A run-to-run framework for prandial insulin dosing: handling real-life uncertainty

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SUMMARY

Individuals with type 1 diabetes require frequent adjustment of their insulin dose to maintain as near to normal glycaemia as possible. This process is not only burdensome but also, for many, difficult to achieve. As a result, control algorithms to facilitate 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 post-prandial blood glucose measurements. For each meal independently, the insulin dose is adjusted based on the performance measure for the same meal the previous day. A robustness analysis is performed which considers the sources of uncertainty typically encountered in clinical use. This shows that the system remains stable even with large uncertainty.

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KEY WORDS: type 1 diabetes; run-to-run control; robustness; insulin dosing; biomedical control

1. INTRODUCTION

The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus [1] defines diabetes mellitus as a group of metabolic diseases which are characterized by hyperglycaemia (high levels of blood glucose). This hyperglycaemia results from defects in insulin secretion, insulin action, or both. Type 1 diabetes is caused by an absolute deficiency of insulin secretion, which is primarily due to β cell destruction. People with type 1 diabetes are prone to
ketoacidosis and fully depend on exogenous insulin. It is estimated that 17 million people worldwide had type 1 diabetes in 2000 [2, 3], with a clear rising trend in the worldwide incidence of the disease of about 3% per year [4, 5].

The chronic hyperglycaemia 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 main complications being heart disease, stroke, 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 when critically ill.

The efficacy of intensive treatment in preventing diabetic complications has been established by the Diabetes Control and Complications Trial (DCCT) [6] and the United Kingdom Prospective Diabetes Study (UKPDS) [7]. In both trials the treatment regimens that reduced average glycosylated haemoglobin \( A_1c \) (a clinical measure of glycaemic control, which reflects average blood glucose levels over the preceding 2–3 months) 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 [8, 9].

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), and activity and exercise patterns changed.

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 were those of Skyler et al. [10] and Jovanovic and Peterson [11]. Both set heuristic rules based on practical experience; the main difference between these two is that Skyler et al. [10] relies on pre-prandial blood glucose measurements exclusively, while Jovanovic and Peterson [11] uses pre- and post-prandial measurements to adjust the insulin dosing.

The algorithm proposed by Jovanovic and Peterson [11] was used as the basis to program a pocket computer, which was tested in five type 1 diabetic subjects. They demonstrate that computer-assisted insulin delivery decision making is feasible [12]. This computer program was then compared to the standard approach for new continuous subcutaneous insulin infusion pump users. Peterson et al. [13] 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. [14] programmed a portable computer to adjust dosing of short- and intermediate-acting insulin in a two-injection per day strategy, using pre-prandial blood glucose measurements. Even within the limitations of the therapy regimen used, they saw marked improvements in glycaemic control when using the computer. Chiarelli et al. [15] compares this computer method with a manual method; while they find no differences in glycaemic control, they did notice fewer instances of hypoglycaemia in the computer users. Peters et al. [16] adapts this algorithm and compares its effectiveness against manual adjustments, finding that metabolic control and safety were comparable in both.
Taking the heuristic algorithm of Skyler et al. [10] as their starting point, Beyer et al. [17] 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 [18].

In the work reviewed above, none of the computer algorithms make use of the newer monomeric insulin formulations. Owens et al. [19] 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 min after the start of the meal in lieu of the maximum and minimum. Two-thirds of the subjects converged to, or maintained, good glycaemic control, but the rest diverged in their responses due to various factors [20].

In this work, the algorithm is modified 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 addition, formal robustness is evaluated theoretically. In Section 2 the basis of the run-to-run algorithm is presented, followed by the specific implementation for insulin dosing. Simulation results using this method are presented in Section 3, followed by a robustness analysis in Section 4 which considers the expected sources of uncertainty.

2. RUN-TO-RUN ALGORITHM

The original formulation for the run-to-run control applied to insulin bolus dosing and timing is described in Reference [19]. 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 [21, 22].

The general run-to-run control algorithm is as follows.

