Mealtime Correction Insulin Advisor for CGM-Informed Insulin Pen Therapy*

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Abstract—With improvements in the accuracy and reliability of continuous glucose monitoring (CGM), the stage is set for new algorithmic approaches to the treatment of Type 1 diabetes. While recent efforts to build a closed-loop artificial pancreas device are encouraging, the artificial pancreas will not apply to patients who prefer to inject insulin manually or who simply will not submit to fully automatic closed-loop control. Therefore, it is of interest to see whether non-pump users can benefit from algorithmic insulin advisory systems. In this paper we present a mealtime correction bolus advisor for patients on “multiple daily injection” (MDI) therapy, taking advantage of the ability to estimate the patient’s metabolic state in real time using both CGM and manual reports of insulin delivery. The state estimation process for this is informed by knowledge of the patient’s daily injection of long-acting insulin through the novel concept of a virtual basal rate profile. Preliminary in silico trials indicate that the advisor can result in significantly improved control (reduction of up to 1% saturation of hemoglobin A1C) for patients on insulin pens consistently struggling with sustained hyperglycemia.

I. INTRODUCTION

As many as three million Americans have Type 1 diabetes [1], an autoimmune disease that destroys the insulin-producing pancreatic beta cells, disrupting the hormonal network responsible for maintaining blood glucose concentration (BG) within normal levels. Longitudinal studies, such as the Diabetes Control and Complications Trial (DCCT) [2], have shown that intensive insulin therapy reduces the risk of long-term complications. Prior to the 1970s, intensive therapy was defined primarily by multiple daily injections (MDI) of insulin, in which the timing and dosage of each injection was chosen to satisfy insulin requirements throughout the day. Over the years MDI therapy has evolved to include the use of both long-acting insulin (e.g., glargine and detemir) given once or twice daily to satisfy insulin requirements between meals and rapid-acting insulin (e.g., lispro and aspart) to cover insulin requirements associated with meals. Many patients find insulin pens to be a convenient mechanism for manual injections of insulin. [3] An insulin pen consists of a vial of insulin (either long- or rapid-acting insulin), hypodermic needle, and a plunger mechanism integrated into a single pen-like form factor, allowing patients to “dial in” the desired dose. In the 1970s, continuous subcutaneous insulin infusion (CSII, a.k.a. insulin pump) therapy became a viable alternative to MDI. While CSII therapy is associated with lower glycosylated hemoglobin (HbA1c), lower glycemic variability, and lower incidence of hypoglycemia [4], many patients remain on MDI due in part to the higher cost associated with insulin pumps and the need for trained supervision of the use of insulin pumps.

The technology for BG sensing has similarly undergone a transformation over the years. Replacing the relatively crude and non-specific methods of BG urinalysis, self-monitoring of blood glucose (SMBG), involving the use of a lancet and chemical test strip for each sample, arrived in the 1960s. SMBG is to this day the primary mechanism for assessing BG for treatment, often used to make corrections to mealtime insulin doses based on out-of-range BG. Within the last decade, continuous glucose monitoring (CGM), with BG samples every five minutes or less, has become available to patients as an adjunct to SMBG, giving patients a more complete understanding of glycemic variability throughout the day. Interestingly, the introduction of CGM has led many research groups to work toward the development of a safe and effective “artificial pancreas” in which CGM informs closed-loop adjustment of CSII insulin delivery in real time. [5], [6], [7], [8], [9], [10], [11], [12], [13]

While many patients will certainly want to benefit from the reduced burden of control that would come with an artificial pancreas, it is clear that such devices will be expensive (at least initially) and will appeal mainly to technologically savvy patients. It also seems likely that many patients would remain in control themselves, possibly looking for CGM-informed advice about insulin injections rather than automation. In our prior work, we investigated systems for real time advice to insulin pump users [14], focusing on optimal between-meal correction bolus recommendations on demand. In this paper, we explore the opportunity to provide CGM-informed advice to MDI patients at mealtimes. Specifically, as illustrated in Fig. 1, we work toward a “smart insulin pen” that can provide real time advice about corrections to mealtime rapid-acting boluses based on (i) CGM (in addition to the requisite SMBG reading) and (ii) an internal representation of the pharmacokinetic characteristics of long-acting insulin. We seek to determine the extent to which MDI patients could benefit from algorithmic support for computing optimal correction boluses, leading possibly to the possibility of an automated insulin pen that could provide optimal mealtime correction boluses in real time.
to the investment needed to develop an integrate insulin pen / CGM receiver for the smart insulin pen platform.

