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Applying the Distributional Data Analysis Tool, Biomarker Density, with the Collected Daily Data from 2 Types of Glucose Over the Past 3.5 Years of a Patient with Chronic Diseases to Investigate his Glucose Conditions Based on GH-Method: Math-Physical Medicine (No. 518)

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Abstract

Recently, the author conducted a series of medical research projects by applying a distributional data density analysis tool on his weight, glucose, blood pressure (BP), and heart conditions, while using his collected big data regarding certain biomarker's density distribution for the selected years. In this article, he investigates his collected glucose data density via two different collection methods, finger-piercing and continuous glucose monitoring (CGM) sensor device, within a time span of 3.5 years (5/8/2018-9/13/2021). With this data, he can interpret the results and explore additional and in-depth information since he is most familiar with his own health conditions. The findings from his own data are applicable to other patients with type 2 diabetes (T2D). The main purpose of writing this series of research articles is to further demonstrate the applicability and power of the specific distributional data density analysis tool. When he previously researched certain biomarkers and their relationship with other influential factors, he generally used the average values of those biomarkers. We know that most biomarkers, including glucose, could fluctuate along the time scale in the form of a wave. Each wave has its own unique amplitude and a specific measuring unit that is associated with this particular biomarker. However, there are two other key factors, frequency and wavelength, to be considered as well. Particularly, the frequency component is associated with energy and excessive energy causes damage to the internal organs. Therefore, without focusing on the waveform of a biomarker and depending only on its mean value, we would lose many vital, interesting, and useful hidden information. This type of mean value, such as HbA1C, can only provide partial views of our overall diabetic conditions. These biomarkers still have missing information which carries certain hidden internal turmoil or vital signs, e.g., biomarker variation or its severe stimulation due to all types of external and/or internal stimulators. Therefore, by applying this basic knowledge of distributional data analysis[(1)] by defining another term known as the general biomarker density or bio-density% (BMD%), he can explore additional, different, in-depth, and useful hidden information from collected biomarker data and their associated waveforms. The term biomarker density percentage (BMD%) is defined as the occurrence frequency at a specific person's biomarker value. With this, he can calculate and examine each biomarker's occurrence rate within a certain range over a selected timespan. This selected timespan is dependent on the study which is applied to specific patients (in this case, himself). As of 1/1/2012, he started to track his daily weight and daily finger glucose and began collecting his CGM sensor glucose on 5/8/2018. As a result, his selected timespan for this particular study commenced on 5/8/2018 and ended on 9/13/2021. By investigating the changes of the peak biomarker value with their associated BMD% from year to year, he can easily observe his biomarker's moving trend and understand his actual health problems or necessary health improvement effort clearly. The above description provides the reason he keeps searching for applicable tools to analyze the collected big data of any biomarker. If this type of biomarker examination method is accepted by the medical community, it can be an extremely beneficial tool for doctors to quickly study the health conditions of their patients. Furthermore, the author programmed this algorithm into an iPhone app software. Through the combination of his published papers and medical books along with a widely distributed app for patient's use in the future, he believes that worldwide patients with chronic diseases can benefit from his research work. Hopefully, his research papers would not be limited within the scope of a "descriptive style

