Developing a Meal Detection Algorithm and Meal Content for Patients with Type I Diabetes Using Continued Glucose Monitoring Data

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On our honor, we have neither given
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Developing a Comprehensive Meal Detection Algorithm and Meal Content Analysis for Patients with Type I Diabetes Using Continued Glucose Monitoring Data

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Abstract

Type 1 Diabetes (T1D) is a chronic ailment afflicting more than 1.25 million patients in the United States alone with increasing costs in both direct and indirect care every year. In an attempt to manage diabetes, patients typically undergo extreme lifestyle and/or dietary changes. In order for T1D-afflicted patients to maintain proper nutrition, professional help in the form of clinicians and deviants is often recommended. However, these professionals require accurate patients' meal records in providing the critical care that T1D patients require. Unfortunately, the meal records provided by patients are often incomplete, either lacking in correct time stamps or missing meals altogether. A system that retrospectively reviews a patient's continued glucose monitoring (CGM) data and reconstructs the meal record would significantly improve patient outcome and better T1D management. To that effect, we have developed a meal detection algorithm that utilizes peak identification alongside first and second derivative curves of the CGM trace to retrospectively identify meal occurrences. Similarly, the glucose minimal model is used to quantify the appearance of glucose in the bloodstream. Model parameters were compared with the meal's content using computational techniques to establish overall trends and correlations. This pipeline for meal record reconstruction can be further improved to identify meal times and meal types with high accuracy, enabling this comprehensive framework to be converted into a real-time tool to be implemented within an Artificial Pancreas (AP) systems.

Keywords: meal detection; type 1 diabetes; physiological modeling; unannounced meals; glucose minimal model

Introduction

Type I diabetes (T1D) is an autoimmune disorder that results in the degradation of pancreatic β-cells, inhibiting an individual's ability to produce insulin, and leading to several chronic health implications[1]. Although T1D accounts for only 10% of all diabetes cases, its incidence continues to increase – from 1.25 million Americans in 2017 to a predicted patient population of 5 million by 2050[2]. These trends are especially worrisome as insulin spending per patient has increased from $2,900 in 2012 to $5,700 in 2016, pointing to not only the physiological, but also the immense financial burdens associated with juvenile diabetes.

Currently, T1D management is achieved through various clinical and at-home approaches. Although contemporary methods such as surgical interventions (i.e. islet transplantation) and novel immunotherapeutic methods show promise, these techniques are invasive and much more involved than current protocols. Effective management of diabetes also requires the patient to continuously pay attention to insulin administration, blood glucose monitoring, and timely meal planning[4]. These management techniques are burdensome as patients are required to manually interact with their insulin delivery system with frequent blood glucose checks and daily insulin injections[1]. Scientific analysis of diabetic patients also proves difficult because an accurate meal record alongside a complete meal content classification (i.e. nutritional composition, macronutrients, micronutrients, etc.) is crucial for reliable clinical studies. Unfortunately, the records provided by patients are either inaccurate or missing meals entirely, indicating a great need for a system that can retrospectively reconstruct patients' meal records. Modern advances in the biotechnological realm have led to implementations of computational approaches and meal detecting algorithms (MDA) in reconstructing a patients' meal occurrence based solely on continuous glucose monitoring (CGM) data collected via wearable sensors[5]. Various factors such as meal quantity, frequency, and *especially* meal content is being considered as studies have indicated limitations in insulin dosing based on carbohydrate counting alone[6]. Therefore, the goals of this study are to:

1. Develop and optimize meal record reconstruction tool by:

- *Identifying peaks utilizing 2nd derivatives of the CGM data, correlating to a sharp rise in blood glucose, which would indicate a meal occurrence.*
- *Optimizing peak identification method by adjusting the importance of CGM feature and algorithm parameters*
- *Comparing predicted meal occurrence with known occurrence to increase accuracy*

2. Determine effect of meal content on CGM trends and post-prandial peaks by:

- *Fitting a compartmentalized model (DTTM) following each meal and optimizing its overall fit*
- *Investigating the relationship between each meal's recorded content and optimized model parameters by performing linear regression on each model parameter individually with different meal content variables*

Further fine tuning these algorithms and analysis on improved approaches will pave the way for development of a real-time system that identifies a meal occurrence and type simultaneously. This will hopefully ultimately be culminating with a mock concept of an Artificial Pancreas (AP) system offering automated regulation of blood glucose concentration among individuals afflicted with juvenile diabetes.

Introduction to Meal Detection Algorithms (MDA)

Detecting meals via CGM data is not a novel concept as various meal detection algorithms for Artificial Pancreases (AP) systems have previously been proposed[5,9,10,21,22]. The algorithms being employed in the development of closed-loop systems in particular can be classified into four types of models[9,11]. Model predictive control algorithms attempt to predict glucose levels in the near future and attempt to adjust insulin delivery accordingly. Proportional integral derivative algorithm is a well-known control loop which responds to real-time measured glucose values. Similarly, fuzzy logic algorithms determine insulin doses based on various parameters to mimic a clinician making real-time adjustments based on the CGM data[1,11]. Lastly, bio-inspired mathematical models are also being considered to determine dosing based on how β cells would act in response to blood glucose activity. These models all have varying degrees of success, but typically are able to predict a meal detection with a high level of accuracy. Despite the high performance, it should be noted that many of these predictive models are generated utilizing *in silico* data, which may not account for the metabolic variability observed in clinical settings. Furthermore, many of these models fail in instances of small meals and often report false positive rates, which would clinically translate to an AP system dosing insulin despite little to no spikes in blood glucose levels[12]. Regardless, the proposed meal detection methods for this project do not deviate from the current published works, primarily relying on monitoring the rate of change in glucose levels and utilizing first and second derivative peaks to reach the decision of whether a meal has occurred[5].

