An Evolutionary Approach for Estimating the Blood Glucose by Exploiting Interstitial Glucose Measurements

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Abstract: The diabetes is correlated to a malfunction of the pancreas that produces very little or no insulin. A way to improve the quality of life of people with diabetes is to implement an artificial pancreas able to inject an insulin bolus when necessary. The aim of this paper is to devise a possibly step in constructing the fundamental element of such an artificial pancreas - estimation of the blood glucose (BG) through interstitial glucose (IG) measurements. In particular, a new methodology is presented to derive a mathematical relationship between BG and IG by exploiting the ability of the evolutionary techniques in solving this regression task. An automatic procedure is used to estimate the missing BG values within this database. To validate the discovered model a comparison with other models is carried out during the experimental phase.

1 INTRODUCTION

Diabetes mellitus (DM) is a group of heterogeneous disorders, which share the common trait of elevated blood glucose level (BG). A number of medical risks are associated with diabetes ranging from retinopathy, neuropathy, and nephropathy or even more serious complications such as the increased risk of heart disease and stroke (World Health Organization, 2013). A large part of the world population is affected by the diabetes that is a disease with no cure. Therefore, a methodology able to help the sick persons is very important not only to improve the patient's quality of life, but also to abate the costs of the treatment that lasts for many years. To succeed in controlling BG, we need to obtain as precise as possible BG-estimate to establish the right amount of insulin to inject.

Several devices have been introduced to accomplish the task but most of them are invasive. Patients are reluctant to invasive solution because of the associated pain. Moreover, they usually provide measures in intervals that ranges from about 15 minutes to a couple of hours with no BG measurements taken during the night. All this prevents to adequately take care of the patient. Instead there is a wide availability of easier-to-use Continuous Glucose Monitoring System (CGMS) devices (Vashist, 2013) for the measurement of the IG, i.e., the glucose in the subcutaneous tissue.

CMGS is minimally-invasive and can be programmed to take measures with a prefixed frequency for a number of days, also during the night. Nevertheless, CGMS needs BG to calibrate - to transform the measured electric current to glucose level. Patient has to calibrate at least two times a day, when BG and IG are steady. While the patient collects only a few BGs, CGMS provides 288 measurements a day.

BG and IG can differ considerably due to physiological reasons. Therefore, there is a need for efficient methodologies to derive a precise estimation of BG by exploiting the large amount of available IG values.

Several studies (Rossetti et al., 2010) have proved that the complexity of the relationship between glucose dynamics in BG and IG is far too complex to be captured in the simple calibration algorithms implemented in CGMS devices available in the market, and this affects the measurement accuracy. CGMS is a low-power device that implies low computational capabilities. Although IG is not considered a perfect BG indicator, nonetheless it is the only one to be available with continuous and non-invasive measurements.

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Some analytical models have been introduced in the literature attempting to describe mathematical relationship of IG and BG, as detailed in Section 2. All these models represent a basic step to design and implement an *artificial pancreas*, i.e., an artificial device able to automatically drive insulin injections in case of necessity. This device must be able to perform a glycemic control by forecasting BG course through the analysis of the IG signal.

The first contribution of the paper is the introduction of an innovative methodology to put out new BG values without performing additional measurements. This methodology allows increasing the number of the BG values contained in the database which is a critical problem when searching for a prediction model. The second contribution consists in exploiting such a modified database to symbolically derive a law able to describe BG values by starting from IG measurements. These estimation problems are known as *regression problems*. Considered the complexity, we exploit the capability of the Genetic Programming (GP) (Koza, 1992) in tackling regression problems to find an effective approximation of relationship between IG and BG values. The experiments are carried out over a real-world database containing both BG and IG measurements for several subjects suffering from Type 1 DM, i.e., the case in which the pancreas fails to produce insulin. The scope is to extract an explicit relationship, i.e., a mathematical expression, between BG and IG values that could be the core of the knowledge base of an artificial pancreas.

The paper is structured as follows. In Sect. 2 a short description of the related work is given. Section 3 outlines the methodology employed, along with an innovative procedure to enrich the original database presenting too many missing BG values in Sect. 3.1, and the genetic-based regression model in Sect. 3.2. A discussion on the achieved results and a comparison with other models is reported in Sect. 4. Conclusions and future work are exposed in Sect. 5.

