

Computational modeling enables individual assessment of postprandial glucose and insulin responses after bariatric surgery

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This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)

This study utilizes Gaussian process-based methods to fit data points from patients and compare characteristics of glucose dynamics between two groups: RYGB and OAGB. The approach is meaningful as the data exhibit substantial noise and non-linear patterns, necessitating advanced techniques to derive significant results.

The study presents extensive analytical results for curve analysis. However, from a methodological perspective, it represents a straightforward application of established methods rather than the development of novel techniques. Although the authors assert the novelty of their approach, this claim is not substantiated by the methods employed.

Relevant references include:

Li, Ping, and Songcan Chen. "Hierarchical Gaussian processes model for multi-task learning." *Pattern Recognition*, 74 (2018): 134-144.

W. Cho, Y. Kim, and J. Park, "Hierarchical Anomaly Detection Using a Multioutput Gaussian Process," *IEEE Transactions on Automation Science and Engineering*, vol. 17, no. 1, pp. 261-272, Jan. 2020.

Cuesta Ramírez, Jhouben Janyk. "Hierarchical and Multiple Output Gaussian Process for the Analysis of Colombian Cellular Networks." (2015).

Thus, while the study may provide meaningful results, the methodological novelty remains questionable.

Additionally, to enhance clinical impact, the results should explicitly identify which characteristics influence the choice of surgical procedure between RYGB and OAGB.

Reviewer #2

(Remarks to the Author)

Manuscript Review:

The manuscript entitled: "Computational modeling enables individual assessment of postprandial glucose and insulin responses after bariatric surgery" by Onur Poyraz and colleagues explores the mathematical modeling of postprandial glycemic and insulinemic responses to oral tests. This approach aims to reduce data variability and improve data predictability. The model was applied to two patient cohorts who underwent bariatric procedures: Roux-en-Y gastric bypass (RYGB) or One-anastomosis gastric bypass (OAGB).

The use of mathematical modeling is a fundamental tool in health sciences and research. It can improve our understanding of biological phenomena associated with metabolic diseases and their improvement after pharmacological or surgical treatments. Bariatric surgery is a well-established treatment for obesity and type 2 diabetes mellitus. Understanding the mechanisms of action of different surgical procedures is essential to choose the best technique to address patients' metabolic dysfunctions.

Comments to the Authors:

1. The text appears somewhat disconnected. It is unclear whether the main objective is to present a new mathematical

model for analyzing OGTT/MTT metabolic responses or to compare surgical techniques. Consequently, it does not clearly compare the data generated by the model with classical approaches (e.g., plasma glucose and insulin levels, time curves, peak time, area under the curve, and others) or with other mathematical models. Additionally, it does not analyze how the proposed model provides new insights into the typical outcomes of bariatric surgery.

2. The inclusion/exclusion criteria for the study population are not clearly described. It is also unclear how patients were assigned to different procedures or whether the population is entirely new or partially derived from previous projects.

3. The results section is too extensive and sometimes repetitive. It does not fully address the effects of the mathematical model or bariatric surgery. For example, while time curves were not analyzed, only derived data from these curves were used.

4. The discussion section does not compare the results generated by the model with those obtained from other mathematical or classical approaches. It is unclear if the calculated variables align with or differ from those obtained through other methods. The discussion should emphasize whether the model offers any advantages to encourage others to adopt this methodology.

Minor Comments and Suggestions for Improvement:

- The inclusion and selection criteria for the study population should be clarified. If this is a retrospective study, provide a brief explanation of patient selection. In addition, Table G1, which presents the clinical, anthropometric, and metabolic features of patients, lacks units of measurement. If possible, consider showing T2DM subjects in a separate column.

- It is unclear whether the glucose and insulin levels shown in the time-course graphs represent raw data or modeled data. Please clarify.

- Parameters derived from the oral glucose tolerance test (OGTT) or meal tolerance test (MTT) time curves (Figure 1) should specify whether they are based on modeled or raw data.

- Throughout the text, insulin is presented in mmol/L as the unit of measurement. If this is correct, explain the conversion factor used.

- Graphs and table legends should include more information to improve clarity. For instance, in the graphs, explain what the shaded areas represent.

- Table G1 lacks units of measurement and information about the data type. Also, consider displaying T2DM subjects in a separate column.

- Section 2.4 of the methods cites Heinonen et al., 2015, for blood sample collection. However, it incorrectly states: "A fasting blood sample was collected before ingestion of the glucose drink, and post-glucose samples were collected at 0, 30, 60, 120, and 180 min." Time zero should be the sample collected before glucose or meal ingestion, which contradicts Section 2.5 of this manuscript.

