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DRAFT: CHANCE CONSTRAINT BASED DESIGN OF IV INSULIN CONTROL FOR TYPE 1 DIABETIC PATIENTS UNDER MODEL & MEAL UNCERTAINTIES

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ABSTRACT

The focus of this paper is on the development of a chance constrained controller for type 1 diabetic patients in the presence of model, meal and initial condition uncertainty. Since the chance constraints require the mean and variance of the evolving uncertain blood-glucose, a conjugate unscented transform based approach is used to estimate the blood-glucose statistics. The proposed approach is demonstrated on the classic Bergman model augmented with a gut dynamics model.

1 INTRODUCTION

The American Diabetes Association (ADA) [1] estimates that 1.25 million Americans have been diagnosed with Type 1 diabetes which is also called Juvenile diabetes. There are about 40 thousand additional diagnosis every year. Type 1 diabetes is a chronic ailment which without careful regulation results in micro-vascular complications such as retinopathy, neuropathy & nephropathy and macro-vascular complications such as cardio-vascular disease & strokes [2]. The ADA estimates that the cost associated with the treatment and productivity loss of patients (with diabetes) has risen from $174 billion in 2007 to $245 billion in 2012, a 41% increase. There is a clear motivation from a quality of life and from a health care economics point of view, to develop controllers which can emulate the human pancreas as closely as possible. This has motivated the Juvenile Diabetes Research Foundation to launch a consortium in 2006 [3]. The European Union provided additional impetus by initiating the AP@Home effort in 2010 [4], to develop an *Artificial Pancreas*.

Since the development of the first insulin pump by Arnold Kadish [5] which was essentially a backpack, significant progress has been made in reducing the size of the pump. The first commercial pump called *AutoSyringe* provided the impetus leading to numerous manufacturers currently providing pager sized insulin pumps [5]. The current insulin pumps use a catheter to subcutaneously provide basal insulin infusion in conjunction with bolus doses and correction doses.

There has also been a long term effort at developing reliable Continuous Glucose Monitoring (CGM) systems. Many of the current continuous glucose monitoring devices are invasive and are electroenzymatic and need to be periodically replaced. The sensor reading from these electroenzymatic sensors can be transmitted every 1-5 minutes to an insulin pump to facilitate the implementation of a closed loop control system. Finger-prick readings are required to periodically calibrate the CGM although a newer version of a CGM sensor claims to be calibration free [6]. Various non-invasive sensing approaches, based on technologies such as bio-impedance, Near Infrared Spectroscopy, Raman spectroscopy etc. [7] have also been tested to gauge their potential to serve as a reliable, calibration free approach for blood-glucose sensing.

With the maturation of sensing technology in conjunction with the availability of rapid and long acting insulin, the implementation of closed-loop control to eliminate if not minimize the

potential of hypo- and hyperglycemic events is becoming a reality. This goal of the closed-loop control is challenged by the fact that the blood-glucose insulin dynamics for Type 1 diabetic patients is characterized by uncertainties that can be attributed to diurnal variations, meal uncertainties, level of exercise and illness [8]. There is therefore a need to formulate control problems that can account for the uncertainties to synthesize insulin infusion profiles which can emulate a healthy pancreas.

This paper presents a probabilistic problem formulation for the design of optimal controllers for type 1 diabetic patients in the presence of model and meal uncertainties. The classical Bergman model is used to illustrate the proposed control formulation. Since the traditional exponentially decaying models for glucose appearance in the Bergman model seem to depart from the glucose appearance rates from the FDA approved T1DMS simulator, a gut-dynamic model is included resulting in a sixth order model. A chance constraint, which only requires information of the mean and variance of the distribution of the blood-glucose is used to impose an acceptable risk level. We assume five uncertain parameters in the model, uncertainty in the meal size and uncertainty in the blood glucose at the time of insulin bolusing. Since, we only require information about the mean and variance of the evolving blood-glucose, the recently developed Conjugate Unscented Transform (CUT) approach [9] is used to estimate the blood-glucose statistics. A sequential cone programming problem is then solved to determine the optimal insulin infusion profile to track an *ideal* glucose trajectory for the nominal meal.

This document is organized as follows. Section 1 introduces the problem statement and presents some background in the field. Section 2 elaborates the dynamic systems as well as outlays the environment used for the simulations. Section 3 provides a brief overview of the CUT and how it can be used to determine statistics of stochastic variables. This is followed by section 4 where the concept of chance constraints are introduced. Then, in section 5 the method to determine the statistics of blood glucose using CUT is explained. Section 6 combines results from the previous two sections to present the implementation of the chance constraints on blood glucose. The sequential cone programming algorithm is outlined in section 7 where the final results are presented. The paper ends with concluding remarks in section 8.

