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Detailed Investigation of 4 Annual Datasets from the Continuous Glucose Monitoring Sensor Glucoses Collected by a Long-Term Type 2 Diabetes Patient Using the Concept of Distributional Data Analysis to Develop a Specific Analysis Method Regarding Glucose Density Based on GH-Method: Math-Physical Medicine (No. 508)

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Abstract

The author read an article, "Glucodensities: a new representation of glucose profiles using distributional data analysis," dated August 19, 2020, from arxiv.org (see Reference 1). He decided to perform a research task using the Glucodensity (GD) concept but with his own developed software algorithm and collected glucose data via a continuous glucose monitoring (CGM) sensor over four pseudo-annual periods of 2018, 2019, 2020, and 2021.

In clinical practice, most medical doctors use HbA1C as the golden standard to evaluate the disease conditions of their type 2 diabetes (T2D) patients. The HbA1C value represents the average glucose value of all glucoses over the past 90 to 120 days or perhaps 115 days based on the red blood cell's lifespan; however, the A1C alone cannot tell doctors additional information other than the mean value. Other biomarkers such as the glucose variability (GV) or the glucose fluctuation (GF) can provide more data regarding the damage of a patient's internal organs via glucose excursion which causes many diabetic complications. Furthermore, the American Diabetes Association (ADA) issued guidance on time in range (TIR), time above range (TAR), and time below range (TBR) which can offer a general idea of how glucoses are distributed in three different ranges: TIR for normal conditions, TAR for hyperglycemic conditions, and TBR for hypoglycemic conditions.

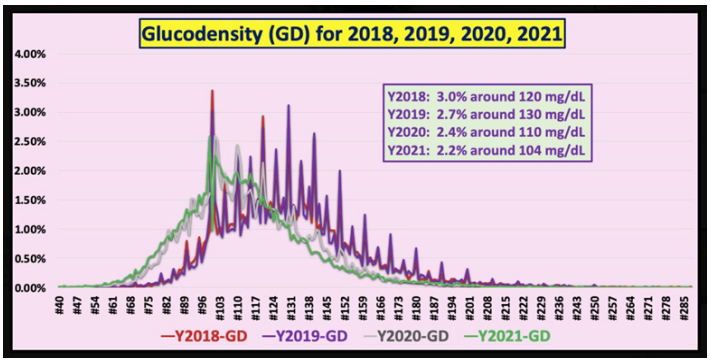
However, the three biomarkers, HbA1C, GF, and Time in/above/below Range (TxR), are still missing the ability to provide more detailed glucose variations, even when using these three defined ranges. Based on the observed shortcomings, GD can fill in certain gaps of "missing information" from the three biomarkers, HbA1C, GF, and TxR.

In conclusion, by using the author's own CGM sensor glucose data and developed APP program for the iPhone to calculate his GD data and curves for the four annual datasets, the key observation made from this study is:

His GD% lumps of "densely populated glucoses" or "majority of glucoses" are moving from higher glucose values with higher GD% during 2018-2019 to lower glucose values with lower GD% during 2020-2021. This observation offers clear proof that his diabetic conditions are not only under good control but also his T2D conditions are improving over time.

The GD analysis can identify more detailed information regarding his glucoses and T2D conditions compared to the traditional biomarkers such as HbA1C and TxR. It should be noted here that GF can offer additional insights regarding his risk probabilities of developing various diabetic complications. Similarly, GD can also present indications regarding diabetic complications.

Furthermore, his own GD waveforms are extremely similar in shape with the GD waveforms from Reference 1, except for ***his peak GD percentages are within 2% to 3% (with only 1 T2D patient, himself) while the peak GD percentages in Reference 1 are within 2% to 6% (with many more severe T2D patients).***



Introduction

The author read an article, "Glucodensities: a new representation of glucose profiles using distributional data analysis," dated August 19, 2020, from arxiv.org (see Reference 1). He decided to perform a research task using the Glucodensity (GD) concept but with his own developed software algorithm and collected glucose data via a continuous glucose monitoring (CGM) sensor over four pseudo-annual periods of 2018, 2019, 2020, and 2021.

