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RESEARCH ARTICLE

Impact of Nutritional Factors in Blood Glucose Prediction in Type 1 Diabetes Through Machine Learning

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ABSTRACT Type 1 Diabetes (T1D) is an autoimmune disease that affects millions of people worldwide. A critical issue in T1D patients is the managing of Postprandial Glucose Response (PGR), through the dosing of the insulin bolus to inject before meals. The Artificial Pancreas (AP), combining autonomous insulin delivery and blood glucose monitoring, is a promising solution. However, state-of-the-art APs require several information for bolus delivery, such as the estimated carbohydrate intake over the meals. This is mainly related to the limited knowledge of the determinants of PGR. Although meal carbohydrates are mostly considered as the major factor into, uencing PGR, other food components play a relevant role in PGRs, and thus, should be taken into account. Based on these considerations, a study to determine the effect of nutritional factors (i.e., carbohydrates, proteins, lipids, fibers, and energy intake) in the short and middle term on Blood Glucose Levels (BGLs) prediction was conducted by Machine Learning (ML) methods. A ML model able to predict the BGLs after 15, 30, 45, and 60 minutes from the meal leveraging on insulin doses, blood glucose, and nutritional factors in T1D patients on AP systems was implemented. More specifically, to investigate the impact of the nutritional factors on the model predictions, a Feed-Forward Neural Network, was fed with several dispositions of BGLs, insulin, and nutritional factors. Both public and self-produced data were used to validate the proposal. The results suggest that patient-specific information about nutritional factors can be significant for middle term postprandial BGLs predictions.

INDEX TERMS Artificial intelligence, neural networks, artificial pancreas, blood glucose, health 4.0, machine learning, nutritional factors, patient monitoring, postprandial glucose response, prediction model, statistical attributes, type 1 diabetes.

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I. INTRODUCTION

Type 1 Diabetes (T1D) is an autoimmune chronic condition, in which the immune system of the affected individual attacks and destroys insulin-making cells (β cells) in the pancreas [1]. The etiology of T1D is complex and depends on different factors, including genetic, immunologic and environmental factors [1], [2]. Based on recent epidemiological studies [3], [4], T1D incidence is 15 per 100,000 people and the worldwide prevalence is 9.5 per 10000 people. In addition to a regular exogenous administration of insulin, patients with T1D have to adhere to a healthy lifestyle and be very careful in monitoring and managing their blood sugar levels to prevent and avoid acute complications, such as severe hypoglycemia, severe hyperglycemia, and ketoacidosis [5], [6], as well as the severe chronic complications involving eye, kidney, and cardiovascular system. In particular, a main issue for T1D patients is managing postprandial glucose response [7].

Technological advances have facilitated the development of closed-loop systems better known as Artificial Pancreas (AP) [8], which combines an insulin pump, Continuous Glucose Monitoring (CGM) and a control system which automates insulin release [9]. In AP systems, the CGM monitors continually glucose levels and sends these data to a control system; this, in turn, uses an algorithm based on heuristic and theoretical knowledge to compute the insulin dosage required to reestablish baseline glucose levels [10]. Hence, not only does AP monitor glucose levels in the body but it also automatically adjusts the delivery of insulin to prevent hypoglycemia and hyperglycemia episodes. Therefore, APs can be a promising solution for T1D treatment. However, although fully-closed loop systems are desirable, delays in insulin absorption and other physiological factors lead to the adoption of Hybrid-Closed Loop Systems (HCLSs) in clinical practice. HCLS automates the delivery of basal insulin but it requires inputs from the patient for bolus insulin delivery due to poor modeling of postprandial glucose response [11].

In this context, the glucose control algorithm seems to represent the key element of AP systems since it keeps blood glucose concentration within the healthy physiological range. Different control algorithms have been developed and proposed, including *model predictive control*, *proportional-integral-derivative control*, and *fuzzy logic control* [12], [13]. However, the modeling of Postprandial Glucose Response (PGR), and the insulin delivery regulation at meal remains major challenges in APs [14]. In particular, carbohydrates are mostly considered in these control algorithms, but also other nutritional factors, like lipids and proteins, should be taken into account. In addition, it must be managed the inter-individual variability and the problem of long-term glucose management influenced by psychological and physical factors (e.g., during physical activity) [15], [16]. In this regard, Artificial Intelligence (AI), especially Machine Learning (ML), has opened new perspectives in AP systems due thanks to the possibility of successfully extracting knowledge from data [17], [18], [19].

A possible AI-based approach for forecasting future glucose values is the use of ML with Artificial Neural Networks (ANNs), allowing to anticipate hypo-/hyperglycemia events and to take appropriate action (e.g., eating sugar or taking insulin). Furthermore, such information could be integrated into closed-loop devices such as AP to improve insulin administration [20], [21]. However, these models based on ANNs mostly considered carbohydrates without taking into account other nutritional factors, like lipids and proteins [22]. As a matter of fact, the nutritional properties of different meals (e.g., lipids, proteins, and carbohydrates) can impact Blood Glucose Level (BGL) in different ways, significantly affecting PGR. It has been demonstrated that the main effect of dietary fat was late postprandial hyperglycemia, showing that high-fat/protein meals require more insulin than lower-fat/protein meals with identical carbohydrate content. These results highlight the importance of developing models based on meal composition rather than carbohydrate quantity alone [23].

Based on these considerations, in this work, a study of the impact of nutritional factors in the short and middle term after a meal was conducted by Machine Learning (ML) methods. The goal was to determine the effect of nutritional factors such as carbohydrates, proteins, lipids, and fibres, as well as meal energy intake, on postprandial blood glucose response. To this aim, a set of experiments exploiting a supervised ML system on data collected across several T1D patients was carried out. Leveraging on the models proposed in [24] and [25], in this study a blood glucose level predictor was proposed. However, differently from other models, in the proposed architecture nutritional factors were taken into account. More in detail, a model able to predict the blood glucose level after 15, 30, 45, and 60 minutes from the meal was implemented. To investigate the impact of the nutritional factors, the model was fed with a different combination between glucose level, insulin, and nutritional factors. The developed architecture was tested on both public and self-produced data.

