Probabilistic Fitting of Glucose Models with Real-Coded Genetic Algorithms

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***Abstract*—Type 1 Diabetes patients have to control their blood glucose levels using insulin therapy. Numerous factors (such as carbohydrate intake, physical activity, time of day, etc.) greatly complicate this task. In this article we propose a modeling method that will allow us to make predictions of blood glucose level evolution with a time horizon of 24 hours. This may allow the adjustment of insulin doses in advance and could help to improve the living conditions of diabetes patients. Our approach starts from a system of finite difference equations that characterizes the interaction between insulin and glucose (in the field, this is known as a minimal model). This model has several parameters whose values vary widely depending on patient characteristics and time. Thus, in the first phase of our strategy, We will enrich the patient's historical data by adding white Gaussian noise, which will allow us to perform a probabilistic fitting with a 95% confidence interval. Then, the model's parameters are adjusted based on the history of each patient using a genetic algorithm and dividing the day into 12 time intervals. In the final stage, we will perform a whole-day forecast from an ensemble of the models fitted in the previous phase. Th e validity of our strategy will be tested using the Parkers' error grid analysis. Our experimental results based on data from real diabetic patients show that this technique is capable of robust predictions that take into account all the uncertainty associated with the interaction between insulin and glucose.**

***Index Terms*—Diabetes, Glucose prediction, genetic algorithms, Evolutionary computation**

I. Introduction

Diabetes mellitus is a disease characterized by the detection of very high blood glucose (sugar) levels in the patient. Blood glucose is obtained from the food we eat and is absorbed by the cells thanks to the action of insulin. In this context, the pancreas is of vital importance as it is responsible, among other things, for generating insulin. Without insulin, glucose remains in the blood and does not reach the cells properly. Prolonged excess of glucose in the blood (hyperglycemia) can lead to diseases affecting different organs and tissues. In type 1 diabetes, the beta cells of the pancreas produce virtually no insulin, so glucose accumulates in the bloodstream and can only be reduced by injecting artificial insulin. It is important to underscore that the use of synthetic insulin is not without risk since an excessive dose causes a low glucose level (hypoglycemia) that can lead to the patient's loss of consciousness and even coma.

The goal of this study is to predict blood glucose levels in patients with Type 1 Diabetes Mellitus from a personalized study, analysis and adjustment of historical data including: glucose, carbohydrates and insulin. The mathematical modeling of diabetes is a very active research topic with many studies published [1], [2] In many cases, mathematical models are used to measure and predict glucose levels in the human body and help the patient avoid the hyperglycemia issue by using synthetic insulin without reaching the dangerous hypoglycemia threshold. We start from what is known in this field as a minimal model [3]. The minimal model is a system of finite difference equations that characterizes the interaction between insulin and glucose from the parameters normally used in regular therapy: insulin sensitivity, glucose sensitivity, instant glucose level, etc. These parameters vary considerably throughout the day. For this reason, and in order to achieve a finer adjustment, we have divided the samples taken in one day into 12 equally sized sections. Thus, when forecasting a complete day, we will do so based on the models of each of these twelve sections.

The adjustment of the parameters of the system of equations is performed using a genetic algorithm. First, the amount of initial data is enriched using a basic data augmentation technique: the addition of white Gaussian noise. This allows us to perform a probabilistic fitting on the results of the genetic algorithm that will provide us with an ensemble of many models for each of the sections into which we have divided the day. Lastly, the final prediction for each of the sections is obtained by averaging the predictions of the models.

The remainder of the paper is organized as follows: section

II places our work in the context of other related state-of-the-art research in this field. Section III elaborates on the methodology used. Subsection III-A details the process for obtaining data from actual diabetes patients. Subsection III-B explains the minimal model and all its parameters. Subsections III-C and III-D, respectively, will give us an insight into the genetic algorithm and the probabilistic fitting technique used to obtain the models. In Section IV we will present the experimental results and their discussion. Finally, in Section V we present the conclusions of this study and the planned future work.

II. Related Work

The problem of modeling and predicting blood glucose levels has been an area of intensive research in recent years. These studies have two main objectives:

- Some of them attempt to predict glucose levels with a time horizon of up to two hours, the usual time for the normal course of digestion of a meal and for the action of synthetic insulin to reach its peak.
- There are also some researchers interested in identifying 24-hour models. The usefulness of this approach, on which the present study is focused, is different and is usually more effective when programming an automatic insulin pump or establishing an insulin profile for longer periods. In the literature, we can find some approaches that provide models for the average case [4]. However, there are hardly any approaches adapted to the particularities of each patient. Most of the articles in the literature apply classical modeling techniques, resulting in models or profiles defined by linear equations with a limited set of input [5], [6].

