Hormone Circuits lecture notes

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Lecture 5

Transition from health to disease as a bifurcation

How does health transition into disease? In this lecture we consider prediabetes, a state in which fasting glucose is between 6mM and 7mM. It is a **subclinical** state - without symptoms, but dangerous enough in the sense that it can transition to diabetes with a yearly conversion rate of 5-10%. Studies that followed people over decades revealed what happens to people before the onset of diabetes. Glucose rises slowly, and then when it crosses a threshold, rises very quickly. For example, a rare study by Mason et al of people over decades gave participants a glucose oral tolerance tests every few years, drinking glucose and measuring blood glucose after 2h (Fig 5.1). A 2h glucose level above 11mM (200mg/dL) is defined as diabetes, above 7.8mM (140mg/dL) is prediabetes. In people who got diabetes, the 2h glucose rose about linearly with age decades before. Once 2h glucose entered the prediabetes phase, it rose much faster. [source: Mason 2007 https://diabetes.diabetesjournals.org/content/56/8/2054.long]

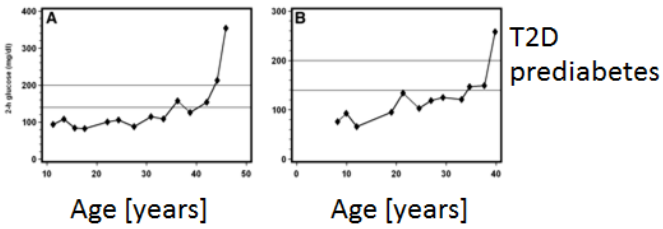


Figure 5.1

When full blown diabetes breaks out, glucose levels can reach 20mM (400mg/dl), with people drinking a lot and urinating a lot to get rid of the excess glucose (polydipsia and polyuria).

A note about units: in Israel and the US, glucose is measured in mg/dL, and in the UK in mM (90mg/dL=5mM).

Also in humans, large-data cohorts collected by Eran Segal allow a population view of glucose in people with prediabetes (Fig 5.2). It is seen that as insulin sensitivity drops, that is as insulin resistance rises, glucose rises above 5mM. When it reaches about 7mM, people transition to very high levels with 20mM not uncommon.

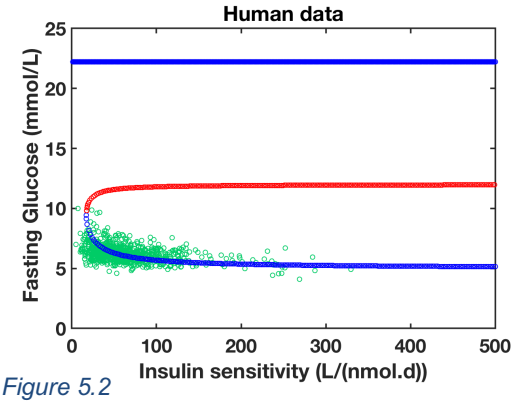


Figure 5.2

What about insulin and beta cells? It turns out that insulin begins to rise even before glucose rises but is compensated fully by the rise of beta cell mass. In prediabetes insulin continues to rise together with glucose. But when the threshold to diabetes is crossed, insulin and beta cell mass begin to decline. There is insufficient insulin and glucose skyrockets. At end stages, there are no more beta cells and insulin, and patients depend on insulin injections.

How can we understand prediabetes? How do you get a continuum of steady states, with higher than 5mM glucose, that can last for years? What is the subclinical state, and how does it break down?

Our plan will be to use the BIG model, and see that although it explains important aspects, it cannot show prediabetes - it can only have a low and a high glucose fixed point, no a continuum.
We will then modify the BIG model and show that a limit to compensation is at the root to prediabetes and the transition to diabetes. We will learn a neat mathematical way to understand this, using a bifurcation plot.

