Dynamic Models and Open-Loop Control of Blood-Glucose for Type 1 Diabetes Mellitus

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Abstract: Type 1 diabetes mellitus must rely on daily insulin injection/infusion for the control of blood glucose. The treatments on those patients to maintain their blood glucose within an acceptable level is thus of essential importance. A good mathematical model of blood glucose may facilitate such a control. In this research, modeling and open-loop control of blood glucose for a type-1 patient using a model extended from the works of Hovorka and his coworkers (Hovorka *et al*., 2002; Hovorka *et al*., 2004; Wilinska *et al*., 2005) are studied. Clinical data from a continuous glucose monitoring system is used to develop the model for such use. Open-loop control strategies for patients that use basal and bolus subcutaneous infusions via an insulin pump are presented.

1. INTRODUCTION

Some relevant studies indicate that good metabolic control of diabetes may decrease the risk of chronic complications. The averaged blood glucose (BG) levels as reflected by the HAb1c levels are generally considered an indication of goodness of such a control. Nevertheless, a good control in terms of HAb1c levels is only necessary but not sufficient, because, high glycemic excursion can not be detected by measuring the HAb1c values only. Recently, a system known as CGMS (Continuous Glucose Monitoring System) has been available for continuously measuring glucose concentrations in subcutaneous tissue. Clinic physicians can make uses of the recorded continuous profiles to learn the excursion of BG and modify their treatments on the patients. Meanwhile, the appearing of real time CGMS on the market also provides a basis for implementation of on-line blood glucose control in the future.

The motivation of this paper is to show, by making uses of a modification to the Harvoka's model (Hovorka *et al*., 2002; Hovorka *et al*., 2004; Wilinska *et al*., 2005) and real CGMS data, an open-loop control that aims to desired HAb1c and blood glucose levels for type 1 patients can be developed.

2. MODEL DESCRIPTIONS

As mentioned, many physiological models have been proposed that describe glucose and/or insulin dynamics. In this paper, the model for study is based on the works of Hovorka and his coworkers (Hovorka, *et al*. ,2002; Hovorka, *et al*. ,2004; and Wilinska *et al*. ,2005). The reasons that this model is adopted for study is due to the inclusion of more detail insulin action that describes the physiological effect of insulin on glucose transport, removal and endogenous glucose production. Also it provides the insulin absorption through two compartmental channels that can be used to model the short acting and long acting effects from the bolus and basal insulin. Two subsystems are used to describe the glucose concentrations in the accessible compartment such as vein and organs, where measurements are made, and the inaccessible compartment such as tissue in human body, where measurements are not made. The insulin action describes the physiological effect of insulin on glucose transport, removal and endogenous glucose production. The original Harvokal model for IVGTT test is given as the following:

$$\frac{dQ_1}{dt} = -F_{01}^{c} - x_1(t)Q_1 + k_{12}Q_2(t) - F_R + U_G + \mathrm{W}\cdot EGP_0\left[1 - x_3(t)\right]; \quad (1)$$

$$\frac{dQ_2}{dt} = x_1(t)Q_1(t) - \left[k_{12} + x_2(t)\right]Q_2(t) \quad (2)$$

$$U_G = \sum_{i=1}^{N} \frac{D_G A_G (t - T_i) e^{\frac{-(t-T_i)}{t_{\max,G}}}}{t_{\max,G}^2} S(t - T_i); \quad T_i, i = 1, \cdots, M \quad (3)$$

$$F_R = \begin{cases} 0.003(G-9)V_G \cdot W & \text{, for G} \geq 9 mmole/L \\ 0 \text{ , else} \end{cases};$$

$$F_{01}^{c} = \begin{cases} F_{01} \cdot W & \text{; if } G \geq 4.5 mmole/L \\ F_{01} G \cdot W / 4.5 & \text{; otherwise} \end{cases};$$

and $G(t) = \dfrac{Q_1}{V_G W}$ $(mmole/L)$

$$\frac{dq_{1a}}{dt} = k_{ba}u_{ba} + k_{bo}\sum_i \frac{u_{bo,i}}{\tau}\exp\left\{-\frac{(t-T_i)}{\tau}\right\} - k_{a1^*}\cdot q_{1a} - \frac{V_{\max,LD}q_{1a}}{\left(k_{M,LD}+q_{1a}\right)} \quad (4)$$

