Characterization of Linear Predictability and Non-stationarity of Subcutaneous Glucose Profiles

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Abstract—Continuous glucose monitoring is increasingly used in the management of diabetes. Subcutaneous glucose profiles are characterized by a strong non-stationarity, which limits the application of correlation-spectral analysis. We derived an index of linear predictability by calculating the autocorrelation function of time series increments and applied detrended fluctuation analysis to assess the non-stationarity of the profiles. Time series from volunteers with both type 1 and type 2 diabetes and from control subjects were analysed. The results suggest that in control subjects, blood glucose variation is relatively uncorrelated, and this variation could be modelled as a random walk with no retention of 'memory' of previous values. In diabetes, variation is both greater and smoother, with retention of inter-dependence between neighboring values. Essential components for adequate longer term prediction were identified via a decomposition of time series into a slow trend and responses to external stimuli. Implications for diabetes management are discussed.

***Keywords* — Autocorrelation, Continuous glucose monitoring systems, Detrended fluctuation analysis, Diabetes Mellitus, Non-stationarity.**

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I. INTRODUCTION

Diabetes mellitus is a state of relative or absolute insulin deficiency, with or without insulin resistance [1]. Insulin is the hormone that controls blood glucose levels (glycaemia), and untreated diabetes is characterised by chronic hyperglycaemia (high levels of blood glucose). Control of hyperglycaemia is important to prevent long term complications, including effects on the eyes, kidneys, peripheral nerves, and cardiovascular system. Reduction of blood glucose levels through both lifestyle and pharmacological interventions is the main therapeutic goal in the management of diabetes. However, low levels (hypoglycaemia) are also dangerous, setting patients and their clinicians a difficult challenge: the achievement and maintenance of glycaemic stability.

People with diabetes are broadly categorised into ‘type 1’ and ‘type 2’. Individuals with type 1 become dependent on injected insulin at or soon after diagnosis and they have no tissue resistance to insulin. For type 1 diabetes the artificial pancreas approach (automated closed loop feedback between blood or subcutaneous glucose and insulin delivery) has attracted much attention with significant progress but many remaining challenges [2]. ‘Type 2’ is typically associated with obesity and insulin resistance, usually treatable without insulin but requiring insulin in a proportion of patients. The rising global prevalence of type 2 diabetes, due both to changes in lifestyle patterns and increasing life expectancy emphasizes the need for early detection and intervention in individual patients. In contrast to type 1 diabetes (where the artificial pancreas approach is of increasing interest), type 2 requires attention to the insulin resistance element which can be modified by lifestyle changes as well as drug therapy.

Glycaemic stability requires a satisfactory mean glucose value, a reasonably narrow range (typically between about 4.0 and 7 mmol L^{-1}), and additionally, an adequate time horizon over which blood glucose behaviour may be predicted into the future. This time horizon is related to the degree of inter-dependence (correlation) between neighboring glucose values in the profile.

Understanding the interconnection of glucose values in a profile and the predictability of future values are therefore important aspects of glycaemic control, enabling the individual to take appropriate corrective action.

Glycosylated haemoglobin (HbA1c) is the most commonly used index to characterize glycaemic control, and reflects average blood glucose values over 2-3 months [3]. However patients with similar HbA1c values may display very different dynamical patterns. Therefore, HbA1c is not an adequate measure of glycaemic stability and variability [3]. Determinants of glycaemic variation include carbohydrate intake, exercise, insulin levels, insulin sensitivity, and other factors.

Continuous monitoring [4] of subcutaneous glucose values taken every 3-5 minutes over several days provides a detailed picture of glucose variability. Such profiles have been shown to correlate well with blood glucose levels [3], although there is a lag between a change in blood value (e.g. after food intake) and the response of the subcutaneous value [3, 5].

The main obstacles to statistical analysis are that subcutaneous glucose time series are relatively short (few days), and their statistical characteristics demonstrate behaviour typical for non-stationary processes [6]. As a result, certain measures including power spectrum and autocorrelation function (ACF) [7, 8] are associated with significant errors and their use is questionable [9]. The term stationarity/non-stationarity refers to the underlying process, not to a particular realisation of it. Therefore, the property of ergodicity is usually assumed which considers a single realization (time series) to be representative of the entire stochastic process [6, 7, 10]. In order to characterize these properties, however such a single time series must be much longer than the longest characteristic time scale [6]. An obvious time scale in glucose profiles is diurnal periodicity, therefore typically available 24-72 hour time series cannot be used to assess the non-stationarity of the process in full. For such short realizations it is only possible to define whether a particular profile is stationary or not.

In this paper we consider glucose time-series as realizations of a non-stationary stochastic process with *stationary increments* [7, 8, 10, 11]. This enables us to remove non-stationarity and assess dynamical characteristics of the profiles. The aim is to develop descriptive non-parametric tools that are universally applicable to characterize linear predictability in subcutaneous profiles both of people with diabetes and controls. The non-stationarity itself is assessed through the use of detrended fluctuation analysis (DFA) [12].

