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Multi-objective Parametric Control of Blood Glucose Concentration for Type 1 Diabetes

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Abstract—The main objective of automatic blood glucose concentration controllers is to avoid hypo- and hyper-glycemia, i.e. maintain the concentration levels between 60 and 120 mg/dL, by optimally manipulating the insulin infusion rates. In the medical literature, hypoglycemia is considered to be more harmful to an individual's health than hyperglycemia. In this work, a multiobjective controller that can take into account this asymmetry in the objective function and can be implemented with minimal computational effort, by using parametric programming techniques, is proposed. An alternative technique that gives higher priority to the satisfaction of constraints on hypoglycemia than on hyperglycemia is also presented. The performance of both the controllers is analyzed under meal disturbances.

I. INTRODUCTION

TYPE 1 diabetes is characterized by inadequate control of blood glucose concentration due to the destruction of insulin producing beta cells in the pancreas. People with type 1 diabetes therefore rely on regular insulin injections for controlling the blood glucose concentration between the desired range of 60 to 120 mg/dL [1] and at the target level of 81 mg/dL. The amounts and times of insulin intake usually depend on the amounts and the times of meal respectively. This usually leads to significant deviations of the blood glucose concentration from the target level due to the manual and open loop nature of the control. A shortage in the insulin supply may lead to the concentration levels rising above 120 mg/dL, a state known as hyperglycemia, whereas an excessive supply may lead to concentration levels falling well below 60 mg/dL, a state known as hypoglycemia. Both these states are harmful to an individual's health but negative deviations from the target value are considered to be more harmful than the positive deviations.

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A number of control techniques that can overcome some of these limitations have been proposed in the literature. For a given blood glucose concentration measured by a sensor the main objective of a control algorithm is to compute the optimal amount of insulin that can be infused via a mechanical pump – see Fig. 1. Proportional Integral (PI) control is one of the oldest control techniques [2] but it can not take into account the constraints on the blood glucose concentration and insulin infusion rates. Model based controllers have the advantage of being able to take into account the detailed and dynamic model of patient and constraints on insulin infusion rates and blood glucose concentration [3][4][5] but require extensive on-line computational effort. Model based parametric controllers provide optimal insulin infusion rates as a set of explicit functions of the current state of the patient and the corresponding polyhedral regions in the space of the state variables [6]. The key advantage of the parametric controllers is that they provide same performance as the model based controllers and yet require minimal computational effort.
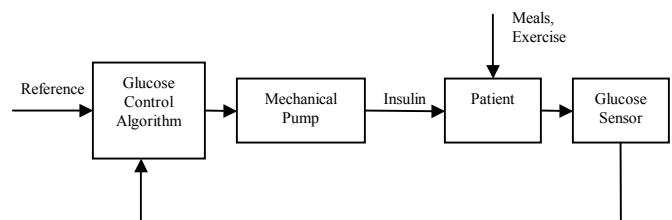

Fig. 1. Automatic control of blood glucose concentration.

The motivation behind the current work is that traditional approaches to characterizing engineering "performance" are rarely equated to a physician's characterization of patient "performance". In particular, the asymmetry between the previously described states of hypo- and hyper-glycemia is noteworthy [7]. In this work, two multiobjective control techniques for addressing this issue are presented. The first technique addresses the issue by designing an asymmetric objective function in the model based control framework with more weighting given to the negative deviations from the setpoint, 81 mg/dL, than to the positive deviation. The problem is then reformulated as a multi-parametric quadratic program and solved to obtain the optimal insulin infusion

rate as an explicit function of the state of the patient. The second technique is concerned with the prioritization of objectives [8]. The "objective" that the constraint corresponding to the hypoglycemic state is not violated has a higher priority than the constraint corresponding to the hyperglycemic state. Similarly, a number of such constraints are identified and prioritized. The constraint prioritization corresponding to various objectives are formulated by using boolean variables that results in a mixed integer program. This problem can then be recast as a multi-parametric mixed integer program by treating state variables as parameters and control and integer variables as optimization variables. The final solution is given by the insulin delivery rate as an explicit function of the state of patient. Since the on-line solution of a mixed integer program is computationally expensive, the parametric programming approach can be used for the incorporation of the prioritized objectives that can significantly improve the performance of blood glucose control.

