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

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Abstract: People with type 1 diabetes require frequent adjustment of their insulin dose to maintain as near normal glycemia 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 glycemia. 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 Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (2003) defines diabetes mellitus as a group of metabolic diseases which are characterized by hyperglycemia. This hyperglycemia results from defects in insulin secretion, insulin action, or both. Type 1 diabetes is caused by an absolute deficiency of insulin secretion. It includes cases primarily due to β-cell destruction, and who are prone to ketoacidosis. These cases are those attributable to an autoimmune process, as well as those with β-cell destruction for which no pathogenesis is known (i.e. idiopathic). People with type 1 diabetes fully depend on exogenous insulin. It is estimated that 17.1 million people world wide had type 1 diabetes in 2000 (Wild *et al.*, 2004; Eisele *et al.*, 2004).

The chronic hyperglycemia in diabetes is associated with long-term complications due to damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels. The three main complications being retinopathy, nephropathy and neuropathy. These can eventually lead to renal failure, blindness, amputation and other types of morbidity. Subjects with diabetes are at higher risk of cardiovascular disease, and face increased morbidity and mortality.

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

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measure of glycemic control, which reflects average blood glucose levels over the preceding 2-3 months) A_{1C} to approximately 7% (normal range is 4-6%) were associated with fewer long term microvascular complications. Recent evidence even suggests that these target levels might not be low enough (Khaw *et al.*, 2001).

Intensive treatment requires multiple (3 or more) daily injections of insulin, or treatment with an insulin infusion pump. In any case, this tight control (*i.e.* as close to normal as possible) should be maintained for life in order to accrue the full benefits. Many factors influence the insulin dose requirements over time, 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 (such as alteration in the timing, frequency and content of the meals), as well as changes in activity and exercise patterns.

With the advent of home blood glucose monitoring technologies becoming available, physicians started to seek ways to use this information to fine-tune the therapeutic regimen. Among the first heuristic algorithms in the literature, we highlight those of Skyler *et al.* (1981) and Jovanovic and Peterson (1982). Both set heuristic rules 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.

The algorithm proposed by Jovanovic and Peterson (1982) is taken as the basis to program a pocket computer, which was tested in 5 type 1 diabetic subjects. They demonstrate that computer-assisted insulin-delivery decision making is feasible (Chanoch *et al.*, 1985). This computer program was then compared to the standard approach for new continuous subcutaneous insulin infusion pump users. Peterson *et al.* (1986) found the approach to be feasible, although it did not fully normalize blood glucose levels. Still, computer users achieved lower average blood glucose and A_{1C} values over the course of the study.

Schiffrin *et al.* (1985) programmed a portable computer to adjust dosing of short and intermediate acting insulin in a 2-injection per day strategy, using pre-prandial blood glucose measurements. Even within the limitations of the therapy regimen used, they saw marked improvements in glycemic control when using the computer. Chiarelli *et al.* (1990) compared this computer method with a manual method; while they found no differences in glycemic control, they did notice fewer instances of hypoglycemia in the computer users. Peters *et al.* (1991) adapts this algorithm and compared its effectiveness against manual adjustments, finding that metabolic control and safety were comparable in both.

Taking the heuristic algorithm of Skyler *et al.* (1981) as their starting point, Bellazzi *et al.* (1990) create their own algorithms; as the original, they use pre-prandial blood glucose measurements. In a clinical trial of 50 subjects they clearly show that the computer group did much better than the regular intensive treatment group (Schrezenmeir *et al.*, 2002).

So far, none of these computer algorithms make use of the newer monomeric insulins. Owens *et al.* (2005) propose a run-to-run control algorithm to adjust the timing and dose of meal related insulin boluses, taking advantage of these fast acting insulin formulations. The basic assumption is that there is a sensor available from which frequent blood glucose measurements can be taken, and thus the maximum and minimum blood glucose excursions in the prandial period can be determined. The feasibility of the algorithm was studied in a clinical setting, making some changes to allow for fingerstick blood glucose determinations at 60 and 90 minutes after the start of the meal, in lieu of the maximum and minimum. Two-thirds of the subjects maintained acceptable glycemic control, but the rest diverged in their responses due to various factors (Zisser *et al.*, 2005).

