Anticipatory Behavior in Blood Glucose Control: Using Meal Prior Probabilities to Prepare for Future Meal Disturbances

Fraser Cameron*, B. Wayne Bequette*
Bruce A. Buckingham**, Darrell M. Wilson**, Hyunjin Lee*, Günter Niemeyer**

*Rensselaer Polytechnic Institute, Troy, NY 12180 USA (Tel: 650-450-0908; e-mail: fmccamer@gmail.com).
**Stanford University, Stanford, CA 94305 USA
***Willow Garage & Stanford University

Abstract: Automatic regulation of blood glucose in patients with Type 1 Diabetes is challenged by unknown or unannounced food consumption. Yet we know most food is ingested in discrete meals, spaced by brief periods of fasting. Treating meals as discrete events, this paper proposes a set of prior probabilities relating distinct meals independently of daily patterns. Using these prior probabilities, closed-loop blood glucose control can attain anticipatory behavior, implicitly lowering glucose levels when patients should be hungry and meals are most likely to occur. This improves overall performance and individual meal responses. The benefits occur because blood glucose prediction, which anticipates future food intake, can achieve near zero mean errors even over a long prediction horizon. As a side effect, such predictors can easily be tuned or tested against unrestricted out-patient data which, by definition, contains unknown meals. We validate our approach in both prediction and control of blood glucose levels. We see improved prediction accuracy over 1-4 hour horizons and a significant reduction in the blood glucose risk index for simulated closed-loop control.

Keywords: Probabilistic models, Adaptive control, Feedforward, Biomedical systems, Biomedical control

1. INTRODUCTION

Patients with Type 1 Diabetes Mellitus must explicitly regulate their blood glucose (BG) levels to remain healthy. When done manually, this effort can be separated into two components: a continuous insulin infusion (basal) to maintain an appropriate steady-state glucose level and discrete infusions (bolus) to counteract the effects of meals. Since meals act roughly as fast as infused insulin, early action is crucial to preventing large blood glucose excursions. In fact (Cobry et al. 2010) conclude that boluses should be given 20 minutes before the meal.

In reality, manual BG control is tedious and bolusing is error prone. (Burdick et al. 2004) show that, on average, teenagers under manual control forget to compensate for 2.1 meals per week. New automatic control algorithms aim to supplant manual attention using insulin pumps and continuous glucose monitors (CGMs). As with manual control, one of the primary challenges to achieving tight BG regulation is the rejection of unknown or unannounced meal disturbances. For a review of other challenges see (Kumareswaran et al. 2009; B Wayne Bequette 2005; Claudio Cobelli et al. 2009). Relying only on feedback control implies a delayed response to meals and associated significant glucose deviations.

Patients could assist feedback controllers by announcing meals and/or explicitly administering insulin. However, we fear the illusion of safety presented by automatic regulation would only worsen the manual error rate of missed meal announcements. Automatic control algorithms should be designed to handle unannounced meals.

Current controllers handle unannounced meals through explicit or implicit meal detection (Eyal Dassau et al. 2008; Lee & B Wayne Bequette 2009). These controllers can use one of several meal detection algorithms (Cameron & Niemeyer 2010; Cameron et al. 2009; E. Dassau et al. 2008; Lee et al. 2009). The meal detection algorithms search for the signature of a meal in the sensor measurements. By definition, they can provide detection only after a meal has occurred.

Fortunately meals are not entirely unpredictable. We know an individual meal follows a consistent shape (Livesey et al. 1998; A Basu et al. 2003; Vella et al. 2007). We also know that meal times and sizes follow particular patterns and rules. This has led (Patek et al. 2009) to predict meal times based on daily patterns. A possible concern is the detrimental effect if a patient deviates from a consistent routine.

In this paper we propose an alternate method of anticipation. We declare meal prior probabilities as a function of time since previous meals, effectively encoding brief periods of fasting between meals. While such anticipation cannot match the certainty of meal announcements, it does allow preparatory lowering of glucose levels when we expect patients to be hungry and meals to occur, regardless of historical patterns.

