A Phenomenological Model of Plasma FFA, Glucose, and Insulin Concentrations During Rest and Exercise

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Abstract—A phenomenological mathematical model for predicting FFA-glucose-insulin dynamics during rest and exercise was developed. The dynamical effects of insulin on glucose and FFA were divided into three parts: (i) insulin-mediated glucose uptake by tissues, (ii) insulin-mediated suppression of endogenous glucose production, and (iii) antilipolytic effects of insulin. Labeled and unlabeled intravenous glucose tolerance test data were used to estimate the parameters of the glucose model, which facilitated separation of insulin action on glucose utilization and production. The model successfully captured the FFA-glucose interactions at the systemic level. The model also successfully predicted mild-to-moderate exercise effects on FFA, glucose, and insulin dynamics. Model predictions of FFA, glucose and insulin profiles were validated with existing literature data. This composite model provides a new test platform for the development of closed-loop glucose control algorithms.

I. INTRODUCTION

Absolute or partial deficiency in insulin secretion by the pancreas, lack of gluco-regulatory action of insulin, or both, leads to a metabolic disease known as diabetes mellitus (DM) [1]. DM is normally associated with wide blood glucose fluctuation. In order to prevent major health complications, it is important to maintain blood glucose concentration within the normoglycemic range (70 – 120 mg/dl) [2], [3]. In the present work, the focus is the insulin-dependent (or Type I) form of DM.

Since the 1960s, mathematical models have been used to describe glucose-insulin dynamics [4], [5], [6], [7]. Majority of these models are glucose-based and have ignored the contribution of free fatty acid (FFA) metabolism, which is an important source of energy for the body. Also, significant interactions exist among FFA, glucose, and insulin. It is important to consider these metabolic interactions in order to characterize the endogenous energy production of a healthy or diabetic patient. In addition, physiological exercise induces fundamental metabolic changes in the body; this topic has also been largely overlooked by the diabetes modeling community.

Previously in our laboratory, two different metabolic models were developed by modifying the Bergman minimal model [5] in order to incorporate various physiological effects of FFA and exercise on the insulin-glucose system [8], [9]. The extended minimal model developed by Roy and Parker [8] is capable of predicting FFA along with glucose dynamics during pre- and post-prandial states. The model is also equipped to capture the inhibitory effects of FFA on glucose uptake rate by the peripheral and hepatic tissues. However, the extended minimal model does not consider the exercise effects on insulin, glucose, and FFA kinetics. In a separate work by Roy and Parker [9], an exercise minimal model was developed to capture the effects of exercise on glucose and insulin dynamics. The model successfully captured insulin-glucose concentrations during and immediately after mild-to-moderate exercise. The model is also capable of predicting the plasma glucose excursion towards hypoglycemia during prolonged exercise periods. The major drawback of this model is the absence of FFA dynamics and its interactions with glucose and insulin.

Instead of having two different models capturing the effects of FFA and exercise on the glucose-insulin system separately, a single low-order metabolic model capturing all the physiological effects on the glucose-insulin system can be developed. Hence, in this work a composite metabolic model capable of predicting plasma glucose, insulin, and FFA dynamics at rest, as well as during mild-to-moderate exercise was developed. To make the composite model more biologically relevant, necessary modifications were made to the original model structures.

In the following section, a detailed description of the structure of the composite model is introduced. Inputs are infusions (insulin, glucose, or FFA), meals (glucose and FFA appearance) and exercise; models describing these input functions can be found in [8], [9], [10] and are not reproduced here due to space constraints. Most of the parameter values were estimated from published data by using the nonlinear least square technique, as described in [8], and the rest were directly obtained from the literature. All the parameter values of the composite model in its final form are provided in Table I[10].

