The effect of food on triggering type II diabetes: modeling a CBD Pancreas

Mohamed Raef Smaoui

School of Computer Science, McGill University, Montreal, QC, Canada

Abstract

Type II diabetes affects around 350 million people worldwide. It is a disease that results in the failure of the pancreas to produce enough insulin in the human body. This failure of meeting the body's insulin demands results in high glucose concentration in the blood and low glucose absorption into the heart, muscles and adipose tissue. As such, patients with the disease are required to inject insulin daily to survive. The pancreas fails to produce enough insulin due to the death of its overworked and overstressed β-cells. In this paper, we use Causal Block Diagrams to model the cooperation of β-cells to produce insulin upon the detection of glucose in the blood. We simulated a pancreas of 100 β-cells that responds to a glucose release of a 3 meals / day metabolic behavior. Our model suggests that a daily intake of 1300 - 1850 calories keeps the pancreas in the best health. We show that any added stress starts to kill the β-cells, and at a rate of 4500 calories / day diabetes becomes inevitable if serious measures to improve one's health are not taken.

Keywords: Pancreas, Causal Block Diagram, type II diabetes, β-cells, AToM^3, Insulin, Glucose

1. Introduction

Upon having a meal, the body digests food into glucose for energy consumption.Glucose levels increase in the blood and signal the pancreas' β-cells to generate insulin and amylin proteins as a response. Insulin is secreted to instruct body organs such as the hearth and muscles to absorb and metabolize glucose, hence lowering its level in the blood. Amylin is released with Insulin at a ratio of 1:100 Westermark et al. (2011). Interestingly, Amylin

has a tendency to change its protein form into a destructive form known as amyloid. It reshapes itself into an amyloid. This amyloid finds other malformed amylin amyloids and aggregates. These amyloids stack on top of each other to create a unified long structure called a fibril.

If the fibril is short due to the low concentration of aggregating amyloids, the cell can eventually degrade these bad structures over time. However, if a person stresses their body by eating too much, the pancreas produces more and more insulin causing amylin's concentration to become high enough for long fibrils to form. Once these fibrils get too large, the cell loses its capability of degrading them. The fibrils then weaken their β-cell, rupture it, and attempt to infect the neighboring cells.

Once a β-cell breaks, it can no longer produce insulin. If many β-cells die, there is not enough insulin to lower glucose levels in the body and the person becomes diagnosed with type II diabetes Marzban et al. (2003). Such individuals require daily insulin injections (after meals) to survive.

In this paper, we intend to model and simulate this diabetes phenomenon using Causal Block Diagrams (CBD) in AToM^3 Lara and Vangheluwe (2002). In section 2.1, we present an ordinary differential equation (ODE) relating physiological insulin and amylin concentrations in human blood. In section 2.2, we explain how to construct CBDs for β-cells of the pancreas that respond to the ODE output of insulin. In section 3, we present and discuss the results of our modeling and simulation. We conclude this paper by discussing the limitations of our model and the plans for future development.

2. Methods

2.1. Insulin and Glucose relation

Many mathematical models that relate the concentrations of insulin to glucose have been published in the last century Boutayeb and Chetouani (2006). Among the famous models is the following one suggested by Bolie (1961),

$$\frac{dI}{dt} = p - \alpha I + \beta G \tag{1}$$

$$\frac{dG}{dt} = q - \gamma I - \delta G \tag{2}$$

where I is the concentration of Insulin in the blood, G the concentration of glucose in the blood, p is the insulin injection function into the blood, q is

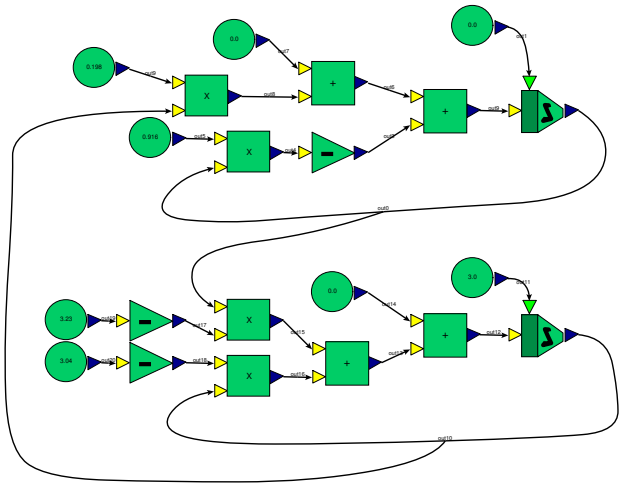


Figure 1: Physiological insulin / glucose relation in the blood. Top integral block models the concentration of insulin at time t, and the lower integral block models the concentration of glucose at time t.

the body's glucose intake function, and the rest of the variables are constants used to calibrate the model with observed experimental data. We model Eqs [1] and [2] as CBDs in AToM^3 as presented in Figure 1.

