Math 636 - Mathematical Modeling

Modeling Diabetes

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Outline

Introduction

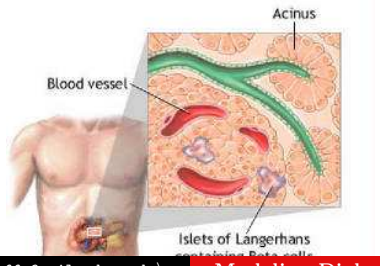
Introduction

- **Diabetes** is a disease, characterized by excessive glucose in the blood stream.
- Currently, there is an epidemic of diabetes.
  - Modern unhealthy lifestyles are dramatically different from how humans survived when they evolved from small nomadic hunter-gatherer societies.
  - Then food was difficult to find.
- There are two forms of diabetes.
  - ***Type 1***, often called ***juvenile diabetes***.
  - ***Type 2***, often referred to as ***adult onset diabetes*** (which now occurs in children as young as 5).
- Our studies concentrate on Type 1 diabetes, which is an autoimmune disease and represents only 10% of all cases of diabetes.

Glucose Metabolism

Glucose Metabolism

- Ingest food, which breaks down to simple sugars.
- Blood absorbs sugar, which raises blood ***glucose concentration***.
- β ***cells*** in pancreas respond and ***insulin*** is released.
- Cells increase glucose uptake.
  - Insulin facilitates glucose transport across cell membranes, especially in skeletal muscles.
  - Glucose converted to glycogen, the preferred energy storage of cells.
  - Blood sugar level decreases.
- Body tightly regulates glucose levels.



Type 1 or Juvenile Diabetes - Overview

Type 1 or Juvenile Diabetes - Overview

- ***Diabetes mellitus*** results from the loss of β cells, an auto-immune disease.
  - Hereditary disease - about 4-20 per 100,000 people.
  - Peak diagnosis occurs around age 14.
- Insulin production is severely reduced.
- 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.
- ***Modern modeling methods*** and ***implanted devices*** allow continuous monitoring of the body glucose levels and computer controlled release of insulin (still ***experimental***).

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Type 1 or Juvenile Diabetes - Symptoms and Diseases

Type 1 or Juvenile Diabetes - Symptoms and Diseases

- Classic Symptoms
  - Polyphagia (hungry)
  - Polydipsia (thirsty)
  - Polyuria (frequent urination)
  - Other symptoms
    - Blurred vision, fatigue, weight loss, poor wound healing
- Diseases
  - Increased heart disease - Atherosclerosis from low insulin
  - Blindness (retinopathy) - Increased pressure in eye
  - Nerve damage (neuropathy)
  - Kidney damage (nephropathy)
- Current prognosis is ***premature death***.

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Modeling Glucose Metabolism

Modeling Glucose Metabolism: The regulation of glucose in the blood begins with the ingestion of food.

Hormones: β-cells in the pancreas to release insulin into the blood (along with a number of other hormones), where insulin facilitates of glucose transport across cell membranes and conversion of glucose to glycogen in the liver.

- ***Other hormones*** include:
  - Epinephrine (adrenalin) is released to break down the glycogen.
  - Glucocorticoids help metabolize carbohydrates.
  - Growth hormone can block the effects of insulin.
- Many other hormones regulate glucose levels in the blood, creating a complex regulatory system.

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Diabetes Detection

Diabetes Detection: There are **3** common tests.

- Type 1 diabetes runs in families, so family members are tested.
- ***FPG (Fasting Plasma Glucose)*** examines blood after an 8-hour fast - over 126 mg/dL is diabetic, while under 100 mg/dL is normal.
- ***A1C (Glycated Hemoglobin)*** examines blood after an 8-hour fast - over 6.5% is diabetic, while under 5.7% mg/dL is normal.
- ***OGTT (Oral Glucose Tolerance Test)*** fast for 8 hr, then given large amount of glucose and tested over 2 hrs - over 200 mg/dL on any test is diabetic, while under 140 mg/dL is normal.

Glucose Tolerance Test is a more accurate follow-up test for diabetes.

