Enhancing Theoretical Understanding of the Onset of Type 1 Diabetes

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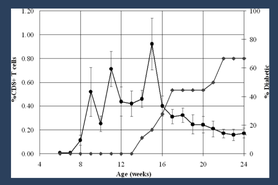
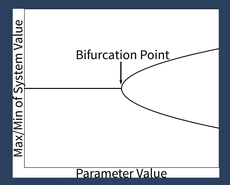
Introduction

In type 1 diabetes, also known as autoimmune diabetes, the body's own immune system attacks and destroys insulin-producing pancreatic beta cells, leading to an insulin shortage and causing symptoms [1]. Currently, the causes and cures are largely unknown [2]. However, previous experiments have shown that in NOD (non-obese diabetic) mice, a standard model for diabetic research, the level of T cells (a specific type of immune cell) fluctuates cyclically in the weeks leading up to the appearance of symptoms, as depicted in the graph (below left): after the "spikes" occur (black), the percentage of diabetic mice increases dramatically (in gray) [[3] cited in [4]]. To better understand the mechanism underlying these oscillations, Mahaffy and Edelstein-Keshet constructed a mathematical model of the immune–pancreas system. One parameter in the model is the level of pancreatic beta cells, which slowly decreases over time; at a certain level, the fluctuations described experimentally occur, and then diabetes appears [4].





Left: from [4]; experimental measurement of T cell levels (black) in NOD mice over time, with diabetes occurring after "spikes" (percentage of mice that are diabetic in gray). Right: example of a Hopf bifurcation.

Originally, the researchers analyzed the model's behavior at various constant parameter values [4]; in particular, they searched for *bifurcations*, or qualitative changes in behavior that occur when a parameter reaches a certain threshold [5]. For instance, a system may remain constant at one parameter value; if the parameter reaches a certain level, the system may then oscillate between two defined values (see diagram) [5]. This experiment will improve the model by applying research demonstrating that in certain systems, slowly varying the parameter value while the model runs can change the qualitative nature of the system [6]. This more accurately reflects what occurs biologically, as the original paper explicitly stated that the parameter should continuously slowly fall. To summarize: for the original *static* analysis, the authors re-ran the model multiple times, each time setting the parameter to a fixed value. For the *continuous* analysis here, the parameter starts at a given value and then continuously decreases over time. Thus, this experiment will help scientists and medical professionals better understand and apply the theoretical results of Mahaffy and Edelstein-Keshet's work as well as the experimental results they cited in predicting and understanding the onset of type 1 diabetes and the behavior of the immune system in this disease.

Research Question

How does treating the peptide clearance rate δ_p (essentially, the level of pancreatic beta cells) as a *continuously* and slowly varying parameter affect the qualitative behavior of the scaled reduced immune model developed by Mahaffy and Edelstein-Keshet [4], and how can those findings be applied to understanding and predicting the onset of type 1 diabetes?

Hypothesis

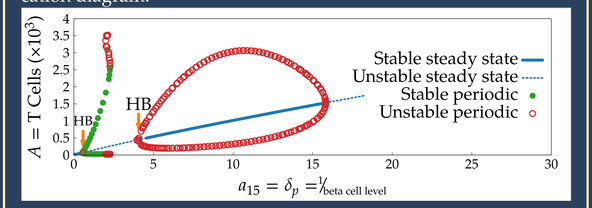
If the model for the level of immune cells in the weeks before the onset of type 1 diabetes is analyzed with both a continuously varying and a static peptide clearance rate δ_p, then in the former analysis, the oscillations present in the original model that indicate the onset of diabetes will begin later than in the latter model because previous research has shown this behavior is delayed in other systems when similarly analyzed with a continuously varying parameter.

Experimental (Materials)

- Computer (x86-64 architecture running a Linux distribution) The exact specifications and the operating system do not matter, as the software used runs on all platforms. A relatively recent (past 5 years or so) computer will suffice.
- Computer Software
  - Python 3.3.3 with `mpmath` (http://www.python.org, http://www.mpmath.org), used to calculate the data for the plots.
  - XPP AUTO 7.0 (http://www.math.pitt.edu/~bard/xpp/xpp.html), used to calculate the data for the bifurcation diagrams.
  - ConTEXt 2014.01.03 (http://wiki.contextgarden.net), used to generate the plots and bifurcation diagrams.
  - Gnuplot 4.6.4 (http://www.gnuplot.info), used to generate plots.

Experimental (Procedures)

XPP AUTO, used in the original paper, is used to compute a bifurcation diagram:



This shows, at a particular level of beta cells, possible states of the model (i.e. level of T cells). The higher the T cell level, the more beta cells can be destroyed. On a steady state, the system remains at a fixed level of T cells; in contrast, the level oscillates on a periodic state. If a state is steady, then introducing a small deviation will result in the system returning to the original state, while an unstable state will move towards another state. The points labeled "HB" are *Hopf bifurcations*, points at which the system changes qualitative behavior—from stable to periodic or vice-versa.

Now, for the *continuous* analysis, the model starts at a particular a_{15} (= 1/beta cell) level, which varies linearly over time. Because this variation is linear, at each time the a_{15} level is unique, and thus the A vs t plot of this model can be overlaid on the bifurcation diagram as a A vs a_{15} plot, allowing them to be compared (see the diagrams below).

