Blood Glucose Regulation and Control of Insulin and Glucagon Infusion Using Single Model Predictive control for T1DM

Cifha Crecil Dias¹, Surekha Kamath¹⁺, Sudha Vidyasagar²
¹ Department of Instrumentation and Control, Manipal Academy of Higher Education, Manipal Institute of Technology, Manipal, India
² Department of Medicine, Manipal Academy of Higher Education, Kasturba Medical College, Manipal, India
* E-mail: surekha.kamath@manipal.edu

Abstract: This paper elaborates on the design of Artificial pancreas using Model Predictive Control (MPC) algorithm for a comprehensive physiological model like the Sorenson model, which regulates the blood glucose and can have a longer control time in normal glycemic range. The main objective of the proposed algorithm is to eliminate the risk of hyper and hypoglycemia and have a precise infusion of hormones: insulin and glucagon. A single model predictive controller is developed to control the bi-hormones, insulin, glucagon for such a development unmeasured disturbance is considered for a random time. The simulation result for the proposed algorithm performed good regulation lowering the hypoglycemia risk and maintaining the glucose level within the normal glycemic range. To validate the performance of the tracking of output and setpoint, Average Tracking Error (ATE) is used and 4.4mg/dl results are obtained while compared with standard value (14.3mg/dl).

1 Introduction

Diabetes Mellitus is a metabolic disease that is incurable and requires regular monitoring and good control for a good quality of life. The blood glucose of such a patient is always abnormal and may lead to life-threatening risks. Diabetes can be categorized into Type 1, Type 2 and gestational diabetes. Among the three categories Type 1 is said to be quite risky because the pancreatic beta cells are destructed and such a patient is insulin-dependent and external insulin need to be infused in regular regime[1]. The importance of monitoring and regulating the blood glucose level in a diabetic patient is required to avoid the risk of hyper and hypoglycemia. Hyper glycaemia is the condition where blood glucose raises above the normal range and requires insulin to regulate and hypoglycaemia is a condition where blood glucose falls below the normal range and requires glucagon hormone to regulate it[2],[3]. The normal blood glucose range is considered to be 70 – 110mg/dl. Insulin and glucagon are the two pancreatic hormones that play a major role in the regulation of blood glucose[4]. Several types of research are being carried out to include the glucagon in therapies, which could be a challenge because it will be difficult to preserve glucagon for a long time under normal room temperature due to its chemical property[/3],[5]. Even though a Type 1 diabetic patient fails to produce insulin from the pancreas, they still can produce glucagon which makes the design complicated.

Hence controlling and regulation of blood glucose in a diabetic patient is an open research challenge. The commonly used therapy is multiple dosages of injection, where a patient has to calculate the dosage intake manually each time before or after meal[6]. In the existing design of insulin pumps which require sufficient information of meal intake, the amount of carbohydrates intake that makes the design semi-closed loop. For complete automatic or closed-loop control an automatic controller needs to be designed in such a way that if the blood glucose deviates from the desired threshold, the controller needs to take action immediately to maintain in the state of normal glycemic range for a long time[7]. Semi-closed-loop type insulin pumps are those which require manual interruption to set the amount of meal consumed along with the amount of carbohydrate and the bolus is manually calculated and fed into the system[7],[8]. When such a system is used the patient should have complete knowledge on how to calculate the bolus dose for each day, which makes the design complicated. In complete automatic closed-loop control the disturbance is measured and the dose is calculated automatically for the infusion[9]. Unmeasured disturbance at random time should be considered if the controller can regulate the blood glucose varied by unmeasured disturbance. If this attains a good regulation then an Artificial pancreas can be developed using MPC.

MPC is an efficient control strategy developed in recent technology for the control design. This control model predicts the future system outputs, taking into account the past as well as current values, and on proposed control action of the future[10],[11],[12]. It has many unique features which makes it more competitive for blood glucose regulation such as:

• Prediction property that enables for anticipatory and measured insulin delivery.
• This type of strategy can surpass the physiological delays associated with the subcutaneous flow.
• The most important feature of the strategy is the compensation of the dead time, commonly seen in the glucose concentration problem.
• Efficient Feedforward control technique to compensate for the known disturbances, like meal intake or metabolic changes.
• It can easily handle constraints on system inputs and outputs.

The control parameters in the model predictive controller are particularly tuned for a patient. The controller can perform well with no external information like time and quantity of meal intake, providing this information the controller will reach the acceptable performance with feedback and feed-forward controller[13],[14]. The control model collects the data from past inputs as well as outputs and then combines it with the future inputs predicted and gives a predicted output for that particular time. This attained predicted output can be combined with the referral trajectory, then giving the predicted future errors possible by the system[15]. To eliminate the error, the attained error can be fed into an optimizer, which can implement the present constraints of the system on to the predicted outputs and then minimizes the operating cost function[16]. This will give the predicted future inputs, which can be used as feedback of the main model and by restarting the process again[17],[18],[19]. Dual control of insulin and glucagon is easily designed with such an algorithm. In this research, we have considered a comprehensive physiological
model developed by Sorenson, a control algorithm Model predic-
tive control. We have developed a single Model predictive control
for dual model infusion of insulin and glucagon with an unmeasured
disturbance at a random time. Such a method performs a good and
better solution for the regulation of blood glucose. The performance
of the proposed controller is measured using ATE, which gives the
average blood glucose deviated from the threshold. The setpoint is
considered as 90mg/dl and the standard value for the limit where
the blood glucose can deviate for good performance is 14.4mg/dl.

This paper is structured into 6 Sections, in Section 2 Background
Study of existing mathematical model and controller design is being
explained. Section 3 contains problem formulation with a subsection
of mathematical model and control objectives. In Section 4 the MPC
design is formulated which is followed by the Results obtained in
Section 5 and the Concluding remarks in Section 6.

2 Background Study

Every year millions of diabetic patients enhance their eminence of
life through the usage of a device that involves many glucose meters.
The insulin pump plays a role in the functioning of the normal human
pancreas. Currently, the implantable device is used to extend the
quality of life of a human by implanting it in different parts of the
body[20],[21]. The dual control insulin delivery system offers several
advantages over conventional syringe dosages. These devices allow siting specific delivery of insulin or glucagon
required by continuous glucose monitoring[22]. This may also allow
significantly lower doses of insulin, which can minimize potential
side effects. The most important advantage is patient conformity, as
the treatment routine associated with a prototype device is generally
less arduous than pills or injections[23],[24].

Numerous research works has been carried out for type 1 DM by
the essential automated control of the level of blood glucose which
could diminish the load therapy and hence improve the risk factors
associated with it. Model predictive control is the emerg-
ing controller[25]. Though several researches are carried on, the risk
of hyperglycemia and hypoglycemia is a big threat. Enhancement
of such a controller can make the prototype system much robust
and achieve better performance. The model predictive controller pre-
dicts the future output variables using current measurements[26].
The predictions can be predicted for different time delays. Also,
the calculations of the control are mainly based on both predictions done
for future and present measurement and the measured disturbances
are included in the control calculation[27],[28].

Blood glucose monitoring is an imperative technique for people with
diabetes to evaluate their physiological state and take the proper dose
for medication. The good property of detection and quick action of
the controller when the blood glucose level is not in the desired
range could prevent acute brain damage or death[29]. A variety of
technologies are available to assist patients with detecting hypo-
glycaemia and hyperglycaemia separately. To make the controller
completely automatic and avoid the manual calculation of the daily
dosage, there is a need to develop complete closed-loop control,
which is an important research domain.