2 RELATED WORK

Several models have been devised to find a reciprocal relationship between BG and IG values.
The first, and most widely used, model attempting to relate BG and IG was proposed by Steil and Rebrin (Rebrin et al., 1999). It is represented by the following equation:

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

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 that the precision of the model can be improved.

Makroglou et al. (Makroglou et al., 2006) presented an overview of several mathematical models aimed at describing the glucose-insulin regulatory system with reference to DM. The described models ranged from ordinary differential equations to partial differential equations, to delay differential equations to the integro-differential ones.

Peréz-Gandía (Pérez-Gandía et al., 2010) employed an artificial neural network for the prediction of the blood glucose concentration. The accuracy of the tool was estimated by using the root mean square error and the prediction delay.

Del Favero et al. (Del Favero et al., 2014) proposed a model that tries to improve that by Steil and Rebrin. Basically, they supposed that the value of g is equal to 1, and added a way to calibrate the model so that a true IG, represented by $i_t(t)$, can be restored. This calibration is expressed by the equation:

$$i_i(t) = \frac{i(t) - \beta - \gamma \cdot \Delta t(t)}{\alpha}; \Delta t(t) = t - tcal \qquad (2)$$

where α, β, and γ are calibration parameters, and their values must be recomputed each time the CGMS is calibrated.

Koutny (Koutny, 2014) struggled to improve 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. This model heavily relies on biological considerations, as for instance the importance of capillaries and the fact they have different permeabilities in different compartments. By means of the proposed model tested on hyperglycemic-clamp data, he succeeded in attaining an improved model to compute the BG levels.

All the analytic models introduced presents the problem of estimation of several parameters. This estimation is usually performed by exploiting mathematical, biological or physiological considerations or, in some cases, by performing an a-posteriori manual tuning. Despite its importance, only in the last years some attempts have been carried out to automatically extrapolate the parameter estimation by means of techniques able to deal with this optimization problem such as the evolutionary methods. Two of these attempts are reported in the following.

Koutny (Koutny, 2016) combined the analytic method proposed in 2014 with meta-Differential Evolution (DE) (Price and Storn, 1997). Namely, starting from a continuously measured level of IG for human

Type-1 diabetic patients, he computed a continuous BG level. He used six different scenarios to ensure robust validation of the calculation, and made use of DE to evaluate the parameters for his model. All the six scenarios, even the simplest ones, performed better than CGMS in estimating BG values.

De Falco et al. (De Falco et al., 2017) proposed a GP tool to estimate the BG values starting from the easily available IG values. A relationship under a form of an explicit mathematical expression was excerpted. The experimentation was carried out on a real-world database containing subjects suffering from Type 1 diabetes. The comparison against state-of-the-art models attested the effectiveness of the proposed evolutionary approach.

3 THE METHODOLOGY

The methodology proposed within this paper can be summarized in two basic steps: i) the definition of a novel automatic procedure to enrich the database with estimated BG values by exploiting an evolutionary optimizer for the calculation of the model parameters; ii) the use of an appropriate evolutionary technique, i.e., a GP algorithm, for solving the regression model and extracting an explicit symbolic model.

3.1 Database Enrichment

The poor availability of BG values with respect to the IG ones is one of the major problem in excerpting a reciprocal and effective mathematical relationship between them. To overcome this problem we devise a new procedure able to estimate a number of missing BG values within the database used to solve the related regression problem.

