Systems Medicine Lecture notes

Uri Alon (BE333, Fall 2021)

Lecture 1

The insulin circuit, part 1

Hormone Theme song (Animals animals)

There's hormones in the thyroid for our metabolic rate
And gonadotropins that help women ovulate
There's hormones in our kidneys and hormones in our brains
Hormones help us sleep at night
And help us stand the pain

There's hormones in the pancreas to control metabolites
And leptin form the fat to control our appetites
There's feedback loops and circuits
That are beautiful to watch
And in this course we'll study them a lot
But not too much

Hormones, hormones, Hormones here and there
Hormones x4 everywhere

Frame Setting for the course

Hi I'm Uri Alon, a professor from the Weizmann Institute in Israel. I did a PhD in physics, finding patterns in turbulent mixing; towards the end of it I looked for new subjects where the physics way of thinking might help to find new laws of nature. When I read a textbook on cell biology, I fell in love with biology and resolved to see if there are laws to be found. In the first decade of research my group discovered that complex networks of biological interactions are actually simpler than they appear - they are made of a handful of recurring, basic circuits, which we named "network motifs" because they show up again and again in different systems. We used bacteria as a model organism to do experiments and understand what each motif does. Ten years ago I fell in love again, with human medicine and physiology, and how physics-style thinking can help make sense of our bodies in health and illness.

I'm excited to start this course with you, on systems medicine.

It's good to think about the goal of this course. **The goal is to see how starting from basic principles or 'laws' we can derive why physiology is built the way it is, and why certain diseases happen while others don't. By the end of the course you will be able to use simple but powerful mathematical models to describe physiological circuits.**

The models are powerful because they turn facts and details into useful understanding, and hopefully new ways to think about treating diseases. And in this course we will

[1] song, welcome, me, goal,structure exercises, project, office hr,arc,breath loop,you,breath, glucose, diabetes, tight control, GTT,insulin, beta cells,feedback, nullclines, minimal model, q, Hill, half-life, s, insulin resistance, obesity paradox, next, song breath.

understand the fundamental causes of some of the most deadly and common diseases: diabetes, autoimmune diseases, and age-related diseases like lung fibrosis and cancer.
I'd like to describe the logistics of the course. There will be 10 lectures of about 90 minutes, the last on Dec 3, 2021. The course is pass/fail. Every 2-3 lectures will have an exercise that should take a few hours to solve. The exercises will be self-evaluated, I'll give you the solutions.
There is no final exam, instead a final project that you can do in groups of 2-3. I will post lecture notes online. Office hour will be on Tuesdays at 10am at Peets at Clark, my email is urialonw@gmail.com.

The trajectory of the course begins with basic principles, derives circuits and their fragility to disease, and culminates in a grand **periodic table of diseases.**
The topics are

part 1 Hormone circuits (diabetes)
part 2 Immune System (autoimmunity, inflammation)
part 3 Ageing (lung fibrosis, osteoarthritis, cancer)
part 4 Periodic table of diseases

Some Rules: As you saw from the song, this course is built to be fun. We will also use physiological knowledge to enhance learning, as we can see with our first feedback loop (Fig. 1). We can be in a relaxed state of mind, which is good for listening, learning and memory. In the relaxed state our body behaves in specific ways. For example, we take slow deep breaths. The wonderful thing is that as human beings we can decide to take a deep breath, and this increases the chances we will enter a relaxed state.
Because the relaxed state is good for learning, we will practice taking nice deep sighs of relief in this course from time to time. Let's practice now: you don't have to, but if you do, I promise you will enjoy it- let's all together take *a nice deep sigh of relief*.

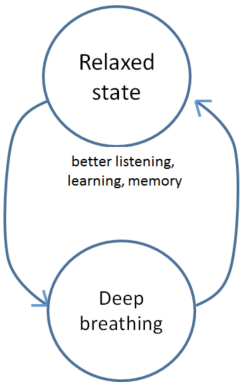

Figure 1.1

About your roles:
This is a heterogeneous class. You are from biology, engineering, physics, math, chemistry and other subjects.
Some things are basic for some of you and hard for others. For some of you the following equation is easy, some need brushing up

$$\frac{dx}{dt} = -\alpha x$$

Whose solution is an exponential decay

$$x(t) = x(0)e^{-\alpha t}$$

This equation will play a role in this course describing degradation of molecules and cells. The half-life of x is log(2)/α.
For others among you, the difference between 'transcription' and' translation' is obvious, for others mysterious. Transcription is decoding DNA into RNA, translation is decoding RNA into proteins.

We will use our heterogeneity to our advantage! I will do pair-and share moments where you can learn from each other.

In this first lecture I want to teach some basic tools and concepts. And also, a fascinating bit of physiology. * So, let's take a nice deep sigh of relief * - here we go!

The insulin-glucose circuit

The insulin circuit: In this lecture and the next, we will focus on the 'hydrogen atom' of hormone circuits: the glucose-insulin control circuit. When I say hydrogen atom, I mean the best-understood system which provides the conceptual tools to understand more complex cases, just as hydrogen was the testing ground for quantum mechanics. The glucose circuit 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).

