Machine-Learning Based Model to Improve Insulin Bolus Calculation in Type 1 Diabetes Therapy

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Abstract*—*Objective: **This paper aims at proposing a new machine-learning based model to improve the calculation of mealtime insulin boluses (MIB) in type 1 diabetes (T1D) therapy using continuous glucose monitoring (CGM) data. Indeed, MIB is still often computed through the standard formula (SF), which does not account for glucose rate-of-change (ΔG), causing critical hypo/hyperglycemic episodes. *Methods:* Four candidate models for MIB calculation, based on multiple linear regression (MLR) and least absolute shrinkage and selection operator (LASSO) are developed. The proposed models are assessed *in silico*, using the UVa/Padova T1D simulator, in different mealtime scenarios and compared to the SF and three ΔG-accounting variants proposed in the literature. An assessment on real data, by retrospectively analyzing 218 glycemic traces, is also performed. *Results:* All four tested models performed better than the existing techniques. LASSO regression with extended feature-set including quadratic terms (LASSO_Q) produced the best results. In silico, LASSO_Q reduced the error in estimating the optimal bolus to only 0.86 U (1.45 U of SF and 1.36–1.44 U of literature methods), as well as hypoglycemia incidence (from 44.41% of SF and 44.60–45.01% of literature methods, to 35.93%). Results are confirmed by the retrospective application to real data. *Conclusion:* New models to improve MIB calculation accounting for CGM-ΔG and easy-to-measure features can be developed within a machine learning framework. Particularly, in this paper, a new LASSO_Q model was developed, which ensures better glycemic control than SF and other literature methods. *Significance:* MIB dosage with the proposed LASSO_Q model can potentially reduce the risk of adverse events in T1D therapy.**

***Index Terms*— Continuous glucose monitoring, least absolute shrinkage and selection operator, linear regression, glycemic control, hypoglycemia.**

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I. Introduction

TYPE 1 diabetes (T1D) is a chronic disease caused by the progressive autoimmune destruction of pancreatic beta cells. The lack of endogenous insulin production results in elevated blood glucose (BG) levels and, in particular, in hyperglycemia (BG $>$ 180 mg/dL), a condition that can lead to several pathologies, such as cardiovascular complications, retinopathy and nephropathy [1]. Therefore, T1D individuals need lifelong therapy based on exogenous insulin administrations, whose excessive dosing induces hypoglycemia (BG $<$ 70 mg/dL) and also short-term complications, including fainting, weakness, coma and, even, death [2].

According to the Diabetes Control and Complications Trial (DCCT), proper glycemic control is mandatory for T1D management and treatment [3]. One of the most critical steps in current standard therapy for exogenous insulin administration is accurate and effective estimation of the meal-insulin bolus (MIB) amount, in order to avoid post-prandial hypo/hyperglycemia. MIB is commonly calculated through an empirical standard formula (SF) [4]:

$$MIB_{SF} = \frac{CHO}{CR} + \frac{G_c - G_t}{CF} - IOB \tag{1}$$

where MIB_{SF} is the mealtime insulin bolus (MIB) computed through the SF, CHO (g) is the meal carbohydrate intake, CR (g/U) and CF (mg/dL/U) are the insulin-to-carbohydrates ratio and the correction factor, i.e., two therapy parameters tuned, by the clinician, through a trial-and-error procedure [5], G_c (mg/dL) is the current BG level, G_t (mg/dL) is the target BG level, IOB (U) is the insulin on board at mealtime [6], i.e., an estimate of the amount of previously injected insulin that is still acting in the organism. However, estimating MIB using the SF can be suboptimal [7]. In particular, MIB_{SF} does not include any information on glucose dynamics at mealtimes. Indeed, the only term reflecting the BG status is G_c, which, however, is a static measurement of BG concentration. Intuitively, knowing whether BG is stable or increasing/decreasing, can be useful for more effective MIB calculation and, consequently, might be able to improve post-prandial glycemic control. Currently, such information on BG dynamics and, in particular, its rate-of-change (ΔG) is provided, in real-time, by continuous glucose monitoring (CGM) sensors. CGM systems are minimally invasive

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devices that are becoming a key element in T1D therapy. In fact, not only can CGM sensors improve the detection of hypo and hyperglycemic episodes [8]–[10], but they can also be used to take treatment decisions, for example insulin dosing, without requiring confirmatory BG measurements through invasive, and uncomfortable, fingerprick devices [11].

The real-time availability of information on glucose dynamics provided by CGM systems, along with the possibility of using the BG measurements they provide for insulin dosing, has encouraged the development of new rules to adjust the MIB_{SF} according to the ΔG provided by these sensors. The Scheiner (SC) [12] and Pettus/Edelman [13] methods, assume that ΔG will be stable by the time the insulin starts to act, and use ΔG as a predictor to infer the future value of BG in the coming 30–60 minutes and then increase/decrease G_c accordingly. The approach proposed by Buckingham (BU) [14] performs a percentage increase/decrease of MIB_{SF} consistent with ΔG magnitude and direction. The methods developed by Klonoff [15], Aleppo/Laffel [16] and Ziegler (ZI) [17] correct MIB_{SF} by adding/subtracting a specified quantity to its value according to ΔG. The two latter methods adjust the dose by taking into account also the patient-specific parameter CF, which individualizes the adjustment.

