Systems medicine Lecture notes

Uri Alon (Spring 2019)

https://youtu.be/a7DvXjUp7cE

Lecture 1 - The Insulin-glucose circuit

Welcome to the Systems Medicine lecture notes. The purpose of this course is to study general principles of tissues, discover the regulatory circuits that are essential for health, and why these circuits fail in diseases. At the end of the course, I hope you will be able to ask questions about human physiology and disease and answer them with appropriate mathematical models.

In this first lecture, we set the stage for the first three lectures. These three lectures will focus on the hydrogen atom of physiological circuits: the glucose-insulin control circuit. This circuit is a good starting point because it highlights several important principles that apply to many other tissues. It is also important medically, because its failure is the basis for diabetes, a disease afflicting about 10% of the world's population (of which 90% is type-2 and 10% type-1 diabetes, see below).

The main variable in this system is the blood concentration of the sugar glucose. Glucose is the energy and carbon source for the cells in our body. Glucose is maintained in the blood within a tight range around 5mM: different healthy people have a concentration of 5+/-1mM.

This tight control is important. If glucose drops below 3mM, the brain does not have enough energy and we can faint. Prolonged low glucose, called hypoglycemia, can be fatal. Similarly, if glucose is too high, above 10-15mM, it damages blood vessels and nerves, and over the years gives rise to the symptoms of type 2 diabetes.

In addition to the tight control over the steady-state level of glucose, the entire glucose dynamics after a meal is tightly regulated. These dynamics are measured, for example, in a clinical test for diabetes, called the glucose tolerance test (GTT). In GTT, you drink 75g of glucose, and measure blood glucose in the following two hours. Glucose rises to about twice its basal level of 5mM, and then falls back to baseline in about 2 hours (Fig 1). Different healthy people have similar glucose dynamics in the GTT. Aberrant

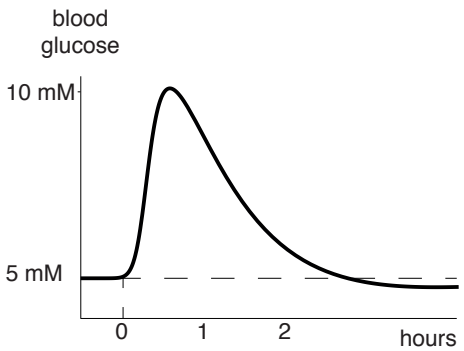

Figure 1.1

dynamics are a sign of diabetes: glucose above 11mM at 2 hours is a clinical criterion for diabetes (Fig 2).

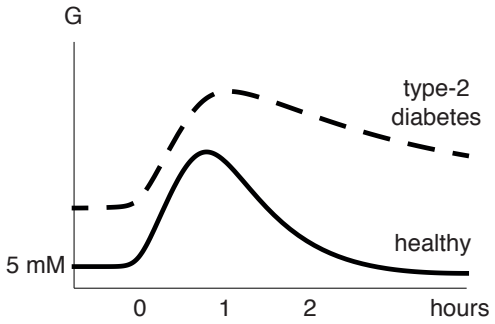

Figure 1.2

How is this tight control of blood glucose concentration achieved? The answer is a feedback circuit involving the hormone insulin, a small protein that is found in the blood. Insulin allows glucose to enter cells in muscle, fat and other tissues, and glucose is thus removed from the blood. Glucose is unable to enter these cells without special glucose transporters on their surface. The transporters are in storage vesicles inside the cell (Fig 3a). When insulin is in the blood, it binds special sensors on the cell surface called insulin receptors (Fig 3b), which bind insulin like a lock and key. When bound, the receptors initiate signaling pathways inside the cell that move the glucose transporters to the cell surface (Fig3b), where they pump glucose into the cell. As a result, insulin binding allows glucose to enter the cell (Fig 3c).