Introduction to Glucose Models

The glucose kinetics minimal model is a dynamic system of equations used to describe changes in both plasma glucose and insulin concentrations in response to rises in blood glucose levels. This model can be used to quantify insulin sensitivity, which is the ability of insulin to enhance glucose uptake into cells.[13] Initial model implementations aimed to describe glucose and insulin behavior in response to intravenous glucose tolerance tests (IVGTT) or oral glucose tolerance tests (OGTT). An IVGTT is used to assess glucose tolerance by recording blood glucose levels in response to an injection of a glucose bolus.[26] Though the test is powerful and provides a clear glucose trace in response, this test is not physiologically realistic, as glucose injections cause immediate and rapid rises in the blood glucose value, while oral consumption of glucose is typically delayed. An OGTT model has also been used to assess glucose tolerance with the subject consuming a glucose solution to determine the bloodstream glucose response.[28] This model also is not physiologically realistic as meal appearances are more delayed than oral glucose appearance due to the breakdown of carbohydrates into glucose. Thus, in order to quantify parameters that are physiologically relevant, the model selected should account for the rate of appearance of the meal into the bloodstream.

Results

Meal Detection Algorithm

Initial Algorithm Development

Our preliminary attempts to design a meal detection tool integrated features identified in prior published works. The accuracy of our algorithm upon validation with a *limited test* set was ~75 percent, with a false positive rate of ~25 percent (Table 1). However, it should be noted the identification window made permissible for detection was quite large, which may have biased the accuracy rates. In spite of these liberal thresholds, the initial model performs poorly relative to published works that boast well over 90 percent accuracy[5,9,10]. This model also relied on an insulin trace as one of the parameters in its detection (See Methods). Since the algorithm is constrained to retrospectively predict meals *solely* based on the CGM trace, it became readily evident that the approaches in the initial algorithm framework needed expansion. Due to the large variability in accuracy among the 10 subjects in dataset, there was a subsequent need to personalize the algorithm's parameters to be more subject specific (discussed below).

Table 1. Confusion Matrix
Predicted meal compared to actual meal occurrence (Prominence = 0.1, n = 7).

		Meals Predicted From MDA		
		Yes	No	Total
Meals Recorded During Admission	Yes	90	32	122
	No	31	91	122
	Total	121	123	244

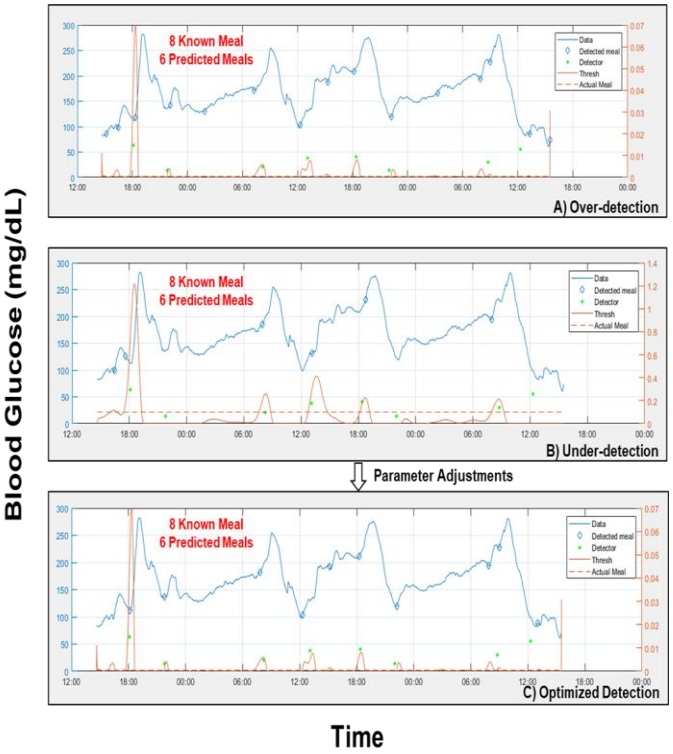

Figure 1. Optimizing for better predictive performance. The designed algorithm and its several parameters were optimized in a subject dependent manner. The two parameters optimized was the respective threshold setting (orange dashed line) and the degree to which the raw data was smoothed. While low thresholding and excessive smoothing leads to overprediction of meals **(A)**, the opposite is true in cased of under detection **(B)**. Optimizing these parameters after several adjustments to the algorithm leads to more reasonable and more accurate meal prediction **(C)**.

Final Algorithm Development and Tuning

An updated algorithm solely dependent on CGM trace was developed through several iterations (see Methods for rationale). On the 10 subjects tested, the designed algorithm performed with varying successes when the parameters were held at a constant.

Enabling some of the parameters to vary and depend on the subject led to far better performance. Figure 1 demonstrates the improvement in the algorithm's accuracy when the primary identified parameters are allowed to vary. The optimal parameter values for each subject is reported in Table S1, while the averaged mean values from each subject are provided in Table 2. These mean parameter levels also serve an important purpose clinically. If a patient is newly administered and their optimal parameter levels are not known, the mean "population" parameter values (Table 2) can be utilized for initialization and adjusted accordingly as more data becomes available.

