Modeling Type 1 Diabetes
in NOD Mice

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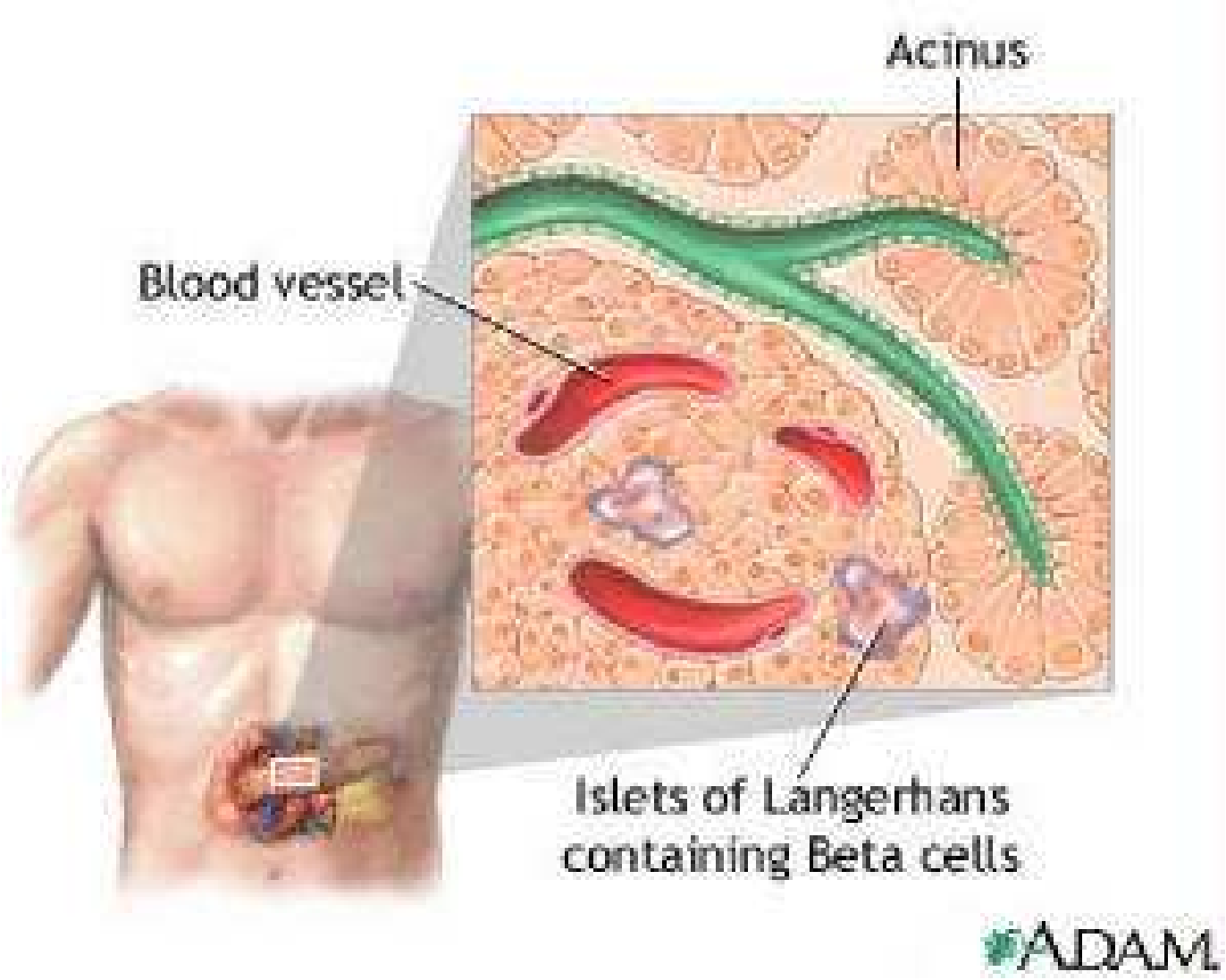
Outline

- Biology - Diabetes and Immune Response
- Mathematical Model
- Bifurcation Analysis
- Simulations
- Discussion and Conclusions

Glucose Metabolism

- Ingest food
  - Breaks down to simple sugars
- Blood absorbs sugar
  - Raises blood glucose concentration
- β cells in pancreas respond
  - Insulin released
- Cells increase glucose uptake
  - Insulin facilitates glucose transport across cell membranes, especially in skeletal muscles
- Glucose converted to glycogen
  - Preferred energy storage of cells
- Blood sugar level decreases
  - Body tightly regulates glucose levels

β Cells - Insulin Release



Type 1 or Juvenile Diabetes - Overview

- Diabetes mellitus results from the loss of β cells
  - An auto-immune disease
- Insulin production is severely reduced
- Hereditary disease - about 4-20 per 100,000 people
- Peak diagnosis occurs around age 14
- 10% of diabetes cases are Type 1, while 90% are Type 2 (where cells become insulin resistant, mostly in obese individuals)
- Treatment is regular injections of insulin - transplants are usually attacked by immune system

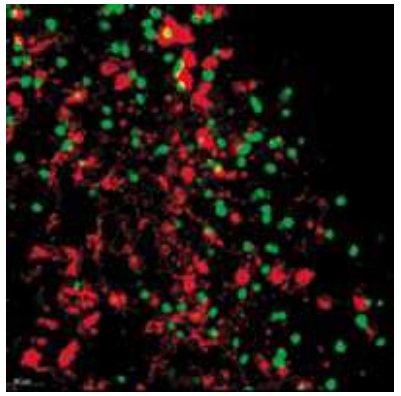
Type 1 or Juvenile Diabetes - Symptoms

- Classic Symptoms
  - Polyphagia (hungry)
  - Polydipsia (thirsty)
  - Polyuria (frequent urination)
- Other Symptoms
  - Blurred vision
  - Fatigue
  - Weight loss
  - Poor wound healing

Type 1 or Juvenile Diabetes - Disease

- Increased heart disease
  - Atherosclerosis from low insulin
- Blindness (retinopathy)
  - Increased pressure in eye
- Nerve damage (neuropathy)
- Kidney damage (nephropathy)

