Dynamic Modeling of Exercise Effects on Plasma Glucose and Insulin Levels

Anirban Roy, M.S., and Robert S. Parker, Ph.D.

Abstract

Background:
Regulation of plasma glucose concentration for type 1 diabetic patients is challenging, and exercise is an added complication. From a metabolic prospective, the significant exercise-induced effects are increased glucose uptake rate by the working tissues, increased hepatic glucose release to maintain overall glucose homeostasis, and decreased plasma insulin concentration. During prolonged exercise, glucose levels drop significantly because of the decrease in hepatic glucose production. With the long-term goal of developing a closed-loop insulin delivery system operating under various physiological conditions, it is necessary to develop a model that is capable of predicting blood glucose concentration at rest and during physical activity.

Methods:
A minimal model developed previously was extended to include the major effects of exercise on plasma glucose and insulin levels. Differential equations were developed to capture the exercise-induced dynamics of plasma insulin clearance and the elevation of glucose uptake and hepatic glucose production rates. The decreasing liver glucose output resulting from prolonged exercise was modeled using an equation depending on exercise intensity and duration.

Results:
The exercise model successfully captured the glucose and insulin dynamics during short- and long-term exercise. Model predictions of glucose and insulin dynamics during the postexercise recovery period were also consistent with literature data.

Conclusion:
The model successfully emulated the physiological effects of exercise on blood glucose and insulin levels. This extended model may provide a new disturbance test platform for the development of closed-loop glucose control algorithms.


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Abbreviations: (CI) confidence interval, (T1DM) type 1 diabetes mellitus

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

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Introduction

Diabetes mellitus is a metabolic disease caused by either the loss of pancreatic insulin secretion (type I) or the resistance developed by the body toward the glucoregulatory action of insulin (type II). In order to prevent major health complications, it is important to maintain the plasma glucose concentration within the normoglycemic range (70–120 mg/dl). The major long-term effects of diabetes are caused by hyperglycemia, where the plasma glucose concentration exceeds 120 mg/dl. Prolonged hyperglycemia can cause complications, which may lead to kidney disease, blindness, loss of limbs, and so on. Of more immediate concern is hypoglycemia, defined by a plasma glucose concentration below 70 mg/dl. Such a condition can lead to dizziness, coma, or even death. Intensive insulin therapy involves three to four daily blood glucose measurements by finger pricking, followed by subcutaneous insulin injection; these usually correspond to meal times and bed time. Although this process is adequate to maintain the blood glucose level within an acceptable range, wide fluctuations persist throughout the day as a consequence of personal daily life activities (such as food intake and exercise) occurring between glucose measurements. In order to achieve tighter glucose control, there is a focus on the synthesis of an automated insulin delivery system composed of a continuous glucose measuring device, an insulin pump, and a control algorithm to govern the system. To have a reliable model-based insulin delivery system operating under various physiological conditions, a model must be developed that can predict blood glucose concentration at rest and during physical activity.

Since the 1960s, mathematical models have been used to describe glucose–insulin dynamics. Bergman and colleagues successfully quantified the pancreatic responsiveness and insulin sensitivity of a diabetic patient using a three-compartmental mathematical model, as shown in Figure 1. Compartments I, X, and G represent plasma insulin (μU/ml), remote insulin (μU/ml), and plasma glucose (mg/dl) concentrations, respectively. The model as written assumes that all the necessary insulin is infused exogenously (u₁), thereby modeling the insulin-dependent diabetic patient. A portion of the infused insulin enters into the remote compartment, X, from the circulatory system, I. The remote insulin (X) actively takes part in promoting the uptake of plasma glucose (G) into the hepatic and extrahepatic tissues.