Since the Steil-Rebrin model (Rebrin et al., 1999) is still one of the most widely used to establish a relation between BG and IG, we have employed it to estimate the missing BG values. To proceed in this direction, it is necessary to estimate the model parameters of Eq. (1), i.e., the steady-state gain g and the equilibration constant τ, so to enhance the model precision. Following the approach of Koutny in (Koutny, 2016), this estimation is performed by using as optimizer an evolutionary algorithm, namely the DE. Such an algorithm works on a population of potential candidate solutions representing the model parameters. Starting from a population of randomly chosen parameter values, the population evolves by performing recombination and mutation of the current solutions through specific evolutionary operators. The details related to these operators can be found in (Price and Storn, 1997). During the evolution the quality of the current parameters is evaluated through a fitness function. This function computes the mean square error between the BG values estimated through the Steil-Rebrin model endowed with the current parameters and the available measured BG values of the original database. The evolutionary procedure is applied iteratively until a fitness of desired quality is achieved or a fixed number of iteration is performed. By exploiting the calculated parameter values at the end of the evolution, we are able to estimate the BG values in correspondence of all the IG values for which they are missing. In this way a complete correspondence between all the IG and BG values is available. Naturally the measured values in the original database are left unchanged. The so-modified database is then used for solving the symbolic regression problem. By considering that the number of estimated BG values in this enriched database are much higher than those truly measured, it will be necessary to introduce a correction factor to avoid a bias in the model extraction. The detail of this correction factor will be reported in the experimental section.

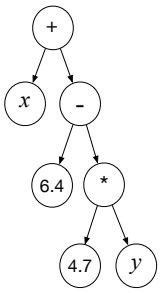

Figure 1: An exemplary tree-structured solution in GP.

3.2 The General GP Framework

Genetic Programming (GP) is a heuristic methodology well suited for optimization purposes (De Falco et al., 2005; De Falco et al., 2006), and has its roots in the implementation in a computer of mechanisms borrowed from the natural evolution process that happens in populations.

Given a problem, GP works on a set, referred to as *population*, of its solutions. Each solution, called *individual*, is a program represented under a tree structure form. The inner nodes in any individual denote elementary functions, while the leaf nodes contain terminals, i.e., either variables of the problem or constant values. By reading a starting tree in pre-order the corresponding program is got. An example is outlined in Fig. 1 in which the tree represents the in-order expression $6.4-(4.7*y)+x$.

In GP the quality of each individual in solving the

Table 1: The set of the elementary functions along with the related symbols.

Symbol	Description
+	Addition
-	Subtraction
*	Multiplication
/	Protected division (is 1 if the denominator is 0)
sqrt	Square root
pow	Power

given problem is evaluated by means of a *fitness function* Φ that should be tailored to the specific problem. The population of solutions evolve iteratively from one generation to the next one by applying evolutionary operators with the aim to improve the fitness function. This evolution ends when a fixed maximum number of generations g_{max} is reached A general pseudo-code describing GP is reported the following:

- randomly generate an initial population with P individuals;
- evaluate the quality of each individual with the help of the appropriate fitness function;
- at each generation create a new population by repeating the steps below:
  - randomly choose an evolutionary operator; i. e., crossover, mutation, and copy;
  - select as many individuals as needed by the operator chosen in the current population;
  - let the selected individuals undergo the operator so as to generate a new individual;
  - insert this latter into the new population being created;
  - assess the quality of the new individual through the fitness function;
- keep on creating a new population at each generation until reaching a preset g_{max}.

The quality of the solutions achieved by GP, in terms of fitness function values, typically improves as the number of generations increases. For a detailed description of the three operators the interested reader can refer to (Koza, 1992).

3.2.1 GP for Regression

Since we wish to tackle a regression task, the population will be constituted by a set of regression models. Each such model is encoded as a 'formula', represented as a tree whose nodes can include either functions or terminals. The complete set of the functions employed within this paper is outlined in Table 1.

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

Aiming at obtaining a (sub)–optimal regression model, a division of the database items into either two or three sets takes typically place for learning purposes. Due to the limited amount of measured items in the available database, we have opted for a two-set division, namely *train* and *test* sets. Learning is carried out over the items of the train set with the goal to attain a model useful to approximate the dependent variable values as a function of the values of the independent problem variables. The quality of the best model (in terms of best fitness value over the train set) provided by GP at the end of the execution is evaluated over the test set, whose items had been never previously displayed to the GP algorithm.

To numerically assess the quality of each regression model S achieved during the GP execution, we have employed the Root Mean Square Error (*RMSE*) as fitness function Φ, i.e:

$$\Phi(S) = \sqrt{\frac{\sum_{i=1}^{n}(y_{calc}(i) - y(i))^2}{n}} \qquad (3)$$

where $y_{calc}(i)$ represents output value for the *i*–th item of the database by the model S under examination, whereas $y(i)$ is the value of the dependent variable for the same *i*–th item. With this choice the regression problem becomes a minimization problem.

