Chapter 1

The insulin circuit

Hormone Theme song

There are hormones in the pancreas to help digest our food, and beta-endorphins that make us feel real good. There’s feedback loops and circuits that are beautiful to watch, and in this book we’ll study them a lot but not too much.

Hormones, hormones, hormones here and there, Hormones, hormones, hormones, hormones Hormones everywhere (music Lynn Kellogg, animals everywhere)

The insulin-glucose circuit

In this chapter and the next, we focus on the glucose-insulin circuit. It is the hydrogen atom of hormone circuits -- the best-understood system which provides the conceptual tools to understand more complex cases, just as hydrogen was the testing ground for quantum mechanics, which provided the tools to understand other atoms and molecules.

The glucose circuit thus provides principles that apply to many other systems. The circuit is also important medically. 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, stay tuned).

Glucose concentration and dynamics is tightly controlled

The main variable in this system is the concentration of the sugar glucose in the blood. Glucose is an energy and carbon source for the cells in our body. It is the major fuel for the brain and for immune cells. **Glucose concentration in the blood is maintained within a tight range around 5mM.** That reads 5 millimolar, or, in more common units, 90 milligrams per deciliter, roughly a teaspoon of glucose per teacup of blood.

Among healthy individuals, glucose steady-state concentrations vary by only about 20%. Such rigorous control is called **homeostasis** in biology - the ability of the body to keep important variables within a tight range. If glucose drops below 3mM, the brain does not have enough energy and we can faint. Prolonged low glucose, called **hypoglycemia**, can be fatal. The body
switches to alternative energy sources such as ketone bodies which can cause blood acidity, which is potentially lethal.

Similarly, if glucose is too high, above 7-10mM, it starts sticking to blood vessels and nerves, damaging them. Over years, this leads to the deadly symptoms of type-2 diabetes. The damaged blood vessels cause heart attacks, kidney disease and, in the retina, blindness. Damaged blood vessels can also lead to amputation of legs and other grim outcomes.

Let’s take a nice deep sigh of relief.

The control is so rigorous that clinical criteria for diabetes are based on glucose blood tests. Blood glucose below 5.6mM (100mg/dL) after fasting for 8h or more is normal. Glucose between 5.6mM and 6.9mM is prediabetes, and above 6.9mM (125 mg/dL) on two separate tests means diabetes.

In addition to the control over the steady-state level of glucose, the entire glucose dynamics after a meal is tightly regulated. These dynamics are measured 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 1.1). Different healthy people have similar glucose dynamics in the GTT. Aberrant dynamics are a sign of diabetes: glucose above 11mM at 2 hours is a clinical criterion for diabetes (Fig 1.2).

We can now ask how such rigorous control is achieved despite vast differences between people. Individuals can vary in weight by a large factor, undergo the changes of pregnancy, vary in activity and diet and so on. Yet most people most of the time have glucose set-points and dynamics that are nearly the same.

Glucose concentration is controlled by insulin

How is the control of blood glucose concentration achieved? The answer is a feedback circuit involving the hormone insulin, a small protein that circulates in the blood. Insulin acts to remove glucose from the blood, by allowing it to enter cells in the muscle, liver and fat where glucose is used or stored.
Glucose is unable to enter these cells without special glucose transporters on the cell surface. The transporters are stored away in storage vesicles inside the cell (Fig 1.3a). When insulin is in the blood, it binds special sensors on the cell surface called insulin receptors (Fig 1.3b). These receptors 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 (Fig 1.3b), where they let glucose into the cell. As a result, insulin shunts glucose out of the blood and into the cells (Fig 1.3c).

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 (Fig 1.4). In this gland there are a billion beta cells, arranged in a million groups of about 1000 cells called islets of Langerhans. The islets also house other types of cells, like alpha cells that secrete glucagon, a hormone that acts to increase glucose in the blood – countering the action of insulin. Glucagon induces the production of glucose in the liver during fasting and sleep.

Beta cells are smart, and only secrete insulin when it is needed. The beta cells sense glucose, and the more glucose around, the more insulin they secrete. 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 1.5). Note the blunt-headed arrow, a symbol of a negative regulation in the world of biological circuits - in this case insulin reducing glucose levels.

