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Research Article

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Multi Objective Nonlinear Model Predictive Control of Diabetes Models Considering the Effects of Insulin and Exercise

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Abstract

Rigorous multiobjective nonlinear model predictive control on the diabetes model incorporating single and multiple control strategies. The amount of glucose is minimized with the Bergman model considering the effects of insulin and exercise. The optimization language pyomo is used in conjunction with the state-of-the-art global optimization solvers IPOPT and Baron. Pareto surfaces are generated. When some optimal control profiles were found to exhibit sharp spikes, an activation factor involving the hyperbolic tangent function was used. It is observed that a greater amount of glucose minimization is achieved when more control procedures were incorporated. This demonstrates that it is more beneficial to use multiple control strategies.

Keywords: Diabetes, Insulin, Optimal Control, Multiobjective.

1. Introduction

The number of people with diabetes in the world has risen substantially during the last few years. Diabetes results in blindness, kidney failure, heart attacks, stroke, and lower limb amputation. For people with diabetes, glucose tends to build up in the bloodstream and may reach dangerously high levels if it is not treated properly. Insulin and other drugs are used to lower blood sugar levels.

A considerable amount of investigation has been performed regarding the use of various strategies to control the glucose level in the human body. The dynamics of the glucose-insulin interaction have been studied by various researchers [1-4]. Bergman et al developed a three-compartment model dealing with the glucose-insulin dynamics [5,6]. This model is very commonly used by researchers and investigators and control strategies have been incorporated into this model to come up with ways to control the damage done by diabetes. A model that studies the effects of glucose production and utilization was developed by Cobelli et al [7,8]. The issues of glucose effectiveness and insulin sensitivity were studied by Cobelli et al [8]. The effects of exercise on glucose were studied by several workers Wasserman et al, Wolfe et al, Wahren et al; Ahlborg et al; Pruett, Zinman) [9-17].

Optimal control has been used to minimize glucose while limiting the use of insulin (Swan, Fisher and Teo, Ollerton, Parker et al, Acikgoz and Diwekar [18-20,2,21]. Hernjak and Doyle III have investigated the use of a PID controller for diabetes models, Dua et al use parametric programming to obtain the insulin delivery rate while [22, 23].

A classic model used to describe glucose reduction with insulin is the Bergman model (1979) [5,6]. Ferjouchia et performed optimal control on the minimalistic Bergman model with one control parameter while Roy et al performed optimal control on the Bergman model with two and three control parameters which are the insulin exogenously and external infusion of glucose and exercise [24,25]. The aim of this work is to perform multiobjective nonlinear model predictive control with the Bergman model using one, two, and three control strategies [5,6].

2. The Bergman Model

The original Bergman model which is used to model the insulin effects on diabetes is given by the following equations [24].

$$\frac{dg}{dt} = -p_1(g(t) - g_b) - x(t)g(t) + ma(t) \quad (1)$$

$$\frac{dx}{dt} = -p_2 x(t) - p_3(IX(t) - I_b) \quad (2)$$

$$\frac{dIx}{dt} = -nIx(t) + u(t) \quad (3)$$

Where the variable values are

- g(t): Blood glucose concentration
- Ix(t): Blood insulin concentration
- X(t) : is effect of active insulin
- u(t): control Variable exogenous insulin
- ma(t): meal disturbance function

2.1 The Bergman Model with One Control Variable

For the original Bergman with one control variable, the original model has a minor modification in equation 1 and is given by the equations [24].

Where the control variable u(t) is again the exogenous insulinIn both these models G(0) = 287 mg/dL. The parameter values for both these models are given in Table 1

Parameter	Value	Units
P1	0.03082	1/min
P2	0.02093	1/min
P3	1.062e-05	$ml/\mu U.\min^2$
n	0.3	1/min
gb	92	mg/dl
Ib	7.3	Mu/dl

Table 1

2.2 The Bergman Model with Two Control Variables

In this model, the two control variables are u_1 and u_2 which represent the insulin is infused exogenously and external infusion of glucose [25].

$$\frac{dg}{dt} = -p_1(g(t)-g_b) - x(t)g(t) + \frac{u_2(t)}{Vol_g} \tag{4}$$

$$\frac{dx}{dt} = -p_2 x(t) + p_3(Ix(t) - I_b) \tag{5}$$

$$\frac{dIx}{dt} = -nIx(t) + p_4 u_1(t) \tag{6}$$

The parameter values are given in table 2

Parameter	Value	Units
P1	0.035	1/min
P2	0.05	1/min
P3	0.000028	$ml/\mu U.\min^2$
	0.3	1/min
P4	0.098	1/ml
n	0.142	1/min
Volg	0.117	dl
gb	80	mg/dl
Ib	7.3	Mu/dl

Table 2

2.3 Bergman Model with Three Control Variables

The equations of the Bergman model with three control variables, u_1,u_2 and u_3 which represent the insulin is infused exogenously and external infusion of glucose and exercise are [25].