1. Parameterize the input profile for run $k$, $u_k(t)$, as $\Psi(t, v_k)$. Also consider a sampled version, $\psi_k$, of the output $y_k(t)$, such that it has the same dimension as the controlled variable vector $v_k$. Thus,

   $\psi_k = F(v_k)$ (1)

2. Choose an initial guess for $v_k$ (when $k = 1$).

3. Complete the run using the input $u_k(t)$ corresponding to $v_k$. Determine $\psi_k$ from the measurements $y_k(t)$.

4. Update the input parameters as

   $v_{k+1} = v_k + K(\Psi' - \psi_k)$ (2)

   where $K$ is an appropriate gain matrix and $\Psi'$ represents the reference values to be attained. Increment $k$ for the next run, and repeat steps 3 and 4 until convergence.
In order to analyse the closed-loop system, a linearization of (1) is used:

\[ \psi_k = Sv_k \]  
\[ S = \frac{\partial F}{\partial v} \]

where \( S \) is the sensitivity matrix. Defining the error of the closed-loop system to be \( e_k = \psi' - \psi_k \), Equation (2) can be written as

\[ v_{k+1} = v_k + Ke_k \]  

Then at time \( k + 1 \), and using (5) and (3), the error can be expressed as

\[ e_{k+1} = \psi' - \psi_{k+1} \]
\[ = \psi' - Sv_{k+1} \]
\[ = \psi' - S(v_k + Ke_k) \]
\[ = \psi' - \psi_k - SKe_k \]
\[ = (I - SK)e_k \]

Thus, the stability and convergence of the algorithm depends on \( S \) and \( K \).

In the context of diabetes management, the natural day-to-day cycle is used 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 glycaemic excursion without overdosing insulin. Thus, the 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, while \( k \) denotes the day (run). Owens et al. [19] show, using an RGA analysis, that there is effectively no coupling between the meals; we also use this assumption, which we verify below, in the algorithm proposed in this paper.

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. In several instances, 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. Furthermore, when using monomeric insulin, the timing of the bolus makes a negligible difference in the post-prandial 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 min after the start of the meal; if the subject for some reason forgot to take either of them and was significantly off on the timing, then the algorithm was not able to correct for the following day [20].

The main change in the algorithm is in the selection of the performance measure used. To have the flexibility of taking blood glucose measurements at different times, a fixed glucose level can no longer be used. Instead, an approximation of the slope of the glycaemic response is used. The only restrictions placed on the patient is that the first glucose measurement must be taken at least 60 min after the start of the meal, and the second one be at least 30 min after the first, but not more than 180 min after the start of the meal. These times are denoted, for each meal, as...
Then, the sampled output vector is

\[
\psi_k = \begin{bmatrix} G(T_{B1}) - G(T_{B2}) \\ G(T_{L1}) - G(T_{L2}) \\ G(T_{D1}) - G(T_{D2}) \end{bmatrix}
\]  

(7)

As the times can change from one meal to the next, and from run to run, a reference value is required that is normalized with respect to time. This reference is defined in terms of units of glucose per minute for each meal, \( \psi_0 \), and then scaled by the actual time between the two measurements. This is expressed as

\[
\psi' = \psi_0 \begin{bmatrix} T_{B2} - T_{B1} \\ T_{L2} - T_{L1} \\ T_{D2} - T_{D1} \end{bmatrix}
\]  

(8)

where \( \otimes \) denotes the Hadamard (elementwise) product.

The manipulated variable \( v_k \) is simply the dose of insulin (per gram of carbohydrate in the meal) corresponding to each meal of day \( k \), \( v_k = [Q_B \ Q_L \ Q_D]^T \). The controller gain, \( K \), is set according to the desired speed of response as well as the insulin sensitivity of the patient.

The rationale for this performance measure is explained by the blood glucose response seen for different doses. For a bolus that is correctly dosed, the peak glucose excursion is expected to be around 60 min, 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 the bolus is under-dosed, 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).