The rest of the paper is organized as follows. In the next section a brief overview of model based control is presented. In section III a parametric programming approach where asymmetry in the objective function is considered is presented to derive the optimal insulin infusion rate as an explicit function of the state of the patient. Section IV considers the case where constraints on blood glucose concentration are prioritized and some concluding remarks are presented in section V.

II. MODEL PREDICTIVE CONTROL (MPC)

MPC is based on the so-called receding horizon philosophy. At each sampling time, an optimal control problem is solved starting at the current state over a finite horizon. At the next time step, the computation is repeated starting from the new state and over a shifted horizon, leading to a moving horizon policy [9]. The solution of linear MPC relies on a linear dynamic model, incorporates all the input and output constraints, and optimizes a quadratic performance index.

Consider the following mathematical model of the patient,

$$x_{t+1} = Ax_t + Bu_t \qquad (1)$$

subject to the following constraints:

$$\begin{aligned} x_{min} &\le x_t \le x_{max} \\ u_{min} &\le u_t \le u_{max} \end{aligned} \qquad (2)$$

where $x_t \in R^n$, $u_t \in R^m$, are the state and input vectors respectively and the subscripts *min* and *max* denote lower and upper bounds respectively. Typically, x_t represents the

glucose and insulin concentrations and u_t represents the insulin delivery rate, at time interval t. The MPC problem can then be posed as the following optimization problem:

$$\begin{aligned} \min_U J(U, x(t)) &= x_{t+N_y|t}^T P x_{t+N_y|t} + \sum_{k=0}^{N_y-1} \left[x_{t+k|t}^T Q x_{t+k|t} + u_{t+k}^T R u_{t+k} \right] \\ s.t. \quad & x_{min} \le x_{t+k|t} \le x_{max}, k = 1,\ldots,N_c \\ & u_{min} \le u_{t+k} \le u_{max}, \quad k = 1,\ldots,N_c \\ & x_{t+k+1|t} = Ax_{t+k|t} + Bu_{t+k}, k \ge 0 \\ & u_{t+k} = Kx_{t+k|t}, N_u \le k \le N_y \end{aligned} \qquad (3)$$

where $U = \left[u_t^T, \ldots, u_{t+N_u-1}^T \right]^T$ and the superscript T denotes transpose of the vector. The tuning parameters are: Q and R, that are constant, symmetric and positive definite matrices, P is given by the solution of the Riccati equation, N_y, N_u and N_c are the prediction, control and constraint horizons respectively and K is some feedback gain. Problem (3) is solved repetitively at each time t for the current state x_t and the vector of predicted state variables, $x_{t+1|t}, \ldots, x_{t+Ny|t}$ at time $t+1,\ldots,t+k$ respectively and corresponding control actions $u_t,\ldots,u_{t+k}$ are obtained.

The main drawback of MPC is its extensive on-line computational effort. This drawback can be overcome by using parametric programming as discussed in the next section.

III. PARAMETRIC PROGRAMMING

A. Multi-parametric Quadratic Program

Parametric programming is a technique which is usually used in an optimization framework where given an objective function, a set of constraints and a vector of parameters, optimal value of the optimization variables is obtained as a set of functions of the parameters and the corresponding regions in the space of parameters where these functions are valid. This is a generic mathematical technique that can be used in the MPC framework to obtain U as a function of x_t by treating U as optimization variables and x_t as parameters as described next [10][11].