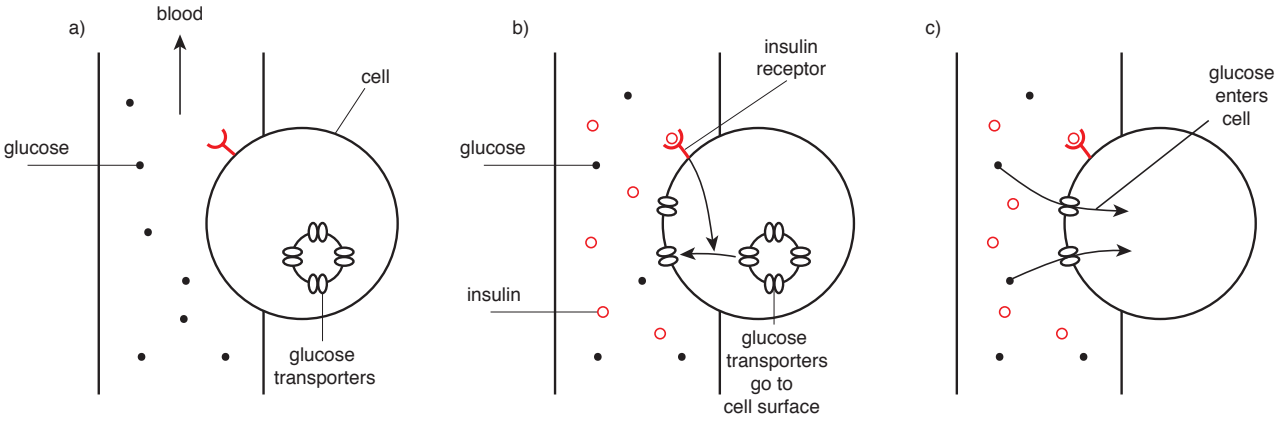

Figure 1.3

Insulin is secreted by special cells in the pancreas called beta-cells. The pancreas is a thin gland about the size of a dollar bill located in our upper abdomen. In this gland are a million groups of cells called islets of Langerhans, each with about a thousand beta cells (Fig 4). The Islets also house other types of cells, like alpha cells that secrete glucagon, a hormone that acts to increase glucose production in the liver, which we will ignore for now. In general, we ignore many details that are not crucial for the principles we wish to describe.

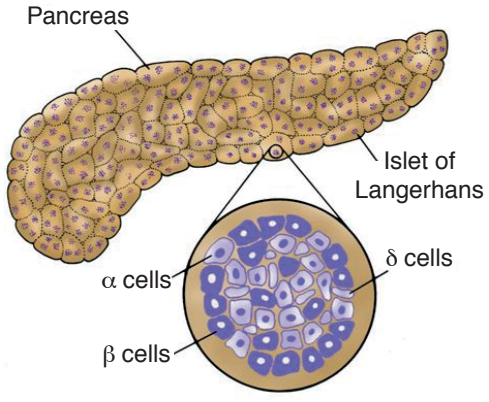

Figure 1.4

Now the beta cells sense glucose, and the more glucose around, the more insulin they secrete. Thus, a rise in glucose leads to more insulin

secreted to the blood. Insulin induces cells in the muscle and fat to take up glucose, and so blood glucose levels drop. This is a negative feedback loop: more glucose, more insulin, and thus less glucose (Fig 5).

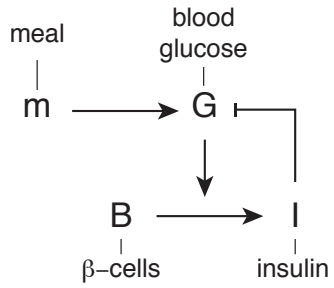

Figure 1.5

Diabetes is a malfunction in this system. In type 1 diabetes (T1D), the immune system attacks beta cells, and kills them off. As a result, there is no insulin and cells cannot obtain the glucose they need. To survive, T1D patients rely on insulin injections. In type 2 diabetes (T2D), beta cells do not secrete enough insulin to remove blood glucose effectively. Glucose rises and over the years causes damage to the body.