Using this performance measure, the steady state gain and the relative gain array can be calculated. If all perturbations to calculate the response are done starting from steady state, the gain matrix is

\[
K_{SS} = \begin{bmatrix} 7.02 & 0 & 0 \\ -0.95 & 6.55 & 0 \\ -0.49 & -1.15 & 5.57 \end{bmatrix}
\]  

(9)

given that the upper-triangular is all zeros, the RGA is the identity matrix, showing no coupling. If for each perturbation the final conditions are used as the initial point for the following day, then the gain matrix is

\[
K_{SS} = \begin{bmatrix} 6.93 & -0.02 & -0.02 \\ -0.98 & 6.42 & -0.10 \\ -0.50 & -1.16 & 5.55 \end{bmatrix}
\]  

(10)
which results in the following RGA

\[
\Lambda = \begin{bmatrix}
1.0007 & -0.0004 & -0.0003 \\
-0.0005 & 1.0038 & -0.0033 \\
-0.0002 & -0.0034 & 1.0036 \\
\end{bmatrix}
\] (11)

Figure 1. (a) Simulation response of run-to-run algorithm over a 24-h period for various runs; and (b) the full profile response over 25 consecutive days.
which although not exactly the identity matrix, it still shows there is no significant coupling. Given that the performance measure is a relative value it makes sense intuitively that this would be the case, as any remaining effect of a previous insulin bolus will affect both glucose measurements by practically the same extent.

3. SIMULATION RESULTS

There are several published models of glucose and insulin dynamics in the literature. For this particular study the one published by Hovorka et al. [23] is used, replacing the subcutaneous insulin infusion model with the one described in Reference [24]. 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 h; with a carbohydrate content of 20, 40 and 70 g, 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 min after the start of the meal, the second one follows 30 to 60 min later.

The reference drop in blood glucose (per minute), was selected for each meal separately, considering the typical amount of carbohydrate consumed in each meal as the main guideline. In this case, \( \psi_0^{[c]} = [0.058\ 0.104\ 0.30]^T \). The controller gain is set at \( K = 0.001 \), and is scaled by 0.5, 2 or 3 for subjects with higher or lower insulin sensitivities. The amount of the insulin bolus is rounded to the nearest 0.1 IU of insulin, which is the resolution of most commercially available 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, the starting dose gives 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. 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 variability observed is due to the changing time points at which blood glucose measurements are taken. The insulin to carbohydrate ratio is used by patients and physicians 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.

In clinical practice, there is ongoing debate on the precise definitions for hyper- and hypoglycaemia. The normal range is accepted to be 70–110 mg/dl, thus strictly speaking anything below 70 mg/dl would be hypoglycaemia, and anything above 110 mg/dl would be hyperglycaemia. In the context of a post-prandial blood glucose excursion, it is accepted that even in a subject without diabetes blood glucose levels can rise above 110 mg/dl. Thus,
Figure 2. Post-prandial maximum (top) and minimum (bottom) blood glucose concentrations for each meal over the full profile response over 25 consecutive days.

Figure 3. Meal insulin bolus converges to the optimal amount for the given meal.
Clinicians usually deem a post-prandial blood glucose excursion kept below 150 mg/dl to be very good control, and thus our choice of a threshold to define hyperglycaemia [25]. Similarly, for hypoglycaemia, the choice of 55 mg/dl corresponds to moderate hypoglycaemia; this is the threshold that clinicians consider to be of concern, while excursions into the range of 55–70 mg/dl are hypoglycaemia but not critical in nature [26].

4. ROBUSTNESS ANALYSIS

The run-to-run algorithm is a model-free paradigm, but for the purpose of robustness analysis we need to identify a model from data. In applying the run-to-run algorithm in real life, there are several sources of variability that must be considered. The main ones encountered are: meal timing changes, meal carbohydrate content variation, incorrect estimate of meal carbohydrate content, and measurement noise.

The effect on the system stability for each of these is considered individually at first, then in combination. As a baseline, a set of 30 runs with no variability is used. The only source of randomness comes from the selection of the time points at which the blood glucose determinations are made. The metrics considered are the minimum and maximum post-prandial blood glucose concentrations for each meal, the number of times the response goes above the desired 150 mg/dl (hyperglycaemic event), and the number of times below 55 mg/dl (hypoglycaemic event). Hypo- and hyperglycaemic events can only happen once after each meal,

Figure 4. The insulin to carbohydrate ratio is what patients and physicians use to determine insulin needs. The algorithm converges to the same ratio, regardless of the carbohydrate content of the meal.
and are counted irrespective of the amount of time blood glucose goes beyond the threshold. The statistics for the baseline case are shown in Table I. In addition to the uncertainty encountered on a daily basis, insulin sensitivity varies from one individual to another. It will also change for a given individual over time; for example, illness will increase the resistance to insulin, thus increasing insulin requirements. The performance of the controller, using a nominal gain setting, as the insulin sensitivity varies from extremely insensitive to very sensitive is also considered.

