SYSTEM IDENTIFICATION AND OPTIMAL CONTROL
Course Project 2018/2019
Advanced Mathematical Model of Glucose-Insulin Concentrations and Implementation of Artificial Pancreas for Patients of 1 Diabetes Using Artificial Neural Network Based

Syed Saad Saif, Alessandro Santopaolo

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SAPIENZA
UNIVERSITÀ DI ROMA

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1 Abstract

An Artificial Pancreas was implemented using an Artificial Neural Network that maintains the glucose levels of patients with type 1 diabetes. The neural network takes as input many parameters of the patient's Glucose-Insulin system and calculates the controller output (insulin flow rate) based only on the current values of the Glucose-Insulin system. In other words, the neural network does not take into account the history of the parameters of the patients. First an accurate representation of the Glucose - Insulin system of human body is modelled. The mathematical used here is the Hovorka model (insert reference here). Hovorka utilises a compartment model which represents the glucoregulatory system and includes submodels representing absorption of subcutaneously administered insulin and gut absorption. To generate the data for training our neural network, an reference controller was used. The reference controller employed was Model Predictive Control. The controller samples the glucose system parameters every 15 minutes and gives the insulin flow rate as output. A custom cost function is used that not only minimises the controller effort but also the rate of change to provide a smoother controller output. Moving target trajectory facilitates slow, controlled normalization of elevated glucose levels and faster normalization of low glucose values. Data is then collected from this control scheme for different initial values of glucose concentrations and different meal times and quantities so that the ANN controller can be effective under diverse conditions. The neural network trained uses multilayer feed-forward back-propagation that relates the output to the inputs by hyperbolic tangent sigmoid transfer function and optimized by Levenberg-Marquardt, the training of the ANN was successfull with R is approaching to 1 (R is a measure of the ANN performance. 1 is best possible result). The generated ANN was then used as a controller and the Insulin - Glucose system was simulated, the ANN was successfully able to maintain normoglycemia. In conclusion, ANN is viable for use as an Artificial Pancreas and this methodology provides many advantages over direct implementation of MPC such as faster speed. (add more reasons here)

2 Introduction

Insulin is a hormone that is crucial to the regulation of glucose concentration in the blood, and without it the blood glucose level is often too high (hyperglycemia), which can cause long-term problems like eye, nerve, kidney diseases, and strokes. On the other hand, low blood glucose (hypoglycemia) can cause the patient to fall into coma or have other immediate consequences. Normally in healthy patients insulin is generated in appropriate quantities. Insulin causes glucose to be absorbed by adipose tissue, e.g. muscles and fat. The insulin also makes the liver absorb glucose as glycogen and therefore can regulate the blood glucose concentration. The blood glucose concentration is also affected when the a meal is consumed. The carbohydrates from the meal are absorbed by the body and are converted into glucose in the blood. This causes the blood glucose concentration to increase.

People with type 1 diabetes(also known as insulin dependent diabetes) are not able to produce sufficient amounts of insulin because body's immune system attacks and destroys insulin producing beta cells of the pancreas. Type 1 diabetes patients must take insulin in order to stay alive, either my manually measuring their glucose levels and injecting insulin accordingly or by a insulin pump and an algorithm to determine the required insulin level.

To create an artificial pancreas, several researches from many disciplines as well as control engineering have participated in this commitment to model the control systems. These studies aimed to acquire the best mathematical models that can be used for prediction, simulation, and control in the very complex glucose-insulin systems. Different classical approaches have been proposed but artificial neural networks techniques are more favourable because it can possibly solve complex physiological system like the dynamics of diabetes that are extremely complex in nature and could auto-correct the accuracy to overcome the disturbances [13]. In this work, an advanced mathematical controller will be developed using artificial neural network to determine insulin flow rate to control the glucose-insulin concentrations at specified time.

3 Insulin - Glucose dynamics Hovorka Model

Hovorka Model is made by Roman Hovorka in order to estimate glucose-insulin concentrations of Type 1 diabetes patients, In this section the details of the mathematical model are provided.