The Bergman minimal model is given mathematically by

\[
\frac{dl}{dt} = -nl(t) + pₙu₁(t); \quad I(0) = Iₛ = \frac{pₛ}{n}u₁b
\]  

Methods and Materials

Bergman Minimal Model

Bergman and colleagues successfully quantified the pancreatic responsiveness and insulin sensitivity of a diabetic patient using a three-compartmental mathematical model, as shown in Figure 1. Compartments I, X, and G represent plasma insulin (μU/ml), remote insulin (μU/ml), and plasma glucose (mg/dl) concentrations, respectively. The model as written assumes that all the necessary insulin is infused exogenously (u₁), thereby modeling the insulin-dependent diabetic patient. A portion of the infused insulin enters into the remote compartment, X, from the circulatory system, I. The remote insulin (X) actively takes part in promoting the uptake of plasma glucose (G) into the hepatic and extrahepatic tissues.

Figure 1. Bergman minimal model of insulin and glucose dynamics, adapted from Bergman and colleagues.

The Bergman minimal model is given mathematically by

\[
\frac{dl}{dt} = -nl(t) + pₙu₁(t); \quad I(0) = Iₛ = \frac{pₛ}{n}u₁b
\]
The maximum rate of oxygen consumption for an individual during exercise is given by VO\textsubscript{2}\textsuperscript{max} (ml/kg/min). Oxygen consumption is approximately linearly proportional to energy expenditure.\textsuperscript{11} Hence, it is possible to indirectly measure the maximum capacity of an individual for aerobic work by measuring oxygen consumption. When physical activity is expressed as a percentage of VO\textsubscript{2}\textsuperscript{max} (PVO\textsubscript{2}\textsuperscript{max}), exercise effects may be compared between individuals of the same sex and similar body weight at the same PVO\textsubscript{2}\textsuperscript{max}. The average PVO\textsubscript{2}\textsuperscript{max} for a person in the basal state is 8%\textsuperscript{12}. Ahlborg and co-workers\textsuperscript{13} demonstrated that PVO\textsubscript{2}\textsuperscript{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\textsubscript{2}\textsuperscript{max} to quantify exercise intensity. The ordinary differential equation for PVO\textsubscript{2}\textsuperscript{max} is given by

\[
\frac{dPVO_2^{\text{max}}}{dt} = -0.8PVO_2^{\text{max}}(t) + 0.8u_3(t);
\]

\[
PVO_2^{\text{max}}(0) = 0.
\]

Here, PVO\textsubscript{2}\textsuperscript{max} is the exercise level as experienced by the individual, and \(u_3(t)\) is the ultimate exercise intensity above the basal level—an input to the model spanning 0 to 92%. The parameter value of 0.8 (1/min) was selected to achieve PVO\textsubscript{2}\textsuperscript{max}(t) settling time of approximately 5 minutes.

### Minimal Exercise Model

Physiological exercise induces several fundamental metabolic changes in the body.\textsuperscript{14} Elevated physical activity promotes a drop in plasma insulin concentration from its basal level.\textsuperscript{12} Dog studies conducted by Wasserman and colleagues\textsuperscript{15} found that an insulin clamp at its basal level disrupted the glucose homeostasis of the dogs during exercise. Similar trends have been observed in human studies.\textsuperscript{13,16}

An increase in exercise intensity also amplifies glucose uptake by the working tissues.\textsuperscript{17} In order to maintain plasma glucose homeostasis, hepatic glucose release also increases with increasing work intensity.\textsuperscript{18} During a mild-to-moderate work load, the major source of increased splanchnic glucose release is contributed by elevated hepatic glycogenolysis. As the duration of exercise increases, the rate of hepatic glycogenolysis diminishes because of the limited supply of liver glycogen stores.\textsuperscript{19} Simultaneously, hepatic gluconeogenesis is stimulated.\textsuperscript{20} However, the rate of glucose produced via liver gluconeogenesis does not fully compensate for the decrease in glucose release by liver glycogenolysis (the former is a slower process), thereby resulting in a net decrease in hepatic glucose release during prolonged exercise.\textsuperscript{21} Because of this imbalance between glucose uptake and hepatic glucose release, the plasma glucose concentration declines and hypoglycemia occurs.\textsuperscript{19,20} As an added complication in glucose regulation, studies have shown that liver glycogen content declines more rapidly with increasing exercise intensity.\textsuperscript{16,22}

During the recovery period after short-term exercise, both the elevated glucose uptake rate by working muscles and the rate of hepatic glucose release decline gradually to their respective basal levels. However, glucose fluxes after prolonged exercise are quite different. Because of the substantial depletion of liver glycogen stores...

