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Modeling Celiac Disease

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To the Graduate Council:

I am submitting herewith a thesis written by Jillian M. Trask entitled "Modeling Celiac Disease." I have examined the final electronic copy of this thesis for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science, with a major in Mathematics.

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Modeling Celiac Disease

A Thesis Presented for the

Master of Science

Degree

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Jillian M. Trask

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I dedicate this work to my Aunt Wanda, who was my inspiration for this project, and to all those who have helped me get to where I am today.

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First and foremost, I would like to thank God for placing me on this incredible path. God, I know that everything happens for a reason, your reason, and I try to learn all that I can from every experience with which you bless me. I thank you for your guidance and strength, without which I could not have completed this work.

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Go down deep enough into anything and you will find mathematics. Dean Schlicter

Abstract

Those who suffer from Celiac Disease have an autoimmune response to the protein complex gluten. The goal of this work is to better understand the biological mechanisms in Celiac Disease through modeling with a system of ordinary differential equations. We first develop a model for the way in which gluten induces a response in zonulin in those with Celiac Disease and estimate parameters for such a model using limited data. We then extend this model to include the interactions between zonulin and the permeability of the intestine, and the effect of this interaction on the immune response. Finally, we perform stability analysis on our model. In doing so, we see that, in our model, a gluten-free diet is always effective in treating the disease. This result may point to the need for additional mechanisms in our model in the future.

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Chapter 1

Introduction and Preliminary Work

1.1 Celiac Disease

Celiac Disease (CD) is an autoimmune disease in which the patient lacks the ability to tolerate gluten, a protein found in wheat, barley, and rye. Celiac Disease affects approximately 1 in 133 people in the United States, though this ratio is believed to be much higher [9]. Those with Celiac Disease suffer damage to the intestinal villi, the long, finger-like structures which protrude from the intestinal wall. This, in turn, changes the resistance of the small intestine. As the resistance of the small intestine declines, gluten passes through the wall of the small intestine, thereby inducing an immune response, which further contributes to the degeneration of the resistance of the small intestine. Celiac Disease has been diagnosed in every country and ethnicity and is unique in that it may be treated, in most cases, with a gluten free diet. In other cases, a gluten free diet will not address the damage; this is referred to as Refractory Celiac Disease (RCD) [11].

Like most autoimmune diseases, Celiac Disease has a genetic component; one must possess the HLA-DQ2 and/or HLA-DQ8 gene(s) in order to develop Celiac Disease [7, 12]. Accordingly, individuals with a relative suffering from Celiac Disease are more likely to suffer from Celiac Disease themselves. However, having the necessary gene(s), does not guarantee that one will suffer from Celiac Disease [8].

Those with Celiac Disease generally suffer the damaging effects of ingested gluten in the small intestine [1, 3]. The wall of the small intestine is made up of tight junctions, which separate the apical side of the intestine from the basolateral side. The apical surface of the small intestine faces the lumen and is specialized for absorption; the basolateral surface, on the other hand, controls the distribution of nutrients to the blood stream [6]. As gluten enters the body, it is broken down into its components, gliadins and glutenins, in the digestive tract. Glutenins are not a driving force in this disease, but there are three types of gliadins to which those with Celiac Disease react. Normally, these gliadins should be too large to fit through the wall of the small

intestine. However, when a person who suffers from Celiac Disease consumes gluten, they have an immune reaction which causes the T-cells to fight off the proteins. The antibodies which are produced then attack the villi of the small intestine causing the structures to lose their form and flatten. Because the permeability of the small intestine is compromised due to damage to the villi, the gliadin proteins are able pass through the wall of the small intestine. As the gliadins escape the small intestine, antibodies react to them, thereby eliciting an even greater immune response. Due to the loss of surface area, the villi are unable to absorb nutrients in a normal manner, often leading to malabsorption. This may lead to ailments such as vitamin deficiencies and osteoporosis [9, 5].

1.1.1 Symptoms

Due to the damage to the villi of the small intestine, those with Celiac Disease may exhibit a wide range of symptoms. The most common symptoms are abdominal pain, diarrhea, weight loss, anemia, and bone or joint pain. Some less common symptoms are fatigue, depression, anxiety, seizures, and infertility. Undiagnosed, these symptoms worsen over time, so early diagnosis is imperative. Unfortunately, these symptoms are common to other ailments, thereby making diagnosis difficult. It is worth noting that many of those who suffer from Celiac Disease have no symptoms at all, which further complicates detection [9].

While those with Celiac Disease mostly suffer the symptoms due to the damage to the small intestine, they can also respond to gluten in other ways. Gluten is present in cosmetics and health items such as lotions, lip balms, lipsticks, medications, toothpaste, and mouthwashes. In this way, gluten could be accidentally ingested or enter the system through cuts on the skin. As a result, those with Celiac Disease may also suffer from dermatitis herpetiformis, an itchy, blistering skin rash, arising from these interactions with gluten [5].

1.1.2 Diagnosis

Several tests, from genetic testing to an endoscopy, can diagnose Celiac Disease. Genetic testing can determine whether or not one has a predisposition to Celiac Disease, while blood testing can determine if it is likely that one's symptoms are a result of Celiac Disease or another ailment. The "gold standard" in the diagnosis of Celiac Disease is an endoscopy, which allows doctors to view portions of the small intestine to inspect for damage to the structure of the villi. Unfortunately, the prospect of an endoscopy keeps many from being diagnosed [9].

While diagnosis can be difficult and unpleasant, it is very important. Undiagnosed, Celiac Disease can cause additional health complications including, but not limited to, Type I Diabetes, autoimmune thyroid disease, autoimmune liver disease, and rheumatoid arthritis. It is also likely to cause malnutrition and vitamin deficiencies, leading to osteoporosis [9].

1.1.3 Treatment

For most Celiac Disease sufferers, avoiding gluten will alleviate their symptoms and allow the small intestine to repair itself. Many foods are naturally gluten-free: fresh fruits and vegetables, rice, dairy products, and organic meats. However, maintaining a gluten-free diet is demanding. While the FDA requires that wheat be identified on packaging, many products, especially health and beauty products, do not identify gluten as a constituent. In addition, gluten-free substitutes for items such as bread and pasta are more expensive than their gluten-containing counterparts. Furthermore, a person can continue to crave the protein for two to eight weeks after beginning a gluten-free diet. As a result, many, especially newly diagnosed, Celiac Disease sufferers deviate from the diet. Dietitians and support groups are available to help those with Celiac Disease maintain a gluten-free diet [9, 10].