The derivation of all previous rules for MIB_{SF} correction has mainly been empirical, suggesting that there would be room for improvement should a systematic modeling methodology be adopted. Moreover, a recent in silico assessment of BU, SC and Pettus/Edelman formulae has shown that all methods performed similarly for all BG and ΔG conditions at mealtime [7], advancing the search for more effective, and possibly personalized, MIB calculation strategies. Some recent proof-of-concept studies have also shown that machine learning techniques can be used to tailor the MIB_{SF} correction to meet patient-specific parameters [18], [19], or could even be used to draw up new rules for MIB estimation, rules which would include ΔG as an input [20], that is, by abandoning the idea of using the MIB_{SF} as an initial estimate to be adjusted according to ΔG.

Thus, this work aims to develop a new approach to MIB calculation which is based not only on the parameters already appearing in equation (1), but also on the glucose ΔG that is provided by CGM and other easily accessible patient-dependent variables, such as body weight (BW) and insulin basal rate (I_b).

Four candidate models based on multiple linear regression (MLR) and the least absolute shrinkage and selection operator (LASSO) have been developed in a simulation environment using both a simple feature set and extended feature sets, which include quadratic and interaction terms. The models have been tested both in silico and, retrospectively, on clinical data collected in T1D individuals versus other approaches in the literature that are currently used for MIB_{SF} correction.

II. Datasets and Features

A. Simulated Dataset

The UVa/Padova T1D Simulator[21], which deploys a mathematical model of glucose, insulin and glucagon dynamics in T1D, has been used to generate synthetic data for 100 virtual adult subjects to train and test the new models. Developing new MIB calculation models within a simulation environment is particularly advantageous for two main reasons. Firstly, a simulation environment makes it possible to generate a unique dataset where patients undergo multiple meal tests while maintaining the same surrounding conditions. This would be impossible to replicate with clinical trials, since a patient's behaviour, and physiological state, do not remain the same. Secondly, extreme conditions, which are difficult and dangerous to obtain in clinical trials, can be simulated without any risk for the patient. This virtual population was subjected to multiple single-meal scenarios in a noise-free ambient [21], which consisted of: using optimal therapy parameters; not permitting either postprandial correction boluses or rescue carbohydrate intakes; and, no errors in either CHO counting, BG measurements or in ΔG estimation. Moreover, we also switched off the intra-patient variability of insulin sensitivity during the meal. All these choices were made in order to eliminate any confounding factors that could have influenced the outcomes of the study.

Each single-meal scenario lasted 12 hours from 7:00 to 19:00. The first part of the simulation (from 7:00 to 13:00) was used to create specific pre-prandial conditions in terms of ΔG and BG in the patient at mealtime, by manipulating both the time and amount of two CHO intakes and one insulin bolus. This generated 108 initial conditions, corresponding to combining 9 different ΔG values (from -2 to $+2$ mg/dL/min with a step equal to 0.5 mg/dL/min) and 12 different preprandial BG values (from 70 to 180 mg/dL with a step equal to 10 mg/dL) for each virtual subject. Then, at 1pm, a meal was set. We then simulated 15 different CHO amounts (from 10 to 150 g with a step of 10 g) for each patient.

Lastly, for each patient and each meal condition (in terms of preprandial BG, ΔG and meal CHO) the optimal MIB dose (MIB_{OPT}) was computed by minimizing the blood glucose risk index (BGRI) [22] that was evaluated during the post-prandial window (from 13:00 to 19:00 PM). BGRI is a risk index with values between 0 and 100, with 0 representing the lowest risk and 100 representing the highest. We chose the BGRI as cost function since this metric, because of the symmetrization of the BG measurement scale, equalizes the amplitude of hyper/hypoglycemic excursions with respect to the risk they carry (a hypoglycemic excursion is much more risky than a hyperglycemic excursion with same amplitude).

Fig. 1 depicts two representative scenarios in terms of BG excursion and MIB_{OPT}. The upper panel shows one example with a mealtime condition of BG $=$ 100 mg/dL, ΔG $=$ $+1$ mg/dL/min, and CHO $=$ 50 g. In the lower panel there is an example with mealtime BG $=$ 150 mg/dL, ΔG $=$ -0.5 mg/dL/min and CHO $=$ 50 g. Note that, in both scenarios, MIB_{OPT} permits proper glycemic control by maintaining the BG within the euglycemic range.

The resulting simulated dataset, with 162000 traces, was divided into training and testing sets. The data on 80 subjects were assigned to the training set, while the remaining data, on 20 subjects, were assigned to the test set. The assignment of each virtual subject either to the training or to the test set was performed randomly. Note, also, that each subject was included

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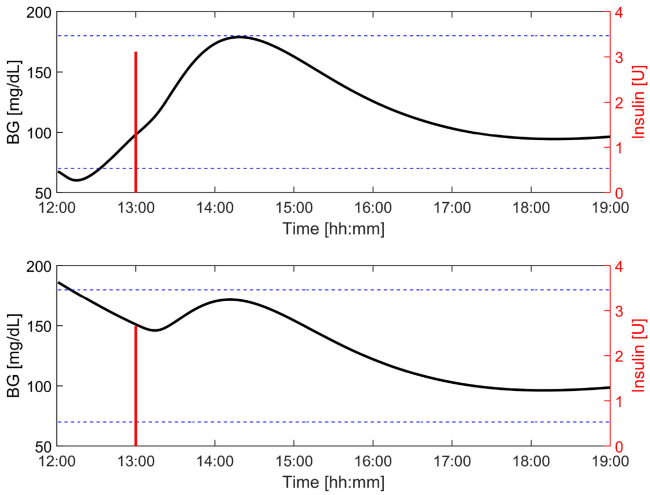

Fig. 1. Two representative simulated scenarios for a virtual subject considering a meal of CHO content equal to 50 g provided at 13:00. The upper panel shows a 7-hour BG curve with BG equal to 100 mg/dL and ΔG equal to +1 mg/dL/min at mealtime and the respective MIB$_{OPT}$ of 3.10 U. The lower panel shows, respectively, a 7-hour BG curve with BG equal to 150 mg/dL and ΔG equal to -0.5 mg/dL/min at mealtime and a MIB$_{OPT}$ of 2.65 U.

either in the training or in the testing set, so as to provide an unbiased evaluation of performance of the model.