For simplicity in presentation assume that $N_y = N_u = N_c$, however, the theory presented is also valid for the case when this does not hold. The equalities in formulation (3) are eliminated by making the following substitution:

$$x_{t+k|t} = A^k x_t + \sum_{j=0}^{k-1} A^j B u_{t+k-1-j} \qquad (4)$$

to obtain the following Quadratic Program (QP):

$$\min_U \frac{1}{2}U^T H U + x_t^T F U + \frac{1}{2}x_t^T Y x_t \tag{5}$$
$$s.t. \quad GU \le W + Ex_t$$

where, $U = \left[u_t^T,....,u_{t+N_u-1}^T\right]^T \in R^s$, is the vector of optimization variables, $s = mN_u$, H is a constant, symmetric and positive definite matrix and H, F, Y, G, W, E are obtained from Q, R and (1) and (2).

The QP problem in (5) can now be reformulated as a multi-parametric quadratic program (mp-QP) [12]:

$$V_z(x) = \min_z \frac{1}{2}z^T H z \tag{6}$$
$$s.t. \quad Gz \le W + Sx_t$$

where, $z = U + H^{-1}F^T x_t, z \in R^s$, and $S = E + GH^{-1}F^T$.

This mp-QP is solved by treating z as the vector of optimization variables and x_t as the vector of parameters to obtain z as a set of explicit functions of x_t. U is then obtained as a set of explicit functions of x_t by using $U = z - H^{-1}F^T x_t$. Each of these functions is valid in a polyhedral region in the space of state variables x_t.

B. Explicit Insulin Delivery Rate

The widely used Bergman model [13] is selected for the controller design. This model captures the glucose-insulin response of the patient by using the minimum number of compartments.

The model comprises of three compartments: plasma glucose compartment, plasma insulin compartment and the effective insulin compartment. Each of these compartments is represented by following equations,

$$\frac{dG}{dt} = -P_1 G - X(G + G_b) + D(t) \tag{7}$$

$$\frac{dI}{dt} = -n(I + I_b) + U(t)/V_1 \tag{8}$$

$$\frac{dX}{dt} = -P_2 X + P_3 I \tag{9}$$

where, G is the plasma glucose concentration above basal value (mg/dL), I is the plasma insulin concentration above basal value (mU/L), X is proportional to plasma insulin concentration in the remote compartment (min^{-1}), D is the meal glucose disturbance (mg/dL min^{-1}), U is the exogenous insulin infusion rate (mU/min), G_b is the nominal value of glucose concentration (mg/dL), I_b is the nominal value of

insulin concentration (mU/L), V_1 is the insulin distribution volume (L) and n is the fractional disappearance rate of insulin (min^{-1}). The plasma insulin compartment is represented by (8) where exogenous insulin is supplied. The output from this compartment goes to the effective insulin compartment, which is represented by (9), where insulin is active in accelerating the glucose disappearance into the periphery and liver as represented by (7).

The states in this model are $x_t = [G \; I \; X]^T$, $u_t = U(t)$ is the control variable and G_b and I_b are nominal values of glucose and insulin concentration. The parameter values that are considered are: $P_1 = 0$ min^{-1}, $P_2 = 0.025$ min^{-1}, $P_3 = 0.000013$ L/mU min^{-2}, $V_1 = 12$ L and $n = 5/54$ min [14].

The model, (7)-(9) is linearized at the steady-state values of $G_b = 4.5$ mmol/L (81 mg/dL), $I_b = 15$ mU/L, $X_b = 0$ and $U_b = 16.66667$ mU/min to obtain the form given in (1): $x_{t+1} = Ax_t + Bu_t + B_d d_t$ where the term d_t represents the input disturbance glucose meal. The sampling time considered is 5 minutes, which is reasonable for the current glucose sensor technology. The discrete state-space matrices A, B and B_d are calculated as follows:

$$A = \begin{bmatrix} 1 & -0.000604 & -21.1506 \\ 0 & 0.6294 & 0 \\ 0 & 0.00004875 & 0.8825 \end{bmatrix}, B = \begin{bmatrix} -0.000088 \\ 0.3335 \\ 0.0000112 \end{bmatrix}, B_d = \begin{bmatrix} 5 \\ 0 \\ 0 \end{bmatrix} \tag{10}$$

The constraints imposed are glucose concentration between 60-120 mg/dL, which is the desired blood glucose concentration range, and insulin infusion rate between 0-100 mU/min, which is suitable for the insulin pumps, i.e., $60 \le G+G_b \le 120$ and $0 \le U+U_b \le 100$.