For all these sources of uncertainty, this can be expressed as

$$\psi_k = S(I + \Delta)v_k$$ (12)

where $\Delta$ represents the multiplicative uncertainty. This will in turn be reflected in the closed-loop system equation (6) as

$$e_{k+1} = (I - S(I + \Delta)K)e_k$$ (13)

The estimate of $S$ for the nominal case is made keeping the measurements fixed at $T_1 = 70$ min and $T_2 = 115$ min, as the variation in the timing of the post-prandial glucose measurements is itself a source of uncertainty. The local sensitivity was computed numerically by changing the insulin bolus dose by up to 5% from the nominal. Given that the system is nonlinear, a global estimate of $S$ is also obtained, this time by changing the insulin bolus dose by up to 40% of the nominal. In both cases, once the data set is generated, a least squares fit is performed using

$$\min_S \sum_{i=1}^N ||\psi_i - S v_i||^2$$ (14)

Figure 5 shows the local and global estimates of the sensitivity, together with the nonlinear relationship. Note that both estimates are very close to each other, and in general they agree quite well with the nonlinear response. The global estimate is used as the nominal sensitivity, so $S = \text{diag}(7.55, 7.14, 5.95)$.

The question now arises as to the validity of a linear analysis, given that the uncertainty is most likely nonlinear [27]. There is evidence that patient dynamics are actually quite linear, even though the underlying structure is not [28]. Thus, the linear approximation should be adequate for this analysis.

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Table I. Statistics for 30 runs of the baseline case, with the only source of variability being the random selection of the post-prandial blood glucose measurement times. Hyper- and hypoglycaemic events are given as a fraction of the total possible. Post-prandial maximum and minimum values are given as the mean (standard deviation). Steady state is assumed to be after 10 days. Run variability is the mean of the standard deviation of each simulation run (and its standard deviation).

<table>
<thead>
<tr>
<th>Metric</th>
<th>All days</th>
<th>After 10 days</th>
<th>Run variability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycaemic events (%)</td>
<td>0.35</td>
<td>0.20 (0.051)</td>
<td></td>
</tr>
<tr>
<td>Hypoglycaemic events (%)</td>
<td>0.01</td>
<td>0.02 (0.020)</td>
<td></td>
</tr>
<tr>
<td>Breakfast minimum (mg/dl)</td>
<td>94.4 (19.04)</td>
<td>84.0 (3.86)</td>
<td>3.37 (0.95)</td>
</tr>
<tr>
<td>Breakfast maximum (mg/dl)</td>
<td>115.6 (15.18)</td>
<td>107.9 (2.16)</td>
<td>1.88 (0.55)</td>
</tr>
<tr>
<td>Lunch minimum (mg/dl)</td>
<td>87.4 (25.19)</td>
<td>73.8 (3.83)</td>
<td>3.49 (1.32)</td>
</tr>
<tr>
<td>Lunch maximum (mg/dl)</td>
<td>146.4 (27.21)</td>
<td>131.3 (5.46)</td>
<td>4.98 (1.58)</td>
</tr>
<tr>
<td>Dinner minimum (mg/dl)</td>
<td>75.1 (28.66)</td>
<td>62.2 (4.79)</td>
<td>4.44 (1.06)</td>
</tr>
<tr>
<td>Dinner maximum (mg/dl)</td>
<td>170.4 (35.37)</td>
<td>152.4 (7.39)</td>
<td>6.95 (1.67)</td>
</tr>
</tbody>
</table>
Given that there is little interaction between the three meals, the matrices in the equations are all diagonal. This means that the eigenvalues of \((I - S(I + \Delta)K)\) all lie on the real axis, and the bounds for \(\Delta\) can be directly calculated to keep them within the unit circle. Then,

\[
I - S(I + \Delta)K = \pm I
\]

