ANALYSIS OF A PARTIAL DIFFERENTIAL EQUATION MODEL FOR NECROTIZING ENTEROCOLITIS

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This thesis presents and analyzes a mathematical model for necrotizing enterocolitis (NEC), a devastating disease that attacks the gastrointestinal tract of pre-term infants. Mathematical models for NEC have been developed in the past. These modes are extremely valuable and provide important insights into the disease. However, all of the models developed previously are one dimensional, ordinary differential equation models and, therefore, simulate only the transient effects of NEC but do not fully model its spatial effects. The mathematical model presented here is a three dimensional model in the form of a system of nonlinear partial differential equations. A three dimensional model is needed to accurately simulate diffusion and advection of the major factors in NEC, to account for the different effects of NEC in the different regions in the body, and to fully integrate all the effects of such mechanisms as epithelial cell degradation and migration.

This thesis presents medical research regarding NEC, constructs inflammatory cascades related to the disease, and develops the system of partial differential equation system. Also, full mathematical analysis of the system of equations. The mathematical analysis of the system of partial differential equations and the associated a mixed finite element analysis are, perhaps, the most important parts of the thesis. The results of this analysis have significance for the NEC system and have significance independent of the NEC system. For example, existence, uniqueness, and regularity analysis is presented in the weak mixed form for the coupled nonlinear equations:

$$
\begin{aligned}
&\frac{\partial u_1}{\partial t} - \nabla \cdot (D_1 \nabla u_1 - u_1 \nabla u_2) \;=\; f_1(u_1, u_2) \\
&\frac{\partial u_2}{\partial t} - \nabla \cdot (D_2 \nabla u_2) \;=\; f_2(u_1, u_2) \qquad (x,t) \in \Omega \times (0,T] \\
&\nabla u_1 \cdot \mathbf{n} = 0 \qquad \text{and} \qquad \nabla u_2 \cdot \mathbf{n} = 0 \qquad \text{on } \Gamma
\end{aligned}
$$

where f_1 and f_2 are nonlinear functions. Furthermore, finite element analysis (using the mixed method) is done on this coupled system and convergence is proven, a new and very important result. No mixed method finite element analysis has previously been published for this system. Similar analysis is done on the rest of the partial differential equations in the system. At the end of the thesis, computer simulations are done using the mathematical model. These simulations demonstrate that the NEC mathematical model presented here produces realistic results consistent with the actual progression of the disease.

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Thanks, above all, be to God, since He Himself gives to all people life and breath and all things; (Acts 17:25 b) and to Jesus Christ who died for us so that we may have the assurance of eternal life (I John 2:25). To Him be all the glory.

Mark D. Tronzo

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1.0 NECROTIZING ENTEROCOLITIS

Necrotizing Enterocolitis(NEC) is a devastating and often fatal disease that attacks the gastrointestinal tract of newborns. NEC is characterized by intestinal inflammation, intestinal tissue death including destruction of the intestine, and sepsis. NEC most often attacks preterm infants. Ironically, as the survival rate of preterm infants increases, so does the incidence of NEC. NEC is diagnosed in about 2 out of 1000 live births per year [6]. NEC occurs in approximately 7% of those infants with birth weights between 1 and 3 pounds. The overall death rate among those infants diagnosed with NEC is between 20% and 30% [101].

The purpose of this thesis is twofold. First of all this work presents a three dimensional mathematical model of Necrotizing Enterocolitis(NEC). This model consists of a system of partial differential equations (PDE) that models both the temporal and spatial aspects of NEC. Secondly, this work analyses that NEC PDE system. That is, existence, uniqueness, and regularity analysis is done on the entire PDE system. Also, a mixed finite element analysis is done on the system of equations. This second purpose has significance for the NEC PDE system and it has significance independent of the NEC PDE system. For the NEC system, this analysis provides a strong mathematical foundation for the equations and their interrelation with each other. On the other hand, some of the classes of equations in the NEC PDE system occur, in a slightly different form, in other contexts but, in some cases, no existence, uniqueness, and regularity results for these equations exist in the literature. Even more importantly, the mixed finite element analysis presented later contains some new and very significant results.

This first chapter will investigate much of the current medical research regarding NEC in order to accumulate information for creating the NEC model. Much more material will

be presented in this chapter than will ultimately be used to build the model. This additional material is included for a number of reasons. First of all, when constructing the NEC model it is important to weigh all of the factors involved in NEC in order to decide what will and what will not be included in the model. This can only be done after each mechanism and player in the disease is investigated and evaluated in order to determine its importance to the model. Therefore, much information is presented in this chapter and, then, in chapter two, the evaluation process will be done and the factors to be included in the model will be determined. Secondly, even though some of this material will not be used *directly* in the NEC model, the material will still be used as a guide for setting simulation runs. Therefore, this material will be of great help for creating realistic the initial conditions for the computer simulations presented in chapter seven as well as for computer simulations in the future. Finally, the additional material will provide background and motivation for a more advanced, extensive NEC model in the future. This will be particularly relevant as new medical discoveries come to light.

1.1 OVERVIEW OF THE DISEASE

NEC usually attacks the intestines resulting in severe, often irreparable damage. Bacteria from the lumen may pass through the protective epithelial cells that line the intestines and seeps into the underlying tissue. This triggers an inflammatory response within and around the intestines that involves bacteria, macrophages, neutrophils, cytokines, as well as many other biological components. If this inflammatory response is left unchecked it will cause tissue death and, ultimately permanent damage to the intestine.

The causes of NEC are multifaceted. The main risk factor for NEC appears to be prematurity - the more premature, the higher the risk for NEC. Formula feeding is another risk factor for NEC which may also contribute to the disease once the disease has been initiated. As mentioned above, the translocation of bacteria from the lumen to the underlying tissue of the intestine is a critical factor in NEC, as well as the breakdown of the epithelial layer of cells that protect the intestines. Many of these causes of NEC are interrelated and it

is not always clear which of these factors is most involved in initiating the disease and which are secondary responses. These causes, their effects, and the physical mechanisms involved will now be investigated.

1.2 SMALL INTESTINE STRUCTURE AND FUNCTION

In general, Necrotizing Enterocolitis strikes the gastrointestinal tract. Usually, NEC may attack either the small or large intestine but the effects of NEC discussed in this thesis will usually apply in either case. In this thesis, the small intestine will be used as the representative organ of the GI tract that NEC attacks. Therefore,it will be worthwhile to study the structure and function of the small intestine in some detail.

The study will begin by considering the components of the small intestine that are directly affected by NEC. The open passage way of the GI tract in the small intestine will here be referred to as the **lumen**. The interior radial surface on the lumen side of the small intestine is covered with finger-like projections called **villi** (singular:villus). Throughout the thesis, the villi will be represented by figure 1. These villi are covered by a gel layer called mucus. On the outer part of the villi is a layer of cells called the epithelium. The epithelium is supported below by the basal lamina or extracellular matrix (ECM). In the central portion of each villus is the lamina propria. These (the mucus layer, the epithelium, the extra cellular matrix, and the lamina propria) together make up what is called the mucosa.

The **mucosa** is responsible for functions critical for digestion such as absorption (of nutrients) and secretion (of mucus). The **epithelium** is a layer of connected cells that covers the villi and protects the underlying tissue. Throughout the thesis, the epithelium will be represented by figure 2. These cells move at approximately 5-10 μm per hour and the cells are renewed every 2 to 5 days [64]. The cells of the epithelium are primarily enterocytes, which absorb nutrients and transfer these nutrients into the underlying tissue. Also included in the epithelium are some goblet cells, which secrete mucus (a thick fluid which serves are a protective layer for the epithelium) as well as intraepithelial lymphocytes (IELs). The small intestine contains one IEL for every four to nine epithelial cells [35]. The regions between

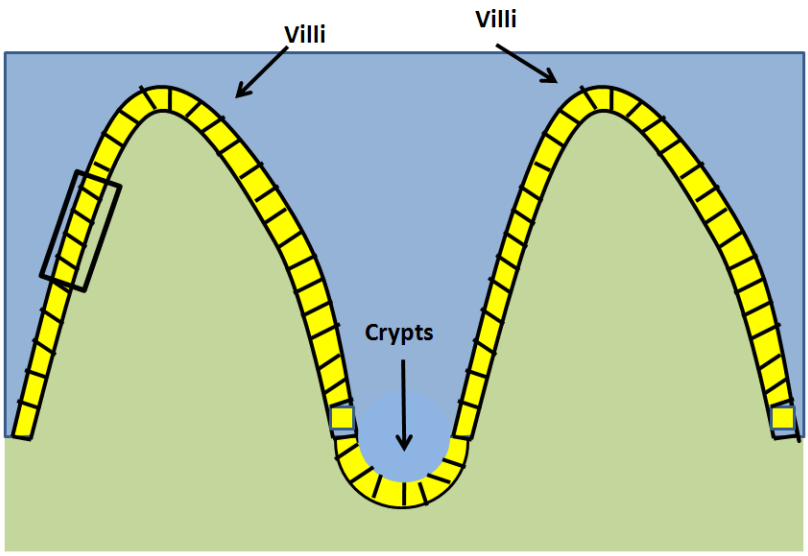


Figure 1: Representation of intestinal villi and crypts. Throughout this thesis, the intestinal villi and crypts will be represented by diagrams similar to this one.

the villi are called the crypts (see figure 1). In the crypts are found Paneth cells, which play an important defensive role. Paneth cells secrete a wide variety of antimicrobial proteins and peptides, such as lysozyme and phospholipase α-defensins, that fight many types of bacteria, viruses, and fungi [106]. They are stimulated to secrete defensins when exposed to bacteria or lipopolysaccharides (LPS) [100]. Paneth cells are also believed to play a major role in protecting epithelial cell proliferation - the Paneth cells' location adjacent to the crypts is an ideal place from which they may protect stem cells from invading bacteria [106], [100]. Between the enterocytes are tight junction proteins (see figure 2), which serve as a barrier that keeps pathogens from passing from the lumen into the underlying tissue, and gap junction proteins, which are important for cell-cell communication.

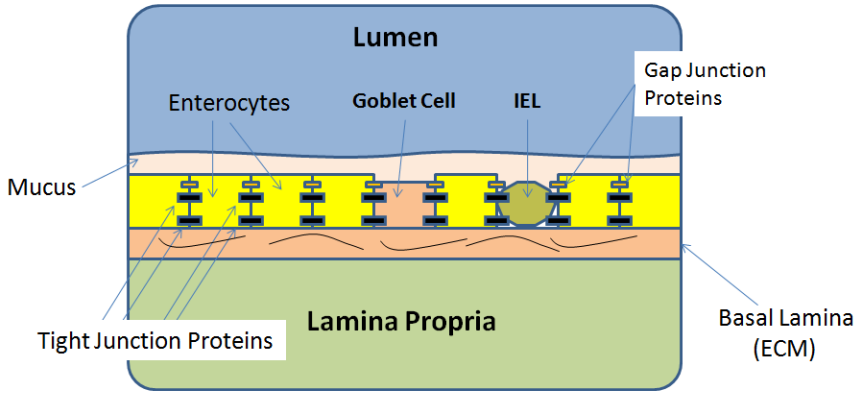


Figure 2: Representation of the epithelium. (This is the region of figure 1 that is enclosed by the rectangle.) Throughout this thesis, the epithelium will be represented by diagrams similar to this one.

The **mucus layer** consists of mucus which is made up of water, lipids, and mucin [6]. Mucins are glycoproteins produced by goblet cells and have the ability to form viscoelastic gels [6], [35]. Mucins provide lubrication and protection of the epithelium from mechanical damage caused by dietary constituents [91]. Mucus forms a continuous covering for the villi. The average mucus layer thickness for the three major sections of the small intestines have been determined to be 170 μm for the duodenum, 123 μm for the jejunum, and 480 μm for the ileum [11]. The mucus layer is the site at which the body first encounters gut bacteria [31]. All bacteria, including commensal bacteria, increase mucus production [60]. The mucus layer serves as protection for the epithelium. Particles, bacteria, and viruses are trapped in the mucus layer and, eventually expelled before they reach the underlying epithelium [131], [140]. Mucus also keeps antimicrobial compounds near the epithelium where they may kill some of the entrapped organisms [140]. Since mucus is continuously created and expelled from the body, any material trapped in the mucus layer, including pathogenic bacteria, is swept away with the exiting mucus [140]. The mucus layer is also a reservoir for secretory immunoglobulin A (IgA). Secretory IgA's bind pathogen and prevents attachment to the

epithelial cells [131].

The mucus layer greatly aids digestion. Mucus forms a constant, unstirred layer thereby keeping digestive enzymes near the epithelium where they may aid normal absorbtion [91]. Molecules in the unstirred layer are, therefore, not taken away by peristalsis [128], [91]. (See discussion of peristalsis later in this chapter.) In addition, mucins lower the diffusion of large pathogenic bacteria but allows the passage of the smaller nutrient molecules [100]. It is most beneficial for the host that the mucus layer be populated by normal flora or indigenous bacteria, that is, the bacteria that is common to that particular host. This bacteria is often referred to as commensal bacteria.

An important resident in the mucus layer is **commensal bacteria**. Commensal Bacteria or Normal Flora plays a protective, beneficial role in the Mucus Layer. The human gut contains between 10 x 10^{12} and 100 x 10^{12} organisms per ml of this commensal bacteria [35],[10]. Whenever it is operating properly, the immune system recognizes commensal bacteria and, therefore, such bacteria does not illicit an inflammatory response. The commensal bacteria protects by: 1) Competing with harmful bacteria for essential nutrients 2) Competing with harmful bacteria for attachment sites 3) Producing substances that kill harmful bacteria [35]. Commensal bacteria also facilitates the digestion, absorption and storage of certain nutrients that would not otherwise be accessible to the host [10], [91].
While population of the mucus layer with commensal bacteria is beneficial to the host, fixation of pathogenic bacteria in the mucus may be good or bad, as Montage [91] points out. Whenever pathogenic bacteria is fixed in the mucus, it cannot reach the underlying epithelial cells and, as long as there are only small amounts of trapped bacteria, the bacteria will be removed together with the mucins during the normal mucus erosion process. On the other hand, if the pathogenic bacterial accumulation in the mucus is at very high levels, so that it exceeds the normal turnover rate of the mucus, then bacterial colonization occurs eventually leading to infection and/or damage to the underlying epithelium [91].

The epithelium lies on what is called basal lamina or **the extra cellular matrix** (ECM). (The ECM may be seen in figure 2.) The extra cellular matrix consists primarily of the protein collagen, elastin, fibronectin. Collagen provides strength to the extra cellular matrix.

Fibronectin binds the epithelial cells to the extracellular matrix and guides cell migration [3].

The **lamina propria mucosae** is the tissue section that lies beneath the epithelium and extra cellular matrix (see figure 2). It consists of smooth muscle cells and fibroblasts [35]. The lamina propria mucosae has been described as 'loose' connective tissue because it does not have a large amount fibrous reinforcement that characterizes more dense connective tissue. Loose connective tissues are easily distorted. Such tissues may move freely with respect to one another.[103] Among the important cells found in the lamina propria are macrophages and dendritic cells [60], [35].

1.3 CELLS OF THE EPITHELIUM

Enterocytes. The majority of cells on the external surface of the small intestine are enterocytes. Enterocytes are formed in the crypts and move out toward the villus tips. These column shaped cells (these are the yellow cells in figures 2 and 3) are responsible for digestion and absorption of nutrients. They transfer substances from the intestinal lumen to the circulatory system. They also obstruct bacteria from entering the underlying lamina propria. Enterocytes release inflammatory cytokines such as IL-6, IL8, and TNF-α and anti-inflammatory cytokines IL-10 and IL-15 [96]. Intestinal enterocytes also secrete antimicrobial peptides such as defensins, cathelicidins, and calprotectins [10].

On top of the enterocytes is the actin-rich microvillar extension surface known as the **brush border** (see figure 3). The brush border serves to impede microbial attachment and invasion. It contains digestive enzymes and transporter systems involved in uptake and metabolism [10].

Goblet Cells. Goblet cells secrete mucus that covers and protects the epithelium (see figure 3). Goblet cells mature in the crypts and, after maturation, travel for 5-7 days to the villus tips. When necessary these cells will secrete large amounts of mucus in response to bacterial insult [100]. Goblet cells have the ability to secrete mucins that promote colo-

nization by commensal bacteria. Also, there is evidence that goblet cells, after coming into contact with specific pathogenic bacteria, can produce mucus to which that bacteria will bind. This will prevent the bacteria from binding to enterocytes [31].

M-Cells. These are specialized epithelial cells that lie over the Peyer's Patch and lymphoid follicles. (The Peyer's Patch consists of bundles of lymphatic tissue. See figure 3. The Peyer's Patch plays some role, not yet fully known, in immune response.) Unlike other epithelial cells, M cells do not have long, fully developed **microvilli** (microvilli are the small fingerlike projections on the top surface of many cells) and they lack certain surface glycoproteins. Instead, their microvilli are short and irregular. All of this means that antigen have easy access to the apical surface of M cells. In fact, the primary function of M cells is to transport material from the lumen, across the epithelium, to the underlying tissue [28]. In particular, M-Cells constantly sample the contents of the lumen and deliver antigen to cells in the underlying tissue where inflammatory cells will be recruited if necessary [10].

Paneth Cells. These cells originate in the crypt stem cell region (see figure 4) but unlike enterocytes, goblet, and M cells, Paneth cells move down toward the base of the crypts [100]. Paneth cells secrete antimicrobial peptides and play a general defensive role. These peptides apparently play a key role in destroying pathogenic bacteria while promoting colonization of favorable bacteria. Therefore, the proper functioning of Paneth cells is critical for intestinal homeostasis [18].

1.4 IMPORTANT MECHANICAL AND PHYSICAL FACTORS.

1.4.1 Cell Death and Renewal of the epithelium

Cell death is an ongoing event of the epithelium. This death may be due to natural causes or due to injury. Three types of **cell death** have been identified:

1. **Apoptosis** (Programmed Cell Death). This is cell death in an organized, well co-

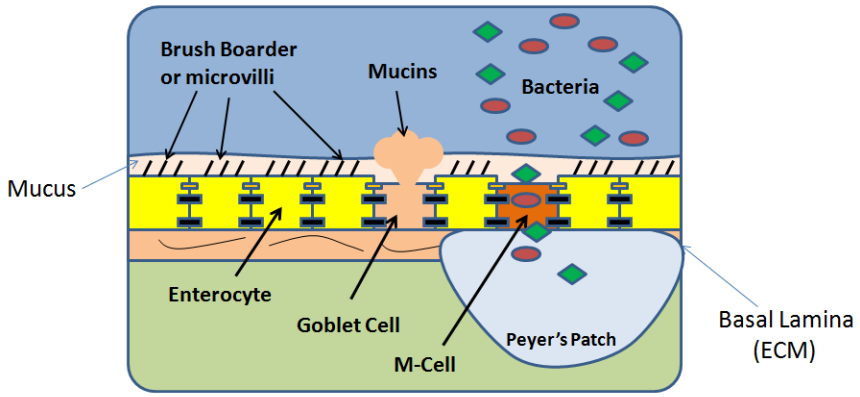


Figure 3: Cells of the epithelium. (This figure is similar to figure 2 but shows different detail.) The brush border on enterocytes prevents microbes from attaching to the enterocytes. Goblet cells secrete mucins. Mucus (mucins) helps to provide lubrication and protection for the epithelium. Mucus also keep enzymes near the epithelium, away from the effects of intestinal peristalsis, so that the enzymes may be easily absorbed. M-Cells constantly sample the lumenal contents and transport bacteria (gram-positive and gram-negative bacteria) to the underlying Peyer's patch.

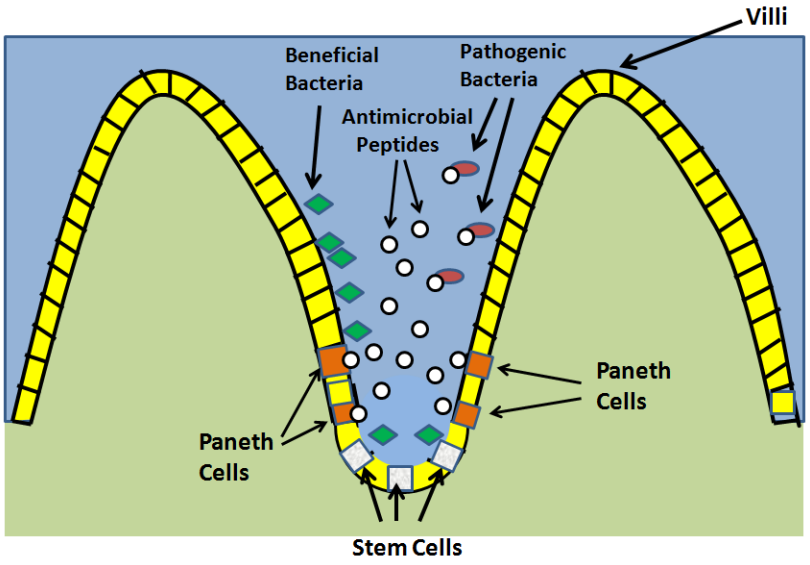


Figure 4: Function of Paneth Cells. Paneth Cells are located in a strategic defensive position near the crypts. There these cells are able to defend the stem cells located in the crypts. Paneth cells secrete antimicrobial peptides that destroy pathogenic bacteria and promote colonization by beneficial bacteria.

ordinated fashion followed by an organized removal of the dying cells. Apoptosis is usually timely and desirable as it removes malfunctioning, senescent, or potentially dangerous cells. However, if apoptosis occurs at too high a rate, the epithelial barrier function may be compromised [122]. It is not clear what causes apoptosis but TNF has been implicated as a major factor in cell apoptosis/cell shedding [58].

2. Cell Shedding (Cell Suicide). Cell shedding is usually restricted to the surface cells or villus tip cells where cells are loosely attached and may be easily shed into the lumen. This shedding may involve single cells or sheets of cells [44]. It must be noted that some believe that cell shedding is the result of apoptosis and, therefore, should not be classified as a distinct form of cell death. On the other hand, others have observed that cell shedding regularly occurs even among cells that have no evidence of initiation of apoptosis [138].

3. Cell Necrosis. This may be the result of injury and is characterized by the rapid breakdown of the membrane integrity. The result is the release of cellular contents which may damage nearby cells and create an unwanted cellular response. For example, HMGB1, which is known to activate TLR4, is often released from damaged cells [44],[122].

An important mechanism in the small intestine is the process of **renewal of the epithelium**. Under normal circumstances, intestinal epithelial cell turnover in nonhuman mammals is about 2 days for adults but 4-5 days for infants [100]. In the absence of injury, cells are shed at the villus tips and they are replaced by cells migrating up the villus from the crypts. As a cell is in the process of being shed it induces its neighboring cells to shed and, in fact, these neighboring cells shed about 5-10 minutes later [48]. In this way, the epithelium is constantly renewed.

There are times during which epithelial cells shed at a higher rate than the rate at which new cells move in to replace them. The result is that there are often gaps in the epithelium. A paper published in 2005 indicated that about 3 % of the epithelium does not have cells covering it at any given time [138]. This result appears to have been widely accepted, however, a more recent study indicates that these gaps amount to a little less than 1 % of the epithelium [48]. Either of these estimates would suggest that large passages exist in the epithelium through which pathogenic bacteria might easily pass. Yet, during this entire process of cell shedding and replacement, the epithelial barrier function is maintained, i.e.,

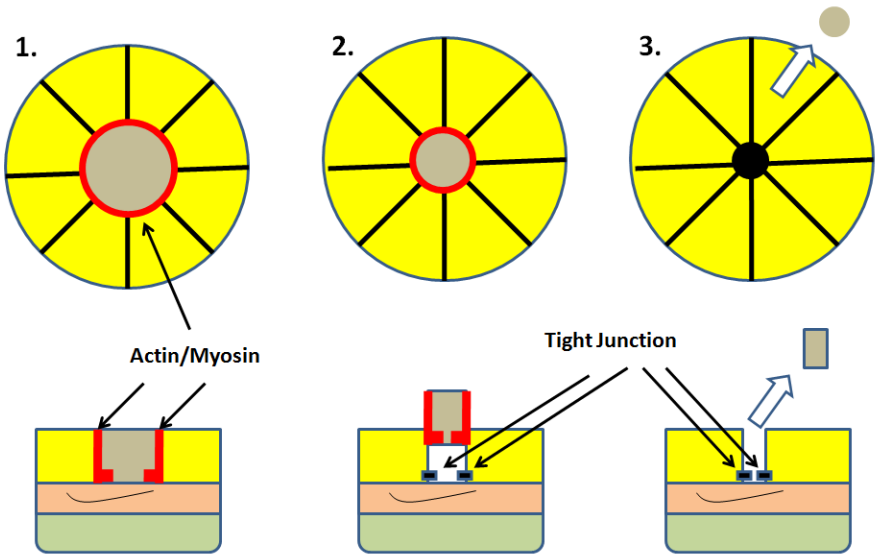


Figure 5: Cell Shedding. The top row shows the top view of the epithelium and the bottom row shows the side view of the epithelium. 1.) An actin/myosin ring forms around and under the dying cell (the dying cell is colored gray). 2.) This actin/myosin ring begins to contract and, thereby, begins to force the dying cell up and out of the epithelium [118]. At the same time, neighboring cells begin to move under the dying cell and tight junctions begin to redistribute under the cell (see Guan,[48]). 3.) The dying cell is forced completely out of the epithelium and the tight junction proteins seal the resulting gap.

the epithelium remains sealed. This can be explained by either (1) cytoplasmic extensions from neighboring cells, (2) an extracellular substance is secreted, perhaps by neighboring epithelial cells, that fills the gap [138], (3) tight junction proteins will form connections between the cells neighboring the departing cell [48]. The most recent research favors a combination of (1) and (3): As a cell leaves the epithelium, its neighboring cells move in underneath the dying cell and ZO1 (a tight junction protein) redistribution occurs. This redistribution seals the gap created by the shed cell [48].

Therefore, current knowledge suggests the following model for cell shedding and the continued maintenance of the epithelium: First, an actin/myosin ring forms around and under the dying cell. Secondly, this actin/myosin ring begins to contract and, thereby, begins to force the dying cell up and out of the epithelium [118]. At the same time, neighboring cells begin to move under the dying cell and tight junctions begin to redistribute under the cell [48]. Thirdly, the dying cell is forced completely out of the epithelium and the tight junction proteins seal the resulting gap. (This model is illustrated in figure 5.)

1.4.2 Wound Healing

NEC is usually accompanied by some injury to the epithelium. Any injury to the epithelium reduces its barrier function, thereby bacteria and other toxins may invade the underlying tissue causing sustained inflammation to the host. Rapid and efficient resealing of the wounded area is, therefore, essential to full recovery from NEC. Proper wound healing depends upon many factors including proper cell migration, proliferation, and differentiation as well as restoration of tight junctions between the cells [94]. Some important features of these processes will be mentioned here.

After injury to the small intestine epithelium, a number of processes (processes which may overlap) go into motion. **1 Villus Contraction.** Almost simultaneous with the injury, the villus dramatically contracts. This contraction greatly reduces the wounded area, thereby aiding the healing process. **2** Within minutes after the injury, epithelial cell **restitution** begins. Epithelial cells adjacent to the injured area begin to migrate to cover the exposed area. This process does not usually involve cell proliferation. **3** About 18-24 hours after

injury, **cell proliferation** occurs in the crypts. This replenishes cells lost during injury. **4** The final, and essential, step in repairing the epithelium and all of its functions is the **restoration of tight junctions** [19], [82].

1. Villus Contraction A most interesting feature of wound healing in the small intestine is the phenomenon of villus contraction which greatly aids restitution. After an injury, the villus actually contracts to reduce the surface area that needs to be resealed by epithelial cells. (see figure 7) Specifically, the villus contracts enough to reduce the "open area" by about one half. It has been discovered that one large contraction of the villus occurs immediately after injury. After that, the villus continues to contract, albeit at a slower rate, in the hours following the injury [92].

2. Restitution Wound healing depends upon the cells' ability to move across the extracellular matrix. Immediately after injury, the cells adjacent to the wound begin to migrate in order to cover the exposed part of the ECM. The leading edge of the cell flattens and stretches forward attaching to the ECM at some point of the uncovered area of the wound. In the process of stretching and reaching, elastic forces are generated in the cell. These elastic forces cause the back of the cell to detach from the ECM. The cell then contracts and the process is repeated. (see figure 6).

The attachment to the ECM is accomplished by activated integrins located at the bottom of the cell. The integrin's proper adherence to the ECM is essential for efficient cell motility. This adherence must be strong enough for the cell to get enough traction to pull itself across the ECM and, yet, it must not be too strong otherwise the integrins at the the back of the cell will not detach from the ECM in a timely manner.

The whole process of cell motility is very complex. However, a crude summary of the process may be presented here: 1) A prerequisite to cell motility is sufficient integrin expression on the bottom of the cell - enough expression to firmly adhere to the ECM. 2) There is a "spreading" or a shape changing of the cell from a round to a flattened shape. This "flattening" tends to be more pronounced at the leading edge of the cell. This front flattened part of the cell is known as a **lamellipod**. 3) Due to the "stretched" state of the cell, forces will be generated within the cell tending to pull the leading edge and trailing edge of the cell toward the middle. 4) The trailing edge of the cell detaches from the ECM. 5) The cell

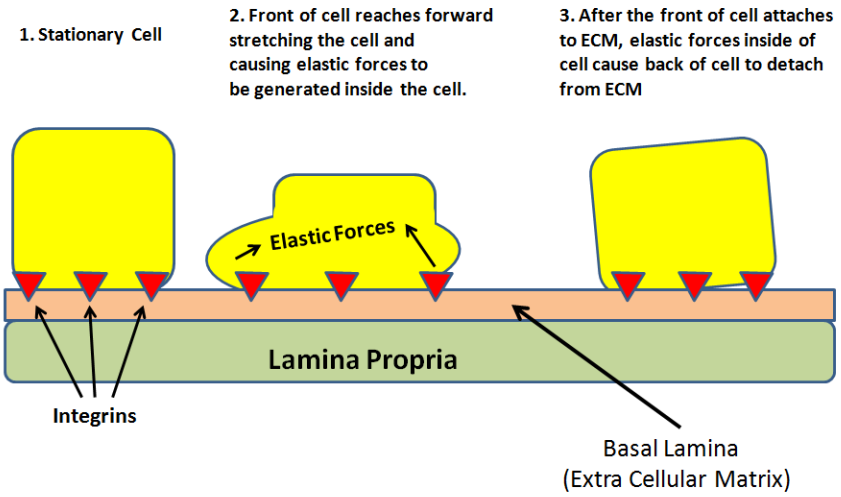


Figure 6: 1. Stationary Cells 2. Cell moves by reaching forward. In the process of stretching, elastic forces are built up in the cell. 3. Elastic forces cause the back of the cell to detach from the ECM.

changes shape again, returning to a somewhat rounded shape. 6) The whole process begins again.

Thus it can be seen that if the adherence of the cell to the ECM is not great enough, i.e. there is not enough integrin expression or the integrins do not bind properly to the ECM, too little "traction" will be generated at the front of the cell for it to grip and pull itself efficiently across the ECM. This results in slow cell movement. On the other hand, if the adherence is too strong, the cells may still have the ability to reach forward, stretch and attach at a forward point on the ECM but the elastic forces generated within the cell will not be strong enough for the trailing edge of the cell to "break free" from the ECM. Again, resulting in little or no cell movement. Experiments have shown that exposing cells to large amounts of bacterial LPS leads to overexpression of integrins and, therefore, greatly inhibited cell movement [113].

Not surprisingly, then, maximum cell migration speed occurs at an intermediate ratio of cell-ECM adhesiveness to intracellular contractile forces. This intermediate ratio occurs at levels at which the cell can both properly adhere at the front end while still being able to

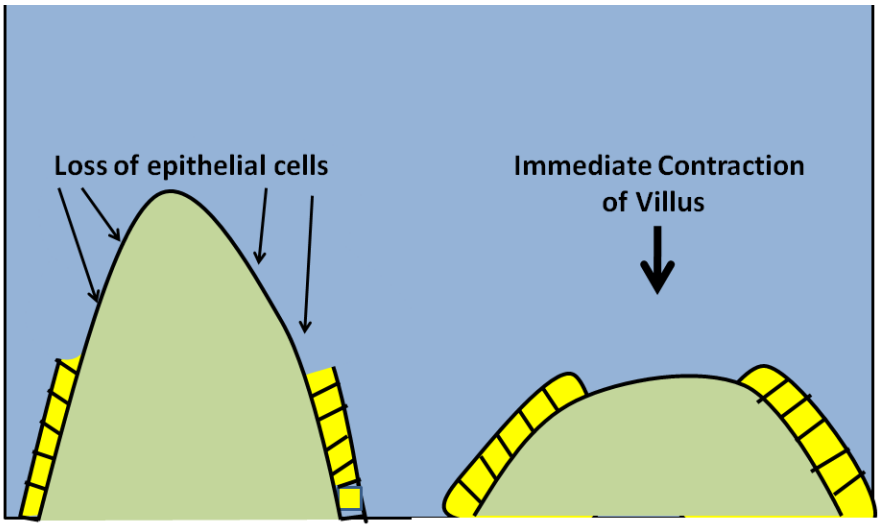


Figure 7: Villus loses epithelial cells due to injury or other insult to the intestinal villi (left), the villus immediately gets shorter (right) thereby reducing the surface area that must be covered by the migrating cells.

detach at the rear of the cell [107].

3 Epithelial Cell proliferation Even though the wound has been covered during the restitution process, many less cells are present in the epithelial. About 18-25 hours after the injury, new cells are formed in the crypts which replenish cells lost during the injury [19].

4 Restoration of Tight Junctions After the wound has been closed, the tight junction proteins begin to be restored. However, studies have determined that adherens junctions are restored prior to the tight junctions. Adherens junctions, which form just below tight junctions, have a belt-like structure and appear to hold adjoining cells together like a thread in clothing even though the cadherins do the actual adhesion. (see figure 8). It is only after the reestablishment of the adherens junctions that the tight junctions begin to be formed [49], [3], [19]. Only after the tight junctions are fully formed is the barrier function of the epithelium restored.

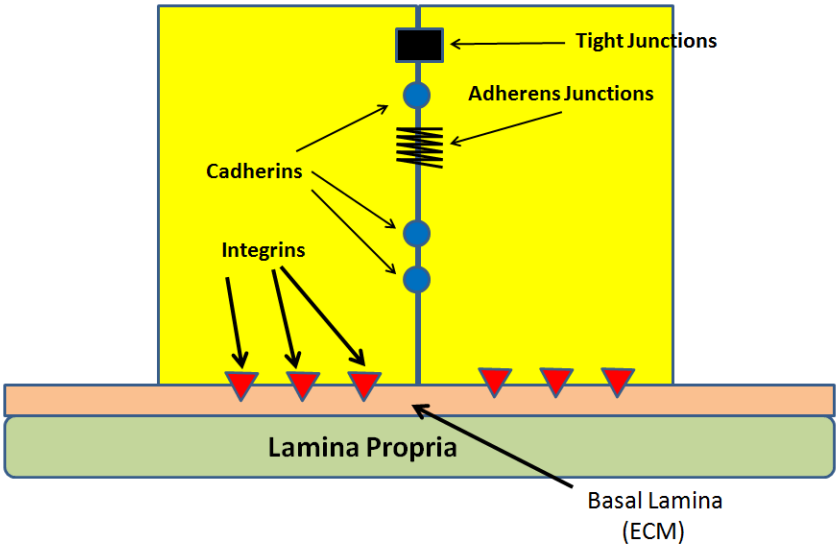


Figure 8: Tight Junction, Adherens, Cadherins, Integrins. During the restitution process, adherens junctions are reestablished. Only after that, do the tight junctions begin to be restored.

Growth Factors and Cytokines that enhance restitution.

Several growth factors and cytokines enhance epithelial restitution. Some of these operate through a transforming growth factor beta (TGF-β) dependent pathway while others work through a TGF-β independent mechanism. TGF-β, which is a product of lamina propria cells and epithelial cells, is required for normal epithelial cell migration even in the absence of injury or insult [32], [82]. TGF-β itself stimulates the migration of intestinal epithelial cells and mediates the work of other migration-promoting growth factors and cytokines [44]. Such growth factors and cytokines act on the basolateral part of the epithelial cells and include TGF-α, EGF, HGF, and FGF peptides as well as the cytokines IL-1, IL-2, IFN-γ [32].

Some of the members of the trefoil factor family (TFF) of peptides play an important role in epithelial restitution. These peptides work from the apical side of the epithelial cells and work in conjunction with glycoproteins through a TGF-β **independent** mechanism [32]. Many of the TFFs are secreted by intestinal goblet cells and remain in the lumen.

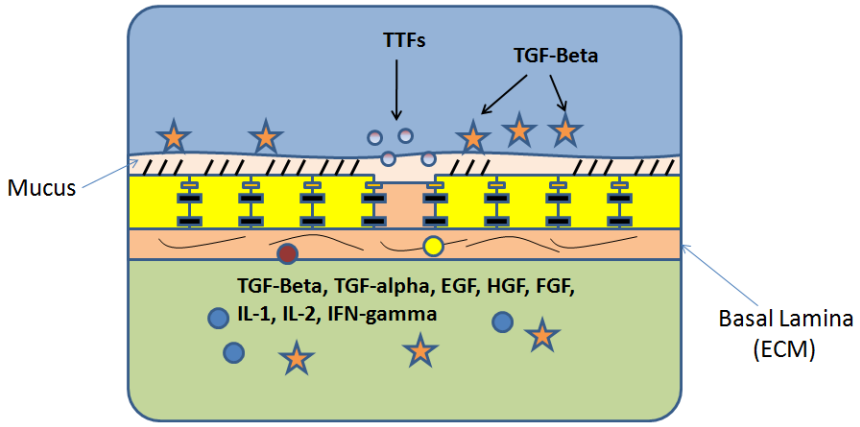


Figure 9: Members of the trefoil factor family (TFF) of peptides are secreted by goblet cells. TGF-Beta is secreted by epithelial cells and lamina propria cells. These, along with the other factors and cytokines shown in the figure, promote epithelial restitution.

Their special structure allow these peptides to survive in the lumen - they are resistant to degradation by luminal enzymes [44]. TFFs interact with the mucus and influence epithelial restitution [82].

EGF which is primarily known to stimulate epithelial cell proliferation (see below), has also been shown to promote epithelial restitution. One study showed that EGF promoted Caco-2 enterocyte sheet migration that was dependent upon the make up of the extracellular matrix. In particular, EGF was observed to stimulate migration over laminin and this migration was independent of cell proliferation [15].

Growth Factors and Cytokines that enhance cell proliferation.

EGF and TGF-α, which is a product of most intestinal epithelial cells, are among the most important stimulators of intestinal epithelial cell (IEC) proliferation. To a much lesser extent, other growth factors, peptides and cytokines stimulate proliferation. These include

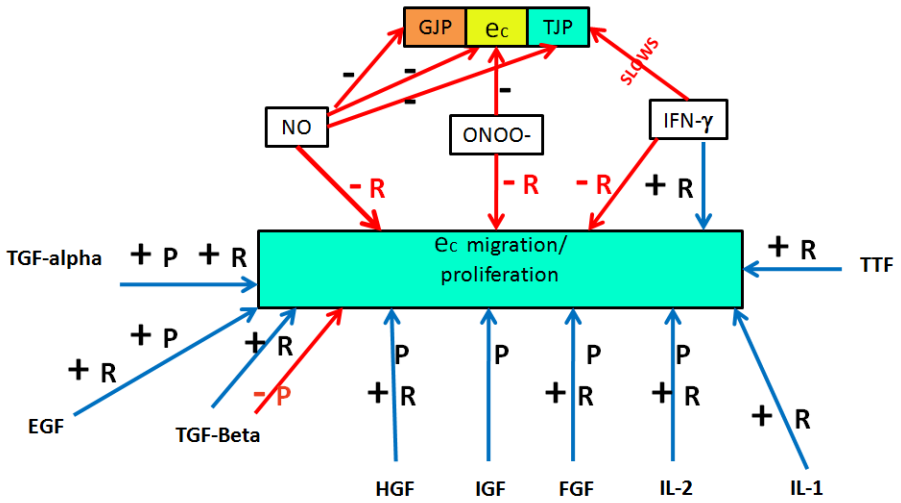


Figure 10: Disruption and restoration of the epithelium. At the top of the illustration we see that nitric oxide destroys gap junction protein (GJP), epithelial cells and tight junction protein(TJP). Also, proxynitrite (ONOO-) destroys epithelial cells and IFN-gamma downregulates the production of tight junction protein. In the middle and the bottom of the illustration, we see the effects on epithelial restitution and proliferation: P means that the cytokine or growth factor contributes somewhat to epithelial proliferation. +P means that the cytokine or growth factor contributes greatly to epithelial proliferation. -P means that the cytokine or growth factor inhibits epithelial proliferation. +R means that the cytokine or growth factor contributes greatly to epithelial restitution . -R means that the cytokine or growth factor inhibits epithelial restitution.

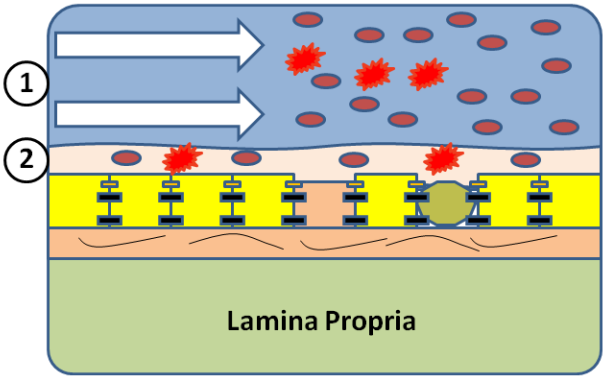


Figure 11: Intestinal Peristalsis. **1.**Peristalsis keeps bacteria and other material moving through the lumen. **2.**Bacteria and other components that are fixed in the mucus layer are not effected by peristalsis.

FGF, IGF, HGF, and IL-2 [32]. Interestingly, TGF-β inhibits cell proliferation. If not for its inhibitory effects, cell growth might continued uncontrolled [32].

1.4.3 Intestinal Peristalsis

. This mechanism is initiated by wave-like muscular contractions that causes contents of the lumen to move along the GI tract. As noted earlier, bacteria and other material that is trapped in the mucus layer will not normally be affected by peristalsis. On the other hand, peristalsis, when working properly, has the effect of limiting the amount of time antigen are able to interact with the epithelial cells thereby limiting bacterial translocation [61] (see figure 11). If this mechanism is impaired or underdeveloped, then bacteria, which is supposed to keep moving through the lumen, may build up and remain in contact with the mucosa for long periods of time possibly resulting in bacterial translocation and damage to the epithelium [6]. As will be seen later (see the subsection on prematurity), intestinal peristalsis is, in fact, underdeveloped in preterm infants and this plays a role in NEC.

1.4.4 Bacterial Translocation

The movement of bacteria (translocation of bacteria) from the lumenal side of the epithelium to the underlying tissue is a key factor in the inflammatory cascade and, therefore, a critical

factor in NEC. Three of the most important bacterial pathways from the lumen into the underlying tissue are A) through a disruption in the epithelium; B) by a paracellular pathway, in between epithelial cells; and C) transcellular pathway, phagocytosis by the enterocytes. (see figure 12.)

Disruption of the epithelium. The intestinal epithelium may be injured in many ways including interaction with microbes, inflammation, oxidative stress, toxic substances in the lumen, as well as by normal functions such as digestion [64]. Any such injury will result in a loss of cells in the epithelium and, therefore, the free flow of bacteria into the underlying tissue.

Paracellular Pathway. As noted above, tight junction proteins prevent large particles, such as whole bacteria, from passing between epithelial cells. (Note: it may be possible for smaller particles, such as LPS, to pass between epithelial cells even when tight junction protein is in tact.) However, any disruption of the tight junction barrier, for example by nitric oxide, will result in increased "leakage" between cells of the epithelium allowing even whole bacteria to pass.

Transcellular Pathway. There is speculation bacteria is able to move through enterocytes of the epithelium. This speculation is the result of studies that prove that enterocytes are capable of phagocytosis of gram-negative bacteria. These same studies indicate that TLR4 is required for the process of enterocyte phagocytosis [97].

1.5 FACTORS CRITICAL TO NEC

1.5.1 Affects of Prematurity

Preterm infants are much more susceptible than term infants to many diseases including NEC. Preterm infants are vulnerable to NEC because many of their bodily systems are severely underdeveloped. The preterm infant suffers from underdeveloped intestinal peristalsis, an immature GI immune system, excessive immune response, immature glycosylation, lower levels of antimicrobial peptides, and lower levels of EGF.

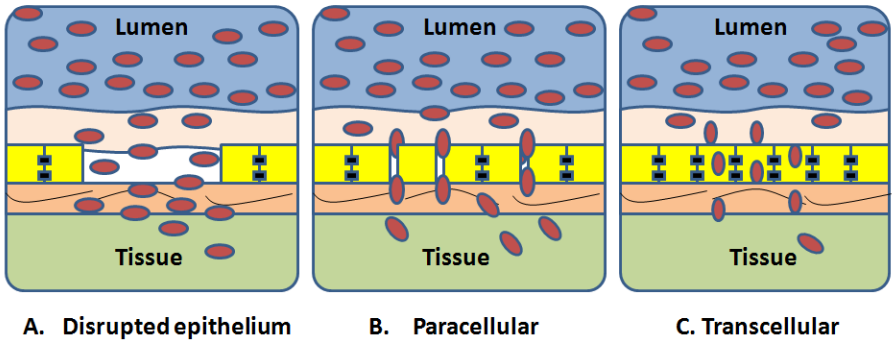


Figure 12: Three important pathways of bacteria from the lumen into the tissue are A) through a disruption in the epithelium B) In-between cells, after tight junction protein is missing or degraded C) phagocytosis by enterocytes.

Underdeveloped Intestinal Peristalsis. As noted above, peristalsis is required for the sustained movement and distribution of luminal contents. In particular, properly working peristalsis keeps bacteria and other antigen from congregating and lingering too long at any one location on the epithelium. Premature infants do not have fully developed peristalsis. The associated migrating complexes are not present in the preterm infant until around 34 weeks gestation [120]. Therefore, in the context of undeveloped or limited peristalsis, large amounts of gram-negative bacteria may congregate near the mucus layer and, if the build-up is great enough, the bacteria may colonize the mucus layer and eventually contact the underlying epithelium. This may result in an inflammatory response, epithelial cell death, and bacterial translocation [6].

Immature Gastrointestinal Immune System The gastrointestinal immune system in the premature infant is underdeveloped. In particular, the premature infant has less protective mucus, less gastric acid production, and lower levels of secretory IgA. In addition, the premature infant has increased mucosal permeability. [26]. Pathogenic organisms are more likely to attach to and translate across the epithelium in immature animals than in mature animals. [26].

The mucin layer is rather sparse in the premature infant. This may be due to the fact that immature goblet cells secrete less mucin than mature cells [51], [99]. As a consequence of this sparse layer, pathogenic bacteria have easier access to the underlying epithelium.

Also, pathogenic bacteria adhere to the complex carbohydrates of mucin, another defence mechanism provided by mucin. Therefore, the reduced mucin levels results in this mechanism being severely handicapped [91].

Bile acids, which play a critical role in digestion, may cause damage to the immature epithelium. The accumulation of Bile acids near the epithelium has been shown to cause damage to the epithelial cells. In particular, bile acids have been shown to reduce the amount of Mucin 2 produced by intestinal goblet cells. Evidence shows that this reduction on mucin secretion by goblet cells is much more pronounced in immature than mature cells [86].

Gastric acid, which acts as a barrier to microorganisms, is much lower in very low birth weight (VLBW) preterm infants, compared to full term normal sized infants [100]. For all preterm infants, the gastric PH levels are initially much higher than for term infants but these levels come back to normal as time passes [62].

Finally, preterm infants have lower levels of secretory IgA, an antibody which binds bacteria [26], [51].

Excessive Immune Response It has been determined that the immature intestine has an exaggerated response to certain stimuli. In particular, studies have shown that both Caco-2 and H4 cells exhibited increased secretion of IL-8 in response to LPS and IL-1β [96].

Immature Glycosylation Glycosylation results in the creation of carbohydrate receptors on the microvilli. These carbohydrate receptors serve as binding sites for gram-negative bacteria. Glycosylation is a developmentally regulated process and, therefore, is not complete in the pre-mature infant [26],[34]. On the one hand, the lack of binding sites for bacteria may seem advantageous (i.e. it may be less likely for bacteria to colonize near the epithelium). On the other hand, these binding sites may also serve as another layer of protection for the epithelium - another obstacle for the bacteria. As a result, immature glycosylation results in more pathogenic bacteria crossing the epithelium and penetrating the underlying tissue. Furthermore, colonization by commensal bacteria is beneficial to the host as it competitively

excludes pathogenic bacteria from congregating near the epithelium. Such colonization by commensal bacteria is not possible without the carbohydrate receptors on the microvilli.

Lower levels of antimicrobial peptides Defensins are antimicrobial peptides of which certain types, such as HD5 and HD6, are produced by Paneth Cells. Like other antimicrobial peptides, these defensins kill pathogenic bacteria and are, therefore, critical to epithelial layer defense. There is strong evidence to suggest that Paneth cell production of defensins is significantly lower in premature infants compared to term infants and increases with gestation age [119].

Low Levels of EGF Epidermal Growth Factor (EGF) is extremely important for epithelial cell proliferation and, in some cases, aids restitution of the epithelium. Therefore, lack of EGF may result in slow repair to the epithelium after injury or insult. EGF may come from many sources but the great majority of EGF is produced in the salivary glands. Studies have shown that infants at earlier gestational ages have lower levels of EGF during their first days of life compared to other infants [136].

Low levels of PAF-degrading enzyme PAF-acetylhydrolase (PAF-AH) As will be noted later in this chapter, Platelet Activating Factor (PAF) plays a large part in the pathology of NEC. In an adult, PAF may normally be kept under control by the PAF-degrading enzyme PAF-acetylhydrolase (PAF-AH). In the newborn, PAF synthesis pathways are increased and the newborn has low circulating activity of PAF-AH [121], [93]. There are strong indications that PAF-AH is found in even lower quantities, or may not exist at all, in the pre-term infant [93].

1.5.2 Advantages of Breast Feeding vs. Formula Feeding in NEC

The advantages of breast feeding over formula feeding are well documented. The incidence of NEC is much higher in formula-fed compared to breast-fed neonates [79]. Richter, et al notes that breast-feeding has antimicrobial, ant-inflammatory, and immunomodulating properties and influences the intestinal flora.

Among the advantages of breast feeding in the case of NEC are: 1) Breast feeding results

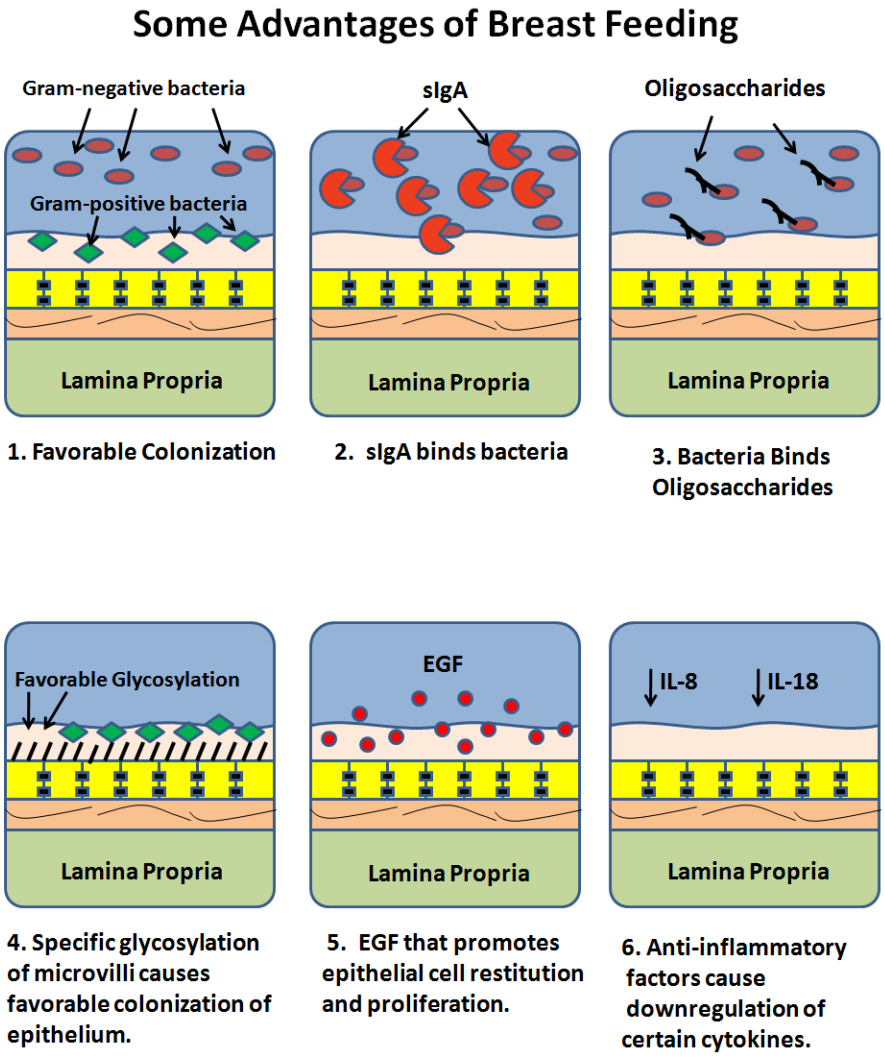


Figure 13: Some of the advantages of breast feeding: 1. Beneficial colonization of the gut competitively excludes pathogenic bacteria. 2. Secretory IgA specifically targets bacteria to which the mother has been exposed. 3. Oligosaccharides have similar structures as binding cites on epithelial cells, therefore, pathogenic bacteria will bind these rather than epithelial cells. 4. Breast feeding causes glycosylation of the epithelial microvilli that attracts favorable bacterial colonization. 5. EGF in breast milk promotes epithelial cell restitution and proliferation. 6. Anti-inflammatory factors cause downregulation of certain cytokines including IL-8 and IL-18.

in a more beneficial colonization of the gut (that is, the gut is colonized with primarily gram-positive bacteria) and, thereby, "competitively excludes" more harmful pathogen from accumulating near the epithelium. 2) There are anti-inflammatory factors in breast milk. 3) Antibodies in breast milk such as secretory IgA bind specific pathogens to which the mother has been exposed. 4) Oligosaccharides in breast milk act as decoys - bacteria binds to the oligosaccharides rather than to the epithelial cells. 5) Breast milk facilitates maturation of the intestinal mucosal barrier and 6) Breast feeding results in favorable glycosylation patterns on the intestinal microvilli.

1. Beneficial bacterial colonization of the GI tract. Current opinion suggests that the gram-positive bacteria bifidobacteria and lactobacilli are the most beneficial bacteria that can colonize the infant gut. On the other hand, staphylococci and clostridia are potentially pathogenic. [111] Breast feeding results, primarily, in gram-positive colonization of the GI tract (e.g colonization primarily bifidobacterium, along with some lactobacillus, streptococcus. In particular, lactoferrin and α-lactalbumin in breast milk stimulate the growth of bifidobacterium [17]). Even though some enterobacteria (gram-negative bacteria) is present in breast-fed infants, it is the bifidobacterium that predominates the breastfed infant gut [102], [51]. Gram-positive bacteria tends to attenuate the growth of gram-negative bacteria and leads to the production of lactic acid which is easily absorbed in the small intestine [83],[112]. Just as importantly, gram-positive bacteria competes with pathogenic bacteria for binding sites and nutrients.

While it is true that there is some gram-positive lactobacilli in the gut of formula-fed infants, there are sufficient pathogenic species such as staphylococcus, escherichia coli, and clostridia to be a potential danger [26], [51]. In general, formula feeding may lead to proliferation of gram-negative bacteria (e.g. coliforms) in the intestine [13]. Gram-negative colonization of the GI tract will intensify any inflammatory cascade and will make the host vulnerable should any insult to the intestine occur. Also, gram-negative bacteria can lead to the production of hydrogen, carbon dioxide, and organic acids. All of which are not easily expelled from the body [112].

Infants delivered vaginally and born at home have the most beneficial gut colonization (the most bifidobacteria and the least C. difficile and E. Coli).Hospitalization and prematu-

rity are both associated with C. difficile. [111] Antibiotics reduced both bifidobacteria and bacteroides [111].

2. Anti-inflammatory factors in human milk. Goldman [45] lists several anti-inflammatory factors in human milk: cytoprotectives, epithelial growth factors, maturational factors, binders of enzymes, modulators of leukocytes, antioxidants. Also, TGF-β1 is in human breast milk. Human milk suppresses IL-1β induced IL-8 production in intestinal epithelial cells [100].

3. Antibodies in breast milk. Among the most important components of human milk that serve as antimicrobial agents include IgA, lactoferrin, and lysozyme [26].

Antibodies in breast milk such as Polymeric IgA (pIgA) and secretory IgA bind antigens, bacteria and endotoxin. In infants, this secretory IgA binds to pathogens before the pathogens attach to the epithelial lining of the intestinal wall [6]. Polymeric IgA and secretory IgA are produced by the mother's immune system and are created to bind the specific pathogens to which the mother has been exposed [26], [102]. It is likely that mother and infant will be exposed to many of the same pathogens, therefore, these antibodies provide a particularly relevant and valuable defensive tool.

Kohler, et. al. [72] report that human milk is rich in immunoglobulins of which about 90% is secretory IgA. The Kohler study showed that IgA concentrations in the feces of breast-fed infants was three times high than in formula-fed infants.

Lactoferrin and lysozyme are nonspecific anti-microbial factors. [26] Lactoferrin has been shown to have anti-microbial activities against a broad range of bacteria but all the types of bacteria and all the conditions under which it is effective have not yet been fully established [39], [102]. Lactoferrin also appears to work synergistically with lysozyme against bacteria [39].

Finally, Goldman [45] notes that these antimicrobial peptides have further advantages: they are resistant to digestive enzymes and they operate without causing an inflammatory response.

Defensins are endogenous antimicrobial peptides produced by the epithelial surface,

which provide nonspecific defense against against a multitude of microorganisms. In the small intestine, $\alpha-$defensins are expressed predominantly by Paneth cells.

4. Oligosaccharides in breast milk act as decoys Human milk oligosaccharides are complex carbohydrate structures that are normally attached to lactose and which survive the passage through the intestine [102]. Oligosaccharides actually bind to bacteria before the bacteria are able to attach to glycoconjugates on the microvillous membrane [102]. Oligosaccharides act as decoys (homologues of of host surface glycoconjugates) so that bacteria bind to the Oligosaccharides rather than to the glycoconjugates on the microvillus membrane. Pathogenic bacteria will bind intestinal epithelial cells via protein adhesions but many oligosaccharides in human milk have the same sugar sequences as the carbohydrate chains of glycolipids and glycoproteins on human epithelial cell surfaces [34]. Thus they prevent binding of pathogen to the intestinal epithelial cells. [26] [102], (Goldman 1993). Oligosaccharides may also act as nutrients for beneficial commensal bacteria [100], [99].

5. Breast Milk Facilitates Maturation of Intestinal Mucosal Barrier EGF is found in large amounts in the breast milk of the mothers of preterm infants (actually it is found in colostrum - milk generated just before giving birth). In fact, the more premature the infant, the higher the level of EGF in breast milk [137]. Not only does EGF promote epithelial cell restitution and proliferation but also downregulates the production of the inflammatory cytokine IL-18 and upregulates the anti-inflammatory cytokine IL-10 [137]. Another study showed that HB-EGF, a member of the EGF family, promoted cell migration/proliferation and resulted in reduced epithelial cell necrosis/apoptosis as well as lower levels of Nitric Oxide [40]. Thus, EGF is particularly important to help prevent and/or relieve NEC.

6. Favorable Glycosylation Patterns As noted above, bacteria binds to the microvilli on the apical side of the epithelial cells. Of course, it is desirable for non-pathogenic bacteria to bing to these cells. According to Bernt [17], certain bacteria will bind to specific glycoconjugate compositions on the microvilli of cells. Specific hormones in breast milk, cortisol in particular, induces glycosylation patterns on the microvilli that results in colonization by non-pathogenic bacteria [17]. Thus, breast feeding results in favorable glycosylation.

7. PAF-degrading enzyme PAF-acetylhydrolase (PAF-AH) As noted above, the newborn has low circulating activity of PAF-AH and evidence suggest that even lower quantities of PAF-AH are found in the pre-term infant [93]. Formula does not contain PAF-AH but human milk contains large quantities of PAF-AH. Interestingly, studies indicate that milk from mothers of pre-term infants contain significantly higher amounts of PAF-AH than even normal breast milk [121], [93].

1.5.3 Particular Advantages of Breast Feeding in case of Prematurity

When one carefully considers the facts given in the last two sections, it is impossible not to notice that for many of the disadvantages of prematurity, there is a corresponding advantage in breastfeeding. For some reason, this fact does not appear to be emphasized in the journal articles. Perhaps because it is so obvious? In any case, this is summarized in the following table.

1.6 DESCRIPTION OF INFLAMMATORY CELLS, CYTOKINES, AND OTHER FACTORS IN NEC

Macrophages. Macrophages reside in the blood stream, epithelial layer, and tissue. These large and powerful phagocytes play a variety of roles. They are antigen presenting cells, they secrete cytokines, they rid the body of dead cells and they ingest pathogens. Macrophages live approximately two to four months [81].

Upon contact with bacterial LPS, macrophages release pro-inflammatory cytokines and Nitric Oxide which can cause destruction to the tight junction protein that seals the para cellular space between epithelial cells. Whenever (resting) macrophages come in contact with cytokines, cytokines bind to the receptors on macrophages to cytokine-receptor complexes. These complexes are then internalized into the macrophages. [12]

Neutrophils. Neutrophils reside in the blood stream until activated. After activation,

Effects of Prematurity	**Corresponding Advantage of Breastfeeding**
Immature glycosylation	Favorable glycosylation patterns
Low levels of IgA production	pIgA and sIgA in breast milk
Lower levels of Antimicrobial peptides	Antimicrobial peptides in breast milk
Low levels of EGF	EGF is found in large amounts in breast milk of mothers of preterm infants
Elevated levels of PAF Low levels of PAF-AH	PAF-AH is found in large amounts in breast milk of mothers of preterm infants
Excessive Immune response	Antimicrobial factors in breast milk

Table 1: Affects of prematurity and the corresponding advantages of breast feeding.

they move to the site of injury/insult through the blood vessels and through tissue. Neutrophils tend to accumulate in the tissue below the epithelium during inflammation [19]. After arriving at the site of injury/insult, the neutrophils phagocyte the pathogens and they aid in sterilizing the wound. Unlike macrophages, neutrophils have a short life, one or two days [81], [19].

Neutrophils can have very positive effects on wound healing such as producing IL-1β which promotes epithelial repair. On the other hand, if the neutrophils do not encounter pathogen in a timely manner, they cause tissue damage, in particular they may damage the extra cellular matrix and they may release elastase which causes epithelial cell death and permanent damage to the tight junctions. Furthermore, they may cross from the tissue side of the epithelium to the lumenal side and in the process cause damage to the epithelium barrier function by increasing the paracellular space. The larger paracellular space makes it easier for toxins to cross the epithelium into the underlying tissue [19].

IL-1. This inflammatory cytokine is released by macrophages. There are two distinct IL-1 genes: IL-1 α and IL-1 β. IL-1 α promotes the inflammatory response. It has been shown that there is a high correlation between IL-1 synthesis and tissue damage and inflammation. In particular, IL-1 α levels in the tissue have been correlated with intestinal necrosis [27]. These findings have been corroborated by studies that have shown significant reduction of inflammatory cell infiltration after the introduction of IL-1ra [27]. (The description of IL-1ra may be found below.) IL-1 helps to promote the inflammatory cascade by stimulating other cells to produce cytokines. [33]. IL-1 β contributes to the production of nitric oxide. In particular, it has been shown that exposing epithelial cells to TNF-α, in combination with IFN-γ and IL-1 β, leads to increased expression of nitric oxide [53]. Increased levels of Nitric Oxide leads to increased epithelial layer permeability (see below). IL-1 β stimulates the production of IL-8 which, in turn, causes neutrophils to congregate near the site of the inflammation [33], [90]. Interestingly, there is some evidence that IL-1 β may have a positive, protective effect on intestinal mucosa integrity by stimulating the increase of Glial cells which are critical to intestinal gut integrity [83].

IL-1ra. Interleukin-1 receptor antagonist binds to the same cell receptors as IL-1 and thereby prevents IL-1 from binding to these sites. Upon binding, IL-1ra produces no biolog-

ical response. Thus, IL-ra has the effect of dampening the inflammatory cascade.

IL-4. This is an anti-inflammatory cytokine. IL-4 serves to dampen the inflammatory cascade. It is produced by T_H2 cells as well as by bone marrow stroma [83]. IL-4 has been found to inhibit human macrophage colony formation [83] [66], IL-4 also inhibits monocyte-derived hydrogen peroxide production [83] and the release of certain inflammatory mediators such as TNF-α and IL-1β. It also reduces the tissue destruction caused by oxygen radicals associated with ischemia and reperfusion injury [83]. IL-4/IL-13 have been shown to inhibit macrophages' ability to phagocyte pathogens [87], [132].

IL-6. IL-6 is produced by T cells, B cells, monocytes, fibroblasts, endothelial cells as well as many other cell types [69]. Studies have found that intestinal epithelial cells, as well, make IL-6 [124]. The release of IL-6 is stimulated by IL-1 and TNF-α as well as by other pro-inflammatory cytokines [83]. IL-6 stimulates B cell growth [42]. There are indications that IL-6 may play a dual role in NEC as studies show that it has both inflammatory and anti-inflammatory effects. The inflammatory effects of IL-6 are well know. High levels of IL-6 have been shown to be associated with NEC severity [83]. Harris showed that IL-6 levels were significantly higher in nonsurvivors compared to survivors of NEC [57]. On the other hand, IL-6 appears to have certain anti-inflammatory affects. IL-6 can drive TGF-β activation. Some research indicates that IL-6 may be responsible for increased local and circulating IL-1ra, increased production of tissue inhibitors of metalloproteinases (TIMPs), and has been shown to inhibit the production of superoxides [83]. As noted above, any up-regulation of IL-1ra competes for the same binding cites as IL-1 but with no inflammatory effects. The increased production of TIMPs results in the inhibition of the enzymes that degrade the extra cellular matrix (see discussion of MMPs below). Finally, superoxides produce tissue damage and, therefore, any inhibition thereof will help protect the host.

IL-8. IL-8 plays a major role in inflammation. IL-8 is a chemokine (a chemokine is a special type of cytokine that is involved in cell migration) produced by enterocytes that causes neutrophils to congregate near the site of inflammation [33], [90], [80]. For example, it has been shown that in the midst of inflammatory cascades, the administration of neutralizing antibodies against IL-8 resulted in reduced neutrophil infiltration and prevented neutrophil-related tissue damage [56]. Studies have shown that, in general, IL-1β induces the production

of IL-8 [33], [90]. Other studies indicate that both IL-1β and endotoxin induce the production of IL-8. [96]. For example, some studies have shown that, in the presence of TNF-α and LPS, the inhibition of IL-1 does not fully eliminate the production of IL-8 and neutrophils leading to speculation that TNF-α and LPS, even without the help of IL-1, may lead directly to the production of IL-8 and neutrophils [56]. In summary, for the case of intestinal epithelial cells (IEC's), both IL-1β and endotoxin may lead to the secretion of IL-8. However, it appears that IL-1β is far more effective than endotoxin in inducing IL-8 secretion by the IECs in both pre-term and full-term infants [90],[96]. Since the IECs are prominent in the study of NEC, IL-1β activation of IL-8 warrants a few more comments.

Studies have shown that IL-1β activation of IL-8 occurs through activation of nuclear factor (NF-κ B). Studies by Claud, et. al. [25],[26] indicate that IL-1β activation of IL-8 is muted by various factors found in breast milk [25]. In particular, it has been shown these factors (e.g. TGF-β1, Epo) in breast milk inhibit the activation of NF-κ and, thereby, results in reduced secretion by IECs [90], [25].

As a side note, one of the studies by Claud [25] indicated that the presence of the anti-inflammatory cytokine IL-10 **did not** inhibit $TNF\alpha$ or IL-1β secretion of IL-8 by IECs. This surprising result conflicted with the expected affects IL-10. However, the authors noted the other anti-inflammatory features of IL-10 may result in reduced inflammation by affecting macrophages and speculate that IL-10 may even affect IECs in an indirect way. (This same study by Claud produced another unexpected result - EGF appears to **increase** secretion of IL-8 by IECs. The authors of the report observed that pretreating IECs with EGF and, afterwards, stimulating the cells with $TNF\alpha$ resulted in increased secretion of IL-8 by IECs. This phenomenon cannot be fully explained at the present time.)

Finally, the presence of high concentrations of IL-8 is a significant indicator of the severity of NEC. For example, studies have shown that within the first day of the onset of the disease, IL-8 concentrations are significantly higher in infants with stage 3 NEC compared to infants with stage 2 NEC [36].

IL-10. This is an anti-inflammatory cytokine that is produced by T_H2 cells, B cells, and monocytes [117]. Like IL-4, this cytokine serves to dampen the inflammatory response. It has been shown that the addition of IL-10 suppressed inducible nitric oxide synthase

(iNOS), messenger RNA (mRNA), and nitric oxide expression in the small bowel, liver, and serum by 60%, 89%, and 11%, respectively (Markel [83] quoting Kling [70]). IL-10 decreases production of IL-2 [125]. It inhibits the activation of macrophages, TNF-α, IL-1β, IL-6, and IL-8. It was discovered that IL-10 decreases the production of metalloproteinases (by inhibiting T cell activation at its earliest stages.) [110]. It inhibits the synthesis of the cytokines IL1, IL-6, IL-8, IL-10, and IL-12 [55]. Furthermore, IL-10 is a good indicator of the severity of NEC, as concentrations of this cytokine were observed to be much higher in infants with stage 3 NEC compared with stage 2 NEC. One study has shown that these differences in concentrations between the stages continued until 72 hours after the onset of the disease [36].

IL-12. This pro-inflammatory cytokine is secreted by B cells and macrophages and induces the release of small amounts of IFN-γ from T cells and natural killer (NK) cells. IL-12 is able, by itself, to stimulate the production of IFN-γ. However, in collaboration with IFN-γ-Inducing Factor (IGIF) causes T cells to produce significantly greater amounts of IFN-γ [2]. This appears to be due to the fact that IL-12 causes the expression of receptor IGIF on certain cell lines [2]. In the same way, IL-12 induces the expression of the IL-18 receptor on Th1 cells. Therefore, IL-12 in collaboration with IL-18 causes T cells to produce exponentially large amounts of IFN-γ [24].

IL-18. This pro-inflammatory cytokine, like IL-12, induces the release of small amounts of IFN-γ but unlike IL-12, it is secreted by macrophages and IECs. Levels of IL-18 tend to increase in step with the increased severity of NEC. [52].

There is some speculation that IL-18 is a negative regulator of TNF-α production by IFN-γ. IFN-γ usually induces the production of TNF-α. However, in the presence of IL-12 and IL-18, even high levels of IFN-γ failed to produce TNF-α.[24].

IL-18 in combination with IL-12 leads to the production of nitric oxide and oxygen radicals in macrophages and neutrophils. These, in turn, have both positive and negative effects - the radicals are toxic to the microbial pathogens but also destructive to tissue [68]. (As noted above, IL-18 and IL-12 together cause the production of IFN-γ. IFN-γ, in turn, induces macrophages and neutrophils to produce nitric oxide and oxygen radicals.)

TNF-α This cytokine can induce other cells to release IL-1, IL-2, IL-6, and IL-8 [139].

Although TNF-α is released from a variety of sources, they mostly come from activated macrophages [139]. TNF-α is not only released by macrophages but is also a major activator of macrophages. For this study, it is particularly important that TNF-α causes macrophages to produce proinflammatory cytokines and nitric oxide [139].

IFN-γ This cytokine is secreted from T cells and NK cells. IL-12 causes T cells to produce IFN-γ while IL-1,IL-2, and TNF together induce NK cells to produce IFN-γ [104]. This induces NO and TNF-α production. It has been shown to cause mucosal inflammation. It has been shown that IL-12 and IL-18 individually induce T cells to produce IFN-γ while together induce the production of very large amounts of IFN-γ (see discussion under IL-12 above). Interestingly, mice injected with large amounts of IFN-γ without the presence of IL-12 or IL-18 did not have pathological effects [24]. There is some speculation that NO inhibits IFN-γ production (see discussion under NO below). It is very important to note that IFN-γ downregulates the production of the tight junction protein ZO1 [53] [35] and IFN-γ reduces gap junction communication [76].

Platelet Activating Factor (PAF) Platelet Activating Factor is a powerful inflammatory mediator and, therefore, an important player in NEC. PAF is produced by neutrophils, macrophages, endothelial cells, and enterocytes in response to endotoxin and hypoxia [121]. PAF leads to the activation of IL-1 β, IL-6, and IL-8 [83], [22].

Its specific role in NEC is unclear. On the one hand, patients with NEC exhibit high levels of PAF. In rat experiments, injection with PAF leads to intestinal necrosis. Also, other experiments on rats have shown that PAF receptor antagonist prevents injury induced by hypoxia, bacteria, and TNF-α [59]. Furthermore, the PAF degrading enzyme PAF-acetylhydrolase (PAF-AH) blocks the initiation of NEC [22]. On the other hand, PAF without the presence of bacteria failed to cause bowel injury in rat experiments [67]. Therefore, PAF plays a major role in NEC but appears to require bacteria to cause inflammation and damage.

PAF activates apoptosis of intestinal epithelial cells[22].

Matrix Metalloproteinases (MMPs). These are enzymes that degrade the extra cellular matrix which supports the intestinal epithelial cells. It has been shown that TNF-α drives the production of the MMPs. It has also been shown that activated lamina propria

T cells will begin a cascade that results in the production of MMPs. On the other hand, IL-10 will inhibit T cell activation thereby reducing the destruction of the ECM by MMPs [110]. Tissue Inhibitor of Metalloproteinases (TIMPs) controls the local activity of MMPs in tissues. However, if the MMP production is too high, an imbalance will result and it will not be possible for the TIMPs to control the MMPs [109],[108].

Nitric Oxide. Nitric oxide plays a number of critical roles in NEC. Nitric Oxide is associated with epithelial barrier dysfunction. In particular, nitric oxide reduces the functional levels of tight junction proteins. In addition, nitric oxide impairs communication between epithelial cells by interfering with the normal function of the gap junction proteins. Nitric oxide is, also, involved in epithelial cell death and has been shown to lead to destruction of the tissue that underlies the epithelial layer.

Nitric oxide is produced from nitrogen oxide synthase (NOS). There are three isoforms of NOS. However, for our study, we are particularly interested in inducible nitric oxide synthase (iNOS). iNOS is produced from macrophages and other inflammatory cells. For example, TNF-α and IFN-γ stimulate macrophages to produce iNOS. Nitric oxide is then produced by oxidation of L-arginine mediated by iNOS [84], [77].

It is very important to note that nitric oxide usually only acts locally. This is partially due to the fact that its metabolic lifespan is, perhaps, only a few seconds [84]. Specifically, Levy et al [77] report that its half life is .1 to 10 seconds. Thus, the effects of nitric oxide are limited to the area near where it is produced. On the other hand, iNOS expression usually leads to the production of large quantities of nitric oxide over an extended period of time [77]. As a result, even though nitric oxide dies out before it moves beyond the local area, its sustained production can have devastating effects in the area near where it is produced.

The body naturally produces some NO and, in fact, moderate amounts of NO are beneficial to the epithelium - nitric oxide plays an anti-microbial role and inhibits the growth of gram-positive bacteria. [65] [77] However, under stressed conditions, large amounts of NO can be produced causing damage to the epithelial layer, the tight junction proteins, and the gap junction proteins [77].

Nitric oxide is strongly linked to epithelial layer permeability. Tight junction proteins are responsible for maintaining a barrier to pathogen attempting to pass between epithelial

cells into the underlying tissue layer. Nitric Oxide has been shown to reduce the functional levels of the tight junction proteins, ZO1, ZO3, and occludin [53].

It is theorized that NO impairs phosphorylation of the gap junction protein Cx43, resulting in reduced cell-to-cell communication. This communication is required for epithelial cell migration. Therefore, NO impairs epithelial cell migration that is required for mucosal repair [5].

Nitric Oxide also reacts with superoxide O_2^- to produce the oxidant peroxynitrite ($ONOO^-$). Peroxynitrite inhibits the proliferation and differentiation of epithelial cells [130].

Gap Junction Proteins. These are intercellular membrane channels that facilitate the passage of ions and solutes between adjacent cells. These membrane channels are composed of the gap junction protein connexin 43 (Cx43). Leaphart, et al [76] have demonstrated that epithelial cells migrate in unison and that gap junction communication plays a crucial role in the migration of intestinal epithelial cells during intestinal healing after injury. They show that epithelial cells, in particular IEC-6 cells, exposed to IFN-γ exhibit reduced gap junction communication and, therefore, greatly reduced migration speed. In particular, they showed that IFN effected this reduced communication by dephosphorylating Cx43 and by causing Cx43 to move inside the cell. Interestingly, inhibited gap junction communication does not appear to reduce epithelial cell proliferation nor does it appear to induce epithelial cell death [76].

A key factor in gap junction communication is the phosphorylation and surface localization of the gap junction protein Cx43. Any inhibition of phosphorylation of Cx43 will lead to an inhibition of epithelial cell migration. Anand, et al [5] has demonstrated that macrophage activation leads to production of nitric oxide. The nitric oxide, in turn, inhibits the phosphorylation of Cx43 resulting in significantly reduced cell migration.

Tight Junction Proteins.(Zonula Occludens) These include occludin, ZO-1,ZO-2, ZO-3, claudin-1, and JAM. [74]. These proteins are formed between adjacent epithelial cells and are closely linked with the actin-based cytoskeleton [53]. Among other functions, Zonula Occludens serve as a barrier to keep bacteria and other molecules from passing through the

epithelial layer into the underlying tissue. It has been discovered that tight junctions restrict passage of molecules based on the size of the particles and, in fact, the size of the solutes that are allowed to pass between cells varies at different locations in the intestine. In particular, the permeability to larger solutes decreases from the crypt to the villus [128]. Also, by restricting transport across the epithelium, the tight junctions serve to prevent equilibrium across on both sides of the epithelium. In this way, a concentration gradient is maintained across the epithelium. This concentration gradient is needed in order that the epithelium can properly absorb and secrete substances [128].

Many factors effect the integrity and health of the tight junction proteins. For example, there is a close connection between the presence of nitric oxide and increased epithelial layer permeability. It is theorized that nitric oxide alters the expression and localization of some of the tight junction proteins, in particular ZO1 [53]. Furthermore, it has been discovered that IFN-γ causes a time-dependent down-regulation of the tight junction protein ZO1 [35], pg. 23. Some studies also indicate that TNF causes increased paracellular permeability [128]. Therefore, TNF may effect the tight junction protein.

DAMPs and Damaged cells. Injured cells send out danger/alarm signals. Cells that send out such signals are cells that are exposed to bacteria, toxins, or cells that have sustained mechanical damage. This is particularly true of cells that are in the process of dying after an insult or injury. [88] Alarm signals might be in the form of any substance made or modified by the dying cell. Cells that die under a normal process will not send out these danger signals. [88] These alarm/danger signals are known as Damage-associated Molecular Pattern molecules [DAMPs]. DAMPs tend to keep inflammation going even when most or all of the invading bacteria has been killed. Therefore, a cycle of damage - inflammation - damage can occur. [134]

LPS. LPS is a glycolipid on the outer membrane of gram-negative bacteria which combines with other components and forms LPS/CD-14 [71], [126], LPS/CD-14 is recognized by and becomes attached to TLR4.

The LPS/CD-14 complex leads to secretion of IL-1, IL-6, and TNF-α in macrophages [89].

TLR4. TLR4 is one member of the group of Toll-like receptors. Also referred to as

pattern recognition molecules (PRMs) or pattern recognition receptors (PRRs). Toll-like receptors are normally expressed on the outside of the cell on what is known as the **cell membrane or plasma membrane** and they recognize large molecules that are associated with pathogens. These large molecules are sometimes referred to as pathogen-associated molecular patterns (PAMPs) or microorganism-associated molecular patterns (MAMPS) [55]. For our study, the only toll-like receptors that we need to consider are TLR4 and TLR9. TLR4 recognizes lipopolysaccharide (LPS) which is on the outer membrane of gram-negative bacteria. TLR4 is expressed on many different types of cells. However, we are most interested in TLR4's role on intestinal epithelial cells (IECs).

It has been discovered that TLR4 mediates phagocytosis of gram-negative bacteria by IECs. This results in IECs translocating bacteria from the mucosa to underneath the epithelial layer in a transcellular manner [97].

On IECs, TLR4-LPS binding begins a signalling cascade inside the cell ultimately resulting in integrin activation. Often TLR4-LPS binding results in over-expression of integrins resulting in reduced cell motility. Other adverse affects of TLR4-LPS binding are increased epithelial cell apoptosis, inhibited cell-cell communication, and decreased cell proliferation [41],[75]. Not surprisingly, there appears to be a strong correlation high levels of TLR4 expression and NEC severity [50]. In particular, high levels of TLR4 have been associated with a decrease in goblet cells and, in turn, a reduction in the protective mucins that goblet cells produce [123].

It has been observed that TLR4 increases during gut development. Fold expression of TLR4 in the gut in mice was shown to increase approximately three-fold from embryonic day 14 to day 18. Then goes back to day 14 levels right after birth. TLR4 expression then increases but falls again after weaning [46],[122].

In humans, at the time of full-term birth, TLR4 expression drops greatly. On the other hand, TLR4 expression remains high at the birth of the pre-term infant and continues to remain high after birth (yet another disadvantage of prematurity) [50].

There are indications that Heat Shock Protein-70 (HsP70) regulates TLR4 signalling resulting in decreased NEC severity [1].

TLR9. TLR9, like TLR4 is a Toll-like receptor. TLR9 is the receptor for bacterial

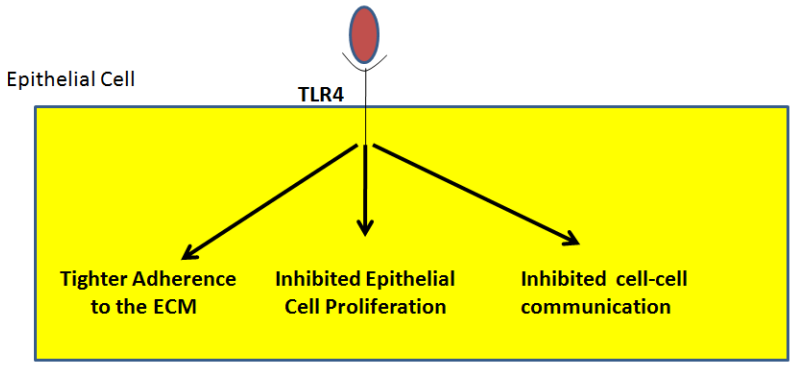


Figure 14: Results of TLR4 signalling.

DNA (CpG-DNA). It has been determined that TLR4 and TLR9 have a reciprocal role, i.e., increased signalling in one TLR is associated with decreased signalling of the other. Studies have shown that, in enterocytes, activating TLR9 with CpG-DNA inhibited LPS-mediated signalling by TLR4 [46]. Furthermore, NEC has been found to develop in a mucosal environment of increased TLR4 expression and decreased TLR9 expression [46].

Integrins. Integrins are cell surface glycoproteins that are responsible for cell adhesion to the extra cellular matrix on which the epithelium resides. Proper integrin expression is critical for proper cell migration after an injury. Signals from inside the cell cause integrins to become activated. Upon TLR4-LPS binding, a signalling cascade begins resulting in integrin activation.

Extracellular ligands of integrins are primarily proteins of the ECM such as fibronectin and collagen. As a result of this binding to proteins of the ECM, the integrins form clusters known as focal adhesions [73]. Integrins then transmit signals across the plasma membrane and, in cooperation with growth-factor initiated signals determine various cell functions [9], [63].

This concludes the survey of the medical research of NEC. The topics in this chapter were presented as they relate to NEC. More general information about these topics may be found in other sources. Janeway's Immunobiology [95] provides a good introduction to the immune system. For cell signalling, see Marks, Klingmuller, and K. Muller-Decker [84].

Tomkins [127] gives a general overview of the role of the cell and its place in creation.

2.0 PREPARATIONS FOR CONSTRUCTION OF A NEC MODEL

Much information related to NEC was presented in the previous chapter. In that chapter, many of the mechanisms and factors involved in NEC were explored and examined. Most of that information will now be organized, summarized, and filtered down into a form that can be used for a 3-D mathematical NEC model. Some of the material in that first chapter will not be used in a direct way to construct the NEC model but will be used to inform the simulation runs later in the thesis. For example, when simulating prematurity in chapter seven, underdeveloped peristalsis, which is a common problem for the pre-term infant, will be simulated by including large amounts of bacteria near the epithelium. On the other hand, some factors presented in chapter one that have common characteristics will be combined into single factors for the purpose of the model. For example, the cytokines that have inflammatory effects will be combined into the general category of cytokines. In addition, certain practical considerations must be kept in mind when constructing this model. This is the first 3-D model for NEC, it will be wise not to include too much detail in this first model. Also, there is currently very little quantitative clinical data concerning some of the specific NEC factors covered in chapter one. As a result, some simplification and/or combining of NEC factors is necessary. Therefore, the main goal of this chapter will be to identify the most essential factors in NEC, generalize these factors as much as possible, and define the interaction among these factors. This work will result in the General Inflammatory Cascade presented in this chapter (see figure 21). In chapter three, this General Inflammatory Cascade will be used as a guide for the construction of the 3-D mathematical NEC model.

The General Inflammatory Cascade will be presented after the construction of intermediate diagrams and cascades. It is possible to construct the General Inflammatory Cascade without these intermediate steps and diagrams. However, it is important that the reader

understand the rationale for many of the simplifications that will be done in this chapter. Also, this intermediate information will provide ideas and motivation for a more advanced NEC model in the future. That is, this intermediate information may supply the next level of detail that can be included in a more extensive NEC model. This information will be particularly relevant as soon as new clinical data becomes available that touches the factors included in these intermediate steps.

2.1 INFLAMMATORY CASCADE

In this section, inflammatory cascades and other diagrams will be developed based on the information presented in chapter 1. An inflammatory cascade which shows the interplay between cytokines, bacteria, etc. is presented in figure 15. (This cascade is a generalization based on the information presented in chapter 1.) In order to preserve clarity, PAF and its role in the inflammatory cascade is not included in figure 15 but in a separate figure (figure 16). In figure 15 we have the following important information (this is all based on the material presented in chapter 1):

1) Beginning along the bottom of the diagram, macrophages eliminate bacteria. At the same time, bacterial contact with macrophages induces the production of IL-12,IL-18, TNF-α.

2) TNF-α induces the production of IL-1, IL-2, IL-6, and IL-8. TNF-α in combination with IL-1, IL-2 induce NK cells to produce IFN-γ (this combination is indicated by the blue ++.) TNF-α also induces the production of MMPs.

3) IL-12 and IL-18 individually induce the production of IFN-γ but in combination IL-12 and IL-18 produce even larger amounts of IFN-γ (this combination is indicated by the blue ++.)

4) IL-18 induces the production of IL-4,5,8,10,13.

5) Both IL-1 and TNF-α induce the production of IL-6.