The prediction horizon was tuned and it was observed that $N_y = 5$ gives a good controller performance; and three different Q/R ratios: 10, 100 and 1000 are considered for deriving the control law – this results in partitioning of the state-space into 54, 60 and 59 polyhedral regions respectively. These regions are known as Critical Regions (CR). Associated with each CR is a control law that is an affine function of the state of the patient. For example, one of the CRs is given by the following state inequalities:

$$-5 \le I \le 25$$
$$0.0478972G - 0.0002712I - X \le 0.104055$$
$$0.0261386G - 0.0004641I - X \le 0.0576751$$
$$-0.00808846G + 0.00119685I + X \le 0$$
$$-0.00660123G + 0.00130239I + X \le 0$$
$$0.00609435G - 0.00134362I - X \le 0$$

where the insulin infusion rate as a function of the state

variables for the next five time intervals is given as follows:

$$U(1) = 30.139G - 0.44597I - 3726.2X$$
$$U(2) = 24.874G - 0.40326I - 3280.4X$$
$$U(3) = 20.16G - 0.35946I - 2842.8X$$
$$U(4) = 16.002G - 0.31571I - 2424.1X$$
$$U(5) = 0$$

Fig. 2 shows the partition of the state space into CRs for fixed values of G, I and X. The implementation of the controller therefore requires identification of the CR corresponding to the current state of the patient and then computing the optimal amount of insulin delivery rate. Similar to MPC, if at any time instant the current state is infeasible, i.e. does not lie within any of the CRs, then the last control action is implemented.
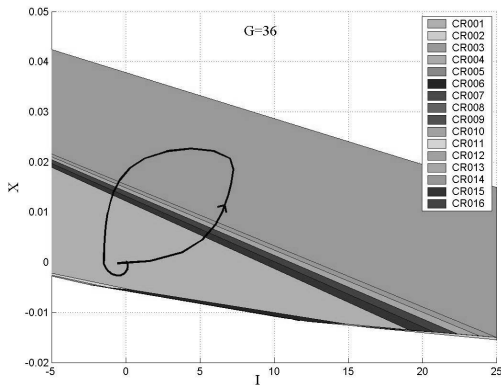

Fig. 2. Critical regions for G = 36. The trajectory depicts the values of I and X for a meal disturbance of 20 g.

The controller implementation therefore requires simple function evaluations, which are much easier to compute than solving an on-line optimization problem. Note that only the first control action, $U(1)$, is implemented. At the next time interval, a new set of state measurements becomes available and the corresponding critical region and the control law is identified and implemented. This sequence is repeated until the desired state of the patient is obtained. The trajectory of the state variables for a meal disturbance of 20 g is also shown in Fig. 2. Another key advantage of the explicit controller is that a complete road-map of all the possible solutions is available a priori.

C. Asymmetric Objective Function

To illustrate the concept of asymmetric objective function, first consider the symmetric case where hypo- and hyper-glycemia are equally weighted. To invoke the occurrence of hypoglycemia a sinusoidal disturbance of the form shown in Fig. 3 is considered. The positive disturbance corresponds to an intake of meal whereas negative disturbance can be attributed to for example excessive bolus of insulin or

