A Genetic Programming-based Regression for Extrapolating a Blood Glucose-Dynamics Model from Interstitial Glucose Measurements and their First Derivatives

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Abstract

This paper illustrates the development and the applicability of an Evolutionary Computation approach to enhance the treatment of Type-1 diabetic patients that necessitate insulin injections. In fact, being such a disease associated to a malfunctioning pancreas that generates an insufficient amount of insulin, a way to enhance the quality of life of these patients is to implement an artificial pancreas able to artificially regulate the insulin dosage. This work aims at extrapolating a regression model, capable of estimating the blood glucose (BG) through interstitial glucose (IG) measurements and their first derivative. Such an approach represents a viable preliminary stage in building the basic component of this artificial pancreas. In particular, considered the high complexity of the reciprocal interactions, an evolutionary-based

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strategy is outlined to extrapolate a mathematical relationship between BG and IG and its derivative. The investigation is carried out about the accuracy of personalized models and of a global relationship model for all of the subjects under examination. The discovered models are assessed through a comparison with other models during the experiments on personalized and global data.

Keywords:
Blood glucose estimation, Interstitial glucose, Regression models, Genetic Programming.

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1. Introduction

Diabetes mellitus (DM) is a metabolic life-long disease characterized by inadequate control of blood glucose concentration in the body that induces a high (hyperglycemia) or a low (hypoglycemia) blood glucose (BG) level over a prolonged period. The glucose amount in the blood is regulated primarily by two hormones produced by the pancreas, i.e, insulin and glucagon, that indirectly affect the blood glucose concentration by lowering it (insulin) or by increasing it (glucagon). Insulin is essential for the conversion of glucose into energy utilized by cells after a food intake when there is an increase in glucose concentration. In absence of insulin, increased concentration of glucose in blood and interstitial fluid, if left untreated, can entail complications, such as the damage and the eventual failure of certain parts of multiple organs or even graver side effects like an increased risk of cardiac heart dysfunctions and failures, and stroke [1, 2, 3]. Instead the glucagon and hepatic production of glucose prevent the glucose concentration from decreasing substantially between meals or during the sleep. The control of this concentration allows avoiding complications as headache, hunger, difficulty in sleeping or more serious consequences like loss of consciousness, seizure and even coma. All these medical problems have a substantial impact on quality and on expectancy of life.

Diabetes is a worldwide growing phenomenon [4]. Since there is currently no cure, such a disease requires daily care and it is extremely important that the patients learn to effectively manage this condition to enhance their quality of life. Diabetic patients must be informed about the disease, instructed towards an appropriate diet, new hygiene habits, and taught about devised therapy and available medical devices, and drugs.

The diabetes is categorized in three major types: Type 1, Type 2 and gestational diabetes. With DM Type 1, there is a complete lack of insulin as pancreas fails to generate it. With DM Type 2, patient presents an insulin resistance as cells necessitate an increment in insulin to operate appropriately. With gestational diabetes, insulin resistance is coupled with an insulin secretory defect. The insulin secretion is too low to comply with the increased requests activated by the insulin resistance.

Within this paper the focus is on Type-1 DM or insulin-dependent diabetes, characterized by an autoimmune destruction of the insulin produced by the pancreatic β-cells. The patients affected by such a chronic disorder are subject to a progressive insulin deficiency and a resultant hyperglycemia, and are totally dependent on an external injection of insulin to regulate their blood-glucose concentration. This regulation is one of the most challenging control problems to tackle in biomedical engineering. Hence, a methodology able to attain to attain a BG estimation as precise as possible assumes a very crucial role to establish the appropriate rate of insulin to infuse.

Proper treatments to control the blood concentration and prevent the complications associated to high BG levels last for many years and the related social costs are very high.

Several invasive estimation devices are present on the market that take BG measures in intervals that range from about 15 minutes to a couple of hours with no measurements taken during the night. Patients are reluctant to be subject to this continuous invasive BG control because of the related pain. Hence, it can become difficult to suitably take care of the sick persons. For such a reason, we need a methodology that obtains continuous BG estimations by using minimally invasive devices. This possibility is offered by the minimally invasive Continuous Glucose Monitoring System (CGMS) devices that in a simpler way measure the IG, i.e., the glucose in the subcutaneous tissue [5].

CGMS are portable devices capable of measuring glycemic levels indirectly from the interstitial space almost continuously for several days with a prefixed frequency. However, CGM sensors are affected by distortion due to the glucose diffusion process across capillary wall between blood and interstitial fluid, and by the time-by-time-varying systematic under/over-estimations due to calibrations, sensor drifts and measurement noise [6, 7]. Most of these devices need to be calibrated - to convert the measured electric current to glucose level. Patient has to calibrate at least two times a day, when BG and IG are steady. At this time, both levels can be considered as equal and thus

CGMS knows what quantity of electric current equals BG. Despite the fact that more and more accurate devices are explored [8, 9], errors in sensors calibration cause the measure inaccuracy of CGMS with respect to BG.

Although IG is not reckoned as a perfect BG indicator, nevertheless it is the only system that permits large number of continuous and non-invasive measurements a day. However, the complexity of the relationship between glucose dynamics in BG and IG is far too complex to be acquired by the calibration algorithms relying on simple linear regression techniques implemented in current CGMS devices [10, 11]. In fact, CGMS is a low-power device that implies low computational capacities and this invalidates the accuracy of the measurements.

Considered that BG and IG can be significantly different due to physiological reasons, the availability of a large amount of IG measures is highly advisable to acquire as much as possible of the BG-to-IG dynamics. In fact, significant progresses with CGMS and insulin pumps have allowed CGMS data to be utilized to regulate insulin delivery [12].

Several analytical models have been suggested attempting to infer a mathematical relationship of IG and BG, as shown in Sect. 2. All these models represent a basic step to design and implement an *artificial pancreas* (AP) [13], i.e., an artificial device capable of automatically regulating insulin injections according to the patients' needs so to ensure them a satisfactory quality of life. This device must be capable of performing a glycemic control by estimating BG values through the analysis of the IG signal. Reliable prediction based on IG only is still beyond the reach since current algorithms are based on supplemental, defective information such as an assessment of carbohydrate intake by the patient.

The paper is a revised and extended version of a conference paper [14]. In particular, a more thorough review of the related works and additional experimentations are included. The aim is to discover a law able to estimate BG values by using IG measurements and their derivative. This law could be the core of the knowledge base of an AP. These estimation problems are known as *regression problems*. Considered the complexity of inducing an analytical model, we leverage the ability of the Genetic Programming (GP) [15] in tackling regression problems [16] to detect an efficient approximation of the relationship between BG and IG values and their first derivative. The experimental phase is carried out over a real-world database including both BG and IG measures for several Type-1 diabetic subjects.

The paper is organized as follows. In Sect. 2 a review of the relevant re-

lated work is given. Section 3 describes the proposed genetic-based approach. A discussion and a comparison with other models on the results attained on personalized and global data is shown in Sect. 4. Conclusions and future work are exposed in Sect. 5.

