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A novel approach for generating physiological interpretations through machine learning

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ABSTRACT

Predicting blood glucose trends and implementing suitable interventions are crucial for managing diabetes. Modern sensor technologies enable the collection of continuous glucose monitoring (CGM) data along with diet and activity records. However, machine learning (ML) techniques are often used for glucose level predictions without explicit physiological interpretation. This study introduces a method to extract physiological insights from ML-based glucose forecasts using constrained programming. A feed-forward neural network (FFNN) is trained for glucose prediction using CGM data, diet, and activity logs. Additionally, a physiological model of glucose dynamics is optimized in tandem with FFNN forecasts using sequential quadratic programming and individualized constraints. Comparisons between the constrained response and ML predictions show higher root mean square error (RMSE) in certain intervals for the constrained approach. Nevertheless, Clarke error grid (CEG) analysis indicates acceptable accuracy for the constrained method. This combined approach merges the generalization capabilities of ML with physiological insights through constrained optimization.

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1. INTRODUCTION

A studies utilized machine learning (ML) algorithms to make predictions regarding the level of glucose in the blood [1] demonstrate the extensive utilization of diverse ML approaches. These encompass neural networks (NN), decision forests (DF), support vector machine (SVM), decision tree (DT), and additional forecasting techniques. Recent research [2] has employed a multi-tiered long short term memory (LSTM) framework to forecast levels of blood glucose in individuals with type 1 diabetes (T1D). This model utilizes the Ohio T1DM dataset [3] and provides predictions for 30 and 60-minute intervals. The aforementioned dataset and LSTM network have been applied in various research endeavors [4]. Furthermore, a novel technique for forecasting blood glucose levels has been developed, utilizing a deep recurrent neural network (RNN) approach with stacked LSTM architecture [5]. This innovative approach incorporates Kalman smoothing to mitigate sensor faults by correcting erroneous readings from continuous glucose monitoring (CGM) devices that result from sensor inaccuracies.

Various ML techniques were employed on a unique T1D dataset, consisting of 29,601 records from 47 individuals [6]. Unexpectedly, the most effective predictor, which combined two Gaussian Process

Regression models, produced surprisingly inaccurate results. This outcome implies that the standard diabetes diary information, routinely gathered, might be insufficient for developing precise blood glucose forecasting models. The study in [7] employed a dataset of 124 CGM traces gathered over a 10-day period using the most recent Dexcom G6 sensor. The researchers evaluated 30 distinct linear and nonlinear predictive algorithms, including established methods such as ARIMA and various ML approaches like SVR, RF, FNNN, and LSTM networks. The findings indicated similar accuracy levels between the most effective linear algorithm (ARIMA) and the top-performing nonlinear algorithm, particularly in terms of hypoglycemia detection. Both methods demonstrated comparable precision and recall rates, with ARIMA achieving 64% precision, 82% recall, and one false alarm daily, while SVR showed 63% precision, 69% recall, and 0.5 false alarms per day.

To aim of predicting blood glucose levels in people who have T1D, a study [8] utilized two different neural network approaches: an optimized feed-forward neural network (FFNN) and a proposed optimal nonlinear autoregressive neural network. The prediction timeframe ranged from 15 to 30 minutes. The models were trained and validated using simulated CGM data generated by AIDA, a mathematical diabetes simulator. Another study [9] examined an innovative multi-component deep learning model for predicting levels of blood glucose in multiple steps ahead. The model underwent comprehensive quantitative and qualitative assessment utilizing actual blood glucose data from 97 patients. Additionally, a study [10] introduced a Dilated RNN for projecting glucose levels with a 30 minutes horizon. This method demonstrated superior performance compared to existing algorithms, including CNN, SVR, and Autoregressive models (ARX). The study emphasized the efficacy of dilated connections in enhancing glucose forecasting precision.

Şahin and Aydın [11] developed an artificial neural network to forecast levels of blood glucose for 30 minutes to 60 minutes intervals. The network was trained utilizing physiological models for insulin administration, carbohydrate consumption, and exercise, in conjunction with historical CGM data from six individuals with T1D. This approach offers reduced computational complexity compared to deep learning methods, rendering it suitable for implementation on portable or embedded systems. The model aims to capture patients' physiological patterns and generate accurate predictions during monitoring.

A separate investigation [12] employed a RNN trained end-to-end forecast the levels of glucose in the blood up to an hour in advance. This method eliminates the necessity for feature engineering or data preprocessing, thereby enhancing computational efficiency. Furthermore, the model provides a confidence measure for predictions, assisting users in interpreting the forecasted values. The study evaluated this approach using standard metrics such as root mean square error (RMSE) and a glucose-specific measure termed the surveillance error grid (SEG). An alternative study [13] constructed a CNN model utilizing causal dilated CNN layers and WaveNet algorithms. This model employed four input fields from the OhioT1DM dataset, with targets representing glucose changes over a 30-minute spanAn evaluation of the model's performance was carried out with the support of the RMSE, and the average of the best RMSE between 6 patients was reported to be 21.72.

The use of these models has not been implemented for making clinical decisions in diabetes care. The only known application of ML -based predictive models appears to be in generating alerts for potential upcoming hypoglycemic events [14]. One significant limitation is that there are no clinical explanations provided for the glucose trajectory that was predicted. Moreover, ML models often overpredict hypoglycemia and underpredict hyperglycemic points in the forecasted glucose trajectory [15]. The discussion now turns to examining the nature of physiological interpretation that contributes to therapeutic decision-making. To illustrate this concept, we consider models developed for diabetes management decisions. The study [16] suggests that numerous predictive models of glucose dynamics, utilized for insulin dosage estimation, are causal and formulated using mathematical equations. These models' parameters represent specific metabolic features, providing physiological insights. However, such mathematical models face challenges in detecting complex patterns embedded within extensive retrospective CGM data, similar to ML models. To date, there appear to be no attempts to extract physiological interpretations from ML-based forecasting approaches.

