Andrew Sullivan 109151173

A Mathematical Model of Glucose-Insulin Dynamics in Healthy and Diabetic Individuals

Development of Glucose Regulation Dynamics in Healthy Individuals

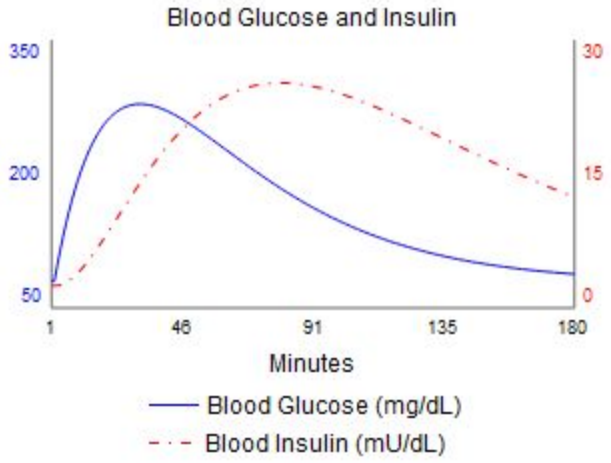
A model was developed in Stella Professional in order to examine the dynamics of the insulin-glucose regulatory system. Glucose levels are typically maintained around 80 mg/dL in healthy individuals during fasting periods.[13] Ingestion of sugar results in a spike in glucose after it is digested and absorbed into the bloodstream, stimulating the β cells of the pancreas to synthesize the hormone insulin. Increases in blood insulin levels stimulate a number of pathways, including cellular uptake by liver and muscle cells, conversion of excess glucose into glycogen, and conversion of glycogen into fat.[16] These effects serve to reduce concentrations of glucose in the blood, returning to homeostatic levels. Should glucose concentrations fall, the opposite effects are induced due to decreased insulin levels and increased levels of the hormone glucagon. As these two hormones are coupled (i.e. a high concentration of one precludes a high concentration of the other),[16] their effects may be considered as a single unit for the purposes of analyzing the system, as glucagon concentrations are implied by insulin levels. As rate constants and values of glucagon have been less extensively studied, this simplification is utilized in the following model.

The model considers five concentrations: blood glucose levels (measured in mg/dL), blood insulin levels (measured in mU/dL), and glucose levels in the digestive system (mg/dL), glycogen storage (mg/dL), and fat (mg/dL). As each of the volumes in these concentrations refer to the total blood volume, these values may also be stated as mass rather than concentration, but the majority of the literature for diabetes studies refers to concentrations.

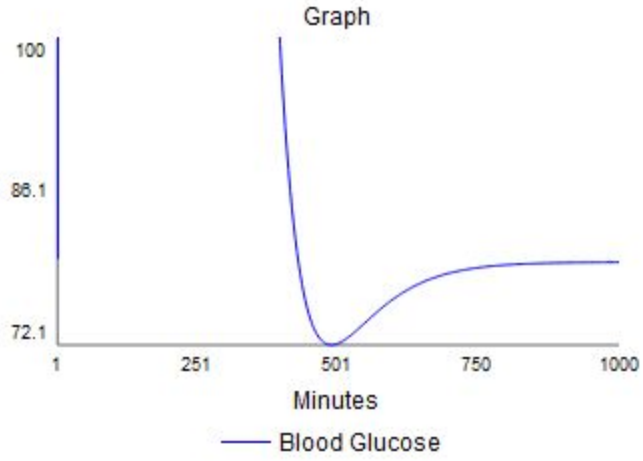
A 1000 mg/dL pulse input to the digestive system is used to provide a bolus to the glucose system, with an initial value of 0 mg present in the digestive tract. The initial glucose level in the blood is taken as a concentration within the normal range of 80 mg/dL, and 10,000 mg/dL is present in the glycogen reserve. The average human body stores approximately 600 g of glycogen between the liver and skeletal muscles,[9] which corresponds to this concentration over 60 dL of blood (i.e. 600,000 mg/60 dL). It is assumed that all of this glycogen may be converted into glucose in a 1:1 ratio for simplicity. Similarly, the initial fat concentration is set as 300,000 mg/dL. This is based on [4], in which the group of non-obese individuals had a body fat content of 19 (taken as 18) kg, which, when normalized over the 60 dL volume, yields 300 g/dL. It is also assumed that this fat may be converted in a 1:1 ratio (i.e. the fat serves simply as an extra storage for glucose). The influence of the fat content will be discussed later in the context of insulin resistance. The initial value of insulin is taken as 2.5 mU/dL, at the upper end of normal levels for fasting.[12] The rate constants for the reactions are obtained from [5]. $\alpha = 0.916/60$ min^{-1} is the rate constant associated with insulin degradation, $\beta = 0.198/60$ is the insulin production rate (mU/min) as a function of glucose concentration (mg), $\gamma = 3.23/60$ is the glucose absorption (mg/min) as a function of insulin concentration (mU), and $\delta = 3.04/60$ is the glucose

