Dynamic Modeling and Model-Based Control of Exercise Disturbances in Type 1 Diabetic Patients

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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 type 1 diabetic patients. From a metabolic prospective, the significant metabolic changes in the body induced by exercise are: increased glucose uptake rate by the working tissues; increased hepatic glucose production to maintain overall glucose homeostasis; and decreased plasma insulin concentration. As a disturbance effect, extended-duration exercise leads to a decrease in hepatic glucose release; the result is an inability to maintain normoglycemia beyond a certain point during prolonged exercise periods. The minimal model developed by Bergman *et al.* [9] was extended to include the major effects on plasma glucose and insulin levels during and after exercise. Model predictions of glucose and insulin dynamics were consistent with the existing literature data. The exercise model was used in the synthesis of linear and nonlinear MPC algorithms for maintaining normoglycemia during and after mild-to-moderate exercise. The closed-loop result of both the MPCs indicated tight glucose control.

Introduction

Type 1 diabetes is a metabolic disease characterized by a lack of endogenous insulin secretion from pancreatic β-cells leading to wide blood glucose variation. It is important to maintain plasma glucose concentration within the normoglycemic range (70 - 120 *mg/dl*), in order to prevent major health complications [1, 2]. The insulin replacement therapy involves 3 to 4 times daily blood glucose measurement followed by subcutaneous insulin injection, usually corresponding to meal times and bed time. Such extensive insulin therapy proves to be inadequate to produce tight glucose control due to daily life activities (such as meal intake, exercise, *etc.*) that occur between the few glucose measurements. In order to produce

tighter glucose control, there is a focus on automated insulin delivery system which would be comprised of a continuous glucose measuring device, an insulin pump, and a control algorithm to govern the system. To have a reliable automated insulin delivery system operating under various physiological conditions, it is necessary to develop an accurate model which is capable of predicting blood glucose concentration at rest, as well as during physiological exercise.

Regulation of plasma glucose concentration for type 1 diabetic patients during exercise can prove to be challenging. Physiological exercise induces several fundamental metabolic changes in the body. Exercise up-regulates glucose uptake by the working muscles [4]. In order to maintain plasma glucose homeostasis, hepatic glucose production also increases with increasing work intensity [5]. During short-term exercise, a significant portion of elevated hepatic glucose production is sustained by accelerated glycogenolysis [5]. However, during prolonged exercise hepatic glycogen stores are depleted to such an extent that the glycogenolysis rate decreases and, as a result, glucose levels drop. During elevated physical activity, the plasma insulin concentration drops significantly below its basal level, which is essential to maintain glucose homeostasis. Studies performed in dogs [3] and humans [6] have revealed that preventing the drop in insulin during exercise can disrupt splanchnic glucose production. During the recovery period after short-term mild-to-moderate exercise, glucose uptake by the working muscles and hepatic glucose production decrease gradually, reaching basal levels within 40–50 *min* [8]. The glucose fluxes behave quite differently during recovery after prolonged exercise. Due to the reduction of glycogenolysis, overall hepatic glucose release is low at the end of prolonged exercise. Hepatic gluconeogenesis, the complement to glycogenolysis in liver glucose release, remains at its elevated level [6]. Liver uptake of lactate also rises significantly after prolonged exercise, with the lactate serving as a substrate for enhanced gluconeogenesis in order to restore normoglycemia [7].

The goal of the present work is to incorporate the fundamental effects of physiological exercise response into the Bergman minimal model [9] in order to capture the plasma glucose and insulin dynamics during and after mild-to-moderate exercise periods. In addition, linear and nonlinear model predictive controllers (MPC) are also synthesized based on the exercise model in order to maintain normoglycemia for simulated Type-1 diabetic patient during and after exercise.

Methods

The minimal model developed by Bergman *et al.* [9] was extended to include the major exercise effects on plasma glucose and insulin levels, as follows:

$$\frac{dI}{dt} = -nI(t) + p_5 u_1(t) - I_e(t) \tag{1}$$

$$\frac{dG}{dt} = -p_1[G(t)-G_b] - p_4X(t)G(t) + \frac{W}{Vol_G}[G_{prod}(t)-G_{gly}(t)] - \frac{W}{Vol_G}G_{up}(t) + \frac{u_2(t)}{Vol_G} \quad (2)$$

Equation (1) represents the plasma insulin dynamics. The only difference in this equation from [9] is the term $I_e(t)$, which captures the rate of insulin removal from the circulatory system due to exercise. The plasma glucose dynamics, represented by (2), differ from [9] by adding the terms $[(G_{prod}(t)-G_{gly}(t))-G_{up}(t)]$. Variables $G_{up}(t)$ and $G_{prod}(t)$ represent the rates of glucose uptake and hepatic glucose production induced by exercise, respectively. Variable $G_{gly}(t)$ represents the decline of glycogenolysis during prolonged exercise due to depletion of glycogen stores. Linear differential equations were added to capture the dynamics of $G_{up}(t)$, $G_{prod}(t)$, and $I_e(t)$ during exercise, and the dynamics of $X(t)$ are identical to [9]. The time dependent dynamics of $G_{gly}(t)$ were modeled as follows:

$$\frac{dG_{gly}}{dt}(t) = \begin{cases} 0 & ;t < t_{gly} \\ k & ;t \geq t_{gly} \\ -\frac{G_{gly}(t)}{T_1} & ;t \geq t_{stop} \end{cases} \quad (3)$$