The paper is organized as follows. Section II provides an overview of the state-of-the-art of ML solutions in the managing of postprandial (after the meal) blood glucose response. Section III describes the datasets employed and the proposed method. The experimental assessment is reported in Section IV, illustrating data preprocessing and the experimental setup. Section V and Section VI reports results and discussion, respectively. Finally, in Section VII, conclusions are drawn and the future steps are outlined.

II. RELATED WORK

In the last years ML has gaining increasing attention in several research fields. Among all the ML techniques available today, ANNs are having particular success in health-related tasks [26], [27], [28]. In particular, several studies [29], [30], [31], [32], [33], [34], [35], [36] have employed ANNs in the prediction of postprandial blood glucose values, using both data from real patients with T1D and

data computer-simulated patients (the latter named *virtual patients*) [37], such as those obtained with UVA/Padova simulator [38].

For instance, Pappada et al. [34] analyzed the performance of a Feed-Forward Neural Network (FFNN) model for real-time predictions of glucose level after 75 minutes (min) from the last input glucose value fed to the network. The adopted FFNN was trained by using an information set including CGM values, insulin dosages, metered glucose values, nutritional intake, lifestyle, and emotional factors collected in 17 patients. The performance was assessed on data belonging to 10 patients outside from the training set. The reported Root-Mean-Square-Error (RMSE) on the whole test set was 43.9 mg/dL ± 6.5 mg/dL. The study proposed by Zecchin et al. [35] provided a short-time glucose prediction algorithm that, in addition to past CGM readings, exploits also information on carbohydrate intakes modeled through a physiological model. The performance of the prediction algorithm was tested both on 20 simulated virtual patients and on 9 real patients. Results on simulated and real data showed RMSE was 14.0 mg/dL ± 4.1 mg/dL for real data and 9.4 mg/dL ± 1.5 mg/dL for simulated data, considering 30 min as prediction horizon (PH). Li et al. [36] proposed a convolutional recurrent neural network for the prediction of blood glucose values with PHs of 30 and 60 min. The adopted network model consisted of two parts: a multilayer convolutional neural network followed by a recurrent neural network with Long Short Term Memory (LSTM) cells. Datasets were composed both of T1D virtual and real patients with CGM sensors. Reported RMSE for real data were 21.07 mg/dL ± 2.35 mg/dL with a PH = 30 min and 33.27 mg/dL ± 4.79 mg/dL with a PH = 60 min

De Bois et al. [39] proposed a comprehensive review of the current state-of-art on glucose predictive models, reporting the descriptions of the most well-known public datasets and glucose predictive models. Furthermore, in the same study nine predictive models were implemented and tested on both virtual and real patients, considering three different temporal horizons (30, 60 and 120 min). All the models were fed with the same input, composed of the glycemic history in the previous 3 hours with 5 min steps, the carbohydrate intake, and the administered insulin boluses. In particular, their results show that, although in favor of complex, non-linear, predictive models (such as neural network-based regression), no model significantly outperforms the other ones for both real and simulated data across the different PHs in all the cases. This can be due to the fact that each model has pros and cons. For instance, when the PH is short, the Support Vector Regression model results to be the most accurate. Instead, neural network-based models, such as LSTM and FFNN are good at making short-term predictions in hyperglycemia and long-term predictions in hypoglycemia, respectively. Moreover, the study highlights the difficulty of predicting future blood glucose values, especially at longer PH.

Another approach was proposed by Alfian et al. [24], where neither insulin boluses nor meal intake were considered in the FFNN model. Instead, FFNN input was built exploiting a 30 min sliding window across the blood glucose values. In addition to the blood glucose values in the previous 30 min, for each window, they calculated eight statistics (i.e. minimum, maximum, mean, standard deviation, difference between highest and lowest, median, kurtosis, and skewness), and these were fed as inputs to the neural network. The adopted neural network achieved a RMSE of 2.82 mg/dL ± 1.00 mg/dL, 6.31 mg/dL ± 2.43 mg/dL, 10.65 mg/dL ± 3.87 mg/dL, and 15.33 mg/dL ± 5.88 mg/dL, respectively considering 15, 30, 45, and 60 min as PHs. However, the model prediction did not consider any information about nutritional factors.

Recently, some studies considered the meal occurrence as an important input of the neural networks [40], [41]. A possible strategy is to predict all the glycemic values starting from the time of the meal to the prediction horizon. Karim et al. [25] implemented a FFNN to predict blood glucose values every 2 min up to 4 hours after the meal. Nevertheless, among the 5 diabetic patients considered for the analysis, only one was affected by T1D. The information on the content of the meal were used in two different ways. In one, the raw values of carbohydrates, lipids, and fibers in grams were directly chosen as inputs for the neural network. In the other one, a glucose absorption model [42] was computed and three numerical parameters of the obtained curve were used as inputs: time elapsed to the peak of the curve, time elapsed to 50 % of the peak of the curve, and rate of absorption at the maximum of the curve. The reported results showed generally better performance when the absorption model was integrated in the computation, with an average RMSE of 1.12 mmol/L (with PH = 60 min), compared to the respective RMSE value of 1.816 mmol/L for the first approach.

It is important to note that, although previous reported studies show that ML techniques can be successfully applied to blood glucose prediction, none of them focused on the impact of nutritional factors in this prediction. For this reason, in this study the impact of several nutritional factors in the short and middle term was investigated by ML methods.

