Project for Math. 224

DETECTION OF DIABETES

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Abstract:

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). This project concerns one of the criteria for interpreting the results of a GTT.

Keywords:

Diabetes, Detection, GTT, Insulin, Glucose, Approximate, Test, Concentration, Pancreas, Secrete

1. Introduction

Diabetes is a syndrome of disordered metabolism, usually due to a combination of hereditary and environmental causes, resulting in abnormally high blood sugar levels. Maybe you didn't care about yourself once time and as time goes by,some problem float to surface and disturb you. At this time, how do you find out that you have Type 2 diabetes? Often, because there may not be noticeable symptoms, the diagnosis is made during an annual physical or checkup. Your doctor may order an Oral Glucose Tolerance Test (OGTT) better know as GTT to help determine whether you have diabetes. What do this tests mean?

The GTT is a glucose challenge test. A fasting blood glucose is usually taken first to establish a baseline level. Then you are given a 75 grams glucose drink. Two hours later another blood sample is drawn to check your glucose level. If your blood glucose is under 140 mg/dl then your glucose tolerance is considered normal. If it is 140 mg/dl to 200 mg/dl, then you have impaired glucose tolerance or pre-218 diabetes. If your glucose is over 200 mg/dl then a diagnosis of type 2 diabetes is made. Again, your doctor will usually perform this test on two different occasions before a definite diagnosis is made. A very serious difficulty associated with this method of diagnosis is that no universal accepted criterion exists for interpreting the results of the GTT.

This project tells you something about GTT.

2. Model for Detection of Diabetes

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

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

where E(t) represents external rate of change for G, and f1 and f2 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, we can show that $f_1(G_0,H_0) = 0 = f_2(G_0,H_0)$.

Proof: Let $G(t) \equiv$ constant G_0 ,$H(t) \equiv$ constant H_0, take it to the equations (a), then we get

$$0 = \frac{dG_0}{dt} = f_1(G_0, H_0) + E(t)$$
$$0 = \frac{dH_0}{dt} = f_2(G_0, H_0)$$

Thus E(t)=const, E(t) represents external rate of change for G as well,thus E(t)=0

Hence,$f_1(G_0,H_0) = 0 = f_2(G_0,H_0)$.

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

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

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" ,

$$\mathrm{f}_1(\mathrm{g}+\mathrm{G}_0,\mathrm{h}+\mathrm{H}_0) \approx \ \mathrm{f}_1(\mathrm{G}_0,\mathrm{H}_0)+\frac{\partial f_1}{\partial G}(G_0,H_0)g+\frac{\partial f_1}{\partial H}(G_0,H_0)h$$

$$\mathrm{f}_2(\mathrm{g}+\mathrm{G}_0,\mathrm{h}+\mathrm{H}_0) \approx \ \mathrm{f}_2(\mathrm{G}_0,\mathrm{H}_0)+\frac{\partial f_2}{\partial G}(G_0,H_0)g+\frac{\partial f_2}{\partial H}(G_0,H_0)h$$

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

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

(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 f1 and f2 are unknown. However, it is possible to determine their signs.

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

When discussing the sign of $\frac{\partial f_1}{\partial G}(G_0,H_0)$,we assume in (3) that $E(t) \equiv 0$, and $h(0) = 0$, $g(0) > 0$ (Biologically,this assumption means there is no more insulin secreted by pancreas initially and without taking glucose but it's more than common case initially.), then we argue that $g'(0) < 0$ by basic biological facts.then we can know that the sign of $\frac{\partial f_1}{\partial G}(G_0,H_0)$ is the same as $g'(0)$ which is negative.

Similarly, we can analyse the signs of the other three.