T Cell Activation

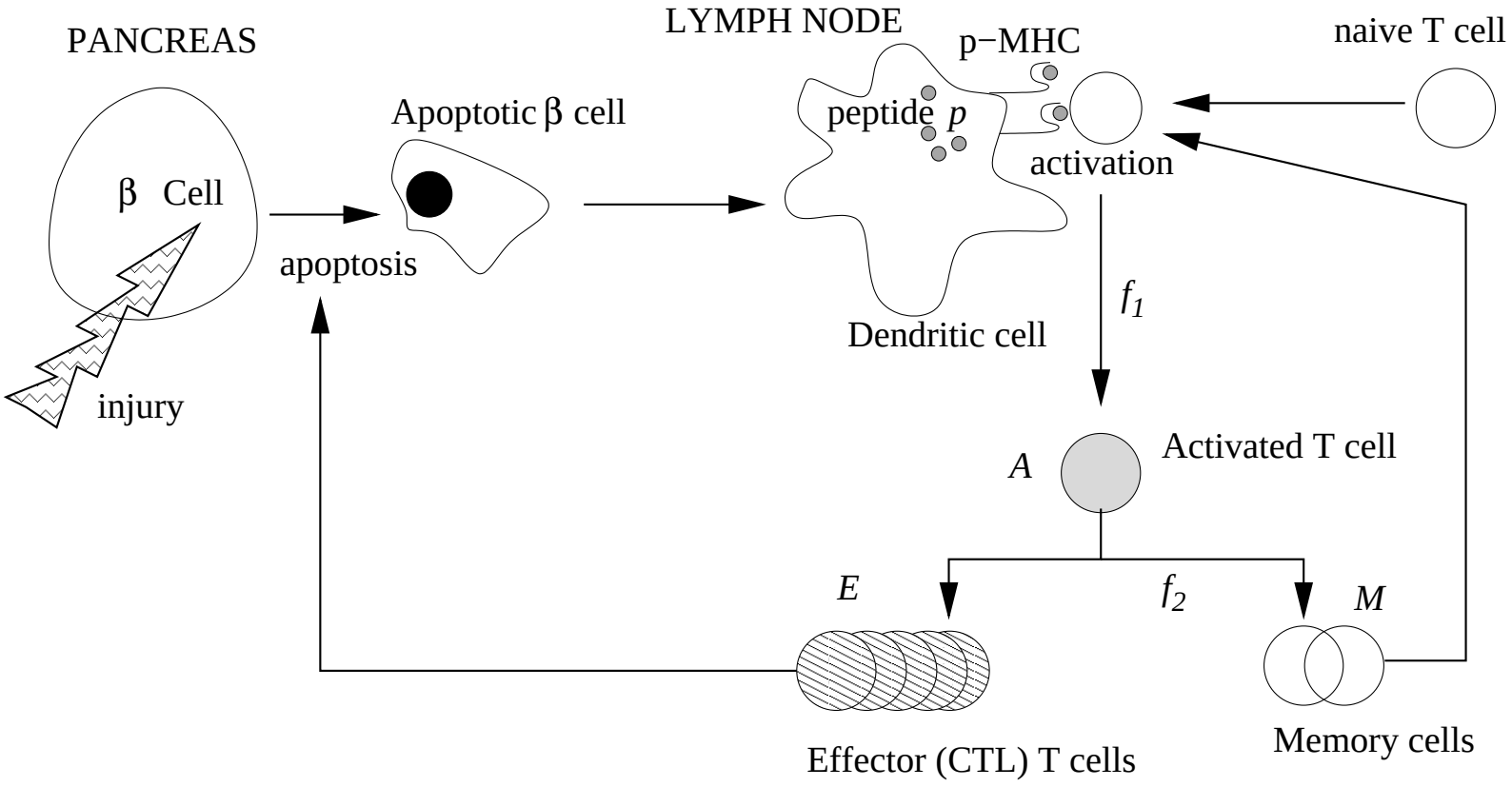


- T cells mature in the thymus
  - Cross-react with self-protein to prevent autoimmunity
- T cells migrate to Lymph nodes
  - Interact with antigen presenting cells (APCs)
  - APCs present antigen protein fragment (about 9 AAs) inside MHC (major histocompatibility complex)
  - The peptide-MHC complex interacts with T cells surface receptors
  - T cells with appropriate specificity become activated
- Most antigens are foreign proteins from viruses and bacteria

T Cell Immune Response

- Activated T cells proliferate about 6 cell divisions
- Most become Effector cells (cytotoxic T-lymphocytes or CTLs)
  - CTLs are efficient specific killers, destroying target cells
  - Relatively short-lived
- Some become Memory cells
  - No immediate effect
  - Long-lived cells
  - New exposure to same antigen, rapidly activated
  - Strategy for vaccines
- Type 1 diabetes when CTLs attack β cells in pancreas
- Other autoimmune diseases are similar

