Spring 2019

Optimal Control Theory and Estimation of Parameters in a Differential Equation Model for Patients with Lupus

Peter Agaba
Western Kentucky University, peter.agaba003@topper.wku.edu

OPTIMAL CONTROL THEORY AND ESTIMATION OF PARAMETERS IN A DIFFERENTIAL EQUATION MODEL FOR PATIENTS WITH LUPUS

A Thesis
Presented to
The Faculty of the Department of Mathematics
Western Kentucky University
Bowling Green, Kentucky

In Partial Fulfillment
Of the Requirements for the Degree
Master of Science

By
Peter Agaba

May 2019

OPTIMAL CONTROL THEORY AND ESTIMATION OF PARAMETERS IN A DIFFERENTIAL EQUATION MODEL FOR PATIENTS WITH LUPUS

Date Recommended 3/26/19

Richard Schugart, Director of Thesis

Ngoc Nguyen

Ngoc Nguyen

Tom Richmond

Tom Richmond

Cheryl D. Davis 4/9/19

Dean, Graduate Studies and Research Date

ACKNOWLEDGMENTS

At the very outset, I would like to thank my advisor, Dr. Schugart for his guidance throughout my thesis project. Not only did he agree to work with me, he was also available whenever I needed his advice. Without his knowledge, guidance, and support, I would not have been able to successfully complete this thesis. I would also like to thank Dr. Richmond and Dr. Nguyen for agreeing to serve in my thesis committee, and for giving me great insights whenever I went to see them with any question. I am grateful to WKU Mathematics staff for their support, not just when I was working on this thesis, but throughout my career in WKU's math department. Their support played a major role in my being able to complete both my undergraduate and Master's math degrees and graduate from Western Kentucky University.

Lastly, a very big thank you to my family and friends for all their uttermost support and encouragement.

CONTENTS

List of Figures

List of Tables

ANALYSIS AND IMPLEMENTATION OF NUMERICAL METHODS FOR SOLVING ORDINARY DIFFERENTIAL EQUATIONS

Peter Agaba May 2019 113 Pages

Directed by: Dr. Schugart Richard, Dr. Thomas Ricmond, and Dr. Ngoc Nguyen

Department of Mathematics Western Kentucky University

System Lupus Erythematosus (SLE) is a chronic inflammatory autoimmune disorder that affects many parts of the body including skin, joints, kidneys, brains and other organs. Lupus Nephritis (LN) is a disease caused by SLE. Given the complexity of LN, we establish an optimal treatment strategy based on a previously developed mathematical model.For our thesis work, the model variables are: Immune Complexes (I), Pro-inflammatory mediators (P), Damaged tissue (D), and Anti-inflammatory mediators (A). The analysis in this research project focuses on analyzing therapeutic strategies to control damage using both parameter estimation techniques (integration of data to quantify any uncertainties associated with parameters) and optimal control with the goal of minimizing time spent on therapy for treating damaged tissue by LN.

CHAPTER 1

INTRODUCTION

1.1. Biology

Systemic Lupus Erythematosus (SLE) is a chronic inflammatory autoimmune disorder that affects many parts of the body including skin, joints, kidneys, brain, and other organs. SLE develops when the body attacks its own immune system and components, confusing them to be the foreign particles attacking the body. One can define Lupus Nephritis (LN) as the kidney disease caused by SLE. LN is mostly characterized by the relapses of the disease, flares, and the remissions that take place after the treatment (Budu-Grajdeanu et al., 2010). Immunity initiates SLE and subsequently LN where the continuous production of auto-antibodies and defects in the clearance system allows immune complexes to deposit in various organs like kidneys in LN (Budu-Grajdeanu et al., 2010).

According to the Avihingsanon and Hirankarn (2010), at least 1.5 million Americans are living with diagnosed lupus, although, the number is believed to be higher given that some people live with undiagnosed lupus. Lupus most affects women. In fact, women make up about nine out of ten adults with the disease. It's also more common in women of African American, Hispanic, Asian, and Native American descent than in Caucasian women (Mu, et al., 2017). Furthermore, SLE is more

prevalent in women than men across all age groups and populations; the female-to-male ratio is highest at reproductive age, ranging between 8:1 and 15:1, and is lowest in prepubertal children at about 4:3 (Smoller & Sundram, 2009).

The prognosis of LN is even worse than non-renal SLE and this can end in chronic kidney disease. The pathogenesis of LN is complex and is influenced by environmental and genetic factors (Budu-Grajdeanu et al., 2010). LN is clinically evident in $50-60\%$ of patients with SLE. Also, people with SLE are more likely to have LN even without clinical manifestations of renal disease. Lupus is developed when Anti-DNA antibodies or immune complexes (that contain these antibodies) are deposited in the kidney and as a result complement tissue is developed which leads to tissue inflammation and damage, and this consequently leads to the release of DNA, nuclear material, and cell debris. These products released lead to the tissue damage which serves as antigens that stimulates the immune system and increases intrarenal inflammation thus leading to LN (Budu-Grajdeanu et al., 2010).

The pathogenesis of LN follows mainly two phases, and these are: systematic events in the immune system and local events in the end organs (Budu-Grajdeanu et al., 2010). The better understanding of pathogenesis would involve studying the molecular pathogenesis of LN and the potential therapeutics. Also, many cells and molecules in these pathogenic cascades serve as attractive therapeutic targets such as T-cells and B-cells whose interactions involve multiple co-stimulatory molecules (Budu-Grajdeanu et al., 2010). That is to say, the pathogenic mechanisms that lead to SLE and lupus are related to genetic predisposition in the environmental settings

and/or stochastic triggers which innate the immune system to activate pathological T-cells and B-cells leading to subsequent inflammation and tissue injury (Mu, et al., 2017).

Lupus is hard to treat and diagnose because its symptoms and signs such as headaches, skin rash especially on cheeks and nose, joint pains, and anemia are same as the symptoms for diseases like HIV, cancer, diabetes and many others. Treatment of LN is more effective when it is done at early remission and prognosis before development and deposition of cascades of flare on the tissue. To better understand Lupus, it is important to study renal disease because it is the most common and serious manifestation of SLE. Renal involvement in SLE adversely affects its ultimate prognosis in terms of patient survival and renal survival rates, as well as quality of life, including work disability (Yazdany & Yelin, 2010). Overall improvements in medical care including the availability of antibiotics, antihypertensive, and renal replacement therapy coupled with the judicious use of glucocorticoid, antimalarial, and immunosuppressive drugs have led to improved survival of SLE patients in the past 50 years (Hirohata, 2018). Recent treatments of LN depend mostly on the severity and type of renal involvement (Littlejohn, et al., 2018).

Recent treatments of LN have involved high dose of corticosteroids accompanied by cytotoxic drugs used in treatment of severe kidney disease. This kind of treatment helps in reducing the harmful effects of humoral or cellular immunity which allows the body to reestablish immunologic homeostasis (Budu-Grajdeanu et

al., 2010). The goal of the treatment of LN is to induce sustained remission, preserve renal parenchyma, and improve the functioning of the kidney. Also, in recent years improved clinical treatments have been based on biomarkers and chemokines. Biomarkers have been used to treat flare cycles immediately before flare, at flare and immediately after flares where urine and serum factors are monitored so as to understand renal flare amounts. On the other hand, chemokines are used to study the change in amount of disease. This is because chemokines and biomarkers are responsible for amplifying the inflammatory response by recruiting additional leukocytes to the kidney, thereby mediating tissue injury and renal dysfunction (Budu-Grajdeanu et al., 2010). The setback in treatment of the LN is that it is very hard to predict when to effectively apply immunosuppressive therapies, and the pathogenesis of LN flare itself.

1.2. Mathematical Modeling

In this project, we analyze a mathematical model using parameter estimation techniques and modify the model to analyze the treatment of LN from an optimal control perspective. Due to the complexity of LN, the primary goal of this thesis is to establish an optimal treatment strategy for LN where we will use as the basis an LN mathematical model data and then add more constraints with the goal of improving their previous results by (Budu-Grajdeanu et al., 2010). In order to control LN, we use four mathematical equations for the primary variables (Immune complexes(I), Pro-inflammatory mediators(P), Damaged tissue(D), and Anti-inflammatory mediators(A) that determine the treatment of LN:

- *Immune Complexes(I)*: These are components of immune system which contribute to the formation of immune complexes (antigens, antigen presenting cells, T cells, B-cells);
- *Pro-inflammatory mediators(P)*: Here we account for the combined effect immune cells such as macrophages and lymphocytes, and components of pro-inflammatory mediators such as MCP-1, TNF-α, IL-1-β;
- *Damaged tissue(D)*: This is the healthy tissue that has been damaged by immune complexes and is undergoing apoptosis or necrosis;
- *Anti-inflammatory mediators(A)*: This represents the combined effect of anti-inflammatory cells, anti-inflammatory cytokines such as IL-10, TGF-β, as well as therapeutics.

The four equations in the mathematical model (Budu-Grajdeanu et al., 2010) are:

$$\frac{dI}{dt} = \underbrace{f(s_i)}_{\text{deposition}} + \underbrace{f(s_{id})\frac{D^2}{k_{id}^2 + D^2}}_{\text{renal production}} - \underbrace{k_{ip} f(P) I)}_{\text{phagocytosis}} \tag{1.1}$$

$$\frac{dP}{dt} = \underbrace{f(k_{pi} I + k_{pp} P)}_{\text{pro-inflammation}} + \underbrace{f(k_{pd} D)}_{\text{infiltration}} - \underbrace{\mu_p P}_{\text{decay}} \tag{1.2}$$

$$\frac{dD}{dt} = \underbrace{k_{dip} f(P) I}_{\text{phagocytosis}} + \underbrace{k_{dp} f(P)}_{\text{collateral damage}} - \underbrace{\mu_d D}_{\text{decay}} \tag{1.3}$$

$$\frac{dA}{dt} = \underbrace{u}_{\text{therapy}} + \underbrace{f(k_{ap} P + k_{ad} D)}_{\text{intrarenal production}} - \underbrace{\mu_a A}_{\text{decay}} \tag{1.4}$$

The above inhibitions are incorporated into the model by taking $f(x) = \frac{x}{1+(\frac{A}{A_{inf}})^2}$.

1.3. Parameter and Model Verification

To ensure that the parameters and model agree with the model in Budu-Grajdeanu et al.(2010), we solve the differential equations using the MATLAB's differential equation solver ode45. Figure 5 in Budu-Grajdeanu et al.(2010) is graphs of the pro-inflammatory mediators (P) and tissue damage (D) (figure 1.1). These graphs were reprinted with permission from Budu-Grajdeanu et al.(2010). We have plotted all 4 state variable for all patients (figure1.2). The graphs of P and D are in agreement with the original work which verifies that we are using the correct form of the mathematical model and corresponding parameter values (Table1.1) and piecewise constant functions (Table1.2).

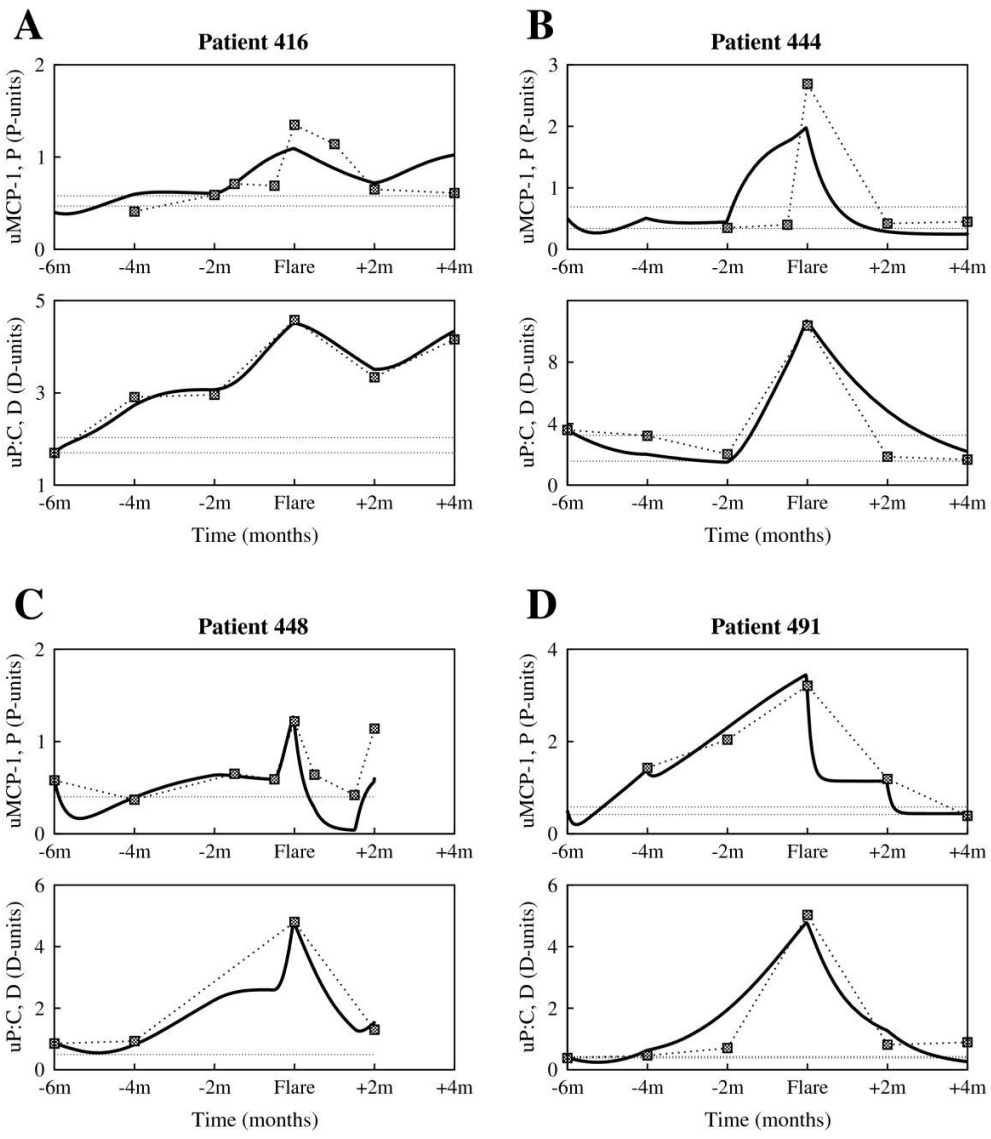

FIGURE 1.1. Model Solution and Data of Pro-inflammatory (P) and Tissue Damage (D). Figure is reproduction from Budu-Grajdeanu et al. (2010), originally published by BioMed Central.

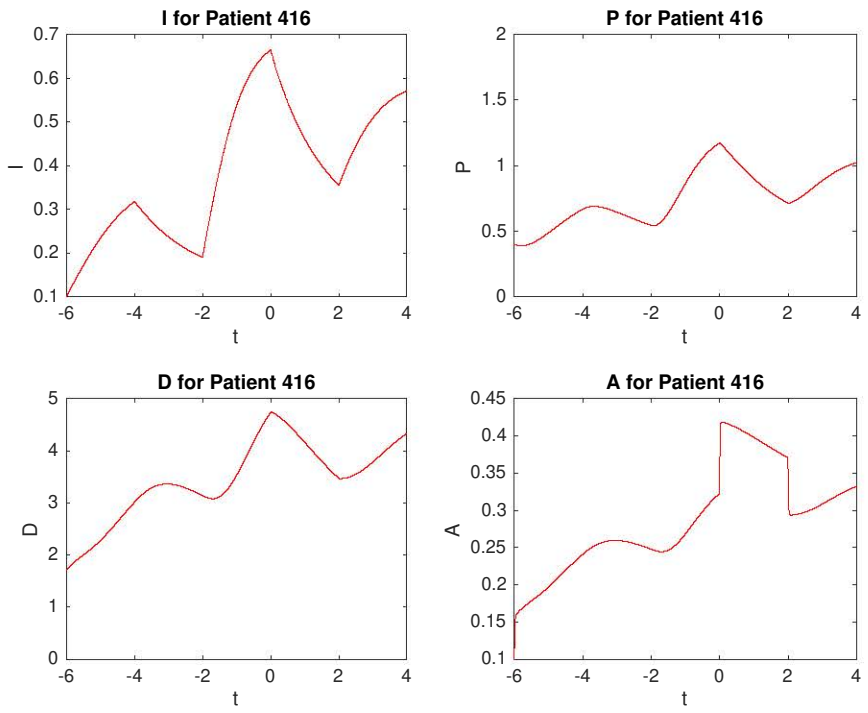

FIGURE 1.2. Model Solution for patient 416

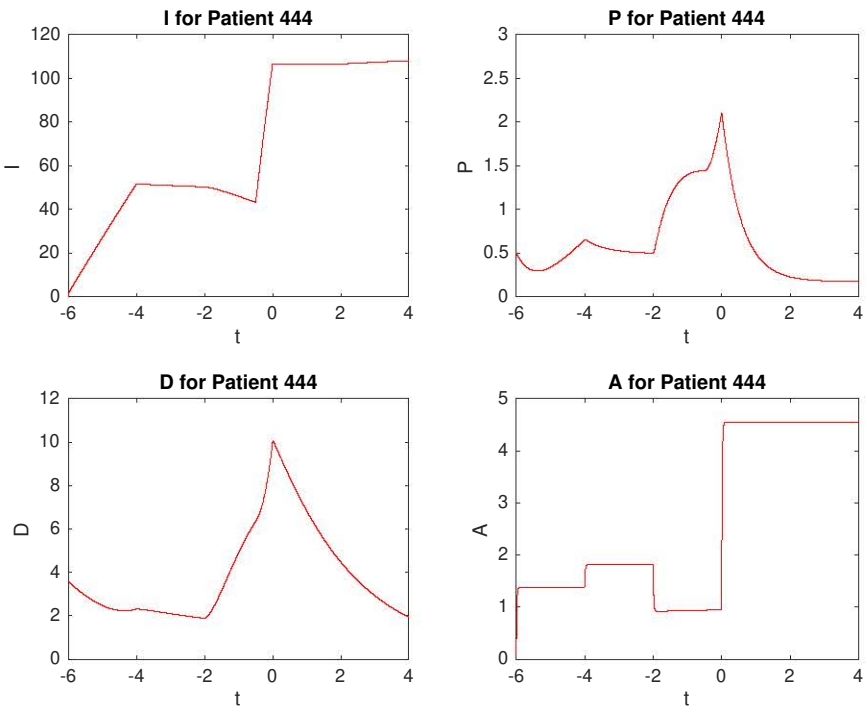

FIGURE 1.3. Model Solution for patient 444

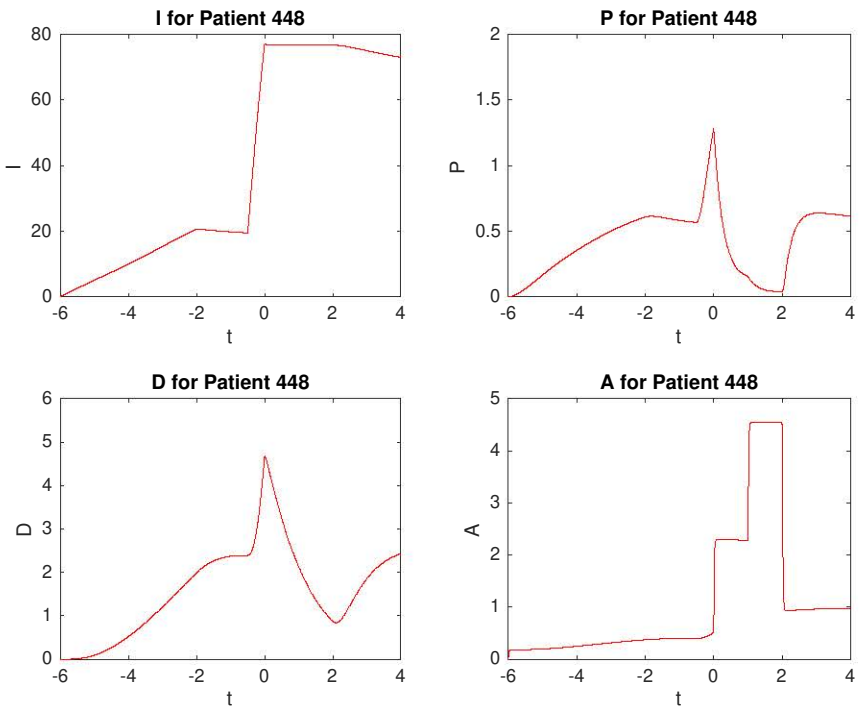

FIGURE 1.4. Model Solution for patient 448

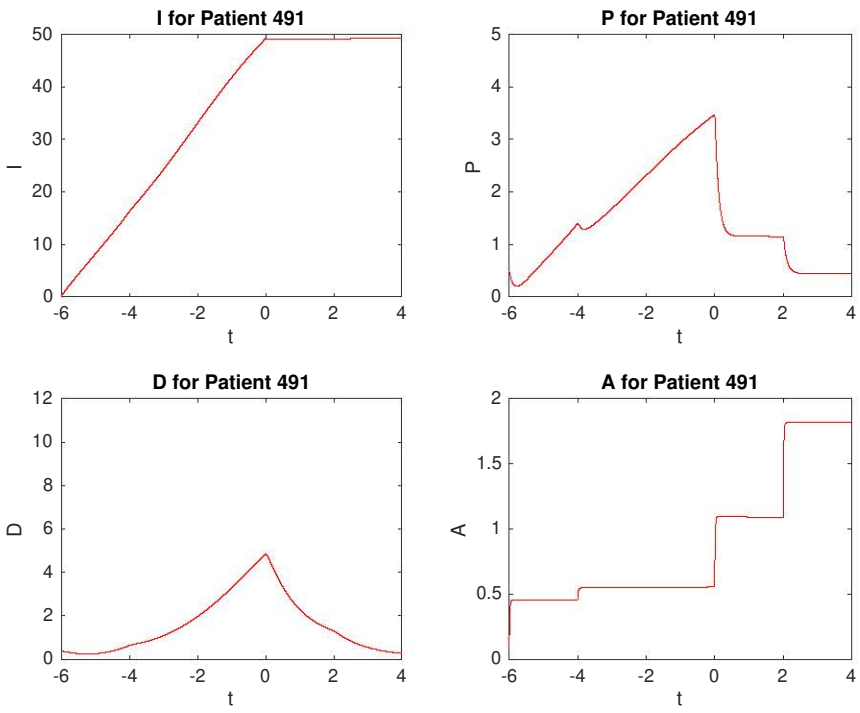

FIGURE 1.5. Model Solution for patient 491

For each patient, parameter estimates are given along with the initial conditions for the best fit of the P and D model solutions to the serial measurements of uMCP-1 and uP:C,respectively. Detailed information on parameter estimates for s_i, s_{id}, and s_a is included in Table1.2. Because parameters s_i, s_{id}, and s_a are used to reflect therapy changes and/or therapy effects on the disease dynamics, they are in general time dependent. All these parameters may vary greatly during the flare cycle (changes in therapy, failure or success), and can also vary greatly from patient to patient (stages of disease, general patient healthy).

TABLE 1.1. Initial conditions and parameter estimates that correspond to the best fit of the model to the data.

Parameters or Initial conditions	Patient 416	Patient 444	Patient 448	Patient 491	Units
I_0	0.1	0.1	0.1	0.1	I-units
P_0	0.4	0.5	0.58	0.5	P-units
D_0	1.7	3.59	0.85	0.38	D-units
A_0	0.1	0.1	0.1	0.1	A-units
s_i	0.001-0.005	0.5-6	0.02-4.5	0.1-0.5	I-units/day
s_{id}	0.002-0.015	0.5-2	0.02-3.8	0.1-0.6	I-units/day
k_{id}	1	1	1	1	D-units
k_{ip}	0.025	0.015	0.01	0.003	P-units/day
k_{pi}	0.13	0.01	0.006	0.05	P-units/C-units/ day
k_{pp}	0.02	0.015	0.02	0.12	per day
k_{pd}	0.001	0.001	0.001	0.01	P-units/D-units/day
μ_p	0.06	0.06	0.13	0.33	per day
k_{dip}	0.025	0.015	0.01	0.003	P-units/ day
k_{dp}	0.27	0.01	0.03	0.015	D-units P-units/ day
μ_d	0.04	0.015	0.03	0.035	per day
S_a	0.05-0.3	2-7	0.4-10	1-4	A-units /day
k_{ap}	0.022	0.006	0.035	0.001	A-units D-units/ day
k_{ad}	0.22	0.06	0.35	0.01	A-units D-units/ day
μ_a	2.2	2.2	2.2	2.2	per day
A_{inf}	0.45	0.45	0.45	0.45	A-units

TABLE 1.2. Parameter estimates for s_i, s_{id}, and s_a, that correspond to the best fit of the model to the data

	Patient416			Patient444			Patient448			Patient491		
Time frame	s_i	s_{id}	s_a	s_i	s_{id}	s_a	s_i	s_{id}	s_a	s_i	s_{id}	s_a
$[-6m, -4m]$	0.002	0.005	0.05	6	1	3	0.2	0.26	0.4	0.5	0.6	1
$[-4m, -2m]$	0.001	0.003	0.1	2	0.5	4	0.2	0.26	0.4	0.5	0.6	1.2
$[-2m, -.5m]$	0.005	0.015	0.05	2	0.5	2	0.02	0.06	0.4	0.5	0.6	1.2
$[-.5m, 0m]$	0.005	0.015	0.05	5	2	2	4.5	3.8	0.4	0.5	0.6	1.2
$[0m, +.5m]$	0.001	0.002	0.3	0.5	0.5	7	0.06	0.02	5	0.1	0.1	2.4
$[0.5m, +.5m]$	0.001	0.002	0.3	0.5	0.5	7	0.06	0.02	10	0.1	0.1	2.4
$[1.5m, +2m]$	0.001	0.002	0.3	0.5	0.5	7	0.06	0.02	2	0.1	0.1	2.4
$[+2m, +4m]$	0.005	0.012	0.1	1.5	0.5	7	0.06	0.02	2	0.1	0.1	4

CHAPTER 2

PARAMETER ESTIMATION

Parameter estimation involves assimilation or integration of data to quantify and update input uncertainties associated with parameters, initial conditions and boundary conditions. The main objective of parameter estimation is to simulate the experiment so as to capture system responses with quantified and reduced uncertainties (Smith, 2014). As part of parameter estimation, we will integrate data so as to quantify the parameters, as well as manipulate data so as to reduce uncertainties associated with parameter estimation. This will also include setting initial conditions, which will help in model prediction and simulations, hence to better capture the results. In general, we use parameter estimation in describing the behavior of mathematical and statistical models using data and the dynamics of the model.