4 EXPERIMENTAL RESULTS

The Database. From the Diabetology Center at the Pilsen Hospital University, we received anonymized datasets of Type 1 diabetic patients. We transformed the datasets into a database. The database comprises 5 different patients. Each patient comprises several time segments. Time segment is a period for which the patient wore CGMS. There are 9, 30, 31, 38 and 38 time segments per patient, respectively. In total, there are 146 time segments, which contain 342 BGs and 36256 IGs.

The Findings. On the database, we apply the methodology described in 3.1 to estimate the missing BG values. This procedure necessitates of the estimation of the parameters of the Steil-Rebrin model. The estimation performed by means of the DE algorithm has resulted in the following values for the parameters: $g = 0.98$ and $\tau = 0.02$. These values have been used to enrich the dataset with the missing BG values. As already said, the truly measured BG are left unchanged. The enriched dataset has been employed

to assess whether or not a general behavior, able to suitably describe all of the involved subjects, can be identified. If it were possible, this would result in an unique model without the necessity to personalize it as a function of the subject. The eventual existence of a single model would simplify also the knowledge base for the artificial pancreas.

To perform all the reported experiments GPTIPS (Searson, 2009), a tool executing GP and running in the MATLAB environment, has been used. The GP parameters have been set at the following values: P= 500, g_{max} = 500, $tourn\_size$ = 30, p_mutate = 0.1, p_cross = 0.9, and p_copy = 0.02 after a preliminary tuning phase. To simplify the results the maximum tree depth and the maximum number of the tree nodes have been set equal to 4 and 8 respectively.

We have assigned the first 70% of its items to the train set (25,370 items) and the remaining 30% of items to the test set. Then we have executed the tool for 10 times. The reason is that GP is a nondeterministic algorithm whose results depends on a random integer value that should be assigned as seed to a random number generator. Different seeds can yield different results. Therefore, GPTIPS has been run 10 times over the dataset. The run reaching the lowest *RMSE* value over the test has been taken into account because its associated final model has the highest ability to correctly compute unseen data.

Furthermore, the GP considers for the independent variable IG a time interval of 30 minutes before and 30 minutes after around a selected time t that is the time at which the dependent variable BG has to be computed. Considered that the IG values are taken with a $\Delta t = 5$ minutes, the values considered with respect to IG at time t, i.e., $i(t)$, ranges from $i(t-\Delta t)$ to $i(t-6\Delta t)$ for the past, and from $i(t+\Delta t)$ to $i(t+6\Delta t)$ for the future total of 14 independent variables, yielding for GPTIPS 13 possible terminals, plus the const node. In addition to these 13 variables, the dataset contains also the estimated BG values $b_s(t)$ and the measured BG values $b_m(t)$.

In Equation (3) $y(i)$ represents the measured BG value in the i–th item of the set, and $y_{calc}(i)$ is its estimate through the use of the IG values.

As explained in Section 3.1, to avoid bias in the model extraction a fitness function with a correction factor p_s has been devised. To this aim a global fitness function $RMSE_{ALL}$ arranged as the sum of two subfitness functions appropriately weighted by an appropriate correction factor p_s is introduced. In formula this function can be expressed as follows:

$$RMSE_{ALL} = (1-p_s)\cdot RMSE_s + p_s \cdot RMSE_m \quad (4)$$

where $RMSE_s$ is the error evaluated on the estimated values while $RMSE_m$ is the error computed on the measured values.

Table 2: $RMSE_m$ values obtained by the different methods.

GP Train	GP Test	IGBG Train	IGBG Test	$S\text{-}R_{opt}$ Train	$S\text{-}R_{opt}$ Test
9.65	10.15	17.17	18.27	14.71	13.82

The correction factor is given by $p_s = n_s/n_t$ where n_s is the number of the estimated values and n_t is the total number of values in the dataset. The choice for the correction factor in Eq. 4 is due to the fact that the number of measured values is about 1% with respect to the number of estimated values. Therefore, considered that $RMSE_s$ weights much more than $RMSE_m$, in order to avoid bias toward the estimated values we have decided to assign to the correction factors values inversely proportional to the weights of the respective sub-fitness functions.