Recent studies have used techniques in the *frequency* domain to take the non-stationarity of glucose profiles into account [13-15]. The Wigner-Ville distribution has been used [13] to illustrate the difference in time-frequency patterns for 24-hour profiles of 4 diabetic patients and 1 control. The wavelet based time-scale distribution has been presented [14] for two non-diabetic 24-hour profiles with different meal regimens. An interesting parametric technique involving frequency band decomposition and short-term forecasting using an autoregressive model has been applied to the 72-hour profiles of nine type 1 diabetic patients [15]. We will consider a non-parametric approach to assess data interconnections and predictability in the *time* domain.

DFA is a non-linear tool applicable to both stationary and non-stationary time series, and was initially suggested to characterize so-called long range correlation for processes with algebraic power-law ACF [12]: $\rho(\tau)\propto\tau^{-\eta}$, in the limit $\tau\to\infty$, i.e. when short-range correlation, for example, exponential form $\rho(\tau)\propto\exp(-\gamma\tau)$ of ACF is not applicable [11, 16]. DFA leads to a scaling index, α, which is less than 1 for a stationary process and greater than 1 for non-stationary [12]. Ogata et al [17] showed that DFA is able to discriminate healthy and diabetic groups and they concluded that glucose profiles show negative long-range correlation for healthy individuals and positive long-range correlation for diabetic patients (largely treated with insulin). While this result and others [18] confirm the usefulness of DFA for characterizing the complexity of glucose profiles, the use of DFA alone to characterize the long-range correlation is

a controversial issue [16]. We investigated the presence of long-range correlation in our glucose profiles by verifying power-law scaling in the ACF of increments of time-series.

A different use of DFA for characterizing the amplitude of fluctuations versus diffusion velocity of the non-stationary data has been suggested [19]. In this case, the value of α is compared with Brownian motion [19], an integrated white noise with uncorrelated increments for which the DFA index is α=1.5. Values of index $\alpha<1.5$ indicate the presence of a fast fluctuating irregular component in the data, and $\alpha>1.5$ indicates the presence of a slower stochastic component and stronger regularity.

Finally, we discuss possible origins and corresponding features of non-stationarity in glucose dynamics as well as essential components for adequate longer term prediction by decomposing the time series into the slow trend and meal time (prandial) events.

II. Materials and Methods

A. Data Collection

We collected data from 15 volunteers, including patients with type 1 and type 2 diabetes, and from controls with no diagnosis of diabetes. Recruitment was purposive to ensure a diverse sample of ages and treatment regimens. Baseline biographical data were obtained on age, sex, body mass index, type of diabetes, treatment regimen, and recent Hba1c value. Subcutaneous glucose values were taken every five minutes over 72 hours using the Medtronic Minimed CGMS (Continuous Glucose Monitoring System) [20]. Time series $G(t_i)=G_i$ are available for each volunteer. G_i mmol L^{-1} is the glucose concentration at time moments $t_i=ih$, where h=5 minutes is the sampling interval, i=1,2,…N and N specifies the length of time series. The participants were asked to keep a diary recording the timing of food intake and exercise. No restrictions were placed on their usual daily activities.

B. Descriptive Statistics of Glucose Time-Series

Each individual was identified as type 1, type 2, or control (without diabetes) based on their known diagnosis and treatment regimen. Continuous glucose monitoring gave us a detailed picture of glucose variability and was used to derive various indices [21]. One of them - standard deviation G_{std} characterises the amplitude of glucose level fluctuations with respect to the mean value, and has been used for diabetes diagnosis on basis of CGMS [21], although not in clinical practice. We consider G_{std} as a reference index and it was obtained using standard Matlab function *std*.

The Mann Whitney U test (matlab function *ranksum*) was performed to assess whether data from the different groups had similar values. The null hypothesis of no difference was tested [22] at the 5% level of significance.

C. The Autocorrelation Function of Differential Increments

ACF is a function that characterises a linear statistical dependence (correlation) between present and past values, defining a memory in the data [7, 8]. The strength of statistical dependence specifies a probability of a given value in future taking into account the prehistory, i.e. it reflects predictability. ACF has been applied to blood glucose time series [9, 23] to analyse linear predictability, but as mentioned above, a major obstacle is the existence of non-stationary behaviour.

To overcome the non-stationarity we considered each glucose profile as a realization of a stochastic process with stationary increments [7, 8, 10, 11]. This approach is an established technique for analysis of time series with a varying (non-stationary) mean value [7, 8]. However, it is very rarely used for characterization of bio-medical data. Because the first difference is a linear operation, the increments (and their ACF) preserve information about the trend. For example, if there is a periodic component, then the ACF of increments shows oscillations;

power-law scaling for long-range correlated processes will be observed in the ACFs of both initial time-series and time-series of first-differences.

As the first step, the presence of a trend in the initial time series and the stationarity of increments are confirmed via a corresponding statistical test of inversion [6], and by DFA. The presence of the trend can also be demonstrated via a decomposition approach described below. The second step involves representing the values from a glucose profile in the form $G_i = G_{i-1}+\Delta G_i$, where differential increments $\Delta G_i=G_i-G_{i\text{-}1}$ correspond to the first differences of G_i,. Since these increments ΔG_i are stationary, calculation of their ACF is straightforward.

