Parametric Analysis of an Initial Multicompartment Model of Type I Diabetes

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Abstract

Mathematical models in biomedical studies are often used to explore the dynamics of biological systems without having to design and perform costly and invasive *in vivo* or *in vitro* studies. Compartment models are especially helpful in simplifying biological dynamics at the cellular level, using high level computational power to model the system *in silico*. In particular, our research focuses on extending previous single compartmental models of the pathogenesis of type 1 diabetes (T1D) to a multicompartmental model. In addition to the previously included pancreas, this research includes both the bloodstream and spleen (lymph nodes) as additional compartments for more nuanced and accurate modelling.

While the additional analysis done on these new compartments inherently enriches understanding of the development of T1D, it also allows for exploration of clinical possibility. It has been documented in recent studies [1], [2] that a proper injection of a dendritic cell (DC) vaccine could halt or slow the progression of T1D and other autoimmune diseases. With integrated depth of the model, it is possible to further the goal of collecting information on the timing and details of these hypothetical treatments for further clinical research.

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Chapter 1

Biological Background

1.1 Prevalence of diabetes and the motivation behind researching it

Diabetes mellitus is a broad term for a set of diseases in which blood glucose levels exceed homeostatic conditions. The name diabetes mellitus comes from the Latin diabainein (to siphon) and the Greek mellitus (sweet), referring to the fact that diabetes was historically diagnosed by tasting the urine of the suspected diabetic person. It is estimated that by 2040 the global population of diabetes mellitus patients (of all types) will be somewhere on the order of 642 million people.

Low estimates (while contested) of type 1 diabetes (T1D) populations yield global prevalence population numbers of 44.94 million people in 2040 [3]. More alarming than the number of T1D cases are the complications associated with T1D: increased risk of having acute myocardial infarctions, end stage renal disease, cardiovascular diseases, retinopathy, neuropathy, and even casual relationships to cancer and early mortality [4]. T1D, unlike other forms of diabetes, is decidedly autoimmune, making potential preventions, treatments, and cures much more difficult.

1.2 Introduction to the idea of T1D's autoimmunity component

The immune system defends against foreign biological agents. Immune system responses are classified by type: innate responses (the general response

against a foreign agent) and the adaptive response (a response specific to the foreign agent in question). Autoimmune diseases are a dysfunction largely of the innate response of the immune system. T1D is an autoimmune disease that targets the beta-cells of the islets of Langerhans, located within the pancreas. Beta cells are responsible chiefly for the production of insulin, a protein hormone that serves as a paragon for the typical enzymatic description of 'lock-and-key' by binding with cells to allow glucose to enter the cell. Beta cells have a sensory component to their activity, whereby glucose levels in the bloodstream determine the activity of beta cells, the production of insulin, and even the creation of new beta cells [5].

Like in other autoimmune diseases (for example, celiac disease, multiple sclerosis, Graves' disease, etc.), cellular function is greatly affected by these immune system effects. In an all types of diabetes mellitus, glucose levels begin to rise and deviate from homeostasis because of reduction (or in some cases, like T1D, termination) in insulin production by beta cells and/or a reduction in the metabolic effectiveness of insulin in stimulating uptake of glucose. In T1D, the patient's own beta cells are destroyed in an autoimmune response rendering the patient without critical hormone and cellular regulation. The immune cells involved with the innate response of the immune system have been shown to have a hand in the eventual development of T1D: in particular, macrophages, T-cells, and dendritic cells. In T1D, beta cells are tagged as autoantigens and the progression of the disease relies heavily on deviation from the normative functions of the immune system [6].

1.3 Summary of the immune system and relevant components

While the immune system is incredibly complex, we simplify the system to encapsulate the most important parts of the immune system in terms of its effect on the pathogenesis of T1D and summarize the biology here (we should also note here that much of this is generalized and simplified beyond what much of the biological literature presents). For a more detailed overview of the immune system as it relates to this model, we suggest [7].

1.3.1 Dendritic Cells (DCs)

Dendritic cells (DCs) roam the bloodstream searching for antigens – defined as any substance that is categorized as foreign and potentially harmful to the organism. If a substance is recognized as an antigen by a DC, a pro-inflammatory response is initiated as the DC engulfs the cell. DCs that are known to incite an inflammatory response (turning on the immune system), the DC is classified as immunogenic. Conversely, DCs that are known to incite an anti-inflammatory response (turning off the immune system), the DC is classified as tolerogenic. Once an antigen is absorbed, however, the DC proceeds to present the antigen to the T-cell system, producing an immunogenic response from the T-cells.

1.3.2 T-cells (effector, memory, regulatory)

T-cells are heavily involved with the destruction of antigens that are identified by the immune system. This model relies on three distinct types of T-cells: effector, memory, and regulatory T-cells. Before being presented with an antigen from a DC, these T-cells wait to be activated before differentiating into their specific type. These T-cells are classified as being naive T-cells. Once the immune response has started, these naive T-cells become immunogenic (as opposed to tolerogenic) and begin to effectuate an immune response. Effector T-cells are responsible for the response to the specific antigen (in the case of T1D, the body's own beta cells). Regulatory T-cells (also known as Treg cells) are involved in slowing immune responses so it does not persist after the antigen has been sufficiently cleared from the body. During this downcycle, memory T-cells are produced, which 'remember' the encountered antigen. Should these memory T-cells encounter the specific antigen, these memory T-cells 'expand' into a large population of effector T-cells to execute the response.

1.3.3 Macrophages (activated, resting)

Macrophages are immune cells that do much of the cleaning at the cellular level by phagocytosing foreign substances and cellular debris. Should a macrophage encounter an antigen, the cell incites a pro-inflammatory response from nearby cells by producing cellular signals called cytokines. By mechanisms that are still being investigated, these 'resting' macrophages can become 'activated' by responding to biochemical signals that accelerate the natural rate of phagocytosis [8]. Thus, activated macrophages work at

higher rates than their resting counterparts, and are much more effective in phagocytosing the antigen.

1.4 The NOD mouse as a proxy for studying human T1D

Studying T1D diabetogenic mechanisms is difficult to do in humans for a number of reasons. First, because it has been long since proven that T1D is not solely a genetically inherited disease and must have an environmental factor in the epigenetics of its expression [9], it is difficult to identify human subjects that will develop the disease. Furthermore, it is not possible to perform controlled studies in human diseases whereby T1D is induced for obvious ethical and scientific reasons. Even if these studies were possible to conduct, the implementation of them would be both invasive and expensive. Scientists looking to study T1D have turned to various animal models to study the appropriately named disease of autoimmune diabetes. Non-obsese diabetic mice (NOD mice) are particularly good proxies for studying the lymphatic components of autoimmune diabetogenesis because of the ease of access to these mice, the relatively quick onset of the disease, and the similarities in NOD autoimmune diabetes genesis and human T1D. In particular, the autoantigens, the number of genes that predispose the patient to the disease, and the constituent immune elements that are involved with pathogenesis are all very comparable [10]. An interesting note of difference, however, is the relation of pathogenesis to sex: while in humans the disease is mostly equitable until puberty (where male subjects are slightly more prone) [11], NOD mice have a high estimate of probability at 90 % of autoimmune diabetes in females compared to a high estimate of 30 % in men for reasons that are still being investigated [12]. For a control organism, much literature uses the Balb/c mouse as a mode of comparison, so we use Balb/c biological factors to compare and contrast biomathematical phenomenons.

1.5 Apoptotic wave, secondary necrosis, and the apoptotic wave in NOD mice

Uninhibited growth in biological systems is unstainable. In the case that the body should find that a particular cell population is no longer needed or is too large in number, cells undergo a ‘programmed cell death‘ called

apoptosis that induces self-destruction [13] [14]. These apoptotic cells are generally cleared by the macrophages of the body as cellular debris. In the case that these apoptotic cell masses accumulate and are not cleared at a sufficient rate, they become necrotic. Necrosis is a type of cell death typically associated with tissue damage by foreign substances. As a result, necrotic cells release biochemical signals to incite an inflammatory response. However, apoptotic cells can become secondary necrotic cells—should the body's clearance system not clear apoptotic cells in a timely fashion, they too can incite an inflammatory response from the immune system. In neonatal NOD mice, several organs undergo an apoptotic wave whereby cell masses within these organs undergo mass destruction and reformation as the body develops and grows. These apoptotic waves have been linked to the autoimmune response that leads to the development of T1D in NOD mice [6] [14] [8].

Chapter 2

Mathematical Model: Full Description

2.1 Variables and parameters

We begin the exploration of the mathematical section by describing the different populations (variables) being studied and the mechanisms by which they are governed (parameters).

As previously compartment models lend themselves easily to mathematical modeling by ordinary differential equations (ODEs), they are also rather easily analysed by non-linear mixed effect modeling software and algorithms [15]. Previous work has been done to create systems of differential equations to model various systems and rates within the NOD mouse and the associated populations and rates associated with diabetogenesis [16] [17] [8] [5] [18] [19] [20] [2] [21], the combination and modification of which has created the model presented herein.

- [16]: models beta, insulin and glucose dynamics only, does not model apoptosis beta cell wave.
- [17] [8]: with Maree, writes thesis about the mathematical modelling of the Copenhagen theory.
  - includes macrophage activation rates, deactivation rates, influx / egress
  - one compartment: pancreas (volume estimated)
  - include necrotic and apoptotic beta cell dynamics
  - does not include healthy beta cells nor glucose and insulin dynamics

  - compares disease dynamics between Balb/c and NOD mice
  - s simple apoptotic wave
- [5] builds off of Topp 2000 and produces glucose, insulin, and beta cell dynamics for type 2 diabetes
- [18] develops dendritic cells and T-cells dynamics in the context of melanoma treatment.
- [19] develops mathematical model for T1D dynamics that involves T-cells and DC with time delay. They assume killing T-cells can remove healthy beta cells in the absence of Tregs (page 47)
- [20] [2] develops a mathematical model for T1D in a well-mixed pancreas compartment that involve macrophages, T-cells, beta cells, glucose and insulin dynamics.
- [21] developed a multi compartment mathematical model of the biological system (includes many trafficking parameters from de Pillis 2013)

2.1.1 Variables

Table 2.1 shows the 12 variables and their meanings.