$$\frac{dg}{dt} = -p_1(g(t)-g_b) - x(t)g(t) + \frac{u_2(t)}{Vol_g} + \frac{W}{Vol_g}(g_{prod}(t) - g_{gly}(t)) - \frac{W}{Vol_g}(g_{up}(t)) + \frac{u_2}{Vol_g} \tag{7}$$

$$\frac{dIx}{dt} = -nIx(t) + p_4 u_1(t) - I_e(t) \tag{8}$$

$$\frac{dx}{dt} = -p_2 x(t) + p_3 (Ix(t) - I_b) \quad (9)$$

$$\frac{dg_{prod}}{dt} = a_1 PVO_2^{\max} - a_2 g_{prod}(t) \quad (10)$$

$$\frac{dg_{up}}{dt} = a_3 PVO_2^{\max} - a_4 g_{up}(t) \quad (11)$$

$$\frac{dI_e}{dt} = a_5 PVO_2^{\max} - a_6 I_e(t) \quad (12)$$

$$A_{TH} = -1.1521[u_3(t)]^2 + 87.471 u_3(t) \quad (13)$$

$$\begin{aligned} \frac{dA}{dt} &= \{u_3(t) \quad if \quad u_3(t) > 0\} \\ &= \{-\frac{A(t)}{0.001} \quad if \quad u_3(t) = 0\} \end{aligned} \quad (14)$$

$$\begin{aligned} \frac{dG_{gly}}{dt} &= \{0 \quad if \quad A(t) < A_{TH}\} \\ &= \{k \quad if \quad A(t) \geq A_{TH}\} \\ &= \{-\frac{G_{gly}(t)}{T_i} \; if \; u_3(t) = 0\} \end{aligned} \quad (15)$$

$G_{up}(t)$ (mg/kg/min) represents the the rates of glucose uptake while (mg/kg/min) $G_{prod}(t)$ is the hepatic glucose production induced by exercise. W (kg) represents the weight of the subject.

Variable $G_{gly}(t)$ (mg/kg/min) is the decline of the glycogenolysis rate during prolonged exercise because of the depletion of li ver glycogen stores.

A(t) is the integrated exercise intensity, while ^{A}TH is the critical threshold value for *A(t)*. $PVO_2^{\max}$ is the power at maximum VO_2

The additional parameters are in table3.

Parameter	Value	Units
a_1	0.035	mg/kg.min²
a_2	0.05	1/min
$PVO_2^{\max}$	40	mL/kg/min
w	80	kg
a_3	0.000028	mg/kg.min2
a_4	0.098	1/min
a_5	0.142	$\mu U / ml.$min
a_6	0.117	1/min
k	80	mg/kg.min²
T_1	7.3	min

Table 3

3. Methodology (MNLMC Method)

The multiobjective nonlinear optimal control (MOOC) method was first proposed by Flores Tlacuahuaz et al14and used by Sridhar [26,27]. This method does not involve the use of weighting functions nor does it impose additional constraints on the problem unlike the weighted function or the epsilon correction method [28]. For a problem that is posed as

$$\begin{aligned} &\min J(x,u) = (x_1, x_2 \ldots . x_k) \\ &subject\ to\ \frac{dx}{dt} = F(x,u) \\ &h(x,u) \le 0 \\ &x^L \le x \le x^U \\ &u^L \le u \le u^U \end{aligned} \tag{16}$$

The MNLMPC method first solves dynamic optimization problems X_i independently. minimizing/maximizing each individually. The minimization/maximization of X_i will lead to the values X_i^*. Then the optimization problem that will be solved is

$$\begin{aligned} &\min \sqrt{\{x_i - x_i^*\}^2} \\ &subject\ to\ \frac{dx}{dt} = F(x,u) \\ &h(x,u) \le 0 \\ &x^L \le x \le x^U \\ &u^L \le u \le u^U \end{aligned} \tag{17}$$

This will provide the control values for various times. The first obtained control value is implemented and the remaining discarded. This procedure is repeated until the implemented and the first obtained control value are the same.

The optimization package in Python, Pyomo , where the differential equations are automatically converted to a Nonlinear Program (NLP) using the orthogonal collocation method [29]. The Lagrange-Radau quadrature with three collocation points is used and 10 finite elements are chosen to solve the optimal control problems. The resulting nonlinear optimization problem was solved using the solvers IPOPT and Baron [30,31]. BARON implements a Branch-and-reduce strategy to provide valid lower and upper bounds for the optimal solution and provides a guaranteed global optimal solution. This algorithm combines constraint propagation, interval analysis, and the duality in it reduces arsenal with enhanced branch and bound concepts as it winds its way through the hills and valleys of complex optimization problems in search of global solutions. BARON is accessed through the Pyomo-GAMS27.2 [32].

To summarize the steps of the algorithm are as follows

1. Minimize/maximize X_i subject to the differential and algebraic equations that govern the process using Pyomo and Baron. This will lead to the value X_i^* at various time intervals t_i.. The subscript *i* is the index for each time step.
2. Minimize $\sqrt{\{x_i - x_i^*\}^2}$ subject to the differential and algebraic equations that govern the process using Pyomo and Baron. This will provide the control values for various times.
3. Implement the first obtained control values and discard the remaining.
4. Repeat steps 1 to 4 until there is an insignificant difference between the implemented and the first obtained value of the control variables.

3.1 Methodology (Tanh Activation Factor)

In the one control problem, the control profile exhibited sharp spikes. These spikes are inconvenient as they make it difficult to implement the control measures. Figure 4a demonstrates the existence of spikes. To circumvent this problem, an activation factor involving the hyperbolic tangent function (tanh) was used and the control variable u(t) was modified to $u(t)tanh(u(t))/\varepsilon$ The newly obtained control profile (figure 4b) shows that the use of the tanh activation factor eliminates the spikes. While the tanh activation factor was not needed in the 2 control problem, it was used as a precautionary measure in the three component problem because of the different constraints for the derivatives $\frac{dA}{dt}, \frac{dG_{gly}}{dt}$ in equations 14 and 15. Here, $u_1(t), u_2(t)$ *and* $u_3(t)$ were replaced by $u_1(t)\tanh(u_1(t))/\varepsilon, u_2(t)\tanh(u_2(t))/\varepsilon$ *and* $u_3(t)\tanh(u_3(t))/\varepsilon$ is chosen to be 10^{-5}.

