DIABETES TECHNOLOGY & THERAPEUTICS
Volume 10, Number 2, 2008
© Mary Ann Liebert, Inc.
DOI: 10.1089/dia.2007.0256

Blood Glucose Dynamics

FARBOD N. RAHAGHI, Ph.D. and DAVID A. GOUGH, Ph.D.

ABSTRACT

Measurement of blood glucose concentration is central to the diagnosis and treatment of diabetes. Although there are large numbers of historic glucose measurements in individuals with diabetes, until recently there have been very few data sets that were recorded continuously or sampled frequently enough to reveal intrinsic blood glucose dynamics, or the change in blood glucose with time. There have even fewer such recordings from individuals not having diabetes to serve as a therapeutic target. As a result, blood glucose dynamics have generally not been used in the diagnosis or treatment of the disease. Although present blood glucose monitoring is based largely on discrete measurements, future monitoring will likely focus on analysis of blood glucose excursions. New measurements are now being obtained, and there is a need for new methods of analysis to extract the maximal information from the data. Several approaches are demonstrated here for characterization of blood glucose dynamics, and a patient profiling system is proposed. An example of new insights is the observation that there are four time scales of blood glucose variations in individuals without diabetes, and these time scales are modified or lost in diabetes.

INTRODUCTION

WHEN BLOOD GLUCOSE is sampled frequently enough to record all its variations, the information effectively becomes continuous and can reveal the *intrinsic blood glucose dynamics*, or the change in blood glucose with time, of an individual. However, for certain individuals with diabetes who experience rapid blood glucose changes and others not having diabetes, the sampling rate must be very frequent—as often as every 12–15 min—to approach continuity and reveal all variations.[1] Further, sampling has to be *automatic* and *independent of user initiative* to capture all blood glucose variations—especially during sleep—and detect hypoglycemic excursions. These sampling requirements are, of course, not tenable by fingersticking or similar methods. There have previously existed few blood glucose data sets in the literature that contain intrinsic dynamic information about individuals with diabetes, and even fewer from individuals not having diabetes for comparison.[2] This situation is being addressed, at least partially, by new studies involving frequent blood sampling[3] and the introduction of continuous glucose sensors into the clinic.[4]

Continuous monitoring may make possible substantive improvements in blood glucose control. The Diabetes Control and Complications Trial[5] was not designed to include information about blood glucose dynamics, as it was based on glycosylated hemoglobin (HbA_{1c}) values, which represent blood glucose averaged over a previous several-month period rather than real-time blood glucose values. Nevertheless, there is a general expectation that dynamic information about blood glucose would allow qualitative and quantitative im-

Department of Bioengineering, University of California San Diego, La Jolla, California.

provements in control. Indeed, parallels with classical control theory[6] suggest that normalization of blood glucose dynamics may be of equal or greater benefit than normalization of average blood glucose alone. Obtaining the maximal advantage from dynamic blood glucose information will require knowledge of the normal dynamic response in those without diabetes and its range of acceptable variation to serve as a performance target.

Prior to the advent of continuous glucose sensors, several approaches had been devised to describe blood glucose variations. A commonly used parameter is the mean average glycemic excursion (MAGE),[7] which provides some insight but does not take advantage of all the information available in the data, as it reflects only statistical averages rather than actual dynamic variations and does not account for the temporal relationship between individual blood glucose values. Another approach based on dynamics is the intravenous glucose tolerance test (IVGTT),[8] in which serial blood glucose measurements are collected in response to a standardized glucose challenge. However, the IVGTT involves a limited glucose challenge that does not represent the size, absorption rates, and timing of actual meals, the result is usually reduced to only a single value to represent the actual dynamic response, and the test reveals little about the range of blood glucose variation of the subject. These considerations indicate that the dynamic aspects of blood glucose concentration have not typically been monitored or used effectively in the diagnosis or treatment of the disease.

Some recent clinical studies have utilized experimental continuous glucose sensors implanted in subcutaneous tissues to monitor glucose variations.[9–11] Preliminary results from these studies suggest an important conclusion: glucose excursions occur much more frequently than was formerly thought, even in presumed well-controlled individuals. They also demonstrate the potential utility of tissue glucose measurements to indicate blood glucose values. However, the sensors used in these studies are at an early stage of development, and the signals often include various types of inaccuracies, such as delays, dampening of signals at certain frequencies and overshoot at other frequencies, artifacts due to variable perfusion of the local microvasculature, and signal drift. As most implanted sensors have thus far not been validated using dynamic criteria and may introduce various forms of distortion, data from these sensors were not used in the present analysis. Nevertheless, continuous glucose sensors, once effectively validated and widely accepted by users, will represent a major advance in glucose monitoring.

Several examples of insights that can be obtained by novel analyses of dynamic blood glucose measurements are given here. These examples are based on historic data from the literature in which blood or plasma glucose samples were collected frequently enough to reconstruct the intrinsic blood glucose dynamics of the research subjects. Comparisons are made between individuals with and without diabetes.

STATISTICAL VERSUS DYNAMIC MONITORING

The approach in conventional statistical analysis is to collect multiple glucose samples for the purpose of obtaining an averaged value at a specific time, whereas analysis of dynamics requires successive glucose measurements obtained in series over an extended period, or a *time series* (see Appendix). As parameters such as the statistical mean and variance do not retain information about the order and timing of the samples, they do not contain dynamic information. The practice, therefore, of averaging a series of measurements over time inherently eliminates dynamic information. For example, HbA_{1c} measurements have no dynamic content. These considerations emphasize that in a standard statistical analysis, each measurement is considered to be fully independent of previous and subsequent measurements.

To include dynamic content, however, individual measurements in a series cannot be mutually independent. The timing of each measurement and its order in the series are crucial. Samples must be collected frequently enough to assure a degree of information carryover, and individual measurements must retain some history of previous measurements. Fur-

ther, a sufficient number of serial measurements must be obtained to observe the evolution of the system over time. Conversely, when samples are separated by more than a certain critical interval characteristic of the subject, the overlapping information between individual measurements is eliminated, measurements become mutually independent, and the dynamic content is lost.

Several metrics of information overlap have been previously proposed. The *Nyquist criterion* applied to blood glucose dynamics[1] is the maximum allowable regular interval between samples that can be used for a distortion-free reconstruction of a subject's blood glucose variations. A specific *Nyquist sampling interval* determined for each individual indicates how frequently samples must be collected to capture all blood glucose variations. Sampling at intervals that are shorter than this characteristic interval provides little additional dynamic information, whereas sampling at greater intervals leads to a very common form of distortion known as *aliasing*, and cannot be relied upon to follow all blood glucose excursions. For example, certain pioneering studies over 50 years ago were based on series samples of blood glucose, but did not sample frequently enough to reveal the undistorted dynamics *of the subject*. For people not having diabetes and those with diabetes who have rapid blood glucose excursions, the critical sampling interval may be 12–15 min.[1] The interval is, of course, greater for individuals in whom excursions are known to be slower,[1] such as many individuals with type 2 diabetes. The *autocorrelation coefficient* is another parameter that indicates overlapping information in successive measurements and has been previously applied to blood glucose data.[2] Autocorrelation of recent blood glucose values can be used to predict blood glucose ahead of the present by as much as 20 min.[2,12]

A more intuitive parameter, the *information half-life*, $i_{1/2}$, is proposed here,[13] which is the time interval between two samples at which the shared information content decreases by half. This parameter provides a more direct indication of the amount of shared information associated with a specified regular sampling regimen.

