BME 301B SPRING 2015

CLab 3: Synaptic Transmissions: Insulin & Glucose Model

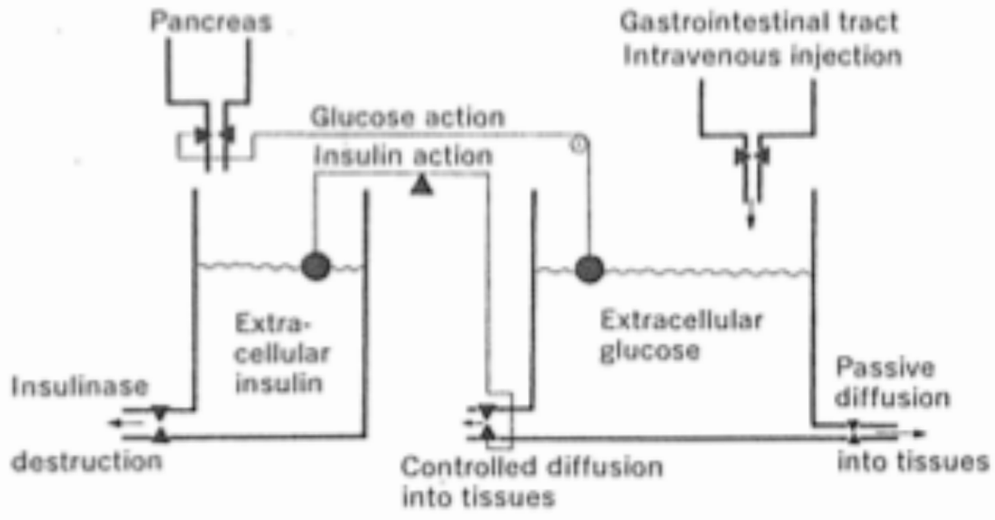

Fig. 57-10. Hydraulic analog of insulin-glucose regulation.

