Enhancing Theoretical Understanding of the Onset of Type 1 Diabetes

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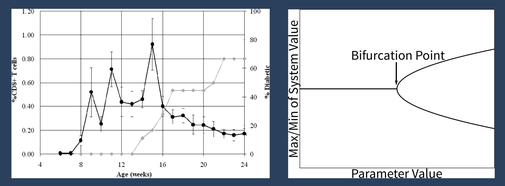
Introduction

In type 1 diabetes (autoimmune diabetes), the immune system attacks and destroys insulin-producing pancreatic beta cells [1]. Currently, the causes and cures are largely unknown [2]. However, a previous experiment has shown that in diabetic mice, the level of T cells fluctuates cyclically in the weeks before the appearance of symptoms (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 underlying mechanism, Mahaffy and Edelstein-Keshet constructed a mathematical model of the immune–pancreas system. One parameter in the model is the pancreatic beta cell level, which slowly decreases over time; at a certain level, the fluctuations described experimentally occur, and thus 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]; 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; at another level, the system may oscillate between two defined values (see diagram, above right) [5]. This experiment improves Mahaffy and Edelstein-Keshet's model by applying research demonstrating that in certain systems, slowly varying the parameter value while the model runs can change the system behavior qualitatively [6]. This more accurately reflects what occurs biologically, as the original paper states the parameter continuously slowly falls. 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 value and then continuously changes over time. Thus, this experiment will help scientists and medical professionals better understand and apply the theoretical results of the model as well as the experimental results cited in predicting and understanding the onset of type 1 diabetes and the behavior of the immune system in this disease.

Furthermore, this experiment will investigate the use of `mpmath` in investigating such models. Previous research demonstrated that numerical error due to rounding can lead to incorrect results [6]; `mpmath` allows the user to set any desired precision to avoid such errors.

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

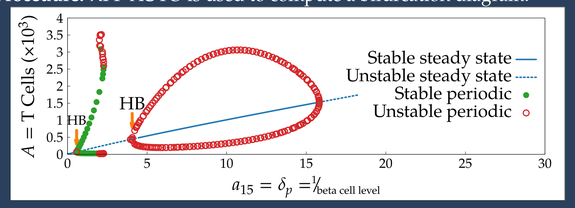
If the model for the level of immune cells in the weeks before the onset of type 1 diabetes is analyzed with both a continuously varying and a static peptide clearance rate δ_p, then in the former analysis, the oscillations present in the original model that indicate the onset of diabetes will begin 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 & Procedures)

Materials.

- Computer (x86-64 architecture running a Linux distribution)
  The software runs on all platforms; a relatively recent (past 5 years or so) computer will suffice.
- Computer Software: Python 3.3.3 with `mpmath`, `matplotlib`; XPP AUTO 7.0; ConTEXt 2014.01.03; Gnuplot 4.6.4
- Code: https://github.com/lidavidm/scifair-type1diabetes-model.

Procedure. XPP AUTO is used to compute a bifurcation diagram:



This shows, at a particular beta cell level, possible model states (T cell levels). The higher the level, the more beta cells can be destroyed. On a steady state, the system remains at a fixed T cell level, while the level oscillates on a periodic state. Introducing a small deviation on a steady state will result in the system returning to the original state, while in an unstable state the system may move towards another state. "HB" indicates a *Hopf bifurcation*, a point at which the system changes from stable to periodic or vice-versa. For the *continuous* analysis, the model starts at a particular a_{15} level, which varies linearly over time. At each time the a_{15} level is unique, and thus the A vs t plot can be overlaid on the bifurcation diagram as a A vs a_{15} plot to compare them (see *Results*). The model equations are

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

$$\frac{dE}{dt} = a_{12}(1 - f_2(p))A - a_{13} E \qquad p = \frac{a_{14}}{a_{15}} EB \qquad f_1 = \frac{p^{a_1}}{a_2^{a_1} + p^{a_1}} \qquad f_2 = \frac{a_4 a_5^{a_3}}{a_5^{a_3} + p^{a_3}}$$

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. Beta cells that undergo apoptosis generate peptide; then, T cells become activated, "recognizing" this peptide. These then become either effector cells, which destroy pancreatic cells, or memory cells, which trigger an immune response.

