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Recurrent Endocrine Cycles

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Abstract

Background: The chaotic nature of blood glucose creates a formidable clinical challenge for diabetes healthcare. The recent discovery of recurrent endocrine cycles offers the advantage of advanced-prediction (proactive) health care.

Methods: Historical studies covering 111 patients and 1 subject collected several months of glucose readings and their daily metrics. Phase portraits and phase analytics can detect recurrent metric cycles and test their ability to anticipate serious glycemic conditions.

Results: Recurrent patterns were detected having a rate of ~7 days per complete cycle. Plots and risk models based on these cycles produced advanced alerts for acute glycemia, capturing greater than 96% of true-positive days with a 5% false-positive rate.

Conclusions: This method can be implemented graphically and functionally within a BG monitoring system to warn doctors and patients of impending serious glycemic levels.

Keywords
diabetes, dynamics, hypoglycemia, hyperglycemia, recurrent cycles, prediction

Two recent ADA abstracts document the discovery of recurrent cycles of blood glucose (BG) metrics.[1,2] The cycles are the collective result of the complex processes of the endocrine network seeking to bound BG levels despite significant fluctuations and the challenges of diabetes.

To view these patterns, one uses time-shifted phase portraits. Given a column of time-ordered data labeled "X," one creates a column labeled "Y" by simply shifting and pairing "X" to its prior values. Hence, plotting Y versus X of a time-evolving (dynamic) endocrine metric creates a pattern of dots. Connecting these dots with a line in time order reveals the portrait cycles as shown for the daily 2% quantile (Q02) of CG data in Figure 1. Each point represents an adjacent pair of time-ordered values of Q02 and is annotated by the week-day name of the first day of each pair. Hence, tracking these labeled days in time order reveals the orbital path from Saturday (Sa) through Friday (F) (with 1 missing day, Wednesday). Note this missing day due to CG malfunction (big black dot in Figure 1) does not impact the predictive flow of the cycles. However, one could position this dot properly using statistical imputation based on the cycle pattern.

The implications of such patterns are interesting. First, they test if the future values (vertical y-axis) versus the past values (horizontal x-axis) of the dynamic variable are mutually independent. Also, point labels may include references to relevant information, for example, day of week reflecting workload activity as in Figure 1. Hence, the "Th" point and the orbital structure imply seriously low impending BG levels on the next-day axis of the "F" point, where indeed Q02 was less than 30 mg/dL on Saturday.

These phase orbits form open polygons as they circulate clockwise about a central average location or centroid (dashed crosshairs in Figure 1), while displaying the impending orbital highs and lows of the metric. So, visually they circulate through the multiday levels of any metric in a predictable manner. In Figure 1 if the centroid were 75, the Saturday Q02 would be below 50. Consider Figure 1 plotting Q98 instead of Q02. If its centroid were 250, the next-day Q98 on Wednesday and Thursday would be near 270. This plot in itself becomes a useful predictive clinical tool for both doctor and patient.

Hence, simple visual inspection of these patterns alerts one to potentially serious zones in the metric cycle, for example, hypoglycemia or hyperglycemia. The key components are cycle shape, size, centroid location, and the cycle position of each point.

To implement this visual process into a risk analysis program requires the geometry of the cycles. The centroid is the average of polygon vertices that capture a central location,

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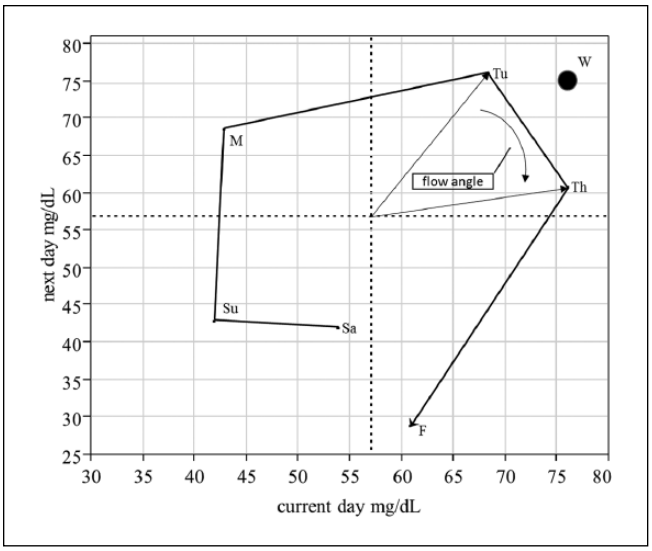