### Table 1. Parameters of the Bergman Minimal Model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Unit</th>
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<td>(\rho_1)</td>
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</tr>
<tr>
<td>(\rho_2)</td>
<td>0.05</td>
<td>1/min</td>
</tr>
<tr>
<td>(\rho_3)</td>
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<td>ml/μU·min(^2)</td>
</tr>
<tr>
<td>(\rho_4)</td>
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<td>1/ml</td>
</tr>
<tr>
<td>(n)</td>
<td>0.142</td>
<td>1/min</td>
</tr>
<tr>
<td>(Vol_g)</td>
<td>117.0</td>
<td>dl</td>
</tr>
<tr>
<td>(G_b)</td>
<td>80.0</td>
<td>mg/dl</td>
</tr>
</tbody>
</table>

**Quantitating Exercise Intensity**

The maximum rate of oxygen consumption for an individual during exercise is given by VO\textsubscript{2}\textsuperscript{max} (ml/kg/min). Oxygen consumption is approximately linearly proportional to energy expenditure.\textsuperscript{11} Hence, it is possible to indirectly measure the maximum capacity of an individual for aerobic work by measuring oxygen consumption. When physical activity is expressed as a percentage of VO\textsubscript{2}\textsuperscript{max} (PVO\textsubscript{2}\textsuperscript{max}), exercise effects may be compared between individuals of the same sex and similar body weight at the same PVO\textsubscript{2}\textsuperscript{max}. The average PVO\textsubscript{2}\textsuperscript{max} for a person in the basal state is 8%\textsuperscript{12}. Ahlborg and co-workers\textsuperscript{13} demonstrated that PVO\textsubscript{2}\textsuperscript{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\textsubscript{2}\textsuperscript{max} to quantify exercise intensity. The ordinary differential equation for PVO\textsubscript{2}\textsuperscript{max} is given by

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During the recovery period after short-term exercise, both the elevated glucose uptake rate by working muscles and the rate of hepatic glucose release decline gradually to their respective basal levels. However, glucose fluxes after prolonged exercise are quite different. Because of the substantial depletion of liver glycogen stores...
during prolonged exercise, the rate of glycogenolysis is suppressed significantly, leading to a net decrease in the hepatic glucose release rate. During the recovery period, the elevated muscle glucose uptake rate gradually declines to the basal level; however, the already suppressed net hepatic glucose release rate is elevated significantly as a consequence of an increase in hepatic gluconeogenesis. In vivo studies have revealed a significant increment in hepatic lactate consumption immediately after prolonged exercise, and this lactate serves as a substrate for enhanced postexercise gluconeogenesis.

The glucose and insulin dynamics, when coupled with the major exercise effects, are given mathematically by

\[
\frac{dI}{dt} = -nI(t) + p_x u_x(t) - I_x(t); \quad I(0) = I_b = \frac{p_x}{n} u_{ib} \tag{5}
\]

\[
\frac{dX}{dt} = -p_x X(t) + p_x[I(t) - I_b]; \quad X(0) = 0 \tag{6}
\]

\[
\frac{dG}{dt} = -p_x [G(t) - G_b] - X(t)G(t) + \frac{W}{Vol_G} [G_{prod}(t) - G_{gly}(t)] + \frac{W}{Vol_G} G_{up}(t) + u_{x}(t); \quad G(0) = G_b \tag{7}
\]

\[
\frac{dG_{prod}}{dt} = a_x PV_{O2}^x(t) - a_x G_{prod}(t); \quad G_{prod}(0) = 0 \tag{8}
\]

\[
\frac{dG_{up}}{dt} = a_x PV_{O2}^x(t) - a_x G_{up}(t); \quad G_{up}(0) = 0 \tag{9}
\]

\[
\frac{dI_x}{dt} = a_x PV_{O2}^x(t) - a_x I_x(t); \quad I_x(0) = 0 \tag{10}
\]

