ORIGINAL ARTICLE

Physical Activity Measured by Physical Activity Monitoring System Correlates with Glucose Trends Reconstructed from Continuous Glucose Monitoring

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Abstract

Background: In type 1 diabetes mellitus (T1DM), physical activity (PA) lowers the risk of cardiovascular complications but hinders the achievement of optimal glycemic control, transiently boosting insulin action and increasing hypoglycemia risk. Quantitative investigation of relationships between PA-related signals and glucose dynamics, tracked using, for example, continuous glucose monitoring (CGM) sensors, have been barely explored.

Subjects and Methods: In the clinic, 20 control and 19 T1DM subjects were studied for 4 consecutive days. They underwent low-intensity PA sessions daily. PA was tracked by the PA monitoring system (PAMS), a system comprising accelerometers and inclinometers. Variations on glucose dynamics were tracked estimating first- and second-order time derivatives of glucose concentration from CGM via Bayesian smoothing. Short-time effects of PA on glucose dynamics were quantified through the partial correlation function in the interval (0, 60 min) after starting PA.

Results: Correlation of PA with glucose time derivatives is evident. In T1DM, the negative correlation with the first-order glucose time derivative is maximal (absolute value) after 15 min of PA, whereas the positive correlation is maximal after 40–45 min. The negative correlation between the second-order time derivative and PA is maximal after 5 min, whereas the positive correlation is maximal after 35–40 min. Control subjects provided similar results but with positive and negative correlation peaks anticipated of 5 min.

Conclusions: Quantitative information on correlation between mild PA and short-term glucose dynamics was obtained. This represents a preliminary important step toward incorporation of PA information in more realistic physiological models of the glucose–insulin system usable in T1DM simulators, in development of closed-loop artificial pancreas control algorithms, and in CGM-based prediction algorithms for generation of hypoglycemic alerts.

Introduction

IN HEALTHY SUBJECTS THE BLOOD GLUCOSE concentration is tightly controlled by a hormonal feedback network, ensuring stable glycemic levels (80–150 mg/dL) and transient limited fluctuations, despite external perturbations, such as meals and physical activity (PA). Indeed, insulin inhibits hepatic glucose production and stimulates glucose uptake by insulin-dependent tissues (principally muscles and adipose tissue). In type 1 diabetes mellitus (T1DM) lack of endogenous insulin secretion necessitates exogenous insulin administration. Intensive insulin therapy designed to maintain tight glucose control to limit diabetes complications unavoidably increases the risk of severe hypoglycemia.^{1,2} Another critical factor that hinders the achievement of optimal glycemic

control is PA, which is known to lower the risk of cardiovascular complications but also causes transient changes in physiological parameters related to glucose–insulin dynamics, increasing insulin sensitivity³ and, consequently, the risk of hypoglycemia. As is understandable, an accurate description of the effect of all these variables on glucose dynamics is crucial to ameliorate therapies for diabetes.

Recently, the introduction of real-time continuous glucose monitoring (CGM) sensors allowed improvement of glucose control and reduction of time spent in the hypo- and hyperglycemic range, thanks to the possibility of detecting hypo- and hyperglycemic events in real time,^{4–7} even if the reliability of CGM sensors is still suboptimal (see Sparacino et al.^{8,9} and Bequette¹⁰ for reviews and Facchinetti et al.¹¹ for the “algorithmically smart sensor” concept, recently proposed to

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overcome these limitations). The real-time availability of glucose measurements promoted the development of several applications aimed not only at detecting but also at preventing hypoglycemia, in both open and closed loop. For instance, glucose prediction algorithms, fed by CGM data streams¹² and coupled with alert generation systems, allow reducing the number and duration of hypoglycemic events, as recently demonstrated in a simulated environment.¹³ Furthermore, closed-loop control algorithms have been demonstrated to be effective in increasing glucose time in target, especially during the overnight period in which steady metabolic conditions are present.^{14–18} However, to be effective, all these CGM-based applications should be also able to describe changes in glucose dynamics caused by perturbing factors, such as meals, insulin injections, exercise, stress, etc. The relationship between these variations and meals/insulin information has been widely investigated in the literature,¹⁹ stimulating their inclusion in short-time glucose prediction algorithms^{20–23} and in control algorithms.^{24,25} Nevertheless, inclusion of PA information is still challenging because dealing with PA is, to the best of our knowledge, less explored, and models describing the effects of PA on glucose dynamics are mainly qualitative or validated on small datasets.