- Subject fasts for 12 hours.
- Subject rapidly ingests a large amount of glucose (100 g of glucose, which is about 2.5× a can of Coke).
- The blood sugar is monitored for 3-6 hrs, and these data are fit to the Ackerman model (below).

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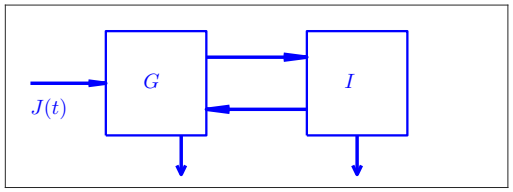
Modeling GTT 1

Modeling GTT: Glucose in the blood, $G(t)$, begins with the rapid ingestion of glucose, $J(t)$.

This stimulates the release of insulin, $I(t)$, and other hormones to regulate $G(t)$.

This can be written as the model:

$$\begin{aligned} \frac{dG}{dt} &= f_1(G, I) + J(t), \\ \frac{dI}{dt} &= f_2(G, I). \end{aligned}$$



Modeling GTT 2

Modeling GTT: Glucose regulation is complex, but we develop a simple model that can be fit with a few parameters.

More complex models have been developed to match different types of food intake for tighter regulation of people with diabetes.

Modeling Assumptions:

- Assume the fasting for 8-12 hours takes the body into a ***homeostasis***.
- The body is in a ***quasi-equilibrium*** with glucose at a level G_0 and insulin at a level I_0.
- Assume the rapid ingestion of glucose makes $J(t)$ like a δ-function only affecting the initial conditions.
- The ***quasi-equilibrium*** assumption allows a ***perturbation analysis*** using

$$g(t) = G(t) - G_0 \qquad \text{and} \qquad i(t) = I(t) - I_0.$$

Linearized GTT Model 1

For the model,

$$\begin{aligned} \frac{dG}{dt} &= f_1(G, I) + J(t), \\ \frac{dI}{dt} &= f_2(G, I), \end{aligned}$$

the ***quasi-equilibrium*** assumption gives:

$$f_1(G_0, I_0) = f_2(G_0, I_0) = 0.$$

Expanding the general model to linear terms with these definitions gives the linearized perturbation mode:

$$\begin{aligned} \frac{dg}{dt} &= \frac{\partial f_1(G_0, I_0)}{\partial g} g + \frac{\partial f_1(G_0, I_0)}{\partial i} i, \\ \frac{di}{dt} &= \frac{\partial f_2(G_0, I_0)}{\partial g} g + \frac{\partial f_2(G_0, I_0)}{\partial i} i, \end{aligned}$$

where $g(t)$ and $i(t)$ are the linearized perturbed variables.

Linearized GTT Model 2

Next we examine the partial derivatives of the functions, f_1 and f_2, with our understanding of the physiology of glucose and insulin.

Physiologically, an increase in glucose in the blood stimulates tissue uptake of glucose and glycogen storage in the liver:

$$\frac{\partial f_1(G_0, I_0)}{\partial g} = -m_1 < 0.$$

An increase in insulin facilitates the uptake of glucose in tissues and the liver:

$$\frac{\partial f_1(G_0, I_0)}{\partial i} = -m_2 < 0.$$

However, increases in blood glucose result in the release of insulin:

$$\frac{\partial f_2(G_0, I_0)}{\partial g} = m_4 > 0.$$

Increases in insulin result increased metabolism of excess insulin:

$$\frac{\partial f_2(G_0, I_0)}{\partial i} = -m_3 < 0.$$

Linearized GTT Model 3

With these definitions, the linearized system is written:

$$\begin{pmatrix} \dot{g} \\ \dot{i} \end{pmatrix} = \begin{pmatrix} -m_1 & -m_2 \\ m_4 & -m_3 \end{pmatrix} \begin{pmatrix} g \\ i \end{pmatrix},$$

where $\dot{g} = dg/dt$ and similarly for $i(t)$.

The ***characteristic equation*** for this linear system is given by

$$\det \begin{vmatrix} -m_1 - \lambda & -m_2 \\ m_4 & -m_3 - \lambda \end{vmatrix} = \lambda^2 + (m_1 + m_3)\lambda + m_1 m_3 + m_2 m_4 = 0.$$

Since the $m_i > 0$, all coefficients of the ***characteristic equation*** are positive.