The insulin dynamics, Equation (5), have been modified from the Bergman minimal model, Equation (1), by adding the final term. Here, \(I(t)\) (µU/ml/min) is the rate of insulin removal from the circulatory system due to exercise-induced physiological changes. The plasma glucose dynamics, Equation (7), differ from Equation (3) of the Bergman minimal model by the addition of the following terms: \(W/Vol_G\) is the weight of the subject. Variables \(G_{gly}(t)\) (mg/kg/min) and \(G_{up}(t)\) (mg/kg/min) represent the rates of glycogenolysis and hepatic glucose production induced by exercise, respectively. \(W\) (kg) represents the weight of the subject. Variable \(G_{gly}(t)\) (mg/kg/min) represents the decline of the glycolysis rate during prolonged exercise due to the depletion of liver glycogen stores. The dynamics of hepatic glucose production, glucose uptake, and plasma insulin removal induced by exercise are represented in Equations (8), (9), and (10), respectively.

The rate of glycogenolysis \([G_{gly}(t)]\) starts to decrease when the energy expenditure exceeds a critical threshold value \(A_{TH}\), which is a function of exercise intensity and duration. \(A_{TH}\) can be represented mathematically as

\[
A_{TH} = u_3(t) t_{gly}(u_3(t)) \tag{11}
\]

where \(t_{gly}(u_3(t))\) is the duration of exercise that can be performed at intensity \(u_3(t)\) before the rate of hepatic glycolysis starts to decrease. The rate of hepatic glycogenolysis increases with increasing exercise intensity. Hence, \(t_{gly}(u_3(t))\) is a function of exercise intensity, as shown in Figure 2. A linear equation, decreasing with increasing work intensity, captures the dependence of \(t_{gly}(u_3(t))\) on \(u_3(t)\) as follows:

\[
t_{gly} = -1.152 ln u_3(t) + 87.471 \tag{12}
\]

By substituting Equation (12) into Equation (11),

\[
A_{TH} = -1.152 [ln u_3(t)]^2 + 87.471 u_3(t) \tag{13}
\]

Hence, the dynamics of glycogenolysis during prolonged exercise can be represented mathematically as follows:

\[
\frac{dG_{gly}}{dt} = \begin{cases} 
0 & A(t) < A_{TH} \\
\frac{T}{k} - \frac{G_{gly}(t)}{T} & A(t) \geq A_{TH}
\end{cases} \tag{14}
\]

Hence, the dynamics of glycogenolysis during prolonged exercise can be represented mathematically as follows:

\[
\frac{dG_{gly}}{dt} = \begin{cases} 
0 & A(t) < A_{TH} \\
\frac{T}{k} & A(t) \geq A_{TH}
\end{cases} \tag{14}
\]
where $A(t)$ is the integrated exercise intensity, $u_3(t)$, which is calculated by the following set of equations:

$$\frac{dA}{dt} = \begin{cases} u_3(t) & u_3(t) > 0 \\ -\frac{A(t)}{0.001} & u_3(t) = 0 \end{cases}.$$ (15)

With the onset of exercise ($u_3(t) > 0$), $A(t)$ will increase at a rate proportional to $u_3(t)$. At the end of physical activity ($u_3(t) = 0$), $A(t)$ will quickly return to its initial condition (which is zero). As long as $A(t)$ is less than the critical threshold value ($A_{th}$), enough glycogen is still available to maintain a sufficient rate of hepatic glucose release. However, once $A(t)$ reaches $A_{th}$, the rate of change of glycogenolysis rate starts to decline at a rate given by $k$ because of the depletion of available liver glycogen stores. The end of exercise (when $u_3(t)$ returns to zero), which is also the beginning of the recovery period, marks the commencement of repletion of glycogen stores via a continued elevation in the rate of hepatic gluconeogenesis. The time required for $G_{gly}$ to return to its basal value after exercise is governed by the pseudo-time constant $T_1$.