3.1 Introduction

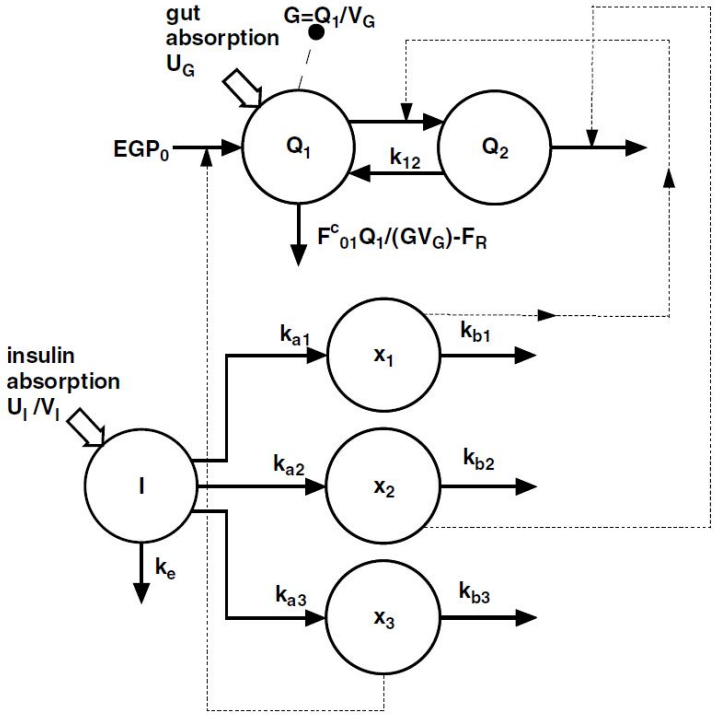

Figure 1: Compartment Model of glucose - insulin System.

In the figure above, $Q1$ and $Q2$ represent masses in accessible (plasma) and non-accessible compartments of glucose, I represents plasma insulin, xi represent insulin action on glucose transport, disposal and endogenous glucose production.

The two compartment model expresses the relation between the insulin injection as an input and the intravenous glucose level which is considered the output of the system. Figure 1 provides the overall view of the system and the interconnection of the various subsystems. The model includes the glucose subsystem (glucose absorption, distribution and disposal), an insulin

subsystem (insulin absorption, distribution, disposal) and an insulin action subsystem (insulin action on glucose transport, disposal and endogenous production).

3.2 Glucose Subsystem

The two mathematical differential equations of the glucose subsystem are as follows.

$$\frac{dQ_1(t)}{dt} = \left[\frac{F_{01}^c}{V_G G(t)} + x_1(t)\right] Q_1(t) + k_{12}Q_2(t) - F_R + U_G(t) + EGP_0[1 - x_3(t)] \tag{1}$$

$$\frac{dQ_2(t)}{dt} = x_1(t)Q_1(t) - [k_{12} + x_2(t)]Q_2(t)y(t)G(t) = Q_1(t)/V_G \tag{2}$$

In the equations above $Q1$ and $Q2$ are the masses of glucose in the accessible and non-accessible compartments respectively. k_{12} is the transfer rate constant from the non-accessible to the accessible compartment, V_G is the distribution volume of the accessible compartment, y and G is the (measurable) glucose concentration, and EGP_0 represents endogenous glucose production (EGP) extrapolated to the zero insulin concentration.

F_{01}^c is the total non-insulin-dependent glucose flux corrected for the ambient glucose concentration.

$$F_{01}^c = \begin{cases} F_{01} & if G \geq 4.4 mmol L^{-1} \\ \frac{F_{01}G}{4.5} & otherwise. \end{cases} \tag{3}$$

F_R is the renal glucose clearance above the glucose threshold of 9 $mmol L^{-1}$.

$$F_R = \begin{cases} 0.03(G - 9) & if G \geq 9 mmol L^{-1} \\ 0 & otherwise. \end{cases} \tag{4}$$

The glucose absorption rate $U_G(t)$ is as follows.

$$U_G(t) = \frac{D_G A_G t e^{-t/t_{max,G}}}{t_{max,G}^2} \tag{5}$$

tmax,G is the time-of-maximum appearance rate of glucose in the accessible glucose compartment, DG is the amount of carbohydrates digested, and AG is carbohydrate bioavailability.

3.3 Insulin subsystem

The differential equation of insulin absorption is as follows.

$$\frac{dS_1}{dt} = u(t) - \frac{S_1(t)}{t_{max,I}} \tag{6}$$

$$\frac{dS_2}{dt} = \frac{S_1(t)}{t_{max,I}} - \frac{S_2(t)}{t_{max,I}} \tag{7}$$

where S1 and S2 are a two-compartment chain representing absorption of subcutaneously administered insulin, u(t) here is the input to the system, i.e the input flow rate of insulin.
The dynamics of insulin concentration are given below.

$$\frac{dI}{dt} = \frac{U_I(t)}{V_I} - k_e I(t) \tag{8}$$

here k_e is the fractional elimination rate and V_I is the distribution volume.