III. MATERIALS AND METHOD

A. DATASET DESCRIPTION

In this section, the used data are presented. First the main characteristics of the public dataset *DirectNet* are briefly reported. Next, the data provided by Federico II University Hospital are described in detail (*AI4PG* data).

1) DirectNet DATA

The *DirectNet* is a public dataset available since 2007 containing CGM measurements. The data were collected with informed consent from eligible subjects and the protocol was approved by the Jaeb Center for Health Research as reported in [43]. It includes data from 50 child-patients with T1D wearing the HCLS device, Medtronic MiniMed Guardian-RT. The Guardian-RT system was designed to measure blood

glucose levels in a range of 40-400 mg/dL. The Guardian-RT system acquires glucose values every 10 seconds through a subcutaneous sensor. Then, the acquired data are averaged and recorded at intervals of 5 min. The dataset includes data from males and females patients, aged between 3 to 7 or 12 to 18 years, with a T1D diagnosis of more than 1 year. The blood glucose data was collected continuously every 5 min for approximately 7 days.

2) AI4PG DATA

The *AI4PG* dataset was provided by the Diabetes Outpatient Clinic of Federico II University Hospital (Naples, Italy). The dataset includes data from 25 T1D patients wearing the HCLS, Medtronic MiniMed 670G system [44], reporting information on dietary habits, insulin doses, and CGM measurements for 6/7 days [45]. Subjects were 12 males and 13 females, age (40 B1 12) years and with a duration of diabetes in the range of (15 B1 12) years. Patients completed at least 7-day food diaries with various information, such as consumed food and drinks. The dataset is organized in breakfasts, lunches, and dinners, each of them represented as time series of pre- and post-meal glycemic levels (mg/dL). Overall, the dataset contains a total of 1264 meals: 398 breakfasts, 441 lunches, 425 dinners. Manual Boluses (MBs) insulin, administered at mealtime, is reported in the dataset. The MB insulin (mmol/L) leverages on the amount of meal's carbohydrates and caloric intake computed by the patient. MetaDieta software [46] was used to calculate energy intake, nutrient composition, glycemic index and glycemic load. The dataset provided glycemia values from CGM every 5 min, from 30 min before meal to 60 min after meal. In particular, the dataset provided an estimate of carbohydrates (g), lipids (g), proteins (g), fibres (g) and energy intake (kcal) associated with each meal. Use of data in the present study was approved by the Ethical Committee of Federico II University and each participant was informed of the study and gave their consent to participate.

B. PROPOSED METHOD

In this work, a ML-based system, via FFNN [47], for postprandial blood glucose prediction at different PHs in T1D patients is proposed. The proposed model was developed leveraging on the results reported in [24] and [25]. In particular, based on the former, a 30 min window of blood glucose values and 8 associated statistical attributes were considered as input. Specifically, the statistics computed were minimum, maximum, mean, standard deviation, difference between highest and lowest, median, kurtosis, and skewness. Furthermore, on the basis of [25], the number of outputs was set equal to the number of PHs to investigate. In the present study, 4 prediction horizons in the short and middle time were considered to predict blood glucose values, i.e. 15, 30, 45, 60 min. A grid search strategy was implemented to set the number of hidden layers and neurons of the FFNN. Finally, a model that predicts at different PHs of interest was obtained.

A preliminary experiment on *DirectNet* data was carried out to assess the performance of the proposed system in blood glucose predictions. Once validated on *DirectNet* data, the proposed model was applied to the self-produced *AI4PG* dataset. In order to investigate the impact of nutritional factors in postprandial glycemic response, several input configurations were tested. More in detail, nine scenarios were considered.

- *#1 No-insulin*: the model took in input:
  - glycemic values (mg/dL) from 30 min before meal until mealtime every 5 min
  - glycemia's statistical attributes, that were minimum, maximum, mean, standard deviation, difference between highest and lowest, median, kurtosis, and skewness calculated on glycemia values before each meal.
- *#2 Insulin, No nutritional factor*: in addition to the aforementioned inputs, the FFNN also took manually-administered insulin bolus MB (mmol/L) before the meal as an input.
- *Single-nutritional factors scenarios*: in these scenarios, a single nutritional factor was taken into account. More in detail, the inputs were composed of glycemic values, statistical attributes, insulin bolus and a nutritional factor across the following:
  - *#3 Carbohydrates* (g),
  - *#4 Proteins* (g),
  - *#5 Fibers* (g),
  - *#6 Lipids* (g), and
  - *#7 Energy* intake (kcal) associated with each meal.
- *#8 Insulin, All nutritional factors*: in these scenario, the model was fed of glycemic values, statistical attributes, insulin bolus and all nutritional factor simultaneously.
- *#9 No insulin, All nutritional factors*: the model took in input glycemic values, statistical attributes and all nutritional factors simultaneously, without considering the MB insulin.

The layout of FFNN model is summarized in Fig.1, wherein the number of the scenario is used to identify the various input combinations. The outputs are postprandial blood glucose values at 15, 30, 45, and 60 min.

Root Mean Square Error (RMSE) was used to evaluate the prediction performances for each PH. RMSE is defined by Eq.1:

$$RMSE = \sqrt{\frac{1}{N}\sum_{N}(\hat{y}_t - y_t)^2} \tag{1}$$

where $\hat{y}_t$ and y_t are the predicted and the measured BGLs at the time instant t, respectively; while N is the total number of blood glucose measurements in the dataset.