The input to this circuit is glucose from meals that goes into the blood. Between meals glucose is produced by the liver. The liver stores glucose in times of plenty in a polymer called glycogen, and breaks it down when we fast. When it runs out of glycogen, at about the middle of the night, the
liver makes glucose out of amino acids taken from muscles, in a process called gluconeogenesis (‘new production of glucose’). We denote both sources by $m$ in Fig 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 glucose can not enter muscle cells. Until the 1920s, type-1 diabetes was a death sentence to the children who got it: about 1% of the population gets T1D, typically at the age of 10-11. With the discovery of insulin, diabetic children survive thanks to insulin injections, and now through continuous insulin pumps. Still, keeping glucose under external control is hard, and type-1 diabetes raises the risk for health complications. We will understand this autoimmune disease in chapter 4.

In the more common disease called type-2 diabetes (T2D), glucose rises and over the years causes damage to the body. A major cause of type-2 diabetes is insulin resistance, which we will describe below.

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

In this book we want to go beyond verbal descriptions by adding 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 foundation for the next chapter in which we will make progress on these questions.

**Mathematical model for the glucose-insulin circuit**

Mathematical models for this circuit, developed since the 1970's, have benefitted clinical practice. They help to define key 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 (R. N Bergman et al. 1979), and we will use a version of this model as a basis for our exploration.

The model was developed using experiments on volunteers in which glucose or insulin were introduced intravenously, and their effects were monitored over time using glucose and insulin blood tests. The model uses differential equations to describe rates of change of glucose and insulin concentrations in the blood.

This model, and all of the models in this book, ignores some of the details of the system and focuses only on the main features essential to understand the principles we are interested in. The simplicity of the models might generate mistrust because one might think "It is more complicated than that! You didn’t take this or that into account". We will see that ignoring some details is not only okay but necessary in order to see underlying principles. By exploring the art of building good
models, we will learn how to tell which features are essential based on their timescale and magnitude.

Let’s begin with the equation for the rate of change of insulin concentration, $I(t)$. The equation has a form we will use throughout the book, where rate of change equals production minus removal

$$\text{Rate of change of insulin} = \frac{dI}{dt} = \text{production - removal}$$

For more details, see solved exercise 7. Insulin is produced by beta cells, and the production rate rises with glucose. Thus, each beta cell makes $q f(G)$ units of insulin concentration per unit time, where $q$ is the maximal production rate per unit biomass of beta cells divided by the blood volume, and $f(G)$ is an increasing function of glucose $G$, that ranges between 0 and 1. It describes how glucose regulates the secretion rate of insulin.$^2$ Experimental measurements show an increasing S-shaped curve that saturates at high glucose, meaning that it reaches a maximal level (Fig 1.6). Such curves are well-described in many biological systems by a Hill function, given by

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

This function reaches half of its maximum value at a glucose concentration of $G = K$. This half-way concentration is about $K = 8mM$ in human islets. The steepness of the Hill function is higher the larger the Hill coefficient parameter, $n$. For beta-cells, $n=2$ is a good approximation (Fig 1.6). Hill functions have a theoretical basis which can be found in most biochemistry textbooks (see solved exercise 8).

All that we need to do now is to multiply the production rate by the total beta cell mass $B$, to get an insulin production rate of $q B f(G)$.

We now turn to insulin removal. Removal of molecules is well described by giving them a constant rate of removal, $\gamma$, so that the number of molecules removed per unit time is $\gamma I$. The difference between production and removal is our equation for insulin:

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

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$^2$ Some additional features of the system are ignored here because they do not affect the core behavior of the feedback loop. This includes the following: Insulin secretion $q$ is amplified by hormones released from the gut such as GLP-1 that sense incoming meals, and from brain inputs that anticipate meals. Insulin is secreted in two pulses, a brief spike of a few minutes followed by a prolonged insulin response to a meal, by beta cells that are heterogeneous with different sizes and secretion rates.
The removal rate $\gamma$ is determined by the insulin half-life, about 5 min. Insulin is removed primarily by degradation in the liver and the remainder is filtered out by the kidneys.

