Glucose Regulation in Diabetes

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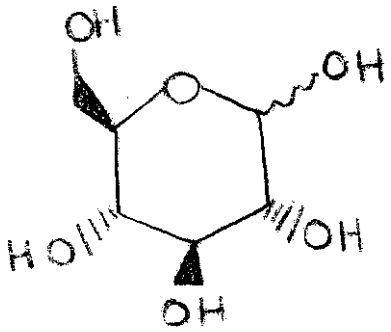

Glucose

Abstract

Complicated and extensive models of glucose regulation, involving several variables, have been developed over the years. Our research specifically focuses on the feedback loop between insulin and glucagon. Although our model is simpler than a model including state variables such as non-esterified fatty acids concentration in the blood plasma, β-cell mass, TAG content of lipocytes, and/or leptin concentrations in the blood plasma, we are still able to simulate most of the key effects of diabetes and other health problems on glucose regulation; such as, hyperglycemia, hyperinsulinism, and insulin shock (hypoglycemia). We are even able to simulate eating a bowl of vanilla ice cream!

Introduction

For most of our qualitative and quantitative experimentations we worked with MATLAB, a computer programming language and data visualization software, which offers a rich set of tools for solving problems in engineering, scientific, computing, and mathematical disciplines, such as a graphical user interface.

Our model is a refinement of a realistic model developed by Cobelli et al. (1982). Despite the fact that the paper is nearly 28 years old, the experimental data of diagnostic tests used by medical professionals, such as the Intravenous Glucose Tolerance Test (IVGTT), correlates with our simulated graphs.

From a Biological Perspective

Regulation in a Healthy System

In order for us to model any biological system, we need to first understand exactly what is happening within a human body. We need to ask what causes this effect and why. To answer these questions we need to identify the key organs and hormones, and then see how they interact within our bodies.

The key organs that control blood glucose are the pancreas and the liver. The key hormones are insulin and glucagon. In the pancreas, there are clusters of endocrine cells scattered throughout the tissue. These are the α-cells and the β-cells. The α-cells produce glucagon and the β-cells produce insulin. The pancreas secretes these antagonistic hormones into the extracellular fluid, which then enters the circulatory system and regulates the concentration of glucose in the blood. For biologists, this is known as a simple endocrine pathway.

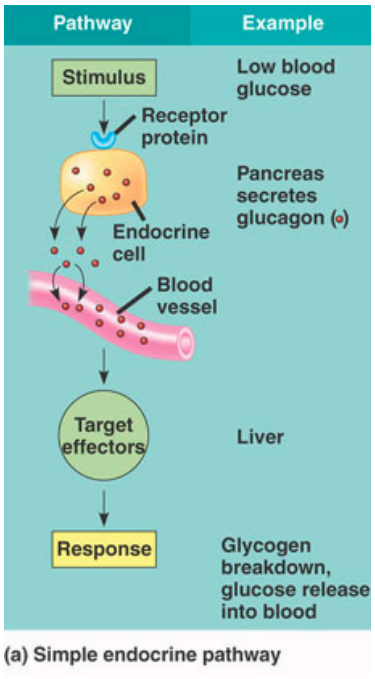

Diagram 1: Simple Endocrine Pathway
Courtesy of Campbell and Reese's Biology

The next question is: How does insulin and glucagon regulate the concentration of glucose in the blood? This is where a diagram is very useful visual tool.

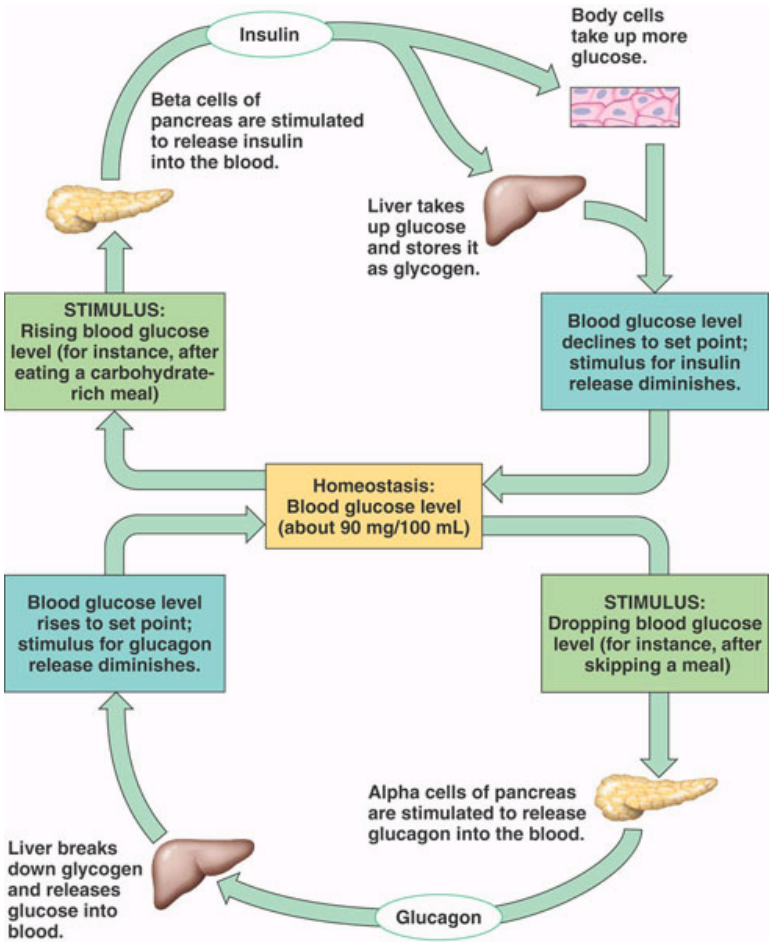

Diagram 2: Glucose Regulation from a Biological Perspective
Courtesy of Campbell and Reese's Biology

Above we observe that homeostasis* in a normal system is achieved by maintaining a blood glucose level of about 90mg glucose/100mL of blood. This balance is disturbed by a stimulus such as eating a meal or skipping a meal.

When we eat a meal, our blood glucose level rises because we absorb sugar and carbohydrates into our blood via our digestive system. Consequently, blood glucose exceeds the set point of 90mg/100mL and the β-cells of the pancreas release insulin into the blood. Insulin then travels through the circulatory system and signals the liver and body cells to take up glucose and store it as glycogen. The blood glucose level declines to the set point and the stimulus for insulin release diminishes as we return to homeostasis.

After we skip a meal, our blood glucose level drops because our bodies have used up most of the glucose that was already in the blood from the previous meal. As a result, blood glucose drops below the set point and the α-cells of the pancreas release glucagon into the blood. Glucagon then travels through the circulatory system and signals the liver to break down its glycogen stores and release them into the blood as glucose. The blood

* The steady-state physiological condition of the body.

glucose level rises to the set point and the stimulus for glucagon release diminishes and we return, yet again, to homeostasis.

