Design of MDIs for Type 1 Diabetes Treatment via Rolling Horizon Cardinality-Constrained Optimisation

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Abstract: Recent results on cardinality constrained optimisation are used to obtain an optimised Multiple Daily Injection (MDI) insulin regimen for Type 1 Diabetes patients. The optimisation is implemented in a rolling horizon fashion to account for unannounced events. A blood glucose model is described and an algorithm developed to illustrate the aforementioned strategy. The impact of varying the number of allowable injections in a given day is also studied. Real patient data is used to obtain the models and simulation results are included.

Keywords: optimisation; diabetes; blood glucose regulation

1. INTRODUCTION

Type 1 Diabetes (T1D) is a major health issue worldwide. It is estimated it affects over 40 million people. Its incidence is increasing at a rate of approximately 3% per annum (International Diabetes Federation, 2015). T1D is caused by the destruction of β-cells within the pancreas rendering it unable to produce insulin. Insulin has various functions one of which is to regulate blood glucose level (BGL). For diabetes patients, external addition of insulin is required to replace the insulin that would otherwise be produced by a functioning pancreas. It is vital that the blood glucose concentration remains regulated in a tight range since excessively high concentrations (hyperglycaemia) or excessively low concentrations (hypoglycaemia) lead to long-term and short-term health complications (Aronoff et al., 2004).

A commonly accepted treatment approach is to use basal-bolus therapy (Farkas-Hirsch, 1995; Kaufman, 2012). This approach divides the insulin requirements into two components: (i) Basal insulin provides the constant background supply needed by insulin dependent cells. It balances the endogenous production and consumption of glucose to maintain normoglycaemia during fasting. (ii) Bolus insulin balances exogenous glucose inputs (or disturbances), such as food ingestion. If food is consumed without extra insulin being supplied then BGL will rise and remain high for an extended period of time. The treatment for this kind of disturbance is typically provided by a bolus (dose) of insulin delivered subcutaneously just prior to, or with, meal consumption.

Current clinical practice determines initial basal and bolus doses based on formulae provided by clinicians. Many alternative formulae have been developed, along with proprietary schemes proposed by individual endocrinologists (King and Armstrong, 2007; Davidson et al., 2008; Walsh et al., 2011). For the most part these formulae are based on body weight. Once these initial parameters have been determined they are revised by incremental adjustments until a desirable level of control is obtained. Thus management of T1D involves the calculation, and adjustment, of appropriate basal and bolus insulin over a significant period of time.

Although this treatment approach is widely adopted it does have several well known shortcomings. The impact of exercise is not easily incorporated into a patient's treatment strategy due to insufficient research in this area and the very individual nature of how exercise impacts BGL. This is a major source of difficulty for many patients. Also, there is the uncertainty and variability of life which patients try to minimise although not always successfully. Unexpected events and situations mean that patients must make an educated guess at how best to compensate. These ad-hoc corrections add to the burden of diabetes management and contribute to complications and poor health outcomes.

Around 80% of type 1 diabetics rely upon multiple daily insulin injections (MDIs) and self-monitoring blood glucose (SMBG) measurements to administer basal-bolus therapy (Pickup, 2011). This treatment is invasive and disruptive to the patient since they need to receive multiple injections per day, with SMBG measurements being obtained through periodic finger prick testing. Although invasive, this is still one of the most cost effective treatment options.

In recent years there has been a large effort aimed at developing a, so called, Artificial Pancreas (AP) (Bequette, 2005; Lee et al., 2009; Klonoff et al., 2009; Harvey et al., 2010; Cefalu and Tamborlane, 2014; Kovatchev et al., 2016). An AP is intended to be a fully operational au-

tonomous closed loop system for regulating blood glucose by interconnecting a continuous glucose monitor (CGM) and an insulin infusion system (IIS). Such systems could potentially reduce the inconveniences associated with MDI treatment. However, the high cost of such devices, and the limited access to them, reduces the availability of such an approach. Indeed, only about 20% of diabetics use an IIS (Pickup, 2011) (which is needed for an AP).