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using 26 alphabets" but instead as a "quantitative style using 10 digits". Numbers do not lie as long as we don't use fake, unorganized, and/or uncleaned data. Statistics is a tricky tool to use for any research work because it has the obvious characteristics of garbage in and garbage out (GIGO). It is also important to know that using statistics with different selected time-windows for certain studies will result in varying conclusions. In summary, the author conducts this research work using the tools of glucose density% (GD%) with his collected 3 daily glucose: estimated average glucose (eAG), postprandial plasma glucose (PPG), and fasting plasma glucose (FPG) from the finger-piercing method and sensor collecting method over the same period of 3.5 years (5/8/2018-9/13/2021). Each of these 6 selected glucose has its own unique glucose range (maximum glucose and minimum glucose) and specifically defined glucose normal conditions, e.g., under 120 mg/dL is non-diabetes, whereas above 180 mg/dL is severe diabetes. This makes a combined study and data presentation quite difficult. In order to combine the 6 glucose into one single diagram for this case, he must redefine a common general-scale of the glucose data range from 40 mg/dL to 260 mg/dL with an equal interval of 1 mg/dL. With this new numbering system, he can then align these 6 different "normal conditions or target values" of glucose based on the following definitions: below the glucose level 70 mg/dL as "hypoglycemic"; between 70 mg/dL and 180 mg/dL as "pre-diabetic or diabetic"; above 180 mg/dL as "hyperglycemic". For the purpose of additional investigation on the various diabetic ranges, he has chosen a narrower dividing line of 140 mg/dL in order to distinguish between the pre-diabetes condition and diabetes condition. Now, he is able to plot all 6-GD% curves into one combined diagram with their relative positions which indicate certain biomedical meanings. Through a closer examination of this combined diagram, he provides the following three conclusive statements: (1) From the time-domain diagram and density-domain diagram, his eAG curves and PPG curves are closer to each other. This is logical since his finger PPG occupies 75% of weight for eAG (3 post-meal tests out of a total of 4 tests per day) and sensor PPG occupies 38% of weight for eAG (9 hours of PPG period vs. 24 hours of eAG per day). On the other hand, his FPG curves are distant from the curves of eAG and PPG. This phenomenon is a result of his finger FPG occupying only 25% of weight for eAG (1 fasting test out of a total of 4 tests per day) and sensor FPG occupying 29% of weight for eAG (7 hours of PPG period vs. 24 hours of eAG per day). The other missing percentages belong to the glucose associated with between-meals and pre-bedtime periods, 0% for finger case (no test conducted) and 33% for sensor case (8 hours out of 24 hours). (2) Examining his time-in-range (TIR) percentages, it is clear that his finger glucose densities within the TIR range are higher than the sensor glucose densities within the same TIR range. In the case of finger vs. sensor between 70 mg/dL-120 mg/dL, 78%>53% for eAG, 77%>44% for PPG, 83%>79% for FPG. In the case of finger vs. sensor between 70 mg/dL-140 mg/dL, 97%>78% for eAG, 96%>73% for PPG, 99%>92% for FPG. In the case of finger vs. sensor between 70 mg/dL-180 mg/dL, 99%>96% for eAG, 99%>96% for PPG, 99%>92% for FPG. (3) With hypoglycemia (<70 mg/dL) and hyperglycemia (>180 mg/dL), his case demonstrates extremely low probabilities for either one. Actually, his TIR percentages for 70 mg/dL-180 mg/dL indicate that his scores are 99% for finger glucose and 97% for sensor glucose. This means that his T2D control has been remarkably effective during the period from 5/8/2018 to 9/13/2021. By combining the two different analysis methods, the traditional time-domain analysis and the newly defined density-domain analysis, he can explore more insights into his glucose.

Keywords: Blood pressure; Type 2 diabetes; Continuous glucose monitoring; Biomarker density; Glucose density; Postprandial plasma glucose; Fasting plasma glucose

Abbreviations: CGM: continuous glucose monitoring; T2D: type 2 diabetes; BMD%: biomarker density percentage; GD%: glucose density%; eAG: estimated average glucose; PPG: postprandial plasma glucose; FPG: fasting plasma glucose; TIR: time-in-range; MPM: math-physical medicine; HbA1C: hemoglobin A1C

1. INTRODUCTION

Recently, the author conducted a series of medical research projects by applying a distributional data density analysis tool on his weight, glucose, blood pressure (BP), and heart conditions, while using his collected big data regarding certain biomarker's density distribution for the selected years.

In this article, he investigates his collected glucose data density via two different collection methods, finger-piercing and continuous glucose monitoring (CGM) sensor device, within a time span of 3.5 years (5/8/2018-9/13/2021).

With this data, he can interpret the results and explore additional and in-depth information since he is most familiar with his own health conditions. The findings from his own data are applicable to other patients with type 2 diabetes (T2D). The main purpose of writing this series of research articles is to further demonstrate the applicability and power of the specific distributional data density analysis tool.