II. MODEL OF MDI THERAPY

Long-acting insulin is often conceptualized as having rapid time to peak concentration (two or three hours) and tapering off slowly over the remaining hours of the day (see [15] for a comparison with a faster-acting insulin analog and [16] for a standalone review). For design purposes, we propose a simple model for subcutaneous long-acting insulin in which we add an extra compartment to a previously existing compartmental model of rapid-acting insulin [17], [18], accounting for the slower absorption of long-acting insulin:

\[
\begin{align*}
I_{SC0}(t) &= J_1(t) - k_{d0}I_{SC0}(t) \\
I_{SC1}(t) &= k_{d0}I_{SC0}(t) + J_2(t) - (k_{a1} + k_d)I_{SC1}(t) \\
I_{SC2}(t) &= k_dI_{SC1}(t) - k_{a2}I_{SC2}(t)
\end{align*}
\]

where \(J_1(t)\) and \(J_2(t)\) are the subcutaneous injections rates (pmol/kg/min) of long- and rapid-acting insulins, respectively; \(k_{a0}, k_d, k_{a1}, \) and \(k_{a2}\) are time constants; and \(I_{SCi}\), \(i = 0, 1, 2\) are the volumes of compartments with the outflow of compartments \(I_{SC1}\), and \(I_{SC2}\) contributing, as in the earlier model, to the concentration of insulin in blood plasma. In the simulation results that follow, we set \(k_{d0} = 2.8e - 4\) as the nominal value for the new model parameter, and then test robustness to +/-25% variation in \(k_{d0}\).

We have incorporated the long-acting insulin model above within a specialized Type 1 computer simulation package, implemented in MATLAB/Simulink. This simulator is based on the oral glucose “meal model” of [19] and is equipped with a population of 100 in silico adult patients, which we assume “covers” interpatient variability observed in real patients. The simulator allows for two types of insulin delivery: (i) daily long-acting insulin injections and (ii) injection of rapid acting insulin at meal times (or between meals) according to a prescribed meal scenario specified by the analyst. (In particular, the parameters \(k_{a1}, k_d, k_{a2}\) are all set on a per-patient basis according to the original Type 1 simulator.) Thus, the simulator is uniquely equipped to support evaluation of both (i) conventional insulin pen therapy and (ii) enhanced smart pen insulin therapy. Fig. 2 shows the plasma insulin concentration for the population average patient, resulting from one bolus of long-acting insulin.

Fig. 3 shows the output of the simulator for the same population average in silico patient in a scenario in which the patient only takes the daily insulin long-acting injection and experiences no other metabolic disturbances over the course of 10 days. (Specifically, the in silico patient does not eat and consequently does not require supplementary rapid-acting insulin at meal times.) Note that the daily long-acting dose (35.23 U) was manually titrated to achieve an average BG of 115 mg/dl. The fluctuations in both BG and plasma insulin concentration are due to the pharmacokinetic characteristic of insulin. Note that it takes several days of simulated time for the patient to settle into a regular 24-hour pattern of BG and plasma insulin fluctuations.

III. SMART INSULIN PEN: MEALTIME CORRECTIONS

A. Virtual Basal Rate Profile

The structure of the subcutaneous long-acting insulin model of (1) makes it possible to interpret the 24-hour pattern of plasma insulin fluctuations as resulting from an equivalent insulin pump (continuously varying) basal rate profile. For example, the 24-hour pattern in plasma insulin concentration for the population average in silico patient in Fig. 3 can be implemented via the equivalent insulin pump basal rate profile: \(1.493 + u^{LA}(t)\), with \(u^{LA}(t)\) being an appropriate, patient-specific basal rate deviation signal,
as shown in Fig. 4. (Here, $t = 0$ corresponds to the time of the last long-acting insulin injection). The notion of a virtual basal rate profile makes it possible to account for the pharmacokinetic properties of long-acting insulin in the algorithmic framework below.

