Automatic Adjustment of Basal Insulin Infusion Rates in Type 1 Diabetes using Run-to-Run Control and Case-Based Reasoning

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Abstract. People with type 1 diabetes mellitus rely on a basal-bolus insulin regimen to roughly emulate how a non-diabetic person’s body delivers insulin. Adjusting such regime is a challenging process usually conducted by an expert clinical. Despite several guidelines exist for such purpose, they are usually impractical and fall short in achieving optimal glycemic outcomes. Therefore, there is a need for more automated and efficient strategies to adjust such regime. This paper presents, and in silico validates, a novel technique to automatically adapt the basal insulin profile of a person with type 1 diabetes. The presented technique, which is based on Run-to-Run control and Case-Based Reasoning, overcomes some of the limitations of previously proposed approaches and has been proved to be robust in front of realistic intra-day variability. Over a period of 5 weeks on 10 virtual adult subjects, a significant reduction on the percentage of time in hyperglycemia (<70mg/dl) (from 14.3±5.6 to 1.6±1.7, p< 0.01), without a significant increase on the percentage of time in hypoglycemia (>180mg/dl) (from 10.2±5.9 to 1.6±1.7, p=0.1), was achieved.

Keywords: Diabetes management, insulin therapy, artificial intelligence, case-based reasoning, run-to-run control.

1 Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune condition characterized by elevated blood glucose levels due to the lack of endogenous insulin production [1]. People with T1DM require exogenous insulin delivery to regulate glucose. Current therapies for T1DM management include the administration of multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) with pumps.

A basal-bolus insulin regimen involves taking a longer acting form of insulin to keep blood glucose levels stable through periods of fasting and separate injections of shorter acting insulin to prevent rises in blood glucose levels resulting from meals. Such regimen attempts to roughly emulate how a non-diabetic person’s body delivers insulin. People with T1DM using insulin pumps are able to pre-program different infusion rates
along the day, hence they are able to achieve a finer control [2]. Fig. 1 shows an example of the plasma insulin profile of a typical MDI basal-bolus regimen.

![Plasma insulin profile of a typical basal-bolus regimen. Dashed lines correspond to meal bolus and solid line to the basal insulin injection.](image)

Fig. 1. Plasma insulin profile of a typical basal-bolus regimen. Dashed lines correspond to meal bolus and solid line to the basal insulin injection.

Several medical guidelines exist for adjusting insulin doses basal-bolus regime [3][4], which usually require a cumbersome process of trial and error conducted by an expert clinical. In addition, this regimen is not static and changes over the time due circadian variation in hormone levels (e.g. dawn phenomenon), physical exercise, psychological stress, recurrent illness, or long-term changes in insulin sensitivity due to lifestyle (e.g. obesity) [1]. Therefore, there is a need for more automated and efficient strategies to adjust such regime.

2 Related Work

In order to automatically adjust the basal insulin regimen of a pump, Palerm et al. proposed a Run-to-Run control algorithm that requires six capillary blood glucose measurements along the day at specific times [5]. However, this approach might be impractical in a real-life scenario due to the numerous capillary measurements required.

In the context of an artificial pancreas (i.e. hybrid closed-loop control), a Run-to-Run approach which adapts the basal insulin delivery during the night and the carbohydrate-to-insulin ratio during the day, based on some performance indices calculated from subcutaneous continuous glucose sensor data has been proposed by Toffanin et al. [6].

It is important to note that, apart from considering intra-day changes in insulin sensitivity due to circadian variations of hormonal levels, none of these approaches take into consideration the variability on insulin requirements due to other factors such as physical exercise, alcohol, stress or menstrual cycle.
3 Methods

In this paper, we present a novel technique to automatically adjust the basal insulin profile of a person with type 1 diabetes. For this purpose, a Run-to-Run algorithm [7] incorporating a new control law, which avoids some of the limitations of previously proposed techniques, is introduced (e.g. number of capillary measurements). Then, Case-Based Reasoning [8] is employed to account for intra-subject insulin sensitivity variability. This is done by storing in a subject-specific case-base representing scenarios with significantly different insulin requirements (e.g. dinner after exercise vs. dinner after watching a movie) and therefore, requiring a different basal insulin dosing. Then, a Run-to-Run algorithm is applied to each one of the cases in the case-base in order to adapt the solutions (i.e. basal rate) if considered to be suboptimal.

3.1 Case-Based Reasoning

Case-Based Reasoning (CBR) is an artificial intelligence problem solving framework that solves a newly encountered problem, based on the information obtained from previously solved problems and stored as cases in a case-base [8]. A case is defined by

\[
\text{Case}_i = \{\text{Problem}_i, \text{Solution}_i, \text{Outcome}_i\}, \tag{2}
\]

where \(\text{Problem}_i\) is the description of the problem to be solved (e.g. controlling basal glucose); \(\text{Solution}_i\) is the solution to \(\text{Problem}_i\) (e.g. basal insulin rate); and \(\text{Outcome}_i\) is the outcome resulting of applying \(\text{Solution}_i\) to \(\text{Problem}_i\) (e.g. glucose outcome).

CBR is usually described in four steps: Retrieve the most similar cases to the problem to be solved from the case-base; Reuse the solutions of retrieved cases; Revise the outcome of the applied solution to the new problem; and Retain the new problem if its solution is considered useful for solving future problems. Figure 4 show the four steps of the CBR cycle (Retrieve, Reuse, Revise, Retain) applied to the problem of basal insulin dosing.