Glucose concentration and dynamics is tightly controlled

The main variable in this system is the blood concentration of the sugar glucose. Glucose is an important energy and carbon source for the cells in our body. It is the major energy source for the brain and for red blood cells. **Glucose concentration in the blood is maintained within a tight range around 5mM**: different healthy people have a concentration of 5+/-1mM. In other common units glucose is at 90 mg/dL. This is different from fat mass or body mass index (BMI) that vary much more (factor of 2-4) between healthy people.

Such rigorous control is important. It 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 damages blood vessels and nerves, and over the years gives rise to the deadly symptoms of type-2 diabetes. The damaged blood vessels can give rise to heart attacks, to kidney diseases and, in the retina, to blindness. Damaged blood vessels can also lead to amputation of legs and other grim outcomes.

deep sigh of relief

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 1.2). 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 1.3).

Clinical criteria for diabetes can also be based on a glucose blood test after at least 8h of fasting. Blood sugar level less than 5.6mM (100mg/dL) is normal, between 5.6mM and 6.9mM is

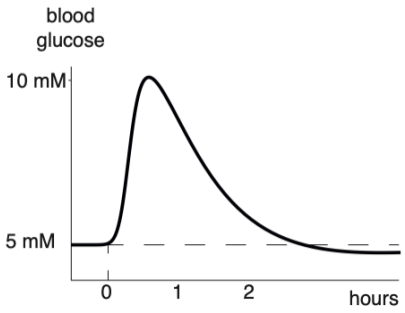

Figure 1.2

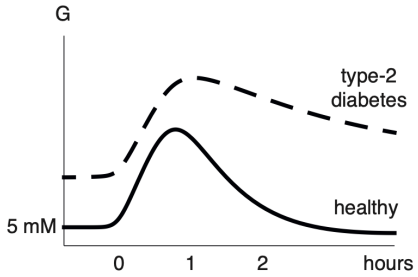

Figure 1.3

prediabetes, and above 6.9mM (125 mg/dL) on two separate tests is diabetes.

Again, people in different states like pregnancy, obesity, age are usually healthy and have glucose setpoints and dynamics that are nearly the same.

Glucose concentration is controlled by insulin

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, liver and fat, and glucose is thus removed from the blood. Glucose is unable to enter these cells without special glucose transporters (pumps) on the cell surface. The transporters are in storage vesicles inside the cell (Fig 1.4a). When insulin is in the blood, it binds special sensors on the cell surface called insulin receptors (Fig 1.4b), 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 (Fig 1.4b), where they pump glucose into the cell. As a result, insulin binding allows glucose to enter from the blood into the cell (Fig 1.4c).

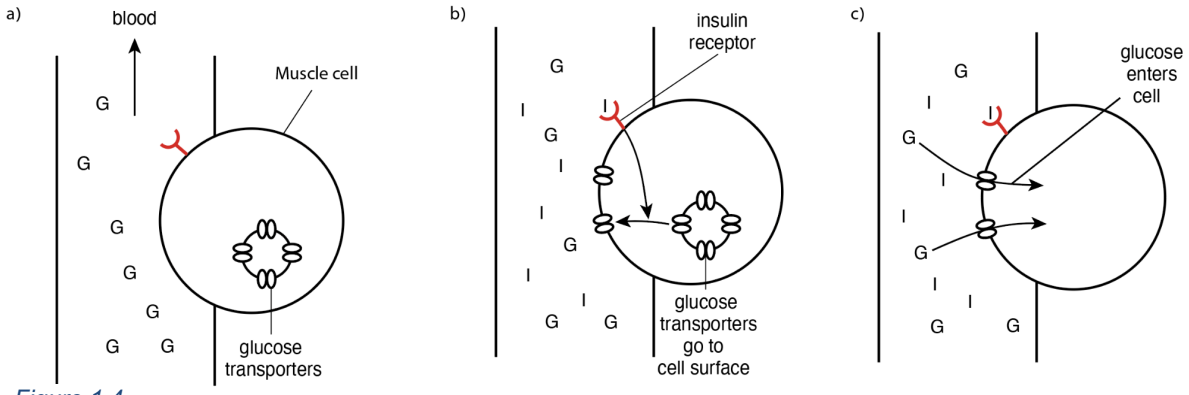

Figure 1.4

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 1.5). 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 during fasting. We will not discuss glucagon and other details for now that are not crucial for the principles we wish to describe.

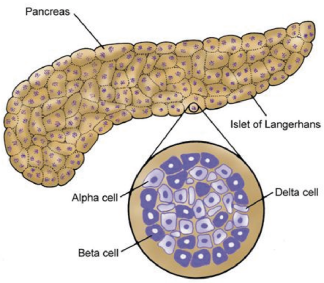

Figure 1.5

The beta cells sense glucose, and the more glucose around, the more insulin they secrete. Thus, a rise in glucose leads to 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 1.6). The input to the blood glucose comes from meals, and from the production of glucose by the liver. We denote these sources by *m* in Fig 1.6.