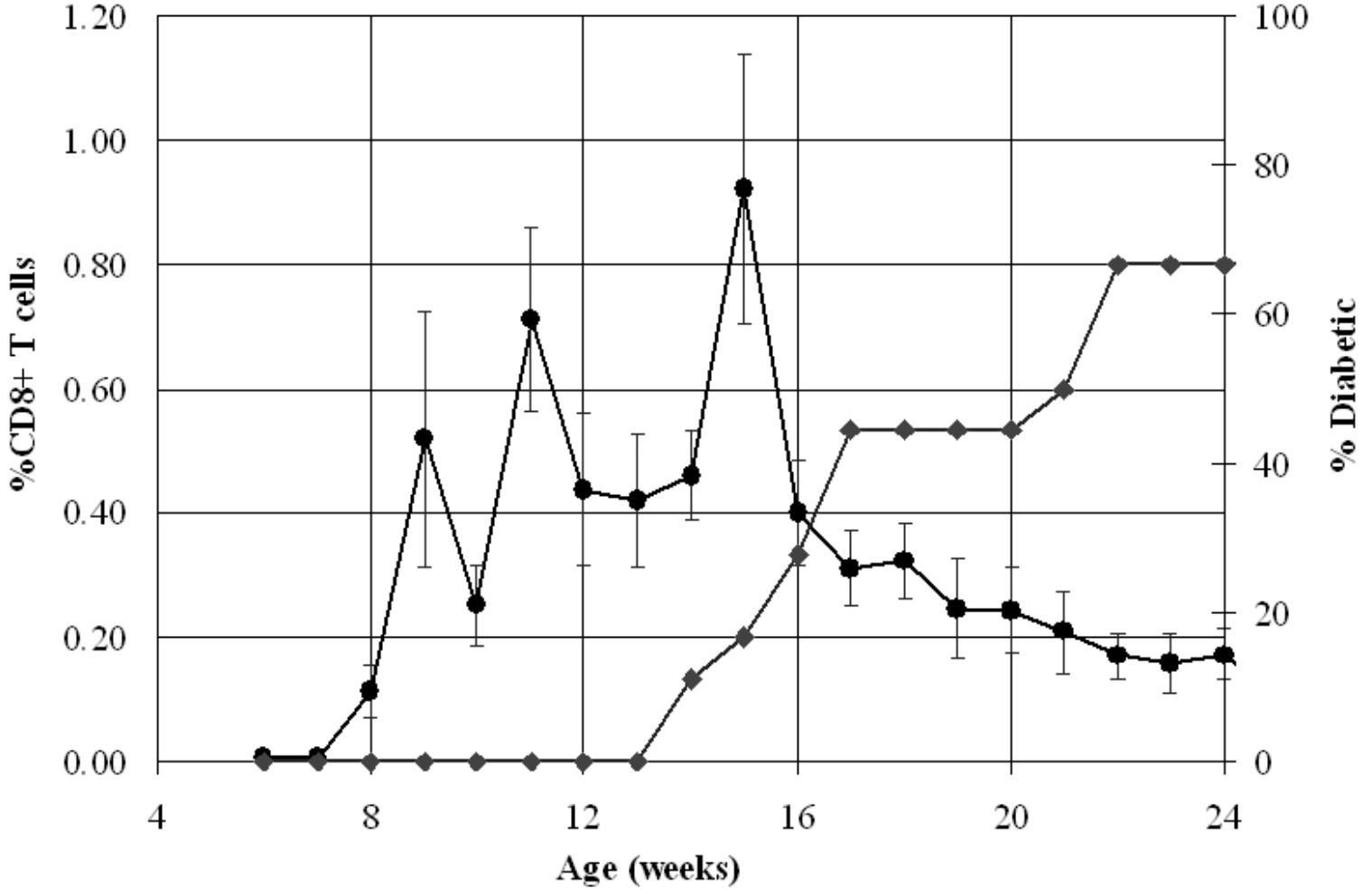
Model Scheme for Diabetes



Animal Model for Diabetes

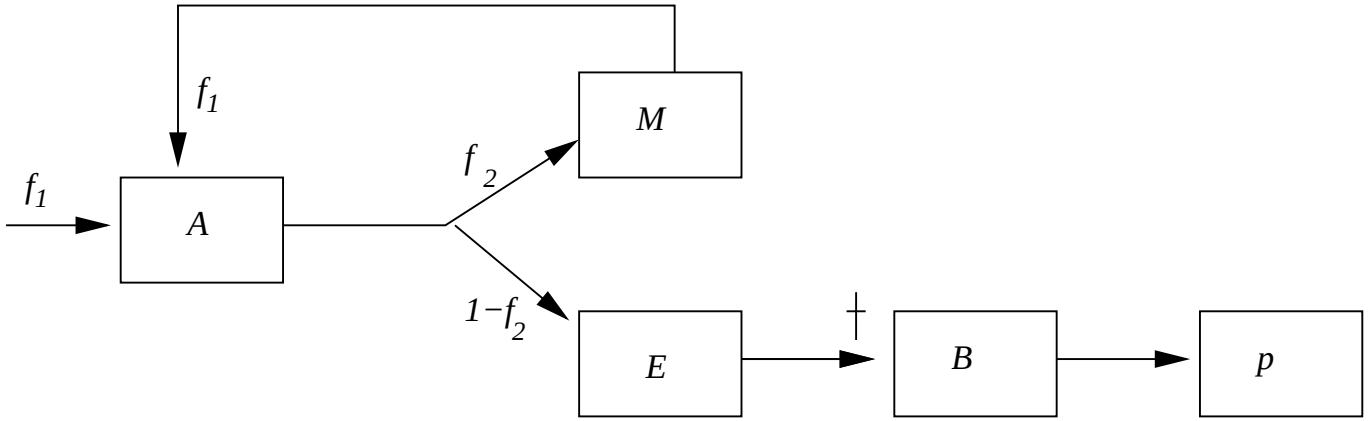
- Non-Obese Diabetic or NOD mice undergo apoptosis or programmed cell death of β cells in the pancreas shortly after birth
- Clearance of apoptotic cells by macrophages is reduced
  - Possibly forms self-antigen
  - Experiments suggest a fragment from IGRP (glucose-6-phosphate catalytic subunit-related protein) produces a dominant antigen
- Experiments designed to find autoreactive CD8+ T cells in pancreas of NOD mice
- Observed three waves of CD8+ T cells before mice became diabetic around 16 weeks

NOD Mice Data



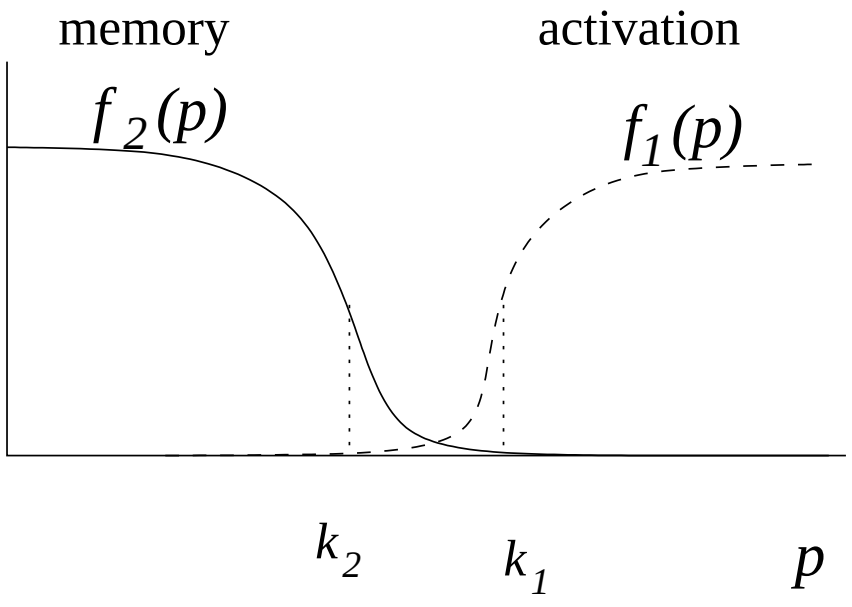
Link to Model Simulation

Simple Model Schematic



- $A =$ Activated T cells
- $M =$ Memory cells
- $E =$ Effector or killer T cells
- $p =$ peptide
- $B =$ Fraction of remaining β cells