Preliminary modeling on Celiac Disease was completed in an undergraduate thesis at Hobart and William Smith Colleges under the supervision of Dr. Jonathan Forde [4]. Working with collaborators, Suzanne Lenhart and Jonathan Forde, we formulate a more detailed model with immunology and intestinal features. The goal of this work is to better understand the biological mechanisms in Celiac Disease through modeling with a system of ordinary differential equations. Ideally, under the appropriate conditions, the model would capture the dynamics of one who does not suffer from Celiac Disease, one who suffers from Celiac Disease, and one who suffers from Refractory Celiac Disease.

In the remainder of this chapter, we consider a preliminary model which addresses the way in which gluten induces zonulin production in the small intestine of a patient suffering from Celiac Disease. In the next chapter, we present an extended model which includes the immune response and the permeability of the small intestine.

1.2 Preliminary Work

1.2.1 Preliminary Model

To investigate the relationships between the components involved, we first built a preliminary model to explore how gluten stimulated zonulin release. Because gliadins are the constituent of gluten to which Celiac Disease sufferers react, we used gliadins in our model to represent gluten. We formulated a simple model of two differential equations, where G_a represented the concentration of gliadins on the apical side of the small intestine and z represented the concentration of zonulin in the intestine. In this model, we assumed that gliadins, G_a, entered the apical side of the small intestine with initial value G_{a0} and then decayed at at rate of d_a. Since gluten in the small intestine causes higher levels of zonulin [2], a protein known to regulate the permeability of the intestine, we considered the gliadins on the apical side of the small intestine to be the source of the protein zonulin, z. We assumed gliadins

induced zonulin at rate c and that zonulin decayed at a rate of d_z. Our preliminary model was as follows:

$$\frac{dG_a}{dt} = -d_a G_a \tag{1.1}$$
$$\frac{dz}{dt} = -d_z z + cG_a. \tag{1.2}$$

1.2.2 Parameter Estimation in the Preliminary Model

Our simple model allowed us to obtain an explicit solution for the way in which gliadins induced zonulin production in the intestine:

$$G_a(t) = G_{a0} e^{-d_a t} \tag{1.3}$$
$$z(t) = \frac{cG_{a0}}{d_z - d_a}\left(e^{-d_a t} - e^{-d_z t}\right) + z_0 e^{-d_z t}. \tag{1.4}$$

The explicit solution had three parameters: the decay rates for the gliadins and zonulin, d_a and d_z respectively; and the rate at which gliadins induced a response in the zonulin, c. The initial conditions used to determine this solution were the initial gliadins, G_{a0}, and initial zonulin, z_0.

In 2003, Clemente et al. published a study in which they determined the effect of gliadins on zonulin release [2]. The team exposed rat intestinal epithelial cells to 0.1 mg/ml of gliadins, in vitro, and observed the zonulin concentrations at 15, 30, 45, and 60 minutes. The results of their experiment can be seen in Figure 1.1; we used this data to determine the parameters and initial conditions in our preliminary model.

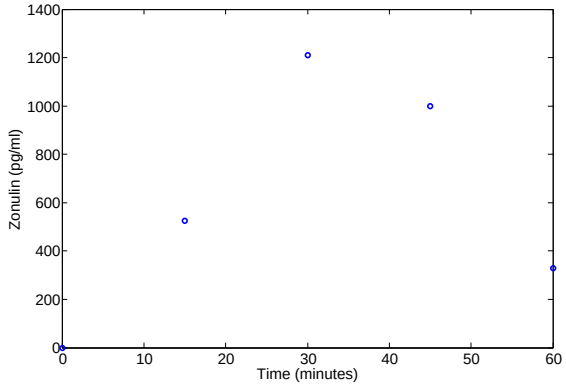

Figure 1.1: Effect of gliadin (0.1 mg/ml) on zonulin release [2].

We used the fminsearchbnd function in MATLAB to estimate the aforementioned parameters by minimizing the difference between the model solution and the five data points from [2], shown in Figure 1.1. In accordance with the experiments carried out by Clemente et al. [2], we first assumed that $G_{a0} = 0.1$ mg/ml and $z_0 = 0$ pg/ml, then estimated the remaining three parameters. Unfortunately, the model with these parameter estimates did not capture the dynamics of the data in an appropriate manner. For example, we noticed that the dynamics of our model would likely not capture the concavity of the graph in Figure 1.1 near the first few data points. In response, we considered starting the response of the zonulin at a later time; i.e. we considered a new variable for the initial time of the zonulin response (t_0). In order for this model to be biologically feasible, we required $z(t) = 0$ on $[0, t_0)$ and then had $z(t)$ pick up Equation 1.2 for $t \in [t_0, 60]$. Again, we used fminsearchbnd, in the same manner as before, to obtain the new parameter estimates found in Table 1.1.

Table 1.1: Parameter estimates with $t_0 \neq 0$; $G_{a0} = 0.1$ mg/ml.

Parameter	**Initial Guess**	**Estimate**
d_a	0.0363	0.0324
d_z	0.3	0.7315
c	0.9065	0.8638
t_0	10	14.6028

As you can see in Figure 1.2, the model with the new parameter estimates captured the shape of the data fairly well. However, the dynamics of our model exhibited a peak both sooner and higher than the experimental data.

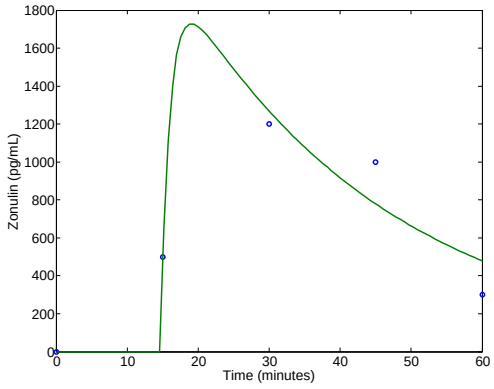

Figure 1.2: Data [2] and Preliminary Model with the parameters in Table 1.1; $G_{a0} = 0.1$ mg/ml.