The model equations are

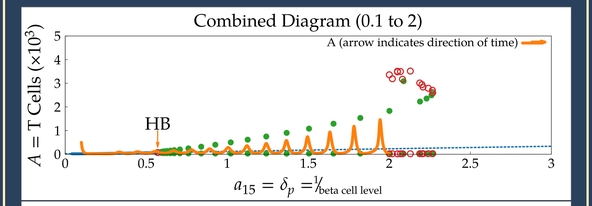
$$\frac{dA}{dt} = (a_6 + a_7 M) f_1(p) - a_8 A - a_9 A^2$$
$$\frac{dM}{dt} = a_{10} f_2(p) A - f_1(p) a_7 a_{16} M - a_{11} M$$
$$\frac{dE}{dt} = a_{12}(1 - f_2(p)) A - a_{13} E$$

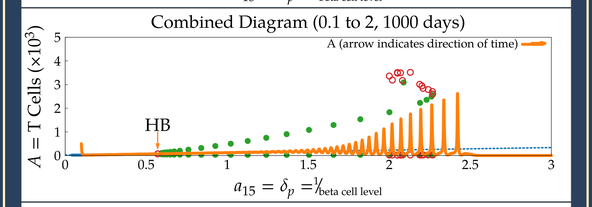
$$p = \frac{a_{14}}{a_{15}} EB \qquad f_1 = \frac{p^{a_1}}{{a_2}^{a_1} + p^{a_1}} \qquad f_2 = \frac{a_4 {a_5}^{a_3}}{{a_5}^{a_3} + p^{a_3}}$$

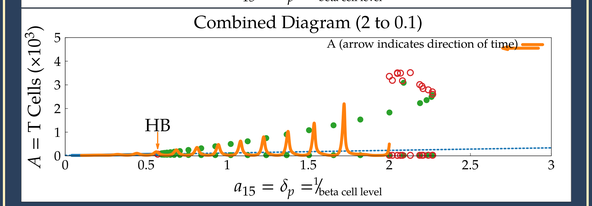
with $a_{15} = \delta_p$ = constant for the bifurcation diagram or $\frac{da_{15}}{dt} = \frac{d\delta_p}{dt}$ = rate of change for the continuous analysis. Here, A is the level of activated T cells, B pancreatic beta cells, E effector T cells, M memory T cells, and p peptide level. In the model, beta cells that undergo apoptosis (cell death) generate peptide; then, T cells become activated, "recognizing" this peptide. These then become either effector cells, which destroy pancreatic cells and produce more peptide, or memory cells that encounter the peptide and trigger an immune response.

A 4th order Runge-Kutta solver is used to solve the continuous system. Runge-Kutta is a standard algorithm for solving differential equations [7], used here because the continuous analysis could lead to numerical precision errors [6], and this implementation allows for arbitrary-precision computations [8].

Results







More T cells (higher A) = more beta cells destroyed
Not all parameter ranges tested are shown for lack of space

Discussion of Results

To read the plots, note that each contains two graphs: the continuous model, in orange, and the bifurcation diagram, in blue/green/red. The latter shows, at a particular δ_p, the level of T cells the static model "settles into" over time. If multiple values are shown for a particular δ_p, then the system oscillates between those values over time (and in this model, oscillations imply symptoms of diabetes [4]). Meanwhile, the continuous model (orange) shows T cell level vs. time; since δ_p varies linearly with time, each δ_p corresponds to exactly one unique time value. The arrow in the upper right indicates the direction of time.

In the original experiments with mice, the appearance of symptoms of diabetes corresponded with cyclic fluctuations in the level of T cells [3]. Looking at the first plot, as the level of T cells decreases over time in the continuous model, some oscillations appear before the point they are expected to (the *Hopf bifurcation* point, labeled "HB"). Given the large error bars in the original experiments, however, such small oscillations may not be of note and may explain why only a few oscillations were found in the mice. When the same amount of beta cell destruction is spread out over a longer timeframe—1000 days rather than 200 (the experiments covered roughly 200 days)—the oscillations occur far later than they should. Thus, theoretically, a way to prevent beta cell destruction would only delay the onset of symptoms.

Conclusion

The results both confirm and refute the hypothesis—depending on the timescale, the oscillations that are indicative of the onset of diabetes may start either earlier or later than expected. Taking into account the error bars on the original data, the simulations here still show the characteristic pattern of low T cell levels that then transition into oscillatory "spiking". Thus, this confirms the veracity of the original model under a more biologically accurate continuous analysis. Furthermore, the results suggest that 1) with sensitive enough tests, the oscillations characteristic of the disease may be detectable earlier than expected, and that 2) slowing the rate of beta cell destruction may delay, but not prevent, those oscillations. Therefore, researchers interested in completely preventing this disease may want to investigate other variables of the model.

Future Research

In this analysis, the level of beta cells varies linearly, but in reality, beta cells regenerate. Thus, extending the system with a model of beta cell regeneration would make it more biologically accurate. For instance, models of type 2 diabetes often account for this and could serve as a starting point for research [Dr. Jiaxu Li, University of Louisville, personal communication, December 6, 2013]. Additionally, conducting further experiments in mice to obtain more data on the oscillations would help fine-tuning the model; note both the large error bars in the original data (see introduction) and the parameter sensitivity of this model [4].

Works Cited

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