Feedback Functions



Activation function

$$f_1(p) = \frac{p^n}{k_1^n + p^n}$$

Inhibition function

$$f_2(p) = \frac{ak_2^m}{k_2^m + p^m}$$

Complete Model

$$
\begin{aligned}
\frac{dA}{dt} &= (\sigma + \alpha M) f_1(p) - (\beta + \delta_A) A - \epsilon A^2 \\
\frac{dM}{dt} &= \beta 2^{m_1} f_2(p) A - f_1(p) \alpha M - \delta_M M \\
\frac{dE}{dt} &= \beta 2^{m_2} (1 - f_2(p)) A - \delta_E E \\
\frac{dp}{dt} &= REB - \delta_p p \\
\frac{dB}{dt} &= -\kappa EB
\end{aligned}
$$

with nonlinear feedback functions

$$
\begin{aligned}
f_1(p) &= \frac{p^n}{k_1^n + p^n} \\
f_2(p) &= \frac{a{k_2}^m}{k_2^m + p^m}
\end{aligned}
$$

Activated T cells

$$
\begin{aligned}
\frac{dA}{dt} &= (\sigma + \alpha M) f_1(p) - (\beta + \delta_A) A - \epsilon A^2 \\
\frac{dM}{dt} &= \beta 2^{m_1} f_2(p) A - f_1(p) \alpha M - \delta_M M \\
\frac{dE}{dt} &= \beta 2^{m_2} (1 - f_2(p)) A - \delta_E E \\
\frac{dp}{dt} &= REB - \delta_p p \\
\frac{dB}{dt} &= -\kappa E B
\end{aligned}
$$

The production of activated T cells, A, from naive T cells and memory cells.

Activated T cells

$$
\begin{aligned}
\frac{dA}{dt} &= (\sigma + \alpha M) f_1(p) - (\beta + \delta_A) A - \epsilon A^2 \\
\frac{dM}{dt} &= \beta 2^{m_1} f_2(p) A - f_1(p) \alpha M - \delta_M M \\
\frac{dE}{dt} &= \beta 2^{m_2} (1 - f_2(p)) A - \delta_E E \\
\frac{dp}{dt} &= REB - \delta_p p \\
\frac{dB}{dt} &= -\kappa EB
\end{aligned}
$$

The production of activated T cells, A, from naive T cells and memory cells.

The loss of activated T cells, A, becoming effector and memory T cells, decaying, and competing with others.

Effector T Cells and β Cells

$$
\begin{aligned}
\frac{dA}{dt} &= (\sigma + \alpha M) f_1(p) - (\beta + \delta_A) A - \epsilon A^2 \\
\frac{dM}{dt} &= \beta 2^{m_1} f_2(p) A - f_1(p) \alpha M - \delta_M M \\
\frac{dE}{dt} &= \beta 2^{m_2} (1 - f_2(p)) A - \delta_E E \\
\frac{dp}{dt} &= REB - \delta_p p \\
\frac{dB}{dt} &= -\kappa EB
\end{aligned}
$$

The effector T cells, E, destroy β cells producing the protein that activates T cells.

Complete Model - Discussion

- 5-Dimensional Model
  - Highly nonlinear
  - Difficult to analyze
- 17 Physiological parameters
  - Many are known or have good estimates
  - Constrains possible solutions
- Time Scale
  - The peptide, p, has fast reaction kinetics
  - This allows Quasi-Steady State Approximations
  - The β cells, B, have slow dynamics
  - This allows consideration of slow changing parameter

Quasi-Steady State Model

The model for analysis consists of three equations:

$$\begin{aligned}
\frac{dA}{dt} &= (\sigma + \alpha M) f_1(p) - (\beta + \delta_A) A - \epsilon A^2 \\
\frac{dM}{dt} &= \beta 2^{m_1} f_2(p) A - f_1(p) \alpha M - \delta_M M \\
\frac{dE}{dt} &= \beta 2^{m_2} (1 - f_2(p)) A - \delta_E E
\end{aligned}$$

together with the QSS peptide expression

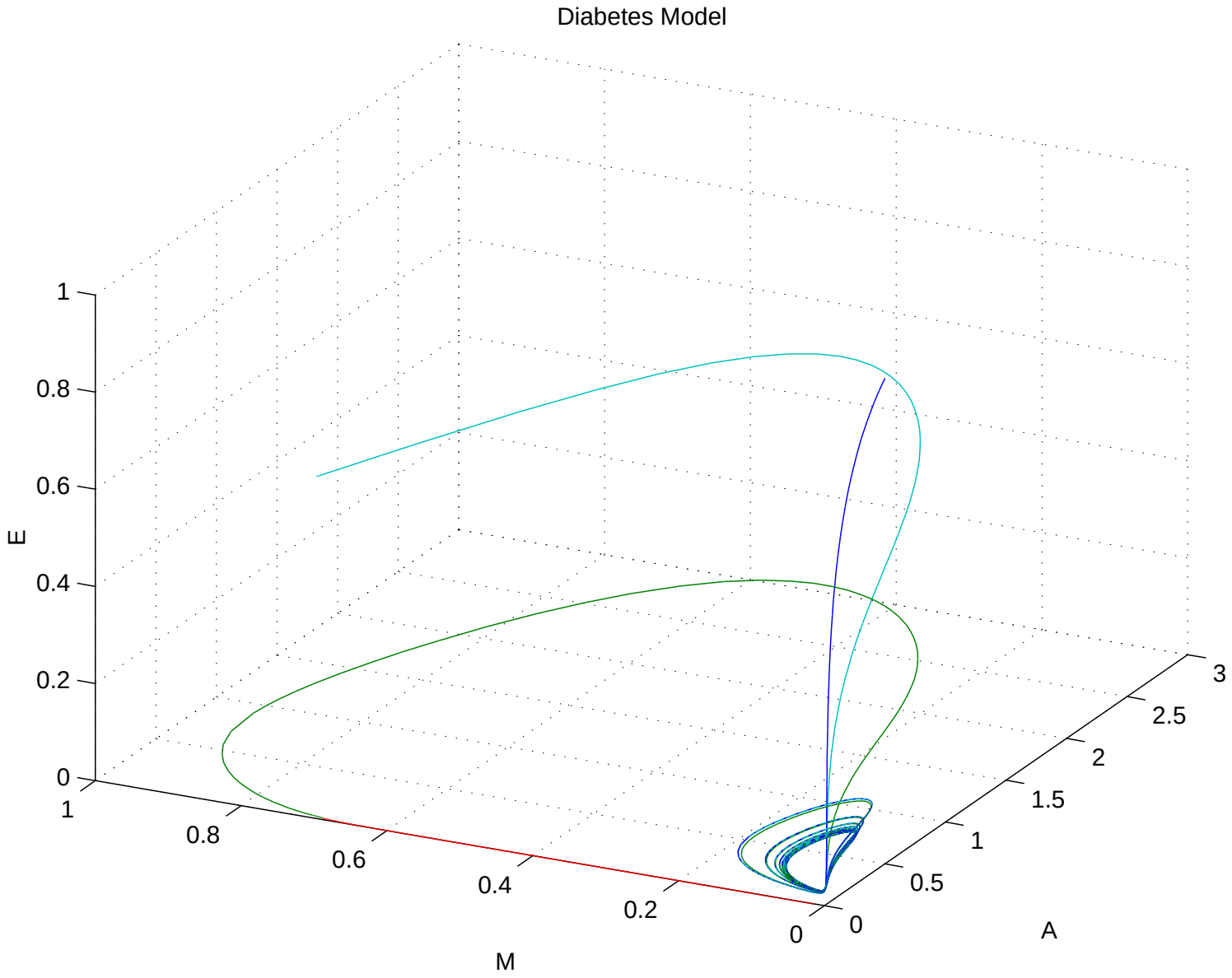
$$p \approx (RB/\delta_p) E$$

3-D system of differential equations permits a more complete analysis.