How does one know if a continuous recording or a time series actually corresponds to the intrinsic blood glucose dynamics *of the subject*? For a continuous recording, the sensor signal must be validated by dynamic testing to show that it is distortion-free and capable of more rapid response than the systemic blood glucose variations of the subject. If discrete sampling is used, the sampling interval must be within the critical sampling interval specific to the subject. For a full appreciation of the dynamics of the subject, it is also important that measurements are taken when the blood glucose is changing rapidly and the subject's full range of response is actually being exercised, such as around mealtime or soon after insulin injection, especially if there is a possibility of a hypoglycemic excursion. If the above conditions are met, the monitoring method is capable of detecting all blood glucose excursions and indicates the subject-specific *blood glucose signal*.

GLUCOSE MONITORING MODES

In practice, there are several modes of glucose monitoring. *Statistical monitoring* (or *non-dynamic monitoring*) occurs when samples are obtained at intervals that are too great to contain subject dynamics, or when the order of the samples is not preserved. *Dynamic monitoring* requires regular sampling within a critical interval, or the use of a qualified continuous sensor. *Integrative monitoring*, such as that achieved with HbA_{1c} measurements, is when a single measured value is proportional to the integral of blood glucose over a previous extended period. A further practical distinction is *automatic monitoring* based on a sensor system that is capable of collecting information regularly even during sleep, in contrast to *initiative-based monitoring*, which requires the subject to initiate each measurement.

METHODS

Data

The examples here are based on historic laboratory blood glucose measurements from subjects with and without diabetes obtained from

literature spanning 30 years. The data used were sampled at regular intervals of 5–20 min for periods up to 50 h. Data were extracted from published figures through a process of reverse digitization.[14] In all cases, several digitization methods were used to insure accuracy of the digitization process, including statistical comparisons and redundant verifications. Means and linear trends of all time series were removed prior to processing, as these features typically obscure dynamic features.

Illustrations of the data in the reversed digitized format used for this study[7,15–17] are given in Figure 1. This particular set of data was obtained from subjects without diabetes having intact glucose management mechanisms, exposed, respectively, to regular meals, continuous enteral feeding, fasting, and sinusoidal glucose infusion. The inclusion of data from control subjects without diabetes illustrates dynamic differences between individuals with and without diabetes as a potential diagnostic tool and suggests a target for improved control of blood glucose. In addition to illustrating the results of reverse digitization, these data demonstrate intrinsic blood glucose dynamics without the complications of extrinsic scheduling of insulin administration. Similar data sets from subjects with diabetes are described later to illustrate clinical features.

Linearity and stationarity

Glucose time series are affected by external perturbations such as meals, insulin injections, and exercise. As the timing and magnitude of these events typically vary from day to day, generalization of dynamic information extracted over multiple days is not expected to be precisely repeatable, that is, to be broad-scale *stationary*. Thus, a crucial question addressed elsewhere[13] must be considered: given a nonstationary system, how generalizable is the extracted dynamic information?

The metabolic system is also not expected to always respond proportionally to the magni-

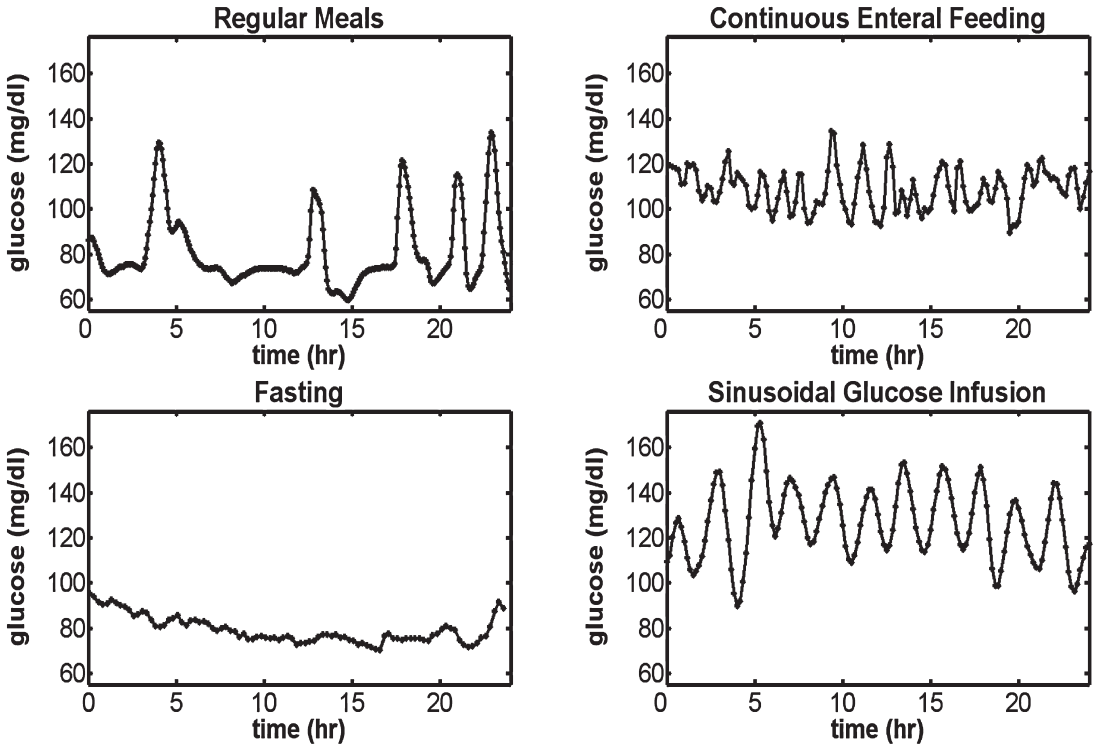

FIG. 1. Blood glucose time series from four subjects without diabetes. Literature data represent responses to different glucose challenges.[7–9] Sampling was at regular intervals ranging from 5 to 15 min over 24-h periods. Data points are based on reverse digitization and are connected by straight lines. Note that the response to fasting contains a rapid, small amplitude signal with a slowly varying baseline. The sinusoidal challenge had a period of 128 min, amplitude of one-third of the mean, and an average infusion rate of 6 mg/kg/min.

tude of the perturbation, that is, to be strictly *linear*. For example, a doubling of meal size may not always produce an exact doubling of the blood glucose response. The key question[13] is again not one of classification, but rather how does nonlinearity affect the generalizability of the dynamic information? Linear analysis tools are used here because nonlinear tools are relatively poorly developed, and the error introduced is proportional to the degree of nonlinearity.