Other personalized control approaches have been presented by the main research groups studying artificial pancreases projects [7]–[10]. They are proposals following clinical practice and therefore produce models which are often inaccurate, since clinical data in type 1 diabetes are not extensive enough to identify exact models [11]. There are also some models used in artificial pancreas systems [12], [13]. They are based on the assumption that it is possible to reach a correct control with approximate models [14]. Our experimental results suggest that in this line of research there is a significant risk of excessive insulin administration that could drive the patient into the hypoglycemic zone. This danger has convinced us of the need to develop accurate individualized models. Therefore, in this article we propose our probabilistic models as a means of dealing with the uncertainty inherent in the evolution of blood glucose levels.

The use of the probabilistic fitting technique is more widespread in the social sciences [15]. In this work, it has been applied to the problem of fitting minimal models for glucose prediction.

In order to perform the probabilistic fitting we need large amounts of data. The process to increase the amount of data available in a synthetic way is known as data augmentation and the original idea is due to Tanner and Wong [16]. It relates to methods for constructing iterative sampling algorithms that introduce unobserved data or latent variables, although more advanced approaches include simulation of data based on dynamic systems [17]. Variations of this technique have been applied to evolutionary strategies for predicting short-term blood glucose levels [2], [18].

III. Methodology

In Figure 2 we can see the complete workflow performed in this research. A database has been recorded from real diabetes patients equipped with an insulin pump and a continuous glucose monitor. Subsection III-A describes this process in more detail. The data collected is preprocessed and enriched by adding white Gaussian noise (see Figure 1). In our workflow this is an important step since this augmented data will be used to perform a probabilistic fitting that will provide us with the final prediction models. All data (original and augmented) are used to feed the genetic algorithm (section III-C) that customizes the parameters of the minimal model (section III-B). Once the minimal model is customized, the probabilistic fitting (section III-D) technique selects models within the confidence interval and we obtain an ensemble of models. The training and testing process has been carried out using the cross-validation technique (section III-F). The final prediction is achieved by averaging the predictions of an ensemble of between 30 and 50 models.

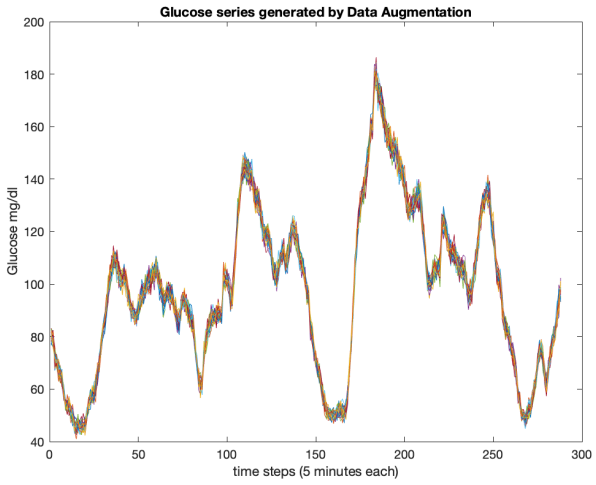

Fig. 1: An example of data augmentation of glucose values. Figure shows 30 glucose time series generated by adding white noise to the original glucose time series.

A. Data

It is important to highlight that here we are using our own dataset, collected by our team thanks to the collaboration of four patients and their medical staff from the public hospital *Principe de Asturias*, located in the Spanish city of *Alcalá de Henares*. The ethical committee of the hospital approved the collection of the data for our studies.

