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HORMONAL EFFECTS ON GLUCOSE REGULATION

Kenneth W. Sulston

Department of Mathematics and Statistics
University of Prince Edward Island
Charlottetown, PEI, C1A 4P3, Canada

William P. Ireland

Department of Biomedical Sciences
Atlantic Veterinary College
University of Prince Edward Island
Charlottetown, PEI, C1A 4P3, Canada

Jeff C. Praught

Department of Mathematics and Statistics
University of Prince Edward Island
Charlottetown, PEI, C1A 4P3, Canada

Abstract. A dynamical-systems model of plasma glucose concentration, and its regulation by insulin and glucagon, is described, as pertains to types 1 and 2 diabetes. The hyperglycemic case is seen to be dependent only on insulin concentration, while the hypoglycemic case requires consideration of both insulin and glucagon concentrations. The role of healthy α cells in maintaining proper levels of glucose and the hormones is also highlighted.

1. **Introduction.** Glucose is a sugar that provides energy to all the cells in the body and consequently the regulation of its plasma levels is of the utmost importance. When glucose concentration in the bloodstream gets too high, the body reacts by storing excess glucose in the liver and muscles as glycogen, a starch made up of many glucose molecules. When blood glucose levels get too low, the liver then converts glycogen back to glucose so that a relatively constant glucose concentration is maintained. To achieve this equilibrium, the body relies primarily on two hormones, insulin and glucagon, which are produced in the β and α cells of the pancreas, respectively. Insulin and glucagon have effects opposing one another: when glucose levels are too high, the pancreas secretes insulin which lowers these levels, and when glucose levels are too low, glucagon is secreted to raise them. Insulin is required by almost all cells in the body, but has the greatest influence on liver cells, fat cells, and muscle cells. By targeting these cells, insulin causes liver and muscle cells to convert glucose to glycogen and fat cells to store fat from fatty acids in the body. Glucagon acts on the same cells as insulin, but has the opposite affect. Glucagon stimulates the liver cells to break down stored glycogen and release glucose into the bloodstream.

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Diabetes mellitus is a disorder characterized by abnormally high blood glucose levels. Diabetes is characterized by two types: insulin-dependent diabetes (type 1) and non-insulin-dependent diabetes (type 2). In type 1 diabetes, more than 90% of the β cells in the pancreas are destroyed, thereby causing the pancreas to produce little or no insulin. Type 1 diabetes is the rarer form and occurs in less than 10% of all cases, while type 2 diabetes accounts for about 90% of all diabetic patients. In type 2 diabetes, the pancreas continues to produce some insulin, sometimes even at the same levels as people without diabetes. However, the body develops a resistance to the insulin and the pancreas can not produce enough insulin to meet the body's requirements. As a result, glucose is not absorbed into muscle and fat cells at a normal rate, and the liver does not function properly, causing glucose levels to be too high.

Mathematical modelling of diabetes is not a new area of research, as there has been an extensive amount of research done for more than 40 years. One of the earliest models was introduced by Bolie [8]; this model was a system of differential equations, with one variable for insulin and one for glucose. Although it was relatively simple, this model provided the foundation on which many of the pioneers of diabetes modelling, such as Cobelli and Ackerman, would base their work. Ackerman *et al.* ([1],[2],[3]) developed a model of the oral glucose tolerance test which measures the ability of a patient to utilize a specific amount of glucose. Much of the subsequent work that followed continued with the glucose-insulin model and variations of it. Bergman *et al.* [7] developed a model to study glucose disappearance and how it affects insulin sensitivity. Their model predicted two linearly connected pools in the pancreas; one pool for stored insulin and the other for promptly releasable insulin. Cobelli *et al.* [13] developed a complex and comprehensive non-linear model to study the short-term blood glucose regulation system. They include crucial processes of glucose, insulin, and glucagon dynamics and their interrelationships. There are limitations to comprehensive models like this one, which are intrinsic in nature, such as variations in the parameters among different individuals and the difficulty of finding data corresponding to all processes included in the model.

Salzsieder *et al.* [19] argued that in order to control long-term glycemic regulation, it is necessary to estimate control parameters for each diabetic patient individually. Their model of glucose and insulin used optimal control theory to find the best estimate for these parameters. They considered physiological relevant processes such as endogenous glucose production, insulin-dependent glucose utilization, and insulin catabolism. Summers and Montani [22] presented a model of glucose homeostasis based on the bihormonal regulation of glucose by glucagon and insulin. Sturis *et al.* [21] developed a model to study oscillations in human insulin over two distinct time periods, rapid (10 - 15 minutes) and ultradian (100 - 150 minutes). Their model used two major feedback loops to describe the effects of insulin on both glucose production and utilization. There have been numerous other models developed to study different aspects of diabetes, including those of Andreassen *et al.* [5], Boroujerdi *et al.* [10], and Cobelli *et al.* [12].