2 MODEL AND SIMULATION ENVIRONMENT

2.1 Dynamic Model

The control design in this work has been implemented on the popular Bergman's Minimal model for glucose-insulin dynamics [10], although the strategy can be easily adapted for more sophisticated models. The minimal model is a two compartment physiological model where the evolution of the model states are defined by

$$\dot{G}(t) = -(X(t)+p_1)G(t) + p_1 G_b + R_{ag}(t)/V_g \tag{1}$$

$$\dot{X}(t) = -p_2 X(t) + p_3(I(t)-I_b) \tag{2}$$

$$\dot{I}(t) = \begin{cases} -p_4 I(t) + \gamma(G(t)-h)(t-t_m) & \text{for } t \geq t_m \text{ and} \\ & G(t) \geq h \\ -p_4 I(t) & otherwise. \end{cases} \tag{3}$$

p_1 (min^{-1}), p_2 (min^{-1}), p_3 $(min^{-2}.L/mU)$, p_4 (min^{-1}), γ $(min^{-2}.mU.dL/mg.L)$ and h (mg/dL) are parameters of the model. p_1 is used to characterize the effective glucose disappearance at basal insulin levels, while p_2 along with p_3 represents the capacity of insulin to increase glucose disappearance and hinder more glucose production. p_4 represents the time constant for insulin disappearance from blood. The states $G(t)$ (mg/dL), $X(t)$ (min^{-1}) and $I(t)$ (mU/L) represent the blood glucose concentration, effective insulin in the remote compartment and the blood insulin concentration respectively. G_b and I_b represent certain basal values of the states $G(t)$ and $I(t)$. The term $\gamma(G(t)-h)(t-t_m)$ mimics the action of the human pancreas, t_m (which has been assumed to be $30\,min$ for all simulations) is time of meal consumption and V_g (dL) is the distribution volume of glucose.

The additional term $R_{ag}(t)$ (mg) (also referred to as the Rate of appearance of glucose in blood) is introduced in the model to replicate a meal intake disturbance. In this work, the dynamics that determine $R_{ag}(t)$ is evaluated from a gut dynamics model adopted from [11]. The model is given by the equations

$$\dot{q}_{sto1}(t) = -k_{21} q_{sto1}(t) + D\delta(t-t_m) \tag{4}$$

$$\dot{q}_{sto2}(t) = -k_{empt} q_{sto2}(t) + k_{21} q_{sto1}(t) \tag{5}$$

$$\dot{q}_{gut}(t) = -k_{abs} q_{gut}(t) + k_{empt} q_{sto2}(t) \tag{6}$$

$$R_{ag}(t) = f k_{abs} q_{gut}(t) \tag{7}$$

$$q_{sto} = q_{sto1} + q_{sto2} \tag{8}$$

$$k_{empt}(q_{sto}) = k_{min} + 0.5(k_{max}-k_{min})(\tanh[\alpha(q_{sto} - bD)] - \tanh[\beta(q_{sto}-cD)] + 2) \tag{9}$$

$$\alpha = \frac{5}{2D(1-b)} \tag{10}$$

$$\beta = \frac{5}{2Dc}. \tag{11}$$

where q_{sto1} (mg) and q_{sto2} (mg) are the amounts of glucose in solid and liquid phases respectively present in the stomach at any time. q_{gut} (mg) is the amount of glucose in the intestines, $\delta(.)$ is the Dirac delta function and D (mg) is the amount of glucose consumed during the meal. k_{21} (min^{-1}) is a constant which determines the rate at which food moves from the first stomach state to the second. k_{empt} (min^{-1}) represents the rate at which the food is drained from the second stomach state to the gut state. It is bounded by maximum and minimum values k_{max} and k_{min} respectively. k_{abs} (min^{-1}) is the rate at which the carbohydrates are absorbed into the body from the gut. α and β are parameters which determine the transition of k_{empt} between its extremities. Finally, b, c and f are other dimensionless parameters of the model.

One of the objectives of the control problem is to make the glucose concentration in a Type 1 diabetic patient track the glucose concentration of a normal person over time after a meal. The variation of glucose concentration for a normal person is referred to as the target glucose trajectory. This target trajectory is generated by simulating the Bergman's model using parameter values fitted to a normal person. Since these parameters vary among people, a set of values are chosen, for illustrative purposes, from literature [12,13]; where the Bergman model and the gut dynamics was actually fit to real data (taken from a normal subject(s)). These values are listed in Table 1. The initial conditions for the trajectory was selected as

$$G(0) = G_b;\ X(0) = 0;\ \text{and}\ I(0) = I_b.$$

It should be noted that during practical implementation, the parameters and initial conditions are not binding and can be altered depending on the target trajectory desired for a patient. In fact, the target trajectory need not be obtained from a model simulation and could be prescribed by the respective physician. However, in this work as mentioned previously, for illustration, the target trajectory is obtained from a simulation.

In case of a person suffering from Type-1 diabetes, the natural pancreas ($\gamma(G(t)-h)(t-t_m)$) is removed and is substituted by an artificial insulin input term $U'(t)$ similar to Lynch and Bequette in [14]. This alters equation (3) to

$$\dot{I}(t) = -p_4 I(t) + U'(t). \tag{12}$$

The diabetic model (comprised of equations (1), (2) and (12)) is now an unstable system in the absence of any insulin control causing the glucose concentration to grow unchecked (which is reasonable to assume: for a Type 1 diabetic patient with no insulin). To stabilize the glucose concentration in such patients,

TABLE 1. Parameter values for a normal subject

Parameter	Value	Parameter	Value
p_1	0.03082	k_{max}	0.0558
p_2	0.02093	k_{min}	0.0080
p_3	1.062×10^{-5}	k_{abs}	0.057
p_4	0.30000	k_{21}	0.0558
γ	0.003349	b	0.82
h	89.5	c	0.00236
G_b	92	f	0.9
I_b	7.3	V_g	146.64

in reality, a basal insulin dosage is given. This concept can be modeled by assuming the control to be of the form

$$U'(t) = U(t) + p_4 I_b \tag{13}$$

where the term $p_4 I_b$ mimics the basal dosage. With this modification, the diabetic model can be summarized as

$$\dot{G}(t) = -(X(t) + p_1)G(t) + p_1 G_b + R_{ag}(t)/V_g \tag{14}$$

$$\dot{X}(t) = -p_2 X(t) + p_3(I(t) - I_b) \tag{15}$$

$$\dot{I}(t) = -p_4(I(t) - I_b) + U(t). \tag{16}$$

Equations (14) through (16) now represent a stable system where the glucose concentration is driven to the desired basal level (G_b). The objective is to determine an insulin trajectory ($U(t)$) to successfully track the target trajectory.

