DOING PHYSICS WITH PYTHON

THE βIG MATHEMATICAL MODEL FOR THE NONLINEAR DYNAMICAL GLUCOSE – INSULIN REGULATORY SYSTEM

Ian Cooper

matlabvisualphysics@gmail.com

SCRIPTS

BIG01P.py

Plots: Gss, Iss, Bss vs k1 GM vs G GH vs G

BIG01A.py

Calculations: Pathological and physiological fixed points and contribution of each term to $d\beta / dt$

Plots: insulin secretion and insulin sensitivity vs glucose level

BIG02A.py

Plot: Time evolution of the βIG system β, I, G vs t

BIG02B.py

Meal response / Plot: Time evolution of the βIG system β, I, G vs t (k_3, k_5)

BIG02C.py

T2D and glucose toxicity:/ Plot: Time evolution of the βIG system β, I, G vs t (k_3, k_5, k_{10})

BIG06.py

Plot: Gss vs k10 physiological and saddle fixed points

Plot: reduction factor in equation for $d\beta / dt$

BIG07.py

Solve ode / plot: G_{ss} and dG_{ss}/dk_5 vs k_5

BIG08.py

Solve ode / plot: G_{ss} Iss Bss dG_{ss}/dk_3 vs k_3 insulin resistance

BIG010.py

Roots of β-cell mass equation using fsolve. Plot: global response curve $d\beta/dt$ vs G

BIG12.py

Plot: Gss, Iss, Bss vs k_1 physiological and saddle fixed points HGP

BIG013.py

Solve ode / plot: G_{ss} Iss Bss dG_{ss}/dk_5 vs k_5 insulin resistance

BIG014.py

Solve ode / plot: G_{ss} Iss Bss dG_{ss}/dk_5 vs k_{10} glucose toxicity

BIG_51.py BIG_52.py BIG_53.py BIG_54.py

Solve ode / Response of glucose regulatory system after the consumption of food Model NGT, IFT, T2D individuals

THE βIG MODEL FOR THE GLUCOSE - INSULIN REGULATORY SYSTEM

The body's regulation of plasma glucose and plasma insulin is amazing in that it can maintain a basal (steady-state) glucose concentration within a narrow range, always returning the basal glucose concentration after food or physical activity. Changes in the plasma glucose concentration are due to the amount of glucose that is removed from the blood (clearance or uptake: utilization and storage) and the amount of glucose that is added to the blood (absorption and production). Glucose homeostasis is achieved autonomically by nutrient sensing and hormonal signalling intracellular mechanisms that control tissue-specific rates of glucose removal and addition continuously throughout each day.

For a healthy individual, the normal plasma glucose concentration is in the range from about 70 to 100 $mg.dL^{-1}$. Normoglycemia is when the plasma glucose is within the normal range and is ideal for the function of our bodies. Too little plasma glucose is called hypoglycaemia and results the body's cells being starved of glucose. Excessive glucose is called hyperglycaemia and it creates a sticky, paralysing effect on cells. The glucose in the blood acts as a fuel when it is transferred into the cells of the body. A delicate balance between hormones of the pancreas, liver, intestines, brain, and even adrenals is required to maintain normal plasma glucose levels.

There is a very wide range of behaviours of the G-I regulatory system for different individuals. Hence, it is convenient to classify people into four categories based upon their basal glucose level: normal glucose tolerant individuals (NGT); impaired glucose tolerant individuals (IGT); type 2 diabetics (T2D); and type 1 diabetics (T1D).

Table 1 shows the ranges for the basal (steady-state) plasma glucose concentrations, insulin concentrations and β-cell mass for NGT, IGT, and T2D individuals when fasting.

Table 1. Basal values of β-cell mass, insulin concentration, and glucose concentration for NGT, IGT, and T2D individuals.

	NGT	IGT	T2D
β-cell mass [mg]	> 300	170 - 300	< 200
Insulin [$mU.L^{-1}$]	10 - 25	7 - 10	< 7
Glucose [$mg.dL^{-1}$]	70 - 100	100 - 125	> 125

Important body systems involved in the control of plasma glucose concentration include the liver, pancreas, intestines, muscles, body cells (tissues), adipose cells (tissues), kidney, and the brain. The most important being the role played by the liver and the pancreas. Figure 1 shows a schematic diagram for a simplified view of the major processes involved in the regulation of the plasma glucose concentration.

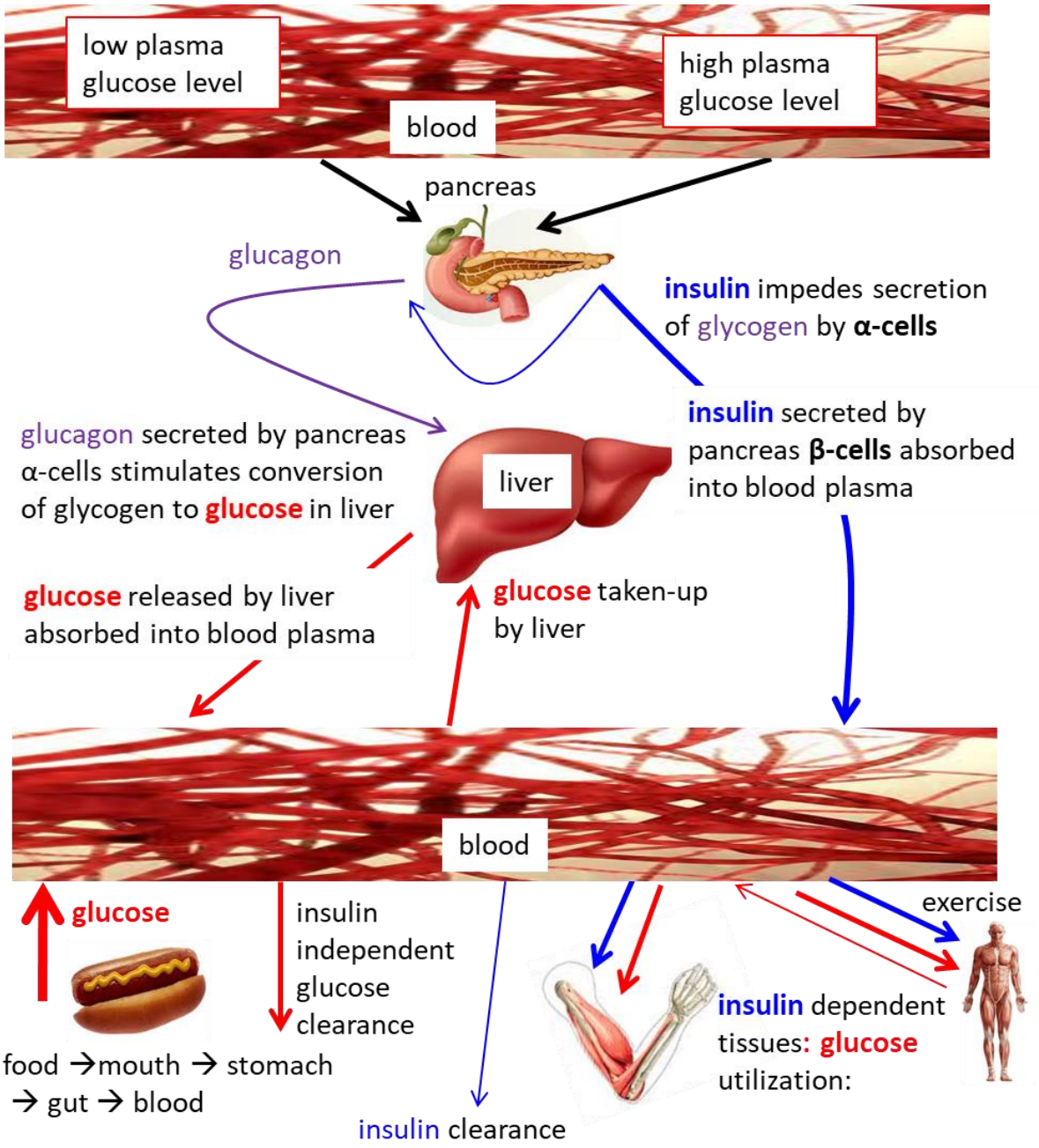


Fig. 1. A schematic diagram of the G-I regulatory system.

BIG_B.pptx

The liver is the body's glucose sink and source and acts to maintain the constant level of glucose in the circulating blood. Glucose is stored in the liver as glycogen. If the plasma glucose concentration is less than its basal value, the α-cells of the pancreas secrete glucagon into the blood. Glucagon causes the liver to engage in glycogenolysis, the process of converting stored glycogen into glucose, which is then released into the bloodstream. If insufficient glucose is released into the blood via glycogenolysis, then glucose can be released into the blood from the breakdown of non-carbohydrates molecules (amino acids, waste products and fat by-products) in a process called gluconeogenesis. Glycogen is a polysaccharide, made and stored primarily in the cells of the liver and it provides an energy reserve that can be quickly mobilized to meet a sudden need for glucose. Glucose that is not immediately used is stored by the body as glycogen in the liver, muscles, and fat tissues.

The pancreas monitors the plasma glucose level and in response secretes the hormones insulin from the β-cells and glucagon from the α-cells. They play a central glucose-dependent counterregulatory role in striving to keep the plasma glucose level within a narrow range.

When the glucose level rises above the basal values, the β-cells of the pancreas secrete the hormone insulin into the bloodstream which reduces the blood glucose levels. The most important role of insulin is that it an essential hormone that is required to allow glucose to be

taken up and used by insulin-dependent tissues by triggering the cells to open up and let the glucose in (figure 2). Once inside, the cells convert glucose into energy or store it to use later. Thus, the insulin increases the rate at which blood glucose is transported into muscles, the liver and adipose tissues. Without insulin, our bodies cannot use or store glucose for energy and the glucose stays in your blood.

Insulin's action in the liver is counter-regulated by glucagon. The insulin helps supress the secretion of glucagon and thus reduces the amount of glucose released into the blood from the liver by glycogenolysis.

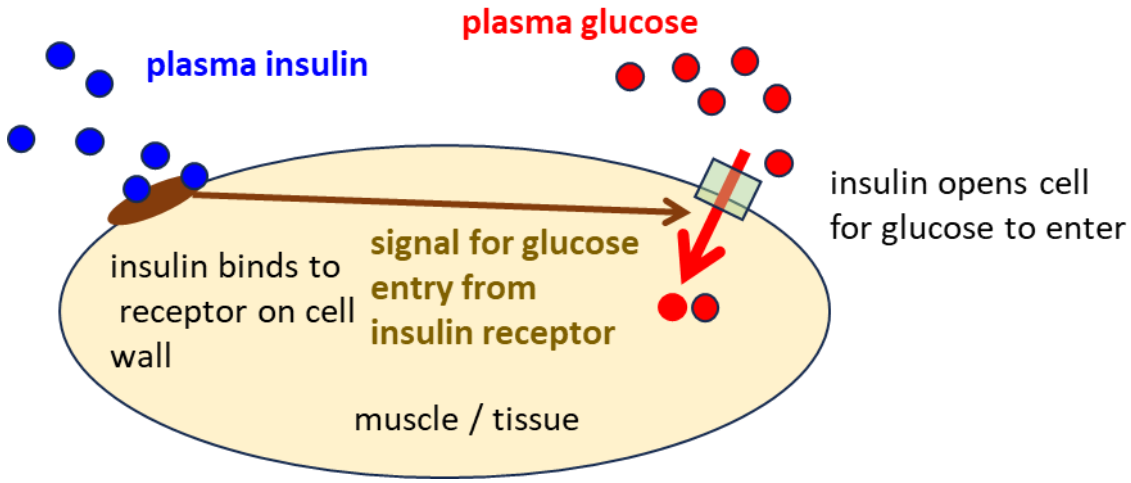


Fig. 2. Insulin triggers a cell that needs energy to open a pathway for glucose to enter. BIG_B.pptx

The role played by the β-cells of the pancreas is of paramount importance in controlling the amount of glucose in the blood. When the plasma glucose level rises, each β-cells secretes insulin at a greater rate and the population of actively secreting β-cells also increases. The greater the level of glucose in the blood, than the greater the secretion rate and the larger the population of actively secreting β-cells. However, there is a maximum rate at which the β-cells can secrete insulin and the population of active secreting insulin β-cells saturates at high plasma glucose concentration. So, there is a limit to which the β-cells can control high levels of glucose in the blood. As the glucose levels fall, both the secretion rate of insulin and the population of active secreting β-cells decrease (figure 3).

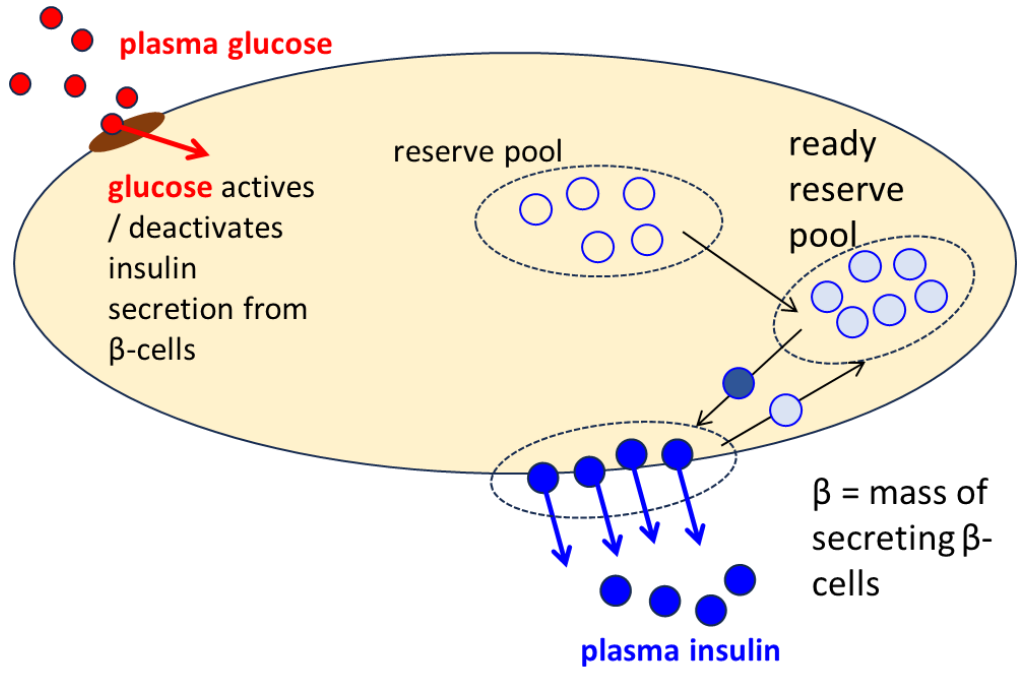


Fig. 3. Pancreas: The secretion rate of insulin from the β-cells into the blood depends upon the plasma glucose concentration.

