ENGN/PHYS 225
Math Modeling Diabetes Diagnositcs: The Glucose Tolerance Test
(Last modified: March 16, 2021)

Introduction and motivation

As we briefly reviewed in class, diabetes continues to be a massive health problem throughout the United States. Diabetes is associated with a range of symptoms including high blood pressure, fatigue, blurred vision, neuropathy, and a poorly functioning immune system Approximately 10% of the population is affected, and per annum health care costs tally upwards of $300 billion dollars (CDC national diabetes statitics report, 2020).

How is diabetes diagnosed? One common method is the Glucose Tolerance Test (GTT). Basically, one starts in a fasted state to bring bring glucose and insulin concentrations to resting baseline levels. Then the patient drinks a glug of sugary drink while glucose and insulin levels are monitored over the next several hours. The trajectory of blood glucose concentration vs time is then used to help make a diagnosis.

What do doctors and patients expect to see? How do they make sense of the data based on fundamental biophysical principles? Enter stage left: math models!

Our goal here is to explore one such classic model originally published circa 1964[1]. It continues to be an extremely useful model. And it's a great entry point into the world of linear algebra via coupled differential equations!

This document serves as a conceptual guide through an admittedly fairly long and involved process. None of the individual steps are tricky, its just that there are a lot of them to navigate to the "other side."

Our specific math aim is to show that the GTT should result in a physiological response of blood glucose concentration $G(t)$, given by:

$$G(t) = G_o + \frac{R}{\omega_d} e^{-\alpha t} \sin \omega_d t \tag{1}$$

The values for α and ω_d are crucial for understanding and interpreting results in context for normal and diabetic individuals to the GTT, as illustrated in Figure 1.

[1] E. Ackerman et al, A mathematical model of the Glucose-tolerance test 1964, *Physics in Medicine and Biology*: 9 203; and E. Ackerman et al, Model studies of blood-glucose regulation 1965, *Bulletin of Mathematical Biophysics*: 27

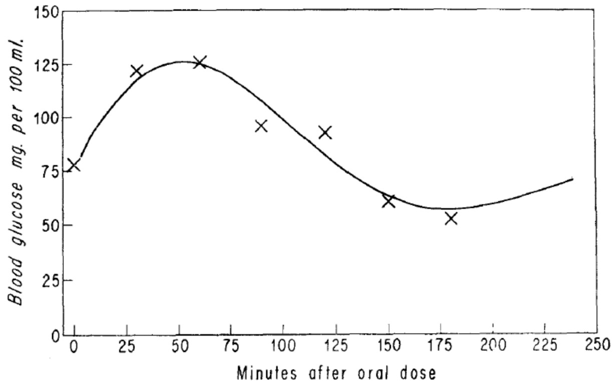

Figure 3. Response of a normal individual to an orally administered glucose load. Curve is determined from model using iterative guessing technique (Hazelrig, *et al.*, 1963)

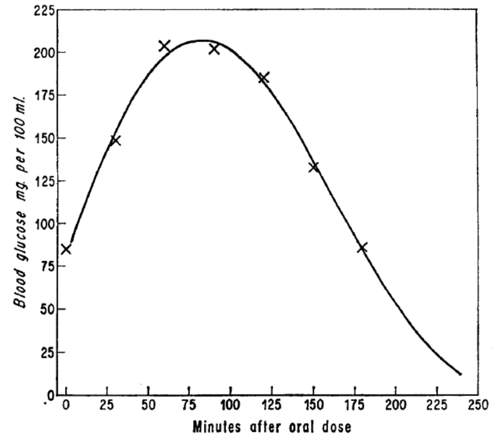

Figure 4. Response of an individual with diabetes to an orally administered glucose load, as Figure 3

Figure 1: GTT test results for normal individual (left) and diabetic (right). After Ackermann et al 1964

Glucose Tolerance Test: Math Model

In the glucose-tolerance test GTT, the subjects fasts overnight, after which their blood glucose and blood glucose-regulating hormone levels (e.g. insulin) reach more or less constant baseline values, G_o and H_o, respectively. These values are controlled by the subject's basic rate of tissue metabolism, diet, body weight, among other factors.

