AMO - Advanced Modeling and Optimization, Volume 20, Number 1, 2018

Optimal Control Applied to Investigate the Effect of Glucose Tolerance Test of Diabetes Mellitus in Human Body

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Abstract

Diabetes mellitus is a metabolic disorder in which the body is unable to respond properly to the consumption of carbohydrates, sugars and starches leading to increased levels of glucose in the blood and urine. In glucose tolerance test (GTT), a patient fasts overnight; the patient is then given a large dose of glucose and the concentration of glucose in the body is monitored for the next three to five hours. In this paper, a mathematical model of optimal control of glucose tolerance test has been discussed. In this control model of GTT, glucose and insulin concentrations have been described for time durations of test. The control model has been analyzed and investigated through analytically and numerically. It is found that the perfect time for GTT is about 4.8 hours and glucose concentration decreases steadily almost linearly while insulin level remains positive.

Keywords: Mathematical model, Optimal control, Glucose, Insulin, Glucose tolerance test (GTT).

Mathematics Subject Classifications (MSC): 34D05, 34D20, 92D25.

1. Introduction

One of the biggest diseases in the world today is diabetes. Many millions suffer from the disease and the number is growing. The number of growing is mostly due to the lifestyle in western world with lots of unhealthy food. Because this is a large problem many researchers try to find methods for diagnosing and treating the disease. One of the approaches is to design a mathematical model describing the glucose-insulin system. Diabetes is a malfunction in exactly this system. These mathematical models can be used to diagnose but also to create simulators to test different treatment types.

Over the past years, mathematics has been used to understand and predict the spread of diseases relating important public health questions to basic infection parameters. Diabetes Mellitus is a disease which is characterized by too high sugar levels in the blood and urine. It is usually diagnosed by means of a glucose tolerance test (GTT). Today there are over 422 million diabetics in the world by 2014. In Bangladesh the number of diabetes is 7.1 million in 2015 [8]. The global prevalence of diabetes has grown from 4.7% in 1980 to 8.5% in 2014, during which time prevalence has increased or at best remained unchanged in every country. Diabetic patients require supplement of insulin in the form of regular injections and tablets in addition to modified diet to regulate glucose input. Glucose plays an important role in the food metabolism of any vertebrate tissue since it is a source of energy for all tissues

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and organs. The majority of mathematical models were devoted to the dynamics of glucose-insulin. So far all the existing models were based on two variables only: glucose and insulin. In the GTT, an individual comes to the hospital after an overnight fast and is given a large dose of glucose. During the next three to five hours several measurements are made on the concentration of glucose in the patient's blood and these measurements are used in the diagnosis of diabetes Mellitus. It is quite conceivable therefore the body will interpret this as an extreme emergency and there after the hormones come in play. Optimal control theory is an outcome of the calculus of variations with a history stretching back over 360 years but interest in it really mushroomed only with the advent of the computer, launched by the spectacular successes of optimal trajectory prediction in aerospace applications in the early1960s. Some geometrical optimization problems were known and solved in classical times such as the line representing the shortest distance between two points or the isoperimetric problem: the shape of the plane curve of given length enclosing the largest area. Lenhart and Workman [9] have developed a new feedback control model of glucose tolerance test. This model considers time variations of GTT for checking the glucose and insulin levels of the patient. We have to find the perfect time for GTT model using control which will indicate the glucose decreasing in the desired level and positive insulin level.

2. Methodology

Methodology is the systematic, theoretical analysis of the methods applied to a field of study. It comprises the theoretical analysis of the body of methods and principles associated with a branch of knowledge. Typically, it encompasses concepts such as paradigm, theoretical model, phases and quantitative or qualitative techniques.

2.1 Glucose Tolerance Test (GTT)

The glucose tolerance test is a medical test in which glucose is given and blood samples taken afterward to determine how quickly it is cleared from the blood. The test is usually used to test for diabetes, insulin resistance, impaired beta cell function, and sometimes reactive hypoglycaemia and acromegaly, or rarer disorders of carbohydrate metabolism. In the most commonly performed version of the test, an oral glucose tolerance test (OGTT), a standard dose of glucose is ingested by mouth and blood levels are checked two hours later.