Analysis

The blood glucose time series from individual subjects were segmented into smaller time series neighborhoods based on comparable events such as meals and analyzed individually to find the relative signal energy in each neighborhood. Well-established methods that do not assume linearity or stationarity were used to analyze energy changes. Methods selected here emphasize intuitive rather than theoretical understanding.

Some useful terminology is the following. The *signal energy* is the squared values of the samples or signal magnitude, and the *total energy* of a signal is the sum of these terms. Energy was chosen as a variable because it remains constant in the face of certain mathematical transformations and can therefore be used to compare signals broadly. The term *time scale* refers to the period of a single sine wave cycle and is used here in place of *frequency*, as it relates more intuitively to clinical experience.

Experimental subjects

The subjects were diagnosed and categorized by the authors of the original publications. In one study, categories included control subjects without diabetes, subjects with "stable" diabetes defined as responding consistently to consistent therapy, and subjects with "unstable" diabetes who responded otherwise. A control group without diabetes was included to help establish a therapeutic performance target.

It has been noted previously[2] that there is a dearth of frequently sampled blood glucose data. Given this situation, the data used here may not necessarily be representative of the respective populations or reflect the range of population variability. Nevertheless, the intent here is show that insights can derive from appropriate analysis of dynamic data and encourage more extensive collection of suitable data.

EXAMPLES

Example 1: response to a meal

Examples of blood glucose signals after a dinner, the largest daily perturbation, are shown in Figure 2. All subjects had comparable meals and exercise, and data from subjects with diabetes included responses to insulin at the subject-specific dosage, timing, and duration of effect. The top panel contains stepwise averaged serial blood glucose measurements after subtraction of the unchanging background and temporal alignment of excursions. The response in those without diabetes shows a rapid rise to approximately 30 mg/dL above baseline and return to baseline within 150 min. The responses in two subjects with diabetes show a comparable rate of rise to 40 and 75 mg/dL above baseline, respectively, but remain elevated much longer and eventually approach the baseline at more than 250 min.

Although these responses are quite familiar to most clinicians, a greater appreciation for the dynamic aspects can be seen in the bottom panel, where the respective rates of change are shown. The initial rates of change of the glucose signals in those with and without diabetes are similar, but the inflection points are readily distinguished, and the negative rates in the diabetes cases persist much longer. As subjects with diabetes rely on exogenous insulin administered according to an external schedule, much of the intrinsic dynamics of glucose are obscured and largely reflect extrinsic perturbations. This complicates the analysis of intrinsic dynamics, but enhances the sensitivity of dynamics as a tool for comparison of potential therapeutic regimen. Other comparisons of these data may lead to further insights, but a larger study population is needed to generalize these observations and define their specific clinical usage.

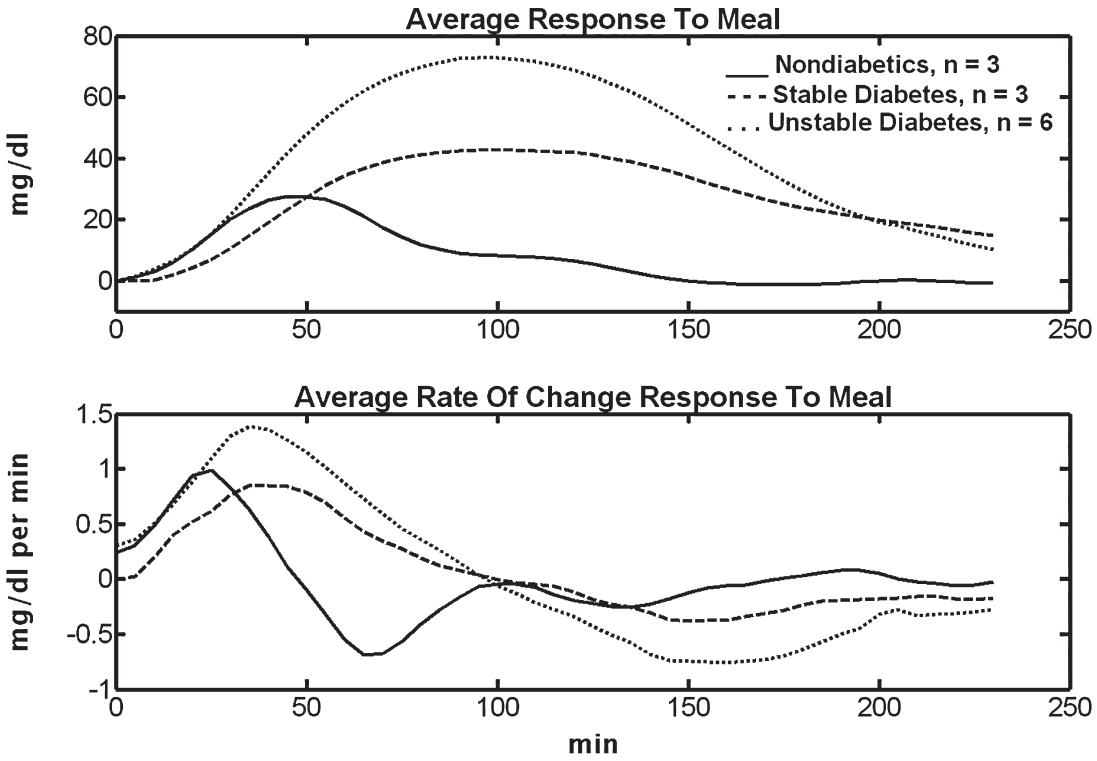

FIG. 2. Response to meals. Averaged responses are shown (**top**) to a meal (dinner) and (**bottom**) rate of change of response to the meal for three subjects without diabetes (solid line), three subjects with stable diabetes (dashed line), and six subjects with unstable diabetes (dotted line). Mean values have been subtracted. The definitions of "stable" and "unstable" were assigned by the original clinician investigators.[7]

The temporal alignment of the signals to coincide with the meal perturbation eliminated the main cause of signal nonstationarity. Variability in the timing of insulin injection remained a nonstationary perturbation, however, as subject-specific dosages varied. The process of stepwise averaging the signals also inherently included information from larger time scales (such as circadian rhythms), thereby introducing some dynamic error. This error can be reduced by segregating the signal components into characteristic time scales, as shown later.