In clinical practice, most medical doctors use HbA1C as the golden standard to evaluate the disease conditions of their type 2 diabetes (T2D) patients. The HbA1C value represents the average glucose value of all glucoses over the past 90 to 120 days or perhaps 115 days based on the red blood cell's lifespan; however, the A1C alone cannot tell doctors additional information other than the mean value. Other biomarkers such as the glucose variability (GV) or the glucose fluctuation (GF) can provide more data regarding the damage of a patient's internal organs via glucose excursion which causes many diabetic complications. Furthermore, the American Diabetes Association (ADA) issued guidance on time in range (TIR), time above range (TAR), and time below range (TBR) which can offer a general idea of how glucoses are distributed in three different ranges: TIR for normal conditions, TAR for hyperglycemic conditions, and TBR for hypoglycemic conditions.

However, the three biomarkers, HbA1C, GF, and Time in/above/below Range (TxR), are still missing the ability to provide more detailed glucose variations, even when using these three defined ranges. Based on the observed shortcomings, GD can fill in certain gaps of "missing information" from the three biomarkers, HbA1C, GF, and TxR.

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 his ~500 published medical papers.

The first paper, No. 386 describes his MPM methodology in a general conceptual format. The second paper, No. 387 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 depicts a general flow diagram containing ~10 key MPM research methods and different tools.

In particular, his paper No. 453 illustrates his GH-Method: math-physical medicine in great details, "Using Topology concept of mathematics and Finite Element method of engineering to develop a mathematical model of Metabolism in medicine in order to control various chronic diseases and their complications via overall health conditions improvement".

The Author'S Case of Diabetes and Complications

The author has been a severe T2D patient since 1996. He weighed 220 lb. (100 kg, BMI 32.5) at that time. By 2010, he still weighed 198 lb. (BMI 29.2) with an average daily glucose of 250 mg/dL (HbA1C of 10%). During that year, his triglycerides reached to 1161 (diabetic retinopathy or DR) and albumin-creatinine ratio (ACR) at 116 (chronic kidney disease or CKD). 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 future high risk of dying from severe diabetic complications. Other than cerebrovascular disease (stroke), he has suffered most known diabetic complications, including both macro-vascular and micro-vascular complications.

In 2010, he decided to launch his self-study on endocrinology, diabetes, and food nutrition in order to save his own life. During 2015 and 2016, he developed four prediction models related to diabetes conditions: weight, PPG, fasting plasma glucose (FPG), and A1C. As a result, from using his developed mathematical metabolism index (MI) model in 2014 and the four prediction tools, by end of 2016, his weight was reduced from 220 lbs. (100 kg, BMI 32.5) to 176 lbs. (89 kg, BMI 26.0), waistline from 44 inches (112 cm, nonalcoholic fatty liver disease /NAFLD) to 33 inches (84 cm), average finger glucose reading from 250 mg/dL to 120 mg/dL, and lab-tested A1C 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 has achieved excellent results on all fronts, especially his 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 and overall metabolism state were somewhat affected during this two-year heavier traveling period.

During 2020 with a COVID-19 quarantined lifestyle, not only has he published ~400 medical papers in 100+ journals, but he has also reached his best health conditions for the past 26 years. By the beginning of 2021, his weight was further reduced to 165 lbs. (BMI 24.4) along with a 6.1% A1C value (daily average glucose at 105 mg/dL), without having any medication interventions or insulin injections. These good results are due to his non-traveling, low-stress, and regular daily life routines. Due to his knowledge of chronic diseases, practical lifestyle management experiences, and developed various high-tech tools contribute to his excellent health status since 1/19/2020, which is the start date of being self-quarantined.