BIG_A.pptx

The kidneys are involved in the regulation of glucose via three different mechanisms: (i) release of glucose into the blood via gluconeogenesis; (ii) uptake of glucose from the blood to satisfy its energy needs; and (iii) glucose absorbed into the kidneys is filter so that the urine is virtually glucose free resulting in the reabsorption of glucose back into the bloodstream.

The brain depends on glucose as its main source of energy. In the brain, neurons have the highest energy demand, requiring continuous delivery of glucose from blood. The brain accounts for ~2% of the body weight, but it consumes ~20% of glucose-derived energy making it the main consumer of glucose. Tight regulation of glucose metabolism is critical for brain physiology and disturbed glucose metabolism in the brain underlies several diseases affecting both the brain itself as well as the entire body.

When we ingest a meal, our intestine secretes hormones that are released into the bloodstream. Amongst these hormones are the incretins hormones which stimulate an increase in the secretion of insulin from β-cells which is essential for the regulation of postprandial glucose concentrations. Approximately 20% of endogenous glucose production is accounted for by the kidneys while the liver accounts for ~80%.

THE βIG MATHEMATICAL MODEL FOR THE GLUCOSE – INSULIN REGULATORY SYSTEM

It is possible to construct mathematical models to better understand this dynamical G-I regulatory system. In the proposed βIG model, four compartments (subsystems) are used to describe the nonlinear dynamical G-I regulatory system: (1) food, (2) glucose, (3) insulin, and (4) β-cell mass.

βIG model

1. Food enters the stomach where digestion begins. The food is broken down into small components including glucose and is then absorbed through the intestines into the bloodstream.
2. The blood glucose concentration increase caused by the glucose absorption induces pancreatic β-cells to secrete insulin.
3. The released insulin is captured by receptor sites on cell membranes which results in opening channels to allow glucose to enter the interior of the cells from the blood stream, reducing the blood glucose levels.
4. If blood glucose levels are too low, pancreatic glucagon-induced hepatic glucose release restores the steady-state homeostatic level.

The three primary model variables are the β-cell mass $\beta(t)$ [mg], plasma insulin concentration $I(t)$ [mU.L^{-1}], and the plasma glucose concentration $G(t)$ [mg.dL^{-1}]. Time t is usually measured in days [d], hours [h], or minutes [min].

The βIG model consists of three nonlinear ordinary differential equations.

Glucose compartment

$$(1) \qquad \frac{dG(t)}{dt} = k_1 - k_2\,G(t) - \frac{k_3\,I(t)G(t)}{k_4\,G(t)+1} + k_{gut}\,G_{gut}(t)$$

Insulin compartment

$$(2) \qquad \frac{dI(t)}{dt} = \beta(t)\,k_5\left(\frac{G(t)^2}{k_6{}^2 + G(t)^2}\right) - k_7\,I(t)$$

β-cell mass compartment

$$(3) \qquad \frac{d\beta(t)}{dt} = \left(-k_8 + k_9\,G(t) - k_{10}\,G(t)^2\right)\beta(t) - k_{11}\tan\left(k_{12}\,\beta(t)\right)$$

The k parameters are variables that can be adjusted to model the βIG system response for individuals with different glucose tolerances. The rate at which glucose enters the bloodstream from the gut is given by the term $k_{gut}\,G_{gut}(t)$

Food compartment

The intake of food is modelled using a two-compartment model where $G_{STO}(t)$ is the food intake to the stomach and $G_{GUT}(t)$ is the variable for the glucose that is absorbed into the blood from the gut. The dynamics is described by equations 4 and 5

$$(4) \qquad \frac{dG_{STO}(t)}{dt} = -k_{STO}\, G_{STO}(t) \qquad k_{STO} = \frac{\log(2)}{t_{STO}}$$

where k_{STO} is a decay constant and t_{STO} is a half-life time for the capture of glucose in the intestines from the food in the stomach. dG_{STO}/dt is the rate at which glucose is transferred from the stomach to the gut.

$$(5) \qquad \frac{dG_{GUT}(t)}{dt} = -k_{GUT}\, G_{GUT}(t) + k_{STO}\, G_{STO}(t) \qquad k_{GUT} = \frac{\log(2)}{t_{GUT}}$$

where k_{GUT} is a decay constant and t_{GUT} is a half-life time for the glucose absorption occurring from the gut to the blood, $k_{STO}\, G_{STO}$ is the rate at which glucose is transferred from the stomach to the gut, and $-k_{GUT}\, G_{GUT}$ is the rate at which glucose is transferred from the gut to the bloodstream.

The food taken in passes through the stomach and into the intestines (gut) as described by equations 4 and 5. For a single meal, we assume that the stomach glucose is given by equation 6.

$$(6) \qquad G_{STO} = G_1 \exp(-k_{STO}\, t) \qquad t_{STO} = \log(2) / k_{STO}$$

where G_1 is the parameter for the food intake of meal 1. For multiple meals, the resultant intake is the sum of the glucose contribution for each meal where $k_{sto}(m) \equiv k_m$ (figure 4).

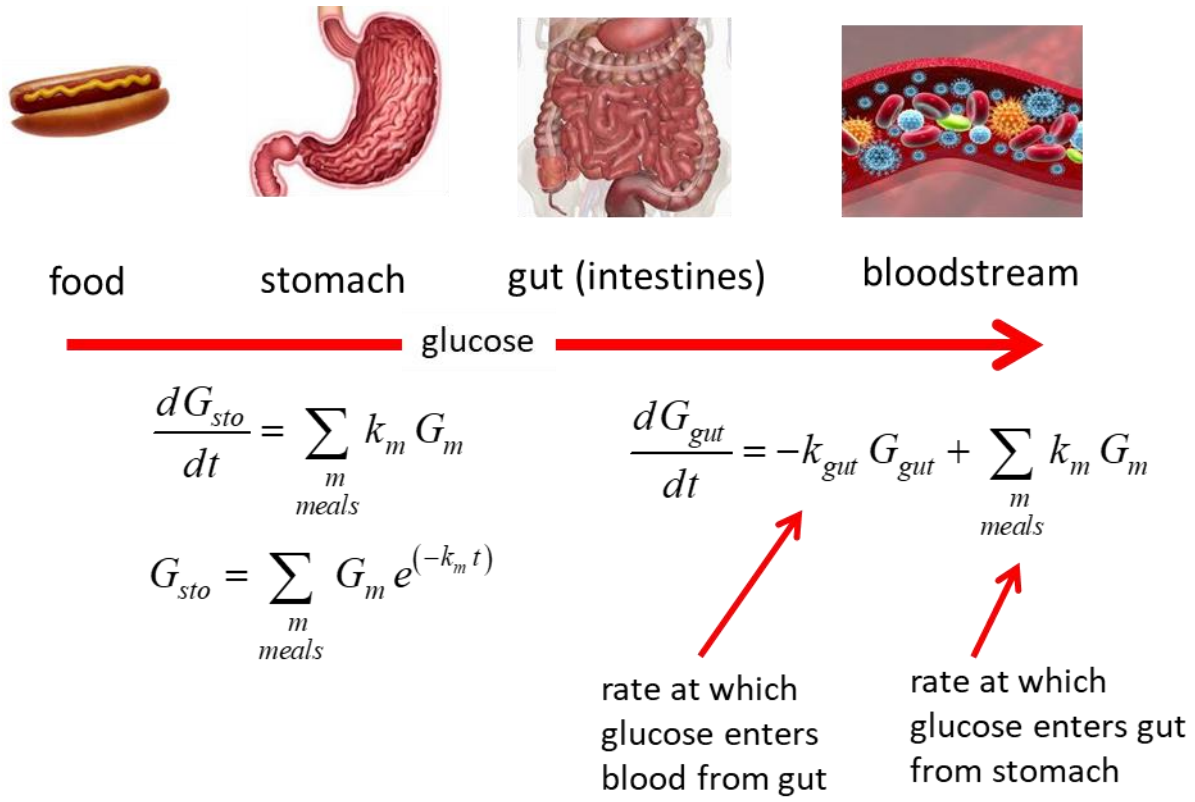


Fig. 4. Food dynamics for multiple meal input.

After the consumption of food, hormones called incretins are secreted from the intestines into the blood. The incretin hormones promote insulin secretion from pancreatic β-cells, inhibit gastric emptying and inhibits glucagon secretion which help in the lowering blood glucose levels after the food.

Glucose dynamics

Glucose is released into the blood mainly from food, liver, muscles, and kidneys and mainly removed from the blood by all the cells of the body and transfer through all the body's functional parts. The rate of change of the plasma glucose concentration depends on the difference between the rate glucose is added into the blood and the rate of uptake of glucose from the blood (figure 5).

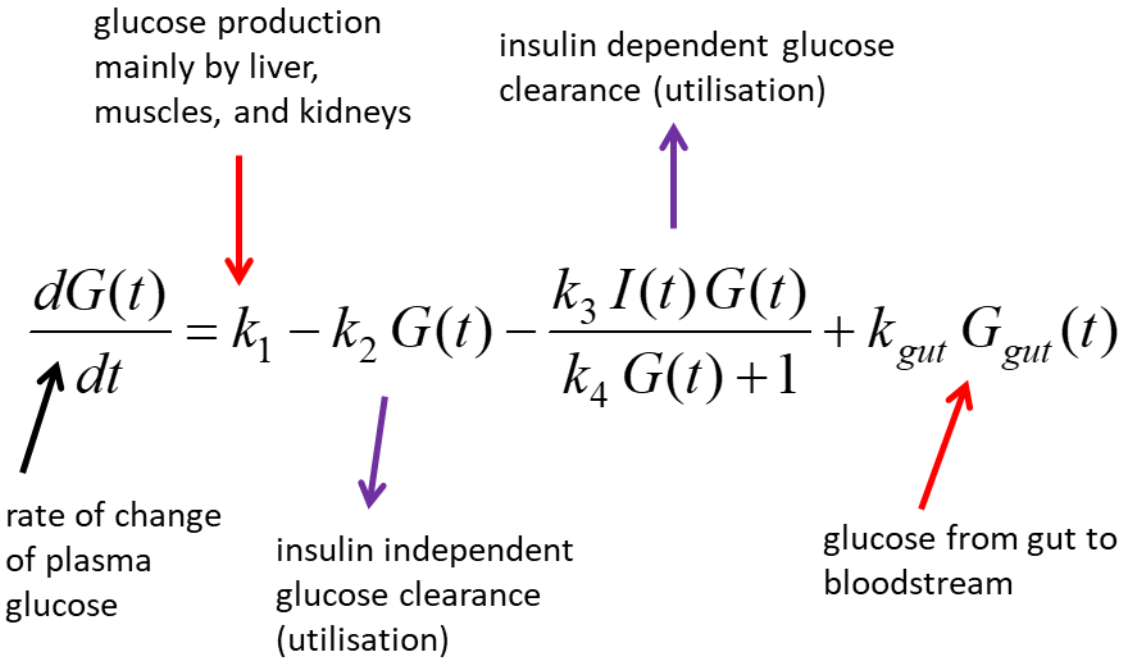


Fig. 5. Schematic diagram of the dynamics of the glucose compartment. BIG_B.pptx

The glucose dynamics – variables and parameters:

- k_1 [mg.dL^{-1}.d^{-1}]: Rate parameter for glucose production mainly by liver, muscles, and kidneys. Glucagon is a hormone released from the α-cells of the pancreas into the blood where it can trigger liver glycogen to convert back to glucose (glycogenolysis). Hence, it will raise the plasma glucose concentration. It the βIG model, the parameter for glucose is assumed to be a constant. But it is more likely that it should be a U shaped-function which has high values for both low and high glucose concentrations.

- k_2 [d-1]: Rate parameter for glucose clearance which is independent of the plasma insulin level.

  A primary purpose of maintaining constant plasma glucose levels is to keep a steady energy supply to the brain, which depends on glucose as its sole energy source. A prolonged decrease in plasma glucose concentrations impairs cerebral function and can cause brain damage and even death. When fasting, the brain accounts for ~50% of glucose utilization, and after a meal ~33%.