Table 2: Optimized Parameter Values

Parameter	Mean ± Std Deviation
Threshold: *thresh*	**$2.19 * 10^{-3} \pm 1.11 * 10^{-3}$**
Smoothing: n_l	**21.5 ± 7.2**

Meal Modeling Analysis

Model Performance

The model used in this study is known as the double triangular minimal model, containing two triangular subsystems to model the meal and insulin rate of appearances in the bloodstream. (Figure 2). These subsystems contain two state compartments that the input travels through to reach the rate of appearance compartment. For example, when a carbohydrate meal input enters state Q_1, the input can go directly to Ra or to Q_2 then Ra. Each of these state-to-state travels is described by a rate constant that, when optimized, improves the shape of the resulting glucose appearance in the bloodstream. The insulin subsystem functions similarly to the meal subsystem. There are six rate parameters: three for the meal subsystem and three for the insulin subsystem. We chose to optimize the meal rate parameters as they modulate the meal input and adjust the shape of the resulting glucose appearance. We also chose to vary insulin sensitivity (SI) as insulin sensitivity is subject specific. We varied the fraction of intestinal absorption (f), in order to adjust the magnitude of the meal rate of appearance to be as close to the actual glucose data as possible.

$$\dot{G} = -S_g(G - G_b) - XS_iG + \frac{f \cdot R_a}{V_g \cdot BW} \quad (1)$$

$$\dot{X} = -p_2X + p_2(I - I_b) \quad (2)$$

$$\dot{Q}_1 = -(k_{m1} + k_{md})Q_1 + m(t) \quad (3)$$

$$IR_a = k_1I_{sc1} + k_2I_{sc2}$$

$$\dot{Q}_2 = -k_{m2}Q_2 + k_{md}Q_1 \quad (4)$$

$$R_a = k_{m1}Q_1 + k_{m2}Q_2$$

$$\dot{I}_{sc1} = -(k_1 + k_d)I_{sc1} + J(t) \quad (5)$$

$$\dot{I}_{sc2} = -k_2I_{sc2} + k_dI_{sc1} \quad (6)$$

$$\dot{I} = -nI + \frac{IR_a}{V_I \cdot BW} \quad (7)$$

Figure 2: Glucose Kinetics Model with a Double Triangular System Set-Up. This model contains seven differential equations, and two inputs: m(t), the rate of carbohydrates consumed in milligrams per minute (3) and J(t), the rate of exogenous insulin infusion delivered (5). G is the rate of glucose appearance in the bloodstream in mg/dL (1). X described the rate of insulin action in the bloodstream in mU/L (2). Q_1 and Q_2 (3 and 4) describe the states in mg of carbohydrates that the meal input can travel through to feed into the meal rate of appearance, Ra. I_{sc1} and I_{sc2} (5 and 6) describe the states in mU that the insulin infusion travels through to feed into the insulin rate of appearance, IRa. I describes the insulin concentration in the bloodstream in mU/L using the insulin rate of appearance (7).

Our initial attempts to model the glucose appearance had many errors, such as the arbitrarily set initial parameters appeared to better fit the model than the model optimized towards the glucose data itself. While the shape of the meal was better described by the optimized parameters, the model optimization was not functioning to decrease the distance between the actual glucose response and simulated glucose response. (Figure 3A) We performed several experiments to improve the optimized model fit (see Methods). We adjusted initial parameters and conditions of the model to be more accurate and reflective of physiological conditions. We also implemented a Bayesian prior on insulin sensitivity to reduce the deviation of SI from a historic mean of $6*10^{-4}$ +/- $8*10^{-5}$ mg/dL.[29] Following all model improvements, we observed a 20-fold decrease in the resulting squared normal residual of the model fit, decreasing from approximately ~20,000 to 1017.21 across all subjects, indicating significant improvement in our algorithm performance. (Figure 3B).

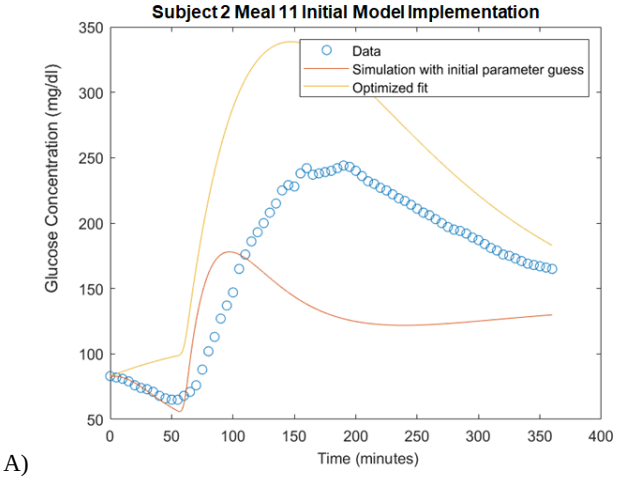

Figure 3. Initial vs Final Model Performance. Blood glucose levels collected every five minutes from the CGM device are represented by the blue data points. The red curve displays the simulated model performance with the initial parameter guess. The yellow curve displays the final model performance after parameter optimization. The resulting normal residual of the initial model (A) was approximately $2*10^5$. The resulting normal residual of the final model (B) was 519.08, indicating a 40-fold improvement of the model in this case

Carb Alignment Utilizing MDA

As meal times were patient-recorded in this study, human error was present in the meal input for the model (Figure 4A). The carbohydrate input was initially set at the time the meal was recorded, which rarely corresponded with the time that the meal propagation would begin. In order to overcome this barrier, the MDA was utilized to detect an accurate meal time in the CGM trace for every given meal. We proceeded to identify the closest carbohydrate input time to the detected meal time and shifted the input accordingly. This pushed the propagation of the simulated glucose bump following the meal input forward by approximately 40 minutes (Figure 4B). The squared normal residual decreased from $1.219*10^4$ to $1.829*10^3$, thus decreasing the squared error ten-fold and improving the overall fit of our model.