B. Real Dataset

Data collected during a randomised crossover trial in patients with T1D [23] were used for a retrospective analysis to assess the effectiveness of the model proposed when applied to real data. In this study, patients were randomized either to 2 months of closed-loop therapy from dinner to waking up, plus open-loop therapy during the day, or, to 2 months of all-day open-loop therapy. Here, we selected only the data collected during the all-day open-loop phase, since we are working on this specific type of therapy setting. Only meals and postprandial intervals lasting 4-hours were considered in the analysis. Intervals containing rescue carbohydrate intakes or correction boluses were excluded. Moreover, only intervals with a combination of positive preprandial ΔG and postprandial hyperglycemic event occurrence (scenario A) and of negative preprandial ΔG postprandial hypoglycemic event occurrence (scenario B) were taken into account because, in these cases, the expected result of an effective ΔG-based MIB calculation is already known: an increased MIB amount, in scenario A, and a decreased MIB amount, in scenario B, when compared to the dose really taken by the patient. We also only selected intervals with a magnitude of hypo- and hyper event greater than 10 % of the total time window, in order to avoid irrelevant episodes. The resulting dataset is made up of 218 glycemic traces, 169 for scenario A, 49 for scenario B.

C. Features Extraction

We extracted 10 easy-to-measure features, informative of patient physiology and status, from both simulated and real dataset. Some of these variables are strictly patient-dependent and could be considered as constant for each individual, i.e. CR, CF, BW, G_t and I_b. The remaining features describe the condition of the subject at mealtimes, i.e. G_c, ΔG, CHO, and IOB. As well as these parameters describing the patient and mealtime condition, we also considered the MIB dose calculated by SF (MIB$_{SF}$) as an additional feature, because this takes into account the non-linear combinations of parameters that are known to be important for MIB calculations. Within a broader perspective, all the features used would be easily accessible in daily life, thus we ensured that the new model could be applied and used by a T1D individual. Lastly, because of differing measurement units and scales in the features, we standardized the variables by removing the mean, and by scaling then to unit variance [24].

III. The New Models for MIB Calculation

Among the possible approaches to target the MIB$_{OPT}$, we chose MLR and LASSO [24] because these methodologies are simple and are able to provide an adequate and interpretable description of how the inputs affect the output. Indeed, each MLR coefficient represents the slope of the linear relationship between the output and that portion of input which is independent from all the others. Moreover, model interpretability represents a desirable feature for clinicians, which could encourage them to use it in clinical practice.

A. MLR Model

The MLR model is:

$$\hat{\boldsymbol{y}} = \hat{\alpha}_0 + \sum_{j=1}^{p} \boldsymbol{x_j} \cdot \hat{\alpha}_j \tag{2}$$

where $\boldsymbol{y}$ is the target variable, i.e. MIB$_{OPT}$, $\boldsymbol{x_j}$ is the j-th feature, α_j the coefficient related to the j-th feature, α_0 is the model intercept and p represents the number of features. Parameters $\hat{\alpha}_j$ are estimated through the least squares estimation method [24], which chooses a vector $\hat{\boldsymbol{\alpha}}$ of coefficients that minimizes the residual sum of squares (RSS):

$$\hat{\boldsymbol{\alpha}} = \underset{\boldsymbol{\alpha}}{\operatorname{argmin}}\, RSS(\boldsymbol{\alpha}) \tag{3}$$

where

$$RSS(\boldsymbol{\alpha}) = \sum_{i=1}^{N} (y_i - \hat{y}_i)^2 \tag{4}$$

and y_i is the i-th observation of MIB$_{OPT}$, $\hat{y}_i$ the corresponding model prediction.

B. LASSO Models

To deal with multicollinearity, we used shrinkage methods. In particular, we resorted to LASSO regression models, which are well known to be robust to multicollinearity [25].LASSO coefficients are estimated by minimizing eq. (4) with the addition of the absolute value of the coefficients magnitude as a penalty

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term:

$$\hat{\boldsymbol{\alpha}} = \underset{\boldsymbol{\alpha}}{\operatorname{argmin}} \left\{ RSS(\boldsymbol{\alpha}) + \lambda \sum_{j=1}^{p} |\alpha_j| \right\} \tag{5}$$

where $\lambda \geq 0$ is a parameter controlling the amount of shrinkage set, through an exhaustive grid search, with cross-validation in the training set. In this paper, we trained three LASSO models on three different feature sets:

- LASSO: trained on the feature set described in Section II-C defined as $\{x_j : j = 1, \ldots p\}$.
- LASSO_Q: trained on an expanded feature set which includes variables reported in Section II-C plus their quadratic values, defined as $\{x_j, x_j^2 : j = 1, \ldots p\}$.
- LASSO_{QI}: trained on an extended feature set which also includes terms of between-features interaction, defined as $\{x_j, x_j^2, x_{ij} : j = 1, \ldots p, i = 1, \ldots p, i \neq j\}$.

Note that, due to the intrinsic nonlinearity of the glucose-insulin system, we also added polynomial transformations of the input variables as features, thus capturing nonlinear relationships between variables while still maintaining model interpretability.

