Lecture Notes in Systems Biology

Lecture 4 - Robustness in the Glucose-Insulin system

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In the previous lectures, we presented the effects of negative and positive feedback on the dynamics of simple biological circuits and how they can act as regulatory motifs. In the following two lectures, we will discuss a topic that is at the core of systems biology (and, in general, control engineering)- the question of how biological systems can be robust in the face of uncertainty in inputs, parameters, etc. We will first discuss this in the context of the regulation of blood sugar homeostasis and, next week, in the context of bacterial navigation. We will see that both systems share core similarities that are related to the important engineering concept of integral feedback.

1 Introduction

Glucose is the main source of energy in the body. Blood glucose levels are regulated by a complex network of hormones, with insulin hormone playing a major role. Insulin is produced and secreted by beta cells in the pancreas and helps move glucose from the bloodstream to peripheral cells (including muscle and fat cells), where it can be stored or used for energy production.

After eating a meal, blood glucose levels rise as the body digests and absorbs carbohydrates. Beta cells release insulin in response to blood glucose levels. Insulin helps to lower blood glucose levels by promoting the uptake of glucose by cells.

Typical trajectories of blood glucose and insulin during the day in healthy individuals are plotted below.

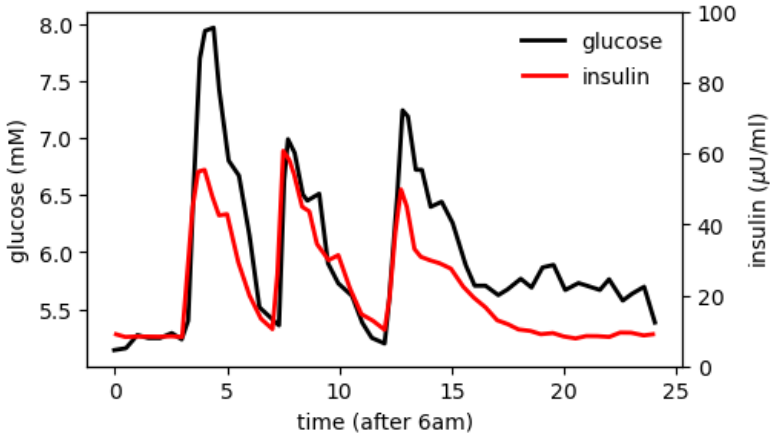

Figure 1: Adapted from Polonsky et al., J Clin Invest. 1988

Both glucose levels and responses to food intake are tightly regulated. In healthy people, fasting glucose levels are about 5mM (or 90mg/dL) with a measurement variability of around 20%. Glucose responses are measured by a standardized test called the glucose tolerance test. In this test, the patient drinks a sugary drink (with about 75 grams of sugar), followed by measurements of blood glucose. In healthy individuals, blood glucose will rise to about 10mM and then drop back to baseline after about two hours.

Blood glucose levels that deviate from the normal range are considered pathological. Large deviations, such as blood glucose levels greater than 6.9 mM or a glycemic response of 11 mM after 2 hours, are considered diabetic. Smaller deviations are indicative of prediabetes.

The tight regulation of blood sugar levels is a remarkable feat considering the complex process involved. Insulin is released by billions of beta cells in the pancreas, which are located in millions of clusters called the Islets of Langerhans. Insulin is then diluted by the blood volume. Finally, the response to insulin depends on the decision-making of many billions of other cells (muscle, fat, and liver cells), each of which decides how much glucose it needs or is willing to take up. This complex process can lead to large variability between different people and between different physiological stages of the same person. For example, body weight, illness, and pregnancy can affect the insulin response to glucose.

To better understand quantitatively the challenge of glucose regulation, we will consider modeling the dynamics of the glucose-insulin system and, in particular, meal responses. The glucose-insulin system has been studied for decades and there are many models that capture its dynamics following a meal response. Here, for simplicity, we will consider a highly simplified model (the principles that we will present will also apply to more complex and detailed models).

