Glucose Dynamics

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A Model of β-Cell Mass, Insulin, and Glucose Kinetics: Pathways to Diabetes

Abstract

- Diabetes is a disease of the glucose regulatory system that is associated with increased morbidity and increased mortality, characterized by **postprandial hyperglycemia**, an exaggerated rise in blood sugar following a meal.
  - Existing models incorporate two dynamical systems: *glucose* and *insulin* dynamics.
  - The model discussed in this paper is novel, as it incorporates a system of **three** nonlinear ordinary differential equations.
    - Glucose and insulin dynamics (fast)
    - β-cell mass dynamics (slow)

Introduction

- There are two major classifications of diabetes based on the etiology of the hyperglycemia.
  - **Type 1 Diabetes**: Also referred to as juvenile onset (or insulin-dependent diabetes) is due to an autoimmune attack on the insulin secreting β-cells.
  - **Type 2 Diabetes**: is a associated with a deficit in the mass of β-cells, reduced insulin secretion, and resistance to the action of insulin.
- Blood glucose levels are regulated by two negative feedback loops
  - Hyperglycemia stimulates a rapid increase in insulin release from the pancreatic β-cells.
  - Recent evidence suggests that chronic hyperglycemia may contribute to a *second* negative feedback loop by increasing the *mass* of insulin secreting β-cells through changes in the rates of β-cell replication.

