Enhancing Theoretical Understanding of the Onset of Type 1 Diabetes

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Research Question

How does treating the level of beta cells as a *continuously* varying slow parameter affect the qualitative behavior of the scaled reduced immune model developed by Mahaffy and Edelstein-Keshet [1], and how can those findings be applied to understanding and predicting 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 will begin at a later time because research has shown this behavior is delayed in other models when analyzed with a continuously varying parameter.

Materials

- Computer
- Software:

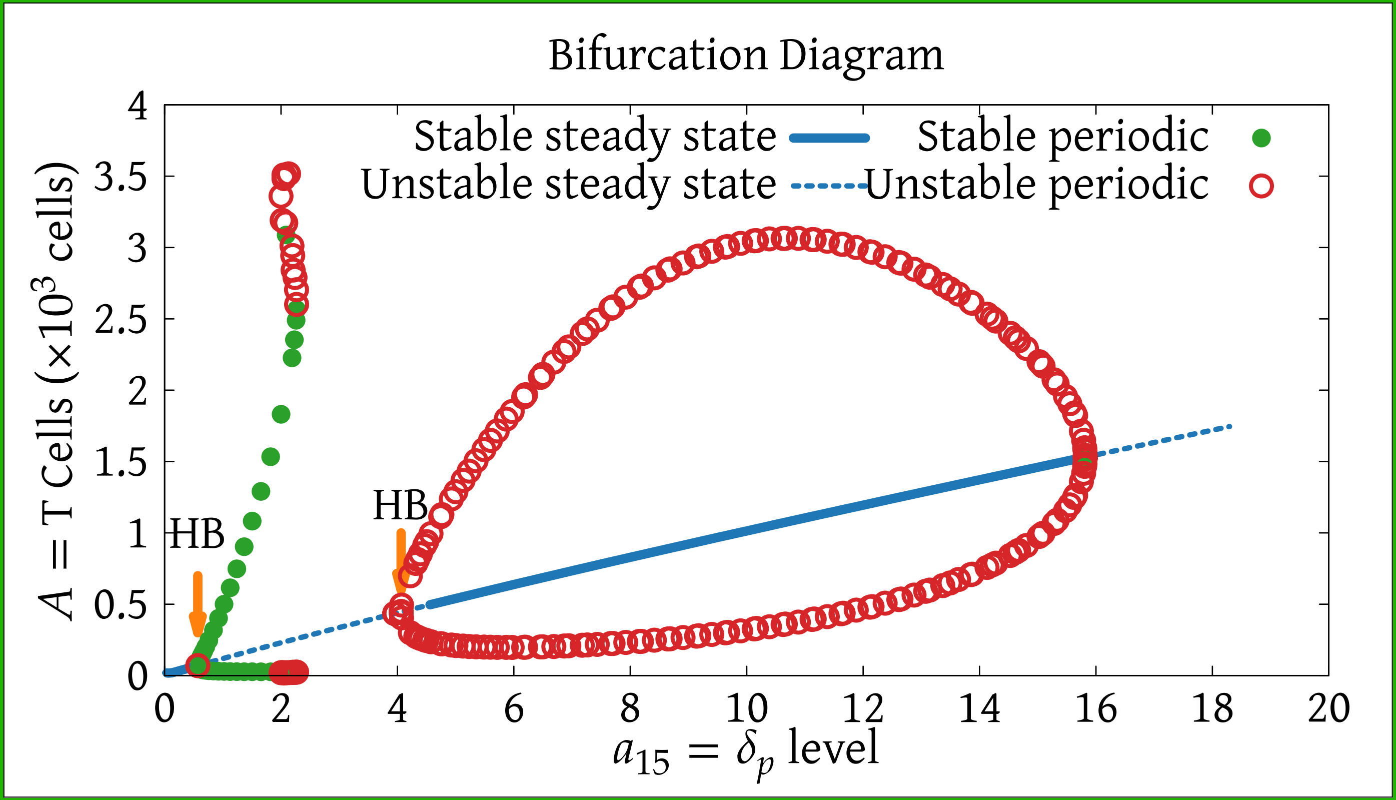
```
% python --version
Python 3.3.3
% ./xppaut -version
XPPAUT Version 7.0
% python -c "import mpmath; print(mpmath.__version__)"
0.17
% gnuplot --version
gnuplot 4.6 patchlevel 4
% context --version
mtx-context     | ConTeXt Process Management 0.60…
mtx-context     | current version: 2014.01.03
00:40
```

