MODELING AUTOIMMUNE DISEASE WITH DIFFERENTIAL EQUATIONS

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ABSTRACT

JENNIFER ANDERSON

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AUGUST 2018

In this project, I will build a mathematical model of a developed autoimmune process considering cell autoimmunity that plays the main role in any autoimmune disorder using a system of three non-linear differential equations. As model variables, I will use the concentration of target cells not bearing dam- age, concentration of cytotoxic T-lymphocytes against given cells, and the con- centration of the tissue-specific antigen formed because of the destruction of the target cells. All concentrations will be expressed in the moles per liter. We will investigate the model over the time interval [0, T] given either by months or days analytically as well as numerically.

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CHAPTER I

INTRODUCTION

The immune system is a highly complex system composed of other systems that function together to keep the human body safe from foreign pathogens. An important part of the process is the recognition of what is foreign and what is self. An autoimmune disease is the result of a breakdown in that process, causing the immune system to see its own cells as invaders and as a result mistakenly attacks itself.

For the first half of the 20th century, scientists believed that it was not possible for the immune system to attack itself based on the theory of German immunologist and Nobel Laureate, Paul Ehrlich. His theory, that the immune system was incapable of attacking itself, was known as *horror autotoxicus*. But in 1951, Noel Rose was completing post doc work at the State University of New York at Buffalo and noticed a shocking result from injecting thyroglobulin originally from rabbit thyroids back into rabbits - the rabbit thyroids were inflamed. Almost all of the rabbits' immune systems had begun to destroy their own thyroid tissue. Rose had proof of what was a revolutionary idea at the time, autoimmune disease [8].

By 1957, the concept of autoimmune disease was accepted. However, be- cause of this early struggle to be recognized, research in autoimmune disease lagged behind during the prolific period of medical discoveries of the early 20th century.

Today, autoimmune disease is recognized and according to the National Institute of Health (NIH) there are as many as 23.5 million people in the US affected by autoimmune disease with an annual direct cost of 100 billion dollars [1]. Furthermore, the prevalence of these diseases is on the rise. However, NIH research funding for autoimmune disease pales in comparison to that of cancer or heart disease and stroke.

Table 1.1

Comparison of Research Funding

	Autoimmune Diseases	Cancer	Heart Disease and Stroke
Number of people affected	23.5 Million	9 Million	22 Million
Annual Direct Health Care cost	$100 Billion	$57 Billion	$200 Billion
NIH Research Funding	$591 Million	$6.1 Billion	$2.4 Billion

The NIH Autoimmune Diseases Research Plan states, Research discoveries of the last decade have made autoimmune research one of the most promising areas of new discovery.

In this paper, I provide an overview of how the immune system works (Chapter 2). I also provide an over view of mathematical tools used to model biological processes (Chapter 3) as well as consider some models that have been presented (Chapter 4). Finally, I investigate one model thoroughly (Chapter 5) and consider conclusions that can be drawn (Chapter 6).

CHAPTER II

THE HUMAN IMMUNE SYSTEM

The Immune System

The immune system is responsible for protecting the body from foreign substances, or pathogens. It is a complex system comprised of smaller systems that interact with one another and protect the body in an efficient and complete manner.

The first line of defense of the immune system is a barrier to keep unwanted pathogens out of the body. The skin is the most obvious component of the immune system's barrier. However, the human body also has many square feet of mucous membranes that help keep pathogens out of the inner workings of our body. If a bacteria, virus, or other pathogen gets past this first layer of defense, then the innate immune system and the adaptive immune system go to work. The innate response is quick and non-specific and involves phagocytes. One type of phagocyte, macrophages, find pathogens and destroy them by engulfing and eating them. After eating the pathogens, the macrophage presents the broken up peptides of the pathogen on their cell surface and become anti- gen presenting cells (APC). The macrophages also release a protein known as interlukin-1 which signals for the production of T-cells and B-cells to fight the foreign cells and antigens. This begins the adaptive immune process.

The adaptive system takes a little more time and involves the recognition of specific antigens. Most cells in the body have proteins on the surface called the major

histocompatibility complex (MHC). These MHC, like fingerprints, are different for each individual. It is these MHC proteins on the bodies' cells that allow the immune system to distinguish between itself and foreign cells. Cells that are foreign have antigens on their surface. B lymphocytes can bind to antigens in the body to attack the foreign invaders. This is called the humoral response. T lymphocytes are able to attack foreign invaders only after the antigens have been processed and presented on the cell membrane with the MHC proteins. This is known as the cell mediated response.

Humoral Response

The humoral response fights pathogens while they are still in the fluids of the body. B-cells, which are created and mature in the bone marrow, are a key component of the humoral response. Because of the way the B cells develop, they each recognize different and specific kinds of pathogens that could invade the body. So when pathogens enter the blood stream, the B- cells "bump" into the pathogen and use their B-cell receptors to determine if the pathogen is a match for the B cells specific antibody formula. If it is a match, then the B cell begins to proliferate and make antibodies to fight the pathogen. These antibodies bind to the pathogen to neutralize it and/or signal for phagocytes to ingest and destroy the pathogen.

Cell Mediated Response

T-cells, which are created in the bone marrow and mature in the Thymus, are a key component of the cell mediated response. Similar to the B cells, the T cells develop in such a way that they respond to specific different kinds of pathogens. However, while

the B-cells attack pathogens that are in the blood, T-cells target pathogens that have already infected cells. Cytotoxic T-cells at- tach to cells that have been infected with a pathogen that matches their specific antibody strand and cause the cell to commit suicide, killing the cell and the pathogen that has infected the cell.

If you consider how many different types of antigens are possible and there- fore how many different T-cells and B-cells there are, it is pretty amazing that the correct B-cell or T-cell finds a pathogen that matches with its specific anti- gen. But this is where the immune system shows one of its best ways of being efficient. The lymphatic system sends lymph from the tissue of the body to the lymph nodes. This lymph includes the pathogens. T and B-cells travel among the lymph nodes looking for matching antigens. So the antigens and T and B-cells are collected in the lymph nodes, making it likely to run into each other.

Autoimmune Disease

The immune system is quite efficient and capable of protecting us against foreign invaders. But in some cases the immune system fails to recognize and tolerate the self-antigens. ”This failure results in the activation of autoreactive T cells and the production of autoantibodies by B cells, causing inflammation and organ damage” [10, p. 1171]. “The normal consequence of an adaptive immune response against a foreign antigen is the clearance of the antigen from the body When an adaptive immune response develops against self-antigens; however, it is usually impossible for immune effector mechanisms to eliminate the antigen completely, and so a sustained response occurs. The consequence

is that the effector pathways of immunity cause chronic inflammatory injury to tissues, which may prove lethal" [7].

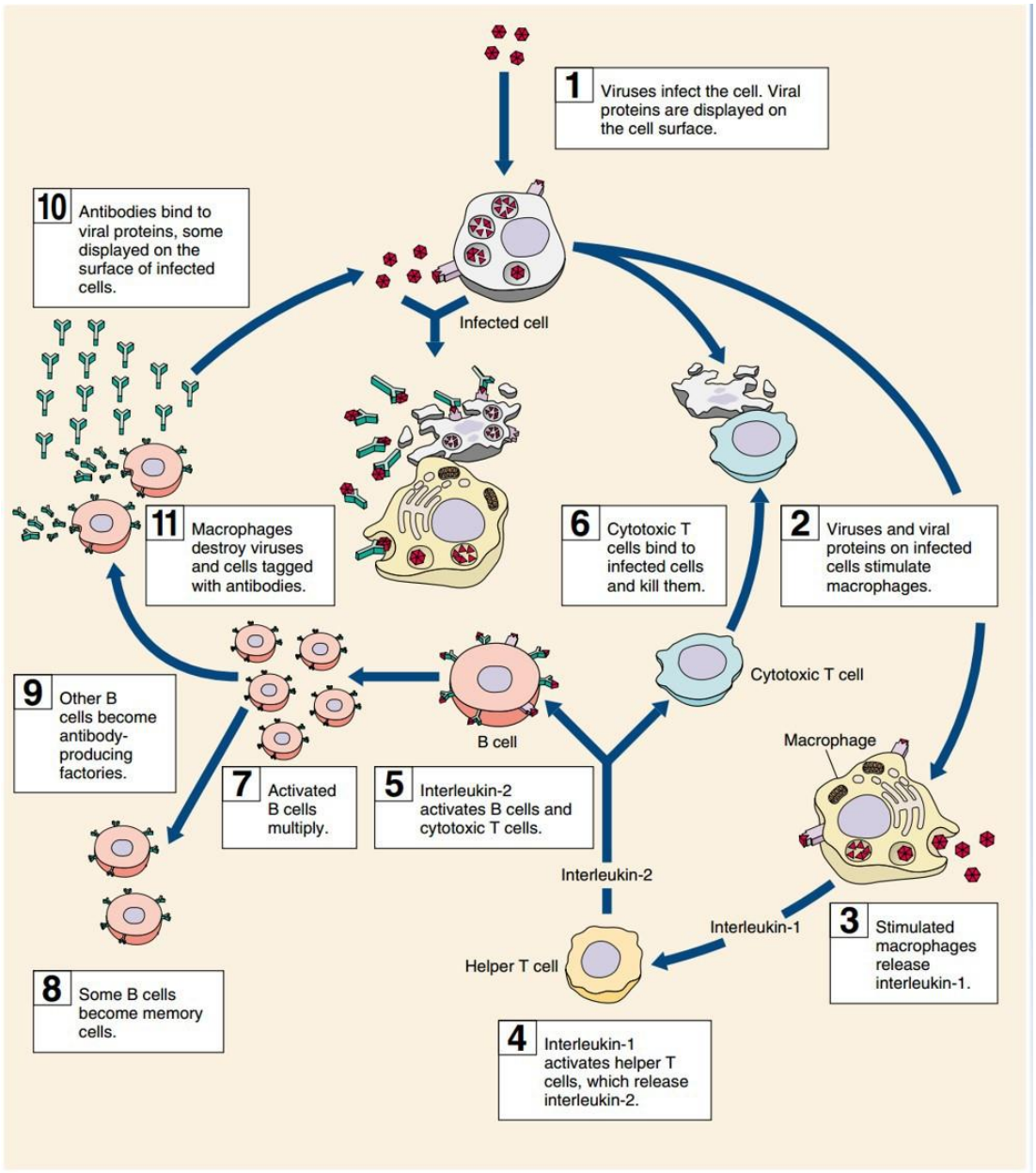

Figure 2.1. The Immune Response [10]

There are over 80 different illnesses caused by autoimmunity. A few of the most common autoimmune diseases are rheumatoid arthritis, celiac, lupus, and psoriasis (see Table 2.1). These autoimmune diseases have much in common and yet they are also quite diverse. They vary based on the type of immune response, the mechanism by which the tissue or organ is damaged, and which tissue or organ is being attacked [7]. But because there are also many general similarities it is beneficial to study them as a group.

There are still many unknowns regarding the cause of an autoimmunity reaction. Theories involve genetic as well as environmental factors. However:

> Nearly all autoimmune illnesses have as their basis a self-sustaining autoimmune reaction directed against some component of the organism, and the course of this reaction is practically independent of the cause of the loss of tolerance of tolerance to the corresponding antigen [12, p. 152].

