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Blood glucose concentration regulation in Type 1 diabetics using multi model multi parametric model predictive control: An empirical approach

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Abstract: A Glucose- Insulin steady state static map is obtained from the Hovorka's 8th order virtual patient model. Three First Order Plus Time Delay (*FOPTD*) models are derived for the three piecewise linear regions in it. Through polyhedral vector space partitioning based on constraint violation, critical regions in state vector space are identified. A state feedback gain based controller is designed for each critical region. The controller design prevents constraint violations and ensures convexity while regulating the state vector to origin. The solution is also globally minimal. The state vector space of each empirical model is subjected to such analysis, resulting in three different set of critical regions and corresponding controllers. Gain Scheduling (*GS*) based on the Blood Glucose Concentration (*BGC*) measurement ensured proper profile selection. Through delay time compensation techniques, the multi model multi-parametric Model Predictive Control (*mp-MPC*) is designed for pure dynamics of each linear region. It is observed that the gain scheduled controller regulates the BGC within the acceptable range (80mg/dL to 160 mg/dL) during multiple meal disturbances. The explicit state feedback gain nature of the controller implies ease of deployment on memory constrained embedded devices.

Keywords: Type 1 diabetes, multi model, multi parametric, explicit MPC, exogenous Insulin Infusion, Lagrangian multipliers.

1. INTRODUCTION

The metabolic disorder in which blood sugar increases beyond its permissible range, owing to insufficient secretion of insulin by the β-cells of the islets of Langerhans present in pancreas is termed Type 1 diabetes or Insulin Dependent Diabetes Mellitus (*IDDM*). A *BGC* outside this range results in chronic and acute complications (Abu-Rmileh et al.,2010). Open loop exogenous infusion of insulin maintains BGC in near normal range.

Virtual Patient models have been constantly updated to improve their representation of the *BGC* – insulin dynamics. The most popular model initially was the 3 differential equation Bergman's minimal model, see Chee et al. (2007). Exogenous Insulin infusion was added only later to this minimal model. Other popular models representing Type 1 diabetics are Sorensen model having 19 differential equations and Hovorka's model having 8 differential equations, see Hovorka et al. (2004). Sorensen's model does not capture the real hyperglycaemic extremes observed in Type 1 diabetics, see Finan et al. (2006). Hovorka model is simple and accurate in representing patients with Type 1 diabetes (Semizer et al., 2012).

Model Predictive Control based on treating the control problem as an online optimization problem at each sampling time is widely adapted in many applications. The benefits of such scheme include constraints inclusion for inputs, outputs and states in finding the optimal solution, see Mayne et al. (2000). Such design of MPC for linear time invariant systems have been studied (Satheesh et al., 2011). They have proven to provide reliable regulatory and tracking solutions to different types of processes (Sivakumaran et al., 2006). Online optimization involves repetitive solution search owing to the implicit feedback. This increases the computational effort (Kouramas et al., 2011). As compared to classical controllers like proportional integral derivative (PID), *MPC* shows better performance but owing to MPC's inability to adapt to faster systems, *PID* controls are still being widely used for such processes. By performing online optimization via offline optimization tools, see Pistikopoulos et al. (2002), *mp-MPC* recasts the problem from a numerical optimization into a parametric optimization (Dua et al., 2008). The hardware-software co-design becomes efficient owing to the simple controller deployment.

A state feedback based *mp-MPC* design has been created for a linearized time invariant (*LTI*) model, see Dua et al. (2006). A *FOPTD* model based *mp-MPC* design facilitates direct field data utilization in *mp-MPC* control law derivation, see Kosmidis et al. (2006).

Hovorka's virtual patient model, exhibits nonlinearity owing to the selection of saturation for certain parameters like non-insulin dependent glucose flux and also renal glucose clearance in it. Insulin dynamics also contribute greatly to this non linearity, see Amjad et al. (2010).

FOPTD based models of the glucose – insulin dynamics are derived from the virtual patient, see Ramprasad et al. (2006). The benefits of multiple model controller based on gain scheduling for nonlinear processes over a nonlinear controller has been discussed greatly, see Amjad et al. (2010). Delay time compensation schemes for control design based on pure dynamics for processes with slow dynamics are widely accepted.

A direct model approach is suggested in Dua et al. (2006) based on a Bergman minimal model. This article deals with difference model based approach to model the dynamics of a Hovorka's virtual patient model. Also, a gain scheduled multiple model adaptive control is designed for the *BGC* control on the virtual patient.