![Figure 4. CBR cycle (Retrieve, Reuse, Revise, Retain) applied to the problem of basal insulin dosing](Image)
In this work, cases are stored in a subject-specific case-base representing scenarios with significantly different insulin requirements (e.g. dinner after exercise vs. dinner after watching a movie) and therefore, requiring different basal insulin rates.

Cases are retrieved from the case-base by computing the Euclidian distance between the current problem and all the cases in the case-base and by selecting the case with the shorter distance.

If the closest retrieved case is still very distant from the current scenario, its solution can be reused (Reuse step) by applying a set of simple rules to guarantee that the applied solution is safe (e.g. reduce basal rate by 30%) and a new case is created for the new scenario. If the retrieved case is equal to the current scenario, then no new case is created.

In order to perform the Revision step, the R2R algorithm presented below is employed, which adapt the solution (i.e. basal rate) of the retrieved, or newly created, case when the glucose outcome is considered sub-optimal based on the analysis of the postprandial CGM measurements.

### 3.2 Run-To-Run control

Run-To-Run (R2R) is a control methodology designed to exploit repetitiveness in the process that is being controlled [7]. Insulin dosing, and in particular basal insulin delivery, has a repetitive nature. Therefore, R2R control can be used to exploit such characteristic.

The proposed R2R algorithm is based on the hypothesis that the time of the day-time when a person is closest to the fasting condition is right before the meals. Therefore, the pre-meal glucose measurement is used to adjust the basal insulin rate of the previous post-prandial period. Regarding the night-time period, this is split in two parts, from dinner time to 6 hours after dinner and from that time to breakfast time. Note that, unlike the six glucose measurements required by the R2R algorithm by Palerm et al. [5], the proposed algorithm only requires four.

The control law used to adjust the basal rates is defined by

\[
\text{Basal}_{i}^{k+1} = \text{Basal}_{i}^{k} + K \cdot (G_{i} - G_{T}),
\]

where sub-index \(i\) indicates the time interval, the super-index \(k\) indicates the iteration, \(K\) is a tuning gain, \(G_{i}\) is the pre-meal glucose value for corresponding interval, and \(G_{T}\) is the glucose target.

It is important to remark that previously proposed R2R algorithms for basal insulin adjustment [5][7] are able deal with intra-day variability due circadian variation, but are not able to deal with inter-day variability due to other factors such as exercise, alcohol, stress, and menstrual cycle. For this purpose, the utilization of Case-Based Reasoning [8] has been proposed in this work.
4 Experimentation and Results

4.1 In Silico Evaluation under Intra-Day Variability

The latest version of the UVa-Padova T1DM simulator (v3.2) [9] was used to evaluate the proposed to automatically adapt basal insulin. 10 adult subjects were used for this purpose. Basal insulin infusion rates were initialised the one provided by the simulator. Meal boluses were computed using a standard bolus calculator [Schmidt 2014] using the default parameters provided by the simulator.

A six-week scenario was selected in order to leave enough time to the basal adaptation mechanism to converge. The selected daily pattern of carbohydrate dose intake was 7am (60g), 1pm (100g) and 7pm (80g).

Intra-day variability and uncertainty were introduced in the simulator as described by Herrero and colleagues [10]. Note that despite all the variability introduced in the simulator, only four different cases were required within the CBR algorithm (i.e. post-breakfast, post-lunch and post-dinner, and night time).

The following glycemic metrics, which are widely accepted by the artificial pancreas community to evaluate glucose controllers, were selected for comparison purposes: mean blood glucose (BG in mg/dl); percentage time in glucose target range [70,180] mg/dl (% in T); percentage time below target (i.e. hypoglycemia) (% < T); percentage time above target (i.e. hyperglycemia) (% > T);

4.2 Glycemic Outcomes

Table 1 shows the results corresponding to the 10 virtual adults after one week of no adaptation and at week 6 after 5 weeks of basal adaptation. Fig. 2 shows a weekly evolution of three of the evaluated glycemic metrics

<table>
<thead>
<tr>
<th>Week</th>
<th>% in T</th>
<th>% &lt; T</th>
<th>% &gt; T</th>
<th>BG</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>75.5±6.7</td>
<td>14.3±5.6</td>
<td>10.2±5.9</td>
<td>118.2±8.6</td>
</tr>
<tr>
<td>#6</td>
<td>84.9±7.6</td>
<td>1.6±1.7</td>
<td>13.4±7.2</td>
<td>137.2±9.0</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt; 0.01</td>
<td>&lt; 0.01</td>
<td>0.1</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Table 1. Glycemic outcomes corresponding to the 10 virtual adult subjects.
When analyzing the weekly evolution of the evaluated glycemic metrics, it can be observed that glycemic metrics take about 3 weeks to converge without significant oscillations towards a steady state value and remain fairly stable along the simulation.

In a real-life scenario, the convergence rate might take longer due to the consideration of more cases representing other scenarios such as exercise, alcohol consumption, hormone cycles or stress.

Clinical trials are required to validate the proposed technique in a real environment. Future work includes the evaluation of the presented technique with a meal bolus adaptation technique.

5 Conclusions

In a virtual T1DM population (10 adults) over a 6-week scenario with intra-day variability, the presented basal insulin adaptation technique significantly reduces hypoglycemia without a significant increase in hyperglycemia.

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References