Managing type 1 diabetes mellitus in ambulatory patients

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Abstract

We present a direct adaptive control/management idea for assisting patients suffering from type 1 diabetes mellitus. It is argued that a static non-linear feedback law is all that can reasonably be implemented given the paucity of the measurement data.

Keywords: non model-based control, constrained control, medical application, diabetes mellitus

1 Introduction

Diabetes management involves strict blood glucose monitoring and insulin therapy, with the guidance of diabetes experts. It is a non-trivial task for most people. It is even more challenging in remote/rural areas where expert advice is not easily obtained. Our aim is to develop an insulin advisory algorithm to be incorporated in hand-held blood glucose meters used by diabetics.

1.1 Problem definition

Diabetes mellitus concerns a dysfunction in the glucose regulation process in the blood stream. Glucose regulation is a control system with hormones as controllers, where insulin plays a major role in keeping blood glucose (BG) level down. When the insulin secretor senses a rise in blood glucose level above the target range (clinically known as the normal glycaemic range), it increases insulin secretion, as illustrated in Figure 1. The inputs to the system include food intake and exercise, which in the diagram are represented as external glucose input. The effects of other hormones, which usually raise BG level when it falls below the target range, are quantities which are not measurable, thus considered as disturbance. This means that the BG plant itself is a closed loop system by nature.

In type 1 diabetes, insulin is absent. BG level must be kept under control by injections of insulin, usually four times a day, before each meal and bedtime. In this case, diabetics measure their BG level, estimates their BG profile given the measured value and their glucose input factors (food and exercise), and estimates the insulin dose required to stabilise their BG back to the target range.

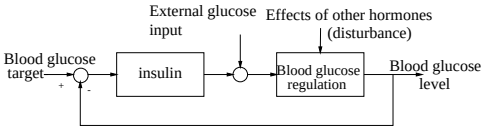

Figure 1: Representation of the glucose regulatory system

There are significant differences between this control scheme and the physiological non-diabetic control. Firstly, daily measurements are very sparse. This means that there is a lot of missing information on the dynamics, as illustrated in Figure 2. Secondly, insulin is injected into fatty tissues under the skin instead of directly into the bloodstream, adding an individual-dependent absorption process into the picture.

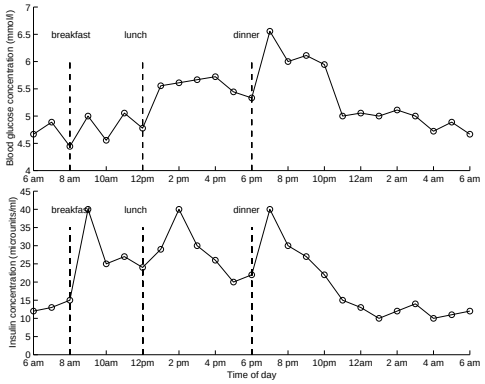

Figure 2: Fluctuations in blood glucose and insulin concentrations in a non-diabetic subject over 24 hours, measured hourly [1]

It is well accepted that these constraints impose limitations to the outcome that can be achieved by this control method. However there is a void in the literature as to what these limits are.

1.2 Model-based approaches

The majority of papers in the literature take the approach of building predictive models of the BG regula-

tion system, where insulin (the controller) is one of the inputs [2, 3], as illustrated in Figure 3.

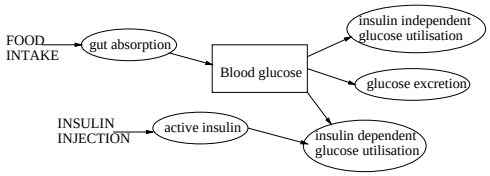

Figure 3: A typical model of the glucose regulatory system

The control algorithm in these systems is usually a set of simple if-then rules with some trial-and-error element incorporated in it. Given a set of conditions, an inference engine decides on an insulin value. The model predicts the BG level given these conditions. If the prediction falls within the target range, it accepts the insulin value, otherwise another guess is generated and tried again in the model.

More naive models have been used to study optimal insulin infusion algorithms [4, 5]. These models are too simplistic to represent the glucose regulation system and are suitable for study design purposes only. The studies involved evaluation of insulin infusion algorithms but did not extend to the investigation of the limits of control outcomes of these algorithms.

Some of the above mentioned models include parameters which are adapted to the individual. These parameters are either computed only at the start of the algorithm [3], or updated periodically [2].

The performance of such systems depends heavily on the model. The glucose regulatory system is complex; it is truly a challenge to develop a quantitative, predictive model that is sufficiently accurate for control purposes. The current models provide good simulation tools for educational and experiment design purposes, however their performance for control purposes is questionable.