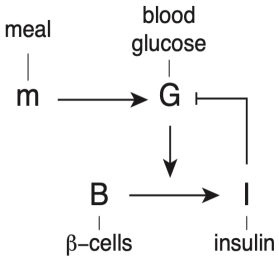

Figure 1.6

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. Until the 1930s' type-1 diabetes was a death sentence to the children who got it (about 1% of the population gets T1D with a typical age of onset of 10-11y). With the discovery of insulin, those children could survive thanks to insulin injections. Still, keeping glucose under control is hard, and type-1 diabetes raises the risk for health complications.

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. A major cause of type-2 diabetes is insulin resistance, which we will describe in detail below.

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 intuitively explain the dynamics, such as the rise and fall after a GTT, and the basic phenomena in diabetes.

<u>*Song: Tangled up in glucose (Dylan)*</u>

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 the developed 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 my dues

getting through

Tangled up in glu-cose.

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.

Mathematical models for the glucose-insulin circuit

In the glucose-insulin circuit, mathematical models developed since the 1970's benefitted clinical practice. 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. An 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.

To begin we will use a graphical tool that is elegant and important. We will use this tool throughout the course. It is called the **phase portrait.**

The phase portrait has two axes, the two variables 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 insulin. One experiment to see this uses IV to inject glucose to 'clamp' blood glucose at some value. Then, let insulin reach a steady state and measure its concentration. Plotting insulin versus glucose reveals an S-shaped function. The more glucose, the more insulin secreted by the beta cells. Insulin saturates (reaches a maximal level) at high glucose levels. This is the black line in Fig 1.7.

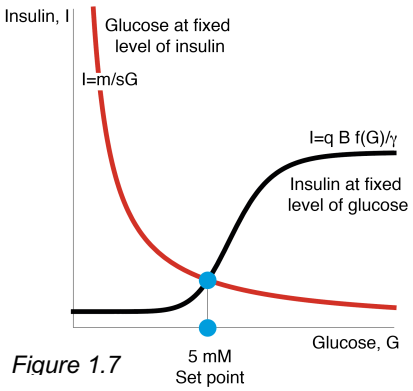

Figure 1.7

The second arm of the feedback loop describes how insulin removes glucose. Imagine injecting insulin to clamp blood insulin at a given level, and waiting till glucose settles down to steady state. The more insulin the less glucose, because insulin helps remove glucose from the blood. This is the decreasing red line in Fig 1.7.

Now we unleash the full feedback loop, without artificially keeping either variable constant. Glucose and insulin now affect each other. The point to watch is where the two lines meet. This is the **fixed point** of the system. It is the point where both glucose and insulin are at steady-state together. At this point, glucose has a steady state G0=5mM, and insulin a steady state Io. These are the values measured with a blood test after fasting, say in the morning.

These types of experiments were used to calibrate the mathematical model we will now describe. To model the dynamics, we use differential equations to describe rates of change of glucose and insulin concentrations in the blood.

Let's begin with an 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 concentration per unit time, where q is the maximal production rate per unit biomass of beta cells, and f(G) is an increasing function of G, that goes between 0 and 1, that describes how glucose regulates the secretion rate.

As in many biological circuits, f(G) is well-described by a Hill function, an S-shaped rising curve given by

$$(1)\quad f(G) = \frac{G^n}{K^n + G^n}$$

This function reaches halfway 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=2-3 is a good approximation, Fig 1.8 (from Alcazar, 2019).

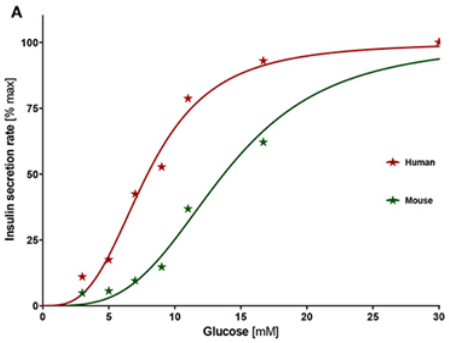

Figure 1.8

Insulin secretion is further amplified by hormones released from the gut (such as GLP-1) that sense the incoming meal, and from brain inputs that can anticipate a meal. We won't deal with these additional inputs in this lecture. Another detail we won't go into is that insulin is secreted in two pulses, a brief spike followed by a prolonged insulin response to a meal.

Note that insulin is secreted into the blood. The higher the blood volume, the more insulin is diluted. Thus, the secretion rate parameter q is the total number of molecules of insulin secreted per unit time per unit biomass, divided by the total blood volume, in order to get units of insulin concentration. Blood volume can change over growth and in pregnancy, for example.

All that we need to do now is to multiply the production rate by the total beta cell mass B, to get a total insulin production of $q\ B\ f(G)$. Insulin is removed at rate γ, so that

$$(2)\quad dI/dt = q\ B\ f(G) - \gamma I$$

you can read this equation as

rate of change of I = production-removal

The removal parameter γ is the probability per unit time of losing an insulin molecule. That is why we wrote the removal term as γ times I. The more insulin the more molecules are removed per unit time. The removal rate γ provides the insulin half-life, about ln(2)/γ=5 min. Insulin is removed primarily by degradation in the liver, where it flows to first; the remaining insulin flows in the circulation and is removed by the kidney which filters the blood.