3.4 Insulin Action Subsystem

$$\frac{dx_3}{dt} = -k_{a1}x_3(t) + k_{b3}I(t) \tag{9}$$

$$\frac{dx_2}{dt} = -k_{a1}x_2(t) + k_{b2}I(t) \tag{10}$$

$$\frac{dx_3}{dt} = -k_{a1}x_3(t) + k_{b3}I(t) \tag{11}$$

3.5 Model Constants and Parameters

Table 1. Model constants.

Symbol	Quantity	Value	Source
k_{12}	Transfer rate	0.066 min^{-1}	Hovorka *et al* 2002
k_{a1}	Deactivation rate	0.006 min^{-1}	Hovorka *et al* 2002
k_{a2}	Deactivation rate	0.06 min^{-1}	Hovorka *et al* 2002
k_{a3}	Deactivation rate	0.03 min^{-1}	Hovorka *et al* 2002
k_e	Insulin elimination from plasma	0.138 min^{-1}	Hovorka *et al* 1993
V_I	Insulin distribution volume	0.12 L kg^{-1}	Hovorka *et al* 1993
V_G	Glucose distribution volume	0.16 L kg^{-1}	Hovorka *et al* 2002
A_G	Carbohydrate (CHO) bioavailability	0.8 (unitless)	Livesey *et al* 1998
$t_{max,G}$	Time-to-maximum of CHO absorption	40 min	Livesey *et al* 1998

Table 2. Model parameters.

Symbol	Quantity	Value[a]	Source
${}^*S_{IT}^f$ [b]	Insulin sensitivity of distribution/ transport	51.2×10^{-4} min^{-1} per mU L^{-1}	Hovorka *et al* 2002
${}^*S_{ID}^f$ [b]	Insulin sensitivity of disposal	8.2×10^{-4} min^{-1} per mU L^{-1}	Hovorka *et al* 2002
${}^*S_{IE}^f$ [b]	Insulin sensitivity of EGP	520×10^{-4} per mU L^{-1}	Hovorka *et al* 2002
EGP_0	EGP extrapolated to zero insulin concentration	0.0161 mmol kg^{-1} min^{-1}	Hovorka *et al* 2002
F_{01}	Non-insulin-dependent glucose flux	0.0097 mmol kg^{-1} min^{-1}	Hovorka *et al* 2002
$t_{max,I}$	Time-to-maximum of absorption of subcutaneously injected short-acting insulin	55 min	Howey *et al* 1994, Rave *et al* 1999

[a] Mean value of the parameter for the purpose of Bayesian parameter estimation.
[b] Alternative parameterization ${}^*S_{IT}^f = k_{b1}/k_{a1}$, ${}^*S_{ID}^f = k_{b2}/k_{a2}$ and ${}^*S_{IE}^f = k_{b3}/k_{a3}$.

Figure 2

4 Implementation of MPC Controller

The concept of model predictive control is shown in the figure below.

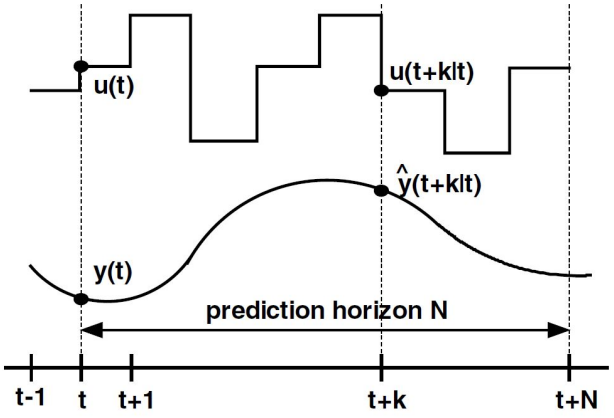

Figure 3: Model Predictive Control

Using the mathematical model of the system the output trajectory $y(t)$ is predicted over prediction horizon N for different control sequences $u(t)$ and a optimal control sequence is selected based on a cost function, here a custom cost function is utilised. Our mathematical model is non-linear and is not linearized around a equilibrium point. Consequently, Non-linear Model Predictive Control Tools are used.

Sampling time period is **15** minutes. Control Horizon of NMPC is **4** and the Prediction Horizon of NMPC is selected **5**. The values are chosen to provide a good balance between the performance of the controller and the processing power required to generate the controller output value. This was a important concern because a lot of data needs to be generated for training the neural network.

The controlled variable of NLMPC is Q1 which is the mass of glucose in accessible compartment of the hovorka model.

The states of the NLMPC are :

$$(Q_1(t), Q_2(t), S_1(t), S_2(t), I(t), x_1(t), x_2(t), x_3(t))^T$$

The output of NLMPC is $u(t)$, insulin flow rate.