The preceding discussion suggests a method to enhance the efficacy of ML predictive models in diabetes management. A metabolically significant period for an individual's physiology typically spans three (03) to six (06) hours of CGM data. By extracting a substantial portion of the predicted profile from an ML-based model and incorporating it into a personalized mathematical framework with constraints, it becomes possible to recreate that segment with physiological interpretation and causal reasoning. The chosen mathematical framework's structure directly influences the quality of the anticipated physiological interpretation. Research has shown the application of operations research (OR) techniques or constrained programming to clinical data. For example, Vahidi [17] demonstrated how sequential quadratic programming, an OR method, could be used to assess organ dysfunction by modeling glucose dynamics in a type 2 diabetic (T2D) patient using clinical data. Furthermore, Bengio *et al.* [18] provide an overview of various strategies for combining ML and OR to address complex problems. It is important to emphasize that successful OR application requires a well-defined mathematical model [19].

This research implements the suggested approach to create a combine model that integrates a number of benefits associated with data-driven and physiological approaches Figure 1. The strategy employs OR techniques in conjunction with ML forecasting. Specifically, a FFNN prediction model is developed using CGM data, dietary information, and activity logs from a T2D patient to generate ML-based predictions. Simultaneously, a constraint based physiological framework for handling glucose, previously developed and validated in a separate study, is utilized for OR [20]. This model captures the metabolic saturation relationship between plasma variables (including glucose, insulin, and glucagon) and metabolic process rates using a hyperbolic tangent function. The entire dataset of actual CGM readings and protocol information is used to optimize the model on a segment-by-segment basis, estimating the magnitude of higher saturation constraints. After determining the final higher saturation constraints, the FFNN model's forecasted sequences are optimized within the same physiological model under The glucose concentration profile was reproduced with a physiological basis relative to these defined restrictions.

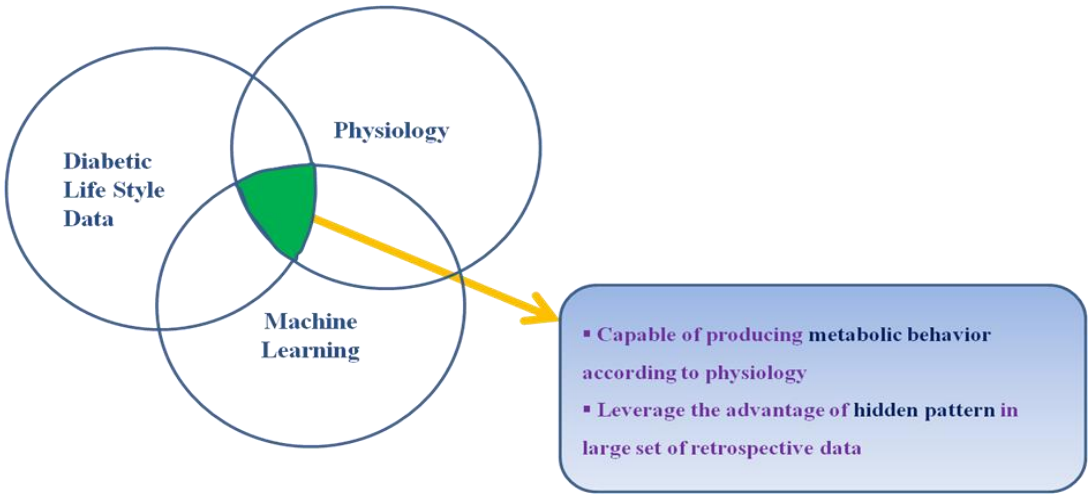


Figure 1. A hybrid prediction model for blood glucose dynamics

The entire process is illustrated in Figure 2. RMSE was used to assess the differences between the trajectories of OR and ML from actual CGM data. The OR response showed an increase in RMSE, which can be attributed to the optimization process involving multiple constraints and the use of fewer plasma variables. However, when compared to the actual glucose profile, the OR response yielded promising results in the Clarke error grid (CEG) analysis, with most points falling within the clinically acceptable region.

The paper's structure is as follows: section 2 provides information about the data set, ML model, the selected physiological model, and various parameters and constraints. Section 3 presents the Results obtained from the proposed models. Section 4 offers a thorough discussion of the experimental findings. In conclusion, the work is brought to a close with concluding observations in section 5.

2. METHODS

2.1. Dataset description

Initially, A FFNN predictive model was developed and validated using a 20-day dataset from a T2D patient. This dataset, referenced in a study by Rollins *et al.* [19], included CGM data, physical activity records, and carbohydrate (CHO) intake events.

The CGM data underwent smoothing using MATLAB functions, with the results displayed for a 24-hour period in Figure 3. As shown in Figure 4, carbohydrate consumption events were recorded as discrete occurrences within the dataset. To represent glucose appearance from the gut as a continuous physiological signal, the carbohydrate quantity was transformed using a farmwork created by Elshoff *et al.* [21].

The sense wear armband's physical activity data was converted into a continuous signal Figure 5 using a differential equation of percentage of the maximum volume of oxygen (PVO2max) from existing literature [22]. This continuous physical activity signal showed a correlation coefficient of -0.00896 with CGM data, with the negative sign indicating an inverse relationship between CGM and on-board activity. Due to the weak correlation between activity data and CGM, a new synthetic activity signal Figure 6 was created for

experimental purposes in this study. This synthetic signal demonstrated a correlation coefficient of -0.1123 with CGM data. The use of synthetic activity signals does not compromise the validity of the research findings.