We have now completed the verbal introduction to this system. It is a basic version of the more intricate verbal description generally taught to doctors and biologists. The verbal description is powerful in that it can explain intuitively the dynamics, such as the rise and fall after a GTT, and the basic phenomena in diabetes.

In this course we want to go beyond verbal descriptions and to write equations. Equations can help us focus on important parameters, and to generalize principles from one system to other systems. Most importantly, equations help us to ask new questions, such as what is the fundamental origin of diseases such as T1D and T2D. In this chapter we lay the foundations for the next two chapters in which we will make progress on these questions.

In the glucose-insulin system, mathematical models developed since the 1970's have had important benefits for clinical practice, because they helped to define important parameters like insulin resistance. They also provide practical ways to estimate these parameters for each patient based on clinical measurements. One important model is the minimal model by Richard Bergman (1979), and we will use a version of this model as a basis for our exploration.

In order to model the dynamics of the system, we use differential equations to describe rates of change of glucose and insulin concentrations in the blood. Blood glucose concentration, G(t), is supplied in two ways: the first is when we eat a meal and glucose enters the blood from the intestinal system. The second way occurs between meals, such as during fasting and sleep. Glucose is then produced by the liver, which stores glucose in times of plenty in a polymer called glycogen, and breaks it down when we fast.

Summing over these two sources, we have the glucose supply m(t). Glucose is removed by the action of insulin. Thus, the rate of change of glucose, dG/dt, is the sum of supply m minus removal

$$(1)\ \frac{dG}{dt} = m - a\,G$$

Let's focus on removal term $-\,a\,G$. The rate parameter a is the probability per unit time to lose a glucose molecule form the blood. For example, suppose we start with glucose concentration of G=G0=5mM, and then totally stop production, m=0. As a result, glucose is only removed,

(2) $\frac{dG}{dt} = -aG$

The solution of this equation is an exponentially decaying concentration which drops over time from its initial level G_0 (Fig 6):

(3) $G(t) = G_0\, exp(-a\, t)$

The half-life of glucose is the time it takes to go halfway down from its initial level. This half-life, t1/2, is when $G(t_{\frac{1}{2}}) = G_0/2$. Plugging this into equation (3), we find $exp(-a\, t_{1/2}) = 1/2$, and thus

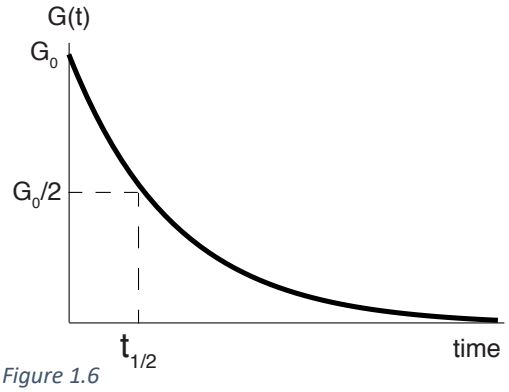

Figure 1.6

(4) $t_{1/2} = ln(2)/a$

This is a general result: the half-life of a molecule is inversely related to its removal rate (faster removal leads to shorter half-life).

In our system, removal is due to insulin, so that a= s I. The parameter s is called **insulin sensitivity**- an important parameter. Insulin sensitivity is the effect of a unit of insulin on glucose removal rate. It can be measured by injecting insulin and noting the reduction in glucose. Thus, our glucose equation is:

(5) $\frac{dG}{dt} = m - s\, I\, G$

Now let's write the equation for the rate of change of insulin concentration in the blood, I(t). Insulin is produced by beta cells, and the production rate rises with glucose. Thus, each beta cell makes q f(G) units of insulin per unit time, where q is the maximal production rate and f(G) is an increasing function of G. As in many biological circuits, f(G) is well described by a Hill function,