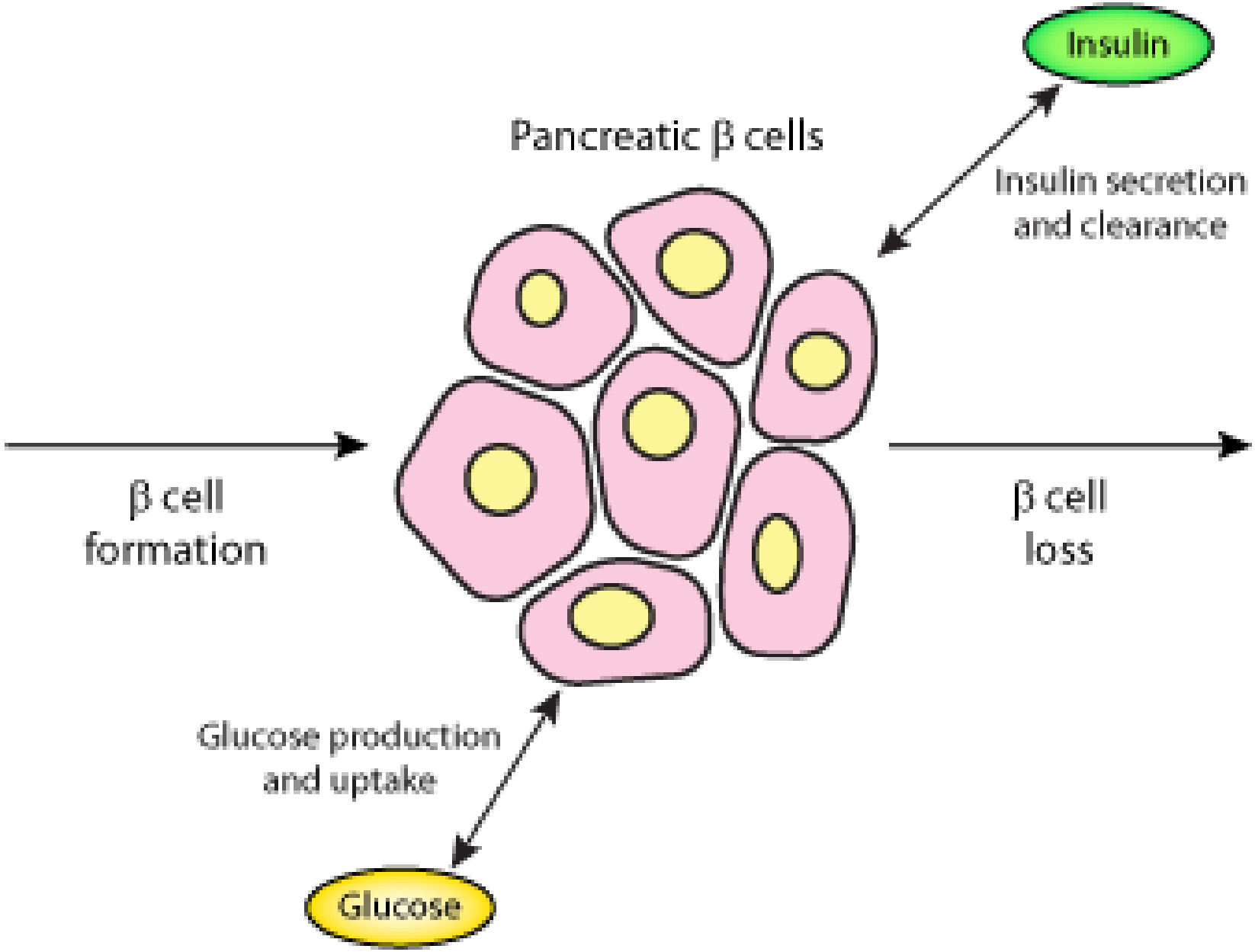
Introduction

- For normal parameter values, the model has two stable fixed points (physiological and pathological steady states), separated on a **slow manifold** by a **saddle point**
- Mild hyperglycemia leads to the growth of the β-cell mass, which secrete insulin to increase cellular glucose uptake, driving blood glucose levels down (negative feedback)
- Extreme hyperglycemia leads to the reduction of the β-cell mass, yielding less insulin and less cellular glucose uptake, driving blood glucose levels up (positive feedback)
- The model predicts that there are three pathways in prolonged hyperglycemia:
  - The physiological fixed point can be shifted to a hyperglycemic level (regulated hyperglycemia)
  - The physiological and saddle points can be eliminated (bifurcation)
  - Progressive defects in glucose and/or insulin dynamics can drive glucose levels up at a rate faster than the adaptation of the β-cell mass which can drive glucose levels down (dynamical hyperglycemia).

Introduction

- Although type 2 diabetes is associated with insulin, insulin secretory defects, and insufficient β-cell mass, *each of these defects can also be found in people without diabetes*.
- Evidence suggests that **normoglycemia** can be maintained in subjects with insulin resistance via increases in blood insulin levels.
  - A defect of insulin secretion is demonstrated in people with Type 2 Diabetes.
- Glucose homeostasis can be maintained despite significant loss of β-cell function when an individual has normal insulin *sensitivity*.
  - Evidence suggests that a great β-cell mass is required in the presence of insulin resistance.

Introduction



Model Development

Underlying Biology

- In the post-absorptive state, glucose is released into the blood by the liver and kidneys, removed from the interstitial fluid by all the cells of the body, and distributed into many physiological compartments.
  - Despite this spatial complexity, it has been shown that a one-compartment model of glucose kinetics, when the kinetics are relatively slow, is sufficient.
- We are primarily concerned with the evolution of fasting blood glucose levels over a time-scale of days to years, glucose dynamics are modeled with a **single-compartment mass balance equation**

Model Development

Glucose Dynamics

The rates of glucose production and uptake depend on blood glucose and insulin levels. At constant insulin levels, glucose production decreases while uptake increases.The rates of glucose **production** and **uptake** depend on blood glucose and insulin levels.

- The slopes of these linear dependencies are the "**glucose effectiveness**" parameters.
- The slope of the glucose effectiveness vs. insulin curve is referred to as **insulin sensitivity**.