The focus of the model presented here is on the effect of glucagon, which has an important, albeit secondary, role in the regulation of glucose. At normal to high levels of plasma glucose, glucagon is secreted at a low rate, and its plasma concentration remains relatively constant. But when glucose levels are low, glucagon secretion increases and its plasma concentration rises significantly. Glucose levels

in diabetics are *usually* in the above-normal range, so that it is the former situation that ordinarily applies, although hypoglycemia is a serious acute complication, with possible long-term effects on health. However, most models have been concerned with hyperglycemic situations, and for this reason, have not incorporated glucagon. Among those that did, Dobbins *et al.* [14] performed compartmental modelling of glucagon in dogs, as part of a theoretical and experimental study examining glucagon metabolism and distribution, although the study was not specifically aimed at diabetes. The main conclusion was that glucagon has a key role in the acute regulation of glucose homeostasis, due to glucagon's rapid equilibration in plasma and its rapid activation of hepatic glucose production. From a modelling perspective, this investigation settled the important question that glucagon kinetics are best described using a model with a single pool for glucagon. Celeste *et al.* [11] studied a (mostly) linear model involving glucagon, insulin, and glucose, which is an extension of the simple Ackerman model so as to include glucagon, with one pool for each substance. Insulin and glucagon were assumed to interact only with glucose, and not with each other. The goals of the study were to show the roles of both insulin and glucagon as co-regulators of glucose, and to simulate the oral glucose tolerance test and insulin infusion test. The simulation of the oral glucose tolerance test suggested that glucagon is not important at higher blood glucose levels, while the simulation of the insulin infusion test showed that glucagon plays a crucial role in recovery from hypoglycemia. They concluded by postulating that glucose levels can be regulated by a weighted combination of insulin and glucagon. Summers and co-workers ([22],[23]) also studied the bihormonal influence of insulin and glucagon on glucose homeostasis, with the aim of developing a broad-based model capable of examining various aspects of glucose metabolism. They adopted a model of three differential equations, one for each of glucose, insulin and glucagon, with the latter two interacting only with glucose, but not with each other, as was also done in Celeste *et al.* [11]. The resulting model was deemed useful for both theoretical analyses and experimental and clinical simulations. Other hormones, such as somatostatin and pancreatic polypeptide, play smaller roles in glucose dynamics, and have received virtually no attention in the modelling literature.

In this paper, we develop a mathematical model of glucose dynamics which includes its interactions with both insulin and glucagon, and with an emphasis on the low-glucose-concentration regime. Novel features not included in other models are the direct influence of insulin and glucagon on each other, and the ingestion of glucose via a meal.

2. **Physiological Description of the Model.**

There are a number of physiological factors that contribute to the concentrations of glucose, insulin, and glucagon in plasma. We develop a dynamic model for their levels, by constructing a differential equation to describe the changes with respect to time t (in minutes) of each of glucose G (in mg/dl), insulin I (in ng/dl), and glucagon E (in ng/dl). Parameter values are selected to be appropriate for a typical 70 kg man, with an assumed plasma volume of 35 dl.

The change in the plasma glucose level can be described phenomenologically by

$$\begin{aligned} dG/dt = &(\textit{hepatic release/uptake}) \\ &-(\textit{uptake by brain and red blood cells}) \\ &-(\textit{uptake by peripherals}) - (\textit{uptake by kidneys}) + (\textit{ingestion}). \end{aligned} \tag{2.1}$$

The terms contributing to (2.1) are as follows. The hepatic uptake/release represents the central role played by the liver in controlling glucose levels. Glucose and insulin serve to increase uptake of glucose by the liver, while glucagon stimulates glucose's release. Uptake by brain and red blood cells represents glucose usage by these areas, and these processes are independent of insulin. Uptake by peripherals represents glucose storage by fat and muscle cells, with these processes being insulin-dependent. Uptake by the kidneys is due to the fact that when glucose levels get too high, excess amounts are passed out of the body in urine by the kidneys. This process is obviously dependent on the concentration of glucose in the blood, but not on that of insulin. Ingestion describes the amount of glucose obtained from a particular meal, and varies depending on the type and amount of food consumed by an individual.

The change in the insulin level can be represented by

$$dI/dt = (secretion) - (degradation) + (injection). \tag{2.2}$$

The first term in (2.2) describes the secretion of insulin, which is known to be stimulated by high levels of glucose and also, to a lesser extent, by glucagon. The degradation term determines how long insulin remains in the blood stream before it is cleared from the body. The injection term is for exogenous insulin externally administered into the bloodstream.

The change in the glucagon level can similarly be described by

$$dE/dt = (secretion) - (degradation). \tag{2.3}$$

The secretion of glucagon in (2.3) depends on both glucose and insulin levels. When glucose is at normal (or higher) levels, the secretion rate is minimal, but when the glucose level falls below a threshold value, glucagon secretion increases (so that the higher glucagon level will spur hepatic release of glucose, thereby raising that level towards the normal range). On the other hand, insulin suppresses the release of glucagon, so that as the insulin concentration rises, the secretion rate of glucagon decreases. The degradation term represents the clearance of glucagon from the bloodstream.

3. **Mathematical Construction of the Model.**

In this section, we reshape the qualitative equations of the last section into differential equations, by modelling each term by an appropriate mathematical form, which mimics the known physiological function. Parameter values are selected, when possible, by performing a least-squares fit of the chosen mathematical form to the corresponding experimental data.

3.1. **Glucose.**

Conversion of glucose into glycogen, or vice versa, by the liver is one of the body's primary methods of regulating glucose concentrations in the bloodstream. High levels of either glucose or insulin serve to increase glucose uptake by the liver, while glucagon stimulates glucose release. To model the dependence of the hepatic release on the glucose concentration, a form that limits the amount of glucose absorbed is needed, because there is a saturation effect at high glucose levels. Thus an appropriate form is

$$k_5 - \frac{k_8 G}{k_9 + G}, \tag{3.1}$$

where k_5 represents the maximum release rate in the (hypothetical) absence of glucose and k_8 and k_9 are the saturation parameters.

The next fact to consider is that rising insulin inhibits the release of glucose from the liver (via glycogen breakdown) up to a threshold point; beyond this point, insulin causes the liver to actually absorb glucose through the synthesis of glycogen. This effect can be modelled conveniently by multiplying k_5 by a "damping" factor to revise (3.1) to

$$\frac{k_5 k_6}{k_6 + I} - \frac{k_8 G}{k_9 + G}, \tag{3.2}$$

where the new factor has a value close to 1 (0) at low (high) insulin concentrations.