2. Related research

Numerous mathematical, statistical and analytical models focused on different aspects of diabetes, ranging from molecular and cellular biology, to clinical science and to health service research have been developed. Several of these modeling approaches aimed at discovering a reciprocal relationship between BG and IG values.

The first, and most widely used, model striving to correlate BG and IG was devised by Steil and Rebrin (SR) in 1999 [17]. It is represented by the following equation:

$$b(t) = \frac{\tau}{g} \cdot \frac{di(t)}{dt} + \frac{1}{g} \cdot i(t) \tag{1}$$

where $b(t)$ and $i(t)$ are the BG and the IG at time t, and the parameters g and τ represent the steady-state gain and the IG equilibration time constant, respectively. An important task is the estimation of the best possible values for g and τ so to enhance the model precision.

Hovorka et al. [18] developed a nonlinear predictive model to preserve normoglycemic Type-1 diabetic patients during fasting conditions such as during overnight fast. The controller employs Bayesian parameter estimation to find time-varying model parameters. The predictive capabilities of the model have been assessed using data from clinical trials for Type 1 diabetic subjects.

Makroglou et al. [19] outlined an overview of several mathematical models in literature aimed at describing the glucose-insulin regulatory system with reference to DM. These models ranged from ordinary differential equations to partial differential equations, to delay differential equations to the integro-differential ones.

Dua et al. [20] presented a model-based control technique for regulating the blood glucose level for Type-1 DM patients. The optimal insulin delivery rate is attained off-line as an explicit function of the current blood glucose concentration of the patient by using parametric programming algorithms.

Kildegaard et al. [21] proposed a physiological model relying on an insulin, a meal and a glucose metabolism model coupled with a Monte Carlo

simulation to predict blood glucose values of diabetic people. Simulations displayed how the variance coefficient for the different model compartments changes over time. For diabetic people the inaccuracies of blood glucose meters and carbohydrate estimates contribute to more than half of the variance. Therefore, the blood glucose prediction is strictly influenced by the inaccuracy in the input variables and by the metabolic oscillations so that an effective prediction model was very arduous to derive.

Facchinetti et al. [22] investigated the reconstruction of plasma glucose from interstitial glucose taken through CGM sensors. Six diabetic volunteers were monitored for two days using a minimally invasive device that returns interstitial glucose concentration on the basis of an initial calibration procedure. At the same time, plasma glucose concentration was also measured every 15 minutes. A nonparametric regularization deconvolution method was used to reconstruct blood values from IG. The findings proved that the quality of the reconstruction was unsatisfactory. Only after a recalibration procedure the relative error in reconstructing blood glucose was significantly reduced.

Leal et al. [23] monitored 18 patients for three days, and extracted the relationship between the IG measured by CGMS and BG by employing an autoregressive model. This resulted in 98.5% of the points being in A and B zones of the Clarke error grid analysis [24].

Peréz-Gandía [25] harnessed an artificial neural network for the prediction of the blood glucose concentration. The network received as inputs the CGM sensor measurements during the preceding 20 minutes and returned as output the prediction of glucose concentration at the selected prediction horizon time. The tool accuracy was estimated by using the root mean square error and the prediction delay.

Koutny [26] suggested a method to assess the BG-to-IG delay based on the hypothesis that the change in the blood glucose level contains information about the estimated rate with which the hypothalamus expects the blood glucose level to return to its normal range. The same author advanced a model of glucose dynamics that allows IG prediction [27]. By accounting the delay, it was possible to relate the present BG and IG to future IG through coefficients of the proposed model of glucose dynamics. An improvement in the devised model of glucose dynamics to reduce its calculation error, especially with rapid changes of BG and IG, e.g., due to short-action insulin, is proposed in [28]. This model is based on biological considerations, as for example the importance of capillaries and the fact that capillaries in differ-

ent compartments have different permeabilities. Through the recommended model tested on hyperglycemic-clamp data, he succeeded in achieving an improved model to calculate the BG levels.

Del Favero et al. [29] investigated a new model that attempts to improve that by Steil and Rebrin. Substatially, they reckoned that the value of g is equal to 1, and added a way to calibrate the model so that a true IG can be restored.

All the above analytic models present the optimization problem of estimating several parameters. This estimation is usually carried out by exploiting mathematical, biological or physiological considerations, or also by performing an a-posteriori manual tuning. However, despite the lavished efforts, an imbalance still remains between the current knowledge attained from experimental approaches and their modeling. To overcome this problem, it is important to revisit the progress made so far toward diabetes modeling.

In the last years some attempts based on evolutionary algorithms have been performed for deriving diabetes modeling by using as inputs the values measured by a GCMS as well as also previous and estimated future carbohydrate intakes and insulin injections [13]. Moreover, there has been an increased interest in the development and application of methods relying on artificial intelligence as decision support systems in diabetes management and knowledge acquisition [30].

Evolutionary techniques have been also used for automatically excerpting the parameter estimation of diabetes modeling. Koutny [31] combined the analytic method proposed in [28] with meta-Differential Evolution. Namely, starting from a continuously measured level of IG for human Type-1 diabetic patients, he computed a continuous BG level. Six different scenarios were employed to guarantee robust validation of the calculation, and a Differential Evolution (DE) [32] was used to evaluate the parameters for the model in all the scenarios. All the six scenarios, even the simplest ones, presented better performance than CGMS in estimating BG values.

De Falco et al. [33, 34] proposed evolutionary-based tools to estimate the BG values harnessing the easily available IG values. Relationships under the form of explicit mathematical expressions were extracted. The experimentation was carried out on a real-world database containing Type-1 diabetic subjects. The comparison against state-of-the-art models stated the effectiveness of the suggested evolutionary approaches. By considering lessons learned in [35], De Falco et al. [36] investigated the ability of evolutionary-based algorithms in finding relationships between IG and BG values for telemedicine

purposes. The paper represents a precursory steps towards the deployment of a web portal aimed at helping people suffering from diabetes by allowing a remote BG estimation.

3. The proposed approach

A GP-based approach for estimating BG levels in diabetic patients, starting from their IG measurements and their corresponding first derivatives is devised for solving such a *symbolic regression* problem.

The proposed approach relies on the structure of the SR model, that is the first and most widely used model trying to relate BG with IG and IG derivative [17]. Nevertheless, there exist situations in which the SR model does not precisely hold, for example in case of rapid changes in BG and IG [28]. Thus, the approach aims at improving the SR model by covering the situations where this latter is not effective. The procedure can be summarized in the following three steps:

1. enrichment of patients' databases;
2. computation of IG first derivative;
3. extraction of the model through GP.

The first step is optional and consists of either a single or a two-level enrichment. The second step calculates the discrete derivatives for the IG measurements. As regards the third step, the genetic approach is employed for extracting patient-oriented models customized on each diabetic subject and general models by unifying the patients' data series.