6) IL-6 induces the production of IL-1ra and TIMPs. IL-1ra in turn reduces the effects of IL-1 by competing for the same binding sites as that cytokine. (IL-6 also leads to TGF-β

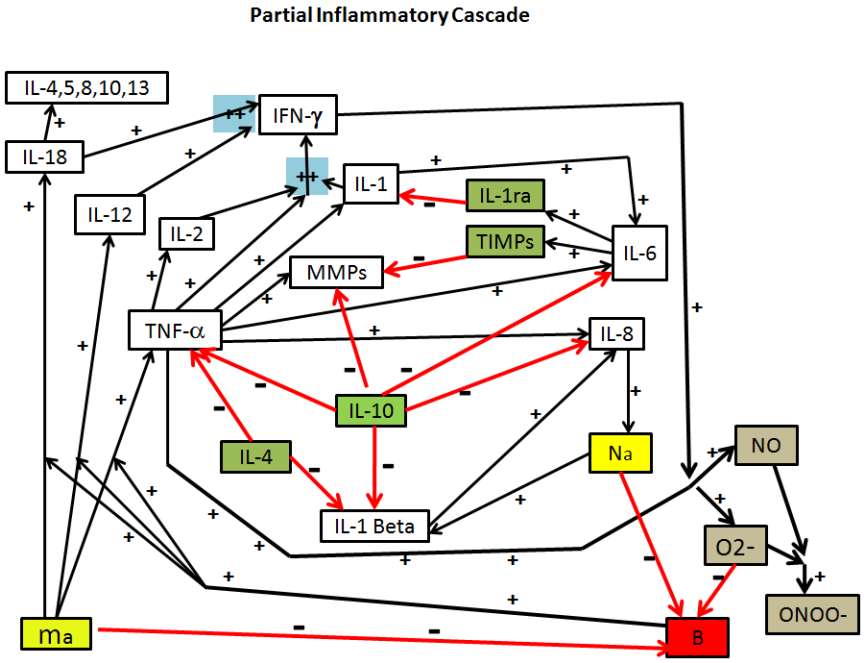


Figure 15: Partial Inflammatory Cascade. See the text for discussion. **Symbols:** Ma stands for activated macrophages, Na for activated neutrophils, B for bacteria, the other symbols are self-explanatory. **Box color designations are as follows:** inflammatory cytokines and other destructive agents have white background boxes; cytokines and other factors that play an anti-inflammatory role have green background boxes; phagocytes have yellow background boxes; free radicals have boxes with gray background. **Arrow color designations are as follows:** a red arrow with a negative sign indicates downregulation or production inhibition; a black arrow with a positive sign indicates upregulation; whenever two or more arrows meet at a plus sign with a blue background, this indicates that two or more factors, when working together, induce the production of a large amount of a substance. Note that activated neutrophils, like activated macrophages, produce cytokines and nitric oxide. For clarity, this function of activated neutrophils is not shown in the figure. Note, also, that some of the intermediate roles of the inflammatory cells are not shown here. For example, the diagram implies that TNF-α and IFN-γ directly produce nitric oxide and O2- but in reality TNF-α and IFN-γ induce macrophages to produce these molecules. Also, IL-10 does not directly inhibit the production of MMP's. Instead, IL-10 inhibits the T cell activation which, in turn, slows the production of MMP's. Finally, the function of IL-4, IL-8, and IL-10 are shown near the middle of the diagram but the production of these cytokines is shown in the upper left hand corner.

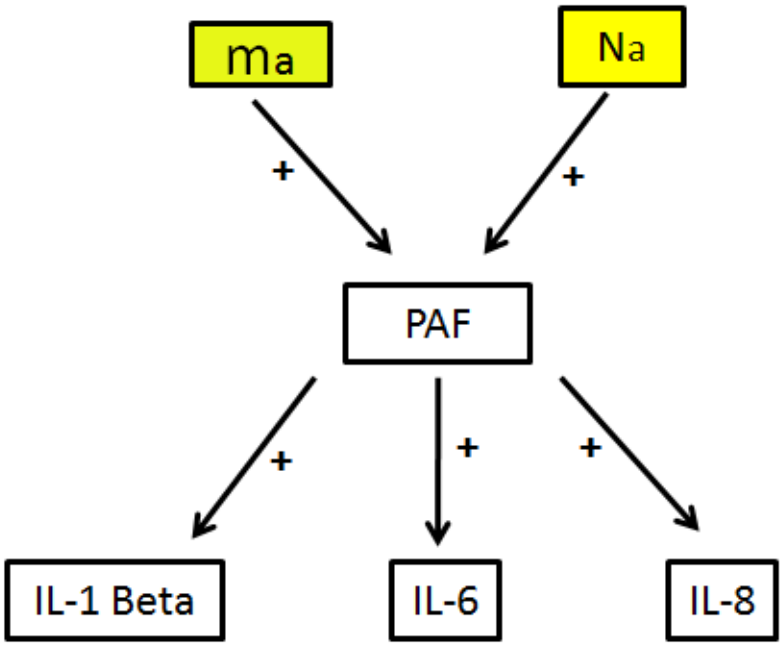


Figure 16: PAF's role in the inflammatory cascade

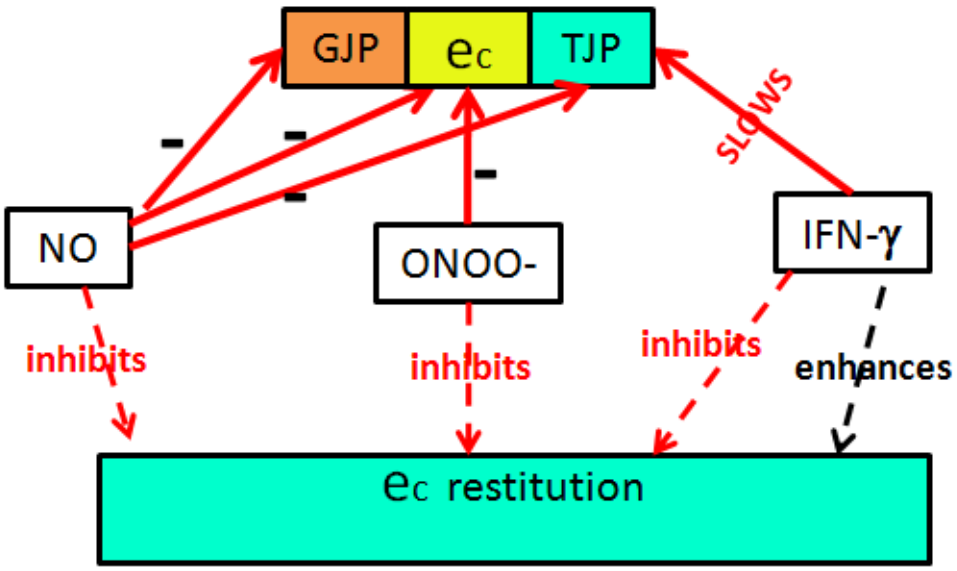


Figure 17: Disruption and restoration of the epithelium. This diagram, unlike the inflammatory cascades, shows the physical effects on the structure of the epithelium. At the top of the illustration we see that nitric oxide destroys gap junction protein (GJP), epithelial cells and tight junction protein(TJP). Also, ONOO- destroys epithelial cells and IFN-γ downregulates the production of tight junction protein. At the bottom, we see that nitric oxide, IFN-γ, and ONOO- inhibits epithelial restitution. Paradoxically, IFN-γ promotes epithelial cell migration and, therefore, also contributes to epithelial restitution.

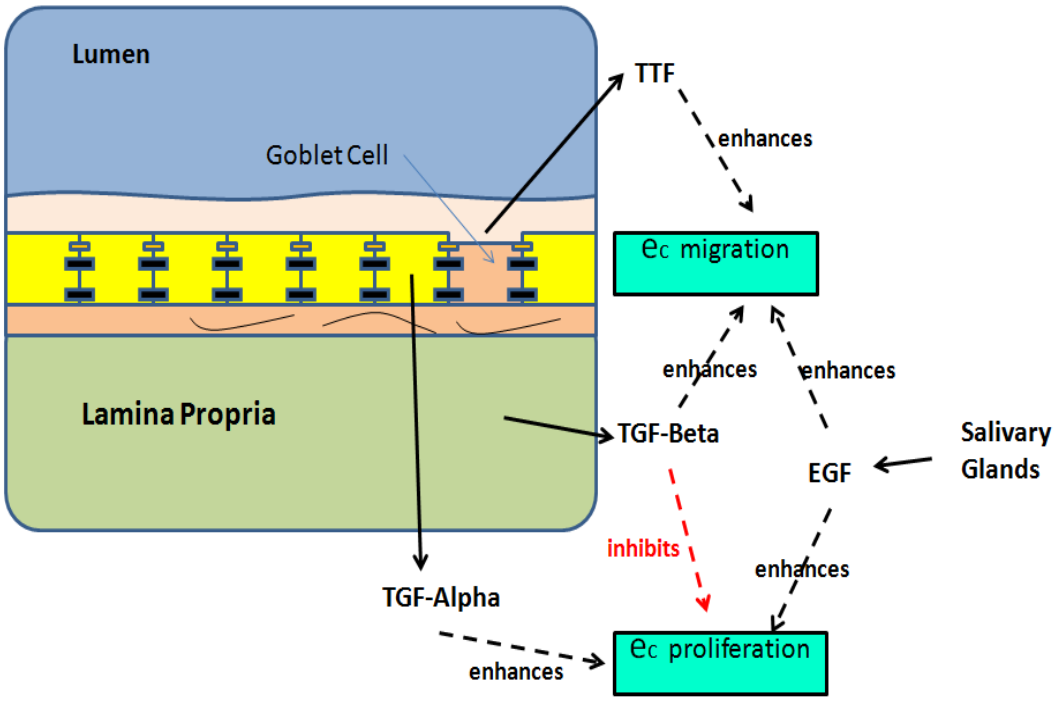


Figure 18: Other factors involved in epithelial restitution/proliferation. Epithelial cells produce TGF-α; Lamina propria cells produce TGF-β; Salivary glands produce EGF; Goblet cells produce TFF. TGF-β, EGF, and TFF all enhance epithelial cell migration. TGF-α and EGF enhance epithelial cell proliferation but TGF-β inhibits epithelial cell proliferation.

activation.)

7) TIMPs inhibit the production of MMPs.

8) IL-1β induces the production of IL-8.

9) IL-8 causes neutrophils to congregate near the site of inflammation.

10) IL-10 inhibits production of TNF-α, IL-1β, IL-6, and IL-8.

11) Not shown is the fact that IL-10 may inhibit MMP production by inhibiting T cell activation.

12) On the bottom right of the diagram, TNF-α and IFN-γ causes macrophages to produce Nitric Oxide and O_2^-.

13) Also on the bottom right of the diagram, Nitric Oxide reacts with O_2^- to produce $ONOO^-$.

Other effects not explicitly shown:

14) IL-4, particularly with IL-13, inhibits macrophages' ability to phagocytize pathogen.

15) IL-4 inhibits macrophages' ability to produce nitric oxide.

PAF's role in the inflammatory cascade is given in figure 16. Here it is shown that activated macrophages and activated neutrophils produce PAF. PAF, in turn, leads to the activation of IL-1β, IL-6, and IL-8.

Disruption of the epithelium. Figure 17 shows how the inflammatory cascade affects the epithelium. Notice that nitric oxide interferes with the normal function of gap junction proteins and, therefore, inhibits epithelial cell-cell communication which in turn inhibits epithelial cell restitution. Nitric oxide also directly reduces the functional levels of tight junction proteins and causes epithelial cell death. ONOO- destroys epithelial cells. IFN-γ downregulates the production of some tight junction protein.

Also, note that figure 17 shows that IFN-γ both inhibits restitution and enhances resti-

tution of the epithelium. This is based on the evidence, presented in chapter one, that IFN-γ reduces gap junction communication [76] and, one would conclude, slows epithelial restitution. Other evidence, also presented in chapter one, suggests that IFN-γ promotes epithelial cell migration [32].

Other factors involved in epithelial restitution/proliferation Figure 18 is a simplification and summary of much of the information that was presented in the last chapter. (See the discussion in chapter one and figure 10 in that chapter.) Recall from chapter one that many of the growth factors such as HGF, and FGF peptides as well as the cytokines IL-1, IL-2, IFN-γ affect the epithelium through TGF-β **dependent** pathways. Therefore, in figure 18 the functions of these particular growth factors, peptides and cytokine are represented simply by TGF-β. On the other hand, the growth factor EGF plays such an important role in epithelial proliferation and restitution that its explicit inclusion in figure 18 is warranted. TGF-α, which is produced by epithelial cells is explicitly included for similar reasons - it plays an important role in epithelial proliferation. Members of the trefoil factor family (TFF), which are produce by goblet cells, work in conjunction with glycoproteins on the apical side (lumenal side) of the epithelium through an TGF-β **independent** pathway (see chapter one) and it is, therefore, explicitly included.

2.2 PHYSICAL DOMAIN FOR THE NEC MODEL.

Based on the discussion in chapter one, the lumen, the mucus, the epithelial layer, the extra cellular matrix (ECM), the underlying tissue, and the blood (or circulatory system) are important regions for the study of NEC. Ideally, all of these regions would be included in the mathematical model. However, a model that includes six regions may be too complex. So, the number of regions considered will be reduced. The mucus will not be included in the mathematical model because it, like the epithelium, is part of the mucosa. Much of what occurs in the mucus can be considered together with the epithelial layer. The integrity of ECM is closely related to the integrity of the epithelium. Recall that the ECM is the

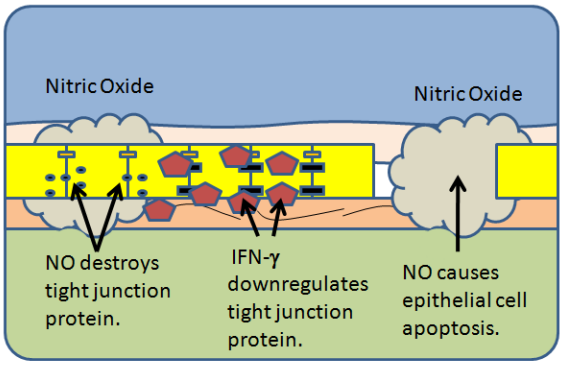


Figure 19: This diagram shows how the presence of nitric oxide and IFN-γ results in epithelial layer permeability.

foundation upon which the epithelial cells stand. Any degradation of the extra cellular matrix will contribute to epithelial layer permeability. Therefore, extra cellular matrix permeability and epithelium permeability will not be treated as separate functions. The extra cellular matrix will not be included in the physical domain for the mathematical model. The function of the ECM will be included in the function of the epithelium. This leaves us with four regions as seen in figure 20.

2.3 GENERAL INFLAMMATORY CASCADE

As we move toward a mathematical model, it is desirable to use the information in figures 15, 16, and 17 to create one simplified General Inflammatory Cascade. Toward this end, we first consider 15 and note the role of MMPs. It was shown in chapter one that the primary action of the MMPs is to destroy the extra cellular matrix (ECM) but, as noted above, ECM integrity will not be included explicitly in our model but will be considered as part of epithelium integrity. Therefore, we will also not include MMPs nor TIMPs (the prime function of which is to downregulate the MMPs). Instead, the MMPs degradation of the epithelium/ECM, will be mathematically modeled, in chapter three, by cytokines

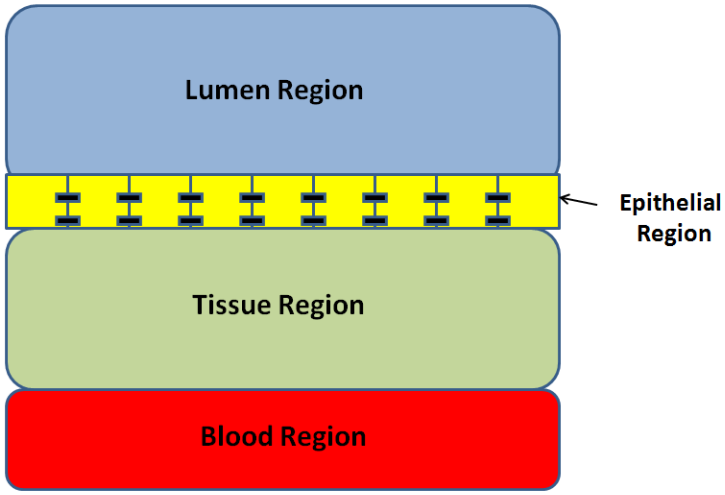


Figure 20: This diagram shows the four regions that will be used in the NEC mathematical model.

affecting epithelial layer integrity. This simplification is reasonable because the cytokine TNF-α induces the production of MMPs as can be seen from figure 15. On the other hand, we will include the immune cells, **activated macrophages, $\mathbf{m_a}$,** and **activated macrophages, $\mathbf{N_a}$,** in the General Inflammatory Cascade. Next note that figures 15 and 16 indicate that activated macrophages and activated neutrophils, either directly or indirectly induce the production of all the inflammatory cytokines. (By "indirectly", it is meant that activated macrophages and activated neutrophils induce the production of some cytokines which, in turn, induce the production of the remaining cytokines shown in the figures.) That is, activated macrophages and activated neutrophils induce the production of TNF-α, IL-1β IL-12, IL-18, PAF, these in-turn induce the production of IL-1,IL-2, IL-4, IL-5, IL-8, IL-10, IL-13, IFN-γ then IL-1 induces the production of IL-6. Therefore, it will be reasonable to group all of the aforementioned inflammatory cytokines under **cytokines, c**. Furthermore, note that in figure 15 that the anti-inflammatory cytokines such as IL-4, IL-10, IL-1ra downregulate most of the inflammatory cytokines. Therefore, these **anti-inflammatory**

cytokines, c_a, may be grouped together.

Note that figure 15 indicates that the same factors that produce NO also produce O2-. Furthermore, NO and O2- together produce ONOO-. Therefore, it is possible to include **nitric oxide, NO,** in the General Inflammatory Cascade and not O2- nor ONOO- as long as we assign the affects of O2- and ONOO- to NO. For example, note that O2- destroys bacteria so in the General Inflammatory Cascade we will indicate that NO destroys bacteria. Also, in figure 17 we see that ONOO- destroys epithelial cells and interferes with epithelial layer restitution but this action mirrors the action of nitric oxide.

In figure 17 we see that nitric oxide (NO) destroys epithelial cells, tight junction protein and gap junction protein. As noted in chapter one, gap junction protein is necessary for epithelial cell communication and for coordinated epithelial cell migration. So, if we model epithelial cell migration and proliferation together, we will not need to include gap junction protein in our General Inflammatory Cascade. That is, we will assume that nitric oxide will cause destruction of the epithelial layer and inhibit its repair.

On the other hand, it would be wise to include **tight junction protein, ZO1,** in the General Inflammatory Cascade because it is possible for enough nitric oxide to be present to destroy the tight junction protein, and therefore, create epithelial layer permeability, without (or before) destroying epithelial cells.

In figure 17, we see that IFN-γ both helps and inhibits epithelial restitution. Based on the evidence presented in chapter one, the net action of IFN-γ is more likely to inhibit epithelial restitution than to promote restitution. Therefore, IFN-γ may be left out of the general inflammatory cascade and its action represented by cytokines, which inhibit epithelial restitution.

epithelial cells, e_c, are essential to the model and, of course will be included in the General Inflammatory Cascade. Note in figure 17 that many of the factors that contribute to epithelial proliferation and restitution originate in the epithelium itself or originate naturally in other parts of the body, i.e., the tissue and salivary glands. It will, therefore, be reasonable to exclude all of the factors in figure 17 from the General Inflammatory Cascade and represent their effects by terms in the epithelial cell equation (this last part will be done in chapter three).

Damage (in the context of DAMPs) was covered in chapter one but it was not included in figures 15, 16, or 17 because as noted in the first chapter, many different components produced or modified by injured or dying cells can play the role of DAMPs. Therefore, DAMPs did not fit in well with the well defined components shown in figures 15, 16, or 17. On the other hand, DAMPs fit well into the General Inflammatory Cascade in which each component may represent a more general class of components. Also, as noted in chapter one, damage is a major player in keeping the inflammatory cascade going, even after all of the bacteria has been destroyed. Therefore, it is necessary to include **damage, d,** in the General Inflammatory Cascade.

Finally, **bacteria, b,** is essential for the model and, therefore, will be included in the general inflammatory cascade. So, the General Inflammatory Cascade is given in figure 21. This General Inflammatory cascade may be though of as occurring in multiple regions, with the understanding, of course, that epithelial cells are present only in the epithelial region. In figure 21, the components are as follows:

b: bacteria - endotoxin, LPS; Interacting with activated neutrophils and activated macrophages, induces the production of cytokines. This effect is indicated by the black dashed lines in the diagram. At the same time, activated neutrophils and activated macrophages destroy bacteria. (This is indicated by the red arrows pointing from activated neutrophils and activated macrophages toward bacteria).

c: pro-inflammatory cytokines. This group includes IL-1, IL-8, IL-12, IL-18, IFN-γ, TNF-α and, perhaps IL-6 (although as indicated in chapter 1, IL-6 may have both inflammatory and anti-inflammatory affects). These cytokines induce macrophages and neutrophils to produce other cytokines (As indicated by the solid black lines going to and from activated neutrophils and activated macrophages). Also, these cytokines induce macrophages and neutrophils to produce nitric oxide. (This is indicated by the black dashed lines). Certain cytokines such as TNF can induce epithelial cell death. (This is indicated by the red line pointing from the cytokines to epithelial cells.)

c_a: anti-inflammatory cytokines - This group includes IL-4 and IL-10. These cytokines tend to reduce the inflammatory response by slowing down the production of cytokines, activated neutrophils and activated macrophages. (This is indicated by the blue dashed

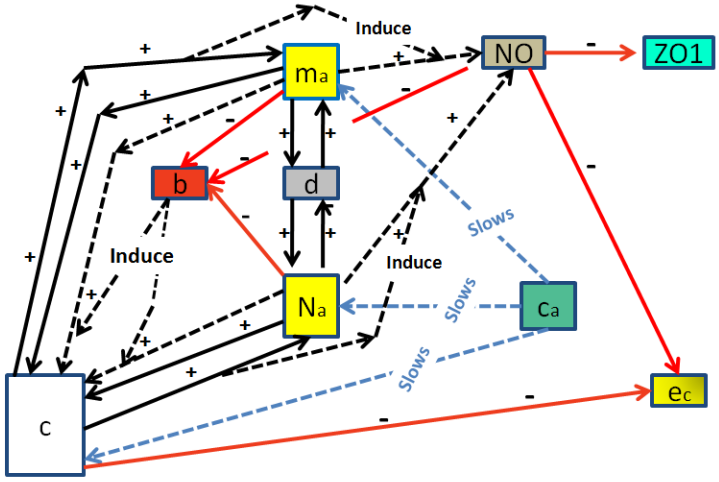


Figure 21: General Inflammatory Cascade. See the text for discussion. **Symbols:** m_a stands for activated macrophages, N_a for activated neutrophils, b for bacteria, C_a for anti-inflammatory cytokines, d for damage, NO nitric oxide, $ZO1$ represents tight junction protein, e_c represents epithelial cells. **Arrow color designations are as follows:** a red arrow with a negative sign indicates downregulation or production inhibition; a black arrow with a positive sign indicates upregulation.

lines in the diagram).

d: damage - Damage was covered in chapter 1 under DAMPs, Damage-associated Molecular Pattern molecules. Damage might be thought of as the measure of the level of severity of the inflammation. DAMPs are induced by inflammation in stressed/injured cells and which serve to perpetuate inflammation in a feed-forward fashion [43], [88], [135].

e_c: epithelial cells - these cells line the intestinal wall and protect the underlying tissue from bacterial invasion. Tight junction proteins, such as ZO1, seal the space between these cells so that pathogen may not pass into the underlying tissue [53], [54].

m: macrophage - resting immune cells. (For clarity, these are not explicitly shown in the diagram but will be included in the PDE model developed in chapter 3.) Macrophages are activated by bacteria, cytokines, and damage.

m_a: activated macrophage - activated immune cells. These cells phagocytose bacteria. These cells release inflammatory cytokines and nitric oxide.

n: neutrophil - resting immune cells normally found in the bloodstream. (For clarity,

these are not explicitly shown in the diagram but will be included in the PDE model developed in chapter 3.) Neutrophils are activated by cytokines and damage.

n_a: activated neutrophil - activated immune cells that move from the blood stream toward the site of infection. These cells release inflammatory cytokines and nitric oxide.

NO: nitric oxide - this chemical is released by activated macrophages and activated neutrophils after these inflammatory cells come in contact with certain cytokines (this is indicated by the black dashed lines coming from activated macrophages and activated neutrophils to nitric oxide. Nitric Oxide destroys the tight junction protein, ZO1, that seals the space between epithelial cells [53], [54]. (This is indicated by the red arrow from the nitric oxide to ZO1). Finally, the presence of nitric oxide in the epithelium leads to epithelial cell apoptosis. (This is indicated by the red arrow from the nitric oxide to the epithelial cells).

$ZO1$: tight junction protein - keeps the epithelial cells in close apposition and prevents the passage of bacteria into the underlying tissue. Nitric Oxide destroys this protein.

2.4 A TYPICAL SCENARIO

At this point, it will be wise to use the information in chapter one to put together a typical NEC scenario, that is, a sequence of events in the progression of the disease. It will be helpful to have such a scenario available when constructing the NEC mathematical model and when doing simulations. There are many possible cases of scenarios. The following example is a typical case of **a premature, formula fed infant with no initial injury to the intestinal barrier**. To be sure, even this case has many possible variations within it but we will pick one variation that includes all of the features of this particular case.

Under this scenario, formula feeding causes bacterial colonization of the lumen. Underdeveloped peristalsis, a common problem in the premature infant, does not clear away the bacteria (figure 22, # **1**). Some of the bacteria that lingers for a long time near the epithelium eventually passes through the protective epithelial cells and invades the underlying tissue (figure 22, # **2**). Note that this bacterial translocation may occur by several

different mechanisms (see figure 12 in chapter 1). Bacteria that gets into the underlying tissue invokes an inflammatory response. Macrophages interacting with the bacteria become activated. The activated macrophages release cytokines, in particular, TNF-α (figure 22, # **3** and # **4**). The TNF-α causes increased production of IL-1 [16] and MMP's [83] (figure 22, # **5**). The activated macrophages also release the cytokines IL-12 and IL-18 which each induce T and NK cells to produce IFN-γ (figure 22, # **6**). Recall from chapter one that IL-12 and IL-18 acting together cause an exponential increase in IFN-γ (figure 22, # **7**).

Many of the cytokines that have been produced then act on the macrophages. In particular, TNF-α and IFN-γ cause macrophages to produce inducible Nitric Oxide synthase (iNOS) which, in turn, produces Nitric Oxide (NO) (figure 23, # **8** and # **9**).

Large amounts of nitric oxide and cytokines near the epithelium lead to its destruction. The nitric oxide causes both the death of epithelial cells as well as destruction of the tight junction protein, such as ZO1, which normally seals the space between the epithelial cells. As noted in chapter one, IFN-γ causes a time-dependent down-regulation of ZO1(figure 23, # **10**). Simultaneously, MMP's cause the degradation of the Basal Lamina that underlies the the epithelial layer (figure 23, # **11**). All of this together results in the greater permeability of the epithelial layer.

The degraded epithelial layer provides only minimal protection for the underlying tissue. Bacteria and other species may easily travel from the lumen into the underlying tissue (figure 23, # **12**). After the bacterial invasion, the tissue becomes the location of a very aggressive inflammatory cascade that involves, among others, IL-1, IL-6, IL-8, IL-12, IL-18, IFN-γ, TNF-α, and HMGB1 (figure 24, # **13** and # **14**).

While this is occurring, the epithelial layer attempts to repair itself. However, as noted earlier, IFN-γ causes a significant reduction in phosphorylated Cx43, a gap junction protein critical to cell-cell communication and epithelial cell migration. Nitric Oxide similarly prevents the phosphorylation of Cx43. Interference with gap junction proteins results in inhibited epithelial cell migration. Furthermore, over-activation of TLR-4 by lumen bacteria results in over-expression of integrins. Too much integrin expression results in the epithelial cells adhering too tightly to extra-cellular matrix (see chapter one). All of this results in greatly reduced cell migration and in a sustained wound (figure 24, # **15**).

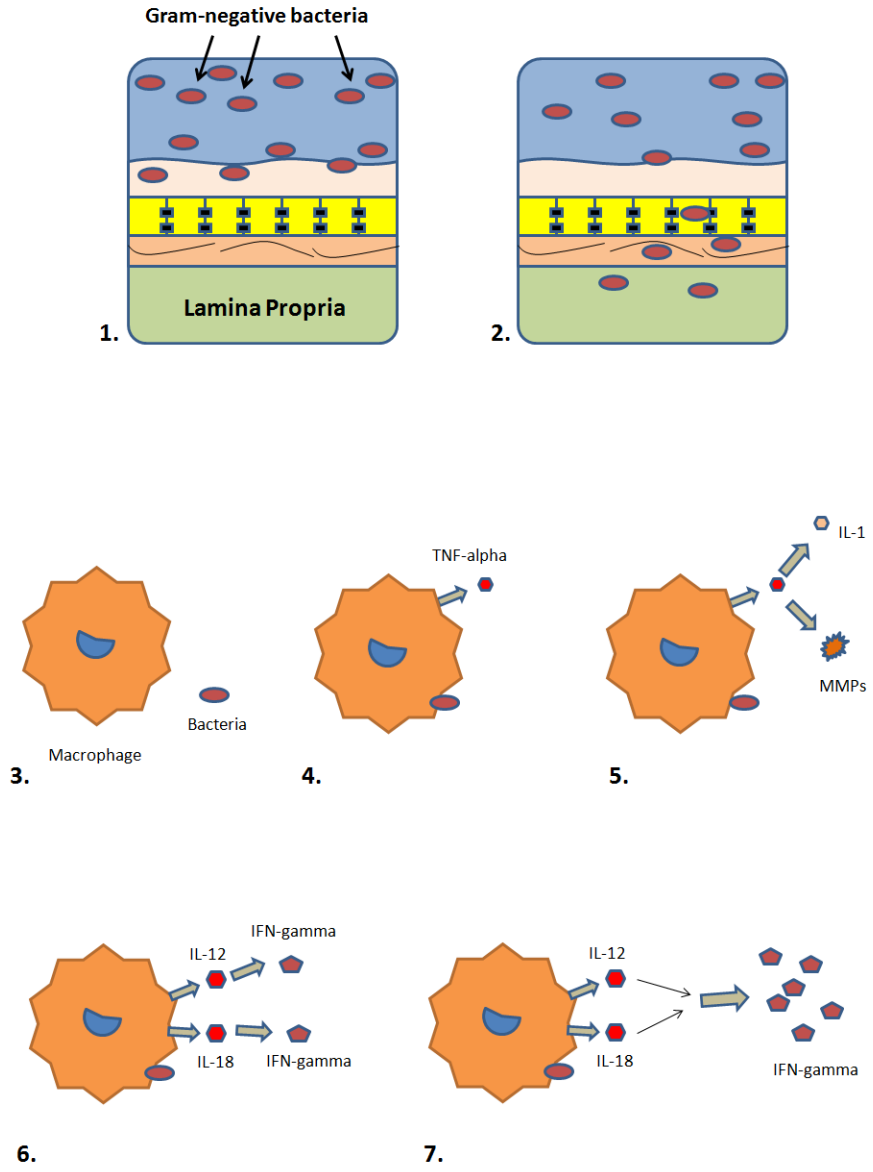


Figure 22: A typical NEC scenario (1 of 3). **1.** Gram-negative bacterial colonization near the epithelium. **2.** Bacteria pass through the epithelium and invades the underlying tissue. **3.** Bacteria in the lumen comes in contact with macrophages. **4.** The macrophages respond by releasing cytokines such as TNF-α. **5.** TNF-α increases production of Metalloproteinases (MMPs) and induces the release of cytokines such as IL-1 . **6.** Macrophages also release other cytokines such as IL-12 and IL-18. IL-12 and IL-18 each provoke the release of IFN-γ. **7.** IL-12 and IL-18 work together to induce the release of large amounts IFN-γ.

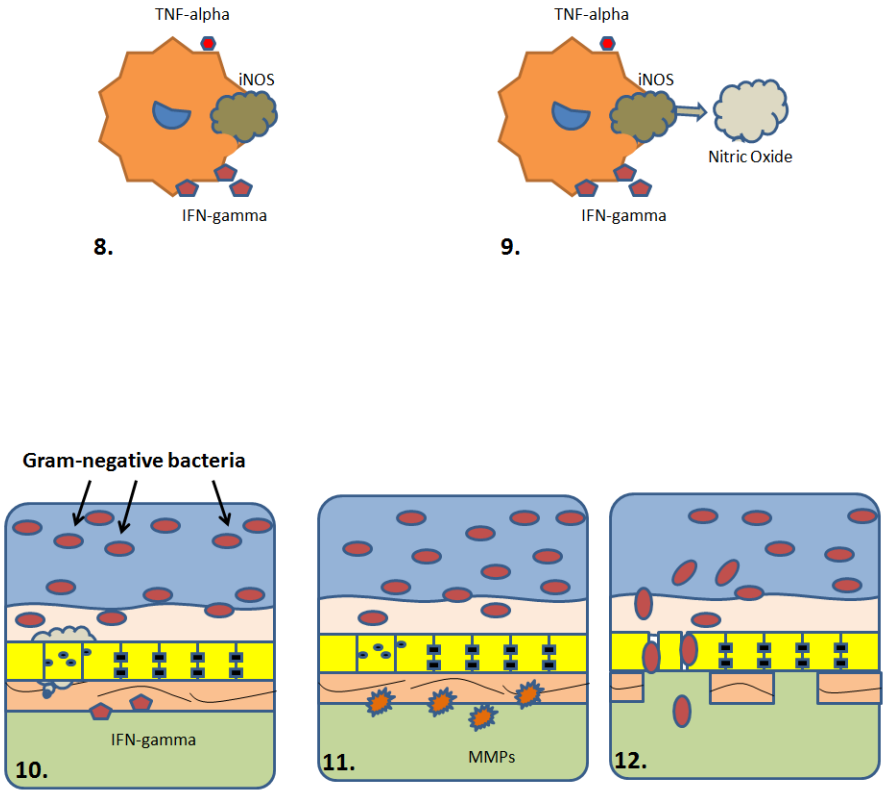


Figure 23: A typical NEC scenario (2 of 3). **8.** and **9.** Macrophage/cytokine interaction leads to the secretion of Nitric Oxide. **10.** Nitric Oxide and IFN-γ lead to epithelial layer permeability. Nitric Oxide destroys the tight junction protein that seals the space between the epithelial cells and IFN-γ downregulates the production of the tight junction protein ZO1. **11.** Metalloproteinases (MMPs) causes degradation of the tissue underlying the epithelial cells. **12.** After destruction of the tight junction protein and degradation of the tissue underlying the epithelial cells, bacteria invades the underlying tissue.

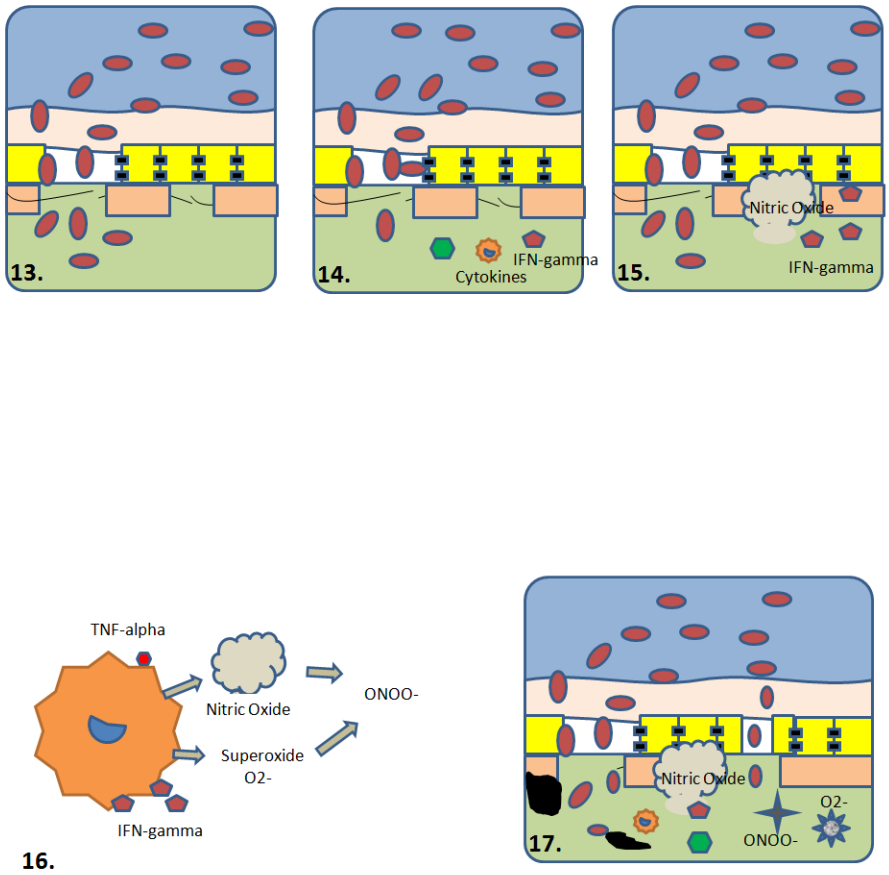


Figure 24: A typical NEC scenario (3 of 3). **13.** and **14.** Bacteria in the tissue results in an aggressive inflammatory response resulting in the release of cytokines such as IL-1, IL-6, IL-8, IL-12, IL-18, IFN-γ, TNF-α, HMGB1. **15.** Nitric oxide and IFN-γ interferes with gap junction proteins. Bacteria contact with the epithelial cells leads to over expression of integrins. All of this leads to reduced epithelial migration. **16.** Macrophages produce nitric oxide and O_2 radicals which, in turn, produce ONOO-. **17.** The NO/ONOO-/O2 Radicals Cause Epithelial Cell Death/Tissue Death.

The inflammatory cascade is now unchecked. The production of nitric oxide and O_2 radicals leads to the production of $ONOO-$. [130](figure 24, # **16**). These work together to cause extensive tissue death (figure 24, # **17**). The ultimate result will be organ failure and possibly death to the infant.

In this chapter, much of the material from chapter one has been organized, summarized, and put into a form that may now be used to construct a NEC model. In particular, the General Inflammatory Cascade (see figure 21) has been constructed. This General Inflammatory Cascade, which shows the interaction among the major players in NEC, will provide the basis for the NEC mathematical model. This cascade can be converted directly into a basic mathematical model. Other information presented in the present chapter will be used to add greater detail to the model. The NEC mathematical model will be constructed in the next chapter.

3.0 A PARTIAL DIFFERENTIAL EQUATION MODEL FOR NEC

This chapter presents a three dimensional mathematical model for NEC. The General Inflammatory Cascade developed in chapter two (see figure 21), will be used as a blueprint for the mathematical model. Other information presented in chapters one and two will be used to create detail in the model.

Mathematical models for NEC and/or inflammation have been developed in the past [116], [29], [8], [129]. These models are extremely valuable and provide important insights into the disease. Furthermore, many of the parameters, mathematical terms, and functions developed in these papers will continue to be used in future NEC mathematical models. In fact, a number of terms developed in Reynold.s et al. [116] that model inflammation will be used in the 3-D mathematical model developed in this chapter. (These will be noted below.)

However, the models mentioned above are all one dimensional, ordinary differential equation (ODE) models and, therefore, simulate only the transient effects of NEC but do not fully model its spatial effects. Only a 3-D model can accurately simulate diffusion and advection of the major players in NEC, account for the different effects of NEC in the different regions in the body (as noted in chapter two, our mathematical model will include four different regions, see figure 20), and fully integrate all the effects of epithelial cell degradation and migration. Therefore, a 3-D model will fill a void in the NEC mathematical models.

Before going forward, it is important to note that several people, over a period of several years, contributed to the development of the NEC PDE system presented in this chapter:

Joshua Sullivan, Ivan Yotov, Mark Tronzo, Christopher Horvat, Jared Barber, Yoram Vodovotz, Jeff Upperman, Gilles Clermont.

The author of this thesis will, here, present the PDE system and attempt to give justification for the structure of each equation. In the process, the close connections between the PDEs and the data presented in chapters one and two will be noted.

3.1 DERIVATION OF PARTIAL DIFFERENTIAL EQUATIONS

In this section, the partial differential equations for the NEC model will be constructed using the General Inflammatory Cascade, figure 21, as a guide.

Activated macrophages. Activated Macrophages will diffuse in the direction of decreasing density of activated macrophages. Thus the activated macrophage equation will have a diffusion term, $\nabla \cdot (-D_{m_a} \nabla m_a)$. Activated macrophages will move in the direction of increasing cytokines and increasing bacteria. So, the advection term may be written as $\nabla \cdot (\gamma_{m_a c} m_a \nabla c + \gamma_{m_a b} m_a \nabla b)$.

The source/sink will include a number of terms:

1) A decay term $-k_{m_a} m_a$.

2) Since macrophages are activated by bacteria, cytokines, and damage, the source terms $k_{mb} bm$, $k_{mc} cm$, and $k_{md} dm$ are included. Therefore, when no anti-inflammatory cytokines are present, the source/sink terms become

$$-k_{ma} m_a + k_{mb} bm + k_{mc} cm + k_{md} dm.$$

However, when anti-inflammatory cytokines are present, they down-regulate the production of activated macrophages. This is modeled by multiplying these last three terms by $R(c_a)$:

$$-k_{m_a} m_a + R(c_a)(k_{mb} bm + k_{mc} cm + k_{md} dm) \quad \text{where} \quad R(c_a) = \frac{1}{1 + k_{R_{c_a}} (c_a / \bar{c}_a)^2}.$$

Note that the equation for $R(c_a)$ is obtained from [116]. Putting this all together, we get

$$\begin{aligned} \frac{\partial m_a}{\partial t} \; - \; & \nabla \cdot (D_{m_a} \nabla m_a - \gamma_{m_a c} m_a \nabla c - \gamma_{m_a b} m_a \nabla b) \\ & = -k_{m_a} m_a + R(c_a)(k_{mb} bm + k_{mc} cm + k_{md} dm). \end{aligned}$$

Macrophages. (Resting) macrophages are normally located in the tissue and are considered to be stationary until they are activated. Therefore, the equation for macrophages does not include diffusion or advection terms but only source/sink terms. Note that every activated macrophage comes from a (resting) macrophage. Therefore, one of the terms from the activated macrophage equation, namely $R(c_a)(k_{mb}bm + k_{mc}cm + k_{md}dm)$, is included here but with a negative sign. Macrophages will be produced up to a maximum. Thus, the source term $k_m(m_{max} - m)$ is included. Putting these together gives us

$$\frac{\partial m}{\partial t} = k_m(m_{max} - m) - R(c_a)(k_{mb}bm + k_{mc}cm + k_{md}dm).$$

Cytokines. The cytokine equation includes a diffusion term but no advection term. The source/sink terms are as follows:

1) There is a decay term $-k_c c$.

2) Activated macrophages and activated neutrophils both produce cytokines. Whenever anti-inflammatory cytokines are absent, this is modeled by $k_{cm_a}m_a + k_{cn_a}n_a$. However, whenever anti-inflammatory cytokines are present, they down-regulate the production of cytokines. This is modeled by multiplying these two terms by $R(c_a)$:

$$R(c_a)(k_{cm_a}m_a + k_{cn_a}n_a) \quad \text{where} \quad R(c_a) = \frac{1}{1 + k_{R_{c_a}}(c_a/\bar{c}_a)^2}.$$

3) Whenever cytokines come in contact with macrophages and neutrophils, the cytokines bind to receptors on these phagocytes to form cytokine-receptor complexes. These complexes are then internalized into the phagocytes. (This was discussed in chapter 1. See under macrophages.) This is modeled by $-k_{nc}cn - k_{mc}cm$ whenever anti-inflammatory cytokines are absent. Note that when anti-inflammatory cytokines are present, they slow the production of cytokines (see figure 21), therefore, the factor

$$-R(c_a)(k_{nc}cn + k_{mc}cm)$$

Putting everything together, we have:

$$\begin{aligned}\frac{\partial c}{\partial t} - \nabla \cdot D_c \nabla c = {} & -k_c c + R(c_a)(k_{cm_a}m_a + k_{cn_a}n_a) \\ & -R(c_a)(k_{nc}cn + k_{mc}cm). \end{aligned} \tag{3.1}$$

Anti-inflammatory cytokines. The equation for anti-inflammatory cytokines contains a diffusion term but no advection term. The source/sink terms are:

1) A decay term $-k_{c_a}c_a$.

2) A constant anti-inflammatory cytokine growth term s_c. This term is usually set to zero (or an extremely small number) unless a known source of anti-inflammatory cytokines, such as breast milk, is present.

3) Activated macrophages, neutrophils, and damage induce the production of anti-inflammatory cytokines. Anti-inflammatory cytokines slow down this production rate. It is reasonable to assume that there will be a saturation point for the anti-inflammatory cytokines.

$$k_{c_aP}\frac{Q}{1+Q} \quad \text{where} \quad Q = R(c_a)(k_{c_am_an_a}n_a + m_a + k_{c_am_ad}d).$$

k_{c_aP} is the rate of anti-inflammatory cytokine production.

$k_{c_am_ad}$ Effectiveness of damage in producing anti-inflammatory cytokine.

$k_{c_am_an_a}$ Effectiveness of activated macrophages and activated neutrophils in producing anti-inflammatory cytokines.

Putting everything together, we have:

$$\frac{\partial c_a}{\partial t} \; - \; \nabla \cdot D_{c_a}\nabla c_a \; = \; -k_{c_a}c_a + s_{c_a} + k_{c_aP}\frac{Q}{1+Q}. \tag{3.2}$$

Bacteria. The equation for bacteria contains a diffusion term but no advection term. The source/sink terms are:

1) In the place of a decay term we use a term from Reynolds, et al. [116] which represents elimination of bacteria due to a baseline local immune response, $-k_b b/(1 + b/\epsilon)$. Decay will be slower with this term than if we had $-k_b b$ alone. This is particularly true whenever the bacteria levels are high. Here ϵ is the range for bacterial death and is usually set at .2. (Obviously, the smaller the value of ϵ, the slower the decay rate.)

2) Also consistent with Reynolds, et al. [116] we include a logistic term $k_{bg}b(1 - b/b_{max})$.

3) Peptides in breast-fed milk causes the destruction of bacteria. This is modeled by $-k_{pp}b$.

4) Both activated macrophages and activated neutrophils phagocyte bacteria (see figure 21). This is modeled by $k_{bm_a} m_a b + k_{bn_a} n_a b$. However, when anti-inflammatory cytokines are present, this is down-regulated in the usual way, so that this term becomes:

$$-R(c_a)(k_{bm_a} m_a b + k_{bn_a} n_a b) - k_{pp} b \quad \text{where} \quad R(c_a) = \frac{1}{1 + k_{R_{c_a}} (c_a/\bar{c}_a)^2}.$$

Putting everything together, we have:

$$\begin{aligned} \frac{\partial b}{\partial t} - \nabla \cdot D_b \nabla b &= k_{bg} b(1 - b/b_{max}) - k_b b/(1 + b/\epsilon) \\ &\quad -R(c_a)(k_{bm_a} m_a b + k_{bn_a} n_a b) - k_{pp} b. \end{aligned} \tag{3.3}$$

Nitric Oxide. The equation for Nitric Oxide includes a diffusion term but no advection term. The source/sink terms are:

1) A decay term $-k_{NO} NO$.

2) Activated macrophages and activated neutrophils both produce cytokines. Certain cytokines then induce macrophages to produce Nitric Oxide. Therefore, both activated macrophages and activated neutrophils induce, directly or indirectly, the production of Nitric Oxide. However, there is a time-delay in the production of the Nitric Oxide. After testing many types of mathematical terms to simulate this time-delay, it was found that the following terms best model this phenomenon:

$$k_{NOm_a} \frac{m_a^{q_1}}{1 + (m_a/\overline{m}_a)^{q_1}} + k_{NOn_a} \frac{n_a^{q_1}}{1 + (n_a/\overline{n}_a)^{q_1}}.$$

where k_{NOm_a} and k_{NOn_a} are the rates at which activated macrophages and activated neutrophils, respectively, produce Nitric Oxide.

Putting everything together, we have:

$$\begin{aligned} \frac{\partial NO}{\partial t} - \nabla \cdot D_{NO} \nabla NO &= -k_{NO} NO + k_{NOm_a} \frac{m_a^{q_1}}{1 + (m_a/\overline{m}_a)^{q_1}} \\ &\quad + k_{NOn_a} \frac{n_a^{q_1}}{1 + (n_a/\overline{n}_a)^{q_1}}. \end{aligned} \tag{3.4}$$

Tight Junction Protein, ZO1. The tight junction protein, ZO1, keeps the space in between epithelial cells sealed so that pathogen may not pass into the underlying tissue. This protein does not move and is not diffused. Therefore, the equation for ZO1 does not contain a diffusion term nor an advection term. Furthermore, ZO1 does not naturally decay. So, no decay term is included. The source/sink terms look like this:

1) Nitric Oxide destroys the tight junction protein, ZO1, this is modeled by the term $-k_{ZN}NO * ZO1$.

2) A certain amount of tight junction protein will be created for each epithelial cell, up to maximum value of zec. (The equation for zec is given below.) This creation of tight junction protein is given by:

$$k_{Z_{e_c}} e_c \, (1 - ZO1/zec).$$

As epithelial cells proliferate (or as they are destroyed), tight junction protein is created (or destroyed) with the epithelial cells. This may be modeled by:

$$k_{Z_{e_{ct}}} \frac{\partial e_c}{\partial t} \, (1 - ZO1/zec).$$

Here zec serves as a limiting value for ZO1. One option would be to set zec to some constant value (such as 1 or .95) but setting zec to some constant value might allow the density of $ZO1$ to grow well beyond the density of epithelial cells. This may be all right - as demonstrated in chapter 1, in some cases $ZO1$ might fill in small open areas of the epithelium where no epithelial cells exists. However, it was apparently decided that $ZO1$ should be modeled to exist only between epithelial cells. Therefore, the expression for zec was made to be

$$zec = (1 - \epsilon_{zec}) + \epsilon_{zec} \left(\frac{1}{e_{c,max}} \right) e_c.$$

Putting everything together, we have:

$$\frac{\partial ZO1}{\partial t} \;=\; \left(k_{Z_{e_c}} e_c + k_{Z_{e_{ct}}} \frac{\partial e_c}{\partial t} \right) (1 - ZO1/zec) - k_{ZN} NO \cdot ZO1 \tag{3.5}$$

where

$$zec = (1 - \epsilon_{zec}) + \epsilon_{zec} \left(\frac{1}{e_{c,max}} \right) e_c. \tag{3.6}$$

Activated neutrophils. For activated neutrophils, we have a diffusion term, $-\nabla\cdot(D_{n_a}\nabla n_a)$. Activated neutrophils will move in the direction of increasing cytokines (see chapter 1). So, the advection term may be written as $\nabla\cdot(\gamma_{n_ac}n_a\nabla c)$.

The source/sink will include a number of terms:

1) A decay term $-k_{n_a}n_a$.

2) Since neutrophils are activated by cytokines and damage (see figure 21), the terms $k_{nc}cn$ and $k_{nd}dn$ are included. Therefore, when no anti-inflammatory cytokines are present, the source/sink terms become

$$-k_{n_a}n_a + k_{nc}cn + k_{nd}dn.$$

However, when anti-inflammatory cytokines are present, they down-regulate the production of activated neutrophils. This is modeled by multiplying these last two terms by $R(c_a)$:

$$-k_{n_a}n_a + R(c_a)(k_{nc}cn + k_{nd}dn) \quad \text{where} \quad R(c_a) = \frac{1}{1+k_{R_{c_a}}(c_a/\bar{c}_a)^2}.$$

Putting this all together, we get

$$\frac{\partial n_a}{\partial t} \; - \; \nabla\cdot(D_{n_a}\nabla n_a - \gamma_{n_ac}n_a\nabla c) = -k_{n_a}n_a + R(c_a)(k_{nc}cn + k_{nd}dn).$$

Damage. Recall from chapters 1 and 2 that damage is correlated with DAMP molecules. These DAMP molecules likely diffuse. So, the damage equation has a diffusion term but no advection term. The source/sink will terms include:

1) A decay term $-k_dd$.

2) Note as defined in chapter 2, damage is the measure of the level of severity of the inflammation. Therefore, even though nitric oxide, activated neutrophils, and macrophages cause tissue destruction (see chapter 1 and figure 21), it is acceptable to include only cytokines in our equation for damage. For that purpose, we use the type of term used in a previous paper [115] (although in that paper, activated phagocytes were used instead of cytokines):

$$k_{dc}\frac{T^{q_2}}{x_{dc}^{q_2}+T^{q_2}} \tag{3.7}$$

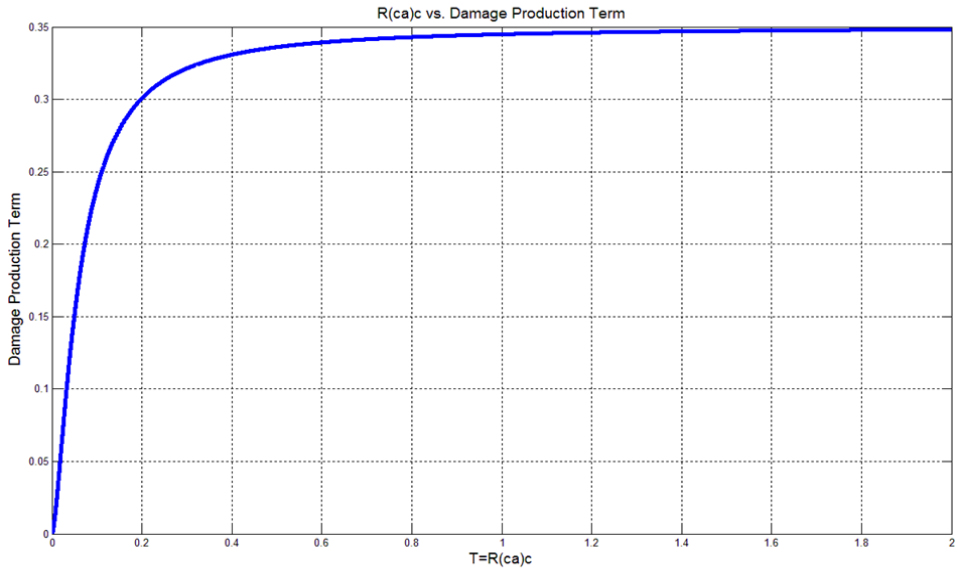


Figure 25: Damage Production Term

here $T = R(c_a)c$ and the constant x_{dc} is the range for damage/DAMP production.

Therefore, the term $T = R(c_a)c$ indicates that cytokines lead to the production of damage while anti-inflammatory cytokines, through $R(c_a)$, moderates this effect. Note that the source term (3.7) has an upper bound of k_{dc}. Using $k_{dc} = .35$,$x_{dc} = .06$, and $q_2 = 1.5$ then $R(c_a)c$ may be plotted against (3.7) to get figure 25.

$$\frac{\partial d}{\partial t} - \nabla \cdot D_d \nabla d = -k_d d + k_{dc} \frac{T^{q_2}}{x_{dc}^{q_2} + T^{q_2}}. \tag{3.8}$$

Epithelial Cells Modeling of the epithelial cells is somewhat more complicated. Epithelial cell migration speed is directly related to integrin activation. Optimum migration speed occurs at some medium/optimal amount of integrin activation. Whenever integrin activation is low, migration speed is low or zero. Likewise, epithelial cell migration speed is low at high levels of integrin activation. Higher migration speeds occur at integrin activation levels between these two extremes.

In this model it will be assumed, in the absence of bacteria that epithelial cells will move at optimal speed, i.e., integrins are adhering at optimal levels. Bacteria is directly related to integrin activation. Higher concentrations of bacteria results in higher levels of integrin activation. Therefore, it will be assumed that the presence of any amount of bacteria will begin a signalling process in the epithelial cells that will result in more than optimal adherence of the integrins to the ECM. The following equation is used to relate bacteria to integrin activation:

$$\alpha(b) = D_{e_c} \frac{(b_{max} - b)^{.25}}{(b_{max} - b)^{.25} + b^{.25}}.$$

Let $\mathbf{u} = -\alpha(b)\nabla e_c$. Note that $\mathbf{u}$ is a velocity and is proportional to $-\nabla e_c$. Therefore, a basic diffusion term would be

$$-\nabla \cdot (\alpha(b)\nabla e_c) = \nabla \cdot \mathbf{u}.$$

This is then multiplied by the Buckley-Leverett equation [23]

$$\beta(e_c) = h(e_c, e_{c,max}, q) = \frac{e_c^q}{e_c^q + (e_{c,max} - e_c)^q}.$$

from two-phase flow (Most usually we will have $q = 2$ and $e_{c,max} = 1$.), to give the diffusion equation

$$-\beta(e_c)\nabla \cdot (\alpha(b)\nabla e_c) = \beta(e_c)\nabla \cdot \mathbf{u}.$$

Advection would, then, be represented by:

$$\nabla(\beta(e_c)\mathbf{u}) = \nabla\beta(e_c) \cdot \mathbf{u} = \frac{\partial \beta}{\partial e_c} \nabla e_c \cdot \mathbf{u}.$$

Note that we have assumed the velocity $\mathbf{u} = -\alpha(b)\nabla e_c$ is constant. Also note that the Buckley-Leverett equation is S-shaped and leads to no advection for $e_c = 0$ and $e_c = e_{c,max}$ since, for $q = 2$, we have

$$\frac{\partial \beta}{\partial e_c} = 2e_c(e_{c,max})^2 - 2e_c^2 e_{c,max}.$$

Figure (26) shows graphs from the Buckley-Leverett equation with exponent values $q = 2, 4, 8$. Figure (27) shows graphs from the Buckley-Leverett equation with fractional exponent values $q = 1/2, 1/4, 1/8$. So the left hand side of the epithelial equation becomes:

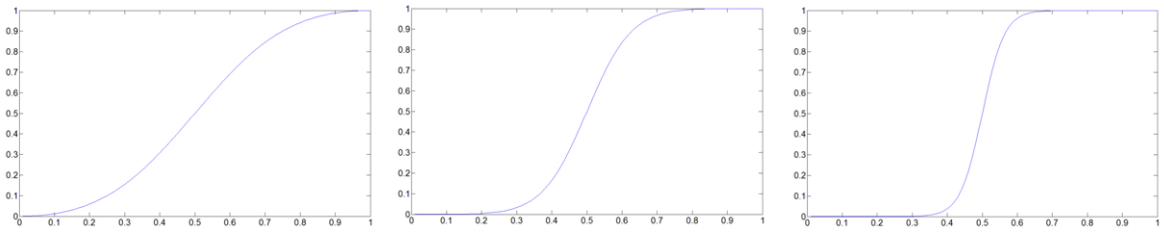


Figure 26: Buckley-Leverett equation. The horizonal axis represents epithelial cells concentration, e_c, ranging from 0 to 1. The vertical axis represents the output of the Buckley-Leverett equation, $\beta(e_c)$. Exponent values for the three graphs are, from left to right, $q = 2, 4, 8$. In each graph, we have $e_{c,max} = 1$.

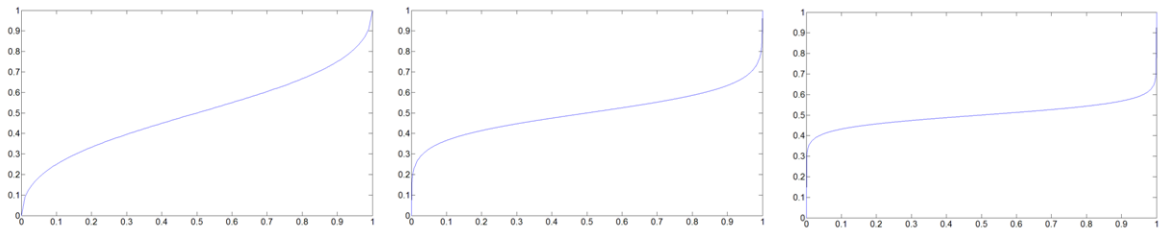


Figure 27: Buckley-Leverett equation. The horizonal axis represents epithelial cells concentration, e_c, ranging from 0 to 1. The vertical axis represents the output of the Buckley-Leverett equation, $\beta(e_c)$. Exponent values for the three graphs are, from left to right, $q = 1/2, 1/4, 1/8$. In each graph, we have $e_{c,max} = 1$.

$$\frac{\partial e_c}{\partial t} + \nabla\beta(e_c) \cdot \mathbf{u} + \beta(e_c)\nabla \cdot \mathbf{u}$$

or

$$\frac{\partial e_c}{\partial t} + \nabla \cdot (\beta(e_c)\mathbf{u}(e_c, b)).$$

For epithelial proliferation, we have $k_p e_c$ multiplied by the logistic term $(1 - e_c/e_{c,max})$. Cytokines, activated neutrophils, and bacteria all contribute to epithelial cell death. Therefore,epithelial cell death is modeled by $-k_a(n_a, c, b)e_c$ where $k_a(n_a, c, b)$ is given by:

$$k_a(n_a, c, b) = \frac{e_{ca}^{q0}(n_a, c, b)}{e_{ca}^{q0}(n_a, c, b) + (e_{ca}(n_{a,max}, c_{max}, b_{max}) - e_{ca}(n_a, c, b))^{q0}}$$

$$\text{and } e_{ca}(n_a, c, b) = n_a + k_{e_c n_a c}c + k_{e_c n_a b}b.$$

Putting everything together, we get

$$\frac{\partial e_c}{\partial t} + \nabla \cdot (\beta(e_c)\mathbf{u}(e_c, b)) = k_p e_c(1 - e_c/e_{c,max}) - k_a(n_a, c, b)e_c.$$

3.2 THE SYSTEM OF PARTIAL DIFFERENTIAL EQUATIONS

The entire system of partial differential equations for the NEC model is given by:

$$\frac{\partial e_c}{\partial t} + \nabla \cdot (\beta(e_c)\mathbf{u}(e_c, b)) = k_p e_c(1 - e_c/e_{c,max}) - k_a(n_a, c, b)e_c$$

Where

$$k_a(n_a, c, b) = \frac{e_{ca}(n_a, c, b)^{q_0}}{e_{ca}(n_a, c, b)^{q_0} + [e_{ca}(n_{a,max}, c_{max}, b_{max}) - e_{ca}(n_a, c, b)]^{q_0}}$$

$$e_{ca}(n_a, c, b) = n_a + k_{e_c n_a} c + k_{e_c n_a} b$$

$$\beta(e_c) = \frac{e_c^2}{e_c^2 + (e_{c,max} - e_c)^2}$$

$$\mathbf{u}(e_c, b) = -\alpha(b)\nabla e_c \qquad \alpha(b) = \frac{(b_{max} - b)^q}{(b_{max} - b)^q + b^q}$$

$$\begin{aligned} \frac{\partial b}{\partial t} - \nabla \cdot D_b \nabla b &= k_{bg} b(1 - b/b_{max}) - k_b b/(1 + b/\epsilon) \\ &\quad - R(c_a)(k_{bm_a} m_a b + k_{bn_a} n_a b) - k_{pp} b \end{aligned}$$

$$\frac{\partial m}{\partial t} = k_m(m_{max} - m) - R(c_a)(k_{mb} bm + k_{mc} cm + k_{md} dm)$$

$$\begin{aligned} \frac{\partial m_a}{\partial t} - \nabla \cdot (D_{m_a} \nabla m_a - \gamma_{m_a c} m_a \nabla c - \gamma_{m_a b} m_a \nabla b) \\ = -k_{m_a} m_a + R(c_a)(k_{mb} bm + k_{mc} cm + k_{md} dm) \end{aligned}$$

$$\frac{\partial c}{\partial t} - \nabla \cdot D_c \nabla c = -k_c c + R(c_a)(k_{cm_a} m_a + k_{cn_a} n_a) - R(c_a)(k_{nc} cn + k_{mc} cm)$$

$$\frac{\partial c_a}{\partial t} - \nabla \cdot D_{c_a} \nabla c_a = -k_{c_a} c_a + s_{c_a} + k_{c_a P} \frac{Q}{1 + Q}$$

$$\frac{\partial NO}{\partial t} \; - \; \nabla \cdot D_{NO} \nabla NO \; = \; -k_{NO} NO + k_{NOm_a} \frac{m_a^{q_1}}{1 + (m_a/\overline{m}_a)^{q_1}} + k_{NOn_a} \frac{n_a^{q_1}}{1 + (n_a/\overline{n}_a)^{q_1}}$$

$$\frac{\partial ZO1}{\partial t} \; = \; \Big(k_{Z_{e_c}} e_c + k_{Z_{e_{ct}}} \frac{\partial e_c}{\partial t} \Big) ZO1_{max} (1 - ZO1/zec) - k_{ZN} NO \cdot ZO1$$

where

$$zec = (1 - \epsilon_{zec}) ZO1_{max} + \epsilon_{zec} \left(\frac{ZO1_{max}}{e_{c,max}} \right) e_c$$

$$\frac{\partial n_a}{\partial t} \; - \; \nabla \cdot (D_{n_a} \nabla n_a - \gamma_{n_a c} n_a \nabla c) = -k_{n_a} n_a + R(c_a)(k_{nc} cn + k_{nd} dn)$$

$$\frac{\partial d}{\partial t} \; - \; \nabla \cdot D_d \nabla d \; = \; -k_d d + k_{dc} \frac{T^{q_2}}{x_{dc}^{q_2} + T^{q_2}}$$

where

$$R(c_a) = \frac{1}{1 + k_{Rc_a} (c_a/\overline{c}_a)^2} \qquad T = R(c_a) c \qquad Q = R(c_a)(k_{c_a m_a n_a} n_a + m_a + k_{c_a m_a d} d)$$

Notes:

1. The physical domain Ω is 3-dimensional consisting of four horizontal regions. The regions from top to bottom are lumen Ω_1, epithelial layer Ω_2, tissue region Ω_3 and circulatory system Ω_4.
2. $D_b, D_c, D_{c_a}, D_d, D_{n_a}, D_{m_a}, D_{NO}$ are diffusion coefficients for bacteria, cytokines, anti-inflammatory cytokines, damage, activated neutrophils, and activated macrophages, respectively.
3. $\gamma_{m_a c}, \gamma_{m_a b}, \gamma_{n_a c}$ are advection coefficients.

3.3 THE NEC EQUATIONS IN THE FOUR REGIONS

Recall that the NEC equations will be applied over four regions (Lumen, Epithelial, Tissue, and Blood). Of course, not all the NEC equations apply to all four regions. For example, the epithelial equation and the ZO1 (tight junction) equation are only valid in the epithelial region. Furthermore, the diffusion coefficients D will be different for each equation and in each region. These diffusion coefficients also play a major role in the communication between the regions. Communication between regions is a very important part of the NEC model and is discussed in more detail in section 7.7 of chapter seven.

3.4 SUGGESTED CHANGES

As noted above, the author of this thesis was involved in the forming and modification of the above PDE model. Yet, the author of this thesis suggests some further changes to the PDE system:

1) **Changes to the nitric oxide equation.** The nitric oxide equation was originally written with no diffusion term. However, the group chose to add a diffusion term to this equation. The author of this thesis suggests that the diffusion term be removed from this equation or, if the diffusion term is retained, other changes to the system should be made. This author's reasoning is as follows:

On the one hand, if nitric oxide in our model is intended to simulate the affects of nitric oxide only, then the diffusion term should be removed. As indicated in the previous chapters, nitric oxide decays very quickly and, therefore, will decay before it diffuses. On the other hand, if nitric oxide in our model is intended to simulate not only nitric oxide but also components formed with the help of nitric oxide such as $ONOO-$ then additional terms must be added. In our current PDE model, nitric oxide destroys tight junction protein but does nothing else. Now, $ONOO-$ is not known to destroy tight junction protein but

$ONOO-$ is known to destroy epithelial cells. However, no such destruction of epithelial cells by nitric oxide is included in our PDE model. (In our model, epithelial cell death by nitric oxide is modeled in an indirect way - bacteria causes epithelial cell death). Therefore, if we wish to retain the diffusion term in the nitric oxide equation, terms should be added to the epithelial equation (and other equations) to model the affects of $ONOO-$ and other components created by nitric oxide.

2) **Changes to the tight junction protein equation.** As noted in chapter 1, in some cases $ZO1$ might fill in small open areas of the epithelium where no epithelial cells exist. In the case of cell shedding, ZO1 moves under the exiting cell in order to fill the newly created space. Therefore, in the equation

$$\frac{\partial e_c}{\partial t} ZO1_{max}(1 - ZO1/zec),$$

it might, in fact, be reasonable to set $zec = ZO1_{max}$. Setting $zec = ZO1_{max}$ was avoided by the group because we did not want there to be tight junction protein in places where no epithelial cells existed. However, in view of the findings noted in chapter 1, we now know that such a condition is possible.

3) **Changes to the equation for Q.** Note that Q was created as:

$$Q = R(c_a)(k_{c_a m_a n_a} n_a + m_a + k_{c_a m_a d} d).$$

It would be more reasonable to multiply $k_{c_a m_a n_a}$ by both n_a and m_a. So that we have:

$$Q = R(c_a)(k_{c_a m_a n_a}(n_a + m_a) + k_{c_a m_a d} d).$$

4.0 ANALYSIS OF THE PDE SYSTEM

In this chapter, the system of partial differential equations will be analyzed.

The most important part of the analysis of the system of partial differential equations in the NEC model is the investigation of the existence of a solution to the system. This particular system of PDEs presents special challenges due unique nonlinearities in some of the equations and the fact that some of the equations are coupled through these non linearities.

Due to the specific coupling involved in the NEC mathematical system, the analysis of the of the partial differential equations may naturally be divided into three parts as follows.

Part I. Part I will consist of eight equations: the equations for bacteria, macrophages, activated macrophages, cytokines, anti-inflammatory cytokines, nitric oxide, activated neutrophils, and damage.

$$\begin{aligned}\frac{\partial b}{\partial t} - \nabla \cdot D_b \nabla b &= k_{bg} b(1 - b/b_{max}) - k_b b/(1 + b/\epsilon) \\ &\quad -R(c_a)(k_{bm_a} m_a b + k_{bn_a} n_a b) - k_{pp} b\end{aligned}$$

$$\frac{\partial m}{\partial t} = k_m(m_{max} - m) - R(c_a)(k_{mb} bm + k_{mc} cm + k_{md} dm)$$

$$\begin{aligned}\frac{\partial m_a}{\partial t} - \nabla \cdot (D_{m_a} \nabla m_a - \gamma_{m_a c} m_a \nabla c - \gamma_{m_a b} R(c_a) m_a \nabla b) \\ = -k_{m_a} m_a + R(c_a)(k_{mb} bm + k_{mc} cm + k_{md} dm)\end{aligned}$$

$$\frac{\partial c}{\partial t} - \nabla \cdot D_c \nabla c = -k_c c + R(c_a)(k_{cm_a} m_a + k_{cn_a} n_a) - R(c_a)(k_{nc} cn + k_{mc} cm)$$

$$\frac{\partial c_a}{\partial t} \; - \; \nabla \cdot D_{c_a} \nabla c_a \; = \; -k_{c_a} c_a + s_{c_a} + k_{c_a P} \frac{Q}{1+Q}$$

$$\frac{\partial NO}{\partial t} \; - \; \nabla \cdot D_{NO} \nabla NO \; = \; -k_{NO} NO + k_{NOm_a} \frac{m_a^{q_1}}{1 + (m_a/\overline{m}_a)^{q_1}} + k_{NOn_a} \frac{n_a^{q_1}}{1 + (n_a/\overline{n}_a)^{q_1}}$$

$$\frac{\partial n_a}{\partial t} \; - \; \nabla \cdot (D_{n_a} \nabla n_a - \gamma_{n_a c} n_a \nabla c) = -k_{n_a} n_a + R(c_a)(k_{nc} cn + k_{nd} dn)$$

$$\frac{\partial d}{\partial t} \; - \; \nabla \cdot D_d \nabla d \; = \; -k_d d + k_{dc} \frac{T^{q_2}}{x_{dc}^{q_2} + T^{q_2}}$$

where

$$R(c_a) = \frac{1}{1 + k_{Rc_a}(c_a/\overline{c}_a)^2} \qquad T = R(c_a)c$$
$$Q = R(c_a)(k_{c_a m_a n_a} n_a + m_a + k_{c_a m_a d} d)$$

Part II. Part II will consist of the epithelial equation:

$$\frac{\partial e_c}{\partial t} + \nabla \cdot (\beta(e_c)\mathbf{u}(e_c, b)) = k_p e_c (1 - e_c/e_{c,max}) - k_a(n_a, c, b) e_c$$

Where

$$k_a(n_a, c, b) = \frac{e_{ca}(n_a, c, b)^{q_0}}{e_{ca}(n_a, c, b)^{q_0} + [e_{ca}(n_{a,max}, c_{max}, b_{max}) - e_{ca}(n_a, c, b)]^{q_0}}$$

$$e_{ca}(n_a, c, b) = n_a + k_{e_c n_a c} c + k_{e_c n_a b} b$$

$$\beta(e_c) = \frac{e_c^2}{e_c^2 + (e_{c,max} - e_c)^2}$$

$$\mathbf{u}(e_c, b) = -\alpha(b) \nabla e_c \qquad \alpha(b) = \frac{(b_{max} - b)^q}{(b_{max} - b)^q + b^q}$$

Part III. Part III consists of the tight junction protein equation:

$$\frac{\partial ZO1}{\partial t} \; = \; \Big(k_{Z_{e_c}} e_c + k_{Z_{e_{ct}}} \frac{\partial e_c}{\partial t}\Big) ZO1_{max}(1 - ZO1/zec) - k_{ZN} NO \cdot ZO1$$

where

$$zec = (1 - \epsilon_{zec})ZO1_{max} + \epsilon_{zec}\left(\frac{ZO1_{max}}{e_{c,max}}\right)e_c.$$

It is not obvious here but the tensor D in each of the equations in Part I depends upon the equation in Part II. (This dependence is more obvious in the computer code for the simulations, which come later in the thesis.) This dependence will be neglected in the following analysis. The equations in Part I do not depend at all on the equation in Part III. Therefore, the existence and uniqueness of solutions for the aforementioned eight equations in Part I may be found independently of the equations in Part II and Part III. This existence and uniqueness study is done in **Analysis of PDEs in Part I**.

Notice that the equation in Part II (the epithelial equation) depends on the equations from part I but does not depend on the equation in Part III (the tight junction protein equation). Therefore, error bounds found in part I may be used to bound the error for the epithelial cells. This study is done in **Analysis of PDEs in Part II**.

The equation in Part III (the tight junction protein equation) depends upon the equations in Part I and Part II. Therefore, error bounds found in part I and Part II may be used to bound the error for the tight junction protein. This study is done in **Analysis of PDEs in Part III**.

4.1 NOTATION

$(\cdot, \cdot)$ is the $L^2(\Omega)$ inner product.

$$L^p(\Omega) = \left\{ f : \Omega \to \mathrm{R} \middle| \int_\Omega |f|^p < \infty \right\} \quad \text{for } 1 \leq p < \infty$$

$$\|f\|_{L^p(\Omega)} = \left[\int_\Omega |f|^p \right]^{1/p} \quad \text{for } 1 \leq p < \infty$$

$$L^\infty(\Omega) = \{ f : \Omega \to \mathrm{R} \mid \text{ess sup}_{\mathbf{x} \in \Omega} |f(\mathbf{x})| < \infty \}$$

$$\|f\|_{L^\infty(\Omega)} = \text{ess sup}_{\mathbf{x}\in\Omega} |f(\mathbf{x})|$$

$$H(div;\Omega) = \{f \in (L^2(\Omega))^n | \nabla \cdot f \in L^2(\Omega)\}$$

$$\|\mathbf{x}\|_\infty = \max_{1\le i\le n} |x_i| \qquad \|A\|_\infty = \sup_{\mathbf{x}\in \mathrm{R}^n, \mathbf{x}\neq 0} \frac{\|A\mathbf{x}\|_\infty}{\|\mathbf{x}\|_\infty} \text{ for } \mathbf{x} \in \mathrm{R}^n \quad A \in \mathrm{R}^{n\times n}$$

Note that the above definition implies $\|A\mathbf{x}\|_\infty \le \|A\|_\infty \|\mathbf{x}\|_\infty$.

$$L^\infty(\mathrm{R}^{n\times n}) = \{A \in \mathrm{R}^{n\times n} \Big| \|A\|_\infty < \infty\}$$

The following two theorems may be found in [38]

Theorem 4.1 (**Banach's Fixed Point Theorem**). *Assume that*

$$A : X \to X$$

where A is a nonlinear mapping and X is a Banach space. Further suppose that

$$\|A[u_1] - A[u_2]\| \le k\|u_1 - u_2\| \quad \forall u_1, u_2 \in X$$

for some constant k such that $k < 1$. Then A has a unique fixed point.

Theorem 4.2 (**Schauder's Fixed Point Theorem - Version 1**). *Suppose that K is a compact and convex space and M is a continuous mapping:*

$$M : K \to K$$

then M has a fixed point in K.

Theorem 4.3 (**Schauder's Fixed Point Theorem - Version 2**). *Let A be a compact and continuous mapping of a bounded, convex set S into S. Then A has a fixed point in S.*

Theorem 4.4 (**Ascoli-Arzela Theorem**). *Let (X, d) be a compact space. A subset $\mathcal{F}$ of $C(X)$ is relatively compact if and only if $\mathcal{F}$ is equibounded and equicontinuous.*

Recall the shift operator $\Delta_{Shift(\overline{\mathbf{h}})} f(\mathbf{x}) = f(\mathbf{x} + \overline{\mathbf{h}})$ where $\overline{\mathbf{h}} \in \mathcal{R}^3$.

The following theorem is found in [21],

Theorem 4.5 (**Kolmogorov-M.Riesz-Frechet**). *Let $\mathcal{F}$ be a bounded set in $L^p(\mathcal{R}^N)$ with $1 \leq p < \infty$. Furthermore, suppose*

$$\lim_{\overline{\mathbf{h}} \to 0} \|\Delta_{Shift(\overline{\mathbf{h}})} f\|_p = 0 \qquad \text{uniformly in } f \in \mathcal{F}$$

where $\Delta_{Shift(\overline{\mathbf{h}})} f(\mathbf{x}) = f(\mathbf{x} + \overline{\mathbf{h}})$ for $\overline{\mathbf{h}} \in \mathcal{R}^3$ is the shift operator.

Then the closure of $\mathcal{F}_{|\Omega}$ in $L^p(\Omega)$ is compact for any measurable set $\Omega \subset \mathcal{R}^N$ with finite measure.

Theorem 4.6 (**Cauchy's inequality with ε**). *Suppose that $a, b > 0$ and $\varepsilon > 0$ then,*

$$ab \leq \varepsilon a^2 + \frac{b^2}{4\varepsilon}.$$

The following theorem may be found in [85]

Theorem 4.7 (**Cauchy-Schwarz inequality**). *For $u, v \in L^2(\Omega)$,*

$$|(u, v)| \leq \|u\| \|v\|.$$

One form of the Gronwall Inequality is given by (see [78]),

Theorem 4.8 (**The Gronwall Inequality**). *For any $t \in [t_0, T)$, if we have*

$$u(t) \leq a(t) + \int_{t_0}^{t} b(s) u(s) ds,$$

where $a(t)$ is not decreasing and $b \geq 0$, then

$$u(t) \leq a(t) e^{\int_{t_0}^{t} b(s) ds}, \qquad \text{for } t \in [t_0, T).$$

Theorem 4.9 (**Aubin-Lions Compactness Criteria**). *Suppose that X, Y, Z are Banach Spaces and $X \subseteq Y \subseteq Z$. Suppose that X and Z are reflective spaces. Furthermore suppose that X is compactly embedded in Y and Y is continuously embedded in Z. Let*

$$Q = \left\{ u \in L^p(0, T; X) \;\middle|\; \frac{\partial u}{\partial t} \in L^q(0, T; Z) \right\} \quad \text{for } 1 < p, q < \infty$$

then Q is compactly embedded into $L^p(0, T; Y)$.

4.2 ANALYSIS OF PDES IN PART I

Representative system

The partial differential equations in Part I are of two general types: (a) those equations that are nonlinear in the "data" only, i.e., the nonlinearities reside in the right hand side functions only. The equations of this type are the bacteria, macrophage, cytokine, anti-inflammatory cytokine, Nitric Oxide, and damage equations; (b) those equations that contain nonlinearities in the advection terms. The equations of this type are activated macrophage and activated neutrophil equations. Such equations are particularly difficult to analyze because these nonlinearities are coupled to other equations in the system.

The particular features mentioned in (a) and (b) above may be represented by the following system of two equations:

$$\frac{\partial u_1}{\partial t} - \nabla \cdot (D_1 \nabla u_1 - u_1 \nabla u_2) = f_1(u_1, u_2) \tag{4.1}$$

$$\frac{\partial u_2}{\partial t} - \nabla \cdot (D_2 \nabla u_2) = f_2(u_1, u_2) \qquad (x,t) \in \Omega \times (0,T] \tag{4.2}$$

$$\nabla u_1 \cdot \mathbf{n} = 0 \qquad \text{and} \qquad \nabla u_2 \cdot \mathbf{n} = 0 \qquad \text{on } \Gamma. \tag{4.3}$$

where f_1 and f_2 are nonlinear functions of u_1 and u_2. Notice that (4.1) might represent the activated macrophage equation or the activated neutrophil equations. On the other hand, (4.2) might represent the bacteria, macrophage, cytokine, anti-inflammatory cytokine, Nitric Oxide, or damage equation. These are the only two types of equations that we have in Part I.

Notice, for example, we do not have any "two-way" coupling in the advection terms, i.e., we **do not** have the following coupling in our system:

$$\frac{\partial u_1}{\partial t} - \nabla \cdot (D_1 \nabla u_1 - u_1 \nabla u_2) = f_1(u_1, u_2)$$

$$\frac{\partial u_2}{\partial t} - \nabla \cdot (D_2 \nabla u_2 - u_2 \nabla u_1) = f_2(u_1, u_2)$$

Therefore, in order to prove that the system of equations in Part I has a solution, it suffices to prove that (4.1), (4.2) has a solution.

4.3 EXISTENCE AND REGULARITY OF WEAK MIXED SOLUTION FOR THE LINEAR PROBLEM

The numerical method that will be used to solve the PDE system will be based on the Mixed Finite Element Method. Therefore, it will be helpful to prove that the PDE system has a weak mixed solution and to establish some regularity for that solution. First, it will be shown that the linear problem has a mixed weak solution. After that, regularity will be established for the weak mixed formulation. Then, in the next subsection, it will be shown that the nonlinear mixed weak form has a solution.

Definition of the Weak Mixed Solution. Consider for $f \in L^2(\Omega)$ the PDE

$$\begin{aligned} &u_t - \Delta u = f \qquad (x,t) \in \Omega \times (0,T] \\ &u(0) = g \\ &\nabla u \cdot \mathbf{n} = 0 \quad \text{on } \Gamma \end{aligned}$$

Set $\mathbf{z} = -\nabla u \Rightarrow \mathbf{z} + \nabla u = 0$

$$\begin{aligned} u_t + \nabla \cdot \mathbf{z} &= f \\ \mathbf{z} + \nabla u &= 0 \end{aligned}$$

Multiply by test functions and integrate. We say $u \in L^2(\Omega), \mathbf{z} \in V^0$ is a **weak mixed solution** if,

$$(u_t, w) + (\nabla \cdot \mathbf{z}, w) = (f, w) \quad \forall w \in L^2(\Omega) \tag{4.4}$$

$$(\mathbf{z}, v) - (u, \nabla \cdot v) = 0 \quad \forall v \in V^0. \tag{4.5}$$

The second equation was obtained by integrating by parts. Here $V = H(\text{div}; \Omega))$ and $V^0 = V \cap \{v : v \cdot n = 0 \text{ on } \Gamma\}$.

4.3.1 Existence of Solution to Finite System.

Consider the basis ϕ_i for V^0 and the orthonormal basis ψ_i for $L^2(\Omega)$. Now, define

$$u_m := \sum_{i=1}^{m} \xi_i \psi_i \quad \Rightarrow \quad u_{m_t} = \sum_{i=1}^{m} \xi_{i_t} \psi_i \tag{4.6}$$

$$\mathbf{z_n} := \sum_{i=1}^{n} \chi_i \phi_i \quad \Rightarrow \quad \mathbf{z_{n_t}} = \sum_{i=1}^{n} \chi_{i_t} \phi_i \tag{4.7}$$

where ξ_i for $i = 1, ..., m$ and χ_i for $i = 1, ..., n$ are functions of t only. Note that $\xi_{i_t} := d\xi_i/dt$ and $\chi_{i_t} := d\chi_i/dt$.

Substitute (4.6) and (4.7) into (4.4) and (4.5) and replace w and v by the basis functions

$$\left(\sum_{i=1}^{m} \xi_{i_t} \psi_i, \psi_j \right) + \left(\nabla \cdot \sum_{i=1}^{n} \chi_i \phi_i, \psi_j \right) = (f, \psi_j) \tag{4.8}$$

$$\left(\sum_{i=1}^{n} \chi_i \phi_i, \phi_j \right) - \left(\sum_{i=1}^{m} \xi_i \psi_i, \nabla \cdot \phi_j \right) = 0 \tag{4.9}$$

For (4.8), set $j = 1, ..., m$ to get

$$\begin{pmatrix} 1 & 0 & \cdots & 0 & 0 \\ 0 & 1 & \cdots & 0 & 0 \\ \cdot & \cdot & \cdots & \cdot & \cdot \\ 0 & 0 & \cdots & 0 & 1 \end{pmatrix} \mathbf{C_t} + \begin{pmatrix} (\nabla \cdot \phi_1, \psi_1) & \cdots & (\nabla \cdot \phi_n, \psi_1) \\ (\nabla \cdot \phi_1, \psi_2) & \cdots & (\nabla \cdot \phi_n, \psi_2) \\ \cdots & \cdots & \cdots \\ (\nabla \cdot \phi_1, \psi_m) & \cdots & (\nabla \cdot \phi_n, \psi_m) \end{pmatrix} \mathbf{X} = \begin{pmatrix} (f, \psi_1) \\ (f, \psi_2) \\ \cdot \\ (f, \psi_m) \end{pmatrix}.$$

For (4.9), set $k = 1, ..., n$ to get

$$\begin{pmatrix} (\phi_1, \phi_1) & \cdots & (\phi_n, \phi_1) \\ (\phi_1, \phi_2) & \cdots & (\phi_n, \phi_2) \\ \cdots & \cdots & \cdots \\ (\phi_1, \phi_n) & \cdots & (\phi_n, \phi_n) \end{pmatrix} \mathbf{X} - \begin{pmatrix} (\psi_1, \nabla \cdot \phi_1) & \cdots & (\psi_m, \nabla \cdot \phi_1) \\ (\psi_1, \nabla \cdot \phi_2) & \cdots & (\psi_m, \nabla \cdot \phi_2) \\ \cdots & \cdots & \cdots \\ (\psi_1, \nabla \cdot \phi_n) & \cdots & (\psi_m, \nabla \cdot \phi_n) \end{pmatrix} \mathbf{C} = \mathbf{0}.$$

Where

$$\mathbf{X} := \begin{pmatrix} \chi_1 \\ \chi_2 \\ . \\ . \\ . \\ \chi_n \end{pmatrix} \qquad \mathbf{C} := \begin{pmatrix} \xi_1 \\ \xi_2 \\ . \\ . \\ . \\ \xi_m \end{pmatrix} \qquad \mathbf{C_t} := \begin{pmatrix} \xi_{1_t} \\ \xi_{2_t} \\ . \\ . \\ . \\ \xi_{m_t} \end{pmatrix}.$$

If we define

$$\mathbf{A} := \begin{pmatrix} (\phi_1, \phi_1) & \cdots & (\phi_n, \phi_1) \\ (\phi_1, \phi_2) & \cdots & (\phi_n, \phi_2) \\ \cdots & \cdots & \cdots \\ (\phi_1, \phi_n) & \cdots & (\phi_n, \phi_n) \end{pmatrix} \qquad \mathbf{B} := \begin{pmatrix} (\nabla \cdot \phi_1, \psi_1) & \cdots & (\nabla \cdot \phi_n, \psi_1) \\ (\nabla \cdot \phi_1, \psi_2) & \cdots & (\nabla \cdot \phi_n, \psi_2) \\ \cdots & \cdots & \cdots \\ (\nabla \cdot \phi_1, \psi_m) & \cdots & (\nabla \cdot \phi_n, \psi_m) \end{pmatrix}$$

$$\mathbf{F} := \begin{pmatrix} (f, \psi_1) \\ (f, \psi_2) \\ . \\ (f, \psi_m) \end{pmatrix} \quad \text{and} \quad \mathbf{G} := \begin{pmatrix} g_1 \\ g_2 \\ . \\ g_m \end{pmatrix}$$

then the system may be written as

$$\mathbf{C_t} + \mathbf{BX} = \mathbf{F} \tag{4.10}$$

$$\mathbf{AX} - \mathbf{B^T C} = \mathbf{0} \tag{4.11}$$

$$\mathbf{C}(0) = \mathbf{G}.$$

So, from (4.11) we have $\mathbf{X} = \mathbf{A^{-1}B^T C}$. Substituting this into (4.10) gives:

$$\mathbf{C_t} + \mathbf{BA^{-1}B^T C} = \mathbf{F}. \tag{4.12}$$

It can be shown that $\mathbf{BA^{-1}B^T}$ is SPD and $\mathbf{BA^{-1}B^T} \in L^\infty(\mathrm{R^{n\times n}})$, i.e., $\exists K$ such that $\|\mathbf{BA^{-1}B^T}\|_\infty \leq K$. Note that (4.12) is a system of ordinary differential equations in the variable t. It is now necessary to show that (4.12) has a solution.

