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Optimal blood glucose level control using dynamic programming based on minimal Bergman model

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Abstract. The purpose of this article is to simulate the glucose dynamic and the insulin kinetic of diabetic patient. The model used in this research is a non-linear Minimal Bergman model. Optimal control theory is then applied to formulate the problem in order to determine the optimal dose of insulin in the treatment of diabetes mellitus such that the glucose level is in the normal range for some specific time range. The optimization problem is solved using dynamic programming. The result shows that dynamic programming is quite reliable to represent the interaction between glucose and insulin levels in diabetes mellitus patient.

1. Introduction

Diabetes mellitus (DM) is a metabolic disorders disease, i.e. carbohydrate metabolism, caused by reduced or unavailability of insulin hormone from beta cells in the pancreas. It may also be caused by or disorders insulin function. In healthy people, normal glucose level for adults after fasting (not eating approximately 8 hours) is 70-110 mg/dl [3]. Thus, diabetes mellitus patients are those who have glucose level outside that normal range.

Patients with DM have too much glucose in the blood and urine, but not enough in the cells. On the other hand, these cells still need glucose, either as food or as a material to produce energy. Insulin produced by beta cells, serves to keep blood glucose in normal range by turning glucose into glycogen and storing it in muscles or tissues as reserves. This hormone works to speed up the transport of glucose from the blood into the cells. Insufficient insulin leads to high glucose level (hyperglycemia) due to the reduction of the transport of glucose into cells. Conversely, insufficient glucagon may lead to low glucose level (hypoglycemia) below the normal range.

Treatment of diabetes mellitus is usually done using oral anti-diabetic drugs (OAD) or insulin injection. However, the use of these drugs may cause side effects and insulin injection is relatively expensive. Therefore, it is necessary to have a good way to control blood glucose so that treatment can be optimal. In this article, the formulated optimal control problem will be solved with dynamic programming method.

2. Minimal Bergman Model

Minimal Bergman model consists of two parts i.e. glucose dynamic and insulin kinetic. The non-linear Minimal Bergman model in Chee and Fernando [1] is as follows

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$$\frac{dG(t)}{dt} = -\big(p_1 + X(t)\big)G(t) + p_1 G_B \tag{1}$$
$$\frac{dX(t)}{dt} = -p_2 X(t) + p_3[I(t) - I_B] \tag{2}$$
$$\frac{dI(t)}{dt} = -n[I(t) - I_B] + u(t) \tag{3}$$

where

$G(t)$ = blood glucose level in plasma [mg/dl] at time t

$X(t)$ = a function that is proportional to the insulin concentration in a remote compartment or insulin level in interstitial [min^{-1}] at time t

$I(t)$ = insulin level in plasma [µU/ml] at time t

G_B = basal glucose level in plasma [mg/dl]

I_B = basal insulin level [µU/ml]

n = fractional disappearance rate constant for endogenous insulin

u = rate of exogenous insulin injection

p_1 = glucose clearance rate independent of insulin

p_2 = rate of clearance of active insulin

p_3 = rate of change of insulin level in interstitial caused by insulin in plasma

From equation (1), it can be seen that glucose will leave or enter plasma compartment when there is a difference between plasma glucose level $G(t)$ and basal glucose level G_B. If plasma glucose level is below basal glucose level, then glucose enters plasma. On the other hand, when plasma glucose level is above basal glucose level, glucose will leave plasma compartment. Glucose also leaves the plasma compartment at a rate proportional to insulin in interstitial tissue $X(t)$. Analogously, from equation (2) and (3), the difference between plasma insulin $I(t)$ and basal insulin I_B will affect the amount of $X(t)$ and $I(t)$.

Parameters of diabetic patient used in this article are for glucose-resistant patient in minimal Bergman model as shown in Chee and Fernando [1] i.e. $p_1 = 0$, $p_2 = 0.025$, $p_3 = 0.000013$, and n=5/54 [2]. Glucose-resistant patients are also called type I diabetic patient. The destruction of pancreas cells that producing insulin in type I diabetic patient leads to insulin dependence. Thus, type I diabetic patient requires more insulin injections than type II. In this case, an optimal insulin injection is really necessary to obtain.