Based on the selected options the `nlmpc` function of MATLAB generates the controller output utilising our customised cost function and target trajectory, the details of which can be seen below. The controller output history is saved and is used to simulate the plant. The simulated state variables are also saved for later use in training the neural network.

4.1 Target Trajectory

The target trajectory is generated at each time step using as the starting point the glucose concentration y(t), The target glucose concentration is 0.96 *mmol* . The slope of the target trajectory depends on the position w.r.t the target value. When starting above the target value, the target trajectory is declining with a maximum decrease set to a conservative value of 2 *mmol* per minute to reduce the risk of undershoot. When starting below the target trajectory, there is bigger slope of the trajectory curve and this reflect the need to recover faster from low glucose values, more dangerous for human body.

4.2 Cost Function

The cost function used is of the following form.

$$J = k_y J_y + k_u J_u + k_\delta J_\delta \tag{12}$$

Where J_y puts the cost on the difference from the desired value. J_u puts the cost on the controller output and J_u puts cost on the rate of change of controller outputs.
Where the definitions of the partial cost functions are

$$J_y = \sum_{n=1}^{P} (y_r ef - y(t+i))^2$$

$$J_u = \sum_{n=1}^{P} u(t+i)^2$$

$$J_\delta = \sum_{n=1}^{P} (u(t+i) - u(t))^2$$

4.3 Simulation Results

Using the aforementioned control architecture, the Glucose-Insulin system was simulated under different conditions. The controller was found to be able satisfactorily maintain normoglycemia. The experiments were performed over a period of 300 minutes, three such experiments with random initial conditions are plotted below to allow the reader to visualise the performance of the control scheme.