Patricia Widder

Chapter 1

CLab 3: Synaptic Transmissions

Due: Tuesday, February 17, 2015, 11:59:59 pm

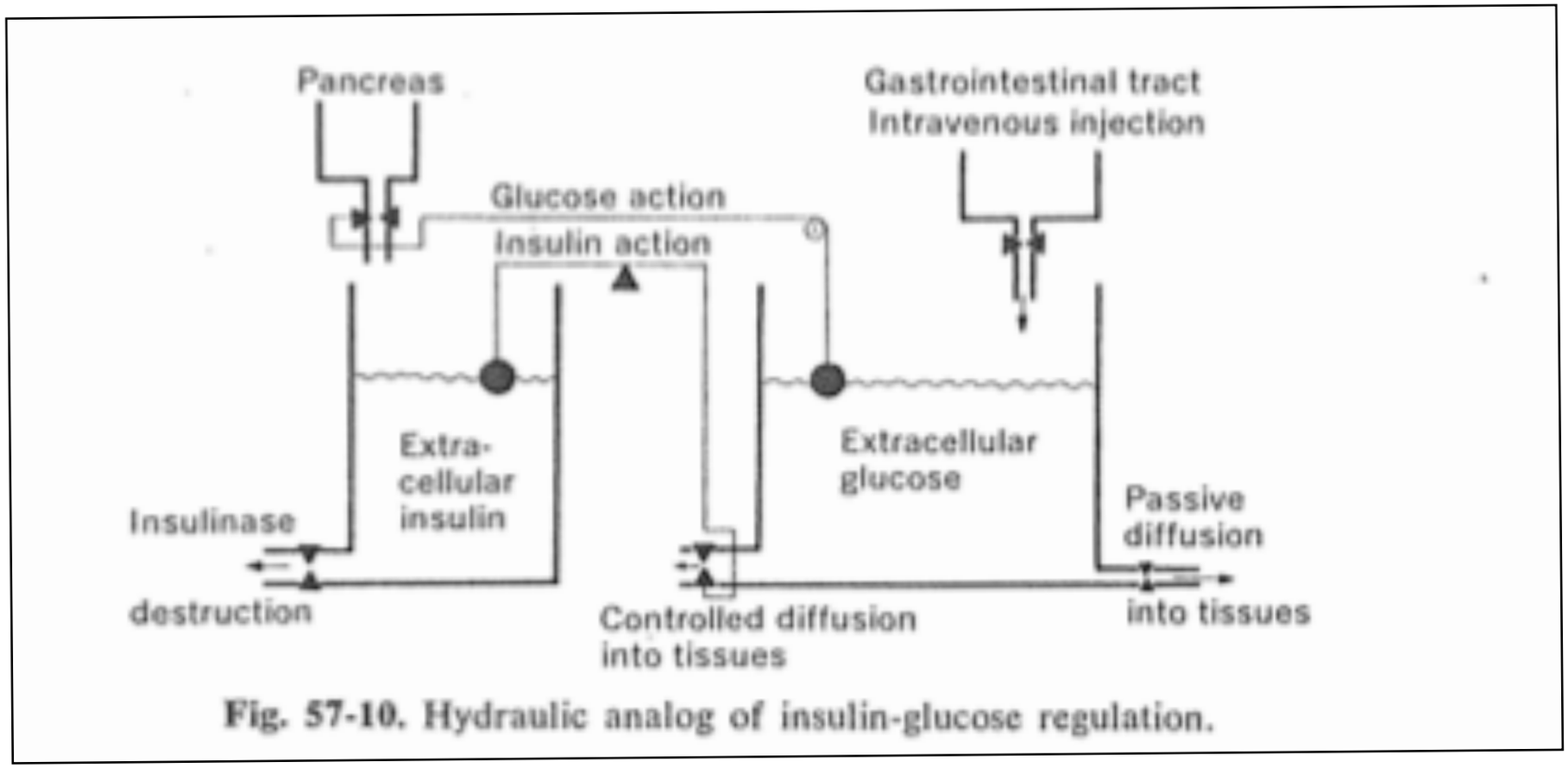

Fig. 57-10. Hydraulic analog of insulin-glucose regulation.

From Stolwijk and Hardy. Regulation and control in physiology. In: Medical Physiology, 13th ed. Mountcastle. CV Mosby, St Louis, 1974, p 1355.

The control system of insulin and glucagon regulates the concentration of glucose in the bloodstream. As blood glucose levels rise, insulin production is increased; low blood glucose concentrations triggers the release of glucagon. Normal glucose regulation as well as Type I and Type II diabetes conditions will be studied and modeled.

Instructions

This lab report should be formatted as if it were a homework assignment, or a CLab report from QP1. No introduction, methods, or results sections are necessary. Just answer the questions with figures and text. Neatness is important. There is no page limit.

Plots must have a title and/or caption which mentions the problem number and sub-question (e.g.: Figure: 1.9 __) . All quantities in figures and answers must be labeled with appropriate units. All MATLAB code must be turned in and must have basic comments. You do not need to turn in your Simulink model(s) unless it is specifically asked for.

All plots must be appropriately zoomed/scaled to clearly show what is happening or important in the simulation. If the important part(s) of a plot is not visible due to scaling, the grader must conclude that the student does not understand the problem.

All work, including code, figures, and text must be your own. Formal and informal references must be clearly stated.

Turn in your report in PDF format to the appropriate location in Blackboard. The report is due at 11:59:59 pm on Tuesday, February 17, 2015.

Contact the lab TA with any questions you have about the lab. Describe your questions clearly and concisely. Please make sure you have done some basic investigation on your own (using Matlab help files, consulting the class references, etc.) before you ask for help.

Background

The physiology control system that relates insulin secretion to glucose levels is both complex and critical to health. Stolwijk and Hardy (1974) developed a mathematical model that described the mechanics of insulin and glucose secretion and uptake. Such models often begin with some basic assumptions, a sketch of the known or predicted physiological interactions, and a conversion to mathematical equivalents. The mathematical model is then tested against experimental data to determine its suitability.

Stolwijk and Hardy first presented an equivalent hydraulic system, with 'vessels' of insulin and glucose, Figure 1.1. The level of the insulin vessel controls the diffusion of extracellular glucose into the tissues, and the level of the glucose vessel controls the release of insulin by the pancreas. These two negative feedback loops work together to maintain a steady-state equilibrium and a controlled response to dynamic changes in the system. Passive removal of insulin and glucose are also shown.