3. Dynamic Programming

To solve the problem, optimal control theory is used to model it. The general problem of optimal control is to

minimize $I(x(0), t_f) = \int_0^{t_f} \psi(x, u, t)\, dt + \phi(x(t_f))$

subject to $\frac{dx}{dt} = f(x, u, t), x(0) = x_0$

$u_a \le u_i(t) \le u_b, \quad i = 1,2,3 \ldots m$

where $\boldsymbol{I}: \boldsymbol{R^n} \times \boldsymbol{R^m} \times \boldsymbol{R} \to \boldsymbol{R}$, $\boldsymbol{f}: \boldsymbol{R^n} \times \boldsymbol{R^m} \times \boldsymbol{R} \to \boldsymbol{R^n}$, $\boldsymbol{x} = (\boldsymbol{x_1}, \cdots, \boldsymbol{x_n}) \in \boldsymbol{R^n}$, $\boldsymbol{u} = (\boldsymbol{u_1}, \cdots, \boldsymbol{u_m}) \in \boldsymbol{R^m}$.

Then, dynamic programming method originally developed by Richard Bellman is applied to the model. Rein Luus in [4] proposes a kind of dynamic programming called the iterative dynamic programming method to solve the general optimal control problem. This method separates the problem with $[0,t_f]$ time interval into several time stages with initial condition placed at stage 1. The first step is the construction of the P time stages with length $L = t_f / P$. The performance index is approximated by

$$I(x(0), P) = \psi(x(t_f)) + \sum_{k=1}^{P} \int_{t_{k-1}}^{t_k} \phi(x(t), u(k-1), t)\, \mathrm{d}t \tag{4}$$

Next step is the construction of grid for state x. At each stage component x_i of state vector x is allowed to take N values except for the first stage. Each control component u_j of control vector u is allowed to take M values. Thus, there are N^n grid points at stages 2, 3, …, P and at each stage M^m values of the control vector u are taken.

The calculation are started from stage P corresponding with time interval $t_f - L \leq t \leq t_f$. For each x-grid point, evaluate M^m values for control u based on the following performance index

$$I(x(t_f - L), 1) = \psi\left(x(t_f)\right) + \int_{t_f-L}^{t_f} \phi\left(x(t), u(P-1)\right)\, dt \tag{5}$$

where M^m control values used for $u(P-1)$. Then compare M^m value of the performance index (5) to determine the control value u giving the minimum value.

The next step is to go backwards to stage $P-1$ associating with time $t_f - 2L \leq t \leq t_f - L$. For each x-grid point, evaluate again M^m values for control u based on the performance index and determine the control value u which gives the minimum value. Then, integration until the final time t_f is done using the control u corresponding to the grid point that is closest to state $x(t_f - L)$ if $x(t_f - L)$ is not one of grid points at state P.

This procedure should be repeated for stages $P - 2$, $P - 3$, and so on until stage 1 which consists of the initial condition $x(0)$ as a single grid point corresponding to the time interval $0 \leq t \leq L$. The process is terminated by comparing the M^m value of the performance index to determine the control u which gives the minimum value.

The process ends with storing the state trajectory. The selected trajectory is traced back by integrating an initial point of state with control u which gives the minimum value at the corresponding time. Finally, forward integration is done until the final time reached.

4. Computer Simulation

The performance index of the problem is to minimize glucose level and insulin injections in the Lagrange form as follows

$$J = \int_0^{t_f} (\rho|u| + (1-\rho)|G - G_T|)\, 10^5 dt \tag{6}$$

with ρ is control weight factor and G_T is blood glucose level target.

Simulation is done using MATLAB over $P = 30$ stages where final time $t_f = 140$ with $L = 140/30$. The number of grid points are $N = 30$. Each stage takes $M = 15$ values of the control vector u with the lower bound of control $u_a = 0$ and the upper bound of control $u_f = 6$. So, the control vector is bounded by $0 \leq u \leq 6$. The initial value of glucose level, the initial value of the interstitial insulin and the initial value of insulin level used in this simulation are $G(0) = 500$, $X(0) = 0$, $I(0) = 30$ respectively. The basal insulin level is set to $I_B = 7$ and basal glucose level is $G_B = 81$.

Therefore, the Minimal Bergman model become as follows

$$\frac{dG(t)}{dt} = -\mathrm{X}(\mathrm{t})G(t) \tag{7}$$

$$\frac{dX(t)}{dt} = -0.025X(t) + 0.000013[I(t) - 7] \tag{8}$$

$$\frac{dI(t)}{dt} = -\frac{5}{54}[I(t) - 7] + u(t) \tag{9}$$

In addition to minimize the use of insulin injection, glucose level of diabetic patients is also maintained to approach as close as possible to target glucose levels i.e. $G_T = 90$ with $\rho = 0.25$. Therefore based on equation (6), the performance index of the problem become as follows

$$J = \int_0^{t_f} (0.25|u| + 0.75|G - 90|)\, 10^5 dt \tag{10}$$

The value of the coefficient $\rho = 0.25$ means that keeping the blood glucose level in the normal range is considered more important than the control of insulin injection. The simulation results are shown in Figure 1, Figure 2, Figure 3 and Figure 4.