4. Results and Discussion (MNLMC of the Bergman Model)

In the Bergman model with one control parameter, the variables g, ix and u are minimized individually while the variable x is maximized. The corresponding resulting objective values are 287, 7.3, 0 and 1.77905. This will lead to the NLMPC problem minimize

$$\sum(x_i - 1.77905)^2 + \sum(g_i - 287)^2 + \sum(Ix_i - 7.3)^2 + \sum(u_i - 0)^2$$

The obtained NLMPC control value of u is 1.79 X 10^{-7}.

In the Bergman model with two control parameter, the variables g, ix of u_1, u_2 are minimized individually while the variable x is maximized. The corresponding resulting objective values are 100.16, 14.6, 0, 0.002 and 0.03568. This will lead to the NLMPC problem minimize

$$\sum(x_i - 0.03568)^2 + \sum(g_i - 100.16)^2 + \sum(Ix_i - 14.6)^2 + \sum(u_{1i} - 0)^2 + \sum(u_{2i} - 0.002)^2$$

The obtained NLMPC control value of u_1, u_2 are 100 and 0.

In the Bergman model with three control parameter, the variables g, ix of u_1, u_2, u_3 are minimized individually while the variable x is maximized. The corresponding resulting objective values are 80 7.3, 0, 0, 0 and 0.02976. This will lead to the NLMPC problem minimize

$$\sum(x_i - 0.02976)^2 + \sum(g_i - 80)^2 + \sum(Ix_i - 7.3)^2 + \sum(u_{1i} - 0)^2 + \sum(u_{2i} - 0.0)^2 + \sum(u_{3i} - 0.0)^2$$

The obtained NLMPC control value of u_1, u_2, u_3 0.0316 0.0243 and 0.003. The increase in the control tasks causes a significant decrease in g, the glucose level from 287 to 100.16 to 80.

Figures 1-3 4a and 4b show the variation of the variables g, ix and x with time while figures 4a and 4b show the control profiles without and with the use of the tanh activation factor. Figure 4a demonstrates the existence of spikes in the control profile while figure 4b shows that the use of the tanh activation factor eliminates the spikes.

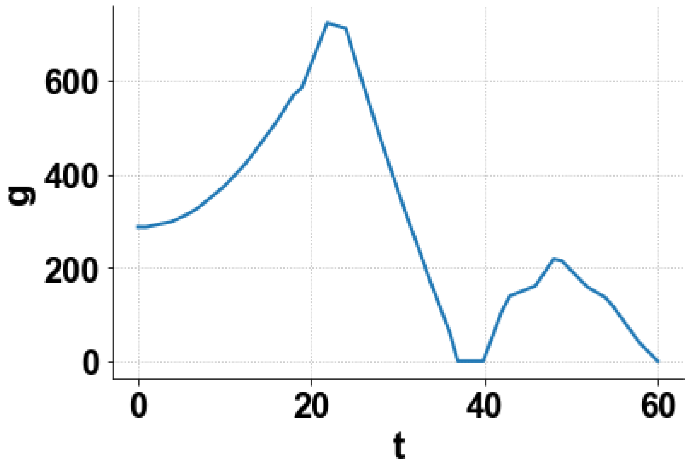

Figure 1: Single control g versus t

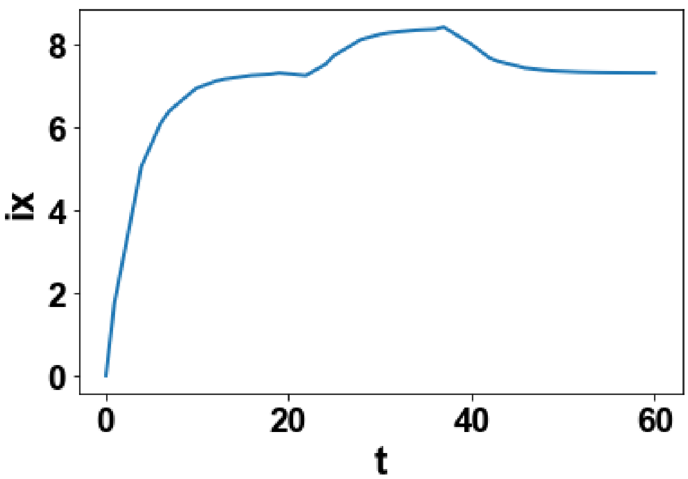

Figure 2: Single control ix versus t

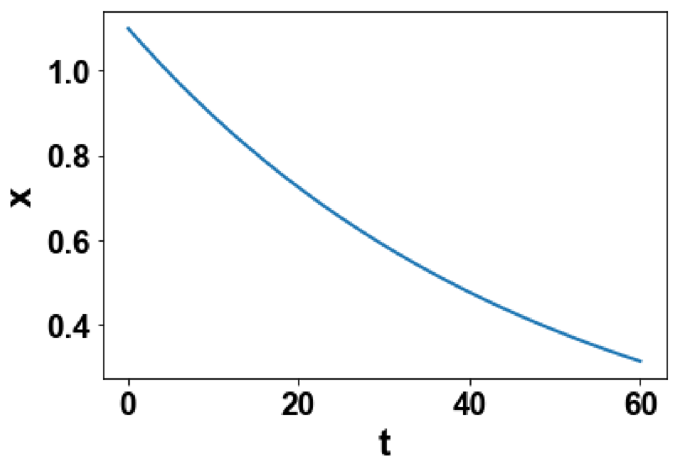

Figure 3: Single control x versus t

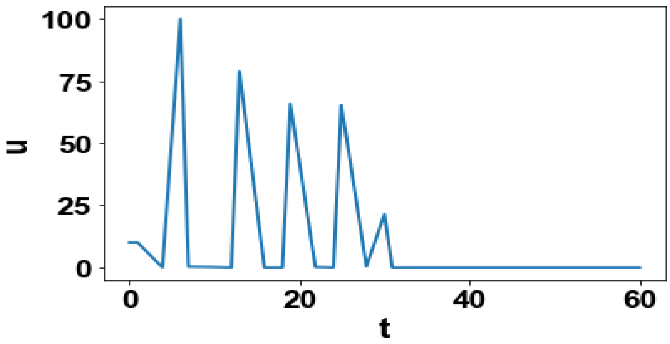

Figure 4a: Single control u versus t (spikes)