Hence, the controller developed is deployed in-silico. The controller has been tuned under varying scenarios of simulation which includes meal disturbances, Insulin sensitivity, and inter-patient variations.

2. VIRTUAL PATIENT MODEL

Hovorka's 8 differential equation model divide the entire operating range into three major subsystems - *glucose* subsystem, the *insulin* subsystem and *insulin action* subsystem, see, Hovorka et al. (2004).

2.1.1 Glucose Subsystem

Glucose kinetics is represented by two compartments Q_1 and Q_2 as in (1) and (2). They represent the masses of glucose in the accessible and non-accessible compartments.

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

$$\frac{dQ_2(t)}{dt} = x_1(t)Q_1(t) - \left[k_{12} + x_2(t)\right]Q_2(t)y(t) \quad (2)$$

where, BGC is obtained as in (3).

$$G(t) = Q_1(t)/V_G \quad (3)$$

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

$$F_{01}^c = \begin{cases} F_{01} & G \geq 4.5\, mmolL^{-1} \\ F_{01}G/4.5 & otherwise \end{cases} \quad (4)$$

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

$$F_R = \begin{cases} 0.003(G-9)V_G & G \geq 9\, mmolL^{-1} \\ 0 & otherwise \end{cases} \quad (5)$$

U_G is the gut absorption rate of glucose. D_G is the amount of carbohydrates digested and A_G is the carbohydrate bio availability.

$$U_G(t) = \frac{D_G A_G\, t \exp(-t/t_{\max,G})}{t_{\max,G}^2} \quad (6)$$

2.1.2.Insulin subsystem

S_1 and S_2 represent the absorption of subcutaneously administered short-acting insulin. *u(t)* represents the administration of insulin. The plasma insulin concentration *I(t)*is given as in (9).

$$\frac{dS_1(t)}{dt} = u(t) - \frac{S_1(t)}{t_{\max,I}} \quad (7)$$

$$\frac{dS_2(t)}{dt} = \frac{S_1(t)}{t_{\max,I}} - \frac{S_2(t)}{t_{\max,I}} \quad (8)$$

$$\frac{dI(t)}{dt} = \frac{U_I(t)}{V_I} - k_e I(t) \quad (9)$$

2.1.3.Insulin action subsystem

Influence of insulin on the glucose kinetics is provided as in (10) to (12).

$$\frac{dx_1}{dt} = -k_{a1}x_1(t) + k_{b1}I(t) \quad (10)$$

$$\frac{dx_2}{dt} = -k_{a2}x_2(t) + k_{b2}I(t) \quad (11)$$

$$\frac{dx_3}{dt} = -k_{a3}x_3(t) + k_{b3}I(t) \quad (12)$$

where x_1 , x_2 and x_3 showcase insulin's effects on glucose transport, production and disposal.

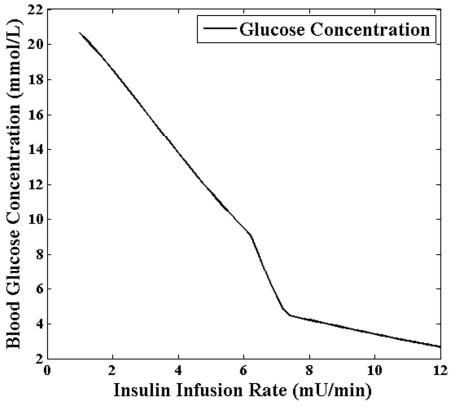

Fig. 1. Steady State BGC – Insulin Interaction for Hovorka's virtual patient

The model constants made use of in this virtual patient is listed in Table 1. The parameters mentioned in Table 1 are taken from Hovorka et al. (2004).

2.2.Non Linearity of Hovorka' virtual patient

The major sources of nonlinearity are due to insulin action on glucose production, distribution and disposal. The steady state Glucose Insulin interaction is obtained as in Fig. 1.

Table 1. Virtual patient model constants

Constant	Description	Value
k_{12}	Transfer Rate	0.066 min^{-1}
k_{a1}	Deactivation rate	0.006 min^{-1}
k_{a2}	Deactivation rate	0.06 min^{-1}
k_{a3}	Deactivation rate	0.03 min^{-1}
k_{b1}	Activation rate	0.3072 x10^{-4} min^{-2} per mU L^{-1}
k_{b2}	Activation rate	0.492 x10^{-4} min^{-2}per mUL^{-1}
k_{b3}	Activation rate	15.6 x10^{-4} min^{-1}per mUL^{-1}
ke	Insulin Elimination rate	0.138 min^{-1}
V_I	Insulin Dist. Vol.	0.12Lkg^{-1}
V_G	Glucose Dist. Vol.	0.16Lkg^{-1}
A_G	Carb. Bio availability (CHO)	0.8(Unit less)
$t_{\max,G}$	Max. CHO absorption Time	40 min
EGPo	EGP Extrapolated to zero insulin concentration	0.0161 mmol kg^{-1} min^{-1}
F_{01}	Non-Insulin dependent glucose flux	0.0097 mmol kg^{-1} min^{-1}
$t_{\max,I}$	Max. Insulin absorption time	55 min

3. MULTI-PARAMETRIC MPC

Multi-parametric optimization problems are vector based optimization problems. Consider a discrete linear time invariant system as in (13).

$$\begin{aligned} x(k+1) &= A\,x(k) + B\,u(k) \\ y(k+1) &= C\,x(k+1) \end{aligned} \tag{13}$$

The linear constraints on the system are as in (14).

$$\begin{aligned} y_{\min} &\le y(k) \le y_{\max} \\ u_{\min} &\le u(k) \le u_{\max} \end{aligned} \tag{14}$$

where, $x(t) \in R^n, u(t) \in R^m, y(t) \in R^p$ represent the state, input and output vectors respectively.

The objective cost function of the model predictive control is as in (15).

$$\min_u J(U, x(t)) = x_{k+N_y|k}^T\, P\, x_{k+N_y|k} + \sum_{m=0}^{N_y-1} x_{k+m|k}^T\, Q\, x_{k+m|k} + u_{k+m|k}^T\, R\, u_{k+m|k} \tag{15}$$

such that

$$x_{\min} \le x_{k+m|k} \le x_{\max} \qquad m = 1,2,3 \ldots N_C$$

$$u_{\min} \le u_{k+m|k} \le u_{\max} \qquad m = 1,2,3 \ldots N_C$$

Q and R are both positive definite matrices. U as in (16) is the set of input vectors

$$U = [u_1^T \quad u_2^T \quad \ldots\ldots \quad u_{k+N_u-1}^T]^T \tag{16}$$

N_y, N_c and N_u are the prediction, constraint and control horizons respectively. The terminal weighing matrix P, is obtained by solving the following algebraic Ricatti equation shown in (17).

$$P = A^T P A + Q - A^T P B (B^T P B + R)^{-1} B^T P A \tag{17}$$

For a prediction horizon of N steps, (13) can be rewritten as in (18).

$$\underbrace{\begin{bmatrix} x(0) \\ x(1) \\ x(2) \\ . \\ x(N) \end{bmatrix}}_{x} = \underbrace{\begin{bmatrix} I \\ A \\ A^2 \\ . \\ A^N \end{bmatrix}}_{S^x} x(0) + \underbrace{\begin{bmatrix} 0 & 0 & .. & 0 \\ B & 0 & .. & 0 \\ AB & B & .. & 0 \\ : & : & .. & : \\ A^{N-1}B & A^{N-2}B & .. & B \end{bmatrix}}_{S^u} \begin{bmatrix} u(0) \\ u(1) \\ u(2) \\ : \\ u(N-1 \end{bmatrix} \tag{18}$$

The quadratic cost function for this problem is now written as in (19).

$$V_N \overset{\Delta}{=} X^T\, \Gamma^x\, X + U^T\, \Gamma^u\, U \tag{19}$$

where,

$$\Gamma^x = \begin{bmatrix} Q & 0 & .. & .. & 0 \\ 0 & Q & .. & .. & 0 \\ : & 0 & . & : & : \\ : & . & . & . & : \\ 0 & 0 & .. & .. & P \end{bmatrix} \qquad \Gamma^u = \begin{bmatrix} R & 0 & .. & .. & 0 \\ 0 & R & .. & .. & 0 \\ : & 0 & . & : & : \\ : & . & . & . & : \\ 0 & 0 & .. & .. & R \end{bmatrix}$$

The multi-parametric optimization problem is recast as in (20).

$$V_z(x) = \min_z \frac{1}{2} z^T\, H\, z \tag{20}$$

s.t.

$$Gz \le W + S\,x(k)$$

where,

$$z = U + H^{-1} g\, x(k) \qquad z \in R^S$$
$$S = E + G H^{-1} g$$

$$H = S^{u^T}\, \Gamma^x\, S^u + \Gamma^u$$
$$g = S^{u^T}\, \Gamma^x\, S^x$$

H is the hessian matrix. g is the gradient.

By optimizing vector z using state vector x(k), explicit functions of state vector provides input decision U as in (21).

$$U = z - H^{-1} g\, x(k) \tag{21}$$

Using the Karush-Kuhn-Tucker condition for optimality, see Bazaraa (1993), the *Lagrangian multipliers* for various points in the state vector space is obtained. The number of multipliers is decided by the number of constraints implemented as in (14). A non-zero positive value to any of the Lagrangian multiplier signifies an active constraint in the assessed state vector space. Such assessment is carried out in the entire state vector space and different sets of such active constraints are utilized to partition the state vector space into polyhedrons.

A state vector is classified into a polyhedral region on satisfying (22).

$$(\tilde{G} H^{-1} \tilde{G}^T)^{-1} \tilde{S} \le (\tilde{G} H^{-1} \tilde{G}^T)^{-1} \tilde{W} \tag{22}$$

The state feedback controller for this polyhedral region is obtained as in (23)

$$u(k) = H^{-1} \tilde{G}^T (\tilde{G} H^{-1} \tilde{G}^T)^{-1} \tilde{S} - H^{-1} g\, x(k) + H^{-1} \tilde{G}^T (\tilde{G} H^{-1} \tilde{G}^T)^{-1} \tilde{W} \tag{23}$$

where,

$\tilde{G}$, $\tilde{S}$ and $\tilde{W}$ are obtained from G, S and W matrices based on the active Lagrangian multipliers.

The control design ensures the convexity and the contiguity of the solution are being preserved in the entire vector space.

The discrete state space model of the pure dynamics of empirical FOPTD model and the deviation of BGC from reference, form the two dimensional state vector space.

To this effect, the difference form of pure dynamics' state space is considered, as in (24).

$$\Delta x(k+1) = A \Delta x(k) + B \Delta u(k)$$
$$\Delta y(k+1) = C \Delta x(k+1) \tag{24}$$

Deviation of BGC is appended to the state as in (25).

$$\begin{bmatrix} \Delta x(k+1) \\ \Delta e(k+1) \end{bmatrix} = \begin{bmatrix} A & 0 \\ CA & I \end{bmatrix} \begin{bmatrix} \Delta x(k) \\ \Delta e(k) \end{bmatrix} + \begin{bmatrix} B \\ CB \end{bmatrix} \Delta u(k) \tag{25}$$

Proper weights on Q ensures, only the deviation is weighed while regulating the system to origin, hence eliminating disturbances.

Offline tuning is hence the process of identifying various combinations of active constraints on the entire state vector space. Controller is tuned by initially setting the Q/R ratio. Both the Q and R matrices in (15) influence the aggression and also the robustness of the controller. Designing controller for each of the critical region completes this procedure.

4. RESULTS AND DISCUSSION

4.1 Empirical modelling and vector space partitioning

The virtual patient model exhibits three distinct regions (Region 1: BGC<80 , Region 2: 80< BGC <160 , Region 3: BGC >160 unit: mg/dL) as seen in Fig. 1. Under steady state conditions in each of the three regions, the subcutaneous insulin infusion rate, which is the input to this process, was varied by 1mU/min as a negative step change and by 0.5 mU/min in the positive direction, from the nominal insulin infusion rate and the transient response of the in–silico patient's BGC, which is the output, is recorded. An FOPTD model is derived out of the transient response in each region. The model thus obtained for region 2 is compared with actual Hovorka model as seen in Fig. 2.

The FOPTD model hence obtained is converted to discrete state space form with a sampling time of 5 minutes. This model is subject to analysis and offline tuning as discussed in *Section 3*. Using (22) and (23), the polyhedrons and control laws are obtained.

The resultant vector space partitioning for region 2 constitutes of three critical regions as seen in Fig.3. Polyhedral classifiers and state feedback controllers are thus obtained for all three FOPTD models.