IV. EXPERIMENTS

In this section a description of the conducted experiments is reported, together with the preprocessing and the experimental setup adopted. As mentioned in Section I, the aim

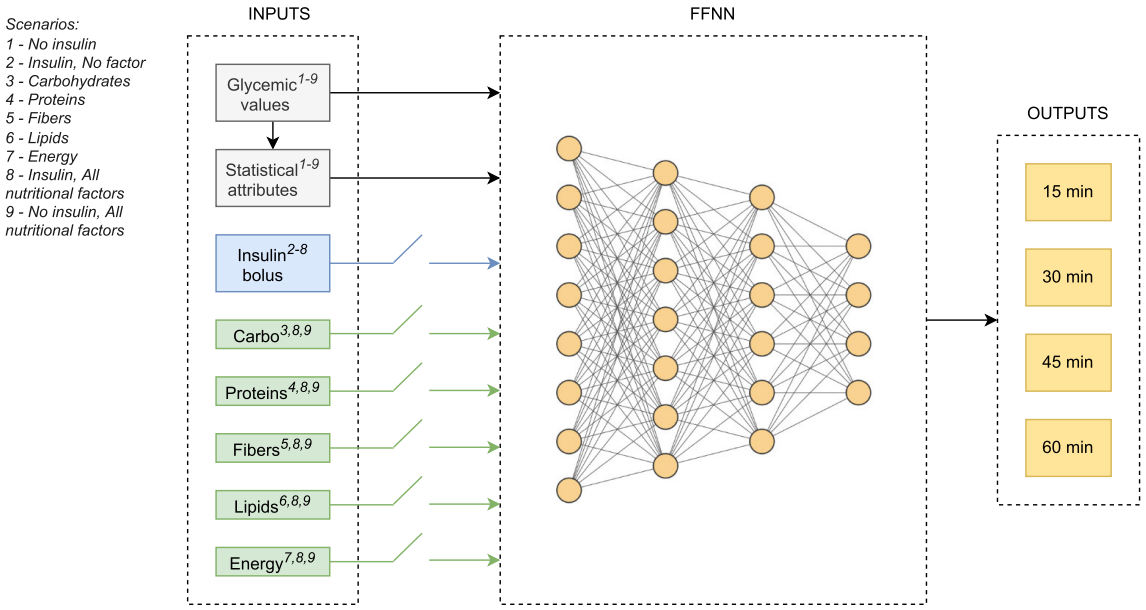

FIGURE 1. The layout of the used FFNN model. The identification number of each scenario identifies each input combination. The outputs are postprandial blood glucose values at 15, 30, 45, and 60 min.

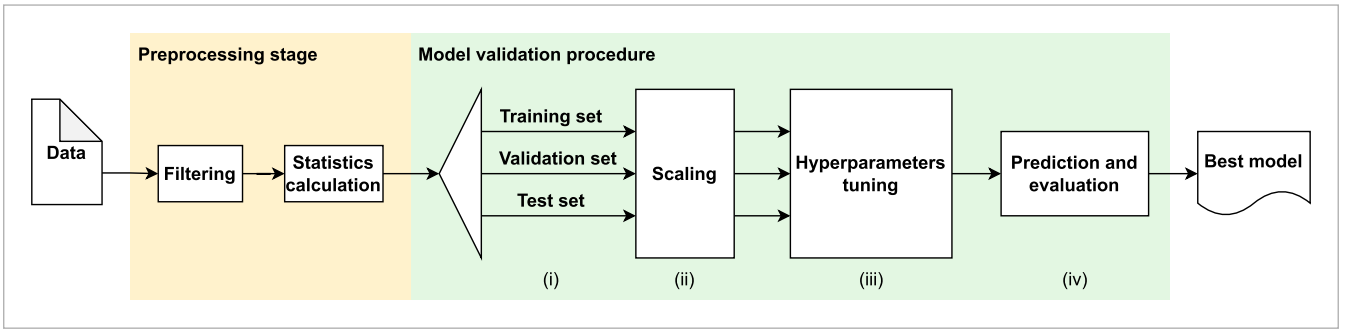

FIGURE 2. Proposed pipeline. It is composed of two main stages: data preprocessing and ML model validation. The data preprocessing stage is composed of the filtering step and the computation of the statistical attributes used together with the other inputs. Instead, the ML model validation stage consists in i) dividing the preprocessed dataset into training, validation and test set, ii) scaling the data using the min-max scaler strategy, iii) tuning the model hyperparameters leveraging on a grid search strategy, and finally iv) predicting the BGL output in several temporal horizons. The obtained prediction are then evaluated to select the best model.

of this work was to evaluate the impact of nutritional factors on the BGL prediction capability. To this end, a preliminary series of experiments was carried out on the public dataset *DirectNet* to experimentally validate the proposed neural network architecture in BGL prediction task. Successively, the proposed architecture was used on the *AI4PG* dataset to evaluate the impact of the nutritional factors, individually and together, on the BGL prediction capability (see Section III). The main stages of the proposed pipeline are reported in Fig. 2. After a first data preprocessing stage (filtering and statistical attributes calculation), a classical ML model validation procedure was carried out. It consisted in (i) dividing the dataset into three parts, that were training, validation and test set, used to train the model and to measure its performance. Then, (ii) data were scaled to adjust the different scales of the involved features. In the (iii) hyperparameters tuning stage, a good set of hyperparameters for the proposed model was searched. Finally, (iv) leveraging on prediction and evaluation on test data, a model able to generalize on new unseen data was provided. In the following of this paper, these stages will be described in detail.

A. DATA PREPROCESSING

1) DirectNet DATA PREPROCESSING

From *DirectNet* dataset, CGM data (mg/dL) of the 12 patients with the highest number of recorded data were considered. It was shown [29], [48] that cleaning the data from noise significantly improves the performance. Therefore, the same preprocessing reported in [24] consisting in the application of the Savitzky Golay technique [49] on the data was made. More in detail, the Savitzky Golay technique

TABLE 1. Tuned hyperparameters and the search space adopted during the grid search.

