



## DYNAMIC MODELING OF EXERCISE EFFECTS ON PLASMA GLUCOSE AND INSULIN LEVELS

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**Abstract:** A mathematical model of the changes in plasma glucose and insulin concentrations during mild-to-moderate physiological exercise was developed for insulin dependent diabetic patients. From a metabolic prospective, the significant exercise induced effects are: increased glucose uptake rate by the working tissues; increased hepatic glucose production to maintain overall glucose homeostasis; and decreased plasma insulin concentration. The minimal mathematical model developed by Bergman *et al.* (1981) was extended to include the major exercise effects on plasma glucose and insulin levels. Model predictions of glucose and insulin dynamics were consistent with the existing literature data. This extended model provides a new disturbance test platform for the development of closed-loop glucose control algorithms.

**Keywords:** diabetes, glucose, insulin, exercise, minimal model.

### 1. INTRODUCTION

Diabetes mellitus is a metabolic disease caused by either the loss of pancreatic insulin secretion (Type-I) or resistance developed by the body towards the glucoregulatory action of insulin (Type-II). In order to prevent major health complications, it is important to maintain plasma glucose concentration within the normoglycemic range ( $70 - 120 \frac{\text{mg}}{\text{dl}}$ ) (DCCT - The Diabetes Control and Complications Trial Research Group, 1993; DCCT - The Diabetes Control and Complications Trial Research Group, 1996). The major long term effects of diabetes are caused due to hyperglycemia, where the plasma glucose concentration exceeds  $120 \frac{\text{mg}}{\text{dl}}$  due to insufficient endogenous insulin secretion (DCCT - The Diabetes Control and Complications Trial Research Group, 1993; DCCT - The Diabetes Control and Complications Trial Research Group, 1996). Prolonged hyperglycemia causes kidney disease, blindness, loss of limbs, etc (DCCT - The Diabetes Control and Complications Trial Research Group, 1993; DCCT - The Diabetes Control and Complications Trial Research Group, 1996). Of more immediate concern is hypoglycemia

when the plasma glucose concentration falls below  $70 \frac{\text{mg}}{\text{dl}}$ . Such conditions can lead to dizziness, coma or even death (DCCT - The Diabetes Control and Complications Trial Research Group, 1993; DCCT - The Diabetes Control and Complications Trial Research Group, 1996).

Since the 1960s, mathematical models have been used to describe glucose-insulin dynamics (Bolte, 1961). Bergman *et al.* (1981) proposed a three compartment minimal model to analyze the glucose disappearance and insulin sensitivity during an intra-venous glucose tolerance test (IVGTT). Modifications have been made to the original minimal model to incorporate various physiological effects of glucose and insulin. Cobelli *et al.* (1986) developed a revised minimal model in order to separate the effects of glucose production from utilization. The overestimation of glucose effectiveness and underestimation of insulin sensitivity by the minimal model was addressed in yet another publication by Cobelli *et al.* (1999), where a second non-accessible glucose compartment was added on to the original model. Hovorka *et al.* (2002) extended the original minimal model by adding three glucose and insulin sub-compartments in order to capture absorption, distribution and disposal dynamics, respectively. However, none of

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these models captures the changes in glucose and insulin dynamics due to exercise.

Physiological exercise induces several fundamental metabolic changes in the body (Wasserman and Cherrington, 1991). An increase in exercise intensity amplifies glucose uptake by the working tissues (Wasserman *et al.*, 1991). In order to maintain plasma glucose homeostasis, hepatic glucose production also increases with increasing work intensity (Wahren *et al.*, 1971). During prolonged exercise, hepatic glycogen stores begin to deplete, which leads to a reduction in hepatic glucose production as the glucose production mechanism shifts from glycogenolysis to gluconeogenesis (Ahlborg *et al.*, 1974). Since the energy requirement at a given exercise intensity is approximately constant, the overall plasma glucose concentration tends to fall well below the normoglycemic range for prolonged exercise durations (Wasserman and Cherrington, 1991). Elevated physical activity also promotes a drop in plasma insulin concentration from its basal level (Wolfe *et al.*, 1986; Wasserman *et al.*, 1989). The goal of the present work is to incorporate the fundamental effects of physiological exercise into the Bergman minimal model (Bergman. *et al.*, 1981) in order to capture the plasma glucose and insulin dynamics during mild-to-moderate exercise.