One of the key features of the LASSO model is that it performs both automatic variable selection simultaneously, setting the coefficients associated to unnecessary features to zero, and, also regularization. In practice, this means that the LASSO model slightly increases the bias to reducing the variance of the predicted values: this leads to an overall improvement in the accuracy of predictions [24]. In this application here, this natural feature selection capability made it possible to considerably reduce the number of features, and to avoid overfitting, especially when quadratic (LASSO_Q) and quadratic plus interaction (LASSO_{QI}) terms were included in the dataset.

IV. In Silico Data: Assessment Criteria

A. Methods From the Literature Adopted for Comparison

In order to carry out a comprehensive evaluation of the new models, their performance was compared to that of three, selected, state-of-the-art methods: BU, SC and ZI. These three models well represent the different approaches, in the literature, that are currently being used for MIB_{SF} correction. BU performs a 20% or 10% increase/decrease of MIB_{SF} according to ΔG magnitude and sign; SC corrects the G_c value used in SF by, respectively, adding/subtracting 25 mg/dL for increasing/decreasing ΔG; while ZI adds/subtracts a constant insulin quantity based on CF value, ΔG magnitude and sign. For further details on these methods, please see the original papers [12], [14], [17].

B. Criteria for in Silico Assessment

The assessment of all the models considered for MIB calculation was performed on the test set. The first evaluation regards the goodness-of-fit of the model. This was carried out by computing both the root mean square error (RMSE) and the coefficient of determination (R^2), between the optimal and the estimated MIB for each model. Next, we tested the effectiveness of the MIB estimates provided by each model in terms of glycemic control. We re-simulated each single-meal scenario (see Section II), created with the UVa/Padova T1D simulator, by using the MIB estimates provided by each model in place of the optimal model. We then evaluated the BG pattern in the 6-hour postprandial time window and assessed the goodness of glycemic control using three metrics that are widely used for such purposes: BGRI (introduced in Section II), and the percentage of time that the BG trace spent in both hyperglycemia (T_{Hyper}) and in hypoglycemia (T_{Hypo}) [26], [27]. The percentage of the incidence of hypoglycemic episodes (I_{Hypo}) was also calculated. These metrics are commonly used to assess glycemic outcomes in T1D [27]. Lastly, to evaluate the statistical significance of the differences in terms of BGRI, T_{Hyper}, T_{Hypo} with respect to SF, a Friedman test was performed with a 5% significance level. We chose this test, which is the nonparametric equivalent of the classical balanced two-way ANOVA, both because metric distributions are not Gaussian, and because there were repeated subjects within the test set (with same physiology, but different initial conditions). We also adjusted the p-values using the Bonferroni method to account for multiple pairwise comparisons.

$$\begin{aligned} MIB_{MLR} &= 4.603 - 0.137\,CR - 0.191\,CF - 0.181\,I_b \\ &\quad - 0.380\,BW + 0.464\,G_t + 0.039\,IOB - 0.065\,G_c \\ &\quad + 0.858\,\Delta G + 0.273\,CHO + 2.686\,MIB_{SF} \end{aligned} \tag{6}$$

$$\begin{aligned} MIB_{LASSO} &= 4.603 - 0.214\,CR - 0.238\,BW + 0.410\,G_t \\ &\quad - 0.032\,G_c + 0.806\,\Delta G + 0.257\,CHO + 2.661\,MIB_{SF} \end{aligned} \tag{7}$$

$$\begin{aligned} MIB_{LASSO_Q} &= 4.603 - 0.198\,CR + 0.789\,\Delta G \\ &\quad + 0.234\,CHO + 2.671\,MIB_{SF} - 0.224\,BW^2 \\ &\quad + 0.403\,{G_t}^2 - 0.020\,{G_c}^2 \end{aligned} \tag{8}$$

$$\begin{aligned} MIB_{LASSO_{QI}} &= 4.603 - 0.150\,CR \cdot G_t - 0.064\,CR \cdot G_c \\ &\quad + 0.007\,CF \cdot MIB_{SF} + 0.043\,I_b \cdot \Delta G + 0.064\,I_b \cdot CHO \\ &\quad + 0.019\,I_b \cdot MIB_{SF} - 0.199\,BW^2 + 0.064\,BW \cdot \Delta G \\ &\quad + 0.236\,{G_t}^2 + 0.632\,G_t \cdot \Delta G \\ &\quad + 0.167\,G_t \cdot CHO + 2.66 G_t \cdot MIB_{SF} \\ &\quad + 0.014\,IOB \cdot SF + 0.079 \Delta G \cdot MIB_{SF} \end{aligned} \tag{9}$$

V. In Silico Data: Results

A. Correlation Analysis of Extracted Features vs. MIB_{OPT}

The first step here was to check whether the extracted features and the optimal bolus MIB_{OPT} were correlated or not. To do this, a correlation analysis was performed, to assess whether the features we had extracted, and presented in II-C were suitable for predicting MIB_{OPT}. Unsurprisingly, the results showed that the most correlated feature was MIB_{SF}, with a Pearson correlation coefficient [28] of $\rho = 0.90$, followed by CHO ($\rho = 0.65$). Also CR and ΔG resulted correlated with the target, with $\rho = -0.41$ and $\rho = 0.39$ respectively.