(6) $f(G) = \frac{G^n}{K^n + G^n}$

which goes between zero and one, and reaches halfway to one at a glucose concentration of G=K. For beta cells, n=2 is a good approximation, so that f(G) has a sigmoidal shape Fig.7. Note that insulin is secreted into the blood. The more blood, the more insulin is diluted. Thus, the secretion rate parameter q is the total number of molecules of insulin secreted per unit time, divided by the total blood volume, in order to get units of insulin concentration. All that we need to do now is to multiply the production rate per cell by the number of beta-cells B, to get a total insulin production of $qBf(G)$. Insulin is removed at rate gamma, so that

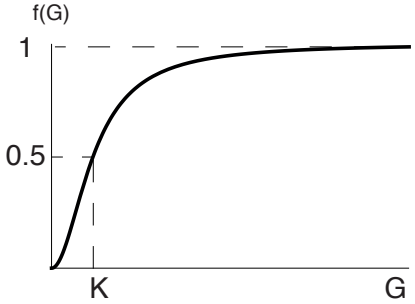

Figure 1.7

(7) $\frac{dI}{dt} = q\, B\, f(G) - \gamma\, I$

The rate parameter gamma provides the insulin half-life in the body, of about 30min.

We now have the minimal model equations. Let's see how they do in the glucose tolerance test. We can solve the equations on the computer, and provide a pulse of input glucose m(t) to describe the glucose going into the body when we drink 75g of glucose solution. As a result, G(t) first rises, and as a result insulin I(t) rises, increasing the removal rate of G until return to baseline (Fig 8). This resembles the measured response of healthy people.

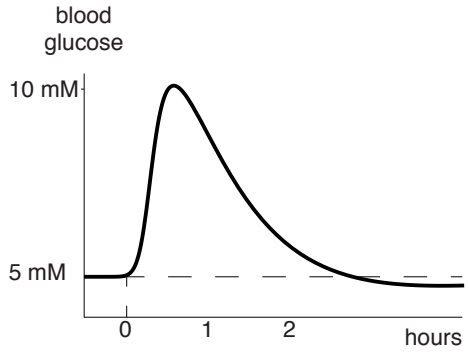

Figure 1.8

Let's now ask about the tightness of glucose regulation. For example, is it plausible that G_{st} and the dynamics G(t) is so constant between people? The parameters to watch is insulin sensitivity, s. Insulin sensitivity varies between people: it is a physiological knob that allows the body to partition glucose resources and determine which tissues get the glucose. For example, when we exercise, muscles need energy, and s rises. The effect of insulin is magnified by higher s, and muscles take up more glucose from the blood.

In contrast, in inflammation, s drops so that more glucose stays in the blood in order to help the immune system fight pathogens. In pregnancy insulin sensitivity also drops, diverting glucose to the fetus. In obesity s drops dramatically, sometimes by a factor of ten. This phenomenon is called insulin resistance, since each unit of insulin works much less effectively than in non-resistant people. Insulin resistance is due to factors secreted by fat cells, and to chronic inflammation that often occurs in obesity. Insulin resistance, as we will see, is an important factor in T2D.

Despite the fact that people vary in s by as much as tenfold, most people have normal glucose levels and dynamics. For example, the majority of people with obesity, which all have low s, have normal 5mm glucose and GTT dynamics.

If we simulate the Minimal model with a 10-fold lower s, we see that steady state rises by factor of about 2, and response time also greatly increases (Fig 9). Thus, the minimal model cannot explain how most people with obesity have normal glucose. In fact no model based on the description of the system we studied so far can do so. We need to add another control loop to make glucose dynamics robust to variations in parameters such as s. We will do this in the next chapter.