## 2. BERGMAN MINIMAL MODEL

Bergman *et al.* (1981) successfully quantified the pancreatic responsiveness and insulin sensitivity of a diabetic patient using a three compartmental mathematical model, as shown in Figure 1.

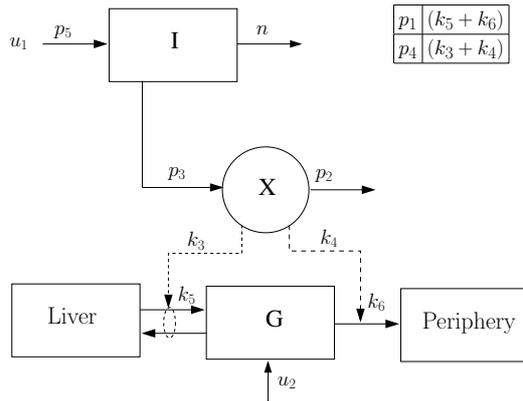


Figure 1: Bergman minimal model of insulin and glucose dynamics, adapted from (Bergman. *et al.*, 1981)

Compartments I, X, and G, represent the plasma insulin ( $\frac{\mu\text{U}}{\text{ml}}$ ), remote insulin ( $\frac{\mu\text{U}}{\text{ml}}$ ), and plasma glucose ( $\frac{\text{mg}}{\text{dl}}$ ) concentrations, respectively. The model assumes that all the necessary insulin is infused exogenously ( $u_1$ ), thereby modeling the insulin-dependent diabetic patients. A portion of the infused insulin enters into the remote compartment, X, from

the circulatory system. The remote insulin (X) actively takes part in promoting uptake of plasma glucose (G) into the hepatic and extra-hepatic tissues.

The deviation form of Bergman minimal model is mathematically given by (Bergman. *et al.*, 1981):

$$\frac{dI}{dt} = -n(I(t) - I_b) + p_5 u_1(t) \quad (1)$$

$$\frac{dX}{dt} = -p_2(X(t) - X_b) + p_3(I(t) - I_b) \quad (2)$$

$$\frac{dG}{dt} = -p_1 G(t) - p_4 X(t) G(t) + p_1 G_b + \frac{u_2(t)}{\text{Vol}_G} \quad (3)$$

Here,  $I_b$ ,  $X_b$  and  $G_b$  are the basal plasma insulin, basal remote insulin, and basal plasma glucose concentrations, respectively. The rate constant  $n$  represents disappearance of plasma insulin above its basal level. The rates of appearance of insulin in, and disappearance of remote insulin from, the remote insulin compartment are governed by the parameters  $p_3$  and  $p_2$ , respectively. Dietary absorption or external infusion of glucose is indicated by  $u_2(t)$ , and the glucose distribution space is indicated by  $\text{Vol}_G$ . Parameter  $p_1$  represents the rate at which plasma glucose above its basal level is removed from the plasma space independent of the influence of insulin. Glucose uptake under the influence of insulin is governed by the parameter  $p_4$ . Parameter values for the minimal model are provided in Table 1.