\[
S(I + \Delta)K = I \mp I
\]

\[
\Delta = \begin{cases} 
-I & \\
2S^{-1}K^{-1} - I 
\end{cases}
\]

using the global estimate for \(S\) and the nominal controller gain \(K = 0.001\), the bounds for \(\Delta\) are

\[
\begin{bmatrix}
-1 & 0 & 0 \\
0 & -1 & 0 \\
0 & 0 & -1 \\
\end{bmatrix}
< \Delta < 
\begin{bmatrix}
282.0 & 0 & 0 \\
0 & 300.5 & 0 \\
0 & 0 & 380.8 \\
\end{bmatrix}
\]

Note that the lower bounds correspond to a change of sign of the system’s sensitivity.

Introducing the variability in the timing of the post-prandial measurements the resulting best-fit sensitivity is calculated. Figure 6 shows the data for the case with the measurement timing variability with its local and global sensitivity estimates, the global sensitivity estimate for the nominal case, and the corresponding stability bounds. In this case, the local and global estimates vary a bit more, but are still in good agreement. For the nominal case with
the variation in the measurement timing the estimated model parameters result in a $\Delta = \text{diag}(-0.064 - 0.070 - 0.119)$, which is practically the same as the nominal system.

4.1. Measurement noise

Current guidelines for blood glucose meters specify that meters have at most a 10% error margin (device and patient error) [29]; some manufacturers actually boast of error in a range of 5–8%, and newer devices are achieving errors below 5% [30]. For this analysis 5, 10, 15 and 20% relative error levels are considered. The noise is assumed to have a normal distribution, with zero mean, and a $3\sigma$ of the per cent error. An inherent advantage in the formulation of the performance measure used is that the noise will tend to cancel out, reducing its effect, than if each measurement were used on its own. The metrics for these cases are shown in Figure 7. As expected, with increasing noise levels there is a higher variability, but it does not increase significantly until the error is higher than the worst expected level of 10%; for the expected noise levels, performance degradation is not significant. The increasing variability going from breakfast to lunch, and lunch to dinner, can be mostly attributed to the larger meal size, and to a lesser extent to carry-over effects from one meal to the next. From these data, estimating the model parameters results in $\Delta = \text{diag}(-0.236 - 0.382 - 0.260)$.

4.2. Meal timing changes

Previously, in standard care, patients were encouraged to follow a strict diet, eating always at the same time of day. This was in part necessary due to the use of insulin formulations whose
action would peak around 2–4 h after the subcutaneous injection. With the current insulin formulations this is no longer necessary, but many physicians maintain this requirement to simplify the adjustment of the insulin dosing. As with any strict imposition of this type, it is hard for an individual to stick to such a regimen, and this is one of the aspects of diabetes care that unduly taxes the individual. As such, allowing the person to eat on an irregular schedule is something that should be easier when using feedback control. Thus, robustness with respect to the timing of the meals must be looked at.

In this case, a uniform distribution is used that will vary the timing of each meal independently from the nominal times (breakfast at 8:00, lunch at 12:00 and dinner at 18:00), by advancing or delaying the meal by up to 60 min. Note that this will result in some cases when the time between two meals (e.g. breakfast and lunch) will be as short as 2 h, or as far apart as 8 h. Figure 8 shows the deviation in the metrics for different magnitudes in the maximum variation of the timing of the meals. In all cases, with the exception of the breakfast minimum, the variability remains practically the same as the baseline case. The reason for the increasing variability for breakfast is that one may have lunch following it by a short time interval; thus, the minimum tends to end up being the blood glucose at the start of lunch, whose timing is changing. In essence, performance degradation is negligible under changes in the meal timing. In this case, $\Delta = \text{diag}(-0.194 \ - 0.450 \ - 0.473)$ when estimating model parameters from these data.