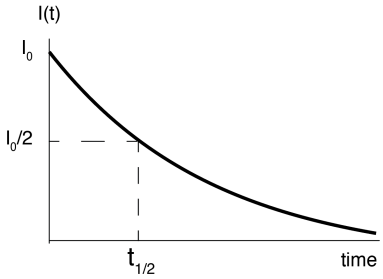

Figure 1.9

To see how the removal rate γ determines the half life, imagine we block insulin production (as in patients with T1D who have no beta cells, or using drugs). In this case, there is no production, only removal and hence

$$dI/dt = -\gamma I$$

The solution of this equation is an exponentially decaying concentration which drops over time from its initial level I(0) (Fig 1.9):

$$(3)\quad I(t) = I(0)\, exp(-\gamma\, t)$$

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

$$(4)\quad t_{1/2} = ln(2)/\gamma$$

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

Note that equation 2 provides a formula for the insulin line in our phase portrait of Fig 1.7. At a given level of G, the steady state of I is given by the condition that it does not change, dI/dt=0. Solving Eq 2 with dI/dt=0 gives I=qBf(G)/gamma. This is the "insulin" line in the phase portrait. It has the same shape as the Hill function f(G).

Officially such lines where one variable is at steady-state are called **nullclines** (this is the dI/dt=0 nullcline). The points where two nullclines meet are the fixed points.

Now let's write the second equation, for glucose. 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 is 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. When it runs out of glycogen, at about the middle of the night, the liver makes glucose out of amino acids taken out of muscles, in a process called gluconeogenesis (new production of glucose).

Summing over meals and liver production of glucose, 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

$$(5)\quad dG/dt = m - a\, G$$

Let's focus on removal term $-\,a\, G$. The rate parameter *a* is the probability per unit time to lose a glucose molecule from the blood. Since high levels of glucose are harmful, it makes sense to remove it quickly after meals- to have a large removal rate *a*. However, this means that at night or during fasting, the liver would need to make more glucose to keep 5mM steady state. The steady-state is *Gst=m/a*, and the higher removal *a* the larger production m needs to be to get a 5mM steady state. 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, but only after meals when glucose is higher than 5mM.

Thus, glucose 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. Insulin sensitivity is more familiar as its inverse, **insulin resistance**. Insulin resistance, defined as 1/s, is the extent to which insulin fails at working.

Insulin sensitivity/resistance can be measured by injecting insulin and noting the reduction in glucose. Thus, our glucose equation is:

$$(6)\quad dG/dt = m - s\,I\,G$$

We can now solve for the glucose nullcline, namely the steady-state amount of glucose in a situation where insulin concentration is fixed, as in an intravenous clamp experiment of Fig 1.7. We simply set dG/dt=0 in Eq 5, to see that glucose level drops inversely with insulin $G_{st} = m/s\,I$, or equivalently $I = m/s\,G_{st}$ where m is steady-state production, such as liver production during fasting (Fig. 1.10).

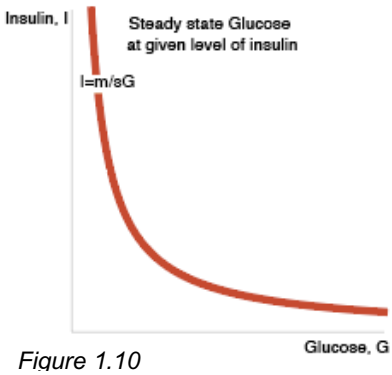

Figure 1.10

Let's see how the equations do in the glucose tolerance test (Fig 1.10). 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, making insulin I(t) rise, increasing the removal rate of G until it returns to baseline. This resembles the measured response of healthy people.

Pair and share. Math people form alliances with bio people.

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 parameter to watch is insulin sensitivity, s. Insulin sensitivity varies between people: 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, 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 infection and inflammation, insulin sensitivity drops so that more glucose stays in the blood in order to help the immune system fight pathogens. Insulin sensitivity also drops during pregnancy, diverting glucose to the fetus. It drops during stress. In obesity, *s* drops dramatically, sometimes by a factor of ten. See figure 1.11 which shows that insulin sensitivity drops with body mass index (BMI), from Kahn, 1993. This phenomenon is called **insulin resistance**, since each unit of insulin works less effectively than in non-resistant people. Insulin resistance in obesity is due to factors secreted by fat cells, and to chronic inflammation that often occurs in obesity. For example, in obesity, excess fatty acids accumulate in muscles and liver causing signals that increase insulin resistance. Overwhelmed fat cells also secrete inflammatory signals which increase insulin resistance. Insulin resistance is usually coordinated between different tissues- muscle, fat and liver have similar resistance. Insulin resistance, as we will see, is an important factor in T2D.

