Mathematical Modeling of CD4+ T-cell and Cytokine Dynamics under Cancerous Conditions

by

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ABSTRACT

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In this study, the mechanism of CD4+ T-cells and their interactions in the immune system are investigated and quantitatively represented by the mathematical model in terms of a set of differential equations. Although it is well recognized that the immune reaction under cancerous conditions is different than that under normal conditions, little is known how these T-cell species affect onto each other. The mathematical model was formulated with an initial value problem based on the dynamics of T-cells and associated cytokines. Each T-cell species and its associated cytokines are denoted by a time dependent function. The interactions between the CD4+ T-cells have been illustrated by a flow chart, which was employed to develop the model using the generalized compartmental method. The literature data and data provided by the University of Texas Health Science Center at San Antonio was used to estimate the model parameters. Three mathematical software - Maple, MatLab, and DEDiscovery - were utilized to solve the system of differential equations. The sensitivity analysis is conducted to study the most influential parameters that control the immune response. This model, after experimental validation, may provide valuable information for the design of new immunotherapy and guide patient's decision-making for immunotherapy.

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CHAPTER 1: INTRODUCTION

Although it is well recognized that the immune-reaction under cancerous conditions is different than under normal conditions, little is known about how CD4+ T-cells affect each other. It is important to investigate these relations for the early cancer detection, better design of immunotherapy, and guidance of decision-making immunotherapeutic treatment.

The goal of this research is to establish biological relevant model that characterize the interactions and dynamics of CD4+ T-cells and their associated cytokines in order to understand how they evolve over a period of time. To develop such a model, a flow chart of the T-cell and cytokine dynamics is constructed and aided in the development of a system of differential equations that models these interactions. The species of T-cells that are included in the model are selected based on whether there are experimental data and how important of their roles in biology. If sufficient data are provided, the species are included in the model for validation purpose. The cytokines that are included in the model are those directly affect or are affected by T-cells or their helper cells. Experimental data collected by Dr. Livi and others are used to estimate the model parameters. Data ranges of the cytokine parameters are collected from published sources. The computational study reveals that, the solution of the system of differential equations allows the most effective search for increasing type 1 T helper (Th1) cells while insuring that other types of T helper cells to be relatively constant so the optimal treatment response could be achieved. The model developed in this study can be used by biologists for efficient design of experiments by pre-selecting immuno-does that maximize the treatment outcome. This model can also be used to aid in the decision making as to whether or not a patient is a good candidate for immunotherapy. The ultimate goal of this research is to lead to personalized medicine decisions when it comes to anti-tumor immunotherapy targeting the right patient population for the treatment.

The rest of this document is organized as follows. In Chapter 2, the thesis statement and specific aims are outlined. In Chapter 3, methods and approach are discussed, which include details of model development, parameter estimation and solution strategies. In Chapter 4, modeling results and discussion are provided. Finally, in Chapter 5, conclusions are made and future studies are discussed.

CHAPTER 2: THESIS STATEMENT

The goal of this thesis study is to investigate the possibility to develop a predictive model based on previously published results and experimental data to guide patient decision making for immunotherapy. The following are specific aims that dictate the overall research throughout this project.

2.1 Specific Aim 1

The first specific aim of this research is to develop a differential equation model based on literature data of the dynamics of CD4+ T-cells and their associated cytokines measured in biological experiments.

2.2 Specific Aim 2

Experimental data provided by the University of Texas Health Science Center at San Antonio will be used to estimate parameters to the modeling system. The model will be adapted to prostate cancer.

2.3 Specific Aim 3

The last specific aim of this research is to conduct sensitivity study and formulate validation strategy with an independent data set when they are made available.

These three specific aims are interrelated. As shown in next chapter, the predictability of a reliable mathematical model relies on accurate estimation of model parameters, which needs to be validated by independent experimental data set.

CHAPTER 3: METHODS AND APPROACH

The development of the modeling system of differential equations requires knowledge in immunology and mathematics. Inspired by [2], the following flow chart represents the dynamics of CD4+ T helper cells and their associated cytokines.

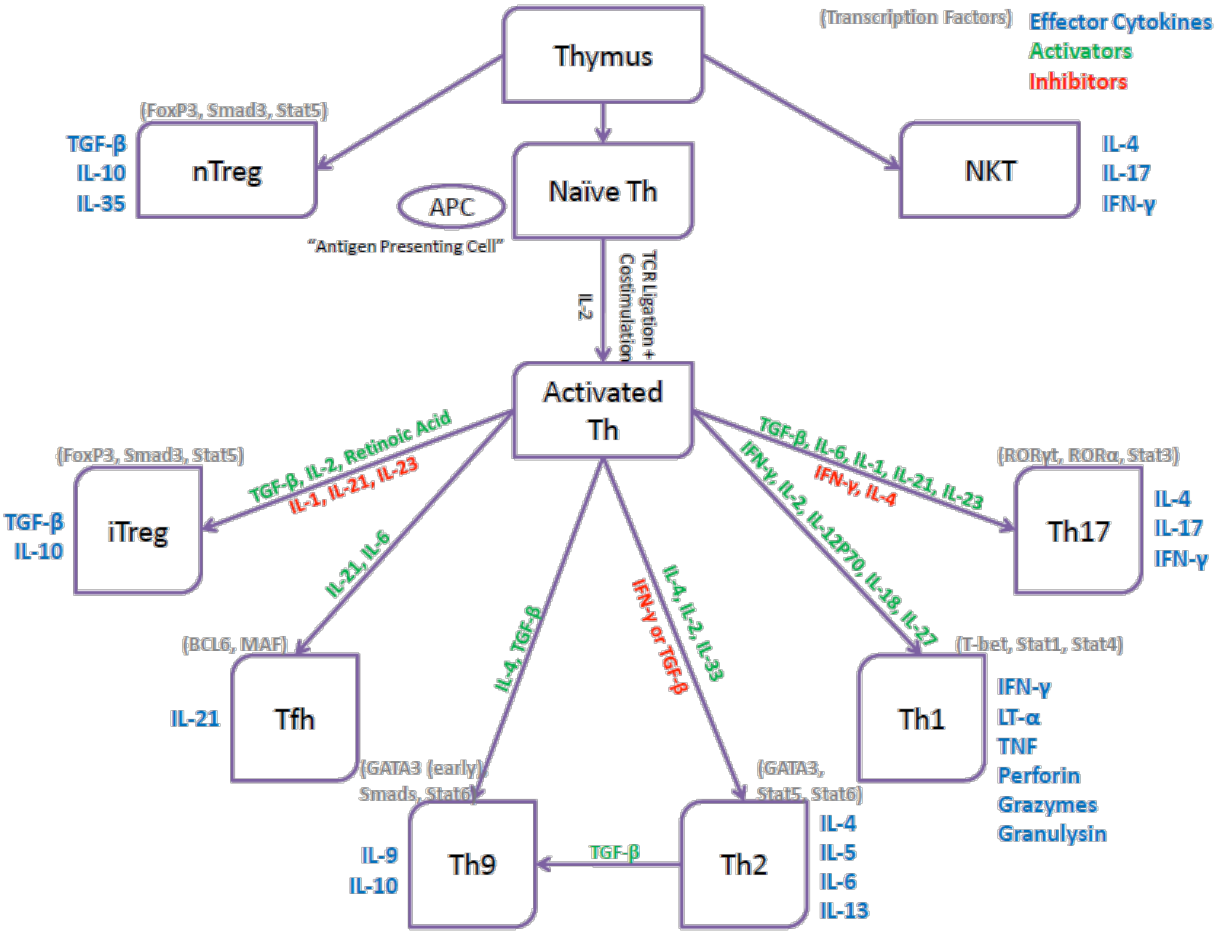


Figure 1. Flow chart of CD4+ T-cell dynamics and their associated cytokines.

Once relevant T-cell species are decided, the reduced flow chart will be used to form the system of differential equations using the compartmentalization method.

3.1 Basic Immunology

Every living, multi-cellular organism has an innate immune system that responds to each pathogen challenge. Jawed vertebrates also have an adaptive immune system that has a pathogen and antigen specific response leading to memory. Memory allows the immune system to respond and clear an

infection much more rapidly the second time a similar pathogen is encountered. The purpose of an immune system is to protect the organism from foreign invaders. The immune system is composed of a network of cells, tissues, and organs that defend the body from infection. One of the most important characteristics of immunity is the ability of the body to distinguish between self and non-self. Self molecules belong in the body and should not be attacked by the immune system. Non-self molecules are the foreign invaders that are targeted and removed by an immune response. Autoimmune disorders occur when self molecules are marked and attached by the immune system. This causes many diseases like psoriasis and multiple sclerosis.

The organs of the immune system are located all throughout the body. Lymphocytes, or white blood cells, can be found in these organs. Some of these lymphoid organs include bone marrow, the spleen, the appendix, and the thymus. The thymus is an important organ in the development of the adaptive immune system. This is the place where T-cells mature. These activated $CD4^+$ T-cells then polarize in response to the presence of cytokines. The types of cytokines present determine what the activated $CD4^+$ T-cell polarizes into. The possible polarized cells included in the model are Th1, Th2, Th17, and T regulatory cells.

The organs of the immune system are connected via a highway of vessels called lymphatic vessels. The lymphatic vessels are separate from blood vessels but tend to run parallel to them. Lymphatic vessels aid in the movement of lymph, a clear fluid that contains lymphocytes and has a composition similar to blood plasma. Along the lymphatic vessels are lymph nodes. They are specialized compartments where lymphocytes gather and where antigens activate immunity cells.

There exists a great extent of types of immunity cells. The most important immunity cells for the development of the model are T helper cells. T helper cells are needed to activate other immune cells such as B-cells and other T-cells. Cytotoxic T-cells, or killer T-cells help rid the body of intracellular infections such as viruses. B-cells are responsible for secreting antibodies. B-cells are mostly found in lymph nodes waiting for a macrophage to present an antigen. The antigen binds to an antibody receptor on the B-cell causing the B-cell to engulf the antigen. The B-cell begins producing millions of copies of an antibody specific to that antigen. Antibodies are shaped like a 'Y' and are also known as immunoglobulins. Among other functions, the antibodies are responsible for activating resting helper T-cells.

Another key feature of immunity are cytokines. They are diverse chemical messengers that are secreted by cells of the immune system. Cytokines play a role in the polarization of T helper cells so they must be included in the immunology model.

3.2 Implemented Immunology

CD4+ T helper cells often work by signaling to macrophages and other antigen presenting cells. The CD4+ T helper cells that will be included in the model are Th1, Th2, Treg (T regulatory cells), and Th17. Th1 CD4+ cells mediate cellular immunity by helping to polarize a cytotoxic response by activating CD8+ cytotoxic T-cells.

Th1 cells also induce B cells to produce opsonizing antibody. This Th1 polarization works against viruses, intracellular parasites, and cancers.

Th2 CD4+ cells mediate humoral immunity. They activate B cells to produce neutralizing antibodies. This Th2 polarization works against extracellular parasites like bacteria.

The primary role for regulatory T-cells is in maintaining peripheral tolerance. Regulatory T-cells have the role of controlling the T-cells response by suppressing the proliferation of other T-cells. This is

also usually indirectly by signaling to antigen presenting cells, although reports of regulatory T-cells directly affecting T-cells have been published.

Much less is known about the role of Th17 cells in healthy individuals. It is involved in the development of several autoimmune diseases and is frequently elevated in cancer. The makes Th17 a great biomarker. If it is found in any amount in the body, there is a great chance that there is something wrong.

3.2.1 Levels of T-cells

The levels of T-cells found in the body are a good indicator of how the body is functioning or responding to an infection. This is what makes the immunology model so important. In order for the body to recognize cancer as a foreign invader, the level of Th1 cells should be elevated. This is a good indicator that the patient's body is fighting the cancer. Increased Th1 causes an increase in the cytokine IFN-γ which is what helps the body recognize cancer as a foreign invader. In contrast, elevated levels of Th2 are bad during cancer. The goal of immunotherapy is to increase the levels of Th1 in the body without increasing the levels of Th2. This can be insured with the validated mathematical model.

If there is a high level of regulatory T-cells, this will decrease the anti-tumor immunity resistance of the body against the cancer. Also, if there is any trace of Th17, there is a good chance that that patient has cancer.