Therefore, there are compelling reasons to study optimal injection algorithms for MDI patients, even more so since the algorithms developed for pumps (including recent closed loop algorithms) are not translatable to MDI therapy since the algorithms developed for pumps rely upon continuous delivery of insulin.

The current paper uses optimisation tools to obtain a treatment regimen for MDI patients. To account for unexpected disturbances, the optimisation is implemented in a rolling horizon fashion (Goodwin et al., 2006).

The problem of choosing the optimal delivery times and dose for MDIs can be considered as a specific instance of cardinality-constrained optimisation (Markovsky, 2011; Lee and Zou, 2014). In particular, cardinality-constrained optimisation allows one to answer the following question: "Given r allowable injections, when is the optimal time and what is the optimal dose to maintain a suitable blood glucose level (BGL) throughout a day?". A priori, it is not obvious when the injections should be delivered. To illustrate this point, say that only 3 injections are allowed within the period 6:00am to 10:00pm, in any one of 5 minute intervals. Under these conditions there are over one million possible combinations for the insulin delivery times. Moreover, for each of the insulin delivery time patterns, the dosage would need to be determined. This would require massive computational effort if solved by brute force. In the current paper, we will use a recently developed algorithm for cardinality-constrained optimisation which allows one to solve general problem scenarios.

Although initially the optimisation could be performed offline for a 24 hour period, many factors could change during the day, making the initial injection strategy inappropriate. A rolling horizon implementation allows one to update the optimal delivery times and doses as new information arrives in the form of BGL data and food consumed.

The treatment strategy described above raises the question, "What is the quantitative trade-off between the number of injections and blood glucose regulation?". This paper studies the impact of varying the number of allowable MDIs in a given day. More specifically, we address the question, "What is the improvement in performance achieved by allowing one extra insulin injection?".

The results will be exemplified by a model obtained from real data from a patient.

The layout for the remainder of the paper is as follows. Section 2 outlines insulin regimens for MDI patients. Section 3 introduces a blood glucose regulation model that accounts for macro-nutrients. Section 4 illustrates the use of cardinality-constrained optimisation when considering a fixed horizon. Section 5 presents algorithms for implementing cardinality-constrained optimisation with a rolling horizon. Results from simulations with a real patient model are included in Section 6. Conclusions are drawn in Section 7.

2. INSULIN REGIMEN FOR MDI PATIENTS

Currently there are two main types of insulin that are available for use: short acting and long acting. Short acting insulin has a quick release and relatively short duration once injected into the body. Long acting insulin has a slow release and long duration once injected into the body. Most treatment regimes use a combination of both types of insulin. Long acting insulin is used to provide the "basal rate" and short acting is used for the "bolus".

The insulin regimen is tailored to the individual. However each regimen is typified by multiple insulin injections and blood glucose monitoring. Type 1 diabetics aim to maintain a constant basal rate, and bolus whenever a meal/food is consumed. The goal of treatment is to regulate a patient's BGL within a range of $4-8$ $[mmol/l]$ $(70-140$ $[mg/dl])$ (Kenny, 2014).

The unit of measurement for doses of insulin is the Unit (U), where 1 $[U]$ is equivalent to 0.01 $[ml]$. An Exchange (EX) measures the amount of carbohydrate content within food, where 1 $[EX]$ is equivalent 15 $[g]$. Note that this does not account for the glycaemic index (GI) content of the food.

Throughout the remainder on the paper the term long acting insulin and basal will be used interchangeably. Similarly, the term short acting insulin and bolus, will be used interchangeably. In the sequel, when referring to MDIs, these only include the bolus component of injections and not the basal injections.

3. LINEAR BLOOD GLUCOSE MODEL WITH MACRO-NUTRIENTS

There are many blood glucose models available in the literature, ranging from simple linear impulse response models to non-linear state-space models. For simplicity a linear blood glucose model will be used in the sequel. The results can, in principle, be extended, mutatis mutandis, to any model.