3.1. Database enrichment

The database enrichment is needed when a database of a diabetic subject collects many IG values measured every few minutes through CGMS but only a few BG measurements taken only a few times per day with glucometers. This situation could be a problem in calculating the IG derivative, depending on the time interval between two consecutive IG measures, and extracting an effective relationship between BG, IG and IG derivative. An enrichment can be performed by estimating the missing BG values by means of the SR model with the parameters optimized through DE [34]. In the following, this model is referred as $\mathrm{SR}_{\mathrm{opt}}$. Thus, the enriched database consists of the original IGs with all the corresponding BGs. These BG values comprehend the truly measured BG values and the larger number of estimated BG values.

Obviously, this enrichment introduces a bias in the dataset as it estimates the missing BGs through SR_{opt}. For this reason, this step is optional and can be omitted if the original database contains a sufficient number of BG measurements.

A further enlargement of the database can be attained by performing a second enrichment before calculating the derivatives, so that these latter are smaller and more precise. This necessity could arise by considering that rapid variations in glucose levels in few minutes intervals can lead to excessively high derivative. Thus, after the first enhancement with SR_{opt}, IG and BG data points are linearly interpolated to have their values in smaller time intervals. The values corresponding to this interval are used to compute the derivatives. Also this second enrichment introduces a bias, as it assumes that IG and BG values change linearly over time. For this reason, this step can be avoided if the database includes a sufficient number of BG and IG values with consecutive IG points that do not excessively differ each other.

3.2. Derivatives computation

The second step basically calculates the discrete derivatives for the IG measurements. To have accurate derivatives, the concentration gradient is applied as derivative to IG values for each instant t [37]:

$$\frac{di(t)}{dt} \simeq \frac{i(t+\Delta t) - i(t-\Delta t)}{2\Delta t},$$

where Δt is the time interval between two consecutive IG measures. If the single-level enrichment with SR_{opt} is performed, the IG derivatives are equal to those that are computed without the enrichment, as this latter only estimates the missing BG values and does not influence the IG ones. Instead, if also the enrichment with interpolation is employed, the IG derivatives are different from those that are evaluated without the enrichment, as this latter interpolates both IG and BG values. This obviously makes the derivatives smaller with respect to the ones calculated without interpolation, but also introduces a bias because it assumes that IG and BG vary linearly over time.

3.3. Model extraction

The solution of a regression problem consists in finding the model that expresses the relationship between a dependent variable and one or more independent variables. An exhaustive enumeration of all the possible models is impracticable due to the considerable amount of time requested to explore

the complete search space. Hence, it is natural to dedicate our attention to evolutionary models, such as GP, that, despite not assuring the achievement of the best model, represent a viable way to discover an appropriate suboptimal solution in a reasonable amount of time.

Specifically, the third step basically concerns the application of GP to the (enriched or not) data series in order to find the explicit expression of the BG level at time t, i.e. $b(t)$, as a function of the two independent variables IG and its derivative at the same time, i.e., $i(t)$ and $\frac{di(t)}{dt}$, respectively.

GP operates on a space of potential solutions, called *individuals*, of the problem under investigation. These solutions consist of randomly generated computer programs represented as tree structures. The inner nodes in any individual denote primitive functions, while the leaf nodes comprehend terminals, i.e., either variables of the problem or constant values. During the evolution, the set of these programs, i.e., the *population*, is iteratively transformed into a new population by applying genetic operators to current individual(s) probabilistically selected with the aim to improve their *fitness function* Φ. Such a fitness explicitly or implicitly measures the quality of the individuals. This evolution terminates when a fixed maximum number of generations g_{max} is obtained. For a detailed description of the genetic operators employed during the evolution, namely selection, mutation, crossover and copy, the interested reader can refer to [15].

For the regression problem tackled within this paper, the population will be composed by a set of regression models. Each model is encoded as a 'formula', represented as a tree whose nodes can entail either functions or terminals.

The set of terminals consists of the set of the independent variables of the problem, plus the symbol that indicates a constant value. This latter is always used in relation to a problem variable, and its value is randomly selected in a range according to the specific involved variable.

To numerically assess the quality of each regression model S attained during the GP execution, we have used as base fitness function the Root Mean Square Error ($RMSE$), i.e:

$$RMSE(S) = \sqrt{\frac{\sum_{i=1}^{n}(b_{comp}(i) - b(i))^2}{n}} \tag{2}$$

where $b_{comp}(i)$ represents the calculated value for the i–th item of the database by the current model S, whereas $b(i)$ is the value of the dependent variable

BG for the same i–th item and n is the total number of BG values collected in the database. With this choice the regression problem becomes a minimization problem.

The model extraction can regard a specific subject or a general law as described in the sections below.

3.3.1. Patient-oriented approach

The patient-oriented approach concerns the model extraction for a specific patient and utilizes only the subject's data series. Depending on whether or not the used dataset has been previously enriched, we can distinguish two situations for the fitness expression, described in the next paragraphs.

Fitness for the original dataset. In this case the database enrichment is not performed, the truly measured BG values are employed for the evaluation of the fitness function by eq. (2).

Fitness for the enriched dataset. When the database enrichment is carried out, to avoid a bias towards the BG values estimated with $\mathrm{SR}_{\mathrm{opt}}$ in the model extraction, a fitness function with a correction factor p_m has been devised. Specifically, the fitness is a weighted sum of two sub-fitness functions, i.e., $RMSE_c$ and $RMSE_m$:

$$\Phi = p_m \cdot RMSE_c + (1 - p_m) \cdot C \cdot RMSE_m \tag{3}$$

where $RMSE_c$ is the error estimated on the computed BG values, while $RMSE_m$ is the error evaluated on the measured BG values. The correction factor is given by $p_m = \frac{n_m}{n_t}$, where n_m is the number of the measured values and n_t is the total number of values (computed and measured ones) in the dataset. The constant C is an additional correction coefficient and can be tuned according to the proportions between the measured and the estimated BG values. The choice for the correction factors p_m and C in eq. (3) is due to the fact that the number of measured BG values is very small with respect to the number of estimated values. Therefore, as $RMSE_c$ weights much more than $RMSE_m$, to avoid a bias towards the BGs estimated by $\mathrm{SR}_{\mathrm{opt}}$, the correction factors are inversely proportional to the weights of their respective sub-fitness functions.

3.3.2. General approach

The general approach unifies all the patients' datasets in a unique database used to extract a relationship between $b(t)$ and the depending variables $i(t)$

and $\frac{di(t)}{dt}$. Two kinds of global fitness functions are proposed: an overall fitness and a mean one, both described in the next paragraphs. The expression of these fitness functions takes into account the fact that the database has not been enriched as it contains a sufficient number of truly measured BG values.

Fitness as an overall RMSE. As the database has not been previously enriched, the global fitness coincides with the RMSE (eq. (2)) computed on all the patients. This kind of fitness treats each data point as contributing equally to the function.

Fitness as a mean of patients' fitnesses. Another possible expression for the global fitness function is a weighted mean, i.e.:

$$\Phi = \frac{\sum_k^P w_k \cdot \Phi_k}{\sum_k^P w_k} \tag{4}$$

where Φ_k and w_k are the fitness and the weight of the k-th patient, respectively. In particular, Φ_k involves the evaluation of the RMSE according to eq. (2). Furthermore, $w_k = n_{t,k}$ is the total number of BG values in the dataset of the k-th subject while P is the total number of patients. Differently from the previous one, this approach considers the fact that patients with more data points in the dataset contribute more than others.