For glucose, we will consider production to be given by a function $u(t)$ (which incorporates both endogenous production and meal inputs). In general, there is insulin-independent removal of glucose (for example, by the brain), and insulin-dependent removal. For simplicity, we will only consider the latter, so the dynamics of glucose (G) and insulin (I) is given by:

$$\dot{G} = u(t) - sGI \tag{1}$$

$$\dot{I} = \beta f(G) - \gamma I \tag{2}$$

For simplicity, the units of I, G are set to (arbitrary) concentration units. The parameter s corresponds to the sensitivity to insulin - this parameter is the aggregate response of the many peripheral cells to insulin. β is the overall beta cell mass, and γ is the clearance rate of insulin from the body. The function $f(G)$ is the secretion rate of insulin per unit of sensed glucose. This is a sigmoid function:

$$f(G) = V\frac{G^2}{G^2 + K^2} \tag{3}$$

where the half-maximal activation is at $G = K$, and the maximal secretion per-cell is V. The activation function depends on the molecular properties of beta cells, namely, the activity of enzymes such as glucokinase, which mediates a key step in glucose sensing.

Eqs. 1,2 capture the main molecular interactions that affect the response to meals. A rise in G causes a rise in I, which helps reduce the level of G. The system will settle at a steady state where both equations solve. This would be at the intersection of two curves (the nullclines for the dynamics):

$$I = \frac{u}{sG} \text{ (nullcline of } \dot{G} = 0) \tag{4}$$

$$I = \beta\gamma^{-1} f(G) \text{ (nullcline of } \dot{I} = 0) \tag{5}$$

We can plot the nullclines in a phase plane. As Eq. 4 is monotonically decreasing and Eq. 5 is monotonically increasing, there will be a single intersection point. We can prove that this intersection is a stable fixed point (the real part of the eigenvalues of the Jacobian around the fixed point is negative, while the imaginary part may be nonzero).

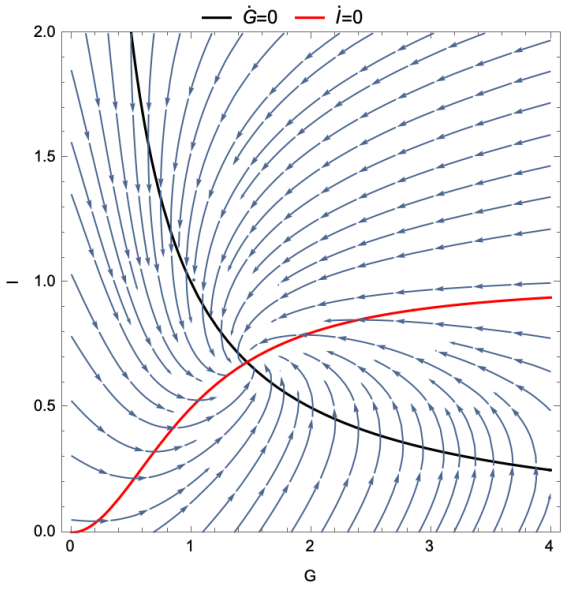

Figure 2: Phase portrait of G-I dynamics

2 The glucose-insulin model is not robust to changes in model parameters

As we mentioned, the parameter s represents the aggregate response of cells (such as fat or muscle cells) to insulin. When s, is high, the body is very sensitive to insulin, while when it is low, there is insulin resistance. Type II diabetes is associated with insulin resistance. However, the converse is not true - many people with insulin resistance do not suffer from hyperglycemia or impaired glucose responses.

How is insulin sensitivity measured? There is a well-established method, called the hyperinsulinemic-euglycemic clamp technique. Here insulin remains constant (through infusion) at some high level I_H, while glucose remains constant at baseline by an additional glucose infusion. The glucose infusion rate would then be roughly proportional to insulin sensitivity. **Experimental measurements show that there can be an order of magnitude of variation in s among healthy individuals with normal glucose levels and normal glycemic responses.**

The hyperinsulinemic-euglycemic clamp technique. Why does the hyperinsulinemic-euglycemic clamp technique measure insulin sensitivity? Consider Eq. 1 when insulin is held constant at a high level I_H, and glucose is infused at a constant (large) rate $\alpha \gg 1$. Let G_0 denote the level of homeostatic glucose, which is the target of the clamp technique (in people this would be about 5mM). Then the equation is now modified to be:

$$\dot{G} = \alpha + u(t) - sGI_H \tag{6}$$

Which, at steady-state, solves at:

$$\alpha = sG_0I_H - u(t) \approx sG_0I_H \tag{7}$$

The latter approximation becomes more accurate when we consider that insulin inhibits the endogenous production of glucose. Since G_0, I_H are fixed within individuals, the rate α will be proportional to the insulin sensitivity parameter s.