Lastly, the stimulative effect of glucagon on hepatic release is thought to be linear (Dobbins *et al.*, [14]). This is due to the fact that glucagon acts by interacting with liver hepatocytes, causing them to secrete glucose [15], suggesting that glucose production increases proportionally to the glucagon concentration. Thus the glucagon effect is modelled as a linear relationship, so that the final form for the hepatic uptake/release (the first term on the right-hand side of (2.1)) is

$$dG_{hep}/dt = \frac{k_5 k_6}{k_6 + I} - \frac{k_8 G}{k_9 + G} + k_7 E. \tag{3.3}$$

The values of the parameters appearing in (3.3) were determined by reference to experiment. The value of k_7 is calculated from the work of Dobbins *et al.* [14], specifically a plot of the net hepatic glucose balance versus glucagon concentration (their fig. 4). This yields a value of $k_7 = 0.4572$ (mg/dl/min of G) per (ng/dl of E). The other parameters (k_5, k_6, k_8, k_9) were estimated by doing a least-squares fit to fig. 2 of Guyton *et al.* [16] of the right-hand side of (3.3) with E set equal to the calculated glucagon fasting level of 8.2 ng/dl (see section 3.3).

The uptake of glucose by the brain and red blood cells is independent of insulin (and glucagon) concentration, but not of glucose concentration. Although some workers have suggested that the uptake rate should be constant, Andreassen *et al.* [5] and Boroujerdi *et al.* [10] argue that it should more realistically be a function of glucose concentration with a saturation limit. Following the latter perspective, the form for this contribution to (2.1) is taken to be

$$dG_{brain}/dt = -\frac{k_4 G}{k_3 + G}. \tag{3.4}$$

Eq. (3.4) indicates that the uptake is effectively 0 at low glucose concentrations, and approaches a limiting value of k_4 at high concentrations.

The parameter values appearing in (3.4) were determined, using the data in fig. 4A of Andreassen *et al.* [5], to be $k_3 = 207.12654$ mg/dl and $k_4 = 9.1119$ mg/dl/min.

The uptake of glucose by the "peripherals" (primarily fat and muscle) is dependent not only on glucose, but also on insulin. Following Andreassen *et al.* [5] this insulin-dependent utilization is close to 0 when $I = 0$, and increases linearly with increasing blood glucose levels, suggesting proportionality to both G and I. Thus a suitable form is

$$dG_{per}/dt = -(k_1 G + k_2) I. \tag{3.5}$$

The values for the parameters in (3.5) were estimated using the data in fig. 5B of Andreassen *et al.* [5] to be $k_1 = 1.0855 \times 10^{-4}$ min^{-1} per (ng/dl of I) and $k_2 = 9.7947 \times 10^{-3}$ (mg/dl/min of G) per (ng/dl of I).

The uptake rate by the kidneys is independent of insulin and glucagon, but not glucose. When G is below the renal threshold level G_r, the uptake rate by the

kidneys is 0. When G is greater that G_r, the rate of uptake increases linearly with increasing G. Thus we have

$$dG_{kid}/dt = -k_r(G - G_r)u(G - G_r), \tag{3.6}$$

where the parameter k_r controls the rate of uptake, and $u(G-G_r)$ is the Heaviside step function.

The value of the renal threshold is well-established as $G_r = 180$ mg/dl [15]. To calculate k_r, we use the fact quoted by Summers and Montani [22] that the uptake by the kidneys increases 230 mg/min for every 180 mg/dl rise in glucose concentration, based on a 70 kg person with an estimated plasma volume of 35 dl. This results in a value of $k_r = 0.0365$ min^{-1}.

The *exogenous* glucose is represented by an input function that describes the amount of glucose ingested and how it is processed in the body. Unlike many models which assume glucose as being given intravenously, we use an approach that models its absorption via a meal. We adopt here the model of Yates and Fletcher [25], which treats this situation as a two-compartment process. The first compartment models the stomach via a trapezoidal function, that describes the glucose flux as the stomach empties into the small intestine, and which has the form

$$G_{empt} = \begin{cases} (V_{max}/T_{asc})t, & t < T_{asc} \\ V_{max}, & T_{asc} < t < T_{asc} + T_{max} \\ V_{max} - (V_{max}/T_{desc})(t - T_{asc} - T_{max}), & T_{asc} + T_{max} < t \\ & \quad < T_{asc} + T_{max} + T_{desc} \\ 0, & \text{otherwise} \end{cases} \tag{3.7}$$

In (3.7), V_{max} is the maximum rate of gastric emptying, and T_{asc} (T_{desc}) is the duration of the ascending (descending) branch of the gastric emptying curve. We let G_{total} represent the total amount of glucose contained in a meal, which is thus a control parameter that depends on the size of the meal and its glucose content. Then

$$T_{max} = \frac{G_{total} - V_{max}(T_{asc} + T_{desc})/2}{V_{max}} \ .$$

The second compartment in the Yates/Fletcher model describes how glucose is processed in the gut, and is governed by the differential equation

$$dG_{gut}/dt = G_{empt} - K_{gabs}G_{gut}. \tag{3.8}$$

From here the exogenous glucose is determined, by virtue of its being proportional to G_{gut}; namely

$$G_{exg} = K_{gabs}G_{gut}. \tag{3.9}$$

Eq (3.8) describes the amount of glucose in the gut, namely G_{gut}, while (3.9) calculates the rate of glucose input into the bloodstream via the gut wall. K_{gabs} is the absorption rate constant of glucose from the gut. The set of equations (3.7) to (3.9) can be solved symbolically (via Maple, for example) to give an explicit, albeit lengthy, expression for $G_{exg}(t)$.