### 4.3. Meal carbohydrate content variation

As with the timing of the meals, the carbohydrate content of the meals is something for which patients are encouraged to adhere to strict guidelines. As with meal timing, this is something that will vary in real-life. Variations in the carbohydrate content of each meal of up to 40% of the nominal (20 g for breakfast, 40 g for lunch and 70 g for dinner) are considered, once again using a uniform distribution. The variation includes both increased and decreased carbohydrate content. Figure 9 shows the deviation in the metrics as the content of the meal is varied from...
only 5% up to 40% of the nominal. Here the variability starts higher for the larger meals, as seen before, and once again increases as the meals are allowed to vary by a larger amount. Again, the degradation in performance is not unreasonable even with the higher variability. In this case, \( D = \text{diag}(-0.281 - 0.496 - 0.414) \) when estimating the system parameters from these data.

4.4. Incorrect estimate of meal carbohydrate content

The algorithm is estimating essentially the carbohydrate to insulin ratio required for the given meal. It is the person that still has to estimate the carbohydrate content of the meal, as there is
no way of measuring this. One way to get around this is to have the person prepare meals using information of the carbohydrate content of the ingredients, and measuring portions. But this defeats one of the central purposes of any closed-loop control algorithm, which is to give more freedom and flexibility to the individual. Thus, the controller has to be robust against erroneous estimates of the carbohydrate content. Fortunately, people tend to be consistent in their estimates, thus reducing the uncertainty introduced into the system. In general, people tend to underestimate the content, thus a uniform distribution of up to 40%, biased so that the most a meal is overestimated is 10%, is used. Figure 10 show the variation in the metrics for these cases. As expected, once again, the more variation in the meal estimates the higher the variation in the metrics. As with all cases before, the controller’s loss of performance is not unreasonable even under the largest variability. For this case $\Delta = \text{diag}(-0.184 - 0.415 - 0.395)$ when estimating the system parameters from these data.

4.5. Combined set of variations

So far the results show variations in each parameter independently, and in some cases taken to extremes that are unlikely to be encountered in real life. In a more realistic scenario the variation will have a normal distribution (in contrast to the uniform distribution used above), and it will be present in several parameters at once. For measurement noise a $3\sigma$ of 10% is assumed, and the meal carbohydrate content is set to vary with a $3\sigma$ of 40% of the nominal value for each meal (20 g for breakfast, 40 g for lunch and 70 g for dinner). Timing of the meals is set for breakfast normally at 8:00, lunch to take place 5 h later, and dinner 6 h after lunch; all with a $3\sigma$ variation of 1.5 h. In general, people tend to underestimate the carbohydrate content of meals by as much as 30%; overestimating the content is not usual. For this reason the meal estimate is set to be nominally 15% underestimated, with a $3\sigma$ of 20%. Given that a person’s activities after a meal vary constantly depending on many external demands for their attention, the variation in the timing of the post-prandial blood glucose measurements is kept with the same uniform

![Figure 10](image-url)

Figure 10. Variation of the post-prandial metrics as a function of different levels of variability in the estimates of the carbohydrate content of meals: (a) hypo- and hyperglycaemic events; and (b) post-prandial minimum and maximum for each meal.
distribution as given before. Table II gives the metrics for a set of 30 runs with these conditions. The variability in the performance metrics is larger than the baseline case, but not unreasonable. The metrics corresponding to dinner are the ones that suffer the most, in large part due to it being the largest meal, and also due to the accumulated effects of the previous two meals. Figure 11 shows the simulation over 30 days for one of the runs. When estimating system parameters from these data $\Delta = \text{diag}(-0.255 \ -0.291 \ -0.286)$.

Table II. Statistics for 30 runs of the real-life case. Hyper- and hypoglycaemic events are given as a fraction of the total possible. Post-prandial maximum and minimum values are given as the mean (standard deviation). Steady state is assumed to be after 10 days. Run variability is the mean of the standard deviation of each simulation run (and its standard deviation).

