Project for Math. 224

DETECTION OF DIABETES

Diabetes is a disease of metabolism which is characterized by too much sugar in the blood and urine. Because of the lack of insulin (a hormone), the patient's body is unable to burn off all its sugar, starches and carbohydrates. Diabetes is usually diagnosed by a glucose tolerance test (GTT). In GTT, the patient comes to the hospital after an overnight fast and is given a large dose of *glucose* (the kind of sugar in the bloodstream). In the next few hours, several measurements of the concentration of blood glucose are made and these measurements are used in diagnosis of diabetes.

This project concerns one of the criteria for interpreting the results of a GTT. The model is based on the following:

Basic Biological Facts: Glucose is a source of energy for all organs and tissues. Each individual has an optimal blood glucose concentration, from which any large deviation would cause a serious pathological condition. The blood glucose concentration is influenced and controlled by various kinds of hormones, among which the predominant factor is *insulin*. (In this project, for the sake of simplicity we shall ignore the effect of other hormones.) Insulin is secreted by the pancreas. After we eat any carbohydrates, the pancreas is signaled to secrete more insulin. Also the glucose in the bloodstream directly stimulates the pancreas to secrete insulin. The insulin in return facilitates tissue uptake of glucose by attaching itself to the impermeable membrane walls, opening the door for glucose to pass through the membrane to the center of cells, where glucose is consumed.

Let $G(t)$ and $H(t)$ be the concentrations of blood glucose and insulin at time t, respectively. Then G and H satisfy

$$(1) \qquad \begin{cases} \dfrac{dG}{dt} = f_1(G,H) + E(t) \ , \\ \dfrac{dH}{dt} = f_2(G,H) \ , \end{cases}$$

where $E(t)$ represents external rate of change for G, and f_1 and f_2 represent internal rate of change for G and H, respectively.

(a) It is known that after an overnight fast, the concentrations of glucose and insulin in the patient's blood stabilize at their optimal values, i.e., $G(t) \equiv$ constant G_0, $H(t) \equiv$ constant H_0. **Using this fact, show that $f_1(G_0, H_0) = 0 = f_2(G_0, H_0)$.**

Let $g = G - G_0$, $h = H - H_0$, then by (1), we have

$$(2) \qquad \begin{cases} \dfrac{dg}{dt} = f_1(g + G_0, h + H_0) + E(t) \ , \\ \dfrac{dh}{dt} = f_2(g + G_0, h + H_0) \ , \end{cases}$$

This system is often hard to solve. In case that g and h are small, (2) can be approximated by a linear system as follows: By the "tangent plane approximation" (taught in Calculus III),

$$f_1(g + G_0, h + H_0) \approx f_1(G_0, H_0) + \frac{\partial f_1}{\partial G}(G_0, H_0)g + \frac{\partial f_1}{\partial H}(G_0, H_0)h \ ,$$

$$f_2(g + G_0, h + H_0) \approx f_2(G_0, H_0) + \frac{\partial f_2}{\partial G}(G_0, H_0)g + \frac{\partial f_2}{\partial H}(G_0, H_0)h \ ,$$

if g and h are small. Thus (2) can be approximated by

$$(3) \qquad \begin{cases} \dfrac{dg}{dt} = \dfrac{\partial f_1}{\partial G}(G_0, H_0)g + \dfrac{\partial f_1}{\partial H}(G_0, H_0)h + E(t) \\ \dfrac{dh}{dt} = \dfrac{\partial f_2}{\partial G}(G_0, H_0)g + \dfrac{\partial f_2}{\partial H}(G_0, H_0)h \ . \end{cases}$$

(Recall $f_1(G_0, H_0) = 0 = f_2(G_0, H_0)$.) This approximation is good if g and h are small. This procedure is called the *linearization* of (2) at point (G_0, H_0).

In system (3),

$$\frac{\partial f_1}{\partial G}(G_0, H_0), \frac{\partial f_1}{\partial H}(G_0, H_0), \frac{\partial f_2}{\partial G}(G_0, H_0), \frac{\partial f_2}{\partial H}(G_0, H_0)$$

are unknown because functions f_1 and f_2 are unknown. However, it is possible to determine their signs.

(b) **By using the *Basic Biological Facts*, show that $\frac{\partial f_1}{\partial G}(G_0, H_0)$, $\frac{\partial f_1}{\partial H}(G_0, H_0)$ and $\frac{\partial f_2}{\partial H}(G_0, H_0)$ are negative and $\frac{\partial f_2}{\partial G}(G_0, H_0)$ is positive.**

[**Hint:** When proving $\frac{\partial f_1}{\partial G}(G_0, H_0) < 0$, assume in (3) that $h = 0$ and $E(t) \equiv 0$ (what does this assumption mean biologically?), then argue that $\frac{dg}{dt} < 0$ if $g > 0$.]

Now (3) can be written as

$$(4) \qquad \begin{cases} \dfrac{dg}{dt} = -a_1 g - a_2 h + E(t) \ , \\ \dfrac{dh}{dt} = -a_3 h + a_4 g \ , \end{cases}$$

where a_1, a_2, a_3 and a_4 are positive constants.

