Modelling Type I Diabetes: Parametric Sensitivity Data Driven Approach with Multi-Compartment Model

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Background

It has been documented in recent studies (Anderson 2013, Shtylla 2019) that an appropriate injection of a dendritic cell (DC) 'vaccine' could halt or slow the progression of autoimmune diabetes in mice. Previous mathematical models involving ordinary differential equations (ODEs) have previously done parametric analysis on a single compartment of the pancreas to model the development of simulated diabetogenesis. This study integrates two new compartments (the spleen and the bloodstream) to develop a much more complex and accurate model with the foundation of a previously developed single compartment model. With proper analysis, parameter sensitivity on this mathematical mode is a conduit for determining effective potential treatments.

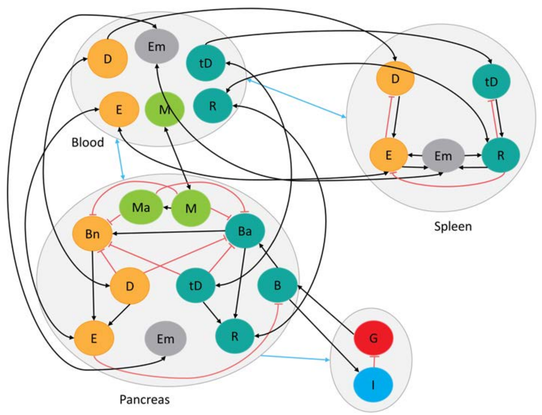


Figure 1 A visual diagram of the three compartment model of the pathogenesis of T1D. With the populations within the blood, spleen, and pancreas compartments, there are 23 populations that are dynamically tracked in this model.

Methods and Results

By modelling the different populations of the system (glucose, insulin, and beta cell populations, for example) with a system of ordinary differential equations, we can produce *in silico* data simulations where we are able to see different model outcomes according to changes in parameter values. Using Balb/c mice data as a control set and using non-obsese diabetic mice (NOD) as an analog for human T1D, we simulate glucose, insulin, and beta-cell population levels in both mice strains. We also model these populations in the event of an apoptotic wave and without.

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

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

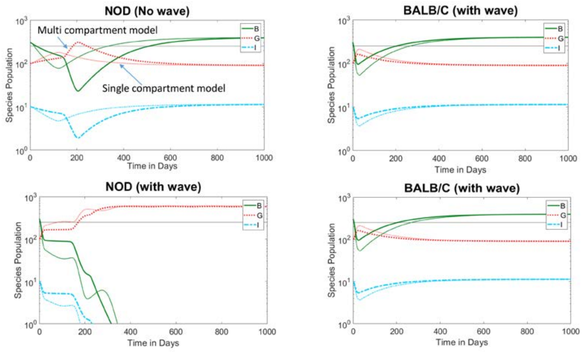
$$W(B,t) = 0.1Be^{-}\left(\frac{t-9}{9}\right)^2$$

$$\frac{d}{dt}B = \alpha_B K_1(G)B - \delta_B B - W(B,t) - \eta K_2(E_{panc}, R_{panc})B$$

$$\frac{d}{dt}B_a = \tilde{W}(B,t) + \tilde{\eta}K_2(E_{panc}, R_{panc})B - f_M M B_a - f_{Ma}M_a B_a - dB_a$$

$$+\tilde{\delta}_B B - f_{tD}(D_{ss} - D_{panc})B_a - f_D D_{panc} B_a$$

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



Comparison single compartment and multi-compartment model simulating glucose level, beta cells and insulin level in NOD and Balb/C with and without apoptotic wave

Figure 2 Beta-cells, glucose, and insulin levels over time for the multicompartmental and single compartmental models. The thinner lines are the multicompartmental model, and the thicker lines are the single compartmental model.

Sensitivity Analysis

The proposed model includes 23 tracked populations and 52 parameters. We began this study by performing in-depth literature reviews on history and derivation of all parameters. After confirming what ranges were biologically reasonable and correct, we began to look at the sensitivity analysis.