This insulin-glucagon negative feedback loop allows for precise regulation of the blood glucose.

Regulation in a Diabetic System

Diabetes Mellitus is an endocrine disorder caused by a deficiency of insulin (Type I Diabetes) or a decreased response to insulin in target tissues (Type II Diabetes).

Type I Diabetes (insulin-dependent diabetes) is an autoimmune disorder in which the immune system destroys the β-cells of the pancreas. As a result, the person's ability to produce insulin is greatly inhibited. Diagnosis usually occurs in early childhood and is treated with insulin injections.

Type II Diabetes (insulin-independent diabetes) is caused by a deficiency of insulin or, more commonly, a reduced responsiveness of insulin target cells due to some change in the insulin receptors. Heredity can play a role, but research indicates that excess body weight and lack of exercise significantly increases risk. It generally appears after age 40, but young people who are overweight and sedentary can develop the disease. More than 90% of people with diabetes have type II and many can manage their blood glucose level with regular exercise and a healthy diet; however, some do require drug therapy.

From a Mathematical Perspective

Regulation in a Healthy System

We worked with the Cobelli et al. (1982) model because it is of intermediate complexity and, as such, this model is sophisticated enough to improve its utility in diagnosis, yet simple enough to pass validation tests. This model incorporates many of the important mechanisms, but it is fit to a particular patient. As a result, this model is parameterized so that it can be scaled around the "normal" operating conditions of the patient. This is achieved by using the hyperbolic tangent function to describe a monotonically decreasing function that corresponds to a negative feedback relation between the dependent and independent variables.

The state variables and auxiliary variables used in the glucose-insulin model are:

Table 1: Variables used in the glucose-insulin model.

STATE VARIABLES	
c	glucagon in plasma and interstitial fluids (nU)
g	glucose in plasma and extracellular fluid (mg)
i	interstitial fluid insulin (μU)
l	liver insulin (μU)
p	plasma insulin (μU)
r	releasable pancreatic insulin (μU)
s	stored pancreatic insulin (μU)

AUXILIARY VARIABLES

NHGB	Net Hepatic (liver) Glucose Balance (F_1-F_2)
F_1	Liver glucose production rate
F_2	Liver glucose uptake rate
F_3	Renal (kidney) glucose excretion rate
F_4	Peripheral system (muscles) glucose use rate
F_5	Non-peripheral system (central nervous system and red blood cells) glucose uptake rate
F_6	Insulin secretion rate
F_7	Glucagon secretion rate
I_g, I_p	Glucose, insulin ingestion rate
W	Insulin synthesis rate

Courtesy of Cobelli et al. 1982 and Haefner's Modeling Biological Systems.

The state variables and auxiliary variables are related by the following differential equations:

$$\frac{dg}{dt} = NHGB - F_3 - F_4 - F_5 + I_g(t) \tag{1}$$

$$\frac{dc}{dt} = -h_{02}c + F_7 \tag{2}$$

$$\frac{di}{dt} = -m_{13}i + m_{31}p \tag{3}$$

$$\frac{dl}{dt} = -(m_{02} + m_{12})l + m_{21}p + F_6 \tag{4}$$

$$\frac{dp}{dt} = -(m_{01} + m_{21} + m_{31})p + m_{12}l + m_{13}i + I_p(t) \tag{5}$$

$$\frac{dr}{dt} = k_{21}s - k_{12}r - F_6 \tag{6}$$

$$\frac{ds}{dt} = -k_{21}s + k_{12}r + W \tag{7}$$

The physiological processes, defined by the auxiliary variables, depend on the concentrations of the state variables in the model. Consequently, we must convert the absolute quantities of the state variables into concentrations by dividing each state variable by the volumes of the tissues in which they are confined. We define the following concentrations:

$\bar{g} = \frac{g}{V_b}$ concentration of glucose in plasma and extracellular fluid

$\bar{p} = \frac{p}{V_p}$ concentration of plasma insulin

$\bar{l} = \frac{l}{V_l}$ concentration of liver insulin

$\bar{i} = \frac{i}{V_i}$ concentration of interstitial fluid insulin

$\bar{c} = \frac{c}{V_b}$ concentration of glucagon in plasma and interstitial fluids

where V_b is the volume of blood and extracellular or interstitial fluids (0.2 of body weight divided by blood density), V_p is the volume of plasma (0.045 of body weight divided by plasma density), V_l is the volume of liver (0.03 of body weight divided by liver density), and V_i is the volume of interstitial fluid (0.10 of body weight divided by interstitial fluid density).

We then standardize each of these concentrations by subtracting the patient's basal (or normal) concentration from the above concentrations:

$\Delta\bar{g} = \bar{g} - g_{basal}$ standardized concentration of glucose

$\Delta\bar{p} = \bar{p} - p_{basal}$ standardized concentration of plasma insulin

$\Delta\bar{l} = \bar{l} - l_{basal}$ standardized concentration of liver insulin

$\Delta\bar{i} = \bar{i} - i_{basal}$ standardized concentration of interstitial fluid insulin

$\Delta\bar{c} = \bar{c} - c_{basal}$ standardized concentration of glucagon

Also, note that the doubly and triply subscripted letters are constants.

The Cobelli et al. (1982) model is based on three major subsystems: insulin, glucose, and glucagon. The systems are related in the diagram below:

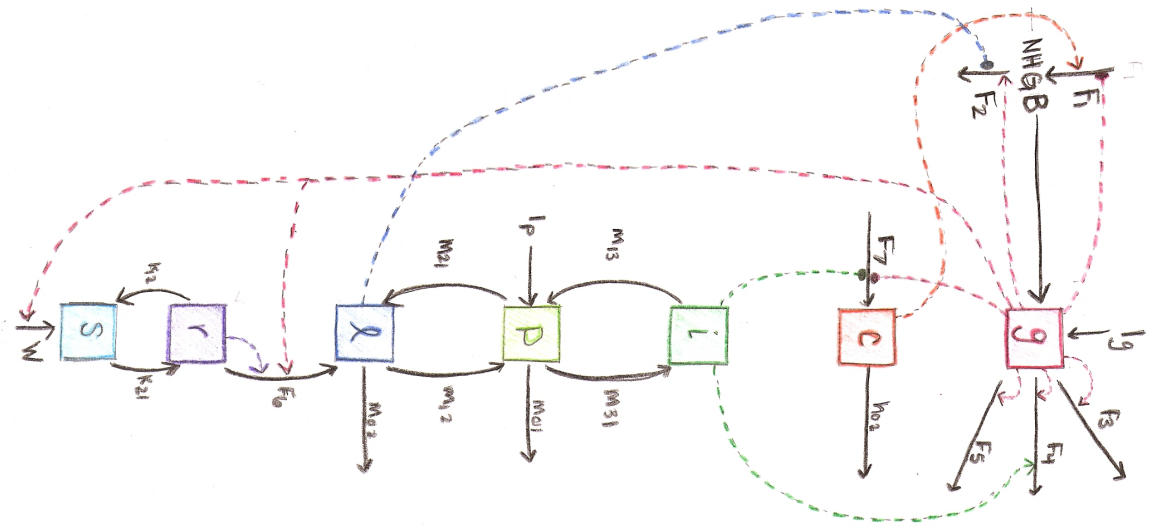

Diagram 3: Model of the glucose-insulin regulation system based on three major subsystems: insulin, glucose, and glucagon.
Note: Fluxes are represented as double arrows. Endocrine interactions are shown as dotted arrows: positive as normal arrowheads, negative as flattened diamonds, modulatory as circles.