The novelty is that the model differentiates the responses to different types of food depending on the GI, i.e. high, moderate, or low. We show that GI content has a significant impact on the BGL response. The model used takes the form:

$$\begin{aligned} y = {} & G_{ba}(s)u_{ba} + G_{bo}(s)u_{bo} + G_h(s)d_h \\ & + G_m(s)d_m + G_l(s)d_l + C \end{aligned} \tag{1}$$

where u_{ba}, u_{bo}, d_h, d_m, and d_l denote the basal insulin flow rate, bolus insulin flow rate, high GI carbohydrate consumption rate, moderate GI carbohydrate consumption rate, and low GI carbohydrate consumption rate. The above inputs and disturbances are respectively linked to the BGL response by the linear transfer functions G_{ba}, G_{bo}, G_h, G_m, and G_l. C is a constant which captures the steady-state balance between endogenous glucose production and its consumption. The output y is the resultant BGL.

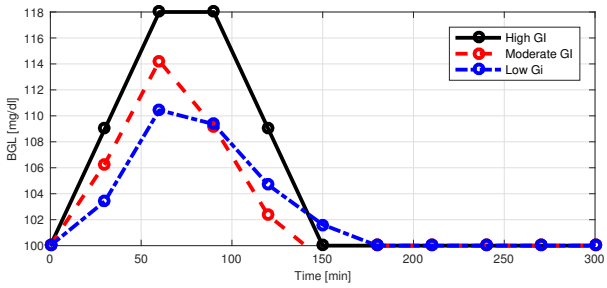

Fig. 1. Patient data. BGL response to 1 $[EX]$ of High, Moderate and Low GI carbs ingested on a short time interval

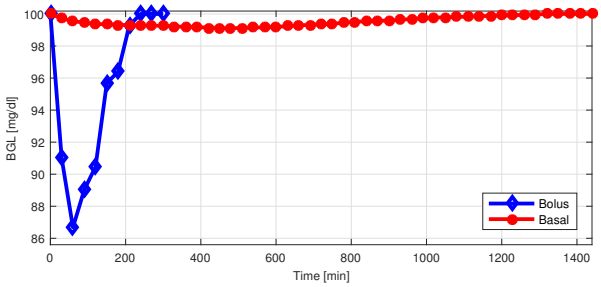

Fig. 2. Patient data. BGL response to 1 $[U]$ of Bolus and Basal Insulin injected on a short time interval

The parameters for this model were obtained by collecting data from a patient (see Fig. 1 and 2) and using standard system identification tools. Figure 1 shows the blood glucose concentration response to 1 $[EX]$ of high, moderate and low GI carbohydrates applied as a discrete impulse at $t = 0$ with no insulin injection. Figure 2 shows the blood glucose response to 1 $[U]$ of bolus and basal insulin applied as discrete impulses.

Note that there is approximately a 2 : 1 difference between responses to a high GI and low GI meal.

The resulting transfer functions obtained from the impulse responses shown in Fig. 1 and 2 are:

$$G_{ba} = \frac{-5.76 \cdot 10^{-4}}{s^2 + 0.0084s + 1.764 \cdot 10^{-5}} \tag{2}$$

$$G_{bo} = \frac{-3.6 \cdot 10^{-2}}{s^2 + 0.0336s + 0.0002822} \tag{3}$$

$$G_h = \frac{4.277 \cdot 10^{-5}}{s^5 + 0.27s^4 + 0.029s^3 + 0.0016s^2 + 4.25 \cdot 10^{-5}s + 4.59 \cdot 10^{-7}} \tag{4}$$

$$G_m = \frac{4.752 \cdot 10^{-3}}{s^3 + 0.12s^2 + 0.004752s + 6.221 \cdot 10^{-5}} \tag{5}$$

$$G_l = \frac{3.24 \cdot 10^{-3}}{s^3 + 0.12s^2 + 0.0045s + 5.4 \cdot 10^{-5}} \tag{6}$$

$$C = 108 \ [mg/dl] \tag{7}$$

Although the identified system is continuous, it is necessary to work in discrete time due to the optimisation algorithm, as shown in Section 4. Therefore we introduce the discretised version of the model as follows:

$$\begin{aligned} y_k = \bar{G}_{ba}(z)u_{bak} + \bar{G}_{bok}(z)u_{bok} + \bar{G}_h(z)d_{hk} \\ + \bar{G}_m(z)d_{mk} + \bar{G}_l(z)d_{lk} + C \end{aligned} \tag{8}$$