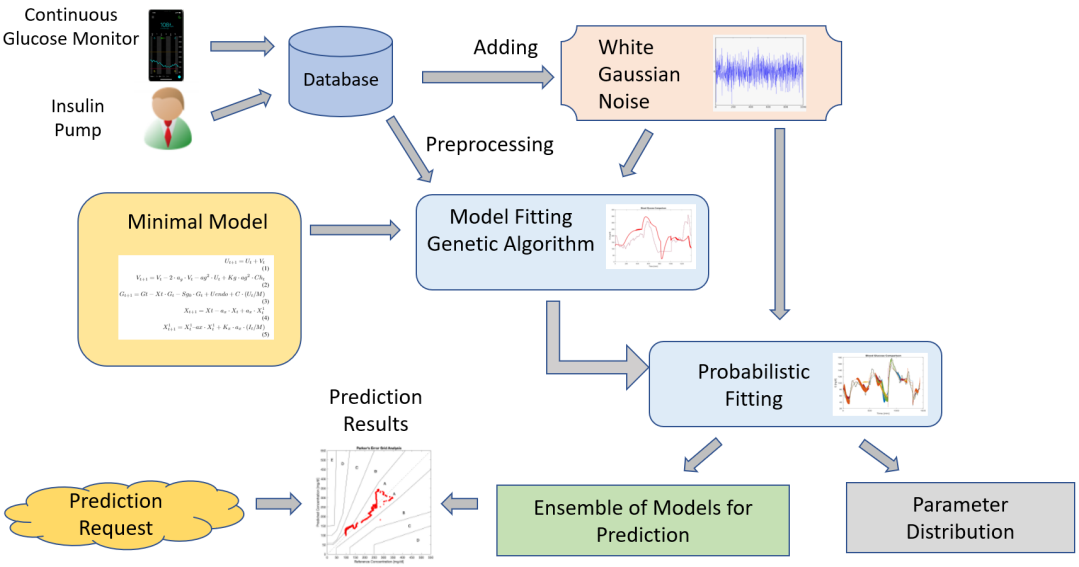

Fig. 2: Full Workflow

TABLE I: Example of recorded data from a patient

# Date	Hour	Glucose	Ch.	Ins S.	Ins. L
16/05/2020	0:00:00	80.0	0.0	0.0125	0.0
16/05/2020	0:01:00	80.0	0.0	0.0125	0.0
16/05/2020	0:02:00	80.0	0.0	0.0125	0.0
16/05/2020	0:03:00	80.0	0.0	0.0125	0.0
16/05/2020	0:04:00	80.0	0.0	0.0125	0.0
...	...	...	...	...	...

Obtaining this data is not an easy task due to different reasons. First, we are dealing with sensitive information, so patients and medical staff have to be closely involved in this task. Patient have to wear devices, take notes and register information over several days with as few disturbances as possible. It is usual to discard part of the data due to patients' mistakes or failures of the electronic devices. Studies in the field usually deal with small datasets, with around ten patients or even fewer.

For this paper, We worked with anonymized data from 4 real patients. We will refer to them as patient$\{1..4\}$. The patients are two women and two men with a mean age of 38 years. The data have been acquired with a *FreeStyle Libre* Continuous Glucose Monitor (CGM) system, and an insulin pump that the patients wore strapped to their body. The sampling period is five minutes. The amount of carbohydrate ingested by the patient and the insulin injected (distinguished by insulin type) were also noted (see Table I). The data consist of five complete days for each patient. The days are not necessarily consecutive, nor are they the same days for all 4 patients. The CGM used is a flash monitoring system that measures interstitial glucose. It should be noted that the values of blood glucose measures (BGM) may differ from CGM measures, since the two are obtained with different techniques and CGM has a delay of approximately 10 to 15 minutes.

B. The Minimal Model

The mathematical model used is an adapted version of the model proposed by Thierry Prud'homme, Alain Bock, Gregory Francois and Denis Gillet [3], which is based on the original model by Bergman et al [19] [20]. The model has the following system of non-linear difference equations:

$$U_{t+1} = U_t + V_t$$

$$V_{t+1} = V_t - 2 \cdot a_g \cdot V_t - ag^2 \cdot U_t + Kg \cdot ag^2 \cdot Ch_t$$

$$G_{t+1} = Gt - Xt \cdot G_t - Sg_0 \cdot G_t + Uendo + C \cdot (U_t/M)$$

$$X_{t+1} = Xt - a_x \cdot X_t + a_x \cdot X_t^1$$

$$X_{t+1}^1 = X_t^1 – ax \cdot X_t^1 + K_x \cdot a_x \cdot (I_t/M)$$

where the parameters are explained as follows:

- U_t: glucose absorption at minute t measured in g/min
- V_t: variation rate of intestinal glucose absorption in g/min^2
- G_t: level of glucose at minute t measured in mg/dl
- X_t: insulin action at instant t
- X_t^1: intermediate insulin action at instant t
- k_x: insulin sensitivity in kg/mU
- k_g: bioavailability of the food (the proportion of the food that is absorbed and utilized by the body). It is unitless.
- a_x: inverse of insulin absorption/action time, it is constant in min^{-1},
- a_g: inverse of the meal's time, constant in min^{-1}
- Ch_t: ingested carbohydrates at instant t in g/min
- $sg0$: glucose effectiveness in min^{-1}
- I_t: insulin injected at time t measured in mU/min
- U_{endo}: endogenous glucose production in mg/(dl min)
- C: constant 50/9 (mg Kg/dl g)
- M: weight of the patient in kg

As we can see, this model uses parameters that are estimated in daily therapy; for example, insulin sensitivity, bioavailability of meals, insulin absorption and endogenous glucose production for instance. Insulin sensitivity varies throughout the day and has a lot of influence on the blood glucose level variability of patients with diabetes. Both insulin sensitivity and endogenous insulin production are difficult to estimate since they vary significantly among different patients and day periods.

