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Local Sensitivity Analysis of Acute Inflammation

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LOCAL SENSITIVITY ANALYSIS OF ACUTE INFLAMMATION

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APPROVAL OF THESIS/DISSERTATION

We, the faculty supervising the work of James N. Martin, affirm that the thesis, Local Sensitivity Analysis of Acute Inflammation, meets the high academic standards for original scholarship and creative work established by the Department of Mathematics and the College of Science. This work also conforms to the editorial standards of our discipline and the Graduate College of Marshall University. With our signatures, we approve the manuscript for publication.

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ABSTRACT

The inflammatory response is the body's response to some pathogen or foreign invader. When infected by a pathogen, a healthy individual will mount a response with immunological factors to eliminate it. An inflammatory response that is either too strong or too weak can be detrimental to the individual's health. We will look at a qualitative mathematical model of the inflammatory response, in scenarios that represent varying disorders of the immune system. Using sensitivity analysis we determine which parameters of this model are most influential in the different scenarios. By determining which parameters are most influential we can suggest possible targets for treatments to these conditions which are traditionally difficult to control.

CHAPTER 1

INTRODUCTION

The human body faces external threats from *pathogens*, or disease causing agents, every day. Pathogens can be viruses, bacteria, fungi, or multi-cellular parasites. The first lines of defense against these invaders are the skin and mucous membranes. If this barrier is breached, be it through a simple cut or ingesting some infected substance, then the second line of defense is activated [7].

The second line of defense is called the innate immune system. The innate immune system is a chemical defense system that is activated by white blood cells called macrophages. When a macrophage detects a pathogen it begins to engulf the pathogen for destruction, a process known as phagocytosis. Macrophages also secretes enzymes, known as cytokines, to begin the process of *inflammation*. Inflammation involves the recruitment of many different chemicals and cells from elsewhere in the body in order to neutralize the pathogens that the macrophages have detected.

Inflammation involves physical symptoms such as heat, redness, swelling, and pain. Symptoms such as these are intended functions of the inflammatory response that strengthen the immune response. One of the earliest components of inflammation is the recruitment neutrophils, a type of white blood cell. Like the macrophages, the neutrophil's function is to engulf the pathogens and destroy them through phagocytosis.

One of the effects of the inflammatory response is to increase the permeability of blood vessels. The increased bloodflow allows a faster exchange of cells and chemicals from the bloodstream to the infected tissues. Swelling and pain is also associated with inflammation. The pain, while uncomfortable, serves to inform the infected party of an injury. Ideally the pain will indicate that the affected area needs rest [3].

The inflammatory response is intended to aggressively attack any and all invading pathogens and eliminate them while causing minimal damage to the healthy parts of the body. Of course, this can go wrong, and when it does there are a wide range of associated consequences. There are numerous conditions and diseases of the immune system in which the inflammatory response does

not function correctly. Too weak of a response allows the invading pathogen to multiply and cause damage and disease. Too strong of a response and healthy tissues can be damaged or destroyed by the immune system.

If there is a systemic infection where a pathogen is present across many different parts of the body, a condition known as *sepsis* can occur. While a general term, sepsis can occur when pathogens, usually bacteria, are present across a large portion of the body. The widespread infection then causes an immune and inflammatory response across many different systems at once. An inflammatory response on this scale is known as septic shock, which can be fatal. There are few known treatments for sepsis, which makes it a prime target for research. Any treatment that could reduce the risk of sepsis, without reducing the efficacy of the immune system, would be valuable.

Autoimmune disorders are another set of conditions under which the immune system can fail. Autoimmune disorders occur when the immune system recognizes itself as a pathogen. Autoimmune disorders include insulin-dependent diabetes mellitus (Type I), multiple sclerosis, lupus, and many others. Furthermore, individuals with these disorders can suffer more severe symptoms when a pathogen invades, as these disorders activate the immune system and cause more healthy cells to be damaged.

Finally, the conditions in which the immune system is insufficient at clearing a pathogenic infection are commonly referred to as *immunodeficiencies*. One of the most well known immunodeficiencies is acquired immune deficiency syndrome (AIDS) caused by the human immunodeficiency virus (HIV). There are also a few other immunodeficiency conditions, such as severe combined immunodeficiency syndrom (SCIDS), and DiGeorge syndrome. These conditions result in an immune system that is either weakened or entirely incapable of defending the body against foreign pathogens. A simple bacterial infection that a healthy individual would clear in a matter of hours could lead to severe illness in a person with an immunodeficiency [7].

The purpose of this study is to take an existing model of the inflammatory response, whether it be healthy, overactive, or immunodeficient, and examine the variables and parameters. Using sensitivity analysis we determine which parameters are most influential on the output of the system. The inflammatory response is a delicate system; if it is too effective, it harms the host

body. If it is not effective enough pathogens can grow unchecked. By determining which parameters of a model of the inflammatory response are most influential, new targets for treatment could be found.

CHAPTER 2

THE MODEL

This chapter presents a basic mathematical model for the inflammatory response. While there are many complex factors that make up the immune system, many of them can be simplified into constants and initial conditions. We are also presenting a few sets of initial conditions that adequately model some common disorders of the immune system.

2.1 Equations

While simple in construction, the system of differential equations presented here adequately models the inflammatory response. This model was presented in the 2004 paper *The Dynamics of Acute Inflammation* [2]. The model is entirely qualitative, and unitless. Here, p represents the pathogen, or infectious agent, m represents early pro-inflammatory mediators, and ℓ is the late pro-inflammatory mediators. The equations are

$$\frac{dp}{dt} = k_p p(1-p) - k_{pm} mp \tag{2.1}$$

$$\frac{dm}{dt} = (k_{mp} p + \ell) m(1-m) - m \tag{2.2}$$

$$\frac{d\ell}{dt} = k_{\ell m} \left[1 + \tanh\left(\frac{m-\theta}{w} \right) \right] - k_\ell \ell. \tag{2.3}$$

All parameters and variables are positive. The general idea is that with the introduction of some initial pathogen, p, we induce a response from the early inflammatory mediators, denoted by m. Part of the function of the early inflammatory mediators is to recruit late inflammatory mediators, ℓ. The late inflammatory mediators strengthen the immune response, and eventually slow the response after the pathogen has been cleared.

The pathogen, p, can represent any invader into the body that would elicit an inflammatory response. Pathogens include viruses, fungi, bacteria, protozoa, etc. The early pro-inflammatory mediators, m, are the first responders to foreign entities. Early mediators include neutrophils, macrophages, Tumor Necrosis Factor-α (TNF-α), Interleukins (IL-1), and others. The late

pro-inflammatory mediators, ℓ, are stimulated by the early effects of inflammation; they include IL-6, High Motility Group Box-1 (HMGB-1), and others [2].

The three variables in this model follow the properties of logistic growth. The equations are similar to those used in modeling populations. That is to say that they each have some carrying capacity defined by the system, past which they can no longer grow. In the case of p and m, the $(1-p)$ and $(1-m)$ components of (2.1) and (2.2) set the carrying capacity of p and m to 1. For ℓ the carrying capacity is more variable and dependent on the value of m through the use of a switching function.

The growth and decay components of these equations include $k_p, k_{pm}, k_{mp}, k_{\ell m}$, and k_ℓ. These parameters represent the growth or decay rates of their respective variables. For instance, in (2.1) the parameter k_p is the fixed growth rate of the pathogen, p. We would expect a high k_p with a particularly virulent invader. The factor k_{pm} represents the capability of the early mediators, m, at destroying the pathogen. A higher k_{pm} represents a more effective inflammatory response. In (2.2) k_{mp} is the recruitment rate of m with respect to p. That is, a higher value of k_{mp}, means more early mediators are recruited in response to the pathogen.

In (2.3) we have $k_{\ell m}$, which is the growth rate of ℓ with respect to m. A higher value of $k_{\ell m}$ represents a stronger late mediator response. The decay rate k_ℓ represents the natural expiration of the late mediators. A high k_ℓ indicates the late mediators do not last long. The value of k_ℓ is fixed at 1 for the purposes of this study.

The hyperbolic tangent in (2.3) serves as a switching function. It "turns on" once a sufficient value of m has been achieved to simulate the recruitment of late mediators by early mediators. Figure 2.1 shows the standard shape and possible changes to $\tanh\left(\frac{m-\theta}{w}\right)$. The activation threshold, θ, is the point in the model where the production of ℓ begins. Increasing θ causes the function to shift left, meaning the production of late mediators is switched on at a lower value of m. The activation width, w, simulates the amount of time it takes for the function to increase. Making the activation width wider would cause a more gradual increase in ℓ starting at an earlier time. Changing the activation width to be more narrow has little effect, but makes the jump to producing late mediators faster.

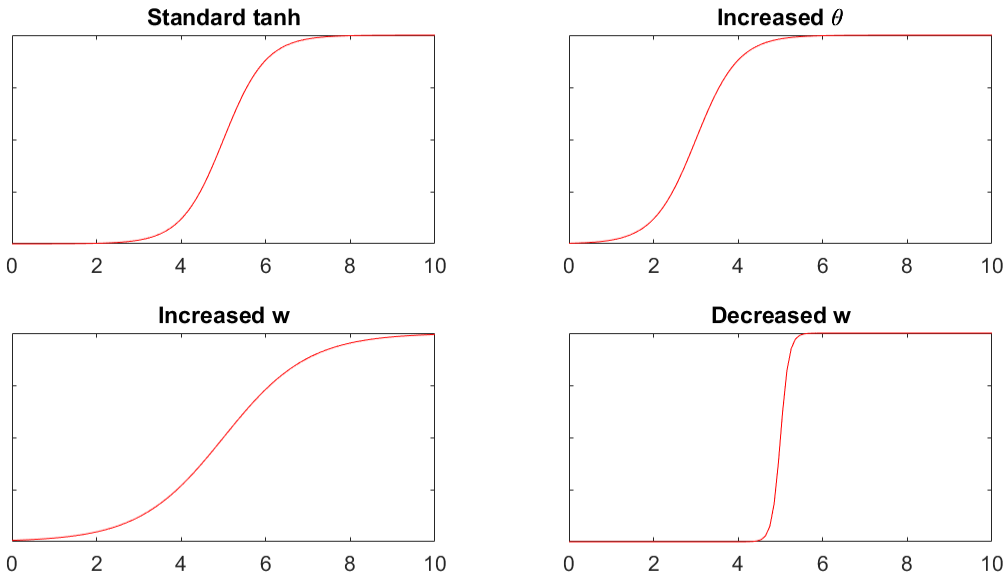

Figure 2.1: Hyperbolic Tangent Functions Examples of the hyperbolic tangent function in (2.3), which is $\tanh\left(\frac{m-\theta}{w}\right)$, and effects of possible changes.

2.2 Immunological Responses

These model equations simulate certain real world conditions. The included simulations are a healthy response to infection, both infectious and non-infectious persistent inflammation, a recurrent infection, and immunodeficiency. The initial conditions and constant parameter values of each of these scenarios can be found in Table A.1. There is also a threshold set for the pathogen of $p = 0.0005$. Once the pathogen drops below this threshold, it is considered to be cleared, and held at zero. At this point the infection is considered to have been eliminated.

Note that the values presented here are all qualitative. In reality, the pathogen, early, and late mediators would correspond to some real valued concentration in an individual's blood serum. For the purposes of this study, however, qualitative values are used. Quantitative information associated with the inflammatory response is much more difficult to process, as it varies greatly between pathogens and affected individuals.

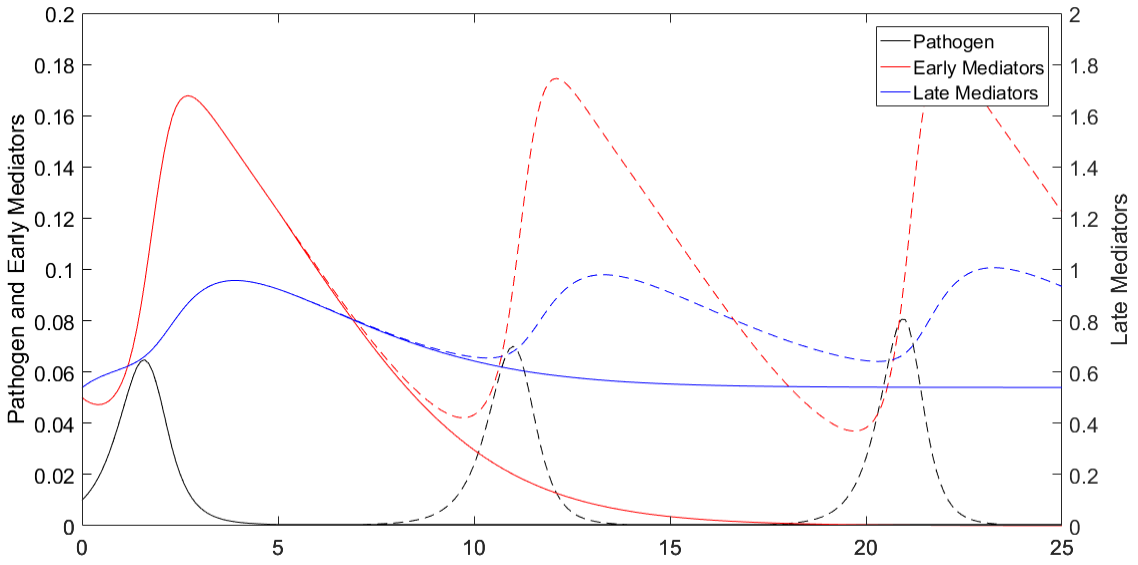

Figure 2.2: Healthy Response In this healthy response the solid line solution holds the value of the pathogen at 0 once it has dropped below a threshold of $p = 0.0005$. The dotted line represents the model without the use of a threshold. Initial conditions are $p(0) = 0.01$, $m(0) = 0.05$, $\ell(0) = 0.539$. Parameter values are $k_p = 3$, $k_{pm} = 30$, $k_{mp} = 25$, $k_{\ell m} = 15$, $k_\ell = 1$, $\theta = 1$, $w = 0.5$. Note that these values are unitless as this is a qualitative model.

