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CONTROVERSIES in
Continuous Glucose Monitoring

Optimum Subcutaneous Glucose Sampling and Fourier Analysis of Continuous Glucose Monitors

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Abstract

Background:

The objective of this article was to focus on the application of harmonic decomposition to continuous glucose monitor (CGM) measurements. We show evidence of an attenuation of fast variations of interstitial glucose when compared to blood in type 1 diabetes mellitus (T1DM) and, using information theory, propose optimal sampling schedules associated with the use and study of CGMs.

Method:

Using a cohort of 26 T1DM subjects, wearing two Navigator™ sensors for 1 to 3 days, we analyzed the frequency content of each glucose signal and derived across subject frequency cutoffs using discrete Fourier transform and common signal processing techniques.

Results:

We observed a significant difference in the frequency content of blood glucose compared to interstitial glucose in T1DM, providing evidence toward the existence of a diffusion process between blood and interstitial glucose, acting as a low-pass filter. Furthermore, we obtained a 15-minutes sampling schedule for optimal comparison of CGM values to blood reference.

Conclusion:

Blood glucose and interstitial glucose have different dynamics, as shown by harmonic analysis, and these differences have consequences on advisable schedules for accuracy studies of CGMS.

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Abbreviations: (BG) blood glucose, (CGM) continuous glucose monitor, (IG) interstitial glucose, (T1DM) type 1 diabetes mellitus

Keywords: blood glucose, Fourier, harmonic analysis, interstitial glucose, Nyquist, optimal sampling schedule

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Introduction

In the last decade, the emergence of subcutaneous continuous glucose monitors (CGMs) has radically changed the information available via glucose measurement.[1,2] While spot measurement blood glucose (BG) indexes are still widely applicable and useful,[3] CGMs, on the basis of their frequent (1–10 minutes) and equally spaced measurements, opened the door to a breadth of signal processing methods.

These methods include, but are not limited to, autoregressive moving average time series analysis, Kalman filtering, and harmonic analysis, in particular discrete Fourier decomposition. All rely on the critical difference between spot and continuous measurement: the identification of time dependency between glucose values or the fact that values in the past can inform values in the present (smoothing, denoising) and in the future (prediction); the latter is of special interest to this article.

Even though it is considered a basic engineering method to analyze signals, discrete Fourier analysis is rather new in the glucose monitoring area and very few studies of its applicability and clinical significance can be found in the literature.[4–8] However, as glucose variability becomes more recognized as an important index of diabetes control, linked to clinical outcomes,[9,10] harmonic decomposition methodologies (e.g., Fourier decomposition, wavelet decomposition) will also become critical to the analysis of glucose traces as these methods provide decomposition of the overall glucose variability into frequency bins (Fourier) or into scales and locations (wavelet). Therefore, these methods further our understanding of the effect of variability on clinical outcomes.

In discrete Fourier analysis, the signal is represented by the strength of each of its frequencies; in optimal conditions, this alternate representation does not suffer from any loss of information. The Fourier transform, in short, identifies *recurring* patterns of particular cycle lengths (periods) and quantifies how important each cycle length is in the glucose trace: if an event or pattern occurs repeatedly and consistently, the corresponding period will be considered important. For example, a 24-hour pattern repetition will most likely be much more important than a 1-hour pattern repetition due to the circadian nature of glucose control[4] (see **Figure 1** for an example).

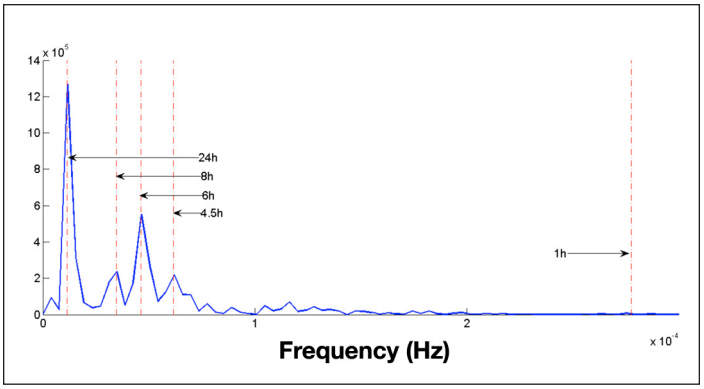

Figure 1. An example of a periodogram showing frequency content of 3 days of CGMs.

Because of the pulsatile nature of some glyco-regulatory hormones and the very fast action of these hormones on BG levels, it is likely that fast (on the scale of minutes) physiologic variations of BG could be observed in health. Fourier analysis can address the following questions: Are these variations still present in type 1 diabetes mellitus (T1DM), despite the lack of endogenous insulin production and therefore lack of feedback glucose control? Are there specific frequencies that can be correlated to diabetes or to diabetes types? Is insulin sensitivity periodic? The discrete Fourier transform is an ideal tool to answer these questions: by comparing the strength of each periodic component (cycles), we can determine what cycles are of importance and eventually link them to clinical outcomes, as demonstrated by Miller and Strange.[4] This could lead to the use of Fourier coefficients in the assessment of clinically relevant components of glucose variability.

Another type of information can be gained from frequency decompositions: the maximum significant frequency of a glucose trace. This relates to the well-known Shannon theorem,[11] but is generally referred to as Nyquist frequency and Nyquist rate; the difference between these two quantities will be made clear in the following sections.

This type of analysis becomes critical when two different fluids (blood and interstitial fluid) are sampled for the assessment of glucose concentration. Indeed, mounting evidence shows[12–14] that blood and interstitial glucose (IG), although interrelated, have different dynamics. The most common hypothesis is that IG is the result of a diffusion process of blood BG into the interstitial fluid, therefore eliminating, or at least attenuating, some of the information contained in BG.

This article focuses on the difference between BG and IG and on the ways of using Fourier decomposition to determine minimal sampling periods and/or maximum information to be expected from a specific sampling schedule of the interstitial fluid. As stated previously, this relates to the application of the Shannon sampling theorem, to continuous glucose monitoring, providing the opportunity for optimal sampling schemes to be determined in accuracy trials and everyday clinical use.

Methods

Discrete Fourier Transform

The discrete Fourier transform is based on a mathematical transformation: the initial signal (glucose trace in mg/dl or mmol/liter) is projected onto a base of sine and cosine functions of different periodicity, which leads to the following representation:

$$\begin{aligned} G(t) = a_0 &+ a_1 \text{ x } \cos\left(2\pi\frac{t}{T}\right) + b_1 \text{ x } \sin\left(2\pi\frac{t}{T}\right) \\ &+ a_2 \text{ x } \cos\left(2\pi\frac{2t}{T}\right) + b_2 \text{ x } \sin\left(2\pi\frac{2t}{T}\right) \\ &\vdots \\ &+ a_N \text{ x } \cos\left(2\pi\frac{Nt}{T}\right) + b_N \text{ x } \sin\left(2\pi\frac{Nt}{T}\right) \end{aligned} \quad (1)$$

Therefore, the glucose signal is decomposed into periodic elements (sine and cosine waves) of different periods (the coefficient within these waves controls their periodicity). The importance, or strength, of each periodic component is represented by the a_i and b_i coefficients (for each $2\pi\frac{i \text{ x } t}{T}$ frequency the strength is $a_i^2 + b_i^2$). The set of frequency strength ($a_i^2 + b_i^2$) is called the spectrum of the glucose trace (much like the spectrum of a light ray is the strength of each color within that light). A common way to represent it is the periodogram, or the plot of estimated strength as a function of frequencies (**Figure 1**). In this particular example we observe the predominant four cycles (1/24, 1/8, 1/6, and 1/4.5 hours), as well as a rapid decay of strength in patterns of periods shorter than about 2 hours. This article focuses on this decay as it pertains to the optimal sampling frequency of the glucose concentration.

The significance of frequencies is determined using the signal-to-noise ratio, e.g., by comparing the power of a specific frequency to the frequency signature of signal noise. Because signal noise is assumed white at high frequency (period shorter than 5 minutes), its frequency signature is flat. The noise level is determined by analyzing the first- and second-order derivatives of the frequency spectrum to determine the frequency onset of the flat spectrum and its characteristics. The white noise assumption is generally inaccurate across the whole spectrum, but is very likely at high frequencies. Nonwhite characteristics of the noise are likely to generate higher peaks at medium frequencies (15- to 30-minute periods),[15] which would inflate the spectrum power at medium frequency and move the cutoff frequency to a higher value, therefore strengthening the conclusions of this article rather than confounding them. Nonetheless, in the absence of a known noise signature, this effect cannot be compensated.

Implication of Sample Frequency in Glucose Monitoring

Fourier analysis can also be used in an information theoretic way, i.e., to determine what information is available in a glucose concentration trace, based on how often glucose was measured. This particular application of harmonic representation is summarized in the Shannon theorem and its corollaries.

The Shannon Theorem

The Shannon theorem[11] states that if a function, $f(t)$, contains no frequencies higher than W cycles per second (used instead of the more modern hertz), it is completely determined by giving its ordinates at a series of points spaced $1/(2W)$ seconds apart.

Therefore, this theorem links the sampling frequency of a discrete signal to the maximum frequency observable in that signal and then, by inference, the optimal sampling frequency of a continuously defined signal (e.g., glucose concentration) to the maximum observed frequency.

Application to Maximum Information with Fixed Sampling Frequency (Nyquist Frequency)

A very common corollary to the aforementioned theorem is that the sampling frequency of a protocol fixes limits to what can be said about a glucose trace. More precisely, no phenomenon faster than half the sampling frequency can be fully characterized. This upper bound on the frequency of observable patterns is called the *Nyquist frequency*.

Application to Maximum Sampling Frequency (Nyquist Rate)

This is the direct application of the theorem: if we know the maximum significant frequency in a subcutaneously measured glucose concentration, ω, then all interstitial glucose characteristics will be accessible by sampling faster than every $1/2\omega$ seconds. For example, if the

highest significant frequency is 1.7×10^{-3} Hz, we only need to measure glucose every 5 minutes. This sampling frequency threshold is called the *Nyquist rate*.

The difficulty here lies in determining the maximum significant frequency in glucose concentration. This can be done by studying the frequency characteristics of a very frequently sampled glucose trace (therefore making sure that the Nyquist frequency is much higher than the expected Nyquist rate).

Data

We used a data set of 26 diabetic subjects wearing two Navigator™ sensors on different sites and in field conditions for periods varying from 21 hours to 3 days. Subcutaneous glucose was recorded every minute. Data were cleaned by selecting the longest segment of uninterrupted data for each subject and trimming each segment to the length of the smallest (this ensures discrete Fourier transform coefficients at the same exact frequencies for all subjects with maximum data retention); we therefore obtained 52 glucose traces, 17 hours long. Each segment was then a posteriori recalibrated (least-square fit using a linear calibration function) to capillary glucose using reference finger sticks (15 ± 5 per day); this recalibration is made necessary by the large potential error caused by online calibration: up to 80% of the error as shown in King *et al*.[16] As this transformation is linear, it has no bearing on the frequency content of the signal. The spectrum of the first-order difference of each recalibrated segment was then estimated using the fast Fourier transform algorithm. Spectra were then averaged across subjects and analyzed; the maximum significant frequency was computed as the last frequency with power significantly different from the base noise.

Results

Difference between Blood Glucose Dynamics and Interstitial Glucose Dynamics

Continuous glucose monitors, as stated previously, measure the glucose concentration in the interstitial fluid (a few millimeters below the skin), but seek to inform about blood glucose concentration. The sensors are calibrated based on capillary blood. This discrepancy, a source of many debates on accuracy and delays,[12–14] also leads to the following question: *are blood glucose dynamics completely accessible from the interstitium?* It is commonly accepted that glucose is transported from one compartment to the other, although the exact model of transport is still being discussed.[16,17] The diffusion of glucose from blood to the interstitium has interesting predicted consequences on the spectrum of the glucose trace. This diffusion process, very often modeled by **Equation (2)**, can be seen as a low-pass filter, i.e., a process that emphasizes low-frequency patterns and attenuates high frequencies, the theoretical cutoff frequency is ω_c in **Equation (2)**.

$$\frac{\partial G_I}{\partial t} = -\alpha G_I + \beta G_B$$

$$\Rightarrow \Gamma_I = \frac{\rho \Gamma_B}{\frac{s}{\omega_c} + 1} \quad \text{where } \omega_c = \alpha \text{ and } \rho = \frac{\beta}{\alpha} \tag{2}$$

Therefore, an attenuation of high frequencies in subcutaneously measured glucose would not only indicate that diffusion is indeed taking place, but also, and most importantly, show an important difference in glucose concentration dynamics between blood and interstitial fluid.

Using data described earlier, we produced an average spectrum of the interstitial glucose, presented in **Figure 2**.

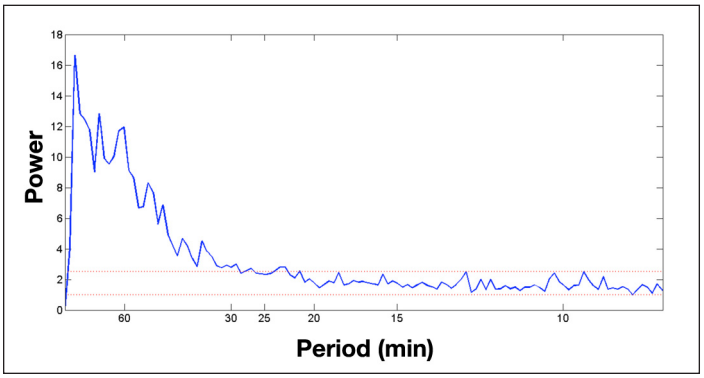

Figure 2. Spectrum of the first-order difference of subcutaneous glucose.

Only a few articles have been published on the subject of glucose spectrum, and none provide a definite answer on the frequency mix of the blood glucose concentration.[4,7,8] Nevertheless, some interesting information has been presented: (i) in healthy individuals, glucose variations are present at fairly high frequencies,[7] periods <5 minutes; this is not surprising as all feedback loops are present and some endogenous glycoregulatory hormones (e.g., insulin) have very fast pulsatile secretion.[18,19] (ii) Diabetic subjects of both types differ from healthy subjects in terms of BG spectrum, as shown in Gough *et al*.[5]; some high frequencies are cut off, resulting in glucose patterns of at least 15–20 minutes.

Our data show the next step in this analysis: the spectrum of interstitial glucose in T1DM presents an

even lower frequency cutoff; the spectrum in **Figure 2** becomes insignificant (the red dotted line represents the significance to background noise) between periods of 20 and 30 minutes (a more precise determination is presented in the next section). This indicates that subcutaneous glucose does not display high-frequency characteristics observed in blood: frequencies corresponding to a pattern between 15 and 30 minutes have mostly disappeared. Therefore, a low-pass filter exists between the two fluids, and the most likely candidate is the transfer of glucose from blood to interstitium.

Optimal Sampling Schedule for IG Dynamics Estimation

Using the spectrum in **Figure 2**, periods shorter than 30 minutes appear to be insignificantly represented in the interstitial glucose signal, but the cutoff point is unclear because of the closeness of the power of periods between 20 and 30 minutes and the noise background. To enhance the visibility of the cutoff point (at which point the spectrum variations are not significant, i.e., it is considered flat), we propose using the first-order difference of the spectrum, presented in **Figure 3**. Again assessing background noise using very high frequencies (period shorter than 5 minutes), this time a very clear cutoff point is seen at a period of approximately 36 minutes.

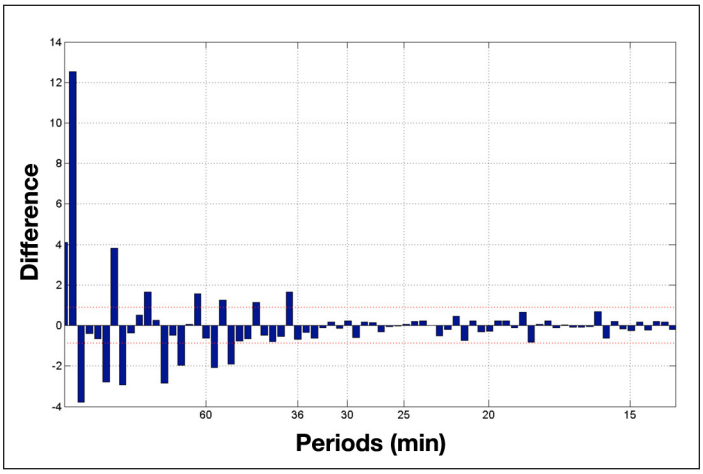

Figure 3. First-order difference of the subcutaneous spectrum.

We therefore conclude that no patterns of a period shorter than 36 minutes are observed in subcutaneously measured glucose. Thus, using the Shannon theorem we can conclude that interstitial glucose levels, as measured by modern subcutaneous continuous sensors, can be perfectly characterized using an *18-minute sampling period.*

Discussion

As continuous subcutaneous sensors become more available and more precise, harmonic analysis of glucose will take a more important place in diabetes technology studies. Identification of clinically relevant harmonic decomposition, by the association of a specific bandwidth to clinical outcome or the comparison of different harmonic methods, should open a new and exciting field in glucose monitoring. Harmonic analysis is a natural extension of the rising variability analysis, offering clinicians powerful, computationally tractable, tools to decompose variability and identify clinically important variations in glucose concentration.

Following the groundbreaking work of Miller and Strange,[4] we demonstrated the versatility of tools such as the Fourier transform, which can be used not only directly to link to clinical outcomes, but also as tools to optimize sampling schedules and identify physiological processes, such as diffusion of glucose from blood.

We showed evidence that the transfer of glucose from the blood to the interstitial fluid has important consequences on the information contained in interstitial glucose and concluded that this process is equivalent to a low-pass filter, attenuating fast variations in the interstitium. These results strengthen the case for a significant difference between blood and interstitial glucose and for the need of a thorough investigation of the relationship between the two fluids. A model, even empirical of BG/IG dynamics could be used to improve the accuracy of CGMs and to optimize calibration procedures and sampling schedules.

Finally, we obtained evidence for the absence of significant variations faster than 36 minutes in interstitial glucose and, using information theory, determined that 18 minutes of sampling (or 15 minutes for ease of use) was the maximum sampling frequency needed to fully register the fluctuations of interstitial glucose. This has a critical importance in accuracy studies: indeed as most CGMs report glucose every 1 to 10 minutes, the Nyquist rate does not apply to the collection of CGM data. It shows, however, that accuracy studies should have reference blood measures every 15 minutes in order to both capture the variability of IG and not introduce additional error due to the faster (but not reflected by IG) blood glucose fluctuations. Indeed, if we compared CGM readings to blood measures, it would be detrimental to observe blood glucose more often: we have proven that dynamics that would be observed because of a faster blood draws schedule are not present in interstitial

glucose. Similarly, we also showed that a slower blood draws schedule, by skipping some significant dynamics, would not capture some of the CGMs characteristics and therefore could ignore some potentially harmful deviations of CGMs from BG.

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References:

1. Mastrototaro J. The MiniMed Continuous Glucose Monitoring System (CGMS). J Pediatr Endocrinol Metab. 1999;12 Suppl 3:751-8.
2. Klonoff DC. Continuous glucose monitoring: roadmap for 21st century diabetes therapy. Diabetes Care. 2005;28(5):1231-9.
3. Kovatchev BP. Is glycemic variability important to assessing antidiabetes therapies? Curr Diab Rep. 2006;6(5):350-6.
4. Miller M, Strange P. Use of Fourier models for analysis and interpretation of continuous glucose monitoring glucose profiles. J Diabetes Sci Technol. 2007;1(5): 630-8.
5. Gough DA, Kreutz-Delgado K, Bremer TM. Frequency characterization of blood glucose dynamics. Ann Biomed Eng. 2003;31(1):91-7.
6. Malinov IA, Denisova TP, Malinova LI, Brook SB, Spectral analysis of time functions of plasma glucose and immunoreactive insulin during intravenous glucose tolerance testing on atherosclerosis and noninsulin-dependent diabetes mellitus. Proc SPIE. 2000; 4001: 416-7.
7. Brodan V, Hájek M, Kuhn E, Anděl M. Analysis of rapid oscillations of glucose and free fatty acids in plasma. Eur J Appl Physiol Occup Physiol. 1979;41(3):159-71.
8. Preoteasa EA, Ionescu B, Ionescu-Tirgoviste C, Georgescu M. FFT analysis and periodic function regression of glycemia time fluctuations in diabetes. Engineering in Medicine and Biology Society, 1996. Bridging disciplines for biomedicine. Proceedings of the 18th Annual International Conference of the IEEE; 1996. Vol. 5, pp. 1834-5.
9. Hirsch IB, Brownlee M. Should minimal blood glucose variability become the gold standard of glycemic control? J Diabetes Complications. 2005;19(3):178-81.
10. Kovatchev BP, Cox DJ, Gonder-Frederick L, Clarke WL. Methods for quantifying self-monitoring blood glucose profiles exemplified by an examination of blood glucose patterns in patients with type 1 and type 2 diabetes. Diabetes Technol Ther. 2002;4(3):295-303.
11. Shannon CE. Communication in the presence of noise. Proc. Institute Radio Engineers. 1949;37(1):10-21. Reprint as classic paper in Proc. IEEE. 1998;86(2).
12. Jansson PA, Fowelin J, Smith U, Lönnroth P. Characterization by microdialysis of intracellular glucose level in subcutaneous tissue in humans. Am J Physiol. 1988;255(2 Pt 1):E218-20.
13. Wentholt IM, Hart AA, Hoekstra JB, Devries JH. Relationship between interstitial and blood glucose in type 1 diabetes patients: delay and the push-pull phenomenon revisited. Diabetes Technol Ther. 2007;9(2):169-75.
14. Kulcu E, Tamada JA, Reach G, Potts RO, Lesho MJ. Physiological differences between interstitial glucose and blood glucose measured in human subjects. Diabetes Care. 2003;26(8):2405-9.
15. Breton MD, Anderson S, Kovatchev BP. Analysis, modeling, and simulation of the accuracy of continuous glucose sensors Proceedings of AIDPIT; 2008, Igls, Austria.
16. King C, Anderson SM, Breton M, Clarke WL, Kovatchev BP. Modeling of calibration effectiveness and blood-to-interstitial glucose dynamics as potential confounders of the accuracy of continuous glucose sensors during hyperinsulinemic clamp. J. Diabetes Sci Technol. 2007;1(3): 317–22.
17. Rebrin K, Steil GM, van Antwerp WP, Mastrototaro JJ. Subcutaneous glucose predicts plasma glucose independent of insulin: implications for continuous monitoring. Am J Physiol. 1999;277(3 Pt 1):E561-71.
18. O'Rahilly S, Turner RC, Matthews DR. Impaired pulsatile secretion of insulin in relatives of patients with non-insulin-dependent diabetes. N Engl J Med. 1988;318(19):1225-30.
19. Bertram R, Sherman A, Satin LS. Metabolic and electrical oscillations: partners in controlling pulsatile insulin secretion. Am J Physiol Endocrinol Metab. 2007;293(4):E890-900.