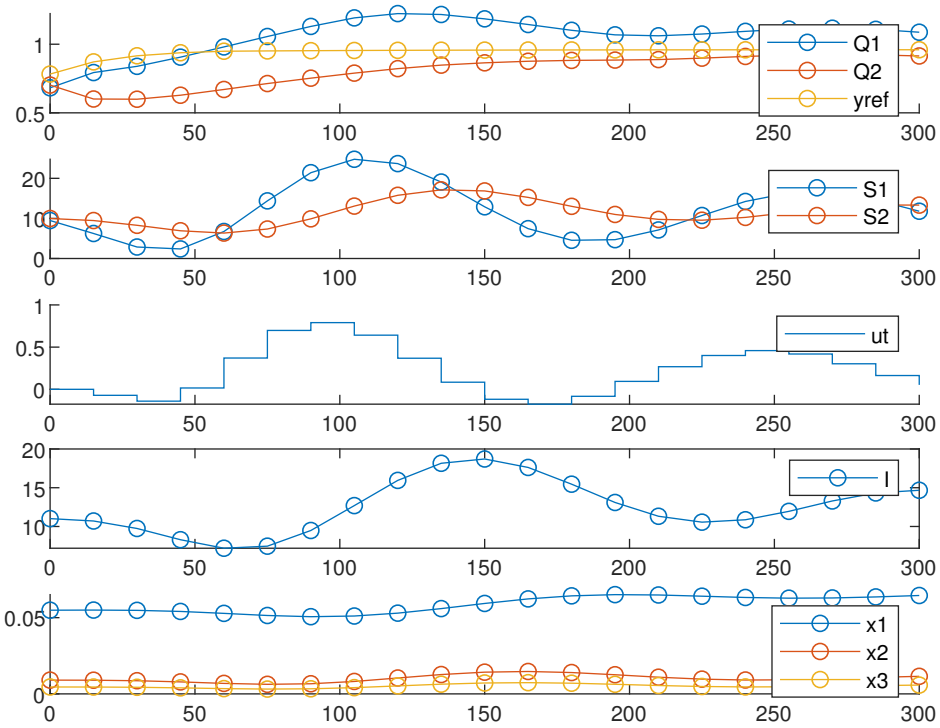

Figure 4: Simulation-1 of Glucose-Insulin System with nlmpc control

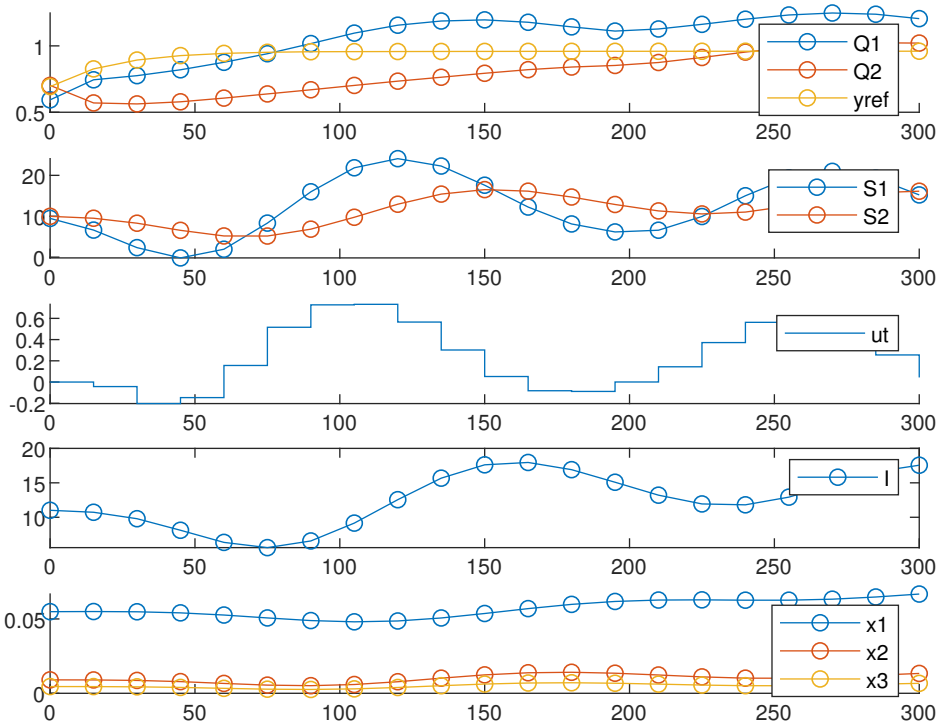

Figure 5: Simulation-2 of Glucose-Insulin System with nlmpc control

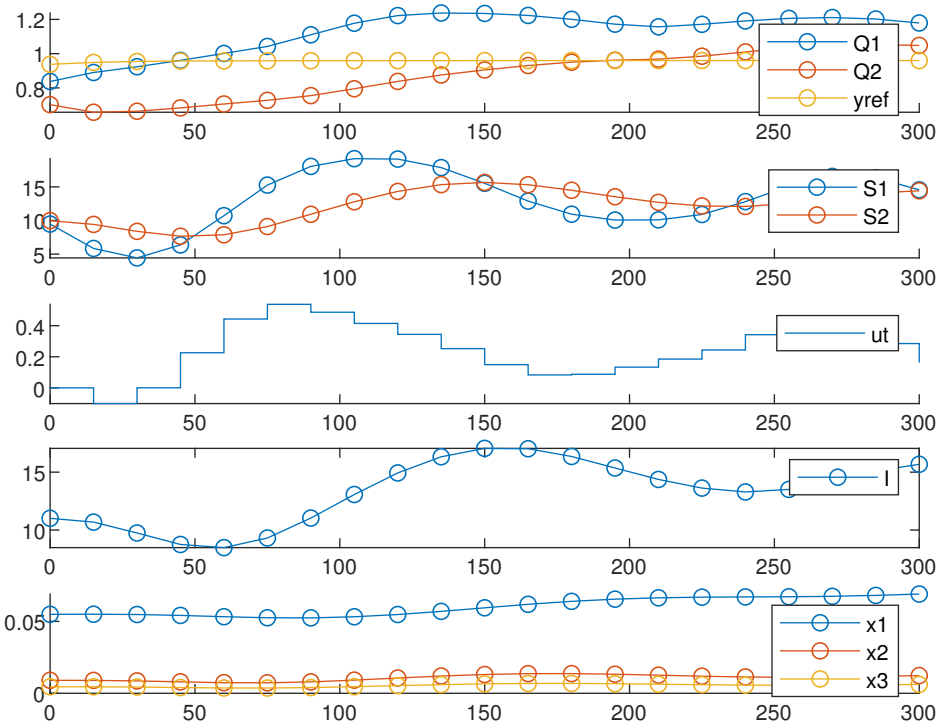

Figure 6: Simulation-3 of Glucose-Insulin System with nlmpc control

The American Diabetic Association recommends that the glucose levels should not exceed 10 $mmolL^{-1}$ after a meal and the fasting condition glucose level should remain above 3.9 $mmolL^{-1}$. these values correspond to the glucose masses of 1.6 $mmol$ and 6.24 $mmol$ respectively for our model. As can be seen that the glucose level Q1 remain within the recommended limits. Apart from the three plots plotted above we have performed simulated further experiments and verified that this limit is not violated.

5 Artificial Neural Network Controller

The data generated from each of the variables has been used as the inputs to the artificial neural network programming.

