IOSR Journal of Engineering (IOSRJEN) **www.iosrjen.org**
ISSN (e): 2250-3021, ISSN (p): 2278-8719
Vol. 10, Issue 4, April 2020, ||Series -II|| PP 30-38

Receding Horizon Control of Blood Glucose Concentration for Type II Diabetes

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Received 21 April 2020; Accepted 06 May 2020

Abstract: In this paper, receding horizon control strategy under model predictive control framework is exploited with the aim to regulate blood glucose concentration for Type II diabetes. The use of model-based control schemes has received a wider acceptance in Biomedical Engineering applications. One of such control schemes is the receding horizon that involves solving a constrained optimization problem repeatedly using past and current state of a system to predict the future control action. Two forms of receding horizon control strategy (Fixed-end and Moving-end) were proposed and applied to a dynamic model. Different disturbance scenarios were generated to evaluate the performance of the two strategies in terms of its efficiency to handle disturbances. The proposed control strategies successfully addressed the issues of the input/external disturbances considered for the patients in a virtual situation and maintained blood glucose level at 80.06 mg/dL.
Key words: Receding horizon control; Blood glucose; concentration; Fixed and Moving-end; model predictive control; type II diabetes.

I. INTRODUCTION

Receding horizon control(RHC) is a type of feedback control mechanism under model predictive control (MPC) that was popular in early1980s [1]. With RHC, a constrained optimization problem is solved at each time step to decide a planof action over a fixed time horizon; then the first input is applied from the plan [2]. The process is repeated to solve a new optimization problem at the next time step, with the timehorizon shifted one step forward [3].

The nonlinear control policy that regulate input/output constraints anddifferent control objectives also known as RHC. In RHC, dynamic systems can be controlled close to their physicallimits while obtaining performances superior to linear control [3]. RHC uses the current glucose concentration and meal input to predict future glucose concentrations [4]. Typically, predictions are made with a linear model. If a high glucose concentration is predicted, more insulin is injected early enough to decrease the glucose concentration to a proper value at the predicted time. RHC predicts the glucose concentration using the insulin infusion rate from only the current time sample.

The optimal insulin infusion rate should then be found to get the best possible predictions.MPC methods found their application in the field ofBiomedical Engineering including clinical anesthesia and diabetes among others [5].The success and efficient conduct of MPCprocedure achieved in these various scientific disciplines, indicates that, MPC methodologies areable to regulate a wide range of systems with great accuracy, for long periods of time [6].Blood glucose regulation (BGC) is now an issue that can be addressed by employing control algorithm that uses the previous and current state measurements of blood glucose concentration to predict the future glucose concentration level and hence compute the actual amount of insulin required.

Despite the usefulness of the model-based algorithms in controlling blood glucose level, state-space models following short insulin tolerance test for diabetics have never been reported in the literature. Moreover, fixed-end receding horizon control has not yet been exploited in research studies involving blood glucose regulation.

1.1 Receding Horizon Control Strategy

Fisher [7] and Ollerton [8] used optimal control theory to obtain the values of input variables u that optimize a cost function J. The change in x (current state vector) is influenced by u on J [9], [10]. The developed optimal control algorithm for linear and nonlinear systems is an extension of RHC as reported in [11], where a fixed-end horizon optimization problem is solved in a sequence of predicted inputs and a prediction horizon is determined by implementation of the first step in the series. The process is repeated by moving a step forward to obtain the prediction time [12].

The methods of RHC is defined by [1] as follows: "At the current time,the optimal control is obtained, either closed-loop type, oropen-loop type on a finite fixed horizon from the current time*k*, say *[k, k + N]*. Among the optimal controls on the entirefixed horizon *[k, k + N]*, only the first one is adopted as thecurrent control law. The procedure is then repeated at the nexttime say, *[k +1, k+1+N]"*.
A typical RHC optimization problem [13] is formulated as follows:

$$\min_{u(0),..u(N)} J = \sum_{k=0}^{N_y} y'(k)Qy + \sum_{k=0}^{N_u} u'(k)Ru(k)$$

$$x(k+1) = l(x(k),u(k))$$

Subject to

$$y(k) = \psi(x(k),u(k))$$

$$x_{\min} \le x(k+1) \le x_{\max}, \qquad k = 0,1,\ldots N_y$$

$$u_{\min} \le u(k+1) \le u_{\max}, \qquad k = 0,1,\ldots N_u \qquad (1)$$

Where: *N* = prediction period, x = current state vector, u = control variable of the system, l = state vector, ψ = output equations, N_y = prediction horizons, N_u = control horizons, Q = deviation weights, R = control variable from the set points, and finally k = is the time step.

