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Frequency Characterization of Blood Glucose Dynamics

DAVID A. GOUGH,[1,3] KENNETH KREUTZ-DELGADO,[2,3] and TROY M. BREMER[1]

[1]Department of Bioengineering, [2]Department of Electrical and Computer Science, [3]Project on Glucose Monitoring and Control, University of California San Diego, San Diego, CA

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Abstract—Examples of the frequency range of blood glucose dynamics of normal subjects and subjects with diabetes are reported here, based on data from the literature. The frequency band edge was determined from suitable, frequently sampled blood glucose recordings using two methods: frequency domain estimation and signal reconstruction. The respective maximum acceptable sampling intervals, or Nyquist sampling periods (NSP), required to accurately represent blood glucose dynamics were calculated. Preliminary results based on the limited data available in the literature indicate that although blood glucose NSP values are higher in most diabetic subjects, values in some diabetic subjects are indistinguishable from those of normal subjects. High fidelity monitoring sufficient to follow the intrinsic blood glucose dynamics of all diabetic subjects requires a NSP of ~ 10 min, corresponding to a continuous frequency band edge of $\sim 1 \times 10^{-3}$ Hz. This analysis provides key information for the design of clinical studies that include blood glucose dynamics and for the design of new glucose monitoring systems. © *2003 Biomedical Engineering Society.*
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Keywords—Blood glucose dynamics, Nyquist sample period.

INTRODUCTION

Diabetes in its various forms is a disease of increasing morbidity characterized by metabolic imbalances and devastating complications.[17] Results of the recent Diabetes Control and Complications Trial (DCCT)[15] and related clinical trials[9,16] have established a causal relationship between time-averaged blood glucose, as indicated by surrogate glycosylated hemoglobin levels (Hb_{A1c}), and the incidence and severity of diabetic complications. The Hb_{A1c} assay provides an index approximately proportional to blood glucose levels averaged over a three-month period.[3] These clinical trials were not, however, designed to include the role of blood glucose dynamics on a short time scale, as the Hb_{A1c} method is inherently incapable of indicating daily blood glucose excursions or of discriminating sustained periods of near normal blood glucose from periods of persistent swings between hyperglycemia and hypoglycemia. Direct blood glucose measurements were not utilized in the DCCT and other studies because the required frequency of blood collection by venipuncture or ''fingersticking'' was substantially greater than could have reasonably been expected of study subjects over the multiyear study period. A study that includes blood glucose dynamics would require direct measurement of blood glucose at a sufficiently regular sampling frequency to reliably report all blood glucose changes in all diabetic subjects. Although some persons with diabetes are willing to perform blood collection multiple times a day when awake, this is not likely to be sufficient to record all blood glucose excursions. Without such frequently sampled blood glucose information, present diabetes treatment modalities cannot systematically incorporate blood glucose dynamics.

New blood glucose sensor systems are under development that may be more acceptable to people with diabetes. Some of these sensors are implantable and make automatic blood glucose determinations that are continuous or near-continuous and do not require user initiative for sample collection. Other sensors are based on methods of discrete sampling and make measurements on demand or at specifiable intervals. In addition to the important advantage of potentially making glucose monitoring more convenient and acceptable to people with diabetes, certain of these new sensing technologies, if properly designed and implemented, may provide the means of monitoring the full range of blood glucose dynamics. This capability may lead to new therapeutic options.

This suggests a key question: How often must blood glucose measurements be made to accurately represent blood glucose dynamics? The question must be addressed for both diabetics and nondiabetic controls, as a potential treatment objective is the return of diabetic blood glucose dynamics to normal by appropriate therapy. The question should also apply to all glucose monitoring technologies, regardless of sensing principle.