Variable name	Units	Meaning	Initial Value
B	mg	Healthy β-cell population	300 mg
G	mg dl^{-1}	Glucose levels	100 mg dl^{-1}
I	μ U	Insulin levels	10 μ U
M	cells ml^{-1}	Macrophage population	$4.77 \cdot 10^5$ cells ml^{-1}
M_a	cells ml^{-1}	Active macrophage population	0 cells ml^{-1}
B_a	cells ml^{-1}	Apoptotic β-cell population	0 cells ml^{-1}
B_n	cells ml^{-1}	Necrotic β-cell population	0 cells ml^{-1}
D	cells ml^{-1}	Immunogenic DC population	0 cells ml^{-1}
tD	cells ml^{-1}	Tolerogenic DC population	0 cells ml^{-1}
E	cells ml^{-1}	Effector T-cell population	0 cells ml^{-1}
R	cells ml^{-1}	Regulatory T-cell population	0 cells ml^{-1}
Em	cells ml^{-1}	Memory T-cell population	0 cells ml^{-1}

Table 2.1 A list of the variables tracked within this model

2.1.2 Parameters

The following is a list of all parameters used in this model. For an explanation of the history, derivation, and justification of these parameters, see Appendix [to be filled in]

ID	Parameter	Balb/c	NOD	Units	Description	Citation	Range
1	s_E	1	1	$ml\ cell^{-1}$	Relative impact of effector T cells on β cell death	Estimated here	Estimate $[1, 100]$
2	s_R	36	36	$ml\ cell^{-1}$	Relative impact of regulatory T cells on β cell death	Estimated here	Estimate $[10, 100]$
3	D_{ss}	1×10^5	1×10^5	$cells\ ml^{-1}$	Steady state DC population	Estimated here	Estimate $[1000, 10^7]$
4	a_{Em}	0.01	0.01	d^{-1}	Death rate of memory T cells	[22]	Estimated $[10^{-3}, 0.1]$
5	η_{basal}	0.02	0.02	d^{-1}	Rate at which T cells eliminate β cells	Estimated here	$[0.01, 0.03]$
6	α_η	0.1	0.1	d^{-1}	Rate of change at which T cells eliminate β cells	Estimated here	$[0.1, 0.5]$
7	β_η	22	22	d^{-1}	Duration T cell effectiveness saturate maximum level	Estimated here	$[11, 30]$
8	f_M	$0.0623 \times 2 \times 10^{-5}$	$0.0623 \times 1 \times 10^{-5}$	$ml\ cells^{-1} d^{-1}$	Rate macrophages engulf necrotic ad apoptotic cells	Modified from [8]	$[0.1, 2] \times .0623 \times 10^{-5}$
9	f_{Ma}	$0.0623 \times 5 \times 10^{-5}$	$0.0623 \times 1 \times 10^{-5}$	$ml\ cell^{-1}\ d^{-1}$	Rate activated macrophages engulf necrotic and apoptotic β cells	[8]	$[0.1, 2] \times .0623 \times 10^{-5}$
10	J_{new}	3.2333×10^3	3.2333×10^3	$cells\ ml^{-1}\ d^{-1}$	Normal resting macrophage influx	[21]	$[3200, 3400]$
	J	$50,000$	$50,000$	$cells\ ml^{-1}\ d^{-1}$	Normal resting macrophage influx	[8]	$10^3 \times [48, 50]$
11	k	0.4	0.4	d^{-1}	Macrophages deactivation rate	[8]	Estimate $[0.1, 1]$
12	b	0.09	0.09	d^{-1}	Recruitment rate of macrophages by activated macrophages	[8]	Estimate $[0.01, 0.1]$
13	c	0.1	0.1	d^{-1}	Macrophages egress rate	[8]	$[0.07, 0.25]$
14	e_1	1×10^{-8}	1×10^{-8}	$cell^{-1} d^{-1}$	Effect of crowding on macrophages	[8]	$[10^{-8}, 10^{-6}]$
15	e_2	1×10^{-8}	1×10^{-8}	$cell^{-1} d^{-1}$	Effect of crowding on macrophages	[8]	$[10^{-8}, 10^{-6}]$
16	α_B	0.0334	0.0334	d^{-1}	Rate β cells are produced from glucose	[5]	$[0.031, 0.035]$
17	δ_B	0.0167	0.0167	d^{-1}	β cell death rate	[5]	$[1/62, 1/58]$
18	G_{hb}	90	90	$mg\ dl^{-1}$	Glucose level of half max β cell production	[5]	$[81, 100]$
19	R_0	864	864	$mg\ dl^{-1}$	Basal rate of glucose production	[16] [23] [24]	Estimate $[500, 1000]$

20	G_0	1.44	1.44	d^{-1}	Rate of glucose decay	[16] [23] [24]	Estimate $[0.1, 2]$
21	S_I	0.72	0.72	ml $\mu\ U^{-1}\ d^{-1}$	Rate of glucose elimination via insulin	[16] [24]	Estimate $[0.1, 1]$
22	σ_I	43.2	43.2	$\mu\ U\ ml^{-1}\ d^{-1}\ mg^{-1}$	Maximum rate of insulin production by β cells	[16] [23] [25]	Estimate $[30, 50]$
23	δ_I	432	432	d^{-1}	Rate of insulin decay	[16] [26] [23]	$[460, 576]$
24	G_I	$\sqrt{20000}$	$\sqrt{20000}$	$mg\ dl^{-1}$	Glucose level of half-max insulin production	[16] [25] [26]	Estimate $[\sqrt{10^2}, \sqrt{10^4}]$
25	Q_{panc}	0.194	0.194	ml	Volume of mouse pancreas	[27]	Estimate $[0.1, 0.5]$
26	b_{DE}	0.487×10^{-5}	0.487×10^{-5}	$ml\ cells^{-1} d^{-1}$	Rate of elimination of DC by effector T cells	[22] [18]	$[0.13 \times 10^{-6}, 0.6 \times 10^{-5}]$
27	b_{IR}	0.487×10^{-5}	0.487×10^{-5}	$ml\ cells^{-1} d^{-1}$	Rate of elimination of DC by regulatory T cells	[22] [18]	$[0.13 \times 10^{-6}, 0.6 \times 10^{-5}]$
28	a_E	0.1199	0.1199	d^{-1}	Rate of initial expansion of naive T cells into effector T cells	[22] [18]	Estimate $[0.1, 0.5]$
29	a_R	0.1199	0.1199	d^{-1}	Rate of initial expansion of naive T cells into regulatory T cells	[22] [18]	Estimate $[0.1, 0.5]$
30	T_{naive}	370	370	$cells\ ml^{-1}$	Density of naive T cells	[22] [18]	Fixed
31	b_P	12	12	d^{-1}	Maximal expansion rate of effector and regulatory T cells due to DC	[22]	$[10, 85]$
32	r_{am}	0.01	0.01	d^{-1}	Reversion rate of effector and regulatory T cells to memory T cells	[22]	$[0.4 \times 10^{-3}, 1.2]$
33	θ_D	2.12×10^5	2.12×10^5	d^{-1}	DC value for half maximal effector T cell expansion	[22] [18]	$[7.5 \times 10^2, 2.12 \times 10^5]$
34	d	0.5	0.5	d^{-1}	β cell rate of necrosis	[8]	$[0.5, 1]$
35	b_E	1×10^{-3}	1×10^{-3}	$ml\ d\ cells^{-1}$	Activation rate for effector T cells from memory T cells	[22]	Estimate $[10^{-4}, 10^{-2}]$
36	b_R	1×10^{-3}	1×10^{-3}	$ml\ d\ cells^{-1}$	Activation rate for regulatory T cells from memory T cells	same as b_E	Estimate $[10^{-4}, 10^{-2}]$
37	μ_{BP}	0.1	0.1	d^{-1}	DC and T cell emigration rate from blood to pancreas	[22] [18]	$[0.05, 0.5]$
38	μ_D	0.51	0.51	d^{-1}	DC and T cell emigration rate from pancreas to blood	[22] [18]	$[0.32, 2]$
39	f_D	1.71×10^{-7}	1.71×10^{-7}	$ml\ cells^{-1} d^{-1}$	Rate DC engulf β cells	MCMC method	Estimate $[10^{-6}, 10^{-5}] \times 5.49 \times 10^{-2}$

40	f_{tD}	1.19×10^{-6}	1.19×10^{-6}	$ml\ cells^{-1}d^{-1}$	Rate naive of tolerogenic DC engulf β cells	MCMC method	Estimate $[10^{-6}, 10^{-5}] \times 3.82 \times 10^{-1}$
41	μ_E	2×10^{-6}	2×10^{-6}	d^{-1}	Rate of effector T cell removal due to regulatory T cells	Estimated here	No range
42	μ_R	2×10^{-6}	2×10^{-6}	d^{-1}	Rate of regulatory T cell removal due to effector T cells	Estimated to be the same as μ_E	No range
43	μ_B	74.56	74.56	ml	DC emigration rate from blood to spleen	[22] [21]	[26.976, 74.56]
44	Q_{blood}	3	3	ml	Volume of blood compartment	[28] [29]	Fixed
45	μ^*_{SB}	0.012	0.012	d^{-1}	CTL migration rate from spleen to blood at equilibrium	[22] [18]	[0.012, 0.08]
46	μ^{normal}_{SB}	0.112	0.112	d^{-1}	normal CTL migration rate from spleen to blood	[22] [18]	[0.1, 100)
47	μ_{BSE}	0.022	0.022	d^{-1}	T cell immigration rate from blood to spleen	[22] [18]	[0.1, 100]
48	a_I	0.2310	0.2310	d^{-1}	Death rate of tolerogenic DC in the spleen	[22] [18]	[0.173, 0.346]
49	a_D	0.2310	0.2310	d^{-1}	Death rate of DC in the spleen	[22] [18]	[0.173, 0.346]
50	B_{conv}	2.59×10^5	2.59×10^5	$cells\ mg^{-1}$	β cells per milligram	[30]	Fixed
51	Q_{spleen}	0.1	0.1	ml	Volume of mouse spleen	[18]	Fixed
52	θ_{shut}	13.65	13.65	$cells\ ml^{-1}$	Threshold in DC density for half-max transfer rate from spleen to blood	[18]	[12.35, 13.65]

2.2 Mathematical model

Each of the equations that we have in this model correspond to a particular compartment and how each of the variables relate to each other through specific parameter values and identities in the different compartments. In this section, each ordinary differential equation is discussed in the context of each compartment in the model.

Spleen / Lymph Node Compartment

As discussed in the biology of this model, the population dynamics of the immune system is fundamental to the current understanding of the pathogenesis of autoimmune diabetes. Therefore, the proposed model includes

dynamics of these immune populations in the compartment that these immune cells are essentially produced in the context of the pathogenesis of T1D.