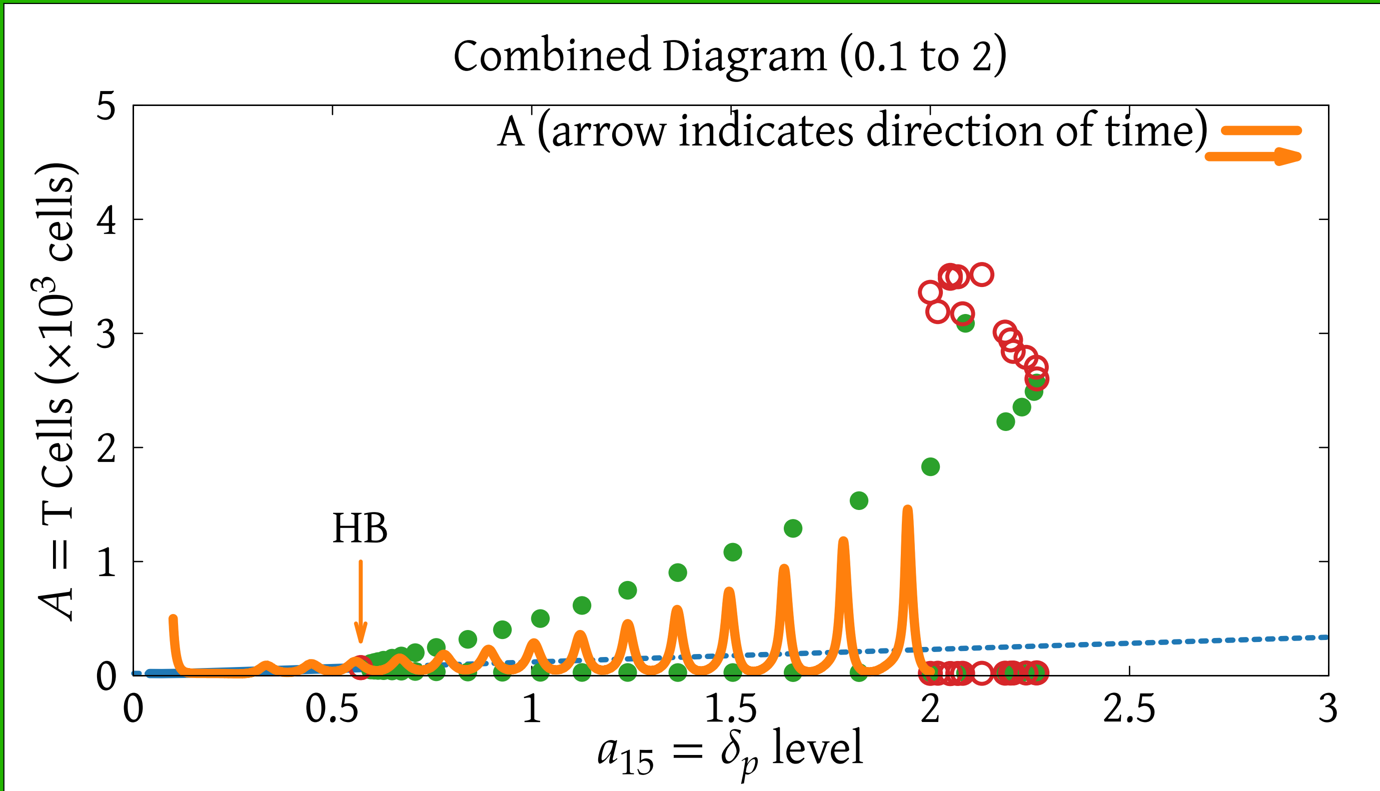
Procedure

1. Using AUTO, compute the data for the bifurcation diagram.
2. For each parameter range:
   a. Run the model with AUTO
   b. Run the model with Python
3. Plot everything