2.2. Modelling the pancreas

The human pancreas consists of millions of β-cells that cooperate to produce insulin. Using CBDs we this cooperation of β-cells in response to glucose levels in the blood. Using the Dirichlet distribution we assign an insulin production rate to each β-cell. The distribution ensures that the sum of all production rates is 1. Each β-cell has a factory for amylin that produces at a rate of 1 amylin protein for every 100 insulin. The factory is modeled with a delay, sum and multiplication blocks. When the concentration of amylin is high enough the cell dies as a result of amylin amyloid fibril formation and its contribution to the total insulin becomes zero, adding more weight to the other β-cell processes to produce the required levels of Insulin. A dead cell does not produce any more insulin (its rate is set to 0), and its amyloid amylins attempt to infect neighboring cells. Life is modeled by a test block and infectivity by a sum block to the neighboring cells. Figure 2 illustrates the CBD model of a single β cell.

We model the entire pancreas by creating 100 β CBD instances of Figure 2 and connect their infecting blocks together. Each restrict each β-cell to

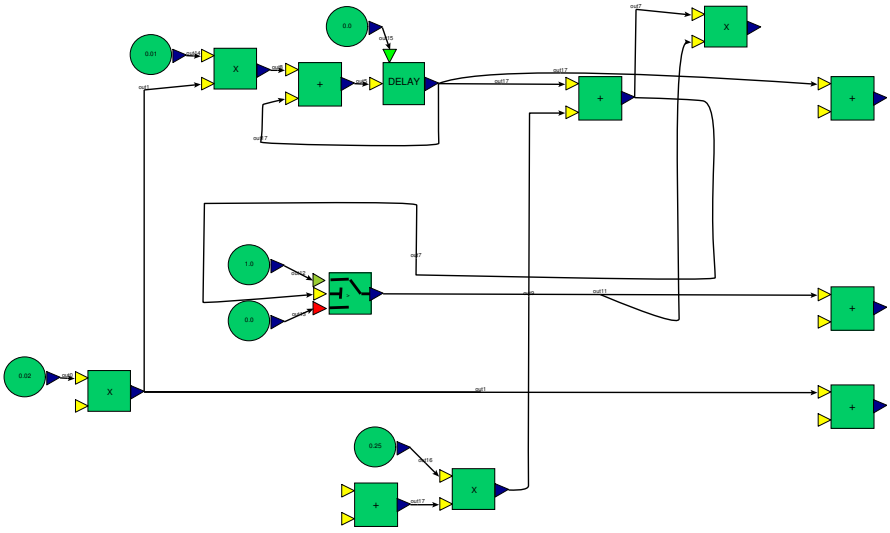


Figure 2: Physiological insulin / glucose relation in the blood. Top integral block models the concentration of insulin at time t, and the lower integral block models the concentration of glucose at time t.

infect two neighbors. The entire 100 CBD models are connected to the ODE CBD of Figure 1. Instead of insulin being fed directly from the insulin integral, we feed insulin required levels to each β-cell and collect the output of the live cells into the glucose CBD. This enables us to keep track on β-cell performance and life throughout time.

3. Results and Discussion

The ODE model explained in section 2.1 and the cooperating 100 β-cells explained in section 2.2 have been modeled into a single CBD that can be simulated from the "myHealth.py" executable found on the course website. The program asks you how many calories you eat for breakfast, lunch, and dinner and calculates the affect of your eating habits on the health of your pancreas. A screen shot of sample run of the executable is shown in Figure 3.

Using the model we built, we have found that a 70 Kg and 170 cm tall person would require a eating habit of 1300 - 1850 calories / day to have a healthy pancres $< 10\%$ β-cell death, as shown in Figure 4. In Figure 5, we show that a diet of 2500 calories / day over the long run can destroy many β-cells in the pancreas. In Figure 6, diabetes is reached when a diet of 4000