Here, t_{gly} (min) is the exercise duration point at which glycogenolysis starts to decrease due to the depletion of hepatic glycogen stores and t_{stop} (min) indicates the end of prolonged exercise. When time, t, is less than t_{gly}, enough glycogen is available to maintain an accelerated rate of hepatic glucose release. However, once the duration of exercise exceeds t_{gly}, glycogenolysis starts to decrease at a constant rate given by k. The end of prolonged exercise ($t \geq t_{stop}$) indicates the commencement of recovery period where repletion of glycogen stores occur due to accelerated hepatic gluconeogenesis. Parameter T_1 represents the time required to reach normoglycemia during the recovery period. Percentage of maximum rate of oxygen consumption (PVO_2^{max}) during exercise was used to quantify the intensity of exercise. A linear differential equation was incorporated in the model to capture the rise of PVO_2^{max} at the onset of exercise.

Two type of MPC algorithms (linear and nonlinear) were employed to close the loop for maintenance of normoglycemia during and after exercise. Taylor series expansion method was employed to linearize the exercise model in order to synthesize the linear MPC [12]. The MPC control algorithm solves an optimization problem at each time step [13]; the result is an optimal insulin delivery sequence that minimizes a user-specified objective function.

Results and Discussion

Data from [10] was used to estimate the parameters of the glucose model in order to capture the effects of exercise on plasma glucose concentration (G, $\frac{mg}{dl}$), where healthy subjects performed mild bicycle exercise (PVO_2^{max} = 40) for 60 minutes. Blood samples were obtained at regular intervals to measure the changes in

glucose uptake rate (G_{up}, $\frac{mg}{kg-min}$) and hepatic glucose production (G_{prod}, $\frac{mg}{kg-min}$) during and after exercise. With the onset of exercise, both G_{up} and G_{prod} gradually increased from their basal states to 3.25 ± 0.25 $\frac{mg}{kg-min}$ and 3.15 ± 0.2 $\frac{mg}{kg-min}$, respectively. During the recovery period ($t > 60$ minutes), both the variables declined back to their basal levels. The dynamics of G_{up} and G_{prod} are represented in deviation form in Figure 1 (top) and (middle), respectively. A comparison between model prediction and experimental data [10] of plasma glucose concentration (G, $\frac{mg}{dl}$) is provided in Figure 1 (bottom). The predictions of the glucose model are in good accordance with the published data.

To evaluate the plasma glucose dynamics during prolonged exercise, data from [7] were considered, where twelve healthy subjects underwent mild exercise ($PVO_2^{max} = 30$) on a bicycle ergometer for 2 hours. Plasma glucose was measured throughout the course of exercise and during a 40 *min* post-exercise recovery period. As the duration of exercise extended beyond the first hour, hepatic glycogenolysis started to decline due to the depletion of available glycogen stores causing a mismatch between G_{up} and G_{prod}, thus resulting in a net decline of G. During the post-exercise recovery period, lactate consumption by the liver increases significantly, serving as a substrate for the accelerated post-exercise gluconeogenesis [11], in order to restore normoglycemia. The model prediction of plasma glucose during prolonged exercise and the restoration of normoglycemia during the post-exercise recovery period are shown in Figure 2.

Closed-loop simulation results are provided in Figure 3, where simulated patients underwent moderate intensity exercise ($PVO_2^{max} = 50$) for a prolonged period (120 *min*). Controller tunings were: $p = 10$, $m = 2$, $\Gamma_y = 1$, and $\Gamma_u = 0.1$; $\triangle T_s$ 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 $\triangle T_s$). Simulation results for both the linear and nonlinear MPC controllers indicated tight G control during the exercise disturbance, and a quick restoration of normoglycemia during the post-exercise recovery period.

Summary

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 (G_{up}) and hepatic glucose production (G_{prod}) 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 post-exercise recovery period. To capture the dynamics of plasma glucose during the various stages of prolonged exercise, variable G_{gly} was incorporated. This time-dependent effect occurred at a fixed time after exercise initiation and captured the decreasing liver glucose output due to the