4. Experimental findings

4.1. The database

The real-world database, containing anonymized datasets of Type-1 diabetic patients, was received from the Diabetology Center at the Pilsen University. The original database comprises 6 different patients, their IDs being 1 to 6 respectively. Each patient comprises several time segments. A time segment is a period in which the patient were wearing a CGMS. The dataset information for each patient is shown in Table 1. In total, there are 184 time segments which include 424 BGs and 45,599 IGs. The IG values are taken with the Medtronic Minimed 640G CSIIS, equipped with an Enlite CGMS, at an interval of $\Delta t = 5$ minutes. In the experiments, the patient with ID 3 has been excluded due to sensor anomalies occurred during the data collection.

Table 1: Dataset information for each patient. The excluded patient is evidenced in italic.

Patient ID	Segments	BGs	IGs
1	9	38	3,082
2	30	76	9,410
3	*37*	*81*	*9,337*
4	32	77	8,446
5	38	76	7,662
6	38	76	7,662

4.2. GP environment and parameters

A tool executing GP and running in the MATLAB environment, i.e., GPTIPS [38], has been employed to perform all the experiments reported throughout this section. It applies a type of symbolic regression called *multigene symbolic regression* that evolves linear combinations of the transformations of the input variables.

Typically, symbolic regression is performed by using GP to evolve a population of trees each of which encodes a mathematical equation. In contrast, in multigene symbolic regression, each member of the GP population, that is a candidate solution, is a weighted linear combination of GP trees. Multigene regression GP can be more accurate and efficient than standard GP for modeling problems [39], so it is used in the proposed approach. For the GP purpose, the chosen method of initialization is the ramped half-and-half. Then, tournament selection, subtree crossover and subtree mutation are chosen as strategies for the three main genetic operations. The terminal set is given by the IG and its derivative, which are the independent variables, to find the expression of the dependent variable BG. Table 2 reports the function set used within all the experiments.

Table 2: The set of the functions along with the corresponding symbols.

Symbol	Description
+	Addition
-	Subtraction
*	Multiplication
/	Protected division (is 1 if the denominator is 0)

The resulting primitive set guarantees type consistency and evaluation safety, as all the functions are type-consistent and do not throw exceptions, while the constants are all positive numeric values. Furthermore, it also ensures sufficiency, because the primitives are capable of expressing a solution to the regression problem, as we know from the SR model. As explained in Sect. 3.3, RMSE has been used as the fitness function.

After a preliminary tuning phase, the GP control parameters have been set as showm in Table 3. The termination criterion is the reaching of either the maximum number of generations or a fitness equal to 0.003.

Table 3: Settings of the GP control parameters

Parameter	Value
Population size	500
Maximum number of generations	300
Tournament size	30
Mutation rate	0.1
Crossover rate	0.9
Copy rate	0
Maximum tree depth	4
Maximum number of tree nodes	8
Subtrees per solution	2

We have subdivided our experiments into two parts. In the former, we have used a personalized approach, so that the goal has been to find the best model for all the subjects by using the enriched dataset with interpolation as described in Sect. 3.1. The relative findings are shown and commented in Sect. 4.3. In the latter part, instead, we have aimed at finding one general model that could work well by using both the global fitness functions described in Sect. 3.3.2. To this end, we have unified the dataset of all the five subjects by using the original enriched datasets without interpolation. These last experiments are described and analyzed in Sect. 4.4.

The estimation of BG values of the enriched database is carried out by means of the DE algorithm. The strategy used is the DE/rand/1/bin [32]. The DE parameters values have been determined by a preliminary tuning as follows: the population size equal to 50, the maximum number of generations equal to 200, the scale factor and the crossover ratio equal to 0.85 and 1, respectively. The best outcome of the DE algorithm over 25 runs has furnished the ensuing values for the Steil-Rebrin parameters: $g = 0.98$ and $\tau = 0.02$. These values have been used to enrich the dataset with the missing BG values. As already explained, the truly measured BG are left unchanged.

The best resulting models of the different experiments are presented along with the tables of the relative errors with respect to the measured BG values, and the Clarke Error Grid analysis (CEG) [24] both for the personalized (patient-oriented) data and for the unified data treatment.

Throughout these experiments, the GP approach is compared with two other methodologies, namely IGBG that utilizes the BG estimation provided by the CGMS through simple regression models thus ignoring the actual BG dynamics and variations, and $\mathrm{SR}_{\mathrm{opt}}$ that is the SR model with the parameters

optimized through DE [34].

4.3. Patient-oriented models

In the patient-oriented procedure, the data of all the single patients are extracted from the original database. Due to the available original data being made up of collections of many IGs and few BGs, each patient's data series is enhanced according to the enrichments described in Sect. 3.1. In other words, the first enrichment is the computation of the missing BGs for every 5 minutes through $\mathrm{SR}_{\mathrm{opt}}$, while the second one is the linear interpolation of the IGs and enriched BGs for every minute. The derivatives are computed on the enhanced data and the GP is then carried out to discover the model.

The GP applied on this enhanced dataset with interpolation is named $\mathrm{GP}_{\mathrm{E,I}}$ (E stands for enrichment, i.e., the database enhancement through $\mathrm{SR}_{\mathrm{opt}}$, and I for the interpolation). Each patient's dataset is divided into a *training* and a *test* sets, containing the 70% and 30% of the ordered data, respectively. The training set is used for learning the model and the test set for evaluating its performance. A validation set is not taken into account due to the fact that there is a limited amount of available BG measurements. The fitness function is a weighted RMSE (eq. (3)), where the constant C is set to 10 after a preliminary tuning. For each patient, 20 runs have been performed.

Although the model extraction has been performed for all the five single patients, for the sake of conciseness, as an example in the following paragraphs we report only the model and the results for the patients with IDs 1, 4 and 6. Lastly, a discussion evaluates the obtained results.

Patient 1. The inferred model for the patient with ID 1 is the following:

$$b_{comp}(t) = 1.21 \cdot i(t) + 6.62 \cdot \frac{di(t)}{dt} - 1.21 \cdot 10^{-4} \cdot i(t)^2 \cdot \frac{di(t)}{di} - \\ -7.18 \cdot 10^{-4} \cdot i(t)^2 - 14.56 \tag{5}$$

The frequency of relative errors for this first patient is shown in Table 4. For the GP approach the 88% of the training items and the 75% of the testing items have a relative error lower than 5%. Moreover, 100% of all the items present a relative error lower than 20%. Instead, IGBG and $\mathrm{SR}_{\mathrm{opt}}$ on the training set never reach the 100% of items, while on the test set they perform better than GP only for a relative error lower than 5%.

Table 4: Frequency of relative errors for patient with ID 1 in $GP_{E,I}$, IGBG and SR_{opt}.