2.1. Local Sensitivity

We use a local sensitivity analysis to determine how independent variable values impact dependent variables so as to assess uncertainty associated with our mathematical model. In particular, we use a local sensitivity analysis where all derivatives are taken at a single point in parameter space (Ratto at el., 2008). The typical sensitivity analysis quantifies and ranks the sensitivities of individual model parameters with respect to other parameters (Krishna et al., 2015). The sensitivity of the

model output y with respect to each individual parameter α_i can be constructed in matrix form (Krishna et al., 2015),

$$M = \frac{\partial y}{\partial \alpha} = \begin{bmatrix} \frac{\partial y_1}{\partial \alpha_1}(t_{11}) & \dots & \frac{\partial y_1}{\partial \alpha_q}(t_{11}) \\ \vdots & \vdots & \vdots \\ \frac{\partial y_1}{\partial \alpha_1}(t_{1k_1}) & \dots & \frac{\partial y_1}{\partial \alpha_q}(t_{1k_1}) \\ \vdots & \vdots & \vdots \\ \frac{\partial y_m}{\partial \alpha_1}(t_{m1}) & \dots & \frac{\partial y_m}{\partial \alpha_q}(t_{m1}) \\ \vdots & \vdots & \vdots \\ \frac{\partial y_m}{\partial \alpha_1}(t_{mk_m}) & \dots & \frac{\partial y_m}{\partial \alpha_q}(t_{mk_m}) \end{bmatrix}$$

.

In order to have better parameter estimation and sensitivities, we need to use parameters values that are of the same order of magnitude (Pope at., 2009). Thus, we computed relative sensitivities by multiplying each element in the sensitivity matrix by a nondimensionalized factor

$$\tilde{M} = \frac{\partial y}{\partial \tilde{\theta}} \frac{1}{y}. \tag{2.1}$$

The sensitivity equations we use in the matrix were constructed using using Gâteaux differentials by differentiating the evolution equation $\frac{du}{dt} = g(t, u(t), q)$ with respect to components q_k of q, and switching the order of integration, to obtain

$$\frac{\partial u_{q_k}}{\partial t} = \frac{\partial g}{\partial u} u_{q_k} + \frac{\partial g}{\partial q_k} \tag{2.2}$$

where $u \equiv \frac{\partial u}{\partial q_k}$ (Smith, 2014). The sensitivity matrix component $\chi_{ik}(q) = C \frac{\partial u_{(t_i,q)}}{\partial q_k}$ is constructed using numerical integration to obtain $u_{qk}(t_i, u)$. The method of Gâteaux differentials is advantageous given that it eliminates the uncertainty

associated with choosing stepsizes h_k to provide more accurate finite difference approximations. On the other hand, this method is tedious because if the original system has N differential equations and P parameters, then the solution will involve $N * P$ additional differential equations to construct sensitivity equations and this can even be more difficult for complex systems (Smith, 2014). The following are 52-differential equations that we constructed to use for the sensitivity matrix:

$$\begin{aligned}\frac{dy_1}{dt} =& - y_1 * \left(\frac{A_{inf}^2 P k_{ip}}{A_{inf}^2 + A^2}\right) - y_2 * \left(\frac{I k_{ip} A_{inf}^2}{A_{inf}^2 + A^2}\right) + y_3 * \left(\frac{2D A_{inf}^2 k_{id}^2 s_{id}}{(A_{inf}^2 + A^2)(D^2 + k_{id}^2)^2}\right) \\ &+ y_4 * \left(\frac{2A A_{inf}^2 (IPk_{ip} - S_i)}{(A^2 + A_{inf}^2)^2} - \frac{2AD^2 s_{id}}{(A^2 + A_{inf}^2)^2 (D^2 + k_{id}^2)}\right) \\ &+ \frac{2A^2 A_{inf}^2 (s_i - IPk_{ip})}{(A^2 + A_{inf}^2)} + \frac{2A^2 D^2 A_{inf} s_{id}}{(A^2 + A_{inf}^2)(D^2 + k_{id}^2)}\end{aligned} \tag{2.3}$$

$$\begin{aligned}\frac{dy_2}{dt} =& y_1 * \left(\frac{A_{inf}^2 k_{pi}}{A_{inf}^2 + A^2}\right) + y_2 * \left(\frac{k_{pp} A_{inf}^2}{A_{inf}^2 + A^2} - \mu_p\right) + y_3 * \left(\frac{k_{pd} A_{inf}^2}{A^2 + A_{inf}^2}\right) \\ &- y_4 * \left(\frac{2A A_{inf}^2 (Dk_{pd} + Ik_{pi} + Pk_{pp})}{(A^2 + A_{inf}^2)^2}\right) \\ &+ \frac{2A^2 A_{inf} (Dk_{pd} + Ik_{pi} + Pk_{pp})}{(A^2 + A_{inf}^2)^2}\end{aligned} \tag{2.4}$$

$$\begin{aligned}\frac{dy_3}{dt} =& y_1 * \left(\frac{A_{inf}^2 P k_{dip}}{A^2 + A_{inf}^2}\right) + y_2 * \left(\frac{A_{inf}^2 (Ik_{dip} + k_{dp})}{A_{inf}^2 + A^2}\right) - y_3 * \mu_d \\ &- y_4 * \left(\frac{2AP A_{inf}^2 (Ik_{dip} + k_{dp})}{(A_{inf}^2 + A^2)^2}\right) + \frac{2A^2 P A_{inf} (Ik_{dip} + k_{dp})}{(A_{inf}^2 + A^2)^2}\end{aligned} \tag{2.5}$$

$$\frac{dy_4}{dt} = y_2 * \left(\frac{k_{ap}A_{inf}^2}{A^2 + A_{inf}^2}\right) + y_3 * \left(\frac{k_{ad}A_{inf}^2}{A^2 + A_{inf}^2}\right) - y_4 * \left(\frac{2AA_{inf}^2(Dk_{ad} + Pk_{ap})}{(A^2 + A_{inf}^2)^2} + \mu_a\right) + \frac{2A^2A_{inf}(Dk_{ad} + Pk_{ap})}{(A^2 + A_{inf}^2)^2} \tag{2.6}$$

$$\frac{dy_5}{dt} = -y_5 * \left(\frac{A_{inf}^2 Pk_{ip}}{A_{inf}^2 + A^2}\right) - y_6 * \left(\frac{Ik_{ip}A_{inf}^2}{A_{inf}^2 + A^2}\right) + y_7 * \left(\frac{2DA_{inf}^2 k_{id}^2 s_{id}}{(A_{inf}^2 + A^2)(D^2 + k_{id}^2)^2}\right) + y_8 * \left(\frac{2AA_{inf}^2(IPk_{ip} - S_i)}{(A^2 + A_{inf}^2)^2} - \frac{2AD^2 s_{id}}{(A^2 + A_{inf}^2)^2(D^2 + k_{id}^2)}\right) - \frac{2D^2A_{inf}^2 k_{id}s_{id}}{(A^2 + A_{inf}^2)(D^2 + k_{id}^2)^2} \tag{2.7}$$

$$\frac{dy_6}{dt} = y_5 * \left(\frac{A_{inf}^2 k_{pi}}{A_{inf}^2 + A^2}\right) + y_6 * \left(\frac{k_{pp}A_{inf}^2}{A_{inf}^2 + A^2} - \mu_p\right) + y_7 * \left(\frac{k_{pd}A_{inf}^2}{A^2 + A_{inf}^2}\right) - y_8 * \left(\frac{2AA_{inf}^2(Dk_{pd} + Ik_{pi} + Pk_{pp})}{(A^2 + A_{inf}^2)^2}\right) \tag{2.8}$$

$$\frac{dy_7}{dt} = y_5 * \left(\frac{A_{inf}^2 Pk_{dip}}{A^2 + A_{inf}^2}\right) + y_6 * \left(\frac{A_{inf}^2(Ik_{dip} + k_{dp})}{A_{inf}^2 + A^2}\right) - y_7 * \mu_d - y_8 * \left(\frac{2APA_{inf}^2(Ik_{dip} + k_{dp})}{(A_{inf}^2 + A^2)^2}\right) \tag{2.9}$$

$$\frac{dy_8}{dt} = y_6 * \left(\frac{k_{ap}A_{inf}^2}{A^2 + A_{inf}^2}\right) + y_7 * \left(\frac{k_{ad}A_{inf}^2}{A^2 + A_{inf}^2}\right) - y_8 * \left(\frac{2AA_{inf}^2(Dk_{ad} + Pk_{ap})}{(A^2 + A_{inf}^2)^2} + \mu_a\right) \tag{2.10}$$

$$\begin{aligned}\frac{dy_9}{dt} = &- y_9 * \left(\frac{A_{inf}^2 Pk_{ip}}{A_{inf}^2 + A^2}\right) - y_{10} * \left(\frac{Ik_{ip}A_{inf}^2}{A_{inf}^2 + A^2}\right) + y_{11} * \left(\frac{2DA_{inf}^2 k_{id}^2 s_{id}}{(A_{inf}^2 + A^2)(D^2 + k_{id}^2)^2}\right) \\ &+ y_{12} * \left(\frac{2AA_{inf}^2(IPk_{ip} - S_i)}{(A^2 + A_{inf}^2)^2} - \frac{2AD^2 s_{id}}{(A^2 + A_{inf}^2)^2(D^2 + k_{id}^2)}\right) \\ &- \frac{I^2 PA_{inf}^2}{A^2 + A_{inf}^2}\end{aligned} \tag{2.11}$$

$$\begin{aligned}\frac{dy_{10}}{dt} = &y_9 * \left(\frac{A_{inf}^2 k_{pi}}{A_{inf}^2 + A^2}\right) + y_{10} * \left(\frac{k_{pp}A_{inf}^2}{A_{inf}^2 + A^2} - \mu_p\right) + y_{11} * \left(\frac{k_{pd}A_{inf}^2}{A^2 + A_{inf}^2}\right) \\ &- y_{12} * \left(\frac{2AA_{inf}^2(Dk_{pd} + Ik_{pi} + Pk_{pp})}{(A^2 + A_{inf}^2)^2}\right)\end{aligned} \tag{2.12}$$

$$\begin{aligned}\frac{dy_{11}}{dt} = &y_9 * \left(\frac{A_{inf}^2 Pk_{dip}}{A^2 + A_{inf}^2}\right) + y_{10} * \left(\frac{A_{inf}^2(Ik_{dip} + k_{dp})}{A_{inf}^2 + A^2}\right) - y_{11} * \mu_d \\ &- y_{12} * \left(\frac{2APA_{inf}^2(Ik_{dip} + k_{dp})}{(A_{inf}^2 + A^2)^2}\right)\end{aligned} \tag{2.13}$$

$$\begin{aligned}\frac{dy_{12}}{dt} = &y_{10} * \left(\frac{k_{ap}A_{inf}^2}{A^2 + A_{inf}^2}\right) + y_{11} * \left(\frac{k_{ad}A_{inf}^2}{A^2 + A_{inf}^2}\right) \\ &- y_{12} * \left(\frac{2AA_{inf}^2(Dk_{ad} + Pk_{ap})}{(A^2 + A_{inf}^2)^2} + \mu_a\right)\end{aligned} \tag{2.14}$$

$$\begin{aligned}\frac{dy_{13}}{dt} = &- y_{13} * \left(\frac{A_{inf}^2 P k_{ip}}{A_{inf}^2 + A^2}\right) - y_{14} * \left(\frac{I k_{ip} A_{inf}^2}{A_{inf}^2 + A^2}\right) \\ &+ y_{15} * \left(\frac{2 D A_{inf}^2 k_{id}^2 s_{id}}{(A_{inf}^2 + A^2)(D^2 + k_{id}^2)^2}\right) \\ &+ y_{16} * \left(\frac{2 A A_{inf}^2 (I P k_{ip} - S_i)}{(A^2 + A_{inf}^2)^2}\right)\end{aligned} \tag{2.15}$$

$$\begin{aligned}\frac{dy_{14}}{dt} = &y_{13} * \left(\frac{A_{inf}^2 k_{pi}}{A_{inf}^2 + A^2}\right) + y_{14}\left(*\frac{k_{pp} A_{inf}^2}{A_{inf}^2 + A^2} - \mu_p\right) + y_{15} * \left(\frac{k_{pd} A_{inf}^2}{A^2 + A_{inf}^2}\right) \\ &- y_{16} * \left(\frac{2 A A_{inf}^2 (D k_{pd} + I k_{pi} + P k_{pp})}{(A^2 + A_{inf}^2)^2}\right) + \frac{I A_{inf}^2}{A^2 + A_{inf}^2}\end{aligned} \tag{2.16}$$

$$\begin{aligned}\frac{dy_{15}}{dt} = &y_{13} * \left(\frac{A_{inf}^2 P k_{dip}}{A^2 + A_{inf}^2}\right) + y_{14} * \left(\frac{A_{inf}^2 (I k_{dip} + k_{dp})}{A_{inf}^2 + A^2}\right) - y_{15} * \mu_d \\ &- y_{16} * \left(\frac{2 A P A_{inf}^2 (I k_{dip} + k_{dp})}{(A_{inf}^2 + A^2)^2}\right)\end{aligned} \tag{2.17}$$

$$\begin{aligned}\frac{dy_{16}}{dt} = &y_{14} * \left(\frac{k_{ap} A_{inf}^2}{A^2 + A_{inf}^2}\right) + y_{15} * \left(\frac{k_{ad} A_{inf}^2}{A^2 + A_{inf}^2}\right) \\ &- y_{16} * \left(\frac{2 A A_{inf}^2 (D k_{ad} + P k_{ap})}{(A^2 + A_{inf}^2)^2} + \mu_a\right)\end{aligned} \tag{2.18}$$

$$\frac{dy_{17}}{dt} = - y_{17} * \left(\frac{A_{inf}^2 P k_{ip}}{A_{inf}^2 + A^2}\right) - y_{18} * \left(\frac{I k_{ip} A_{inf}^2}{A_{inf}^2 + A^2}\right) + y_{19} * \left(\frac{2D A_{inf}^2 k_{id}^2 s_{id}}{(A_{inf}^2 + A^2)(D^2 + k_{id}^2)^2}\right) + y_{20} * \left(\frac{2A A_{inf}^2 (IPk_{ip} - S_i)}{(A^2 + A_{inf}^2)^2}\right) \tag{2.19}$$

$$\frac{dy_{18}}{dt} = y_{17} * \left(\frac{A_{inf}^2 k_{pi}}{A_{inf}^2 + A^2}\right) + y_{18} * \left(\frac{k_{pp} A_{inf}^2}{A_{inf}^2 + A^2} - \mu_p\right) + y_{19} * \left(\frac{k_{pd} A_{inf}^2}{A^2 + A_{inf}^2}\right) - y_{20} * \left(\frac{2A A_{inf}^2 (Dk_{pd} + Ik_{pi} + Pk_{pp})}{(A^2 + A_{inf}^2)^2}\right) + \frac{A_{inf}^2 P}{A^2 + A_{inf}^2} \tag{2.20}$$

$$\frac{dy_{19}}{dt} = y_{17} * \left(\frac{A_{inf}^2 P k_{dip}}{A^2 + A_{inf}^2}\right) + y_{18} * \left(\frac{A_{inf}^2 (I k_{dip} + k_{dp})}{A_{inf}^2 + A^2}\right) - y_{19} * \mu_d - y_{20} * \left(\frac{2AP A_{inf}^2 (I k_{dip} + k_{dp})}{(A_{inf}^2 + A^2)^2}\right) \tag{2.21}$$

$$\frac{dy_{20}}{dt} = y_{18} * \left(\frac{k_{ap} A_{inf}^2}{A^2 + A_{inf}^2}\right) + y_{19} * \left(\frac{k_{ad} A_{inf}^2}{A^2 + A_{inf}^2}\right) - y_{20} * \left(\frac{2A A_{inf}^2 (Dk_{ad} + Pk_{ap})}{(A^2 + A_{inf}^2)^2} + \mu_a\right) \tag{2.22}$$

$$\frac{dy_{21}}{dt} = - y_{21} * \left(\frac{A_{inf}^2 P k_{ip}}{A_{inf}^2 + A^2}\right) - y_{22} * \left(\frac{I k_{ip} A_{inf}^2}{A_{inf}^2 + A^2}\right) + y_{23} * \left(\frac{2D A_{inf}^2 k_{id}^2 s_{id}}{(A_{inf}^2 + A^2)(D^2 + k_{id}^2)^2}\right) + y_{24} * \left(\frac{2A A_{inf}^2 (IPk_{ip} - S_i)}{(A^2 + A_{inf}^2)^2}\right) \tag{2.23}$$

$$\frac{dy_{22}}{dt} = y_{21} * \left(\frac{A_{inf}^2 k_{pi}}{A_{inf}^2 + A^2}\right) + y_{22} * \left(\frac{k_{pp} A_{inf}^2}{A_{inf}^2 + A^2} - \mu_p\right) + y_{23} * \left(\frac{k_{pd} A_{inf}^2}{A^2 + A_{inf}^2}\right) - y_{24} * \left(\frac{2AA_{inf}^2(Dk_{pd} + Ik_{pi} + Pk_{pp})}{(A^2 + A_{inf}^2)^2}\right) + \frac{A_{inf}^2 D}{A^2 + A_{inf}^2} \tag{2.24}$$

$$\frac{dy_{23}}{dt} = y_{21} * \left(\frac{A_{inf}^2 Pk_{dip}}{A^2 + A_{inf}^2}\right) + y_{22} * \left(\frac{A_{inf}^2(Ik_{dip} + k_{dp})}{A_{inf}^2 + A^2}\right) - y_{23} * \mu_d - y_{24} * \left(\frac{2APA_{inf}^2(Ik_{dip} + k_{dp})}{(A_{inf}^2 + A^2)^2}\right) \tag{2.25}$$

$$\frac{dy_{24}}{dt} = y_{22} * \left(\frac{k_{ap} A_{inf}^2}{A^2 + A_{inf}^2}\right) + y_{23} * \left(\frac{k_{ad} A_{inf}^2}{A^2 + A_{inf}^2}\right) - y_{24} * \left(\frac{2AA_{inf}^2(Dk_{ad} + Pk_{ap})}{(A^2 + A_{inf}^2)^2} + \mu_a\right) \tag{2.26}$$

$$\frac{dy_{25}}{dt} = - y_{25} * \left(\frac{A_{inf}^2 Pk_{ip}}{A_{inf}^2 + A^2}\right) - y_{26} * \left(\frac{Ik_{ip} A_{inf}^2}{A_{inf}^2 + A^2}\right) + y_{27} * \left(\frac{2DA_{inf}^2 k_{id}^2 s_{id}}{(A_{inf}^2 + A^2)(D^2 + k_{id}^2)^2}\right) + y_{28} * \left(\frac{2AA_{inf}^2(IPk_{ip} - S_i)}{(A^2 + A_{inf}^2)^2}\right) \tag{2.27}$$

$$\frac{dy_{26}}{dt} = y_{25} * \left(\frac{A_{inf}^2 k_{pi}}{A_{inf}^2 + A^2}\right) + y_{26} * \left(\frac{k_{pp} A_{inf}^2}{A_{inf}^2 + A^2} - \mu_p\right) + y_{27} * \left(\frac{k_{pd} A_{inf}^2}{A^2 + A_{inf}^2}\right) - y_{28} * \left(\frac{2AA_{inf}^2(Dk_{pd} + Ik_{pi} + Pk_{pp})}{(A^2 + A_{inf}^2)^2}\right) - P \tag{2.28}$$

$$\begin{aligned}\frac{dy_{27}}{dt} =& y_{25} * \left(\frac{A_{inf}^2 P k_{dip}}{A^2 + A_{inf}^2}\right) + y_{26} * \left(\frac{A_{inf}^2 (I k_{dip} + k_{dp})}{A_{inf}^2 + A^2}\right) - y_{27} * \mu_d \\ & - y_{28} * \left(\frac{2AP A_{inf}^2 (I k_{dip} + k_{dp})}{(A_{inf}^2 + A^2)^2}\right)\end{aligned} \tag{2.29}$$

$$\begin{aligned}\frac{dy_{28}}{dt} =& y_{26} * \left(\frac{k_{ap} A_{inf}^2}{A^2 + A_{inf}^2}\right) + y_{27} * \left(\frac{k_{ad} A_{inf}^2}{A^2 + A_{inf}^2}\right) \\ & - y_{28} * \left(\frac{2AA_{inf}^2 (D k_{ad} + P k_{ap})}{(A^2 + A_{inf}^2)^2} + \mu_a\right)\end{aligned} \tag{2.30}$$

$$\begin{aligned}\frac{dy_{29}}{dt} =& - y_{29} * \left(\frac{A_{inf}^2 P k_{ip}}{A_{inf}^2 + A^2}\right) - y_{30} * \left(\frac{I k_{ip} A_{inf}^2}{A_{inf}^2 + A^2}\right) + \\ & y_{31} * \left(\frac{2D A_{inf}^2 k_{id}^2 s_{id}}{(A_{inf}^2 + A^2)(D^2 + k_{id}^2)^2}\right) + y_{32} * \left(\frac{2AA_{inf}^2 (IP k_{ip} - S_i)}{(A^2 + A_{inf}^2)^2}\right)\end{aligned} \tag{2.31}$$

$$\begin{aligned}\frac{dy_{30}}{dt} =& y_{29} * \left(\frac{A_{inf}^2 k_{pi}}{A_{inf}^2 + A^2}\right) + y_{30} * \left(\frac{k_{pp} A_{inf}^2}{A_{inf}^2 + A^2} - \mu_p\right) + y_{31} * \left(\frac{k_{pd} A_{inf}^2}{A^2 + A_{inf}^2}\right) \\ & - y_{32} * \left(\frac{2AA_{inf}^2 (D k_{pd} + I k_{pi} + P k_{pp})}{(A^2 + A_{inf}^2)^2}\right)\end{aligned} \tag{2.32}$$

$$\begin{aligned}\frac{dy_{31}}{dt} =& y_{29} * \left(\frac{A_{inf}^2 P k_{dip}}{A^2 + A_{inf}^2}\right) + y_{30} * \left(\frac{A_{inf}^2 (I k_{dip} + k_{dp})}{A_{inf}^2 + A^2}\right) - y_{31} * \mu_d \\ & - y_{32} * \left(\frac{2AP A_{inf}^2 (I k_{dip} + k_{dp})}{(A_{inf}^2 + A^2)^2}\right) + \frac{IP A_{inf}^2}{A^2 + A_{inf}^2}\end{aligned} \tag{2.33}$$

$$\frac{dy_{32}}{dt} = y_{30} * \left(\frac{k_{ap}A_{inf}^2}{A^2 + A_{inf}^2}\right) + y_{31} * \left(\frac{k_{ad}A_{inf}^2}{A^2 + A_{inf}^2}\right) - y_{32} * \left(\frac{2AA_{inf}^2(Dk_{ad} + Pk_{ap})}{(A^2 + A_{inf}^2)^2} + \mu_a\right) \tag{2.34}$$

$$\frac{dy_{33}}{dt} = - y_{33} * \left(\frac{A_{inf}^2 Pk_{ip}}{A_{inf}^2 + A^2}\right) - y_{34} * \left(\frac{Ik_{ip}A_{inf}^2}{A_{inf}^2 + A^2}\right) + y_{35} * \left(\frac{2DA_{inf}^2 k_{id}^2 s_{id}}{(A_{inf}^2 + A^2)(D^2 + k_{id}^2)^2}\right) + y_{36} * \left(\frac{2AA_{inf}^2(IPk_{ip} - S_i)}{(A^2 + A_{inf}^2)^2}\right) \tag{2.35}$$

$$\frac{dy_{34}}{dt} = y_{33} * \left(\frac{A_{inf}^2 k_{pi}}{A_{inf}^2 + A^2}\right) + y_{34}\left(*\frac{k_{pp}A_{inf}^2}{A_{inf}^2 + A^2} - \mu_p\right) + y_{35} * \left(\frac{k_{pd}A_{inf}^2}{A^2 + A_{inf}^2}\right) - y_{36} * \left(\frac{2AA_{inf}^2(Dk_{pd} + Ik_{pi} + Pk_{pp})}{(A^2 + A_{inf}^2)^2}\right) \tag{2.36}$$

$$\frac{dy_{35}}{dt} = y_{33} * \left(\frac{A_{inf}^2 Pk_{dip}}{A^2 + A_{inf}^2}\right) + y_{34} * \left(\frac{A_{inf}^2(Ik_{dip} + k_{dp})}{A_{inf}^2 + A^2}\right) - y_{35} * \mu_d - y_{36} * \left(\frac{2APA_{inf}^2(Ik_{dip} + k_{dp})}{(A_{inf}^2 + A^2)^2}\right) + \frac{PA_{inf}^2}{A^2 + A_{inf}^2} \tag{2.37}$$

$$\frac{dy_{36}}{dt} = y_{34} * \left(\frac{k_{ap}A_{inf}^2}{A^2 + A_{inf}^2}\right) + y_{35} * \left(\frac{k_{ad}A_{inf}^2}{A^2 + A_{inf}^2}\right) - y_{36} * \left(\frac{2AA_{inf}^2(Dk_{ad} + Pk_{ap})}{(A^2 + A_{inf}^2)^2} + \mu_a\right) \tag{2.38}$$

$$\frac{dy_{37}}{dt} = - y_{37} * \left(\frac{A_{inf}^2 P k_{ip}}{A_{inf}^2 + A^2}\right) - y_{38} * \left(\frac{I k_{ip} A_{inf}^2}{A_{inf}^2 + A^2}\right) + y_{39} * \left(\frac{2 D A_{inf}^2 k_{id}^2 s_{id}}{(A_{inf}^2 + A^2)(D^2 + k_{id}^2)^2}\right) + y_{40} * \left(\frac{2 A A_{inf}^2 (I P k_{ip} - S_i)}{(A^2 + A_{inf}^2)^2}\right) \tag{2.39}$$