exercise. For the case when there are equal or symmetric weightings on hypo- and hyper-glycemia, there is violation of the constraint on hypoglycemia and the blood glucose concentration falls below 60 mg/dL – see Fig. 4. This situation can be avoided by solving two parametric programs, one for $G \geq 81$ mg/dL and the other for $G \leq 81$ mg/dL. For the second parametric program, Q, the weighting on blood glucose deviation is taken to be 10 times higher than for the first parametric program. Then the solution of both these programs is combined to provide the parametric controller for the whole range of blood glucose concentration. Fig. 5 shows the variation of blood glucose concentration with time for the sinusoidal disturbance – a much smaller negative deviation from 81 mg/dL is obtained and hypoglycemia is avoided.
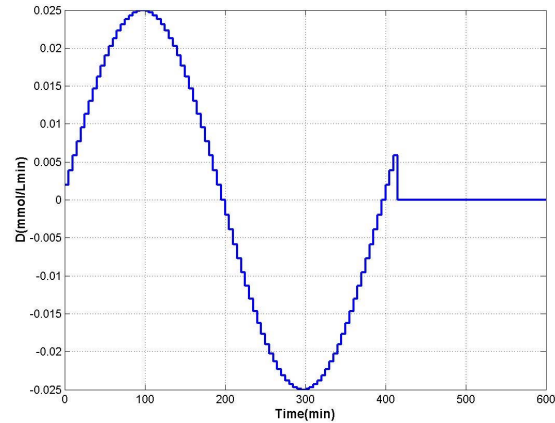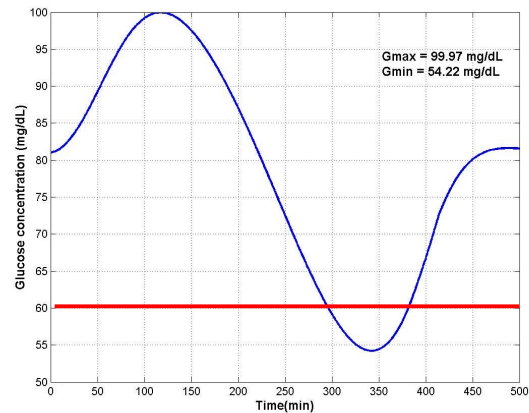

Fig. 3. Sinusoidal disturbance.

Fig. 4. Glucose concentration profile for symmetric objective function.

IV. CONSTRAINT PRIORITIZATION

As an alternative to the asymmetric objective function approach for reducing the hypoglycemic excursions, the problem can be formulated such that we have a set of

objectives O_i, $i = 1, ..., N_o$, which represent constraints on blood glucose concentration. O_i are 0-1 binary variables where a value of 1 implies satisfaction of the constraint and a value of 0 means violation of the objective. For example, an objective, O_1, that G, the blood glucose concentration, should be greater than 70 mg/dL is formulated as: $- G + 70 \leq M*(1-O_1)$, where M is a large positive number. These objectives are arranged in a descending order of priority by introducing the constraints: $P_1 \geq P_2$, $P_2 \geq P_3$, ..., $P_{Np-1} \geq P_{Np}$ where the priorities are denoted by $P_1, ..., P_{Np}$. The priorities P are 0-1 binary variables and a priority is met if and only if the corresponding objective is also met. This condition is formulated as: $O_1 \geq P_1$, $O_2 \geq P_2$, ..., $O_{Np} \geq P_{Np}$.
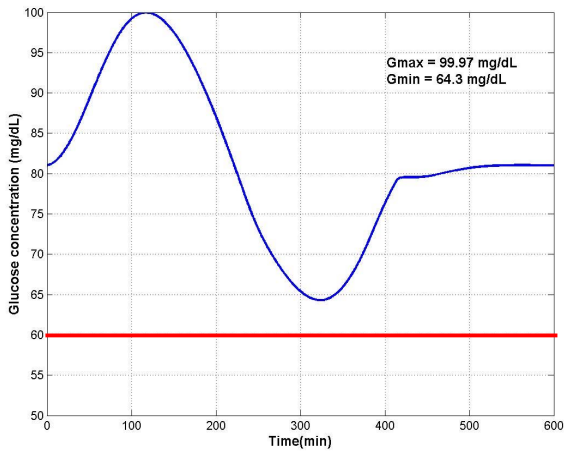

Fig. 5. Glucose concentration profile for asymmetric objective function.