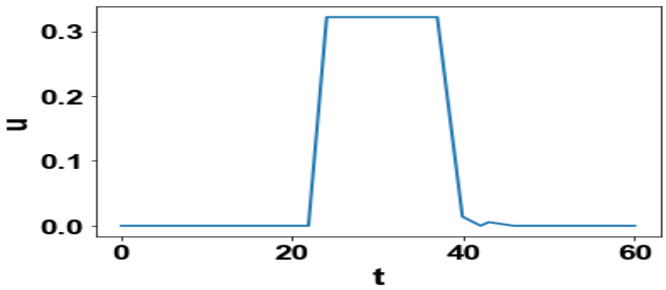

Figure 4b: Single control u versus t (spikes eliminated)

The tanh activation factor was not needed in the 2 control problem. Figures 10-14 show the variation of g, ix, x,   with time. No spikes are observed in the control profiles of   with time. Figures 15-20 show the pareto surfaces for the Bergman model when two control procedures were used. For the three-control problem, Figs 21-23 show the variation of the three control variables   with time while figures 24-26 show the variation of g, ix, x, with time. Figures 27-35 show the pareto profiles for the three-control problem. In the three control problem also, the tanh activation factor was used because of the different constraints for the derivatives $\frac{dA}{dt},\frac{dG_{gly}}{dt}$ in equations 14 and 15.