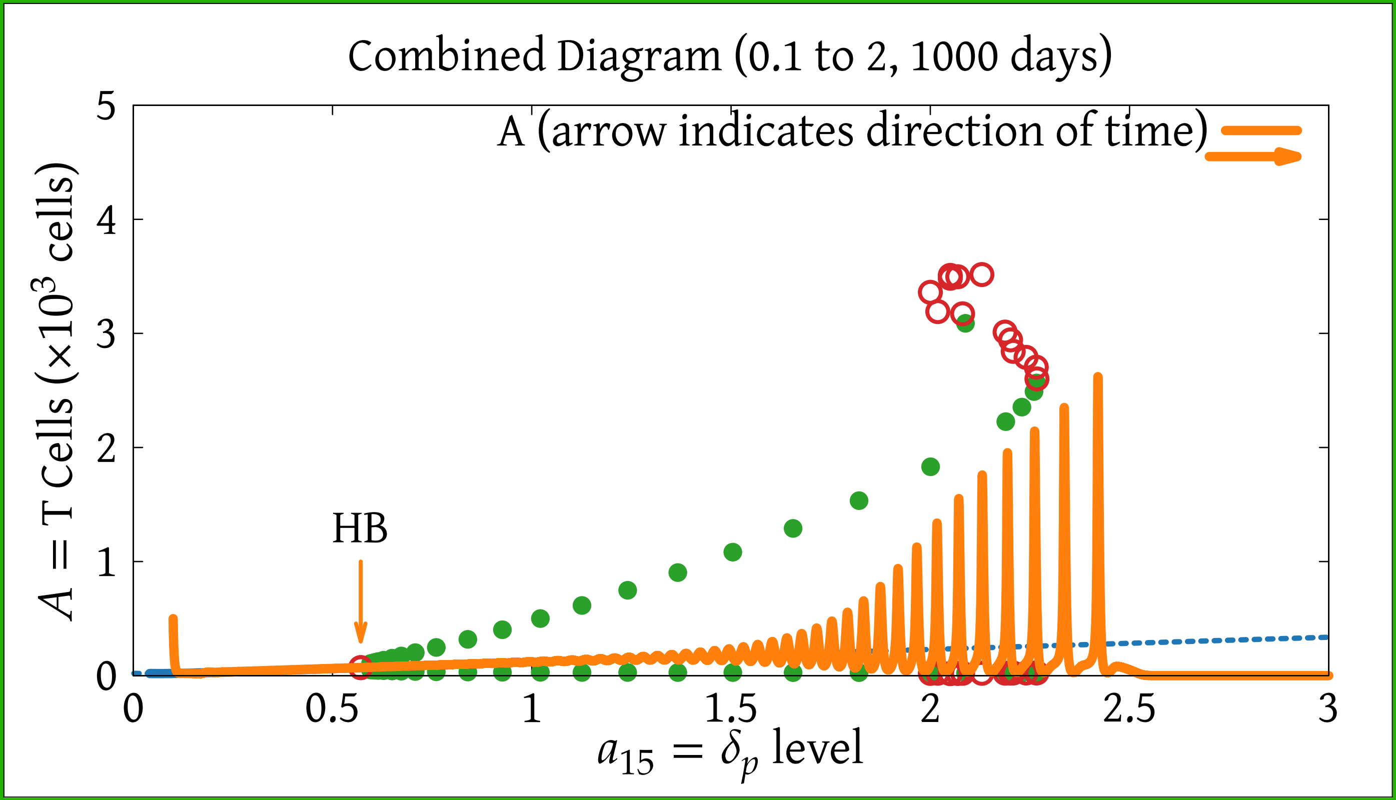
- AUTO is a standard tool for bifurcation and ODE work in mathematical modeling
- `mpmath` is newer and not seen in the field; used to verify results
- ConTEXt and Gnuplot are for generating plots (ConTEXt is a cousin of LaTeX, standard typesetting tool in the sciences)
- Only two "trials", but the experiment is deterministic—repetition unnecessary
- Control group is the bifurcation diagram; comparisons can also be made to Mahaffy's data and the original experiment
- Outside factors: round-off error (reason for Python)