To get some practice with the equation, let’s see how the insulin removal rate $\gamma$ relates to its half-life. Imagine blocking insulin production (as in patients with T1D who have no beta cells, or by using certain drugs). In this case, there is no production, only removal, and hence

$$\frac{dI}{dt} = -\gamma I$$

The solution of this equation is concentration that decays exponentially with time from its initial level $I(0)$:

$$I(t) = I(0) \exp(-\gamma t)$$

The half-life of insulin, $t_{1/2}$, is the time it takes to go halfway down from its initial level. Thus $I(t_{1/2}) = I(0)/2$. Plugging this into equation (3), we find $\exp(-\gamma t_{1/2}) = 1/2$, and our solution for the half-life

$$t_{1/2} = \ln(2)/\gamma$$

This is a general result: the half-life is inversely related to the removal rate -- faster removal leads to shorter half-life. Half-life is not affected by production rate parameters like $q$ and $f(G)$ or by initial conditions.

Now let’s write the second equation, for glucose. Blood glucose concentration, $G(t)$, is produced by meals and by liver production of glucose, whose sum is denoted $m(t)$. Glucose is removed by the action of insulin. The rate of change of glucose is, as before, supply minus removal

$$\frac{dG}{dt} = m - aG$$

Let’s focus on removal term $-aG$. Imagine that you are an engineer that needs to design this circuit. The simplest design is not to have insulin at all, but rather to have a constant glucose removal rate, $a$, the probability per unit time to lose a glucose molecule from the blood. Since high levels of glucose are harmful, it makes sense to remove it quickly after meals, with a large removal rate $a$. However, rapid removal means that at night or during fasting, the liver would need to make more glucose per unit time to keep 5mM steady state.

To see this, notice that the steady-state of Eq 4, that is, when glucose does not change with time, $dG/dt=0$, is $G_{st}=m/a$. Steady state glucose is the ratio of production and removal rates. The higher the removal rate $a$ the larger production $m$ needs to be to maintain a 5mM steady-state glucose concentration. Thus, a constant rapid glucose removal rate creates a wasteful cycle of high production and high removal.

To avoid this wasteful cycle, the body uses insulin to increase the removal rate of glucose when needed. Insulin is made only when glucose is high. This provides a high removal rate after a meal and a low removal rate during fasting. Notably, since insulin is made in tiny amounts compared to glucose, the cost of the insulin system is negligible.

Because glucose removal is enhanced by insulin, we let the removal rate depend on insulin, $a = sI$. The parameter $s$ is called insulin sensitivity. It is an important parameter. Insulin sensitivity is
the effect of a unit of insulin on glucose removal rate. This parameter is more familiar in its inverse form, **insulin resistance**, defined as 1/s. Insulin resistance is the extent to which insulin fails to work. Insulin sensitivity can be measured by injecting insulin and observing the subsequent reduction in glucose.

Thus, our glucose equation is:

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

These equations reach a steady state, which we can find by setting all rates of change to zero, namely \(dG/dt=0\) and \(dI/dt=0\). Solving this precisely yields a messy formula, but a good approximation can be made by assuming that \(f(G) = (G/K)^2\), as described in solved exercise 1. The steady-state glucose concentration is

\[
G_{st} = \frac{\gamma^2 m_{st}}{s q B}^{1/3}
\]

The 5mM steady state can be achieved provided the parameters are right.

Let’s see how these equations 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. In response, \(G(t)\) rises, causing insulin \(I(t)\) to rise in turn, thereby increasing the removal rate of \(G\), until it returns to baseline, as shown in Fig 1.7 (see exercise 6 for more details). This resembles the measured response of healthy people, including a slight glucose undershoot before returning to baseline. The minimal model thus seems to capture the essential behavior.

**A graphical tool to understand the circuit, the phase portrait**

Often we don’t know for sure what is the precise mathematical model to describe a biological circuit. I’d like to present a way in which we can still make progress. This is a graphical tool that we will employ throughout the book, called the **phase portrait**. The phase portrait will show us that the feedback loop can reach a steady state no matter what the exact
parameters or forms of the interaction terms are. Later, we will use it to see how parameters like insulin resistance affect the system.

The phase portrait has two axes, one for each of the variables, in our case insulin and glucose. The idea is to break the feedback loop into two arms. Study each arm separately, and then put them back together.

The first arm describes how glucose induces beta cells to make insulin (black line in Fig 1.8). One experiment to measure this arm of the feedback loop uses intravenous injection of glucose to ‘clamp’ blood glucose to a given value. Then, one allows insulin to reach steady-state and measures its concentration. Plotting insulin versus glucose reveals a rising S-shaped function. The more glucose, the more insulin secreted by the beta cells.