2.2 Model Uncertainties

This subsection is used to outline the uncertainties that have been assumed for the simulation of diabetic patients and present their non-uncertain parameter values. To account for patient variability, model parameters such as $G(0)$, p_1, p_2, p_3, k_{max} and k_{min} are assumed to be uncertain. The non-uncertain Bergman parameter p_4 is taken from literature [14] where the value was identified by fitting the Bergman model to the outputs obtained from the Sorensen diabetic model. The other parameters for diabetic

patients (k_{abs}, b, c, f, V_g G_b and I_b) were obtained from the FDA approved Type 1 Diabetes Metabolic Simulator (T1DMS) software (corresponding to an average adult). The parameters have been tabulated in Table 2.

TABLE 2. Parameter values for a Type 1 Diabetic subject

Parameter	Value	Parameter	Value
$p_1^{nominal}$	0.028735	$k_{max}^{nominal}$	0.0429
$p_2^{nominal}$	0.028344	$k_{min}^{nominal}$	0.0141
$p_3^{nominal}$	5.035×10^{-5}	k_{abs}	0.2062
p_4	$5/54$	k_{21}	0.0558
b	0.7612	c	0.1372
G_b	119.1858	f	0.9
I_b	15.3872	V_g	128.8237

$G(0)$ is the glucose concentration in blood when the simulation starts (i.e. at $t = 0\,min$). Since, the glucose concentration at that instant is unlikely to be exactly the basal value (G_b), $G(0)$ is assumed to be uniformly distributed about G_b with a 30% variation on either side of it. Therefore, $G_0 \in U[83.43, 154.9415]$.

To account for inter-patient variability p_1, p_2, p_3, k_{min} and k_{max} are also assumed to have uniform distributions with a 30% variation about their nominal values. The nominal values (for type 1 diabetic patients) are taken from literature [14] and T1DMS average adult data set (Table 2).

The final uncertainty has been assumed in the meal size consumed by a patient (i.e. the parameter D in equation (4)). According to the 2010 Dietary Guidelines [15] published by the U. S. Department of Agriculture, Health and Human Services, the daily carbohydrate (CHO) intake goal for all ages should be $130\,gm$. Depending on the individual and time of day, meal sizes can vary. Light and heavy meals vary in their CHO counts significantly. The values can vary between $15\,gm$ for a snack to $60\,gm$ for lunch if CHOs from all foods at a meal are added up. A breakdown of the carbohydrate content of recommended foods for diabetic patients can be found in article [16] from the American Diabetes Association. Based on the daily total and mealtime CHO recommendations, D is assumed to have a uniform distribution given by $D \in U[0, 60]\,mg$.

All the aforementioned uncertainties are time invariant and their impact on the evolution of the blood glucose is of interest in the analysis of any controller. Monte Carlo simulations can be used to estimate the evolution of the probability density function of the blood-glucose. However, it is well recognized that this is computationally expensive and will not be suitable for real-time estimation of the time evolution of the statistics of the blood-glucose. A technique such as polynomial chaos [17] presents a powerful approach for the estimation of the statistics, but also suffer from the curse of dimensionality as the number of uncertain variables increase. A powerful deterministic sampling based approach was proposed by Julier and Uhlman [18], called the Unscented Transform (UT). UT permits using $2p+1$ number of samples (sigma points) for p dimensional uncertain inputs to estimate the mean and covariance of the output. One shortcoming of the UT is that as the number of uncertain variable grows, the weights assigned to the sigma points can become negative and the location of the sigma points can lie outside the support of the uncertain variable. For example, if a variable is uniformly distributed, the sigma points could potentially fall outside the support of the uncertain variable. This motivates the use of a more sophisticated method to calculate statistics of random variables. The next section outlines a recently developed sampling scheme that addresses the two mentioned issues.

3 CONJUGATE UNSCENTED TRANSFORM

The Conjugate Unscented Transform for multivariate uniform distributions introduced in [9] is a technique used to calculate statistics of uniform random variables which undergo non-linear transformations. It belongs to a wide class of techniques commonly referred to as sigma-point based estimators. In these methods, a set of points (a.k.a. the sigma points) are selected from the uncertain space (whose statistics are known) such that the mean and the covariance of all the points match with the known statistics. Each of these points are then made to go through the non-linear transformation to yield another set of points in the transformed space. The statistics of the transformed space is now evaluated from the transformed points by weighing them appropriately.

The CUT defines a way to determine the position (x_i) and the associated weights (w_i) of these sigma points. If the non-linear transformation is defined as $y_i = f(x_i)$, then the statistics (mean and covariance) of the transformed space (y) is determined by

$$\bar{y} = \sum_{i=1}^{N} w_i y_i \text{ and} \tag{17}$$

$$P_y = \sum_{i=1}^{N} w_i (y_i - \bar{y})(y_i - \bar{y})^T. \tag{18}$$

where N is the total number of sigma points, $\bar{y}$ and P_y are the mean and the covariance of the transformed space.