Availability of quantitative relationships between PA and glucose dynamics would thus be of help not only to improve glucose prediction algorithms fed by CGM, but also to develop more realistic physiological models of the glucose–insulin system usable in T1DM simulators, as well as to design and test closed-loop control algorithms able to successfully handle effects of PA on glucose dynamics both during and after exercise, which represents one of the major obstacles in the development of the artificial pancreas.¹⁴

So far, the effect of PA on glucose–insulin dynamics has been mainly approached in medical and biological investigational terms. Exercise has been shown to increase the availability of glucose transporter-4 by translocation to the cell membrane^{26–28} and increased transcription in muscle cells,^{29,30} and these changes were demonstrated to be associated with an increase in insulin sensitivity and in insulin-independent glucose uptake.^{3,28,31,32} However, these modifications, although qualitatively well established, are difficult to precisely quantify. Derouich and Boutayeb³³ proposed a simple mathematical model to roughly illustrate the role of PA in improving insulin sensitivity and blood glucose concentration by expanding the so-called minimal model of glucose kinetics.³⁴ Kim et al.³⁵ proposed an extensive mathematical model of the whole-body metabolism, able to predict fuel homeostasis during exercise by using hormonal control over cellular metabolic processes. This model was demonstrated to be able to simulate dynamic changes of hormonal signals and to predict metabolic responses in tissues during exercise. More recently, Breton³⁶ proposed a modification of the minimal model of Bergman et al.³⁴ valid during PA exploiting the heart rate signal, used as a marker of energy expenditure, to increase glucose uptake and modify long-lasting insulin action. This model was further extended taking into account PA duration and intensity³⁷ and preliminarily incorporated into a simulation model of the glucose–insulin system.³⁸

From this overview it emerges that, although effects of PA on glucose metabolism are qualitatively quite well developed, their quantification and incorporation into mathematical

models for topics including, for example, glucose prediction and T1DM simulation, are still existing problems. A limitation in dealing with this is the detection of moderate exercise periods, characterized by increased energy expenditure, by using changes in the heart rate signal. In fact, this signal depends on an individual's fitness level, status of autonomic nervous system, medications, and emotional or environmental stresses.³⁹ Furthermore, T1DM subjects often have autonomic neuropathy, resulting in reduced heart rate variability. In addition, hypoglycemia and a meal can alter heart rate, without concomitant PA. Recently the so-called PA monitoring system (PAMS), a system comprising accelerometers and inclinometers, was proposed to facilitate specific detection and quantification of PA, even at low intensity that mimics activities of daily living.⁴⁰

The purpose of this work is to investigate quantitatively the short-term correlation between glycemic trends and the PA-related signal returned by PAMS. Specifically, glucose concentration trends will be assessed by estimating, from CGM data, the time course of first- and second-order glucose time derivatives, which represent, respectively, how glucose concentration is changing over time and how such a rate of change is itself changing.

Subjects and Methods

Database and protocol

Data used for this analysis were collected in the Clinical Research Unit at the Mayo Clinic (Rochester, MN) as part of an inpatient study designed to detect glycemic patterns and postprandial insulin sensitivity in control and T1DM subjects, in the presence of mild PA.⁴¹ Twenty control and 19 T1DM individuals were studied for 88 h. Each day they were fed with three meals, each one containing approximately 50 g of carbohydrates and similar macronutrient and calorie compositions, without differences between meals or between days. C-peptide-negative T1DM subjects were using an insulin pump and administered an insulin bolus with meals. Each day subjects took part in four to six consecutive sessions of low-intensity PA in which they alternated 26.5 min of walking on a treadmill at 1.2 mph with 33.5 min of sitting. The distance covered daily varied from 3.5 to 4.2 miles. It is noteworthy that the walking velocity was chosen to be consistent with median free-living walking velocity because the protocol wanted to mimic activities of daily living.

PA data were collected using PAMS, a system that captures data on body posture and movements continuously every half second for up to 10 consecutive days.^{40,42,43} The PAMS comprises two tri-axial accelerometers (each captures motion along three orthogonal axes) and four inclinometers (each captures two axes of acceleration against the gravitational field of the Earth) for recording body posture and movements. As schematized in Figure 1 of Levine et al.,⁴⁴ the two accelerometers were placed over the base of the spine; the inclinometers were attached to the left and right outer aspect of the trunk and the left and right outer aspect of the thigh. Specially designed underwear was used to attach the sensors. The accelerometers measure PA data along three orthogonal axes (x , y , z), with the dynamic range to ± 2 g (with g gravitational acceleration). The outcome PAMS signal, expressed in activity units, is obtained summing the instantaneous acceleration over epochs of 1 min.^{44,45}

FIG. 1. (top panels) Continuous glucose monitoring (CGM) time series and **(bottom panels)** physical activity (PA) monitoring system (PAMS) measurements during two workout sessions of a representative subject with type 1 diabetes mellitus (T1DM). Walking sessions are highlighted in gray. AU, activity units.