Glucose Subsystem

Equation (1) describes how glucose in the plasma and extracellular fluid is produced in the liver and the stomach. The net hepatic glucose balance (NHGB) is the difference between liver glucose production (F_1) and uptake (F_2). The liver glucose production rate, F_1, is limited by three factors: the standardized concentrations of glucose, liver insulin, and plasma glucagon. Glucagon stimulates the breakdown of glycogen to glucose (G_1), whereas, liver insulin (H_1) and plasma glucose (M_1) reduce glucose levels. The liver glucose uptake rate, F_2, is limited by the negative effect of liver insulin on glucose uptake (H_2) and the positive effect of glucose concentrations on glucose uptake (M_2).

$$NHGB = F_1 - F_2$$

$F_1 = a_{11} G_1 H_1 M_1$	
$G_1 = 0.5[1 + \tanh(b_{11}(\Delta\bar{c} + c_{11}))]$	positive effect of glucagon concentration
$H_1 = 0.5[1 - \tanh(b_{12}(\Delta\bar{l} + c_{12}))]$	negative effect of liver insulin concentration
$M_1 = 0.5[1 - \tanh(b_{13}(\Delta\bar{g} + c_{13}))]$	negative effect of glucose concentration
$F_2 = H_2 M_2$	
$H_2 = 0.5[1 - \tanh(b_{21}(\Delta\bar{l} + c_{21}))]$	negative effect of liver insulin concentation
$M_2 = a_{221} + a_{222} 0.5[1 + \tanh(b_{22}(\Delta\bar{g} + c_{22}))]$	positive effect of glucose concentration

Referring back to equation (1), we see that there are three other processes in which glucose is used or excreted: kidney excretion (F_3), uptake by fatty tissue and muscles (F_4), and uptake by the blood cells and nerves (F_5). The renal (kidney) excretion rate of glucose (F_3) is controlled by the negative feedback effect of deviations of glucose from

the basal value (M_{31}) (i.e. if there is more glucose than needed in the blood, then it will be excreted from the body until the basal concentration is recovered) and the linear flow rate of glucose from the plasma glucose compartment to urine to excretion (M_{32}):

$$F_3 = M_{31}M_{32}$$

$$M_{31} = 0.5[1 + \tanh(b_{31}(\bar{g} + c_{31}))] \quad \text{positive effect of glucose concentration}$$

$$M_{32} = a_{321}\bar{g} + a_{332} \quad \text{linear rate of excretion}$$

Glucose is removed from the blood plasma by the adipose and muscular tissues (F_4), where interstitial insulin (H_4) and glucose (M_4) promote glucose uptake:

$$F_4 = a_{41}H_4M_4$$

$$H_4 = 0.5[1 + \tanh(b_{41}(\Delta\bar{i} + c_{41}))] \quad \text{positive effect of interstitial insulin concentration}$$

$$M_4 = 0.5[1 + \tanh(b_{42}(\Delta\bar{g} + c_{42}))] \quad \text{positive effect of glucose concentration}$$

Glucose is also removed from the blood plasma by the central nervous system and red blood cells (F_5), where M_{51} and M_{52} model the positive effects of glucose on central nervous system uptake:

$$F_5 = M_{51} + M_{52}$$

$$M_{51} = a_{51}\tanh(b_{51}(\Delta\bar{g} + c_{51})) \quad \text{positive effect of glucose concentration}$$

$$M_{52} = a_{52}\Delta\bar{g} + b_{52} \quad \text{positive effect of glucose concentration}$$

Mostly importantly, we cannot forget that glucose can be added to the blood, either orally or intravenously ($I_g(t)$). This function of time is used for diagnostic tests.

Glucagon Subsystem

The glucagon subsystem is described by equation (2). The control of glucagon production (F_7) depends on the negative effects of plasma glucose (M_7) and insulin concentration (H_7) i.e. elevated concentrations of glucose and/or insulin result in reduced glucagon production:

$$F_7 = a_{71}H_7M_7$$

$$H_7 = 0.5[1 - \tanh(b_{71}(\Delta\bar{i} + c_{71}))] \quad \text{negative effects of interstitial insulin concentration}$$

$$M_7 = 0.5[1 - \tanh(b_{72}(\Delta\bar{g} + c_{72}))] \quad \text{negative effects of glucose concentration}$$

Insulin Subsystem

The insulin subsystem is the most complex because it consists of five compartments: interstitial insulin (equation (3)), liver insulin (equation (4)), plasma insulin (equation (5)), releasable pancreatic insulin (equation (6)), and stored pancreatic insulin (equation(7)). The rate dynamics for equations (3)-(5) are linear, donor-controlled relationships i.e. the various insulin concentrations directly affect each of the

compartment rates. The addition of insulin into the plasma by means of ingestion, intravenously or orally, is represented by $I_p(t)$ in equations (5), (6) and (7).

Recall that insulin is produced in the pancreas and is transported to the liver, where it stimulates the conversion of glucose to glycogen. Cobelli et al. (1982) assumes pancreatic insulin occurs in two forms: a nonlabile, stored form produced by the pancreas at rate W:

$$W = 0.5a_w[1 + \tanh(b_w(\Delta\overline{g} + c_w))] \qquad \text{positive effect of glucose concentration}$$

and a "promptly releasable" form which is secreted from the pancreas at rate F_6:

$$F_6 = 0.5a_6[1 + \tanh(b_6(\Delta\overline{g} + c_6))]r \qquad \text{positive effect of glucose concentration}$$

Note that a_w, b_w, c_w, a_6, b_6, and c_6 are constant parameters. The parameters used in our experiment are defined in the following table:

Table 2: Normal parameter for the glucose-insulin model.