For the diabetes problem in this work, CUT is used to depict the variation in the glucose concentration due to the assumed uncertainties. The number of uncertainties is 7 (i.e.

$\boldsymbol{x} = [p_1, p_2, p_3, G(0), D, k_{max}, k_{min}]^T$). Since, the variable of interest is the glucose concentration, the output y is $G(t)$ and the non-linear function f is the numerical simulation of the diabetic model (equations (14) through (16)). After assuming that the uncertain variables are independent, $N = 686$ sigma points ($\boldsymbol{x}^{(i)}$) and weights ($w^{(i)}$) are generated using the CUT-4 algorithm in [9]. For each of these sigma points, the diabetic model is simulated and the glucose trajectories over time are recorded. The statistics of the glucose concentration (at each time instant) is then evaluated by weighing all the trajectories appropriately (as presented in equations (17) and (18)). Figure 1 shows a 3-sigma bounded variation of the glucose concentration, calculated from the 686 trajectories via CUT.

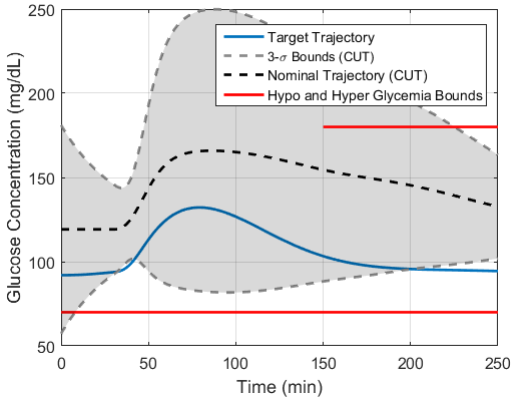

FIGURE 1. Glucose variation with only basal Insulin infusion

It is recommended that blood glucose concentration never falls below a lower bound G_{lb} (hypoglycemia) at any time. According to a joint consensus statement from the ADA and the Endocrine Society regarding hypoglycemia and diabetes [19], G_{lb} should be $70\frac{mg}{dL}$. In addition, after two hours ($120\,min$) of a meal, it is recommended by the American Diabetes Association [20] that the blood glucose concentration be below $180\,\frac{mg}{dL}$. These constraints have been shown (in red) in Figure 1 as well. The objective now is to figure out a way to incorporate these constraints into the control problem. One way to do it would be to pose hard inequality constraints on the blood glucose at the necessary time instants. However, a downside to this approach is that the hypoglycemic as well as the hyperglycemic constraints are treated with equal severity where in reality it is accepted that the hyperglycemic constraint is a comparatively softer constraint (as compared to the hypoglycemic one) in the short term. Moreover, assuming hard constraints may also fail to give a feasible control solution where significant variability in glucose trajectories have been assumed. As a result, these two issues motivate a probabilistic approach towards the glycemic constraints. The next section introduces the concept of chance constraints which is used later to impose the constraints on blood glucose.

4 CHANCE CONSTRAINTS

Calafiore and El Ghaoui in [21] present an approach to rewrite linear probabilistic inequalities as non-probabilistic inequalities. In their work, they prove that if a and b are random variables with known means and variances, then the constraint:

$$\text{Prob}\{a^T x + b \leq 0\} \geq 1 - \varepsilon \tag{19}$$

is equivalent to the convex constraint

$$\sqrt{\frac{1-\varepsilon}{\varepsilon}}\{var[a^T x + b]\}^{1/2} + E[a^T x + b] \leq 0 \tag{20}$$

where ε ($\in (0,1)$) represents the risk level i.e. the probability with which the constraint is permitted to be violated. It should be noted that the constraint is conservative since it subsumes all distributions with the same mean and variance. Therefore, if only the first two moments of the random variables (a,b) are known, equation (20) allows one to enforce equation (19) no matter what the true distribution of (a,b) is. However, since this constraint is robust to all distributions, it yields conservative solutions.

One alternative would be to assume a Gaussian distribution as the probability distribution function (pdf) of $G(t)$ and enforce a chance constraint specific to a Gaussian distribution. However Figure 2 is used to illustrate that the pdf of $G(t)$ is non-Gaussian at all times.

In Figure 2, Gaussian pdfs are generated using the mean and variance obtained from CUT at 3 distinct time instants (shown in red). These pdfs are then compared to the pdfs generated from 10000 Monte Carlo (MC) sample trajectories (shown in blue). It is evident that although the two sets of pdfs have the same first two moments, they are all different. Hence, the robust chance constraint (equation (20)) is chosen for implementation.

The idea here is to: use CUT to obtain accurate measures of the mean and the variance of blood glucose ($G(t)$) over time and then: use these measures to enforce hypoglycemic or hyperglycemic chance constraints.