To obtain this the state of art of Artificial pancreas is shown in figure
1(Fig 1), it consists of a measuring unit for continuous monitor-
ing, a patient model which is developed mathematically, a precise
control algorithm for the infusion of hormones that need to be
developed. The patient model is developed by implanting the
devices, the data is recorded for every 5 minutes and is fed to the
controller[29],[30]. Various plant models mathematically are avail-
able from the previous research. Over the years the behavior of the
interaction of glucose-insulin in a diabetic patient is mathematically
modeled either by an empirical or compartmental technique. In an
empirical process, with the available input-output data without the
physiological knowledge of the system, a model can be developed.
Where in for a compartmental modelling mass balance differential
equations are developed by the interaction of all the components
involved in the physiology[31],[32].

Bergman Minimal Model (BMM) is a nonlinear compartmental
model that comprises of very small number of parameters that could
describe the relationship of the glucose-insulin regulatory system
with adequate accuracy[33],[34]. Sorenson Model (SOM) is the com-
plete model which is composed of 19 differential equations and
describes the action of organs, having to lead to the change in glu-
cose regulation. It also accounts for the glucagon effect which is
opposite to the insulin effect where a dual control can be designed.
Sorenson Model[22] (SoM) is a physiological model that involves all the
changes in the tissues and the organs[35]. This model is been de-
veloped with mass balance equations of the blood flow, the exchange
between the compartmental models and the metabolic process. The
FDA/Food and Drug Administration approved model like Cobelli
was a widely used patient model but failed due to the inability of
varying model parameters during the simulation[36],[37]. Hovorka
model with the 6 states glucose-insulin dynamics is the simplest
nonlinear model which can be used as patient model[38],[39]. The
state represents the glucose, insulin, glucagon and the glucose
concentration in plasma[40]. The comparison of a few compartmental
models used for the study and selection of the available model
is shown in Table 1, these models are simulated and studied in the
research work.

![Fig. 1: General closed loop design for blood glucose regulation](image)

Few black boxes and grey box model techniques are introduced
for the implantable development. Mathematical and clinical trials
on the design of artificial pancreas in diabetes, glucose associated
algorithms. Frequently used control algorithms are Proportional-
Integral-Derivative PID, Fuzzy logic, MPC, advanced control theory,
etc. For a single control of hormone, insulin alone is easily designed
and controlled but the limitation is the risk of hypoglycemia is not yet
eliminated.PID control is said to be the standard control
strategy that can be used for the regulation but dual control of insulin
and glucagon is much efficient using the model predic-
tive control eliminating the risk factors of the regulation of blood
-glucose[45],[46],[47]. Many prototype model can be developed by
considering the physiological model with the relevant control
algorithm. The various control algorithms are, they have different
advantages and disadvantages, to explain few

- Relative Proportional Control Law: This algorithm is mainly based
  on the mode of conveyance of insulin in the weighted pro-
portion by strictly limiting the absolute blood sugar level to the
  magnitude of the desired level. This is a semi closed-loop control
  where the simulation of glucose-insulin metabolism makes use of
  the base data and hence detection and elimination of errors would be
  a challenge [48].
- Fully Closed Loop Controller (MPC): In this, the algorithm was
  mainly used to reduce the risk of hypoglycemia which uses an on-off
  controller with safety rules. In this, a unique model-based strategy
  to develop one-insulin is considered in an account for the uncer-
  tainty and to ensure safety for hypoglycemia. Since the threat of
  hypoglycemia could occur at any time corrective measures to detect
  hypoglycemia was not considered [49],[50].
- MPC Dual Hormone control: In such a control method, MPC is
  developed to take control of the infusion of Insulin and Glucagon.
  Numerous research is being carried out for dual administration espe-
  cially with the switching technique between the hormones. The
# Table 1: Summary of Evolution of Glucose-Insulin Models

<table>
<thead>
<tr>
<th>Type of Model</th>
<th>Structure</th>
<th>Advantage</th>
<th>Limitation</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergman(1981)</td>
<td>3 states, 7 parameters, 1 glucose compartment and 2 insulin compartment</td>
<td>Gives glucose effectiveness and sensitivity and it is a basic model</td>
<td>Minimal Model</td>
<td>Basis of many glucose model and it can be built easily</td>
</tr>
<tr>
<td>Cobelli(1982)[36]</td>
<td>5 states, glucose subsystem, insulin subsystem, glucagon subsystem</td>
<td>Dynamic model for regulation and enables minimum insulin with insulin peripheral infusion</td>
<td>Not adaptable for all types of diabetes as well normal subjects, Meal input is limited to single carbohydrate</td>
<td>Provides just basis for minimal insulin model</td>
</tr>
<tr>
<td>Sorensen(1985)[39]</td>
<td>19 variables and a nonlinear system, additional compartments like brain, heart, kidney and vascular periphery system is included</td>
<td>Glucagon is modelled as ODE, good mass balance modelling with respect to compartment exchange</td>
<td>The estimation of parameters is from rat done clinically</td>
<td>Glucagon modelling insights for validation, incorporates compartment and blood flow</td>
</tr>
<tr>
<td>Sturis(1991)[29]</td>
<td>6 states, negative feed back loops gives insulin effect on glucose</td>
<td>Introduction to insulin degradation time constant and time delays</td>
<td>Disturbances cannot be separated</td>
<td>Understands oscillation due to feedback loops</td>
</tr>
<tr>
<td>Hovorka(2002)[41],[42]</td>
<td>11 variables, endogenous glucose production model</td>
<td>Evaluated clinically for type 1</td>
<td>Requires correction in fasting and overnight</td>
<td>Good insulin model</td>
</tr>
<tr>
<td>Dallamant(2007) [43],[44]</td>
<td>12 states glucose, insulin subsystem</td>
<td>Can simulate both Type 1 and 2</td>
<td>No input for disturbances, meal input is limited</td>
<td>Validation on exercise and including glucagon model is on process</td>
</tr>
</tbody>
</table>

Switching is done by the measurement to the blood glucose, and if the blood glucose is elevated, the controller infuses insulin and switches to glucagon if the blood glucose is fallen below the threshold. Switching technique like hysteresis switch was developed and added the flexibility to the control design [51],[52]. Optimal switching technique used separate MPC’s giving good performance concerning risks associated with diabetes[53]. Such procedure included known disturbances especially the exercise model, which was modeled. These disturbances were known at what time what amount is affected. But the ultimate aim for a Type 1 DM is any unknown disturbance at random time occurs, and the controller should take action and regulate the blood glucose. Such a controller is developed in our research.

- Fading memory proportional derivative: This algorithm doesn’t require human interaction to enter the venous blood sugar level into the system. It mainly uses an adaptive proportional derivative algorithm which keeps an account on the absorption of the subcutaneous substance. It takes the patient’s total daily requirement initially using first glucose reading by the patient and the patient’s basal insulin rate at the beginning [42].
- PID Controller: This is the most widely used controller used to detect the dynamics of the system. Modeling becomes much simpler and feasible. Few assumptions are considered such as the relationship between insulin and the blood glucose along with the disturbance that affects the blood glucose. The risk of hyperglycemia and hypoglycemia was not relatively detected [54],[55].
- Higher Order Sliding Mode Control: This black box model control technique where it only takes into account the knowledge of the moderate degree of the system and the reasonable bounds of an expression. Because of its nonlinear characteristic, it spans of the target system. It is designed in such a way that it does not depend on the parametric or the uncertainties in the system model, which provides robustness [42].
- Fuzzy Logic Control: PID-FLC is an effective strategy that takes into account all the components that are necessary and reacts to the possible changes in glucose concentration in the human body. It helps to raise the patients quality of life and reduces the occurrence of hypoglycemia and hyperglycemia by keeping the glucose level in the ideal range [42].

