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Mixed Meal Modeling and Disturbance Rejection in Type I Diabetic Patients

Anirban Roy and Robert S. Parker

Abstract— **A mixed meal model was developed to capture the gut absorption of glucose, protein, and free fatty acid (FFA) from a mixed meal into the circulatory system. The output of the meal model served as a disturbance to the extended minimal model [3], which successfully captured plasma FFA, glucose and insulin concentration dynamics and interactions. A model predictive controller (MPC) was synthesized to reject meal disturbances and maintain normoglycemia. The dynamic fit of blood glucose after mixed meal consumption was consistent with the published data. The results from the closed-loop simulations were also promising; the MPC was able to maintain the glucose concentration within the normoglycemic range during and after consumption of a mixed meal.**

I. INTRODUCTION

Diabetes is one of the most prevalent diseases in the world today. According to the American Diabetes Association, in the year 2002 about 18 million people were diabetic in the U.S. alone, and the total cost of treatment was approximately $132 billion [1]. These numbers are increasing every year. One of the major characteristics of diabetes is significant blood glucose variation. Prolonged hyperglycemia can cause blindness, loss of limbs, and other complications [2]. Of more immediate concern is hypoglycemia, which can lead to unconsciousness or even death [2]. The most common treatment for type 1 diabetes involves periodic injections of insulin to maintain the blood glucose concentration within the normoglycemic range (70-120 $\frac{mg}{dl}$). Such approaches are adequate, but wide glucose variations still persist.

In order to achieve tighter control, there is a focus on automated insulin delivery pumps driven by control algorithms [4], [5]. In a model-based approach, model quality plays a vital role as controller performance is limited by model accuracy [6]. The mathematical models for diabetic patients proposed in the literature since the early 1960s are primarily glucocentric (glucose-based) [7], [8]. Such glucocentric models focus on the glucose and insulin dynamics. The contribution of free fatty acid (FFA) metabolism and FFA-glucose-insulin interactions have been largely ignored. FFA proves to be an important source of energy, with approximately 90% of muscle energy derived from FFA metabolism when the body is at rest [9]. Previous work from our laboratory extended the Bergman minimal model [7] to include plasma FFA dynamics, as well as its interaction with glucose and insulin dynamics [3]. In this work, a mixed meal model is developed to capture the absorption of carbohydrate (CHO), protein, and FFA from the gut into the circulatory system. The mixed meal serves as a disturbance to the extended minimal model, and a closed loop model predictive control (MPC) algorithm is synthesized for meal disturbance rejection and maintenance of normoglycemia.

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A. Roy is a Ph.D. student in the Department of Chemical Engineering, University of Pittsburgh, Pittsburgh, PA 15261, USA. anr31@pitt.edu

R.S. Parker is an Assistant Professor in the Department of Chemical Engineering, University of Pittsburgh, Pittsburgh, PA 15261, USA. rparker@pitt.edu

Correspondence to R.S. Parker; +1-412-624-7364, Fax +1-412-624-9639

II. EXTENDED MINIMAL MODEL

The minimal model developed by Bergman *et al.* [7] was extended to include FFA dynamics, as well as interactions between FFA, glucose and insulin, as shown in Fig. 1 [3]. The model consists of three accessible compartments, 'I', 'G', and 'F', representing plasma insulin ($\frac{\mu U}{ml}$), glucose ($\frac{mg}{dl}$), and FFA ($\frac{\mu mol}{l}$) concentration, respectively. Compartments 'X' and 'Y' represent the remote insulin (non-accessible) concentration promoting glucose uptake into the periphery, and suppressing FFA release from the adipose tissues (AT) into the circulatory system, respectively. An additional non-accessible compartment, 'Z', was added to the model representing remote FFA concentration impairing glucose uptake dynamics. Exogenously administered insulin is indicated by $u_1(t)$, and the gut absorption of glucose and FFA from a mixed meal is represented by $u_2(t)$ and $u_3(t)$, respectively.