Table 1: Parameters of the Bergman minimal model, from (Bergman. *et al.*, 1981)

Parameter	Value	Unit
$p_1$	0.04	1/min
$p_2$	0.037	1/min
$p_3$	0.000012	1/min
$p_4$	1.0	ml/min· $\mu\text{U}$
$p_5$	0.000568	1/ml
$n$	0.142	1/min
$G_b$	80.0	mg/dl
$\text{Vol}_G$	117.0	dl

## 3. QUANTITATING EXERCISE INTENSITY

The maximum rate of oxygen consumption for an individual is  $\text{VO}_2^{\text{max}}$  ( $\frac{\text{ml}}{\text{kg}\cdot\text{min}}$ ). Oxygen consumption is approximately linearly proportional to the energy expenditure (Åstrand, 1960). Hence, it is possible to indirectly measure an individual's maximum capacity to do aerobic work by measuring oxygen consumption. When physical activity is expressed as a percentage of  $\text{VO}_2^{\text{max}}$ , ( $\text{PVO}_2^{\text{max}}$ ), exercise effects may be compared between individuals of the same sex and similar body weight at the same  $\text{PVO}_2^{\text{max}}$ . The average  $\text{PVO}_2^{\text{max}}$  for a person in the basal state is 8% (Felig and Wahren, 1975). Ahlborg *et al.* (1974) demonstrated that  $\text{PVO}_2^{\text{max}}$  increases rapidly at the onset of exercise,

reaches its ultimate value within 5-6 minutes and remains constant for the duration of exercise. The exercise model developed in this study uses  $PVO_2^{max}$  to quantify exercise level. The ordinary differential equation (ODE) capturing the exercise intensity is given by:

$$\frac{dPVO_2^{max}}{dt} = -0.8PVO_2^{max}(t) + 0.8u_3(t) \quad (4)$$

Here,  $PVO_2^{max}(t)$  is the exercise level as experienced by the individual, and  $u_3(t)$  is the ultimate exercise intensity – an input to the model. The parameter value of 0.8 ( $\frac{1}{\min}$ ) was selected to achieve a  $PVO_2^{max}(t)$  settling time of approximately 5 minutes.

#### 4. MINIMAL EXERCISE MODEL

The aim is to capture the effects of exercise on plasma glucose and insulin concentrations in response to mild-to-moderate aerobic exercise. A rise in glucose uptake by the working tissues occurs in response to exercise, and this is followed by an increase in hepatic glucose production. However, the rate of liver glucose production decreases with prolonged exercise due to the depletion of liver glycogen stores. As the muscle energy demand remains approximately constant for a given exercise level, the overall plasma glucose concentration eventually declines after an initial rise (Ahlborg *et al.*, 1974; Ahlborg and Felig, 1982). The initial rise in plasma glucose concentration with the onset of exercise is due to a several fold of increase in hepatic glucose production exceeding the glucose demand by working tissues (Marliss and Vranic, 2002). There is also an exercise induced decline in plasma insulin level. Wolfe *et al.* (1986) demonstrated that the application of a pancreatic clamp to maintain basal insulin levels during exercise (at 40  $PVO_2^{max}$ ) significantly increases the plasma glucose uptake, thereby disrupting glucose homeostasis. This is consistent with the idea that an increase in exercise level elevates the stimulating effect of insulin on glucose uptake (Wolfe *et al.*, 1986; Wasserman *et al.*, 1989). The ODEs for the exercise minimal model are as follows:

$$\frac{dI}{dt} = -n(I(t) - I_b) + p_5u_1(t) - I_e(t) \quad (5)$$

$$\frac{dX}{dt} = -p_2(X(t) - X_b) + p_3(I(t) - I_b) \quad (6)$$

$$\begin{aligned} \frac{dG}{dt} = & -p_1G(t) - p_4X(t)G(t) + p_1G_b \\ & + G_{prod}(t) - G_{up}(t) + \frac{u_2(t)}{Vol_G} \end{aligned} \quad (7)$$

$$\frac{dG_{prod}}{dt} = a_1PVO_2^{max}(t) - a_2G_{prod}(t) \quad (8)$$

$$\begin{aligned} \frac{dG_{up}}{dt} = & (a_3PVO_2^{max}(t) - a_4)PVO_2^{max}(t) \\ & - a_5G_{up}(t) \end{aligned} \quad (9)$$