In an attempt to obtain a better model, we allowed G_{a0} to be included in the parameter search. The newest parameter estimates are found in Table 1.2; Figure 1.3 shows the model, as compared to the data.

Table 1.2: New parameter estimates; G_{a0} included in parameter search.

Parameter	Model Estimate
d_a	0.0624
d_z	0.0732
c	0.9810
t_0	12.5068
G_{a0}	453.6417

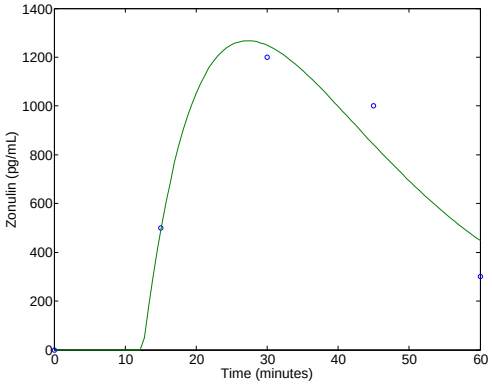

Figure 1.3: Data [2] and the Preliminary Model using parameter estimates in Table 1.2; G_{a0} included in parameter search.

Note that the model with these new parameters better approximated the shape of the data as the peak was more appropriately targeted.

Finally, we observed the dynamics of our model under varying initial concentrations of gliadins. The results are shown in Figure 1.4. Notice that the qualitative behavior of the zonulin release was consistent, exhibiting a peak at approximately thirty minutes after being exposed to the gliadins, despite the initial gluten concentration.

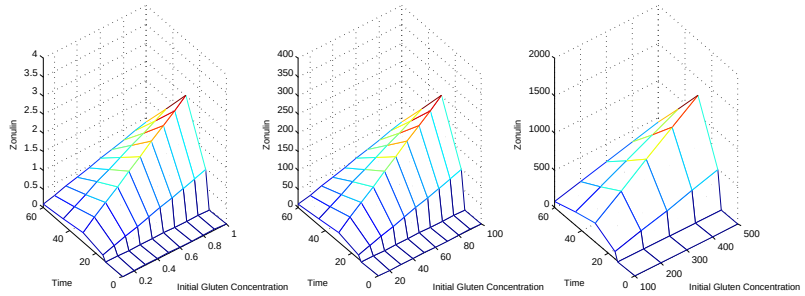

Figure 1.4: 3-D Mesh of Preliminary Model; dynamics at varying initial gliadin concentrations.

1.2.3 Discussion

This work assumed that the initial value of zonulin was zero, indicating that its natural concentration was too small to be detected under normal circumstances. As such, we forced the zonulin level to remain at zero until the initial time when the gliadins induced a response in zonulin, t_0.

We considered two searches for the parameter values in our model, one in which we excluded the initial gliadin concentration, G_{a0}, and one in which we included it. While the search including the initial gliadin concentration better captured the shape of the data, the estimated initial gliadin concentration was far too high to be a viable initial value. We expected that the initial concentration would be, at least, on the same order of magnitude as the initial concentration used in Clemente et al. [2]. Therefore, we chose not to use these parameter values in our model going forward, instead opting to use the parameter estimations from the search excluding the initial gliadin concentration, in order to remain consistent with [2].

Our preliminary work indicated that the estimates for the parameters d_a, d_z, and c appropriately represented the effect which gliadins had on zonulin production in the small intestine of a patient suffering from Celiac Disease. However, we assumed that c, the rate at which gliadins induced a response in zonulin, was linear. Given that the preliminary model did not approximate the data as well as we would have liked, it may be reasonable to consider a nonlinear term in the future.

Finally, our model considered how gliadins on the apical side of the small intestine and zonulin interacted in a person suffering from Celiac Disease. However, a more realistic model for Celiac Disease also requires components for the immune reaction, the resistance of the small intestine, and the gliadins on the basolateral side of the small intestine.

Chapter 2

Working Model

2.1 Model Formulation

We now extend the model to include components for the permeability of the small intestine (p), the gluten which passes through the tight junctions to reach the basolateral side of the small intestine (G_b), and the immune response, represented by the T-cell concentration (T).

The working model is as follows:

$$\frac{dG_a}{dt} = \begin{cases} -d_a G_a, & \text{if } 0 \leq p \leq p_{crit} \\ -d_a G_a - \frac{L(p-p_{crit})^k}{{a_2}^k + (p-p_{crit})^k} G_a, & \text{if } p \geq p_{crit} \end{cases} \tag{2.1}$$

$$\frac{dz}{dt} = - d_z z + c G_a \tag{2.2}$$

$$\frac{dp}{dt} = \left(\frac{az}{b+z} + \frac{a_3 T}{b_2 + T} \right) \frac{1}{1+p} - mp \tag{2.3}$$

$$\frac{dT}{dt} = s \left(1 + \frac{c_2 p}{1+p} \right) + \frac{c_3 G_b}{d + G_b} T - d_T T \tag{2.4}$$

$$\frac{dG_b}{dt} = \begin{cases} -d_b G_b, & \text{if } 0 \leq p \leq p_{crit} \\ -d_b G_b + \frac{L(p-p_{crit})^k}{{a_2}^k + (p-p_{crit})^k} G_a, & \text{if } p \geq p_{crit}. \end{cases} \tag{2.5}$$

Here, the differential equation for the gluten on the apical side of the small intestine (G_a) now includes a term to indicate the transfer of gluten on the apical side of the small intestine to the basolateral side of the small intestine. A hill function has been chosen to represent this transfer because there is a limit to the rate at which gluten may pass through to the basolateral side. Note that, biologically, this transfer cannot take place until the permeability of the small intestine has increased enough to permit the protein to pass through the walls of the small intestine. Accordingly, our model does not allow this transfer until permeability reaches a predefined critical value, p_{crit}.

A differential equation for the permeability of the small intestine (p) has also been included in the extended model. The permeability of the small intestine increases with the increased production of zonulin and the increase in the T-cell concentration. However, these production rates are limited using saturation terms. In addition, the effect that each of these components has on permeability should decrease as permeability increases; the factor $\frac{1}{1+p}$ represents this effect. Finally, the permeability relaxes to its normal level at rate m.