1.3 Rule based approach

An alternative approach can be taken by directly deriving a set of control rules from the data collected. It is also a challenge, considering the nature of these data. However, it bears the advantage of avoiding the model construction stage. These rules are based on those used in clinical practice. Furthermore, the rules are less complex than the actual BG system, thus offering the advantage that it is easier to tune to the individual.

The rule based algorithms described in current literature compute adjustments from a prescribed insulin dose [6, 7]. They are generic rules for the population of diabetics, and are piece-wise linear functions with saturation points at minimum and maximum insulin. The work described in this paper extends this approach by customising the rules to individuals and incorporating an adaptive algorithm to obtain an optimal set of rules.

1.4 Paper outline

This paper addresses the issues surrounding direct design of a controller for diabetes by firstly analysing the data gathered from diabetic subjects. The analyses aim to further understanding of the nature of the problem, explore the limitations imposed by the constraints and investigate the importance of dynamics and history in the control rules. Discussion of the control strategy follows, focusing on direct derivation of control rules from data and the use of probabilistic modelling.

2 Data analysis

Data have been collected from ten subjects, aged 14–65 years, who have contracted type 1 diabetes for periods in the range 2–48 years. The data comprise BG measurements, insulin dose, and qualitative indications of food intake and level of physical activities, as shown in Table 4.

Date / Time	22 Nov 1999				23 Nov 1999			
	BG	Ins	Food	Exc	BG	Ins	Food	Exc
Breakfast	8.3	6	small	light	14.6	8	reg	light
Lunch	15.4	14	v.lrg	light	11.2	12	large	none
Dinner	19	11	reg	light	10.4	10	reg	none
Bedtime	10.5	18		none	9	18		light

Figure 4: Two days of raw data obtained from subject 7. BG is measured in mmol/l and insulin in units.

Information on intended carbohydrate intake and physical activity is a qualitative indication relative to the usual routine. Information on food is categorised into smaller, regular, larger or much larger portion compared to the usual carbohydrate intake. Information on exercise intensity is categorised into no exercise, light, medium or strenuous intensity. These deviations from routine are the factors diabetics use to base their decisions on; we conjecture that the information contained is sufficient for the proposed algorithm. How this information is incorporated into the decision rules will be discussed in Section 3

Quantitative information on food intake does not actually give sufficient information on its effect on the BG dynamics. One gram of sugar, for example, can translate to different amounts of rise in BG concentration in different people. Exercise is a variable that is hard to express quantitatively. We argue that quantitative information will not contribute to better decision rules.

Subjects were not asked to record the actual time of measurement. Instead, they were asked to indicate whether the measurement was taken at pre-meal (and at which meal) or bedtime. The reasons for this will be explain further in this section.

2.1 Preliminary observations

Because BG measurements are taken at intervals longer than its dynamics, it is assumed that it has returned to relative steady state at measurement time. In non-diabetic individuals, BG will have returned to the normal range. Observations of a series of diabetic BG measurements over time (i.e. what is considered to be the outcome of diabetes control) suggest that this is not the case in diabetic individuals. In fact, the fluctuations of BG levels (outside of the normal range) are very large and erratic, as shown in Figure 5.

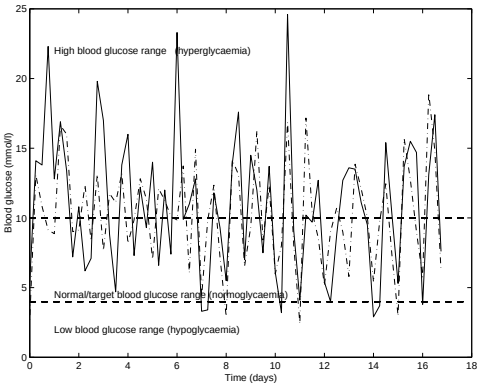

Figure 5: Blood glucose profile over 17 days of subject 7, at four measurements/day, and its predicted values. - = actual data, -. = predicted value by $BG_{k+1} = \alpha_1.BG_k + \alpha_2.BG_{k-3} + \alpha_3.Ins^s_k + \alpha_4.Ins^l_{k-1}$ [8]

BG levels recorded in a period of two months were plotted against exact time of measurement, as recorded by the glucose-meter, as shown in Figure 6, to investigate whether there is any functional relationship between BG levels and time. It is subsequently observed that, firstly, BG measurement is not conducted at regular time intervals. We cannot assume regularity in sampling frequency. Secondly, we can observe the time variant nature of the system. The range of BG level measured at 2 pm during that two months, for example, spans from 2 mmol/l to 27 mmol/l. These observations confirm that the system could be viewed as time variant and stochastic. We cannot reconstruct a "typical" profile of BG dynamics even if information on the exact measurement times is available. Hence we conclude that a record of exact measurement time does not give extra information, and is therefore not considered in the derivation of control rules.