Model Development

Glucose Dynamics

$$\frac{dG}{dt} = Production - Uptake \tag{1}$$

$$Production = P_0 - (E_{G0P} + S_{IP} I)G \tag{2}$$

$$Uptake = U_0 + (E_{G0U} + S_{IU} I)G \tag{3}$$

G is the blood glucose concentration, t is the time, P_0 and U_0 are the rates of glucose production and uptake at zero glucose, E_{G0P} and E_{G0U} are glucose *effectiveness* at zero insulin production and uptake, S_{IP} and S_{IU} are insulin uptake, and I represents blood insulin concentrations. Substituting equations (2) and (3) into equation (1), we arrive at

$$\frac{dG}{dt} = R_0 - (E_{G0} + S_I I)G \tag{4}$$

Model Development

Insulin Dynamics

$$\frac{dI}{dt} = Secretion - Clearance \tag{5}$$

$$Secretion = \beta\sigma - G^2/(alpha + G^2) \tag{6}$$

$$Clearance = kI \tag{7}$$

β is the β-cell mass, σ is the rate at which β-cells secrete insulin, and $G^2/(\alpha + G^2)$ is the rate insulin is secreted at Substituting equations (6) and (7) into equation (5), we arrive at

$$\frac{dI}{dt} = \beta\sigma - G^2/(alpha + G^2) - kI \tag{8}$$

Model Development

β-cell mass Dynamics

$$\frac{d}{dt} = Formation - Loss \tag{9}$$

$$Formation = (r_{1r} - r_{2r}G^2)/\beta \tag{10}$$

$$Loss = (d_0 - r_{1a}G + r_{2a}G)/\beta \tag{11}$$

d_0 is the death rate at zero glucose, r_1 and r_2 are rate constants. Substituting equations (10) and (11) into equation (9), we arrive at

$$\frac{dB}{dt} = (d_0 + r_1 G - r_2 G^2)/\beta \tag{12}$$

Model Development

List of Nine Parameters

1. S_I - Total insulin sensitivity
2. E_{G0} - Total glucose effectiveness
3. R_0 - Net rate of production at zero glucose
4. σ - Maximal rate of secretion
5. α - Dissociation constant of Hill equation (where glucose reaches its maximum rate of change)
6. k - Clearance constant
7. d_0 - Death rate at zero glucose
8. r_1 - Rate constant 1 of replication
9. r_2 - Rate constant 2 of replication

Model Behavior

- After non-dimensionalization, the model was decomposed into "fast" and "slow" systems for stability analysis, representing the dynamics of Glucose and Insulin (G, I), and β cell mass, respectively.
  - When parameterized by a steady state of the "slow" β system, the "fast" (G, I) system nullclines give a globally attracting fixed point. That is, the (G, I) system undergoes damped oscillations to a steady state determined by β.
  - As β increases, the (G, I) system fixed point shifts toward a lower value for glucose (G), and a higher insulin (I) value.

Model Behavior cont.

Slow subsystem stability

- At a given steady state of the (G, I) system, the β system has 3 steady states: The "pathological" state: $\beta = 0$, the "physiological" state $G = 100$, and the "unstable" state: $G = 250$.
- When comparing β cell replication and death rates to glucose levels, 3 distinct system behavior "zones" arise:

Zone 1: In the region where death rate is greater than replication rate and β cell mass decreases, which "regulates" glucose levels to increase back to the "physiological" fixed point $G = 100$. This corresponds biologically to hypoglycemia.

Zone 2: In the region where replication rates are greater than death rates, with increasing β cell mass, glucose is "regulated" to decrease back to the "physiological" fixed point. This corresponds biologically to mild hyperglycemia.

Zone 3: In the region where death rates exceed replication rates and glucose rates are increased, the system is driven to a β cell mass of 0, the "pathological" steady state. This corresponds biologically to extreme hyperglycemia.

Model Behavior cont.