When he previously researched certain biomarkers and their relationship with other influential factors, he generally used the average values of those biomarkers. We know that most biomarkers, including glucose, could fluctuate along the time scale in the form of a wave. Each wave has its own unique amplitude and a specific measuring unit that is associated with this particular biomarker. However, there are two other key factors, frequency and wavelength, to be considered as well. Particularly, the frequency component is associated with energy and excessive energy causes damage to the internal organs. Therefore, without focusing on the waveform of a biomarker and depending only on its mean value, we would lose many vital, interesting, and useful hidden information. This type of mean value, such as HbA1C, can only provide partial views of our overall diabetic conditions. These biomarkers still have missing information which carries certain hidden internal turmoil or vital signs, e.g., biomarker variation or its severe stimulation due to all types of external and/or internal stimulators. Therefore, by applying this basic knowledge of distributional data analysis by defining another term known as the general biomarker density or bio-density% (BMD%), he can explore additional, different, in-depth, and useful hidden information from collected biomarker data and their associated waveforms.

The term biomarker density percentage (BMD%) is defined as the occurrence frequency at a specific person's biomarker value. With this, he can calculate and examine each biomarker's occurrence rate within a certain range over a selected timespan. This selected timespan is dependent on the study which is applied to specific patients (in this case, himself). As of 1/1/2012, he started to track his daily weight and daily finger glucose and began collecting his CGM sensor glucose on 5/8/2018. As a result, his selected timespan for this particular study commenced on 5/8/2018 and ended on 9/13/2021. By investigating the changes of the peak biomarker value with their associated BMD% from year to year, he can easily observe his biomarker's moving trend and understand his actual health problems or necessary health improvement effort clearly.

The above description provides the reason he keeps searching for applicable tools to analyze the collected big data of any biomarker. If this type of biomarker examination method is accepted by the medical community, it can be an extremely beneficial tool for doctors to quickly study the health conditions of their patients. Furthermore, the author programmed this algorithm into an iPhone app software. Through the combination of his published papers and medical books along with a widely distributed app for patient's use in the future, he believes that worldwide patients with chronic diseases can benefit from his research work. Hopefully, his research papers would not be limited within the scope of a "descriptive style using 26 alphabets" but instead as a "quantitative style using 10 digits". Numbers do not lie as long as we don't use fake, unorganized, and/or uncleaned data. Statistics is a tricky tool to use for any research work because it has the obvious characteristics of garbage in and garbage out (GIGO). It is also important to know that using statistics with different selected time-windows for certain studies will result in varying conclusions.

2. METHODS

2.1 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 the biochemical medicine (BCM) approach vs. 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: MPM in great detail, "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".

2.2 The author's case of diabetes and complications

The author has been a severe T2D patient since 1996. He weighed 220 lbs. (100 kg, BMI 32.5) at that time. By 2010, he still weighed 198 lbs. (BMI 29.2) with average daily glucose of 250 mg/dL (HbA1C of 10%). During that year, his triglycerides reached to 1161 (diabetic retinopathy or DR) and the 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 need for kidney dialysis treatment and future high risk of dying from severe diabetic complications. Other than the cerebrovascular disease (stroke), he has suffered most of the 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 condition: weight, postprandial plasma glucose (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 the lab-tested A1C from 10% to ~6.5%. One of his major accomplishments is that he no longer takes any diabetes medication 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 dining 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 condition 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 intervention or insulin injections. These good results are due to his non-traveling, low-stress, and regular daily life routines. His knowledge of chronic diseases, practical lifestyle management experiences and developed various high-tech tools contributed 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 his glucose measurements every 5 minutes for a total of ~288 times each day. He has maintained the same measurement pattern to the present day. In his research work, he uses the CGM sensor glucose at a time-interval of 15

minutes (96 data per day). By the way, the difference of average sensor glucose 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 2/19/20-8/13/21.

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 aim of achieving 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 and FPG prediction models using neuroscience.