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TABLE I
PEARSON CORRELATION COEFFICIENTS CALCULATED BETWEEN EACH COUPLE OF FEATURES (FIRST TEN COLUMNS) AND BETWEEN EACH FEATURE AND THE TARGET VARIABLE (LAST COLUMN)

	CR	CF	I_b	BW	G_t	IOB	G_c	ΔG	CHO	MIB_{SF}	MIB_{OPT}
CR	1.000	0.652	-0.216	-0.008	-0.190	-0.186	< 0.001	< 0.001	< 0.001	-0.413	-0.410
CF		1.000	-0.729	0.034	0.094	-0.138	< 0.001	< 0.001	< 0.001	-0.316	-0.280
I_b			1.000	-0.547	-0.249	0.018	< 0.001	< 0.001	< 0.001	0.154	0.142
BW				1.000	0.255	0.069	< 0.001	< 0.001	< 0.001	-0.042	-0.081
G_t					1.000	0.115	< 0.001	< 0.001	< 0.001	-0.020	0.107
IOB						1.000	-0.196	-0.583	< 0.001	-0.235	-0.290
G_c							1.000	< 0.001	< 0.001	0.257	0.177
ΔG								1.000	< 0.001	0.195	0.392
CHO									1.000	0.740	0.651
MIB_{SF}										1.000	0.900

Furthermore, the between-features correlation was also investigated, to check whether there was multicollinearity. In particular, the features highly correlated each other are CF and I_b ($\rho = -0.73$), CR and CF ($\rho = 0.65$), ΔG and IOB ($\rho = -0.58$), BW and I_b ($\rho = -0.55$). As expected, MIB_{SF} had nonzero correlation with the majority of the variables, especially with CHO ($\rho = 0.74$), CR ($\rho = -0.41$) and CF ($\rho = -0.28$). Table I reports the Pearson correlation coefficients calculated between each couple of features (first ten columns) and between each feature and the target variable (last column).

This preliminary analysis showed that the target MIB_{OPT} was highly correlated with CHO, MIB_{SF}, CR and ΔG, suggesting that these could be the most relevant inputs for the models. Moreover, the effect of multicollinearity should be taken into account during model development, justifying the use of LASSO methodology [25].

B. Identified Models

Here we report the equations of the models identified on the training set. Comments on coefficient meaning and selected features are also provided.

1) MLR: the resulting MLR equation, identified on the training set, is reported in eq. (6). As expected CHO, MIB_{SF} and ΔG contribute positively to the final insulin amount. Moreover, their coefficients are generally bigger than the others (absolute value), thus highlighting the importance of these features for MIB computation. CR, makes a negative contribution since the lower the CR the higher the amount of insulin required to compensate a specific CHO intake. A similar reasoning, but in terms of insulin sensitivity, can be applied to CF, which has a negative sign. On the other hand, IOB and BW coefficients present positive and negative signs, respectively, which are the opposite to those expected from a physiological interpretation of these variables. This result is probably due to the presence of multicollinearity among features (as reported in Section V-A) .

2) LASSO: the LASSO equation identified is reported in eq. (7). Note that variables CF, I_b and IOB were discarded during the LASSO training procedure, by adopting the automatic selection feature offered by this methodology.This result was expected, since correlation analysis had revealed a high correlation between these features and CR, BW, and ΔG, respectively. Note also that the CR, BW and ΔG coefficients had changed in (absolute) magnitude when compared to those of the MLR model. The CR coefficient, in particular, has increased, whereas the BW and ΔG coefficients have decreased, as well as the Gc coefficient.

3) LASSO$_Q$: the final LASSO$_Q$ equation is reported in eq. (8). Note that, by adding the quadratic terms, only the most relevant first-order features (CR, ΔG, CHO, MIB_{SF}) were selected in the training procedure, while BW, Gt and Gc appear within the model only with a quadratic contribution.

4) LASSO$_{QI}$: the LASSO$_{QI}$ equation identified on the training set is reported in eq. (9). More specifically, augmenting the inputs with both quadratic and interaction terms leads to the elimination of all the first-order terms, thus lending more importance to the interaction and quadratic terms. In particular, the highest coefficient is related to (G_t,MIB_{SF}) interaction, followed by (G_t, ΔG), while the other coefficients are very close to zero.

Remark: note that the three LASSO models were trained on three different feature sets. The value of λ was chosen, for all the models, by searching, exhaustively, among 200 equally-spaced values ranging between 0.001 and 10 and by selecting the value that maximized the R^2 in a 5-fold cross validation ($\lambda = 0.05$).

C. Error in Estimating MIB_{OPT}

The aim of this first evaluation, carried out on the simulated test set, was to assess and quantify whether the models developed would be able to estimate MIB_{OPT} more accurately than SF, BU, SC, and ZI. Table II reports the results obtained in terms of RMSE and R^2. Models MLR, LASSO, LASSO$_Q$ and LASSO$_{QI}$ estimate the optimal insulin bolus more accurately when compared with the other methods. Specifically, RMSE is 1.45 U for SF, 1.36–1.44 U for the literature models, and 0.84–0.87 U for the new models, with the best result achieved by LASSO$_{QI}$ (RMSE = 0.84 U).

The R^2 metric also improved with the new models (R^2 = 0.91–0.92), achieving the highest value with LASSO$_{QI}$ (R^2 = 0.92) when compared with SF (R^2 = 0.82) and with the methods described in the literature (R^2 = 0.84–0.85). Note too, that BU, SC and ZI also slightly improved their performances when compared with SF, but both lower RMSE and higher R^2 values were obtained with the proposed new models.