- Thus, the "slow" β cell system has 2 stable steady states and an unstable steady state.
- For the overall βIG system, the 3 steady states are: $(\beta, I, G) = (300, 10, 100)$ stable spiral for the physiological fixed point, $(\beta, I, G) = (37, 2.8, 250)$ saddle point, and $(\beta, I, G) = (0, 0, 600)$ stable node for the pathological fixed point.
- As a planar system in Glucose and Insulin, the attractive null surfaces intersect in a 1-D slow manifold.

Model Behavior cont.

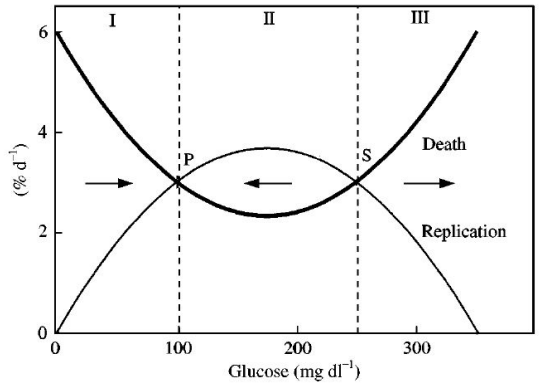


Figure: Slow subsystem Global behavior: Glucose levels vs Replication and Death rates. (P) is physiological fixed point, (S) is saddle point

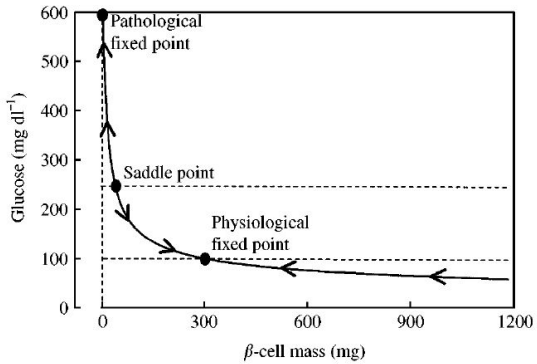


Figure: Overall model global behavior: Slow manifold and β cell mass null surfaces onto G and β plane

Model behavior cont.

- All system solutions follow trajectories perpendicular to the β cell mass axis onto this slow manifold.
- Subsequent behavior then follows the dynamics of the β cell mass, with its three null surfaces being planes at $G = 100 mgdl^{-1}$, $G = 250 mgdl^{-1}$, and $\beta = 0 mg$.
- Solutions of the fast subsystem quickly reach a steady state at the initial β cell mass, which is driven by the β cell dynamics to pathological or physiological steady states.

Effects of Parameter Changes on Global Behavior

- The number of non-trivial steady-state solutions is determined by the parameters of the β-cell mass equation, while the position of these fixed points is determined by all nine-dimensional parameters.
  1. S_I - Total insulin sensitivity
  2. E_{G0} - Total glucose effectiveness
  3. R_0 - Net rate of production at zero glucose
  4. σ - Maximal rate of secretion
  5. α - Dissociation constant of Hill equation
  6. k - Clearance constant
  7. d_0 - Death rate at zero glucose
  8. r_1 - Rate constant 1 of replication
  9. r_2 - Rate constant 2 of replication
- The trivial steady-state solution is fixed at zero β-cell mass and insulin, but has a steady-state glucose level that is dependent on the glucose parameters (R_0, E_{G_0})

Effects of Parameter Changes on Global Behavior

Defects in Glucose Dynamics

- Defects in insulin sensitivity, represented by a reduced S_I, decrease the curvature of the glucose nullcline and thus the slow manifold.
  - This forces the physiological and saddle points to shift to *higher* β-cell mass and insulin levels, but does not affect the *number* of fixed points or the glucose levels at any of these fixed points.
  - Thus, the long-term effects of non-progressive insulin resistance are **hyperinsulinemia**, β-**cell hyperplasia**, and **normoglycemia**.