3.3 Flow Chart

Figure 1, as shown at the beginning of this chapter, is the most detailed representation of the dynamics of T-cells and their associated cytokines. This flow chart was not used to develop the equations for the immunology model since experimental data was not available for some of the cytokines and T-cells. The following flow chart shows the interactions between the T-cells and cytokines that were included in the equations. Since much of the data regarding T-cell polarization and cytokine production is acquired in vitro (ex vivo), the flow chart shows how naïve $CD4^+$ T-cells can be activated by antibodies against CD3 and CD28.

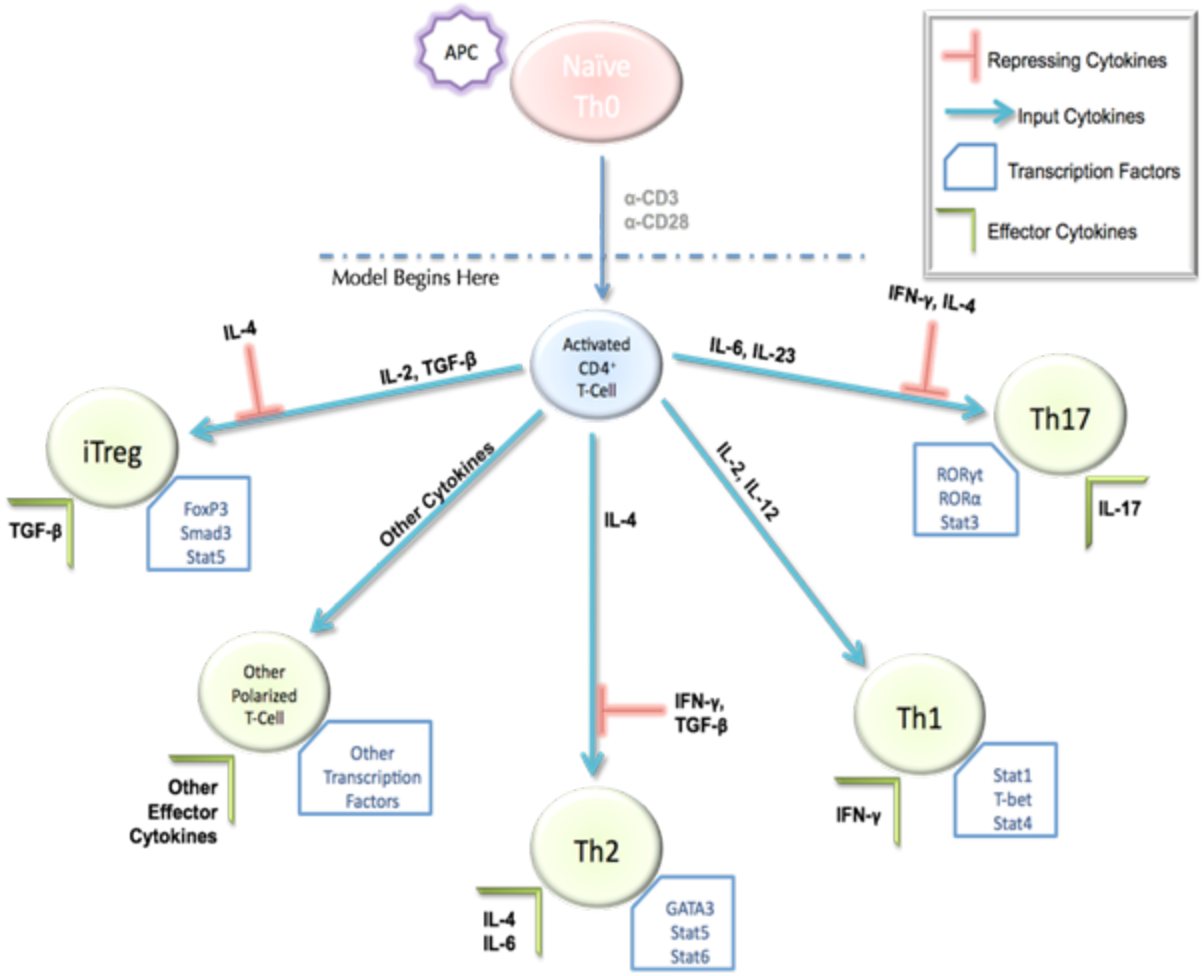


Figure 2. Model T-cell and Cytokine Dynamics.

3.4 Equations Development

The system of differential equations will be produced by a generalized compartmental method, which is an extension of traditional compartmental method (e.g., [3]) with nonlinear model parameters. This is mathematical method that takes the interactions of different species and makes them into a system of differential equations. Once relevant species are determined to be included in the model, a rate equation is formed for each species.

3.4.1 System of Equations

The equations developed are a system of Ordinary Non-Linear Differential equations. The non-linear term is derived from Michaelis-Menten Kinetics. These terms represent inhibitory cytokines.

$$\frac{dT_{reg}}{dt} = \alpha_1 I_\beta (\frac{I_4}{I_4 + c_1}) T_A - \alpha_2 T_{reg}$$

$$\frac{dT_2}{dt} = \alpha_3 I_4 (\frac{I_\gamma + I_\beta}{I_\gamma + I_\beta + c_2}) T_A - \alpha_4 T_2$$

$$\frac{dT_1}{dt} = \alpha_5 I_{12} T_A - \alpha_6 T_1$$

$$\frac{dT_{17}}{dt} = (\alpha_7 I_6 + \alpha_8 I_{23}) (\frac{I_\gamma + I_4}{I_\gamma + I_4 + c_3}) T_A - \alpha_9 T_{17}$$

$$\frac{dT_A}{dt} = -\alpha_1 I_\beta (\frac{I_4}{I_4 + c_1}) T_A - \alpha_3 I_4 (\frac{I_\gamma + I_\beta}{I_\gamma + I_\beta + c_2}) T_A - \alpha_5 I_{12} T_A - (\alpha_7 I_6 + \alpha_8 I_{23}) (\frac{I_\gamma + I_4}{I_\gamma + I_4 + c_3}) T_A$$

Figure 3, T-cell Dynamics

$$\frac{dI_\beta}{dt} = \alpha_2 T_r - \alpha_{10} (\frac{I_4}{I_4 + c_1}) I_\beta - \mu_\beta I_\beta$$

$$\frac{dI_4}{dt} = \alpha_4 T_2 - \alpha_{11} I_4 - \mu_4 I_4$$

$$\frac{dI_\gamma}{dt} = \alpha_6 T_1 - \mu_\gamma I_\gamma$$

$$\frac{dI_6}{dt} = \alpha_4 T_2 - \alpha_{12} I_6 - \mu_6 I_6$$

$$\frac{dI_{12}}{dt} = -\alpha_{13} I_{12} - \mu_{12} I_{12}$$

$$\frac{dI_{23}}{dt} = -\alpha_{14} I_{23} - \mu_{23} I_{23}$$

$$\frac{dI_{17}}{dt} = \alpha_9 T_{17} - \mu_{17} I_{17}$$

Figure 4, Cytokine Dynamics

Variable	Species	Description
T_A	Activated $CD4^+$ T helper cell	Naïve Th0 activated by α-CD3 and α-CD28 (or TCR engagement)
T_{reg}	T regulatory cell	Regulation, tolerance
T_2	Th 2	Immunity to extracellular parasites
T_1	Th 1	Not well characterized; Immunity to viruses, intracellular bacteria, and parasites
T_{17}	Th 17	Immunity to extracellular bacterial and fungal infections
I_β	TGF-β	Transforming growth factor, controls proliferation and cellular differentiation
I_4	IL-4	Interleukin-4, induces differentiation of Th0 to Th2
I_γ	IFN-γ	Interferon-γ, works against intracellular bacterial infections and tumor control
I_6	IL-6	Interleukin-6, mediator of fever and acute phase response
I_{12}	IL-12	Interleukin-12, involved in activation of NK cells and T-cells
I_{23}	IL-23	Interleukin-23, involved with inflammation
I_{17}	IL-17	Interleukin-17, highly inflammatory cytokine

Table 1, Definitions of T-cells and Cytokines

3.5 Parameter Analysis

Parameter analysis will be performed using experimental data. The data will be used to fit the solution of the system of differential equations to prostate cancer.

Name	Range	Definition	Units
α_1	~	T_{reg} by TGF-β	pg/mL
α_2	~	TFG-β by T_{reg}	pg/mL
α_3	(0.8, 50)	T_2 by IL-4	pg/mL
α_4	(2.0, 450)	IL-6 by T_2	pg/mL
α_5	(7.8, 500)	T_1 by IL-12	pg/mL
α_6	(5.1, 500)	IFN-γ by T_1	pg/mL
α_7	(2.0, 450)	T_{17} by IL-6	pg/mL
α_8	~	T_{17} by IL-23	pg/mL
α_9	(9.8, 10000)	IL-17 by T_{17}	pg/mL
α_{10}	~	T_{reg} by TGF-β	pg/mL
α_{11}	(0.8, 50)	T_2 by IL-4	pg/mL
α_{12}	(2.0, 450)	T_{17} by IL-6	pg/mL
α_{13}	(7.8, 500)	T_1 by IL-12	pg/mL
α_{14}	~	Th_{17} by IL-23	pg/mL
μ_β	~	TGF-β decay rate	1/day
μ_4	2.77	IL-4 decay rate	1/day
μ_γ	(2.16, 33.27)	IFN-γ decay rate	1/day
μ_{17}	(3.6968, 7.23)	IL-17 decay rate	1/day
μ_{12}	~	IL-12 decay rate	1/day
μ_6	~	IL-6 decay rate	1/day
μ_{23}	~	IL-23 decay rate	1/day
c_1	(50, 110)	Half-sat, IL-4 on TGF-β	cytokine/mL
c_2	(1, 2)	Half-sat, IFN-γ and TGF-β on IL-4	cytokine/mL
c_3	~	Half-sat, IFN-γ and IL-4 on IL-6 and IL-23	cytokine/mL

Table 2, List of Parameters

The values with a ~ are unavailable so were estimated to be close to given ranges.

3.6 Data Collection

Experimental Data will be used to fit parameters to the system of differential equations. The model must be fit using data collected from both patients and mice. The data used for this research was provided by Dr. Livi and others. The data was obtained from serum samples from prostate cancer patients. The cytokine ranges used to produce the results of the model were from a published source.

3.7 Limitations of Methods and Approach

A limitation of this method is that only species that have data available can be included in the model. Data will have to be split as explained in Section 3.2 , which will make the model more reliable, but an independent data set will still have to be used to validate the model.

3.8 Model Over-Fitting

A reliable mathematical model is one that can be applied to a wide range of patients. Model over fitting occurs when the same data set is used to train as well as to validate the model. This does not represent the entire spectrum of possible interactions, so the datasets will be split to ensure that the model is not over fitted to a particular set of samples provided and instead captures the overall biological properties being modeled.

Once a system of differential equations was developed (each species with its own rate equation), the system was solved using numerical integration. To simplify solving the system, mathematical software was used. This enabled quick changes in parameters to better fit the solution to experimental data and what actually occurs biologically.

3.9. Solving the System of Differential Equations

The mathematical software DEDiscover was used to solve the system of differential equations. The parameters and initial conditions will be chosen according to published data and according to what will make the solution fit collected experimental data of the different species involved in the system. The initial conditions were also determined using biological intuition. The solver name used in DEDiscover was RK45 Solver. It solves non-stiff Ordinary Differential

Equations using the Runge-Kutta 4th order system method. It is a medium-accuracy solver and is useful for dynamic systems which do not change their trajectories violently within a small period of time. The step size used to determine the solution of the system of ordinary non-linear differential equations was fixed and can be found on the following table.

Name	Value
Start Time	0.0000
Stop Time	0.0100
Step Size	1.0000E-03
R Tolerance	1.0000E-03
A Tolerance	1.0000E-06
Max Steps	1.0000E06
Init Step Size	1.0000E-03
Min Step Size	1.0000E-15
Max Step Size	0.1000
Safe Factor	0.9000

Table 3, Solver Configuration

CHAPTER 4: RESULTS AND DISCUSSION

The solution represents the amount of a specific species and how that amount changes in time. This is helpful to the researcher because it shows how different species can affect each other and the concentration of a specific species at any desired time.

