FLEXIBLE RUN–TO–RUN STRATEGY FOR INSULIN DOSING IN TYPE 1 DIABETIC SUBJECTS

Cesar C. Palerm∗ Howard Zisser∗∗ Lois Jovanovic∗∗∗ Francis J. Doyle, III∗∗∗∗

† Dept. of Chemical Engineering, University of California Santa Barabara
** Sansum Diabetes Research Institute, Santa Barbara, CA
*** Biomolecular Science and Engineering Program, University of California Santa Barabara

Abstract: People with type 1 diabetes require frequent adjustment of their insulin dose to maintain as near normal glycaemia as possible. This process is not only burdensome, but for many difficult to achieve. As a result, control algorithms to facilitate the insulin dosage have been proposed, but have not been completely successful in normalizing glycaemia. Here we present a novel run–to–run control algorithm to adjust the meal related insulin dose using only postprandial blood glucose measurements.

Keywords: biomedical control systems, batch control, insulin sensitivity, medical systems, diabetes, run–to–run control

1. INTRODUCTION

The chronic hyperglycaemia in diabetes is associated with long-term complications due to damage, dysfunction and failure of various organs. The Expert Committee on the Diagnosis and age, dysfunction and failure of various organs, Classification of Diabetes Mellitus (2003) defines diabetes mellitus as a group of metabolic disorders which are characterized by hyperglycaemia. Thrombosis, nephropathy, neuropathy. These hyperglycaemia results from defects in insulin secretion, insulin action, or both. Type 1 diabetes is characterized by an absolute deficiency of insulin with diabetes are at higher risk of cardiovascular disease. It includes cases primarily due to disease, and face increased morbidity and mortality, cell destruction, and who are prone to ketoacidosis when critically ill.

The efficacy of intensive treatment in preventing diabetic complications has been established by the Diabetes Control and Complications Trial (DCCT) (Diabetes Control and Complications Trials Research Group, 1993) and the United Kingdom Prospective Diabetes Study (UKPDS) (UK Prospective Diabetes Study Group, 1998). In both trials the treatment regimens that reduced average glycosylated hemoglobin (a clinical

1 Corresponding author (frank.doyle@icb.uscb.edu)
measure of glycemic control, which reflects average blood glucose levels over the preceding 2-3 and compared its effectiveness against manual methods. $A_1C$ to approximately 7% (normal range for adults) and 4-6% were associated with fewer long-term complications. Recent evidence even suggests that these target levels might not be low enough (Khan et al., 2001).

Taking the heuristic algorithm of Skyler et al. (1981) as their starting point, Beyer et al. (1990) created their own algorithm; as the original, they use the pre-prandial blood glucose measurements. In daily injections of insulin, or treatment with a clinical trial of 50 subjects they clearly show that the computer group did much better in the control (i.e., as close to norm as possible) should be maintained for life in order to accrue the full benefits. Many factors influence the insulin dose, requiring adjustments, including weight, physical condition and stress levels. Due to this, frequent blood glucose monitoring is required. Based on these measurements, the insulin dosage must be modified, dietary changes implemented, exercise patterns. With the advent of home blood glucose monitoring technology becoming available, physicians are starting to seek ways to use this information tied in a clinical setting, making some changes to fine-tune the therapeutic regimen. Among the allowances fingerstick blood glucose determinations of the subjects maintained close to normal levels. The main difference between these two is that Skyler et al. (1981) relies on pre-prandial blood glucose measurements exclusively, while Jovanovic and Peterson (1982) uses prandial measurements as well to adjust the insulin dosing.

The algorithm proposed by Jovanovic and Peterson is taken as the basis to program an algorithm (Owens et al., 2005) as well. It is based on practical experience; the main difference between these two is that Skyler et al. (1981) relies on pre-prandial blood glucose measurements exclusively, while Jovanovic and Peterson (1982) uses prandial measurements as well to adjust the insulin dosing.

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### 2. Run-to-Run Algorithm

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cursions in the prandial period can be determined.
Choose an initial guess for \( (\text{when } k = 1) \).

(3) Complete the run using the input \( \psi^k \) corresponding to \( t_k \). Determine \( \psi_k \) from the measurement set \( \psi_k \).

(4) Update the input parameters as

\[
\psi_{k+1} = \psi_k + K (\psi^\dagger - \psi_k)
\]

where \( K \) is an appropriate gain matrix and \( \psi^\dagger \) represents the reference values to be attained. Increment the next run, and repeat steps 3-4 until convergence.