The concepts of RHC strategy is shown in Figure 1, where the sequence of control action is obtained by solving an objective function over a finite time horizon [6]. The main advantage of RHC strategy is that it's a model based, hence, physical and operational constraints on state and control variables can be easily handled. These constraints can be considered to calculate the future control action for being an online optimization method [14].

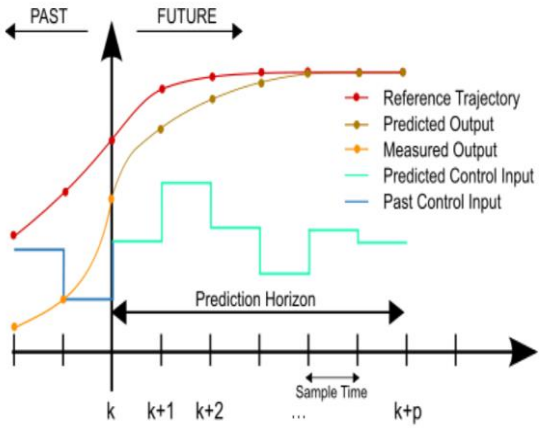


Figure 1: Model predictive control implementation [13].

The strategies of RHC with respect to the prediction horizon are of two types namely; fixed and moving end control strategies. In fixed end RHC, the prediction time equals the entire control period which decreases subsequently as the control advances, while in moving end control strategy, the length of the prediction time remains constant [9], as can be seen in Figures 2 and 3.

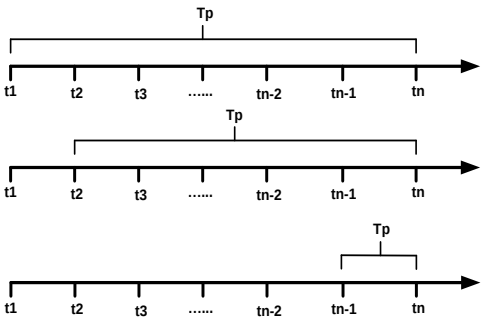


Figure 2: Fixed end receding horizon

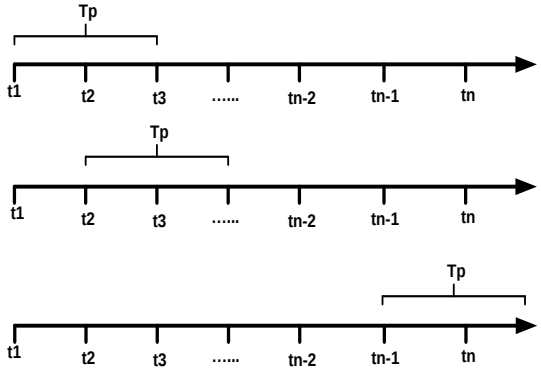


Figure 3: Moving end receding horizon

In this paper, blood glucose concentration is solved over the fixed end, and moving end receding horizon control strategies with the view to developing a control strategy under the model predictive control framework for regulating blood glucose concentration within the range of 70 – 120 mg/dL as recommended by Diabetes Association of Nigeria (2013); American Diabetes Association (2015);[16].

One of the advantages of the proposed control strategies is that they accommodate uncertain parameters (disturbance) which includes large amount of food, like a meal or snack with more carbohydrates than usual, stress which can produce hormones that raise blood glucose levels or too much insulin or oral diabetes medications within the scheduling horizon. Some disturbance scenarios were introduced to evaluate the performances of fixed end and moving end horizon strategies for recommendation to medical and clinical professionals.

II. PROBLEM FORMULATION

2.1 Dynamic model of blood glucose concentration

The interaction of blood glucose concentration in human body can be formulated based on the law of conservation of mass, as follows:

Rate of change = (in – out)/time (2)

From Equation (2), the rate change of glucose concentration can be written as

Rate change of glucose concentration = (Glucose $_{in}$ – Glucose $_{out}$)/time (3)

The rate change of glucose concentration is determined by insulin independent glucose uptake in which the short insulin tolerance test (SITT) was conducted on patients with non-insulin dependent diabetes mellitus within the age range of 25-60 years as reported in [17].