Example 2: rate of change

A method of analyzing the glucose signal that makes very few assumptions about the linearity and stationarity of the data is to simply plot the magnitude and the corresponding rate of change of individual values of the signal. This method involves taking the difference between two successive blood glucose values and dividing by the time interval between them, thus revealing the evolution of the measurements over time. The resulting rate of change can itself be treated as a new time series, with one set of information plotted against another, and its dynamic information content can be estimated by simple statistical methods. The result is a two-dimensional histogram or image known as a phase space map or Poincare map,[18–20] which shows the evolution of the time series. Issues concerning the critical sampling interval (above) remain crucial to the accuracy of this analysis.

The distribution of blood glucose concentration with its corresponding rate of change for each of the three subject groups is shown in Figure 3. When two points fall on the same coordinate, they are added to make a darker point on the graph. The response without diabetes (left panel) is focused asymmetrically at a baseline glucose level with similar rising and falling rates of change, whereas the response with stable diabetes (center panel) is characterized by

a broader glucose excursion and asymmetric rate of change, and the response with unstable diabetes (right panel) has a much broader excursion and a symmetric rate of change. Parametric characterization of these two-dimensional histograms can provide statistical parameters that indicate differences between the groups, but it is unjustified at present to generalize these observations in the absence of additional data.

Example 3: energy spectra of blood glucose signals

A useful approach for summarizing the overall dynamic characteristics of the glucose signal is a plot of the *energy spectrum*, shown in Figure 4. In this plot, the square of the original glucose values at each time, or the *signal energy*, is converted into signal energy *time scales* using a computational implementation of the Fourier transform[21] and is displayed on a semilogarithmic plot. The result is the normalized signal energy in each time scale region, or band. The three panels correspond, respectively, to subjects without diabetes, with stable diabetes, and unstable diabetes. All subjects had comparable meals and exercise, and the glucose values of subjects with diabetes were affected by their respective schedules of insulin administration. The information half-life needed to accurately describe the full dynamic content of each data set is given and is shortest in the subjects without diabetes and longer in the subjects with diabetes.

In the subjects without diabetes, the signal energy segregates into four time scales. The shortest time scale, approximately 5–15 min, is a result of pulsatile secretion of insulin[22] and contains very little of the total energy of the system. This shortest time scale is not shown in Figure 4 but is discussed in detail below. The second time scale, approximately 60–120 min (shaded), reflects the intrinsic oscillatory behavior shown in Figure 1. The third time scale, at about 150–500 min (shaded), which contains

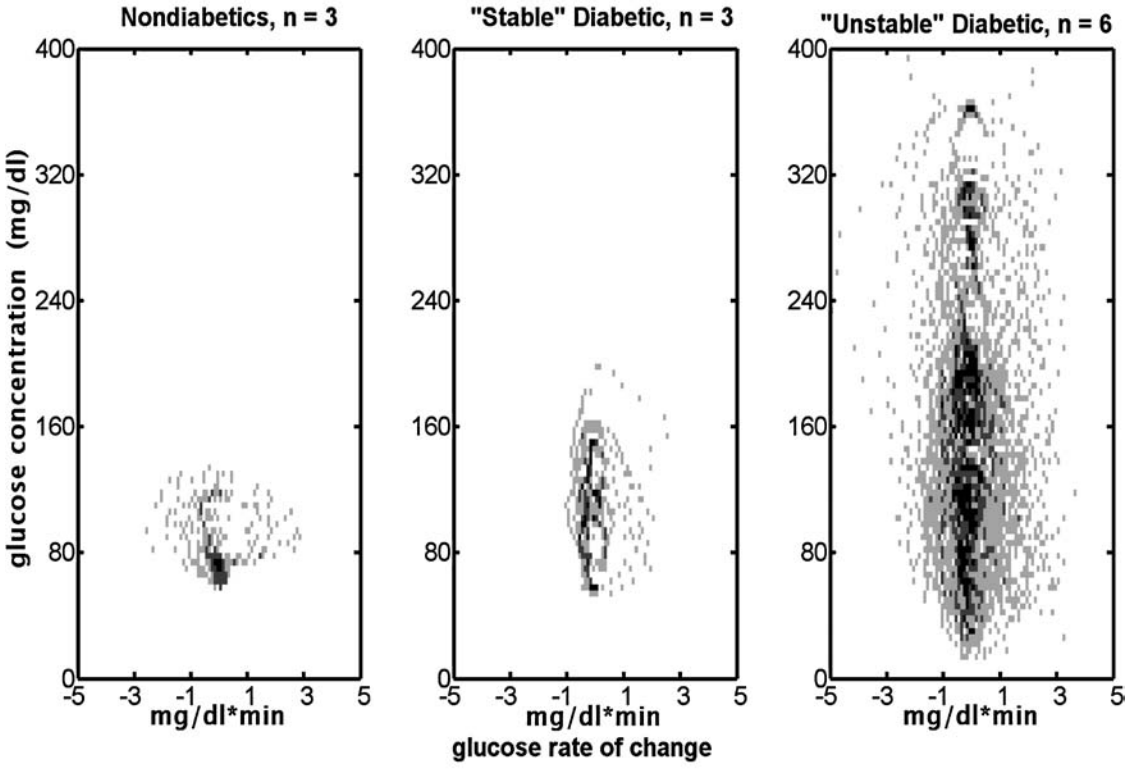

FIG. 3. Distributions of blood glucose (*y*-axis) and its rate of change (*x*-axis) for three groups.[7] (**Left**) Three subjects without diabetes. (**Center**) Three subjects with stable type 1 diabetes. (**Right**) Six subjects with unstable type 1 diabetes. The subjects had comparable meals and exercise, and subjects with diabetes received insulin at variable dosage and timing. Darker data points reflect more samples falling at a given coordinate.