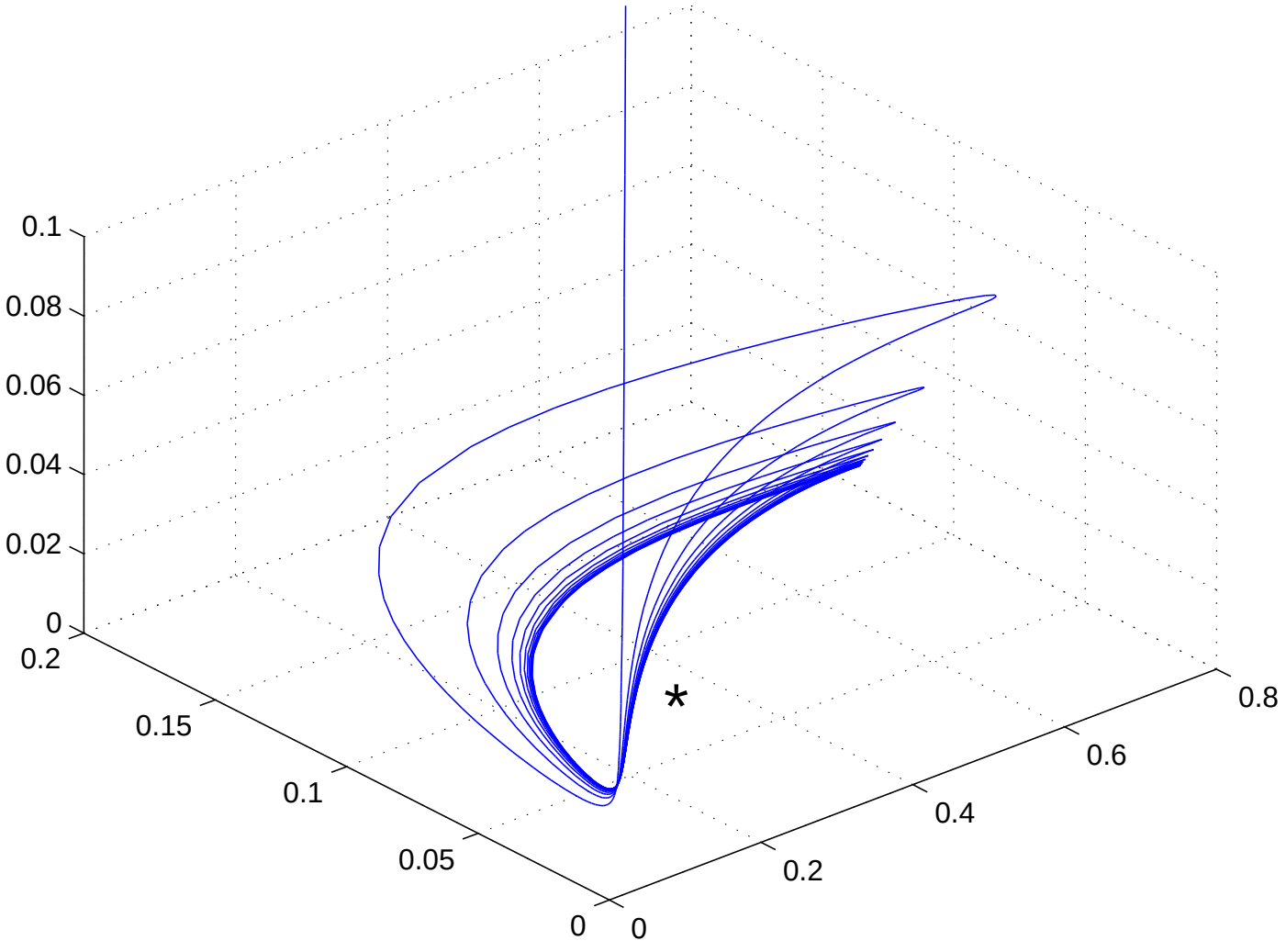
QSS Model - Discussion

- **Equilibria**
  - There are 1-5 equilibria
  - With physiological parameters, 3 equilibria exist
- **Linear Analysis** of 3 Equilibria
  - **Origin** is a Stable Node
  - **Diseased State** is a Node that is Stable or Unstable depending on parameters
  - Third equilibrium is a Saddle Node

3D Phase Portrait



3D Phase Portrait



QSS Model - Parameter Study

- **Parameters**
  - Experimental data compiled by Marée, Santamaria, and Edelstein-Keshet
  - Physiological range of parameters limited by their study for most parameters in the model
  - Several parameters remain unknown, so varied to obtain desired behaviour
  - Sensitivity of the parameters was studied

