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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OBJECTIVE — We propose a novel algorithm to adjust prandial insulin dose using sparse blood glucose measurements. The dose is adjusted on the basis of a performance measure for the same meal on the previous day. We determine the best performance measure and tune the algorithm to match the recommendations of experienced physicians.

RESEARCH DESIGN AND METHODS — Eleven subjects with type 1 diabetes, using continuous subcutaneous insulin infusion, were recruited (seven women and four men, aged 21–65 years with A1C of 7.1 ± 1.3%). Basal insulin infusion rates were optimized. Target carbohydrate content for the lunch meal was calculated on the basis of a weight-maintenance diet. Over a period of 2–4 days, subjects were asked to measure their blood glucose according to the algorithm's protocol. Starting with their usual insulin-to-carbohydrate ratio, the insulin bolus dose was titrated downward until postprandial glucose levels were high (180–250 mg/dl [10–14 mmol/l]). Subsequently, physicians made insulin bolus recommendations to normalize postprandial glucose concentrations. Graphical methods were then used to determine the most appropriate performance measure for the algorithm to match the physician's decisions. For the best performance measure, the gain of the controller was determined to be the best match to the dose recommendations of the physicians.

RESULTS — The correlation between the clinically determined dose adjustments and those of the algorithm is $R^2 = 0.95$, $P < 1e - 18$.

CONCLUSIONS — We have shown how engineering methods can be melded with medical expertise to develop and refine a dosing algorithm. This algorithm has the potential of drastically simplifying the determination of correct insulin-to-carbohydrate ratios.

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A bsolute normalization of blood glucose levels at all times is the ultimate goal of diabetes management. Although this remains a point of debate, there is evidence that reducing glycemic variability is an important factor in reducing long-term complications (1,2). A crucial component of such a strategy is the correct determination of an individual's insulin-to-carbohydrate ratio, defined as the amount of the meal-related carbohydrate (in grams) covered by 1 unit of insulin. The insulin-to-carbohydrate ratio is not fixed; it is influenced by a myriad of different factors, such as time of day, levels of physical activity, and psychological and physical stress. Although guidelines exist to select a starting insulin-to-carbohydrate ratio, optimizing the insulin dosage is a trial-and-error process (3–5).

Since the advent of home glucose monitoring, there has been interest in developing algorithms to guide the adjustment of insulin therapy. Skyler et al. (6) and Jovanovic and Peterson (7) were among the first to introduce such heuristic algorithms. Both adjust insulin dosing using rules based on practical experience. The Skyler et al. (6) algorithm uses only preprandial blood glucose measurements, whereas the Jovanovic and Peterson (7) algorithm uses pre- and postprandial measurements.

Chanoch et al. (8) demonstrated that computer-assisted insulin delivery decision making is feasible. The pocket computer program they tested in five subjects with type 1 diabetes was based on the algorithm proposed by Jovanovic and Peterson (7). In another study, Peterson et al. (9) found the approach to be viable. Computer users in this study achieved lower average blood glucose and A1C values, although blood glucose levels were not completely normalized.

Schiffrin et al. (10) saw significant improvements in glycemic control in subjects who used a portable computer programmed to adjust short- and intermediate-acting insulin dosing. Their algorithm used preprandial blood glucose measurements and was based on a two-injection per day strategy. Chiarelli et al. (11) compared this method with manual dose adjustment, and, although they did not find differences in glycemic control, they did observe a reduction in hypoglycemia in the computer users. Peters et al. (12) adapted this algorithm as well and compared it with manual adjustments. Their conclusion was that metabolic control and safety were comparable.

Beyer et al. (13) created their own algorithms on the basis of the work of Skyler et al. (6). As in the original, only preprandial blood glucose measurements were used. They found that subjects using the computer algorithm did significantly better than subjects in the manually adjusted intensive treatment group (14).

None of these studies used the newer rapid-acting insulin analogs. Owens et al. (15) proposed an algorithm that takes advantage of these monomeric insulin formulations and uses 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 min 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 several diverged in their responses (16).