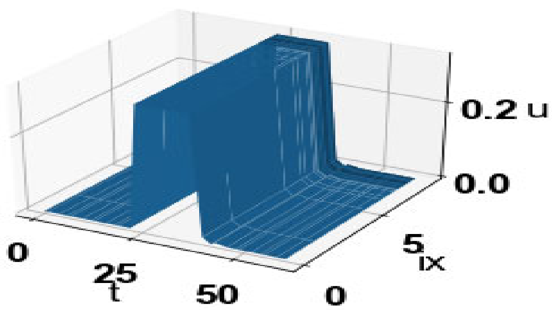

Figure 5: Single control t, ix, u surface

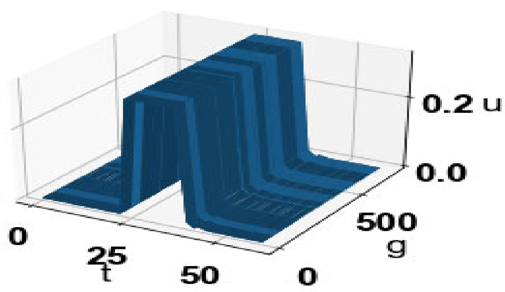

Figure 6: Single control t, g, u surface

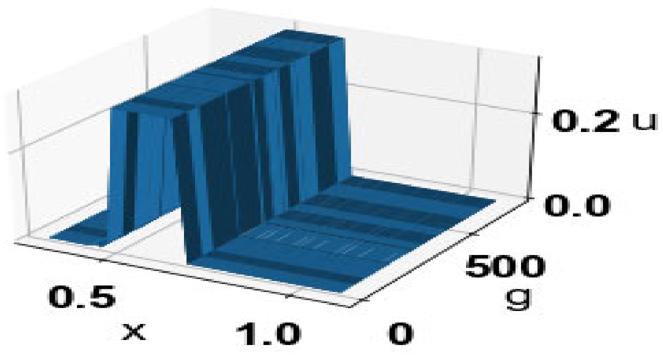

Figure 7: Single control x, g, u surface

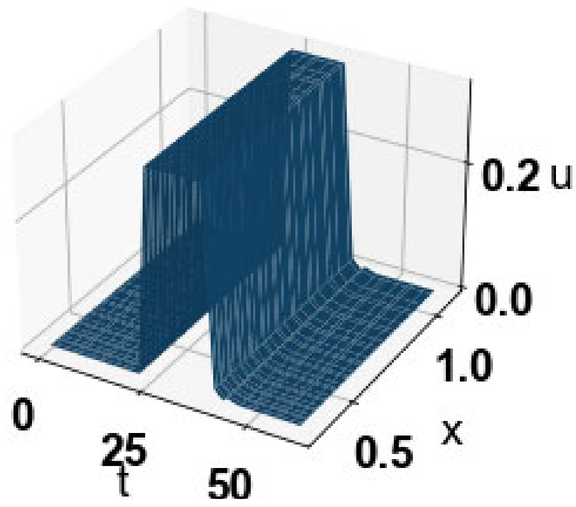

Figure 8: Single control t, x, u surface

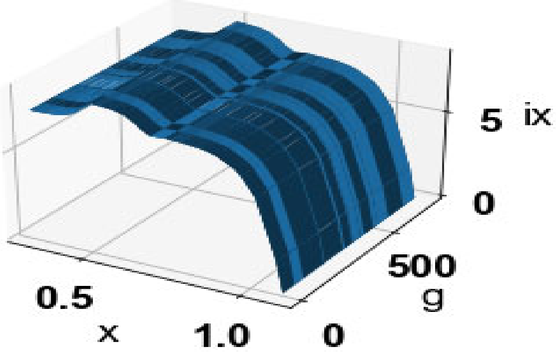

Figure 9: Single control x, g, ix surface

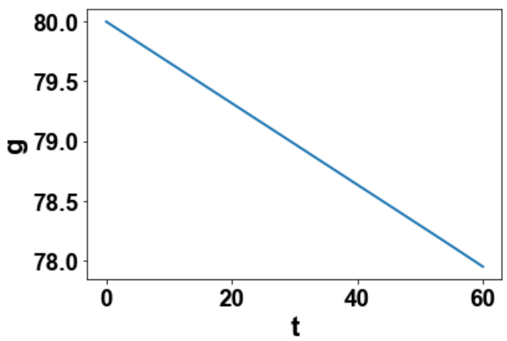

Figure 10: two controls g versus t

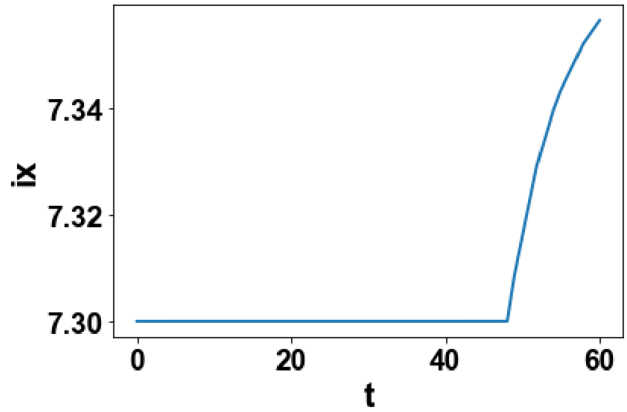

Figure 11: two controls ix versus t

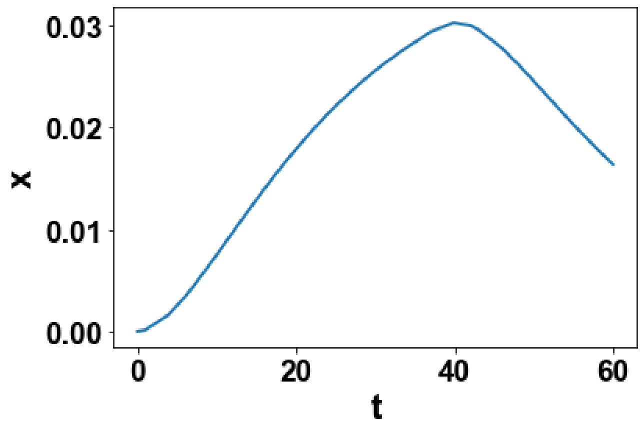

Figure 12: two controls x versus t

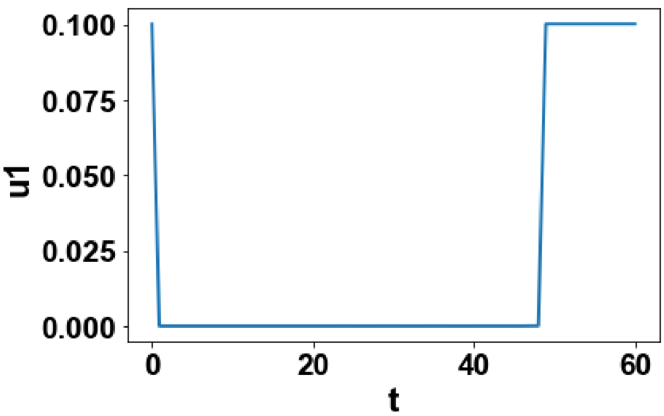

Figure 13: two controls u1 versus t

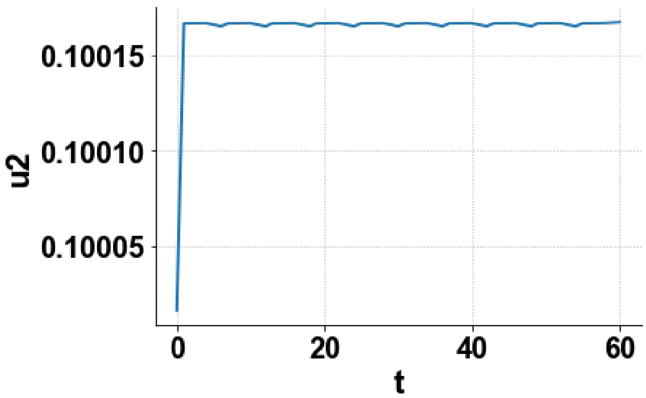

Figure 14: two controls u2 versus t

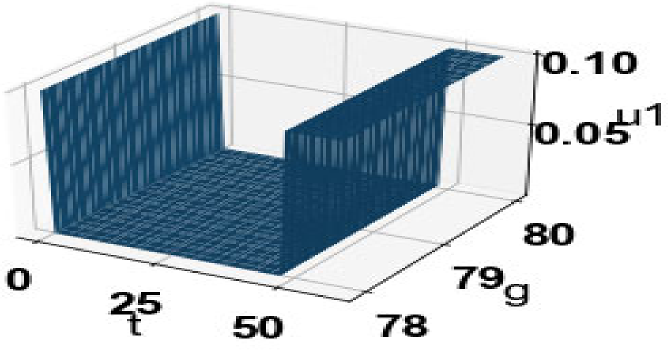