In addressing this question, it is advisable to analyze potentially applicable data from the literature prior to collecting extensive new data. This is because a key

Address correspondence to David Gough, Department of Bioengineering, University of California San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0412. Electronic mail: dgough@bioeng.ucsd.edu

experimental design parameter, the sampling frequency needed to capture all dynamic features, has not been previously established and directions are needed for rational design of new study protocols. Moreover, data collected with new glucose sensors under development may not be appropriate for these definitive studies because, in most cases, these sensors have not been validated and remain to be optimized for frequency response. It is also essential that direct blood glucose recordings are used to establish a sensor-independent dynamic standard, rather than employing information from tissue fluids or other indirect sources on which some sensing strategies are based, as it remains to be shown that glucose from such sources closely follows blood glucose.[1]

In this article, we give examples of spectral analysis methods applied to frequently sampled, benchmark blood glucose measurement sets in the literature collected from normal and diabetic subjects.[2] Frequency domain and signal reconstruction methods are applied to the data to generate information power spectra, the band edges of which provide estimates of the Nyquist sampling period (NSP),[7] or maximum acceptable sampling interval required to accurately represent continuous blood glucose dynamics. Results are shown for diabetic subjects receiving various treatment modalities and two nondiabetic control subjects. The NSP values may provide insights about intrinsic dynamics of blood glucose regulation, indicate sampling protocols for new clinical studies, and suggest performance standards for new glucose sensors.

BACKGROUND

Several *ad hoc* approaches have been proposed for characterizing blood glucose excursions. In previous studies,[12] blood glucose excursions were classified in terms of the number of wide swings, the extent of high and variable diurnal averages, and the frequency of hypoglycemic episodes. Metrics used previously have been: means and standard deviations, mean amplitude of glycemic excursions exceeding one standard deviation, and the ratio of blood glucose measurements to a reference blood glucose concentration weighted to emphasize hypoglycemia. These approaches provide some information about the extent of glycemic excursions, but reveal little information about blood glucose dynamics. Other approaches such as oral and intravenous glucose tolerance tests commonly used in diagnosis of the disease contain some dynamic information, but are fixed, limited challenges. These challenges may be useful for diagnosis but are of little value for indicating the range of blood glucose dynamics associated with typical daily activities. Ideal challenges for characterizing blood glucose dynamics should include blood glucose determinations frequent enough to detect all variations over a period of several days while the subject is undergoing a wide range of activities.

METHODS

Data

It has previously been pointed out that there are very few published examples of frequently sampled blood glucose measurements that are suitable for dynamic analysis,[1] and a solicitation for the collection of additional data sets has been made. Benchmark quality data sets from the literature[2] used in the present analysis consisted of frequently sampled, nonaveraged blood glucose measurements collected over periods of 10–48 h from subjects with type 1 diabetes,[5,6,11,13,14] pregnant female subjects with type 1 and type 2 diabetes,[10] and nondiabetic subjects.[8,11] Blood glucose determinations were made at regular intervals of 2–5 min in respective studies. The data sets were digitized directly from the published figures and are available in a digital format from the present authors.[4] General characteristics of these data sets and their suitability for reference dynamic measurements have been described elsewhere.[2] It is important to note that these data represent natural or intrinsic blood glucose dynamics as opposed to blood glucose excursions created by nonphysiologic challenges.

Frequency Range Estimation: Frequency Domain

The frequency ranges were estimated indirectly using time series reconstruction and directly using frequency domain representations of the recordings. Specifically, power spectrum estimates were used to represent the information contained in the serial blood glucose measurements at a finite number of frequencies. To obtain the power spectrum estimates, the data were linearly detrended and the estimate calculated using Welch's averaged periodogram method that was weighted to be asymptotically unbiased.[7] The power spectrum estimation was implemented in Matlab (The Mathworks, Inc.).

The band edge frequency of each blood glucose data set was iteratively defined by the intersection of the main lobe of the power spectrum estimate with the upper edge of a confidence interval about the noise floor. The noise floor frequency range was defined as the interval from the band edge frequency to the highest frequency included in the power spectrum estimate. The upper edge of the confidence interval about the noise floor was defined as the sample mean plus two standard deviations of the noise floor. The intersection of the noise floor upper bound with the main lobe of the power spectrum estimate was used to redefine the band edge frequency and thus the noise floor range. This process was repeated

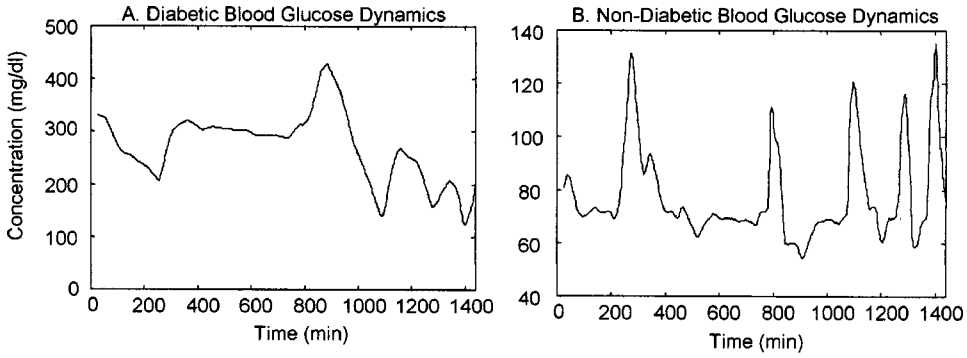

FIGURE 1. (A) and (B) Examples of a 24 h segment of frequently-sampled blood glucose recordings from the literature. Individual data points were collected at fixed sample intervals of 5 min and connected by straight lines. These data are representative of responses to a typical daily schedule of meals, exercise, sleep, and other activities. (A) Subject with type 1 diabetes receiving one injection of regular insulin per day; (B) nondiabetic subject.

until the band edge was consistently defined by the upper edge of the confidence interval about the identified noise floor.

Frequency Range Estimation: Reconstruction Method

An alternative criterion for establishing the frequency range of a dynamic signal is based on signal reconstruction. In the present analysis, the frequency range of the blood glucose dynamics was also estimated by implementing sequential low pass filtering to determine the minimum frequency range that allowed a specified fraction of the total power in the original discrete measurement set to be represented after the low pass filtering. The 3 dB cutoff frequency of a low pass filter was used to demarcate the effective 95% or 99% reconstruction frequency at which only 50% of the power of the original signal was allowed to pass. The power content of the original signal at frequencies greater than the cutoff frequency of the low pass filter was essentially eliminated.

Sequential band edge reduction was performed using a fifth-order Chebyshev type II digital low-pass filter[7] designed with 20 dB of side lobe suppression. The filter was implemented in an anticausal manner using Matlab to achieve a near-ideal, low-pass filter with precisely zero-phase distortion and 40 dB of stop-band attenuation. This eliminated 99% of the power in the signal for frequencies higher than the band edge of the low pass filter. The frequency range of the filter was iteratively adjusted until the reconstruction error of the original measurement sequences had, for example, 5% variance or equivalently, a root mean squared error of 2.2%, as given by the following equation:

$$e_{\mathrm{rms}}\% = 100\times \sqrt{\frac{1}{N}\sum_{k=1}^{N-1}\left(\frac{[y(k)-\hat{y}_f(k)]}{y(k)}\right)^2}. \qquad (1)$$

Both methods were validated by application to simulated data having the same characteristics as the original data.

Nyquist Sampling

The maximum sampling period that is necessary and sufficient for discrete representation of the unfiltered and the filtered measurement sequences was then determined for the band edge frequency and the bandwidth defined using 95% or 99% effective signal reconstruction. The maximum sampling period for both criteria was defined in accordance with the Nyquist sampling theorem,[7] which states that the necessary and sufficient sampling rate to represent a continuous band-limited sequence with discrete samples is greater than or equal to twice the maximum band-limited frequency, or the band edge frequency:

$$w_{\mathrm{NSR}} \geqslant 2\times w_{\mathrm{BE}}. \qquad (2)$$

From the above, the maximum necessary and sufficient sampling period or Nyquist sampling period (NSP), is defined:

$$\mathrm{NSP} = \frac{1}{w_{\mathrm{NSR}}} \leqslant \frac{1}{2w_{\mathrm{BE}}}. \qquad (3)$$

RESULTS

Examples of Data

Examples of recordings of blood glucose dynamics from the literature are given in Figs. 1(A) and 1(B). Figure 1(A) shows a 24 h segment of blood glucose measurements obtained from a diabetic subject at a fixed sample collection interval of 5 min, with data points connected by straight lines. The ordinate is time in minutes and the abscissa is blood glucose concentration in mg/dl. These data are representative of large and sus-

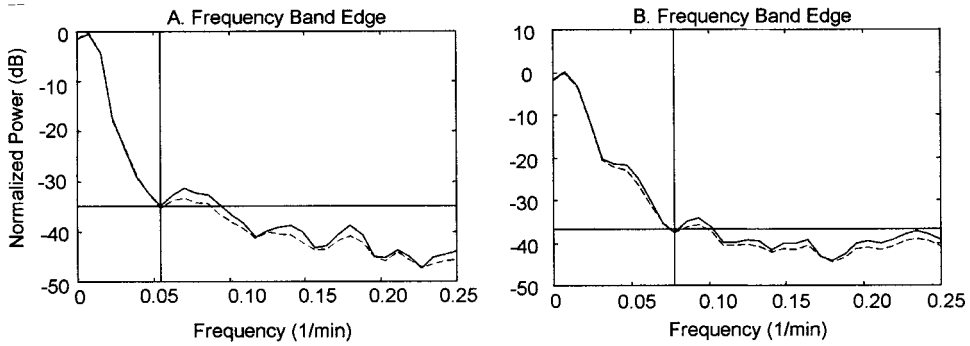

FIGURE 2. (A) and (B) Band edge of blood glucose dynamics determined using the frequency domain method, corresponding to data in Figs. 1(A) and 1(B), respectively. Solid data line: unfiltered data. Broken data line: filtered data, horizontal line: noise floor, vertical line: band edge.

tained blood glucose excursions characteristic of type 1 diabetes in response to a typical daily schedule of meals, exercise, sleep, and once-daily insulin injection. Figure 1(B) contains blood glucose measurements obtained from a nondiabetic subject under the same conditions and at the same fixed sample collection interval as in Fig. 1(A), showing relatively brief blood glucose excursions corresponding to a typical daily schedule of meals, exercise, sleep, and other activities. The qualitative differences between diabetic and nondiabetic blood glucose variations, and the observation that diabetic excursions are usually much larger and prolonged are consistent with clinical experience.

Frequency Domain

Results of the power spectrum estimate method are illustrated in Figs. 2(A) and 2(B), based, respectively, on the data in Figs. 1(A) and 1(B). The ordinate is frequency in minutesand the abscissa is signal power expressed in decibels (dB). The power spectrum estimate based directly on the signal is indicated by the solid line, and the estimate based on the signal filtered as described above is indicated by the broken line. The horizontal line indicates the noise floor of the original signal, maintained at constant amplitude to the maximum frequency of the power spectrum estimate. The intersection of the dynamic signal and the noise floor is the band edge, indicated by the vertical line, which occurs for the diabetic subject [Fig. 2(A)] at 5.5×10^{-2} min^{-1} or 0.9×10^{-3} Hz, corresponding to a NSP value of about 9 min, and for the nondiabetic subject [Fig. 2(B)] at 7.8×10^{-2} min^{-1} or 1.3×10^{-3} Hz, corresponding to a NSP value of about 7 min. The sampling interval of 2–5 min used originally in collection of these data was sufficiently short to avoid compromising the conclusion that NSP values of 7–9 min are adequate to record all dynamic characteristics of these data.

Reconstruction

Results of 95% signal reconstruction are illustrated in Figs. 3(A) and 3(B), based on data in Figs. 1(A) and 1(B), respectively. The ordinate is frequency in minutes and the abscissa is signal power expressed in decibels. The power spectrum estimate from the signal is indicated by the solid line, and the estimate based on the low pass filtered signal determined to allow for 95% signal recon-

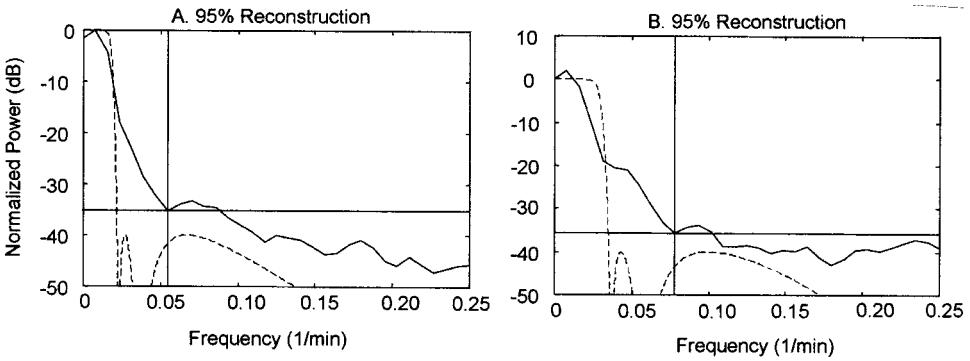

FIGURE 3. (A) and (B) Frequency extent of blood glucose dynamics determined using the 95% reconstruction method, corresponding to data in Figs. 1(A) and 1(B), respectively. Solid data line: unfiltered data; broken data line: filtered data; horizontal line: noise floor; vertical line: band edge.

struction is indicated by the broken line. The 95% effective band edge is indicated by the vertical line, which passes through the 3 dB cutoff frequency of the low pass filter. The band edge frequency for the diabetic subject [Fig. 3(A)] is 5.6×10^{-2} min^{-1} or 0.9×10^{-3} Hz, corresponding to a NSP value of about 9 min. The band edge frequency is defined using the noise floor. For the nondiabetic subject [Fig. 3(B)], the band edge frequency is 7.7×10^{-2} min^{-1} or 1.3×10^{-3} Hz, corresponding to a NSP value of about 7 min.

Although values of blood glucose band edge frequency and NSP values differed between the diabetic and nondiabetic subjects, the frequency domain method and reconstruction method gave comparable results for the respective cases. Therefore, from practical considerations of sensor operation rather than mathematical imperatives, the reconstruction method based on the 99% reconstruction criteria, which gives a closer approximation of the frequency band edge corresponding to a slightly greater value for NSP, is recommended for further studies. This represents a compromise of somewhat less frequent sampling, which is desirable for sensors requiring discrete sampling, while still maintaining specifiable accuracy,

The values of the band edge determined here are typical of the available data, but the generality of the values is limited more by the paucity of available data than the analysis methods. Although the two methods gave confirmatory results, it is clear that substantially more clinical data is needed for final recommendations. In the absence of sufficient data, a conservative recommendation is that practical sensor systems should be overdesigned if possible to respond to the most rapid blood glucose dynamic characteristics observed here.

Summary of Observations

Figure 4 shows NSP values corresponding to the bandwidth needed to achieve less than 1% rms reconstruction error (99% criteria) for individuals in five relevant clinical groups and nondiabetic controls. These data represent subjects where blood glucose values were determined sufficiently frequently over periods of many hours to days.[2] The groups listed in the abscissa are: nondiabetic subjects (NDB, $n=2$); type 1 and type 2 diabetic subjects intensively treated with intravenous insulin under automatic feedback control (DB1, $n=11$); type 1 diabetic subjects treated intensively with four or more insulin injections per day (DB2, $n=6$); type 1 and type 2 diabetic subjects treated moderately with intravenous insulin under automatic feedback control and decreased insulin infusion rate (DB3, $n=3$); type 1 diabetic subjects treated with two insulin injections per day (DB4, $n=17$); and all subjects ($n=37$) in groups DB1 through DB4 (DB 1–4).

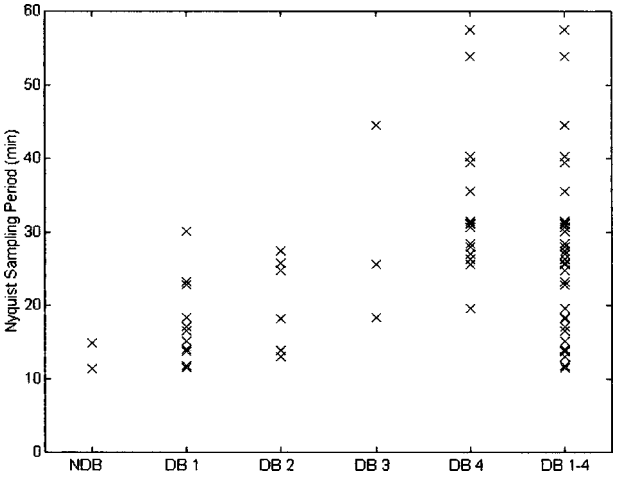

FIGURE 4. Nyquist sampling period for less than 1% rms reconstruction error of blood glucose dynamics in diabetic and nondiabetic subjects. (NDB) Nondiabetic subjects; (DB1) type 1 and type 2 diabetic subjects intensively treated with intravenous insulin under automatic feedback control; (DB2) type 1 diabetic subjects treated intensively with four or more insulin injections per day; (DB3) type 1 and type 2 diabetic subjects treated moderately with intravenous insulin under automatic feedback control and decreased insulin infusion rate; (DB4) type 1 diabetic subjects treated with two insulin injections per day; (DB 1–4) All subjects in groups DB1–DB4.