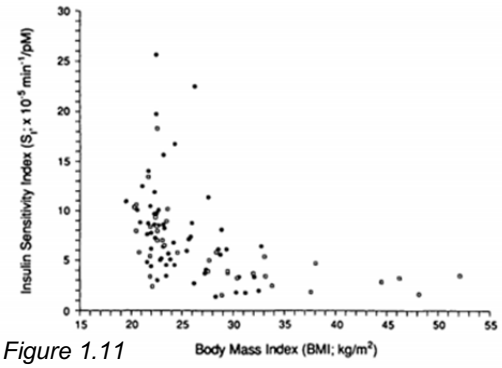

Figure 1.11

Despite the fact that people vary in *s* by as much as ten-old, 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.

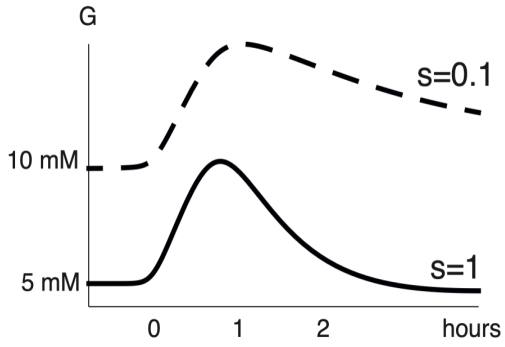

Figure 1.12

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, and response time also increases substantially (Fig 1.12). 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.

We can see how insulin resistance increases glucose above 5mM in this model, using the phase portrait approach (Fig. 1.13). Suppose that s drops by a factor of 10: insulin is 10 times less effective at removing glucose. This does not affect the insulin line, but it does shift the glucose line to a higher level, because that line is inversely proportional to s: I=m/sG. As a result, the glucose set point shifts to higher levels, far above 5mM. **This creates a problem for the model, because most people with obesity have insulin resistance but normal glucose levels.**

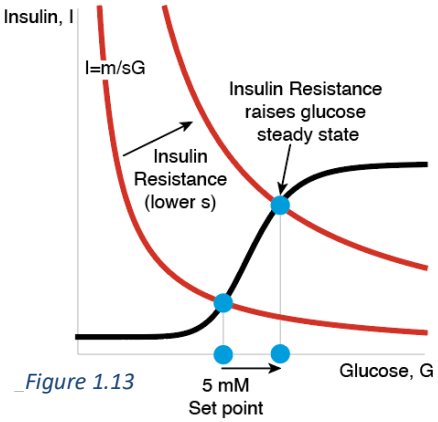

Figure 1.13

A second, more quantitative way to see how sensitive the minimal model is to variations in parameters, is to solve for the steady-state glucose, as done in the solved exercises below

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 concentration and its dynamics with respect to physiological parameters. We need to explain why most people with obesity, pregnancy or athletic lifestyles have very different insulin resistance but normal 5mM glucose and normal dynamics in the glucose tolerance test.

In the next lecture we will see how answering the question of robustness of glucose dynamics opens up general principles for feedback control in tissues. This new feedback will have unavoidable fragilities that explain why beta cells fail in T2D, as we will see in the next lecture, and why the body attacks its own beta cells in T1D, as well see later on in the course. In the next lecture we will also reveal the three basic 'laws' that will carry us throughout the course.

See you next week:)

deep sigh of relief

Solved exercise 1: 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 the time derivatives to zero: $dG/dt = 0$ and $dI/dt = 0$. We find from Equation (5), that

$$(8) \quad s\, I_{st} G_{st} = m_{st}$$

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

Incidentally, this is the origin of the commonly used **HOMA-IR equation** used in research 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].

To find the steady-state solution of the insulin equation Eq. 7, 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 of Eq. 6, with n=2 and is valid when $(G/K)^2 << 1$. This is not a terrible approximation, since (G/K)^2~(⅝)^2~0.3. As an aside, if Gst was larger than K, insulin secretion would saturate at 5mM glucose and beta cells would not be able to change their insulin secretion to match blood glucose. Thus, from the insulin Eq 7, solved at steady-state by setting with dI/dt=0, we find that $q\ B\ (G_{st}/K)^2 = \gamma I_{st}$. Plugging this into Eq 8, 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):

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

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 2 is the cube root of 8, $8=2^3$). 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.

Also, we see from Eq 9 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 can also change because beta cell metabolism depends on many factors such as time of day, inflammation and age. 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 changes during childhood growth, and in other physiological conditions. So being robust to q is also biologically important in order to achieve 5mM strict control.

Note that when s becomes very small, the glucose nullcline hits the insulin line when it sturates. Then, the expression becomes simpler. We have at the fixed point m/sG=qBf(G)/gamma=qB/gamma since f(G)=1. Thus

Gst= m gamma/qBs.

The predicted rise in Gst when insulin resistance is large is dramatic, Gst~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 also 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: $I_{st} = (\,{m_{st}}^2\, q\, B/s^2\,\gamma K^2\,)^{1/3}$ and thus the half life is $t_{1/2} = ln(2)/s$ Ist=$ln(2)/(s\,{m_{st}}^2\, q\, B/\gamma K^2\,)^{1/3}$. Therefore, glucose half-life depends inversely on the cube root of insulin sensitivity, $s^{-1/3}$. Half-life doubles if s shrink 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, which is at odds with the majority of insulin resistant people.