NORMAL PARAMETERS

GLUCOSE

a_{11}=1.51	a_{221}=1.95*10^{-3}	a_{321}=1.43*10^{-5}
b_{11}=2.14	a_{222}=5.21*10^{-3}	a_{322}=-1.3`*10^{-5}
b_{12}=7.84*10^{-2}	b_{21}=1.11*10^{-2}	b_{31}=20
b_{13}=2.75*10^{-2}	b_{22}=1.45*10^{-2}	c_{31}=-180
c_{11}=-0.85	c_{12}=7	c_{21}=51.3
c_{22}=-108.5	c_{13}=20	a_{41}=2.87*10^{-2}
a_{51}=1.01*10^{-3}	a_{52}=4.6*10^{-6}	b_{41}=3.1*10^{-2}
b_{42}=1.44*10^{-2}	b_{51}=2.78*10^{-2}	b_{52}=4.13*10^{-4}
c_{41}=-50.9	c_{42}=-20.2	c_{51}=1.002

INSULIN

k_{12}=0.01	k_{21}=4.34*10^{-3}	m_{01}=0.125
m_{02}=0.185	m_{12}=0.209	m_{13}=0.02
m_{21}=0.268	m_{31}=0.042	a_w=0.287
a_6=1.3	b_w=1.51*10^{-2}	b_6=9.23*10^{-2}
c_w=-92.3	c_6=-19.68	

GLUCAGON

a_{71}=2.35	b_{71}=6.86*10^{-3}	b_{72}=3.00*10^{-2}
c_{71}=99.2	c_{72}=40	h_{02}=0.086

Courtesy of Cobelli et al. 1982 and Haefner's Modeling Biological Systems.

Regulation in a Diabetic System

To construct a diabetic model, we need only (1) change some variables from our healthy model to parameters and (2) decrease a few of our previously defined parameters.

Table 3: Parameters for diabetic subjects. All other parameters as in Table 2.

DIABETES PARAMETERS

F_2=0.037
H_4=0.0012
b_{42}=7*10^{-3}
c_{42}=-40.47
b_w=4.5*10^{-3}
b_6=5*10^{-3}
c_6=-363.55
c_w=-306.25

Courtesy of Cobelli et al. 1982 and Haefner's Modeling Biological Systems.

In a diabetic system, liver uptake and peripheral utilization of glucose is less sensitive to insulin (approximately one-half the normal state). To simulate the reduced sensitivity of liver uptake of glucose to insulin, we replace F_2 with a constant. Likewise, to simulate the reduced sensitivity of peripheral utilization of glucose to insulin, we replace H_4 with a constant. When we replace H_4 with a constant we reduce the positive effects of interstitial insulin on the removal of glucose from the blood plasma by adipose and muscular tissue. In addition, decreasing the constants b_{42} and c_{42} by half, also effects the removal of glucose from the blood plasma by adipose and muscular tissue by decreasing the positive effects of glucose on this subsystem.

Diabetes is also noted by considerably reduced insulin secretion and enhanced glucagon secretion (about two times). Cobelli et al. model simulates a reduced insulin secretion by decreasing the parameters b_w, b_6, c_6, and c_w. The reduction of the parameters b_w and c_w reduces the rate at which stored insulin is produced by the pancreas, W. The reduction of the parameters b_6 and c_6 reduces the rate at which releasable insulin is secreted from the pancreas, F_6.

The combination of these variable and parameter adjustments affects the quantity of glucagon secreted in the system because glucagon production, F_7, is determined by the new concentrations of insulin and glucose in the blood plasma. In particular, since insulin secretion is reduced in a diabetic system, the negative effects of interstitial insulin on glucose production, H_7, is reduced.

Simulations

Diagnostic Tests

Intravenous Glucose Tolerance Test

The intravenous glucose tolerance test, or IVGTT, is a diagnostic test, in which a rapid intravenous injection of glucose is given to the subject. For our experiments, we injected the patient with 0.33g glucose/(kg body weight) in 3 minutes. Observing the graph for the normal system, we note that both plasma glucose and plasma insulin return to homeostasis about 90 minutes after the pulse of glucose. In addition, notice that the liver and plasma insulin increase almost immediately after the glucose pulse.

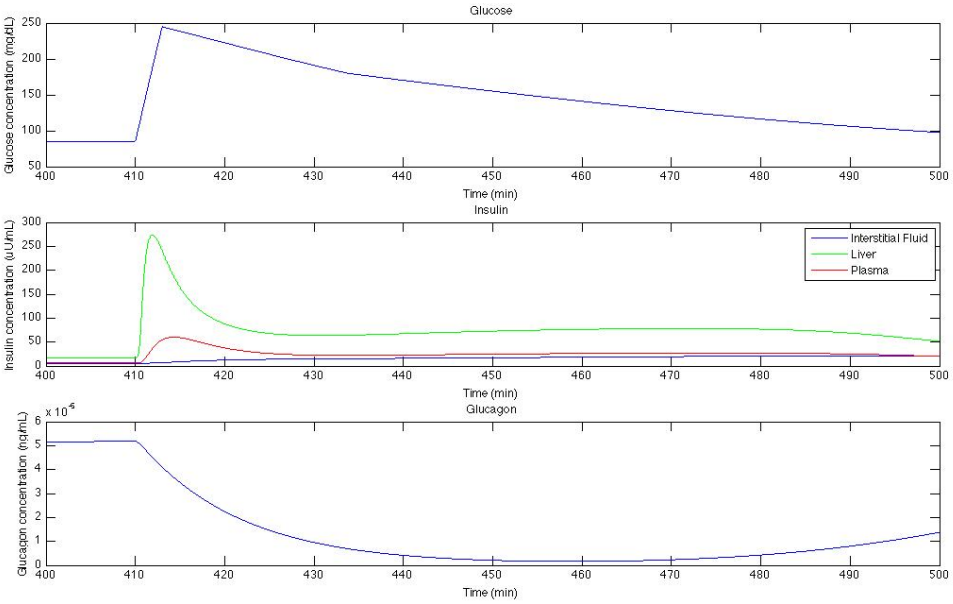

Figure 1: Normal IVGTT

People with diabetes have a much higher basal level of glucose (about 250mg/100mL) than a normal individual, and their insulin levels are much lower (maximum of 50uU/mL in the diabetic study of this experiment compared to a maximum of 300uU/mL in the normal study of this experiment). Consequently, the response of a diabetic to an IVGTT is much slower i.e. the recovery period is much longer (30 minutes) than a normal individual (15 minutes). The system takes almost twice as long to return to homeostasis.