- If parameters derived from OGTT or MTT time curves were calculated from the model, comparing them with classical parameters derived from raw glucose and insulin response time curves would help to understand the differences between the methods.

- The first paragraph of the results section states that both tests used the same amount of carbohydrates, which contradicts Section 2.5 of the methods.

I sincerely appreciate the effort and dedication invested in this manuscript. The topic is highly relevant, and the use of computational modeling in this context is promising. I believe addressing the points mentioned will significantly enhance the clarity and impact of your work.

Thank you for the opportunity to review this study, and I look forward to seeing its final version.

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)

It seems that all my concerns have been resolved. Thank you.

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Rebuttal Letter

Comments of Reviewer 1 (expert on machine learning)

RC: This study utilizes Gaussian process-based methods to fit data points from patients and compare characteristics of glucose dynamics between two groups: RYGB and OAGB. The approach is meaningful as the data exhibit substantial noise and non-linear patterns, necessitating advanced techniques to derive significant results.

AR: [We thank the reviewer for the appreciative comments.](#)

RC: The study presents extensive analytical results for curve analysis. However, from a methodological perspective, it represents a straightforward application of established methods rather than the development of novel techniques. Although the authors assert the novelty of their approach, this claim is not substantiated by the methods employed.

AR: [Thank you for this comment. It is true that the model itself has been introduced before but we have adapted it to a novel application by modeling human postprandial OGTT and MMT data. We show that the modeling gives biologically meaningful results in revealing clinical differences during weight loss between two surgical operation types, sexes and patients with and without type 2 diabetes. Many of the observed differences would remain hidden in simpler analyses, such as modeling the curves by linear interpolation between observation points, which nonetheless are still widely used in human postprandial glucose data analysis, and we have added a comparison to demonstrate this \(Results section 3.7, and Table H.1 of the manuscript\). Hence, we need more accurate models to assess and predict responses of the individual patients. The presentation of such a model is another contribution of the manuscript. We have now tried to clarify this in the text and removed the word “novel” in relation to the model itself from the first and last paragraphs of the discussion.](#)

RC: Relevant references include:
Li, Ping, and Songcan Chen. "Hierarchical Gaussian processes model for multi-task learning." *Pattern Recognition*, 74 (2018): 134-144.
W. Cho, Y. Kim, and J. Park, "Hierarchical Anomaly Detection Using a Multioutput Gaussian Process," *IEEE Transactions on Automation Science and Engineering*, vol. 17, no. 1, pp. 261-272, Jan. 2020.
Cuesta Ramírez, Jhouben Janyk. "Hierarchical and Multiple Output Gaussian Process for the Analysis of Colombian Cellular Networks." (2015).
Thus, while the study may provide meaningful results, the methodological novelty remains questionable.

AR: [Thank you for pointing out that these important works were missing. We have now incorporated the references in the introduction on page 2, rows 50-52:](#)

“Similar techniques to HMOGP have been successfully applied before in different domains such as anomaly detection (Cho 2019), multi-task learning (Li 2018), and mobile cellular network analysis (Cuesta 2015), performing better than MOGP and GP. We expanded these techniques to the medical domain in OGTT and MMT responses with necessary adaptations.”

RC: Additionally, to enhance clinical impact, the results should explicitly identify which characteristics influence the choice of surgical procedure between RYGB and OAGB.

AR: We have now tried to improve the text in this aspect and modified the discussion paragraph on RYGB and OAGB followingly on page 10, lines 288-297:

“Our findings suggest that the more pronounced glucose-insulin peak in RYGB stems from its anatomical differences, where nutrients reach key gut areas more rapidly, leading to faster glucose absorption and a sharper insulin response compared to OAGB. This accelerated glycemic response may enhance early glucose control. In contrast, OAGB’s more gradual glucose absorption presents a smoother curve and may thus lower post-bariatric hypoglycemia risk, making it a preferable option for participants with preserved beta-cell function or milder metabolic disturbances. Although higher glycemic peaks in RYGB are linked to vascular risks like atherosclerosis and hypertension (Temelkova-Kurktschiev 2000, Anan 2008), studies indicate better hypertension improvement and reduced antihypertensive medication use post-RYGB (Heinonen 2023). Given these dynamics, OAGB could, however, be a safer choice for individuals with a history of cardiovascular disease. Nonetheless, bariatric surgery remains a powerful metabolic intervention, providing substantial glycemic benefits regardless of the procedure (Sinclair 2018).”

In the conclusion, we have now added:

“Our study suggests that based on postprandial glucose dynamics, RYGB may be favorable over OAGB in hyperglycemic patients without risk for hypoglycemia or vascular diseases, where OAGB could be preferred.”