ACF is defined by the following expression [6]

$$\rho(\tau_j)=\frac{\langle (X_i - X_{mean})(X_{i-j} - X_{mean})\rangle}{X_{std}^2}\ , \qquad (1)$$

where the brackets <> mean time averaging, $\tau_j=jh$, j=0,1,2…, h is the sampling period, and X_i is analysed time-series with mean value X_{mean}. This was calculated using the standard Matlab function *xcorr*. The resulting function $\rho(\tau_j)$ belongs to the range [–1:1]: values close to 1 suggest a strong correlation between subsequent points separated by time interval (lag) τ_j, and values close to zero suggest an absence of correlations.

Exponential function $\rho(\tau_j)$= exp(-$\gamma\tau_j$) was used to fit an initial decay of ACF and to determine the ACF decay exponent γ. The initial decay relates to an interval of $\tau_j\in$[0:30h]. The exponent γ was then used to characterize the strength of correlation in the time series of increments ΔG_i. Smaller values of γ correspond to less rapid decay and hence stronger correlation and longer memory in the data.

D. Detrended Fluctuation Analysis

DFA exploits several parameters which can be varied and the choice of parameters influences the final results and their interpretation. A detailed analysis of applicability of these parameters and ways to interpret the DFA outputs are outside the scope of the current paper. Here we follow an established numerical scheme [17]. A general calculation scheme for DFA index α has been published [12, 19] and the corresponding code is freely available [24]. This involves scaling of detrended fluctuations of amplitude $F(n)$ as a function of window size n: $F(n) \propto n^{\alpha}$.

For a meaningful comparison between our results and those of Ogata et al [17], each glucose profile was divided into non-overlapping 24 hour segments. This led to 15 segments for the control group, and 13 and 12 segments for type 1 and type 2 diabetes groups respectively. Following Ogata et al [17] the function $F(n)$ was calculated for $n \in [8:70]$ using a third order detrending polynomial and overlapping windows. For some profiles there is a crossover point, n_c, where $F(n)$ changes its scaling, and therefore two scaling indices α_1 and α_2 were used for fitting: $F(n) \propto n^{\alpha}{}_1$ for short range $n \in [8:n_c]$ and $F(n) \propto n^{\alpha}{}_2$ for long range $n \in [n_c:70]$. A minimum of the error between piece-wise two-line fitting and $F(n)$ has been used to determine the crossover point n_c. Thus, the outputs of the procedure are the presence/absence of the crossover point and its location n_c (if present); two scaling indices α_1 and α_2, which were considered as equal if there was no crossover effect.

E. Trend Extraction

To consider long term prediction (usually defined as beyond one hour [4, 17]) and dynamic behaviour, we decomposed the glucose time series into two parts. One part is a trend, and another part corresponds to meal time (prandial) events. The data did not include an accurate quantification of food intake, so the exact amount of carbohydrate in each meal is unknown.

The trend was derived as a level connecting local minima and by taking into account the fact that there is no food intake during night time. Prandial events can be considered as responses to glucose intake and a number of mathematical models exist [25,26] for describing glucose-insulin dynamics in such situations. A comprehensive discussion of the prandial events is beyond the scope of this paper. The events were fitted for the purpose of illustration by the function $G(t-t_e)=B_1(\exp[\beta_1(t-t_e)]-\exp[\beta_2(t-t_e)])-G(t_e)$, where t_e corresponds to the onset of the event, and B_1, β_1 and β_2 are constants. The first term is a particular solution of a linear second order differential equation. This solution describes the impulse response of a linear system, i.e. a response to an external perturbation changing $\dot{G}(t_e)$ at a given time moment t_e. The solution corresponds to a linearized version of a glucose homeostatic model recently suggested by Watson et al [25]. Matlab function *nlinfit*, which performs nonlinear square regression, was used for fitting.

III. RESULTS

A. Data collection and descriptive statistical analysis

The CGMS device was well tolerated with only minor problems reported, for instance keeping the probe attached during very hot weather. In two cases the device was removed before completing the 72 hours, but these nevertheless contained 648 and 674 consecutive glucose measurements. There were no missing values in any of the profiles apart from profile 14, in which there were difficulties with initial attachment of the monitoring system. Because this interruption would have affected the analysis, the first 38 minutes of data were excluded prior to an interlude of 19 minutes, still leaving a continuous series of 797 data points. In one participant (profile 1) the device was kept on voluntarily (on the independent advice of the patient's clinician) for more than six days to assist in clinical care, providing 1936 data points.

The biographical data are given in Table 1. The 15 participants had a median age of 57 years, range 22-74 years. Twelve were women. Five were controls with no diagnosis of diabetes, four had type 1 diabetes and six had type 2. Two of the type 1 participants were using an insulin pump; the other two were using a regimen of glargine (basal) and aspart (bolus) insulin analogues. Of the six type 2 participants, one was using glargine in addition to metformin, all the others were using oral medications only except for participant No 15, who was diagnosed with diabetes at entry to the study and was not using any medication for diabetes. Hba1c measurements ranged from 38 to 89mmol/mol, with median 53mmol/mol. The approximate mapping [3] of HbA1c values to mean glucose level gives the range 6.3 to 13.8 mmol L^{-1} with median 8.5 mmol L^{-1}.

TABLE 1

FIGURE 1.