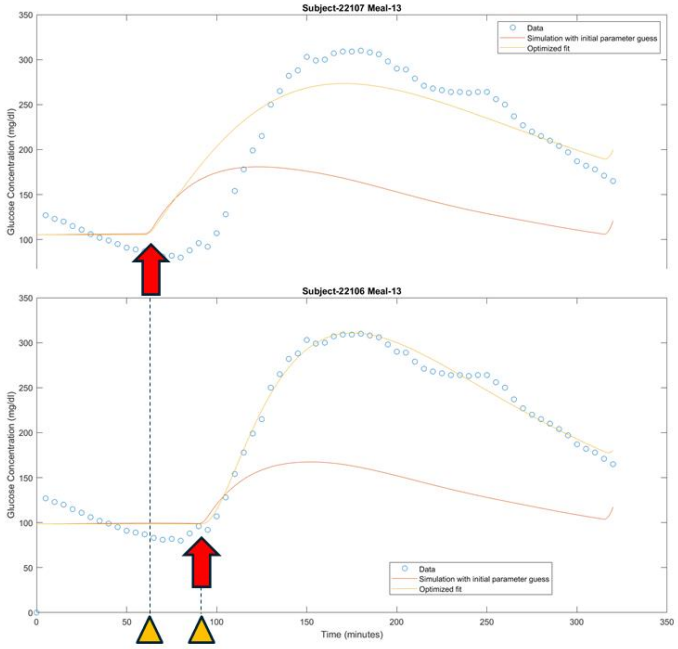

Figure 4: Carbohydrate Alignment using Meal Detection Algorithm. Initial model implementation without carbohydrate alignment began meal propagation approximately 50 minutes after the first CGM value, while the CGM data was still decreasing in value. (above) Final model implementation with carbohydrate alignment began meal propagation 90 minutes after the first CGM value while the CGM value was beginning to rise. (below)

Optimized Parameters

Once the final model performance was thoroughly optimized, the final algorithm was run on all 107 pre-screened meals to calculate estimates for the five varied parameters: Si, k_{m1}, k_{md}, k_{m2}, and f. (Table 3). Before computing the average and standard deviation of the parameter estimates, we removed all estimates for which the squared normal residual was over 4000 in order to only analyze the values for which the model optimization was successful. This step removed 25 meals from analysis due to poor fit. The resulting parameter estimates are computed over 82 meals across 11 subjects. The resulting SI value was found to be slightly smaller than historic values, in comparison to 0.0006 +/- 0.000087 mg/dL. Average values of k_{md} were much larger than the averages found for both k_{m1} and k_{m2}. As k_{md} describes movement from state Q_1 to Q_2, the large value for k_{md} relates to faster movement from Q_1 to Q_2. It does not have as significant of an impact on the resulting Ra as Ra is more dependent on k_{m1} and k_{m2}. indicating that the faster component of the model is not as relevant, and the slow movement is more relevant (k_{m1}). Lastly, the fraction of intestinal absorption, f, has the largest value with the most variation. As f acts as a gain on the rate of appearance, Ra, f adjusts the meal rate of appearance to push the simulated glucose response towards the glucose data during the model optimization.

Table 3: Model Parameter Estimates Following Optimization.	
MODEL PARAMETER	**MEAN +/- STD DEVIATION**
Insulin Sensitivity: S_i	4.2089 E-4 +/- 5.33 E-4 {$L*mU^{-1}*min^{-1}$}
Meal Rate Parameter: k_{m1}	0.006972 +/- 0.0348 {min^{-1}}
Meal Rate Parameter: k_{md}	0.2443 +/- 0.439 {min^{-1}}
Meal Rate Parameter: k_{m2}	0.01840 +/- 0.0198 {min^{-1}}
Fraction of Intestinal Absorption: f	3.667 +/- 7.42

Meal Content Analysis

Preliminary studies were performed to investigate the effect meal content on the qualitative appearance of the resulting glucose trace. (Figure 5) Data collected for each meal also contained meal content information i.e. amount of carbohydrates, fat, protein, fiber, and sugar. Content data was normalized within each content variable to quantitatively identify which meals had a higher than normal presence of carbohydrates, fat, and protein to classify a meal as high carbohydrate, protein, or fat. Three meals were selected to be qualitatively analyzed with respect to the glucose appearance. High carb meals can be seen to follow the traditional glucose appearance, with an even increase and decrease of glucose values with respect to time. High protein meal profiles contain a rapid increase of blood glucose levels, followed by a short postprandial peak and slow decay of the BG value back to the initial BG level. High fat meal profiles are characterized by long plateaus at the peak value of the postprandial glucose response.

Discussion

Meal Detection Algorithm Analysis

Although we were able to establish a general framework for our meal detection algorithm, accurately utilizing the meal detection tool for validation purposes remains a challenge. Continual improvements on our meal detection tool stagnated primarily due to a lack of access to larger datasets (n = 10). Furthermore, the recorded data for these 10 subjects were over a 2-day period--an extremely small sample size as most patients did not consume more than 5 “meals” per day. Limitations in the size of the data also implied that traditional machine learning methods could not be appropriately applied. Since most of the samples were initially required in “training” the model, there was limited data to fully test and validate the model and its assumption. To mitigate this issue, we attempted to test the algorithm on the complementary dataset (Launchpad) utilized in meal content analysis. Unfortunately, the meal times provided and classified within Launchpad may not be accurate as those are manually-inputted meal times. Without an accurate classifier for the actual conditions (i.e. actual meal times), testing the accuracy of the model and validating its results become practically impossible. In the future, more data should be integrated into the system to test the viability of our algorithm in accurately predicting a meal occurrence across a wide range of patient scenarios. Instances of constant snacking as opposed to complete meals as well as fluctuating dietary states are interesting

test cases that may further highlight some flaws in the currently built meal detection tool.