2016: PPG and 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 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 his time and effort on medical research work and shared his findings and learnings with other patients worldwide.

2.3 Glucose density (GD)

For the case of one particular patient i, the collected biomarker data can be expressed by pairs of data in the format of (t ij, X ij), j = 1 … T, where the t ij represents the recording time and X ij is the biomarker level at time instant t ij, and T is the overall observation length of the selected biomarker. For the case in this article, the total T is 221 (e.g., from 40 mg/dL to 260 mg/dL with an equal interval of 1 mg/dL between two glucose end-points).

Therefore, he can describe the above mathematical problem in a more simplified equation for one patient only. The glucose density% (GD%) for one patient can be defined in terms of a continuous format as follows:

$$GD(x) = \int_{1}^{T} (Y(t)\,dt)/T \quad \text{with} \quad x1 < Y(t) < x2$$

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:

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

with $x1 < Y(t) < x2$

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

He then developed his app software program using the above-described algorithm.

3. RESULTS

Figure 1 shows the comparison between his finger glucose and his CGM sensor glucose using a time-domain analysis. It should be pointed out that the correlations between the finger curves and sensor curves are within a high range of 77%-89%.

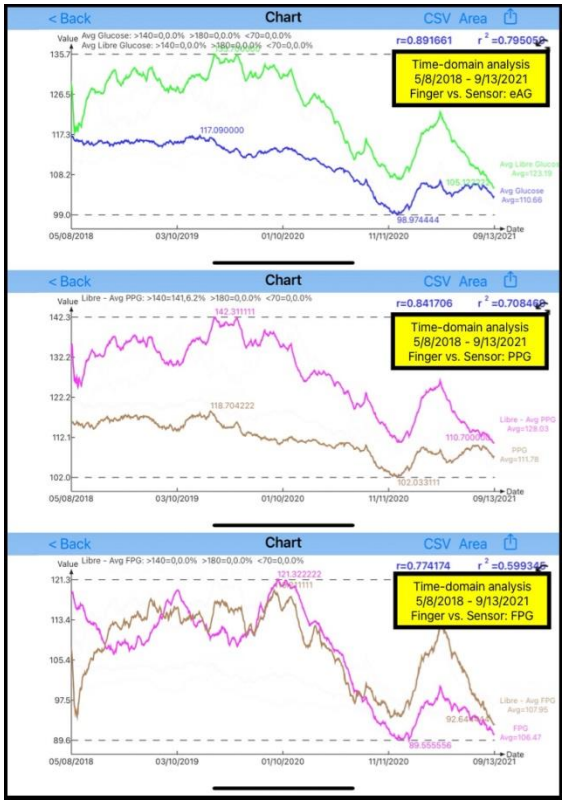


Figure 1: Time-domain analysis of his eAG, PPG, FPG curves within a period of 3.5 years (5/8/2018-9/13/2021).

Figure 2 illustrates the comparison between finger glucose and sensor glucose along with estimated average glucose (eAG), PPG, and FPG using a density-domain analysis. The 3 diagrams are generated on his app with different glucose ranges that contain varying minimum glucose and maximum glucose; however, they have similar patterns between eAG and PPG as well as different patterns between FPG and eAG/PPG which are evident.