Tuned hyperparameters	Search Space
number of hidden layers	{1, 2, 3}
number of neurons in each layer	{32, 64, 128, 256}
optimization algorithm	{Stochastic Gradient Descent (SGR) [50], Adam [51]}
learning rate	{0.0001, 0.0005, 0.001, 0.005, 0.01}

with a first-order polynomial and a 15-step filtering window on blood glucose values was employed. Then, a 30-minute sliding window across the blood glucose data was used to construct the model input. In addition, based on [24], statistical features were calculated on each window of glycemic data and added as inputs. In particular, minimum, maximum, mean, standard deviation, difference between highest and lowest values, median, kurtosis and skewness were used.

2) AI4PG DATA PREPROCESSING

The blood glucose values (mg/dL), the MB (mmol/L), and the following nutritional factors were considered: total energy intake (kcal) of the meal, total protein (g), total carbohydrates (g), total lipids (g), total fiber (g). To avoid patients with a low number of acquisitions, subjects with less than 30 meals records were removed. For the remaining patients, only the first 100 meals were considered. Therefore, data from 15 patients were used, for a total 1036 meal records. Subsequently, the Savitzky Golay technique with a first-order polynomial and a 15-step filtering window was applied on BGLs. Therefore, glycemic values from (30 min) before meal until mealtime were used as part of inputs of the adopted FFNN. The second part of the input was composed of the 8 statistics previously discussed, computed on preprandial BGLs and used as network's inputs.

B. EXPERIMENTAL SETUP

As mentioned in Section III, FFNN was used as a predictor of postprandial blood glucose levels at different PHs. In order to select optimal hyperparameters, for the adopted FFNN model, a grid search strategy was exploited. More specifically, Table 1 reports the tuned hyperparameters and the search spaces. For each hidden layer of the network, the ReLU activation function [52] was chosen. In addition, regularization term with weight decay (L2 penalty) parameter was set to 0.0001, and the maximum number of epochs was set to 1000 with a patience of 20 as an usual trade-off between computational complexity and generalization capability [47].

The experiments were conducted both intra-subject and inter-subject on both *DirectNet* and *AI4PG* data.

1) INTRA-SUBJECTIVE APPROACH

The intra-subjective approach considered each subject individually, building a different a model for each patient. In this case, an hold-out validation strategy was performed to validate the method. In the Hold-Out strategy the dataset was split into three non-overlapping parts: training, validation, and testing sets. More in detail, 70 % of the data was used for training, 10 % for validation, and the remaining 20 % for testing. Since the model had to predict future BGL values relying on past ones, the temporal order of the data was maintained during the hold-out split procedure, letting the most recent ones in the test set. Furthermore, all data were scaled using min-max scaling. The minimum and maximum values were computed of the training data. The models were trained using the training set, while the validation set was used to avoid overfitting on the training data insofar as it allows to select the best model in terms of generalization capability [47]. The testing set was used for the final model evaluation to achieve the best model for each patient.

2) INTER-SUBJECTIVE APPROACH

In the inter-subjective case, a single model was built using data belonging to all the considered subjects, therefore all the data were used regardless of the subject to whom they belong. This was done to verify if and how much a model trained using data acquired from several subjects was able to generalize on new data. In this case, a 5-fold cross-validation (CV) was performed to validate the method. For each iteration of the CV process, a portion of the training data was used as validation set following a 70 %/10 % split. Furthermore, all data were scaled using min-max scaling using the minimum and maximum values of the training data.

Each model was evaluated on the test set by using RMSE as described in Section III.

V. EXPERIMENTAL RESULTS

In this section the experimental results both for intra-subject and inter-subject cases are reported. In the first part the results on *DirectNet* data are shown. Next, the findings on *AI4PG* data are presented.

A. DirectNet RESULTS

The model's performance on *DirectNet* dataset was assessed by calculating RMSE between actual and predicted values at the four PHs of interest (15, 30, 45, and 60 min). As no information on patient's administered insulin or meal intakes were reported in *DirectNet* dataset, the predictions were based only on daily BGL trend. Table 2 reports means and standard deviations of the RMSEs for the blood glucose prediction.

In the intra-subjective case, the reported results are the average on the test data of all the considered patients. An increasing average RMSE was observed as the PH increases, starting at 15 min with 4.14 mg/dL to a maximum of 16.69 mg/dL at 60 min. Moreover, standard deviation increased along with the PH (up to 5.86 mg/dL), due to high performance variability across different patients.

In the inter-subjective case, the RMSE averaged on the 5 folds is reported in Table 2. The results obtained are similar to the subject-dependent condition, with mean of RMSE increasing as PH increases. However, since each fold contains data from different patients, the variability of performance

TABLE 2. Mean RMSE with standard deviation of BGL prediction with intra-subjective and inter-subjective approach for various settings at different PHs on *DirecNet* dataset.

	15 min	30 min	45 min	60 min
	mean ± std	mean ± std	mean ± std	mean ± std
Intra-subjective	4.14 ± 1.30	8.30 ± 2.37	13.72 ± 4.03	16.69 ± 5.86
Inter-subjective	4.63 ± 0.36	8.01 ± 0.62	14.20 ± 1.07	21.32 ± 1.59

TABLE 3. Performance reported by the proposed approach and the analyzed literature.

Study	Inputs	PH (min)	RMSE (mg/dL)
Perez-Gandia et al. [29]	CGM data	15	9.74 ± 2.71
		30	17.45 ± 5.44
		45	25.08 ± 8.73
Ben Ali et al. [30]	CGM data	30	7.45 ± 2.63
		45	8.13 ± 2.76
		60	9.03 ± 2,83
Alfian et al. [24]	CGM data, statistical attributes	15	2.82 ± 1.00
		30	6.31 ± 2.43
		45	10.65 ± 3.87
		60	15.33 ± 5.88
Zecchin et al. [35]	CGM Data, glucose rate after meal	30	14.00 ± 4.10
Proposed method on *DirecNet* dataset	CGM data, statistical attributes	15	4.14 ± 1.30
		30	8.30 ± 2.37
		45	13.72 ± 4.03
		60	16.69 ± 5.86

between folds was minimal, resulting in a lower standard deviation respect to the intra-subject case.