From here, Stolwijk and Hardy used experimental data and estimations of physiological activity to devise mathematical representations of the insulin and glucose processes. Others (Sturis 1991, Tolic 2000, and Bennett 2004) have since expanded Stolwijk's model to include additional detail and complexity.

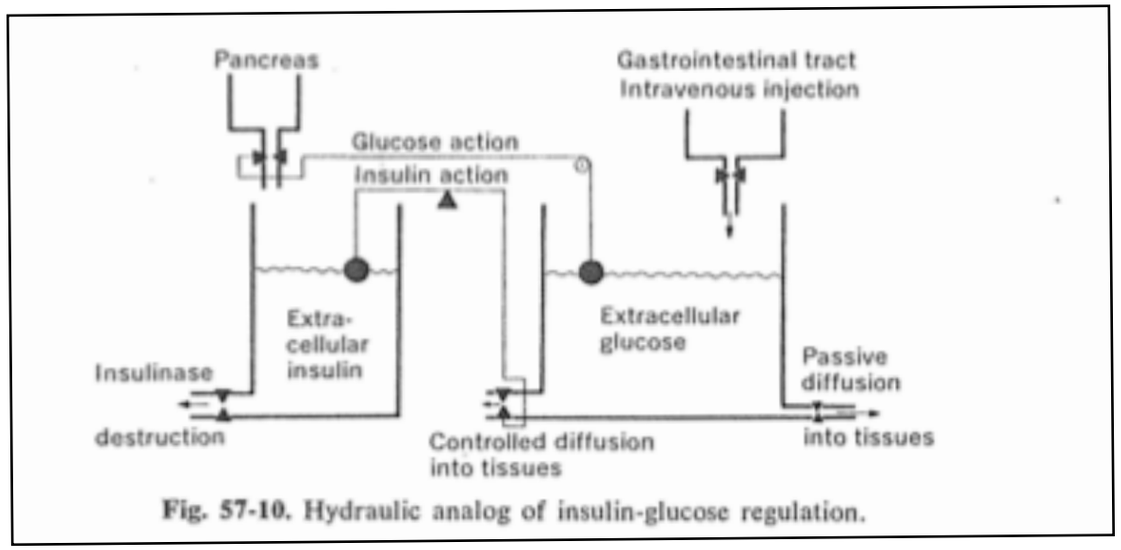

Figure 1.1 Stolwijk and Hardy's (1974) hydraulic analog.

Problem 1: Steady-State Conditions

Glucose Concentration

Glucose enters the bloodstream primarily in three ways: through absorption from the GI tract (from food consumption), intravenous infusion, or supplied by the liver. For the steady-state case, we'll consider only the last two pathways, which will be combined into one constant term Q_L, representing the inflow of glucose.

Glucose leaves the bloodstream by passive diffusion into tissues (insulin-independent), controlled diffusion into tissues (insulin-dependent), and elimination by the kidneys. Let's consider each of these.

In the insulin-independent passive diffusion, the movement of glucose is driven only by the concentration gradient:

$$\text{Insulin-independent tissue utilization} = \lambda G$$

Insulin aids glucose uptake in muscle and adipose tissue, so that movement depends on both the glucose concentration and the concentration of insulin in the blood:

$$\text{Insulin-dependent tissue utilization} = \nu IG$$

Finally, glucose can be excreted by the urine. This happens only when the blood glucose concentration exceeds a threshold level, due to saturation of the transport proteins in the proximal convoluted tubule that ferry glucose from the glomerular filtrate back into the blood. The rate of renal elimination is thus proportional to the difference between blood glucose and the threshold level θ:

$$\text{Renal loss rate:} \quad \begin{array}{ll} = \mu(G-\theta) & G > \theta \\ = 0 & G \leq \theta \end{array}$$

We presume that at steady state, the glucose entering the system is equal to the glucose leaving the system. We can write a mass balance set of equations, incorporating the renal threshold:

$$\begin{array}{ll} Q_L = \lambda G + \nu IG + \mu(G-\theta) & G > \theta \\ Q_L = \lambda G + \nu IG & G \leq \theta \end{array} \tag{1.1}$$

So, λ, ν, and μ are constant coefficients related to glucose utilization, G is the blood glucose concentration, and I is the blood insulin concentration.