(c) **By eliminating h and $\frac{dh}{dt}$ from (4), show that $g(t)$ satisfies**

$$\frac{d^2 g}{dt^2} + (a_1 + a_3)\frac{dg}{dt} + (a_1 a_3 + a_2 a_4) g = a_3 E(t) + \frac{dE}{dt} \ .$$

Except for the very short time interval in which glucose load is being ingested after the arrival of the patient at the hospital, $E(t)$ and hence $\frac{dE}{dt}(t)$ are identically zero. Set $t = 0$ at the time of the completion of the ingestion. Then for $t \geq 0$, $g(t)$ satisfies

$$(5) \qquad g'' + 2\alpha g' + \beta^2 g = 0 \ ,$$

where $\alpha = \frac{a_1 + a_3}{2}$, $\beta^2 = a_1 a_3 + a_2 a_4$. β is called the *natural frequency* of equation (5). This is exactly the equation for the spring–mass system.

(d) **Using (5), show in detail that every solution $g(t)$ of (5) is of the form**

$$g(t) = \begin{cases} \mu e^{-\alpha t}\cos(wt - \delta), & \text{if } \alpha^2 - \beta^2 < 0 \text{ (underdamped case)} \\ C_1 e^{-\alpha t} + C_2 t e^{-\alpha t}, & \text{if } \alpha^2 - \beta^2 = 0 \text{ (critically damped case)} \\ C_1 e^{\lambda_1 t} + C_2 e^{\lambda_2 t}, & \text{if } \alpha^2 - \beta^2 > 0 \text{ (overdamped case)} \end{cases}$$

where $w = \sqrt{\beta^2 - \alpha^2}$, $\lambda_1 = -\alpha + \sqrt{\alpha^2 - \beta^2}$, $\lambda_2 = -\alpha - \sqrt{\alpha^2 - \beta^2}$, and μ, δ, C_1 and C_2 are constants. This part is a repeat of what you learned in the class.

(e) **Show that $\lim_{t\to\infty} G(t) = G_0$.**

Now we have for $t \geq 0$,

$$G(t) = \begin{cases} G_0 + \mu e^{-\alpha t}\cos(wt - \delta), & \text{if } \alpha^2 - \beta^2 < 0 \ , \\ G_0 + C_1 e^{-\alpha t} + C_2 t e^{-\alpha t}, & \text{if } \alpha^2 - \beta^2 = 0 \ , \\ G_0 + C_1 e^{\lambda_1 t} + C_2 e^{\lambda_2 t}, & \text{if } \alpha^2 - \beta^2 > 0 \ . \end{cases}$$

(It should be reminded that this formula holds only approximately because we derive it by using (4) which is an approximation of the "precise" model (1).) The constants G_0, α, β, δ, μ, C_1 and C_2 are unknown constants. They can be determined by taking several measurements of the patient's blood glucose.

(f) **How can G_0 be found experimentally; i.e., what measurements, under what conditions, should be taken to estimate G_0?**

(g) In the overdamped case ($\alpha^2 - \beta^2 > 0$), how would you find α, β, C_1 and C_2?

In numerous experiments, it was observed that β is insensitive to experimental errors in measuring G. Therefore we choose β as the basic descriptor of the response to a glucose tolerance test. Let $T = 2\pi/\beta$. T is called the *natural period* of the system (5). The data from many doctors and hospitals lead to the following.

Criterion for Diabetes: $T < 4$ *hours implies normalcy,* $T > 4$ *hours indicates mild diabetes.*

Remark: The model we discussed above can only be used to diagnose mild diabetes, since the linearized system (3) is a good approximation of (2) only if g and h are small. Very large deviations g of G from its optimal value G_0 imply severe diabetes.

Before using data to determine T $(= 2\pi/\beta)$ of a patient as discussed in (g), we have to know if we are in the underdamped, critically damped, or overdamped case. What distinguishes the underdamped case from the other two cases is that in the former, any nontrivial solution $g(t)$ of (5) changes the sign infinitely many times, while in the latter cases, $g(t)$ can change its sign at most once. (By a nontrivial solution of (5), we mean a solution of (5) which is not identically zero.)

(h) **Show that in the critically damped or overdamped case, any nontrivial solution $g(t)$ of (5) can change its sign at most once.**

Thus, if data indicate that $g(t)$ changes its sign more than once, we know we are in the underdamped case.

Now let's look at two examples.

Example 1. After an overnight fast, this patient's blood glucose concentration is 75 mg glucose/100 ml blood. His blood glucose concentration 1 hour, 2 hours and 3 hours after fully absorbing a large amount of glucose is 90, 62, 81 mg glucose/100 ml blood, respectively.

(i) **Argue by using** (h) **that this is the underdamped case.**

(j) **Show that in the underdamped case, the time interval between any consecutive zeros of any nontrivial solution** $g(t)$ **of** (5) **is greater than** $T/2$**.**

(k) **Now show that the patient in** Example 1 **is normal.**

Example 2. A patient's blood glucose concentration is 70 mg glucose/100 ml blood after an overnight fast. His blood glucose concentration 1 hour, 2 hours, 3 hours and 4 hours after fully absorbing a large amount of glucose is 95, 70, 65, 65 mg glucose/100 ml blood.

(l) **Using** (f) **and** (g)**, determine if this patient is a diabetic. Assume** $\alpha^2 - \beta^2 > 0$**.**

Solving the system you wrote for C_1, C_2, λ_1, λ_2 in (g) is pretty difficult. The reasonable thing to do is to introduce two new variables instead of λ_1, λ_2, namely, $x_1 = e^{\lambda_1}$, $x_2 = e^{\lambda_2}$ (after you find x_1, x_2, you just take $\lambda_i = \ln x_i$). Write the system for the unknowns C_1, C_2, x_1, x_2.

The new system is simpler, but still difficult to solve.

You may try to eliminate C_1, C_2 by dividing all equations by C_1.

Alternatively, you can use Matlab to solve the algebraic equations–see its manual.