The parameter V_{max} is the maximum rate of gastric emptying, for which Yates and Fletcher [25] give a value of 360 mg/min. The parameters T_{asc} and T_{desc} vary with the individual, and are here both assumed to have a value of 15 minutes. G_{total} is a control parameter which can be varied to simulate different glucose contents of a meal. The rate constant K_{gabs} is taken to be 1/60 min^{-1} [25].

Inserting the results of eqs. (3.3) to (3.6), and (3.9) into (2.1) gives the final form for the glucose equation to be

$$dG/dt = \frac{k_5 k_6}{k_6 + I} - \frac{k_8 G}{k_9 + G} + k_7 E - \frac{k_4 G}{k_3 + G} - (k_1 G + k_2) I \\ -k_r (G - G_r) u(G - G_r) + G_{exg}(t). \tag{3.10}$$

3.2. **Insulin.** Insulin is secreted by the β cells in the pancreas. It is well-known that both glucose and glucagon have stimulative effects on insulin release, and it is thought that either can act in the absence of the other. Thus the secretion term in (2.2) is modelled as having two terms, one for each of glucose and glucagon dependence. The rate of insulin release is considered to increase proportionally with the glucagon concentration in the blood, suggesting a simple linear relationship. On the other hand, the glucose dependence is more complicated; the rate of release rises with glucose concentration, but with a saturation effect. Consequently, an approach equivalent to that of Sturis *et al.* [21] is adopted, whereby the dependence on glucose is described by a hyperbolic tangent function. Thus the secretion term in (2.2) is modelled by

$$dI_{sec}/dt = (a_1/2)[\tanh(a_2(G - a_3)) + 1] + b_1 E, \tag{3.11}$$

where a_1 is the maximum secretion rate in the absence of glucagon.

The parameter b_1 in (3.11) is estimated using the work of Kawai *et al.* [17], and specifically their fig. 1 wherein they plot the dependence of insulin on glucagon. Thus is obtained a value of $b_1 = 0.14545$ (ng/dl/min of I) per (ng/dl of E). The other parameters are taken from the work of Sturis *et al.* [21], considering that the *tanh* term in (3.11) is equivalent to the *exponential*-type form used therein, yielding $a_1 = 248.81$ ng/dl/min, $a_2 = 0.01667$ (mg/dl)$^{-1}$, and $a_3 = 198$ mg/dl.

The degradation rate for insulin is clinically known to be proportional to the insulin concentration, so the second term in (2.2) has the form

$$dI_{deg}/dt = -b_2 I. \tag{3.12}$$

A value of b_2 is estimated from the work of Cobelli *et al.* [13], where their multi-pool submodel for insulin is treated as one effective pool with a decay constant $b_2 = 0.206$ min^{-1}.

The injection term in (2.2), the so-called exogenous insulin, is modelled by an input function that varies according to the type of insulin administered, the duration of its effectiveness, the size of the dosage, and the time at which the dosage is given. Here, the mathematical form for the exogenous insulin is taken from the work of Basov *et al.* [6], which appears to be satisfactory for longer-acting insulin types (such as NPH and Lente), but less so for shorter term types (such as Regular). The Basov approach models a series of m insulin injections as

$$I_{exg}(t) = \sum_{j=1}^{m} i_j(t), \tag{3.13}$$

with

$$i_j(t) = \begin{cases} B_j \sin[\pi(t - t_j)/T_j], & t_j \le t \le t_j + T_j, \\ 0, & \text{otherwise}, \end{cases} \tag{3.14}$$

where t_j corresponds to the time at which dosage j is given, T_j is the duration of its effectiveness, and $B_j = (\pi I_0)/(2T_j)$, with I_0 being the actual size of the dosage. Typical values of T_j are 24 hours for Lente and 20 hours for NPH. I_0 and t_j are control parameters, whose chosen values are discussed in section 4.

Substituting eqs. (3.11) to (3.13) into (2.2) produces the final form for the insulin equation, viz.,

$$dI/dt = (a_1/2)[\tanh(a_2(G - a_3)) + 1] + b_1 E - b_2 I + I_{exg}(t). \tag{3.15}$$

3.3. **Glucagon.** The degradation rate of glucagon in plasma is known from clinical experiments to be proportional to the glucagon concentration, so that the second term in (2.3) has the form

$$dE_{deg}/dt = -c_3 E. \tag{3.16}$$

The value of the degradation constant is well-known to be $c_3 = 0.08$ min^{-1} [13].

Glucagon is secreted in the α cells of the pancreas, with the secretion increasing at low glucose levels but being suppressed by high insulin levels. At normal fasting levels of glucose, there is a basal level of glucagon secretion, taken here to be a constant c_0. At higher glucose concentrations, additional secretion is suppressed, but when the glucose concentration falls below a threshold level G_E, glucagon secretion should increase linearly with decreasing G. Thus an initial form for the secretion term in (2.3) is

$$c_0 + c_1(G_E - G)u(G_E - G), \tag{3.17}$$

with the Heaviside step function u serving to switch the secretion on or off at the threshold value G_E. When $I = 0$, the glucagon secretion rate is at its maximum, and as I increases, the secretion rate should decrease. This fact suggests that (3.17) should be modified to

$$dE_{sec}/dt = c_0 + \frac{c_1}{c_2 + I}(G_E - G)u(G_E - G). \tag{3.18}$$

The fasting level of glucagon is known to be $\bar{E} = 8.2$ ng/dl [9], from which c_0 is determined from the relationship $\bar{E} = c_0/c_3$ to be $c_0 = 0.656$ ng/dl/min. The threshold value of glucose below which glucagon secretion occurs is well-established to be $G_E = 75$ mg/dl [15]. The values of c_1 and c_2 were determined by fitting to data extracted from fig. 1 of Bolli *et al.* [9], yielding $c_1 = 2.5441$ (ng/dl/min of E)(ng/dl of I) per (mg/dl of G) and $c_2 = -5.2523$ ng/dl (of I).