In this work we modify the algorithm to overcome the difficulties encountered in clinical practice. The run-to-run formulation described here gives more flexibility to the subject, as blood glucose measurements are not required to be taken at specific times. In section 2 we present the basis of the run-to-run algorithm, followed by the specific implementation for insulin dosing. We present simulation results using this method in section 3.

2. RUN-TO-RUN ALGORITHM

The original formulation for the run-to-run control applied to insulin bolus dosing and timing is described in (Owens *et al.*, 2005). It is based on the application of a constraint control scheme in the run-to-run framework to optimize the operation of batch processes in the chemical industry (Srinivasan *et al.*, 2003*a*; Srinivasan *et al.*, 2003*b*).

The general run-to-run control algorithm is:

(1) Parameterize the input profile for run k, $u_k(t)$, as $U(t, \nu_k)$. Also consider a sampled version, ψ_k, of the output $y_k(t)$, such that it has the same dimension as the controlled variable vector, c_k. Thus we have

$$\psi_k = F(\nu_k) \tag{1}$$

(2) Choose an initial guess for ν_k (when $k = 1$).
(3) Complete the run using the input $u_k(t)$ corresponding to ν_k. Determine ψ_k from the measurements $y_k(t)$.
(4) Update the input parameters as

$$\nu_{k+1} = \nu_k + K\,(\psi^r - \psi_k) \qquad (2)$$

where K is an appropriate gain matrix and ψ^r represents the reference values to be attained. Increment k for the next run, and repeat steps 3-4 until convergence.

In the context of diabetes management, we use the natural 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 overdosing insulin. Thus, our manipulated variable, $u_k(t)$, corresponds to the insulin profile, and the measurement profile, $y_k(t)$, corresponds to glucose measurements. Time, t, is within a given day, k, which is also a run. Owens *et al.* (2005) show, using an RGA analysis, that there is effectively no coupling between the meals, and we also use this assumption in the new algorithm.

There were two drawbacks to the original implementation when evaluated in a clinical setting. The first was the changing of the timing of the insulin bolus with respect to the start of the meal. Many times this resulted in a bolus being administered in the middle of a meal; at other times, the administration before the start of the meal was inconvenient to the subject, and was not adhered to. Besides, when using monomeric insulin, the timing of the bolus makes a negligible difference in the postprandial profile when compared with the effect of the dose. For these reasons it was decided to fix the timing to always coincide with the beginning of the meal. The second drawback was the need for blood glucose determinations at 60 and 90 minutes after the start of the meal; if the subject for some reason forgot to take either of them, then the algorithm was not able to correct for the following day (Zisser *et al.*, 2005).

The main change is in the selection of the performance measure used. To have the flexibility of taking blood glucose measurements at different times, we can no longer use a fixed glucose level. Instead, we use an approximation of the slope of the glycemic response. The only restrictions we place on the patient is that the first glucose measurement must be taken at least 60 minutes after the start of the meal, and the second one be at least 30 minutes after the first, but not more than 180 minutes after the start of the meal. We denote these times, for each meal, as T_{B_1}, T_{B_2}, T_{L_1}, T_{L_2}, T_{D_1}, T_{D_2}. Then, our sampled output vector is

$$\psi_k = \begin{bmatrix} G(T_{B_1}) - G(T_{B_2}) \\ G(T_{L_1}) - G(T_{L_2}) \\ G(T_{D_1}) - G(T_{D_2}) \end{bmatrix} \qquad (3)$$

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, ψ_0^r, and then scale by the actual time between the two measurements. We can write this as

$$\psi^r = \psi_0^r \begin{bmatrix} T_{B_2} - T_{B_1} \\ T_{L_2} - T_{L_1} \\ T_{D_2} - T_{D_1} \end{bmatrix} \qquad (4)$$

where $\circ$ denotes the Hadamard (element-wise) product.