2.2.1 Healthy Response

In a healthy response to a pathogen, as shown in Figure 2.2, we start with a small infection, and some early and late mediators set to simulate a healthy individual. As expected we see a rapid growth of the pathogen after initial infection followed by an equally quick spike in the early inflammatory mediators. As the late mediators begin to rise we see the pathogen levels drop off. The pathogen crosses the minimum threshold around $t = 5$ and is considered to be cleared at that point.

The late mediators end at an equilibrium value near their initial value. As a consequence of the pathogen value being set to zero, the value of the early mediators drop to zero as well, which occurs due to the nature of the model. In reality a healthy individual would see early mediator levels return to their initial value as well. The dashed line indicates the solution without the use of the threshold.

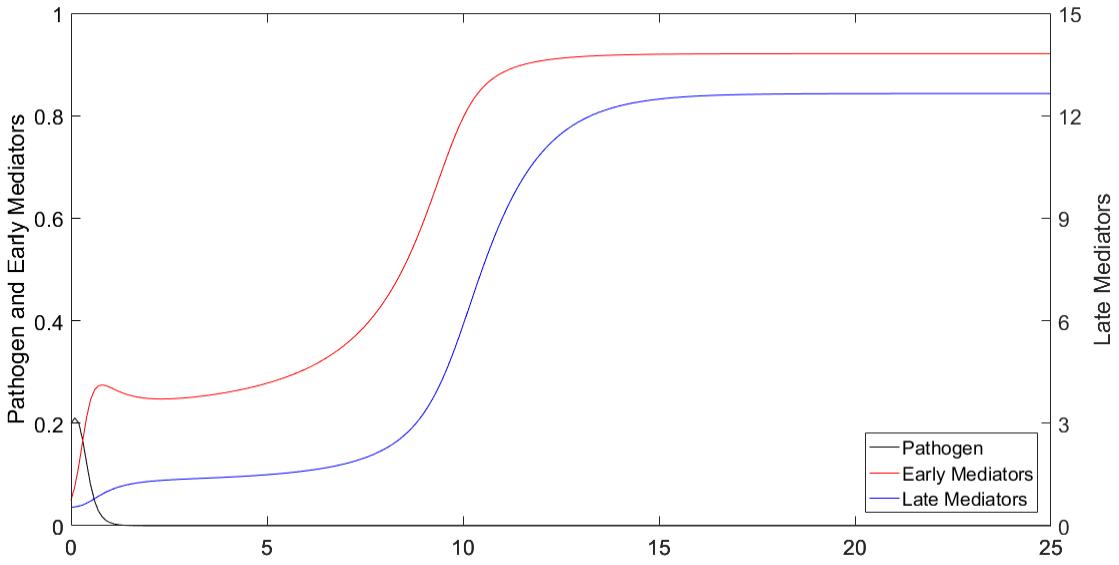

Figure 2.3: Persistent Non-Infectious Inflammation In persistent non-infectious inflammation the pathogen is successfully cleared, but the inflammatory response continues anyway. Initial conditions and parameters are the same as healthy response except for $p(0) = 0.2$.

2.2.2 Persistent Non-Infectious Inflammation

Looking at Figure 2.3, we have an example of persistent non-infectious inflammation. Persistent non-infectious inflammation is what we expect in the case of an autoimmune disorder, where after clearing the pathogen, the immune system remains activated attacking healthy cells. The initial conditions of this scenario are the same as in the healthy response, with the exception of the initial pathogen, which is $p(0) = 0.2$.

The large amount of initial pathogen causes an overly aggressive response by the immune system. Despite the pathogen being completely cleared, the inflammatory response does not return to baseline levels. The early mediators come to an equilibrium value around 0.9, which is near the carrying capacity. The late mediators reach a final value of about 12.5.

2.2.3 Persistent Infectious Inflammation

Moving on to Figure 2.4, we see a case of persistent infectious inflammation. Persistent infectious inflammation is where the infection is not able to be cleared, and the immune response remains active. Here we use everything from the healthy example, but change the value of k_{pm} to 3 (down

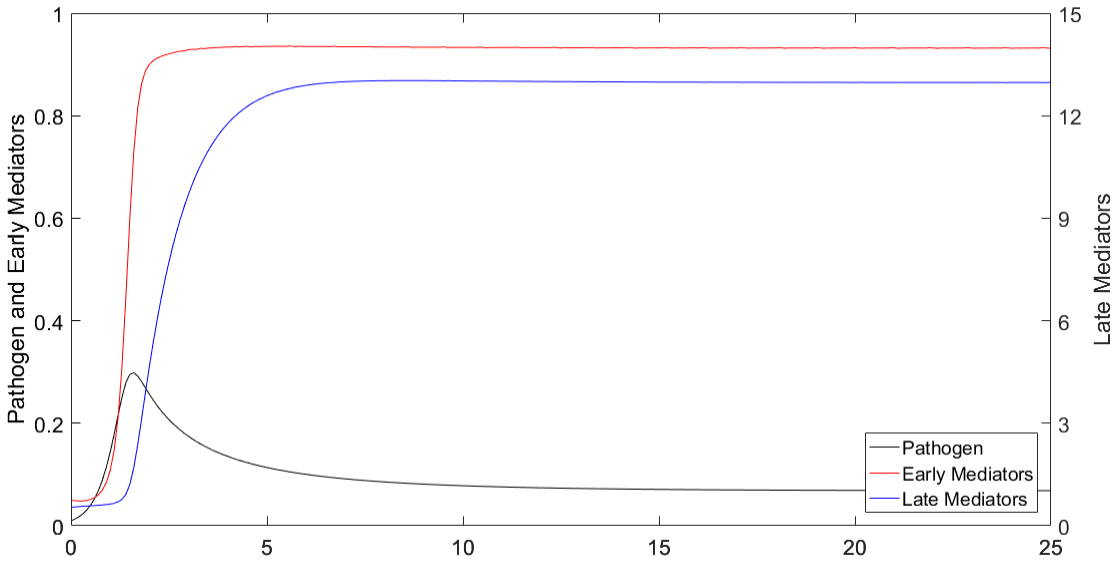

Figure 2.4: Persistent Infectious Inflammation With persistent infectious inflammation, the inflammatory response escalates very aggressively to a pathogen that cannot be entirely eliminated. Initial conditions and parameters are the same as healthy response except for $k_{pm} = 3$.

from 30). Recall that k_{pm} is the rate at which the early mediators are able to kill the pathogen, thus the ability to clear infection is reduced.

The level of pathogen drops from the initial value, but never fully clears, and stays constant around $p = 0.1$. A constant presence of pathogen causes the equilibrium values of early and late mediators to remain elevated, around 0.95 and 12.5. These levels are similar to that of the non-infectious case seen in Section 2.2.2.

2.2.4 Recurrent Infection

In Figure 2.5 we have a recurrent infection, where the pathogen is never eliminated and is able to grow again at regular intervals. Thus the infection flares up after the immune response dies down and the cycle continues. In this scenario the value of $k_{\ell m}$ has been lowered to 5 (down from 15). The initial amount of late mediators has also been lowered to $\ell(0) = 0.179$. Note that $k_{\ell m}$ is the parameter responsible for recruiting late inflammatory mediators. As a result too few late mediators are recruited and the infection is able to return.

The value of the pathogen, while constantly fluctuating, reaches an equilibrium around 0.03.

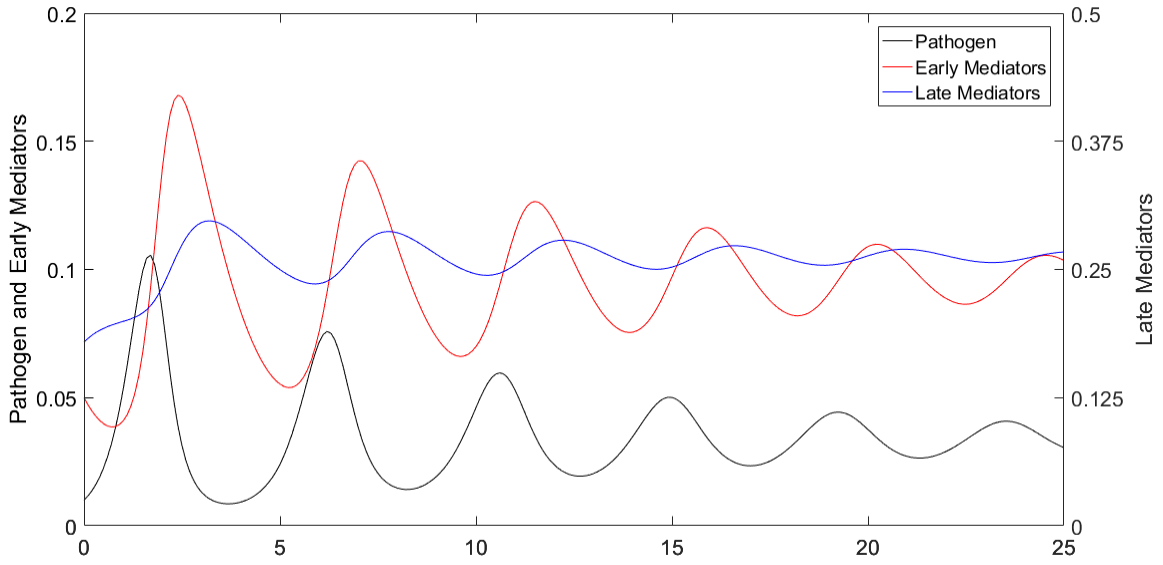

Figure 2.5: Recurrent Infection With recurrent infection a pathogen keeps coming back despite the inflammatory response. The recurring inflammation results in cycles of pathogen levels and responses from the early and late mediators. Initial conditions and parameters are the same as healthy response except for $\ell(0) = 0.179$ and $k_{\ell m} = 5$.

The early mediators fluctuate around 0.1, which is double their initial values. The late mediators become the most stable component of this system, leveling off almost exactly at 0.26.

2.2.5 Severe Immunodeficiency

Figure 2.6 shows the case of immunodeficiency. Recall that this is meant to simulate an inflammatory response that has been weakened. The value of k_{mp} is now $k_{mp} = 0.4$ which is down from 25 in the other examples. A lower k_{mp} causes fewer early mediators to be recruited from the presence of the pathogen, which in turn causes a vastly reduced inflammatory response.

The reduced inflammatory response results in the pathogen growing to nearly the carrying capacity, 1.0. In an individual this would mean the infection is spreading to other parts of the body. The early mediators, despite having the same initial value as the other examples, drop to very near zero. The late mediators have a slight bump at the start, due to the presence of m, but quickly return to their starting value of around 0.54.

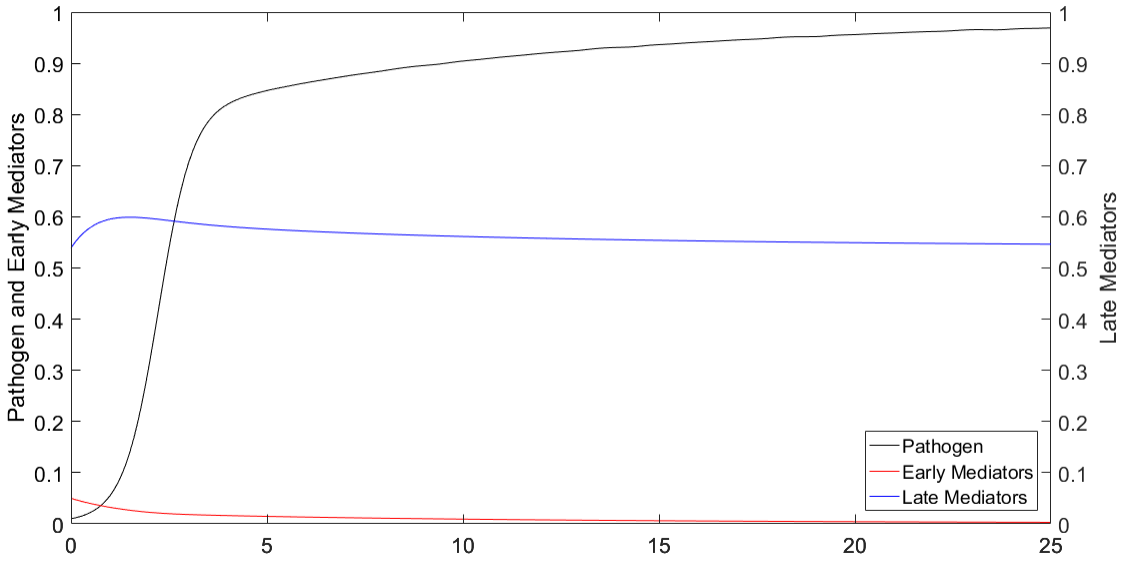

Figure 2.6: Severe Immunodeficiency With severe immunodeficiency we have a reduced response from the late mediators. The reduced late mediators in turn leads to the pathogen growing to carrying capacity rapidly. Initial conditions and parameters are the same as healthy response except for $k_{mp} = 0.4$.

CHAPTER 3

LOCAL SENSITIVITY ANALYSIS

Utilizing these model equations, the next component of this study is the application of local sensitivity analysis. Using sensitivity analysis, we will look more closely at the described model to determine which of the parameters are the most influential.

3.1 What is sensitivity analysis?

Sensitivity analysis is a method used for determining the importance of parameters on a system of equations or model. It encompasses varying techniques that help determine which inputs in a system have a significant effect on the output and which do not. In a system that has multiple inputs, both in the form of fixed constants and initial conditions of variables, it may not be obvious how changes to these parameters could impact the output of the model. Sensitivity analysis attempts to both qualitatively and quantitatively assess what role each factor plays in a given model.