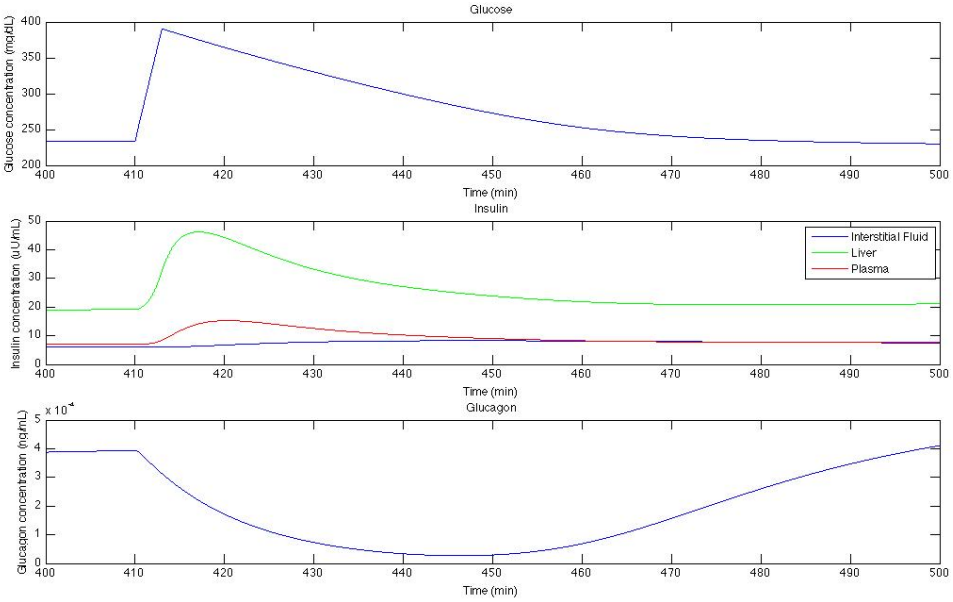

Figure 2: Diabetic IVGTT

Consecutive Glucose Injections

Another test applies repeated pulses of glucose at intervals less than that needed to clear the previous pulse from the system. We administered seven increasingly larger doses (0.5, 1.0, 2.5, 5, 10, 20, and 40 grams) of intravenous glucose at intervals of 0, 30, 70, 100, 180. 270, and 400 minutes, respectively. If repeated and increasing pulses are injected, glucose levels do not decay exponentially as they did in the single IVGTT. A "hump" in insulin concentration following pulse 6 forms which greatly delays the recovery of the insulin system to homeostasis.

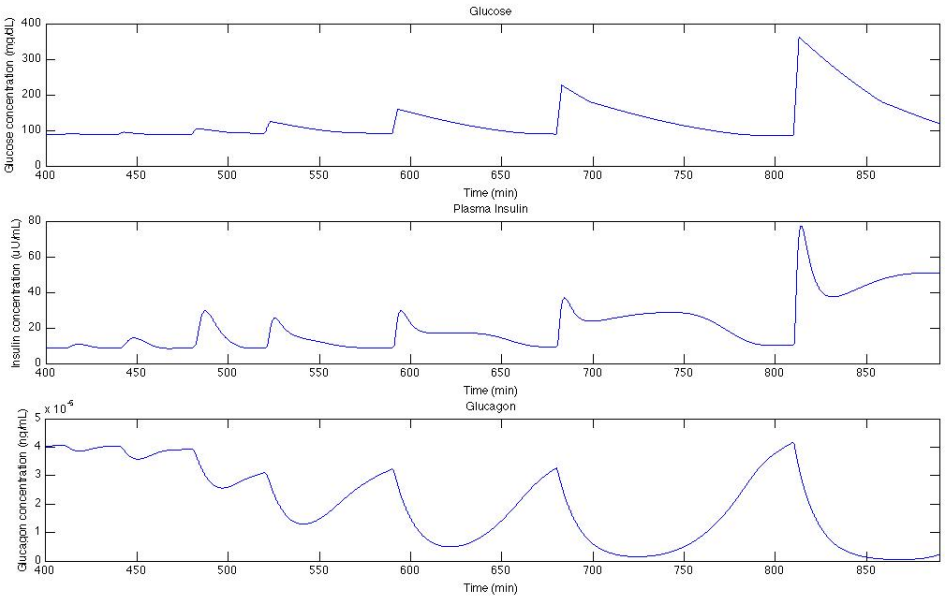

Figure 3: Normal Pulses

Note that no hump in insulin concentration forms after pulse 6 in the diabetic study. Why? Recall that diabetes reduces the pancreatic secretion rate of insulin into the blood, F_6. A decreased rate of pancreatic insulin secretion, F_6, reduces the concentration of liver insulin in the blood, l, which then lowers the concentration of plasma insulin in the blood. In other words, diabetics cannot "work harder" to remove glucose from the

blood by releasing more insulin because their bodies have a limited insulin secretion rate.

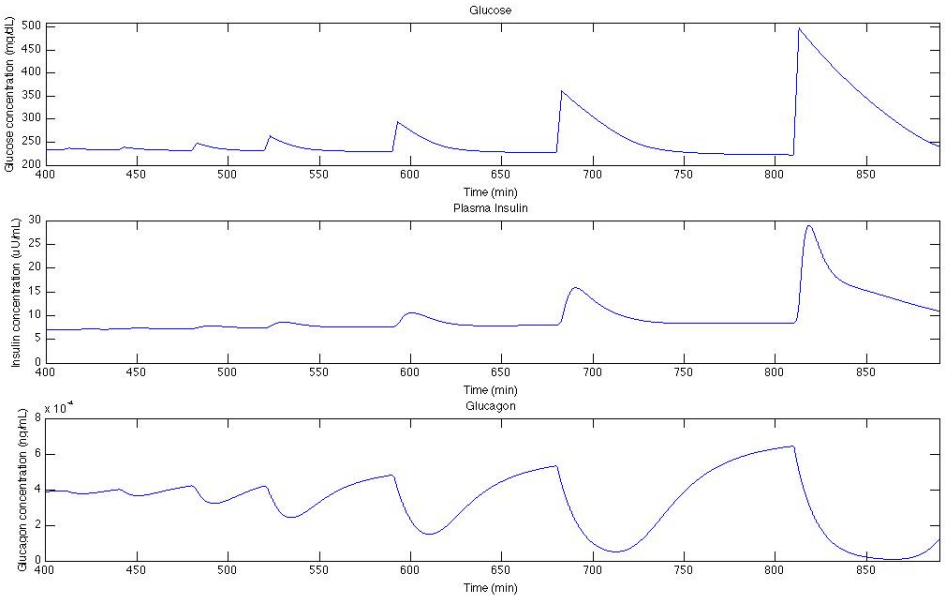

Figure 4: Diabetic Pulses

Meals—Glucose Infusion

To simulate eating a meal, we add glucose as a constant input spread out over an interval of time. We administered 25g of glucose over 60 minutes.