### B. LTI Design Model

We adopt a linear discrete-time model derived from the “minimal model” of Bergman et al. [20], extended to account for subcutaneous sensing, subcutaneous injection of rapid acting insulin, and oral consumption of carbohydrates.

\[
x(k+1) = Ax(k) + Bu(k) + Bu^{LA}(k) + G\omega(i),
\]

where $k$ is a discrete time index corresponding to sampling at regular intervals of $T_s$ (here $T_s = 5$ min.), $x$ is a vector of metabolic state variables, $u$ and $u^{LA}$ (both mU/min) are insulin actuation signals, $\omega$ (mg-CHO/min) is a meal disturbance process. To arrive at this model, we linearize the extended minimal model (with population average parameters) about the target operating point (BG = 115mg/dl) assuming a constant rate of insulin infusion, so that $u(k) > 0$ accounts for injections of rapid-acting insulin, and $\omega(k) > 0$ accounts for meals. Let $C$ be such that

\[
y(k) = Cx(k)
\]

is the patient’s plasma BG value at stage $k$ relative to the operating point. Note that we superimpose the differential virtual basal rate signal $u^{LA}$ (with a zero-order hold), so that $k = 0$ corresponds to the discrete stage of the last long-acting insulin injection. In this way we are able to account for the pharmacokinetic properties of long-acting insulin within the Kalman filter used for state estimation.

### C. LQ Optimization Model

At mealtimes the patient will compute a carb-related bolus in the usual way by applying his or her carbohydrate ratio (CR) to an estimate of the size of the meal. However, instead of using his/her correction factor, we compute an insulin correction, which adjusts for the patient’s current state (e.g. high or low BG at the time of the meal), by minimizing the objective function

\[
F(u) = u^T R u + \sum_{k=\kappa}^{\kappa+N} (C\tilde{x}(k) - \Delta)'^T Q (C\tilde{x}(k) - \Delta)
\]

where $\kappa$ is the stage in which the patient intends to deliver a mealtime bolus of rapid-acting insulin, $N$ is the planning horizon (here $N = 72$ five minute intervals, i.e. 6 hours), $Q$ and $R$ are positive semidefinite and definite weighting matrices, respectively, $\Delta$ is a desired BG offset, and $\{\tilde{x}(k)\}_{k=\kappa}^{\kappa+N}$ is governed by

\[
\begin{align*}
\tilde{x}(\kappa) &= \hat{x}(\kappa) \\
\tilde{x}(\kappa+1) &= Ax(\kappa) + Bu + Bu^{LA}(\kappa) \\
\tilde{x}(\kappa+2) &= Ax(\kappa+1) + Bu^{LA}(\kappa+1) \\
&\vdots \\
\tilde{x}(\kappa+N) &= Ax(\kappa+N-1) + Bu^{LA}(\kappa+N-1).
\end{align*}
\]

Note in the above that the correction insulin bolus $u$ is applied only in stage $\kappa$, and the only other variation in insulin is due to the pharmacokinetic characteristics of the long-acting insulin injected at $k = 0$. Note also that $x(\kappa)$ is taken to be the Kalman filter estimate $\hat{x}(\kappa)$ of the patient’s state. Finally, observe that the meal itself is not reflected in the objective function; the objective function essentially assumes that the meal is perfectly compensated for by the CR calculation made by the patient.