$$\frac{dy_{38}}{dt} = y_{37} * \left(\frac{A_{inf}^2 k_{pi}}{A_{inf}^2 + A^2}\right) + y_{38}\left(* \frac{k_{pp} A_{inf}^2}{A_{inf}^2 + A^2} - \mu_p\right) + y_{39} * \left(\frac{k_{pd} A_{inf}^2}{A^2 + A_{inf}^2}\right) - y_{40} * \left(\frac{2 A A_{inf}^2 (D k_{pd} + I k_{pi} + P k_{pp})}{(A^2 + A_{inf}^2)^2}\right) \tag{2.40}$$

$$\frac{dy_{39}}{dt} = y_{37} * \left(\frac{A_{inf}^2 P k_{dip}}{A^2 + A_{inf}^2}\right) + y_{38} * \left(\frac{A_{inf}^2 (I k_{dip} + k_{dp})}{A_{inf}^2 + A^2}\right) - y_{39} * \mu_d - y_{40} * \left(\frac{2 A P A_{inf}^2 (I k_{dip} + k_{dp})}{(A_{inf}^2 + A^2)^2}\right) - D \tag{2.41}$$

$$\frac{dy_{40}}{dt} = y_{38} * \left(\frac{k_{ap} A_{inf}^2}{A^2 + A_{inf}^2}\right) + y_{39} * \left(\frac{k_{ad} A_{inf}^2}{A^2 + A_{inf}^2}\right) - y_{40} * \left(\frac{2 A A_{inf}^2 (D k_{ad} + P k_{ap})}{(A^2 + A_{inf}^2)^2} + \mu_a\right) \tag{2.42}$$

$$\frac{dy_{41}}{dt} = - y_{41} * \left(\frac{A_{inf}^2 P k_{ip}}{A_{inf}^2 + A^2}\right) - y_{42} * \left(\frac{I k_{ip} A_{inf}^2}{A_{inf}^2 + A^2}\right) + y_{43} * \left(\frac{2 D A_{inf}^2 k_{id}^2 s_{id}}{(A_{inf}^2 + A^2)(D^2 + k_{id}^2)^2}\right) + y_{44} * \left(\frac{2 A A_{inf}^2 (I P k_{ip} - S_i)}{(A^2 + A_{inf}^2)^2}\right) \tag{2.43}$$

$$\frac{dy_{42}}{dt} = y_{41} * \left(\frac{A_{inf}^2 k_{pi}}{A_{inf}^2 + A^2}\right) + y_{42} * \left(\frac{k_{pp} A_{inf}^2}{A_{inf}^2 + A^2} - \mu_p\right) + y_{43} * \left(\frac{k_{pd} A_{inf}^2}{A^2 + A_{inf}^2}\right) - y_{44} * \left(\frac{2AA_{inf}^2(Dk_{pd} + Ik_{pi} + Pk_{pp})}{(A^2 + A_{inf}^2)^2}\right) \tag{2.44}$$

$$\frac{dy_{43}}{dt} = y_{41} * \left(\frac{A_{inf}^2 Pk_{dip}}{A^2 + A_{inf}^2}\right) + y_{42} * \left(\frac{A_{inf}^2(Ik_{dip} + k_{dp})}{A_{inf}^2 + A^2}\right) - y_{43} * \mu_d - y_{44} * \left(\frac{2APA_{inf}^2(Ik_{dip} + k_{dp})}{(A_{inf}^2 + A^2)^2}\right) \tag{2.45}$$

$$\frac{dy_{44}}{dt} = y_{42} * \left(\frac{k_{ap} A_{inf}^2}{A^2 + A_{inf}^2}\right) + y_{43} * \left(\frac{k_{ad} A_{inf}^2}{A^2 + A_{inf}^2}\right) - y_{44} * \left(\frac{2AA_{inf}^2(Dk_{ad} + Pk_{ap})}{(A^2 + A_{inf}^2)^2} + \mu_a\right) + \frac{A_{inf}^2 P}{A^2 + A_{inf}^2} \tag{2.46}$$

$$\frac{dy_{45}}{dt} = -y_{45} * \left(\frac{A_{inf}^2 Pk_{ip}}{A_{inf}^2 + A^2}\right) - y_{46} * \left(\frac{Ik_{ip} A_{inf}^2}{A_{inf}^2 + A^2}\right) + y_{47} * \left(\frac{2DA_{inf}^2 k_{id}^2 s_{id}}{(A_{inf}^2 + A^2)(D^2 + k_{id}^2)^2}\right) + y_{48} * \left(\frac{2AA_{inf}^2(IPk_{ip} - S_i)}{(A^2 + A_{inf}^2)^2}\right) \tag{2.47}$$

$$\frac{dy_{46}}{dt} = y_{45} * \left(\frac{A_{inf}^2 k_{pi}}{A_{inf}^2 + A^2}\right) + y_{46}\left(*\frac{k_{pp} A_{inf}^2}{A_{inf}^2 + A^2} - \mu_p\right) + y_{47} * \left(\frac{k_{pd} A_{inf}^2}{A^2 + A_{inf}^2}\right) - y_{48} * \left(\frac{2AA_{inf}^2(Dk_{pd} + Ik_{pi} + Pk_{pp})}{(A^2 + A_{inf}^2)^2}\right) \tag{2.48}$$

$$\frac{dy_{47}}{dt} = y_{45} * \left(\frac{A_{inf}^2 P k_{dip}}{A^2 + A_{inf}^2}\right) + y_{46} * \left(\frac{A_{inf}^2 (I k_{dip} + k_{dp})}{A_{inf}^2 + A^2}\right) - y_{47} * \mu_d - y_{48} * \left(\frac{2AP A_{inf}^2 (I k_{dip} + k_{dp})}{(A_{inf}^2 + A^2)^2}\right) \tag{2.49}$$

$$\frac{dy_{48}}{dt} = y_{46} * \left(\frac{k_{ap} A_{inf}^2}{A^2 + A_{inf}^2}\right) + y_{47} * \left(\frac{k_{ad} A_{inf}^2}{A^2 + A_{inf}^2}\right) - y_{48} * \left(\frac{2AA_{inf}^2 (D k_{ad} + P k_{ap})}{(A^2 + A_{inf}^2)^2} + \mu_a\right) + \frac{A_{inf}^2 D}{A^2 + A_{inf}^2} \tag{2.50}$$

$$\frac{dy_{49}}{dt} = - y_{49} * \left(\frac{A_{inf}^2 P k_{ip}}{A_{inf}^2 + A^2}\right) - y_{50} * \left(\frac{I k_{ip} A_{inf}^2}{A_{inf}^2 + A^2}\right) + y_{51} * \left(\frac{2D A_{inf}^2 k_{id}^2 s_{id}}{(A_{inf}^2 + A^2)(D^2 + k_{id}^2)^2}\right) + y_{52} * \left(\frac{2AA_{inf}^2 (IP k_{ip} - S_i)}{(A^2 + A_{inf}^2)^2}\right) \tag{2.51}$$

$$\frac{dy_{50}}{dt} = y_{49} * \left(\frac{A_{inf}^2 k_{pi}}{A_{inf}^2 + A^2}\right) + y_{50} * \left(\frac{k_{pp} A_{inf}^2}{A_{inf}^2 + A^2} - \mu_p\right) + y_{51} * \left(\frac{k_{pd} A_{inf}^2}{A^2 + A_{inf}^2}\right) - y_{52} * \left(\frac{2AA_{inf}^2 (D k_{pd} + I k_{pi} + P k_{pp})}{(A^2 + A_{inf}^2)^2}\right) \tag{2.52}$$

$$\frac{dy_{51}}{dt} = y_{49} * \left(\frac{A_{inf}^2 P k_{dip}}{A^2 + A_{inf}^2}\right) + y_{50} * \left(\frac{A_{inf}^2 (I k_{dip} + k_{dp})}{A_{inf}^2 + A^2}\right) - y_{51} * \mu_d - y_{52} * \left(\frac{2AP A_{inf}^2 (I k_{dip} + k_{dp})}{(A_{inf}^2 + A^2)^2}\right) \tag{2.53}$$

$$\begin{aligned}\frac{dy_{52}}{dt} =& y_{50} * \left(\frac{k_{ap}A_{inf}^2}{A^2 + A_{inf}^2}\right) + y_{51} * \left(\frac{k_{ad}A_{inf}^2}{A^2 + A_{inf}^2}\right) \\ & - y_{52} * \left(\frac{2AA_{inf}^2(Dk_{ad} + Pk_{ap})}{(A^2 + A_{inf}^2)^2} + \mu_a\right) - A\end{aligned} \tag{2.54}$$

Cubic Splines

In Buddu-Grajdeanu et al, (2010) parameters s_i, s_{id} , and s_a are given as piecewise functions. Thus, to be able to calculate sensitivities (i.e., a partial derivative of each parameter with respect to each model variable) for these parameters, we construct cubic splines on each time subinterval to obtain a function that has a continuous derivative on each interval (Burden, 1997). To be specific, we use cubic spline interpolation by finding a piecewise polynomial approximation whenever there is a jump between two successive time points. For example, for the following given piecewise function:

$$S_i(t) = \begin{cases} 0.5 & 0 \leq t < 6 \\ 0.1 & 6 \leq t < 10. \end{cases} \tag{2.55}$$

To construct a cubic spline between 0.5 and 0.1, we use a generalized form of a piecewise function with cubic splines as follows:

$$S_i(t) = \begin{cases} p & 0 \leq t_1 < t_1 - \epsilon \\ at^3 + bt^2 + ct + d & t_1 - \epsilon \leq t_1 < t_1 + \epsilon \\ q & t_1 + \epsilon \leq t < t_2 - \epsilon \end{cases} \tag{2.56}$$

where $p = 0.5$, and $q = 0.1$

We can solve for the coefficients the cubic spline a, b, c, and d by using the following equations:

$$a(t_0 - \epsilon)^3 + b(t_0 - \epsilon)^2 + c(t_0 - \epsilon) + d = 0.5 \tag{2.57}$$

$$a(t_0+\epsilon)^3 + b(t_0+\epsilon)^2 + c(t_0+\epsilon) + d = 0.1 \tag{2.58}$$

$$3a(t_0-\epsilon)^2 + 2b(t_0-\epsilon) + c = 0 \tag{2.59}$$

$$3a(t_0+\epsilon)^2 + 2b(t_0+\epsilon) + c = 0 \tag{2.60}$$

We obtain equations 59 and 60 by taking the derivatives of equations 57 and 58 respectively. This is to create two extra equations as well as satisfying the conditions of a cubic spline. Solving the system of the four equations and setting $t_0 = 6$, and $\epsilon = 0.1$, we get $a = 100, b = -1800, c = 10797$, and $d = -21581.7$. Thus, the piecewise function (equation 55) can be written with a cubic spline that connects points 0.1 and 0.5 as follows:

$$S_i(t) = \begin{cases} 0.5 & 0 \le t < 6-\epsilon \\ 100t^3 - 1800t^2 + 10797t - 21581.7 & 6-\epsilon \le t < 6+\epsilon \\ 0.1 & 6+\epsilon \le t < 10 \end{cases} \tag{2.61}$$

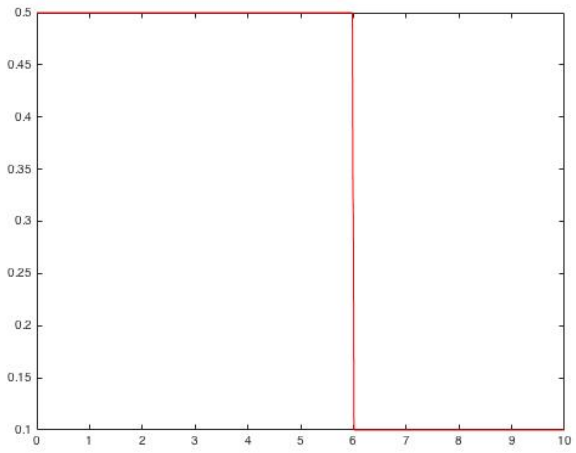

FIGURE 2.1. Cubic spline for the function 2.61

From the figure 2.1, we see that numerical solution for both piecewise function without a cubic spline and the piecewise function with cubic spline match, because the two solutions overlap.

Also, the sensitivities of the piecewise parameters can be formed by taking the derivative of the generalized piecewise function with cubic spline as shown below:

$$sip(t) = \frac{\partial S_i(t)}{\partial p} = \begin{cases} 1 & 0 \leq t_1 < t_1 - \epsilon \\ \frac{\partial a}{\partial p}t^3 + \frac{\partial b}{\partial p}t^2 + \frac{\partial c}{\partial p}t + \frac{\partial d}{\partial p} & t_1 - \epsilon \leq t_1 < t_1 + \epsilon \\ 0 & t_1 + \epsilon \leq t < t_f \end{cases} \tag{2.62}$$

$$siq(t) = \frac{\partial S_i(t)}{\partial q} = \begin{cases} 0 & 0 \leq t_1 < t_1 - \epsilon \\ \frac{\partial a}{\partial q}t^3 + \frac{\partial b}{\partial q}t^2 + \frac{\partial c}{\partial q}t + \frac{\partial d}{\partial q} & t_1 - \epsilon \leq t_1 < t_1 + \epsilon \\ 1 & t_1 + \epsilon \leq t < t_f \end{cases} \tag{2.63}$$

Thus, the following twelve sensitivity equations were formulated after incorporating cubic splines in the piecewise parameters

$$\begin{aligned} \frac{dy_{53}}{dt} = &- y_{53} * \left(\frac{A_{inf}^2 P k_{ip}}{A_{inf}^2 + A^2} \right) - y_{54} * \left(\frac{I k_{ip} A_{inf}^2}{A_{inf}^2 + A^2} \right) + \\ &y_{55} * \left(\frac{2DA_{inf}^2 k_{id}^2 s_{id}}{(A_{inf}^2 + A^2)(D^2 + k_{id}^2)^2} \right) \\ &+ y_{56} * \left(\frac{2AA_{inf}^2 (IPk_{ip} - S_i)}{(A^2 + A_{inf}^2)^2} - \frac{2AD^2 s_{id}}{(A^2 + A_{inf}^2)^2 (D^2 + k_{id}^2)} \right) \\ &+ \frac{A_{inf}}{A^2 + A_{inf}^2} * (sip(t) + siq(t)) \end{aligned} \tag{2.64}$$

$$\frac{dy_{54}}{dt} = y_{53} * \left(\frac{A_{inf}^2 k_{pi}}{A_{inf}^2 + A^2}\right) + y_{54} * \left(\frac{k_{pp} A_{inf}^2}{A_{inf}^2 + A^2} - \mu_p\right) + y_{55} * \left(\frac{k_{pd} A_{inf}^2}{A^2 + A_{inf}^2}\right) - y_{56} * \left(\frac{2AA_{inf}^2(Dk_{pd} + Ik_{pi} + Pk_{pp})}{(A^2 + A_{inf}^2)^2}\right) \tag{2.65}$$

$$\frac{dy_{55}}{dt} = y_{53} * \left(\frac{A_{inf}^2 Pk_{dip}}{A^2 + A_{inf}^2}\right) + y_{54} * \left(\frac{A_{inf}^2(Ik_{dip} + k_{dp})}{A_{inf}^2 + A^2}\right) - y_{55} * \mu_d - y_{56} * \left(\frac{2APA_{inf}^2(Ik_{dip} + k_{dp})}{(A_{inf}^2 + A^2)^2}\right) \tag{2.66}$$

$$\frac{dy_{56}}{dt} = y_{54} * \left(\frac{k_{ap} A_{inf}^2}{A^2 + A_{inf}^2}\right) + y_{55} * \left(\frac{k_{ad} A_{inf}^2}{A^2 + A_{inf}^2}\right) - y_{56} * \left(\frac{2AA_{inf}^2(Dk_{ad} + Pk_{ap})}{(A^2 + A_{inf}^2)^2} + \mu_a\right) \tag{2.67}$$

$$\begin{aligned}\frac{dy_{57}}{dt} = &- y_{57} * \left(\frac{A_{inf}^2 Pk_{ip}}{A_{inf}^2 + A^2}\right) - y_{58} * \left(\frac{Ik_{ip} A_{inf}^2}{A_{inf}^2 + A^2}\right) + \\ &y_{59} * \left(\frac{2DA_{inf}^2 k_{id}^2 s_{id}}{(A_{inf}^2 + A^2)(D^2 + k_{id}^2)^2}\right) \\ &+ y_{560} * \left(\frac{2AA_{inf}^2(IPk_{ip} - S_i)}{(A^2 + A_{inf}^2)^2} - \frac{2AD^2 s_{id}}{(A^2 + A_{inf}^2)^2(D^2 + k_{id}^2)}\right) \\ &+ \frac{A_{inf} D62}{(A^2 + A_{inf}^2)(D^2 + k_{id}^2} * (sidp(t) + sidq(t))\end{aligned} \tag{2.68}$$

$$\frac{dy_{58}}{dt} = y_{57} * \left(\frac{A_{inf}^2 k_{pi}}{A_{inf}^2 + A^2}\right) + y_{58} * \left(\frac{k_{pp} A_{inf}^2}{A_{inf}^2 + A^2} - \mu_p\right) + y_{59} * \left(\frac{k_{pd} A_{inf}^2}{A^2 + A_{inf}^2}\right) - y_{60} * \left(\frac{2AA_{inf}^2(Dk_{pd} + Ik_{pi} + Pk_{pp})}{(A^2 + A_{inf}^2)^2}\right) \tag{2.69}$$

$$\frac{dy_{59}}{dt} = y_{57} * \left(\frac{A_{inf}^2 Pk_{dip}}{A^2 + A_{inf}^2}\right) + y_{58} * \left(\frac{A_{inf}^2(Ik_{dip} + k_{dp})}{A_{inf}^2 + A^2}\right) - y_{59} * \mu_d - y_{60} * \left(\frac{2APA_{inf}^2(Ik_{dip} + k_{dp})}{(A_{inf}^2 + A^2)^2}\right) \tag{2.70}$$

$$\frac{dy_{60}}{dt} = y_{58} * \left(\frac{k_{ap} A_{inf}^2}{A^2 + A_{inf}^2}\right) + y_{59} * \left(\frac{k_{ad} A_{inf}^2}{A^2 + A_{inf}^2}\right) - y_{60} * \left(\frac{2AA_{inf}^2(Dk_{ad} + Pk_{ap})}{(A^2 + A_{inf}^2)^2} + \mu_a\right) \tag{2.71}$$

$$\frac{dy_{61}}{dt} = - y_{61} * \left(\frac{A_{inf}^2 Pk_{ip}}{A_{inf}^2 + A^2}\right) - y_{62} * \left(\frac{Ik_{ip} A_{inf}^2}{A_{inf}^2 + A^2}\right) + y_{63} * \left(\frac{2DA_{inf}^2 k_{id}^2 s_{id}}{(A_{inf}^2 + A^2)(D^2 + k_{id}^2)^2}\right) + y_{60} * \left(\frac{2AA_{inf}^2(IPk_{ip} - S_i)}{(A^2 + A_{inf}^2)^2} - \frac{2AD^2 s_{id}}{(A^2 + A_{inf}^2)^2(D^2 + k_{id}^2)}\right) \tag{2.72}$$

$$\frac{dy_{62}}{dt} = y_{61} * \left(\frac{A_{inf}^2 k_{pi}}{A_{inf}^2 + A^2}\right) + y_{62} * \left(\frac{k_{pp} A_{inf}^2}{A_{inf}^2 + A^2} - \mu_p\right) + y_{63} * \left(\frac{k_{pd} A_{inf}^2}{A^2 + A_{inf}^2}\right) - y_{64} * \left(\frac{2AA_{inf}^2(Dk_{pd} + Ik_{pi} + Pk_{pp})}{(A^2 + A_{inf}^2)^2}\right) \tag{2.73}$$

$$\frac{dy_{63}}{dt} = y_{61} * \left(\frac{A_{inf}^2 Pk_{dip}}{A^2 + A_{inf}^2}\right) + y_{62} * \left(\frac{A_{inf}^2(Ik_{dip} + k_{dp})}{A_{inf}^2 + A^2}\right) - y_{63} * \mu_d - y_{64} * \left(\frac{2APA_{inf}^2(Ik_{dip} + k_{dp})}{(A_{inf}^2 + A^2)^2}\right) \tag{2.74}$$

$$\frac{dy_{64}}{dt} = y_{62} * \left(\frac{k_{ap} A_{inf}^2}{A^2 + A_{inf}^2}\right) + y_{63} * \left(\frac{k_{ad} A_{inf}^2}{A^2 + A_{inf}^2}\right) - y_{64} * \left(\frac{2AA_{inf}^2(Dk_{ad} + Pk_{ap})}{(A^2 + A_{inf}^2)^2} + \mu_a\right) + (sap(t) + saq(t)) \tag{2.75}$$

The description for $y_1 - y_{64}$, $sap(t)$, $saq(t)$, $sidq(t)$, $sidp(t)$, $sip(t)$, and $siq(t)$ are provided in appendix A.

Local Sensitivity Results

We computed a 2-norm so as to evaluate the total sensitivity, $\tilde{M}_j$ of the j^{th} parameter (Krishna et al., 2015)

$$\tilde{M}_j = (\frac{1}{K} \sum_{i=1}^{K} M_{i,j}^2)^{\frac{1}{2}}. \tag{2.76}$$

Also, we computed relative sensitivity where we divided the largest 2-norm total sensitivity to each individual j^{th} parameter so as to determine the relativity of each parameter with respect to each model variable.

$$\tilde{M}_j = \sqrt{(\frac{1}{L}\sum_{i=1}^{l} M_{j,l}^2)^{\frac{1}{2}}}. \tag{2.77}$$

To determine sensitive and insensitive parameters, we rank them according to size of the magnitude of relative sensitivity with respect to each model variable with most sensitive parameter having the value of one. Using numerical methods and MATLAB code solver, we found corresponding sensitivity numerical values of each parameter with the corresponding state variable. We used the two-norm of sensitivities values to rank parameters on how sensitive they are to the model variables for every patient. The sensitivities were plotted for each patient with respect to the time to see how sensitivities change with time.

The following plots are graphs of sensitivities of each parameter with respect to state variables for patient 416 and 491. The sensitivity graphs of patient 444 and 448 are included in the Appendix.