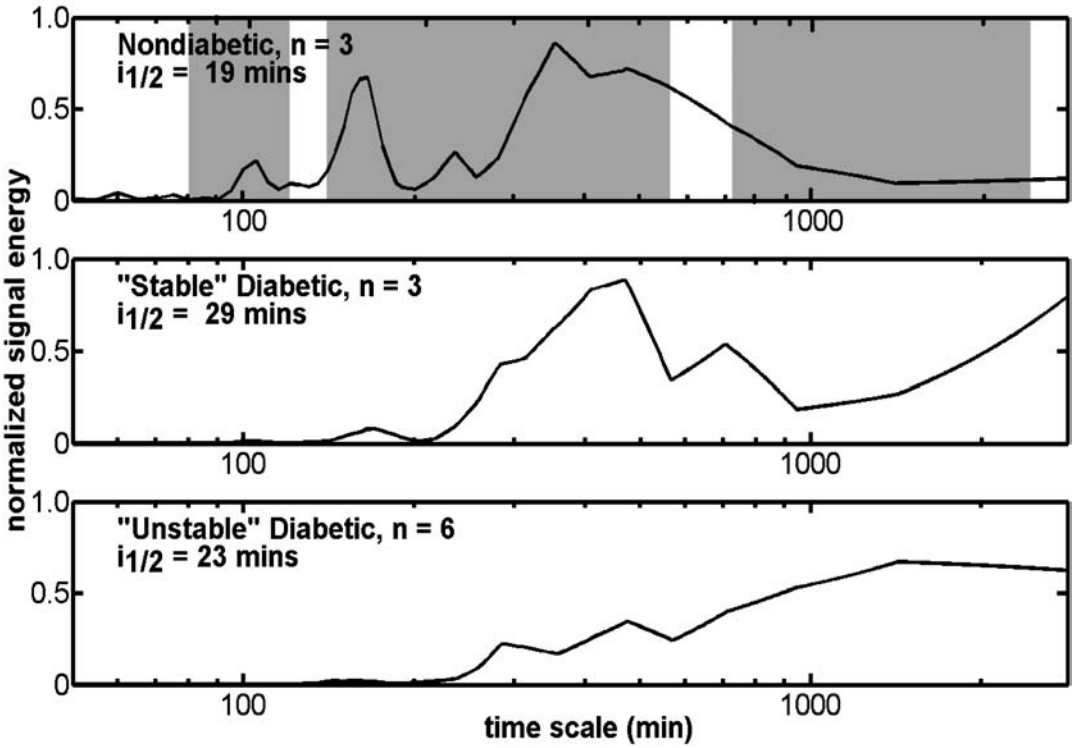

FIG. 4. Spectral comparisons of blood glucose dynamics. (**Top**) Three subjects without diabetes. (**Middle**) Three subjects with stable diabetes. (**Bottom**) Six subjects with unstable diabetes.

a large fraction of signal energy, is caused by external perturbations such as meals and insulin injections. The fourth time scale (>700 min, shaded) corresponds to modulation of other time scales and a circadian rhythm of the blood glucose baseline. These time scales are summarized in Table 1.

The panels representing subjects with diabetes show either a substantial reduction or total loss of the glucose signal energy in the first two time scales, with the remaining energy shifted to peaks corresponding to scheduled meals. For the subjects with unstable diabetes, the signal energy is dictated by the larger daily swings corresponding to insulin injection and absorption, as manifested by a shift toward the slower time scale. This shift represents a loss of normal insulin release, in particular as it affects the signal energy between meals, and a gradually increasing role of insulin injection. As individuals with diabetes rely on exogenous insulin administered mainly according to external schedules and having relatively slow absorption rates, many aspects of the intrinsic glucose dynamics of these subjects may be obscured by extrinsic perturbations. Nevertheless, the shift of energy distribution toward that of the control response may serve as a metric of the restoration of normal glucose regulation.

Example 4: very short time scale glucose signals

Very rapid oscillations in insulin secretion (5–15 min) due to pulsatile secretion have been

Table 1. Time Scales of Blood Glucose Dynamics

Time scale	*Range (min)*	*Physical event*
1	5–15	Pulsatile secretion of insulin
2	60–120	Intrinsic oscillatory phenomena
3	150–500	Meals, insulin injection, external schedules
4	>700	Circadian rhythm

the subject of intense study and can affect the glucose signal,[22,23] although most glucose data sets in the literature have not been sampled frequently enough to capture such perturbations. To ascertain the possible contribution of very short time scale glucose signal components, the few data sets from the literature based on sample intervals of 4 min or less were included. These blood glucose data sets were obtained from control subjects without diabetes,[15,23,24] mostly in response to meal challenges. Normalized signal energy components corresponding to periods of 30 min or less are listed in Table 2.

Although the results indicate that very short time-scale oscillations contribute little to the total glucose signal energy, this does not lead to the conclusion that sampling at <30 min provides little additional information. Indeed, singular events (such as hypoglycemic excursions) can occur rapidly and may not constitute a substantial portion of the overall signal, but frequent sampling is still necessary for the purposes of hypoglycemia detection. It does imply, however, that for the purpose of spectral analysis, data sampled at 15-min intervals consistent with the various sampling interval criteria (above) are likely to be sufficient.

Example 5: signal energy comparisons

The previous approach to characterization of blood glucose dynamics relied on normal meals and exercise as challenges. An alternative approach is to employ a larger range of perturbations designed to explore the full dynamic response. In the following examples, methods of time-scale analysis are applied to four subject groups using different specified perturbations.

The upper two panels of Figure 5 contain results from, respectively, fasting[16] and constant intravenous infusion of glucose, comparing responses from control subjects without diabetes, subjects having impaired glucose tolerance, and subjects with type 2 diabetes.[25–27] As was the case with continuous enteral feeding (Fig. 1, upper right panel), both fasting and continuous intravenous glucose infusion lead to an oscillatory response with a period of about 100 min in subjects without diabetes. In subjects with impaired glucose tolerance, the energy in these oscillations is shifted toward longer time scales.

Similarly, sinusoidal intravenous infusion of glucose can serve as a tool for distinguishing between normal and abnormal states.[17,28,29] The normalized energy profile is shown in the lower left panel for a control subject without diabetes and a subject with type 2 diabetes during sinusoidal infusion at a period of approximately 100 min. *Entrainment*, or the spontaneous synchronization of the system dynamics to the input dynamics, occurs to a quite different extent in these two subjects. As in the previous example, the energy distribution is shifted to longer periods in the subject with type 2 diabetes. The lower right panel shows results from two patients prior to and after the removal of insulin-secreting tumors that led to

Table 2. Contribution of High-Frequency Oscillation Component to Total Blood Glucose Signal Energy

Reference	*Sample period (min)*	*Conditions during recording*	*Total energy*	*Energy in <30 min component*	*Percentage of total energy*
Sturis et al.[24]	2	Fasting	700	120	16.8
Simon et al.[15]	2	Continuous feeding	20,000	500	2.5
Simon et al.[23]	4	Meal challenge	7,240	290	4.0
Simon et al.[23]	4	Meal challenge	5,880	120	2.0
Simon et al.[23]	4	Meal challenge	22,300	850	3.8
Simon et al.[23]	4	Meal challenge	24,100	820	3.4
Simon et al.[23]	4	Meal challenge	27,500	270	1.0
Simon et al.[23]	4	Meal challenge	32,700	920	2.8
Simon et al.[23]	4	Meal challenge	43,400	160	0.4
Simon et al.[23]	4	Meal challenge	94,500	430	0.5

Data means and linear trends have been removed. Total energy is dependent on the cumulative number of samples.

