

# Physiological Simulations: Plasma Glucose Regulation<sup>1</sup>

Physiology – Biology 390

## **I. An Introduction to this Lab and to Models<sup>2</sup> in General:**

The purpose of this exercise is to use a computer simulation to enhance your understanding of diabetes mellitus. It is assumed that you have basic familiarity with a glucose tolerance test (GTT) from lab and that you know the differences between:

- (i) Insulin-dependent diabetes mellitus (IDDM or Type I)
- (ii) Non-insulin dependent diabetes mellitus (NIDDM or Type II).

You should also find out the difference between *diabetes mellitus* and *diabetes insipidus*.

! One good source for additional information (although it is somewhat dated at present) is a review article on diabetes mellitus by Bennett (1983). *Annual Review of Medicine*. **34**, 295-309. This is in the stacks in the CHC Science Library

**About Simulations in General (Models):** Simulations are abstractions of a process used:

- to allow someone to increase their understanding of the process by seeing if they can correctly predict the result or various changes in variables that affect the process
- to generate testable hypotheses in the case of systems that are relatively complex. The individual elements of the simulation (constants, functions and the inter-relationships of these) are either known parameters or represent hypotheses in themselves. The model (simulation) is tested by seeing how well it behaves in accordance with actual observation.

With the advent of digital computing, simulation became a powerful tool in both education and research. In principle, any process that can be abstracted into one or more inter-related equations can be modeled or simulated.

### **About this Simulation:**

Your introduction to simulations is based on the work of Stolwijk and Hardy (1974 -- *Regulation and Control in Physiology*. Ch. 57 in *Medical Physiology*, 13th edition by V.B. Montcastle, ed. Mosby, St. Louis MO). James Randall constructed a simulation in the computer language BASIC (see *Microcomputers and Physiological Simulation*, 1980, Addison-Wesley, Reading MA) and I have translated ("ported" in computerese) the program to LabView and made some modifications and additions.

Your simulation calculates the concentration of glucose in the total extracellular body fluid ("the extracellular fluid compartment"). Plasma is part of this compartment. One uses the extracellular fluid compartment because glucose can freely move between the plasma in the capillaries to the extracellular fluid that bathes all of the solid tissues. So, if glucose is added to the plasma, some of it will quickly diffuse into the non-plasma extracellular space (intercellular fluid) and the entire compartment will come into equilibration.

Calculations are based (surprise) on the difference between gains to this fluid and losses.

---

<sup>1</sup> Copyright © 2015 by K. N. Prestwich, Dept. Biology, Holy Cross College, Worcester MA 01610, kprestwi@holycross.edu

<sup>2</sup> "Simulation" and "model" are similar terms and can usually be taken as synonyms. Most properly, a model is a series of equations and input parameters that may or may not be on a computer. A simulation uses a model within a computer program or some other type of device.

I. **Gains to the extracellular fluid compartment's glucose pool are seen to come from two sources:**

(a) infused glucose -- in this experiment we will assume that we infuse glucose over a 30 minute period at some rate instead of by ingestion. You will be able to vary that rate

(b) Glycogenolysis in the liver.

? How is glycogenolysis controlled? (from class)

II. **Losses from the extracellular fluid compartment are:**

(a) "**First order losses**": even without insulin, glucose can be taken into cells and metabolized. These are passive losses -- no active (~P-utilizing) processes are required. Entry into cells (a loss from the extracellular fluid compartment) is determined by:

- the concentration gradient between the cell and extracellular fluid
- the permeability or conductance,  $G$ , of the cell to glucose.

We will symbolize the non-insulin dependent conductance of glucose into cells as  $G_1$  and we'll call it the "**first-order rate constant for glucose uptake into cells**". It will have units of glucose / time).