We show substantial performance improvements, lowering the average blood glucose risk index (BGR1) (Clarke & B. Kovatchev 2009; Boris P. Kovatchev et al. 1997) from 6.92 to 2.83 when adding meal priors for a set of ten simulated patients. Simultaneously, we show that glucose levels remain reasonable even with two consecutive skipped meals.
The control benefits result from the meal priors improving prediction of longer prediction horizons including unknown future meals. In contrast to other predictors that assume no meals (Bergman et al. 1979; Hovorka et al. 2004), or stay limited to short prediction horizons (Gillis et al. 2007), our prediction can achieve causal zero-mean long-term prediction errors. As an additional benefit, we can test, tune, and validate the prediction on existing free-living outpatient data.

After a brief background of relevant prior work, we propose the novel meal prior probabilities, determine appropriate parameter selections, and examine the resultant expected meal behavior. We finally validate our approach in both prediction and closed-loop control before concluding.

2. BACKGROUND

(Patek et al. 2009) provide a Model Prediction Control (MPC)-like method that anticipates meals when augmented with a meal pattern and either meal announcement or a meal detector. The meal pattern used is generated from historical data and uses the regime of breakfast in the morning, lunch around noon, and dinner in the evening. This allows insulin to be safely administered before a meal, yielding improved controller performance and safety in the event of a missed meal. This work is based on historical patterns and so has reduced benefit for non-standard days.

An alternate implementation by (Cameron & Niemeyer 2010) avoids historical patterns such as the breakfast, lunch, and dinner regime. They generate predictions and uncertainties that can be incorporated into MPC like controllers. (Cameron 2010; Cameron et al. 2011) use the generated predictions and uncertainties in an MPC-like controller. The probabilistic framework used for meals is, however, simplistic, and is not readily based upon actual human behaviour.

(Strubbe & Woods 2004) report on human behaviour from extensive work characterising the eating behaviour of rats. They report that food intake occurs as discrete bouts or meals, and then continue to suggest that circadian activity pattern, changes in the light cycle, and the size of the previous meal can have discernable effects. An authoritative textbook on human physiology (Guyton & Hall 2006) provides some fundamental biological evidence. They state that the hypothalamus stimulates the desire for food which is then quenched by stomach stretch. Further it states that stomach emptying and thus reinvigoration of hunger is governed by the small intestine to ensure adequate absorption of the nutrients in food.

(Winkler et al. 1999; Winkler et al. 1995) actually observed human behaviour for German men aged between 45-64 over 6293 days. They report a significant variance in the number of meals eaten each day, with only 19% of patient days containing 3 meals. 34.4% patient days contained 4 meals, while 32% had 5 meals.

3. MEAL PRIOR PROBABILITY

The meal prior probabilities should reflect what we know about how humans consume meals. Consequently, we work from what we know: a) meals are only eaten when awake, and c) meals inhibit new meals while being digested.

Figure 1. Published Glucose Appearance vs. Time Profiles

3.1 Meals are discrete

We model meals as discrete events that occur entirely in a single sample period, have a default size of effect $\mu_m$ in mg/dL, and an uncertainty $\sigma_m$.

3.2 Patients eat when they are awake

To represent the fact that we do not eat while asleep we begin by defining a base probability function $\Gamma(k)$ for each time step $k$ that is zero at night, and non-zero during the daytime. Meals are assumed to only start every $T_\text{s}$ time steps. Since we are ignoring meal patterns, $\Gamma(k)$ is set to a constant probability $\Gamma_d$ during the day. $\Gamma_d$ represents the probability of a meal in a given sampling period when there are no meals in the recent past. The mathematical formulation of $\Gamma(k)$ is:

$$\Gamma(k) = \begin{cases} 
\Gamma_d T_\text{s} & \text{if awake and } k \mod T_\text{s} = 0 \\
0 & \text{otherwise} 
\end{cases}$$

(1)

This formulation assumes that we know that when the patient is awake. In the more general case we would need to determine the patient’s status through announcement, accelerometers, a prolonged absence of detected meals, or assumed using a historical pattern.