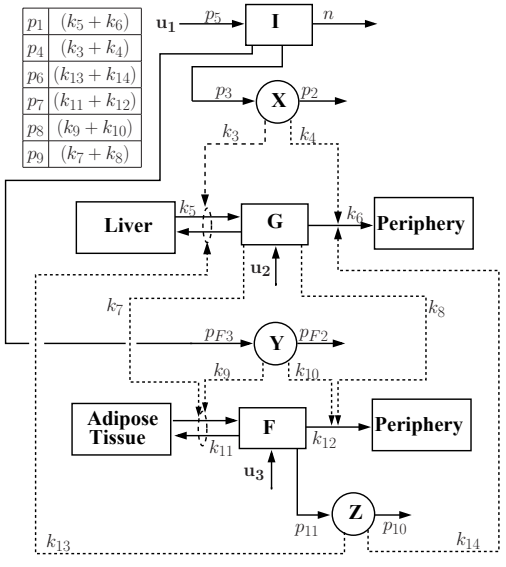

Fig. 1. Extended model of insulin, glucose, and free fatty acid dynamics

Deviations from the basal condition can be represented mathematically as follows:

$$\dot{I}(t) = -n[I(t) - I_b] + p_5 u_1(t) \quad (1)$$

$$\dot{X}(t) = -p_2[X(t) - X_b] + p_3[I(t) - I_b] \quad (2)$$

$$\dot{Y}(t) = -p_{F2}[Y(t) - Y_b] + p_{F3}[I(t) - I_b] \quad (3)$$

$$\dot{G}(t) = -p_1[G(t) - G_b] - p_4[X(t)G(t) - X_b G_b] + p_6[G(t)Z(t) - G_b Z_b] + \frac{u_2(t)}{Vol_G} \quad (4)$$

$$\dot{F}(t) = -p_7[F(t) - F_b] - p_8[Y(t)F(t) - Y_b F_b] + p_9[F(t)G(t) - F_b G_b] + \frac{u_3(t)}{Vol_F} \quad (5)$$

$$\dot{Z}(t) = -p_{10}[Z(t) - Z_b] + p_{11}[F(t) - F_b] \quad (6)$$

Basal levels of the state variables are denoted by the subscript, b. Plasma insulin dynamics and remote insulin effects on glucose and FFA concentrations are given by (1), (2), and (3), respectively. Plasma glucose dynamics are given by (4), where the passive glucose disposal is represented by parameter p_1, and the glucose uptake under the influence of insulin is represented by parameter p_4. In addition, the impairing action of plasma FFA on glucose uptake is represented by p_6. The equations representing plasma FFA and remote FFA dynamics are given by (5) and (6), respectively. The combined rate of FFA uptake by peripheral and AT is represented by p_7. The insulin induced suppression of FFA release by AT is represented by p_8. Finally, the lipolytic effect of plasma glucose concentration is given by p_9. The extended model successfully captured the plasma FFA, glucose and insulin concentration dynamics, as well as the interactions that exist between these species. Further details regarding the extended minimal model can be found in [3]. For the simulations below, all estimated parameters from (1) to (6) were held constant.

To validate the extended minimal model an Intra-Venous Glucose Tolerance Test (IVGTT) simulation was performed, where the model was subjected to a bolus of glucose, as shown in Fig. 2. Exogenous insulin infusion (bolus at t = 0, then constant infusion at 24 $\frac{mU}{min}$) yielded a decline in plasma glucose concentration until it returned to its basal level. Comparison between the model predictions of plasma insulin and glucose concentrations with published data [7] are shown in Fig. 2 (top and middle). It can be observed that the simulated results are consistent with the published data. In response to the IVGTT, the simulated plasma FFA concentration declined significantly below its basal level.

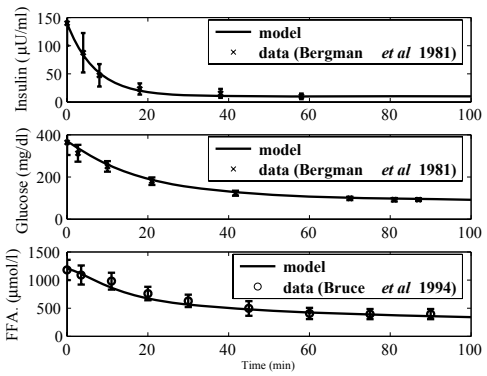

Fig. 2. Model validation simulation versus published data ($\mu \pm \sigma$) of plasma insulin (top), glucose (middle), and FFA (bottom) concentrations in response to an IVGTT

Comparison between the model prediction and published data [10] of FFA concentration in response to an IVGTT with identical conditions are shown in Fig. 2 (bottom). It can be observed that the model was consistently within one std. dev. of the data mean at all time points.