The GTT math model is primarily interested in solving deviations away from resting baseline values, $g(t)$ and $h(t)$ respectively. Plus, doing so makes the math a little bit easier to solve. Specifically, we define:

$$g(t) = G(t) - G_o \tag{2}$$
$$h(t) = H(t) - H_o \tag{3}$$

Again, note that $G(t)$ is the concentration of blood glucose measured at time t, while little $g(t)$ expresses the deviation away from baseline value G_o. A similar statement applies for hormone concentration.

Next, we introduce the math model (per Ackerman et al);

$$\frac{dg}{dt} = -m_1 g - m_2 h + J(t) \tag{4}$$
$$\frac{dh}{dt} = -m_3 h + m_4 g + K(t) \tag{5}$$

where the rate constants $m_k \geq 0$.

The ***rate constants*** signify the following biophysical/physiological phenomena:

m_1 = removal of glucose due to its own concentration being above baseline level
m_2 = removal of glucose above initial baseline level by insulin
m_3 = removal of hormone (insulin) due to its own concentration being above baseline level
m_4 = release of hormone due to increased levels of glucose above baseline levels

The ***forcing terms*** have also included for completeness on the RHS (we'll deal with these more in a second) $J(t)$ is rate of ingested glucose (per unit time)
$K(t)$ represents the rate of extrinsic hormone introduced per unit time (e.g. an insulin shot)

In practice for the GTT, no hormone is extrinsically introduced, thus, $K(t) = 0$. While, $J(t)$ could be vary in time, wiggle and waggle around as a patient eats a meal, we'll assume the glug of ingested glucose happens so fast that there is an ***delta function impulse*** to the system at $t = 0$, thus $J(t) = R\delta(t)$, where $\delta(t)$ denotes the Kroenecker delta function. It is infinitely thin and infinitely high; the area under it's curve is 1 and all the action is focused at $t = 0$ and the forcing is 0 for all time otherwise

One nice way to mathetmically handle this funky looking impulse function is to realize that it essentially imposes an "initial velocity" condition: $\dot{g}(0) = \dot{g}_o$. This is similar to saying you have a mass and springs connected on a table, and you give one of them a whack with a mallet. Just at the moment the mallet strikes, the initial position is 0, but the mass has been put into motion—it has initial velocity.

The summary of all of this hefty dose of math is that we now have the following model to solve:

$$\frac{dg}{dt} = -m_1 g - m_2 h \tag{6}$$

$$\frac{dh}{dt} = -m_3 h + m_4 g \tag{7}$$

subject to the initial conditions:

$$g(0) = 0 \tag{8}$$

$$\dot{g}(0) = \dot{g}_o = R \tag{9}$$

$$h(0) = 0 \tag{10}$$

$$\dot{h}(0) = \dot{h}_o \tag{11}$$

A little interlude

Before our deep deep, let's take a quick little math breather solving a quadratic equation. Spoiler alert: This cool little math cat will reappear in a later act!

Imagine you are have a quadratic equation in λ:

$$\lambda^2 + 2\alpha\lambda + \omega_o^2 = 0$$

Show that

$$\lambda = -\alpha \pm \sqrt{\alpha^2 - \omega_o^2}$$

Solution Method for the GTT: Make a good guess!

Our goal now is to solve the system of ***coupled ODEs*** in Eqn 6.

How do we do this? Just guess a good guess and see if it works!

1. Let's make a (very good) guesses for solutions:

   $$g(t) = a_1 e^{\lambda t}$$

   and

   $$h(t) = a_2 e^{\lambda t}$$

   We are on the hunt for the values λ, a_1, a_2 which might solve our system of equations!

   One very important note here is that λ is the *same* constant used for both $g(t)$ and $h(t)$. Physically, this means they evolve with the *same* time course. Pause for a minute and think why this should be so, then briefly justify in 1-2 sentences why this is a good and reasonable conjecture. It may help to consider counterexamples, for example if glucose concentration varies on a time scale of 30 min, does it make any sense that hormone concentration, being sensitive to glucose, would vary on a scale of say 90 min? As a spoiler alert, we'll soon see that λ are the ***eigenvalues*** of the system.

   One other very important note, the amplitudes a_1 and a_2 are not the same. What does it physically mean if a_1 is half as big as a_2, for example; or 4× as big? Soon we'll see see the ratio of these two values is critically important. We often bundle these up into a vector $[a_1, a_2]^T$. Spoiler alert, these are the ***eigenvectors*** of the system. This is a linear algebra based solution, so this should come as no surprise.