RMSE values obtained from intra-subjective models were comparable with the literature, as shown in Table 3. It is important to notice that different experimental conditions, such as preprocessing or hyperparameters setting, can in turn affect the results, making an unbiased comparison among the methods proposed in literature hard to be made. In spite of these differences, preliminary results showed that the proposed ML-model predicts blood glucose levels comparable with the state-of-the-art methods reported in literature on a CGM public dataset *DirectNet*. After validating the prediction capability of the proposed model, the impact of nutritional factors on the predictions was investigated. This aspect is still an open issue, and it has been scarcely investigated in literature.

B. AI4PG RESULTS

Table 4 and Table 5 report the performance of the proposed method for intra-subjective and inter-subjective approaches, respectively. In both cases, RMSE between the real glycemic values at the 15^{th}, 30^{th}, 45^{th}, 60^{th} min after the meals and the predicted ones is reported. More in detail, the intra-patient results were averaged on the test data of the considered patients, and Table 4 reports mean and standard deviation (std) of RMSEs for each considered scenario. Instead, the inter-patient results, reported in Table 5, were computed averaging the RMSEs on 5-folds.

To asses the influence of nutritional factors and insulin on the predictions, a *statistical t-test* was used to determine the statistical significance of the results obtained. More in detail, a *paired t-test* was used to compare the *#1 No-insulin* scenario, where only blood glucose values and associated statistics features are used, with the other ones. The statistical significance of our results was interpreted through *p-value*. In particular, if the *p-value* was less than significance level α, the null hypothesis, i.e. zero mean difference between *#1 No-insulin* scenario and the other ones, was rejected and the mean difference was considered statistically significant. For this analysis, the adopted α was 0.05.

For intra-subjective approach, the t-test *p-value* between *#1 No-insulin* case and the other scenarios are also reported in Table 4. More in detail:

- for PH = 15 min, a negative statistical significance was obtained in *#2 Insulin, No nutritional factor* and in *#8 Insulin, All nutritional factors*.
- from PH = 30 min, a positive statistical significance were obtained when the nutritional factors were individually considered as input of FFNN, demonstrating that meal composition had a significant effect on postprandial blood glucose. As expected, *#3 Carbohydrates* remained the factor that abruptly impacts BGL predictions [45], but also *#4 Proteins* and *#5 Fibers* played an important role from 30 min after the meal [53].
- nutritional factors uniformly impact on BGL prediction when the temporal horizon was greater than or equal to 45 min.

For inter-subjective approach, as *p-value* was always greater than *alpha*, no statistical significance was found. This result reflects the need to model inter-individual variability. Indeed, a significant part of postprandial glucose variability is generally related to individual characteristics [53].

As a further validation of the obtained results, the Relative Squared Errors (RSEs) were calculated for intra-subjective and inter-subjective cases. The RSEs values are summarized in Table 6: for all the experimental cases, the RSEs are consistent with RMSEs values.

VI. DISCUSSION

As a first remark, it should be noted that the obtained results on *DirecNet* and *AI4PG* data suggest that a single classifier can be developed to obtain BGL predictions on multiple temporal horizons at once, as also proposed in [25].

The aim of this study is to verify the impact of the nutritional factors in the final predictions. Indeed, the importance of the nutritional factors on the BGL reported in the literature [53] can lead toward the hypothesis that nutritional factors can affect the BGL predictions. The preliminary results on *DirecNet* showed that the proposed ML-model predicts blood glucose levels comparable with the state-of-the-art methods reported in literature. The greatest part of the current

TABLE 4. Experimental results in intra-subject approach for various settings at different PHs on *AI4PG* dataset. RMSE averaged on all the subjects with standard deviation of BGL prediction is reported. The t-test p-values between the *1 No-insulin* scenario and the other ones are also reported. In bold the p-values less than the significance level α.

	15 min		30 min		45 min		60 min	
	mean $\pm$ *std*	*p-value*	*mean* $\pm$ *std*	*p-value*	*mean* $\pm$ *std*	*p-value*	*mean* $\pm$ *std*	*p-value*
#1 No insulin	2.80 $\pm$ 0.18		8.66 $\pm$ 0.31		16.27 $\pm$ 0.54		24.02 $\pm$ 0.73	
#2 Insulin, No nutritional factor	2.95 $\pm$ 0.22	**0.046**	8.58 $\pm$ 0.40	0.54	16.04 $\pm$ 0.81	0.34	23.65 $\pm$ 1.21	0.36
#3 Carbohydrates	2.81 $\pm$ 0.23	0.81	8.31 $\pm$ 0.36	**0.011**	15.72 $\pm$ 0.48	**0.0067**	23.23 $\pm$ 0.72	**0.0060**
#4 Proteins	2.86 $\pm$ 0.19	0.36	8.33 $\pm$ 0.34	**0.0087**	15.63 $\pm$ 0.60	**0.0043**	23.06 $\pm$ 0.83	**0.0028**
#5 Fibers	2.83 $\pm$ 0.19	0.60	8.38 $\pm$ 0.27	**0.011**	15.62 $\pm$ 0.50	**0.0036**	23.15 $\pm$ 0.79	**0.0064**
#6 Lipids	2.91 $\pm$ 0.24	0.16	8.24 $\pm$ 0.43	0.055	15.55 $\pm$ 0.63	**0.0087**	22.98 $\pm$ 0.92	**0.0075**
#7 Energy	2.87 $\pm$ 0.16	0.37	8.43 $\pm$ 0.32	0.11	15.72 $\pm$ 0.58	**0.030**	23.22 $\pm$ 0.87	**0.025**
#8 Insulin, All nutritional factors	3.00 $\pm$ 0.24	**0.0073**	8.50 $\pm$ 0.41	0.23	15.85 $\pm$ 0.73	**0.046**	23.38 $\pm$ 1.06	**0.035**
#9 No insulin, All nutritional factors	2.98 $\pm$ 0.28	0.085	8.66 $\pm$ 0.29	0.99	16.14 $\pm$ 0.57	0.41	23.93 $\pm$ 0.82	0.70

TABLE 5. Experimental results in inter-subjective approach for various settings at different PHs on *AI4PG* dataset. RMSE averaged on the test folds of a 5-fold CV procedure with standard deviation of BGL prediction is reported.