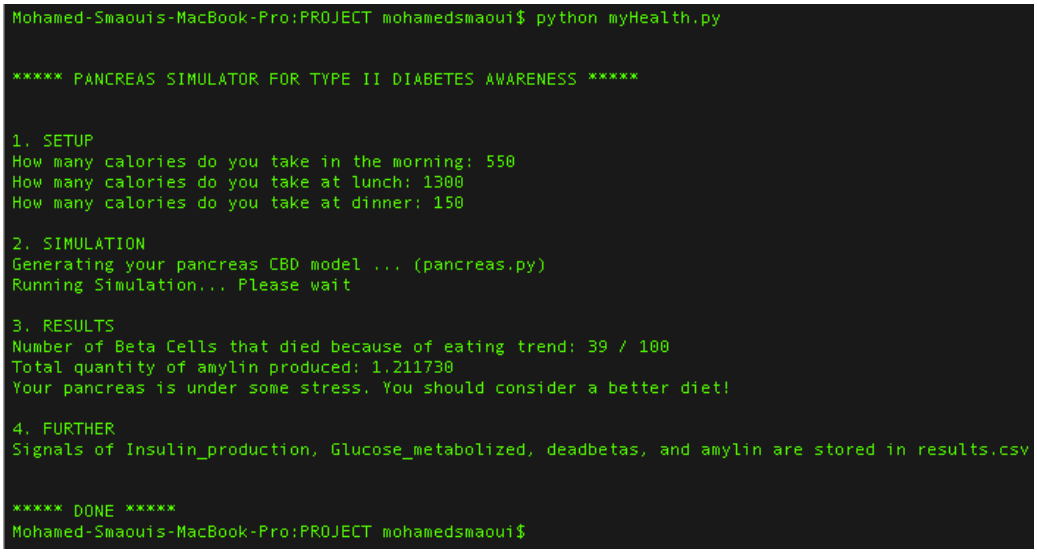


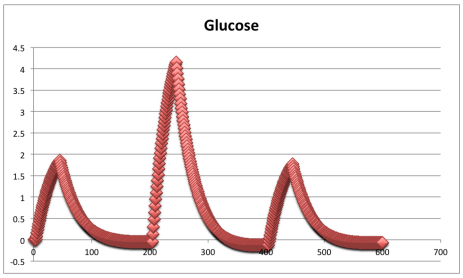
Figure 3: Screenshot of the myHealth.py program

calories / day generates enough amylin amyloids to kill most of the β-cells. Years of pancreatic stress due to the high glucose level in the blood results in type II diabetes.

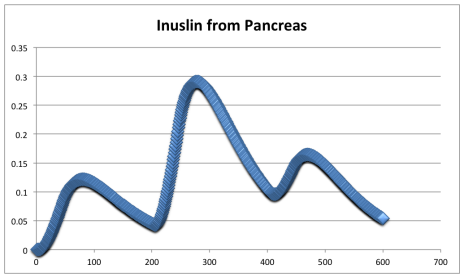
We highly recommend that an individual takes between 1300 and 1850 calories / day to stay healthy.

4. Conclusion and Future direction

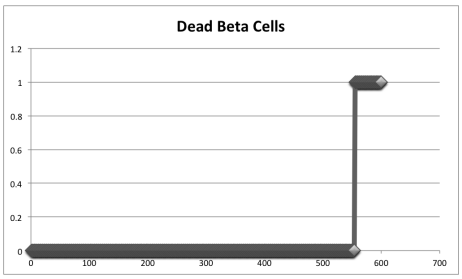
We aimed at producing a model that captures the phenomenon of β-cell death due to high glucose demand. The current ODE relating insulin to glucose does not take into account glucagon levels in the blood and does not take into account that glucose should not fall under a level of 5. We plan to substitute the ODE in section 2.1 with one given by the Minimal Model of Insulin. We plan to increase the number of β-cells to better simulate the real size of the pancreas. We also plan to add a lysosome mechanism in the β-cells to model destruction of small amyloids. Adding these features will slow down the simulations and require clusters to compute the output results. Nevertheless, more detail can be captured and more accurate findings can be made.