From ODEs (think damped spring mass system), this implies that all the ***eigenvalues***, λ, are either complex with negative real parts or both ***eigenvalues*** are negative.

A ***stable node*** is expected of a self-regulatory system.

Linearized GTT Model 3

The ***characteristic equation*** is:

$$\lambda^2 + (m_1 + m_3)\lambda + m_1 m_3 + m_2 m_4 = 0.$$

Only the blood glucose level in the GTT is measured, so only need the linearized solution for $g(t)$.

We expect the underdamped situation with complex eigenvalues.

Physiologically, think of the body's response to a "sugar high" (maximum of blood glucose), which is followed after an hour or two by a "sugar low" (minimum of blood glucose below equilibrium) that encourages more eating.

Thus, the general solution satisfies:

$$g(t) = e^{-\alpha t}(c_1 \cos(\omega t) + c_2 \sin(\omega t)),$$

where

$$\alpha = \frac{m_1 + m_3}{2} \qquad \text{and} \qquad \omega = \frac{1}{2}\sqrt{4(m_1 m_3 + m_2 m_4) - (m_1 + m_3)^2}.$$

Linearized GTT Model 4

From the general solution:

$$g(t) = e^{-\alpha t}(c_1 \cos(\omega t) + c_2 \sin(\omega t)),$$

if we take

$$c_1 = A\cos(\omega\delta) \qquad \text{and} \qquad c_2 = A\sin(\omega\delta),$$

then we can approximate the blood glucose level by

$$G(t) = G_0 + Ae^{-\alpha t}\cos(\omega(t - \delta)).$$

- This solution has five unknown parameters to be fit to the data.
- G_0 represents the equilibrium blood sugar level.
- α measures the ability of the system to return to equilibrium state after being perturbed.
- ω gives a frequency response to perturbations.
- A gives the amplitude of the response.
- δ represents a delay in the response.

Ackerman Model

The **Ackerman model** is given by:

$$G(t) = G_0 + Ae^{-\alpha t}\cos(\omega(t - \delta)).$$

- α was found to have large errors from the many subjects tested by Ackerman *et al.*
- A more robust measure was the natural frequency of the system, ω_0.
- The ***natural frequency*** from forced damped oscillators is defined

$$\omega_0^2 = \omega^2 + \alpha^2 \qquad \text{and} \qquad T_0 = \frac{2\pi}{\omega_0},$$

  where T_0 is the natural period of the system.
- The natural period is a good predictor of diabetes.
- Ackerman found that if $T_0 < 4$, then a person was generally normal, while if $T_0 > 4$, then the person is likely to have diabetes.
- Physiologically, this relates to the idea that normally people get hungry every 3-4 hours.

Example 1

Example: We examine the theory with a normal and a diabetic subject given the GTT.

t (hr)	Subject A	Subject B	t (hr)	Subject A	Subject B
0	70	100	2	75	175
0.5	150	185	2.5	65	105
0.75	165	210	3	75	100
1	145	220	4	80	85
1.5	90	195	6	75	90

Table: Data from the Glucose Tolerance Test. Subject A is a normal subject, while Subject B has diabetes.

A nonlinear least squares best fit is performed with the ***Ackerman model***.

Parameter	Subject A	Subject B	Parameter	Subject A	Subject B
G_0	79.1814	95.2124	ω	1.81274	1.03037
α	0.99272	0.63349	δ	0.90056	1.51604
A	171.5474	263.1528	$LSSE$	225.6757	718.6180

Table: Best Fitting Parameters to GTT Model. Subject A is a normal subject, while Subject B has diabetes.