D. Assessment of Glycemic Control

MLR and LASSO models were also compared against SF, BU, SC and ZI in terms of glycemic outcome. BGRI, T_{Hyper}, T_{Hypo},

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TABLE II
COMPARISON OF METRICS FOR PREDICTION ACCURACY AND GOODNESS OF FIT EVALUATION. VALUES RELATED TO SF, STATE-OF-ART METHODS AND THE MODELS PROPOSED ARE REPORTED

Metric	SF	BU	SC	ZI	MLR	LASSO	LASSO_Q	LASSO_{QI}
$RMSE$ U	1.45	1.44	1.36	1.44	0.87	0.87	0.86	0.84
R^2	0.82	0.84	0.85	0.85	0.91	0.91	0.91	0.92

TABLE III
COMPARISON OF METRICS ASSESSING GLYCEMIC CONTROL FOR SF, STATE-OF-THE-ART METHODOLOGIES AND THE MODELS PROPOSED. METRICS RELATED TO MIB_{OPT} ARE REPORTED AS REFERENCE VALUES. MEDIAN AND INTERQUARTILE RANGE ARE REPORTED FOR BGRI, T_{Hypo}, T_{Hyper}

Metric	MIB_{OPT}	SF	MLR	LASSO	LASSO_Q	LASSO_{QI}	BU	SC	ZI
BGRI	8.23 (3.97-14.03)	9.93 (4.85-17.46)	9.10* (4.68-15.50)	9.09* (4.67-15.45)	9.08* (4.68-15.43)	8.97* (4.59-15.31)	9.53 (4.67-17.34)	9.72 (4.74-17.28)	9.68 (4.69-17.76)
T_{Hypo} %	0.00 (0.00-0.00)	0.00 (0.00-28.53)	0.00* (0.00-14.68)	0.00* (0.00-13.99)	0.00* (0.00-13.57)	0.00* (0.00-10.25)	0.00 (0.00-28.81)	0.00 (0.00-28.25)	0.00 (0.00-28.81)
T_{Hyper} %	29.92 (12.19-39.34)	29.09 (13.30-37.95)	29.92 (12.19-39.06)	29.92 (11.91-39.06)	29.92 (11.90-39.34)	30.19 (11.63-39.34)	29.09 (13.60-37.67)	29.09 (13.30-37.81)	29.36 (14.13-37.95)
I_{Hypo}%	24.24	44.41	36.28	36.15	35.93	33.87	44.93	44.60	45.01

[1] *Statistically significant compared to SF with p-value < 0.0071 (Bonferroni-corrected threshold).

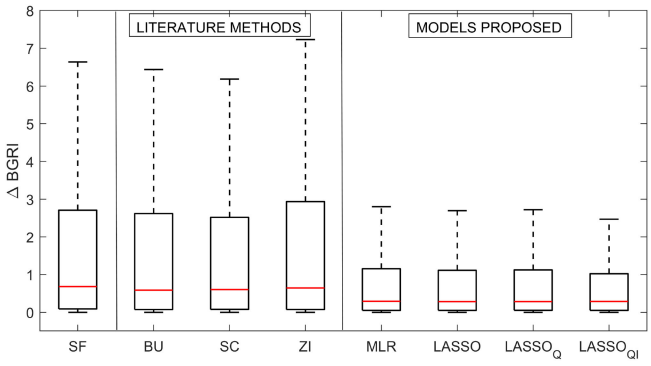

Fig. 2. Distribution of the difference between BGRI of SF, MLR, LASSO, LASSO_Q, LASSO_{QI}, BU, SC, ZI methods versus MIB_{OPT}.

and I_{Hypo} were computed. The results obtained are reported in Table III. When considering BGRI, SF revealed the highest median risk (9.93) with regard to all the other methods, followed by BU, SC and ZI which showed a median BGRI of 9.53, 9.72 and 9.68 respectively. The lowest median BGRI values were obtained by LASSO_Q (9.08) and LASSO_{QI} (8.97), both of which were close to the BGRI value that was obtained using MIB_{OPT} (8.23). Fig. 2 shows the distributions of difference in BGRI (ΔBGRI) between each of the MIB calculation methods and MIB_{OPT}. Since the optimal insulin bolus minimizes the BGRI function, the ΔBGRI distributions are in the positive half-plane. Note that the BGRI distributions of our models are closer to that of MIB_{OPT} (lower ΔBGRI values) compared to the other methodologies.

As regards hypoglycemia, median T_{Hypo} values proved not to be informative as they were equal to 0 for all methods. On the other hand, considering the 75th percentile of T_{Hypo}, together with the I_{Hypo} values, it could be stated that the magnitude and occurrence of hypoglycemic events is considerably reduced for the models proposed when compared to SF, BU, SC and ZI. The 75^{th} percentile of T_{Hypo} in particular, decreases from about 28% with SF, BU, SC and ZI to a value between 10.25% and 14.68% obtained with the new models. In addition, also I_{Hypo} is reduced, from about 44% of SF and literature methods to a value ranging between 36.28–33.87% for the models proposed. Best results were achieved by LASSO_{QI} (75^{th} percentile of T_{Hypo} equal to 10.25% and $\text{I}_{Hypo} = 33.87\%$). The improvement in terms of BGRI and T_{Hypo} given by MLR, LASSO, LASSO_Q and LASSO_{QI} is statistically significant (p-value < 0.0071) when compared to SF. Regarding hyperglycemia, the median T_{Hyper} values slightly increased for all new models when compared with the existing methods. This result was expected since BGRI, which is the cost function minimized to compute MIB_{OPT}, assigns a higher risk to hypoglycemia than it does to hyperglycemia, thus resulting in higher T_{Hyper} values for MIB_{OPT} (and, consequently, also for the models proposed, which target MIB_{OPT}) when compared to the methodologies proposed in the literature. However, the T_{Hyper} increase is moderate and is not statistically significant when compared with SF. Moreover, it does not negatively affect overall glycemic control in terms of BGRI. The only new model that increases median T_{Hyper} when compared with MIB_{OPT} is the LASSO_{QI} model. In conclusion, amongst all developed new models, we have selected LASSO_Q as the final model, because it permits the greatest reduction of BGRI and THypo when compared with the existing methods and does not increase median T_{Hyper} when compared with MIB_{OPT}. Fig. 3 shows two representative postprandial BG curves, after administration of MIB, computed through LASSO_Q, MIB_{OPT} and the existing methods. Note that only LASSO_Q has been considered for reasons of better visualization, since it is the final, selected model in this study. As shown in the upper panel, SF, BU and SC all induce hypoglycemia, while LASSO_Q and ZI permit proper glycemic control, approaching that of MIB_{OPT}, and, despite the initial hyperglycemia that was mainly due to the meal, and to high pre-prandial BG. The lower panel shows the occurrence of hyperglycemic events after the application of SF, BU, ZI and SC methodologies, while LASSO_Q permitted optimal glycemic control.