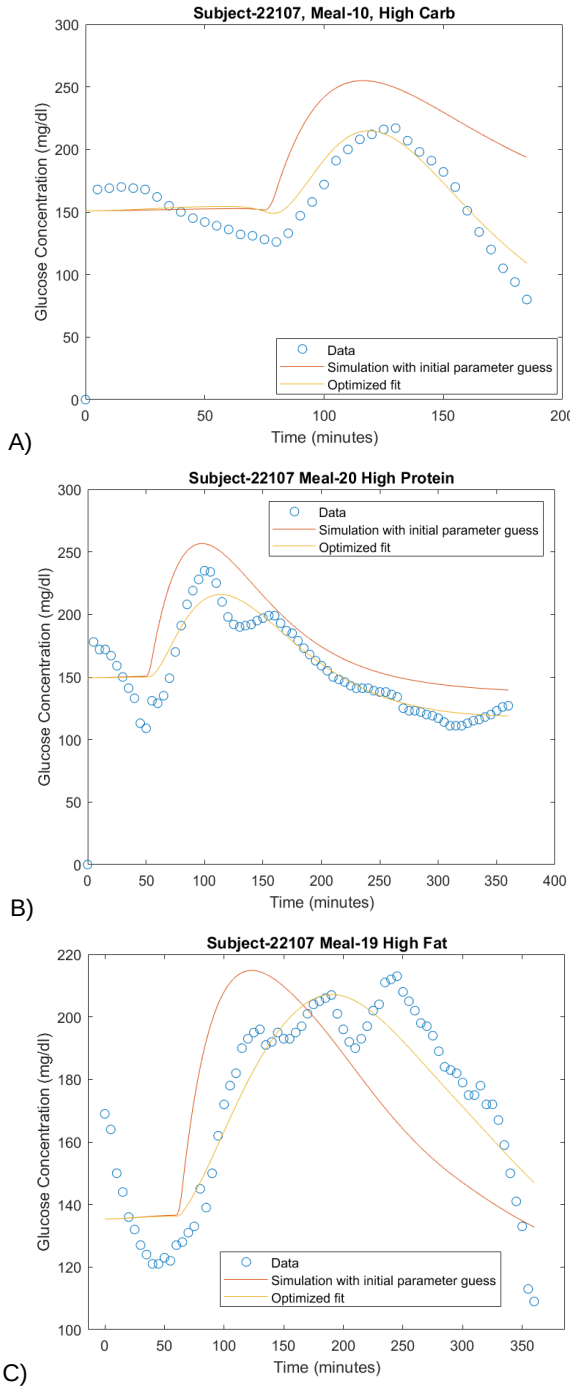

Figure 5: Meal Content CGM Profiles with Optimized Model Fits. A: High carb meal profile with 41 grams of carbohydrates, 7 grams of fat, and 11 carbohydrates. **B:** High protein meal profile with 33 grams of carbohydrates, 5 grams of fat, and 21 grams of protein. **C:** High fat meal profile with 21 grams of carbohydrates, 8 grams of fat and 3 grams of protein.

Meal Modeling Analysis

The primary goal for the glucose minimal model is to quantify a subject-specific insulin sensitivity value. Insulin sensitivity provides insight on glucose utilization that occurs within each subject. In this study, we found that insulin sensitivity did not vary greatly over subjects, with standard deviations typically being the same magnitude as the mean value itself. In order to increase the clinical relevance of the identified value of insulin sensitivity, further model improvement is necessary. Future studies could investigate the effects of imposing additional constraints on SI within the optimization cost function that take into account all previously determined SI values for that specific subject.

Theoretically, k_{m1}, the meal rate parameter describing movement from state Q_1 to Ra, correlates with the total amount of carbohydrates in a given meal. In order to test this theory, we ran a basic linear regression model to predict carbohydrate content based on a given k_{m1} value. This model produced a p-value of 0.446, indicating that the k_{m1} values observed in this study did not have a significant impact on the amount of carbohydrates in the given meal. Imposing a larger constraint on k_{m1} within the optimization function might allow this value to be less varied and have a more significant impact on carbohydrate content.

The final algorithm significantly improved the characterization of model parameters for meals where the CGM data was prescreened to be well defined with minimal anomalies. However, in clinical usage, not all data will be pre-screened for usability. Improving the algorithm's performance to optimize the model fit for data that may be classified as messy or unclean is essential to increase clinical usability. Future work could include any method of filtering the CGM data prior to running any sort of model analysis to smooth out resulting data.

Another study conducted to determine the impact of meal content on postprandial glucose control correlated meals with higher fat and protein content with increased more insulin dosing in comparison to meals with lower fat and protein, but identical carbohydrate content.[6] The meal profiles generate in our study displayed similar findings, such as delayed postprandial hyperglycemia for high fat meals. Further investigation into the relationship between varied model parameters and meal content can be helpful in eventually identifying the meal type based on resulting parameters from the optimized minimal model.

Clinical Relevance: Artificial Pancreas System

The artificial pancreas system strives to closely mimic the regulatory function of the pancreas in blood glucose management. In an idealized model, AP systems utilize closed-loop control, which enables the designed algorithm to automatically adjust insulin delivery based on continuous glucose monitoring (CGM) trends[8]. Due to limitations in design, current AP systems primarily utilize hybrid closed-loop systems, which require users to check glucose values at least twice daily to calibrate the CGM device[1,12,15]. Furthermore, the greatest barrier to an efficient AP system lies in regulating glucose levels following a meal[23]. Current controller systems have attempted to combat the meal detection dilemma using the *feed-forward approach*, where a user informs the controller of a meal occurrence, initiating an insulin bolus. In contrast, a *feedback control* only boluses after sensing an increase in glucose levels. This method is limited, however, due to a delay in insulin absorption, placing the patient at risk for postprandial

hyperglycemia. The *discrete meal detection* is a more novel approach, which attempts to trigger an insulin bolus as part of an algorithm using continuous feedback from a CGM device, enabling a more *real-time* controller system[5]. The transition from a hybrid closed-loop systems to fully closed-loop systems that implement discrete meal detection strategies is contingent on a well-tested meal detection tool[5,18]. The algorithmic frameworks proposed here and in existing literature therefore serves two critical and innovative functions: 1) MDA will automate the AP system controllers to accommodate for meals and bolus without the assistance of *any* patient input and 2) Retracing of meals that patients are unable to accurately record allows clinicians and dietitians access to significantly more data for preventive diabetes medicine and intervention.