Throughout our experiments, we compare our GP-based method endowed the new methodology to estimate the missing BG values against a GP approach which makes use of the measured IG values as if they were the exact measured values of the BG. This method is denoted as IGBG. The last comparison is performed with the state-of-the art Steil-Rebrin model (Rebrin et al., 1999) with the parameters optimized through DE. Hereinafter this model is named $S\text{-}R_{opt}$. The best model found for the global database is:

$$b(t) = 1.16\cdot i(t+\Delta t)) - 0.00369\cdot i(t-6\Delta t) - 0.141\cdot i(t-\Delta t) + \frac{(10.6\cdot (i(t)+(i(t)-\Delta t))}{i(t+3\Delta t)} - 20.6$$

where i is the measured IG and b is the computed BG.

The obtained model uses five out of the thirteen inputs, namely the IG values at times t, $t-\Delta t$, $t-6\Delta t$, $t+\Delta t$ and $t+3\Delta t$. This confirms the statement in (Boyne et al., 2003; Steil et al., 2000) that delays of up to 13 minutes take place between IG and BG.

From a quantitative viewpoint, Table 2 shows the $RMSE_m$ of the different models over train and test sets. Of course, for the IGBG method there is no learning. Our method has the best performance with respect to the other models, and obtains an $RMSE_m$ value equal to 9.65 over the train set, and to 10.15 over the test set. This is a very good result, because this means that the difference between a BG value estimated by this model and the real BG value is about 10 mg/dl in a typical range between 50 and 400. This relatively small $RMSE_m$ ensures that the use of the above model can be of great help in assessing whether the subject is in a normal state, or is undergoing a hyperglycemic or a hypoglycemic episode.

Figure 2 shows how well the BG values estimated by the computed model fit the BG measured data over both train and test sets. As a general comment, fitting is very satisfactory also over test set data, never shown

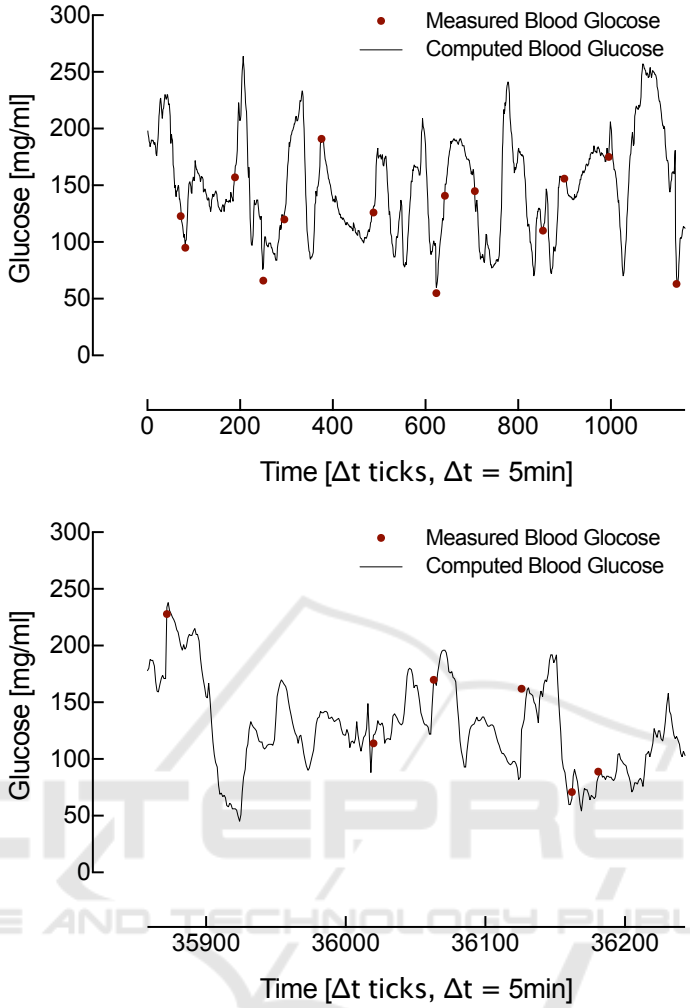

Figure 2: The estimate of the values through GP. Top: first 2 segments on train set. Bottom: last 4 segments on test set.

to the system during learning, BG peaks are very often caught in terms of both time and magnitude.