$$\frac{dq_{1b}}{dt} = (1-k_{ba})u_{ba} + (1-k_{bo})\sum_i \frac{u_{bo,i}}{\tau}\exp\left\{-\frac{(t-T_i)}{\tau}\right\} - k_{a2^*}\cdot q_{1b} - \frac{V_{\max,LD}q_{1b}}{\left(k_{M,LD}+q_{1b}\right)} \quad (5)$$

$$\frac{dq_2}{dt} = k_{a1^*}q_{1a} - k_{a1^*}q_2 \quad (6)$$

$$\frac{dq_3}{dt} = k_{a1^*}q_2 + k_{a2^*}q_{1b} - k_e q_3 \quad (7)$$

$$\frac{dx_1}{dt} = -k_{a1}x_1(t) + \frac{k_{a1}S_{IT}^f q_3}{V_1\cdot W} \quad (8)$$

$$\frac{dx_2}{dt} = -k_{a2}x_2(t) + \frac{k_{a2}S_{ID}^f q_3}{V_1\cdot W} \quad (9)$$

$$\frac{dx_3}{dt} = -k_{a3}x_3(t) + \frac{k_{a3}S_{IE}^f q_3}{V_1\cdot W} \quad (10)$$

where, Q_1 and Q_2 (*mmole/l*) represent the glucose in accessible and non-accessible compartments, G (*mmole/l*) is the measurable glucose concentration, k_{12} represents the transfer rate constant from non-accessible to accessible compartment, V_G represents the distribution volume of the accessible compartment, and EGP_0 represents endogenous glucose production at the zero insulin concentration. F_{01}^c is the non-insulin-dependent glucose flux and F_R is the renal glucose clearance thresholds of 9 mmol/L. W is the patient's weight. U_G is the gut absorption rate, $t_{\max,G}$ is the time-of-maximum appearance rate of glucose in the accessible glucose compartment, D_G is the amount of carbohydrates (CHO) digested and A_G is the carbohydrate bioavailability. Variable q_2 represents the insulin mass (mU) in the nonaccessible subcutaneous compartment, q_3 represents the insulin mass (mU) in the plasma compartment. The quantities q_{1a} and q_{1b} represent the masses of insulin administered as continuous infusion (mU) through the slow and fast compartment channels (Wilinska *et al*. 2005). The variable u represents the basal insulin input (mU/min). The parameters k_{a1^*}, k_{a2^*}, and k_e are transfer rates ($\min^{-1}$), $V_{\max,LD}$ is the saturation level (mU/min) for Michaelis-Menten dynamics of insulin degradation, $k_{M,LD}$ is the value of insulin mass (mU) at which insulin degradation is equal to half of its maximal value for continuous infusion. The dimensionless constant k and $1-k$ represent the proportions of the total input flux of insulin passing through the slower and faster compartment channels, respectively. The variables, x_1, x_2, and x_3 represent the (remote) effects of insulin on glucose distribution/transport, glucose disposal and endogenous glucose production (Harvoka, *et al*. 2002). Finally, k_{ai}, i=1,⋯,3, represent the deactivation rate constants.

The modeling form given above is based on the work of Seborg and his coworkers (2008). On this basis, the addition of carbohydrates in-take from different meals (i.e. Eq.(3)) and the basal insulin and bolus insulin infusion/injection at different times (i.e. Eq.(4) and Eq.(5)) are considered as an extensions to the original model. Notations u_{ba} and u_{bo} are used to designate the quantities of basal insulin and bolus insulin, respectively.

The complete model for modelling the BG consists of equations from Eq.(1) through Eq.(10). V_G and A_G are assumed to be constant as: V_G=0.16 ($L^{-1}\cdot kg$) and A_G=0.8. Totally seventeen parameters in the model will be determined:

F_{01}, k_{12} ,EGP_0, k_{a1^*}, k_{a2^*}, $t_{MAX,G}$, S_{IT}^f/V_I, S_{ID}^f/V_I, S_{IE}^f/V_I, $V_{\max,LD}$, $k_{M,LD}$, k_{ba}, $k_{bo,}$ k_e, k_{a1}, k_{a2}, k_{a3}

For patient undertaking same insulin in basal and bolus injections, k_{ba} and k_{bo} in the model are assumed to have the same value.

