Introduction

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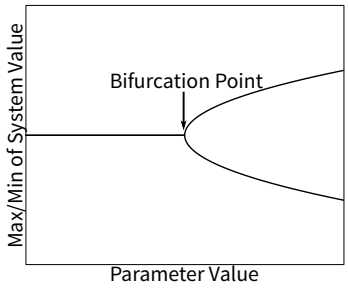
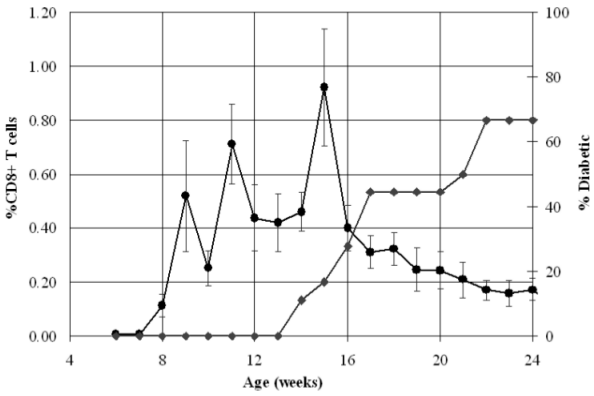
In type 1 diabetes, also known as autoimmune diabetes, the body's own immune system attacks and destroys insulin-producing pancreatic beta cells, leading to an insulin shortage and causing symptoms [1]. Currently, the causes and cures are largely unknown [2]. However, previous experiments have shown 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 [[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 as the disease progresses; at a certain level, the fluctuations described experimentally appear [4].

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.



Example of a Hopf bifurcation



Reproduced from [4]; experimental measurement of T cell levels in NOD mice over time, with diabetes occurring after the three "spikes"

[1]: Wisse, Brent (2013). Type 1 Diabetes. In *A.D.A.M. Medical Encyclopedia*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001350/.

[2]: Daneman, D. (2006). Type 1 diabetes. *The Lancet, 367*.

[3]: Trudeau, J. D. & Kelly-Smith, C. & Verchere, C. B. & Elliott, J. F. & Dutz, J. P. & Finegood, D. T. & Santamaria, P. & Tan, R. (2003). Prediction of spontaneous autoimmune diabetes in NOD mice by quantification of autoreactive T cells in peripheral blood. *Journal of Clinical Investigation, 111*.

[4]: Mahaffy, J. M. & Edelstein-Keshet, L. (2007). Modeling Cyclic Waves of Circulating T Cells in Autoimmune Diabetes. *SIAM Journal on Applied Mathematics, 67*.

[5]: Voorn, G. (2006). PhD mini course: introduction to bifurcation analysis. Retrieved from http://www.bio.vu.nl/thb/research/project/globif/Globif_text.pdf.

[6]: Baer, S. & Erneux, T. & Rinzel, J. (1989). The Slow Passage Through a Hopf Bifurcation: Delay, Memory Effects, and Resonance. *SIAM Journal on Applied Mathematics, 49*.