Let G_1 denote the amount of glucose concentration in the body and G_2 denotes the blood glucose concentration at time $t \geq 0$. From the information available, assuming the reaction kinetics follows first order, Equation (3) can be mathematically written as:

$$\frac{dG_1}{dt} = -k_1 G_1 \tag{4}$$

$$\frac{dG_2}{dt} = k_1 G_1 - k_2 (G_2 - G_0) \tag{5}$$

Where G_1 (mg/dL) is the glucose concentration in the body, G_2 (mg/dL) is the plasma blood glucose concentration, G_0 is the initial blood glucose concentration during the fasting period (baseline value) at $t = 0$. The initial conditions are $G_1(0) = G_2(0) = G_0$, the rate constant $k_1(\min^{-1})$ is the rate of glucose absorption and $k_2(\min^{-1})$ is the rate of disappearance of glucose and t is the time taken during the experiment (min). Equations (4) and (5) represent the glucose-insulin system following the short insulin tolerance test (SITT). Note that in Equation (4), the short insulin tolerance test was done at a fasting level, therefore there has been no flow of glucose into the body.

2.2 State space model of blood glucose concentration.

The dynamic model developed was built up from SITT data obtained from [17]. According to the model, the relationship between the rate changes of blood glucose concentration and insulin administered during the test is a linear first order differential equation. The model equation describing the system dynamic was identified by the

system identification toolbox in MATLAB as a continuous state space model. Each of the states was chosen to represent a patient's plasma glucose concentration data (system dynamics). Equation (6) shows the model structure and matrices of the model.

$$\frac{dx}{dt} = Ax(t) + Bu(t) + Ke(t)$$
$$y(t) = C(t) + e(t) \tag{6}$$

Where:

$$x(t) = [x_1(t), x_2(t)...x_8(t)]^T$$
$$u(t) = [I(t)]^T$$

$$A = \begin{bmatrix} 0.8145 & -0.6768 & -0.007007 & 0.2212 & -0.1378 & 0.2756 & 0.1406 & -0.2134 \\ 1.173 & -0.07853 & 19.95 & 8.244 & -12.9 & 21.6 & 3.462 & -9.414 \\ 0.1671 & -10.19 & -5.211 & -28.76 & 12.97 & -36.74 & -3.436 & 12.49 \\ 0.0424 & 0.1859 & 17.23 & 1.364 & 12.26 & -51.04 & 1.446 & 5.967 \\ 0.1548 & 0.6689 & 1.33 & -4.288 & -3.122 & 58.06 & 0.592 & -8.538 \\ -0.3731 & -0.329 & -0.5628 & 1.51 & -3.108 & -8.311 & 2.562 & 61.5 \\ -0.2807 & -0.3408 & 0.1154 & 0.8775 & 0.671 & -19.63 & -6.866 & -91.57 \\ 0.01318 & 0.2577 & -0.434 & -0.7708 & 0.8672 & -31.47 & 87.91 & -2.587 \end{bmatrix}$$

$$B = \begin{bmatrix} -1.441e-06 \\ -0.001224 \\ 0.001832 \\ 0.001948 \\ -0.002119 \\ -0.002934 \\ 0.005491 \\ 0.006215 \end{bmatrix} \quad K = \begin{bmatrix} 0.1241 \\ -0.6815 \\ -0.5361 \\ 0.04596 \\ 0.04931 \\ -0.08173 \\ -0.1935 \\ 0.03915 \end{bmatrix}$$

$$C = [4674 \quad -28.02 \quad -7.984 \quad 2.53 \quad 2.14 \quad -0.05628 \quad 0.003985 \quad 0.07942]$$

The input to the models (u) is insulin ($\mu U/dL$), and the output (y) is blood glucose concentration (mg/dL). x is the vector of the eight states. The sampling time is 10 minutes which is suitable for the measurement sensor.