Insulin Concentration

We can establish a similar mass balance for insulin. The pancreas produces insulin based on the blood glucose concentration. Below a certain threshold (ϕ) of glucose concentration, no insulin is produced. So:

$$\text{Insulin production rate:} \quad \begin{array}{ll} = 0 & G \leq \phi \\ = \beta(x-\phi) & G > \phi \end{array}$$

Insulin is destroyed by the insulinase enzyme, at a rate proportional its concentration in the blood:

$$\text{Insulin destruction rate} = \alpha I$$

If we presume that at steady state, insulin production is equal to its destruction, we can create a mass balance equation for insulin, relating the steady-state level of insulin to that of glucose:

$$\begin{aligned} I &= 0 & G &\le \phi \\ I &= \frac{\beta}{\alpha}(G-\phi) & G &> \phi \end{aligned} \qquad \textbf{1.2}$$

For a normal healthy adult, we can use the following parameter values:

θ	2.5	mg/ml
μ	7200	ml/h
λ	2470	ml/h
ν	139000	1/(mU*h)
ϕ	0.51	mg/ml
β	1430	mU*ml/(mg*h)
α	7600	ml/h
Q_L	8400	mg/h

(Notice that insulin is given in 'units'; a unit of insulin is approximately 1/24 mg.)

For this problem, you can use either MATLAB or Simulink, as you wish. Turn in your MATLAB code or your Simulink model.

Problem 1.1

Use equations 1.1 and 1.2 to plot insulin vs glucose concentrations at steady state in a healthy adult. Vary your insulin concentration from 0 to 0.2 mU/mL, and vary the glucose concentration from 0 to 2 mg/mL. Determine the steady state operating point; that is, where the two equations are equal to each other. Verify that your operating point is reasonable for a normal adult (provide a reference if necessary).

Problem 1.2

In Type 1 or insulin-dependent diabetes, the main defect is the inability of the islet cells of the pancreas to produce enough insulin. Determine which parameter represents the production rate of insulin, modify it to reflect Type 1 diabetic conditions, and create a new plot showing the changed operating point of a juvenile diabetic. Describe which parameter you changed and why this operating point reflects the condition of juvenile diabetes.

Problem 1.3

In Type 2 or adult-onset diabetes, the main defect is a drastic reduction in the ability of insulin to stimulate glucose uptake by the muscle and adipose tissues. Determine which parameter reflects this ability, modify it appropriately, and create a new plot showing the changed operating point. Describe which parameter you changed and why this operating point reflects the condition of adult-onset diabetes. According to your graph, would treatment with insulin be a useful approach to Type 2 diabetes? Explain.

Problem 1.4

How would you adjust the parameters or variables of this model to reflect each of the three conditions described in Homework 2, problem 6? Present your reasoning for each along with a new plot showing the revised operating point.

Problem 2: Dynamic Conditions

From Stolwijk, we can extend the steady state equations for glucose to include dynamic response (notation changed from Stolwijk to match previous section):

$$C_G\frac{dG}{dt} = U(t) + Q_L - \lambda G - \nu GI \qquad G \le \theta \qquad \textbf{1.3}$$
$$C_G\frac{dG}{dt} = U(t) + Q_L - \lambda G - \nu GI - \mu(G-\theta) \quad G > \theta$$

where C_G is the glucose capacitance in the extracellular space and U(t) is the time course of the addition of glucose into the bloodstream (through food consumption, for example). The equations in 1.3 basically state that the rate at which the glucose concentration of the blood increases or decreases is equal to the difference between the rate at which glucose is added and the rate at which it is eliminated.

Similarly, we can extend the insulin equations to be:

$$C_I\frac{dI}{dt} = -\alpha I \qquad G \le \phi \qquad \textbf{1.4}$$
$$C_I\frac{dI}{dt} = -\alpha I + \beta(G-\phi) \quad G > \phi$$

where C_I is the insulin capacitance of the extracellular space.