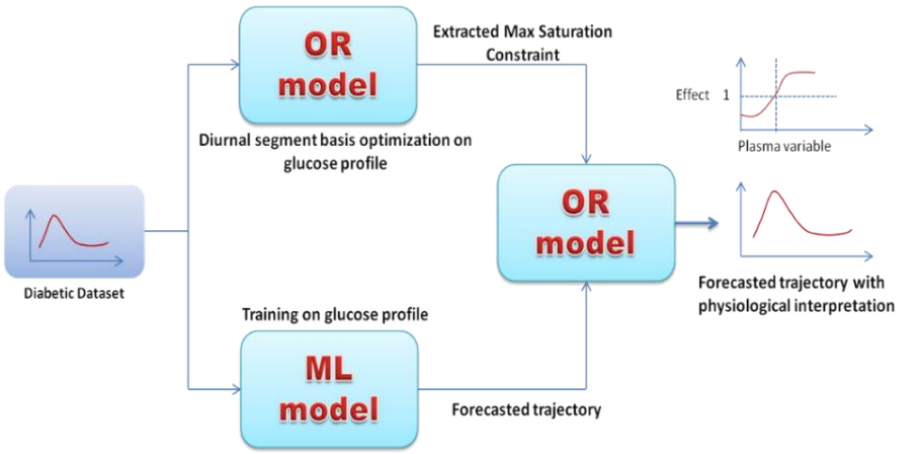


Figure 2. The process of carrying out OR on ML-based glucose predicting method

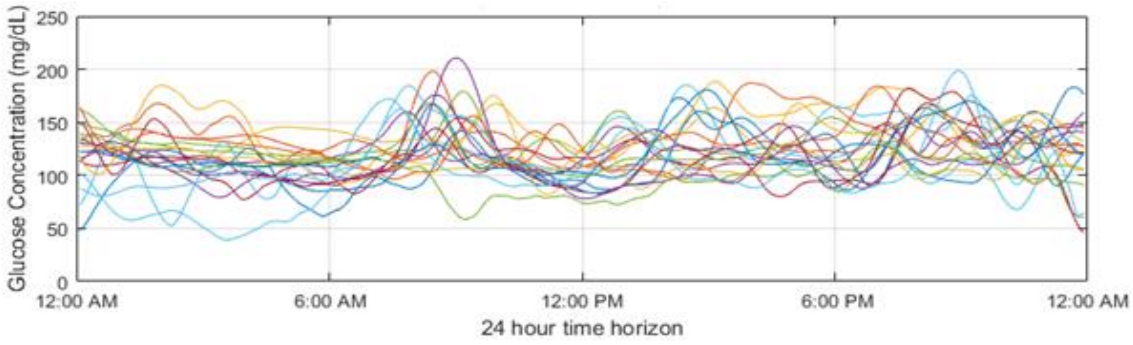


Figure 3. Continuous glucose monitoring data of a T2D patient over twenty (20) days

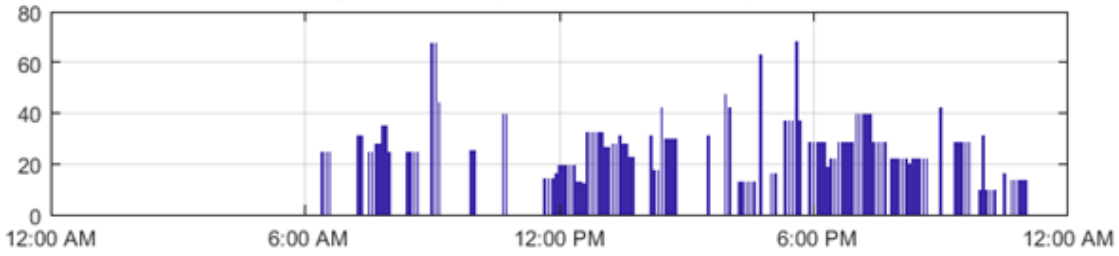


Figure 4. Logged diet events of a T2D patient over twenty (20) days

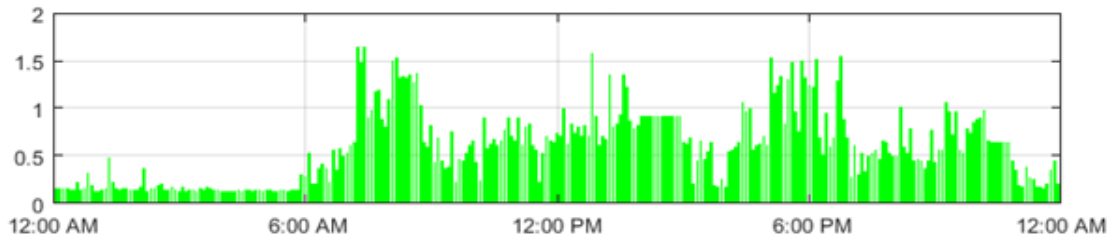


Figure 5. Daily pattern of physical activity (%VO2max) over 20 days

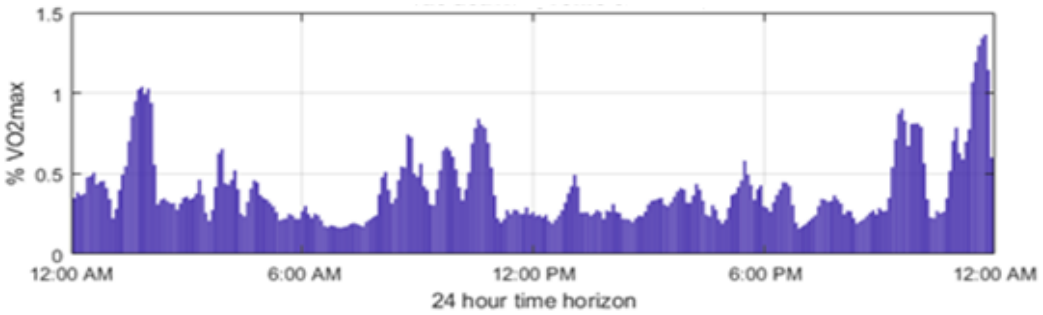


Figure 6. Synthetic activity profile over 20 days

2.2. Building the ML model

A review of the literature revealed that FFNNs were the preferred choice for developing predictive models to forecast short-term glucose levels. Consequently, this study employed FFNNs to create a ML model using the previously described dataset. The ML model structure, shown in Figure 7, was determined by analyzing prior model architectures and evaluating the correlation between sequences in the diabetic dataset. The FFNN model correlates glucose data at time t+N with glucose levels and the sum of carbohydrate intake and physical activity from time t to t-5. N denotes the number of time points, calculated by dividing the prediction horizon (PH) by the sampling frequency. The model also incorporates timestamps to account for daily fluctuations in plasma glucose concentration. The FFNN design is made up of a single concealed layer that has 10 neurons and a layer for output that contains a single neuron, using hyperbolic tangent and linear activation functions, respectively. On a total of fifteen days' worth of data, the Bayesian Regularization Backpropagation algorithm was utilized to train the predictive algorithm, and the remaining information were utilized for testing purposes [23]. The predefined settings of the "fitnet" program can be found in the MATLAB toolbox.