Now (3) can be written as

$$\begin{cases} \dfrac{dg}{dt}=-a_1g-a_2h+E(t) \\ \dfrac{dh}{dt}=-a_3h+a_4g \end{cases} \qquad (4)$$

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

$$\frac{d^2g}{dt^2}+\left(a_1+a_3\right)\frac{dg}{dt}+\left(a_1a_3+a_2a_4\right)g=a_3E(t)+\frac{dE}{dt}$$

Proof:

$$\begin{cases}\dfrac{dg}{dt}=-a_1g-a_2h+E(t)\\ \dfrac{dh}{dt}=-a_3h+a_4g\end{cases}$$

$$\begin{aligned}&\frac{d^2g}{dt^2}=-a_1\frac{dg}{dt}-a_2\frac{dh}{dt}+\frac{dE}{dt}\\ &=-a_1\frac{dg}{dt}-a_2\left(-a_3h+a_4g\right)+\frac{dE}{dt}\\ &=-a_1\frac{dg}{dt}-a_2\left(-a_3\left(\frac{-\frac{dg}{dt}-a_1g+E(t)}{a_2}\right)+a_4g\right)+\frac{dE}{dt}\\ &thus\\ &\frac{d^2g}{dt^2}+\left(a_1+a_3\right)\frac{dg}{dt}+\left(a_1a_3+a_2a_4\right)g=a_3E(t)+\frac{dE}{dt}\end{aligned}$$

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 dE/dt are identically zero. Set t = 0 at the time of the completion of the ingestion. Then for $t \geq 0$, g(t) satisfies

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

where $\alpha = (a_1+a_3)/2$, $\beta^2 = a_1a_3 + a_2a_4$. 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

$$g(t)=\begin{cases}\mu e^{-\alpha t}\cos(\omega t-\delta), if\,\alpha^2-\beta^2<0(underdamped-case)\\ \left(C_1+C_2t\right)e^{-\alpha t}, if\,\alpha^2-\beta^2=0(critically-damped-case)\\ C_1e^{\lambda_1 t}+C_2e^{\lambda_2 t}, if\,\alpha^2-\beta^2>0(overdamped-case)\end{cases}$$

$$where\,\omega=\sqrt{\beta^2-\alpha^2},\lambda_1=-\alpha+\sqrt{-\beta^2+\alpha^2},\lambda_2=-\alpha-\sqrt{-\beta^2+\alpha^2}, and\,\mu,\delta,C_1\,\&\,C_2 are\_constants$$

Proof:

Particular equation of the system is $\lambda^2+2\alpha\lambda+\beta^2=0$

if $\triangle=(2\alpha)^2-4\beta^2>0$, then it has two solutions:

$$\lambda_1 = -\alpha + \sqrt{-\beta^2 + \alpha^2}, \lambda_2 = -\alpha - \sqrt{-\beta^2 + \alpha^2}$$

Thus the solution of the equation are

$$C_1 e^{\lambda_1 t} + C_2 e^{\lambda_2 t}$$

if △=$(2\alpha)^2 - 4\beta^2 = 0$, then it has only one solutions:

$$\lambda = -\alpha$$

Thus one of the solution of the equation is

$$C_1 e^{-\alpha t}$$

However,we can verify that it is also the solution of g'(t), thus

$$\mathrm{t} C_1 e^{-\alpha t}$$

Is the solution as well

Thus the solution of the equation are

$$\left(C_1 + C_2 t\right) e^{-\alpha t}$$

if △=$(2\alpha)^2 - 4\beta^2 < 0$, then it has two solutions:

$$\lambda_1 = -\alpha + \sqrt{\beta^2 - \alpha^2}\, i, \lambda_2 = -\alpha - \sqrt{\beta^2 - \alpha^2}\, i$$

$$\lambda_1 = -\alpha + \omega i, \lambda_2 = -\alpha - \omega i$$

Thus the solution of the equation are

$$\mu e^{-\alpha t} \cos(\omega t - \delta)$$

QED

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

We can easily verify that $\lim_{t \to \infty} g(t) = 0$

if △=$(2\alpha)^2 - 4\beta^2 > 0$, the solution of the equation are

$$C_1 e^{\lambda_1 t} + C_2 e^{\lambda_2 t}$$

When t→infinity，then g(t)→0 for λ_1&λ_2 are both negative and C_1 C_2 are positive.

if △=$(2\alpha)^2 - 4\beta^2 = 0$,the solution of the equation are

$$\left(C_1 + C_2 t\right) e^{-\alpha t}$$

When t→infinity，then g(t)→0 for -α is negative and C_1 C_2 are positive.

if △=$(2\alpha)^2 - 4\beta^2 < 0$, the solution of the equation are

$$\mu e^{-\alpha t} \cos(\omega t - \delta)$$

When t→infinity，then g(t)→0 for -α is negative and μ are positive.