The BIG model can explain the continuum of steady states seen in prediabetes

The BIG model has three equations. We add an insulin-independent removal αG, which will prove useful later. It is removal at zero insulin, as in the urine and sweat. This is valid for the diseases we will discuss today when glucose gets very high. The BIG model is thus

$$(1)\ \frac{dG}{dt} = m - (s\ I + \alpha)G$$
$$(2)\ \frac{dI}{dt} = qB\ f(G) - \gamma G$$
$$(3)\ \frac{dB}{dt} = B(p(G) - r(G))$$

Three equations are hard to analyze. But we can make progress by reducing them to two equations, so we can use the phase portrait approach. To do so, we notice that the insulin equation has a much faster timescale ($1/\gamma$~5min) than the glucose equation (~1 hour) and the B equation (weeks). This allows us to reduce to two equations, which will allow us to use nullclines.
The idea is that insulin responds so fast, it can be determined by the other two variables G and B - it reaches steady state so quickly that it tracks them. Thus, we need to get rid of the insulin equation

$$\frac{dI}{dt} = qBf(G) - \gamma\ I$$

by setting it to quasi steady state using dI/dt=0

$$I_{st} = qBf(G)/\gamma$$

Plugging in this steady state insulin I_{st} into to Eq 1 and 3, we end up with two equations, the "BG" model (the BGs were a disco band, "staying alive")

$$(4)\ \frac{dG}{dt} = m - \frac{qs}{\gamma}Bf(G)G - \alpha G = m - (c\ B\ f(G) + \alpha)G \quad c = qs/\gamma$$
$$(5)\ \frac{dB}{dt} = B(p(G) - r(G))$$

Let's now draw the phase portrait (Fig. 5.3). The glucose nullcline $dG/dt = 0$ (red line) is a reducing line

$$B = \frac{\gamma}{sq}\ (m - \alpha\, G)/Gf(G)$$

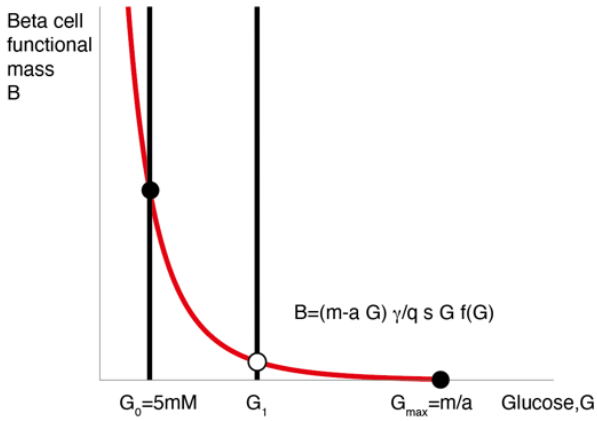


Figure 5.3

Which means that a high given level of beta cells B gives a low level of steady-state G, due to increased insulin. Note that this nullcline intersects the x-axis at a very high level of glucose $G = m/\alpha$ in which removal is due to the insulin-independent mechanisms. This is the level with zero beta-cells, as occurs in untreated T1D or end stage T2D. This is when glucose is removed primarily from the urine and sweat, at a level of 20-25mM (400 mg/dl).

The second nullcline, dB/dt, has a special shape. Since proliferation equals removal at two points, $G = Go = 5mM\ and\ G = G_1$, we have two vertical lines as the possible steady-state solutions for $dB/dt = 0$, together with the line $B = 0$. There are now three crossing points of the nullclines, and therefore three fixed points. One fixed point is stable, at $G = 5mM$. The other is unstable, at the glucotoxicity level G_1. There is a third stable fixed point at very high glucose (~20-25mM) and zero beta cells.

This model works well to compensate for insulin resistance, or in fact any change in the parameter $c = qs/\gamma$, which combines insulin sensitivity, insulin removal and beta cell secretion capacity. Changes in the combination c shift the glucose nullcline (Fig 5.4). Insulin resistance, which means reduced s, causes the glucose nullcline to shift up (more glucose at given beta-cell level). Since glucose dynamics are much faster than beta cell dynamics, glucose snaps within hours to the red nullcline and climbs back to steady state over weeks.