C. Genetic Algorithm for Model Fitting

To obtain the customized parameters of the minimal model explained in the previous section based on a patient's historical data, we implemented a genetic algorithm in Matlab [21]. The genetic algorithm uses real coding of individuals, a representation widely used in numerical optimization problems [22] [23]. In the next subsections, we are going to describe the main aspects of this evolutionary algorithm:

- Representation of the solutions or individuals, subsection III-C1.
- Quality or fitness of the solutions, subsection III-C2.
- Operators and parameters used in the algorithm, subsection III-C3.

1) Representation of individuals: Individuals are represented as a sequence of 50 real values corresponding to the parameters used in the model. These 50 parameters are:

- k_{x_i} with $i = 1$ to 12, and $k_{x_i} \in [0.01, 500]$
- k_{g_i} with $i = 1$ to 12, and $k_{g_i} \in [0.01, 500]$
- a_{x_i} with $i = 1$ to 12, and $a_{x_i} \in [0.01, 5]$
- a_{g_i} with $i = 1$ to 12, and $a_{g_i} \in [0.01, 5]$
- $s_g \in [0.01, 5]$
- $U_{endo} \in [0.01, 10]$

Four of these fifty-one parameters are further fine-tuned in two-hour sections. This way, we provide the model with the ability to vary insulin sensitivity according to the time of day. This emulates the specialists' practice and their ability to program different injection patterns and different levels of insulin sensitivity throughout the day. The parameters affected are k_x, k_g, a_x and a_g. For the algorithm to work, we set a lower and upper limit for each of the 50 parameters.

2) Fitness Function: To obtain the quality or fitness of a solution we use the value of the mean square error (MSE) calculated by comparing the result obtained in the model (optimized with the evolutionary algorithm) against the real value obtained with the patient's data. Equation 1 shows the calculation of the MSE, where Yi are predicted values, Xi original values of glucose and n is the number of samples. We can think of it as the average of the squares of the Euclidean distance between the prediction time series and the actual data time series.

$$MSE = \frac{1}{n}\sum_{i=1}^{n}(X_i - Y_i)^2 \tag{1}$$

3) Parameters: Table II lists the parameters used to run the genetic algorithm employed to fit the minimal model.

TABLE II: Experimental Parameters

Parameter	Value
Population	200
Generation	1200
Selection	25%
Crossover probability	0.8
Mutation probability	0.15

D. Probabilistic fitting

The first part of the probabilistic fitting process consists of fitting a series of model parameters, which can be done by different techniques and for which we have used a genetic algorithm. At the end of this first stage, we have the list of model parameters that have been fitted to a sample of the data, ordered by their fitness (here, the mean squared error). In the left column of Figure 3 we can see the result of this phase. As we can see, the output of the model still does not accurately fit the real data from the patient. To achieve a much finer fit we decided to extend the workflow by adding a stage with probabilistic fitting.

Now, starting from the patient data we resample each glucose value using a Gaussian distribution centered on the glucose value at each instant and with a standard deviation of 5%. This 5% corresponds to the error added by the glucose sensor. Thus we have new time series with glucose values that follow the behavior of the patient's original time series. The result of this stage is shown on the center and right columns of Figure 3. As can be seen in the figure, the fit is now much more accurate and we can say that the twelve models throughout the day are able to capture the general trend and patient-specific temporal behaviors.

E. Parkers' Grid Analysis

Predicting the glucose level in a diabetes patient is a special case of forecasting because forecasting errors can have a very different impact depending on whether the actual blood glucose level is in the hypoglycemic, hyperglycemic, or healthy range.

If our prediction points to the hyperglycemic zone, the patient will inject a higher insulin dose. If this prediction is wrong and the patient actually has a glucose level close to the hypoglycemic zone, that higher insulin dose can have catastrophic consequences. To study this type of situation, two options are available in the literature: the Clarke's error grid [24] and the Parkes' error grid (PEG) [25] [26] . In this study we have opted for the PEG as a way of measuring the accuracy of the predictions produced by our method since it is the one advised in the guidelines of the ISO15197:2013 [27].