One use of sensitivity analysis is the identification of which parameters in a given system are the most important. Sensitivity analysis allows the identification of which parameters should be prioritized for more accurate measurement or further study. Sensitivity analysis can help identify which inputs give the largest variability to the output of the system. Once determined these factors can then be fixed at the value where they least impact the system, offering less overall variance in the system [1].

Global sensitivity analysis is a method that helps determine how different input factors work realative to one another[5]. For example, does parameter x have a larger or smaller impact on the output of the system when parameter y is small? What if parameter y is large? Global sensitivity analysis is a valuable tool, but for systems with many different inputs this can be computationally expensive, and as such will not be the method used in this study.

Local sensitivity analysis uses a one-at-a-time (OAT) approach to examining model parameters. Each factor is looked at individually, with the others held constant. We accomplish this by taking derivatives with respect to the desired parameter. The sensitivities are then normalized to look at

the impact of each factor relative to the scale of the model [6]. Local sensitivity analysis is ideal for this study, since we are modeling specific scenarios where each parameter is fixed.

3.2 Applying local sensitivity analysis to our model

First, we want to identify which parameters of our model to analyze. Looking at (2.1), (2.2) , and (2.3) we have the factors k_p, k_{pm}, k_{mp}, $k_{\ell m}$, k_ℓ, θ, and w. The values for these parameters will vary based on the particular simulation we are running, as shown in Table A.1.

To find the sensitivities of each parameter we will use derivatives. We begin by stating our entire output of the system, presented in (2.1), (2.2), and (2.3) as y, thus

$$y' = \begin{bmatrix} p' \\ m' \\ \ell' \end{bmatrix} = \begin{bmatrix} k_p p(1-p) - k_{pm} mp \\ (k_{mp} p + \ell) m(1-m) - m \\ k_{\ell m} \left[1 + \tanh\left(\frac{m-\theta}{w}\right)\right] - k_e l l \ell \end{bmatrix}.$$

For an arbitrary parameter κ we call S_κ the *sensitivity* of κ and $S_\kappa = \frac{\partial y}{\partial \kappa}$. Taking the derivative of the sensitivity, with respect to t, gives us $S'_\kappa = \frac{\partial}{\partial t}\left(\frac{\partial y}{\partial \kappa}\right)$. Now, by utilizing the symmetry of second derivatives, or Schwarz's Theorem, we can say that $S'_\kappa = \frac{\partial}{\partial \kappa}\left(\frac{\partial y}{\partial t}\right)$ [8]. Notice that $\frac{\partial y}{\partial t}$ is our original system of differential equations. So, the derivative of the sensitivity of a specific parameter is just the derivative of our system with respect to that parameter.

From here we will use a specific variable, p, and parameter, k_p. We have that the derivative of the sensitivity of p to k_p is

$$\frac{\partial S^p_{k_p}}{\partial t} = \frac{\partial}{\partial k_p}\left(\frac{\partial p}{\partial t}\right).$$

Note that $\frac{\partial p}{\partial t}$ is (2.1), and is a function, say g, of k_p, p, m, and ℓ. Also note that p, m, and ℓ are also functions of k_p. So, we have that

$$\frac{\partial p}{\partial t} = k_p p(1-p) - k_{pm} mp = g(k_p, p(k_p), m(k_p), \ell(k_p)).$$

Now we take to total derivative of g with respect to k_p and we get

$$\frac{\partial}{\partial k_p} g(k_p, p(k_p), m(k_p), \ell(k_p)) = \frac{\partial g}{\partial k_p}\frac{\partial k_p}{\partial k_p} + \frac{\partial g}{\partial p}\frac{\partial p}{\partial k_p} + \frac{\partial g}{\partial m}\frac{\partial m}{\partial k_p} + \frac{\partial g}{\partial \ell}\frac{\partial \ell}{\partial k_p}.$$

Here we have that $\frac{\partial g}{\partial k_p}$ is the derivative of g with respect to k_p, and $\frac{\partial k_p}{\partial k_p}$ is 1. The terms $\frac{\partial p}{\partial k_p}$, $\frac{\partial m}{\partial k_p}$,

and $\frac{\partial \ell}{\partial k_p}$ are the sensitivities of each variable with respect to k_p. Plugging this in we now have

$$\frac{\partial S^p_{k_p}}{\partial t} = p(1-p) + \frac{\partial g}{\partial p} S^p_{k_p} + \frac{\partial g}{\partial m} S^m_{k_p} + \frac{\partial g}{\partial l} S^\ell_{k_p}.$$

Now we want to apply this technique to the whole system. Let $\frac{\partial y}{\partial t} = f(k_p, p(k_p), m(k_p), \ell(k_p))$, a function representing our three model equations. Note that y is a vector containing p, m, and ℓ. Using this we have that

$$S'_{k_p} = \frac{\partial f}{\partial k_p} + \frac{\partial f}{\partial p} S^p_{k_p} + \frac{\partial f}{\partial m} S^m_{k_p} + \frac{\partial f}{\partial \ell} S^\ell_{k_p}.$$

As before we have $\frac{\partial f}{\partial k_p}$, which is the derivative of our system with respect to k_p. The terms $\frac{\partial f}{\partial p}$, $\frac{\partial f}{\partial m}$, and $\frac{\partial f}{\partial \ell}$ are components of the Jacobian of y, which we will show later. The sensitivities $S^p_{k_p}$, $S^m_{k_p}$, and $S^\ell_{k_p}$ make up our total sensitivity of k_p. Putting all of this together gives us

$$S'_{k_p} = \frac{\partial f}{\partial k_p} + \frac{\partial f}{\partial y} \cdot S_{k_p}.$$

Where $\frac{\partial f}{\partial t}$ is the Jacobian of the system,

$$\frac{\partial f}{\partial t} = \begin{bmatrix} k_p(1-2p) - k_{pm} m & -k_{pm} p & 0 \\ k_{pm} m(1-m) & k_{mp} p(1-2m) + \ell - 2m\ell - 1 & m(1-m) \\ 0 & \frac{k_{\ell m} \operatorname{sech}^2(\frac{m-\theta}{w})}{w} & -k_e ll. \end{bmatrix}$$

Applying this process for every parameter gives us

$$\begin{aligned} S'_{k_p} &= \tfrac{\partial f}{\partial t} S_{k_p} + [p(1-p), 0, 0]^T \\ S'_{k_{pm}} &= \tfrac{\partial f}{\partial t} S_{k_{pm}} + [-mp, 0, 0]^T \\ S'_{k_{mp}} &= \tfrac{\partial f}{\partial t} S_{k_{mp}} + [0, pm(1-m), 0]^T \\ S'_{k_{\ell m}} &= \tfrac{\partial f}{\partial t} S_{k_{\ell m}} + \left[0, 0, 1 + \tanh(\tfrac{m-\theta}{w})\right]^T \\ S'_{\theta} &= \tfrac{\partial f}{\partial t} S_{\theta} + \left[0, 0, -\frac{k_{\ell m} \operatorname{sech}^2(\frac{m-\theta}{w})}{w}\right]^T \\ S'_{w} &= \tfrac{\partial f}{\partial t} S_{w} + \left[0, 0, -\frac{k_{\ell m}(m-\theta) \operatorname{sech}^2(\frac{m-\theta}{w})}{w^2})\right]^T \\ S'_{k_\ell} &= \tfrac{\partial f}{\partial t} S_{k_\ell} + [0, 0, -l]^T. \end{aligned}$$

We now have a differential equation for the sensitivity of each parameter. We assume that the

parameter values do not affect the initial conditions of the model, and so the initial conditions of each sensitivity is zero. The sensitivities were solved using the ode45 function in MATLAB. The time step for each solution was $dt = 0.1$.

These sensitivities will vary greatly, based on the output of the model. Since the output is dimensionless, the relative difference between these sensitivities and the model output, or elasticity, will be more useful. So, the sensitivities presented in the next chapter are normalized in the following way. For an arbitrary parameter κ we have the normalized sensitivity as

$$\hat{S}_\kappa = S_\kappa \cdot \left(\frac{\kappa}{y}\right) = \frac{\partial y}{\partial \kappa}\left(\frac{\kappa}{y}\right).$$

Where k is the value of the parameter and y is the output vector of the model. The normalization is applied pointwise for every time step. For example, at some arbitrary time t^* we have that the sensitivity of an arbitrary parameter κ is a vector containing the sensitivities for each variable at time t^* as such: $S_\kappa = \left[S_\kappa^{p*}, S_\kappa^{m*}, S_\kappa^{\ell*}\right]^T$. To obtain the normalized sensitivity at t^* we multiply each of these by the fixed scalar κ, and divide by the output vector of the model at time t^*, which is $y^* = [p^*, m^*, \ell^*]^T$. Thus at time t^* we have that the normalized sensitivity is

$$\hat{S}_\kappa^* = \left[S_\kappa^{p*}, S_\kappa^{m*}, S_\kappa^{\ell*}\right]^T \cdot \frac{\kappa}{[p^*, m^*, \ell^*]^T}.$$

CHAPTER 4

RESULTS

Presented here are the results of the local sensitivity analysis for each of the simulation cases from Chapter 2. The sensitivities are displayed based on the associated variable, so each simulation has figures for sensitivities with respect to p, m, and ℓ. The value of the sensitivity indicates the effect of that parameter. A positive sensitivity means that an increase in the parameter causes an increase in the variable. A negative sensitivity indicates that an increase in that parameter's value will cause a decrease in value for a respective variable. For example, if the sensitivity of k_p with respect to p is positive at some point in time, then increasing the value of k_p would lead to a higher value of p at that same point in time.

4.1 Healthy Response

The healthy response was the first model simulation we looked at. The healthy response scenario was established to represent the standard way in which an infection could be cleared. The conditions are set to represent the response of a healthy individual to a standard infectious agent. The output of this model was presented in Figure 2.2. Recall that in this scenario the value of p was fixed at zero once it dropped below the threshold of $p = 0.0005$. We fix p to simulate the infection being "cleared" and thus unable to return. The threshold is crossed around $t = 5$.

Starting with Figure 4.1 we have the sensitivities of p with respect to the healthy response. After the threshold for p is crossed the value of p is fixed at 0. Thus the sensitivities of p are zero once the threshold is passed, since the parameters no longer affect the model. In Figure 4.1 the sensitivities are not shown once $p = 0$, for clarity.

We see k_p with a strong positive swing at the outset of the healthy response, which is expected as it is the growth rate of the pathogen, p. However, once the early mediator, m, builds up, the sensitivity dips to strongly negative, as m has a strong negative influence on p.

We see k_{pm} start with a negative influence on p, which is expected since k_{pm} is the decay rate of p with respect to m. In the same way that k_p shifts negative, we see that k_{pm} shifts to the positive with the decline of p and the rise of m. For k_{mp}, the growth rate of m with respect to p,

we see a decreasing negative sensitivity that starts to increase when the value of m peaks.

As for the rest, we have θ with an increasing positive sensitivity, since an increase in θ causes a decrease in ℓ, which causes an increase in p. Similarly, k_ℓ is always positive and increasing in sensitivity towards p since it is the decay rate of ℓ. A lower value of ℓ causes there to be less m and thus more p. The activation width, w, is always negative and decreasing, because a higher w will cause ℓ to rise which leads to lower p. The growth rate of ℓ with respect to m, $k_{\ell m}$, also has a negative and decreasing trend. Higher $k_{\ell m}$ leads to more ℓ which causes lower p.

In Figure 4.2 and Figure 4.3 we have the sensitivities of m in the healthy response scenario, with the latter being the same data with a smaller y-axis. We see w and $k_{\ell m}$ with increasing positive sensitivities as both of these only serve to increase ℓ. Increased ℓ causes increased m. The pathogen growth rate, k_p, has an early spike that lines up with the growth of the pathogen in the model. Since p stimulates growth in m, the effect of k_p on m is relative to the value of p. The sensitivity of k_p stabilizes after p is cleared, maintaining positive sensitivity. The growth rate of m with respect to p, k_{mp}, has a sensitivity near zero throughout the model. The negative sensitivities of k_{pm}, θ, and k_ℓ is due to θ and k_ℓ reducing the value of ℓ which lowers m, and similarly k_{pm} reduces p which also reduces m.

The sensitivity of ℓ is shown in Figure 4.4. Here we see that k_p, k_{pm}, and k_{mp} have sensitivities very near to zero throughout. For $k_{\ell m}$ we see a generally positive sensitivity, as this is the growth rate of ℓ with respect to m. For k_ℓ we see a generally negative sensitivity as expected due to its role as a decay rate for ℓ. For w and θ we have that θ has a negative sensitivity, and w has a positive sensitivity.