2.2 Optimal Control System

Since the birth of the optimal control, several authors proposed different basic mathematical formulations of OCPs (fixed time problems) [3, 4, 5]. For fixed time problems there are three major mathematical formulations of optimal control problems: Bolza form, Lagrange form and Mayer form.

We start with the general form of Bolza problem:

$$(P_B)\quad \begin{cases} \text{Minimize } \; l\big(x(a),x(b)\big)+\int_b^a L\big(t,x(t),u(t)\big)\,dt \\ \text{subject to} \\ \dot{x}(t)= f\big(t,x(t),u(t)\big),\; a.e.\;\; t\in[a,b] \\ u(t)\in U(t),\; a.e.\;\; t\in[a,b] \\ \big(x(a),x(b)\big)\in E \end{cases}$$

Here $[a,\, b]$ is a fixed interval. The function $f:[a,b]\times\mathbb{R}^n\times\mathbb{R}^m\to\mathbb{R}^n$ describes the system dynamics and $U:[a,b]\to\mathbb{R}^m$ is a multifunction. Furthermore, the closed set $E\subset\mathbb{R}^n\times\mathbb{R}^n$ and the functions $l:\mathbb{R}^n\times\mathbb{R}^n\to\mathbb{R}$ and $L:[a,b]\times\mathbb{R}^n\times\mathbb{R}^m\to\mathbb{R}$ specify the endpoint constraints and cost. The functional

$$l\left(x(a),x(b)\right)+\int_{b}^{a}L\left(t,x(t),u(t)\right)dt \tag{1}$$

to be minimized is called the payoff or cost functional. The aim of this problem is to find the pair $(x,\ u)$ comprising two functions where $u:[a,b]\to\mathbb{R}^m$ (the control function) and the corresponding state trajectory x which is an absolutely continuous function $x:[a,b]\to\mathbb{R}^n$ (called the state function) satisfying all the constraints of the problem (P_B) and minimizing the cost. A pair (x, u), where x is an absolutely continuous function and u is a function belonging to a certain space U (U can be L^1, C, the space of measurable functions, the space of piecewise continuous functions, etc.), such that $\dot{x}(t)=f\left(t,x(t),u(t)\right)$ *a.e.*, is called a process. A process satisfying all the constraints of the problem (P_B) is called an admissible process. We say that $\left(x^*,u^*\right)$ is an optimal solution if it minimizes the cost over all admissible processes. For optimal control problems one may speak of local or global minimizers.

If the function $l:\mathbb{R}^n\times\mathbb{R}^n\to\mathbb{R}$ is absent from the cost functional (1) and all others data remain the same, we obtain the optimal control problem in Lagrange form; the cost in such case is simply

$$J(x,u)=\int_{a}^{b}L\left(t,x(t),u(t)\right)dt \tag{2}$$

On the other hand, if the Lebesgue integrable function $L:[a,b]\times\mathbb{R}^n\times\mathbb{R}^m\to\mathbb{R}$ is absent from the cost functional (1) and all others constraints remain the same, we obtain the Mayer form with cost

$$J(x,u)=l\left(x(a),x(b)\right) \tag{3}$$

However, we can reformulate Bolza form (1) into Mayer form by state augmentation.

Let us define,

$$\begin{aligned}&\dot{y}(t)=L\left(t,x(t),u(t)\right)\ a.e.\\&y(a)=0\end{aligned} \tag{4}$$

Then the problem (P_B) can be rewritten as following

$$(P_M)\quad\begin{cases}Minimize\ l(x(a),x(b))+y(b)\\ subject\ to\\ \dot{x}(t)=f(t,x(t),u(t))\ a.e.\ t\in[a,b]\\ \dot{y}(t)=L(t,x(t),u(t))\ a.e.\ t\in[a,b]\\ u(t)\in U(t)\ a.e.\ t\in[a,b]\\ \left(x(a),x(b),y(a)\right)\in E\times\{0\}\end{cases}$$

This new problem (P_M) is now in Mayer form.

