Prandial insulin dosing using run-to-run control: application of clinical data and medical expertise to define a suitable performance metric

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For all people with type 1 diabetes, managing their disease is a daily challenge. As of 2000 an estimated 17.1 million people were afflicted with type 1 diabetes (Eiselein *et al.*, 2004; Wild *et al.*, 2004), with a clear rising trend in the incidence of the disease (Gale, 2005). The associated cost of the disease is staggering (American Diabetes Association, 2003; Ettaro *et al.*, 2004). Starting with the Diabetes Control and Complications Trial (Diabetes Control and Complications Trials Research Group, 1993), the accumulated clinical evidence is that blood glucose levels must be normalized in order to prevent the complications associated with diabetes (Cefalu, 2005). Maintaining normoglycemia entails frequent monitoring of blood glucose levels, together with frequent adjustments to the treatment strategy, including changing insulin dosing, meal composition, and exercise routines.

One of the components for normalizing blood glucose is determining and using the correct dosing of insulin to cover the carbohydrate content of meals. The insulin-to-carbohydrate (IC) ratio is not a fixed ratio; it depends on the time of day, and will change as the person's insulin sensitivity changes due to myriad different factors, such as levels of physical activity and stress. Although guidelines exist to select a starting IC ratio, optimizing the insulin dosage is a trial and error process (Jovanovic, 2002; Walsh and Roberts, 2003; Bode, 2004).

Since the advent of home glucose monitoring, there has been interest in developing algorithms to guide the adjustment of insulin therapy. Skyler *et al.* (1981) and Jovanovic and Peterson (1982) were among the first to introduce such heuristic algorithms. Both algorithms adjust insulin dosing using rules based on practical experience. The Skyler *et al.* (1981) algorithm uses only pre-prandial blood glucose measurements, while the Jovanovic and Peterson (1982) algorithm uses pre- and postprandial measurements.

Chanoch *et al.* (1985) demonstrated that computer-assisted insulin delivery decision making is feasible. The pocket computer program they tested in five type 1 subjects with diabetes was based on the algorithm proposed by Jovanovic and Peterson (1982). In another study Peterson *et al.* (1986) found the approach to be viable. Computer users in this study achieved lower average blood glucose and glycated hemoglobin (A_{1c}) values, although blood glucose levels were not completely normalized.

Several other studies (Schiffrin *et al.*, 1985; Chiarelli *et al.*, 1990; Peters *et al.*, 1991; Beyer *et al.*, 1990; Schrezenmeir *et al.*, 2002) found benefits from the use of similar algorithms. In the worst of cases no differences in overall glycemic control were observed, with only a reduction in the instances of hypoglycemia. None of these studies used the newer rapid-acting insulin analogs.

Owens *et al.* (2006) propose an algorithm that takes advantage of these monomeric insulin formulations, and use a run-to-run control framework adopted from the chemical process industry. The concept was tested in a clinical setting, using blood glucose determinations at 60 and 90 minutes after the start of the meal to adjust the dose and timing of the insulin bolus. The majority of the subjects converged to, or maintained, good glycemic control, but the rest diverged in their responses (Zisser *et al.*, 2005).

Based on the results from this trial, the run-to-run formulation was modified to overcome the difficulties encountered, such as changing the timing of the insulin bolus with respect to the beginning of the meal and the required fixed timing for the blood glucose determinations (Palerm *et al.*, 2006). The proposed revision to the algorithm adjusts only the dose of the insulin bolus, keeping the timing to coincide with the beginning of the meal. The algorithm was tested *in silico* using the mathematical model proposed by Hovorka *et al.* (2004), giving quite satisfactory results.

Mathematical models are very useful tools in research and development, but their limitations must be considered in the process. In this case it is known that the glucose absorption from a mixed meal is a weak point of the model, in part because the model is based only on data from liquid oral glucose loads. Given the central role of the meal absorption in relation to insulin dosing it was imperative that the *in silico* results be verified *in vivo*.

Eleven subjects with type 1 diabetes mellitus were recruited for a study to test the algorithm. There were seven females and four males, with a range of age from 21 to 65 years (43.5 ± 15.6 years,

mean±SD), a BMI of 25.5 ± 4.8 kg/m^2, and a glycated hemoglobin (A$_{1c}$) of $7.1 \pm 1.3\%$. Duration of diabetes was 16.7 ± 12.5 years (range of 1–39 years). All subjects had undetectable C-peptide levels. The study was approved by the Cottage Health System Office of Research Institutional Review Board, and informed witnessed consent was obtained from all subjects.

In the initial phase of the trial, subjects were given a target carbohydrate content for their lunch meal based on a weight maintenance diet calculation. Lunch was determined to account for 40% of the subject's calculated total daily caloric requirement, and for carbohydrate to account for 30% of the meal. Total daily caloric requirements were calculated based on weight, gender and activity levels.

During a baseline period of two to four days subjects were asked to measure their blood glucose according to the protocol the dose adjustment algorithm uses. The subjects all measured their blood glucose at the start of the meal. Two additional postprandial blood glucose determinations were taken: the first one at 60–90 minutes after the start of the meal and the second one at least 30 minutes after the first, but no later than 180 minutes after the start of the meal. On test days, they were asked to start the lunch meal with a blood glucose level within 70–130 mg/dl. Starting with their usual IC ratio, their insulin bolus dose was titrated downward until their postprandial glucose levels were high (180–250 mg/dl).