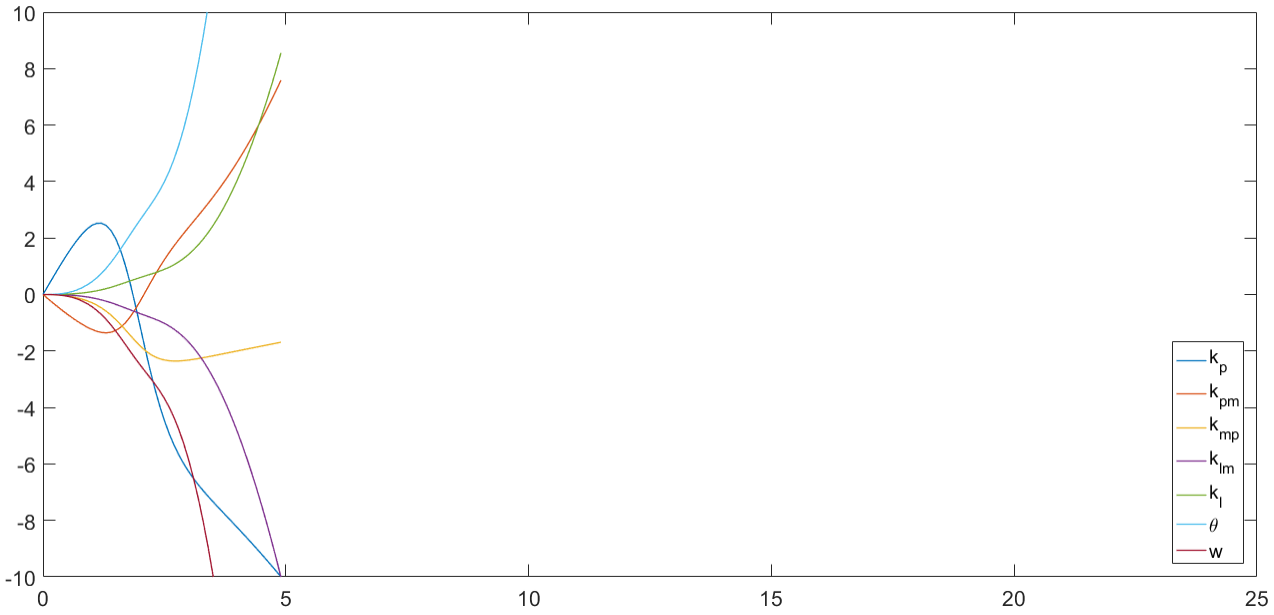

Figure 4.1: Sensitivities of p in Healthy Response Since p becomes zero near $t = 5$ the sensitivities would also become zero. They are not displayed after $t = 5$ for clarity.

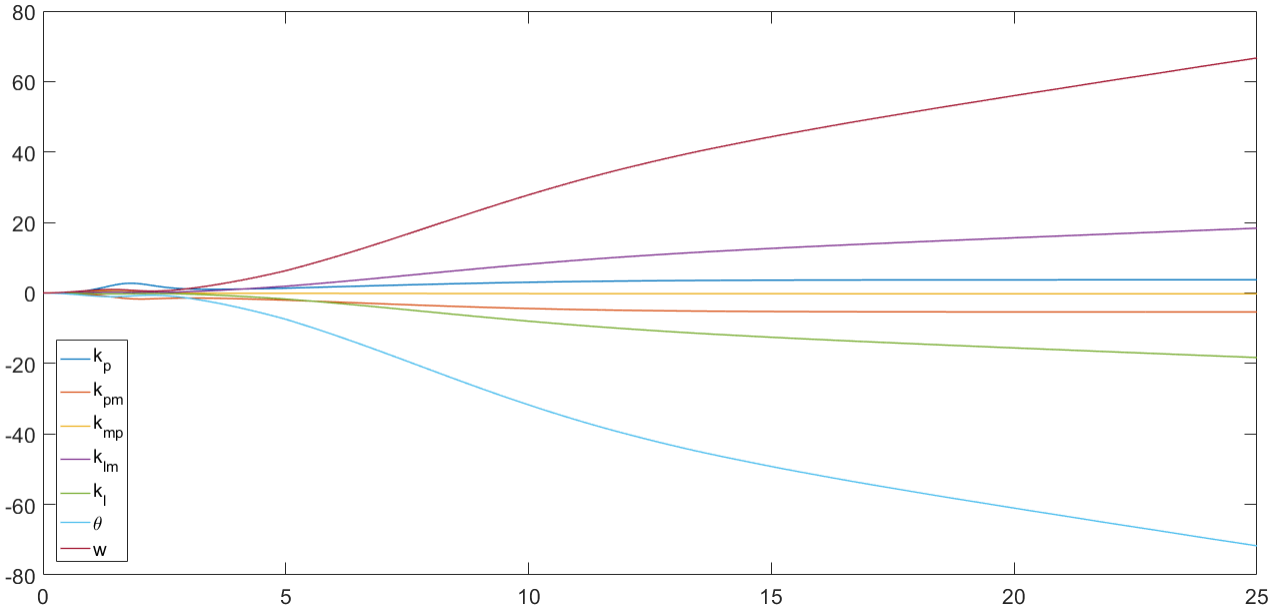

Figure 4.2: Sensitivities of m in Healthy Response

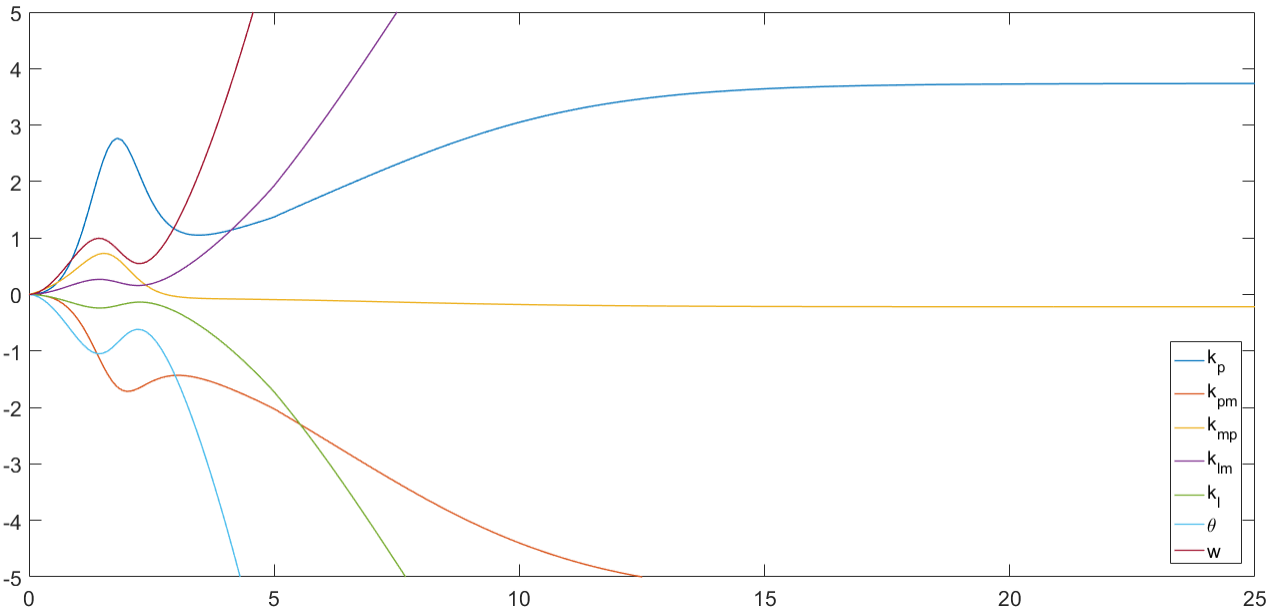

Figure 4.3: Sensitivities of m in Healthy Response (Alternative) The y-axis has been constrained here for clarity in the early portions of the graph.

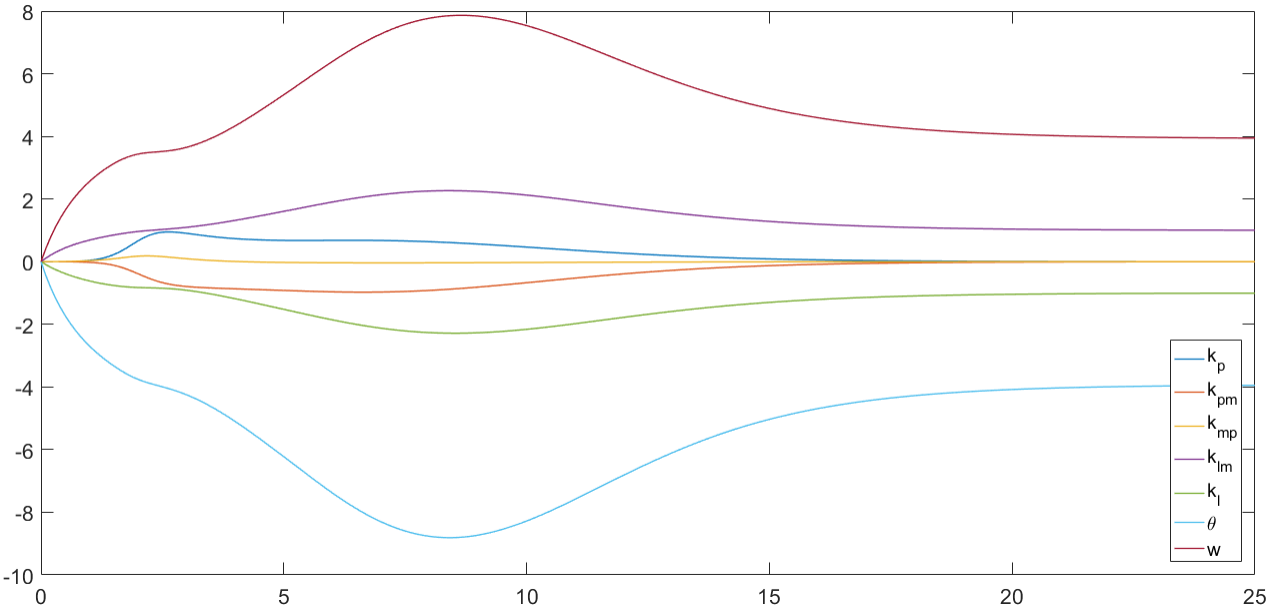

Figure 4.4: Sensitivities of ℓ in Healthy Response

4.2 Persistent Non-Infectious Inflammation

Recall that persistent non-infectious inflammation is the case where the immune system clears the infection, but the inflammatory response continues despite the infection being gone. The output of the model was presented in Figure 2.3. The sensitivity of p in non-infectious inflammation is shown in Figure 4.5. Since the infection is cleared completely, the value of the pathogen is fixed at zero once it drops below the threshold of $p = 0.0005$. Once again, the sensitivities are not shown past this point for clarity, but they are zero once the threshold is crossed.

The sensitivities of p are very similar to the healthy response case. We see k_p starts positive, but quickly turns negative, as once the value of m is high enough, k_p becomes a decay factor. For k_{pm} we see it begin negative, then increase, similar to the healthy response. The increased sensitivity of k_{pm} is again due to m becoming significantly larger than p. The sensitivity of k_{mp} is different from the healthy response, rather than increasing it continues to decrease over the entire time for which p is active. The increasing sensitivity is due to the value of m being unchanging here, while in the healthy response m declines.

The sensitivities of $k_{\ell m}$ and k_ℓ are similar to the healthy response. We have that k_ℓ is positive because it is a decay rate of ℓ, and $k_{\ell m}$ is negative as it is the decay rate. Similarly θ is positive, and w is negative. These sensitivities indicate that ℓ affects p similarly here as it does in the healthy response.

The sensitivity of m in non-infectious inflammation is shown in Figures 4.6 and 4.7 where the latter has a smaller y-axis. We again have a lot of similarities to the healthy response, with θ and w having sensitivities nearly double in magnitude to the nearest counterpart. Around $t = 0.5$ we see a small peak in the sensitivity of k_{mp}. All of the sensitivities of m approach zero once the system reaches equilibrium.

Figures 4.8 and 4.9 show the sensitivities of ℓ in persistent non-infectious inflammation. The overall shape and position of the curves is nearly identical to the sensitivities of m. The parameters more specific to ℓ play a larger role, so the magnitudes of k_ℓ, $k_{\ell m}$, θ, and w are larger. The final state of the sensitivities are larger than in m, but still relatively near zero. We again have that around $t = 10$ is when the sensitivities are largest, and after $t = 15$ they become

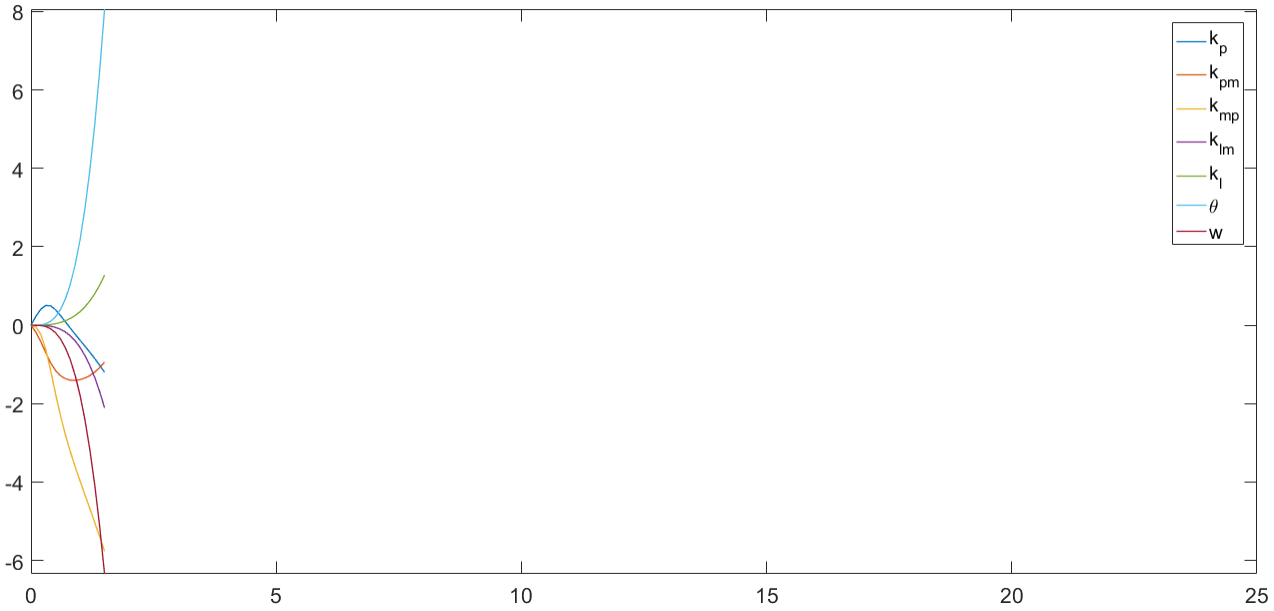

Figure 4.5: Sensitivities of p in Persistent Non-Infectious Inflammation A threshold of $p < 0.0005$ is used here, similar to the healthy response. Without it, the sensitivities are very erratic as p is very near zero.

negligible.