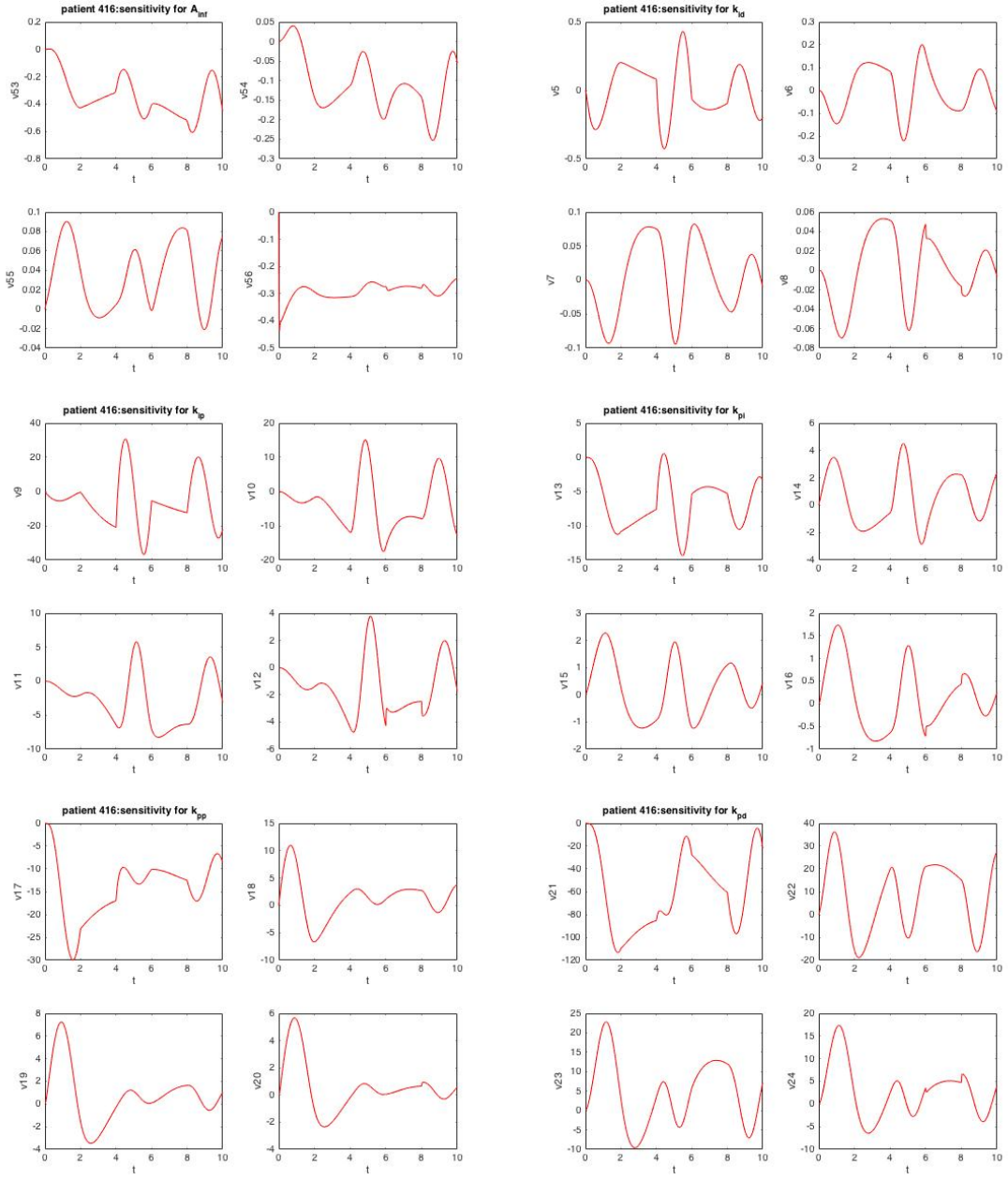

FIGURE 2.2. Sensitivities plots for parameters A_{inf}, k_{id}, k_{ip}, k_{pi}, k_{pp}, and k_{pd} for patient 416 with respect to model variables showing how they change over time

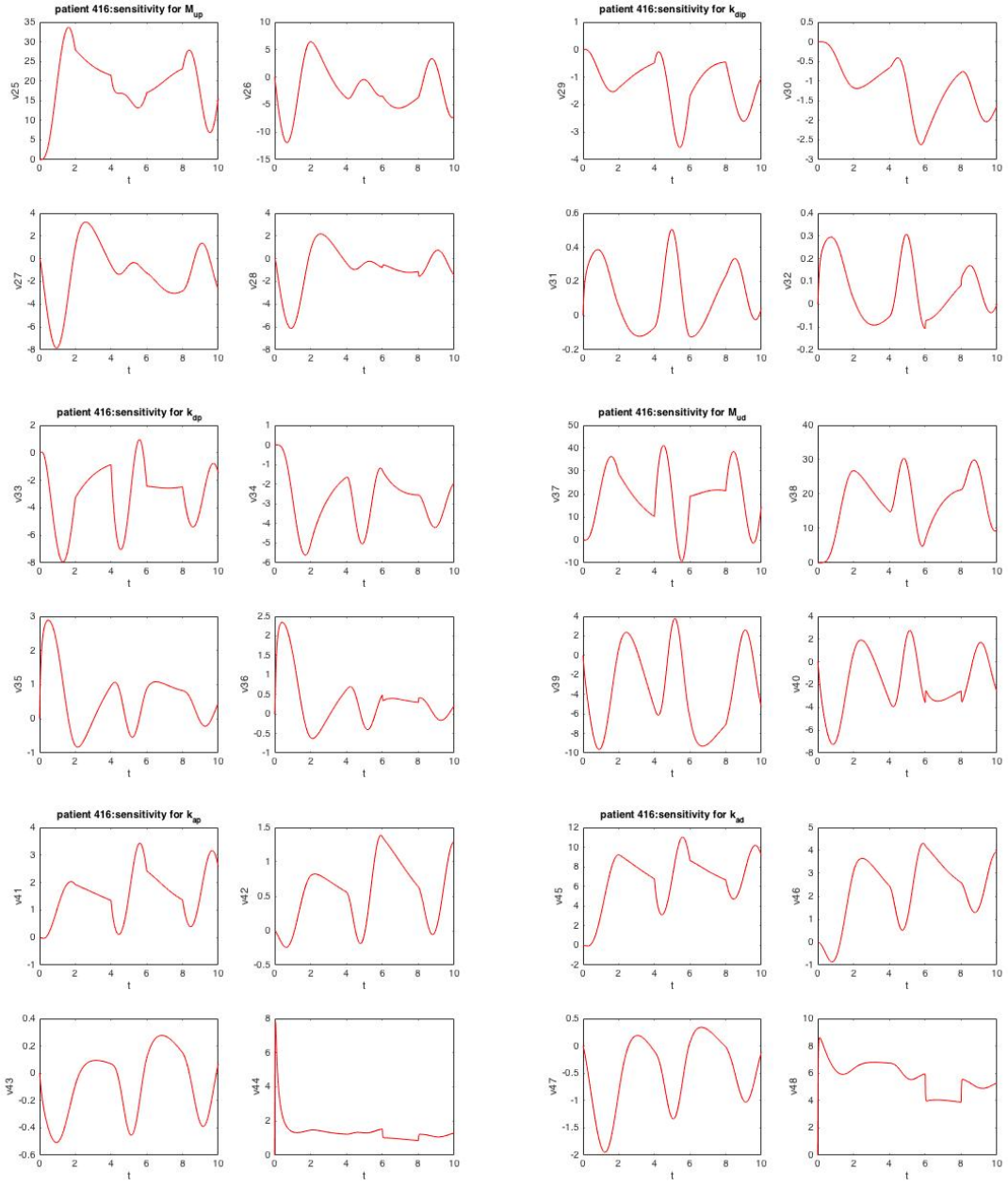

FIGURE 2.3. Sensitivities plots for parameters μ_p, k_{dip}, k_{dp}, μ_d, k_{ap}, and k_{ad} for patient 416 with respect to model variables showing how they change over time

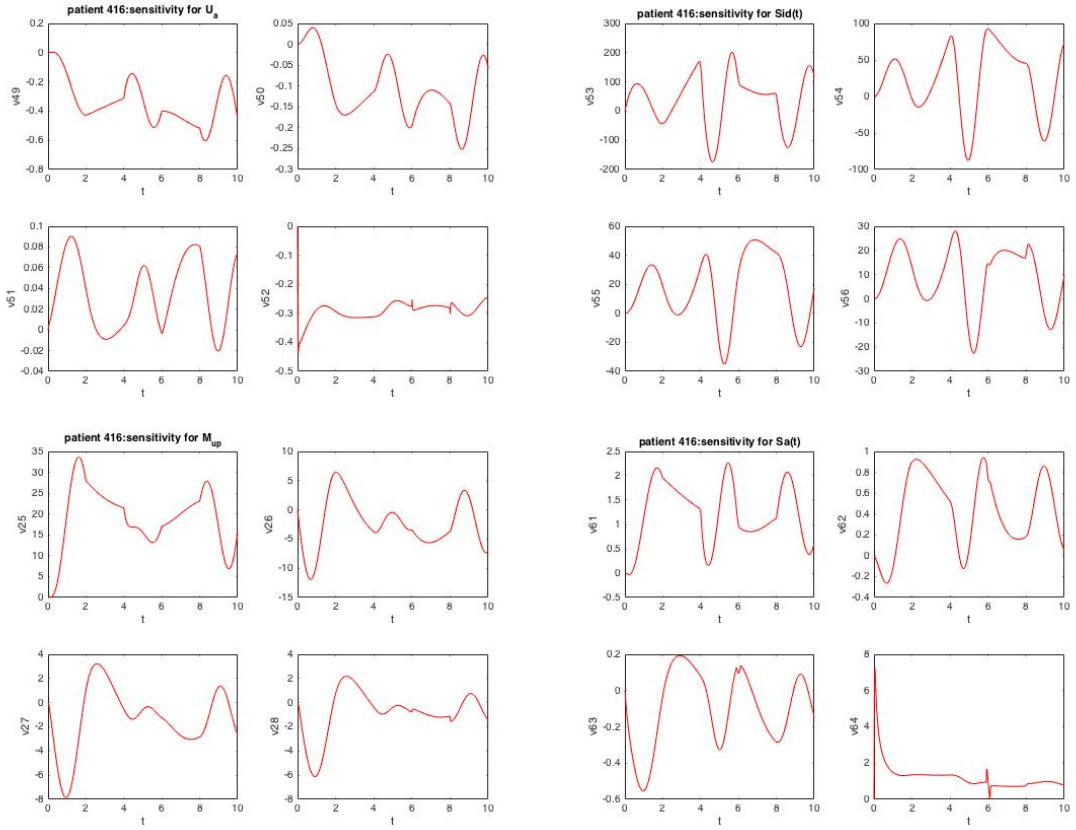

FIGURE 2.4. Sensitivities plots for parameters μ_a, $s_i(t)$, $s_{id}(t)$, and $s_a(t)$ for patient 416 with respect to model variables showing how they change over time

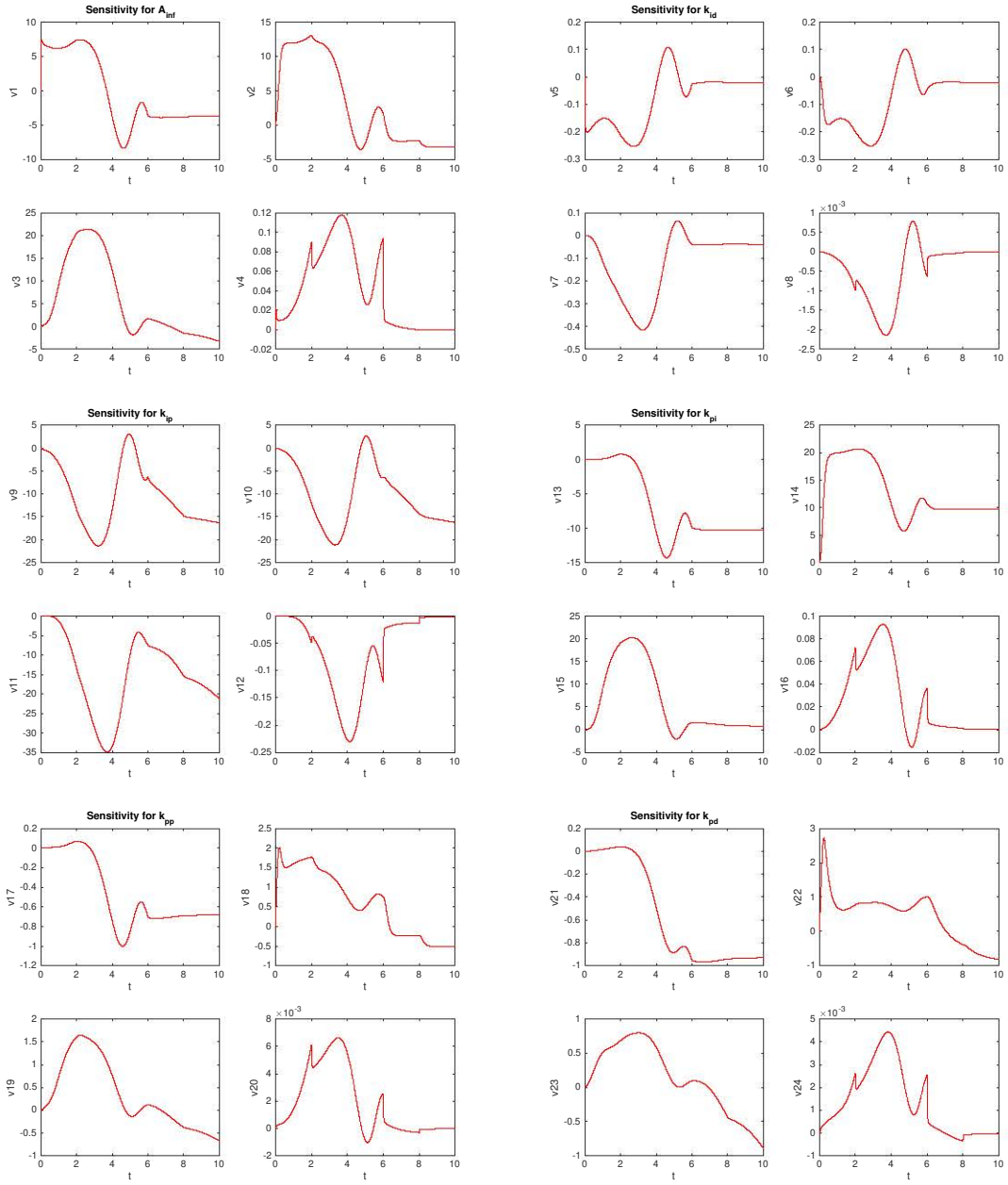

FIGURE 2.5. Sensitivities plots for parameters A_{inf}, k_{id}, k_{ip}, k_{pi}, k_{pp}, and k_{pd} for patient 491 with respect to model variables showing how they change over time

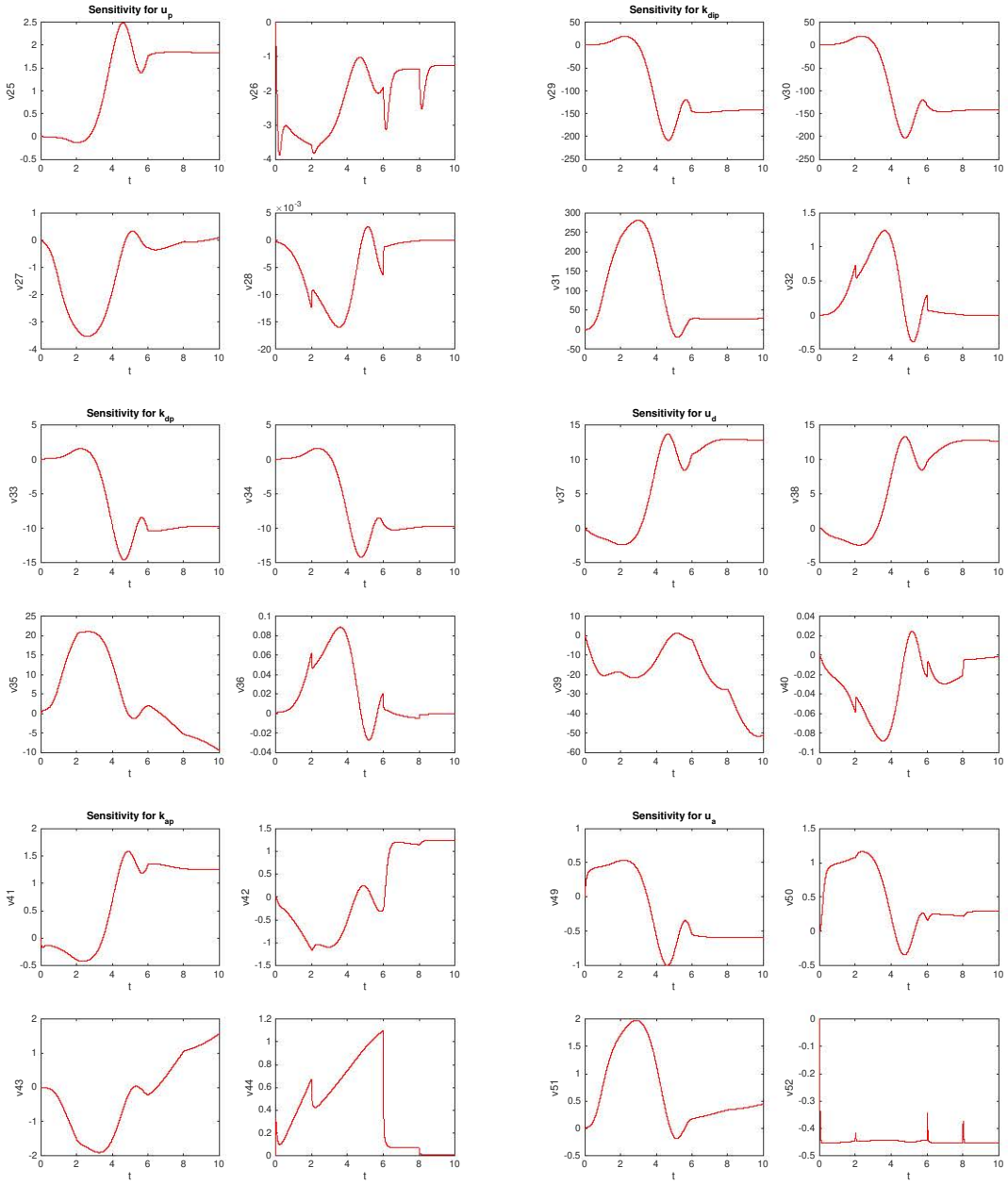

FIGURE 2.6. Sensitivities plots for parameters μ_p, k_{dip}, k_{dp}, μ_d, k_{ap}, and k_{ad} for patient 491 with respect to model variables showing how they change over time

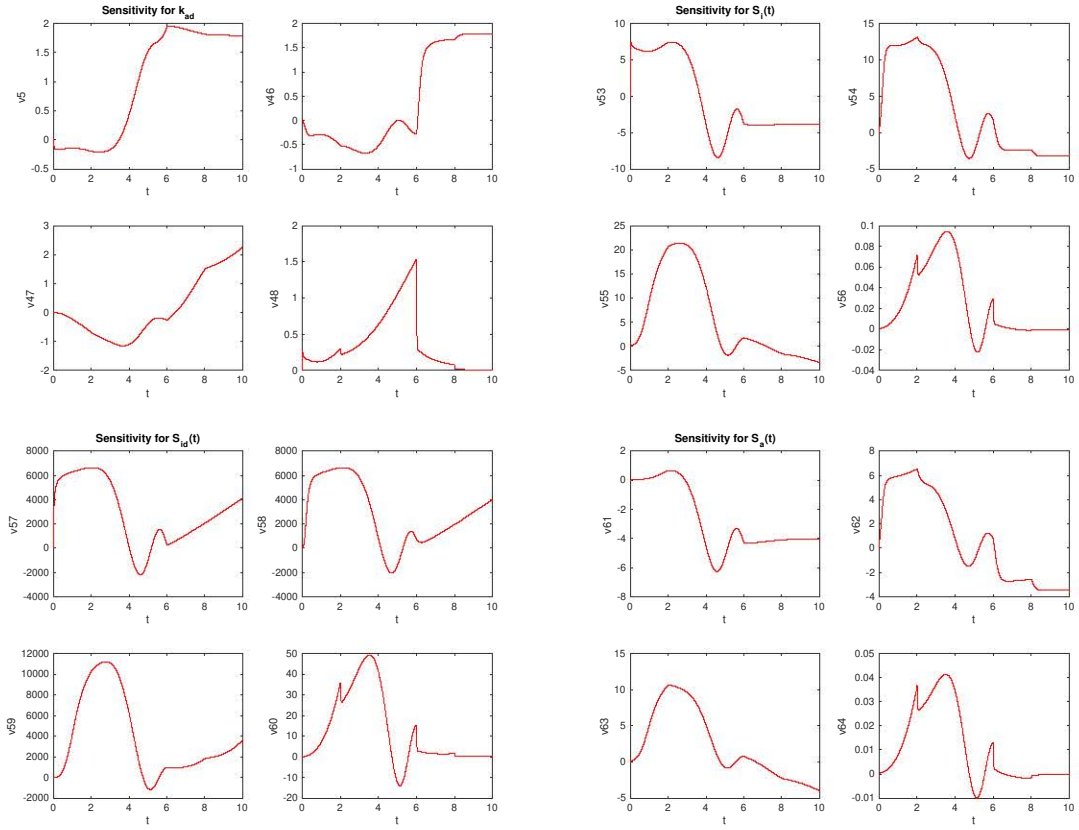

FIGURE 2.7. Sensitivities plots for parameters μ_a, $s_i(t)$, $s_{id}(t)$, and $s_a(t)$ for patient 491 with respect to model variables showing how they change over time

TABLE 2.1. Sensitivities: Patient 416

	Sensitivity				Two-Norm		
Parameter	I	P	D	A	$\tilde{M}_j$	$\frac{\tilde{M}_j}{91.4196}$	Rank
s_i	155.2659	81.0371	45.8090	25.6362	91.4196	1.0000	1
s_{id}	95.2329	50.0821	28.4274	15.3605	56.1729	0.6145	2
k_{id}	0.1916	0.1009	0.0541	0.0351	0.1129	0.0012	16
k_{ip}	15.2887	7.9619	4.5326	2.4038	8.9925	0.0984	6
k_{pi}	7.5798	1.9544	1.0777	0.7349	3.9678	0.0434	10
k_{pp}	15.5145	3.8633	2.5182	1.8805	8.1471	0.0891	7
k_{pd}	68.3929	16.9602	9.6756	6.2927	35.7017	0.3905	3
μ_p	20.4776	4.7846	2.8876	2.0529	10.6627	0.1166	5
k_{dip}	1.5293	1.3391	0.2188	0.1403	1.0246	0.0112	13
k_{dp}	8.3174	6.9886	2.3779	1.6797	5.6235	0.0615	8
μ_d	22.5101	19.4830	5.4266	3.0533	15.2065	0.1663	4
μ_a	0.3716	0.1302	0.0477	0.2939	0.2468	0.0027	14
s_a	1.0458	0.5517	0.2282	1.4566	1.0458	0.0114	12
k_{ap}	1.8172	0.7207	0.2548	1.5663	1.5663	0.0171	11
k_{ad}	7.2969	2.6747	0.8094	5.8147	4.8699	0.0533	9
A_{inf}	0.3711	0.1300	0.0480	0.2936	0.2466	0.0027	15

TABLE 2.2. Sensitivities: Patient 444

	Sensitivity				Two-Norm		
Parameter	I	P	D	A	$\tilde{M}_j$	$\frac{\tilde{M}_j}{91.4196}$	Rank
s_i	7.4169	5.2896	1.0929	0.0155	4.5876	0.0607	7
s_{id}	7.2021	5.1436	1.0798	0.0150	4.4579	0.0590	8
k_{id}	0.1431	0.0952	0.0393	0.0008	0.0882	0.0012	16
k_{ip}	21.0844	13.6105	4.4828	0.1021	12.7466	0.1687	4
k_{pi}	89.1206	116.8626	35.3145	0.6661	75.5760	1.0000	1
k_{pp}	1.9983	1.6442	0.66404	0.0134	1.3329	0.0176	11
k_{pd}	4.0568	6.2086	2.0620	0.0343	3.8489	0.0509	9
μ_p	11.3337	22.1140	4.8557	0.0839	12.6605	0.1675	5
k_{dip}	72.6974	46.4612	26.0960	0.4935	45.0688	0.5963	2
k_{dp}	1.4231	0.9339	0.4419	0.0074	0.8793	0.0116	13
μ_d	26.0346	20.9754	46.2030	0.1171	28.5153	0.3773	3
μ_a	3.2149	2.5648	1.1288	0.4421	2.1438	0.0284	10
s_a	1.3122	0.9935	1.0925	0.2756	0.9973	0.0131	12
k_{ap}	0.3283	0.1950	0.1053	0.0510	0.1997	0.0026	15
k_{ad}	1.0121	0.5583	0.3969	0.2027	0.6194	0.0082	14
A_{inf}	14.9004	11.9950	5.3051	0.1268	9.9255	0.1313	6

TABLE 2.3. Sensitivities: Patient 448

	Sensitivity				Two-Norm		
Parameter	I	P	D	A	$\tilde{M}_j$	$\frac{\tilde{M}_j}{61.3905}$	Rank
s_i	4.6145	3.6866	4.1741	0.8562	3.6415	0.0593	8
s_{id}	1.0523	0.8326	0.9633	0.1309	0.8326	0.0136	12
k_{id}	0.1705	0.1291	0.1447	0.0402	0.1306	0.0021	16
k_{ip}	14.5079	11.9458	13.9278	1.1996	11.7111	0.1908	4
k_{pi}	76.6816	89.8175	32.1539	9.6980	61.3905	1.0000	1
k_{pp}	1.7560	2.8620	1.2000	0.3390	1.7909	0.0292	9
k_{pd}	5.2083	8.5441	2.9244	0.8295	5.2289	0.0852	5
μ_p	3.0094	6.6094	1.7224	0.4641	3.7391	0.0609	6
k_{dip}	35.8978	36.4865	19.1362	4.7518	27.4258	0.4467	2
k_{dp}	1.7840	1.8154	2.2920	0.59197	1.7322	0.0282	7
μ_d	9.6625	8.9342	26.5880	1.9732	14.8661	0.2422	3
μ_a	0.2727	0.2887	0.2933	0.3589	0.3052	0.0050	14
s_a	0.6610	0.5053	0.5943	0.7915	0.6465	0.0105	13
k_{ap}	0.3175	0.2279	0.2486	0.2124	0.2548	0.0042	15
k_{ad}	0.9777	0.6644	0.7243	0.6437	0.7642	0.0124	11
A_{inf}	1.2232	1.3994	1.3990	0.557	1.1947	0.0195	10

TABLE 2.4. Sensitivities: Patient 491

	Sensitivity				Two-Norm		
Parameter	I	P	D	A	$\tilde{M}_j$	$\frac{\tilde{M}_j}{20.8376}$	Rank
s_i	2.3349	2.2756	3.3875	0.0129	2.3508	0.1128	5
s_{id}	0.1764	0.1722	0.2405	0.0011	0.1722	0.0082	14
k_{id}	0.1261	0.1223	0.1857	0.0008	0.1278	0.0061	16
k_{ip}	11.5280	20.2273	34.5655	0.0551	20.8376	1.0000	1
k_{pi}	8.4758	13.7374	9.7901	0.0405	9.4393	0.4530	3
k_{pp}	0.5840	1.0111	0.8045	0.0030	0.7090	0.0340	12
k_{pd}	0.7055	0.8332	0.5060	0.0020	0.6017	0.0289	13
μ_p	1.5001	2.3965	1.6864	0.0070	1.6460	0.0790	7
k_{dip}	1.1296	1.0784	0.5006	0.0938	0.8213	0.0394	11
k_{dp}	2.3975	2.1773	1.1927	0.2885	1.7316	0.0831	6
μ_d	9.4914	9.2356	24.9491	0.0396	14.1230	0.6777	2
μ_a	0.3040	0.0906	0.1126	0.0684	0.1718	0.0082	15
s_a	1.0328	1.2864	1.9591	0.7137	1.3294	0.0638	8
k_{ap}	1.0121	0.9021	1.0976	0.5207	0.9102	0.0437	10
k_{ad}	1.3230	1.0750	1.0460	0.5278	1.0342	0.0496	9
A_{inf}	2.4425	2.3979	3.6534	0.0254	2.5032	0.1201	4

Local Sensitivity Analysis

Based on the parameter estimates for all the patients, we found the numerical sensitivity value of each parameter with respect to each model variable. We plotted sensitivities with respect to time and we see that overall we get good plots over time as shown in the figure 2.1.3. To be able to understand which parameters are more sensitive in our model, we find the two norm of each parameter with respect to all the model variables (I, P, D, and A). Also, we divide all the two norm numerical values of each parameter to the largest value so as to find relativity of each parameter to the model variables. We rank the relative sensitivities from the most sensitive to the least sensitive (Table 2.1.4). Based on our results, we find that the parameters were ranked as follows:

Patient416: $s_i, s_{id}, k_{pd}, \mu_d, \mu_p, k_{ip}, k_{pp}, k_{dp}, k_{ad}, k_{pi}, k_{ap}, s_a, k_{dip}, \mu_a, A_{inf}$,and k_{id}

Patient444: $k_{pi}, k_{dip}, \mu_d, k_{ip}, k_{pd}, \mu_p, k_{dp}, s_i, k_{pp}, A_{inf}, k_{ad}, s_{id}, s_a, \mu_a, k_{ap}$,and k_{id}

Patient448: $k_{pi}, k_{dip}, \mu_d, k_{ip}, \mu_p, A_{inf}, s_i, s_{id}, k_{pd}, \mu_a, k_{pp}, s_a, k_{dp}, k_{ad}, k_{ap}$,and k_{id}

Patient491: $k_{ip}, \mu_d, k_{pi}, A_{inf}, s_i, k_{dp}, \mu_p, s_a, k_{ad}, k_{ap}, k_{dip}, k_{pp}, k_{pd}, s_{id}, \mu_a,$ and k_{id}

To find the most sensitive parameter across all the patients, we find the average of all sensitivities of each parameter across all the patients. These averaged sensitivities are computed and shown in the table 2.1.5

Using the parameter estimates for our mathematical model, the numerical values for the average of relative sensitivities of each parameter were computed across all the patients and were ranked from the most sensitive to the least sensitive (Table 2.1.5). These parameters were ranked in order of their magnitude across all patients. These ranked sensitivities tell us which parameters affect the model most and help us in explaining any uncertainties associated with the model.