**Parameter Estimation**

Parameters for the minimal exercise model were estimated using nonlinear least squares, as described elsewhere. The normalized residual is obtained as

$$\chi^2 = \sum_{i=1}^{N} \left[ \frac{y_i - \bar{y}(t_i,a_1,\ldots,a_M)}{\sigma_i} \right]^2.$$ (16)

Here $y_i$ is the measured data at time $t_i$ which has standard deviation $\sigma_i$. The model prediction is given by $\bar{y}(t_i,a_1,\ldots,a_M)$, where $a_j$ represent model parameters, with $j \in [1,M]$. Equation (16) can be considered a weighted minimization over $N$ data points using $(1/\sigma^2)$ as weights. $\chi^2$ is often denoted as “weighted sum squared error,” and the aim is to estimate $a_j$ such that $\chi^2$ is minimized.

The quality of the model fits was assessed by measuring the statistical correlation between experimental data and model predictions using the $R^2$ technique. $R^2$ can be defined as

$$R^2 = 1 - \frac{\chi^2}{SST},$$ (17)

where $\chi^2$ is the weighted sum squared error from Equation (16) and $SST$ is the weighted sum of squares about the data mean. $SST$ can be calculated using the following equation:

$$SST = \sum_{i=1}^{N} \frac{[y_i - \bar{y}]^2}{\sigma_i},$$ (18)

where $N$ is the number of data points and $\bar{y}$ is the grand mean of all data points. $R^2$ takes values between 0 and 1, with a value closer to 1 indicating a better fit. Calculated $R^2$ values for every model fit and validation are provided in the figure legends.

**Experimental Data from Literature Used in Parameter Estimation**

Data from Wolfe and colleagues were used to investigate the plasma insulin dynamics during exercise, where healthy subjects performed a continuous bicycle exercise for 60 minutes ($P_{VO2}^{max} = 40$). Blood samples were taken at regular intervals to measure the plasma insulin level. In order to capture the depletion of plasma insulin during exercise and its repletion during the recovery period, parameters $a_5$ and $a_6$ in Equation (10) were estimated (Figure 3). After fixing $a_5$ and $a_6$, 95% confidence intervals (CI) were calculated by using the nlparci.m function from the MATLAB Statistics Toolbox (©2006 The MathWorks Inc., Natick, MA). Data from a separate study by Ahlborg et al. were used to validate the insulin model (see Figure 4), where healthy subjects performed light exercise ($P_{VO2}^{max} = 30$) for 120 minutes, and the removal of plasma insulin from the circulatory system was observed.
In the glucose model, parameters $a_3$ and $a_4$ for the $G_{up}$ [Equation (9)], along with their 95% CIs (calculated using the nlparsi.m MATLAB function), were estimated from data collected by Wolfe and colleagues\textsuperscript{16} (see Figure 5, top). In this study, healthy subjects performed mild bicycle exercise ($PVO_2^{\text{max}} = 40$) for 60 minutes. Blood samples were obtained at regular intervals to measure the changes in glucose uptake rate ($G_{up}$, mg/kg/min) and hepatic glucose production rate ($G_{prod}$, mg/kg/min) during and after exercise. After fixing $a_3$ and $a_4$, parameters $a_1$ and $a_2$ for $G_{prod}$ [Equation (8)] were estimated from the same data set\textsuperscript{16} (see Figure 5, bottom). Using the same technique as for $a_3$ and $a_4$, 95% CIs were calculated for $a_1$ and $a_2$. After fixing parameters $a_{1-6}$ and their 95% CIs, model estimation of plasma glucose was compared with data obtained from the same study\textsuperscript{16} (see Figure 6).