Data were separated according to injection time (eg pre-breakfast, pre-lunch, etc), to further observe its distribution. Examples of the distribution of insulin against the distribution of BG are illustrated in Figure 8. The distribution of insulin dose seemed to centre around a certain level for each injection time. This reflects the prescribed level for that dosage; a typical insulin regime generally comprises a set of different dosages at

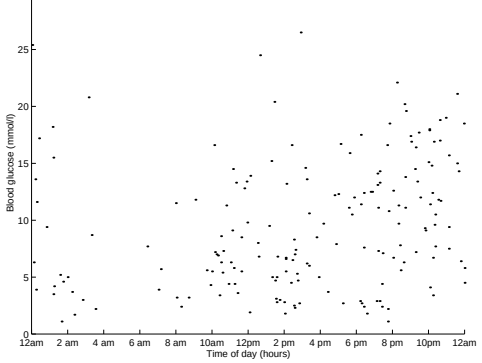

Figure 6: Blood glucose of subject 3 against time of day, from two months of data

different times of injection. In deriving rules for insulin, therefore, separate rules are computed for each injection time.

2.2 Correlation analysis of BG data

We attempted to build predictive models of BG employing system identification methodologies, taking into account both past BG and insulin values. This exercise aimed to establish the significance of BG and insulin history on the control rules. The results, as illustrated in Figure 5, show that linear models of BG can, at best, replicate the general trend of BG fluctuation, but cannot reproduce the actual values, especially the peaks. Literature in time series analysis of BG data further confirm that time series model of BG cannot be constructed using such sparse data [8], possibly because there is much missing information.

The next logical step was to investigate the correlation between BG measurements. The results of this analyses have revealed that each measurement does not have high correlation to past measurements, which explains why a predictive model could not be constructed. An example of this correlation plot is shown in Figure 7. The analyses extended to investigation of the correlation between BG and functions of BG (quadratic, cubic and logarithmic), with similar results. These confirm that the BG system has short memory, hence we cannot build deterministic predictive models for it.

These observations are consistent with medical information that the average settling time of BG dynamics is shorter than the sampling interval. Based on these observations, we conclude that static rules are sufficient to control this system.

3 Control rule design

A classically known rule based control for diabetes is the control strategy employed in clinical practice, by

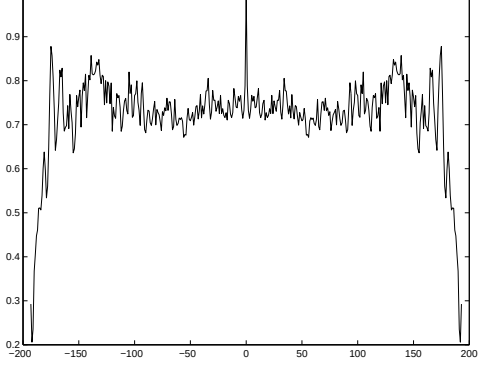

Figure 7: Autocorrelation of BG values for subject 3

physicians and patients. Essentially, rule based control algorithms are based around this method. This section, therefore, begins by studying the clinical control methodology before continuing to elaborate on the derivation of the control rules.

3.1 Clinical control regime

Clinical management of diabetes can be summarised as an adaptive rule-based control with an aim of optimising BG performance. The physician prescribes an insulin regime to the patient. On average, the patient consults the physician every three months, at which times insulin dose may be adjusted, depending on the BG profile during that period. In making these decisions, the physician considers BG distribution at each injection time and an average BG profile over the three month period. This average profile is measured through a blood test which indicates the percentage of glucose-impregnated red blood cells.

The physician's ultimate control objective is minimising BG fluctuations and the occurrence of BG levels outside the normal range. The reality is that the majority of diabetic people experience episodes of high BG level frequently. A naive solution to this would be an increase in insulin dose. However, it has been interesting to observe that physicians are reluctant to prescribe a dose which they consider to be too high, in caution that patients may fall into low BG episodes, which invariably do happen. These low episodes are equally perilous to the patient, if not more so. In fact, many physicians tolerate relatively high BG profiles in preference to risking drastic drops to the low range. This indicates that they are aware of the limitations of the current clinical control strategies, that it may be unrealistic to expect consistently normal BG levels as the outcome. However, it is not clear what the extent of the limitations are, thus one should aim for the ultimate goal and hope for the best, often resulting in frustration for physician and patient alike.