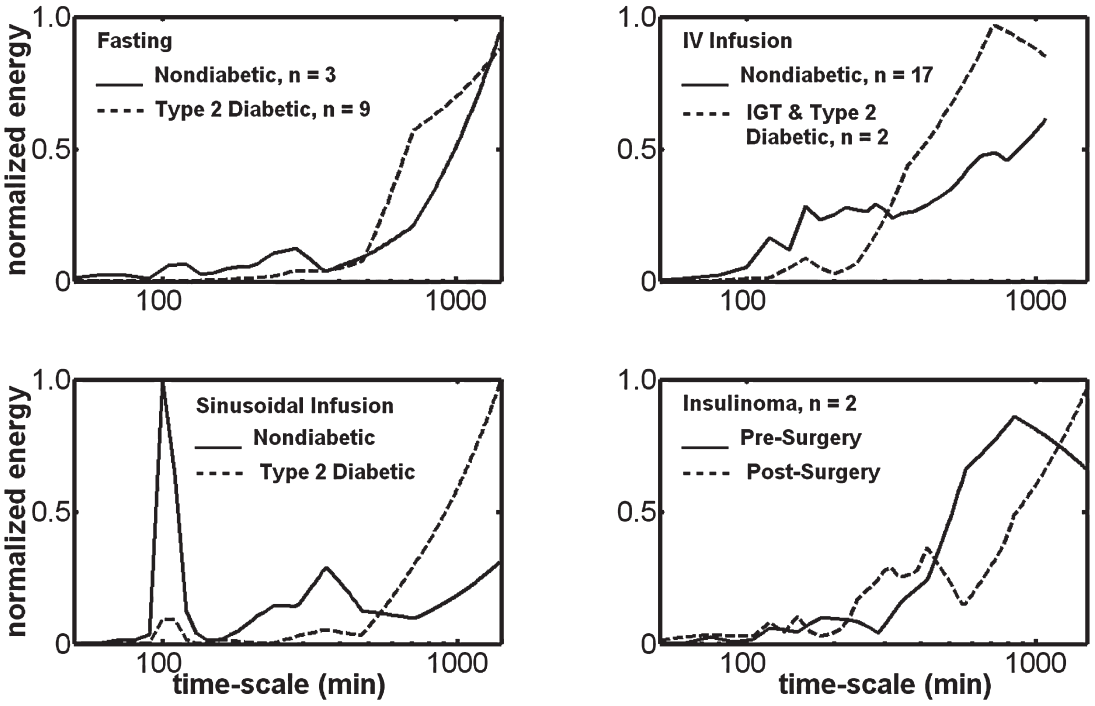

FIG. 5. Comparisons of time scales of four subgroups under different perturbations. (**Top left**) Spectral comparisons between subjects without diabetes and those with type 2 diabetes during fasting[16] show a shift in energy distribution towards slower dynamics. (**Top right**) Similar trends are shown in subjects during intravenous (IV) infusion.[25–27] IGT, impaired glucose tolerance. (**Lower left**) Sinusoidal infusion leading to entrainment in controls without diabetes, denoted by a large singular peak, and loss of entrainment in the subject with type 2 diabetes.[17,28,29] (**Lower right**) Changes in time-scale energy profiles are also observed in two patients with insulinoma prior to and after removal of the tumor.[30]

hypoglycemia. The patients received frequent meals and glucose monitoring. The relative energy distribution shift is presumed due to removal of the abnormal insulin source.

Example 6: movement of the signal energy time scale

Although the Fourier transform has an elegant physical underpinning and is well suited for signals that are strictly repeated in time, the periodic content of blood glucose signals with external perturbations is not usually constant, because of nonlinearity of the system and nonstationarity of the perturbations. It has been assumed here that the dynamic time scales are constant during individual recordings, but it is important to realize that time scales themselves may be time-dependent.[31] Other methods of time-frequency analysis should therefore be used to view the signal in different ways that allow visualization of time-localized events.

Figure 6 shows the results of such an analysis of data from a subject without diabetes using the method of continuous wavelet transforms. The blood glucose signal (above) shows oscillations caused by continuous enteral feeding.[15] Previous investigators have noted that these oscillations change in amplitude over time, even in the absence of changes in glucose infusion pattern.[15] Below, the signal is decomposed into multiple time scales of a preselected waveform (the Morelet waveform,[32] in this case), and the energy in each time scale is estimated for sequential segments of the time series. The distribution of time scales is shown as a function of time bands, with the intensity indicating where the data appear. As time advances, the time scale energy content of the oscillations changes. The change itself may contain inherent structure that can be exploited further for blood glucose prediction and controller design.

This plot can also be used to examine the

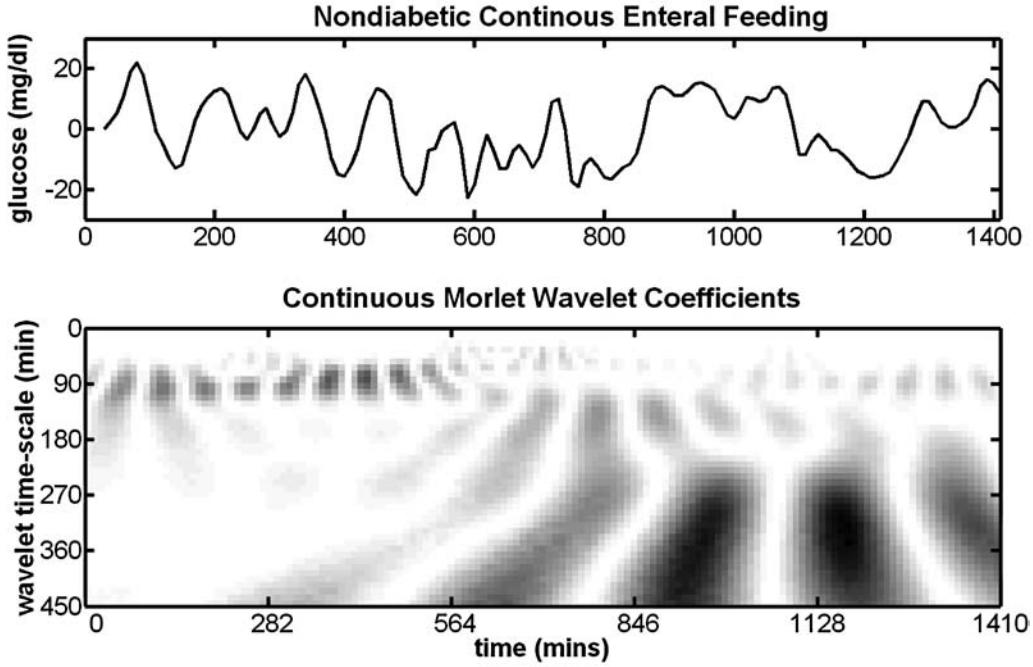

FIG. 6. Wavelet analysis of a time series. (**Top**) Glucose values as a function of time in a subject without diabetes undergoing continuous enteral feeding. A gradual shift toward a longer time scale is noted near the end of the time series. (**Bottom**) The wavelet scale is plotted as a function of energy shift, with the intensity (gray scale) indicating the energy of time domains in the respective time scales.

gradual change in the frequency content of the oscillatory response as a function of other variables (in this case, time of day and sleep). This time series demonstrates both the approximately 100-min time scale and the circadian time scale observed in controls without diabetes.