2. Plugging these guesses for $g(t)$ and $h(t)$ back into the coupled ODEs (see starting Eqn 6), show that we get the following:

   $$-m_1\, g(t) - m_2\, h(t) - \lambda\, g(t) = 0 \quad (12)$$
   $$m_4\, g(t) - m_3\, h(t) - \lambda\, h(t) = 0 \quad (13)$$

3. Next write these coupled ODEs (starting Eqn 12) in matrix form

   $$B\vec{x} = \vec{0}$$

   were we define:

   $$\vec{x}(t) = \begin{bmatrix} g(t) \\ h(t) \end{bmatrix} = e^{\lambda t} \begin{bmatrix} a_1 \\ a_2 \end{bmatrix} = e^{\lambda t}\vec{a} \quad (14)$$

   which just bundles $g(t)$ and $h(t)$ together. We'll see soon that λ and $\vec{a}$ are ***eigenvalues*** and ***eigenvectors*** of our system!

Be explicit in carefully writing out each element in matrix B. Note that $\vec{0}$ denotes a vector with all elements equal to zero, in this case a 2×1 column vector.

4. Next, a little math massage. Show that we can write $B\vec{x} = \vec{0}$ another form

$$(A - \lambda I)\, \vec{x}(t) = \vec{0} \tag{15}$$

where I denotes the (2×2) identity matrix. Be explicit in carefully writing out each element in matrix A.

5. Remember we're on the hunt for values of λ, a_1 and a_2 that solve our coupled ODEs. We are getting tantalizing close now. Show/argue that we can use Eqn 15 to write the following.

$$(A - \lambda I)\, \vec{a} = \vec{0} \tag{16}$$

The key conceptual question moving from Eqn 15 to 16: Why was it fair game to ditch the time-dependent term $e^{\lambda t}$?

Eqn 15 expresses the classic ***eigenvalue problem***! It looks like a humble little equation, but it is not an exaggeration to say it is one of the most important forms that appears across all branches of math, physics, and engineering! It pops up when solving everything from how buildings vibrate during earthquakes to page ranking systems for google searches; from natural speech analysis and facial recognition (daily things at human size scales) to quantum physics (a wonderful world operating at a different size scale!).

6. "OK, that's nice and cute and all", you say, "but how do I actually solve it?!" Well, you've come to the right place.

The crux of the ***eigenvector/value problem*** is this: Eqn 16 says we have two options in math life:

(a) $\vec{a} = [a_1, a_2]^T = \vec{0}$. This is the ***trivial solution***. It's boring. It says nothing actually changes in time. That's not helpful at all for diagnosing diabetes either!

(b) We find eigenvalues λ of matrix A such that the matrix $A - \lambda I$ *cannot* be inverted. This precludes the trivial solution because we *cannot* get a solution $\vec{a} = \text{inv}(A - \lambda I)\, \vec{0} = \vec{0}$.

OK, so how do we *guarantee* this 2nd case comes to fruition? It involves the ***determinant*** of $A - \lambda I$. What is the condition of $det(A - \lambda I)$ which ensures that it is ***non-invertible*** (or ***singular***). For a refresher, look back at problems 3 and 4 of the matrix math/linear algebra worksheet

7. Now solve for the eigenvalues λ.

The math can be a bit grindy with all the m's running around, so let's clean things up a bit defining the following parameters, each of which has intuitive physical meaning in terms of damping and natural frequency of oscillation (evident by looking back at the solution to the model on the first page)

$$2\alpha = m_1 + m_3$$

$$\omega_o^2 = m_1 m_3 + m_2 m_4$$

$$\omega_d^2 = \omega_o^2 - \alpha^2$$

Given we expect oscillations based on GTT results, we'll assume here that $\omega_o^2 > \alpha^2$.

It might not be just a co-ink-ee-dink if you just so happen to stumble on a familiar looking solution (see section "A little interlude"). Note that there are two unique eigenvalues here, denoted λ_1 and λ_2. This is no coincidence: after all, have 2 coupled ODE's bundles up in a 2×2 matrix.