To address this issue this research is being carried on for bihormonal control with insulin and glucagon infusion and maintain normal glycemia for a longer time. Such a control algorithm is developed in our research using MPC control and Sorensen model. In choosing an appropriate mathematical model various criteria are used to ensure the implementation: "Complexity of the model", "Related
meal model", "Validated by literature", "Modifiability" and "Accessibility". In choosing a model a decision matrix was used as shown in table 2, Where,  

- Complexity (+) means: appropriate for realization and (-) means: Too complex.
- Related meal model (+) means: available and (-) means no meal model.
- Validated (+) means: used in research and (-) means: not used in research studies.
- Modifiability (+) means: can modify for type 2 and (-) means: cannot be modified.
- Accessibility (+) means: unrestricted access to the original model and (-) means: limited access.

After the evaluation of the decision matrix, the Sorenson model was considered to be the most appropriate model for the implementation in further work. Though the model is complex it has a meal model, it is validated in the literature and research, easy to modify to type 2 model and the major advantage is, it incorporates the glucagon model. Other models need extra development of glucagon model for the bihormonal development. The selection of plant models from the above criteria helped in efficiently choosing the plant model for the further development of the Artificial Pancreas using MPC.

3 Problem Formulation

In this section, a brief introduction and modeling of a comprehensive physiological Sorenson model for Type 1 Diabetes (T1DM) are presented with Ordinary Differential Equation (ODE). Next Section describes the control algorithm and the main objectives are stated and formulated.

3.1 Mathematical Model

We have considered a comprehensive model which consists of a glucose, insulin and glucagon model in ordinary differential equation form. The entire model is simulated for few cases like an empty stomach, with meal, with bolus and the difference of each is observed and the steady-state analysis of the model is checked for the Sorenson Model. The model is linearized and the state-space model of it is considered for the control algorithm development [38],[39],[40]. We have considered a continuous time model:

\[ x'(t) = Ax(t) + Bu(t); y(t) = Cx(t) + Du(t) \]  

(1)

Where A is the state matrix, B is the input Matrix, X are the states of the model, y is the output, C is the output matrix and D is the feed-forward matrix. The Sorensen model (Sorensen, 1985) is an extensive non-linear model consisting of eleven ODE to describe the glucose subsystem, ten ODE to describe the insulin subsystem and one ODE to describe the glucagon subsystem. However, three ODE of the insulin subsystem describes endogenous insulin production and secretion which are to be omitted for the T1DM condition. The number of equations and sub equations make the model hard to comprehend. Therefore, the Sorensen model was rewritten to state-space form while incorporating all sub equations in their corresponding equation and grouping parameters as much as possible. The Modified and Linearised state-space equation are given below:

\[ G^*_G = 0.901(G_H - G_G) \]  

(5)

\[ G^*_L = 0.099G_H + 0.402G_G - 0.501G_L + 2.755M^*_HGP - 5.299f_2 - 8.467M^*_HGU + 4.354G^*_6 \]  

(6)

\[ G^*_K = 1.53(G_H - G_K) \]  

(7)

\[ G^*_PV = 1.451G_H - 2.748G_PV + 1.296G_PRI \]  

(8)

\[ G^*_PI = 0.2G_PV - 0.204G_PRI - 0.007I_PRI \]  

(9)

\[ M^*_HGP = -0.04M^*_HGP + 0.077I_L \]  

(10)

\[ M^*_HGU = -0.04M^*_HGU + 0.002I_L \]  

(11)

\[ f^2 = -0.045f_2 - 0.006I \]  

(12)

\[ I^*_H = 1.73(I_H - I_B) \]  

(13)

\[ I^*_H = 0.454I_H + 0.909I_L + 0.727I_K + 1.061I_PV - 3.154I_H \]  

(14)

\[ I^*_G = 0.765(I_H - I_G) \]  

(15)

\[ I^*_L = 0.094I_H + 0.378I_G - 0.789I_L \]  

(16)

\[ I^*_K = 1.411I_H - 1.835I_K \]  

(17)

\[ I^*_PV = 1.418I_H - 1.874I_PV + 0.455I_PRI \]  

(18)

\[ I^*_PI = 0.05I_PV - 0.111I_PRI + U_1 \]  

(19)

\[ \Gamma^* = -0.08\Gamma - 0.0000069G_H + 0.0016I_H + U_2 \]  

(20)

The parameter description is is briefed in appendix. The state vector considered is

\[ x = [x_1, x_2, ..., x_19]^T \]  

(21)

The control input

\[ U(t) = [U_1(t), U_2(t)]^T \]  

(22)

where U_1(t) is insulin and U_2(t) is the glucagon input variable and U_1(t) \geq 0 is infused exogenously with rate (mU/min) and U_2(t) \geq 0 is also infused exogenously with rate (mg/min). The disturbance is considered to be unmeasured at a random time to develop the control algorithm but for the model check, the disturbance is considered to be the meal intake in terms of grams. The output i.e the amount of glucose in the body is measured at the state
variable $G_{DI}$ glucose at the periphery region. The steady-state analysis of the model is checked when the inputs $U_I(t) = U_G(t) = 0$ and such a condition is called a basal condition for a diabetic patient. This condition is totally dependent on the model parameters and the glucose level can be observed with the initial conditions of each state.

- **Case 1: Complete Model simulation of Sorenson**
  The figure 2 shows the complete simulation of the Sorenson model includes the entire differential equation of each compartment for steady-state analysis. Simulation is done with MATLAB 2018 software. The x-axis represents the time in minutes and the y-axis represents the blood glucose, insulin, and glucagon compartment parameters. The blood glucose of different parts is measured with mg/dl, insulin is measured with mU/min and the glucagon is measured with mg/min. It is observed that the entire system attains steady state within 800 minutes. A disturbance of meal and input of insulin is also included in the design to check the steady-state analysis. The individual parameter can be examined by plotting the graph to observe the changes with and without a meal as well as the input as insulin.

- **Case 2: Simulation of Sorenson Model for empty stomach**
  The model is simulated for an empty stomach condition, in a T1DM usually the blood glucose level will be high and they don’t produce insulin to regulate the blood glucose level. Figure 3 shows the glucose simulation of the model in an empty stomach, the x-axis represents the time in minutes and the y-axis represents the blood glucose in mg/dl. It is observed that the blood glucose is above the normal range and it remains high throughout, the measured blood glucose level is 145 mg/dl. When observed in figure 4 the insulin in body is zero, this is because the pancreas lacks the production of insulin in T1DM. The x-axis is time in minutes and the y-axis is units per minute. There is some amount of glucagon secreted in the body and it is observed in figure 5. The x-axis is time in minutes and the y-axis is mg per minute. To regulate this blood glucose level for a normal range infusion of insulin is necessary.