On 5/5/2018, he applied a CGM sensor device on his upper arm

and checks glucose measurements every 5 minutes for a total of ~288 times each day. He has maintained the same measurement pattern to present day. In his research work, he uses the CGM sensor glucose at time-interval of 15 minutes (96 data per day). By the way, the difference of average sensor glucoses between 5-minute intervals and 15-minute intervals is only 0.4% *(average glucose of 114.81 mg/dL for 5-minutes and average glucose of 114.35 mg/dL for 15-minutes with a correlation of 93% between these two sensor glucose curves) during the period from 2/19/20- to 8/13/21.*

Therefore, over the past 11 years, he could study and analyze the 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.

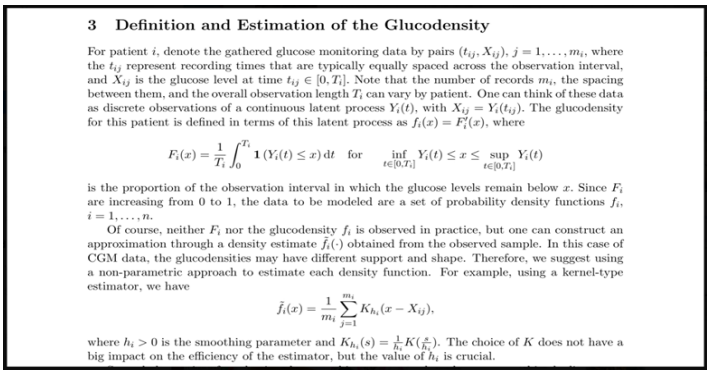
The following timetable provides a rough sketch of the emphasis of his medical research during each stage:

- 2000-2013: Self-study diabetes and food nutrition, developing a data collection and analysis software.
- 2014: Develop a mathematical model of metabolism, using engineering modeling and advanced mathematics.
- 2015: Weight & FPG prediction models, using neuroscience.
- 2016: PPG & HbA1C prediction models, using optical physics, artificial intelligence (AI), and neuroscience.
- 2017: Complications due to macro-vascular research such as cardiovascular disease (CVD), coronary heart disease (CHD) and stroke, using pattern analysis and segmentation analysis.
- 2018: Complications due to micro-vascular research such as chronic kidney disease (CKD), bladder, foot, and eye issues such as diabetic retinopathy (DR).
- 2019: CGM big data analysis, using wave theory, energy theory, frequency domain analysis, quantum mechanics, and AI.
- 2020: Cancer, dementia, longevity, geriatrics, DR, hypothyroidism, diabetic foot, diabetic fungal infection, linkage between metabolism and immunity, and learning about certain infectious diseases such as COVID-19.
- 2021: Applications of linear elastic glucose theory (LEGT) and perturbation theory from quantum mechanics on medical research subjects, such as chronic diseases and their complications, cancer, and dementia. Using metabolism and immunity.it's as the base, he expands his research into cancers, semantic, and COVID-19.

To date, he has collected more than two million data regarding his medical conditions and lifestyle details. In addition, he has written 498 medical papers and published 400+ articles in 100+ various medical journals, including 6 special editions with selected 20-25 papers for each edition. Moreover, he has given ~120 presentations at ~65 international medical conferences. He has continuously dedicated time and effort on medical research work and shared his findings and learnings with other patients worldwide.

Glucose Density or Glucodensity (GD)

The author took the following photo directly from the beginning part of Section 3 in the Glucodensities' paper (Reference 1), because he does not know how to write articles with LATAX math symbols on his iPAD Page application.



3 Definition and Estimation of the Glucodensity

For patient i, denote the gathered glucose monitoring data by pairs (t_{ij}, X_{ij}), $j = 1, \ldots, m_i$, where the t_{ij} represent recording times that are typically equally spaced across the observation interval, and X_{ij} is the glucose level at time $t_{ij} \in [0, T_i]$. Note that the number of records m_i, the spacing between them, and the overall observation length T_i can vary by patient. One can think of these data as discrete observations of a continuous latent process $Y_i(t)$, with $X_{ij} = Y_i(t_{ij})$. The glucodensity for this patient is defined in terms of this latent process as $f_i(x) = F_i'(x)$, where

$$F_i(x) = \frac{1}{T_i}\int_0^{T_i} \mathbf{1}\left(Y_i(t) \le x\right) dt \quad \text{for} \quad \inf_{t\in[0,T_i]} Y_i(t) \le x \le \sup_{t\in[0,T_i]} Y_i(t)$$

is the proportion of the observation interval in which the glucose levels remain below x. Since F_i are increasing from 0 to 1, the data to be modeled are a set of probability density functions f_i, $i = 1, \ldots, n$.