5.1 ANN Architecture

The architecture of the ANN implemented through the *Machine learning toolbox* of Matlab is described below. The multilayer feed-forward back propagation artificial neural network is build in **5** hidden layers, composed by **5** neurons each. Each node is an adaptive network that executes a static mapping from its inputs to the output. There are no dynamic or internal states in each node which means a node's output depends only on its current inputs. The activation function chosen is the hyperbolic tangent sigmoid transfer function and the optimizer is the Levenberg-Marquardt optimization method.

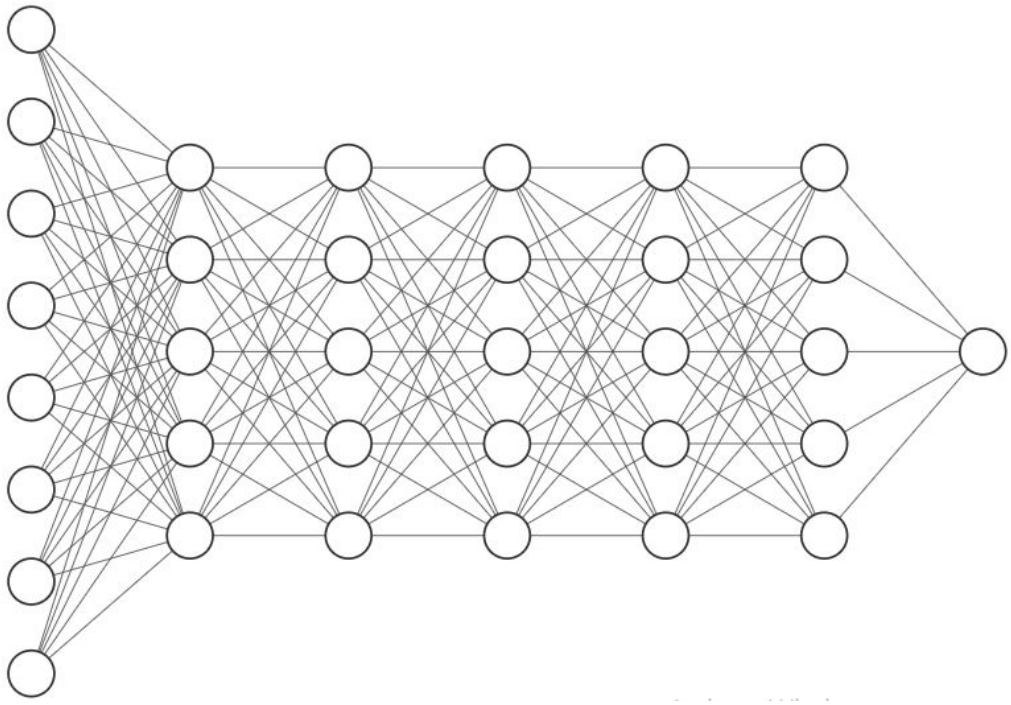

Figure 7: Architecture of the Artificial Neural Network

5.2 ANN Training and Performance

From the nlmpc controller 211 samples of controller outputs and corresponding states were selected. And the neural network was trained using the architecture described in the section above. The data was divided into three parts 70% training, 15% Validation and 15% for the Testing of the Neural Network. With repeated training we were able to achieve an R value of more that 0.99 which represents a very good result. Below we plot the regression graph to demonstrate the neural network quality.