Prove that there exists a solution to the system (4.12) of ODEs.

A solution to (4.12) will now be constructed on an arbitrary interval $[0, T]$. Integrate (4.12) from 0 to $T_1 \leq T$ to get:

$$\mathbf{C} - \mathbf{C}(0) + \int_0^{T_1} \mathbf{B}\mathbf{A}^{-\mathbf{1}}\mathbf{B}^{\mathbf{T}}\mathbf{C}\, ds = \int_0^{T_1} \mathbf{F}\, ds. \tag{4.13}$$

So,

$$\mathbf{C} = \mathbf{G} + \int_0^{T_1} \mathbf{F}\, ds - \int_0^{T_1} \mathbf{B}\mathbf{A}^{-\mathbf{1}}\mathbf{B}^{\mathbf{T}}\mathbf{C}\, ds. \tag{4.14}$$

Now, we may define the mapping:

$$\mathbf{H}(\mathbf{C}) := \mathbf{G} + \int_0^{T_1} \mathbf{F}\, ds - \int_0^{T_1} \mathbf{B}\mathbf{A}^{-\mathbf{1}}\mathbf{B}^{\mathbf{T}}\mathbf{C}\, ds. \tag{4.15}$$

Banach's fixed point theorem (**Theorem 4.1**) will be used to prove that this mapping has a fixed point. In order to do this, choose two $\mathbf{C}$'s, say $\mathbf{C_1}$ and $\mathbf{C_2}$. Then

$$\mathbf{H}(\mathbf{C_2}) - \mathbf{H}(\mathbf{C_1}) = \int_0^{T_1} \mathbf{B}\mathbf{A}^{-\mathbf{1}}\mathbf{B}^{\mathbf{T}}(\mathbf{C_1} - \mathbf{C_2})\, ds. \tag{4.16}$$

Since $\mathbf{B}\mathbf{A}^{-\mathbf{1}}\mathbf{B}^{\mathbf{T}}$ and $\|\mathbf{B}\mathbf{A}^{-\mathbf{1}}\mathbf{B}^{\mathbf{T}}\|_\infty \leq K$ is SPD, we have:

$$\|\mathbf{H}(\mathbf{C_2}) - \mathbf{H}(\mathbf{C_1})\|_{MaxNorm(T_1)} \leq KT_1\|\mathbf{C_2} - \mathbf{C_1}\|_{MaxNorm(T_1)} \tag{4.17}$$

$$\text{where } \|\cdot\|_{MaxNorm(T^*)} := \sup_{0\leq t\leq T^*} \|\cdot\|_\infty \quad \text{and} \quad K \text{ is a constant.}$$

Now pick T_1 so that $KT_1 < 1$. Then by Banach's fixed point theorem (**Theorem 4.1**) there exists a $\mathbf{C}$ such that $\mathbf{H}(\mathbf{C}) = \mathbf{C}$ on $[0, T_1]$. Thus, there exists a solution to (4.12) on $[0, T_1]$.

Next, choose T_2 so as to get a similar contraction, and therefore establish a solution, on the interval $[T_1, T_2]$. Continue to prove the existence of solutions on these subintervals until the entire interval $[0, T]$ is covered. In this way, a solution to (4.12) may be constructed on any interval $[0, T]$.

Thus, we have established that for any finite integers, m and n, the system

$$(u_{m_t}, \psi_j) + (\nabla \cdot \mathbf{z_n}, \psi_j) = (f, \psi_j) \tag{4.18}$$

$$(\mathbf{z_n}, \phi_k) - (u_m, \nabla \cdot \phi_k) = 0 \tag{4.19}$$

has a solution $(u_m, \mathbf{z_n}) \in L^\infty(0,T;L^2(\Omega)) \times L^\infty(0,T;V^0)$.

4.3.2 Establish Bounds for Various Terms

In order to prove any regularity for the solution to the PDE system, it will first be necessary to establish bounds on various terms.

Establishment of a bound for $\|u_m\|_{L^\infty(0,T;L^2(\Omega))}$ and $\|\mathbf{z_n}\|_{L^2(0,T;L^2(\Omega))}$.

Multiply (4.18) by ξ_j and multiply (4.19) by χ_k to get:

$$(u_{m_t}, \xi_j\psi_j) + (\nabla \cdot \mathbf{z_n}, \xi_j\psi_j) = (f, \xi_j\psi_j) \tag{4.20}$$

$$(\mathbf{z_n}, \chi_k\phi_k) - (u_m, \nabla\chi_k\phi_k) = 0. \tag{4.21}$$

Summing $j = 1, ..., m$ and summing $k = 1, ..., n$ and recalling (4.6),(4.7) gives:

$$(u_{m_t}, u_m) + (\nabla \cdot \mathbf{z_n}, u_m) = (f, u_m) \tag{4.22}$$

$$(\mathbf{z_n}, \mathbf{z_n}) - (u_m, \nabla\mathbf{z_n}) = 0. \tag{4.23}$$

Substitute (4.23) into (4.22),use the Cauchy-Schwarz inequality (theorem 4.7) and Cauchy's inequality (theorem 4.6) to get,

$$\frac{1}{2}\frac{d}{dt}\|u_m\|^2 + \|\mathbf{z_n}\|^2 = (f, u_m) \leq \frac{1}{2}\|f\|^2 + \frac{1}{2}\|u_m\|^2. \tag{4.24}$$

Multiply by 2 and integrate from 0 to t, for $0 < t \leq T$,

$$\|u_m\|^2(t) + 2\int_0^t \|\mathbf{z_n}\|^2 \leq \int_0^t \|f\|^2 + \int_0^t \|u_m\|^2 + \|u_m\|^2(0).$$

Applying the Gronwall Inequality, theorem 4.8,

$$\sup_{0\le t\le T}\|u_m\|^2+2\int_0^T\|\mathbf{z_n}\|^2\le C\left(\int_0^T\|f\|^2+\|u_m\|^2(0)\right).$$

Thus, if $u_m(0)\in L^2(\Omega)$ and $f\in L^2(0,T;L^2(\Omega))$ then

$$\{u_m\}_{m=1}^{\infty}\text{ is bounded in }L^\infty(0,T;L^2(\Omega)) \tag{4.25}$$

$$\{\mathbf{z_n}\}_{n=1}^{\infty}\text{ is bounded in }L^2(0,T;L^2(\Omega)). \tag{4.26}$$

Establishment of a bound for $\|u_{m_t}\|_{L^2(0,T;L^2(\Omega))}$ and $\|\mathbf{z_n}\|_{L^\infty(0,T;L^2(\Omega))}$

Now, multiply (4.18) by ξ_{j_t}. Then, take the derivative of (4.19) with respect to t and then multiply it by χ_k to get

$$(u_{m_t},\xi_{j_t}\psi_j)+(\nabla\cdot\mathbf{z_n},\xi_{j_t}\psi_j)=(f,\xi_{j_t}\psi_j) \tag{4.27}$$

$$(\mathbf{z_{n_t}},\chi_k\phi_k)-(u_{m_t},\nabla\chi_k\phi_k)=0. \tag{4.28}$$

Summing $j=1,...,m$ and $k=1,...,n$ gives:

$$(u_{m_t},u_{m_t})+(\nabla\cdot\mathbf{z_n},u_{m_t})=(f,u_{m_t}) \tag{4.29}$$

$$(\mathbf{z_{n_t}},\mathbf{z_n})-(u_{m_t},\nabla\cdot\mathbf{z_n})=0. \tag{4.30}$$

Substitute (4.30) into (4.29),

$$\|u_{m_t}\|^2+\frac{1}{2}\frac{d}{dt}\|\mathbf{z_n}\|^2=(f,u_{m_t})\le\frac{1}{2}\|f\|^2+\frac{1}{2}\|u_{m_t}\|^2. \tag{4.31}$$

Move $\frac{1}{2}\|u_{m_t}\|^2$ to the left hand side, multiply by 2 and integrate from 0 to t, for $0<t\le T$,

$$\int_0^t\|u_{m_t}\|^2+\|\mathbf{z_n}\|^2(t)\le\int_0^t\|f\|^2+\|\mathbf{z_n}\|^2(0). \tag{4.32}$$

Thus, if $\mathbf{z_n}(0)\in L^2(\Omega)$, which is true if $g\in H^1(\Omega)$, and $f\in L^2(0,T;L^2(\Omega))$ then

$$\{\mathbf{z_n}\}_{n=1}^{\infty}\text{ is bounded in }L^\infty(0,T;L^2(\Omega)) \tag{4.33}$$

$$\{u_{m_t}\}_{m=1}^{\infty}\text{ is bounded in }L^2(0,T;L^2(\Omega)). \tag{4.34}$$

We will fix P and Q and choose

$$w = \sum_{j=1}^{P} c_j \psi_j \qquad \text{and} \qquad v = \sum_{k=1}^{Q} y_k \phi_k. \tag{4.35}$$

Where c_j and y_k are functions of t only.

Now, multiply (4.18) by c_j and (4.19) by y_k to get

$$(u_{m_t}, c_j\psi_j) + (\nabla \cdot \mathbf{z_n}, c_j\psi_j) = (f, c_j\psi_j) \tag{4.36}$$

$$(\mathbf{z_n}, y_k\phi_k) - (u_m, \nabla y_k\phi_k) = 0. \tag{4.37}$$

Summing $j = 1, ..., P$ and $k = 1, ..., Q$ gives

$$(u_{m_t}, w) + (\nabla \cdot \mathbf{z_n}, w) = (f, w) \qquad \forall w \in \text{span}\{\psi_j\}_{j=1}^{m} \tag{4.38}$$

$$(\mathbf{z_n}, v) - (u_m, \nabla \cdot v) = 0 \qquad \forall v \in \text{span}\{\phi_k\}_{k=1}^{n}. \tag{4.39}$$

Since w, v are constructed from the basis functions ψ_j, ϕ_j and there is a solution to (4.18),(4.19), this implies that there exists a solution to (4.38),(4.39).

Establishment of a bound on $\|\nabla \cdot \mathbf{z_n}\|_{L^2(0,T;L^2(\Omega))}$

Now, in (4.38) set $w = \nabla \cdot \mathbf{z_n}$,

$$(u_{m_t}, \nabla \cdot \mathbf{z_n}) + (\nabla \cdot \mathbf{z_n}, \nabla \cdot \mathbf{z_n}) = (f, \nabla \cdot \mathbf{z_n}). \tag{4.40}$$

Then

$$\|\nabla \cdot \mathbf{z_n}\|^2 \leq \|f\|\|\nabla \cdot \mathbf{z_n}\| + \|u_{m_t}\|\|\nabla \cdot \mathbf{z_n}\|. \tag{4.41}$$

Dividing,

$$\|\nabla \cdot \mathbf{z_n}\| \leq \|f\| + \|u_{m_t}\|. \tag{4.42}$$

This implies,

$$\|\nabla \cdot \mathbf{z_n}\|^2 \leq 2\|f\|^2 + 2\|u_{m_t}\|^2.$$

Integrate from 0 to t and use (4.32)

$$\int_0^t \|\nabla \cdot \mathbf{z_n}\|^2 \leq 2\int_0^t \|f\|^2 + 2\int_0^t \|f\|^2 + 2\|\mathbf{z_n}\|^2(0). \tag{4.43}$$

Thus, if $f \in L^2(0,T;L^2(\Omega))$ and $\mathbf{z_n}(0) \in L^2(\Omega)$ (which is true if $g \in H^1(\Omega)$) then

$$\{\nabla \cdot \mathbf{z_n}\}_{n=1}^{\infty} \text{ is bounded in } L^2(0,T;L^2(\Omega)). \tag{4.44}$$

4.3.3 Convergence to a Solution of Linear Weak Mixed System

Now, integrate (4.38) and (4.39) from 0 to T.

$$\int_0^T (u_{m_t}, w) + \int_0^T (\nabla \cdot \mathbf{z_n}, w) = \int_0^T (f, w) \tag{4.45}$$

$$\int_0^T (\mathbf{z_n}, v) - \int_0^T (u_m, \nabla \cdot v) = 0. \tag{4.46}$$

Note that from (4.25), (4.26), (4.33),(4.34), (4.44) all of the relevant sequences are bounded in the appropriate spaces. Therefore, each of these sequences has a weakly convergent subsequence in that space. Choose convergent subsequences $\{\mathbf{u_{m_L}}, \mathbf{z_{n_L}}\}$ of $\{\mathbf{u_m}, \mathbf{z_n}\}$ such that $u_{m_L} \rightharpoonup u$ weakly and $\mathbf{z_{n_L}} \rightharpoonup \mathbf{z}$ weakly. Set $m = m_L, n = n_L$ and take $m_L \to \infty, n_L \to \infty$ in (4.38) - (4.39). Then

$$\int_0^T (u_t, w) + \int_0^T (\nabla \cdot \mathbf{z}, w) = \int_0^T (f, w) \qquad \forall w \in L^2(\Omega) \tag{4.47}$$

$$\int_0^T (\mathbf{z}, v) - \int_0^T (u, \nabla \cdot v) = 0 \qquad \forall v \in V^0(\Omega). \tag{4.48}$$

By choosing test functions $\phi(t)w$ and $\psi(t)v$ where $\phi, \psi \in C_0^{\infty}(0,T)$ one can show that

$$(u_t, w) + (\nabla \cdot \mathbf{z}, w) = (f, w) \qquad \forall w \in L^2(\Omega) \tag{4.49}$$

$$(\mathbf{z}, v) - (u, \nabla \cdot v) = 0 \qquad \forall v \in V^0(\Omega). \tag{4.50}$$

$$u(0) = g$$

holds for a.e. $t \in (0,T]$.

Establishment of a bound for $\|u_t\|_{L^\infty(0,T;L^2(\Omega))}$ and $\|\mathbf{z_t}\|_{L^2(0,T;L^2(\Omega))}$

In (4.49) and (4.50) take the derivative with respect to t and set $w = u_t, v = \mathbf{z_t}$

$$(u_{tt}, u_t) + (\nabla \cdot \mathbf{z_t}, u_t) = (f_t, u_t) \tag{4.51}$$

$$(\mathbf{z_t}, \mathbf{z_t}) - (u_t, \nabla \cdot \mathbf{z_t}) = 0. \tag{4.52}$$

Substitute (4.52) into (4.51),

$$\frac{1}{2}\frac{d}{dt}\|u_t\|^2 + \|\mathbf{z_t}\|^2 = (f_t, u_t) \leq \frac{1}{2}\|f_t\|^2 + \frac{1}{2}\|u_t\|^2. \tag{4.53}$$

Multiply by 2 and integrate from 0 to t,

$$\|u_t\|^2(t) + \int_0^t \|\mathbf{z_t}\|^2 \leq \int_0^t \|f_t\|^2 + \|u_t\|^2(0). \tag{4.54}$$

Thus, if $g \in L^2(\Omega))$, $f \in L^\infty(0,T;L^2(\Omega))$ and $f_t \in L^2(0,T;L^2(\Omega))$ then

$$\begin{aligned} &\mathbf{z_t} \in L^2(0,T;L^2(\Omega)) \\ &u_t \in L^\infty(0,T;L^2(\Omega)). \end{aligned} \tag{4.55}$$

Establishment of a bound for $\|u_{tt}\|_{L^2(0,T;L^2(\Omega))}$ and $\|\mathbf{z_t}\|_{L^\infty(0,T;L^2(\Omega))}$

Take the derivative, with respect to t, of (4.49). Take two derivatives, with respect to t, of (4.50) then set $w = u_{tt}, v = \mathbf{z_t}$

$$(u_{tt}, u_{tt}) + (\nabla \cdot \mathbf{z_t}, u_{tt}) = (f_t, u_{tt}) \tag{4.56}$$

$$(\mathbf{z_{tt}}, \mathbf{z_t}) - (u_{tt}, \nabla \cdot \mathbf{z_t}) = 0. \tag{4.57}$$

Substitute (4.57) into (4.56),

$$\|u_{tt}\|^2 + \frac{1}{2}\frac{d}{dt}\|\mathbf{z_t}\|^2 = (f_t, u_{tt}) \leq \frac{1}{2}\|f_t\|^2 + \frac{1}{2}\|u_{tt}\|^2. \tag{4.58}$$

Move $\frac{1}{2}\|u_{tt}\|^2$ to the left hand side, multiply by 2 and integrate from 0 to t,

$$\int_0^t \|u_{tt}\|^2 + \|\mathbf{z_{n_t}}\|^2(t) \leq \int_0^t \|f_t\|^2 + \|\mathbf{z_t}\|^2(0). \tag{4.59}$$

Thus, if $\mathbf{z_t}(0) \in L^2(\Omega)$ (which is true if $g \in H^3(\Omega)$), $f \in L^\infty(0,T;L^2(\Omega))$ and $f_t \in L^2(0,T;L^2(\Omega))$ then

$$\begin{aligned} &\mathbf{z_t} \in L^\infty(0,T;L^2(\Omega)) \\ &u_{tt} \in L^2(0,T;L^2(\Omega)). \end{aligned} \tag{4.60}$$

Establishment of a bound on $\|\nabla \cdot \mathbf{z_t}\|_{L^2(0,T;L^2(\Omega))}$

Take derivative of (4.49) with respect to t to get,

$$(u_{tt}, w) + (\nabla \cdot \mathbf{z_t}, w) = (f_t, w)$$

Set $w = \nabla \cdot \mathbf{z_t}$

$$(u_{tt}, \nabla \cdot \mathbf{z_t}) + (\nabla \cdot \mathbf{z_t}, \nabla \cdot \mathbf{z_t}) = (f_t, \nabla \cdot \mathbf{z_t})$$

then

$$\|\nabla \cdot \mathbf{z_t}\|^2 \leq \|f_t\|\|\nabla \cdot \mathbf{z_t}\| + \|u_{tt}\|\|\nabla \cdot \mathbf{z_t}\|$$

and

$$\|\nabla \cdot \mathbf{z_t}\| \leq \|f_t\| + \|u_{tt}\|$$

Finally

$$\int_0^T \|\nabla \cdot \mathbf{z_t}\|^2 \leq 2\int_0^T \|f_t\|^2 + 2\int_0^T \|u_{tt}\|$$

We know from (4.60) that the last term on the right hand side is bounded. So if we have that $f_t \in L^2(0,T;L^2(\Omega))$

$$\nabla \cdot \mathbf{z_t} \in L^2(0,T;L^2(\Omega)) \tag{4.61}$$

Establishment of a bound on $\|\nabla \cdot \mathbf{z_n}\|_{L^\infty(0,T;L^2(\Omega))}$

Go back to (4.40) and take the derivative with respect to t,

$$(u_{tt}, \nabla \cdot \mathbf{z}) + (u_t, \nabla \cdot \mathbf{z_t}) + 2(\nabla \cdot \mathbf{z}, \nabla \cdot \mathbf{z_t}) \\ = (f_t, \nabla \cdot \mathbf{z_n}) + (f, \nabla \cdot \mathbf{z_t}).$$

Rearranging,

$$\frac{d}{dt}\|\nabla \cdot \mathbf{z}\|^2 \leq \|f_t\|\|\nabla \cdot \mathbf{z}\| + \|f\|\|\nabla \cdot \mathbf{z_t}\| \\ +\|u_{tt}\|\|\nabla \cdot \mathbf{z_n}\| + \|u_t\|\|\nabla \cdot \mathbf{z_t}\|$$

then

$$\frac{d}{dt}\|\nabla \cdot \mathbf{z}\|^2 \leq C\|f_t\|^2 + C\|\nabla \cdot \mathbf{z}\|^2 + C\|f\|^2 \\ +C\|\nabla \cdot \mathbf{z_t}\|^2 + C\|u_{tt}\|^2 + C\|u_t\|^2$$

Integrating from 0 to t:

$$\|\nabla \cdot \mathbf{z}\|^2 \leq C\int_0^T \|f_t\|^2 + C\int_0^T \|\nabla \cdot \mathbf{z}\|^2 + C\int_0^T \|f\|^2 \\ +C\int_0^T \|\nabla \cdot \mathbf{z_t}\|^2 + C\int_0^T \|u_{tt}\|^2 + C\int_0^T \|u_t\|^2 + \|\nabla \cdot \mathbf{z}\|^2(0)$$

Apply the Gronwall Inequality, theorem 4.8, to get:

$$\sup_{0\leq t\leq T} \|\nabla \cdot \mathbf{z}\|^2 \leq C\int_0^T \|f_t\|^2 + C\int_0^T \|f\|^2 + C\int_0^T \|\nabla \cdot \mathbf{z_t}\|^2 \\ +C\int_0^T \|u_{tt}\|^2 + C\int_0^T \|u_t\|^2 + \|\nabla \cdot \mathbf{z_n}\|^2(0)$$

If $f, f_t \in L^2(0,T;L^2(\Omega))$ and because of the bounds (4.61), (4.34), and (4.60) we have

$$\{\nabla \cdot \mathbf{z_n}\}_{n=1}^{\infty} \text{ is bounded in } L^\infty(0,T;L^2(\Omega)) \tag{4.62}$$

Establishment of a bound for $\|\mathbf{u_{ttt}}\|_{L^2(0,T;L^2(\Omega))}$ and $\|\mathbf{z_{tt}}\|_{L^\infty(0,T;L^2(\Omega))}$

Take two derivatives, with respect to t, of (4.49). Take three derivatives, with respect to t, of(4.50) and set $w = u_{ttt}, v = \mathbf{z_{tt}}$ to get

$$(u_{m_{ttt}}, u_{m_{ttt}}) + (\nabla \cdot \mathbf{z_{n_{tt}}}, u_{m_{ttt}}) = (f_{tt}, u_{m_{ttt}}) \tag{4.63}$$

$$(\mathbf{z_{ttt}}, \mathbf{z_{tt}}) - (u_{ttt}, \nabla \cdot \mathbf{z_{tt}}) = 0. \tag{4.64}$$

Substitute (4.64) into (4.63),

$$\|u_{ttt}\|^2 + \frac{1}{2}\frac{d}{dt}\|\mathbf{z_{tt}}\|^2 = (f_{tt}, u_{ttt}) \leq \frac{1}{2}\|f_{tt}\|^2 + \frac{1}{2}\|u_{ttt}\|^2. \tag{4.65}$$

Move $\frac{1}{2}\|u_{ttt}\|^2$ to the left hand side, multiply by 2 and integrate from 0 to T,

$$\int_0^t \|u_{ttt}\|^2 + \|\mathbf{z_{tt}}\|^2 \leq \int_0^t \|f_{tt}\|^2 + \|\mathbf{z_{tt}}\|^2(0). \tag{4.66}$$

Thus, if $\mathbf{z_{tt}}(0) \in L^2(\Omega)$ (which is true if $g'' \in H^1(\Omega)$) and $f_{tt} \in L^2(0,T;L^2(\Omega))$ then

$$\begin{aligned} &\mathbf{z_{tt}} \in L^\infty(0,T;L^2(\Omega)) \\ &u_{ttt} \in L^2(0,T;L^2(\Omega)). \end{aligned} \tag{4.67}$$

Establishment of a bound on $\|\nabla \cdot \mathbf{z_{n_{tt}}}\|_{L^2(0,T;L^2(\Omega))}$

Take two derivatives of (4.38) with respect to t to get,

$$(u_{ttt}, w) + (\nabla \cdot \mathbf{z_{tt}}, w) = (f_{tt}, w)$$

Set $w = \nabla \cdot \mathbf{z_{tt}}$

$$(u_{ttt}, \nabla \cdot \mathbf{z_{tt}}) + (\nabla \cdot \mathbf{z_{tt}}, \nabla \cdot \mathbf{z_{tt}}) = (f_{tt}, \nabla \cdot \mathbf{z_{tt}})$$

then

$$\|\nabla \cdot \mathbf{z_{tt}}\|^2 \leq \|f_{tt}\|\|\nabla \cdot \mathbf{z_{tt}}\| + \|u_{ttt}\|\|\nabla \cdot \mathbf{z_{tt}}\|$$

and

$$\|\nabla \cdot \mathbf{z_{tt}}\| \leq \|f_{tt}\| + \|u_{ttt}\|$$

Finally

$$\int_0^T \|\nabla \cdot \mathbf{z_{tt}}\|^2 \leq 2\int_0^T \|f_{tt}\|^2 + 2\int_0^T \|u_{ttt}\|^2$$

We know from (4.67) that the last term on the right hand side is bounded. So if we have that $f_{tt} \in L^2(0,T;L^2(\Omega))$

$$\nabla \cdot \mathbf{z_{tt}} \in L^2(0,T;L^2(\Omega)) \tag{4.68}$$

Establishment of a bound on $\|\nabla \cdot \mathbf{z_t}\|_{L^\infty(0,T;L^2(\Omega))}$

Take derivative of (4.49) with respect to t to get,

$$(u_{tt}, w) + (\nabla \cdot \mathbf{z_t}, w) = (f_t, w)$$

Set $w = \nabla \cdot \mathbf{z_{tt}}$

$$(u_{tt}, \nabla \cdot \mathbf{z_{tt}}) + (\nabla \cdot \mathbf{z_t}, \nabla \cdot \mathbf{z_{tt}}) = (f_t, \nabla \cdot \mathbf{z_{tt}})$$

then

$$\frac{1}{2}\frac{d}{dt}\|\nabla \cdot \mathbf{z_t}\|^2 \leq \|f_t\|\|\nabla \cdot \mathbf{z_{tt}}\| + \|u_{tt}\|\|\nabla \cdot \mathbf{z_{tt}}\|$$

and

$$\frac{1}{2}\frac{d}{dt}\|\nabla \cdot \mathbf{z_t}\|^2 \leq C\|f_t\|^2 + C\|\nabla \cdot \mathbf{z_{tt}}\|^2 + C\|u_{tt}\|^2$$

and

$$\|\nabla \cdot \mathbf{z_{n_t}}\|^2 \leq C\int_0^t \|f_t\|^2 + C\int_0^t \|\nabla \cdot \mathbf{z_{n_{tt}}}\|^2 + C\int_0^T \|u_{tt}\|^2 + \|\nabla \cdot \mathbf{z_t}\|^2(0)$$

We know from (4.67) and (4.68) that the right hand side is bounded. So if we have that $f_t \in L^2(0,T;L^2(\Omega))$

$$\nabla \cdot \mathbf{z}_{\mathbf{n_t}} \in L^\infty(0,T;L^2(\Omega)) \tag{4.69}$$

4.3.4 Regularity of Linear Weak Mixed System

Based on all of the foregoing bounds and convergence, we can state the following theorems:

Theorem 4.10 (**Theorem A**). *Suppose* $g \in H^1(\Omega)$ *and* $f \in L^2(0,T;L^2(\Omega))$ *then*

$$\begin{aligned}
&(u_t, w) + (\nabla \cdot \mathbf{z}, w) = (f, w) \qquad \forall w \in L^2(\Omega) \\
&(\mathbf{z}, v) - (u, \nabla \cdot v) = 0 \qquad\quad \forall v \in V^0(\Omega). \\
&u(0) = g \\
&\nabla u \cdot \mathbf{n} = 0 \quad \textit{on } \Gamma
\end{aligned}$$

has a weak solution with $\mathbf{z} \in L^\infty(0,T;L^2(\Omega))$, $\nabla \cdot \mathbf{z} \in L^2(0,T;L^2(\Omega))$, $u \in L^\infty(0,T;L^2(\Omega))$, $u_t \in L^2(0,T;L^2(\Omega))$.

Theorem 4.11 (**Theorem B**). *Suppose* $g \in H^3(\Omega)$ *and* $f_t \in L^2(0,T;L^2(\Omega))$ *then*

$$\begin{aligned}
&(u_t, w) + (\nabla \cdot \mathbf{z}, w) = (f, w) \qquad \forall w \in L^2(\Omega) \\
&(\mathbf{z}, v) - (u, \nabla \cdot v) = 0 \qquad\quad \forall v \in V^0(\Omega). \\
&u(0) = g \\
&\nabla u \cdot \mathbf{n} = 0 \quad \textit{on } \Gamma
\end{aligned}$$

has a weak solution with $\mathbf{z_t} \in L^\infty(0,T;L^2(\Omega))$, $u_t \in L^\infty(0,T;L^2(\Omega))$, $u_{tt} \in L^2(0,T;L^2(\Omega))$, $\nabla \cdot \mathbf{z} \in L^\infty(0,T;L^2(\Omega))$,$\nabla \cdot \mathbf{z_t} \in L^2(0,T;L^2(\Omega))$.

Theorems 4.10 and 4.11 afford a certain amount of regularity to the solution of the equations in Part I, later in the thesis more regularity of the solution will be required. The proof of the following theorem follows from the classical elliptic regularity theory [47].

Theorem 4.12 (**Theorem C**). .

I. *Suppose for $m \geq 0$, we have*

$$g \in H^{m+1}(\Omega) \text{ and } f \in L^2(0,T;H^m(\Omega)) \quad \text{then}$$

$$(u_t, w) + (\nabla \cdot \mathbf{z}, w) = (f, w) \qquad \forall w \in L^2(\Omega) \tag{4.70}$$

$$(\mathbf{z}, v) - (u, \nabla \cdot v) = 0 \qquad \forall v \in V^0(\Omega) \tag{4.71}$$

$$u(0) = g \tag{4.72}$$

$$\nabla u \cdot \mathbf{n} = 0 \quad \text{on } \Gamma \tag{4.73}$$

has a weak solution with

$$u \in L^2(0,T;H^{m+2}(\Omega)) \qquad z \in L^2(0,T;H^{m+1}(\Omega)).$$

$$u \in L^\infty(0,T;H^{m+1}(\Omega)) \qquad z \in L^\infty(0,T;H^m(\Omega)).$$

II. *Suppose for $k = 1, 2, 3, \ldots$ and $m \geq 2(k-1)$, we have*

$$g \in H^{m+1}(\Omega) \quad \text{and} \quad \frac{d^L f}{dt^L} \in L^2(0,T;H^{m-2L}(\Omega)) \quad \text{for} \quad L = 0, 1, \ldots, k-1$$

then the system (4.70),(4.71),(4.72),(4.73) has a weak solution with

$$\frac{d^k u}{dt^k} \in L^2(0,T;H^{m-2(k-1)}(\Omega)) \qquad \frac{d^k z}{dt^k} \in L^2(0,T;H^{m-1-2(k-1)}(\Omega)).$$

$$\frac{d^k u}{dt^k} \in L^\infty(0,T;H^{m-1-2(k-1)}(\Omega)) \qquad \frac{d^k u}{dt^k} \in L^\infty(0,T;H^{m-2-2(k-1)}(\Omega)).$$

4.4 THE NONLINEAR WEAK MIXED SYSTEM

In this section, we will establish the fact that the representative system of equations in **mixed form** has a weak solution. No published analysis exists for this particular system of equations in the weak mixed form. Analysis has been done in the weak form (but not the weak mixed form) by A. Boy [20] on the following system:

$$\frac{\partial u_1}{\partial t} - \nabla \cdot (D_1 \nabla u_1 - u_1 \nabla u_2) \;=\; 0 \tag{4.74}$$

$$\frac{\partial u_2}{\partial t} - \nabla \cdot (D_2 \nabla u_2) \;=\; C_1 u_1 + C_2 u_2 \qquad (x,t) \in \Omega \times (0,T] \tag{4.75}$$

$$\nabla u_1 \cdot \mathbf{n} = 0 \qquad \text{and} \qquad \nabla u_2 \cdot \mathbf{n} = 0 \qquad \text{on } \Gamma. \tag{4.76}$$

As can be seen, the system in the Boy paper has the nonlinearity in the advection term but lacks the nonlinear functions f_1 and f_2 that appear in our system (see (4.77),(4.78) below). For that reason, the analysis of our system will be more difficult. Furthermore, the fact that our analysis will done in the weak mixed form, makes the work here somewhat different than the work in the Boy paper.

4.4.1 Development and Proof of nonlinear Theorems

As noted previously, we will consider the representative system:

$$\frac{\partial u_1}{\partial t} - \nabla \cdot (D_1 \nabla u_1 - u_1 \nabla u_2) \;=\; f_1(u_1, u_2) \tag{4.77}$$

$$\frac{\partial u_2}{\partial t} - \nabla \cdot (D_2 \nabla u_2) \;=\; f_2(u_1, u_2) \qquad (x,t) \in \Omega \times (0,T] \tag{4.78}$$

$$\nabla u_1 \cdot \mathbf{n} = 0 \qquad \text{and} \qquad \nabla u_2 \cdot \mathbf{n} = 0 \qquad \text{on } \Gamma \tag{4.79}$$

$$u_1(x,0) = u_1^0(x), \quad u_2(x,0) = u_2^0(x), \quad x \in \Omega.$$

We assume that D is sufficiently smooth, so that the theory from the last section applies.

Let,

$$\mathbf{z}_1 = -D_1 \nabla u_1 \quad \text{and} \quad \mathbf{z}_2 = -D_2 \nabla u_2 \tag{4.80}$$

$$\text{So, } D_1^{-1}\mathbf{z}_1 = -\nabla u_1 \quad \text{and} \quad D_2^{-1}\mathbf{z}_2 = -\nabla u_2. \tag{4.81}$$

Multiplication by test functions and integration in Ω gives,

$$(u_{1_t}, w) - (\nabla \cdot (D_2^{-1}\mathbf{z}_2 u_1), w) + (\nabla \cdot \mathbf{z}_1, w) = (f_1, w) \qquad \forall w \in W \tag{4.82}$$

$$(u_{2_t}, w) + (\nabla \cdot \mathbf{z}_2, w) = (f_2, w) \qquad \forall w \in W \tag{4.83}$$

$$(D_1^{-1}\mathbf{z}_1, v) = -(\nabla u_1, v) \Rightarrow (D_1^{-1}\mathbf{z}_1, v) = (u_1, \nabla \cdot v) - \langle u_1, v \cdot \mathbf{n} \rangle_\Gamma \qquad \forall v \in V^0 \tag{4.84}$$

$$(D_2^{-1}\mathbf{z}_2, v) = -(\nabla u_2, v) \Rightarrow (D_2^{-1}\mathbf{z}_2, v) = (u_2, \nabla \cdot v) - \langle u_2, v \cdot \mathbf{n} \rangle_\Gamma \qquad \forall v \in V^0 \tag{4.85}$$

where

$$W = L^2(\Omega) \quad V = H(\mathrm{div}; \Omega)) \quad V^0 = V \cap \{v : v \cdot \mathbf{n} = 0 \text{ on } \Gamma\}.$$

The last term in each of (4.84) and (4.85) is zero by the definition of V^0. Then the **weak mixed formulation** of (4.77), (4.78), and (4.79) may be stated as :

Find $u_1, u_2 \in W$ and $\mathbf{z}_1, \mathbf{z}_2 \in V^0$ such that

$$(u_{1_t}, w) - (\nabla \cdot (D_2^{-1}\mathbf{z}_2 u_1), w) + (\nabla \cdot \mathbf{z}_1, w) = (f_1, w) \qquad \forall w \in W \tag{4.86}$$

$$(u_{2_t}, w) + (\nabla \cdot \mathbf{z}_2, w) = (f_2, w) \qquad \forall w \in W \tag{4.87}$$

$$(D_1^{-1}\mathbf{z}_1, v) = (u_1, \nabla \cdot v) \qquad \forall v \in V^0 \tag{4.88}$$

$$(D_2^{-1}\mathbf{z}_2, v) = (u_2, \nabla \cdot v) \qquad \forall v \in V^0 \tag{4.89}$$

We will first prove that solution to this system (4.86), (4.87), (4.88),(4.89) exists under certain regularity assumptions on f_1, f_2. Then we will prove that these regularity assumptions hold for each of the equations in Part I of the NEC PDE system.

Assumption 1. For all $\xi_1 \in L^2(0, T; H^2(\Omega))$ and $\xi_2 \in L^2(0, T; H^3(\Omega))$ we have $f_2(\xi_1, \xi_2) \in L^2(0, T; H^2(\Omega))$.

Assumption 2. For all $\xi_1 \in L^2(0, T; H^2(\Omega))$ and $\xi_2 \in L^2(0, T; H^3(\Omega))$ we have $f_1(\xi_1, \xi_2) \in L^2(0, T; H^1(\Omega))$ and $f_2(\xi_1, \xi_2) \in L^2(0, T; H^2(\Omega))$.

Theorem 4.13 (**Existence and Regularity for second set of equations**). *For any* $\mathbf{u}_1 \in L^2(0,T;H^2(\Omega))$, *under* ***Assumption 1***, *the system*

$$(u_{2_t}, w) + (\nabla \cdot \mathbf{z}_2, w) = (f_2(u_1, u_2), w) \qquad \forall w \in W \tag{4.90}$$

$$(D_2^{-1}\mathbf{z}_2, v) = (u_2, \nabla \cdot v) \qquad \forall v \in V^0 \tag{4.91}$$

$$u_2(x,0) = u_2^0(x) \quad x \in \Omega.$$

such that f_2 *is Lipschitz continuous has a solution* $(u_2, \mathbf{z}_2)$ *such that*

$$u_2 \in L^2(0,T;H^4(\Omega)) \quad \mathbf{z}_2 \in L^2(0,T;H^3(\Omega)).$$

$$u_{2_t} \in L^2(0,T;H^2(\Omega)) \quad \mathbf{z}_{2_t} \in L^2(0,T;H^1(\Omega)).$$

$$\mathbf{z}_2 \in L^\infty(0,T;H^2(\Omega)) \quad \nabla \cdot \mathbf{z}_2 \in L^\infty(0,T;H^1(\Omega)).$$

Proof. Let $u_1 \in L^2(0,T;H^2(\Omega))$ be fixed. For any $u_2 \in L^2(0,T;H^3(\Omega))$ by **Assumption 1**, $f_2(u_1,u_2) \in L^2(0,T;H^2(\Omega))$. Then by the Theorem 4.12 developed in the previous section, the linearized form of (4.90) and (4.91),

$$(\phi_{2_t}, w) + (\nabla \cdot \psi_2, w) = (f_2(u_1, u_2), w) \tag{4.92}$$

$$(D_2^{-1}\psi_2, v) = (\phi_2, \nabla \cdot v) \tag{4.93}$$

has a solution $\phi_2 \in L^2(0,T;H^4(\Omega)) \quad \psi_2 \in L^2(0,T;H^3(\Omega))$.
$d\phi_2/dt \in L^2(0,T;H^2(\Omega)) \quad d\psi_2/dt \in L^2(0,T;H^1(\Omega))$
(Note that since $u_2 \in L^2(0,T;H^3(\Omega))$ then $z_2 \in L^2(0,T;H^2(\Omega))$.)
So, the above defines a mapping M such that:

$$M : (u_2, \mathbf{z_2}) \to (\phi_2, \psi_2)$$

$$M : (L^2(0,T;H^3(\Omega)), L^2(0,T;H^2(\Omega))) \to (L^2(0,T;H^4(\Omega)), L^2(0,T;H^3(\Omega))).$$

Now, since H^4 is compactly imbedded in H^3 and H^3 is continuously imbedded in H^2 then by the Aubin-Lions Compactness Criteria, **Theorem 4.9**.

$$\{u_2 \in L^2(0,T;H^4(\Omega) : u_{2_t} \in L^2(0,T;H^2(\Omega)\}$$

$$\text{is compactly imbedded into } L^2(0,T;H^3(\Omega)).$$

Now, since H^3 is compactly imbedded in H^2 and H^2 is continuously imbedded in H^1 then by the Aubin-Lions Compactness Criteria, **Theorem 4.9**.

$$\{\mathbf{z_2} \in L^2(0,T;H^3(\Omega) : \mathbf{z_{2_t}} \in L^2(0,T;H^1(\Omega)\}$$

$$\text{is compactly imbedded into } L^2(0,T;H^2(\Omega)).$$

Then by Schauder's Fixed Point Theorem **4.2**, the mapping, M has a fixed point. Thus, there exists a solution, $(u_2, \mathbf{z_2})$, to (4.92),(4.93) and

$$u_2 \in L^2(0,T;H^4(\Omega)) \quad \mathbf{z_2} \in L^2(0,T;H^3(\Omega)). \tag{4.94}$$

Now that a solution has been established, we may claim the additional regularity from Theorem 4.12:

$$\mathbf{z}_2 \in L^\infty(0,T;H^2(\Omega)) \quad \nabla \cdot \mathbf{z}_2 \in L^\infty(0,T;H^1(\Omega)).\mathbf{Q.E.D.}$$

Strategy for proving that the system (4.86), (4.87),(4.88), and (4.89) has a solution. Before stating the next theorem, which gives the existence of the solution of (4.1), (4.2), it will be helpful to first show in diagram form the main idea of the theorem:

Choose $(u_1, u_2$ $\mathbf{z_1}, \mathbf{z_2})$	$\rightarrow$	Theorem 4.13 gives solution $\widetilde{u_2}, \widetilde{\mathbf{z_2}}$ to second equation.	$\rightarrow$	Use the $\widetilde{u_2}, \widetilde{\mathbf{z_2}}$ just found and $u_1, \mathbf{z_1}$ to find a solution ϕ_1, ψ_1 to first equation.

$\rightarrow$ The result is a solution $(\phi_1, \psi_1, \widetilde{u_2}, \widetilde{\mathbf{z_2}})$ to the **linearized** system.

The above defines a mapping:

$$T : (u_1, u_2, \mathbf{z_1}, \mathbf{z_2}) \longrightarrow (\phi_1, \psi_1 \widetilde{u_2}, \widetilde{\mathbf{z_2}}). \tag{4.95}$$

It will, then be proved that this mapping has a fixed point.

Theorem 4.14 (Existence and Regularity for the coupled equations). *Consider the system of equations,*

$$(u_{1_t}, w) - (\nabla \cdot (D_2^{-1}\mathbf{z}_2 u_1), w) + (\nabla \cdot \mathbf{z}_1, w) = (f_1(u_1, u_2), w) \ \forall w \in W \tag{4.96}$$

$$(u_{2_t}, w) + (\nabla \cdot \mathbf{z}_2, w) = (f_2(u_1, u_2), w) \qquad \forall w \in W \tag{4.97}$$

$$(D_1^{-1}\mathbf{z}_1, v) = (u_1, \nabla \cdot v) \qquad \forall v \in V^0 \tag{4.98}$$

$$(D_2^{-1}\mathbf{z}_2, v) = (u_2, \nabla \cdot v) \qquad \forall v \in V^0 \tag{4.99}$$

$$u_1(x, 0) = u_1^0(x), u_2(x, 0) = u_2^0(x), \quad x \in \Omega.$$

under ***Assumption 2****, and if f_1 and f_2 are Lipschitz continuous then the system (4.96),(4.97),(4.98), and (4.99) has a solution $(u_1, u_2, \mathbf{z}_1, \mathbf{z}_2)$ such that*

$$u_1 \in L^2(0, T; H^3(\Omega)), \ u_2 \in L^2(0, T; H^4(\Omega)),$$

$$\mathbf{z}_1 \in L^2(0, T; H^2(\Omega)), \ \mathbf{z}_2 \in L^2(0, T; H^3(\Omega)).$$

Proof. Re-write (4.96),(4.97),(4.98), and (4.99) as

$$(u_{1_t}, w) + (\nabla \cdot \mathbf{z}_1, w) = (f_1(u_1, u_2), w) + (\nabla \cdot (D_2^{-1}\mathbf{z}_2 u_1), w) \ \forall w \in W \tag{4.100}$$

$$(u_{2_t}, w) + (\nabla \cdot \mathbf{z}_2, w) = (f_2(u_1, u_2), w) \qquad \forall w \in W \tag{4.101}$$

$$(D_1^{-1}\mathbf{z}_1, v) = (u_1, \nabla \cdot v) \qquad \forall v \in V^0 \tag{4.102}$$

$$(D_2^{-1}\mathbf{z}_2, v) = (u_2, \nabla \cdot v) \qquad \forall v \in V^0 \tag{4.103}$$

Linearize by

$$(\phi_{1_t}, w) + (\nabla \cdot \psi_1, w) = (f_1(u_1, u_2), w) + (\nabla \cdot (D_2^{-1}\mathbf{z}_2 u_1), w) \tag{4.104}$$

$$(\phi_{2_t}, w) + (\nabla \cdot \psi_2, w) = (f_2(u_1, u_2), w) \qquad \forall w \in W \tag{4.105}$$

$$(D_1^{-1}\psi_1, v) = (\phi_1, \nabla \cdot v) \tag{4.106}$$

$$(D_2^{-1}\psi_2, v) = (\phi_2, \nabla \cdot v) \qquad \forall v \in V^0 \tag{4.107}$$

and choose

$$u_1 \in L^2(0,T;H^2(\Omega)),\ u_2 \in L^2(0,T;H^3(\Omega)),$$

$$\mathbf{z}_1 \in L^2(0,T;H^1(\Omega)), \mathbf{z}_2 \in L^2(0,T;H^2(\Omega)).$$

Then by Theorem 4.13,(4.105) and (4.107) has a solution

$$u_2 \in L^2(0,T;H^4(\Omega)) \quad \mathbf{z}_2 \in L^\infty(0,T;H^3(\Omega)) \quad \nabla\cdot\mathbf{z_2} \in L^\infty(0,T;H^2(\Omega))$$

$$u_{2_t} \in L^2(0,T;H^2(\Omega)) \quad \mathbf{z}_{2_t} \in L^2(0,T;H^1(\Omega)).$$

Define $f_1^* := f_1(u_1,u_2) + \nabla\cdot(D_2^{-1}\mathbf{z}_2u_1)$ and note that

$$\begin{aligned}
\|f_1^*\|^2_{L^2(0,T;H^1(\Omega))} &= \int_0^T \|f_1(u_1,u_2) + \nabla\cdot(D_2^{-1}\mathbf{z}_2u_1)\|^2_{H^1(\Omega)} \\
&\le \int_0^T \Big(\|f_1(u_1,u_2)\|_{H^1(\Omega)} + \|(\nabla\cdot D_2^{-1}\mathbf{z}_2)u_1\|_{H^1(\Omega)} + \|D_2^{-1}\mathbf{z}_2\nabla u_1\|_{H^1(\Omega)}\Big)^2 \\
&\le C\int_0^T \Big(\|f_1(u_1,u_2)\|^2_{H^1(\Omega)} + \|(\nabla\cdot D_2^{-1}\mathbf{z}_2)\nabla u_1\|^2_{L^2(\Omega)} + \|(\triangle D_2^{-1}\mathbf{z}_2)u_1\|^2_{L^2(\Omega)} \\
&\qquad + \|D_2^{-1}\mathbf{z}_2\triangle u_1\|^2_{L^2(\Omega)} + \|(\nabla\cdot D_2^{-1}\mathbf{z}_2)u_1\|^2_{L^2(\Omega)} + \|D_2^{-1}\mathbf{z}_2\nabla u_1\|^2_{L^2(\Omega)}\Big) \\
&\le C\int_0^T \|f_1\|^2_{H^1(\Omega)} + C\int_0^T\int_\Omega |\nabla\cdot D_2^{-1}\mathbf{z}_2|^2|\nabla u_1|^2 + C\int_0^T\int_\Omega |\triangle D_2^{-1}\mathbf{z}_2|^2|u_1|^2 \\
&\qquad + C\int_0^T\int_\Omega |D_2^{-1}\mathbf{z}_2|^2|\triangle u_1|^2 + C\int_0^T\int_\Omega |\nabla\cdot D_2^{-1}\mathbf{z}_2|^2|u_1|^2 \\
&\qquad + C\int_0^T\int_\Omega |D_2^{-1}\mathbf{z}_2|^2|\nabla u_1|^2 \\
&\le C\int_0^T \|f_1\|^2_{H^1(\Omega)} + C\int_0^T \|\nabla\cdot D_2^{-1}\mathbf{z}_2\|^2_{L^\infty(\Omega)}\int_\Omega |\nabla u_1|^2 \\
&\qquad + C\int_0^T \|u_1\|^2_{L^\infty(\Omega)}\int_\Omega |\triangle D_2^{-1}\mathbf{z}_2|^2 \\
&\qquad + C\int_0^T \|D_2^{-1}\mathbf{z}_2\|^2_{L^\infty(\Omega)}\int_\Omega |\triangle u_1|^2 \\
&\qquad + C\int_0^T \|\nabla\cdot D_2^{-1}\mathbf{z}_2\|^2_{L^\infty(\Omega)}\int_\Omega |u_1|^2 \\
&\qquad + C\int_0^T \|D_2^{-1}\mathbf{z}_2\|^2_{L^\infty(\Omega)}\int_\Omega |\nabla u_1|^2 \\
&\le C\int_0^T \|f_1\|^2_{H^1(\Omega)} + C\int_0^T \|\nabla\cdot D_2^{-1}\mathbf{z}_2\|^2_{L^\infty(\Omega)}\|\nabla u_1\|^2_{L^2(\Omega)} \\
&\quad + C\int_0^T \|u_1\|^2_{L^\infty(\Omega)}\|\mathbf{z}_2\|^2_{H^2(\Omega)} + C\int_0^T \|D_2^{-1}\mathbf{z}_2\|^2_{L^\infty(\Omega)}\|\triangle u_1\|^2_{L^2(\Omega)}
\end{aligned}$$

$$+C\int_0^T \|\nabla\cdot D_2^{-1}\mathbf{z}_2\|^2_{L^\infty(\Omega)}\|u_1\|^2_{L^2(\Omega)} + C\int_0^T \|D_2^{-1}\mathbf{z}_2\|^2_{L^\infty(\Omega)}\|\nabla u_1\|^2_{L^2(\Omega)}.$$

Since $\mathbf{z}_2$, $\nabla\cdot\mathbf{z}_2$, and $\Delta\mathbf{z}_2$ are in L^∞ in time, we can say

$$\begin{aligned}\|f_1^*\|^2_{L^2(0,T;H^1(\Omega))} \leq\ & C\int_0^T \|f_1\|^2_{H^1(\Omega)} + C\|\nabla\cdot D_2^{-1}\mathbf{z}_2\|^2_{L^\infty(0,T;L^\infty(\Omega))}\int_0^T \|\nabla u_1\|^2_{L^2(\Omega)}\\ &+C\|\mathbf{z}_2\|^2_{L^\infty(0,T;H^2(\Omega))}\int_0^T \|u_1\|^2_{L^\infty(\Omega)} + C\|D_2^{-1}\mathbf{z}_2\|^2_{L^\infty(0,T;L^\infty(\Omega))}\int_0^T \|\triangle u_1\|^2_{L^2(\Omega)}\\ &+C\|\nabla\cdot D_2^{-1}\mathbf{z}_2\|^2_{L^\infty(0,T;L^\infty(\Omega))}\int_0^T \|\nabla u_1\|^2_{L^2(\Omega)} + C\|D_2^{-1}\mathbf{z}_2\|^2_{L^\infty(0,T;L^\infty(\Omega))}\int_0^T \|\nabla u_1\|^2_{L^2(\Omega)}.\end{aligned}$$

All of the terms on the right hand side of the inequality are bounded (for example, by **Assumption 2**, $\int_0^T \|f_1(u_1,u_2)\|^2_{H^1(\Omega)}$ is bounded). Therefore,

$$f_1^* \in L^2(0,T;H^1(\Omega)) \text{ and by } \textbf{Assumption 2} \text{ we have } f_2 \in L^2(0,T;H^2(\Omega)).$$

Then by the Theorem 4.12 from the previous section, the linearized system (4.104),(4.105),(4.106), and (4.107) has a solution

$$\phi_1 \in Q = L^2(0,T;H^3(\Omega)) \tag{4.108}$$

$$\phi_2 \in Q = L^2(0,T;H^4(\Omega)) \tag{4.109}$$

$$\psi_1 \in Q = L^2(0,T;H^2(\Omega)) \tag{4.110}$$

$$\psi_2 \in Q = L^2(0,T;H^3(\Omega)). \tag{4.111}$$

We will the use these spaces to define the space Q,

$$Q := L^2(0,T;H^3(\Omega)) \times L^2(0,T;H^4(\Omega)) \times L^2(0,T;H^2(\Omega)) \times L^2(0,T;H^3(\Omega)).$$

Recall that we chose,

$$u_1 \in L^2(0,T;H^2(\Omega)),\ u_2 \in L^2(0,T;H^3(\Omega)),$$

$$\mathbf{z}_1 \in L^2(0,T;H^1(\Omega)),\ \mathbf{z}_2 \in L^2(0,T;H^2(\Omega)).$$

We will the use these spaces to define the space QW,

$$QW := L^2(0,T;H^2(\Omega)) \times L^2(0,T;H^3(\Omega)) \times L^2(0,T;H^1(\Omega)) \times L^2(0,T;H^2(\Omega))$$

The above defines a mapping T such that:

$$T : (u_1, u_2, \mathbf{z_1}, \mathbf{z_2}) \to (\phi_1, \phi_2, \psi_1, \psi_2)$$

$$T : QW \to Q.$$

Since H^4 is compactly imbedded in H^3 and H^3 is continuously imbedded in H^2
and
Since H^3 is compactly imbedded in H^2 and H^2 is continuously imbedded in H^1, then by the Aubin-Lions Compactness Criteria, **Theorem 4.9**. Q is compactly imbedded into QW.
Thus, T is a continuous mapping T such that:

$$T : Q \to Q.$$

Then by Schauder's Fixed Point Theorem **4.2**, the mapping, T has a fixed point. Thus, there exists a solution, $(u_1, u_2, \mathbf{z_1}, \mathbf{z_2})$, to this system the system (4.100),(4.101),(4.102), and (4.103) with regularity given by (4.108),(4.109),(4.110), and (4.111). Based on this regularity, we have, in particular that,

$$u_1 \in L^2(0, T; H^3(\Omega)),\ u_2 \in L^2(0, T; H^4(\Omega)),$$

$$\mathbf{z}_1 \in L^2(0, T; H^2(\Omega)),\ \mathbf{z}_2 \in L^2(0, T; H^3(\Omega)).$$

Now that a solution has been established, we may claim the additional regularity from Theorem 4.12:

$$\mathbf{z}_1 \in L^\infty(0, T; H^2(\Omega)) \quad \nabla \cdot \mathbf{z}_1 \in L^\infty(0, T; H^1(\Omega)),$$

$$\mathbf{z}_2 \in L^\infty(0, T; H^3(\Omega)) \quad \nabla \cdot \mathbf{z}_2 \in L^\infty(0, T; H^2(\Omega)).$$

4.4.2 Uniqueness Mixed Weak Solution

Now that it has been shown that a solution exists to the Part I equations, it is necessary to prove the uniqueness of that solution:

$$(u_{1_t}, w) - (\nabla \cdot (D_2^{-1}\mathbf{z}_2 u_1), w) + (\nabla \cdot \mathbf{z}_1, w) = (f_1(u_1, u_2), w) \tag{4.112}$$

$$(u_{2_t}, w) + (\nabla \cdot \mathbf{z}_2, w) = (f_2(u_1, u_2), w) \qquad \forall w \in W \tag{4.113}$$

$$(D_1^{-1}\mathbf{z}_1, v) = (u_1, \nabla \cdot v) \tag{4.114}$$

$$(D_2^{-1}\mathbf{z}_2, v) = (u_2, \nabla \cdot v) \qquad \forall v \in V^0 \tag{4.115}$$

Suppose $(u_1, \mathbf{z_1}, u_2, \mathbf{z_2})$ is one solution and $(u_1^*, \mathbf{z_1^*}, u_2^*, \mathbf{z_2^*})$ is another solution.
Take the difference between the two solutions:

$$\begin{aligned}((u_1 - u_1^*)_t, w) + (\nabla \cdot (\mathbf{z}_1 - \mathbf{z}_1^*), w) \\ = (f_1(u_1, u_2) - f_1(u_1^*, u_2^*), w) \\ +(\nabla \cdot (D_2^{-1}(\mathbf{z}_2 u_1 - \mathbf{z}_2^* u_1^*), w)\end{aligned} \tag{4.116}$$

$$\begin{aligned}((u_2 - u_2^*)_t, w) + (\nabla \cdot (\mathbf{z}_2 - \mathbf{z}_2^*), w) \\ = (f_2(u_1, u_2) - f_2(u_1^*, u_2^*), w)\end{aligned} \tag{4.117}$$

$$(D_1^{-1}(\mathbf{z}_1 - \mathbf{z}_1^*), v) - (u_1 - u_1^*, \nabla \cdot v) = 0 \tag{4.118}$$

$$(D_2^{-1}(\mathbf{z}_2 - \mathbf{z}_2^*), v) - (u_2 - u_2^*, \nabla \cdot v) = 0 \tag{4.119}$$

First Bound

Consider (4.117) and (4.119). Take the derivative with respect to t of (4.119)

$$\begin{aligned}((u_2 - u_2^*)_t, w) + (\nabla \cdot (\mathbf{z}_2 - \mathbf{z}_2^*), w) \\ = (f_2(u_1, u_2) - f_2(u_1^*, u_2^*), w)\end{aligned} \tag{4.120}$$

$$(D_2^{-1}(\mathbf{z}_2 - \mathbf{z}_2^*)_t, v) - ((u_2 - u_2^*)_t, \nabla \cdot v) = 0 \tag{4.121}$$

Set $w = \mathbf{z_2} - \mathbf{z_2^*}$ and $v = (u_2 - u_2^*)_t$

$$((u_2 - u_2^*)_t, (u_2 - u_2^*)_t) + (\nabla \cdot (\mathbf{z}_2 - \mathbf{z}_2^*), (u_2 - u_2^*)_t)$$

$$= (f_2(u_1, u_2) - f_2(u_1^*, u_2^*), (u_2 - u_2^*)_t) \tag{4.122}$$

$$(D_2^{-1}(\mathbf{z}_2 - \mathbf{z}_2^*)_t, \mathbf{z}_2 - \mathbf{z}_2^*) - ((u_2 - u_2^*)_t, \nabla \cdot (\mathbf{z}_2 - \mathbf{z}_2^*)) = 0 \tag{4.123}$$

Substitute (4.123) into (4.122) and use the Cauchy-Schwarz inequality (theorem 4.7) and the fact that f_2 is Lipschitz,

$$\|(u_2 - u_2^*)_t\|^2 + \frac{1}{2}\frac{d}{dt}\|(D_2^{-1/2}(\mathbf{z}_2 - \mathbf{z}_2^*)\|^2 \\ \leq (C\|u_1 - u_1^*\| + C\|u_2 - u_2^*\|)\|(u_2 - u_2^*)_t\|. \tag{4.124}$$

Use Cauchy's inequality (theorem 4.6) and then hide $\|(u_2 - u_2^*)_t\|^2$ on the left hand side to get

$$\frac{1}{2}\|(u_2 - u_2^*)_t\|^2 + \frac{1}{2}\frac{d}{dt}\|(D_2^{-1/2}(\mathbf{z}_2 - \mathbf{z}_2^*)\|^2 \\ \leq C\|u_1 - u_1^*\|^2 + C\|u_2 - u_2^*\|^2. \tag{4.125}$$

Multiply by 2 and then integrate from 0 to t,

$$\int_0^t \|(u_2 - u_2^*)_t\|^2 + \|(D_2^{-1/2}(\mathbf{z}_2 - \mathbf{z}_2^*)\|^2(t) \\ \leq C\int_0^t \|u_1 - u_1^*\|^2 + C\int_0^t \|u_2 - u_2^*\|^2 + \|(D_2^{-1/2}(\mathbf{z}_2 - \mathbf{z}_2^*)\|^2(0). \tag{4.126}$$

Second Bound

Consider (4.117)

$$((u_2 - u_2^*)_t, w) + (\nabla \cdot (\mathbf{z}_2 - \mathbf{z}_2^*), w) \\ = (f_2(u_1, u_2) - f_2(u_1^*, u_2^*), w)$$

set $w = \nabla \cdot (\mathbf{z}_2 - \mathbf{z}_2^*)$

$$((u_2 - u_2^*)_t, \nabla \cdot (\mathbf{z}_2 - \mathbf{z}_2^*)) + (\nabla \cdot (\mathbf{z}_2 - \mathbf{z}_2^*), \nabla \cdot (\mathbf{z}_2 - \mathbf{z}_2^*)) \\ = (f_2(u_1, u_2) - f_2(u_1^*, u_2^*), \nabla \cdot (\mathbf{z}_2 - \mathbf{z}_2^*)).$$

Rearranging,and using the fact that f_2 is Lipschitz,

$$\|\nabla \cdot (\mathbf{z}_2 - \mathbf{z}_2^*)\|^2 \leq (\|(u_2 - u_2^*)_t\| + C\|u_1 - u_1^*\| + C\|u_2 - u_2^*\|)\|\nabla \cdot (\mathbf{z}_2 - \mathbf{z}_2^*)\|.$$

Dividing,

$$\|\nabla \cdot (\mathbf{z}_2 - \mathbf{z}_2^*)\| \leq \|(u_2 - u_2^*)_t\| + C\|u_1 - u_1^*\| + C\|u_2 - u_2^*\|.$$

Square, integrate from 0 to t, and use (4.126)

$$\int_0^t \|\nabla \cdot (\mathbf{z}_2 - \mathbf{z}_2^*)\|^2 \leq \|(D_2^{-1/2}(\mathbf{z}_2 - \mathbf{z}_2^*)\|^2(0) + C\int_0^t \|u_1 - u_1^*\|^2 + C\int_0^t \|u_2 - u_2^*\|^2. \tag{4.127}$$

This bound will be used shortly.

Now, consider again (4.116),(4.117),(4.118),(4.119) and set $w = u_1 - u_1^*$ and $v = \mathbf{z}_2 - \mathbf{z}_2^*$ to get,

$$\begin{aligned}
&((u_1 - u_1^*)_t, u_1 - u_1^*) + (\nabla \cdot (\mathbf{z}_1 - \mathbf{z}_1^*), u_1 - u_1^*) \\
&\quad = (f_1(u_1, u_2) - f_1(u_1^*, u_2^*), u_1 - u_1^*) \\
&\qquad + (\nabla \cdot (D_2^{-1}(\mathbf{z}_2 u_1 - \mathbf{z}_2^* u_1^*), u_1 - u_1^*) \qquad (4.128) \\
&((u_2 - u_2^*)_t, u_2 - u_2^*) + (\nabla \cdot (\mathbf{z}_2 - \mathbf{z}_2^*), u_2 - u_2^*) \\
&\qquad = (f_2(u_1, u_2) - f_2(u_1^*, u_2^*), u_2 - u_2^*) \qquad (4.129) \\
&(D_1^{-1}(\mathbf{z}_1 - \mathbf{z}_1^*), \mathbf{z}_1 - \mathbf{z}_1^*) = (u_1 - u_1^*, \nabla \cdot (\mathbf{z}_1 - \mathbf{z}_1^*)) \qquad (4.130) \\
&(D_2^{-1}(\mathbf{z}_2 - \mathbf{z}_2^*), \mathbf{z}_2 - \mathbf{z}_2^*) = (u_2 - u_2^*, \nabla \cdot (\mathbf{z}_2 - \mathbf{z}_2^*)) \qquad (4.131)
\end{aligned}$$

Substitute (4.130) into (4.128), use the Lipschitz continuity of f_1, and use the Cauchy-Schwarz inequality (theorem 4.7)

$$\begin{aligned}
&\frac{1}{2}\frac{d}{dt}\|u_1 - u_1^*\|^2 + \|D_1^{-1/2}(\mathbf{z}_1 - \mathbf{z}_1^*)\|^2 = (f_1(u_1, u_2) - f_1(u_1, u_2^*), u_1 - u_1^*) \\
&\qquad + (f_1(u_1, u_2^*) - f_1(u_1^*, u_2^*), u_1 - u_1^*) \\
&\qquad + (\nabla \cdot (D_2^{-1}(\mathbf{z}_2 u_1 - \mathbf{z}_2 u_1^* + \mathbf{z}_2 u_1^* - \mathbf{z}_2^* u_1^*), u_1 - u_1^*) \\
&\leq (C|u_2 - u_2^*|, |u_1 - u_1^*|) + (C|u_1 - u_1^*|, |u_1 - u_1^*|) \\
&\quad + \int_\Omega (\nabla \cdot D_2^{-1}\mathbf{z}_2)(u_1 - u_1^*)^2 + \int_\Omega (D_2^{-1}\mathbf{z}_2(\nabla \cdot (u_1 - u_1^*))(u_1 - u_1^*) \\
&\quad + \int_\Omega \nabla \cdot D_2^{-1}(\mathbf{z}_2 - \mathbf{z}_2^*)u_1^*(u_1 - u_1^*) + \int_\Omega D_2^{-1}(\mathbf{z}_2 - \mathbf{z}_2^*)(\nabla u_1^*)(u_1 - u_1^*)
\end{aligned}$$

$$\leq C\frac{\varepsilon_1}{2}\|u_2-u_2^*\|^2+\frac{C}{2\varepsilon_1}\|u_1-u_1^*\|^2+C\|u_1-u_1^*\|^2$$
$$+\|\nabla\cdot D_2^{-1}\mathbf{z}_2\|_{L^\infty(\Omega)}\|u_1-u_1^*\|^2+\|D_2^{-1}\mathbf{z}_2\|_{L^\infty(\Omega)}\int_\Omega(\nabla\cdot(u_1-u_1^*))(u_1-u_1^*)$$
$$+\|u_1^*\|_{L^\infty(\Omega)}\|\nabla\cdot D_2^{-1}(\mathbf{z}_2-\mathbf{z}_2^*)\|\|u_1-u_1^*\|$$
$$+\|\nabla u_1^*\|_{L^\infty(\Omega)}\int_\Omega D_2^{-1}(\mathbf{z}_2-\mathbf{z}_2^*)(u_1-u_1^*).$$

Substitute $\nabla\cdot(u_1-u_1^*)=D_1^{-1}(\mathbf{z}_1-\mathbf{z}_1^*)$, then use the Cauchy-Schwarz inequality (theorem 4.7) and Cauchy's inequality (theorem 4.6)

$$\frac{1}{2}\frac{d}{dt}\|u_1-u_1^*\|^2+\|D_1^{-1/2}(\mathbf{z}_1-\mathbf{z}_1^*)\|^2$$
$$\leq C\frac{\varepsilon_1}{2}\|u_2-u_2^*\|^2+\frac{C}{2\varepsilon_1}\|u_1-u_1^*\|^2+C\|u_1-u_1^*\|^2$$
$$+C\|u_1-u_1^*\|^2+C\frac{\varepsilon_2}{2}\|D_1^{-1}(\mathbf{z}_1-\mathbf{z}_1^*)\|^2+\frac{C}{2\varepsilon_2}\|u_1-u_1^*\|^2$$
$$+C\frac{\varepsilon_3}{2}\|\nabla\cdot D_2^{-1}(\mathbf{z}_2-\mathbf{z}_2^*)\|^2+\frac{C}{2\varepsilon_3}\|u_1-u_1^*\|^2$$
$$+C\frac{\varepsilon_4}{2}\|D_2^{-1}(\mathbf{z}_2-\mathbf{z}_2^*)\|^2+\frac{C}{2\varepsilon_4}\|u_1-u_1^*\|^2$$
$$\leq C\frac{\varepsilon_1}{2}\|u_2-u_2^*\|^2+(C+\frac{C}{2\varepsilon_1}+\frac{C}{2\varepsilon_2}+\frac{C}{2\varepsilon_3}+\frac{C}{2\varepsilon_4})\|u_1-u_1^*\|^2$$
$$+C\frac{\varepsilon_2}{2}\|D_1^{-1}(\mathbf{z}_1-\mathbf{z}_1^*)\|^2+C\frac{\varepsilon_3}{2}\|\nabla\cdot D_2^{-1}(\mathbf{z}_2-\mathbf{z}_2^*)\|^2+C\frac{\varepsilon_4}{2}\|D_2^{-1}(\mathbf{z}_2-\mathbf{z}_2^*)\|^2.$$

Finally,

$$\frac{1}{2}\frac{d}{dt}\|u_1-u_1^*\|^2+C\|(\mathbf{z}_1-\mathbf{z}_1^*)\|^2$$
$$\leq C\frac{\varepsilon_1}{2}\|u_2-u_2^*\|^2+(C+\frac{C}{2\varepsilon_1}+\frac{C}{2\varepsilon_2}+\frac{C}{2\varepsilon_3}+\frac{C}{2\varepsilon_4})\|u_1-u_1^*\|^2$$
$$+C\frac{\varepsilon_2}{2}\|\mathbf{z}_1-\mathbf{z}_1^*\|^2+C\frac{\varepsilon_3}{2}\|\nabla\cdot(\mathbf{z}_2-\mathbf{z}_2^*)\|^2+C\frac{\varepsilon_4}{2}\|(\mathbf{z}_2-\mathbf{z}_2^*)\|^2. \tag{4.132}$$

Now, go to the other set of equations. That is, Substitute (4.131) into (4.129)

$$\frac{1}{2}\frac{d}{dt}\|u_2-u_2^*\|^2+\|D_2^{-1/2}(\mathbf{z}_2-\mathbf{z}_2^*)\|^2=(f_2(u_1,u_2)-f_2(u_1,u_2^*),u_2-u_2^*)$$
$$+(f_2(u_1,u_2^*)-f_2(u_1^*,u_2^*),u_2-u_2^*)$$
$$\leq(C|u_2-u_2^*|,|u_2-u_2^*|)+(C|u_1-u_1^*|,|u_2-u_2^*|)$$
$$\leq C\frac{\varepsilon_5}{2}\|u_1-u_1^*\|^2+\frac{C}{2\varepsilon_5}\|u_2-u_2^*\|^2+C\|u_2-u_2^*\|^2.$$

Finally,

$$\frac{1}{2}\frac{d}{dt}\|u_2 - u_2^*\|^2 + C\|(\mathbf{z}_2 - \mathbf{z}_2^*)\|^2 \leq C\|u_1 - u_1^*\|^2 + C\|u_2 - u_2^*\|^2. \tag{4.133}$$

Add (4.132) and (4.133)

$$\begin{aligned}
&\frac{1}{2}\frac{d}{dt}(\|u_1 - u_1^*\|^2 + \|u_2 - u_2^*\|^2) + C\|(\mathbf{z}_1 - \mathbf{z}_1^*)\|^2 + C\|(\mathbf{z}_2 - \mathbf{z}_2^*)\|^2 \\
&\leq (C + C\frac{\varepsilon_1}{2})\|u_2 - u_2^*\|^2 + (C + \frac{C}{2\varepsilon_1} + \frac{C}{2\varepsilon_2} + \frac{C}{2\varepsilon_3} + \frac{C}{2\varepsilon_4})\|u_1 - u_1^*\|^2 \\
&\quad + C\frac{\varepsilon_2}{2}\|\mathbf{z}_1 - \mathbf{z}_1^*\|^2 + C\frac{\varepsilon_3}{2}\|\nabla\cdot(\mathbf{z}_2 - \mathbf{z}_2^*)\|^2 + C\frac{\varepsilon_4}{2}\|(\mathbf{z}_2 - \mathbf{z}_2^*)\|^2.
\end{aligned} \tag{4.134}$$

Choose $\varepsilon_2, \varepsilon_4$ to hide terms and set $\varepsilon_3 = 1$

$$\begin{aligned}
&\frac{1}{2}\frac{d}{dt}(\|u_1 - u_1^*\|^2 + \|u_2 - u_2^*\|^2) + C\|(\mathbf{z}_1 - \mathbf{z}_1^*)\|^2 + C\|(\mathbf{z}_2 - \mathbf{z}_2^*)\|^2 \\
&\qquad \leq C\|u_1 - u_1^*\|^2 + C\|u_2 - u_2^*\|^2 + C\|\nabla\cdot(\mathbf{z}_2 - \mathbf{z}_2^*)\|^2.
\end{aligned} \tag{4.135}$$

Integrate 0 to t,

$$\begin{aligned}
&(\|u_1 - u_1^*\|^2(t) + \|u_2 - u_2^*\|^2(t)) + C\int_0^t (\|(\mathbf{z}_1 - \mathbf{z}_1^*)\|^2 + \|(\mathbf{z}_2 - \mathbf{z}_2^*)\|^2) \\
&\qquad \leq C\int_0^t (\|u_1 - u_1^*\|^2 + \|u_2 - u_2^*\|^2) + C\int_0^t \|\nabla\cdot(\mathbf{z}_2 - \mathbf{z}_2^*)\|^2 \\
&\qquad\qquad + \|u_1 - u_1^*\|^2(0) + \|u_2 - u_2^*\|^2(0).
\end{aligned} \tag{4.136}$$

Use (4.127)

$$\begin{aligned}
&(\|u_1 - u_1^*\|^2(t) + \|u_2 - u_2^*\|^2(t)) + C\int_0^t (\|(\mathbf{z}_1 - \mathbf{z}_1^*)\|^2 + \|(\mathbf{z}_2 - \mathbf{z}_2^*)\|^2) \\
&\qquad \leq C\int_0^t (\|u_1 - u_1^*\|^2 + \|u_2 - u_2^*\|^2) + C\|(D_2^{-1/2}(\mathbf{z}_2 - \mathbf{z}_2^*)\|^2(0) \\
&\qquad\qquad + \|u_1 - u_1^*\|^2(0) + \|u_2 - u_2^*\|^2(0).
\end{aligned} \tag{4.137}$$

Use the Gronwall Inequality, theorem 4.8,

$$\begin{aligned}
&(\|u_1 - u_1^*\|^2(t) + \|u_2 - u_2^*\|^2(t)) + C\int_0^t (\|(\mathbf{z}_1 - \mathbf{z}_1^*)\|^2 + \|(\mathbf{z}_2 - \mathbf{z}_2^*)\|^2) \\
&\qquad \leq e^{ct}(\|(D_2^{-1}(\mathbf{z}_2 - \mathbf{z}_2^*)\|^2(0) + \|u_1 - u_1^*\|^2(0) + \|u_2 - u_2^*\|^2(0)).
\end{aligned} \tag{4.138}$$

Obviously, if the initial conditions are the same, the solutions will be the same.

4.4.3 Application of the Theorems to Individual Equations

In this section we will show that the right hand side functions in each equation of our PDE system meets the hypothesis of theorems 4.13 and 4.14.

Bounds on various terms. There are certain terms that will occur repeatedly throughout the thesis. Therefore, it will be helpful to find bounds on these terms and then refer to these bounds whenever necessary.

It is obvious by inspection of the Part I NEC equations that the variables in the equations will always be non-negative. In any case, we list that fact as an assumption:

$$\textbf{Assumption 3} \qquad e_c,\ b,\ m,\ m_a,\ c,\ c_a,\ NO,\ n_a,\ d \geq 0. \tag{4.139}$$

Now, consider the terms

$$T = R(c_a)c \text{ and } \quad R(c_a) = \frac{1}{1 + k_{Rc_a}(c_a/\overline{c}_a)^2}.$$

Note that since $k_{Rc_a} \geq 0$ and our assumption (4.139), we have

$$0 < R(c_a) \leq 1 \quad \text{and} \quad T = R(c_a)c \geq 0. \tag{4.140}$$

Since $x_{dc} \geq 0$ and $q_2 > 0$, then

$$0 \leq \frac{T^{q_2}}{x_{dc}^{q_2} + T^{q_2}} \leq 1. \tag{4.141}$$

Consider

$$Q = R(c_a)(k_{c_a m_a n_a} n_a + m_a + k_{c_a m_a d} d). \tag{4.142}$$

Since $k_{c_a m_a n_a} > 0$, $k_{c_a m_a d} > 0$, (4.139) and (4.140) we have

$$Q \geq 0 \quad \text{and} \quad 0 \leq \frac{Q}{1+Q} \leq 1. \tag{4.143}$$

Consider the terms

$$\frac{m_a^{q_1}}{1 + (m_a/\overline{m}_a)^{q_1}} \quad \text{and} \quad \frac{n_a^{q_1}}{1 + (n_a/\overline{n}_a)^{q_1}}. \tag{4.144}$$

Since the constants $q_1 > 0$, $\overline{m}_a > 0$ and $\overline{n}_a > 0$ and (4.139),

$$0 \leq \frac{m_a^{q_1}}{1 + (m_a/\overline{m}_a)^{q_1}} \leq \overline{m}_a^{q_1} \leq C \quad \text{and} \quad 0 \leq \frac{n_a^{q_1}}{1 + (n_a/\overline{n}_a)^{q_1}} \leq \overline{n}_a^{q_1} \leq C \tag{4.145}$$

for some $C > 0$.

Consider

$$k_b b/(1 + b/\epsilon). \tag{4.146}$$

Since $k_b > 0$, $\epsilon > 0$, and (4.139) ,

$$k_b b/(1 + b/\epsilon) \leq k_b \epsilon \leq C \tag{4.147}$$

for some $C > 0$.

Application to Individual Equations. Now, we apply theorems 4.13 and 4.14 to the individual equations of the NEC model. The equations will be analyzed in the ideal order, i.e., so that the regularity established for some equations may be used in the subsequent analysis of the other equations. Such an ordering, will require the least possible assumptions.

Damage Equation

$$\frac{\partial d}{\partial t} \; - \; \nabla \cdot D_d \nabla d \; = \; -k_d d + k_{dc} \frac{T^{q_2}}{x_{dc}^{q_2} + T^{q_2}}. \tag{4.148}$$

Define

$$f_d := \; -k_d d + k_{dc} \frac{T^{q_2}}{x_{dc}^{q_2} + T^{q_2}} \quad \text{and choose } d \in L^2(0,T;H^3(\Omega)), \text{then,}$$

$$\begin{aligned} \|f_d\|^2_{L^2(0,T;H^2(\Omega))} \; &= \; \int_0^T \left\| -k_d d + k_{dc} \frac{T^{q_2}}{x_{dc}^{q_2} + T^{q_2}} \right\|^2_{H^2(\Omega)} \\ \leq \; C \int_0^T \|k_d d\|^2_{H^2(\Omega)} &+ C \int_0^T \|k_d d\|_{H^2(\Omega)} \left\| k_{dc} \frac{T^{q_2}}{x_{dc}^{q_2} + T^{q_2}} \right\|_{H^2(\Omega)} \\ &+ C \int_0^T \left\| k_{dc} \frac{T^{q_2}}{x_{dc}^{q_2} + T^{q_2}} \right\|^2_{H^2(\Omega)}. \end{aligned}$$

Using (4.141),

$$\begin{aligned}\|f_d\|^2_{L^2(0,T;H^2(\Omega))} \leq\ & Ck_d^2\int_0^T \|d\|^2_{H^2(\Omega)} + Ck_{dc}k_d\int_0^T \|d\|_{H^2(\Omega)} + Ck_{dc}^2T \\ \leq\ & (Ck_d^2 + Ck_{dc}k_d)\|d\|^2_{L^2(0,T;H^2(\Omega))} + Ck_{dc}^2T.\end{aligned}$$

So, $f_d \in L^2(0,T;H^2(\Omega))$. Then by **Theorem** 4.13, (4.148), has a solution with

$$d \in L^2(0,T;H^4(\Omega)). \tag{4.149}$$

Nitric Oxide Equation

$$\begin{aligned}\frac{\partial NO}{\partial t} - \nabla\cdot D_{NO}\nabla NO =\ & -k_{NO}NO + k_{NOm_a}\frac{m_a^{q_1}}{1+(m_a/\overline{m}_a)^{q_1}} \\ & + k_{NOn_a}\frac{n_a^{q_1}}{1+(n_a/\overline{n}_a)^{q_1}}.\end{aligned} \tag{4.150}$$

Define

$$f_{NO} := -k_{NO}NO + k_{NOm_a}\frac{m_a^{q_1}}{1+(m_a/\overline{m}_a)^{q_1}} + k_{NOn_a}\frac{n_a^{q_1}}{1+(n_a/\overline{n}_a)^{q_1}}$$

and choose $NO \in L^2(0,T;H^3(\Omega))$, then,

$$\|f_{NO}\|^2_{L^2(0,T;H^2(\Omega))} =$$
$$\int_0^T \left\| -k_{NO}NO + k_{NOm_a}\frac{m_a^{q_1}}{1+(m_a/\overline{m}_a)^{q_1}} + k_{NOn_a}\frac{n_a^{q_1}}{1+(n_a/\overline{n}_a)^{q_1}}\right\|^2_{H^2(\Omega)}.$$

Then by (4.145)

$$\begin{aligned}\|f_{NO}\|^2_{L^2(0,T;H^2(\Omega))} \leq\ & C\int_0^T \|NO\|^2_{H^2(\Omega)} + CT \\ \leq\ & C\|NO\|^2_{L^2(0,T;H^2(\Omega))} + CT.\end{aligned}$$

So, $f_{NO} \in L^2(0,T;H^2(\Omega))$. Then by **Theorem** 4.13, (4.150), has a solution with

$$NO \in L^2(0,T;H^4(\Omega)). \tag{4.151}$$

Anti-inflammatory Cytokine Equation

$$\frac{\partial c_a}{\partial t} \; - \; \nabla \cdot D_{c_a} \nabla c_a \; = \; -k_{c_a} c_a + s_{c_a} + k_{c_a P} \frac{Q}{1+Q} \tag{4.152}$$

Define

$$f_{c_a} := \; -k_{c_a} c_a + s_{c_a} + k_{c_a P} \frac{Q}{1+Q} \quad \text{and choose } c_a \in L^2(0,T;H^3(\Omega)).$$

Then,

$$\|f_{c_a}\|^2_{L^2(0,T;H^2(\Omega))} \; = \; \int_0^T \left\| -k_{c_a} c_a + s_{c_a} + k_{c_a P} \frac{Q}{1+Q} \right\|^2_{H^2(\Omega)}.$$

Using (4.143) and noting that k_{c_a}, s_{c_a} and $k_{c_a P}$ are constants,

$$\|f_{c_a}\|^2_{L^2(0,T;H^2(\Omega))} \leq \; C \int_0^T \|c_a\|^2_{H^2(\Omega)} + CT \leq \; C\|c_a\|^2_{L^2(0,T;H^2(\Omega))} + CT.$$

So, $f_{c_a} \in L^2(0,T;H^2(\Omega))$. Then by **Theorem** 4.13, (4.152), has a solution with

$$c_a \in L^2(0,T;H^4(\Omega)). \tag{4.153}$$

Cytokine Equation

$$\frac{\partial c}{\partial t} \; - \; \nabla \cdot D_c \nabla c \; = \; -k_c c + R(c_a)(k_{cm_a} m_a + k_{cn_a} n_a) - R(c_a)(k_{nc} cn + k_{mc} cm) \tag{4.154}$$

Define

$$f_c := \; -k_c c + R(c_a)(k_{cm_a} m_a + k_{cn_a} n_a) - R(c_a)(k_{nc} cn + k_{mc} cm)$$

$$\text{choose } c \in L^2(0,T;H^3(\Omega)) \text{ and choose } m, m_a, n, n_a \in L^2(0,T;H^2(\Omega)).$$

(Since each of these are solutions to their respective PDEs, we can say,
$c \in L^\infty(0,T;H^2(\Omega))$ and $m, m_a, n, n_a \in L^\infty(0,T;H^1(\Omega))$, see theorem 4.12.)

$$\text{Then} \|f_c\|^2_{L^2(0,T;H^2(\Omega))} \; =$$
$$\int_0^T \left\| -k_c c + R(c_a)(k_{cm_a} m_a + k_{cn_a} n_a) - R(c_a)(k_{nc} cn + k_{mc} cm) \right\|^2_{H^2(\Omega)}$$

$$\leq\ C\int_0^T \Big\|c+m_a+n_a+cn+cm\Big\|^2_{H^2(\Omega)}$$
$$\leq C\int_0^T \|c\|^2_{H^2(\Omega)} +\ C\int_0^T \|m_a\|^2_{H^2(\Omega)} +\ C\int_0^T \|n_a\|^2_{H^2(\Omega)}$$
$$+\ C\int_0^T \|cn\|^2_{H^2(\Omega)} +\ C\int_0^T \|cm\|^2_{H^2(\Omega)}$$
$$\leq C\int_0^T \|c\|^2_{H^2(\Omega)} +\ C\int_0^T \|m_a\|^2_{H^2(\Omega)} +\ C\int_0^T \|n_a\|^2_{H^2(\Omega)}$$
$$+C\int_0^T\int_\Omega |cn|^2 + C\int_0^T\int_\Omega |(\nabla c)n|^2 + C\int_0^T\int_\Omega |c\nabla n|^2$$
$$+C\int_0^T\int_\Omega |(\nabla c)\nabla n|^2 + C\int_0^T\int_\Omega |(\triangle c)n|^2 + C\int_0^T\int_\Omega |c\triangle n|^2$$
$$+C\int_0^T\int_\Omega |cm|^2 + C\int_0^T\int_\Omega |(\nabla c)m|^2 + C\int_0^T\int_\Omega |c\nabla m|^2$$
$$+C\int_0^T\int_\Omega |(\nabla c)(\nabla m)|^2 + C\int_0^T\int_\Omega |(\triangle c)m|^2 + C\int_0^T\int_\Omega |c\triangle m|^2$$
$$\leq C\int_0^T \|c\|^2_{H^2(\Omega)} +\ C\int_0^T \|m_a\|^2_{H^2(\Omega)} +\ C\int_0^T \|n_a\|^2_{H^2(\Omega)}$$
$$+C\int_0^T \|c\|^2_{L^\infty(\Omega)}\int_\Omega |n|^2 + C\int_0^T \|n\|^2_{L^\infty(\Omega)}\int_\Omega |\nabla c|^2 + C\int_0^T \|c\|^2_{L^\infty(\Omega)}\int_\Omega |\nabla n|^2$$
$$+C\int_0^T \|\nabla c\|^2_{L^4(\Omega)}\|\nabla n\|^2_{L^4(\Omega)} + C\int_0^T \|n\|^2_{L^\infty(\Omega)}\int_\Omega |(\triangle c)|^2$$
$$+C\int_0^T \|c\|^2_{L^\infty(\Omega)}\int_\Omega |\triangle n|^2 + C\int_0^T \|c\|^2_{L^\infty(\Omega)}\int_\Omega |m|^2 + C\int_0^T \|m\|^2_{L^\infty(\Omega)}\int_\Omega |\nabla c|^2$$
$$+C\int_0^T \|c\|^2_{L^\infty(\Omega)}\int_\Omega |\nabla m|^2 + C\int_0^T \|\nabla c\|^2_{L^4(\Omega)}\|\nabla m\|^2_{L^4(\Omega)}$$
$$+C\int_0^T \|m\|^2_{L^\infty(\Omega)}\int_\Omega |(\triangle c)|^2 + C\int_0^T \|c\|^2_{L^\infty(\Omega)}\int_\Omega |\triangle m|^2.$$

In the last inequality above, the $L^4(\Omega)$ norms come from applying Cauchy-Schwarz, for example,

$C\int_0^T\int_\Omega |(\nabla c)(\nabla m)|^2 \leq C\int_0^T \Big(\int_\Omega (|\nabla c|^2)^2\Big)^{1/2}\Big(\int_\Omega |\nabla m|^2)^2\Big)^{1/2}$

$= C\int_0^T \Big(\Big(\Big(\int_\Omega (|\nabla c|^2)^2\Big)^{1/2}\Big)^{1/2}\Big)^2\Big(\Big(\Big(\int_\Omega |\nabla m|^2)^2\Big)^{1/2}\Big)^{1/2}\Big)^2 = C\int_0^T \|\nabla c\|^2_{L^4(\Omega)}\|\nabla m\|^2_{L^4(\Omega)}.$

Now, note that since $c\in L^\infty(0,T;H^2(\Omega))$, we have $\nabla c\in L^\infty(0,T;L^6(\Omega))$ and since $m,n\in L^2(0,T;H^2(\Omega))$ we have $\nabla m,\nabla n\in L^2(0,T;L^6(\Omega))$ and $\triangle m,\triangle n\in L^2(0,T;L^6(\Omega))$. All of this is used to say,

$$\|f_c\|^2_{L^2(0,T;H^2(\Omega))}\ \leq C\int_0^T \|c\|^2_{H^2(\Omega)} +\ C\int_0^T \|m_a\|^2_{H^2(\Omega)} +\ C\int_0^T \|n_a\|^2_{H^2(\Omega)}$$

$$+C\|c\|^2_{L^\infty(0,T;L^\infty(\Omega))}\int_0^T\int_\Omega |n|^2 + C\|n\|^2_{L^\infty(0,T;L^\infty(\Omega))}\int_0^T\int_\Omega |\nabla c|^2$$
$$+C\|c\|^2_{L^\infty(0,T;L^\infty(\Omega))}\int_0^T\int_\Omega |\nabla n|^2 + C\|\nabla c\|^2_{L^\infty(0,T;L^4(\Omega))}\int_0^T \|\nabla n\|^2_{L^4(\Omega)}$$
$$+C\|n\|^2_{L^\infty(0,T;L^\infty(\Omega))}\int_0^T\int_\Omega |(\triangle c)|^2 + C\|c\|^2_{L^\infty(0,T;L^\infty(\Omega))}\int_0^T\int_\Omega |\triangle n|^2$$
$$+C\|c\|^2_{L^\infty(0,T;L^\infty(\Omega))}\int_0^T\int_\Omega |m|^2 + C\|m\|^2_{L^\infty(0,T;L^\infty(\Omega))}\int_0^T\int_\Omega |\nabla c|^2$$
$$+C\|c\|^2_{L^\infty(0,T;L^\infty(\Omega))}\int_0^T\int_\Omega |\nabla m|^2 + C\|\nabla c\|^2_{L^\infty(0,T;L^4(\Omega))}\int_0^T \|\nabla m\|^2_{L^4(\Omega)}$$
$$+C\|m\|^2_{L^\infty(0,T;L^\infty(\Omega))}\int_0^T\int_\Omega |(\triangle c)|^2 + C\|c\|^2_{L^\infty(0,T;L^\infty(\Omega))}\int_0^T\int_\Omega |\triangle m|^2.$$

Each of the terms above are bounded. So, $f_c \in L^2(0,T;H^2(\Omega))$. Then by **Theorem** 4.13, (4.154), has a solution with

$$c \in L^2(0,T;H^4(\Omega)). \tag{4.155}$$

Bacteria Equation

$$\begin{aligned}\frac{\partial b}{\partial t} \; - \; \nabla \cdot D_b \nabla b \; &= \; k_{bg} b(1 - b/b_{max}) - k_b b/(1 + b/\epsilon) \\ &\quad -R(c_a)(k_{bm_a} m_a b + k_{bn_a} n_a b) - k_{pp} b \end{aligned} \tag{4.156}$$

Define

$$f_b := \; k_{bg} b(1 - b/b_{max}) - k_b b/(1 + b/\epsilon) - R(c_a)(k_{bm_a} m_a b + k_{bn_a} n_a b) - k_{pp} b$$

$$\text{choose } b \in L^2(0,T;H^3(\Omega)) \text{ and choose } m_a, n_a \in L^2(0,T;H^2(\Omega)).$$

(Since each of these are solutions to their respective PDEs, we can say,
$b \in L^\infty(0,T;H^2(\Omega))$ and $m_a, n_a \in L^\infty(0,T;H^1(\Omega))$, see theorem 4.12.)
It has been shown that $b \geq 0$, therefore, it is reasonable to assume that

$$|1 - b/b_{max}| \leq 1.$$

$$\|f_b\|^2_{L^2(0,T;H^2(\Omega))} = \int_0^T \Big\| k_{bg} b(1 - b/b_{max}) - k_b b/(1 + b/\epsilon) - R(c_a)(k_{bm_a} m_a b + k_{bn_a} n_a b) - k_{pp} b \Big\|^2_{H^2(\Omega)}$$
$$\leq C \int_0^T \|b^2\|^2_{H^2(\Omega)} + C \int_0^T \|m_a b\|^2_{H^2(\Omega)} + C \int_0^T \|n_a b\|^2_{H^2(\Omega)} + C \int_0^T \|b\|^2_{H^2(\Omega)}. \quad (4.157)$$

Notice that in each term, at least one of the functions is in $L^2(0,T;H^3(\Omega))$. Therefore, using techniques similar to those in the analysis of the cytokine equation above, it can be shown that all of the terms in (4.157) are bounded. So, $f_b \in L^2(0,T;H^2(\Omega))$. Then by **Theorem** 4.13, (4.156), has a solution with

$$b \in L^2(0,T;H^4(\Omega)). \quad (4.158)$$

Macrophage Equation

$$\frac{\partial m}{\partial t} = k_m(m_{max} - m) - R(c_a)(k_{mb} bm + k_{mc} cm + k_{md} dm). \quad (4.159)$$

Define

$$f_m := k_m(m_{max} - m) - R(c_a)(k_{mb} bm + k_{mc} cm + k_{md} dm).$$

Choose $m \in L^2(0,T;H^2(\Omega))$. Then $m \in L^\infty(0,T;H^1(\Omega))$, see theorem 4.12.