In regards to the spleen, it is important to discuss the populations of the two DC populations monitored (immunogenic and tolerogenic DCs) as well as the effector, regulatory, and memory T-cells here. All of these equations are modeled after equations produced in [18], which borrowed heavily from [22].

$$\frac{d}{dt}D_s = \mu_B \left(\frac{Q_{blood}}{Q_{spleen}}\right) D_{blood} - a_D D_s - b_{DE} D_s E_s \tag{2.1}$$

This equation represents the immunogenic population of dendritic cells in the spleen. All parameters of the form μ are parameters that govern the particular rate and trafficking of different immune cell populations into and out of a compartment. In this case, μ_B is a parameter used to denote the rate that immunogenic dendritic cells enter the spleen from the bloodstream. See the section on parameters for more information about their history, calculation, etc.

The first term represents the influx of DCs from the blood to the spleen parameter multiplied by a conversion factor to account for the volume of the compartments multiplied by the variable that represents the population of immunogenic DCs in the bloodstream. This accounts for the positive change in the number of immunogenic DCs in the blood. The negative change in this number comes from the second term (the death rate of the DCs in the spleen) and the third term (dendritic cells being eliminated by T-cells).

Similarly, the tolerogenic DC population is modeled by a nearly identical equation:

$$\frac{d}{dt}D_s = \mu_B \left(\frac{Q_{blood}}{Q_{spleen}}\right) tD_b - a_I tD_s - b_{IR} tD_s R_s \tag{2.2}$$

Apart from the different population being modeled using different variables, the second and third terms are modified with the appropriate death and elimination rate parameters, respectively.

T-cells in the spleen have a more complicated modelling process. First, studies have shown that DC density within the spleen is critical when it

comes to allowing T-cells to leave the spleen [31], [32]. This is often called a gating or trapping effect, and was modelled effectively by [22] by the following equation:

$$\mu_{SB}(DC) = \mu^{*}_{SB} + \frac{\mu^{normal}_{SB} - \mu^{*}_{SB}}{1 + \frac{DC}{\theta_{shut}}} \tag{2.3}$$

$\mu_{SB}(DC)$ is a function of the dendritic cell population, where θ_{shut} represents a DC threshold density, and the numerator of the fraction is the difference of CTL normal migration rates and DC-reduced CTL migration rates.

Second, T-cells go through various forms and rates of differentiation, activation, and death that involve other cell populations.

The following equation represents the differential equation for effector T-cells in the spleen:

$$\frac{d}{dt}E_s = \mu BSE\left(\frac{Qblood}{Q_{spleen}}\right)E_b - \mu SB(Ds)E_s + b_E D_s Em_s + a_E\left(\frac{T_{naive}}{Q_{spleen}} - E_s\right) - \mu_e E_s R_s - r_{am}E_s + b_p\frac{D_s E_s}{\theta_D + D_s} \tag{2.4}$$

The first term is similar to the first terms seen in the equations for DC populations. The second term represents the rate of immigrating from the spleen to the blood, which is altered by the gating/trapping function described above. Effector T-cells are activated from memory T-cells at a rate of $b_E$and is dependent on the population of immunogenic DC population in the spleen and the memory T-cell population in the spleen (third term). Naive T-cells expand to effector T-cells at rate a_E, which is dependent on the population density of naive T-cells that produce effector and regulatory T-cells minus the effector T-cell population density in the spleen (fourth term). Effector T-cells are removed from competition due to other effector and regulatory T-cells in the spleen (fifth term). Effector T-cells revert back to memory cells at a rate r_{am} (sixth term), but are activated due to the presence of dendritic cells (seventh term).

The other T-cell populations in the spleen (R_s, regulatory, and Em_s, memory) are modeled by similar equations:

$$\frac{d}{dt}E_s = \mu BSE\left(\frac{Qblood}{Q_{spleen}}\right)E_b - \mu SB(Ds)E_s + b_E D_s Em_s + a_E(\frac{T_{naive}}{Q_{spleen}} - E_s) - \mu_e E_s R_s - r_{am}E_s + b_p\frac{D_s E_s}{\theta_D + D_s} \tag{2.5}$$

The only necessary changes for the regulatory T-cell population equation are the population being modelled, trafficking parameter rates, and the inclusion of tolerogenic dendritic cells being the specific population gating the migration of regulatory T-cells leaving the spleen.

$$\frac{d}{dt}Em_s = \mu_{BSE}\left(\frac{Q_{blood}}{Q_{spleen}}\right)Em_b - \mu_{SB}\left(D_s\right)Em_s + r_{am}\left(E_s + R_s\right) - \left(a_{Em} + b_E D_s + b_R t D_s\right)Em_s \tag{2.6}$$

Again, memory T-cell populations in the spleen can be modelled similarly. The gating specific population of dendritic cells for memory T-cells are the immunogenic dendritic cells, and the rate of conversion of other T-cell equations back to memory cells contributes positively to the population size in this case. On the other hand, T-cell death rate, as well as activation and expansion rates of regulatory and effector T-cells due to the presence of immunogenic and tolerogenic DC populations, subtract from the overall population size of the memory cells in the spleen.

2.2.1 Blood / bloodstream compartment

The bloodstream is an important compartment to model in terms of various immune cell populations travelling between compartments and being present. Again, we present equations for DC populations and T-cell populations being modelled, with the addition of macrophage populations within the bloodstream.

$$\frac{d}{dt}D_b = -\mu_B D_b + \mu_{PB}\left(\frac{Q_{panc}}{Q_{blood}}\right)D_{panc} \tag{2.7}$$

We begin again with the immunogenic dendritic cell population. Each of these populations have specific parameters to represent the rate of trafficking, and are changed as necessary throughout the equations. The first term represents the flow of these DCs out of the bloodstream into the pancreas. The second term represents the flow of these DCs out of the pancreas and back into the bloodstream, with the addition of a scaling factor of the volume of

the pancreas to the volume of the bloodstream to account for the differences in volume.

Similarly, tolerogenic dendritic cell populations are modeled identically and incorporate various change in parameters and variables where necessary:

$$\frac{d}{dt}tD_b = -\mu_B tD_b + \mu_{PB}\left(\frac{Q_{panc}}{Q_{blood}}\right)tD_{panc} \tag{2.8}$$

T-cell populations in the blood are modelled almost identically here as well, with different parameters and variables as necessary:

$$\frac{d}{dt}E_b = \mu_{SB}\left(D_s\right)\left(\frac{Q_{spleen}}{Q_{blood}}\right)E_s + \mu_{PB}\left(\frac{Q_{panc}}{Q_{blood}}\right)E_{panc} - \left(\mu_{BP} + \mu_{BSE}\right)E_b \tag{2.9}$$

$$\frac{d}{dt}R_b = \mu_{SB}\left(tD_s\right)\left(\frac{Q_{spleen}}{Q_{blood}}\right)R_s + \mu_{PB}\left(\frac{Q_{panc}}{Q_{blood}}\right)R_{panc} - \left(\mu_{BP} + \mu_{\ BSE}\right)R_b \tag{2.10}$$

$$\frac{d}{dt}Em_b = \mu_{SB}\left(D_s\right)\left(\frac{Q_{spleen}}{Q_{blood}}\right)Em_s + \mu_{PB}\left(\frac{Q_{panc}}{Q_{blood}}\right)Em_{panc} - \left(\mu_{BP} + \mu_{BSE}\right)Em_b \tag{2.11}$$

The first term represents the influx of the T-cells into the bloodstream dependent on their specific gating DC population. The second term represents the influx of T-cells into the bloodstream from the pancreas dependent on the T-cell populations within the pancreas. The third term represents the outflow of various T-cell populations out of the bloodstream and into the pancreas or the spleen.

Macrophages within the bloodstream are a relatively simple population to model. While this equation is a newly designed one for the purposes of this multi-compartment model, the initial modelling of macrophage population dynamics come from [17] and [8], and is modified from that:

$$\frac{d}{dt}M_b = -J_{new} + c\left(\frac{Q_{panc}}{Q_{blood}}\right)M \tag{2.12}$$

The first term represents the influx of macrophages out of the bloodstream and into the pancreas, while the second term represents the egress rate from the pancreas into the bloodstream.

2.2.2 Pancreas compartment

We begin again with immune system cell populations within the pancreas. As dendritic cell populations in the pancreas have slightly different dynamics due to interacting with beta cells, these equations become slightly more complex than previous forms of DC, T-cell, and macrophage dynamic equations.

Again, beginning with the immunogenic DC population, we have:

$$\frac{d}{dt}D_{panc} = f_{tD}B_n(D_{ss} - D_{panc} - tD_{panc}) + f_{tD}B_n tD_{panc} - \mu_{PB}D_{panc} \quad (2.13)$$

The third term is familiar: it is the decrease in immunogenic DC populations from the pancreas to the bloodstream. The first and second terms are more nuanced. Starting with the second term, the immunogenic DC population is increased when tolerogenic DCs encounter necrotic beta-cells. Finally, the first term represents the phenomenon by which immunogenic DC populations are increased at a rate proportional to the rate at which immunogenic DCs engulf necrotic beta cells with respect to the remaining DCs (i.e., the steady state dendritic cell population minus the tolerogenic and immunogenic cell populations).

Tolerogenic DC populations are modelled similarly:

$$\frac{d}{dt}D_{panc} = f_{tD}B_a(D_{ss} - D_{panc} - tD_{panc}) - f_{tD}B_n tD_{panc} - \mu_{PB}tD_{panc} \quad (2.14)$$

The differences between this first and second DC equation arise from the fact that immunogenic DCs, when encountering an apoptotic cell, revert back to being tolerogenic, increasing the population. Additionally, as more necrotic beta cells are encountered by tolerogenic DCs, these tolerogenic DCs change to being immunogenic, thus increasing the immunogenic population and decreasing the tolerogenic populations.

T-cells in the pancreas, again, are modelled very similarly. The first term of each of the following equations represents the volume-scaled influx of the T-cell population from the bloodstream into the pancreas and the second term represents the migration from the pancreas back into the bloodstream.

$$\frac{d}{dt}E_{panc} = \mu_{BP}E_b(\frac{Q_{blood}}{Q_{panc}})\mu_{PB}E_{panc} \tag{2.15}$$

$$\frac{d}{dt}R_{panc} = \mu_{BP}R_b(\frac{Q_{blood}}{Q_{panc}})\mu_{PB}R_{panc} \tag{2.16}$$

$$\frac{d}{dt}Em_{panc} = \mu_{BP}Em_b(\frac{Q_{blood}}{Q_{panc}})\mu_{PB}Em_{panc} \tag{2.17}$$

Macrophages in the pancreas are divided into two broad categories: resting and activated macrophages. The rates at which beta cells are engulfed by macrophages not only differ by species of mice, but also by whether or not these macrophages are activated or not. By a mechanism that is not entirely understood, resting macrophages when provided with a sufficient amount of presented antigen will become activated, engulfing the antigen at much faster rates. In any case, we present here a simplified analogue of this activation and deactivation process with the resting macrophage population and activated macrophage population.