3. PARAMETER ESTIMATION FOR MODELING

The model described above was applied to one real patient who has type-1 diabetes. The subject undergoing the experiment weighted 55kg and wore an insulin pump for insulin infusion. She also wore the MiniMed CGMS for five days during the experiment period. During that period, the meal contents and the insulin doses were recorded on a diary. These meal contents then were quantified by a dietician. No special arrangement was made for this experiment. The patient was asked to live on her normal way with meals and works as usual. The data from the patient accompanied with a complete diary on meals and insulin dosages are recorded. These data are then fitted into the model abovementioned. The modelling is aimed to find the parameters that minimize the sum of squares of the output errors. To compute these output errors, BG is computed by integrating the modified Hovorka model described in Section 2, starting with a set of parameters and initial conditions. The initial parameters are taken from the parameters of Marchetti *et al*. (2008). The steady-states values of the modified Hovorka model which correspond to a fasting level of BG are prepared in advance from the same model and are taken to initiate the integration for optimization. These initial states for integration are then updated from iteration to iteration using the resulted states in the last fasting stage of the previous run.

The modelling starts to fit themodel to the CGMS data of the first two days by making uses of the reported quantified CHOs and insulin doses. The parameters thus obtained are given as follows:

Parameter	Value	Unit	Parameter	Value	Unit
S_{IT}^{f}/V_I	0.019	Min^{-1} • mU^{-1} • kg	k_{12}	0.237	min^{-1}
S_{ID}^{f}/V_I	0.003	Min^{-1} • mU^{-1} • kg	k_{a1}	0.017	min^{-1}
S_{IE}^{f}/V_I	0.052	mU^{-1} • kg	k_{a2}	0.273	min^{-1}
EGP_0	0.051	mmole • kg^{-1} • min^{-1}	k_{a3}	0.128	min^{-1}
F_{01}^{c}	1.899	mmole • min^{-1}	k_e	0.036	min^{-1}
k	0.34	–	$t_{MAX,G}$	22.91	min
$V_{MAX,LD}$	2.156	mU • min^{-1}	k_{a1*}	0.005	min^{-1}
$k_{M,LD}$	64.182	mU	k_{a2*}	0.054	min^{-1}

With the resulting parameters, the fitting of the real CGMS data to the model is shown in Figure 1. In this figure, the fitting of the model to the reported CGMS data in the first 48 hours looks good. The model is then used to predict the blood glucose in the remaining days. Figure 2 shows that the fitting is not good enough, but the trend is alright. The lack of fit in the extending time horizon is due to imprecise quantification of CHO intakes. If the remaining CHOs are allowed for some modifications, the fitting turns out to be more satisfactory (see Figure 3).

4. OPEN-LOOP CONTROL VIA SUBCUTANEOUS INSULIN INFUSION/INJECTION

Using an artificial pancreas, subcutaneous infusion of insulin according to a pre-programmed basal and bolus dosages is one approach to control the blood glucose of a type-1 diabetic patient in an open-loop manner. However, artificial pancreas is somewhat an expensive device that most of the patients may not afford. Fortunately, due to the availability of effective long acting insulin, the pre-programmed subcutaneous insulin injection can also be applied to patients who do not use artificial pancreas. The multiple subcutaneous injections with long acting and short acting insulin can be used to mimic the insulin secretions in a normal body. The basal insulin rate is aimed to maintain a given fasting level of blood glucose (e.g. 100 mg/dl). The bolus insulin dose is taken to enhance the control of blood glucose at each CHO intake.

4.1 Development of bolus dosage plan for Prandial CHO-uptake

While planning the bolus dosage under a prandial condition, some constraints should be considered. These constraints come from clinical demands for normal control of blood glucose. For example,

(1). Fasting blood glucose ≤ 100 mg/dl (≤ 5.6 mmol/l)

(2). Two-hour Post-prandial blood glucose $\leq$ 120 mg/dl

(3). In all time, blood glucose $\geq$ 70 mg/dl and never less than 50 mg/dl

The above standards may not be achievable by a type-1 diabetic patient in real practice. Apart from keeping patients from a hyperglycemia status, type-1 diabetic patient should be cautious to keep from having hypoglycaemia, especially during midnight (i.e. approx. 6 hours after dinner). Thus, in order to accommodate properly the blood glucose concerns in many aspects, the determination of bolus dosage for a CHO-intake is thus formulated as the problem of the following:

$$\underset{u_{bo}}{Min}\left\{\left|G_{av}(t^*,u_{bo}(x_i))-\gamma_1^*\right| \text{ given } |\, CHO=x_i \text{ and } G_{fasting}=\gamma_o\right\} \quad (13)$$

$$s.t. \quad \begin{cases} (1)\ G(t)\geq \gamma_*, \\ (2)\ G(t)<\gamma^* \ \forall t\geq 0\ , \end{cases}$$