Table 2.1

Common Autoimmune Diseases

Some common autoimmune diseases classified by immunopathogenic mechanism		
Syndrome	**Autoantigen**	**Consequence**
Type II antibody to cell-surface or matrix antigens		
Autoimmune hemolytic anemia	Rh blood group antigens, I antigen	Destruction of red blood cells by complement and FcR^+ phagocytes, anemia
Autoimmune thrombocytopenic purpura	Platelet integrin GpIIb:IIIa	Abnormal bleeding
Goodpasture's syndrome	Noncollagenous domain of basement membrane collagen type IV	Glomerulonephritis, pulmonary hemorrhage
Pemphigus vulgaris	Epidermal cadherin	Blistering of skin
Acute rheumatic fever	Streptococcal cell-wall antigens. Antibodies cross-react with cardiac muscle	Arthritis, myocarditis, late scarring of heart valves
Type III immune-complex disease		
Mixed essential cryoglobulinemia	Rheumatoid factor IgG complexes (with or without hepatitis C antigens)	Systemic vasculitis
Systemic lupus erythematosus	DNA, histones, ribosomes, snRNP, scRNP	Glomerulonephritis, vasculitis, rash
Rheumatoid arthritis	Rheumatoid factor IgG complexes	Arthritis
Type IV T cell-mediated disease		
Insulin-dependent diabetes mellitus	Pancreatic β-cell antigen	β-Cell destruction
Rheumatoid arthritis	Unknown synovial joint antigen	Joint inflammation and destruction
Experimental autoimmune encephalomyelitis (EAE), multiple sclerosis	Myelin basic protein, proteolipid protein, myelin oligodendrocyte glycoprotein	Brain invasion by CD4 T cells, weakness

CHAPTER III

USING MATHEMATICAL MODELS FOR BIOLOGICAL DISCOVERY

As previously stated, the immune system is a complex system. By "system," we mean it has multiple interacting components and a boundary [5]. Further, when we call the system complex, we mean that the "overall behavior of the system cannot be intuitively understood in terms of the individual components or interactions...That is, behavior can be drastically altered by seemingly in- significant changes in features" [5, p. 5].

In recent years, there have been many scientific and technological discoveries that allow us to study the cellular and molecular processes. However, it is still difficult and expensive to conduct laboratory research on cellular and molecular processes. For this reason mathematical modeling is used to gain a better understanding of the processes and dynamics of a system. Mathematical models can be used to predict a system's dynamics under different conditions to help guide experimental design:

> Although model simulations will never replace laboratory experiments, a model can be used to probe system behavior in ways that would not be possible in the laboratory. Model simulations can be carried out quickly (often in seconds) and incur no real cost. Model behavior can be explored in conditions that could never be achieved in a laboratory. Every aspect of model behavior can be observed at all-time points. Furthermore, model analysis yields insights into why a system behaves the way it does, thus providing links between net- work structure and behavior [5, p. 6].

Ordinary differential equations are an extremely useful tool for modeling biological processes. If we can construct a model that accurately represents the cellular or molecular biological processes, then we can use general theorems and analytical methods to examine the systems behavior and interpret the results in biological terms.

Analysis of Linear Systems

Consider the system

$$\frac{dx}{dt} = ax + by$$

$$\frac{dy}{dt} = cx + dy \tag{3.1}$$

where *a*, *b*, *c*, and *d* are constants.

Definition 3.1.1. An *equilibrium point* is a point where there is no change in the *x* or *y* value of the system, that is $\frac{dx}{dt} = ax + by$. *Steady state* and *singular point* are synonyms.

Definition 3.1.2. If all the trajectories of a system are moving towards an equilibrium point, it is *stable*.

Definition 3.1.3. If all the trajectories of a system are moving away from an equilibrium point, it is *unstable* and called a *source*.

Definition 3.1.4**.** If some of the trajectories of a system are moving toward and some are moving away from an equilibrium point, it is called a *saddle*.

This system can also be written in matrix form as

$$\frac{d}{dt}\begin{bmatrix} x \\ y \end{bmatrix} = \begin{bmatrix} a & b \\ c & d \end{bmatrix}\begin{bmatrix} x \\ y \end{bmatrix}$$

The eigenvalues of the coefficient matrix can be used to determine the behavior of the system. The eigenvalues of the coefficient matrix are found from $\det(a - \lambda I)X = 0$. As a result, we get

$$(a - \lambda)(d - \lambda) - bc = 0$$

or

$$\lambda^2 - (a + d)\lambda + (ad - bc) = 0$$

Using the quadratic equation, we see that the eigenvalues are

$$\lambda = \frac{(a + d) \pm \sqrt{(a + d)^2 - 4(ad - bc)}}{2}$$

Definition 3.1.5. The sum of the diagonal entries of a matrix is known as the *trace*, trA.

Definition 3.1.6. The *determinant* of a 2x2 matrix, $\begin{bmatrix} a & b \\ c & d \end{bmatrix}$ is $ad - bc$.

Using these definitions, we can see that the eigenvalues are actually,

$$\lambda = \frac{(a+d) \pm \sqrt{(trA)^2 - 4detA}}{2}$$

Definition 3.1.7. The *discriminant*, D, of a quadratic equation is the value under the radical of the quadratic formula, $D = b^2 - 4ac$. It allows us to deduce properties of the roots without actually computing them.

The *discriminant* of our eigenvalue is $(trA)^2 - 4detA$. Therefore:

- if $D > 0$, the eigenvalues are Real
- if $D < 0$, the eigenvalues are Imaginary
- if $D = 0$, there are two eigenvalues of the same value.

Now, using the eigenvalues, we can determine the behavior of the system of linear ordinary differential equations.

- If both eigenvalues are real and positive, then the equilibrium point (0,0) is a solution is a source.
- If both eigenvalues are real and negative, then the equilibrium point is a sink.
- If the eigenvalues are real and opposite signs, then the equilibrium point is a saddle.
- If the $trA > 0$ and $D < 0$, then the equilibrium point is a spiral source.
- If the $trA < 0$ and $D < 0$, then the equilibrium point is a spiral sink.
- If the $trA = 0$ and $D < 0$, then the equilibrium point is a center.

Thus, we can discern much about the behavior of the system by considering the trace and the determinant.

Linearization of Nonlinear Models

Most models used for biological systems are nonlinear and have many variables and parameters. These systems are far too complex to solve explicitly to achieve detailed global analysis. Instead, we will determine the qualitative behavior of the system at specific points and then use that information to estimate the global behavior. The specific points that we will use are called equilibrium points. We can approximate the local behavior around the equilibrium points as linear and then use the tools of linear analysis. By considering the approximated linear behavior at all the equilibrium points, we can get a fairly good picture of the global behavior.

Theorem 3.2.1**.** Close to the steady state, the nonlinear model can be approximated by a linear one [3].

Equilibrium Points and Stability

Jacobian Matrix

We can use the Jacobian matrix and its eigenvalues to determine the behavior of the function at the equilibrium points. This is especially helpful when we have a system of more than 2 equations.

Theorem 3.4.1. *Let* $x^t = f(x)$ *be a nonlinear system of n first-order equations with an equilibrium solution and* $\boldsymbol{f}$ *a sufficiently smooth vector function. Let* $\boldsymbol{J}$ *be the Jacobian (the matrix of partial derivatives) evaluated at this equilibrium solution:*

$$J(x^2) = \begin{bmatrix} \frac{\partial f_1}{\partial f_1} & \frac{\partial f_1}{\partial x_2} & \cdots & \frac{\partial f_2}{\partial x_n} \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x2} & \cdots & \frac{\partial f_2}{\partial x_n} \\ & \vdots & \ddots & \\ \frac{\partial f_n}{\partial x_1} & \frac{\partial f_2}{\partial x_2} & \cdots & \frac{\partial f_n}{\partial x_n} \end{bmatrix}$$

Let $\{\lambda_1, \lambda_2, ..., \lambda_n\}$ be the n (real or complex, possibly repeated) eigenvalues of the Jacobian matrix.//

1. *If the real part of the eigenvalue $\mathbb{R}(\lambda_i) < 0$ for all i, then the equilibrium is stable*

2. *If the real part of the eigenvalue $\mathbb{R}(\lambda_i) < 0$ for at least one i and $\mathbb{R}(\lambda_i) > 0$ for at least one j, then the equilibrium is a saddle*

3. *If the real part of the eigenvalue $\mathbb{R}(\lambda_i) > 0$ for all i, then the equilibrium is unstable.*

4. *If any of the eigenvalues are complex, then the stable or unstable equilibria is a spiral; if all of the eigenvalues are real, it is a node.*

5. *If a pair of complex conjugate eigenvalues, λ_i, λ_i satisfy $\mathbb{R}(\lambda_i) = 0$, then the equilibrium is a linear center in the plane containing the corresponding eigenvectors [13].*

Phase Plane and Vector Field

We continue our analysis by considering a graphical approach to gain a better understanding of how the system is behaving. The right hand side of (3.1) tells us how the

system is changing at each point $(\frac{dx}{dt}, \frac{dy}{dt})$.

Definition 3.5.1**.** The *phase plane* is the *xy* plane where *x* and *y* are two variables in the system [13].

Definition 3.5.2**.** For each point (*x*, *y*) in the *phase plane*, we can assign a vector, $(\frac{dx}{dt}, \frac{dy}{dt})$ to describe the change. The collection of these vectors is the *vector field* [13]. *Direction Field* is a synonym for vector field.

Using the *Vector Field,* we can sketch the possible solution curves depending on the initial condition. It shows the concentrations at the initial state and converging to the steady state. This can be extremely helpful for analysis. Using these methods, "The qualitative behavior of a system of equations can be understood without solving the equation explicitly" [14].

Bifurcation Analysis

Definition 3.6.1. When a change in the value of a parameter changes the qualitative behavior of the solution, it is called a *bifurcation.*

Saddle node, transcritical, pitchfork, and hopf are different types of bifurcation. It is important to know when and how a bifurcation occurs for under- standing a mathematical model [14].

Common Models

Verhulst

In modeling biological processes, we need to be able to model the growth and decay of cells. Exponential growth, however, is not an appropriate model since there will be a point at which the growth will no longer have enough resources to continue at a high population level. For this reason, we alter the logistical growth equation and get what is referred to as the Verhulstequation [14]

$$N' = rN, \qquad \text{(Exponential Growth)}$$

$$N' = rN\left(1 - \frac{N}{K}\right), \qquad \text{(Verhulst Equation)}$$

Figure 3.1 shows the direction field for a Verhulst Model. Notice that any initial condition with an x value below 5, will move up to 5. And any *x* value above 5, will move down to 5. In this example, 5 is the critical point where growth will no longer occur.

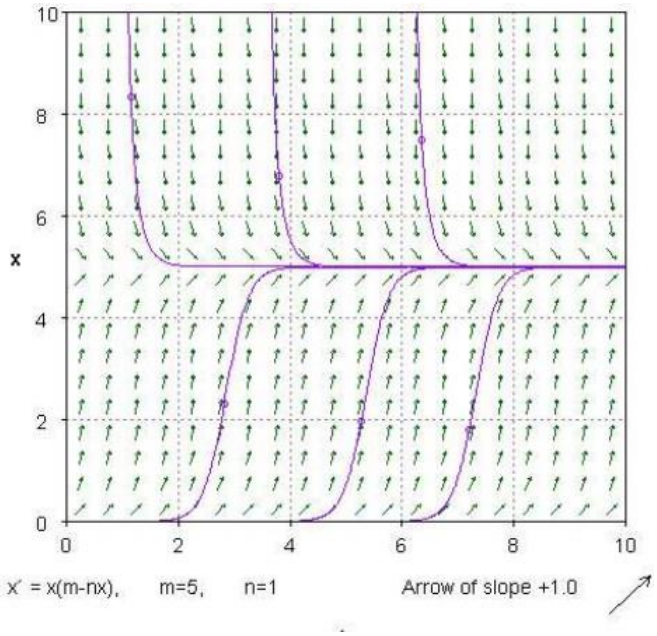

Figure 3.1. Direction Field of Verhulst Model

Lotka-Volterra

The *Lotka-Voltera* also often referred to as *predator-prey model* is a well-known system for modeling two competing populations. The populations tend to oscillate as each species inhibits the other's growth. The Lotka-Volterra equations are

$$\frac{dx}{dt} = ax - \beta xy$$

$$\frac{dy}{dt} = \sigma xy - \gamma y$$

These equations have been heavily studies and modified for different purposes or to include more realistic prey growth rates through the years [3].