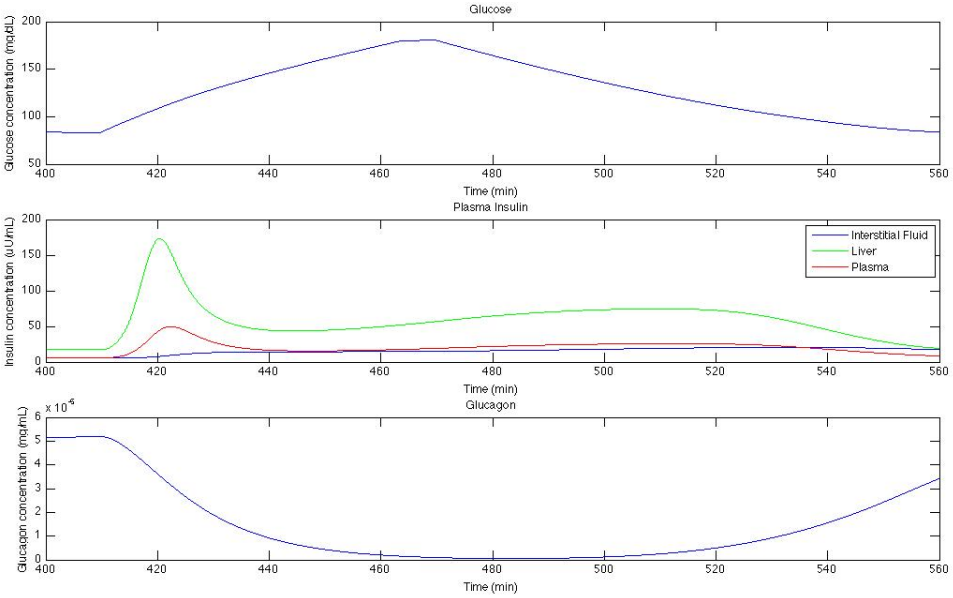

Figure 5: Normal Glucose Infusion

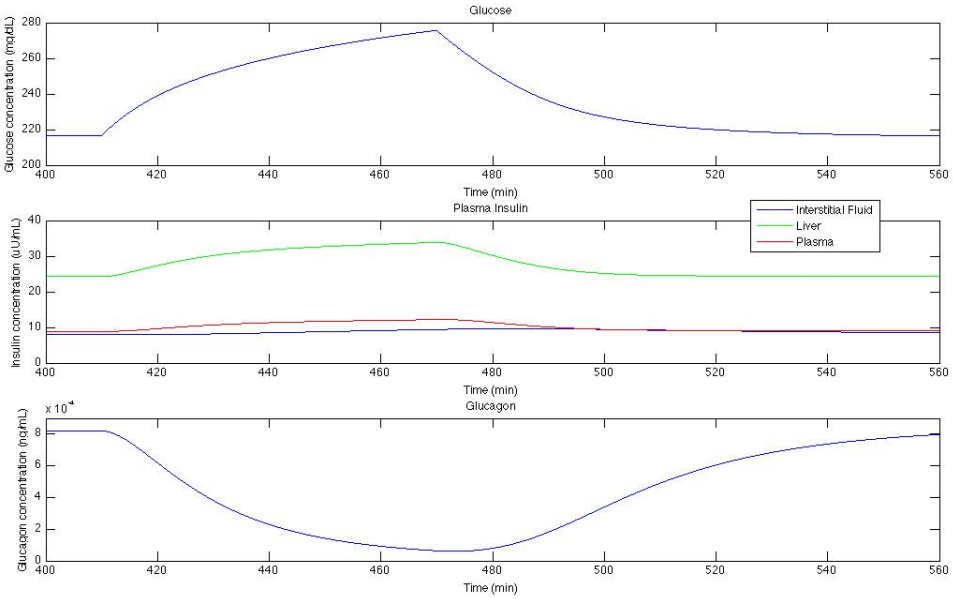

Figure 6: Diabetic Glucose Infusion

How do these dynamics compare to the IVGTT? In the normal glucose infusion, the initial response of insulin to the glucose infusion closely resembles the initial response of insulin to the glucose injection in the IVGTT; however, in the glucose infusion experiment, the response amplitude is lower and the increasing curve is more gradual. Also, in the normal and diabetic cases, the initial response of glucagon to the

glucose infusion looks like the initial response of glucagon to the glucose injection in the IVGTT; although, the decreasing curve is less severe.

Insulin Shock

Insulin shock is also known as hypoglycemia, or low plasma glucose concentrations. Unlike hyperinsulinism and diabetes, insulin shock is not considered a disease; instead, it is a symptom of other problems such as (1) your body's glucose is used up too quickly, (2) glucose is released into the blood plasma too slowly, and/or (3) too much insulin is released into the blood plasma (chronic in hyperinsulinism). Also, since the central nervous system depends almost exclusively on plasma glucose for energy, low concentrations of glucose (about 70mg/100mL) will begin to produce erratic behavior and loss of motor control. In severe cases, when plasma glucose concentration falls below 20-50mg/100mL, the patient becomes convulsive and eventually falls into a coma. Short-term treatment of insulin shock is to supply the patient with large concentrations of intravenous glucose.

Moreover, it is important to note that hypoglycemia is relatively common in people with diabetes and occurs when you (1) inject too much insulin, (2) do not eat enough, and/or (3) suddenly increase you exercise without increasing the amount of calories you intake.

For this experiment, we simulate insulin shock by injecting an abundance of insulin into the blood plasma; specifically, 0.10U/(kg body weight) over 2 minutes.

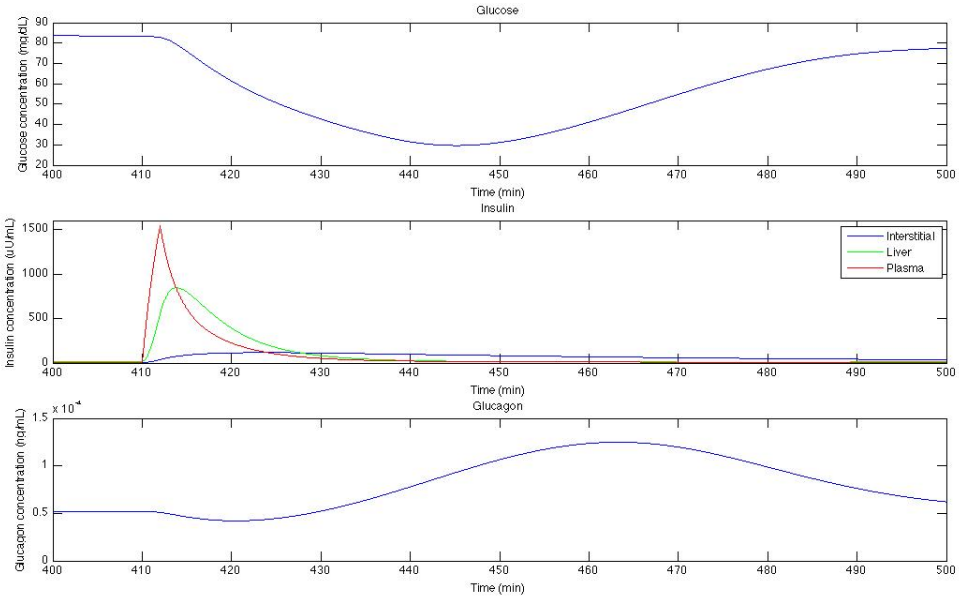

Figure 7: Normal Insulin Shock

Observe the momentary hypoglycemia that resulted in Figure 7 (the sudden decrease in glucose concentration above). Did our subject die? No, because we see that

glucagon reacted to the sudden decrease in glucose (the sudden increase in glucagon concentration above) by releasing glucose into the blood plasma from body stores to stop the decrease in blood plasma glucose (the glucose concentration does not fall below 30mg/100mL) in order to return the body's glucose concentration to around normal levels (about 80mg/100mL).