To simplify notation, let

\[
\tilde{x}(\kappa) = [\tilde{x}'(\kappa) \tilde{x}'(\kappa+1) \cdots \tilde{x}'(\kappa+N)]'
\]

\[
\bar{u}^{LA}(\kappa) = [u^{LA}(\kappa) u^{LA}(\kappa+1) \cdots u^{LA}(\kappa+N-1)]'
\]

Note that $\tilde{x}(\kappa)$ can be expressed compactly as

\[
\tilde{x}(\kappa) = A\hat{x}(\kappa) + B\bar{u}^{LA}(\kappa) + B_0 u,
\]

where

\[
A = \begin{bmatrix} I \\ A \\ A^2 \\ \vdots \\ A^{N-1} \end{bmatrix} \quad B = \begin{bmatrix} 0 & 0 & \cdots & 0 \\ 0 & 0 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & 0 \end{bmatrix} \quad B_0 = \begin{bmatrix} 0 \\ B \\ AB \\ \vdots \\ A^{N-2}B \\ A^{N-2}B \\ \vdots \end{bmatrix}
\]

Defining $C$ and $\tilde{\Lambda}$ as

\[
C = \begin{bmatrix} C & 0 & \cdots & 0 \\ 0 & C & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & C \end{bmatrix}
\]

\[
\tilde{\Lambda} = \begin{bmatrix} \Delta \\ \Delta \\ \vdots \\ \Delta \end{bmatrix}
\]

we can express $F(u)$ compactly as

\[
F(u) = (C\tilde{x}(\kappa) - \tilde{\Lambda})'^T Q (C\tilde{x}(\kappa) - \tilde{\Lambda}) + u^T R u
\]

where $Q = q \cdot J^{N x N}$.

**Proposition 1** The optimal correction amount for a meal bolus at stage $k$ is

\[
u_{\text{correction}}^* = T_s \cdot u^*/1000 \text{ (U)}
\]

where

\[
u^* = K_1 x(k) + K_2 \Delta + K_3 \bar{u}^{LA}(k),
\]
where
\[ K_1 = \Phi^{-1} \Theta_1, \quad K_2 = \Phi^{-1} \Theta_2, \quad K_3 = \Phi^{-1} \Theta_3, \quad (10) \]

with
\[ \Phi = \begin{pmatrix} BBB' & 0 & CCC' & QQQCCCBBB & 0 \\ 0 & CCC' & QQQ & CCCBBB & 0 + R \end{pmatrix} \quad (11) \]
\[ \Theta_1 = -BBB' & 0 & CCC' & QQQCCCAAA \]

All subjects are run under 2-day scenarios with the meal plan of:

- First day:

Proof: Using (7) and (8), we have that
\[ F(u) = (C_{\hat{x}} - \hat{\Delta})' Q (C_{\hat{x}} - \hat{\Delta}) + u'Ru \]
\[ = (CAx + CB_{LA}^L)' Q (CAx + CB_{LA}^L) \]
\[ + (CAx + CB_{LA}^L)' - (CAx + CB_{LA}^L) - \hat{\Delta}) QCB_{LA} u \]
\[ + u' (B_{0x} C_{LA} QCB_{LA} + R) u \]
\[ - (CAx + CB_{LA}^L)' Q \hat{\Delta} \]
\[ - \hat{\Delta} Q (CAx + CB_{LA}^L) + \hat{\Delta} Q \hat{\Delta}, \]

which, after taking the gradient with respect to \( u \) and collecting terms, gives rise to (9)-(14). □

D. Smart Insulin Pen Algorithm

Proposition 1 implies that mealtime correction bolus algorithm can be devised along the lines of Fig. 5. To interpret the figure, suppose that the patient is interested in advice about an optimal correction bolus at discrete time \( \kappa \). The first step of the algorithm is to compute an estimate \( \hat{x}(\kappa) \) of the patient’s metabolic state based on both CGM measurements and the patient’s virtual basal deviation \( u_{LA}^L \) rate up to \( \kappa \).