Law of Mass Action

Reaction kinetics, which rely on the *law of mass action* are crucial for modeling many physiological processes including modeling populations. The *law of mass action* is originally from chemistry and states that “the rate of molecular collisions of two chemical species in a dilute gas or solution is proportional to the product of the two concentrations” [3].

CHAPTER IV

IMMUNE SYSTEM MODELS

The first mathematical models of immunological processes and phenomena were developed in the 1970s. G.I. Bell published papers about a model of clonal selection and antibody production in three parts in the Journal of Theoretical Biology. In addition, Olga Smirnova published papers in Russian of a model of immune reactions ([11], [12]).

In the past 10 years, there has been an increase in the number of papers published about modeling immunological processes. One of the most cited immunology papers has been S. Gordon and P. Taylor's "Monocyte and Macrophage heterogeneity" from 2005 [4].

Frameworks of Immunology Models

Mathematical models of autoimmunity can be categorized in several ways. One way is to consider whether the model is focused on molecular, cellular, or tissue level. Most of the models at the molecular level involve non-spatial ordinary differential equations (ODEs). While the models that work at the cellular level are usually simple ODEs and are made of fewer equations than those at the molecular level. As a result, the cellular level models with fewer equations are easier to investigate using analytical tools [4]. An excellent paper investigating autoimmunity at the cellular level was "The role of tunable activation thresholds in the dynamics of autoimmunity" in the Journal of Theoretical Biology in 2012 [2].

Another way to group mathematical models of autoimmunity is by what part of the process they are modeling. For example, is the model addressing the start of the disease or the self-sustaining autoimmune reaction?

Modeling Tolerance, Flare-Ups, and Dormancy

In 2007, Shingo Iwami et al. published a paper [6] with a simple mathematical model for autoimmune disease based on the personal immune response function and the target cell growth function. Iwami et al. showed how these functions explain tolerance, repeated flare-ups, and dormancy and how their model captures the overall essence of autoimmune disease. Their model is

$$\begin{cases} T' = g(T) - \beta TC \\ D' = \beta TC - \alpha D \\ C' = f(D) - \gamma C \end{cases} \tag{4.1}$$

where T is the population size of the target cells, D is the damaged cells (anti- gens), and C is the immune cells. These target cells, damaged cells, and immune cells die at the rate of μ, α, and γ respectively and β represents the efficacy of damage resulting when immune cells attack target cells. $g(T)$ is:

$$g_1(T) = \lambda - \mu T \text{ or}$$

$$g_2(T) = \lambda - \mu T + pT\,(1 - \frac{T}{L})$$

where λ is the rate at which new target cells are produced and μ is the death rate of target cells. In g_2, p is the maximum proliferation rate and L is the target cell population density where p shuts off and $f(D)$ is:

$$f_1(D) = kD \text{ or}$$

$$f_2(D) = \frac{mD^2}{h^2 + D^2}$$

where *k* is the magnitude of activation of immune response form the antigen presenting cells (APG) which means that *kD* is the proliferation rate of immune cells by APCs at time *t*. In f_2, *m* is the maximum proliferation rate of immune cells by APCs and *h* is the number of damaged cells at which proliferation of immune cells is half the maximum, *m* [6].

A Model of Inflammatory Bowel Disease

In 2016, Anna Park and Il Hyo Jung published a paper [9] with a mathematical model of inflammatory bowel disease (IBD) using ordinary differential equations to show the relationship between T-cells and cytokines in the immune system.

Their model is:

$$\begin{cases} \frac{dN}{dt} = bN\left(1 - \frac{N}{K}\right) - (\gamma S + c)N - \mu_1 N \\ \frac{dT}{dt} = \alpha_1 \gamma SN + \alpha_2 cN - \mu_2 T \\ \frac{dS}{dt} = \omega T - \beta NS - \mu_3 S \end{cases} \tag{4.2}$$

where the three variables are the concentration of Naive T-cells $N(t)$, the con- centration of Helper T-cells, $T(t)$ and the cytokines secreted by the helper T- cells, $S(t)$ and all parameters are assumed to be positive. The parameters are: *b*, growth rate of Naive T-

cells; *K*, Carrying capacity: γ, the loss of N from encounters with *S*; *c*, rate of production for T differentiation; α_1 the rate of proliferation and differentiation into N by S; α_2 the rate of proliferation and differentiation into *N* by *c*; ω, the rate of *S* production from *T*; β, the loss of *S* from encounters with *N*; μ_1 the rate of excretion and elimination of *N*; μ_2 the death rate for *T*;μ_3 the death rate for *S* [9].

CHAPTER V

A MODEL OF CELLULAR AUTOIMMUNITY

As explained in Section 2.2 on autoimmune disease, there are still a variety of competing theories as to how autoimmune diseases develop. But once developed, most autoimmune diseases involve a self-sustaining autoimmune reaction directed against some tissue or organ of the individual. This model is of this final stage of the autoimmune process. Because of its role in long-term autoimmune diseases, cellular autoimmunity is considered. The model consists of three differential equations representing the concentration of healthy tissue cells that will be targeted, *x*; the concentration of T lymphocytes, *y*; and the concentration of the tissue specific antigen, *z*.

This model is from "Environmental Radiation Effects on Mammals: A Dynamical Modeling Approach" by Olga Smirnova and incorporates the Verhulst equation (see section 3.7.1), Lotka Volterra equation (3.7.2), and the Law of Mass Action (3.7.3).

$$\begin{cases} \frac{dx}{dt} = \mu x - \nu x^2 - \beta xy \\ \frac{dy}{dt} = \psi zy - \beta xy - \alpha y \\ \frac{dz}{dt} = \sigma\beta xy - \gamma z \end{cases} \tag{5.1}$$

Table 5.1
Description of parameter for the model

Description of Parameter Notation	
μ	multiplicity rate of the tissue cells
vx^2	the rate of natural death of the tissue cells.
βxy	represents the mutual annihilation of tissue cells and T lymphocyte cells
$\sigma\beta xy$	the rate of production of tissue specific autoantigen and is proportional to βxy
ψz	the antigen concentration
α	the death rate of T lymphocytes
γ	the rate the antigen is removed from the organism

The $\mu x - vx^2$ portion of the $\frac{dx}{dt}$ is from the Verhulst equation and gives a limit to the growth of the system. The $-\beta xy$ in the $\frac{dx}{dt}$ and $\frac{dy}{dt}$ equations is from the Lotka Volterra equation. It is a result of the competition between the tissue cells and T-cells.

In her book [12], Olga Smirnova investigated the system by reducing it to 2 equations. I summarize Smirnova's approach below and then do my own investigation of the 3d system.

Reducing the 3D system to 2D

The time required for the antigen to reach equilibrium is measured in days. However, the time of the autoimmune process and tissue growth are measured in months. Therefore, we can conclude that $\frac{dz}{dt}$ is "fast" and can be replaced by its stationary solution, $z = \frac{\sigma\beta}{\gamma} xy$, which is acquired after setting $\frac{dz}{}$ equal to zero and solving for z.

Now inserting this new expression for z into the second equation of the system (5.1) Smirnova created a new system with only 2 equations.

$$\frac{dx}{dt} = \mu x - vx^2 - \beta xy$$

$$\frac{dy}{dt} = \frac{\psi\sigma\beta}{\gamma} xy^2 - \beta xy - \alpha y$$

Next, Smirnova inserted the dimensionless variables and parameters

$$\xi = \frac{v}{\mu}x \;\; \eta = \frac{\beta}{\gamma}\tau = \mu t$$

$$a = \frac{\psi\sigma\mu}{\gamma v} \; b = \frac{\beta\gamma}{\psi\sigma\mu} \; c = \frac{a\gamma v}{\mu^2\psi\sigma}$$

And now the new system of differential equations is

$$\frac{d\xi}{d\tau} = \xi(1 - \xi - \eta)$$

$$\frac{d\eta}{d\tau} = a\eta(\xi\eta - b\xi - c)$$

Smirnova [12] used qualitative theory of differential equations, oscillation theory, and bifurcation theory to investigate the system. Below is a phase plane of that system. The dimensionless variable representing the tissue cell concentration, ξ, is graphed on the horizontal axis. And the dimensionless variable representing the killer T cell concentration, η, is graphed on the vertical axis.

Smirnova [12] found that "the trivial singular point ($\xi_1 = 0, \eta_1 = 0$) is always unstable (a saddle). The singular point 2 with coordinates $\xi_2 = 1$ and $\eta_2 = 0$ is always stable (a node). It corresponds to a steady state of the healthy organism in which the target tissue has normal size and is not damaged. The singular points 3 and 4 are in the positive quadrant when $b < 1 - 2\sqrt{c}$. The point 3 is always unstable (a saddle), and the point 4 is either a node or a focus. When $c < (1/a - b)(1 - 1/a)$, the point 4 becomes unstable" [12, p. 154].

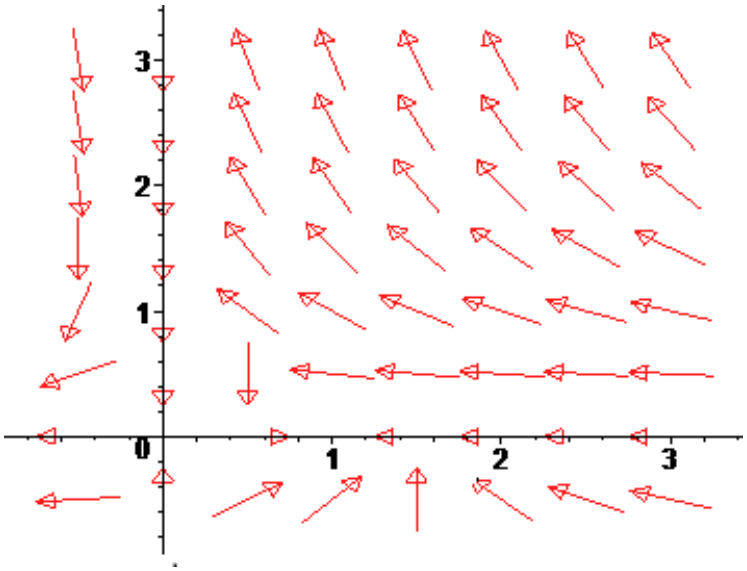

Figure 5.1 Phase Plane of Smirnova's system

Investigating the 3D Nonlinear System

While I am using the model from Smirnova [12], I analytically investigated the dynamics of this system as a 3D system instead of reducing it to a 2D system. This is a system of three nonlinear differential equations with seven positive parameters. The seven positive parameters (μ, ν, β, ψ, σ, γ, α) depend on the patient.

$$\begin{cases} \frac{dx}{dt} = \mu x - \nu x^2 - \beta xy = F(x,y,z) \\ \frac{dy}{dt} = \psi zy - \beta xy - ay = G(x,y,z) \\ \frac{dz}{dt} = \sigma\beta xy - \gamma z = H(x,y,z) \end{cases} \tag{5.2}$$

Because this system is nonlinear it is difficult to determine its behavior. Therefore, we find the equilibrium points of the system and then linearize the system in the neighborhood of each equilibrium point to classify the behavior of the system. In order to find the equilibrium points, I set the three derivatives equal to zero. Now we have a

nonlinear algebraic system, solving which we can find all the equilibrium points of system (5.2). Our system is

$$\begin{cases} \mu x - \nu x^2 - \beta xy = x(\mu - \nu x - \beta y) = 0 \\ \psi zy - \beta xy - a\gamma = y(\psi z - \beta x - a) = 0 \\ \sigma\beta xy - \gamma z = 0 \end{cases} \tag{5.3}$$

Equilibrium Points

First Equilibrium Point

The first equilibrium point is easy to see from (5.3), $x^* = 0$, $y^* = 0$, and $z^* = 0$, or (0, 0, 0). This equilibrium point represents values of 0 for the number of tissue cells, T-cells, and antigen. Thus, it is trivial for biological interpretation as a patient would die before getting to this point. However, mathematically this equilibrium point is important because it affects the overall behavior of the system.