Using Simulink, build a model representing the equations of 1.3 and 1.4. Use the constants from Problem 1, along with $C_G = C_I = 15000mg$.

Set the simulation time to 5 hours. Note that you do NOT need to enter that as 5*60*60 seconds in the simulation time window. Because all of our variables have time units of hours, setting the simulation time to just '5' will mean 5 hours when you run it, even though the default time unit is given as seconds. If you put 5*60*60 seconds in the time window, you'll have to convert all of the variables to be in terms of seconds also. (In other words, think of the time unit for this simulation to be hours, even though it's called seconds.)

Use a pulse generator block for U(t), with an amplitude of 100000 mg/h, period 5 hours, time step 0.01 hour, duty cycle 5%, starting at t=0.5 hours. This represents a glucose infusion occurring for a duration of 0.25 hours, starting at t=0.5 hours.

Think carefully about the initial conditions for your integrator blocks.

There are at least two ways to implement the threshold conditions of θ and ϕ; you can either use saturation blocks or 'Compare to Constant' blocks. Saturation blocks are a good way to set upper or lower limits to an output. The Compare to Constant block outputs a 0 if the comparison is false and a 1 if the comparison is true.

Problem 2.1

Plot the time course of the response of glucose and insulin concentrations to the glucose input U(t), for both the normal and the Type 2 diabetic condition. Describe your findings. How does this correlate with your plots in Problem 1?

Problem 2.2

Review the Stolwijk article, beginning with the last two paragraphs at the bottom of page 1354 and continuing until the middle of page 1357.

What major physiological process involved in glucose regulation is not represented in this model? Why do you think it was not included in the model (other than perhaps the researchers were exhausted from empirically determining all of the constants in the existing model)?

List at least two other simplifications that were made when creating the model, and why they are justified.

Problem 2.3

What terms of the model create nonlinearities? Using your graphs from Problem 1, estimate what range of insulin and glucose concentrations might be 'linear enough' to apply frequency response analysis, a linear technique. How might frequency response analysis be useful?

Shown in Figure 1.2 are frequency responses generated for our model using the Spectrum Analyzer block of Simulink. The top panel relates glucose infusion to glucose concentration; the middle relates glucose infusion to insulin concentration; and the bottom panel relates glucose concentration as the input to insulin concentration as the output. What can you deduce from these three graphs about the dynamic behavior of insulin and glucose?