Additionally, in the abstract, we have now added:

“Higher glucose and insulin responses were observed after RYGB compared with OAGB, suggesting differences between the procedures that may influence the clinical practice.”

Comments of Reviewer 2 (expert on diabetes, insulin, and glucose measurement)

Summary: The manuscript entitled: "Computational modeling enables individual assessment of postprandial glucose and insulin responses after bariatric surgery" explores the mathematical modeling of postprandial glycemic and insulinemic responses to oral tests. This approach aims to reduce data variability and improve data predictability. The model was

applied to two patient cohorts who underwent bariatric procedures: Roux-en-Y gastric bypass (RYGB) or One-anastomosis gastric bypass (OAGB).

The use of mathematical modeling is a fundamental tool in health sciences and research. It can improve our understanding of biological phenomena associated with metabolic diseases and their improvement after pharmacological or surgical treatments. Bariatric surgery is a well-established treatment for obesity and type 2 diabetes mellitus. Understanding the mechanisms of action of different surgical procedures is essential to choose the best technique to address patients' metabolic dysfunctions.

RC: The text appears somewhat disconnected. It is unclear whether the main objective is to present a new mathematical model for analyzing OGTT/MTT metabolic responses or to compare surgical techniques. Consequently, it does not clearly compare the data generated by the model with classical approaches (e.g., plasma glucose and insulin levels, time curves, peak time, area under the curve, and others) or with other mathematical models. Additionally, it does not analyze how the proposed model provides new insights into the typical outcomes of bariatric surgery.

AR: [Thank you for this important comment.](#)

[Our primary aim is to produce novel knowledge on individual postprandial glucose and insulin responses between different metabolic cohorts. For this purpose, the simple statistical methods were unsatisfactory, and hence we used the HMOGP modeling. We present results that could influence the choice between RYGB and OAGB, and take into account differences between sexes and metabolic disorders. We have now tried to clarify the novel results of the study in relation to when and to which patients should RYGB be favored over OAGB and vice versa, and clarified the differences found between sexes and persons with and without T2DM.](#)

[Our secondary aim was to test whether the used HMOGP modeling is suitable and reliable in analyzing the complex OGTT and MMT data and to provide clinically meaningful results in this aspect. We present that this modeling approach can be used for the OGTT and MMT data.](#)

[Additionally, we now present results in **Table H.1**, where we describe the advantage of this modeling over a simpler data analysis, where the curves are approximated by linear interpolation. In table 1 it is of note that the conventional methods give unreliable peaking time and peak values for the analysed curves compared with HMGOP modeling. Area under the curve and time in the risk zone are also more inaccurate with conventional calculations. These data are now presented in the first paragraph of the results-section.](#)

[We have also now added in the abstract:](#)

[“Higher glucose and insulin responses were observed after RYGB compared with OAGB, suggesting clinical differences between the procedures that may influence patient selection.”](#)

[In the conclusions we have now added:](#)

“Our study suggests that based on postprandial glucose dynamics RYGB may be favorable over OAGB in hyperglycemic patients without risk for hypoglycemia or vascular diseases, where OAGB could be preferred.”

We have done revisions throughout the manuscript to clarify the primary and secondary aims.

We have also tried to improve the readability of the results section.

RC: The inclusion/exclusion criteria for the study population are not clearly described. It is also unclear how patients were assigned to different procedures or whether the population is entirely new or partially derived from previous projects.

AR: Thank you for this important question. The inclusion and exclusion criteria of the population are explained in two previous publications (Heinonen Obesity 2023 and Saarinen Trials 2019). We have now better referred to these works and added a sentence to explain the used criteria on page 2, lines 71-72:

“All participants from Helsinki University Hospital with OGTT data available were included in the current study. No data or participants were removed from the analysis.”

RC: The results section is too extensive and sometimes repetitive. It does not fully address the effects of the mathematical model or bariatric surgery. For example, while time curves were not analyzed, only derived data from these curves were used.

AR: Thank you for this comment. We do believe that addressing this will greatly improve the readability of the manuscript. We have now tried to rewrite the results as more fluent in this aspect and to emphasize the effects of both the model and that of bariatric surgeries. We have reduced redundancy and removed data rather referring to tables and figures in the results section. We hope that this has enhanced readability. Additionally, we have tried to shorten and improve the discussion section accordingly.

RC: The discussion section does not compare the results generated by the model with those obtained from other mathematical or classical approaches. It is unclear if the calculated variables align with or differ from those obtained through other methods. The discussion should emphasize whether the model offers any advantages to encourage others to adopt this methodology.