Figure 15: two controls g t u1 surface

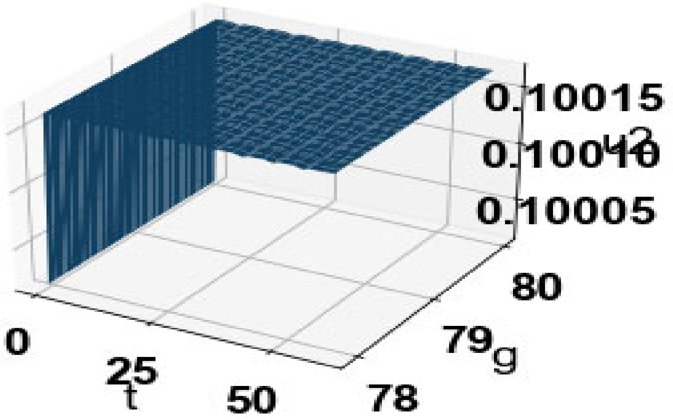

Figure 16: two controls g t u2 surface

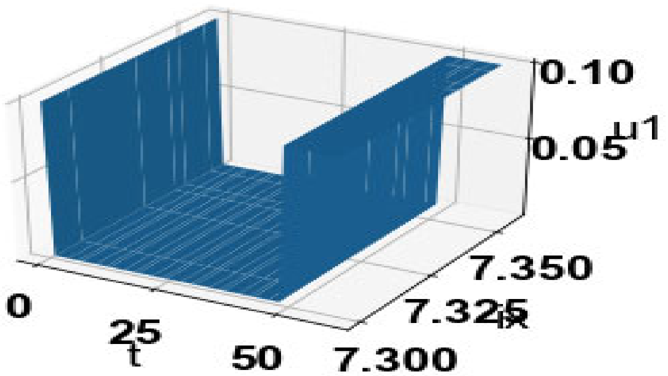

Figure 17: two controls ix t u1 surface

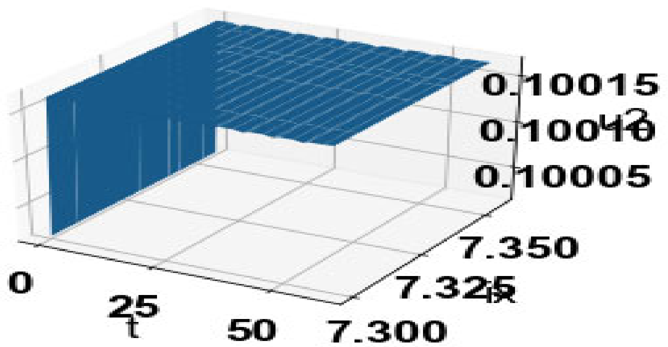

Figure 18: two controls ix t u2 surface

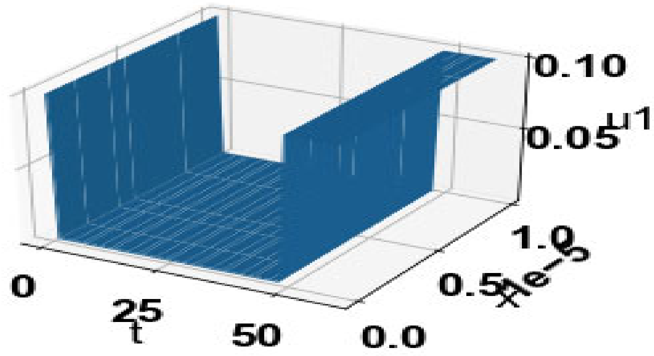

Figure 19: two controls x t u1 surface

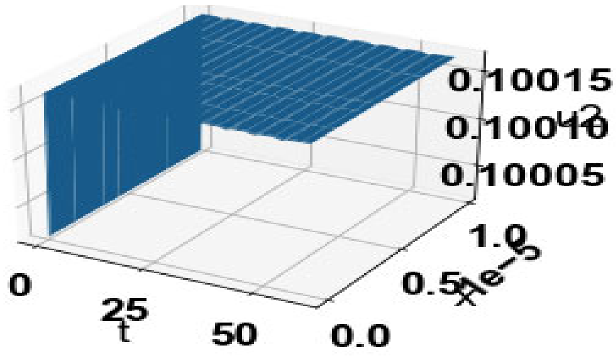

Figure 20: two controls x t u2 surface

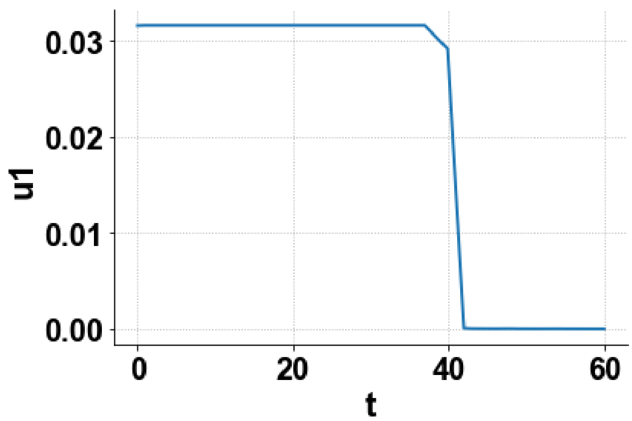

Figure 21: 3 controls u1 versus t

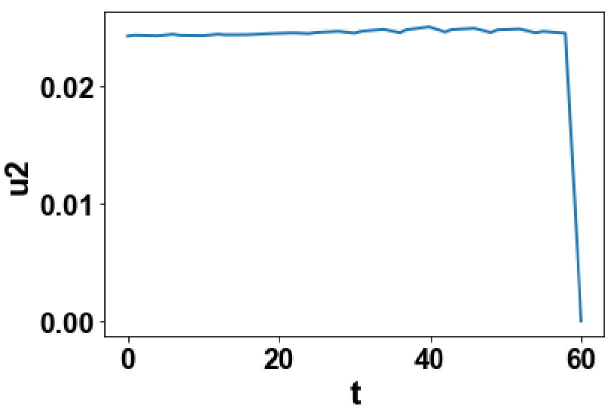

Figure 22: 3 controls u2 versus t

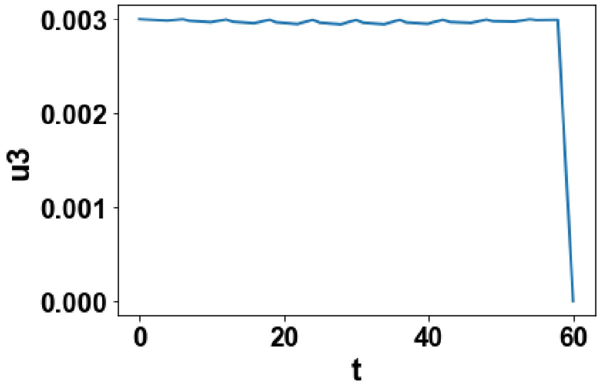

Figure 23: 3 controls u3 versus t

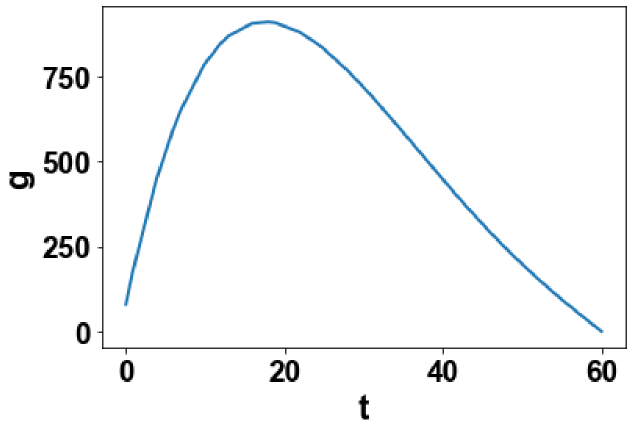

Figure 24: 3 controls g versus t

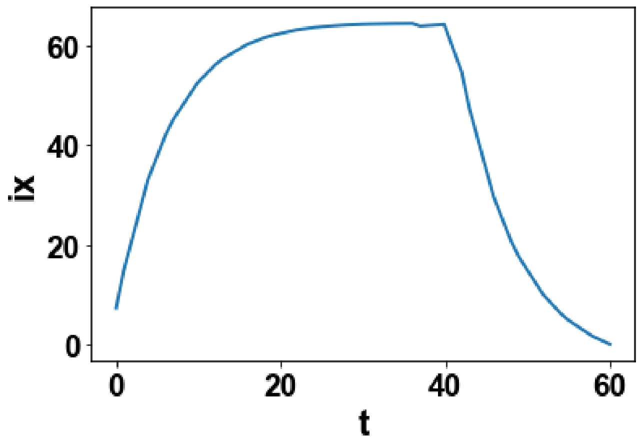

Figure 25: 3 controls ix versus t