Effects of Parameter Changes on Global Behavior

Defects in Glucose Dynamics

- Defects in glucose dynamics represented by an increase in R_0 or a decrease in E_{G0} cause the glucose nullsurface and the associated slow manifold to shift upwards.
  - There are also shifts of the physiological and saddle fixed points to higher $/beta$-cell mass and insulin levels, as well as a shift of the pathological fixed point to a higher glucose level.
  - Experimental augmentation of R_0, via continuous glucose infusion, has been shown to increase β-cell mass and plasma insulin levels.
- Glucose dynamics have no effect on the model's physiologically regulated glucose level, but do affect the β-cell mass and insulin levels which are required to maintain normal fasting glucose levels.

Effects of Parameter Changes on Global Behavior

Defects in Insulin Dynamics

- An increase in the insulin clearance rate or a decrease in the insulin secretion rate per active β cell, modeled by an increase in k or a decrease in σ, respectively, compresses the insulin null surface along he direction of the insulin axis.
  - This changes the curvature of the slow manifold, shifting the physiological and saddle points to higher β-cell mass decreases and β-cell mass increases with age.
    - Consistent with experimental data: Maximal insulin secretion rate per of β-cell mass decreases and β-cell mass increases with age in non-diabetic rats. (More cells, less insulin per cell)

Effects of Parameter Changes on Global Behavior

Defects in Insulin Dynamics

- Defects in the recruitment of β cells from an inactive to an active state, represented by an increase in α, stretch the insulin nullsurface along the direction of the glucose axis, changing the curvature of the slow manifold.
  - This also shifts the physiological and saddle points to higher β-cell mass values
  - It is not known whether α can be manipulated specifically
- Insulin dynamics do no affect the glucose or insulin levels at the physiological fixed point, but do affect the β-cell mass required to maintain normal fasting glucose and insulin levels.

Effects of Parameter Changes on Global Behavior

Defects in β-Cell Mass Dynamics

- Defects in β-cell replication and/or death rates, represented by an increase in d_0 or r_2, or by a decrease in r_1, cause the non-trivial $\beta - cell$ mass null surfaces to move closer together along the direction of the glucose axis.
  - The physiological fixed point shifts to a point with higher glucose, lower insulin, and lower β-cell mass, while the saddle point shifts to a point with lower glucose, higher insulin, and higher β-cell mass, increasing the volume of the basin of pathological attraction.
  - If a defect in β-cell mass parameters progresses to the point where death rates exceed replication rates at all glucose levels, then there is only **one steady-state solution**, namely the globally attractive pathological steady state with **zero β-cell mass**.

Effects of Parameter Changes on Global Behavior

Defects in β-Cell Mass Dynamics

- Experimentally, a relationship between plasma glucose levels and mild defects in β-cell replication and/or death rates has *not* been observed
  - It has been shown that a large increase in the β-cell death rate drives β-cell mass towards zero, which then generates extreme hyperglycemia.
- The β-cell mass parameters determine the number of fixed points, as well as the glucose levels at the physiological and saddle points, **when they exist**.

Pathways into Diabetes

- There are three general pathways into diabetes (persistent hyperglycemia) according the to βIG model:
  1. **Regulated Hyperglycemia**: Move the physiological fixed point to a hyperglycemic level
  2. **Bifurcation**: Eliminate the physiological and saddle points
  3. **Dynamical Hyperglycemia**: Drive a trajectory across a separatrix (also referred to as *catch and pass*)

Pathways into Diabetes

Regulated Hyperglycemia

- Steady-state glucose levels are determined by β-cell mass dynamics, thus there are two possible ways to shift the physiological fixed point to a hyperglycemic levels:
  1. A defect in β-cell mass regulation
     - e.g. a decrease in the response of replication and/or an increase in the response of death rates
  2. A loss of β-cell mass regulation combined with a defect in glucose and/or insulin dynamics

Pathways into Diabetes

Regulated Hyperglycemia: Defect in β-cell mass regulation

- Small defects in *any* of the β-cell mass parameters cause the physiological fixed point to shift to a hyperglycemic level
  - The β-cell mass is responsive to changes in plasma glucose concentration and has a basin of attraction, but the physiologically regulated glucose level is now hyperglycemic.