Figure 1 shows boxplots with *p*-values for calculated characteristics of all 15 profiles. If there is a significant difference in medians between any two groups then the values are marked by a star. It can be seen that standard deviation G_{std} (Fig. 1, *b*) differs significantly between diabetes and controls, as expected.

FIGURE 2.

B. ACF Analysis

Fig. 1, *b* shows box plots for ACF exponents, but before we discuss them, let us give an illustration of ACF shapes and reaffirm the case for using the increments $\Delta G(t_i)$ instead of initial time series $G(t_i)$ in the correlation analysis. In Figure 2, *a*, ACFs calculated for initial time series $G(t_i)$ and for differential increments $\Delta G(t_i)$ are shown for a diabetes patient. A periodic

component, related to diurnal activities, is clearly seen for glucose time-series $G(t_i)$, but not for $\Delta G(t_i)$, where ACF has a non-oscillatory shape. Another example of ACF is shown in Figure 2, *b* for a person from the control group (profile 3). In contrast to the first case, this graph does not show a clear diurnal oscillatory component and the shape of ACF is typical for a long-range correlation process. However ACF obtained using differential increments looks similar to the diabetes case and both cases show fast decay to zero indicating only short-range memory. Let us stress that a power-scaling in the case of long-range correlation must be observed for both the initial data $G(t_i)$, and for increments $\Delta G(t_i)$ [11]. Therefore, these two pictures demonstrate the absence of long-range memory. This demonstrates the limitations of using ACF for analysis of time-series $G(t_i)$ and its applicability to increments $\Delta G(t_i)$. However, if the focus of interest is specifically to identify periodicities, then spectral analysis [13, 14] of the original time series may also be useful.

The box plots shown in Fig. 1, *b* demonstrate that ACF exponent γ is smaller in the diabetic groups, indicating stronger correlation of data with time, and higher in the control group indicating uncorrelated dynamics.

C. Detrended Fluctuation analysis

The DFA indices α_1 and α_2 (Fig. 1, *c*, and *d*) are greater than *1* for all profiles indicating the presence of non-stationary behaviour in the time series.

The crossover effect has been observed in most of the segments (39 out of 47). The index α_1 for the short range is not statistically different (Fig. 1, *c*), whereas the index α_2 is statistically different for control and diabetes groups (Fig. 1, *d*). For a comparison to the previous investigation by Ogata et al [17], results of both type 1 and type 2 diabetes groups were combined. The results are presented in the format of mean value plus-minus standard deviation.

Ogata et al [17] gave the following results: α_1=1.77±0.32, α_2=1.25±0.29 for the control group; α_1=1.72±0.21, α_2=1.65±0.30 for the diabetes group. Our results are the following: α_1=1.84±0.23, α_2=1.44±0.30 for the control group; α_1=1.95±0.36, α_2=1.83±0.31 for the combined diabetes group. There is a qualitative correspondence between these two investigations since both show that the difference is not significant for α_1 (p=0.278 for our data) but it is significant for α_2 (p=0.0004 for our data). However, values of indices α_1 and α_2 for our data are larger than in Ogata et al's study [17]. Several factors may explain this difference. Their participants were asked to follow certain prescriptions for food intake, refraining from all forms of caffeine, limitations on physical activity and scheduled times to wake up and go to sleep. Our participants had no such restrictions. Perhaps more importantly, fourteen of their fifteen participants with diabetes were using insulin. Our sample included more diverse treatment regimens: five using insulin, four using tablet treatment alone, and one using neither (Table 1).

Index α_2 as already mentioned is significantly different for control and diabetic groups. The value of α_2 is close to 1.5 for controls which in combination with the ACF index, allows us to present the dynamics as a random walk with independent increments, i.e. as Brownian motion. For diabetic groups, α_2 is higher than 1.5, suggesting a slow variation of the corresponding time series.

FIGURE 3.

D. Glucose Variation as a Stochastic Process

Thus, ACF exponent, DFA index and standard deviation all show clear differences between control and diabetes groups. Figure 3 suggests monotonic nonlinear dependences between the 3 parameters meaning that any one of them is sufficient for differentiation between the diabetes and control groups. However, these characteristics are complementary to each other as they

reflect different properties of the glucose profiles: linear predictability (γ), non-stationary behaviour (α) and amplitude of variation (G_{std}). Interestingly, the combination of two indices, G_{std} and γ, leads to a two-dimensional map (Fig. 3, *a*). Here, indices of control and diabetic groups form distinct clusters with a hypothetical boundary represented by a dashed line whereas we see overlap of values if only one of the indices is considered at a time (Fig 1 and Fig 3), particularly for α.

FIGURE 4.

E. Decomposition and Trend Extraction

Figure 4 demonstrates the presence of prandial excursions in the profiles (two profiles for type 2 diabetes are shown as examples) superimposed on a slow component, a trend, and this is typical for all our time series. There are no clear regular patterns in the slow components and the predictability of the trends is an open question.