where u_{bak}, u_{bok}, d_{hk}, d_{mk}, and d_{lk} denote the basal insulin, bolus insulin, high GI carbohydrates, moderate GI carbohydrates, and low GI carbohydrates consumed within the given time interval $(k-1)\Delta \leq t < k\Delta$, where $k \in \mathbb{N}_{>0}$ and Δ is the sample period. $\bar{G}_{ba}$, $\bar{G}_{bo}$, $\bar{G}_h$, $\bar{G}_m$, and $\bar{G}_l$ are discrete transfer functions linked to the aforementioned inputs and disturbances. y_k is the resultant BGL at time sample k.

4. CARDINALITY CONSTRAINED OPTIMISATION

Cardinality Constrained Optimisation is a class of optimisation problems where the cardinality of the free variable is constrained. This class of optimisation problems is generally non-convex. Computing the optimal solution is NP-hard. This is because the number of combinations to be tested rises exponentially with the size of the problem.

In the case of MDI therapy, the number of injections is limited. Therefore, using the model (8), the problem of selecting the delivery times, and the associated doses, can be formulated as follows:

$$\begin{aligned} \mathcal{P}: \quad & u_i = \underset{u}{\operatorname{argmin}} \sum_{i=1}^{k} (y_i - y^*)^2 \\ & u = u_0, \ldots, u_{N-1} \\ & u_i \in [0, u_{max}] \\ & y_i \geq y_{min} \\ & \text{card}\ (u_i) \leq r \end{aligned}$$

where y_{min} is a lower bound and y^* is the reference value.

This problem is a quadratic program that includes a cardinality constraint. There are several existing tools to solve this problem. For example, by using Mixed Integer Quadratic Programming or cardinality-constraint optimisation. In this paper we adopt the latter approach. In particular we follow the approach described in Dattorro (2005); Delgado et al. (2016) that reformulates a problem with a cardinality constraint as an optimisation problem subject to bilinear constraints. The approach in Delgado et al. (2016) is based on the fact that for $x \in \mathbb{R}^n$, then $\text{card}(x) \leq r$ is equivalent to $\exists w \in \{w \in \mathbb{R}^n | 0 \leq w_i \leq 1, \sum_{i=1}^{n} w_i = n - r\}$, such that $x_i w_i = 0$ for $i = 1, \ldots, n$.

The main advantage of this approach is that the resulting problem can be solved with standard tools in non-linear programming. Based on this idea, the solution of problem $\mathcal{P}$ is equivalent to the solution of the following optimisation problem:

$$\begin{aligned} \mathcal{P}_{equiv}: \quad & \min_{u,w} \sum_{i=1}^{k} (y_i - y^*)^2 \\ & u_i \in [0, u_{max}] \\ & y_i \geq y_{min} \\ & \sum_{i=1}^{k} w_i = k - r \\ & 0 \leq w_i \leq 1 \qquad \text{for } i = 1, \ldots, k \\ & u_i w_i = 0 \qquad \text{for } i = 1, \ldots, k \end{aligned}$$

This problem can be solved using known techniques in non-linear programming (Bertsekas, 1999).

In summary, given a food profile $\{d_{hk}, d_{mk}, d_{lk}\}_{k=0}^{N-1}$, a basal insulin profile $\{u_{bak}\}_{k=0}^{N-1}$, and restricting the number of allowable MDIs over a specific time period to r, the

optimal delivery times and dose for the bolus insulin are obtained by solving $\mathcal{P}_{equiv}$.

5. ROLLING HORIZON IMPLEMENTATION

5.1 Event Triggered Rolling Horizon

Implementing an optimisation-based control algorithm in a rolling horizon fashion allows the system to account for any update of relevant information. In the case of MDI therapy, the main source of state information are SMBG measurements. However, rolling horizon optimisation also allows the system to respond to unexpected changes in the daily routine, such as missing a meal, missing an injection or performing unanticipated exercise.

A key point is that a re-calculation of the optimal insulin delivery times is carried out only when triggered by an external event. In addition, a special strategy is needed to ensure the cardinality-constraint does not become redundant.