Second Equilibrium Point

The second equilibrium point is found by considering when $y^* = 0$ $z^* = 0$. Then $\mu x - \nu x^2 = 0$ and $x^* = \frac{\mu}{\nu}$. So the second equilibrium point is $(\frac{\mu}{\nu}, 0, 0)$

Third and Fourth Equilibrium Points

We can solve the third equation of (5.3) for z and get

$$z = \frac{\sigma\beta xy}{\gamma} \tag{5.4}$$

Now by substituting this value for z into a simplified version of the second equation of (5.3), we get

$$\psi z - \beta x - a = 0$$

$$\psi\left(\frac{\sigma\beta xy}{\gamma}\right) - \beta x - a = 0$$

$$\psi\sigma\beta - \beta x\gamma - a\gamma = 0$$

From the first equation of (5.3) we know that

$$\beta xy = \mu x - vx^2$$

So we continue

$$\psi\sigma(\mu x - vx^2) - \beta x\gamma - a\gamma = 0$$
$$\psi\sigma\mu x - \psi\sigma vx^2 - \beta x\gamma - a\gamma = 0$$
$$\psi\sigma vx^2 - (\psi\sigma\mu - \beta\gamma)x + a\gamma = 0$$

After dividing by $\varphi\sigma$ ($\psi\sigma \neq 0$) and simplifying, we get,

$$vx^2 - \left(\mu - \frac{\beta\gamma}{\sigma\psi}\right)x + \frac{\alpha y}{\sigma\psi} = 0 \qquad (5.5)$$

This is a quadratic equation of variable x in the form $ax^2 + bx + c = 0$ with the following coefficients:

$$a = v$$

$$b = -(\mu - \frac{\beta\gamma}{\sigma\psi})$$

$$c = \frac{a\gamma}{\psi\sigma}$$

We can use the quadratic formula to solve this quadratic equation and we know that the number of roots is determined by the discriminant, D.

$$D = b^2 - 4ac = \left(\mu - \frac{\beta\gamma}{\sigma\psi}\right)^2 - 4\frac{vay}{\psi\sigma} \qquad (5.6)$$

If $D > 0$ there will be two real roots, if $D = 0$ there will be one real root, and if $D < 0$ there will be 2 imaginary roots. We are not interested in the case of two imaginary roots since our model is restricted to the positive first quadrant. But we need to consider the two other cases that result from this quadratic equation.

Table 5.2

Possible Number of Equilibrium Points based on the Discriminant

Equilibrium Points		
$D < 0$	$D = 0$	$D > 0$
2 Equilibrium Points	3 Equilibrium Points	4 Equilibrium Points

We continue by finding the third and fourth equilibrium points from our quadratic equation, (5.5). But first, let us consider what we know about these roots from Vieta's Theorem.

Theorem 5.2.1. *For the roots,* x_1 *and,*x_2 *of a quadratic equation,* $ax^2 + bx + c = 0$, *we know that* $x_1 + x_2 = -\frac{b}{a}$ *and* $x_1 \cdot x_2 = \frac{c}{a}$.

Since we are investigating a system of cellular growth, we are only concerned with positive values for the roots. Using Vieta's theorem and remembering that all the parameters are positive, we see that

$$x_3^* \cdot x_4^* = \frac{a\gamma}{\upsilon\psi\sigma} > 0$$

$$x_3^* + x_4^* = \left(\mu - \frac{\beta\gamma}{\sigma\psi}\right)\frac{1}{v} > 0 \text{ when } \mu > \frac{\beta\gamma}{\sigma\psi}$$

Thus, we can see that both roots are positive as long as

$$\mu > \frac{\beta\gamma}{\sigma\psi}. \tag{5.7}$$

Now, we determine the actual roots using the quadratic formula,

$$x_3^* = \frac{\mu - \frac{\beta\gamma}{\sigma\psi} + \sqrt{(\mu - \frac{\beta\gamma}{\sigma\psi})^2 - 4\frac{v\alpha\gamma}{\psi\sigma}}}{2v} \tag{5.8}$$

And now we can substitute the new found values for x^* back into the system (5.3) to find the corresponding values for y^* and z^*.

In order to do that, we solve the first equation of (5.3) for y and get

$$\mu - vx - \beta\gamma = 0$$

$$y = \frac{\mu - vx}{\beta} \tag{5.10}$$

And now we substitute x^* into this equation and get

$$Y_{3,4}^* = \frac{\mu}{\beta} - \frac{v}{\beta}\left(\frac{\mu - \frac{\beta\gamma}{\sigma\psi} \pm \sqrt{\left(\mu - \frac{\beta\gamma}{\sigma\psi}\right)^2 - 4\frac{v\alpha\gamma}{\psi\sigma}}}{2v}\right)$$

Thus,

$$y_3^* = \frac{\mu}{\beta} - \frac{1}{2\beta}\left(\frac{\mu-\beta\gamma}{\sigma\psi} + \sqrt{\left(\mu - \frac{\beta\gamma}{\sigma\psi}\right)^2 - 4\frac{v\alpha\gamma}{\psi\sigma}}\right) \tag{5.11}$$

$$y_4^* = \frac{\mu}{\beta} - \frac{1}{2\beta}\left(\frac{\mu-\beta\gamma}{\sigma\psi} - \sqrt{\left(\mu - \frac{\beta\gamma}{\sigma\psi}\right)^2 - 4\frac{v\alpha\gamma}{\psi\sigma}}\right) \tag{5.12}$$

Similarly, we can use equation (5.4), which has already been solved for *z* and substitute x^* and y^* in. We get

$$z_3^* = \frac{\sigma\beta}{\gamma}\left(\left(\frac{\mu-\frac{\beta\gamma}{\sigma\psi}+\sqrt{\left(\mu-\frac{\beta\gamma}{\sigma\psi}\right)^2-4\frac{v\alpha\gamma}{\psi\sigma}}}{2v}\right)\cdot\left(\frac{\mu}{\beta}-\frac{1}{2\beta}\left(\frac{\mu-\beta\gamma}{\sigma\psi}+\sqrt{\left(\mu-\frac{\beta\gamma}{\sigma\psi}\right)^2-4\frac{v\alpha\gamma}{\psi\sigma}}\right)\right)\right) \tag{5.13}$$

$$z_4^* = \frac{\sigma\beta}{\gamma}\left(\left(\frac{\mu-\frac{\beta\gamma}{\sigma\psi}+\sqrt{\left(\mu-\frac{\beta\gamma}{\sigma\psi}\right)^2-4\frac{v\alpha\gamma}{\psi\sigma}}}{2v}\right)\cdot\left(\frac{\mu}{\beta}-\frac{1}{2\beta}\left(\frac{\mu-\beta\gamma}{\sigma\psi}+\sqrt{\left(\mu-\frac{\beta\gamma}{\sigma\psi}\right)^2-4\frac{v\alpha\gamma}{\psi\sigma}}\right)\right)\right) \tag{5.14}$$

Third equilibrium point

We just found the third and fourth equilibrium points that occur when the Discriminant, D, is positive (D ¿ 0). However, if D = 0, then there will only be 1 real root from our quadratic equation (5.5), and therefore, only 3 equilibrium points (see Table 5.2). Now, we find the equilibrium point that occurs when D = 0.

$$\left(\mu - \frac{\beta\gamma}{\sigma\psi}\right)^2 - 4\frac{va\gamma}{\psi\sigma} = 0$$

$$x^* = \frac{-b}{2a} = \frac{1}{2v}\left(\mu - \frac{\beta\gamma}{\sigma\psi}\right)$$

And now using this value for x^*, and equations (5.3) and (5.4), we find y^* and $_{z^*}$

$$\beta y^* = \mu - vx^*$$

$$\beta y^* = \mu - \frac{v}{2v}\left(\mu - \frac{\beta\gamma}{\psi\sigma}\right)$$

$$y^* = \frac{1}{2}\left(\frac{\mu}{\beta} + \frac{\gamma}{\psi\sigma}\right)$$

$$z^* = \frac{\sigma\beta xy}{\gamma}$$

$$z^* = \frac{\sigma\beta}{\gamma}\left(\frac{1}{2v}\left(\mu - \frac{\beta\gamma}{\sigma\psi}\right)\right)\left(\frac{1}{2}\left(\frac{\mu}{\beta} + \frac{\gamma}{\psi\sigma}\right)\right)$$

$$z^* = \frac{1}{4v}\left(\frac{\sigma\mu^2}{\gamma} - \frac{\beta^2}{\sigma\psi^2 v}\right)$$

And the equilibrium point

$$(x_3^*, y_3^*, z_3^*) = \left(\frac{1}{2v}\left(\mu - \frac{\beta\gamma}{\sigma\psi}\right), \frac{1}{2}\left(\frac{\mu}{\beta} + \frac{\gamma}{\psi\sigma}\right), \frac{1}{4v}\left(\frac{\sigma\mu^2}{\gamma} - \frac{\beta^2\gamma}{\sigma\psi^2 v}\right)\right)$$

Table 5.3.