- **Case 3: Simulation of Sorenson Model with meal intake**
  In this case, some amount of disturbance in terms of the meal is been given, the amount of meal intake is 50 mg, for the disturbance induced in figure 6 we observe the changes in the blood glucose level. The induced food requires some time to digest and the delay is seen in the beginning. The blood glucose level slowly increases as the effect of disturbance is being sensed. It is observed that blood glucose is raised with respect to the meal intake to 160 mg/dl. This increase in blood glucose also keeps increasing at the high level due...
Fig. 4: Simulation of Sorenson Model for empty stomach-Insulin plot

Fig. 5: Simulation of Sorenson Model for empty stomach-Glucagon plot

Fig. 6: Simulation of Sorenson Model with meal intake-Glucose

Fig. 7: Simulation of Sorenson Model with insulin infusion-Glucose

to absence of insulin infusion, the next case is explained with the infusion of insulin. The insulin in body still remains the same as in figure 4 and the glucagon also remains the same as observed in figure 5.

• Case 4: Simulation of Sorenson Model with insulin infusion
For a T1DM external infusion of insulin is required for regulating the blood glucose level and maintaining it within the threshold range. In figure 7 we observe the decrease of blood glucose level when insulin is given as an external source. The blood glucose range is 140 mg/dl and decreases due to the effect of insulin and once the effect on the body decreases the blood glucose level again increases above the normal range. In figure 8 we observe the infusion of insulin in mU per minutes, some amount of insulin is infused to bring down the elevated blood glucose. It is said that, 1 Unit of Insulin can decrease 50 mg/dl of blood glucose in body. In figure 9 it is observed that glucagon is decreased when compared with the previous cases. Glucagon is an counter hormone used for regulation, when insulin is conveyed the glucagon decreases. Hence to continuously maintain the blood glucose within the threshold a good controller need to be developed.

• Case 5: Comparison of individual cases together
All the 3 cases are compared together in figure 10 to observe the difference in the blood glucose level in an empty stomach, with only meal as a disturbance and with an infusion of insulin. From this comparison, we can conclude that it is very necessary to develop a good controller that can predict the blood glucose level and take immediate action in regulating blood glucose. The three conditions are in the basal condition with attained initial condition. This model physiology is and the working condition is mimicking the semi closed-loop condition, hence such a model is used further to develop the MPC algorithm.

3.2 Control Algorithm Developed
A MPC algorithm is formulated by considering two main goals:

1. Predict the blood glucose level
2. Take immediate action to regulate the blood glucose level

The MPC algorithm is designed to predict the blood glucose level and take immediate action to regulate it. This algorithm is further used to develop the MPC algorithm.
The main aim is to regulate blood glucose and have control by eliminating the risk of hyperglycemia and hypoglycemia for a longer time, irrespective of random disturbance. The infusion of insulin and glucagon should be precise and limited.

The proposed work uses a linear state space plant model, under which a linear MPC algorithm is developed. An MPC uses a linear model to calculate glucose concentration predictions. The linear approximation in MPC is used when calculating the predictions because it is simpler and faster than using the non-linear model. It is important that the calculation is fast since new computations are made within the short interval\[17],[18]. MPC has a standard technique to be followed, the MPC controller is developed with respect to the model used, the model used is a linear model, hence we went for a direct linear MPC approach. MPC technique is just not confined to one single technique rather it has a different range of methods to be controlled to a process model by the best minimization of the objective function\[56],[57]. The summary of model predictive control is:

- With the process model the output can be predicted at future horizon.
- With the help of control sequence the objective function can be minimized.
- A receding horizon strategy is used where only the first move is calculated and fed this strategy applies the primary control signal to form at each instance.

The implementation for the plant is by the linearised control which is an added advantage. The advantage of using linear prediction is that a linear model can be more robust where an optimization problem based on a non-linear model. Few advantages of MPC is. Even with the lesser knowledge of the process model the tuning of the parameters is easy. Variety of process either simple or complex dynamics can be controlled with the strategy. Multi variable cases can be implemented easily. Compensation with the dead time is done in a natural way. By inducing the feed forward technique the disturbances that can be measured can be compensated. Constraints in the design can be easily added. The prediction property of the strategy makes the design very useful to eliminate the error\[18],[19].

In this section, the model used only to describe the dynamic relationship between insulin, glucose and glucagon. Thus, this model treats meals as unmeasured, unmodeled disturbances\[37]. Here the state at a certain time \( t_{k+1} \) is calculated from the state and the insulin infusion rate of the previous time \( t_k \). The glucose concentration, \( y_k \) can be calculated from the state. Consider the state-space model equation \( 23 \) and \( 24 \):

\[
x_{k+1} = Ax_k + Bu_k
\]

\[
y_k = Cx_k + e_k
\]

where:

\( A \) is a \( 19 \times 19 \) state matrix, \( B \) is a \( 19 \times 2 \) input matrix, \( C \) is a \( 1 \times 19 \) output matrix, \( e_k \) is the difference between the actual glucose and the predicted glucose. The prediction is from \( x_{k|k-1} \) state at the time \( t_{k-1} \). Now the glucose concentration for the next time measure can be predicted by using this error to calculate the next state. For the next \( j \) time measurements, the glucose concentration can be predicted by using the state-space model with no noise term. In the case of any model if this term is not used then the model can be predicted with a small noise term.

\[
x_{k+1|k} = Ax_{k|k-1} + Bu_{k|k}
\]
\[ \dot{y}_{k+1|k} = C\hat{x}_{k+1|k} \]  
\text{(26)}

For the j measurements: where \( j=1,2,3,\ldots, N-1 \), N is the prediction horizon.
\[ \dot{x}_{k+1+j|k} = A\hat{x}_{k+1+j|k} + B\hat{u}_{k+j|k} \]  
\text{(27)}

\[ \hat{y}_{k+1+j|k} = \hat{C}\hat{x}_{k+1+j|k} \]  
\text{(28)}

The optimal glucose concentration should be as close as possible to the threshold. That is the preferable level of glucose, called normoglycemia, a person should have in a fasting state. The optimal insulin infusion rate is now estimated to minimize the least-squares difference between the predicted glucose trajectory and the set point[54]. This is the objective function in equation 29 which will be minimized for each time measure. To prevent too large changes in the insulin infusion rate, a damping parameter, \( \lambda \) is introduced[18]. It is multiplied with the difference, \( \Delta u_{k+j|k} \) between the insulin infusion rate at time \( t_{k+j} \) and \( u_{k+j|k} = u_{k+j|k} - u_{k+j|k-1} \).

The objective function is given as:
\[ \phi = \frac{1}{2} \sum_{j=0}^{N-1} \|y_{k+1+j|k} - r_{k+1+j|k}\|^2 + \lambda \|u_{k+j|k}\|^2 \]  
\text{(29)}

Where \( r_{k+1+j|k} \) is the set point at time \( t_{k+1+j} \) so \( r \) is the desired glucose level, which may or may not be varying time. The predicted glucose concentration in the objective function has to be constrained, since these are the model predictions. The glucose concentration predictions only depend on \( \hat{x}_{k|k-1}, y_{k} \) and the insulin infusion rates. The \( u \) which is the manipulated variable has 2 control variables \( U_{1} \) and \( U_{2} \) which is infusion of insulin and glucagon. This means that each state prediction at time \( k \) can be calculated from the prediction made at time \( k-1 \), the error term, and the predicted insulin infusion rate from time \( k \) to time \( k + N \). This will now be shown for \( N = 4 \).