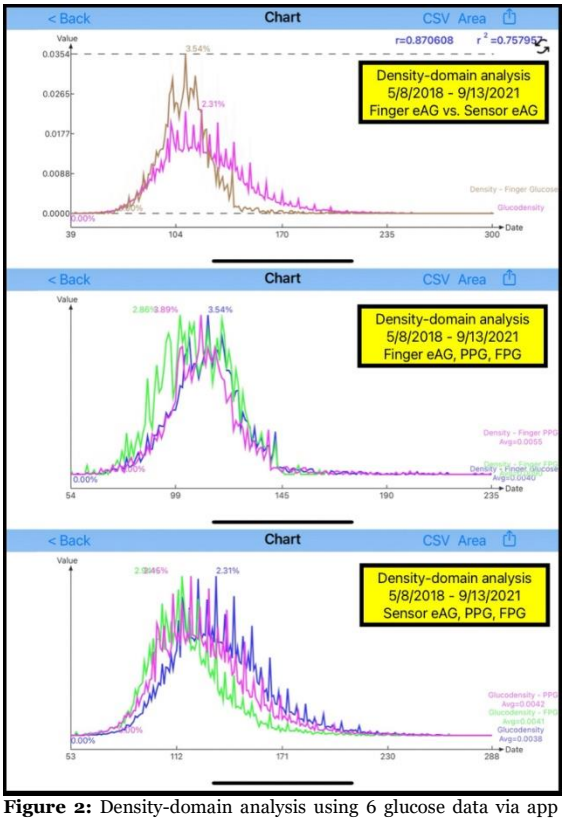


Figure 2: Density-domain analysis using 6 glucose data via app software within a period of 3.5 years (5/8/2018-9/13/2021).

Figure 3 reflects the combined glucose densities of the 6 glucose into one diagram which has a consistent glucose range from 40 mg/dL to 260 mg/dL. Again, they have similar patterns between eAG and PPG as well as different patterns between FPG and eAG/PPG which are obvious. Furthermore, the higher GD peaks are associated with the finger glucose compared to the GD peaks of sensor glucose that can be found if we examine them closely from this combined figure.

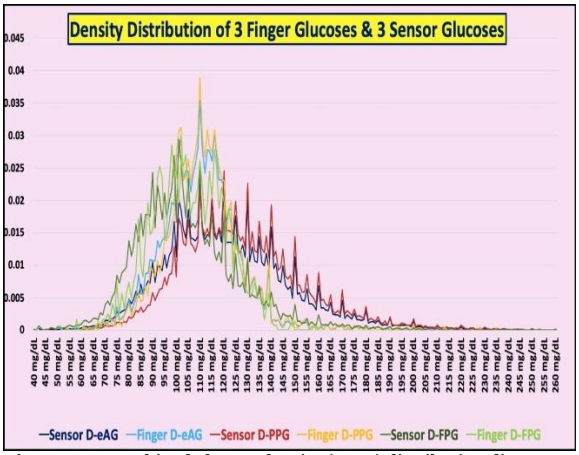


Figure 3: A combined glucose density (GD%) distribution diagram of 6 selected glucose based on the same data range within a common period of 3.5 years (5/8/2018-9/13/2021).

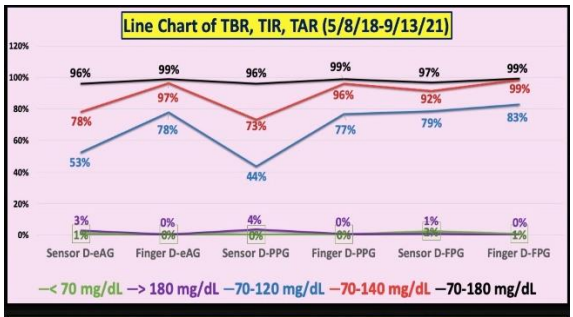
Figure 4 uses the line chart and bar chart to display more hidden information from the above GD diagrams. By examining the time-in-range (TIR) percentages, it is clear that his finger glucose densities within the TIR range are higher than the sensor glucose densities within the same TIR range.

In the case of finger vs. sensor between 70 mg/dL-120 mg/dL, 78%>53% for eAG, 77%>44% for PPG, 83%>79% for FPG.

In the case of finger vs. sensor between 70 mg/dL-140 mg/dL, 97%>78% for eAG, 96%>73% for PPG, 99%>92% for FPG.

In the case of finger vs. sensor between 70 mg/dL-180 mg/dL, 99%>96% for eAG, 99%>96% for PPG, 99%>92% for FPG.

Furthermore, with hypoglycemia (<70 mg/dL) and hyperglycemia (>180 mg/dL), his case demonstrates having extremely low probabilities. Actually, both his TIR percentages for 70 mg/dL-180 mg/dL have indicated that his scores are 99% for finger glucose and 97% for sensor glucose. This means that his T2D control has been very effective during the period from 5/8/2018 to 9/13/2021.