II. COMPOSITE MODEL STRUCTURE

A. Insulin Dynamics

The model assumes an absolute deficiency of the pancreatic β-cells to secrete any insulin; hence, all of the gluco-regulatory hormone is externally infused ($\mu t(t)$). Exercise (incorporated as external input $\mu_E(t)$ and quantitated as percentage of $VO_2\max$ in decimal form) promotes the clearance of insulin, causing a drop in the plasma insulin level. This phenomenon is essential to enhance the hepatic glucose production and lipolysis during exercise [11]. The insulin dynamics along with exercise...
effects can be mathematically written as:

\[
\frac{dI(t)}{dt} = -nI(t) - y_{IU}(t)I(t) + \frac{u_I(t)}{V_I} \quad (1)
\]

\[
\frac{dPV_{O2}^{\text{max}}(t)}{dt} = m_{PV}(u_{E_3}(t) - PV_{O2}^{\text{max}}(t)) \quad (2)
\]

\[
\frac{dy_{IU}(t)}{dt} = m_{IU1} PV_{O2}^{\text{max}}(t) - m_{IU2} y_{IU}(t) \quad (3)
\]

Here, equation (1) captures the plasma insulin concentration \(I(t)\), \(\frac{u_I(t)}{V_I}\). The insulin clearance rate, \(n\), and the insulin distribution space, \(V_I\), are directly obtained from the literature [5]. Equation (2) quantifies the exercise intensity above its basal level by considering the percentage of maximum rate of oxygen consumption \(PV_{O2}^{\text{max}}\) for an individual, which is approximately linearly proportional to the energy expenditure [9]. The dynamics of the unobserved variable \(y_{IU}(t)\) \(\left(\frac{\text{mol}}{\text{min}}\right)\) is represented by equation (3). Parameters \(m_{IU1}\) and \(m_{IU2}\) were estimated by utilizing data obtained from Wolfe et al. [11], where healthy subjects performed bicycle exercise for 60 min at an intensity \(PV_{O2}^{\text{max}} = 40\%\). Blood samples were collected during exercise and the recovery period to measure the plasma insulin concentration, as shown in Fig. 1. With the onset of exercise, plasma insulin declined below its basal level due to the elevated clearance rate and remained low until the end of exercise. During the recovery period, plasma insulin climbed back to its basal value.

### B. FFA Dynamics

FFA is released from the adipose tissue (AT) into the plasma via the lipolytic process. The circulating FFA is consumed by the various organs and tissues mostly for oxidation, except the AT where it is consumed for storage purposes. Insulin is one of the major hormones that regulates the lipolytic process by suppressing the activation of hormone sensitive lipase (HSL), which is the primary enzyme responsible for lipolysis [12]. The following equations capture the FFA dynamics at rest:

\[
\frac{dF(t)}{dt} = -p_{F1} F(t) + EFP(t) + \frac{u_F(t)}{V_F} \quad (4)
\]

\[
EFP(t) = EFP_0 \left(1 - \frac{k_{EFP} \cdot x_{EFP2}(t)}{x_{EFP2}(t) + \sigma_{EFP}}\right) \quad (5)
\]

\[
\frac{dx_{EFP1}(t)}{dt} = p_{F2}(I(t) - x_{EFP1}(t)) \quad (6)
\]

\[
\frac{dx_{EFP2}(t)}{dt} = p_{F3}(x_{EFP1}(t) - x_{EFP2}(t)) \quad (7)
\]

\[
x_{EFP2}(t) = \frac{x_{EFP3}(t)}{x_{EFP2b}} \quad (8)
\]

Here, equation (4) represents the plasma FFA concentration \(F(t)\), \(\frac{u_F(t)}{V_F}\), and FFA appearance as a function of meal consumption is given by \(u_F(t)\). The plasma FFA distribution volume \((V_F, I)\) is directly obtained from the literature [13]. Parameter \(p_{F1}\) represents the rate at which FFA is consumed by the tissues. The rate of endogenous FFA production \(i.e.,\) lipolysis) is captured by the variable \(EFP(t)\) \(\left(\frac{\text{mol}}{\text{min}}\right)\), which is a function of insulin concentration as shown in equations (5)–(8). The unobserved variables \(x_{EFP1}\) and \(x_{EFP2}\) \(\left(\frac{\text{mol}}{\text{min}}\right)\) represent the effect of remote insulin concentration on lipolysis. Variable \(x_{EFP2}(t)\) is the remote insulin concentration normalized with respect to its basal level \(\left(\frac{x_{EFP2b}}{\text{mol}}\right)\), as shown in equation (8).