Data

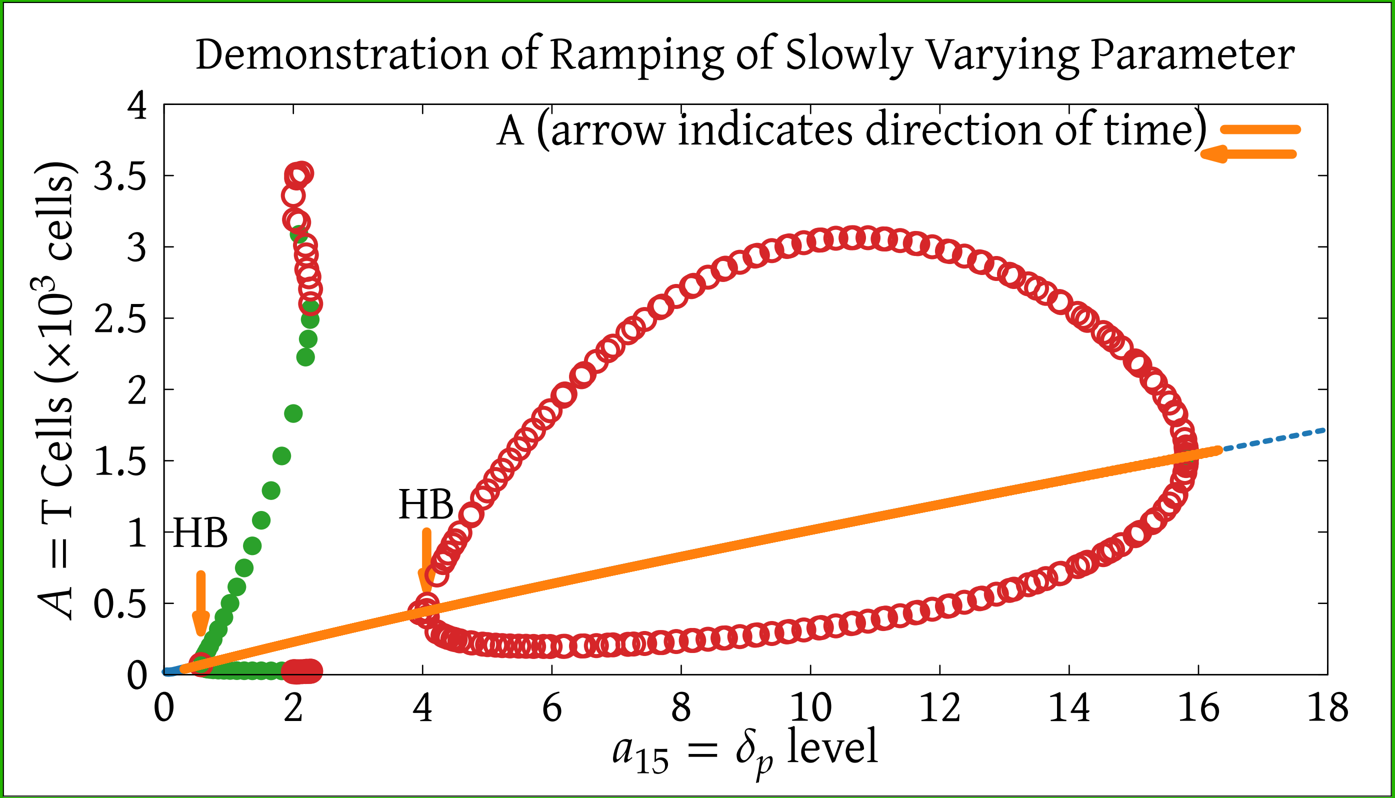

Bifurcation Diagram
Stable steady state
Unstable steady state
Stable periodic
Unstable periodic
HB
HB
A = T Cells ($\times 10^3$ cells)
$a_{15} = \delta_p$ level
0
0.5
1
1.5
2
2.5
3
3.5
4
0
2
4
6
8
10
12
14
16
18
20



Oscillations start *before* the bifurcation point, but don't become noticeable until after



On a less realistic time scale (1000 days vs 200), the oscillations start much later. If the beta cell decline can somehow be slowed...