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TABLE IV

COMPARISON OF METRICS OBTAINED FROM SCENARIO A, FOR SF, STATE-OF-THE-ART METHODOLOGIES AND LASSO$_Q$. MEDIAN AND INTERQUARTILE RANGE ARE REPORTED FOR T_{Hypo}, T_{Hyper}, MEAN AND STANDARD DEVIATION FOR T_{Target}

Metric	Original bolus	LASSO$_Q$	SF	BU	SC	ZI
T_{Hypo} %	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
T_{Hyper} %	41.67 (20.83-62.50)	38.54 (20.83-70.83)	41.67 (22.92-70.83)	39.58 (20.83-13)	40.63 (20.83-66.67)	39.58 (18.75-62.50)
T_{Target} %	54.72 ($\pm$ 27.11)	54.45 ($\pm$ 27.88)	53.05 ($\pm$ 27.87)	54.47 ($\pm$ 28.08)	54.15 ($\pm$ 27.73)	54.47 ($\pm$ 28.07)

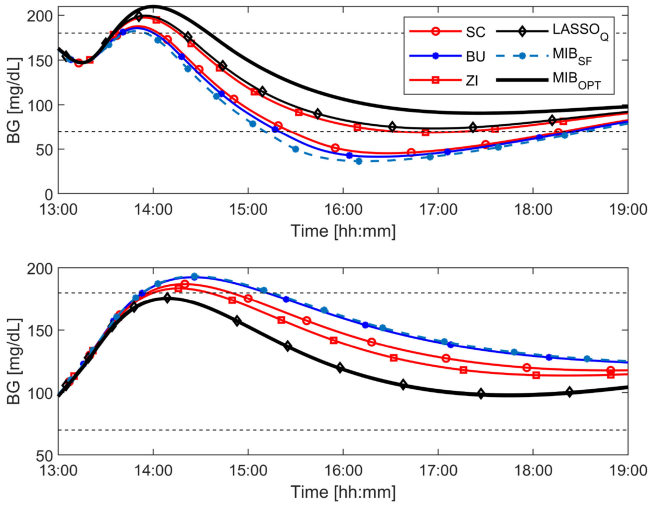

Fig. 3. Representative examples of BG curves during postprandial time window for different methods of insulin bolus computation and different mealtime conditions. For a better visualization, only LASSO$_Q$ among the models proposed is reported. In the upper panel, mealtime ΔG is negative (-1.5 mg/dL/min), starting BG $= 160$ mg/dL and meal CHO is 60 g. The calculated MIB doses are MIB$_{OPT} = 1.89$ U, MIB$_{SF} = 3.62$ U, MIB$_{LASSO_Q} = 1.94$ U, MIB$_{BU} = 3.26$ U, MIB$_{SC} = 3.02$ U, MIB$_{ZI} = 2.12$ U. In the lower panel, mealtime ΔG is positive (1.5 mg/dL/min), starting BG $= 100$ mg/dL and meal CHO is 30 g. The MIB doses are MIB$_{OPT} = 2.80$ U, MIB$_{SF} = 0.72$ U, MIB$_{LASSO_Q} = 2.74$ U, MIB$_{BU} = 0.79$ U, MIB$_{SC} = 1.34$ U, MIB$_{ZI} = 1.71$ U. Dashed lines indicate the euglycemic range.

VI. REAL DATA: ASSESSMENT CRITERIA

Assessing the impact of LASSO$_Q$ on already acquired glucose traces is important since such data cannot be manipulated. To overcome this limitation, we decided to resort to a model-based strategy. This approach consisted of two main steps: first, a state-of-the-art composite physiological model of glucose-insulin dynamics [29] was fitted on each meal-portion datum; second, the model was used to simulate glucose concentration during the meal by replacing the real injected insulin bolus with the insulin dose provided by LASSO$_Q$.

Briefly, the physiological model of choice uses the glucose-insulin minimal model proposed by Bergman *et al.* [30] as the core to describe both the effect of the insulin action and the glucose rate of appearance on plasma glucose dynamics through time. However, since neither the insulin action or the glucose rate of appearance are usually available (as in our case), the model has been expanded with the models of Schiavon *et al.* [31] and Dalla Man *et al.* [32], which allow the final, composite model to take, as inputs, (available) exogenous insulin infusion and meal carbohydrate intakes.