For validation of the glucose model, model predictions of $G_{prod}$, $G_{up}$, and $G$ were compared with data from another exercise study performed by type 1 diabetes mellitus (T1DM) patients conducted by Zinman and colleagues\textsuperscript{25} (see Figures 7 and 8). Here, T1DM patients performed moderate level exercise on a bicycle ergometer for 45 minutes at $PVO_2^{\text{max}} = 50$. Blood samples were taken at regular intervals to measure $G_{up}$, $G_{prod}$, and $G$.

Finally, the effects of glycogen depletion during prolonged exercise and recovery were modeled. In order to capture these effects, data from Ahlborg and colleagues\textsuperscript{20} were used to estimate the parameters $k$ and $T_1$ only, from Equation (14) (see Figure 9). In this study, 12 healthy subjects underwent mild exercise ($PVO_2^{\text{max}} = 30$) on a bicycle ergometer for 2 hours. Plasma glucose was measured throughout the course of exercise and during a 40-minute postexercise recovery period. After estimating $T_1$ and $k$, the MATLAB function nlparsi.m was used to calculate 95% CIs for these parameters. For further validation of the model during prolonged exercise, plasma glucose concentration was compared with data from another study performed by...
Ahlborg et al.,19 where healthy subjects performed exercise at a higher intensity \( \text{PVO}_2^{\text{max}} = 60 \) (see Figure 10). Blood samples were taken during and after the exercise to measure plasma glucose concentration. All the parameter values, along with their \( 95\% \) CIs for the minimal exercise model, are given in Table 2.

Simulations in Figures 3, 5, 6, and 9 include confidence interval bounds (dotted lines) on the output profile of interest (e.g., \( I, G, G_{\text{wp}}, G_{\text{prod}} \) and \( [G_{\text{prod}} - G_{\text{gly}}] \)). These bounds are “worst case” bounds, in that the induced effect of multiple parameter uncertainty was maximized by selecting parameter pairs that lead to the largest possible deviation from the nominal profile.
Table 2. Parameters of the Minimal Exercise Model with 95% Confidence Intervals (CI), in Addition to Those in Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
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<th>Lower limit 95% CI</th>
<th>Upper limit 95% CI</th>
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<td>$a_1$</td>
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<td>$a_4$</td>
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<td>$a_5$</td>
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<td>$k$</td>
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<td>$T_1$</td>
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Results

Plasma Insulin Dynamics during Exercise

A simulation study of mild exercise (PVO$_{2\text{max}}$ = 40) for 60 minutes was performed to evaluate the physiological effects of exercise on plasma insulin concentration. With the onset of exercise, plasma insulin declined from its basal state (12.2 µU/ml) and continued to do so along a first-order-type response trajectory until the end of the experiment, as shown in Figure 3. During the recovery period (t > 60 minutes), the plasma insulin concentration climbed back to its basal level. Quantitatively, model predictions were consistently within one standard deviation of the mean of experimental data from which the relevant parameters ($a_s$ and $a_g$) were estimated. The 95% CI bounds of plasma insulin concentration were simulated by choosing a set of parameter values from Table 2 that had the maximum underestimation ($a_s = 0.0015$, $a_g = 0.0019$, $a = 0.0013$, $a_g = 0.0617$) and maximum overestimation ($a_s = 0.0024$, $a_g = 0.0355$) of plasma insulin concentration, as shown in Figure 3 (dotted lines).

For validation of the model, a separate simulation study was performed by keeping the parameter values of $a_s$ and $a_g$ unchanged and using a different exercise intensity level (PVO$_{2\text{max}}$ = 30) and a longer time duration (t$_{ex} = 0$ to 120 minutes). With the onset of exercise, the insulin level declined well below the basal level (10.2 µU/ml); this hypoinsulinemic state persisted until the end of the experiment. A comparison between model prediction of insulin and experimental data on the same exercise protocol is shown in Figure 4. Plasma insulin gradually returned back to the basal level during the recovery period (t > 120 minutes). Overall, the insulin model fits the experimental data sets.