Substituting (3.16) and (3.18) into (2.3) produces the final form of the glucagon equation as

$$dE/dt = c_0 + \frac{c_1}{c_2 + I}(G_E - G)u(G_E - G) - c_3 E. \tag{3.19}$$

Note that when $G > G_E$, the Heaviside function is switched off, setting the middle term of (3.19) to 0, resulting in an equilibrium value of glucagon being achieved when $dE/dt = 0$, i.e., at $\bar{E} = c_0/c_3$.

3.4. **Diabetes.** The model of glucose utilization represented by equations (3.10), (3.15), and (3.19) pertains to a healthy individual. To simulate the different forms of diabetes requires modification of certain terms, which we discuss here.

Type 1 diabetes is characterized by the destruction of most of the β cells, with the result that little insulin is produced. Although this effect could be modelled in various ways, we do so in a simple manner whereby the insulin secretion terms (3.11) are replaced by a single constant term b_3 so that the insulin equation (3.15) in the model is replaced by

$$dI/dt = b_3 - b_2 I + I_{exg}(t). \tag{3.20}$$

The value of b_3 can be expected to vary with the severity of the individual's condition, but here we choose $b_3 = 3.914$ ng/dl/min, corresponding to an equilibrium level of insulin of 19 ng/dl. Type 1 diabetes is known to have complications, such

as renal failure and liver disease, which occur over the long term; such factors are not incorporated into the model.

In type 2 diabetes, the β cells continue to produce insulin, although at a reduced level. Moreover, the body develops a resistance to insulin thus reducing its effectiveness. The former effect can be modelled by multiplying the insulin secretion terms (3.11) by a reduction factor $0 \leq InsRed \leq 1$. The value of $InsRed$ would vary with the individual, so here we choose an intermediate value of $InsRed = 0.5$. The latter effect can be modelled by multiplying usage-related occurrences of $I(t)$ by an effectiveness factor. Specifically we change the peripheral uptake (3.5) to

$$dG_{per}/dt = -(k_1 G + k_2) I(InsEff), \tag{3.21}$$

and the hepatic uptake/release (3.3) to

$$dG_{hep}/dt = \frac{k_5 k_6}{k_6 + I(InsEff2)} - \frac{k_8 G}{k_9 + G} + k_7 E, \tag{3.22}$$

where the effectiveness factors are such that $0 \leq InsEff, InsEff2 \leq 1$. The actual values of the factors will depend upon the individual, and here we take them to be $InsEff = InsEff2 = 0.2$.

The final situation that we simulate is that of damage to the α cells (which secrete glucagon), which is believed to be of possible importance in many diabetic cases. This is due to the fact that the sensitivity of the α cells to glucose is apparently diminished over time, so that more glucose is needed in order for suppression of glucagon secretion to occur, resulting in an increase in the value of G_E. For our purposes here, we take that revised value to be $G_E = 125$ mg/dl. In addition, the α cells may be desensitized to insulin, which may be modelled by multiplying $I(t)$ in (3.19) by an effectiveness factor $InsEff3$ so that the glucagon equation becomes

$$dE/dt = c_0 + \frac{c_1}{c_2 + I(InsEff3)}(G_E - G)u(G_E - G) - c_3 E. \tag{3.23}$$

We take $InsEff3 = 0.2$.

4. **Results and Discussion.** In this section, we look at some representative results for the model, for both healthy and diabetic individuals. The starting point is the set of equations (3.10), (3.15) and (3.19) for a healthy individual, with parameter values as indicated in sections 3.1-3.3. These equations form a *dynamical system*, which can be solved numerically for arbitrary initial conditions. It can be shown that the system has just one equilibrium (i.e., steady-state solution), occurring at $\bar{G} = 93.6$, $\bar{I} = 41.6$, $\bar{E} = 8.2$. The equilibrium can be shown to be *stable*, which indicates physiologically that, at least for modest deviations from the steady-state values, the system returns itself to equilibrium, as would be expected in a healthy individual; i.e., when the plasma concentration of one or more of the substances deviates from equilibrium, the system readjusts itself so as to drive the concentrations back to equilibrium. This behaviour is illustrated in Figure 1, where neither food nor insulin is given, while the initial values are taken to be $G_0 = 60$, $I_0 = \bar{I}$, $E_0 = \bar{E}$ (i.e., glucose initially below equilibrium, insulin and glucagon at equilibrium). The graphs show that the glucose level very quickly (within 15 minutes) returns to the equilibrium level, due to a combination of a short-term drop in the insulin level (by about 25%) and a rise in the glucagon level (of about 20%). This behaviour is expected because of the known effect of glucagon to raise glucose levels and of insulin to lower them. When the calculation was repeated, but with insulin and glucagon levels held constant at their equilibrium values, it took about