9/17/21	5/8/18-9/13/21					
Glucose	Sensor D-eAG	Finger D-eAG	Sensor D-PPG	Finger D-PPG	Sensor D-FPG	Finger D-FPG
< 70 mg/dL	1%	0%	0%	0%	2%	1%
> 180 mg/dL	3%	0%	4%	0%	1%	0%
70-120 mg/dL	53%	78%	44%	77%	79%	83%
70-140 mg/dL	78%	97%	73%	96%	92%	99%
70-180 mg/dL	96%	99%	96%	99%	97%	99%

Figure 4: TBR/TIR/TAR analysis using combined glucose density (GD%) distribution of 6 selected glucose within a period of 3.5 years (5/8/2018-9/13/2021).

4. CONCLUSION

In summary, the author conducts this research work using the tools of GD% with his collected 3 daily glucose: eAG, PPG, and FPG from the finger-piercing method and sensor collecting method over the same period of 3.5 years (5/8/2018-9/13/2021).

Each of these 6 selected glucose has its own unique glucose range (maximum glucose and minimum glucose) and specifically defined glucose normal conditions, e.g., under 120 mg/dL is non-diabetes, whereas above 180 mg/dL is severe diabetes. This makes a combined study and data presentation quite difficult. In order to combine the 6 glucose into one single diagram for this case, he must redefine a common general-scale of the glucose data range from 40 mg/dL to 260 mg/dL with an equal interval of 1 mg/dL. With this new numbering system, he can then align these 6 different "normal conditions or target values" of glucose based on the following definitions:

Below the glucose level 70 mg/dL as "hypoglycemic";

Between 70 mg/dL and 180 mg/dL as "pre-diabetic or diabetic";

Above 180 mg/dL as "hyperglycemic".

For the purpose of additional investigation on the various diabetic ranges, he has chosen a narrower dividing line of 140 mg/dL in order to distinguish between the pre-diabetes condition and diabetes condition.

Now, he is able to plot all 6-GD% curves into one combined diagram with their relative positions which indicate certain biomedical meanings. Through a closer examination of this combined diagram, he provides the following three conclusive statements:

(1) From the time-domain diagram and density-domain diagram, his eAG curves and PPG curves are closer to each other. This is logical since his finger PPG occupies 75% of weight for eAG (3 post-meal tests out of a total of 4 tests per day) and sensor PPG occupies 38% of weight for eAG (9 hours of PPG period vs. 24 hours of eAG per day). On the other hand, his FPG curves are distant from the curves of eAG and PPG. This

phenomenon is a result of his finger FPG occupying only 25% of weight for eAG (1 fasting test out of a total of 4 tests per day) and sensor FPG occupying 29% of weight for eAG (7 hours of PPG period vs. 24 hours of eAG per day). The other missing percentages belong to the glucose associated with between-meals and pre-bed time periods, 0% for finger case (no test conducted) and 33% for sensor case (8 hours out of 24 hours).

(2) Examining his TIR percentages, it is clear that his finger glucose densities within the TIR range are higher than the sensor glucose densities within the same TIR range. In the case of finger vs. sensor between 70 mg/dL-120 mg/dL, 78%>53% for eAG, 77%>44% for PPG, 83%>79% for FPG. In the case of finger vs. sensor between 70 mg/dL-140 mg/dL, 97%>78% for eAG, 96%>73% for PPG, 99%>92% for FPG. In the case of finger vs. sensor between 70 mg/dL-180 mg/dL, 99%>96% for eAG, 99%>96% for PPG, 99%>92% for FPG.

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By combining the two different analysis methods, the traditional time-domain analysis and the newly defined density-domain analysis, he can explore more insights into his glucose.

5. 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) Matabuena M, Petersen A, Vidal JC, et al. Glucodensities: A new representation of glucose profiles using distributional data analysis. Stat Methods Med Res. 30(6);1445–1464:2021.

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