To establish the correlation between endogenous FFA production rate and insulin concentration, data was obtained from Campbell et al. [14], where the lipolytic rate of healthy humans was measured at various steady state hyperinsulinemic levels. The rate of lipolysis at zero insulin in equation (5), \(EFP_0\) \(\left(\frac{\text{mol}}{\text{min}}\right)\), was obtained from the literature [14]. The value of \(EFP_0\) and \(k_{EFP}\) in equation (5) were directly obtained from the literature [14]. Only the saturation constant \(\sigma_{EFP}\) was estimated to fit the data.

In order to capture the dynamical effects of insulin on endogenous FFA production, parameters \(p_{F2}\) and \(p_{F3}\) in equations (6) and (7) were estimated by utilizing data from two different studies simultaneously [15], [16]. In Howard et al. [15], euglycemic-hyperinsulinemic clamps were employed on normal subjects. Plasma insulin concentration was elevated to 20, 30, and 100 \(\frac{\text{IU}}{\text{mL}}\), as shown in the top, middle, and bottom panels in Fig. 2, respectively. Due to the antilipolytic action of elevated insulin levels, plasma FFA was suppressed in all the three cases. In the second study [16], a modified insulin frequently sampled intravenous glucose tolerance test (MI-FSIGT) was performed, where boluses of insulin at time \(t = 0\) and 20 min were administered to normal subjects, as indicated by the top panel of Fig. 3. Due to the insulin boluses, plasma FFA concentration was suppressed well below its basal level as shown in the bottom panel of Fig. 3. The two separate filter equations in the insulin dynamics could be visualized as the lag associated with transport of insulin in the adipocyte from the circulatory system and the lag associated with the action of insulin on deactivation of HSL, due to which lipolysis is suppressed.
Exercise increases FFA uptake, as well as production in the body. In order to incorporate the effects of exercise on FFA dynamics, equation (4) can be re-written as follows:

\[
\frac{dF(t)}{dt} = -p_{IF}(t) - \frac{W}{V_F} y_{IFU}(t) + E_{FP}(t) + \frac{W}{V_F} y_{IFP}(t) + \frac{W}{V_F} y_{IFY}(t)
\]

\[
\frac{dy_{IFU}(t)}{dt} = m_{FU1} PV_2^{max}(t) - m_{FU2} y_{IFU}(t) - m_{FU3} y_{IFU}(t) - y_{IFU}(t)
\]

\[
\frac{dy_{IFP}(t)}{dt} = m_{FP1} PV_2^{max}(t) - m_{FP2} y_{IFP}(t) - m_{FP3} (y_{IFP}(t) - y_{IFP}(t))
\]