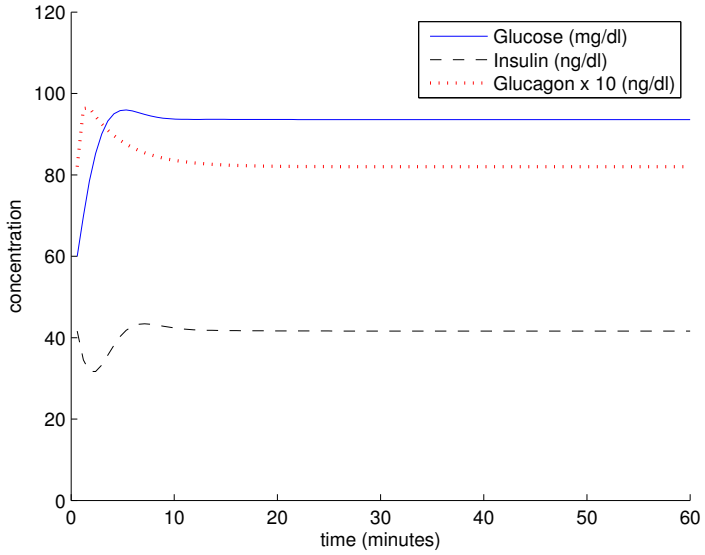

FIGURE 1. $G(t)$, $I(t)$, and $E(t) \times 10$ for a healthy individual, given no food ($G_{total} = 0$) and no insulin ($I_{total} = 0$).

2-3 times longer for the glucose level to return to equilibrium. However, with just glucagon kept constant, the equilibration process is only modestly slower than when glucagon is allowed to vary. This is indicative of the fact (Unger [24], Kruger *et al.* [18]) that insulin is the primary regulator of the bloodstream's glucose levels, with glucagon acting in a secondary role as one (but not the only) counterbalance to insulin's actions. The role of glucagon becomes more pronounced when the glucose level falls even further below the secretion threshold of $G_E = 75$ mg/dl, than the $G_0 = 60$ mg/dl of Figure 1. The distinction between holding glucagon constant, versus letting it vary, becomes greater with lower glucose levels. The importance of glucagon in correcting such situations of hypoglycemia is thus emphasized.

The situation that is normal for healthy individuals is ingestion of a meal, but with no administration of exogenous insulin. This case is illustrated in Figure 2, for a meal with a content of $G_{total} = 200000$ mg of glucose, and with all levels initially at their equilibrium values. As might be anticipated, the glucose level rises to a maximum of over 125 mg/dl and remains elevated over a period of several hours, before dropping back to equilibrium level. Correspondingly, the insulin level rises over the same time period, acting to bring the glucose levels down. The glucagon level (not shown) remains constant at $\bar{E} = 8.2$ ng/dl because the glucose concentration always remains above the threshold value $G_E = 75$ mg/dl, below which additional glucagon secretion commences (c.f. (3.17)). This circumstance would be the usual one for hyperglycemia wherein glucose levels are high resulting in glucagon levels remaining constant. The modellistic implication is that glucagon as a dynamic variable can be removed from the model, in such cases. Such is *not* the case for hypoglycemia, where glucagon levels may change significantly.

We turn now to type 1 diabetes, with the model modifications outlined in section 3.4. Figure 3 illustrates a typical situation where a meal with $G_{total} = 200000$ mg

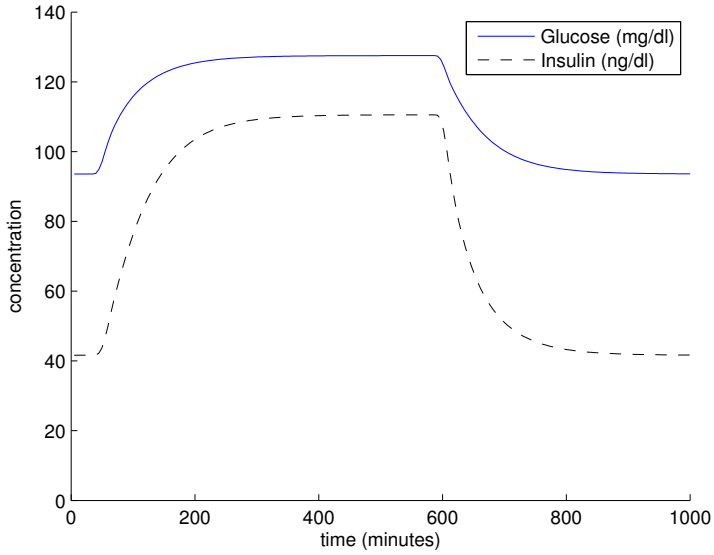

FIGURE 2. $G(t)$ and $I(t)$ for a healthy individual, with ingestion of a meal ($G_{total} = 200000$) but no insulin ($I_{total} = 0$). $E(t) =$ constant is not shown.

glucose content is taken (at $t = 0$) followed an hour later by an administration of 27778 ng/dl Lente insulin, corresponding to $\frac{1}{3}$ U per kg bodyweight. (The standard clinical unit for measurement of insulin is 1 U which corresponds to 1/24 mg of insulin.) The initial values are taken to be the new equilibrium levels of equations (3.10), (3.19), and (3.20), namely $\bar{G} = 120$, $\bar{I} = 19$, and $\bar{E} = 8.2$. As expected, the meal causes the modelled glucose level to rise quickly to almost 200 mg/dl. The insulin injection an hour later immediately raises the plasma insulin level $I(t)$, which the model responds with a steep decline in $G(t)$. In this case, the insulin serves to decrease the glucose to a very low level (eventually around 50 mg/dl), thus causing the glucagon secretion to increase dramatically at $t = 600$ in order to drive $G(t)$ back up to equilibrium. Thus the model predicts that glucagon plays a crucial role in correcting this hypoglycemic situation. Qualitatively similar results are obtained for other meal sizes and insulin doses and types. For example, a larger meal with higher glucose content (G_{total}) would cause more glucose to be in the body, and the predicted duration of any glucagon secretion would be considerably decreased. Figure 3 can be compared with Figure 2 (for a healthy person), where it can be noted that the return to equilibrium takes approximately twice as long for a diabetic as for a healthy person, and with noticeably more variation in the function values, especially $G(t)$.