2.3 Controller Design and implementation

Based on this state space model identified above, the controller is designed and afterwards implemented under the Model Predictive Control framework in MATLAB.The objective function of the RHC to maintain blood glucose concentration around 100 mg/dL in this paper is formulated as follows:

For moving end strategy $[t, t+N_y]$

$$\min_{u(0),..u(N)} J = \sum_{k=0}^{N_y} y'(k)Qy + \sum_{k=0}^{N_u} u'(k)Ru(k)$$

Subject to prediction model:

$$\dot{x}_{t+k+1|t} = A_t \dot{x}_{t+k|t} + Bu_{t+k|t} + ke[t] \tag{7}$$

$$y_{t+k|t} = C\dot{x}_{t+k|t} + y(t)$$

Where $\dot{x}_{t+k|t}$, k= 0, 1,…, N_y, represents the predicted blood glucose concentration over finite horizon [t, $t+N_y$], N_y is the prediction horizon defined in Equation (1). $k \neq 0$, the matrices A, B, C, k are given in Equation (1). The manipulated variables constraint: $u_{k|t} = u_{N_u|t}$ for $k = N_u + 1,..., N_y$ where N_u is the control horizon; $0 \le u \le u_{t+k|t} \le \bar{u}$ for k = 0, 1,…, N_u. Where u and $\bar{u}$ are lower and upper bounds of the manipulated variable (insulin) respectively. The bounds are set to avoid hypoglycemia. The output constraints: $\dot{y}_{t+k|t} \ge y^*$ for k = 0, 1, …, N_y and y^* is set to be 80 mg/dL.

In the case of fixed end horizon strategy: $[t+1]$, the prediction model is subject to:

$$\hat{x}_{t+1|t} = Ax(t) + Bu(t) + Ke(t)$$
$$y_{t+1|t} = Cx(t) + y(t) \quad (8)$$

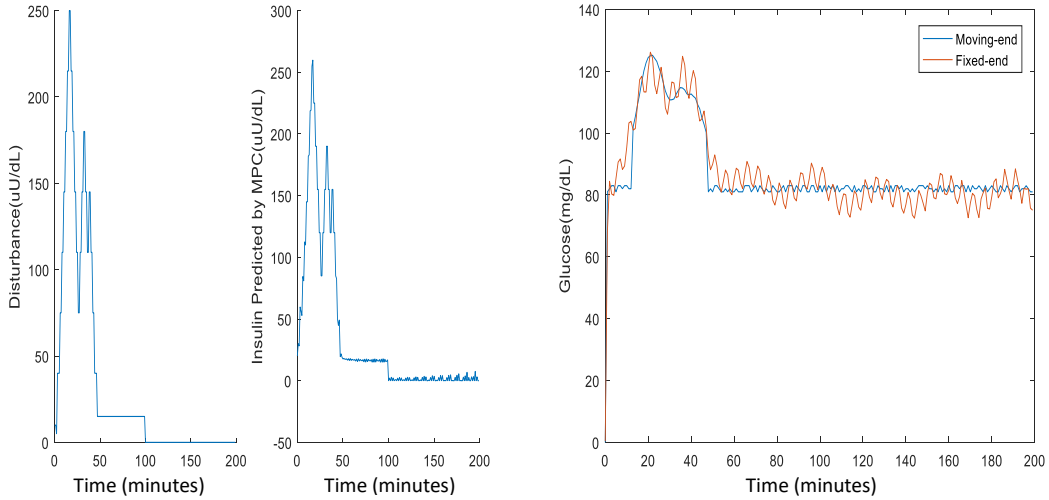
Where $\hat{x}_{t+1|t}$, k= 0, 1,…, N_y, represents the predicted blood glucose concentration over finite horizon $[t+1]$, N_y is the prediction horizon defined in Equation (1).

The control algorithms proposed in this paper to calculate the actual doses of insulin were based on a mathematical model of the patient dynamics. Moreover, they used predictions of the blood glucose concentration to take decisions about insulin intakes. A linear state-space model was used in a prediction algorithm to predict future blood glucose concentration. The model structure, describing the patients' dynamics was used within an optimization-based control algorithm to determine the amounts of insulin to be applied to the patient.In order to demonstrate the performance of the fixed-end and moving-end horizon approaches, the state space model in Equation (6) with the set of constraints were deployed into the MATLAB workspace and modified to suit both control strategies. Sets of simulation scenarios were performed, as will be presented in the later part of this section, in order to serve as a comparative analysis between the fixed and moving-end horizon control strategies.