Equilibrium Points of System 5.2

Equilibrium Points		
$D < 0$	$D = 0$	$D > 0$
(0, 0, 0)	(0, 0, 0)	(0, 0, 0)
$\left(\frac{\mu}{\nu}, 0, 0\right)$	$\left(\frac{\mu}{\nu}, 0, 0\right)$	$\left(\frac{\mu}{\nu}, 0, 0\right)$
	$\left(\frac{1}{2v}\left(\mu - \frac{\beta\gamma}{\sigma\psi}\right), \frac{1}{2}\left(\frac{\mu}{\beta} + \frac{\gamma}{\psi\sigma}\right), \frac{1}{4v}\left(\frac{\sigma\mu^2}{\gamma} - \frac{\beta^2\gamma}{\sigma\psi^2 v}\right)\right)$	
		(x_3^*, y_3^*, z_3^*)
		(x_4^*, y_4^*, z_4^*)

Investigation of the Types of Equilibrium Points

Having found all of the equilibrium points, we now linearize our system and investigate the behavior in the neighborhood of the equilibrium points and classify the behavior of the system. We use the Jacobian matrix to classify the behavior in the neighborhood of the equilibrium points

The Jacobian is

$$J(x^*, y^*, z^*) = \begin{bmatrix} \frac{\partial F}{\partial x} & \frac{\partial F}{\partial y} & \frac{\partial F}{\partial z} \\ \frac{\partial G}{\partial x} & \frac{\partial G}{\partial y} & \frac{\partial G}{\partial z} \\ \frac{\partial H}{\partial x} & \frac{\partial H}{\partial y} & \frac{\partial H}{\partial z} \end{bmatrix} = \begin{bmatrix} \mu - 2vx - \beta y & -\beta x & 0 \\ -\beta y & \psi z - \beta x - a & \psi y \\ \sigma\beta y & \sigma\beta x & -\gamma \end{bmatrix} \quad (5.15)$$

Investigating 1st Equilibrium Point (x_1^*, y_1^*, z_1^*)

The Jacobian (5.9) at (0, 0, 0) is

$$J(0,0,0) = \begin{bmatrix} \mu & 0 & 0 \\ 0 & -a & 0 \\ 0 & 0 & -\gamma \end{bmatrix}$$

Thus, system (5.2) in the neighborhood of (0, 0, 0) has the following linearized form

$$\begin{cases} \frac{dx}{dt} = \mu x \\ \frac{dy}{dt} = -ay \\ \frac{dz}{dt} = y\gamma z \end{cases}$$

Because the Jacobian matrix is diagonal, we know that its eigenvalues are its diagonal entries. That is, $\lambda_1 = \mu, \lambda_2 = -a, \lambda_3 = -\gamma$. Since one eigenvalue is real and positive and the other two are real and negative, (0, 0, 0) is an unstable node for all parameter values.

Investigating 2nd Equilibrium Point $(x_2^*,\ y_2^*,\ z_2^*)$

The Jacobian (5.9) at $(\frac{\mu}{\nu}, 0, 0)$ is

$$J_{\left(\frac{\mu}{\nu},0,0\right)} = \begin{bmatrix} -\mu & \frac{-\beta\mu}{\nu} & 0 \\ 0 & \frac{-\beta\mu}{\nu} - a & 0 \\ 0 & \frac{\sigma\beta\mu}{\nu} & -\gamma \end{bmatrix} \tag{5.16}$$

Thus, system (5.2) in the neighborhood of $(\frac{\mu}{\nu}, 0, 0)$ has the following linearized form

$$\begin{cases} \frac{dx}{dt} = -\mu x - \frac{\beta\mu}{\nu} y \\ \frac{dy}{dt} = \left(\frac{-\beta\mu}{\nu} - a\right) y \\ \frac{dz}{dt} = \frac{\sigma\beta\mu}{\nu} y - \gamma z \end{cases}$$

We can find the characteristic equation of matrix (5.10),

$$\left| J_{\left(\frac{\mu}{\nu},0,0\right)} - \lambda I \right| = 0$$

$$\begin{vmatrix} -\mu - \lambda & \frac{-\beta\mu}{\nu} & 0 \\ 0 & \frac{-\beta\mu}{\nu} - a - \lambda & 0 \\ 0 & \frac{\sigma\beta\mu}{\nu} & -\gamma - \lambda \end{vmatrix} = 0 \tag{5.17}$$

Evaluating the determinant, we obtain the characteristic equation in factorized form

$$(-\mu - \lambda) \cdot \left(\frac{-\beta\mu}{\nu} - a - \lambda\right) \cdot (-\gamma - \lambda) = 0 \tag{5.18}$$

from which it follows that $\lambda_1 = -\mu < 0, \lambda_2 = \frac{-\beta\mu}{\nu} - a < 0$, and $\lambda_3 = -\gamma < 0$. Because all the eigenvalues are negative, $\left(\frac{\mu}{\nu}, 0,0\right)$ is an asymptotically stable node.

Investigating 3rd of 3 Equilibrium Points $(x_3^*,\ y_3^*,\ z_3^*)$

When $D = 0$ the resulting equilibrium point is

$$(x_3^*, y_3^*, z_3^*) = \left(\frac{1}{2v}\left(\mu - \frac{\beta\gamma}{\sigma\psi}\right), \frac{1}{2}\left(\frac{\mu}{\beta} + \frac{\gamma}{\psi\sigma}\right), \frac{1}{4}\left(\frac{\sigma\mu^2}{\gamma} - \frac{\beta^2\gamma}{\sigma\psi^2 v}\right)\right) \quad (5.19)$$

We can simplify the Jacobian matrix (5.9).

$$J_{(x^*,y^*,z^*)} = \begin{bmatrix} \mu - 2vx - \beta y & -\beta x & 0 \\ -\beta y & \psi z - \beta x - a & \psi y \\ \sigma\beta y & \sigma\beta x & -\gamma \end{bmatrix}$$

Notice that the element in the second row and second column, j_{22}, is the same as the second equation of (5.3) and since $y \neq 0$, this term must be 0. This does not occur for the first and second equilibrium points. But it is true for the third equilibrium that occurs when the discriminant is zero and for the third and fourth equilibrium points that occur when the discriminant is positive. We can also simplify j_{11}. Remember from the first equation of (5.3), we know that $\beta y = \mu - vx$, and therefore

$$\begin{aligned} j_{11} &= \mu - 2vx - \beta y \\ &= \mu - 2vx - (\mu - vx) \\ &= -vx \end{aligned}$$

Now, our simplified Jacobian is

$$J_{(x^*,y^*,z^*)} = \begin{bmatrix} -vx^* & -\beta x^* & 0 \\ -\beta y^* & 0 & \psi y^* \\ \sigma\beta y^* & \sigma\beta x^* & -\gamma \end{bmatrix} \quad (5.20)$$

By substituting in our values for x_3^*, y_3^*, z_3^*, we get the Jacobian at this point

$$J_{(x_3^*,y_3^*,z_3^*)} = \begin{bmatrix} \frac{-1}{2}\left(\mu - \frac{\beta\gamma}{\sigma\psi}\right) & \frac{-\beta\mu}{2v} + \frac{\beta^2\gamma}{2\sigma\psi v} & 0 \\ -\frac{\beta}{2}\left(\frac{\mu}{\beta} + \frac{\gamma}{\sigma\psi}\right) & 0 & \frac{\psi}{2}\left(\frac{\mu}{\beta} + \frac{\gamma}{\sigma\psi}\right) \\ \frac{\sigma\mu}{2} + \frac{\sigma\beta\gamma}{2\sigma\psi} & \frac{\sigma\beta\mu\psi - \beta^2\gamma}{2\psi v} & -\gamma \end{bmatrix}$$

But we will use the simplified Jacobian with x^*, y^* (5.13) to find the characteristic equation.

$$\left|J_{(x_3^*,y_3^*,z_3^*)} - \lambda I\right| = 0$$

$$\begin{vmatrix} -vx^* - \lambda & -\beta x^* & 0 \\ -\beta y^* & -\lambda & \psi y^* \\ \sigma\beta y^* & \sigma\beta x^* & -\gamma - \lambda \end{vmatrix} = 0$$

$$-\lambda(\lambda + \nu x^*)(\lambda + \gamma) - \beta^2\psi\sigma {y^*}^2 x^* + (\lambda + \gamma)\cdot\beta^2 x^* y^* + (\lambda + \nu x^*)\cdot\psi\sigma\beta x^* y^* = 0$$

$$-\lambda^3 - \lambda^2\gamma - \lambda^2\nu x - \lambda\nu x\gamma - \beta^2\psi\sigma {y^*}^2 x + \beta^2 x^* y^*\lambda + \beta^2 x^* y^*\gamma + \lambda\psi\sigma\beta x^* y^* + \nu x^*\psi\sigma\beta x^* y^* = 0$$

$$\lambda^3 + (\gamma + \nu x^*)\lambda^2 - (\beta^2 x^* y^* + \psi\sigma\beta x^* y^* - \nu x^*\gamma)\lambda + \beta^2\psi\sigma {y^*}^2 x - \gamma\beta^2 x^* y^* - \nu\psi\sigma\beta x^* y^* = 0 \quad (5.21)$$

The characteristic equation is in the form, $\lambda^3 + a\lambda^2 + b\lambda + c = 0$. We will now evaluate the constant term, c.

$$\begin{aligned} c &= \beta^2\psi\sigma {y^*}^2 x^* - \gamma\beta^2 x^* y^* - \nu\psi\sigma\beta x^* y^* \\ &= x^* y^*\beta(\beta\psi\sigma y^* - \beta\gamma - \nu\psi\sigma x^*) \end{aligned} \quad (5.22)$$

Now, calculating the expression in the parenthesis, we see that

$$= \psi\sigma\beta y^* - \beta\gamma - \nu\psi\sigma x^2$$

$$= \beta\psi\sigma\left(\frac{\mu}{2\beta} - \frac{\gamma}{2\psi\sigma}\right) - \beta\gamma - \nu\psi\sigma\left(\frac{\mu}{2\nu} - \frac{\beta\gamma}{2\nu\sigma\psi}\right)$$

$$= \frac{\psi\sigma\mu}{2} + \frac{\gamma\beta}{2} - \frac{\psi\sigma\mu}{2} - \frac{\beta\gamma}{2} = 0$$

We can see that the constant term of (5.21) is zero. Thus, one of the eigenvalues will always be 0 (λ = 0) and it is not possible to find the type of this equilibrium point (5.19) using the linearization method and local analysis.

Investigating 3rd and 4th Equilibrium Points (x_3^*, y_3^*, z_3^*) and (x_4^*, y_4^*, z_4^*)

When the discriminant is positive, there will be two more equilibrium points that result from solving the quadratic equation. The Jacobian matrix for these two equilibrium points is the same type as (5.13).

$$J_{(x_3^*, y_3^*, z_3^*)} = J_{(x_4^*, y_4^*, z_4^*)} \begin{bmatrix} -\nu x^* & -\beta x^* & 0 \\ -\beta y^* & 0 & \psi y^* \\ \sigma\beta y^* & \sigma\beta x^* & -\gamma \end{bmatrix}$$

And since the Jacobian matrix is the same type as (5.13), the characteristic polynomial will have the same type as (5.14) depending only on the values of the equilibrium point (x_3^*, y_3^*, z_3^*) or (x_4^*, y_4^*, z_4^*). However, the constant term will not be 0 ($c \neq 0$).

$$\lambda^3 + (\gamma + \nu x^*)\lambda^2 - (\beta^2 x^* y^* + \psi\sigma\beta x^* y^* - \nu x^* \gamma)\lambda + \beta^2 \psi\sigma y^{*2} x - \gamma\beta^2 x^* y^* - \nu\psi\sigma\beta x^* y^* = 0$$

The constant term also depends on the equilibrium point.

$$c = x^* y^* \beta(\beta\psi\sigma y^* - \beta\gamma - \nu\psi\sigma x^*)$$

Here x^* and y^* represent x_3^* and y_3^* or x_4^* and y_4^*. We evaluated this term numerically in Chapter 6.

Now, we know more information about this system and the possible equilibrium points as shown in Table 5.4.

Table 5.4.