In the model, this line is given by setting $dl/dt=0$ in Eq 2, corresponding to zero change in insulin. This is called the insulin nullcline. Its formula is $I=qBf(G)/\gamma$, and so the nullcline has essentially the same shape as the induction function $f(G)$.

The second arm of the feedback loop (red line in Fig 1.8) describes how insulin removes glucose. Imagine clamping blood insulin at a given level and waiting till glucose settles down to its steady state. At each level of insulin, you record the steady-state level of glucose, and plot this to get the decreasing blue line in Fig 1.7. The curve decreases because the more insulin, the less glucose since insulin removes glucose from the blood. Its equation can be derived by setting $dG/dt=0$ in Eq 5, to get the glucose nullcline, $I=m/s G$.

Now we unleash the full feedback loop without artificially clamping one of the variables. Glucose and insulin now affect each other. The point to watch is where the two lines intersect. This is the fixed point of the system, where both glucose and insulin are at steady state simultaneously. These are the values you can measure with blood tests after fasting, say in the morning.

We can add to the phase portrait little arrows that indicate the dynamics (Fig 1.9). The arrows show the direction of change for insulin and glucose. They converge into the fixed point, showing that all initial conditions flow to it -- it is a stable fixed point. The orange trajectory in Fig 1.9 shows how glucose and insulin evolve when we start with an initial excess of glucose. Glucose makes insulin rise, pushing glucose down towards its steady state of 5mM, and both return to baseline.

The phase portrait can help us arrive at conclusions even if we don’t know the mathematical functions or parameters in the model and hence the precise shapes of the nullclines. No matter what the exact shape of the curves, we know that one curve must increase –

Figure 1.9: The phase portrait shows arrows that indicate insulin and glucose dynamics. One trajectory is shown in orange which begins with high glucose and flows into the fixed point.
glucose induces insulin production—and the other curve must decrease – insulin removes glucose. This guarantees a steady state where the two curves intersect.

So far so good. The minimal model provides a glucose set point, and the observed rise and fall of glucose and insulin in response to a meal. We can take a nice deep sigh of relief for making it this far.

**Insulin sensitivity varies widely between people**

With our model in hand, let’s now ask about the tightness of glucose regulation. A striking observation is that one of the model parameters varies widely between individual people, but empirical evidence shows that the glucose steady state and dynamics remain constant. Is our current model capable of capturing this kind of consistency?

The varying parameter is insulin sensitivity, $s$. Insulin sensitivity varies between people and over time because it is a physiological knob that allows the body to allocate glucose resources and determine which tissues get the glucose. For example, when we exercise or during caloric restriction, we need to use or store glucose, and signals are secreted that cause insulin sensitivity $s$ to rise. The effect of insulin is magnified by higher $s$, and muscles and fat take up more glucose from the blood.

In contrast, during infection and inflammation, insulin sensitivity drops due to inflammatory signals in the circulation. Instead of storing it in muscle and fat, more glucose stays in the blood to help the immune system fight pathogens. Insulin sensitivity also drops during pregnancy, diverting glucose to the fetus. A further condition that leads to low insulin sensitivity is chronic stress, through the action of the hormone cortisol that we will discuss in chapter 3. A common cause of insulin resistance is obesity -- $s$ drops dramatically, often by a factor of ten, with body mass index (weight divided by height squared) as shown in Fig 1.10 (from Kahn et al. 1993). Obesity causes fat accumulation in muscle and liver that triggers inflammation and insulin resistance (James, Stöckli, and Birnbaum 2021).

Thus inflammation, pregnancy, chronic stress and obesity lead to **insulin resistance**. Recall that insulin resistance is defined as $1/s$. Each unit of insulin works less effectively than in non-resistant people. Insulin resistance, as we will see in the next chapter, is an important factor in T2D.