The frequency of relative errors for the three investigated models is reported in Table 3. As it can be appreciated from the table, for our model 87.74% of the items has a relative error lower than 10%, which is an excellent result. Moreover, more than 95% of the items has an error lower than 20%, which is also good with respect to ISO 15197:2003 and 15197:2013 accuracy standards for blood glucose meters. The table also evidences that these results are much better than those achieved when IG is used as the real value of BG, and better also than $S\text{-}R_{opt}$ model for the items with relative errors lower than 10% and 20%. $S\text{-}R_{opt}$ model has slightly better values than GP for a relative error lower than 5% while the results are the same for the other relative errors. This means that the proposed GP-based approach can actually help in better estimating BG.

Table 3: The frequency of relative errors: cumulative probability of lower than or equal to relative error.

Relative error	GP	IGBG	$S\text{-}R_{opt}$
≤5%	59.43%	41.51%	60.38
≤10%	87.74%	72.64%	83.02
≤15%	90.57%	84.91%	90.57
≤20%	95.28%	90.57%	92.45
≤25%	98.11%	93.40%	98.11
≤30%	98.11%	96.23%	98.11
≤35%	98.11%	96.23%	98.11
≤40%	100.0%	98.11%	100.0
≤45%	100.0%	98.11%	100.0
≤50%	100.0%	100.0%	100.0

Figure 3 shows the results in terms of the Clarke Error Grid analysis (Clarke et al., 1987), that is widely used in the studies about diabetes. Basically, the 2D-estimate space is subdivided into five zones labeled from A to E. The higher the number of points falling in zones A and B, the better the estimate. Points

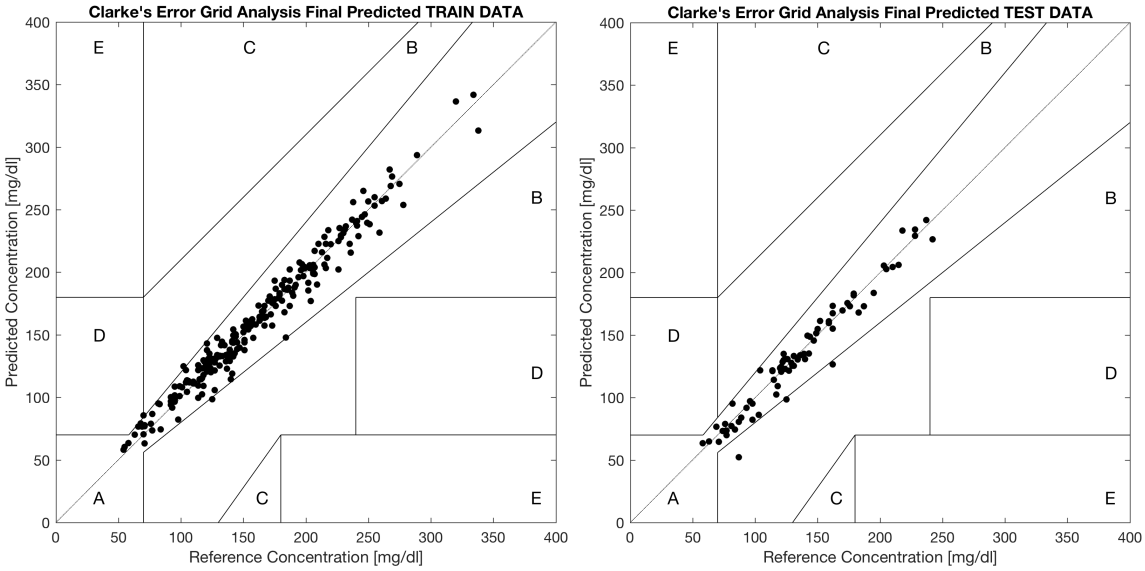

Figure 3: Clarke grid analysis. Left: train set. Right: test set.

falling in the other zones represent different types of situations that should be avoided. As it can be seen, almost all of the points lie in the zones A and B, and this holds true not only for the train set but for the test set too, which is a hint of a very good estimate. Numerically, the percentage of points falling in the different zones is reported in Table 4 for the test set, and this for all the models. For GP we report also the results over the train set, and for IGBG the results are related to the whole database.