Where, x_i, i=1, 2, 3 is the grams of CHO-intake in each meal, $\gamma^*, and\ \gamma_*$ are parameters to be assigned, which may vary according to the physician on a patient-to-patient basis for constraining blood glucose. Notice that, here, γ_* is taken as 70mg/dl. In other words, $\underline{G}\geq 70\ mg/dl$ is a hard constraint for patient to avoid from having hypoglycemia. The value of t^* is taken as 6hrs, since each meal is usually 6 hours apart from one to the other. $G_{av}(6hrs,u_{bo}(x_i))$ is the average value of G in a 6-hours period with x_i CHO-intake and $u_{bo}(x_i)$ bolus dosage.

To solve the problem in Eq. (13), first, we need the function $u_{bo}(x_i)$ and a basal insulin amount, $u_{ba}(G_{fasting})$, to maintain the blood glucose at a specified fasting level. The latter is used to mimic the secretion of the basal insulin in a normal human body. Mathematically, basal insulin can be considered as a step dose lasting for 24 hours a day that leads G to a fasting level. In fact, this value can be obtained by solving the set of algebraic equations obtained from setting the derivatives in the extended Hovorka model to zeros. The fasting glucose to mimic the effect of the secretion of basal insulin in a normal human body is taken as 100 mg/dl in this study (γ_0=100 mg/dl). A lower value may also be taken, however, a too low value may lead Eq.(13) without having feasible solution. Based upon this basal insulin amount (or, in other words, the targeting blood glucose) the bolus dosage plan will then be computed.

Next, we need to develop the function, $u_{bo}(x_i)$, which describes the required bolus dosage to a CHO intake from meals. The parameters $\gamma^*, and\ \gamma_1^*$ are considered for type-1 diabetic patients to have an acceptable glycated hemoglobin (i.e., hemoglobin HbA_{1c} or, simply, A1c) value. The use of hemoglobin A1c for monitoring the degree of control of glucose metabolism in diabetic patients was proposed in 1976 by Koenig and coworkers. A buildup of A1c within the red cell reflects the average level of glucose to which the cell has been exposed during its life cycle (approx. 120 days). Thus,

the A1c level is proportional to the averaged blood glucose concentration over the previous four weeks to three months. According to ADA (American Diabetes Association), the mean plasma glucose concentration (MPG) is related to HbA_{1c} with an empirical equation of the following:

MPG (mg/dl) = (35.6* HbA_{1c}) - 77.3, or, MPG (mmol/l) = (1.98* HbA_{1c}) - 4.29 (14)

A simpler and approximately equivalent formula can also be written as:

$$MPG(mg/dl) = 35*(A1c-5)+100 \quad (15)$$

Where, MPG is the mean plasma glucose concentration in the last three months. Thus,

$$A1c = \left(MPG-100\right) \div 35+5 \quad (16)$$

If the daily average blood glucoses (i.e. $G_{av}(24hrs)$) are equal from day to day in a period of at least three months, the MPG will equal to its daily time-average. Notice that the glucose concentration in the plasma is higher than the glucose concentration in the whole blood by about 11%. In the mathematical model, the glucose concentration G is referred to the whole blood. As a result, in terms of blood glucose as described by the model, Eq.(16) needs to be updated as:

$$A1c \cong \left[G_{av}(24hrs)\times 1.1-100\right] \div 35+5 \quad (17)$$

For easier application, one may consider to replace the $G_{av}(24hrs)$ with the following:

$$G_{av}(24hrs) \cong \left[\sum_{i=1}^{3} G_{av}(6hrs, u_{bo}(x_i)) + G_{fasting}\right] * 0.25 \quad (18)$$

And,

$$A1c \cong \left[\left\{\sum_{i=1}^{3} G_{av}(6hrs, u_{bo}(x_i)) + G_{fasting}\right\} * 0.25\times 1.1-100\right] \div 35+5 \quad (19)$$

Where, x_1, x_2, x_3 are CHO amounts in terms of grams taken from the daily three meals. Eq.(18) compute the mean BG by assuming that daily BG has a level at $G_{av}(6hrs)$ in a period of three meals (i.e.18 hours) and at 100mg/dl in the fasting period (i.e. another 6 hrs). Thus, specifying γ_1^* in Eq.(13) is to specify the target A1c as shown in Figure 4. An effective control of blood glucose should make this A1c value to remain below 7. In practical treatment, the values of γ^*, and γ_1^* may differ from subject to subject. If a bolus-to-CHO relation is available, then, given a daily CHO-plan, the average blood glucose can be computed from integrating the model. A graphical approach to the solution of a bolus-to-CHO relation will be demonstrated in the example that follows.