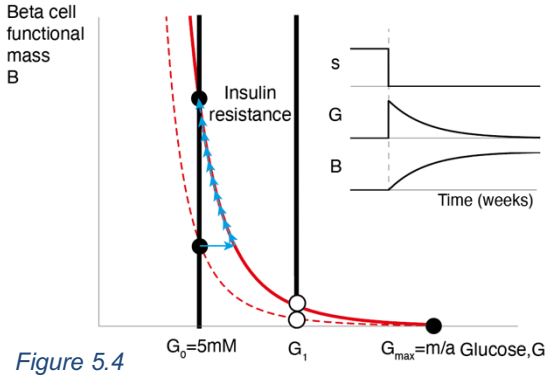


Figure 5.4

Therefore, during the 'climbing period, which is a transient period of several weeks, glucose levels are higher than normal, but when the beta cells rise to reach their new steady state, G=5mM again. Insulin and beta cells are both 1/s times higher.

There is no level of insulin resistance that can break this compensation in this model (Fig 5.5). The only way to break compensation is to reduce beta cell levels so low that the glucose rise crosses the separatrix, and beta cell decline. This can be due to autoimmune destruction in T1D.

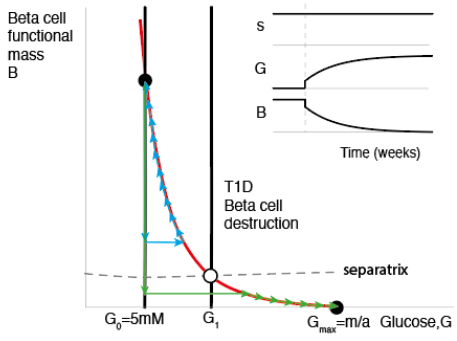


Figure 5.5

This requires removing most of the beta cells as seen in postmortems of T1D patients who died soon after diagnosis (85% beta cell destruction for T1D, even though 40% may be enough in 20yo). This makes sense with the sharp threshold-like transition of T1D, where kids can come in with very high sugar (20mM). Organs have a **'spare capacity'** in this sense: you can remove 85% of the pancreas, ⅔ of the liver and 90% of the kidneys for example, and still function.

Breakdown of compensation due to beta cell carrying capacity can explain prediabetes

The model cannot, therefore, describe the progression usually leading up to T2D. T2D is a progressive disease, and takes years. There is typically a slow linear rise in glucose that creeps into the prediabetes range, and then a sharp rise into the glucose range of diabetes. This can be seen for example in glucose at 2 hours after a glucose tolerance test, Fig 5.6 [Figure legend: Longitudinal glucose at 2H after oral glucose test, versus age in years. Note the linear rise followed by sharp rise, horizontal lines are criteria for prediabetes and diabetes, source: Mason 2007 https://diabetes.diabetesjournals.org/content/56/8/2054.long]
)
Apparently, insulin resistance grows slowly, and ageing has slow effects. The hallmarks are (1) compensated state where glucose is normal, but insulin is high, (2) prediabetes: a creeping rise in insulin above 5.9mM and a rise in insulin, (3) diabetes with a sharp rise in glucose but fall in insulin (4) end-stage diabetes with no insulin and very high glucose.
So, we need to understand how a continuum of steady states can exist with glucose above 5mM.

To do so, we can assume that beta cells hit a carrying capacity They can only make so much insulin per cell and increase their mass by only so much (mass rises in humans by 30-60%, tenfold more in mice). The carrying capacity reduces the growth rate when B approaches carrying capacity K. Such a carrying capacity effect is seen in studies of carrying capacity of fibroblasts (Adler, Xu, Medzhitov, Cell 2018). Thus, the proliferation term p(G) becomes $p(G)(1 - B/K)$ which is zero when $B = K$.
The beta-cell equation with carrying capacity is thus