Even though people vary in $s$ by as much as a factor of ten, most people have normal glucose levels and dynamics. For example, most people with obesity, which all have low $s$, have normal 5mM glucose and GTT dynamics.
The minimal model fails to explain how people with insulin resistance maintain normal glucose levels

Let’s see what the model predicts for insulin resistance. Suppose that $s$ drops by a factor of 10 -- or equivalently insulin resistance rises by a factor of 10, making insulin 10 times less effective at removing glucose. In the phase portrait (Fig 1.11), the glucose nullcline shifts to a higher level, because that nullcline is inversely proportional to $s$, $I = m/sG$. As a result, the glucose set-point shifts to higher levels, far above 5mM.

The phase portrait shows that this is a general effect, no matter what the exact shape of the curves. Insulin resistance shifts the glucose nullcline up because a given insulin level results in more glucose, and hence steady-state glucose rises.

*This creates a problem for the model because most people with obesity have insulin resistance but normal glucose levels.*

Indeed, if we simulate the minimal model with a 10-fold lower $s$, we see that steady-state glucose concentration rises by a factor of about 2 (Fig 1.12 blue line is the model prediction). You can see this from the solution of Eq 6, where $G_{st}$ depends on $1/s^3$, and the cube root of 10 is about 2. In fact, glucose steady state depends on all model parameters.

The response time after a glucose tolerance test also increases substantially in the model when $s$ is low (Fig 1.12 blue line). See solved exercise 2 for an analytic solution for the response time, which also depends on all model parameters.

Thus, the minimal model cannot explain how most people with obesity have normal glucose (their observed dynamics is like that predicted for $s=1$, black line). 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.

**Summary and outlook**

The prose description of the insulin-glucose circuit found in textbooks seems to work qualitatively well. But when we write the equations, we see that we need additional mechanisms to explain how glucose stays under tight control despite variations in physiological parameters. We need to explain why most people with obesity, pregnancy or chronic stress have very different insulin resistances but normal 5mM glucose and normal dynamics in the glucose tolerance test.
In the next chapter we will see how answering this question opens up general principles for feedback control in tissues. This new feedback has unavoidable fragilities that explain why beta cells fail in type-2 diabetes, as we will see in the next chapter, and why the body attacks its own beta cells in type-1 diabetes, as we will see later in chapter 4. In the next chapter we will also reveal the three basic ‘laws’ that will carry us throughout the book.

Let’s take a deep sigh of relief.
Exercises:

Solved exercise 1: Show that the minimal model has steady-state glucose that depends on insulin sensitivity $s$ and all other model parameters.

Let’s write the minimal model equations again,

\begin{align*}
(7) \quad \frac{dg}{dt} &= m - sI_G \\
(8) \quad \frac{dl}{dt} &= qBf(G) - \gamma l
\end{align*}

Steady state means no change with time, and thus we set the time derivatives to zero: $dG/dt = 0$ and $dl/dt = 0$. We find from Equation (7), that

\begin{equation}
(9) \quad s I_{st}G_{st} = m_{st}
\end{equation}

where $m_{st}$ is the fasting production of glucose from the liver. The subscripts "st" denote steady-state throughout this book.

Incidentally, this is the origin of the HOMA-IR equation used in research and in the clinic to estimate insulin sensitivity from steady-state glucose and insulin measurements:

$$s = m_{st} / I_{st} G_{st}$$

using the estimated parameter $m_{st} = 22.5$ whose units assume that glucose is measured in mM and insulin in $\mu U/ml$ [https://en.wikipedia.org/wiki/Homeostatic_model_assessment].

Similarly, there is a useful equation for beta cell function, based on the steady state of Eq 8, given by $qB = \gamma I / f(G)$. Often researchers use an approximation for $f(G)$, a straight line describing the slope near 5mM glucose, $f(G)$~$G^{-3.5}$, providing the HOMA-B equation $qB = c I/(G^{-3.5})$ with $c=20$ in the units above.

To find the steady-state solution of the insulin equation Eq. 8, let’s approximate the regulation function $f(G)$ as $(G/K)^2$, as suggested by (Topp et al. 2000). This approximation is derived from the Hill function $f(G) = \frac{G^n}{K^n + G^n}$ with n=2 and is valid when $(G/K)^2 \ll 1$.