Figure 4 reports the same diagram on all the dataset. For GP the zones A and B contain more than 99% of the points in test set (ISO 15197:2013 requirement), which is very good and is superior to IGBG, and slightly outperforms also the *S*-R_{opt} method. Also the absence of points related to situations C and E is an excellent outcome of the proposed model. As a comparison, GP has a lower number of points lying in the zone D than IGBG and the *S*-R_{opt} models. This is a very important outcome because zone D points out a possible risky inadequacy for hypoglycemia or hyperglycemia identification.

Summarizing, the results obtained seem to imply that a unique model extracted by using GP can fit all of the subjects involved in this study, and the artificial pancreas for all of them could be based on evolutionary-devised models.

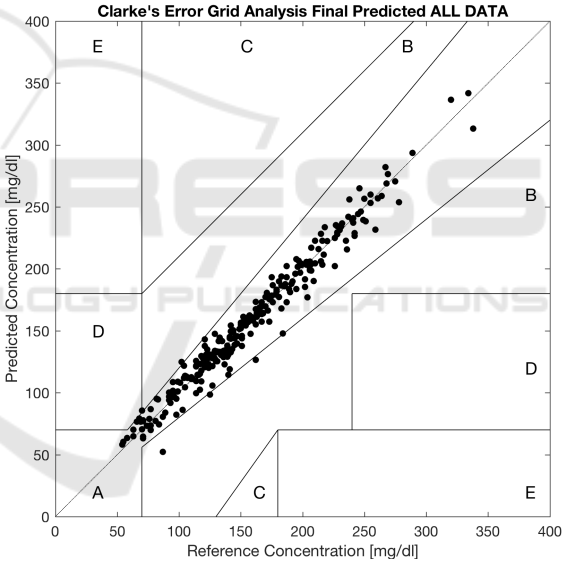

Figure 4: Clarke grid analysis on the whole dataset.

5 CONCLUSIONS

The main problem for a regression model in finding a relationship between variables is the absence of a sufficient number of value of the variables to be correlated. This situation is usual in the field of diabetes research where the easily available number of IG values contrast with the low number of corresponding number of BG values. Within this paper, to overcome the problem we have devised an evolutionary procedure to enrich the database made up of many missing BG values by exploiting the Steil-Rebrin model and the DE technique to estimate these missing BG values. Afterward, a GP algorithm has been used to excerpt an explicit relationship between BG and IG values under the form of a mathematical expression.

This model has been compared both against a GP approach which makes use of the measured IG val-

Table 4: The Percentage of Points Falling in the Different Zones of the Clarke Error Grid.

Zone	GP Train	GP Test	IGBG Train	IGBC Test	*S-R$_{opt}$* Train	*S-R$_{opt}$* Test
A	98.73%	95.28%	94.49%	90.57%	97.46%	93.40%
B	0.85%	4.72%	4.24%	8.49%	1.69%	6.60 %
A + B	99.58%	100%	98.73%	99.06%	99.15%	100%
C	0.00 %	0.00%	0,00%	0.0%	0%	0%
D	0.42%	0%	1.27%	0.94%	0.85%	0%
E	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%

ues as if they were the exact measured values of the BG, and against the state-of-the-art Steil-Rebrin model with optimized parameters. The results have shown its superiority in terms of lower *RMSE*, and of better fitting in the Clarke Error Grid. The findings obtained seem to imply that a unique model can fit all of the subjects involved in this study, and the artificial pancreas for all of them could be based on evolutionary-devised model.

Future work implies the use of evolutionary-devised model in a clinical trial to estimate the BG values of the involved subjects, so as to further test its effectiveness. In the positive case, this model could be added to an under-development artificial pancreas device for a real experimentation.

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