Equilibrium Points and their Classifications

Equilibrium Points			**Classification**
$D < 0$	$D = 0$	$D > 0$	
$(0, 0, 0)$	$(0, 0, 0)$	$(0, 0, 0)$	unstable node
$\left(\frac{\mu}{\nu}, 0, 0\right)$	$\left(\frac{\mu}{\nu}, 0, 0\right)$	$\left(\frac{\mu}{\nu}, 0, 0\right)$	stable node
	$\left(\frac{1}{2\nu}\left(\mu - \frac{\beta\gamma}{\sigma\psi}\right), \frac{1}{2}\left(\frac{\mu}{\beta} + \frac{\gamma}{\psi\sigma}\right), \frac{1}{4\nu}\left(\frac{\sigma\mu^2}{\gamma} - \frac{\beta^2\gamma}{\sigma\psi^2\nu}\right)\right)$	(x_3^*, y_3^*, z_3^*)	
		(x_4^*, y_4^*, z_4^*)	

CHAPTER VI

NUMERICAL ANALYSIS OF THE MODEL

In Chapter 5, we found that our model could have two, three, or four equilibrium points depending on the parameters. Now, we demonstrate the behavior of the system (5.2) with parameter values for each of these cases.

2 Equilibrium Points (Discriminant ¡ 0)

Selecting, $\mu = 5$, $\nu = 1$, $\beta = 1$, $\psi = 1$, $\alpha = 2$, $\sigma = 1$, $\gamma = 2$, we see by formula (5.6) that the discriminant,

$$D = \left(\mu - \frac{\beta\gamma}{\sigma\psi}\right)^2 - 4\frac{\nu a\gamma}{\psi\sigma}$$
$$D = \left(5 - \frac{1 \cdot 2}{1 \cdot 2}\right)^2 - 4\,\frac{1 \cdot 2 \cdot 2}{1 \cdot 1}$$
$$D = -7 < 0$$

The Jacobian at (0,0,0) is

$$J_{(0,0,0)} = \begin{bmatrix} 5 & 0 & 0 \\ 0 & -2 & 0 \\ 0 & 0 & -2 \end{bmatrix}$$

The $tr(J) = 1$ and $\det J = 20$. Because this is a diagonal matrix, we can see the characteristic equation is $(5 - \lambda)(-2 - \lambda)(-2 - \lambda)$ and the eigenvalues are $\lambda_1 = 5$, $\lambda_2 = -2$, $\lambda_3 = -2$. We have one real positive and 2 real negative eigenvalues. This confirms

what we found analytically in section 5.2.2, that (0, 0, 0) is an asymptotically unstable node.

The Jacobian at (5, 0, 0) is

$$J_{(5,0,0)}= \begin{bmatrix} -5 & -5 & 0 \\ 0 & -7 & 0 \\ 0 & 5 & 2 \end{bmatrix}$$

The $tr(J) = -14$, the det $J = -70$, and the characteristic equation is $\lambda^3 + 14\lambda^2 + 59\lambda + 70 = 0$. Thus, we know the eigenvalues are $\lambda_1 = -5$, $\lambda_2 = -7$, $\lambda_3 = -2$. All of the eigenvalues are real and negative, confirming what we found analytically in section 5.2.2, that (5, 0, 0) is an asymptotically stable node. Figures 6.1 - 6.3 show $x(t)$, $y(t)$, and $z(t)$ as a function of time on the time interval (0, 10) or (0, 20) for Figure 6.3 . Notice that for all of these initial conditions, the system goes to the stable point, (5, 0, 0). Figure 6.3 required more time to get there because of the aggressive autoimmune reaction that occurred early. The T-cells (green line) peaked to a maximum value of almost 24 before going to 0. And with the increase of the T-cells and antigens, the tissue cell went to 0. So, even though the system eventually made it to the equilibrium point, in reality a patient would have died because of the loss of the tissue cells before the system could get back to the healthy stable equilibrium point. Figure 6.1 represents a healthy individual without a self-sustaining autoimmune reaction. Figure 6.4 gives a 3d view of the trajectories of this system with the three different initial conditions from Figures 6.1 - 6.3. The blue trajectory represents the initial conditions of Figure 6.1, the green trajectory represents the initial conditions of Figure 6.2, and the red trajectory represents the initial conditions

of Figure 6.3. Notice, in Figure 6.4 we can see all the trajectories in time approaching the stable equilibrium point $(\frac{\mu}{\nu}, 0, 0) = (5, 0, 0)$. And finally Figure 6.6 is the 3d field plot of the system.

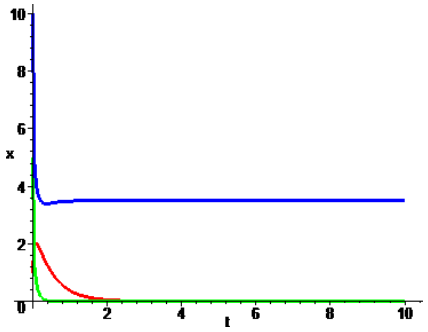

Figure 6.1. x(0) = 10, (blue) y(0) = 5 (green), z(0) = 1 (red)

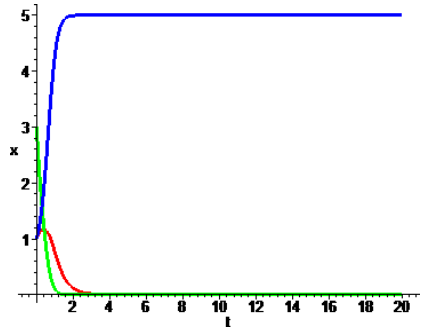

Figure 6.2. x(0) = 1 (blue) y(0) = 3 (green), z(0) = 1 (red)

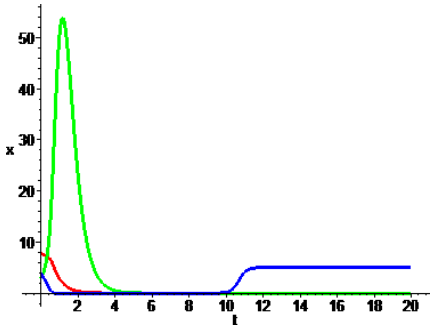

Figure 6.3. x(0) = 4 (blue) y(0) = 3 (green), z(0) = 8 (red)

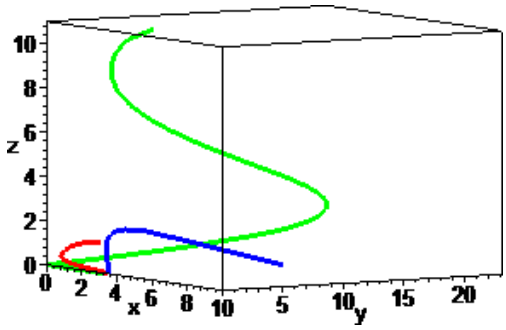

Figure 6.4. 3d graph of the system trajectories Blue-Figure 6.1 initial conditions Green-Figure 6.2 initial conditions Red-Figure 6.3 initial conditions

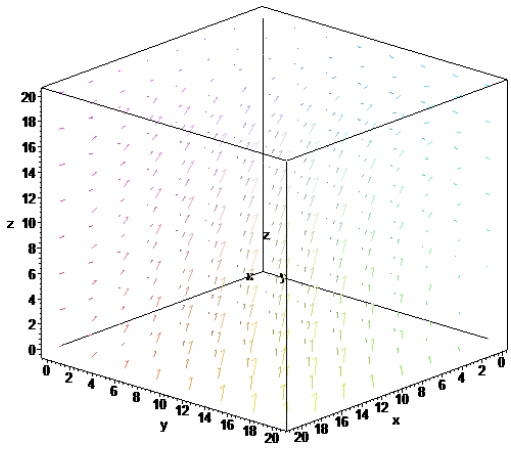

Figure 6.5. 3d field plot

3 Equilibrium Points (Discriminant = 0)

Selecting, $\mu = 3.5$, $v = 1$, $\beta = 3$, $\psi = 1$, $\alpha = 2$, $\sigma = 4$, $\gamma = 2$, we see that the discriminant is 0 ($D = 0$)

$$D = \left(\mu - \frac{\beta\gamma}{\sigma\psi}\right)^2 - 4\frac{va\gamma}{\psi\sigma}$$

$$D = \left(3.5 - \frac{3 \cdot 2}{4 \cdot 1}\right)^2 - 4\frac{1 \cdot 2 \cdot 2}{1 \cdot 4} = 0$$

The first equilibrium point is $(x_1^*, y_1^*, z_1^*) = (0, 0, 0)$. We know from the analytical investigation that this is an asymptotically unstable node. The second equilibrium point is $(x_2^*, y_2^*, z_2^*) = (\frac{\mu}{v}, 0, 0) = (\frac{3.5}{1}, 0, 0) = (3.5, 0, 0)$. We know from the analytical investigation that this is an asymptotically stable node.

And the third equilibrium point is

$$x_3^* = \frac{1}{2v}\left(\mu - \frac{\beta\gamma}{\sigma\psi}\right) + \frac{1}{2 \cdot 1}\left(3.5 - \frac{3 \cdot 2}{4 \cdot 1}\right) = 1$$
$$y_3^* = \frac{1}{2}\left(\frac{\mu}{\beta} + \frac{\gamma}{\psi\sigma}\right) = \frac{1}{2}\left(\frac{3.5}{3} + \frac{2}{4 \cdot 1}\right) = 0.8\overline{33}$$
$$(x_3^*, y_3^*, z_3^*) = (1, 0.8\overline{33}, 5)$$

The Jacobian (5.9) at (x_3^*, y_3^*, z_3^*) is

$$J_{(1,0.8\overline{33},5)} = \begin{bmatrix} -1 & -3 & 0 \\ -2.5 & 0 & .8\overline{33} \\ 10 & 12 & -2 \end{bmatrix}$$

The $tr(J) = -3$ and $\det J = 75$ and the characteristic equation is $\lambda^3 + 3\lambda^2 - 15.5\lambda = 0$. And so, we know the eigenvalues are $\lambda_1 = 0, \lambda_2 \approx 2.713, \lambda_3 \approx -5.713$. There is one root that is 0, one positive real root, and one negative real root. As we established

analytically, one of the eigenvalues is zero so in order to classify this equilibrium point we need to do further analysis such as investigation of the Lyapunov function.

Figures 6.6 - 6.8 show $x(t)$, $y(t)$, and $z(t)$ as a function of time on the interval (0,10). Notice that for all of these initial conditions, the system goes to the stable node, (3.5, 0, 0). Figures 6.7 and 6.8 represent a person experiencing an autoimmune reaction. The peak of the green line represents an increase in T- Lymphocytes. At the same time as the increase in T-Lymphocytes, there is a smaller increase in antigen levels and a decrease in tissue cells. While these figures will eventually get to the stable equilibrium point mathematically, this healthy condition would not be realized as the patient would die as a result of the loss of tissue cells. Notice also that the initial conditions of Figure 6.6 are just below the third unclassified equilibrium point while the initial conditions of Figure 6.7 are above the same point.

Figure 6.9 gives a 3d view of the three trajectories of this system with the initial conditions from figures 6.6 - 6.8. The blue trajectory represents the initial conditions of Figure 6.6, the green v trajectory represents the initial conditions of Figure 6.7, and the red trajectory represents the initial conditions of Figure 6.8. In Figure 6.9, we see all the trajectories in time $t[0, 1000]$ approaching the stable equilibrium point $(\frac{\mu}{}, 0, 0) = (3.5, 0, 0)$. And finally, Figure 6.10 is the 3d field plot of the system.