The change in resting macrophage population within the pancreas are:

$$\frac{d}{dt}M = J_{new}(\frac{Q_{blood}}{Q_{panc}}) + (k+b)M_a cMf_M MB_a f_M MB_n e_1 M(M+M_a) \tag{2.18}$$

The first term represents the volume-scaled resting macrophage influx into the pancreas. The second term represents the activated macrophage-dependent increase in resting macrophages due to deactivation of the activated macrophages as well as the generalized recruitment of resting macrophages by the activated macrophage population. The third term represents the generalized egress rate out of the pancreas, decreasing the resting macrophage population size. Additionally, encountering necrotic or apoptotic beta cell populations decreases the resting macrophage population size within the population as it leaves or becomes activated. Finally, the sixth term represents the biological constraint that the total macrophage density cannot exceed a certain cell density (as the parameter e_1 represents an anti-crowding effect).

Similarly, the activated macrophage population is modelled as the following:

$$\frac{d}{dt}M_a = f_M MB_a + f_M MB_n - kM_a - e_2 M_a(M + M_a) \tag{2.19}$$

When resting macrophage populations encounter apoptotic and necrotic beta cells, the activated macrophage populations increase as these resting macrophages become activated. The third term represents the deactivation rate of the activated macrophages, and the last term as before is the biological macrophage density constraint and includes an anti-crowding effect.

The remaining model of the pancreas compartment includes dynamics more typically associated with general diabetogenesis: beta cell population, glucose levels, and insulin levels. In regards to the modelling of the healthy beta cell population, several nested functions are involved that will be described now.

Glucose levels are known to be related to healthy beta-cell growth, and beta-cell growth is maximized when glucose levels are at the baseline level (indicating homeostasis is key for beta-cell growth). This function comes from [5]. It is modelled by the Hill function:

$$K1(G) = \frac{G^2}{G^2 + G_{hb}^2} \tag{2.20}$$

Secondly, T-cells eliminate beta-cells at different rates dependent on the type of T-cell the beta-cell is eliminated by. This function comes from [19]. This second nested function is modelled as:

$$K2(E_{panc}, R_{panc}) = \frac{(s_E E_{panc})^2}{1 + (s_E E_{panc})^2 + (s_R R_{panc})^2} \tag{2.21}$$

Finally, the apoptotic wave that initially induces major beta-cell death is incorporated into the population dynamics of healthy beta-cell population decline. The following function is a modified version from [17] and [8].

$$W(B, t) = 0.1Be^{(\frac{t9}{9})^2} \tag{2.22}$$

With all of these nested functions defined, the differential equation for healthy beta-cells within the pancreas is the following:

$$\frac{d}{dt}B = \alpha_B K_1(G)\, B \;\; \delta_B B \;\; W(B, t) \;\; \eta K_2\left(E_{panc},\, R_{panc}\right) B \tag{2.23}$$

The first term represents beta-cell growth incited by glucose levels. The second term represents the non-specific death of beta-cells that occurs. The third and fourth term respectively decrease the healthy beta-cell population by the apoptotic wave and the targeting of the healthy beta-cells by T-cells.

The apoptotic beta-cell population is modelled by the following equation:

$$\frac{d}{dt}B_a = \tilde{W}(B,t)+\tilde{\eta}K2(E_{panc},R_{panc})B-f_M M B_a-f_{Ma}M_a B_a-dB_a+\tilde{\delta}_B B-f_{tD}(D_{ss}-D_{panc})B_a-f_D D_{panc}B_a \tag{2.24}$$

The inclusion of a tilde (above a function or parameter in the above equation is used to denote a multiplication factor of $\frac{B_{conv}}{Q_{panc}}$. As the apoptotic wave occurs, the number of apoptotic beta-cells increase (first term). Similarly, as T-cell mediated destruction of healthy beta-cells occurs, the apoptotic population increases (second term). It is decreased, however, by the resting macrophage populations and activated macrophage populations phagocytosing the apoptotic cells (third and fourth term). It is decreased by the transition from apoptosis to necrotic beta-cells (fifth term) and increased by natural beta-cell death. Finally, it is decreased by the rates of engulfment by currently active and recruited DC populations within the pancreas.

Necrotic beta cells are simpler to model:

$$\frac{d}{dt}B_n = dB_a f_M M B_n f_{Ma}M_a B_n f_{tD}(D_{ss}D_{panc})B_n f_D D_{panc}B_n \tag{2.25}$$

Necrotic beta cell populations are increased by secondary necrosis (first term), but are decreased as macrophages and dendritic cells phagocytize and clear necrotic beta-cells.

Finally, glucose and insulin dynamics are pulled primarily from [16] and [5]. Glucose is modeled by the following equation:

$$\frac{d}{dt}G = R_0(G_0 + S_I I)G \tag{2.26}$$

The first term represents basal glucose production, while the second term represents the decrease in glucose due to natural glucose decay and insulin

production.

Insulin is modeled by the following equation:

$$\frac{d}{dt}I = \sigma_I \frac{G^2}{G^2 + GI^2} B\delta_I I \tag{2.27}$$

The first term represents the beta-cell population dependent rate of insulin production, while the second term represents the natural decay of insulin.

2.3 Mathematical theory behind parameter sensitivity

The idea behind creating a compartment model simulating the pathogenesis of type 1 diabetes is to understand what is most sensitive to the disease's progression. In such: understanding what parameters are most sensitive to change is a conduit for finding the most direct component to potentially target within the pathogenesis of type 1 diabetes.

We describe here the mathematical theory necessary to understand the algorithims we present to perform parameter sensitivity

2.3.1 Mathematical description of the theory behind LHS (and potential applications)

Latin hypercube sampling (LHS) is a statistical method to generate sample of parameter values from multi-dimensional distribution. In brief, LHS partition each parameter range into n subintervals with equal probability which are then sampled independently without replacement. A model output of interest is simulated for each parameter combination. LHS has proven to be more efficient to estimate the average model output with fewer parameter combination than simple random sampling. A robust overview of the theory behind Latin hypercube sampling can be found within [33].

2.3.2 Theory behind nonlinear mixed effect modeling

The nonlinear mixed effect modeling has been widely used for it can characterized first the biological phenomena observed for each individual and second the variability seen between individuals, which is a common challenge in modeling biological system. The previous result from [2] has shown that the model can impressively predict the average glucose dynamics seen

in NOD mice. Our goal of applying the non-linear mixed effect model is to capture the intervariability in glucose level in each individual mouse seen in experimental data.

Now, let us assume that each individual dynamic can be represented by the same model but not necessarily the exact same parameter values. Thus, each individual i has a corresponding set of parameters ϕ_i, randomly selected from a distribution p_ϕ. The distribution p_ϕ has mean θ (population parameter) and standard deviation ω (random effect). In this context the model is the joint distribution of the observation and individual parameters:

$$p(y, \phi, \theta, t) = p(y|\phi, t)p(\phi, \theta)$$

where ϕ represents the individual parameters where $p(\phi, \theta)$ represents the parametric distribution of individual parameters where $p(y|\phi, t)$ represents the distribution of observation y given parameter ϕ

Briefly, our goal is to infer the mean and standard deviation of the distribution, where the individual parameters will be sampled from using a Stochastic Approximation Expectation Maximization (SAEM) algorithm from the existing data. From here, we are able to more effectively fit the model and parameter values to the data. Mixed-effect modeling is particularly helpful when the data dealt with has very distinct differences depending on the categorical data it is grouped with. While simple data sets have the potential to be modified in a rather straightforward fashion through linear mixed effect modelling, should the data take on exponential growth or decay, a sigmoid shape, an asymptotic location, or other not as easily modelled data sets, nonlinear mixed effects modelling can be an appropriate tool. In particular, nonlinear mixed effect modelling has been noted to be especially powerful with mechanistic compartment models, the parameters of which are seldom linear.

The nonlinear mixed effect modelling system typically relies on the modification of covariates based on iterated conditional mode (ICM) algorithms, a set of algorithms designed to optimize Markov Random Fields. These algorithms are based on the assumption that data local to a datum are relatively close by quantitatively, and the assumption that data are independent of other data points (i.e. no data point influences another data point) [34]. Further, by using a structural model, equations that mitigate error in the measurement and parameter ranges can be formed by aggregating the equations that have been formed through these predictive algorithms.

2.3.3 EFAST and first-order sensitivity index

eFAST, developed by [35] is a variance decomposition method that identifies the contribution of the input parameter X the total output variation. The sampling procedure implemented in eFAST defines a sinusoidal function of a particular frequency for each input parameter (search curve), $X_i = f(j), j = 1, 2, \ldots, N_S$ (where N_S is the sample size). Due to the symmetry property of sinusoidal functions, the eFAST algorithm is repeated N_R times by introducing a random phase shift to each sinusoidal function. The model output of interest is then simulated for each parameter combination.

From here, the algorithm determines what fraction of this variance can be explained by the variation in each input parameter using Fourier analysis. eFAST calculates both first-order and total-order sensitivity indices for each input parameter. The first order sensitivity measures the main contribution of the parameter input X to the output variance and the total order sensitivity index accounts for both the main and higher order effect contribution to the output variance due to interaction of other parameters with the input parameter X. This index is invaluable in analyses of the model, as it can prove the significance (or insignifiance) of particular input components. In medical applications, this can be applied to what parts of a system should be targeted for optimal treatment [36].

[35] proposed the use dummy parameter to determine the significance of the sensitivity indices for each parameter input. Dummy parameter neither appear in the model nor affect the model in any way. Therefore any parameters with sensitivity indexes equal or less than that of the dummy parameter should be considered insignificant to the model. A two sample t-test on data generated by resampling eFAST search curve is used to compare the distribution of the first order (S_i) and total order (S_{Ti}) sensitivity index with S_{dummy} and $S_{T_{dummy}}$.

Chapter 3

Parameters

The following chapter is a description of all parameters included in this model. Details on how these parameters were determined and the origin of their values are found here. In addition, citations in the parameter table in the previous section refer to further papers to read beyond the history presented here.