$$(6)\ \frac{dB}{dt} = B\left(p(G)\left(1 - \frac{B}{K}\right) - r(G)\right)$$

The new nullcline dB/dt=0 is

$$(7)\ B = K\left(1 - \frac{r(G)}{p(G)}\right)$$

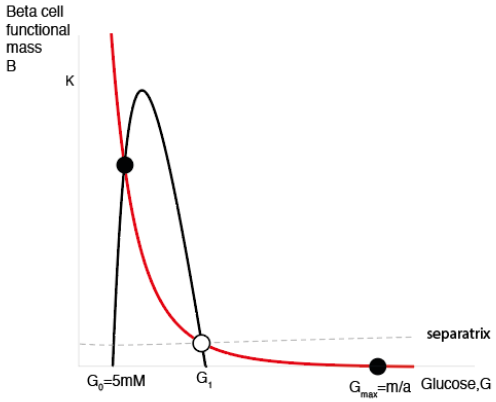


Figure 5.7

It has a mountain shape (Fig 5.7): at very low glucose and very high glucose there are no beta cells at steady-state due to removal that exceeds proliferation. At middle glucose levels, beta cells rise and then fall.

Now we can have a gradual prediabetes state. In insulin resistance, s drops and the red nullcline rises (more glucose at given beta cell level due to the lower effect of each unit of insulin). The fixed-point creeps up to higher levels of glucose, beta cells (and insulin) (Fig 5.8).
But at a critical level of insulin resistance, the stable and unstable fixed points collide, and annihilate. Above this insulin resistance, the only fixed point is the high one at 25mM!

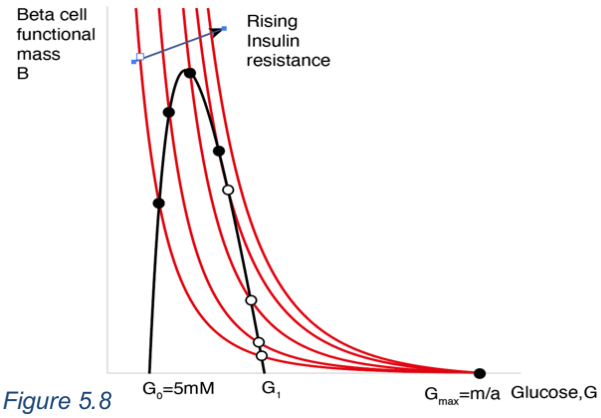


Figure 5.8

We can look at this transition to diabetes by using a useful plot called a **bifurcation plot (Fig. 5.9).** We plot insulin sensitivity on the x axis, and the glucose levels of the fixed points on the y axis. This helps us to track how the fixed points change with insulin resistance.
The bifurcation plot has three lines at high levels of s (low insulin resistance) - the top line is the 20mM high fixed point, the bottom blue line is the fixed point near 5mM, and the red line is the unstable middle fixed point. When insulin sensitivity approaches a critical point, the 5mm and unstable fixed points come closer and collide and annihilate. The only remaining fixed point at low s is 20mM.
Gratifyingly, data on rats in a genetic rat model that develops diabetes [Topp 2007], follows the bifurcation plots qualitatively (Fig 5.9). Incidentally, this data was collected by the same group who did the seminal BIG model.
We can also compare the bifurcation plot to large scale data on human participants with prediabetes, collected by the lab of Eran Segal (Fig 5.10). Insulin sensitivity was estimated using the HOMA model from fasting insulin and glucose tests (s=const/I G). We see that glucose rises as insulin sensitivity s drops, rising to an apparent critical point. (Work of Aurore Woller).