In order to determine whether the solution to the model is biologically sound, it was necessary to play around with the parameters and see how the model reacts. If the model reacts in a mechanism that corroborates with how the cells react in the body, then the model is biologically sound.

CHAPTER 5: CONCLUSIONS

The T helper cell lineages listed where chosen by taking into consideration the information available to us as well as their role in cancer diagnosis and prognosis. We opted to utilize a single or double cytokine for polarization of each T helper cells subtype for this first model. However, this model can be scaled to account for the large complexity of the immune system.

5.1 Solutions

The developed system of Ordinary Differential Equations represents the polarization of an activated $CD4^+$ T-cell into different types of T-cells in response to the types of cytokines in the environment. In order to test the validity of the model, specific cytokines were increased. If the corresponding T-cell increased, then the polarization of the model is working correctly. First to test if the rate equation for Th17 was working, the parameters a7 and a8 were increased. These parameters represent the input cytokines IL-6 and IL-23.

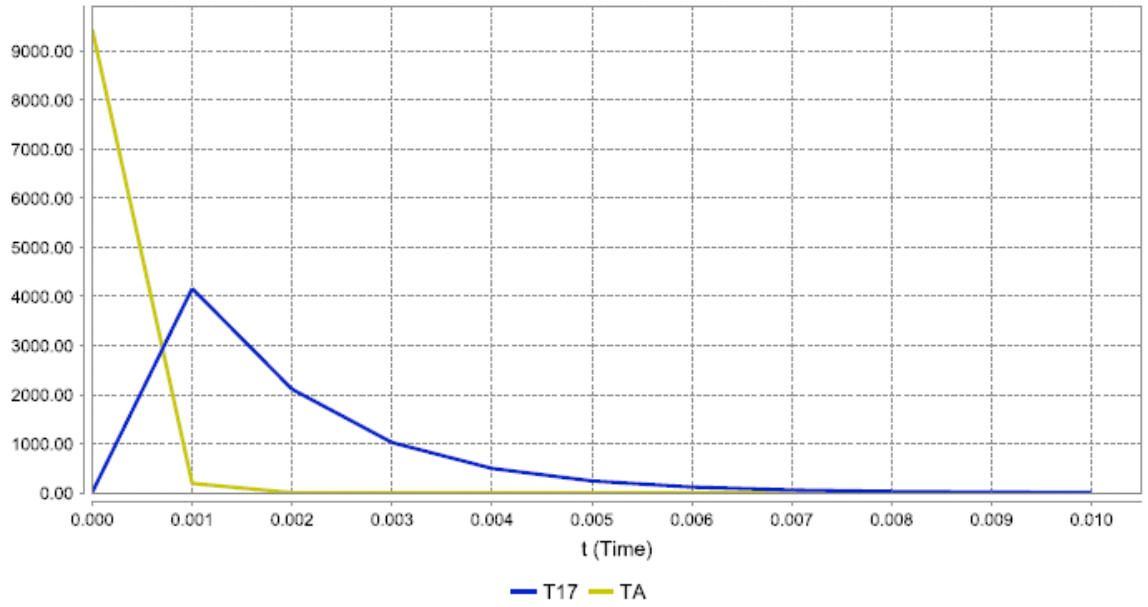


Figure 5, Th17 solution

The above solution shows an increase in Th17 as the parameters a_7 and a_8 were increased. The solution also shows a decrease in the level of Activated T-cells. This is biologically sound because Activated T-cells decrease as they polarize into other T-cells. To test if the rate equation for T regulatory cells was biologically correct, the parameter a1 was increased. This parameter represents the input cytokine TGF-β.

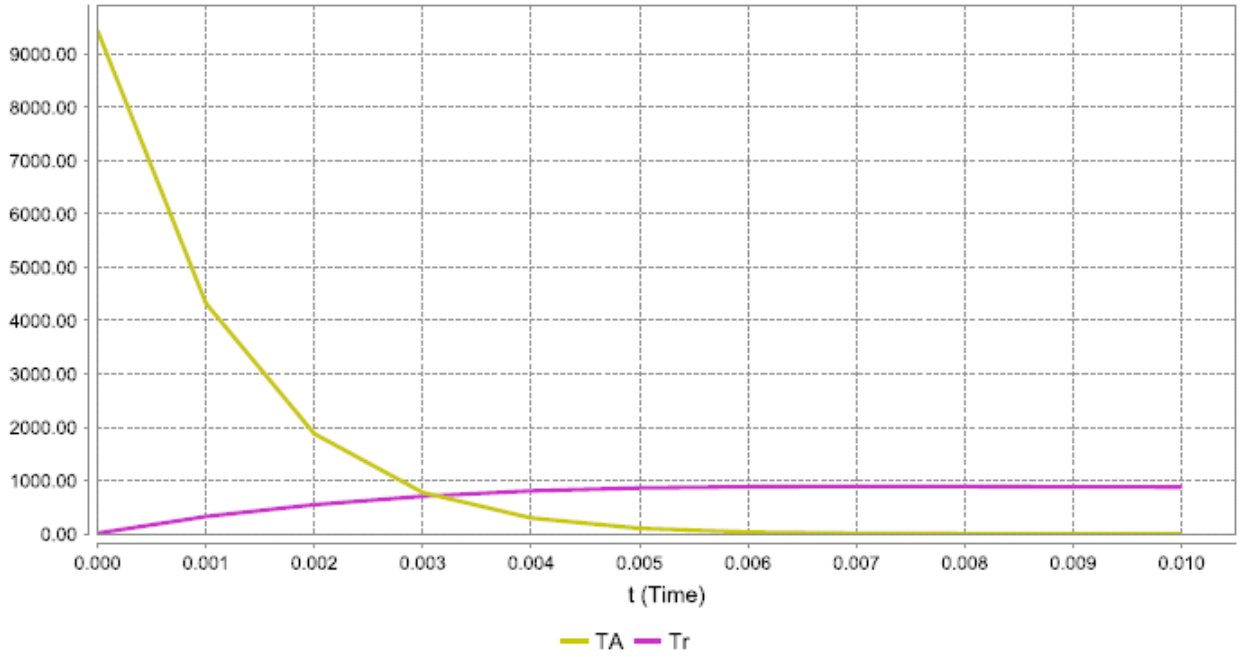


Figure 6, T regulatory cells solution

To test if the rate equation for Th1 was correct, the parameter a5 was increased. This parameter represents the input cytokine IL-12.

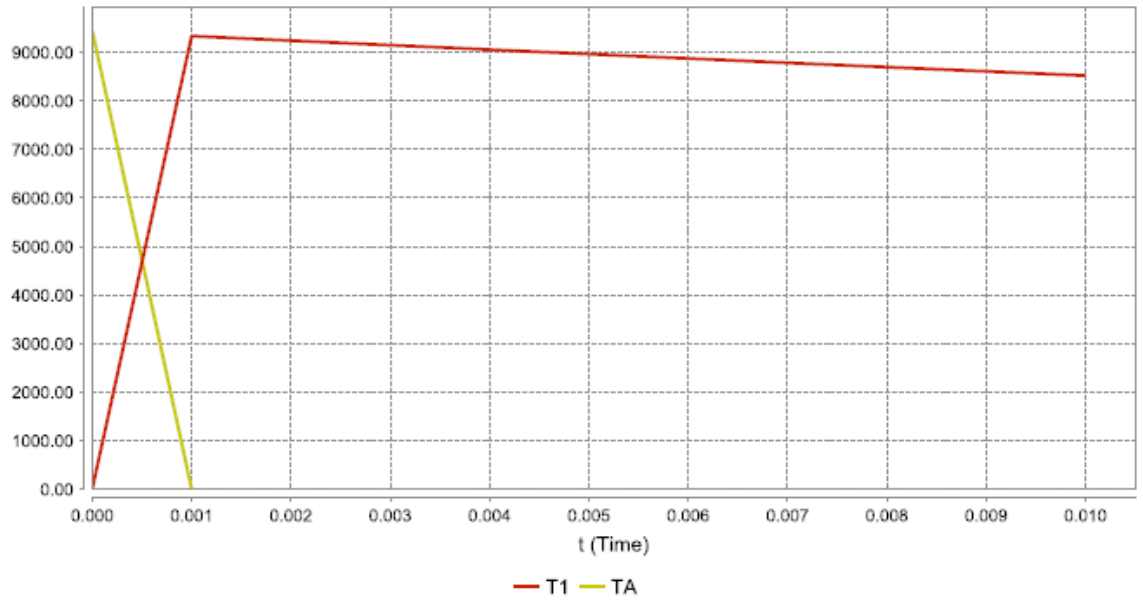


Figure 7, Th1 solution

To test if the rate equation for Th2 was correct, the parameter a3 was increased. This parameter represents the input cytokine IL-4.

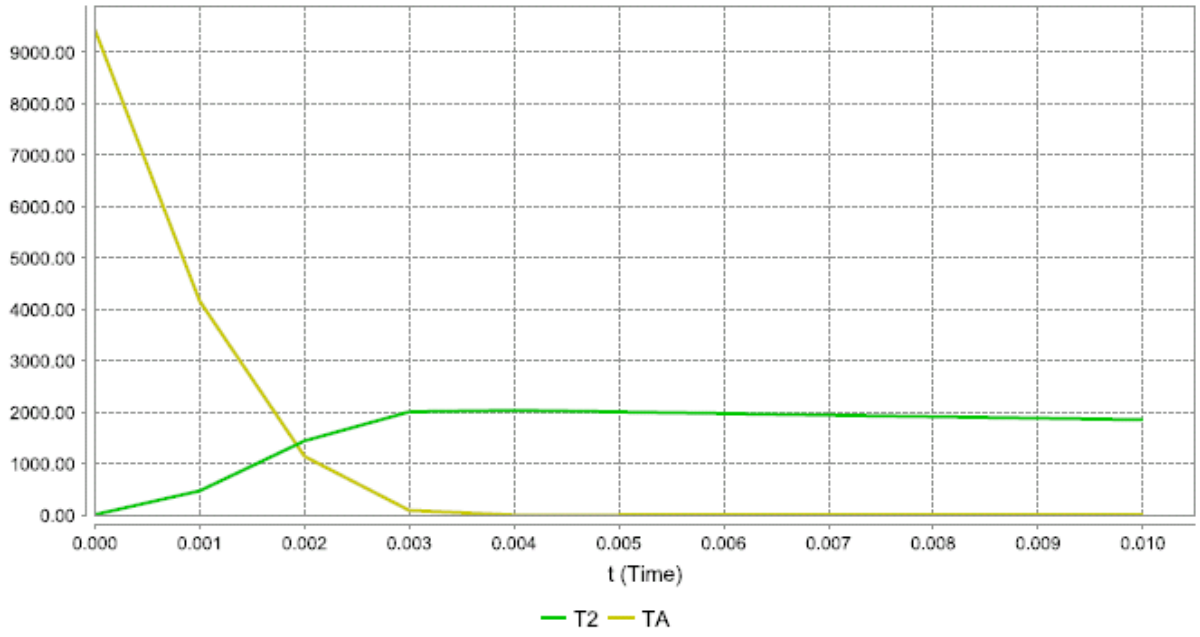


Figure 8, Th2 solution.

The solutions show an increase in the T-cells while their associated cytokines are increased. The graphs also show the solution of the activate T-cell. This amount should decrease as it polarizes into a different T-cell. The solution shows that as the polarized T-cells increase, the activated T-cell decreases.

CHAPTER 6: IMPLICATIONS OF RESEARCH

In this thesis, we have developed a mathematical model that represents the dynamics of T-cells and associated cytokines, which are important to immunotherapy. The biological applications include improved efficiency for immune system experiments by pre-selecting the relevant to clinical practice. Once the model is constructed and validated with independent sets of experimental data, information can be provided for the design of new immunotherapy. This model could prevent the misuse of immunotherapy in patients that are unlikely to benefit from this treatment and guide patient decision-making. Since the major target of immunotherapy is to increase the level of Th1 cells, this model may be used to study the dependency and reactions of other T-cells and cytokines by doing so. Thus, side-effect of undesirable response can be prevented. In addition, this model can be used to distinguish individuals if they are suitable for the immuno-therapy.