- k_3 [mU^{-1}.L.d^{-1}]: Insulin sensitivity parameter for glucose clearance which is insulin dependent (figure 6).

$$\left(\frac{dG_{\text{sensitivity}}}{dt}\right) / I = S_G = \frac{-k_3\, G}{k_4\, G + 1}$$

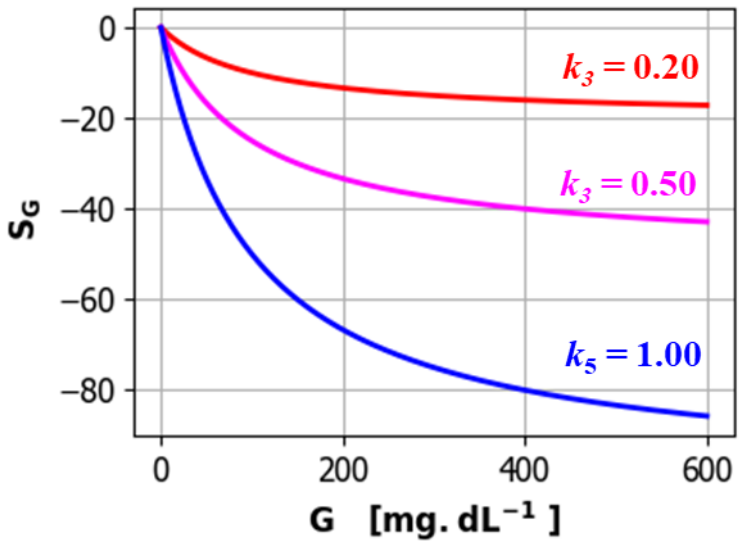


Fig. 6. Glucose uptake (utilisation) due to insulin sensitivity parameter k_3. The larger the value of k_3, then the greater the clearance of glucose from the blood. BIG_B.pptx

Clearence of glucose from the blood by insulin binding to receptors on the surface of a cell which causes a signal to the cell membrane to allow glucose molecules to across the membrane into the cell. The insulin sensitivity parameters k_3 determines the rate of clearance of the plasma glucose by the plasma insulin. The rate of clearance of the plasma glucose is slower for smaller values of the insulin sensitivity parameter k_3. There is a negative feedback cycle: if the glucose level rises, then the clearance rate of glucose from the blood increases due to the plasma insulin.

- k_4 [mg^{-1}.dL]: Michaelis function $G_H = G/(k_4 G + 1)$. The Michaelis function limits the range of the glucose in the blood which contributes to the insulin dependent clearance of the plasma glucose (figure 7).

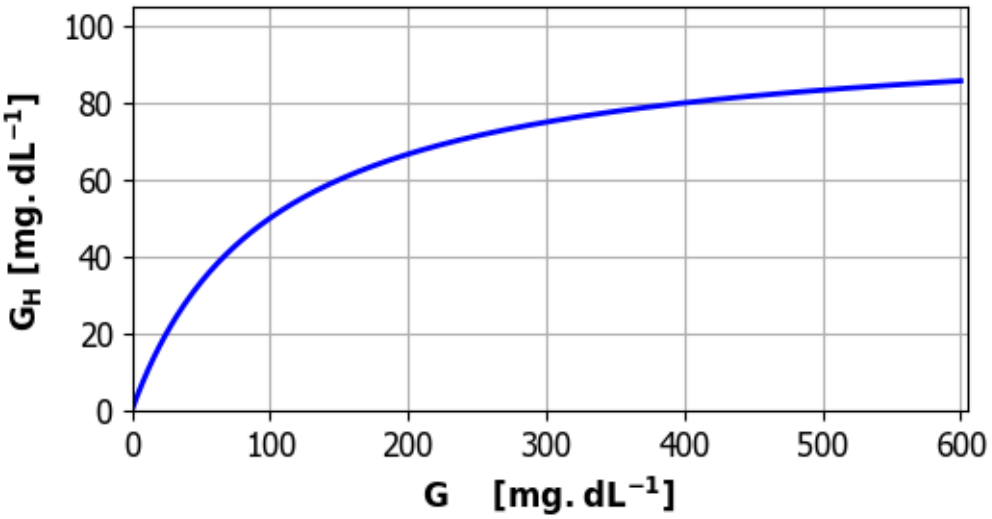


Fig. 7. Michaelis function: glucose uptake (utilisation) due to insulin sensitivity parameter k_4. BIG01P.py

The muscle and adipose tissues are major sites for insulin-mediated glucose removal from the blood stream, and the ability of these tissues to increase their glucose uptake in response to insulin is critical for maintaining normal blood glucose levels. Under fasting conditions these tissues account for ~25% of glucose utilization and for ~33% after a carbohydrate rich meal. In response to rising levels of insulin, glucose uptake in muscle and adipose tissue is increased. In periods of increased glucose demand, like in exercise, glucose uptake by skeletal muscle is greatly enhanced. The muscle also releases amino acids into the blood circulation that are used by the liver as

substrates for gluconeogenesis. Adipose tissue contributes to whole body glucose homeostasis by releasing free fatty acids and glycerol that can be taken up by the liver and used as substrates for gluconeogenesis, and also by secretion of adipokines that influence insulin sensitivity in muscle and liver.

Insulin dynamics

The pancreas is a major contributor to whole body glucose homeostasis, as it controls the secretion of both insulin and glucagon. When blood glucose levels rise, insulin is secreted from pancreatic β-cells to stimulate glucose clearance in muscle and adipose tissue and to suppress hepatic glucose production. In addition, hyperinsulinemia suppresses glucagon secretion from pancreatic α-cells. When blood glucose levels fall, insulin levels are suppressed and glucagon is secreted in response to catecholamines and glucocorticoids to promote hepatic glucose production and maintain glucose homeostasis.

The insulin subsystem is very complex. For example, when there is a glucose spike after eating food, there is a rapid release of insulin into the blood, lasting about 10 minutes, followed by a steady secretion of insulin for a much longer period. This biphasic behaviour leads to oscillations in the fasting glucose and insulin levels. The proposed model is very much simplified and excludes this biphasic behaviour.

In the βIG model, the rate of change of the insulin concentration depends only on the difference between the rate of secretion of insulin from the pancreas into the blood plasma and the rate of clearance of insulin from the blood plasma.

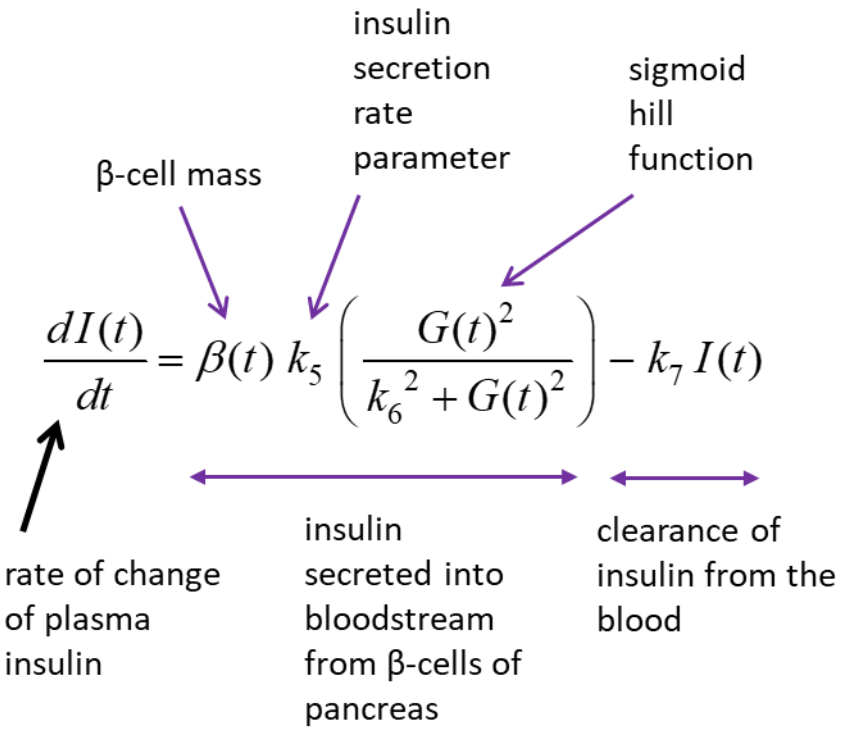


Fig. 8. Schematic diagram of the dynamics of the insulin compartment. BIG_B.pptx

The insulin dynamics - variables and parameters:

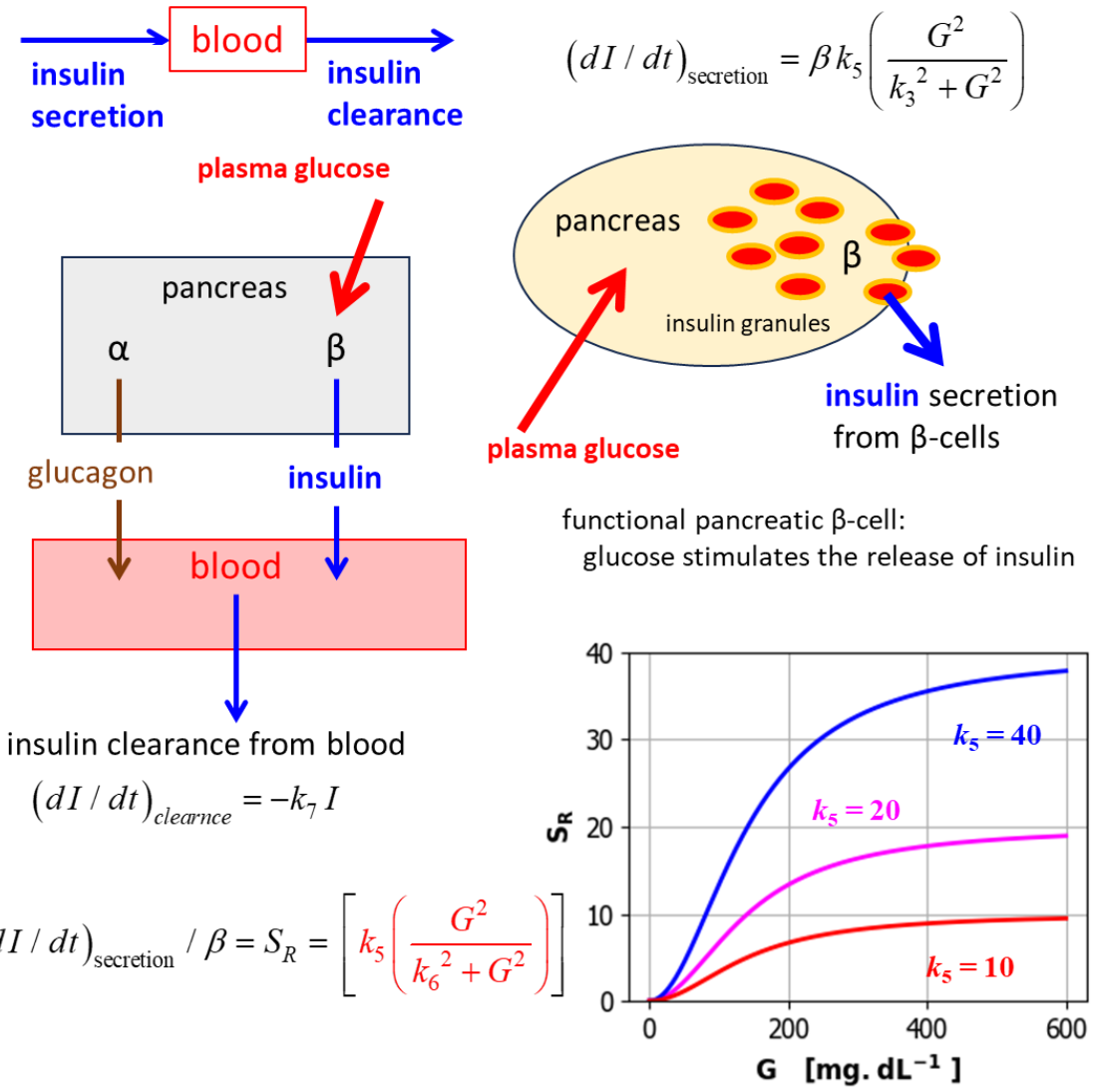
The rate of insulin released from the pancreas into the blood depends upon the plasma glucose concentration and is modelled a sigmoidal function, the β-cell mass and the maximum insulin secretion rate of eachβ-cell. Glucose from the blood can enter a β-cell and stimulate the release of insulin into the blood from pancreatic insulin granules.

- k_5 [mU.L^{-1}.d^{-1}]: insulin secretion rate. Assume all active β-cells secretion insulin at the same maximum rate.

- k_6 [mg.dL^{-1}]: Parameter for defining a Hill function that describes a sigmoid ranging from 0 to 1 which reaches a maximum at $G = k_6$

- k_7[d^{-1}]: Insulin clearance parameter which represents the combined insulin uptake at the liver, kidneys and insulin receptors. The liver helps in the clearance of insulin and this rate of clearance is assumed to be proportional to the plasma insulin concentration with k_7 being the constant of proportionality and we can define a clearance half-time t_I where $t_I = \log(2) / k_7$.

$$dI/dt = (dI/dt)_{\text{secretion}} + (dI/dt)_{clearance}$$



$$(dI/dt)_{\text{secretion}} / \beta = S_R = \left[k_5 \left(\frac{G^2}{k_6^2 + G^2} \right) \right]$$

Fig. 9. Insulin secretion from β-cell and insulin clearance from blood.

BIG01P.py BIG_A.pptx

β-cell dynamics

A hypothesis that can be drawn from the βIG model is that the population of β-cells that secrete insulin is the main factor that controls the dynamics of the glucose regulatory system. β is a dynamical quantity that represents the instantaneous mass of β-cells that are actively secreting insulin. A β-cell that secretes will be referred to as an active β-cell and that all active β-cells secrete insulin at the same rate. The β-cell mass responds to changes in the demand for insulin. For example, if more insulin is needed to reduce the glucose concentration, then the population of β-cells secreting will increase.

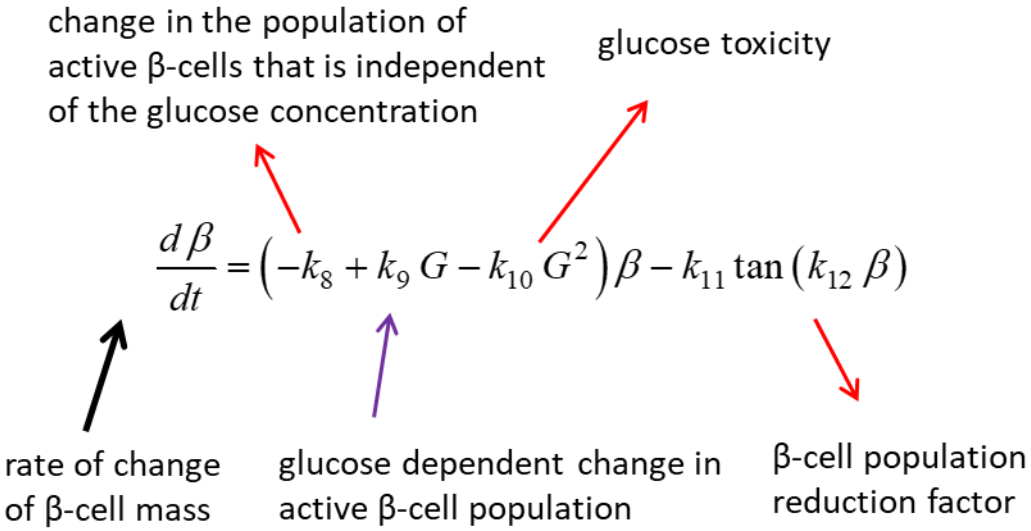


Fig. 10. β-cell dynamics.