Of course, neither F_i nor the glucodensity f_i is observed in practice, but one can construct an approximation through a density estimate $\hat{f}_i(\cdot)$ obtained from the observed sample. In this case of CGM data, the glucodensities may have different support and shape. Therefore, we suggest using a non-parametric approach to estimate each density function. For example, using a kernel-type estimator, we have

$$\hat{f}_i(x) = \frac{1}{m_i}\sum_{j=1}^{m_i} K_{h_i}(x - X_{ij}),$$

where $h_i > 0$ is the smoothing parameter and $K_{h_i}(s) = \frac{1}{h_i}K(\frac{s}{h_i})$. The choice of K does not have a big impact on the efficiency of the estimator, but the value of h_i is crucial.

For the case of one patient of himself (i=1), he can then ignore the index i and only use j=1,…..T, where T is the overall observation length of glucoses. For the case in this article, the total T is 245 (from 40 mg/dL to 285 mg/dL).

His gathered CGM glucose data by pairs (tj, Xj), j=1,…,T, where the tj represents recording times (every 15 minutes for 96 times each day). Therefore, he can simplify the above equation in the photo into the following simplified equation for one patient only. The GD for himself can be defined in terms of a ***continuous format*** as follows where Xj = Y(tj) = CGM glucose.

$$GD(x) = \int_1^T (Y(t)\,dt) / T$$

with x1 < Y(t) < x2

where x1 and x2 are ∫ boundaries of his selected glucose range.

The glucose density % (GD%) equation for one patient, such as himself, can also be defined in terms of a discrete format as follows:

$$GD(x) = \left(\sum_{j=1}^{T} Y(tj)\right) / T$$

with x1 < Y(t) < x2

where x1 and x2 are boundaries of his selected glucose range.

He then programs the above algorithm into his APP software on the iPhone device to be used for calculating GD values and curves.

Results

Figure 1 shows his glucose density (GD) curves for 4 pseudo-annual periods of Y2018, Y2019, Y2020, and Y2021.

The left diagram is generated by using his algorithm on the Phone APP which has different glucose ranges for each period:

Y 2018: 50 (x1) to 288 (x2)
Y 2018: 50 (x1) to 300 (x2)
Y 2018: 42 (x1) to 287 (x2)
Y 2018: 39 (x1) to 272 (x2)

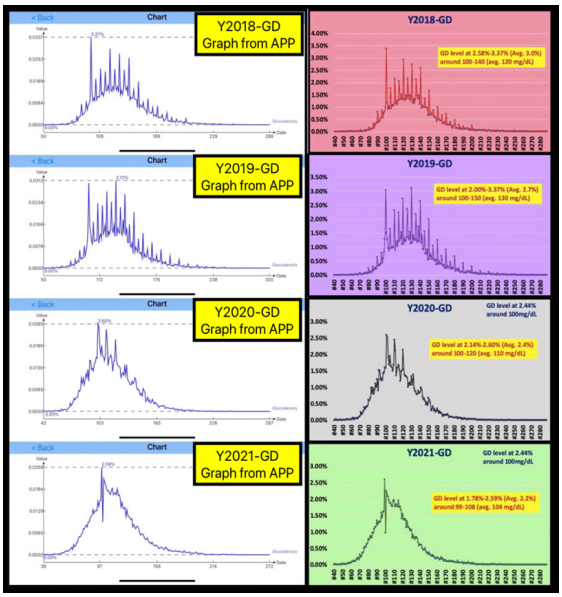


Figure 1: Glucose density (GD) curves of Y2018, Y2019, Y2020, and Y2021

The right diagram is created by using Excel on his Mac PC which has the ***same glucose ranges for each period, i.e., 40 (x1) to 280 (x2).*** He compiles these 4 different glucose ranges into 1 consistent glucose range for the purpose of easier and accurate results comparison by plotting the 4 curves on one diagram (Figure 2). It is clear that the left diagram and right diagram are almost identical to each other except for the glucose areas near x1 and near x2 which have 0% of GD%.