Materials and Methods

Data Collection

Meal Detection Algorithm: GV2 Dataset

The dataset considered in the development of the algorithm was collected by the Center for Diabetes Technology (CDT) in a clinical study that attempted to reduce patients' glucose variability[24]. T1D subjects were included based on various inclusion criteria in a randomized crossover 48-hour visit. Although 15 total subjects were administered in the study, only 10 data sets were deemed complete and compatible for this study. The CGM data was collected through the Dexcom Share AP CGM device, while an accurate meal record was simultaneously recorded for the 48 hours that subjects remained at the CDT research house. Since the meal records for these patients are known and accurately recorded, this dataset is ideal in testing the accuracy of our meal detection algorithm.

Meal Content and Modeling Analysis: Launchpad Dataset

The dataset considered in the development of the meal modeling and meal content analysis was also collected by the Center for Diabetes Technology (CDT) in a separate clinical study that attempted to study the underlying glycemic variability across the menstrual cycle in women with T1DM. This study enrolled premenopausal women for approximately three-month outpatient study where the subject wore CGM devices and self-monitored blood glucose levels utilizing insulin pump to capture insulin dosing. The Launchpad set had longitudinal data with many separate recorded meals, making it an ideal set for meal content and meal modeling analysis.[25]

Meal Detection Algorithm: Model Development

Initial Algorithm Development

The raw CGM curve was filtered utilizing a moving average window filter over 2 hours for each data point and smoothed. A peak was subsequently identified in the filtered CGM data by finding the local maxima with the largest prominence (Fig. S1A). Potential instances when insulin was delivered to the patient was also plotted under the assumption that insulin levels twice greater than the basal rate indicated a bolus (Fig. S1B). Upon filtering the collected CGM data, peaks in the 2nd derivative was identified to isolate sharp rises in the raw data (Fig. S1C). The separated peaks were subsequently analyzed by studying the postprandial effect on CGM features, including: the blood glucose value, prominence of 2nd derivative peak, and the trend of the 1st derivative of the raw CGM following a meal. Since the 2nd derivative of CGM values tend to fluctuate significantly, a prominence of 0.1 was selected due to its ability to best capture all large 2nd derivative peaks that are typically indicative of a meal occurrence. Each identified 2nd derivative peak was predicted as a meal if the following circumstances were met (Fig. S1D):

- *If an insulin peak (bolus) occurred within 3 hours of the identified 2nd derivative peak*
- *CGM value at peak time was recorded to be <= 95 mg/dL*
- *Postprandial peak in the CGM data occurred between the identified peak and the next 2nd derivative peak*

Final Algorithm Development

In the redesigned approach, the detection of meal is based solely on the CGM values and no longer dependent on an insulin trace. The algorithm inputs patient's CGM data (collected at 5-minute intervals), interpolates it over time point of every minute. A non-causal filter is utilized to smooth out the data, which allows the algorithm to more easily observe the changes of blood glucose concentrations caused by potential meals. Filtering also helps to reduce the effects of CGM sensor noise. Meal information is subsequently extracted from the filtered CGM signal; however, filtering the data disrupts the original trace—the larger the filtration parameter, the larger the disruption. Identifying the appropriate smoothing parameter was thus one of the values optimized in the re-developed algorithm.

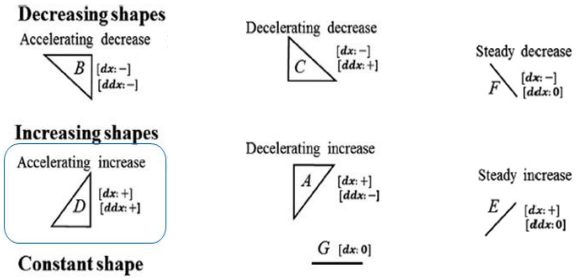

Figure adapted from: Samadi et al., *IEEE Biomedical and Health Informatics*

Fig. 6. Trends in the CGM Trace. The seven possible unique 1st and 2nd derivative combinations in describing CGM trends. The algorithm designed herein operates under the assumption that meals are most prevalent in instances of positive 1st and 2nd derivative (Schema D)

The possible changes (i.e. derivative) in blood glucose levels that is representative of the unique 1st and 2nd derivative combinations are expressed in Figure 6. In particular, the possibility of a meal is most likely to occur in instances of case D—an accelerating increase in the glucose profile (positive 1st, '*dx'*, and positive 2nd, '*ddx',* derivative). Therefore, only time points with positive trend in both the 1st and 2nd derivative were flagged as potential meal options. If the product of the 1st and 2nd derivative crossed an arbitrarily defined threshold (another parameter optimized in the study), the algorithm proceeds to identify the maximum peak of the 2nd derivative within the vicinity (± 20 mins) of the timepoint, pinpointing that timestamp as a potential meal. Figure S2 shows a more comprehensive flowchart of the designed algorithm.