On the basis of 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 (17). The proposed revision to the algorithm adjusts only the dose of the insulin bolus, fixing the timing of the bolus to coincide with the beginning of the meal. The algorithm was tested in silico using the mathematical model proposed by Hovorka et al. (18). Given the uncertainty inherent in any mathematical model, and, in particular, in the meal absorption component of the model used, it was imperative that the proposed algorithm metric be tested in vivo. The main purpose of this study was to test and refine, using clinical data, the performance measure used in determining how appropriate the bolus dose is. Medical expertise was also used to tune the controller. The corrections the algorithm would recommend were compared with what an experienced physician would do in the same cases. This study reports that our algorithm, using a revised performance measure, is able to match the dose adjustment recommendations of the physicians.

RESEARCH DESIGN AND METHODS

Eleven subjects with type 1 diabetes were recruited for this study. Inclusion criteria were a diagnosis of type 1 diabetes for at least 1 year, use of a continuous subcutaneous insulin infusion pump with a rapid-acting insulin analog, and willingness to participate for up to 2 years. Exclusion criteria included being pregnant or planning to become pregnant, being younger than 18 years of age, being unwilling to perform repeated blood glucose measurements or unwilling to take insulin as directed, or having abnormal thyroid, kidney, or liver function. There were seven women and four men,

with a range of age from 21 to 65 years (43.5 ± 15.6 [mean ± SD] years), a BMI of 25.5 ± 4.8 kg/m^2, and A1C of 7.1 ± 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.

Data collection protocol

To optimize the basal insulin infusion rates, subjects wore a continuous glucose sensor (CGMS; Medtronic MiniMed, Northridge, CA) for a period of 3 days. On each day they skipped a meal (breakfast one day, lunch the next day, and dinner on the third day) to be able to determine basal insulin infusion rates during these mealtime periods, when there are usually prandial insulin boluses present. Using these data, the basal insulin infusion rates were adjusted to a target of 90 mg/dl (5 mmol/l). The process was repeated as necessary until all preprandial glucose concentrations were in the target range (19).

Once basal rates were optimized, the subjects were given a target carbohydrate content for their lunch meal on the basis of a weight maintenance diet calculation (adjusted for sex, exercise pattern, and stress level). Lunch was determined to account for 40% of the subject's calculated total daily caloric requirement and carbohydrates to account for 30% of the meal. Total daily caloric requirements were calculated on the basis of weight, sex, and activity levels (20). The composition of the meal (beyond the carbohydrate content) was left to the subjects to determine according to their personal preferences.

Subjects were provided with a One-Touch UltraSmart blood glucose monitoring system (LifeScan, Milpitas, CA), which was selected for its memory capacity and its event logging functions. During the baseline period of 2–4 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 min after the start of the meal and the second one at least 30 min after the first but no later than 180 min after the start of the meal. On test days, subjects were asked to start the lunch meal with a blood glucose

level within 70 and 130 mg/dl (3.9 and 7.2 mmol/l). Starting with their usual insulin-to-carbohydrate ratio, their insulin bolus dose was titrated downward until their postprandial glucose levels were high (180–250 mg/dl [10–14 mmol/l]).

Dose adjustment algorithm

The run-to-run algorithm considers each day as a "run." Each meal of the day (i.e., breakfast, lunch, and dinner) is adjusted independently. The insulin dosage correction is based on a performance measure (denoted by ψ) that quantifies the postprandial glucose excursion as a scalar quantity. The performance measure corresponding to the ideal postprandial response is denoted by ψ^r. The algorithm then takes the current insulin-to-carbohydrate ratio (denoted in the equation below as ν_k, with the subscript k indicating the current day) and makes an adjustment to calculate the new insulin-to-carbohydrate ratio for the next day (denoted as ν_{k+1}) using

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

where the gain K is a tuning parameter that determines how aggressive the algorithm is in making a correction. The new insulin-to-carbohydrate ratio is used on the following day, and the procedure is repeated.