Glucose concentration was monitored continuously with the DexCom (San Diego, CA) SEVEN[®] Plus CGM sensor, a device with expected accuracy measured by mean absolute relative deviation around $16.5 \pm 6.7\%$.⁴⁶ Figure 1 shows two typical pieces of data, measured in a T1DM subject, with walking sessions highlighted in gray; the top panels represent the CGM time course, whereas the bottom panels show the PAMS signal.

Data preprocessing

Changes in glucose dynamics were quantified by computing the first- and second-order time derivatives of glucose concentration. In particular, a Bayesian smoothing approach, similar to that already used by Facchinetti et al.^{47,48} to denoise CGM data, was used to face ill-conditioning of derivatives calculation and limit artifacts due to measurement noise affecting CGM readings. Some details on the method and its implementation are reported in the Appendix. For readers with limited mathematical background, it might be useful to clarify that the first-order time derivative represents a rate of change, whereas the second-order time derivative represents an acceleration. Thus, for example, a positive glucose concentration first-order time derivative at a certain time t indicates that glucose concentration at time t is increasing. If, at the same time t , the glucose concentration second-order time derivative is positive, the increase of glucose concentration over time is becoming steeper; otherwise, if the glucose concentration second-order time derivative is negative, the slope of glucose concentration is dropping. Because we wished to assess the effects of PA on variations of glucose dynamics, quantified via first- and second-order glucose time derivatives, only pieces of data relative to consecutive PA sessions (i.e., repetitions of 26.5 min of active time and 33.5 min of sedentary time) were considered, without including any long sedentary period. In the rest of this article, we will refer to these portions of data as workout sessions. According to the protocol, for each patient three or four workout sessions were recorded. In addition, a time alignment of the signals was performed; this procedure simply consisted of down-sampling PAMS recordings whose original sampling time was of 1 min, considering only those values measured at the same time instants at which the CGM signal, whose sampling time was 5 min, was also available.

Partial correlation analysis

For each workout session, the relationship between PAMS and glucose concentration derivatives was quantified by partial correlation computed at various time shifts (τ) in the range of 0–60 min. We could not choose time shifts greater than 60 min because of constraints of our protocol; indeed, because the subject starts a PA session (walking on treadmill plus resting) every hour, restricting our analysis to time shifts shorter than or equal to 60 min is essential to avoid superimposition of effects of consecutive PA sessions. Partial correlation measures the degree of association between two signals, removing the effect of a set of controlling signals. Specifically, the controlling signals were CGM-, meal-, and insulin (the last one only for T1DM patients)-related information. In particular, meal intakes were preprocessed with

the physiological model⁴⁹ to generate carbohydrate rate of appearance in the blood, whereas insulin dosages were used to calculate the so-called insulin on board with the formulas described by Patek et al.⁵⁰ Using partial instead of conventional correlation guarantees that results are not affected by any collateral effects of glucose concentration value, meal, or insulin injections and that results quantify exclusively the correlation between PAMS and glucose derivatives.

Mathematically, the partial correlation between X (in our case PAMS) and Y (in our case first- or second-order glucose derivative), given a set of n controlling variables $Z = \{Z_1, Z_2, \dots, Z_n\}$ (in our case, CGM, meal rate of appearance, and insulin on board), indicated as $\rho_{XY,Z}$, is the correlation between the residuals r_X and r_Y resulting from the linear regression of X with Z and of Y with Z , respectively. Solving the linear regression problem requires finding the n -dimensional weight vectors

$$\begin{aligned} \omega_X^* &= \arg \min_{\omega} \left\{ \sum_{i=1}^N (x_i - \langle \omega, z_i \rangle)^2 \right\} \\ \omega_Y^* &= \arg \min_{\omega} \left\{ \sum_{i=1}^N (y_i - \langle \omega, z_i \rangle)^2 \right\} \end{aligned} \quad (1)$$

where N is the length of the time series and $\langle \omega, z_i \rangle$ represents the internal product between vector ω and vector z_i . Given the weight vectors of Eq. 1, the residuals can then be computed as

$$\begin{aligned} r_{X,i} &= x_i - \langle \omega_X^*, z_i \rangle \\ r_{Y,i} &= y_i - \langle \omega_Y^*, z_i \rangle \end{aligned} \quad (2)$$

and the partial correlation is finally given by the formula

$$\hat{\rho}_{XY,Z} = \frac{N \sum_{i=1}^N r_{X,i} r_{Y,i} - \sum_{i=1}^N r_{X,i} \sum_{i=1}^N r_{Y,i}}{\sqrt{N \sum_{i=1}^N r_{X,i}^2 - (\sum_{i=1}^N r_{X,i})^2} \sqrt{N \sum_{i=1}^N r_{Y,i}^2 - (\sum_{i=1}^N r_{Y,i})^2}} \quad (3)$$