Example 2

Example: **MatLab** is used to find the best fitting parameters to fit the ***GTT data*** with the program `fminsearch`, using

```
[p1,J,flag] = fminsearch(@diabetes_err,p,[],td,gn)
```

```
function J = diabetes_err(p,td,gd)
% Least squares error
y = GTT(td,p);
err = y - gd;
J = err*err';
end
```

```
function y = GTT(t,p)
% GTT function
y  = p(1)+p(2)*exp(-p(3)*t).*cos(p(4)*(t-p(5)));
end
```


Example 3

Example: The graph is produced with

```
td = [0 0.5 0.75 1 1.5 2 2.5 3 4 6];
gn = [70 150 165 145 90 75 65 75 80 75];
gd = [100 185 210 220 195 175 105 100 85 90];

xlab = '$t$ (hr)';      % X-label
ylab = 'Glucose (mg/dl)';           % Y-label
mytitle = 'GTT Model';  % Title

xx = linspace(0,6,200);
pn = [79.1814 171.5474 0.99272 1.81274 0.90056];
pd = [95.2124 263.1528 0.63349 1.03037 1.51604];
yn = pn(1)+pn(2)*exp(-pn(3)*xx)...
     .*cos(pn(4)*(xx-pn(5)));
yd = pd(1)+pd(2)*exp(-pd(3)*xx)...
     .*cos(pd(4)*(xx-pd(5)));
```


Example 4

```
plot(xx,yn,'b-');
hold on;
plot(xx,yd,'r-');
plot(td,gn,'ob',td,gd,'or');
grid
xlim([0 6]);
ylim([0 250]);
fontlabs = 'Times New Roman';
xlabel(xlab,'FontSize',14,'FontName',fontlabs,...
    'interpreter','latex');
ylabel(ylab,'FontSize',14,'FontName',fontlabs,...
    'interpreter','latex');
title(mytitle,'FontSize',16,'FontName',...
    'Times New Roman','interpreter','latex');
set(gca,'FontSize',12);

print -depsc GTT_modelA.eps
```

Example 5

The graph below shows that the best parameter fit does very well matching the model to the data.

From the definitions of ω_0 and T_0, Subject A has:

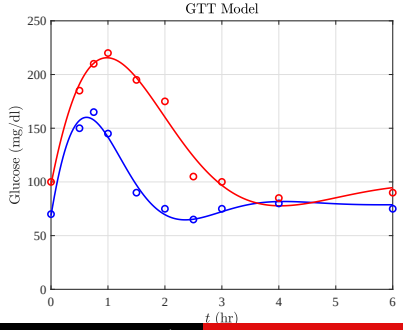
$$\omega_0 = 2.0668 \qquad \text{and} \qquad T_0 = 3.0401,$$

so according to the criterion by the ***Ackerman model***, this subject is normal.

For Subject B,

$$\omega_0 = 1.2095 \qquad \text{and} \qquad T_0 = 5.1947,$$

so according to the criterion by the ***Ackerman model***, this subject is diabetic.

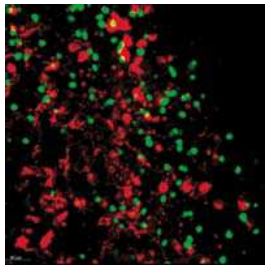


Diabetes in NOD Mice

Diabetes in NOD Mice

- With diabetes a significant disease in humans we need an animal model.
- An important animal with a diabetic tendency is the ***non-obese diabetic (NOD) mouse***.
- ***Type 1 diabetes*** arises in NOD mice when ***T cells*** from the immune system become primed to specifically target and kill ***β-cells***.
- These ***cytotoxic T cells*** belong to a class of lymphocytes displaying a surface marker called CD8 (denoted ***$CD8^+$ T cells***).

T Cell Activation



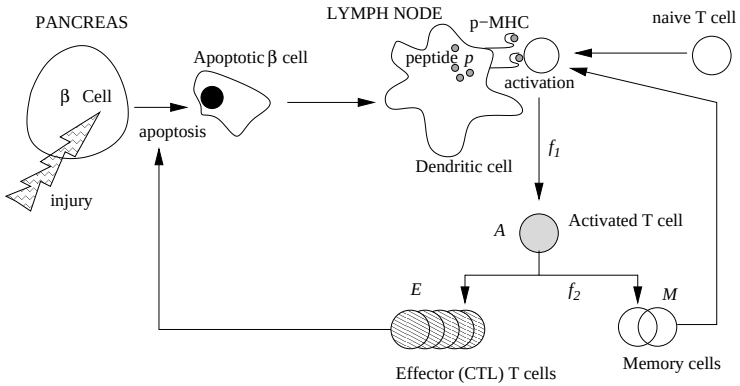
- T cells mature in the thymus.
  - Cross-react with self-protein to prevent autoimmunity.
- T cells migrate to Lymph nodes.
  - Interact with antigen presenting cells (APCs).
  - APCs present antigen protein fragment (about 9 AAs) inside MHC (major histocompatibility complex).
  - The peptide-MHC complex 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

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.