Since immune system is so complex, only species that have experimental data available are included in the model, the model developed in this thesis could leave out some important species. Therefore, there is one unknown function corresponding to the lump sum of "others" species is built-in in this model and left the door open for future expansion as more species are discovered or as more experimental data are available. For that purpose, the block 'Others' in the flow chart is the designated spot for new species to be added and to show that there are other T helper cells that play a part in immunity.

The method of developing a system of differential equations to represent the interactions between different species in a system can be applied to many different biological systems. Along with this research, the interaction of cells involved with Tuberculosis and the propagation of Heat Shock Proteins have both been modeled using flow charts and the compartmentalization

method. The results of this research can be applied to many biological systems so researchers can learn more about the interactions. Since the cells included in this model play a part in immunology as a whole, small modifications can be made to apply the model to not only cancer, but also to autoimmune disease and parasitic infections.

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APPENDICES

Model: Increase Th17

- Formula:

  dTr/dt=a1*Ib*(I4/(I4+c1))*TA-a2*Tr
  dT2/dt=a3*I4*((Ig+Ib)/(Ig+Ib+c2))*TA-a4*T2
  dT1/dt=a5*I12*TA-a6*T1
  dT17/dt=(a7*I6+a8*I23)*((Ig+I4)/(Ig+I4+c3))*TA-a9*T17
  dTA/dt=-a1*Ib*(I4/(I4+c1))*TA-a3*I4*((Ig+Ib)/(Ig+Ib+c2))*TA-a5*I12*TA-(a7*I6+a8*I23)*((Ig+I4)/(Ig+I4+c3))*TA
  dIb/dt=a2*Tr-a10*(I4/(I4+c1))*Ib-mb*Ib
  dI4/dt=a4*T2-a11*I4-m4*I4
  dIg/dt=a6*T1-mg*Ig
  dI6/dt=a4*T2-a12*I6-m6*I6
  dI12/dt=-a13*I12-m12*I12
  dI23/dt=-a14*I23-m23*I23
  dI17/dt=a9*T17-m17*I17

- Parameter Configuration:

Name	Current	Min	Default	Max
a1	11.1224	2.0000	200.0000	300.0000
a10	11.1224	2.0000	200.0000	300.0000
a11	2.3061	0.8000	25.4000	50.0000
a12	13.4285	2.0000	226.0000	450.0000
a13	30.4008	7.8000	253.9000	500.0000
a14	8.0816	2.0000	200.0000	300.0000
a2	6.5612	2.0000	200.0000	300.0000
a3	1.5531	0.8000	25.4000	50.0000
a4	15.7142	2.0000	226.0000	450.0000
a5	477.3992	7.8000	253.9000	500.0000
a6	10.1500	5.1000	252.5500	500.0000
a7	8.8571	2.0000	226.0000	450.0000
a8	6.5612	2.0000	200.0000	300.0000
a9	723.3900	9.8000	5004.9000	10000.0000
c1	53.9796	50.0000	80.0000	110.0000
c2	1.7551	1.0000	1.5000	2.0000
c3	16.0255	1.0000	10.0000	20.0000
m12	5.0000	0.0000	5.0000	10.0000
m17	5.9306	3.6968	5.4634	7.2300
m23	6.3223	0.0000	5.0000	10.0000

m4	2.7700	2.7700	2.7700	2.7700
m6	5.0000	0.0000	5.0000	10.0000
mb	5.0000	0.0000	5.0000	10.0000
mg	10.0018	2.1600	17.7150	33.2700

- Initial Condition Configuration:

Name	Current	Min	Default	Max
I12	37.9345	7.8000	253.9000	500.0000
I17	9.8000	9.8000	5000.0000	10000.0000
I23	10.0000	10.0000	10.0000	10000.0000
I4	0.8000	0.8000	25.4000	50.0000
I6	8.8571	2.0000	226.0000	450.0000
Ib	10.0000	10.0000	10.0000	10000.0000
Ig	5.1000	5.1000	252.5500	500.0000
T1	10.0000	10.0000	5000.0000	10000.0000
T17	10.0000	10.0000	10.0000	1000.0000
T2	10.0000	10.0000	5000.0000	10000.0000
TA	9439.3412	10.0000	10000.0000	10000.0000
Tr	10.0000	10.0000	5000.0000	10000.0000

- Macro Configuration:

Simulation Method

- Solver Name:

  RK45 Solver

- Solver Description:

  Solve non-stiff ODE problems. This is a medium-accuracy solver. It issuitable for dynamic systems which do NOT change their trajectories violently within a small period of time. Since the step size is adaptive, a higher accuracy of numerical results can be achieved than that of Runge-Kutta 4th order solver with fixed step size.

- Solver Configuration:

Name	Value
Start Time	0.0000
Stop Time	0.0100
Step Size	1.0000E-03
R Tolerance	1.0000E-03

A Tolerance	1.0000E-06
Max Steps	1.0000E06
Init Step Size	1.0000E-03
Min Step Size	1.0000E-15
Max Step Size	0.1000
Safe Factor	0.9000

Simulation Results

- Predefined Parameter Set:

Name	Current	Default
Simulate	false	true
Visible	false	false
a1	11.1224	200.0000
a10	11.1224	200.0000
a11	2.3061	25.4000
a12	13.4285	226.0000
a13	30.4008	253.9000
a14	8.0816	200.0000
a2	6.5612	200.0000
a3	1.5531	25.4000
a4	15.7142	226.0000
a5	477.3992	253.9000
a6	10.1500	252.5500
a7	8.8571	226.0000
a8	6.5612	200.0000
a9	723.3900	5004.9000
c1	53.9796	80.0000
c2	1.7551	1.5000
c3	16.0255	10.0000
m12	5.0000	5.0000
m17	5.9306	5.4634
m23	6.3223	5.0000
m4	2.7700	2.7700
m6	5.0000	5.0000
mb	5.0000	5.0000
mg	10.0018	17.7150
I12	37.9345	253.9000
I17	9.8000	5000.0000
I23	10.0000	10.0000
I4	0.8000	25.4000

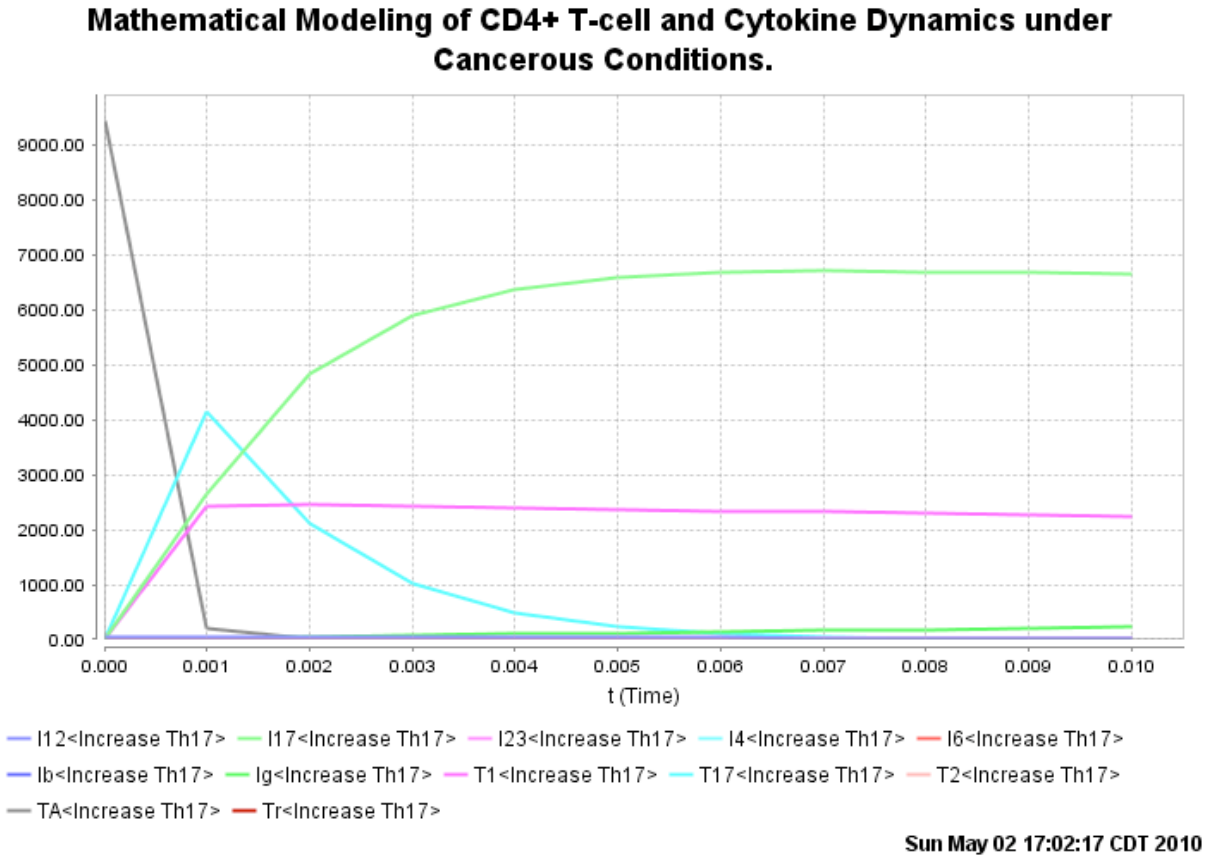
I6	8.8571	226.0000
Ib	10.0000	10.0000
Ig	5.1000	252.5500
T1	10.0000	5000.0000
T17	10.0000	10.0000
T2	10.0000	5000.0000
TA	9439.3412	10000.0000
Tr	10.0000	5000.0000

- User Defined Parameter Set:

Name	Th17 Increase&Decrease 1	set2	set3	0 at t=0	Increase Th17	Increase Treg	Increase Th2	Increase Th1
Simulate	true	true	true	true	false	false	false	false
Visible	false	false	false	false	true	false	false	false
a1	200.0000	200.0000	200.0000	200.0000	9.6020	284.7960	11.1224	11.1224
a10	200.0000	200.0000	200.0000	200.0000	11.1224	11.1224	11.1224	11.1224
a11	25.4000	25.4000	25.4000	25.4000	2.3061	2.3061	2.3061	2.3061
a12	226.0000	74.1983	74.1983	74.1983	13.4285	13.4285	13.4285	13.4285
a13	253.9000	253.9000	253.9000	253.9000	30.4008	30.4008	30.4008	30.4008
a14	200.0000	196.5621	196.5621	196.5621	8.0816	8.0816	8.0816	8.0816
a2	200.0000	200.0000	200.0000	200.0000	6.5612	6.5612	6.5612	6.5612
a3	25.4000	25.4000	25.4000	25.4000	2.5571	2.0551	47.2388	1.5531
a4	226.0000	226.0000	226.0000	226.0000	15.7142	15.7142	15.7142	15.7142
a5	253.9000	253.9000	253.9000	253.9000	22.8672	17.8448	17.8448	477.3992
a6	252.5500	252.5500	252.5500	252.5500	10.1500	10.1500	10.1500	10.1500
a7	450.0000	450.0000	450.0000	450.0000	450.0000	8.8571	8.8571	8.8571
a8	295.8992	295.8992	295.8992	295.8992	300.0000	6.5612	6.5612	6.5612
a9	9.8000	9.8000	9.8000	9.8000	723.3900	723.3900	723.3900	723.3900
c1	54.9541	54.9541	54.9541	54.9541	93.7755	53.9796	53.9796	53.9796
c2	1.0550	1.0550	1.0550	1.0550	1.7551	1.7551	1.7551	1.7551
c3	2.4817	2.4817	2.4817	2.4817	16.0255	16.0255	16.0255	16.0255
m12	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000
m17	5.4634	5.9306	5.9306	5.9306	5.9306	5.9306	5.9306	5.9306
m23	5.0000	6.3223	6.3223	6.3223	6.3223	6.3223	6.3223	6.3223
m4	2.7700	2.7700	2.7700	2.7700	2.7700	2.7700	2.7700	2.7700

m6	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000
mb	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000
mg	17.7150	10.0018	10.0018	10.0018	10.0018	10.0018	10.0018	10.0018
I12	253.9000	253.9000	375.9331	367.8832	37.9345	37.9345	37.9345	37.9345
I17	5000.0000	5000.0000	5000.0000	220.1237	9.8000	9.8000	9.8000	9.8000
I23	0.0000	0.0000	7561.9800	7561.9800	10.0000	10.0000	10.0000	10.0000
I4	25.4000	42.0711	25.8066	25.8066	0.8000	0.8000	0.8000	0.8000
I6	226.0000	226.0000	229.7023	229.7023	8.8571	8.8571	8.8571	8.8571
Ib	0.0000	0.0000	0.0000	0.0000	10.0000	10.0000	10.0000	10.0000
Ig	252.5500	252.5500	254.5949	254.5949	5.1000	5.1000	5.1000	5.1000
T1	5000.0000	5000.0000	5000.0000	0.0000	10.0000	10.0000	10.0000	10.0000
T17	0.0000	0.0000	0.0000	0.0000	10.0000	10.0000	10.0000	10.0000
T2	5000.0000	5000.0000	5000.0000	0.0000	10.0000	10.0000	10.0000	10.0000
TA	10000.0000	10000.0000	10000.0000	10000.0000	9439.3412	9439.3412	9439.3412	9439.3412
Tr	5000.0000	5000.0000	5000.0000	0.0000	10.0000	10.0000	10.0000	10.0000