Can the experimental observation of normal glycemia, in the face of the large variation in s, be

reconciled with the GI model? The graphical depiction of Eqs. 4, 5 is helpful for understanding how the steady state of the system depends on parameter values. We can see that changing s changes the location of the G nullcline and that the steady-state of G increases in rough proportion to a decrease in s. Thus, wide variation in G should translate to a wide variation in G, which is not observed experimentally.

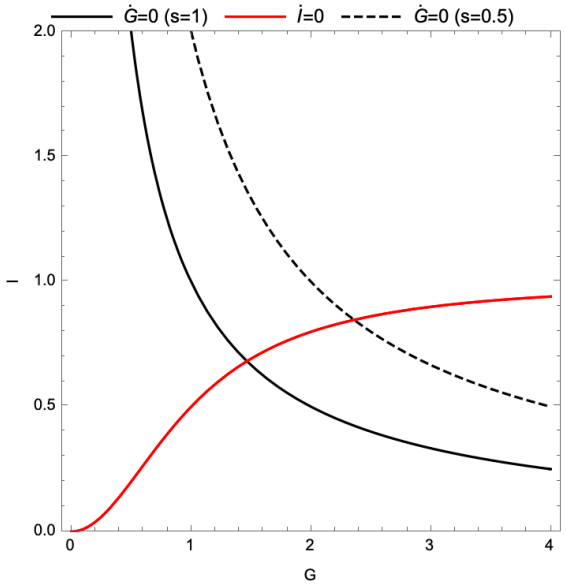

Figure 3: Phase portrait with nullclines for baseline (solid) and insulin resistance (dashed)

Experimentally, insulin resistance is compensated by increased insulin secretion. There is a well-established experimental observation that for healthy individuals, insulin secretion at baseline (denoted I_{st}), as well as insulin responses, follow a hyperbolic relation with insulin sensitivity, that is, the product $I_{\text{st}}s = D$ where D is a constant known as the disposition index. For diabetic individuals, the product is smaller than the disposition index. How does the body know how to adjust insulin secretion in the face of insulin resistance?

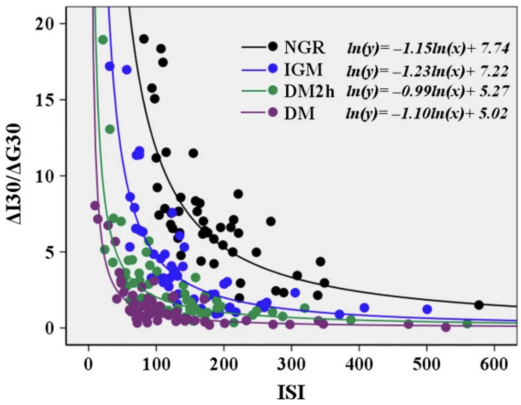

Figure 4: From Chen et al., Diabetology and Metabolic Syndrome, 2013

Another relevant observation has to do with glucose responses. Polonsky et al. measured glucose responses throughout the day in non-obese and obese subjects (obese subjects generally have insulin resistance, i.e. lower s). They observe that glucose baseline **and** responses remain largely unaltered. Furthermore, while insulin baseline and responses are higher in obese subjects, they are effectively identical to non-obese subjects when normalized by their baseline (Figure 8). It appears that insulin secretion adapts in some way precisely to the degree of insulin resistance.

How does this adaptation happen?