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History of minimal model:

Bergemann (2020) https://www.frontiersin.org/articles/10.3389/fendo.2020.583016/full

HOMA estimates based on minimal model:

Insulin resistance: HOMA-IR=I G/c where c=22.5 mM mIU/ml

Beta-cell function: HOMA-B=20 I/(G-3.5)

Appendix (for the mathematically curious):

Exactly solvable approximation for response time in the minimal model

$$dG/dt = m - s\ I\ G$$

$$dI/dt = qB\ f(G) - \gamma\ I$$

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

$$I_1 = q\ B/\gamma$$

Glucose when the meal ends 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 is repressed by insulin.

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

Response time is $t_{1/2}$=ln(2) γ/s q B – depends on all parameters. Area under the G(t) curve in the decline phase is about G_1 $t_{1/2}$~m_1 $(\gamma/sq\ B)^2$; goes up very high with s and q. In the BIG model, in contrast,

$$dB/dt = B\ \mu(G)$$

G_{st}=G_o, and hence I_{st}=m_0/s G_o, and B_{st}=γm_o/(s q G_o f(G_o))

Response time is $t_{1/2}$=ln(2) γ/sq B=ln(2) G_o f(G_o)/m_o independent on s,q,γ

G_1=m_1/s I_1 = m_1 γ/ s q B =m_1 G_o f(G_o)/m_o, area under curve independent on s and q.

Biological appendix (for true enthusiasts):

Source: https://link.springer.com/referenceworkentry/10.1007%2F978-3-319-45015-5_8

In order to appreciate the multiple pathophysiologic disturbances responsible for the development of impaired glucose metabolism in individuals with type 2 diabetes mellitus (T2DM), a review of the whole body, organ, and cellular mechanisms involved in the maintenance of normal glucose homeostasis in the postabsorptive state (10–12-h overnight fast) and following ingestion of a typical mixed meal is warranted (DeFronzo 1998, 1997, 2009; DeFronzo and Ferrannini 2010). During the sleeping and throughout the postabsorptive state, the great majority of total body glucose disposal takes place in insulin independent tissues, primarily the brain and other neural tissues which account for ~50% of all glucose utilization. Brain glucose utilization is insulin independent and saturates at a plasma glucose concentration of ~40 mg/dl (DeFronzo and Ferrannini 2010; Grill 1990). Since the normal fasting plasma glucose (FPG) concentration is ~70–80 mg/dl, this provides a large window of protection against cerebral neuroglycopenia. During the postabsorptive state, ~25% of glucose disposal takes in the splanchnic area (liver plus gastrointestinal tissues) and is insulin independent. Insulin-dependent tissues, primarily muscle and to a lesser extent adipose tissue, account for the remaining ~25% of glucose utilization. Basal glucose utilization averages ~2.0 mg/kg per min and is precisely matched by the rate of endogenous glucose production. Approximately 85% of endogenous glucose production is contributed by the liver and the remaining ~15% by the kidney. The ratio of insulin to glucagon in the portal circulation is the primary regulator of hepatic glucose production (Cherrington 1999), while in the kidney insulin is the primary regulator of renal glucose production (Meyer et al. 1998a). Glucagon has been reported to have no effect on renal glucose production (Stumvoll et al. 1998). Glycogenolysis and gluconeogenesis contribute approximately equally to the basal rate of hepatic glucose production, while gluconeogenesis is responsible for all renal glucose production (Cherrington 1999; Gerich et al. 2001).

Following ingestion of glucose or a mixed meal, the plasma glucose concentration rises resulting in the stimulation of insulin secretion by the pancreatic beta cells (DeFronzo and Ferrannini 2010; Ferrannini and DeFronzo 2015). The combination of hyperinsulinemia and hyperglycemia (i) stimulates glucose uptake by splanchnic (liver and gut) and peripheral (muscle and adipose) tissues and (ii) suppresses endogenous (hepatic and renal) glucose production (DeFronzo 1998, 1997, 2009; DeFronzo and Ferrannini 2010, 1987; Ferrannini and DeFronzo 2015; DeFronzo et al. 1985, 1981; Ferrannini et al. 1985; Mandarino et al. 2001). Muscle accounts for the majority (~80–85%) of glucose uptake by peripheral tissues, with a small amount (~5%) being disposed of by adipocytes. Although fat accounts for only a small amount of glucose disposal, it contributes to the maintenance of total body glucose homeostasis by regulating the release of free fatty acids (FFA) from stored triglycerides and through the production of adipocytokines that influence insulin sensitivity in muscle and liver (Bays et al. 2004; Groop et al. 1989; Bergman 2000). Lipolysis is highly sensitive to insulin, and the rise in plasma insulin concentration following glucose/meal ingestion results in a decline in plasma FFA concentration (Groop et al. 1989). FFA inhibits glucose uptake in muscle and stimulates hepatic glucose production (Belfort et al. 2005; Bajaj et al. 2005; Groop et al. 1991). As the plasma FFA concentration declines following glucose/meal ingestion, muscle glucose uptake is increased and hepatic glucose production is inhibited. Thus, the