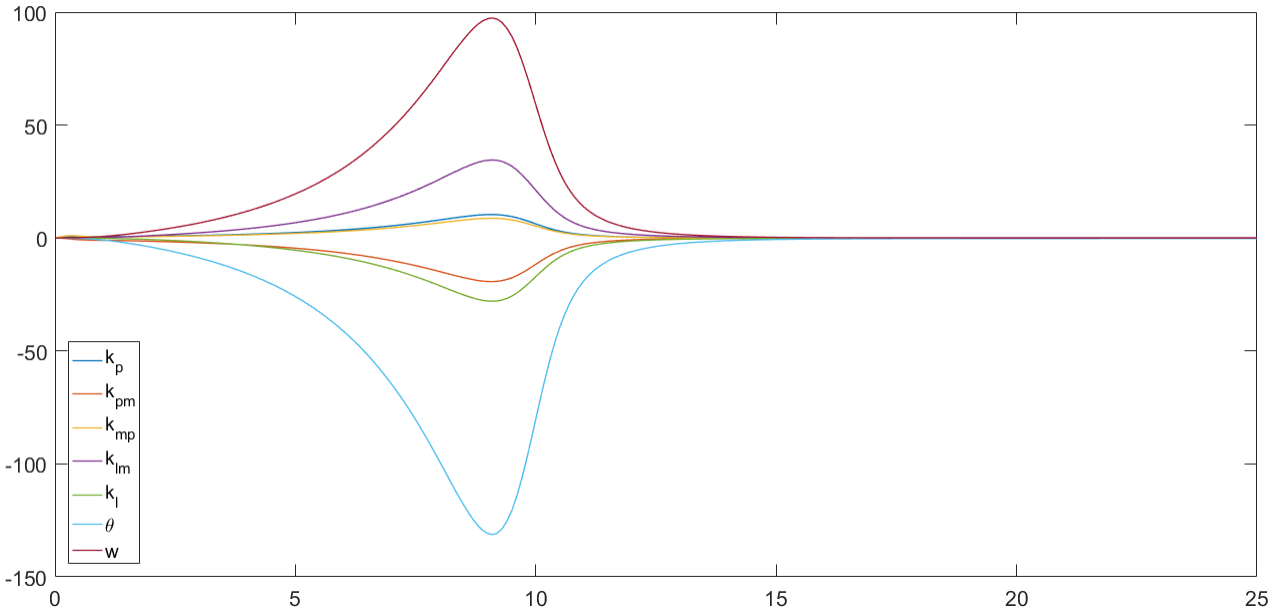

Figure 4.6: Sensitivities of m in Persistent Non-Infectious Inflammation

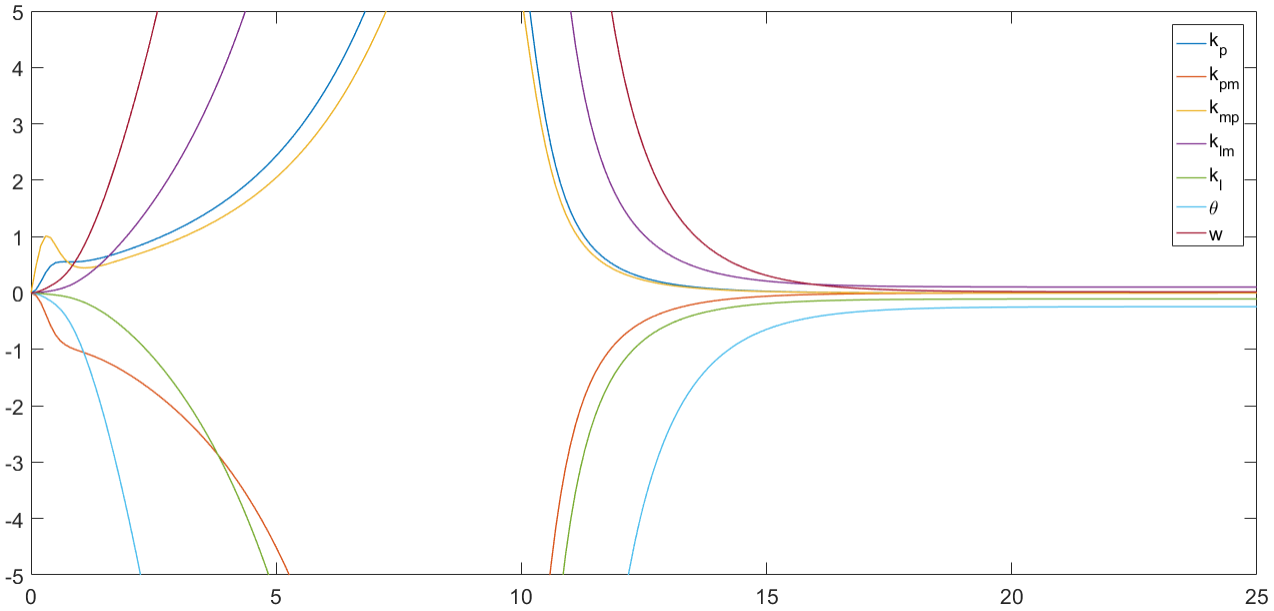

Figure 4.7: Sensitivities of m in Persistent Non-Infectious Inflammation (Alternative)
Reproduction of Figure 4.6 with restricted y-axis for clarity.

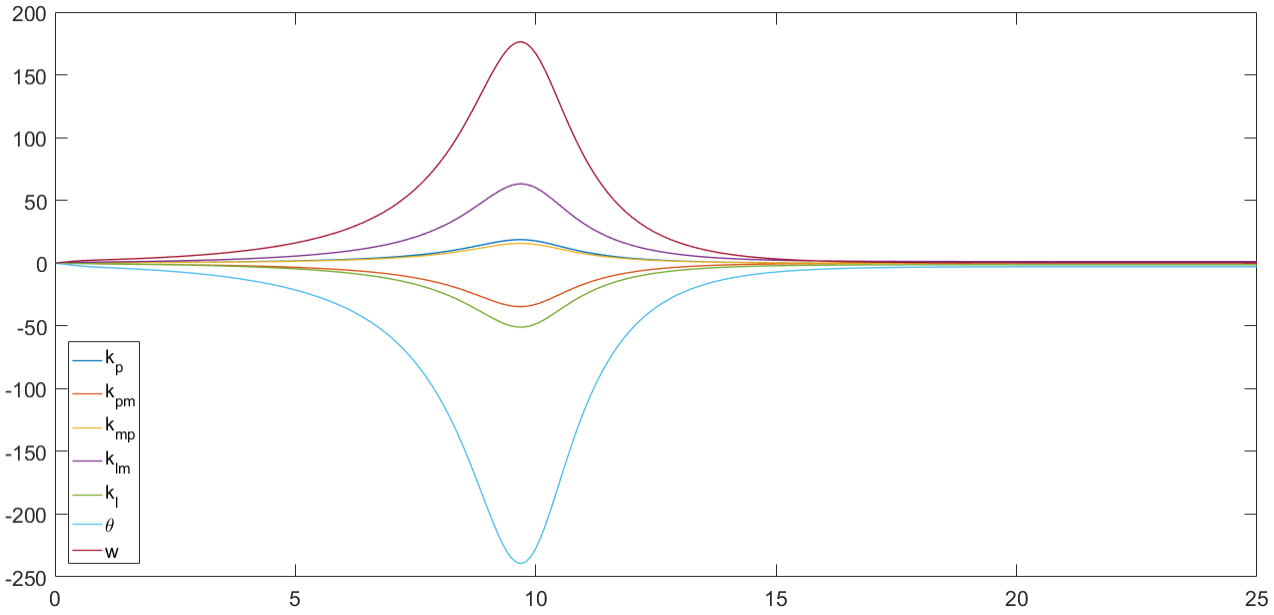

Figure 4.8: Sensitivities of ℓ in Persistent Non-Infectious Inflammation

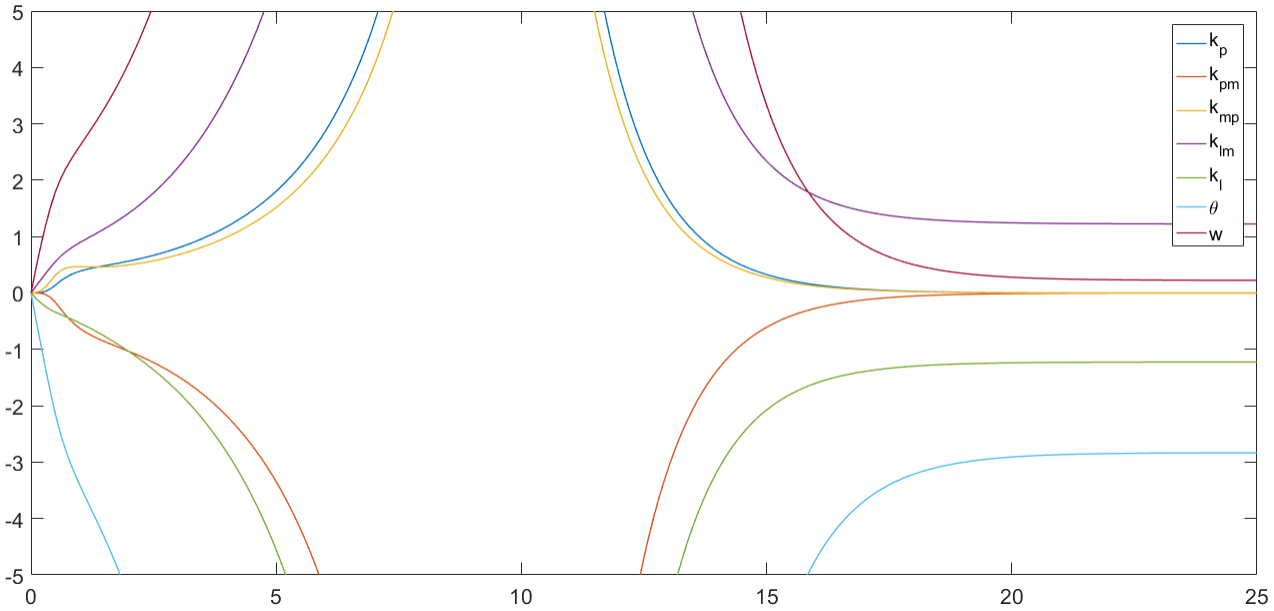

Figure 4.9: Sensitivities of ℓ in Persistent Non-Infectious Inflammation (Alternative)
Reproduction of Figure 4.8 with restricted y-axis for clarity.

4.3 Persistent Infectious Inflammation

The model for persistent infectious inflammation, presented in Figure 2.4, is similar to persistent non-infectious inflammation. One difference is that the pathogen is never fully cleared, despite the early and late mediators rising to levels similar to non-infectious inflammation. Since the infection remains, the threshold of $p = 0.0005$ is never reached, unlike the previous two simulations.

The sensitivities of p with persistent infectious inflammation are shown in Figure 4.10. At the beginning we see k_p is the only parameter with significant sensitivity. Since it is the growth factor of p, this seems reasonable. Around $t = 2$ the other parameters spread out a small amount, with θ and k_ℓ being slightly positive while w, k_{mp}, and $k_{\ell m}$ are slightly negative. Another parameter of note for p is k_{pm}, as it becomes strongly negative as the system reaches equilibrium. Since k_{pm} is a decay rate of p with respect to m this is expected.

For the sensitivities of m in persistent infectious inflammation we have Figure 4.11. We have that m is only significantly sensitive to the parameters very early in the model, around $t = 2$. The parameter k_p has the most significant positive influence on m. It is the growth factor for p and a higher value of k_p would lead to a higher value of p which would recruit more m. By $t = 2.5$ all the sensitivities are very near zero.

Figure 4.12 has the sensitivities of ℓ for persistent infectious inflammation. Again we see w and θ quickly become respectively positive and negative, as we have seen in previous sensitivities. However, as this system reaches equilibrium, w falls below $k_{\ell m}$. The parameter k_p has the largest positive sensitivity around $t = 2.5$ which means it has the greatest positive sensitivity at some point for all three variables.