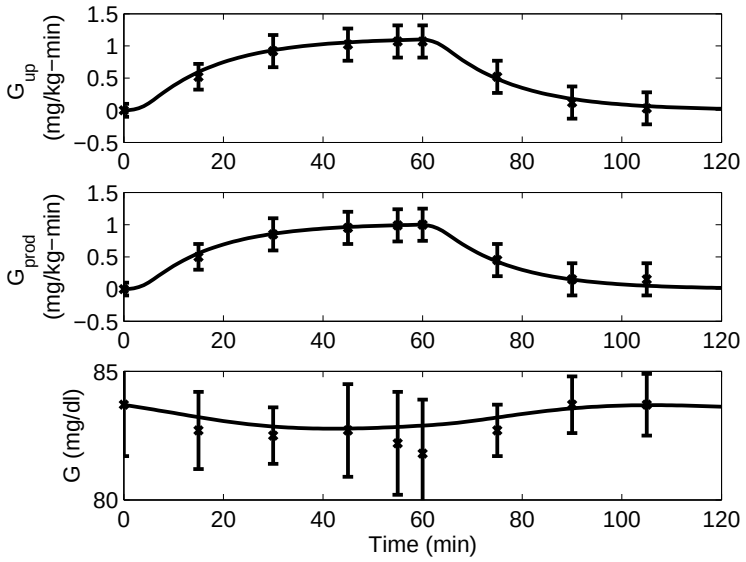

Figure 1: Model fit (—) versus published data (×) [10] in response to mild exercise (PVO_2^{max} = 40) which lasted from 0 to 60 minutes. Top: glucose uptake rate (G_{up}); Middle: hepatic glucose production rate (G_{prod}); Bottom: plasma glucose concentration (G). Both G_{prod} and G_{up} are shown in deviation form.

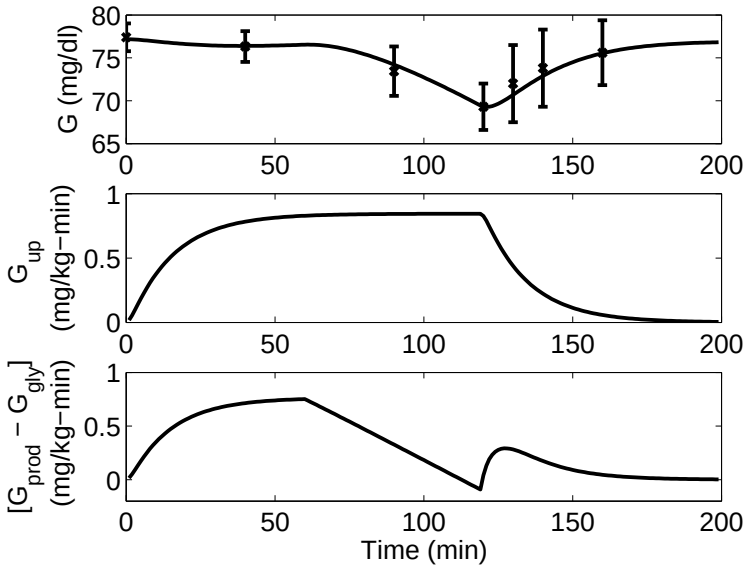

Figure 2: Model fit (—) versus published data (×) [7] in response to mild exercise (PVO_2^{max} = 30) which lasted from 0 to 120 minutes. Top: plasma glucose (G); Middle: hepatic glucose production rate (G_{prod}); Bottom: glucose uptake rate along with glycogen depletion [G_{up} - G_{gly}] (bottom). Both G_{prod} and [G_{up} - G_{gly}] are shown in deviation form.

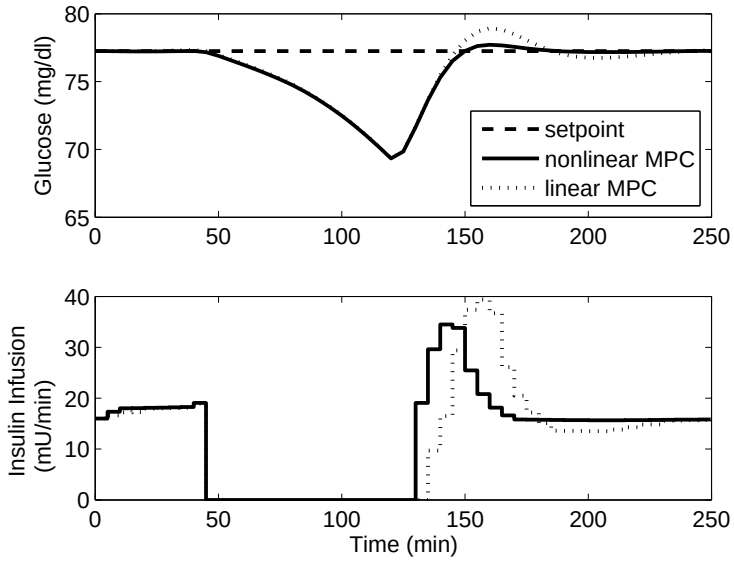

Figure 3: Nonlinear and linear MPC simulation results of moderate exercise (PVO_2^{max} = 50) which lasted from 0 to 120 minutes.

shift from glycogenolysis to gluconeogenesis. The model also successfully captured the removal of plasma insulin from the circulatory system during physiological exercise. The exercise model was used in the synthesis of linear and nonlinear MPC algorithms for maintaining normoglycemia during and after mild-to-moderate exercise. The closed-loop result of both the MPCs indicated tight glucose control.

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