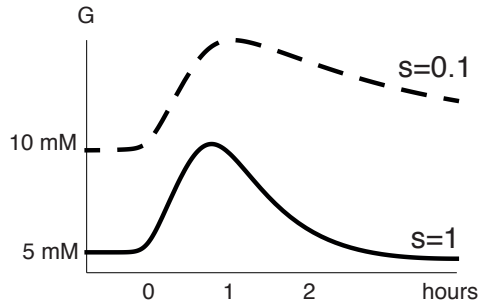

Figure 1.9

To see explicitly how sensitive the minimal model is to variations in parameters, we can solve for the steady state glucose:

Solved exercise: Show that the minimal model has steady state glucose that depends on insulin sensitivity s and all other model parameters

Steady-state means no change with time, and thus we set dG/dt=0 and dI/dt=0. We find from Equation (5), that $s\, I_{st}\, G_{st} = m_{st}$, where m_{st} is the fasting production of glucose form the liver. The subscripts "st" denote steady state. To find the steady state solution of the insulin equation Eq.7, lets approximate the regulation function as $(G/K)^2$. Thus, from Eq.7, we find that $q\, B\, (G/K)^2 = \gamma\, I_{st}$. Hence $qB(G/K)^2 = \gamma\, I_{st} = \gamma\, m_{st}/(s\, G_{st})$ and we obtain a steady state glucose level that depends as a cube root on all parameters (the cube root comes from the G^2 regulation):

$$G_{st} = \left(\frac{K^2\, \gamma\, m_{st}}{s\, q\, B}\right)^{\frac{1}{3}} .$$

Let's consider the case of insulin resistance due to an 8-fold drop in s, keeping all other parameters the same. This will result in a 2-fold rise in G_{st} (because $8 = 2^3$). G_{st} is not robust to insulin resistance, or to any of the other parameters in the model.

Thus, the prose description of the insulin-glucose circuit seems to work qualitatively well. But when we write the equations, we can see that we need additional mechanisms to explain the robustness of glucose dynamics with respect to physiological parameter.

In the next two chapters we will see how answering the question of robustness of G dynamics leads to general principles for a feedback control in tissues. This new feedback will have unavoidable fragilities that explain why beta cells fail in T2D, as we will see in chapter 2, and why the body attacks its own beta cells in T1D, as well see in chapter 3.

Appendix:

Exactly solvable approximation for response time in the minimal model

$$\frac{dG}{dt} = m - s\ I\ G$$

$$\frac{dI}{dt} = qB\ f(G) - \ c\ I$$

Suppose a big long meal, $m(t) = m_1$. Glucose rises and maximizes $f(G)$ to $f(G) = 1$ for enough time that I reach its high steady state

$$I_1 = q\ B/c$$

When the meal ends, glucose is at its high level

$$G_1 = \frac{m_1}{s\ I_1}.$$

Now meal ends and m(t) drops to its basal level m_0 (liver glucose production repressed by insulin).

$$G(t) = G_0 + (G_1 - G_0)exp(-s\ I_1\ t) = G_0 + (G_1 - G_0)\ exp(-[s\ q\ B\ /c]\ t)$$

Response time is $t_{1/2} = ln(2)\ c/(s\ q\ B)$ → depends on all parameters

Area under the m(t) curve in the decline phase is about $G_1\ t_{1/2}$~$\mathrm{m_1}\ (\mathrm{c}\ /\mathrm{s}\ \mathrm{q}\ \mathrm{B})^2$; goes up very high with s and q.

In the BIG model,

$$\frac{dB}{dt} = B\ \mu(G)$$

$G_{st} = G_0$, and hence $I_{st} = m_0/(s\ G_0)$, and $B_{st} = c\ m_0/(s\ q\ G_0\ f(G_0))$

Response time is $t_{1/2} = ln(2)\ c/sq\ B = ln(2)G_0\ f(G_0)/m_0$ → independent on s,q,c

$G_1 = m_1/(s\ I_1) = \ m_1\ c/\ s\ q\ B\ = m_1\ G_0\ f(G_0)/m_0$, area under curve independent on s and q.