- Simulation Result:
    - Combined Plot



- Tabular Data

Number of Variables: 12
Number of Time Points: 11

Time	I12	I17	I23	I4	I6	Ib	Ig	T1	T17	T2	TA	Tr
0.0000	37.9345	9.8000	10.0000	0.8000	8.8571	10.0000	5.1000	10.0000	10.0000	10.0000	9439.3412	10.0000
1.0000E-03	36.6150	27.1427	9.8570	0.9602	8.8585	10.0188	94.5631	9332.8221	17.6752	10.4289	1.6054E-04	10.7844
2.0000E-03	35.3415	36.0529	9.7160	1.1175	8.8579	10.0371	187.4001	9238.5736	8.5743	10.2663	7.9823E-07	10.7138
3.0000E-03	34.1123	40.2400	9.5771	1.2715	8.8547	10.0545	278.3662	9145.2767	4.1594	10.1062	5.8394E-07	10.6438
4.0000E-03	32.9258	42.1366	9.4401	1.4222	8.8491	10.0711	367.4895	9052.9220	2.0178	9.9487	6.9798E-07	10.5742
6.0000E-03	30.6752	43.1715	9.1721	1.7141	8.8311	10.1018	540.3187	8871.0012	0.4748	9.6409	1.4075E-06	10.4363
7.0000E-03	29.6083	43.1599	9.0409	1.8554	8.8188	10.1159	624.0791	8781.4163	0.2303	9.4905	9.5830E-07	10.3681
8.0000E-	28.5785	43.0229	8.9116	1.9936	8.8044	10.1292	706.1058	8692.7361	0.1117	9.3426	5.8429E-	10.3003

03											07	
9.0000E-03	27.5844	42.8259	8.7842	2.1288	8.7879	10.1417	786.4251	8604.9514	0.0542	9.1969	1.7133E-06	10.2329
0.0100	26.6250	42.6004	8.6585	2.2610	8.7695	10.1535	865.0629	8518.0532	0.0263	9.0535	7.1411E-08	10.1660

Model: Increase T regulatory cells

- Formula:

  dTr/dt=a1*Ib*(I4/(I4+c1))*TA-a2*Tr
  dT2/dt=a3*I4*((Ig+Ib)/(Ig+Ib+c2))*TA-a4*T2
  dT1/dt=a5*I12*TA-a6*T1
  dT17/dt=(a7*I6+a8*I23)*((Ig+I4)/(Ig+I4+c3))*TA-a9*T17
  dTA/dt=-a1*Ib*(I4/(I4+c1))*TA-a3*I4*((Ig+Ib)/(Ig+Ib+c2))*TA-a5*I12*TA-(a7*I6+a8*I23)*((Ig+I4)/(Ig+I4+c3))*TA
  dIb/dt=a2*Tr-a10*(I4/(I4+c1))*Ib-mb*Ib
  dI4/dt=a4*T2-a11*I4-m4*I4
  dIg/dt=a6*T1-mg*Ig
  dI6/dt=a4*T2-a12*I6-m6*I6
  dI12/dt=-a13*I12-m12*I12
  dI23/dt=-a14*I23-m23*I23
  dI17/dt=a9*T17-m17*I17

- Parameter Configuration:

Name	Current	Min	Default	Max	Description
a1	11.1224	2.0000	200.0000	300.0000	
a10	11.1224	2.0000	200.0000	300.0000	
a11	2.3061	0.8000	25.4000	50.0000	
a12	13.4285	2.0000	226.0000	450.0000	
a13	30.4008	7.8000	253.9000	500.0000	
a14	8.0816	2.0000	200.0000	300.0000	
a2	6.5612	2.0000	200.0000	300.0000	
a3	1.5531	0.8000	25.4000	50.0000	
a4	15.7142	2.0000	226.0000	450.0000	
a5	477.3992	7.8000	253.9000	500.0000	
a6	10.1500	5.1000	252.5500	500.0000	
a7	8.8571	2.0000	226.0000	450.0000	
a8	6.5612	2.0000	200.0000	300.0000	
a9	723.3900	9.8000	5004.9000	10000.0000	
c1	53.9796	50.0000	80.0000	110.0000	
c2	1.7551	1.0000	1.5000	2.0000	

c3	16.0255	1.0000	10.0000	20.0000	
m12	5.0000	0.0000	5.0000	10.0000	
m17	5.9306	3.6968	5.4634	7.2300	
m23	6.3223	0.0000	5.0000	10.0000	
m4	2.7700	2.7700	2.7700	2.7700	
m6	5.0000	0.0000	5.0000	10.0000	
mb	5.0000	0.0000	5.0000	10.0000	
mg	10.0018	2.1600	17.7150	33.2700	

- Initial Condition Configuration:

Name	Current	Min	Default	Max	Description
I12	37.9345	7.8000	253.9000	500.0000	
I17	9.8000	9.8000	5000.0000	10000.0000	
I23	10.0000	10.0000	10.0000	10000.0000	
I4	0.8000	0.8000	25.4000	50.0000	
I6	8.8571	2.0000	226.0000	450.0000	
Ib	10.0000	10.0000	10.0000	10000.0000	
Ig	5.1000	5.1000	252.5500	500.0000	
T1	10.0000	10.0000	5000.0000	10000.0000	
T17	10.0000	10.0000	10.0000	1000.0000	
T2	10.0000	10.0000	5000.0000	10000.0000	
TA	9439.3412	10.0000	10000.0000	10000.0000	
Tr	10.0000	10.0000	5000.0000	10000.0000	

- Macro Configuration:

Simulation Method

- Solver Name:

  RK45 Solver

- Solver Description:

  Solve non-stiff ODE problems. This is a medium-accuracy solver. It issuitable for dynamic systems which do NOT change their trajectories violently within a small period of time. Since the step size is adaptive, a higher accuracy of numerical results can be achieved than that of Runge-Kutta 4th order solver with fixed step size.

- Solver Configuration:

Name	Value

Start Time	0.0000
Stop Time	0.0100
Step Size	1.0000E-03
R Tolerance	1.0000E-03
A Tolerance	1.0000E-06
Max Steps	1.0000E06
Init Step Size	1.0000E-03
Min Step Size	1.0000E-15
Max Step Size	0.1000
Safe Factor	0.9000

Simulation Results

- Predefined Parameter Set:

Name	Current	Default
Simulate	false	true
Visible	false	false
a1	11.1224	200.0000
a10	11.1224	200.0000
a11	2.3061	25.4000
a12	13.4285	226.0000
a13	30.4008	253.9000
a14	8.0816	200.0000
a2	6.5612	200.0000
a3	1.5531	25.4000
a4	15.7142	226.0000
a5	477.3992	253.9000
a6	10.1500	252.5500
a7	8.8571	226.0000
a8	6.5612	200.0000
a9	723.3900	5004.9000
c1	53.9796	80.0000
c2	1.7551	1.5000
c3	16.0255	10.0000
m12	5.0000	5.0000
m17	5.9306	5.4634
m23	6.3223	5.0000
m4	2.7700	2.7700
m6	5.0000	5.0000
mb	5.0000	5.0000
mg	10.0018	17.7150

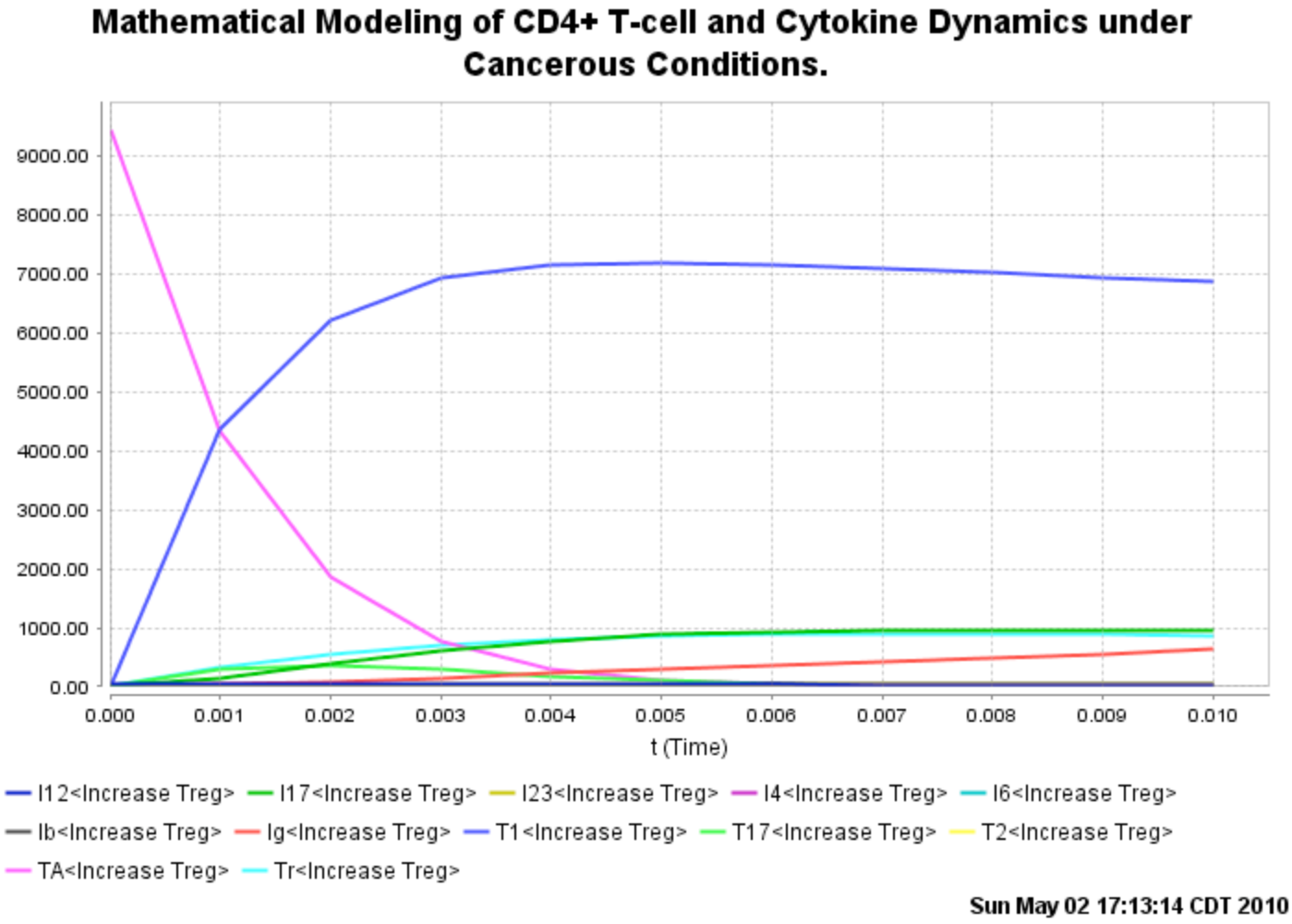
I12	37.9345	253.9000
I17	9.8000	5000.0000
I23	10.0000	10.0000
I4	0.8000	25.4000
I6	8.8571	226.0000
Ib	10.0000	10.0000
Ig	5.1000	252.5500
T1	10.0000	5000.0000
T17	10.0000	10.0000
T2	10.0000	5000.0000
TA	9439.3412	10000.0000
Tr	10.0000	5000.0000