In the initial development, the performance measure used is the rate of change of blood glucose estimated from the two postprandial blood glucose measurements and is calculated using

$$\psi_k = \frac{G_2 - G_1}{T_2 - T_1},$$

where T_1 and T_2 are the minutes elapsed since the beginning of the meal at the time of the first and second postprandial blood glucose measurements (G_1 and G_2), respectively. This performance measure is further normalized by the carbohydrate content of the meal. Although performance is quite satisfactory in the in silico testing, the glucose absorption from a mixed meal is a weak point of the model used and therefore required in vivo validation (17).

Data analysis and gain selection

Independently, two physicians skilled in intensified insulin delivery (H.Z. and L.J.) studied the datasets collected and made a specific recommendation for each meal as to how the insulin bolus dose should be

corrected for the following day. The physicians' new insulin recommendation was targeted to normalize the postprandial glucose levels on the following day, whereas the algorithm could be tuned to converge to the correct insulin-to-carbohydrate ratio over a set period of days. The physicians would not make a change to the insulin-to-carbohydrate ratio for the following day if the subject's preprandial glucose concentration was not in the range of 70–120 mg/dl (3.9–6.7 mmol/l). Prandial blood glucose concentrations were excluded from the decision to adjust the insulin-to-carbohydrate ratio if they were above or below this target to minimize other variables that may affect the postprandial glucose excursion. The physicians increased the following day's meal-related dosage if either of the two postprandial glucose levels was >120 mg/dl (6.7 mmol/l). Dosages were increased in a proportional fashion above this level. The physicians would recommend a decrease in the insulin dosage if any of the postprandial glucose levels were <70 mg/dl (3.9 mmol/l). Additionally, no adjustment to the insulin-to-carbohydrate ratio would be made if the first postprandial glucose concentration was >150 mg/dl (8.3 mmol/l) and the second postprandial glucose level was <70 mg/dl (3.9 mmol/l); the physicians would instead recommend lowering the total carbohydrate content of the meal for the following day.

Graphical methods were then used to determine whether the performance measure proposed from the in silico testing (17) correctly clustered the data points according to the clinical adjustment (increase, decrease, or no change to dose). Other possibilities were also considered, including the rate of increase in blood glucose in the first phase of the postprandial response (estimated from the premeal and first postmeal measurements), the deviations from baseline for the two postprandial determinations, the difference between the rate of increase and the rate of decrease, and the blood glucose at 60 and 90 min from the start of the meal as interpolated from the measured values. For the performance measure best able to cluster the collected data in accordance with the medical expertise, the gain for the controller was determined to best match the dose recommendation of the physicians over the full dataset.

RESULTS — Of the 43 datasets collected during this portion of the study,
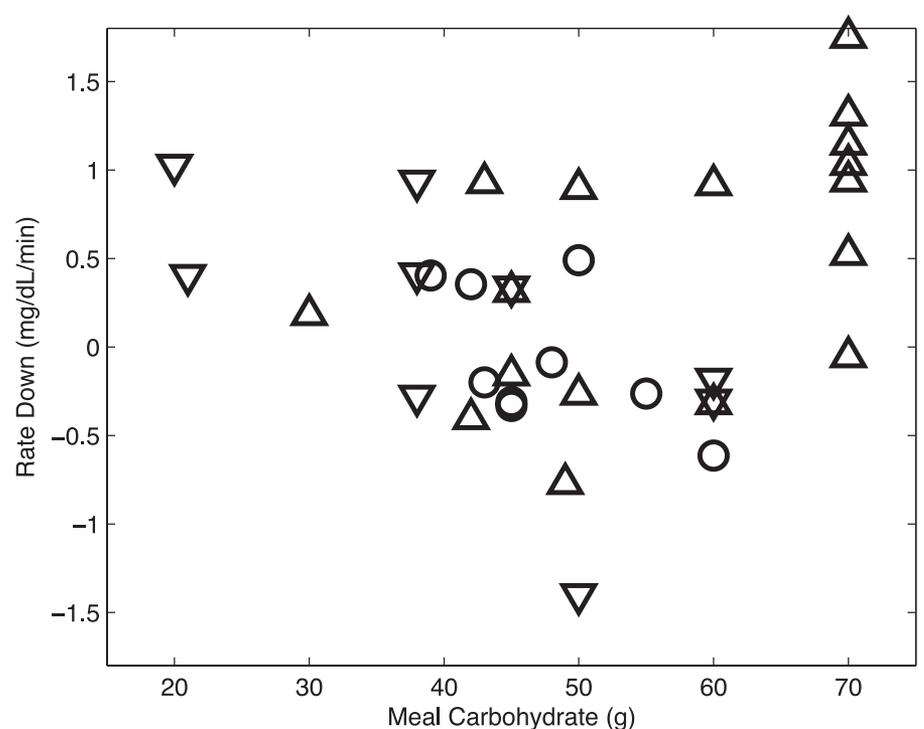