absorption as a function of the glucose concentration (min^{-1}). In the model from which these constants were obtained, the concentrations entering into the equations are not the absolute values, but rather deviations from the mean (i.e. $i = I-I_0$ and $g = G-G_0$). These mean values were taken to be the same as the initial starting values (i.e. assuming the system is initially at a steady state, so I_0 = 2.5 mU/dL and G_0 = 80 mg/dL). The rate constant for glucose uptake into glycogen storage is assumed to be equal to that for fat uptake, since, as previously discussed, fat is essentially acting as a reserve pool for the reserve pool. The hydrolysis rate constants are also assumed to be the same, meaning that, whenever the value of the forward rate is negative, it is instead set to zero and the reverse rate is used to obtain glucose from storage. A modification of the model from which the rate constants were obtained was required due to the lack of partitioning of the constants into different compartments, i.e. for glycogen uptake versus cellular uptake. Thus, based on [9], ⅔ of the intake was assumed to be placed in glycogen storage, while the remaining ⅓ was used by the cells. Another issue with this approach is that it assumes there is no glucose- and insulin-independent glucose absorption from tissues, which is known to be false. Cells like neurons absorb glucose dependent on their metabolic requirements. To account for this, a value of 2.59*70/(60) mg/(dL*min) was introduced into the uptake rate, based on [8], and with the 70 and 60 accounting for the kg and lack of dL present in the units, respectively. Finally, the absorption constant from the digestive tract is taken as 0.018 min^{-1}.[17]

Dynamics of the Healthy Individual Model



The figure at the left displays the insulin and glucose dynamics for a healthy individual with the above parameters over three hours after the glucose is ingested. The dynamics of this model are approximately consistent with known values for glucose tolerance tests, in which initial glucose concentrations are elevated, stimulating insulin release, which returns the glucose back to normal levels.[3] After the three hour time period, the glucose levels have nearly returned to normal (~88 mg/dL), while the insulin concentrations remain elevated for longer. The absolute value and point of the maximum insulin concentration is also consistent with normal range.[12] The threshold value for prediabetes is typically taken to be 140 mg/dL.[7] It should also be noted that the system displays overshoot-and-collapse behavior if the pulse is too large (75 g), wherein the system jumps to a very large value, before overcorrecting below the steady-state value. Due to the presence of glucose reserves, the system is then able to return to its steady-state value.



Incorporation of Insulin Sensitivity- Type II Diabetes

Insulin resistance is a phenomenon in which the cellular response to plasma insulin is attenuated, thus reducing the amount of uptake by cells and prolonging elevated blood glucose concentrations. This may eventually develop into Type II Diabetes Mellitus. The mechanisms of insulin resistance are believed to be the result of disruptions in the insulin signaling cascade triggered in healthy individuals, including signaling protein downregulation, disruption of GLUT4 glucose transporter function, or defects in the action of various protein kinases involved in phosphorylation cascades and second messenger synthesis.[16]

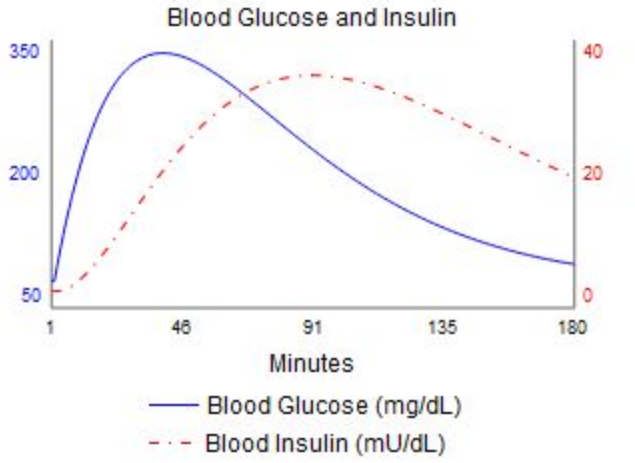
One of the primary factors commonly correlated with insulin resistance is obesity, in which increased visceral adipose tissue raises body levels of pro-inflammatory cytokines and free fatty acids, which are released in greater amounts from visceral adipocytes than other fatty tissues and are thought to accumulate in muscles and the liver, ultimately disrupting the insulin cascade and inducing insulin resistance.[16]