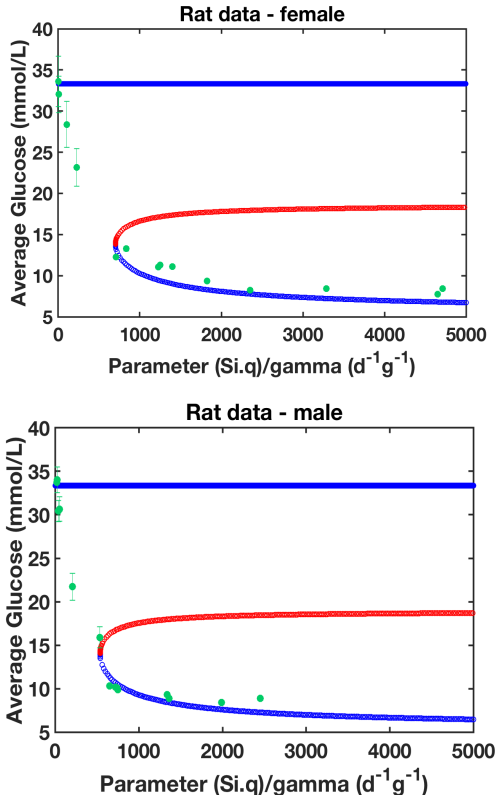


Figure 5.9

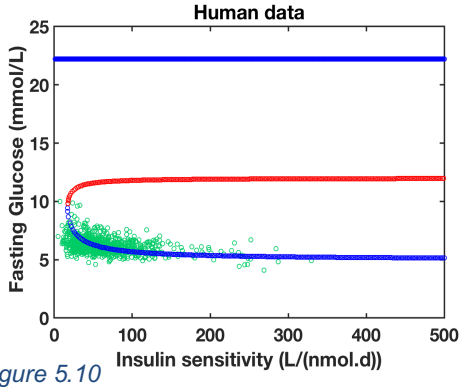


Figure 5.10

Diabetes is easier to prevent than to treat.
In the stable region, glucose homeostasis is kept (5mM~100 mg/dl). Above a threshold, positive feedback sets in due to glucotoxicity. It takes acute caloric restriction or gastric bypass surgery to get back below the unstable fixed point [Figure 5.11 from Ha and Sherman 2020]

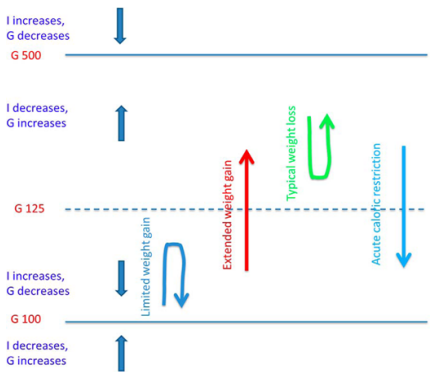


Figure 5.11

The model can help to explain how diabetes drugs work, and perhaps to suggest new conceptual targets for drugs.
An early drug family includes sulfonylurea, which increases beta cell insulin secretion capacity q (Fig. 5.12). Since q multiplies s in the nullcline equation, increasing q is like increasing insulin sensitivity in the model, which pushes the nullcline down and away from the bifurcation

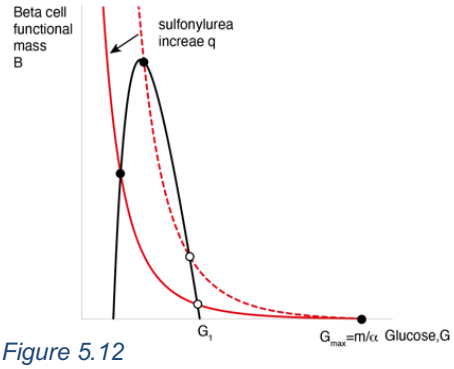


Figure 5.12

Another class of drugs increase glucose removal rate alpha (Fig. 5.13). They do by inhibiting the transporter that returns glucose from the forming urine to the body, a process known as **reabsorption**. The kidney filters blood by moving it at high pressure through thin capillaries. The pressure pushes out substances from the plasma to the forming urine. Normally, the body recovers important substances like glucose and salts using special transporters. SGLT2 **inhibitors** are important blood **glucose** lowering agents for use in diabetes treatment. They primarily function by altering **glucose reabsorption** via SGLT2 in the proximal tubule of the kidney where urine begins to form. They also improve body weight and composition, uric acid levels and blood pressure in patients. Since alpha is raised, the high glucose fixed point, G_hi=m/alpha, moves down and this pushes the nullcline away from the bifurcation point.