T Cell Immune Response

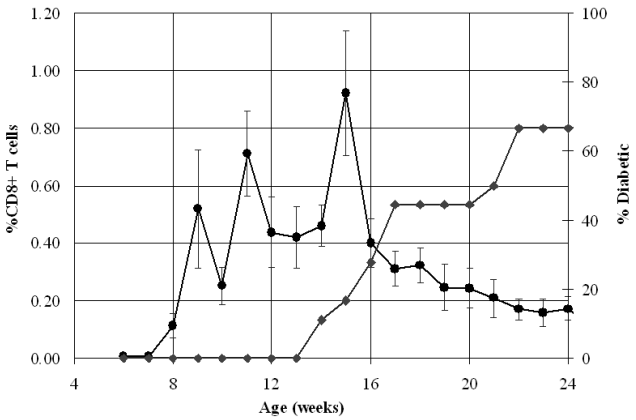


Animal Model for Diabetes

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.

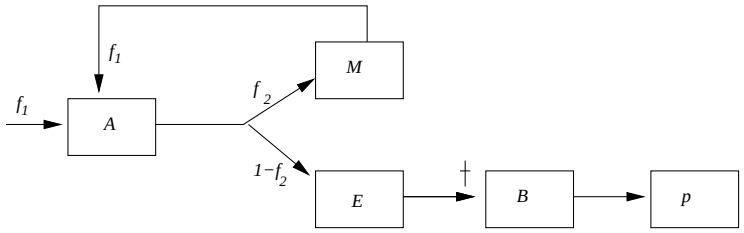
NOD Mice Data



Pooled data had mice aligned to time of high blood sugar onset at 16-weeks.

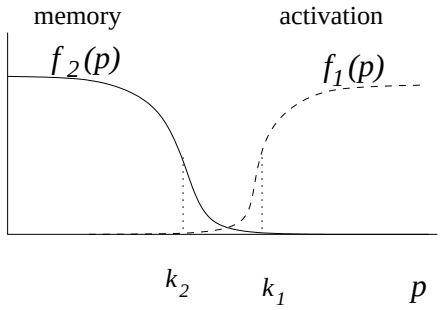
Link to Model Simulation

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

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

$$\begin{aligned}
f_1(p) &= \frac{p^n}{k_1^n + p^n} \\
f_2(p) &= \frac{ak_2{}^m}{k_2^m + p^m}
\end{aligned}$$

Activated T cells

Activated T cells

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

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

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

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 1

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 ***Quasi-Steady State*** peptide expression

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

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

Quasi-Steady State Model 2

With $p=(RB/\delta_p)E$, the model is written:

$$\begin{aligned}\frac{dA}{dt} &= (\sigma+\alpha M)\tilde{f}_1(E)-(\beta+\delta_A)A-\epsilon A^2 \;=\; F_1(A,M,E),\\ \frac{dM}{dt} &= \beta 2^{m_1}\tilde{f}_2(E)A-\tilde{f}_1(E)\alpha M-\delta_M M \;=\; F_2(A,M,E),\\ \frac{dE}{dt} &= \beta 2^{m_2}(1-\tilde{f}_2(E))A-\delta_E E \;=\; F_3(A,E),\end{aligned}$$

where $\tilde{f}_1(E)$ and $\tilde{f}_2(E)$ are the appropriately scaled nonlinear functions.

From the positive feedback form of $\tilde{f}_1(E)$, it is easy to see that there exists the ***disease-free equilibrium***,

$$(A_e, M_e, E_e) = (0,0,0).$$

Quasi-Steady State Model – Equilibria 3

Equilibria are found by solving the three highly nonlinear equations:

$$F_1(A_e,M_e,E_e)=0, \qquad F_2(A_e,M_e,E_e)=0, \qquad F_3(A_e,E_e)=0,$$

which beyond the ***disease-free equilibrium*** may have **0**–**4** other ***equilibria***.