Example 7: toward a patient profile

An important objective of this approach to blood glucose monitoring is to provide a simple-to-use clinical tool for diagnostic and therapeutic decisions. Perhaps the first step to the clinical introduction of dynamic analysis is to establish a patient profile that provides multiple views of the glucose signal. An example of such a proposed profile is given in Figure 7, which employs several of the tools described here. The software for generation of this profile and other graphs described in this communication can be found on-line (downloadable software that can be used to generate these figures from regularly sampled blood glucose data can be found at http://glucosedynamics.ucsd.edu.).

CONCLUSIONS AND RECOMMENDATIONS

Diagnosis and therapy in diabetes have historically been based on statistical glucose monitoring where measurements are independent, rather than on dynamic monitoring where measurements are mutually related. However, there is untapped information about blood glucose dynamics in continuous or frequently sampled serial measurements, and new sensor systems intended to provide this information are entering clinical practice. Nevertheless, new methods are needed for qualification of these sensors to assure that they faithfully capture subject-specific blood glucose dynamics. New sensors can lead to a variety of innovative studies using relevant perturbations such as exercise and normal activity, repeated on individuals over time, tracking the results of therapy, and exploring a range of subject demographics. Similar studies are also needed on a broad range of individuals not having diabetes. With a deeper understanding, the incorporation of blood glucose dynamics into clinical

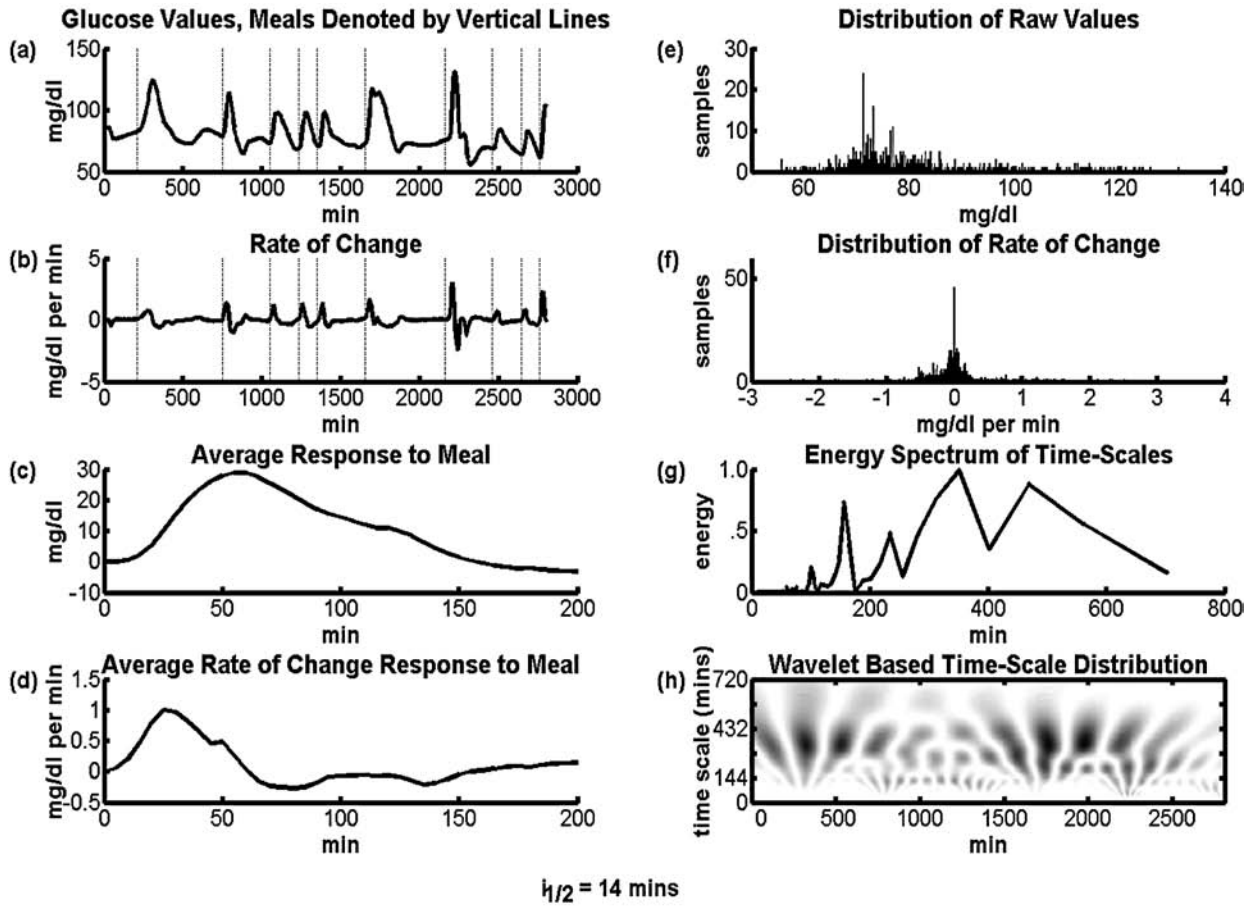

FIG. 7. Proposed dynamic profile. (**a**) A blood glucose time series with meals denoted by vertical lines.[7] (**b**) One of the simplest forms of dynamic information, the derivative of the signal estimated by subtracting sequential data points and dividing by the sampling interval, shows the rate of rise and fall of glucose. (**c**) The averaged responses to meals, the most prominent events in the signal. (**d**) The rate of change of the averaged meal events. (**e**) Histogram of the distribution of measured values from (a). (**f**) Histogram of the distribution of the rate of change values from (b). In normal subjects, blood glucose rises and falls rapidly, the rate of change is rapid, and the distributions of these measurements are grouped around the mean. (**g**) A Fourier transform[21] represents the signal energy at successive time scales. (**h**) Graph of wavelet basis functions,[32] an alternative to the Fourier transform, where both the timing and the time scale are considered. The information half-life applied for all data shown.

practice may be an important step toward qualitative and quantitative improvements in blood glucose control.

APPENDIX

Certain definitions have been summarized in a mathematical format elsewhere.[13]

autocorrelation function: An index of how much a given measurement at a specified time correlates with another measurement at another time.

average mutual information: The amount information shared between two data points. A measure of predictability of a future signal value based on the current value.

entrainment: The process by which a system adopts dynamics at the same time scale as another system connected to it.

Fourier transform: An algorithm for converting samples in a time series into an equivalent frequencies.

linear system: A system in which inputs are strictly additive to produce proportional outputs.

stationarity: A system property in which the dynamic character does not change with time.