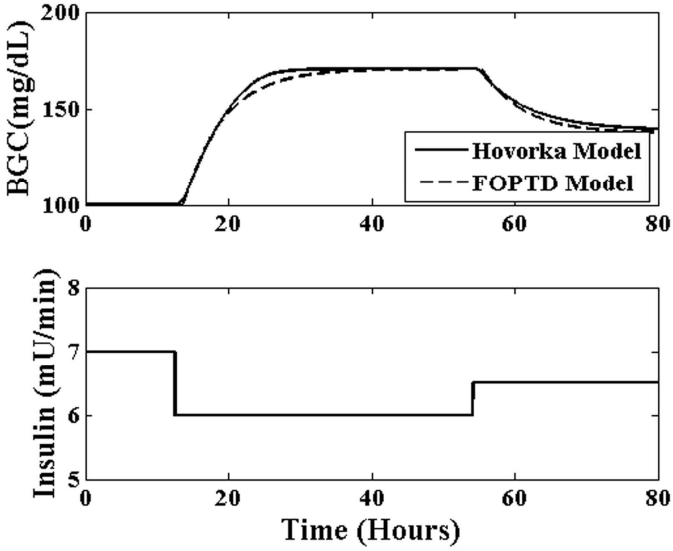

Fig. 2. Comparison of Empirical FOPDT model to Hovorka's virtual patient model.

The FOPTD model for Region 2 constitutes of a gain of -70.51, a time delay of 25 minutes and a time constant of

magnitude 125 minutes. As indicated in Percival et al. (2011), the time delay values for all three regions are similar and hence considered to be same. The controller is designed based on pure dynamics. A Smith predictor based time delay compensation is performed in closed loop. Gain scheduling determines the model/controller selection during closed loop control. Based on region classification provided in *Section 4.1*, the scheduling is executed.

The pure dynamics of the FOPTD model is converted to continuous time state space representation. This model is further discretized with a sample time of 5 minutes. The discrete state space models for the three regions are provided in Table 2. A Q/R ratio of 5 has been used in design of the three controllers.

Table 2. Discrete Time State Space models

Region	A	B	C	D
Region 1	0.9355	4.837	-0.4813	0
Region 2	0.9608	4.901	-0.5641	0
Region 3	0.8669	4.659	-0.2136	0

Table 3. Meal Disturbance

Meal Time	8:00 am	12:00 pm	7:00 pm
D_G (mmol/kg)	3	5	4

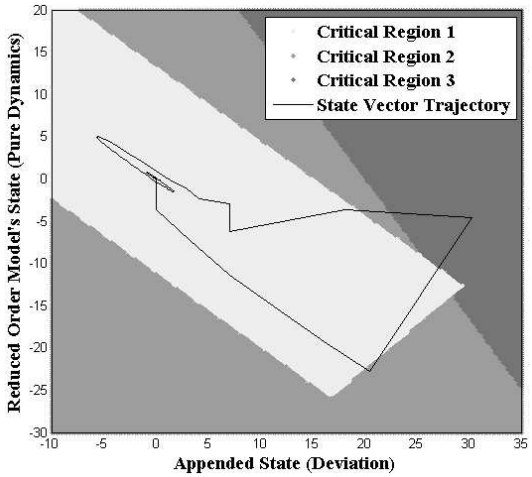

Fig. 3. Polyhedral partitioning of vector space (Region 2) and Trajectory of state vector in the vector space for a 5 mmol/kg meal disturbance.

4.2 Regulation of meal disturbances

BGC control is approached as a regulatory problem owing to no changing of the reference.

Another explicit form of *MPC* is the unconstrained *MPC* (U MPC) derived from (21). Hard input saturation is used before deploying it on the virtual patient. The constraint employed on the given *mp-MPC* is on the rate of change of insulin infusion rate. Considering the patient's weight to be 165 pounds, the total daily dose (TDD) of insulin is calculated to be 41.25 units.