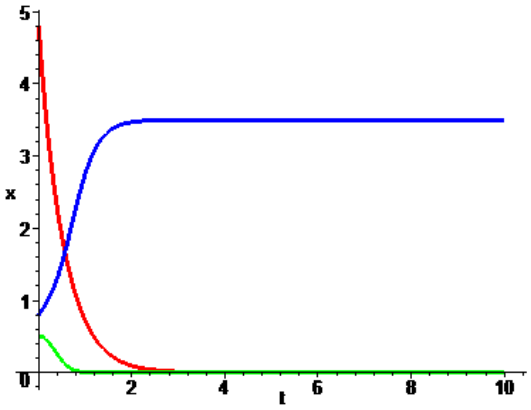

Figure 6.6. x(0) = .8 (blue) y(0) = .5 (green), z(0) = 4.8 (red) below eq point $(x_3^*, y_3^*, z_3^*) = (1, 0.8\overline{3}, 5)$

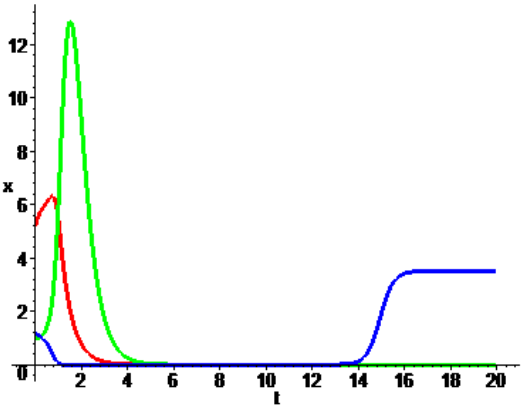

Figure 6.7. x(0) = 1.2 (blue) y(0) = 1 (green), z(0) = 5.2 (red) above eq point $(x_3^*, y_3^*, z_3^*) = (1, 0.8\overline{3}, 5)$

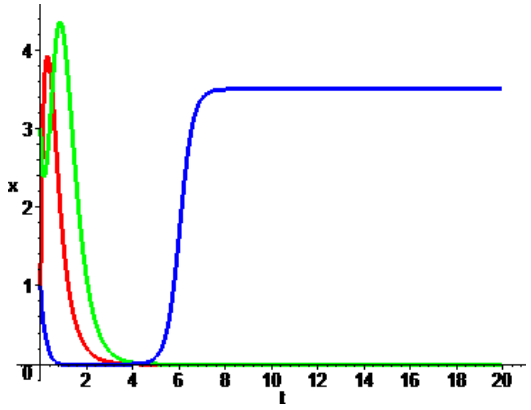

Figure 6.8. x(0) = 1 (blue) y(0) = 3 (green), z(0) = 1 (red)

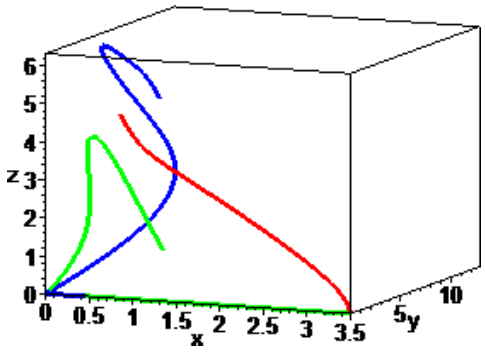

Figure 6.9. 3d graph of the system trajectories

Blue-Figure 6.6 initial conditions

Green-Figure 6.7 initial conditions

Red-Figure 6.8 initial conditions

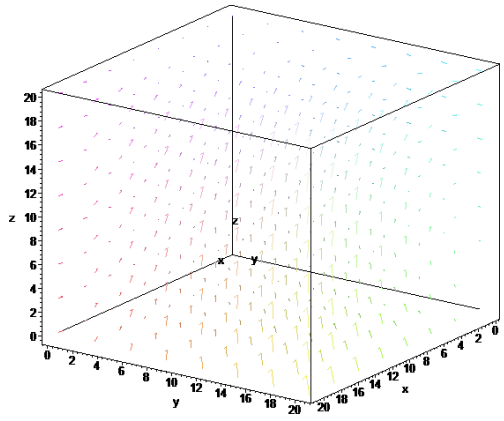

Figure 6.10. 3d field plot

4 Equilibrium Points (Discriminant > 0)

Selecting, $\mu = 5$, $\nu = 1$, $\beta = 1$, $\psi = 1$, $\alpha = 1$, $\sigma = 1$, $\gamma = 2$, we see by formula (5.6) that the discriminant,

$$D = \left(\mu - \frac{\beta\gamma}{\sigma\psi}\right)^2 - 4\frac{va\gamma}{\psi\sigma}$$

$$D = \left(3.5 - \frac{3 \cdot 2}{4 \cdot 1}\right)^2 - 4\frac{1 \cdot 2 \cdot 2}{1 \cdot 4} = 0$$

The first equilibrium point is $(x_1^*, y_1^*, z_1^*) = (0, 0, 0)$. We know from the analytical investigation that this is an asymptotically unstable node. The second equilibrium point is $(x_2^*, y_2^*, z_2^*) = (\frac{\mu}{\nu}, 0, 0) = (\frac{3.5}{1}, 0, 0) = (5, 0, 0)$. We know from the analytical investigation that this is an asymptotically stable node.

The third equilibrium point is

$$x_3^* = \frac{\mu - \frac{\beta\gamma}{\sigma\psi} + \sqrt{\left(\mu - \frac{\beta\gamma}{\sigma\psi}\right)^2 - 4\frac{va\gamma}{\psi\sigma}}}{2\nu}$$

$$x_3^* = \frac{5 - \frac{1 \cdot 2}{1 \cdot 1} + \sqrt{\left(5 - \frac{1 \cdot 2}{1 \cdot 1}\right)^2 - 4\frac{1 \cdot 1 \cdot 2}{1 \cdot 1}}}{2 \cdot 1} = 2$$

$$y_3^* = \frac{\mu}{\beta} - \frac{1}{2\beta}\left(\frac{\mu - \beta\gamma}{\sigma\psi} + \sqrt{\left(\mu - \frac{\beta\gamma}{\sigma\psi}\right)^2 - 4\frac{va\gamma}{\psi\sigma}}\right)$$

$$y_3^* = \frac{5}{1} - \frac{1}{2 \cdot 1}\left(\frac{5 - 1 \cdot 2}{1 \cdot 1} + \sqrt{\left(5 - \frac{1 \cdot 2}{1 \cdot 1}\right)^2 - 4\frac{1 \cdot 1 \cdot 2}{1 \cdot 1}}\right) = 3$$

$$z_3^* = \frac{\sigma\beta}{\gamma}\left[\left(\frac{\mu - \frac{\beta\gamma}{\sigma\psi} + \sqrt{\left(\mu - \frac{\beta\gamma}{\sigma\psi}\right)^2 - 4\frac{v\alpha\gamma}{\psi\sigma}}}{2v}\right)\right.$$
$$\left.\cdot\left(\frac{\mu}{\beta} - \frac{1}{2\beta}\left(\frac{\mu - \beta\gamma}{\sigma\psi} + \sqrt{\left(\mu - \frac{\beta\gamma}{\sigma\psi}\right)^2 - 4\frac{v\alpha\gamma}{\sigma\psi}}\right)\right)\right]$$

$$z_3^* = \frac{1\cdot 1}{2}\left[\left(\frac{5 - \frac{1\cdot 2}{1\cdot 1} + \sqrt{\left(5 - \frac{1\cdot 2}{1\cdot 1}\right)^2 - 4\frac{11\cdot 2}{1\cdot 1}}}{2\cdot 1}\right)\right.$$
$$\left.\cdot\left(\frac{5}{1} - \frac{1}{2\cdot 1}\left(\frac{5 - 1\cdot 2}{1\cdot 1} + \sqrt{\left(5 - \frac{1\cdot 2}{1\cdot 1}\right)^2 - 4\frac{1\cdot 1\cdot 2}{1\cdot 1}}\right)\right)\right] = 3$$

$$(x_3^*, y_3^*, z_3^*) = (2,3,3)$$

Substituting these coordinates into (5.16)

$$\begin{aligned} c &= x^* y^* \beta(\beta\psi\sigma y^* - \beta\gamma - \nu\psi\sigma x^*) \\ &= 2\cdot 3\cdot 1\cdot(1\cdot 1\cdot 1\cdot 3 - 1\cdot 2 - 1\cdot 1\cdot 1\cdot 2) = -6 \end{aligned} \tag{6.1}$$

And the Jacobian (5.9) at this point is

$$J_{(2,3,3)} = \begin{bmatrix} -2 & -2 & 0 \\ -3 & 0 & 3 \\ 3 & 2 & -2 \end{bmatrix}$$

The $tr(J) = -4$ and $\det J = 6$ and the characteristic equation is $\lambda^3 + 4\lambda^2 - 8\lambda - 6 = 0$. The constant term of the characteristic polynomial is -6 as we saw above in (6.1). Solving the characteristic equation for its zeros, we find the eigenvalues are

$\lambda_1 \approx 1.8945$, $\lambda_2 \approx -5.2965 - 1 \cdot 10^{-10} \cdot i$, and $\lambda_3 \approx -.59795 - 1 \cdot 10^{-10} \cdot i$. Thus, it has 1 positive real root and 2 complex roots in which the real part is negative so it is an asymptotically unstable spiral.

The fourth equilibrium point is

$$x_4^* = \frac{\mu - \frac{\beta\gamma}{\sigma\psi} - \sqrt{\left(\mu - \frac{\beta\gamma}{\sigma\psi}\right)^2 - 4\frac{va\gamma}{\psi\sigma}}}{wv}$$

$$x_4^* = \frac{5 - \frac{1 \cdot 2}{1 \cdot 1} - \sqrt{\left(5 - \frac{1 \cdot 2}{1 \cdot 1}\right)^2 - 4\frac{1 \cdot 1 \cdot 2}{1 \cdot 1}}}{2 \cdot 1} = 1$$

$$y_4^* = \frac{\mu}{\beta} - \frac{1}{2\beta}\left(\frac{\mu - \beta\gamma}{\sigma\psi} - \sqrt{\left(\mu - \frac{\beta\gamma}{\sigma\psi}\right)^2 - 4\frac{va\gamma}{\psi\sigma}}\right)$$

$$z_4^* = \frac{\sigma\beta}{\gamma}\left[\left(\frac{\mu - \frac{\beta\gamma}{\sigma\psi} - \sqrt{\left(\mu - \frac{\beta\gamma}{\sigma\psi}\right)^2 - 4\frac{va\gamma}{\psi\sigma}}}{2v}\right)\right.$$

$$\left. \cdot \left(\frac{\mu}{\beta} - \frac{1}{2\beta}\left(\frac{\mu - \beta\gamma}{\sigma\psi} + \sqrt{\left(\mu - \frac{\beta\gamma}{\sigma\psi}\right)^2 - 4\frac{va\gamma}{\sigma\psi}}\right)\right)\right]$$

$$z_4^* = \frac{1 \cdot 1}{2}\left[\left(\frac{5 - \frac{1 \cdot 2}{1 \cdot 1} - \sqrt{\left(5 - \frac{1 \cdot 2}{1 \cdot 1}\right)^2 - 4\frac{11 \cdot 2}{1 \cdot 1}}}{2 \cdot 1}\right)\right.$$

$$\left. \cdot \left(\frac{5}{1} - \frac{1}{2 \cdot 1}\left(\frac{5 - 1 \cdot 2}{1 \cdot 1} + \sqrt{\left(5 - \frac{1 \cdot 2}{1 \cdot 1}\right)^2 - 4\frac{1 \cdot 1 \cdot 2}{1 \cdot 1}}\right)\right)\right] = 2$$

$$(x_4^*, y_4^*, z_4^*) = (1,4,2)$$

Substituting these coordinates into (5.16)

$$\begin{aligned} c &= x^* y^* \beta(\beta\psi\sigma y^* - \beta\gamma - \nu\psi\sigma x^*) \\ &= 1 \cdot 4 \cdot 1 \cdot (1 \cdot 1 \cdot 1 \cdot 4 - 1 \cdot 2 - 1 \cdot 1 \cdot 1 \cdot 1) = 4 \end{aligned} \tag{6.2}$$

And the Jacobian (5.9) is

$$J_{(1,4,2)} = \begin{bmatrix} -1 & -1 & 0 \\ -4 & 0 & 4 \\ 4 & 1 & 2 \end{bmatrix}$$

The $tr(J) = -3$, the det $J = -4$, and the characteristic equation is $\lambda^3 + 3\lambda^2 - 6\lambda + 4 = 0$. The constant term of the characteristic polynomial is 4 as we saw above in (6.2). Solving the characteristic equation for its zeros, we find the eigenvalues are $\lambda_1 \approx -4.5223$, $\lambda_2 \approx .7612 - .5524 \cdot i$, and $\lambda_3 \approx .7612 + .5524 \cdot i$. It has 1 negative real root and 2 complex roots with positive real parts. Thus, we can classify this equilibrium point as an asymptotically unstable spiral.