In the following we will use the results (4.149),(4.155),and (4.158)
(i.e. $d, c, b \in L^2(0,T;H^4(\Omega))$ which implies $d, c, b \in L^\infty(0,T;H^3(\Omega))$, see theorem 4.12).

$$\|f_m\|^2_{L^2(0,T;H^2(\Omega))} =$$
$$\int_0^T \Big\| k_m(m_{max} - m) - R(c_a)(k_{mb} bm + k_{mc} cm + k_{md} dm) \Big\|^2_{H^2(\Omega)}$$
$$\leq C \int_0^T \|m\|^2_{H^2(\Omega)} + C \int_0^T \|bm\|^2_{H^2(\Omega)} + C \int_0^T \|cm\|^2_{H^2(\Omega)} + C \int_0^T \|dm\|^2_{H^2(\Omega)} + C. \quad (4.160)$$

Notice that in each term, at least one of the functions is in $L^2(0,T;H^3(\Omega))$. Therefore, using techniques similar to those in the analysis of the cytokine equation above, it can be shown that all of the terms in (4.160) are bounded. So, $f_m \in L^2(0,T;H^2(\Omega))$. Then by **Theorem** 4.13, (4.159), has a solution with

$$m \in L^2(0,T;H^4(\Omega)). \tag{4.161}$$

Activated Macrophage Equation (coupled with the cytokine and bacteria equations)

$$\begin{aligned}\frac{\partial m_a}{\partial t} \; - \; \nabla \cdot (D_{m_a}\nabla m_a - \gamma_{m_a c} m_a \nabla c - \gamma_{m_a b} R(c_a) m_a \nabla b) \\ = -k_{m_a} m_a + R(c_a)(k_{mb} bm + k_{mc} cm + k_{md} dm).\end{aligned} \tag{4.162}$$

$$\frac{\partial c}{\partial t} \; - \; \nabla \cdot D_c \nabla c \; = \; -k_c c + R(c_a)(k_{cm_a} m_a + k_{cn_a} n_a) - R(c_a)(k_{nc} cn + k_{mc} cm) \tag{4.163}$$

$$\begin{aligned}\frac{\partial b}{\partial t} \; - \; \nabla \cdot D_b \nabla b \; = \; k_{bg} b(1 - b/b_{max}) - k_b b/(1 + b/\epsilon) \\ - R(c_a)(k_{bm_a} m_a b + k_{bn_a} n_a b) - k_{pp} b\end{aligned} \tag{4.164}$$

Define

$$f_c := \; -k_c c + R(c_a)(k_{cm_a} m_a + k_{cn_a} n_a) - R(c_a)(k_{nc} cn + k_{mc} cm),$$

$$f_{m_a} := \; -k_{m_a} m_a + R(c_a)(k_{mb} bm + k_{mc} cm + k_{md} dm) \text{ and}$$

$$f_b := \; k_{bg} b(1 - b/b_{max}) - k_b b/(1 + b/\epsilon) - R(c_a)(k_{bm_a} m_a b + k_{bn_a} n_a b) - k_{pp} b.$$

Choose $m_a \in L^2(0,T;H^2(\Omega))$.

In the following we will use the results (4.149),(4.155),(4.158), and (4.161) (i.e. $d, c, b, m \in L^2(0,T;H^4(\Omega))$ and since each of these are solutions to their respective PDEs, we can say, $d, c, b, m \in L^\infty(0,T;H^3(\Omega))$, by theorem 4.12).

$$\|f_{m_a}\|^2_{L^2(0,T;H^1(\Omega))} \; = \; \int_0^T \Big\| \; -k_{m_a} m_a + R(c_a)(k_{mb} bm + k_{mc} cm + k_{md} dm)\|^2_{H^1(\Omega)}$$

$$\leq C\int_0^T \|m_a\|^2_{H^1(\Omega)} + C\int_0^T \|bm\|^2_{H^1(\Omega)} + C\int_0^T \|cm\|^2_{H^1(\Omega)} + C\int_0^T \|dm\|^2_{H^1(\Omega)} \quad (4.165)$$

Using techniques similar to those in the analysis of the cytokine equation above, it can be shown that all of the terms in (4.165) are bounded. So, $f_{m_a} \in L^2(0,T;H^1(\Omega))$. We have already shown that $f_c, f_b \in L^2(0,T;H^2(\Omega))$ (see **cytokines** and **bacteria** above). So, we may apply **Theorem** 4.14 to conclude that the system (4.162), (4.163),(4.164) has a solution with

$$m_a \in L^2(0,T;H^3(\Omega)) \;\; c \in L^2(0,T;H^4(\Omega))$$
$$b \in L^2(0,T;H^4(\Omega)). \quad (4.166)$$

Activated Neutrophil Equation (coupled with the cytokine equation)

$$\frac{\partial n_a}{\partial t} - \nabla\cdot(D_{n_a}\nabla n_a - \gamma_{n_a c} n_a \nabla c) = -k_{n_a} n_a + R(c_a)(k_{nc} cn + k_{nd} dn). \quad (4.167)$$

$$\frac{\partial c}{\partial t} - \nabla\cdot D_c \nabla c = -k_c c + R(c_a)(k_{cm_a} m_a + k_{cn_a} n_a) - R(c_a)(k_{nc} cn + k_{mc} cm) \quad (4.168)$$

Define

$$f_{n_a} := -k_{n_a} n_a + R(c_a)(k_{nc} cn + k_{nd} dn) \text{ and}$$
$$f_c := -k_c c + R(c_a)(k_{cm_a} m_a + k_{cn_a} n_a) - R(c_a)(k_{nc} cn + k_{mc} cm).$$

Choose $n, n_a \in L^2(0,T;H^2(\Omega))$.

In the following we will use the results (4.149) and (4.155) (i.e. $d, c \in L^2(0,T;H^4(\Omega))$ and since each of these are solutions to their respective PDEs, we can say, $d, c \in L^\infty(0,T;H^3(\Omega))$, by theorem 4.12.)

$$\|f_m\|^2_{L^2(0,T;H^1(\Omega))} = \int_0^T \Big\| - k_{n_a} n_a + R(c_a)(k_{nc} cn + k_{nd} dn)\|^2_{H^1(\Omega)}$$
$$\leq C\int_0^T \|n_a\|^2_{H^1(\Omega)} + C\int_0^T \|cn\|^2_{H^1(\Omega)} + C\int_0^T \|dn\|^2_{H^1(\Omega)}. \quad (4.169)$$

Using techniques similar to those in the analysis of the cytokine equation above, it can be shown that all of the terms in (4.169) are bounded. So, $f_{n_a} \in L^2(0,T;H^1(\Omega))$ and we have already shown that $f_c \in L^2(0,T;H^2(\Omega))$ (see **cytokines** above). So, we may apply **Theorem** 4.14 to conclude that the system (4.167), (4.168) has a solution with

$$n_a \in L^2(0,T;H^3(\Omega)) \quad c \in L^2(0,T;H^4(\Omega)). \tag{4.170}$$

4.4.4 Conclusion

We have shown that Theorems 4.13 and 4.14 may be applied the eight equations in PDE Analysis - Part I. **Therefore, the system of eight equations in PDE Analysis - Part I has a weak solution.**

4.5 ANALYSIS OF PDES IN PART II

In this section we will consider the epithelial equation. This equation is challenging for two reasons. First of all, it contains a difficult nonlinearity in its diffusion term. Secondly, the diffusion term may go to zero in some cases. In this case, this PDE is a **degenerate parabolic** PDE.

In this chapter, we will consider both the non-degenerate and the degenerate cases for this PDE. Existence analysis will be provided for the non-degenerate case. An equation similar to, but much more general than our equation, has been analyzed by by Alt and Luckhaus [4]. However, the analysis in that paper is much more complicated than we require. So, the analysis presented here will use many ideas from Alt and Luckhaus as well as from other works but will be tailored to the specifics in our equation.

For the degenerate case of our equation, many cite Alt and Luckhaus, although their paper does not fully address the degeneracy the occurs. For example, Arbogast, Wheeler, and Zhang [7] rely heavily on the Alt and Luckhaus paper. We will do the same here. Therefore, there will be no need to do new analysis for the degenerate case in this thesis. Instead, the degenerate case will be covered by making appropriate references to the work of the aforementioned authors. After referencing the work of these authors, further regularity will be established for the mixed weak form of the degenerate case.

Epithelial Equation

The epithelial equation is given by:

$$\frac{\partial e_c}{\partial t} \; + \; \nabla \cdot (\beta(e_c)\mathbf{u}(e_c, b)) \; = \; k_p e_c(1 - e_c/e_{c,max}) - k_a(n_a, c, b)e_c \tag{4.171}$$

where

$$\beta(e_c) = \frac{e_c^2}{e_c^2 + (e_{c,max} - e_c)^2} \qquad \mathbf{u}(e_c, b) \; = \; -\alpha(b)\nabla e_c \tag{4.172}$$

$k_a(n_a, c, b) :=$

$$\frac{(n_a + k_{e_c n_a c} c + k_{e_c n_a b} b)^{.45}}{(n_a + k_{e_c n_a c} c + k_{e_c n_a b} b)^{.45} + ((n_{a,max} - n_a) + k_{e_c n_a c}(c_{max} - c) + k_{e_c n_a b}(b_{max} - b))^{.45}}$$

$$\alpha(b) = \frac{(b_{max} - b)^q}{(b_{max} - b)^q + b^q}.$$

Equation (4.171) may be written as

$$\frac{\partial e_c}{\partial t} - \nabla \cdot (\beta(e_c)\alpha(b)\nabla e_c) \ = f_{e_c}(e_c, b, n_a). \tag{4.173}$$

Define

$$f_{e_c}(e_c, b, n_a) := \ k_p e_c(1 - e_c/e_{c,max}) - \mathcal{A} e_c$$

where

$$\mathcal{A} = k_a(n_a, c, b).$$

Note that (4.173) equation may be written as

$$\frac{\partial e_c}{\partial t} - \nabla \cdot (\alpha(b)\nabla P(e_c)) \ = f_{e_c}(e_c, b, n_a) \tag{4.174}$$

where $P(e_c)$ is the Kirchhoff transformation given by:

$$P(e_c) = \int_0^{e_c} \beta(s) \, ds$$

so that

$$\nabla P(e_c) \ = \ \frac{\partial P}{\partial e_c} \nabla e_c \ + \ \nabla_x P(e_c) \ = \ \beta(e_c)\nabla e_c \ + \ \int_0^{e_c} \nabla_x \beta(s) \, ds \ = \ \beta(e_c)\nabla e_c.$$

Note that e_c may, at times, be zero. $B(e_c)$ and $\nabla P(e_c)$ will be zero whenever $e_c = 0$. Such a PDE is classified as a **degenerate parabolic** PDE. So, analysis of the epithelial equation will include two cases: 1) the **non-degenerate case** (conditions under which e_c will never be zero) and 2) the **degenerate case** (conditions under which e_c may be zero).

4.5.1 Properties that apply to both the Non-Degenerate Case and the Degenerate Case

Before considering these two cases note that the right hand side of the epithelial equation (4.173) is **Lipschitz Continuous** in both the degenerate case and the non-degenerate case:

$$\begin{aligned}|f_{e_c}(e_{c_2}) - f_{e_c}(e_{c_1})| \;&=\; |\, k_p(e_{c_2} - e_{c_1}) - \frac{1}{e_{c,max}}(e_{c_2}^2 - e_{c_1}^2) - \mathcal{A}(e_{c_2} - e_{c_1})| \\ &= \left| k_p(e_{c_2} - e_{c_1}) - \frac{1}{e_{c,max}}(e_{c_2}^2 - e_{c_1}^2) - \mathcal{A}(e_{c_2} - e_{c_1}) \right| \\ &= \left| k_p - \frac{1}{e_{c,max}}(e_{c_2} + e_{c_1}) - \mathcal{A} \right| |e_{c_2} - e_{c_1}|.\end{aligned}$$

Since e_c is bounded, we have

$$|f_{e_c}(e_{c_2}) - f_{e_c}(e_{c_1})| \;\leq\; \mathcal{C}|e_{c_2} - e_{c_1}|. \tag{4.175}$$

For some $\mathcal{C} \geq 0$.

Further, since $e_c \geq 0$ we have

$$P(e_c) = \int_0^{e_c} \frac{s^2}{s^2 + (1-s)^2}\, ds \leq (1) \int_0^{e_c} ds \;=\; e_c.$$

So, we can say

$$\|P(e_c)\|^2 \leq \|e_c\|^2. \tag{4.176}$$

4.5.2 Properties that apply only to Non-Degenerate Case

Now, we consider the non-degenerate case. Once again consider (4.173). Note that $n_a,\ k_{e_c n_a c},\ c,\ k_{e_c n_a b},\ b,\ k_{a0}$ are all non-negative. If we assume that we have $n_{a,max} \geq n_a,\ c_{max} \geq c,\ b_{max} \geq b$ then

$$0 \leq \mathcal{A} \leq 1.$$

So, (4.173) may be written as

$$\frac{\partial e_c}{\partial t} - \nabla \cdot (a(\nabla e_c, e_c)) \ = f_{e_c}(e_c, b, n_a) \tag{4.177}$$

where $a(\nabla e_c, e_c) = \beta(e_c)\alpha(b)\nabla e_c$.

Several properties for this epithelial equation, such as monotonicity and a growth condition, can only be proved for the non-degenerate case. This is done here:

For the non-degenerate case, there exists some constants $e_{c,min}, \alpha_{min}$ such that:

$$e_c \geq e_{c,min} > 0 \quad \forall e_c \quad \text{and} \quad \alpha(b) \geq \alpha_{min} > 0 \quad \forall b.$$

So, obviously, we also have $\alpha_{max} = 1$. Then

$$\beta(e_c) = \frac{e_c^2}{e_c^2 + (e_{c,max} - e_c)^2} \geq \frac{e_{c,min}^2}{e_{c,min}^2 + (e_{c,max} - e_{c,min})^2}.$$

So, we may say,

$$\beta_{min} := \frac{e_{c,min}^2}{e_{c,min}^2 + (e_{c,max} - e_{c,min})^2} > 0$$

and, obviously $\beta_{max} = 1$. Then

$$0 < \beta_{min} < \beta_{max} = 1.$$

Monotonicity

In the non-degenerate case, we can establish monotonicity of $a(\cdot, \cdot)$

$$\begin{aligned}(a(\nabla e_{c_1}, e_c) - a(\nabla e_{c_2}, e_c)) \cdot (\nabla e_{c_1} - \nabla e_{c_2}) \\ = \beta(e_c)\alpha(b)(\nabla e_{c_1} - \nabla e_{c_2}) \cdot (\nabla e_{c_1} - \nabla e_{c_2})\end{aligned}$$

$$\geq \beta_{min}\alpha_{min}|\nabla e_{c_1} - \nabla e_{c_2}|^2.$$

Growth Condition

In the non-degenerate case, we can also establish a growth condition. First note that

$$\begin{aligned}|f_{e_c}(e_c)| = \ |k_p e_c(1 - e_c/e_{c,max}) - \mathcal{A}e_c| &\leq k_p|e_c||(1 - e_c/e_{c,max})| + |\mathcal{A}e_c| \\ &\leq C|e_c| + C|e_c| \leq 2C|e_c|.\end{aligned}$$

Therefore,

$$|f_{e_c}(e_c)|^2 \leq C_1 e_c^2. \tag{4.178}$$

Also, we have

$$a(\nabla e_c, e_c) = \beta(e_c)\alpha(b)\nabla e_c \leq \beta_{max}\alpha_{max}\nabla e_c \leq C\nabla e_c.$$

Therefore,

$$|a(\nabla e_c, e_c)|^2 \leq C|\nabla e_c|^2. \tag{4.179}$$

So, by (4.178) and (4.179), there exists a C such that,

$$|a(\nabla e_c, e_c)|^2 + |f_{e_c}(e_c)|^2 \leq C\Big(1 + |\nabla e_c|^2 + \frac{e_c^2}{2}\Big). \tag{4.180}$$

Lower Bound for $\|P(e_c)\|$

Further, since $0 \leq e_c \leq 1$ we have

$$P(e_c) = \int_0^{e_c} \frac{s^2}{s^2 + (1-s)^2}\, ds \geq \frac{e_c^3}{12} \geq \frac{e_{c,min}^2}{12} e_c \geq Ce_c$$

for some $C > 0$.

So, we can say

$$\|P(e_c)\| \geq C\|e_c\|.$$

Holder Continuity

Holder continuity is usually required in order to establish uniqueness of the solution. Unfortunately, it is not possible to establish Holder continuity for the epithelial equation, even in the non-degenerate case. First note that

$$\begin{aligned}
&\beta(e_{c_1}) - \beta(e_{c_2}) = \frac{e_{c_1}^2}{e_{c_1}^2 + (e_{c,max} - e_{c_1})^2} - \frac{e_{c_2}^2}{e_{c_2}^2 + (e_{c,max} - e_{c_2})^2} \\
&= \frac{(e_{c_1} - e_{c_2})(e_{c,max}^2(e_{c_1} + e_{c_2}) - 2e_{c,max}e_{c_1}e_{c_2})}{(e_{c_1}^2 + (e_{c,max} - e_{c_1})^2))(e_{c_2}^2 + (e_{c,max} - e_{c_2})^2)} \\
&\leq \frac{(e_{c_1} - e_{c_2})(1^2(e_{c_1} + e_{c_2}) - 2(1)e_{c_1}e_{c_2})}{(.5)(.5)} \leq \frac{(e_{c_1} - e_{c_2})(e_{c_1} + e_{c_2})}{.25}.
\end{aligned}$$

In the above, we used the fact that $e_{c_1}, e_{c_2} \geq 0$ and $e_{c,max} = 1$. Now, the best we can get is

$$\left|\beta(e_{c_1})\alpha(b)\nabla e_c - \beta(e_{c_2})\alpha(b)\nabla e_c\right| \leq \left|\alpha(b)\nabla e_c \frac{(e_{c_1} - e_{c_2})(e_{c_1} + e_{c_2})}{.25}\right|.$$

Thus, we cannot establish Holder Continuity.

4.6 NON-DEGENERATE CASE - EXISTENCE OF A SOLUTION.

Here, it will be demonstrated that a solution exists in the non-degenerate case, (4.177). (In this analysis, various standard techniques for analyzing PDEs will be used. Most of the techniques used here may be found in Evans [38] and/or Alt and Luckhaus [4].) Consider the orthonormal basis $\{\psi_i\}_{i=1}^{\infty}$ for $H^1(\Omega)$. We will look for a solution to (4.177) of the form:

$$e_{c_m} := \sum_{i=1}^{m} \xi_i \psi_i \tag{4.181}$$

where ξ_i for $i = 1, ..., m$ is a function of t only.

Substituting into:

$$\frac{\partial e_c}{\partial t} - \nabla \cdot (a(\nabla e_c, e_c)) \ = f_{e_c}(e_c, b, n_a)$$

multiplying by the basis functions ψ_j and integrating by parts, we get:

$$\left(\frac{\partial e_c}{\partial t}, \psi_j\right) + (a(\nabla e_{c_m}, e_{c_m}), \nabla \psi_j) \ = (f_{e_{c_m}}, \psi_j)$$

for $j = 1, ..., m$.

Consider the time interval $[0, h]$ for small h. Use backward Euler in place of the time derivative in the previous equation.

$$\left(\frac{e_{c_m}(t) - e_{c_m}(t-h)}{h}, \psi_j\right) + (a(\nabla e_{c_m}, e_{c_m}), \nabla \psi_j) \ = (f_{e_{c_m}}, \psi_j).$$

We can say,

$$\left(\frac{e_{c_m}(t) - e_c(0)}{h}, \psi_j\right) + (a(\nabla e_{c_m}, e_{c_m}), \nabla \psi_j) \ = (f_{e_{c_m}}, \psi_j).$$

Now define: $\mathbf{C} := (\xi_1, ..., \xi_m)$ and define:

$$v_j(\mathbf{C}) := \left(\frac{e_{c_m}(t) - e_c(0)}{h}, \psi_j\right) + (a(\nabla e_{c_m}, e_{c_m}), \nabla \psi_j) \ - (f_{e_{c_m}}, \psi_j).$$

Then $\mathbf{v}_m = (v_1, ..., v_m)$.

$$\begin{aligned}
\mathbf{v}_m(\mathbf{C}) \cdot \mathbf{C} &= \left(\frac{e_{c_m}(t) - e_{c_m}(0)}{h}, e_{c_m}\right) + (a(\nabla e_{c_m}, e_{c_m}), \nabla e_{c_m}) \ - (f_{e_{c_m}}, e_{c_m}) \\
&\geq \left(\frac{e_{c_m}(t)}{h}, e_{c_m}\right) - \left(\frac{e_{c_m}(0)}{h}, e_{c_m}\right) + c_1 \|\nabla e_{c_m}\|^2 \ - c_2 \|e_{c_m}\|^2 \\
&\geq \frac{1}{h}|\mathbf{C}|^2 - \frac{1}{2h}\|e_{c_m}(0)\|^2 - \frac{1}{2h}\|e_{c_m}\|^2 + c_1 \|\nabla e_{c_m}\|^2 \ - c_2 \|e_{c_m}\|^2 \\
&= \frac{1}{2h}(|\mathbf{C}|^2 - \|e_{c_m}(0)\|^2) + c_1 |\mathbf{C}|^2 \ - c_2 |\mathbf{C}|^2.
\end{aligned}$$

Note that $\|e_{c_m}(0)\|^2$ is known. Now choose $\mathbf{C}$ so that $|\mathbf{C}|^2 - \|e_{c_m}(0)\|^2 > 0$, then take h small enough so that the right hand side becomes positive. Thus, $\mathbf{v}_m(\mathbf{C}) \cdot \mathbf{C} \geq 0$ for $|\mathbf{C}| > 0$.

Therefore, there exists a solution $\mathbf{C}$ to $\mathbf{v}_m(\mathbf{C}) = 0$ on the interval $[0, h]$. So, there exists a solution at $t = h$. Therefore, the same process may be applied to the interval $[h, h + k]$, etc. In this way, a solution may be established on $[0, T]$.

Thus, there exists a solution e_{c_m} of the form (4.181) to the equation:

$$\left(\frac{\partial e_{c_m}}{\partial t}, \psi_j\right) + (a(\nabla e_{c_m}, e_{c_m}), \nabla \psi_j) \ = (f_{e_{c_m}}, \psi_j) \ \text{ for } j = 1, ..., m. \tag{4.182}$$

Now, it will be necessary to bound the sequences that appear in this equation. Using (4.182) we can say:

$$\left(\frac{\partial e_{c_m}}{\partial t}, e_{c_m}\right) + (a(\nabla e_{c_m}, e_{c_m}), \nabla e_{c_m}) \ = (f_{e_{c_m}}, e_{c_m}). \tag{4.183}$$

$$\frac{1}{2}\frac{d}{dt}\|e_{c_m}\|^2 + c_1\|\nabla e_{c_m}\|^2 \ \leq (f_{e_{c_m}}, e_{c_m}) \leq \|f_{e_{c_m}}\|\|e_{c_m}\| \leq c_2\|e_{c_m}\|^2.$$

$$\|e_{c_m}\|^2 + 2c_1\int_0^T \|\nabla e_{c_m}\|^2 \ \leq \|e_{c_m}\|^2(0) + 2c_2\int_0^T \|e_{c_m}\|^2.$$

Apply the Gronwall Inequality, theorem 4.8,:

$$\sup_{0\leq t\leq T}\|e_{c_m}\|^2 + c_1\int_0^T \|\nabla e_{c_m}\|^2 \ \leq c_3\|e_{c_m}\|^2(0).$$

So,

$$\{e_{c_m}\}_{m=1}^{\infty} \text{ is bounded in } L^\infty(0, T; L^2(\Omega)) \tag{4.184}$$

$$\{\nabla e_{c_m}\}_{n=1}^{\infty} \text{ is bounded in } L^2(0, T; L^2(\Omega)). \tag{4.185}$$

Putting (4.184) and (4.185) together, we have

$$\{e_{c_m}\}_{m=1}^{\infty} \text{ is bounded in } L^2(0, T; H^1(\Omega)). \tag{4.186}$$

In order to bound the time derivative consider,

$$(e_{c_{m_t}}, \psi_j) + (a(\nabla e_{c_m}, e_{c_m}), \nabla \psi_j) \ = (f_{e_{c_m}}, \psi_j).$$

Here we will use a technique given by Evans [38]. Fix $v \in H^1(\Omega)$ with $\|v\|_{H^1(\Omega)} \leq 1$ where $v = v^1 + v^2$. With the the property $v^1 \in \text{span}\{\psi_j\}_{j=1}^m$ and $(v^2, \psi_j) = 0$ for all j. Now,

$$\begin{aligned}(e_{c_{m_t}}, v^1) + (a(\nabla e_{c_m}, e_{c_m}), \nabla v^1) &= (f_{e_{c_m}}, v^1)\\ (e_{c_{m_t}}, v^1) &= -(a(\nabla e_{c_m}, e_{c_m}), \nabla v^1) + (f_{e_{c_m}}, v^1).\end{aligned}$$

Since $e_{c_{m_t}}$ is in $\text{span}\{\psi_j\}_{k=1}^m$, we have $(e_{c_{m_t}}, v^2) = 0$. So,

$$\begin{aligned}(e_{c_{m_t}}, v) &= -(a(\nabla e_{c_m}, e_{c_m}), \nabla v^1) + (f_{e_{c_m}}, v^1)\\ |(e_{c_{m_t}}, v)| &\leq \|\nabla e_{c_m}\|\|\nabla v^1\| + \|f_{e_{c_m}}\|\|v^1\|\\ |(e_{c_{m_t}}, v)| &\leq \|\nabla e_{c_m}\|\|v^1\|_{H^1(\Omega)} + \|f_{e_{c_m}}\|\|v^1\|_{H^1(\Omega)}\\ |(e_{c_{m_t}}, v)| &\leq \|\nabla e_{c_m}\| + \|f_{e_{c_m}}\|.\end{aligned}$$

Since this last inequality is true for all $\|v\|_{H^1(\Omega)} \leq 1$, we have

$$\begin{aligned}\|e_{c_{m_t}}\|_{H^{-1}(\Omega)} &\leq \|\nabla e_{c_m}\| + \|f_{e_{c_m}}\|\\ \int_0^T \|e_{c_{m_t}}\|_{H^{-1}(\Omega)} &\leq \int_0^T \|\nabla e_{c_m}\| + \int_0^T \|f_{e_{c_m}}\|.\end{aligned}$$

So,

$$\left\{\frac{d}{dt} e_{c_m}\right\}_{n=1}^{\infty} \text{ is bounded in } L^2(0, T; H^{-1}(\Omega)). \tag{4.187}$$

In view of (4.179), we can say $a(\nabla e_{c_m}, e_{c_m}) \leq C|\nabla e_{c_m}|$. So, by (4.185),

$$\{a(\nabla e_{c_m}, e_{c_m})\}_{m=1}^{\infty} \text{ is bounded in } L^2(0, T; L^2(\Omega)). \tag{4.188}$$

Thus, by (4.184),(4.185),(4.187), and (4.188) the solution to (4.182) is bounded, i.e., $\{e_{c_m}\}_{n=1}^{\infty}, \{\nabla e_{c_m}\}_{n=1}^{\infty}, \left\{\frac{d}{dt} e_{c_m}\right\}_{n=1}^{\infty}$ and $\{a(\nabla e_{c_m}, e_{c_m})\}_{m=1}^{\infty}$ are all bounded.

Therefore, there exists a subsequence $\{e_{c_{m_L}}\}_{L=1}^{\infty}$ of $\{e_{c_m}\}_{m=1}^{\infty}$ that converges weakly to some y_1 and such that $\{\frac{d}{dt} e_{c_{m_L}}\}_{L=1}^{\infty}$ converges weakly to some y_2.

Now, we must show that y_2 is the weak derivative of y_1. That is, we must show that (see Evans [38], page 285.):

$$\int_0^T \frac{dh}{dt} y_1 \, dt = -\int_0^T h y_2 \, dt$$

for all test functions $h \in C_c^{\infty}(0, T)$.

So, let $h \in C_c^\infty(0,T)$ and $w \in H^1(\Omega)$

$$\left(\int_0^T \frac{dh}{dt} y_1 \, dt, w \right) = \int_0^T \left(\frac{dh}{dt} y_1, w \right) dt = \int_0^T \left(y_1, \frac{dh}{dt} w \right) dt$$
$$= \lim_{L\to\infty} \int_0^T \left(e_{c_{m_L}}, \frac{dh}{dt} w \right) dt = \lim_{L\to\infty} \left(\int_0^T e_{c_{m_L}} \frac{dh}{dt} \, dt, w \right)$$
$$= \lim_{L\to\infty} \left(- \int_0^T h \frac{de_{c_{m_L}}}{dt} \, dt, w \right) = \left(- \int_0^T h y_2 \, dt, w \right).$$

Here, change the name y_1 to e_c and change y_2 to $\frac{d}{dt} e_c$.

In order to deal with the convergence of $a()$, we will use the method of Browder and Minty. This method is usually applied to elliptic equations (see for example Zhang [142]) but here we will apply it to our parabolic equation following the same basic steps.

By (4.184),(4.185),(4.187), and (4.188) we know that there exists an a^* such that $a(\nabla e_{c_{m_L}}, e_{c_{m_L}}) \to a^*$ weakly. So that we can say

$$\left(\frac{\partial e_{c_m}}{\partial t}, \psi_j \right) + (a^*, \nabla \psi_j) \ = (f_{e_{c_m}}, \psi_j). \tag{4.189}$$

is satisfied for each j. So,

$$\left(\frac{\partial e_{c_m}}{\partial t}, w \right) + (a^*, \nabla w) \ = (f_{e_{c_m}}, w). \tag{4.190}$$

From monotonicity we have

$$\begin{aligned} &((a(\nabla e_{c_m}, e_{c_m}) - a(\nabla w, w)), (\nabla e_{c_m} - \nabla w)) \geq 0 \\ &(a(\nabla e_{c_m}, e_{c_m}), \nabla e_{c_m}) - (a(\nabla e_{c_m}, e_{c_m}), \nabla w) \\ &\qquad -(a(\nabla w, w), \nabla e_{c_m}) + (a(\nabla w, w) \cdot \nabla w)) \geq 0. \end{aligned} \tag{4.191}$$

Now, recall (4.183),

$$(a(\nabla e_{c_m}, e_{c_m}), \nabla e_{c_m}) \ = (f_{e_{c_m}}, e_{c_m}) - \left(\frac{\partial e_{c_m}}{\partial t}, e_{c_m} \right). \tag{4.192}$$

Substitute (4.192) into (4.191) to get:

$$(f_{e_{c_m}}, e_{c_m}) - \left(\frac{\partial e_{c_m}}{\partial t}, e_{c_m}\right) - (a(\nabla e_{c_m}, e_{c_m}), \nabla w) \\ -(a(\nabla w, w), \nabla e_{c_m}) + (a(\nabla w, w), \nabla w)) \geq 0.$$

Substituting the subsequences $\{e_{c_{m_L}}\}$ and taking limits gives:

$$(f_{e_{c_m}}, e_c) - \left(\frac{\partial e_c}{\partial t}, e_c\right) - (a^*, \nabla w) \\ -(a(\nabla w, w), \nabla e_c) + (a(\nabla w, w), \nabla w)) \geq 0. \tag{4.193}$$

In (4.190) set $w = e_c$ to get

$$(f_{e_{c_m}}, e_c) - \left(\frac{\partial e_{c_m}}{\partial t}, e_c\right) \;=\; (a^*, \nabla e_c). \tag{4.194}$$

Substituting this into (4.193), we get

$$(a^*, \nabla e_c) - (a^*, \nabla w) - (a(\nabla w, w), \nabla e_c) + (a(\nabla w, w), \nabla w)) \geq 0$$
$$(a^*, \nabla e_c - \nabla w) + (a(\nabla w, w), \nabla w - \nabla e_c) \geq 0$$
$$(a^* - a(\nabla w, w), \nabla e_c - \nabla w) \geq 0.$$

For $v \in H^1(\Omega)$ we set $w := e_c - (1/n)v$ where n is a natural number, and get

$$\left(a^* - a\Big(\nabla e_c - \frac{1}{n}\nabla v, e_c - \frac{1}{n}v\Big), \nabla e_c - \nabla e_c + \frac{1}{n}\nabla v\right) \geq 0$$
$$\left(a^* - a\Big(\nabla e_c - \frac{1}{n}\nabla v, e_c - \frac{1}{n}v\Big), \frac{1}{n}\nabla v\right) \geq 0$$
$$\left(a^* - a\Big(\nabla e_c - \frac{1}{n}\nabla v, e_c - \frac{1}{n}v\Big), \nabla v\right) \geq 0.$$

Now take $\lim_{n\to\infty}\ 1/n$, to get

$$(a^* - a(\nabla e_c, e_c), \nabla v) \geq 0. \tag{4.195}$$

Using the same $v \in H^1(\Omega)$ and set $w := e_c + (1/n)v$ where n is a natural number, we get

$$\left(a^* - a\Big(\nabla e_c + \frac{1}{n}\nabla v, e_c + \frac{1}{n}v\Big), \nabla e_c - \nabla e_c - \frac{1}{n}\nabla v\right) \geq 0$$
$$\left(a^* - a\Big(\nabla e_c + \frac{1}{n}\nabla v, e_c + \frac{1}{n}v\Big), -\frac{1}{n}\nabla v\right) \geq 0$$
$$-\left(a^* - a\Big(\nabla e_c + \frac{1}{n}\nabla v, e_c + \frac{1}{n}v\Big), \nabla v\right) \geq 0.$$

Now take $\lim_{n\to\infty}\ 1/n$, to get

$$-(a^* - a(\nabla e_c, e_c), \nabla v) \geq 0 \quad \text{or} \quad (a^* - a(\nabla e_c, e_c), \nabla v) \leq 0. \tag{4.196}$$

Putting (4.195) and (4.196) together we see that

$$(a^* - a(\nabla e_c, e_c), \nabla v) = 0. \tag{4.197}$$

Thus, we conclude that $a^* = a(\nabla e_c, e_c)$. So, we can substitute $a^* = a(\nabla e_c, e_c)$ into (4.189).

For the rest, we will follow the standard techniques used for a linear parabolic PDE, (see, for example, Evans page 357 [38]):

Now, fix P and choose:

$$w := \sum_{i=1}^{P} c_i \psi_i \tag{4.198}$$

where c_i for $i = 1, ..., m$ is a function of t only.

Multiply

$$(e_{c_{m_t}}, \psi_j) + (a(\nabla e_{c_m}, e_{c_m}), \nabla \psi_j) \ = (f_{e_{c_m}}, \psi_j) \tag{4.199}$$

by c_j to get:

$$(e_{c_{m_t}}, c_j\psi_j) + (a(\nabla e_{c_m}, e_{c_m}), \nabla c_j\psi_j) \ = (f_{e_{c_m}}, c_j\psi_j).$$

Summing $j = 1, ..., P$ gives:

$$(e_{c_{m_t}}, w) + (a(\nabla e_{c_m}, e_{c_m}), \nabla w) \ = (f_{e_{c_m}}, w).$$
$$\int_0^T (e_{c_{m_t}}, w) + \int_0^T (a(\nabla e_{c_m}, e_{c_m}), \nabla w) \ = \int_0^T (f_{e_{c_m}}, w).$$

Substituting subsequences $\{e_{c_{m_L}}\}$ and take limits to find that

$$\int_0^T (e_{c_t}, w) + \int_0^T (a(\nabla e_c, e_c), \nabla w) \ = \int_0^T (f_{e_c}, w).$$

Thus, **there exists a weak solution in the non-degenerate case,(4.177).**

4.7 DEGENERATE CASE

As noted above, the degenerate case has been studied by others. Therefore, we will begin by noting the results of these authors. After that, we will establish some regularity.

Near the beginning of this chapter, we put our equation into the form of (4.177) so that we may apply the work done by Alt and Luckhaus [4] as well as work by Otto [105]. We will use these works directly as well as Arbogast, Wheeler, and Zhang's [7] interpretation of the work by Alt and Luckhaus.

Alt and Luckhaus analyze the following PDE in their paper.

$$\frac{\partial b^j(u)}{\partial t} - \nabla \cdot (a^j(b(u), \nabla u)) \ = f^j(b(u)). \tag{4.200}$$

Alt and Luckhaus identify the solution space for this type of equation as:

$$\int_0^T \int_\Omega (\Psi(b(u)) + |\nabla u|^r < \infty$$

where

$$\Psi(z) := \sup_{\sigma \in R} \int_0^\sigma (z - b(s)) ds.$$

In our case, $b(e_c)$ is just the identity function. So,

$$\Psi(b(e_c)) = \Psi(e_c) = \frac{e_c^2}{2}.$$

Therefore, our growth condition, (4.180), may be written as:

$$|a(\nabla e_c, e_c)|^2 + |f_{e_c}(e_c)|^2 \leq C(1 + |\nabla e_{c_1}|^2 + \Psi(e_c)). \tag{4.201}$$

4.7.1 Degenerate Case - Regularity

Therefore, based on the conditions listed above and the assumption that for (4.174) we have $f_{e_c} \in L_2\{(0,T]; L_2(\Omega)\}$, then according to Arbogast, Wheeler, and Zhang [7], the epithelial PDE has a solution with:

$$e_c \in L_\infty\{(0,T]; L_1(\Omega)\} \qquad \frac{\partial e_c}{\partial t} \in L_2\{(0,T]; H^{-1}(\Omega)\} \tag{4.202}$$

$$\mathbf{z} \in L_2\{(0,T]; (L_2(\Omega))^3\}. \tag{4.203}$$

Now, we will attempt to establish higher regularity as well as regularity for the mixed weak form.

4.7.2 Degenerate Case - Regularity of the Weak Form

Note that (4.202) and (4.203) give the minimum regularity for the degenerate parabolic equation. It is normal to assume more regularity than what is given in (4.202). In fact, Arbogast, Wheeler, and Zhang [7] themselves as well as well as Woodward and Dawson [141] assume more regularity than (4.202). Here, the following regularity will be assumed:

$$e_c \in L_2\{(0,T]; L_2(\Omega)\} \qquad \frac{\partial e_c}{\partial t} \in L_2\{(0,T]; L_2(\Omega)\}. \tag{4.204}$$

Using this as a starting point, more regularity will be developed here.

To begin with, we may use (4.176) along with (4.204) to get:

$$P(e_c) \in L^2(0,T; L^2(\Omega)). \tag{4.205}$$

Weak Mixed Form

Recalling (4.174)

$$\frac{\partial e_c}{\partial t} - \nabla \cdot (\alpha(b) \nabla P(e_c)) \ = f_{e_c}(e_c, b, n_a). \tag{4.206}$$

Set $\alpha^{-1}\mathbf{z} = \nabla P(e_c)$. Then the weak form becomes

$$(e_{c_t}, w) + (\nabla \cdot \mathbf{z}, w) \ = (f_{e_c}(e_c, b, n_a), w) \tag{4.207}$$

$$(\alpha^{-1}\mathbf{z}, v) = (-\nabla P(e_c), v). \tag{4.208}$$

In the weak system (4.207), (4.208), integrate the second equation (4.208) by parts then set $w = P(e_c)$ and $v = \mathbf{z}$:

$$(e_{c_t}, P(e_c)) + (\nabla \cdot \mathbf{z}, P(e_c)) \ = (f_{e_c}, P(e_c))$$

$$(\alpha^{-1}\mathbf{z}, \mathbf{z}) = (P(e_c), \nabla \cdot \mathbf{z}).$$

Combining these and applying the Cauchy-Schwarz inequality (theorem 4.7) we get,

$$C\|\mathbf{z}\|^2 \ \leq \|f_{e_c}\|\|P(e_c)\| + \|e_{c_t}\|\|P(e_c)\|.$$

Apply Cauchy's inequality (theorem 4.6):

$$\|\mathbf{z}\|^2 \leq C\bigg(\|f_{e_c}\|^2 + \|P(e_c)\|^2 + \|e_{c_t}\|^2\bigg). \tag{4.209}$$

Integrate (4.209) then using (4.176), (4.178), (4.204), and (4.205)

$$\begin{aligned}\int_0^t \|\mathbf{z}\|^2 &= C\int_0^t \bigg(\|f_{e_c}\|^2 + \int_0^t \|P(e_c)\|^2 + \int_0^t \|e_{c_t}\|^2\bigg) \\ &\leq C\int_0^t \bigg(\|f_{e_c}\|^2 + \int_0^t \|e_c\|^2 + \int_0^t \|e_{c_t}\|^2\bigg)\end{aligned}$$

we can say

$$\mathbf{z} \in L^2(0,T;(L^2(\Omega))^3). \tag{4.210}$$

In (4.207), set $w = \nabla \cdot \mathbf{z}$

$$(e_{c_t}, \nabla\cdot\mathbf{z}) + (\nabla\cdot\mathbf{z}, \nabla\cdot\mathbf{z}) = (f_{e_c}, \nabla\cdot\mathbf{z}).$$

Apply the Cauchy-Schwarz inequality (theorem 4.7)

$$\|\nabla\cdot\mathbf{z}\|^2 \leq \|f_{e_c}\|\|\nabla\cdot\mathbf{z}\| + \|e_{c_t}\|\|\nabla\cdot\mathbf{z}\|.$$

Apply Cauchy's inequality (theorem 4.6) and hide terms:

$$\|\nabla\cdot\mathbf{z}\|^2 \leq C\bigg(\|f_{e_c}\|^2 + \|e_{c_t}\|^2\bigg). \tag{4.211}$$

Integrate (4.211)

$$\int_0^t \|\nabla\cdot\mathbf{z}\|^2 = C\int_0^t \bigg(\|f_{e_c}\|^2 + \|e_{c_t}\|^2\bigg) \tag{4.212}$$

using (4.204), we have

$$\nabla\cdot\mathbf{z} \in L^2(0,T;L^2(\Omega)). \tag{4.213}$$

In (4.207), set $w = e_c$

$$(e_{c_t}, e_c) + (\nabla\cdot\mathbf{z}, e_c) = (f_{e_c}, e_c).$$

Cauchy-Schwarz inequality (theorem 4.7),

$$\frac{1}{2}\frac{d}{dt}\|e_c\|^2 \ = \|f_{e_c}\|\|e_c\| + \|\nabla \cdot \mathbf{z}\|\|e_c\|.$$

Cauchy's inequality (theorem 4.6):

$$\frac{d}{dt}\|e_c\|^2 \ = C\|f_{e_c}\|^2 + C\|e_c\|^2 + C\|\nabla \cdot \mathbf{z}\|^2.$$

Integrate from 0 to T:

$$\|e_c\|^2(t) \ = C\int_0^T \|f_{e_c}\|^2 + C\int_0^T \|e_c\|^2 + C\int_0^T \|\nabla \cdot \mathbf{z}\|^2 + \|e_c\|^2(0).$$

apply the Gronwall Inequality, theorem 4.8,

$$\sup_{0\le t\le T} \|e_c\|^2(t) \ = C\left(\int_0^T \|f_{e_c}\|^2 + \int_0^T \|\nabla \cdot \mathbf{z}\|^2 + \|e_c\|^2(0)\right). \tag{4.214}$$

Using (4.178) and (4.213) in (4.214) gives

$$e_c \in L^\infty(0,T;L^2(\Omega)). \tag{4.215}$$

4.8 ANALYSIS OF PDES IN PART III

In this section, we will consider the $ZO1$ equation. Recall,

$$\frac{\partial ZO1}{\partial t} = \left(k_{Z_{e_c}} e_c + k_{Z_{e_{ct}}} \frac{\partial e_c}{\partial t}\right) ZO1_{max}(1 - ZO1/zec) - k_{ZN} NO \cdot ZO1$$

where

$$zec = (1 - \epsilon_{zec}) ZO1_{max} + \epsilon_{zec} \left(\frac{ZO1_{max}}{e_{c,max}}\right) e_c$$

We will show that this equation has a solution by explicitly finding the solution.

In order to simplify the notation we will replace all of the parameters with their actual values:

$$ZO1_t + \left(\frac{.03e_c + 2e_{c_t}}{.95 + .05e_c} + .75NO\right) ZO1 = .03e_c + 2e_{c_t}$$

We will solve this using an integrating factor

$$I^* = e^{\int_0^t ((.03e_c + 2e_{c_t})/(.95 + .05e_c) + .75NO)\, dt} = e^{(1/.05)(.03t + 2\ln(.95 + .05e_c) - .03 \int_0^t .95/(.95 + .05e_c) + \int_0^t .75NO)}$$

If we apply I^* to our differential equation, we get:

$$I^* ZO1 = \int_0^t I^*(.03e_c + 2e_{c_t})\, dt + IC$$

$$ZO1 = \frac{\int_0^t I^*(.03e_c + 2e_{c_t})\, dt + IC}{I^*} \tag{4.216}$$

$$\|ZO1\|_\infty \leq \left\| \frac{\int_0^t I^*(.03e_c + 2e_{c_t})\, dt}{I^*} \right\|_\infty + \left\| \frac{IC}{I^*} \right\|_\infty . \tag{4.217}$$

We proved in PDE Analysis Part I that $NO \in W^{1,2}([0,T]; L^2(\Omega))$ thus I^* is just a number. Therefore, (4.216) implies that the ZO equation has a solution and (4.217) indicates that $ZO \in L^\infty(\Omega)$. In the appendix it is demonstrated that the right hand side functions of each of the equations in Part I are Lipschitz continuous. Lipschitz continuity is a necessary condition for the numerical analysis that will done later in the thesis.

Equation	**Regularity**	**Equation**	**Regularity**
Bacteria	$b \in L^2(0,T;H^3(\Omega))$	Nitric Oxide	$NO \in L^2(0,T;H^3(\Omega))$
Macrophage	$m \in L^2(0,T;H^3(\Omega))$	Tight Junction	$ZO1 \in C([0,T];H^2(\Omega))$
Activated Macrophage	$m_a \in C([0,T];H^2(\Omega))$	Activated Neutrophils	$n_a \in C([0,T];H^2(\Omega))$
Cytokine	$c \in L^2(0,T;H^3(\Omega))$	Damage	$d \in L^2(0,T;H^3(\Omega))$
Anti-Infl. Cytokine	$c_a \in L^2(0,T;H^3(\Omega))$	Epithelial	$e_c \in L^\infty(0,T;L_2(\Omega))$ $e_{c_t} \in L^2(0,T;H^{-1}(\Omega))$ $\mathbf{z} \in L^2(0,T;((L^2(\Omega))^3)$ $\nabla \cdot \mathbf{z} \in L^2(0,T;L^2(\Omega))$

Table 2: Regularity of the weak solution of the NEC PDE system.

5.0 FINITE ELEMENT ANALYSIS (CONVERGENCE ANALYSIS FOR THE FULLY COUPLED SYSTEM OF PDES)

The purpose of this chapter is to prove that the numerical approximation of the PDE system using the mixed finite element method will converge to the true solution of the system. For each of the ten variables in our NEC PDE system, it will be demonstrated that the numerical error $v - v_h$ is bounded, in some norm, by some power of h multiplied by a constant not dependent upon h. This will then show that as h gets smaller, the numerical error gets smaller and convergence to the true solution may be achieved.

Much of the analysis in this chapter, particularly the analysis for the eight equations in Part I of the PDE system, is new. In particular, no mixed finite element method exists for the particular type of coupled equations, represented by the system (5.6), (5.7) below. There does exist a mixed finite element method for a similar equation:

$$\frac{\partial u_1}{\partial t} - \nabla \cdot (u_1 u_2 - D \nabla u_1) \;=\; f_1(u_1) \tag{5.1}$$

(see Dawson[30] and Vassilev and Yotov[133]). However, in (5.1) u_2 is the Darcy velocity, a known quantity, which makes the analysis somewhat simpler than what we will have in our system, (5.6), (5.7) below. On the other hand, Epshteyn and Kurganov [37] do a finite element analysis on a coupled system very similar to our system. However, they use a discontinuous Galerkin finite element method, a method somewhat different from the mixed finite element method. Furthermore, the solution in this last paper was found in an unbounded space, we will find the solution in a bounded space. In any case, our analysis will utilize some ideas from each of the above mentioned papers.

A mixed finite element method for an equation very similar to the equation in Part II has been done in Arbogast, Wheeler, and Zhang [7]. Therefore, the analysis of the Part II

equation will not add anything new to the general knowledge. Yet, in order that the analysis for all of the equations in the NEC PDE system are included in this thesis, the analysis for the Part II equation will be done here. Of course, our analysis will closely follow Arbogast, Wheeler, and Zhang.

The Part III equation, although unique, does not pose any significant challenges. The analysis of the Part III equation is presented below.

The numerical analysis on the NEC PDE system will be done in three parts, according to the natural grouping of the types of PDEs. This grouping is identical to the grouping listed in the PDE analysis chapter. For convenience, that listing is repeated here:

Part I. Part I will consist of eight equations: the equations for bacteria, macrophages, activated macrophages, cytokines, anti-inflammatory cytokines, nitric oxide, activated neutrophils, and damage.

$$\frac{\partial b}{\partial t} - \nabla \cdot D_b \nabla b = k_{bg} b(1 - b/b_{max}) - k_b b/(1 + b/\epsilon) - R(c_a)(k_{bm_a} m_a b + k_{bn_a} n_a b) - k_{pp} b$$

$$\frac{\partial m}{\partial t} = k_m(m_{max} - m) - R(c_a)(k_{mb} bm + k_{mc} cm + k_{md} dm)$$

$$\frac{\partial m_a}{\partial t} - \nabla \cdot (D_{m_a} \nabla m_a - \gamma_{m_a c} m_a \nabla c - \gamma_{m_a b} R(c_a) m_a \nabla b) = -k_{m_a} m_a + R(c_a)(k_{mb} bm + k_{mc} cm + k_{md} dm)$$

$$\frac{\partial c}{\partial t} - \nabla \cdot D_c \nabla c = -k_c c + R(c_a)(k_{cm_a} m_a + k_{cn_a} n_a) - R(c_a)(k_{nc} cn + k_{mc} cm)$$

$$\frac{\partial c_a}{\partial t} - \nabla \cdot D_{c_a} \nabla c_a = -k_{c_a} c_a + s_{c_a} + k_{c_a P} \frac{Q}{1 + Q}$$

$$\frac{\partial NO}{\partial t} - \nabla \cdot D_{NO} \nabla NO = -k_{NO} NO + k_{NOm_a} \frac{m_a^{q_1}}{1 + (m_a/\overline{m}_a)^{q_1}} + k_{NOn_a} \frac{n_a^{q_1}}{1 + (n_a/\overline{n}_a)^{q_1}}$$

$$\frac{\partial n_a}{\partial t} \; - \; \nabla \cdot (D_{n_a} \nabla n_a - \gamma_{n_a c} n_a \nabla c) = -k_{n_a} n_a + R(c_a)(k_{nc} cn + k_{nd} dn)$$

$$\frac{\partial d}{\partial t} \; - \; \nabla \cdot D_d \nabla d \; = \; -k_d d + k_{dc} \frac{T^{q_2}}{x_{dc}^{q_2} + T^{q_2}}$$

where

$$R(c_a) = \frac{1}{1 + k_{Rc_a}(c_a/\bar{c}_a)^2} \qquad T = R(c_a)c$$
$$Q = R(c_a)(k_{c_a m_a n_a} n_a + m_a + k_{c_a m_a d} d).$$

Part II. Part II will consist of the epithelial equation:

$$\frac{\partial e_c}{\partial t} + \nabla \cdot (\beta(e_c)\mathbf{u}(e_c, b)) = k_p e_c (1 - e_c/e_{c,max}) - k_a(n_a, c, b) e_c$$

where

$$k_a(n_a, c, b) = \frac{e_{ca}(n_a, c, b)^{q_0}}{e_{ca}(n_a, c, b)^{q_0} + [e_{ca}(n_{a,max}, c_{max}, b_{max}) - e_{ca}(n_a, c, b)]^{q_0}}$$

$$e_{ca}(n_a, c, b) = n_a + k_{e_c n_a c} c + k_{e_c n_a b} b$$

$$\beta(e_c) = \frac{e_c^2}{e_c^2 + (e_{c,max} - e_c)^2}$$

$$\mathbf{u}(e_c, b) = -\alpha(b) \nabla e_c \qquad \alpha(b) = \frac{(b_{max} - b)^q}{(b_{max} - b)^q + b^q}.$$

Part III. Part III consists of the tight junction protein equation:

$$\frac{\partial ZO1}{\partial t} \; = \; \left(k_{Z_{e_c}} e_c + k_{Z_{e_{ct}}} \frac{\partial e_c}{\partial t}\right) ZO1_{max}(1 - ZO1/zec) - k_{ZN} NO \cdot ZO1$$

$$\text{where} \qquad zec = (1 - \epsilon_{zec}) ZO1_{max} + \epsilon_{zec} \left(\frac{ZO1_{max}}{e_{c,max}} \right) e_c.$$

Note that the tensor D in each of the equations in Part I depends upon the equation in Part II. In the analysis of this chapter, this dependence will be neglected. The equations in Part I do not depend at all on the equation in Part III. Therefore, the error bounds for

the aforementioned eight equations in Part I may be found independently of the equations in Part II and Part III. These error bounds are derived in **Analysis of PDEs in Part I**.

Notice that the equation in Part II (the epithelial equation) depends on the equations from part I but does not depend on the equation in Part III (the tight junction protein equation). Therefore, error bounds found in part I may be used to bound the error for the epithelial cells. This study is done in **Analysis of PDEs in Part II**.

The equation in Part III (the tight junction protein equation) depends upon the equations in Part I and Part II. Therefore, error bounds found in part I and Part II may be used to bound the error for the tight junction protein. This study is done in **Analysis of PDEs in Part III**.

Strategy for demonstrating convergence. In order to prove convergence of the numerical approximation to the true solution for the NEC PDE system, it will be necessary to determine the convergence rates in a specific order. First, the convergence rates for the PDEs in Part I of the PDE system will be determined. It is most logical to analyze the Part I equations first because they are not dependent upon the equations in Part II and III. The convergence rate of the Part I equations will be shown to be in some power of h in terms of the L^2 norm for each of the variables in Part I. Next, the equation in Part II, the epithelial equation, will be analyzed. This equation is dependent upon three equations from Part I. Namely, the bacteria, activated neutrophil and cytokine equations. Therefore, the error bounds found in Part I for these three equations will be used to find the error bound for the numerical approximation of the epithelial equation of Part II. However, due to the fact that the epithelial equation is degenerate parabolic, the numerical error will be bounded in terms of the H^{-1} norm. Existing tools do not allow us to bound this error in any stronger norm. Finally, the equation in Part III, the ZO1 equation, will be analyzed. The ZO1 equation is dependent upon an equation from Part I, the NO equation, and the epithelial equation from Part II. Since the numerical error for epithelial equation can only be bounded in the H^{-1} norm, it will not be possible to bound the ZO1 error in the L^2 norm. Instead, a bound for the $ZO1$ error will be found in the H^{-1} norm. Thus, convergence for the fully coupled system will be demonstrated in this chapter.

5.1 CONDITIONS AND NOTATION FOR FEM SECTION.

Let Ω be a bounded domain in $\mathtt{R}^d$ where $d = 1, 2$ or 3. Let $(\cdot, \cdot)$ denote the $L_2(\Omega)$ inner product and $\|\cdot\|$ the $L_2(\Omega)$ norm. Define the spaces

$$W = L^2(\Omega) \quad V = H(\mathrm{div}; \Omega) \quad V^0 = V \cap \{v : v \cdot \mathbf{n} = 0 \text{ on } \Gamma\}.$$

Let τ_h be a quasiuniform family of finite element partitions of Ω. Such that for $E \in \tau_h$,

$$h_E = \max_{x,y \in E} \|x - y\|_{\mathtt{R}^d} \qquad h = \max_{h_E \in \tau_h} h_E$$

$$\text{and there exists a } K_{\tau_h} \text{ such that } K_{\tau_h} \geq \frac{h_E}{\rho_E} \quad \forall E \in \tau_h$$

where ρ_E is the diameter of the largest circle (in 3-D, the largest sphere) that will fit inside the element E.

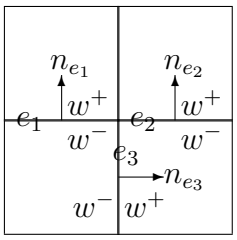
Let W_h, V_h denote mixed finite element approximating subspaces of W and V, respectively, e.g., the Raviart-Thomas-Nedelec [98], [114] finite element spaces. Let $V_h^0 = V_h \cap V^0$. Furthermore, we have:

$$\nabla \cdot V_h = W_h \quad \text{and} \quad \nabla_h W_h \subset (W_h)^n.$$

(Where ∇_h is the element-wise gradient.) The functions u_1 and u_2 are approximated by $u_{1,h} \in W_h$ and $u_{2,h} \in W_h$, respectively. On any element $E \in \tau_h$, $w \in W_h$ is a polynomial, discontinuous across the element boundaries.

In this paper, it will be necessary to utilize two different definitions for the normals to the element boundaries. On each edge, e, in the finite element mesh a **fixed** normal vector, $\mathbf{n}_e$, is assigned. Since this normal is fixed, it will be the same no matter which element is under consideration. Then for any point, x, on each edge, the functions $w^+(x)$ and $w^-(x)$ will be defined as follows

$$w^+(x) = \lim_{c \to 0^+} (w(x + c\mathbf{n}_e)) \qquad\qquad w^-(x) = \lim_{c \to 0^-} (w(x + c\mathbf{n}_e))$$



The 'jump' and 'average' terms will be defined in this way:

$$[w] = w^+ - w^- \qquad \overline{w} = \frac{1}{2}(w^+ + w^-) \qquad \text{in } \Omega.$$

On the boundary, Γ, we will assign $\mathbf{n_e}$ so that it points outward. Thus,

$$[w] = w^- \qquad \overline{w} = w^- \qquad \text{on } \Gamma.$$

In this paper, we also define an outward normal $\mathbf{n}_E$ on each element boundary. When considering any particular element, E, this normal will always point outward. Therefore, its direction will be different depending upon the element under consideration.

We must define the following projections:

1) The "π" or Raviart-Thomas projection. There exists a projection operator $\Pi_h : (H^1(\Omega))^d \to V_h$. If $\mathbf{q} \in (H^1(\Omega))^d$ then $\Pi_h \mathbf{q} \in V_h$ and

$$(\nabla \cdot (\Pi_h \mathbf{q} - \mathbf{q}), w_h) \;=\; 0 \quad \forall w_h \in W_h. \tag{5.2}$$

2) The L^2 projection. There exists a projection operator $Q_h : L_2(\Omega) \to W_h$. If $u \in L^2(\Omega)$ then $Q_h u \in W_h$ and

$$(Q_h u - u, w_h) \;=\; 0 \qquad \forall w_h \in W_h. \tag{5.3}$$

3) The Π_0 projection. If $u \in L^2(\Omega)$ then $\Pi_0 u$ is the projection of u into piecewise constants and

$$(\Pi_0 u - u, 1) \;=\; 0. \tag{5.4}$$

4) Weighted projection. (The weighted projected will be used in the Part II equations.)We define a weighted projection operator $\mathbf{P_h} : (L_2(\Omega))^d \to V_h$. If $\mathbf{v} \in (L^2(\Omega))^d$ then $\mathbf{P}_h\mathbf{v} \in V_h$ and

$$(a(\cdot,t)(\mathbf{P}_h\mathbf{v} - \mathbf{v}), v_h) \;=\; 0 \quad \forall v_h \in V_h. \tag{5.5}$$

($a(\cdot,t)$ will be defined Part II).

Special Notation. In the following sections, we will use $\theta_x = x - \Pi_h x$ and $\psi_x = x_h - \Pi_h x$.

$s_{u_1}, s_{u_2}, s_{\mathbf{z_1}}, s_{\mathbf{z_2}}$ are the regularities of $u_1, u_2, \mathbf{z_1}, \mathbf{z_2}$ respectively in $H^s(\Omega)$.

$s_{u_1,\infty}, s_{u_2,\infty}, s_{\mathbf{z_1},\infty}, s_{\mathbf{z_2},\infty}$ are the regularities of $u_1, u_2, \mathbf{z_1}, \mathbf{z_2}$ respectively in $W^s_\infty(\Omega)$.

$r_{u_1}, r_{u_2}, r_{\mathbf{z_1}}, r_{\mathbf{z_2}}$ are the polynomial degrees of $u_1, u_2, \mathbf{z_1}, \mathbf{z_2}$ respectively.

Approximation Results: In this paper, the following approximation results will be used,

$$\|u_1 - Q_h u_1\|_m \le C\frac{h^{\mu_{u_1}-m}}{r_{u_1}^{s_{u_1}-m}}\|u\|_{s_{u_1}} \qquad \|\nabla\cdot(\mathbf{z_1} - \Pi_h\mathbf{z_1})\|_m \le C\frac{h^{\mu_{\mathbf{z_1}}-m}}{r_{\mathbf{z_1}}^{s_{\mathbf{z_1}}-m}}\|\nabla\cdot\mathbf{z_1}\|_{s_{\mathbf{z_1}}}$$

$$\|u_1 - Q_h u_1\|_{m,\infty} \le C\frac{h^{\mu_{u_1,\infty}-m}}{r_{u_1}^{s_{u_1}-m}}\|u\|_{s_{u_1},\infty}$$

$$\|u_2 - Q_h u_2\|_m \le C\frac{h^{\mu_{u_2}-m}}{r_{u_2}^{s_{u_2}-m}}\|u\|_{s_{u_2}} \qquad \|\nabla\cdot(\mathbf{z_2} - \Pi_h\mathbf{z_2})\|_m \le C\frac{h^{\mu_{\mathbf{z_2}}-m}}{r_{\mathbf{z_2}}^{s_{\mathbf{z_2}}-m}}\|\nabla\cdot\mathbf{z_2}\|_{s_{\mathbf{z_2}}}$$

$$\|u_2 - Q_h u_2\|_{m,\infty} \le C\frac{h^{\mu_{u_2,\infty}-m}}{r_{u_2}^{s_{u_2}-m}}\|u\|_{s_{u_2},\infty}$$

$$\text{for } 0 \le m \le \mu_\alpha.$$

In the above we have $\mu_\alpha = \min(r_\alpha + 1, s_\alpha)$ and $\mu_{\alpha,\infty} = \min(r_\alpha + 1, s_{\alpha,\infty})$
where $\alpha = u_1, u_2, \mathbf{z_1},$ or $\mathbf{z_2}$ as appropriate.

Inverse Inequalities:

For any polynomial, w, we have

$$\|w\|_\infty \le Ch^{-1}\|w\| \qquad \|w\|_{H^1(E)} \le Ch^{-1}\|w\|_E \qquad \|w\|_e \le Ch^{-1/2}\|w\|_E.$$

Trace Inequalities:

$$\|w\|_e \leq Ch^{-1/2}(\|w\|_E + h\|\nabla w\|_E) \qquad \|\nabla w \cdot \mathbf{n}\|_e \leq Ch^{-1/2}(\|\nabla w\|_E + h\|\nabla^2 w\|_E).$$

5.2 FINITE ELEMENT ANALYSIS OF THE PDES IN PART I

We may properly analyze the equations from Part I by considering the following coupled partial differential equations:

$$\frac{\partial u_1}{\partial t} - \nabla \cdot (D_1 \nabla u_1 - u_1 \nabla u_2) \;=\; f_1(u_1, u_2) \tag{5.6}$$

$$\frac{\partial u_2}{\partial t} - \nabla \cdot (D_2 \nabla u_2) \;=\; f_2(u_1, u_2) \qquad (x,t) \in \Omega \times (0,T] \tag{5.7}$$

$$\nabla u_1 \cdot \mathbf{n} = 0 \qquad \text{and} \qquad \nabla u_2 \cdot \mathbf{n} = 0 \qquad \text{on } \Gamma, \tag{5.8}$$

where $T > 0$; D_1 and D_2 are positive definite tensors; f_1 and f_2 are nonlinear functions of u_1 and u_2 but f_1 and f_2 are each Lipschitz continuous in both u_1 and u_2, i.e., there exist constants L_{11},L_{12},L_{21}, and L_{22} such that

$$|f_1(x_1, y) - f_1(x_2, y)| \leq L_{11}|y||x_1 - x_2| \tag{5.9}$$

$$|f_1(x, y_1) - f_1(x, y_2)| \leq L_{12}|x||y_1 - y_2| \tag{5.10}$$

$$|f_2(x_1, y) - f_2(x_2, y)| \leq L_{21}|y||x_1 - x_2| \tag{5.11}$$

$$|f_2(x, y_1) - f_2(x, y_2)| \leq L_{22}|x||y_1 - y_2|. \tag{5.12}$$

(Recall that in chapter 4, it was proven that conditions (5.9) through (5.12) hold for each and every one of the equations in Part I.)
The initial condition is given by:

$$u_1(x,0) = u_1^0(x) \qquad \text{and} \qquad u_2(x,0) = u_2^0(x) \quad \text{in} \quad \Omega.$$

These initial conditions will often be represented by u_1^0 and u_2^0, respectively. In a previous chapter, it was shown that a unique solution u_1, u_2 exists.

Mixed Method Formulation

Considering our system (5.6), (5.7), and (5.8) we set

$$\mathbf{z}_1 = -D_1 \nabla u_1 \quad \text{and} \quad \mathbf{z}_2 = -D_2 \nabla u_2 \tag{5.13}$$

$$\text{So, } D_1^{-1}\mathbf{z}_1 = -\nabla u_1 \quad \text{and} \quad D_2^{-1}\mathbf{z}_2 = -\nabla u_2. \tag{5.14}$$

Then the weak formulation of (5.6), (5.7), and (5.8) may be stated as :

Find $u_1, u_2 \in W$ and $\mathbf{z}_1, \mathbf{z}_2 \in V^0$ such that $\forall w \in W$,

$$(u_{1_t}, w) - (\nabla \cdot (u_1 D_2^{-1}\mathbf{z}_2), w) + (\nabla \cdot \mathbf{z}_1, w) = (f_1, w) \tag{5.15}$$

$$(u_{2_t}, w) + (\nabla \cdot \mathbf{z}_2, w) = (f_2, w) \tag{5.16}$$

and $\forall v \in V^0$,

$$(D_1^{-1}\mathbf{z}_1, v) = -(\nabla u_1, v) \Rightarrow (D_1^{-1}\mathbf{z}_1, v) = (u_1, \nabla \cdot v) - \langle u_1, v \cdot \mathbf{n}\rangle_\Gamma \tag{5.17}$$

$$(D_2^{-1}\mathbf{z}_2, v) = -(\nabla u_2, v) \Rightarrow (D_2^{-1}\mathbf{z}_2, v) = (u_2, \nabla \cdot v) - \langle u_2, v \cdot \mathbf{n}\rangle_\Gamma \tag{5.18}$$

The last term in each of (5.17) and (5.18) is zero by the definition of V^0.

The second term on the left hand side of (5.15) may be written as

$$-(\nabla \cdot (u_1 D_2^{-1}\mathbf{z}_2), w) = -\sum_E (\nabla \cdot (u_1 D_2^{-1}\mathbf{z}_2), w)_E.$$

Integration by parts on this term gives,

$$-(\nabla \cdot (u_1 D_2^{-1}\mathbf{z}_2), w) = \sum_E (u_1 D_2^{-1}\mathbf{z}_2, \nabla w)_E + \sum_e ((u_1 D_2^{-1}\mathbf{z}_2) \cdot \mathbf{n}_e, [w])_e \tag{5.19}$$

If we substitute (5.19) into (5.15), we get $\forall w \in W$ and $\forall v \in V$

$$(u_{1_t}, w) + \sum_E (u_1 D_2^{-1}\mathbf{z}_2, \nabla w)_E + \sum_e ((u_1 D_2^{-1}\mathbf{z}_2) \cdot \mathbf{n}_e, [w])_e + (\nabla \cdot \mathbf{z}_1, w) = (f_1, w) \tag{5.20}$$

$$(u_{2_t}, w) + (\nabla \cdot \mathbf{z}_2, w) = (f_2, w) \tag{5.21}$$

$$(D_1^{-1}\mathbf{z}_1, v) = (u_1, \nabla \cdot v) \tag{5.22}$$

$$(D_2^{-1}\mathbf{z}_2, v) = (u_2, \nabla \cdot v). \tag{5.23}$$

Discrete Formulation

For the discrete formulation, we replace u_1, u_2 by $u_{1,h}, u_{2,h} \in W_h$, respectively and replace $\mathbf{z}_1, \mathbf{z}_2$ by $\mathbf{z}_{1,h}, \mathbf{z}_{2,h} \in V_h^0$, respectively, with the exception that on each edge e, replace u_1 and u_2 by their respective "upwind" values:

$$u_{1,h}^u = \begin{cases} u_{1,h}^- \text{ if } D_2^{-1}\mathbf{z}_{2,h} \cdot \mathbf{n}_e < 0 \\ u_{1,h}^+ \text{ if } D_2^{-1}\mathbf{z}_{2,h} \cdot \mathbf{n}_e \geq 0. \end{cases}$$

At $t = 0$ we define $u_{1_h}(x, 0) := u_{1_h}^0 \in W_h$ and $u_{2_h}(x, 0) := u_{2_h}^0 \in W_h$ by

$$(u_{1_h}^0 - u_1^0, w) = 0 \text{ and } (u_{2_h}^0 - u_2^0, w) = 0 \qquad \forall w \in W_h. \tag{5.24}$$

This results in the following discrete formulation. Find $u_{1,h}, u_{2,h} \in W_h$ and $\mathbf{z}_{1,h}, \mathbf{z}_{2,h} \in V_h$ such that for all $w \in W_h$ and for all $v \in V_h$,

$$(u_{1,h_t}, w) + \sum_E (D_2^{-1}\mathbf{z}_{2,h}u_{1,h}, \nabla w)_E + \sum_e ((D_2^{-1}\mathbf{z}_{2,h}) \cdot \mathbf{n}_e, u_{1,h}^{up}[w])_e$$
$$+(\nabla \cdot \mathbf{z}_{1,h}, w) = (f_1(u_{1,h}, u_{2,h}), w) \tag{5.25}$$

$$(u_{2,h_t}, w) + (\nabla \cdot \mathbf{z}_{2,h}, w) = (f_2(u_{1,h}, u_{2,h}), w) \tag{5.26}$$

$$(D_1^{-1}\mathbf{z}_{1,h}, v) = (u_{1,h}, \nabla \cdot v) \tag{5.27}$$

$$(D_2^{-1}\mathbf{z}_{2,h}, v) = (u_{2,h}, \nabla \cdot v). \tag{5.28}$$

Stability and Error Analysis. In order to do the stability and error analysis for the mixed finite element method we will use an approach that is similar to Epshteyn and Kurganov [37]. This approach involves creating a set, a mapping, and then finding a fixed point of the mapping within the set. However, Epshteyn and Kurganov used the approach on a discontinuous Galerkin application. We will be using this approach on the mixed method. Therefore, the details in our analysis will be completely different from the details in the Epshteyn and Kurganov paper. Furthermore, Epshteyn and Kurganov were satisfied finding their solution in an unbounded set. We will prove that our solution exists in a bounded set, a somewhat more lengthy process.

Define the following space, S, (notice that S is the space of functions of a given error estimate):

$$S = \Bigg\{ (\phi^{u_1}, \phi^{u_2}, \phi^{\mathbf{z_1}}, \phi^{\mathbf{z_2}}) \in H^1([0,T]) \cap L^\infty([0,T]) \cap \mathcal{W}_h^{u_1} \times \mathcal{W}_h^{u_2} \times \mathcal{W}_h^{\mathbf{z_1}} \times \mathcal{W}_h^{\mathbf{z_2}}, \tag{5.29}$$

such that there exists constants $C_{u_1}, C_{u_2}, C_{\mathbf{z_1}}, C_{\mathbf{z_2}}$, and

$$\sup_{t\in[0,T]} \|\phi^{u_1} - Q_h u_1\|^2 \leq C_{u_1}\beta_1,$$
$$\sup_{t\in[0,T]} \|\phi^{u_2} - Q_h u_2\|^2 \leq C_{u_2}\beta_2,$$
$$\int_0^T \|\phi^{\mathbf{z_1}} - \Pi_h \mathbf{z_1}\|^2 \leq C_{\mathbf{z_1}}\beta_3,$$
$$\sup_{t\in[0,T]} \|\phi^{\mathbf{z_2}} - \Pi_h \mathbf{z_2}\|^2 + \int_0^T \|\phi^{\mathbf{z_2}} - \Pi_h \mathbf{z_2}\|^2 + \int_0^T \|\nabla\cdot(\phi^{\mathbf{z_2}} - \Pi_h \mathbf{z_2})\|^2 \leq C_{\mathbf{z_2}}\beta_4 \Bigg\}$$

where

$$\beta_1 = \beta_2 = \beta_3 = \beta_4 = h^{2\mu_{u_1}-2} + h^{2\mu_{u_2}} + h^{2\mu_{\mathbf{z_1}}} + h^{2\mu_{\mathbf{z_2}}-2}$$

For $T \leq \widetilde{t}$, the value $\widetilde{t}$ is defined in the lines immediately after (5.77) below.

$\mathcal{W}_h^{u_1}, \mathcal{W}_h^{u_2}, \mathcal{W}_h^{\mathbf{z_1}}, \mathcal{W}_h^{\mathbf{z_2}}$ are the respective Raviart-Thomas spaces of piecewise polynomials of degrees $r_{u_1}, r_{u_2}, r_{\mathbf{z_1}}, r_{\mathbf{z_2}}$, respectively. $C_{u_1}, C_{u_2}, C_{\mathbf{z_1}}, C_{\mathbf{z_2}}$ are positive constants independent of h and the polynomial degrees $r_{u_1}, r_{u_2}, r_{\mathbf{z_1}}, r_{\mathbf{z_2}}$.

Note that the constants, $C_{u_1}, C_{u_2}, C_{\mathbf{z_1}}, C_{\mathbf{z_2}}$, are determined below.

Definition. Define the norm

$$\|(\phi^{u_1}, \phi^{u_2}, \phi^{\mathbf{z_1}}, \phi^{\mathbf{z_2}})\|_S = \sup_{t\in[0,T]} \|\phi^{u_1}\| + \sup_{t\in[0,T]} \|\phi^{u_2}\| + \left(\int_0^t \|\phi^{\mathbf{z_1}}\|\right)^{1/2} + \sup_{t\in[0,T]} \|\phi^{\mathbf{z_2}}\| + \left(\int_0^t \|\phi^{\mathbf{z_2}}\|\right)^{1/2} + \left(\int_0^t \|\nabla\cdot\phi^{\mathbf{z_2}}\|\right)^{1/2} \tag{5.30}$$

Theorem 5.1. *For any* $(\phi^{u_1}, \phi^{u_2}, \phi^{\mathbf{z_1}}, \phi^{\mathbf{z_2}}) \in S$ *there exist positive constants* $M_{u_1}, M_{u_2}, M_{\mathbf{z_1}}, M_{\mathbf{z_2}}$ *independent of* $h, r_{u_1}, r_{u_2}, r_{\mathbf{z_1}}, r_{\mathbf{z_2}}$ *such that*

$$\sup_{t\in[0,T]} \|\phi^{u_1}\|_\infty \leq M_{u_1} \quad \sup_{t\in[0,T]} \|\phi^{u_2}\|_\infty \leq M_{u_2} \quad \sup_{t\in[0,T]} \|\phi^{\mathbf{z_1}}\|_\infty \leq M_{\mathbf{z_1}} \quad \sup_{t\in[0,T]} \|\phi^{\mathbf{z_2}}\|_\infty \leq M_{\mathbf{z_2}}.$$

Proof. See Epshteyn and Kurganov [37]), proof of Lemma 5.1.

Linearized System:

In this section, the linearized system will be considered. Define A on S as follows:

$$\forall(\phi^{u_1}, \phi^{\mathbf{z}_1}, \phi^{u_2}, \phi^{\mathbf{z}_2}) \in S \qquad A(\phi^{u_1}, \phi^{\mathbf{z}_1}, \phi^{u_2}, \phi^{\mathbf{z}_2}) = (\phi_L^{u_1}, \phi_L^{\mathbf{z}_1}, \phi_L^{u_2}, \phi_L^{\mathbf{z}_2})$$

the initial conditions are $(\phi^{u_1,0}, \phi^{\mathbf{z}_1,0}, \phi^{u_2,0}, \phi^{\mathbf{z}_2,0}) = (Q_h u_1^0, \Pi_h \mathbf{z}_1^0, Q_h u_2^0, \Pi_h \mathbf{z}_2^0)$.

$(\phi_L^{u_1}, \phi_L^{\mathbf{z}_1}, \phi_L^{u_2}, \phi_L^{\mathbf{z}_2})$ is the solution to the linearized system:

$$((\phi_L^{u_1})_t, w) + \sum_E (D_2^{-1}\phi^{\mathbf{z}_2}\phi_L^{u_1}, \nabla w)_E + \sum_e ((D_2^{-1}\phi^{\mathbf{z}_2} \cdot \mathbf{n}_e, \phi_{L_{up}}^{u_1}[w])_e$$
$$+(\nabla \cdot \phi_L^{\mathbf{z}_1}, w) = (f_1(\phi_L^{u_1}, \phi^{u_2}), w) \tag{5.31}$$
$$(D_1^{-1}\phi_L^{\mathbf{z}_1}, v) = (\phi_L^{u_1}, \nabla \cdot v) \tag{5.32}$$

$$((\phi_L^{u_2})_t, w) + (\nabla \cdot \phi_L^{\mathbf{z}_2}, w) = (f_2(\phi^{u_1}, \phi_L^{u_2}), w) \tag{5.33}$$
$$(D_2^{-1}\phi_L^{\mathbf{z}_2}, v) = (\phi_L^{u_2}, \nabla \cdot v) \tag{5.34}$$

where $\phi^{u_2}, \phi^{z_2} \in S$ (these were inserted to linearize the system).

Theorem 5.2. *For each* $(\phi^{u_1}, \phi^{\mathbf{z}_1}, \phi^{u_2}, \phi^{\mathbf{z}_2}) \in S$ *there exists a unique* $(\phi_L^{u_1}, \phi_L^{\mathbf{z}_1}, \phi_L^{u_2}, \phi_L^{\mathbf{z}_2}) = A(\phi^{u_1}, \phi^{\mathbf{z}_1}, \phi^{u_2}, \phi^{\mathbf{z}_2})$.

Proof. The proof follows from the analysis in section 4.3.1.

Before moving on to the next theorem, the following notation will be introduced:

$$\xi^{u_1} = u_1 - Q_h u_1 \qquad \tau^{u_1} = \phi_L^{u_1} - Q_h u_1$$
$$\xi^{u_2} = u_2 - Q_h u_2 \qquad \tau^{u_2} = \phi_L^{u_2} - Q_h u_2$$
$$\xi^{\mathbf{z_1}} = \mathbf{z_1} - \Pi_h \mathbf{z_1} \qquad \tau^{\mathbf{z_1}} = \phi_L^{\mathbf{z_1}} - \Pi_h \mathbf{z_1}$$
$$\xi^{\mathbf{z_2}} = \mathbf{z_2} - \Pi_h \mathbf{z_2} \qquad \tau^{\mathbf{z_2}} = \phi_L^{\mathbf{z_2}} - \Pi_h \mathbf{z_2}.$$

Theorem 5.3. *For any* $(\phi^{u_1}, \phi^{\mathbf{z}_1}, \phi^{u_2}, \phi^{\mathbf{z}_2}) \in S$ *we have* $A(\phi^{u_1}, \phi^{\mathbf{z}_1}, \phi^{u_2}, \phi^{\mathbf{z}_2}) \in S$. *(That is,* $A : S \to S$.*)*

Proof. Let $(\phi^{u_1}, \phi^{\mathbf{z}_1}, \phi^{u_2}, \phi^{\mathbf{z}_2}) \in S$ then, as we have proven there exists a unique $(\phi_L^{u_1}, \phi_L^{\mathbf{z}_1}, \phi_L^{u_2}, \phi_L^{\mathbf{z}_2}) = A(\phi^{u_1}, \phi^{\mathbf{z}_1}, \phi^{u_2}, \phi^{\mathbf{z}_2})$. Now, it will be proven that this unique solution $(\phi_L^{u_1}, \phi_L^{\mathbf{z}_1}, \phi_L^{u_2}, \phi_L^{\mathbf{z}_2})$ is, in fact, in S.