	15 min	30 min	45 min	60 min
	mean $\pm$ *std*	*mean* $\pm$ *std*	*mean* $\pm$ *std*	*mean* $\pm$ *std*
#1 No insulin	3.04 $\pm$ 0.42	8.89 $\pm$ 0.33	16.70 $\pm$ 0.50	24.70 $\pm$ 0.73
#2 Insulin, No nutritional factor	3.44 $\pm$ 0.96	8.99 $\pm$ 0.41	16.55 $\pm$ 0.87	24.32 $\pm$ 1.42
#3 Carbohydrates	3.34 $\pm$ 0.91	8.72 $\pm$ 0.60	16.34 $\pm$ 0.63	24.20 $\pm$ 1.03
#4 Proteins	3.41 $\pm$ 0.41	8.79 $\pm$ 0.68	16.27 $\pm$ 1.36	23.97 $\pm$ 2.00
#5 Fibers	3.01 $\pm$ 0.38	8.64 $\pm$ 0.39	16.36 $\pm$ 0.62	24.14 $\pm$ 0.81
#6 Lipids	3.05 $\pm$ 0.41	8.60 $\pm$ 0.15	16.29 $\pm$ 0.24	24.08 $\pm$ 0.50
#7 Energy	3.02 $\pm$ 0.18	8.85 $\pm$ 0.53	16.43 $\pm$ 1.06	24.12 $\pm$ 1.45
#8 Insulin, All nutritional factors	3.12 $\pm$ 0.18	8.68 $\pm$ 0.44	16.26 $\pm$ 0.96	24.15 $\pm$ 1.37
#9 No insulin, All nutritional factors	3.38 $\pm$ 0.44	8.89 $\pm$ 0.19	16.50 $\pm$ 0.22	24.33 $\pm$ 0.30

literature on the BGL prediction deals with proposing innovative methods to improve the prediction performance. However, the importance of nutritional factors is not considered in these works. Therefore, understanding if this hypothesis is verified or not, could help achieving more effective BGL predictors.

As regarding the impact of the nutritional factors, for the intra-subjective case on the *AI4PG* data, it is interesting to note that the results reported in Table 4 indicate that nutritional factors uniformly impact on BGL prediction when the temporal horizon is greater than or equal to 45 min. This can be interpreted as a confirmation that BGL values are influenced by nutritional factors in the middle term [45].

For shorter time, one can observe that just some of them have an impact on BGL prediction. In particular, Proteins and Fibers seem already give a contribution in the prediction to 30 min, in spite of they do not result in a statistically positive influence to 15 min. The lack of performance improvements using nutritional factors in the short term can be due to the high correlation between the preceding and immediately following blood glucose values, as reported in [24], [54], and [55]. Therefore, the use of nutritional factors in the short term may not give any improvement over using BGL values alone. Instead, after 30 min, all the nutritional factors give a positive impact on the BGL predictions.

However, it is interesting to notice that using together all the considered nutritional factors in the input leads to a lower impact on the performance respect to using just one nutritional factor at once. For example, in Table 4 using all the analyzed nutritional factors there is a lower improvement respect to using only the lipids. This can be due to at least two possible reasons: the former is that the proposed model is subject to the Peaking Phenomenon [47], [56] where, for training sets of finite size, the performance of a given model does not keep on improving as the number of features (in this case, the nutritional factors) is increased. The latter, instead, can be due to a negative interaction between nutritional factors in the predictions.

Consistently with the findings in [45], [53], and [57], it results that some nutritional factors (such as fibers and lipids) can have a greater impact in middle term prediction respect to other ones.

TABLE 6. RSE results in intra-subjective and inter-subjective approach for the different PHs on *AI4PG* dataset.

	Intra-subjective approach				Inter-subjective approach			
	15 min	**30 min**	**45 min**	**60 min**	**15 min**	**30 min**	**45 min**	**60 min**
	mean ± *std*	*mean* ± *std*	*mean* ± *std*	*mean* ± *std*	*mean* ± *std*	*mean* ± *std*	*mean* ± *std*	*mean* ± *std*
#1 No insulin	0.007 ± 0.001	0.056 ± 0.005	0.15 ± 0.02	0.23 ± 0.03	0.007 ± 0.002	0.061 ± 0.009	0.18 ± 0.02	0.31 ± 0.04
#2 Insulin, No nutritional factor	0.009 ± 0.001	0.054 ± 0.007	0.15 ± 0.01	0.22 ± 0.02	0.010 ± 0.006	0.061 ± 0.004	0.17 ± 0.02	0.29 ± 0.04
#3 Carbohydrates	0.007 ± 0.001	0.052 ± 0.005	0.14 ± 0.01	0.22 ± 0.01	0.007 ± 0.001	0.053 ± 0.003	0.16 ± 0.01	0.27 ± 0.03
#4 Proteins	0.007 ± 0.001	0.051 ± 0.005	0.14 ± 0.01	0.21 ± 0.01	0.010 ± 0.002	0.058 ± 0.006	0.18 ± 0.04	0.30 ± 0.06
#5 Fibers	0.051 ± 0.005	0.052 ± 0.006	0.14 ± 0.01	0.22 ± 0.01	0.007 ± 0.001	0.057 ± 0.006	0.17 ± 0.02	0.31 ± 0.05
#6 Lipids	0.007 ± 0.001	0.058 ± 0.007	0.14 ± 0.01	0.21 ± 0.01	0.007 ± 0.002	0.059 ± 0.009	0.18 ± 0.02	0.33 ± 0.04
#7 Energy	0.007 ± 0.001	0.051 ± 0.006	0.14 ± 0.01	0.22 ± 0.02	0.007 ± 0.002	0.061 ± 0.009	0.18 ± 0.02	0.29 ± 0.01
#8 Insulin, All nutritional factors	0.008 ± 0.002	0.054 ± 0.007	0.15 ± 0.02	0.23 ± 0.03	0.008 ± 0.001	0.057 ± 0.004	0.17 ± 0.01	0.32 ± 0.02
#9 No insulin, All nutritional factor	0.008 ± 0.002	0.058 ± 0.007	0.15 ± 0.01	0.24 ± 0.01	0.009 ± 0.002	0.058 ± 0.006	0.18 ± 0.01	0.30 ± 0.02