Since the objective was to describe the effect of carbohydrate intakes and insulin bolus on glucose concentration, the physiological model was identified separately for each of the 218 traces by adopting the Bayesian framework, described in [29], which makes it possible to, effectively, circumvent any undesired non-identifiability issues and, also, provides point estimates of unknown model parameters by exploiting a Markov-Chain Monte Carlo strategy. Other details regarding both the physiological model and its identification procedure can be found in [29]. Consequently, we obtained 218 different parameter sets (PS), one for each trace. We then analyzed, trace-by-trace, the results obtained from this identification procedure. In particular, we decided to discard those traces whose pre-prandial BG value was outside the euglycemic range from the final evaluation for two main reasons: i) they do not belong to our bolus calculator domain of validity, since it was trained only on glucose traces with this initial condition; ii) we observed that glucose traces with pre-prandial BG concentrations outside the euglycemic range resulted in model parameters which were not physiologically plausible. Therefore, the resulting dataset is composed of 129 glycemic traces, 110 in scenario A and 19 in scenario B.

Then, in order to quantify, for each of the 129 traces, the glycemic outcomes resulting from the use of LASSO$_Q$, we set up a 4-hour long scenario where we simulated the corresponding trace 5 times using the real insulin dose input and the doses computed with LASSO$_Q$, BU, SC, ZI and SF respectively. For each simulation, we quantified glycemic control in terms of T_{Hypo}, T_{Hyper}, and in percentage time within glucose target range (T_{Target}).

VII. REAL DATA: RESULTS

The performance of LASSO$_Q$ model was assessed separately on scenario A and the scenario B (see Section II for the division). The times in each glycemic range are reported either as mean ($\pm$standard deviation) for Gaussian distributed metrics and median [interquartile range] otherwise. For this purpose, the non-Gaussian nature of each distribution was checked using Lilliefors test with a 1% confidence level. The resulting metrics are reported in Table IV for scenario A, and Table V for scenario B.

In order to compare the results obtained through the adoption of LASSO$_Q$ in scenario A versus the other methods considered, we reduced T_{Hyper} while maintaining comparable results in terms of T_{Target} and /but without inducing hypoglycemia. However, in scenario B, LASSO$_Q$ considerably increased T_{Target}

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TABLE V
COMPARISON OF METRICS OBTAINED FROM SCENARIO B, FOR SF, STATE-OF-THE-ART METHODOLOGIES AND $LASSO_Q$. MEDIAN AND INTERQUARTILE RANGE ARE REPORTED FOR T_{Hypo}, T_{Hyper}, MEAN AND STANDARD DEVIATION FOR T_{Target}

Metric	Original bolus	$LASSO_Q$	SF	BU	SC	ZI
T_{Hypo} %	28.83 (15.10-39.98)	20.83 (10.94-29.17)	27.08 (12.50-44.27)	25.00 (12.50-44.27)	22.92 (12.50-44.27)	22.92 (9.38-44.27)
T_{Hyper} %	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-9.38)	0.00 (0.00-9.38)	0.00 (0.00-9.38)	0.00 (0.00-9.38)
T_{Target} %	69.74 (± 19.19)	72.26 (± 20.55)	67.76 (± 22.10)	67.65 (± 22.15)	67.76 (± 22.10)	67.21 (± 22.47)

but reduced T_{Hypo}. Indeed, while the $LASSO_Q$ median value of 20.83% was equal to the value obtained with the administered bolus, both the 25^th and the 75^th percentiles were about 5% lower. This same result was also observed when $LASSO_Q$ was compared with the other methods considered. In conclusion, the application of the proposed $LASSO_Q$ model to the real data supports the positive results obtained *in silico*.

VIII. CONCLUSION

By adopting machine learning techniques, we developed four models for MIB calculation, with the aim of improving the SF traditionally used for insulin dosage and, hence, improving the quality of glycemic control. A comparison was performed using three state-of-the-art methods described in the literature (BU, SC and ZI) which have the same objective. We assessed the performance of these models by evaluating the goodness-of-fit (RMSE, R^2), by quantifying each model ability to approximate the optimal insulin dose (MIB_{OPT}), and then compared them with commonly adopted glycemic control indices (T_{Hypo}, T_{Hyper}, BGRI and I_{Hypo}). We found that the improvements offered by the new models were significant when compared with SF, BU, SC and ZI. The *in silico* test also showed that $LASSO_Q$ and $LASSO_{QI}$ performed better than MLR and LASSO models, being able to better approach the MIB_{OPT} thanks to the addition of quadratic and interaction terms between the features as input variables. In particular, $LASSO_Q$ and $LASSO_{QI}$ reduced hypoglycemia duration and incidence, indeed, the 75^{th} percentile of T_{Hypo} was halved with the two models, and, furthermore, I_{Hypo} decreased when compared with both SF and the state-of-the-art methods. This latter result suggests that the models proposed could result in a safer glycemic control. However, $LASSO_{QI}$ did slightly increase T_{Hyper} compared to MIB_{OPT}. For this reason, we selected $LASSO_Q$ as our final model, as it offered the best compromise for reducing hypoglycemia without increasing hyperglycemia. Positive results, obtained through simulations, were confirmed by retrospective analysis on real data. Indeed, the application of $LASSO_Q$ provided a reduced T_{Hyper} value in meals with postprandial hyperglycemia (scenario A) and a lower T_{Hypo} in meals with postprandial hypoglycemia (scenario B).

To conclude, this work suggests that information on BG dynamics at mealtime are the key to reduce the risk of hypo/hyperglycemia after the meal. Future developments will include further investigations of the new model within a multi-meal scenario [33], including additional error sources, such as errors in patient behavior [34], carbohydrates miscalculations [35] and sensor readings [36], [37].

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