Independently, two physicians skilled in intensified insulin delivery (H. Zisser and L. Jovanovič) went through the data sets collected, and made a specific recommendation for each meal as to how the insulin bolus dose should be corrected for the following day. The physician's new insulin recommendation was targeted to normalize the postprandial glucose levels the following day, whereas the algorithm could be tuned to converge to the correct IC ratio over a set period of days.

Of the 43 data sets collected during this portion of the study, only 35 met the pre-meal blood glucose target requirement. For these, the mean pre-meal blood glucose was 98.5 ± 16.9 mg/dl. At the first postprandial time-point, which occurred at 74 ± 15 min after the start of the meal, mean blood glucose was 133.0 ± 50.7 mg/dl. For the second postprandial time-point — at 120 ± 25 min after the start of the meal, 47 ± 18 min after the first determination — mean blood glucose was 117.9 ± 30.1 mg/dl. For nine of these sets the physicians determined that the insulin bolus dose was appropriate, thus requiring no change. Another nine required a reduction in the bolus dose, and 17 required that the dose be increased.

Using the original performance measure proposed by Palerm *et al.* (2006), we found that clustering was impossible to match the clinical decisions. In particular some decisions had the same performance measure, but required opposite actions to the insulin dose. This is, using this performance measure the algorithm could end up making the wrong decision, increasing the insulin dose when a decrease was needed or *vice versa*.

Most of the other possibilities tested also fell in this category, with only a few showing the possibility of discrimination. The best of the tested performance measures uses the deviation from the pre-prandial blood glucose of the blood glucose estimated at 60 minutes after the start of the meal (calculated using the rate-of-change from the pre-meal and first post-meal blood glucose determinations), together with the difference in blood glucose between the pre-meal and second post-meal time points. Since the performance measure must be a scalar value, the length of the vector from the origin to the point defined by the two measures is used. Regions that determine the action to take based on the performance measure were defined. Mathematically, this is expressed as

$$G_{60 \text{ min}} = 60 \cdot \frac{G_1 - G_0}{T_1}$$
$$\Delta G_{60 \text{ min}} = G_{60 \text{ min}} - G_0$$
$$\Delta G_{T_2} = G_2 - G_0$$
$$\psi = \sqrt{\Delta G_{60 \text{ min}}^2 + \Delta G_{T_2}^2}$$

where G_0 is the pre-prandial blood glucose, G_1 and G_2 are the blood glucose determinations at the first and second postprandial time points (at T_1 and T_2 minutes after the start of the meal), respectively.

The gain for the algorithm was calculated using linear regression to best match the clinically determined dose adjustment. The dose calculated with the algorithm over the data set was then compared with the clinical determinations. The correlation between the two is $R^2 = 0.95$.

As part of the clinical influence on the run-to-run algorithm implementation, further heuristics were incorporated. Under certain conditions, when an increase in the insulin dose could result in hypoglycemia, a reduction in the meal's carbohydrate content is recommended instead of changing the IC ratio. Special handling of the correction is also taken when the post-meal measurements show hypoglycemia (defined as a blood glucose below 60 mg/dl for our purposes), thus adding a level of safety to the algorithm.

After the baseline period, the next phase focused on the lunch meal, for which carbohydrate content was personalized. For each subject, the daily caloric requirement was calculated according to gender, weight and activity levels. Subjects were asked to keep lunch consistent at this carbohydrate content through the test period.

The algorithm testing was started once their postprandial blood glucose levels were high (180-250 mg/dl). The algorithm then adjusted the IC ratio over two weeks. The average number of days it took the algorithm to converge to an appropriate IC ratio was 5.4 ± 3.6 days. On the first day the pre-prandial blood glucose was 101.7 ± 22.4 mg/dl and at 60 min post-prandial blood glucose was 176.5 ± 41.6 mg/dl, starting IC ratio was 1U to 14.15 ± 3.95 g carbohydrate. On convergence, the pre-prandial blood glucose was 94.7 ± 23.9 mg/dl and the 60 min post-prandial blood glucose was 109.5 ± 25.3 mg/dl, the IC ratio was 1U to 9.47 ± 2.27 g carbohydrate. Over 118 meals, only two hypoglycemic (<55 mg/dl) events were reported (a 1.7% incidence rate), and none were below 50 mg/dl.

The results from the initial testing of the algorithm are very satisfactory. In particular the low incidence of hypoglycemia is quite good, as this is a significant improvement over what subjects will usually experience when following standard treatment strategies. Further testing in the second phase removes the constraints on the fixed carbohydrate content of the meals. Preliminary analysis of the data from this second phase is promising as well.

We have shown how traditional methods from engineering can be melded with medical expertise to develop and refine a dosing algorithm. Given how well the algorithm matches the clinical decisions using only sparse blood glucose measurements bodes well for a new tool that could soon be made available. Such a tool will simplify the current trial and error method of determining the correct insulin-to-carbohydrate ratios.

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