The β-cell mass dynamics - variables and parameters:

- $d\beta / dt$ is the rate of change in the β-cell mass [mg.day^{-1}] due to changes in the population of β-cells that are actively secreting at that instant.

- k_8 [day^{-1} d^{-1}]: change in the population of active β-cells that is independent of the glucose concentration. $\left(k_8 \downarrow \Rightarrow d\beta / dt \uparrow\right)$.

- k_9 [mg^{-1}.dL.d^{-1}]: glucose dependent change in active β-cell population. $\left(k_9 \uparrow \Rightarrow d\beta / dt \uparrow\right)$. There is a feedback loop between the plasma glucose concentration and the β-cells of the pancreas. When the plasma glucose level rises, a signal is detected by the pancreas to increase the population of active β-cells. So, more β-cells secrete insulin resulting in an increase in level of the plasma insulin concentration.

- k_{10} [mg^{-2}.dL^2.d^{-1}]: glucose toxicity factor (glucotoxicity). When the plasma glucose level rises to high values, the result is that the active β-cell population decreases and reduces the amount of insulin secreted into the bloodstream. $\left(k_{10} \uparrow \Rightarrow d\beta / dt \downarrow\right)$

- $\beta_R \equiv -k_{11} \tan\left(k_{12}\, \beta\right)$ (k_{11} [d^{-1}] k_{12} [mg^{-1}]): This term does not appear in the Topp model. In the Topp model there is no upper

limit to the value of the β-cell mass. To describe a more realistic dynamical behaviour of the β-cell mass the term β_R is added to the Topp equation for β-cell dynamics. This function β_R reduces the growth of the β-cell population slowly when β is small but rises rapidly as β-cell becomes larger. There may be better functions to use which has a gradual increase in slope followed by a rapidly increasing slope (figure 11). Why include this term? It seems reasonable that as demand grows for more and more insulin to be secrete by increasing the β-cell population, the β-cells population becomes stressed and this stress limits or even reverses the size of the active β-cell population.

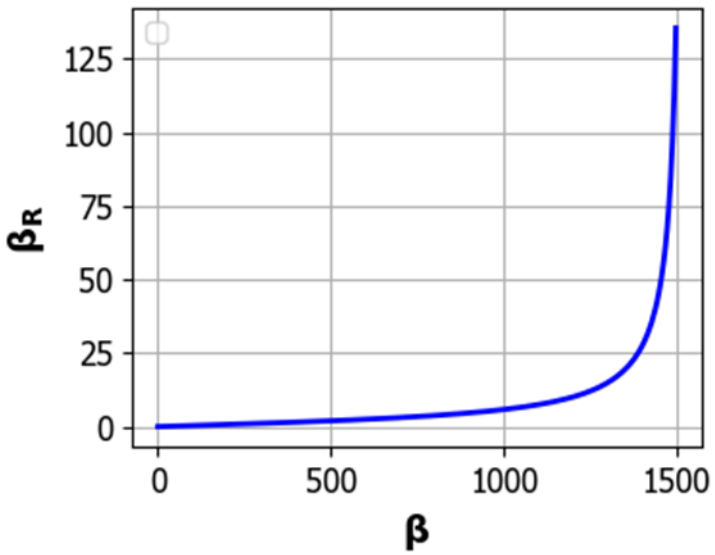


Fig. 11. Population reduction factor $\beta_R \equiv \left|-k_{11}\tan\left(k_{12}\,\beta\right)\right|$ as a function of β. BIG06.py

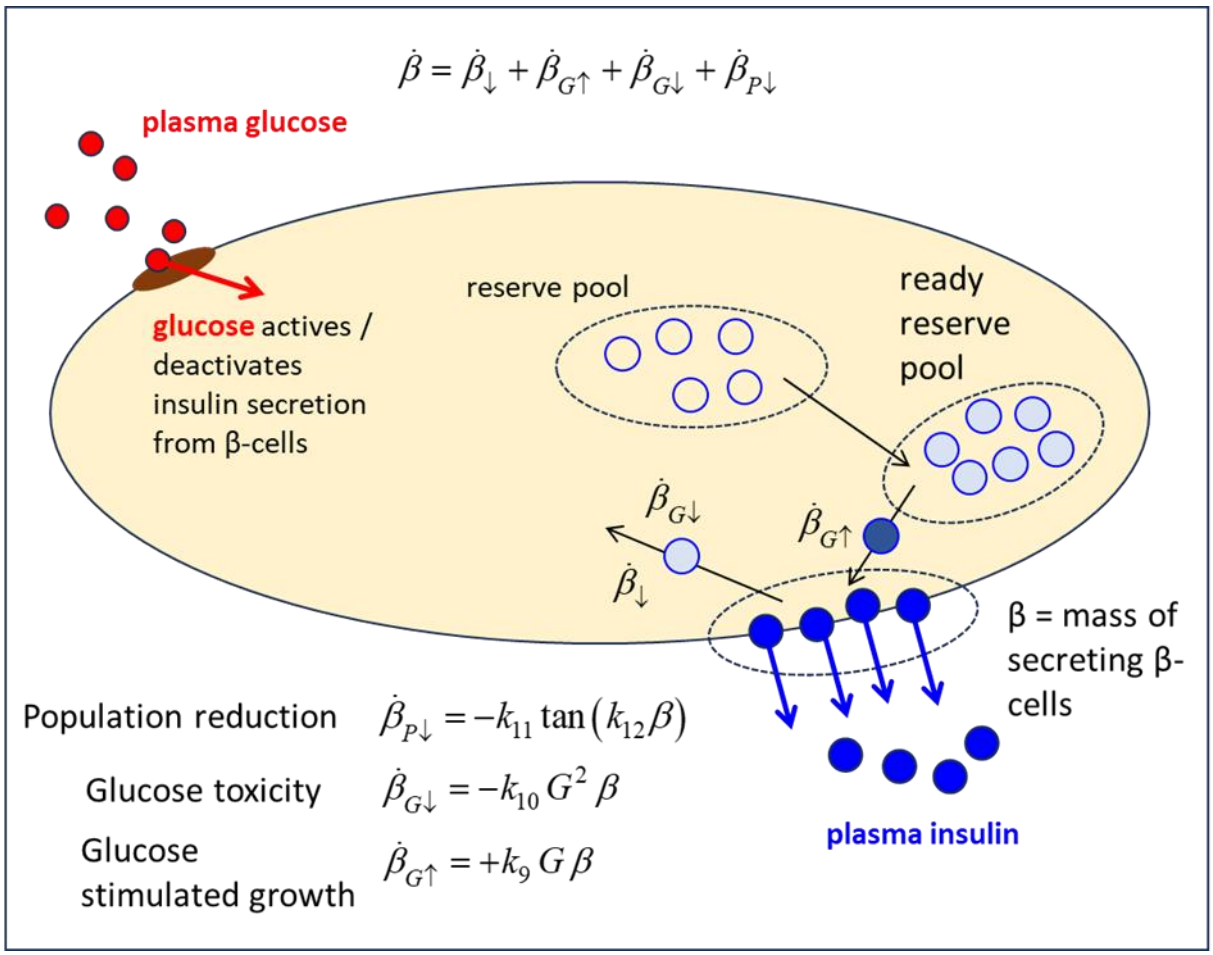


Fig. 12. β-cell dynamics.

Fixed points of the βIG regulatory system

Maintaining blood glucose concentration within a relatively narrow range through periods of fasting or excess nutrient availability is essential to the survival of the organism. This is achieved through an intricate balance between glucose uptake and endogenous glucose production to maintain constant glucose concentrations. This is specifically challenging in periods of reduced energy supply such as after prolonged fasting or exercise. In the fed state, circulating glucose is derived primarily from dietary sources and is distributed to

the brain, the muscle and fat, and the liver. After an overnight fast when dietary glucose supply is not available, glucose is produced primarily from glycogenolysis, the release of glucose from glycogen breakdown, or from gluconeogenesis, the synthesis of glucose from noncarbohydrates precursors (i.e., pyruvate, lactate, glycerol and amino acids). The low glucose levels are sensed by pancreatic α-cells and the adrenal medulla that secrete glucagon and catecholamines, respectively. An increase in blood concentrations of these hormones promotes hepatic glucose production (HGP) in the fasted state and during exercise. Under overnight fasting conditions, the contribution of glycogenolysis and gluconeogenesis to overall glucose production is approximately equal. Glycogen content in the liver is limited and is largely depleted after an overnight fast. Therefore, gluconeogenesis becomes the predominant source of glucose after prolonged fasting.

So, it is very important to know to predict the basal values for glucose and insulin and to decide whether a person is NGT, IGT or T2D. When an equilibrium situation exists, the levels of the glucose and insulin are equal to their basal values. When disturbed, the glucose regulatory system will always evolve to a stable fixed points which correspond to the basal values or steady-state values provided there are no further disturbances.

The fixed points or steady state values $(\beta_{ss}, I_{ss}, G_{ss})$ can be found from the set of simultaneous nonlinear equations when the rates of change of the β-cell mass, insulin and glucose are all zero (equation 7).

(7a) $$k_1 - k_2 G_{ss} - \frac{k_3 I_{ss} G_{ss}}{k_6 G_{ss} + 1} = 0$$

(7b) $$\beta_{ss} k_5 \left(\frac{{G_{ss}}^2}{{k_6}^2 + {G_{ss}}^2} \right) - k_7 I_{ss} = 0$$

(7c) $$\left(-k_8 + k_9 G_{ss} - k_{10} {G_{ss}}^2 \right) \beta_{ss} - k_{11} \tan\left(k_{12} \beta_{ss} \right) = 0$$

An obvious solution is the trivial stable fixed point known as the pathological fixed point where

(5) $$\beta_{ss} = 0 \quad I_{ss} = 0 \quad G_{ss} = \frac{k_1}{k_2}$$

When the βIG system is attracted to the pathological fixed point, the β-cell mass and insulin level converge to zero and the glucose level to its maximum value since there is zero insulin to control the glucose level.

The other stable fixed points $(\beta_{ss}, I_{ss}, G_{ss})$ if they exist are the stable physiological fixed point and an unstable saddle point. The Python function fsolve can be used to find the numerical values for the physiological fixed point.

PATHWAYS TO DIABETES

With a rapid economic development, dramatic changes in lifestyles, and an aging population, T2D has become a leading global public health problem in advanced as well as developing countries. The global prevalence of T2D in adults is estimated to be ~ 600 million in 2023 and more than 800 million by 2050. So, by 2050 more than 12% of the world's population will be living with T2D.

T1D is an autoimmune condition that can develop suddenly and may be caused by genetics and other unknown factors. In T1D, zero insulin is secreted from the β-cells of the pancreas, therefore the body has no mechanism for controlling blood glucose levels. T2D is a serious condition where the blood basal glucose level is too high. It may develop over time due to a decrease in β-cell function as your body doesn't produce enough insulin and/or the insulin it produces isn't effective. T2D is a progressive disease of hyperglycaemia which may result increase the risk of myocardial infarction, stroke, microvascular events, and death.

The current increase in the prevalence of T2D is believed to be a result of increases in food consumption and in sedentary lifestyle. T2D is a multifactorial disease characterized by postprandial and postabsorptive hyperglycaemia, insulin resistance, insulin dysfunction (reduced insulin secretion), and a declining active β-cell population.

In the diabetic state, the muscle becomes resistant to insulin, and glucose clearance is reduced. However, a more serious problem is that it is likely that there is decrease in brain glucose clearance (normally the brain clears ~60% of the plasma glucose). In the diabetic state, the liver also becomes resistant to the actions of insulin, resulting in an increase in the hepatic glucose production. The increase in HGP during fasting in the diabetic state is primarily the result of an increase in gluconeogenesis and that glycogenolysis remains unchanged.

Altered glucose homeostasis in T2D glucose homeostasis in diabetic patients is disturbed both in insulin secretion from pancreatic β-cells and in insulin sensitivity of liver, muscle and adipocytes (insulin resistance). Insulin resistance is acquired early in the progression of T2D, but initially glucose tolerance is normal due to a compensatory increase in insulin secretion. In individuals with mild fasting hyperglycaemia (<140 $mg.dL^{-1}$) insulin concentration is up to 2.5 times higher compared to non-diabetic individuals. When fasting hyperglycaemia exceeds 140 $mg.dL^{-1}$, pancreatic β-cells can no longer maintain elevated insulin secretion, and plasma concentrations of insulin start to drop and HGP starts to rise.

The vast majority of diabetic patients are obese and are characterized by elevated plasma levels of free fatty acids and glycerol. Insulin is a potent antilipolytic hormone, and in T2D adipose tissue becomes

resistant to insulin, leading to increased lipolysis and release of glycerol to the circulation.