3.3 Meals in the recent past inhibit meals now

The speed of meal digestion is dependent on the fat content of the meal since fat is digested much more slowly than protein or carbohydrates (Guyton & Hall 2006) and the stomach empties at a rate that ensures efficient absorption of the meal. So, carbohydrates in high fat meals flow into the small intestine slower, and are absorbed slower. Fig. 1 shows several examples with the lower fat meals finishing faster (R. Basu et al. 2006; A Basu et al. 2004; Livesey et al. 1998; Vella et al. 2007).

Continuous glucose monitors provide poor information about the fat content of a meal. Consequently, we assume the same digestion pattern $m(k - k_0)$ for all meals. Specifically, we assume that all meals follow the glucose appearance vs. time profile published in (R. Basu et al. 2006). Here, $k_0$ represents
the start time of the meal in minutes and \( m(k - k_0) \) is normalized to sum to 1. The default effect of a meal is equal to \( \mu_m m(k - k_0) \). 

\[
P(meal, k) \equiv \Gamma(k) \prod_{p=1}^{Q} \left( 1 - e^{-\left(k_p - k\right)^2} \right) \quad (2)
\]

where, \( Q \) represents the number of past meals (practically there are 1 to 3 meals in the last 6 hours), \( k_p \) is the starting time in minutes for meal \( p \), and \( \tau \) is the time constant that parameterizes the digestion pattern for meals. An example penalty for a single meal is shown in Fig. 2.

Fig. 2: Probability penalty function for a single past meal

The digestion of the previous meal inhibits the eating of meals now, meaning that the probability of eating a meal now can be the base probability \( \Gamma(k) \) multiplied by a penalty for each past meal:

\[ P(meal, k) \equiv \Gamma(k) \prod_{p=1}^{Q} \left( 1 - e^{-\left(k_p - k\right)^2} \right) \]

4. PARAMETER SELECTION

These prior probabilities are defined by several parameters: \( \mu_m, \sigma_m, m(k - k_0), T_s, \Gamma_d, \) and \( \tau \). Here we describe the values we used and why.

\( \mu_m \) and \( \sigma_m \) represent the mean and standard deviation of the effect of a meal in mg/dL. This will depend upon the person, the situation, and the model. For instance, an athlete eating 4 standard meals per day will have a high \( \mu_m \), and a low \( \sigma_m \). Alternately, if the model lumps the suppression of endogenous glucose production (removal of glucose) with the meal effect (addition of glucose) then \( \mu_m \) will be decreased.

For the control validation we use \( \mu_m = 240 \) mg/dL, and \( \sigma_m = 90 \) mg/dL based on the known carbohydrate intake. For the prediction validation in patients aged 3-18, we use \( \mu_m = 210 \) mg/dL, and \( \sigma_m = 75 \) mg/dL. For reference we derive \( \mu_m \) for a generic adult. In general 50% of the caloric intake should come from carbohydrates (Anderson et al. 2004). With a standard diet of 2,000 Calories per day, and 4 Calories per gram of carbohydrate that corresponds to 250 grams of carbohydrate (g CHO) per day. Using a conversion between g CHO and mg/dL of 3.25, based on the insulin to carb ratio and correction factor in (Walsh & Roberts 1994), the average adult takes in 812 mg/dL from carbohydrates per day. Assuming 4 meals per day (Winkler et al. 1999) \( \mu_m = 203 \) mg/dL. Diabetics tend to eat fewer carbohydrates to shrink meal disturbances and ease blood glucose control. Here we handle the harder case of the average healthy diet. Diabetics may have a lower \( \mu_m \), but only because they have adapted to facilitate manual blood glucose control. We seek to not require this adaptation.

Table 1. Published and fitted meal frequencies

<table>
<thead>
<tr>
<th>Number of Meals per Day</th>
<th>Number of Reported Days</th>
<th>Reported %</th>
<th>Fitted %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>0.1</td>
<td>1.3</td>
</tr>
<tr>
<td>2</td>
<td>71</td>
<td>1.1</td>
<td>6.3</td>
</tr>
<tr>
<td>3</td>
<td>1194</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>2162</td>
<td>34</td>
<td>34</td>
</tr>
<tr>
<td>5</td>
<td>2012</td>
<td>32</td>
<td>27</td>
</tr>
<tr>
<td>6</td>
<td>847</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>0</td>
<td>1.8</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0.1</td>
</tr>
<tr>
<td>Mean</td>
<td>4.1</td>
<td>4.2</td>
<td></td>
</tr>
</tbody>
</table>

\( T_s \) is the sampling period for potential meal start times. We arbitrarily set \( T_s = 5 \) min. For reference (Patek et al. 2009) set a similar value to 15 minutes.