When we repeat our experiment with a diabetic subject, we see that normal hypoglycemia does not result because our subject's basal glucose concentration is already at an elevated state compared to a normal subject. Instead, a "diabetic hypoglycemia" results and our subject's glucagon returns their body's glucose concentration to "diabetic normal." Furthermore, our diabetic subject will not die because our insulin injection only lowers our diabetic's glucose concentration to 190mg/100mL, which is well above the level that produces erratic behavior (about 70mg/100mL).

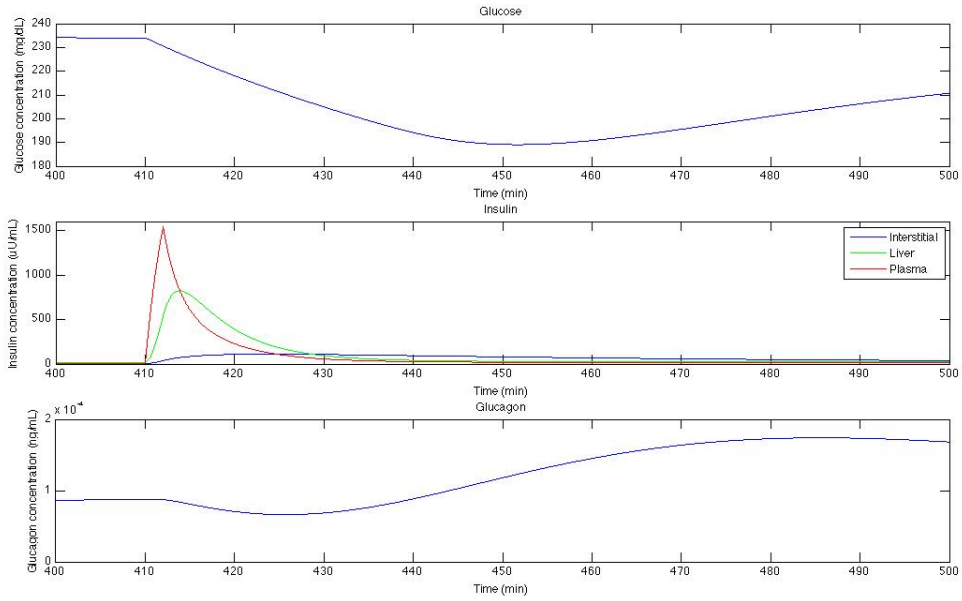

Figure 8: Diabetic Insulin Shock

Meals—Vanilla Ice Cream

For fun, let us simulate eating a delicious bowl of vanilla ice cream. For this experiment, we chose everybody's favorite ice cream (or at least mine), Ben and Jerry's Vanilla Ice Cream.

Ben and Jerry's Vanilla Ice Cream
Courtesy of Google Images.

According to the nutrition facts, there are 19g of sugar (glucose) per ½ cup serving (one scoop). Typically, we cannot have just one scoop so we assume we eat 2 scoops or 38g of glucose. We also suppose that we eat these 2 scoops over 20 minutes because (1) it is delicious and (2) we do not want it to melt! Therefore, we eat 38g of glucose over 20 minutes.

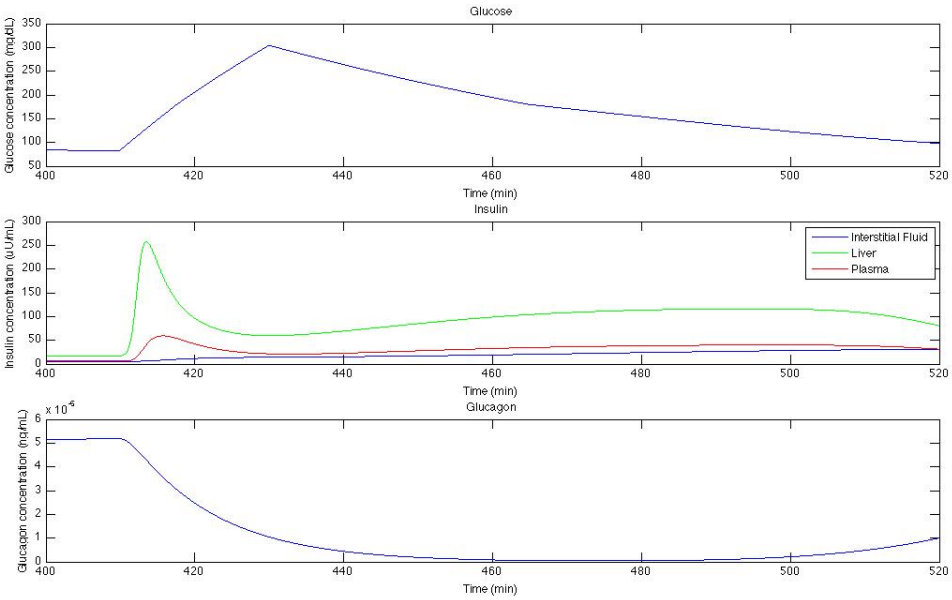

Figure 9: Normal Meal—Vanilla Ice Cream

Notice that this experiment parallels our previous meal simulation experiment if we qualitatively examine the results of the normal case. However, when we examine the results quantitatively, we see that concentrations increase and decrease on a much larger scale. For example, in the meal—glucose infusion experiment, glucose reaches a maximum under 200mg/100mL. Comparatively, in the meal—vanilla ice cream experiment, glucose reaches a maximum above 400mg/100mL. Similarly, an increase can be observed when comparing insulin and glucagon maximums in each experiment.