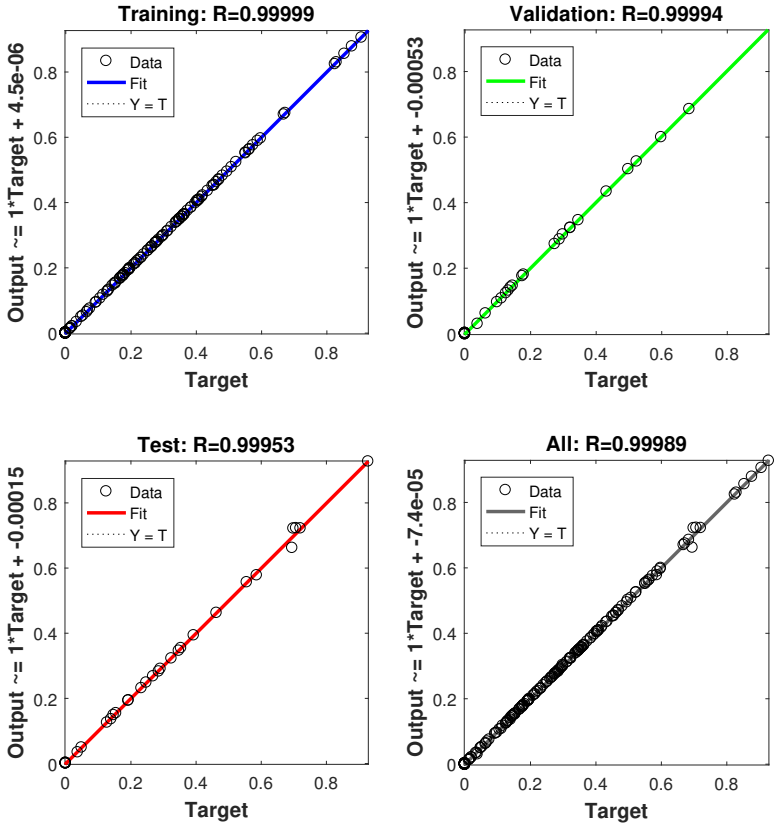

Figure 8: Regression graph for Neural Network

5.3 Simulations with ANN Controller

Finally we use the neural network to control the diabetes patient's model. Below we plot three simulations of glucose-insulin evolution with different initial conditions.