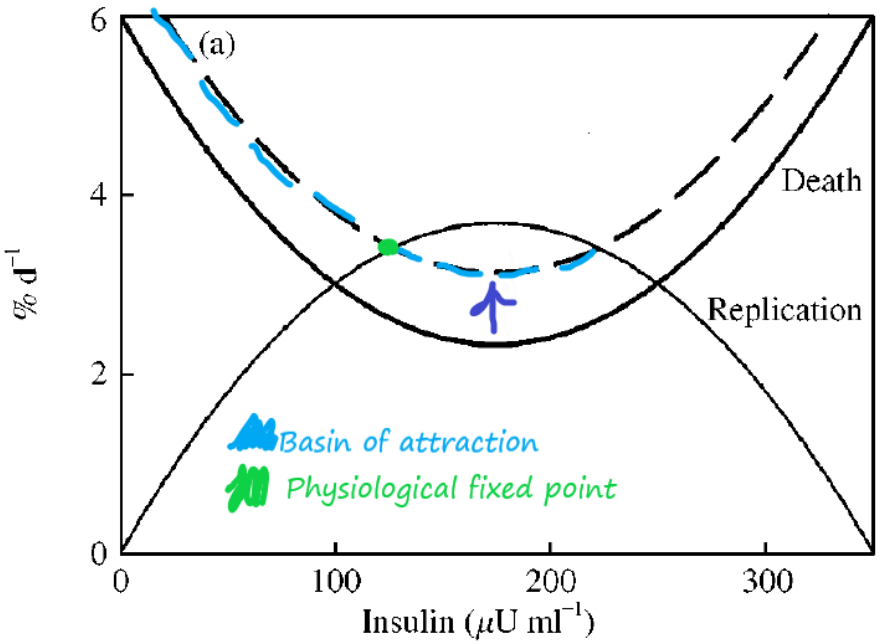


Figure 3: A small upward shift of death rate curve moves the physiological fixed point to a higher glucose level and shrinks the basin of attraction

Pathways into Diabetes

Regulated Hyperglycemia: Coupling a loss of β-cell regulation with a defect in glucose/insulin dynamics

- Setting each of the β-cell mass parameters to zero yields equal replication and death rates at all glucose levels, and as a result, the β-cell mass becomes non-responsive
  - The βIG model is reduced to the two-dimensional fast subsystem (IG) and any defects in insulin or glucose parameters generate hyperglycemia.

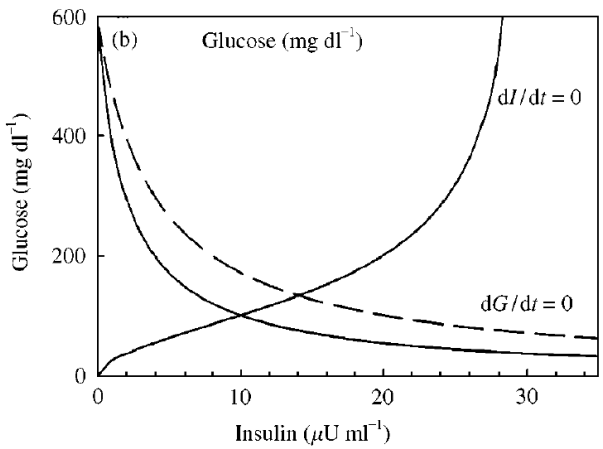


Figure 4: A reduction in insulin sensitivity changes the curvature of the glucose nullcline and shifts the steady state of the fast subsystem to a hyperglycemic level