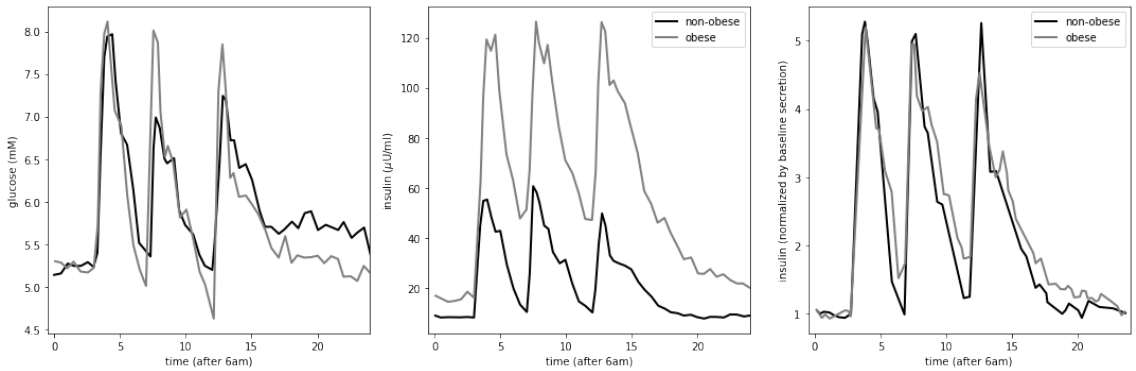

Figure 5: Adapted from Polonsky et al., J Clin Invest. 1988

3 βIG model explains adaptation to insulin resistance

To see how adaptation occurs in the glucose-insulin system, we need to consider the role of the beta cell mass (the term β in Eqs. 1,2). It is well established that the overall mass of beta cells is greater in individuals with insulin resistance and that it can dynamically adapt to physiological changes associated with insulin resistance, such as pregnancy.

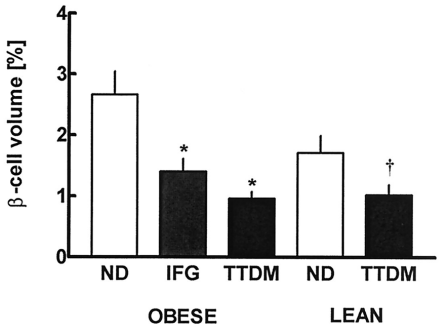

Figure 6: From Butler et al., Diabetes, 2003

We will therefore add to Eqs. 1,2 an additional equation for the dynamics of β, first devised by Topp et al. It is inspired by the observation that, when cultured in a plate, beta cells appear to be very sensitive to the precise glucose concentration (Efanova et al.) - if glucose is just below the homeostatic 5mM concentration, they die! This observation is important since it suggests a feedback loop from glucose to beta cell mass.

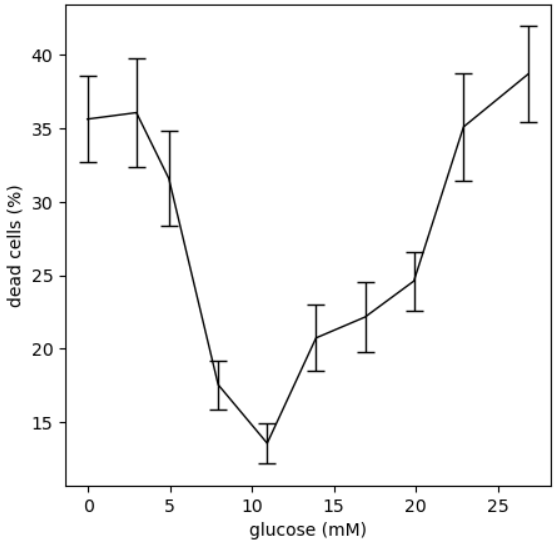

Figure 7: Adapted from Efanova et al., JBC 1998

To model the dependence of beta cell mass on glucose, we will add an equation of the form $\dot{\beta}$ = production − removal. Beta cells are produced from other beta cells, and removal is also proportional to the current beta cell mass. We can therefore model beta cell dynamics as:

$$\dot{\beta} = \beta \left(h_+(G) - h_-(G) \right) \tag{8}$$

where $h_+(G), h_-(G)$ corresponds to the growth and removal rates (per cell) of β cells. Fixed points of the system occur when $h_+(G) = h_-(G)$. Since glucose inhibits β cell death in a fast and step-like manner around $G = 5mM$, there will be a fixed point around $G_0 \approx 5$, and this fixed point will be stable (at the moment we ignore the increase in the death rate of beta cells at high glucose levels).

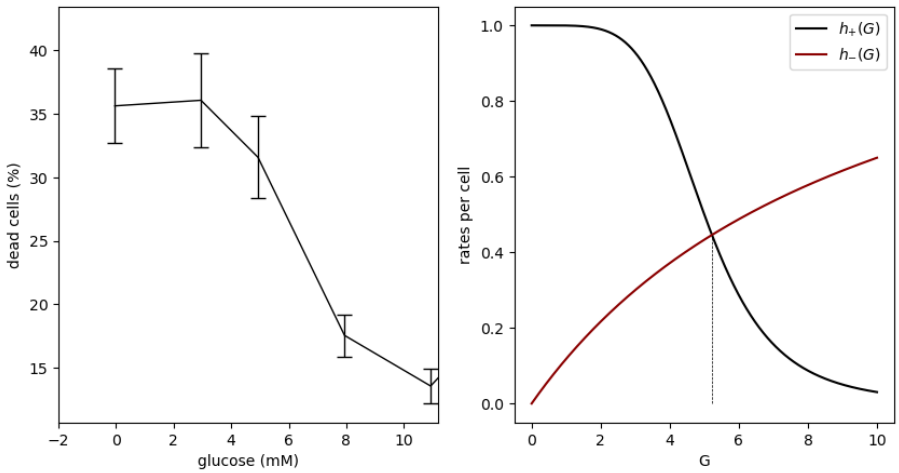

Figure 8: Left panel - adapted from Efanova et al., JBC 1998

We, therefore, add to the GI model one additional equation:

$$\dot{\beta} = \beta h(G) \tag{9}$$

where $h(G)$, the growth rate of the beta cells, is monotonically decreasing and is zero at

$G \approx 5mM$. Eqs. 1,2,9 together comprise the βIG model.

Eq. 9 causes the beta-cell mass to adapt in response to changes in parameters. A drop in s increases glucose levels, resulting in beta-cell expansion until glucose returns to baseline. On the other hand, an increase in s leads to beta cell contraction. In all cases, glucose homeostasis is ensured.

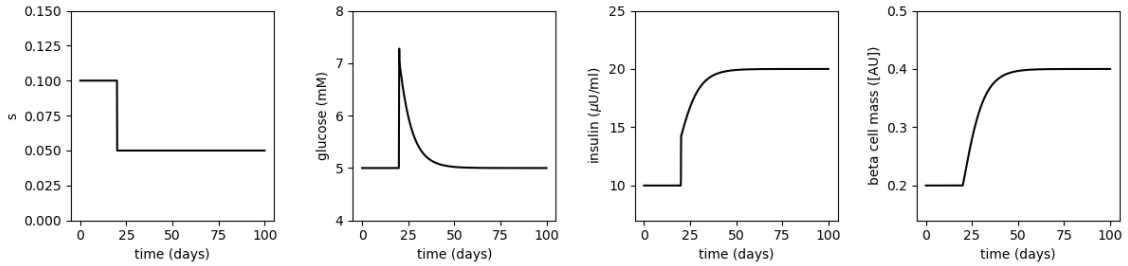

Figure 9: Response to a 2-fold drop in s.

In addition to the robustness of the steady state of G, in fact, the robustness of the entire glycemic response is ensured. Therefore, the βIG model can explain the observation that most individuals maintain proper glycemic levels and responses despite large variations in insulin sensitivity.

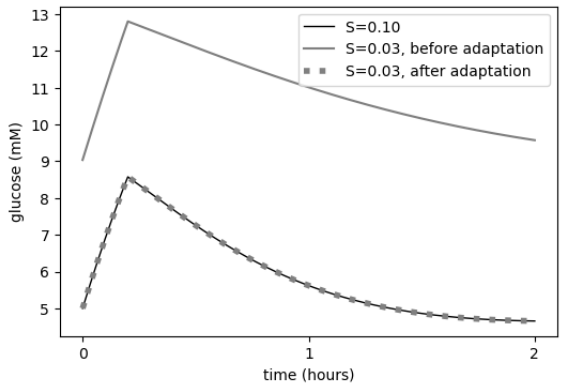

Figure 10: Glycemic responses during the adaptation process to insulin resistance.

Eq. 9 result in the adaptation of the entire dynamics of glucose to inputs following changes in insulin sensitivity. We call this robustness of dynamics in the face of changes in parameters *dynamical compensation*. To see why the βIG model has dynamical compensation, consider rewriting Eqs. 1, 2, 9 with a change of variables: $\hat{I} = sI, \hat{\beta} = s\beta$:

$$\dot{G} = u(t) - G\hat{I} \tag{10}$$

$$\dot{\hat{I}} = s\dot{I} = \beta s f(G) - \gamma s I = \hat{\beta} f(G) - \gamma \hat{I} \tag{11}$$

$$\dot{\hat{\beta}} = s\dot{\beta} = s\beta h(G) = \hat{\beta} h(G) \tag{12}$$

Eqs. 10,11,12 are independent of s. Now, it is also fairly straightforward to show that due to the exact adaptation of G, the steady states of I, β scale with s, and thus at steady state the variables $\hat{I}, \hat{\beta}$ are independent of s. Thus, the entire dynamics after any input $u(t)$ is independent of s.

Exercise: Show that the βIG model provides dynamical compensation to the increase in plasma volume during growth.