Hence，

$$\lim_{t\to\infty} G(t) = \lim_{t\to\infty}\left(g(t)+G_0\right) = \lim_{t\to\infty} g(t) + G_0 = G_0$$

QED

Now we have for t ≥ 0,

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

(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?
Solution： We can measure a common person after lunch for a long time, we can find a limit value which is the G_0.

(g) In the overdamped case ($\alpha^2 - \beta^2 > 0$), we can find α, β, C_1 and C_2 with some initial value take into the function. 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 = 2π/β. 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 (= 2π/β) 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 non-trivial 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 non-trivial 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.

In the ritically damped or overdamped case, we may find that

$$g'(t)=\begin{cases}\left[C_2-\alpha\left(C_1+C_2t\right)\right]e^{-\alpha t}<0, if\, \alpha^2-\beta^2=0\\ C_1\lambda_1e^{\lambda_1 t}+C_2\lambda_2e^{\lambda_2 t}<0, if\, \alpha^2-\beta^2>0\end{cases}$$

For g(0)>0,thus if data indicate that g(t) changes its sign more than once, we know we are in the underdamped case.

QED

3. Examples

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.

Sol: For 90>70,62<70,81>70,we know that there two times for the value cross the sign-change line. thus it's not the situation in (h),i.e. 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.

Sol: In the underdamped case,

$$g(t)=\mu e^{-\alpha t}\cos(\omega t-\delta)$$

Let g(t)=0,it means $\cos(\omega t-\delta)$=0,the least distance between two zero point is

$$\frac{\pi}{\omega}=\frac{\pi}{\sqrt{\beta^2-\alpha^2}}>\frac{\pi}{\sqrt{\beta^2}}=\frac{\pi}{\beta}=\frac{T}{2}$$

QED

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

In this case, we know that T<3 which is smaller than 4, thus 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 we 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 we find x_1 , x_2 , we just take $\lambda_i = \ln x_i$). Write the system for the unknowns C_1 , C_2 , x_1 , x_2 .

Sol: we have system as follow:

$$\begin{cases} C_1 x_1 + C_2 x_2 = 25 \\ C_1 x_1^2 + C_2 x_2^2 = 0 \\ C_1 x_1^3 + C_2 x_2^3 = -5 \\ C_1 x_1^4 + C_2 x_2^4 = -5 \end{cases}$$

Using **Mathematica**,we can solve these equations:

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In[2]:= Solve[{c1 x1 + c2 x2 == 25, c1 x1^2 + c2 x2^2 == 0, c1 x1^3 + c2 x2^3 == -5,
         c1 x1^4 + c2 x2^4 == -5}, {c1, x1, x2, c2}]
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Out[2]= $\left\{\left\{c1 \to \frac{25}{2}\left(5 - 3\sqrt{5}\right),\ c2 \to \frac{125}{2} + \frac{75\sqrt{5}}{2},\ x2 \to \frac{1}{10}\left(5 - \sqrt{5}\right),\ x1 \to \frac{1}{10}\left(5 + \sqrt{5}\right)\right\},\ \left\{c1 \to \frac{25}{2}\left(5 + 3\sqrt{5}\right),\ c2 \to \frac{25}{2}\left(5 - 3\sqrt{5}\right),\ x2 \to \frac{1}{10}\left(5 + \sqrt{5}\right),\ x1 \to \frac{1}{10}\left(5 - \sqrt{5}\right)\right\}\right\}$

Because of symmetry, we take one of these solutions.

Thus

$$\lambda_1 = \ln[\frac{1}{10}(5-\sqrt{5})] \& \lambda_1 = \ln[\frac{1}{10}(5+\sqrt{5})]$$

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