So, the equation for the first order loss of glucose from the extracellular fluid compartment to cell is:

eq. 1. **First order loss =  $\Delta[\text{glucose}] * G_1$**

(b) **Renal Losses**: If plasma glucose concentrations reach a high enough value, losses can occur via the kidney. We will learn how the kidney handles glucose in more detail later in the course but for the moment we can simply say that it operates by filtering the blood such that all small particles, including glucose, pass through the filter. Next, the kidneys reabsorb needed substances such as glucose. With normal levels of plasma glucose, all the glucose that ends up in the filtrate is transported back by specific transport proteins. However, like any protein system, the transport system can become saturated. If glucose concentrations in the plasma (and therefore the filtrate) are too high, not all of the glucose in the filtrate will be captured and some will be lost in the urine. The point where this first occurs is called the **renal threshold**,  $T_{GL}$ . The actual rate of loss will be proportional to the difference between this level and the actual [plasma glucose].

As with all other equations, we will also need a rate constant which gives the rate at which glucose is lost per unit the [plasma glucose] exceeds  $T_{GL}$ . We'll call this rate constant  $L_{kidney}$ .

Here is the equation:

eq. 2. **Loss in the urine =  $([\text{plasma glucose}] - T_{GL}) * L_{kidney}$**

(c) "**Insulin Controlled Losses**": Clearly glucose removal from the extracellular space can also be altered by insulin on any of its target cells (e.g., mostly muscle, liver, and adipose). In this case, insulin causes the conductance of the cell to glucose to increase by unleashing a transport system (it is also passive). The insulin-controlled loss is a function of:

- the glucose concentration gradient
- the insulin activity,  $I$ , where insulin is given in activity units (mg glucose transported / (hour \* conc. gradient)). This is simply a measure of the amount of insulin present, just as enzyme activity, although given as a reaction rate, is a measure of the amount of enzyme present.

- the sensitivity of the cells to insulin,  $S_I$ . This factor can be seen as a dimensionless number that relates to the number of functional **insulin receptors on the target cells**.

Thus the controlled loss (in mg) is the product of

**eq. 3. Controlled loss =  $\Delta[\text{glucose}] * I * S_I$**

Notice that the **solution to this equation is strongly dependent on the concentration (activity) of insulin**. So, the controlled loss will depend on what the pancreas is doing -- how much insulin does it release in response to a given change in the concentration of glucose. Although not usually a variable factor, the insulin concentration will also depend on the rate of insulin loss. This is covered in more detail in the next paragraph.

### III. Factors that Affect the Concentration (Activity) of Insulin:

The rate insulin is released by the pancreas into the blood is proportional to the difference between the plasma glucose present at some moment and a genetically set reference value. We will symbolize the genetically set reference concentration of glucose as  $[\text{glu}]_{\text{ref}}$ .

! Note that in this model  $[\text{glu}]_{\text{ref}}$  is not the same thing as the set point or set range that we considered earlier with negative feedback models. This reference value is very much lower than the actual set range for [plasma glucose]. The reason is that the pancreas always releases insulin so as to facilitate the uptake of glucose. Even at dangerously low [plasma glucose], the pancreas still releases insulin, albeit in very small amounts. So, the  $[\text{glu}]_{\text{ref}}$  value is the value where zero insulin would be released (very close to a fatally low concentration). At any [plasma glucose] above this, the release is greater.

Insulin release is also proportional to a rate constant we'll call the absolute insulin release rate  $R_{\text{insulin}}$ . This parameter gives the rate of release of insulin for a unit difference in the [plasma glucose] from the  $[\text{glu}]_{\text{ref}}$ . So, the addition of insulin to the extracellular fluid is given as

**eq. 4. Addition of Insulin =  $([\text{glucose}]_{\text{plasma}} - [\text{glu}]_{\text{ref}}) * R_{\text{insulin}}$**

The removal of insulin is a function of a **degradation rate**  $D_{\text{insulin}}$  determined by general protein degradative processes and by the rate that insulin binds to insulin receptors. It is also a function of plasma insulin concentration (since insulin is taken up by receptors at a higher rate when insulin is in higher concentrations). Thus:

**eq. 5. Degradation of Insulin =  $[\text{insulin}] * D_{\text{insulin}}$**

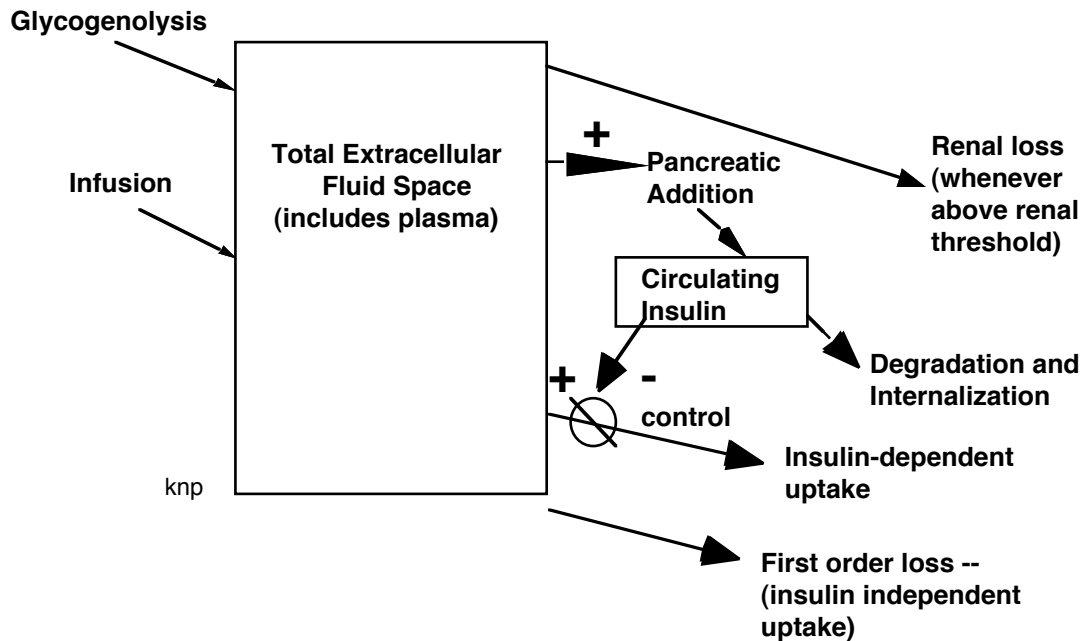
So, at any moment in time, the amount of insulin present is a function of the concentration a moment ago plus the any added insulin minus the removed (what an awesome conclusion!).

#### Calculations in the Simulation :

The actual simulation works by starting with the present glucose concentration and then adds any glucose added by infusion or glycogenolysis. It next subtracts the renal, first order and insulin-controlled losses and finally it calculates the new level of insulin (for the next iteration) by adding whatever has come from the pancreas in the past time interval to what was already there and then by subtracting whatever insulin had been lost.