In each profile several peaks corresponding to prandial events were chosen and fitted (red thin lines in Figure 4) as described in the Methods section. The fit in the form of the impulse response of a linear system works well for all control cases, however it gives inconsistent results for diabetic time series of both type 1 and type 2. In our example in Figure 4 the fit is good for *a* but poor for *b*: peaks in *a* have an asymmetric shape, whereas peaks are more symmetrical in *b*. Values of the fitting coefficients vary from peak to peak for each profile indicating a strong nonlinear dependence on the amplitude of external stimuli. Therefore, for the control group and for some of the participants with diabetes the response to food intake can be effectively modelled by a second order linear equation, however specific non-linear and/or high dimensional models [26, 27] need to be applied for other cases.

IV. DISCUSSION

A. *Summary of Principal Findings*

Our results suggest that subcutaneous glucose variation can be modeled as a stochastic process with stationary increments. ACF analysis of the increments indicates the presence of short-range memory using an exponential decay function for ACF fitting. Long-range trends in the original glucose profiles are removed effectively by this technique, enabling comparison between diabetic and control profiles, and the value of DFA is confirmed.

We found that 3 characteristics (standard deviation G_{std}, ACF exponent γ and DFA index α) differentiate between control and diabetic groups, and uniquely define independent properties of the glucose profiles. These complementary parameters suggest that in the control state, blood glucose variations are small in amplitude and relatively uncorrelated over time scales of 10 to 20 minutes, during which ACF decays rapidly. These variations could be modelled as a random walk, with no retention of 'memory' of previous values, i.e. Brownian motion. In diabetes, by contrast, variation is greater in amplitude and smoother, with retention of inter-dependence between neighbouring values in a profile; ACF decays less abruptly, suggesting persistence of correlated structure over short time scales of 30 minutes to one hour. ACF exponent γ is shown to be a qualitative indicator of linear predictability.

Our use of increments rather than the original time series enables us to compare the glucose dynamics of both healthy individuals and diabetic patients. Further natural extension of this technique is an application of *spectral* analysis and probability measures of the increments.

The decomposition of time series to the slow trend related to intrinsic dynamics and responses to external stimuli has demonstrated an event-driven character of glucose variation, highlighting the importance of explicit inclusion of external stimuli into prediction models, as is used in artificial pancreas systems [2]. Additionally, it suggests that long term predictions (beyond one hour) may be limited by the slow trend related to the intrinsic dynamics. These conclusions agree

well with a previously published finding [4] that the use of short time windows can support simple auto-regressive models for short-term forecasting [4, 23]. Longer term prediction may require a better understanding of the slow trend. For some time series the trend can be represented by an oscillatory function related to a diurnal component, but for most of the profiles in our study a clear diurnal periodicity was absent.

B. Limitations of the Study

This is an exploratory study investigating the potential for time series analysis to support a dynamical definition of glycaemic stability. It is inevitably limited by the relatively small sample of profiles available, but has confirmed the ability of such data to support this approach in the clinical setting. A larger study would involve more participants preferably using a broader range of therapies including different insulin replacement regimens, as well as newer anti-diabetic agents such as GLP-1 analogues, which were not included in our study. This would identify the effects of different therapies on the glucose dynamics. Longer time series (over weeks or months rather than days) would allow the detection of longer term patterns (including weekly and monthly periodicities [28]) but are more difficult to collect unless the sampling frequency is significantly reduced or new technologies emerge [29].

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TABLE 1. Biometric indices, treatment regimens, hba1c values and corresponding approximate glucose levels [3] of participants

Profile No.	**Age** (years)	**Sex**	**BMI** ($kg/m^{2)}$	**Diabetes status**	**Treatment regimen**	**HbA1c** (mmol/mol)	**Glucose level** (mmol L^{-1})
1	57	F	20.5	Type 1	Basal bolus (glargine plus aspart)	63	10.0
2	27	F	19.2	Control	N/A	N/A	N/A
3	59	F	27.3	Control	N/A	N/A	N/A
4	49	F	21.9	Control	N/A	N/A	N/A
5	32	F	29.4	Type 1	Insulin pump	55	9.0
6	74	M	20.5	Type 2	Metformin, gliclazide and rosiglitazone	61	9.7
7	66	F	25.9	Type 1	Insulin pump	38	6.3
8	75	M	23.4	Type 2	Metformin	46	7.6
9	68	F	32.7	Type 1	Basal bolus (glargine plus aspart)	48	7.8
10	39	F	21.3	Control	N/A	N/A	N/A
11	61	F	32.6	Type 2	Metformin	52	8.4
12	56	M	30.0	Type 2	Metformin and gliclazide	68	10.8
13	52	F	44.5	Type 2	Metformin and glargine	89	13.8
14	22	F	19.6	Control	N/A	N/A	
15	63	F	27.0	Type 2	Newly diagnosed diet only	42	7.0