Comparison of Results from Diabetic and Nondiabetic Subjects

NSP values extend over a much greater range in diabetic subjects, although this conclusion can only be tentative as the number of individuals in the two groups is substantially different (two nondiabetic vs. 37 diabetic subjects). Nevertheless, the sampling period needed to represent the dynamics of certain members of some diabetic groups appears comparable to the sampling period requirements of the nondiabetic subjects. This figure shows that a NSP of $\sim$10 min is needed for a reconstruction to within 1% rms error of the most rapid anticipated blood glucose dynamics of all subjects. This tentative conclusion is consistent with conventional wisdom, but the analysis further demonstrates the need for additional data, especially from the nondiabetic group.[1]

DISCUSSION

Limited Availability of Data

The biggest difficulty in identifying the frequency range of blood glucose dynamics in diabetic and nondiabetic individuals was finding appropriate, frequently sampled blood glucose data, especially for the nondiabetic controls. There is a substantial volume of blood glucose data in the literature, but the vast majority of data are collected with sampling periods that are far too long to be useful for characterizing the total dynamic

content. Moreover, multiple data points at a given time are often averaged, as is typically required by journal publication policies, masking the connectivity of individual excursions. Although few suitable data are available for nondiabetic subjects, clinical experience suggests that the dynamic response of diabetic subjects to typical daily glycemic challenges extends over a much broader range than that of nondiabetic individuals. Collection of additional data from nondiabetic controls is of great importance to define the mean and range of performance standards for new therapies intended to restore normal blood glucose dynamics.

The problem of insufficient data representing nondiabetic control subjects was circumvented in the DCCT by the use of data from respective diabetic subjects as control data prior to receiving the test treatment. As the Hb_{A1c} assay is insensitive to short time-scale blood glucose dynamics, it is clear that such dynamics were not considered either in the control or treatment phases of the study. An assumption that there were no treatment-induced differences in the blood glucose dynamics in a given subject was not testable by the data used in the study. It is of interest to determine if there are dynamic differences between normal subjects and well-controlled diabetic subjects, a question to be resolved by future studies.

Nyquist Sampling Period

It is nevertheless of interest that NSP values of a small fraction of diabetic subjects appear indistinguishable from those of nondiabetic subjects. However, these preliminary conclusions are limited by the availability of nondiabetic data, of which there are little. Furthermore, based on these data alone, it is also not possible to determine whether diabetic subjects with apparently near-normal blood glucose dynamics reflect intrinsic characteristics of those individuals, or whether subjects with previously less favorable dynamics have benefited from improved therapy. New studies are needed to resolve these important questions. The availability of the metrics described here for dynamic blood glucose provides a basis for the design and interpretation of such studies.

Application to New Sensor Systems

Certain new glucose sensor systems under development may be more convenient, unobtrusive, automatic, and acceptable to patients over the long term. However, each of these sensor systems has respective dynamic response properties, including transient response to blood glucose, lags, and sampling frequency. There is a need to establish rational performance standards based on anticipated blood glucose monitoring requirements to effectively design and evaluate sensors. It is important to include information in the standards representing normal blood glucose dynamics and the normal range of variability of blood glucose. The requirements for frequency band edge and corresponding NSP values are applicable to all glucose sensing systems, regardless of the mode of operation.

Sensing systems that have dynamic characteristics insufficient to follow the most rapid diabetic blood glucose excursions may nevertheless still be of use in diabetes therapy for the majority of diabetic subjects with slower blood glucose variations, or wheretime-averaged blood glucose values are clinically acceptable. However, it may not be possible to control dynamic modes of insulin delivery from adjustable rate insulin replacement pumps and related devices if the sensor frequency response is inadequate.

CONCLUSIONS

The role of blood glucose dynamics in diabetes is not well understood. This analysis suggests methods of frequency domain estimation and signal reconstruction that can be used to establish sampling frequency requirements and identify the maximum acceptable sampling interval, NSP, or its frequency equivalent. This leads to the tentative conclusion that accurate monitoring of blood glucosedynamics in the most rapidly responding diabetic subjects and in nondiabetic subjects requires sampling at approximately every 10 min or use of a continuous sensor system with a band edge of about 1×10^{-3} Hz. This tentative conclusion is based on the limited amount of available data, and collection of additional appropriate data is needed. These results suggest blood glucose sampling requirements for future clinical studies and identify dynamic performance goals for new blood glucose sensor systems.

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