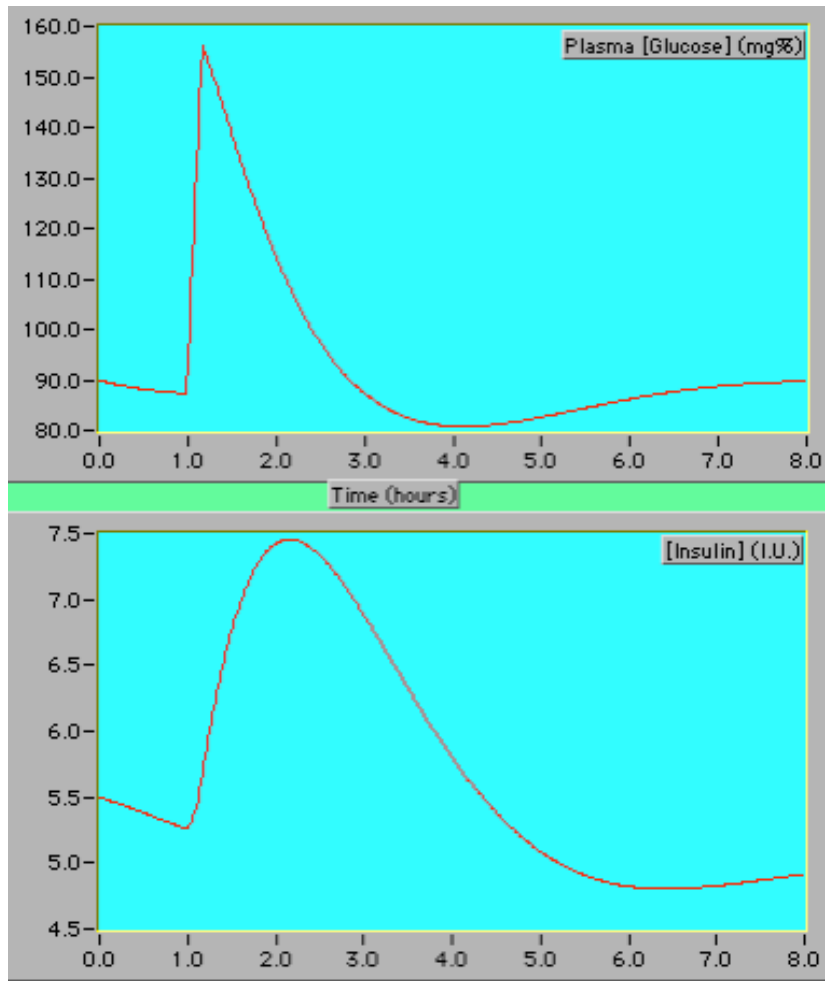
This process can be viewed as a series of inputs and outputs into two pools -- the total glucose and insulin pools. The balance between the inputs and outputs determine the size of each of these pools. In addition they interact by determining the amount of insulin secreted and by altering the rate of insulin dependent tissue uptake. This is summarized on the next page:

**Plasma [glucose] and [insulin] regulation. Inputs and outputs to the circulating pools as envisioned by the simulation.**



**Using the Simulation:**

**Plots:** In the simulation, you will see two plots. The top plot is of plasma glucose concentration and the lower plot is insulin activity (concentration). **The values on the Y axes will be automatically redefined as you change conditions** so that the plots will always fill most of the available space on the graph. You can see a picture of the graphical display on the next page:



**Variables Under Your Control and Some Suggestions:**

The simulation will enable you to control the following variables (and some others):

**1. Time (amount) of glucose infused into a subject.** You will control the total infusion time with two inputs, total time and rate. The greater the amount of time used or the greater the concentration, the more total glucose will enter the subject (tough, huh!). You can easily calculate the actual amount of glucose entering given the rate of infusion (80 g/h) and the time of infusion. For most experiments, you will probably want to use a constant amount of glucose, that is, a constant infusion interval and rate. The default setting is adequate for most situations. However, you will also want to see what happens in normal and abnormal situations when both very large and very small infusions are made.

? How would you make an infusion of 0 glucose?

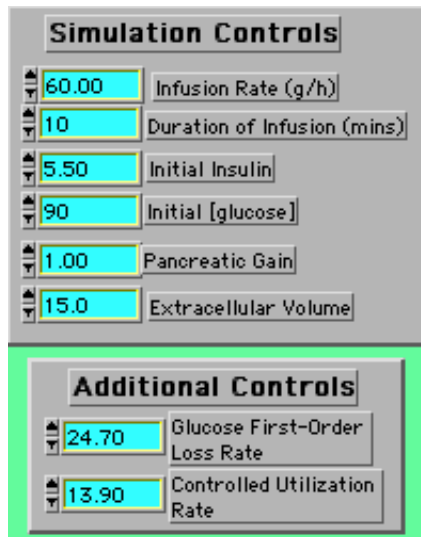
**2. Initial amounts of insulin.** The default value is a good one for someone who has not eaten recently and is not a diabetic. Think about what you would expect for type I and II diabetics who had not eaten recently. (Note: we are assuming uncontrolled diabetes).