Figure 1—*Distribution of data points using the original performance measure based on the rate of fall of postprandial blood glucose. The clinical decision of the physicians is denoted as a dose increase (△), dose unchanged (○), or a dose decrease (▽). A negative rate indicates that blood glucose was still rising at the second postprandial blood glucose determination. There is no way to draw boundaries that group and segregate all the data points for each clinical decision category; thus, the measure cannot discriminate accordingly.*

only 35 met the premeal blood glucose target requirement. For these, the mean premeal blood glucose was 98.5 ± 16.9 (mean ± SD) mg/dl (5.47 ± 0.94 mmol/l). 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 (7.39 ± 2.82 mmol/l). 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 (6.55 ± 1.67 mmol/l). For 9 of these sets, the physicians determined that the insulin bolus dose used was appropriate, thus requiring no change. Another 9 required a reduction in the bolus dose, and 17 required that the dose be increased.

The rate of change of blood glucose concentration in the postprandial period is a common metric physicians look at; this metric was the basis of the original performance measure proposed in ref. 17. Using this performance measure, we found that clustering to match the clinical decisions was impossible (Fig. 1); there is no way to draw boundaries that group and segregate the data points for the three clinical decision categories of increase,

decrease, or no change of dose. In particular, some decisions at 45 and 60 g of carbohydrate had the same performance measure but required opposite actions on the insulin dose adjustment. Therefore, if this performance measure were used, 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 used the deviation from the preprandial blood glucose at two distinct time points. The first is the deviation at 60 min after the start of the meal, which is calculated using the first postmeal blood glucose determination (calculated using the rate of change from the premeal and first postmeal blood glucose determinations). The second deviation is that at the second postmeal time point. Because the performance measure must be a single scalar value, the distance from the origin to the point defined by the two measures is used. Figure 2 shows these data, together with the regions that determine the action to take on the basis of the perfor-
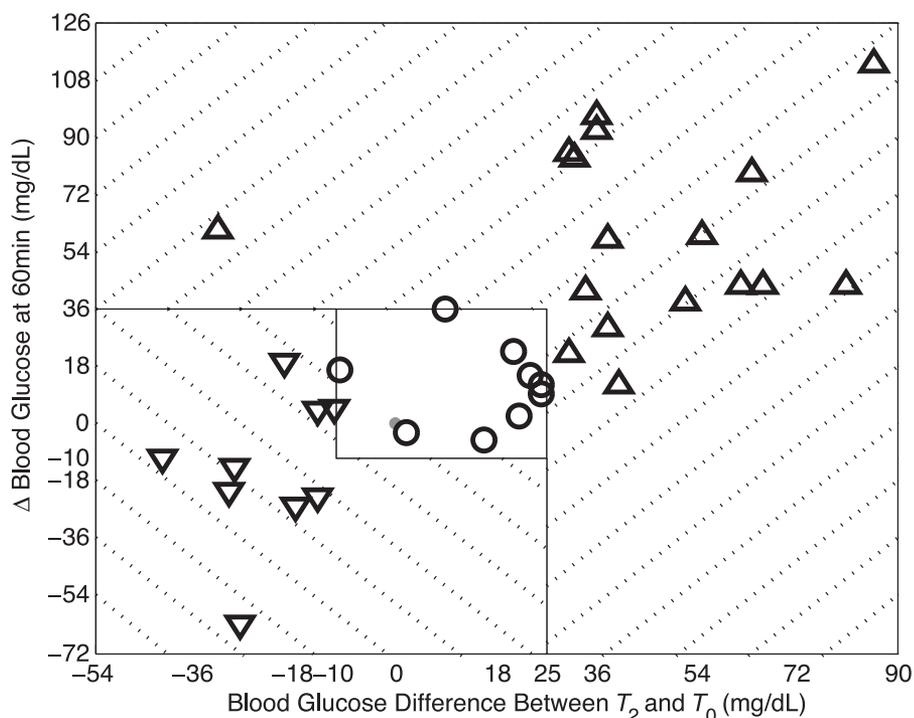
Figure 2—*Clustering of data when using the estimated blood glucose at 60 min postprandial and the differential between the baseline and final blood glucose levels. The clinical decisions of the physicians are denoted as a dose increase ($\triangle$), dose unchanged ($\bigcirc$), or a dose decrease ($\triangledown$). The center box (no hatch marks) indicates the desired region corresponding to no dose change, the upper right-hand region (positive slope hatch marks) corresponds to a dose increase, and the lower left-hand region (negative slope hatch marks) corresponds to a dose decrease.*