III. MIXED MEAL MODEL

Meals generally consist of all three major nutrient groups: glucose, protein and fat. After ingestion, the stomach converts the meal contents to chyme via a mechanico-chemical process. The partly digested meal then empties into the intestine for further digestion and absorption into the circulatory system. As discussed in Section II, meal-induced disturbances drive the glucose and FFA equations separately based on overall meal content. The meal models proposed in the literature typically focus on the gut absorption of glucose [11]. Thus, a mixed meal model describing CHO, protein, and FFA absorption is needed to drive the extended minimal model. The present study employs the Lehman and Deutsch meal model [11] structure to explicitly account for protein, fat, and CHO, absorption from the gut.

A. Mixed Meal Model Structure

The model assumes that the gastric emptying rate (G_{emp}) has a trapezoidal shape (adapted from [11]), as follows:

$$G_{emp}(t) = \begin{cases} (V_{max}/T_{asc})t & t < T_{asc} \\ V_{max} & T_{asc} < t \leq T_{asc} + T_{max} \\ V_{max} - (V_{max}/T_{des})(t - T_{asc} - T_{max}) & T_{asc} + T_{max} \leq t < T_{max} + T_{asc} + T_{des} \\ 0 & otherwise \end{cases} \quad (7)$$

$$V_{max} = 2N_{tot}/(T_{asc} + 2T_{max} + T_{des}) \quad (8)$$

Here, V_{max} is the maximum rate of gastric emptying. The duration for which G_{emp} is maximum (V_{max}) and constant is given by T_{max} (min). T_{asc} (min) and T_{des} (min) are the respective ascending and descending periods of G_{emp}. Total nutrient consumed is given by N_{tot} (g). The gastric emptying function is an input to the model of intestinal absorption. Nutrient absorption from the gut into the circulatory system is given by the following differential equations:

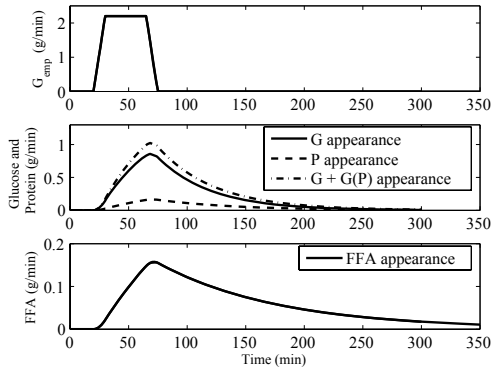

Fig. 3. Model simulation of total meal gastric emptying rate (top); glucose (G) appearance, protein (P) appearance, and G plus glucose derived from protein (G(P)) appearance (middle); and FFA appearance (bottom), in response to 108 g mixed meal tolerance test

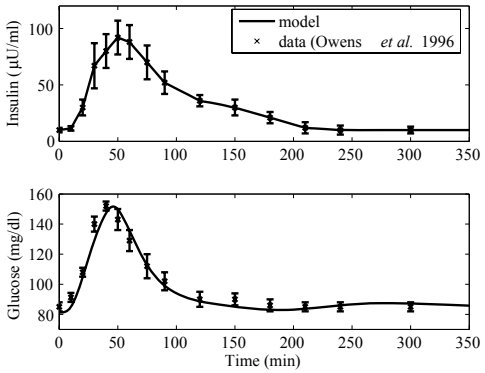

Fig. 4. Insulin concentration data from normal subjects ($\mu \pm \sigma$) and piecewise linear approximation (top), model simulation versus published data ($\mu \pm \sigma$) of plasma glucose concentration dynamics in response to mixed meal (bottom) tolerance test