1. s_E

   This parameter represents the relative impact that effector T-cells have on beta-cell death. The mathematical modelling theory behind this is from [19], which is incorporated into a differential equation describing beta-cell population dynamics. This parameter was estimated here through data-fitting completed in the forthcoming [2].

2. s_R

   This parameter represents the relative impact that regulatory T-cells have on beta-cell death. See s_E for a description of the history of how this parameter was determined. The mathematical modelling theory behind this is from [19], which is incorporated into a differential equation describing beta-cell population dynamics. This parameter was estimated here through data-fitting completed in the forthcoming [2].

3. D_{ss}

This parameter represents the parameter that describes numerically the steady-state dendritic cell population.

4. a_{Em}

   This parameter represents the memory T-cell death rate. This value was originally reported in [22] within an equation defining the half-life of resting memory cells. This equation is modelled in the following way:

   where t^E is the half-life of resting memory T-cells

   where α_{Em} is the decay constant (what our model defines as a_{Em})

   then:

   $\alpha_{Em} = \frac{ln\ 2}{t^E}$

   [22] measured the half-life of these resting 'memory'T-cells, and from there the decay constant is easily computed.

5. η_{basal}

   This parameter represents the rate at which T-cells eliminate beta-cells. In the forthcoming paper by [2], this parameter was estimated to be around 0.02 as the range (where this parameter was estimated to be effective was between 0.01 and 0.025). Based on the biological data that seems to indicate that the effectiveness of T-cell mediated beta-cell destruction follows an inverse tangent function, this parameter was created by [2] and values were chosen ad-hoc. Further investigation needs to be carried out (potentially using time-series data from [37] or [38]) in order to figure out a biologically accurate range of values.

6. α_η

   This parameter represents the rate of change at which T-cells eliminate beta cells. This was parameter was estimated from the data used from [38]. Based on the biological data that seems to indicate that the effectiveness of T-cell mediated beta-cell destruction follows an inverse tangent

function, this parameter was created by [2]and values were chosen ad-hoc. This paper includes analysis as to what values of this parameter make biological sense.

7. β_η

   This parameter represents the duration of T-cell effectiveness saturation at maximum levels. This was parameter was estimated from the data used from [38]. Based on the biological data that seems to indicate that the effectiveness of T-cell mediated beta-cell destruction follows an inverse tangent function, this parameter was created by [2]and values were chosen ad-hoc. This paper includes analysis as to what values of this parameter make biological sense.

8. f_M

   This parameter represents the basal phagocytosis rate of macrophages. Note that there are two different values in this paper: one for the Balb/c mouse and one for the NOD mouse. [8] presents phagocytosis rates done through *in vitro* experiments and data fitting. Interpreting rate factors as multipliers for the baseline rate of engulfment, Balb/c mice resting macrophages tended to have between 1.5 and 2 times as fast a basal phagocytosis rate as NOD mice macrophages did. However, note that the current model has a new scaling factor: because [8]does not include dendritic cells within the context of the model, modifications were necessary to the original engulfment rates.

9. f_{Ma}

   This parameter represents the activated phagocytosis rate of macrophages. Note that there are two different values in this paper: one for the Balb/c mouse and one for the NOD mouse. [8] presents phagocytosis rates done through *in vitro* experiments and data fitting. The data presented that the activated macrophages in Balb/c mice had a rate of 3 to 6 times as fast as activated macrophages in NOD mice. However, note that the current model has a new scaling factor: because [8]doesn not include dendritic cells within the context of the model, modifications were necessary to the original engulfment rates.

10. J_{new}

    This parameter is a modified version of the parameter J (seen in earlier papers) that represents the influx of macrophages into the system. Because earlier versions of this model used only a single compartment of the pancreas, the influx for the multi-compartment system must be reduced proportionally to the volume of area that it is now entering through in order to retain accuracy. Therefore, J, the original parameter value calculated for the normal influx rate of macrophages into the pancreas, is multiplied by a ratio of the ratio of the volume of the pancreas to the volume of the bloodstream to assume that the macrophages start in the bloodstream and enter the pancreas at this modified parameter rate.

    $$J_{new} = J \cdot \frac{Q_{panc}}{Q_{blood}}$$

    The macrophage influx rate was originally computed by ([17] 2005). Using [28] and the *in vivo* experimental data of finding 20 mL to the total volume of mouse tissue, the total number of macrophages in the body to be 10^6 cells, and the randoming leaving of the macrophages from the blood to be 0.04 per hour, [17] calculates J as the following:

    $$J = (1 \times 10^6 cells)(0.04h^1)\frac{1}{20ml} \approx 2000\ cells\ ml^1\ hr^1$$

    When multiplying this by 24 hours to get the daily rate, this comes out to be around 48,000 cells per ml per day. To get the J_{new} we have in this model, we multiply this parameter by the proportional scaling factor.

11. k

    This parameter represents the net rate of macrophage deactivation. This value comes from a study performed by [39], where a mathematical model was developed to study the effects of tuberculosis on the immune system in humans. [8]and [17] look at various estimates for this macrophage deactivation rate and found the value that seemed to not only be biologically accurate but allowed congruency in the mathematical model being developed.

12. b

This parameter represents the macrophage recruitment rate by the activated macrophage population. In [8], ϕ is the fraction of activated macrophages to total macrophages, 1ϕ is the fraction of resting macrophages to total macrophages. This is the saddle point of 'chronic' infection, where the immune system is just getting ready to mount a response:

$J + b\phi c(1\phi)(M + M_a) = 0$

Solving for b:

$b = \frac{J+c(M+M_a)(1\phi)}{\phi(M+M_a)}$

Then, assuming reasonable values for each of the remaining populations:

$\phi = 0.5$ $M_{tot} = 10^7$ $J = 48,000$ (from the original single-compartment model that [17] and [8])

$b = 0.09$

While there are other assumptions and estimations that could be made, this is a stable and trusted value, so this model continues to use this value. However, we do note that other values for b could be used as well (by adjusting, for example, the total number of macrophages or ϕ).

13. c

This parameter represents the macrophage egress rate. Macrophage turnover rate is largely unknown, but was studied in [40] and is thought to be somewhere between 3.8 and 14.9 days. [17] rounded these numbers to have a turnover range of between 4 and 15 days, which in turn makes the egress constant equal to:

$c = \frac{1}{turnover\ time\ in\ days}$

For simplicity's sake, [17]/ [8]assumed the turnover time in days to be 10 days, yielding a c value of 0.1

14. e_1

This parameter represents the anti-crowding effect for the resting macrophage population. As stated in [17] and [8], there can only be around 10^8 cells per ml in terms of the total number of macrophages. In order to make sure the model does not overrepresent the number of cells that can fit, [8]included these terms in order to prevent overestimates in the cell density equations. Note that e_1 and e_2 are estimated to be around the same.

15. e_2

This parameter represents the anti-crowding effect for the active macrophage population. As stated in [17] and [8], there can only be around 10^8 cells per ml in terms of the total number of macrophages. In order to make sure the model does not overrepresent the number of cells that can fit, [8] included these terms in order to prevent overestimates in the cell density equations. Note that e_1 and e_2 are estimated to be around the same.

16. α_B

This parameter represents the growth rate of beta cells. This was derived from glucose dynamics written in [5], as the following:

let k_b be the beta cell turnover rate of $1/60$ (per day (value taken from [41]
let G_0 be the baseline glucose level of the mouse (reported as 5.0 mM, which converts to 90 mg/d) (value taken from
[41]) let G_{hb} be the half-maximal glucose stimulation of beta cell replication.
[41] shows a Hill function that shows that optimal pancreatic function happens when blood sugar is at the healthy baseline (5.0 mM)

Then, beta cell growth rate can be defined as the following: $\frac{k_b(G_0^2+G_{HB})}{G_0^2}$

While the number we give for this is 90 mg/dl, [42] found that this number was likely in the range from 81 to 100 mg/dl (4.5 to 5.5 mM). Further, this postulates that beta-cell growth and function is largely dependent on the homeostasis of the blood glucose levels within the organisms. This is proven by the sigmoid function provided in [16], that describes this phenomenon in greater detail.

17. δ_B

This parameter represents the rate at which beta-cells die. [41] cites beta-cell turnover rate to be in the range of 60 days, which gives a beta-cell death rate to be around $\frac{1}{60}$.

18. G_{hb}

This parameter represents the glucose level of half-maximal beta-cell production. As this was previously described in the discussion of α_B, this is related to the fact that beta-cell production and growth is maximized at healthy (normalized) glycemia ranges. While the number we give for this is 90 mg/dl, [42] found that this number was likely in the range from 81 to 100 mg/dl (4.5 to 5.5 mM).

Using the other parameters we have, a reverse calculation of G_{hb} could be found as the following:

$$G_{hb} = \pm\sqrt{\frac{h_b G_0^2 k_b G_0^2}{k_b}}$$

19. R_0

This parameter represents the basal rate of glucose production. [16] compiles a list of equations to describe the dynamics of glucose, insulin, and beta cells in mathematical diabetes modelling. [16] defines R_0 as the following: where P_0 is the rate of glucose production where U_0 is the rate of glucose uptake $R_0 = P_0 R_0$

Using the dynamics presented in [16], this parameter value was calculated in [16].

20. G_0

This parameter represents the rate of glucose decay. [16] compiles a list of equations to describe the dynamics of glucose, insulin, and beta cells in mathematical diabetes modelling. Here, [16] defines the rate of glucose decay, E_{G0} as the following: where E_{G0P} is the glucose effectiveness of production at zero insulin where E_{G0U} is the glucose effectiveness of uptake at zero insulint zero $E_{G0} = E_{G0P} + E_{G0U} + E_{G0U} + E_{G0U}$

Using the dynamics presented in [16], this parameter value was calculated in [16].

21. S_I

    This parameter represents the insulin rate of glucose elimination. [16] compiles a list of equations to describe the dynamics of glucose, insulin, and beta cells in mathematical diabetes modelling. Here, [16] defines the insulin rate of glucose elimination as the following:

    where S_{IP} is the insulin sensitivity to glucose production

    where S_{IU} is the insulin sensitivity to glucose uptake

    then:

    $S_I = S_{IP} + S_{IU}$

    Using the dynamics presented in [16], this parameter value was calculated in [16].

