Post-prandial Plasma Glucose Prediction in Type I Diabetes Based on Impulse Response Models

F. Ståhl, R. Johansson and Eric Renard

Abstract—In this paper the impact of different meals and rapid insulin were estimated as Finite Impulse Response Models from a data set of 18 patients. Based on these models short-term individualized predictors were tested for 20 and 60 minute prediction. The predictors were evaluated using Clarke Grid Analysis and had on average more than 94 % and 75 % in the A zone and less than 1 % and 3 % in the erroneous C/D/E zones, which in comparison to other published results is competitive.

I. INTRODUCTION

Type I Diabetes Mellitus is a chronic metabolic disease characterized by impaired plasma glucose regulation normally treated with intense insulin therapy. To determine the quantity and timing of the insulin injections various approaches are used. Currently, mostly qualitative and semi-quantitative models and reasoning are used to design such a therapy. The closed-loop regime is evolving as a powerful alternative using a Continuous Glucose Monitor (CGM) sensor together with an insulin pump [1]. Whichever approach is considered a model of the impact of the main control variables is of utmost importance. To this purpose, this paper addresses the identification of the impact of different meals and rapid insulin on plasma glucose dynamics from patient data. Such models could be used for the design and implementation in a closed-loop context [2], or as a predictive tool per se to facilitate for patients and clinicians to understand the consequences of different actions [3], [4], [5], [6], [7]. In the European DIAadvisor project such a predictive advisory tool is pursued [8].

II. DATA ACQUISITION

The data were collected within the European FP7 project DIAadvisor at the Montpellier University Hospital [8]. The study was conducted in-hospital during a three-day visit. Standard meals were served for breakfast (08:00), lunch (13:00) and dinner (19:00), the amount of carbohydrates included being about 45, 70 and 70 grams, respectively. No specific intervention on the usual diabetes treatment was scheduled being about 45, 70 and 70 grams, respectively. No specific

A. Signals

Data collection consisted of CGMS measurements obtained with the Abbott FreeStyle Navigator™[9], fingerstick measurements with a personal glucose meter (HemoCue™[10], average 38 measurements/day), and carbohydrate intake and insulin administration reported in a personal patient logbook. The HemoCue measurements were interpolated using a shape preserving interpolation method (pchip in Matlab [11]) to retrieve an equidistant sampled signal.

In Fig. 1, an example of a patient data set can be seen.

III. MODELS AND IDENTIFICATION METHOD

Due to the lack of data and the opposing effects of meal and insulin, empirical identification of each module is difficult, often resulting in merged models or that assumptions have to be made on intermediate model levels. Previous attempts at meal and insulin impact modeling and identification often rely on structured models, where compartment models dominate. A nice summary of PK models for insulin diffusion following a subcutaneous injection is found in [12]. Modeling the digestion process and the flux of glucose from the gut from a meal has been initiated in [13]. In this paper no such models are imposed. Instead, black-box Finite Impulse Response (FIR) models were considered for each input.

\[
\Delta y_k = \sum_{i=k-N_1}^{k-1} H_i \cdot u_i + \sum_{j=k-N_2}^{k-1} H_j^2 \cdot u_j^2
\]
where $\Delta y_k$ is the difference in plasma glucose between sample $k$ and $k-1$, $u_k^1$ and $u_k^2$ are the insulin and meal intakes at sample $k$, and $H_k^1$, $H_k^2$ are the impulse response terms for each input.

To guarantee qualitatively correct responses, i.e., negative response to insulin infusion and positive for meals, the identification was constrained giving the following least-squares optimization problem over the time set $[T_1, T_N]$.

\[
\hat{p} = \arg \min_p p^T Q p \qquad (2)
\]
\[
Q = \begin{bmatrix} -\Delta Y & U_1^T \\ -\Delta Y & U_2^T \end{bmatrix}, \quad Ap \leq 0 \qquad (3)
\]

where \( \hat{p} = [1 \ H_1 \ldots H_{N,1} \ H_1^2 \ldots H_{N,2}] \), \( \Delta Y = [y_1 - y_0 \ldots y_N - y_{N-1}]^T \), \( U_1 = [u_1^1 \ldots u_N^1]^T \), \( U_2 = [u_1^2 \ldots u_N^2]^T \) and $A$ is a diagonal matrix of $1$:s and $-1$:s in relevant positions.

A. Insulin and Meal Impulse Estimation

The estimation for each patient was divided into two parts; identification of the insulin response and thereafter the impulse response of each meal. To estimate the insulin response the entire data set was considered. This yields an average insulin and meal impulse response. The average meal response was discarded as a dummy parameter set, whereas the average insulin response was considered as the estimate of the insulin impact.

Thereafter each meal was considered separately. Using the estimated insulin impulse response model, the residuals in glucose change corresponding to the meal impact were used to estimate each meal impulse response. For each type of meal (breakfast, lunch, dinner), the average impulse response was thereafter retrieved.