Due to the association of fat and insulin resistance, body levels of fat in the above model were coupled to the various insulin-dependent pathways throughout the model. Though this does not affect insulin production, it reduces the sensitivity of the model to increased insulin levels, thereby giving rise to the symptoms commonly associated with type II diabetes. The coupling factor was derived based on the information in [4], which surveyed a population of normal and obese individuals in terms of body fat content and free fatty acid concentration in the blood. A linear relationship was developed to relate the amount of fat on the individual in the model to their free fatty acid concentration. Based on the "healthy" mean level of 573 μEq/L in this study, the insulin resistance factor was taken as 573/[FFA]. This factor was multiplied into the glycogen and cellular uptake pathways in order to account for resistance to insulin-mediated processes.

Dynamics of the Insulin-Resistance Model

The figure below displays the behavior of an individual with a body fat content of 40 kg, which raises the free fatty acid concentration above 800 μEq/L, thus increasing the insulin resistance of the individual. This is evident from the plot, which displays similar behavior in terms of shape but the magnitude of each curve is quite different. Whereas the individual with an initial body weight of 19 kg finishes the three hour time point with concentrations of 88.2 mg/dL and 12.5 mU/dL for glucose and insulin, respectively, the heavier individual has values of 98.9

mg/dL and 19.5 mU/dL. At the two hour time point, at which the glucose tolerance test is typically measured, this individual has a concentration of 164 mg/dL, above the 140 mg/dL threshold for prediabetes. Individuals with starting weights of 55 kg body fat or more are approximately at or above the 200 mg/dL threshold at this time point. However, depending on factors such as the individual's starting glucose levels (80 mg/dL is in the lower half of the range) and genetic predispositions, these symptoms may manifest at lower weights. Additionally, synergistic interactions with destruction of pancreatic β cells, as discussed below, may also contribute.



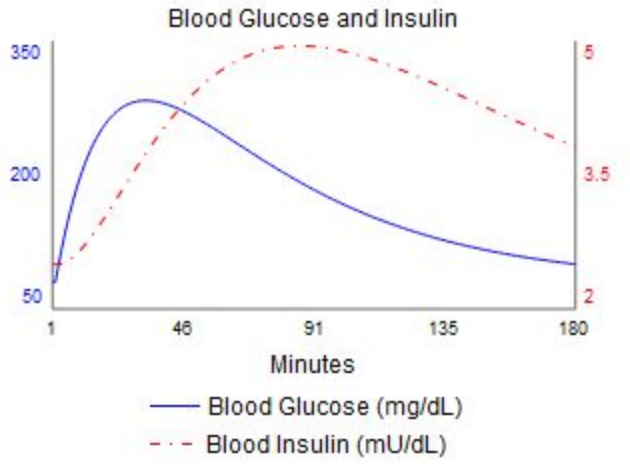
Incorporation of Autoimmune Destruction of Pancreatic Cells- Type I Diabetes

Type I diabetes, rather than being an acquired disorder as a consequence of tolerance mechanisms, is an autoimmune disease in which the body's own immune cells attack the pancreatic cells responsible for synthesizing insulin.[15] This results in a decreased production of insulin, precluding the cell's ability to take up glucose, despite a potentially high concentration in the blood stream. Though the outcome is quite similar to that of Type II diabetes, insulin levels for the autoimmune disorder are abnormally low, unlike their normally elevated state in Type II.