Nyquist criterion: States that a signal must be

sampled at least twice the frequency (one-half the time scale) of its fastest component to avoid distortion.

signal energy: The magnitude of individual glucose measurements squared and summed.

time scale: The time or the inverse of frequency required for a specific change to occur in the system.

time series: A series of measurements of a dynamic system in which each measurement occurs after a fixed, specified time interval.

wavelet transform: A mathematical process that converts time series measurements into time scales and shows how the time scales evolve with time.

CONFLICT OF INTEREST STATEMENT

D.A.G. is founder and advisor to GlySens, Inc., a company that develops glucose sensor technology. This arrangement is approved by the University of California San Diego in accordance with its conflict of interest policies.

ACKNOWLEDGMENTS

This work was funded by grants DK64570 and DK77101 from the National Institutes of Health.

REFERENCES

1. Gough DA, Kreutz-Delgado K, Bremer TM: Frequency characterization of blood glucose dynamics. Ann Biomed Eng 2003;31:91–97.
2. Bremer T, Gough DA: Is blood glucose predictable from previous values? A solicitation for data. Diabetes 1999;48:445–451.
3. The Diabetes Research in Children Network (DirecNet) Study Group: The accuracy of the CGMS in children with type 1 diabetes: results of the Diabetes Research in Children Network (DirecNet) accuracy study. Diabetes Technol Ther 2003;5:781–789.
4. Rahaghi FN, Gough DA: Glucose sensors. In: Webster J, ed. Encyclopedia of Medical Devices and Instrumentation. New York: John Wiley & Sons, 2006: 393–406.
5. 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.
6. Palm WJ III: Modeling, Analysis and Control of Dynamic Systems. New York: John Wiley & Sons, 1999.
7. Service FJ, Molnar GD, Rosevear JW, Ackerman E, Taylor BW, Cremer GM, Moxness KE: Mean amplitude of glycemic excursions, a measure of diabetic instability. Diabetes 1970;19:644–655.
8. Hosker JPM, Rudenski DR, Burnett AS, Darling MA, Bown EG, Turner RC: Continuous infusion of glucose with model assessment: measurement of insulin resistance and beta-cell function in man. Diabetologia 1985;28:401–411.
9. Geiger MC, Ferreira JV, Hafiz MM, Froud T, Baidal DA, Meneghini LF, Ricordi C, Alejandro R: Evaluation of metabolic control using a continuous subcutaneous glucose monitoring system in patients with type 1 diabetes mellitus who achieved insulin independence after islet cell transplantation. Cell Transplant 2005;14:77–84.
10. Kerssen A, de Valk HW, Visser GH: Day-to-day glucose variability during pregnancy in women with Type 1 diabetes mellitus: glucose profiles measured with the Continuous Glucose Monitoring System. BJOG 2004;111:919–924.
11. Rebrin K, Steil GM: Can interstitial glucose assessment replace blood glucose measurements? Diabetes Technol Ther 2000;2:461–472.
12. 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.
13. Rahaghi FN: Blood Glucose Dynamics in Diabetes [Ph.D. Thesis]. San Diego, CA: University of California San Diego, 2007.
14. Bremer TM, Edelman SV, Gough DA: Benchmark data from the literature for evaluation of new glucose sensing technologies. Diabetes Technol Ther 2001;3:409–418.
15. Simon C, Brandenberger G, Follenius M: Ultradian oscillations of plasma glucose, insulin, and C-peptide in man during continuous enteral nutrition. J Clin Endocrinol Metab 1987;64:669–674.
16. Shapiro ET, Polonsky KS, Copinschi G, Bosson, D, Tillil H, Blackman J, Lewis G, van Cauter E: Nocturnal elevation of glucose levels during fasting in non-insulin-dependent diabetes. J Clin Endocrinol Metab 1991;72:444–454.
17. Sturis J, van Cauter E, Blackman JD, Polonsky KS: Entrainment of pulsatile insulin secretion by oscillatory glucose infusion. J Clin Invest 1991;87:439–445.
18. Abarbanel HDI: Analysis of Observed Chaotic Data. New York: Springer, 1996.
19. Marple SL: Digital Spectral Analysis with Applications. Englewood Cliffs, NJ: Prentice-Hall, 1987.
20. Kay SM: Fundamentals of Statistical Signal Processing. Englewood Cliffs, NJ: Prentice-Hall, 1993.
21. Oppenheim AV, Schafer RW: Digital Signal Processing. Englewood Cliffs, NJ: Prentice-Hall, 1975.

22. Porksen N: The in vivo regulation of pulsatile insulin secretion. Diabetologia 2002;45:3–20.
23. Simon C, Follenius M, Brandenberger G: Postprandial oscillations of plasma glucose, insulin and C-peptide in man. Diabetologia 1987;30:769–773.
24. Sturis J, Polonsky KS, Shapiro ET, Blackman JD, O'Meara NM, van Cauter E: Abnormalities in the ultradian oscillations of insulin secretion and glucose levels in type 2 (non-insulin-dependent) diabetic patients. Diabetologia 1992;35:681–689.
25. Shapiro ET, Tillil H, Polonsky KS, Fang VS, Rubenstein AH, van Cauter E: Oscillations in insulin secretion during constant glucose infusion in normal man: relationship to changes in plasma glucose. J Clin Endocrinol Metab 1988;67:307–314.
26. Frank SA, Roland DC, Sturis J, Byrne MM, Refetoff S, Polonsky KS, van Cauter E: Effects of aging on glucose regulation during wakefulness and sleep. Am J Physiol 1995;269:E1006–E1016.
27. Scheen AJ, Sturis J, Polonsky KS, van Cauter E: Alterations in the ultradian oscillations of insulin secretion and plasma glucose in aging. Diabetologia 1996;39:564–572.
28. Sturis J, O'Meara NM, Shapiro ET, Blackman JD, Tillil H, Polonsky KS, van Cauter E: Differential effects of glucose stimulation upon rapid pulses and ultradian oscillations of insulin secretion. J Clin Endocrinol Metab 1993;76:895–901.
29. O'Meara NM, Sturis J, van Cauter E, Polonsky KS: Lack of control by glucose of ultradian insulin secretory oscillations in impaired glucose tolerance and in non-insulin-dependent diabetes mellitus. J Clin Invest 1993;92:262–271.
30. Villaume C, Beck B, Dollet JM, Pointel JP, Drouin P, Debry G: 28-hour profiles of blood glucose (BG), plasma immunoreactive insulin (IRI) and IRI/BG ratio in four insulinomas. Ann Endocrinol (Paris) 1984;45:155–60.
31. Cohen L: Time-Frequency Analysis. Englewood Cliffs, NJ: Prentice-Hall, 1995.
32. Mallat SG: A Wavelet Tour of Signal Processing. San Diego, CA: Academic Press, 1998.

Address reprint requests to:
David Gough, Ph.D.
Department of Bioengineering
University of California San Diego
9500 Gilman Drive
La Jolla, CA 92093-0412

E-mail: dgough@ucsd.edu