To analyze the performance of fixed and moving-end horizon control, five scenarios of input disturbance were simulated. As discussed earlier, disturbance was measured in terms of glucose concentration (mg/dL) in the blood stream resulting from direct injection of raw glucose over a specified time interval. However, all the simulation scenarios presented below served to demonstrate the controller action in the presence of input disturbance and therefore do not represent any practical/real-time scenario. As such, all the input values were used in some cases to demonstrate the robustness of the developed controller.

III. SIMULATION RESULTS AND DISCUSSIONS

The controller's action in five different disturbance scenarios are presented in Figures 4 to 8. In all the scenarios, the desired target is to minimize the variation in glucose level in the presence of input disturbances. However, the reference point was chosen to be 80 mg/dL, therefore, the glucose concentration (control variable) is expected to remain within 80 mg/dL when the external disturbance is suppressed. It was observed that the moving-end horizon control strategy presents a better stability/reference tracking than the fixed-end strategy.

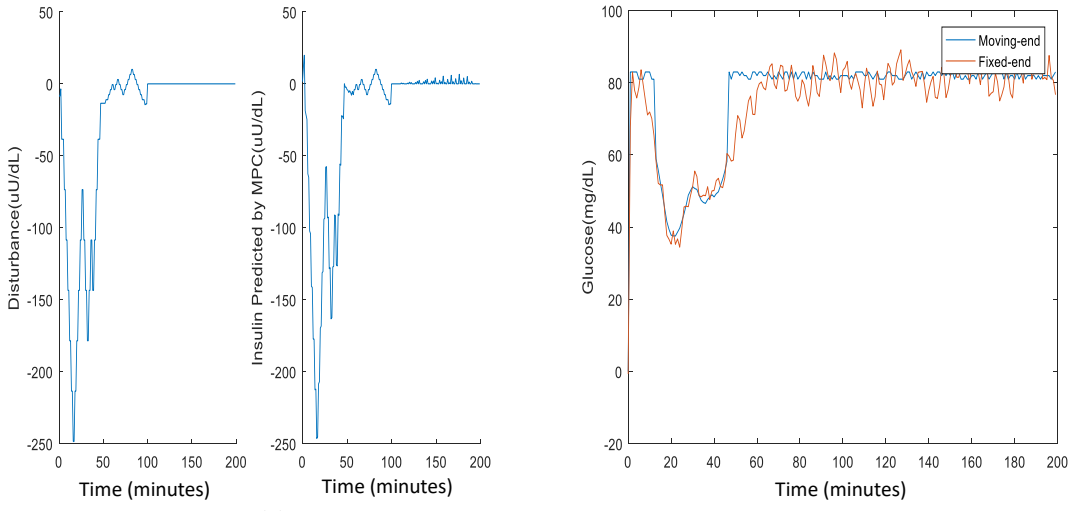


(a) **(b)**

Figure 4: (a) Disturbance scenario for a diabetic subject fed with large quantity of carbohydrate. (b)Perfo rmance of RHC controller with fixed-end (red) and moving-end (blue) for a diabetic subject fed with larg e quantity of (carbohydrate) disturbance.

As can be seen in Figure 4, the moving-end strategy stabilized in about 50 minutes, whereas the counter part approach doesn′t settle (presented a poor tracking of the reference point (80 mg/dL) and the controller was a ble to calculate the actual amount of insulin (0.13 $\mu U/dL$) required to regulate the blood glucose concentration . The results obtained were compared with [10] to evaluate the performance of the receding horizon control strat egies. It was observed in [10] that the fixed end was suitable strategy unlike the one obtained here, which demon strate that moving end strategy is better alternative for blood glucose regulation. This happens as a result of diffe rences in the set of data used in two of the such studies.