There are relatively stringent biological constraints on the parameters.

In the biological parameter range, there are **2** additional equilibria.

These are found numerically, having no analytic solution.

Quasi-Steady State Model – Linear Analysis 4

Linear Analysis of this model uses the ***Jacobian matrix*** at the equilibria, where

$$J(A,M,E) = \begin{pmatrix} \frac{\partial F_1(A,M,E)}{\partial A} & \frac{\partial F_1(A,M,E)}{\partial M} & \frac{\partial F_1(A,M,E)}{\partial E} \\ \frac{\partial F_2(A,M,E)}{\partial A} & \frac{\partial F_2(A,M,E)}{\partial M} & \frac{\partial F_2(A,M,E)}{\partial E} \\ \frac{\partial F_3(A,E)}{\partial A} & 0 & \frac{\partial F_3(A,E)}{\partial E} \end{pmatrix}$$

From the ***Quasi-Steady State Model***,

$$J(A,M,E) = \begin{pmatrix} -(\beta+\delta_A) - 2\epsilon A & \alpha\tilde{f}_1(E) & (\sigma+\alpha M)\tilde{f}\,'_1(E) \\ \beta 2^{m_1}\tilde{f}_2(E) & -(\alpha\tilde{f}_1(E)+\delta_M) & \beta 2^{m_1} A\tilde{f}\,'_2(E) - \alpha M\tilde{f}\,'_1(E) \\ \beta 2^{m_2}(1-\tilde{f}_2(E)) & 0 & -(\beta 2^{m_2} A\tilde{f}\,'_2(E)+\delta_E) \end{pmatrix}$$

Provided $n > 1$ (which is expected, since $\tilde{f}_1(E)$ is a type of switch), then $\tilde{f}_1(0) = \tilde{f}\,'_1(0) = 0$ and

$$J(0,0,0) = \begin{pmatrix} -(\beta+\delta_A) & 0 & 0 \\ \beta 2^{m_1}\tilde{f}_2(0) & -\delta_M & 0 \\ \beta 2^{m_2}(1-\tilde{f}_2(0)) & 0 & -\delta_E \end{pmatrix}$$

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Quasi-Steady State Model – Linear Analysis 5

Characteristic Equation: At the ***disease-free equilibrium***, $(A_e, M_e, E_e) = (0,0,0)$, it is easy to solve

$$\det|J(0,0,0) - \lambda I| = -(\lambda+\beta+\delta_A)(\lambda+\delta_M)(\lambda+\delta_E) = 0.$$

This ***characteristic equation*** shows that the ***disease-free equilibrium*** has purely negative ***eigenvalues***:

$$\lambda_1 = -\beta - \delta_A, \qquad \lambda_2 = -\delta_M, \qquad \lambda_3 = -\delta_E.$$

It follows that the ***disease-free equilibrium*** is a ***stable node***.

Since the origin is an ***attractor***, a sufficiently weak disturbance that provokes the immune system should be resolved.

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Quasi-Steady State Model – Linear Analysis 6

Linear Analysis: A ***second equilibrium*** represents the ***diseased state***.

- This equilibrium corresponds to a state of elevated immune cell levels.
  - Effector T cells are continuously killing β-cells.
  - This corresponds to an autoimmune attack, leading to diabetes.
- This equilibrium has various stability properties that depend on the parameters.
  - For some parameters this equilibrium is a ***stable node***.
  - This equilibrium can undergo a ***supercritical Hopf bifurcation*** leading to an ***unstable node*** and a ***stable periodic orbit***.
  - This equilibrium can simply be an ***unstable node*** with only the origin being an ***attractor***.
  - Other more exotic behaviors occur away from physiological relevant parameters.