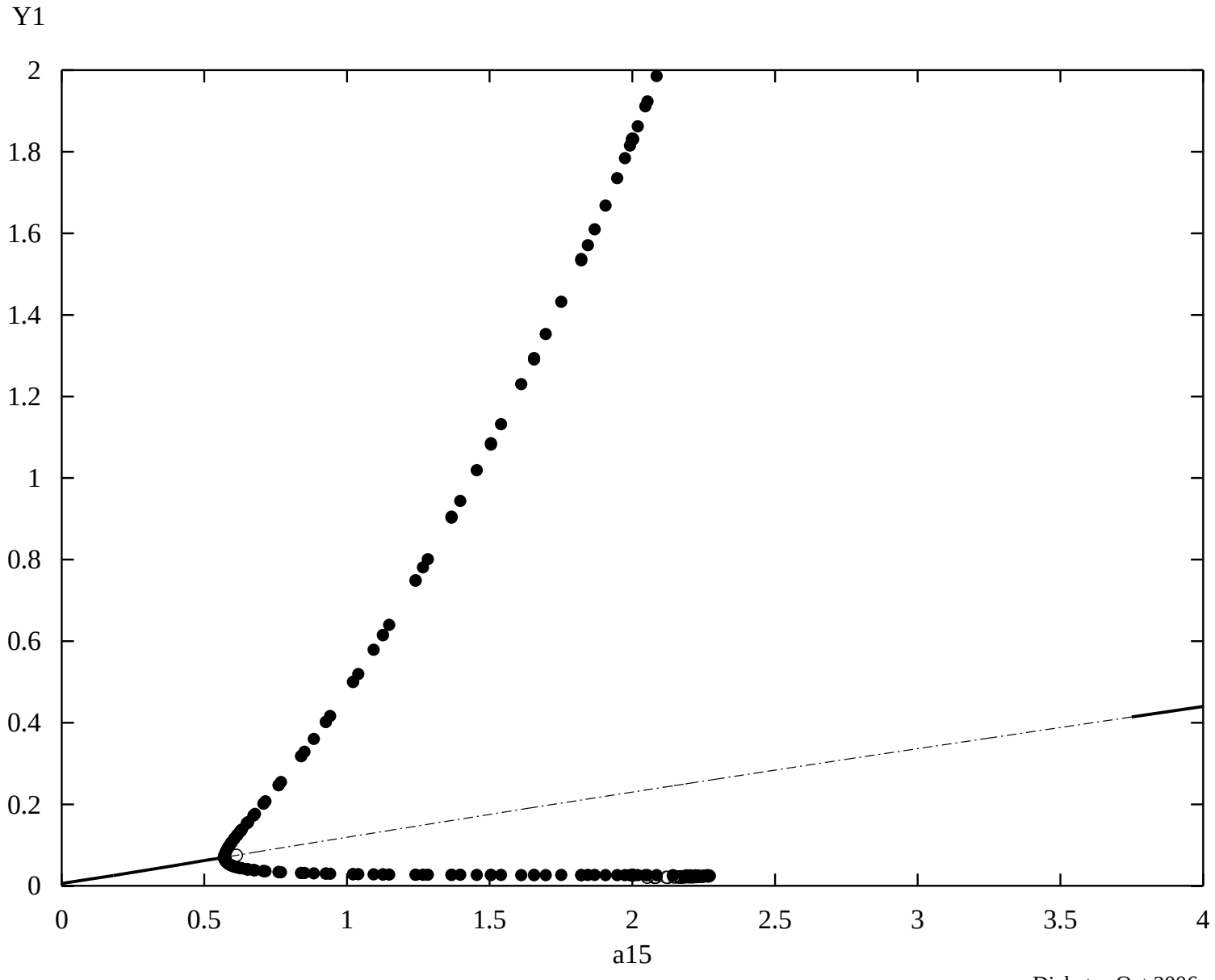
QSS Model - Bifurcation Study

- **Bifurcation Analysis**
  - Many parameters investigated using **AUTO** with **XPP**
  - Chose peptide clearance rate δ_p as it is believed that poor clearance could induce diabetes
  - In the normal range of clearance, the most solutions approached the **Origin**
  - When halved, the many solutions oscillated about the **Diseased State**
  - The **QSS** approximation is