As reflected in the figure, the CGM input to the Kalman filter is relative to an algorithm parameter \( \hat{B} \), which could, for example, be initialized based on patient’s daily average blood glucose concentration and adjusted thereafter as the patient achieves better glycemic outcomes. Note that in practice, the mealtime SMBG sample would be used to adjust the CGM history (to eliminate the effect of sensor drift) prior to computing the estimate \( \hat{x}(\kappa) \). The next step of the algorithm is to compute an LQ optimal discrete correction bolus per Proposition 1, based on (i) the current estimate of the patient’s metabolic state, (ii) future values of the virtual basal rate signal \( u_{LA}^L \), and (iii) a desired offset \( \Delta \). Note that \( \Delta \) allows the patient to compensate for a poorly titrated long-acting insulin dose. That is, if the long-acting dose is too low (resulting in a high average BG), then correction boluses can be designed to achieve a BG offset that apply at least for the duration of action for the correction bolus. The parameters \( q \) and \( \Delta \) can be regarded as tuning parameters for the algorithm. Finally, note that use of the future values of the relative virtual basal rate signal \( u_{LA}^L \) allows one to adjust for the transient effect of the timing of the most recent long-acting insulin injection.

IV. PRECLINICAL IN SILICO TRIALS

The Kalman filter and linear quadratic control gains for the algorithm of Section III-D have been implemented with the customized MDI simulation environment of Section II. Our general strategy for in silico evaluation of the algorithm has been to superimpose self-treatment behaviors onto the in silico population to recover BG traces that are representative of patients under MDI therapy. Within the simulator we are free to titrate daily long-acting insulin doses, as well as parameters relating to mealtime rapid-acting insulin (correction factors and carbohydrate ratios), to achieve any desired HbA1c and/or measure of BG variability.

A. MDI Reference Therapy Model

As a preliminary evaluation, we have created a reference MDI therapy model in which daily long-acting doses (taken at 6AM) and rapid-acting mealtime correction factors and carb ratios have been titrated to achieve (as a population) an average HbA1c of 7.98% (standard deviation = .52), an average percentage time above 180 mg/dl of 46.6%, and an average percentage time below 70 mg/dl of 0%. This primary reference treatment model could be taken to represent a hypoglycemia-fearing group, where the objective of the algorithm is to reduce HbA1c without significantly increasing the risk of hypoglycemia.

For the preliminary evaluation here, we have chosen a scenario with just one long-acting injection a day, which occurs in the morning at 6:00 AM with 100% compliance. To titrate individual subjects, we randomly generated values of HbA1c around 8% and assigned them to our cohort. Then the average two-day BG value which would lead to such an HbA1c was calculated. After that, each subject was titrated to reach that average BG over a two-day meal scenario (see below). The carbohydrate ratio for each patient in the reference model is derived from the subject’s ideal CR, and, for each subject, a random factor (between 1.0 and 1.1) was applied to the ideal CR. The correction factor for each in silico patient was modified similarly.

All subjects are run under 2-day scenarios with the meal plan of:

- First day:
- 0.5 g CHO(carbohydrates)/kg for breakfast at 8:00 AM
- 0.9 g CHO/kg for lunch at 2:00 PM
- 0.7 g CHO/kg for dinner at 8:00 PM

- Second day:
  - 0.5 g CHO/kg for breakfast 8:00 AM
  - 0.9 g CHO/kg for the dinner 8:00 PM

where the second day is designed to test the system’s behavior in the case of a skipped meal. For all of the in silico results we use a universal formula for choosing an appropriate $q$-parameter for each patient:

$$q = 10^{d_0 + \beta_1 BW + \beta_2 TDI}$$

(15)

where BW refers to the patients body weight in kilograms and TDI is the patient’s total daily insulin requirement in Units. In practice this formula would be taken as an initial starting point for patients encountering the algorithm for the first time. For the experiments here $BG$ was taken as 150 (mg/dl), and $\Delta$ was individually numerically tuned for each in silico patient.

B. In Silico Results - Nominal Case

Some representative in silico trial results are illustrated in Fig. 6. Each plot shows a comparison between (i) the reference MDI therapy model (black “std” trace) and (ii) the algorithm of Section III-D (red “opt” trace). Note that hour 0 corresponds to 6:00 AM (assumed to be the time of the daily injection of long-acting insulin). Five meals are administered over the course of two days, as described above, and are easily identifiable on the plots by the corresponding BG spikes that follow them. From the plots one can see the difference in the pairs of traces leading to lower average glycemia under the smart insulin pen therapy. The smart pen algorithm, informed by continuous monitoring and, with its patient-adapted parameters $q$ and $\Delta$, makes different decisions about the amount of insulin to be injected as the correction part of the mealtime bolus compared to the decision made by the reference therapy model.