$$\dot{N_G}(t) = x_G G_{emp}(t) - k_G N_G(t) \quad (9)$$

$$\dot{N_P}(t) = x_P G_{emp}(t) - k_P N_P(t) \quad (10)$$

$$\dot{N_F}(t) = x_F G_{emp}(t) - k_F N_F(t) \quad (11)$$

Here, $N_G(t)$, $N_P(t)$, and $N_F(t)$ are the amount of glucose, protein and FFA in the gut, respectively. The mass fraction of glucose, protein and FFA in the meal are given by x_G, x_P, and x_F, respectively. Similarly, the intestinal absorption rate constant for glucose, protein, and FFA are given by k_G, k_P, and k_F, respectively. The model assumes that 60% of the protein is converted to glucose [12]. Hence, the rates of appearance of glucose and FFA in the circulatory system, *i.e.*, $u_2(t)$ from (4) and $u_3(t)$ from (5), are given by:

$$u_2(t) = k_G N_G(t) + 0.6[k_P N_P(t)] \quad (12)$$

$$u_3(t) = k_F N_F(t) \quad (13)$$

Graphical representations of the G_{emp} of the total meal, and rate of appearance of the three nutrients in the circulatory system are given in Fig. 3, based on the simulation conditions described in Section III *B*.

B. Mixed Meal Tolerance Test (MTT)

A mixed meal (CHO = 70 g, protein = 18 g, and FFA = 20 g) was consumed by healthy subjects in 10 min in an MTT study by Owens *et al.* [13]. Blood samples were taken at various times after the meal consumption to measure glucose and insulin concentrations. To investigate MTT response in simulation, the mixed meal model was coupled with the extended minimal model. Since insulin concentration measurements were available, the insulin dynamics, (1), were replaced by a piecewise linear approximation of the normal patient's insulin profile (Fig. 4, top). Parameters T_{max}, k_G, k_P, and k_F of the mixed meal model were estimated to fit the glucose profile (as shown in Fig. 4), whereas parameters of the extended minimal model were directly obtained from [3]. The parameter values of the meal model are T_{max} = 35 min, k_G = 0.022 min^{-1}, k_P = 0.0097 min^{-1}, and k_F = 0.015 min^{-1}. V_{max} calculated from (8) is 2.2 $\frac{g}{min}$. This is similar in value to other maximum G_{emp} rates reported in the literature using similar meal sizes [14]. Literature data also suggested that the time to reach V_{max} for a medium size mixed meal, such as the one used here, is typically 10 - 15 min [15]. Based on that, the T_{asc} and T_{des} values were fixed at 10 min. It can be observed that the meal model when coupled to the extended minimal model, yielded glucose concentration predictions consistent with experimental data. The slight underprediction of glucose in the first 50 *min* could be due to differences in dynamics between the patients modeled in [3], [7] and the patient responses in Fig. 4. More accurate glucose predictions could be achieved by reducing T_{asc} to a lower value; however this would violate generally accepted physiological limits on T_{asc} [15].

IV. CLOSING THE LOOP

One objective in synthesizing the extended minimal model is to evaluate the effects of FFA dynamics on closed-loop (CL) glucose control. A CL insulin delivery system would require a glucose sensor, an insulin pump, and a (model-based) control algorithm that would adjust insulin infusion based on the glucose measurement. In this study, a MPC algorithm was synthesized to maintain normoglycemia in the presence of mixed meal challenges. The controller solves an optimization problem at each time step; the result is an optimal insulin delivery sequence that minimizes a user-specified objective. MPC algorithms are well-suited for biological system applications due to the straight forward incorporation of constraints.

A. Linear Model Predictive Controller

A linear MPC algorithm was developed to control blood glucose concentration about a setpoint of 81 $\frac{mg}{dl}$. The extended minimal model was linearized using a first-order Taylor series expansion.