In the present contribution the partial correlation is computed using the MATLAB[®] R2011b Statistics Toolbox (Mathworks, Natick, MA). Before computing partial correlation coefficients, each time series v was normalized by subtracting the mean and dividing by the SD, that is, applying the formula

$$v_{\text{normalized}} = \frac{v - \text{mean}(v)}{\text{standard deviation}(v)} \quad (4)$$

so that it had zero mean and unitary variance. Note that partial correlation analysis was not computed during long sedentary periods. Indeed, those pieces of data are not informative because during non-activity periods the PAMS signal is very close to 0, smooth, and not affected by noise and artifacts that could trigger false PA sessions.

Results

Correlation between PAMS and first-order glucose derivative

Figure 2 shows four correlation curves between PAMS and the first-order glucose derivative, relative to the

FIG. 2. Four correlation curves between the physical activity monitoring system (PAMS) and the first-order glucose concentration time derivative computed for various time shifts τ in the range (0, 60 min). Continuous curves are relative to the two workout sessions shown in Figure 1; dotted curves are relative to the other two workout sessions for the same subject with type 1 diabetes mellitus shown in Figure 1.

representative subject with diabetes shown in Figure 1. Continuous curves correspond to the two workout sessions shown in Figure 1; dotted curves correspond to the other two workout sessions of that subject. As we can observe, at an individual level, all the four estimated correlation curves present a similar time course. In particular, there is a negative

correlation for τ lower than 30 min and a positive correlation for τ belonging to the interval (30, 50 min). The negative correlation is maximal, in absolute value, for τ equals 10–15 min, whereas the positive correlation reaches its maximum for τ equals 40–45 min. This means that the glucose concentration begins to decrease as the PA session starts and the subject begins walking, and the decrease is particularly evident after 10–15 min. Analogously, as the sitting period begins, the glucose concentration begins to increase again, and this increase is maximal after 10–15 min. It is interesting that the four curves show temporal dynamics very similar to each other, although their amplitudes are different. It is worth observing that, even if the glucose concentration was in different ranges during the two workout sessions plotted in Figure 1, correlation curves are not influenced, confirming the independence of first- and second-order derivative time courses from the absolute glucose concentration value.

Median results computed for the 19 T1DM and the 20 control subjects are graphically shown in Figure 3. In subjects with diabetes (Fig. 3, left), as observed in the representative example of Figure 2, there is a negative correlation between the first-order glucose concentration derivative and PAMS for τ lower than 30 min, with a maximum, in absolute terms, for τ equals 15 min. For τ in the range (30, 60 min) the correlation becomes positive and is maximal when τ equals 40–45 min. Results relative to control subjects (Fig. 3, right) are similar; however, the degree of correlation is smaller (in absolute terms), and correlation peaks are anticipated of 5–10 min compared with what we observed for T1DM. These results suggest that low-intensity PA decreases glucose concentration in the short term (approximately 15 min) and that as exercise stops glucose tends to increase in approximately 15 min.

FIG. 3. Median correlation curves (and 25th and 75th percentiles [dotted lines]) between the physical activity monitoring system (PAMS) and first-order continuous glucose monitoring derivatives, computed for (left) the 19 subjects with type 1 diabetes mellitus (T1DM) and (right) the 20 control subjects.

FIG. 4. Four correlation curves between the physical activity monitoring system (PAMS) and the second-order glucose concentration time derivative computed for various time shifts τ in the range (0, 60 min). Continuous curves are relative to the two workout sessions shown in Figure 1; dotted curves are relative to the other two workout sessions for the same subject with type 1 diabetes mellitus shown in Figure 1.

Correlation between PAMS and second-order glucose derivative

Figure 4 shows correlation curves between PAMS and the second-order glucose derivative relative to the four workout sessions of the same representative subject with diabetes shown in Figures 1 and 2. (Line meanings are as in Figure 2.) It

is noteworthy that correlation is, in absolute terms, lower than for the first-order time derivative, but the various curves are coherent and present a well-defined time course (i.e., intra-individual variability is limited). Indeed, we can observe that the correlation is negative for τ lower than 15 min and reaches its maximum absolute value for τ equals 5 min; then it slowly increases becoming positive for τ in the range (20, 45 min) and is negative again for τ values belonging to (50, 60 min). These results imply that, as the PA session begins, almost instantaneously glucose rate-of-change becomes more negative or, at least, less positive. In practical terms, if the glucose concentration was increasing, it starts decreasing, or at least it continues to increase less rapidly than before starting to walk, whereas if the glucose concentration was decreasing, it decreases more rapidly. In contrast, after 30–35 min from the beginning of the PA session (i.e., as the sitting period begins), the CGM trend becomes less negative or more positive. In practical terms, if the glucose concentration was decreasing, it decreases less rapidly, or it begins increasing, whereas if it was increasing, it starts increasing more rapidly.