The control problem similar to (3) can then be formulated. In this work we consider, minimization of a linear objective function, consisting of weighted summation of the terms corresponding to: glucose concentration deviation over a time horizon, insulin infusion rates over the time horizon, priorities and objectives, given by:

$$\min_{U,P,O} \alpha^T P + \beta^T O + \gamma \sum_{k=0}^{N_y} \left| x_{t+k|t} \right| + \delta \sum_{k=0}^{N_y-1} \left| u_{t+k} \right| \tag{11}$$

where α and β are constant vectors and γ and δ are constant scalars. This function is minimized subject to the model and constraints in (1) and (2) and the constraints mentioned in the previous paragraph. This results in a mixed-integer linear program (MILP) that can be reformulated as a multi-parametric mixed integer linear program (mp-MILP) [15] by treating the state variable as parameters and the control and integer variables as optimization variables, similar to that discussed in section III.A.

Consider the case when there are 9 objectives in the

descending order of priority as shown in Table I [7]. $G(k+\theta)$ is the blood glucose concentration at the $k+\theta$ time interval where k is the current time interval and θ is the number of steps over which the objective is not enforced. Fig. 6 shows the performance of the controller, which although is not as good as observed for the asymmetric case (Fig. 5) but is much better than for the symmetric case (Fig. 4) and hypoglycemia is avoided.

TABLE I
OBJECTIVES AND PRIORITIES

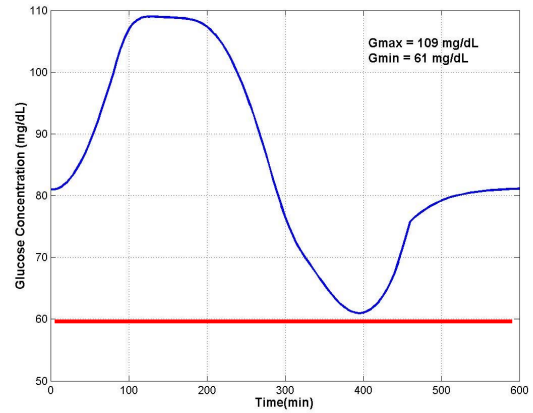| Priorities	Objectives
1	$G(k+\theta) > 70$, $\theta = 2$
2	$G(k+\theta) > 70$, $\theta = 1$
3	$G(k+\theta) > 70$, $\theta = 0$
4	$G(k+\theta) > 75$, $\theta = 2$
5	$G(k+\theta) > 75$, $\theta = 1$
6	$G(k+\theta) > 75$, $\theta = 0$
7	$G(k+\theta) < 110$, $\theta = 2$
8	$G(k+\theta) < 110$, $\theta = 1$
9	$G(k+\theta) < 110$, $\theta = 0$

Fig. 6. Glucose concentration profile for prioritized constraints.

V. CONCLUDING REMARKS

In this work, advanced model based parametric controllers for the regulation of blood glucose concentration have been proposed. The key advantages of these controllers are that they require minimal on-line computational effort and can take into account the physician's performance criteria. The reduction in the on-line computational effort is due to the parametric programming techniques that provide the optimal insulin infusion rate as an explicit function of the state of the

patient. The physician's performance criteria are given by minimization of the blood glucose concentration from the target value as well as placing more emphasis on reducing the negative excursions from the target value than on the positive excursions. Two approaches for addressing this problem were proposed. In the first approach, a control objective function consisting of asymmetric weights on positive and negative deviations was constructed. This resulted in reduced negative deviations and hypoglycemia was avoided. The second approach relies on introducing 0-1 binary variables to enforce and prioritize constraints on blood glucose concentration. This approach also resulted in a reduction in negative deviations and avoided hypoglycemia. These developments are expected to improve the automation of the blood glucose control and significant reduction in the patient inconvenience.

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