2.3. Description of the adopted physiological model

This section presents a concise summary of the constraint-based mathematical model [20] utilized in the paper. The model, rooted in blood glucose regulation physiology [24], recognizes that glucose and hormone concentrations in plasma reflect the cumulative effects of changes in metabolic rates, which are in turn significantly affected by these same concentrations. This reciprocal interaction creates a metabolic ecosystem, illustrated in Figure 8. This ecosystem functions within a framework of rate-balance-concentration principles. The model consists of four compartments, including three plasma variables (glucose, insulin, and glucagon) and eight metabolic process rates. External factors like exercise directly affect these metabolic processes.

A hyperbolic tangent function, shown in Figure 9 [25], characterizes the connection between plasma variables and metabolic process rates. This function is employed for two main reasons within the rate-balance concentration model. Firstly, it enables the incorporation of clinical and saturation constraints. Second, it allows for the representation of a metabolic spectrum that illustrates how plasma variables influence metabolic processes, facilitating physiological interpretation.

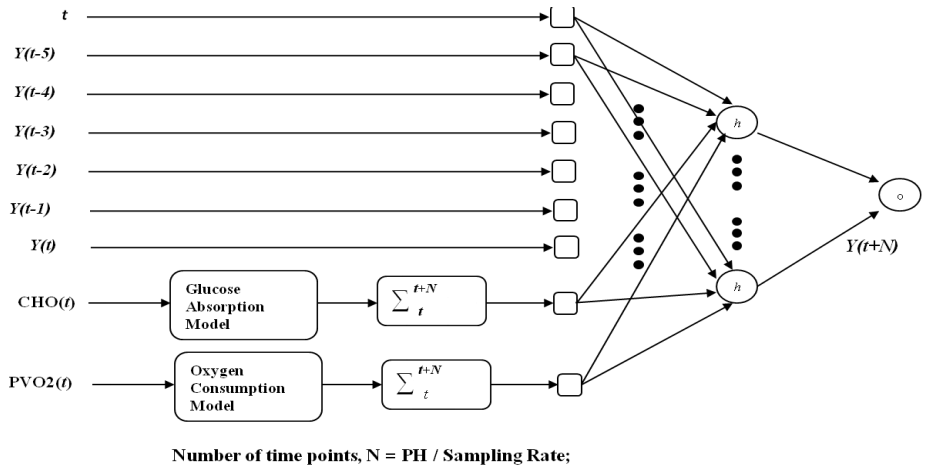


Figure 7. Architecture of FFNN based predictive model

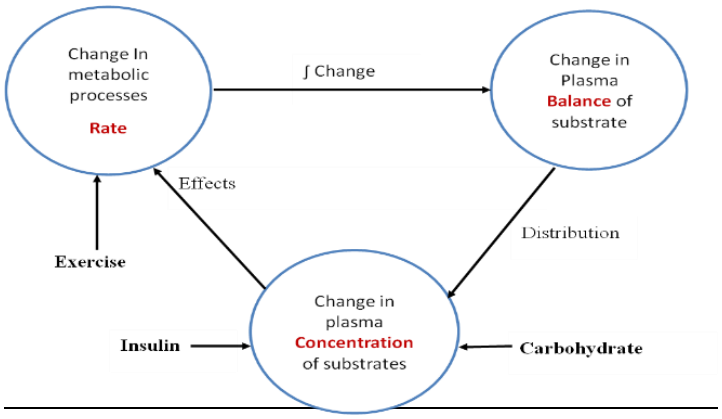


Figure 8. A paradigm of glucose dynamics based on rate-balance-concentration

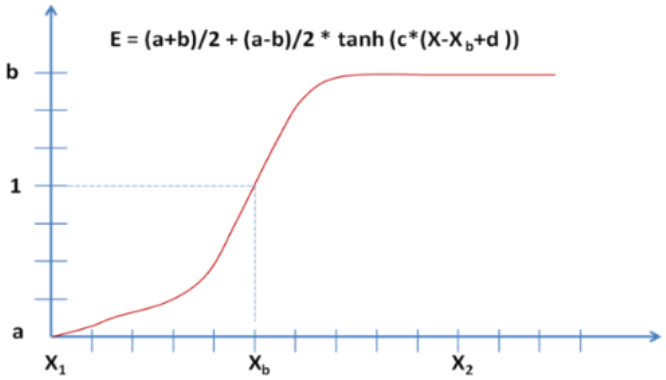


Figure 9. A sigmoid relationship takes place between the concentration and the effects

The physiological structure of the adopted model is presented in tabular format in Table 1. Each cell within the table specifies the nature of the hyperbolic tangent function representing the effect of corresponding plasma variables or external stimuli on the relevant process rate.

$$E_x = \frac{(a+b)}{2} + \frac{(a-b)}{2} \times \tanh(c \times (X - X_b + d)) \quad (1)$$

In this context, X denotes the concentration of glucose, insulin, glucagon, or exercise. The term "Ex" signifies the impact of X on the rate of a specific metabolic process, as depicted in Figure 8. Ex induces a multiplicative influence on the basal rate of each metabolic process.

Table 1. The metabolic relationship among plasma attributes and the processes of metabolism within the logical compartments considered

Plasma variables	Liver		Muscle tissue	Pancreas		Plasma compound		
Metabolic operations	Release of glucose	Uptake of glucose	Uptake of glucose	Secretion of insulin	Secretion of glucagon	Degradation of insulin	Uptake of nerve	Uptake of RBC
Glucose molecules								
Substance insulin								
Hormone glucagon								
Exercise								

2.3.1. Glucose dynamics

- Release of liver glucose: Adoption Rate of HTP = rate of basal × Eglucose× Eglucagon × Einsulin;
- Uptake of glucose by the liver: HPT Uptake Rate = rate of basal × Einsulin × Eglucose;
- Muscle blood glucose uptake: Adoption Rate of MT= rate of basal × Eglucose × Eexercise × Einsulin;
- Uptake of glucose by the central nervous system: Adoption Rate of NS = rate of basal × Eglucose;
- Red blood cell glucose uptake: Adoption Rate of RBC = rate of basal × Eglucose;
- Urination glucose extraction: Rate of Spilling Urine = 0.5 × (level of glucose - cutoff);
- Net Change = Presence Rate of the GUT + Discharge Rate of HPT – Adoption Rate of HPT–Adoption - -
- Rate of MT – Adoption Rate of NS – Rate of Spilling Urine – Adoption Rate of RBC;
- Plasma Glucose Storage = Initial Plasma Glucose Level + ∫Net Change
- Plasma Glucose Concentration = Plasma Glucose Storage / (Volume of Distribution × 10);
- Volume of Distribution = 20% × (Body Weight);