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<th>Run variability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycaemic events (%)</td>
<td>0.30</td>
<td>0.18 (0.054)</td>
<td></td>
</tr>
<tr>
<td>Hypoglycaemic events (%)</td>
<td>0.05</td>
<td>0.07 (0.032)</td>
<td></td>
</tr>
<tr>
<td>Breakfast minimum (mg/dl)</td>
<td>86.0 (18.08)</td>
<td>77.0 (5.32)</td>
<td>4.79 (1.11)</td>
</tr>
<tr>
<td>Breakfast maximum (mg/dl)</td>
<td>113.4 (15.88)</td>
<td>106.0 (5.16)</td>
<td>4.79 (1.08)</td>
</tr>
<tr>
<td>Lunch minimum (mg/dl)</td>
<td>83.0 (23.98)</td>
<td>72.6 (8.44)</td>
<td>7.68 (2.59)</td>
</tr>
<tr>
<td>Lunch maximum (mg/dl)</td>
<td>139.2 (26.76)</td>
<td>126.7 (10.68)</td>
<td>10.21 (2.16)</td>
</tr>
<tr>
<td>Dinner minimum (mg/dl)</td>
<td>82.1 (35.82)</td>
<td>70.2 (20.16)</td>
<td>19.09 (5.26)</td>
</tr>
<tr>
<td>Dinner maximum (mg/dl)</td>
<td>165.1 (35.03)</td>
<td>151.7 (17.58)</td>
<td>16.53 (4.02)</td>
</tr>
</tbody>
</table>

Figure 11. A sample run of 30 days using realistic settings for the variability of meal timing, carbohydrate content, estimates of meal carbohydrates and noise levels.
4.6. **Insulin sensitivity**

As noted earlier, the sensitivity to insulin varies from one individual to another, and it can also change over time (from weeks to months) for a given individual. The controller must then be able to perform satisfactorily for a wide range of insulin sensitivities. The nominal case, in which the only variation comes from the timing of the post-prandial glucose measurements, is used for this case. A set of 30 runs is done for each of the sensitivity settings. In these simulations, 100% corresponds to a healthy, extremely insulin sensitive diabetic subject. This is scaled down to 5%, which corresponds to an extremely insulin resistant individual. The nominal for a diabetic subject is set at 50%, and is what has been used so far in the rest of the tests. Figure 12 shows the metrics for this case. The higher incidence of hyperglycaemia for the lower sensitivities reflects the slower convergence of the algorithm, as at day 10 it still has not converged. As the sensitivity increases the incidence of hypoglycaemia increases, reflecting the more aggressive action. The same is true for the post-prandial variability.

A sample of the responses for a low, nominal and high sensitivity are shown in Figure 13. Note that although the high sensitivity seems to perform much better, the performance will be worse once other sources of uncertainty come into play.

For the extremely insulin insensitive case \( \Delta = \text{diag}(-0.837 - 0.986 - 0.900) \), and for the extremely insulin sensitive case \( \Delta = \text{diag}(-0.356 - 0.461 - 0.775) \). In both cases these are still within the stability bounds for \( \Delta \) from the nominal sensitivity. It is interesting to note that the case with the lower insulin sensitivity has a \( \Delta \) that is much closer to the stability bound than the higher insulin sensitivity case, which is counterintuitive at first. At this low insulin sensitivity, the dose required is much higher when compared to the nominal case; thus, the peak of the post-prandial glucose excursion is shifted farther into the future, putting the performance measure \( \psi \) in an operating region that is nonlinear with respect to the changes in the dosing. The sensitivity is also closer to zero, and thus closer to the stability bound corresponding to the change of sign of the sensitivity. In this case, if the sensitivity to insulin kept decreasing, it would approach zero in the limit, but never change sign.

![Figure 12](image-url)  
*Figure 12. Variation of the post-prandial metrics as a function of insulin sensitivity; nominal case is 50%: (a) hypo- and hyperglycaemic events; and (b) post-prandial minimum and maximum for each meal.*
5. CONCLUSIONS

The feasibility of using run-to-run control to determine the optimal insulin bolus dose and timing was shown by Zisser et al. [20], 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 min; 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.

A new performance measure is proposed, which gives the patient the freedom of taking post-prandial glucose measurements at times that are more flexible and do not require them to adhere rigidly to the clock. Even with this variation in the timing, the controller is able to converge within a couple of days, significantly improving the degree of glycaemic control. This new formulation of the algorithm has proven to be quite robust. Even in the face of large uncertainty the controller always remains stable under the conditions tested. Under realistic conditions (which are still more on the higher extreme of variability) performance remains satisfactory. It is expected that the actual variability encountered in use will not be as significant as the testing conditions. The algorithm is currently being evaluated in a clinical setting.
REFERENCES