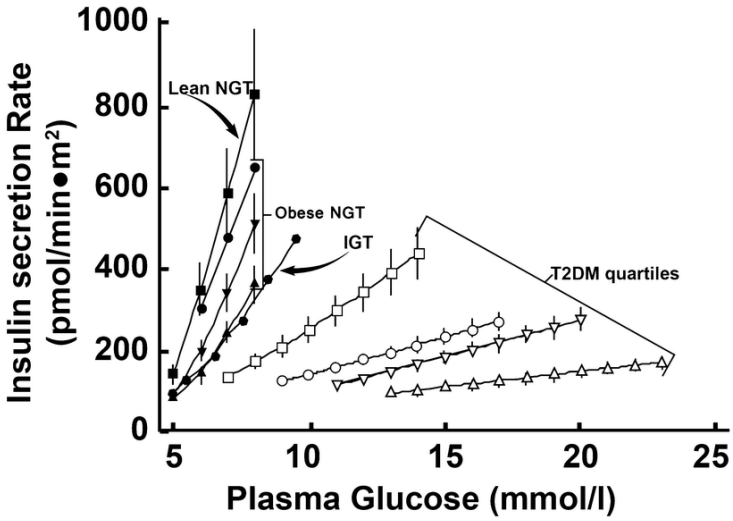
reduction in plasma FFA concentration in response to the increases in plasma insulin and glucose concentrations plays an important role in the maintenance of normal glucose homeostasis (Bays et al. 2004; Groop et al. 1989; Bergman 2000; Belfort et al. 2005).

Glucagon secretion by the alpha cell also plays a central role in the regulation of fasting and postprandial glycemic (Cherrington 1999; Baron et al. 1987). During fasting conditions, approximately half of total hepatic glucose output is dependent upon glucagon, and inhibition of basal glucagon secretion with somatostatin reduces hepatic glucose output and plasma glucose concentration. After a meal glucagon secretion is inhibited by insulin, and the decline in plasma glucagon plays a pivotal role in the suppression of hepatic glucose production and maintenance of normal postprandial glucose tolerance. If, following a meal, glucose enters from both the liver and gastrointestinal tract, postprandial hyperglycemia will ensue. Within the pancreas, approximately 70% of the beta cells are in direct communication with nonbeta cells, including alpha cells, through gap junctions containing connexin proteins (Bosco et al. 2010; Orci et al. 1975; Benninger and Piston 2014). In addition, beta cells can influence alpha cell secretion via intraislet blood flow (Jain and Lammert 2009). Thus, the local paracrine effect of insulin, as well as the rise in circulating plasma insulin concentration, conspires to inhibit glucagon secretion.

Following oral glucose administration, the amount of insulin which is secreted is 2.5–3 fold greater than if glucose were given intravenously to mimic the plasma glucose concentration observed following glucose ingestion. This is referred to as the incretin effect and is related to the release of glucagon-like peptide-1 (GLP-1) from the L cells in the distal small bowel/large intestine and glucose-dependent insulinotropic polypeptide (previously called gastric inhibitory polypeptide) (GIP) from the K cells in the early part of the small intestine (Drucker 2006, 2013; Holst 2007; Nauck and Meier 2016). Collectively, GLP-1 plus GIP account for 60–70% of the insulin that is secreted during a meal. All nutrients (glucose, protein, fat) stimulate GLP-1 and GIP secretion, but glucose is the most potent. GLP-1, but not GIP, also inhibits glucagon secretion, and the decline in plasma glucagon concentration contributes to suppression of hepatic glucose production following meal ingestion. Within minutes after ingestion of a meal, circulating levels of GLP-1 and GIP increase. This occurs long before nutrients can reach the K cells in the duodenum and the L cells in the more distal intestine. This rapid release of GLP-1 and GIP is mediated via neural impulses that are carried to the hypothalamus and back to the intestinal cells via the vagus nerve (Nauch and Meier 2016). GLP-1 and GIP bind to their respective receptors on the β cell, leading to activation of adenyl cyclase and an increase in insulin secretion (Drucker 2006, 2013; Holst 2007; Nauck and Meier 2016). Importantly, the stimulation of insulin secretion by GLP1 and GIP is glucose-dependent; that is, insulin release is augmented in the presence of hyperglycemia and wanes as the blood glucose concentration returns to normoglycemic levels. Similarly, the inhibitory effect of GLP-1 on glucagon secretion wanes as the plasma glucose concentration returns to its baseline level, allowing hepatic glucose production to increase, thereby preventing hypoglycemia.