This is not a terrible approximation, since $(\frac{G}{K})^2 \sim (\frac{2}{8})^2 \sim 0.3$. Using this in the insulin Eq 8, solved at steady state by setting $dl/dt=0$, we find that $q B (G_{st} / K)^2 = \gamma I_{st}$. Plugging this into Eq 9, we obtain a steady state glucose level $G_{st}$ that depends on the cube root of all parameters (the cube root comes from the $(G/K)^2$ regulation):

\begin{equation}
(10) \quad G_{st} = (\gamma K^2 m_{st} / s q B)^{1/3}
\end{equation}

Let’s consider the case of insulin resistance due to an 8-fold drop in $s$, keeping all other parameters the same. This results in a 2-fold rise in $G_{st}$ because 2 is the cube root of 8. This is a rise from 5mM to 10mM, way past the criterion for diabetes. We see that $G_{st}$ is not robust to changes in insulin resistance, which means it is sensitive to changes in this parameter, or to any of the other parameters in the model.
We also see from Eq 10 that glucose steady state is not robust to any of the other model parameters, including q, the maximal insulin production rate per beta cell. This parameter also changes because beta cell metabolism depends on many factors such as time of day, inflammation, and age. The parameter q also depends on total blood volume, as mentioned above, which dilutes the number of insulin molecules to give rise to insulin concentration. Blood volume, which is about 5L in adults, increases by 50% in pregnancy. It rises during childhood growth, in chronic exercise and in other physiological conditions. So being robust to q is also biologically important to achieve strict 5mM control.

Note that when s becomes very small, the glucose nullcline hits the insulin nullcline line when it saturates, that is when it flattens out. The expression becomes simpler. Because in this regime \( f(G) = 1 \), we have at the fixed-point \( \frac{m}{sG} = \frac{qBf(G)}{\gamma} = qB/\gamma \). Thus

\[
G_{st} = m_{st}\gamma/sqB
\]

The predicted rise in \( G_{st} \) when insulin resistance is large is dramatic, \( G_{st} \approx 1/s \), emphasizing the ‘paradox’ of normal glucose in people with obesity.

Solved exercise 2: Show that half-life of glucose in the blood is not robust to insulin sensitivity in the minimal model

Likewise, the half-life of glucose in the blood is not robust. To see this, let’s recall the removal term of glucose, namely s I G. The removal parameter- the factor multiplying G that has units of 1/time - is \( a = s I \). The half-life, as discussed in the beginning of the chapter, is therefore \( t_{1/2} = ln(2)/a = ln(2)/s I \). Let’s consider the case that the system is at steady-state, and now a small amount of glucose is added to the blood, that hardly affects insulin concentration. Since at steady state \( I = I_{st} \), the half-life is \( ln(2)/s I_{st} \). We can compute \( I_{st} \) from Eq. 8 and 9: \( I_{st} = \left( m_{st}^2 q B/s^2 \gamma k^2 \right)^{1/3} \) and thus the half life is \( t_{1/2} = ln(2)/s I_{st} = ln(2)/(s m_{st}^2 q B/\gamma k^2)^{1/3} \). Therefore, glucose half-life depends inversely on the cube root of insulin sensitivity, \( s^{-1/3} \). Half-life doubles if s shrinks by a factor of 8. Instead of returning to baseline within an hour of a meal, G stays high for two hours, surpassing criteria for diabetes. This is at odds with most insulin resistant people.

3. Additional biological features of the glucose-insulin circuit and diabetes.

The goal of this exercise is to expand your knowledge of the glucose circuit and acquaint you with a nice video resource used by medical students. Watch the 19-minute video from osmosis.com on diabetes. Diabetes mellitus (type 1, type 2) & diabetic ketoacidosis (DKA) https://www.youtube.com/watch?v=B-RVybvfU

(a) Choose one element of the glucose system or diabetes (except glucagon) that we did not cover in class in detail. Read about it and summarize its role in the glucose control and/or diabetes in 100 words.

(b) Read about the hormone glucagon. Describe its role in 100 words.

(c) Speculate on why the body needs two opposing hormones, insulin and glucagon? (100 words)
4. Brain uptake of glucose

The brain takes up glucose from the blood at an insulin-independent rate. Modify the insulin-glucose model with a term describing this effect.

(a) Write a formula for the steady states of glucose and insulin.

(b) Is the steady-state blood glucose level GST affected by the brain's uptake rate?

(c) Plot the nullclines in this case. Is there still a single fixed point?