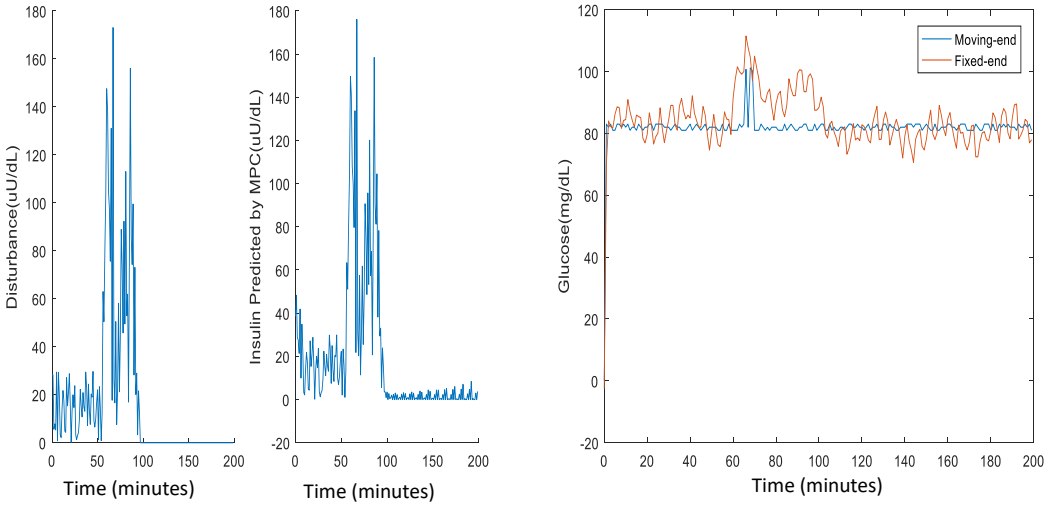
It can be observed from Figure 5, that the moving-end strategy stabilizes in about 50 minutes under different disturbance scenario, the fixed-end doesn't settle (presented a poor tracking of the reference point 80 mg/dL), and the controller was able to calculate the actual amount of insulin of (0.13 $\mu U/dL$) required to regulate the blood glucose concentration. This could happen as a result of much exercise where blood glucose concentration goes below normal value.



(a) **(b)**

Figure 5: (a) Disturbance scenario for a diabetic subject fed with small quantity of carbohydrate. (b) Perf ormance of RHC controller with fixed-end (red) and moving-end (blue) for a diabetic subject fed with sm all quantity of (carbohydrate) disturbance.

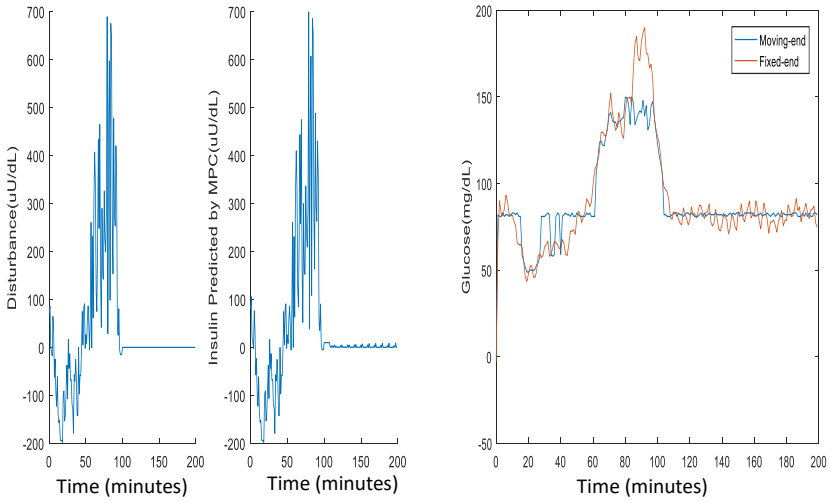
In Figure 6, the disturbance only resulted in a slight variation in the output of glucose concentration level (especially at the interval between 60 and 80 minutes). This means that the controller is robust enough to counter this effect, but in [10] the disturbance scenario affects the performance of RHC which makes the fixed end strategy a better alternative than the moving end.