Here, \(y_{IFU}(t) (\mu\text{mol/kg/min})\) represents the rate of disappearance of FFA by the working tissues due to exercise. Exercise-induced production of FFA is captured by \(y_{IFP}(t) (\mu\text{mol/kg/min})\). \(W (kg)\) is the weight of the patient. In order to estimate the parameters of equations (10)–(13), data was obtained from an experiment performed by Klein et al. [13] where healthy subjects performed exercise at \(PV_2^{max} = 45\%\) intensity for 240 min. FFA kinetics were measured during and immediately after the physical activity, to measure the whole-body plasma FFA appearance rate, \(R_{DF} (\mu\text{mol/min/kg})\), and plasma disappearance rate, \(R_{DF} (\mu\text{mol/min/kg})\), was measured along with the FFA concentration at the systemic level. With the onset of exercise, both \(R_{DF}\) and \(R_{AF}\) increased rapidly over the first 30 min. Thereafter, \(R_{DF}\) and \(R_{AF}\) gradually increased until the end of exercise. As \(R_{AF}\) exceeded \(R_{DF}\), plasma FFA concentration increased steadily throughout the duration of exercise. During the recovery period, the FFA returned to its basal level slowly. On the RHS of equation (9), the first two terms represent the rate of disappearance of plasma FFA \((R_{DF})\); whereas, the third and fourth terms represent the rate of appearance of plasma FFA \((R_{AF})\). Parameters \((m_{FU1-FU3} \text{ and } m_{FP1-FP3})\) capturing the exercise effects on FFA kinetics were estimated by using data from Klein et al. [13] to obtain the model predictions as shown in Fig. 4. It should be noted that the exercise levels used in the insulin model above \((PV_2^{max} = 40\%)\) and for the FFA model \((PV_2^{max} = 45\%)\) are different. Unfortunately, without control of the experiments (we are fitting to already published literature data), it was not possible to fit both models to data at the same intensity. Given the fit quality of the existing model (see Fig. 1 and Fig. 2), it is unlikely that a dramatic improvement in data capture would be provided by such data sets.

C. Glucose Dynamics

Glucose is taken up from the circulating pool by hepatic tissues for storage (primarily) and by the peripheral tissue for oxidation purposes. Glucose influences its own uptake in the hepatic and extra-hepatic tissue (known as glucose effectiveness [6]). Glucose uptake into the tissues is further facilitated by insulin (known as insulin sensitivity [6]). To maintain plasma glucose homeostasis, stored glucose in the liver is released back into the circulatory system via glycogenolysis. The rate of hepatic glucose production (HGP) is indirectly regulated by insulin [17]. Plasma insulin inhibits glucagon secretion from the pancreatic \(\alpha\)-cells, and the latter is a crucial hormone for maintaining HGP [18]. Furthermore, increased availability of FFA has an inhibitory effect on tissue glucose uptake [19], [20]. The dynamics of plasma glucose at rest along with the actions of insulin on
glucose uptake and endogenous glucose production, plus the inhibitory effect of FFA on glucose uptake at the systemic level can be mathematically expressed as given below:

\[
\frac{dG(t)}{dt} = (-p_{G1}G(t) - x_{G}(t)G(t)) f_{FG}(t) + EGP(t) + \frac{u_{G}(t)}{V_{G}}
\]  
(14)

\[
\frac{dx_{G}(t)}{dt} = p_{G2}I(t) - p_{G3}x_{G}(t)
\]  
(15)

\[
f_{FG}(t) = f_{FG0} \left(1 - k_{FG} \left(\frac{F_{N}^{3}(t)}{F_{N}(t) + s_{FGN}^{3}}\right)\right)
\]  
(16)

\[
F_{N}(t) = \frac{F(t)}{F_{B}}
\]  
(17)

\[
EGP(t) = EGP_{0} \left(1 - \frac{k_{EGP} \cdot x_{EGP}_{N}(t)}{x_{EGP}_{N}(t) + s_{EGP}^{3}}\right)
\]  
(18)

\[
\frac{dx_{EGP}_{N}(t)}{dt} = p_{GA}(I(t) - x_{EGP}_{N}(t))
\]  
(19)

Here, equation (14) represents plasma glucose concentration, \(G(t)\) (\(\frac{\text{mg}}{\text{dl}}\)), and glucose appearance as a function of meal consumption or glucose infusion is given by \(u_{G}(t)\). The first term in the parenthesis on the RHS of equation (14) represents the glucose uptake rate under its own influence. The bilinear term, \(x_{G}(t)G(t)\), captures glucose uptake under the influence of insulin; \(x_{G}(t)\) (\(\frac{\text{mg}}{\text{dl}}\)) represents the action of insulin on tissue glucose uptake. The dynamics of \(x_{G}(t)\) are captured by equation (15). The multiplier function \(f_{FG}(t)\) is a dimensionless variable that captures the inhibitory effect of FFA on glucose uptake rate (\(Rd_{G}\)). Variables \(x_{EGP}_{N}\) and \(F_{N}\) are the remote insulin and FFA concentrations normalized with respect to their basal levels, \(x_{EGP}_{N}\) and \(F_{B}\), respectively.