5 COMPUTATION OF MEAN AND VARIANCE

The formulation of the chance constraints is designed only for linear constraints (Equation (19)). Such a formulation would need the mean of $G(t)$ to be a linear function of $G(0)$ and $U(t)$ as well as the variance of $G(t)$ to be a quadratic function of $G(0)$ and $U(t)$. This is not the case here as can be seen from the model equations. Therefore, the first objective of this section

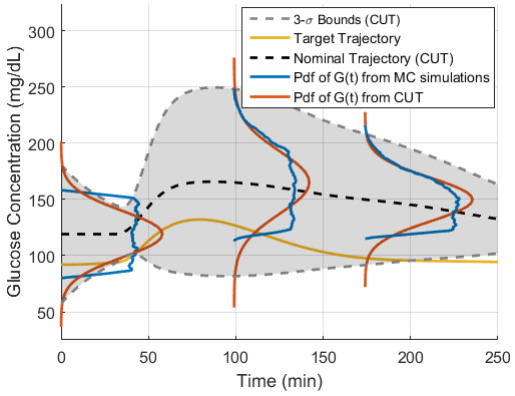

FIGURE 2. Pdfs obtained from CUT and MC sampling at times: $t = 0$, 99 and 174 min. (Pdfs have been scaled for illustration)

is to present a linear approximation for $G(t)$ which can cater to the chance constraint needs. The second objective is to derive a way in which the statistics of blood glucose can be determined after the control input has been slightly changed.

To deal with the issue of non-linearity, the non linear model is linearized about the trajectories generated from the N sigma points (also called the nominal trajectories). The mean and the variance of $G(t)$ are then calculated from these linearized models by appropriately weighing them. This entire process is elaborated in this section.

5.1 Linearization

Let the non-linear diabetes model be described by the equation

$$\dot{\boldsymbol{z}} = \boldsymbol{f}(\boldsymbol{z}, U) \tag{21}$$

where $\boldsymbol{z} = [G, X, I, q_{sto1}, q_{sto2}, q_{gut}]^T$. This system is linearized about the N nominal trajectories $\overline{\boldsymbol{z}}^{(i)}$. $\overline{\boldsymbol{z}}^{(i)}$ are generated from N sigma points using $\dot{\overline{\boldsymbol{z}}}^{(i)} = \boldsymbol{f}(\overline{\boldsymbol{z}}^{(i)}, \overline{U})$, where $\overline{U}$ (also referred to as the nominal input) is an initial guess of the control input U. The error dynamics of the linearized systems is given by

$$\Delta\dot{\boldsymbol{z}}^{(i)} = \left.\frac{\partial \boldsymbol{f}}{\partial \boldsymbol{z}}\right|_{\boldsymbol{z}=\overline{\boldsymbol{z}}^{(i)}, U=\overline{U}} \Delta\boldsymbol{z}^{(i)} + \left.\frac{\partial \boldsymbol{f}}{\partial U}\right|_{\boldsymbol{z}=\overline{\boldsymbol{z}}^{(i)}, U=\overline{U}} \Delta U \tag{22}$$

where (i) represents the system corresponding to the i^{th} sigma point and varies from 1 to N. This linear system is now discretized so that linear algebraic chance constraints on the blood glucose can be exercised.

5.2 Discretization

The discretized version of equation (22) assuming a Zero Order Hold setting can be written as

$$\Delta\boldsymbol{z}^{(i)}(k+1) = G_k^{(i)} \Delta\boldsymbol{z}^{(i)}(k) + H_k^{(i)} \Delta U(k) \tag{23}$$

where k is the k^{th} time step, $G_k^{(i)}$ and $H_k^{(i)}$ are state dependent discretized system matrices for the i^{th} sigma point trajectory. Equation (23) can be simplified to

$$\Delta\boldsymbol{z}^{(i)}(k+1) = \left(\prod_{j=0}^{k} G_j^{(i)}\right) \Delta\boldsymbol{z}^{(i)}(0) + H_k^{(i)} \Delta U(k) + \sum_{j=0}^{k-1} \left(\prod_{m=j+1}^{k} G_m^{(i)}\right) H_j^{(i)} \Delta U(j) \tag{24}$$

where $\Delta\boldsymbol{z}^{(i)}(0)$ represents the initial perturbation state of each trajectory and is equal to 0.

For the entire work, the simulation time has been assumed to be $T_f = 250\,min$ and the sampling time to be $T_s = 1\,min$. This makes k vary between 0 and 249. Correspondingly, the number of inputs is 250, i.e. $U(0)$ through $U(249)$. If the entire control profile is defined by the vector $\boldsymbol{U} = [U(0), U(1), \ldots, U(249)]^T$, the entire blood glucose profile by $\boldsymbol{G} = [G(1), G(2), \ldots, G(250)]^T$), the error dynamics can be given by the equation

$$\Delta\boldsymbol{G}^{(i)} = M^{(i)} \Delta\boldsymbol{U} \tag{25}$$

where $M^{(i)} =$

$$\begin{bmatrix} C_{glu} H_0^{(i)} & \cdots & \\ C_{glu} G_1^{(i)} H_0^{(i)} & C_{glu} H_1^{(i)} & \\ \vdots & \vdots & \ddots \\ C_{glu} \left(\prod_{j=1}^{k} G_j^{(i)}\right) H_0^{(i)} & \cdots & \cdots\ C_{glu} H_{249}^{(i)} \end{bmatrix} \tag{26}$$

and $C_{glu} = [1, 0, 0, 0, 0, 0]^T$. Thus, equation (25) allows us to write the blood glucose perturbation along each sigma point trajectory as a linear function of the input perturbation, accomplishing the first objective of the section.

