Dynamics of Glucose-Insulin Regulation: Insulin Injection Regime for Patients with Diabetes Type 1[1]

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Abstract
A healthy human body regulates blood glucose concentration via regulating the insulin concentration. Diabetes type 1 patients' bodies cannot produce insulin. Therefore, blood glucose needs to be regulated by insulin injections. This is not an easy task because there are dynamic complexities such as accumulation processes, delays, nonlinearities, and feedback loops in the system. Moreover, the task is a critical one because both low and high levels of glucose are harmful for the body. In this work, we first developed and calibrated a system dynamics model for "the two time delay model" as described by Li et al., 2006. Later, we introduced a penalty formulation to be able to evaluate different cases. We also deleted the insulin production flow and added insulin injections to the base model in order to obtain the model for a diabetes type 1 patient. According to the initial results of the study, the suggested decision making heuristic would yield satisfactory results. However, further tests under different glucose infusion rate patterns and improvement to the heuristic are necessary.

Keywords: glucose-insulin regulation; control problem; diabetes type 1; insulin injections; medical modeling; decision making heuristic.

Introduction

Diabetes Mellitus is a disease associated with body insulin deficiency or inefficient use of it. A patient with diabetes either cannot produce insulin to absorb glucose and turn it into energy (diabetes type 1) or cannot properly respond to insulin (diabetes type 2) (Alberti and Zimmet, 1998). Regulation of glucose is very critical because both hyperglycemia (high blood glucose) and hypoglycemia (low blood glucose) are harmful for the organs (Cryer, 2001; Ruderman et al., 1992, Sanlioglu et al., 2008). In a healthy human body, glucose is regulated via regulating the blood insulin concentration. However, diabetes type 1 patients' bodies cannot produce insulin, which leaves glucose

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unregulated. Insulin injection is the main treatment for such patients (Sanlioglu et al., 2008). However, one should be very careful with insulin injections because if more insulin than necessary is injected, this may lead to hypoglycemia and, if less insulin than necessary is injected, this may lead to hyperglycemia (Cryer, 2001; Sanlioglu et al., 2008). Regulating the blood glucose and insulin concentrations by insulin injections is not a simple task because of the existing dynamic complexities in the regulatory system.

There are many studies and different models on the glucose-insulin regulatory system (Makroglou et al., 2006). According to experiments, insulin secretion rate has three different oscillatory patterns superimposed on each other. The first oscillatory pattern is the fastest and it has a period of tens of seconds; The second oscillatory pattern is called *rapid oscillation* and has a period of 5-15 minutes; The third oscillatory pattern is called *ultradian oscillations* and has a period of 50-120 minutes (Makroglou et al., 2006). Sturis et al. (1991) developed a six dimensional differential equation model to analyze the ultradian oscillations. The model introduced by Sturis et al. (1991) separates insulin stock (compartment) into two distinct stocks and contains a third order delay of insulin effectiveness and a glucose stock. Tolic et al. (2000) improved the model developed by Sturis et al. (1991) by simplifying it[2]. Li et al. (2006) proposed a delay-differential-equation model that uses the same functions and parameter values as in the models of Sturis et al. (1991) and Tolic et al. (2000). This model is named as the *two time delay model* and includes two distinct time delays for both insulin effectiveness and glucose effectiveness (Li et al., 2006).

In this work, we first constructed a system dynamics model of the two time delay model introduced by Li et al. (2006). We run our model for the different cases discussed in the Li et al. (2006) paper and confirmed that our model produces the same dynamics as the Li et al. (2006) model in all cases. In order to save some space, we did not provide those runs in the paper. After the calibration of the system dynamics model, we set the delay parameters equal to the values used in section 3 of the Li et al. (2006) paper and obtained base run dynamics for a healthy person as a benchmark. We introduced a penalty formulation to be able to evaluate different cases. Later, we adapted the base model for diabetes type 1 patients. In order to obtain the model for a diabetes type 1 patient, we deleted the insulin production flow from and added insulin injections to the base model. We also suggested a decision heuristic for insulin injections.