Figure 1. Time-shifted phase portrait of 2% quantile (Q02) for a patient.

typically a moving average spanning 1 or 2 cycles. One can locate each point by its radial distance relative to this centroid and its positive clockwise angle from the right x-axis, known as radial coordinates. A time-ordered angular transition between 2 adjacent polygon vertices produces a "flow angle," shown in Figure 1. A polygonal orbit completes a cycle when the sum of its flow angles exceeds 2π radians over a set of ordered days. Note Figure 1 implies a 7-day orbit cycle. For comparison a "regular" polygon has sides of equal length and vertices equidistant from its centroid. Each patient's lifestyle-regimen activities cause distortions in such ideal orbital regularity with an occasional negative-angle transition. The impact of chaos is evident since orbits are nonclosed and nonduplicating.

Objective

This study seeks to detect and characterize multiday recurrent cycles of endocrine metrics and evaluate their ability to predict impending risk of serious acute glycemic conditions, for example, hypoglycemia, where a hypoglycemic day occurs if CG levels produce a 2% quantile (denoted Q02) less than 61 mg/dL, and hyperglycemia, where a hyperglycemic day occurs if 2% of readings exceed 259 mg/dL.

Materials and Methods

We collected historical data composed of BG readings from 111 patients covering several months of observation in 3 studies, totaling 261 893 continuous glucose (CG) measurements and 29 278 daily event readings. To ensure deidentification, the data provided only BG readings and general type of medications for each subject. Two data sets are associated with designed studies on 41 type 1 and type 2 patients, A1C 7% to 11%.[3,4] The third data set comes from a collection of 70 outpatients, donated for diabetes research.[5]

For comparison, 7 months of twice daily self-monitor readings were collected before breakfast (fasting blood glucose) and at bedtime by a nondiabetic subject, A1C near 5.8%.

The CG data from 41 patients provide the daily average (DA), standard deviation (DS), the 2% quantile (Q02), and the 98% quantile (Q98). The SMBG data from 111 patients are the source of morning fasting blood glucose (FB) readings. The nondiabetic subject provided the DA of before breakfast fasting and bedtime blood glucose readings (DAn).

Note a flow angle calculation requires a series of 3 ordered days of data. As in Figure 1, we anticipate that cycle conditions of any phase point can predict next-day conditions at the next phase point, and the stable structure of the orbits would enable effective prediction regardless of missing adjacent days.

To verify this recurrent structure, we calculate the mean flow angle and radial size using data restricted to 3 adjacent dates of metrics. Consequently, 95% CIs and regression methods are used to analyze and compare these parameters.

More generally, logistic function models are used to establish the ability of orbits to alert subjects to impending serious conditions. These models use an exponential function to predict such risk. The exponential argument for recurrent cycles must be a general circular (trigonometric) function. Hence, for each subject we try a simple extension of the common linear format "m + b * X" to the form "a + b * cosine(angle) + c * sine(angle) + d * centroid * centroid," where a, b, and c are linear functions of the centroid and radial position of each point, that is, a = "A_a + B_a * radius + C_a * centroid." "Angle" is its angular position. The "d term" accounts for curvature in the range of average glucose. Hence, there are 10 coefficients in the risk model. A regression fit using orbital points to predict next-day acute glycemia optimizes all coefficients for each subject.

In summary one can predict next-day acute glycemia (ACG) by visual inspection of the recurrent orbits of daily Q02 and Q98 levels. For general validation this visual process is represented by our models, where the key graphical components of the flow cycles become multiple predictors in risk estimation methods such as generalized or logistic regression. Final prediction accuracy combined from every patient evaluates total model performance. Robustness is tested by predicting next-day hypoglycemia for days excluded from the model optimization.

Results

The data provided ~3600 monitored days for graphical and risk analysis of recurrent endocrine cycles. Tables 1 and 2 report the estimation and significance of the cycle parameters for all endocrine metrics. All flow angles are significantly

Table 1. Flow Angle Statistics of Metrics.