Note that the exact solution satisfies:

$$(u_{1_t}, w) + \sum_E (D_2^{-1}\mathbf{z}_2 u_1, \nabla w)_E + \sum_e ((D_2^{-1}\mathbf{z}_2) \cdot \mathbf{n}_e, u_1^{up}[w])_e$$
$$+(\nabla \cdot \mathbf{z}_1, w) = (f_1(u_1, u_2), w) \tag{5.35}$$
$$(D_1^{-1}\mathbf{z}_1, v) - (u_1, \nabla \cdot v) = 0 \tag{5.36}$$

$$(u_{2_t}, w) + (\nabla \cdot \mathbf{z}_2, w) = (f_2(u_1, u_2), w) \tag{5.37}$$
$$(D_2^{-1}\mathbf{z}_2, v) - (u_2, \nabla \cdot v) = 0 \tag{5.38}$$

Add and subtract $Q_h u_1$,$Q_h u_2$,$\Pi_h \mathbf{z}_1$ or $\Pi_h \mathbf{z}_2$ in the appropriate terms of (5.35),(5.36), (5.37) and (5.38) to get:

$$
\begin{aligned}
&(u_{1_t} - Q_h u_{1_t} + Q_h u_{1_t}, w) + \sum_E (D_2^{-1}\mathbf{z}_2(u_1 - Q_h u_1 + Q_h u_1), \nabla w)_E \\
&+ \sum_e ((D_2^{-1}\mathbf{z}_2)\cdot \mathbf{n}_e, (u_1^{up} - Q_h u_1^{up} + Q_h u_1^{up})[w])_e + (\nabla\cdot(\mathbf{z}_1 - \Pi_h\mathbf{z_1} + \Pi_h\mathbf{z_1}), w) \\
&\qquad -(f_1(u_1,u_2) - f_1(Q_h u_1, u_2) + f_1(Q_h u_1, u_2), w) = 0 \\
&\qquad (D_1^{-1}(\mathbf{z}_1 - \Pi_h\mathbf{z_1} + \Pi_h\mathbf{z_1}), v) - (u_1 - Q_h u_1 + Q_h u_1, \nabla\cdot v) = 0
\end{aligned}
$$

$$
\begin{aligned}
&(u_{2_t} - Q_h u_{2_t} + Q_h u_{2_t}, w) + (\nabla\cdot(\mathbf{z}_2 - \Pi_h\mathbf{z_2} + \Pi_h\mathbf{z_2}), w) \\
&\qquad -(f_2(u_1,u_2) - f_2(u_1, Q_h u_2) + f_2(u_1, Q_h u_2), w) = 0 \\
&\qquad\qquad (D_2^{-1}(\mathbf{z}_2 - \Pi_h\mathbf{z_2} + \Pi_h\mathbf{z_2}), v) - (u_2 - Q_h u_2 + Q_h u_2, \nabla\cdot v) = 0
\end{aligned}
$$

Use $\xi^{u_1} = u_1 - Q_h u_1$,etc.

$$
\begin{aligned}
&(Q_h u_{1_t}, w) + \sum_E (D_2^{-1}\mathbf{z}_2 Q_h u_1, \nabla w)_E \\
&+ \sum_e (D_2^{-1}\mathbf{z}_2\cdot\mathbf{n}_e, Q_h u_1^{up}[w])_e + (\nabla\cdot\Pi_h\mathbf{z_1}, w) - (f_1(Q_h u_1, u_2), w) = \\
&-((\xi^{u_1})_t, w)) - \sum_E (D_2^{-1}\mathbf{z}_2\xi^{u_1}, \nabla w)_E - \sum_e ((D_2^{-1}\mathbf{z}_2)\cdot\mathbf{n}_e, (\xi^{u_1}_{up})[w])_e \\
&\qquad -(\nabla\cdot\xi^{\mathbf{z}_1}, w) + (f_1(u_1,u_2) - f_1(Q_h u_1, u_2), w) \qquad (5.39) \\
&(D_1^{-1}\Pi_h\mathbf{z_1}, v) - (Q_h u_1, \nabla\cdot v) = -(D_1^{-1}\xi^{\mathbf{z}_1}, v) + (\xi^{u_1}, \nabla\cdot v) \qquad (5.40)
\end{aligned}
$$

$$
\begin{aligned}
&(Q_h u_{2_t}, w) + (\nabla\cdot\Pi_h\mathbf{z_2}, w) - (f_2(u_1, Q_h u_2), w) = \\
&\qquad -((\xi^{u_2})_t, w)) - (\nabla\cdot\xi^{\mathbf{z}_2}, w) + (f_2(u_1,u_2) - f_2(u_1, Q_h u_2), w) \qquad (5.41) \\
&(D_2^{-1}\Pi_h\mathbf{z_2}, v) - (Q_h u_2, \nabla\cdot v) = -(D_2^{-1}\xi^{\mathbf{z}_2}, v) + (\xi^{u_2}, \nabla\cdot v) \qquad (5.42)
\end{aligned}
$$

Subtract (5.39) from (5.31) and (5.40) from (5.32) to get:

$$
\begin{aligned}
&((\phi_L^{u_1})_t - Q_h u_{1_t}, w) + \sum_E (D_2^{-1}(\phi^{\mathbf{z}_2}\phi_L^{u_1} - \mathbf{z}_2 Q_h u_1), \nabla w)_E \\
&+ \sum_e (D_2^{-1}\phi^{\mathbf{z}_2}\cdot\mathbf{n}_e\phi^{u_1}_{L_{up}}, [w])_e - \sum_e (D_2^{-1}\mathbf{z}_2\cdot\mathbf{n}_e Q_h u_1^{up}, [w])_e
\end{aligned}
$$

$$
\begin{aligned}
&+(\nabla\cdot(\phi_L^{\mathbf{z}_1}-\Pi_h\mathbf{z_1}),w)-(f_1(\phi_L^{u_1},\phi^{u_2})-f_1(Q_hu_1,u_2),w) \qquad =\\
((\xi^{u_1})_t.w))&+\sum_E(D_2^{-1}\mathbf{z}_2\xi^{u_1},\nabla w)_E+\sum_e((D_2^{-1}\mathbf{z}_2)\cdot\mathbf{n}_e,(\xi_{up}^{u_1})[w])_e\\
&+(\nabla\cdot\xi^{\mathbf{z}_1},w)-(f_1(u_1,u_2)-f_1(Q_hu_1,u_2),w)\\
&(D_1^{-1}(\phi_L^{\mathbf{z}_1}-\Pi_h\mathbf{z_1}),v)-(\phi_L^{u_1}-Q_hu_1,\nabla\cdot v)=(D_1^{-1}\xi^{\mathbf{z}_1},v)-(\xi^{u_1},\nabla\cdot v)
\end{aligned}
$$

And Subtract (5.41) from (5.33) and (5.42) from (5.34) to get:

$$
\begin{aligned}
&((\phi_L^{u_2})_t-Q_hu_{2_t},w)+(\nabla\cdot(\phi_L^{\mathbf{z}_2}-\Pi_h\mathbf{z_2}),w)-(f_2(\phi^{u_1},\phi_L^{u_2})-f_2(u_1,Q_hu_2),w) \;=\\
&\qquad((\xi^{u_2})_t,w))+(\nabla\cdot\xi^{\mathbf{z}_2},w)-(f_2(u_1,u_2)-f_2(u_1,Q_hu_2),w) \qquad (5.43)\\
&(D_2^{-1}(\phi_L^{\mathbf{z}_2}-\Pi_h\mathbf{z_2}),v)-(\phi_L^{u_2}-Q_hu_2,\nabla\cdot v)=(D_2^{-1}\xi^{\mathbf{z}_2},v)-(\xi^{u_2},\nabla\cdot v) \quad (5.44)
\end{aligned}
$$

Add and subtract the appropriate terms:

$$
\begin{aligned}
&((\phi_L^{u_1})_t-Q_hu_{1_t},w)+\sum_E(D_2^{-1}\phi^{\mathbf{z}_2}\tau^{u_1},\nabla w)_E+\sum_e(D_2^{-1}\phi^{\mathbf{z}_2}\cdot\mathbf{n}_e\tau_{up}^{u_1},[w])_e\\
&+\sum_E(D_2^{-1}Q_hu_1(\phi^{\mathbf{z}_2}-\Pi_h\mathbf{z_2}),\nabla w)_E+\sum_e(D_2^{-1}(\phi^{\mathbf{z}_2}-\Pi_h\mathbf{z_2})\cdot\mathbf{n}_e,Q_hu_1^{up}[w])_e\\
&-\sum_E(D_2^{-1}Q_hu_1\xi^{\mathbf{z}_2},\nabla w)_E-\sum_e(D_2^{-1}\xi^{\mathbf{z}_2}\cdot\mathbf{n}_e,Q_hu_1^{up}[w])_e\\
&\quad+(\nabla\cdot(\phi_L^{\mathbf{z}_1}-\Pi_h\mathbf{z_1}),w)-(f_1(\phi_L^{u_1},\phi^{u_2}),w)+(f_1(Q_hu_1,\phi^{u_2}),w)\\
&-(f_1(Q_hu_1,\phi^{u_2}),w)+(f_1(Q_hu_1,u_2),w) \qquad =\\
&\sum_E(D_2^{-1}\mathbf{z}_2\xi^{u_1},\nabla w)_E+\sum_e((D_2^{-1}\mathbf{z}_2)\cdot\mathbf{n}_e,(\xi_{up}^{u_1})[w])_e\\
&\qquad\qquad-(f_1(u_1,u_2)-f_1(Q_hu_1,u_2),w) \qquad (5.45)
\end{aligned}
$$

$$
(D_1^{-1}(\phi_L^{\mathbf{z}_1}-\Pi_h\mathbf{z_1}),v)-(\phi_L^{u_1}-Q_hu_1,\nabla\cdot v)=(D_1^{-1}\xi^{\mathbf{z}_1},v) \qquad (5.46)
$$

$$
\begin{aligned}
&((\phi_L^{u_2})_t-Q_hu_{2_t},w)+(\nabla\cdot(\phi_L^{\mathbf{z}_2}-\Pi_h\mathbf{z_2}),w)-(f_2(\phi^{u_1},\phi_L^{u_2}),w)+(f_2(\phi^{u_1},Q_hu_2),w)\\
&-(f_2(\phi^{u_1},Q_hu_2),w)+(f_2(u_1,Q_hu_2),w)=\\
&-(f_2(u_1,u_2)-f_2(u_1,Q_hu_2),w) \qquad (5.47)
\end{aligned}
$$

$$(D_2^{-1}(\phi_L^{\mathbf{z}_2} - \Pi_h \mathbf{z_2}), v) - (\phi_L^{u_2} - Q_h u_2, \nabla \cdot v) = (D_2^{-1}\xi^{\mathbf{z}_2}, v) \tag{5.48}$$

Set $w = \tau^{u_1}$ in (5.45), $v = \tau^{\mathbf{z}_1}$ in (5.46), $w = \tau^{u_2}$ in (5.47), and $v = \tau^{\mathbf{z}_2}$ in (5.48)to get:

$$\begin{aligned}
&((\phi_L^{u_1})_t - Q_h u_{1_t}, \tau^{u_1}) + \sum_E (D_2^{-1}\phi^{\mathbf{z}_2}\tau^{u_1}, \nabla\tau^{u_1})_E + \sum_e (D_2^{-1}\phi^{\mathbf{z}_2} \cdot \mathbf{n}_e \tau_{up}^{u_1}, [\tau^{u_1}])_e \\
&+ \sum_E (D_2^{-1} Q_h u_1 (\phi^{\mathbf{z}_2} - \Pi_h \mathbf{z_2}), \nabla\tau^{u_1})_E + \sum_e (D_2^{-1}(\phi^{\mathbf{z}_2} - \Pi_h \mathbf{z_2}) \cdot \mathbf{n}_e, Q_h u_1^{up}[\tau^{u_1}])_e \\
&- \sum_E (D_2^{-1} Q_h u_1 \xi^{\mathbf{z}_2}, \nabla\tau^{u_1})_E - \sum_e (D_2^{-1}\xi^{\mathbf{z}_2} \cdot \mathbf{n}_e, Q_h u_1^{up}[\tau^{u_1}])_e \\
&\quad + (\nabla \cdot \tau^{\mathbf{z}_1}, \tau^{u_1}) - (f_1(\phi_L^{u_1}, \phi^{u_2}), \tau^{u_1}) + (f_1(Q_h u_1, \phi^{u_2}), \tau^{u_1}) \\
&- (f_1(Q_h u_1, \phi^{u_2}), \tau^{u_1}) + (f_1(Q_h u_1, u_2), \tau^{u_1}) \qquad = \\
&\sum_E (D_2^{-1}\mathbf{z}_2 \xi^{u_1}, \nabla\tau^{u_1})_E + \sum_e ((D_2^{-1}\mathbf{z}_2) \cdot \mathbf{n}_e, (\xi_{up}^{u_1})[\tau^{u_1}])_e \\
&\qquad\qquad - (f_1(u_1, u_2) - f_1(Q_h u_1, u_2), \tau^{u_1})
\end{aligned} \tag{5.49}$$

$$(\tau^{u_1}, \nabla \cdot \tau^{\mathbf{z}_1}) = (D_1^{-1}(\phi_L^{\mathbf{z}_1} - \Pi_h \mathbf{z_1}), \tau^{\mathbf{z}_1}) - (D_1^{-1}\xi^{\mathbf{z}_1}, \tau^{\mathbf{z}_1}) \tag{5.50}$$

$$\begin{aligned}
&((\phi_L^{u_2})_t - Q_h u_{2_t}, \tau^{u_2}) + (\nabla \cdot (\phi_L^{\mathbf{z}_2} - \Pi_h \mathbf{z_2}), \tau^{u_2}) - (f_2(\phi^{u_1}, \phi_L^{u_2}), \tau^{u_2}) + (f_2(\phi^{u_1}, Q_h u_2), \tau^{u_2}) \\
&-(f_2(\phi^{u_1}, Q_h u_2), \tau^{u_2}) + (f_2(u_1, Q_h u_2), \tau^{u_2}) = -(f_2(u_1, u_2) - f_2(u_1, Q_h u_2), \tau^{u_2})
\end{aligned} \tag{5.51}$$

$$(\tau^{u_2}, \nabla \cdot \tau^{\mathbf{z}_2}) = (D_2^{-1}(\phi_L^{\mathbf{z}_2} - \Pi_h \mathbf{z_2}), \tau^{\mathbf{z}_2}) - (D_2^{-1}\xi^{\mathbf{z}_2}, \tau^{\mathbf{z}_2}) \tag{5.52}$$

Consider the third term on the left hand side of (5.49):

$$\begin{aligned}
&\sum_e (D_2^{-1}\phi^{\mathbf{z}_2} \cdot \mathbf{n}_e \tau_{up}^{u_1}, [\tau^{u_1}])_e = \sum_e (D_2^{-1}\phi^{\mathbf{z}_2} \cdot \mathbf{n}_e (\tau_{up}^{u_1} - \frac{1}{2}\tau_{down}^{u_1} + \frac{1}{2}\tau_{down}^{u_1}), [\tau^{u_1}])_e \\
&= \frac{1}{2}\sum_e (D_2^{-1}\phi^{\mathbf{z}_2} \cdot \mathbf{n}_e (\tau_{up}^{u_1} - \tau_{down}^{u_1}), [\tau^{u_1}])_e + \frac{1}{2}\sum_e (D_2^{-1}\phi^{\mathbf{z}_2} \cdot \mathbf{n}_e (\tau_{up}^{u_1} + \tau_{down}^{u_1}), [\tau^{u_1}])_e
\end{aligned}$$

Note that whenever $D_2^{-1}\phi^{\mathbf{z}_2} \cdot \mathbf{n}_e \geq 0$

$$(\tau_{up}^{u_1} - \tau_{down}^{u_1}), [\tau^{u_1}] = (\tau^{u_1,+} - \tau^{u_1,-})(\tau^{u_1,+} - \tau^{u_1,-}) = (\tau^{u_1,+} - \tau^{u_1,-})^2 = [\tau^{u_1}]^2$$

So,

$$\frac{1}{2}\sum_e (D_2^{-1}\phi^{\mathbf{z}_2}\cdot\mathbf{n}_e(\tau_{up}^{u_1}-\tau_{down}^{u_1}),[\tau^{u_1}])_e = \frac{1}{2}\sum_e (|D_2^{-1}\phi^{\mathbf{z}_2}\cdot\mathbf{n}_e|,[\tau^{u_1}]^2)_e$$

Note that whenever $D_2^{-1}\phi^{\mathbf{z}_2}\cdot\mathbf{n}_e < 0$

$$(\tau_{up}^{u_1}-\tau_{down}^{u_1}),[\tau^{u_1}] = (\tau^{u_1,-}-\tau^{u_1,+})(\tau^{u_1,+}-\tau^{u_1,-}) = -(\tau^{u_1,+}-\tau^{u_1,-})^2$$

So,

$$\begin{aligned}\frac{1}{2}\sum_e (D_2^{-1}\phi^{\mathbf{z}_2}\cdot\mathbf{n}_e(\tau_{up}^{u_1}-\tau_{down}^{u_1}),[\tau^{u_1}])_e &= \frac{1}{2}\sum_e (-|D_2^{-1}\phi^{\mathbf{z}_2}\cdot\mathbf{n}_e|,-[\tau^{u_1}]^2)_e \\ &= \frac{1}{2}\sum_e (|D_2^{-1}\phi^{\mathbf{z}_2}\cdot\mathbf{n}_e|,[\tau^{u_1}]^2)_e\end{aligned}$$

Note that whenever $D_2^{-1}\phi^{\mathbf{z}_2}\cdot\mathbf{n}_e \geq 0$

$$(\tau_{up}^{u_1}+\tau_{down}^{u_1}),[\tau^{u_1}] = (\tau^{u_1,+}+\tau^{u_1,-})(\tau^{u_1,+}-\tau^{u_1,-}) = (\tau^{u_1,+})^2-(\tau^{u_1,-})^2$$

Note that whenever $D_2^{-1}\phi^{\mathbf{z}_2}\cdot\mathbf{n}_e < 0$

$$(\tau_{up}^{u_1}+\tau_{down}^{u_1}),[\tau^{u_1}] = (\tau^{u_1,-}+\tau^{u_1,+})(\tau^{u_1,+}-\tau^{u_1,-}) = (\tau^{u_1,+})^2-(\tau^{u_1,-})^2$$

So, we have

$$\begin{aligned}\sum_e (D_2^{-1}\phi^{\mathbf{z}_2}\cdot\mathbf{n}_e\tau_{up}^{u_1},[\tau^{u_1}])_e &= \frac{1}{2}\sum_e (|D_2^{-1}\phi^{\mathbf{z}_2}\cdot\mathbf{n}_e|,[\tau^{u_1}]^2)_e \\ &+\frac{1}{2}\sum_e (D_2^{-1}\phi^{\mathbf{z}_2}\cdot\mathbf{n}_e,(\tau^{u_1,+})^2-(\tau^{u_1,-})^2)_e\end{aligned}$$

Apply the divergence theorem:

$$\begin{aligned}\sum_e (D_2^{-1}\phi^{\mathbf{z}_2}\cdot\mathbf{n}_e\tau_{up}^{u_1},[\tau^{u_1}])_e &= \frac{1}{2}\sum_e (|D_2^{-1}\phi^{\mathbf{z}_2}\cdot\mathbf{n}_e|,[\tau^{u_1}]^2)_e \\ &-\frac{1}{2}\sum_E (\nabla\cdot D_2^{-1}\phi^{\mathbf{z}_2},(\tau^{u_1})^2)-\sum_E (D_2^{-1}\phi^{\mathbf{z}_2}\tau^{u_1},\nabla\tau^{u_1})\end{aligned} \tag{5.53}$$

Substitute (5.50) and (5.53) into (5.49) and rearranging:

$$\frac{1}{2}\frac{d}{dt}\|\tau^{u_1}\|^2-\frac{1}{2}\sum_E (\nabla\cdot D_2^{-1}\phi^{\mathbf{z}_2},(\tau^{u_1})^2)_E+\frac{1}{2}\sum_e (|D_2^{-1}\phi^{\mathbf{z}_2}\cdot\mathbf{n}_e|,[\tau^{u_1}]^2)_e$$

$$
\begin{aligned}
+\|D_1^{-1/2}\tau^{\mathbf{z}_1}\|^2 = &-\sum_E (D_2^{-1}Q_h u_1(\phi^{\mathbf{z}_2}-\Pi_h\mathbf{z_2}),\nabla\tau^{u_1})_E\\
&-\sum_e (D_2^{-1}(\phi^{\mathbf{z}_2}-\Pi_h\mathbf{z_2})\cdot\mathbf{n}_e, Q_h u_1^{up}[\tau^{u_1}])_e\\
&+\sum_E (D_2^{-1}Q_h u_1\xi^{\mathbf{z}_2},\nabla\tau^{u_1})_E+\sum_e (D_2^{-1}\xi^{\mathbf{z}_2}\cdot\mathbf{n}_e, Q_h u_1^{up}[\tau^{u_1}])_e\\
&+(f_1(\phi_L^{u_1},\phi^{u_2}),w)-(f_1(Q_h u_1,\phi^{u_2}),w)\\
&+(f_1(Q_h u_1,\phi^{u_2}),w)-(f_1(Q_h u_1,u_2),w)\\
&+\sum_E (D_2^{-1}\mathbf{z}_2\xi^{u_1},\nabla\tau^{u_1})_E+\sum_e ((D_2^{-1}\mathbf{z}_2)\cdot\mathbf{n}_e,(\xi_{up}^{u_1})[\tau^{u_1}])_e\\
&-(f_1(u_1,u_2)-f_1(Q_h u_1,u_2),\tau^{u_1})+(D_1^{-1}\xi^{\mathbf{z}_1},\tau^{\mathbf{z}_1})
\end{aligned}
\tag{5.54}
$$

Substitute (5.52) into (5.51):

$$
\begin{aligned}
\frac{1}{2}\frac{d}{dt}\|\tau^{u_2}\|^2+\|D_2^{-1/2}\tau^{\mathbf{z}_2}\|^2 = &(f_2(\phi^{u_1},\phi_L^{u_2})-f_2(\phi^{u_1},Q_h u_2),\tau^{u_2})\\
&+(f_2(\phi^{u_1},Q_h u_2)-f_2(u_1,Q_h u_2),\tau^{u_2})\\
&-(f_2(u_1,u_2)-f_2(u_1,Q_h u_2),\tau^{u_2})+(D_2^{-1}\xi^{\mathbf{z}_2},\tau^{\mathbf{z}_2})
\end{aligned}
\tag{5.55}
$$

Rearranging (5.54):

$$
\begin{aligned}
&\frac{1}{2}\frac{d}{dt}\|\tau^{u_1}\|^2+\frac{1}{2}\sum_e (|D_2^{-1}\phi^{\mathbf{z}_2}\cdot\mathbf{n}_e|,[\tau^{u_1}]^2)_e+\|D_1^{-1/2}\tau^{\mathbf{z}_1}\|^2\\
&=\sum_E (D_2^{-1}\mathbf{z}_2\xi^{u_1},\nabla\tau^{u_1})_E+\sum_e ((D_2^{-1}\mathbf{z}_2)\cdot\mathbf{n}_e,(\xi_{up}^{u_1})[\tau^{u_1}])_e\\
&-\sum_E (D_2^{-1}Q_h u_1(\phi^{\mathbf{z}_2}-\Pi_h\mathbf{z_2}),\nabla\tau^{u_1})_E-\sum_e (D_2^{-1}(\phi^{\mathbf{z}_2}-\Pi_h\mathbf{z_2})\cdot\mathbf{n}_e,Q_h u_1^{up}[\tau^{u_1}])_e\\
&+\sum_E (D_2^{-1}Q_h u_1\xi^{\mathbf{z}_2},\nabla\tau^{u_1})_E+\sum_e (D_2^{-1}\xi^{\mathbf{z}_2}\cdot\mathbf{n}_e,Q_h u_1^{up}[\tau^{u_1}])_e\\
&+\frac{1}{2}\sum_E (\nabla\cdot D_2^{-1}\phi^{\mathbf{z}_2},(\tau^{u_1})^2)_E+(f_1(\phi_L^{u_1},\phi^{u_2})-f_1(Q_h u_1,\phi^{u_2}),\tau^{u_1})\\
&\quad+(f_1(Q_h u_1,\phi^{u_2})-f_1(Q_h u_1,u_2),\tau^{u_1})-(f_1(u_1,u_2)-f_1(Q_h u_1,u_2),\tau^{u_1})\\
&+(\phi^{u_2}\tau^{u_1},\tau^{u_1})-(Q_h u_1(\phi^{u_2}-u_2),\tau^{u_1})-(\xi^{u_1}u_2,\tau^{u_1})+(D_1^{-1}\xi^{\mathbf{z}_1},\tau^{\mathbf{z}_1})
\end{aligned}
\tag{5.56}
$$

We will consider the third and fourth terms on the right hand side of (5.56). Integrating by parts and rewriting terms, we get:

$$
-\sum_E (D_2^{-1}Q_h u_1(\phi^{\mathbf{z}_2}-\Pi_h\mathbf{z_2}),\nabla\tau^{u_1})_E-\sum_e (D_2^{-1}(\phi^{\mathbf{z}_2}-\Pi_h\mathbf{z_2})\cdot\mathbf{n}_e,Q_h u_1^{up}[\tau^{u_1}])_e
$$

$$
\begin{aligned}
&= \sum_E ((\nabla \cdot D_2^{-1}(\phi^{\mathbf{z}_2} - \Pi_h \mathbf{z_2}))Q_h u_1, \tau^{u_1})_E + \sum_E ((D_2^{-1}(\phi^{\mathbf{z}_2} - \Pi_h \mathbf{z_2})) \cdot \nabla Q_h u_1, \tau^{u_1})_E \\
&+ \sum_E ((D_2^{-1}(\phi^{\mathbf{z}_2} - \Pi_h \mathbf{z_2})) \cdot \mathbf{n}_e Q_h u_1^+, \tau^{u_1,+})_E - \sum_E ((D_2^{-1}(\phi^{\mathbf{z}_2} - \Pi_h \mathbf{z_2})) \cdot \mathbf{n}_e Q_h u_1^-, \tau^{u_1,-})_E \\
&- \sum_e (D_2^{-1}(\phi^{\mathbf{z}_2} - \Pi_h \mathbf{z_2}) \cdot \mathbf{n}_e, Q_h u_1^{up} \tau^{u_1,+})_e + \sum_e (D_2^{-1}(\phi^{\mathbf{z}_2} - \Pi_h \mathbf{z_2}) \cdot \mathbf{n}_e, Q_h u_1^{up} \tau^{u_1,-})_e \\
&= \sum_E ((\nabla \cdot D_2^{-1}(\phi^{\mathbf{z}_2} - \Pi_h \mathbf{z_2}))Q_h u_1, \tau^{u_1})_E + \sum_E ((D_2^{-1}(\phi^{\mathbf{z}_2} - \Pi_h \mathbf{z_2})) \cdot \nabla Q_h u_1, \tau^{u_1})_E \\
&\quad + \sum_E ((D_2^{-1}(\phi^{\mathbf{z}_2} - \Pi_h \mathbf{z_2})) \cdot \mathbf{n}_e (Q_h u_1^+ - Q_h u_1^{up}), \tau^{u_1,+})_E \\
&\quad + \sum_E ((D_2^{-1}(\phi^{\mathbf{z}_2} - \Pi_h \mathbf{z_2})) \cdot \mathbf{n}_e (Q_h u_1^{up} - Q_h u_1^-), \tau^{u_1,-})_E
\end{aligned} \tag{5.57}
$$

We will consider the fifth and sixth terms on the right hand side of (5.56). Integrating by parts and rewriting terms, we get:

$$
\begin{aligned}
&\sum_E (D_2^{-1} Q_h u_1 \xi^{\mathbf{z}_2}, \nabla \tau^{u_1})_E + \sum_e (D_2^{-1} \xi^{\mathbf{z}_2} \cdot \mathbf{n}_e, Q_h u_1^{up}[\tau^{u_1}])_e \\
&= -\sum_E ((\nabla \cdot (D_2^{-1} \xi^{\mathbf{z}_2}))Q_h u_1, \tau^{u_1})_E - \sum_E ((D_2^{-1} \xi^{\mathbf{z}_2}) \cdot \nabla Q_h u_1, \tau^{u_1})_E \\
&- \sum_E ((D_2^{-1} \xi^{\mathbf{z}_2}) \cdot \mathbf{n}_e Q_h u_1^+, \tau^{u_1,+})_E + \sum_E ((D_2^{-1} \xi^{\mathbf{z}_2}) \cdot \mathbf{n}_e Q_h u_1^-, \tau^{u_1,-})_E \\
&+ \sum_e (D_2^{-1} \xi^{\mathbf{z}_2} \cdot \mathbf{n}_e, Q_h u_1^{up} \tau^{u_1,+})_e - \sum_e (D_2^{-1} \xi^{\mathbf{z}_2} \cdot \mathbf{n}_e, Q_h u_1^{up} \tau^{u_1,-})_e \\
&= -\sum_E ((\nabla \cdot (D_2^{-1} \xi^{\mathbf{z}_2}))Q_h u_1, \tau^{u_1})_E - \sum_E ((D_2^{-1} \xi^{\mathbf{z}_2}) \cdot \nabla Q_h u_1, \tau^{u_1})_E \\
&+ \sum_E ((D_2^{-1} \xi^{\mathbf{z}_2}) \cdot \mathbf{n}_e (Q_h u_1^{up} - Q_h u_1^+), \tau^{u_1,+})_E \\
&+ \sum_E ((D_2^{-1} \xi^{\mathbf{z}_2}) \cdot \mathbf{n}_e (Q_h u_1^- - Q_h u_1^{up}), \tau^{u_1,-})_E
\end{aligned} \tag{5.58}
$$

Substitute (5.57) and (5.58) into (5.56),

$$
\begin{aligned}
&\frac{1}{2}\frac{d}{dt}\|\tau^{u_1}\|^2 + \frac{1}{2}\sum_e (|D_2^{-1}\phi^{\mathbf{z}_2} \cdot \mathbf{n}_e|, [\tau^{u_1}]^2)_e + \|D_1^{-1/2}\tau^{\mathbf{z}_1}\|^2 \\
&= \sum_E (D_2^{-1}\mathbf{z}_2 \xi^{u_1}, \nabla \tau^{u_1})_E + \sum_e ((D_2^{-1}\mathbf{z}_2) \cdot \mathbf{n}_e, (\xi_{up}^{u_1})[\tau^{u_1}])_e \\
&\quad + \sum_E ((\nabla \cdot D_2^{-1}(\phi^{\mathbf{z}_2} - \Pi_h \mathbf{z_2}))Q_h u_1, \tau^{u_1})_E \\
&\quad + \sum_E ((D_2^{-1}(\phi^{\mathbf{z}_2} - \Pi_h \mathbf{z_2})) \cdot \nabla Q_h u_1, \tau^{u_1})_E
\end{aligned}
$$

$$
\begin{aligned}
&+\sum_e((D_2^{-1}(\phi^{\mathbf{z}_2}-\Pi_h\mathbf{z_2}))\cdot\mathbf{n}_e(Q_hu_1^+-Q_hu_1^{up}),\tau^{u_1,+})_e\\
&+\sum_E((D_2^{-1}(\phi^{\mathbf{z}_2}-\Pi_h\mathbf{z_2}))\cdot\mathbf{n}_e(Q_hu_1^{up}-Q_hu_1^-),\tau^{u_1,-})_e\\
&-\sum_E((\nabla\cdot D_2^{-1}\xi^{\mathbf{z}_2})Q_hu_1,\tau^{u_1})_E-\sum_E((D_2^{-1}\xi^{\mathbf{z}_2})\cdot\nabla Q_hu_1,\tau^{u_1})_E\\
&+\sum_e((D_2^{-1}\xi^{\mathbf{z}_2})\cdot\mathbf{n}_e(Q_hu_1^{up}-Q_hu_1^+),\tau^{u_1,+})_e\\
&+\sum_e((D_2^{-1}\xi^{\mathbf{z}_2})\cdot\mathbf{n}_e(Q_hu_1^--Q_hu_1^{up}),\tau^{u_1,-})_e\\
&+\frac{1}{2}\sum_E(\nabla\cdot D_2^{-1}\phi^{\mathbf{z}_2},(\tau^{u_1})^2)_E\\
&+(f_1(\phi_L^{u_1},\phi^{u_2})-f_1(Q_hu_1,\phi^{u_2}),\tau^{u_1})\\
&+(f_1(Q_hu_1,\phi^{u_2})-f_1(Q_hu_1,u_2),\tau^{u_1})\\
&-(f_1(u_1,u_2)-f_1(Q_hu_1,u_2),\tau^{u_1})\\
&+(\phi^{u_2}\tau^{u_1},\tau^{u_1})-(Q_hu_1(\phi^{u_2}-u_2),\tau^{u_1})\\
&-(\xi^{u_1}u_2,\tau^{u_1})+(D_1^{-1}\xi^{\mathbf{z}_1},\tau^{\mathbf{z}_1})
\end{aligned}
$$

$$
=: T_1+T_2+T_3+\cdots+T_{16}+T_{17}+T_{18} \tag{5.59}
$$

From (5.55):

$$
\begin{aligned}
\frac{1}{2}\frac{d}{dt}\|\tau^{u_2}\|^2+\|D_2^{-1/2}\tau^{\mathbf{z}_2}\|^2&=(f_2(\phi^{u_1},\phi_L^{u_2})-f_2(\phi^{u_1},Q_hu_2),\tau^{u_2})\\
&+(f_2(\phi^{u_1},Q_hu_2)-f_2(u_1,Q_hu_2),\tau^{u_2})-(f_2(u_1,u_2)-f_2(u_1,Q_hu_2),\tau^{u_2})\\
&+(D_2^{-1}\xi^{\mathbf{z}_2},\tau^{\mathbf{z}_2})=: T_{19}+T_{20}+T_{21}+T_{22}
\end{aligned} \tag{5.60}
$$

Bounds on the terms $T_1, T_2, ...$

Here bounds for both equations, (5.59) and (5.60) will be computed.

$$T_1 = \sum_E (D_2^{-1}\mathbf{z}_2\xi^{u_1}, \nabla\tau^{u_1})_E = \sum_E (D_2^{-1}\mathbf{z}_2\xi^{u_1} - \Pi_0 D_2^{-1}\mathbf{z}_2\xi^{u_1}, \nabla\tau^{u_1})_E$$
$$\leq C\sum_E h\|\mathbf{z}_2\|_{1,\infty,E}\|\xi^{u_1}\|_E\|\nabla\tau^{u_1}\|_E \leq C\sum_E h\|\xi^{u_1}\|_E h^{-1}\|\tau^{u_1}\|_E$$
$$\leq C\sum_E h^{\mu_{u_1}}\|u_1\|_{s_{u_1},E}\|\tau^{u_1}\| \leq C\sum_E h^{\mu_{u_1}}\|\tau^{u_1}\|_E \leq \varepsilon_1 C h^{2\mu_{u_1}} + \frac{1}{\varepsilon_1}\|\tau^{u_1}\|^2$$
$$\leq \varepsilon_1 C h^{2\mu_{u_1}} + \frac{1}{\varepsilon_1}\|\tau^{u_1}\|^2$$

$$T_2 = \sum_e ((D_2^{-1}\mathbf{z}_2)\cdot\mathbf{n}_e, (\xi_{up}^{u_1})[\tau^{u_1}])_e$$
$$\leq \sum_e \|(D_2^{-1}\mathbf{z}_2)\cdot\mathbf{n}\|_{0,\infty,e}\|\xi_{up}^{u_1}\|_e(\|\tau^{u_1,+}\|_e + \|\tau^{u_1,-}\|_e)$$
$$\leq C\sum_E h^{-1/2}\|\xi^{u_1}\|_E(h^{-1/2}\|\tau^{u_1}\|_E + h^{-1/2}\|\tau^{u_1}\|_E)$$
$$\leq C\sum_E h^{\mu_{u_1}-1}\|u_1\|_{s_{u_1},E}\|\tau^{u_1}\|_E \leq \varepsilon_2 C h^{2\mu_{u_1}-2} + \frac{1}{\varepsilon_2}\|\tau^{u_1}\|^2$$
$$\leq \varepsilon_2 C h^{2\mu_{u_1}-2} + \frac{1}{\varepsilon_2}\|\tau^{u_1}\|^2$$

$$T_3 = \sum_E ((\nabla\cdot D_2^{-1}(\phi^{\mathbf{z}_2} - \Pi_h\mathbf{z_2}))Q_h u_1, \tau^{u_1})_E$$
$$\leq \sum_E \|(\nabla\cdot D_2^{-1}(\phi^{\mathbf{z}_2} - \Pi_h\mathbf{z_2})\|_E\|Q_h u_1\|_{\infty,E}\|\tau^{u_1}\|_E$$
$$\leq \sum_E C\|(\nabla\cdot D_2^{-1}(\phi^{\mathbf{z}_2} - \Pi_h\mathbf{z_2})\|_E\|\tau^{u_1}\|_E$$
$$\leq \varepsilon_3\|\nabla\cdot((\phi^{\mathbf{z}_2} - \Pi_h\mathbf{z_2})\|^2 + \frac{1}{\varepsilon_3}\|\tau^{u_1}\|^2$$

For T_4, we will use the inverse inequality

$$T_4 = \sum_E ((D_2^{-1}(\phi^{\mathbf{z}_2} - \Pi_h\mathbf{z_2}))\cdot\nabla Q_h u_1, \tau^{u_1})_E$$
$$\leq \sum_E \|(D_2^{-1}(\phi^{\mathbf{z}_2} - \Pi_h\mathbf{z_2})\|_E\|\nabla Q_h u_1\|_{\infty,E}\|\tau^{u_1}\|_E$$
$$\leq \sum_E C\|(D_2^{-1}(\phi^{\mathbf{z}_2} - \Pi_h\mathbf{z_2})\|_E\|\tau^{u_1}\|_E$$

$$\leq \sum_E C\|\phi^{\mathbf{z}_2} - \Pi_h \mathbf{z_2}\|_E \|\tau^{u_1}\|_E \leq \varepsilon_4 C\|\phi^{\mathbf{z}_2} - \Pi_h \mathbf{z_2}\|^2 + \frac{1}{\varepsilon_4}\|\tau^{u_1}\|^2$$

$$\begin{aligned}
T_5 &= \sum_e ((D_2^{-1}(\phi^{\mathbf{z}_2} - \Pi_h \mathbf{z_2})) \cdot \mathbf{n}_e (Q_h u_1^+ - Q_h u_1^{up}), \tau^{u_1,+})_e \\
&\leq \sum_e \|((D_2^{-1}(\phi^{\mathbf{z}_2} - \Pi_h \mathbf{z_2})) \cdot \mathbf{n}_e\|_e \|Q_h u_1^+ - Q_h u_1^{up}\|_{0,\infty,e} \|\tau^{u_1,+}\|_e \\
&\leq \sum_E C h^{-1/2} \|(D_2^{-1}(\phi^{\mathbf{z}_2} - \Pi_h \mathbf{z_2}))\|_E \|u_1 - Q_h u_1\|_{0,\infty,E} h^{-1/2} \|\tau^{u_1}\|_E \\
&\leq \sum_E C h^{-1/2} \|(D_2^{-1}(\phi^{\mathbf{z}_2} - \Pi_h \mathbf{z_2}))\|_E h^{\mu_{u_1,\infty}} \|u_1\|_{s_{u_1},\infty,E} h^{-1/2} \|\tau^{u_1}\|_E \\
&\leq \sum_E C h^{\mu_{u_1,\infty}-1} \|((\phi^{\mathbf{z}_2} - \Pi_h \mathbf{z_2}))\|_E \|\tau^{u_1}\|_E \\
&\leq \varepsilon_5 h^{2\mu_{u_1,\infty}-2} C \|((\phi^{\mathbf{z}_2} - \Pi_h \mathbf{z_2}))\|^2 + \frac{1}{\varepsilon_5}\|\tau^{u_1}\|^2
\end{aligned}$$

In the same way:

$$T_6 \leq \varepsilon_6 h^{2\mu_{u_1,\infty}-2} C \|((\phi^{\mathbf{z}_2} - \Pi_h \mathbf{z_2}))\|^2 + \frac{1}{\varepsilon_6}\|\tau^{u_1}\|^2$$

$$\begin{aligned}
T_7 &= -\sum_E ((\nabla \cdot (D_2^{-1}\xi^{\mathbf{z}_2})) Q_h u_1, \tau^{u_1})_E \leq \sum_E \|\nabla \cdot (D_2^{-1}\xi^{\mathbf{z}_2})\|_E \|Q_h u_1\|_{\infty,E} \|\tau^{u_1}\|_E \\
&\leq \sum_E C h^{\mu_{\mathbf{z_2}}} \|\nabla \cdot \mathbf{z_2}\|_E \|\tau^{u_1}\|_E \\
&\leq \sum_E \varepsilon_7 C h^{2\mu_{\mathbf{z_2}}} \|\nabla \cdot \mathbf{z_2}\|_E^2 + \frac{1}{\varepsilon_7}\|\tau^{u_1}\|_E^2 \leq \varepsilon_7 h^{2\mu_{\mathbf{z_2}}} C + \frac{1}{\varepsilon_7}\|\tau^{u_1}\|^2
\end{aligned}$$

$$\begin{aligned}
T_8 &= -\sum_E ((D_2^{-1}\xi^{\mathbf{z}_2}) \cdot \nabla Q_h u_1, \tau^{u_1})_E \leq \sum_E \|D_2^{-1}\xi^{\mathbf{z}_2}\|_E \|\nabla Q_h u_1\|_{\infty,E} \|\tau^{u_1}\|_E \\
&\leq \sum_E \|D_2^{-1}\xi^{\mathbf{z}_2}\|_E \|\nabla Q_h u_1\|_{\infty,E} \|\tau^{u_1}\|_E \leq \sum_E C\|\xi^{\mathbf{z}_2}\|_E \|\tau^{u_1}\|_E \\
&\leq \varepsilon_8 C h^{2\mu_{\mathbf{z_2}}} \|\mathbf{z_2}\|^2 + \frac{1}{\varepsilon_8}\|\tau^{u_1}\|^2 \leq \varepsilon_8 h^{2\mu_{\mathbf{z_2}}} C + \frac{1}{\varepsilon_8}\|\tau^{u_1}\|^2
\end{aligned}$$

$$\begin{aligned}
T_9 &= \sum_e ((D_2^{-1}\xi^{\mathbf{z}_2}) \cdot \mathbf{n}_e (Q_h u_1^{up} - Q_h u_1^+), \tau^{u_1,+})_e \\
&\leq \sum_e \|(D_2^{-1}\xi^{\mathbf{z}_2}) \cdot \mathbf{n}_e\|_e \|Q_h u_1^+ - Q_h u_1^{up}\|_{0,\infty,e} \|\tau^{u_1,+}\|_e \\
&\leq \sum_E C h^{-1/2} \|(D_2^{-1}\xi^{\mathbf{z}_2})\|_E \|u_1 - Q_h u_1\|_{0,\infty,E} h^{-1/2} \|\tau^{u_1}\|_E
\end{aligned}$$

$$\leq \sum_E Ch^{-1/2}h^{\mu_{\mathbf{z_2}}}\|\mathbf{z_2}\|_E C\|u_1\|_{\infty,E}h^{-1/2}\|\tau^{u_1}\|_E$$
$$\leq \sum_E Ch^{\mu_{\mathbf{z_2}}-1}\|\mathbf{z_2}\|_E\|\tau^{u_1}\|_E \leq \sum_E \varepsilon_9 Ch^{2\mu_{\mathbf{z_2}}-2}\|\mathbf{z_2}\|_E^2 + \frac{1}{\varepsilon_9}\|\tau^{u_1}\|_E^2$$
$$\leq \varepsilon_9 h^{2\mu_{\mathbf{z_2}}-2}C + \frac{1}{\varepsilon_9}\|\tau^{u_1}\|^2$$

In the same way,

$$T_{10} \leq \varepsilon_{10}h^{2\mu_{\mathbf{z_2}}-2}C + \frac{1}{\varepsilon_{10}}\|\tau^{u_1}\|^2$$

$$T_{11} = \frac{1}{2}\sum_E(\nabla\cdot D_2^{-1}\phi^{\mathbf{z}_2},(\tau^{u_1})^2)_E \leq C\sum_E\|\nabla\cdot D_2^{-1}\phi^{\mathbf{z}_2}\|_{\infty,E}\|\tau^{u_1}\|_E^2$$
$$\leq C\sum_E\|\phi^{\mathbf{z}_2}\|_{\infty,E}\|\tau^{u_1}\|_E^2 \leq C\|\tau^{u_1}\|^2$$

$$T_{12} = (f_1(\phi_L^{u_1},\phi^{u_2}) - f_1(Q_hu_1,\phi^{u_2}),\tau^{u_1}) \leq \|f_1(\phi_L^{u_1},\phi^{u_2}) - f_1(Q_hu_1,\phi^{u_2})\|\|\tau^{u_1}\|$$
$$\leq (|f_1(\phi_L^{u_1},\phi^{u_2}) - f_1(Q_hu_1,\phi^{u_2})|,|\tau^{u_1}|) \leq (C|\phi^{u_2}||\phi_L^{u_1} - Q_hu_1|,|\tau^{u_1}|)$$
$$\leq C\|\phi^{u_2}\|_\infty\|\tau^{u_1}\|^2 \leq C\|\tau^{u_1}\|^2$$

$$T_{13} = (f_1(Q_hu_1,\phi^{u_2}) - f_1(Q_hu_1,u_2),\tau^{u_1}) \leq C\|Q_hu_1\|_\infty\|\phi^{u_2} - u_2\|\|\tau^{u_1}\|$$
$$\leq C\|\phi^{u_2} - Q_hu_2 + Q_hu_2 - u_2\|\|\tau^{u_1}\|$$
$$\leq C\|\phi^{u_2} - Q_hu_2\|\|\tau^{u_1}\| + Ch^{\mu_{u_2}}\|u_2\|_{s_{u_2}}\|\tau^{u_1}\|$$
$$\leq \varepsilon_{13}C\|\phi^{u_2} - Q_hu_2\|^2 + \frac{2}{\varepsilon_{13}}\|\tau^{u_1}\|^2 + \varepsilon_{13}Ch^{2\mu_{u_2}}\|u_2\|_{s_{u_2}}^2$$
$$\leq \varepsilon_{13}C\|\phi^{u_2} - Q_hu_2\|^2 + \frac{2}{\varepsilon_{13}}\|\tau^{u_1}\|^2 + \varepsilon_{13}h^{2\mu_{u_2}}C$$

$$T_{14} = (f_1(u_1,u_2) - f_1(Q_hu_1,u_2),\tau^{u_1}) \leq \|u_2\|_\infty\|u_1 - Q_hu_1\|\|\tau^{u_1}\|$$
$$\leq Ch^{\mu_{u_1}}\|u_1\|_{s_{u_1}}\|\tau^{u_1}\| \leq \varepsilon_{14}Ch^{2\mu_{u_1}}\|u_1\|_{s_{u_1}}^2 + \frac{1}{\varepsilon_{14}}\|\tau^{u_1}\|^2$$
$$\leq \varepsilon_{14}h^{2\mu_{u_1}}C + \frac{1}{\varepsilon_{14}}\|\tau^{u_1}\|^2$$

$$T_{15} = (\phi^{u_2}\tau^{u_1},\tau^{u_1}) \leq \|\phi^{u_2}\|_\infty\|\tau^{u_1}\|^2 \leq C\|\tau^{u_1}\|^2$$

$$T_{16} = -(Q_h u_1(\phi^{u_2} - u_2), \tau^{u_1}) \leq \|Q_h u_1\|_\infty \|\phi^{u_2} - u_2\| \|\tau^{u_1}\|$$
$$\leq C\|\phi^{u_2} - Q_h u_2 + Q_h u_2 - u_2\| \|\tau^{u_1}\|$$
$$\leq C\|\phi^{u_2} - Q_h u_2\| \|\tau^{u_1}\| + Ch^{\mu_{u_2}} \|u_2\|_{s_{u_2}} \|\tau^{u_1}\|$$
$$\leq \varepsilon_{16} C\|\phi^{u_2} - Q_h u_2\|^2 + \frac{2}{\varepsilon_{16}} \|\tau^{u_1}\|^2 + \varepsilon_{16} Ch^{2\mu_{u_2}} \|u_2\|^2_{s_{u_2}}$$
$$\leq \varepsilon_{16} C\|\phi^{u_2} - Q_h u_2\|^2 + \frac{2}{\varepsilon_{16}} \|\tau^{u_1}\|^2 + \varepsilon_{16} h^{2\mu_{u_2}} C$$

$$T_{17} = -(\xi^{u_1} u_2, \tau^{u_1}) \leq \|u_2\|_\infty \|\xi^{u_1}\| \|\tau^{u_1}\| \leq \varepsilon_{17} Ch^{2\mu_{u_1}} \|u_1\|^2_{s_{u_1}} + \frac{1}{\varepsilon_{17}} \|\tau^{u_1}\|^2$$
$$\leq \varepsilon_{17} Ch^{2\mu_{u_1}} + \frac{1}{\varepsilon_{17}} \|\tau^{u_1}\|^2$$

$$T_{18} = (D_1^{-1} \xi^{\mathbf{z}_1}, \tau^{\mathbf{z}_1}) \leq \|D_1^{-1} \xi^{\mathbf{z}_1}\| \|\tau^{\mathbf{z}_1}\| \leq Ch^{\mu_{\mathbf{z}_1}} \|\mathbf{z_1}\|_{s_{\mathbf{z}_1}} \|\tau^{\mathbf{z}_1}\|$$
$$\leq \frac{C}{\varepsilon_{18}} h^{2\mu_{\mathbf{z}_1}} \|\mathbf{z_1}\|^2_{s_{\mathbf{z}_1}} + \varepsilon_{18} \|\tau^{\mathbf{z}_1}\|^2 \leq \frac{C}{\varepsilon_{18}} h^{2\mu_{\mathbf{z}_1}} + \varepsilon_{18} \|\tau^{\mathbf{z}_1}\|^2$$

$$T_{19} = (f_2(\phi^{u_1}, \phi_L^{u_2}) - f_2(\phi^{u_1}, Q_h u_2), \tau^{u_2})$$
$$\leq \|\phi^{u_1}\|_\infty \|\phi_L^{u_2} - Q_h u_2\| \|\tau^{u_2}\| \leq C\|\tau^{u_2}\|^2$$

$$T_{20} = (f_2(\phi^{u_1}, Q_h u_2) - f_2(u_1, Q_h u_2), \tau^{u_2})$$
$$\leq \|Q_h u_2\|_\infty \Big(\|\phi^{u_1} - Q_h u_1\| + \|Q_h u_1 - u_1\| \Big) \|\tau^{u_2}\|$$
$$\leq C\|\phi^{u_1} - Q_h u_1\| \|\tau^{u_2}\| + Ch^{\mu_{u_1}} \|u_1\|_{s_{u_1}} \|\tau^{u_2}\|$$
$$\leq \varepsilon_{20} \|\phi^{u_1} - Q_h u_1\|^2 + \frac{C}{\varepsilon_{20}} \|\tau^{u_2}\|^2 + \varepsilon_{20} h^{2\mu_{u_1}} \|u_1\|^2_{s_{u_1}}$$

$$T_{21} = -(f_2(u_1, u_2) - f_2(u_1, Q_h u_2), \tau^{u_2}) \leq \|u_1\|_\infty \|u_2 - Q_h u_2\| \|\tau^{u_2}\|$$
$$\leq Ch^{\mu_{u_2}} \|u_2\|_{s_{u_2}} \|\tau^{u_2}\| \leq Ch^{2\mu_{u_2}} + C\|\tau^{u_2}\|^2$$

$$T_{22} = (D_2^{-1} \xi^{\mathbf{z}_2}, \tau^{\mathbf{z}_2}) \leq \|D_2^{-1} \xi^{\mathbf{z}_2}\| \|\tau^{\mathbf{z}_2}\| \leq Ch^{\mu_{\mathbf{z}_2}} \|\mathbf{z_2}\|_{s_{\mathbf{z}_2}} \|\tau^{\mathbf{z}_2}\|$$
$$\leq C \frac{h^{2\mu_{\mathbf{z}_2}}}{\varepsilon_{22}} \|\mathbf{z_2}\|^2_{s_{\mathbf{z}_2}} + \varepsilon_{22} \|\tau^{\mathbf{z}_2}\|^2$$

Put $T_1, T_2, T_3, \cdots, T_{16}, T_{17}, T_{18}$ into (5.59) assuming that $h < 1$ and noting that $r \geq 1$, and D_1, D_2 are SPD,

$$\begin{aligned}
&\frac{1}{2}\frac{d}{dt}\|\tau^{u_1}\|^2 + \frac{1}{2}\sum_e (|D_2^{-1}\phi^{\mathbf{z}_2}\cdot\mathbf{n}_e|, [\tau^{u_1}]^2)_e + C\|\tau^{\mathbf{z}_1}\|^2 \\
&\leq \left(\frac{1}{\varepsilon_1}+\frac{1}{\varepsilon_2}+\frac{1}{\varepsilon_3}+\frac{1}{\varepsilon_4}+\frac{1}{\varepsilon_5}+\frac{1}{\varepsilon_6}+\frac{1}{\varepsilon_7}+\frac{1}{\varepsilon_8}\right. \\
&\qquad\left.+\frac{1}{\varepsilon_9}+\frac{1}{\varepsilon_{10}}+\frac{2}{\varepsilon_{13}}+\frac{1}{\varepsilon_{14}}+\frac{2}{\varepsilon_{16}}+\frac{1}{\varepsilon_{17}}+C\right)\|\tau^{u_1}\|^2 \\
&\quad +\varepsilon_{18}\|\tau^{\mathbf{z}_1}\|^2 + (\varepsilon_1+\varepsilon_{14}+\varepsilon_{17})Ch^{2\mu_{u_1}} + \varepsilon_2 Ch^{2\mu_{u_1}-2} \\
&+(\varepsilon_{13}+\varepsilon_{16})Ch^{2\mu_{u_2}} + \frac{C}{\varepsilon_{18}}h^{2\mu_{\mathbf{z_1}}} + (\varepsilon_7+\varepsilon_8)Ch^{2\mu_{\mathbf{z_2}}} + (\varepsilon_9+\varepsilon_{10})Ch^{2\mu_{\mathbf{z_2}}-2} \\
&+(\varepsilon_{13}+\varepsilon_{16})C\|\phi^{u_2}-Q_h u_2\|^2 + \left(\varepsilon_4 C + (\varepsilon_5+\varepsilon_6)Ch^{2\mu_{u_1,\infty}-2}\right)\|((\phi^{\mathbf{z}_2}-\Pi_h\mathbf{z_2}))\|^2 \\
&+\varepsilon_3 C\|\nabla\cdot((\phi^{\mathbf{z}_2}-\Pi_h\mathbf{z_2})\|^2 \qquad (5.61)
\end{aligned}$$

Define:

$$\frac{1}{\varepsilon'} := \frac{1}{\varepsilon_1}+\frac{1}{\varepsilon_2}+\frac{1}{\varepsilon_3}+\frac{1}{\varepsilon_4}+\frac{1}{\varepsilon_5}+\frac{1}{\varepsilon_6}+\frac{1}{\varepsilon_7}+\frac{1}{\varepsilon_8}+\frac{1}{\varepsilon_9}+\frac{1}{\varepsilon_{10}}+\frac{2}{\varepsilon_{13}}+\frac{1}{\varepsilon_{14}}+\frac{2}{\varepsilon_{16}}+\frac{1}{\varepsilon_{17}}.$$

Since $u_1 \in L^2(0,T;H^3(\Omega))$, then $\nabla u_1 \in L^2(0,T;H^2(\Omega))$ and $\nabla u_1 \in L^2(0,T;L^\infty(\Omega))$ we have $\mu_{u_1,\infty} = 1$. Using this information, multiplying (5.61) by 2, choosing ε_{18} carefully, integrating with respect to time, and noting that $h < 1$ gives:

$$\begin{aligned}
&\|\tau^{u_1}\|^2 + \int_0^t \sum_e (|D_2^{-1}\phi^{\mathbf{z}_2}\cdot\mathbf{n}_e|, [\tau^{u_1}]^2)_e + C\int_0^t \|\tau^{\mathbf{z}_1}\|^2 \\
&\leq \left(\frac{1}{\varepsilon'}+C\right)\int_0^t \|\tau^{u_1}\|^2 + (\varepsilon_1+\varepsilon_{14}+\varepsilon_{17}+\varepsilon_2)C\int_0^t h^{2\mu_{u_1}-2} \\
&\quad +(\varepsilon_{13}+\varepsilon_{16})C\int_0^t h^{2\mu_{u_2}} + \frac{C}{\varepsilon_{18}}\int_0^t h^{2\mu_{\mathbf{z_1}}} + (\varepsilon_7+\varepsilon_8+\varepsilon_9+\varepsilon_{10})C\int_0^t h^{2\mu_{\mathbf{z_2}}-2} \\
&\quad +(\varepsilon_{13}+\varepsilon_{16})C\int_0^t \|\phi^{u_2}-Q_h u_2\|^2 + (\varepsilon_4+\varepsilon_5+\varepsilon_6)C\int_0^t \|((\phi^{\mathbf{z}_2}-\Pi_h\mathbf{z_2}))\|^2 \\
&\quad +\varepsilon_3 C\int_0^t \|\nabla\cdot((\phi^{\mathbf{z}_2}-\Pi_h\mathbf{z_2})\|^2 + \|\tau^{u_1}\|(0)
\end{aligned}$$

Apply the Gronwall Inequality, theorem 4.8, while noting that $\|\tau^{u_1}\|(0) = 0$:

$$\|\tau^{u_1}\|^2 + \int_0^t \sum_e (|D_2^{-1}\phi^{\mathbf{z}_2}\cdot\mathbf{n}_e|, [\tau^{u_1}]^2)_e + C\int_0^t \|\tau^{\mathbf{z}_1}\|^2$$

$$\leq e^{(\frac{1}{\varepsilon'}+C)t}\Bigg[(\varepsilon_1+\varepsilon_{14}+\varepsilon_{17}+\varepsilon_2)C\int_0^t h^{2\mu_{u_1}-2}$$
$$+(\varepsilon_{13}+\varepsilon_{16})C\int_0^t h^{2\mu_{u_2}}+\frac{C}{\varepsilon_{18}}\int_0^t h^{2\mu_{\mathbf{z_1}}}+(\varepsilon_7+\varepsilon_8+\varepsilon_9+\varepsilon_{10})C\int_0^t h^{2\mu_{\mathbf{z_2}}-2}$$
$$+(\varepsilon_{13}+\varepsilon_{16})C\int_0^t \|\phi^{u_2}-Q_hu_2\|^2+\Big(\varepsilon_4+\varepsilon_5+\varepsilon_6)C\int_0^t \|((\phi^{\mathbf{z}_2}-\Pi_h\mathbf{z_2}))\|^2$$
$$+\varepsilon_3C\int_0^t \|\nabla\cdot((\phi^{\mathbf{z}_2}-\Pi_h\mathbf{z_2})\|^2\Bigg]$$

Using the definition of the space, S,

$$\|\tau^{u_1}\|^2+\int_0^t\sum_e(|D_2^{-1}\phi^{\mathbf{z}_2}\cdot\mathbf{n}_e|,[\tau^{u_1}]^2)_e+C\int_0^t\|\tau^{\mathbf{z}_1}\|^2$$
$$\leq e^{(\frac{1}{\varepsilon'}+C)t}\Bigg[(\varepsilon_1+\varepsilon_{14}+\varepsilon_{17}+\varepsilon_2)Ch^{2\mu_{u_1}-2}$$
$$+(\varepsilon_{13}+\varepsilon_{16})Ch^{2\mu_{u_2}}+\frac{C}{\varepsilon_{18}}h^{2\mu_{\mathbf{z_1}}}+(\varepsilon_7+\varepsilon_8+\varepsilon_9+\varepsilon_{10})Ch^{2\mu_{\mathbf{z_2}}-2}$$
$$+\Big((\varepsilon_{13}+\varepsilon_{16})CC_{u_1}+(\varepsilon_4+\varepsilon_5+\varepsilon_6+\varepsilon_3)CC_{\mathbf{z_2}}\Big)(h^{2\mu_{u_1}-2}+h^{2\mu_{u_2}}+h^{2\mu_{\mathbf{z_1}}}+h^{2\mu_{\mathbf{z_2}}-2})\Bigg]$$

So,

$$\|\tau^{u_1}\|^2+\int_0^t\sum_e(|D_2^{-1}\phi^{\mathbf{z}_2}\cdot\mathbf{n}_e|,[\tau^{u_1}]^2)_e+C\int_0^t\|\tau^{\mathbf{z}_1}\|^2$$
$$\leq e^{(\frac{1}{\varepsilon'}+C)t}\Bigg[C^*(h^{2\mu_{u_1}-2}+h^{2\mu_{u_2}}+h^{2\mu_{\mathbf{z_1}}}+h^{2\mu_{\mathbf{z_2}}-2})$$
$$+\Big((\varepsilon_{13}+\varepsilon_{16})CC_{u_1}+(\varepsilon_4+\varepsilon_5+\varepsilon_6+\varepsilon_3)CC_{\mathbf{z_2}}\Big)(h^{2\mu_{u_1}-2}+h^{2\mu_{u_2}}+h^{2\mu_{\mathbf{z_1}}}+h^{2\mu_{\mathbf{z_2}}-2})\Bigg]$$

Finally,

$$\|\tau^{u_1}\|^2+\int_0^t\sum_e(|D_2^{-1}\phi^{\mathbf{z}_2}\cdot\mathbf{n}_e|,[\tau^{u_1}]^2)_e+C'\int_0^t\|\tau^{\mathbf{z}_1}\|^2$$
$$\leq e^{(\frac{1}{\varepsilon'}+C)t}\Bigg[C^*+\Bigg((\varepsilon_{13}+\varepsilon_{16})CC_{u_1}$$
$$+(\varepsilon_4+\varepsilon_5+\varepsilon_6+\varepsilon_3)CC_{\mathbf{z_2}}\Bigg)\Bigg](h^{2\mu_{u_1}-2}+h^{2\mu_{u_2}}+h^{2\mu_{\mathbf{z_1}}}+h^{2\mu_{\mathbf{z_2}}-2}). \tag{5.62}$$

Define $C_{u_1} := 2C^* + 2$.

Define $C_{\mathbf{z}_1} := 2C^*/C' + 2/C'$.

Now, if $\varepsilon_3, \varepsilon_4, \varepsilon_5, \varepsilon_6, \varepsilon_{13}, \varepsilon_{16}$ are chosen small enough then there exists a t_1 such that for $t \leq t_1$ the sum of the constants on the right hand side of (5.62) is less than C_{u_1} and less than $C'C_{\mathbf{z}_1}$.

Thus, (5.62) gives us a bound for $\|\tau^{u_1}\|^2(t), \int_0^t \|\tau^{\mathbf{z}_1}\|^2$. We will also require bounds for $\|\tau^{u_2}\|^2(t), \int_0^t \|\tau^{\mathbf{z}_2}\|^2, \|\nabla \cdot \tau^{\mathbf{z}_2}\|$. This will be done below.

Equation for $\|\tau^{u_2}\|^2(t)$

Put $T_{19}, T_{20}, T_{21}, T_{22}$ into (5.60) assuming that $h < 1$ and noting that $r \geq 1$, and D_1, D_2 are singular positive definite (SPD),

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}\|\tau^{u_2}\|^2 + C\|\tau^{\mathbf{z}_2}\|^2 \leq \left(C + \frac{2}{\varepsilon_{20}}\right)\|\tau^{u_2}\|^2 + \varepsilon_{22}\|\tau^{\mathbf{z}_2}\|^2 + \varepsilon_{20}h^{2\mu_{u_1}}\|u_1\|^2_{s_{u_1}} \\ +\varepsilon_{21}Ch^{2\mu_{u_2}}\|u_2\|^2_{s_{u_2}} + \frac{1}{\varepsilon_{22}}h^{2\mu_{\mathbf{z}_2}}\|\mathbf{z_2}\|^2 + \varepsilon_{20}\|\phi^{u_1} - Q_h u_1\|^2 \qquad (5.63)\end{aligned}$$

Multiply (5.63) by 2 and choose ε_{21} carefully then integrate

$$\begin{aligned}\|\tau^{u_2}\|^2 + C\int_0^t \|\tau^{\mathbf{z}_2}\|^2 \leq 2\int_0^t \left(C + \frac{2}{\varepsilon_{20}}\right)\|\tau^{u_2}\|^2 + 2\varepsilon_{20}C\int_0^t h^{2\mu_{u_1}}\|u_1\|^2_{s_{u_1}} \\ +2\varepsilon_{21}C\int_0^t h^{2\mu_{u_2}}\|u_2\|^2_{s_{u_2}} + \frac{2C}{C_{\varepsilon_{22}}}\int_0^t h^{2\mu_{\mathbf{z}_2}}\|\mathbf{z_2}\|^2 + 2\varepsilon_{20}\int_0^t \|\phi^{u_1} - Q_h u_1\|^2 + \|\tau^{u_2}\|^2(0)\end{aligned}$$

Using the regularity noted above, note that $\|\tau^{u_2}\|^2(0) = 0$, and apply the Gronwall Inequality, theorem 4.8,

$$\begin{aligned}\|\tau^{u_2}\|^2 + C\int_0^t \|\tau^{\mathbf{z}_2}\|^2 \leq e^{(2C+\frac{4}{\varepsilon_{20}})t}\Bigg[C^{**}\left(h^{2\mu_{u_1}} + h^{2\mu_{u_2}} + h^{2\mu_{\mathbf{z}_2}}\right) \\ +2\varepsilon_{20}\int_0^t \|\phi^{u_1} - Q_h u_1\|^2\Bigg]\end{aligned}$$

Using the definition of the space S and noting that $h < 1$,

$$\|\tau^{u_2}\|^2 + C\int_0^t \|\tau^{\mathbf{z}_2}\|^2 \leq e^{(2C+\frac{4}{\varepsilon_{20}})t}\Bigg[(C^{**} + 2\varepsilon_{20}C_{u_1})\Big(h^{2\mu_{u_1}-2} + h^{2\mu_{u_2}}$$

$$+h^{2\mu_{\mathbf{z_1}}}+h^{2\mu_{\mathbf{z_2}}-2}\Big)\Big] \tag{5.64}$$

Define $C_{u_2}:=2C^{**}+2C_{u_1}$.

Note that for small enough ε_{20} there exists a t_2 such that for $t\le t_2$, we have

$$e^{(2C+\frac{4}{\varepsilon_{20}})t}(C^{**}+2\varepsilon_{20}C_{u_1})\le 2C^{**}+2C_{u_1}.$$

Equation for $\int_0^t\|\tau_t^{u_2}\|^2(t)$

Go back to (5.43) and (5.44), noting that $(\xi^{u_2},\nabla\cdot v)=0$,$(\nabla\cdot\xi^{\mathbf{z}_2},w)=0$ $((\xi^{u_2})_t,w))=0$:

$$\begin{aligned}((\phi_L^{u_2})_t-Q_hu_{2_t},w)+(\nabla\cdot(\phi_L^{\mathbf{z}_2}-\Pi_h\mathbf{z_2}),w)-(f_2(\phi^{u_1},\phi_L^{u_2})-f_2(u_1,Q_hu_2),w)\ =\\ -(f_2(u_1,u_2)-f_2(u_1,Q_hu_2),w)\end{aligned} \tag{5.65}$$

$$(D_2^{-1}(\phi_L^{\mathbf{z}_2}-\Pi_h\mathbf{z_2}),v)-(\phi_L^{u_2}-Q_hu_2,\nabla\cdot v)=(D_2^{-1}\xi^{\mathbf{z}_2},v) \tag{5.66}$$

Take the derivative with respect to t of (5.66), then (5.65) and (5.66) become:

$$\begin{aligned}(\tau_t^{u_2},w)+(\nabla\cdot\tau^{\mathbf{z}_2},w)-(f_2(\phi^{u_1},\phi_L^{u_2})-f_2(u_1,Q_hu_2),w)\ =\\ -(f_2(u_1,u_2)-f_2(u_1,Q_hu_2),w)\end{aligned} \tag{5.67}$$

$$(D_2^{-1}\tau_t^{\mathbf{z}_2},v)-(\tau_t^{u_2},\nabla\cdot v)=(D_2^{-1}\xi_t^{\mathbf{z}_2},v) \tag{5.68}$$

Set $v=\tau^{\mathbf{z}_2}$ and $w=\tau_t^{u_2}$, then substitute the (5.68) into (5.67) and add/subtract appropriate terms:

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}\|D_2^{-1/2}\tau^{\mathbf{z}_2}\|^2+\|\tau_t^{u_2}\|^2=(D_2^{-1}\xi_t^{\mathbf{z}_2},\tau^{\mathbf{z}_2})+(f_2(\phi^{u_1},\phi_L^{u_2}),\tau_t^{u_2})-(f_2(\phi^{u_1},Q_hu_2),\tau_t^{u_2})\\ +(f_2(\phi^{u_1},Q_hu_2),\tau_t^{u_2})-(f_2(u_1,Q_hu_2),\tau_t^{u_2})-(f_2(u_1,u_2)-f_2(u_1,Q_hu_2),\tau_t^{u_2})\end{aligned}$$

Then

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}\|D_2^{-1/2}\tau^{\mathbf{z}_2}\|^2+\|\tau_t^{u_2}\|^2&\le\|\xi_t^{\mathbf{z}_2}\|\|\tau^{\mathbf{z}_2}\|+\|\phi^{u_1}\|_\infty\|\phi_L^{u_2}-Q_hu_2\|\|\tau_t^{u_2}\|\\ &+\|\phi^{u_1}-Q_hu_1+Q_hu_1-u_1\|\|Q_hu_2\|_\infty\|\tau_t^{u_2}\|+\|u_1\|_\infty\|u_2-Q_hu_2\|\|\tau_t^{u_2}\|\\ &\le\frac{1}{2}\|\xi_t^{\mathbf{z}_2}\|^2+\frac{1}{2}\|\tau^{\mathbf{z}_2}\|^2+\frac{C}{\varepsilon_1^*}\|\phi_L^{u_2}-Q_hu_2\|^2+\varepsilon_1^*\|\tau_t^{u_2}\|^2\end{aligned}$$

$$+\frac{C}{\varepsilon_2^*}\|\phi^{u_1}-Q_hu_1\|^2+\frac{C}{\varepsilon_3^*}\|Q_hu_1-u_1\|^2+(\varepsilon_2^*+\varepsilon_3^*)\|\tau_t^{u_2}\|^2$$
$$+\frac{C}{\varepsilon_4^*}\|u_2-Q_hu_2\|^2+\varepsilon_4^*\|\tau_t^{u_2}\|^2$$

Choose $\varepsilon_1^*,\varepsilon_2^*,\varepsilon_3^*,\varepsilon_4^*$ carefully

$$\frac{1}{2}\frac{d}{dt}\|D_2^{-1/2}\tau^{\mathbf{z}_2}\|^2+C\|\tau_t^{u_2}\|^2\leq\frac{1}{2}h^{2\mu_{\mathbf{z_2}}}+\frac{1}{2}\|\tau^{\mathbf{z}_2}\|^2+\frac{C}{C_{\varepsilon_1^*}}\|\tau^{u_2}\|^2$$
$$+\frac{C}{C_{\varepsilon_2^*}}\|\phi^{u_1}-Q_hu_1\|^2+C\frac{h^{2\mu_{u_1}}}{C_{\varepsilon_3^*}}+C\frac{h^{2\mu_{u_2}}}{C_{\varepsilon_4^*}}$$

Multiply by 2 and integrate with respect to t, and apply the Gronwall Inequality, theorem 4.8:

$$\|\tau^{\mathbf{z}_2}\|^2+2C\int_0^t\|\tau_t^{u_2}\|^2\leq e^t\left[2\frac{C}{C_{\varepsilon_1^*}}\int_0^t\|\tau^{u_2}\|^2+2\frac{C}{C_{\varepsilon_2^*}}\int_0^t\|\phi^{u_1}-Q_hu_1\|^2\right.$$
$$\left.+\int_0^t\left(2Ch^{2\mu_{\mathbf{z_2}}}+2C\frac{h^{2\mu_{u_1}}}{C_{\varepsilon_3^*}}+2C\frac{h^{2\mu_{u_2}}}{C_{\varepsilon_4^*}}\right)\right] \tag{5.69}$$

Equation for $\int_0^t\|\nabla\cdot\tau^{\mathbf{z}_2}\|^2$

Go back to (5.67):

$$(\tau_t^{u_2},w)+(\nabla\cdot\tau^{\mathbf{z}_2},w)-(f_2(\phi^{u_1},\phi_L^{u_2})-f_2(u_1,Q_hu_2),w)\ =$$
$$-(f_2(u_1,u_2)-f_2(u_1,Q_hu_2),w)$$

Set $w=\nabla\cdot\tau^{\mathbf{z}_2}$:

$$\|\nabla\cdot\tau^{\mathbf{z}_2}\|^2\leq\|\tau_t^{u_2}\|\|\nabla\cdot\tau^{\mathbf{z}_2}\|+\|f_2(\phi^{u_1},\phi_L^{u_2})-f_2(u_1,Q_hu_2)\|\|\nabla\cdot\tau^{\mathbf{z}_2}\|$$
$$+\|f_2(u_1,u_2)-f_2(u_1,Q_hu_2)\|\|\nabla\cdot\tau^{\mathbf{z}_2}\|$$

$$\|\nabla\cdot\tau^{\mathbf{z}_2}\|^2\leq(\varepsilon_1^{**}+\varepsilon_2^{**}+\varepsilon_3^{**})\|\nabla\cdot\tau^{\mathbf{z}_2}\|^2+C\|\tau_t^{u_2}\|^2+C\|\tau^{u_2}\|^2+C\|\phi^{u_1}-Q_hu_1\|^2$$
$$+Ch^{2\mu_{u_1}}+Ch^{2\mu_{u_2}}$$

Choose $\varepsilon_1^{**}, \varepsilon_2^{**}, \varepsilon_3^{**}$ carefully and integrate from 0 to t:

$$C\int_0^t \|\nabla\cdot\tau^{\mathbf{z}_2}\|^2 \le C\int_0^t \|\tau_t^{u_2}\|^2 + C\int_0^t \|\tau^{u_2}\|^2 \\ +C\int_0^t \|\phi^{u_1} - Q_h u_1\|^2 + C\int_0^t h^{2\mu_{u_1}} + C\int_0^t h^{2\mu_{u_2}} \tag{5.70}$$

Substitute (5.69) into (5.70):

$$\int_0^t \|\nabla\cdot\tau^{\mathbf{z}_2}\|^2 \le e^t\left[2\frac{C}{C_{\varepsilon_1^*}}\int_0^t \|\tau^{u_2}\|^2 + 2\frac{C}{C_{\varepsilon_2^*}}\int_0^t \|\phi^{u_1} - Q_h u_1\|^2 \right. \\ \left. + \int_0^t \left(2Ch^{2\mu_{\mathbf{z_2}}} + 2C\frac{h^{2\mu_{u_1}}}{C_{\varepsilon_3^*}} + 2C\frac{h^{2\mu_{u_2}}}{C_{\varepsilon_4^*}}\right)\right] \\ +C\|\tau^{u_2}\|^2 + C\|\phi^{u_1} - Q_h u_1\|^2 + Ch^{2\mu_{u_1}} + Ch^{2\mu_{u_2}} \tag{5.71}$$

.

More Bounds.

Consider (5.64),

$$\|\tau^{u_2}\|^2 + C\int_0^t \|\tau^{\mathbf{z}_2}\|^2 \leq e^{(2C+\frac{4}{\varepsilon_{20}})t}\Bigg[(C^{**}+2\varepsilon_{20}C_{u_1})\Big(h^{2\mu_{u_1}-2}+h^{2\mu_{u_2}} +h^{2\mu_{\mathbf{z_1}}}+h^{2\mu_{\mathbf{z_2}}-2}\Big)\Bigg] \tag{5.72}$$

Combine equations (5.72), (5.69) and (5.71),

$$\begin{aligned}
&\|\tau^{u_2}\|^2 + \|\tau^{\mathbf{z}_2}\|^2 + C\int_0^t \|\tau^{\mathbf{z}_2}\|^2 + \int_0^t \|\nabla\cdot\tau^{\mathbf{z}_2}\|^2 + C\int_0^t \|\tau_t^{u_2}\|^2 \\
&\quad\leq e^{(2C+\frac{4}{\varepsilon_{20}})t}\Bigg[(C^{**}+2\varepsilon_{20}C_{u_1})\Big(h^{2\mu_{u_1}-2}+h^{2\mu_{u_2}} \\
&\qquad +h^{2\mu_{\mathbf{z_1}}}+h^{2\mu_{\mathbf{z_2}}-2}\Big)\Bigg] \qquad (5.73)\\
&+e^t\Bigg[2\frac{C}{C_{\varepsilon_1^*}}\int_0^t \|\tau^{u_2}\|^2 + 2\frac{C}{C_{\varepsilon_2^*}}\int_0^t \|\phi^{u_1}-Q_hu_1\|^2 \\
&\qquad +\int_0^t\left(2Ch^{2\mu_{\mathbf{z_2}}}+2C\frac{h^{2\mu_{u_1}}}{C_{\varepsilon_3^*}}+2C\frac{h^{2\mu_{u_2}}}{C_{\varepsilon_4^*}}\right)\Bigg] \\
&e^t\Bigg[2\frac{C}{C_{\varepsilon_1^*}}\int_0^t \|\tau^{u_2}\|^2 + 2\frac{C}{C_{\varepsilon_2^*}}\int_0^t \|\phi^{u_1}-Q_hu_1\|^2 \\
&\qquad +\int_0^t\left(2Ch^{2\mu_{\mathbf{z_2}}}+2C\frac{h^{2\mu_{u_1}}}{C_{\varepsilon_3^*}}+2C\frac{h^{2\mu_{u_2}}}{C_{\varepsilon_4^*}}\right)\Bigg] \\
&+C\int_0^t \|\tau^{u_2}\|^2 + C\int_0^t \|\phi^{u_1}-Q_hu_1\|^2 + C\int_0^t h^{2\mu_{u_1}} + C\int_0^t h^{2\mu_{u_2}}
\end{aligned}$$

Now,

$$\begin{aligned}
&\|\tau^{u_2}\|^2 + \|\tau^{\mathbf{z}_2}\|^2 + C\int_0^t \|\tau^{\mathbf{z}_2}\|^2 + \int_0^t \|\nabla\cdot\tau^{\mathbf{z}_2}\|^2 + C\int_0^t \|\tau_t^{u_2}\|^2 \\
&\quad\leq \Bigg[e^{(2C+\frac{4}{\varepsilon_{20}})t}(C^{**}+2\varepsilon_{20}C_{u_1})\Big(h^{2\mu_{u_1}-2}+h^{2\mu_{u_2}} \\
&\qquad +h^{2\mu_{\mathbf{z_1}}}+h^{2\mu_{\mathbf{z_2}}-2}\Big)\Bigg] + \Big(4e^t\frac{C}{C_{\varepsilon_1^*}}+C\Big)\int_0^t \|\tau^{u_2}\|^2 \qquad (5.74)
\end{aligned}$$

$$+2e^t\int_0^t\left(2Ch^{2\mu_{\mathbf{z_2}}}+2C\frac{h^{2\mu_{u_1}}}{C_{\varepsilon_3^*}}+2C\frac{h^{2\mu_{u_2}}}{C_{\varepsilon_4^*}}\right)\Bigg]$$
$$+4e^t\Big(\frac{C}{C_{\varepsilon_2^*}}+C\Big)\int_0^t\|\phi^{u_1}-Q_hu_1\|^2+C\int_0^t h^{2\mu_{u_1}}+C\int_0^t h^{2\mu_{u_2}}$$

Apply the Gronwall Inequality, theorem 4.8, take the sup of both sides and use the definition of the space S,

$$\|\tau^{u_2}\|^2+\|\tau^{\mathbf{z}_2}\|^2+C\int_0^t\|\tau^{\mathbf{z}_2}\|^2+\int_0^t\|\nabla\cdot\tau^{\mathbf{z}_2}\|^2+C\int_0^t\|\tau_t^{u_2}\|^2$$
$$\leq e^{\left(4e^t\frac{C}{C_{\varepsilon_1^*}}+C\right)t}\Bigg[\Big(e^{(2C+\frac{4}{\varepsilon_{20}})t}(C^{**}+2\varepsilon_{20}C_{u_1})+Ce^t\Big)\Big(h^{2\mu_{u_1}-2}+h^{2\mu_{u_2}}$$
$$+h^{2\mu_{\mathbf{z_1}}}+h^{2\mu_{\mathbf{z_2}}-2}\Big)\Bigg] \tag{5.75}$$

Noting that all factors on the right hand side are constants except for h, there exists a C^{II}, C^{III} and C^{IV} such that

$$\sup_{t\in[0,T]}\Big(\|\tau^{u_2}\|^2+\|\tau^{\mathbf{z}_2}\|^2\Big)+C\int_0^T\|\tau^{\mathbf{z}_2}\|^2+\int_0^T\|\nabla\cdot\tau^{\mathbf{z}_2}\|^2+C\int_0^T\|\tau_t^{u_2}\|^2$$
$$\leq\left[\Big(C^{II}C^{**}+C^{III}C_{u_1}+C^{IV}\Big)\Big(h^{2\mu_{u_1}-2}+h^{2\mu_{u_2}}+h^{2\mu_{\mathbf{z_1}}}+h^{2\mu_{\mathbf{z_2}}-2}\Big)\right] \tag{5.76}$$

Since $\|\tau^{u_2}\|^2$ is non-negative, we can say

$$\sup_{t\in[0,T]}\|\tau^{\mathbf{z}_2}\|^2\leq\sup_{t\in[0,T]}\Big(\|\tau^{u_2}\|^2+\|\tau^{\mathbf{z}_2}\|^2\Big)$$

Therefore, from (5.76), we can say

$$\sup_{t\in[0,T]}\|\tau^{\mathbf{z}_2}\|^2+C\int_0^T\|\tau^{\mathbf{z}_2}\|^2+\int_0^T\|\nabla\cdot\tau^{\mathbf{z}_2}\|^2+C\int_0^T\|\tau_t^{u_2}\|^2$$
$$\leq\left[\Big(C^{II}C^{**}+C^{III}C_{u_1}+C^{IV}\Big)\Big(h^{2\mu_{u_1}-2}+h^{2\mu_{u_2}}+h^{2\mu_{\mathbf{z_1}}}+h^{2\mu_{\mathbf{z_2}}-2}\Big)\right] \tag{5.77}$$

Define $C_{\mathbf{z_2}}:=C^{II}C^{**}+C^{III}C_{u_1}+C^{IV}$.

Now, the constants in the space S have been defined. Furthermore, we can now define $\widetilde{t}=\min(t_1,t_2)$. (Note that t_1 is defined immediately after (5.62) and t_2 is defined immediately after (5.64)).

Therefore, we can say $(\phi_L^{u_1},\phi_L^{\mathbf{z}_1},\phi_L^{u_2},\phi_L^{\mathbf{z}_2})\in S$.

Now, prove that the mapping, A, has a fixed point in S.