Between consultations, diabetic individuals are in charge of their own BG control. They have their own control rules in place. They may vary their insulin dose from the prescription. Firstly, they consider the BG level measured at the time of injection. If it is a higher level than a pre-determined range, they are likely to inject more insulin, and vice versa. They also estimate the rate of change of glucose according to what they are going to eat or do. For example, if their BG measurement is high or if they expect a steeper rise in BG level due to larger carbohydrate consumption, insulin dose is increased and vice versa. There are maximum/minimum insulin dosages that are recommended by the physician, which they mostly adhere to.

These rules can be summarised as follows: $ins = f(BG)(1 + g(F, E))$, where f is a monotonically increasing function, with saturation at both minimum and maximum insulin values, and g is determined by food and exercise. The parameterisation of these rules will be discussed in the following section.

3.2 Control rules based on clinical management

A control strategy based on clinical management practice described in Section 3.1 comprise an initial set of rules, derived from patient data, and an adaptation procedure, based on the optimal control objective. In this discussion, we will consider the rules to have the generic form as expressed above, with parameters which can be updated to achieve optimal outcome.

Looking at that generic form, it is clear that $f(BG)$ forms the backbone of the control rule. We therefore need to establish an underlying structure suitable for $f(BG)$ by analysing the insulin-BG relationship of the data.

Initial observations suggested a stochastic functional relationship between distribution of insulin and distribution of BG [9]. The distributions indicated a bounded positive correlation between insulin and BG, with saturation levels for maximum and minimum insulin dose. It was further established that a piece-wise linear function can be derived from the means of the distribution of $p(ins|BG)$ [10] The shape of this function is consistent with those used in other rules of insulin adjustment, $\Delta ins = f(BG)$ [6, 7].

Observations of the ins-BG plots of different subjects show that the generic shape of the rules holds. However, the ranges of insulin and BG distribution vary significantly, highlighting differences in minimum and maximum points, threshold and slope of the distribution. It is more appropriate, therefore, to extract rules for individuals rather than a universal rule for the diabetic population.

Further analysis of ins-BG relationship revealed that an insulin rule can be parameterised by

$f(BG) = \theta_1 . (\log(BG))^{\theta_2}$, where θ_1 takes mean(insulin) as an initial value and $0 < \theta_2 \leq 1$. θ_1 and θ_2 are computed iteratively until $f(BG)$ sits in the centre of the ins-BG distribution. Both $f(BG)$ functions (piece-wise linear and logarithmic) are illustrated in Figure 8.

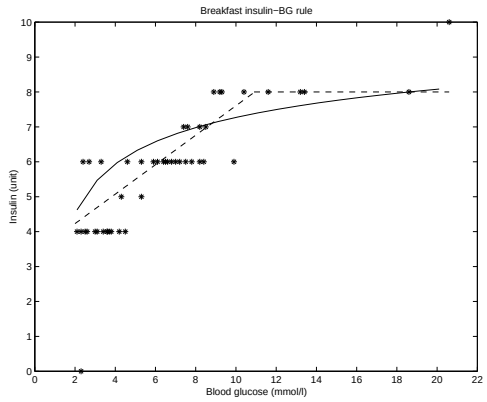

Figure 8: Decision rules based on insulin-BG distribution. * = insulin-BG data, dashed line = piece-wise linear $f(BG)$, solid line = logarithmic $f(BG)$, $(\theta_1, \theta_2) = (0.9\ \mu_{ins}, 0.4)$.

Consider the function $g(F, E)$ to be parameterised by $g(F, E) = \theta_3 . g'(F, E)$, $0 < \theta_3 < 0.5$, and g' is determined by food and exercise as described in [10]. The initial value of θ_3 is taken to be a default value of 0.1, which is a figure recommended by physicians.

The insulin rule described above is derived from current data, therefore it essentially parameterises the current rule used by the diabetic person. This may or may not be the optimal rule for this person. This initial rule will be optimised along a cost function $J(\boldsymbol{\theta})$ with minimal cost in the desired range and rising outside of the range [2], by computing $\boldsymbol{\theta_{k+1}} = \boldsymbol{\theta_k}$ - $\gamma . \frac{\delta J}{\delta \theta} . J$, where $\boldsymbol{\theta}$ is a vector of parameters $(\theta_1, \theta_2, \theta_3)$. The aim is to optimise the long term outcome, therefore γ must be chosen to be sufficiently small [11].