As the times can change from one meal to the next, and from run to run, we need a reference value that is normalized with respect to time. We define this reference in terms of units of glucose per minute for each meal \( t_k \), and then scale by the actual time between the two measurements. We can write this as

\[
\psi^\dagger = \left[ \begin{array}{c}
T_{B_1} - T_{B_t} \\
T_{L_1} - T_{L_t} \\
T_{D_1} - T_{D_t}
\end{array} \right]
\]

The manipulated variable is simply the dose of insulin corresponding to each meal of day \( k \) for a day-to-day cycle as a run; within this run, there are three separate meals (namely breakfast, lunch, and dinner), for which an appropriate insulin bolus has to be determined. The objective is to minimize the prandial glycemic excursion, without overusing insulin. Thus, our manipulated variable, \( \psi_k \), corresponds to the insulin profile, and the measurement \( \psi_k \), corresponds to glucose measurements. Time is within a given day, which is also a run. We assume no coupling between the meals; therefore, the reference for the next run, and from run to run, we need a reference value that is normalized with respect to time. For this reason, we define this reference in terms of units of glucose per minute for each meal \( t_k \), and then scale by the actual time between the two measurements. We can write this as

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The reasoning for this performance measure is based on the blood glucose response seen for different doses. For a bolus that is correctly dosed, we expect the peak glucose excursion to be around 60 minutes, and to drop from that point on until it reaches the basel level. If the bolus is under-dosed, this moves the peak into the future. Thus, if we have under-dosage, the difference in blood glucose levels between the first and second measurements will be negative, or positive but very small. As the dose approaches the ideal level, this difference will increase. This is illustrated in Figure 1(a).

3. SIMULATION RESULTS

The main change is in the selection of the performance measure used. To have the flexibility of delivering (as is the case with insulin infusion pumps), the absorption of insulin from a subcutaneous delivery (as is the case with insulin infusion pumps), and the appearance of glucose in plasma from a fixed meal. Instead, we use an approximation of the slope of the glycemic response. The only restriction for each day, the simulation has the meals at place on the patient is that the first glucose is at 8:00, 12:00 and 18:00 hours, with a carbohydrate content of 20, 40 and 70 grams, respectively. After the start of the meal, and the second one before each day and meal, the time points at which at least 30 minutes after the first, but not more than 60 minutes after the start of the meal, and the second one after each meal, \( T_{B_1}, T_{B_2}, T_{L_1}, T_{L_2}, T_{D_1}, T_{D_2} \). Then, our sampled output vector is
Fig. 1. In (a) it can clearly be seen that the time between sampling times changes for the different meals, and shows how the run-to-run algorithm is able to bring the dosing within the desired bounds. (b) shows the full profile over 25 consecutive days.

The reference drop in blood glucose (per minute) $\psi_0 = [0.058 \ 0.104 \ 0.30]^T$. The controller gain is set at $K = 0.0005$, and is scaled by 2, 3 or 4 for subjects with lower insulin sensitivities. The chosen meal is the main guideline. We have selected...
1:10). Thus we start giving much less insulin than is actually required for the first run. (0).

Figure 1(b) shows the simulation for 25 days, with figure 1(a) highlighting a couple of days only. The dotted lines show the desired bounds for the blood glucose excursions; note that we are more aggressive in keeping blood glucose below 150 mg/dl than preventing it from going below 70 mg/dl.

Even though the algorithm does not directly consider them minimum and maximum excursions after a meal, these are still relevant clinical markers. Figure 2 shows them minimum and maximum values after each meal, where once again the dotted lines represent the desirable bounds. The amount of the insulin bolus and the corresponding insulin to carbohydrate ratios are shown in figures 3 and 4, respectively. The insulin to carbohydrate ratio is what the patients and physicians use to calculate their insulin requirements for a given meal; this shows clearly that the algorithm converges to the ideal ratio. It is important to note that although in this case they converge to approximately the same value, it is not necessarily the case in real life, as insulin sensitivity has a circadian variation which is not captured by the simulation model used.

4. CONCLUSIONS

The feasibility of using run-to-run control to determine the optimal insulin bolus dose and timing was shown by Zisser et al. (2005), but some hurdles were identified. Changing the timing of the insulin bolus was one of them, which coupled with the small difference it makes when using monomeric insulin, it was decided to keep it fixed to coincide with the beginning of the meal. The second was the requirement that blood glucose measurements be taken at 60 and 90 minutes; besides imposing additional burden on the patient to keep close track of times after a meal, it also meant that when the patient missed these time points the algorithm could no longer make a correction for the dosing the following day.

We have proposed a new performance measure, which gives the patient the freedom of taking post-prandial glucose measurements at times that are more flexible and do not require them to be constrained to the clock. We have shown that even with this variation in the timing, the controller is able to converge within a couple of days, significantly improving the degree of glycemic control.

Further simulation studies must be done to incorporate other sources of variability that are expected, including measurement noise, mismatch ratio of 1:33 (a more typical value is around 1:10).
the meal and the actual value, and variation in the timing and carbohydrate content of the meals. Initial results (not shown) are quite encouraging. We are currently undertaking a robustness analysis that takes into account all of these sources of uncertainty.

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