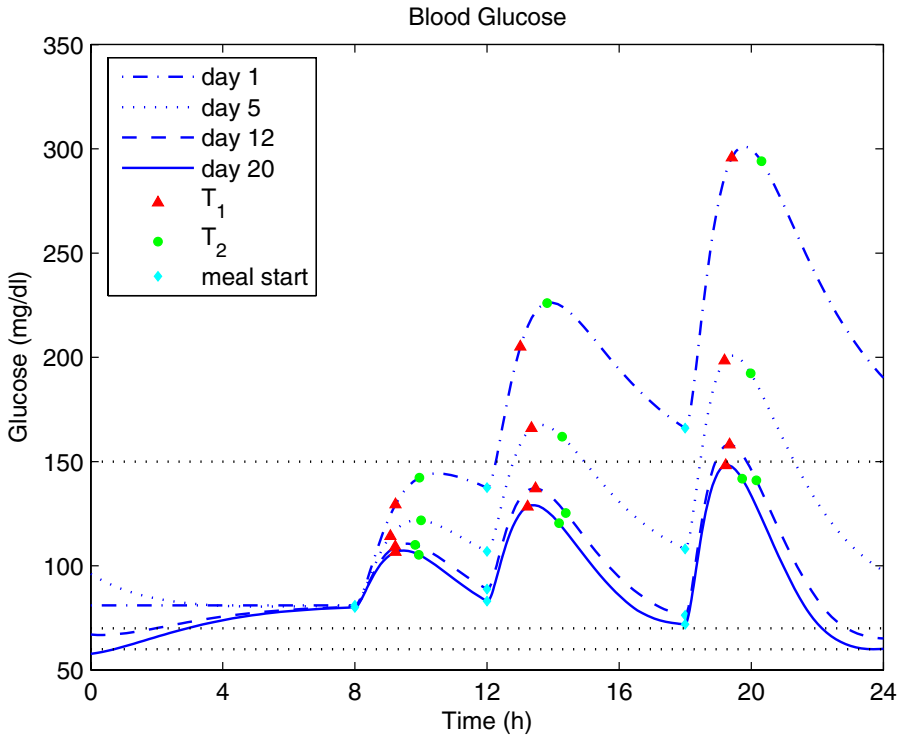
The manipulated variable, u_k, is simply the dose of insulin corresponding to each meal of day k, $\nu_k = \begin{bmatrix} Q_B & Q_L & Q_D \end{bmatrix}^T$. The controller gain, K, is set depending on the insulin sensitivity of the patient.

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 basal level. If the bolus is under-dosed, this moves the peak into the future. Thus, if we have under-bolused, 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 all illustrated in figure 1(a).

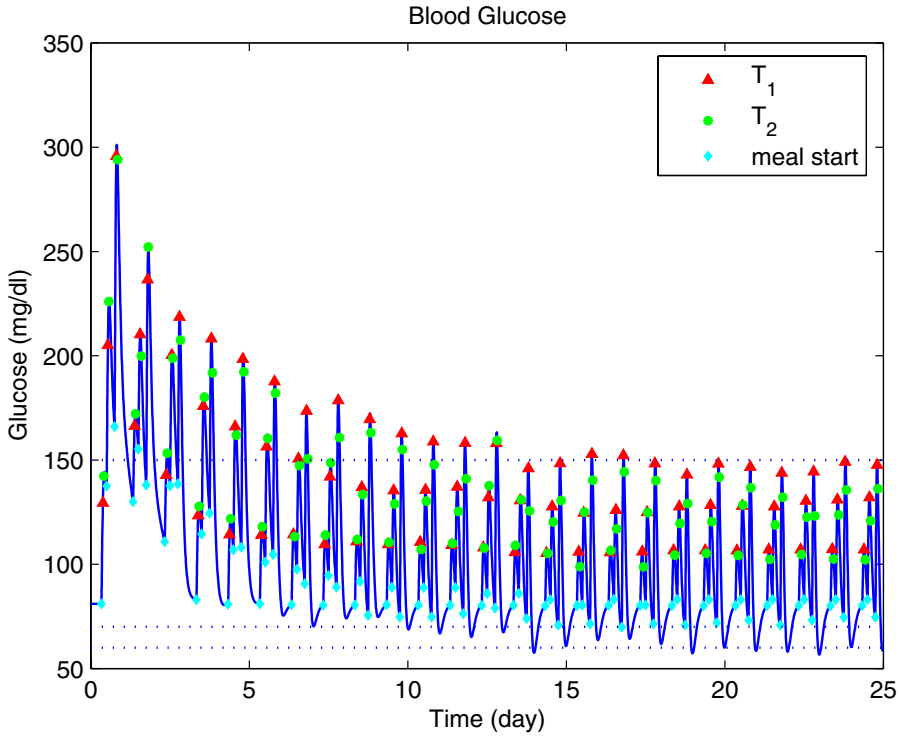
3. SIMULATION RESULTS

There are several published models of glucose and insulin dynamics in the literature. For this particular study we have selected the one published by Hovorka *et al.* (2004), replacing the subcutaneous insulin infusion model with the one described in (Wilinska *et al.*, 2005). The model captures not only the dynamics of glucose and insulin, but also 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 mixed meal.