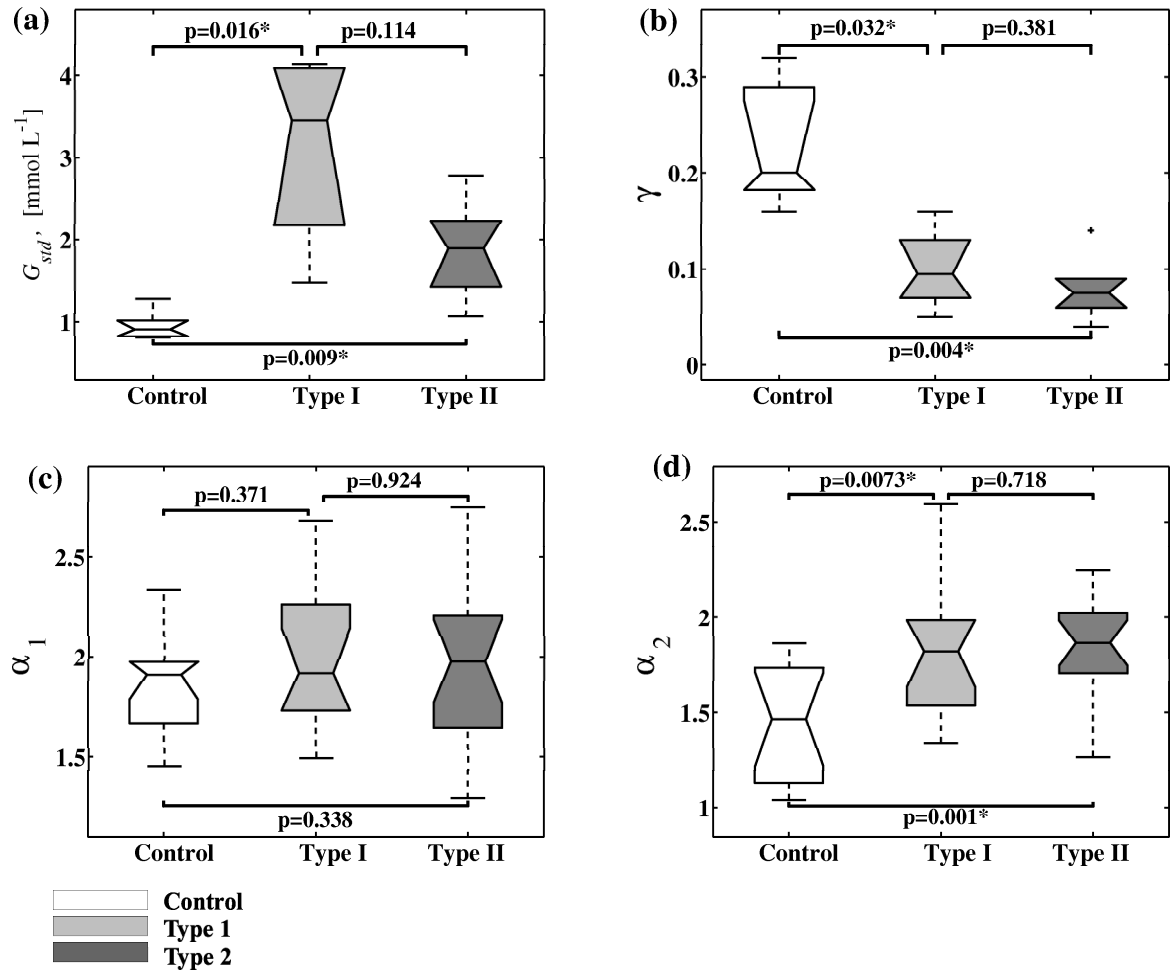

Fig. 1. Box plots of (*a*) standard deviation values, (*b*) ACF decay exponents, γ, and DFA indices (*c*) α_1, (*d*) α_2. All grouped by diabetes status.