22. σ_I

    This parameter represents the maximum rate of insulin production by beta-cells. [16] compiles a list of equations to describe the dynamics of glucose, insulin, and beta cells in mathematical diabetes modelling. Here, [16] defines this parameter to be a part of a differential equation describing the derivative of blood insulin concentrations (I) with respect to time:

    where I represents blood insulin concentrations

    k is a clearance constant which represents the combined insulin uptake at liver, kidneys, and insulin receptors

    β is the mass of pancreatic beta cells

G represents the concentration of glucose in the blood

t is time measured

σ represents the maximal secretion rate of the beta cells

$G^2/(\alpha + G^2)$ represents a Hill function with coefficient 2, ranging from 0 to 1 and reaches the half maximal rate

then:

$\frac{dI}{dt} = \frac{\beta\sigma G^2}{\alpha+G^2}kI$
Solving for σ (what we define as σ_I) and using the dynamics presented in [16], this parameter value was calculated in [16].

23. δ_I

This parameter represents the rate of insulin decay. [16] compiles a list of equations to describe the dynamics of glucose, insulin, and beta cells in mathematical diabetes modelling. Here, [16] defines this parameter to be a part of a differential equation describing the derivative of blood insulin concentrations (I) with respect to time: where I represents blood insulin concentrations

k is a clearance constant which represents the combined insulin uptake at liver, kidneys, and insulin receptors

β is the mass of pancreatic beta cells

G represents the concentration of glucose in the blood

t is time measured

σ represents the maximal secretion rate of the beta cells

$G^2/(\alpha + G^2)$ represents a Hill function with coefficient 2, ranging from 0 to 1 and reaches the half maximal rate

where we define δ_I to be parameter k in [16]

then:

$\frac{dI}{dt} = \frac{\beta\sigma G^2}{\alpha+G^2}kI$
Solving for k (what we define as δ_I) and using the dynamics presented in [16], this parameter value was calculated in [16].

24. GI

This parameter represents the glucose level of half-max insulin production. [16] compiles a list of equations to describe the dynamics of glucose, insulin, and beta cells in mathematical diabetes modelling. Here, [16] defines this parameter to be a part of a differential equation describing the derivative of blood insulin concentrations I with respect to time:

where I represents blood insulin concentrations

k is a clearance constant which represents the combined insulin uptake at liver, kidneys, and insulin receptors

β is the mass of pancreatic beta cells

G represents the concentration of glucose in the blood

t is time measured

σ represents the maximal secretion rate of the beta cells

$G^2/(\alpha + G^2)$ represents a Hill function with coefficient 2, ranging from 0 to 1 and reaches the half maximal rate

our parameter GI is defined as the square root of α

then:

$\frac{dI}{dt} = \frac{\beta\sigma G^2}{\alpha+G^2}kI$

Using the dynamics presented in [16], this parameter value was calculated in [16].

25. Q_{panc}

This parameter represents the volume of the pancreas of the *in silico* mice for this mathematical model. This came from [27]G, which explored a way of estimating pancreatic volume of mice using MRI (such that the determination of this volume would not invasive and disruptive to experiments). Given the details that know regarding the age and body weight of the mice that we are simulating, the value given here will be given as a constant 0.194 ml.

26. b_{DE}

This parameter represents the dendritic cell elimination rate by effector T-cells. This parameter comes from [22]. [22] makes the large assumption that both b_{DE} and b_{IR} have the same value, and were fitted to data collected within their own study. [22] fit these parameters to data collected from *in vivo* experiments carried out in conjunction with compiling mathematical models to fit to the data.

27. b_{IR}

This parameter represents the dendritic cell elimination rate by regulatory T-cells. This parameter comes from [22]. [22] makes the large assumption that both b_{DE} and b_{IR} have the same value, and were fitted to data collected within their own study. [22] fit these parameters to data collected from *in vivo* experiments carried out in conjunction with compiling mathematical models to fit to the data.

28. a_E

This parameter represents the rate of initial expansion of naive T-cells to effector T-cells. [22] fit parameters to data collected from *in vivo*

experiments carried out in conjunction with compiling mathematical models to fit to the data. For this parameter specifically, [22] reports the half-life of activated T-cells ($t^E_{1/2}$) as 5.78 days. a_E is the decay constant of this exponential decay function, and is calculated as such:

$a_E = \frac{ln\ 2}{t^E_{1/2}}$

Because the reported half-life in [22] is 5.78 days, the decay constant (the parameter we are trying to calculate here) is .1199. Since [22] reports this half-life as the general half-life of activated T-cells, it is assumed that $a_E = a_R$.

29. a_R

    This parameter represents the rate of initial expansion of naive T-cells to regulatory T-cells. [22] fit parameters to data collected from *in vivo* experiments carried out in conjunction with compiling mathematical models to fit to the data. For this parameter specifically, [22] reports the half-life of activated T-cells ($t^E_{1/2}$) as 5.78 days. a_R is the decay constant of this exponential decay function, and is calculated as such:

    $a_R = \frac{ln\ 2}{t^E_{1/2}}$

    Because the reported half-life in [22] is 5.78 days, the decay constant (the parameter we are trying to calculate here) is .1199. Since [22] reports this half-life as the general half-life of activated T-cells, it is assumed that $a_E = a_R$.

30. T_{naive}

    This parameter represents the number of naive T-cells contributing to initial production of effector and regulatory T-cells. This value was pulled from [22] as E^{naive}, which is defined as the of naive gp-33-specific CTL contributing to primary clonal expansion. [22] fit these parameters to data collected from *in vivo* experiments carried out in conjunction with compiling mathematical models to fit to the data.

31. b_p

    This parameter represents the maximum expansion rate of effector T-cells due to DCs. This was originally defined in [22] as the maximal

expansion factor of activated CTL per day. [22] fit these parameters to data collected from *in vivo* experiments carried out in conjunction with compiling mathematical models to fit to the data.

32. r_{am}

This parameter represents the reversion rate of effector and regulatory T-cells to memory T-cells. This was originally defined in [22] as the activated CTL reversion rate into resting 'memory' cells. [22] fit these parameters to data collected from *in vivo* experiments carried out in conjunction with compiling mathematical models to fit to the data.

33. θ_D

This parameter represents the DC value for half-maximal effector T-cell expansion. This was originally defined in [22] as the threshold in DC density in the spleen for half-maximal proliferation rate of CTL. [22] fit these parameters to data collected from *in vivo* experiments carried out in conjunction with compiling mathematical models to fit to the data.

34. d

This parameter represents the beta cell death rate. This was originally derived by [17]and [8]using a study from van Nieuwenhuijze-2003 that originally stated that the non-specific beta cell death rate was at a rate of 1 to 2 days. Again, to find the decay constant from this, the inverse of the day length was taken. Because [43] showed a large skew towards the higher value of two days, the parameter for d is taken to be $\frac{1}{2}$.

35. b_E

This parameter represents the activation rate for effector T-cells from memory T-cells. This was originally defined in [22] as b_a, the activation rate of quiescent CTL by DC. It is noted as an ad-hoc fixed value for the purposes of parameter fitting. [22] fit these parameters to data collected from *in vivo* experiments carried out in conjunction with compiling mathematical models to fit to the data. Note the important assumption made here that $b_E = b_R$.

36. b_R

    This parameter represents the activation rate for regulatory T-cells from Em T-cells. This was originally defined in [22] as b_a, the activation rate of quiescent CTL by DC. It is noted as an ad-hoc fixed value for the purposes of parameter fitting. [22] fit these parameters to data collected from *in vivo* experiments carried out in conjunction with compiling mathematical models to fit to the data. Note the important assumption made here that $b_R = b_E$.

37. μ_D

    This parameter represents the emigration rate of DCs and T-cells from the blood to the pancreas. Note, as above, that this value comes from [22] and was originally measured to be the net emigration rate of DCs and T-cells from the blood to the liver.

38. μ_{PB}

    This parameter represents the emigration rate of DCs and T-cells from the pancreas to the blood. Note that while this value still comes from [22], it is originally reported in as the measured rate of T-cell and DC emigration from the liver to the blood.

39. f_D

    This parameter represents the rate that naive dendritic cells engulf necrotic beta cells. This was done by taking estimated values for engulfment from the original data estimates from [44], and multiplying by a scaling factor estimated in [20]. A full description of how this parameters was determined can be found in the forthcoming [2].

40. f_{tD}

    This parameter represents the rate that naive dendritic cells engulf apoptotic beta cells. This was done by taking estimated values for engulfment from the original data estimates from [44], and multiplying by a scaling factor estimated in [20]. A full description of how this parameters was determined can be found in the forthcoming [2].

41. μ_E

This parameter represents the effector T-cell removal rate due to competition. [22] reports the parameter α_{Em} as the half-life of memory T-cells. To calculate the decay constant of this parameter, we calculate:

$\alpha_{Em} = \frac{ln\ 2}{t_{1/2}^{Em}}$

The value of this parameter was calculated by taking the decay constant of this exponential decay equation and dividing it by 5000. This last calculation was done ad-hoc in order for the data to be fit with the parameters.

42. μ_R

This parameter represents the regulatory T-cell removal rate due to competition. In the forthcoming paper [2], the value of these parameters were fitted to data within the mathematical model proposed.

This parameter represents the effector T-cell removal rate due to competition. [22] reports the parameter α_{Em} as the half-life of memory T-cells. To calculate the decay constant of this parameter, we calculate:

$\alpha_{Em} = \frac{ln\ 2}{t_{1/2}^{Em}}$

The value of μ_R was calculated by taking the decay constant of this exponential decay equation and dividing it by 5000. This last calculation was done ad-hoc in order for the data to be fit with the parameters.

43. μ_B

This parameter represents the net dendritic cell emigration rate from the blood to the spleen. It was originally calculated by ([22]). Using biological labeling methods, mice dendritic cell populations and their associated e/immigration rates were tracked and mathematical modeling helped estimate from the data a parameter value that would fit both the structural model used and the biological data found. [22] reports this value in hours, while this report uses the hourly value. As the hourly rate had a mean of 1.124 per hour with a standard deviation of 5.9 per hour, our previous methods determined that the value that best fit the model proposed herein (74.56 per hour) would only correlate to being around 0.336 standard deviations above the originally reported [22] mean.

44. Q_{blood}

    This parameter represents the volume of the bloodstream in the mouse model. The volume of the bloodstream is useful for helping create conversion factors, as the volumes of the compartments change. To stay consistent with the other numbers given, the estimation of the mouse bloodstream volume being 3ml remained the same [28], [17], and [8].

45. μ_{SB}^{*}

    This parameter represents the activated cytotoxic T lymphocytes (CTLs) rate of entering the bloodstream from the spleen at equilibrium. Again, this was from [22], so few numbers needed calculation for any of them.