**3. Initial plasma glucose concentration ([glu]).** The default value is typical for a normal individual who has fasted for 6 hours. How would these values look in uncontrolled diabetics?

**4. Pancreatic Gain:** the sensitivity of the pancreas to a change in plasma [glu]. A gain of 1 is normal, gains below 1 mean that the pancreas releases less than normal (including no) insulin in response to an increase in [glu]. It is multiplied by the rate constant used in eq. 4,  $R_{insulin}$ .

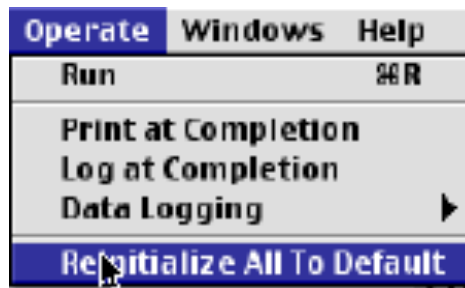
**5. The first-order and insulin-controlled utilization rates** (see previous discussion). How would these change in different disease or activity states?

**Changing Values:** The controls display looks something like this:



You can change values by simply moving the mouse pointer over the value you want to change. An insertion bar (something like `]]`) appears. If you drag across the present value you can then re-enter an entire value. Or, if you only want to change part of the number, place your insertion point just to the right of what you want to change, delete and then re-enter.

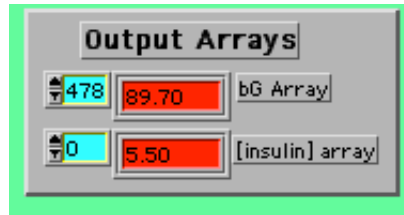
You can reset the values of all of the controls to their original default mode by going to the top menu and looking under **operate** and then select **Set All To Default Values**:



If you wish to reset a single value only to its default ("normal") value then:

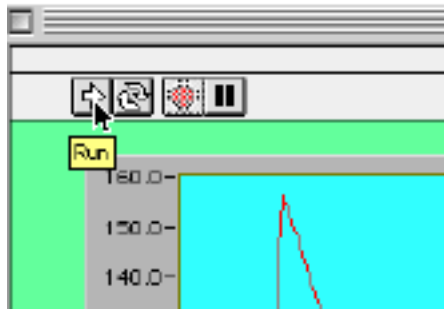
- (i) put the mouse POINTER ON THE CONTROL YOU WISH TO ALTER,
- (ii) press the MOUSE BUTTON AND HOLD it, also press the COMMAND key
- (iii) CAREFULLY select "RE-INITIALIZE TO DEFAULT"

**The Output Array Boxes:** We won't use these but they look like this:



You can use them to find exact numerical values for any point. However, we will probably not use them.

**To Run the Program:** After you have set the values, run the program by clicking on the single (right facing) arrow icon:



It stops automatically after running a given simulation.

## II. Try These Simulations:

1. Get familiar with the model by running it using the default values and then modifying each value, one at a time to get a feel for both the general effect of the modification and for the relationship between the size of the response and the size of the perturbation that you have selected.

**DO NOT HURRY THROUGH THIS PART, IT IS PROBABLY THE MOST IMPORTANT PART OF THE EXERCISE.**

2. Make several simulations of IDDM and NIDDM. Before you come to lab, decide and write down which of the variables are most important to modify to simulate these disease states. Decide the size of the change based on your knowledge of these diseases and on what you have observed about the responsiveness of the computer.

3. Given an IDDM state, see what happens if you try to cure it with extra insulin. See what happens in NIDDM.

4. Try at least one additional thing that you are interested in doing.

Take notes on what you see: look at all aspects of each simulation. Do not treat this like it was a video game and hurriedly run from one simulation to the next. It can be an excellent learning tool if you use it as one. Generally, you will need several minutes for adequate study of each simulation.