- User Defined Parameter Set:

Name	Th17 Increase&Decrease 1	set2	set3	0 at t=0	Increase Th17	Increase Treg	Increase Th2	Increase Th1
Simulate	true	true	true	true	false	false	false	false
Visible	false	false	false	false	false	true	false	false
a1	200.0000	200.0000	200.0000	200.0000	9.6020	284.7960	11.1224	11.1224
a10	200.0000	200.0000	200.0000	200.0000	11.1224	11.1224	11.1224	11.1224
a11	25.4000	25.4000	25.4000	25.4000	2.3061	2.3061	2.3061	2.3061
a12	226.0000	74.1983	74.1983	74.1983	13.4285	13.4285	13.4285	13.4285
a13	253.9000	253.9000	253.9000	253.9000	30.4008	30.4008	30.4008	30.4008
a14	200.0000	196.5621	196.5621	196.5621	8.0816	8.0816	8.0816	8.0816
a2	200.0000	200.0000	200.0000	200.0000	6.5612	6.5612	6.5612	6.5612
a3	25.4000	25.4000	25.4000	25.4000	2.5571	2.0551	47.2388	1.5531
a4	226.0000	226.0000	226.0000	226.0000	15.7142	15.7142	15.7142	15.7142
a5	253.9000	253.9000	253.9000	253.9000	22.8672	17.8448	17.8448	477.3992
a6	252.5500	252.5500	252.5500	252.5500	10.1500	10.1500	10.1500	10.1500
a7	450.0000	450.0000	450.0000	450.0000	450.0000	8.8571	8.8571	8.8571
a8	295.8992	295.8992	295.8992	295.8992	300.0000	6.5612	6.5612	6.5612
a9	9.8000	9.8000	9.8000	9.8000	723.3900	723.3900	723.3900	723.3900
c1	54.9541	54.9541	54.9541	54.9541	93.7755	53.9796	53.9796	53.9796
c2	1.0550	1.0550	1.0550	1.0550	1.7551	1.7551	1.7551	1.7551
c3	2.4817	2.4817	2.4817	2.4817	16.0255	16.0255	16.0255	16.0255

m12	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000
m17	5.4634	5.9306	5.9306	5.9306	5.9306	5.9306	5.9306	5.9306
m23	5.0000	6.3223	6.3223	6.3223	6.3223	6.3223	6.3223	6.3223
m4	2.7700	2.7700	2.7700	2.7700	2.7700	2.7700	2.7700	2.7700
m6	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000
mb	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000
mg	17.7150	10.0018	10.0018	10.0018	10.0018	10.0018	10.0018	10.0018
I12	253.9000	253.9000	375.9331	367.8832	37.9345	37.9345	37.9345	37.9345
I17	5000.0000	5000.0000	5000.0000	220.1237	9.8000	9.8000	9.8000	9.8000
I23	0.0000	0.0000	7561.9800	7561.9800	10.0000	10.0000	10.0000	10.0000
I4	25.4000	42.0711	25.8066	25.8066	0.8000	0.8000	0.8000	0.8000
I6	226.0000	226.0000	229.7023	229.7023	8.8571	8.8571	8.8571	8.8571
Ib	0.0000	0.0000	0.0000	0.0000	10.0000	10.0000	10.0000	10.0000
Ig	252.5500	252.5500	254.5949	254.5949	5.1000	5.1000	5.1000	5.1000
T1	5000.0000	5000.0000	5000.0000	0.0000	10.0000	10.0000	10.0000	10.0000
T17	0.0000	0.0000	0.0000	0.0000	10.0000	10.0000	10.0000	10.0000
T2	5000.0000	5000.0000	5000.0000	0.0000	10.0000	10.0000	10.0000	10.0000
TA	10000.0000	10000.0000	10000.0000	10000.0000	9439.3412	9439.3412	9439.3412	9439.3412
Tr	5000.0000	5000.0000	5000.0000	0.0000	10.0000	10.0000	10.0000	10.0000

- Simulation Result:
    - Combined Plot



- Tabular Data

Number of Variables: 12
Number of Time Points: 11
Link to simulation result file

Time	I12	I17	I23	I4	I6	Ib	Ig	T1	T17	T2	TA	Tr
0.0000	37.9345	9.8000	10.0000	0.8000	8.8571	10.0000	5.1000	10.0000	10.0000	10.0000	9439.3412	10.0000
1.0000E-03	36.6150	27.1427	9.8570	0.9602	8.8585	10.0188	94.5631	9332.8221	17.6752	10.4289	1.6054E-04	10.7844
2.0000E-03	35.3415	36.0529	9.7160	1.1175	8.8579	10.0371	187.4001	9238.5736	8.5743	10.2663	7.9823E-07	10.7138
3.0000E-03	34.1123	40.2400	9.5771	1.2715	8.8547	10.0545	278.3662	9145.2767	4.1594	10.1062	5.8394E-07	10.6438
4.0000E-03	32.9258	42.1366	9.4401	1.4222	8.8491	10.0711	367.4895	9052.9220	2.0178	9.9487	6.9798E-07	10.5742
6.0000E-03	30.6752	43.1715	9.1721	1.7141	8.8311	10.1018	540.3187	8871.0012	0.4748	9.6409	1.4075E-06	10.4363

7.0000E-03	29.6083	43.1599	9.0409	1.8554	8.8188	10.1159	624.0791	8781.4163	0.2303	9.4905	9.5830E-07	10.3681
8.0000E-03	28.5785	43.0229	8.9116	1.9936	8.8044	10.1292	706.1058	8692.7361	0.1117	9.3426	5.8429E-07	10.3003
9.0000E-03	27.5844	42.8259	8.7842	2.1288	8.7879	10.1417	786.4251	8604.9514	0.0542	9.1969	1.7133E-06	10.2329
0.0100	26.6250	42.6004	8.6585	2.2610	8.7695	10.1535	865.0629	8518.0532	0.0263	9.0535	7.1411E-08	10.1660

Model: Increase Th2

- Formula:

  dTr/dt=a1*Ib*(I4/(I4+c1))*TA-a2*Tr
  dT2/dt=a3*I4*((Ig+Ib)/(Ig+Ib+c2))*TA-a4*T2
  dT1/dt=a5*I12*TA-a6*T1
  dT17/dt=(a7*I6+a8*I23)*((Ig+I4)/(Ig+I4+c3))*TA-a9*T17
  dTA/dt=-a1*Ib*(I4/(I4+c1))*TA-a3*I4*((Ig+Ib)/(Ig+Ib+c2))*TA-a5*I12*TA-(a7*I6+a8*I23)*((Ig+I4)/(Ig+I4+c3))*TA
  dIb/dt=a2*Tr-a10*(I4/(I4+c1))*Ib-mb*Ib
  dI4/dt=a4*T2-a11*I4-m4*I4
  dIg/dt=a6*T1-mg*Ig
  dI6/dt=a4*T2-a12*I6-m6*I6
  dI12/dt=-a13*I12-m12*I12
  dI23/dt=-a14*I23-m23*I23
  dI17/dt=a9*T17-m17*I17

- Parameter Configuration:

Name	Current	Min	Default	Max	Description
a1	11.1224	2.0000	200.0000	300.0000	
a10	11.1224	2.0000	200.0000	300.0000	
a11	2.3061	0.8000	25.4000	50.0000	
a12	13.4285	2.0000	226.0000	450.0000	
a13	30.4008	7.8000	253.9000	500.0000	
a14	8.0816	2.0000	200.0000	300.0000	
a2	6.5612	2.0000	200.0000	300.0000	
a3	1.5531	0.8000	25.4000	50.0000	
a4	15.7142	2.0000	226.0000	450.0000	
a5	477.3992	7.8000	253.9000	500.0000	
a6	10.1500	5.1000	252.5500	500.0000	
a7	8.8571	2.0000	226.0000	450.0000	
a8	6.5612	2.0000	200.0000	300.0000	

a9	723.3900	9.8000	5004.9000	10000.0000	
c1	53.9796	50.0000	80.0000	110.0000	
c2	1.7551	1.0000	1.5000	2.0000	
c3	16.0255	1.0000	10.0000	20.0000	
m12	5.0000	0.0000	5.0000	10.0000	
m17	5.9306	3.6968	5.4634	7.2300	
m23	6.3223	0.0000	5.0000	10.0000	
m4	2.7700	2.7700	2.7700	2.7700	
m6	5.0000	0.0000	5.0000	10.0000	
mb	5.0000	0.0000	5.0000	10.0000	
mg	10.0018	2.1600	17.7150	33.2700	

- Initial Condition Configuration:

Name	Current	Min	Default	Max	Description
I12	37.9345	7.8000	253.9000	500.0000	
I17	9.8000	9.8000	5000.0000	10000.0000	
I23	10.0000	10.0000	10.0000	10000.0000	
I4	0.8000	0.8000	25.4000	50.0000	
I6	8.8571	2.0000	226.0000	450.0000	
Ib	10.0000	10.0000	10.0000	10000.0000	
Ig	5.1000	5.1000	252.5500	500.0000	
T1	10.0000	10.0000	5000.0000	10000.0000	
T17	10.0000	10.0000	10.0000	1000.0000	
T2	10.0000	10.0000	5000.0000	10000.0000	
TA	9439.3412	10.0000	10000.0000	10000.0000	
Tr	10.0000	10.0000	5000.0000	10000.0000	

- Macro Configuration:

Simulation Method

- Solver Name:

  RK45 Solver

- Solver Description:

  Solve non-stiff ODE problems. This is a medium-accuracy solver. It issuitable for dynamic systems which do NOT change their trajectories violently within a small period of time. Since the step size is adaptive, a higher accuracy of numerical results can be achieved than that of Runge-Kutta 4th order solver with fixed step size.

- Solver Configuration:

Name	Value
Start Time	0.0000
Stop Time	0.0100
Step Size	1.0000E-03
R Tolerance	1.0000E-03
A Tolerance	1.0000E-06
Max Steps	1.0000E06
Init Step Size	1.0000E-03
Min Step Size	1.0000E-15
Max Step Size	0.1000
Safe Factor	0.9000

Simulation Results

- Predefined Parameter Set:

Name	Current	Default
Simulate	false	true
Visible	false	false
a1	11.1224	200.0000
a10	11.1224	200.0000
a11	2.3061	25.4000
a12	13.4285	226.0000
a13	30.4008	253.9000
a14	8.0816	200.0000
a2	6.5612	200.0000
a3	1.5531	25.4000
a4	15.7142	226.0000
a5	477.3992	253.9000
a6	10.1500	252.5500
a7	8.8571	226.0000
a8	6.5612	200.0000
a9	723.3900	5004.9000
c1	53.9796	80.0000
c2	1.7551	1.5000
c3	16.0255	10.0000
m12	5.0000	5.0000
m17	5.9306	5.4634
m23	6.3223	5.0000
m4	2.7700	2.7700