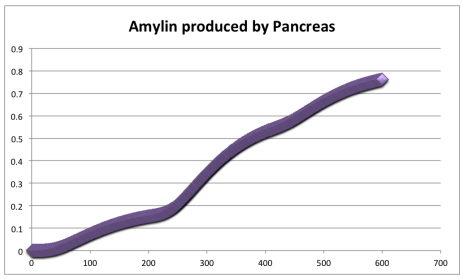
(a) 3 meals / day



(b) 3 insulin spikes / day

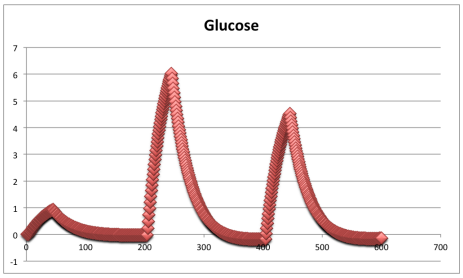


(c) 1 dead cell

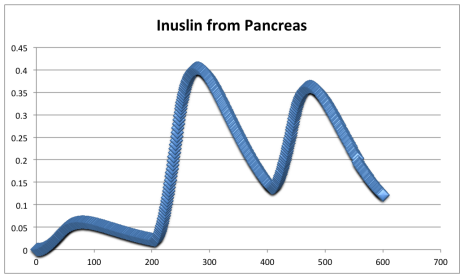


(d) low amylin concentration

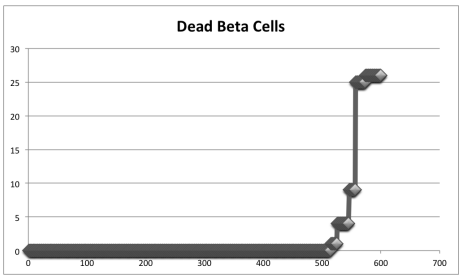
Figure 4: Output of model for a healthy diet pattern of 1700 calories / day consisting of 400 calories for breakfast, 900 for lunch, and 400 for dinner.



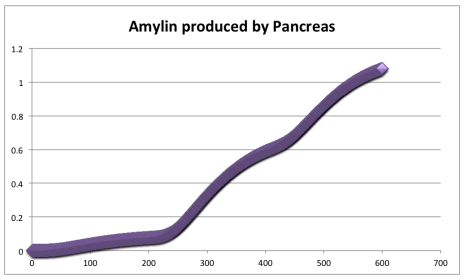
(a) 3 meals / day



(b) 3 insulin spikes / day

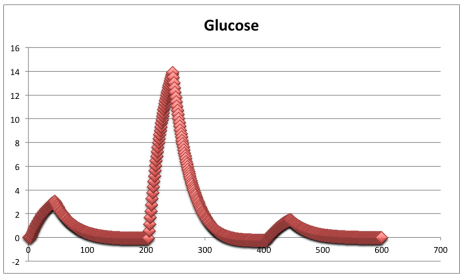


(c) 1 dead cell

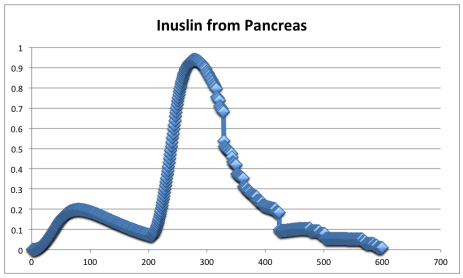


(d) low amylin concentration

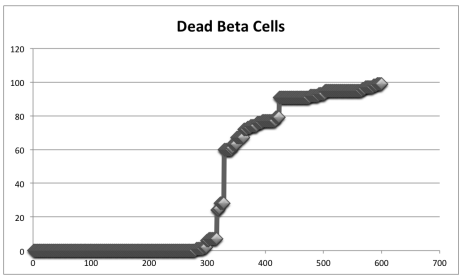
Figure 5: Output of model for a diet pattern of 2500 calories / day consisting of 200 calories for breakfast, 1300 for lunch, and 1000 for dinner.



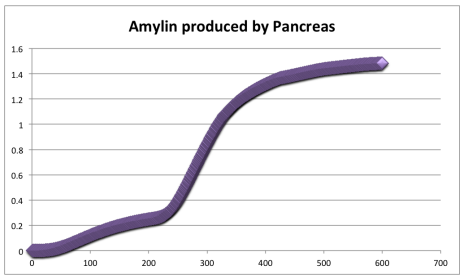
(a) 3 meals / day



(b) 3 insulin spikes / day



(c) 1 dead cell



(d) low amylin concentration

Figure 6: Output of model for a diet pattern of 4000 calories / day consisting of 650 calories for breakfast, 3000 for lunch, and 350 for dinner.

5. References

Bolie, V. W., Sep 1961. Coefficients of normal blood glucose regulation. J Appl Physiol 16, 783–8.

Boutayeb, A., Chetouani, A., 2006. A critical review of mathematical models and data used in diabetology. Biomed Eng Online 5, 43.

Lara, J., Vangheluwe, H., 2002. Atom3: A tool for multi-formalism and meta-modelling. European Joint Conference on Theory And Practice of Software (ETAPS), Fundamental Approaches to Software Engineering (FASE) 2306, 174–188.

Marzban, L., Park, K., Verchere, C. B., Apr 2003. Islet amyloid polypeptide and type 2 diabetes. Exp Gerontol 38 (4), 347–51.

Westermark, P., Andersson, A., Westermark, G. T., Jul 2011. Islet amyloid polypeptide, islet amyloid, and diabetes mellitus. Physiol Rev 91 (3), 795–826.