4.2 Case study

As mentioned, the basal insulin amount versus the fasting blood glucose levels can be calculated from the steady-state solution to the modified Hovorka model given in Section 2. For this case, the basal insulin amounts corresponding to each possible fasting glucose level are prepared and plotted in Figures 4. On the other hand, under a basal dose that leads to a fasting glucose of 100mg/dl, the responses of the blood glucose to different CHO intakes are computed. Based on these responses, the average blood glucoses at 4hrs and 6 hrs, together with maximum and minimum values under the same dosage are computed and plotted in Figure 5 and Figure 6, , with an insulin increment of 0.5 unit. The values of γ^*, and γ_1^* are then specified in order to obtain the bolus dose. As an example in this case, they are selected as 320, and 120, respectively.

The feasible regions to satisfy condition (1) and condition (2) of Eq. (13) are plotted for specific CHO intakes, starting from 15grams to 60grams, with an increment of 15grams. As shown in Figure 5, the feasible region that satisfies condition (1) and condition (2) is the region spanned by the pink and red lines. In each case (e.g. Figure 5 and Figure 6), there is u_{bo} that corresponding to the given CHO value, x . However, in case there is no feasible solution exists that will give $G_{av}(6hrs)$ exactly at 120 mg/dl, the bolus dosage at the boundary of the feasible region will be taken. By increasing the CHO amount, x , at an increment of 15 grams, a curve of bolus insulin required for different prandial CHOs can be obtained as shown in Figure 7. Thus, under a give basal insulin amount, the bolus dosage required for each CHO-intake can be read from these curves. If, a CHO meal-plan is taken (e.g., breakfast: 30gm, lunch: 60gm, dinner:60gm) with the bolus dosage plan as shown in Fig. 7 (e.g. breakfast: 1.05U, lunch: 2.1U, dinner: 2.1U), the averaged blood glucose could be expected to be 113.5 which gives 5.76 for the A1c value. Compared to the current record from the CGMS, the A1c value as well as the blood glucose could be significantly improved.

5. CONCLUSIONS

Modeling glucose-insulin interactions with real CGMS data and a model extended from Hovorka and his coworkers (Hovorka *et al*., 2002; Hovorka *et al.*, 2004) are studied. Using the mathematical model as a frame work, dynamic models are built for a case study. Data from a continuous glucose monitoring system (CGMS, MiniMed) are used to estimate the parameters in the model. As the CHO contents in various foods are fuzzy due to natural language, the CHO values thus quantified are subject to certain extent of uncertainties. As a result, during the parameter estimation, these quantified CHO values need to be modified. The resulting models are then used to determine the daily basal and bolus dosages to mimic the secretion of insulin of a human body and control the blood glucose to an acceptable level. The basal amount is to be determined to maintain the fasting glucose value at a given level. The bolus dosage is then determined based upon this basal insulin and the CHO intake in each meal. The bolus is aimed to keep the blood glucose within upper and lower bounds. The lower bound is

70 mg/dl which is normally considered in medical treatment to prevent the occurrence of hypoglycermia. The upper bound can be considered on a person-to-person basis. Besides setting the glucose value in the upper/lower bounds, the bolus dosage plan is also aimed to have a targeted A1c value, which is normally less than 7.0 in general medical treatments for the diabetes patients. The basal insulin amount and the bolus dosage plan are demonstrated with the utilization of the developed models.

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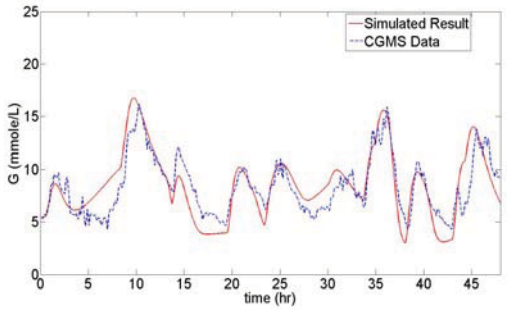