	Average of Sensitivities	
Parameter	Average	Rank
k_{ip}	0.3645	1
k_{pi}	0.36241	2
μ_d	0.3534	3
s_i	0.3082	4
k_{dip}	0.2734	5
k_{pd}	0.1389	6
μ_p	0.1060	7
A_{inf}	0.0684	8
k_{dp}	0.0461	9
k_{pp}	0.0425	10
s_{id}	0.0358	11
s_a	0.0352	12
k_{ad}	0.0309	13
k_{ap}	0.0169	14
μ_a	0.0111	15
k_{id}	0.0032	16

TABLE 2.5. Average of sensitivities for all patients

Local sensitivity analysis depends on the baseline of the parameter values. Thus, the calculated sensitivities can help us in examining the space that we wish

to fit since were are able to distinguish between which parameters are most and least sensitive. Also, the most sensitive parameters of the model are the ones that have the greatest impact on the model.

Based on our model, we can see that the most sensitive parameters are associated with immune complexes, pro-inflammatory mediators, and damaged tissue equations and on the other hand, the least sensitive parameters are associated with the anti-inflammatory mediators equation. This gives a reason to hypothesize that as self-antigens accumulate in kidney glomeruli, more biological mediators will be released by the damaged cells and there will be more collateral damage. This may be counterbalanced by decay rates (μ_a, μ_p, and μ_d) but this not enough to outlast the growth in the damage of the tissue.

The explanation for anti-inflammatory mediators having the least sensitive values may be that the damage effects by immune complexes and pro-inflammatory mediators weakens the response of the therapy (anti-inflammatory mediators). Also, anti-inflammatory mediators are associated with the least sensitive parameters because it is hard to understand prognosis of Systemic Lupus Erythematosus and is thus hard to treat.

CHAPTER 3

OPTIMAL CONTROL THEORY

3.1. Non-Linear Control Theory

In an optimal control model, we define a set of variables which are to be controlled. Using optimal control theory will help us make decisions about when to adjust a control variable. The other dependent variables in an optimal control problem are state variables. State variables describe the behavior of the dynamical system (Daulton, 2013). We change the behavior of the state variables by adjusting the control function with the goal of minimizing the treatment (requirements) of LN. In particular, we will be controlling the damage of the flare. In order to control LN, we also use state variables from our LN model, which are immune complexes, pro-inflammatory mediators, damaged tissue, and anti-inflammatory mediators which are modeled by differential equations 1.1, 1.2, 1.3, and 1.4 respectively in chapter one. Our goal for using optimal control theory is to set up a control to identify the optimal time to administer therapy as well as the magnitude of the therapy. Also, as part of mathematical modeling, we set up an objective functional which we minimize. In our case, the objective functional is $\int [D(t) + \frac{1}{2}cu^2]dt$, where u is the control variable.

The control variable u, which is given as parameter s_a in equation 1.4 in chapter one is the therapy drug that is given to LN patients to keep inflammation under

control.

To better understand the optimality problem, we define a control set for a given

$a, b, t_1 t_0, \geq 0$, and

$U \equiv \{u(t) : a \leq u(t) \leq b, t_0 \leq t \leq t_1, u(t)$ is Lebesque measurable$\}$ (Lukes,1982) and state variable $x(t)$, where $x(t)$ depends on the control variable $u \in U$ satisfying a differential equation:

$x'(t) = g(t, x(t), u(t))$.

The basic optimal control problem consists of finding a piecewise continuous control $u(t)$ and associated state variable $\vec{x}(t)$ to minimize (or maximize) the given objective functional:

$$\min_{a \leq u \leq b} \int_{t_0}^{t_1} f(t, x(t), u(t)) dt$$
$$\text{subject to } x'(t) = g(t, x(t), u(t)),$$
$$x(t_0) = x_0, \text{ and } x(t_1) \text{ free.}$$

$x(t_1)$ free means that the value of $x(t_1)$ is unrestricted so that functions f and g are continuously differentiable in all three arguments (Daulton, 2013). Thus, the control variable will be piecewise continuous and the associated state variable will be piecewise differentiable (Daulton, 2013). The necessary and sufficient conditions for our control are derived using Pontryagin's Minimum (or Maximum) principle based on the following Theorem 1.1.1 provided in the work by Lenhart and Workman (2007):

THEOREM 3.1.1. *For the control* $\vec{u} = (u_1, ..., u_m)^{\mathcal{T}}$ *belonging to the admissible control set* U *and related trajectory* $\vec{x} = (x_1, ..., x_m)^{\mathcal{T}}$ *that satisfies*

$$\frac{d\vec{x}}{dt_i} = g_i(\vec{x}, \vec{u}, t) \text{ (state equation)}$$

$$\vec{x}_i(a) = c_i \text{ (initial conditions)}$$

but with free end conditions, to minimize the performance criterion

$$J = \phi(\vec{x}, t)|_a^b + \int_a^b f(\vec{x}, \vec{u}, t)dt$$

it is necessary that a vector $\vec{\lambda} = \vec{\lambda}(t)$ *exists such that*

$$\frac{d\vec{\lambda}}{dt} = -\frac{\partial H}{\partial \vec{x}} \text{ (adjoint equations),}$$

$$\vec{\lambda}(b) = \phi_x[\vec{x}(b), b] \text{(adjoint final conditions),}$$

where the Hamiltonian

$$H(t, \vec{x}, u) = f(t, \vec{x}, u) + \vec{\lambda}^{\mathcal{T}} \cdot \vec{g}(t, \vec{x}, u), = integrand + adjoint \cdot RHSofDE$$

for all $t, a \leq t \leq b$, *and all* $\vec{u} \in U$, *satisfies*

$$H[\vec{\lambda}(t), \vec{x}^*(t), \vec{u}] \geq H[\vec{\lambda}(t), \vec{x}^*(t), \vec{u}^*].$$

The adjoint functions add constraints to the function to be minimized or maximized.

3.2. Forming The Hamiltonian Equations for the Control

Given the objective functional $J[u(t)] : \int [D(t) + \frac{1}{2}cu^2]dt$,

we can form the following Hamiltionian using the differential equations (1.1-1.4) and using the theorem 3.1.1:

$$\begin{aligned} H &= [D + 0.5cu^2] \\ &+ \lambda_1\left(\frac{s_i}{1+(\frac{A}{A_{inf}})^2} + \frac{s_{id}}{1+(\frac{A}{A_{inf}})^2}\frac{D^2}{{k_{id}}^2+D^2} - \frac{k_{ip}IP}{1+(\frac{A}{A_{inf}})^2}\right) \\ &+ \lambda_2\left(\frac{k_{pi}I + k_{pp}P}{1+(\frac{A}{A_{inf}})^2} + \frac{k_{pd}D}{1+(\frac{A}{A_{inf}})^2} - \mu_p P\right) \\ &+ \lambda_3\left(\frac{k_{dip}IP}{1+(\frac{A}{A_{inf}})^2} + \frac{k_{dp}P}{1+(\frac{A}{A_{inf}})^2} - \mu_d D\right) \\ &+ \lambda_4\left(u + \frac{k_{ap}P + k_{ad}D}{1+(\frac{A}{A_{inf}})^2} - \mu_a A\right) \end{aligned} \tag{3.1}$$

The corresponding adjoint equations using theorem 3.1.1 are as follows:

$$\begin{aligned} \lambda_1' &= -\frac{\partial H}{\partial I} \\ &= -\left[-\lambda_1\left(\frac{k_{ip}A_{inf}^2 P}{A_{inf}^2 + A^2}\right) + \lambda_2\left(\frac{k_{pi}A_{inf}^2}{A_{inf}^2 + A^2}\right) + \lambda_3\left(\frac{k_{dip}A_{inf}^2 P}{A^2 + A_{inf}^2}\right)\right] \end{aligned} \tag{3.2}$$

$$\begin{aligned} \lambda_2' &= -\frac{\partial H}{\partial P} \\ &= -\left[-\lambda_1\left(\frac{k_{ip}A_{inf}^2 I}{A_{inf}^2 + A^2}\right) + \lambda_2\left(\frac{k_{pp}A_{inf}^2}{A^2 + A_{inf}^2} - \mu_p\right) + \lambda_3\left(\frac{k_{dip}A_{inf}^2 I}{A_{inf}^2 + A^2} + \frac{k_{dp}A_{inf}^2}{A^2 + A_{inf}^2}\right)\right. \\ &\left. + \lambda_4\left(\frac{k_{ap}A_{inf}^2}{A^2 + A_{inf}^2}\right)\right] \end{aligned} \tag{3.3}$$

$$
\begin{aligned}
\lambda_3' &= -\frac{\partial H}{\partial D} \\
&= -\Bigg[1 + \lambda_1\left(\frac{2s_{id}k_{id}^2A_{inf}^2D}{(A_{inf}^2+A^2)(k_{id}^2+D^2)^2}\right) + \lambda_2\left(\frac{k_{pd}A_{inf}^2}{A_{inf}^2+A^2}\right) \\
&\quad - \lambda_3\mu_d + \lambda_4\left(\frac{k_{ad}A_{inf}^2}{A_{inf}^2+A^2}\right)\Bigg]
\end{aligned} \tag{3.4}
$$

$$
\begin{aligned}
\lambda_4' &= -\frac{\partial H}{\partial A} \\
&= -\Bigg[\lambda_1\left(\frac{2AA_{inf}^2(IPk_{ip}(D^2+k_{id}^2) - s_i(D^2+k_{id}^2) - D^2s_{id})}{(A^2+A_{inf}^2)^2(D^2+k_{id}^2)}\right) \\
&\quad - \lambda_2\left(\frac{2AA_{inf}^2(k_{pi}I + k_{pp}P + k_{pd}D)}{(A^2+A_{inf}^2)^2}\right) \\
&\quad + \lambda_3\left(\frac{-2AA_{inf}^2P(k_{dip}I + k_{dp})}{(A^2+A_{inf}^2)^2}\right) \\
&\quad + \lambda_4\left(\frac{-2AA_{inf}^2(k_{ad}D + k_{ap}P)}{(A^2+A_{inf}^2)^2} - \mu_a\right)\Bigg]
\end{aligned} \tag{3.5}
$$

The optimality condition $\frac{\partial H}{\partial u} = cu + \lambda_4$ and the optimality control is given by :

$$
u^*(t) = \begin{cases} 0 & \text{means } cu + \lambda_4 \geq 0 \text{ at t,} \\ 0 < -\frac{\lambda_4}{c} < b & \text{means } cu + \lambda_4 = \text{ at t,} \\ M2 & \text{means } cu + \lambda_4 \leq 0 \text{ at t.} \end{cases} \tag{3.6}
$$

3.3. Non Linear Existence of an Optimal Control

The boundedness of the solution system (1), (2), (3), and (4) can used to prove the existence of the optimal control as stated in Joshi (2002) using supersolutions

technique. The super solution for $\bar{I}$, $\bar{P}$, $\bar{D}$, and $\bar{A}$ satisfying

$$\frac{d\bar{I}}{dt} = \bar{s_i} + \frac{\bar{s}_{id}\bar{D}^2}{{k_{id}}^2 + \bar{D}^2} \tag{3.7}$$

$$\frac{d\bar{P}}{dt} = k_{pi}\bar{I} + k_{pp}\bar{P} + k_{pd}\bar{D} \tag{3.8}$$

$$\frac{d\bar{D}}{dt} = k_{dip}\bar{I}\bar{P} + k_{dp}\bar{P} \tag{3.9}$$

$$\frac{d\bar{A}}{dt} = u + k_{ap}\bar{P} + k_{ad}\bar{D} \tag{3.10}$$

is bounded on a finite time interval.

To show the existence of an optimal control, u^*, we use the theorem by Fleming and Rishel (1975) provided in Daulton (2013) stated below:

THEOREM 3.3.1. *The Cauchy problem* $\frac{dx}{dt} = g(t, x(t)), x|_{t=\tau} = \xi$ *where* $(\tau, \xi) \in D$, *with* D *a nonempty open subset of* $\mathbb{R} \times \mathbb{R}^n$ *and* $f : D \to \mathbb{R}^n$ *has a solution if for some* $R_{a,b} = \{(t, x) : |t - \tau| \leq a, |x - \xi| \leq b, a, b > 0\} \subset D$ *centered about* (τ, ξ) *the restriction of* g *to* $R_{a,b}$ *is continuous in* x *for a fixed* t, *measurable in* t *for a fixed* x, *and satisfies* $|g(t, x)| \leq |m(t)|, (t, x) \in R_{a,b}$ *for some* m *integrable over the interval* $[\tau - a, \tau + a]$.

In order to prove the existence of a nonlinear solution for our optimal control using the theorem above, we check the following five properties given in Joshi (2002) and stated in Daulton (2013).

1. The set of controls and corresponding state variables is non-empty.

2. The Control set U is convex and closed.

3. The RHS of the state system is bounded by a linear function in the state and control variables.

4. The integrand of the objective functional is concave on U.

5. There exist constants $c_1, c_2 > 0$, and $\beta > 1$ such that the integrand $L(t, u_1, u_2)$ of the objective functional satisfies $L(t, u_1, u_2) \geq c_2 - c_1|u_1|^\beta$.

THEOREM 3.3.2. *Let L be the integrand of the objective functional, $\vec{g}$ be the right-hand side of the differential equation, U be a closed subset of E^n, the space of n tuples $x = (x_1, ..., x_n)$ of real numbers. Let $\mathscr{F}'$ be the class of all (x_0, u) such that u is a Lebesque-integrable function on the interval $[t_0, t_1]$ with values in U and the solution of the differential equations satisfying the end conditions $e \in S$. Let S be a given subset of E^{2n+2} and $J(x_0, u) = \phi_j(t_0, t_1, x(t_0), x(t_1)) = \phi(e)$ for $j = 2, ..., k$ where e denotes a $(2n+2)$-tuple of end points. For each $(t, x) \in E^{n+1}$, let $\tilde{F}(t, x) = \tilde{z} : z = g(t, x, u), z_{n+1} \geq L(t, x, u), u \in U$.*

Suppose that $\vec{g}$ is continuous; there exists positive constants C_1, C_2 such that

(a) $|\vec{g}(t, x, u)| \leq C_1(1 + |x| + |u|)$,

(b) $|\vec{g}(t, x', u) - \vec{g}(t, x, u)| \leq C_2|x' - x|(1 + |u|)$ for all $t \in E^1, x, x' \in E^n$, and $u \in U, L$ is continuous,

and that:

1. $\mathscr{F}'$ is not empty;

2. U is closed;

3. S is compact and ϕ is continuous on S;

4. $\tilde{F}(t,x)$ is convex for each $(t,x) \in E^{n+1}$;

5. $L(t,x,u) \geq h(u)$, where h is continuous and $|u|^{-1}h(u) \to +\infty$ as $|u| \to \infty, u \in U$.

Then there exist (x_0^*, u^*) minimizing $J(x_0, u)$ on $\mathscr{F}'$.

We use Theorem 3.3.2 to prove the existence of a non-linear solution for our optimal problem by satisfying the five conditions by Joshi (2002) as follows:

Proof

1. The theorem by Lukes gives the existence of ODE solutions with bounded coefficients. The piecewise constant coefficients s_i, s_{id} are bounded by $\bar{s}_i$ and $\bar{s}_{id}$.

2. The control set U is convex and closed given that our differential equation in u is linear and closed since $0 \leq u \leq b$.

3. Since the state variables I, P, D, and A are bounded by $\bar{I}$, $\bar{P}$, $\bar{D}$, and $\bar{A}$, respectively, in a finite time, the right hand side is bounded by a linear function in the state variables. The control is also bounded since since $a \leq$ u $\leq$ b.

4. The integrand of our objective function $D(t) + \frac{c}{2}u^2\chi$ is convex on U. Using the theorem by Rudin (1976) which states that "If $f(x)$ has a second derivative in $[a,b]$, then a necessary and sufficient condition for it to be convex on that interval is that the second derivative $f''(x) \geq 0$ for all $x \in [a,b]$. Based on the theorem, it is easy to see that our objective function is convex since the second derivative of $D(t) + \frac{c}{2}u^2\chi = c > 0$.

5. Let $c_1 = c > 0, c_2 > 0$. Then $D + cu^2 \geq c_1|u|^2 - c_2$.

Thus, we can conclude that there exists an optimal control solution to our system.

3.4. Uniqueness of the Optimality System

To show the uniqueness of the optimality system, we use the Theorem 3.4 provided in Daulton (2013). Our optimality system is defined by the state variables, adjoint system, initial conditions, transversality conditions, and the optimal control characterization.

In our system, we consider the following boundary value problem.

$$f(t) = \begin{cases} \vec{x}(t)' = \vec{p}(t, x, \lambda) = (I(t)', P(t)', D(t)', A(t))^\tau \\ \vec{\lambda}(t) = \vec{q}(t, x, \lambda) = (\lambda_1(t)', \lambda_2(t)', \lambda_3(t)', \lambda_4(t)')^\tau \\ \vec{x}(0) = \vec{x_0}, \vec{\lambda}(T) = \vec{\lambda_T}, \end{cases} \tag{3.11}$$

where $\vec{x} \in \mathbb{R}^m, \vec{\lambda} \in \mathbb{R}^n$, $\vec{p} : \mathbb{R} \times \mathbb{R}^m \times \mathbb{R}^n \to \mathbb{R}^m$, and $\vec{q} : \mathbb{R} \times \mathbb{R}^m \times \mathbb{R}^n \to \mathbb{R}^n$ are continuous.

THEOREM 3.4.1. *Assume that $\vec{p}$ and $\vec{q}$ are bounded and satisfy a Lipschitz condition relative to $\vec{x}$ and $\vec{\lambda}$ with a constant $C > 0$. Then solutions of system above are unique if T is sufficiently small.*

Proof: Consider the two-point boundary value problem (equation (3.1.1)) where the solution to the equation is a pair such that

$$f(t) = \begin{cases} \vec{x}(t)' = \vec{p}(t, x, \lambda) = (I(t)', P(t)', D(t)', A(t))^\tau \\ \vec{\lambda}(t) = \vec{q}(t, x, \lambda) = (\lambda_1(t)', \lambda_2(t)', \lambda_3(t)', \lambda_4(t)')^\tau \\ \vec{x}(0) = \vec{x_0}, \vec{\lambda}(T) = \vec{\lambda_T} \end{cases} \tag{3.12}$$

If we have a solution $(x(t), \lambda(t))$ defined on an interval $[0, T]$, then, integrating the expression $x'(t) = \frac{dx}{dt} = p(t, x(t), \lambda(t))$ we obtain

$\int_0^t x'(s)ds = \int_0^t p(s, x(s), \lambda(s))ds$

$\implies x(t) - x(0) = \int_o^t p(s, x(s), \lambda(s))ds$

So, $x(t) = x_0 + \int_0^t p(s, x(s), \lambda(s))ds$.

Similarly: $\int_T^t \lambda'(s)ds = \int_T^t q(s, x(s), \lambda(s))ds$

$\implies \lambda(t) - \lambda(T) = \int_0^t q(s, x(s), \lambda(s))ds$.

So, $\lambda(t) = \lambda_T - \int_t^T p(s, x(s), \lambda(s))ds$.

Now suppose we have two solutions $(x_1(t), \lambda_1(t))$ and $(x_2(t), \lambda_2(t))$ to our boundary equation. Then,

$x_1(t) - x_2(t) = x_0 + \int_0^t p(s, x_1(s), \lambda_1(s))ds - x_0 - \int_0^t p(s, x_2(s), \lambda_2(s))ds$ and

$\lambda_1(t) - \lambda_2(t) = \lambda_T + \int_t^T q(s, x_1(s), \lambda_1(s))ds - \lambda_T + \int_t^T q(s, x_2(s), \lambda_2(s))ds$.

Simplifying the above equations we get:

$x_1(t) - x_2(t) = \int_0^t p(s, x_1(s), \lambda_1(s))ds - p(s, x_2(s), \lambda_2(s))ds$ and

$\lambda_1(t) - \lambda_2(t) = \int_t^T q(s, x_1(s), \lambda_1(s))ds - q(s, x_2(s), \lambda_2(s))ds$.

So, $||x_1(t) - x_2(t)|| \leq \int_0^t ||p(s, x_1(s), \lambda_1(s))ds - p(s, x_2(s), \lambda_2(s))||ds$ and

$||\lambda_1(t) - \lambda_2(t)|| \leq \int_t^T ||q(s, x_1(s), \lambda_1(s))ds - q(s, x_2(s), \lambda_2(s))||ds$.

The two inequalities are a consequence of $|| \int_a^b F(t)dt|| \leq \int_a^b ||F(t)||dt$ valid for every vector function $F : [a, b] \to \mathbb{R}^N$.

Suppose that $\vec{p}$ and $\vec{q}$ are bounded and satisfy a Lipschitz condition relative to $\vec{x}$ and $\vec{y}$ with a constant $c > 0$. In that case we have that:

$||p(s, x_1(s), \lambda_1(s)) - p(s, x_2(s), \lambda_2(s))|| \leq C(||x_1(s) - x_2(s)|| + ||\lambda_1(s) - \lambda_2(s)||)$ and

$||q(s, x_1(s), \lambda_1(s)) - q(s, x_2(s), \lambda_2(s))|| \leq C(||x_1(s) - x_2(s)|| + ||\lambda_1(s) - \lambda_2(s)||)$.

Then, $||x_1(t) - x_2(t)|| \leq C \int_0^t (||x_1(s) - x_2(s)|| + ||\lambda_1(s) - \lambda_2(s)||)ds$ and

$||\lambda_1(t) - \lambda_2(t)|| \leq C \int_t^T (||x_1(s) - x_2(s)|| + ||\lambda_1(s) - \lambda_2(s)||)ds$.

If we add the two equations above, we get:

$||x_1(t) - x_2(t)|| + ||\lambda_1(t) - \lambda_2(t)|| \leq C \int_0^T (||x_1(s) - x_2(s)|| + ||\lambda_1(s) - \lambda_2(s)||)ds$

Now, we apply the Mean Value Theorem of integrals: If f is continuous on $[a, b]$ there exists a value c on the interval (a, b) such that $\int_a^b f(t)dt = f(c)(b - a)$. Thus, there exists an α ; $0 \leq \alpha \leq T$ such that

$||x_1(t) - x_2(t)|| + ||\lambda_1(t) - \lambda_2(t)|| \leq T * C(||x_1(\alpha) - x_2(\alpha)|| + ||\lambda_1(\alpha) - \lambda_2(\alpha)||)$ for all $t \in [0, T]$.

If we take T such that $TC < 1$, we obtain that for all $t \in [0, T]$,

$||x_1(t) - x_2(t)|| + ||\lambda_1(t) - \lambda_2(t)|| < T * C(||x_1(\alpha) - x_2(\alpha)|| + ||\lambda_1(\alpha) - \lambda_2(\alpha)||)$. This gives us a contradiction and thus completing our proof.

3.5. Numerical Solution for the Optimal Control

Using the numerical methods, Matlab ode solvers, and iterative methods techniques, we were able to to solve our optimal system using the Hamiltonian given by equation (3.1). We solved the state system with initial conditions forward-in-time and then the adjoint equations is solved backward-in-time (Agaba, 2016). The control u is run for several iterations and updated at the end of each iteration.

Our control u, the therapy is updated by a simple average $u = 0.5 * (u1 + oldu)$ where $u1$ is the current iterative value of $u1$ and $oldu$ is the previous iterative value of u. Our control has lower bound of $a = 0$ and upper bound of $b = 35$. We continue to run the iterations until the convergence criterion is met. From work

by Budu-Grajdeanu et al., 2010, the therapy is administered for 30 days. So, in our work we develop a strategy where therapy is only administered when there is damage of the kidney tissue. First, we find numerical results when therapy is administered so as to track the prognosis of flare damage in the kidney glomerulus.

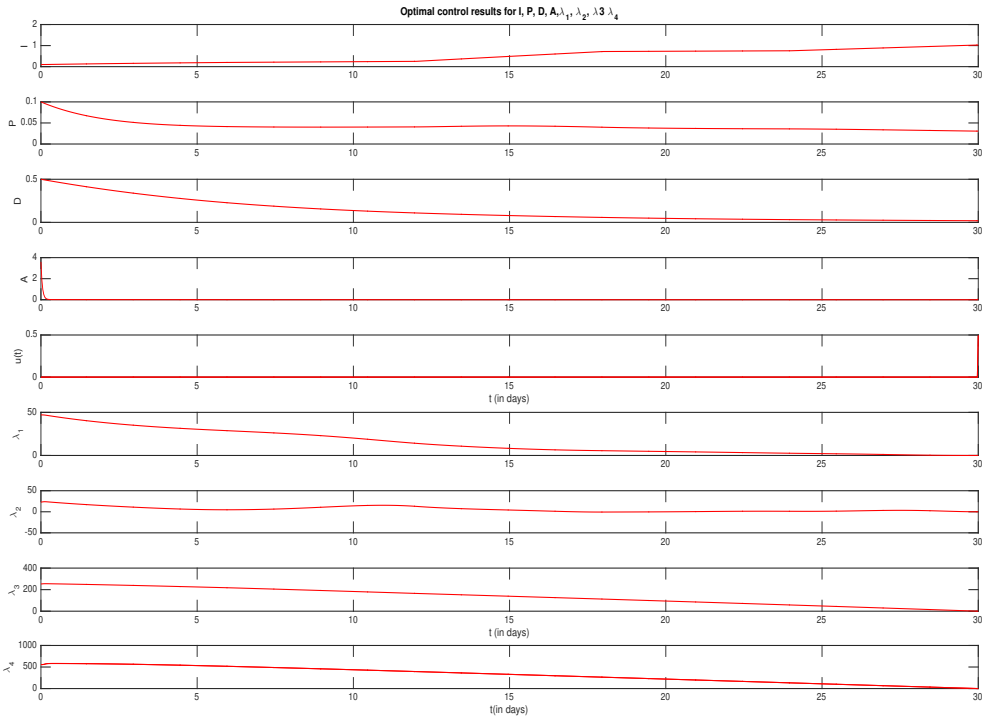

FIGURE 3.1. Results for patient 444. Damage naturally goes to zero.