A 4th order Runge-Kutta solver (RK4) written in Python using `mpmath` is used to solve the continuous system. RK4 is standard 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

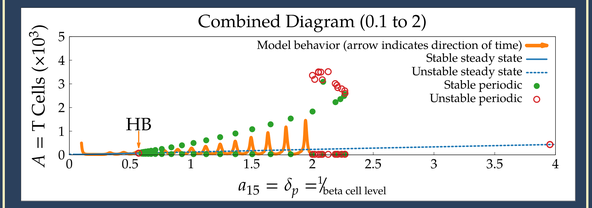


Figure 1. Combined diagram showing T cell level over time (as beta cell level decreases), over a duration of 200 days

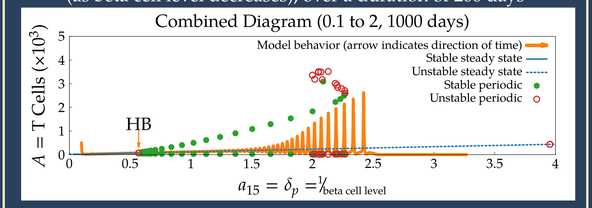


Figure 2. Combined diagram showing T cell level over time (as beta cell level decreases), but over a duration of 1000 days

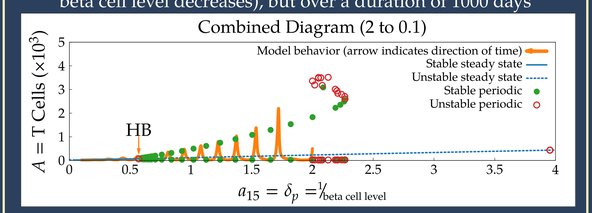


Figure 3. Combined diagram showing T cell level over time (as beta cell level *increases*), over a duration of 200 days

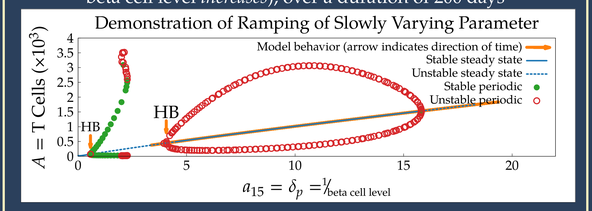


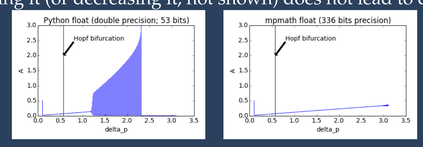
Figure 4. Combined diagram showing T cell level over time (as beta cell level *increases*), over a duration of 3200 days

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), which is the focus of this experiment, 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]. (See the diagram in the introduction.) Looking at figure 1, 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 experimentally in the mice. In figure 2, when the same amount of beta cell destruction occurs over a longer timeframe—1000 days rather than 200 (note the experiments covered roughly 200 days)—the oscillations occur far later than they should. This implies that theoretically, a way to slow down beta cell destruction would delay the onset of symptoms. Meanwhile, in figure 3, the beta cell level increases at a rate that outpaces the destruction caused by the immune system. In this scenario, the immune system still displays the response characteristic of the onset of diabetes—but as beta cell level is increasing, this response does not matter. Figure 4 examines the other Hopf bifurcation present, passing through it slowly; no oscillations occur, as expected: a high δ_p is normal [4] and increasing it (or decreasing it; not shown) does not lead to disease.



As for numerical precision, this experiment compared results from XPP and Python; no qualitative difference was found. Further tests found that running this model at double precision with certain parameter values leads to incorrect results: at left is double precision, at right a higher precision. The former incorrectly shows oscillations that begin too early and that oscillate too frequently.

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. However, the results herein further 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, and being able to theoretically detect the onset of type 1 diabetes earlier than expected before would allow more time for treatment and hopefully a higher quality of life for those affected.

Experimental error in this model may result from round-off due to finite numerical precision. To address this, `mpmath` with Python allowed the calculations to be conducted at higher precision for comparison with the result from XPP. Multiple trials were not necessary as the calculations were deterministic. (Internally, `mpmath` represents values with an integer mantissa and exponent and guarantees the correctness of basic arithmetic operations, the only ones used here [8].) This experiment thus demonstrated the viability of Python in research by comparing it to the standard tool XPP and showing when it is more capable.

Future Research

In this analysis, the level of beta cells linearly and monotonically varies, but beta cells regenerate; accounting for this would make the model more biologically accurate. Models of type 2 diabetes often consider 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-tune the model; note both the large error bars in the original data (see introduction) and the parameter sensitivity of this model [4]. Finally, the WKB method could be applied to approximate when exactly the oscillations begin [Dr. Stephen Baer, Arizona State University, personal communication, January 3, 2014].

Works Cited

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Acknowledgements

Thanks to Dr. Michael McKelvy, Dr. Stephen Baer, Dr. Joseph Mahaffy, Dr. Jiaxu Li