Median results are plotted in Figure 5 and are consistent with what we observed in Figure 4. In subjects with diabetes (Fig. 5, left) there is a negative correlation between PAMS and the second-order glucose derivative for τ lower than 20 min, and this correlation is maximal (in absolute terms) for τ equals 5 min, whereas there is a positive correlation for τ in the interval (25, 45 min), and this correlation is maximal for τ equals 35 min. In control subjects (Fig. 5, right) the degree of correlation is slightly lower (in absolute value), and correlation peaks are anticipated relative to T1DM patients. Results relative to correlation between PAMS and the second-order glucose concentration derivative suggest that, even in case the glucose concentration does not decrease during walking, at least it increases at a lower rate; furthermore, in case the

FIG. 5. Median correlation curves (and 25th and 75th percentiles [dotted lines]) between the physical activity monitoring system (PAMS) and second-order continuous glucose monitoring derivatives, computed for (left) the 19 subjects with type 1 diabetes mellitus (T1DM) and (right) the 20 control subjects.

glucose concentration does not increase during rest, at least it decreases less rapidly.

Discussion

PA has been demonstrated to have positive effects for T1DM subjects, lowering the overall risk of cardiovascular events in the long term.⁵¹ However, exercise in all forms can increase the risk of hypoglycemia during activity and post-exercise,⁵² rendering glucose control challenging.

A preliminary but necessary step before building quantitative models of PA effects on glucose concentration (e.g., for prediction or closed-loop control purposes) requires assessing the presence of correlation between these two variables. Indeed, the aim of the present article was to quantitatively assess if PA causes measurable variations of glucose dynamics and if those variations follow a typical pattern. For pursuing such a topic, we quantified correlation between mild PA that reproduces everyday life activity and glucose trends, the first measured using the PAMS signal and the second quantified estimating first- and second-order glucose time derivatives from the CGM signal. Results obtained for 19 T1DM and 20 control subjects confirm a tendency of glucose concentration to decrease during exercise and to increase during rest periods. It is interesting that correlation is higher, in absolute value, in T1DM than in control subjects, suggesting that in diabetes patients PA causes greater excursions of glucose concentration, as suggested by Manohar et al.⁴¹ Moreover, in diabetes subjects response to PA in terms of glucose dynamics modification is slower than in control subjects. This is very likely due to the fact that the impact of PA on glucose concentrations is dependent on prevailing insulin status, and a lower concurrent insulin level is reflected in T1DM by a higher glucose concentration for longer time periods. This can have immediate clinical implications for T1DM patients in open-loop therapy. Patients on multiple daily insulin injections may have to wait to increase PA until their blood glucose level is lower. Patients on continuous subcutaneous insulin infusion therapy with a high pre-PA glucose concentration can continue with their usual basal insulin during PA, whereas patients whose pre-PA glucose concentration is closer to their target glycemia should decrease their basal insulin. Currently, most providers advise their patients along similar lines. Accessory implications for closed-loop control can also be considered. In particular, the slower impact of PA on lowering the glucose level will have to be accounted for in PA modules developed for closed-loop algorithms based on model predictive control.

To conclude, our results indicate that, not surprisingly, PA affects glucose trends. Even if the correlation between PA and first- and second-order glucose concentration time derivatives exhibits some intra-individual variability, a certain regular pattern, displayed in Figures 3 and 5, is maintained. The presence of short-term correlation between changes in glucose dynamics and mild exercise suggests the potential utility of including PA information in short-time prediction models, to infer more precisely the future glucose concentration in the presence of PA. The ability of predicting effects of exercise on glucose concentration could be very helpful because it would allow adapting insulin infusion during and after PA and it could forewarn against hypoglycemic events, by alerting the patient before their occurrence. Furthermore,

the findings of the present study confirm the importance of modeling the effects of PA on the glucose–insulin system and incorporating them in simulators of T1DM patients, for designing closed-loop control algorithms able to improve artificial pancreas performance during changing metabolic conditions due to exercise. Of course, the effective quantitative incorporation of PA information within glucose predictors and closed-loop systems will require in-depth future investigations. For instance, with regard to prediction algorithms, PA information could be exploited to dynamically modulate the forgetting factor typically used in low-order time-varying autoregressive/polynomial models (e.g., the forgetting factor of simple time-varying prediction algorithms as those proposed by Eren-Oruklu et al.^{23,53} and Sparacino et al.⁵⁴ could be decreased in real time in the presence of PA).