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Quasi-Steady State Model – Linear Analysis 7

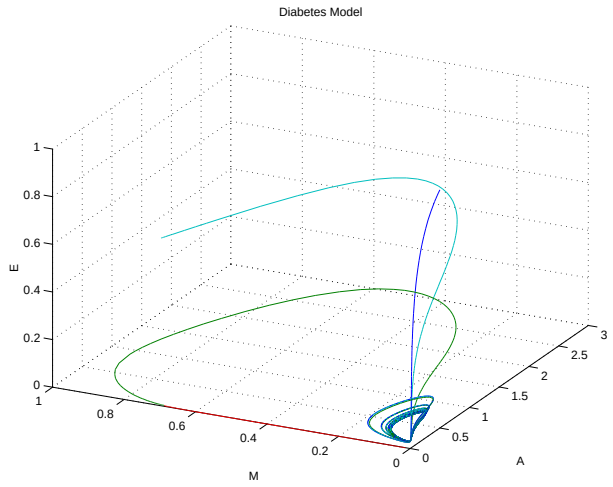
Linear Analysis: The ***third equilibrium*** is a ***saddle node***.

- It has a ***2D stable manifold***, which for some parameters separates the healthy and diseased equilibria.
- For these parameters, stimuli that fall on the wrong side of this ***separatrix*** will be attracted to the ***diseased equilibrium***.
- For other parameter values, the ***unstable manifold*** of the diseased state connects to the ***stable manifold*** of the saddle point.
- In this case, almost all positive initial conditions asymptotically, approach the healthy state.
- This would represent a ***normal state***, where the immune system is damped and no ***autoimmune*** response persists.

SDSU

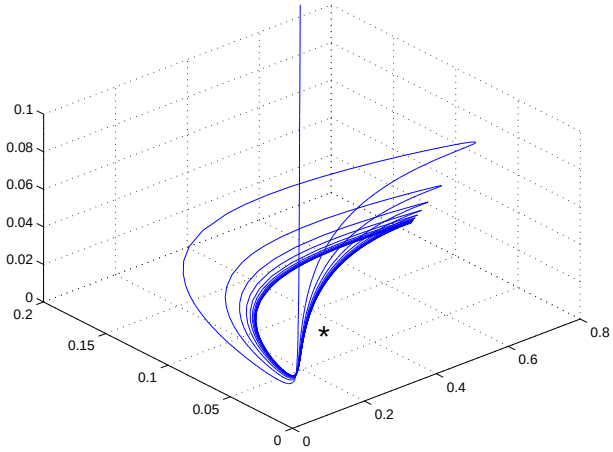
Quasi-Steady State Model – Simulation 8

Simulation: The QSS Model is simulated where stable oscillations occur around the *diseased state*.



Quasi-Steady State Model – Simulation 9

Simulation: Zooming in on the previous plot the stable oscillations around the *diseased state* are readily seen.



Parameters and Bifurcation 1

Parameter study

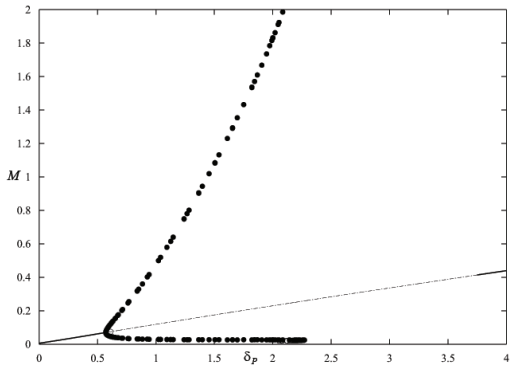
- Experimental data compiled by Marée, Santamaria, and Edelstein-Keshet.
- Physiological range of parameters limited by their study for most parameters in the model.
- Several parameters remain unknown, so varied to obtain desired behavior.
- Sensitivity of the parameters was studied.

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.

Bifurcation Study 2

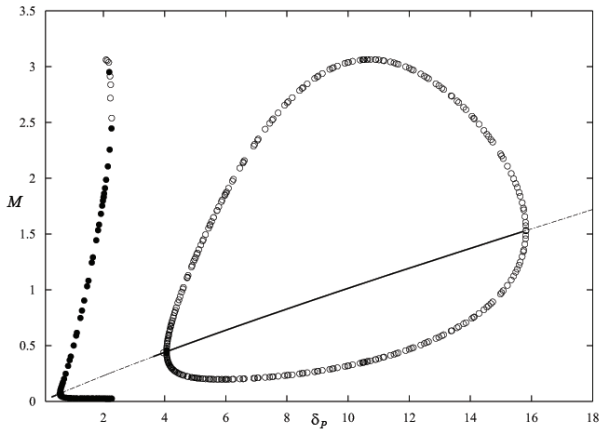
Bifurcation Study: Steady-state of M as the peptide clearance rate δ_p is varied.