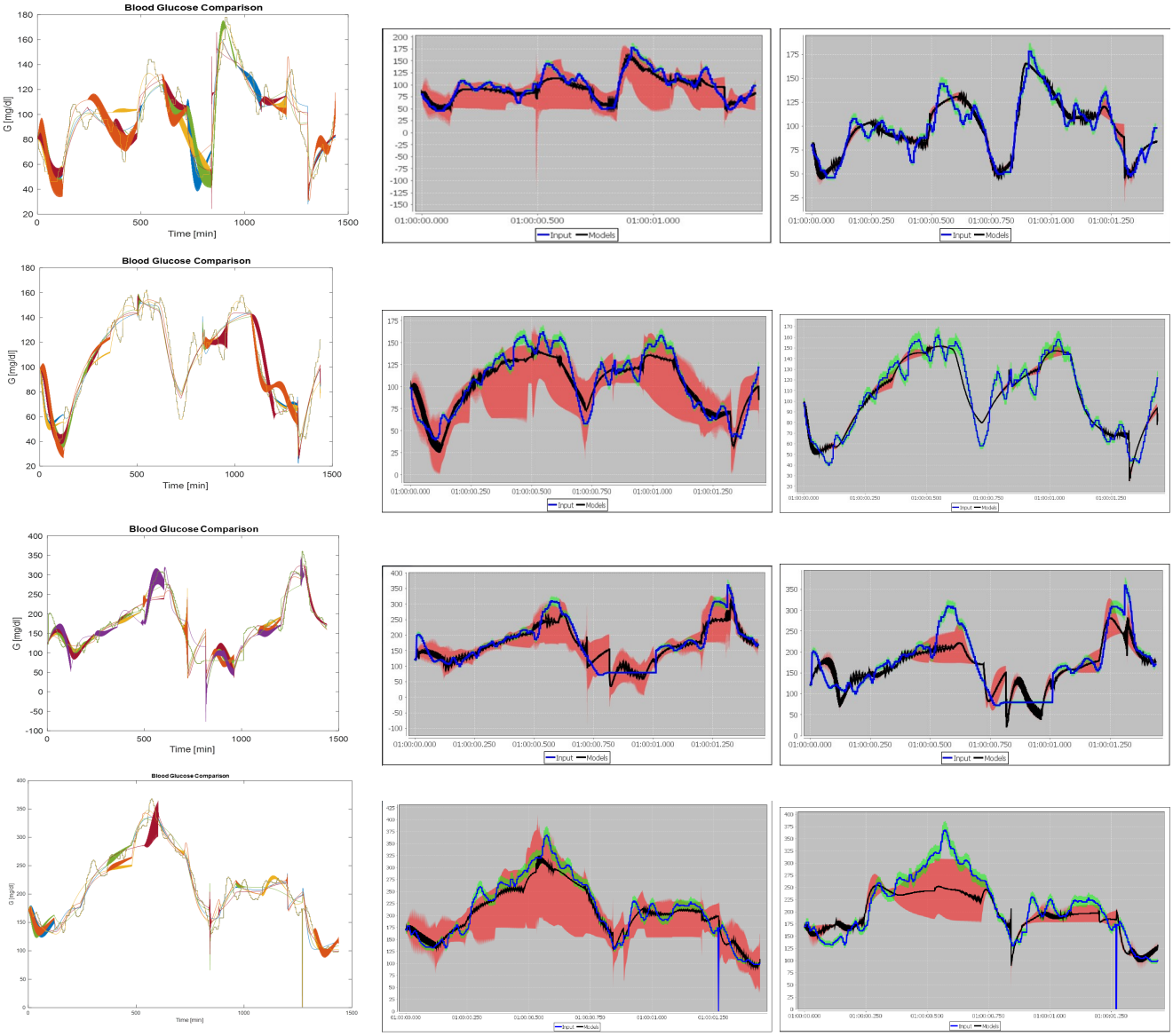

Fig. 3: Example of Model fitting (left) and Probabilistic Fitting (right) for four days from patient1

Following the PEG method we draw a scatterplot of the experimental results, Figure 4. On one axis, we have the real observations and on the other, the values obtained through a forecasting method. The main diagonal represents the perfect prediction and depending on the severity of the misprediction, the rest of the points can fall into five regions:

- Region A (dark green color) are those values within 20% of the actual values,
- Region B (bright green color) contains errors that are greater than 20% but would not lead to inappropriate treatment,
- Region C (orange color) are those points leading to unnecessary treatment,
- Region D (pink color) are those points indicating a potentially dangerous failure to detect hypoglycemia or hyperglycemia, and
- Region E (red color) are those points that would confuse treatment of hypoglycemia with hyperglycemia.