[2] If correctly applied model simplification increases the usefulness of models (Saysel and Barlas, 2006; Yasarcan, 2010).

Base Model for a Healthy Person

We constructed a system dynamics model of the two time delay model introduced by Li et al. (2006). The stock-flow diagram of this model is given in Figure 1. Note that the equations (1-37) of this model are all taken from Li et al. (2006) and we also tried to provide the related information presented in the Li et al. (2006) paper by adding footnotes to the equations. Note that this model represents the glucose-insulin regulatory system for a healthy person.

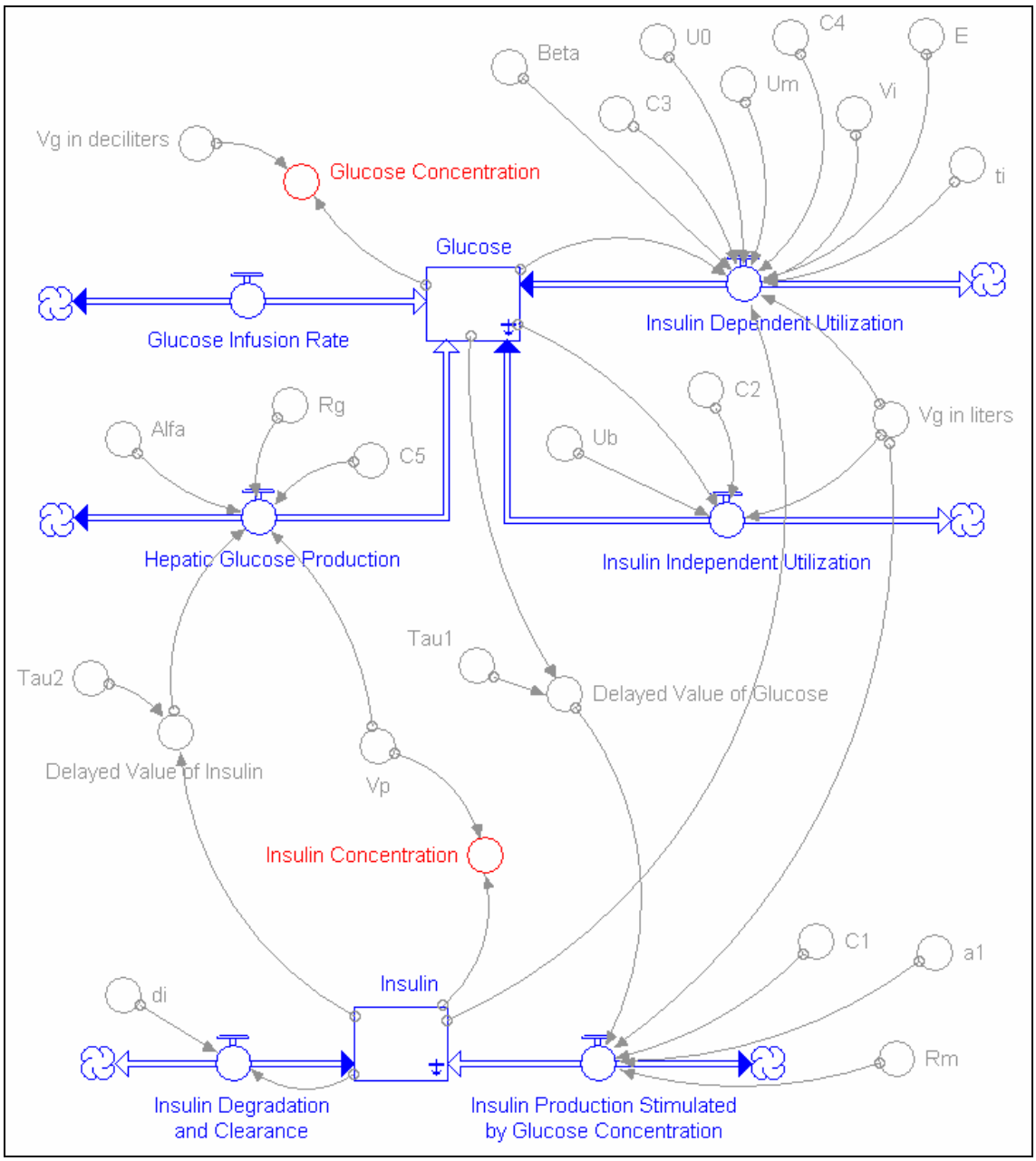

Figure 1. Stock-flow diagram of the two time delay model

- Initial values and approximate integral equations for the stock variables:

$$Glucose_0 = 10{,}500\ [milligram] \tag{1}$$

$$Glucose_{t+DT} = Glucose_t + \begin{pmatrix} Glucose\ Infusion\ Rate \\ + Hepatic\ Glucose\ Production \\ - Insulin\ Dependent\ Utiliation \\ - Insulin\ Independent\ Utilization \end{pmatrix} \bullet DT\ [milligram] \tag{2}$$

$$Insulin_0 = 90\ [milliunit] \tag{3}$$

$$Insulin_{t+DT} = Insulin_t + \begin{pmatrix} Insulin\ Production\ Stimulated\ by \\ Glucose\ Concentration \\ - Insulin\ Degradation\ and\ Clearance \end{pmatrix} \bullet DT\ [milliunit] \tag{4}$$

- Flow variables:

$$Glucose\ Infusion\ Rate = 108\ [milligram/minute] \tag{5}$$

$$Hepatic\ Glucose\ Production = \frac{Rg}{1 + e^{Alfa \bullet (Delayed\ Value\ of\ Insulin/Vp - C5)}} \left[\frac{milligram}{minute}\right] \tag{6}$$

$$Insulin\ Dependent\ Utilization = \left(\frac{Glucose}{C3 \bullet Vg\ in\ liters)}\right) \bullet \left(U0 + \frac{(Um - U0)}{1 + e^{-Beta \bullet LOGN\left(\frac{Insulin}{C4 \bullet (1/Vi + 1/(E \bullet ti))}\right)}}\right) \left[\frac{milligram}{minute}\right] \tag{7}$$

$$Insulin\ Independent\ Utilization = Ub \bullet \left(1 - e^{-\left(\frac{Glucose}{C2 \bullet Vg\ in\ liters)}\right)}\right) \left[\frac{milligram}{minute}\right] \tag{8}$$

$$\begin{pmatrix} Insulin\ Production\ Stimulated \\ by\ Glucose\ Concentration \end{pmatrix} = \frac{Rm}{1 + e^{\frac{(C1 - Delayed\ Value\ of\ Glucose/Vg\ in\ liters)}{a1}}} \left[\frac{milliunit}{minute}\right] \tag{9}$$

$$Insulin\ Degrdation\ and\ Clearance = Insulin \bullet di \left[\frac{milliunit}{minute}\right] \tag{10}$$

- Other variables:

$$Delayed\ Value\ of\ Glucose = \text{DELAY}\left(Glucose, Tau1, Glucose\right)\left[milligram\right] \quad (11)^{3}$$

$$Delayed\ Value\ of\ Insulin = \text{DELAY}\left(Insulin, Tau2, Insulin\right)\left[milliunit\right] \quad (12)$$

$$Glucose\ Concentration = Glucose/Vg\ in\ deciliters\ \left[milligram/deciliter\right] \quad (13)$$

$$Insulin\ Concentration = Insulin/Vp\ \left[milliunit/liter\right] \quad (14)$$

- Parameters:

$$a1 = 300\ \left[milligram/liter\right] \quad (15)$$

$$Alfa = 300\ \left[milligram/liter\right] \quad (16)^{4}$$

$$Beta = 1.77\ \left[dimensionless\right] \quad (17)^{5}$$

$$C1 = 2000\ \left[milligram/liter\right] \quad (18)$$

$$C2 = 144\ \left[milligram/liter\right] \quad (19)$$

$$C3 = 1000\ \left[milligram/liter\right] \quad (20)$$

$$C4 = 80\ \left[milliunit/liter\right] \quad (21)$$

$$C5 = 26\ \left[milliunit/liter\right] \quad (22)$$

$$C5 = 26\ \left[milliunit/liter\right] \quad (23)$$

$$di = 0.06\ \left[1/minute\right] \quad (24)^{6}$$

$$E = 0.2\ \left[liter/minute\right] \quad (25)^{7}$$

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[3] DELAY(input, delay time, initial value) is a function that creates a delayed version of the input as its output such that if Y = DELAY(X, t1, Y_0), this means that $Y_{t+t1} = X_t$.

[4] The software that we used to develop the system dynamics model does not allow symbols. In the Li et al. (2006) paper *Alfa* is represented with the symbol α.

[5] In the Li et al. (2006) paper *Beta* is represented with the symbol β.

[6] *di* is the clearance fraction.

[7] *E* is the diffusion transfer rate.

$$Rg = 180\ [milligram/minute] \quad (26)$$

$$Rm = 210\ [milliunit/minute] \quad (27)$$

$$Tau1 = 7\ [minute] \quad (28)^{8}$$

$$Tau2 = 12\ [minute] \quad (29)^{9}$$

$$ti = 100\ [minute] \quad (30)^{10}$$

$$U0 = 40\ [milligram/minute] \quad (31)$$

$$Ub = 72\ [milligram/minute] \quad (32)$$

$$Um = 940\ [milligram/minute] \quad (33)$$

$$Vg\ in\ deciliters = 100\ [deciliter] \quad (34)^{11}$$

$$Vg\ in\ liters = 10\ [liter] \quad (35)$$

$$Vi = 11\ [liter] \quad (36)^{12}$$

$$Vp = 3\ [liter] \quad (37)^{13}$$

We simulated the model for 1440 minutes (1 day) in order to obtain the benchmark dynamics. The glucose and insulin concentration dynamics for this run is given in Figure 2. Glucose concentration level varies approximately between 83 and 106. Insulin concentration level varies approximately between 25-43. According to Li et al. (2006), the oscillatory behavior observed in Figure 2 is in agreement with physiological data.

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[8] In the Li et al. (2006) paper *Tau1* is represented with the symbol τ_1 and it is the insulin transportation delay time.

[9] In the Li et al. (2006) paper *Tau2* is represented with the symbol τ_2 and it is the time lag for insulin effect on liver.

[10] *ti* is the insulin degradation time constant.

[11] *Vg in deciliters* and *Vg in liters* are actually the same parameter. We separated *Vg* into two parameters because the software that we used cannot handle unit transformation.

[12] *Vi* is the effective volume of the intercellular space.

[13] *Vp* is the plasma insulin distribution volume.