External events provide an update of information to the system at infrequent times. The new information, which may include actual BGL, food, and insulin data, is used to obtain a new state estimate of the system. Such an implementation is non-standard since the information update does not occur at regular times. This can be overcome with a non-equal sampling Kalman filter.

Another matter of importance is the window of the horizon. The only control action in this system is insulin, which acts to lower blood glucose. Insulin cannot be removed nor can a control action be used to increase the blood glucose. The use of glucagon has been considered as a control action to raise BGL, however it is not currently used in practice due to complications with its storage at room temperature. For this reason it is vital that the rolling horizon window looks far enough into the future to ensure any delivered insulin does not cause a hypoglycaemic event at a later time. Here a 24 hour window is used.

5.2 Enforcing Cardinality-Constraint

Care must be taken to ensure that the cardinality-constraint is enforced, i.e. taking into account injections that have already been delivered. Thus, the following additional constraints are added to $\mathcal{P}_{equiv}$:

$$u_d \leq r \qquad \text{for } t = [k_o, k_i] \tag{9}$$

$$u_a = r - u_d \qquad \text{for } t = [k_{i+1}, k_N] \tag{10}$$

$$u_p = r \qquad \text{for } t = [k_{N+1}, k_{N+i}] \tag{11}$$

where k_i is the current sample, N is the number of samples within a day, u_d is the number of MDIs delivered so far within the current day, u_a is the number of MDIs remaining within the current day, and u_p is the number of MDIs allowed for the next day.

6. SIMULATIONS

In this section we illustrate how the Cardinality Constrained Optimisation algorithm described above can be applied to MDI therapy. We study the incremental performance gain due to allowing an extra insulin injection. We then illustrate the impact of rolling horizon implementation with several daily scenarios.

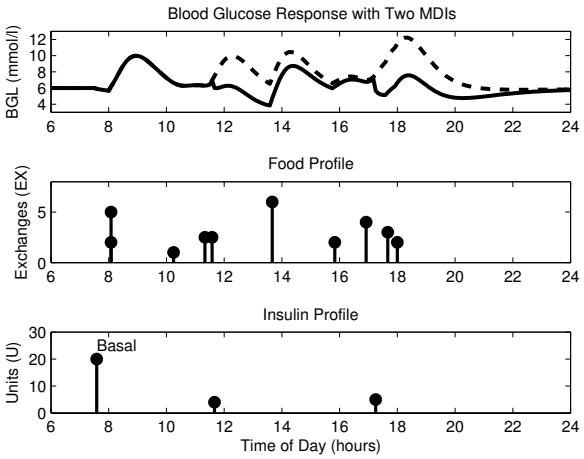

Fig. 3. Blood Glucose Response and Optimisation Results for Two MDIs $r = 2$ (solid). No injections (dashed)

6.1 Fixed Horizon

Using the algorithm described in Section 4 and the model described in Section 3, we obtain the resulting insulin injection schedule for a specific daily food profile, i.e. a combination of low, moderate and high GI food throughout the day. Figure 3 shows the result for $r = 2$ (2 MDIs) The solid line in subplot 1 represents the blood glucose response of the model when the given MDIs are allowed and the dashed line represents the blood glucose response of the model without any injections ($r = 0$). The latter is included for comparison purposes. The food profile is shown in subplot 2. The resulting insulin injection schedule is shown in subplot 3.

6.2 Incremental Performance Gain

The next question studied is what is the quantitative gain achieved by increasing the number of MDIs? To study this question, offline optimisations were performed for $r = 0, \ldots, 10$. The performance of each optimisation was determined by calculating the blood glucose response deviation from the ideal (but unattainable) result of a constant blood glucose response ($y = 6.0$) throughout the whole day. These were then normalised against the blood glucose response for no MDIs. Hence an error of 1 corresponds to the worst blood glucose response (when disturbances are not dealt with) and an error of 0 corresponds to the best blood glucose response (when disturbances are completely mitigated). The results are shown in Fig. 4.