Figure 1. Fitting of the CGMS data to the model

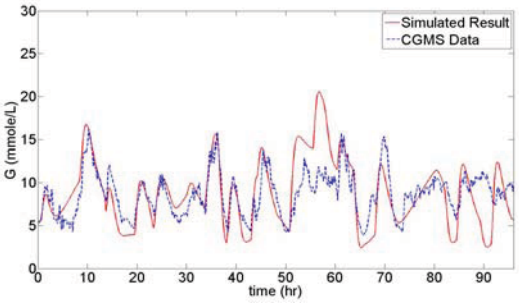

Figure 2. Validation of model using the original CHO and insulin data (case 1)

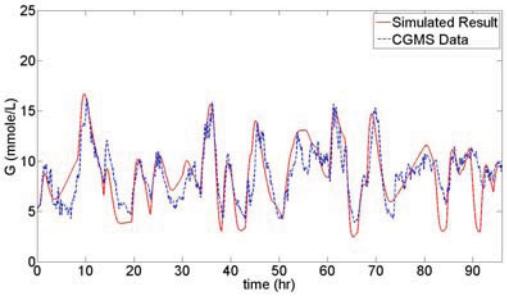

Figure 3. The blood glucose excursions after meal CHO being modified (Case 1).

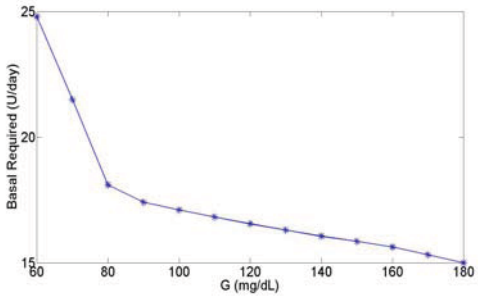

Figure 4. The basal dose for fasting blood glucose

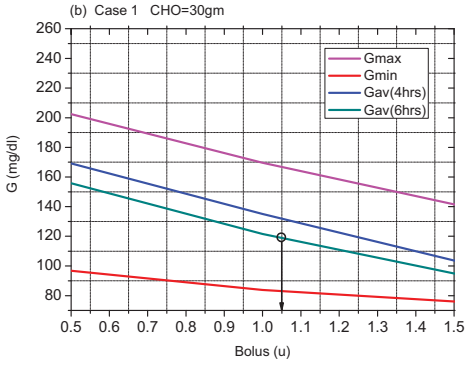

Figure 5. Graphical solution to Eq.(13), CHO intakes at 30gms.

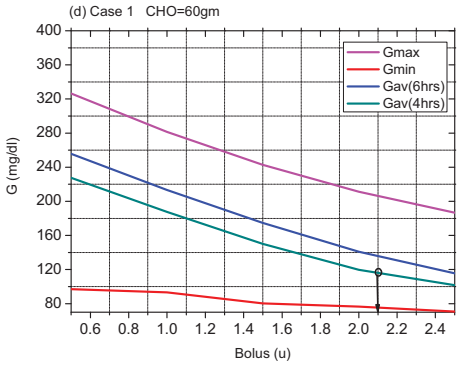

Figure 6. Graphical solution to Eq.(13), CHO intakes at 60gms.

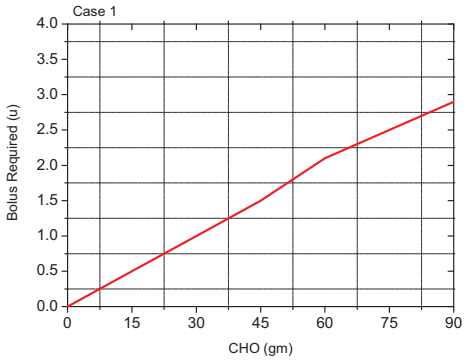

Figure 7. Bolus dose v.s. CHO for Case 1 ($G_{fasting}$=100mg/dl)

Table 4. CHO-plans vs A1c for Case 1

A1c*: computed from G_{av}(6hrs)

CHO-plan (g)			MG (24hr)	MPG (24hr)	A1c	A1c*
B	L	D	mg/dL			
15	45	45	114.52	125.97	5.7	5.7
15	45	60	113.94	125.33	5.7	5.7
15	60	45	111.58	122.74	5.6	5.7
15	60	60	111.22	122.35	5.6	5.7
30	45	45	112.39	123.62	5.7	5.7
30	45	60	111.94	123.14	5.7	5.7
30	60	45	110.63	121.70	5.6	5.7
30	60	60	110.35	121.39	5.6	5.7