mance measure. Mathematically, this is expressed as

$$G_{60\,min} = 60 \cdot \frac{G_1 - G_0}{T_1}$$

$$\Delta G_{60\,min} = G_{60\,min} - G_0$$

$$\Delta G_{T_2} = G_2 - G_0$$

$$\psi = \sqrt{\Delta G^2_{60\,min} + \Delta G^2_{T_2}},$$

where G_0 is the preprandial blood glucose and 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. Mathematically, there is no reason for the relationship between the dose adjustment and the performance measure chosen to be linear. Therefore, the dose calculated with the algorithm over the dataset was then compared with the clinical determinations (Fig. 3). The correlation between the two is $R^2 = 0.95$, $P < 1e - 18$. This result confirms that the choice of the linear relationship for the

dose adjustment used by the algorithm, together with the performance measure, is satisfactory.

CONCLUSIONS — The reason for selecting the first postprandial blood glucose determination to be at 60 min is that, on the basis of previous clinical experience, this is the expected time of the peak glucose excursion. Recent evidence from other studies demonstrated that the actual time to peak is closer to 70–75 min (21,22). The actual time to peak will vary, in part on how closely the insulin bolus dose is matched to the carbohydrate content of the meal. A grossly underdosed (or missed) bolus will result in the peak being pushed to a later time. The use of the second postprandial measurement was originally conceived to verify if indeed the blood glucose had peaked and was on its way back to baseline and not still increasing.

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.

To this end, data were gathered according to the desired timing of postprandial blood glucose measurements in relation to the start of the meal. Experienced physicians determined whether the insulin bolus dose needed to be increased, kept the same, or decreased. Although the initial performance measure worked well for in silico testing, it failed to discriminate among the in vivo datasets. Different prospective performance measures were tested for their ability to cluster the in vivo data in the same way as the experienced physicians did.

The best performance measure not only differentiates the clinical data correctly but it is also intuitive from the physiological standpoint. It uses blood glucose at 60 min as one of the parameters, which is close to the time of the peak blood glucose excursion. Thus, too large of a positive deviation from baseline indicates that the insulin dose was insufficient.

Certainly penalizing only this excursion can conceivably lead to hypoglycemia resulting from too strong a dose. Therefore, the deviation at the second postprandial determination from basal serves to balance this effect and not only to confirm that the blood glucose has indeed peaked. It is expected that at this point the blood glucose will be close to the baseline value when we have the perfect bolus dose.