A basal insulin infusion rate of 7mU/min is maintained. Based on BGC deviation during continuous glucose measurement (CGM) the bolus insulin infusion rate is varied

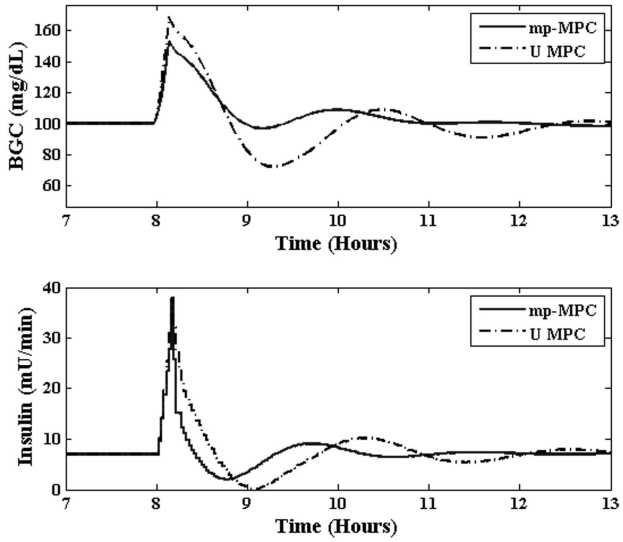

Fig. 4. Regulation of 5 mmol/kg meal disturbance.

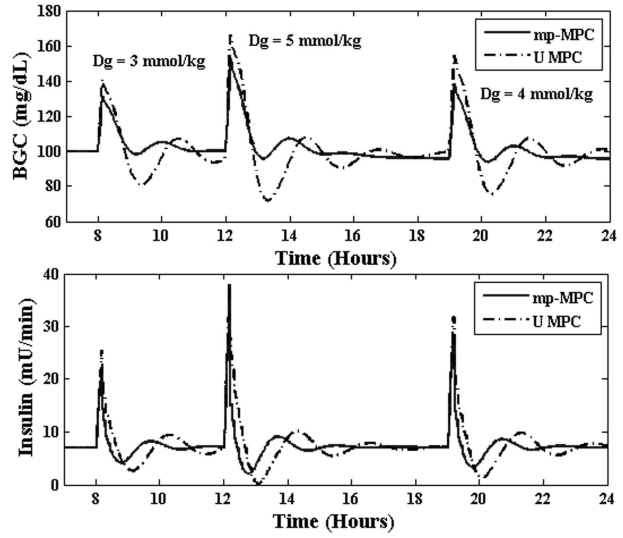

Fig. 5. Regulation of multiple meal disturbances. Meal Disturbances as listed in Table 3.

For the given meal sizes, the control action shown in Fig.5 the total insulin infused is found to be 34.729 units by the *mp-MPC*. Whereas, the insulin infused by the unconstrained *MPC* is 36.809 units.

It is evident from the comparison of graphs in Fig. 4 and Fig. 5 and also, the mean square error values as seen in Table 3, the *mp-MPC* performs better. A control variability grid analysis (CVGA) shown in Fig. 6.

It shows that for varying meal sizes, the *mp-MPC* maintains the control in regions a and b and hence imparting better control in comparison to *U MPC.* Meanwhile, input cost is also contained by *mp-MPC* as indicated by the standard deviation mentioned of in Table 4.

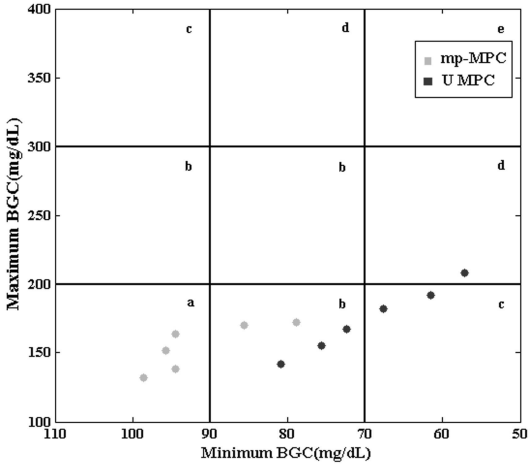

Fig. 6. CVGA analysis of various meal sizes.

Table 4. Qualitative Analysis of Regulation of multiple meal disturbances

Controller	mp-MPC	Unconstrained MPC
MSE	13.6043	51.7476
Standard Deviation of Insulin Infusion Rate	1.01	1.95

5. CONCLUSION

A Hovorka's virtual patient model has been used. Multiple *FOPDT* models based on piecewise linearity have been obtained. Vector space partitioning based on active constraints using Lagrangian multipliers has been performed. Gain Scheduling based on *BGC* measured from virtual patient selects the controller profile. A multi model multi parametric MPC based on empirical models has been designed and deployed in-silico on a virtual patient. The explicit nature of the controller obtained, coupled with the simplicity of the control solution makes it an ideal choice for embedded deployment while preserving the benefits of *MPC*.

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