The rate of endogenous glucose production is represented by \(EGP(t)\), which is a function of plasma insulin as shown in equation (18). \(EGP_{0}\) (\(\frac{\text{mg}}{\text{dt}}\)) is the rate of hepatic glucose production in the absence of insulin. The dynamical effect of insulin on \(EGP(t)\) is captured by the unobserved remote insulin concentration, \(x_{EGP}(t)\) (\(\frac{\text{mg}}{\text{dl}}\)).

To establish the correlation between HGP and insulin concentration, data was obtained from [21], [22]. In these studies, the rate of glucose production was estimated by measuring the arterial-venous glucose concentration difference across the liver along with the hepatic blood flow rate. Due to the nature of the \(EGP\) dynamics with respect to the normalized remote insulin concentration \(s_{EGP_{N}}\), a 3rd order Hill function was selected for superior model accuracy, as indicated in equation (18). The value of \(EGP_{0}\) and \(k_{EGP}\) were directly obtained from the literature [22]. Only the saturation constant \(s_{EGP_{N}}\) was estimated to fit the data.

Randle et al. were the first to introduce the glucose-FFA cycle [19] to explain the interaction between CHO and fat metabolism. It was proposed that an increase in FFA availability will enhance fat oxidation, thus causing an increase in acetyl-CoA production, which will result in downregulating the rate-limiting CHO metabolizing enzymes. Due to this phenomenon, tissue glucose uptake will decrease [23]. From equation (14), plasma glucose uptake \((Rd_{G})\) rate can be written as:

\[
Rd_{G} = -[(-p_{G1}G(t) - x_{G}(t)G(t)) f_{FG}(t)]
\]  
(21)

The correlation between glucose uptake rate, \(Rd_{G}\), and plasma FFA was captured by utilizing data from [24], [25], where experiments were performed on healthy subjects by employing euglycemic-hyperinsulinemic clamps. The overall glucose uptake rate was measured at various plasma FFA levels. The gain parameter, \(k_{FG}\), from equation (16) was directly obtained from the data [24], [25]. Only the saturation constant, \(s_{FGN}\), was estimated to fit the data.

Parameters \(p_{G2}\) and \(p_{G3}\) from equation (15), representing the insulin action on tissue glucose uptake, and parameter \(p_{GA}\) from equation (19), capturing the dynamical effect of insulin mediated-suppression on hepatic glucose production, were estimated by using data from Regittin et al. [26]. In this study, a labeled-IVGTT was performed in T1DM patients. At time \(t=0\) min, a bolus of glucose labeled with a stable isotope tracer, D-[6,6-H\(_{2}\)]glucose, (hot glucose) was administered intravenously. A bolus of insulin was also injected at \(t=0\) min, followed by a continuous insulin infusion at constant rate to maintain the basal level. Blood samples were gathered at regular intervals to measure the concentrations of plasma insulin, tracer glucose, and total glucose (endogenous glucose plus the labeled exogenous glucose), as shown in Fig. 5. Parameters estimated from the labeled-IVGTT data provide a significant advantage over the unlabeled-IVGTT [6]. Due to the presence of tracer, it is
possible to monitor the dynamics of glucose disappearance only. Hence, labeled IVGTT data can separate the individual contributions of insulin on glucose production and utilization, which is impossible to achieve from unlabeled-IVGTT data. This technique was first introduced by Cobelli et al. [6] to minimize model errors and ambiguities that may arise when estimating parameters of the classical minimal model [5] from the unlabeled data only.