Normal range of δ_p is likely between 2.5 and 3.5, while the *diseased state* is likely less than half that value.

Bifurcation Study 3

Bifurcation Study: Extending the peptide clearance rate δ_p shows other bifurcations. However, the higher range is unrealistic.

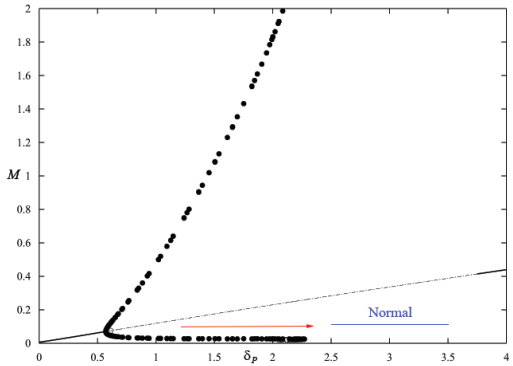


Bifurcation Study 4

Bifurcation Study: Most solutions approach the ***Origin*** in the normal range.

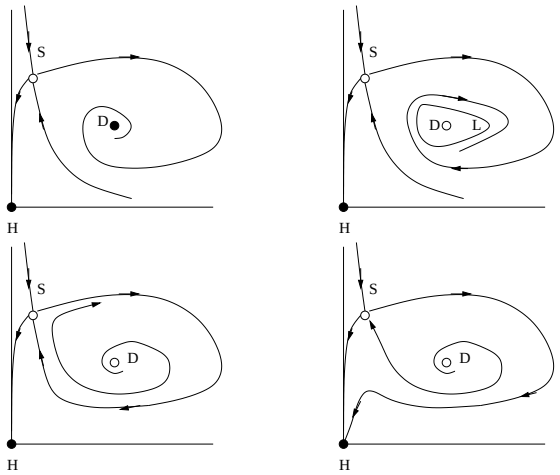
Suspected that δ_p is less than half ***normal*** in the ***diseased state***.

With $p \approx \frac{RB}{\delta_p} E$, the ***red arrow*** shows increasing δ_p, which is similar to B decreasing or β-cells dying.



Homoclinic Bifurcation 5

Homoclinic Bifurcation: 2D cartoon illustrating model behavior as δ_p increases.

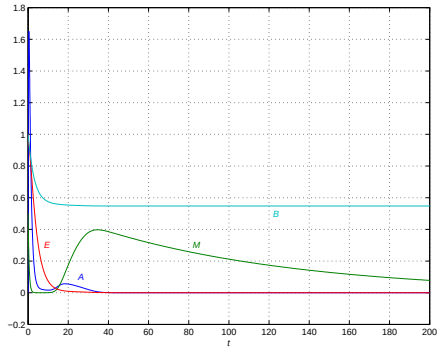


Link to Diabetic SimulationLink to Normal Simulation

Complete NOD Mouse Model (Normal) 1

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

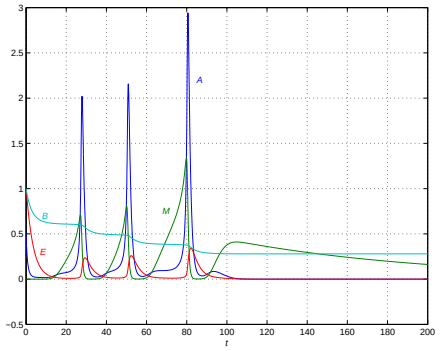


Link to Homoclinic Diagram

Complete NOD Mouse Model (Diabetic) 2

Simulated complete model for a ***diabetic mouse*** with lower peptide clearance

- Assumed an initial response of ***Effector T cells***
- 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



Link to Experimental dataLink to Homoclinic Diagram

Conclusions

Conclusions

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