AR: We have now added Table H.1, where we compare analysis through conventional methods and HMOGP modeling. We discuss this in the Result section 3.7 and have also incorporated a line on this in the discussion section on page 10, lines 250-255.

Minor Comments and Suggestions for Improvement:

RC: The inclusion and selection criteria for the study population should be clarified. If this is a retrospective study, provide a brief explanation of patient selection. In addition, Table G1, which presents the clinical, anthropometric, and metabolic features of patients, lacks units of measurement. If possible, consider showing T2DM subjects in a separate column.

AR: Thank you for these important notions. We now have in the methods referred to the publications where the inclusion and exclusion criteria of the study population are explained; see also a question by a reviewer presented earlier.

We apologize that the metabolic units were missing and have now added them to Table G.1. Additionally, we have now presented data of the persons with and without T2DM in separate columns.

RC: It is unclear whether the glucose and insulin levels shown in the time-course graphs represent raw data or modeled data. Please clarify.

AR: Thank you for this observation! We have now clarified that these graphs represent modeled data and added more explanation in the figure legends.

RC: Parameters derived from the oral glucose tolerance test (OGTT) or meal tolerance test (MTT) time curves (Figure 1) should specify whether they are based on modeled or raw data.

AR: We have now clarified this in Figure 1. These curves represent modeled data.

RC: Throughout the text, insulin is presented in mmol/L as the unit of measurement. If this is correct, explain the conversion factor used.

AR: Thank you for this observation. We now present insulin in mU/L (milliunit per liter) throughout the manuscript.

RC: Graphs and table legends should include more information to improve clarity. For instance, in the graphs, explain what the shaded areas represent.

AR: We have now added more explanation to the graphs and the figures. The shaded areas represent 95% confidence intervals of the modeled data.

RC: Table G1 lacks units of measurement and information about the data type. Also, consider displaying T2DM subjects in a separate column.

AR: We apologize that the metabolic units were missing and have now added them to Table G1 and presented individuals with and without T2DM in separate columns.

RC: Section 2.4 of the methods cites Heinonen et al., 2015, for blood sample collection. However, it incorrectly states: “A fasting blood sample was collected before ingestion of the glucose drink, and post-glucose samples were collected at 0, 30, 60, 120, and 180 min.” Time zero should be the sample collected before glucose or meal ingestion, which contradicts Section 2.5 of this manuscript.

AR: We have now modified sections 2.4 and 2.5 accordingly. Section 2.4 states only Hba1c and lipids, while section 2.5 (OGTT and MMT) states the measurement of glucose and insulin, including also the fasting samples of 0 minutes, that was indeed measured before the ingestion of the glucose drink or the liquid meal.

RC: If parameters derived from OGTT or MMT time curves were calculated from the model, comparing them with classical parameters derived from raw glucose and insulin response time curves would help to understand the differences between the methods.

AR: We have now added Table H.1, where we present comparisons between our modeling results and the results derived from conventional analysis of the data. We have presented this in the 1st paragraph of the results section.

These results clearly show that with conventional analyses, estimating peaking time or peaking values gives unreliable data. Those values will always lie on the data measurement points and, therefore, do not reveal differences between the cohorts. The area under the curve by the conventional linear trapezoid method, as well as time in the risk zone, are also more inaccurate reflections of reality compared with the current modeling strategy.

RC: The first paragraph of the results section states that both tests used the same amount of carbohydrates, which contradicts Section 2.5 of the methods.

AR: We have now corrected the text as follows: “In MMT, glucose (76g) was combined with protein and fats, while OGTT had 75g of glucose.”

Final Note: I sincerely appreciate the effort and dedication invested in this manuscript. The topic is highly relevant, and the use of computational modeling in this context is promising. I believe addressing the points mentioned will significantly enhance the clarity and impact of your work.

Thank you very much for the kind words. We appreciate both reviewers' time and effort in giving us the feedback to improve and clarify this manuscript. With the modified work we hope to clarify the improvements in patient selection for bariatric procedures but also better present why HMOGP modeling is suitable for OGTT/MMT and other postprandial data. In due course this approach can, for example, enable better glucose prediction control in insulin devices or enable new metrics used to evaluate T2DM status and the effects of the treatments in the clinic.

Author's Note:

We fixed a mistake that affected the results in Table F.1. Now, all the mean values (and CI values) were reduced by 1. The difference between them remained unchanged. Additionally, we fixed a small bug that was affecting the p-values calculations in peaking times (PT, Table F.1) and time in the risk zone (TiH, Table F.4). We updated all figures with corrected (and added if it is missing) units and more detailed explanations for improved clarity.