The control algorithm minimized the following 2-norm squared objective function:

$$\min_{\triangle U(k|k)} \|\Gamma_y(Y(k+1|k) - R(k+1|k)\|_2^2 + \|\Gamma_u \triangle U(k|k)\|_2^2 \quad (14)$$

Here, vectors $R(k+1|k)$ and $Y(k+1|k)$ of length p are the desired future glucose trajectory and the future model prediction resulting from the open-loop optimal control sequence

vector $\triangle U(k|k)$ of length m (where, $m \leq p$). The goal is to minimize the error in setpoint tracking and variation in the control sequence. Γ_y and Γ_u are the weighing matrices for glucose setpoint tracking and insulin move penalization, respectively. Controller tuning involves adjustments to the four parameters p, m, Γ_y, and Γ_u.

At the current sampling time ($\triangle T_s$), unmodeled disturbances are estimated from the difference between the plant measurement (the nonlinear extended minimal model in this work), $y_m(k)$, and the linear model prediction, $\hat{y}(k|k-1)$. The algorithm solves for an m-length input move sequence based on the linear model output prediction; the first calculated move is implemented, and the algorithm repeats.

B. Mixed Meal Disturbance Rejection

A mixed meal (CHO = 70 g, protein = 18 g, and FFA = 20 g) was consumed by the simulated patient (SP-1), at t = 20 min. Controller tunings were: p = 10, m = 2, Γ_y = 1, and Γ_u = 0.2; $\triangle T_s$ was set at 5 min. Safety constraints were simulated by bounding the insulin input magnitude ($0 \leq U(k|k) \leq 90\frac{mU}{min}$). In order to make sure that the maximum change in insulin delivery rate is not higher than the mechanical characteristics of the pump, a maximum input rate constraint was employed ($|\triangle U(k)| \leq 45\ \frac{mU}{min}$ per $\triangle T_s$). For comparison, a second simulated patient (SP-2) consumed a meal of equal total mass (108 g), where the mixed meal absorption model (9), (10), and (11) was replaced by a single glucocentric absorption equation, given by:

$$\dot{N_G}(t) = (x_G + 0.6x_P + x_F)G_{emp}(t) - k_G N_G(t) \quad (15)$$

Just like the mixed meal model, the combined meal model assumes that 60% of the total protein consumed is converted to glucose. Closed-loop simulation results of both meal models are shown in Fig. 5. It can be observed that the maximum glucose concentration is much less for SP-1 than SP-2 (SP-1 = 117.4$\frac{mg}{dl}$; SP-2 = 132.2 $\frac{mg}{dl}$). However, the minimum glucose concentrations for both responses are similar (SP-1 = 71.9$\frac{mg}{dl}$; SP-2 = 72.2 $\frac{mg}{dl}$). The 99% settling time is much faster for SP-1 than SP-2 (SP-1 = 258 min; SP-2 = 306 min). Total insulin infused over 6 hr following meal ingestion for SP-1 is 5.9% higher than SP-2. Finally, the sum squared error of glucose from the setpoint for SP-1 is 52% less than SP-2. Based on these results, the incorporation of FFA does impact CL controller performance.

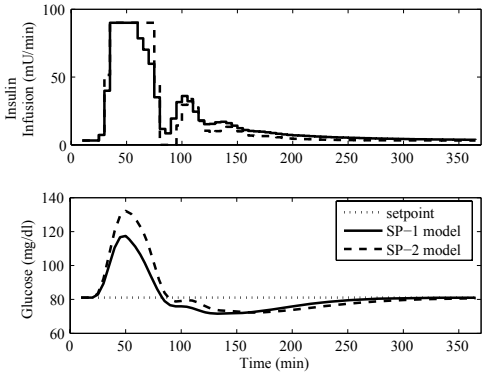

Fig. 5. Linear MPC meal disturbance rejection with mixed meal (SP-1) and glucocentric meal (SP-2)

V. SUMMARY

A mixed meal model was developed to capture the gut absorption of glucose, protein, and FFA into the circulatory system. The outputs of the meal model served as disturbances for the extended minimal model [3]. In a MTT, the extended minimal model with mixed meal disturbance successfully captured plasma glucose concentration dynamics. A linear MPC algorithm was developed to maintain normoglycemia during and after meal consumption. Tighter glucose control was obtained when FFA effects were explicitly incorporated in the meal disturbance. This more complete model description, capturing all the major nutrient groups provides superior blood glucose regulation under model-based control for a simulated type 1 diabetic patient.

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