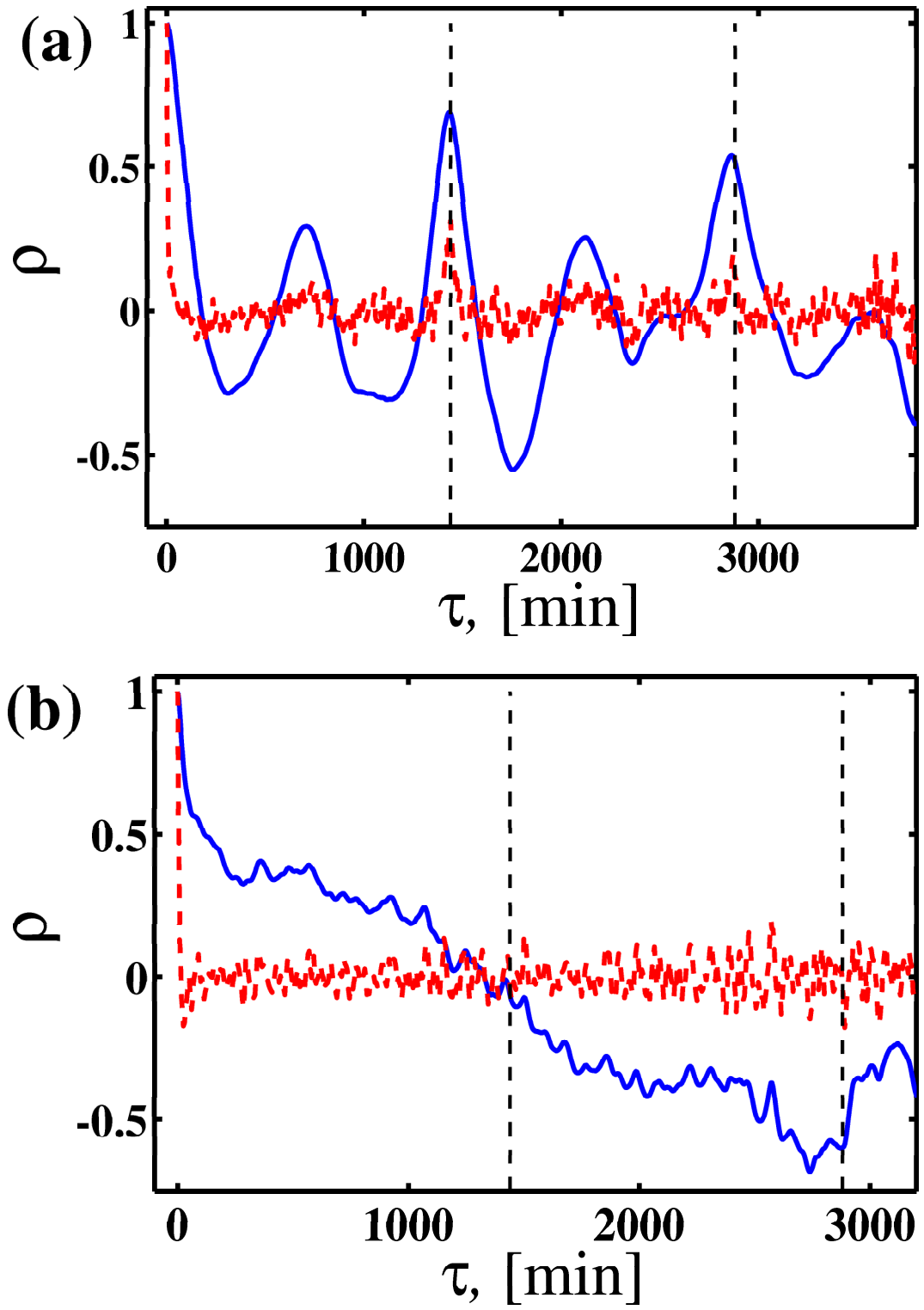

Fig. 2. ACF for (*a*) a diabetic patient (profile 11) and for (*b*) a person without diabetes (profile 3). The solid blue and dashed red lines correspond to ACF calculated for time series $G(t_i)$ and $\Delta G(t_i)$ respectively. The dot-dashed vertical lines correspond to 24 and 48 hours lags.