Figure 4 shows that each additional allowable MDI improves the blood glucose response. With 4 MDIs a 90% improvement has been achieved with respect to blood glucose regulation. Interestingly, no significant benefit is obtained by increasing the MDIs beyond 4 (for this particular food and basal insulin profile). Of course this result could change if different food and basal insulin profiles were adopted. However, it raises the question whether there is an acceptable performance trade-off between the number of insulin injections and continuous insulin supply.

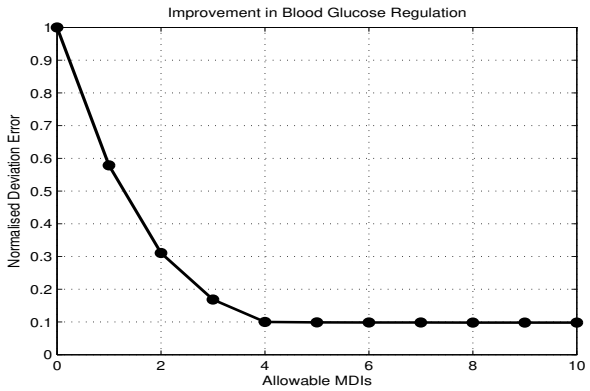

Fig. 4. Effect of Increasing MDIs on the BGL

6.3 Rolling Horizon

In this section we illustrate the benefits of a rolling horizon implementation. Consider a typical day for a patient having breakfast at 08:00 (90g CHO), lunch at 13:00 (75g CHO), an afternoon snack at 16:00 (15g CHO) and dinner at 19:00 (75g CHO). All moderate GI meals. We will consider three scenarios. In Figures 5, 6 and 7 the top, mid and bottom panels show the food profile, the insulin profile and the simulated BGL trace.

Scenario 1 The patient has a normal lunch at 13:00 but forgets to inject the corresponding insulin bolus. At 14:00 the algorithm is updated. The results are shown in Figure 5.

The mid panel in Figure 5 shows the original injection schedule with a dashed line. The bottom panel shows the BGL trace for the updated injection schedule (solid line) and the BGL trace if the original injection schedule had been used as planned.

It can be seen that, given the update at 14:00, the algorithm recalculates the new optimal time and injection dose, which is to bolus 1.9 units of insulin at 14:00. Most importantly, note that this bolus is not the same size as the originally planned bolus. Had the same bolus been administered, the patient would have had a hypoglycaemic event. Note that the delayed injection of insulin has led to an unavoidable decrease in performance.

Scenario 2 The patient has an unscheduled snack of 120 $[g]$ at 18:30, right before dinner. The algorithm is updated immediately. The results are shown in Figure 6.

The top panel in Figure 6 shows the additional unscheduled meal. The mid panel shows the updated insulin profile, with the original injection schedule shown with a dashed line. The bottom panel shows the BGL traces had the original injection schedule occurred (dashed) despite the new meal, i.e. assuming the algorithm was not updated regarding the unscheduled meal, and the BGL trace corresponding to the updated injection schedule (solid). Note that the rolling horizon optimisation has significantly improved the BGL response. In particular, it can be seen that informing the algorithm immediately about the unscheduled snack shifts the third injection to the current time and increases the dosing by almost double. This