In this case, u is initially 0.4 and initial conditions $(I, P, D, A) = (0.1, 0.5, 3.59, 0.1)$. Damage naturally goes to zero around the twenty sixth day and pro-inflammatory

mediators persist. On the other hand, immune complexes persist and keep circulating in the kidneys. The anti-inflammatory mediators go to zero on the first day of the therapy. The control u which is the therapy is not administered until the thirtieth day.

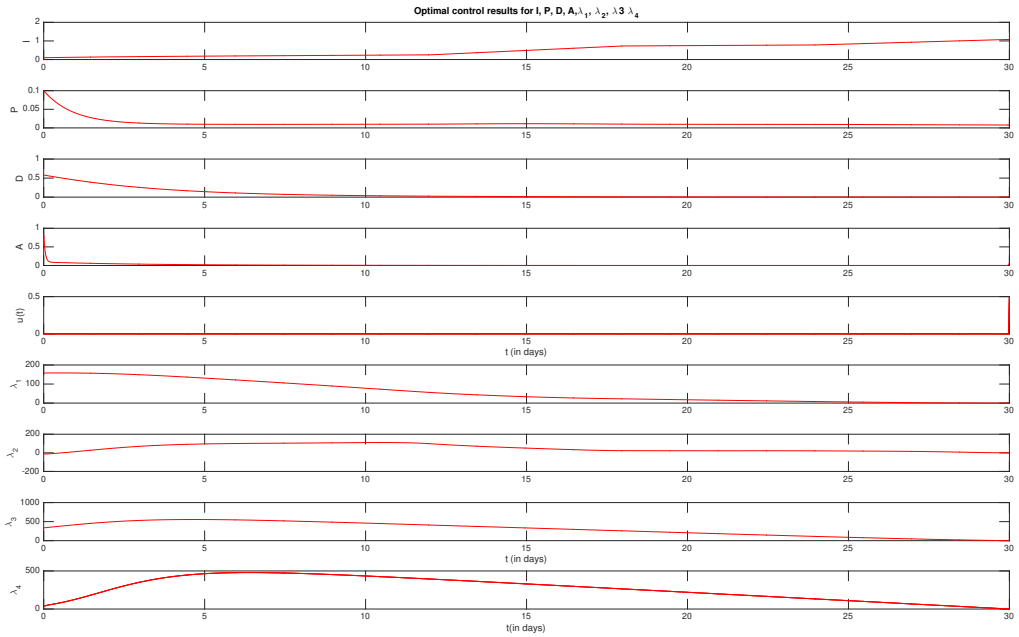

FIGURE 3.2. Results for patient 448. Damage naturally goes to zero.

Results for u is initially 0.4 and $(I, P, D, A) = (0.1, 0.58, 0.85, 0.1)$. Damage naturally goes to zero on the tenth day and pro-inflammatory mediators go to zero in 2.5 days. On the other hand, immune complexes stay at zero for the first 5 days and after that grow and keep circulating in the kidneys. The anti-inflammatory mediators quickly goes to zero on the first day. The control u which is the therapy stays at zero for the entire period. This is biologically reasonable given that damage naturally goes to zero. It makes sense for therapy to stay at zero so that there will not be there any damage coming from dose misuses.

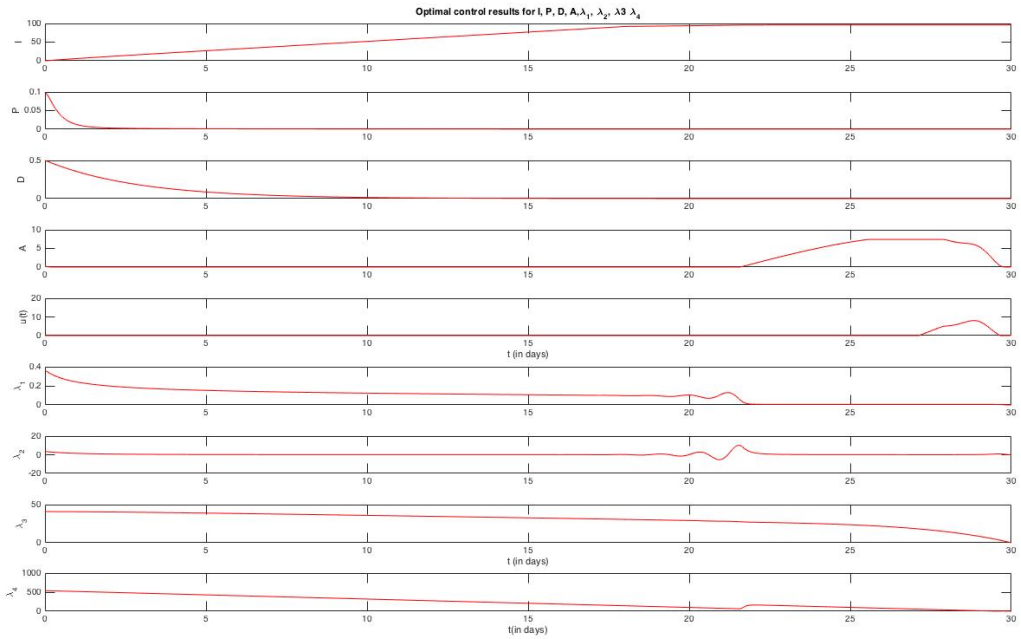

FIGURE 3.3. Results for patient 491. Damage naturally goes to zero.

Here u is initially 0.4 and $(I, P, D, A) = (0.1, 0.5, 0.38, 0.1)$. Damage goes to zero in 9-days while pro-inflammatory mediators go to zero on the second day. The therapy, u is only applied for 2 days from the twenty-eighth day and goes back to zero on the thirtieth day. The anti-inflammatory stays at zero until the twenty-second day and stays at an average of 5 and goes back to zero on thirtieth day. Again this is not biologically reasonable since therapy is applied when damage is already zero.

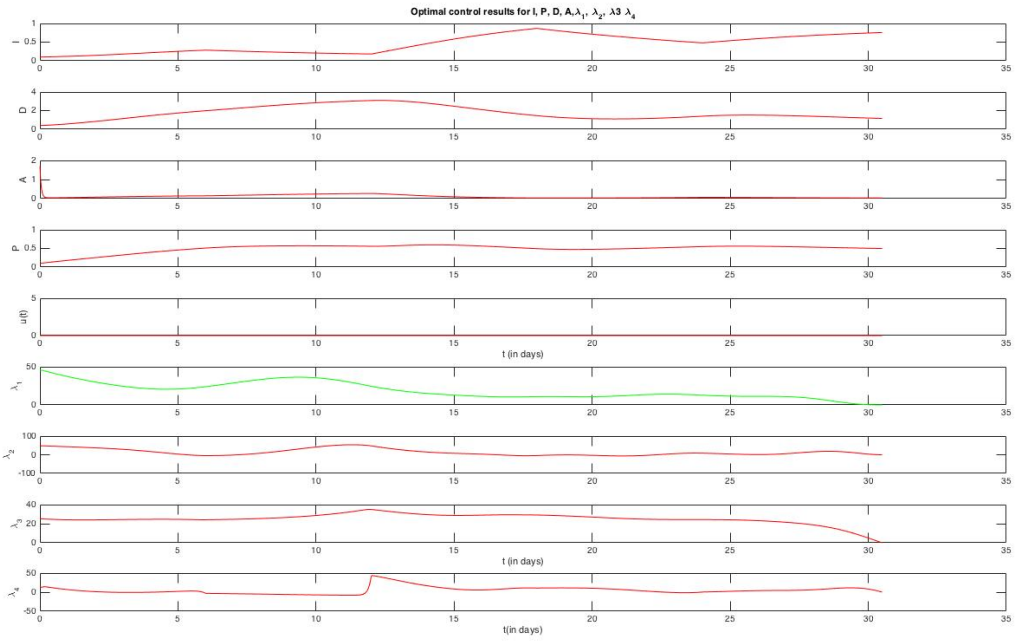

FIGURE 3.4. Results for patient 416. Damage persists.

Here u is initially 0.4 and $(I, P, D, A) = (0.1, 0.4, 1.7, 0.1)$. In this case, damage, pro-inflammatory, and immune complexes persist in the kidney. The anti-inflammatory mediators are held close, or at zero for the entire therapy period. Also, therapy kept at zero for 30 days. This case shows that without therapy, damage persists.

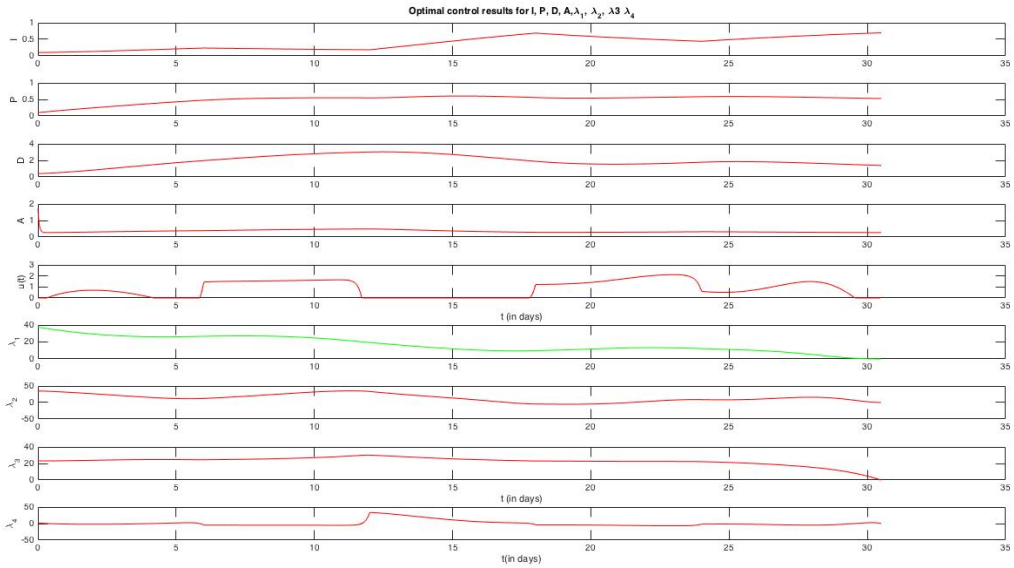

FIGURE 3.5. Results for patient 416. In this case damage persists.

Numerical results for patient 416 when therapy is administered and u is initially at 0.5. Flare damage of the tissue still persists and starts decreasing after the fifteenth day. The therapy remains at zero for the first six days and then runs again for 6 days and then goes back to zero. After eighteenth day, therapy runs up to the twenty-ninth day. Though, damage does not completely go to zero, this is biologically reasonable because when therapy starts running, the flare damage keeps on decreasing as it is being counter-interacted by the therapy. To find a better solution, we need to find amount of therapy/control that would make damage go to zero.

Given that the damage persists in the wound for the case when therapy is not administered and when therapy is administered when u is initially 0.5, we try a case when therapy is administered and see what happens to flare damage of the

tissue. This is done for patient 416, the case when damage persists and we also let our MATLAB code run for as many as 25,000 iterations. We use different values of u and also adjust the values of c (c is initially 0.000001), where c is the constant multiplied to the control.

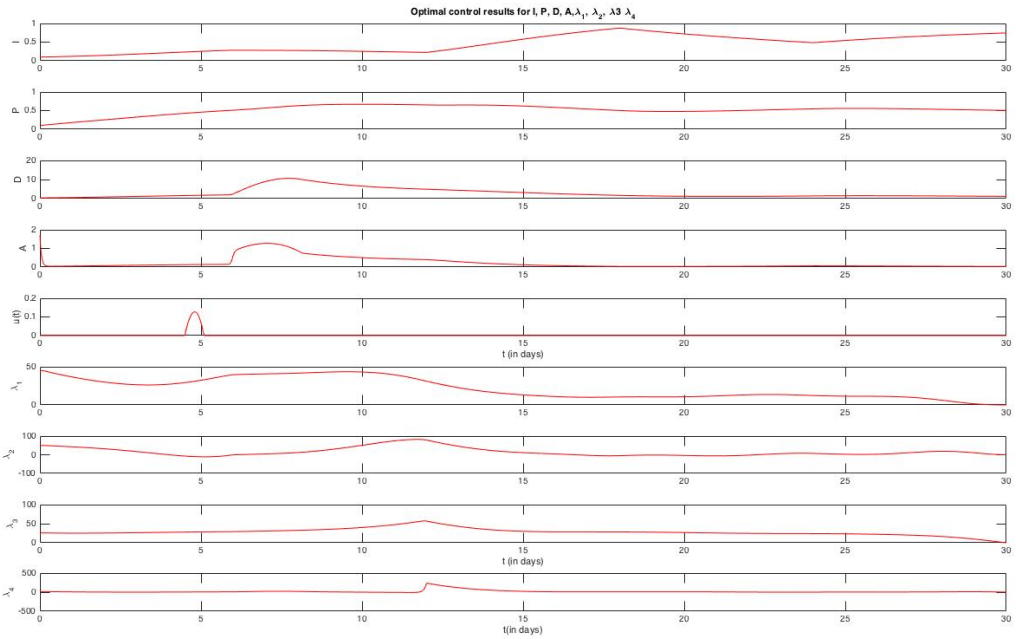

FIGURE 3.6. Results for patient 416. In this case damage does not go to zero.

For this case u is initially 0.4 and $(I, P, D, A) = (0.1, 0.4, 1.7, 0.1)$. The therapy is kept at a small amount close to zero and damage is driven to zero on the eighth day. The anti-inflammatory mediators also go to zero. For this case, we added $0.5u$ to pro-inflammatory mediators and the reason for doing this is that, pro-inflammatory mediators play a key role in healing of lupus nephritis. This is biologically applicable since adding a therapy will strengthen the existing immune cells which fight to kill immune complexes and flare damage in the kidneys.

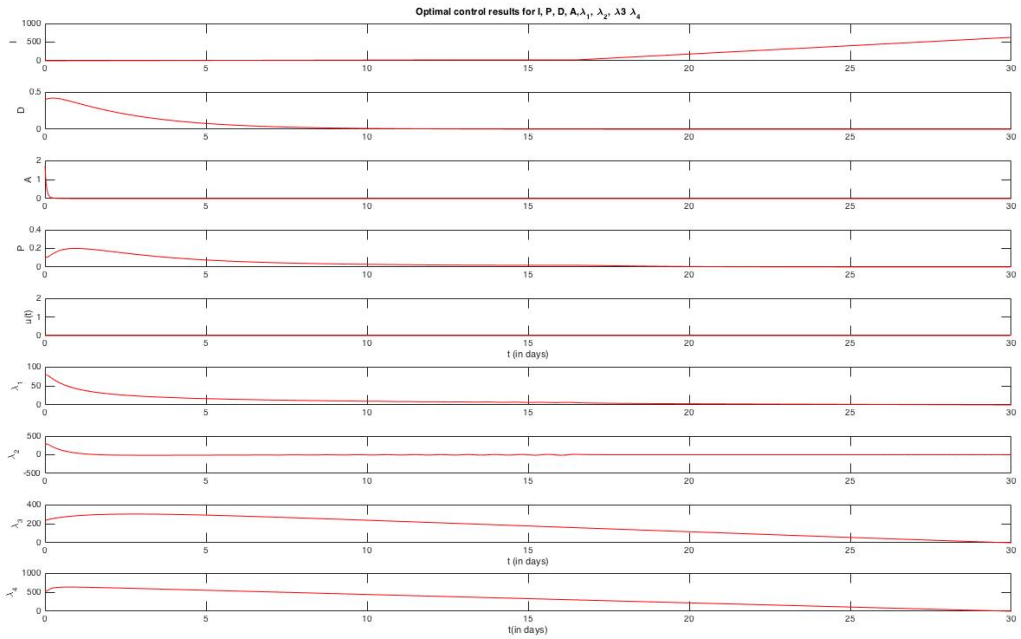

FIGURE 3.7. Results for patient 416. In this case damage goes to zero.

For this case u is initially 0.3 and $(I, P, D, A) = (0.1, 0.4, 1.7, 0.1)$. The therapy is kept at a small amount close to zero and damage is driven to zero on the eighth day. The anti-inflammatory mediators also go to zero. For this case, we added $0.5u$ to pro-inflammatory mediators and the reason for doing this is that, pro-inflammatory mediators play a key role in healing of lupus nephritis. This is biologically applicable since adding a therapy will strengthen the existing immune cells which fight to kill immune complexes and flare damage in the kidney.

Summary of Results		
Patient	Damage goes to zero	Initial value of u
416	no	0
416	no	0.5
416	no	0.4
416	yes	0.3
444	yes	0.4
448	yes	0.4
491	yes	0.4

TABLE 3.1. Summary of the results for all the patients.

From our findings, we are still seeking better therapy for lupus nephritis. We need to find a better value for our control u (therapy) that would have much impact on the dynamics of the flare damage in the kidney. As much as we have been able to find cases where damage goes to zero, most of these cases had damage naturally go to zero and thus, we did not apply as much therapy as expected. This explains the reason why it is hard to treat LN in these cases with aggressive therapy.

One of the significant findings is that adding therapy to pro-inflammatory mediators plays a key role in pathogenesis and explaining treatment of LN. Therapy strengthens the immune system which in turn helps to fight the immune complexes. Therefore, this provides us information on the control/biomarkers for diagnosis, pathogenesis, and therapeutics that can help track and treat flare cycle and damage in the kidney.

CHAPTER 4

CONCLUSIONS AND FUTURE WORK

4.1. Parameter Estimation: Local Sensitivity

In our work, we used a local (derivative-based approach) sensitivity analysis to rank parameters based on their significance to the model. Using local sensitivity analysis, we were able to rank and quantify the sensitivities of individual model parameters with respect to other parameters. We computed a 2-norm to evaluate the total and relative sensitivities of each parameter with respect to the state variables. Also, we found average relative sensitivities of each parameter across all patients to determine which parameters needed to be considered most in our model. For the parameters (s_a, s_i, and s_{id}) that are given as piecewise functions, we constructed cubic splines at each time subinterval to obtain a continuous derivative on each subinterval.

Our results for sensitivities helped us find which parameters are most and least sensitive. The numerical values of the sensitivities of each parameter with respect to each model were plotted. This explains the dynamics of each parameter and how they change over time. Our results indicate that decay parameters are relatively more sensitive when compared to other parameters across all patients. Thus, we can hypothesize that decay rates have a significant effect on the dynamics of the biological system.

Also, the ability to establish the border line that helped us separate most sensitive from least sensitive parameters Thus, the local sensitivity results indicate that we need to explore a small space to know which parameters are sensitive and the role they play in explaining the prognosis of the Lupus. Numerical values from our sensitivities show that the sensitive parameters are associated with immune complexes, pro-inflammatory mediators, and damaged tissue and insensitive parameters with anti-Inflammatory mediators (therapy). This matches our expectations since it is very hard to understand the prognosis of the Lupus Nephritis. Also, immune complexes, pro-inflammatory mediators, and damaged tissue play a key role in growth and decay rates of flare in kidneys and, as such, parameters associated with these variables will be sensitive.

For future work, we will explore three areas to improve parameter estimation for our model: Parameter Identifiability, Global Sensitivity analysis, and a Bayesian algorithm, Delayed Rejection Adaptive Metropolis (DRAM).

Parameter identifiability as will enable us to uniquely recover the model parameters from a given set of data. In parameter identifiability, one is able to incorporate parameter estimation with issues that come with real data such as noise and bias (Smith, 2014). That is, identifiability explores this question: given an input u, model and experimental output y, is it possible to uniquely identify the parameters p? (Eisenberg and Hayashi, 2014). Thus, parameter identifiability can be used quantify and update input uncertainties associated with parameters, initial conditions and boundary conditions.

For our sensitivity analysis, we will also to explore a global sensitivity analysis. We will explore a global sensitivity analysis to ascertain how uncertainty in model outputs can be apportioned to uncertainties in model inputs, taken either singly or in combination, when considered over the entire range of input values (Smith, 2014). The advantage of using "global" is that it is independent of parameter estimates and covers a wide range of the parameter space unlike a local sensitivity analysis that is infeasible for complex models where taking partial derivatives is nontrivial given that it explores a small fraction of the design space especially when they are many parameters.

Under DRAM, many different implementations and proposals for covariance are suggested. Then, we demonstrate one straight forward possibility algorithm. This implemented possibility is tested and if it fails, a modified version of the first proposal is done. When first proposal fails, a second proposal can be adapted and this can be with a smaller covariance. And as such, DRAM is better for parameter estimation since it makes several runs for code and uses the most efficient correlation/proposal (Smith, 2014). This provides a good parameter estimation by updating uncertainties associated with the model.

4.2. Optimal Control

We have been able to develop non-linear optimal control therapy for the treatment of the LN. Also, we proved the existence and uniqueness of non-linear optimal control. We found the optimal values for the control u that we able to drive damage to zero. Our results indicate that it is good to stop administering

the therapy when damage goes to zero. This is done to minimize both time spent administering therapy and the costs of the therapy.

From our results, we found an optimal solution for the control variable through the simulations. Our control model provided relevant information on how the complexes are related to LN. Also, as anticipated that to treat LN needs a lot of drugs, through simulations we were able to realize that it needs high immunosuppressive drugs and therapy to treat LN. We also realized that though aggressive treatments are applied to treat LN, it takes a long time to completely eliminate flare damage from the kidneys. It is better to administer high amounts to harness the flare damage in the kidneys.

For our future work on this project, we can explore the linear optimal control theory. The linear objective functional problem can be written as follows: $J = \int [D + \frac{1}{2} cu] dt$. In this case, therapy/dose will need to be given at the maximum value for the entire time of treatment (Lenhart and Workman, 2007). This would be ideal treatment for LN given that LN needs aggressive treatment. Also linear control means that therapy will be administered to the affected area and this is advantageous in that it helps in minimizing the costs and time of the therapy.

Also, the other areas we will consider exploring are adding the control to pro-inflammatory mediators and also trying other objective functions. Pro-inflammatory mediators come as a result of prolonged immune complexes in the

body organs and as such immune cells are generated which fight the damage and immune complexes. So, adding therapy/control to the pro-inflammatory mediators will help strengthen the immune system and thus, increases the ability of the kidney to fight flare damage.

We did not consider minimizing other objective functions such as $J = \int [D + \frac{1}{2} c u^2 e^{-\delta t}] dt$. $e^{-\delta t}$ works as a Lagrange multiplier which adds constraints to our control and this is done in a way that therapy is only applied for a certain length of time each day (Agaba, 2016). Adding more constraints to the objective function will work to minimize our problem. The only disadvantage of using a harder objective functions is that we will need to run more iterations which is hard sometimes for computers to run and be able to find the convergence criterion.

BIBLIOGRAPHY

[1] Budu-Grajdeanu, P., Schugart, R. C., Friedman, A., Birmingham, D. J., & Rovin, B. H. (2010). Mathematical framework for human SLE Nephritis: disease dynamics and urine biomarkers. *Theoretical Biology and Medical Modelling*,7(1), 14. doi:10.1186/1742-4682-7-14.

[2] Smoller, B., & Sundram, U. (2009). Faculty of 1000 evaluation for Subcutaneous panniculitis-like T-cell lymphoma with overlapping clinicopathologic features of lupus erythematosus: Coexistence of 2 entities. *Post-publication Peer Review of the Biomedical Literature*. doi:10.3410/f.1164784.626603.

[3] Mu, Q., Tavella, V. J., Kirby, J. L., Cecere, T. E., Chung, M., Lee, J., & Luo, X. M. (2017). Antibiotics ameliorate lupus-like symptoms in mice. *Scientific Reports*, 7(1). doi:10.1038/s41598-017-14223-0.

[4] Avihingsanon, Y., and Hirankarn, N. (2010). Major lupus organ involvement: Severe lupus nephritis. *Lupus*, 19(12), 1391-1398. doi:10.1177/0961203310376522.

[5] Hirohata, S. (2018). Epidemiology of Neuropsychiatric Systemic Lupus Erythematosus. Neuropsychiatric Systemic Lupus Erythematosus,1-13. doi:10.1007/978-3-319-76496-21.

[6] Yazdany, J., & Yelin, E. (2010). Health-related quality of life and employment among persons with systemic lupus erythematosus. Rheumatic disease clinics of North America, 36(1), 15-32. doi:10.1016/j.rdc.2009.12.006.

[7] Schugart, R. C., Friedman, A., Zhao, R., & Sen, C. K. (2008). Wound angiogenesis as a function of tissue oxygen tension: a mathematical model. *Proceedings of the National Academy of Science USA*, 105(7):2628-2633.

[8] Littlejohn, E., Marder, W., Lewis, E., Francis, S., Jackish, J., Mccune, W. J., & Somers, E. C. (2018). The ratio of erythrocyte sedimentation rate to C-reactive protein is useful in distinguishing infection from flare in systemic lupus erythematosus patients presenting with fever. *Lupus*, 27(7), 1123-1129. doi:10.1177/096120331876373.

[9] Krishna, N. A., Pennington, H. M., Coppola, C. D., Eisenberg, M. C., and Schugart, R. C., (2015) *Connecting Local and Global Sensitivities in a Mathematical Model for Wound Healing*, Bulletin of Mathematical Biology, **77** (12), 2294-2324. doi:10.1007/s11538-015-0123-3

[10] Daulton, D. L. *Using Optimal Control Theory to Optimize the Use of Oxygen Therapy in Chronic Wound*, Maters Thesis, 2013.

[11] Saltelli, A., Ratto, M., Andres, T., Campolongo, F., Cariboni, J., Gatelli, D., Saisana, M., & Tarantola, S. *Global Sensitivity Analysis.*, The Primer, John Wiley and Sons, 2008.