From a clinical point of view, further studies should focus on longer sessions with higher levels of PA, investigating possibly both short- and long-term effects of strenuous exercise on the glucose concentration–time course. Moreover, because PAMS does not discriminate between different fitness levels, future protocols should also complement PAMS with additional information on the patient's fitness level (e.g., objective maximum O₂ volume measurements).

Appendix

Here we report some technical information on how the first- and second order time derivatives of glucose concentration are estimated. In a matrix-vector embedding, the N -size vector $\mathbf{y}$ containing the (uniformly spaced) CGM samples is modeled as

$$\mathbf{y} = \mathbf{G}\mathbf{u} + \mathbf{v} \quad (5)$$

where $\mathbf{u}$ is the N -size vector containing the samples of the (unknown) time derivative, $\mathbf{v}$ is the random vector of the measurement errors (assumed uncorrelated, with zero mean and constant unknown variance), and $\mathbf{G}$ is an N -size lower triangular square Toeplitz matrix having as its first column $T_s \cdot [1, 1, \dots, 1]$ or $T_s^2 \cdot [1, 2, \dots, N]$, respectively, if the vector of the first-order or second-order time derivative is estimated (T_s is the sensor sampling period). Because of ill-conditioning, least squares estimation of $\mathbf{u}$ given $\mathbf{y}$ in Eq. 5 is unreliable, and a Bayesian regularization approach,^{55,56} similar to that applied by Guerra et al.,⁵⁷ for glucose trend estimation from CGM data, is used. According to this approach, the estimated $\hat{\mathbf{u}}$ is computed as

$$\hat{\mathbf{u}} = (\mathbf{G}^T \mathbf{G} + \gamma \mathbf{F}^T \mathbf{F})^{-1} \mathbf{G}^T \mathbf{y} \quad (6)$$

where γ is the regularization parameter, whose value is determined according to a maximum likelihood/consistency criterion, and $\mathbf{F}$ is a squared N -size lower triangular Toeplitz matrix that, according to considerations on CGM data explained in detail by Facchinetti et al.,^{47,48} has a first column equal to $[1, -2, 1, 0, \dots, 0]^T$.