5. Circadian changes in beta cells

Cells have clocks that track the time of day called circadian clocks. Beta cells secrete more insulin for a given level of glucose during the day than during the night. This can be modeled as a change in the parameter q in the insulin-glucose model. Suppose that during the day \( q = q_1 \) and during the night \( q = q_2 \) with \( q_1 > q_2 \).

(a) What does the model predict for steady-state glucose and insulin during the day and night? Use the phase plot.

(b) Is it unhealthy to eat big late-night meals?

6. Simulate the glucose-insulin circuit

Write a computer code to simulate the dynamics of the glucose insulin circuit, Eq 7-8 in exercise 1. Use the following parameters \( q = B = s = \gamma = 1, m = 0.5, \) and \( f(G) = \frac{G^2}{1 + G^2} \).

(a) Show that the steady state solution is \( G_{st} = 1, I_{st} = 0.5 \).

(b) Simulate the glucose tolerance test by adding a glucose input term that rises and falls with time, representing glucose arriving to the circulation from the gut, namely \( m(t) = 0.5 + e^{-(t-5)^2} \). This glucose input function peaks at \( t=5 \). Start the simulation at time \( t = 0 \) at steady state. Plot glucose and insulin as a function of time.

(c) Simulate insulin resistance by setting \( s=0.1 \). Repeat the simulation of the glucose tolerance test.

7. Solved exercise: Why is the rate of change equal to production minus removal?

Here is an explanation of the equations in this book in which rate of change equals production rate minus removal rate. Suppose there are \( X(t) \) molecules in the body at time \( t \). Suppose that molecules are produced at rate \( p \) per unit time, and removed at rate \( r \) per unit time. In a small time increment \( \Delta t \), \( p \Delta t \) molecules will be added and \( r \Delta t \) will be removed, for a total of \( (p-r) \Delta t \). Therefore at time \( t+\Delta t \), the number of molecules is \( X(t+\Delta t)=X(t)+(p-r)\Delta t \). Rearranging this we find \( (X(t+\Delta t)-X(t))/\Delta t = p-r \). If \( \Delta t \) is very small, the term on the right is just the differential \( dX/dt \). We find that the rate of change of \( X \) is \( dX/dt=p-r=\text{production rate-removal rate} \).

8. Solved exercise: Why is the Hill equation justified biologically?

Here is a simple case in which the Hill equation applies. Suppose that a receptor R is activated only when it binds \( n \) molecules of ligand L. It can either be unbound and inactive R, or bound to \( n \) molecules at once and active RL\( n \). The equilibrium constant for this
reaction, $R+nL\rightleftharpoons RL_n$, is $K_d = [R][L]^n/[RL_n]$, where $[R]$ is the unbound receptor concentration, $[RL_n]$ is the bound receptor concentration and $[L]$ is the molecular concentrations of the ligand. Now since the receptor can only be in one of the two states, bound and unbound, we have $[R]+[RL_n]=[R_t]$ where $[R_t]$ is the total receptor concentration. The fraction of active receptors is $f(L) = [RL_n]/[R_t]=[RL_n]/(R+[RL_n])$. Using the expression for $K_d$, we find that the fraction of active receptors is $f(L) = L^n/(K^n+L^n)$, where the halfway point $K$ is defined by $K^n = K_d$. Thus $f(L)$ has the form of the Hill equation. The Hill equation is a good approximation also in much more complex situations.
References and further reading:

Insulin resistance: (James, Stöckli, and Birnbaum 2021)

type 2 diabetes: (DeFronzo et al. 2015)

Osmosis video on Diabetes Mellitus: https://www.youtube.com/watch?v=B-RVybfffU

Review on homeostatic circuits and inflammation: (Kotas and Medzhitov 2015)


History of minimal model: (Richard N. Bergman 2021)


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**Tangled up in glucose (Dylan)**

Early one morning the sun was shining, I was sleeping in
Wondering if my beta cells were still making insulin
What with the rise of type-1 diabetes, and type-2 as well
all over this crazy world, you know you never can tell
I was standing on the side of the road, rain falling down on my shoes
heading out for the clinic, god knows I paid some dues
getting through
Tangled up in glu-cose.

We both had type 1 diabetes with an insulin syringe
Split up on a dark sad night after an eating binge
I felt my glucose rise, my world began to fade away
Heard her say over my shoulder, we'll meet again someday
On the avenue
Tangled up in glu-cose.