C_{glu} can also be used to write the nominal blood glucose trajectories as

$$\overline{\boldsymbol{G}}^{(i)} = C_{glu} \boldsymbol{z}^{(i)}. \tag{27}$$

Therefore, the blood glucose profile $\boldsymbol{G}$ due to a $\Delta\boldsymbol{U}$ change in the control input profile $\overline{\boldsymbol{U}}$ can be finally written as

$$\boldsymbol{G} = \overline{\boldsymbol{G}} + \Delta\boldsymbol{G} \tag{28}$$

where $\overline{\boldsymbol{G}}$ is the stochastic nominal blood glucose trajectory due to the control input $\overline{\boldsymbol{U}}$ and $\Delta\boldsymbol{G}$ is the stochastic perturbation about $\overline{\boldsymbol{G}}$ due to a perturbation in the control input $\Delta\boldsymbol{U}$. The statistics of $\boldsymbol{G}$ can now be easily calculated using relations similar to (17) and (18) since we have sigma-point realizations of $\overline{\boldsymbol{G}}$ as well as $\Delta\boldsymbol{G}$. This completes the second objective.

However, the statistics of most interest is the mean and the variance of $\boldsymbol{G}$ because the mean and the variance are the only two moments necessary for the robust chance constraints. The next section details the development of the chance constraints using the said two moments.

6 CHANCE CONSTRAINTS ON GLUCOSE

As expressed previously, this work seeks to implement chance constraints on the hypoglycemic and hyperglycemic blood glucose concentration levels. It is desired that the hypoglycemic constraint is always satisfied, i.e. $G(k) \geq G_{lb}$ for all k. It is also desired that the hyperglycemic constraint is satisfied after two hours of the meal, i.e. $G(k) \leq G_{ub}$ for $k > 150$ since meal time is $t_m = 30\,min$. In this section, the derivation of only the hypoglycemic chance constraint at a particular time instant j is shown, as the other constraints are almost identical. The objective of this section is to derive a convex inequality as a function of $\Delta\boldsymbol{U}$ to represent the chance constraints.

The blood glucose concentration at the j^{th} minute is given by the j^{th} row of equation (28) and is summarized as $G(j) = \overline{G}(j) + \Delta G(j)$. The goal is to effectively implement the following probabilistic constraint

$$\text{Prob}\{-G(j) + G_{lb} \leq 0\} \geq 1 - \varepsilon_1 \text{ for } j = 1, \ldots, 250. \tag{29}$$

Ideally, ε_1 should be 0 since we want the hypoglycemic constraint to be satisfied with probability 1. However, since the chance constraints are conservative to begin with, a 10 % violation is allowed, i.e. $\varepsilon_1 = 0.1$. Equation (29) is equivalent to the constraint

$$\sqrt{\frac{1-\varepsilon_1}{\varepsilon_1}}\{\text{var}[-G(j) + G_{lb}]\}^{1/2} + E[-G(j) + G_{lb}] \leq 0 \tag{30}$$

similar to equation (20). Now,

$$E[-G(j) + G_{lb}] = -E[\overline{G}(j) + \Delta G(j)] + G_{lb} = \underbrace{-\sum_{i=1}^{N} w^{(i)} \overline{G}^{(i)}(j)}_{E[\overline{G}(j)]} \underbrace{-\sum_{i=1}^{N} w^{(i)} M_j^{(i)} \Delta\boldsymbol{U}}_{E[\Delta G(j)]} + G_{lb} \tag{31}$$

where $\overline{G}^{(i)}(j)$ is the j^{th} element of $\overline{\boldsymbol{G}}^{(i)}$ and $M_j^{(i)}$ is the j^{th} row of $M^{(i)}$. Moreover,

$$\text{var}[-G(j) + G_{lb}] = \text{var}[-G(j)] = \text{var}[\overline{G}(j) + \Delta G(j)] \tag{32}$$

since G_{lb} is a number and not a random variable. Equation (32) can be expanded as

$$\text{var}[\overline{G}(j) + \Delta G(j)] = \text{var}[\overline{G}(j)] + \text{var}[\Delta G(j)] + 2\text{cov}[\overline{G}(j), \Delta G(j)]. \tag{33}$$

The variances can be found using the following relations

$$\text{var}[\overline{G}(j)] = \underbrace{\sum_{i=1}^{N} w^{(i)} (\overline{G}^{(i)}(j) - E[\overline{G}(j)])^2}_{C} \text{ and} \tag{34}$$

$$\text{var}[\Delta G(j)] = \sum_{i=1}^{N} w^{(i)} (\Delta G^{(i)}(j) - E[\Delta G(j)])^2. \tag{35}$$

Equation (35) can be simplified in terms of $\Delta\boldsymbol{U}$ as

$$\text{var}[\Delta G(j)] = \Delta\boldsymbol{U}^T \underbrace{\left(\sum_{i=1}^{N} (M_j^{(i)} - M_j) w^{(i)} (M_j^{(i)} - M_j)^T \right)}_{A} \Delta\boldsymbol{U}. \tag{36}$$

where $M_j = \sum_{i=1}^{N} w^{(i)} M_j^{(i)}$. The covariance term in equation (33) is found using

$$\text{cov}[\overline{G}(j), \Delta G(j)] = \sum_{i=1}^{N} w^{(i)} (\overline{G}^{(i)}(j) - E[\overline{G}(j)])(\Delta G^{(i)}(j) - E[\Delta G(j)]). \tag{37}$$

Once again, equation (37) can be simplified in terms of $\Delta \boldsymbol{U}$ as

$$\text{cov}[\overline{G}(j), \Delta G(j)] = \underbrace{\left(\sum_{i=1}^{N} w^{(i)} (\overline{G}^{(i)}(j) - E[\overline{G}(j)])(M_j^{(i)} - M_j) \right)}_{B} \Delta \boldsymbol{U}. \quad (38)$$