46. μ_{SB}^{normal}

    This parameter is used to show the normal CTL migration rate from the spleen to the blood. Again, this was taken from [22].

47. μ_{BSE}

    This parameter represents the emigration rate from the blood to the spleen of T-cells. As this is again a number cited from [22], we take this measured number from there.

48. a_I

    This parameter represents the rate of tolerogenic cell death in the spleen. ([22]) measured the half-life of dendritic cells in the spleen of a mouse, and found it to be three days. Using the following formula, the parameter values were estimated:

    $decay\ constant = \frac{ln(2)}{halflife}$, where half-life is three days.

    Note that it is assumed that both immunogenic and tolerogenic dendritic cell populations have the same half-life and thus the same decay constant.

49. a_D

This parameter represents the rate of immunogenic cell death in the spleen. ([22]) measured the half-life of dendritic cells in the spleen of a mouse, and found it to be three days. Using the following formula, the parameter values were estimated:

$decay\ constant = \frac{ln(2)}{halflife}$, where half-life is three days.

Note that it is assumed that both immunogenic and tolerogenic dendritic cell populations have the same half-life and thus the same decay constant.

50. B_{conv}

This parameter represents the density of beta-cells (in cells per milligram). The value of this parameter comes from [30], which did a cell count of alpha and beta cells in the pancreatic tail of mice.

51. Q_{spleen}

This parameter was taken from [45]. [22] borrows heavily from the methodology of [45] by combining existing mathematical models and *in vivo* experiments to determine parameter values. [45] looked at modelling viral infections in mice, and to do so measured the volume of various organs in mice. Specifically for the spleen, the assumption is used that mice tissue has a mass-to-volume ratio of 1 $g\ ml^{-1}$, and the spleen of the average mouse weighs around 100 grams. Converting units, the estimated volume of the mouse spleen is 0.1 ml.

52. θ_{shut}

This parameter represents the DC threshold density for half-maximal transfer rate from the spleen to the blood. It was originally defined in [22] as the threshold in DC density in the spleen for half-maximal transfer rate of CTL from spleen to blood (primary response). [22] fit these parameters to data collected from *in vivo* experiments carried out in conjunction with compiling mathematical models to fit to the data.

Parameter Sensitivity: Results The reasoning behind describing all of these parameters is two-fold: one, to introduce the reader to the elements

that are incorporated into this model and two, to describe the motivation behind the analysis done on these parameters.

The idea behind creating a compartment model simulating the pathogenesis of type 1 diabetes is to understand what is most sensitive to the disease's progression. Previous, single compartment models like in the forthcoming [2] have done this analysis with success, finding that small changes in specific parameters caused dramatic changes in the outcome of the mouse. It has been hypothesized that a deficiency in the macrophage clearance rate of apoptotic beta-cells is an important factor in the body's mounting of the autoimmune responses on beta-cells [6] [44] [8]. In single compartment *in silico* models, this was confirmed as well: in one calculation from [2], it was estimated that diabetogenesis could be prevented with just a

0.75

increase.

Codes used for this research

3.1 eFAST-multicompartmental

The eFast algorithm originally comes from a paper Marino and colleagues published in 2008. The code was first modified by An Do for the single compartmental model, then that code was modified for the multicompartmental model. Ultimately, the eFAST algorithm will give the first order sensitivity indices and total order sensitivity indexes which can then be plotted.

The first order sensitivity index will examine the individual parameter's variance on the output model variance.

The total order sensitivity index will look at the individual parameter's variance on 1) the output model variance and 2) higher order variance, which is how the individual parameter's variance will affect the variance of the other parameters.

The dummy parameter acts as a 0 in this algorithm. We do a two sample t-test to determine parameters with significant sensitivity indexes. The parameters with Si's and Sti's that have a p-value < 0.05 are significant, and there is variation in the mean compared to the dummy parameter.

Any parameters with Si's and STi's with a p > 0.05 are filtered out as their sensitivity indexes are not significant in comparison to the dummy parameter.

There is a .csv file that will match the number ID to parameter names. Or consult the parameters table in the Summer 2019 REU Report to match the ID number with the parameter name.

3.1.1 Model_efast_T1D.m

Model _ efast _ T1D.m will run the eFAST algorithm. For each parameter variance, there will be 30 points that are resampled 65 times. Once the code finishes running, it will output a .mat file, Model_efast_T1D.mat.

```
% First order and total effect indices for a given
% model computed with Extended Fourier Amplitude
% Sensitivity Test (EFAST).
% Andrea Saltelli, Stefano Tarantola and Karen Chan.
% 1999. % "A quantitative model-independent method for global
% sensitivity analysis of model output". % Technometrics 41:39-56
clear;
close all;

%% efast Parameters setting
Parameter_settings_EFAST_T1D;
K = size(pmax,1); % # of input factors (parameters varied) + dummy
     parameter


%% INPUT
NR = 30; %: no. of search curves - RESAMPLING
NS = 65; % # of samples per search curve
wantedN=NS*K*NR; % wanted no. of sample points


% OUTPUT
% SI[] : first order sensitivity indices
% STI[] : total effect sensitivity indices
% Other used variables/constants:
% OM[] : vector of k frequencies
% OMi : frequency for the group of interest
% OMCI[] : set of freq. used for the compl. group
% X[] : parameter combination rank matrix
% AC[],BC[]: fourier coefficients
% FI[] : random phase shift
% V : total output variance (for each curve)
% VI : partial var. of par. i (for each curve)
% VCI : part. var. of the compl. set of par...
% AV : total variance in the time domain
% AVI : partial variance of par. i
% AVCI : part. var. of the compl. set of par.
```

```
% Y[] : model output

MI = 4; %: maximum number of fourier coefficients
        % that may be retained in calculating the partial
        % variances without interferences between the
        % assigned frequencies



% Computation of the frequency for the group
% of interest OMi and the # of sample points NS (here N=NS)

OMi = floor(((wantedN/NR)-1)/(2*MI)/K);
NS = 2*MI*OMi+1;

if(NS*NR < 65)
    fprintf(['Error: sample size must be >= ' ...
    '65 per factor.\n']);
    return;
end

%% Wave
wave = 1;

%% Pre-allocation of the output matrix Y
%% Y will save only the points of interest specified in
%% the vector time_points

time_points=[70 273]; % time points of interest in days

%Y(NS,length(time_points),length(y0),length(pmin),NR)=0;  % pre-
    allocation


 % pre-allocation glucose signal
Y(NS,length(time_points),1,length(pmin),NR)=0;



% Loop over k parameters (input factors)
for i=1:K % i=# of replications (or blocks)
    % Algorithm for selecting the set of frequencies.
    % OMci(i), i=1:k-1, contains the set of frequencies
    % to be used by the complementary group.

    OMci = SETFREQ(K,OMi/2/MI,i);
    % Loop over the NR search curves.

```

```
84      for L=1:NR
85          % Setting the vector of frequencies OM
86          % for the k parameters
87          cj = 1;
88          for j=1:K
89              if(j==i)
90                  % For the parameter (factor) of interest
91                  OM(i) = OMi;
92              else
93                  % For the complementary group.
94                  OM(j) = OMci(cj);
95                  cj = cj+1;
96              end
97          end
98          % Setting the relation between the scalar
99          % variable S and the coordinates
100         % {X(1),X(2),...X(k)} of each sample point.
101         FI = rand(1,K)*2*pi; % random phase shift
102         S_VEC = pi*(2*(1:NS)-NS-1)/NS;
103         OM_VEC = OM(1:K);
104         FI_MAT = FI(ones(NS,1),1:K)';
105         ANGLE = OM_VEC'*S_VEC+FI_MAT;
106
107         X(:,:,i,L) = 0.5+asin(sin(ANGLE'))/pi; % between 0 and 1
108
109         % Transform distributions from standard
110         % uniform to general.
111
112         %%this is what assigns 'our' values rather than 0:1 dist
113         X(:,:,i,L) = parameterdist(X(:,:,i,L),pmax,pmin,0,1,NS,'
    unif');
114
115         %% Loading Model Parameters
116         ParametersLHS;
117
118         % Do the NS model evaluations.
119         for run_num=1:NS
120             [i run_num L] % keeps track of [parameter run NR]
121
122             % Assign parameter values
123              assignParameters(X(:,:,i,L),run_num);
124              dummy=X(run_num,end); %dummy variable
125              ParametersLHS; % Load parasmeter values into
    Paramters file
126
127
128             % ODE solver call
```

```
129             [t,y]=ode15s(@(t,y)ODE_efast(t, y, fMat, fMt, wave),
    tspan,y0,[]);
130
131 %           retrieve glucose level
132             glucose = y(:,22);
133 %           plot the glucose dynamics
134 %           plot(t,glucose);hold on;
135
136             % It saves only  at the time points of interest
137            Y(run_num,:,:,i,L)=glucose(time_points+1,:);
138
139         end %run_num=1:NS
140     end % L=1:NR
141 end % i=1:k
142
143 save Model_efast.mat;
144
145
146 % Calculate Coeff. of Var. for Si and STi for Viral load (variable
      4). See
147 % online Supplement A.5 for details.
148 %[CVsi CVsti]=CVmethod(Si, rangeSi,Sti,rangeSti,4)
```

3.1.2

Codes used for this research

Bibliography

[1] R. P. Anderson and B. Jabri, "Vaccine against autoimmune disease: Antigen-specific immunotherapy," *Current Opinion in Immunology*, vol. 25, no. 3, pp. 410–417, Jun. 2013.

[2] B. Shtylla, M. Gee, A. Do, S. Shabahang, L. Eldevik, and L. de Pillis, "A mathematical model for DC vaccine treatment of type I diabetes," *Frontiers*.

[3] K. Ogurtsova, J. D. da Rocha Fernandes, Y. Huang, U. Linnenkamp, L. Guariguata, N. H. Cho, D. Cavan, J. E. Shaw, and L. E. Makaroff, "IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040," *Diabetes Research and Clinical Practice*, vol. 128, pp. 40–50, Jun. 2017.

[4] J. L. Harding, M. E. Pavkov, D. J. Magliano, J. E. Shaw, and E. W. Gregg, "Global trends in diabetes complications: A review of current evidence," *Diabetologia*, vol. 62, no. 1, pp. 3–16, Jan. 2019.

[5] E. J. Graham, "Mathematical Models of Mechanisms Underlying Long-Term Type 2 Diabetes Progression," Thesis, The University of Utah, Salt Lake City, Utah, Aug. 2012.

