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A Review of Mathematical Model Describing Insulin Delivery System for Type 1 Diabetes

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Abstract: Even though technologies on diabetes treatment keep expanding from time to time, blood glucose control problem is still being a crucial issue raised by scientists and researchers. Most of the Diabetes do not achieve an optimum blood glucose level despite of persistent treatment taken. Therefore, an efficient control is essential to enhance diabetes treatment. A comprehensive, accurate, reliable and simple mathematical model is being focused in developing a control algorithm on blood glucose level. It is hoped that the insulin delivery mechanism can be simplified and the life quality of patient can be improved. A good working mathematical model should be able to mimic the dynamic and complexity of insulin glucose interactions so as to provide valuable information on safety and effectiveness of the control system in patient's body. In this paper, we review the mathematical model which describes insulin delivery mechanism for Type 1 Diabetes and present the results of the simulation work representing insulin-glucose interactions in the body.

Key words: Diabetes, mathematical model, optimization, insulin

INTRODUCTION

Mathematical model describes a system that employs mathematical concepts and language. A simple but comprehensive three-compartmental model, limited to Intravenous Glucose Tolerance Test (IVGTT) has been proposed (Bergman *et al*., 1981). Then, Derouich and Boutayeb (2002) introduced parameters related to physical exercises. Extension of Bergman's minimal model which introduced partitioning during IVGTT was then developed (Hovorka *et al*., 2002). In 2004, a nonlinear model predictive controller was developed to maintain optimum blood glucose level in Type 1 Diabetes patients during fasting conditions (Hovorka *et al*., 2004). Man *et al*. (2007) were also responsible in developing a closed- loop control system in artificial pancreas research. In this paper, we will discuss further in diabetic mathematical model describing insulin delivery system specifically for Type 1 Diabetes.

MATERIALS AND METHODS

Equations 1 to 8 from Hovorka model (Hovorka *et al*., 2004) were employed to represent mass of glucose in accessible compartment (Q1), mass of glucose in non-accessible compartment (Q2), insulin absorption on compartment 1 (S1), insulin absorption on compartment 2 (S2), plasma insulin concentration (I), effect of insulin on glucose distribution/transport (x1), effect of insulin on glucose disposal (x2) and effect of insulin on endogenous glucose production (x3), respectively (Table 1, 2). Figure 1 depicts schematic flow diagram for glucose and insulin subsystem of Hovorka model. Simulation works in this study were carried out using MATLAB programming. All parameter values are specified as follows:

- Glucose subsystem:

Table 1: Model constants

Symbol	Quantity	Value
k_{12}	Transfer rate (min^{-1})	0.066
k_{a1}	Deactivation rate (min^{-1})	0.006
k_{a2}	Deactivation rate (min^{-1})	0.06
k_{a3}	Deactivation rate (min^{-1})	0.03
k_e	Insulin elimination from plasma (min^{-1})	0.138
V_I	Insulin distribution volume (L kg^{-1})	0.12
V_G	Glucose distribution volume (L kg^{-1})	0.16
A_G	Carbohydrate(CHO)bioavailability (unitless)	0.8
$t_{max,G}$	Time-to-maximum of CHO absorption (min)	40

Source: Hovorka model (Hovorka *et al*., 2004)

Table 2: Model parameters

Symbol	Quantity	Value[a]	Source
$*S_{IT}^{fb}$	Insulin sensitivity of distribution/transport	51.2×10^{-4} min^{-1} per mU L^{-1}	Hovorka *et al*. (2002)
$*S_{ID}^{fb}$	Insulin sensitivity of disposal	8.2×10^{-4} min^{-1} per mU L^{-1}	Hovorka *et al*. (2002)
$*S_{IE}^{fb}$	Insulin sensitivity of EGP	520×10^{-4} per mU L^{-1}	Hovorka *et al*. (2002)
EGP_0	EGP extrapolated to zero insulin concentration	0.0161 mmol kg^{-1} min^{-1}	Hovorka *et al*. (2002)
F_{01}	Non-insulin-dependent glucose flux	0.0097 mmol kg^{-1} min^{-1}	Hovorka *et al*. (2002)
$t_{max,I}$	Time-to-maximum of absorption of subcutaneously injected short-acting insulin	55 min	Howey *et al*. (1994), Rave *et al*. (1999)

[a]Mean value of the parameter for the purpose of Bayesian parameter estimation. [b]Alternative parameterization. $*S_{IT}^{f} = k_{b1}/k_{a1}$, $*S_{ID}^{f} = k_{b2}/k_{a2}$ and $*S_{IE}^{f} = k_{b3}/k_{a3}$