In optimizing the fit, a parameter sweep was conducted on the two most sensitive parameters—threshold and smoothing. Due to the algorithm responding at different accuracy rates across subjects, these parameters were allowed to vary and a ROC curve analysis was conducted at several different values—threshold values

ranging from 0.0001 to 0.1 and the smoothing filter parameter ranging from 1 to 100. Based on the optimally identified values, these parameters were re-adjusted per subject, resulting in a far more refined algorithm than the initial implementation.

Development of Minimal Model

Data Preprocessing

Data from the Launchpad study was preprocessed and screened prior to performing model optimization. Each subject in this study recorded given an array of patient recorded meal times, we aligned CGM data, insulin infusion data, carbohydrate data with the datetime values from 30 minutes before the given meal time to 4 hours following the meal time or until the next meal. This was done for all 613 meal times across 13 subjects. The resulting pre-processed data was then qualitatively screened in order to isolate meals with a clean CGM trace on which model performance would be successful. A maximum of 10 meals were identified per subject based on the following criterion: 1) there was a clear initial state prior to the consumption of a meal, 2) the consumption of a meal could be clearly identified by a sharp rise in glucose value, 3) the propagation of the CGM value following a meal was smooth and began to trend downwards by the end of the time series, and 4) there were no anomalies in the CGM trace that couldn't be remedied by computational methods. A total of 107 meals across 11 subjects were identified as suitable for further analysis. Two subjects were found to have zero usable meals. Further data analysis was performed to account for CGM values that may not have been obtained properly, resulting in a BG value of 0. For these cases, the average of data points before and after the loss of signal was applied to these BG values of 0.

Model Development

The model used is known as the double triangular minimal model. The traditional glucose minimal model is described by equation 1 for glucose modeling, and equation 2 for insulin action. The first input to the model is m(t) which is fed into the state equations for the meal rate of appearance. The second input is J(t) which is fed into the state equations for the Insulin rate of appearance, which is fed into equation 7, the insulin concentration equation. Ra and I are then fed into equations 1 and 2 to generate a simulated glucose response. The fixed model parameters for this study are Sg (the fraction of glucose effectiveness), Vg (distribution volume of glucose), BW (subject body weight), p_2 (rate constant of insulin action), the rate constants for the insulin state equations (k_1, k_d, and k_2), Vi (distribution volume of insulin), n (clearance rate of insulin concentration). G_b and I_b were initially fixed as well, but were adjusted dependent on the data in the final model implementation. G_b was set as the calculated average of all glucose values prior to the beginning of meal propagation. I_b was set as the calculated average of all basal insulin injection concentrations divided by n, Vi and BW in order to adjust the units from mU/min into mU/L. The initial parameters of the ODE are set as seen in Table S2. The initial conditions of the model for the ODE are set based on the steady state solutions of the model;

$$G = G_b . X = 0, I = I_b, Q_1 = 0, Q_2 = 0$$

$$I_{sc1} = \frac{n * I}{V_i * BW * (k_1 + k_d)}$$

$$I_{sc2} = I_{sc1} * \frac{k_d}{k_2}$$

Model Adjustments

We adjusted the lower and upper bounds of varied parameters within the cost function from 0 to 1 to 1/100 and 100 times the initial parameter estimates. We also adjusted the calculation of the model input values within the model script to improve the models fit. The initial model implementation used MATLAB function interp1 to calculate the input value at each increment of t within the differential equation solver (ode45). Though interp1 functioned well for the meal input, it forced the insulin input to be interpolated across both basal and bolus injections. We changed this function from *interp1* to *find* to find the last datetime value within the input data that is less than the current increment of t. This improved the model performance as the insulin action curve was impacted more by boluses.

Carb Alignment

We used the MDA we developed to identify potential meal times. In the case that there was more than one detected meal time, we chose the meal time that occurred earliest as this model performance is geared towards identifying the meal type of one meal. Once the meal time was ascertained, the closest carb input was shifted to the detected meal time. In the case that no meal time was detected, we made no changes to the carbohydrate input.