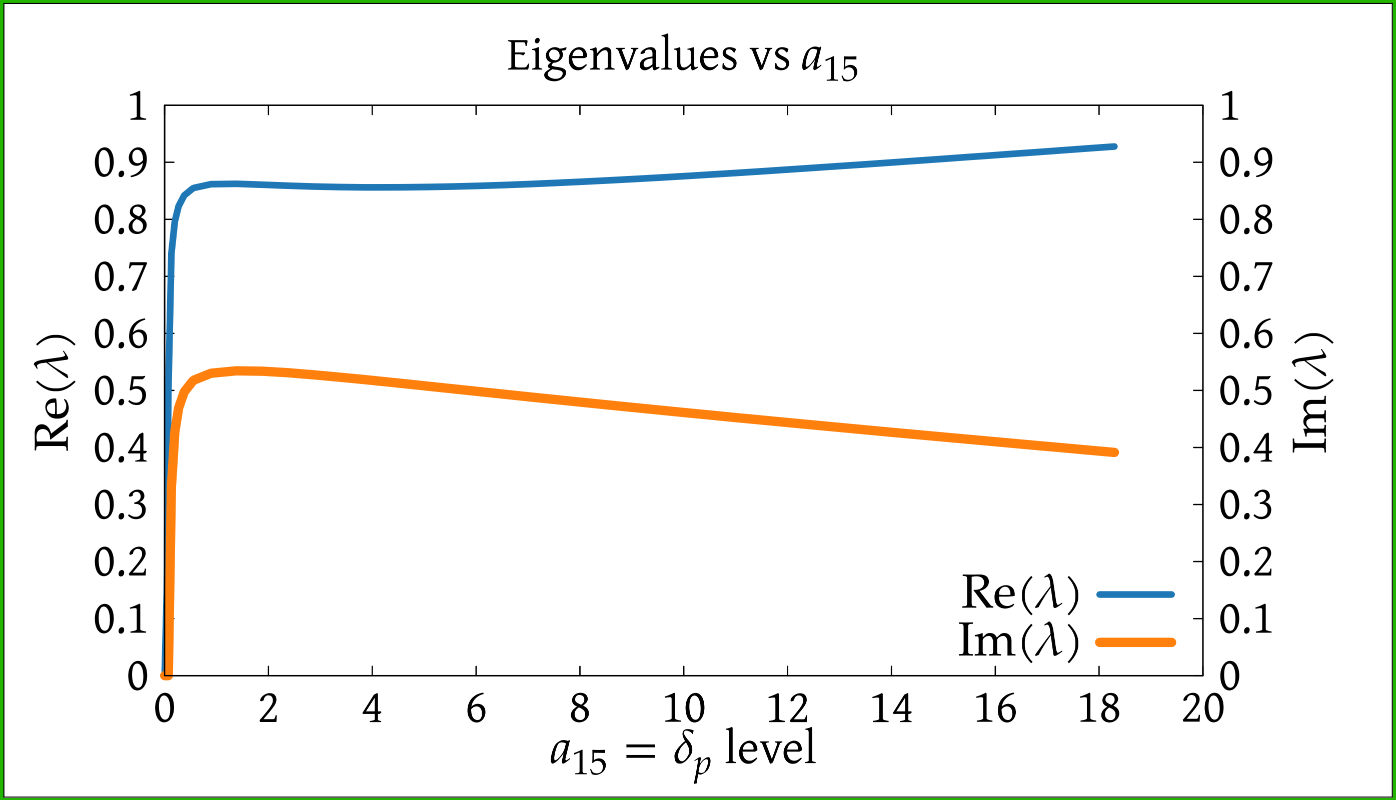
Starting from a condition with few beta cells/a high clearance rate shows no oscillations. Biologically, the disease has already set in...trying to lower δ_p doesn't help

Potential Impact

- Two interpretations: δ_p vs B (equivalent effect)
- Sufficiently lowering δ_p could delay the onset
- Increasing B or decreasing δ_p too late does nothing, of course
- Impact: speed of increase affects onset time; may contribute to explanation of individual variance
- Applications: look for treatments that can manipulate these variables, tests that can monitor them...
- Future work: address Mahaffy's concerns with his model to make it more accurate
- Having the original experimental data for comparison would be helpful

Further Analysis

- Dr. Baer pointed me to the WKB method, used to determine exact point at which oscillations begin in such studies
- Also suggested the idea of a $\mathrm{Re}(\lambda)$ vs δ_p graph, another way to tell when oscillations begin (contained in his paper)
- One issue with the latter...



$\mathrm{Re}(\lambda)$ never crosses the axis!