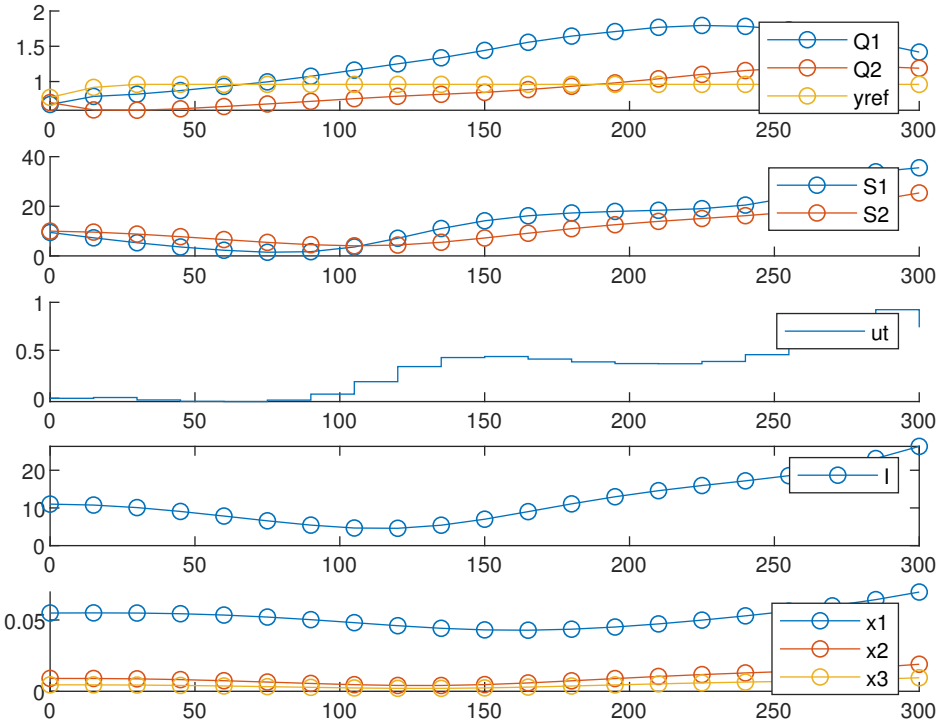

Figure 9: Simulation-1 of Glucose-Insulin System with machine learning control

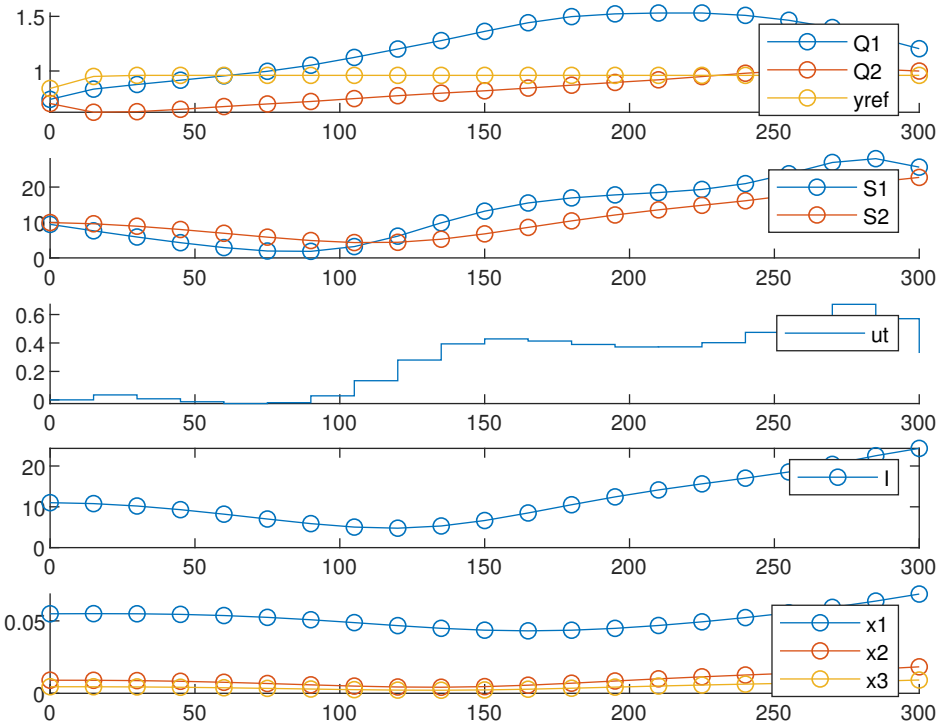

Figure 10: Simulation-2 of Glucose-Insulin System with machine learning control

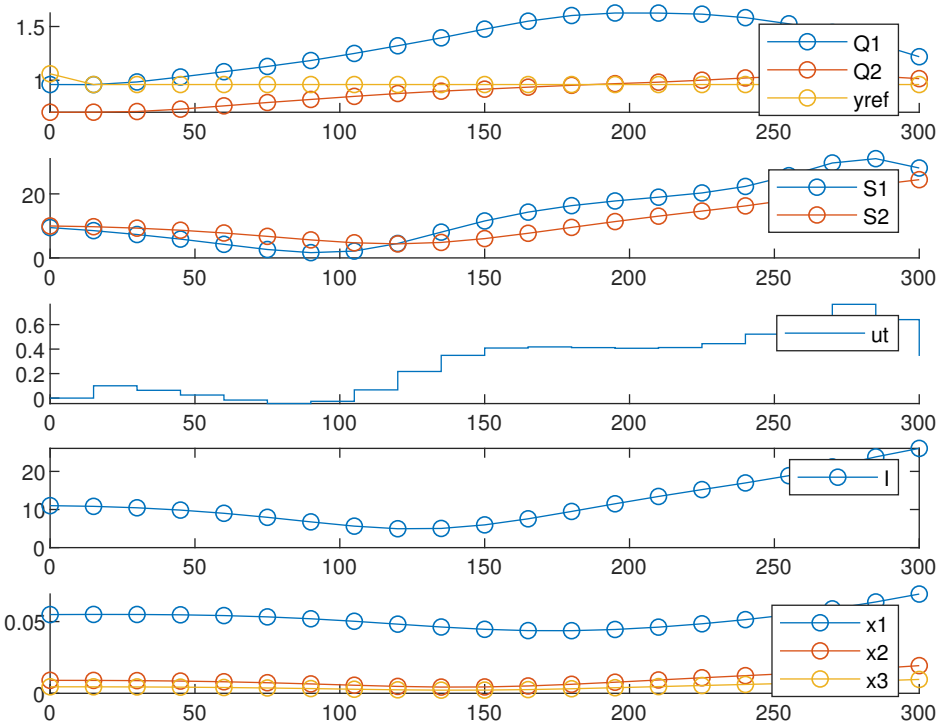

Figure 11: Simulation-3 of Glucose-Insulin System with machine learning control

6 Conclusion

In conclusion, we were able to realise a non-linear model predictive control strategy that was successfully able to maintain normoglycemia in a mathematical model of type 1 diabetes patients during fasting conditions as well as regulate the glucose of the patient after consumption of meals whilst maintaining the glucose mass within safe levels. The system was simulated for various initial conditions to demonstrate that the controller is robust to variations in meal times, meal quantities as well as initial glucose levels of the patient's mathematical model. Furthermore, a an Artificial Neural Network controller was trained using data previously collected from nlmpc controller and the performance of the neural network was verified using Machine Learning performance metrics. Finally, the neural network was used to regulate the glucose levels of diabetes-1 patient's mathematical model and again we were able to verify that the controller was able to robustly maintain glucose levels within safe limits. As a matter of fact, the glucose level regulation of $Q1$ by the nlmpc and ANN Controller was very close to each other. Using ANN to as a controller offers many benefits over conventional strategies.First, ANN based controller is less computationally expensive compared to NLMPC. Recently silicon that is optimised to run ANN efficiently on embedded devices has become available which is suitable for a portable artificial pancreas device. Secondly the same ANN architecture can be modified to run a reinforcement learning algorithm and can provide a even better controller that the one based on NLMPC.

References