Parameter	Balb/c	NOD	Units	Description	Citation	Range
s_E	1	1	ml $cell^{-1}$	Relative impact of effector T cells on β cell death	Estimated here	Estimate [1, 100]
s_R	36	36	ml $cell^{-1}$	Relative impact of regulatory T cells on β cell death	Estimated here	Estimate [10, 100]
D_{ss}	1×10^5	1×10^5	cells ml^{-1}	Steady state DC population	Estimated here	Estimate $[1000, 10^7]$
a_{Em}	0.01	0.01	d^{-1}	Death rate of memory T cells	[1]	Estimated $[10^{-3}, 0.1]$
η_{basal}	0.02	0.02	d^{-1}	Rate at which T cells eliminate β cells	Estimated here	[0.01, 0.03]
α_η	0.1	0.1	d^{-1}	Rate of change at which T cells eliminate β cells	Estimated here	[0.1, 0.5]
β_η	22	22	d^{-1}	Duration T cell effectiveness saturate maximum level	Estimated here	[11, 30]
f_M	$0.0623 \times 2 \times 10^{-5}$	$0.0623 \times 1 \times 10^{-5}$	$mlcells^{-1}d^{-1}$	Rate macrophages engulf necrotic ad apoptotic cells	Modified from [2]	$[0.1, 2] \times .0623 \times 10^{-5}$
f_{Ma}	$0.0623 \times 5 \times 10^{-5}$	$0.0623 \times 1 \times 10^{-5}$	ml $cells^{-1}d^{-1}$	Rate activated macrophages engulf necrotic and apoptotic β cells	[2]	$[0.1, 2] \times .0623 \times 10^{-5}$
J_{new}	3.2333×10^3	3.2333×10^3	cells ml^{-1} d^{-1}	Normal resting macrophage influx	Gianna Wu's thesis	[3200, 3400]
J	50, 000	50, 000	cells ml^{-1} d^{-1}	Normal resting macrophage influx	[2]	$10^3 \times [48, 50]$
k	0.4	0.4	d^{-1}	Macrophages deactivation rate	[2]	Estimate [0.1, 1]
b	0.09	0.09	d^{-1}	Recruitment rate of macrophages by activated macrophages	[2]	Estimate [0.01, 0.1]
c	0.1	0.1	d^{-1}	Macrophages egress rate	[2]	[0.07, 0.25]
e_1	1×10^{-8}	1×10^{-8}	$cell^{-1}d^{-1}$	Effect of crowding on macrophages	[2]	$[10^{-8}, 10^{-6}]$
e_2	1×10^{-8}	1×10^{-8}	$cell^{-1}d^{-1}$	Effect of crowding on macrophages	[2]	$[10^{-8}, 10^{-6}]$
α_B	0.0334	0.0334	d^{-1}	Rate β cells are produced from glucose	[3]	[0.031, 0.035]
δ_B	0.0167	0.0167	d^{-1}	β cell death rate	[3]	[1/62, 1/58]
$G_{0.5}$	90	90	mg dl^{-1}	Glucose level of half max β cell production	[3]	[81, 100]
R_0	864	864	mg dl^{-1}	Basal rate of glucose production	[4, 5, 6]	Estimate [500, 1000]
G_0	1.44	1.44	$d^{-1}4$	Rate of glucose decay	[4, 5, 6]	Estimate [0.1, 2]

Figure 3 Sample of parameter list used in this report. This table contains the first 20 parameters out of 52 in total.