[6] J. Nerup, T. Mandrup-Poulsen, J. Mølvig, S. Helqvist, L. Wogensen, and J. Egeberg, "Mechanisms of pancreatic beta-cell destruction in type I diabetes," *Diabetes Care*, vol. 11 Suppl 1, pp. 16–23, 1988 Nov-Dec.

[7] J. Parkin and B. Cohen, "An overview of the immune system," *Lancet (London, England)*, vol. 357, no. 9270, pp. 1777–1789, Jun. 2001.

[8] A. F. M. Marée, R. Kublik, D. T. Finegood, and L. Edelstein-Keshet, "Modelling the onset of Type 1 diabetes: Can impaired macrophage

phagocytosis make the difference between health and disease?" *Philosophical Transactions. Series A, Mathematical, Physical, and Engineering Sciences*, vol. 364, no. 1842, pp. 1267–1282, May 2006.

[9] B. Freiesleben De Blasio, P. Bak, F. Pociot, A. E. Karlsen, and J. Nerup, "Onset of type 1 diabetes: A dynamical instability," *Diabetes*, vol. 48, no. 9, pp. 1677–1685, Sep. 1999.

[10] J. A. Pearson, F. S. Wong, and L. Wen, "The importance of the Non Obese Diabetic (NOD) mouse model in autoimmune diabetes," *Journal of Autoimmunity*, vol. 66, pp. 76–88, Jan. 2016.

[11] E. A. Gale and K. M. Gillespie, "Diabetes and gender," *Diabetologia*, vol. 44, no. 1, pp. 3–15, Jan. 2001.

[12] M. Bao, Y. Yang, H.-S. Jun, and J.-W. Yoon, "Molecular Mechanisms for Gender Differences in Susceptibility to T Cell-Mediated Autoimmune Diabetes in Nonobese Diabetic Mice," *The Journal of Immunology*, vol. 168, no. 10, pp. 5369–5375, May 2002.

[13] J. C. Reed, "Mechanisms of Apoptosis," *The American Journal of Pathology*, vol. 157, no. 5, pp. 1415–1430, Nov. 2000.

[14] J. D. Trudeau, J. P. Dutz, E. Arany, D. J. Hill, W. E. Fieldus, and D. T. Finegood, "Neonatal beta-cell apoptosis: A trigger for autoimmune diabetes?" *Diabetes*, vol. 49, no. 1, pp. 1–7, Jan. 2000.

[15] C. W. Tornøe, H. Agersø, E. Jonsson, H. Madsen, and H. A. Nielsen, "Non-linear mixed-effects pharmacokinetic/pharmacodynamic modelling in NLME using differential equations," *Computer Methods and Programs in Biomedicine*, vol. 76, no. 1, pp. 31–40, Oct. 2004.

[16] B. Topp, K. Promislow, G. deVries, R. M. Miura, and D. T. Finegood, "A model of beta-cell mass, insulin, and glucose kinetics: Pathways to diabetes," *Journal of Theoretical Biology*, vol. 206, no. 4, pp. 605–619, Oct. 2000.

[17] R. A. Kublik, "Modeling the onset of type 1 diabetes," 2005.

[18] L. DePillis, A. Gallegos, and A. Radunskaya, "A Model of Dendritic Cell Therapy for Melanoma," *Frontiers in Oncology*, vol. 3, 2013.

[19] J. R. Moore, "Mathematical Modeling of Autoimmune Disease," Thesis, The University of Utah, Salt Lake City, Utah, 2015.

[20] M. Gee, "Modeling type 1 Diabetes and Immune Cell Dynamics in the Pancreas," Thesis, Harvey Mudd College, Claremont, California, 2018.

[21] G. Wu, "Mathematical Modeling for Type 1 Diabetes," Thesis, Pomona College, Claremont, California, 2019.

[22] B. Ludewig, P. Krebs, T. Junt, H. Metters, N. J. Ford, R. M. Anderson, and G. Bocharov, "Determining control parameters for dendritic cell-cytotoxic T lymphocyte interaction," *European Journal of Immunology*, vol. 34, no. 9, pp. 2407–2418, Sep. 2004.

[23] R. N. Bergman, L. S. Phillips, and C. Cobelli, "Physiologic evaluation of factors controlling glucose tolerance in man: Measurement of insulin sensitivity and beta-cell glucose sensitivity from the response to intravenous glucose," *The Journal of Clinical Investigation*, vol. 68, no. 6, pp. 1456–1467, Dec. 1981.

[24] D. T. Finegood, L. Scaglia, and S. Bonner-Weir, "Dynamics of beta-cell mass in the growing rat pancreas. Estimation with a simple mathematical model," *Diabetes*, vol. 44, no. 3, pp. 249–256, Mar. 1995.

[25] W. Malaisse, F. Malaisse-Lagae, and P. H. Wright, "A new method for the measurement in vitro of pancreatic insulin secretion," *Endocrinology*, vol. 80, no. 1, pp. 99–108, Jan. 1967.

[26] G. Toffolo, R. N. Bergman, D. T. Finegood, C. R. Bowden, and C. Cobelli, "Quantitative estimation of beta cell sensitivity to glucose in the intact organism: A minimal model of insulin kinetics in the dog," *Diabetes*, vol. 29, no. 12, pp. 979–990, Dec. 1980.

[27] J. L. Paredes, A. I. Orabi, T. Ahmad, I. Benbourenane, K. Tobita, S. Tadros, K. T. Bae, and S. Z. Husain, "A non-invasive method of quantifying pancreatic volume in mice using micro-MRI," *PloS One*, vol. 9, no. 3, p. e92263, 2014.

[28] R. Van Furth, M. C. Diesselhoff-den Dulk, and H. Mattie, "Quantitative study on the production and kinetics of mononuclear phagocytes during an acute inflammatory reaction," *The Journal of Experimental Medicine*, vol. 138, no. 6, pp. 1314–1330, Dec. 1973.

[29] N. Kaliss and D. Pressman, "Plasma and Blood Volumes of Mouse Organs, As Determined with Radioactive Iodoproteins." *Experimental Biology and Medicine*, vol. 75, no. 1, pp. 16–20, Oct. 1950.

[30] M. Chintinne, G. Stangé, B. Denys, Z. Ling, P. In 't Veld, and D. Pipeleers, "Beta cell count instead of beta cell mass to assess and localize growth in beta cell population following pancreatic duct ligation in mice," *PloS One*, vol. 7, no. 8, p. e43959, 2012.

[31] M. M. Zatz, "The distribution of 51CR-labeled lymphocytes into antigen-stimulated mice," *Journal of Experimental Medicine*, vol. 134, no. 1, pp. 224–241, Jul. 1971.

[32] A. Martín-Fontecha, S. Sebastiani, U. E. Höpken, M. Uguccioni, M. Lipp, A. Lanzavecchia, and F. Sallusto, "Regulation of Dendritic Cell Migration to the Draining Lymph Node: Impact on T Lymphocyte Traffic and Priming," *The Journal of Experimental Medicine*, vol. 198, no. 4, pp. 615–621, Aug. 2003.

[33] M. D. Mckay, R. J. Beckman, and W. J. Conover, "A Comparison of Three Methods for Selecting Values of Input Variables in the Analysis of Output From a Computer Code," *Technometrics*, vol. 42, no. 1, pp. 55–61, Feb. 2000.

[34] D. M. Bates and J. C. Pinheiro, "Linear and Nonlinear Mixed-Effects Models," *Conference on Applied Statistics in Agriculture*, Apr. 1998.

[35] S. Marino, I. B. Hogue, C. J. Ray, and D. E. Kirschner, "A methodology for performing global uncertainty and sensitivity analysis in systems biology," *Journal of Theoretical Biology*, vol. 254, no. 1, pp. 178–196, Sep. 2008.

[36] C. Xu and G. Z. Gertner, "A general first-order global sensitivity analysis method," *Reliability Engineering & System Safety*, vol. 93, no. 7, pp. 1060–1071, Jul. 2008.

[37] C. E. Mathews, S. Xue, A. Posgai, Y. L. Lightfoot, X. Li, A. Lin, C. Wasserfall, M. J. Haller, D. Schatz, and M. A. Atkinson, "Acute Versus Progressive Onset of Diabetes in NOD Mice: Potential Implications for Therapeutic Interventions in Type 1 Diabetes," *Diabetes*, vol. 64, no. 11, pp. 3885–3890, Nov. 2015.

[38] A. Li, J. Chen, M. Hattori, E. Franco, C. Zuppan, O. Ojogho, Y. Iwaki, and A. Escher, "A therapeutic DNA vaccination strategy for autoimmunity and transplantation," *Vaccine*, vol. 28, no. 8, pp. 1897–1904, Feb. 2010.

[39] J. E. Wigginton and D. Kirschner, "A Model to Predict Cell-Mediated Immune Regulatory Mechanisms During Human Infection with *Mycobacterium tuberculosis*," *The Journal of Immunology*, vol. 166, no. 3, pp. 1951–1967, Feb. 2001.

[40] R. van Furth, "Origin and turnover of monocytes and macrophages," *Current Topics in Pathology. Ergebnisse Der Pathologie*, vol. 79, pp. 125–150, 1989.

[41] C. J. Rhodes, "Type 2 diabetes-a matter of beta-cell life and death?" *Science (New York, N.Y.)*, vol. 307, no. 5708, pp. 380–384, Jan. 2005.

[42] A. De Gaetano, T. Hardy, B. Beck, E. Abu-Raddad, P. Palumbo, J. Bue-Valleskey, and N. Pørksen, "Mathematical models of diabetes progression," *American Journal of Physiology. Endocrinology and Metabolism*, vol. 295, no. 6, pp. E1462–1479, Dec. 2008.

[43] A. E. M. van Nieuwenhuijze, T. van Lopik, R. J. T. Smeenk, and L. A. Aarden, "Time between onset of apoptosis and release of nucleosomes from apoptotic cells: Putative implications for systemic lupus erythematosus," *Annals of the Rheumatic Diseases*, vol. 62, no. 1, pp. 10–14, Jan. 2003.

[44] A. F. M. Marée, M. Komba, C. Dyck, M. Łabecki, D. T. Finegood, and L. Edelstein-Keshet, "Quantifying macrophage defects in type 1 diabetes," *Journal of Theoretical Biology*, vol. 233, no. 4, pp. 533–551, Apr. 2005.

[45] G. Bocharov, P. Klenerman, and S. Ehl, "Modelling the Dynamics of LCMV Infection in Mice: II. Compartmental Structure and Immunopathology," *Journal of Theoretical Biology*, vol. 221, no. 3, pp. 349–378, Apr. 2003.