2.3.2. Insulin dynamics

- Release of insulin from the pancreas: I_ Release Rate = rate of basal × Eglucose × Echange
- Echange = (a+b)/2+(a-b)/2 × tanh (c × (Change the levels of presence glucose – Basal + d));
- Depletion of insulin in plasma: I_ Depletion Rate = 0.075 × (Amount of Net Insulin) × Eexercise;
- Net Change = I_ Release Rate – I_ Depletion Rate +I_Presence Rate;
- Total Insulin = Initial Plasma Insulin Level + ∫ Net Change;
- Plasma Insulin Concentration = Total Insulin / Volume of Distribution.
- Volume of Distribution = 20% × (Body Weight);
- Apparent concentration of glucose = Plasma Glucose Level + Presence Rate of the GUT × 0.20;
- Perceived glucose change = (Apparent concentration of glucose (t) – Apparent concentration of glucose (t-1))/0.1; There, a timestamp is denoted by t.

2.3.3. Glucagon dynamics

- Release of pancreatic glucagon: G_ Release Rate = rate of basal × Eglucose;
- Degradation of glucagon: G_ Depletion Rate = 0.20 × (Net Plasma Glucagon Amount);
- Net Change = G_ Release Rate – G_ Depletion Rate;
- Plasma Glucagon Concentration = Total Glucagon / Volume of Distribution.
- Volume of Distribution = 20% × (Body Weight);
- According to [24], the basal rates of a number of different metabolic processes and constants were obtained.

2.3.4. Parameter and constraint estimation

The physiological framework dynamics involve 14 effects and 56 adjustable attributes. However, by utilizing physiological knowledge and insights from numerous optimization attempts, it became clear that some attributes can be assumed without the optimization process. These included parameters linked to the smallest effect magnitude for a specific plasma variable's concentration based on a specific rate of the procedure, either the 'a' or 'b' parameter in the equation which describes the hyperbolic tangent effect Figure 9. A further, such attribute was 'd', that determined the plasma variable concentration's operating range midpoint. As a result, excluding these assumable parameters, only 24 attributes needed to be optimized and fine-tuned over the entire experimental dataset.

These targeted attributes included the highest effect magnitude equations ('a'/'b' parameter) and the trigger slope ('c'). The parameter estimation optimization problem began with predetermined basal and initial state variable values, according to data and underlying assumptions. The optimization process involved applying constraints to the chosen model parameters.

In every case, the attributes 'a' or 'b' exhibited positive values. During the estimation of individualized constraints and subsequent OR implementation, the range for attributes with greater values ('a' nor 'b') was defined as one to infinity. Parameters with lower values were determined based on physiological knowledge. The parameter 'c' consistently displayed negative values across all effect equations. Its range was established through extensive experimentation and refinement.

Xm = [Xb – (±d)] ensured that 'd' represented when the concentration of the substrate is at its middle point within the operational range, Xb denoted concentration of the basal. Consequently, Xm remained within the interval [X1, X2]. In the context of nonlinear optimization issues with constraints, the objective function seeks to reduce the overall disparity between the results of the model and the reference data source. An optimal set of model parameters produces results that closely match the reference information. The objective function can be expressed as follows:

$$\min_{\theta} \sum_{i=1}^{n} \left(\left| G_m^i - G_{cgm}^i \right| \right) \quad (2)$$

where G_m^i represents concentrations of the plasma glucose at time i; while G_{cgm}^i is signifies the pertinent clinical assessments. 'n' represents the volume of the data, and Θ denotes the value comprising framework attributes.

2.3.5. Performing OR on ML response

In applying OR to ML-based responses, the forecasted glucose trajectories were divided into segments corresponding to a three-hour PH. Each day's forecasted profile was further partitioned into eight intervals. Subsequently, each segment from all intervals was subjected to optimization within the constrained model, alongside the carbohydrates that are pertinent on board, continuously occurring activity signal, and previously outlined individualized limitations and restrictions. The optimization problem was addressed using the procedure detailed in the preceding subsection. Subsequently, both the optimized response (OR response) and the ML forecast of glucose concentration were integrated for comparison with the actual plasma glucose concentration sequence. Evaluation was conducted using RMSE and CEG analysis [26] as performance metrics.

2.3.6. In silicon operations for therapeutic decision

In making therapeutic decisions, the estimation of CHO intake, physical activity intensity, or insulin dosage is crucial to controlling levels of plasma glucose during the normoglycemic the scope of for a specific duration. Conducting multiple in silico operations within the optimized physiological model allows for the calibration of glucose trajectories within an expected range. As an illustrative example, this article conducts in silico operations involving three CHO ingestion events (50g, 75g, and 100g, respectively) to observe the corresponding glucose variations. Each amount of CHO is considered an appropriate action dose for a particular moment, aimed at achieving an acceptable glucose trajectory in the in silico operation.

3. RESULTS

Figure 10 displays the OR for ML forecasting during the 12:00 pm to 3:00 pm period on day first, generated from the testing subset utilized by the dataset. Figures 11 and 12 showcase the metabolic characteristics outlined in the physiological model's architecture, obtained by applying constraint programming to the ML response. Specifically, Figure 11 demonstrates how liver metabolism, specifically hepatic release and uptake, is influenced by plasma concentrations of glucagon, glucose, and insulin. The curve indicates in Figure 11(a) that hepatic release increases with rising glucagon levels, showing a stimulatory effect at higher concentrations.

As plasma glucose concentration increases, hepatic glucose release decreases, indicating an inhibitory effect (Figure 11(b)). The effect decreases as insulin levels rise, signifying insulin's suppressive role in glucose release from the liver (Figure 11(c)). Figure 11(d) shows a positive correlation, with higher glucose concentrations leading to increased hepatic uptake. Finally, as insulin levels rise, hepatic uptake of glucose also increases, underscoring insulin's stimulatory effect on this metabolic pathway (Figure 11(e)).