	$GP_{E,I}$		IGBG		SR_{opt}	
Relative error	Training	Test	Training	Test	Training	Test
< 0.05	0.88	0.75	0.72	0.83	0.85	0.92
< 0.10	0.96	1	0.84	1	0.88	1
< 0.15	0.96	1	0.88	1	0.92	1
< 0.20	1	1	0.92	1	0.96	1
< 0.25	1	1	0.96	1	0.96	1
< 0.30	1	1	0.96	1	0.96	1
< 0.35	1	1	0.96	1	0.96	1
< 0.40	1	1	0.96	1	0.96	1
< 0.45	1	1	0.96	1	0.96	1
< 0.50	1	1	0.96	1	0.96	1

Figure 1 depicts the CEGs for this patient on the entire dataset: at top-left the $GP_{E,I}$ approach, at top-right the IGBG, at the bottom the SR_{opt}. We can note that the concentrations estimated by the proposed GP fall in zone A, while the other approaches present a point between zones B and D.

Patient 4. The model for the patient with ID 4 is:

$$b_{comp}(t) = 1.02 \cdot i(t) + 7.06 \cdot \frac{di(t)}{dt} - 0.03 \cdot i(t) \cdot \frac{di(t)}{dt} + 0.03 \cdot \left(\frac{di(t)}{dt}\right)^2 + 0.34 \tag{6}$$

Table 5 reports the frequency of relative errors for this patient. For the $GP_{E,I}$ approach, the 60% of training and the 68% of test items have a relative error lower than 5%. $GP_{E,I}$ training reaches 100% items with relative error lower than 25%, while IGBG training and SR_{opt} training never achieve this percentage. Moreover, $GP_{E,I}$ Test reaches 100% of items with 15% of relative error while IGBG Test attains 100% only for a relative error of 45% and SR_{opt} Test reaches 100% for a relative error of 35%.

Figure 2 illustrates the CEGs for such a patient on the complete dataset: all the points estimated by $GP_{E,I}$ fall within zone A, except for two points on the borders between zones A and B, and A and D respectively. We can note that the points are concentrated in the area near the bisector, thus meaning that the predictions are accurate. This is a very good result if compared with the other two strategies. Indeed, for IGBG and SR_{opt}, several points fall in zones B and D and exhibit a sparse behaviour, thus indicating less accurate BG estimations or even mispredictions.

Figure 1: CEGs for patient 1. Top-left: $\mathrm{GP_{E,I}}$, top-right: IGBG, bottom: $\mathrm{SR_{opt}}$.

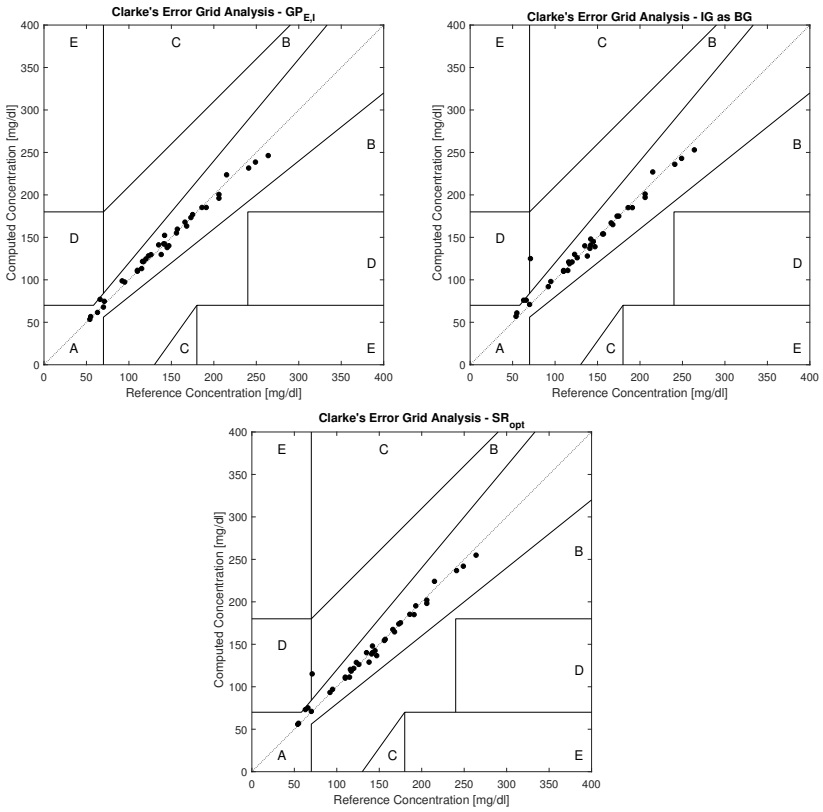


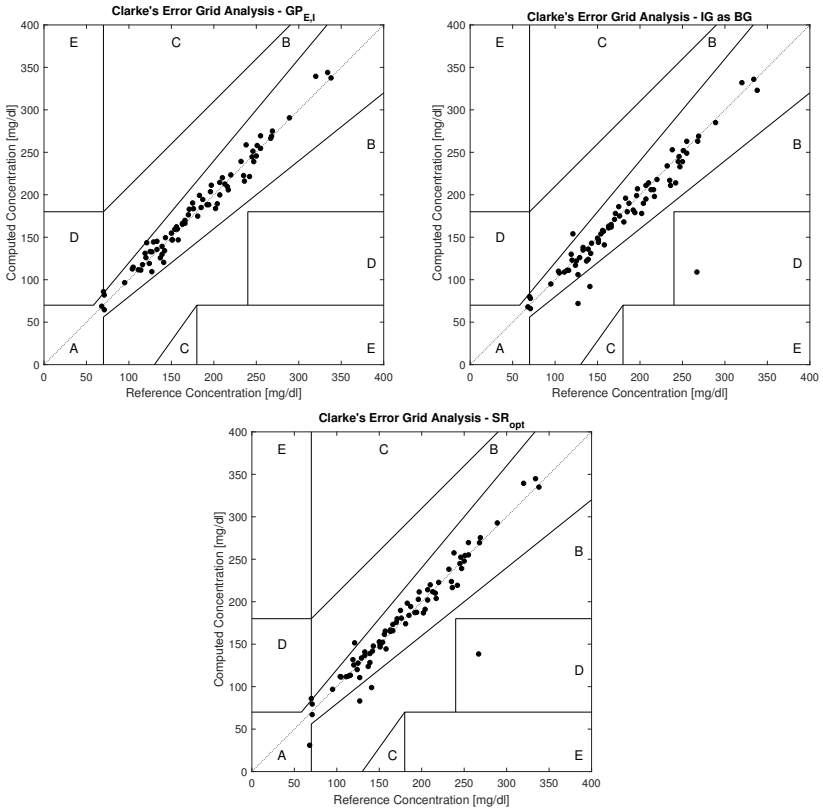
Table 5: Frequency of relative errors for the patient with ID 4 in $\mathrm{GP_{E,I}}$, IGBG and $\mathrm{SR_{opt}}$.