Plasma Glucose Dynamics during Exercise

To evaluate the exercise effects on plasma glucose concentration, a 60-minute simulation study of mild exercise was performed (PVO$_{2\text{max}}$ = 40). With the onset of exercise, G$_{sp}$ increased from its basal state to 1.15 mg/kg/min. During the recovery period (t > 60 minutes), G$_{sp}$ returned to its basal level. Model prediction of G$_{sp}$, along with experimental data on the same exercise protocol from which parameters $a_s$ and $a_g$ were estimated, is shown in Figure 5 (top). The 95% CIs of G$_{sp}$ were simulated by choosing a set of parameter values from Table 2 that had the maximum underestimation ($a_s = 0.0015$, $a_g = 0.0617$) and maximum overestimation ($a_s = 0.0024$, $a_g = 0.0355$) of glucose uptake rate, as shown by the dotted lines in Figure 5 (top). In order to maintain plasma glucose homeostasis, the hepatic glucose production rate (G$_{prod}$ mg/kg/min) also increased from its basal level to 0.95 mg/kg/min for the duration of exercise. In conjunction with the glucose uptake rate, G$_{prod}$ decreased to its basal level after the end of exercise. Parameters $a_s$ and $a_g$ were estimated to fit the data, as shown in Figure 5 (bottom). Again, 95% CIs of G$_{prod}$ were simulated by choosing a set of parameter values from Table 2 that had the maximum underestimation ($a_s = 0.0013$, $a_g = 0.0679$) and maximum overestimation ($a_s = 0.0019$, $a_g = 0.0441$) of glucose production rate, as shown by the dotted lines in Figure 5 (bottom). Both G$_{sp}$ and G$_{prod}$ are represented in deviation form in Figure 5.

The accelerated glucose uptake rate during exercise is compensated for by enhanced hepatic glucose production; hence, normoglycemia is maintained throughout the course of physical activity. A comparison between the model prediction of glucose concentration, including G$_{sp}$ plus G$_{prod}$ effects, and experimental data is provided in Figure 6. The predictions of the glucose model are in good accordance with published data. In order to simulate the 95% CIs for plasma glucose concentration, a combination of parameter values were chosen from Table 2 that generated the maximum underestimation ($a_s = 0.0013$, $a_g = 0.0679$, $a_s = 0.0024$, $a_g = 0.0355$, $a_s = 0.001$, $a_g = 0.0912$) and maximum overestimation ($a_s = 0.0019$, $a_g = 0.0441$, $a_s = 0.0015$, $a_g = 0.0617$, $a_s = 0.0015$, $a_g = 0.0588$) of plasma glucose, as indicated by the dotted lines in Figure 6.

For validation of the glucose model, another simulation test was performed using a 45-minute bout of moderate-level exercise (PVO$_{2\text{max}}$ = 50). Again, with the onset of exercise, both G$_{sp}$ and G$_{prod}$ increased. During the recovery period (t > 45 minutes), G$_{sp}$ and G$_{prod}$ gradually declined to.
their respective basal levels. Model validation simulations (i.e., no model parameter changes) are plotted alongside experimental data of TIDM patients in Figure 7, top and bottom (both in deviation form). Figure 8 shows the model prediction of plasma glucose concentration, including the combined effects of $G_{up}$ and $G_{prod}$ during exercise, along with experimental data.