(a) **(b)**

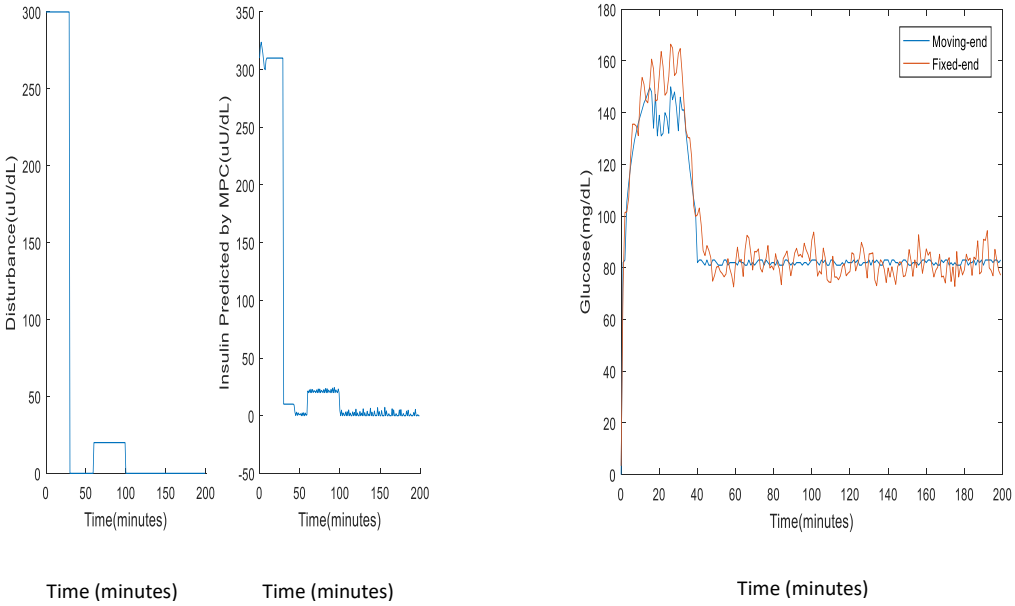
Figure 6: (a) Disturbance scenario for a diabetic subject fed with large quantity of carbohydrate. (b) Performance of RHC controller with fixed-end (red) and moving-end (blue) for a control subject fed with large quantity of (carbohydrate) disturbance.

In Figure 7, due to the large quantity of disturbance, the moving-end based control strategy stabilizes (at about 92 mg/dL) immediately the disturbance was suppressed (100 minutes). Whereas, in Figure 8, the system settles in less than 40 minutes. The performance of the moving end strategy was compared with [9], and it was observed that moving end provides a better alternative even with the effect of disturbance for blood glucose regulation.



(a) **(b)**

Figure 7: (a) Disturbance scenario for a diabetic subject fed with large quantity of carbohydrate. (b) Performance of RHC controller with fixed-end (red) and moving-end (blue) for a male diabetic subject fed with large quantity of (carbohydrate) disturbance



(a) **(b)**

Figure 8: (a) Disturbance scenario for a diabetic subject fed with large quantity of carbohydrate. (b) Performance of RHC controller with fixed-end (red) and moving-end (blue) for a male control subject fed with large quantity of (carbohydrate) disturbance.

IV. CONCLUSIONS AND RECOMMENDATIONS

In this study, the use of receding horizon control schemes for blood glucose regulation was investigated with the view to finding the best control structure to adopt for treating type II diabetes. The proposed approach enables calculating the actualamount of insulin dose required for blood glucose regulation. Controller performance has been analyzed with respectsto two control strategies (fixed and moving-end control strategies). The results show themoving end control strategy is a suitable alternative to control dynamic of blood glucoseconcentration. Moving end strategy represents better performance and stabilized with thegiven reference trajectory under different disturbance scenarios. The controller was assessedfor its ability to track the normoglycemic set point of 80.06 mg/dL for blood glucose level.

The results obtained can be improved by using other global optimization techniques. The system can be programmed into DSP chip to enable simulation of real-life scenarios; this can aid in the development of real-time data acquisition systems of blood glucose control (BGC). A variable control algorithmcould also be used with some stopping criteria such as multi-single-output strategies to get a better impression for patient variability.

With the presence of AI techniques such as the ANN, large data sets can be used for training and the resulting model can be converted to the desired form and fed into MPC controller. This approach can be more accurate and additive to the changing body system.

Conflict of interest

There is no known conflict of interest that may arise from the publication of this manuscript.

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Abdul-AlimG. Ibrahim,etal. "Receding Horizon Control of Blood Glucose Concentration for Type II Diabetes." *IOSR Journal of Engineering (IOSRJEN)*, 10(4), 2020, pp. 30-38.