As permeability increases past its critical value, gluten on the apical side of the small intestine (G_a) is able to pass through the wall of the small intestine, thereby transferring to the basolateral side of the small intestine, G_b. Thus, the transfer term from the differential equation for the gluten on the apical side of the small intestine, G_a, is the source term for the differential equation for the gluten on the basolateral side, G_b. Additionally, G_b decays at rate d_b.

Finally, the T-cell concentration (T), in addition to its natural source s, increases as a function of both permeability (p) and the amount of gluten present on the basolateral side of the small intestine (G_b). Again, the increase with respect to each of these components is limited using the Michaelis-Menten type terms. Naturally, T-cells die at a rate d_T.

2.2 Parameter Estimation and Simulations

Just as for the preliminary model, we first assume that the initial amount of gluten on the apical side of the small intestine, G_a, is 0.1 mg/ml. The extended model includes eighteen unique parameters, three of which (d_a, d_z, and c) were in the preliminary model. The list of parameters and their units is listed in Table 2.1.

Table 2.1: Parameters and their Units.

Parameter	Description	Units
d_a	decay rate of G_a	$\frac{1}{time}$
d_z	decay rate of z	$\frac{1}{time}$
c	rate at which G_a induces zonulin production	$\left(\frac{1}{time}\right)\left(\frac{pg}{ml}\right)$
a	maximum rate at which z affects p	$\frac{1}{time}$
b	half-saturation constant	$\frac{pg}{ml}$
m (d_p)	relaxation rate of p	$\frac{1}{time}$
c_2	scalar	dimensionless
d_T	natural death rate of T-cells	$\frac{1}{time}$
c_3	maximum rate at which G_b affects T-cell production	$\frac{1}{time}$
d	half-saturation constant	mg/ml
d_b	decay rate of G_b	$\frac{1}{time}$
L	maximum transfer rate of G_a to G_b	$\frac{1}{time}$
k	parameter to control slope of dG_b/dt near a_2	dimensionless
a_2	half-saturation constant	dimensionless
p_{crit}	critical p value at which G_a passes through intestine	dimensionless
a_3	maximum rate at which G_b affects T-cell production	$\frac{1}{time}$
b_2	half-saturation constant	$\frac{cells}{mm^3}$
s	production rate of T-cells	$\left(\frac{1}{time}\right)\left(\frac{cells}{mm^3}\right)$

Using the results from the preliminary model, the extended model already has estimates for three of its parameters: $d_a = 0.0324$, $d_z = 0.7315$, and $c = 0.8638$. We then use the literature to approximate the additional parameter values [3, 12]. A list of the parameter values can be found in Table 2.3; we use the ode45 function in MATLAB to obtain all of our numerical solutions using the parameter values presented in this table. The numerical solution to the model using the parameters from the preliminary model and the initial conditions found in Table 2.2 is shown in Figure 2.1.

Table 2.2: Initial Conditions

Variable	Description	Initial Condition	Units
G_a	apical gluten	0.1	mg/ml
z	zonulin	0	pg/ml
p	gut permeability	0.01	dimensionless
T	T-cell concentration	0.2	cells/mm^3
G_b	basolateral gluten	0.01	mg/ml

Table 2.3: Parameter Values for Figures 2.1 - 2.8.

Parameter	**Value (Fig. 2.1)**	**Value (Fig. 2.2, 2.4, 2.6, 2.7, 2.8)**	**Value (Fig. 2.3, 2.5)**
d_a	0.0324	0.0363	0.0363
d_z	0.7315	0.3	0.3
c	0.8638	0.9065	0.9065
a	0.1	0.1	0.1
b	3	3	3
m (d_p)	0.015	0.008	0.008
c_2	4	4	0
d_T	.4	5	.4
c_3	2	2	0
d	1	10	1
d_b	0.001	0.001	0.001
L	1	10	1
k	2	2	2
a_2	0.5	5	0.5
p_{crit}	0.1	0.1	0.15
a_3	0.01	0.01	0.01
b_2	2	2	2
s	0.1	0.5	0.1

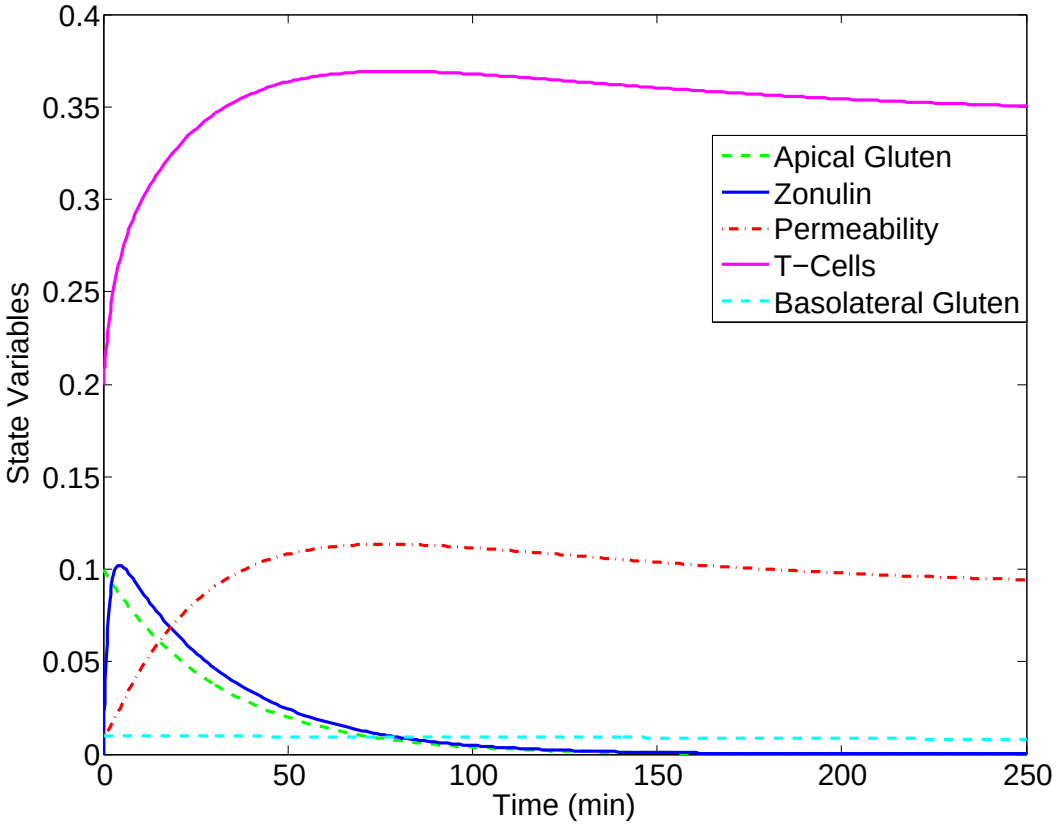

Figure 2.1: Solution to Model with Parameter Values from our Preliminary Model 2.3.