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Author Disclosure Statement

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References

- Cryer PE: Hypoglycemia: the limiting factor in the glycaemic management of Type I and Type II diabetes. *Diabetologia* 2002;45:937–948.
- The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977–986.
- Brun JF, Guinrand-Hugret R, Boegner C, Bouix O, Orsetti A: Influence of short-term submaximal exercise on parameters of glucose assimilation analyzed with the minimal model. *Metabolism* 1995;44:833–840.
- Battelino T, Philip M, Bratina N, Nimri R, Oskarsson P, Bolinder J: Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. *Diabetes Care* 2011;34:795–800.
- Chase H, Fiallo-Scharer R, Messer L, Gage V, Burdick P, Laffel L, Milaszewski K, Pratt K, Bismuth E, Keady J: Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med* 2008;359:1464–1476.
- Mauras N, Fox L, Englert K, Beck RW: Continuous glucose monitoring in type 1 diabetes. *Endocrine* 2013;43:41–50.
- Lane JE, Shivers JP, Zisser H: Continuous glucose monitors: current status and future developments. *Curr Opin Endocrinol Diabetes Obes* 2013;20:106–111.
- Sparacino G, Facchinetti A, Cobelli C: Smart continuous glucose monitoring sensors: on-line signal processing issues. *Sensors* 2010;10:6751–6772.
- Sparacino G, Zanon M, Facchinetti A, Zecchin C, Maran A, Cobelli C: Italian contributions to the development of continuous glucose monitoring sensors for diabetes management. *Sensors* 2012;12:753–780.
- Bequette BW: Continuous glucose monitoring: real-time algorithms for calibration, filtering, and alarms. *J Diabetes Sci Technol* 2010;4:404–418.
- Facchinetti A, Sparacino G, Guerra S, Luijck Y, Devries J, Mader J, Ellmerer M, Benesch C, Heinemann L, Bruttomesso D, Avogaro A, Cobelli C: Real-time improvement of continuous glucose-monitoring accuracy: the smart sensor concept. *Diabetes Care* 2013;36:793–800.
- Sparacino G, Facchinetti A, Maran A, Cobelli C: Continuous glucose monitoring time series and hypo/hyperglycemia prevention: requirements, methods, open problems. *Curr Diabetes Rev* 2008;4:181–192.
- Zecchin C, Facchinetti A, Sparacino G, Cobelli C: Reduction of number and duration of hypoglycemic events by glucose prediction methods: a proof-of-concept in silico study. *Diabetes Technol Ther* 2013;15:66–77.
- Breton M, Farret A, Bruttomesso D, Anderson S, Magni L, Patek S, Dalla Man C, Place J, Demartini S, Del Favero S, Toffanin C, Hughes-Karvetski C, Dassau E, Zisser H, Doyle FJ 3rd, De Nicolao G, Avogaro A, Cobelli C, Renard E, Kovatchev B; International Artificial Pancreas Study Group: Fully integrated artificial pancreas in type 1 diabetes: modular closed-loop glucose control maintains near normoglycemia. *Diabetes* 2012;61:2230–2237.
- Russell SJ, El-Khatib FH, Nathan DM, Magyar KL, Jiang J, Damiano ER: Blood glucose control in type 1 diabetes with a bi-hormonal bionic endocrine pancreas. *Diabetes Care* 2012;35:2148–2155.
- Phillip M, Battelino T, Atlas E, Kordonouri O, Bratina N, Miller S, Biester T, Stefanija MA, Muller I, Nimri R, Danne T: Nocturnal glucose control with an artificial pancreas at a diabetes camp. *N Engl J Med* 2013;368:824–833.
- Kumareswaran K, Evans ML, Hovorka R: Closed loop insulin delivery: towards improved diabetes care. *Discov Med* 2012;13:159–170.
- Weinzimer SA: Closed-loop artificial pancreas: current studies and promise for the future. *Curr Opin Endocrinol Diabetes Obes* 2012;19:88–92.
- Cobelli C, Dalla Man C, Sparacino G, Magni L, De Nicolao G, Kovatchev BP: Diabetes: models, signals and control. *IEEE Rev Biomed Eng* 2009;2:54–96.
- Finan D, Doyle F, Palerm C, Bevier W, Zisser H, Jovanovic I, Seborg D: Experimental evaluation of a recursive model identification technique for type 1 diabetes. *J Diabetes Sci Technol* 2009;5:1192–1202.
- Pappada SM, Cameron BD, Rosman PM, Bourey RE, Papadimos TJ, Olorunto W, Borst MJ: Neural network-based real-time prediction of glucose in patients with insulin-dependent diabetes. *Diabetes Technol Ther* 2011;13:135–141.
- Zecchin C, Facchinetti A, Sparacino G, De Nicolao G, Cobelli C: Neural network incorporating meal information improves accuracy of short-time prediction of glucose concentration. *IEEE Trans Biomed Eng* 2012;59:1550–1560.
- Eren-Oruklu M, Cinar A, Rollins D, Quinn L: Adaptive system identification for estimating future glucose concentrations and hypoglycemia alarms. *Automatica* 2012; 48:1892–1897.
- Bequette BW: Challenges and recent progress in the development of a closed-loop artificial pancreas. *Annu Rev Control* 2012;36:255–266.
- Dassau E, Zisser H, Harvey RA, Percival MW, Grosman B, Bevier W, Atlas E, Miller S, Nimri R, Jovanovic L, Doyle FJ 3rd: Clinical evaluation of a personalized artificial pancreas. *Diabetes Care* 2013;36:801–809.
- Goodyear LJ, Hirshman MF, Horton ES: Exercise-induced translocation of skeletal muscle glucose transporters. *Am J Physiol* 1991;261:E795–E799.
- Thorell A, Hirshman MF, Nygren J, Jorfeldt L, Wojtaszewski JF, Dufresne SD, Horton ES, Ljungqvist O, Goodyear LJ: Exercise and insulin cause GLUT-4 translocation in human skeletal muscle. *Am J Physiol* 1999;277:E733–E741.
- Henriksen EJ: Invited review: effects of acute exercise and exercise training on insulin resistance. *J Appl Physiol* 2002; 93:788–796.
- Dohm GL: Invited review: regulation of skeletal muscle GLUT-4 expression by exercise. *J Appl Physiol* 2002;93:782–787.
- Ren JM, Semenkovich CF, Gulve EA, Gao J, Holloszy JO: Exercise induces rapid increases in GLUT4 expression, glucose transport capacity, and insulin-stimulated glycogen storage in muscle. *J Biol Chem* 1994;269:14396–14401.
- Borghouts LB, Keizer HA: Exercise and insulin sensitivity: a review. *Int J Sports Med* 2000;21:1–12.
- Goodyear LJ, Kahn BB: Exercise, glucose transport, and insulin sensitivity. *Annu Rev Med* 1998;49:235–261.
- Derouich M, Boutayeb A: The effect of physical exercise on the dynamics of glucose and insulin. *J Biomech* 2002;35: 911–917.