For the 1st step prediction the output is given as
\[ \hat{y}_{k+1|k} = C\hat{x}_{k+1|k} \]  
\text{(30)}

By substituting equation (25) in equation (30) we get the output as:
\[ \hat{y}_{k+1|k} = C(A\hat{x}_{k|k-1} + B\hat{u}_{k|k}) \]  
\text{(31)}

For \( j=1 \)
\[ \hat{x}_{k+2|k} = A\hat{x}_{k+1|k} + B\hat{u}_{k+1|k} \]  
\text{(32)}

\[ \hat{y}_{k+2|k} = C\hat{x}_{k+2|k} \]  
\text{(33)}

For value of \( \hat{x}_{k+1|k} \) and \( \hat{x}_{k+2|k} \) the previous equation values can be substituted. For \( j=2 \)
\[ \hat{x}_{k+3|k} = A\hat{x}_{k+2|k} + B\hat{u}_{k+2|k} \]  
\text{(34)}

\[ \hat{y}_{k+3|k} = C\hat{x}_{k+3|k} \]  
\text{(35)}

For \( j=3 \)
\[ \hat{x}_{k+4|k} = A\hat{x}_{k+3|k} + B\hat{u}_{k+3|k} \]  
\text{(36)}

\[ \hat{y}_{k+4|k} = C\hat{x}_{k+4|k} \]  
\text{(37)}

For \( j=4 \) For \( j=3 \)
\[ \hat{x}_{k+5|k} = A\hat{x}_{k+4|k} + B\hat{u}_{k+4|k} \]  
\text{(38)}

\[ \hat{y}_{k+5|k} = C\hat{x}_{k+5|k} \]  
\text{(39)}

From these calculations it is seen that for an 1 step prediction at time \( k \), where \( i \leq N \) the prediction of the glucose concentration can be calculated directly from the prediction of the state at time \( k \), the error and all the previously predicted insulin infusion rates as shown in equation 40:
\[ \hat{y}_{k+1+i|k} = CA^i\hat{x}_{k+1|k} + HI\hat{u}_{k+i|k} + H_{i-1}\hat{y}_{k+i+1|k} + H_{i-2}\hat{u}_{k+i+2|k} + \ldots + H_{1}\hat{u}_{k+i+1|k} \]  
\text{(40)}

Expanding the equation 40 in matrix form:
\[ \begin{bmatrix} \hat{y}_{k+1|k} \\ \hat{y}_{k+2|k} \\ \hat{y}_{k+3|k} \\ \hat{y}_{k+4|k} \end{bmatrix} = \begin{bmatrix} CA \\ CA^2 \\ CA^3 \\ CA^4 \end{bmatrix} \begin{bmatrix} \hat{x}_{k|k-1} \\ H_{1} \\ H_{2} \\ H_{3} \end{bmatrix} + \begin{bmatrix} \hat{u}_{k+1|k} \\ \hat{u}_{k+2|k} \\ \hat{u}_{k+3|k} \end{bmatrix} \]  
\text{(41)}

We can consider: \( \begin{bmatrix} CA \\ CA^2 \\ CA^3 \\ CA^4 \end{bmatrix} \) as \( \Phi \) and \( \begin{bmatrix} H_{1} \\ H_{2} \\ H_{3} \end{bmatrix} \) as \( \Gamma \)
and the above equation 41 can be written as:
\[ Y_{k} = \Phi \hat{x}_{k|k-1} + \Gamma U_{k} \]  
\text{(42)}

while considering the infusion of the insulin and glucagon the infusion rates should be within the physical limits and this type of implementation is Constrained MPC with constraint added to the manipulated variables. u for general form with constraints can be considered as:
\[ u_{\min} \leq u_{k+j|k} \leq u_{\max} \]  
\text{(43)}

By considering \( U \) with 2 manipulated variable and for \( N=4 \) can be expressed as:
\[ U_{\min} \leq U_{k} \leq U_{\max} \]  
\text{(44)}

where:
\[ U_{\min} = \begin{bmatrix} u_{k+1|k} \\ u_{k+2|k} \\ u_{k+3|k} \end{bmatrix} \]  
\text{(45)}

By using these constraints it can, for instance, be ensured that the insulin infusion rate and glucagon infusion are never negative. This is a necessary limit since insulin and glucagon cannot be extracted from the blood. There is also a limit to how much the insulin infusion rate should be changed between two consecutive time measures[56],[57]. This means that there should be similar constraints on \( \Delta u_{k+j|k} \). The constraints on the difference between the insulin infusion rate at two consecutive time measures can now be re-written to linear constraints containing \( U_{k} \) so it can be inserted into the optimization problem[19]. The two boundaries for \( \Delta U_{k} \) are called \( \Delta U_{\min} \) and \( \Delta U_{\max} \), respectively. The constraints for the rate of flow for infusion are given in equation 46:
\[ \Delta U_{\min} \leq \Delta U_{k} \leq \Delta U_{\max} \]  
\text{(46)}

The constraints are developed based on the manipulated variables. Output of the system and the rate of infusion of insulin and glucagon. The control strategy for automated insulin delivery is through enhancement of model predictive control. Such a controller can take action on a predicted hyperglycemia or hypoglycemia and even for the hard constraints on input and outputs. A cost function has to be defined for the controller to maintain the regulation of blood glucose[57]. Then an optimal control law is formulated subjected to the prediction model, control inputs and output constraints. The main objective is to avoid and to reduce the occurrence of hyperglycemia and hypoglycemia. The main plant and a process model are connected in parallel. In order to predict the controlled variable,
the MPC uses a dynamic process. The predicted controlled variable is taken as feedback to the controller where it is then optimized, this minimizes a relevant cost function which is used to determine the manipulated variable. The controller output is implemented in real-time for every sampling time with actual process data repetitively. The difference between the plant measurement and the model output is also fed to the controller to abolish the steady-state offset. This cost function usually depends on the quadratic error between the future reference variable and the future controlled variable within a limited time horizon.

MPC strategy in loop Algorithm is shown as flow chart in figure 11:

- Step 1: Measure current state $x_t$ from developed state Matrix of the model.
- Step 2: Compute the cost function by checking the error of the predicted and desired output.
- Step 3: Decision of infusion of insulin and glucagon is calculated by the cost function.
- Step 4: Constraints are put for the infusion of insulin and glucagon and the rate of flow of both.
- Step 5: The manipulated variables are infused according to the correction of error.
- Step 6: Apply Receding Horizon and feed the first control input to the process.
- Step 7: Check the output measurement Blood glucose and take action
- Step 8: Provide feedback by the output measurement to the next step and repeat the algorithm.

Mathematical model used in the research is a physiological model of Sorenson which is derived and clinically tested. The decision of choosing a cost function which is also called as the objective function is very important because the variation in MPC can be clearly seen in the control algorithm. The major aim of developing a control is to ensure that the future output will reach the desired trajectory as close as possible. Finding the solution to the problem using MPC is optimization. This technique minimizes the cost function of the defined problem. The solution obtained from the minimization is the input signal that would make the output of the system to follow the trajectory. The trajectory is set as the $X_{ref}$ reference which is decided in prior and each state has a input reference which is referred as $U_{ref}$. Constraints are the control values or the limitations that is given to the system to execute. The constraints are used usually to maintain or to regulate the output of the system within the required range and for safety[18],[19].

MPC depends on an iterative and finite horizon advancement of a plant model display. Whenever at time $t$, the present plant state is inspected and a cost minimization calculation is done for a moderately brief time horizon in the future $[t, t+T]$. Just the initial step of the control calculation is actualized and after that the plant state is inspected once more. The iterations are repeated from the start point that is the current state till a new predicted value is attained. The prediction horizon keeps being shifted forward and for this reason model predictive control is also called receding control horizon as shown in figure 12[8].