For the inter-subject case, instead, from Table 5 one can observe that no nutritional factor contributes in improving the BGL predictions significantly. This can be due to the subjective response of each single patient with respect to nutritional factors, making hard to build a inter-subject classifier able to find relationships between nutritional factors and BGL shared among different subjects. In other words, postprandial glucose responses seem strongly related on individual characteristics of the subject. This is consistent with the findings in [53], [58], and [59], reporting that, in general, the human postprandial glucose response is almost constant in the same subject, while it changes across different ones.

The obtained findings contribute to the advancement of knowledge on the timing of the effects on blood glucose of the different nutritional factors. The time dependence of the predicting value of the nutritional factors is evident with very early effects of carbohydrates but also early effects of proteins and immediately after of lipids and energy intake. Therefore, understanding the contribution over time by different nutrients with AI could compensate for more complex kinetic studies. Moreover, a better knowledge of nutritional factor impact should be used to enhance the algorithms driving insulin infusion rate in hybrid closed loop systems, and the individual insulin bolus calculation.

VII. CONCLUSION

The aim of this research work was to experimentally investigate the impact of nutritional factors on the capability to obtain postprandial BGL predictions, in the short and middle term after a meal, by machine learning methods. In particular, the impact of nutritional factors such as carbohydrates, proteins, lipids, and fibres, as well as meal energy intake, on postprandial blood glucose response was investigated. A series of experiments to predict BGLs was carried out on the self-produced *AI4PG* dataset containing both CGM measurements and meal nutritional factors of a set of patients. Experiments were made using a Feed Forward Neural Network model as predictor. Initially, the model was validated with a preliminary experiments on the well-Known *DirectNet* dataset, obtaining performance results comparable with the current literature. Next, an analysis on the prediction performance on the *AI4PG* was conducted, taking into account also several nutritional factors as input.

In particular, nutritional factors were considered individually as inputs to the proposed system to the aim of investigating the impact of each of them. Furthermore, a final experiment on the adoption of all the nutritional factors together as input was investigated.

The results suggested that information about nutritional factors can be significant for middle-term postprandial BGL predictions, but these information have to be used in a subject dependent way. This approach is in agreement with a patient centered vision to support precision medicine. Hence, a customized system is required to meet the individual needs of the subject. The recent literature already proposed some prototypes of personalized devices [60]. On the other hand, an alternative machine learning strategy could be based on transferring the knowledge among different inter-subjective datasets, such as in the case of Transfer Learning methods (e.g., [61], [62]).

This study focused on the impact on BGL predictions of several nutritional factors considered individually or all together. However, the impact of different scenarios also should be considered. This can be investigated considering classical features selection strategies or more recent eXplainable Artificial Intelligence (XAI) methods [63], [64], able to give explanations about the input-output relationships of an AI system. Indeed, despite of XAI systems are usually used in other tasks, such as image classification [64], [65] and text classification [66], recent literature is investigating on the use of XAI methods also on different type of signals, as biological ones [67]. Furthermore, literature [68], [69], [53] reports that nutritional factors can have a significant impact in longer time predictions, since the shape of glucose response can be significant also over 6 h from the meal. Therefore, further studies have to be carried out to investigate prediction performances of ML systems in longer temporal horizons. In addition, the adoption of more advanced neural network models, such as recursive (LSTM) and convolutional architectures, can help produce better results.

AUTHORS' CONTRIBUTION

Conceptualization: Andrea Apicella, Roberto Prevete. Data collection: Giovanni Annuzzi, Lutgarda Bozzetto. Data curation: Sabatina Criscuolo, Marisa Pesola, Ersilia Vallefuoco. Formal analysis: Andrea Apicella, Sabatina Criscuolo, Marisa Pesola. Funding acquisition: Giovanni Annuzzi, Egidio De Benedetto, Roberto Prevete. Interpretation of results: Giovanni Annuzzi, Egidio De Benedetto, Roberto Prevete. Draft manuscript preparation: Andrea Apicella, Sabatina Criscuolo, Marisa Pesola, Ersilia Vallefuoco. Writing–review & editing: Pasquale Arpaia, Egidio De Benedetto, Roberto Prevete. Software: Andrea Apicella, Sabatina Criscuolo, Marisa Pesola. Supervision: Pasquale Arpaia, Egidio De Benedetto, Roberto Prevete. Validation: Andrea Apicella, Sabatina Criscuolo, Marisa Pesola. Visualization: Sabatina Criscuolo, Marisa Pesola, Ersilia Vallefuoco.

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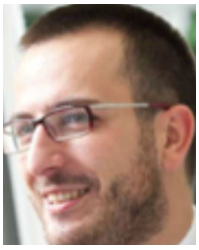

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