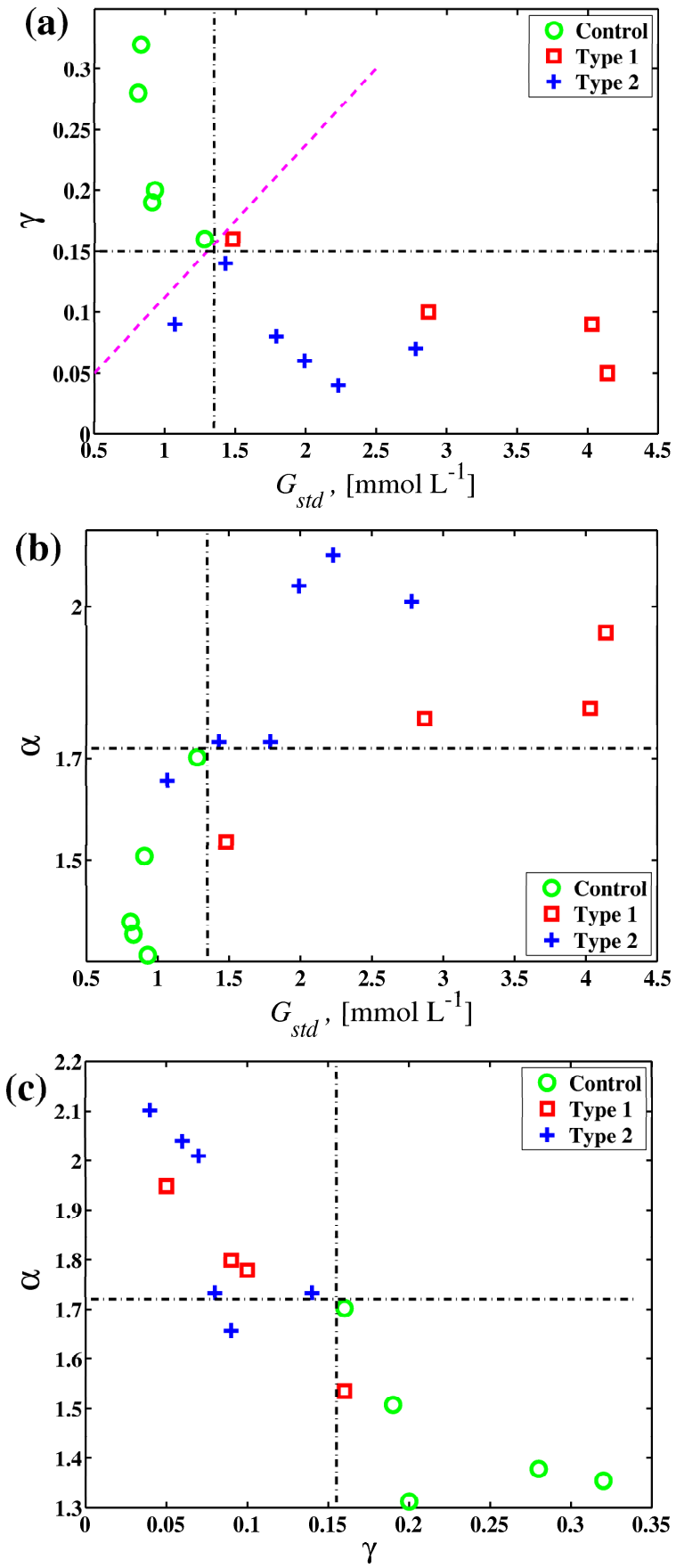

Fig.3. Scatter plots of (*a*) standard deviation, G_{std}, (x-axis) versus ACF decay exponent, γ; (*b*) G_{std} (x-axis) versus DFA index, α; (*c*) ACF decay exponent, γ (x-axis) versus DFA index α. The results are shown by green circles, red squares and blue pluses for the control, type1 and type 2 groups respectively. Dash-dot lines show boundaries for one parametric analysis; the dashed line in (a) shows a boundary for two-parametric analysis.

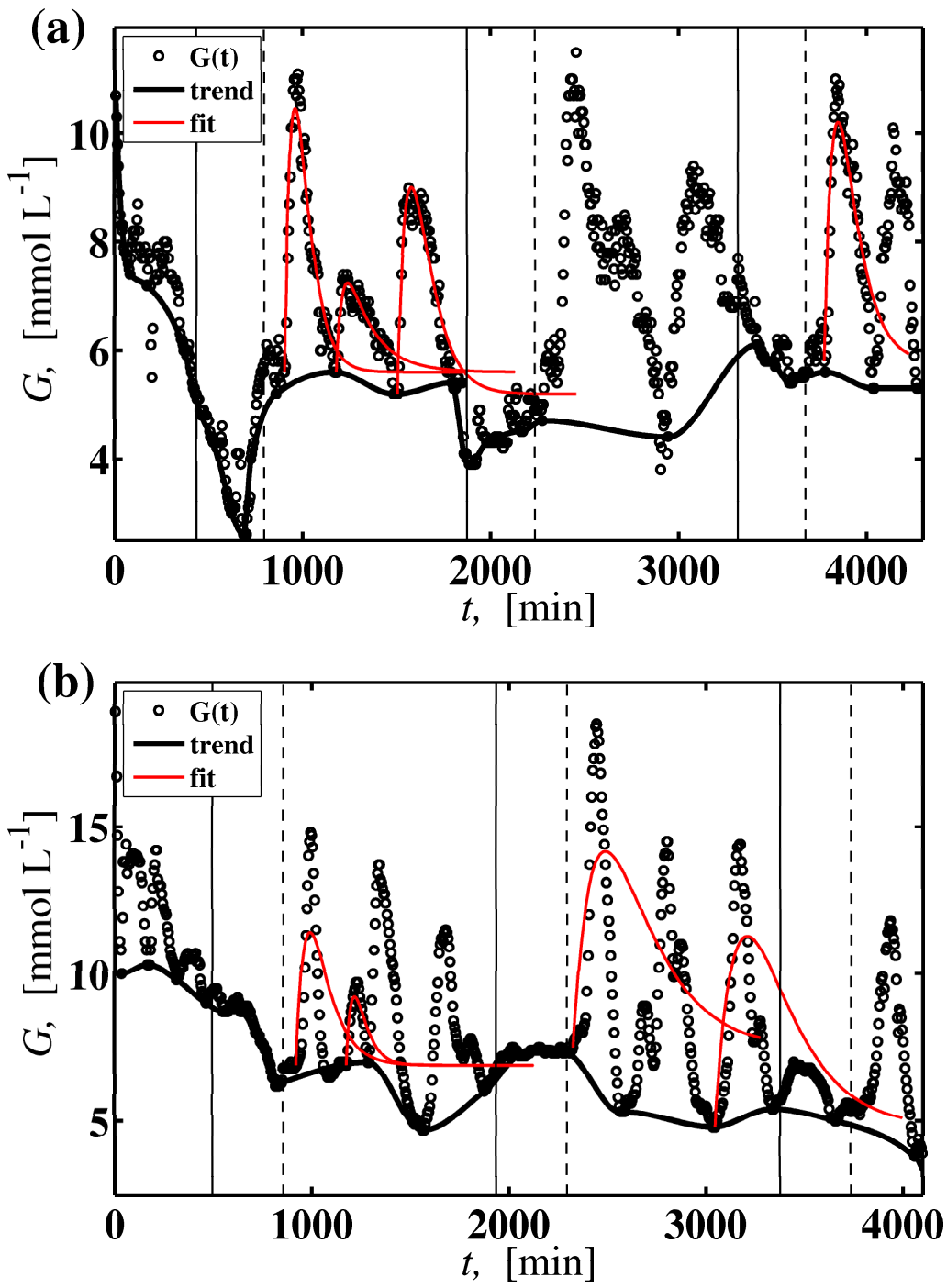

Fig. 4. The glucose time series are shown for profile 8 (*a*) and profile 15 (*b*) of type 2 diabetes group. The solid thick black line corresponds to the trend; measured glucose values are shown by circles; fitting curves are shown by thin red lines. The dashed and solid vertical lines correspond to 6am and midnight respectively.