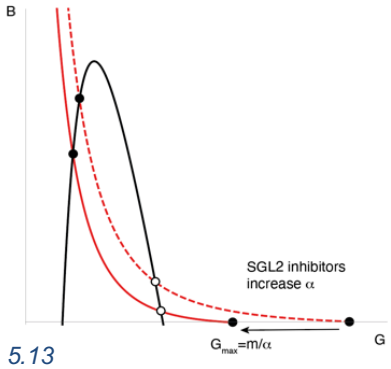


Figure 5.13

One of the most commonly used drugs is **metformin**, which reduces liver glucose production m, and raises insulin sensitivity s (Fig. 5.14). These shifts both the intersection point at high glucose, and the slope of the nullcline. This pushes the glucose fixed point away from the bifurcation point.

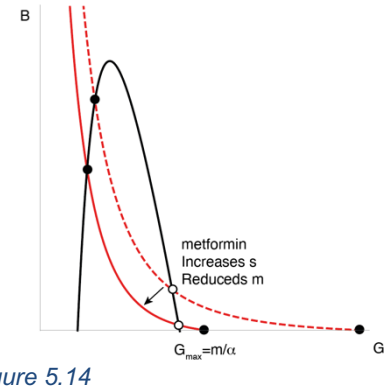


Figure 5.14

It would be important to investigate other parameters in the model: the beta cell carrying capacity K and the glucotoxicity curve r(G). Increasing carrying capacity or reducing glucotoxicity are predicted to be effective ways to address diabetes.

To summarize: A basic biological law (and law of life in general) is that all processes have a limit. Limit of beta cell compensation causes a continuum of glucose steady states known as prediabetes, and a sudden bifurcation to a state with only a single very high glucose setpoint, signaling the loss of beta cells and the rise of glucose to damaging levels.

In fact, we can say that **three basic biological laws** are at the bottom of glucose homeostasis and breakdown. Law 1, *all cells come from cells*, so a feedback loop must keep organ size control. That's why glucose controls beta cell mass growth, allowing compensation of insulin resistance. Law 2, however, is that *cells mutate*. Thus, mutants will arise that fool the feedback, by sensing too much glucose, dividing and secreting insulin, and threaten to take over. To resolve this, glucotoxicity evolved, to kill those mutants. But glucotoxicity is a fragility for diabetes, because when compensation reaches a limit, according to law 3 that *all biological processes have a limit* or saturate, beta cells begin to be killed by the high glucose, leading to diabetes.

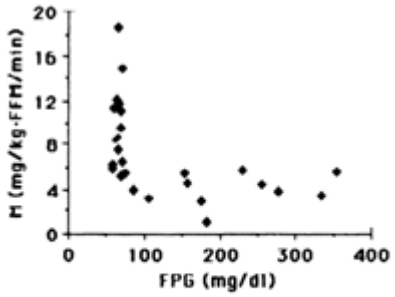


FIG. 3. Nonlinear relationship between insulin sensitivity (M) and fasting plasma glucose levels (FPG) in all subjects. Greatest variability in M rate was found in the normoglycemic subjects (< 100 mg/dl); in those subjects with FPG > 100 mg/dl, M rates decreased to < 6 mg·kg $^{-1}$·FFM·min $^{-1}$.

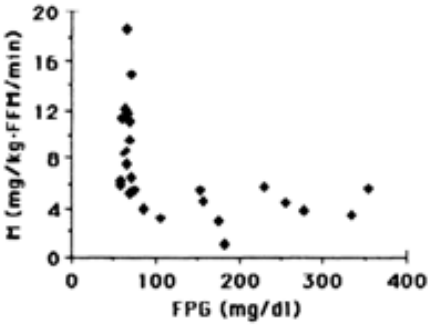
Appendix:

A bifurcation like phenomenon is also seen in data from monkeys that get diabetes. Fasting plasma glucose (FPG) is compensated until insulin sensitivity drops below a threshold.

[https://journals.physiology.org/doi/pdf/10.1152/ajpendo.1989.256.5.E676]

Note: beta cell mass increases faster than body weight, and 85% destruction needed for T1D in 5yo, but only 40% in 20yo

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2147725/



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