$$\frac{dI_e}{dt} = a_6PVO_2^{max}(t) - a_7I_e(t) \quad (10)$$

The insulin dynamics, (5), have been modified from the Bergman minimal model, (1), by the addition of the final term. Here  $I_e(t)$  is the rate of insulin removal from the circulatory system due to exercise. The plasma glucose dynamics, (7), differ from (3) of the Bergman minimal model by the terms, ( $G_{prod}(t) - G_{up}(t)$ ). Variables  $G_{up}(t)$  and  $G_{prod}(t)$  represent rates of glucose uptake and hepatic glucose production induced by exercise, respectively. The dynamics of hepatic glucose production, glucose uptake, and removal of plasma insulin, induced by exercise are given by (8), (9), and (10), respectively.

Parameters for the minimal exercise model were estimated using the nonlinear ‘Least Square’ technique as described in (Carson and Cobelli, 2001). The normalized residual is obtained as:

$$\chi^2 \equiv \sum_{i=1}^N \left[ \frac{y_i - y(t_i, a_1 \dots a_M)}{\sigma_i} \right]^2 \quad (11)$$

Here  $y_i$  is the measured data at time  $t_i$  which has standard deviation of  $\sigma_i$ . The model prediction is given by  $y(t_i, a_1 \dots a_M)$ , where  $a_i$  represent model parameters. Equation (11) can be considered a weighted minimization using  $(\frac{1}{\sigma})^2$  as the weights.  $N$  is the number of data points and  $M$  is the total number of model parameters.  $\chi^2$  is often denoted as ‘weighted sum squared error’. The aim is to estimate  $a_i$  in order to minimize  $\chi^2$ .

Table 2: Parameters of the minimal exercise model in addition to those in Table 1

Parameter	Value	Unit
$a_1$	0.011	mg/dl·min
$a_2$	0.9	–
$a_3$	0.000001	mg/dl·min
$a_4$	0.00013	mg/dl·min
$a_5$	0.00002	–
$a_6$	0.00025	$\mu$ U/ml·min
$a_7$	0.009	–

Data from (Ahlborg *et al.*, 1974) and (Ahlborg and Felig, 1982) were used to estimate the parameters  $a_6$  and  $a_7$ , thereby quantifying the exercise induced removal of plasma insulin from the circulatory system. After fixing  $a_6$  and  $a_7$ , the insulin model was validated by comparing with the data from (Wolfe *et al.*, 1986). In fitting plasma glucose parameters, initially  $a_3$  was set to zero. Parameters  $a_1$ ,  $a_2$ ,  $a_4$ , and  $a_5$  were estimated from (Ahlborg *et al.*, 1974) and (Marliss and Vranic, 2002). The model was validated by comparing the predictions of plasma glucose concentration with the data from (Ahlborg and Felig, 1982). In order to improve the model fit, the bilinearity was introduced in the glucose uptake ODE (9) by estimating  $a_3$  (where,  $a_3 \neq 0$ ) and re-estimating  $a_4$ , using (Ahlborg

*et al.*, 1974) and (Ahlborg and Felig, 1982). The parameter values for the minimal exercise model are given in Table 2.

## 5. RESULTS

### 5.1 Plasma Insulin Dynamics During Exercise

To study the plasma insulin dynamics during prolonged exercise periods, Ahlborg *et al.* (1974) conducted an experiment where healthy subjects were studied in a continuous bicycle exercise for 4 hours ( $PVO_2^{max} = 30$ ). Blood samples were taken at regular intervals to measure the plasma insulin level. With the onset of exercise, plasma insulin level declined from its basal level ( $14 \pm 1.9 \frac{\mu U}{ml}$ ), and continued to do so until the end of the experiment, as shown in Figure 2. It can be observed that the model under predicts insulin concentration in short terms, followed by slight over prediction at long times. Quantitatively, however, the model was consistently within one standard deviation of the mean. Parameters  $a_6$  and  $a_7$  had values as given in Table 2.