Figures 6.11 - 6.13 show $x(t)$, $y(t)$, and $z(t)$ as a function of time on the interval (0,10). Notice that for all of these initial conditions, the system goes to the stable point, (5, 0, 0). However, the activity on the interval (0, 4) varies greatly depending on the initial conditions and is interesting. Figure 6.11 shows activity similar to Figure 6.3 (when there

were only 2 equilibrium points). Notice that the maximum of the T-Lymphocytes coincides with a level near or at 0 for the healthy tissue(x) and antigens (z). While the system mathematically recovers and moves toward the stable equilibrium point, in reality a person would die before getting back to the healthy equilibrium point because of the loss of healthy tissue. The initial conditions of Figure 6.11 are just below the third equilibrium point, while the initial conditions of 6.12 are just above it. The initial conditions of 6.13 are just below the 4th equilibrium point. The initial conditions of 6.14 are just above the fourth equilibrium point. Notice in Figure 6.14 there is a peak in the t-cells, but the population of tissue cells is able to recover before getting to zero.

Figure 6.15 gives a 3d view of the three trajectories of this system with the initial conditions from figures 6.11 - 6.14. The blue trajectory represents the initial conditions of Figure 6.11, the green trajectory represents the initial conditions of Figure 6.12, the red trajectory represents the initial conditions of Figure 6.13, and the black trajectory represents the initial conditions of Figure 6.14. Figure 6.16 is a 3d field plot of the system. Table 6. 1 provides a summary of the results of the numerical analysis

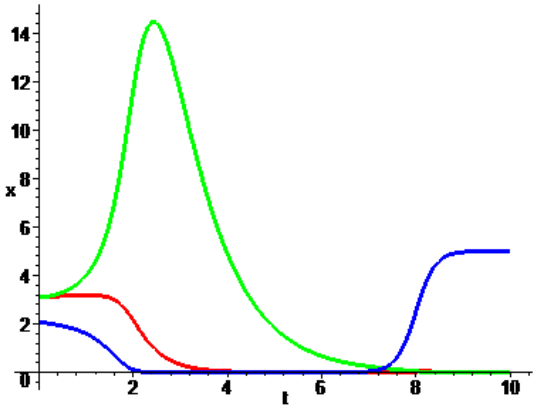

Figure 6.11. x(0) = 2.1 (blue)

y(0) = 3.1 (green), z(0) = 3.1 (red)

above eq. point (x_3^*, y_3^*, z_3^*) = (2, 3, 3)

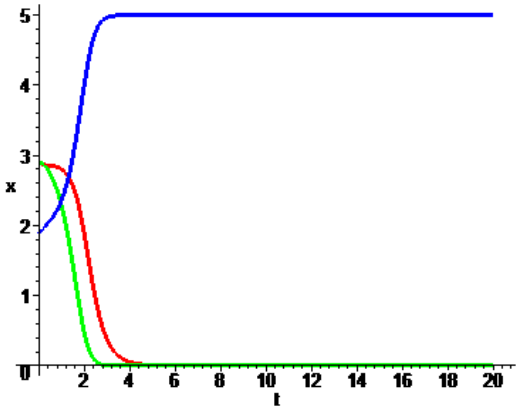

Figure 6.12. x(0) = 1.9 (blue)

y(0) = 2.9 (green), z(0) = 2.9 (red)

below eq. point (x_3^*, y_3^*, z_3^*) = (2, 3, 3)

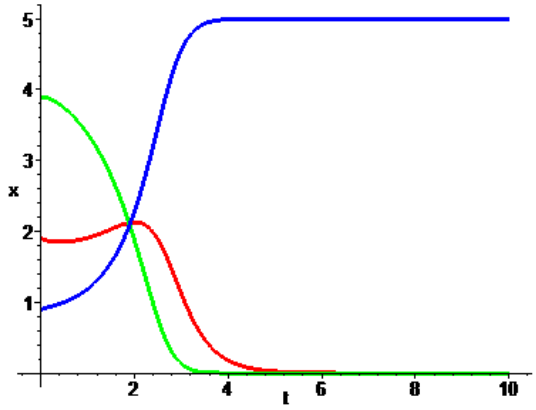

Figure 6.13. x(0) = .9(blue)

y(0) = 3.9 (green), z(0) = 1.9 (red)

below eq. point (x_4^*, y_4^*, z_4^*) = (1, 4, 2)

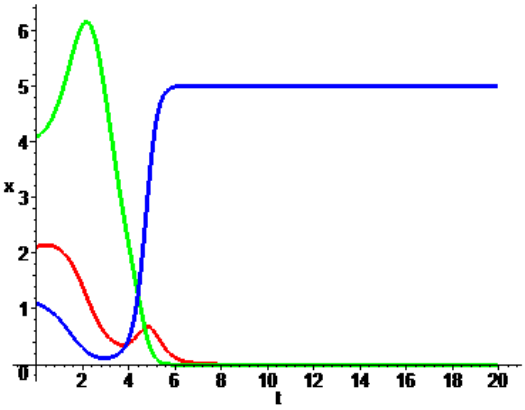

Figure 6.14. x(0) = 1.1 (blue)

y(0) = 4.1 (green), z(0) = 2.1 (red)

above eq. point (x_4^*, y_4^*, z_4^*) = (1, 4, 2)

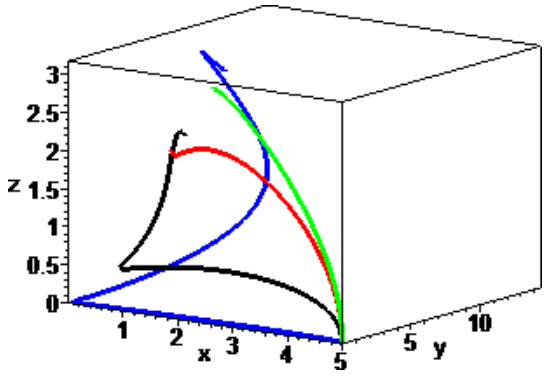

Figure 6.15. 3d graph of the system trajectories

Blue-Figure 6.11 initial conditions

Green-Figure 6.12 initial conditions

Red-Figure 6.13 initial conditions

Black-Figure 6.14 initial conditions

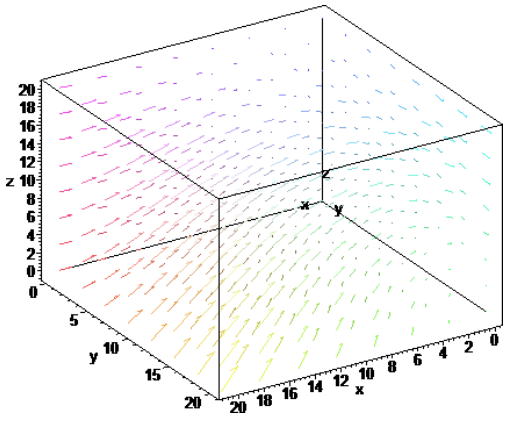

Figure 6.16. 3d field plot

Table 6.1.

Equilibrium Points and their Classification from Numerical Analysis

Equilibrium Points			**Classification**
$D < 0$	$D = 0$	$D > 0$	
(0, 0, 0)	(0, 0, 0)	(0, 0, 0)	unstable node
(5, 0, 0)	(3.5, 0, 0)	(5, 0, 0)	stable node
	$(1, 0.8\overline{33}, 5)$		need more analysis
		(2, 3, 3)	unstable spiral
		(1, 4, 2)	unstable spiral

CHAPTER VII

CONCLUSIONS

I investigated a model of autoimmunity at the cellular level. During this investigation, I saw how the production of T lymphocyte cells and their mutual destruction of healthy tissue cells affect the concentration of healthy tissue cells. This model was focused on the self-sustaining autoimmune reaction involving T lymphocyte killer cells, antigens, and the healthy tissue cells that are being attacked. This model represents a part of the cell mediated response of the adaptive immune system. Further models can be created and investigated to consider the humoral response of the adaptive immune system or the cause of the autoimmune response. There are many unanswered questions in the study of immunology and autoimmune disease that can be answered with further mathematical study.

Interpretation of the Equilibrium Points

In the investigation of the system of nonlinear ODEs, we found situations that resulted in 2, 3, or 4 equilibrium points and used a Jacobian matrix to classify these equilibrium points. In this section, I consider the biological application of that classification.

First Equilibrium Point

The first equilibrium point was $(0, 0, 0)$ and we found it to always be asymptotically unstable. This is trivial as it represents a case where the concentration of healthy tissue cells, T lymphocytes, and tissue specific antigens are all 0.

Second Equilibrium Point

The second equilibrium point was $(\frac{\mu}{\nu}, 0, 0)$ and we found that it is an asymptotically stable equilibrium point. This equilibrium point represents a healthy individual with a normal size of healthy tissue cell and minimal number of T lymphocytes or tissue specific antigens. This represents a healthy individual in which the self-sustaining autoimmune reaction has not started and therefore cytotoxic T-cells are not reproducing. Medically our goal is to get all individuals to this equilibrium point.

Third and Fourth Equilibrium Points

The third and fourth equilibrium points resulted from the quadratic formula. After investigating with some possible parameter values, we found that x_3^* and x_4^* are asymptotically unstable spirals. Based on our bifurcation analysis, these points are not always part of the system. They only occur when $\left(\mu - \frac{\beta\gamma}{\sigma\psi}\right)^2 - 4\frac{va\gamma}{\sigma\psi} > 0$ and we are only concerned when both roots are positive which means that $\mu > \frac{\beta\gamma}{\sigma\psi}$.

When the system tends towards these equilibrium points, it represents situations with a self-sustaining autoimmune reaction at varying levels. The system will eventually get to the stable node, $(\frac{\mu}{\nu}, 0, 0)$ mathematically. However, biologically, the patient will not survive the loss of tissue cells.

When $\left(\mu\ \frac{\beta\gamma}{\sigma\psi}\right)^2 - 4\frac{va\gamma}{\sigma\psi} = 0$. There are only 3 equilibrium points. However, because one of the eigenvalues will always be zero, we need to do further analysis in order to classify this equilibrium point. This model appears to be a good and accurate

representation of the features of the autoimmune reaction. This is a good model to continue to work with and to develop further for other theories of autoimmunity.

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