The route of glucose entry into the body also plays an important role in glucose homeostasis (Cherrington 1999; DeFronzo et al. 1978a; Ferrannini et al. 1980). IV glucose exerts a modest effect to increase splanchnic glucose uptake, and the increase in SGU is directly proportional to

the increase in plasma glucose concentration (DeFronzo et al. 1985). Similarly, intravenous insulin exerts only a small stimulatory effect on splanchnic (liver plus gut) glucose uptake. In contrast, when glucose is ingested, splanchnic glucose uptake increases markedly in direct proportion to the negative hepatic artery-portal vein glucose concentration gradient (Cherrington 1999). As this gradient widens, a neural reflex is activated in which vagal activity is enhanced and sympathetic nerves innervating the liver are inhibited. These neural changes stimulate hepatic glycogen synthase, inhibit glycogen phosphorylase, and augment liver glucose uptake and glycogen formation. Consequently, following oral glucose administration, splanchnic tissues remove ~30–40% of the ingested glucose. This is in marked contrast to IV glucose/insulin administration, where muscle accounts for the majority (~85%) of glucose disposal.



Plot of insulin secretion rate against the concomitant plasma glucose concentration in subjects with normal glucose tolerance (NGT), impaired glucose tolerance (IGT), and type 2 diabetes (T2D) by quartile of fasting hyperglycemia. The mean slope of the fitting functions measures β-cell glucose sensitivity. (Source: Ferrannini et al., J Clin Endocrinol Metab 90:493–500, 2005)

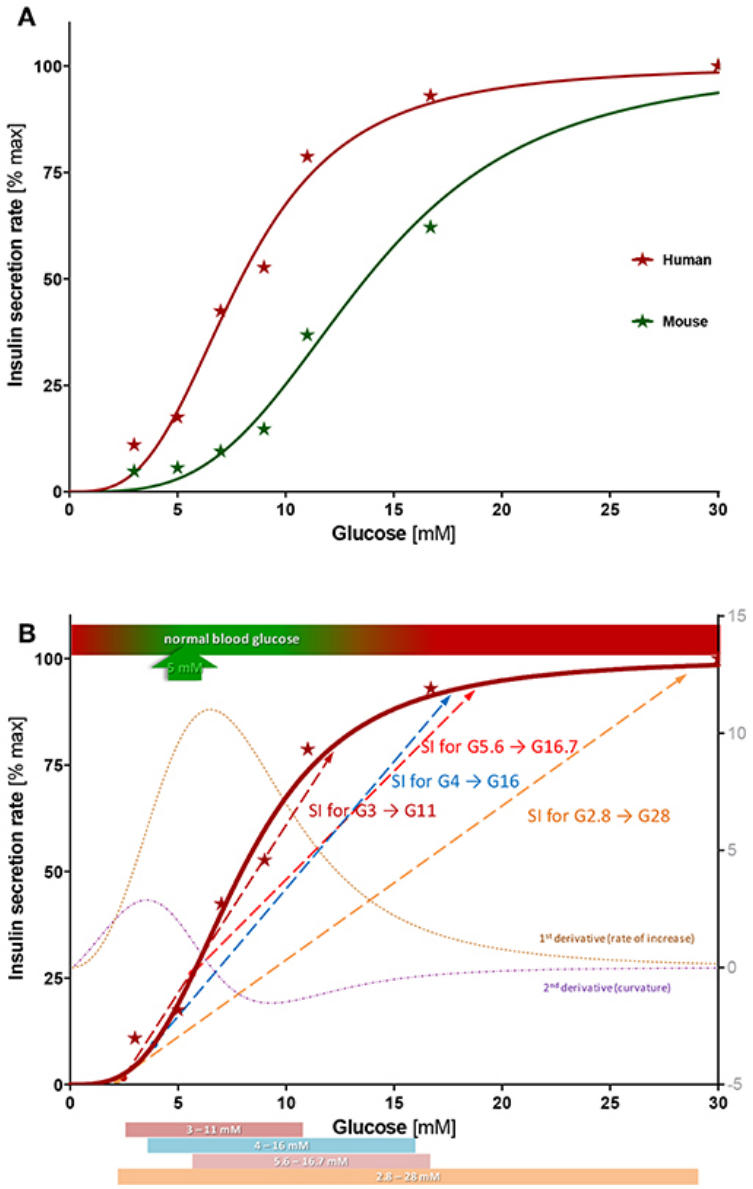


Figure 5. Concentration-response of insulin secretion. **(A)** Average insulin secretion rate (first- and second phase) at different glucose steps expressed as percent of maximum value (at G30) and fitted with a sigmoidal dose response function (Hill function, Equation 1). Compared to human islets, mouse islets have a similar Hill slope (n = 3.4 ± 0.4 vs. 3.2 ± 0.4), but a right-shifted response (half-maximal concentration C_{50} = 13.7 ± 0.6 vs. 7.9 ± 0.4 mM). **(B)** Best-fit sigmoid function describing percent insulin secretion rate in function of the high glucose challenge for human islets (Equation 1; n = 3.2, C_{50} = 7.9 mM) overlapped with its first and second derivative (right axis) and some commonly used stimulation indices (SIs). See text for details

.source:https://www.frontiersin.org/articles/10.3389/fendo.2019.00680/full