Theorem 5.4. *The mapping A is continuous.*

Proof. Choose any sequence

$$\{(\phi_n^{u_1}, \phi_n^{u_2}, \phi_n^{\mathbf{z}_1}, \phi_n^{\mathbf{z}_2})\} \in S \qquad \text{such that}$$

$$\lim_{n\to\infty} \sup_{t\in[0,T]} \|(\phi_n^{u_1}, \phi_n^{u_2}, \phi_n^{\mathbf{z}_1}, \phi_n^{\mathbf{z}_2}) - (\phi^{u_1}, \phi^{u_2}, \phi^{\mathbf{z}_1}, \phi^{\mathbf{z}_2})\|_S = 0.$$

Recall the mapping, $A(\phi^{u_1}, \phi^{\mathbf{z}_1}, \phi^{u_2}, \phi^{\mathbf{z}_2}) = (\phi_L^{u_1}, \phi_L^{\mathbf{z}_1}, \phi_L^{u_2}, \phi_L^{\mathbf{z}_2})$ defined by (5.31),(5.32),(5.33),(5.34):

$$(\phi_{L_t}^{u_1}, w) + \sum_E (\phi_L^{u_1} D_2^{-1} \phi^{\mathbf{z}_2}, \nabla w)_E + \sum_e (D_2^{-1}\phi^{\mathbf{z}_2} \cdot \mathbf{n}_e \phi_{L_{up}}^{u_1}, [w])_e$$
$$+(\nabla \cdot \phi_L^{\mathbf{z}_1}, w) - (f_1(\phi_L^{u_1}, \phi^{u_2}), w) = 0 \tag{5.78}$$

$$(D_1^{-1}\phi_L^{\mathbf{z}_1}, v) = (\phi_L^{u_1}, \nabla \cdot v) \tag{5.79}$$

$$(\phi_{L_t}^{u_2}, w) + (\nabla \cdot \phi_L^{\mathbf{z}_2}, w) - (f_2(\phi^{u_1}, \phi_L^{u_2}), w) = 0 \tag{5.80}$$

$$(D_2^{-1}\phi_L^{\mathbf{z}_2}, v) = (\phi_L^{u_2}, \nabla \cdot v). \tag{5.81}$$

We may also do $A(\phi_n^{u_1}, \phi_n^{\mathbf{z}_1}, \phi_n^{u_2}, \phi_n^{\mathbf{z}_2}) = (\phi_{L,n}^{u_1}, \phi_{L,n}^{\mathbf{z}_1}, \phi_{L,n}^{u_2}, \phi_{L,n}^{\mathbf{z}_2})$ where:

$$(\phi_{L,n_t}^{u_1}, w) + \sum_E (\phi_{L,n}^{u_1} D_2^{-1} \phi_n^{\mathbf{z}_2}, \nabla w)_E + \sum_e (D_2^{-1}\phi_n^{\mathbf{z}_2} \cdot \mathbf{n}_e \phi_{L,n_{up}}^{u_1}, [w])_e$$
$$+(\nabla \cdot \phi_{L,n}^{\mathbf{z}_1}, w) - (f_2(\phi_{L,n}^{u_1}, \phi_n^{u_2}), w) = 0 \tag{5.82}$$

$$(D_1^{-1}\phi_{L,n}^{\mathbf{z}_1}, v) = (\phi_{L,n}^{u_1}, \nabla \cdot v) \tag{5.83}$$

$$(\phi_{L,n_t}^{u_2}, w) + (\nabla \cdot \phi_{L,n}^{\mathbf{z}_2}, w) - (f_2(\phi_n^{u_1}, \phi_{L,n}^{u_2}), w) = 0 \tag{5.84}$$

$$(D_2^{-1}\phi_{L,n}^{\mathbf{z}_2}, v) = (\phi_{L,n}^{u_2}, \nabla \cdot v). \tag{5.85}$$

Subtract (5.82),(5.83).(5.84), and (5.85) from (5.78),(5.79).(5.80), and (5.81), respectively

$$\begin{aligned}
&(\phi_{L_t}^{u_1} - \phi_{L,n_t}^{u_1}, w) + \sum_E (D_2^{-1}(\phi_L^{u_1}\phi^{\mathbf{z}_2} - \phi_{L,n}^{u_1}\phi_n^{\mathbf{z}_2}), \nabla w)_E \\
&+ \sum_e (\phi_{L_{up}}^{u_1} D_2^{-1}\phi^{\mathbf{z}_2} - \phi_{L,n_{up}}^{u_1} D_2^{-1}\phi_n^{\mathbf{z}_2}) \cdot \mathbf{n}_e, [w])_e \\
&\qquad +(\nabla \cdot (\phi_L^{\mathbf{z}_1} - \phi_{L,n}^{\mathbf{z}_1}), w) - (f_1(\phi_L^{u_1}, \phi^{u_2}) - f_1(\phi_{L,n}^{u_1}, \phi_n^{u_2}), w) = 0
\end{aligned}$$

$$(D_1^{-1}(\phi_L^{\mathbf{z}_1} - \phi_{L,n}^{\mathbf{z}_1}), v) = (\phi_L^{u_1} - \phi_{L,n}^{u_1}, \nabla \cdot v)$$

$$(\phi_{L_t}^{u_2} - \phi_{L,n_t}^{u_2}, w) + (\nabla \cdot (\phi_L^{\mathbf{z}_2} - \phi_{L,n}^{\mathbf{z}_2}), w) - (f_2(\phi^{u_1}, \phi_L^{u_2}) - f_2(\phi_n^{u_1}, \phi_{L,n}^{u_2}), w) = 0$$

$$(D_2^{-1}(\phi_L^{\mathbf{z}_2} - \phi_{L,n}^{\mathbf{z}_2}), v) = (\phi_L^{u_2} - \phi_{L,n}^{u_2}, \nabla \cdot v).$$

Add and subtract the appropriate terms to get:

$$\begin{aligned}
&(\phi_{L_t}^{u_1} - \phi_{L,n_t}^{u_1}, w) + \sum_E (D_2^{-1}(\phi_L^{u_1}\phi^{\mathbf{z}_2} - \phi^{\mathbf{z}_2}\phi_{L,n}^{u_1} + \phi^{\mathbf{z}_2}\phi_{L,n}^{u_1} - \phi_{L,n}^{u_1}\phi_n^{\mathbf{z}_2}), \nabla w)_E \\
&+ \sum_e (\phi_{L_{up}}^{u_1} D_2^{-1}\phi^{\mathbf{z}_2} - \phi_{L,n_{up}}^{u_1} D_2^{-1}\phi^{\mathbf{z}_2} + \phi_{L,n_{up}}^{u_1} D_2^{-1}\phi^{\mathbf{z}_2} - \phi_{L,n_{up}}^{u_1} D_2^{-1}\phi_n^{\mathbf{z}_2}) \cdot \mathbf{n}_e, [w])_e \\
&\qquad +(\nabla \cdot (\phi_L^{\mathbf{z}_1} - \phi_{L,n}^{\mathbf{z}_1}), w) - (f_1(\phi_L^{u_1}, \phi^{u_2}) - f_2(\phi_{L,n}^{u_1}, \phi_n^{u_2}), w) = 0
\end{aligned}$$

$$(D_1^{-1}(\phi_L^{\mathbf{z}_1} - \phi_{L,n}^{\mathbf{z}_1}), v) = (\phi_L^{u_1} - \phi_{L,n}^{u_1}, \nabla \cdot v)$$

$$(\phi_{L_t}^{u_2} - \phi_{L,n_t}^{u_2}, w) + (\nabla \cdot (\phi_L^{\mathbf{z}_2} - \phi_{L,n}^{\mathbf{z}_2}), w) - (f_2(\phi^{u_1}, \phi_L^{u_2}) - f_2(\phi_n^{u_1}, \phi_{L,n}^{u_2}), w) = 0$$

$$(D_2^{-1}(\phi_L^{\mathbf{z}_2} - \phi_{L,n}^{\mathbf{z}_2}), v) = (\phi_L^{u_2} - \phi_{L,n}^{u_2}, \nabla \cdot v).$$

Define $\widehat{\phi}_L^{u_1} := \phi_L^{u_1} - \phi_{L,n}^{u_1}$ $\widehat{\phi}_L^{u_2} := \phi_L^{u_2} - \phi_{L,n}^{u_2}$ $\widehat{\phi}_L^{\mathbf{z}_1} := \phi_L^{\mathbf{z}_1} - \phi_{L,n}^{\mathbf{z}_1}$ $\widehat{\phi}_L^{\mathbf{z}_2} := \phi_L^{\mathbf{z}_2} - \phi_{L,n}^{\mathbf{z}_2}$ and set $w = \widehat{\phi}_L^{u_1}$ and $v = \widehat{\phi}_L^{\mathbf{z}_1}$ and rearrange the terms:

$$\begin{aligned}
&(\widehat{\phi}_{L_t}^{u_1}, \widehat{\phi}_L^{u_1}) + \sum_E (\widehat{\phi}_L^{u_1} D_2^{-1}\phi^{\mathbf{z}_2}, \nabla \widehat{\phi}_L^{u_1})_E + \sum_e (\widehat{\phi}_{L_{up}}^{u_1} D_2^{-1}\phi^{\mathbf{z}_2} \cdot \mathbf{n}_e, [\widehat{\phi}_L^{u_1}])_e \\
&+ \sum_E (\phi_{L,n}^{u_1} D_2^{-1}(\phi^{\mathbf{z}_2} - \phi_n^{\mathbf{z}_2}), \nabla \widehat{\phi}_L^{u_1})_E + \sum_e (\phi_{L,n_{up}}^{u_1} D_2^{-1}(\phi^{\mathbf{z}_2} - \phi_n^{\mathbf{z}_2}) \cdot \mathbf{n}_e, [\widehat{\phi}_L^{u_1}])_e
\end{aligned}$$

$$+(\nabla\cdot\widehat{\phi}_L^{\mathbf{z}_1},\widehat{\phi}_L^{u_1})-(f_1(\phi_L^{u_1},\phi^{u_2})-f_2(\phi_{L,n}^{u_1},\phi_n^{u_2}),\widehat{\phi}_L^{u_1})=0 \tag{5.86}$$

$$(D_1^{-1}\widehat{\phi}_L^{\mathbf{z}_1},\widehat{\phi}_L^{\mathbf{z}_1})=(\widehat{\phi}_L^{u_1},\nabla\cdot\widehat{\phi}_L^{\mathbf{z}_1}) \tag{5.87}$$

$$(\widehat{\phi}_{L_t}^{u_2},\widehat{\phi}_L^{u_2})+(\nabla\cdot\widehat{\phi}_L^{\mathbf{z}_2},\widehat{\phi}_L^{u_2})-(f_2(\phi^{u_1},\phi_L^{u_2})-f_2(\phi_n^{u_1},\phi_{L,n}^{u_2}),\widehat{\phi}_L^{u_2})=0 \tag{5.88}$$

$$(D_2^{-1}\widehat{\phi}_L^{\mathbf{z}_2},\widehat{\phi}_L^{\mathbf{z}_2})=(\widehat{\phi}_L^{u_2},\nabla\cdot\widehat{\phi}_L^{\mathbf{z}_2}). \tag{5.89}$$

Substituting (5.87) into (5.86) and (5.89) into (5.88) and rewriting terms, we get:

$$\begin{aligned}
&\frac{1}{2}\frac{d}{dt}\|\widehat{\phi}_L^{u_1}\|^2+\sum_E(\widehat{\phi}_L^{u_1}D_2^{-1}\phi^{\mathbf{z}_2},\nabla\widehat{\phi}_L^{u_1})_E+\sum_e(\widehat{\phi}_{L_{up}}^{u_1}D_2^{-1}\phi^{\mathbf{z}_2}\cdot\mathbf{n}_e,[\widehat{\phi}_L^{u_1}])_e\\
&+\sum_E(\phi_{L,n}^{u_1}D_2^{-1}(\phi^{\mathbf{z}_2}-\phi_n^{\mathbf{z}_2}),\nabla(\phi_L^{u_1}))_E+\sum_e(\phi_{L,n_{up}}^{u_1}D_2^{-1}(\phi^{\mathbf{z}_2}-\phi_n^{\mathbf{z}_2})\cdot\mathbf{n}_e,[\phi_L^{u_1}])_e\\
&+\sum_E(\phi_{L,n}^{u_1}D_2^{-1}(\phi_n^{\mathbf{z}_2}-\phi^{\mathbf{z}_2}),\nabla(\phi_{L,n}^{u_1}))_E+\sum_e(\phi_{L,n_{up}}^{u_1}D_2^{-1}(\phi_n^{\mathbf{z}_2}-\phi^{\mathbf{z}_2})\cdot\mathbf{n}_e,[\phi_{L,n}^{u_1}])_e\\
&+\|D_1^{-1/2}\widehat{\phi}_L^{\mathbf{z}_1}\|^2=(f_1(\phi_L^{u_1},\phi^{u_2})-f_2(\phi_{L,n}^{u_1},\phi_n^{u_2}),\widehat{\phi}_L^{u_1})
\end{aligned} \tag{5.90}$$

$$\frac{1}{2}\frac{d}{dt}\|\widehat{\phi}_L^{u_2}\|^2+\|D_1^{-1/2}\widehat{\phi}_L^{\mathbf{z}_2}\|^2=(f_2(\phi^{u_1},\phi_L^{u_2})-f_2(\phi_n^{u_1},\phi_{L,n}^{u_2}),\widehat{\phi}_L^{u_2}). \tag{5.91}$$

Consider the seventh term on the left hand side of (5.90) (note that $\phi^{\mathbf{z}_2}-\phi_n^{\mathbf{z}_2}$ has already been replaced by $\phi_n^{\mathbf{z}_2}-\phi^{\mathbf{z}_2}$ in that term in order to make the sign in front of the summation positive).

$$\begin{aligned}
&\sum_e(\phi_{L,n_{up}}^{u_1}D_2^{-1}(\phi_n^{\mathbf{z}_2}-\phi^{\mathbf{z}_2})\cdot\mathbf{n}_e,[\phi_{L,n}^{u_1}])_e\\
&=\sum_e D_2^{-1}(\phi_n^{\mathbf{z}_2}-\phi^{\mathbf{z}_2})\cdot\mathbf{n}_e,(\phi_{L,n_{up}}^{u_1}-\frac{1}{2}\,\phi_{L,n_{down}}^{u_1}+\frac{1}{2}\,\phi_{L,n_{down}}^{u_1})[\phi_{L,n}^{u_1}])_e\\
&=\frac{1}{2}\sum_e D_2^{-1}(\phi_n^{\mathbf{z}_2}-\phi^{\mathbf{z}_2})\cdot\mathbf{n}_e,(\phi_{L,n_{up}}^{u_1}-\,\phi_{L,n_{down}}^{u_1})[\phi_{L,n}^{u_1}])_e\\
&+\frac{1}{2}\sum_e D_2^{-1}(\phi_n^{\mathbf{z}_2}-\phi^{\mathbf{z}_2})\cdot\mathbf{n}_e,(\phi_{L,n_{up}}^{u_1}+\,\phi_{L,n_{down}}^{u_1})[\phi_{L,n}^{u_1}])_e.
\end{aligned} \tag{5.92}$$

Note that whenever $D_2^{-1}(\phi_n^{\mathbf{z}_2}-\phi^{\mathbf{z}_2})\cdot\mathbf{n}_e\geq 0$,we have

$$(\phi_{L,n_{up}}^{u_1}-\,\phi_{L,n_{down}}^{u_1})[\phi_L^{u_1}]=(\phi_{L,n}^{u_1,+}-\,\phi_{L,n}^{u_1,-})(\phi_{L,n}^{u_1,+}-\,\phi_{L,n}^{u_1,-})=[\phi_{L,n}^{u_1}]^2$$

and

$$(\phi^{u_1}_{L,n_{up}} + \phi^{u_1}_{L,n_{down}})[\phi^{u_1}_L] = (\phi^{u_1,+}_{L,n} + \phi^{u_1,-}_{L,n})(\phi^{u_1,+}_{L,n} - \phi^{u_1,-}_{L,n}) = ((\phi^{u_1,+}_{L,n})^2 - (\phi^{u_1,-}_{L,n})^2).$$

Also, whenever $D_2^{-1}(\phi_n^{\mathbf{z}_2} - \phi^{\mathbf{z}_2}) \cdot \mathbf{n}_e < 0$,we have

$$(\phi^{u_1}_{L,n_{up}} - \phi^{u_1}_{L,n_{down}})[\phi^{u_1}_L] = (\phi^{u_1,-}_{L,n} - \phi^{u_1,+}_{L,n})(\phi^{u_1,+}_{L,n} - \phi^{u_1,-}_{L,n}) = -[\phi^{u_1}_{L,n}]^2$$

and

$$(\phi^{u_1}_{L,n_{up}} + \phi^{u_1}_{L,n_{down}})[\phi^{u_1}_L] = (\phi^{u_1,-}_{L,n} + \phi^{u_1,+}_{L,n})(\phi^{u_1,+}_{L,n} - \phi^{u_1,-}_{L,n}) = ((\phi^{u_1,+}_{L,n})^2 - (\phi^{u_1,-}_{L,n})^2).$$

Therefore, (5.92) may be written as,

$$\begin{aligned}
&\sum_e (\phi^{u_1}_{L,n_{up}} D_2^{-1}(\phi_n^{\mathbf{z}_2} - \phi^{\mathbf{z}_2}) \cdot \mathbf{n}_e, [\phi^{u_1}_L])_e \\
&= \frac{1}{2}\sum_e (|D_2^{-1}(\phi_n^{\mathbf{z}_2} - \phi^{\mathbf{z}_2}) \cdot \mathbf{n}_e|, [\phi^{u_1}_L]^2)_e \\
&+ \frac{1}{2}\sum_e D_2^{-1}(\phi_n^{\mathbf{z}_2} - \phi^{\mathbf{z}_2}) \cdot \mathbf{n}_e, (\phi^{u_1,+}_{L,n})^2 - (\phi^{u_1,-}_{L,n})^2)_e.
\end{aligned}$$

After applying the divergence theorem, we find that

$$\begin{aligned}
&\sum_e (\phi^{u_1}_{L,n_{up}} D_2^{-1}(\phi_n^{\mathbf{z}_2} - \phi^{\mathbf{z}_2}) \cdot \mathbf{n}_e, [\phi^{u_1}_L])_e \\
&= \frac{1}{2}\sum_e (|D_2^{-1}(\phi_n^{\mathbf{z}_2} - \phi^{\mathbf{z}_2}) \cdot \mathbf{n}_e|, [\phi^{u_1}_L]^2)_e \\
&- \frac{1}{2}\sum_E \int (\nabla \cdot D_2^{-1}(\phi_n^{\mathbf{z}_2} - \phi^{\mathbf{z}_2}))(\phi^{u_1}_{L,n})^2 \, dx - \sum_E \int \phi^{u_1}_{L,n}(\nabla \cdot D_2^{-1}(\phi_n^{\mathbf{z}_2} - \phi^{\mathbf{z}_2})) \cdot \nabla \phi^{u_1}_{L,n} \, dx.
\end{aligned}$$

Do the same things to the third term on the left hand side of (5.92). After making these substitutions, (5.92) then becomes:

$$\begin{aligned}
&\frac{1}{2}\frac{d}{dt}\|\widehat{\phi}^{u_1}_L\|^2 - \frac{1}{2}\sum_E (\nabla \cdot D_2^{-1}\phi^{\mathbf{z}_2}, (\widehat{\phi}^{u_1}_L)^2)_E + \frac{1}{2}\sum_e (|D_2^{-1}\phi^{\mathbf{z}_2} \cdot \mathbf{n}_e|, [\widehat{\phi}^{u_1}_L]^2)_e \\
&- \frac{1}{2}\sum_E (\nabla \cdot D_2^{-1}(\phi_n^{\mathbf{z}_2} - \phi^{\mathbf{z}_2}), (\phi^{u_1}_{L,n})^2)_E + \frac{1}{2}\sum_e (|D_2^{-1}(\phi_n^{\mathbf{z}_2} - \phi^{\mathbf{z}_2}) \cdot \mathbf{n}_e|, [\widehat{\phi}^{u_1}_{L,n}]^2)_e \\
&\quad + \|D_1^{-1/2}\widehat{\phi}^{\mathbf{z}_1}_L\|^2 = (f_1(\phi^{u_1}_L, \phi^{u_2}) - f_2(\phi^{u_1}_{L,n}, \phi^{u_2}_n), \widehat{\phi}^{u_1}_L) \\
&- \sum_E (\phi^{u_1}_{L,n} D_2^{-1}(\phi^{\mathbf{z}_2} - \phi^{\mathbf{z}_2}_n), \nabla(\phi^{u_1}_L))_E - \sum_e (\phi^{u_1}_{L,n_{up}} D_2^{-1}(\phi^{\mathbf{z}_2} - \phi^{\mathbf{z}_2}_n) \cdot \mathbf{n}_e, [\phi^{u_1}_L])_e
\end{aligned}$$

$$\frac{1}{2}\frac{d}{dt}\|\widehat{\phi}_L^{u_2}\|^2 + \|D_1^{-1/2}\widehat{\phi}_L^{\mathbf{z}_2}\|^2 = (f_2(\phi^{u_1},\phi_L^{u_2}) - f_2(\phi_n^{u_1},\phi_{L,n}^{u_2}),\widehat{\phi}_L^{u_2}).$$

Now,

$$\begin{aligned}
&\frac{1}{2}\frac{d}{dt}\|\widehat{\phi}_L^{u_1}\|^2 + \frac{1}{2}\sum_e(|D_2^{-1}\phi^{\mathbf{z}_2}\cdot\mathbf{n}_e|,[\widehat{\phi}_L^{u_1}]^2)_e + \frac{1}{2}\sum_e(|D_2^{-1}(\phi_n^{\mathbf{z}_2}-\phi^{\mathbf{z}_2})\cdot\mathbf{n}_e|,[\widehat{\phi}_{L,n}^{u_1}]^2)_e\\
&+\|D_1^{-1/2}\widehat{\phi}_L^{\mathbf{z}_1}\|^2 = (f_1(\phi_L^{u_1},\phi^{u_2}) - f_2(\phi_{L,n}^{u_1},\phi^{u_2}) + f_2(\phi_{L,n}^{u_1},\phi^{u_2}) - f_2(\phi_{L,n}^{u_1},\phi_n^{u_2}),\widehat{\phi}_L^{u_1})\\
&-\sum_E(\phi_{L,n}^{u_1}D_2^{-1}(\phi^{\mathbf{z}_2}-\phi_n^{\mathbf{z}_2}),\nabla(\phi_L^{u_1}))_E - \sum_e(\phi_{L,n_{up}}^{u_1}D_2^{-1}(\phi^{\mathbf{z}_2}-\phi_n^{\mathbf{z}_2})\cdot\mathbf{n}_e,[\phi_L^{u_1}])_e\\
&+\frac{1}{2}\sum_E(\nabla\cdot D_2^{-1}\phi^{\mathbf{z}_2},(\widehat{\phi}_L^{u_1})^2)_E + \frac{1}{2}\sum_E(\nabla\cdot D_2^{-1}(\phi_n^{\mathbf{z}_2}-\phi^{\mathbf{z}_2}),(\phi_{L,n}^{u_1})^2)_E\\
&\le C\|\widehat{\phi}_L^{u_1}\|^2\|\phi^{u_2}\|_{\infty,\Omega} + C\|\phi_{L,n}^{u_1}\|_{\infty,\Omega}\|(\phi^{u_2}-\phi_n^{u_2})\|\|\widehat{\phi}_L^{u_1}\| \qquad (5.93)\\
&+C\|\phi_{L,n}^{u_1}\|_{\infty,\Omega}\|\phi^{\mathbf{z}_2}-\phi_n^{\mathbf{z}_2}\|\|\nabla(\phi_L^{u_1})\| - \sum_e(\phi_{L,n_{up}}^{u_1}D_2^{-1}(\phi^{\mathbf{z}_2}-\phi_n^{\mathbf{z}_2})\cdot\mathbf{n}_e,[\phi_L^{u_1}])_e\\
&+C\|\nabla\cdot D_2^{-1}\phi^{\mathbf{z}_2}\|_{\infty,\Omega}\|\widehat{\phi}_L^{u_1}\|^2 + C\|\nabla\cdot D_2^{-1}(\phi_n^{\mathbf{z}_2}-\phi^{\mathbf{z}_2})\|\|\phi_{L,n}^{u_1}\|_{\infty,\Omega}\|\phi_{L,n}^{u_1}\|
\end{aligned}$$

and

$$\frac{1}{2}\frac{d}{dt}\|\widehat{\phi}_L^{u_2}\|^2 + \|D_1^{-1/2}\widehat{\phi}_L^{\mathbf{z}_2}\|^2 \le C\|\widehat{\phi}_L^{u_2}\|^2\|\phi^{u_1}\|_{\infty,\Omega} + C\|\phi_{L,n}^{u_2}\|_{\infty,\Omega}\|(\phi^{u_1}-\phi_n^{u_1})\|\|\widehat{\phi}_L^{u_2}\| \quad (5.94)$$

Since $\phi^{u_1},\phi^{u_2},\phi_{L,n}^{u_1},\widehat{\phi}_L^{u_1},\phi^{\mathbf{z}_2}\in S$, then $\|\phi^{u_1}\|_{\infty,\Omega}$, $\|\phi^{u_2}\|_{\infty,\Omega}$, $\|\phi_{L,n}^{u_1}\|$, $\|\phi_{L,n}^{u_1}\|_{\infty,\Omega}$, $\|\widehat{\phi}_L^{u_1}\|$, $\|\nabla(\phi_L^{u_1})\|$, $\|\nabla\cdot D_2^{-1}\phi^{\mathbf{z}_2}\|_{\infty,\Omega}$ are bounded. After combining (5.93) and (5.94) we get,

$$\begin{aligned}
&\frac{1}{2}\frac{d}{dt}(\|\widehat{\phi}_L^{u_1}\|^2 + \|\widehat{\phi}_L^{u_2}\|^2) + \frac{1}{2}\sum_e(|D_2^{-1}\phi^{\mathbf{z}_2}\cdot\mathbf{n}_e|,[\widehat{\phi}_L^{u_1}]^2)_e\\
&+\frac{1}{2}\sum_e(|D_2^{-1}(\phi_n^{\mathbf{z}_2}-\phi^{\mathbf{z}_2})\cdot\mathbf{n}_e|,[\widehat{\phi}_{L,n}^{u_1}]^2)_e + \|D_1^{-1/2}\widehat{\phi}_L^{\mathbf{z}_1}\|^2 + \|D_1^{-1/2}\widehat{\phi}_L^{\mathbf{z}_2}\|^2\\
&\le C(\|\widehat{\phi}_L^{u_1}\|^2 + \|\widehat{\phi}_L^{u_2}\|^2) + C\|(\phi^{u_1}-\phi_n^{u_1})\| + C\|(\phi^{u_2}-\phi_n^{u_2})\| + C\|\phi^{\mathbf{z}_2}-\phi_n^{\mathbf{z}_2}\| \qquad (5.95)\\
&+\sum_e C\|D_2^{-1}(\phi^{\mathbf{z}_2}-\phi_n^{\mathbf{z}_2})\|_e\|[\phi_L^{u_1}]\|_e + C\|\nabla\cdot D_2^{-1}(\phi_n^{\mathbf{z}_2}-\phi^{\mathbf{z}_2})\|.
\end{aligned}$$

Consider the fifth term on the right hand side of (5.95):

$$\begin{aligned}
&\sum_e C\|D_2^{-1}(\phi^{\mathbf{z}_2}-\phi_n^{\mathbf{z}_2})\|_e\|[\phi_L^{u_1}]\|_e \le \sum_e C\|D_2^{-1}(\phi^{\mathbf{z}_2}-\phi_n^{\mathbf{z}_2})\|_e(\|(\phi_L^{u_1})_e^{E^1}\|_e + \|(\phi_L^{u_1})_e^{E^2}\|_e)\\
&\le \sum_E C\|D_2^{-1}(\phi^{\mathbf{z}_2}-\phi_n^{\mathbf{z}_2})\|_E(\|\phi_L^{u_1}\|_{E^1} + \|\phi_L^{u_1}\|_{E^2}) \le \sum_E C\|D_2^{-1}(\phi^{\mathbf{z}_2}-\phi_n^{\mathbf{z}_2})\|. \qquad (5.96)
\end{aligned}$$

Substitute (5.96) into (5.95) and treat h as a constant:

$$\begin{aligned}
&\frac{1}{2}\frac{d}{dt}(\|\widehat{\phi}_L^{u_1}\|^2+\|\widehat{\phi}_L^{u_2}\|^2)+\frac{1}{2}\sum_e(|D_2^{-1}\phi^{\mathbf{z}_2}\cdot\mathbf{n}_e|,[\widehat{\phi}_L^{u_1}]^2)_e\\
&+\frac{1}{2}\sum_e(|D_2^{-1}(\phi_n^{\mathbf{z}_2}-\phi^{\mathbf{z}_2})\cdot\mathbf{n}_e|,[\widehat{\phi}_{L,n}^{u_1}]^2)_e+\|D_1^{-1/2}\widehat{\phi}_L^{\mathbf{z}_1}\|^2+\|D_1^{-1/2}\widehat{\phi}_L^{\mathbf{z}_2}\|^2\\
&\le C(\|\widehat{\phi}_L^{u_1}\|^2+\|\widehat{\phi}_L^{u_2}\|^2)+C\|(\phi^{u_1}-\phi_n^{u_1})\|+C\|(\phi^{u_2}-\phi_n^{u_2})\|+C\|\phi^{\mathbf{z}_2}-\phi_n^{\mathbf{z}_2}\|\\
&\quad+\sum_E C\frac{r^2}{h}\|D_2^{-1}(\phi^{\mathbf{z}_2}-\phi_n^{\mathbf{z}_2})\|+C\|\nabla\cdot D_2^{-1}(\phi_n^{\mathbf{z}_2}-\phi^{\mathbf{z}_2})\|. \qquad (5.97)
\end{aligned}$$

Multiply (5.97) by 2 and integrate from 0 to t,

$$\begin{aligned}
&(\|\widehat{\phi}_L^{u_1}\|^2+\|\widehat{\phi}_L^{u_2}\|^2)+\int_0^t\sum_e(|D_2^{-1}\phi^{\mathbf{z}_2}\cdot\mathbf{n}_e|,[\widehat{\phi}_L^{u_1}]^2)_e\\
&+\int_0^t\sum_e(|D_2^{-1}(\phi_n^{\mathbf{z}_2}-\phi^{\mathbf{z}_2})\cdot\mathbf{n}_e|,[\widehat{\phi}_{L,n}^{u_1}]^2)_e+2\int_0^t\|D_1^{-1/2}\widehat{\phi}_L^{\mathbf{z}_1}\|^2+2\int_0^t\|D_1^{-1/2}\widehat{\phi}_L^{\mathbf{z}_2}\|^2\\
&\le C\int_0^t(\|\widehat{\phi}_L^{u_1}\|^2+\|\widehat{\phi}_L^{u_2}\|^2)+C\int_0^t\|(\phi^{u_1}-\phi_n^{u_1})\|+C\int_0^t\|(\phi^{u_2}-\phi_n^{u_2})\|\\
&\quad+C\int_0^t\|\phi^{\mathbf{z}_2}-\phi_n^{\mathbf{z}_2}\|+\int_0^t\sum_E C\frac{r^2}{h}\|D_2^{-1}(\phi^{\mathbf{z}_2}-\phi_n^{\mathbf{z}_2})\|\\
&\quad+C\int_0^t\|\nabla\cdot D_2^{-1}(\phi_n^{\mathbf{z}_2}-\phi^{\mathbf{z}_2})\|+\|\widehat{\phi}_L^{u_1,t=0}\|^2+\|\widehat{\phi}_L^{u_2,t=0}\|^2.
\end{aligned}$$

Apply the Gronwall Inequality, theorem 4.8,

$$\begin{aligned}
&(\|\widehat{\phi}_L^{u_1}\|^2+\|\widehat{\phi}_L^{u_2}\|^2)+\int_0^t\sum_e(|D_2^{-1}\phi^{\mathbf{z}_2}\cdot\mathbf{n}_e|,[\widehat{\phi}_L^{u_1}]^2)_e\\
&+\int_0^t\sum_e(|D_2^{-1}(\phi_n^{\mathbf{z}_2}-\phi^{\mathbf{z}_2})\cdot\mathbf{n}_e|,[\widehat{\phi}_{L,n}^{u_1}]^2)_e+2\int_0^t\|D_1^{-1/2}\widehat{\phi}_L^{\mathbf{z}_1}\|^2+2\int_0^t\|D_1^{-1/2}\widehat{\phi}_L^{\mathbf{z}_2}\|^2\\
&\quad\le C\Bigg(\int_0^t\|(\phi^{u_1}-\phi_n^{u_1})\|+C\int_0^t\|(\phi^{u_2}-\phi_n^{u_2})\|+C\int_0^t\|\phi^{\mathbf{z}_2}-\phi_n^{\mathbf{z}_2}\|\\
&\qquad+\int_0^t\sum_E C\frac{r^2}{h}\|D_2^{-1}(\phi^{\mathbf{z}_2}-\phi_n^{\mathbf{z}_2})\|+C\int_0^t\|\nabla\cdot D_2^{-1}(\phi_n^{\mathbf{z}_2}-\phi^{\mathbf{z}_2})\|\Bigg). \qquad (5.98)
\end{aligned}$$

As

$$\lim_{n\to\infty}\sup_{t\in[0,T]}\|(\phi_n^{u_1},\phi_n^{u_2},\phi_n^{\mathbf{z}_1},\phi_n^{\mathbf{z}_2})-(\phi^{u_1},\phi^{u_2},\phi^{\mathbf{z}_1},\phi^{\mathbf{z}_2})\|_S=0 \qquad (5.99)$$

the right hand side of (5.98) goes to zero. Thus, we have

$$\|\widehat{\phi}_L^{u_1}\|^2 + \|\widehat{\phi}_L^{u_2}\|^2 + 2\int_0^t \|D_1^{-1/2}\widehat{\phi}_L^{\mathbf{z}_1}\|^2 + 2\int_0^t \|D_1^{-1/2}\widehat{\phi}_L^{\mathbf{z}_2}\|^2 = 0.$$

In a similar way, it can be shown that for 5.99

$$\sup_{t\in[0,T]} \|\widehat{\phi}_L^{\mathbf{z_2}}\| + \int_0^t \|\nabla \cdot \widehat{\phi}_L^{\mathbf{z_2}}\| = 0.$$

So,

$$\lim_{n\to\infty} \sup_{t\in[0,T]} \|A(\phi_n^{u_1}, \phi_n^{u_2}, \phi_n^{\mathbf{z}_1}, \phi_n^{\mathbf{z}_2}) - A(\phi^{u_1}, \phi^{u_2}, \phi^{\mathbf{z}_1}, \phi^{\mathbf{z}_2})\|_S = 0.$$

By this, the continuity of A is established. **Q.E.D.**

Theorem 5.5. *The mapping A is compact.*

Proof. Let

$$(\phi^{u_1}, \phi^{u_2}, \phi^{\mathbf{z}_1}, \phi^{\mathbf{z}_2}) \in S.$$

Recall the mapping, $A(\phi^{u_1}, \phi^{\mathbf{z}_1}, \phi^{u_2}, \phi^{\mathbf{z}_2}) = (\phi_L^{u_1}, \phi_L^{\mathbf{z}_1}, \phi_L^{u_2}, \phi_L^{\mathbf{z}_2})$, defined by (5.31),(5.32),(5.33),(5.34):

$$(\phi_{L_t}^{u_1}, w) + \sum_E (\phi_L^{u_1} D_2^{-1}\phi^{\mathbf{z}_2}, \nabla w)_E + \sum_e (D_2^{-1}\phi^{\mathbf{z}_2}\cdot \mathbf{n}_e \phi_{L_{up}}^{u_1}, [w])_e$$
$$+(\nabla \cdot \phi_L^{\mathbf{z}_1}, w) - (f_1(\phi_L^{u_1}, \phi^{u_2}), w) = 0 \tag{5.100}$$

$$(D_1^{-1}\phi_L^{\mathbf{z}_1}, v) = (\phi_L^{u_1}, \nabla \cdot v) \tag{5.101}$$

$$(\phi_{L_t}^{u_2}, w) + (\nabla \cdot \phi_L^{\mathbf{z}_2}, w) - (f_2(\phi^{u_1}, \phi_L^{u_2}), w) = 0 \tag{5.102}$$

$$(D_2^{-1}\phi_L^{\mathbf{z}_2}, v) = (\phi_L^{u_2}, \nabla \cdot v). \tag{5.103}$$

Recall the shift operator $\Delta_{Shift(\overline{\mathbf{h}})} f(\mathbf{x}) = f(\mathbf{x} + \overline{\mathbf{h}})$ where $\overline{\mathbf{h}} \in \mathcal{R}^3$. If we apply the shift operator to (5.100),(5.101),(5.102),(5.103) and follow the same steps as in the proof of theorem 5.4, we get something similar to (5.98),

$$(\|\Delta_{Shift(\overline{\mathbf{h}})}\phi_L^{u_1}\|^2 + \|\Delta_{Shift(\overline{\mathbf{h}})}\phi_L^{u_2}\|^2) + \int_0^t \sum_e (|D_2^{-1}\phi^{\mathbf{z}_2}\cdot \mathbf{n}_e|, [\Delta_{Shift(\overline{\mathbf{h}})}\phi_L^{u_1}]^2)_e$$

$$
\begin{aligned}
&+\int_0^t \sum_e (|D_2^{-1}(\Delta_{Shift(\overline{\mathbf{h}})}\phi^{\mathbf{z}_2})\cdot \mathbf{n}_e|, [\Delta_{Shift(\overline{\mathbf{h}})}\phi_L^{u_1}]^2)_e \\
&\quad +2\int_0^t \|D_1^{-1/2}\Delta_{Shift(\overline{\mathbf{h}})}\phi_L^{\mathbf{z}_1}\|^2 + 2\int_0^t \|D_1^{-1/2}\Delta_{Shift(\overline{\mathbf{h}})}\phi_L^{\mathbf{z}_2}\|^2 \qquad (5.104)\\
&\leq C\Bigg(\int_0^t \|\Delta_{Shift(\overline{\mathbf{h}})}\phi^{u_2}\| + C\int_0^t \|\Delta_{Shift(\overline{\mathbf{h}})}\phi^{u_2}\| + C\int_0^t \|\Delta_{Shift(\overline{\mathbf{h}})}\phi^{\mathbf{z}_2}\| \\
&+\int_0^t \sum_E C\|D_2^{-1}\Delta_{Shift(\overline{\mathbf{h}})}\phi^{\mathbf{z}_2}\| + C\int_0^t \|\nabla\cdot D_2^{-1}\Delta_{Shift(\overline{\mathbf{h}})}\phi^{\mathbf{z}_2}\|\Bigg).
\end{aligned}
$$

In a similar way, it can be shown that,

$$
\begin{aligned}
&\sup_{t\in[0,T]} \|\Delta_{Shift(\overline{\mathbf{h}})}\phi_L^{\mathbf{z}_2}\| + \int_0^t \|\nabla\cdot\Delta_{Shift(\overline{\mathbf{h}})}\phi_L^{\mathbf{z}_2}\| \qquad (5.105)\\
&\qquad \leq \int_0^t C\|\Delta_{Shift(\overline{\mathbf{h}})}\phi^{\mathbf{z}_2}\| + C\int_0^t \|\nabla\cdot(\Delta_{Shift(\overline{\mathbf{h}})}\phi^{\mathbf{z}_2})\|. \qquad (5.106)
\end{aligned}
$$

Since the functions $\phi^{u_2}, \phi^{\mathbf{z}_2}$ that appear on the right hand side of (5.104),(5.106)are in the space S, these functions are Lipschitz continuous. Thus we may can conclude that

$$
\lim_{\overline{\mathbf{h}}\to 0} \|\Delta_{Shift(\overline{\mathbf{h}})}\phi_L^{u_1}\| = 0 \qquad \text{uniformly.}
$$

The same may be said of $\|\Delta_{Shift(\overline{\mathbf{h}})}\phi_L^{\mathbf{z}_2}\|$, etc. Thus we may apply **Kolmogorov-M.Riesz-Frechet**, theorem 4.5, and conclude that the mapping A is compact. **Q.E.D.**

Therefore, by the Schauder's Fixed Point Theorem - Version 2, theorem 4.3, the mapping A has at least one fixed point in S.

Error Analysis. Based on the previous analysis, we can say,

$$
\begin{aligned}
&\|u_{1,h} - Q_h u_1\|_{L^\infty([0,T];L^2(\Omega))} + \|u_{2,h} - Q_h u_2\|_{L^\infty([0,T];L^2(\Omega))} \\
&+\|\mathbf{z_{2,h}} - \Pi_h \mathbf{z_2}\|_{L^\infty([0,T];L^2(\Omega))} + \left(\int_0^T \|\mathbf{z_{1,h}} - \Pi_h \mathbf{z_1}\|^2\right)^{1/2} \\
&+\left(\int_0^T \|\mathbf{z_{2,h}} - \Pi_h \mathbf{z_2}\|^2\right)^{1/2} + \left(\int_0^T \|\nabla\cdot(\mathbf{z_{2,h}} - \Pi_h \mathbf{z_2})\|^2\right)^{1/2} \\
&\qquad \leq C(h^{\mu_{u_1}-1} + h^{\mu_{u_2}} + h^{\mu_{\mathbf{z_1}}} + h^{\mu_{\mathbf{z_2}}-1}). \qquad (5.107)
\end{aligned}
$$

5.3 FINITE ELEMENT ANALYSIS OF THE PDES IN PART II

Recall the epithelial equation:

$$\frac{\partial e_c}{\partial t} + \nabla \cdot (\beta(e_c)\mathbf{u}(e_c, b)) = k_p e_c(1 - e_c/e_{c,max}) - k_a(n_a, c, b)e_c \tag{5.108}$$

Where

$$k_a(n_a, c, b) = \frac{e_{ca}(n_a, c, b)^{q_0}}{e_{ca}(n_a, c, b)^{q_0} + [e_{ca}(n_{a,max}, c_{max}, b_{max}) - e_{ca}(n_a, c, b)]^{q_0}}$$

$$e_{ca}(n_a, c, b) = n_a + k_{e_c n_a c} c + k_{e_c n_a b} b$$

$$\beta(e_c) = \frac{e_c^2}{e_c^2 + (e_{c,max} - e_c)^2}$$

$$\mathbf{u}(e_c, b) = -\alpha(b)\nabla e_c \qquad \alpha(b) = \frac{(b_{max} - b)^q}{(b_{max} - b)^q + b^q} \tag{5.109}$$

Equation (5.108) may be written as

$$\frac{\partial e_c}{\partial t} - \nabla \cdot (\beta(e_c)\alpha(b)\nabla e_c) \ = \gamma(e_c, b, n_a, c) \tag{5.110}$$

Where

$$\gamma(e_c, b, n_a, c) \ = \ k_p e_c(1 - e_c/e_c^{max}) - k_a(n_a, c, b)e_c$$

This equation may be written as

$$\frac{\partial e_c}{\partial t} - \nabla \cdot (\alpha(b)\nabla P(e_c)) \ = \gamma(e_c, b, n_a, c) \tag{5.111}$$

where $P(e_c)$ is the Kirchhoff transformation given by:

$$P(e_c) = \int_0^{e_c} \beta(s)\, ds$$

$$\text{so that } \ \nabla P(e_c) \ = \ \frac{\partial P}{\partial e_c}\nabla e_c \ + \ \nabla_x P(e_c)$$

$$= \ \beta(e_c)\nabla e_c \ + \ \int_0^{e_c} \nabla_x \beta(s)\, ds \ = \ \beta(e_c)\nabla e_c$$

Note that e_c may, at times, be zero. $B(e_c)$ and $\nabla P(e_c)$ will be zero whenever $e_c = 0$. Therefore, (5.111) is a **degenerate parabolic** PDE.

Assumptions

In the PDE Analysis Part I, it was proven that n_a, b and c are at least in $L^\infty(\Omega)$. Following Arbogast, Wheeler, and Zhang [7] as well as Woodward and Dawson [141], we will assume that:

$$e_c \in L_\infty((0,T); L_\infty(\Omega)) \text{ and } e_{c_t} \in L_2((0,T); H^{-1}(\Omega))$$

Assume that there exists a constant $C_0 > 0$, independent of time such that

$$\|P(\phi_1) - P(\phi_2)\|^2 \leq C_0(P(\phi_1) - P(\phi_2), \phi_1 - \phi_2) \quad \forall \phi_1, \phi_2 \in L_2(\Omega) \tag{5.112}$$

(This implies, among other things, that P is Lipschitz continuous)

Assume that for the function γ we have $\forall \phi_1, \phi_2 \in L_2(\Omega),\ \exists\, C > 0$ such that

$$\|\gamma(\phi_1, b, n_a, c) - \gamma(\phi_2, b, n_a, c)\|^2 \leq C(P(\phi_1) - P(\phi_2), \phi_1 - \phi_2) \tag{5.113}$$

$$\|\gamma(\phi_1, b, n_a, c) - \gamma(\phi_2, b, n_a, c)\| \leq C\|\phi_1 - \phi_2\| \tag{5.114}$$

and $\forall b_1, b_2 \in L_2(\Omega),\ \exists\, C > 0$

$$\|\gamma(\phi, b_1, n_a, c) - \gamma(\phi, b_2, n_a, c)\| \leq C\|b_1 - b_2\| \tag{5.115}$$

and $\forall n_{a_1}, n_{a_2} \in L_2(\Omega),\ \exists\, C > 0$

$$\|\gamma(\phi, b, n_{a_1}, c) - \gamma(\phi, b, n_{a_2}, c)\| \leq C\|n_{a_1} - n_{a_2}\| \tag{5.116}$$

and $\forall c_1, c_2 \in L_2(\Omega),\ \exists\, C > 0$

$$\|\gamma(\phi, b, n_a, c_1) - \gamma(\phi, b, n_a, c_2)\| \leq C\|c_1 - c_2\| \tag{5.117}$$

Let

$$\mathbf{z} \;=\; -\alpha(b)\nabla P(e_c). \tag{5.118}$$

Note that $\alpha(b)$ as given by (5.109) has an inverse, in particular,

$$\alpha^{-1} = b(\alpha) = \frac{b_{max}(\frac{1-\alpha}{\alpha})^{1/q}}{1+(\frac{1-\alpha}{\alpha})^{1/q}}. \tag{5.119}$$

Using (5.110),(5.118), and (5.119) we can find the variational formulation:

$$\langle e_{c_t}, w\rangle + \langle \nabla\cdot\mathbf{z}, w\rangle \;= \langle \gamma(e_c, b, n_a, c), w\rangle \qquad \forall w \in H_0^1(\Omega) \tag{5.120}$$

$$\langle \alpha^{-1}\mathbf{z}, v\rangle \;+\; \langle \nabla P(e_c), v\rangle = 0 \qquad \forall v \in H(\Omega; div) \tag{5.121}$$

Using Green's,

$$\langle e_{c_t}, w\rangle + \langle \nabla\cdot\mathbf{z}, w\rangle \;= \langle \gamma(e_c, b, n_a, c), w\rangle \tag{5.122}$$

$$\langle \alpha^{-1}\mathbf{z}, v\rangle \;-\; \langle P(e_c), \nabla\cdot v\rangle \;=\; -\langle P(e_{c_D}), v\cdot\mathbf{n}\rangle \tag{5.123}$$

Where $\mathbf{n}$ is normal to the boundary.

Integrating (5.110), from 0 to t

$$\int_0^t \frac{\partial e_c}{\partial s} ds + \nabla\cdot\int_0^t \mathbf{z}\; ds \;=\; \int_0^t \gamma(e_c, b, n_a, c)\; ds \tag{5.124}$$

$$e_c(t) + \nabla\cdot\int_0^t \mathbf{z}\; ds \;=\; \int_0^t \gamma(e_c, b, n_a, c)\; ds + e_c(0) \tag{5.125}$$

The variational formulation becomes,

$$\langle e_c, w\rangle + \left\langle \nabla\cdot\int_0^t \mathbf{z}\; ds, w\right\rangle = \left\langle \int_0^t \gamma(e_c, b, n_a, c)\; ds, w\right\rangle + \langle e_c(0), w\rangle \qquad \forall w \in L_2(\Omega) \tag{5.126}$$

$$\langle \alpha^{-1}\mathbf{z}, v\rangle \;-\; \langle P(e_c), \nabla\cdot v\rangle \;=\; -\langle P(e_{c_D}), v\cdot\mathbf{n}\rangle \tag{5.127}$$

$$\forall v \in H(\Omega; div)$$

Semi-discrete mixed finite element method

Let $(e_{c_h}, \mathbf{z}_h)$ be the approximation of $(e_c, \mathbf{z})$. Where $(e_{c_h}, \mathbf{z}_h) \in \mathbf{W_h} \times \mathbf{V_h}$ such that

$$\langle e_{c_h}, w_h \rangle + \left\langle \nabla \cdot \int_0^t \mathbf{z}_h \, ds, w_h \right\rangle = \left\langle \int_0^t \gamma(e_{c_h}, b_h, n_{a_h}, c_h) \, ds, w_h \right\rangle + \langle e_c(0), w_h \rangle \quad (5.128)$$

$$\langle \alpha^{-1} \mathbf{z}_h, v_h \rangle - \langle P(e_{c_h}), \nabla \cdot v_h \rangle = -\langle P(e_{c_D}), v_h \cdot \mathbf{n} \rangle \quad (5.129)$$

For all $w_h \in \mathbf{W_h} \subset L_2(\Omega)$ and for all $v_h \in \mathbf{V_h} \subset H(\Omega, div)$

5.3.1 Analysis of semi-discrete scheme

The following analysis depends heavily on a paper by Arbogast, Wheeler, and Zhang [7].

Let e_c be the true solution of the variational form (5.126),(5.127) and e_{c_h} be the solution of the semi-discrete form (5.128),(5.129). Subtracting (5.126),(5.127) from (5.128),(5.129), we get

$$(e_{c_h} - e_c, w_h) + \left(\nabla \cdot \int_0^t (\mathbf{z}_h - \mathbf{z}) \, ds, w_h \right) = \left(\int_0^t [\gamma(e_{c_h}, b_h, n_{a_h}, c_h) - \gamma(e_c, b, n_a, c)] \, ds, w_h \right)$$

$$(\alpha^{-1}(\mathbf{z}_h - \mathbf{z}), v_h) - (P(e_{c_h}) - P(e_c), \nabla \cdot v_h) = 0$$

Using the notation of Arbogast, Wheeler, and Zhang [7]:

$$\Phi = \mathbf{z}_h - \mathbf{z} \qquad \acute{\Phi} = \int_0^t \Phi \, ds \qquad \acute{\mathbf{z}} = \int_0^t \mathbf{z} \, ds$$

the last two equations become

$$(e_{c_h} - e_c, w_h) + \left(\nabla \cdot \acute{\Phi}, w_h \right) = \left(\int_0^t [\gamma(e_{c_h}, b_h, n_{a_h}, c_h) - \gamma(e_c, b, n_a, c)] \, ds, w_h \right)$$

$$(\alpha^{-1}\Phi, v_h) - (P(e_{c_h}) - P(e_c), \nabla \cdot v_h) = 0$$

By (5.2),

$$(e_{c_h} - e_c, w_h) + (\nabla \cdot \Pi_h \acute{\Phi}, w_h)$$
$$= \left(\int_0^t [\gamma(e_{c_h}, b_h, n_{a_h}, c_h) - \gamma(e_c, b, n_a, c)] ds, w_h) \right) \quad \forall w_h \in \mathbf{W}_h \tag{5.130}$$

$$(a\Phi, v_h) - (Q_h P(e_{c_h}) - Q_h P(e_c), \nabla \cdot v_h) = 0 \qquad \forall v_h \in \mathbf{V}_h \tag{5.131}$$

Set $w_h = Q_h P(e_{c_h}) - Q_h P(e_c) \in W_h$

Set $v_h = \mathsf{P}_h \acute{\Phi} = \Pi_h \acute{\Phi} + (\Pi_h - \mathsf{P}_h)\acute{\mathbf{z}} \in \mathbf{V}_h$ this is because $\mathsf{P}_h \acute{\mathbf{z}_h} = \Pi_h \acute{\mathbf{z}_h} = \acute{\mathbf{z}_h}$

Important! From this point on, we let $a = \alpha^{-1}$.

$$(e_{c_h} - e_c, Q_h P(e_{c_h}) - Q_h P(e_c)) + (\nabla \cdot \Pi_h \acute{\Phi}, Q_h P(e_{c_h}) - Q_h P(e_c))$$
$$= \left(\int_0^t [\gamma(e_{c_h}, b_h, n_{a_h}, c_h) - \gamma(e_c, b, n_a, c)] ds, Q_h P(e_{c_h}) - Q_h P(e_c)) \right)$$

$$(a\Phi, \mathsf{P}_h \acute{\Phi}) - (Q_h P(e_{c_h}) - Q_h P(e_c), \nabla \cdot \mathsf{P}_h \acute{\Phi}) = 0$$

Use $\mathsf{P}_h \acute{\Phi} = \Pi_h \acute{\Phi} + (\Pi_h - \mathsf{P}_h)\acute{\mathbf{z}}$

$$(e_{c_h} - e_c, Q_h P(e_{c_h}) - Q_h P(e_c)) + (Q_h P(e_{c_h}) - Q_h P(e_c), \nabla \cdot \Pi_h \acute{\Phi})$$
$$= \left(\int_0^t [\gamma(e_{c_h}, b_h, n_{a_h}, c_h) - \gamma(e_c, b, n_a, c)] ds, Q_h P(e_{c_h}) - Q_h P(e_c)) \right)$$

$$(a\Phi, \mathsf{P}_h \acute{\Phi}) - (Q_h P(e_{c_h}) - Q_h P(e_c), \nabla \cdot \Pi_h \acute{\Phi} + \nabla \cdot (\Pi_h - \mathsf{P}_h)\acute{\mathbf{z}}) = 0$$

$$(e_{c_h} - e_c, Q_h P(e_{c_h}) - Q_h P(e_c)) + (Q_h P(e_{c_h}) - Q_h P(e_c), \nabla \cdot \Pi_h \acute{\Phi})$$
$$= \left(\int_0^t [\gamma(e_{c_h}, b_h, n_{a_h}, c_h) - \gamma(e_c, b, n_a, c)] ds, Q_h P(e_{c_h}) - Q_h P(e_c)) \right)$$

$$(a\Phi, \mathsf{P}_h \acute{\Phi}) - (Q_h P(e_{c_h}) - Q_h P(e_c), \nabla \cdot \Pi_h \acute{\Phi}) - (Q_h P(e_{c_h}) - Q_h P(e_c), \nabla \cdot (\Pi_h - \mathsf{P}_h)\acute{\mathbf{z}}) = 0$$

Add these two equations

$$\begin{aligned}&(e_{c_h}-e_c, Q_hP(e_{c_h})-Q_hP(e_c))+(a\Phi, \mathsf{P}_h\acute{\Phi})\\&\quad=\left(\int_0^t[\gamma(e_{c_h},b_h,n_{a_h},c_h)-\gamma(e_c,b,n_a,c)]ds, Q_hP(e_{c_h})-\Pi P(e_c))\right)\\&\qquad\qquad+\Big(Q_hP(e_{c_h})-Q_hP(e_c), \nabla\cdot(\Pi_h-\mathsf{P}_h)\acute{\mathbf{z}}\Big)\end{aligned}$$

Now, note that since $\mathbf{z}\in L_2(J;(L_2(\Omega))^d)$ we have $\Phi=\mathbf{z}_h-\mathbf{z}\in L_2(J;(L_2(\Omega))^d)$ and since $\mathsf{P}_h\acute{\Phi}\ \in\mathbf{V}_h$, we can use (5.5) to say that:

$$(a(\mathsf{P}_h\Phi-\Phi),\mathsf{P}_h\acute{\Phi}))=0\quad\text{ and so }\quad(a\mathsf{P}_h\Phi,\mathsf{P}_h\acute{\Phi})=(a\Phi,\mathsf{P}_h\acute{\Phi})\quad\forall v_h\in\mathbf{V}_h.$$

In our equation, we now have

$$\begin{aligned}&(e_{c_h}-e_c, Q_hP(e_{c_h})-Q_hP(e_c))+(a\mathsf{P}_h\Phi, \mathsf{P}_h\acute{\Phi})\\&=\left(\int_0^t[\gamma(e_{c_h},b_h,n_{a_h},c_h)-\gamma(e_c,b,n_a,c)]ds, Q_hP(e_{c_h})-Q_hP(e_c))\right)\\&\qquad+\Big(Q_hP(e_{c_h})-Q_hP(e_c), \nabla\cdot(\Pi_h-\mathsf{P}_h)\acute{\mathbf{z}}\Big)\end{aligned}\tag{5.132}$$

Consider the first term on the left hand side of the error equation, (5.132) :

$$\begin{aligned}&(e_{c_h}-e_c, Q_hP(e_{c_h})-Q_hP(e_c))=(e_{c_h}-Q_he_c, Q_hP(e_{c_h})-Q_hP(e_c))\\&=(e_{c_h}-Q_he_c, P(e_{c_h})-P(e_c))=(e_{c_h}-e_c+e_c-Q_he_c, P(e_{c_h})-P(e_c))\\&=(e_{c_h}-e_c, P(e_{c_h})-P(e_c))-(Q_he_c-e_c, P(e_{c_h})-P(e_c))\end{aligned}$$

If we integrate from 0 to t,

$$\begin{aligned}\int_0^t(e_{c_h}-e_c, Q_hP(e_{c_h})-Q_hP(e_c))\,ds\ &=\\&=\int_0^t(e_{c_h}-e_c, P(e_{c_h})-P(e_c))\,ds\\&\quad-\int_0^t(Q_he_c-e_c, P(e_{c_h})-P(e_c))\,ds\end{aligned}\tag{5.133}$$

Before considering the second term on the left hand side of (5.132) recall

$$(a(\cdot,t)(\mathsf{P}_h(t)v - v), v_h)) = 0 \quad \forall v_h \in \mathbf{V}_h$$

Set $v = \acute{\Phi}$

$$(a(\cdot,t)(\mathsf{P}_h(t)\acute{\Phi} - \acute{\Phi}), v_h)) = 0 \quad \forall v_h \in \mathbf{V}_h$$

Take the derivative with respect to time, recalling that $\frac{d}{dt}\acute{\Phi} = \frac{d}{dt}\int_0^t \Phi \, ds = \Phi$

$$(a_t(\mathsf{P}_h(t)\acute{\Phi} - \acute{\Phi}), v_h)) + (a((\mathsf{P}_h(t)\acute{\Phi})_t - \Phi), v_h)) = 0 \quad \forall v_h \in \mathbf{V}_h$$

Set $v_h = \mathsf{P}_h\acute{\Phi}$

$$(a_t(\mathsf{P}_h(t)\acute{\Phi} - \acute{\Phi}), \mathsf{P}_h\acute{\Phi})) + (a((\mathsf{P}_h(t)\acute{\Phi})_t - \Phi), \mathsf{P}_h\acute{\Phi})) = 0$$

Using (5.5), we say

$$(a_t(\mathsf{P}_h(t)\acute{\Phi} - \acute{\Phi}), \mathsf{P}_h\acute{\Phi})) + (a((\mathsf{P}_h(t)\acute{\Phi})_t - \mathsf{P}_h\Phi), \mathsf{P}_h\acute{\Phi})) = 0$$

$$(a_t(\mathsf{P}_h(t)\acute{\Phi} - \acute{\Phi}), \mathsf{P}_h\acute{\Phi})) + (a(\mathsf{P}_h(t)\acute{\Phi})_t, \mathsf{P}_h\acute{\Phi})) - (a\mathsf{P}_h\Phi, \mathsf{P}_h\acute{\Phi})) = 0$$

$$(a\mathsf{P}_h\Phi, \mathsf{P}_h\acute{\Phi})) = (a_t(\mathsf{P}_h(t)\acute{\Phi} - \acute{\Phi}), \mathsf{P}_h\acute{\Phi})) + (a(\mathsf{P}_h(t)\acute{\Phi})_t, \mathsf{P}_h\acute{\Phi})) \tag{5.134}$$

Note that

$$\frac{d}{dt}(a\mathsf{P}_h\acute{\Phi}, \mathsf{P}_h\acute{\Phi}) = \int a_t\mathsf{P}_h\acute{\Phi}\mathsf{P}_h\acute{\Phi} \; + \; 2\int a\mathsf{P}_h\acute{\Phi}(\mathsf{P}_h\acute{\Phi})_t$$

This gives,

$$(a(\mathsf{P}_h\acute{\Phi})_t, \mathsf{P}_h\acute{\Phi}) \; = \frac{1}{2}\left[\frac{d}{dt}(a\mathsf{P}_h\acute{\Phi}, \mathsf{P}_h\acute{\Phi}) \; - \; (a_t\mathsf{P}_h\acute{\Phi}, \mathsf{P}_h\acute{\Phi})\right]$$

Put this into equation (5.134), we get

$$\begin{aligned}(a\mathsf{P}_h\Phi, \mathsf{P}_h\acute{\Phi}) = {} & (a_t(\mathsf{P}_h(t)\acute{\Phi} - \acute{\Phi}), \mathsf{P}_h\acute{\Phi}) \\ & + \frac{1}{2}\left[\frac{d}{dt}(a\mathsf{P}_h\acute{\Phi}, \mathsf{P}_h\acute{\Phi}) \; - \; (a_t\mathsf{P}_h\acute{\Phi}, \mathsf{P}_h\acute{\Phi})\right]\end{aligned} \tag{5.135}$$

$$\begin{aligned}(a\mathsf{P}_h\Phi, \mathsf{P}_h\acute{\Phi}) = {} & (a_t(\mathsf{P}_h(t)\acute{\Phi} - \acute{\Phi}), \mathsf{P}_h\acute{\Phi}) \\ & + \frac{1}{2}\,\frac{d}{dt}\|a^{1/2}\mathsf{P}_h\acute{\Phi}\|^2 \; - \; \frac{1}{2}(a_t\mathsf{P}_h\acute{\Phi}, \mathsf{P}_h\acute{\Phi})\end{aligned} \tag{5.136}$$

Integrating from 0 to t, we get

$$\int_0^t (a\mathsf{P}_h\Phi, \mathsf{P}_h\acute{\Phi})\ ds = \int_0^t (a_t(\mathsf{P}_h(t)\acute{\Phi}\ - \acute{\Phi}), \mathsf{P}_h\acute{\Phi})\ ds + \frac{1}{2}\ \|a^{1/2}(\cdot,t)\mathsf{P}_h\acute{\Phi}(t)\|^2$$

$$- \frac{1}{2}\ \|a^{1/2}(\cdot,0)\mathsf{P}_h\acute{\Phi}(0)\|^2\ -\ \frac{1}{2}\int_0^t (a_t\mathsf{P}_h\acute{\Phi}, \mathsf{P}_h\acute{\Phi})\ ds \tag{5.137}$$

Integrating (5.132) in time from 0 to t, substituting (5.133) and (5.137) gives

$$\int_0^t (e_{c_h} - e_c, P(e_{c_h}) - P(e_c))\ ds\ -\ \int_0^t (Q_h e_c - e_c, P(e_{c_h}) - P(e_c))\ ds$$

$$\int_0^t (a_t(\mathsf{P}_h(t)\acute{\Phi}\ - \acute{\Phi}), \mathsf{P}_h\acute{\Phi})\ ds + \frac{1}{2}\ \|a^{1/2}(\cdot,t)\mathsf{P}_h\acute{\Phi}(t)\|^2$$

$$- \frac{1}{2}\ \|a^{1/2}(\cdot,0)\mathsf{P}_h\acute{\Phi}(0)\|^2\ -\ \frac{1}{2}\int_0^t (a_t\mathsf{P}_h\acute{\Phi}, \mathsf{P}_h\acute{\Phi})\ ds$$

$$= \int_0^t \left(\int_0^t [\gamma(e_{c_h}, b_h, n_{a_h}, c_h) - \gamma(e_c, b, n_a, c)]ds, Q_hP(e_{c_h}) - Q_hP(e_c)) \right) ds$$

$$+ \int_0^t (Q_hP(e_{c_h}) - Q_hP(e_c), \nabla\cdot(\Pi_h - \mathsf{P}_h)\acute{\mathbf{z}})ds.$$

Moving some terms to the right hand side, we get the following **error equation**:

$$\int_0^t (e_{c_h} - e_c, P(e_{c_h}) - P(e_c))\ ds\ + \frac{1}{2}\ \|a^{1/2}(\cdot,t)\mathsf{P}_h\acute{\Phi}(t)\|^2$$

$$= \int_0^t \left(\int_0^s [\gamma(e_{c_h}, b_h, n_{a_h}, c_h) - \gamma(e_c, b, n_a, c)]ds_1, Q_hP(e_{c_h}) - Q_hP(e_c)) \right) ds$$

$$+ \int_0^t (Q_hP(e_{c_h}) - Q_hP(e_c), \nabla\cdot(\Pi_h - \mathsf{P}_h)\acute{\mathbf{z}})ds$$

$$+\ \int_0^t (Q_he_c - e_c, P(e_{c_h}) - P(e_c))\ ds - \int_0^t (a_t(\mathsf{P}_h(t)\acute{\Phi}\ - \acute{\Phi}), \mathsf{P}_h\acute{\Phi})\ ds$$

$$+\frac{1}{2}\int_0^t \|a^{1/2}(\cdot,0)\mathsf{P}_h\acute{\Phi}(0)\|^2\,ds+\frac{1}{2}\int_0^t(a_t\mathsf{P}_h\acute{\Phi},\mathsf{P}_h\acute{\Phi})\,ds$$

$$=T_1+T_2+T_3+T_4+T_5 \tag{5.138}$$

Bounding the terms

$$\begin{aligned}
T_1&=\int_0^t\left(\int_0^s[\gamma(e_{c_h},b_h,n_{a_h},c_h)-\gamma(e_c,b,n_a,c)]ds_1,Q_hP(e_{c_h})-\Pi P(e_c)\right)ds\\
&\le\int_0^t\|\int_0^s[\gamma(e_{c_h},b_h,n_{a_h},c_h)-\gamma(e_c,b,n_a,c)]ds_1\|\|Q_hP(e_{c_h})-Q_hP(e_c)\|\,ds\\
&\le\int_0^t\frac{1}{2\varepsilon_3}\|\int_0^s[\gamma(e_{c_h},b_h,n_{a_h},c_h)-\gamma(e_c,b,n_a,c)]ds_1\|^2ds\\
&\qquad+\frac{\varepsilon_3}{2}\int_0^t\|Q_hP(e_{c_h})-Q_hP(e_c))\|^2\,ds
\end{aligned}$$

Add and subtract the appropriate terms with the function γ and apply (5.115) through (5.117):

$$\begin{aligned}
T_1&\le\int_0^t\frac{1}{2\varepsilon_3}\|\int_0^s[\gamma(e_{c_h},b,n_a,c)-\gamma(e_c,b,n_a,c)]ds_1\|^2ds\\
&\quad+\int_0^t\frac{C}{2\varepsilon_3}\|\int_0^s|n_a-n_{a_h}|ds_1\|^2ds+\int_0^t\frac{C}{2\varepsilon_3}\|\int_0^s|c-c_h|ds_1\|^2ds\\
&+\int_0^t\frac{C}{2\varepsilon_3}\|\int_0^s|b-b_n|ds_1\|^2ds+\frac{\varepsilon_3}{2}\int_0^t\|Q_hP(e_{c_h})-Q_hP(e_c))\|^2\,ds
\end{aligned}$$

By the assumption on γ, see (5.113),

$$\begin{aligned}
T_1&\le\int_0^t\frac{1}{2\varepsilon_3}\|\int_0^s[C_0(P(e_{c_h})-P(e_c),e_{c_h}-e_c)]ds_1\|^2ds\\
&\quad+\int_0^t\frac{C}{2\varepsilon_3}\|\int_0^s\|b-b_n\|ds_1\|^2ds+\int_0^t\frac{C}{2\varepsilon_3}\|\int_0^s|n_a-n_{a_h}|ds_1\|^2ds\\
&\quad+\int_0^t\frac{C}{2\varepsilon_3}\|\int_0^s|c-c_h|ds_1\|^2ds+\frac{\varepsilon_3}{2}\int_0^t\|Q_hP(e_{c_h})-Q_hP(e_c))\|^2\,ds\\
T_2&=\int_0^t(Q_hP(e_{c_h})-Q_hP(e_c),\nabla\cdot(\Pi_h-\mathsf{P}_h)\acute{\mathbf{z}})ds\\
&\le\int_0^t\|Q_hP(e_{c_h})-Q_hP(e_c)\|\|\nabla\cdot(\Pi_h-\mathsf{P}_h)\acute{\mathbf{z}}\|ds\\
&\le\frac{\varepsilon_2}{2}\int_0^t\|Q_hP(e_{c_h})-Q_hP(e_c)\|^2+\frac{1}{2\varepsilon_2}\|\nabla\cdot(\Pi_h-\mathsf{P}_h)\acute{\mathbf{z}}\|^2ds
\end{aligned}$$

$$
\begin{aligned}
T_3 &= \int_0^t (Q_h e_c - e_c, P(e_{c_h}) - P(e_c))\, ds \\
&\leq \int_0^t \|Q_h e_c - e_c\| \|P(e_{c_h}) - P(e_c))\|\, ds \\
&\leq \int_0^t \frac{1}{2\varepsilon_1} \|Q_h e_c - e_c\|^2 + \frac{\varepsilon_1}{2} \|P(e_{c_h}) - P(e_c))\|^2\, ds \\
T_4 &= -\int_0^t (a_t(\mathsf{P}_h(t)\acute{\Phi} - \acute{\Phi}), \mathsf{P}_h\acute{\Phi})\, ds \\
&= -\int_0^t (a_t(\mathsf{P}_h(t) \int_0^t (\mathbf{z}_h - \mathbf{z}) ds - \int_0^t (\mathbf{z}_h - \mathbf{z}) ds), \mathsf{P}_h\acute{\Phi})\, ds \\
&= -\int_0^t (a_t(\mathsf{P}_h(t)(\acute{\mathbf{z}_h} - \acute{\mathbf{z}}) - (\acute{\mathbf{z}_h} - \acute{\mathbf{z}})), \mathsf{P}_h\acute{\Phi})\, ds \\
&= -\int_0^t (a_t(\mathsf{P}_h(t)\acute{\mathbf{z}_h} - \acute{\mathbf{z}_h}), \mathsf{P}_h\acute{\Phi})\, ds \\
&\qquad\qquad - \int_0^t (a_t(\mathsf{P}_h(t)(-\acute{\mathbf{z}}) - (-\acute{\mathbf{z}})), \mathsf{P}_h\acute{\Phi})\, ds \\
&= -\int_0^t (a_t(\mathsf{P}_h(t)\acute{\mathbf{z}_h} - \acute{\mathbf{z}_h}), \mathsf{P}_h\acute{\Phi})\, ds + \int_0^t (a_t(\mathsf{P}_h(t)\acute{\mathbf{z}} - \acute{\mathbf{z}}), \mathsf{P}_h\acute{\Phi})\, ds
\end{aligned}
$$

By (5.5), the first term on the right hand side is zero, so we have

$$
T_4 = \int_0^t (a_t(\mathsf{P}_h(t)\acute{\mathbf{z}} - \acute{\mathbf{z}}), \mathsf{P}_h\acute{\Phi})\, ds
$$

Assume that a_t is bounded above,

$$
T_4 \leq \int_0^t C_1 \|\mathsf{P}_h(t)\acute{\mathbf{z}} - \acute{\mathbf{z}}\| \|\mathsf{P}_h\acute{\Phi}\|\, ds
$$

$$
\leq \int_0^t \frac{C_2}{2} \|\mathsf{P}_h(t)\acute{\mathbf{z}} - \acute{\mathbf{z}}\|^2 + \frac{C_3}{2} \|\mathsf{P}_h\acute{\Phi}\|^2\, ds
$$

$$
T_5 = +\frac{1}{2} \int_0^t (a_t \mathsf{P}_h\acute{\Phi}, \mathsf{P}_h\acute{\Phi})\, ds \leq \frac{1}{2} C_1 \int_0^t \|\mathsf{P}_h\acute{\Phi}\|^2\, ds
$$

Substituting T_1 through T_5 into (5.138), we get

$$
\begin{aligned}
&\int_0^t (e_{c_h} - e_c, P(e_{c_h}) - P(e_c)) ds + \|a^{1/2}\mathsf{P}_h\acute{\Phi}\|^2 \\
&\leq \int_0^t \frac{1}{2\varepsilon_1} \|Q_h e_c - e_c\|^2\, ds + \int_0^t \frac{\varepsilon_1}{2} \|P(e_{c_h}) - P(e_c))\|^2\, ds
\end{aligned}
$$

$$
\begin{aligned}
&+ C_4 \int_0^t \|\mathsf{P}_h \acute{\Phi}\|^2 \, ds + \int_0^t \frac{C_2}{2} \|\mathsf{P}_h(t)\acute{\mathbf{z}} \ - \acute{\mathbf{z}}\|^2 ds \\
&+ \frac{\varepsilon_2}{2} \int_0^t \|Q_h P(e_{c_h}) - Q_h P(e_c)\|^2 + \frac{1}{2\varepsilon_2} \|\nabla \cdot (\Pi_h - \mathsf{P}_h)\acute{\mathbf{z}}\|^2 ds \\
&+ \int_0^t \frac{1}{2\varepsilon_3} \| \int_0^s [C_0(P(e_{c_h}) - P(e_c), e_{c_h} - e_c)] ds_1 \|^2 ds \\
&\quad + \int_0^t \frac{C}{2\varepsilon_3} \| \int_0^s \|b - b_n\| ds_1 + \int_0^t \frac{C}{2\varepsilon_3} \| \int_0^s |n_a - n_{a_h}| ds_1 \|^2 ds \\
&\quad + \int_0^t \frac{C}{2\varepsilon_3} \| \int_0^s |c - c_h| ds_1 \|^2 ds + \frac{\varepsilon_3}{2} \int_0^t \|Q_h P(e_{c_h}) - Q_h P(e_c))\|^2 ds
\end{aligned}
$$

Before continuing, note that from (5.112), we can say,

$$
\|P(e_{c_h}) - P(e_c)\|^2 \leq C_0(P(e_{c_h}) - P(e_c), e_{c_h} - e_c) \tag{5.139}
$$

This will be used in what follows.

Using the fact that $\|Q_h P(e_{c_h}) - Q_h P(e_c)\| \leq C\|P(e_{c_h}) - P(e_c)\|$, we have

$$
\begin{aligned}
&\int_0^t (e_{c_h} - e_c, P(e_{c_h}) - P(e_c)) ds + \|a^{1/2} \mathsf{P}_h \acute{\Phi}\|^2 \\
&\leq \int_0^t \frac{1}{2\varepsilon_1} \|Q_h e_c - e_c\|^2 \, ds + \int_0^t \frac{\varepsilon_1}{2} \|P(e_{c_h}) - P(e_c))\|^2 \, ds \\
&\quad + C_4 \int_0^t \|\mathsf{P}_h \acute{\Phi}\|^2 \, ds + \int_0^t \frac{C_2}{2} \|\mathsf{P}_h(t)\acute{\mathbf{z}} \ - \acute{\mathbf{z}}\|^2 ds \\
&+ C\frac{\varepsilon_2}{2} \int_0^t \|P(e_{c_h}) - P(e_c)\|^2 ds + \int_0^t \frac{1}{2\varepsilon_2} \|\nabla \cdot (\Pi_h - \mathsf{P}_h)\acute{\mathbf{z}}\|^2 ds \\
&+ \int_0^t \frac{1}{2\varepsilon_3} \| \int_0^s [C_0(P(e_{c_h}) - P(e_c), e_{c_h} - e_c)] ds_1 \|^2 ds \\
&+ \int_0^t \frac{C}{2\varepsilon_3} \| \int_0^s \|b - b_n\| ds_1 \|^2 ds + \int_0^t \frac{C}{2\varepsilon_3} \| \int_0^s |n_a - n_{a_h}| ds_1 \|^2 ds \\
&+ \int_0^t \frac{C}{2\varepsilon_3} \| \int_0^s |c - c_h| ds_1 \|^2 ds + \frac{\varepsilon_3}{2} \int_0^t \|P(e_{c_h}) - P(e_c))\|^2 \, ds
\end{aligned} \tag{5.140}
$$

Using (5.139):

$$
\begin{aligned}
&\int_0^t (e_{c_h} - e_c, P(e_{c_h}) - P(e_c)) ds + C_9 \|\mathsf{P}_h \acute{\Phi}\|^2 \\
&\leq \int_0^t \frac{1}{2\varepsilon_1} \|Q_h e_c - e_c\|^2 \, ds + \int_0^t \frac{\varepsilon_1}{2} C_0(P(e_{c_h}) - P(e_c), e_{c_h} - e_c) \, ds
\end{aligned}
$$

$$
\begin{aligned}
&+ C_4 \int_0^t \|\mathsf{P}_h \acute{\Phi}\|^2 \, ds + \int_0^t \frac{C_2}{2} \|\mathsf{P}_h(t)\acute{\mathbf{z}} \ - \acute{\mathbf{z}}\|^2 ds \\
&+ C\frac{\varepsilon_2}{2} \int_0^t C_0(P(e_{c_h}) - P(e_c), e_{c_h} - e_c) ds + \int_0^t \frac{1}{2\varepsilon_2} \|\nabla \cdot (\Pi_h - \mathsf{P}_h)\acute{\mathbf{z}}\|^2 ds \\
&+ \int_0^t \frac{1}{2\varepsilon_3} \int_0^s [C_0(P(e_{c_h}) - P(e_c), e_{c_h} - e_c)] ds_1 ds \\
&+ \frac{\varepsilon_3}{2} \int_0^t C_{00}(P(e_{c_h}) - P(e_c), e_{c_h} - e_c) \, ds \\
&+ \int_0^t \frac{C}{2\varepsilon_3} \| \int_0^s \|b - b_n\| ds_1 \|^2 ds + \int_0^t \frac{C}{2\varepsilon_3} \| \int_0^s |n_a - n_{a_h}| ds_1 \|^2 ds \\
&+ \int_0^t \frac{C}{2\varepsilon_3} \| \int_0^s |c - c_h| ds_1 \|^2 ds
\end{aligned} \tag{5.141}
$$

Choosing $\varepsilon_1, \varepsilon_2$, and ε_3 carefully,

$$
\begin{aligned}
&C_5 \int_0^t (e_{c_h} - e_c, P(e_{c_h}) - P(e_c)) \, ds + C_9 \|\mathsf{P}_h \acute{\Phi}\|^2 \\
&\leq \int_0^t C_6 \|Q_h e_c - e_c\|^2 \, ds + \ C_4 \int_0^t \|\mathsf{P}_h \acute{\Phi}\|^2 \, ds \\
&+ \int_0^t \frac{C_2}{2} \|\mathsf{P}_h(t)\acute{\mathbf{z}} \ - \acute{\mathbf{z}}\|^2 ds + C_7 \int_0^t \|\nabla \cdot (\Pi_h - \mathsf{P}_h)\acute{\mathbf{z}}\|^2 ds \\
&+ C_8 \int_0^t \int_0^s [C_0(P(e_{c_h}) - P(e_c), e_{c_h} - e_c)] ds_1 ds \\
&\quad + \int_0^t \frac{C}{2\varepsilon_3} \| \int_0^s \|b - b_n\| ds_1 \|^2 ds + \int_0^t \frac{C}{2\varepsilon_3} \| \int_0^s |n_a - n_{a_h}| ds_1 \|^2 ds \\
&\quad + \int_0^t \frac{C}{2\varepsilon_3} \| \int_0^s |c - c_h| ds_1 \|^2 ds
\end{aligned}
$$

Note that the Gronwall Inequality, theorem 4.8, can be applied to the terms that have the constants C_5 and C_8. Also, the Gronwall Inequality can be applied to the terms that have the constants C_9 and C_4 to get:

$$
\begin{aligned}
&C_5 \int_0^t (e_{c_h} - e_c, P(e_{c_h}) - P(e_c)) \, ds + C_9 \|\mathsf{P}_h \acute{\Phi}\|^2 \\
&\leq \ C_{10} \Bigg\{ \int_0^t C_6 \|Q_h e_c - e_c\|^2 \, ds + \int_0^t \frac{C_2}{2} \|\mathsf{P}_h(t)\acute{\mathbf{z}} \ - \acute{\mathbf{z}}\|^2 ds \\
&\qquad + C_7 \|\nabla \cdot (\Pi_h - \mathsf{P}_h)\acute{\mathbf{z}}\|^2 ds \quad + \int_0^t \frac{C}{2\varepsilon_3} \| \int_0^s |b - b_n| ds_1 \|^2 ds \\
&\qquad\qquad + \int_0^t \frac{C}{2\varepsilon_3} \| \int_0^s |n_a - n_{a_h}| ds_1 \|^2 ds
\end{aligned}
$$

$$+\int_0^t \frac{C}{2\varepsilon_3}\|\int_0^s |c-c_h|ds_1\|^2 ds\Bigg\} \tag{5.142}$$

Using (5.113) and the definition of $\|\mathsf{P}_h\acute{\Phi}\|$

$$\begin{aligned}
&C_5\int_0^t \|\gamma(e_{c_h},b,n_a,c)-\gamma(e_c,b,n_a,c)\|^2\,ds + C_9\|\int_0^t \mathbf{z}_h\,ds - \int_0^t P_h\mathbf{z}\,ds\|^2\\
&\leq\ C_{10}\Bigg\{\int_0^t C_6\|Q_he_c-e_c\|^2\,ds + \int_0^t \frac{C_2}{2}\|\mathsf{P}_h(t)\acute{\mathbf{z}}-\acute{\mathbf{z}}\|^2 ds\\
&\quad +C_7\|\nabla\cdot(\Pi_h-\mathsf{P}_h)\acute{\mathbf{z}}\|^2 ds \quad + \int_0^t \frac{C}{2\varepsilon_3}\|\int_0^s |b-b_n|ds_1\|^2 ds\\
&\qquad + \int_0^t \frac{C}{2\varepsilon_3}\|\int_0^s |n_a-n_{a_h}|ds_1\|^2 ds\\
&\qquad\quad + \int_0^t \frac{C}{2\varepsilon_3}\|\int_0^s |c-c_h|ds_1\|^2 ds\Bigg\}
\end{aligned} \tag{5.143}$$

Furthermore, since all the terms are positive, we get:

Bound 1 (Degenerate Case)

$$\begin{aligned}
&\int_0^t \|\gamma(e_{c_h},b,n_a,c)-\gamma(e_c,b,n_a,c)\|\,ds + \|\int_0^t \mathbf{z}_h\,ds - \int_0^t P_h\mathbf{z}\,ds\|\\
&\leq\ C_{11}\Bigg\{\int_0^t \|Q_he_c-e_c\|\,ds + \int_0^t \|\mathsf{P}_h(t)\acute{\mathbf{z}}\ -\acute{\mathbf{z}}\|ds\\
&+\|\nabla\cdot(\Pi_h-\mathsf{P}_h)\acute{\mathbf{z}}\|^2 ds\ + \int_0^t \|\int_0^s |b-b_n|ds_1\|^2 ds\\
&+\int_0^t \|\int_0^s |n_a-n_{a_h}|ds_1\|^2 ds\ + \int_0^t \|\int_0^s |c-c_h|ds_1\|^2 ds\Bigg\}.
\end{aligned} \tag{5.144}$$

We may also go back to (5.142) and use (5.112) and the definition of $\|\mathsf{P}_h\acute{\Phi}\|$ and, again, use the fact that all terms are positive, to get:

Bound 2 (Degenerate Case)

$$\begin{aligned}
&\int_0^t \|P(e_{c_h})-P(e_c)\|\,ds + C_9\|\int_0^t \mathbf{z}_h\,ds - \int_0^t P_h\mathbf{z}\,ds\|\\
&\leq\ C_{12}\Bigg\{\int_0^t \|Q_he_c-e_c\|\,ds + \int_0^t \|\mathsf{P}_h(t)\acute{\mathbf{z}}\ -\acute{\mathbf{z}}\|ds
\end{aligned}$$

$$+\|\nabla\cdot(\Pi_h-\mathsf{P}_h)\acute{\mathbf{z}}\|^2ds \;+\int_0^t\|\int_0^s|b-b_n|ds_1\|^2ds$$
$$+\int_0^t\|\int_0^s|n_a-n_{a_h}|ds_1\|^2ds \;+\int_0^t\|\int_0^s|c-c_h|ds_1\|^2ds\Bigg\}. \tag{5.145}$$

Bound in the H^{-1} Norm

So far, we have succeeded in finding a bound in the error $P(e_{c_h})-P(e_c)$ in the L_2 norm. We now desire to find a bound in the error $e_{c_h}-e_c$ in some norm. Once again, we follow Arbogast, Wheeler, and Zhang [7] to get such a bound in the H^{-1} norm.

Let $\varphi\in H_0^1$ and $Q_h\varphi\in W_h$. Where $\Pi\varphi$ is the L_2 projection of φ onto W_h. Then

$$\begin{aligned}\langle e_{c_h}-e_c,\varphi\rangle &= \langle e_{c_h}-e_c,\varphi-Q_h\varphi+Q_h\varphi\rangle\\ &=\langle e_{c_h}-e_c,\varphi-Q_h\varphi\rangle \;+\; \langle e_{c_h}-e_c,Q_h\varphi\rangle\\ &=\langle e_{c_h}-Q_he_c+Q_he_c-e_c,\varphi-Q_h\varphi\rangle \;+\; \langle e_{c_h}-e_c,Q_h\varphi\rangle\\ &=\langle e_{c_h}-Q_he_c,\varphi-Q_h\varphi\rangle \;+\; \langle Q_he_c-e_c,\varphi-Q_h\varphi\rangle \;+\; \langle e_{c_h}-e_c,Q_h\varphi\rangle\end{aligned}$$

Note that $e_{c_h}-Q_he_c\in W_h$ and $\varphi-Q_h\varphi$ is orthogonal to W_h. So, the first term on the right hand side is zero. So, we have

$$\langle e_{c_h}-e_c,\varphi\rangle \;=\; \langle Q_he_c-e_c,\varphi-Q_h\varphi\rangle \;+\; \langle e_{c_h}-e_c,Q_h\varphi\rangle$$

Then by (5.130),

$$\begin{aligned}\langle e_{c_h}-e_c,\varphi\rangle &= (Q_he_c-e_c,\varphi-Q_h\varphi)\\ &+\left(\int_0^t[\gamma(e_{c_h},b_h,n_{a_h},c_h)-\gamma(e_c,b,n_a,c)]ds,Q_h\varphi\right)-(\nabla\cdot\Pi_h\acute{\Phi},Q_h\varphi)\end{aligned}$$

Since $\nabla\cdot\Pi_h\acute{\Phi}\in W_h$, we have $\langle\nabla\cdot\Pi_h\acute{\Phi},Q_h\varphi\rangle=\langle\nabla\cdot\Pi_h\acute{\Phi},\varphi\rangle$

$$\begin{aligned}\langle e_{c_h}-e_c,\varphi\rangle &= (Q_he_c-e_c,\varphi-Q_h\varphi)\\ &+\left(\int_0^t[\gamma(e_{c_h},b_h,n_{a_h},c_h)-\gamma(e_c,b,n_a,c)]ds,Q_h\varphi\right)-(\nabla\cdot\Pi_h\acute{\Phi},\varphi)\end{aligned}$$

Integration by parts gives

$$\begin{aligned}\langle e_{c_h} - e_c, \varphi\rangle \;&=\; (Q_h e_c - e_c, \varphi - Q_h\varphi)\\ &+\left(\int_0^t [\gamma(e_{c_h}, b_h, n_{a_h}, c_h) - \gamma(e_c, b, n_a, c)]ds, Q_h\varphi\right) + (\Pi_h\acute{\Phi}, \nabla\varphi) - (\Pi_h\acute{\Phi}, \varphi)_{\partial\Omega}\end{aligned}$$

Since $\varphi \in H_0^1$, the last term on the right hand side is zero. So, we have

$$\begin{aligned}\langle e_{c_h} - e_c, \varphi\rangle \;&\leq\; \langle Q_h e_c - e_c, \varphi - Q_h\varphi\rangle\\ &+\left(\int_0^t [\gamma(e_{c_h}, b_h, n_{a_h}, c_h) - \gamma(e_c, b, n_a, c)]ds, Q_h\varphi\right) + (\Pi_h\acute{\Phi}, \nabla\varphi)\\ &\leq\; \|Q_h e_c - e_c\|\|\varphi - Q_h\varphi\|\\ &+\int_0^t \|\gamma(e_{c_h}, b_h, n_{a_h}, c_h) - \gamma(e_c, b, n_a, c)\|ds\|Q_h\varphi\| + \|\Pi_h\acute{\Phi}\|\|\nabla\varphi\|\end{aligned}$$

For a projection, $\|Q_h\varphi\| \leq \|\varphi\|$. The approximation result gives us

$$\|\varphi - Q_h\varphi\| \leq h^{1-0}K\|\varphi\|_{H^1(\Omega)}$$

Also, we have

$$\|\nabla\varphi\|_{L^2} \leq \|\varphi\|_{H^1} \text{ and } \|\varphi\|_{L^2} \leq \|\varphi\|_{H^1}$$

$$\begin{aligned}\langle e_{c_h} - e_c, \varphi\rangle \;&\leq\; C\Bigg(\|Q_h e_c - e_c\|h\\ &+\int_0^t \|\gamma(e_{c_h}, b_h, n_{a_h}, c_h) - \gamma(e_c, b, n_a, c)\|ds + \|\Pi_h\acute{\Phi}\|\Bigg)\|\varphi\|_{H^1(\Omega)}\end{aligned}$$

$$\begin{aligned}\frac{\langle e_{c_h} - e_c, \varphi\rangle}{\|\varphi\|_{H^1(\Omega)}} \;&\leq\; C\Bigg(\|Q_h e_c - e_c\|h\\ &+\int_0^t \|\gamma(e_{c_h}, b_h, n_{a_h}, c_h) - \gamma(e_c, b, n_a, c)\|ds + \|\Pi_h\acute{\Phi}\|\Bigg)\end{aligned}$$

Since this is true for all $\varphi \in H_0^1(\Omega)$,

$$\begin{aligned}\sup_{\varphi\in H_0^1(\Omega)} \frac{\langle e_{c_h} - e_c, \varphi\rangle}{\|\varphi\|_{H^1(\Omega)}} \;&\leq\; C\Bigg(\|Q_h e_c - e_c\|h\\ &+\int_0^t \|\gamma(e_{c_h}, b_h, n_{a_h}, c_h) - \gamma(e_c, b, n_a, c)\|ds + \|\Pi_h\acute{\Phi}\|\Bigg)\end{aligned}$$

$$\|e_{c_h} - e_c\|_{H^{-1}(\Omega)} \leq C\Bigg(\|Q_h e_c - e_c\| h + \int_0^t \|\gamma(e_{c_h}, b_h, n_{a_h}, c_h) - \gamma(e_c, b, n_a, c)\| ds + \|\Pi_h \acute{\Phi}\| \Bigg)$$

Add and subtract the appropriate functions of γ within the second term on the right hand side. Add and subtract $\int_0^t P_h \mathbf{z} ds$ inside the last term on the right hand side and using (5.115) through (5.117), we get,

$$\|e_{c_h} - e_c\|_{H^{-1}(\Omega)} \leq C\Bigg(\|Q_h e_c - e_c\| h + \int_0^t \|n_a - n_{a_h}\| ds + \int_0^t \|c - c_h\| ds + \int_0^t \|b_h - b\| ds + \int_0^t \|\gamma(e_{c_h}, b, n_a, c) - \gamma(e_c, b, n_a, c)\| \, ds + \| \int_0^t \mathbf{z}_h \, ds - \int_0^t P_h \mathbf{z} \, ds\| + \| \int_0^t P_h \mathbf{z} \, ds - \int_0^t \Pi_h \mathbf{z} \, ds\| \Bigg).$$

Substitute (5.144)

$$\|e_{c_h} - e_c\|_{H^{-1}(\Omega)} \leq C\Bigg(\|Q_h e_c - e_c\| h + \int_0^t \|n_a - n_{a_h}\| ds + \int_0^t \|c - c_h\| ds + \int_0^t \|b_h - b\| ds + \int_0^t \|Q_h e_c - e_c\| \, ds + \int_0^t \|\mathsf{P}_h(t) \acute{\mathbf{z}} - \acute{\mathbf{z}}\| ds + \int_0^t \|\nabla \cdot (\Pi_h - \mathsf{P}_h) \acute{\mathbf{z}}\| ds + \| \int_0^t P_h \mathbf{z} \, ds - \int_0^t \Pi_h \mathbf{z} \, ds\| + \int_0^t \| \int_0^s |b - b_n| ds_1\|^2 ds + \int_0^t \| \int_0^s |n_a - n_{a_h}| ds_1\|^2 ds + \int_0^t \| \int_0^s |c - c_h| ds_1\|^2 ds$$

$$\leq C\Bigg(\|Q_h e_c - e_c\| h + \int_0^t \|b_h - b\| ds + \int_0^t \|Q_h e_c - e_c\| \, ds + \int_0^t \|n_a - n_{a_h}\| ds + \int_0^t \|c - c_h\| ds + \int_0^t \|\mathsf{P}_h(t) \acute{\mathbf{z}} - \acute{\mathbf{z}}\| ds + \int_0^t \|\nabla \cdot (\Pi_h \acute{\mathbf{z}} - \acute{\mathbf{z}} + \acute{\mathbf{z}} - \mathsf{P}_h \acute{\mathbf{z}})\| ds + \| \int_0^t P_h \mathbf{z} \, ds - \int_0^t \mathbf{z} \, ds + \int_0^t \mathbf{z} \, ds - \int_0^t \Pi_h \mathbf{z} \, ds\|$$

$$+\int_0^t \| \int_0^s |n_a - n_{a_h}| ds_1 \|^2 ds \; + \int_0^t \| \int_0^s |c - c_h| ds_1 \|^2 ds$$
$$+ \int_0^t \| \int_0^s |b - b_n| ds_1 \|^2 ds \Bigg)$$

$$\leq \; C \Bigg(\|Q_h e_c - e_c\| h \; + \int_0^t \|b_h - b\| ds + \int_0^t \|Q_h e_c - e_c\| \; ds$$
$$+ \int_0^t \|n_a - n_{a_h}\| ds \; + \int_0^t \|c - c_h\| ds$$
$$+ \int_0^t \|\mathsf{P}_h(t)\acute{\mathbf{z}} \; - \acute{\mathbf{z}}\| ds + \int_0^t (\|\nabla \cdot (\Pi_h \acute{\mathbf{z}} - \acute{\mathbf{z}})\| + \|\nabla \cdot (\acute{\mathbf{z}} - \mathsf{P}_h \acute{\mathbf{z}})\|) ds$$
$$+ \| \int_0^t (P_h \mathbf{z} \; - \mathbf{z}) \; ds\| + \| \int_0^t (\mathbf{z} - \Pi_h \mathbf{z}) \; ds\| + \int_0^t \| \int_0^s |b - b_n| ds_1 \|^2 ds$$
$$+ \int_0^t \| \int_0^s |n_a - n_{a_h}| ds_1 \|^2 ds \; + \int_0^t \| \int_0^s |c - c_h| ds_1 \|^2 ds \Bigg). \tag{5.146}$$

Bound 3 (Error bound in H^{-1} Norm - Degenerate Case)

Thus, (5.146) gives an error bound for $e_{c_h} - e_c$ in the H^{-1} norm. Note that in (5.146) the terms $\|Q_h e_c - e_c\|, \|\mathsf{P}_h(t)\acute{\mathbf{z}} \; - \acute{\mathbf{z}}\|, \|\nabla \cdot (\acute{\mathbf{z}} - \mathsf{P}_h \acute{\mathbf{z}})\|, \|\nabla \cdot (\Pi_h \acute{\mathbf{z}} - \acute{\mathbf{z}})\|, \| \int_0^t (\mathbf{z} - \Pi_h \mathbf{z}) \; ds\|$, and $\| \int_0^t (P_h \mathbf{z} \; - \mathbf{z}) \; ds\|$ will be bounded using approximation results. Bounds on the terms $\|b_h - b\|$,$\|n_{a_h} - n_a\|$, and $\|c_h - c\|$ were found in the numerical analysis for the equations in Part I of the PDE system.

Note: A careful look at **Bound 3** indicates that in order to get convergence of at least h, it is required that $P(e_c) \in H^3(\Omega)$.

5.4 FINITE ELEMENT ANALYSIS OF THE PDES IN PART III

In this section we will do the final error bound, the bound on the error of $ZO1$. Recall,

$$\frac{\partial ZO1}{\partial t} = \left(k_{Z_{e_c}} e_c + k_{Z_{e_{ct}}} \frac{\partial e_c}{\partial t}\right) ZO1_{max}(1 - ZO1/zec) \\ -k_{ZN} NO \cdot ZO1 \tag{5.147}$$

where

$$zec = (1 - \epsilon_{zec}) ZO1_{max} + \epsilon_{zec} \left(\frac{ZO1_{max}}{e_{c,max}}\right) e_c. \tag{5.148}$$

The initial condition is given by:

$$ZO1(x, 0) := ZO1^0(x) \quad \text{on } \Omega$$

(Note that $ZO1^0(x)$ will usually be represented by $ZO1^0$.)

Note that the right hand side of (5.147) is dependent upon an equation (the NO equation) from Part I of PDE equations and upon the equation (the epithelial equation) from Part II of PDE equations. We found an error bound for the numerical approximation of the Part I equations in terms of the L^2 norm but the error bound for Part II equation was found in terms of the H^{-1} norm. Therefore, it will probably not be possible to find an error for the numerical approximation of $ZO1$ in a norm any stronger than H^{-1}. Therefore, the goal in this section is to find an error bound in that norm.