Therefore, the fewer points that appear in the C area, the better, it being of utmost importance to avoid areas D and E.

F. Cross-validation

We have chosen the K-fold cross-validation technique because it usually results in a less biased estimate of the model's performance than a simple train/test division. It could be argued that the random partitioning of the training set into much smaller subsets to be validated would produce models with a high variance, but recent research has not found empirical proof of this [28]. After shuffling the data, the total data set is divided into K subsets. Over k iterations, the models are tested on one of the subsets and trained on the other (k-1) subsets. The final results are averaged over the k iterations.

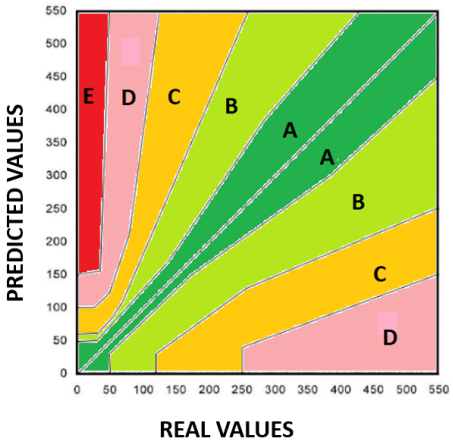

Fig. 4: Parkers' Error Grid (also known as Consensus Error Grid)

In this article K is equal to the number of days recorded for each patient, i.e. five. Thus, in each iteration, each model is trained using the data corresponding to four days and tested using the remaining day.

IV. Results and discussion

As we have seen in section III-F, to test the validity of our proposal we have used the k-fold cross-validation technique, where k = 1 day of data. Thus, we have iteratively tested on each of the five days of the dataset and trained the models on the remaining four days.

In Figures 5 to 8 we post the results obtained for the four patients shown within the PEG (for reasons of space we only show four days). Let us analyze these plots for each patient:

- Patient 1 (Figure 5) shows excellent results. All the points fall into A and B areas. In addition, we have a majority of points that follow the bisector that represents a perfect prediction. The only exception is an isolated point in the leftmost plot that is located in zone D .
- In Patient 2 (Figure 6) we find a very different situation. As can be observed, this patient monitors his glucose level very well and, in fact, has a clear tendency to be close to hypoglycemia. Although our models manage to be in zones A and B for a high percentage of time, we also find a considerable percentage of points in zone C (unnecessary treatment) and on the border of this area and zone D (erroneous treatment).
- Patient 3 (Figure 7) has a similar behavior to patient2; however our models achieve much more optimal results. Most of the points are located in zone B, with a small percentage of points on the border between zones B and C.
- The high variability of Patient 4's behavior (Figure 8) is similar to patient1's. However, in this case, our models are not able to predict glucose level excursions with sufficient reliability. This is attested to by the considerable percentage of points in zone C and by the majority of points far from the perfect prediction line.

In view of these results, we can draw several conclusions and at the same time raise several questions:

The results of our strategy differ greatly for similar patient behaviors. This suggests the need to include new variables representing latent factors in the models.

For some patients, the daily time division into twelve time slots seems to be sufficient to capture patient-specific peculiarities in the daily behavior of their glucose levels. But for other patients, this division is clearly insufficient. To remedy this situation, we can map out two options:

- Increase the number of time slots into which to divide the hours of the day.
- Make a flexible division with a variable number of time slots and/or with time slots of variable length. The latter approach seems to be perfectly suited to an evolutionary strategy.

V. Summary, Conclusions and Future Work

In this paper we have presented a strategy for 24-hour time horizon prediction of blood glucose levels in patients with Type 1 Diabetes Mellitus. Our proposal consists of several stages:

- Data are augmented using white Gaussian noise.
- Daily samples are divided into 12 identically sized slots.
- Using real data from diabetic patients, a genetic algorithm adjusts the parameters of a minimal model that characterizes the interaction between glucose and insulin based on parameters such as: insulin sensitivity, glucose sensitivity, instant glucose level, etc, for each of the 12 time slots.
- All the time series resulting from the previous stage are adjusted using Probabilistic Fitting in order to produce an ensemble of models for prediction.
- The final prediction is obtained by averaging the individuals' predictions of the ensemble's models.