[12] Smith, R. C (2014). *Uncertainty quantification: Theory, implementation, and applications.*, Philadelphia: Society for Industrial and Applied Mathematics.

[13] Pope, S.R., Ellwein, L.M., Zapata, C.L., Novak, V., Kell, C.T., Olufsen, M.S., (2009) *Estimation and identification of parameters in a lumped cerebrovascular model.*, Math Biosci Eng, 6(1):93-115.

[14] Olufsen, M.S., & Ottesen, T.J., (2013) *A practical approach to parameter estimation applied to model predicting heart rate regulation.* J Math Bio, 67(1):39-68.

[15] Burden, R. L., Faires, J. D., & Reynolds, A. C (1997). *Numerical Analysis, 6th ed.* Boston, MA: Brooks/Cole, pp. 120-121.

[16] Lenhart, S. & Workman, J.T. (2007). Optimal Control Applied to Biological Models. Chapman & Hall/CRC: Boca Raton, FL.

[17] Joshi, H. R. (2002). Optimal control of an HIV immunology model. *Optimal Control Application Methods* 23: 199-213.

[18] Fleming W., & Rishel, R. (1975) Deterministic and stochastic optimal control. *Springer-Verlag: New York, NY.*

[19] Rudin, W. *Principles of Mathematical Analysis, 3rd ed.* New York: McGraw-Hill, 1976.

[20] Eisenberg, M. C., & Hayashi, M. A. (2014). Determining identifiable parameter combinations using subset profiling. *Mathematical Biosciences*, 256, 116-126. doi:10.1016/j.mbs.2014.08.008.

APPENDIX A

Appendix on Local Sensitivity Analysis

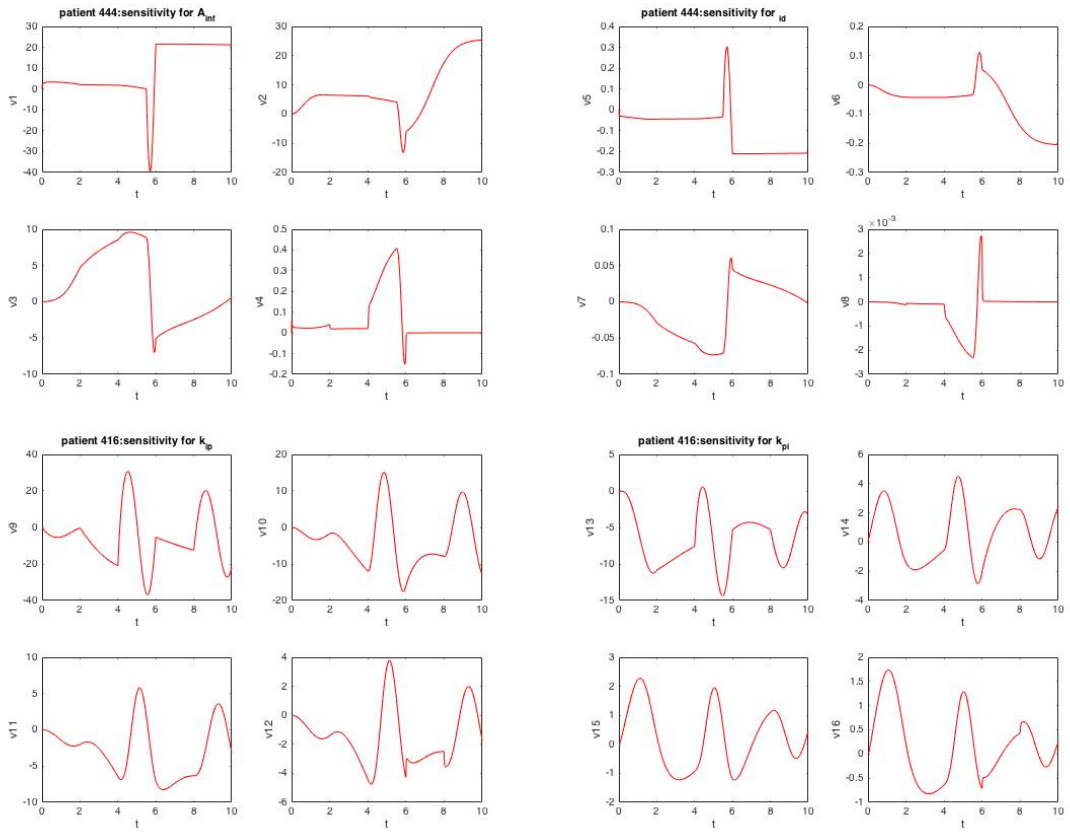

FIGURE A.1. Sensitivities plots for parameters A_{inf}, k_{id}, k_{ip}, k_{pi}, k_{pp}, and k_{pd} for patient 444 with respect to model variables showing how they change over time

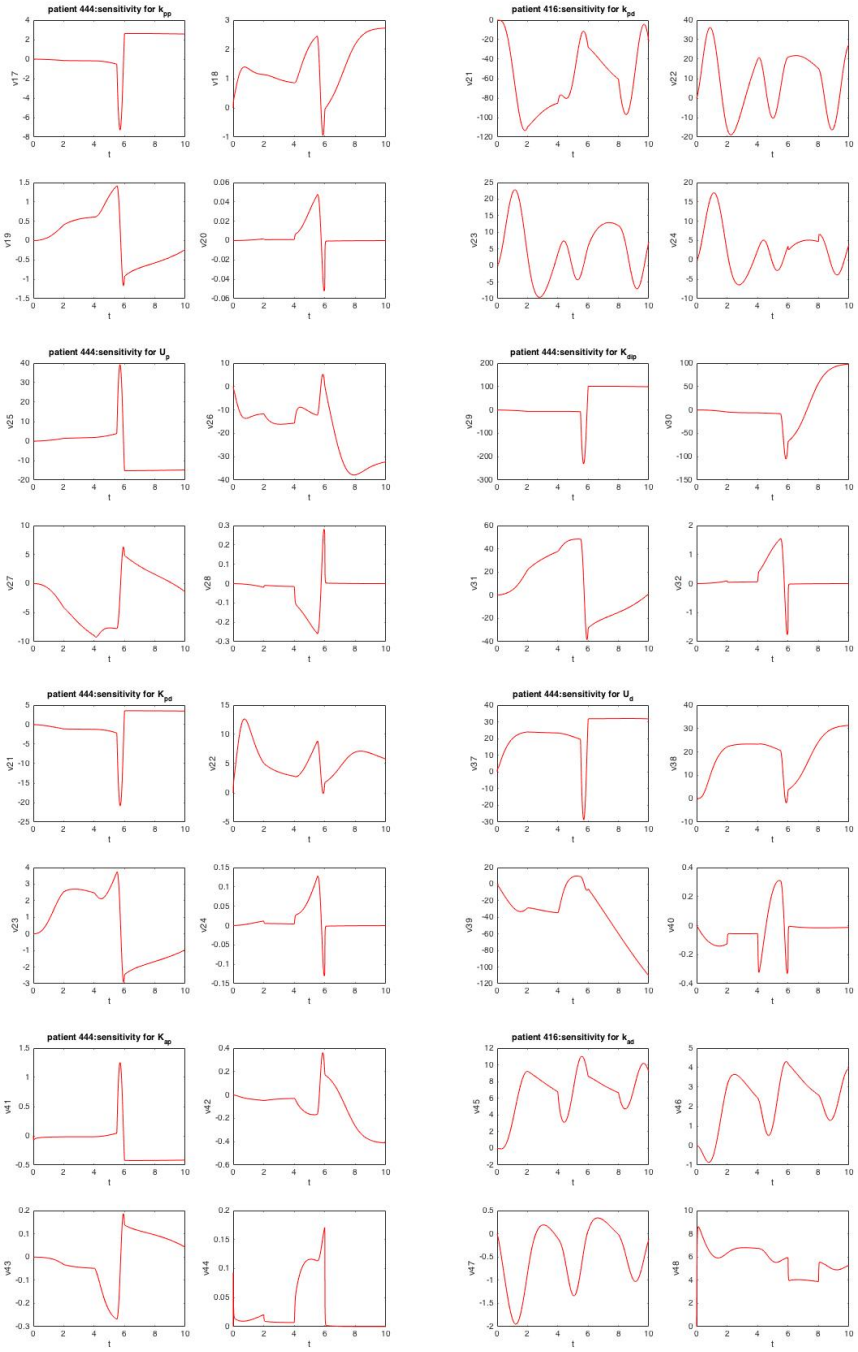

FIGURE A.2. Sensitivities plots for parameters μ_p, k_{dip}, k_{dp}, μ_d, k_{ap}, and k_{ad} for patient 444 with respect to model variables showing how they change over time

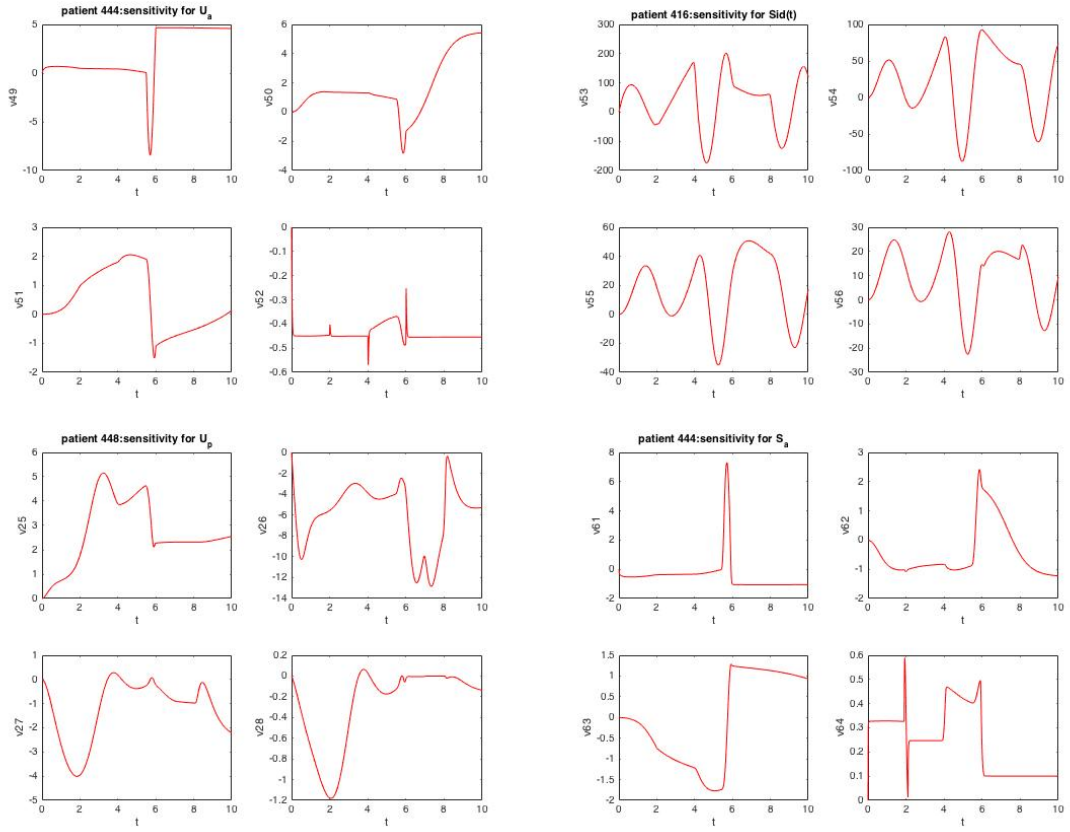

FIGURE A.3. Sensitivities plots for parameters μ_a, $s_i(t)$, $s_{id}(t)$, and $s_a(t)$ for patient 444 with respect to model variables showing how they change over time

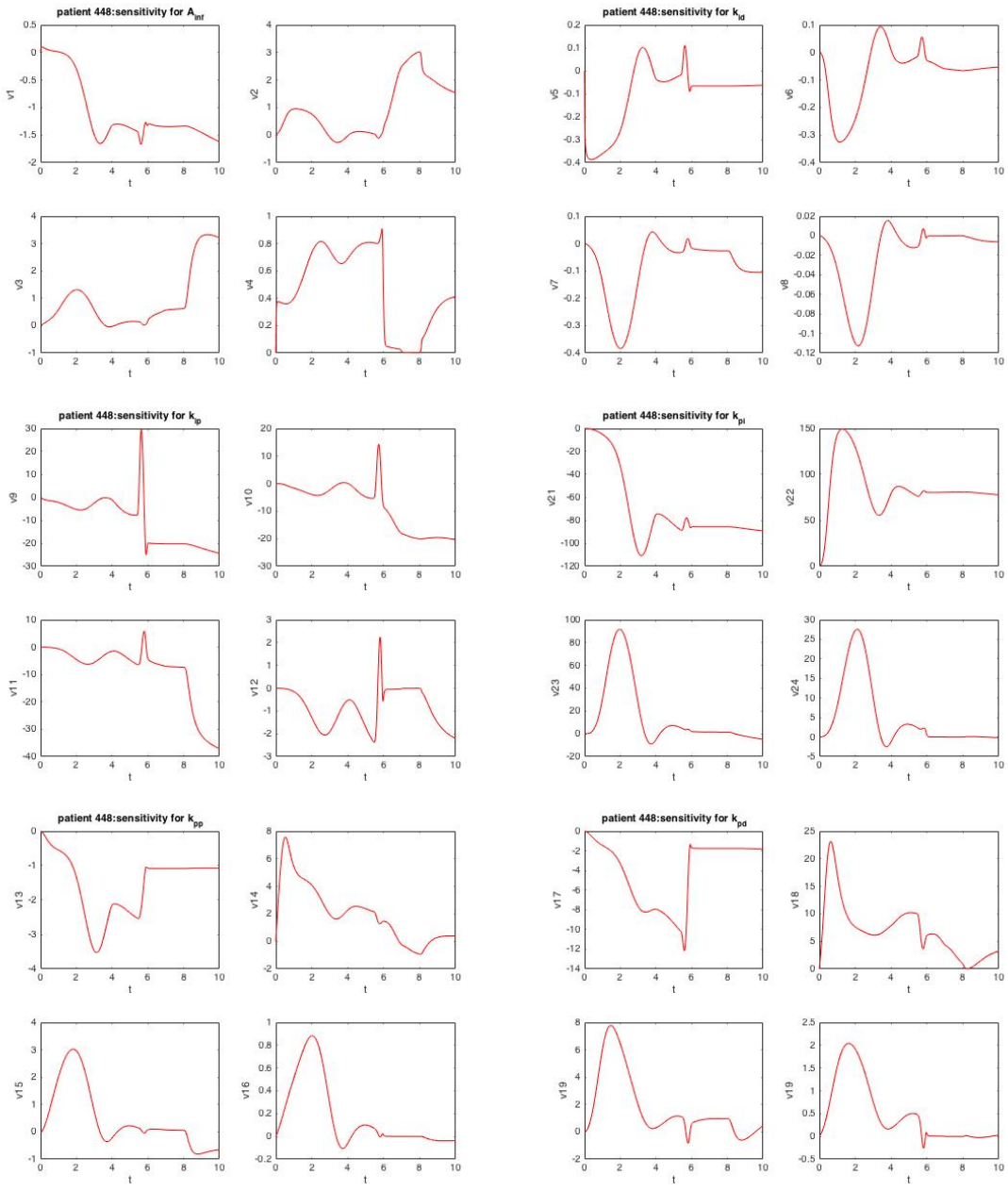

FIGURE A.4. Sensitivities plots for parameters A_{inf}, k_{id}, k_{ip}, k_{pi}, k_{pp}, and k_{pd} for patient 448 with respect to model variables showing how they change over time

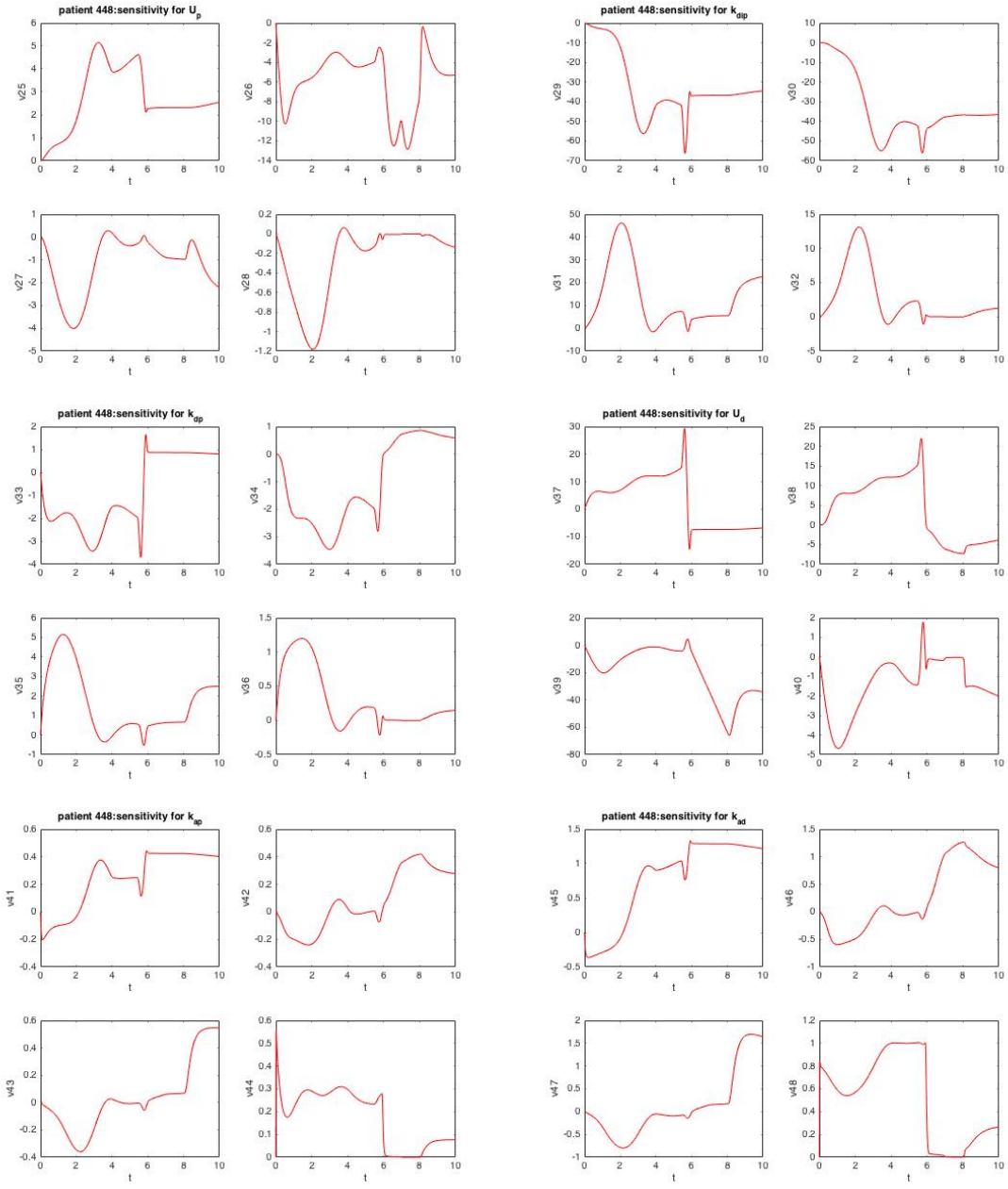

FIGURE A.5. Sensitivities plots for parameters μ_p, k_{dip}, k_{dp}, μ_d, k_{ap}, and k_{ad} for patient 448 with respect to model variables showing how they change over time

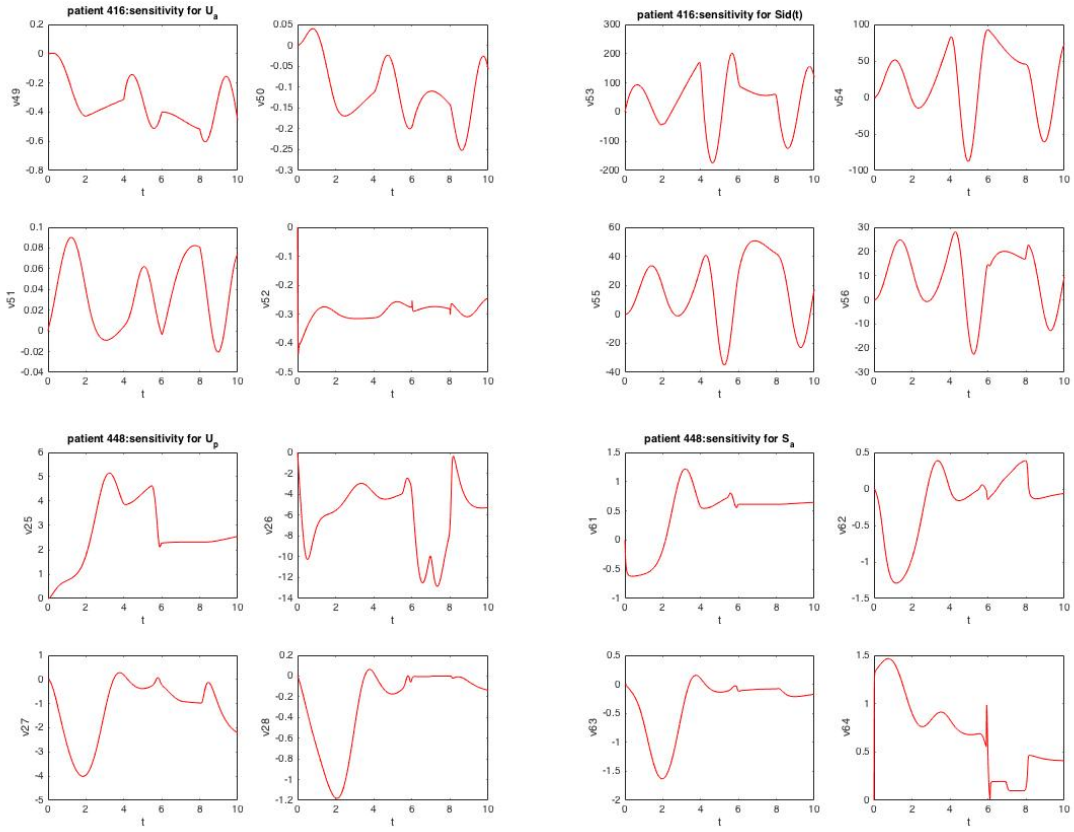

FIGURE A.6. Sensitivities plots for parameters μ_a, $s_i(t)$, $s_{id}(t)$, and $s_a(t)$ for patient 444 with respect to model variables showing how they change over time

The following are the descriptions of sensitivities provided in chapter 2:

$$y_1 = \frac{\partial I}{dk_{id}},\ y_2 = \frac{\partial P}{dk_{id}},\ y_3 = \frac{\partial D}{dk_{id}},\ y_4 = \frac{\partial A}{dk_{id}},\ y_5 = \frac{\partial I}{dk_{ip}},\ y_6 = \frac{\partial P}{dk_{ip}},\ y_7 = \frac{\partial D}{dk_{ip}},\ y_8 = \frac{\partial A}{dk_{ip}},$$

$$y_9 = \frac{\partial I}{dk_{pi}},\ y_{10} = \frac{\partial P}{dk_{pi}},\ y_{11} = \frac{\partial D}{dk_{pi}},\ y_{12} = \frac{\partial A}{dk_{pi}},\ y_{13} = \frac{\partial I}{dk_{pp}},\ y_{14} = \frac{\partial P}{dk_{pp}},\ y_{15} = \frac{\partial D}{dk_{pp}},$$

$$y_{16} = \frac{\partial A}{dk_{pp}},\ y_{17} = \frac{\partial I}{dk_{pd}},\ y_{18} = \frac{\partial P}{dk_{pd}},\ y_{19} = \frac{\partial D}{dk_{pd}},\ y_{20} = \frac{\partial A}{dk_{pd}},\ y_{21} = \frac{\partial I}{d\mu_p},\ y_{22} = \frac{\partial P}{d\mu_p},$$

$$y_{23} = \frac{\partial D}{d\mu_p},\ y_{24} = \frac{\partial A}{d\mu_p},\ y_{25} = \frac{\partial I}{dk_{dip}},\ y_{26} = \frac{\partial P}{dk_{dip}},\ y_{27} = \frac{\partial D}{dk_{dip}},\ y_{28} = \frac{\partial A}{dk_{dip}},\ y_{29} = \frac{\partial I}{dk_{dp}},$$

$$y_{30} = \frac{\partial P}{dk_{dp}},\ y_{31} = \frac{\partial D}{dk_{dp}},\ y_{32} = \frac{\partial A}{dk_{dp}},\ y_{33} = \frac{\partial I}{d\mu_d},\ y_{34} = \frac{\partial P}{d\mu_d},\ y_{35} = \frac{\partial D}{d\mu_d},\ y_{36} = \frac{\partial A}{d\mu_d},$$

$$y_{37} = \frac{\partial I}{dk_{ad}},\ y_{38} = \frac{\partial P}{d_{ad}},\ y_{39} = \frac{\partial D}{dk_{ad}},\ y_{40} = \frac{\partial A}{dk_{ad}},\ y_{41} = \frac{\partial I}{dk_{ap}},\ y_{42} = \frac{\partial P}{d_{ap}},\ y_{43} = \frac{\partial D}{dk_{ap}},$$

$$y_{44} = \frac{\partial A}{dk_{ap}},\ y_{45} = \frac{\partial I}{d\mu_a},\ y_{46} = \frac{\partial P}{d\mu_a},\ y_{47} = \frac{\partial D}{d\mu_a},\ y_{48} = \frac{\partial A}{d\mu_a},\ y_{49} = \frac{\partial I}{ds_i},\ y_{50} = \frac{\partial P}{ds_i},\ y_{51} = \frac{\partial D}{ds_i},$$

$y_{52} = \frac{\partial A}{ds_i}$, $y_{53} = \frac{\partial I}{ds_{id}}$, $y_{54} = \frac{\partial P}{ds_{id}}$, $y_{55} = \frac{\partial D}{ds_{id}}$, $y_{56} = \frac{\partial A}{ds_{id}}$, $y_{57} = \frac{\partial I}{ds_a}$, $y_{58} = \frac{\partial P}{ds_a}$, $y_{59} = \frac{\partial D}{ds_a}$,

$y_{60} = \frac{\partial A}{ds_a}$, $y_{61} = \frac{\partial I}{dA_{inf}}$, $y_{62} = \frac{\partial P}{\partial A_{inf}}$, $y_{63} = \frac{\partial D}{dA_{inf}}$, and $y_{64} = \frac{\partial A}{dA_{inf}}$.