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Supplemental Figures

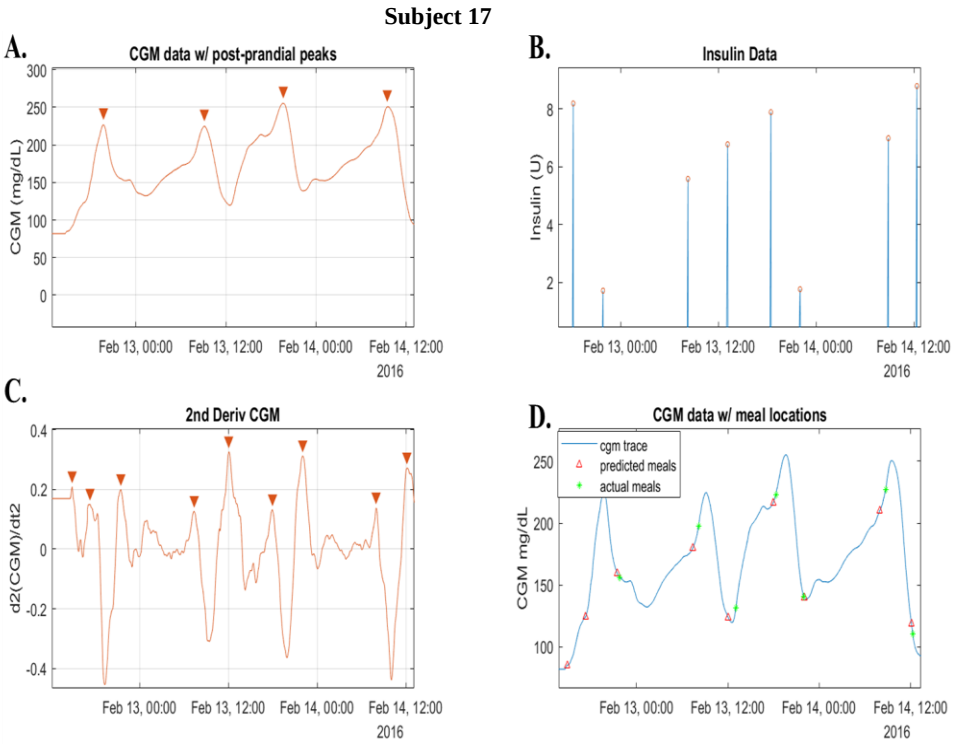

Fig S1. Initial Meal Detection Algorithm Development. Raw CGM data was filtered and peak was identified based on local maxima (A). Bolus was identified under the presumption that insulin levels doubling relative to basal concentrations was indicative of insulin being delivered to patient (B). 2nd derivative peaks were identified to isolate sharp rise in CGM (C), with only peaks meeting the required thresholds being identified as meals. (D) shows filtered CGM trace, overlapped with instances of both actual meal (green) and predicted meal (red) occurrence.

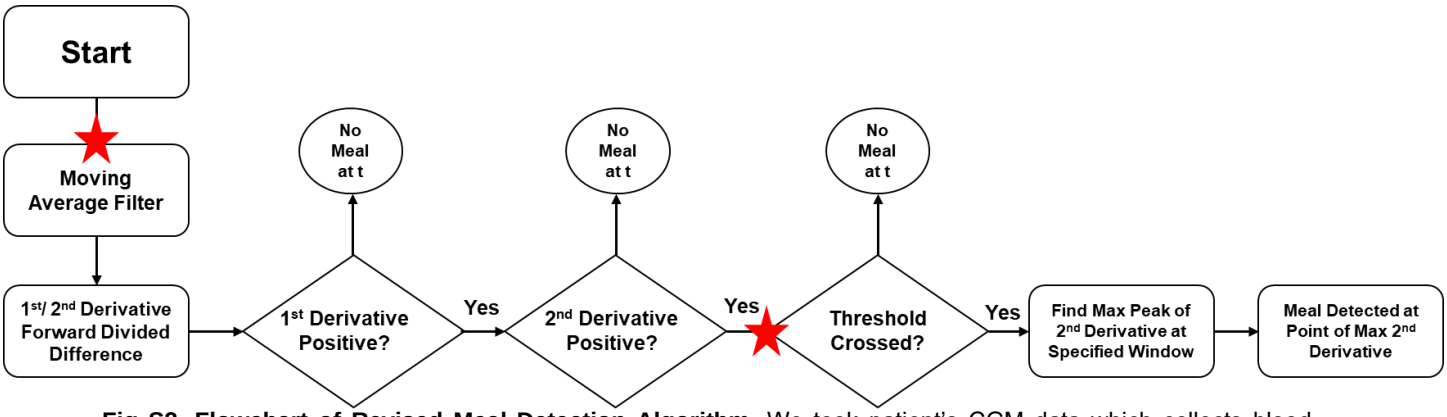

Fig S2. Flowchart of Revised Meal Detection Algorithm. We took patient's CGM data which collects blood glucose levels every 5 minutes, interpolating it over a time point of every minute and applying a non-causal filter that smooths out the data. As expected, smoothing the data disrupts the original signal, but becomes necessary to derive smoother and more prominent 1^{st} and 2^{nd} derivative curves. The derivative curves serves as the primary rationale behind our meal detection algorithm (see methods). Only timepoints where both the 1^{st} and 2^{nd} derivatives of the CGM trace are positive *and* the product of those two derivatives crosses an arbitrarily set threshold are identified as potential meal flags. The algorithm then proceeds to identify the max second derivative near the vicinity of where threshold is crossed, identifying that as a possible meal. The red star indicates parameters in the algorithm (thresholding and filtering settings) that were allowed to be varied across patients.

Although the model performs fairly well, there are more adjustments that could be made including (but not limited to): further optimizing the parameters, incorporation of different numerical methods in derivative calculations, surveying different windowing options, and altering filtering techniques.

Supplemental Tables

Table S1: Optimized Parameter Values in Meal Detection Algorithm Across Patients

Subject	Threshold	Smoother
1	0.00285	22
2	0.00185	18
4	0.0011	36
7	0.00115	25
11	0.00215	19
13	0.00015	27
16	0.00275	27
17	0.00315	13
20	0.0031	19
23	0.0036	9

Table S2: Initial Parameter Estimates

Symbol	Meaning	Value	Units
S_g	Fractional glucose effectiveness	0.01	min^{-1}
G_b	Basal glucose	Calculated	$mg*dL^{-1}$
V_g	Distribution volume of glucose	1.7	$dL*kg^{-1}$
Si	Insulin sensitivity	0.0001	$L*mU^{-1}*min^{-1}$
p_2	Rate constant of the remote insulin compartment	0.02	min^{-1}
I_b	Basal insulin	Calculated	$mU*L^{-1}$
k_{m1}	Rate constant of meal transport	0.02	min^{-1}
k_{md}	Rate constant of meal transport	0.015	min^{-1}
k_{m2}	Rate constant of meal transport	0.01	min^{-1}
k_1	Rate constant of nonmonomeric insulin absorption	0.0018	min^{-1}
k_d	Rate of constant insulin dissociation	0.0164	min^{-1}
k_2	Rate constant of monomeric insulin absorption	0.0182	min^{-1}
n	Insulin clearance	Calculated from BSA	min^{-1}
V_i	Distribution volume of insulin	Calculated from BSA	$L*kg^{-1}$
BW	Body weight	specific	kg
f	Fraction of intestinal absorption	0.9	