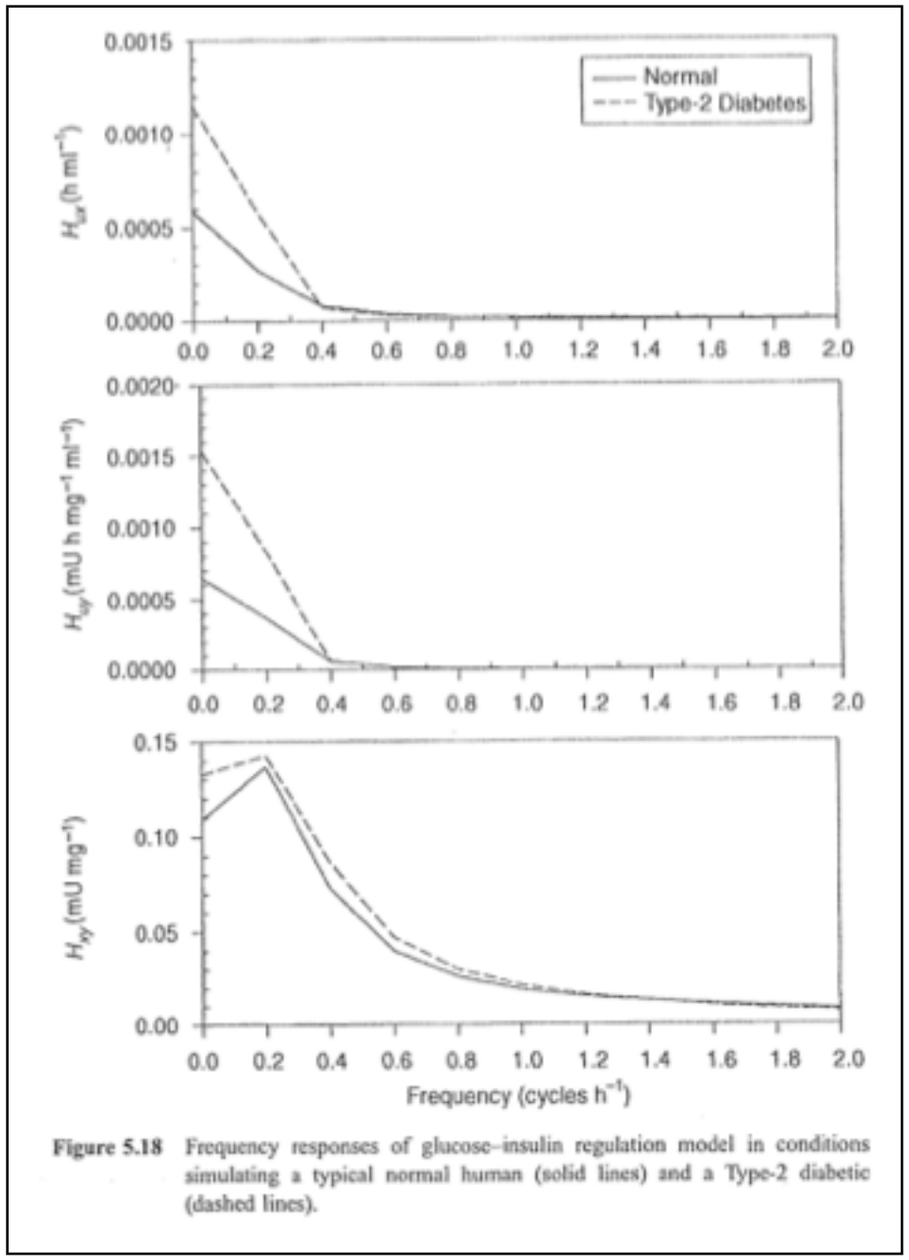

Figure 5.18 Frequency responses of glucose–insulin regulation model in conditions simulating a typical normal human (solid lines) and a Type-2 diabetic (dashed lines).

Figure 1.2 Frequency response of glucose-insulin model. From Khoo,2000.

Problem 3: Ultradian Oscillations of Insulin and Glucose

It has been observed experimentally that the secretion of insulin in normal conditions is not a smooth ramp dynamic; in fact, secretion of insulin occurs in at least two oscillatory modes, one rapid (period 8-15 min) and one ultradian (period 100-150 min). Experimental studies show that the rapid oscillations of insulin secretion are of small magnitude and are superimposed upon the longer and larger amplitude ultradian oscillations (Simon, 1987). The cause of these rapid and ultradian oscillations is not well understood.

Some studies (Stagner, 1980) suggest that the rapid oscillations of insulin are due to the activity of an intrinsic pancreatic pacemaker. Other researchers (Simon, 1987 and others) suggest that the oscillations are a dynamic property of the insulin-glucose feedback system, without the need for a pancreatic pacemaker.

Sturis et al (1991) proposed a mathematical model of insulin-glucose regulation that could predict and describe the oscillatory behavior of insulin and glucose as an intrinsic part of the insulin-glucose feedback system. Their model suggests that the existence and properties of the oscillations can be entirely accounted for within the insulin-glucose feedback system, without the need to postulate a pancreatic pacemaker.

Two important elements were added to the original model from Stolwijk that bring oscillatory behavior into the system. One is the separation of insulin into two compartments, plasma insulin and interstitial insulin. The other is the introduction of a time delay between the introduction of insulin into the plasma and the resulting production of glucose by the liver.

Sturis modeled this time delay as a three-stage filter. Bennett (2004) presented a different approach to the time delay by representing it as an explicit delay in the hepatic production function.