APPENDIX B

Code for Sensitivity Analysis

This is the code we used for sensitivity analysis

```
function sensetivity % Patient 491
tic
t=0:0.001:300;
ic=[0.1,0.5,0.38,0.1];
ic2=[0,0,0,0];
warning('off')
Ainf=0.45;
Kid=1;
Kip=0.025;
Kpi=0.13;
Kpp=0.02;
Kpd=0.001;
Mup=0.06;
Kdip=0.025;
Kdp=0.27;
Mud=0.04;
Kap=0.022;
Kad=0.22;
Mua=2.2;
params=[Ainf,Kid, Kip, Kpi, Kpp, Kpd,Mup,Kdip,Kdp,Mud,...
```

```
    Kap,Kad,Mua];
options=odeset('Stats','on','RelTol',1e-4,'AbsTol',...
    [1e-4,1e-4,1e-4,1e-4]);
options2 = odeset('Stats','on','RelTol',1e-5,...
    'AbsTol',[1e-5,1e-5,1e-5,1e-5]);

[T1,u] = ode15s(@trial_func_ode,t,ic,options,params);

[T2,sensitivities] = ...
    ode15s(@sensitivities_ode,t,ic2,options2,params,t,u);
size(sensitivities(:,1))
size(u(:,1))
fIdy=sensitivities(:,1)./(u(:,1)+10^(-10));
fPdy=sensitivities(:,2)./(u(:,2)+10^(-10));
fDdy=sensitivities(:,3)./(u(:,3)+10^(-10));
fAdy=sensitivities(:,4)./(u(:,4)+10^(-10));
w=(norm(fIdy,2)/sqrt(length(fIdy)))
x=(norm(fPdy,2)/sqrt(length(fPdy)))
y= (norm(fDdy,2)/sqrt(length(fDdy)))
z =(norm(fAdy,2)/sqrt(length(fAdy)))
A= [fIdy;fPdy;fDdy;fAdy]
B=length(A)
n=norm(A,2)/sqrt(B)
w
x
y
```

```
z
%E=n./B
%p=normest(A)
%m= y+z+w+x
%q=size(A)

min(abs(fDdy))
min(abs(fIdy))
min(abs(fPdy))
min(abs(fAdy))

figure(12)
%title('A_{inf} for Patient 491')
subplot(2,2,1)
plot(T1./30,fIdy,'r-')
title('patient 416:sensitivity for Sid(t)')
xlabel('t')
ylabel('v53')
subplot(2,2,2)
plot(T1./30,fPdy,'r-')
xlabel('t')
ylabel('v54')
subplot(2,2,3)
plot(T1./30,fDdy, 'r-')
xlabel('t')
ylabel('v55')
```

```
subplot(2,2,4)
plot(T1./30,fAdy, 'r-')
xlabel('t')
ylabel('v56')

figure(15)
plot(T1,u,'r--')
title('Patient 491')
axis([-6 4 0 7])
hold on;
subplot(2,2,1)
plot(T1,u(:,1),'r -')
xlabel('t')
ylabel('I')
title('I for Patient 491')
subplot(2,2,2)
plot(T1,u(:,2),'r-')
%axis([0 30 0 4])
xlabel('t')
ylabel('P')
title('P for Patient 491')
subplot(2,2,3)
plot(T1,u(:,3),'r-')
%axis([0 30 0 4])
xlabel('t')
ylabel('D')
```

```
title('D for Patient 491')
subplot(2,2,4)
plot(T1,u(:,4),'r-')
xlabel('t')
ylabel('A')
title('A for Patient 491')
figure(16)
subplot(2,2,1)
plot(T2,sensitivities(:,1))
subplot(2,2,2)
plot(T2,sensitivities(:,2))
subplot(2,2,3)
plot(T2,sensitivities(:,3))
subplot(2,2,4)
plot(T2,sensitivities(:,4))

toc
function dy = trial_func_ode(t,y,params)
k1=params(1);
k2=params(2);
k3=params(3);
k4=params(4);
k5=params(5);
k6=params(6);
k7=params(7);
k8=params(8);
```

```
k9=params(9);
k10=params(10);
k11=params(11);
k12=params(12);
k13=params(13);

I=y(1);
P=y(2);
D=y(3);
A=y(4);

dy=[Si(t)./(1+(A/k1)^2) + ...
    (Sid(t)./(1+(A/k1)^2))*(D^2/(k2^2+D^2)) -...
    (k3*I*P)/(1+(A/k1)^2);...
(k4*I +k5*P)/(1+(A/k1)^2)+ k6*D/(1+(A/k1)^2)-k7*P;...
k8*I*P/(1+(A/k1)^2) + k9*P/(1+(A/k1)^2)-k10*D;...
Sa(t)+(k11*P+k12*D)/(1+(A/k1)^2)-k13*A];

function dy = sensitivities_ode(t,y,params,tt,u)

k1=params(1);
k2=params(2);
k3=params(3);
k4=params(4);
k5=params(5);
```

```
k6=params(6);
k7=params(7);
k8=params(8);
k9=params(9);
k10=params(10);
k11=params(11);
k12=params(12);
k13=params(13);



u1 = u(:,1);
u2 = u(:,2);
u3 = u(:,3);
u4 = u(:,4);
I = interp1(tt,u1,t,'cubic');
P = interp1(tt,u2,t,'cubic');
D = interp1(tt,u3,t,'cubic');
A = interp1(tt,u4,t,'cubic');
%u1 = u(:,1);
u11 = interp1(tt,u1,t,'cubic');


v9 = y(1); %dI/dSi(t)
v10 = y(2); %dyP/dSi(t)
v11 = y(3); %dD/dSi(t)
v12 = y(4); %dA/dSi(t)
```

```
dy=[(-v9)*((k1^2*P*k3)/(k1^2+A^2))-...
      (v10)*((I*k3*k1^2)/(k1^2+A^2))
      +(v11)*((2*D*k1^2*Sid(t))/((k1^2+A^2)*(D^2+k2^2)^2)...
      -(2*D^3*k1^2*Sid(t))/((A^2+k1^2)*(D^2+k2^2)))+...
v12*((2*A*I*k1^2*P*k3)/(A^2+k1^2)^2-...
(2*A*D^2*Sid(t)*k1^2)/((A^2+k1^2)^2*(D^2+k2^2))....
-2*A*k1^2*Si(t)/(A^2+k1^2)^2)+(Sidp(t)+Sidq(t)...
+Sidr(t)+Sids(t)+SidT(t)*(k1/(k1^2+A^2)));...
      v9*((k1^2*k4)/(k1^2+A^2))+...
      (v10)*((k5*k1^2)/(k1^2+A^2)-k7)...
      +v11*((k6*k1^2)/(k1^2+A^2))...
      -v12*((2*A*k1^2*(D*k6+I*k4+P*k5))/(A^2+k1^2)^2);
v9*((k1^2*P*k8)/(k1^2+A^2))...
+v10*((k1^2*(I*k8+k9))/(k1^2+A^2))-v11*k10-...
v12*(2*A*P*k1^2*(I*k8+k9)/(k1^2+A^2)^2);...
      v10*((k1^2*k11)/(k1^2+A^2))...
      +v11*((k1^2*k12)/(k1^2+A^2))-...
      v12*((2*A*k1^2*(D*k12+P*k11)/(k1^2+A^2)^2)...
      +k13)];
      function S=Si(t)
t=t/30;
m=0.1;
if (t>=0&&t<4-m)
      S=0.001;
elseif(t>=4-m&&t<4+m)
      S=-1.7499999999927205*t.^3+20.99999999991264*t.^2.
```

```
        -83.94749999965076*t+111.79449999953486;
elseif(t>=4+m&&t<6-m)
    S=0.008;
elseif(t>=6-m&&t<6+m)
    S=-0.0603448*t.^3+0.905172*t.^2-4.37922*t
        +6.72993;
elseif(t>=6+m&&t<8-m)
    S=0.001;
elseif(t>=8-m&&t<8+m)
    S=-1*t.^3+24*t.^2-191.97*t+511.763;
elseif(t>=8+m&&t<10)
    S=0.005;
else
    S=0.005;
end
function S=Sid(t)
t=t/30;
m=0.1;
if(t>=0&&t<2-m)
    S=0.0075;
elseif (t>=2-m&&t<2+m)
    S=1.62500000*t^3-9.7500000000*t^2+...
        19.45125*t-12.89825;
elseif(t>=2+m&&t<4-m)
    S=0.0001;
elseif(t>=4-m&&t<4+m)
```

```
        S=-3.7250*t^3+44.7*t^2-178.688249999*t+...
            237.9605499990;
    elseif(t>=4+m&&t<6-m)
        S=0.015;
    elseif(t>=6-m&&t<6+m)
        S=3.500000000*t^3-63.000000000*t^2+...
            377.894999998*t...
            -755.3619999952;
    elseif(t>=6+m&&t<8-m)
        S=0.001;
    elseif(t>=8-m&&t<8+m)
        S=-2.75000*t^3+65.9999999976*t^2....
            -527.9174999810*t+1407.346499949;
    else
        S=0.012;
    end
    function S=Sa(t)
    t=t/30;
    m=0.1;
    if (t>=0&&t<6-m)
        S=0.005;
    elseif(t>=6-m&&t<6+m)
        S=-86.249999999*t^3+1552.499999990*t^2....
            -9312.4124999405*t+18614.6524998812;
    elseif(t>=6+m&&t<8-m)
        S=0.35;
```

```
elseif(t>=8-m&&t<8+m)
    S=62.499999998*t^3-1499.9999999459*t^2....
        +11998.124999568*t-31984.774998848;
elseif(t>=8+m&&t<10)
    S=0.1;
else
    S=0.1;
end


function S=Sidp(t)
t=t/30;
m=0.1;
if (t>=0&&t<2-m)
    S= 1;
elseif(t>=2-m&&t<2+m)
    m=0.1;
    x0=2;
    S=(1/(4*m^3))*t^3-((3*x0)/(4*m^3))*t^2....
        -(3*(m^2-x0^2)/(4*m^3))*t-...
        (x0^3-2*m^3-3*m^2*x0)/(4*m^3);
elseif(t>=2+m&&t<10)
    S=0;
else
    S=0;
end
```

```
function S=Sidq(t)
t=t/30;
m=0.1;
if (t>=0&&t<2-m)
    S= 0;
elseif(t>=2-m&&t<2+m)
    m=0.1;
    x0=2;
    S=(1/(4*m^3))*t^3-((3*x0)/(4*m^3))*t^2....
        -(3*(m^2-x0^2)/(4*m^3))*t-...
        (x0^3-2*m^3-3*m^2*x0)/(4*m^3);
elseif(t>=2+m&&t<4-m)
    S=1;
elseif(t>=4-m&&t<4+m)
    x0=4;
    m=0.1;
    S=(-1/(4*m^3))*t^3+((3*x0)/(4*m^3))*t^2-...
        (3*(x0^2-m^2)/(4*m^3))*t-...
        (3*m^2*x0-2*m^3-x0^3)/(4*m^3);
elseif(t>=4+m&&t<10)
    S=0;
else
    S=0;
end
```

```
function S=Sidr(t)
t=t/30;
m=0.1;
if (t>=0&&t<4-m)
    S= 0;
elseif(t>=4-m&&t<4+m)
    x0=4;
    m=0.1;
    S=(1/(4*m^3))*t^3-((3*x0)/(4*m^3))*t^2-...
        (3*(m^2-x0^2)/(4*m^3))*t-(x0^3-...
        2*m^3-3*m^2*x0)/(4*m^3);
elseif(t>=4+m&&t<6-m)
    S=1;
elseif(t>=6-m&&t<6+m)
    x0=6;
    m=0.1;
    S=(1/(4*m^3))*t^3-((3*x0)/(4*m^3))*t^2-...
        (3*(m^2-x0^2)/(4*m^3))*t-...
        (x0^3-2*m^3-3*m^2*x0)/(4*m^3);
elseif(t>=6+m&&t<10)
    S=0;
else
    S=0;
end

function S=Sids(t)
```

```
t=t/30;
m=0.1;
if (t>=0&&t<6-m)
    S= 0;
elseif(t>=6-m&&t<6+m)
    x0=6;
    m=0.1;
    S=(1/(4*m^3))*t^3-((3*x0)/(4*m^3))*t^2-....
        (3*(m^2-x0^2)/(4*m^3))*t...
        -(x0^3-2*m^3-3*m^2*x0)/(4*m^3);
elseif(t>=6+m&&t<8-m)
    S=1;
elseif(t>=8-m&&t<8+m)
    x0=8;
    m=0.1;
    S=(1/(4*m^3))*t^3-((3*x0)/(4*m^3))*t^2-...
        (3*(m^2-x0^2)/(4*m^3))*t-...
        (x0^3-2*m^3-3*m^2*x0)/(4*m^3);
elseif(t>=6+m&&t<10)
    S=0;
else
    S=0;
end

function S=SidT(t)
t=t/30;
```

```
m=0.1;
if (t>=0&&t<8-m)
    S= 0;
elseif(t>=8-m&&t<8+m)
    x0=8;
    m=0.1;
    S=(-1/(4*m^3))*t^3+((3*x0)/(4*m^3))*t^2-...
        (3*(x0^2-m^2)/(4*m^3))*t-...
        (3*m^2*x0-2*m^3-x0^3)/(4*m^3);
elseif(t>=8+m&&t<10)
    S=1;
else
    S=1;
end
```

APPENDIX C

Code for Optimal Control

This is the MATLAB code we used for our optimal control theory problem

```
function y=params1(I0,P0,D0,A0)
% assigns variable I0, P0, D0 and A0 as
% inputs, y as output


warning('off','all')
%patient = 416;
 %patient = 448;
%patient = 491;
patient = 444;
test = -1; % convergence test variable-
%begins the while loop with a neg
tf=300;
zeta = .1; % convergence criterion
N = 1000; % number of nodes
t = linspace(0,tf,N+1);
% creates N+1=1001 equally spaced nodes
t1=linspace(tf,0,N+1);
h = tf/N; % spacing is assigned as h
h2 = h/2; % short-hand for Runge-Kutta
%subroutine (h2 short for h/2)
```

```
M2 = 16.32; %max bound of u see page 82
M1 =0; %min bound of u see pg 82
k = 0;
chi = 1;

Sa=0.5.*ones(1,N+1);


%error('Stop Program')
while k < 30;
    k = k+1;
     u = 0.5.*ones(1,N+1);
end


%u = zeros(1,N+1);
%u = -M2*t/tf +M2;
%u1 = 0.5*zeros(1,N+1).*Sa(t);
%u1=Sa(t).*ones(1,N+1);
%u1=0*ones(1,N+1);
u1=Sa;
%Sa =0';
%u1=Sa;
I = zeros(1,N+1); %vector I and size
I(1)=I0;%
P= zeros(1,N+1);
```

```
P(1)=P0;
D= zeros(1,N+1);
D(1)=D0;
A = zeros(1,N+1);
A(1)=A0;
lambda1 = zeros(1,N+1); % lamda1 and size
lambda2 = zeros(1,N+1);
lambda3 = zeros(1,N+1);
lambda4 = zeros(1,N+1);
k=0; %k is my counter
j=0;
while(test < 0 && k<1500)%25000)
    % when convergence occurs
   % test will become non-negative
    k = k+1;
   c = 0.01;

    oldu = u; % previous value of u
    oldlambda1 = lambda1; % previous value of lambda1
    oldlambda2 = lambda2; % previous value of lambda2
    oldlambda3 = lambda3; % previous value of lambda3
    oldlambda4 = lambda4;% previous value of lambda4
    %I0=0.1;
   % A0=0.1;
    Kid=1;
    MUa=2.2;
```

```
Ainf=0.45;

switch patient
    case 416
        % P0=0.4;
        % D0=1.7;
         Kip=0.025;
         Kpi=0.13;
         Kpp=0.02;
         Kpd=0.001;
         MUp = 0.06;
         Kdip=0.025;
         Kdp=0.27;
         MUd=0.04;
         Kap=0.022;
         Kad=0.22;

    case 444
        % P0=0.5;
         %D0=3.59;
          Kip=0.015;
         Kpi=0.01;
         Kpp=0.015;
         Kpd=0.001;
         MUp = 0.06;
         Kdip=0.015;
```

```
        Kdp=0.01;
        MUd=0.015;
        Kap=0.006;
        Kad=0.06;

case 448
    %P0 = 0.58;
    %D0 = 0.85;
    Kip = 0.01;
    Kpi=0.006;
    Kpp = 0.02;
    Kpd = 0.001;
    MUp = 0.13;
    Kdip = 0.01;
    Kdp = 0.03;
    MUd = 0.03;
    Kap = 0.035;
    Kad = 0.35;

case 491
   %I0=0.1;
   %P0=0.5;
    %D0=0.38;
   % A0=0.1;
      Kip = 0.003;
      Kpi = 0.05;
```

```
            Kpp = 0.12;
            Kpd =0.01;
            MUp =  0.33;
            Kdip =0.003;
            Kdp = 0.015;
            MUd = 0.035;
             Kap = 0.001;
             Kad = 0.01;
%%
        otherwise
            error('invalid patient number')
    end

    oldj = j;
    params1=[Ainf,Kid,Kip,Kpi,Kpp,Kpd,MUp,...
        Kdip,Kdp,MUd,Kap,Kad,MUa];


     [T1,x]=firstfunction(I0,A0,D0,P0,t,t,...
         u1,params1);
    if t~=T1'
        error('time values for x do not match')
    end
    I=x(:,1)';
    P=x(:,2)';
    D=x(:,3)';
```

```
    A=x(:,4)';

    [T2,lambda]=secondfunction(I,P,D,A,t1,...
        t1,params1);
  %t
  T2
    if t~=T2'
      t
       T2
  error('time values for lambda do not match')
    end
   lambda1=flipud(lambda(:,1))';
   lambda2=flipud(lambda(:,2))';
   lambda3=flipud(lambda(:,3))';
   lambda4=flipud(lambda(:,4))';

u1 = max(M1, min(u1 - h*(c*u1+lambda4),M2));
n=size(u1);
size(D);
j = sum((D+(c/2)*chi*u1.^2+1));
temp2 = abs(j-oldj);
test = 0.15-temp2

    if floor(k/10)==k/10;
        display(test)
```

```
    end
end

%end



y(1,:) = t; % defines t
y(2,:) = I; % defines I
 y(3,:) = P; % defines P
 y(4,:) = D; % defines D
 y(5,:) = A; % defines A
y(6,:) = lambda1; % defines lambda1
y(7,:) = lambda2; % defines lambda2
y(8,:) = lambda3; % defines lambda3
y(9,:) = lambda4; % defines lambda4
y(10,:) = u1; % defines u


 J=sum((D+(c/2)*chi*u1.^2+1));
 t=t./10;
 display(J)
 figure(1)
 figure(2)
 hold on;
 subplot(9,1,1)
```

```
plot(t,I,'r-')
ylabel('I')
plot(t,P,'r-')
ylabel('P')
subplot(9,1,3)
plot(t,D,'r-')
ylabel('D')
subplot(9,1,4)
plot(t,A,'r-')
ylabel('A')
subplot(9,1,5)
plot(t,u1,'r-')
 %axis([0  30  0  2])
ylabel('u(t)')
%ylim([0,10])
xlabel('t (in days)')
figure(2)
hold on;
subplot(9,1,6)
plot(t,lambda1,'r-')
ylabel('\lambda_1')

subplot(9,1,7)
plot(t,lambda2,'r-')
ylabel('\lambda_2')
%ylim([-20,200])
```

```
subplot(9,1,8)
plot(t,lambda3,'r-')
ylabel('\lambda_3')
 %ylim([0,00])
xlabel('t (in days)')
subplot(9,1,9)
plot(t,lambda4,'r-')
ylabel('\lambda_4')
 %ylim([-70,800])
xlabel('t(in days)')

%  display('k =')
%  display(k)
end
```

```
    function [T1,x] = firstfunction(I0,A0,D0,P0,...
        t,tt,u1,params1)
    ic= [I0 A0 P0 D0];
    options = odeset('RelTol',1e-4,'AbsTol',...
        [1e-4, 1e-4, 1e-4, 1e-4]);
    [T1,x]= ode15s(@firstfunctionode, ...
        t,ic,options,tt,u1,params1);
end
```

```
function dx = firstfunctionode(t,x,tt,u,params1)
k1=params1(1);
k2=params1(2);
k3=params1(3);
k4=params1(4);
k5=params1(5);
k6=params1(6);
k7=params1(7);
k8=params1(8);
k9=params1(9);
k10=params1(10);
k11=params1(11);
k12=params1(12);
k13=params1(13);
u1=interp1(tt,u,t,'cubic');

dx =[Si(t)/(1+(x(4)/k1)^2)+
      Sid(t)/(1+(x(4)/k1)^2)*x(3)^2/(k2^2+x(3)^2)
   -k3*x(2)/(1+(x(4)/k1)^2)*x(1);...
   (k4*x(1)+k5*x(2))/(1+(x(1)/k1)^2)+...
   k6*x(3)/(1+(x(1)/k1)^2)
   -k7*x(2);
    k8*x(1)*x(2)/(1+(x(1)/k1)^2)...
    +k9*x(2)/(1+(x(1)/k1)^2)
    -k10*x(3);
    u1+(k11*x(2)+k12*x(3))/(1+(x(1)/k1)^2)-k13*x(4)];
```

```
end
function [T2,y] = secondfunction(I,P,D,A,t,tt,params1)
ic=[0 0 0 0];
options = odeset('RelTol',1e-4,'AbsTol',...
    [1e-4, 1e-4, 1e-4, 1e-4]);
[T2,y] = ode15s(@secondfunctionode,t,ic,...
    options,tt,I,P,D,A,params1);
end


function dy=secondfunctionode(t,y,tt,I,P,D,A,params1)
 k1=params1(1);
k2=params1(2);
k3=params1(3);
k4=params1(4);
k5=params1(5);
k6=params1(6);
k7=params1(7);
k8=params1(8);
k9=params1(9);
k10=params1(10);
k11=params1(11);
k12=params1(12);
k13=params1(13);
ttt = flipud(tt')';
I1=interp1(ttt,I,t,'cubic');
P1=interp1(ttt,P,t,'cubic');
```

```
D1=interp1(ttt,D,t,'cubic');
A1=interp1(ttt,A,t,'cubic');
 size (I1);
 %display(A1);
 %display(D1);
 %display(P1);
 %display(I1);
dy=[y(1)*(k1*P1*k3/(k1.^2+A1.^2))-y(2)*(k1.^2*k3/(A1.^2+k1.^2))
    -y(3)*k1.^2*k8*P1/(A1.^2+k1.^2);...
    y(1)*I1*k1.^2./(A1.^2+k1.^2)-y(2)*((k1.^2*k5/(A1^2+k1.^2))
    -y(3)*((I1*k1.^2*k8/(k1.^2+A1.^2))+k1.^2*k9/(A1.^2+k1.^2))
    -y(4)*k11*k1.^2/(k1.^2+A1.^2);...
    -1+y(1)*((2*D1*k1.^2*Sid(t)./((A1.^2+k1.^2)*(D1.^2+k2.^2))
    (2*D1.^3*k1.^2*Sid(t)./((A1.^2+k1.^2)*(D1.^2+k2.^2).^2))))
    y(2)*k1.^2*k6./(A1.^2+k1.^2)+y(3)*k10
    -y(4)*k11*k1.^2./(A1.^2+k1.^2);
    y(1)*((2*A1*I1*k1.^2*P1*k3./(A1.^2+k1.^2).^2)....
    -(2*A1*k1.^2*Si(t)./(A1.^2+k1.^2).^2)-...
    (2*A1*D1.^2*k1.^2*Sid(t)./(A1.^2+k1.^2)^2*(D1.^2
+k2.^2)))
    -y(2)*(-2*A1*D1*k1.^2*k6/(A1.^2+k1.^2).^2
    ((2*A1*k1.^2*(I1*k4+P1*k5))/(A1.^2+k1.^2).^2))
    (y(3)*((-2*A1*I1*k1.^2*P1*k8)./(A1.^2+k1.^2).^2
    (2*A1*k1.^2*P1*k9)./(A1.^2+k1.^2).^2))-...
    y(4)*(((-2*A1*k1.^2*(D1*k12+P1*k11))/(A1.^2...
+k1.^2).^2))...
```

```
    -k13];

end

function S=Si(t)
t=t/30;
if (t>=0&&t<2)
    S=0.001;
elseif(t>=2&&t<4)
    S=0.001;
elseif(t>=4&&t<4.5)
    S=0.008;
elseif(t>=4.5&&t<5.5)
    S=0.008;
elseif(t>=5.5&&t<6)
    S=0.008;
elseif(t>=6&&t<7.0)
    S=0.001;
elseif(t>=7.0&&t<8)
    S=0.001;
else
    S=0.005;
end
```

```
end
function S=Sid(t)
t=t/30;
if (t>=0&&t<2)
    S=0.0075;
elseif(t>=2&&t<4)
    S=0.0001;
elseif(t>=4&&t<4.5)
    S=0.015;
elseif(t>=4.5&&t<5.5)
    S=0.015;
elseif(t>=5.5&&t<6)
    S=0.015;
elseif(t>=6&&t<7)
    S=0.001;
elseif(t>=7&&t<8)
    S=0.001;
else
    S=0.012;
end
end
function S=Sa(t)
t=t/30;
if (t>=0&&t<2)
    S=0.005;
elseif(t>=2&&t<4)
```

```
        S=0.005;
elseif(t>=4&&t<4.5)
        S=0.005;
elseif(t>=4.5&&t<5.5)
        S=0.005;
elseif(t>=5.5&&t<6)
        S=0.005;
elseif(t>=6&&t<7)
        S=0.35;
elseif(t>=7&&t<8)
        S=0.35;
else
        S=0.1;
end
end
```