A summary of the key statistics of the nominal in silico evaluation appears in Table I. As can be seen, the smart insulin pen algorithm is capable of reducing estimated HbA1c (based on time-average BG) by over one percentage point, without significantly increasing the risk of hypoglycemia, even under +/-25% variation in the absorption parameter $k_{d0}$. The in silico results suggest that the combination of CGM with MDI can be very effective in improving glycemic control for patients with Type 1 diabetes, extracting many of the benefits of fully closed-loop pump-oriented systems (e.g. the artificial pancreas).

It is worth mentioning that to obtain our in silico results we constructed a rough model of self-treatment for a population of Type 1 subjects, in which each patient is assigned (i) a daily long-acting insulin dose and (ii) a carbohydrate ratio and correction factor so that the overall group achieves a mean HbA1c of 7.98%. After imposing this self-treatment model on the population, we tuned the reference therapy model to achieve a reduction in HbA1c, keeping the risk of hypoglycemia as a secondary criterion. In ongoing work we are studying other models of patient self-treatment behavior, including a group of patients with very low average BG, where it appears necessary to tune the parameters of the algorithm differently, i.e. with the risk of hypoglycemia as the primary metric. In general, we are finding that the appropriate method of tuning the algorithm depends on the behavioral “type” of the patient.

Finally, since no CGM-enabled insulin pens are currently on the market, it would appear that the embodiment of our algorithm within a commercial application is a long way

### TABLE I

<table>
<thead>
<tr>
<th>LBGI</th>
<th>HBGI</th>
<th>HbA1c</th>
<th>&gt; 180</th>
<th>&lt; 70</th>
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<tbody>
<tr>
<td>Ref</td>
<td>0.001</td>
<td>8.64</td>
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<td>46.6%</td>
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<tr>
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### TABLE II

<table>
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<th>LBGI</th>
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<th>HbA1c</th>
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<th>&lt; 70</th>
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</table>

### V. Conclusions

In this paper we have presented a nominal model of the pharmacokinetic properties of once-daily long-acting insulin, which has been incorporated into a computer simulation environment for MDI therapy of Type 1 diabetes. Further, based on the structure of our pharmacokinetic model, we have introduced the notion of a virtual basal rate profile associated with daily long-acting insulin injections, facilitating the estimation of the patient’s metabolic state via Kalman filtering. Using this state estimate we compute correction bolus recommendations for mealtime rapid-acting boluses in MDI therapy. We have evaluated the correction advisor for an in silico Type 1 population whose self-treatment strategies achieve an HbA1c of 7.98% on average (with a standard deviation of 0.52), and the algorithm results in a reduction of over one percent saturation without significantly increasing the risk of hypoglycemia, even under +/-25% variation in the absorption parameter $k_{d0}$. The in silico results suggest that the combination of CGM with MDI can be very effective in improving glycemic control for patients with Type 1 diabetes, extracting many of the benefits of fully closed-loop pump-oriented systems (e.g. the artificial pancreas).
Fig. 6. Examples of reducing HbA1c with the smart pen algorithm off. However, a path to preliminary clinical studies may be found through the hardware/software platforms currently in development to support the artificial pancreas. For example, the UVA Center for Diabetes Technology is developing an Android-based platform for ambulatory studies of artificial pancreas technology, including (i) establishing a reliable, real-time link to the CGM and (ii) providing a validated human user interface that supports mealtime insulin decision-making. The same hardware/software platform could be the basis for implementation of an advisory system for MDI patients. In such an implementation: (1) the system would have real time access to CGM data, (2) the patient would acknowledge delivered insulin (both long- and rapid-acting) through the user interface, (3) the system would continuously update the estimate of the patient’s metabolic state based on acknowledged insulin and the CGM data, and (4) the system would be ready to provide advice about a meal time boluses at any time.

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