Type 2 diabetes differs from type 1 because more significant amounts of insulin are produced, but the insulin's effectiveness is reduced, thus leading to the model implications discussed in section 3.4. Figure 4 displays a typical scenario wherein a meal with glucose content $G_{total} = 200000$ mg is ingested at $t = 0$, but no insulin is administered (because type 2 diabetics usually do not take insulin). After the meal, the plasma glucose level $G(t)$ increases rapidly to over 190 mg/dl and

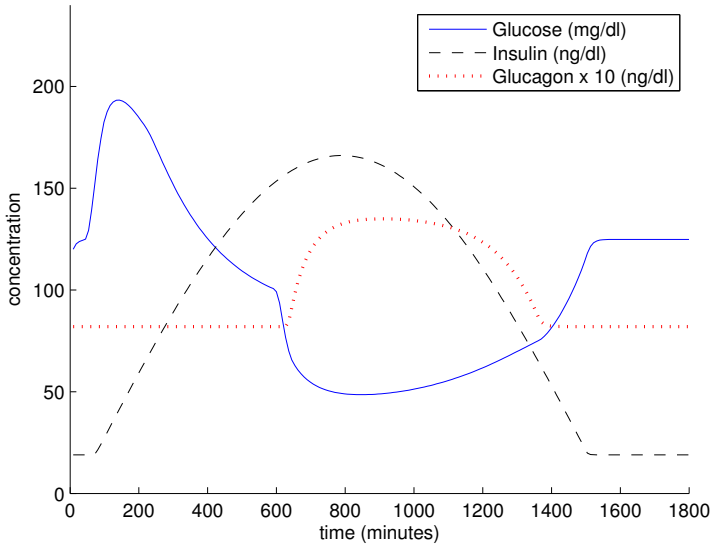

FIGURE 3. $G(t)$, $I(t)$, and $E(t) \times 10$ for a type 1 diabetic, given both food ($G_{total} = 200000$) and insulin ($I_{total} = 27778$).

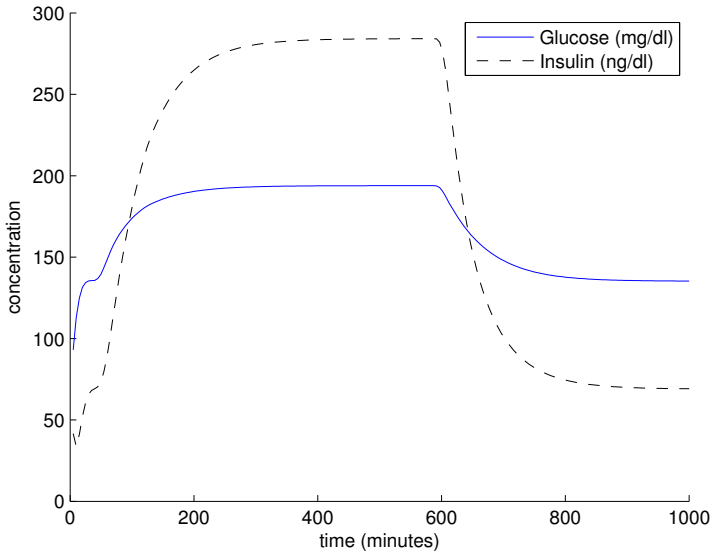

FIGURE 4. $G(t)$ and $I(t)$ for a type 2 diabetic, given food ($G_{total} = 200000$) but no insulin ($I_{total} = 0$). $E(t) =$ constant is not shown.

remains high over the course of several hours. As a consequence, the plasma insulin level $I(t)$ rises to very high levels (albeit more slowly than the rise in $G(t)$), and eventually lowers $G(t)$ to its equilibrium level (around 140 mg/dl) after about 10

hours. Comparison with Figure 2 shows that the equilibration process here takes about the same length of time as in a healthy person, but that the glucose levels go much higher. Due to the reduced effectiveness of the insulin, $I(t)$ has its maximum value at over 250 ng/dl, much higher than in the corresponding situation for healthy subjects (Figure 2, where $I(t)$ has a maximum of about 125 ng/dl), or even for type 1 diabetics (Figure 3, where the maximum of $I(t)$ is about 160 ng/dl). Nonetheless, the individual's natural insulin is sufficient to control hyperglycemia (although at elevated equilibrium levels of glucose), without resorting to administration of exogenous insulin. The glucagon level (not shown in figure) remains constant at the equilibrium value $\bar{E} = 8.2$ ng/dl, because the glucose levels always remain above $G_E = 75$ mg/dl. Below this level, additional glucagon secretion occurs. The relevance of glucagon to type 2 diabetes can be seen by examining a hypoglycemic situation (induced by a period of fasting, for instance). This situation is shown in Figure 5, where the initial plasma glucose concentration is taken to be $G_0 = 60$ mg/dl. This is below G_E, and leads to a sharp rise in the glucagon level, and a