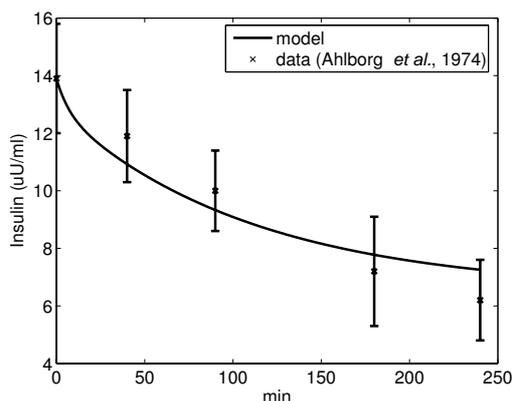


Figure 2: Published (mean  $\pm$  std. dev.) and model fit to data of plasma insulin concentration in response to mild exercise ( $PVO_2^{max} = 30$ )

In another study, Ahlborg *et al.* (1982) conducted a similar leg exercise experiment at a higher exercise level ( $PVO_2^{max} = 60$ ). Plasma insulin concentration declined consistently with the onset of exercise, as shown in Figure 3. It can be observed that the model prediction for plasma insulin concentration was generally better than that of Figure 2, although under prediction occurred at longer times. Parameters  $a_6$  and  $a_7$  had values as given in Table 2. The model predictions were within one standard deviation of the mean, thus validating the insulin model.

Data from a separate study by Wolfe *et al.* (1986) was used to validate the insulin model. Light exercise ( $PVO_2^{max} = 40$ ) was performed to observe the removal of plasma insulin from the circulatory system. With the onset of exercise the insulin level declined well below the basal level ( $13.2 \pm 3 \frac{\mu U}{ml}$ ), and this hypoinsulinemic state persisted until end of the experiment, as shown in Figure 4.

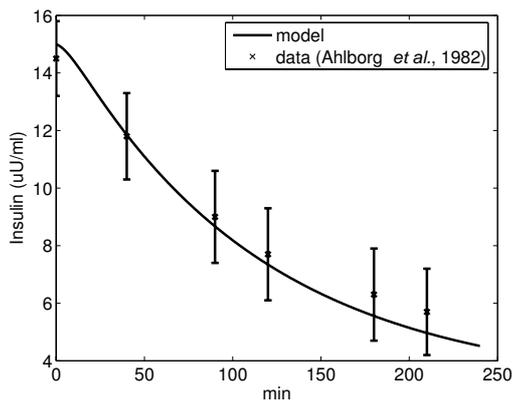


Figure 3: Published (mean  $\pm$  std. dev.) and model fit to data of plasma insulin concentration in response to moderate exercise ( $PVO_2^{max} = 60$ )

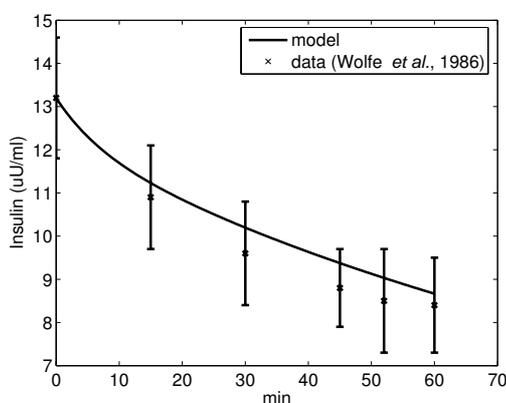


Figure 4: Model simulation validation versus published data (mean  $\pm$  std. dev.) of plasma insulin concentration in response to mild exercise ( $PVO_2^{max} = 40$ )

### 5.2 Plasma Glucose Dynamics During Exercise

The plasma glucose dynamics during a short duration (40 minute) of moderate level exercise ( $PVO_2^{max} = 50$ ), are shown in Figure 5 (Marliss and Vranic, 2002). Healthy subjects performed a full-body exercise, where blood samples were collected at regular intervals to measure the plasma glucose concentration. With the onset of exercise, the plasma glucose level increased slightly from its basal state ( $89 \pm 4.5 \frac{mg}{dl}$ ) to  $95 \pm 5 \frac{mg}{dl}$  and then started to decrease towards the end of the experiment. The resulting model predictions of plasma glucose were quantitatively consistent with the published data. Parameters  $a_1$ ,  $a_2$ ,  $a_4$  and  $a_5$  had values as given in Table 2.