To estimate the parameters ($p_{G2}$, $p_{G3}$, and $p_{Ga}$) from the labeled-IVGTT data [26], two glucose models were used simultaneously. The total glucose concentration was captured by using equations (14), (15), (18), (19), and (16); this forms the cold glucose model. On the other hand, the tracer glucose concentration was captured by a new ODE as shown below:

$$\frac{dG(t)}{dt} = (-p_{G1}G(t) - x(t)G(t))f_{FG}(t)$$  

Equation (22), along with equations (15) through (17) to capture FFA effects, forms the hot glucose model. Simultaneous fitting of the total and tracer glucose data (as shown in Fig. 5) by using the cold and hot glucose models, respectively, should provide better informed parameter estimates.

Exercise induces an elevation in glucose uptake rate, $Rd_G$ (mg/min), by the working muscles. To maintain glucose homeostasis in the systemic level, glucose production rate ($Ra_G$, mg/min) is also elevated during exercise due to the accelerated rate of glycogenolysis. Two new variables, $y_GU(t)$ and $y_GP(t)$ (mg/kg/min), were added to equation (14) representing the exercise-induced glucose uptake and production rates, respectively, as follows:

$$\frac{dG(t)}{dt} = (-p_{G1}G(t) - x(t)G(t))f_{FG}(t) - \frac{W}{V_G}y_GU(t) + EG(t) + \frac{W}{V_G}y_GP(t) + \frac{u_G(t)}{V_G}$$  

From equation (23), plasma glucose uptake ($Rd_G$) and production ($Ra_G$) rate can be rewritten as:

$$Rd_G = (p_{G1}G(t) + x(t)G(t))f_{FG}(t) + \frac{W}{V_G}y_GU(t)$$  

$$Ra_G = EG(t) + \frac{W}{V_G}y_GP(t)$$

Coupling this to the definitions of the added variables, $y_GU(t)$ and $y_GP(t)$,

$$\frac{y_GU(t)}{dt} = m_{GU1}PV_{O_2}^{max}(t) - m_{GU2}y_GU(t)$$  

$$\frac{y_GP(t)}{dt} = m_{GP1}PV_{O_2}^{max}(t) - m_{GP2}y_GP(t)$$  

$$b = \frac{PV_{O_2}^{max}(t)}{PV_{O_2}^{max}(t) + sp_V}$$

yields a revised model to capture glucose homeostasis during short-duration exercise. In order to model the exercise-induced changes in glucose kinetics, data was procured from Wolfe et al. [11]. Further detail of the exercise effects on the glucose dynamics can be found in Roy [10].

### III. SUMMARY AND DISCUSSION

The primary goal of this work was to characterize the dynamics of the major energy-providing substrates and insulin at rest, as well as during exercise. The model successfully captured the physiological effects of FFA and mild-to-moderate exercise on plasma glucose concentration.

The model consisted of four parts capturing the insulin, glucose, FFA, and exercise dynamics. The dynamical effects of insulin on glucose and FFA were divided into three sections: the anti-lipolytic action to suppress endogenous FFA release; the gluco-regulatory action to promote glucose uptake in the tissues; and, the suppression of hepatic glucose production. Parameters of the insulin action on glucose were fitted by using labeled-IVGTT data which facilitated separation of insulin action on glucose utilization and production. Exercise effects on insulin, glucose, and FFA were divided into five sections. Mainly, these effects are the exercise-mediated plasma insulin clearance, elevated glucose uptake and production rate during exercise, and elevated FFA uptake and production rate during exercise. An extensive validation of the model was performed by conducting various simulation experiments and comparing the results with published literature data.

This novel approach of incorporating both FFA and exercise effects in the glucose-insulin metabolic model provides the diabetes research community with an excellent tool to investigate the fluctuations in glucose dynamics after consumption of mixed meal or performing exercise.