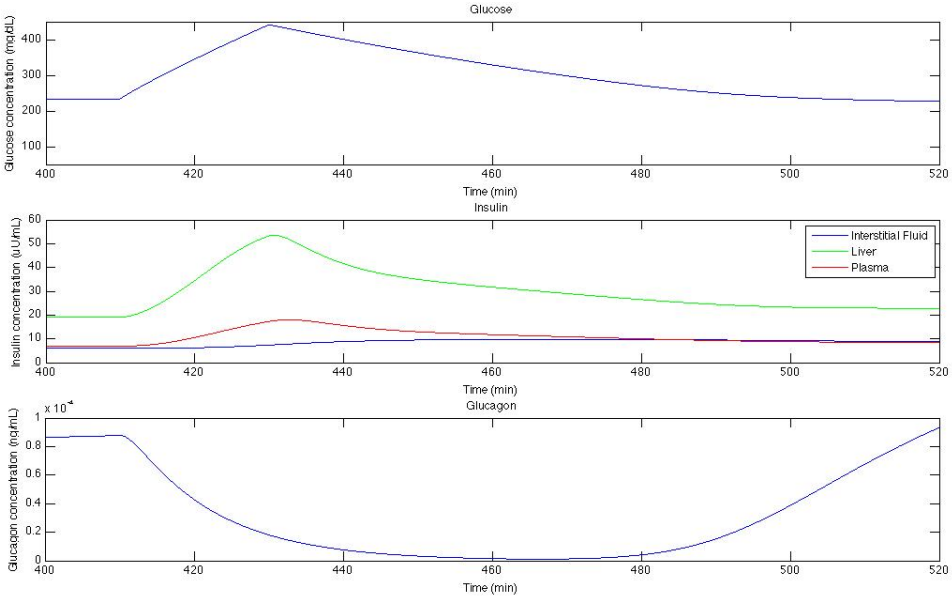

Figure 10: Diabetic Meal—Vanilla Ice Cream

Compared to the normal simulations, the behavior in the diabetic meal—glucose infusion experiment does not correlate with the behavior in the diabetic meals—vanilla ice cream experiment. Instead, the diabetic curves of glucose, insulin, and glucagon for the meals—vanilla ice cream experiment look like subtler normal meals—glucose infusion experiment curves. We observe this behavior because diabetics already have an elevated glucose set point and, in order to, simulate the same effects of the experiment, normal meals—glucose infusion, for a diabetic subject we need to inject a greater amount of glucose, which is what the experiment, meals—vanilla ice cream, accomplishes. In fact, the meals—glucose infusion experiment injects .4167g glucose/min, whereas the meals—vanilla ice cream experiment injects 1.9g glucose/min, which is more than four times the rate of glucose infusion in the meals—glucose infusion experiment!

Conclusions and Further Research

Hyperinsulinism (Hypoglycemia)

In our "insulin shock" experiments, we simulated hypoglycemia by injecting an overabundance of insulin into the blood. However, our experiments only simulated a temporary hypoglycemia in an otherwise normal system for a healthy or diabetic individual i.e. normal concentration levels, rates, and parameters for their particular system. Contrary to "insulin shock," hyperinsulinism is a chronic disorder, which results in an overproduction of insulin that drives down the plasma glucose concentrations (chronic hypoglycemia).

To simulate hyperinsulinism, we could begin by adjusting the appropriate parameters in Table 2. Maybe we could try increasing a_6 in F_6. Although, other adjustments may be needed.

Extended Models

We observe that even a simple model involving only glucose, insulin, and glucagon allows us to simulate some complex disorders, such as diabetes and hyperinsulinism; as well as, simpler situations, such as eating a bowl of vanilla ice cream. Imagine if we extended our model to incorporate variables such as non-esterified acid concentrations in the blood plasma, β-cell mass, TAG (triglyceride) content of lipocytes, and/or leptin concentrations in the blood plasma, then we would be able to work towards a better understanding of concepts such as why obesity sometimes leads to diabetes. Then we could even try to integrate exercise into our new model as a treatment for diabetes. With our simple model, we could simulate a "meal plan," but we could only vary the amount of sugar (glucose) ingested, the time ingested, and the duration of ingestion. With a more complex model, we could simulate more components of a typical meal, such as protein and fat content. Essentially, we would be able to construct a basic diet for our subject and then we could attempt to find a diet that could help treat or negate some of the effects of diabetes.

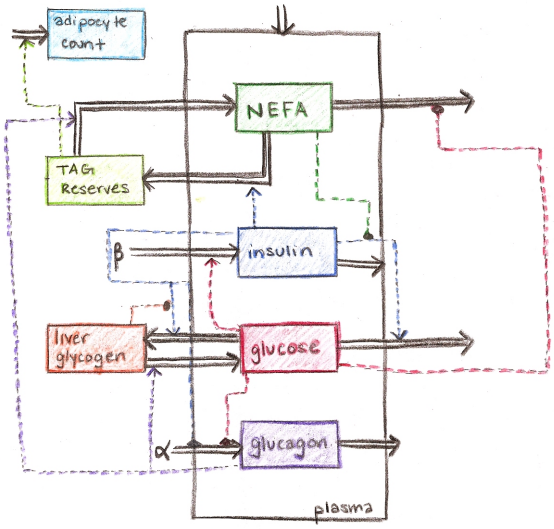

Diagram 4: Insulin-Glucose Model extended with the glucose-fatty acid cycle.
Note: Fluxes are represented as double arrows. Endocrine interactions are shown as dotted arrows: positive as normal arrowheads, negative as flattened diamonds, modulatory as circles. 'α' represents pancreatic α-cells and 'β' represents pancreatic β-cells.

In addition, our new complex model would be able to simulate some additional consequences of diabetes. For example, without sufficient glucose available to meet the needs of most body cells, fat becomes the main substrate for cellular respiration. We could observe fat metabolism in diabetes with a new model that incorporates TAG (triglyceride) content of lipocytes. Also, in severe cases, acidic metabolites formed during fat breakdown accumulate in the blood, threatening life by lowering blood pH, which impedes affinity of hemoglobin for oxygen so less oxygen is carried to vital

organs. We could see this result in a new model that includes non-esterified fatty acid concentration in the blood plasma.

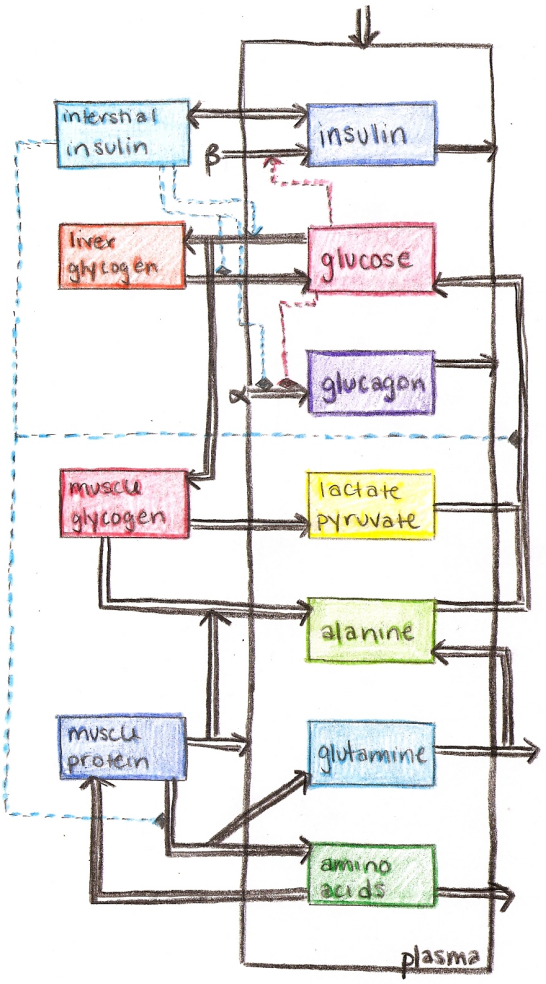

Diagram 5: Insulin-Glucagon-glucose model integrated with protein metabolism.
Note: Fluxes are represented as double arrows. Endocrine interactions are shown as dotted arrows: positive as normal arrowheads, negative as flattened diamonds, modulatory as circles. 'α' represents pancreatic α-cells and 'β' represents pancreatic β-cells.

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