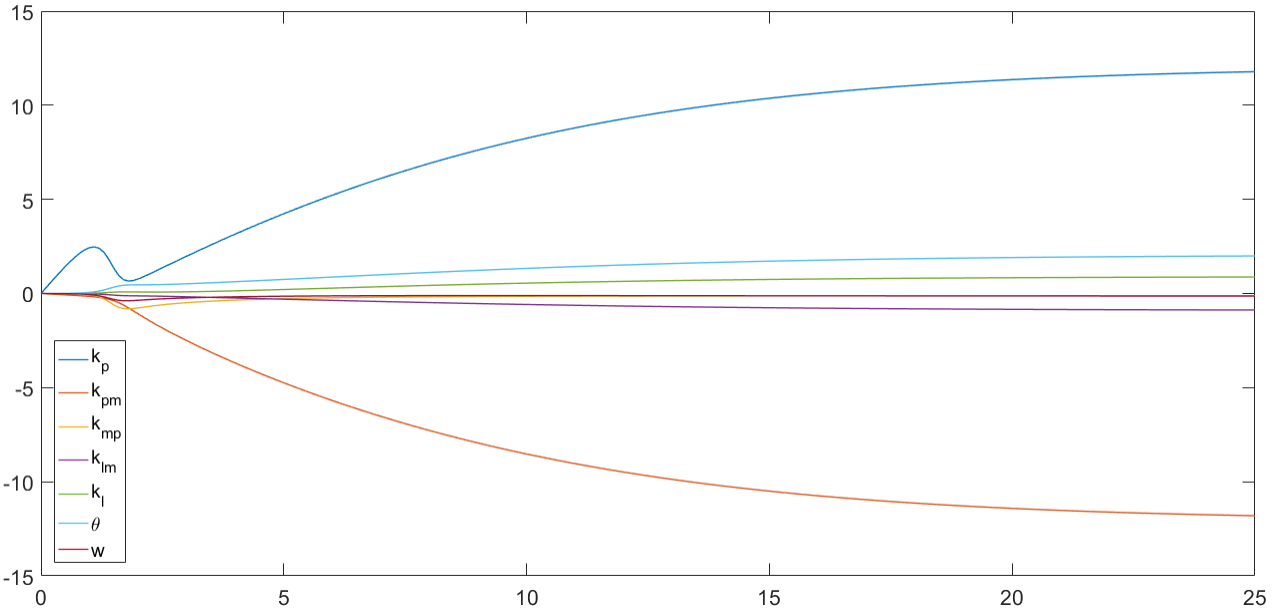

Figure 4.10: Sensitivities of p in Persistent Infectious Inflammation

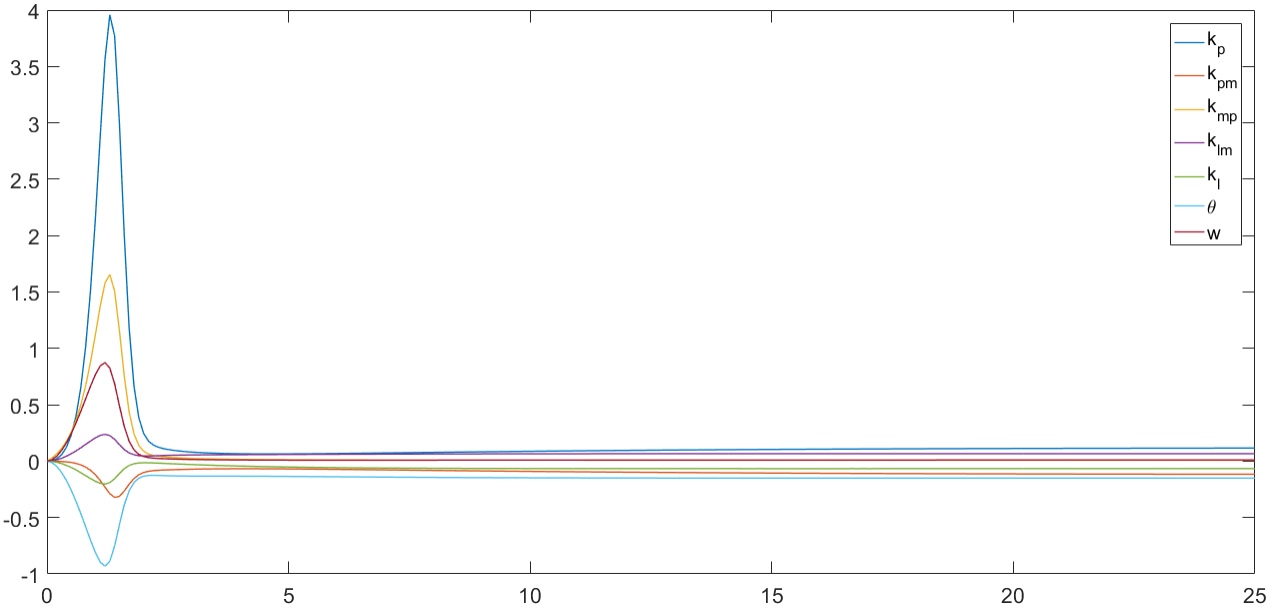

Figure 4.11: Sensitivities of m in Persistent Infectious Inflammation

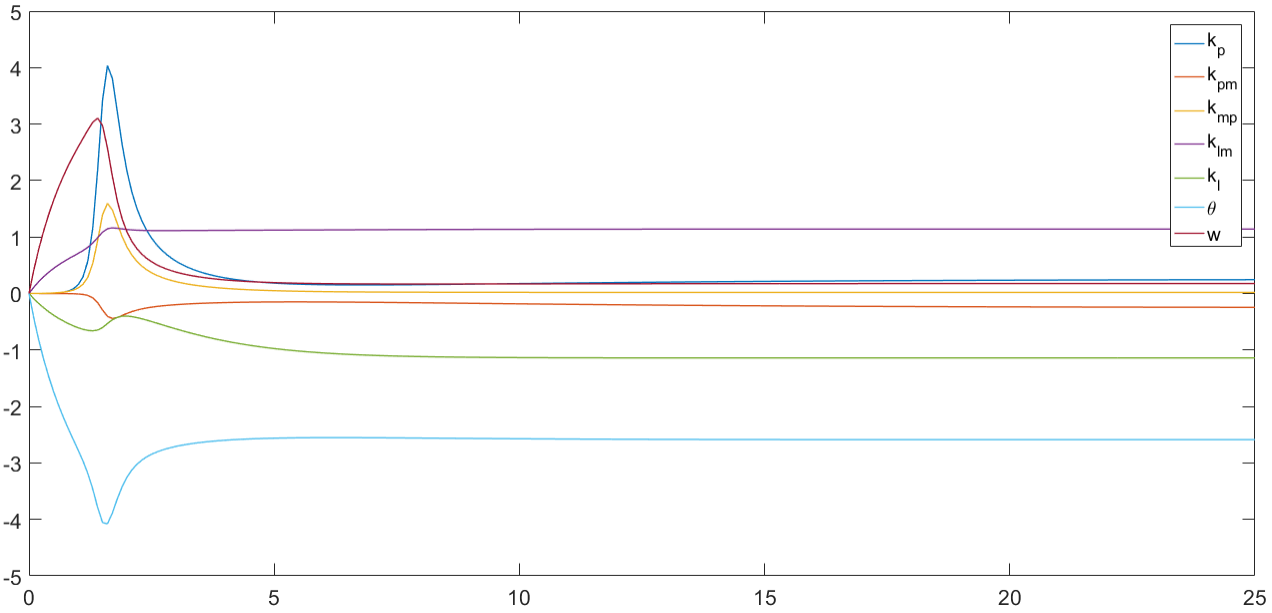

Figure 4.12: Sensitivities of ℓ in Persistent Infectious Inflammation

4.4 Recurrent Infection

Recurrent infection is the simulation where the pathogen has recurrent spikes of growth throughout, which in turn causes the early and late mediators to rise and fall in value. The pathogen is never cleared completely, so it is able to recover from the effects of the inflammatory mediators. The recurrent infection scenario was presented in Figure 2.5.

The sensitivities of p in recurrent infection are shown in Figure 4.13. While very busy at first glance, most of these sensitivities are fairly intuitive. For instance, the sensitivity of k_p rises and falls with p. We have k_p at its maximum value when p is increasing, and is at its lowest value while p is decreasing.

After the system stabilizes around $t = 5$, θ, k_ℓ, and k_{pm} have peaks at the same time as k_p, implying that these parameters are most sensitive when p is increasing. Similarly, k_{mp} also moves in phase with the rest of the system but is always negatively valued. Parameters w and $k_{\ell m}$ peak when the value of p is decreasing.

The sensitivities of m, shown in Figure 4.14, are similar to those of p, only they line up with m. For example k_p is most sensitive when m is increasing and least sensitive while m decreases. The same is true of k_{mp}. After $t = 5$ the parameters k_ℓ, k_{mp}, and w have peaks with k_p and k_{mp} as

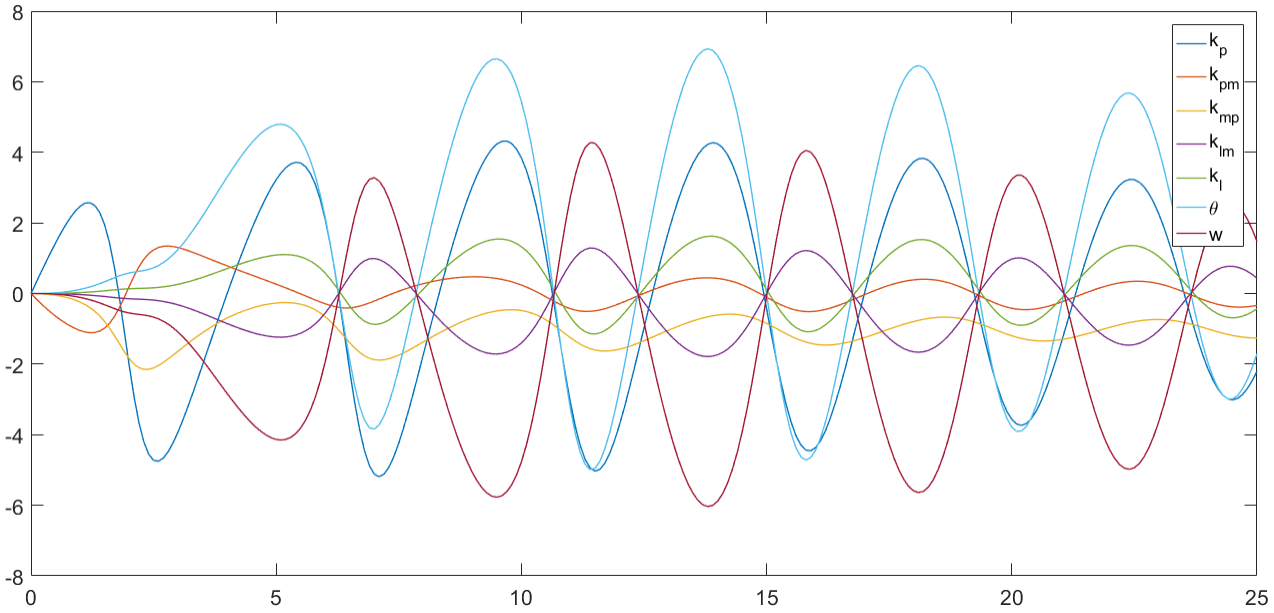

Figure 4.13: Sensitivities of p in Recurrent Infection

well. Note, though, that k_ℓ and k_{mp} are positive when m is increasing, while w is always negative. Thus, w is least sensitive when m is increasing, while k_ℓ and k_{mp} are most sensitive at this time.

However, before $t = 5$ we have that θ and k_{pm} have troughs where m is increasing, while k_ℓ is effectively zero. The troughs could be caused by the high value of p at this time or the rapidly increasing value of ℓ. A similar effect occurs with w and k_ℓ which have small peaks for the first rise of m, but both are strongly negative every other time m increases.

Figure 4.15 shows the sensitivities of ℓ in recurrent infection, which are significantly different than p and m. While the sensitivities of ℓ still cycle up and down, the sensitivities retain their values relative to one another. Similar to the other sensitivities of ℓ we have that w and θ are the most sensitive, with w being positive, and θ negative. Also, $k_{\ell m}$ is the second most positive sensitivity, with k_p right below it. Likewise, k_ℓ is the second strongest negative sensitivity, followed by k_{pm}.

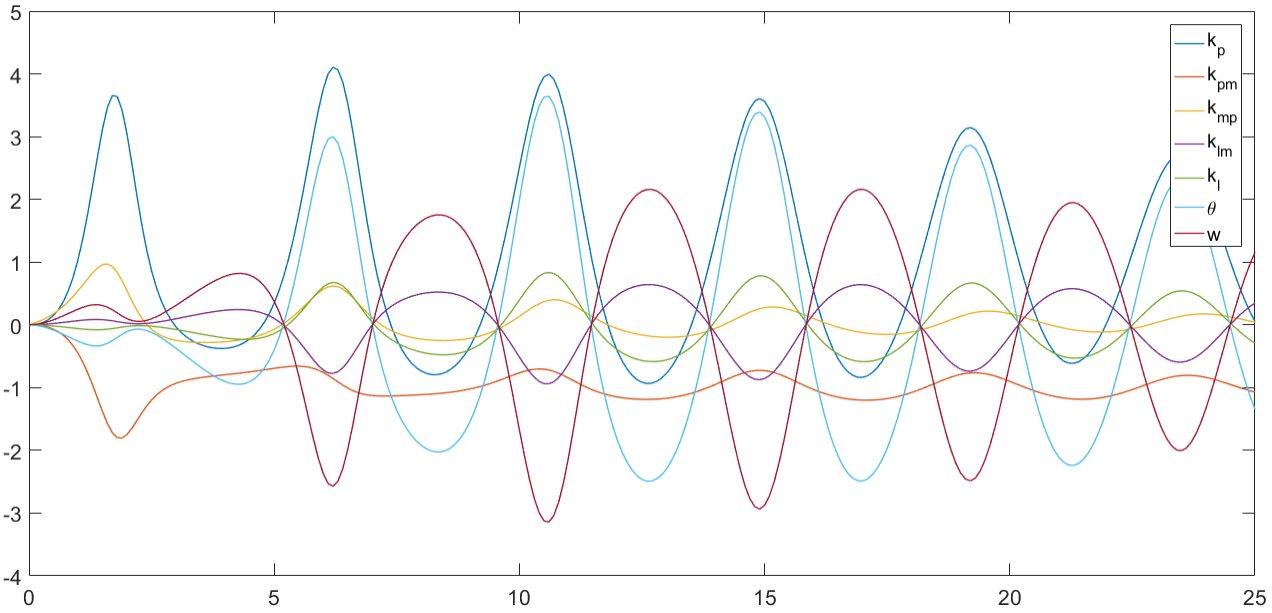

Figure 4.14: Sensitivities of m in Recurrent Infection

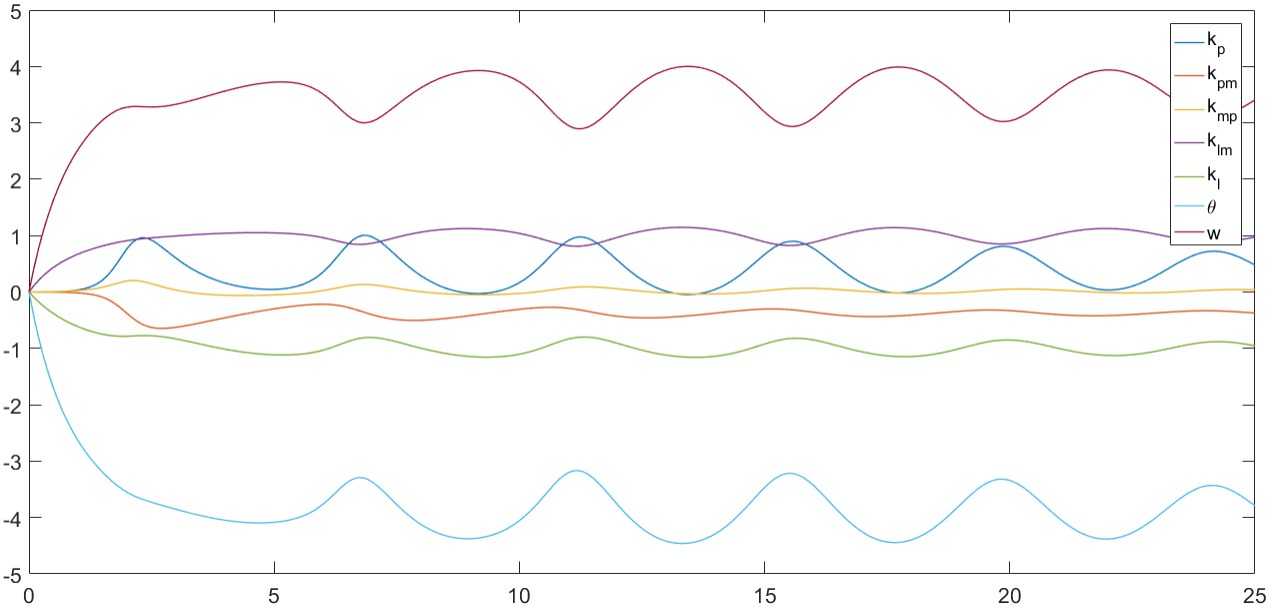

Figure 4.15: Sensitivities of ℓ in Recurrent Infection

4.5 Severe Immunodeficiency

The model of immunodeficiency was shown in Figure 2.6. Recall that it had rapid proliferation of pathogen with almost no rise in m or ℓ due to a very low value of k_{mp}. The scenario is meant to simulate the effects of an immunodeficiency disorder, such as AIDS.

The sensitivities of p, shown in Figure 4.16, begin with a strong positive sensitivity of k_p and negative sensitivity for k_{pm}. Both of these parameters, however, are very nearly zero by $t = 10$ as p approaches its carrying capacity. As with the other sensitivities for p, we have positive sensitivities for θ and k_ℓ and negative sensitivities for $k_{\ell m}$ and k_{mp}. The sensitivity of k_{mp} is negligible, though, as it is almost always zero.

Figure 4.17 has the sensitivities of m with immunodeficiency. Since the value of the early mediators is very small and relatively unchanging in this case, we have that the sensitivities are almost identical to that of the healthy response. The parameters w, $k_{\ell m}$ and k_{mp} are positive, while θ and k_ℓ are negative. Similar to the healthy case, k_p and k_{pm} are negligible.

The sensitivities of ℓ in immunodeficiency, shown in Figure 4.18, are also very similar to the healthy counterparts. The parameters w and $k_{\ell m}$ are again positive, while θ and k_ℓ are negative. The others, however, are different from what we have seen before, as k_{pm}, k_{mp}, and k_p are all effectively zero for all t. The low sensitivities likely arise from how static the late mediators are in immunodeficiency, as ℓ does not change significantly from its starting value.

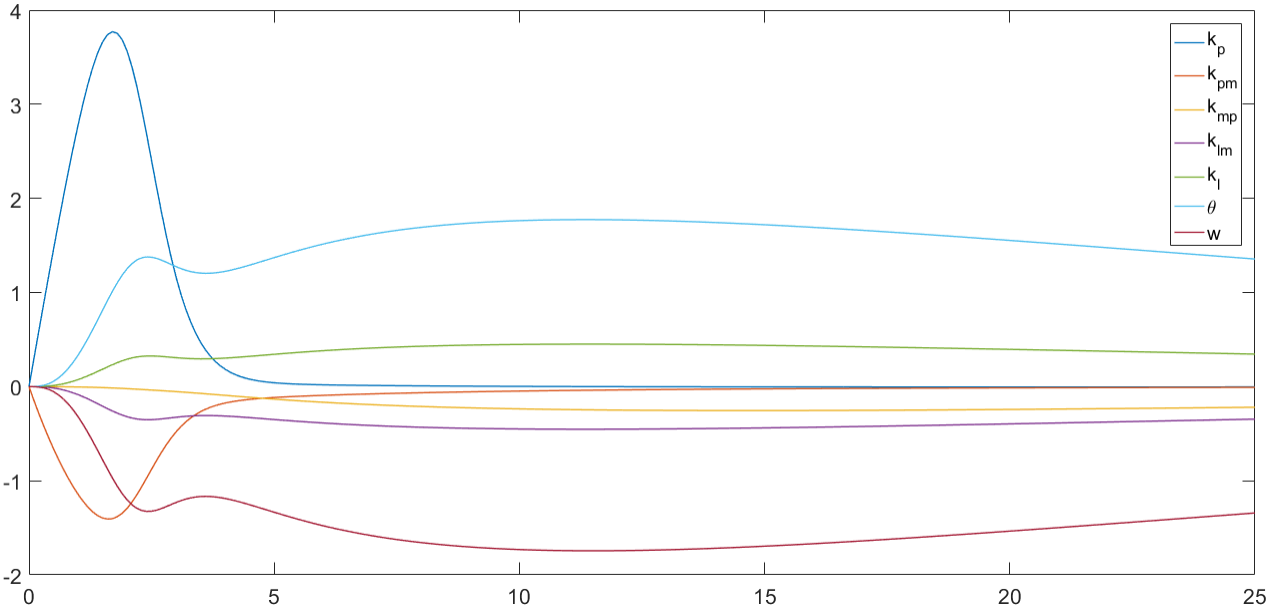

Figure 4.16: Sensitivities of p in Severe Immunodeficiency

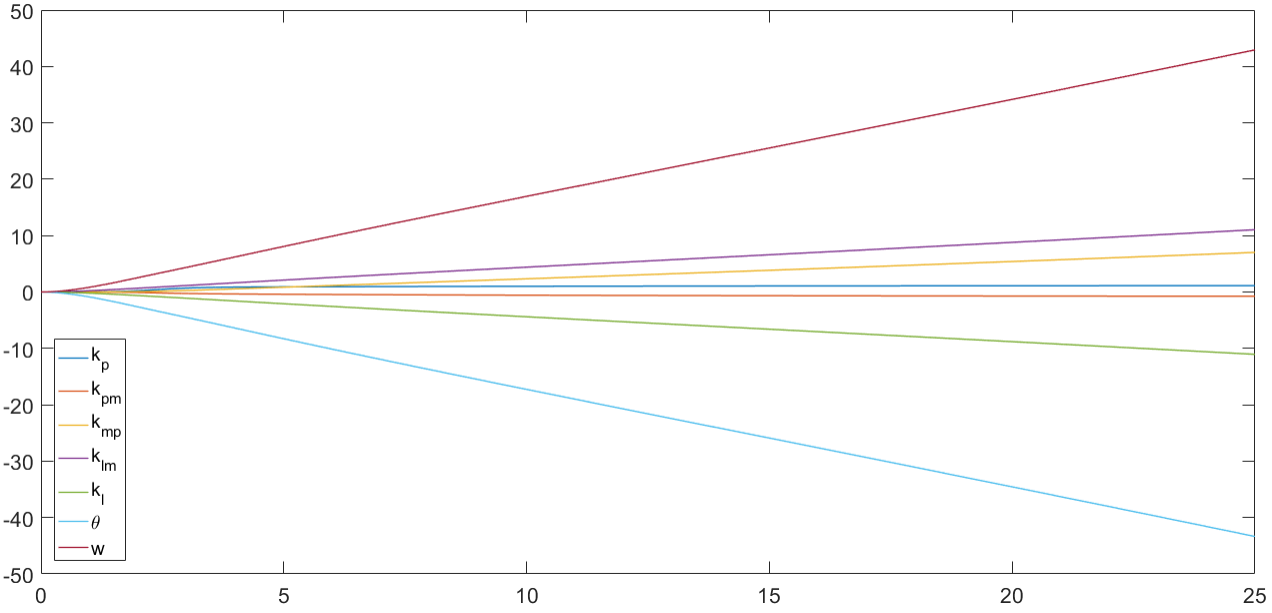

Figure 4.17: Sensitivities of m in Severe Immunodeficiency

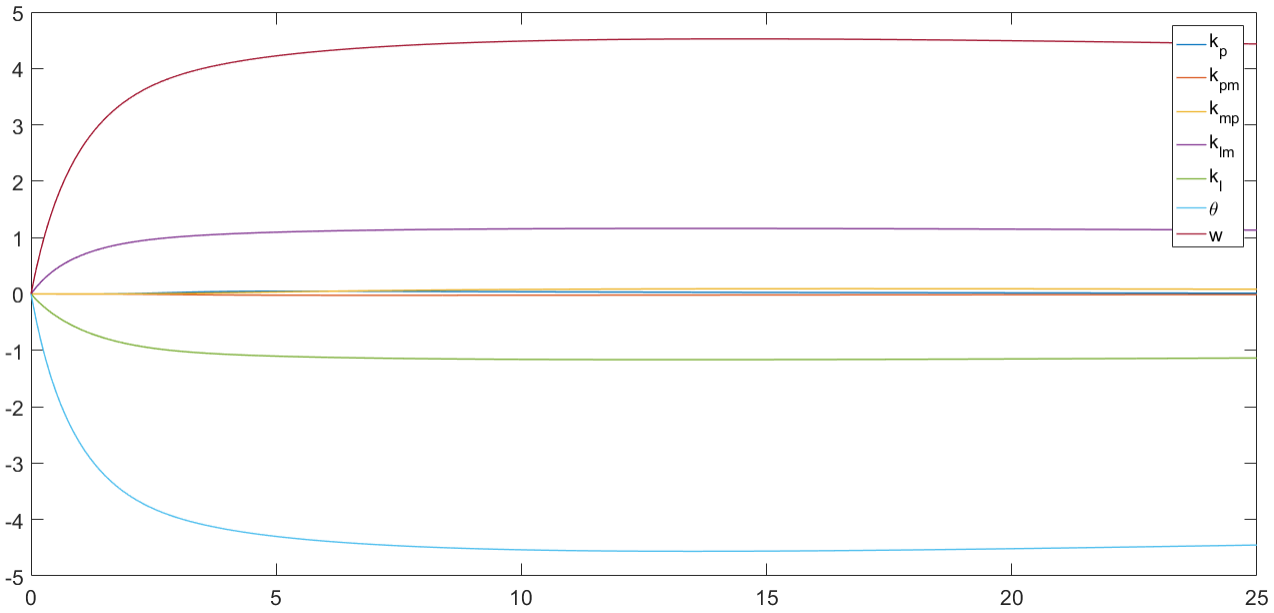

Figure 4.18: Sensitivities of ℓ in Severe Immunodeficiency

CHAPTER 5

DISCUSSION

One of the first things worth addressing is the overall impact of each parameter in our model. Across most of the scenarios presented here there are clear patterns in the sensitivities of the parameters. We will also compare the overall sensitivities as they pertain to the three variables, p, m, and ℓ. It is also worth noting that there are other models of the inflammatory response that better emulate the biological processes involved. We will look at one of those models and compare the differences to the one we used.

5.1 Parameters

The growth rate of the pathogen, k_p, is unsurprisingly positive at the start of every simulation. Since we always begin at similar values of m and ℓ, we have that k_p has a positive influence on all three variables at the start. The sensitivity of k_p only becomes negative in a few cases. In Figures 4.1 and 4.5 p becomes a negative influence on itself causing the sensitivity of k_p to be negative until the threshold is reached. The sensitivity of k_p is also negative in parts of Figures 4.13 and 4.14 due to the periodic nature of those sensitivities.

The positive sensitivity of k_p is because p is necessary for the growth of m and ℓ, so while k_p is the direct growth rate of p, it indirectly causes growth in m and ℓ as well. A decrease in k_p would have the effect of both lowering the growth of p and preventing an inflammatory response. The parameter k_p is not an ideal target for treatment, however, as it is generally a property of the pathogen itself. Thus k_p is not easily controlled and will vary based on the pathogen.

For k_{pm}, which is the value of the effectiveness at which m is able to destroy p, we see that its sensitivity is generally negative for p, m, and ℓ in every scenario. The only place where k_{pm} has a positive sensitivity is in Figures 4.1 and 4.13. In Figure 4.1 the negative sensitivity is due to the previously explained nature of p in the healthy response, and in Figure 4.13 the negative sensitivity is due to the nature of recurrent infection.

The effect of k_{pm} opposes k_p, and since it is the decay rate of p this is expected. In terms of treatment for sepsis, increasing the value of k_{pm} would suppress the inflammatory response and

could still allow for the pathogen to be cleared. Care needs to be taken, though, to ensure that the immune response is left strong enough to effectively clear the pathogen.

Moving on to k_{mp}, which is the growth rate of m due to p, we have that the sensitivity is mostly negative for p, while positive for m and ℓ. While this holds across every scenario, it is also the case that k_{mp} is almost always the least sensitive parameter as well. It frequently holds a value of zero, and outside of a few spikes, is almost always the sensitivity of the lowest magnitude.

Increasing k_{mp} both increases the immune response, and ultimately suppresses the growth of the pathogen. The combined effect makes it an ideal avenue for potential treatment of the case of immunodeficiency. The parameter k_{mp} is the only value lowered in the model from the healthy response to produce the immunodeficient case, so this may be obvious. However, the low magnitude of the sensitivities could indicate that k_{mp} might not be enough by itself.

Recall that $k_{\ell m}$ is the growth rate of ℓ due to m. Similar to k_{mp} the sensitivities of $k_{\ell m}$ are generally negative for p and positive for m and ℓ. The only exception here is the recurrent infection case where $k_{\ell m}$ cycles from positive to negative in the sensitivities of p and m. Also, the magnitude of the sensitivities are generally higher than k_{mp}.

Since $k_{\ell m}$ is dependent on m, it is likely not suitable for use as a treatment for immunodeficiency, as there is little change in m to stimulate a growth for ℓ. For the septic cases, $k_{\ell m}$ could be more useful. Within our model ℓ has a fixed decay rate and will correct for itself. Thus, increasing $k_{\ell m}$ stimulates higher ℓ, lowering the value of p. Then ℓ will decay back to equilibrium on its own. However, a high value of ℓ could cause unintended damage, initiating secondary inflammatory responses, which this model does not account for.

The death rate of ℓ, which is k_ℓ, opposes the effect of $k_{\ell m}$. The sensitivities of k_ℓ are generally positive for p and negative for m and ℓ. Similar to k_ℓ the sensitivities of p and m switch back and forth in the recurrent infection case. The magnitude of the sensitivities of k_ℓ are generally similar to that of $k_{\ell m}$ as well.

Increasing k_ℓ could be a viable treatment for the septic cases, as it lowers ℓ which should also bring m down as well. Care would need to be taken, however, as lowering ℓ too far could lead to a proliferation of p. Another opportunity would be to increase both $k_{\ell m}$ and k_ℓ in tandem. Doing both would cause a larger response of ℓ to eliminate the pathogen followed by a faster decline in ℓ.

Balancing the two together could be a challenge, but it could be an effective way to clear the pathogen in a way that prevents sepsis from occurring.

Recall that θ and w are the activation threshold and width, respectively. The activation threshold, θ, controls when ℓ is recruited in response to m. The activation width, w, represents how quickly this occurs once the threshold is crossed. We have that the sensitivities of these two parameters are generally opposed to one another. The sensitivities of θ are mostly positive for p and negative for m and ℓ, while w is generally has a negative sensitivity for p and positive for m and ℓ.

While these two parameters seems to be mostly linked to ℓ, and their sensitivities are similar to $k_{\ell m}$ and k_ℓ, the magnitudes indicate that the effects for θ and w are much more significant. In terms of treating potential septic situations, increasing θ, or decreasing w, would drastically reduce the response of m and ℓ, but would also have a large positive effect on the growth of the pathogen.

5.2 A Different Model

It has already been discussed that the model presented here is not completely consistent with the biology of inflammation. Recall that the late mediators, which involve both pro and anti-inflammatory components, are difficult to simulate with one equation. A more advanced model could be constructed which better simulates the underlying biology. One such model already exists [4].

The model presented in [4] separates the pro and anti-inflammatory elements of the late mediators and has separate equations for each. It also includes a fourth variable to account for tissue damage, which can be a significant cause of further inflammation. In addition, it takes into account the availability of inflammatory factors that have not been activated.

The primary drawbacks of this more biologically accurate model are that it has more than 20 different parameters. That is more than three times the amount in the model used in this study. It is also a four-dimensional system, which further increases complexity. So while the model better fits the biological process of inflammation, it is more difficult to utilize numerically.

5.3 Conclusion

While the model presented is not the most biologically accurate one available, the output of it is consistent with what is expected biologically. The numerous variables and factors involved with the inflammatory response make accurate models difficult to construct. In addition, every step to make the model better emulate biology adds more numerical complexity to the system.

All of the parameters of this model correspond to some real-world factors, and local sensitivity analysis has shown which of these parameters are more influential in certain scenarios. The positive feedback involved with inflammation makes sepsis a difficult condition to treat, but further work with modeling it could indicate the best factors to target.

APPENDIX A

Model Parameter Values

Model	$p(0)$	$m(0)$	$\ell(0)$	k_p	k_{pm}	k_{mp}	$k_{\ell m}$	k_ℓ	θ	w
Healthy Response	0.01	0.05	0.539	3	30	25	15	1	1	0.5
Persistent Non-Infectious Inflammation	0.2	0.05	0.539	3	30	25	15	1	1	0.5
Persistent Infectious Inflammation	0.01	0.05	0.539	3	3	25	15	1	1	0.5
Recurrent Infection	0.01	0.05	0.179	3	30	25	5	1	1	0.5
Severe Immunodeficiency	0.01	0.05	0.539	3	30	0.4	15	1	1	0.5

Table A.1: Scenario Parameter Values and Initial Conditions These are the parameter values for each scenario presented in Chapter 2. These scenarios and their initial condtions are presented in the 2004 paper *The Dynamics of Acute Inflammation*[2].

APPENDIX B

MATLAB Code for Model Solutions

```
%The following code solves the model equations
%presented in Chapter 2

global kpm kp kmp klm kl theta w;
kpm = 30; %Parameters for Healthy Response
kp = 3.1; %Replace with values in Table A.1
kmp = 25; %To recreate other simulations
klm = 15;
kl = 1;
theta = 1;
w = 0.5;
p0 = 0.01; %Initial pathogen
m0 = 0.05; %Initial early mediator
l0 = 0.539;%Initial late mediator
 initialt = 0; %Initial time
 finalt = 25; %Final time
dt = 0.1; %Time-step interval
tspan = initialt :dt: finalt ; %Construct time vector
y0 = [p0,m0,l0]; %Vector of initial conditions

[t,y] = ode45(@odefun,tspan,y0); %Solve system without threshold
[a,b] = ode45(@odesol,tspan,y0); %Solve system with threshold

%This function solves the system as is
%without the use of the threshold for p
function dydt = odefun(t,y)
    global kpm kp kmp klm kl theta w;
    dydt = zeros (3,1); %non-threshold output vector
    dydt(1) = kp*y(1)*(1-y(1))-kpm*y(2)*y(1); %Equation 2.1 for pathogen
    dydt(2) = (kmp*y(1) + y(3))*y(2)*(1-y(2))-y(2); %Equation 2.2 for early mediators
    dydt(3) = klm*(1+tanh((y(2) - theta)/w)) - kl*y(3); %Equation 2.3 for late mediators
```

```
end

%This function is for solving the system with threshold
%p is held at 0 after dropping below 0.0005, note this
%will only effect Healthy response and persistent
%non-infectious inflammation
function dbdt = odesol(a,b)
    global kpm kp kmp klm kl theta w;

    if b(1) < 0.0005 %Apply threshold
        b(1) = 0;
    end
        dbdt = zeros (3,1); %threshold output vector
        dbdt(1) = kp*b(1)*(1-b(1))-kpm*b(2)*b(1); %Equation 2.1 for pathogen
        dbdt(2) = (kmp*b(1) + b(3))*b(2)*(1-b(2))-b(2); %Equation 2.2 for early mediators
        dbdt(3) = klm*(1+tanh((b(2) - theta)/w)) - kl*b(3); %Equation 2.3 for late mediators

end
```

APPENDIX C

MATLAB Code for Sensitivities

```
%The following code calculates the
% sensitivities presented in Chapter 4

y0 = zeros(1,24); %Define Container vector
%Initial Conditions
y0(1) = 0.01; %Initial pathogen
y0(2) = 0.05; %Initial early mediators
y0(3) = 0.539;%Initial late mediators
%The previous three IC's are for the healthy response
%Update with value from Table A.1 for other simulations
 initialt  = 0;
dt = .1;
 finalt  = 25;
tspan =  initialt :dt: finalt ;
%%Parameter Definition$$
kpm = 30; %Along with variable IC's
kp = 3;     %these are for  Healthy Response
kmp = 25; %For other simulations update
klm = 15;  %with values from Table A.1
kl  = 1;
th = 1;
w = 0.5;
para = [kp kpm kmp klm kl th w]; %parameter vector

%%Solve the DE set up in the JacCalc function%%
[t,y] = ode45(@JacCalc,tspan,y0,[],para);

%Threshold for sensitivities of p below 0.0005
%this prevents divergence
for i = 1 : length(y(:,1))
    if y(i,1) < 0.0005
```

```
32            y(i ,1:3:24)  = 0;
33        end
34    end
35
36    % Normalize Sensitivities by dividing by parameter and variable value
37    yfixed (:,4:6)  = y(:,4:6) .*(para(1)./y (:,1:3) );  % kp
38    yfixed (:,7:9)  = y(:,7:9) .*(para(2)./y (:,1:3) );  % kpm
39    yfixed (:,10:12)  = y(:,10:12) .*(para(3)./y (:,1:3) );  % kmp
40    yfixed (:,13:15)  = y(:,13:15) .*(para(4)./y (:,1:3) );  % klm
41    yfixed (:,16:18)  = y(:,16:18) .*(para(5)./y (:,1:3) );  % kl
42    yfixed (:,19:21)  = y(:,19:21) .*(para(6)./y (:,1:3) );  % th
43    yfixed (:,22:24)  = y(:,22:24) .*(para(7)./y (:,1:3) );  % w
44    %Note the positions for output of  sensitivities
45    %They are arranged by paramaeter so yfixed(:,4) is the
46    %sensitivity of kp with respect to p, and yfixed(:,5) is
47    %the sensitivity of kp with respect to m
48    %For all sensitivities of p use yfixed (:,4:3:24)
49    %yfixed(:,5:3:24) for all sensitivities of m
50    %and yfixed(:,6:3:24) for all sensitivities of l
51
52
53    function dydt = JacCalc(t,y,para) %Function to update system
54        %Redefine parameters
55        kp = para(1);
56        kpm = para(2);
57        kmp = para(3);
58        klm = para(4);
59        kl = para(5);
60        th = para(6);
61        w = para(7);
62
63        %Threshold for pathogen below 0.0005
64        if y(1) < 0.0005
65            y(1:3:24)  = 0;
66        end
```

```
67
68      %Apply initial condtions
69      p = y(1);
70      m = y(2);
71      l = y(3);
72
73      dp = kp*y(1)*(1-y(1))-kpm*y(2)*y(1); %Equation 2.1 for pathogen
74      dm = (kmp*y(1) + y(3))*y(2)*(1-y(2))-y(2); %Equation 2.2 for early mediators
75      dl = klm*(1+tanh((y(2) - th)/w)) - kl*y(3); %Equation 2.3 for late mediators
76
77      %Jacobian Definition
78      Jaco = zeros(3);
79      Jaco(1,1) = kp*(1-2*p)-kpm*m;
80      Jaco(1,2) = -kpm*p;
81      Jaco(1,3) = 0;
82      Jaco(2,1) = kmp*m*(1-m);
83      Jaco(2,2) = kmp*p*(1-2*m)+l-2*m*l-1;
84      Jaco(2,3) = m*(1-m);
85      Jaco(3,1) = 0;
86      Jaco(3,2) = (klm*(sech((m-th)/w))^2)/w;
87      Jaco(3,3) = -kl;
88
89      %Derivative vectors for  sensitivies
90      dkp = [p*(1-p);0;0];                                    %4,5,6
91      dkpm = [-m*p;0;0];                                      %7,8,9
92      dkmp = [0;p*m*(1-m);0];                                 %10,11,12
93      dklm = [0;0;1+tanh((m-th)/w)];                          %13,14,15
94      dkl = [0;0;-l];                                         %16,17,18
95      dth = [0;0;-(klm*(sech((m-th)/w)^2))/w];                %19,20,21
96      dw = [0;0;-(klm*(m-th)*(sech((m-th)/w)^2))/(w^2)]; %22,23,24
97
98      %Sensitivity equations
99      skp = y(4:6);
100     skpprime = Jaco * skp + dkp;
101     skpm = y(7:9);
```

```
102         skpmprime = Jaco * skpm + dkpm;
103         skmp = y(10:12);
104         skmpprime = Jaco * skmp + dkmp;
105         sklm = y(13:15);
106         sklmprime = Jaco * sklm + dklm;
107         skl  = y(16:18);
108         sklprime = Jaco * skl + dkl;
109         sth  = y(19:21);
110         sthprime = Jaco * sth + dth;
111         sw = y(22:24);
112         swprime = Jaco * sw + dw;
113
114         % Vector for exporting the model equation and sensitivity  data
115         dydt = [dp;dm;dl;skpprime;skpmprime;skmpprime;sklmprime;sklprime;sthprime;swprime];
116
117   end
```

APPENDIX D

LETTER FROM INSTITUTIONAL RESEARCH BOARD

MARSHALL UNIVERSITY
www.marshall.edu

Office of Research Integrity

March 15, 2017

James N. Martin
RR 3 Box 81
Ona, WV 25545

Dear Mr. Martin:

This letter is in response to the submitted thesis abstract entitled *"Local Sensitivity Analysis of Acute Inflammation."* After assessing the abstract it has been deemed not to be human subject research and therefore exempt from oversight of the Marshall University Institutional Review Board (IRB). The Code of Federal Regulations (45CFR46) has set forth the criteria utilized in making this determination. Since the information in this study does not involve human subjects as defined in the above referenced instruction it is not considered human subject research. If there are any changes to the abstract you provided then you would need to resubmit that information to the Office of Research Integrity for review and a determination.

I appreciate your willingness to submit the abstract for determination. Please feel free to contact the Office of Research Integrity if you have any questions regarding future protocols that may require IRB review.

Sincerely,

Bruce F. Day, ThD, CIP
Director

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Publications

1. *Local Sensitivity Analysis of Acute Inflammation.* Master's thesis, Marshall University, August 2017.