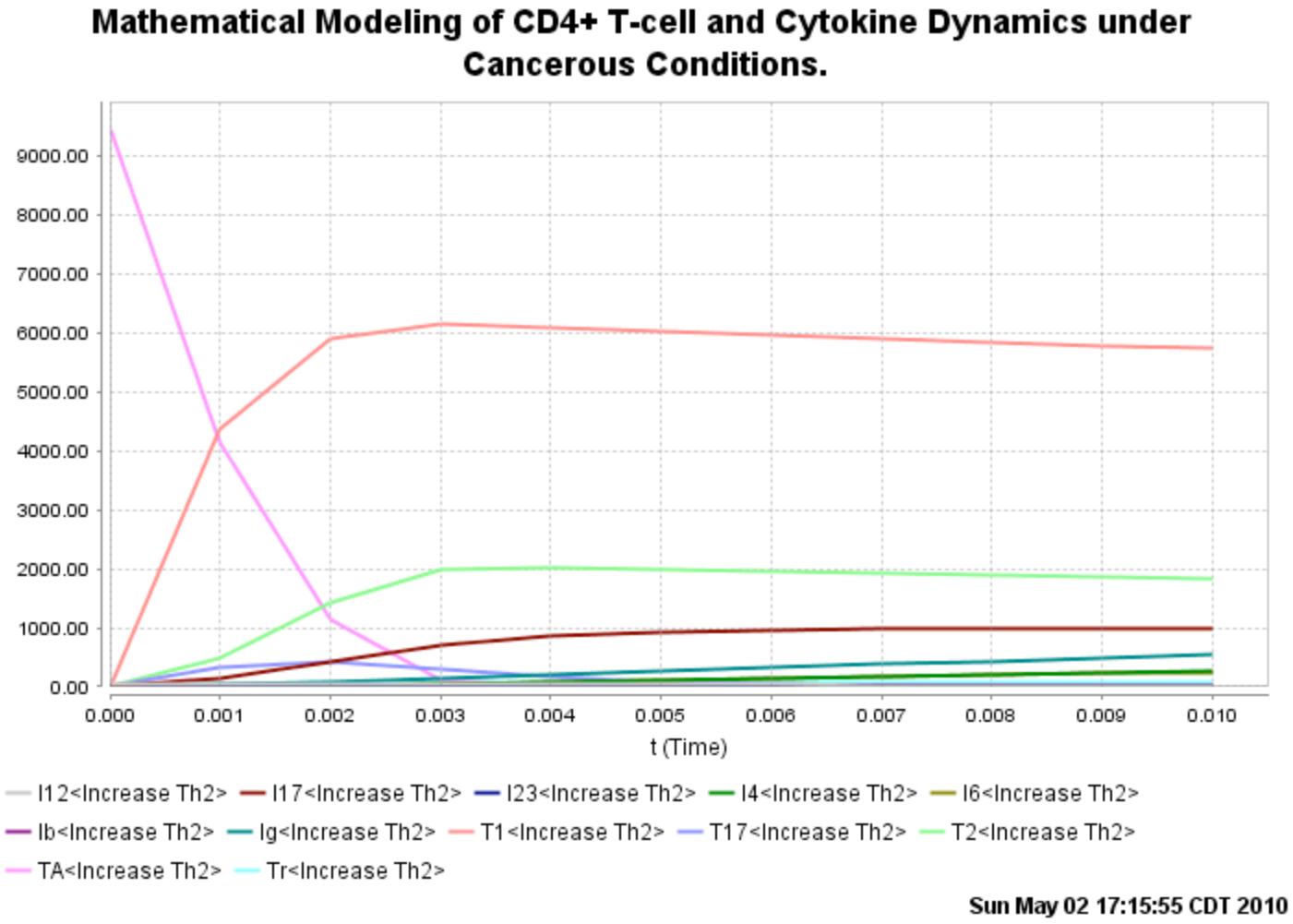
m6	5.0000	5.0000
mb	5.0000	5.0000
mg	10.0018	17.7150
I12	37.9345	253.9000
I17	9.8000	5000.0000
I23	10.0000	10.0000
I4	0.8000	25.4000
I6	8.8571	226.0000
Ib	10.0000	10.0000
Ig	5.1000	252.5500
T1	10.0000	5000.0000
T17	10.0000	10.0000
T2	10.0000	5000.0000
TA	9439.3412	10000.0000
Tr	10.0000	5000.0000

- User Defined Parameter Set:

Name	Th17 Increase&Decrease 1	set2	set3	0 at t=0	Increase Th17	Increase Treg	Increase Th2	Increase Th1
Simulate	true	true	true	true	false	false	false	false
Visible	false	false	false	false	false	false	true	false
a1	200.0000	200.0000	200.0000	200.0000	9.6020	284.7960	11.1224	11.1224
a10	200.0000	200.0000	200.0000	200.0000	11.1224	11.1224	11.1224	11.1224
a11	25.4000	25.4000	25.4000	25.4000	2.3061	2.3061	2.3061	2.3061
a12	226.0000	74.1983	74.1983	74.1983	13.4285	13.4285	13.4285	13.4285
a13	253.9000	253.9000	253.9000	253.9000	30.4008	30.4008	30.4008	30.4008
a14	200.0000	196.5621	196.5621	196.5621	8.0816	8.0816	8.0816	8.0816
a2	200.0000	200.0000	200.0000	200.0000	6.5612	6.5612	6.5612	6.5612
a3	25.4000	25.4000	25.4000	25.4000	2.5571	2.0551	47.2388	1.5531
a4	226.0000	226.0000	226.0000	226.0000	15.7142	15.7142	15.7142	15.7142
a5	253.9000	253.9000	253.9000	253.9000	22.8672	17.8448	17.8448	477.3992
a6	252.5500	252.5500	252.5500	252.5500	10.1500	10.1500	10.1500	10.1500
a7	450.0000	450.0000	450.0000	450.0000	450.0000	8.8571	8.8571	8.8571
a8	295.8992	295.8992	295.8992	295.8992	300.0000	6.5612	6.5612	6.5612
a9	9.8000	9.8000	9.8000	9.8000	723.3900	723.3900	723.3900	723.3900

c1	54.9541	54.9541	54.9541	54.9541	93.7755	53.9796	53.9796	53.9796
c2	1.0550	1.0550	1.0550	1.0550	1.7551	1.7551	1.7551	1.7551
c3	2.4817	2.4817	2.4817	2.4817	16.0255	16.0255	16.0255	16.0255
m12	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000
m17	5.4634	5.9306	5.9306	5.9306	5.9306	5.9306	5.9306	5.9306
m23	5.0000	6.3223	6.3223	6.3223	6.3223	6.3223	6.3223	6.3223
m4	2.7700	2.7700	2.7700	2.7700	2.7700	2.7700	2.7700	2.7700
m6	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000
mb	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000
mg	17.7150	10.0018	10.0018	10.0018	10.0018	10.0018	10.0018	10.0018
I12	253.9000	253.9000	375.9331	367.8832	37.9345	37.9345	37.9345	37.9345
I17	5000.0000	5000.0000	5000.0000	220.1237	9.8000	9.8000	9.8000	9.8000
I23	0.0000	0.0000	7561.9800	7561.9800	10.0000	10.0000	10.0000	10.0000
I4	25.4000	42.0711	25.8066	25.8066	0.8000	0.8000	0.8000	0.8000
I6	226.0000	226.0000	229.7023	229.7023	8.8571	8.8571	8.8571	8.8571
Ib	0.0000	0.0000	0.0000	0.0000	10.0000	10.0000	10.0000	10.0000
Ig	252.5500	252.5500	254.5949	254.5949	5.1000	5.1000	5.1000	5.1000
T1	5000.0000	5000.0000	5000.0000	0.0000	10.0000	10.0000	10.0000	10.0000
T17	0.0000	0.0000	0.0000	0.0000	10.0000	10.0000	10.0000	10.0000
T2	5000.0000	5000.0000	5000.0000	0.0000	10.0000	10.0000	10.0000	10.0000
TA	10000.0000	10000.0000	10000.0000	10000.0000	9439.3412	9439.3412	9439.3412	9439.3412
Tr	5000.0000	5000.0000	5000.0000	0.0000	10.0000	10.0000	10.0000	10.0000

- Simulation Result:
    - Combined Plot



- Tabular Data

Number of Variables: 12
Number of Time Points: 11
Link to simulation result file

Time	I12	I17	I23	I4	I6	Ib	Ig	T1	T17	T2	TA	Tr
0.0000	37.9345	9.8000	10.0000	0.8000	8.8571	10.0000	5.1000	10.0000	10.0000	10.0000	9439.3412	10.0000
1.0000E-03	36.6150	27.1427	9.8570	0.9602	8.8585	10.0188	94.5631	9332.8221	17.6752	10.4289	1.6054E-04	10.7844
2.0000E-03	35.3415	36.0529	9.7160	1.1175	8.8579	10.0371	187.4001	9238.5736	8.5743	10.2663	7.9823E-07	10.7138
3.0000E-03	34.1123	40.2400	9.5771	1.2715	8.8547	10.0545	278.3662	9145.2767	4.1594	10.1062	5.8394E-07	10.6438
4.0000E-03	32.9258	42.1366	9.4401	1.4222	8.8491	10.0711	367.4895	9052.9220	2.0178	9.9487	6.9798E-07	10.5742
6.0000E-03	30.6752	43.1715	9.1721	1.7141	8.8311	10.1018	540.3187	8871.0012	0.4748	9.6409	1.4075E-06	10.4363

7.0000E-03	29.6083	43.1599	9.0409	1.8554	8.8188	10.1159	624.0791	8781.4163	0.2303	9.4905	9.5830E-07	10.3681
8.0000E-03	28.5785	43.0229	8.9116	1.9936	8.8044	10.1292	706.1058	8692.7361	0.1117	9.3426	5.8429E-07	10.3003
9.0000E-03	27.5844	42.8259	8.7842	2.1288	8.7879	10.1417	786.4251	8604.9514	0.0542	9.1969	1.7133E-06	10.2329
0.0100	26.6250	42.6004	8.6585	2.2610	8.7695	10.1535	865.0629	8518.0532	0.0263	9.0535	7.1411E-08	10.1660

Model: Increase Th1

- Formula:

  dTr/dt=a1*Ib*(I4/(I4+c1))*TA-a2*Tr
  dT2/dt=a3*I4*((Ig+Ib)/(Ig+Ib+c2))*TA-a4*T2
  dT1/dt=a5*I12*TA-a6*T1
  dT17/dt=(a7*I6+a8*I23)*((Ig+I4)/(Ig+I4+c3))*TA-a9*T17
  dTA/dt=-a1*Ib*(I4/(I4+c1))*TA-a3*I4*((Ig+Ib)/(Ig+Ib+c2))*TA-a5*I12*TA-(a7*I6+a8*I23)*((Ig+I4)/(Ig+I4+c3))*TA
  dIb/dt=a2*Tr-a10*(I4/(I4+c1))*Ib-mb*Ib
  dI4/dt=a4*T2-a11*I4-m4*I4
  dIg/dt=a6*T1-mg*Ig
  dI6/dt=a4*T2-a12*I6-m6*I6
  dI12/dt=-a13*I12-m12*I12
  dI23/dt=-a14*I23-m23*I23
  dI17/dt=a9*T17-m17*I17

- Parameter Configuration:

Name	Current	Min	Default	Max	Description
a1	11.1224	2.0000	200.0000	300.0000	
a10	11.1224	2.0000	200.0000	300.0000	
a11	2.3061	0.8000	25.4000	50.0000	
a12	13.4285	2.0000	226.0000	450.0000	
a13	30.4008	7.8000	253.9000	500.0000	
a14	8.0816	2.0000	200.0000	300.0000	
a2	6.5612	2.0000	200.0000	300.0000	
a3	1.5531	0.8000	25.4000	50.0000	
a4	15.7142	2.0000	226.0000	450.0000	
a5	477.3992	7.8000	253.9000	500.0000	
a6	10.1500	5.1000	252.5500	500.0000	
a7	8.8571	2.0000	226.0000	450.0000	

a8	6.5612	2.0000	200.0000	300.0000	
a9	723.3900	9.8000	5004.9000	10000.0000	
c1	53.9796	50.0000	80.0000	110.0000	
c2	1.7551	1.0000	1.5000	2.0000	
c3	16.0255	1.0000	10.0000	20.0000	
m12	5.0000	0.0000	5.0000	10.0000	
m17	5.9306	3.6968	5.4634	7.2300	
m23	6.3223	0.0000	5.0000	10.0000	
m4	2.7700	2.7700	2.7700	2.7700	
m6	5.0000	0.0000	5.0000	10.0000	
mb	5.0000	0.0000	5.0000	10.0000	
mg	10.0018	2.1600	17.7150	33.2700	

- Initial Condition Configuration:

Name	Current	Min	Default	Max	Description
I12	37.9345	7.8000	253.9000	500.0000	
I17	9.8000	9.8000	5000.0000	10000.0000	
I23	10.0000	10.0000	10.0000	10000.0000	
I4	0.8000	0.8000	25.4000	50.0000	
I6	8.8571	2.0000	226.0000	450.0000	
Ib	10.0000	10.0000	10.0000	10000.0000	
Ig	5.1000	5.1000	252.5500	500.0000	
T1	10.0000	10.0000	5000.0000	10000.0000	
T17	10.0000	10.0000	10.0000	1000.0000	
T2	10.0000	10.0000	5000.0000	10000.0000	
TA	9439.3412	10.0000	10000.0000	10000.0000	
Tr	10.0000	10.0000	5000.0000	10000.0000	

- Macro Configuration:

Simulation Method

- Solver Name:

  RK45 Solver

- Solver Description:

  Solve non-stiff ODE problems. This is a medium-accuracy solver. It issuitable for dynamic systems which do NOT change their trajectories violently within a small period of time. Since the step size is adaptive, a higher accuracy of numerical results can be achieved than that of Runge-Kutta 4th order solver with fixed step size.