\( \Gamma_d \) and \( \tau \) representing the base meal probability and the meal digestion time constant respectively are set to best match the published frequency of meals per day as published in (Winkler et al. 1999) and shown in Table 1. The resultant values are \( \Gamma_d = 3.1 \text{ min}^{-1} \) and \( \tau = 128 \text{ min} \).

4.1 Reality check

The tuning of the meal prior probabilities only forces them to fit the expected number of meals per day. So, we predict three other behaviours to check agreement with reality. a) does the predicted breakfast behaviour match Winkler et al.

b) How long do we expect between meals and c) what is the distribution of meals within a day?

(Winkler et al. 1995) show that the first meal of the day, breakfast, is eaten on 98.5% of days, and is eaten according to Fig. 3. Fig. 3 shows a wide spread of times for breakfast. The meal priors expect that the first meal of the day (breakfast) is eaten within 2 hours of awakening 98.5% of the time. If we assume that the spread in breakfast times are due
in large part to the variation in wake up times for the participants, then this number can match.

Assuming that a meal has just occurred then the next meal is penalized. As time passes the probability of the next meal increases while the penalty drops, and then decreases due to the chance that it has already occurred. Assuming that \( k_0 = 0 \) and that the patient is awake, the equation is:

\[
P(\text{next meal, } k) = \Gamma_d T_s (1 - e^{-k^2}) \prod_{k_n}(1 - P(\text{next meal, } k_n))
\]

With reference to Fig 4 That shows the time profile of the probability of the next meal, the most likely spacing between successive meals is 100 minutes.

\hspace{1cm}

**Fig. 4: The probability of the next meal \( T_s=5 \text{ min} \)**

(Winkler et al. 1999; Winkler et al. 1995) report the average number of meals per person eaten in a given hour of the day as shown in blue in Fig 5. To get the simulated version (shown in green) we simulated using the meal prior probabilities for 16 hour days with wake up times uniformly distributed between 6 and 8 AM.

Though roughly similar, these two distributions are not identical. This is due in large part to the fact that these meal priors do not include the societal pattern of eating lunch at noon or 1 PM, and eating dinner between 6 and 8 PM. However, since we are seeking to use human physiology instead of patterns, this is acceptable.

5. VALIDATION

We validate the meal prior probabilities in prediction of blood glucose profiles containing unknown meals (B. Buckingham et al. 2007) and in closed-loop control.

5.1 Validation in prediction

(Cameron & Niemeyer 2010) previously published a prediction algorithm without these meal priors. To prevent skewing from the unknown future meals they were forced to alter the future insulin when showing results on clinical data. Now we show results for the same prediction algorithm using these meal priors to predict and estimate the effects of the next meal.

To calculate the expected effects of the next meal we simply convolved the probability of the next meal, generated using the meal priors and the meal knowledge provided by the prediction algorithm, with the default meal effect \( \mu_m m(k - k_0) \). Note that we can also estimate the uncertainty of the effect of the next meal.

\hspace{1cm}

**Fig. 6: Root mean squared error vs. prediction horizon**

**Fig. 7: Mean error vs. prediction horizon**

Figs. 6 and 7 shows how the error behaves versus the length of the prediction on clinical data. None of the algorithms are provided with any information about meals. The first prediction in black assumes a Kalman filter augmented state-space model that assumes that there are no meals. The error grows steadily due to known insulin that is not offset by estimates of the unknown meals in the recent past and in the future.
The second algorithm (red) also uses a single state-space model with a Kalman filter. It differs from the first algorithm by including a two-state meal model. The Kalman filter updates the state estimates to fit meals that were occurring. This algorithm can thus adapt to existing meals, but assumes that there are no future meals. The effect of adapting to the existing meals is to lessen the initial growth in the error. It does not affect the error growth at the longer prediction horizons.

