Glucose Regulation in Diabetes

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Glucose
The next question is: How does insulin and glucagon regulate the concentration of glucose in the blood? This is where a diagram is very useful visual tool.
Above we observe that homeostasis* in a normal system is achieved by maintaining a blood glucose level of about 90mg glucose/100mL of blood. This balance is disturbed by a stimulus such as eating a meal or skipping a meal.

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

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

* The steady-state physiological condition of the body.
glucose level rises to the set point and the stimulus for glucagon release diminishes and we return, yet again, to homeostasis.

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

**Regulation in a Diabetic System**

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

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

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

**From a Mathematical Perspective**

**Regulation in a Healthy System**

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

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>c</td>
<td>glucagon in plasma and interstitial fluids (nU)</td>
</tr>
<tr>
<td>g</td>
<td>glucose in plasma and extracellular fluid (mg)</td>
</tr>
<tr>
<td>i</td>
<td>interstitial fluid insulin (µU)</td>
</tr>
<tr>
<td>l</td>
<td>liver insulin (µU)</td>
</tr>
<tr>
<td>p</td>
<td>plasma insulin (µU)</td>
</tr>
<tr>
<td>r</td>
<td>releasable pancreatic insulin (µU)</td>
</tr>
<tr>
<td>s</td>
<td>stored pancreatic insulin (µU)</td>
</tr>
</tbody>
</table>
To simulate hyperinsulinism, we could begin by adjusting the appropriate parameters in Table 2. Maybe we could try increasing $a_6$ in $F_6$. Although, other adjustments may be needed.

Extended Models

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

Diagram 4: Insulin-Glucose Model extended with the glucose-fatty acid cycle.

Note: Fluxes are represented as double arrows. Endocrine interactions are shown as dotted arrows: positive as normal arrowheads, negative as flattened diamonds, modulatory as circles. ‘$\alpha$’ represents pancreatic $\alpha$-cells and ‘$\beta$’ represents pancreatic $\beta$-cells.

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

**Diagram 5**: Insulin-Glucagon-glucose model integrated with protein metabolism.

*Note*: Fluxes are represented as double arrows. Endocrine interactions are shown as dotted arrows: positive as normal arrowheads, negative as flattened diamonds, modulatory as circles. ‘α’ represents pancreatic α-cells and ‘β’ represents pancreatic β-cells.

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References