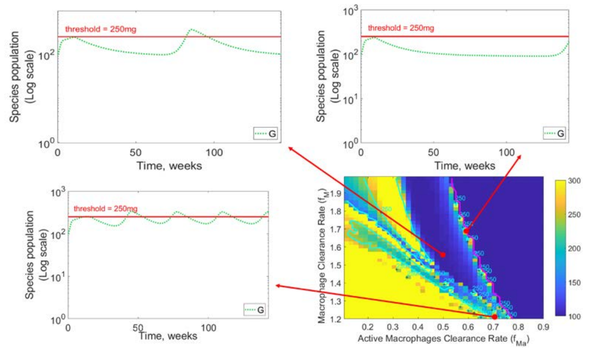


Figure 4 Heatmap displaying glucose readings from varying macrophage clearance rates. The yellow region of the heatmap represents the diabetic state, and the blue region shows the healthy state. In between the diabetic and healthy state is a "hyperglycemic" region where the glucose levels oscillate and repeatedly transition between healthy states and diabetic states. A diabetic state is defined as having a consistent blood sugar glucose level at or above 250 mg/dl.

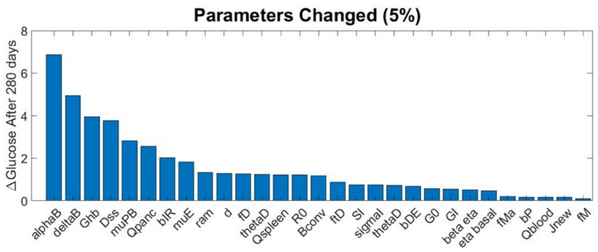


Figure 5 Global to local sensitivity analysis. Parameter combinations are sampled using Latin Hypercube Sampling scheme. For each set of parameter combinations, one parameter value is varied by 5% at a time while others are held fixed. We display the average change in the end result glucose over 10,000 samples with respect to each parameter in descending order.

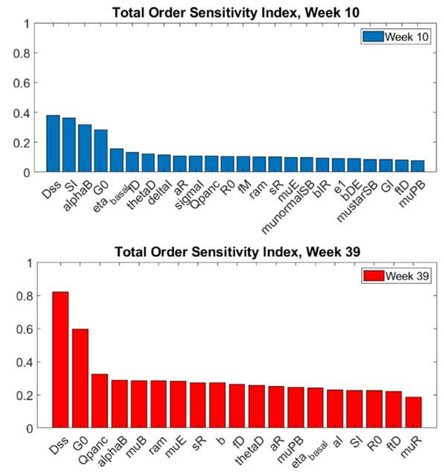


Figure 6 Extended Fourier Analysis Test (eFAST) performed on multi-compartment T1D model. Input parameter values are sampled according to a sinusoidal function. Glucose level at week 10 and week 39 is solved for each parameter combination. Total sensitivity index measures the model variance explained by the input variance of a given parameter. The higher the index is, the more sensitive the model outcomes are to the given parameter.

Conclusions and Future Work

Through the parameter sensitivity, we were able to assert the multicompartment models validity by comparing our simulations, models, data, and methods to previously heuristically-proved models.
There is still more research to be done on this project:

1. Using a data-driven approach to fine-tuning and adjusting parameter values
2. Finding consistencies between previous models and the proposed model as a conduit for finding efficient treatment options
3. Incorporating population and random effects into the currently proposed model to capture the inter-variability of glucose levels between subjects
4. Adding compartments to the model that are known biologically to have a large effect on the pathogenesis of T1D (for example, the liver)
5. Simulating hypothetical treatments within the proposed model to improve understanding of how these potential treatments would be implemented

Overall, the multicompartment model shared parametric similarity, indicating that the incorporation of these new compartments retains the original modelling and allows for a more nuanced approach to how specific biological agents can be manipulated to treat, prevent, and eventually cure autoimmune diabetes.

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References

Anderson, R. et al. Vaccine against autoimmune disease: antigen-specific immunotherapy. Current Opinion in Immunology 25 (2013).
Marino, S. et al. A Methodology for Performing Global Uncertainity and Senstivity in Systems Biology. Journal of Theoretical Biology 254 (2008).
Shtylla, B. et al. A Mathematical Model for DC Vaccine Treatment for Type I Diabetes. forthcoming (2019).