The stochastic gradient algorithm [11] is used, which estimates $\frac{\delta J}{\delta \theta} = \frac{J(\theta + \Delta\theta . e_i) - J(\theta - \Delta\theta . e_i)}{2\Delta\theta}$, and $\Delta\theta$ is independently generated at random. Since the cost function has only one minimum region, $\boldsymbol{\theta}$ should move towards optimality, provided γ is small.

3.3 Probabilistic modelling

Results of the analyses described in section 2 suggest that the diabetic system is a stochastic system with short memory. There is low correlation between BG_k and BG_{k+1}, and little information about its transition, therefore it is impossible to construct a deterministic model of BG using only the available data.

Considering the fact that the mapping of both BG_k to BG_{k+1} and BG_k to ins are probabilistic in nature, we propose a probabilistic model to represent the system. From further analysis of the data, we have strong reasons to believe that this system can be modelled as a Markov Decision Process (MDP) [12], which is homogeneous to a reasonable degree.

The features of an MDP are as follows: it only requires current state to determine the next state, each link in the chain is composed of a probability distribution of states, and it bears an ability to optimise a long term reward. These features suggest that an MDP model is suitable to the BG system, which is a stochastic system with short memory, and whose control objective is optimising long term outcome.

To construct an MDP for the BG control system, we firstly need to define the elements of the chain and a set of actions. For simplicity, we start with the minimum number of states required, which is low, normal and high BG levels, denoted by $\{BG^l, BG^n, BG^h\}$, with the normal range arbitrarily defined as BG levels between 4–10 mmol/l. The transition matrix A is a 3×3 matrix of probability distributions; functions of insulin, food and exercise. We start with a simplified version of this function, limiting it to a function $h(ins)$ of insulin only. In summary, our chain is denoted by $BG_{k+1} = \mathrm{A}.BG_k$, where $\mathrm{A} = [h(ins)]$.

The desirable state is BG^n. Thus we define the action set to be a set of decisions on insulin dose, with the aim of maximising the probability of transitions to state BG^n. Large, erratic BG fluctuations are very undesirable, therefore we want to avoid transitions $BG^l \rightarrow BG^h$ and $BG^h \rightarrow BG^l$. The cost function reflects this by assigning maximum cost to transitions $BG^l \rightarrow BG^h$ and $BG^h \rightarrow BG^l$, and minimum cost to any transitions to BG^n.

4 Discussion

The blood glucose regulation system is indeed complex, with some inputs and associated physiological processes which are not very well defined or easily measured, and various individual specific parameters. On top of the complex nature of the system, the fact that available data is sparse, consisting of little information, with no dynamical information at all, makes blood glucose control a very challenging task. The saving grace is the fact that the control objective is relatively flexible, and the system itself is robust, making it possible for a controller to be designed for the system. Considering the nature of the system and the practical constraints, the use of non-conventional control techniques is warranted.

With this scenario, it is crucial to understand the nature of the problem and clearly define the information at hand (parameters, constraints and limitations that

these impose) before tackling the problem, in order to establish an angle from which it should be approached. It is observed that one known and considerably successful BG control system is the clinical management strategy. This clinical practice has been studied to gain insight into the characteristics of the control rule, and how the control objective is defined and achieved. The observation further indicates that the ultimate control objective is often not achieved, and that the realistic optimal outcome is not well defined or understood. The issue of how the constraints limit system performance and what this realistic optimal outcome is pose questions that are worth addressing. This knowledge will not only give an understanding of the limitations of this control strategy, but would also provide better means to set a concrete control goal and performance criteria.

In our observation of clinical diabetic management, we have noted that the decision rules employed are static rule, and have raised a question whether information on current state only is sufficient to make a decision. Through correlation analysis and unsuccessful attempts to construct a time series model $BG_{k+1} = \sum_{i=0}^{M} \alpha_i.BG_{k-i} + \sum_{j=0}^{N} \beta_j.ins_{k-j}$, it is revealed that the system has short memory, possibly because the dynamics are expected to have settled at sampling time. Hence static rules are appropriate to implement in this situation. The general rule takes the form of $ins = f(BG)(1 + g(F, E))$.

The short memory nature of this BG system also suggests its suitability for Markov decision process modelling. One desirable feature of the MDP is its ability to optimise performance over a period of time, which is consistent with clinical control objectives.

5 Concluding remarks

At present, data analysis indicates that static control rules are the only scientific option for management of type 1 diabetes mellitus. With stochastic sampling of a time variant system, there is not sufficient information on the dynamics. This simplifies the design of control rules and adaptation technique, but it limits the outcome that can be achieved. These limits remain a subject of continuing study.

Further analysis indicates a promise in the use of Markov Decision Process framework. This is currently being explored.

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