Therefore, the variance term in equation (30) can be written as a quadratic function of the $\Delta \boldsymbol{U}$ vector as

$$\text{var}[-G(j) + G_{lb}] = \Delta \boldsymbol{U}^T A \Delta \boldsymbol{U} + 2B\Delta \boldsymbol{U} + C \quad (39)$$

where A, B and C are defined through equations (36), (38) and (34) respectively. Since $\text{var}[-G(j) + G_{lb}] \geq 0$, a factorization can be found of the form

$$\text{var}[-G(j) + G_{lb}] = (P\Delta \boldsymbol{U} + Q)^T (P\Delta \boldsymbol{U} + Q) \quad (40)$$

leading to

$$\text{var}[-G(j) + G_{lb}]^{1/2} = ||P\Delta \boldsymbol{U} + Q||_2. \quad (41)$$

On substituting equation (41) and (31) in (30), the chance constraint finally boils down to the cone constraint

$$\underbrace{\sqrt{\frac{1-\varepsilon_1}{\varepsilon_1}} ||P\Delta \boldsymbol{U} + Q||_2 - E[\overline{G}(j)] - E[\Delta G(j)] + G_{lb}}_{HypoCon(j)} \leq 0. \quad (42)$$

Equation (42) represents the hypoglycemic glucose chance constraint for the j^{th} time instant or minute. By considering varying values of j, the hypoglycemic constraint can be imposed for every minute. A similar inequality can also be derived for the hyperglycemic constraint

$$\underbrace{\sqrt{\frac{1-\varepsilon_2}{\varepsilon_2}} ||P\Delta \boldsymbol{U} + Q||_2 + E[\overline{G}(j)] + E[\Delta G(j)] - G_{ub}}_{HyperCon(j)} \leq 0. \quad (43)$$

in which case j would vary from 150 to 250. ε_2 is used to denote the risk level for the hyperglycemic constraint and since it is a much softer constraint, the value was fixed to be 0.3, i.e. allowing a 30 % violation.

Now that all the components necessary to solve the optimal control problem have been defined, the next section focuses on the sequential cone programming algorithm (which uses results from all the previous sections) to finally solve it.

7 SEQUENTIAL CONE PROGRAMMING

This section presents the iterative sequential algorithm that can be used to determine a solution to the optimal control problem.

The algorithm starts with an initial guess of the entire IV insulin control profile. This profile is also termed as the nominal control trajectory and is represented by $\overline{\boldsymbol{U}} = [\overline{U}(0), \overline{U}(1), ..., \overline{U}(249)]^T$. In the problem it is assumed that the control $\overline{\boldsymbol{U}}$ results in the stochastic state $\overline{\boldsymbol{G}}$ and the control $\boldsymbol{U} = \overline{\boldsymbol{U}} + \Delta \boldsymbol{U}$ results in the stochastic state $\boldsymbol{G} = \overline{\boldsymbol{G}} + \Delta \boldsymbol{G}$.

Using $\overline{\boldsymbol{U}}$ as the control input trajectory, N nominal state trajectories $\overline{z}^{(i)}$ are determined based on the N sigma points. The sigma point trajectories now allow the determination of the mean and the variance of $\overline{\boldsymbol{G}}$ as weighted sums of the nominal glucose trajectories ($\overline{\boldsymbol{G}}^{(i)}$).

This step is followed by linearizing the state space model about those N nominal state trajectories to obtain N time-varying continuous linear systems. The N time-varying continuous linear systems are then discretized to obtain N time-varying discrete linear systems with system matrices $G_k^{(i)}$ and $H_k^{(i)}$ (as explained in sections 5.1 and 5.2).

These N sets of system matrices are then used to construct N special matrices ($M^{(i)}$), which map the control perturbation profile ($\Delta \boldsymbol{U}$) to the glucose perturbations ($\Delta \boldsymbol{G}^{(i)}$) about the N nominal glucose trajectories ($\overline{\boldsymbol{G}}^{(i)}$). This allows the determination of the mean and the variance of $\Delta \boldsymbol{G}$ as a linear and a quadratic function of $\Delta \boldsymbol{U}$ respectively. At this point in the development, the following optimization problem is solved:

$$\begin{array}{lll} \text{minimize}_{\Delta \boldsymbol{U}} & ||E[\boldsymbol{G}] - \boldsymbol{G}_{target}||_2 & \\ \text{subject to} & HypoCon(j) \leqslant 0 & \text{for } j = 1, ..., 250 \\ & HyperCon(j) \leqslant 0 & \text{for } j = 150, ..., 250 \\ & \boldsymbol{U} \geqslant 0. & \end{array}$$

The cost function of the problem is designed to minimize the error norm between the expected value of the glucose trajectory ($E[\boldsymbol{G}]$) and the target glucose trajectory ($\boldsymbol{G}_{target}$) shown in blue in Figure 1 so that the control solution drives the mean glucose of the Type 1 diabetic patient towards a glucose profile seen in normal patients. The first two constraints refer to the hypoglycemic and the hyperglycemic chance constraints derived in the previous section (summarized by the inequalities (42) and (43)). The final constraint is to enforce the fact that insulin can only be added to the bloodstream (and not removed).

The optimization problem is convex since the cost is a 2-norm error function (where the error function is linearly dependent on the optimization variable $\Delta \boldsymbol{U}$), the chance constraints are cone constraints and the final constraint is a linear inequality. There are many efficient convex solvers available to solve such problems. For this work however, the CVX MATLAB toolbox

[22] was used. Once the solution $\Delta \boldsymbol{U}^*$ is obtained, the control input solution is updated using the relation: $\boldsymbol{U}^{*(1)} = \overline{\boldsymbol{U}} + \Delta \boldsymbol{U}^*$.