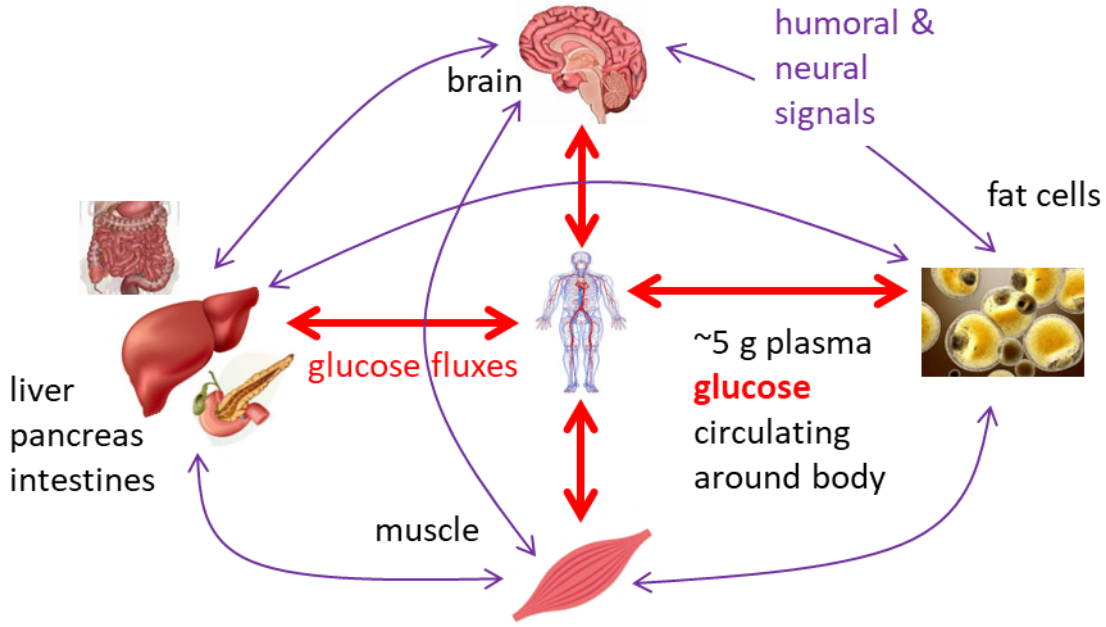


Fig. 13 To maintain glucose homeostasis by direct control of glucose flux, it is necessary that there exists two-way communication between organs and an integration of these humoral and neural signals.

BIG_B.pptx

Some of the factors that may be associated with progression from NGT to IGT to T2D include: elevated fasting plasma glucose levels; high plasma insulin levels; insulin resistance; β-cell dysfunction (lower insulin secretion rate), decline in the functional β-cell population; older age; overweight or obese (body mass index - BMI); hypertension (high blood pressure); dyslipidaemia (imbalance of lipids such as cholesterol, low-density lipoprotein cholesterol, (LDL-C), triglycerides, and high-density lipoprotein (HDL).

The βIG model can be used for simulations of the G-I regulatory system for some of these factors such as insulin resistance, β-cell function and population, and enhanced glucose production from the liver.

SIMULATIONS

A better understanding through the use of mathematical models can be gained by modelling the role played by deteriorating β-cell function, β-cell mass, insulin resistance and other abnormalities linked with the progression of T2D. An improved understanding of the glucose regulatory system may provide insight into new and novel therapies for achieving and maintaining good glycaemic control.

The dynamics of the βIG glucose regulatory system depends upon the set of values for the *k* parameters and the initial conditions for the glucose, insulin and β-cell mass. The default values for the simulations of the βIG regulatory system for a NGT individual are shown in Table 2.

Table 2. Default values of the model parameters for a NGT individual and the fixed-point values.

$k_1 = 864$ mg.dL^{-1}.d^{-1} $k_2 = 1.44$ d^{-1}

$k_3 = 1.00$ mU^{-1}.L.d^{-1} $k_4 = 0.010$ mg^{-1}.dL

$k_5 = 40.0$ mU.L^{-1}.d^{-1} $k_6 = 150$ mg.dL

$k_7 = 432$ d^{-1} $k_8 = 0.060$ d^{-1}

$k_9 = 10.00\text{x}10^{-4}$ mg^{-1}.dL.d^{-1} $k_{10} = 2.4\text{e-}6$ mg^{-2}.dL^2.d^{-1}

$k_{11} = 3.49$ d^{-1} $k_{12} = \pi/3050$ mg^{-1}

Pathological fixed-point

$\beta_{ss} = 0$ mg $I_{ss} = 0$ mU.L^{-1} $G_{ss} = 600.00$ mg.dL^{-1}

Physiological fixed-point

$\beta_{ss} = 816.45$ mg $I_{ss} = 16.81$ mU.L^{-1} $G_{ss} = 80.22$ mg.dL^{-1}

BIG01A.py

Endogenous hepatic glucose production

One pathway to diabetes is due to the excessive conversion of glycogen to glucose in the liver resulting in elevated basal glucose levels.

The liver plays a major role in maintaining glucose homeostasis, as it is the main organ for glucose storage, in the form of glycogen. The liver maintains normal whole body glucose levels by regulating the processes of glucose production (gluconeogenesis) and glycogen breakdown (glycogenolysis), thus controlling the levels of hepatic

glucose release. Anomalous regulation of hepatic glucose production (HGP) can result in deleterious outcomes, and excessive HGP is a major contributor to the hyperglycaemia observed in T2D individuals.

When nutrients are available, insulin is secreted from pancreatic β cells and promotes hepatic glycogen synthesis and lipogenesis. When nutrients become scarce, insulin levels are decreased and glucagon is secreted from pancreatic α-cells to promote HGP to meet the body's energetic demands. However, increased rates of HGP are observed in people T2D who have significantly impair glucose homeostasis and significantly contribute to hyperglycaemia.

Although acquired late in the progression of T2D, excessive HGP is a major contributor to the pathogenesis of this disease. It is believed that in the diabetic state the chronically elevated HGP is a result of increased gluconeogenesis, rather than glycogenolysis. The widely used drug metformin is primary used for the suppression of HGP by the inhibition of gluconeogenesis.

The effects of greater glucose released into the bloodstream by hepatic glucose production can be simulated by increasing the parameter k_1. Figure 14 shows the steady-state glucose G_{SS} vs k_1 plot: unstable saddle point (red) and stable physiological fixed point (blue), the steady-state insulin I_{SS} plot, and the steady-state β-cell mass plot, using the default values for the other k parameters.

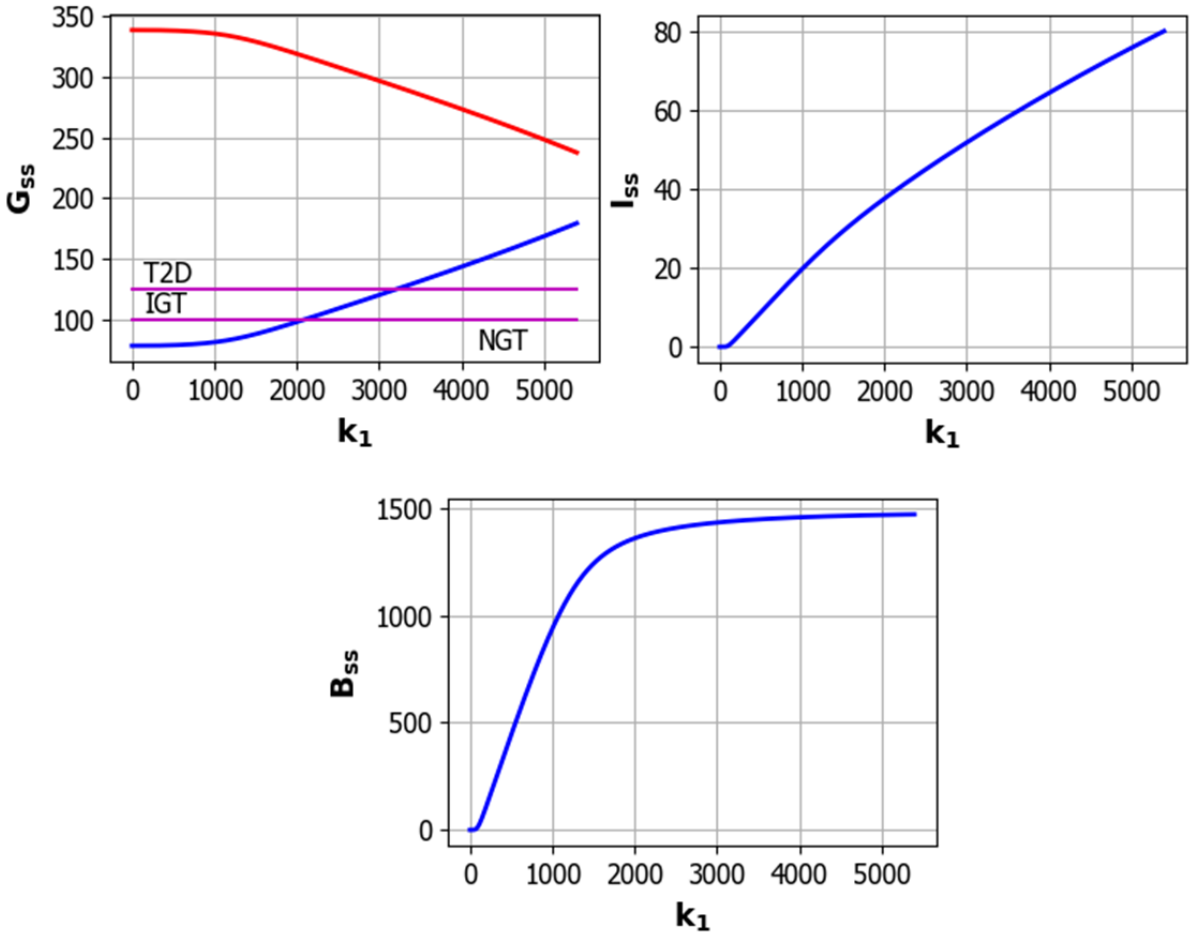


Fig. 14. HGP: G_{ss} vs k_1 plot: saddle point (red) and physiological fixed point (blue), the steady-state insulin, and the steady-state β-cell mass plots. BIG12.py

Provided $k_1 < \sim 2000$, the insulin secreted from the β-cells can maintain normal glucose homeostasis. As k_1 continually increases above 2000, increasing insulin must be secreted from an increasing active β-cell population. For $k_1 > \sim 2000$, the β-cell mass starts to saturate at its maximum value which limits the insulin secretion, so the basal glucose level rises. When $k_1 > 5397$, the saddle point and

physiological fixed-point merge and the basal glucose level spirals to the pathological fixed-point, $G_{SS} = 600$.

Increased rates of hepatic glucose production in the diabetic state are a result of an imbalance in several factors affecting the different aspects involved in the regulation of HGP as discussed above. These factors include: 1) increased availability of gluconeogenic substrates that ultimately leads to increased gluconeogenesis; 2) resistance of the liver to the action of insulin leading to improper suppression of hepatic glucose output; 3) elevated levels of glucagon leading to hyperactivation of signalling pathways that are normally activated in the fasted state when glucose supply is needed.

Insulin resistance

Insulin is a hormone made by the pancreas that helps glucose in your blood enter cells in your muscle, fat, and liver. Insulin resistance is when cells in your muscles, adipose tissue (connective tissue that extends throughout your body found under your skin as subcutaneous fat, visceral fat between your internal organs and even in the inner cavities of bones), and liver don't respond well to insulin and can't easily take up glucose from your blood. Tissue inflammation is an established cause of insulin resistance and is considered a main driver of insulin resistance in adipose tissue.

With insulin resistance, the β-cells in the pancreas secrete more insulin to help glucose enter your cells. As long as your β-cells can secrete enough insulin to overcome your cells' weak response to insulin, your blood glucose levels will stay in the healthy range. It is not fully understood what causes insulin resistance but excess weight and lack of physical activity are the most likely major factors.

Insulin resistance is characteristic of both lean and obese diabetic people and is considered the main driver of T2D. However, the development of insulin resistance is tightly correlated with obesity.

Insulin resistance plays a major role in determining glucose tolerance status over time. During the onset of insulin resistance, normal glucose concentrations will stay in a healthy range provided there is a compensatory increase in insulin secretion from the β-cells. When the insulin secretion becomes insufficient to maintain normal plasma glucose levels, there is a progression to IGT and if this worsens, T2D will be the outcome.

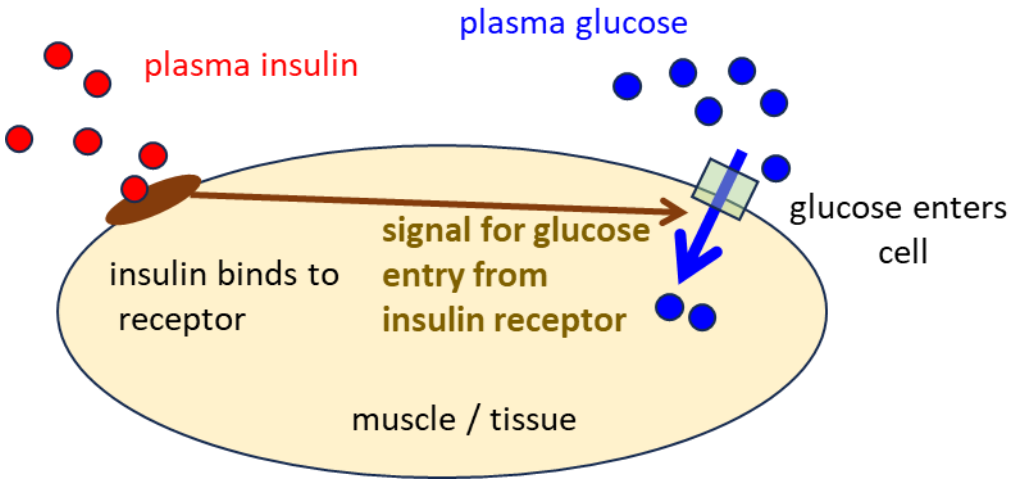


Fig. 15. There are insulin receptors on the surface of cells. When insulin binds to the receptors, signals are sent to the cell's membrane so that it is permeable to glucose molecules. BIG_A.pptx

The glucose dynamics is described by equation 1 where dG/dt is the rate of the plasma glucose concentration. The utilization of glucose which is insulin dependent is govern by the term

$$-\frac{k_3 I G}{k_4 G + 1}$$

The insulin sensitivity parameter k_3 relates to how well the cells are activated to clear glucose from the blood. Increasing insulin resistance can be modelled by decreasing the value of the k_3 parameter (a cells' ability to take up glucose is diminished). Figure 16 shows the results of the insulin resistance simulation where the default k parameters are used except for parameter k_3.