For each day, the simulation has the meals at 8:00, 12:00 and 18:00 hours, with a carbohydrate content of 20, 40 and 70 grams, respectively. For each day and meal, the time points at which blood glucose measurements are taken are selected randomly (using a uniform distribution); the first one can take place from 60 to 90 minutes after the start of the meal, the second one follows 30 to 60 minutes later.



(a) Glucose profile for selected days



(b) Glucose profile over a period of 25 days

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) $\psi_0^r = \begin{bmatrix} 0.058 & 0.104 & 0.30 \end{bmatrix}^T$. The controller gain is was selected for each meal separately, considering set at $K = 0.0005$, and is scaled by 2, 3 or 4 the typical amount of carbohydrate consumed in for subjects with lower insulin sensitivities. The each meal as the main guideline. We have selected

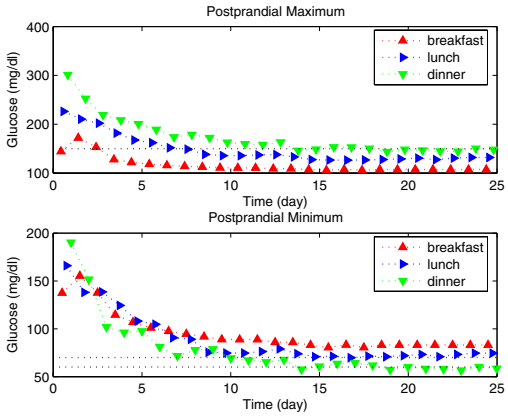


Fig. 2. Maximum and minimum glucose excursions after a meal converge to clinically acceptable bounds.

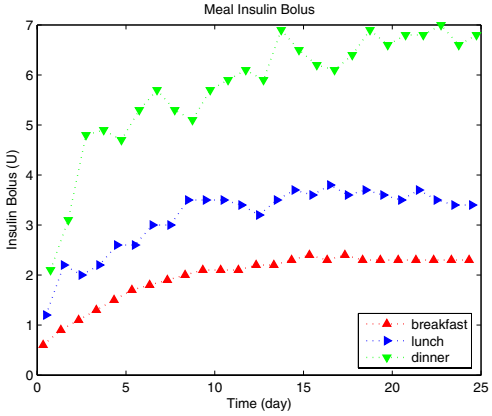


Fig. 3. Meal insulin bolus converges to the optimal amount for the given meal.

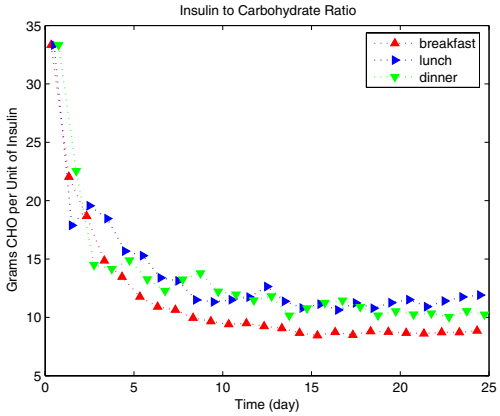


Fig. 4. The algorithm converges to the same insulin to carbohydrate ratio, regardless of the carbohydrate content of the meal.

amount of the insulin bolus is rounded to the nearest 0.1 U of insulin, which is the resolution of most infusion pumps.

The initial guess for the insulin requirement for each meal is set at an insulin to carbohydrate ratio of 1:33 (a more typical value is around 1:10). Thus we start giving much less insulin than is actually required for the first run ($k=0$). 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 the minimum and maximum excursions after a meal, these are still relevant clinical markers. Figure 2 shows the maximum and minimum 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 time 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 become slaves 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 between the estimated carbohydrate content of

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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