The third algorithm (blue) follows (Cameron & Niemeyer 2010) except using the new meal priors. This algorithm both adapts to the existing meals, lessening the error growth at short prediction horizons, and anticipates the effect of future meals, lessening error growth at longer prediction horizons.

5.2 Validation in control

Using a control algorithm as described in (Cameron 2010), a prediction algorithm as described in (Cameron & Niemeyer 2010), and the meal priors as described here we simulated using the 10 adult patients in the UVa/Padova Metabolic simulator for Type 1 Diabetes (B.P. Kovatchev et al. 2009). Each of the 10 patients was simulated for 34.5 hours containing 6 meals of 50, 70, 90, 25, 50, 70 g CHO at 9:00, 13:00, 5:30, 8:00, 9:00, and 13:00 hours respectively. The controller starts after 1.5 hours and is told that the patient is asleep between 22:00 and 6:00.

We show results for this controller with and without the meal priors, and also for an optimized basal/bolus controller. Since this controller explicitly minimizes the expected, combined clinical risk of hypoglycaemia and hyperglycemia there are no performance related tuning parameters. The basal/bolus controller has a single basal rate and optimized boluses at the start of each meal. The boluses were optimized retrospectively and thus represent a rough lower bound on the achievable BGRI. The BGRI is defined in (Boris P. Kovatchev et al. 1997; Clarke & B. Kovatchev 2009). The BGRI and the time spent in the euglycemic range are shown in Table 2.

<table>
<thead>
<tr>
<th>Controller</th>
<th>BGRI</th>
<th>% BG 70-180 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without meal priors</td>
<td>6.92</td>
<td>64</td>
</tr>
<tr>
<td>With meal priors</td>
<td>2.83</td>
<td>90</td>
</tr>
<tr>
<td>Basal/Bolus</td>
<td>1.64</td>
<td>97</td>
</tr>
</tbody>
</table>

Since this controller anticipates meals, it is possible that it will provide insulin for an upcoming meal that is dangerous when the meal is missed. A sample case where dinner and the evening snack were missed is shown in Fig 8. The top plot shows the CGM sensor signal (blue) and the true blood glucose level (green). The middle plot shows the insulin injected by the controller. The bottom plot shows the ingested carbohydrates. Recall that the controller anticipates meals between 3 PM and 10 PM, where there are none in this case. The lowest blood glucose level in this example is 73 mg/dL, which is in the euglycemic range.

By comparison the performance for the same patient without use of the meal priors to anticipate the next meal is shown in Fig. 9. Here the lowest value is 98, 25 mg/dL higher than when anticipating a non-existent meal. However, the postprandial peaks are uniformly 34 mg/dL higher.

6. CONCLUSIONS

This paper develops a mathematical expression for meal prior probabilities that does not rely on historical eating patterns. As a result it can adapt to days where the eating schedule is abnormal.

Predictions using these meal priors achieve significantly improved long-term prediction accuracy. Specifically, it removes the prediction bias associated with the effect of future meals. This enables tuning to patient data where the future effects of meals are unknown.

Simulations of closed-loop control using these meal priors significantly reduced the blood glucose risk index. The benefits come with marginally lower blood glucose values when patients abstain from meals for long time periods.

We hope such anticipatory behavior will make practical controllers both more effective and robust, improving the lives of diabetes patients.

ACKNOWLEDGEMENTS

This work is supported by funding from the Juvenile Diabetes Research Foundation’s Artificial Pancreas Project.
REFERENCES
http://purl.stanford.edu/jf647rq8653.
Cameron, Fraser, and Günter Niemeyer. 2010. Predicting Blood Glucose Levels around Meals for Patients with Type 1 Diabetes. In Dynamic Systems and Control Conference. Cambridge, MA.
Patek, S D, C Hughes, M Breton, and B P Kovatchev. 2009. Anticipating Meals with Behavioral Profiles : Towards Stochastic Model Predictive Control of T1DM. In IFAC Symposium on Modelling, 37-42. Aalborg, Denmark.