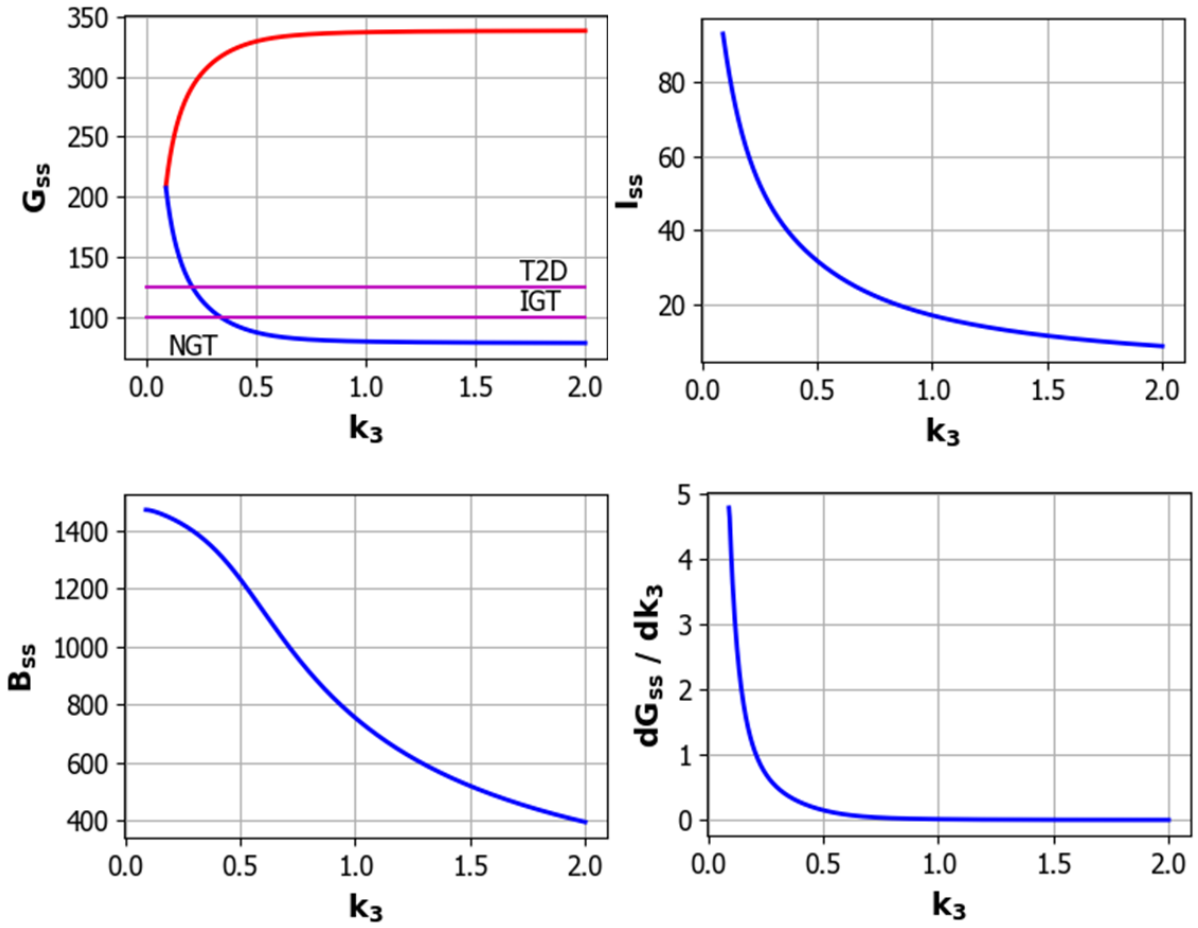


Fig. 16. Insulin resistance increases as the insulin sensitivity parameter k_3 is reduced. BIG_08.py

As the insulin sensitivity parameter k_3 decreases and a cell's ability to utilize glucose becomes less, there is an increase in the plasma glucose and insulin concentrations and as the demand for insulin secretion rises, a larger population of active β-cells is required. The plots show why fully fledged T2D occurs slowly. At first as the insulin sensitivity declines there is only small increases in the plasma glucose and insulin concentrations and the rate of change of the steady-state glucose concentration with decreasing insulin sensitivity k_3 is very small $\left(dG_{SS} / dk_3 \approx 0\right)$. When $k_3 < 0.5$, the sensitivity factor

dG_{SS} / dk_3 rapidly increases resulting a dramatic change in the glucose dynamics. Even for a small decrease in insulin sensitivity, there can be a large increase in the basal glucose concentration.

The insulin sensitivity parameter k_3 is a bifurcation parameter. When $k_3 < 0.08$, the saddle point and physiological fixed-point merge and the basal glucose level spirals to the pathological fixed-point, $G_{SS} = 600$. Thus, for a NGT person, even a relatively large decrease in the insulin resistance parameter k_3 has little impact upon the steady-state glucose concentration. However, this is not the case for individuals who are IGT or T2D. Even a small decrease in the insulin resistance parameter k_3 will lead to a relatively large increase in the fasting glucose level. This explains why the deterioration in diabetes occurs slowly at first before a rapid worsening in the severity of the disease.

Active β-cell population and secretion rate

With β-cell dysfunction, insulin secretion is impaired because of inadequate glucose sensing to stimulate insulin secretion from the active β-cells resulting in hyperglycaemia. So, the β-cell functional population does not increase sufficiently to meet the insulin requirements to keep glucose levels in the healthy range. Generally, β-cell dysfunction follows insulin resistance in T2D. Both pathological states of insulin resistance and impaired insulin secretion influence each other and together exacerbate diabetes. T2D never develops

unless β-cells fail to compensate insulin resistance where a deficit of β-cell functional mass is an essential component of the pathophysiology of T2D. Reducing β-cell workload appears to be the most effective way to preserve β-cell functional mass.

To model a reduction in the rate of insulin secretion, the parameter k_5 is reduced in value. For a NGT person, even a relatively large decrease in the insulin secretion rate has little impact upon the steady-state glucose concentration. However, this is not the case for individuals who are IGT or T2D. Even a small decrease in the secretion rate of insulin will lead to a relatively large increase in the fasting glucose level. This explains why the deterioration in diabetes occurs slowly at first before a rapid worsening in the severity of the disease (figure 17).

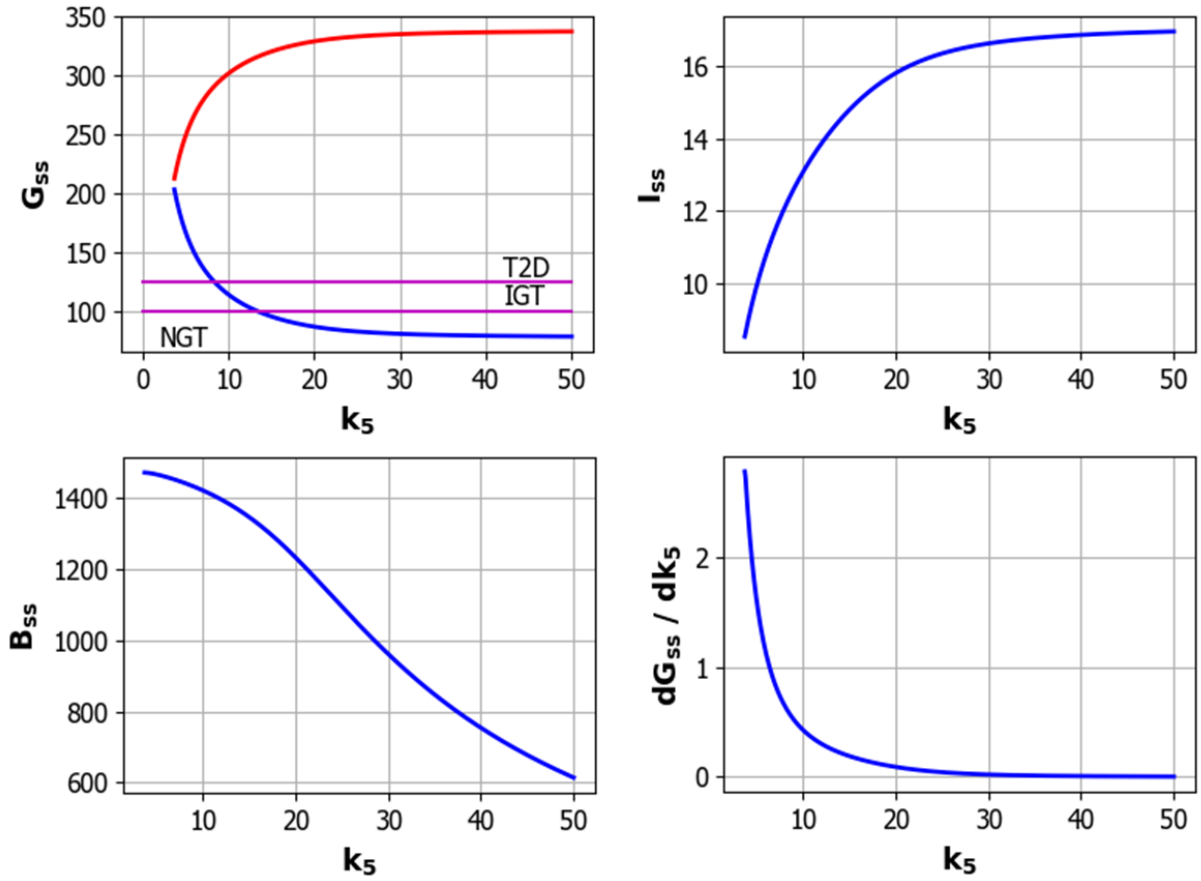


Fig. 17. The steady-state glucose and insulin concentration as a function of the parameter k_5 for insulin secretion. The blue curve is for the physiological fixed-points, and the red curve for the saddle points. The lower graphs show the β-cell mass, and the rate of change of the physiological steady-state glucose concentration with respect to the insulin secretion parameter k_5 ($\left|dG_{ss} / dk_5\right|$ *vs* k_5).

BIG13.py BIG_B.pptx

The dynamics of the βIG glucose regulatory system for changes in insulin secretion rates is very similar to the dynamics of changing the insulin sensitivity factor. A person who is T2D, even a further small decrease in the insulin secretion rate will lead to a large increase in the basal glucose concentration.

Glucose toxicity

We can model the effects of too much plasma glucose causing glucose toxicity by incrementing the parameter k_{10} as shown in figure 18.

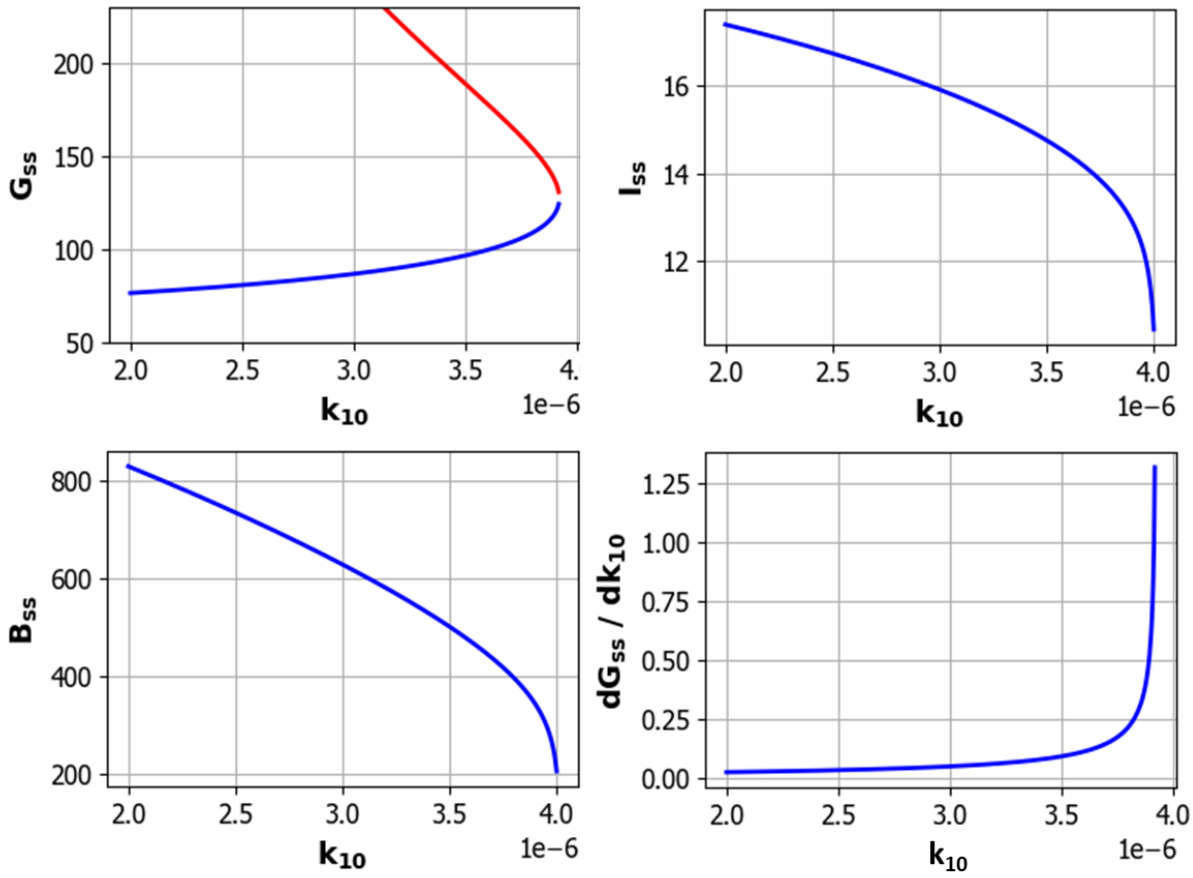


Fig. 18. The steady-state glucose and insulin concentration as a function of the parameter k_{10} for glucose toxicity. The blue curve is for the physiological fixed-points, and the red curve for the saddle points. The lower graphs show the β-cell mass, and the rate of change of the physiological steady-state glucose concentration with respect to the glucose toxicity parameter k_{10} ($dG_{ss} / dk_{10} vs\ k_{10}$).

