Introduction

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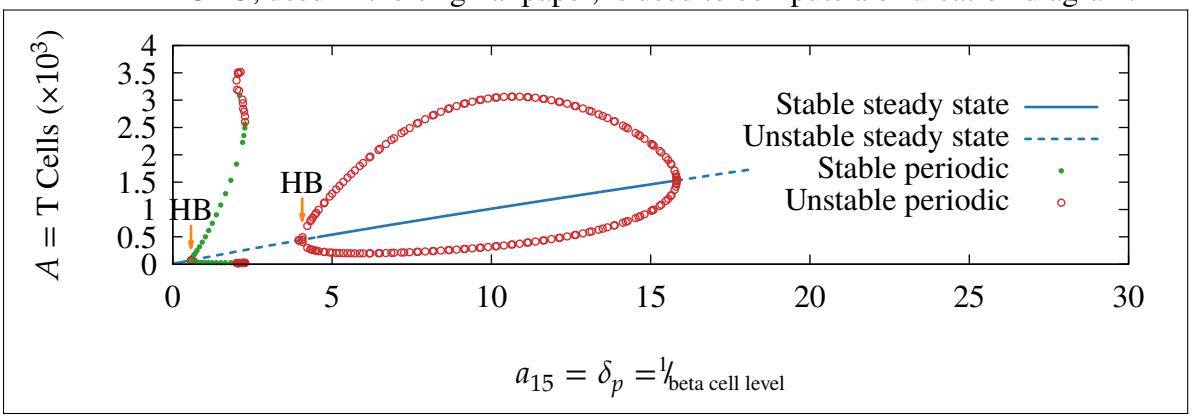
- Computer (x86-64 architecture running a Linux distribution)
  The exact specifications and the operating system do not matter, as the software used runs on all platforms. A relatively recent (past 5 years or so) computer will suffice.
- Computer Software
  - Python 3.3.3 with `mpmath` (http://www.python.org, 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.

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

$$\frac{dA}{dt} = (a_6 + a_7 M) f_1(p) - a_8 A - a_9 A^2$$

$$\frac{dM}{dt} = a_{10} f_2(p) A - f_1(p) a_7 a_{16} M - a_{11} M$$

$$\frac{dE}{dt} = a_{12}(1 - f_2(p)) A - a_{13} E$$

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

with $a_{15} = \delta_p = \text{constant}$ for the bifurcation diagram or $\frac{da_{15}}{dt} = \frac{d\delta_p}{dt} = \text{rate of change}$ 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 [1], used here because the continuous analysis could lead to numerical precision errors [2], and this implementation allows for arbitrary-precision computations [3].

[1]: Gonsalves, Richard J (2009). Runge-Kutta Methods for ODE Systems. *Computational Physics*. Retrieved on October 24, 2013 from http://www.physics.buffalo.edu/phy410-505-2009/topic3/lec-3-2.pdf.

[2]: 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*.

[3]: Johansson, F. (2011). Precision and representation issues. *mpmath v0.17 documentation*. Retrieved on September 14, 2013 from http://mpmath.googlecode.com/svn/trunk/doc/build/technical.html.