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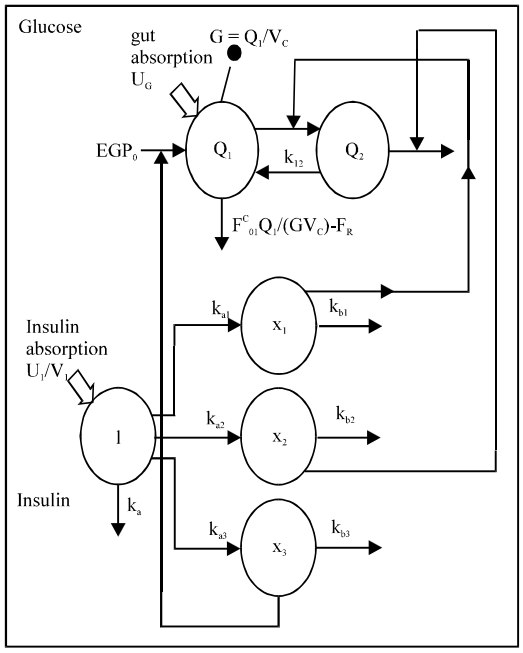

Fig. 1: Schematic flow diagram for glucose and insulin subsystem of Hovorka model

$$\frac{dQ_1(t)}{dt} = -\left[\frac{F^c_{01}}{V_G G(t)} + x_1(t)\right]Q_1(t) + k_{12}Q_2(t) - F_R + U_G(t) + EGP_0[1 - x_3(t)] \quad (1)$$

$$\frac{dQ_1(t)}{dt} = x_1(t) + Q_1(t) - [k_{12} + x_2(t)]Q_2(t)y(t)G(t) \quad (2)$$

- Insulin subsystem:

$$\frac{dQ_1(t)}{dt} = \mu(t) - \frac{S_1(t)}{t_{max,1}} \quad (3)$$

$$\frac{dQ_1(t)}{dt} = \frac{S_1(t)}{t_{max,1}} - \frac{S_2(t)}{t_{max,1}} \quad (4)$$

$$\frac{dI(t)}{dt} = \frac{U_1(t)}{V_1} - k_{e1}I(t) \quad (5)$$

- Insulin action subsystem:

$$\frac{dx_1(t)}{dt} = -k_{a1}I(t) + k_{b1}I(t) \quad (6)$$

$$\frac{dx_2}{dt} = -k_{a2}x_2(t) + k_{b2}I(t) \quad (7)$$

$$\frac{dx_3}{dt} = -k_{a3}x_3(t) + k_{b3}I(t) \quad (8)$$

RESULTS AND DISCUSSION

Interaction of each variable with time: This study focuses on interaction of each variable involved in Hovorka diabetic model in order to have better understanding upon reaction between insulin and glucose in achieving near normal glycemic control for Type 1 Diabetes patient. As in recent medical practice, insulin is infused into patient's body using a subcutaneous method, which causes a time lag about 30 min before the insulin can reduce the high glucose level with optimum performance. Thus, all interactions are simulated within 25 min.

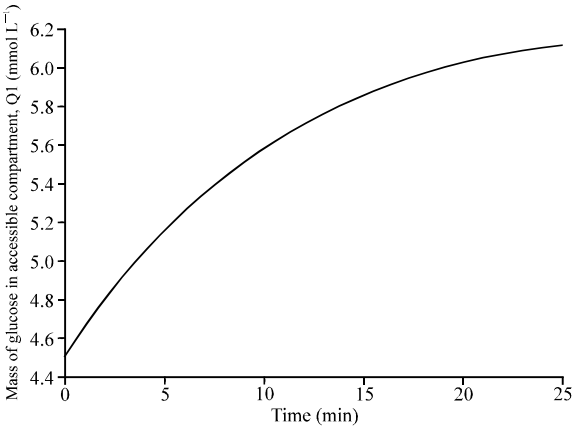

Fig. 2: Mass of glucose in accessible compartment, (Q1)