BIG14.py BIG_B.pptx

An increase in the glucose toxicity parameter k_{10} does not have a dramatic effect on the basal plasma glucose concentration until the toxicity effect becomes very strong when there is a rapid decline in active β-cell population which then leads to the sharp falloff in the plasma insulin concentration.

NGT, IGT and T2D individuals

There can be a range of k parameters to give basal glucose concentration within each of the categories NGT, IFG, and T2D. This helps explain why not all people who are obese develop T2D. This is because the β-cells of the people who are obese but are not T2D have sufficient insulin in the blood to have better control over glucose levels. Table 3 gives the prediction of the βIG model for the steady-state values for glucose, insulin and β-cell mass for changes in the parameters k_1 (endogenous glucose production), k_3 (insulin resistance – insulin sensitivity), and k_5 (insulin secretion).

Table 3. Steady-values for the progression from NGT to IGT, and T2D.

	k_1	k_3	k_5	B_{ss}	I_{ss}	G_{ss}
NGT	864	1.00	40.0	816	16.8	80.2
IGT	864	0.35	40.0	1383	40.5	102
T2D	1300	0.35	40.0	1444	56.7	129
T2D	1000	0.35	20.0	1465	35.9	159

The progression from NGT to IFG is due to insulin resistance where the body's cells are less effective in the uptake of glucose due to the action of insulin. The progression from IGT to T2D is due to the greater endogenous glucose production which may be a result of the insulin resistance. The T2D may progress to a more serve state where the active β-cells become stress and their population decreases. The smaller population can no longer produce enough insulin, so the steady-state glucose concentration shifts to a dangerous level.

GLUCOSE REGULARLY SYSTEM RESPONSE TO FOOD INTAKE

After digestion of a meal, in the fed state, glucose levels are sensed by pancreatic β cells that secrete insulin while secretion of glucagon from pancreatic α cells is suppressed. The increase in circulating insulin strongly suppresses HGP and promotes energy storage by increasing glycogenesis and lipogenesis. After a carbohydrate meal, ~33% of the glucose is taken up by the liver, another ~33% is taken up by muscle and adipose tissues, and the remaining glucose is taken up by the brain, kidney and red blood cells.

Single meal G-I dynamics

The G-I dynamics is different for NGT, IGT, and T2D individuals. Some of these differences can be investigated by modelling the G-I dynamic response for a 12-hour period with the simple meal consumed at time 2.00 hours. The meal quantity is 250 and the half-life is 20 minutes (figure 19). Figure 20 shows the time evolution of the glucose and insulin concentrations and figure 2, the variation in the β-cell mass.

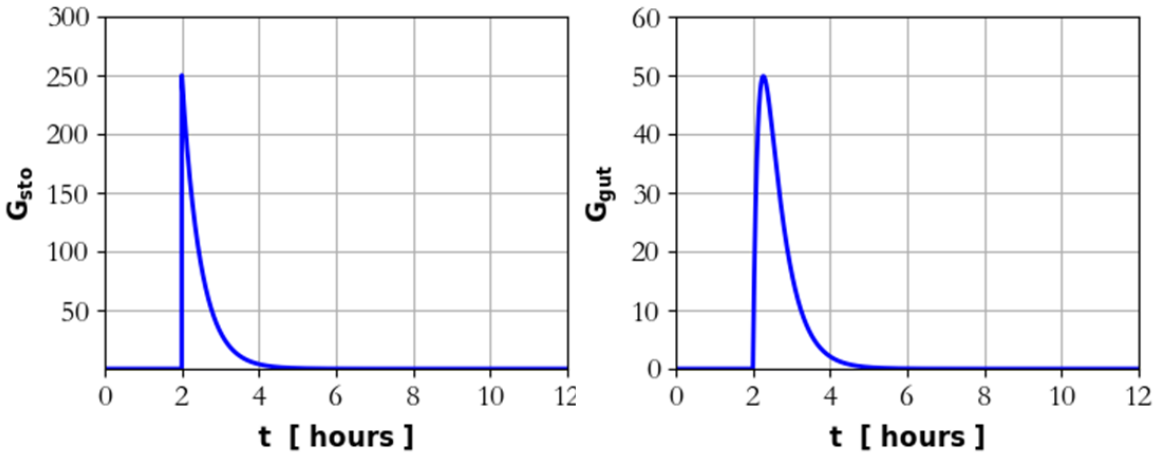


Fig. 19. The stomach (G_{sto}) and gut (G_{gut}) dynamics for the consumption of the meal at time 2.00 hours. The gut peak (G_{gut} = 50) occurs 16 minutes after the stomach peak (G_{sto} = 250).

BIG_51.py BIG_B.pptx

The input and output parameters for the simulation are presented in Table 4. The output parameters are: the steady-state values for the pathological and physiological fixed points; peak values for the glucose and insulin concentration (G_{peak} [mg.dL^{-1}], I_{peak} [mU.L^{-1}]); the average glucose and insulin concentrations averaged over 12 hours (G_{avg}, I_{avg}); full width at half maximum of glucose and insulin peaks (G_{fwhm}, I_{fwhm} [h]); time intervals between start of meal and peaks ($G_{peak\ delay}$, $I_{peak\ delay}$ [h]); time to return to 1.05 x steady-state values (5% return G, 5% return I [h]).

Table 4 and figure 20 clearly demonstrate the different responses for NGT, IGT and T2D individuals after the consumption of a meal. The more serious the diabetic condition then the greater the glucose and

insulin loads on the body. There are very significant spikes in the glucose and insulin concentrations and it take a much longer time for the levels to return to their steady-state values.

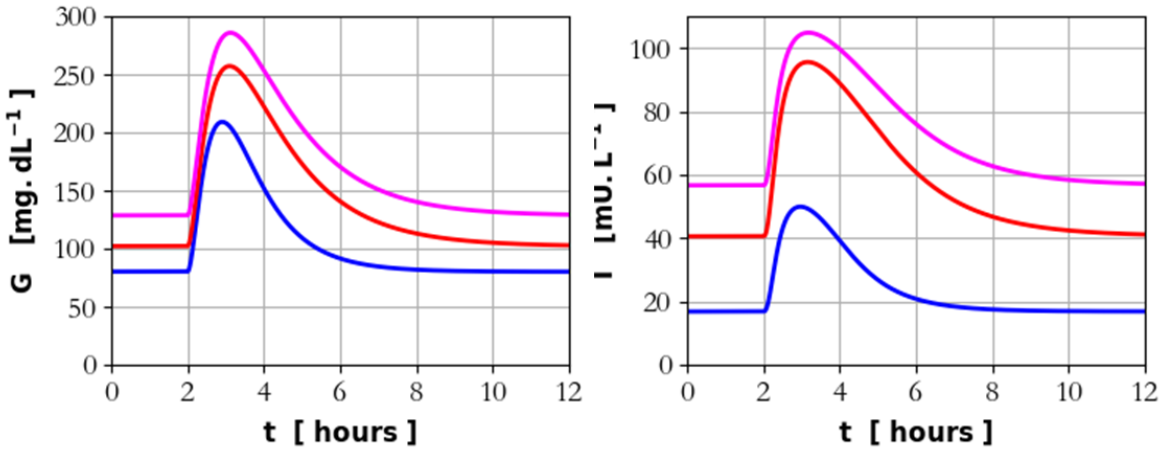


Fig. 20. Single meal; time evolution of the glucose and insulin concentrations for **NGT**, **IGT**, and **T2D** individuals.

BIG_51.py BIG_B.pptx

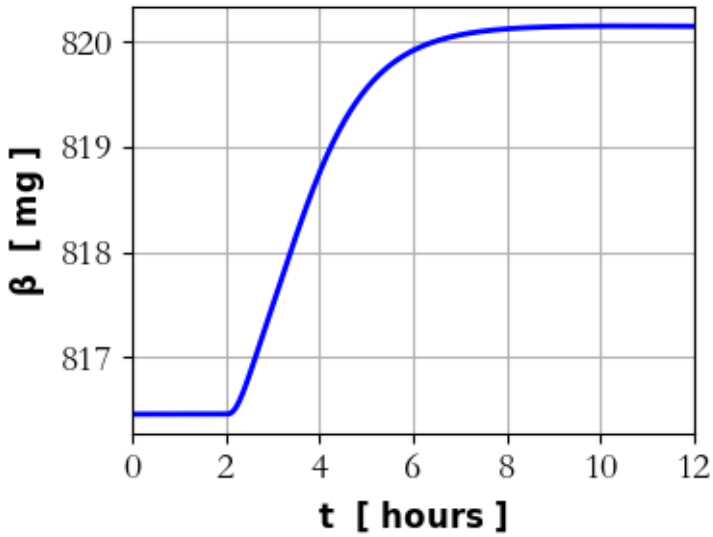


Fig 21. The dynamics of the β-cell mass is very slow, so there is only a slight change of the β-cell mass after the consumption of the meal.

Table 4. βIG response to a single meal.

Parameter	NGT	IGT	T2D
k_1	864	864	1300
k_3	1.00	0.35	0.35
Pathological fixed point	Bss = 0 Iss = 0 Gss = 600	Bss = 0 Iss = 0 Gss = 600	Bss = 0 Iss = 0 Gss = 903
Physiological fixed point	Bss = 816 Iss = 17 Gss = 80	Bss = 1383 Iss = 41 Gss = 102	Bss = 1444 Iss = 57 Gss = 129
Gpeak	209	257	286
Gavg	102	139	167
Gfwhm	1.81 h	2.49 h	2.57 h
Gpeak delay	0.91 h	1.10 h	1.12 h
5% return G	5.09 h	7.17 h	6.91 h
Ipeak	50	96	105
Iavg	23	56	71
Ifwhm	2.09 h	3.08 h	3.23 h
Ipeak delay	0.97 h	1.16 h	1.18 h
5% return I	5.70 h	7.85 h	7.23 h

The single meal parameters $G_1 = 200$ and $t_{sto} = 10$ min for the simulation give a reasonable approximation to the OGTT (oral glucose tolerance test: 75 g glucose load). From the results of the simulation, we can predict the glucose and insulin concentrations 1, 2 3, and 4 hours after the administration of the glucose (Table 5).

Table 5. Glucose (first line) and insulin (second line) concentrations 1, 2, 3 and 4 hours after start of OGTT. BIG_54.py

	1 h	2 h	3 h	4 h
NGT Gss = 80 Iss = 17	 191 47	 126 32	 97 23	 87 19
IGT Gss = 102 Iss = 41	 240 93	 187 79	 148 64	 127 54
T2D Gss = 129 Iss = 57	 269 102	 217 91	 178 79	 155 70

The results of the OGTT as a screening test for type 2 diabetes can be interpreted as follows:

NGT: The 2-hour plasma glucose level <140 mg/dL.

IGT: The 2-hour plasma glucose level 40-199 mg/dL.

T2D: The 2-hour plasma glucose level ≥200 mg/dL.

The results clearly indicate the sustained higher glucose and insulin concentrations in the blood the worst the diabetic condition of an individual.

Glycemic Index

The glycaemic index (GI) is a value assigned to foods based on how slowly or how quickly those foods increase the blood glucose concentration. Foods are classified as low, medium, or high glycaemic foods and ranked on a scale of 0 – 100 (low < 56, medium 56–69, high > 69. Foods high in refined carbs and sugar are digested more quickly and often have a high GI, while foods high in protein, fat, or fibre typically have a low GI. Foods that contain no carbs are not assigned a GI and include meat, fish, poultry, nuts, seeds, herbs, spices, and oils.

We can stimulate the response of the G-I regulatory system for a NGT individual for a single meal by using the half-life parameter t_{STO} (half-life time for the capture of glucose in the intestines from the food in the stomach). The values used are: $t_{sto} = 20$ min for a high glycaemic index and $t_{sto} = 80$ min for a low glycaemic index. Results are summarized in Table 6 and figures 22, 23.

Table 6. NGT individual response to changes in the G-I index for a single meal consumed. Steady state values: Bss = 816, Iss =17, and Gss = 80.