Pathways into Diabetes

Bifurcation

- The bifurcation pathway consists of any combination of parameter changes that result in the elimination of the physiological and saddle fixed point.
  - Large defects in β-cell mass dynamics (e.g. changes replication and/or death curves) causes a saddle-node bifurcation, resulting in a single globally attractive pathological fixed point at zero β-cell mass.
    - This occurs when death rates exceed replication rates at all glucose levels

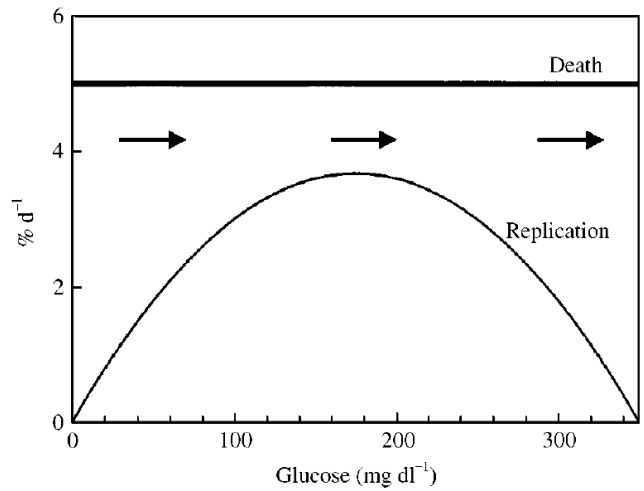


Figure 5: Here, the physiological and saddle-points are eliminated

Pathways into Diabetes

Bifurcation

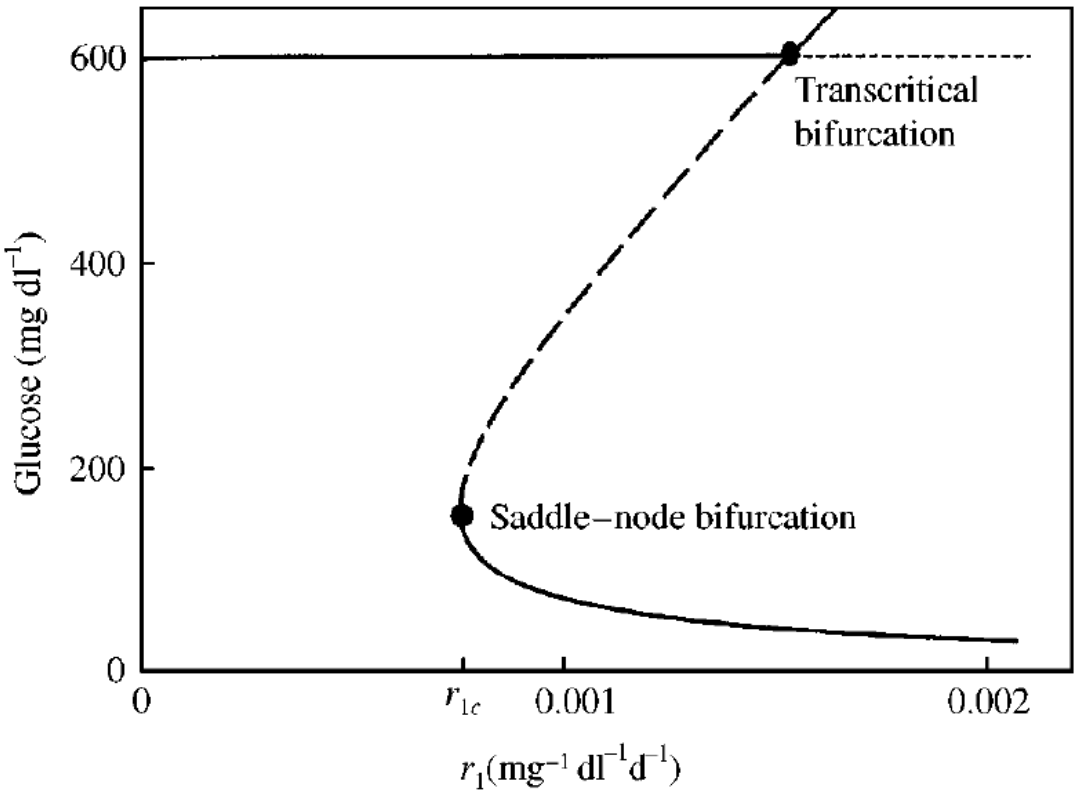


Figure 6: The glucose levels of the stable fixed points (—) and the saddle point (- - - -) are plotted as functions of the parameter r_1.