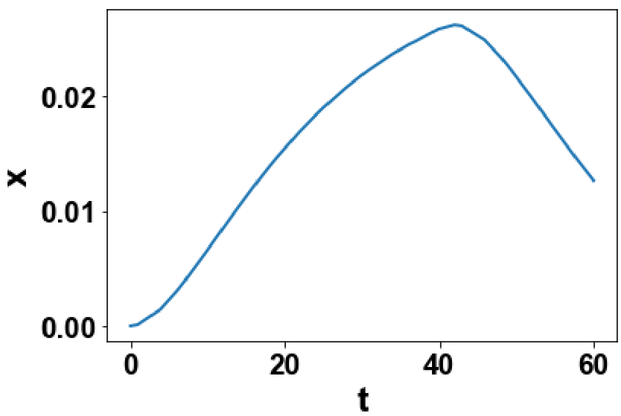

Figure 26: 3 controls x versus t

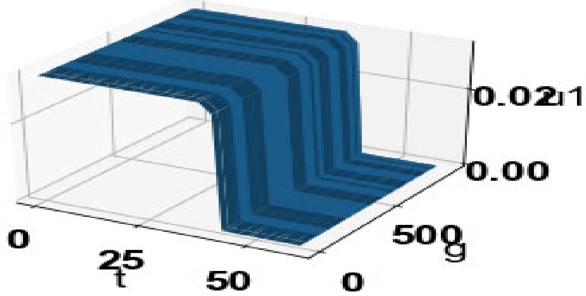

Figure 27: 3 controls t g u1 surface

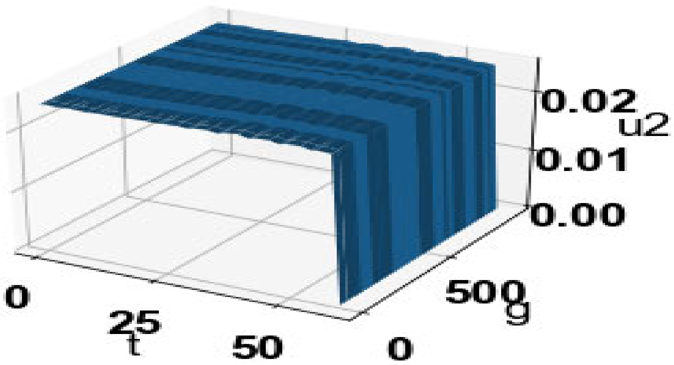

Figure 28: 3 controls t g u2 surface

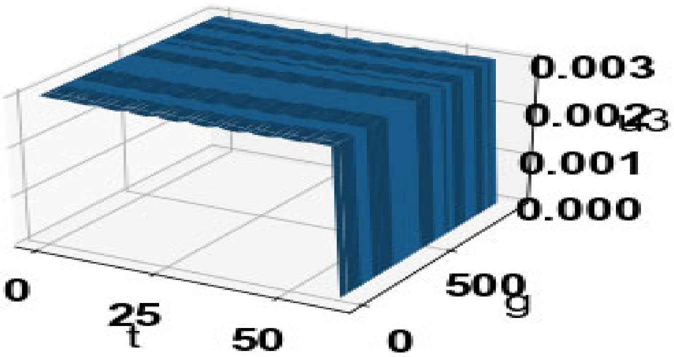

Figure 29: 3 controls t g u3 surface

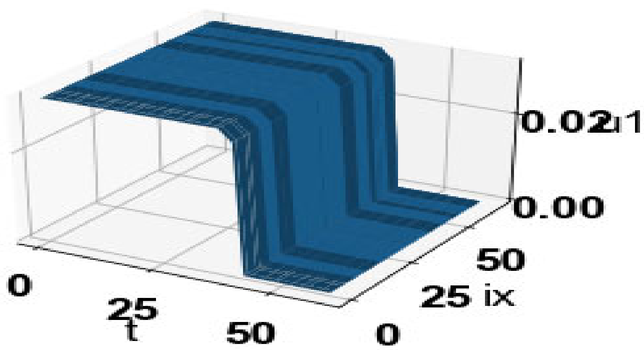

Figure 30: 3 controls t ix u1 surface

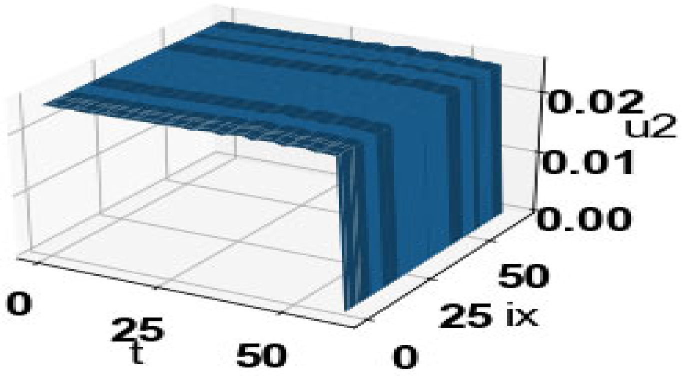

Figure 31: 3 controls t ix u2 surface

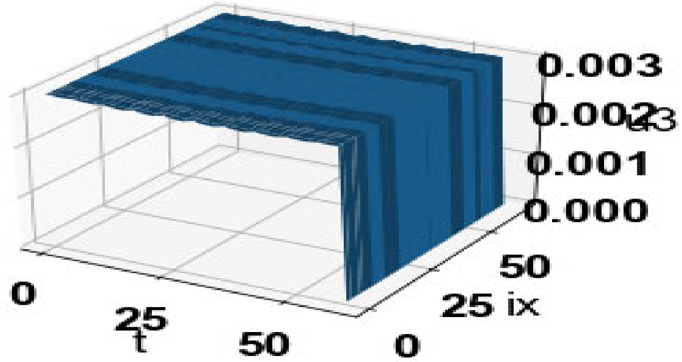

Figure 32: 3 controls t ix u3 surface

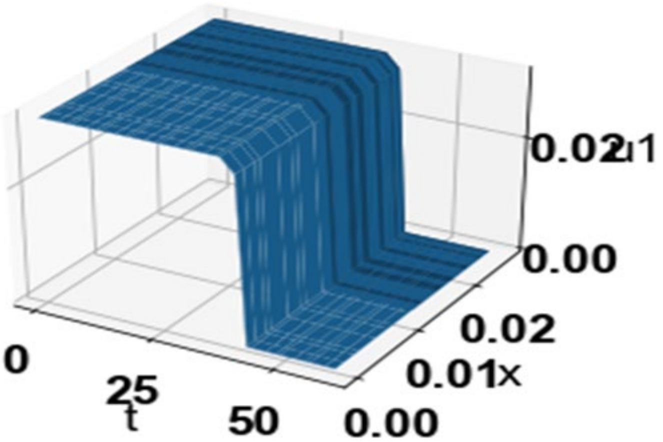

Figure 33: 3 controls t x u1 surface

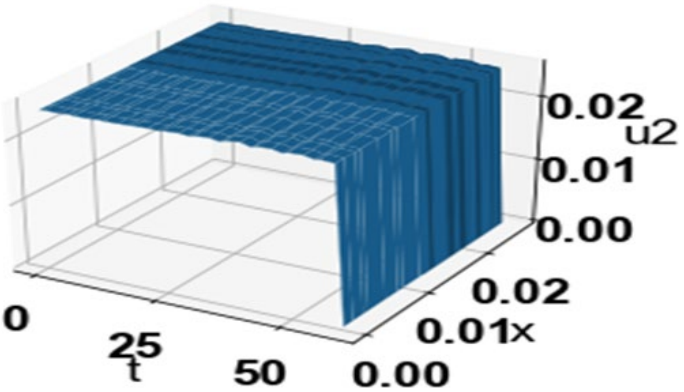

Figure 34: 3 controls t x u2 surface

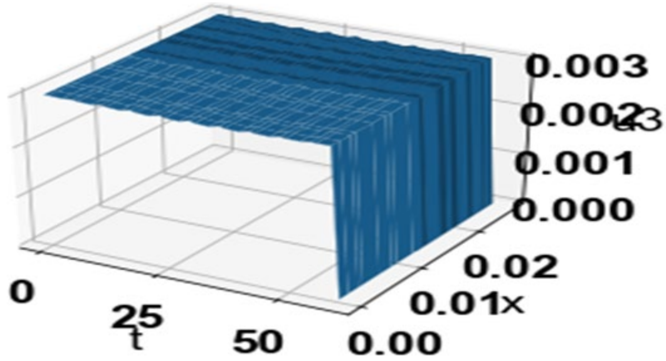

Figure 35: 3 controls t x u3 surface

Conclusions

A rigorous multiobjective nonlinear model predictive control of the diabetes model involving one, two and three control strategies was performed. In the one-control problem, the control profile exhibited spikes making the incorporation of the control strategy difficult. This was remedied by using an activation factor involving the hyperbolic tangent function. Such an activation factor was not needed in the two-control problem. In the three control problem the activation strategy was used as a precautionary measure because of different constraints for the differential equations under different conditions. The results indicate that the use of more than one control strategy was more efficient in minimizing the blood glucose concentration and controlling the damage done by diabetes.

Data Availability Statement

All data used is presented in the paper

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