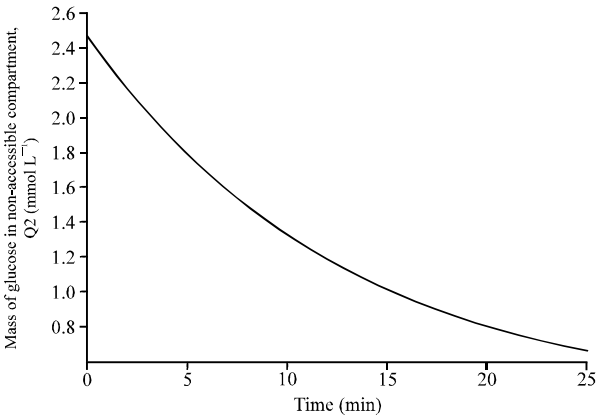

Fig. 3: Mass of glucose in non-accessible compartment, (Q2)

Mass of glucose in accessible compartment,Q1 and mass of glucose in non-accessible compartment,Q2: Figure 2 shows the behaviour of mass of glucose in accessible compartment, Q1 from the beginning of reaction until 25th min. At the beginning, mass of glucose in body is about 4.5 mmol L^{-1}. The mass of glucose can be seen increasing sharply as the reaction starts and eventually stops at about 6.1 mmol L^{-1}. However, the behaviour of mass of glucose in non-accessible compartment, Q2 is in contrast to the condition in the accessible compartment as seen in Fig. 3. The mass of glucose reduced rapidly and reached

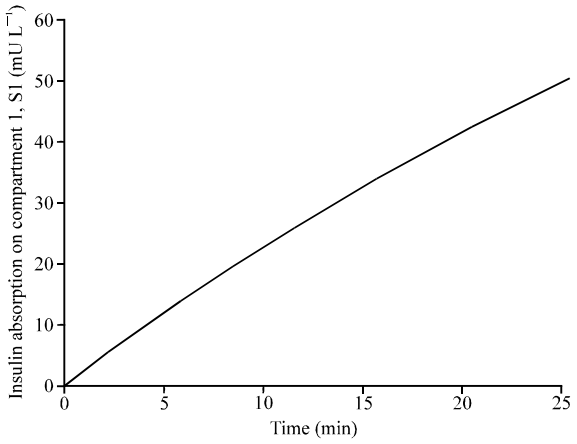

Fig. 4: Insulin absorption on compartment 1, (S1)

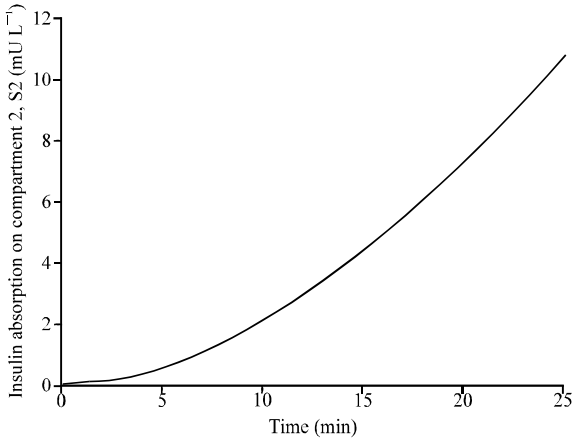

Fig. 5: Insulin absorption on compartment 2, (S2)

about 0.5 mmol L^{-1} at the point of time equals to 25 min. We can see that the insulin reacts faster and easier in lowering the level of glucose in non-accessible compartment compared to condition in the accessible compartment. The glucose level in accessible compartment is still at increasing tendency as the insulin needs time lag to response to the glucose. Blood glucose profiles also can be referred to these works (Lee *et al*., 2012; Mougiakakou *et al*., 2005; Nguyen and Jones, 2010).

Insulin absorption on compartment 1, (S1) and insulin absorption on compartment 2, (S2): In Fig. 4 and 5, we can see the behaviour of insulin from outside (exogenous) which is infused inside the patient's body starting from the time of 0 min until 25th min. Both graphs show a sharp rise from the beginning until the end of reaction. This is due to smooth absorption of insulin through the skin layer of patient's body throughout the infusion process.

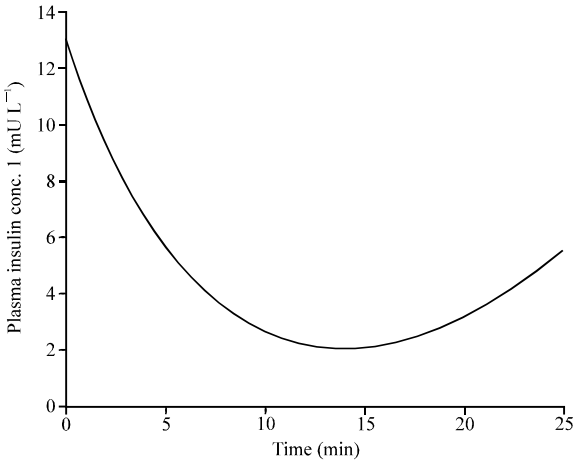

Fig. 6: Plasma insulin concentration, (I)