Exercise: Identify the general conditions on the dynamics of I, G, β for dynamical compensation.

4 Integral Feedback

Equation 9 is an example of a very important concept of control engineering: integral feedback control. The task of many controllers is to remove disturbances from a system. For example, a thermostat needs to keep a room at a constant temperature, and a cruise control system needs to keep a car moving at a desired speed.

Typically, such a system will have two elements: proportional feedback (P), which provides negative feedback that is proportional to the error, and integral feedback (I), which is proportional to the integral of the error. Together, these are known as PI control. The idea is that the proportional term stabilizes the output of the system, while the integral term eliminates the steady-state error. There may also be a term that increases in proportion to the derivative (D) of the error.

Insulin in Equations 1 and 2 plays a role somewhat analogous to the proportional controller, as it is secreted in rough proportion to glucose levels. Equation 9, on the other hand, implements an integral feedback control. Beta cell mass effectively integrates the error on glucose (the difference between the homeostatic set point and the sensed levels) and feeds it back through increased insulin secretion. This eliminates the steady-state error due to variation in s and other parameters. The property of dynamical compensation does not occur in linear integral feedback controllers but results from the specific nonlinear nature of the regulation of gland mass.

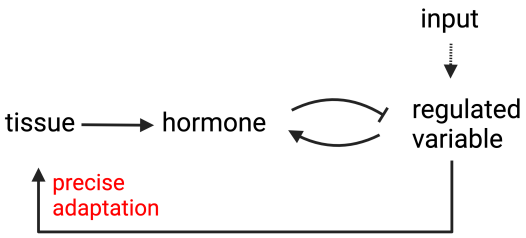

Figure 11: Motif for dynamical compensation

The two-step feedback mechanism for hormone regulation is widespread throughout the body. The first step is a rapid feedback loop in which a gland secretes a hormone in response to a change in a factor. The second step is a slower feedback loop in which the gland's mass is regulated by the factor. This two-step mechanism provides essential robustness to the hormonal system against variations in parameters such as blood volume and responses of remote cells.

5 Diabetes

If the beta cell adaptation mechanism ensures the robustness of glucose dynamics, why do some people develop diabetes? And why is diabetes so hard to reverse? An intriguing answer, consistent with our current understanding of the disease, was given by Topp et al., who noticed that, in addition to the suppression of beta cell death at low glucose concentration, there is an increase in the death rate of beta cells at high glucose concentration (Figure 7). This phenomenon is known as *glucotoxicity*. Incorporating glucotoxicity into the dynamics of beta cells (Eq. 9) results in a biphasic growth rate $h(G)$ (Figure 12). What are the implications of this biphasic growth rate?

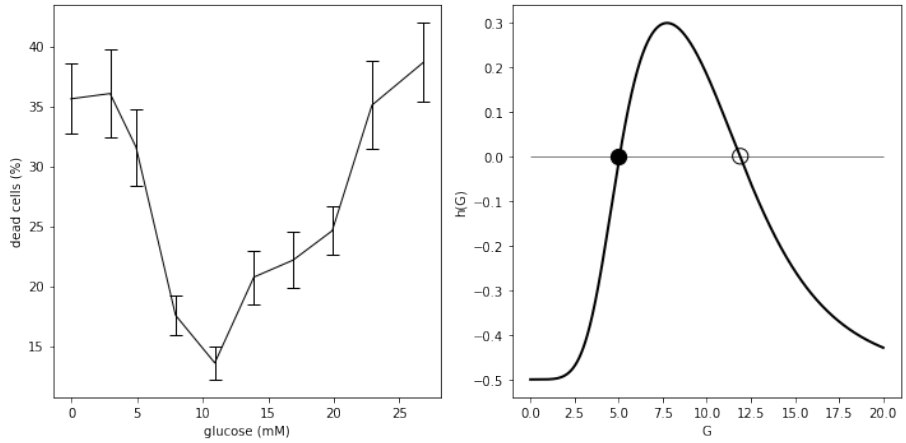

Figure 12: Glucotixicity results in biphasic growth of beta cells

The main idea is that as long as glycemia is maintained stably in the vicinity of the 5mM concentration, the beta cell feedback loop can adapt the beta cell mass to changes in s. On the other hand, a large change in glycemia (for example, due to a sudden increase in beta cell death, as occurs in type 1 diabetes) will activate a positive feedback loop that reduces beta cell mass even further, preventing the reestablishment of the beta cell mass and adaptation of glycemia.

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