Figure 12 illustrates the metabolic and physiological discipline of glucose and insulin and activity on muscle, pancreas, and plasma. In the Figure Muscle 12(A) (a), can observe the effect of glucose activity in muscle molecules, indicating the reactions of muscle tissues with respect to different glucose levels. Figure 12A(b) shows the role of insulin in regulating muscle activity, emphasizing its importance in glucose uptake and energy utilization on the other hand, Figure 12A(c) covers the relationship between glucose and muscle absorption, representing the minimal dynamical response of muscle absorption in regards to circulating glucose.

For the Pancreas in Figure 12(B), Glucose Regulation and Hormone Secretion Panel Figure 12B(a) explores the plasma glucose changes and their disruption of the ability of the pancreas to perform metabolic homeostasis. Figure 12B(b) shows how increasing plasma glucose concentrations stimulate the pancreas to secrete insulin, emphasizing the key feedback between glucose and insulin. In Figure 12B(c), this represents the negative feedback loop by which glucagon secretion must be inhibited at high glucose levels to maintain blood sugar homeostasis.

In terms of the Plasma Figure 12(C) reflects tissue/systemic effects of activity and glucose. Figure 12C(a) shows that physical activity alters the insulin lifespan in plasma, which further suggests the presence of exercise-mediated regulation in insulin turnover. The Figure 12C(b) investigate the effects of plasma glucose levels on RBC absorption, implying a glucose regulated RBC function. Lastly, Figure 12C (c) features the reliance of the nervous system on glucose and how the plasma glucose concentration directly drives its uptake and provides energy for the nervous system.

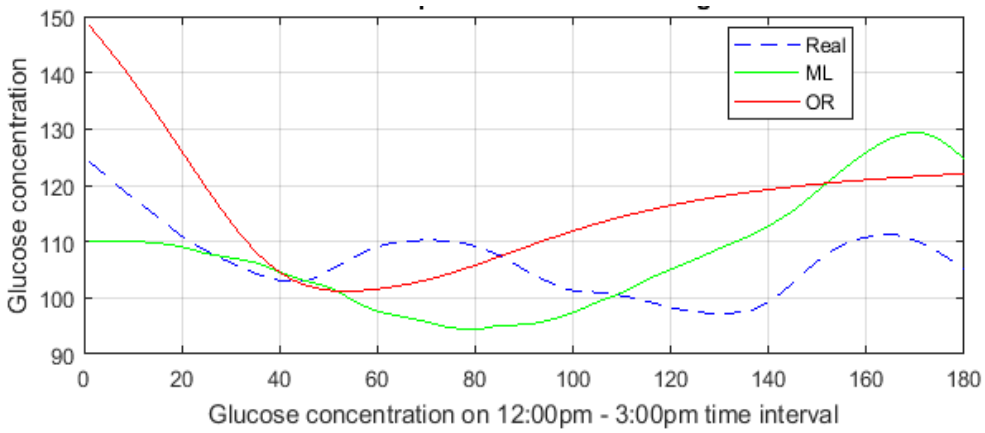


Figure 10. Producing OR response by optimizing physiological model

Similar spectra with varying intensities are estimated by performing equivalent operations for forecasting over five complete days. Table 2 presents the comparative outcome of ML and OR framework across eight distinct intervals of time, for a period of five full days. Furthermore, Figure 13 displays a scatter plot illustrating the CEG Analysis findings for both OR and ML responses.

Figure 14(a) demonstrate the results of the in silico operation within the optimized OR model for therapeutic decision-making. The simulated glucose appearance rate following oral glucose consumption of 50g, 75g, and 100g is shown in Figure 14(b) illustrates the resultant effect of these glucose ingestions on plasma glucose levels.

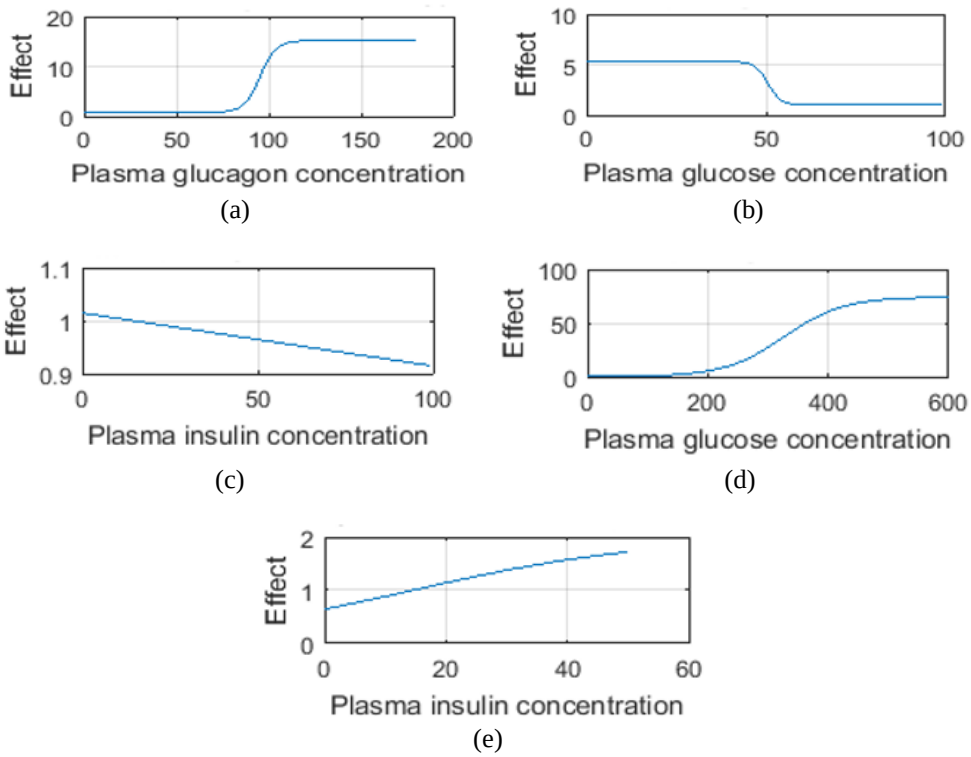


Figure 11. Liver - Hepatic release is impacted by the presence of glucagon; (a), glucose, (b) insulin, (c) hepatic uptake is affected by glucose, (d) and insulin, and (e) respectively.