In order to simplify the following calculations the parameters in (5.147) and (5.148) will be replaced with their actual values:

$$ZO1_t = (.03e_c + 2e_{c_t})(1 - ZO1/zec) - .75NO \cdot ZO1 \tag{5.149}$$

$$zec = .95 + .05e_c. \tag{5.150}$$

Now, substitute (5.150) into (5.149) and integrate with respect to t to obtain:

$$ZO1 = .03 \int_0^t e_c + 2e_c - 2e_c(0) - .03 \int_0^t \frac{e_c ZO1}{.95 + .05e_c} \\ - 2 \int_0^t \frac{e_{c_t} ZO1}{.95 + .05e_c} - .75 \int_0^t NO \cdot ZO1 + ZO1(0).$$

Weak Formulation

Set $W := H_0^1(\Omega)$. The weak formulation of the above equation may be stated as follows: find $ZO1 \in W$ such that

$$\begin{aligned}(ZO1, w) &= .03 \int_0^t (e_c, w) + 2(e_c, w) \\ &+ .03 \int_0^t \left(\frac{-e_c ZO1}{.95 + .05e_c}, w \right) + 2 \int_0^t \left(\frac{-e_{c_t} ZO1}{.95 + .05e_c}, w \right) \\ &-.75 \int_0^t (NO \cdot ZO1, w) + (ZO1(0), w) \quad \forall w \in H_0^1(\Omega). \end{aligned} \tag{5.151}$$

Discrete Formulation

Let W_h denote the finite element approximating subspace of W. Then the semidiscrete formulation may be described as: find $ZO1_h \in W_h$ such that

$$\begin{aligned}(ZO1_h, w) &= .03 \int_0^t (e_{c_h}, w) + 2(e_{c_h}, w) \\ &+ .03 \int_0^t \left(\frac{e_{c_h} ZO1_h}{.95 + .05e_{c_h}}, w \right) + 2 \int_0^t \left(\frac{e_{c_{t_h}} ZO1_h}{.95 + .05e_{c_h}}, w \right) \\ &-.75 \int_0^t (NO_h \cdot ZO1_h, w) + (ZO1_h(0), w) \quad \forall w \in W_h \end{aligned} \tag{5.152}$$

At $t = 0$ define $ZO1_h(x, 0) := ZO1_h^0 \in W_h$ by:

$$(ZO1_h^0 - ZO1^0, w) = 0 \qquad \forall w \in W_h. \tag{5.153}$$

The subtracting (5.152) from (5.151) and using (5.153) we get the error equation,

$$\begin{aligned}(ZO1 - ZO1_h, w) &= .03 \int_0^t (e_c - e_{c_h}, w) + 2(e_c - e_{c_h}, w) \\ &+ .03 \int_0^t \left(\frac{-e_c ZO1}{.95 + .05e_c} + \frac{e_{c_h} ZO1_h}{.95 + .05e_{c_h}}, w \right)\end{aligned}$$

$$
\begin{aligned}
&+2\int_0^t \left(\frac{-e_{c_t} ZO1}{.95 + .05e_c} + \frac{e_{c_{t_h}} ZO1_h}{.95 + .05e_{c_h}}, w \right) \\
&+.75\int_0^t (-NO \cdot ZO1 + NO_h \cdot ZO1_h, w) \\
:= .03\int_0^t T_1 + 2T_2 + .03\int_0^t T_3 + 2\int_0^t T_4 + .75\int_0^t T_5 \quad &\forall w \in W_h.
\end{aligned}
$$

Bounds on each term

In the following analysis, we will need the following three assumptions:

Assumption 1. For the functions f where f is $ZO1, ZO1_h, e_{c_t}$ or $e_{c_{t_h}}$ there exists a constant $C_{f,\Omega}$ such that:

$$
\sup_{w \in H^1(\Omega)} \frac{(fu, w)}{\|w\|_{H^1(\Omega)}} \leq C_{f,\Omega} \sup_{w \in H^1(\Omega)} \frac{(u, w)}{\|w\|_{H^1(\Omega)}} \tag{5.154}
$$

where $C_{f,\Omega}$ is a constant that depends only on f and Ω.

Note that any functions that are in $L^\infty(\Omega)$, such as $ZO1$, will automatically satisfy (5.154).

Based on the results of Part I of the PDE analysis, we know that $\|NO\|_{L^\infty(\Omega)}$ is bounded and using the results of Part I of the numerical analysis, we know that $\|NO_h\|$ is bounded. Here we will make the further assumption:

Assumption 2. $\|NO_h\|_\infty$ is bounded.

We previously assumed that e_c is a non-negative function. Therefore, it is reasonable to make the following assumption:

Assumption 3. $-4 \leq e_{c_h}$.

Note that the terms T_1 and T_2 are already in a form that may be analyzed. For T_3 and T_4, we will find a common denomination, add and subtract the appropriate terms to get:

$$\begin{aligned}T_3 &= \left(\frac{-.95e_{c_h}(ZO1 - ZO1_h)}{(.95+.05e_c)(.95+.05e_{c_h})}, w\right) + \left(\frac{-.95ZO1(e_c - e_{c_h})}{(.95+.05e_c)(.95+.05e_{c_h})}, w\right) \\ &\quad + \left(\frac{-.05e_{c_h}e_c(ZO1 - ZO1_h)}{(.95+.05e_c)(.95+.05e_{c_h})}, w\right) \\ &= (f_{31}(ZO1 - ZO1_h), w) + (f_{32}(e_c - e_{c_h}), w) + (f_{33}(ZO1 - ZO1_h), w).\end{aligned}$$

$$\begin{aligned}T_4 &= \left(\frac{-.95e_{c_{t_h}}(ZO1 - ZO1_h)}{(.95+.05e_c)(.95+.05e_{c_h})}, w\right) + \left(\frac{-.95ZO1(e_{c_t} - e_{c_{t_h}})}{(.95+.05e_c)(.95+.05e_{c_h})}, w\right) \\ &\quad + \left(\frac{-.05e_{c_{t_h}}e_c(ZO1 - ZO1_h)}{(.95+.05e_c)(.95+.05e_{c_h})}, w\right) + \left(\frac{.05ZO1_h e_t(e_c - e_{c_h})}{(.95+.05e_c)(.95+.05e_{c_h})}, w\right) \\ &\quad + \left(\frac{-.05ZO1_h e_c(e_{c_t} - e_{c_{t_h}})}{(.95+.05e_c)(.95+.05e_{c_h})}, w\right) \\ &= (f_{41}(ZO1 - ZO1_h), w) + (f_{42}(e_{c_t} - e_{c_{t_h}}), w) + (f_{43}(ZO1 - ZO1_h), w) \\ &\quad + (f_{44}(e_c - e_{c_h}), w) + (f_{45}(e_{c_t} - e_{c_{t_h}}), w).\end{aligned}$$

$$\begin{aligned}T_5 &= (-NO \cdot ZO1 + NO_h \cdot ZO1 - NO_h \cdot ZO1 + NO_h \cdot ZO1_h, w) \\ &= ((-NO_h)(ZO1 - ZO1_h), w) + (ZO1(NO_h - NO), w) \\ &\leq ((-NO_h)(ZO1 - ZO1_h), w) + \|ZO1\|_{L^\infty}\|NO_h - NO\|\|w\| \\ &\leq ((-NO_h)(ZO1 - ZO1_h), w) + \|ZO1\|_{L^\infty}\|NO_h - NO\|\|w\|_{H^1(\Omega)}.\end{aligned}$$

Put these terms into the error equation to get:

$$\begin{aligned}(ZO1 - ZO1_h, w) &\leq C\int_0^t (e_c - e_{c_h}, w) + 2(e_c - e_{c_h}, w) \\ &\quad + C\int_0^t ((f_{31} + f_{33} + f_{41} + f_{43})(ZO1 - ZO1_h), w) \\ &\quad + C\int_0^t ((f_{32} + f_{44})(e_c - e_{c_h}), w) + C\int_0^t ((f_{42} + f_{45})(e_{c_t} - e_{c_{t_h}}), w) \\ &\quad + C\|NO_h\|_{L^\infty}\int_0^t ((ZO1 - ZO1_h), w) \\ &\quad + C\int_0^t \|ZO1\|_{L^\infty}\|NO_h - NO\|\|w\|_{H^1(\Omega)}.\end{aligned}$$

Take the sup and note that the functions f_{31} and f_{33} are bounded. Apply (5.154) to the terms that contain $f_{32}, f_{41}, f_{42}, f_{43}$, and f_{44} to get:

$$\sup_{w\in H^1(\Omega)} \frac{(ZO1 - ZO1_h, w)}{\|w\|_{H^1(\Omega)}} \leq C\int_0^t \sup_{w\in H^1(\Omega)} \frac{(e_c - e_{c_h}, w)}{\|w\|_{H^1(\Omega)}}$$
$$+2 \sup_{w\in H^1(\Omega)} \frac{(e_c - e_{c_h}, w)}{\|w\|_{H^1(\Omega)}} + C\int_0^t \sup_{w\in H^1(\Omega)} \frac{((ZO1 - ZO1_h), w)}{\|w\|_{H^1(\Omega)}}$$
$$+C\int_0^t \sup_{w\in H^1(\Omega)} \frac{((e_c - e_{c_h}), w)}{\|w\|_{H^1(\Omega)}} + C\int_0^t \sup_{w\in H^1(\Omega)} \frac{((e_{c_t} - e_{c_{t_h}}), w)}{\|w\|_{H^1(\Omega)}}$$
$$+C\|NO_h\|_{L^\infty}\int_0^t \sup_{w\in H^1(\Omega)} \frac{((ZO1 - ZO1_h), w)}{\|w\|_{H^1(\Omega)}}$$
$$+C\int_0^t \|ZO1\|_{L^\infty}\|NO_h - NO\|.$$

In the PDE section Part III, we proved that $\|ZO1\|_{L^\infty}$ is bounded. By **Assumption 2**, $\|NO_h\|_{L^\infty}$ is bounded. So, the above simplifies to:

$$\|ZO1 - ZO1_h\|_{H^{-1}(\Omega)} \leq C\int_0^t \|e_c - e_{c_h}\|_{H^{-1}(\Omega)} + C\|e_c - e_{c_h}\|_{H^{-1}(\Omega)}$$
$$+C\int_0^t \|e_{c_t} - e_{c_{t_h}}\|_{H^{-1}(\Omega)} + C\int_0^t \|ZO1 - ZO1_h\|_{H^{-1}(\Omega)}$$
$$+C\int_0^t \|NO_h - NO\|.$$

Result - Bound in H^{-1} norm.

Finally, apply the Gronwall Inequality, theorem 4.8, to get

$$\|ZO1 - ZO1_h\|_{H^{-1}(\Omega)} \leq C\Bigg(\int_0^t \|e_c - e_{c_h}\|_{H^{-1}(\Omega)} + C\|e_c - e_{c_h}\|_{H^{-1}(\Omega)}$$
$$+C\int_0^t \|e_{c_t} - e_{c_{t_h}}\|_{H^{-1}(\Omega)} + C\int_0^t \|NO_h - NO\|\Bigg). \tag{5.155}$$

For (5.155), the bound on $\|e_{c_t} - e_{c_{t_h}}\|_{H^{-1}(\Omega)}$ with convergence of h (as long as $P(e_c) \in H^3(\Omega)$) was found in the numerical analysis of the Part II equations. A bound on $\|NO_h - NO\|$ with convergence $h^{2\mu_{NO}}$ was found in the numerical analysis of the Part I equations. Thus, $\|ZO1 - ZO1_h\|_{H^{-1}(\Omega)}$ is bounded by h, as long as the regularity of NO and the power of r_{NO} is great enough.

5.5 CONCLUSION FOR FINITE ELEMENT ANALYSIS CHAPTER

It was demonstrated in this chapter that convergence for the fully coupled NEC system is attainable. Convergence for the equations in Part I, using the L^2 norm, was $O(h^{2\mu_\alpha})$ for $\alpha = b, m, c, c_a, NO, d, e_c, ZO1$ and $O(h^{2\mu_\alpha - 2})$ for $\alpha = m_a, n_a$. By using this result, it was found that convergence for the epithelial equation in Part II, using the H^{-1} norm, was $O(h)$ (as long as we have $P(e_c) \in H^3(\Omega)$). Finally, using the results of Part I and Part II, it was found that convergence for the tight junction equation in Part III, using the H^{-1} norm, was $O(h)$. All of these results are summarized in the following two tables.

Equation	**Error**	**Norm**	**Conv Rate**	**Notes**
Bacteria	$\|b_h - b\|$	$L^2(\Omega)$	$h^{2\mu_b}$	
Macrophage	$\|m_h - m\|$	$L^2(\Omega)$	$h^{2\mu_m}$	
Activated Macrophage	$\|m_{a_h} - m_a\|$	$L^2(\Omega)$	$h^{2\mu_{m_a}-2}$	
Cytokine	$\|c_h - c\|$	$L^2(\Omega)$	$h^{2\mu_c}$	
Anti-Infl. Cytokine	$\|c_{a_h} - c_a\|$	$L^2(\Omega)$	$h^{2\mu_{c_a}}$	

Table 3: Convergence Rates for fully coupled system (1 of 2).

Equation	**Error**	**Norm**	**Conv Rate**	**Notes**
Nitric Oxide	$\|NO_h - NO\|$	$L^2(\Omega)$	$h^{2\mu_{NO}}$	
Activated Neutrophils	$\|n_{a_h} - n_a\|$	$L^2(\Omega)$	$h^{2\mu_{n_a}-2}$	
Damage	$\|d_h - d\|$	$L^2(\Omega)$	$h^{2\mu_d}$	
Epithelial	$\|e_{c_h} - e_c\|_{H^{-1}(\Omega)}$	$H^{-1}(\Omega)$	h	Requires $P(e_c) \in H^3(\Omega)$
Tight Junction	$\|ZO1_h - ZO1\|_{H^{-1}(\Omega)}$	$H^{-1}(\Omega)$	h	

Table 4: Convergence Rates for fully coupled system (2 of 2).

6.0 CONVERGENCE TESTS

6.1 CODE TO TEST COUPLED ADVECTION EQUATION

The author of this thesis wrote MATLAB code in order to do convergence tests on the system

$$\frac{\partial u}{\partial t} - \nabla \cdot (D_1 \nabla u - u \nabla v) = f_1(u, v) \tag{6.1}$$

$$\frac{\partial v}{\partial t} - \nabla \cdot (D_2 \nabla v - v \nabla u) = f_2(u, v). \tag{6.2}$$

Note that this system is more general than the system in our NEC model in that (6.2) contains the term $\nabla \cdot (D_2 \nabla v - v \nabla u)$ instead of just $\nabla \cdot D_2 \nabla v$. The test runs below will include this more general case as well as cases similar to the NEC model.

Even though the purpose of these tests is determine the convergence of the mixed method, for comparison purposes code was also written for the Implicit Finite Difference Method, Explicit Finite Difference Method, and Cell-Centered Finite Difference Method. Due to the unusual non-linearities in the PDE system, a short description of equations for each of these methods is given here.

6.1.1 Implicit Finite Difference

This section covers the Implicit Finite Difference Method. The left hand side of equation (6.1) is discretized as follows:

$$\frac{u_{ix,iy}^{m+1} - u_{ix,iy}^{m}}{\Delta t} + C_{11} \left(\frac{u_{ix,iy}^{m+1} - u_{ix-1,iy}^{m+1}}{\Delta x} \right) \left(\frac{v_{ix+1,iy}^{m+1} - v_{ix-1,iy}^{m+1}}{2\Delta x} \right)$$

$$
\begin{aligned}
&+C_{12}\left(\frac{u^{m+1}_{ix,iy}-u^{m+1}_{ix,iy-1}}{\Delta y}\right)\left(\frac{v^{m+1}_{ix,iy+1}-v^{m+1}_{ix,iy-1}}{2\Delta y}\right)\\
+C_{11}&\left(u^{m+1}_{ix,iy}\frac{v^{m+1}_{ix-1,iy}-2v^{m+1}_{ix,iy}+v^{m+1}_{ix+1,iy}}{(\Delta x)^2}\right)\\
&+C_{12}\left(u^{m+1}_{ix,iy}\frac{v^{m+1}_{ix,iy-1}-2v^{m+1}_{ix,iy}+v^{m+1}_{ix,iy+1}}{(\Delta y)^2}\right)\\
-C_{21}&\left(\frac{u^{m+1}_{ix-1,iy}-2u^{m+1}_{ix,iy}+u^{m+1}_{ix+1,iy}}{(\Delta x)^2}\right)\\
&-C_{22}\left(\frac{u^{m+1}_{ix,iy-1}-2u^{m+1}_{ix,iy}+u^{m+1}_{ix,iy+1}}{(\Delta y)^2}\right).
\end{aligned}
\tag{6.3}
$$

The left hand side of equation (6.2) is discretized as follows:

$$
\begin{aligned}
&\frac{v^{m+1}_{ix,iy}-v^{m}_{ix,iy}}{\Delta t}+\\
D_{11}&\left(\frac{v^{m+1}_{ix,iy}-v^{m+1}_{ix-1,iy}}{\Delta x}\right)\left(\frac{u^{m+1}_{ix+1,iy}-u^{m+1}_{ix-1,iy}}{2\Delta x}\right)\\
&+D_{12}\left(\frac{v^{m+1}_{ix,iy}-v^{m+1}_{ix,iy-1}}{\Delta y}\right)\left(\frac{u^{m+1}_{ix,iy+1}-u^{m+1}_{ix,iy-1}}{2\Delta y}\right)\\
+D_{11}&\left(v^{m+1}_{ix,iy}\frac{u^{m+1}_{ix-1,iy}-2u^{m+1}_{ix,iy}+u^{m+1}_{ix+1,iy}}{(\Delta x)^2}\right)\\
&+D_{12}\left(v^{m+1}_{ix,iy}\frac{u^{m+1}_{ix,iy-1}-2u^{m+1}_{ix,iy}+u^{m+1}_{ix,iy+1}}{(\Delta y)^2}\right)\\
-D_{21}&\left(\frac{v^{m+1}_{ix-1,iy}-2v^{m+1}_{ix,iy}+v^{m+1}_{ix+1,iy}}{(\Delta x)^2}\right)\\
&-D_{22}\left(\frac{v^{m+1}_{ix,iy-1}-2v^{m+1}_{ix,iy}+v^{m+1}_{ix,iy+1}}{(\Delta y)^2}\right).
\end{aligned}
\tag{6.4}
$$

The next few pages will make more sense if we first rearrange in this way:

$$
\begin{aligned}
&\frac{u^{m+1}_{ix,iy}-u^{m}_{ix,iy}}{\Delta t}+\\
C_{11}&\left(\frac{u^{m+1}_{ix,iy}-u^{m+1}_{ix-1,iy}}{\Delta x}\right)\left(\frac{v^{m+1}_{ix+1,iy}-v^{m+1}_{ix-1,iy}}{2\Delta x}\right)\\
&+C_{12}\left(\frac{u^{m+1}_{ix,iy}-u^{m+1}_{ix,iy-1}}{\Delta y}\right)\left(\frac{v^{m+1}_{ix,iy+1}-v^{m+1}_{ix,iy-1}}{2\Delta y}\right)
\end{aligned}
$$

$$
\begin{aligned}
&-C_{21}\left(\frac{u^{m+1}_{ix-1,iy}-2u^{m+1}_{ix,iy}+u^{m+1}_{ix+1,iy}}{(\Delta x)^2}\right)\\
&\qquad -C_{22}\left(\frac{u^{m+1}_{ix,iy-1}-2u^{m+1}_{ix,iy}+u^{m+1}_{ix,iy+1}}{(\Delta y)^2}\right)\\
&+C_{11}\left(u^{m+1}_{ix,iy}\frac{v^{m+1}_{ix-1,iy}-2v^{m+1}_{ix,iy}+v^{m+1}_{ix+1,iy}}{(\Delta x)^2}\right)\\
&\qquad +C_{12}\left(u^{m+1}_{ix,iy}\frac{v^{m+1}_{ix,iy-1}-2v^{m+1}_{ix,iy}+v^{m+1}_{ix,iy+1}}{(\Delta y)^2}\right).
\end{aligned}
\tag{6.5}
$$

$$
\begin{aligned}
&\frac{v^{m+1}_{ix,iy}-v^{m}_{ix,iy}}{\Delta t}+\\
&D_{11}\left(\frac{v^{m+1}_{ix,iy}-v^{m+1}_{ix-1,iy}}{\Delta x}\right)\left(\frac{u^{m+1}_{ix+1,iy}-u^{m+1}_{ix-1,iy}}{2\Delta x}\right)\\
&\qquad +D_{12}\left(\frac{v^{m+1}_{ix,iy}-v^{m+1}_{ix,iy-1}}{\Delta y}\right)\left(\frac{u^{m+1}_{ix,iy+1}-u^{m+1}_{ix,iy-1}}{2\Delta y}\right)\\
&-D_{21}\left(\frac{v^{m+1}_{ix-1,iy}-2v^{m+1}_{ix,iy}+v^{m+1}_{ix+1,iy}}{(\Delta x)^2}\right)\\
&\qquad -D_{22}\left(\frac{v^{m+1}_{ix,iy-1}-2v^{m+1}_{ix,iy}+v^{m+1}_{ix,iy+1}}{(\Delta y)^2}\right)\\
&+D_{11}\left(v^{m+1}_{ix,iy}\frac{u^{m+1}_{ix-1,iy}-2u^{m+1}_{ix,iy}+u^{m+1}_{ix+1,iy}}{(\Delta x)^2}\right)\\
&\qquad +D_{12}\left(v^{m+1}_{ix,iy}\frac{u^{m+1}_{ix,iy-1}-2u^{m+1}_{ix,iy}+u^{m+1}_{ix,iy+1}}{(\Delta y)^2}\right).
\end{aligned}
\tag{6.6}
$$

The first partial differential equation

Thus, the discretization of equation (6.1) simplifies to:

$$
\begin{aligned}
&g := K_1\ u_{ix,iy} + K_2\ u_{ix,iy}v_{ix+1,iy} + K_3\ u_{ix,iy}v_{ix-1,iy} + K_4\ u_{ix-1,iy}v_{ix+1,iy} +\\
&K_5\ u_{ix-1,iy}v_{ix-1,iy} + K_6\ u_{ix,iy}v_{ix,iy+1} + K_7\ u_{ix,iy}v_{ix,iy-1} + K_8\ u_{ix,iy-1}v_{ix,iy+1} +\\
&K_9\ u_{ix,iy-1}v_{ix,iy-1} + K_{10}\ u_{ix-1,iy} + K_{11}\ u_{ix,iy} + K_{12}\ u_{ix+1,iy} + K_{13}\ u_{ix,iy-1} +\\
&K_{14}\ u_{ix,iy} + K_{15}\ u_{ix,iy+1} + K_{18}\ v_{ix-1,iy}u_{ix,iy} + K_{19}\ v_{ix,iy}u_{ix,iy} + K_{20}\ v_{ix+1,iy}u_{ix,iy} +\\
&K_{18}\ v_{ix,iy-1}u_{ix,iy} + K_{19}\ v_{ix,iy}u_{ix,iy} + K_{20}\ v_{ix,iy+1}u_{ix,iy} - f_1(x,y,t) + K_{17}u^m_{ix,iy}
\end{aligned}
\tag{6.7}
$$

Where $K_1 = 1/(\triangle t),\ K_2 = C_{11}/(2*(\triangle x)^2),\ K_3 = -K_2,\ K_4 = -K_2,\ K_5 = K_2,\ K_6 = C_{12}/(2*(\triangle y)^2),\ K_7 = -K_6,\ K_8 = -K_6,\ K_9 = K_6,\ K_{10} = -C_{21}/(\triangle x)^2,\ K_{11} = (-2)*K_{10},\ K_{12} = K_{10},\ K_{13} = -C_{22}/(\triangle y)^2,\ K_{14} = (-2)*K_{13},\ K_{15} = K_{13},\ K_{17} = -K_1,\ K_{18} = C11/(\triangle x)^2,\ K_{19} = (-2)*K_{18},\ K_{20} = K_{18},\ K_{21} = C_{12}/(\triangle y)^2,\ K_{22} = (-2)*K_{21},\ K_{23} = K_{21}.$

Note that $f_1(x,y,t)$ is term number 16. Therefore $K_{16} = 1$ and is not shown here. K_{17} is shown last here for clarity because it is associated with the "m" time step. Unless otherwise noted all superscripts are $m+1$.

The second partial differential equation

Likewise, the discretization of equation (6.2) simplifies to:

$$\begin{aligned} h \ = \ & J_1\ v_{ix,iy} + J_2\ v_{ix,iy}u_{ix+1,iy} + J_3\ v_{ix,iy}u_{ix-1,iy} + J_4\ v_{ix-1,iy}u_{ix+1,iy} + \\ & J_5\ v_{ix-1,iy}u_{ix-1,iy} + J_6\ v_{ix,iy}u_{ix,iy+1} + J_7\ v_{ix,iy}u_{ix,iy-1} + J_8\ v_{ix,iy-1}u_{ix,iy+1} + \\ & J_9\ v_{ix,iy-1}u_{ix,iy-1} + J_{10}\ v_{ix-1,iy} + J_{11}\ v_{ix,iy} + J_{12}\ v_{ix+1,iy} + J_{13}\ v_{ix,iy-1} + \\ & J_{14}\ v_{ix,iy} + J_{15}\ v_{ix,iy+1} + J_{18}\ u_{ix-1,iy}v_{ix,iy} + J_{19}\ u_{ix,iy}v_{ix,iy} + J_{20}\ u_{ix+1,iy}v_{ix,iy} + \\ & J_{18}\ u_{ix,iy-1}v_{ix,iy} + J_{19}\ u_{ix,iy}v_{ix,iy} + J_{20}\ u_{ix,iy+1}v_{ix,iy} - f_2(x,y,t) + J_{17}v^m_{ix,iy}. \end{aligned} \tag{6.8}$$

Where $J_1 = 1/(\triangle t),\ J_2 = D_{11}/(2*(\triangle x)^2),\ J_3 = -J_2,\ J_4 = -J_2,\ J_5 = J_2,\ J_6 = D_{12}/(2*(\triangle y)^2),\ J_7 = -J_6,\ J_8 = -J_6,\ J_9 = J_6,\ J_{10} = -D_{21}/(\triangle x)^2,\ J_{11} = (-2)*J_{10},\ J_{12} = J_{10},\ J_{13} = -D_{22}/(\triangle y)^2,\ J_{14} = (-2)*J_{13},\ J_{15} = J_{13},\ J_{17} = -J_1,\ J_{18} = C11/(\triangle x)^2,\ J_{19} = (-2)*J_{18},\ J_{20} = J_{18},\ J_{21} = D_{12}/(\triangle y)^2,\ J_{22} = (-2)*J_{21},\ J_{23} = J_{21}.$

Note that $f_2(x,y,t)$ is term number 16. Therefore $J_{16} = 1$ and is not shown here. J_{17} is shown last here for clarity because it is associated with the "m" time step. Unless otherwise noted all superscripts are $m+1$.

Define

$$\mathbf{FF} := \begin{pmatrix} g_1 \\ ... \\ g_n \\ h_1 \\ ... \\ h_n \end{pmatrix} \qquad \text{and} \qquad \mathbf{u} := \begin{pmatrix} u_1 \\ ... \\ u_n \\ v_1 \\ ... \\ v_n \end{pmatrix}.$$

We need to find a vector $\mathbf{u}$ such that $\mathbf{FF}(\mathbf{u}) = 0$. Due to the non-linearities, this system of equations will be solved using Newton's method, i.e., $\mathbf{u}$ will be found by iteratively solving:

$$\mathbf{u} = \mathbf{u} - \mathbf{A^{-1}}(\mathbf{x})\mathbf{FF}(\mathbf{x}).$$

The Jacobian $\mathbf{A}(\mathbf{x})$ is given by:

$$\mathbf{A}(\mathbf{x}) = \begin{pmatrix} \frac{\partial g_1}{\partial u_1}(\mathbf{x}) & ... & \frac{\partial g_1}{\partial u_n}(\mathbf{x}) & \frac{\partial g_1}{\partial v_1}(\mathbf{x}) & ... & \frac{\partial g_1}{\partial v_n}(\mathbf{x}) \\ ... & ... & ... & ... & ... & ... \\ \frac{\partial g_n}{\partial u_1}(\mathbf{x}) & ... & \frac{\partial g_n}{\partial u_n}(\mathbf{x}) & \frac{\partial g_n}{\partial v_1}(\mathbf{x}) & ... & \frac{\partial g_n}{\partial v_n}(\mathbf{x}) \\ \frac{\partial h_1}{\partial u_1}(\mathbf{x}) & ... & \frac{\partial h_1}{\partial u_n}(\mathbf{x}) & \frac{\partial h_1}{\partial v_1}(\mathbf{x}) & ... & \frac{\partial h_1}{\partial v_n}(\mathbf{x}) \\ ... & ... & ... & ... & ... & ... \\ \frac{\partial h_n}{\partial u_1}(\mathbf{x}) & ... & \frac{\partial h_n}{\partial u_n}(\mathbf{x}) & \frac{\partial h_n}{\partial v_1}(\mathbf{x}) & ... & \frac{\partial h_n}{\partial v_n}(\mathbf{x}) \end{pmatrix}.$$

Therefore, the derivatives of g and h will be required:

Partial derivatives of g with respect to each variable that has "m+1" superscript

$$\begin{aligned} \frac{\partial g}{\partial u_{ix,iy}} &= K_1 + K_{11} + K_{14} + (K_{19} + K_{22})v_{ix,iy} + (K_3 + K_{18})v_{ix-1,iy} \\ &\quad +(K_2 + K_{20})v_{ix+1,iy} + (K_7 + K_{21})v_{ix,iy-1} + (K_6 + K_{23})v_{ix,iy+1} \\ \frac{\partial g}{\partial u_{ix-1,iy}} &= K_{10} + K_5 v_{ix-1,iy} + K_4 v_{ix+1,iy} \\ \frac{\partial g}{\partial u_{ix+1,iy}} &= K_{12} \end{aligned}$$

$$\frac{\partial g}{\partial u_{ix,iy-1}} = K_{13} + K_9 v_{ix,iy-1} + K_8 v_{ix,iy+1}$$
$$\frac{\partial g}{\partial u_{ix,iy+1}} = K_{15}$$
$$\frac{\partial g}{\partial v_{ix,iy}} = (K_{19} + K_{22}) u_{ix,iy}$$
$$\frac{\partial g}{\partial v_{ix-1,iy}} = (K_3 + K_{18}) u_{ix,iy} + K_5 u_{ix-1,iy}$$
$$\frac{\partial g}{\partial v_{ix+1,iy}} = (K_2 + K_{20}) u_{ix,iy} + K_4 u_{ix-1,iy}$$
$$\frac{\partial g}{\partial v_{ix,iy-1}} = (K_7 + K_{21}) u_{ix,iy} + K_9 u_{ix,iy-1}$$
$$\frac{\partial g}{\partial v_{ix,iy+1}} = (K_6 + K_{23}) u_{ix,iy} + K_8 u_{ix,iy-1}.$$

Partial derivatives of h with respect to each variable that has "m+1" superscript

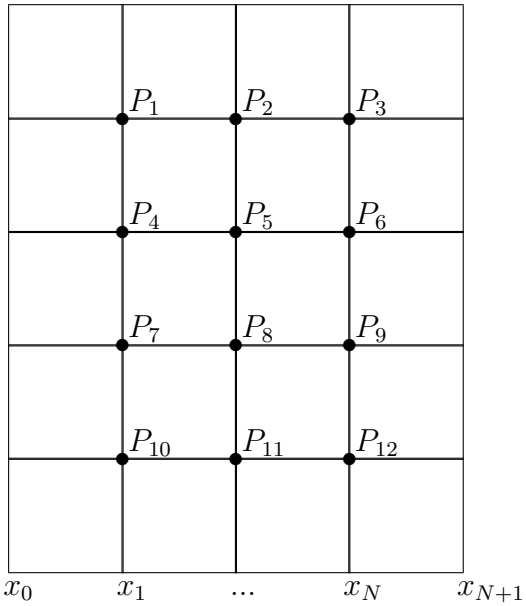
$$\frac{\partial h}{\partial v_{ix,iy}} = J_1 + J_{11} + J_{14} + (J_{19} + J_{22}) u_{ix,iy} + (J_3 + J_{18}) u_{ix-1,iy}$$
$$+ (J_2 + J_{20}) u_{ix+1,iy} + (J_7 + J_{21}) u_{ix,iy-1} + (J_6 + J_{23}) u_{ix,iy+1}$$
$$\frac{\partial h}{\partial v_{ix-1,iy}} = J_{10} + J_5 u_{ix-1,iy} + J_4 u_{ix+1,iy}$$
$$\frac{\partial h}{\partial v_{ix+1,iy}} = J_{12}$$
$$\frac{\partial h}{\partial v_{ix,iy-1}} = J_{13} + J_9 u_{ix,iy-1} + J_8 u_{ix,iy+1}$$
$$\frac{\partial h}{\partial v_{ix,iy+1}} = J_{15}$$
$$\frac{\partial h}{\partial u_{ix,iy}} = (J_{19} + J_{22}) v_{ix,iy}$$
$$\frac{\partial h}{\partial u_{ix-1,iy}} = (J_3 + J_{18}) v_{ix,iy} + J_5 v_{ix-1,iy}$$
$$\frac{\partial h}{\partial u_{ix+1,iy}} = (J_2 + J_{20}) v_{ix,iy} + J_4 v_{ix-1,iy}$$
$$\frac{\partial h}{\partial u_{ix,iy-1}} = (J_7 + J_{21}) v_{ix,iy} + J_9 v_{ix,iy-1}$$
$$\frac{\partial h}{\partial u_{ix,iy+1}} = (J_6 + J_{23}) v_{ix,iy} + J_8 v_{ix,iy-1}.$$

These will result in equations $g_1, g_2, ..., g_n, h_1, h_2, ..., h_n$.

.

Node Numbering for the Implicit and Explicit Finite Difference Method Dirichlet Boundary Conditions

The nodes are numbered using $L1 = ix + (\text{Nodes in y direction} - iy) * (\text{Nodes in x direction})$. For example, these will look like:



Note that in the MATLAB code, the vector **u** is represented by:

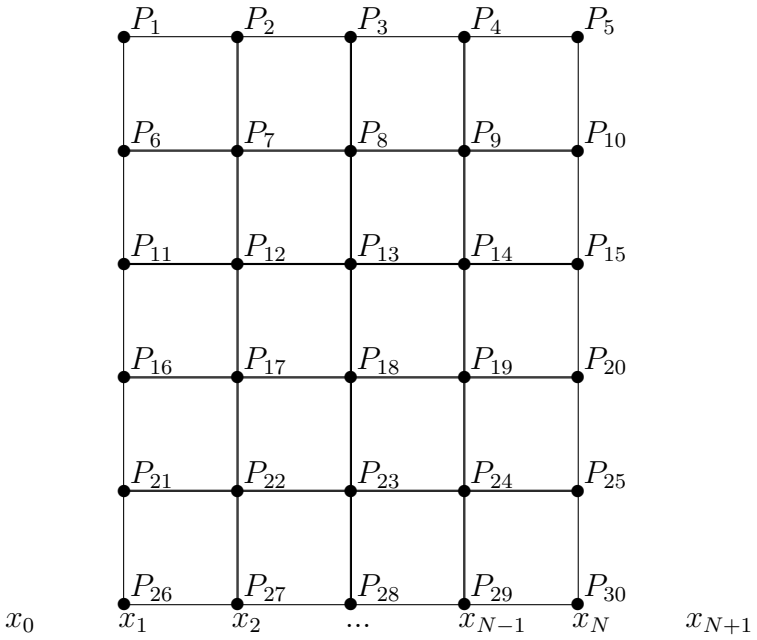
$$\begin{pmatrix} u(1) \\ ... \\ u(n) \\ u(n+1) \\ ... \\ u(2n) \end{pmatrix}$$

where the $u_1, ..., u_n$ are represented by $u(1), ..., u(n)$ and the $v_1, ..., v_n$ are represented by $u(n+1), ..., u(2n)$.

.

Node Numbering for the Implicit and Explicit Finite Difference Method Neumann Boundary Conditions

The nodes are numbered using $L1 = ix + (\text{Nodes in y direction} - iy) * (\text{Nodes in x direction})$. For example, these will look like:



Note that in the MATLAB code, the vector **u** is represented by:

$$\begin{pmatrix} u(1) \\ \dots \\ u(n) \\ u(n+1) \\ \dots \\ u(2n) \end{pmatrix}$$

where the $u_1, ..., u_n$ are represented by $u(1), ..., u(n)$ and the $v_1, ..., v_n$ are represented by $u(n+1), ..., u(2n)$.

6.1.2 Explicit Finite Difference

$$
\begin{aligned}
&K_1\ u^m_{ix,iy} + K_2\ u_{ix,iy}v_{ix+1,iy} + K_3\ u_{ix,iy}v_{ix-1,iy} + K_4\ u_{ix-1,iy}v_{ix+1,iy} + \\
&K_5\ u_{ix-1,iy}v_{ix-1,iy} + K_6\ u_{ix,iy}v_{ix,iy+1} + K_7\ u_{ix,iy}v_{ix,iy-1} + K_8\ u_{ix,iy-1}v_{ix,iy+1} + \\
&K_9\ u_{ix,iy-1}v_{ix,iy-1} + K_{10}\ u_{ix-1,iy} + K_{11}\ u_{ix,iy} + K_{12}\ u_{ix+1,iy} + K_{13}\ u_{ix,iy-1} + \\
&K_{14}\ u_{ix,iy} + K_{15}\ u_{ix,iy+1} + K_{18}\ v_{ix-1,iy}u_{ix,iy} + K_{19}\ v_{ix,iy}u_{ix,iy} + K_{20}\ v_{ix+1,iy}u_{ix,iy} + \\
&K_{18}\ v_{ix,iy-1}u_{ix,iy} + K_{19}\ v_{ix,iy}u_{ix,iy} + K_{20}\ v_{ix,iy+1}u_{ix,iy} + K_{17}u_{ix,iy} = f_1(x,y,t).
\end{aligned}
\tag{6.9}
$$

Where $K_1 = 1/(\triangle t),\ K_2 = C_{11}/(2*(\triangle x)^2),\ K_3 = -K_2,\ K_4 = -K_2,\ K_5 = K_2,\ K_6 = C_{12}/(2*(\triangle y)^2),\ K_7 = -K_6,\ K_8 = -K_6,\ K_9 = K_6,\ K_{10} = -C_{21}/(\triangle x)^2,\ K_{11} = (-2)*K_{10},\ K_{12} = K_{10},\ K_{13} = -C_{22}/(\triangle y)^2,\ K_{14} = (-2)*K_{13},\ K_{15} = K_{13},\ K_{17} = -K_1,\ K_{18} = C11/(\triangle x)^2,\ K_{19} = (-2)*K_{18},\ K_{20} = K_{18},\ K_{21} = C_{12}/(\triangle y)^2,\ K_{22} = (-2)*K_{21},\ K_{23} = K_{21}.$

Note that $f_1(x,y,t)$ is term number 16. Therefore $K_{16} = 1$ and is not shown here. K_{17} is shown last here for clarity because it is associated with the "m" time step. Unless otherwise noted all superscripts are $m-1$.

$$
\begin{aligned}
&J_1\ v^m_{ix,iy} + J_2\ v_{ix,iy}u_{ix+1,iy} + J_3\ v_{ix,iy}u_{ix-1,iy} + J_4\ v_{ix-1,iy}u_{ix+1,iy} + \\
&J_5\ v_{ix-1,iy}u_{ix-1,iy} + J_6\ v_{ix,iy}u_{ix,iy+1} + J_7\ v_{ix,iy}u_{ix,iy-1} + J_8\ v_{ix,iy-1}u_{ix,iy+1} + \\
&J_9\ v_{ix,iy-1}u_{ix,iy-1} + J_{10}\ v_{ix-1,iy} + J_{11}\ v_{ix,iy} + J_{12}\ v_{ix+1,iy} + J_{13}\ v_{ix,iy-1} + \\
&J_{14}\ v_{ix,iy} + J_{15}\ v_{ix,iy+1} + J_{18}\ u_{ix-1,iy}v_{ix,iy} + J_{19}\ u_{ix,iy}v_{ix,iy} + J_{20}\ u_{ix+1,iy}v_{ix,iy} + \\
&J_{18}\ u_{ix,iy-1}v_{ix,iy} + J_{19}\ u_{ix,iy}v_{ix,iy} + J_{20}\ u_{ix,iy+1}v_{ix,iy} + J_{17}v_{ix,iy} = f_2(x,y,t).
\end{aligned}
\tag{6.10}
$$

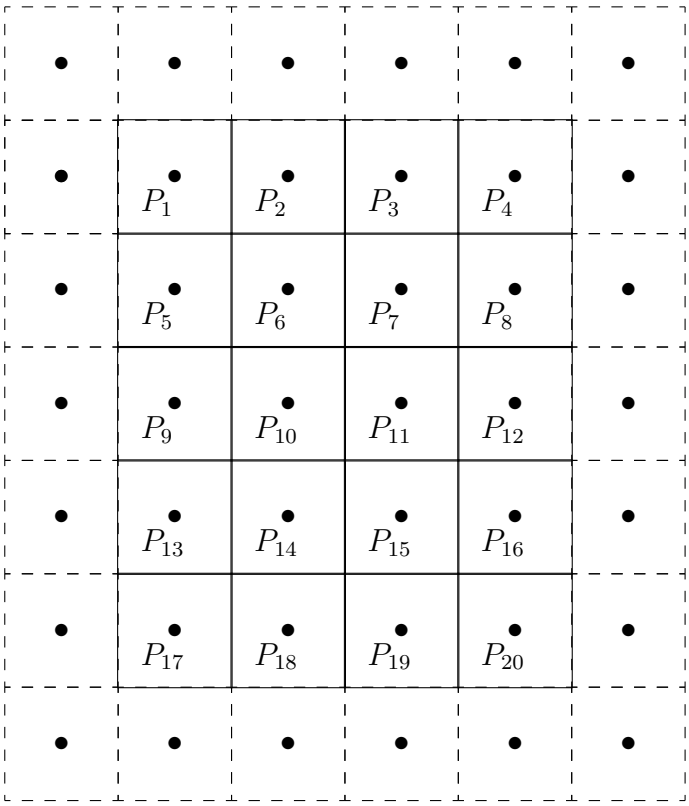
Where $J_1 = 1/(\triangle t),\ J_2 = D_{11}/(2*(\triangle x)^2),\ J_3 = -J_2,\ J_4 = -J_2,\ J_5 = J_2,\ J_6 = D_{12}/(2*(\triangle y)^2),\ J_7 = -J_6,\ J_8 = -J_6,\ J_9 = J_6,\ J_{10} = -D_{21}/(\triangle x)^2,\ J_{11} = (-2)*J_{10},\ J_{12} = J_{10},\ J_{13} = -D_{22}/(\triangle y)^2,\ J_{14} = (-2)*J_{13},\ J_{15} = J_{13},\ J_{17} = -J_1,\ J_{18} = C11/(\triangle x)^2,\ J_{19} = (-2)*J_{18},\ J_{20} = J_{18},\ J_{21} = D_{12}/(\triangle y)^2,\ J_{22} = (-2)*J_{21},\ J_{23} = J_{21}.$

Note that $f_2(x,y,t)$ is term number 16. Therefore $J_{16} = 1$ and is not shown here. J_{17}

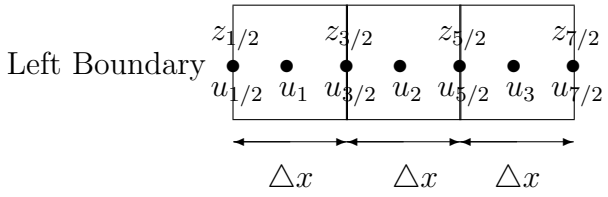
is shown last here for clarity because it is associated with the "m" time step. Unless otherwise noted all superscripts are $m-1$.

6.1.3 Cell-Centered Finite Difference Method

Cell Numbering for Cell-centered finite difference



Left Boundary



So, if we have $\nabla \cdot D\nabla u$. Set $z = D\nabla u$. Then

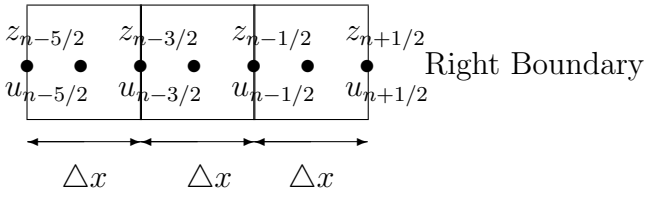
$$z_{1/2} = D_{1/2}\frac{u_1 - u_{1/2}}{(\triangle x/2)} \quad \text{and} \quad z_{3/2} = D_{3/2}\frac{u_2 - u_1}{\triangle x}$$

$$\nabla \cdot D\nabla u_1 = \frac{z_{3/2} - z_{1/2}}{\triangle x} = \frac{D_{3/2}\frac{u_2 - u_1}{\triangle x} - D_{1/2}\frac{u_1 - u_{1/2}}{(\triangle x/2)}}{\triangle x}$$
$$= \frac{D_{3/2}u_2 - D_{3/2}u_1 - 2D_{1/2}u_1 + 2D_{1/2}u_{1/2}}{(\triangle x)^2}$$

If $D = 1$. Then

$$\nabla \cdot \nabla u_1 = \frac{u_2 - 3u_1 + 2u_{1/2}}{(\triangle x)^2}$$

Right Boundary



So, if we have $\nabla \cdot D\nabla u$. Set $z = D\nabla u$. Then

$$z_{n+1/2} = D_{n+1/2}\frac{u_{n+1/2} - u_n}{(\triangle x/2)} \quad \text{and} \quad z_{n-1/2} = D_{n-1/2}\frac{u_n - u_{n-1}}{\triangle x}$$

If $D = 1$. Then

$$\nabla \cdot \nabla u_1 = \frac{2u_{n+1/2} - 3u_n + u_{n-1}}{(\triangle x)^2}$$

6.2 TEST RUNS

The following pages contain convergence tests based on various test equations, methods, and boundary conditions for the types of equations in Part I of the PDE system. The methods include implicit finite difference, explicit finite difference, and cell centered finite difference.

Even though the typical equations in Part I of the PDE system include an equation with an advection term coupled with an equation with no advection term, other cases are included in the tests which follow. For example in Cases 1 and 3 both of the coupled equations contain advection terms. These are of particular interest because it has not been proven that such PDEs (nor the associated numerical methods) always have solutions. Case 4 contains two coupled equations neither of which has an advection term. Case 2, contains the typical coupling of the equations in Part I of the PDE system - one equation with an advection term, and one equation with no advection term.

In the following tests, we have:

$$SRSS = \sqrt{\frac{\Sigma_{Nodes}(\text{True Solution-numerical solution})^2}{\text{Number of Node Points}}}.$$

$$SAV = \frac{\Sigma_{Nodes}|\text{True Solution-numerical solution}|}{\text{Number of Node Points}}.$$

Most importantly, the maximum error is given by:

$$MAXError = \max_{Nodes} |\text{True Solution-numerical solution}|.$$

The convergence rates are based on the maximum error and are calculated by:

$$p = \frac{\ln(MAXError2) - \ln(MAXError1)}{\ln(h_2) - \ln(h_1)}.$$

Case 1

$$\begin{aligned}
\frac{\partial u_1}{\partial t} - \nabla \cdot (D_1 \nabla u_1 - u_1 \nabla u_2) &= -\frac{e^{-2x-3y}}{(1+t)^2} - 13\frac{e^{-2x-3y}}{1+t} + 28\frac{e^{-6x-4y}}{(1+t)^2} \\
\frac{\partial u_2}{\partial t} - \nabla \cdot (D_2 \nabla u_2 - u_2 \nabla u_1) &= -\frac{e^{-4x-y}}{(1+t)^2} - 17\frac{e^{-4x-y}}{1+t} + 24\frac{e^{-6x-4y}}{(1+t)^2} \\
\text{on } [0,1] \times [0,1] \qquad & 2 \le t \le 7 \\
u_1 = \frac{e^{-2x-3y}}{1+t} \qquad \text{and} \qquad & u_2 = \frac{e^{-4x-y}}{1+t} \qquad \text{on } \partial\Omega \\
u_1 = \frac{e^{-2x-3y}}{3} \qquad \text{and} \qquad & u_2 = \frac{e^{-4x-y}}{3} \qquad \text{at } t = 2.
\end{aligned}$$

x = 0.00 to 1.00 and y = 0.00 to 1.00 Time = 2.00 sec to 7.00 sec.

Dirichlet Boundary Conditions.

Implicit Finite Difference ——— Function Numbers 8 and 9

Delta X	Delta Y	Delta T	SRSS	SAV	MAX Error
0.20000	0.20000	0.024876	0.00043062	0.00034962	0.00086695
0.16667	0.16667	0.024876	0.00028619	0.00022819	0.00062912
0.14286	0.14286	0.024876	0.00020176	0.00015824	0.00046375
0.07692	0.07692	0.024876	0.00004734	0.00003438	0.00011859

Convergence Rate = 2.16 (Based on the Maximum Error).

Explicit Finite Difference - No Upwinding — Function Numbers 8 and 9

Delta X	Delta Y	Delta T	SRSS	SAV	MAX Error
0.20000	0.20000	0.000500	0.00043034	0.00034933	0.00086646
0.16667	0.16667	0.000500	0.00028592	0.00022792	0.00062862
0.14286	0.14286	0.000050	0.00020151	0.00015798	0.00046322
0.07692	0.07692	0.000050	0.00004711	0.00003416	0.00011806

Convergence Rate = 2.16 (Based on the Maximum Error)

Cell Centered Finite Difference - Upwinding – Function Numbers 8 and 9

Delta X	Delta Y	Delta T	SRSS	SAV	MAX Error
0.20000	0.20000	0.000050	0.00140068	0.00087865	0.00451430

0.16667	0.16667	0.000050	0.00101304	0.00062353	0.00354081
0.14286	0.14286	0.000050	0.00076371	0.00046374	0.00283941
0.07692	0.07692	0.000050	0.00023244	0.00013494	0.00106125

Convergence Rate = 1.56 (Based on the Maximum Error).

Case 2

$$\frac{\partial u_1}{\partial t} - \nabla \cdot (D_1 \nabla u_1 - u_1 \nabla u_2) = (2t - 4t^2(1 + x^2 + y^2))e^{x^2+y^2} + (18 + 8x + 8y^2)t^3 e^{4x+x^2+2y^2}$$

$$\frac{\partial u_2}{\partial t} - \nabla \cdot (D_2 \nabla u_2) = (1 - 18t - 4y^2 t)e^{4x+y^2}$$

$$\text{on } [0, .5] \times [0, .5] \qquad 2 \le t \le 7$$

$$u_1 = t^2 e^{x^2+y^2} \quad \text{and} \quad u_2 = te^{4x+y^2} \quad \text{on } \partial\Omega$$

$$u_1 = 4e^{x^2+y^2} \quad \text{and} \quad u_2 = 2e^{4x+y^2} \quad \text{at } t = 2.$$

Results

x = 0.00 to 0.50 and y = 0.00 to 0.50 Time = 2.00 sec to 7.00 sec.

Dirichlet Boundary Conditions.

Implicit Finite Difference ——— Function Numbers 12 and 13

Delta X	Delta Y	Delta T	SRSS	SAV	MAX Error
0.10000	0.10000	0.098039	0.52831048	0.37976163	1.13428824
0.03846	0.03846	0.098039	0.23052810	0.15107538	0.55326673
0.03125	0.03125	0.098039	0.18987872	0.12304563	0.47302421
0.02500	0.02500	0.098039	0.15369333	0.09859691	0.39135379
0.02174	0.02174	0.098039	0.13446556	0.08579368	0.34693499

Convergence Rate = 0.85 (Based on the Maximum Error).

Explicit Finite Difference - No Upwinding – Function Numbers 12 and 13

Delta X	Delta Y	Delta T	SRSS	SAV	MAX Error
0.10000	0.10000	0.000500	0.52818714	0.37967200	1.13410669
0.03846	0.03846	0.000050	0.23039674	0.15098086	0.55305044
0.03125	0.03125	0.000050	0.18974669	0.12295091	0.47281510
0.02500	0.02500	0.000050	0.15356077	0.09850211	0.39115397
0.02174	0.02174	0.000050	0.13433274	0.08569888	0.34673113

Convergence Rate = 0.85 (Based on the Maximum Error).

Cell Centered Finite Difference - Upwinding – Function Numbers 12 and 13

Delta X	Delta Y	Delta T	SRSS	SAV	MAX Error
0.10000	0.10000	0.000050	0.60547023	0.48115077	1.30528104
0.03846	0.03846	0.000050	0.22996059	0.16125296	0.58496432
0.03125	0.03125	0.000050	0.18800082	0.12888287	0.48879547
0.02500	0.02500	0.000050	0.15152485	0.10171055	0.40131272
0.02174	0.02174	0.000050	0.13239148	0.08784893	0.35162598

Convergence Rate = 0.91 (Based on the Maximum Error).

Neumann Boundary Conditions for Case 2

Spatial Domain – x = 0.00 to 0.50 and y = 0.00 to 0.50 Time = 2.00 sec to 7.00 sec

Neumann Boundary Conditions

Explicit Finite Difference - No Upwinding – Function Numbers 12 and 13

Delta X	Delta Y	Delta T	SRSS	SAV	MAX Error
0.10000	0.10000	0.000005	12.77238570	10.33884141	18.92834610
0.04167	0.04167	0.000005	2.26910258	1.97228186	3.28782200
0.03333	0.03333	0.000005	1.47215238	1.31112482	2.10428574
0.02632	0.02632	0.000005	0.93706418	0.85777338	1.31156866
0.02273	0.02273	0.000005	0.71139595	0.66248244	0.97826721

Convergence Rate = 2.00 (Based on the Maximum Error).

Case 3

$$\begin{aligned}
\frac{\partial u_1}{\partial t} - \nabla \cdot (D_1 \nabla u_1 - u_1 \nabla u_2) &= (2t - 4t^2(1 + x^2 + y^2))e^{x^2+y^2} \\
&\quad +(18 + 8x + 8y^2)t^3 e^{4x+x^2+2y^2} \\
\frac{\partial u_2}{\partial t} - \nabla \cdot (D_2 \nabla u_2 - u_2 \nabla u_1) &= (1 - 18t - 4y^2 t)e^{4x+y^2} \\
&\quad +2t^3(2 + 4x + 2x^2 + 4y^2)e^{4x+x^2+2y^2}
\end{aligned}$$

$$\text{on } [0, .5] \times [0, .5) \qquad 2 \le t \le 7$$

$$u_1 = t^2 e^{x^2+y^2} \qquad \text{and} \qquad u_2 = te^{4x+y^2} \qquad \text{on } \partial\Omega$$

$$u_1 = 4e^{x^2+y^2} \qquad \text{and} \qquad u_2 = 2e^{4x+y^2} \qquad \text{at } t = 2$$

Note that these are functions 12 and 14 in the code.

Results

Implicit Finite Difference ——— Function Numbers 12 and 14

x = 0.00 to 0.50 and y = 0.00 to 0.50 Time = 2.00 sec to 7.00 sec.

Dirichlet Boundary Conditions.

Delta X	Delta Y	Delta T	SRSS	SAV	MAX Error
0.10000	0.10000	0.098039	0.22152365	0.19252587	0.42037679
0.03846	0.03846	0.098039	0.09096140	0.07646009	0.19700125
0.03125	0.03125	0.098039	0.07429931	0.06196773	0.16254211
0.02500	0.02500	0.098039	0.05969120	0.04941398	0.13205175
0.02174	0.02174	0.098039	0.05201304	0.04287958	0.11566309

Convergence Rate = 0.94 (Based on the Maximum Error).

,

Explicit Finite Difference - No Upwinding – Function Numbers 12 and 14

No Solution

Delta X	Delta Y	Delta T	SRSS	SAV	MAX Error
0.10000	0.10000	0.000005	**No Solution**		
0.03846	0.03846	0.000005	**No Solution**		

Cell Centered Finite Difference - Upwinding – Function Numbers 12 and 14

No Solution

Case 4 (Diffusion Only, Equations not coupled)

$$\begin{aligned}
\frac{\partial u_1}{\partial t} - \nabla \cdot (D_1 \nabla u_1) &= (2t - 4t^2(1 + x^2 + y^2))e^{x^2+y^2} \\
\frac{\partial u_2}{\partial t} - \nabla \cdot (D_2 \nabla u_2) &= (2t - 4t^2(1 + x^2 + y^2))e^{x^2+y^2} \\
&\text{on } [0,1] \times [0,1] \qquad 2 \le t \le 7 \\
u_1 = t^2 e^{x^2+y^2} \qquad &\text{and} \qquad u_2 = t^2 e^{x^2+y^2} \qquad \text{on } \partial\Omega \\
u_2 = 4e^{x^2+y^2} \qquad &\text{and} \qquad u_2 = 4e^{x^2+y^2} \qquad \text{at } t = 2
\end{aligned}$$

Note that these are functions 11 and 11 in the code.

Results

Implicit Finite Difference —— Function Numbers 11 and 11

x = 0.00 to 1.00 and y = 0.00 to 1.00 Time = 2.00 sec to 7.00 sec

Dirichlet Boundary Conditions

Delta X	Delta Y	Delta T	SRSS	SAV	MAX Error
0.20000	0.20000	0.024876	0.97960738	0.92570389	1.44478352
0.16667	0.16667	0.024876	0.67174248	0.62781339	1.05640592
0.14286	0.14286	0.024876	0.48812595	0.45194552	0.77341119
0.07692	0.07692	0.024876	0.13695343	0.12249615	0.23645546
0.06250	0.06250	0.024876	0.09008938	0.07981570	0.15812972

Convergence Rate = 1.92 (Based on the Maximum Error).

Explicit Finite Difference - No Upwinding – Function Numbers 11 and 11

Delta X	Delta Y	Delta T	SRSS	SAV	MAX Error
0.20000	0.20000	0.000500	0.97721845	0.92337131	1.44132091
0.16667	0.16667	0.000050	0.66945500	0.62560563	1.05312373
0.14286	0.14286	0.000050	0.48588182	0.44980142	0.77035057
0.07692	0.07692	0.000050	0.13483303	0.12054486	0.23320608
0.06250	0.06250	0.000050	0.08799651	0.07790955	0.15484686

Convergence Rate = 1.94 (Based on the Maximum Error).

Cell Centered Finite Difference - Upwinding – Function Numbers 11 and 11

Delta X	Delta Y	Delta T	SRSS	SAV	MAX Error
0.20000	0.20000	0.000050	2.79983922	2.28396678	7.00094784
0.16667	0.16667	0.000050	1.98465021	1.61033163	5.24666498
0.14286	0.14286	0.000050	1.47663050	1.19412742	4.06794314
0.07692	0.07692	0.000050	0.43921360	0.35271975	1.36536394
0.06250	0.06250	0.000050	0.29101280	0.23346200	0.93007695

Convergence Rate = 1.79 (Based on the Maximum Error).

7.0 SIMULATION RESULTS

Simulation results are presented in this chapter. These simulations were created in MATLAB using the PDE system from chapter three. The PDE system was discretized using a cell-centered finite difference method. Which, technically, is a form of the Mixed Finite Element Method. **Unlike all of the other code in this thesis, which was written solely by the author, the writing of the code in this chapter was a collaborative effort. Among those who contributed to the writing of the code:**

Joshua Sullivan, Ivan Yotov, Chris Horvat, and Mark Tronzo (the author of this thesis).

The purpose of this chapter is to show that the most critical features of NEC are reasonably modeled by the PDE system presented in this thesis. It must be noted that there is currently not enough data available to accurately determine the parameters in the NEC model. Furthermore, it is very likely that new NEC discoveries will prompt further changes to the equations in the PDE system. **Therefore, we are not claiming that the computer runs presented here exactly match actual disease conditions. Instead, we hope to demonstrate that our NEC PDE system is flexible enough that with proper parameter selection and minor changes to the equations the model will be able to simulate the general patterns of the disease.** So one should not focus upon the actual numbers shown in the following graphs but upon the general patterns.

(For those interested in "the next step", i.e. an attempt to more accurately simulate NEC with the PDE model presented in this chapter, we point out that **Jared Barber has significantly updated and refined the MATLAB code presented in this chapter. His results are presented in our paper** [14].)

Computer runs were made in order to simulate actual NEC conditions. In particular, different combinations of the following were used:

1) **Two Types of feedings:** formula-fed and breastfed. Within the breastfed category, several levels of anti-microbial peptides were used. (These different levels are simulated by using different values of the parameter k_{pp}, which is the rate of the destruction of bacteria by the anti-microbial peptides in breast milk.)

2) **Two different levels of infant maturity:** Premature infants and term infants.

3) **Three different epithelial injury levels:** no injury to the epithelium, partial injury to the epithelium and total injury to the epithelium.

Various combinations of the conditions in 1) through 3) above are represented in the cases which follow.

For the most part, the initial conditions are the same for each NEC component in all four regions with the following exceptions: (resting) macrophages are set to 0 in the lumen and to their maximum value in the other three regions; (resting) neutrophils are set to their maximum value in the blood and to 0 in the other three regions; epithelial cell density and ZO1 density is zero in all regions except the epithelial layer.

7.1 NORMAL CASE - TERM INFANT, NO INJURY TO THE EPITHELIUM.

We will begin by presenting a normal case. Of course, many cases might be considered normal. Here we are defining our normal case as a term infant with no injury to the epithelium but the epithelium is not perfect, its density is not quite 100 %. (Recall from chapter one that during the process of natural cell death and proliferation, gaps in the epithelium of 1%

to 3 % are very common.) k_{pp} is set at .25, higher than with formula feeding but lower than with regular breast feeding. The results are shown in figures 28 and 29. Notice that the epithelial density begins at .98 and ZO1 begins at .99, indicating the imperfection in the epithelial layer. Immediately, this epithelial density drops to .95 but levels off while ZO1 rises to 1. (Recall from chapter one that it is believed that ZO1 will fill in small gaps in the epithelium created by missing cells. That would explain why ZO1 is slightly greater than the epithelial density in some cases.) The run begins with bacteria in the tissue, lumen, and epithelial layer but approaches zero in all of those layers except the lumen where it levels off at a positive value. At the beginning of the run, damage is zero in all four layers but quickly rises in the tissue, lumen, and epithelial layer but approaches zero in all of those layers. Cytokines rise in all four layers but eventually level off. Similar observations may be made of the other components.

So, what we see in our normal case is **not** perfection but the players in NEC **under control.** The epithelium is not perfectly sealed but is dense enough to prevent any significant bacterial invasion into the underlying tissue. Bacteria is either eliminated or remains at a constant, non-threatening level. Damage occurs in several regions but is quickly repaired.

7.2 CASE - PREMATURITY, NO INJURY TO THE EPITHELIUM.

These cases will consider the premature infant that has no injury to the epithelium. The main assumption of this group of runs is that the premature infant has reduced peristalsis. Recall from chapter one that peristalsis aids in moving bacteria and other material along the lumen. When peristalsis is not fully functioning or underdeveloped, as is often the case in the premature infant, gram-negative bacteria may, over time, build up near the epithelium. Therefore, these runs will begin with high levels of gram-negative bacteria near the epithelium (simulated by setting $b_{max} = 5.0$).

Formula Fed $k_{pp} = .05,\ b_{max} = 5$. The first simulation under this case was run with formula feeding. It was assumed that with formula feeding only a very small amount of anti-

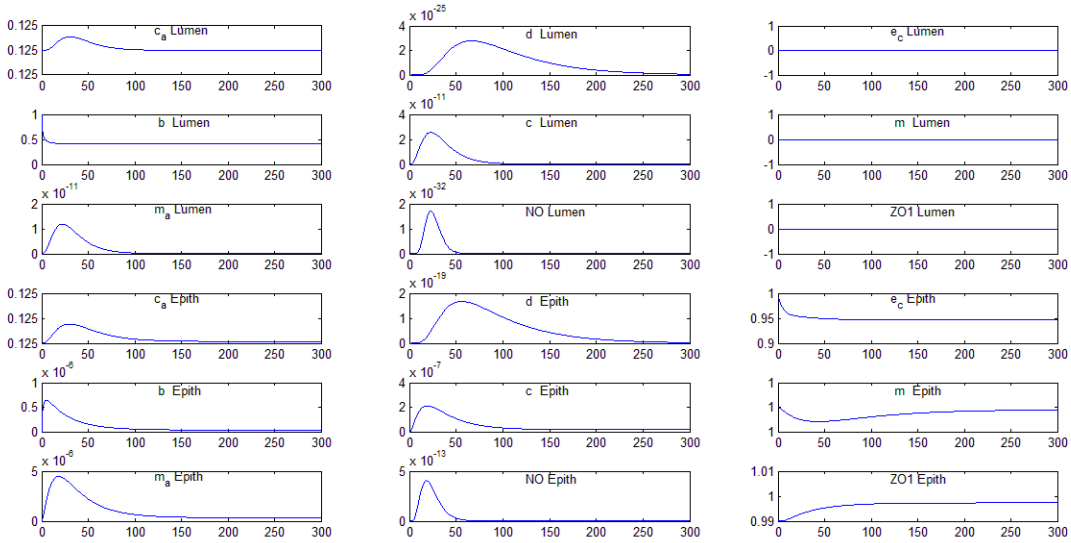


Figure 28: Normal Case - Term Infant, No Injury to the epithelium (1 of 2). The 18 graphs shown in this figure show the amount of each component in the **epithelial** and **lumen** layers. (For example, the graph in the bottom left corner shows the amount of activated macrophages in the epithelial layer.) For each graph, the vertical axis indicates the quantity of the substance and the horizontal axis indicates time, in hours.

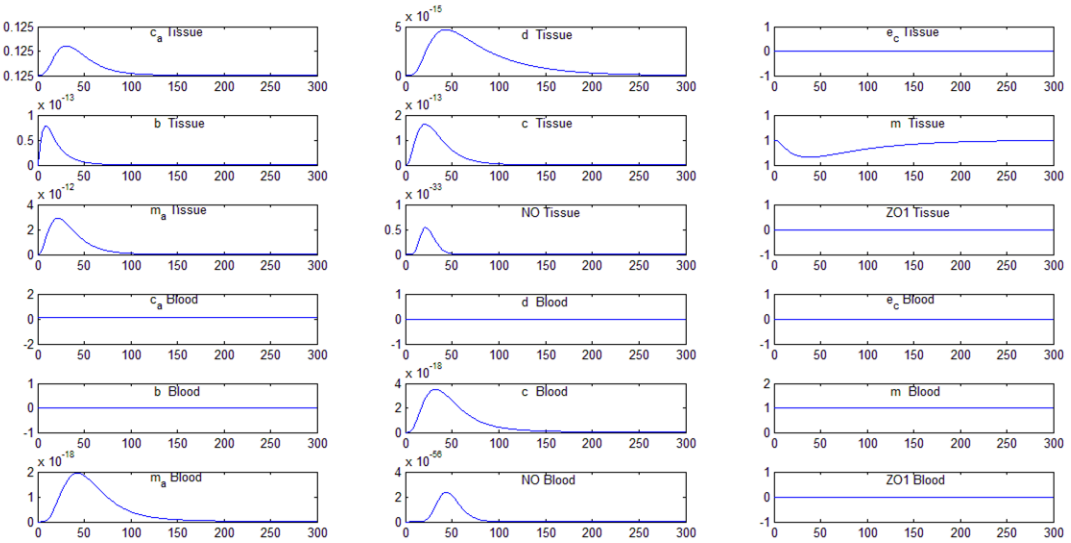


Figure 29: Normal Case - Term Infant, No Injury to the epithelium (2 of 2). The 18 graphs shown in this figure show the amount of each component in the **blood** and **tissue** layers. (For example, the graph in the bottom left corner shows the amount of activated macrophages in the blood layer.)

microbial peptides will be present, simulated by setting $k_{pp} = .05$. The results are shown in figure 30, 31, and 32. Figure 30 indicates that epithelial layer density is dropping steadily. This is very bad. Recall from chapter two that the resulting permeability of that layer will lead to bacterial invasion of the underlying tissue and usually a very bad outcome. Further bad indicators are that damage and nitric oxide are rising in certain layers.

Breast Fed $k_{pp} = .5,\ b_{max} = 5$. This run was made assuming breast feeding. In this case, moderate levels of anti-microbial peptides were assumed, simulated by setting $k_{pp} = .5$. The results are shown in figure 33, 34, and 35. This case does is not good. Unlike the previous case, the epithelial density is not dropping quickly but not quite stable either. Furthermore, damage is rising in that layer. At the same time, rising cytokines, damage, and nitric oxide in the blood and tissue are serious problems.

Breast Fed $k_{pp} = .7,\ b_{max} = 5$. This run was made assuming breast feeding. In this case, higher levels of anti-microbial peptides were assumed, simulated by setting $k_{pp} = .7$. The results are shown in figure 36, 37, and 38. Toward the end of the run, many NEC factors are approaching normal levels (compare to the normal case in the last section). Rising epithelial density is a very good sign. However, increasing damage in the blood, if continued unchecked, will be a problem.

Breast Fed $k_{pp} = 1,\ b_{max} = 5$. This run was made assuming breast feeding. In this case, high levels of anti-microbial peptides was assumed, simulated by setting $k_{pp} = 1$. The results are shown in figure 39, 40, and 41. The results in this case are extremely good. The epithelium is approaching full density and, similar to the normal case from the last section, and all of the NEC factors are either approaching zero or under control.

The epithelial layer for the four cases in this section are shown in figure 42.

7.3 CASE - TERM INFANT, PARTIAL INJURY TO EPITHELIUM.

In these runs, a full term infant with a partial injury to the epithelium will be simulated. Note that 'partial injury' will indicate that there is a circular area in the epithelial layer that is at 33% of its maximum density and 'total injury' means that there is a circular area in

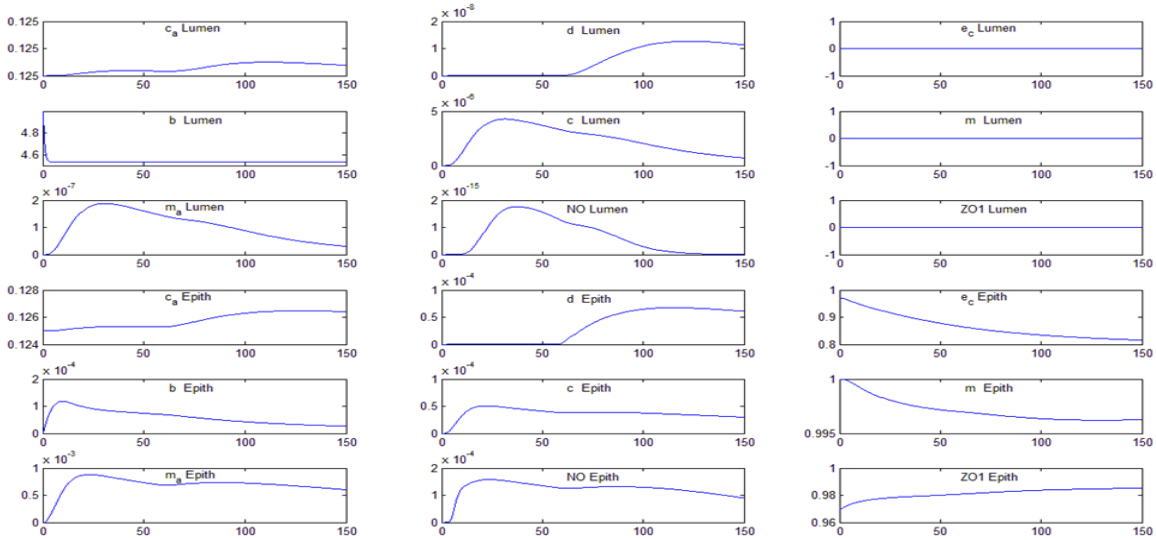


Figure 30: Simulation for Prematurity, No Injury, Formula Fed $k_{pp} = .05$, $b_{max} = 5$ (1 of 2). The 18 graphs shown in this figure show the amount of each component in the **epithelial** and **lumen** layers. (For example, the graph in the bottom left corner shows the amount of activated macrophages in the epithelial layer.) For each graph, the vertical axis indicates the quantity of the substance and the horizontal axis indicates time, in hours. In this particular case, the steady decrease in epithelial layer density will allow bacterial invasion of the underlying tissue which can lead to a very bad outcome.

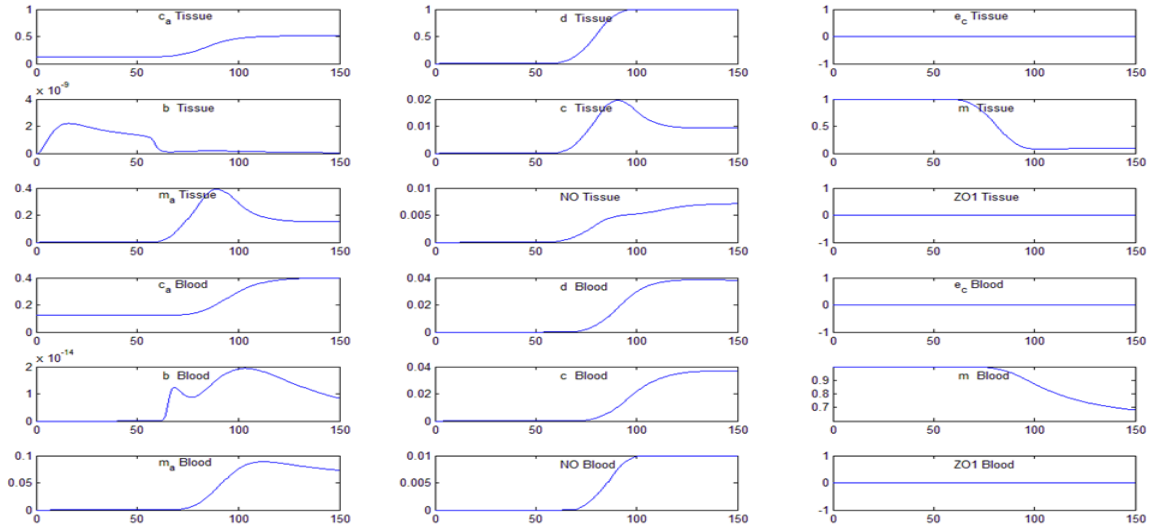


Figure 31: Simulation for Prematurity, No Injury, Formula Fed $k_{pp} = .05,\ b_{max} = 5$ (2 of 2). The 18 graphs shown in this figure show the amount of each component in the **blood** and **tissue** layer. (For example, the graph in the bottom left corner shows the amount of activated macrophages in the blood layer.) In this case, nitric oxide and damage are increasing in some layers.

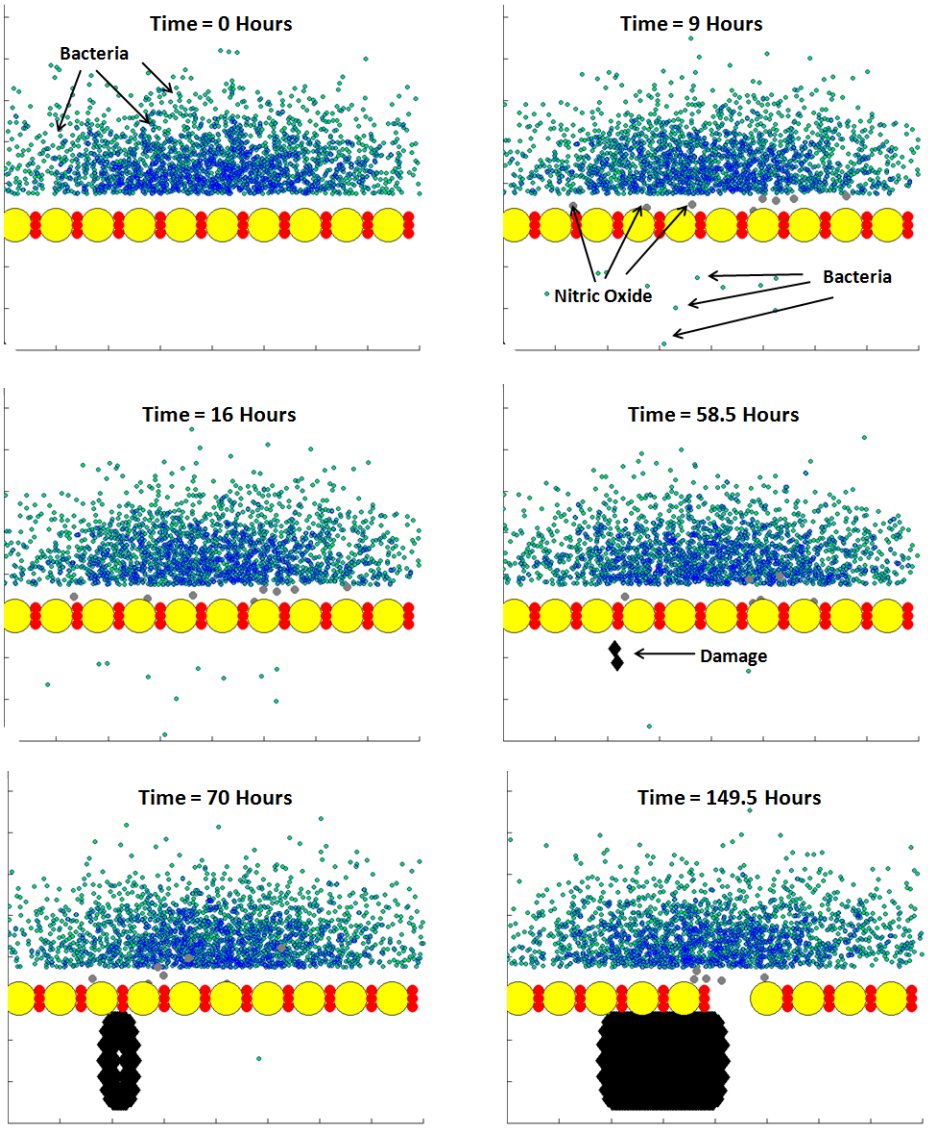


Figure 32: Simulation for Prematurity, No Injury, Formula Fed $k_{pp} = .05$, $b_{max} = 5$. The purpose of this figure is to give an average visual picture of what is happening physically. This graph should not be considered as accurate as the other graphs for this simulation. In order not to clutter the diagram, only a limited number of components are shown: bacteria in the lumen, nitric oxide in the epithelium (represented by the small gray balls), epithelial cells (represented by the yellow balls), tight junction protein (represented by the red bars), bacteria in the tissue, and damage to the tissue (represented by the black areas).

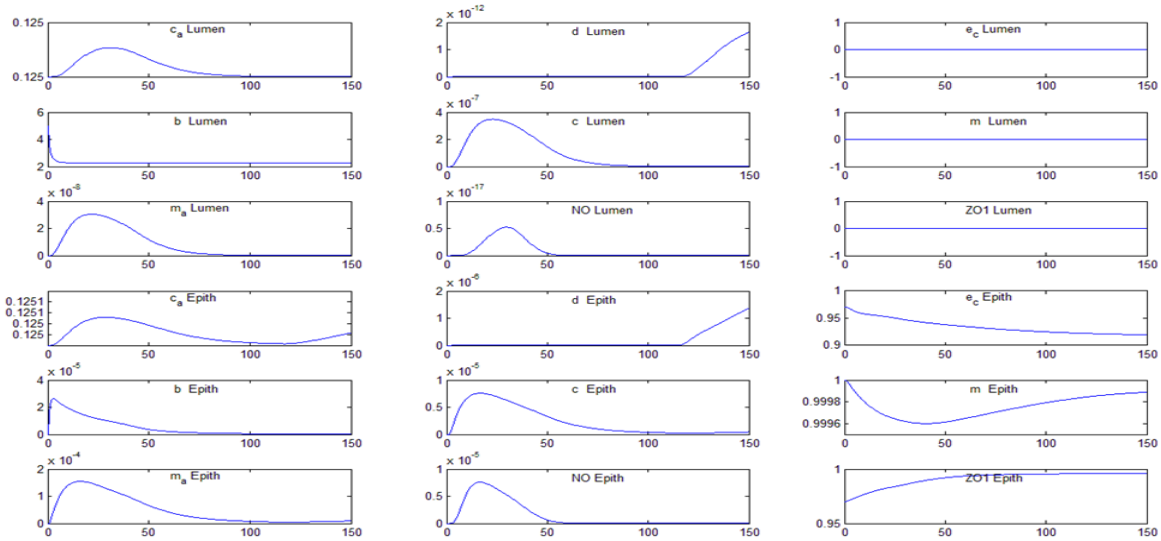


Figure 33: Simulation for Prematurity, No Injury, Breast Fed $k_{pp} = .5$, $b_{max} = 5$ (1 of 2). The 18 graphs shown in this figure show the amount of each component in the **epithelial** and **lumen** layers. (For example, the graph in the bottom left corner shows the amount of activated macrophages in the epithelial layer.) For each graph, the vertical axis indicates the quantity of the substance and the horizontal axis indicates time, in hours. In this case, epithelial density is not dropping quickly but not quite stable either. Damage is rising in the epithelial layer.

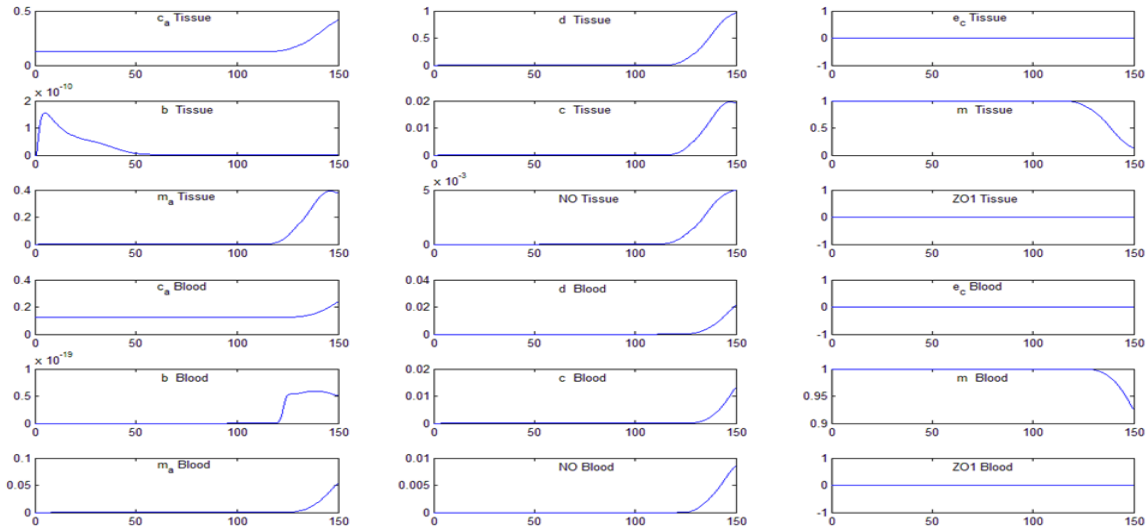


Figure 34: Simulation for Prematurity, No Injury, Breast Fed $k_{pp} = .5$, $b_{max} = 5$ (2 of 2). The 18 graphs shown in this figure show the amount of each component in the **blood** and **tissue** layer. (For example, the graph in the bottom left corner shows the amount of activated macrophages in the blood layer. In this case, rising cytokines, damage, and nitric oxide in the blood and tissue are serious problems.)

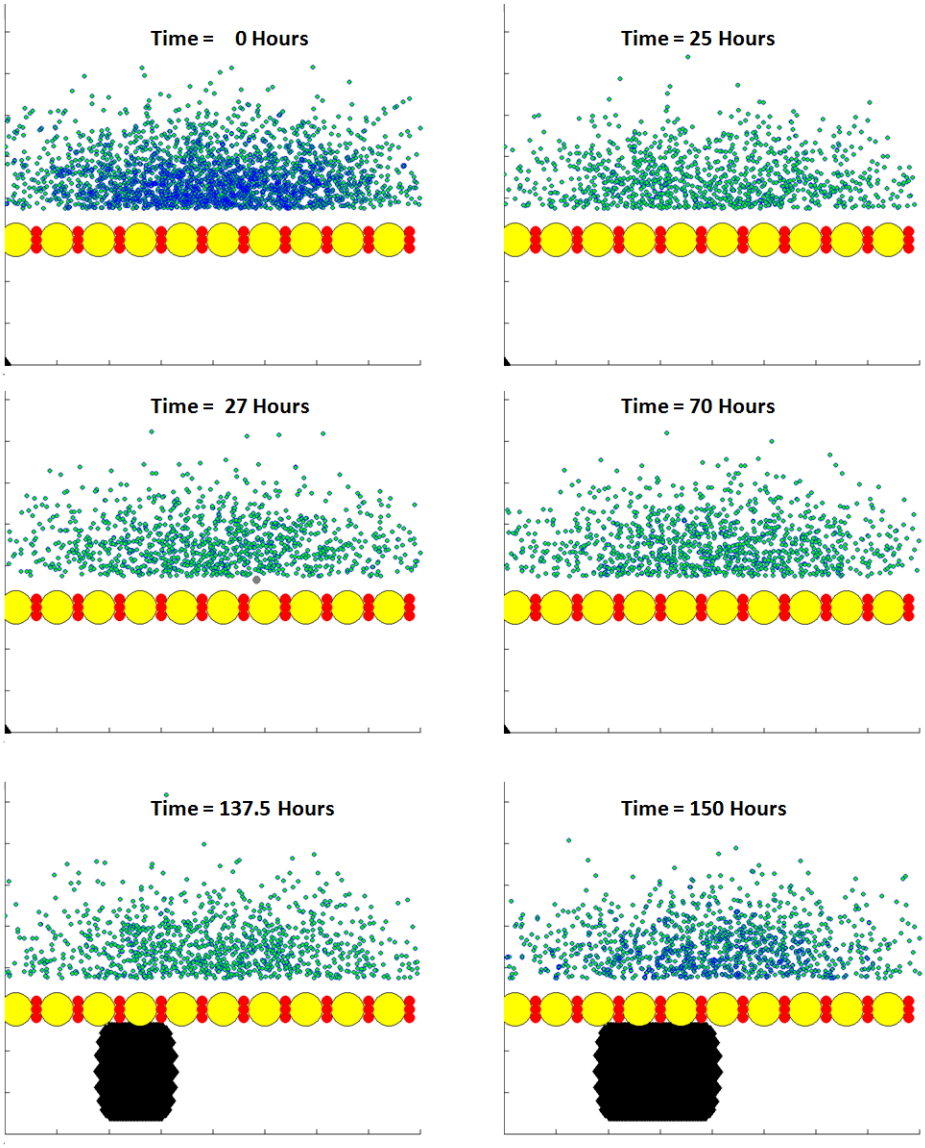


Figure 35: Simulation results for Prematurity, No Injury, Breast Fed $k_{pp} = .5$, $b_{max} = 5$. The purpose of this figure is to give an average visual picture of what is happening physically. This graph should not be considered as accurate as the other graphs for this simulation. In order not to clutter the diagram, only a limited number of components are shown: bacteria in the lumen, nitric oxide in the epithelium (represented by the small gray balls), epithelial cells (represented by the yellow balls), tight junction protein (represented by the red bars), bacteria in the tissue, and damage to the tissue (represented by the black areas).

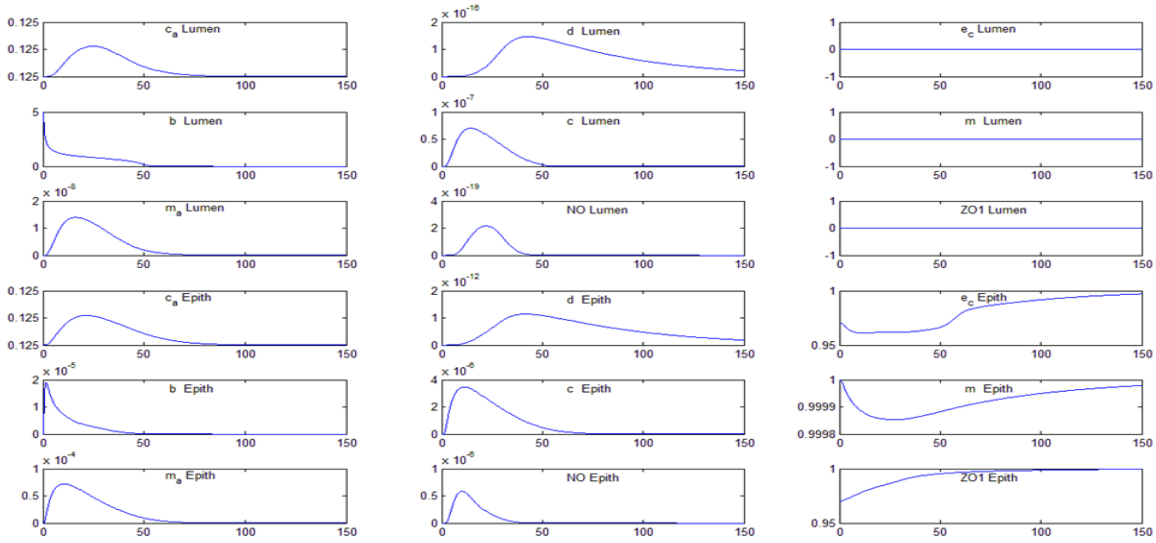


Figure 36: Simulation results for Prematurity, No Injury, Breast Fed $k_{pp} = .7$, $b_{max} = 5$ (1 of 2). The 18 graphs shown in this figure show the amount of each component in the **epithelial** and **lumen** layers. (For example, the graph in the bottom left corner shows the amount of activated macrophages in the epithelial layer.) For each graph, the vertical axis indicates the quantity of the substance and the horizontal axis indicates time, in hours. In this case, rising epithelial density is a very good sign.