The experiment conducted by Ahlborg *et al.* (1974) was considered to observe the plasma glucose dynamics during prolonged exercise periods. Blood samples were taken at regular intervals to measure the plasma glucose level. With the onset of exercise, the plasma glucose level increased slightly from  $81.8 \pm 2.5 \frac{mg}{dl}$  to  $83.5 \pm 3 \frac{mg}{dl}$  at the 40 minute mark. This

degree of change is consistent with the data of Marliss *et al.* (2002) shown in Figure 5.

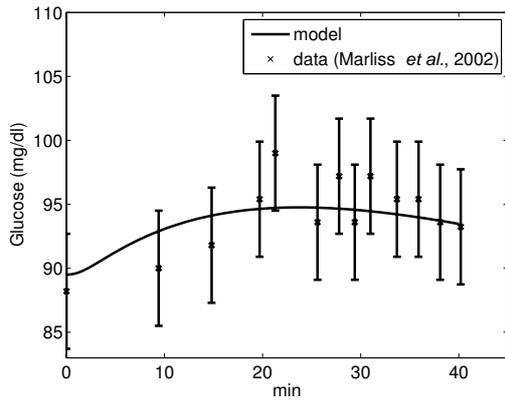


Figure 5: Published (mean  $\pm$  std. dev.) and model fit to data of plasma glucose concentration in response to moderate exercise ( $PVO_2^{max} = 50$ )

Beyond that, plasma glucose level decreased consistently until the end of the experiment, as shown in Figure 6. It can be observed that, during the short term response the model under predicted the mean data, and with eventual over prediction for  $t \geq 180$  min. However, quantitatively the model was consistently within one standard deviation of the mean. Again, parameters  $a_1$ ,  $a_2$ ,  $a_4$  and  $a_5$  had values as given in Table 2. Note that  $a_3$  was set to zero, as discussed in Section 4.

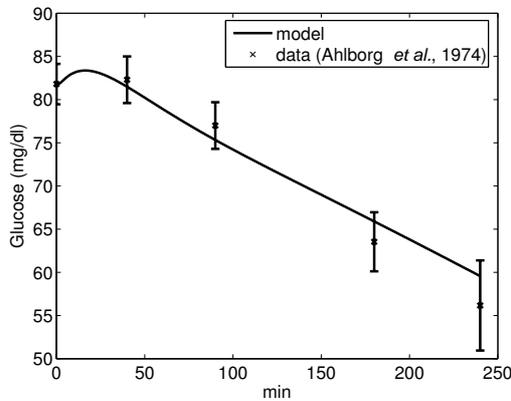


Figure 6: Published (mean  $\pm$  std. dev.) and model fit to data of plasma glucose concentration in response to mild exercise ( $PVO_2^{max} = 30$ )

To test the glucose model for moderate exercise intensity ( $PVO_2^{max} = 60$ ), data from another similar leg exercise study conducted by Ahlborg *et al.* (1982) was considered. Throughout the duration of the experiment, glucose uptake was higher than splanchnic glucose production. Hence, from the onset of exercise, overall plasma glucose concentration decreased consistently, as shown in Figure 7. With  $a_3 = 0$ , the model over predicted plasma glucose dynamics significantly at all times (Figure 7).