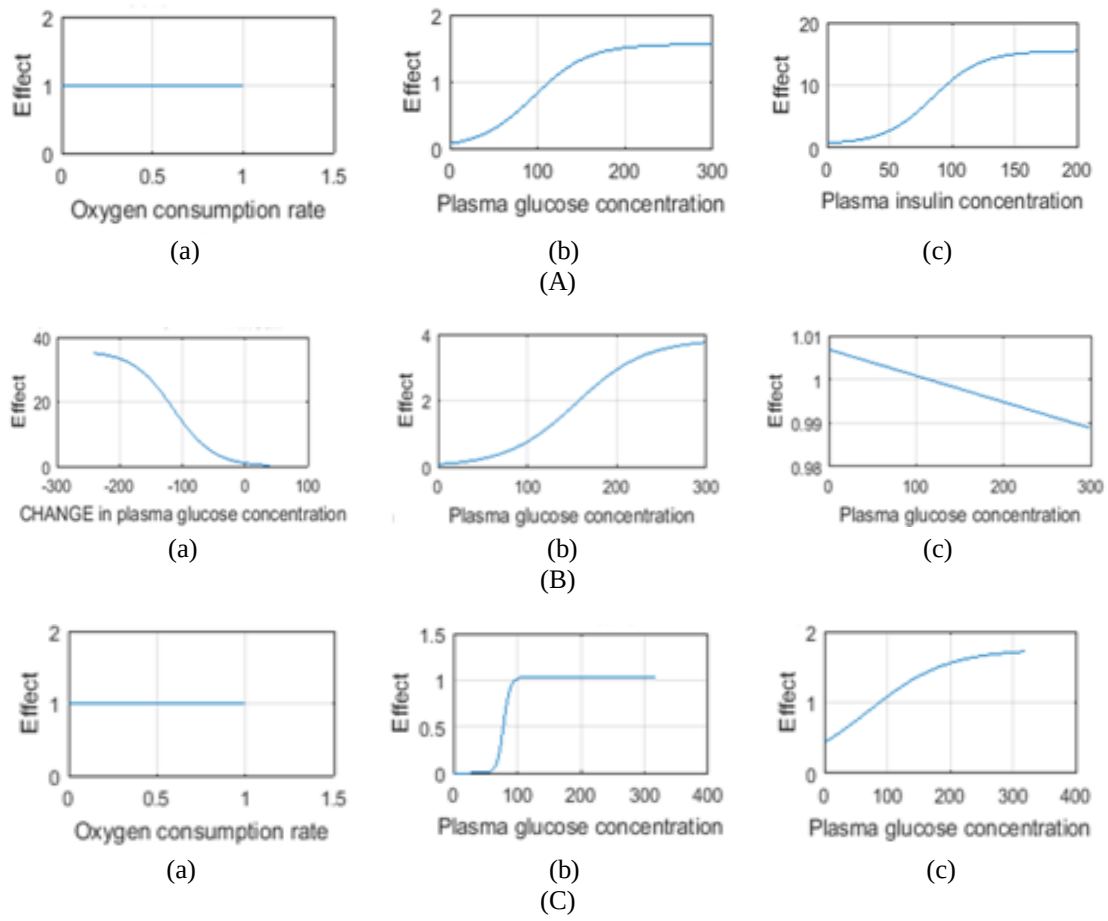


Figure 12. Muscle (A) - Impact of (a) glucose activity (b) on insulin and (c) glucose absorption by the muscle, Pancreas (B) – (a) Changes in glucose levels and their effects on glucose (b) on the release of insulin, (c) The impact of glucose on the release of glucagon, Plasma (C) – (a) Impact of activity on the degradation of insulin. (b) Impact of glucose on the absorption of RBC, (c) Impact of glucose on the nervous system's absorption of glucose

Table 2. Comparison of OR response vs. goal and ML response vs. goal across 05 complete days at 03 hours PH

Period	Approach	RMSE	Area (A)	Area (B)	Area (C)	Area (D)	Area (E)
9:00 pm – 12:00 am	OR	25.9 ±12.8	64.4 ± 21.7	33.4 ± 21.04	0	2.1 ± 4.8	0
	ML	29.5 ± 7.6	53.2 ± 12.9	45.8 ± 11.5	0	1 ± 2.2	0
6:00 pm – 9:00 pm	OR	31.8 ± 10.4	49.8 ± 19.5	50.2 ± 19.5	0	0	0
	ML	23.9 ± 8.4	53.2 ± 31.3	46.8 ±3 1.3	0	0	0
3:00 pm – 6:00 pm	OR	22.4 ± 8.93	61.2 ± 30.3	38.8 ± 30.3	0	0	0
	ML	25.6 ± 7.2	57 ± 21.38	43 ± 21.4	0	0	0
12:00 pm – 3:00 pm	OR	22.9 ± 11.3	57.3 ± 42.3	42.7 ± 42.3	0	0	0
	ML	22.4 ± 16.1	64 ± 39.8	36 ± 39.8	0	0	0
9:00 am – 12:00 pm	OR	30 ± 5.8	27.4 ± 29.2	68.4 ± 25.6	0	4.1 ± 9.2	0
	ML	24.4 ± 6.5	56 ± 28.9	39.9 ± 20.4	0	4.1 ± 9.2	0
6:00 am – 9:00 am	OR	19.7 ± 7	70.7 ± 24	28.4 ± 23.4	0	0.9 ± 2	0
	ML	17.3 ± 7.6	78.2 ± 30.2	20.9 ± 29.3	0	0.9 ± 2	0
3:00 am – 6:00 am	OR	13.6 ± 7.7	74.3 ± 30.3	25.7 ± 30.3	0	0	0
	ML	10.6 ± 4	91.2 ± 12.3	8.8 ± 12.3	0	0	0
12:00 am – 3:00 am	OR	20.6 ± 14.1	65.7 ± 44.8	34.3 ± 44.8	0	0	0
	ML	21 ± 11.9	65.1 ± 37.8	34.9 ± 37.8	0	0	0