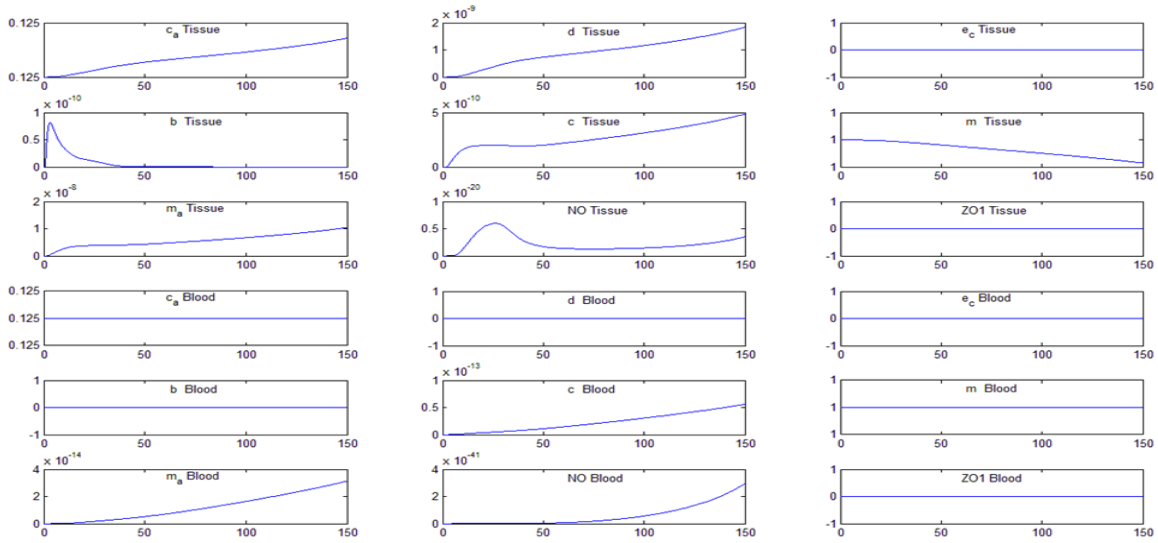


Figure 37: Simulation results for Prematurity, No Injury, Breast Fed $k_{pp} = .7$, $b_{max} = 5$ (2 of 2). The 18 graphs shown in this figure show the amount of each component in the **blood** and **tissue** layer. (For example, the graph in the bottom left corner shows the amount of activated macrophages in the blood layer.) In this case, increasing damage in the blood, if continued unchecked, will be a problem.

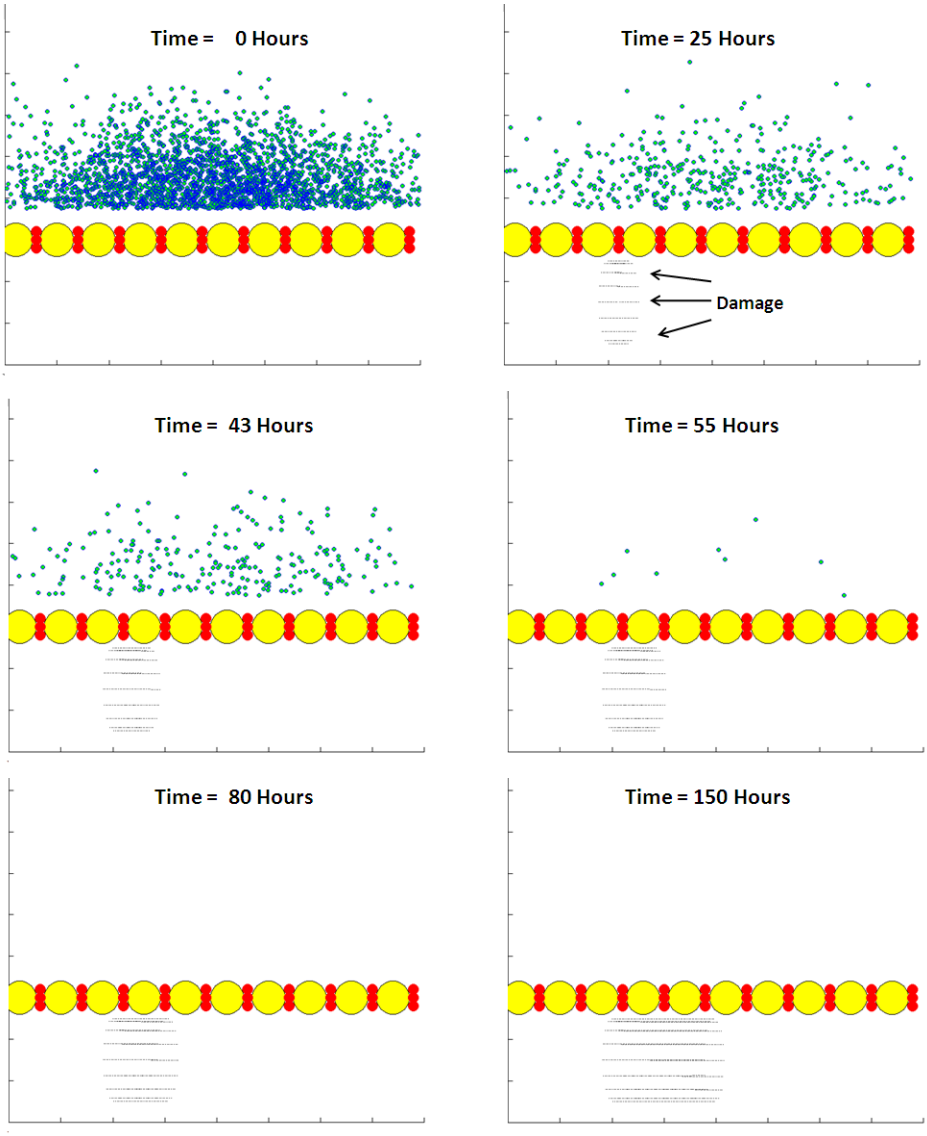


Figure 38: Simulation results for Prematurity, No Injury, Breast Fed $k_{pp} = .7$, $b_{max} = 5$. The purpose of this figure is to give an average visual picture of what is happening physically. This graph should not be considered as accurate as the other graphs for this simulation. In order not to clutter the diagram, only a limited number of components are shown: bacteria in the lumen, nitric oxide in the epithelium (represented by the small gray balls), epithelial cells (represented by the yellow balls), tight junction protein (represented by the red bars), bacteria in the tissue, and damage to the tissue (represented by the black areas).

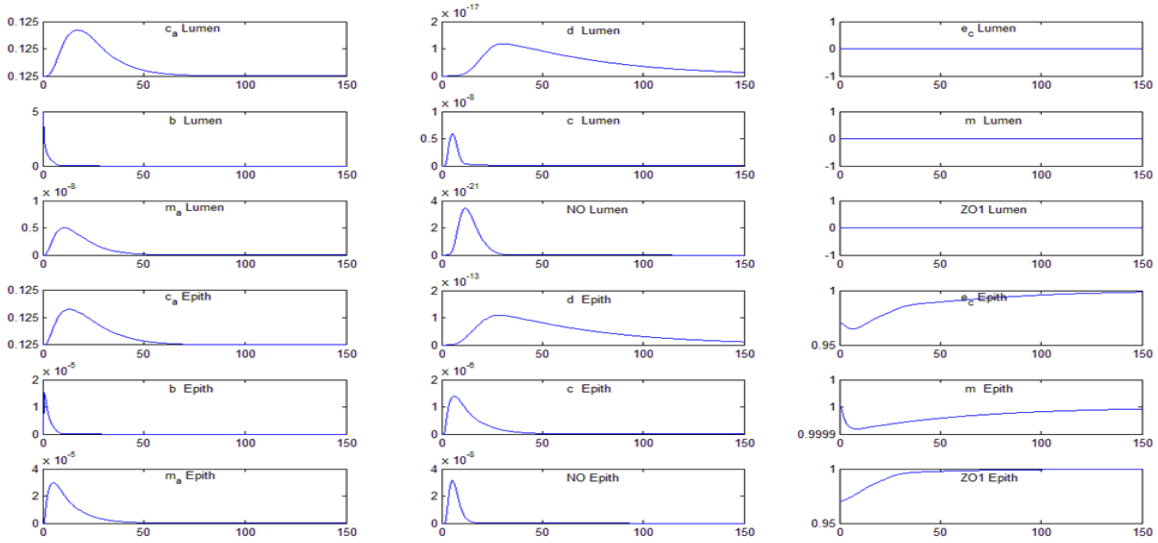


Figure 39: Simulation for Prematurity, No Injury, Breast Fed $k_{pp} = 1$, $b_{max} = 5$ (1 of 2). The 18 graphs shown in this figure show the amount of each component in the **epithelial** and **lumen** layers. (For example, the graph in the bottom left corner shows the amount of activated macrophages in the epithelial layer.) The results in this case are extremely good. The epithelium is approaching full density and, similar to the normal case from the last section, and all of the NEC factors are either approaching zero or under control. For each graph, the vertical axis indicates the quantity of the substance and the horizontal axis indicates time, in hours. The colored vertical graphs are logs of, from left to right, $c_a, d, e_c, b, c, m, m_a, NO, ZO1$,

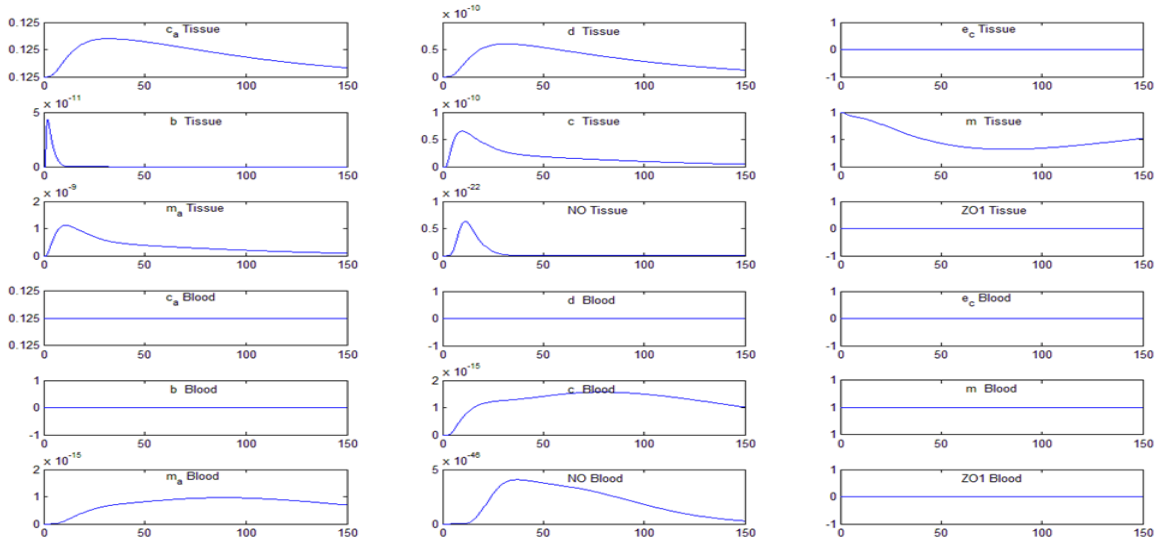


Figure 40: Simulation for Prematurity, No Injury, Breast Fed $k_{pp} = 1$, $b_{max} = 5$ (2 of 2). The 18 graphs shown in this figure show the amount of each component in the **blood** and **tissue** layer. (For example, the graph in the bottom left corner shows the amount of activated macrophages in the blood layer.)

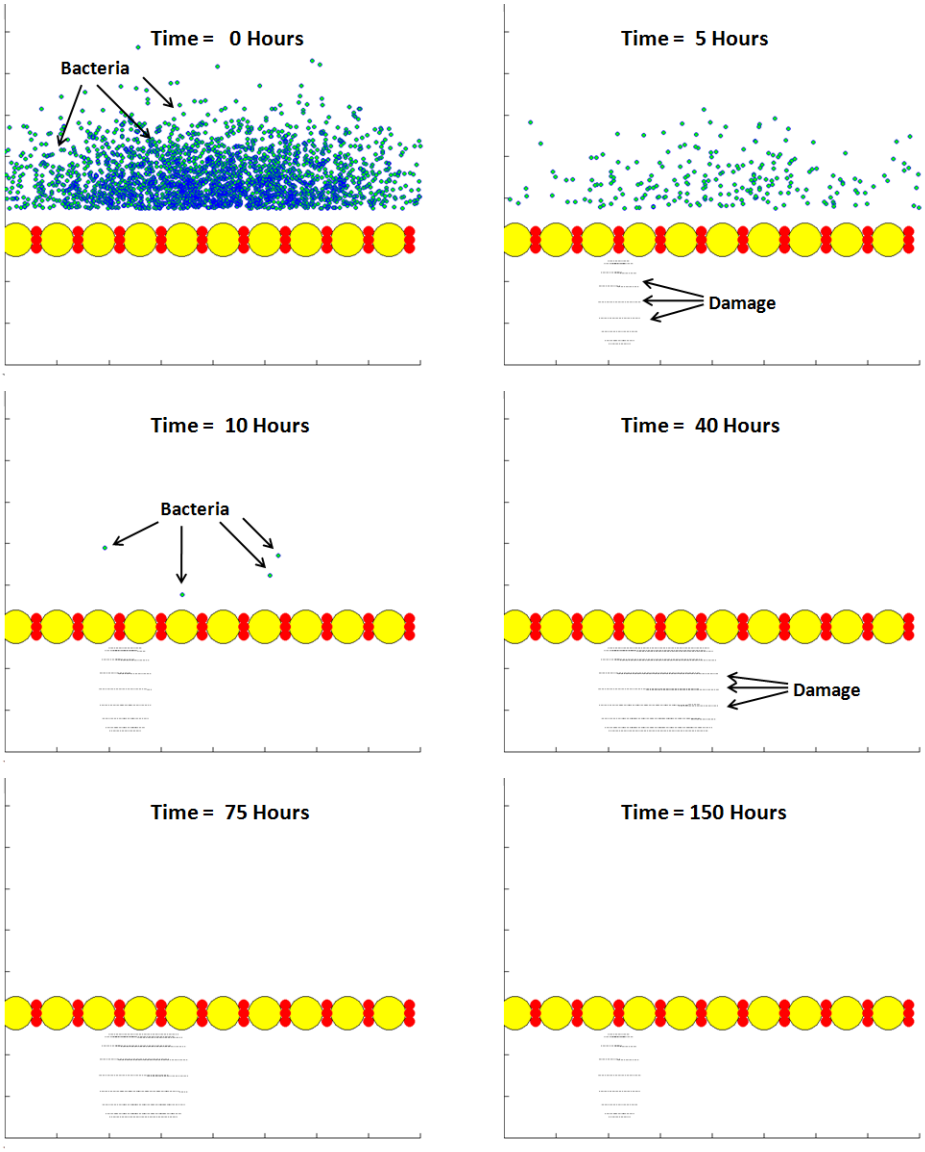


Figure 41: Simulation for Prematurity, No Injury, Breast Fed $k_{pp} = 1$, $b_{max} = 5$. The purpose of this figure is to give an average visual picture of what is happening physically. This graph should not be considered as accurate as the other graphs for this simulation. In order not to clutter the diagram, only a limited number of components are shown: bacteria in the lumen, nitric oxide in the epithelium (represented by the small gray balls), epithelial cells (represented by the yellow balls), tight junction protein (represented by the red bars), bacteria in the tissue, and damage to the tissue (represented by the black areas).

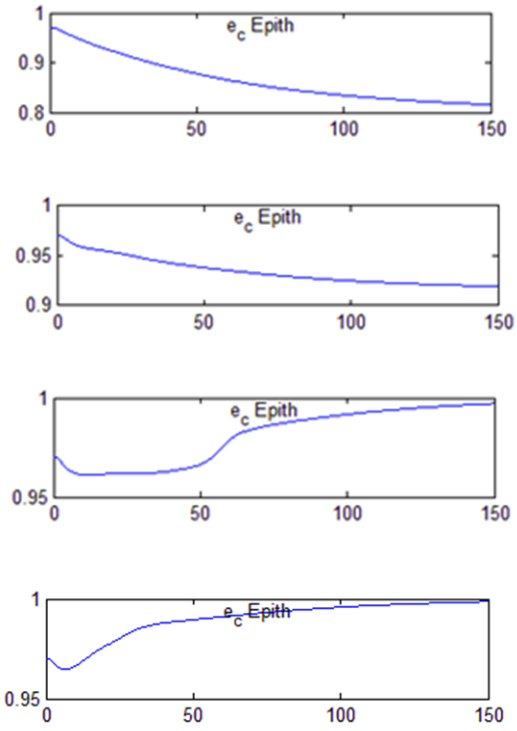


Figure 42: Comparison between formula fed and breast fed for prematurity and no injury. All of these cases use $b_{max} = 5$. These graphs show the epithelial layer. The top graph is the formula fed case. Next, is breast fed with $k_{pp} = .5$. The third graph from the top, is breast fed with $k_{pp} = .7$. The bottom graph is breast fed with $k_{pp} = 1$.

the epithelial layer that has zero density.

Formula Fed $k_{pp} = 0$. The simulation run using the initial conditions of a partial injury and formula feeding is shown in figure 43. The end result is sustained inflammation. High levels of bacteria remain in the lumen. Epithelial cells reach a steady state of 87% concentration, indicating an injury that has not healed completely and the injury is no longer in the process healing. This unhealed injury will provide a permanent pathway for the bacteria in the lumen to pass through the epithelial layer into the underlying tissue. Notice that damage is high and sustained in both the lumen and epithelial layer (the graphs marked d lumen and d epith in figure 43). Damage is also high and sustained in the tissue layer (the time graph of the tissue layer is not shown here). High concentrations of cytokines in the epithelial layer indicate an ongoing pro-inflammatory response that contributes to damage in that layer. One of the few favorable indicators is the tight junction protein, ZO1 nearing 100 % concentration, an indication that the para cellular space between epithelial cells is being sealed with functional ZO1. Overall, however, this is a very unhealthy outcome. Figure 46 shows several snapshots in time of the epithelial layer density. Notice that the wound, at first, appears to be healing but, by the end of the run, a substantial wound remains. (Note that the color scale is changing in each graph. In the last graph, red represents .88, yellow represents .86, and blue represents .83.) The average, visual representation of this case is given in figure 44.

Breast Fed $k_{pp} = .7$. Figure 45 shows the results of starting with a partial injury and breast feeding. In contrast to the formula fed case, we see here a healthy outcome. Epithelial layer concentration has reached 100% indicating that this layer is completely healed. Damage has decreased to zero in the two layers shown in the time graph. (The damage is also zero in the time graph of the tissue layer which is not shown here.) The bacterial concentration is zero in both layers. We can see that the body's anti-inflammatory immune response is aiding the healing process, as evidenced by the zero concentration of pro-inflammatory cytokines. The tight junction protein is at 100 % concentration, indicating that the cell walls are being fully repaired. Figure 47 shows snapshots of the epithelial layer. The wound closes very quickly and is fully healed by the end of the run. (Note that the color scale is changing

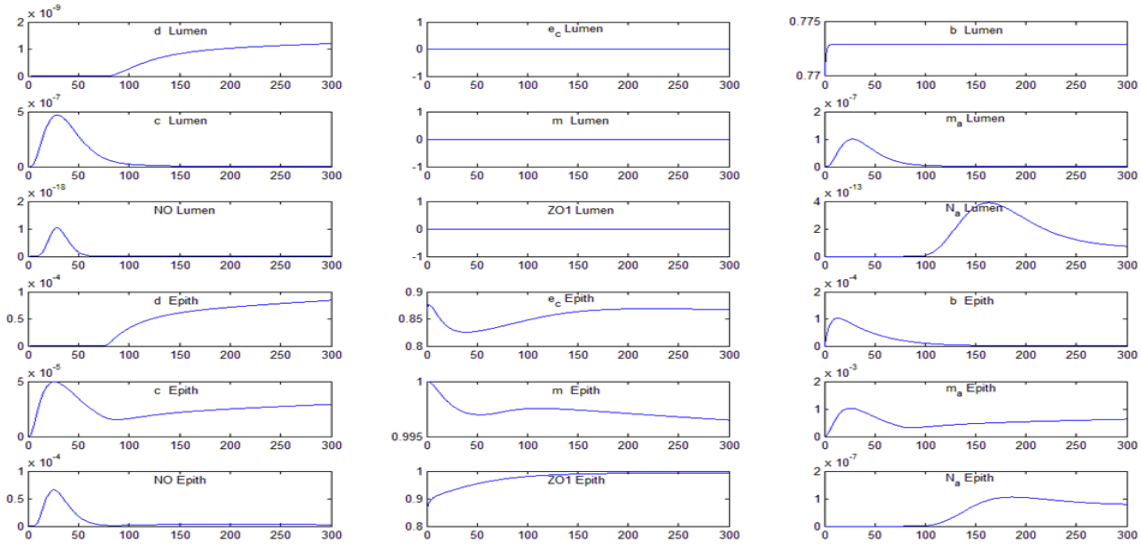


Figure 43: Simulation results for Case Partial Injury, Formula Fed. The 18 graphs shown in this figure show the amount of each component in the **epithelial** and **lumen** layers. (For example, the graph in the bottom left corner shows the amount of activated macrophages in the epithelial layer.) For each graph, the vertical axis indicates the quantity of the substance and the horizontal axis indicates time, in hours.

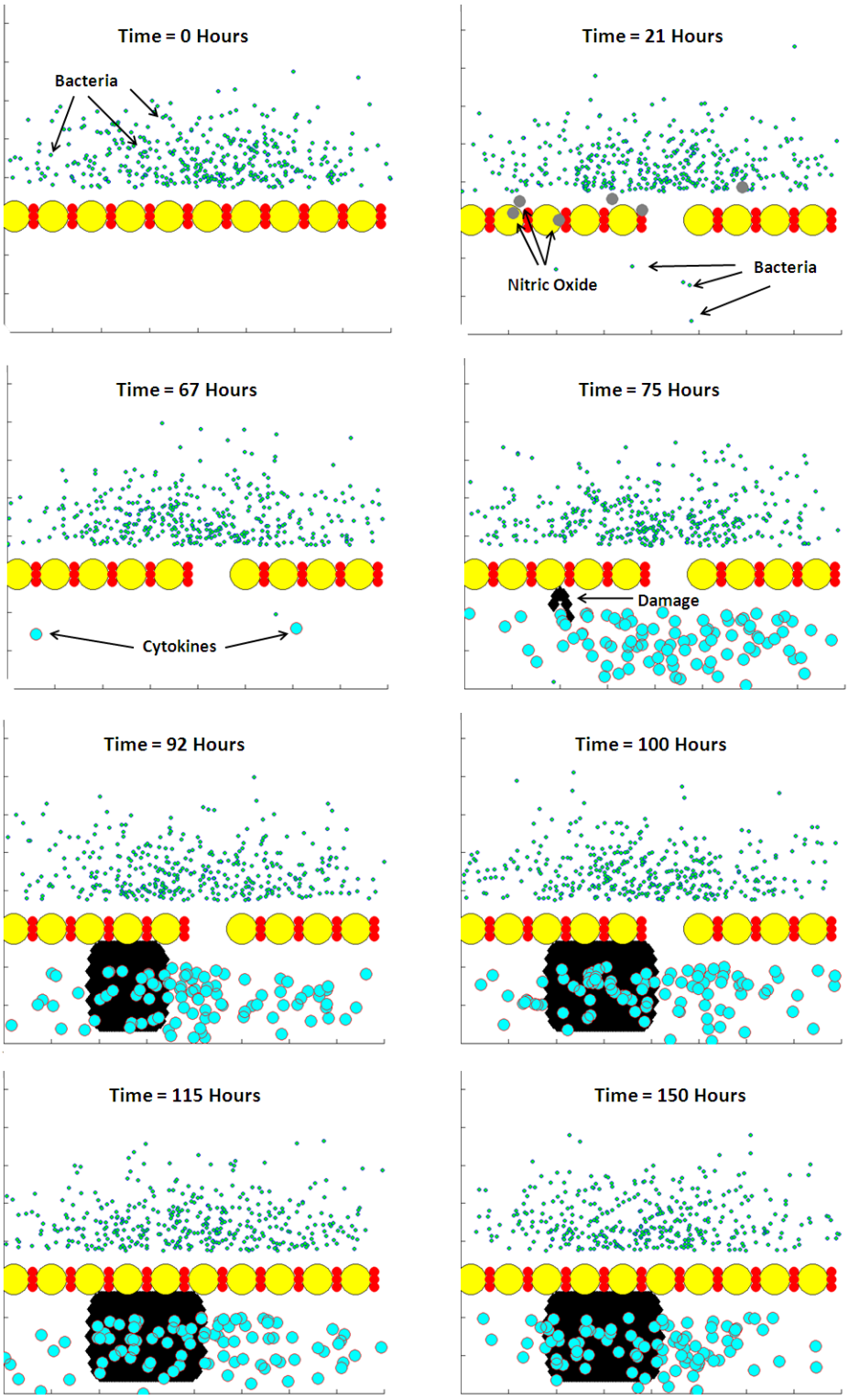


Figure 44: Case - Partial Injury Formula Fed. The purpose of this figure is to give an average visual picture of what is happening physically. This graph should not be considered as accurate as the other graphs for this simulation. In order not to clutter the diagram, only a limited number of components are shown: bacteria in the lumen, nitric oxide in the epithelium (represented by the small gray balls), epithelial cells (represented by the yellow balls), tight junction protein (represented by the red bars), bacteria in the tissue, and damage to the tissue (represented by the black areas). Also, unlike the some of the previous graphs, cytokines in the tissue are shown here.

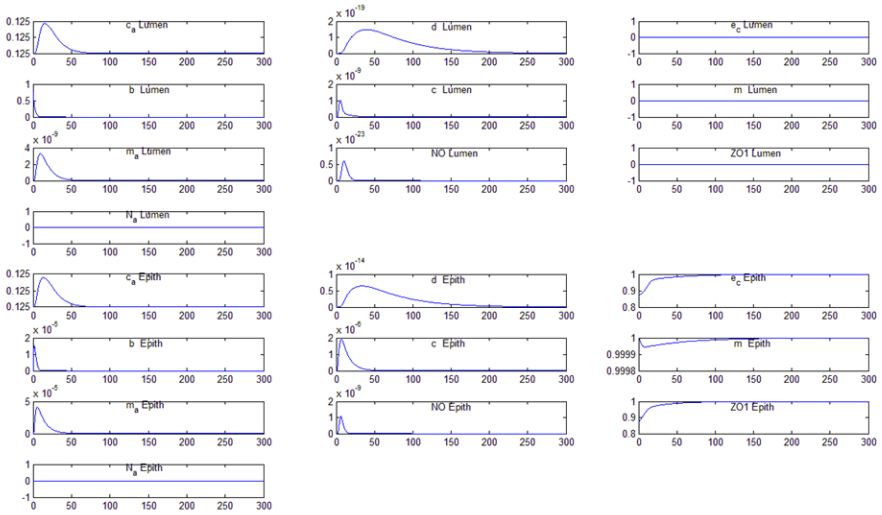


Figure 45: Simulation results for Case Partial Injury, Breastfed, $k_{pp} = .7$. The 18 graphs shown in this figure show the amount of each component in the **epithelial** and **lumen** layers. (For example, the graph in the bottom left corner shows the amount of activated macrophages in the epithelial layer.) For each graph, the vertical axis indicates the quantity of the substance and the horizontal axis indicates time, in hours.

in each graph. In the last graph, red/yellow/green represents .99999 and blue represents .9999.) This is in stark contrast to the slow, inefficient wound closing in Case Partial Injury Formula Fed (Figure 46).

The epithelial layer for these cases are shown in figure 48.

7.4 CASE - TERM INFANT, TOTAL INJURY TO EPITHELIUM.

In these runs, a full term infant with a total injury to the epithelium will be simulated. Note that 'total injury' indicate that there is a circular area in the epithelial layer that has zero density.

Formula Fed $k_{pp} = 0$. The case of formula fed is shown in figure 49. Again we see an unhealthy outcome. This example shows the epithelial layer concentration rising at about $t = 40$, but at about $t = 190$ it begins to slowly but steadily fall. This is a very bad

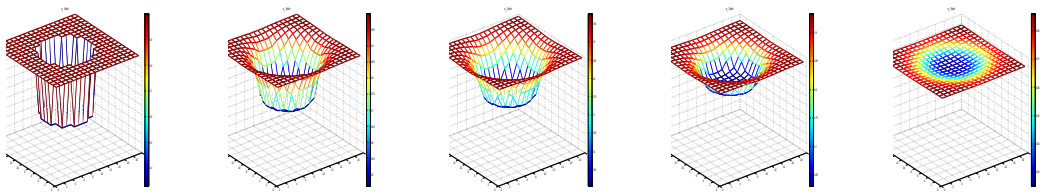


Figure 46: Wound Closing for Case Partial Injury, Formula Fed. These snapshots show the progression of the wound. The wound, at first, appears to be healing but, by the end of the run, a substantial wound remains.

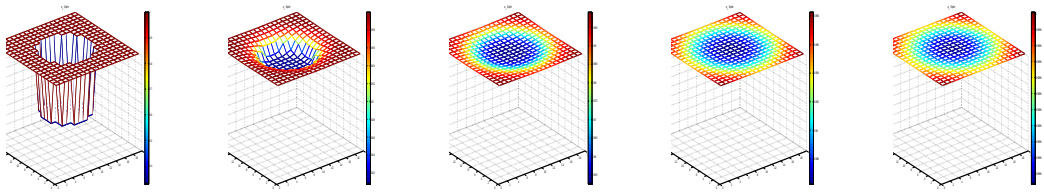


Figure 47: Wound Closing for Case Partial Injury, Breastfed. These snapshots show the progression of the wound. The wound heals very quickly.

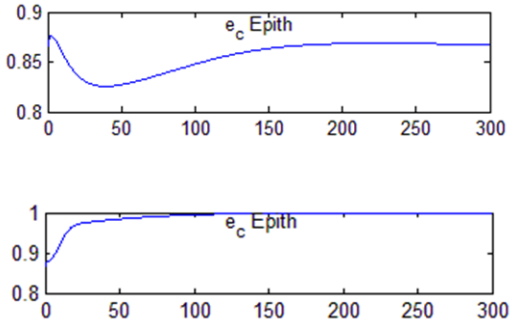


Figure 48: Comparison between formula fed and breast fed for term infant and partial injury. These graphs show the epithelial layer. The top graph is the formula fed case. $k_{pp} = 0$. The bottom graph is breast fed with $k_{pp} = .7$.

sign, indicating that the injury to the epithelial layer is actually getting worse. The tight junction protein, ZO1, is also deteriorating near the end of the run, further increasing the permeability of the epithelial layer. Nitric oxide levels are also on the rise. Nitric oxide will cause further damage to the tight junction protein. Damage, as in the previous formula fed case, is high and is increasing over time. Damage does not exhibit any asymptotic behavior, indicating it will continue to increase if the system is stimulated further. Bacteria is again not eliminated fully in the epithelial layer and remains at high levels in the lumen. The cytokine presence in the lumen and epithelial layers is non-zero and increasing over time, indicating an increasing, self-sustaining pro-inflammatory response that contributes to the increasing damage throughout the system.

Breast Fed, $k_{pp} = .7$. Figure 50. We see here a system approaching full recovery. Unlike the total injury formula fed case, the epithelial cell concentration is very close to 100%, indicating that the injury is practically fully healed. Damage is approaching zero everywhere. Bacterial content is eliminated swiftly in both layers. As a direct result of the anti-inflammatory cytokines, the pro-inflammatory cytokine presence has decreased to zero in the system. This decrease in inflammation leads to reduced damage, leading to system recovery. Figure 51 shows snapshots of the epithelial layer. Notice how the wound closes smoothly and efficiently. (Note that the color scale is changing in each graph. In the last graph, red represents .9999, yellow represents .9997, and blue represents .9995.)

We next examine two cases that vary the effect of the anti-microbial peptides in breast milk. These simulations were carried out using total injury. The parameter involved is k_{pp}. For normal cases, $k_{pp} = .7$. The following two cases show how first by reducing k_{pp} by several orders of magnitude and secondly by doubling k_{pp} affects the system outlook.

Breast Fed, $k_{pp} = .000125$ and $k_{pp} = 1.25$, respectively. Notice that when the effect of the anti-microbial peptides is reduced, by setting $k_{pp} = .000125$, Figure 52, the system recovery appears to slow down. The epithelial cell concentration is approximately 83 %, and still rising - it appears that recovery is only a matter of time. On the other hand, when the effect of the anti-microbial peptides is increased, by setting $k_{pp} = 1.25$ (see Figure 53), the system recovery appears to speed up slightly as compared with the $k_{pp} = .7$ case. The epithelial cell layer reaches its full concentration, 100 %, very quickly.

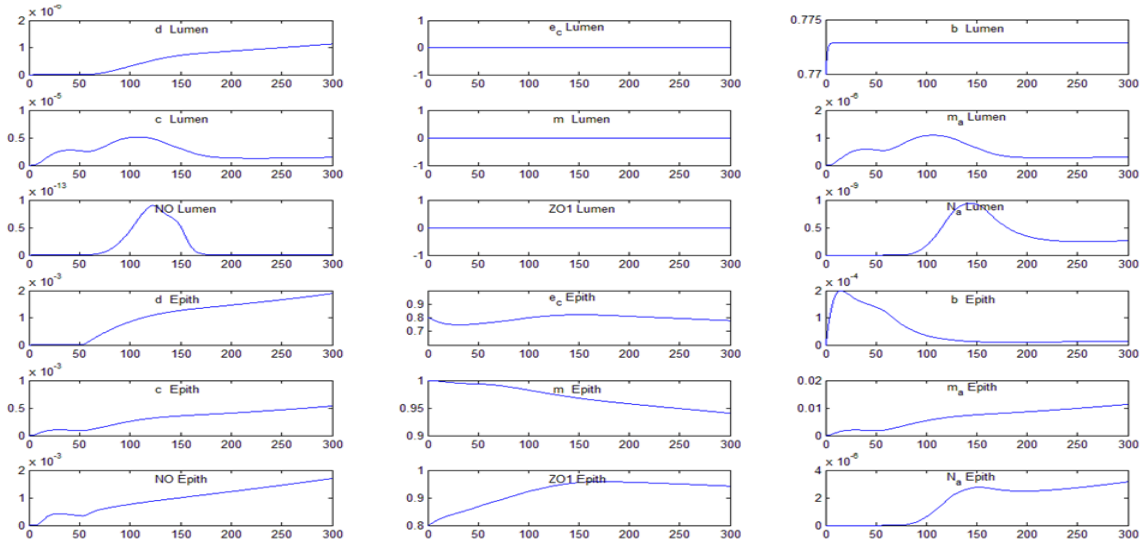


Figure 49: Simulation results for Case Total Injury, Formula Fed. The 18 graphs shown in this figure show the amount of each component in the **epithelial** and **lumen** layers. (For example, the graph in the bottom left corner shows the amount of activated macrophages in the epithelial layer.) For each graph, the vertical axis indicates the quantity of the substance and the horizontal axis indicates time, in hours.

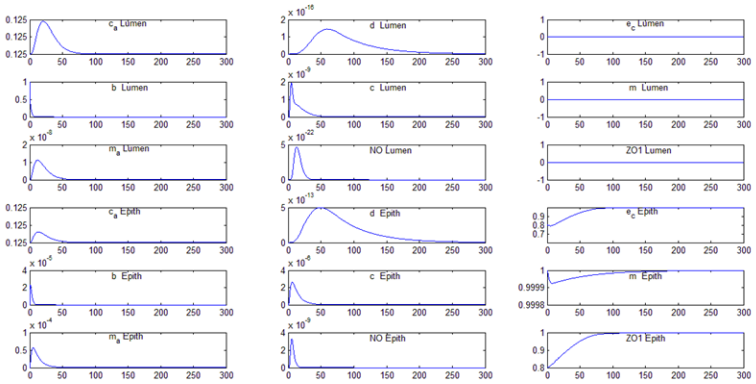


Figure 50: Simulation results for Case Total Injury, Breast Fed $k_{pp} = .7$. The 18 graphs shown in this figure show the amount of each component in the **epithelial** and **lumen** layers. (For example, the graph in the bottom left corner shows the amount of activated macrophages in the epithelial layer.) For each graph, the vertical axis indicates the quantity of the substance and the horizontal axis indicates time, in hours.

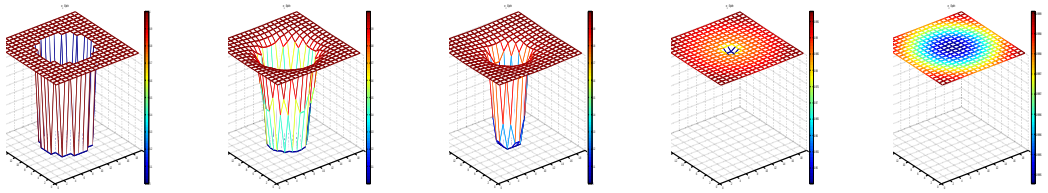


Figure 51: Wound Closing for Case Total Injury, Breast Fed $k_{pp} = .7$. These snapshots show the progression of the wound. The wound closes very quickly.

Therefore, it appears that changing the effects of the anti-microbial peptides relates only to the *speed* of the recovery, not the *fact* of the recovery. However, when we look at the damage to the tissue for the three cases Case Total Injury, breastfed with $k_{pp} = .7$, Case Total Injury, breastfed with $k_{pp} = .000125$ and Case Total Injury, breastfed with $k_{pp} = 1.25$ (see Figure 54), we notice something very important: damage is high and sustained for Case Total Injury, breastfed with $k_{pp} = .000125$, which uses the lowest value of k_{pp}. On the other hand, damage is under control for the two cases of high k_{pp}.

These test cases show the direct effect of varying the presence of anti-microbial peptides in breast milk. Based on these cases, we can say that below some value of k_{pp}, the parameter that simulates anti-microbial peptides in the computer code, the system has an unhealthy outcome. On the other hand, above some critical concentration of k_{pp} the system has a healthy outcome. As one continues to increase k_{pp} above this critical value, recovery will be proportionally faster.

7.5 SUMMARY OF SIMULATIONS

The simulations in this chapter show several things. First of all, a good result is characterized by the quantities of all components staying within reasonable limits and all the components staying under control. A good result does not necessarily mean that all NEC quantities remain at ideal levels. For example in section 7.1 (the normal case), the steady state epithelial density is 95 %. This is not perfect but is dense enough to prevent a pathogen invasion into the underlying tissue. In this same simulation, bacteria in the lumen are never eradicated. However, they do attain a manageable steady state level. On the other hand, a bad result is characterized by at least some of the undesirable NEC factors continuing to increase throughout the simulation or leveling off at too high of a value toward the end of the simulation. This can be seen in section 7.2 (prematurity, no injury) in the circumstance of formula feeding. Here, damage in the tissue and the blood remains high at the end of the run. Furthermore, nitric oxide remains high in some regions. Another characteristic of a bad result is low epithelial density throughout the entire simulation. This can be seen in section

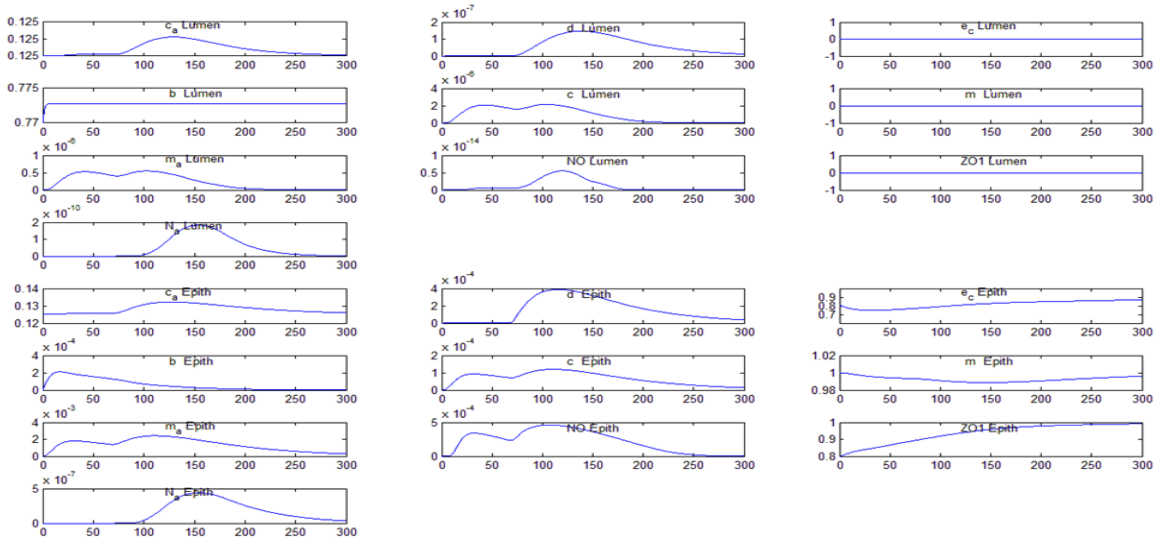


Figure 52: Simulation results for Case Total Injury, Breast Fed $k_{pp} = .000125$. The 18 graphs shown in this figure show the amount of each component in the **epithelial** and **lumen** layers. (For example, the graph in the bottom left corner shows the amount of activated macrophages in the epithelial layer.) For each graph, the vertical axis indicates the quantity of the substance and the horizontal axis indicates time, in hours.

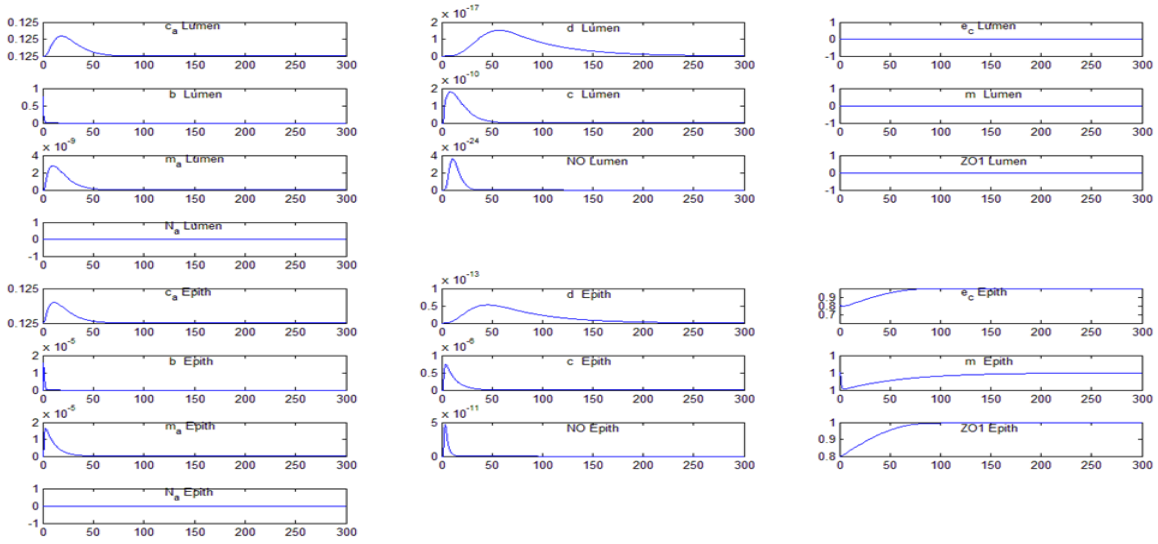


Figure 53: Simulation results for Case Total Injury, Breast Fed $k_{pp} = 1.25$. The 18 graphs shown in this figure show the amount of each component in the **epithelial** and **lumen** layers. (For example, the graph in the bottom left corner shows the amount of activated macrophages in the epithelial layer.) For each graph, the vertical axis indicates the quantity of the substance and the horizontal axis indicates time, in hours.

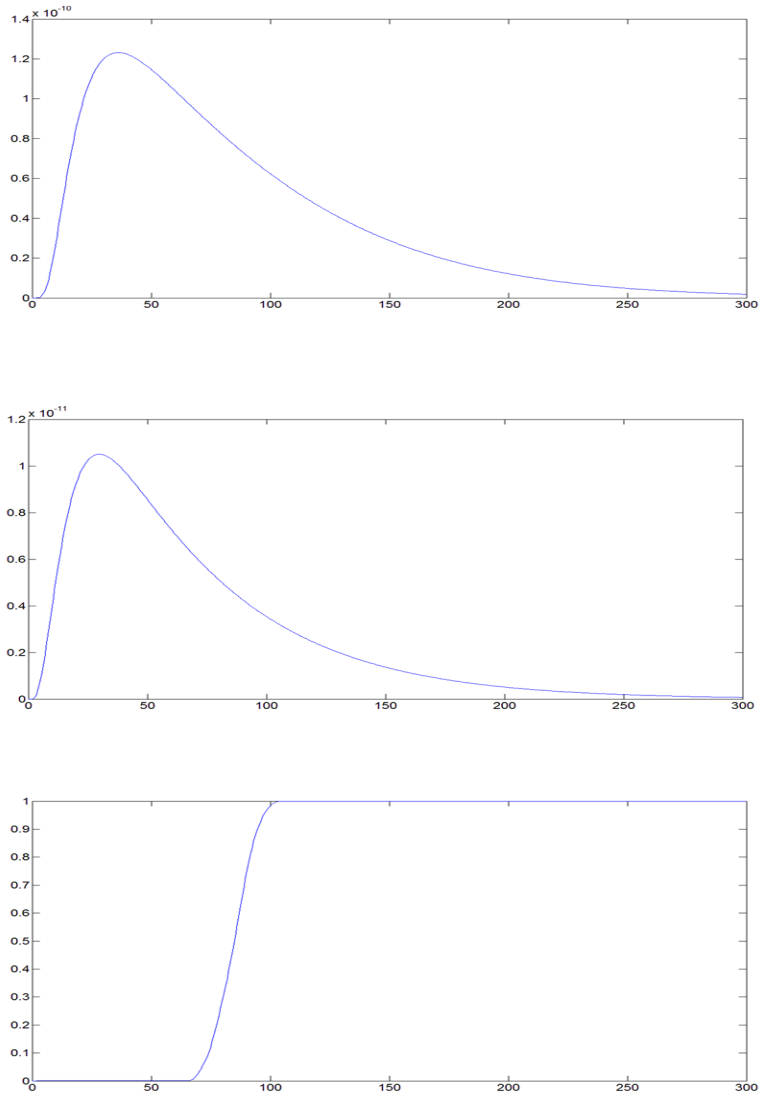


Figure 54: Tissue Damage for Case Total Injury, breastfed with $k_{pp} = .000125$ (Top), Case Total Injury, breastfed with $k_{pp} = .7$ (Middle), and Case Total Injury, breastfed with $k_{pp} = 1.25$ (Bottom).

7.3 (term infant, partial injury) in the circumstance of formula feeding. In this simulation, the epithelial density appears to be reaching a level density. However, the density is not high enough to prevent bacterial invasion of the underlying tissue.

Secondly, consistent breast feeding, simulated in these runs by high values of k_{pp}, will usually lead to good results. This fact can be seen throughout the cases in this chapter. Even in the difficult case of total injury to the epithelium, consistent breast feeding led, eventually, to a good outcome.

Thirdly, an unhealthy NEC outcome is the result of at least two undesirable events or factors. One bad factor is not enough for an unhealthy NEC outcome. For example, in section 7.2 (prematurity, no injury), the high levels of bacteria near the epithelium led to a bad NEC outcome when combined with formula feeding. On the other hand, in this same section it was shown that high levels of bacteria near the epithelium did not lead to an unhealthy outcome in the circumstance of consistent breast feeding, (simulated by $k_{pp} = 1$). Furthermore, a survey of the other simulations in this chapter will reveal the fact that injury alone, prematurity alone, or formula feeding alone will not result in a bad NEC outcome.

7.6 CONCLUSIONS

The general pattern of the graphs generated by our NEC model very closely resembles what one would expect under actual disease conditions. For example, it was shown that an initial large injury to the epithelial layer followed by formula feeding resulted in an ever-escalating inflammatory cascade with a very bad outcome. On the other hand, an initial small injury to the epithelial layer combined with breast feeding resulted in a very positive outcome. In the cases studied, the peaks and valleys of each graph occurred in very realistic patterns. However, the actual value of the peaks and valleys in the graphs as well as the relative time at which they occur are areas for future study and refinement. This refinement may be achieved through better parameter estimation and better evaluation of the uncertainties in the parameter values.

7.7 A COMPUTATIONAL NOTE OF THE APPLICATION OF THE NEC EQUATIONS TO DIFFERENT DOMAINS

The calculations done in this chapter were done in three dimensions, using the cell-centered finite difference method. For computational purposes, each region was divided into computational cells. The computational domain, discretized into a grid of computational cells, is shown in figure 55. (The third dimension, going into the page, is not shown.) As the cells get smaller, the number of cells increases and so does the accuracy of the solution. However, decreasing the size of the cells greatly increases the computation time.

Obviously, some of the equations in the NEC model apply only in certain domains, for example, the epithelial equation and the ZO1 (tight junction) equation are only valid in the epithelial layer. (That is why these components are zero in other regions.) Even though some of the NEC equations are valid in all four regions, they have different vertical and horizontal diffusion coefficients, D, depending upon the region. For example, the bacteria equation's diffusion coefficient is greater in the blood region than in the tissue region.

These vertical and horizontal diffusion coefficients affect the rates at which the NEC components move from computational cell to computational cell within each region. The vertical diffusion coefficients also effect how the NEC components move from region to region. Diffusion coefficients for computational cells along the interface of two regions are calculated by finding the harmonic average of the diffusion coefficients in both of the regions.

Another consideration for diffusion coefficients is epithelial layer permeability. In the computer code, diffusion coefficients into and out of the epithelial region increase as ZO1 (the tight junction protein) decreases. Recall from chapters one through three that tight junction protein seals the para cellular space between epithelial cells. So, as ZO1 is destroyed, epithelial layer permeability increases. Furthermore, ZO1 density is highly correlated to epithelial cell density - as epithelial cells die and create "holes" in the epithelium, ZO1 decreases. Therefore, it is reasonable to inversely correlate ZO1 density with epithelial permeability, i.e., we increase diffusion coefficients into and out of the epithelial region as ZO1 decreases and we decrease diffusion coefficients into and out of the epithelial region as ZO1 increases.

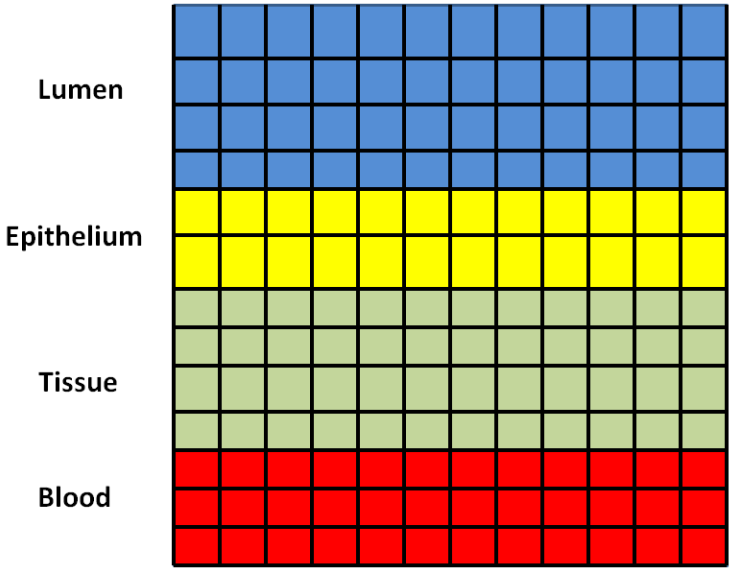


Figure 55: The computational domain, discretized into grid of computational cells. Two dimensions are shown, the third dimension which goes into the page, is not shown.

Finally, we consider the tissue/blood barrier. Under normal circumstances, this barrier has a low level of permeability. However, as damage in the tissue increases, this barrier will be compromised. Therefore, in the code, the vertical diffusion coefficient between these two layers increases as damage increases.

8.0 CONCLUSIONS AND FUTURE WORK

As noted in the introduction, the purpose of this thesis is twofold. First of all this work presents a three dimensional mathematical model of Necrotizing Enterocolitis(NEC). NEC models published previously were all one dimensional, ordinary differential equation models. These one dimensional models are extremely valuable, however, they do not model important spatial aspects of the disease. The model in this thesis consists of a system of partial differential equations (PDEs) that models both the temporal and spacial aspects of NEC. Secondly, this work analyses that NEC PDE system. That is, existence, uniqueness, and regularity analysis is done on the entire PDE system. Also, a mixed finite element analysis is done on the system of equations. This second purpose has significance for the NEC PDE system and it has significance independent of the NEC PDE system. For the NEC system, this analysis provides a strong mathematical foundation for the equations and their interrelation with each other. On the other hand, some of the classes of equations in the NEC PDE system occur, in a slightly different form, in other contexts but, in some cases, no existence, uniqueness, and regularity results for these equations exist in the literature. The same may be said of the mixed finite element analysis of some of the equations in the system - no published analysis exists. Therefore, the PDE analysis and the finite element analysis include new and important results.

As seen in the last chapter, the NEC model presented in this thesis incorporates the most significant features of NEC. Furthermore, the simulations presented in that chapter are consistent with the progression of the disease as seen in actual NEC patients. The model may now be used to simulate other NEC scenarios.

The existence, uniqueness, and regularity for the NEC PDE system was developed in

chapter four. The analysis of the nonlinear coupled system in Part I,

$$\begin{aligned}
&\frac{\partial u_1}{\partial t} - \nabla \cdot (D_1 \nabla u_1 - u_1 \nabla u_2) \;=\; f_1(u_1, u_2) \\
&\frac{\partial u_2}{\partial t} - \nabla \cdot (D_2 \nabla u_2) \;=\; f_2(u_1, u_2) \qquad (x,t) \in \Omega \times (0,T] \\
&\nabla u_1 \cdot \mathbf{n} = 0 \qquad \text{and} \qquad \nabla u_2 \cdot \mathbf{n} = 0 \qquad \text{on } \Gamma
\end{aligned}$$

where f_1 and f_2 are nonlinear functions is new. It was proven that the system does indeed have a weak solution and regularity was established. Furthermore, regularity was established for all of the NEC variables.

Furthermore, mixed finite element convergence was established for each of the NEC variables. The mixed method finite analysis for the Part I equations is new and it is perhaps the most significant result of the thesis. That analysis consisted of finding a solution in the bounded set S.

Future Work.

There are many possibilities for future work for the NEC model. For example, it may be helpful to include more detail in the epithelial layer and extra cellular matrix. This may mean including cell migration in the model as well adding an extra cellular matrix region to the model.

Further work may also be done in the area of analysis. The PDEs analyzed in chapters four and five were relevant to the NEC system. However, it would be beneficial to do existence, uniqueness, and regularity studies as well as finite element analysis on a more general system that contains more complicated coupling. For example, instead of the Part I type equations (see chapter four), one might study a system that has "two-way" coupling in the advection terms:

$$\begin{aligned}
&\frac{\partial u_1}{\partial t} - \nabla \cdot (D_1 \nabla u_1 - u_1 \nabla u_2) \;=\; f_1(u_1, u_2) \\
&\frac{\partial u_2}{\partial t} - \nabla \cdot (D_2 \nabla u_2 - u_2 \nabla u_1) \;=\; f_2(u_1, u_2)
\end{aligned}$$

Some computer convergence tests were done for the system above and it was found that there was no convergence in some cases(see chapter six) when using the explicit finite difference method. On the other hand, there was convergence for all of the implicit cases that were

tested. However, no formal analysis was done on this system. Such an analysis would be interesting but very difficult in view of the challenges that the two-way coupling presents.

The existence and regularity analysis for the PDE in part II was presented in chapter four. The results for the degenerate case heavily depended on the excellent paper by Alt and Luckhaus [4]. However, Alt and Luckhaus, make certain assumptions that do not always apply to the degenerate case. For example, for our Part II equation, (see equation (4.177) in chapter four :

$$\frac{\partial e_c}{\partial t} - \nabla \cdot (a(\nabla e_c, e_c)) \ = f_{e_c}(e_c, b, n_a)$$

Alt and Luckhaus would make the assumption that

$$(a(\nabla e_{c_1}, e_c) - a(\nabla e_{c_2}, e_c)) \cdot (\nabla e_{c_1} - \nabla e_{c_2}) \geq \beta_{min}\alpha_{min}|\nabla e_{c_1} - \nabla e_{c_2}|^2.$$

(See [4], page 314 assumption 3.) We showed that this assumption is, in fact, valid for the non-degenerate case but it will often not be true for the degenerate case. Therefore, further work can be done to eliminate such assumptions for the Part II equations for the degenerate case.

APPENDIX A

FEM ANALYSIS PART II NON-DEGENERATE CASE

In chapter 5 of this thesis, the mixed finite element analysis of the degenerate case of PDEs in Part II of the NEC system were presented. Below is the analysis of the non-degenerate case.

Assumptions Following Arbogast, Wheeler, and Zhang, we assume for the non-degenerate case we have,

$$0 < C' \leq P_{e_c} \leq C'' \tag{A.1}$$

For some positive constants C' and C''. Which, of course, implies that

$$0 < C' \leq \frac{P(e_{c_h}) - P(e_c)}{e_{c_h} - e_c} \leq C'' \tag{A.2}$$

and

$$C'|e_{c_h} - e_c| \leq |P(e_{c_h}) - P(e_c)| \leq C''|e_{c_h} - e_c| \tag{A.3}$$

$$\frac{1}{2}C_A(e_{c_h} - e_c)^2 \leq \int_{e_c}^{e_{c_h}} (P(\mu) - P(e_c))\, d\mu \leq \frac{1}{2}C_B(e_{c_h} - e_c)^2 \tag{A.4}$$

We may replace the first term on the left hand side of (5.145) with (A.3) to get the following error bound:

$$\int_0^t C'\|e_{c_h} - e_c\|\, ds + \| \int_0^t \mathbf{z}_h\, ds - \int_0^t P_h\mathbf{z}\, ds\|$$

$$
\begin{aligned}
&\leq C_{12}\Bigg\{ \int_0^t \|\Pi e_c - e_c\|\, ds + \int_0^t \|\mathsf{P}_h(t)\acute{\mathbf{z}} - \acute{\mathbf{z}}\| ds + \int_0^t \|\nabla\cdot(\Pi_h - \mathsf{P}_h)\acute{\mathbf{z}}\| ds \Bigg\} \\
&\leq C_{12}\Bigg\{ \int_0^t \|\Pi e_c - e_c\|\, ds + \int_0^t \|\mathsf{P}_h(t)\acute{\mathbf{z}} - \acute{\mathbf{z}}\| ds \\
&\qquad\qquad + \int_0^t \|\nabla\cdot(\Pi_h\acute{\mathbf{z}} - \acute{\mathbf{z}} + \acute{\mathbf{z}} - \mathsf{P}_h\acute{\mathbf{z}})\| ds \Bigg\} \\
&\leq C_{12}\Bigg\{ \int_0^t \|\Pi e_c - e_c\|\, ds + \int_0^t \|\mathsf{P}_h(t)\acute{\mathbf{z}} - \acute{\mathbf{z}}\| ds \\
&\qquad\qquad + \int_0^t \|\nabla\cdot(\Pi_h\acute{\mathbf{z}} - \acute{\mathbf{z}}\| ds + \int_0^t \|\acute{\mathbf{z}} - \mathsf{P}_h\acute{\mathbf{z}})\| ds \Bigg\}
\end{aligned}
$$

Bound 4 (Error bound in L^2 Norm - Non-Degenerate Case)

$$
\begin{aligned}
&\int_0^t C'\|e_{c_h} - e_c\|\, ds + \| \int_0^t \mathbf{z}_h\, ds - \int_0^t P_h\mathbf{z}\, ds\| \\
&\leq C_{13}\Bigg\{ \int_0^t \|\Pi e_c - e_c\|\, ds + \int_0^t \|\mathsf{P}_h(t)\acute{\mathbf{z}} - \acute{\mathbf{z}}\| ds \\
&\qquad\qquad + \int_0^t \|\nabla\cdot(\Pi_h\acute{\mathbf{z}} - \acute{\mathbf{z}}\| ds \Bigg\} \qquad \text{(A.5)}
\end{aligned}
$$

Thus, (A.5) gives an error bound for $e_{c_h} - e_c$ in the L^2 norm.

Terms $\|\Pi e_c - e_c\|, \|\mathsf{P}_h(t)\acute{\mathbf{z}} - \acute{\mathbf{z}}\|, \|\nabla\cdot(\Pi_h\acute{\mathbf{z}} - \acute{\mathbf{z}})\|$ will be bounded using approximation results.

APPENDIX B

RENAMING OF PARAMETERS

During the update of the NEC computer code, many of the parameters in the code were renamed and a few new parameters were added. The old and new parameter names are listed in the next three tables along with the current numerical values of these parameters.

New Name	**Value**	**Old Name**	Checked
k_{bg}	0.9	k_{bg}	*
k_b	1.5	k_b	*
$k_{R_{ca}}$	1.0	k_{nc}	*
k_{bm_a}	1.8	k_{ab}	*
k_{bn_a}	1.8	k_{N_ab}	*
k_{pp}	0-.25	k_{cab}	*
k_m	0.12	k_m	*
k_{mb}	0.1	k_{bm}	*
k_{mc}	0.076	k_{cm}	*
k_{md}	0.02	k_{dm}	*
k_{m_a}	0.05	k_{ma}	*
k_c	1.0	k_c	*
k_{cm_a}	0.2	k_{m_ac}	*
k_{cn_a}	0.05	k_{N_ac}	*
k_{nc}	0.04	k_{cN}	*
$k_{c_am_an_a}$	0.25	**NEW**	*

Table 5: Renaming of parameters (1 of 3).

New Name	**Value**	**Old Name**	Checked
$k_{c_a m_a d}$	48	k_{cnd}	*
k_{c_a}	0.1	k_{c_a}	*
$k_{c_a P}$	0 or .04	k_{cnn}	*
k_{NO}	2.0	k_{NO}	*
k_{NOm_a}	10,000	k_{maNO}	*
k_{NOn_a}	10,000	$k_{n_a NO}$	*
k_{n_a}	0.05	k_{N_a}	*
k_{nd}	0.018	k_{dN}	*
k_d	0.02	k_d	*
k_{dc}	0.35	k_{dn}	*
$k_{Z_{ec}}$	0.03	k_{ZO1}	*
$k_{Z_{ec_t}}$	2.0	**NEW**	Previously 1
k_{ZN}	0.75	k_{NZ}	*
k_P	0.25	k_P	*
$k_{e_c n_a b}$	0.25	**NEW**	*
$k_{e_c n_a c}$	0.5	**NEW**	*

Table 6: Renaming of parameters (2 of 3).

New Name	**Value**	**Old Name**	Checked
b_{max}	20	b_{max}	*
$\overline{c}_a$	0.2800	k_b	*
c_{max}	0.3500	c_{max}	*
d_{max}	.92	d_{max}	*
$e_{c,max}$	1.0000	$e_{c,max}$	*
ϵ	0.2	ϵ	*
D_{e_c}	0.000003	D_{e_c}	*
ϵ_{zec}	0.05	γ_{zec}	*
$\gamma_{m_a c}$	.0001	γ_0	*
$\gamma_{n_a c}$	0.0001	γ_2	*
$\gamma_{m_a b}$	0.0001	γ_1	*
$\overline{m}_a$	0.01	$\overline{m}_a$	*
m_{max}	0.67	m_0	*
$\overline{n}_a$	0.01	$\overline{n}_a$	*
$n_{a,max}$	0.62	$n_{a,max}$	*
n_b	1	n_b	*
q_0	0.45	New	*
q_1	3.5	q_1	*
q_2	1.5	q_2	*
s_{c_a}	0 or .0125	s_c	*
x_{dc}	0.06	x_{dn}	*
$ZO1_{max}$	1	$ZO1_{max}$	*

Table 7: Renaming of parameters (3 of 3).

APPENDIX C

LIPSCHITZ CONTINUITY RELATED TO PDES IN PART I

In this section, we will show that the right hand side functions of each of the equations in Part I are Lipschitz continuous. Lipschitz continuity is a necessary condition for the numerical analysis that will done later in the thesis.

Anti-inflammatory Cytokine Equation

$$\frac{\partial c_a}{\partial t} \; - \; \nabla \cdot D_{c_a} \nabla c_a \; = \; -k_{c_a} c_a + s_{c_a} + k_{c_a P} \frac{Q}{1+Q} \tag{C.1}$$

where

$$Q = R(c_a)(k_{c_a m_a n_a} n_a + m_a + k_{c_a m_a d} d) \quad \text{and} \quad R(c_a) = \frac{1}{1 + k_{Rc_a}(c_a/\overline{c}_a)^2}$$

Define

$$f_{c_a} := \; -k_{c_a} c_a + s_{c_a} + k_{c_a P} \frac{Q}{1+Q}$$

Set $\mathcal{A} \; = \; k_{c_a m_a n_a} n_a + m_a + k_{c_a m_a d} d$. We previously showed that n_a, m_a, c_a are bounded and non-negative, also, $k_{c_a m_a n_a} n_a$ and $k_{c_a m_a d} d$ are non-negative constants therefore, $\mathcal{A}$ is bounded and non-negative. Now,

$$\frac{Q}{1+Q} \; = \; \frac{\mathcal{A}}{(1 + k_{Rc_a}(c_a/\overline{c}_a)^2)(1 + \frac{\mathcal{A}}{(1+k_{Rc_a}(c_a/\overline{c}_a)^2)})} \; = \; \frac{\mathcal{A}}{1 + k_{Rc_a}(c_a/\overline{c}_a)^2 + \mathcal{A}}$$

$$|f_{c_a}(c_{a_2}) - f_{c_a}(c_{a_1})| \; = \; \left| - k_{c_a} c_{a_2} + k_{c_a P} \frac{\mathcal{A}}{1 + k_{Rc_a}(c_{a_2}/\overline{c}_a)^2 + \mathcal{A}} \right.$$

$$
\begin{aligned}
&\qquad\qquad -\Big(- k_{c_a} c_{a_1} + k_{c_a P} \frac{\mathcal{A}}{1 + k_{Rc_a}(c_{a_1}/\overline{c}_a)^2 + \mathcal{A}} \Big) \Bigg| \\
&= \left| - k_{c_a} c_{a_2} + k_{c_a} c_{a_1} + \frac{k_{c_a P}\mathcal{A}(1 + k_{Rc_a}(c_{a_1}/\overline{c}_a)^2 + \mathcal{A}) - k_{c_a P}\mathcal{A}(1 + k_{Rc_a}(c_{a_2}/\overline{c}_a)^2 + \mathcal{A})}{(1 + k_{Rc_a}(c_{a_2}/\overline{c}_a)^2 + \mathcal{A})(1 + k_{Rc_a}(c_{a_1}/\overline{c}_a)^2 + \mathcal{A})} \right| \\
&= \left| - k_{c_a} c_{a_2} + k_{c_a} c_{a_1} + \frac{k_{c_a P}\mathcal{A} k_{Rc_a}(c_{a_1}^2 - c_{a_2}^2)}{\overline{c}_a^2 (1 + k_{Rc_a}(c_{a_2}/\overline{c}_a)^2 + \mathcal{A})(1 + k_{Rc_a}(c_{a_1}/\overline{c}_a)^2 + \mathcal{A})} \right|
\end{aligned}
$$

$$
\text{Set } \mathcal{B} = \frac{k_{c_a P}\mathcal{A} k_{Rc_a}}{\overline{c}_a^2 (1 + k_{Rc_a}(c_{a_2}/\overline{c}_a)^2 + \mathcal{A})(1 + k_{Rc_a}(c_{a_1}/\overline{c}_a)^2 + \mathcal{A})}
$$

then

$$
\begin{aligned}
|f_{c_a}(c_{a_2}) - f_{c_a}(c_{a_1})| &= | - k_{c_a} c_{a_2} + k_{c_a} c_{a_1} - \mathcal{B}(c_{a_1} + c_{a_2})(c_{a_2} - c_{a_1})| \\
&= |(-k_{c_a} - \mathcal{B}(c_{a_1} + c_{a_2}))(c_{a_2} - c_{a_1})| \\
&\leq \mathcal{C}|(c_{a_2} - c_{a_1})| \qquad \text{(C.2)}
\end{aligned}
$$

This last inequality is true because the terms in the denominator of $\mathcal{B}$ are all positive, $\overline{c}_a$ is constant and c_a was previously shown to be bounded.

Epithelial Equation

$$
\frac{\partial e_c}{\partial t} \; + \; \nabla \cdot (\beta(e_c)\mathbf{u}(e_c, b)) \; = \; k_p e_c(1 - e_c/e_{c,max}) - k_{a0} k_a(n_a, c, b) e_c \qquad \text{(C.3)}
$$

where

$$
\beta(e_c) = \frac{e_c^2}{e_c^2 + (e_{c,max} - e_c)^2} \qquad \mathbf{u}(e_c, b) \; = \; \alpha(b)\nabla e_c \qquad \text{(C.4)}
$$

$k_a(n_a, c, b) :=$

$$
\frac{(n_a + k_{e_c n_a c} c + k_{e_c n_a b} b)^{.45}}{(n_a + k_{e_c n_a c} c + k_{e_c n_a b} b)^{.45} + ((n_{a,max} - n_a) + k_{e_c n_a c}(c_{max} - c) + k_{e_c n_a b}(b_{max} - b))^{.45}}
$$

Define

$$
f_{e_c} := \; k_p e_c(1 - e_c/e_{c,max}) - \mathcal{A} e_c
$$

where

$$\mathcal{A} = k_{a0} k_a(n_a, c, b)$$

Note that $n_a,\ k_{e_c n_a c},\ c,\ k_{e_c n_a b},\ b,\ k_{a0}$ are all non-negative and if we can assume that we have $n_{a,max} \geq n_a,\ c_{max} \geq c,\ b_{max} \geq b$ then

$$0 \leq \mathcal{A} \leq 1$$

$$\begin{aligned}
|f_{e_c}(e_{c_2}) - f_{e_c}(e_{c_1})| \ &= \ | \ k_p(e_{c_2} - e_{c_1}) - \frac{1}{e_{c,max}}(e_{c_2}^2 - e_{c_1}^2) - \mathcal{A}(e_{c_2} - e_{c_1})| \\
&= \left| \ k_p(e_{c_2} - e_{c_1}) - \frac{1}{e_{c,max}}(e_{c_2}^2 - e_{c_1}^2) - \mathcal{A}(e_{c_2} - e_{c_1}) \right| \\
&= \left| \ k_p - \frac{1}{e_{c,max}}(e_{c_2} + e_{c_1}) - \mathcal{A} \right| |e_{c_2} - e_{c_1}|
\end{aligned}$$

Since e_c is bounded, we have

$$|f_{e_c}(e_{c_2}) - f_{e_c}(e_{c_1})| \ \leq \ \mathcal{C}|e_{c_2} - e_{c_1}| \tag{C.5}$$

For some $\mathcal{C} \geq 0$.

Bacteria Equation

$$\begin{aligned}
\frac{\partial b}{\partial t} \ - \ \nabla \cdot D_b \nabla b \ &= \ k_{bg} b(1 - b/b_{max}) - k_b b/(1 + b/\epsilon) \\
&\quad -R(c_a)(k_{bm_a} m_a b + k_{bn_a} n_a b) - k_{pp} b
\end{aligned} \tag{C.6}$$

Define

$$f_b := \ k_{bg} b(1 - b/b_{max}) - k_b b/(1 + b/\epsilon) - R(c_a)(k_{bm_a} m_a b + k_{bn_a} n_a b) - k_{pp} b$$

$$\begin{aligned}
|f_b(b_2) - f_b(b_1)| \ = \ | \ & k_{bg} b_2(1 - b_2/b_{max}) - k_b b_2/(1 + b_2/\epsilon) \\
& +b_2(-R(c_a)k_{bm_a} m_a - R(c_a)k_{bn_a} n_a - k_{pp}) \\
& - k_{bg} b_1(1 - b_1/b_{max}) + k_b b_1/(1 + b_1/\epsilon) \\
& -b_1(-R(c_a)k_{bm_a} m_a - R(c_a)k_{bn_a} n_a - k_{pp})|
\end{aligned}$$

$$
\begin{aligned}
&= \Big| \; k_{bg}(b_2 - b_1) - \frac{k_{bg}}{b_{max}}(b_2 - b_1) - k_b \frac{b_2 + b_1 b_2/\epsilon - b_1 - b_1 b_2/\epsilon}{(1 + b_1/\epsilon)(1 + b_2/\epsilon)} \\
&\qquad\qquad + (b_2 - b_1)(-R(c_a) k_{bm_a} m_a - R(c_a) k_{bn_a} n_a - k_{pp}) \Big| \\
&= \Big| k_{bg} - \frac{k_{bg}}{b_{max}} - k_b \frac{1}{(1 + b_1/\epsilon)(1 + b_2/\epsilon)} \\
&\qquad\qquad - R(c_a) k_{bm_a} m_a - R(c_a) k_{bn_a} n_a - k_{pp} \Big| |b_2 - b_1| \\
&\qquad |f_b(b_2) - f_b(b_1)| \; \leq \; \mathcal{C} |b_2 - b_1|
\end{aligned}
\tag{C.7}
$$

Since the bacteria equation is coupled with the activated macrophage equation, we will also have to show that f_b is Lipschitz continuous in m_a:

$$
|f_b(m_{a_2}) - f_b(m_{a_1})| \; = \; | \; - R(c_a) k_{bm_a} b (m_{a_2} - m_{a_1})|
$$

$$
|f_b(m_{a_2}) - f_b(m_{a_1})| \; \leq \; \mathcal{C} |m_{a_2} - m_{a_1}| \tag{C.8}
$$

Activated Neutrophil Equation

$$
\frac{\partial n_a}{\partial t} \; - \; \nabla \cdot (D_{n_a} \nabla n_a - \gamma_{n_a c} n_a \nabla c) = -k_{n_a} n_a + R(c_a)(k_{nc} c n + k_{nd} d n)
$$

Define

$$
f_{n_a} := \; -k_{n_a} n_a + R(c_a)(k_{nc} c n + k_{nd} d n)
$$

Note that the last two terms on the right hand side do not depend on n_a and also note that $k_{n_a} \geq 0$, so

$$
|f_d(n_{a_2}) - f_d(n_{a_1})| \; = \; | - k_{n_a} n_{a_2} - (-k_{n_a} n_{a_1})| \; = \; k_{n_a} |n_{a_2} - n_{a_1}| \tag{C.9}
$$

Since the activated neutrophil equation is coupled with the cytokine equation, we will also have to show that f_{n_a} is Lipschitz continuous in c:

$$
|f_{n_a}(c_2) - f_{n_a}(c_1)| \; = \; | \; R(c_a) k_{nc} n (c_2 - c_1)|
$$

$$|f_{n_a}(c_2) - f_{n_a}(c_1)| \ \leq \ \mathcal{C}|c_2 - c_1| \tag{C.10}$$

Activated Macrophage Equation

$$\frac{\partial m_a}{\partial t} \ - \ \nabla \cdot (D_{m_a} \nabla m_a - \gamma_{m_a c} m_a \nabla c - \gamma_{m_a b} m_a \nabla b)$$
$$= -k_{m_a} m_a + R(c_a)(k_{mb} bm + k_{mc} cm + k_{md} dm)$$

Define

$$f_{m_a} := \ -k_{m_a} m_a + R(c_a)(k_{mb} bm + k_{mc} cm + k_{md} dm)$$

Note that the last three terms on the right hand side do not depend on m_a and also note that $k_{m_a} \geq 0$, so

$$|f_{m_a}(m_{a_2}) - f_{m_a}(m_{a_1})| \ = \ |-k_{m_a} m_{a_2} - (-k_{m_a} m_{a_1})| \ = \ k_{m_a}|m_{a_2} - m_{a_1}| \tag{C.11}$$

Since the activated macrophage equation is coupled with the cytokine equation, we will also have to show that f_{m_a} is Lipschitz continuous in c:

$$|f_{m_a}(c_2) - f_{m_a}(c_1)| \ = \ | \ R(c_a) k_{mc} m (c_2 - c_1)|$$

$$|f_{m_a}(c_2) - f_{m_a}(c_1)| \ \leq \ \mathcal{C}|c_2 - c_1| \tag{C.12}$$

The activated macrophage equation is also coupled with the bacteria equation, so we will also have to show that f_{m_a} is Lipschitz continuous in b:

$$|f_{m_a}(b_2) - f_{m_a}(b_1)| \ = \ | \ R(c_a) k_{mb} m (b_2 - b_1)|$$

$$|f_{m_a}(b_2) - f_{m_a}(b_1)| \ \leq \ \mathcal{C}|b_2 - b_1| \tag{C.13}$$

Damage Equation

$$\frac{\partial d}{\partial t} \; - \; \nabla \cdot D_d \nabla d \; = \; -k_d d + k_{dc} \frac{T^{q_2}}{x_{dc}^{q_2} + T^{q_2}} \tag{C.14}$$

Define

$$f_d := \; -k_d d + k_{dc} \frac{T^{q_2}}{x_{dc}^{q_2} + T^{q_2}}$$

Note that the second term on the right hand side does not depend on d and also note that $k_d \geq 0$, so

$$|f_d(d_2) - f_d(d_1)| \; = \; |-k_d d_2 - (-k_d d_1)| \; = \; k_d |d_2 - d_1| \tag{C.15}$$

Nitric Oxide Equation

$$\frac{\partial NO}{\partial t} \; - \; \nabla \cdot D_{NO} \nabla NO \; = \; -k_{NO} NO + k_{NOm_a} \frac{m_a^{q_1}}{1 + (m_a/\overline{m}_a)^{q_1}} + k_{NOn_a} \frac{n_a^{q_1}}{1 + (n_a/\overline{n}_a)^{q_1}} \tag{C.16}$$

Define

$$f_{NO} := \; -k_{NO} NO + k_{NOm_a} \frac{m_a^{q_1}}{1 + (m_a/\overline{m}_a)^{q_1}} + k_{NOn_a} \frac{n_a^{q_1}}{1 + (n_a/\overline{n}_a)^{q_1}}$$

$$|f_{NO}(NO_2) - f_{NO}(NO_1)| \; = \; |-k_{NO} NO_2 - (-k_{NO} NO_1)| \; = \; k_{NO} |NO_2 - NO_1| \tag{C.17}$$

Cytokine Equation

$$\frac{\partial c}{\partial t} \; - \; \nabla \cdot D_c \nabla c \; = \; -k_c c + R(c_a)(k_{cm_a} m_a + k_{cn_a} n_a) - R(c_a)(k_{nc} cn + k_{mc} cm) \tag{C.18}$$

Define

$$f_c := \; -k_c c + R(c_a)(k_{cm_a} m_a + k_{cn_a} n_a) - R(c_a)(k_{nc} cn + k_{mc} cm)$$

$$|f_c(c_2) - f_c(c_1)| \; = \; |-k_c c_2 - R(c_a)(k_{nc} c_2 n + k_{mc} c_2 m) - (-k_c c_1 - R(c_a)(k_{nc} c_1 n + k_{mc} c_1 m))$$

$$= |c_2(-k_c - R(c_a)k_{nc}n - R(c_a)k_{mc}m) - c_1(-k_c - R(c_a)k_{nc}n - R(c_a)k_{mc}m))$$
$$= |-k_c - R(c_a)k_{nc}n - R(c_a)k_{mc}m||c_2 - c_1|$$

Using (4.140), the fact that n is fixed and $m \leq m_{max}$, a constant. So,

$$|f_c(c_2) - f_c(c_1)| \leq C|c_2 - c_1| \tag{C.19}$$

Since the cytokine equation is coupled with the activated macrophage equation, we will also have to show that f_c is Lipschitz continuous in m_a:

$$|f_c(m_{a_2}) - f_c(m_{a_1})| = |R(c_a)k_{cm_a}c(m_{a_2} - m_{a_1})|$$

$$|f_c(m_{a_2}) - f_c(m_{a_1})| \leq \mathcal{C}|m_{a_2} - m_{a_1}| \tag{C.20}$$

The cytokine equation is coupled with the activated neutrophil equation, we will also have to show that f_c is Lipschitz continuous in n_a:

$$|f_c(n_{a_2}) - f_c(n_{a_1})| = |R(c_a)k_{cn_a}(n_{a_2} - n_{a_1})|$$

$$|f_c(n_{a_2}) - f_c(n_{a_1})| \leq \mathcal{C}|n_{a_2} - n_{a_1}| \tag{C.21}$$

Macrophage Equation

$$\frac{\partial m}{\partial t} = k_m(m_{max} - m) - R(c_a)(k_{mb}bm + k_{mc}cm + k_{md}dm)$$

Define

$$f_m := k_m(m_{max} - m) - R(c_a)(k_{mb}bm + k_{mc}cm + k_{md}dm)$$

$$|f_m(m_2) - f_m(m_1)| \leq k_m|m_2 - m_1| + R(c_a)(k_{mb}b + k_{mc}c + k_{md}d)|m_2 - m_1|$$
$$\leq C|m_2 - m_1|.$$

APPENDIX D

VERTICAL GRAPHS FOR THE SIMULATION CHAPTER.

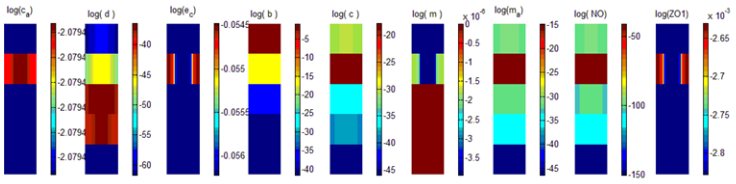


Figure 56: Normal Case - Term Infant, No Injury to the epithelium. The colored vertical graphs are logs of, from left to right, $c_a, d, e_c, b, c, m, m_a, NO, ZO1$. This graph is associated with figure 28 in the Simulation Results chapter.

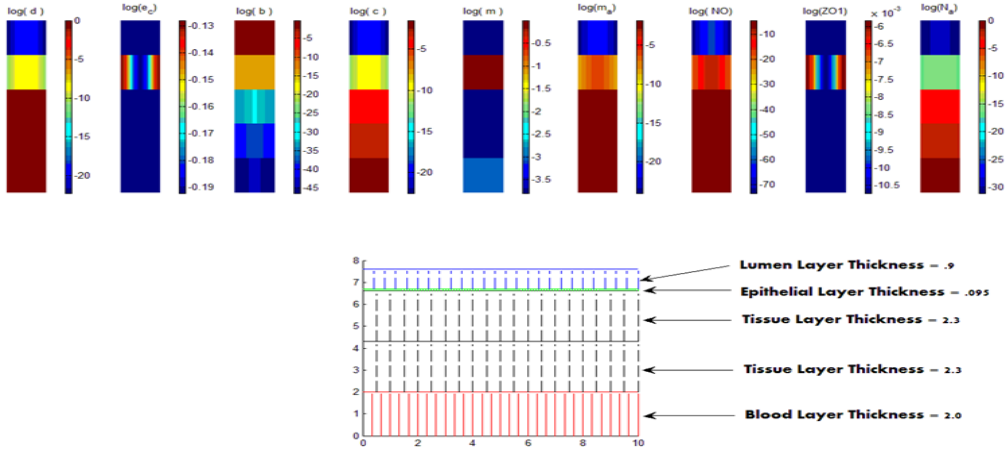


Figure 57: Simulation results for Case Partial Injury, Formula Fed. The colored vertical graphs are logs of, from left to right, $c_a, d, e_c, b, c, m, m_a, NO, ZO1$. This graph is associated with figure 43 in the Simulation Results chapter.

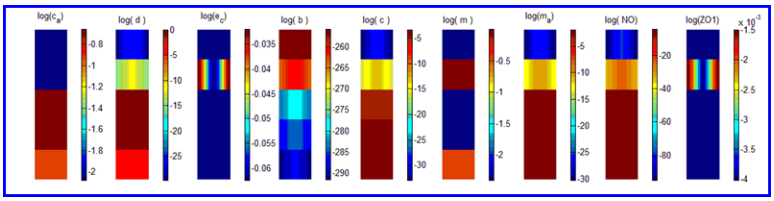


Figure 58: Simulation results for Case Partial Injury, Breastfed. $k_{pp} = .7$. The colored vertical graphs are logs of, from left to right, $c_a, d, e_c, b, c, m, m_a, NO, ZO1$. This graph is associated with figure 45 in the Simulation Results chapter.

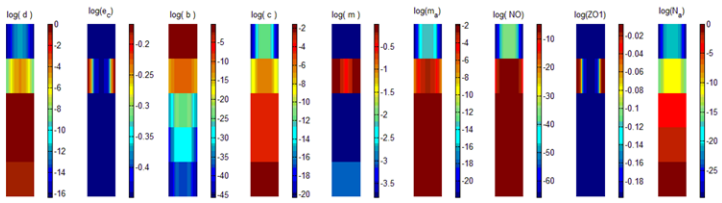


Figure 59: Simulation results for Case Total Injury, Formula Fed. The colored vertical graphs are logs of, from left to right, $c_a, d, e_c, b, c, m, m_a, NO, ZO1$. This graph is associated with figure 49 in the Simulation Results chapter.

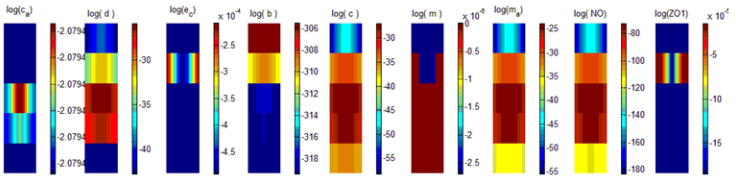


Figure 60: Simulation results for Case Total Injury, Breast Fed $k_{pp} = .7$. The colored vertical graphs are logs of, from left to right, $c_a, d, e_c, b, c, m, m_a, NO, ZO1$. This graph is associated with figure 50 in the Simulation Results chapter.

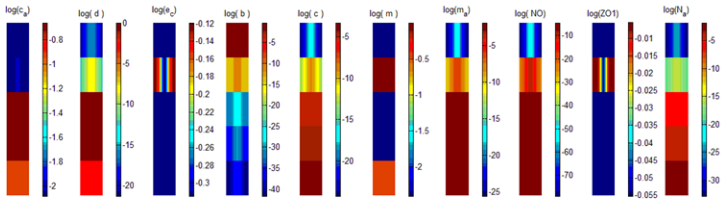


Figure 61: Simulation results for Case Total Injury, Breast Fed $k_{pp} = .000125$. The colored vertical graphs are logs of, from left to right, $c_a, d, e_c, b, c, m, m_a, NO, ZO1$. This graph is associated with figure 52 in the Simulation Results chapter.

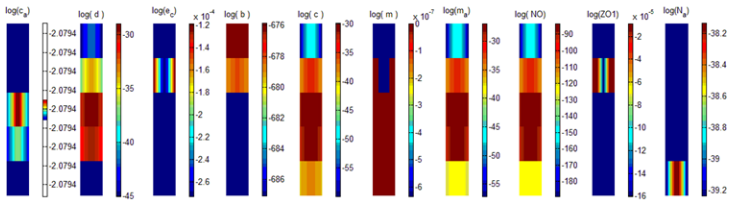


Figure 62: Simulation results for Case Total Injury, Breast Fed $k_{pp} = 1.25$. The colored vertical graphs are logs of, from left to right, $c_a, d, e_c, b, c, m, m_a, NO, ZO1$. This graph is associated with figure 53 in the Simulation Results chapter.

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