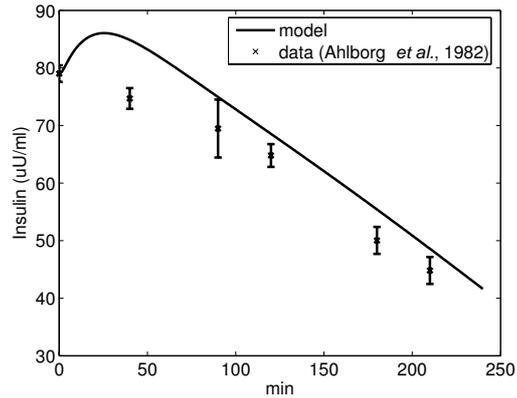


Figure 7: Published (mean  $\pm$  std. dev.) and model fit to data of plasma glucose concentration in response to moderate exercise ( $PVO_2^{max} = 60$ ), where  $a_3 = 0$  and  $a_4 = 0.00017$

In order to capture the plasma glucose dynamics during moderate intensity exercise ( $PVO_2^{max} = 60$ ), the parameter  $a_4$  was modified to incorporate an effect linear with exercise intensity,  $a_3PVO_2^{max}(t) - a_4$ . Parameters  $a_3$  and  $a_4$  in the glucose uptake ODE (9) were re-estimated with  $a_3 \neq 0$  using the data from (Ahlborg and Felig, 1982). Comparison of plasma glucose concentrations between the revised model and literature data (Ahlborg and Felig, 1982) are shown in Figure 8. It can be observed that the short term response of the model does not capture the data adequately.

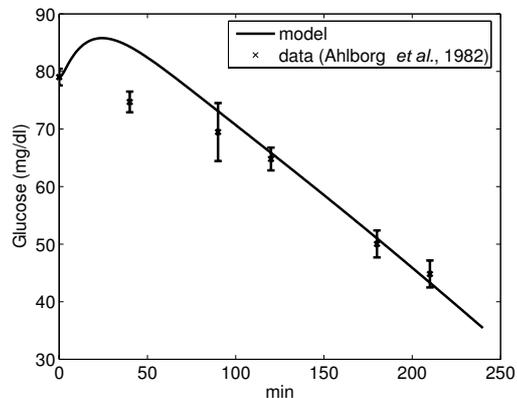


Figure 8: Published (mean  $\pm$  std. dev.) and model fit to data of plasma glucose concentration in response to moderate exercise ( $PVO_2^{max} = 60$ ), where  $a_3 = 0.000001 \frac{mg}{dl \cdot min}$  and  $a_4 = 0.00013 \frac{mg}{dl \cdot min}$

It is interesting to note that the short term data from (Ahlborg and Felig, 1982), in Figure 8, is inconsistent with that of (Marliss and Vranic, 2002) and (Ahlborg *et al.*, 1974), in Figures 5 and 6, respectively. Hence the model behaviors are inherently limited by the data quality, and additional experimental and simulation studies are required to refine and validate the model.

## 6. SUMMARY AND DISCUSSION

A minimal model of exercise effects on plasma glucose-insulin dynamics was developed. The model successfully captured the effects of mild-to-moderate aerobic exercise on plasma glucose and insulin concentrations. Inclusion of separate dynamics in the model for glucose uptake (9) and hepatic glucose production (8) induced by exercise made it possible to capture the initial rise (due to higher hepatic glucose production than tissue glucose uptake) and eventual decline of plasma glucose level with prolonged exercise (due to shortage of glycogen storage and a shift in glucose production mechanism). It was necessary to introduce a bilinear term in the glucose uptake ODE (9) in order to capture the full set of observed glucose dynamics induced by mild-to-moderate exercise. Given the small values for  $a_3$  and  $a_4$ , changes in model structure may be warranted. The model also successfully captured the removal of plasma insulin from the circulatory system during physical exercise. This model provides the control community with an alternative benchmark problem in glucose control for diabetic patients by allowing the analysis of meal and exercise disturbances alone or in combination.

Some of the parameters ( $a_6$  and  $a_7$ ) were estimated using data from (Ahlborg *et al.*, 1974) and (Ahlborg and Felig, 1982), where healthy subjects were used in the experiments. Ideally, this data would be from a diabetic population; however the majority of exercise studies are on healthy subjects. Additional experimental studies, ideally in a diabetic population, would improve model fidelity.

## 7. ACKNOWLEDGMENT

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