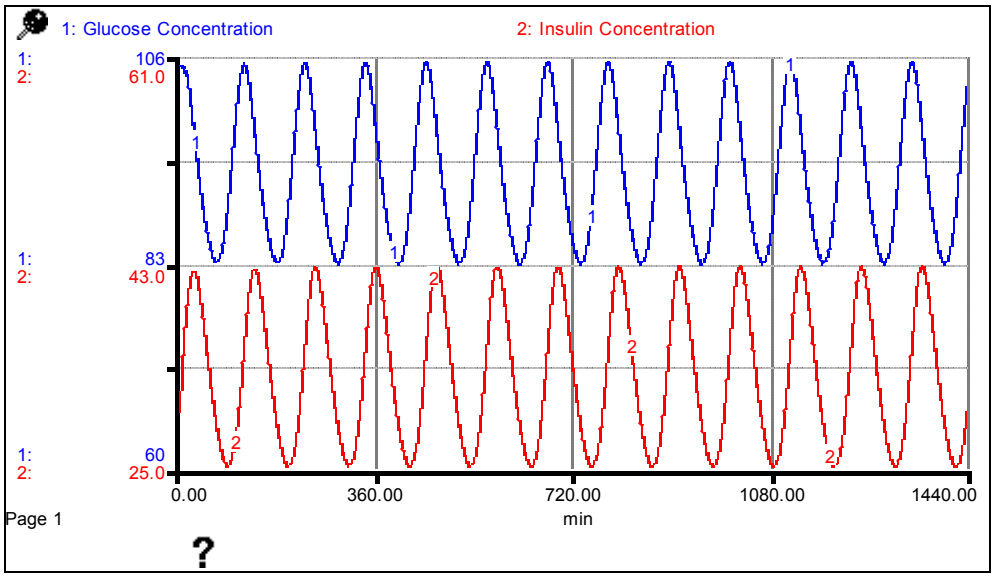

Figure 2. Base run: glucose and insulin concentration dynamics for a healthy person

Suggested Penalty Formulation

We introduced the following penalty formulation (equations 38-40):

$$Penalty_0 = 0 \quad [milligram \cdot minute / deciliter] \tag{38}$$

$$Penalty_{t+DT} = Penalty_t + Penalty\ Generation \bullet DT \quad \left[\frac{(milligram \cdot minute)}{deciliter}\right] \tag{39}$$

$$Penalty\ Generation = \left|94.25 - Glucose\ Concentration\right| \quad [milligram / deciliter] \tag{40}$$

Approximately, 94.25 is the average glucose concentration. *Penalty* is the accumulated absolute difference between 94.25 and *Glucose Concentration* (equations 38-40). Penalty is 10,179 for the base run in Figure 2.

Changes in the Model for a Diabetes Type 1 Patient

We changed Equation 4 to the following (Equation 41) by replacing the inflow of *Insulin* stock, which is *Insulin Production Stimulated by Glucose Concentration*, with *Insulin Injections*:

$$Insulin_{t+DT} = Insulin_t + \begin{pmatrix} Insulin\ Injections \\ - Insulin\ Degradation\ and\ Clearance \end{pmatrix} \bullet DT \ [milliunit] \tag{41}$$

We assumed that the actual value of *Glucose Concentration* is not available to the decision maker. Hence, the following equations (42-45) are added to the model:

$$Measured\ Glucose\ Concentration_0 = Glucose\ Concentration \left[\frac{milligram}{deciliter}\right] \quad (42)$$

$$\begin{pmatrix} Measured \\ Glucose \\ Concentration \end{pmatrix}_{t+DT} = \begin{pmatrix} Measured \\ Glucose \\ Concentration \end{pmatrix}_{t} + \begin{pmatrix} Measurement \\ Formation \end{pmatrix} \bullet DT \left[\frac{milligram}{deciliter}\right] \quad (43)$$

$$\begin{pmatrix} Measurement \\ Formation \end{pmatrix} = \frac{\begin{pmatrix} Glucose \\ Concentration \end{pmatrix} - \begin{pmatrix} Measured \\ Glucose \\ Concentration \end{pmatrix}}{Measurement\ Delay\ Time} \quad \left[\frac{milligram}{deciliter \bullet minute}\right] \quad (44)$$

$$Measurement\ Delay\ Time = 2 \quad [minute] \quad (45)$$

We assume that a dynamic decision making heuristic control the automatic insulin injection unit attached to the patient. Patient should use the unit 24 hours a day. The equations for the suggested dynamic decision making heuristic, which controls the injections, are given below (equations 46-52):

$$Insulin\ Injections = \left\{\begin{array}{l} \text{IF } (Measured\ Glucose\ Concentration > 94.25) \\ \quad \text{AND NOT}(Remaining\ Time > 0) \\ \text{THEN } Amount\ of\ Injection/\text{DT} \\ \text{ELSE } 0 \end{array}\right\} \left[\frac{milliunit}{minute}\right] \quad (46)$$

$$Amount\ of\ Injection = 200\ [milliunit] \quad (47)$$

$$Remaining\ Time_0 = 10\ [minute] \quad (48)$$

$$\begin{pmatrix} Remaining \\ Time \end{pmatrix}_{t+DT} = \begin{pmatrix} Remaining \\ Time \end{pmatrix}_{t} + \begin{pmatrix} Restart\ Remaining\ Time \\ -\ Count\ Down \end{pmatrix} \bullet DT\ [minute] \quad (49)$$