- As r_1 decreases to r_{1c}, the saddle and physiological points move closer together, eventually meeting at a saddle-node bifurcation,

Pathways into Diabetes

Dynamical Hyperglycemia

Dynamical Hyperglycemia (catch and pass) occurs when the level of required β-cell mass moves slower than the required β-cell levels. This can be caused by a rapid increase in insulin resistance or a fast, sustained increase in glucose.

Pathways into Diabetes

Dynamical Hyperglycemia: Fast increase of insulin resistance.

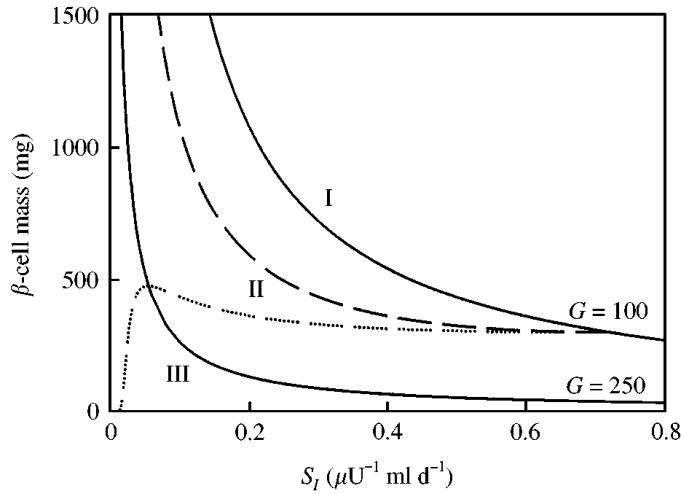


Figure 7: $d\beta/dt$ is positive on Zones I and III and negative on Zone II. The segmented line (—) is how β-cell mass changes if we go decreasing S_I by 0.01 ml/ μ U d per day. And The dotted line ($\cdots$) shows β-cell mass if we decrease insulin sensitivity by 0.05 ml/ μ U d per day. Both starting from the steady state at G=100 for S_I=0.72

- With the increasing insulin resistance (decrease of S_I) there's an immediate increase in glucose and a slower increase in β-cells.
- If the decrease of S_I is fast enough, β-cell mass will eventually cross to Zone III and into the *positive* feedback loop.

Conclusion

Model achievements and use-cases

- *In vivo* β-cell mass approximation.
  The authors suggest that with better parameters β-cell mass could be measured indirectly.
- The model does reflect the effects of β-cell "exhaustion" and, to some extent, the change in insulin levels to insulin resistance.
- Although it is a very simple model, it explains the dynamics seen in previous experiments.

Conclusion

Important Assumptions

- Effects of extreme Hyperglycemia on βIG dynamics are not considered.
  - Geogenesis
  - *Insulin* secretion and sensitivity.
  - etc.
- Hormonal effects not included
- Insulin clearance rate assumed constant with respect to changes in insulin resistance.

These assumptions were made because, (1) there was not enough experimental data to make accurate quantification of their effects. And (2) the available data indicated that the effects of this assumptions would not change the dynamics.

Conclusion

Author-suggested improvements

The authors cite several papers that suggest that insulin dynamics play an important role in lipid metabolism. And lipid dynamics and levels affect β-cell mass dynamics and insulin resistance respectively.
Thus, adding lipid dynamics to the βIG model might affect the pathways to diabetes or even show additional ones.