To evaluate the plasma glucose dynamics during prolonged exercise, data from Ahlborg et al. were considered (see Figure 9). With the onset of exercise, both $G_{up}$ and $G_{prod}$ rates were elevated from the basal level; this resulted in the maintenance of glucose homeostasis during the first hour of exercise. As the integrated exercise intensity exceeded a critical threshold (which is a function of exercise intensity and duration), the hepatic glycogenolysis rate started to decline as a result of which net liver glucose production rate, $|G_{prod} - G_{gly}|$, decreased until the end of exercise (Figure 9, bottom). However, $G_{up}$ remained elevated because of continuing physical activity (Figure 9, middle). This mismatch between $G_{up}$ and $G_{prod}$ resulted in a net decrease of plasma glucose level (Figure 9, top). During the postexercise recovery period, lactate consumption by the liver increased significantly, serving as a substrate for accelerated postexercise gluconeogenesis. It is believed that the purpose of this elevated gluconeogenesis is to replete the liver glycogen stores and restore normoglycemia. Keeping parameters $a_{1-6}$ unchanged, parameters $k$ and $T_1$ from Equation (14) were adjusted to capture the dynamical behavior of plasma glucose concentration. To simulate the 95% CIs for plasma glucose concentration during prolonged exercise, the same combination of parameter values was chosen from Table 2 as in Figure 6, with the addition of $(k = 0.0131, T_1 = 10.14)$ for maximum underestimation and $(k = 0.0085, T_1 = 1.86)$ for maximum overestimation, as shown by the dotted lines in Figure 9 (top). To simulate the CIs for $G_{up}$, the same parameter value sets as those used in Figure 5 (top) were chosen (see Figure 9, middle). Finally, to simulate the 95% CIs of net liver glucose production rate, a combination of parameter values were chosen from Table 2 to generate the maximum underestimation ($a_1 = 0.0013, a_2 = 0.0679, k = 0.0131, T_1 = 10.14$) and maximum overestimation ($a_1 = 0.0019, a_2 = 0.0441, k = 0.0085, T_1 = 1.86$) of $|G_{prod} - G_{gly}|$, as shown by the dotted lines in Figure 9 (bottom).

In order to validate the model during prolonged exercise, a separate simulation study was performed where exercise was performed for 3 hours at a moderate exercise intensity ($PVO_{2\text{max}} = 60$). Because of the higher exercise intensity, glycogen stores depleted at a faster rate; the result is an inability to maintain glucose homeostasis beyond $t_{ex} = 30$ minutes (see Figure 10, top). A comparison between model simulations (without changing any parameters) and data is given in Figure 10.

**Discussion**

A model of exercise effects on plasma glucose–insulin dynamics was developed. The principal goal was to extend the Bergman minimal model by adding suitable dynamics to capture the observed physiological phenomenon induced by exercise. Based on validation data, the extended model is able to predict plasma glucose and insulin concentrations in response to mild-to-moderate exercise challenges. All the added equations in the proposed model are linear in nature, thus maintaining the simplistic approach of the original minimal model. 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 [Equation (9)] and hepatic glucose production [Equation (8)] made it possible to capture the simultaneous rise of these rates with the onset of short-term exercise in order to maintain glucose homeostasis. These equations were also successful in capturing the dynamics of glucose fluxes during the postexercise recovery period. As the integrated exercise intensity extends beyond a critical threshold (which is a function of exercise intensity and duration), a decline in splanchnic glucose release is expected. As glucose uptake rate remains elevated, maintenance of glucose homeostasis is no longer possible. Because of this, plasma glucose continues to decline until the end of physical activity. At the end of prolonged exercise, the hepatic gluconeogenesis rate is increased, which facilitates the repletion of glycogen stores and helps achieve normoglycemia. A substantial amount of lactate is released from the postexercising muscles during the recovery period, which serves as a substrate for gluconeogenesis. To capture the dynamics of plasma glucose during the various stages of prolonged exercise, Equation (14) was incorporated. The model also successfully captured the clearance of plasma insulin from the circulatory system during physical exercise due to the addition of Equation (10).

With a focus on closed-loop insulin delivery systems for type 1 diabetic patients, it is necessary to develop models that can accurately predict plasma glucose concentration during rest, as well as during physical exercise. Hence, 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. The exercise model can also be used to predict the duration of exercise at a given intensity that can be executed while keeping plasma glucose within the normoglycemic range. However,
a prospective validation of the components of the minimal exercise model is necessary before the model, or a model-based controller, is employed in any clinical setting.

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References: