ISSN: 2689-1204

Research Article

Journal of Applied Material Science & Engineering Research

Estimating Cardiovascular Disease Risk and Insulin Resistance via Transforming Glucose Wave Fluctuations from Time Domain into Associated Energy in Frequency Domain and Applying the Linear Elastic Glucose Theory of GH-Method: Math-Physical Medicine, LEGT Part 21 (No. 403)

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Submitted: 16 July 2021; **Accepted**: 23 July 2021; **Published**: 03 Aug 2021

Citation: *Gerald C Hsu (2021) Estimating Cardiovascular Disease Risk and Insulin Resistance via Transforming Glucose Wave Fluctuations from Time Domain into Associated Energy in Frequency Domain and Applying the Linear Elastic Glucose Theory of GH-Method: Math-Physical Medicine, LEGT Part 21 (No. 403). J App Mat Sci & Engg Res, 5(2), 1-11.*

Abstract

In this article, the author provides his personal perceptions and opinions regarding the concept and approach of "Glycemic Variability" (GV). Instead of using certain newly defined biomarkers by other research scientists, such as the mean amplitude glycemic excursions (MAGE), he chose to study the glucose wave fluctuations via a simple yet straightforward expression of the magnitude of glucose wave variances. He uses his simple definition of ***a glucose wave fluctuation equals to the maximum glucose value minus the minimum glucose value****. Furthermore, he selected the postprandial plasma glucose (PPG) wave fluctuations from two distinctive periods consisting of 230 days each: the beginning collection of his sensor glucose data of Period A from 5/15/2018 to 12/31/2018 (Y2018) and the most recent Period B from 7/1/2020 to 2/16/2021 (Y2020).*

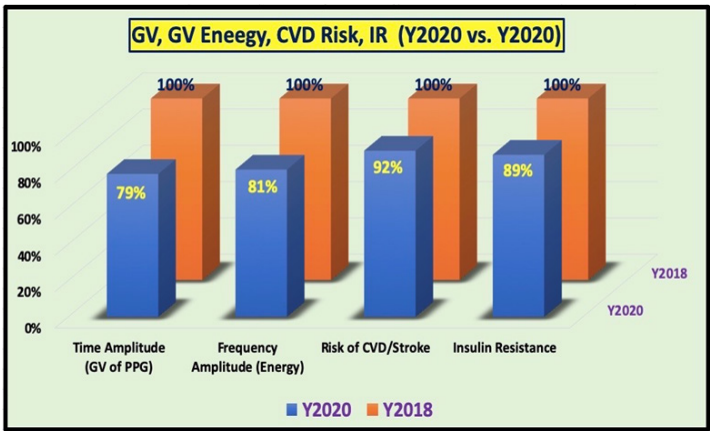
The key conclusion from this study is that, using Y2020 as the baseline data, Y2018 has the following similar pattern of value reductions (or improvements):

Time domain amplitude (GV of PPG): 79%
Frequency domain amplitude (Energy of GV): 81%
Risk Probability of CVD or Stroke: 92%
Insulin Resistance (IR): 89%

There are also three observations from this study:

1. Either more carbs/sugar intake amount or less post-meal exercise level would increase the PPG amplitude and the magnitude of glucose fluctuation, for example, after having his lunch meals. This higher time domain's amplitude would result into a higher magnitude, i.e., the Y-axis strength, of the frequency domain's amplitude. This Y-axis strength is the building block of energy associated with glucose fluctuation.
2. Once the Y-axis magnitude of frequency domain is driven higher, then the total energy associated with the glucose fluctuations would also increase, regardless of the different calculation formulas applied. The numerical values derived from these three equations are "estimated relative level" of the total energy associated with GV.
3. From the viewpoints of both CVD risk and insulin resistance, a lower total energy associated with glucose fluctuation would decrease the risk of having a CVD or stroke, and insulin resistance.

This article provides these three key conclusions using real data from the clinical case of the author and his developed GH-method: math-physical medicine research methodology including the linear elastic glucose theory. This analysis provides quantitative proof of his findings with a higher precision regarding glycemic fluctuations induced diabetic complications, such as CVD or stroke, and insulin resistance.



Introduction

In this article, the author provides his personal perceptions and opinions regarding the concept and approach of "Glycemic Variability" (GV). Instead of using certain newly defined biomarkers by other research scientists, such as the mean amplitude glycemic excursions (MAGE), he chose to study the glucose wave fluctuations via a simple yet straightforward expression of the magnitude of glucose wave variances. He uses his simple definition of ***a glucose wave fluctuation equals to the maximum glucose value minus the minimum glucose value***. Furthermore, he selected the postprandial plasma glucose (PPG) wave fluctuations from two distinctive periods consisting of 230 days each: the beginning collection of his sensor glucose data of Period A from 5/15/2018 to 12/31/2018 (Y2018) and the most recent Period B from 7/1/2020 to 2/16/2021 (Y2020).

Methods

MPM Background

To learn more about his developed GH-Method: math-physical medicine (MPM) methodology, readers can read the following three papers selected from the published 400+ medical papers.

The first paper, No. 386 (Reference 1) describes his MPM methodology in a general conceptual format. The second paper, No. 387 (Reference 2) outlines the history of his personalized diabetes research, various application tools, and the differences between biochemical medicine (BCM) approach versus the MPM approach. The third paper, No. 397 (Reference 3) depicts a general flow diagram containing ~10 key MPM research methods and different tools.

The Author'S Case of Diabetes

The author was a severe type 2 diabetes patient since 1996. He weighed 220 lb. (100 kg) at that time. By 2010, he still weighed 198 lb. with an average daily glucose of 250 mg/dL (HbA1C of 10%). During that year, his triglycerides reached to 1161 and albumin-creatinine ratio (ACR) at 116. He also suffered from five cardiac episodes within a decade. In 2010, three independent physicians warned him regarding his needs of kidney dialysis treatment and his future high risk of dying from his severe diabetic complications.

In 2010, he decided to self-study endocrinology, diabetes and food nutrition. During 2015 and 2016, he developed four prediction models related to diabetes conditions, i.e., weight, postprandial plasma glucose (PPG), fasting plasma glucose (FPG), and HbA1C (A1C). As a result, from using his developed mathematical metabolism index (MI) model and those four prediction tools, by end of 2016, his weight was reduced from 220 lbs. (100 kg) to 176 lbs. (89 kg), waistline from 44 inches (112 cm) to 33 inches (84 cm), averaged finger glucose from 250 mg/dL to 120 mg/dL, and HbA1C from 10% to ~6.5%. One of his major accomplishments is that he no longer takes any diabetes medications since 12/8/2015.

In 2017, he had achieved excellent results on all fronts, especially glucose control. However, during the pre-COVID period of 2018 and 2019, he traveled to approximately 50+ international cities to attend 65+ medical conferences and made ~120 oral presentations. This hectic schedule inflicted damage to his diabetes control, through dinning out frequently, post-meal exercise disruption, jet lag, and along with the overall metabolism impact due to his irregular life patterns through a busy travel schedule; therefore, his glucose control was affected during this two-year period.

By 2020, his weight was further reduced to 165 lbs. (BMI 24.4) and his HbA1C was at 6.2% without any medications intervention or insulin injection. Actually, during 2020 with the special COVID-19 quarantined lifestyle, not only has he published approximately 400 medical papers in journals, but he has also achieved his best health conditions for the past 26 years. These good results are due to his non-traveling, low-stress, and regular daily life routines. Of course, his rich chronic diseases knowledge, practical lifestyle management experiences, and his developed various high-tech tools also contribute to his excellent health status since 1/19/2020.

On 5/5/2018, he applied a continuous glucose monitoring (CGM) sensor device on his upper arm and checks his glucose measurements every 15 minutes for a total of ~96 times each day. He has maintained the same measurement pattern to present day. Therefore, during the past 11 years, he could study and analyze his collected ~2 million data regarding his health status, medical conditions, and lifestyle details. He applies his knowledge, models, and tools from mathematics, physics, engineering, and computer science to conduct his medical research work. His medical research work is based on the aims of achieving both "high precision" with "quantitative proof" in the medical findings, not just through linguistic expressions of qualitative words, vague statements, or complex terminologies.

Other GV Research Work

There are many available articles regarding GV; however, the author decided to combine five published articles into one excerpt (References 4, 5, 6, 7 and 8). These five references cite 200+ published papers where the readers do not need to search for key information from a long list of the cited reference articles.

Reference 4 concentrates on the comparison of many published GV articles. Reference 5 focuses on an algorithm, method, and firmware design of a web-based APP software in calculating the GV values. Reference 6 evaluates the relationship between GV and pancreatic beta cell dysfunction. Reference 7 from the American Diabetes Association (ADA) describes the overall picture of GV.

Reference 8 defines the mathematical equation of MAGE.

Here is the combined excerpt:

"Several pathophysiological mechanisms were reported, unifying the two primary mechanisms: excessive protein glycation end products and activation of oxidative stress, which causes vascular complications. Intermittent high blood glucose exposure, rather than constant exposure to high blood glucose, has been shown to have deleterious effects in experimental studies. In in-vitro experimental settings and in animal studies, glycemic fluctuations display a more deleterious effect on the parameters of CV risk, such as endothelial dysfunction. There is a significant association between GV and the increased incidence of hypoglycemia. Hypoglycemic events may trigger inflammation by inducing the release of inflammatory cytokines. Hypoglycemia also induces increased platelet and neutrophil activation. The sympathoadrenal response during hypoglycemia increases adrenaline secretion and may induce arrhythmias and increase the cardiac workload. Underlying endothelial dysfunction leading to decreased vasodilation may contribute to CV risk. Published studies have demonstrated that ***GV, particularly when associated with severe hypoglycemia, could be harmful not only to people with diabetes but also to non-diabetic patients in critical care settings.*** *Overall, the pathophysiological evidence appears to be highly suggestive of* ***GV being an important key determinant of vascular damage.*** *In addition to HbA1c, GV may have a predictive value for the development of T1DM complications. In insulin-treated T2DM, the relevance of GV varies according to the heterogeneity of the disease, the presence of residual insulin secretion and insulin resistance. HbA1c is a poor predictor of hypoglycemic episodes because it only considers 8% of the likelihood of severe hypoglycemia; on the contrary, GV can account for an estimated 40% to 50% of future hypoglycemic episodes. HbA1c is a poor predictor of hypoglycemic risk, whereas GV is a strong predictor of hypoglycemic episodes.* ***GV was an independent predictor of chronic diabetic complications, in addition to HbA1c. We should note that PPG and GV are not identical, even if they are closely related.*** *The attention dedicated to GV is derived from the above evidence concerning its effects on oxidative stress and, from the latter, on chronic diabetes complications. Control of GV has been the focus of a number of interventional studies aimed at reducing this fluctuation.* ***Diet and weight reduction are the first therapeutic instrument that can be used for reducing GV.***

Despite the various formulas offered, simple and standard clinical tools for defining GV have yet to evolve and different indexes of GV should be used, depending on the metabolic profile of the studied population. Moreover, the absence of a uniformly accepted standard of how to estimate postprandial hyperglycemia and GV adds another challenge to this debate.

The majority of these studies have used time-averaged glucose values measured as glycosylated hemoglobin (HbA1c), an indicator of the degree of glycemic control, which is why HbA1c has become the reference parameter for therapies aimed at reducing the risk of complications from diabetes. ***Chronic hyperglycemia is almost universally assessed by HbA1c which has been shown to correlate closely with mean glucose levels over time, as determined by continuous glucose monitoring (CGM). However, the relative contribution of postprandial glycemic excursions and fasting to overall hyperglycemia has been the subject of considerable debate.*** *Monnier et al. suggested that the relative contributions of fasting and postprandial glucose differ according to the level of overall glycemic control.* ***Fasting glucose concentrations present the most important contribution to hemoglobin glycosylation, whereas at lower levels of HbA1c, the relative contribution of postprandial hyperglycemia becomes predominant. Collectively, GV is likely to be incompletely expressed by HbA1c, particularly in patients with good metabolic control.***

GV is a physiological phenomenon that assumes an even more important dimension in the presence of diabetes because it not only contributes to increasing the mean blood glucose values but it also favors the development of chronic diabetes complications. ***It appears that GV is poised to become a future target parameter for optimum glycemic control over and above standard glycemic parameters, such as blood glucose and HbA1c.*** *Avoiding both hyperglycemia and hypoglycemia by careful use of SMBG and the availability of new agents to correct hyperglycemia without inducing hypoglycemia is expected to reduce the burden of premature mortality and disabling CV events associated with diabetes mellitus. However,* ***defining GV remains a challenge primarily due to the difficulty of measuring it and the lack of consensus regarding the most optimal approach for patient management.***

The risk of developing diabetes-related complications is related not only to long-term glycemic variability, but may also be related to short-term glucose variability from peaks to nadirs. *Oscillating glucose concentration may exert more deleterious effects than sustained chronic hyperglycemia on endothelial function and oxidative stress, two key players in the development and progression of cardiovascular diseases in diabetes. Percentages of hyperglycemia (levels between 126 and 180 mg/dl) and hypoglycemia (levels below 70.2 mg/dl) episodes should be used in the GV related research.*

Mean amplitude of glycemic excursions (MAGE), together with mean and SD, is the most popular parameter for assessing glycemic variability and is calculated based on the arithmetic mean of differences between consecutive peaks and nadirs of differences greater than one SD of mean glycemia. It is designed to assess major glucose swings and exclude minor ones.

The features discouraging use of glycemic variability as a parameter in clinical practice and trials are the difficulty of interpreting numerous parameters describing this phenomenon and a limited number of computational opportunities allowing rapid calculation of glycemic variability parameters in CGM data.

The UK Prospective Diabetes Study (UKPDS) showed that after an initial improvement, glycemic control continues to deteriorate despite the use of oral agents to enhance insulin secretion and to reduce insulin resistance. This deterioration can be attributed to the progressive decline of β-cell function. Even in subjects with well-controlled type 2 diabetes, 70% of the variability of A1C can

be explained by abnormalities in postprandial glucose. ***Chronic sustained hyperglycemia has been shown to exert deleterious effects on the β-cells and the vascular endothelium. In vivo studies have convincingly demonstrated that hyperglycemic spikes induce increased production of free radicals and various mediators of inflammation, leading to dysfunction of both the vascular endothelium and the pancreatic β-cell."***

Mean Amplitude of Glycemic Excursions (MAGE)

Furthermore, such a measure should be simple in concept and faithful to the physiological basis for the glucose swings. ***Because interest lay in the amplitude of glycemic swings and not in the dispersion of all the glucose data, SD was considered to be unsuitable.*** *The criterion, which did recognize all of the meal-related glucose excursions for all of the normal subjects, was the SD of the mean BG for each 24-h period of study (288 values taken q5min from the continuous record) for each individual. In contrast, 0.5 SD and 1.5 SD were less inclusive/exclusive. Although the numerical value of 1 SD will perforce differ in absolute value from person to person, it nevertheless acts as an individualized standard.* ***By convention, a glycemic excursion (both trough-to-peak and peak-to-trough) must exceed 1 SD of the respective 24-h BG profile.*** *For continuous recordings exceeding 24 h, the use of 1 SD calculated for the whole period of study may result in the inclusion of the same excursions as use of the separate 24-h SDs, since SDs from successive days do not differ by much (even in type 1 diabetic patients as long as therapy has not changed during the period of monitoring). Only one limb of the excursion, ascending or descending, determined by the initial excursion (which is not always an inflection especially in type 1 diabetic patients) is used for calculation of subsequent excursions. Should the subsumed excursion be of a magnitude observed for normal subjects its exclusion may be inconsequential relevant to the risk for the development of microvascular complications of diabetes. The arithmetic mean of the glycemic excursions for the period of study (24 h, 48 h, or longer) is the value of mean amplitude of glycemic excursions (MAGE). An automated algorithm has been created for the calculation of MAGE. Although created for determination from continuous BG analysis, MAGE has been applied to intermittent (7- and 22-point sampling/24 h) measurements as well as continuous interstitial glucose monitoring.*

The author's view on Glucose Wave Fluctuations (Glycemic Excursions)

There is a concluding remark from one of the reference articles, which was expressed above and now is copied again at below.

"The features discouraging use of glycemic variability as a parameter in clinical practice and trials are the difficulty of interpreting numerous parameters describing this phenomenon and a limited number of computational opportunities allowing rapid calculation of glycemic variability parameters in CGM data."

The author also believes that any newly created biomarker should accurately describe the biomedical phenomena of a disease, but at the same time, it should be easily enough for physicians and/or patients to comprehend and apply it to their day-to-day diabetes control.

The concept and discussion of GV have existed more than a decade based on the clinical usage and results of the continuous glucose monitoring (CGM) device to monitor severe diabetes patients and insulin treatments in hospitals. The self-monitored glucose devices (SMGD) became available and popular to outpatients for general public's diabetes control usage starting from 2016-2017. As a result, most of the published research reports are based on glucose data collected during a relatively short analysis period of 2 to 3 days from hospitalized diabetes patients. Although many GV medical papers have been published based on a larger patient numbers, who were probably hospitalized, it lacks the needed longer time period. Furthermore, there are only few of those research papers that provide connections to the intuitive comprehension and easy application on daily diabetes control. That is why the subject of GV is only a research topic in the medical research community, instead of being truly utilized as a clinical tool for practical usage by both diabetes patients and their physicians. For example, the author has had type 2 diabetes (T2D) for 26 years and has been under the care of multiple physicians associated with renown medical institutes. For the past decade, he has attended 65 medical conferences and met more than 1,000 medical doctors, professors, and clinical physicians, but he has never heard of GV mentioned once or its related discussions by the physicians he has met.

Starting on 5/5/2018, he placed a SMGD on his arm to collect two sets of glucose data. The first set of data are measured every 15 minutes with a total of 96 data per day. In addition, since 2/19/2020, he has applied Bluetooth technique to collect his second set of data which are measured every 5 minutes with a total of 288 data per day. In this article, he decided to use the 15-minute dataset with 96 data per day for his analysis due to its longer time period of available glucose data. With a longer time span, he can observe more changes on both glucose and insulin resistance situations. Statistics analysis based on 1000+ patients with only a few days can certainly provide some useful information. However, the author offers a similar analysis from a perpendicular angle, i.e., one patient with big data associated with a much longer period of time. His data include a span of ~2.8 years (~32 months, 971 days) and 93,216 daily glucose or 37,869 PPG values. The reason he chose PPG wave as his research target in this article because its fluctuations are usually the most "violent" kind in comparison with glucoses in other segments in a day.

Defining GV remains a challenge primarily due to the difficulty of data collection with its associated follow-on necessary tasks, such as data transfer, data cleansing, data processing, and data analysis that can lead into the ambiguity of GV's existing interpretations, different versions of expressions, along with the lack of consensus regarding the optimal approach for its clinical management. For example, one of the major GV derivations, mean amplitude of glycemic excursion (MAGE), involves the usage of standard deviation (SD) from statistics. Although SD is widely used in statistics, it has some limitations since its inherited assumption of measured data are normally distributed, which is typically not the case for most glucose data and waves.

All of the above-mentioned tasks are still challenging for most diabetes patients, physicians, and even some medical research

scientists. Due to the lack of professional training and academic knowledge in this domain, most patients and clinical physicians have encountered difficulties in understanding and applying the GV related materials.

The author is a professionally trained mathematician, physicist, and engineer. He has further used multiple analytical approaches to analyze his own health data and glucose waveforms from many different research angles. Therefore, he thoroughly understands the behaviors and characteristics of those glucose data and waves collected from his own body.

Based on the theoretical and technical viewpoints, the author decided to conduct this study on applying the ***basic concept, not the other definitions*** of GV (i.e., glucose fluctuation between peak and trough) in combination with the ***primary characteristics*** of wave theory (mainly frequencies, amplitudes, phases, and associated energies of glucoses). This would assist in his investigation of the self-recovery of his pancreatic beta cells and various internal organ impacts from the energy associated with glucose waves, including GV (i.e., glucose fluctuations). It also benefits his research on the subject of risk probability of having complications, e.g., cardiovascular diseases or stroked, from chronic diseases. In this article, the author applies the following simple formula of glucose fluctuation rate to use for his GV study where the glucose fluctuation is defined as ***the glucose wave's peak as the maximum glucose minus the glucose wave's trough as the minimum glucose.***

Glucose fluctuation rate= [Summation (i = 1 to n) of :
((maximum glucose - minimum glucose) / average glucose)] / n

Stress, Strain, & Young's Modulus
The following excerpts come from the internet public domain, including Google and Wikipedia:

Strain - ε

Strain is the "deformation of a solid due to stress" - change in dimension divided by the original value of the dimension - and can be expressed as
ε = dL / L
where
ε = strain (m/m, in/in)
dL = elongation or compression (offset) of object (m, in)
L = length of object (m, in)

Stress - σ

Stress is force per unit area and can be expressed as
σ = F / A
where
σ = stress (N/m2, lb/in2, psi)
F = applied force (N, lb)
A = stress area of object (m2, in2)

Stress includes tensile stress, compressible stress, shearing stress, etc.

E, Young's Modulus
It can be expressed as:

E = stress / strain = σ / ε

where
E = Young's Modulus of Elasticity was named after the 18th-century English physicist Thomas Young.

Elasticity:
Elasticity is a property of an object or material indicating how it will restore it to its original shape after distortion. A spring is an example of an elastic object - when stretched, it exerts a restoring force which tends to bring it back to its original length.

Young's modules in the above table are ranked from soft material (low E) to stiff material (higher E)."

Highlights of Linear Elastic Glucose Theory

If readers are interested in the step-by-step explanation for the predicted PPG equation using linear elastic glucose theory, they can read the author's papers listed in References 10 through 25.

The following explains the key components of his developed linear elastic glucose theory:

1. Baseline PPG equals to 97% (an upper-bound) of FPG value, or 97% * (weight * GH.f-Modulus). He also uses 60% as his lower-bound analysis.
2. Baseline PPG plus increased amount of PPG due to food, i.e., plus (carbs/sugar intake amount * GH.p-Modulus).
3. Baseline PPG plus increased PPG due to food, and then subtracts reduction amount of PPG due to exercise, i.e., minus (post-meal walking k-steps * 5).
4. The Predicted PPG equals to Baseline PPG plus the food influences, and then subtracts the exercise influences.

The Linear Elastic Glucose Equation is defined as

Predicted PPG =(0.97 * GH.f-modulus * Weight) +(GH.p-modulus * Carbs&sugar) - (post-meal walking k-steps * 5)

Where
(1) Incremental PPG = Predicted PPG - Baseline PPG + Exercise impact
(2) GH.f-modulus = FPG / Weight
(3) GH.p-modulus = Incremental PPG / Carbs intake

Therefore,

GH.p-modulus = (PPG - (0.97 or 0.6 * FPG) + (post-meal walking k-steps * 5)) / (Carbs&Sugar intake)

By using this linear equation, a diabetes patient only needs the input data of body weight, carbs & sugar intake amount, and post-meal walking steps in order to calculate the predicted PPG value without obtaining any measured glucose data.

Time Domain to frequency domain via Fourier Transform

The following is excerpt from Reference 19 regarding signal processing which includes concepts related to time domain, frequency

domain, wave theory, and energy theory:

"Fourier methods are named after Joseph Fourier, a French mathematician and physicist that lived from 1768 to 1830. He pioneered the use of sinusoids for representing arbitrary functions.

It is relatively easy to represent an arbitrary signal, or a wave, as a combination or sum of multiple sinusoids of different frequencies. A frequency spectral analysis is an important aspect of signal processing. The goal is to start with a signal, usually in a "time domain", and identify the strength of the sinusoidal components that make up the signal. The strength or amplitude of the sinusoids are displayed as a function of frequency which is the "frequency domain".

Fourier methods are used for two primary purposes: mathematical analysis of problems and numerical analysis of data. The Fourier transform is used to analyze problems involving continuous-time signals or mixtures of continuous- and discrete-time signals. The fast Fourier transform algorithm or FFT, is not a distinct Fourier method, but is an efficient computational technique for evaluating the discrete Fourier transform. The discrete Fourier transform may be computed very efficiently using an FFT algorithm. The computational efficiency of FFT algorithms is a direct consequence of the properties of complex sinusoids. The FFT algorithm was published by Cooley and Tukey in 1965. Computational power was quite limited in those early days of digital computing, and the FFT opened up possibilities for computer analysis of signals that were previously unimaginable. Thus, FFT algorithms fueled the rapid growth of the new field of signal processing. The FFT remains a cornerstone of modern signal processing as it allows solution of problems that are "large" with respect to available computing power.

In summary, Fourier methods are based on representing arbitrary signals as weighted sums of complex sinusoids, with both a real part and an imaginary part. They are intuitive, apply to a large class of interesting signal processing systems and physical effects, and numerical Fourier analysis can be performed very efficiently. They play a huge role in signal processing and are worthy of study."

The Author'S Analysis Procedures

First step, the author calculates his "glucose fluctuation" value, defined as "the maximum glucose value minus the minimum glucose value", of his three meals' PPG values. He then assembles them into a daily PPG fluctuation value in time domain. After that, he calculates the square of the glucose fluctuation amplitude first since the energy associated with a wave is "proportional to" (not "equal to") the square of amplitude in time domain, i.e., the square of daily glucose fluctuation value.

Second step, he uses his developed software program based on FFT algorithm to transform 3 meals and daily glucose fluctuation signals or waves into the frequency domain. In the frequency domain, he then calculates the following two energy values:
(4) By hand, he takes the strength of frequency domain, i.e. the average Y-amplitude value, then multiply the total number of frequency components (N or n).
(5) Using computer, he calculates the total area underneath the frequency curve or frequency wave in the frequency domain.

Since the above two methods are based on the same equation but different tools, they would produce two energy values which are remarkably close to each other due to those minor difference of accuracy between hand and computer.

However, the estimated energy based on the square of glucose Y-amplitude in time domain multiplied with the total number of days (N), which is the same as the total number of frequency components in frequency domain would result into different numerical results, but with the same data trend or pattern. This is due to the associated energy in a particular wave is proportional to, but not equal to, the square of amplitude of this wave.

From the three calculated associated energies, we can then compare them against the risk probabilities of having cardiovascular disease (CVD), stroke, diabetic chronic kidney disease (DKD or CKD), and insulin resistance.

Risk of having CVD or Stroke

In 2014, the author applied the topology concept of mathematics and finite-element method of engineering, to develop a ten-dimensional complex mathematical model of metabolism which contains four output categories (weight, glucose, BP, and lipids) and other lab-tested data (ACR, TSH, and others), and six input categories (food, water intake, exercise, sleep, stress, and routine life patterns), and ~500 detailed elements. He further defined two new parameters, metabolism index (MI), as the combined score of the above 10 metabolism categories (dimensions) and 500 detailed elements, and general health status unit (GHSU), as the 90-days moving average value of MI. Please noted that Mi (where i = 1 through 10) represents individual metabolism score of each category. Since 2012, he has collected ~2 million data of his own biomedical conditions and personal lifestyle details. He only utilized a part of his big database for analysis work in this article.

Next, he developed a few suitable algorithms containing some different weighting factors which include a patient's baseline data (gender, age, race, family genetic history, medical history, bad habits, BMI, weight, and waistline), medical conditions (diabetes, hypertension, and hyperlipidemia), and lifestyle details (food, exercise, and others). After continuously collecting sufficient input data for a decade, he can then conduct the following three sets of calculations:

(A) Medical conditions - individual M2 through M4 for diabetes, hypertension, hyperlipidemia and others. These 3 metabolic disorder values include a patient's self-collected biomedical data and the lab-tested medical examination results. Through his previous research for the past 5-years, he already detected that glucose is the "principal criminal" and blood pressure with lipids are the "accessory criminals" in terms of induced complications from chronic diseases, specifically CVD, stroke, renal problems, diabetic retinopathy, and even cancers. More precisely, his mathematical model for CVD or stroke includes two biomedical scenarios.

The first scenario is the artery blockage situation which involves diabetes (glucose), hypertension (blood pressure or BP), and hyperlipidemia (lipids) where he applied his acquired fluid dynamics concepts for his engineering modeling of artery blockage. The second biomedical scenario is the artery rupture situation which involves diabetes (glucose), and hypertension (BP) where he applied his acquired solid dynamics and fracture mechanics concepts for his engineering modeling of artery rupture.

(B) Lifestyle details - individual M5 through M10 which affect medical conditions directly or indirectly. In this category, he includes the following three sub-categories with a total of nine detailed elements. (B-1) 3 foods: quantity, quality, and carbs/sugar intake amount; (B-2) two exercises: daily walking steps and post-meal waking steps; (B-3) 4 others: water intake, sleep, stress, and daily life routines.

(C) MI & GHSU scores - MI is a combined score of M1 through M10 using engineering finite element method. GHSU is the 90-days moving average MI curve which can show the MI's trend clearly. The break-even point for MI is 73.5%, while *the break-even level of risk percentage for the separated groups of medical conditions and lifestyle details are 62%.* In other words, an undesirable situation is being above the break-even line while staying below the break-even line is an ideal situation.

With this developed mathematical risk assessment tool, he can obtain three separate risk probability percentages associated with each of these three calculation models mentioned above. As a result, this tool would offer a range of the risk probability predictions of having CVD or stroke, depending on the patient's medical conditions, lifestyle details, or the combined metabolism impact on the human body.

Pancreatic Beta-Cells Study

Since 2019, the author focused on his continuous medical research work for the "self-recovery" of his pancreatic beta cells. He uses the term "self-recovery" because he has kept his carbs/sugar intake amount less than 15 grams per meal and his post-meal walking exercise more than 4,000 steps for the past five years. Since 12/8/2015, he has also ceased taking any diabetes medication, which is the strongest influential factor for the phenomena of glucose fluctuations. Therefore, his body is totally free of any external chemical intervention that may alter or interrupt the internal organ's biochemical process and reactions. Under this strict controlled lifestyle and environment, his damaged pancreatic beta cells must go through the self-repairing process in order to show any meaningful improvement signs of his diabetes conditions through glucose value changes. This is his chosen approach since 2016 that "fixing his diabetes conditions from their root causes via a stringent lifestyle management" instead of "using a tranquilizer to calm down the external symptom or behavior of his glucose problems".

Furthermore, during the FPG period, e.g., between 00:00 midnight through 07:00 next morning, glucose is not under any influence from external factors, mainly food and exercise. However, the FPG values would still fluctuate through the hours of sleep. Of course, there are some other factors, such as sleep conditions, stress, illness, or room environments that can alter FPG, which are secondary influential factors. The weight is the major influential factor of FPG which occupies ~85% of FPG formation. However, we also know that weight is highly correlated to insulin resistance phenomenon. The left-over and major influential factor of FPG formation is "insulin" which is produced by the pancreatic beta cells. Therefore, the ability to analyze and interpret FPG and then extend it to connect with PPG is important for understanding his situation of insulin resistance.

Data used in this Analysis

The author has collected 96 glucose data per day (every 15 minutes) using a CGM device since 5/5/2018 and 288 glucose data collected per day (every 5 minutes) since 2/17/2020. During the past 971 days (5/5/2018 - 12/31/2020), he has collected 93,216 glucose data, using the 15-minute model. He decided to use this model for his analysis due to its sufficient long time period of data collection.

In this article, he chose two distinctive periods to conduct his analysis. The first period is the beginning phase of his SMGD sensor glucose collection which has 230 days from 5/15/2018 to 12/31/2018. The second period is the most recent 230 days period from 7/1/2020 to 2/16/2021. The reason he selected these two periods is that his average glucose values are quite different between them with the recent period having better and improved glucoses. Besides, the same time period would provide the same number of 230 frequency components (N or n) which would alter the total energy values.

Results

Figure 1 and Figure 2 show the PPG fluctuation (maximum minus minimum) in both time domain and frequency domain for the two periods, respectively. These two figures provide the necessary input information and data comparison for those necessary follow-on calculations.

Figure 3 depicts the table containing input data of FPG and PPG along with the calculation table for the procedures outlined in the method section. It is clear that his lunch, which is the heaviest meal of the day, produced not only the highest average glucose amplitude (the mean value) but also the most "violent" in terms of glucose wave fluctuations. The lunch's GV contribution is around 36%, i.e., the largest glycemic variability. The next meal contributions are his dinner at 33% of GV, and the lightest meal is his breakfast at 32% of GV. The associated energy distribution ratios among the three meals are extremely similar to the glucose fluctuation amplitude distribution. Another key observation is that frequency domain's Y-axis values times number of frequency (N) are remarkably close to the calculated frequency domain area. But both of them have quite different numerical values from taking the square of time-domain's Y-axis amplitude (glucose fluctuation) times the number of days (N), but the distribution patterns are similar. Again, according to the wave theory of physics, a particular wave's associated energy is proportional to, not equal to, the square of amplitude of this wave. Figures 1, 2, & 3 have demonstrated an example of applying the signal processing techniques

with Fourier transform on bio-medical research.

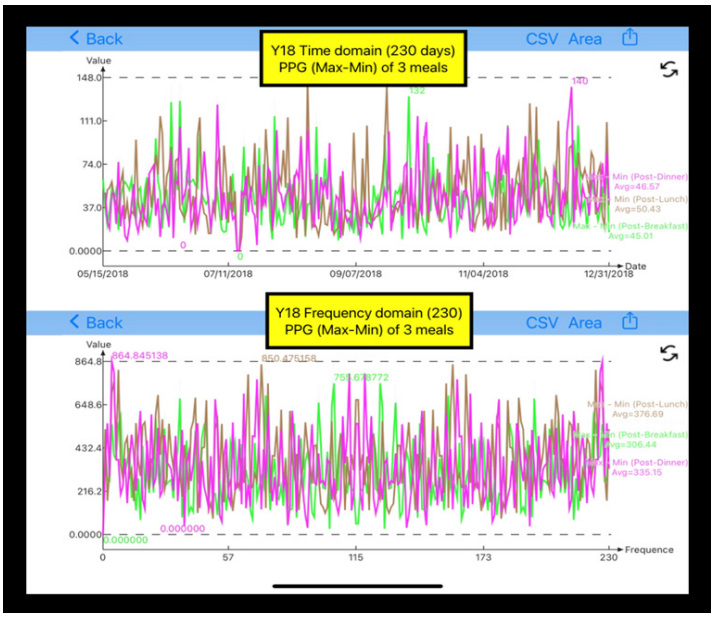


Figure 1: Y-amplitudes from both Time domain and Frequency domain of Y2018 (230 days)

PPG (Max-Min) Comparison	Period 2018	% of Y2018	Period 2020	% of Y2020	Y2020 / Y2018 Ratio
Days / Freq (N)	230		230		
Bkfst Time PPG (Max-Min)	45	32%	27	24%	60%
Lunch Time PPG (Max-Min)	50	36%	43	38%	84%
Dinner Time PPG (Max-Min)	47	33%	42	38%	90%
Daily Time PPG (Max-Min)	47	33%	37	33%	78%
Sum of Time PPG (Max-Min)	142	100%	111	100%	78%
Bkfst Freq Y (Max-Min)	306	30%	213	26%	69%
Lunch Freq Y (Max-Min)	377	37%	290	35%	77%
Dinner Freq Y (Max-Min)	335	33%	321	39%	96%
Daily PPG Freq Y (Max-Min)	339	33%	275	33%	81%
Sum of Freq Y (Max-Min)	1018	100%	824	100%	81%
Bkfst (Freq Y * N)	70481	30%	48880	26%	69%
Lunch (Freq Y * N)	86639	37%	66741	35%	77%
Dinner (Freq Y * N)	77085	33%	73862	39%	96%
Daily PPG (Freq Y * N)	78068	33%	63161	33%	81%
Sum of (Freq Y * N)	234204	100%	189483	100%	81%
Bkfst (Freq Area)	70554	30%	48950	26%	69%
Lunch (Freq Area)	86752	37%	66825	35%	77%
Dinner (Freq Area)	77254	33%	73794	39%	96%
Daily PPG (Freq Area)	78187	33%	63190	33%	81%
Sum of (Freq Area)	234560	100%	189570	100%	81%
Bkfst (PPG**2 * N)	465957	30%	165072	17%	35%
Lunch (PPG**2 * N)	584933	38%	416611	42%	71%
Dinner (PPG**2 * N)	498816	32%	406106	41%	81%
Daily PPG (PPG**2 * N)	516568	33%	329263	33%	64%
Sum of (PPG **2 * N)	1549705	100%	987790	100%	64%

Figure 2: Y-amplitudes from both Time domain and Frequency domain of Y2020 (230 days)

PPG (Max-Min) Comparison	Period 2018	% of Y2018	Period 2020	% of Y2020	Y2020 / Y2018 Ratio
Days / Freq (N)	230		230		
Bkfst Time PPG (Max-Min)	45	32%	27	24%	60%
Lunch Time PPG (Max-Min)	50	36%	43	38%	84%
Dinner Time PPG (Max-Min)	47	33%	42	38%	90%
Daily Time PPG (Max-Min)	47	33%	37	33%	78%
Sum of Time PPG (Max-Min)	142	100%	111	100%	78%
Bkfst Freq Y (Max-Min)	306	30%	213	26%	69%
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Daily PPG (PPG**2 * N)	516568	33%	329263	33%	64%
Sum of (PPG **2 * N)	1549705	100%	987790	100%	64%

Figure 3: Data table of input data and calculation results for 2 time periods

Figure 4 uses bar-diagrams to illustrate two results from the data table in Figure 3. The top diagram reveals the comparison between two periods of both glucose fluctuations from time domain and their associated energies from frequency domain. The bottom diagram indicates the comparison between the two periods using three different calculation methods to obtain the total energies associated with GV.

The table below re-lists the conclusion for Figures 3 and 4 in the format of (GV amplitude, GV associated energy amplitude, total energy using Frequency Y*N, total energy using Frequency Area, total energy using GV**2*N):

Y2018
(47, 339, 78068, 78187, 516568)
Y2020
(37, 275, 63161, 63190, 329263)

It is evident that all of numbers in Y2020 are lower than Y2018. The following table lists the ratio of lower values in Y2020 over higher numbers in Y2018:

Time amplitude: 78%
Frequency amplitude: 81%
Total energy (Freq Y * N) 81%

Total energy (Freq Area) 81%
*Total energy (Time Y**2*N) 64%*

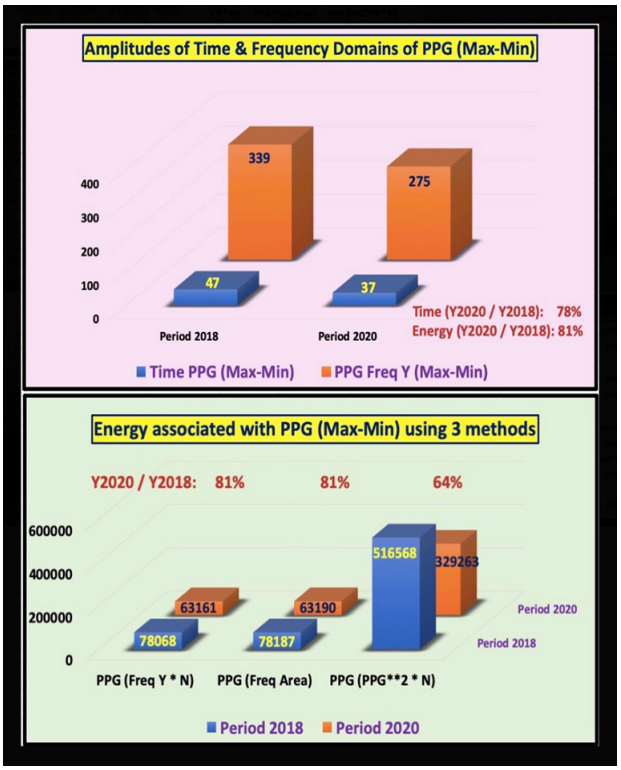

Figure 4: Amplitudes of Time & Frequency domains and associated energies with PPG fluctuations using 3 different formulas

Figure 5 displays the results of his risk probability of having CVD or stroke during these two different periods. Using the metabolism index (MI) approach as he mentioned in the section of Methods for risk of CVD/Stroke, his beginning period of Y2018 has a risk of 55.51% and his recent period of Y2020 has a risk of 50.81%. Therefore, we can safely conclude that he has a 4.7% improvement or reduction on his risk probability of having CVD or stroke. In other words, his CVD risk in Y2020 is at 92% level of his CVD risk in Y2018.

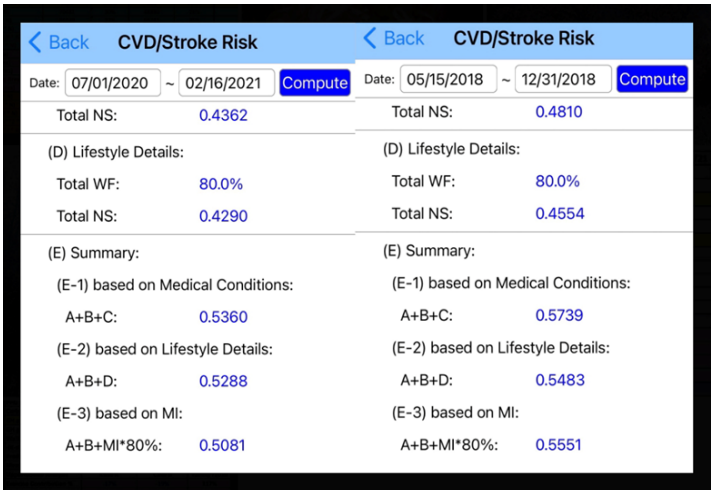

Figure 5: Risk probabilities of having a CVD or stroke during Y2018 and Y2020

Figure 6 shows a data table related to his insulin resistance using his developed linear elastic glucose theory. It is a complicated data table to comprehend. However, let us focus on two variables. The first variable is the GH-p Modulus and the second variable is his FPG values between these two periods. His two calculated GH-p moduli through numerical iterations are 3.0 for the upper-bound case (using 0.97 as the GH-f) and 5.5 for the lower-bound case (using 0.6 as the GH-f). It has two "near-constant" values for both Y2018 and Y2020. This observed phenomenon of his constant GH Modulus is due to the two time periods are fairly close to each other in a broad time scale, and he has possessed quite similar lifestyles. However, the second variable is his FPG between the two periods which have 11% difference. This observed phenomenon of FPG reduction is due to his improvement on insulin resistance (IR) mainly resulted from his pancreatic beta cells self-repair. His FPG does not involve food and exercise during sleep hours and he has not taking any medication or insulin injection since12/8/2015. It is the strong influential power from his pancreatic beta cells of both insulin secretion (quantity) and insulin resistance (quality). Therefore, we can safely conclude that his insulin resistance situation has also being improved by ~11% during the recent period of Y2020 in comparison with the beginning period of Y2018

(2/16/2021) Upper Bound	5/15/18-12/31/18	7/1/20-2/16/21	Y2020/Y2018
Daily Sensor Glucose	130	113	87%
FPG	112	100	89%
GH.f	0.97	0.97	
PPG Baseline = (GH.f*FPG)	109	97	89%
Carbs/Sugar	16.0	14.6	92%
GH.p	3.0	3.0	100%
GH.p*Carbs	48	44	92%
Walking K-steps	4.5	4.6	103%
-(K-steps*5)	-22	-23	
Predicted PPG	134.84	117.88	87%
Measured PPG	134.84	117.88	87%
Upper-Bound Analysis	Case A	Case B	Y2020/Y2018
Exercise Contribution %	-17%	-19%	117%
Diet Contribution %	36%	37%	105%
Baseline Contribution %	81%	82%	101%
Total %	100%	100%	100%
Pancreatic Beta Cells	100%	100%	100%
(2/16/2021) Lower Bound	5/15/18-12/31/18	7/1/20-2/16/21	Y2020/Y2018
Daily Sensor Glucose	130	113	87%
FPG	112	100	89%
GH.f	0.60	0.60	
PPG Baseline = (GH.f*FPG)	67	60	89%
Carbs/Sugar	16.0	14.6	92%
GH.p	5.6	5.5	98%
GH.p*Carbs	90	81	90%
Walking K-steps	4.5	4.6	103%
-(K-steps*5)	-22	-23	
Predicted PPG	134.84	117.88	87%
Measured PPG	134.84	117.88	87%
Lower-Bound Analysis	Case A	Case B	Y2020/Y2018
Exercise Contribution %	-17%	-19%	117%
Diet Contribution %	67%	69%	103%
Baseline Contribution %	50%	51%	101%
Total %	100%	100%	100%
Pancreatic Beta Cells	100%	98%	98%

Figure 6: Calculation of Insulin Resistance situations through glucoses during Y2018 and Y2020

Figure 7 signifies the summary bar diagrams for time amplitude

(GV), frequency amplitude (energy of GV), CVD risks, and insulin resistance between Y2018 and Y2020. It should be emphasized again that risk of CVD/Stroke is related to weight, glucose, look pressure, lipid and 6 different lifestyle details, while insulin resistance situation can be reflected via his FPG changes. Although these four sets of values have some numerical differences among them, but they still possess similar data trend and data pattern.

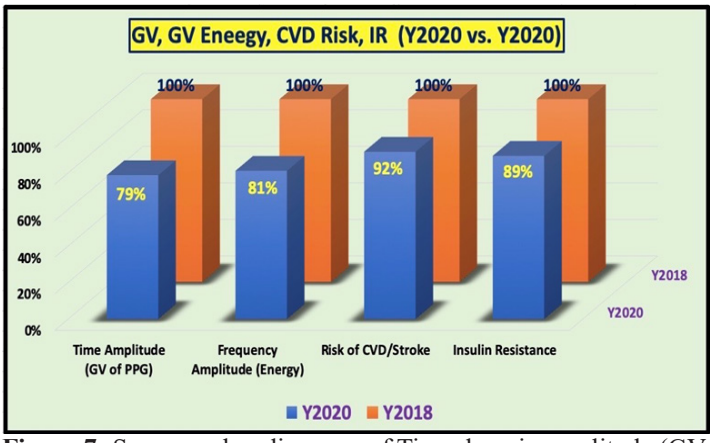

Figure 7: Summary bar diagrams of Time domain amplitude (GV of PPG), Energy domain amplitude (Energy of GV), CVD/Stroke risk and IR situations between Y2018 and Y2020

Conclusions

The key conclusion from this study is that, using Y2020 as the baseline data, Y2018 has the following similar pattern of value reductions (or improvements):

Time domain amplitude (GV of PPG): 79%
Frequency domain amplitude (Energy of GV): 81%
Risk Probability of CVD or Stroke: 92%
Insulin Resistance (IR): 89%

There are also three observations from this study:

(1) Either more carbs/sugar intake amount or less post-meal exercise level would increase the PPG amplitude and the magnitude of glucose fluctuation, for example, after having his lunch meals. This higher time domain's amplitude would result into a higher magnitude, i.e., the Y-axis strength, of the frequency domain's amplitude. This Y-axis strength is the building block of energy associated with glucose fluctuation.
(2) Once the Y-axis magnitude of frequency domain is driven higher, then the total energy associated with the glucose fluctuations would also increase, regardless of the different calculation formulas applied. The numerical values derived from these three equations are "estimated relative level" of the total energy associated with GV.
(3) From the viewpoints of both CVD risk and insulin resistance, a lower total energy associated with glucose fluctuation would decrease the risk of having a CVD or stroke, and insulin resistance.

This article provides these three key conclusions using real data from the clinical case of the author and his developed GH-method: math-physical medicine research methodology including the linear elastic glucose theory. This analysis provides quantitative proof of his findings with a higher precision regarding glycemic fluctuations induced diabetic complications, such as CVD or stroke, and insulin resistance [1-18].

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