In Fig. 2 there is a single point in the upper left-hand quadrant; in this case the meal had 70 g carbohydrates, and the bolus administered was 6.5 units of insulin. Before the meal the blood glucose was 115 mg/dl (6.4 mmol/l), at 85 min after the start of the meal it was 202 mg/dl (11.2 mmol/l), and at 175 min it was 85 mg/dl (4.7 mmol/l). The clinical decision was to increase the dose by 0.5 unit. Although it was safe to make this small adjustment, this dose is very close to the point at which an increase could be dangerous. To avoid such a possibility, dose changes can be overruled if the blood glucose difference between the second postprandial and baseline measurements is < -10 mg/dl (-0.56 mmol/l). Other such safety checks are easily implemented as well.

The gain of the controller was calculated to best match the clinical recommendation. By using this gain, the correlation between the algorithm's dose
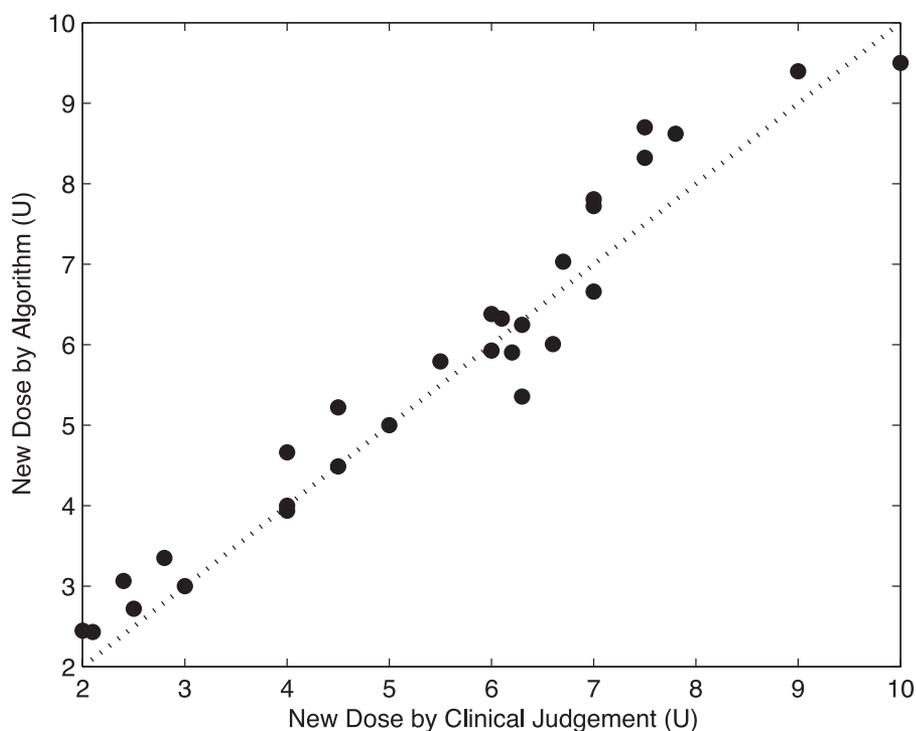
Figure 3—*Comparison of the new dose as determined by the algorithm (using the gain derived from the clinical data) and the physician:* $R^2 = 0.95$, $P < 1e - 18$.

recommendation and that of the physician is very high. For safety, this gain can also be "detuned" (i.e., scaled back) so that recommendations are not as aggressive as the physician's, who will generally have additional information to consider when making dose adjustments.

The resulting algorithm, with the defined regions determining the action to take on the basis of simple linear rules, is similar to the concept of parametric programming (23). Such a structure has the advantage of making it possible to exhaustively test all possible actions by the algorithm a priori. The resulting algorithm also suggests that the underlying behavior may be low order (i.e., simple dynamics), which has other implications that could influence more complex algorithms such as those developed for an artificial β-cell.

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 clinical decisions using only sparse blood glucose measurements, a new tool that will simplify the current trial-and-error method of determining correct insulin-to-carbohydrate ratios could soon be available.

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