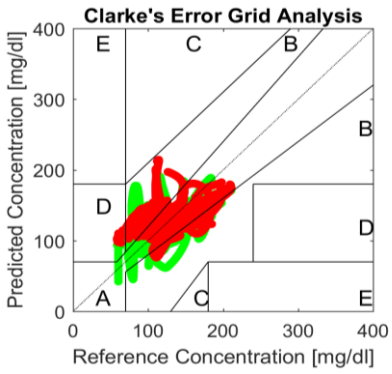
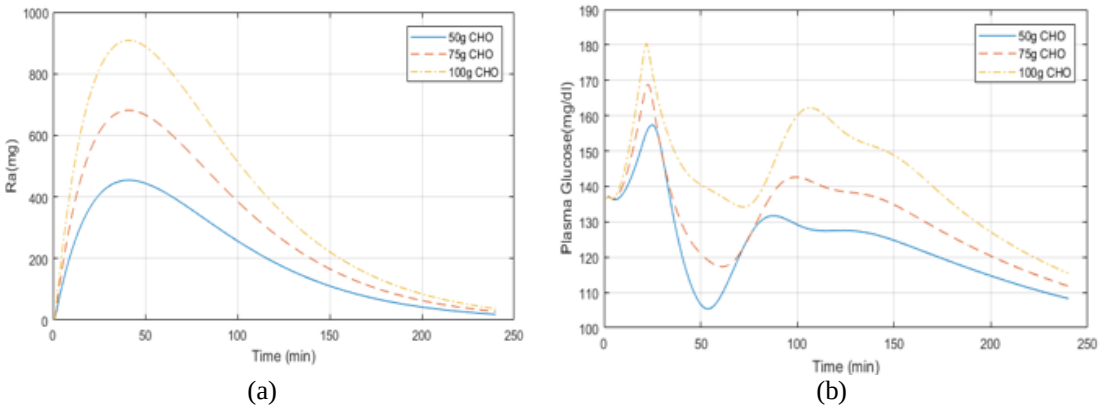


Figure 13. Examination of the error grid over five days, comparing the OR response (red) to the ML response (green)



(a) (b)

Figure 14. CHO rate of appearance (a) Plasma glucose excursion and (b) for 50g, 75g, and 100g oral glucose ingestion

4. DISCUSSION

OR enables the conversion of data-driven predicted glucose concentration profiles into metabolic signals, as shown in Figure 10. This signal offers a physiological interpretation by approximating the connection between plasma variables and metabolic process rates, as outlined in Table 1 and demonstrated in Figures 11 and 12. When a forecasted glucose concentration sequence undergoes constrained nonlinear optimization within the physiological model, the model's metabolic parameters are fine-tuned to ensure that sigmoid functions represent the operational trajectory of effects stemming from plasma variable concentration changes. Following optimization under limits, the integrated hyperbolic tangent functions demonstrate a metabolic profile controlling of blood glucose for the designated duration of time. This spectrum often demonstrates the nonlinear impact of insulin, glucagon, plasma glucose and exercise concentrations on metabolic processes across many organs and tissues. The constraints act as upper limits for the estimated effects on an actual profile for a particular individual. Programming with these constraints improves the reliability and personalization of the resulting OR response.

Examination of the condensed results Table 2 indicates that RMSE generally increases when performing OR in most instances. Nevertheless, the CEG analysis Figure 13 shows that blood glucose responses largely remain within practically suitable ranges (Area-A and Area-B) for most time periods. The 9:00 am to 12:00 pm interval is the only exception, where both ML and OR responses exhibit some clinically risky outcomes. This suggests that both models struggle to accurately predict actual plasma glucose responses during this timeframe. Table 2 also reveals that RMSE outcomes are significantly better from 9:00 pm to 9:00 am compared to 9:00 am to 9:00 pm. This enhancement is due to the first twelve hours (9:00 pm to 9:00 am) coinciding with nighttime, when glucose regulation is less affected by external influences than the following twelve hours (9:00 am to 9:00 pm). The rise in RMSE for OR responses is linked to the quest for solutions while complying with four (04) constraint types during optimization. Moreover, the physiological model only accounts for a limited number of factors causing glycemic fluctuations. As a result,

it becomes difficult to accurately replicate real trajectories in OR responses while simultaneously meeting all considered constraints.

After configuring the OR model for predicting glucose levels, it is expected to run simulations under various external factors to evaluate the response and determine appropriate diabetes management strategies. Figure 14 shows the results of a virtual experiment involving three CHO consumption events. In the optimal OR model, the glucose level in the plasma was first measured at 140 mg/dl. This level is then tracked over the subsequent three (03) hours following the consumption of 50g, 75g, and 100g of CHOs, as shown in Figure 14. This virtual experiment aids in deciding the ideal CHO intake amount to achieve the desired normal blood sugar state. The findings suggest that consuming 50g of glucose would be preferable to ingesting 75g or 100g of CHO. Nevertheless, substantial work remains to confirm the effectiveness of the proposed approach for practical application. A key step in accomplishing this goal is to perform experiments using a comprehensive dataset that includes crucial factors affecting plasma glucose concentration. All necessary data, models, and scripts can be found in [27] for replicating the experimental results presented in this article.

5. CONCLUSION

This study explores a new method for deriving physiological interpretations from ML -based predictions through optimization and reconstruction (OR). The approach utilizes a constraint based clinical framework founded according to the paradigm of the rate balance concentration as the expected interpretation is dependent on the model's architecture. Results indicate that the OR process successfully generated clinically acceptable forecasts in most instances. However, a significant increase in RMSE was observed during periods when glucose regulation was more disrupted by external factors. The absence of physiological reasoning in predictive models may result in less effective glucose management, potentially elevating the risk of hypoglycemic or hyperglycemic episodes. Employing physiologically constrained models to address this issue helps bridge the gap between predictions and clinical reality, possibly leading to better health outcomes for diabetic individuals.

Subsequent research could concentrate on enhancing the constraint-based physiological model to reduce RMSE while preserving clinical accuracy. Moreover, integrating more sophisticated ML algorithms, such as LSTM or deep convolutional networks, could enhance the performance of hybrid models. It is also essential to expand the model's evaluation using larger, more diverse datasets to ensure validation and generalization.

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