Blood glucose metrics	Mean radian	Lower 95%	Upper 95%	# of flow angles	Estimated days/cycle
Q02 CG 2% quantile	0.92	0.80	1.04	502	6.83
DA CG daily mean	0.93	0.81	1.04	504	6.79
DS CG daily standard deviation	0.93	0.80	1.05	504	6.78
FB SM daily fasting BG	0.94	0.89	0.99	2913	6.68
DAn nondiabetic daily mean	0.83	0.63	1.03	198	7.56

Table 2. Subject Impact on cycle properties.

Orbit parameter	Factor	Degrees of freedom	Prob > *F*	Factor significant
DA flow angle	Subject	40	.27	No
FB flow angle	Subject	62	.20	No
DA radius	Subject	40	0	Yes
DS radius	Subject	40	0	Yes

positive supporting the concept of clockwise cycles. Table 1 also shows the overlap of the 95% CIs indicating equivalence of cycle rates among all subjects. Table 2 displays the significance of subject-specific impact on all cycle parameters. Consequently, all metrics have the same estimated rate of 6 to 7 days per cycle for all subjects. The orbit sizes reflecting metric volatility however are specific to each patient.

The cycle geometry enabled effective functional prediction despite missing days, up to 9 days in specific cases. Using CG data, the logistic model predicted 126 of 129 next-day hypoglycemia days within 937 monitored days with a false-positive rate of 5%. The 3 missed alerts had next-day Q02 levels of 52, 58, and 40 mg/dL. Ten hypoglycemic days were excluded from the model regression but were predicted correctly. The hyperglycemia model predicted 192 of 199 true positives within 916 monitored days with a false positive rate of 5%.

All 10 factor coefficients for all subjects where highly significant.[2]

Discussion

The results support the diagnostic value of BG flow patterns to anticipate impending episodes of acute glycemia. The graphical approach presents a simple diagnostic platform accessible to anyone or device capable of XY plotting. As exemplified by Figure 1, one gets an overview of disease status, management, and trends. Such graphics can be a basis for patient education, group discussions, diagnostics, and biofeedback, all effective tools for preventative medicine and research. For example, achieving polygon regularity in the cycles could be a goal for guiding lifestyle habits and balancing dosing of long-acting (24-hour) insulin with prandial insulin.

The regression results provide general significance for the graphical connections of cycle flow factors to impending glycemic risk. Using CG data, the logistic models produced accurate predictions, missing 3 mild-to-moderate levels of 129 next-day hypoglycemia and missing 7 of 199 next-day hyperglycemia both with 5% false positives. Ten excluded hypoglycemic days were correctly predicted.

For clinical application these simple risk models enable optimization and implementation within any device capable of least squares programming. Concepts of statistical design-of-experiments applied to the function models show 2 cycles are adequate to initiate prediction of next-day ACG levels. This is an initial step toward developing a comprehensive ACG alert system for each patient.

Conclusions

The predictive power of the orbitals achieved clear statistical significance despite the observational nature and noise level of the data collections. The nondiabetic data imply these cycles may impact healthy subjects as well, perhaps causing short transient episodes of ACG.

To test if multiday recurrent orbits can be combined with intraday CG patterns to enable intraday predictions of ACG and also for further general validation, a properly designed clinical study is desirable, which includes lifestyle/regimen factors.

An unpublished pharmacokinetics/dynamics model supporting these recurrent endocrine cycles is beyond the scope of this article but available on request.[6] A comprehensive search of the literature and patent documents revealed no prior art concerning endocrine cycles as originally reported.[1,2]

Orbitals diagnostics may be useful in other areas such as cardiovascular diseases, mental illness, pulmonary diseases, and economics.

Abbreviations

ACG, acute glycemia, either hyper- or hypoglycemia; CG, continuous glucose readings; DA, CG daily mean; DAn, nondiabetic SM

daily mean; DS, CG daily standard deviation; FB, SM daily fasting BG; Q02, 2% quantile or maximum of lowest 2% of daily glucose readings; Q98, 98% quantile or minimum of highest 2% of daily glucose readings. SM, self-monitor glucose readings.

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Declaration of Conflicting Interests

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