Experimental data have been gathered using a k-fold cross-validation technique and the results have been analyzed using the Parkes' Error Grid framework. The discussion of the latter has draw the following conclusions:

- The division of the daily glucose samples into 12 time intervals has produced a very significant improvement in the final adjustment of the minimal model used. For some patients, this has proven to be a good technique for capturing the uncertainty of their daily glucose evolution.
- However, for other patients this division seems insufficient. To remedy this situation and as future work, we plan to test a larger number of slots, time intervals of varying length and other evolutionary algorithms such as Particle Swarm Optimization.

Acknowledgment

We acknowledge support from Spanish Ministry of Economy and Competitiveness under project RTI2018-095180-B-I00 and Madrid Regional Goverment - FEDER grants

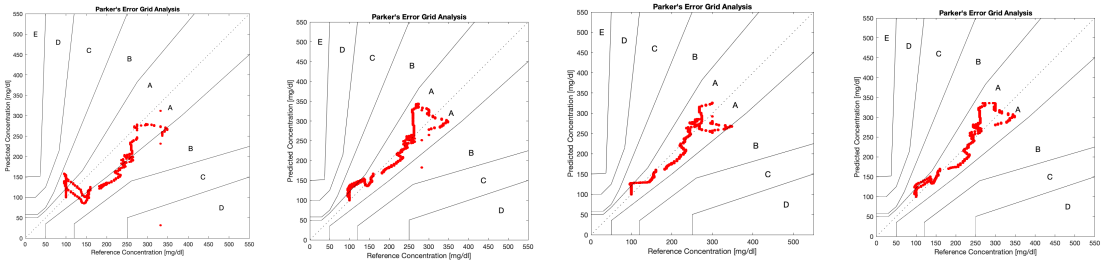

Fig. 5: Patient1. PEG Results for four different days

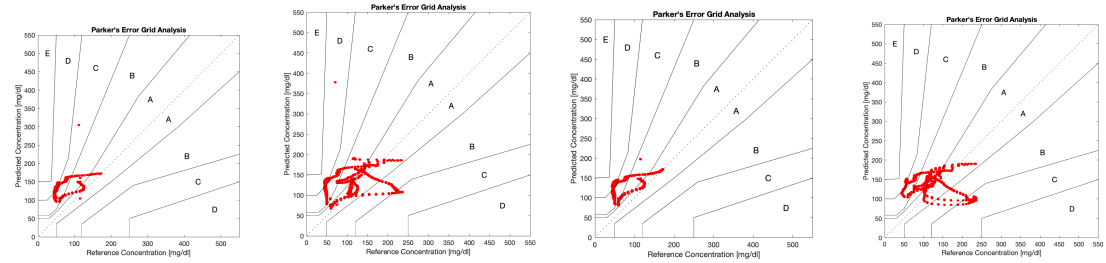

Fig. 6: Patient2. PEG Results for four different days

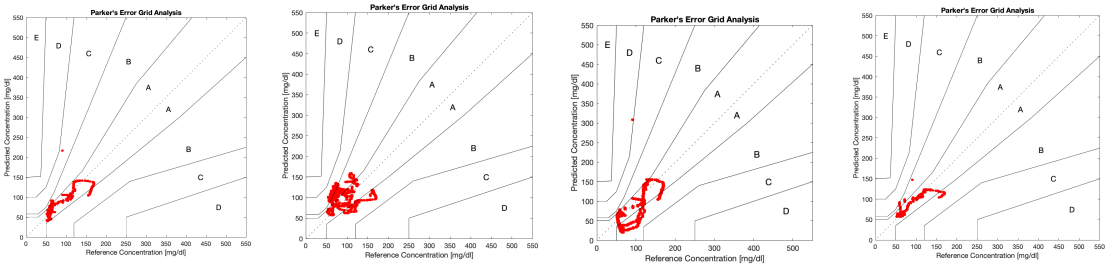

Fig. 7: Patient3. PEG Results for four different days

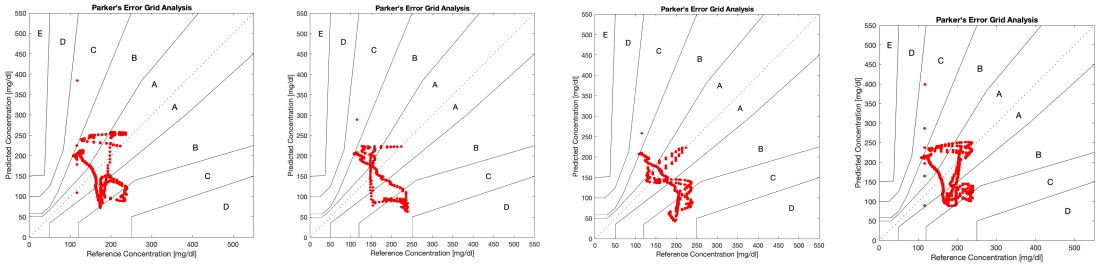

Fig. 8: Patient4. PEG Results for four different days

B2017/BMD3773 (GenObIA-CM) and Y2018/NMT-4668 (Micro-Stress- MAP-CM). Devices for adquiring data from patients were adquired with the support of Fundación Eugenio Rodriguez Pascual 2019 grant - *Desarrollo de sistemas adaptativos y bioinspirados para el control glucémico con infusores subcutáneos continuos de insulina y monitores continuos de glucosa (Development of adaptive and bioinspired systems for glycaemic control with continuous subcutaneous insulin infusors and continuous glucose monitors).*

REFERENCES

[1] Hrushikesh N Mhaskar, Sergei V Pereverzyev, and Maria D van der Walt. A deep learning approach to diabetic blood glucose prediction. *Frontiers in Applied Mathematics and Statistics*, 3:14, 2017.

[2] José Ignacio Hidalgo, Marta Botella, J. Manuel Velasco, Oscar Garnica, Carlos Cervigón, Remedios Martínez, Aranzazu Aramendi, Esther Maqueda, and Juan Lanchares. Glucose forecasting combining markov chain based enrichment of data, random grammatical evolution and bagging. *Appl. Soft Comput.*, 88:105923, 2020.