In order to incorporate the effects of pancreatic cell degradation, an extra parameter was introduced into the insulin production rate corresponding to the fraction of insulin-producing cells alive. For a healthy individual, this factor is one, so the dynamics of the system are unchanged. The rate of β cell destruction has been found to vary widely between individuals, with the average age of onset peaking at 10-14 years, but in some cases may be as early as 0-4 years or into adulthood.[11] A study of insulin secretion rates in Type I diabetic patients found an approximate secretion rate of 52% of the non-diabetic rate at diagnosis, dropping to 28% two years later.[15] Thus, a 12% decrease in insulin secretion was used per year in the cell fraction parameter. The underlying mechanisms governing this reduction in insulin production are still a matter of debate, with some findings reporting that percentage of β cell destruction is an insufficient predictor of the onset of Type I diabetes and that the threshold reduction is a function of age with a large variance.[10] Additionally, the effects of elevated FFA concentrations are hypothesized to affect the viability of pancreatic cells, and may thus contribute to further worsening of diabetic symptoms.[16]

Dynamics of the Type I Diabetes Model

The plot for an individual beginning with only 10% β cell function is displayed to the left. This point is typically within the range of the fraction of cells left at which the symptoms of Type I diabetes manifest.[15] Though the trend is similar, the scale of the insulin concentration is drastically reduced, peaking at a concentration nearly five times lower than the normal model. The trend of glucose absorption, as the model considers not only the effects of insulin but of non-insulin dependent factors, including glucose-dependent factors, still follows a similar pattern to the normal individual, but the time course in returning to steady state conditions is longer, with a glucose concentration of 100 mg/dL after three hours, despite an insulin concentration of only 3.82 mU/dL. This is consistent with the symptoms of Type I diabetes, namely, severely reduced insulin levels and elevated glucose levels.



Obese individuals with elevated FFA concentrations and degradation of pancreatic insulin-secreting cells may experience factors of both types of diabetes that make further dysregulate the glucose balance of the body. Insulin tolerance, developed by FFA-dependent pathways, will necessitate higher insulin levels to produce the same effect. However, degradation of β cells reduces the available insulin concentrations. As an example, an individual with a 40 kg body fat content and 10% cell function will have concentrations of 120 mg/dL of glucose but only 4.65 mU/dL of insulin after three hours. At the two hour time point, the individual is nearly at the threshold for diabetes, with a glucose concentration of 190 mg/dL.

A New Method for Testing for Diabetes

For a long time, the oral glucose tolerance test (OGTT) was the standard for diagnosing diabetes. However, there are certain aspects of the test that make it less than desirable for an accurate and safe diagnosis of diabetes and associated diseases, such as impaired glucose tolerance and cardiovascular disease (CVD). A lack of reproducibility has been cited as one of the most significant failures of the method, with less than 50% of the mandated second tests corroborating the results of the first.[6] Additionally, the results of the test do not permit accurate discrimination between various types of disorders associated with glucose elevation. From a mechanistic standpoint, this method does not actually investigate the underlying cause of the glucose tolerance, which is the impaired insulin response.[14]

Updates and alternative testing methods have been developed in order to resolve the issues present in the OGTT, including fasting blood glucose (FBG) and A1C tests, the latter of which measures blood glucose concentration based on percentage of glucose bound to

hemoglobin.[1] This value reflects an average over three months, the average lifespan of a red blood cell, yielding a more reliable overall value than a single time point after two hours.[2] Even so, cases have occurred in which the glucose tests have been more reliable than A1C, and vice versa.

The symptoms of diabetes reflect a confluence of underlying causes that may all be separately assessed. Thus, a single glucose test should not be the primary determining factor in diagnosis of diabetes. As discussed above, elevated free fatty acid levels have been implicated as a cause of insulin resistance, and pancreatic degradation is commonly the result of genetic causes. Therefore, a proper diabetes test should examine each of these factors: glucose, insulin, and FFA levels, along with potential genetic causes. Similarly to the diagnosis of depression or CVD, a certain number of abnormal levels for each of these factors, either over acute or chronic timescales, should be required for diagnosis of diabetes. Acute timescales, such as surveying glucose levels every fifteen minutes or half hour after eating permits discrimination of shorter dynamics that may give the same final result at the two hour time point, while chronic timescales, such as those probed by the A1C test, examine the relative baseline or average values. Assessing both timescales for multiple symptoms will permit more accurate diagnosis not subject to the same variations of only using a single time point OGTT.

A slight modification to the above paradigm for diagnosis is to ensure that the recorded time points for each variable sample as many frequencies as possible; that is, they do not follow only one regular pattern. This pseudorandom sampling of the system permits an accurate reconstruction of the impulse-response function over the duration of the testing, rather than relying on one time point or a regularly spaced array of time points that may be unable to internal oscillations of the system depending on their frequency. This permits the approximation of the response that the system would have to a large bolus, without posing as much of a medical risk for diabetic patients.

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