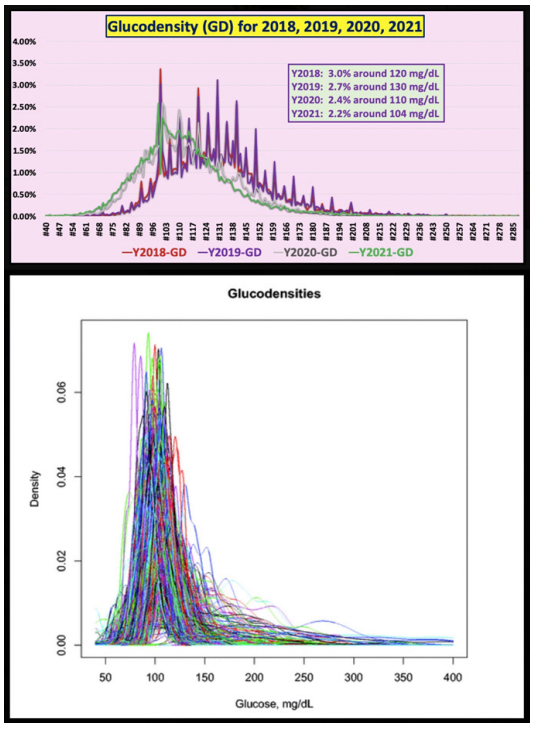


Figure 2: The combined 4 GD% curves of the author and Reference 1's displayed GD% curve

In Figure 1, the readers should focus on the middle "peak lumps" of each year's curve. ***The "peak lumps" are the glucose values which have elevated numbers of occurrence (i.e. higher GD%).***

The top diagram in Figure 2 illustrates the combined GD% curves of the 4 annual glucose data with the following highlights:

Y2018: GD 3.0% around 120 mg/dL
Y2019: GD 2.7% around 130 mg/dL
Y2020: GD 2.4% around 110 mg/dL
Y2021: GD 2.2% around 104 mg/dL

It is evident that ***his GD% and average glucose values are decreasing year after year, except for having 130 mg/dL in Y2019.*** *The busy travel schedule of attending medical conferences in Y2019 made his conditions worse than Y2018. During the on-going COVID-19 quarantine lifestyle, his performance in Y2021 is better than Y2020.*

The lower diagram in Figure 2 is taken directly from the paper in Reference 1. It has a similar GD% peak lump as the author's GD% except that it has ***a higher GD% (up to 6%) compared to the author's GD% (up to 3% only).*** The peak lump spread in Reference 1 is between 90 mg/dL and 140 mg/dL, while the author's peak lump spread is between 104 mg/dL and 130 mg/dL (via visual check). It should be noted that ***Reference 1 uses many more patients' data in a short time period, whereas the author has only one patient's data but with a much longer time period of ~4 years.***

Conclusions

In conclusion, by using the author's own CGM sensor glucose data and developed APP program for the iPhone to calculate his GD data and curves for the four annual datasets, the key observation made from this study is:

His GD% lumps of "densely populated glucoses" or "majority of glucoses" are moving from higher glucose values with higher GD% during 2018-2019 to lower glucose values with lower GD% during 2020-2021. This observation offers clear proof that his diabetic conditions are not only under good control but also his T2D conditions are improving over time.

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References

For editing purposes, majority of the references in this paper, which are self-references, have been removed for this article. Only references from other authors' published sources remain. The bibliography of the author's original self-references can be viewed at www.eclairemd.com.

1. Marcos Matabuena1, Alexander Petersen, Juan C Vidal, Francisco Gude (2020) Glucodensities: a new representation of glucose profiles using distributional data analysis. https://arxiv.org/pdf/2008.07840.pdf