8. Next up, we need to find the eigenvectors $\vec{a}$ associated with each of the eigenvalues λ. How do we find them? Just recall our original eigenvalue problem:

$$(A - \lambda I)\,\vec{a} = \vec{0} \qquad \text{equivalently} \qquad A\,\vec{a} = \lambda\,\vec{a}$$

   First plug in λ_1 to find its associated eigenvector $\vec{a}^{(1)}$.
   Similarly, pin λ_2 to solve for its associated eigenvector $\vec{a}^{(2)}$.

   Note the superscript index on the eigenvectors; this is used to avoid consusion with the individual components of the vector a_1 and a_2. To make this more explicit, we could say, for instance, that $a_1^{(2)}$ is the first component of the second eigenvector.

   In solving, you may immediately and vociferously object "But I only have 1 equation for 2 unknowns!" And you'd be absolutely correct. What's the out? Eigenvectors are really all about ratios, in this case the ratio of a_1 to a_2. We don't really care about arbitrary scale factors. So a common choice–the first easy out–is to just choose $a_1 = 1$. Make that choice here.

   Let's pause here and note that a crucial math fact; ***eigenvectors and eigenvalues always come in pairs***: λ_n and $\vec{a}^{(n)}$, often called ***a mode of the system***. We have 2 of them here ($n = 1, 2$). If we were solving a 5 dimensional problem, we'd have 5 eigenvector/value combinations; for N dimensions, we'd have N eigenvalues, each with its own eigenvector (assuming they exist, which for pretty much every physical system is the case).

9. Getting closer now! We have now solved for the eigenvalues and eigenvectors we needed for our initial (and very good guess) for a solution per Eqn 14: $\vec{x}(t) = e^{\lambda_n t}\vec{a}^{(n)}$.

   Both of these ($n = 1, 2$) solve the original ODEs. The total solution is just a ***linear combination*** of these, aka the ***superposition*** of the individual modes

$$\begin{bmatrix} g(t) \\ h(t) \end{bmatrix} = \sum_n c_n\, e^{\lambda_n t}\vec{a}^{(n)}$$

   Here, the c_n are the "weights" specifying how much each individual mode of the system mixes into the total solution. Larger magnitude $|c_n|$ indicate a more prominent/dominant mode.

   Though this compact notation is very handy, it is also unnervingly dense. So let's unpack! Write out the RHS of this equation in full and glorious detail, one equation for $g(t)$ and another for $h(t)$.

10. Since the GTT is focused on the glucose response vs. time, for now we'll solve out for just $G(t)$. Solving for $H(t)$ follows the same exactly process, but will save that for another day.

    As a penultimate step to solving for $g(t)$, hence $G(t)$, apply initial conditions to find any remaining constants.

    Hint: At this point, you may recognize a very familiar form for $g(t)$, shockingly similar to our mountain biker ODEs problem.

11. Finally, the big finale! Show that we can put everything together to write the final solution of our math puzzle per Eqn 1.

12. Before we say night-night to this math model, let's recall the real world reason why we are doing this in the first place: to help diagnose diabetes so that the individual can get good and proper treatment (hopefully!). A GTT response time of ≥ 4 hrs is normally interpreted as strong indicator the individual has diabetes. Likewise, the maximum rise in blood glucose sugar of ≥ 100 mg/mL is a strong diagnostic indicator. To tie everything together, we'll plot a glucose response curves for a normal vs. diabetic individual. This allows easy compare and contrast.

    Using the data illustrated in Figure 1, estimate approximate values for parameters:
    G_o, R, ω_o, α, and ω_d.
    Make a table to help compare and contrast values for normal vs. diabetic.
    Hint: A good iterative strategy to finding parameter values would be to start with an eyeball estimate of parameters, plot the resulting curve for $G(t)$ vs. t, then revise your estimates, plot again; rinse, lather, repeat.[2]

13. The big claim to the GTT is the following, per Ackermann et al 1964: *On the basis of measurements on over 750 persons, it is suggested that the value of ω_o, can be used to distinguish normal from diabetic persons more closely than any other parameter [see Fig 5].*

    In view of the results for model parameter estimates (step 12 above), evaluate this claim. Does it seem to be true based on your an $N = 1$ basic comparison?

Final remark

Wow, we just did a lot of work to solve a math model for diabetes. We still have a lot of work to do collectively as a society of scientists, mathematicians and policy makers to actually solve diabetes.

[2] There is another wonderful branch of math that deals with curve fitting aka regression fitting. It is a very useful tool to have your math toolbox, but sadly we won't have enough time to approach it this winter.