Linear MPC with constraints is developed with following specifications:

- Output of the process: Glucose at Peripheral- we are observing the output at peripheral region, this is because usually a finger prick method is done at the peripheral region. In case an minimal invasive or a Continuous glucose monitoring is used, they are mounted at the peripheral region.
- Manipulated Control variables: Insulin and Glucagon- these are our control variables, externally we infuse insulin to bring down the elevated glucose and Glucagon is infused to rise the blood glucose in order to avoid hypoglycemia.
- Disturbance: Random disturbance of meal (Unannounced Meal)
- Set point: 90mg/dl- this set point is considered as a safe zone, if the blood glucose is maintained at this value the quality of life would be better and this is a normal glycemic region.

- Prediction Horizon:25 sampling time- Prediction horizon is the number of future control intervals the MPC controller must evaluate by prediction while optimizing manipulated variable.
- Control Horizon:15 sampling time- the number of Manipulated variable moves to be optimized at control interval.
- Sampling time:5 minutes-depends on the plant dynamic characteristics, Mainly we choose 5 minutes is because, present CGM records time every 5 minutes and the control action is also taken accordingly. We need to keep in mind the open loop and closed loop simulation too while choosing the sampling time. For any LTI system, controller inherits its time unit from the plant model with Time Unit property.
- Output constraints: $80mg/dl \leq g(k) \leq 120mg/dl$
- Insulin constraints: $0mU/min \leq u_1(k) \leq 80mU/min$
- Glucagon constraints: $0mg/ml \leq u_2(k) \leq 0.5mg/ml$
- Rate of infusion of Insulin: $\Delta U = 16.7mU\ min$
- Rate of infusion of Glucagon: $\Delta U = 0.1mg$

### 4 Results

In this section, the simulation of the MPC algorithm implemented with constraint and parameter values are described in graphical form. The initial conditions are set for the plant and the blood glucose is starting at $110mg/dl$ for the considered model which corresponds to the target that is set by clinical trials. Considering from the data the initial condition in which basal glucose is set to be $100mg/dl$ for a type 1 patient[59]. This is observed in the steady-state analysis without meal intake. The output glucose constraints is considered to be $70 \leq G(t) \leq 110mg/dl$. The control horizon and prediction horizon is considered in sampling instant with 5 mins. The inputs insulin and glucagon are constrained which are associated with objective function. The hormones have the opposite effect in the regulation so that it can be controlled and balanced easily. In our research we have considered the safe range for blood glucose as $70mg/dl – 180mg/dl$ and the stages that of immense threat are:

- Hyperglycemia, is a situation where the excessive amount of blood glucose starts to circulate in the blood, and is identified in two categories:
  - Fasting hyperglycemia is a condition where the blood glucose rises above $130mg/dl$ for 8 hours of fasting.
  - Postprandial hyperglycemia is a condition where the blood glucose rises above $180mg/dl$ after 2 hours of meal intake.
- Hypoglycemia, is a state where the blood glucose becomes lower than the acceptable range and is categorized in two terms:
  - Slight hypoglycemia where the blood glucose range is $55 - 70mg/dl$.
  - Severe hypoglycemia where the blood glucose range is below $50mg/dl$.

The performance of the controller is evaluated with the Average Tracking Error (ATE)[43]

$$ATE = \frac{1}{N} \sum_{n=0}^{N} \frac{|\hat{y} - y_{setpoint}|}{N}$$

(47)

Where $N$ is the number of samples(2000 considered in the research), $\hat{y}$ is the Glucose output, $y_{setpoint}$ is the setpoint (90mg/dl). The simulation is carried out for 2000 minutes nearly for one and a half-day. The implementation of closed-loop is initiated from the first day, while the simulation is being performed unmeasured disturbance is given to the system and the control is observed in figures 13 and 14 concerning real cases. The simulation gives a good performance according to a few existing clinical studies when compared from existing literature. The statistical data for the performance evaluation are shown in table 3 and also the risk ranges are being recorded along with ATE.

- Case 1: Disturbance 1
  Figure 13 is simulated for an unmeasured random disturbance, the
If BG > 120 mg/dl

1. Process Model
2. Acquire data of control, manipulated and disturbance
3. Update model prediction
4. Determine control structure
5. Check for condition

- If BG > 120 mg/dl, go to Basal Infusion of insulin.
- If BG < 80 mg/dl, go to Infusion of Glucagon.

MPC control action

Calculation of set point/target

- Yes: MPC control action
- No: Check output BG

Fig. 11: Flowchart of MPC algorithm

Fig. 12: Receding Horizon Control[58]

The effect of disturbance is observed within 200 minutes. The x-axis represents the time in minutes and the simulation is carried for 2000 minutes which is almost for 1 and a half days. The subplot represents the simulation of blood glucose level with the unit mg/dl, this is observed through the peripheral region of the system. The control units insulin and glucagon are plotted in the next subplots with the unit mU/min and mg/min respectively. It is observed that the disturbance applied is affecting the system but the control units insulin is brought to zero and the glucagon is infused to regulate the blood glucose level to the threshold. The threshold is considered as 90 mg/dl, and if the blood glucose elevates from the threshold the insulin is infused and when it starts decreasing glucagon is infused and the blood glucose is maintained in the normal glycemic range for a longer time. The performance of the controller is evaluated with ATE, the attained ATE for Case 1 is 4.31 mg/dl. This shows that the controller has taken immediate action and maintained the blood glucose in the normal range for a long time with a deviation of 4.31 mg/dl, wherein the standard value should be within the limit of 14.4 mg/dl.

- Case 2: Disturbance 2
  Retaining the same disturbance and including another disturbance at random time is shown in figure 14. The disturbance is given at 1600 minutes. The performance of the controller is evaluated with ATE, the attained ATE for Case 1 is 4.72 mg/dl. This shows that the controller has taken immediate action and maintained the blood glucose in the normal range for a long time with a deviation of 4.72 mg/dl, wherein the standard value should be within the limit of 14.4 mg/dl.

The statistical data for the performance evaluation with the comparison of two cases are shown in table 3 and also the risk ranges are being recorded along with ATE.

Table 3 Statistic of Control Performance

<table>
<thead>
<tr>
<th>Algorithm used</th>
<th>% BG</th>
<th>% BG</th>
<th>ATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy</td>
<td>&lt; 70mg/dl</td>
<td>&gt; 180mg/dl</td>
<td>mg/dl</td>
</tr>
<tr>
<td>MPC Dual control (Disturbance 1)</td>
<td>0</td>
<td>0</td>
<td>4.31</td>
</tr>
<tr>
<td>MPC Dual control (Disturbance 2)</td>
<td>0</td>
<td>0</td>
<td>4.72</td>
</tr>
</tbody>
</table>

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The table 3 explains the performance of controller using statistical data, the Standard value for ATE is 14.4 mg/dl, while our proposed MPC algorithm tracking performance ATE is 4.3 mg/dl and no cases of hyper glycemia and hypoglycemia is observed throughout the simulation. Hence proposed single MPC for dual control improves the control performance and regulated the blood glucose for long time.