	$\mathrm{GP_{E,I}}$		IGBG		$\mathrm{SR_{opt}}$	
Relative error	Training	Test	Training	Test	Training	Test
< 0.05	0.60	0.68	0.64	0.55	0.56	0.73
< 0.10	0.91	0.91	0.89	0.73	0.89	0.86
< 0.15	0.95	1	0.96	0.86	0.92	0.91
< 0.20	0.98	1	0.96	0.91	0.92	0.91
< 0.25	1	1	0.96	0.91	0.95	0.91
< 0.30	1	1	0.98	0.91	0.96	0.91
< 0.35	1	1	0.98	0.95	0.96	1
< 0.40	1	1	0.98	0.95	0.96	1
< 0.45	1	1	0.98	1	0.96	1
< 0.50	1	1	0.98	1	0.98	1

Patient 6. The model for the patient with ID 6 is:

$$b_{comp}(t) = 0.88 \cdot i(t) + 5.50 \cdot \frac{di(t)}{dt} + 10.61 + 3.69 \cdot 10^{-4} \cdot \left(i(t) + \frac{di(t)}{dt} \right)^2 \tag{7}$$

Figure 2: CEGs for the patient with ID 4. Top-left: $GP_{E,I}$, top-right: IGBG, bottom: SR_{opt}.



The frequency of relative errors for such a patient is shown in Table 6. As we can see, the 59% of the $GP_{E,I}$ training items and the 74% of the $GP_{E,I}$ testing items have a relative error lower than 5%, which is better than the corresponding values of IGBG and SR_{opt}. Again, $GP_{E,I}$ training and $GP_{E,I}$ Test reach the 100% items at lower relative errors compared with IGBG and SR_{opt} approaches.

Figure 3 outlines the CEGs for this patient on the total dataset. As in the previous cases, it is possible to observe that almost the totality of the estimations done by $GP_{E,I}$ is located in zone A and just two points fall in zone B. The other two methods exhibit various and sparse points in zone B, and this means that they are less accurate than $GP_{E,I}$. Moreover, in the CEGs of IGBG and SR_{opt} the points assume a sparse behaviour, while the $GP_{E,I}$ points are more concentrated along the graph bisector, thus representing a

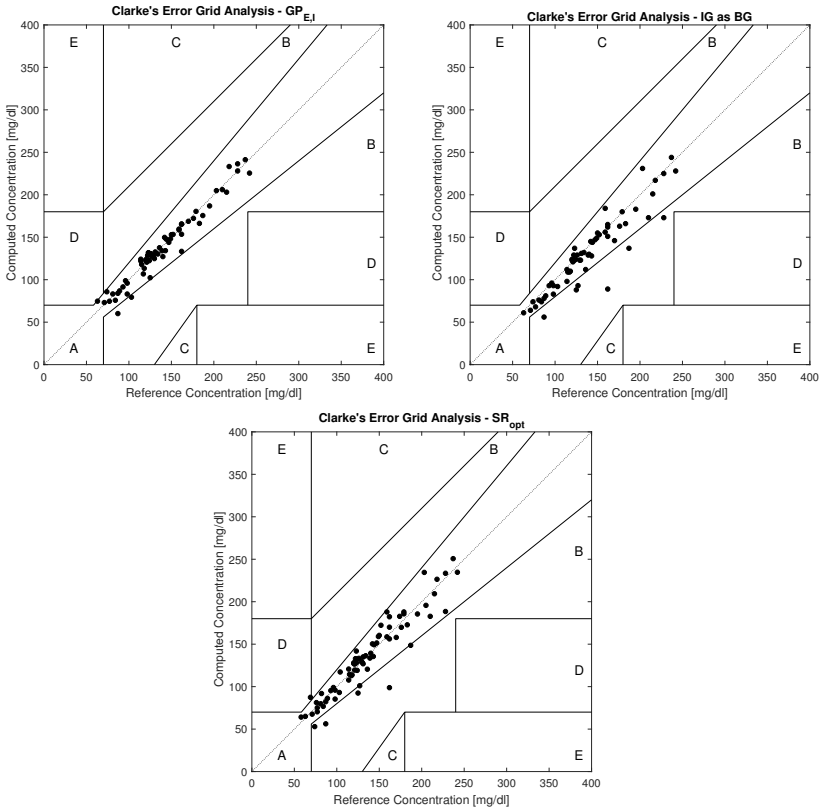
better estimation.

Table 6: Frequency of relative errors for the patient with ID 6 in $GP_{E,I}$, IGBG and SR_{opt}.

	$GP_{E,I}$		IGBG		SR_{opt}	
Relative error	Training	Test	Training	Test	Training	Test
< 0.05	0.59	0.74	0.43	0.42	0.5	0.42
< 0.10	0.93	0.79	0.70	0.68	0.75	0.75
< 0.15	0.93	0.79	0.84	0.84	0.88	0.79
< 0.20	1	0.89	0.93	0.84	0.92	0.88
< 0.25	1	0.95	0.93	0.89	0.96	0.88
< 0.30	1	0.95	1	0.89	1	0.92
< 0.35	1	1	1	0.89	1	0.92
< 0.40	1	1	1	0.95	1	1
< 0.45	1	1	1	0.95	1	1
< 0.50	1	1	1	1	1	1

Discussion. For all the scenarios, the model discovered by $GP_{E,I}$ show a proportional dependency of $b_{comp}(t)$ on $i(t)$ and $\frac{di(t)}{dt}$, thus recalling the SR model [17]. The constants that multiply $i(t)$ are in the range 0.88 – 1.21, whereas the constants that multiply $\frac{di(t)}{dt}$ are in the range 5.17 – 7.05. Each model differs from the other ones in the correction factors and biases depending on the specific case. These factors improve the basic SR model which fails in computing the $i(t)$ derivatives in case of rapid glucose variations. In fact, in the tables of relative errors, $GP_{E,I}$ generally reaches higher percentages of items for the same relative error values, when compared with IGBG and SR_{opt}. Also, the 100% of items is achieved by $GP_{E,I}$ at lower relative errors with respect to the other two methods. From a medical viewpoint, it is to point out that the CEGs report very good results for the proposed GP methodology in all the patients, as almost the totality of the estimated concentrations falls in zone A, except for a small number of points in zone B. In fact, zones A and B represent accurate clinical estimations with a corresponding high probability of correct clinical treatments. Instead, IGBG and SR_{opt} show many more points in zone B and even some points in D. This latter zone represents estimations that are far from being acceptable and could lead to incorrect clinical treatments. The obtained findings imply that the evolutionary approach allows better estimations than other methods and thus could be effectively employed in AP devices.

Figure 3: CEGs for the patient with ID 6. Top-left: $GP_{E,I}$, top-right: IGBG, bottom: SR_{opt}.