IV. Evaluation Criteria

To evaluate the predictive performance of the models 20 and 60 minute predictions were considered. The correspondence to the reference HemoCue measurements were assessed using the Clarke Pointwise Error Grid Analysis (pCGA) [14], standard deviation and maximum absolute error.

V. Results

A. Impulse Responses

In Fig. 2 the average impulse responses to the different kinds of inputs can be seen for each patient as well as over the entire population.

B. Prediction

The predictive capacity of the model was evaluated for all patients using a 20 minute and a 60 minute predictor. In Table I the different metrics are summarized. As reference a zero-order hold (ZOH) predictor with the same prediction horizons was given. An example of the 20 and 60 min predictions for each meal using the patient specific average meal input models can be found in Fig. 3.

An example of a Clarke Grid plot is found in Fig. 4.

### Table I

<table>
<thead>
<tr>
<th></th>
<th>pCGA[%]</th>
<th>STD [mg/dl]</th>
<th>max [e] [mg/dl]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model 20</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>94.2</td>
<td>5.0</td>
<td>11.8</td>
</tr>
<tr>
<td>std</td>
<td>8.2</td>
<td>7.1</td>
<td>12.0</td>
</tr>
<tr>
<td><strong>ZOH 20</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>86.2</td>
<td>12.5</td>
<td>19.0</td>
</tr>
<tr>
<td>std</td>
<td>13.4</td>
<td>11.6</td>
<td>19.4</td>
</tr>
<tr>
<td><strong>Model 60</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>75.7</td>
<td>21.7</td>
<td>22.1</td>
</tr>
<tr>
<td>std</td>
<td>23.9</td>
<td>20.8</td>
<td>22.8</td>
</tr>
<tr>
<td><strong>ZOH 60</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>51.3</td>
<td>41.3</td>
<td>41.4</td>
</tr>
<tr>
<td>std</td>
<td>23.8</td>
<td>20.3</td>
<td>43.0</td>
</tr>
</tbody>
</table>

VI. Discussion

A. Impulse Estimates

The insulin impulse responses differ, especially in terms of magnitude, among different patients, and this difference is expected due to patient specific insulin kinetics and dynamics, including insulin sensitivity. Apart from a few outliers, the dynamic response in temporal aspect seems to be more similar though. Looking at the meal impulse responses the breakfast seems to be a somewhat homogeneous meal and could maybe serve as a meal classifier. It is also significantly different from the other meals, and this is probably due to a combination of factors, such as the so called dawn phenomena [15], to the high content of carbohydrates of low complexity typically digested for breakfast, and probably to the fact that many people tend to have the same breakfast routines every day. The lunch and dinner meals seem to be more heterogenous, with a slightly faster response to the lunch meal. It seems that other meal markers than just the attributes lunch and dinner need to be used to classify these meals. As the prediction results indicate, however, some information, at least on a patient-specific basis, could be retrieved from this classification.

B. Prediction

The predictors are generally doing well, clearly outperforming the ZOH predictor, and the 20-minute predictor keeps up with rapid glucose changes in all regions of glucose levels with a CGA-value of 94.2 % in zone A and less than 1 % in the deviating zones. The relatively large standard deviations of both the C/D/E score as well as the maximum absolute error may indicate that the general performance is good but that these average metric values are heavily influenced by a few poorer predictors. Further analysis is thus required to evaluate the overall population performance. In comparison to earlier published results on prediction based on neural networks [7], AR-models [16] and sub-space identification [5] the prediction is competitive. Short-term predictors will be utilized in the DIAdvisor project for advisory purposes [8].
Fig. 2. Thick Solid line: Average over all patients. Upper Left: Average Impulse Response to 1 IU of rapid insulin. Upper Right: Average Impulse Response to 1 gram of Breakfast Carbohydrate. Lower Left: Average Impulse Response to 1 gram of Lunch Carbohydrate. Lower Right: Average Impulse Response to 1 gram of Dinner Carbohydrate.

Fig. 3. Solid line: Interpolated Plasma Glucose Measurements (BG), Magenta dashed: 20 minutes prediction, Green dash-dotted: 60 minute prediction. (Patient 0125).
This paper addressed the estimation of meal and insulin impact on plasma glucose dynamics in type 1 diabetic patients. The results indicate that the outlined methodology could be used to estimate patient-specific FIR models of different meals and insulin response. Implementing these models in a predictor enables reliable short-term predictions of post-prandial glucose excursions following different kinds of meals. Further work on glucose prediction and control will be pursued in the European FP7 IST-216592 DIAdvisor™ project [8].

VIII. ACKNOWLEDGMENT

The authors are grateful for the data provided by the Montpellier University Hospital and for the financial support from the European Union.

REFERENCES