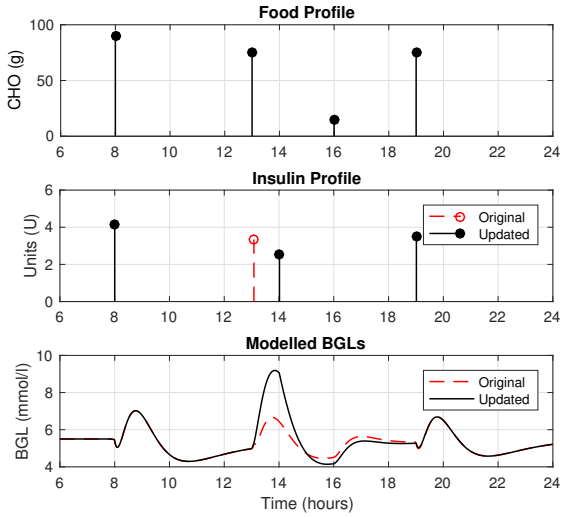

Fig. 5. Traces for Scenario 1

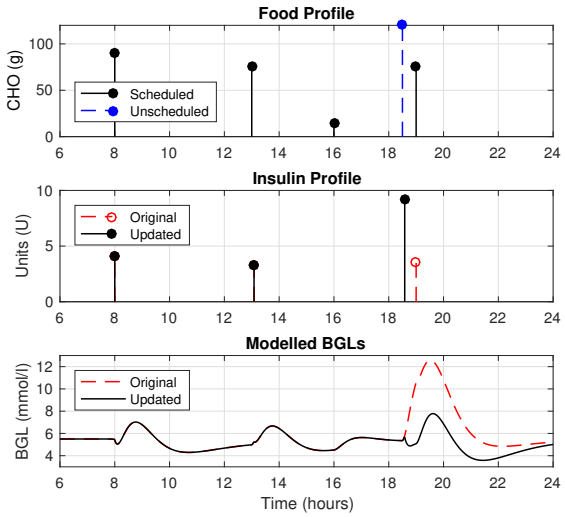

Fig. 6. Traces for Scenario 2

avoids a considerable hyperglycaemic event had the event not been informed.

Scenario 3 The patient has an unscheduled snack of 120 $[g]$ at 18:30, right before dinner. The original dinner and the third insulin injection occur as planned. However, importantly the algorithm is not updated until 19:30 with the new information about the unscheduled snack. The results are shown in Figure 7.

Since the three allowed daily injections have already occurred, the two options for the algorithm are to do nothing or to suggest a fourth injection. The mid panel in Figure 7 shows the timing and dosage of the additional injection, if allowed. The bottom panel shows the BGL traces corresponding to the original three injection schedule (dashed) and the four injection schedule (solid).

It can be seen that, although the unscheduled snack is much bigger in comparison to the other meals, the extra injection is smaller than the other ones. The algorithm

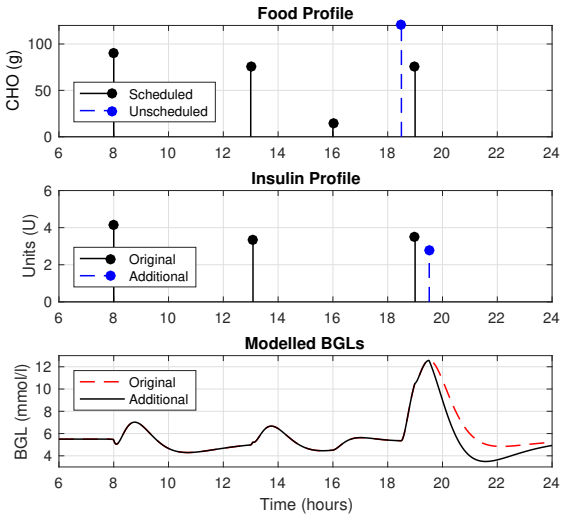

Fig. 7. Traces for Scenario 3

takes into account the difference in time and the fact that the meal was compensated when the algorithm was updated. Had a normal dose for that snack been injected at 19:30 the patient would have had a severe hypoglycaemic event. Indeed, this exact scenario was taken from a real life experience. The patient, a 9 year old child in this case, did not immediately inform his parents of two chocolate bars he ate. When he told his parents several hours later the parents injected the same dose they would have used had the snacks been ingested at that time. He ended up having an hypoglycaemic event and taken to the hospital.

These scenarios provide typical complex scenarios that a patient may have to address in the course of their daily activity. Current treatment strategies do not provide an objective patient response to these scenarios as there are no stipulated rules for the actions required in such situations. We believe that they would provide a significant challenge to even the most attentive patient or health care professional.

7. CONCLUSION

In this paper we have shown how Cardinality Constrained Optimisation can be applied to the problem of Multiple Daily insulin Injections in Type 1 Diabetes therapy. We have also introduced a rolling horizon scheme that allows for updates as the patient's day evolves. Simulations have shown the advantages of the algorithm as well as the versatility to deal with unexpected situations. We have shown that the proposed algorithm is capable of diminishing the complexity of decision making by providing systematic, quantitative advice. Moreover, the receding horizon implementation addresses changing daily situations.

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