4.4. General model on enriched database

In the previous section, we have presented the patient-oriented approach that is customized for the specific diabetic subject. However, it can be useful to find a general law able to describe the glycemia behaviour as a function of time independently on the target patient. This could be employed in those kinds of healthcare medical devices that have to be general-purpose and adaptable to specific subjects. The general model extracted from the enhanced database takes into account the data series of the patients with IDs 1, 2, 4, 5 and 6. These data are unified and then enriched through the SR_{opt} approach. Indeed, as mentioned before, the original data is a collection of several IG measurements and a small amount of real BG ones. Therefore, SR_{opt} estimates the missing BG values. After the enhancement, the IG derivatives are computed. In particular, as the database is a collection

of data from several time segments of different subjects, the IG derivative between two IG points belonging to different patients is not truly measured. Indeed, the final segment of a patient and the initial segment of the next one differ from each other in a period of time much longer than 5 minutes. To avoid extremely high and inaccurate derivatives in those discontinuities, $\frac{di(t)}{dt}$ is set to 0 if t is the first or the last index of the initial and last time segment of two consecutive patients, otherwise it equals the gradient. A second level enrichment, i.e. through interpolation, has not been considered as the five patients' unified database contains a sufficient number of measurements. The GP is carried out with 20 runs on the enriched database. For the GP purpose, the unified series of the five patients is divided into three sets, i.e. *training*, *validation* and *test* sets, containing the 60% (first three patients), 22% (fourth patient) and 18% (last patient) of the ordered data, respectively. The training set is used to fit the model. The validation set provides an unbiased evaluation of the model fitting. Finally, the test set is used to assess the quality of the best model (in terms of best fitness achieved over the previous sets).

In this general method, two fitness functions are proposed, namely an overall fitness (eq. (3)), and a mean fitness (eq. (4)). In both cases, the constant C appearing in their formulas is set to 10 on the basis of a preliminary tuning phase. The GP approach using the overall fitness is referred to as $\mathrm{GP_{E,all}}$, while the one using the mean fitness is referred to as $\mathrm{GP_{E,mean}}$. The extracted models are outlined in the following paragraphs, together with a final discussion that compares GP-based models with IGBG and $\mathrm{SR_{opt}}$ models.

Fitness as an overall weighted RMSE. The model in case of using an overall weighted fitness, with the form of the eq. (3), is:

$$b_{comp}(t) = 1.05 \cdot i(t) + 0.93 \cdot \frac{di(t)}{dt} + 4.2 \cdot 10^{-8} \cdot \left(i(t) \cdot \frac{di(t)}{dt} \right)^2 - 4.72 \quad (8)$$

Fitness as a mean of patients' fitness. The model in case of using a weighted mean fitness, with the form of the Equation (4), is the following:

$$b_{comp}(t) = 1.05 \cdot i(t) + 1.05 \cdot \frac{di(t)}{dt} - 4.78 - 3.901 \cdot 10^{-8} \cdot i(t)^3 \cdot \frac{di(t)}{dt} + \\ + 3.901 \cdot 10^{-8} \cdot \left(i(t) \cdot \frac{di(t)}{dt} \right)^2 \quad (9)$$

To evaluate the proposed general models, the frequency of relative errors is shown in Table 7, together with IGBG and SR_{opt}.

Table 7: Frequency of relative errors for the general model in $GP_{E,all}$, $GP_{E,mean}$, IGBG and SR_{opt} for the training, validation (Val) and test sets.

	$GP_{E,all}$			$GP_{E,mean}$			IGBG			SR_{opt}		
Relative error	Training	Val	Test	Training	Val	Test	Training	Val	Test	Training	Val.	Test
< 0.05	0.64	0.57	0.59	0.63	0.57	0.58	0.59	0.41	0.42	0.59	0.47	0.48
< 0.1	0.88	0.88	0.89	0.88	0.87	0.87	0.84	0.73	0.70	0.84	0.76	0.74
< 0.15	0.95	0.89	0.90	0.95	0.89	0.90	0.93	0.85	0.84	0.92	0.86	0.85
< 0.2	0.99	0.95	0.94	0.98	0.95	0.94	0.95	0.91	0.90	0.95	0.91	0.91
< 0.25	0.99	0.99	0.98	0.99	0.99	0.98	0.96	0.93	0.92	0.95	0.94	0.94
< 0.3	0.99	0.99	0.99	0.99	0.99	0.98	0.97	0.97	0.97	0.97	0.97	0.97
< 0.35	1	0.99	0.98	1	0.99	0.98	0.98	0.97	0.97	0.98	0.97	0.97
< 0.4	1	1	1	1	1	1	0.98	0.99	0.98	0.98	1	1
< 0.45	1	1	1	1	1	1	0.99	0.99	0.98	0.98	1	1
< 0.5	1	1	1	1	1	1	0.99	1	1	0.99	1	1

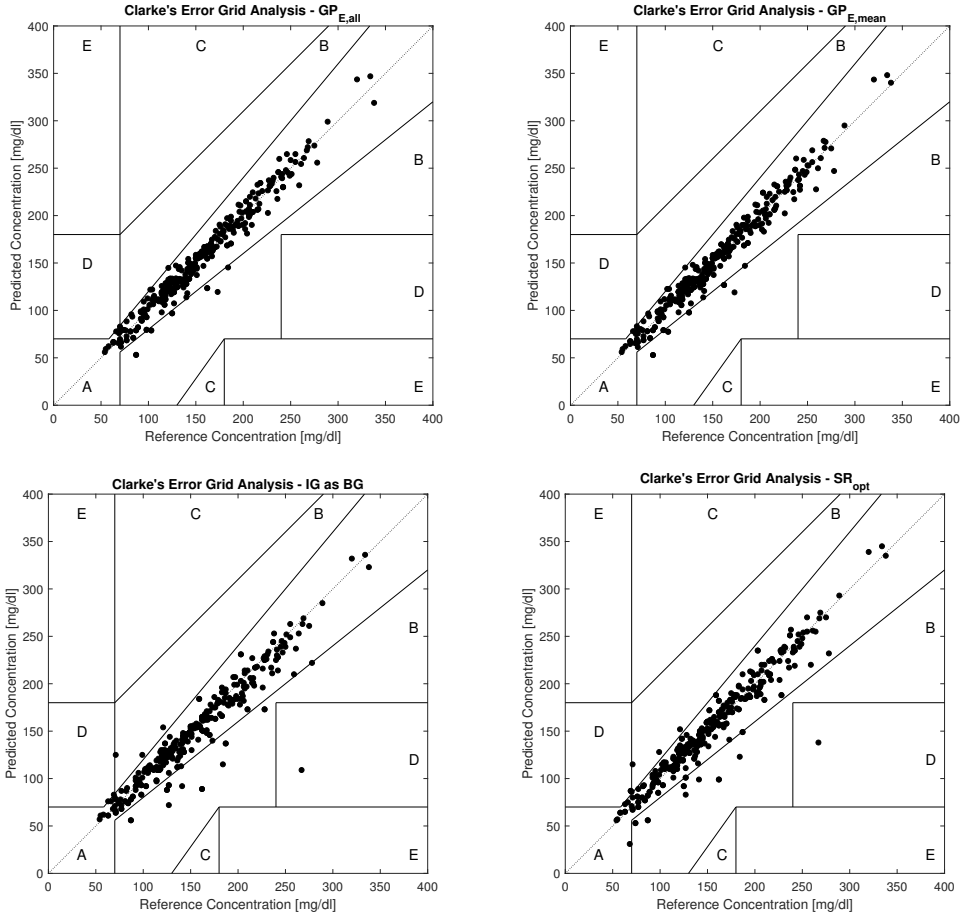
Table 8 depicts the percentages of points falling in the respective zones of the CEGs for the compared methods on the entire database.