- Solver Configuration:

Name	Value
Start Time	0.0000
Stop Time	0.0100
Step Size	1.0000E-03
R Tolerance	1.0000E-03
A Tolerance	1.0000E-06
Max Steps	1.0000E06
Init Step Size	1.0000E-03
Min Step Size	1.0000E-15
Max Step Size	0.1000
Safe Factor	0.9000

Simulation Results

- Predefined Parameter Set:

Name	Current	Default
Simulate	false	true
Visible	false	false
a1	11.1224	200.0000
a10	11.1224	200.0000
a11	2.3061	25.4000
a12	13.4285	226.0000
a13	30.4008	253.9000
a14	8.0816	200.0000
a2	6.5612	200.0000
a3	1.5531	25.4000
a4	15.7142	226.0000
a5	477.3992	253.9000
a6	10.1500	252.5500
a7	8.8571	226.0000
a8	6.5612	200.0000
a9	723.3900	5004.9000
c1	53.9796	80.0000
c2	1.7551	1.5000
c3	16.0255	10.0000
m12	5.0000	5.0000
m17	5.9306	5.4634
m23	6.3223	5.0000
m4	2.7700	2.7700

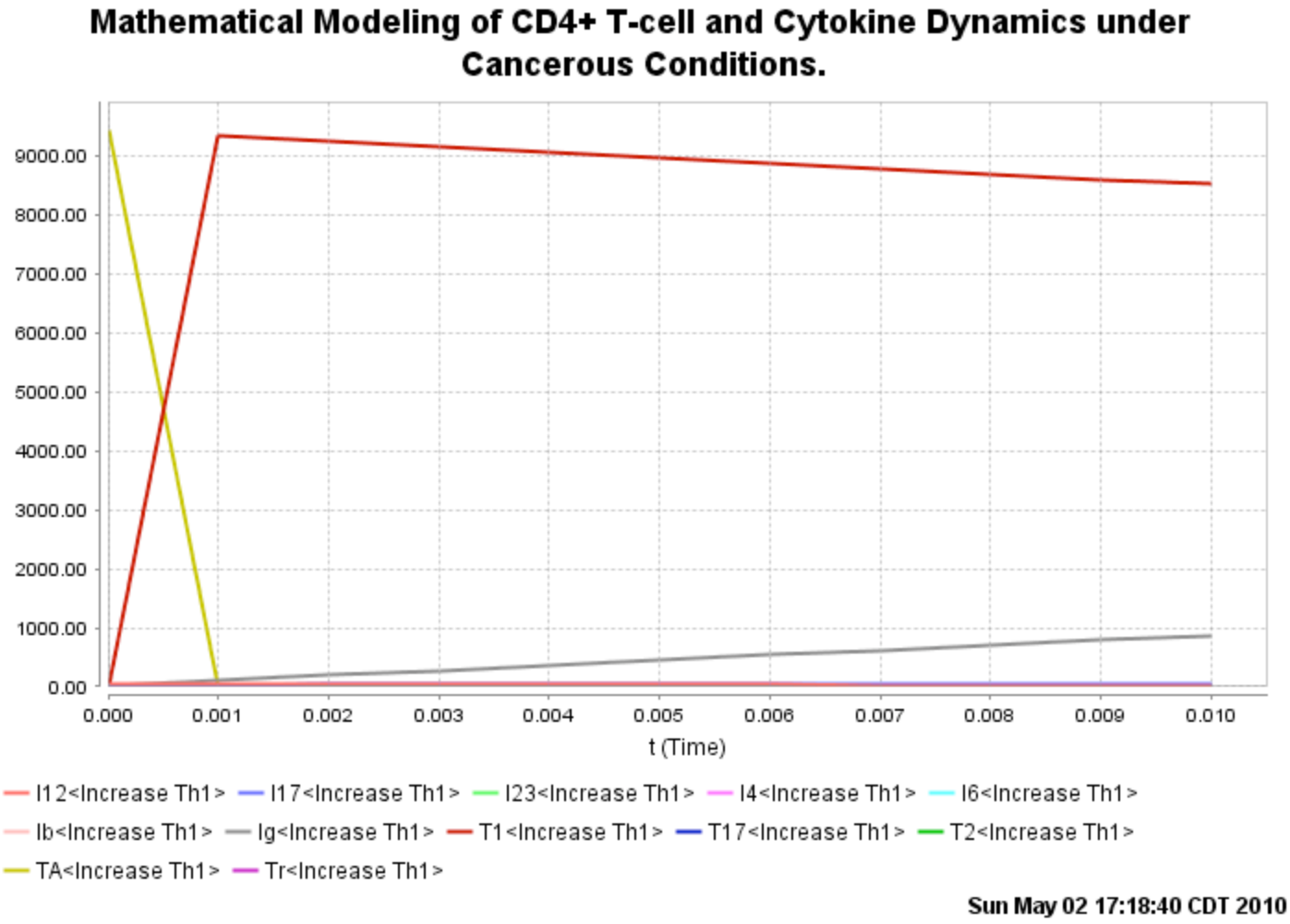
m6	5.0000	5.0000
mb	5.0000	5.0000
mg	10.0018	17.7150
I12	37.9345	253.9000
I17	9.8000	5000.0000
I23	10.0000	10.0000
I4	0.8000	25.4000
I6	8.8571	226.0000
Ib	10.0000	10.0000
Ig	5.1000	252.5500
T1	10.0000	5000.0000
T17	10.0000	10.0000
T2	10.0000	5000.0000
TA	9439.3412	10000.0000
Tr	10.0000	5000.0000

- User Defined Parameter Set:

Name	Th17 Increase&Decrease 1	set2	set3	0 at t=0	Increase Th17	Increase Treg	Increase Th2	Increase Th1
Simulate	true	true	true	true	false	false	false	false
Visible	false	false	false	false	false	false	false	true
a1	200.0000	200.0000	200.0000	200.0000	9.6020	284.7960	11.1224	11.1224
a10	200.0000	200.0000	200.0000	200.0000	11.1224	11.1224	11.1224	11.1224
a11	25.4000	25.4000	25.4000	25.4000	2.3061	2.3061	2.3061	2.3061
a12	226.0000	74.1983	74.1983	74.1983	13.4285	13.4285	13.4285	13.4285
a13	253.9000	253.9000	253.9000	253.9000	30.4008	30.4008	30.4008	30.4008
a14	200.0000	196.5621	196.5621	196.5621	8.0816	8.0816	8.0816	8.0816
a2	200.0000	200.0000	200.0000	200.0000	6.5612	6.5612	6.5612	6.5612
a3	25.4000	25.4000	25.4000	25.4000	2.5571	2.0551	47.2388	1.5531
a4	226.0000	226.0000	226.0000	226.0000	15.7142	15.7142	15.7142	15.7142
a5	253.9000	253.9000	253.9000	253.9000	22.8672	17.8448	17.8448	477.3992
a6	252.5500	252.5500	252.5500	252.5500	10.1500	10.1500	10.1500	10.1500
a7	450.0000	450.0000	450.0000	450.0000	450.0000	8.8571	8.8571	8.8571
a8	295.8992	295.8992	295.8992	295.8992	300.0000	6.5612	6.5612	6.5612
a9	9.8000	9.8000	9.8000	9.8000	723.3900	723.3900	723.3900	723.3900

c1	54.9541	54.9541	54.9541	54.9541	93.7755	53.9796	53.9796	53.9796
c2	1.0550	1.0550	1.0550	1.0550	1.7551	1.7551	1.7551	1.7551
c3	2.4817	2.4817	2.4817	2.4817	16.0255	16.0255	16.0255	16.0255
m12	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000
m17	5.4634	5.9306	5.9306	5.9306	5.9306	5.9306	5.9306	5.9306
m23	5.0000	6.3223	6.3223	6.3223	6.3223	6.3223	6.3223	6.3223
m4	2.7700	2.7700	2.7700	2.7700	2.7700	2.7700	2.7700	2.7700
m6	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000
mb	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000
mg	17.7150	10.0018	10.0018	10.0018	10.0018	10.0018	10.0018	10.0018
I12	253.9000	253.9000	375.9331	367.8832	37.9345	37.9345	37.9345	37.9345
I17	5000.0000	5000.0000	5000.0000	220.1237	9.8000	9.8000	9.8000	9.8000
I23	0.0000	0.0000	7561.9800	7561.9800	10.0000	10.0000	10.0000	10.0000
I4	25.4000	42.0711	25.8066	25.8066	0.8000	0.8000	0.8000	0.8000
I6	226.0000	226.0000	229.7023	229.7023	8.8571	8.8571	8.8571	8.8571
Ib	0.0000	0.0000	0.0000	0.0000	10.0000	10.0000	10.0000	10.0000
Ig	252.5500	252.5500	254.5949	254.5949	5.1000	5.1000	5.1000	5.1000
T1	5000.0000	5000.0000	5000.0000	0.0000	10.0000	10.0000	10.0000	10.0000
T17	0.0000	0.0000	0.0000	0.0000	10.0000	10.0000	10.0000	10.0000
T2	5000.0000	5000.0000	5000.0000	0.0000	10.0000	10.0000	10.0000	10.0000
TA	10000.0000	10000.0000	10000.0000	10000.0000	9439.3412	9439.3412	9439.3412	9439.3412
Tr	5000.0000	5000.0000	5000.0000	0.0000	10.0000	10.0000	10.0000	10.0000

- Simulation Result:
    - Combined Plot



- Tabular Data

Number of Variables: 12
Number of Time Points: 11
Link to simulation result file

Time	I12	I17	I23	I4	I6	Ib	Ig	T1	T17	T2	TA	Tr
0.0000	37.9345	9.8000	10.0000	0.8000	8.8571	10.0000	5.1000	10.0000	10.0000	10.0000	9439.3412	10.0000
1.0000E-03	36.6150	27.1427	9.8570	0.9602	8.8585	10.0188	94.5631	9332.8221	17.6752	10.4289	1.6054E-04	10.7844
2.0000E-03	35.3415	36.0529	9.7160	1.1175	8.8579	10.0371	187.4001	9238.5736	8.5743	10.2663	7.9823E-07	10.7138
3.0000E-03	34.1123	40.2400	9.5771	1.2715	8.8547	10.0545	278.3662	9145.2767	4.1594	10.1062	5.8394E-07	10.6438
4.0000E-03	32.9258	42.1366	9.4401	1.4222	8.8491	10.0711	367.4895	9052.9220	2.0178	9.9487	6.9798E-07	10.5742
6.0000E-03	30.6752	43.1715	9.1721	1.7141	8.8311	10.1018	540.3187	8871.0012	0.4748	9.6409	1.4075E-06	10.4363

7.0000E-03	29.6083	43.1599	9.0409	1.8554	8.8188	10.1159	624.0791	8781.4163	0.2303	9.4905	9.5830E-07	10.3681
8.0000E-03	28.5785	43.0229	8.9116	1.9936	8.8044	10.1292	706.1058	8692.7361	0.1117	9.3426	5.8429E-07	10.3003
9.0000E-03	27.5844	42.8259	8.7842	2.1288	8.7879	10.1417	786.4251	8604.9514	0.0542	9.1969	1.7133E-06	10.2329
0.0100	26.6250	42.6004	8.6585	2.2610	8.7695	10.1535	865.0629	8518.0532	0.0263	9.0535	7.1411E-08	10.1660