2.3 Optimal Control of GTT Model

Optimal control allows the incorporation of functional constraints and requirements as a departure point for the design process. A control system for optimal insulin delivery in a type I diabetic patient is presented based on the linear quadratic control problem theory [9]. The glucose–insulin dynamics is first represented by a linear model whose state variables are the glucose and the insulin concentrations in the blood. These variables allow the formulation of an appropriate cost function for a diabetes treatment in terms of the deviation from the normal glucose level and the dosage of exogenous insulin. We have the general GTT model.

$$g'(t) = -ag - bh, \tag{5}$$

$$h'(t) = -cg + dh. \tag{6}$$

Our goal is to find the insulin injection level $u(t)$ which will minimize the difference between $g(t)$ and desired constant glucose level l. Also it was shown that for diabetics $c = 0$ is reasonable assumption [7]. Then we have optimal control problem as (see [1, 6, 12, 13, 14, 15, 16] for more analysis.)

$$(P)\begin{cases} \underset{u}{\text{Minimize}} \int_0^T A(g-l)^2 + u^2 dt \\ \text{subject to} \\ g' = -ag - bh, \\ h' = -dh + u, \\ g(0) = g_0 > 0,\ h(0) = h_0 \end{cases}$$

where

- g is the concentration of blood glucose
- h is the concentration of hormone
- u is the control variable
- g_0 is an initial glucose level
- A is the weight parameter
- l is the desired glucose level
- t is the time parameter.

The problem (P) can be rewritten as the following optimal control problem

$$(P_D)\begin{cases} \underset{u}{\text{Minimize}} \int_0^T L(x,u)\, dt \\ \text{subject to} \\ \dot{x}(t) = f(t,x,u), \\ u(t) \in U, \\ x(0) = x_0 \end{cases}$$

where, $L(x,u) = A\left(g-l\right)^2 + u^2,\ x(t) = \left(g(t), h(t)\right)$

$f(t,x,u) = \left(-ag - bh, -dh + u\right),\ x(0) = \left(g(0), h(0)\right)$

2.4 Analytical Solution:

The Hamiltonian of the system (P_D) is given by

$$H\left(t, g, h, \lambda_1, \lambda_2\right) = A(g-l)^2 + u^2 - \lambda_1 ag - \lambda_1 bh - \lambda_2 dh + \lambda_2 u \tag{7}$$

The optimality condition of (7) is

$$\left.\frac{\partial H}{\partial u}\right|_{u=u^*} = 0$$

$$\Rightarrow u^* = -\frac{\lambda_2}{2} \tag{8}$$

Again,

$$\frac{\partial^2 H}{\partial u^2} = 2 > 0.$$

So the problem is a minimization problem. Now the adjoint equations are

$$\lambda_1'\left(t\right) = -\frac{\partial H}{\partial g} = -2A(g-l) + a\,\lambda_1 \tag{9}$$

$$\lambda_2'(t) = -\frac{\partial H}{\partial h} = b\lambda_1 + d\,\lambda_2. \tag{10}$$

Also using u^* from in the given subjective functions, we get

$$g'\left(t\right) = -ag - bh \tag{11}$$

$$h'\left(t\right) = -dh - \frac{1}{2}\lambda_2. \tag{12}$$

From (9)-(12), we get the following system

$$\begin{pmatrix} g \\ h \\ \lambda_1 \\ \lambda_2 \end{pmatrix}' = \begin{bmatrix} -a & -b & 0 & 0 \\ 0 & -d & 0 & -\frac{1}{2} \\ -2a & 0 & a & 0 \\ 0 & 0 & b & d \end{bmatrix} \begin{bmatrix} g \\ h \\ \lambda_1 \\ \lambda_2 \end{bmatrix}. \tag{13}$$

For simplification we consider $a = 2, b = 1, d = 1, A = 2.$ Then the equation (13) becomes

$$\begin{pmatrix} g \\ h \\ \lambda_1 \\ \lambda_2 \end{pmatrix}' = \begin{bmatrix} -2 & -1 & 0 & 0 \\ 0 & -1 & 0 & -\frac{1}{2} \\ -4 & 0 & 2 & 0 \\ 0 & 0 & 1 & 1 \end{bmatrix} \begin{bmatrix} g \\ h \\ \lambda_1 \\ \lambda_2 \end{bmatrix} \tag{14}$$

Say $X' = MX$ where,

$$M = \begin{bmatrix} -2 & -1 & 0 & 0 \\ 0 & -1 & 0 & -\frac{1}{2} \\ -4 & 0 & 2 & 0 \\ 0 & 0 & 1 & 1 \end{bmatrix} \text{and } X = \begin{bmatrix} g \\ h \\ \lambda_1 \\ \lambda_2 \end{bmatrix}.$$

Then the eigen values of the co-efficient matrix of (14) is

$$\left|\lambda I_4 - M\right| = 0$$

$$\Rightarrow \begin{bmatrix} \lambda+2 & 1 & 0 & 0 \\ 0 & \lambda+1 & 0 & \frac{1}{2} \\ 4 & 0 & \lambda-2 & 0 \\ 0 & 0 & -1 & \lambda-1 \end{bmatrix} = 0$$

$$\Rightarrow \lambda^4 - 4\lambda^2 - \lambda^2 + 6 = 0$$

$$\Rightarrow \left(\lambda^2 - 3\right)\left(\lambda^2 - 2\right) = 0$$

$$\therefore \lambda = \pm\sqrt{3}, \pm\sqrt{2}.$$

We consider the following system (i.e. eigen vectors) from (14)

$$\begin{bmatrix} -\lambda-2 & -1 & 0 & 0 \\ 0 & -\lambda-1 & 0 & -.5 \\ -4 & 0 & -\lambda+2 & 0 \\ 0 & 0 & 1 & -\lambda+1 \end{bmatrix} \begin{bmatrix} k_1 \\ k_1 \\ k_3 \\ k_4 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \tag{15}$$

where, k_1, k_2, k_3 and k_4 are variables that are chosen for solving 4×4 matrix corresponding to the eigen values λ. We have to find the ratios of the form $k_1 : k_2 : k_3 : k_4$. Now for $\lambda = \sqrt{3} = 1.7321$, we get from the system (15)

$$\Rightarrow \begin{bmatrix} -3.7321 & -1 & 0 & 0 \\ 0 & -2.7321 & 0 & -.5 \\ -4 & 0 & .2679 & 0 \\ 0 & 0 & 1 & -.7321 \end{bmatrix} \begin{bmatrix} k_1 \\ k_2 \\ k_3 \\ k_4 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}. \tag{16}$$

Solving (16), we get

$k_1 : k_2 : k_3 : k_4 = .0547 : -.18301 : .7324 : 1.$

Now for $\lambda = -\sqrt{3} = -1.7321,$ we get from the system (15)

$$\Rightarrow \begin{bmatrix} -.2679 & -1 & 0 & 0 \\ 0 & .7321 & 0 & -.5 \\ -4 & 0 & 3.7321 & 0 \\ 0 & 0 & 1 & 2.7321 \end{bmatrix} \begin{bmatrix} k_1 \\ k_2 \\ k_3 \\ k_4 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}. \qquad (17)$$

Solving (17), we get

$k_1 : k_2 : k_3 : k_4 = -3.7327 : 1 : .73241.4642 : -4.0005.$

Again for $\lambda = \sqrt{2} = 1.4142,$ we get from the system (15)

$$\Rightarrow \begin{bmatrix} -3.4142 & -1 & 0 & 0 \\ 0 & -2.4142 & 0 & -.5 \\ -4 & 0 & .5858 & 0 \\ 0 & 0 & 1 & -.4142 \end{bmatrix} \begin{bmatrix} k_1 \\ k_2 \\ k_3 \\ k_4 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}. \qquad (18)$$

Solving (18), we get

$k_1 : k_2 : k_3 : k_4 = .06066 : -.20711 : .4142 : 1.$

And for $\lambda = -\sqrt{2} = -1.4142,$ we get from the system (15)

$$\Rightarrow \begin{bmatrix} -.5858 & -1 & 0 & 0 \\ 0 & .4142 & 0 & -.5 \\ -4 & 0 & 3.4142 & 0 \\ 0 & 0 & 1 & 2.4142 \end{bmatrix} \begin{bmatrix} k_1 \\ k_2 \\ k_3 \\ k_4 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}. \qquad (19)$$

Solving (19), we get

$k_1 : k_2 : k_3 : k_4 = -2.0608 : 1.2072 : -2.4142 : 1.$

Now using the ratios of $k_1 : k_2 : k_3 : k_4$ for each eigen value (λ), we get the analytic solution of the control system (A) of the form

$$\begin{pmatrix} g \\ h \\ \lambda_1 \\ \lambda_2 \end{pmatrix} = C_1 \begin{pmatrix} .05427 \\ -.18301 \\ .7324 \\ 1 \end{pmatrix} e^{1.7721t} + C_2 \begin{pmatrix} -3.7327 \\ 1 \\ 1.4642 \\ -4.0005 \end{pmatrix} e^{-1.7321t} + C_3 \begin{pmatrix} .06066 \\ -.20711 \\ .4142 \\ 1 \end{pmatrix} e^{-1.4142t} + C_4 \begin{pmatrix} -2.0608 \\ 1.2072 \\ -2.4142 \\ 1 \end{pmatrix} e^{-1.4142t} \qquad (20)$$

where C_1, C_2, C_3 and C_4 are arbitrary constants.

$$\therefore g(t) = .05427C_1e^{\sqrt{3}t} - 3.7327C_2e^{-\sqrt{3}t} + .06066C_3e^{\sqrt{2}t} - 2.0608C_4e^{-\sqrt{2}t} \tag{21}$$

$$\therefore h(t) = -.18301C_1e^{\sqrt{3}t} + C_2e^{-\sqrt{3}t} - .20711C_3e^{\sqrt{2}t} + 1.2072C_4e^{-\sqrt{2}t} \tag{22}$$

$$\therefore \lambda_1(t) = .7324C_1e^{\sqrt{3}t} + 1.4642C_2e^{-\sqrt{3}t} + .4142C_3e^{\sqrt{2}t} - 2.4142C_4e^{-\sqrt{2}t} \tag{23}$$

$$\therefore \lambda_2(t) = C_1e^{\sqrt{3}t} - 4.0005C_2e^{-\sqrt{3}t} + C_3e^{\sqrt{2}t} + C_4e^{-\sqrt{2}t} \tag{24}$$

Now from the equation (8), the control equation of the problem is

$$\therefore u(t) = -\frac{\lambda_2(t)}{2}$$

$$= -\frac{1}{2}(C_1e^{\sqrt{3}t} - 4.0005C_2e^{-\sqrt{3}t} + C_3e^{\sqrt{2}t} + C_4e^{-\sqrt{2}t}). \ \text{[using (24)]} \tag{25}$$

The equations (21), (22) and (25) represent glucose concentration, insulin concentration and control of the model respectively.

3. Results and Discussions

A GTT requires the monitoring of glucose for only three two to five hours. Our work requires the accurate prediction of glucose level for weeks or even months. Now we will try to interpret the optimal control, Insulin and Glucose concentration with fixed values of a, b, c, x_0 and A and the changing values of time parameter t. **Figs.** 3.1-3.4 represent these properties. Firstly we take $a = 2,\ b = 1,\ c = 1,\ x_0 = .75,\ A = 2$ and $l = .5$ with the time $T = 20$ days. It has been shown in **Fig.** 3.1.

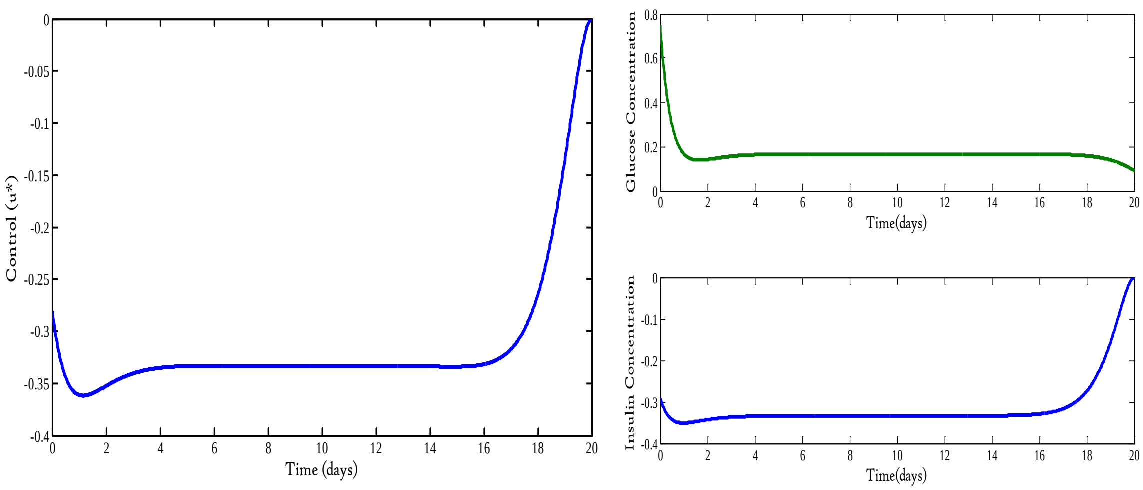

Fig. 3.1: The optimal control u^* and the glucose and insulin concentration for $T = 20$ with $a = 2,\ b = 1,\ c = 1,$ $x_0 = .75,\ A = 2$ and $l = .5$ respectively.

From **Fig.** 3.1, we observe the optimal control behaviour for 20 days. Though the control is initially negative, optimal control increases with increase of time. Also we see that the insulin level is negative. Actually this gives the situation of physical impossibility. Also the behaviour of glucose level seems to oppose our goal as it decreases to the desired 0.5 level and reaches under level 0.5.

We need to show that control tends to zero with increase of time. But from **Fig. 3.1**, control does not do so. The variation of the model is actually the parameters we have used, mainly the length of time. When we take $T = 0.2$ days means 4.8 hours, we get reasonable result as shown in **Fig. 3.2**.

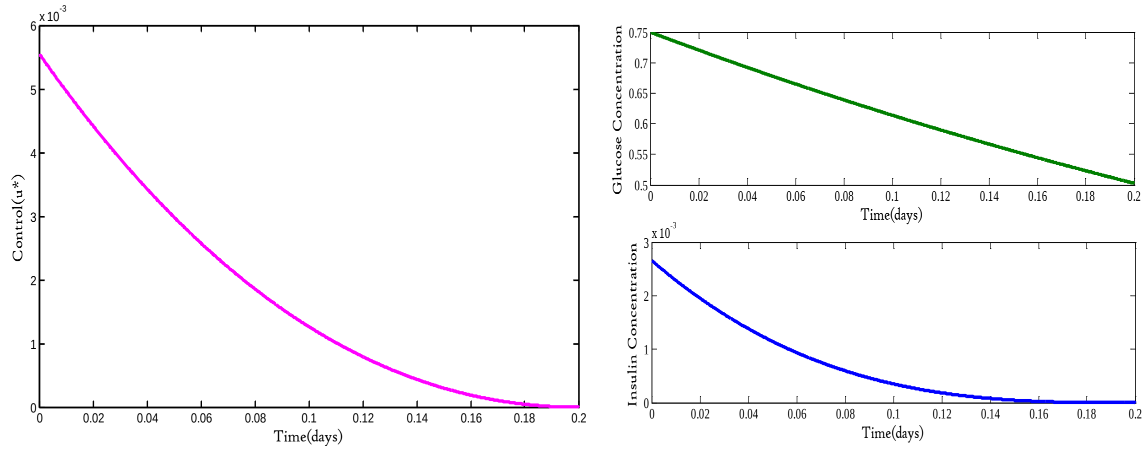

Fig. 3. 2: The optimal control u^* and the glucose and insulin concentration for $T = 0.2$ with $a = 2$, $b = 1$, $c = 1$, $x_0 = .75$, $A = 2$ and $l = .5$ respectively.

From **Fig. 3.2**, we observe the optimal control behaviour for 0.2 days or 4.8 hours. Initially the control is positive. But optimal control decreases with increase of time and it tends to zero at 4.8 hours. Also we see that the results are reasonable. The glucose concentration is steadily decreased almost linearly and insulin level is positive. Now we consider $T = 0.3$ and observe the control, glucose and insulin concentrations in **Fig. 3.3**. From **Fig. 3.3**, we observe that control tends to zero with increase of time likely for time $T = .2$.

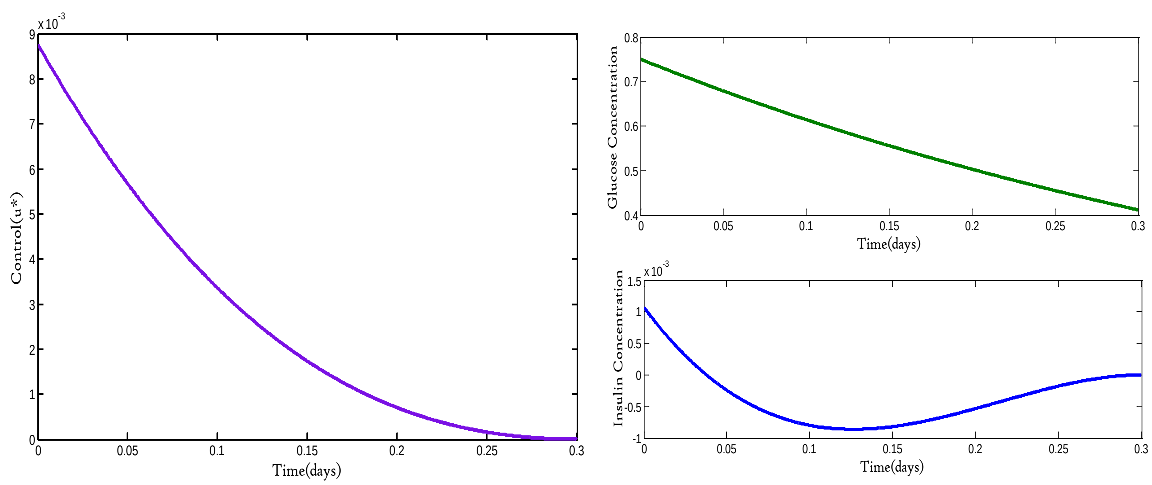

Fig. 3.3: The optimal control u^* and the glucose and insulin concentration for $T = 0.3$ with $a = 2$, $b = 1$, $c = 1$, $x_0 = .75$, $A = 2$ and $l = .5$ respectively.

Also we see that the glucose concentration is steadily decreased and insulin level tends to zero with increase of time. But in the process the insulin level becomes negative. This is a physical impossibility. Again we take $T = .4$ and observe the control, glucose and insulin concentrations.

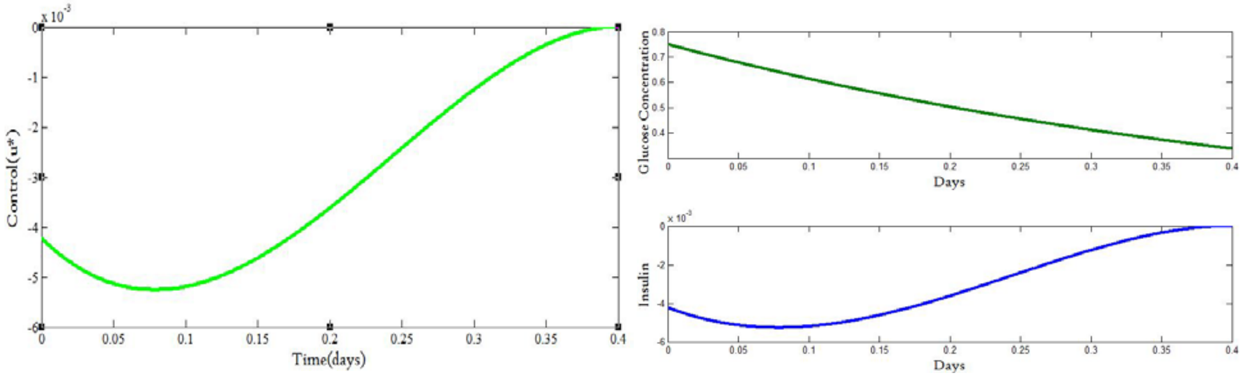

Fig. 3.4: The optimal control u^* and the glucose and insulin concentration for $T = 0.4$ with $a = 2,\ b = 1,\ c = 1,$ $x_0 = .75,\ A = 2$ and $l = .5$ respectively.

From **Fig. 3.4**, we observe that control variable primarily starts from negative and tends to zero with increase of time. This contradicts our assumption of positivity of control. Also **Fig. 3.4** indicates that glucose concentration is decreasing and insulin level is negative. We see that for time $T = .4$ days control is initially negative which contradicts the optimality condition. So we do not need to examine the model for the times more than .4 days.

4. **Conclusions**

We have presented optimal control of general GTT model. A GTT requires the monitoring of glucose for only three to five hours. Our work is related to obtain the accurate prediction of glucose level. For various time periods (i.e. time parameter T), we have examined the control problem of GTT taking other fixed parametric values (i.e. $a = 2,\ b = 1,\ c = 1,\ x_0 = 0.75,\ A = 2$ and $l = 0.5$) and we have also observed glucose and insulin concentration for corresponding time T. If it is taken long time period (i.e. 20 days), the control becomes inconsistent to the model (i.e. control becomes negative). For proper time prediction, we have also taken $T = .2,\ .3$ and .4 days and have observed control of the model. Actually for .2 days (4.8 hours), the control behaves more accurately means it tends to zero. The glucose concentration decreases steadily almost linearly and insulin level remains positive. This gives the desired time for GTT. The desired time is 4.8 hours. We can also conclude that the model becomes inconsistent for time more than 4.8 hours. Mathematical model and optimal control are the large fields of calculus of variations but our work has touched a little part of it. Especially the applications of optimal control models to the real world are every moment needs. There are many questions in control of GTT for human perspectives still unstudied. We believe that extensive and continuous involvement in optimal control research may result in to answer many questions for the development of this topic.

5. Acknowledgements

The authors would like to thank the anonymous reviewers for their fruitful comments which help our manuscript for further improvement. While preparing this manuscript, all sorts of logistic supports provided by Mathematics Discipline of Khulna University, Bangladesh are also acknowledged.

References

[1] Adekunle, A. I. and Olotu, O. (2013). Optimal Control of Myocardial due to Diabetes, *Advanced Modeling and Optimization*, 15(2):223-233.

[2] Baynest, H. W. (2015). Classification, Pathophysiology, Diagnosis and Management of Diabetes Mellitus, *Journal of Diabetes and Mellitus*, 6(5):1-9.

[3] Biswas, M. H. A. (2013). "Necessary Conditions for Optimal Control Problems with State Constraints: Theory and Applications", PhD Thesis, Department of Electrical and Computer Engineering, Faculty of Engineering, University of Porto, Portugal.

[4] Biswas, M. H. A. (2011). Necessary Conditions for Optimal Control Problems with and without State Constraints: A Comparative Study. *WSEAS Transactions on Systems and Control*, 6(6):217–228.

[5] Biswas, M. H. A. and de Pinho, M. D. R. (2011). A Nonsmooth Maximum Principle for Optimal Control Problems with State and Mixed Constraints – Convex Case, *Discrete and Continuous Dynamical Systems*, 174-183.

[6] Chalishajar, D. and Stanford, C. A. C. (2014). Mathematical Analysis of Insulin-Glucose Feedback System of Diabetics, *International Journal of Engineering and Applied Sciences*, 5(2).

[7] Helal, A. Z., Rehbock, V. and Loxton, R. (2015). Modelling and Optimal Control of Blood Glucose Levels in The Human Body, *Journal of Industrial and Management Optimization*, 11(4):1149-1164.

[8] IDF Report on Diabetes in Bangladesh, International Diabetes Federation, 2011.

[9] Lenhart, S. and Workman, J. T. (2007), ''Optimal Control Applied to Biological Models'', CRC Press, Taylor & Francis Group, London.

[10] Murray, J. D. (1993), ''Mathematical Biology'', Second Edition, Springer-Verlag, Berlin.

[11] Naidu, D. S. (2003), ''Optimal Control Systems'', CRC Press, Boca Raton, London.

[12] Naidu, D. S., Fernando, T. and Fister, K. R. (2011). Optimal control in diabetes, *Optima Control Applications and Method*, 32:181-184.

[13] Neilan, R. M. and Lenhart, S. (2010), ''An Introduction to Optimal Control and Theoretical Computer Science with an Application in Disease Modeling'', DIMACS Series in Discrete Mathematics, Vol. 75.

[14] Pinch, E. B. (1993), 'Optimal control and the Calculus of Variations', Oxford University Press Inc., New York.

[15] Sargent, R.W.H. (2000). Optimal control, *Journal of Computational and Applied Mathematics,* 124:361-371.

[16] Sussmann, H. J. and Willems, J. C. (1997). 300 years of Optimal Control: From the Brachystochrone to the Maximum Principle, *IEEE Control Systems*, 0272-1708.