Table 8: Percentages of points falling in the zones of the CEG for the general model in $GP_{E,all}$, $GP_{E,mean}$, IGBG and SR_{opt}.

	$GP_{E,all}$			$GP_{E,mean}$			IGBG			SR_{opt}		
Zone	Training	Val	Test	Training	Val	Test	Training	Val	Test	Training	Val.	Test
A	98.95	94.67	93.65	97.89	94.67	93.65	95.26	90.67	90.48	95.48	91.03	90.91
B	1.05	5.33	6.35	2.11	5.33	6.35	3.68	8	9.52	3.02	7.69	9.09
A+B	100	100	100	100	100	100	98.94	98.67	100	98.50	98.71	100
C	0	0	0	0	0	0	0	0	0	0	0	0
D	0	0	0	0	0	0	0.91	1.05	1.34	1.51	1.28	0
E	0	0	0	0	0	0	0	0	0	0	0	0

Discussion. As it can be seen from the extracted models shown in eqs. 8 and 9, according to the employed fitness function, the proposed GP approach is capable of reconstructing different general laws describing the BG trend as a function of IG and its derivative. These laws rely on the SR model but improve it with appropriate correction factors and constants that are not taken into account by IGBG and SR_{opt}. In fact, IGBG considers the IG trend as if it was the exact BG trend, thus ignoring the real BG dynamics and variations, while SR_{opt} does not hold in case of rapid BG changes, as

Figure 4: CEGs for the general model on enhanced dataset. Top-left: $GP_{E,all}$, top-right: $GP_{E,mean}$, bottom-left: IGBG, bottom-right: SR_{opt}.



we know from theory. Moreover, from the Table 7, we can observe that generally $GP_{E,all}$ and $GP_{E,mean}$ reach similar percentages of items for the same relative error, percentages that are higher than those attained by the other two strategies. For example, for a relative error less than 5%, $GP_{E,all}$ reaches 64% in training, 57% in validation and 59% in test, while $GP_{E,mean}$ achieves 63%, 57% and 58%, respectively. For the same relative error, IGBG reaches 59%, 41% and 42% while SR_{opt} reaches 59%, 47% and 48% of items. Furthermore, the GP approaches reach 100% of training items for a relative error less than 35%, that is a percentage achieved by IGBG and SR_{opt} at higher relative errors. The effectiveness of the GP approaches is confirmed

by their small RMSEs. The best RMSE values for the general models on the enriched database are reported in Table 9.

Table 9: Best RMSE for the general models on the enriched database.

	$GP_{E,all}$	$GP_{E,mean}$	IGBG	SR_{opt}
Training	10.61	10.64	18.05	15.58
Validation	10.35	10.43	17.25	15.50
Test	10.75	10.82	18.47	15.83

As we can see from Table 8, for the GP methodologies, almost the totality of the predictions falls in zone A except for few points in B. Instead, IGBG and SR_{opt} present more points in zone B and also a percentage of points in zone D, thus revealing dangerous mispredictions. It is to remark that the ability of the GP approach to avoid incorrect estimates in zone D is of a prominent importance from a medical viewpoint. In fact, erroneous predictions in this latter zone could have fatal consequences for diabetic patients subject both to manual and to automatic treatment of the insulin regulation. Furthermore, it is worth noting that both the GP methods reach a greater percentage of predicted BG values in zone A than IGBG and SR_{opt} on the test set, as it is possible to observe from Fig. 4. The picture shows the CEGs in the different situations: at the top-left $GP_{E,all}$, at the top-right $GP_{E,mean}$, at the bottom-left IGBG, and at the bottom-right SR_{opt}.

In conclusion, the proposed GP approach outperforms IGBG and SR_{opt} both from a numerical and, even more importantly, from a medical viewpoint.

5. Conclusions and future works

The present paper has introduced an innovative evolutionary methodology for estimating BG from IG measurements and their derivatives. Specifically, through the GP, the proposed approach derives a law able to forecast the BG trend of diabetic subjects by starting from their past BG and IG measurements. To demonstrate the effectiveness of this method, several experiments have been carried out over a real-world database containing both BG and IG measurements from five diabetic patients. The final goal of these experiments has been the extraction of an explicit relationship between BG, IG and IG derivative at the same time under the form of a mathematical expression. The excerpted model could be the core of the knowledge base of intelligent medical devices, such as the AP.

Experiments have been performed on the personalized datasets enriched through the SR model and the interpolation, and on the global enriched database without interpolation. These experiments have allowed finding both patient-oriented models and general models able to describe the glycemia behaviour as a function of time independently of a specific patient. The personalized models could be applicable in medical devices that have to precisely fit the individual glycemic dynamics. The global relationship could be employed in those kinds of healthcare devices that have to be general purpose and adaptable to the target subjects.

The findings have shown a similarity between the performances of the GP on personalized and global data. In fact, in all the extracted models it is evident a proportional dependency of BG on IG and IG derivative at the same time. This behaviour recalls the basic SR model that has been the reference model for the present work. However, each extracted model differs from the other ones in correction factors and biases depending on the particular situation. These factors improve the SR model, which in fact does not hold in case of rapid glucose variations. Furthermore, the results also prove that it can be useful to enrich the data through estimation of the missing BGs with the SR model and, in case of necessity, with linear interpolation.

Throughout the experiments, the effectiveness of the proposed evolutionary approach has been ascertained by comparison with two state-of-the-art methods, namely IGBG and $\mathrm{SR}_{\mathrm{opt}}$ under different points of view and with different methods of analysis, like the frequency of the relative errors, the CEGs and the RMSE evaluation. All the results show that the GP variants always outperform the other two approaches, in terms of quality of the BG estimations. Moreover, it is to point out that the performance of the GP is particularly valid from a medical viewpoint since it permits avoiding dangerous inaccuracies in BG estimations.

In conclusion, the presented GP methodology could be useful in different contexts and for several purposes to improve the future diabetes healthcare and the quality of life of diabetic people.

In the future works we intend to investigate the correction factors discovered by the GP-based models to determine which factors are specific to the patient, and which ones model CGMS's errors. Further future developments include the use of evolutionary-devised models in a clinical study to estimate the BG values of the involved subjects. This implies an extension of the methodology under different aspects. The proposed patient-oriented

approach could be extended to take into account other interesting variables as the carbohydrate intakes and the insulin boluses of the subject, in order to perform a prediction of future glycemic levels. After supplementary experiments, it could be exploited in forthcoming special-purpose medical devices for the diabetes healthcare. On the other hand, the general approach could be expanded to larger datasets to extract a more and more accurate general relationship. This latter could be utilized in general-purpose devices for the estimation of the BG trend without dealing with the cost related to the necessity of learning over each subject.

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