This step concludes the first iteration with $\boldsymbol{U}^{*(1)}$ representing the control solution determined from the iteration. Since the solution at the end of iteration 1 is obtained as a perturbation about an initial guess nominal control trajectory $\overline{\boldsymbol{U}}$, it depends on the choice of $\overline{\boldsymbol{U}}$. To converge to at least a locally minimal control solution, the entire process is made iterative where the nominal trajectory $\overline{\boldsymbol{U}}$ for the second iteration is made equal to the control solution from the previous iteration, i.e. $\boldsymbol{U}^{*(1)}$. Therefore, we get $\overline{\boldsymbol{U}}|_{iter+1} = \boldsymbol{U}^{*(iter)}$ where $iter$ represents the iteration number in the algorithm. As the entire control problem is resolved by solving convex cone optimizations sequentially at each iteration, the phrase Sequential Cone Programming (SCP) is used to justify the process.

Figure 1 shows the variation of glucose (with the mean $\boldsymbol{G}$ in black dashed line) when no insulin control is present. We can see that a large fraction of the grey area (which shows a $3-\sigma$ glucose variability bound) violates the hyperglycemic glucose constraint beyond the $150\,min$ mark, thus motivating the need for an insulin control.

Results from the SCP are now presented. The SCP algorithm is started with an initial nominal guess for the control. The nominal guess is chosen based on the pre-meal bolus principle where an insulin bolus is given prior to the consumption of every meal [23]. Therefore, the initial control guess is assumed to be $\overline{\boldsymbol{U}} = [40, 0, \ldots, 0]^T$.

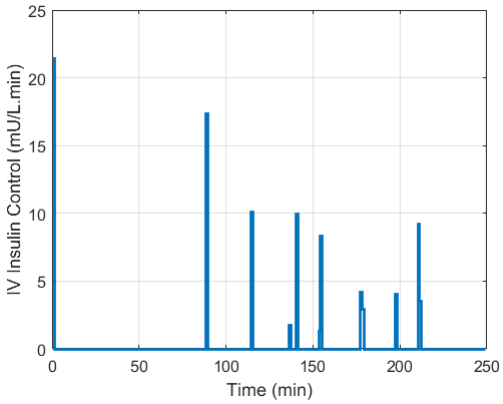

FIGURE 3. Control Solution $\boldsymbol{U}$ obtained after 6 iterations of the SCP

It should be pointed out that the optimization assumes a linear approximation of the true non-linear model. Therefore finding a control solution for the linearized model which satisfies all the constraints does not imply that the same control on the true system would also satisfy those constraints. Hence, the SCP algorithm is terminated only if it is observed that the control solution is able to satisfy all the constraints even for the true non-linear system. This is verified by determining the mean and the variance of blood glucose via the non-linear model using CUT and checking if the desired constraints are met. In the illustrated case, the true glucose variation satisfied the desired constraints at the end of the 6^{th} iteration. The control solution obtained at the end of the 6^{th} iteration is shown in Figure 3. The associated glucose variation is shown in Figure 4. In this figure we see that the glucose variation lies within the stipulated bounds (presenting the success of the SCP algorithm). It is seen that the nominal trajectory hovers above the blue curve instead of tracking it. This is because perfect tracking would cause the grey region to violate the glucose lower bound.

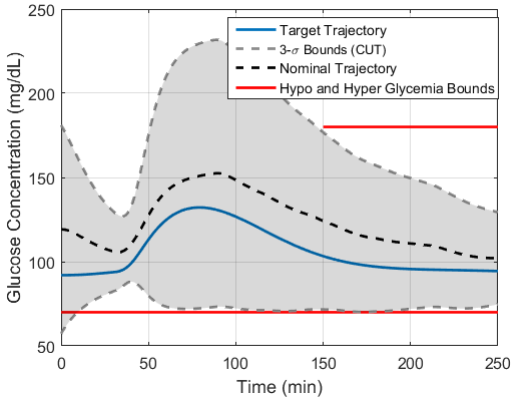

FIGURE 4. Glucose variation $\boldsymbol{G}$ obtained after 6 iterations of the SCP

It should also be mentioned that although the optimization problem being solved is a convex one, the final solution obtained need not be globally optimal. This is because the optimization problem tries to determine a perturbation profile about a pre-established control trajectory and not estimate the entire control input. Therefore, the optimization problem posed in this section only provides the best perturbation profile. Repeatedly solving this optimization problem (by updating the nominal control input) however, allows us to converge to a reasonable solution. It must also be mentioned that for an assumed $\overline{\boldsymbol{U}}$, a solution might not be feasible. This does not mean that a control input solution does not exist, but it just motivates the algorithm to select a better $\overline{\boldsymbol{U}}$.

8 CONCLUSION

A probabilistic approach for the design of insulin profiles to regulate blood glucose in Type 1 diabetic patients is studied. Chance constraints, which are functions of the mean and variance of the uncertain blood-glucose are used to impose acceptable probabilities of hypo- and hyperglycemic events. A sequential cone programming approach is used to design a controller for

a model for Type 1 diabetes with uncertainties in model parameters, meal size and initial blood glucose. Numerical results are encouraging to warrant studying more complex models including subcutaneous insulin infusion.

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