Parameter	$t_{sto} = 20$ min high GI	$t_{sto} = 80$ min low GI
Gpeak	209	146
Gavg	102	102
Gfwhm	1.81 h	3.46 h
t_Gpeak	2.91 h	3.55 h
dt_G	0.91 h	1.55 h
dt_G5	5.09 h	8.41
Ipeak	50	37
Iavg	23	24
Ifwhm	2.09 h	3.65
dt_I	0.97	1.61
dt_I5	5.70 h	9.55

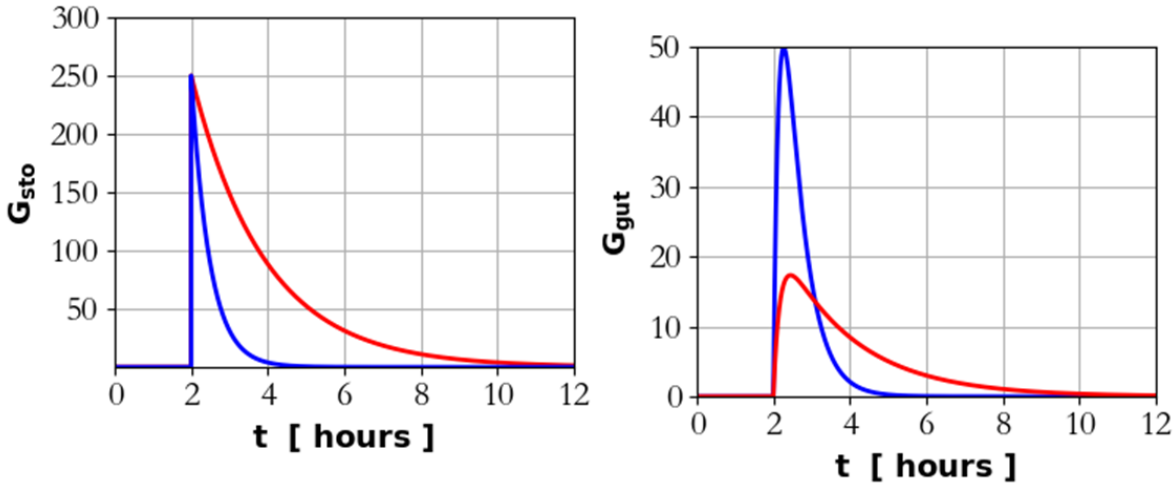


Fig. 22. Meal half-life parameters: t_{sto} = **20** (high GI index) and t_{sto} = **80** (low GI index). BIG_52.py BIG_B.pptx

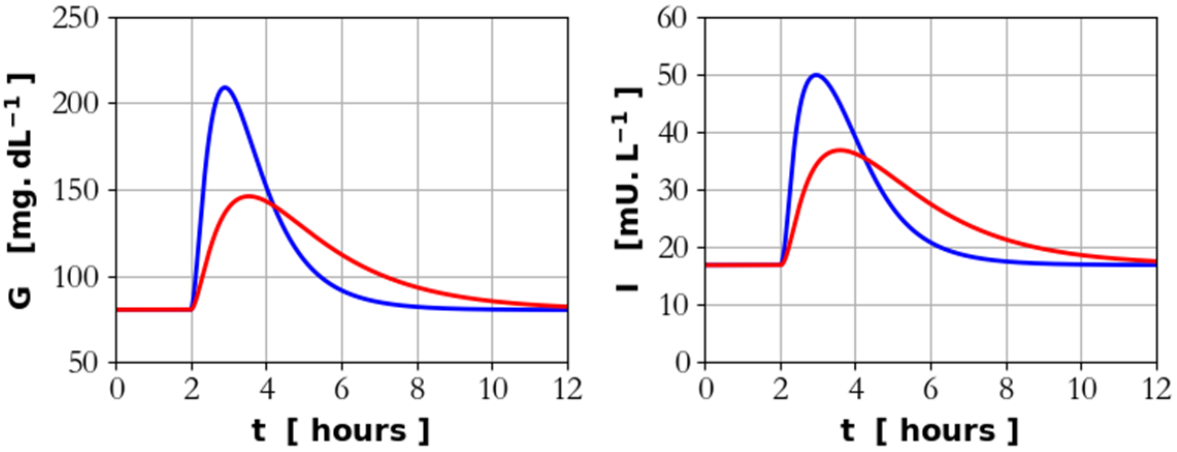


Fig. 23. G-I response to meals with different half-life parameters: t_{sto} = **20** (high GI index) and t_{sto} = **80** (low GI index). BIG_52.py BIG_B.pptx

The average glucose and insulin concentrations and the load parameters are independent of the GI index. This is the case since the same amount of glucose that is added to and cleared from the bloodstream is the same.

However, the rate at which the glucose is absorbed into the bloodstream is very different. The high GI index meal results in sharp spikes in both the glucose and insulin levels (the spikes being higher and narrow) compared with the response to the low GI index meal:

G_{peak}(high GI) / G_{peak}(low GI) = 1.43

I_{peak}(high GI) / I_{peak}(low GI) = 1.35

G_{fwhm}(high GI) / G_{fwhm}(low GI) = 0.52

I_{fwhm}(high GI) / I_{fwhm}(low GI) = 0.52

The time taken for the glucose concentration to return to the basal value is much longer for the low GI food. Hence, the low GI index food results in the glucose being release more slowly and steadily then the food with a high GI index and this slower and steady release of glucose helps maintain better glucose control.

The concern with high GI foods is that it produces a narrow spike in the glucose level and this stimulates a rapid increase in insulin release from the pancreatic β cells. Over a long period of time, the repeated narrow insulin spikes that are stimulated by high GI foods may lead to a deterioration in the ability of the pancreas to secrete sufficient insulin.

It is the quantity of the food consumed that matters most

We can simulate the G-I response to eating a small meal compared (Q_1 = 150) with eating a large meal (Q_1 = 250) where the two meals have the same glycaemic index (t_{sto} = 20). Results summarized in Table 7 and figure 24.

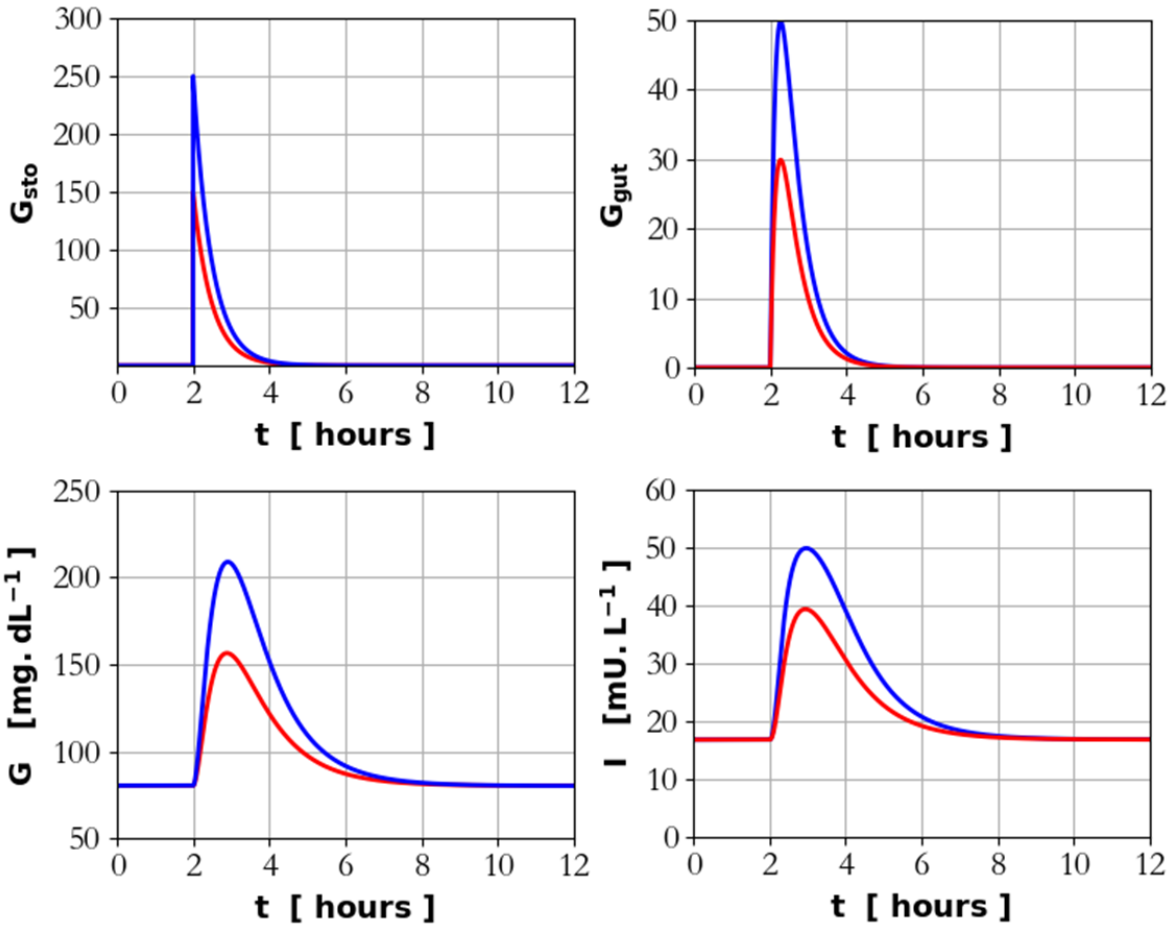


Fig. 24. The smaller the quantity of food consumed then the lower demands are placed on the G-I regulatory system. Large meal: Q_1 = 250 and small meal Q_1 = 150 where the two meals have the same glycaemic index (t_{sto} = 20).

Table 7. NGT individual G-I response to meals of different quantity and same glycaemic index.

	$Q_1 = 250$	$Q_1 = 150$
Gpeak	209	156
Gavg	102	93
dt_G5	5.09 h	4.56 h
Ipeak	50	39
Iavg	23	21
dt_I5	5.70 h	5.09 h

Comparing the two meals, it is obvious that the smaller the quantity of the glucose content in the meal then the smaller the amount of glucose that enters the blood and therefore reducing the quantity of insulin required to be secreted into the blood. The peak values and parameters for the glucose and insulin are significant greater for the larger meal compared with the smaller meal. It also takes longer for the glucose and insulin levels to return to their basal values after the larger meal.

The model confirms the well-established principles: (1) carbohydrates with low GI values are more slowly digested, absorbed and metabolised and cause a lower and slower rise in blood glucose and hence insulin levels. (2) The smaller the portion of food eaten then the smaller the spikes in the glucose and insulin levels.

Eating Patterns

The model can be used to examine the G-I dynamics for three different meal patterns for a NGT individual. The same total quantity of food is consumed with the glycaemic index (t_{sto} = 30 min):

1 meal: t_1 = 2 h, Q_1 = 600

2 meals: t_1 = 2 h, Q_1 = 200, t_2 = 8 h, Q_2 = 400

3 meals: t_1 = 2 h, Q_1 = 100, t_2 = 6 h, Q_2 = 200, t_2 = 12 h, Q_2 = 300

The results of the simulation are shown in Table 8 and figure 25.

Table 8. G-I response to different eating patterns.

	1 meal	2 meals	3 meals
Gpeaks	371	42, 57	124, 170, 214
Gavg	112	107	106
Ipeaks	65	42, 57	31, 43, 51
Iavg	24	24	25

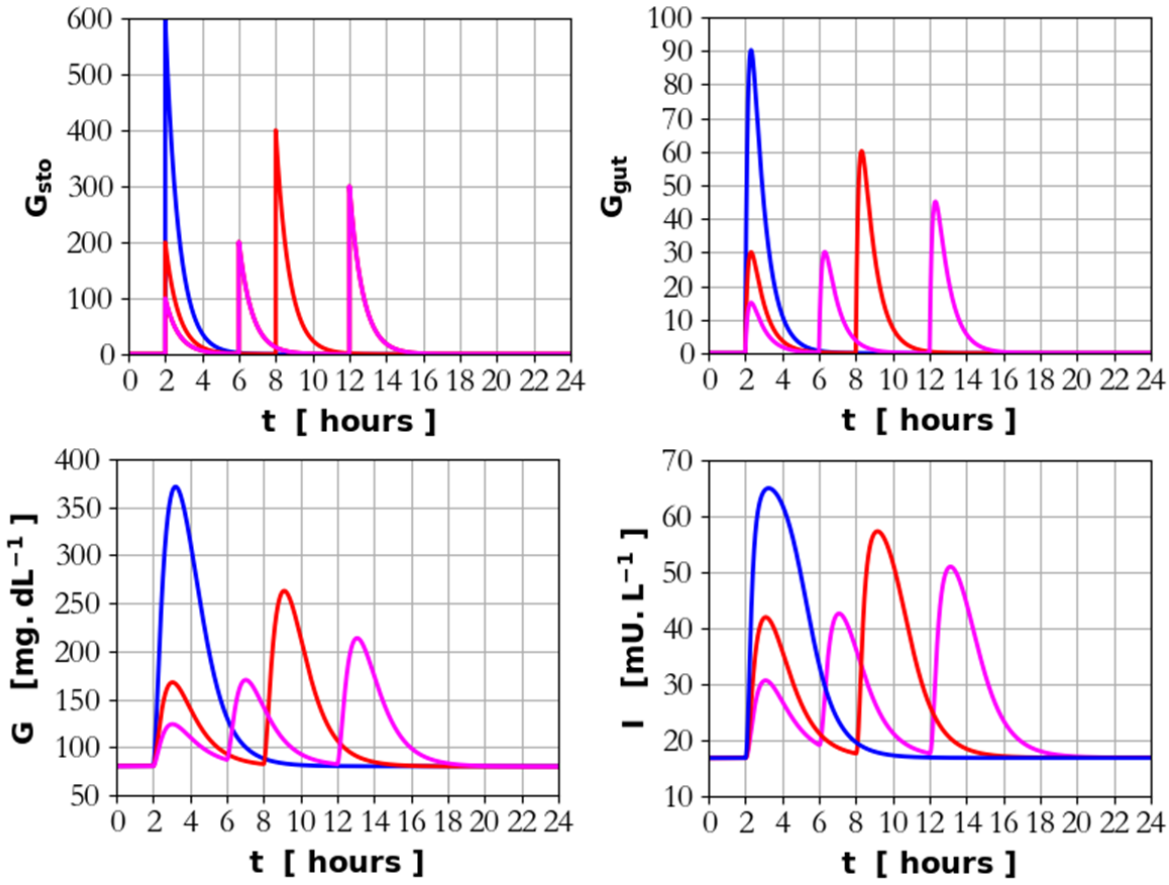


Fig. 25. The G-I response to three different eating patterns.

BIG_51.py BIG_52.py BIG_53.py BIG_54.py

The results of the βIG model indicate that the average glucose and insulin concentrations are relatively independent of eating the one, two or three meals. The same quantity of food was consumed in each case. The amount of glucose that was absorbed into the bloodstream and cleared from the bloodstream are the same, so it is not surprising the same average concentrations are predicted by the βIG model. If anything, the single meal is the worst case because of the significantly larger glucose and insulin spikes.

REFERENCES

Topp, B., Promislow, K., deVries, G., Miura, R.M., Finegood, D.T
A model of beta-cell mass, insulin, and glucose kinetics: pathways to diabetes
J Theor Biol (2000) **206**, 605-619.

Boutayeb, W., Lamlili,M.E.N., Boutayeb, A., Derouich, M.
Mathematical Modelling and Simulation of β-Cell Mass, Insulin and Glucose Dynamics: Effect of Genetic Predisposition to Diabetes
Journal of Biomedical Science and Engineering (2014) Vol.7 No.6, May 2014, 330-342.