$$\begin{pmatrix} Restart \\ Remaining \\ Time \end{pmatrix} = \left\{\begin{array}{l} \text{IF } Insulin\ Injections > 0 \\ \text{THEN } \dfrac{Minimum\ Time\ Between\ Injections}{\text{DT}} \\ \text{ELSE } 0 \end{array}\right\} [dimensionless] \quad (50)$$

$$Minimum\ Time\ Between\ Injections = 15\ [minute] \quad (51)$$

$$Count\ Down = \{\text{IF } Remaining\ Time > 0 \text{ THEN } 1 \text{ ELSE } 0\}\ [dimensionless] \qquad (52)$$

The resulting behavior can be seen in Figure 3. The associated penalty is approximately 8,801, which is even less than the penalty (10,179) obtained for a healthy person. Thus, we can conclude that the proposed heuristic is successful under the conditions presented in this paper.

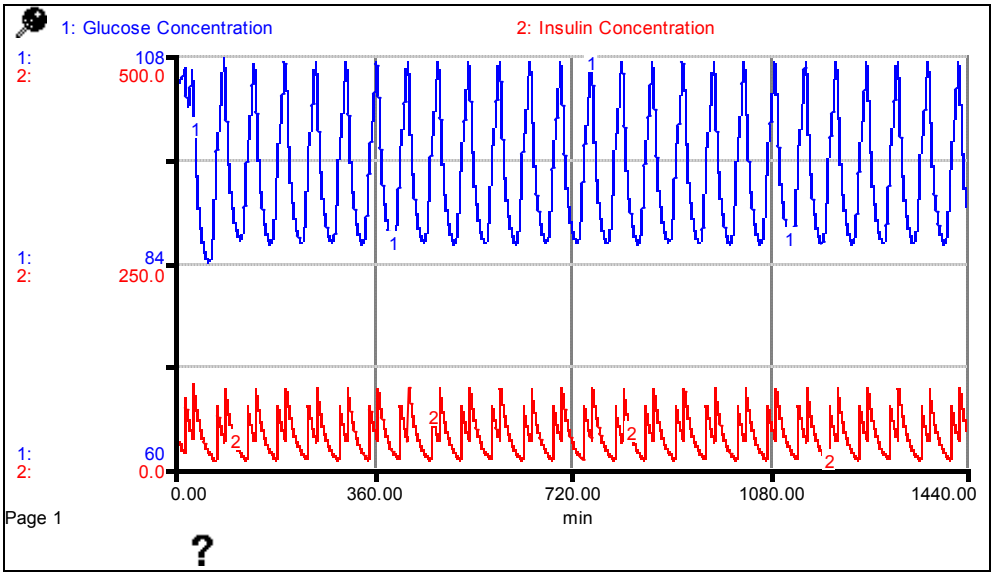

Figure 3. Run for a diabetes type 1 patient

Conclusions

In this work, we first constructed a system dynamics model of the two time delay model introduced by Li et al. (2006). This model represents the glucose-insulin regulatory system in a healthy person. We simulated the model for 1440 minutes (1 day) and obtained the benchmark dynamics given in Figure 2. Later, we introduced a penalty formulation and calculated the penalty as 10,179 for the benchmark.

We adapted the model for a diabetes type 1 patient by replacing the insulin production with *Insulin Injections*. We assumed that an automatic insulin injection unit is attached to the patient 24 hours a day. We also introduced a dynamic decision making heuristic that can be utilized in the control of the unit. The suggested decision making heuristic generated a penalty value (8,801) less than the benchmark penalty (10,179). Hence, we conclude that the proposed heuristic is successful under the conditions presented in this paper. However, further tests under different glucose infusion rate patterns would be required before utilizing the heuristic. Moreover, the performance of the heuristic should be improved by optimizing its parameters.

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