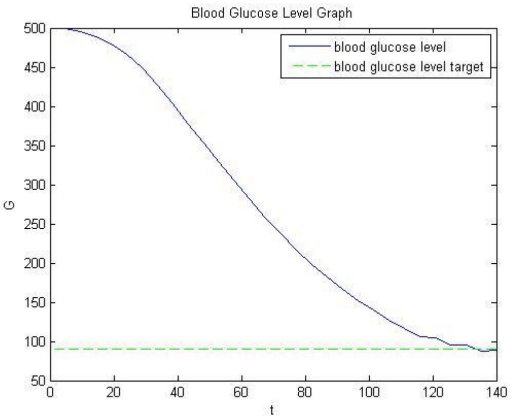

Figure 1. Glucose level graph

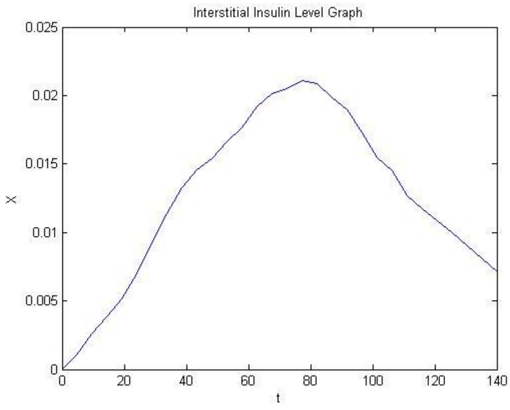

Figure 2. Interstitial insulin level graph

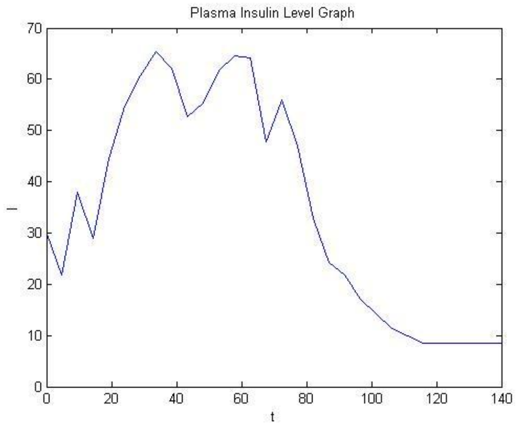

Figure 3. Plasma insulin level graph

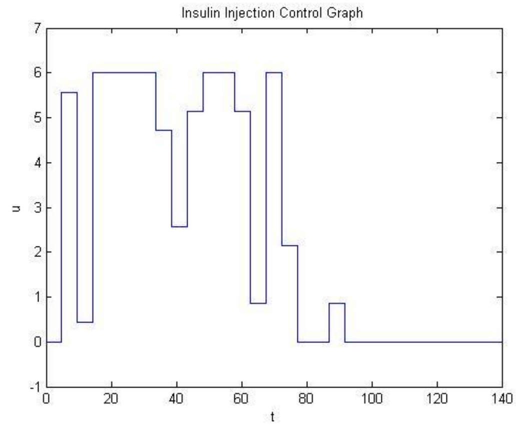

Figure 4. Insulin injection control graph

From the graphs, it is seen that at $t < 80$ the glucose level decreases rapidly due to the increase of injected insulin. Consequently, this increases the insulin either in plasma or interstitial cells as well. On the other hand, when the injected insulin becomes zero ($t > 80$) the plasma and interstitial insulin start to decrease and cause the decrease of the blood glucose level more slowly than before. Interstitial insulin level increases and reaches the highest point at time t = 80. At the final time the glucose level of diabetic patient can decrease until $G(t_f) = 88.2005$, whereas insulin interstitial is $X(t_f) = 0.0072$ and insulin level is $I(t_f) = 8.4407$. The minimum performance index (6) achieved is 1.69251. Thus, the glucose change is 411.7995. Glucose level at final time reaches the desired glucose level located around the target glucose level and the required insulin injection is 69.4286.

5. Conclusion

Based on the results of the simulation program it can be concluded that Minimal Bergman model could represent well the glucose dynamic and the insulin kinetic in people with diabetes mellitus. Optimal control problem with Minimal Bergman model could be solved by applying dynamic programming method. Glucose level of diabetic patients can reach the desired target and the dynamic of glucose is around the target glucose level by minimizing the performance index in Lagrange form. Hence, dynamic programming can be used to control glucose level in diabetic patients with an insulin infusion therapy based on the resulted insulin injection control behaviour.

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