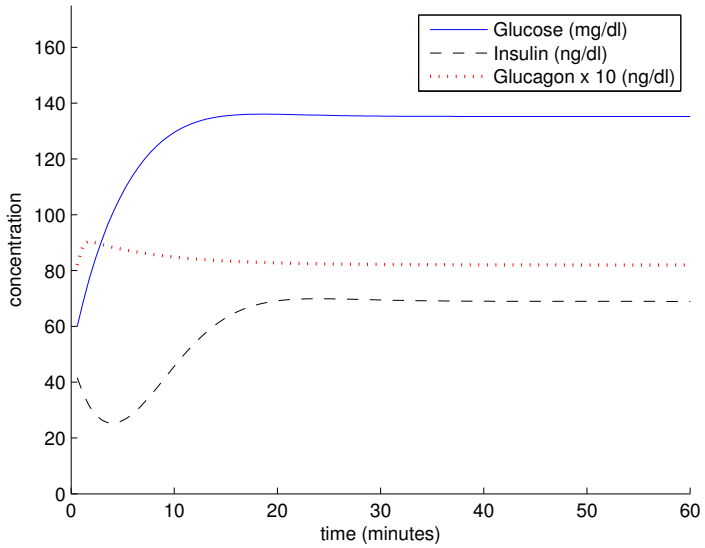

FIGURE 5. $G(t)$, $I(t)$, and $E(t) \times 10$ for a type 2 diabetic, given no food ($G_{total} = 0$) and no insulin ($I_{total} = 0$).

corresponding drop in the insulin level, thus producing the desired increase in the glucose level to its equilibrium level, over a reasonably short time period of about 30 minutes. Figure 5 shows a strong qualitative resemblance to the corresponding situation for a healthy person (Figure 1), differing primarily in that the return to equilibrium in the diabetic case takes about 1.5-2 times as long as it does in the healthy case. The equilibria for the two cases are obviously different, most importantly in that the equilibrium for the diabetic case has a significantly elevated level of glucose compared to that for a healthy person. The well-known counterbalancing effects of the two hormones (Unger [24], Kruger *et al.* [18]) are again illustrated (in both Figures 1 and 5), where glucagon acts to help correct the hypoglycemic

situation, but the rise in glucose levels is restricted by the counter-effect of insulin, which acts to prevent hyperglycemia.

The importance of healthy α cells, with their complicated dependence on glucose and insulin concentrations determining the glucagon secretion rate, is demonstrated by looking at the consequences of the improper functioning of damaged α cells. This situation is shown in Figure 6, using the model modifications discussed in section 3.4, and with initial glucose concentration being very low, $G_0 = 60$ mg/dl. As

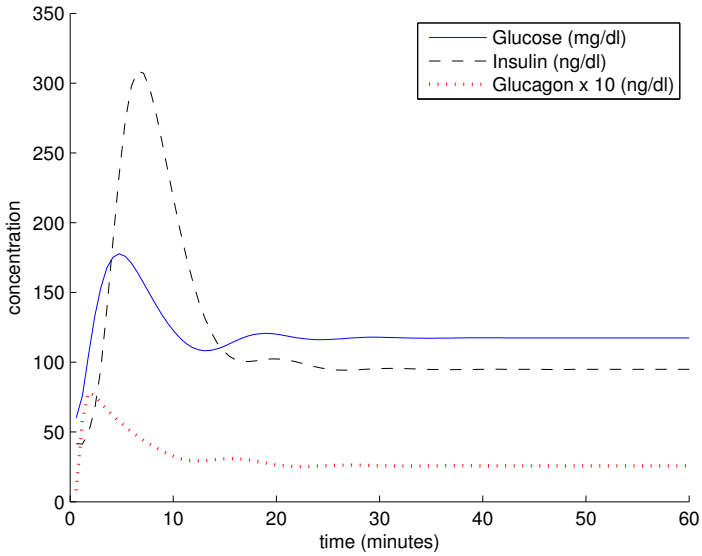

FIGURE 6. $G(t)$, $I(t)$, and $E(t)\times 10$ for an individual with damaged α cells, given no food ($G_{total} = 0$) and no insulin ($I_{total} = 0$).

expected, the model predicts that a glucagon concentration increase occurs, and in fact this increase happens quickly and sharply. Because of the reduced sensitivity to glucose (higher G_E), glucagon secretion continues even when glucose levels are in the range 75-125 mg/dl. As a result, the glucose concentration increases as high as 180 mg/dl, before dropping to a new, elevated equilibrium value of about 120 mg/dl. The equilibrium values of insulin and glucose are now elevated to several times their values in the healthy case (c.f. Figure 1), and once again the return to equilibrium takes about twice as long as in a healthy person. Figure 6 emphasizes the role of the α cells, and their production of glucagon, in the regulation of plasma glucose concentration. Damage to the α cells, often believed to be a long-term effect of diabetes, has a significant impact on the glucose levels. There is experimental support for these theoretical results. Shah *et al.* [20] showed that in type 2 diabetics, a lack of suppression of glucagon is a contributory factor to hyperglycemia after a meal. Ahren and Larsson [4] reached a similar, and perhaps stronger, conclusion that impaired glucose tolerance is indeed associated with reduced suppression of glucagon secretion, which is insulin-induced and possibly caused by α cell resistance to insulin. In both cases, they emphasized that treatment of diabetes would be aided by the development of agents to inhibit glucagon secretion or counteract glucagon action.

In summary, the model developed in this paper demonstrates the strong dependence of plasma glucose levels on the concentrations of the key hormones, insulin and glucagon. In the hyperglycemic situation that is most important to diabetics, the glucagon concentration stays constant and can be removed from consideration, as is done by most models. For the hypoglycemic case, which is a serious acute complication, consideration of the role of glucagon is vital to an accurate calculation of the glucose level. The oft-ignored α cells are shown to play an essential role in glucose regulation, and their malfunction can have a significant effect by raising glucose levels.

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E-mail address: sulston@upei.ca; ireland@upei.ca; jpraught@dal.ca