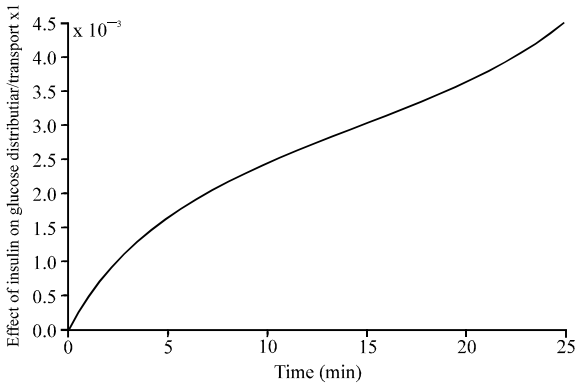

Fig. 7: Effect of insulin on glucose distribution/ transport, (x1)

Plasma insulin concentration: Plasma insulin is the insulin that exists and is produced in patient body which is different with the exogenous insulin. As depicted in Fig. 6, plasma insulin began to reduce gently until it levelled off at 4 mU L^{-1} within 10 to 15 min. Then, it started to rise up again until it reached its peak at 25 min. During this interaction, insulin in the body decreased as the plasma insulin utilised it in response to lowering glucose level. Then, as the exogenous insulin gradually infused, the insulin in the body tend to increase, accordingly. Insulin concentration profiles after insulin injected into body subcutaneously can be referred to Heinemann *et al*. (2000) previous work.

Effect of insulin on glucose distribution/transport, (x1), effect of insulin on glucose disposal, (x2) and effect of insulin on endogenous glucose production, (x3): From Fig. 7 to 9, it can be deduced that insulin does have effect on each glucose distribution/transport, glucose disposal

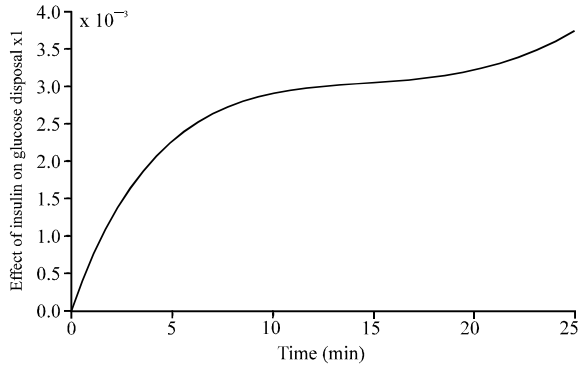

Fig. 8: Effect of insulin on glucose disposal, (x2)

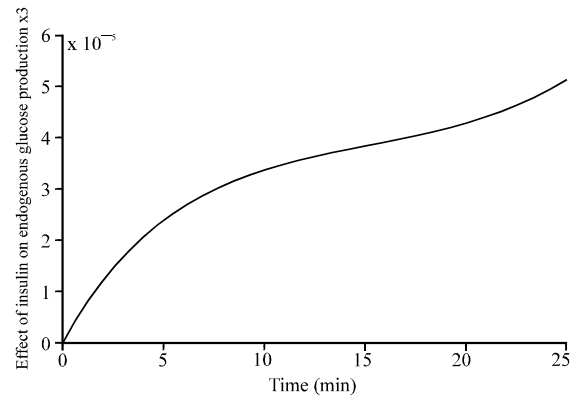

Fig. 9: Effect of insulin on endogenous glucose production, (x3)

and endogenous glucose production since all graphs show continuous increment from the beginning until the 25th min of the reaction. However, the effect of insulin on glucose disposal as shown in Fig. 8 demonstrated smooth increase from the beginning of reaction and a slow decrease prior to getting stabilized from the 10th to 20th min. Then, slowly the insulin continues to give effect on the glucose disposal.

CONCLUSION

The study of each interaction with time and the observation of behavior of all graphs from the simulation works are very important in order to have better understanding in effective treatment of Type 1 Diabetes. From the results, it is understood that insulin needs a time lag to response efficiently to glucose when the insulin is infused subcutaneously (through skin layer). Also, it can be concluded that the mathematical model proposed by Roman Hovorka (Hovorka *et al*., 2004) is useful and convenient for artificial pancreas research since the simulated results produced from this study is in agreement, fully justified with the expected reaction of insulin and glucose in diabetes therapy.

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