5 Conclusion

MPC has the advantage that it uses predictions of the glucose concentration, so it can react before changes occur. The proposed algorithm Single MPC for dual control shows excellent performance and control from the simulation and the statistical data. The Simulation is designed in such a way that it imitates the clinical trials. To reject disturbances, insulin boluses can be administered simultaneously with the disturbance. MPC infuses the exact amount of bolus required for the correction of the error of blood glucose. Simulations have shown that the Sorenson model with MPC can give a good insulin and glucagon infusion rate with unannounced disturbances, such as changes in insulin sensitivities. Simulation results confirm that the Sorenson model handles changes in the insulin sensitivities well. Here the controller returns the simulated patient to a normoglycemic steady state after the changes. However, with a change in the endogenous glucose production at zero insulin, a parameter in the model, the controller gives few oscillations in glucose concentration. Due to the subcutaneous delay, the glucagon and insulin infusion takes time to increase or decrease the flow. The MPC optimization problem has two sets of constraints, a minimum, and a maximum value for the calculated insulin infusion rate and minimum and maximum value for the change of insulin infusion rate between two consecutive time measures[60],[61]. There is a natural minimum of the insulin infusion rate at zero because insulin cannot be extracted from the blood. The maximum insulin infusion rate should be high to ensure the possibility of giving large insulin boluses. The maximum insulin infusion rates and the constraints on change in the insulin infusion rate should be based on the actual mechanical limitations of the insulin pump.

Using linear predictions give larger irregularities due to the linear approximation, while a non-linear model if used directly would be more accurate. On the other hand, the linear predictions are computed much faster and do not require as much calculation capacity as a non-linear model. This is an advantage when calculations are made in a small computer controlling an insulin pump. The fast calculations are necessary to get a relatively small sample size of 5 seconds. It can be seen from the simulations that MPC gives a better insulin infusion rate profile. MPC gives better results when it is used with a linear Sorenson model. When a disturbance is applied the absorption is dependent on the duration of the Disturbance. Simulations show that the differences in the resulting glucose concentration trajectory are small. Therefore disturbance can be regarded as impulses, which makes it easier for the user in the sense that it is not necessary to know the duration of the disturbance. Hence it is concluded that a single MPC can be used for the dual infusion and control of insulin and glucagon to regulate blood glucose. The ATE is used for performance tracking and shows a good performance by maintaining the normal range.
6 Acknowledgments

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7 References


22 Khalid Benkhadra, Fares Alalabah, Shrikant U Tambhe, Rozalina G McCoy, Larry J Pippy, and Thank Tun Department of Medical Electronics, Kasturba Medical College, Manipal for their extensive support for this research. The authors significantly appreciate and thank the anonymous referees and the editor’s positive and valuable comments that have improved the quality of this research article.
When the glucose, insulin and glucagon concentrations are shown in figure 1,2,3 [39],[40].

8 Appendices
8.1 Mathematical Model

The entire Sorenson model with the model diagram and the equations derived from it is explained below. Dr. John Thomas Sorensen developed a physiologic model using anatomical organ and tissue compartments for simulating glucose metabolism and its regulation by insulin and glucagon in normal man. Mass balance equations were written to account for blood flow, exchange between compartments, and metabolic processes causing addition or removal of glucose, insulin, and glucagon, yielding 19 ordinary differential equations. The body has been divided into six physiologic compartments [39],[40]:

- Brain, which represents the central nervous system
- Heart and Lungs, which represent the rapidly mixing vascular volumes of the heart, lungs, and arteries
- Periphery, which includes skeletal muscle and adipose tissue
- Gut
- Liver
- Kidney

In general, Subscripts distinguish physiologic compartments and, if required, a second subscript is included to indicate fluid spaces within compartments. Superscripts indicate respective models (glucose, insulin, or glucagon). The physiologic process are modelled as metabolic sources and sinks which can occur at a constant rate or at a rate which is mediated in a nonlinear manner by relevant changes in glucose, insulin, and glucagon concentrations which are shown in figure 1,2,3 [39],[40].

![Fig. 15: Representation of Sorensen Glucose model](image-url)

The mathematical patient model given by J.T. Sorensen was divided into three parts: Glucose model, insulin model, and glucagon model each having a set of differential equations for describing its metabolism. The glucose model contains tissues including heart, brain, liver, kidney and muscle where the glucose is used for energy. Glucose excretion by kidney and gastrointestinal tract where the exogenous glucose enters the blood, are also included. The glucose model consists of 8 differential equations describing the glucose metabolism of the body. The insulin model includes subcutaneous tissue as a source for insulin. It is assumed that pancreas completely lacks the insulin production. Removal and degradation of insulin occurs mostly in liver, kidney and peripheral tissue, they degrade one-half, one-third and one-sixth, respectively, of the insulin presented to them, regardless of the plasma concentration of insulin. The glucagon model is a little simplified as compared to the Glucose and Insulin Model consisting of a single differential equation modelled as shown below. When the glucose, insulin and
glucagon model are converted into a subsystem, and the intercon-nections between them are made, then a complete Sorensen model is obtained. Mass balance equations were written to account for blood flow, exchange between compartments, and metabolic pro-cesses causing addition or removal of glucose, insulin, and glucagon, yielding 19 differential equations.

Mass balances for the glucose model result in a set of 8 simulta-neous ordinary differential equations which are nonlinear as a result of metabolic source and sink rates. In addition, it is through these metabolic rates which depend on insulin and glucagon concentra-tions that the glucose model is coupled to the insulin and glucagon models, respectively. The mass balance equation of glucose model is given below:

**BRAIN:**

\[
V^G_L \frac{dG^L}{dt} = Q^G_A(G^H - G^L) + Q^G_B(G^L) + Q^G_P(G_pv) + S_{HGP} - \sum BGU
\]  

**KIDNEY:**

\[
V^G_K \frac{dG^K}{dt} = Q^G_A(G^H - G^K) - \sum RBCU
\]

**PERIPHERY:**

\[
V^G_P \frac{dG^P}{dt} = \frac{V^G_P}{TP}(G_{PV} - G^P) - \sum PGU
\]

Where,

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Variable description for Glucose Subsystem [6]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
<td>Description</td>
</tr>
<tr>
<td>G</td>
<td>Glucose concentration</td>
</tr>
<tr>
<td>Q</td>
<td>Vascular water flow rate</td>
</tr>
<tr>
<td>T</td>
<td>Transcapillary diffusion time</td>
</tr>
<tr>
<td>V</td>
<td>Volume</td>
</tr>
<tr>
<td>( \sum )</td>
<td>Metabolic sources nd sink rate</td>
</tr>
<tr>
<td>t</td>
<td>Time</td>
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</table>

<table>
<thead>
<tr>
<th>Table 5</th>
<th>First Subscript: Physiologic Compartment for Glucose Subsystem</th>
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</thead>
<tbody>
<tr>
<td>Variables</td>
<td>Description</td>
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<tr>
<td>B</td>
<td>Brain</td>
</tr>
<tr>
<td>G</td>
<td>Gut</td>
</tr>
<tr>
<td>H</td>
<td>Heart</td>
</tr>
<tr>
<td>K</td>
<td>Kidney</td>
</tr>
<tr>
<td>L</td>
<td>Liver</td>
</tr>
<tr>
<td>P</td>
<td>Periphery</td>
</tr>
<tr>
<td>A</td>
<td>Hepatic Artery</td>
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</table>