34. Bergman RN, Ider YZ, Bowden CR, Cobelli C: Quantitative estimation of insulin sensitivity. *Am J Physiol* 1979;236: E667–E677.
35. Kim J, Saidel GM, Cabrera ME: Multi-scale computational model of fuel homeostasis during exercise. *Ann Biomed Eng* 2007;35:69–90.
36. Breton MD: Physical activity—the major unaccounted impediment to closed loop control. *J Diabetes Sci Technol* 2008;2:169–174.
37. Dalla Man C, Breton MD, Cobelli C: Physical activity into the meal glucose–insulin model of type 1 diabetes: in silico studies. *J Diabetes Sci Technol* 2009;3:56–67.
38. Kovatchev BP, Breton MD, Cobelli C, Dalla Man C: Method, system and computer simulation environment for testing of monitoring and control strategies in diabetes. Patent WO/2008/1577881. December 24, 2008.
39. Chen KY, Janz KF, Zhu W, Brychta RJ: Re-defining the roles of sensors in objective physical activity monitoring. *Med Sci Sports Exerc* 2012;44(1 Suppl 1):S13–S23.
40. Levine A, Lanningham-Foster LM, McCrady SK, Krizan AC, Olson LR, Kane PH, Jensen MD, Clark MM: Interindividual variation in posture allocation: possible role in human obesity. *Science* 2005;307:584–586.
41. Manohar C, Levine JA, Nandy DK, Saad A, Dalla Man C, McCrady-Spitzer SK, Basu R, Cobelli C, Carter RE, Basu A, Kudva YC: The effect of walking on postprandial glycemic excursion in patients with type 1 diabetes and healthy people. *Diabetes Care* 2012;35:2493–2499.
42. Levine JA, Baukol PA, Westerterp KR: Validation of the Tracmor triaxial accelerometer system for walking. *Med Sci Sports Exerc* 2001;33:1593–1597.
43. Levine J, Melanson EL, Westerterp KR, Hill JO: Tracmor system for measuring walking energy expenditure. *Eur J Clin Nutr* 2003;57:1176–1180.
44. Levine JA, McCrady SK, Lanningham-Foster LM, Kane PH, Foster RC, Manohar CU: The role of free-living daily walking in human weight gain and obesity. *Diabetes* 2008;57:548–554.
45. Manohar C, McCrady S, Pavlidis IT, Levine JA: An accelerometer-based earpiece to monitor and quantify physical activity. *J Phys Act Health* 2009;6:781–789.
46. Damiano ER, El-Khatib FH, Zheng H, Nathan DM, Russell SJ: A comparative effectiveness analysis of three continuous glucose monitors. *Diabetes Care* 2013;36:251–259.
47. Facchinetti A, Sparacino G, Cobelli C: An online self-tunable method to denoise CGM sensor data. *IEEE Trans Biomed Eng* 2010;57:634–641.
48. Facchinetti A, Sparacino G, Cobelli C: Online denoising method to handle intraindividual variability of signal-to-noise ratio in continuous glucose monitoring. *IEEE Trans Biomed Eng* 2011;58:2664–2671.
49. Dalla Man C, Camilleri M, Cobelli C: A system model of oral glucose absorption: validation on gold standard data. *IEEE Trans Biomed Eng* 2006;53:2472–2478.
50. Patek S, Magni L, Dassau E, Karvetski C, Toffanin C, De Nicolao G, Del Favero S, Breton M, Dalla Man C, Renard E: Modular closed-loop control of diabetes. *IEEE Trans Biomed Eng* 2012;59:2986–2999.
51. Burr JF, Shephard RJ, Riddell MC: Physical activity in type 1 diabetes mellitus. Assessing risks for physical activity clearance and prescription. *Can Fam Physician* 2012;58:533–535.
52. Riddell M, Perkins BA: Exercise and glucose metabolism in persons with diabetes mellitus: perspectives on the role for continuous glucose monitoring. *J Diabetes Sci Technol* 2009;3:914–923.
53. Eren-Oruklu M, Cinar A, Quinn L, Smith D: Estimation of future glucose concentrations with subject-specific recursive linear models. *Diabetes Technol Ther* 2009;11:243–253.
54. Sparacino G, Zanderigo F, Corazza S, Maran A, Facchinetti A, Cobelli C: Glucose concentration can be predicted ahead in time from continuous glucose monitoring sensor time-series. *IEEE Trans Biomed Eng* 2007;54:931–937.
55. De Nicolao G, Sparacino G, Cobelli C: Nonparametric input estimation in physiological systems: problems, methods and case studies. *Automatica* 1997;33:851–870.
56. Sparacino G, Cobelli C: A stochastic deconvolution method to reconstruct insulin secretion rate after a glucose stimulus. *IEEE Trans Biomed Eng* 1996;43:512–529.
57. Guerra S, Sparacino G, Facchinetti A, Schiavon M, Dalla Man C, Cobelli C: A dynamic risk measure from continuous glucose monitoring data. *Diabetes Technol Ther* 2011;13:843–852.

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