This model seems appropriate in its dynamics regarding the interaction between apical gluten and zonulin: the apical gluten decays while the zonulin release sees a sharp increase in response to the initial gluten and then decays over the remaining four hours. In addition, the permeability appears to increase as expected; however, it does not relax back to *normal* in an appropriate manner. Since the permeability never reaches the critical level (set to be 0.01), gluten does not pass through the wall of the small intestine and an immune response is not elicited. Therefore, we expect that the permeability will decay much faster over the 250 minutes than we see when we use these particular parameter values.

In order to address the decay of the permeability, we modify some of the parameters and run the simulation again. In Table 2.3 we see the new values of d_a, d_z, c, m, d_T, d, L, a_2, and s; the simulation results are shown in Figure 2.2. Here, we see the sharper decay of the permeability that we were expecting.

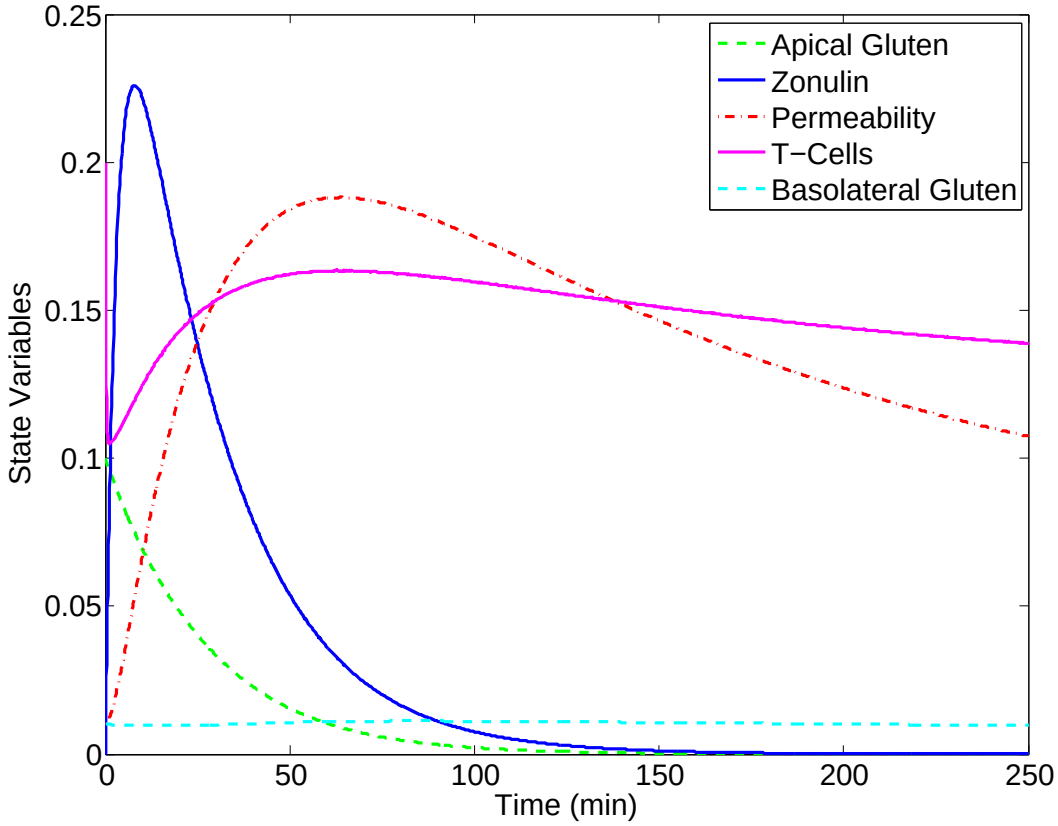

Figure 2.2: Solution to Model with Modified Parameter Values seen in Table 2.3; specifically, the parameters d_a, d_z, c, m, d_T, d, L, a_2, and s have been modified.

Next, we begin to examine our model under the assumption that one is not suffering from Celiac Disease. We do this in order to ensure that our model will not exhibit the same dynamics in one without the genetic predisposition to Celiac Disease as it does in one with the predisposition. In this case, it should be that neither the permeability level nor any gluten that passes through the wall of the small intestine should have an effect on one's T-cell response. Therefore, the parameters c_2 and c_3 must both be zero, as seen in Table 2.3. Figure 2.3 allows us to visualize the results.

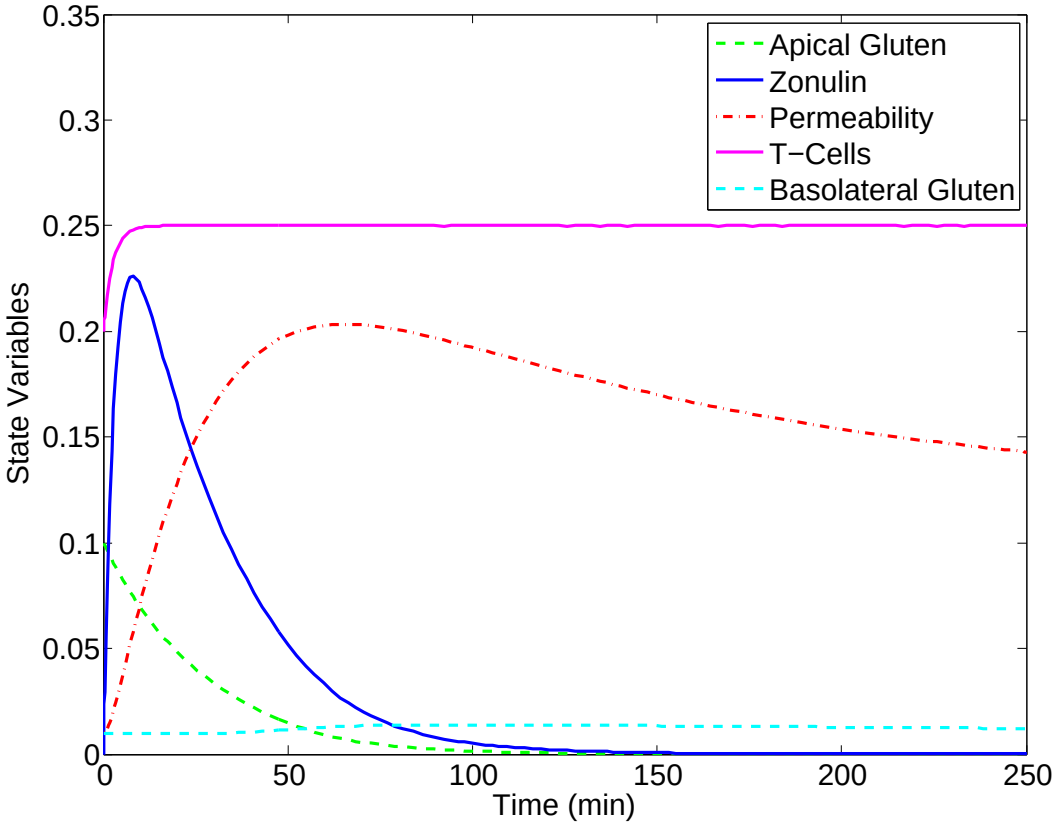

Figure 2.3: Solution to Model for a patient without the genetic predisposition to Celiac Disease.

Here, we see that the T-cell concentration remains constant, despite the intake of gluten. This is the expected behavior in one without the genetic predisposition to Celiac Disease.

Since individuals may consume gluten several times a day, we should consider the effect of this behavior in our model. In order to do so, gluten is periodically introduced into our model using a pulse source. This pulse introduces more gluten (G_a) to the system at a predetermined time (e.g., every 250 minutes). We first run the original simulation for 250 minutes; at 250 minutes, we add 0.1 mg/ml of gluten to the value of the gluten at the end of the first run and then use the values of the other four variables at the ending time as the new initial conditions for the next run. We continue in this fashion for as many runs as we see fit (e.g. three runs). This is representative of a person consuming gluten three times a day, approximately four hours apart. Using the parameter values from Table 2.3, we pulse twice to get the results shown in Figure 2.4.

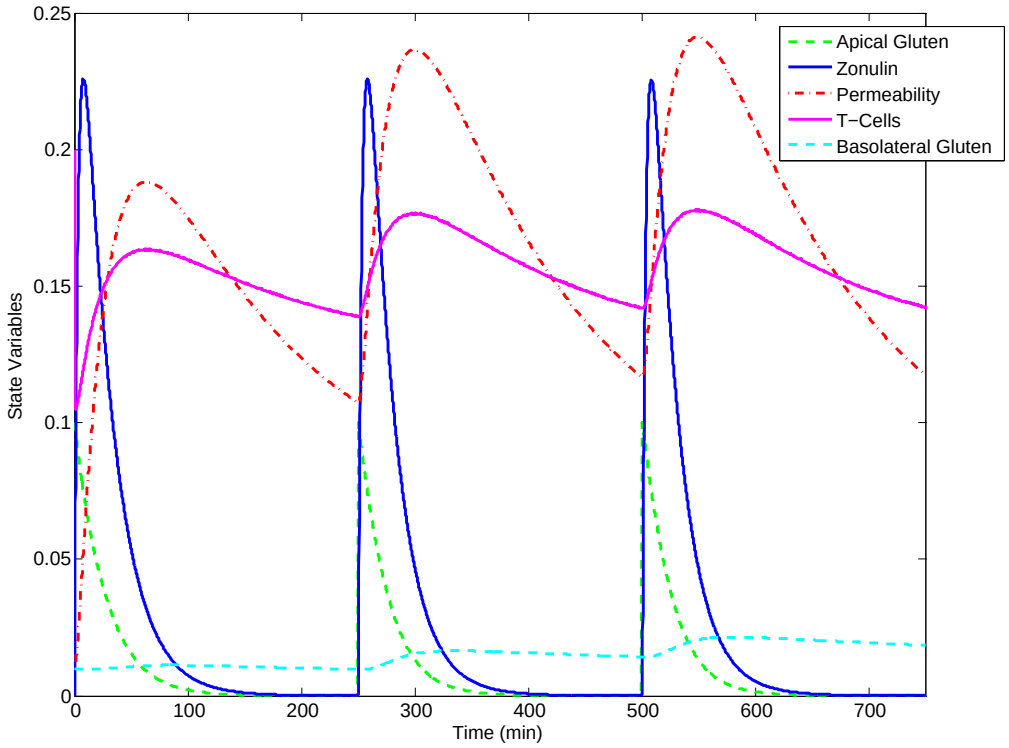

Figure 2.4: Pulsed solution to Model for a patient with Celiac Disease.

Again, the apical gluten decays as expected and, consistent with [2], the zonulin peaks approximately thirty minutes into each run before it decays. Also, the permeability reaches its critical value in each run, thereby allowing the apical gluten to pass to the basolateral side of the intestine (i.e. basolateral gluten increases). Initially, the T-cell concentration increases in response to the gluten passing to the basolateral side, then decays, as expected.

We may perform the same analysis on our model depicting those without Celiac Disease to demonstrate that there is not an immune response to the gluten over time. Figure 2.5 exhibits this behavior. Here, we see that apical gluten continues to decay and that the zonulin level still peaks approximately thirty minutes into each run, as expected. In addition, the permeability peaks, reaching its critical value, before decaying. Again, this forces the basolateral gluten to increase. However, the T-cell concentration remains level indicating that there is not an immune response to the gluten in the system, which is expected for those without the predisposition to Celiac Disease.

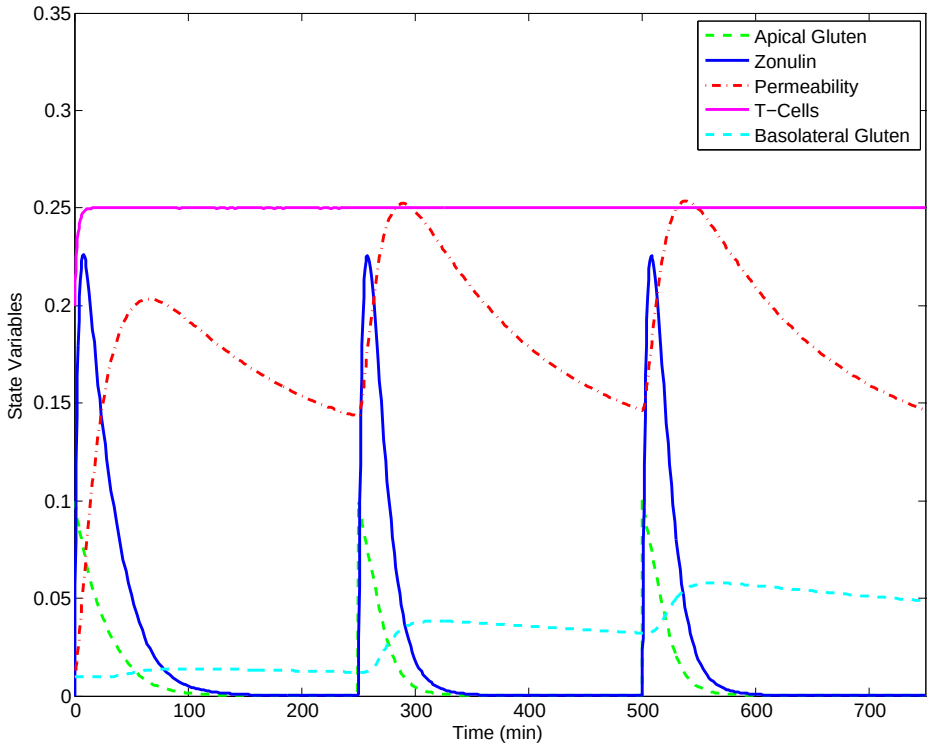

Figure 2.5: Pulsed solution to Model for a patient without Celiac Disease.

Generally, changes in the length of time between meals results in similar dynamics. However, longer periods of time between meals allows the permeability to decay back to more normal levels, which affects both the amount of gluten which is able to pass through the intestine to the basolateral side, as well as the T-cell response. Accordingly, allowing shorter periods of time between meals prevents permeability from relaxing back to normal; thus driving permeability up with each pulse. This, in turn, increases the amount of gluten which may pass through to the basolateral side, thereby increasing the T-cell response.

2.3 Stability Analysis

To determine the stability of our model, we consider the steady states of the system when no gluten is introduced into the system. In order to do so, we set each of the five differential equations equal to zero and solve for the state variables. When we do this, it is easy to see that G_a, z, and G_b must be zero. This leaves only p and T to solve for. Note that these variables are interdependent, which makes the system difficult

to solve explicitly. However, we can solve the system for our set of parameters. First, we set each of the two differential equations equal to zero and solve each for T, as is shown in Equations 2.6 and 2.7 below. T_p is the equation resulting from setting the differential equation for p equal to zero and solving for T; T_T is the equation which results from setting the differential equation for T equal to zero and solving for T:

$$T_p = 0.1\left(1 + \frac{4p}{1+p}\right) \tag{2.6}$$

$$T_T = \frac{1.6p(1+p)}{1 - 0.8p(1+p)}. \tag{2.7}$$

To find the intersection points, we graph the solutions of these two equations. Upon doing so, we can show that there will be one viable steady state, provided that our parameters are all greater than zero. For our parameters, the steady state occurs when $p = 0.069$ and $T = 0.126$; this result is shown in Figure 2.6.

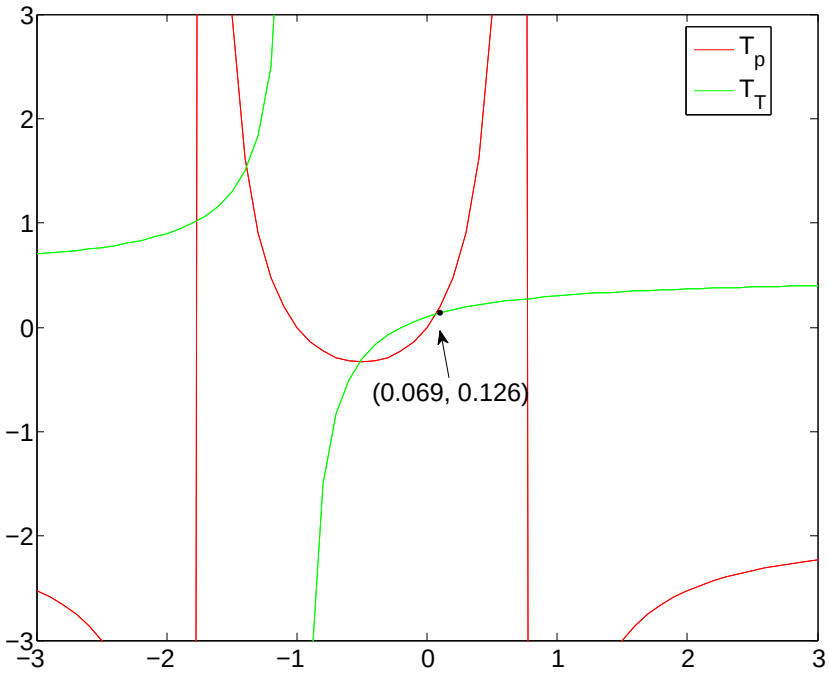

Figure 2.6: Plot of Equations 2.6 and 2.7, showing the intersection point in the first quadrant. This plot shows that there will be one biologically feasible steady state. This plot specifically shows the intersection for the parameter values in column two of Table 2.3.

We can also see this in the following figures, where we graph the solution to our system in the absence of gluten, using the parameter values in Table 2.3. Figure 2.7 shows the steady states when we begin with a permeability level below the critical value, p_{crit}; Figure 2.8 portrays the steady state when we begin with a permeability level above the critical value. Observe that the graphs for both the permeability and the T-cell concentration tend toward the steady state mentioned above.

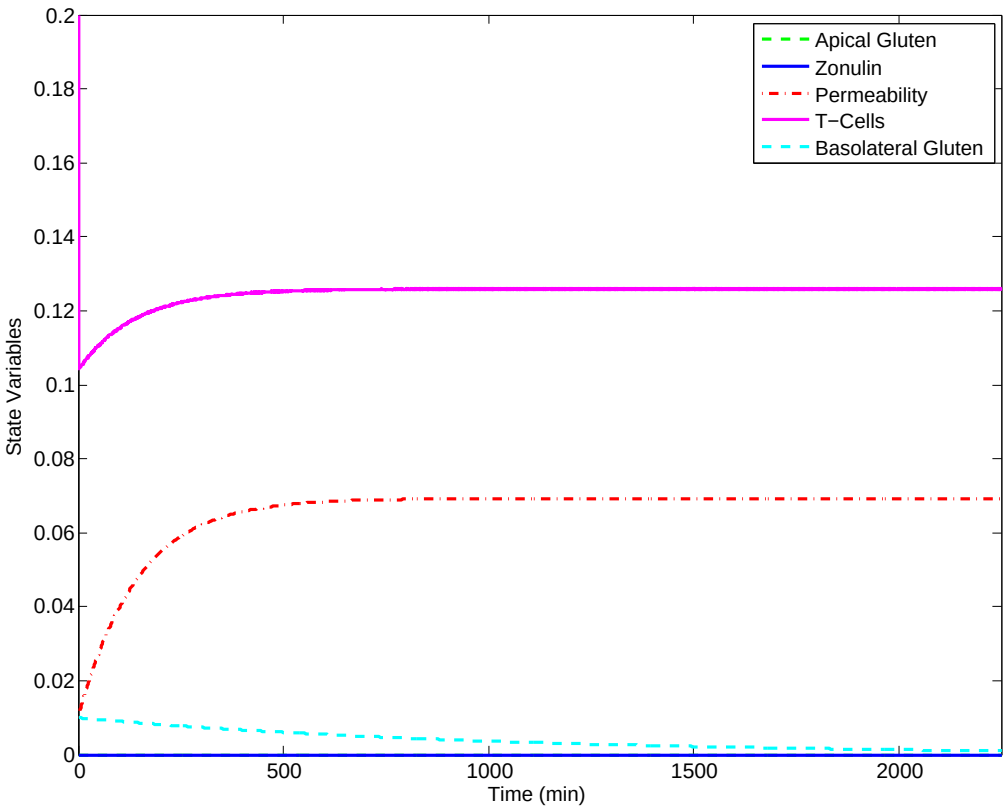

Figure 2.7: Steady State of Model using Parameter Values from column two of Table 2.3; $p_0 < p_{crit}$.

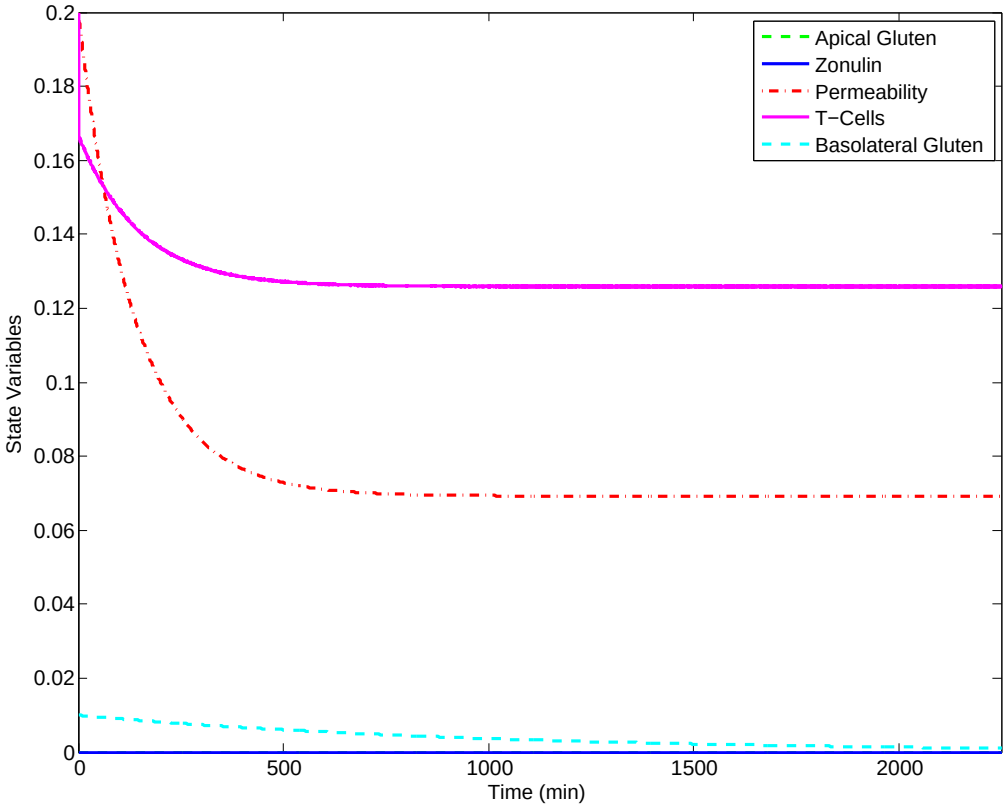

Figure 2.8: Steady State of Model using Parameter Values from column two of Table 2.3; $p_0 > p_{crit}$.

The stability analysis of our model indicates that we will have the same steady state whether or not permeability reaches a critical level; in both cases, the permeability will relax to normal in the absence of gluten. Thus, in our model, a gluten-free diet is always effective. Therefore, our model is limited in that it cannot demonstrate a situation in which a patient reaches Refractory Celiac Disease.

2.4 Conclusion

In this work, we present a system of five differential equations to model several components of Celiac Disease. In summary, a patient with a genetic predisposition to Celiac Disease may consume gluten, which increases the production of zonulin in one's small intestine. This decreases the permeability of their small intestine, which allows large gliadin proteins to escape the small intestine, thereby triggering an immune response brought on by the increased production in T-cells due to the stimulus.

After developing the system of differential equations, we estimate the parameter values using both the fminsearchbnd function in MATLAB and the literature. With parameter estimates, we are able to run simulations to determine the long-term behavior of the model under specific conditions, namely, those which are favorable to the development of Celiac Disease and those which are not.

Finally, we perform stability analysis on our model in order to determine the steady state and long-term behavior of the model in the absence of gluten. Through this analysis, we learned that our model is limited in that it cannot reach a state in which a patient would develop Refractory Celiac Disease. This is a deficiency that we are interested in addressing in the near future by including additional features or mechanisms in our model.

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Vita

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