<table>
<thead>
<tr>
<th>Table 6</th>
<th>Second Subscript: Physiologic Compartment for Glucose Subsystem</th>
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</thead>
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<td>Variables</td>
<td>Description</td>
</tr>
<tr>
<td>I</td>
<td>Interstitial fluid space</td>
</tr>
<tr>
<td>V</td>
<td>Vascular blood water space</td>
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<table>
<thead>
<tr>
<th>Table 7</th>
<th>Metabolic rate Subscript for Glucose Subsystem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
<td>Description</td>
</tr>
<tr>
<td>BGU</td>
<td>Brain glucose uptake</td>
</tr>
<tr>
<td>GGU</td>
<td>Gut glucose uptake</td>
</tr>
<tr>
<td>HGP</td>
<td>Hepatic glucose production</td>
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<td>HGU</td>
<td>Hepatic glucose uptake</td>
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<td>KGE</td>
<td>Kidney glucose uptake</td>
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<td>PGE</td>
<td>Periphery glucose uptake</td>
</tr>
<tr>
<td>RBCU</td>
<td>Red blood cell glucose uptake</td>
</tr>
</tbody>
</table>

The sources and sinks of glucose subsystem is characterised as:

Mass balances for the insulin formulation result in a set of 7 simultaneous differential equations which are linear except for the liver where the rate of pancreatic insulin release as an insulin source.
term is computed from an additional set of three ordinary differential equations which constitute the model pancreas formulation BRAIN:

\[
V^I_B \frac{dI_B}{dt} = Q^I_B(I_H - I_B)
\]  
(56)

**HEART AND LUNGS**

\[
V^I_H \frac{dI_H}{dt} = Q^I_H B + Q^I_K L + Q^I_P V - Q^H_B I_H + U
\]  
(57)

**GUT:**

\[
V^G_G \frac{dI_G}{dt} = Q^G_I(I_H - I_G)
\]  
(58)

**LIVER:**

\[
V^L_L \frac{dI_L}{dt} = Q^L_A I_H + Q^L_G I_G - Q^L_P I_L + S_{PRI} - \sum LIC
\]  
(59)

**KIDNEY:**

\[
V^K_K \frac{dI_K}{dt} = Q^K_K(I_H - I_K) + \sum KIC
\]  
(60)

**PERIPHERY:**

\[
V^P_P \frac{dI_P}{dt} = Q^P_P(I_H - I_P) + \frac{V^P_I}{T^P}(I_PV - I_P)
\]  
(61)

\[
V^P_I \frac{dI_P}{dt} = \frac{V^P_I}{T^P}(I_PV - I_P) - \sum PIC
\]  
(62)

Where,

### Table 10: Variable description for Insulin Subsystem [6]

<table>
<thead>
<tr>
<th>Variables</th>
<th>Description</th>
<th>Unit</th>
</tr>
</thead>
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<tr>
<td>I</td>
<td>Insulin concentration</td>
<td>mU/dL</td>
</tr>
<tr>
<td>Q</td>
<td>Vascular blood water flow rate</td>
<td>l/min</td>
</tr>
<tr>
<td>d</td>
<td>Transcapillary diffusion time</td>
<td>min</td>
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<tr>
<td>V</td>
<td>Volume</td>
<td>L</td>
</tr>
<tr>
<td>Γ</td>
<td>Metabolic sources nd sink rate</td>
<td>mU/min</td>
</tr>
<tr>
<td>t</td>
<td>Time</td>
<td>min</td>
</tr>
</tbody>
</table>

The sources and sinks of Insulin subsystem is characterised as:

### Table 11: First Subscript: Physiologic Compartment for Insulin Subsystem

<table>
<thead>
<tr>
<th>Variables</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Brain</td>
</tr>
<tr>
<td>G</td>
<td>Gut</td>
</tr>
<tr>
<td>K</td>
<td>Kidney</td>
</tr>
<tr>
<td>L</td>
<td>Liver</td>
</tr>
<tr>
<td>P</td>
<td>Periphery</td>
</tr>
<tr>
<td>A</td>
<td>Hepatic Artery</td>
</tr>
</tbody>
</table>

### Table 12: Second Subscript: Physiologic Compartment for Insulin Subsystem

<table>
<thead>
<tr>
<th>Variables</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Interstitial fluid space</td>
</tr>
<tr>
<td>V</td>
<td>Vascular blood water space</td>
</tr>
</tbody>
</table>

The glucagon model is described using a one compartment formulation that represents the whole body fluid distribution volume for glucagon. Glucagon is cleared from the body at a rate which is a linear function of its plasma level, and glucagon is released from the pancreas as a nonlinear function of arterial glucose and insulin concentrations. The glucagon mass balance equation is given by [6]:

\[
V^G \frac{dI_G}{dt} = S_{PRI} - \sum PTC
\]  
(63)

Where,

### Table 13: Metabolic rate Subscript for Insulin Subsystem

<table>
<thead>
<tr>
<th>Variables</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIC</td>
<td>Kidney insulin clearance</td>
</tr>
<tr>
<td>LIC</td>
<td>Liver insulin clearance</td>
</tr>
<tr>
<td>PIR</td>
<td>Pancreatic insulin release</td>
</tr>
</tbody>
</table>

### Table 14: Superscript for Insulin Subsystem

<table>
<thead>
<tr>
<th>Variables</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Insulin</td>
</tr>
</tbody>
</table>

### Table 15: Sources and sinks of Insulin subsystem

<table>
<thead>
<tr>
<th>Physiologic Process</th>
<th>Rate is a function of</th>
<th>Process is</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smks</td>
<td>Liver clearance</td>
<td>Linear</td>
</tr>
<tr>
<td></td>
<td>Kidney Clearance</td>
<td>Linear</td>
</tr>
<tr>
<td></td>
<td>Peripheral clearance</td>
<td>Linear</td>
</tr>
<tr>
<td>Sources</td>
<td>Pancreatic insulin release</td>
<td>Linear</td>
</tr>
</tbody>
</table>

### Table 16: Variable description for Glucagon Subsystem

<table>
<thead>
<tr>
<th>Variables</th>
<th>Description</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>G</td>
<td>Glucagon concentration</td>
<td>pg/ml</td>
</tr>
<tr>
<td>V</td>
<td>Glucagon distribution Volume</td>
<td>ml</td>
</tr>
<tr>
<td>S_{PRI}</td>
<td>Pancreatic glucagon release rate</td>
<td>pg/min</td>
</tr>
<tr>
<td>PTC</td>
<td>Plasma glucagon clearance rate</td>
<td>pg/min</td>
</tr>
</tbody>
</table>

These Equations are linearised with an operating point and initial conditions are found and the linear equations are developed to get the state model.
8.2 Expansion of variable in figure 2

In figure 2 the legend consists of state variables, these 19 state variables are expanded in the table below and the differential equation from (2 to 20) contains the same state variables these are expanded in the same table. The detailed explanation of the parameters are available in the [29].

**Table 17** Superscript for Glucose Subsystem

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>G</td>
<td>Glucose</td>
</tr>
</tbody>
</table>

**Table 18** First Subscript: Physiologic Compartment for Glucose Subsystem

<table>
<thead>
<tr>
<th>Variables</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Brain</td>
</tr>
<tr>
<td>G</td>
<td>Gut</td>
</tr>
<tr>
<td>H</td>
<td>Heart</td>
</tr>
<tr>
<td>K</td>
<td>Kidney</td>
</tr>
<tr>
<td>L</td>
<td>Liver</td>
</tr>
<tr>
<td>P</td>
<td>Periphery</td>
</tr>
<tr>
<td>A</td>
<td>Hepatic Artery</td>
</tr>
</tbody>
</table>

**Table 19** Second Subscript: Physiologic Compartment for Glucose Subsystem

<table>
<thead>
<tr>
<th>Variables</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Interstitial Fluid space</td>
</tr>
<tr>
<td>V</td>
<td>Vascular blood water space</td>
</tr>
</tbody>
</table>