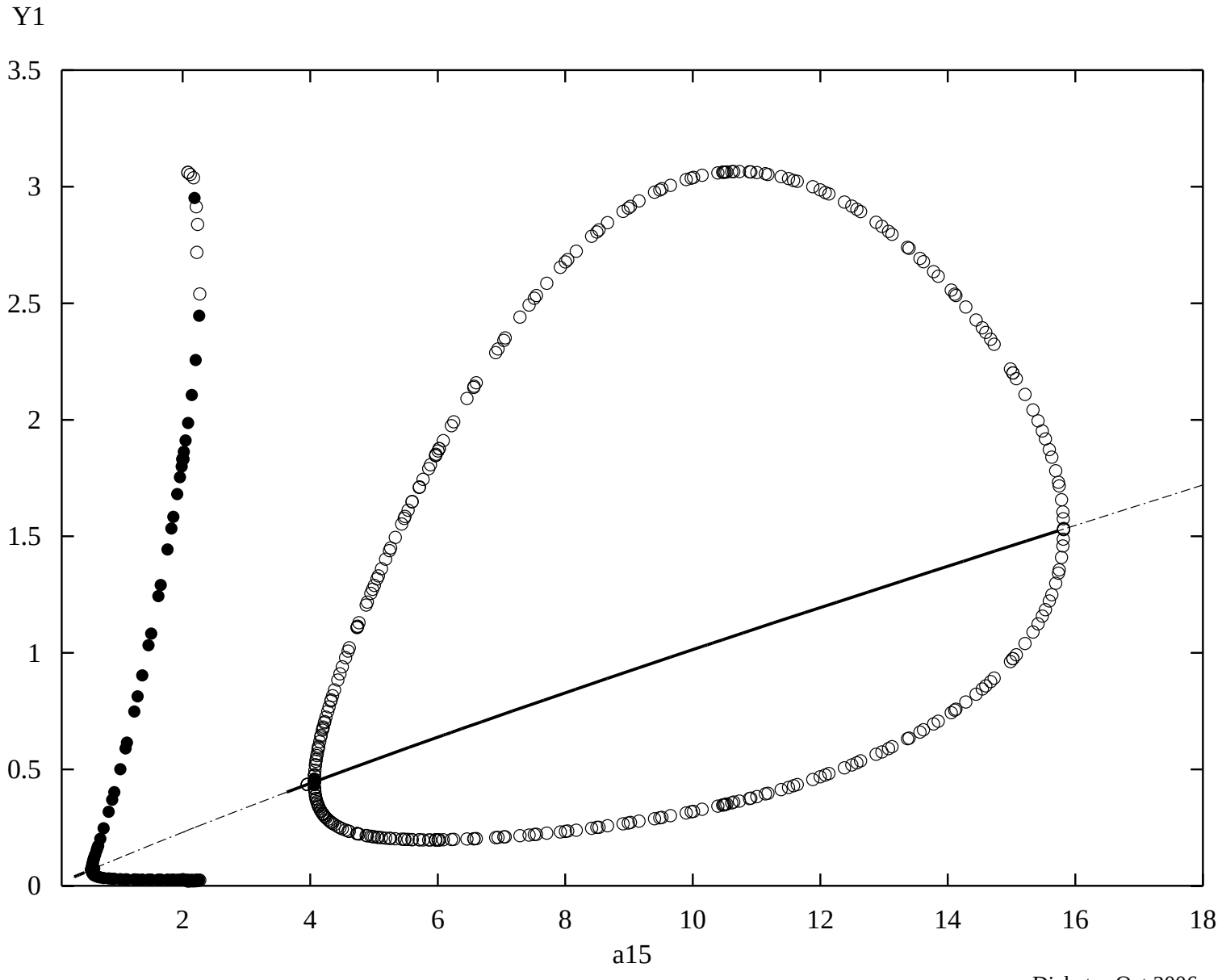
$$p \approx \frac{RB}{\delta_p} E,$$

so δ_p increasing is similar to B decreasing

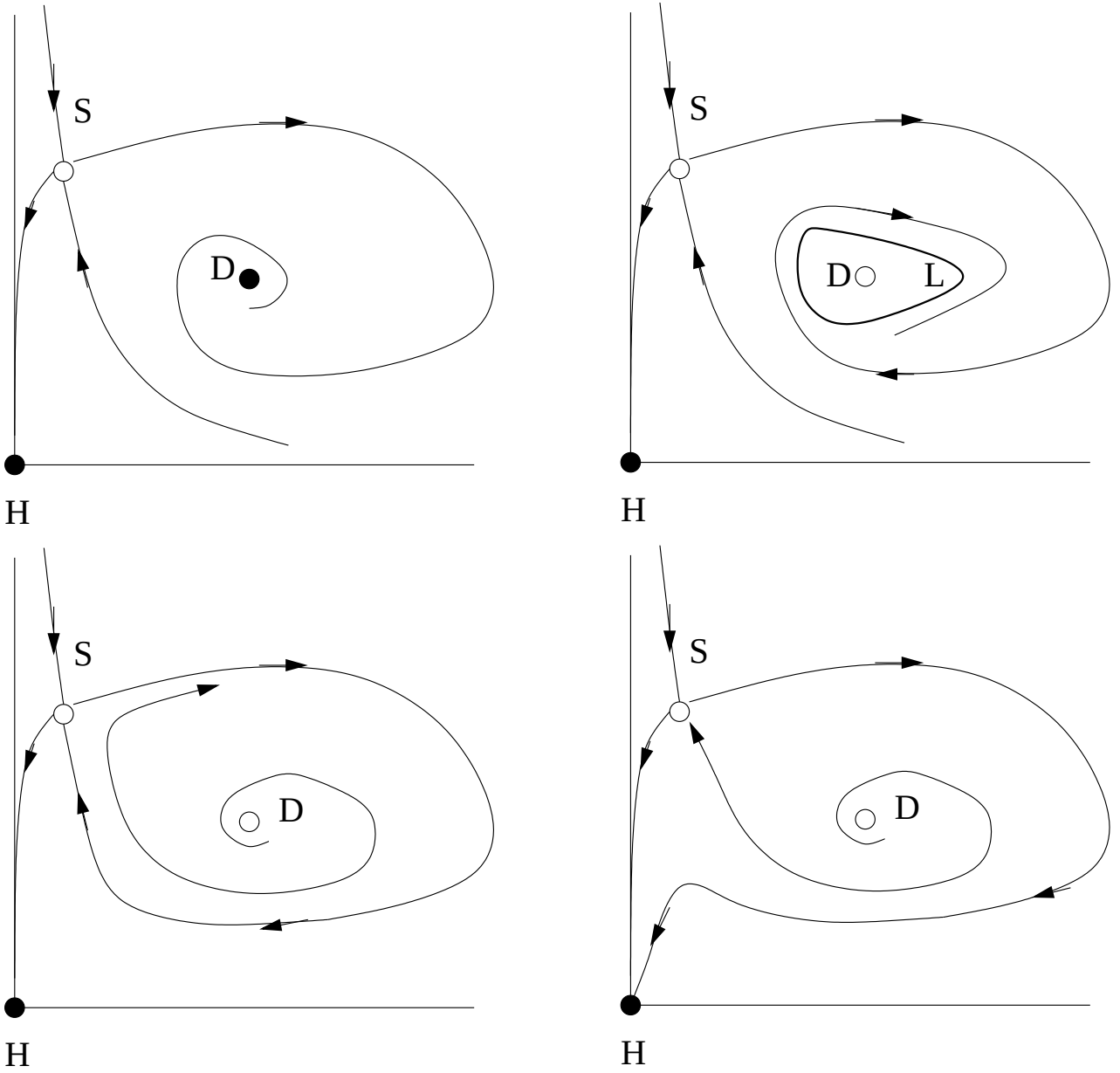
Bifurcation Diagram



Bifurcation Diagram



Homoclinic Bifurcation

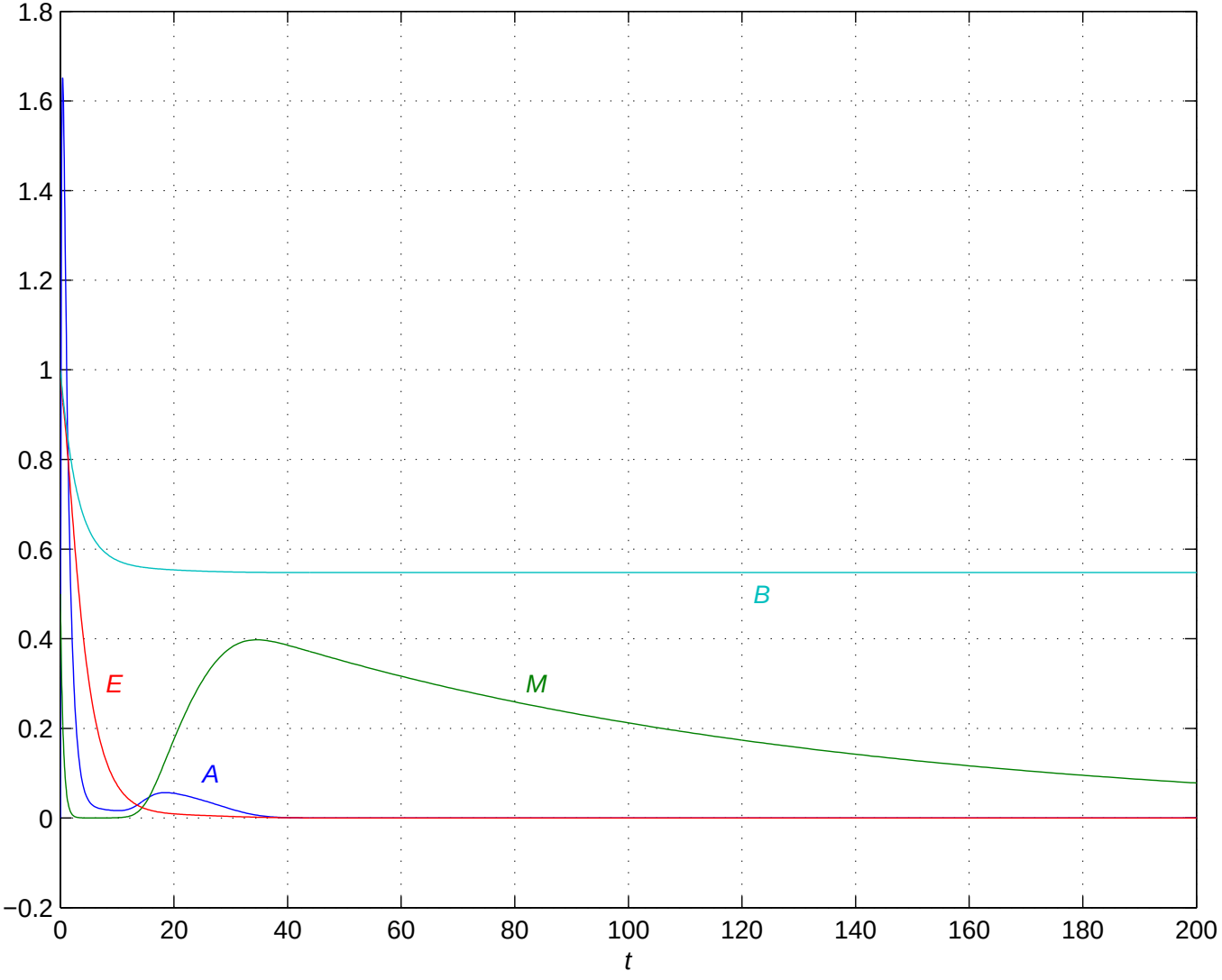


Link to Diabetic SimulationLink to Normal Simulation

Complete Model - Normal Mouse

- Simulated complete model for a normal mouse
  - Assumed an initial response of **Effector T cells**
  - Normal parameter values
  - Some β cells die, but levels at high equilibrium

Simulation - Normal Mouse

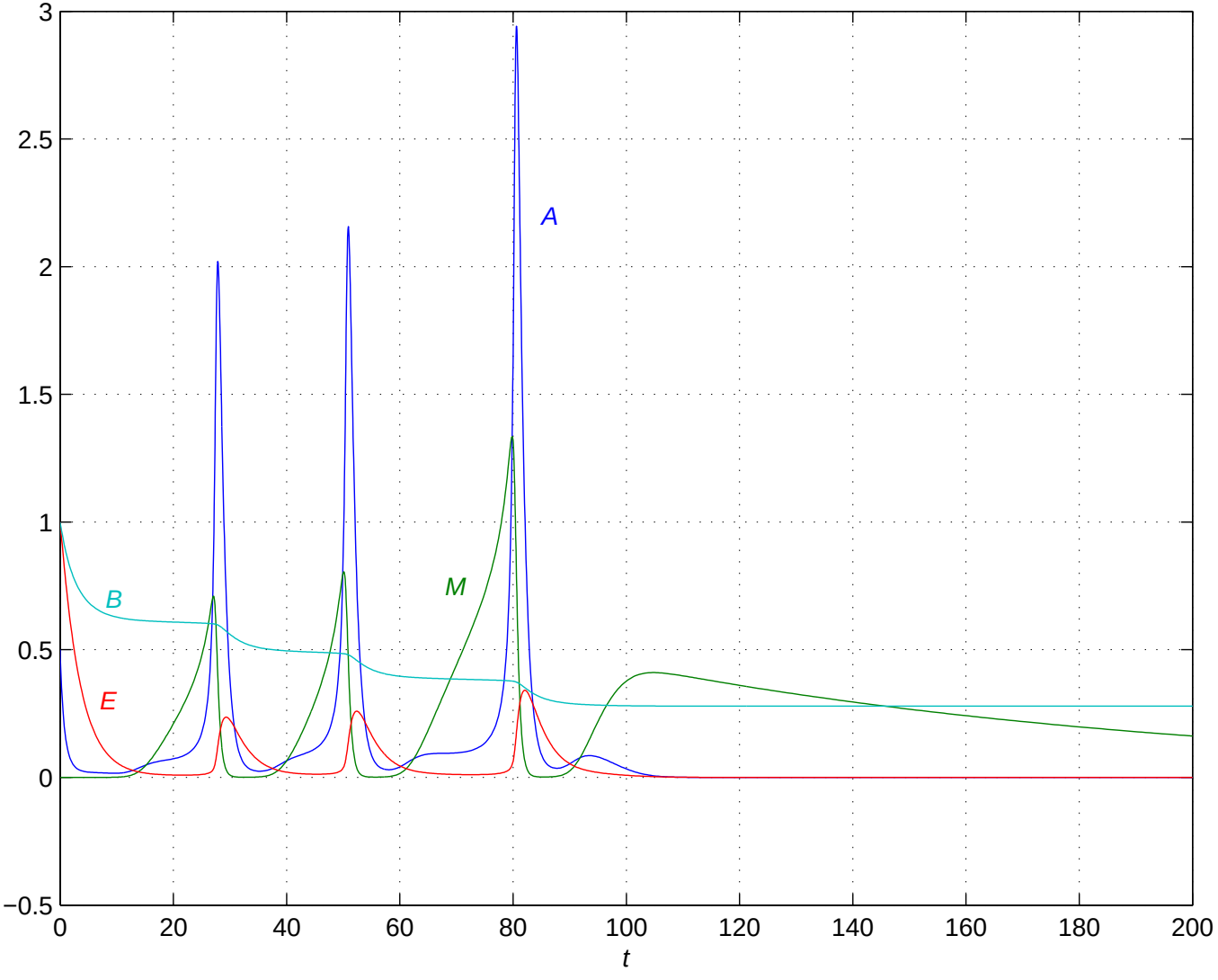


Link to Homoclinic Diagram

Complete Model - Diabetic Mouse

- Simulated complete model for a diabetic mouse
  - Assumed an initial response of **Effector T cells**
  - Lower peptide clearance
  - Increasing spikes of **Activated T cells**
  - Waves of short-lived **Effector T cells**
  - High **Memory cell** populations allow new response
  - Slow decline of β cells until diabetic

Simulation - Diabetic Mouse



Link to Experimental dataLink to Homoclinic Diagram

Discussion and Conclusions

- Designed a reasonable model for NOD mice
- Parameters fit physiological data
- Simulations indicate parameters and initial conditions may be too sensitive
- Excellent qualitative behaviour of the model
- Good example of a homoclinic bifurcation
- Model supports biological theory of defective clearance after apoptosis