Problem 3.1

Compare the terms in the differential equation for glucose in Equation 1.3 (assume $G \leq \theta$) to the differential equation for glucose in Bennett Equation 2.1, page 190. Identify which terms in each equation correspond to external glucose input, glucose production by the liver, insulin-dependent glucose uptake, and insulin-independent glucose uptake.

Execution of a model of the systems of equations in Sturis and Bennett shows that the oscillatory behavior of insulin and glucose in the model disappears if the insulin compartments are combined or if the time delay is too large or too small. Why do you think the addition of these two elements allows oscillatory behavior to occur?

Problem 3.2

Using the MATLAB script and Simulink model given to you, plot the time course of insulin and glucose concentrations at three different external glucose infusion rates with tau=12 minutes.

Next, show how different values of tau affect the oscillatory behavior of the response. Determine a range a values for tau where oscillatory behavior occurs.

Problem 3.3

Create plots of f_1 vs G, f_2 vs G, f_4 vs I_i, and f_5 vs I_p. (You can copy and paste the functions out of the Simulink function blocks.) Use a range of 0 to 40000 mg for G, 0 to 2000 mU for I_i, and 0 to 200 mU for I_p.

The exact terms of the f functions are not physiologically significant, but instead were chosen to give the correct relative quantitative behavior. Relate the shape of each function curve to the physiological process that it is intended to represent.

Problem 3.4

In response to a pulse of glucose, the rate of insulin release shows a biphasic response, as shown in the left side of Figure 1.3. Describe the physiological processes that lead to this biphasic secretion, and the effects of each phase.

How would you begin constructing a mathematical model of this behavior? You can begin with the equations from the Bennett or Stolwijk papers, or design your own equations. This can be very general; the idea is to think about the dynamic processes and how they should look, similar to the f functions of Problem 3.3. There will be many possible answers; just lay out a basic plan.

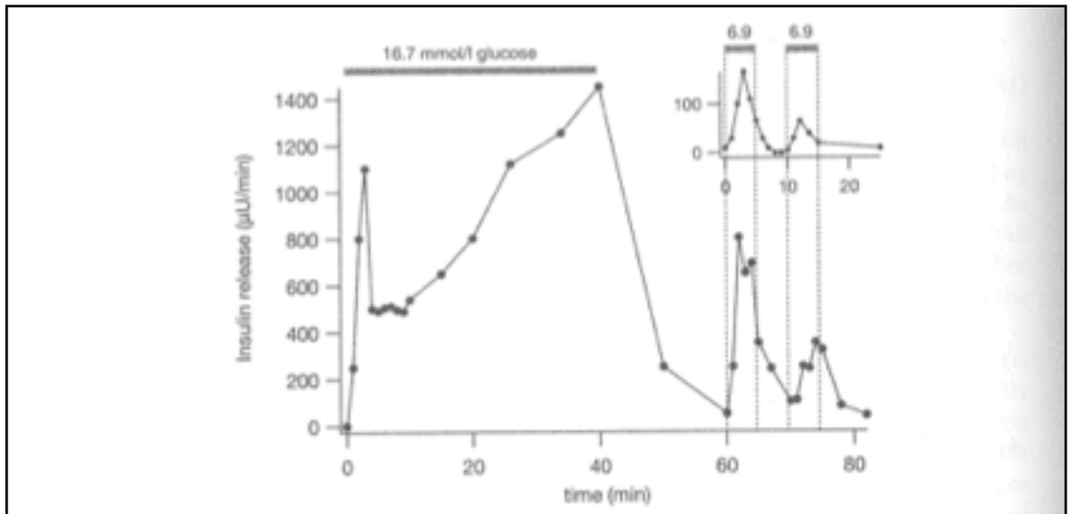

Figure 16.25 The response to glucose of the rate of insulin release in the perfused rat pancreas. The inset at the top right show the response to two glucose steps (each of size 6.9 mmol/l) while directly below the inset is shown the response to two identical glucose steps, but after the pancreas has been primed by the prior addition of 16.7 mmol/l glucose for 40 minutes (Nesher and Cerasi, 2002). We thank Professor Erol Cerasi for providing the original data for this figure.

Figure 1.3 Biphasic release of insulin, from Keyner & Sneed (2009).

References

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