[3] Thierry Prud'homme, Alain Bock, Grégory François, and Denis Gillet. Preclinically assessed optimal control of postprandial glucose excursions for type 1 patients with diabetes. In *IEEE Conference on Automation Science and Engineering, CASE 2011, Trieste, Italy, Aug. 24-27, 2011*, pages 702–707. IEEE, 2011.

[4] Lucy Mays. Diabetes mellitus standards of care. *Nursing Clinics of North America*, 50(4):703 – 711, 2015. Pathophysiology and Care Protocols for Nursing Management.

[5] Mirko Messori, Chiara Toffanin, Simone Del Favero, Giuseppe De Nicolao, Claudio Cobelli, and Lalo Magni. Model individualization for artificial pancreas. *Computer Methods and Programs in Biomedicine*, pages –, 2016.

[6] Christina-Maria Kastorini, George Papadakis, Haralampos J. Milionis, Kallirroi Kalantzi, Paolo-Emilio Puddu, Vassilios Nikolaou, Konstantinos N. Vemmos, John A. Goudevenos, and Demosthenes B. Panagiotakos. Comparative analysis of a-priori and a-posteriori dietary patterns using state-of-the-art classification algorithms: A case/case-control study. *Artificial Intelligence in Medicine*, 59(3):175 – 183, 2013.

[7] Roman Hovorka, Janet M Allen, Daniela Elleri, Ludovic J Chassin, Julie Harris, Dongyuan Xing, Craig Kollman, Tomas Hovorka, Anne Mette F Larsen, Marianna Nodale, Alessandra De Palma, Malgorzata E Wilinska, Carlo L Acerini, and David B Dunger. Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial. *The Lancet*, 375:743 – 751, 2010.

[8] B. Kovatchev, C. Cobelli, E. Renard, S. Anderson, M. Breton, S. Patek, W. Clarke, D. Bruttomesso, A. Maran, S. Costa, A. Avogaro, C. Dalla Man, A. Facchinetti, L. Magni, G. De Nicolao, J. Place, and A. Farret. Multinational study of subcutaneous model-predictive closed loop control in type 1 diabetes mellitus: Summary of the results. *Diabetes Sci Technol*, 4:1374–1381, 2010.

[9] F.H. El-Khatib, S.J. Russell, D.M. Nathan, R.G. Sutherlin, and E.R. Damiano. A bihormonal closed-loop artificial pancreas for type 1 diabetes. *Sci Transl Med.*, 2 (27), 2010.

[10] Lalo Magni, Marco Forgione, Chiara Toffanin, Chiara Dalla Man, Boris Kovatchev, Giuseppe De Nicolao, and Claudio Cobelli. Run-to-run tuning of model predictive control for type 1 diabetes subjects: In silico trial. *Journal of Diabetes Science and Technology*, 3(5):1091–1098, 2009. PMID: 20144422.

[11] Chengxia Yu and Chunhui Zhao. Rapid model identification for online glucose prediction of new subjects with type 1 diabetes using model migration method. {*IFAC*} *Proceedings Volumes*, 47(3):2094 – 2099, 2014. 19th {IFAC} World Congress.

[12] E. Dassau, H. Zisser, B. Grosman, W. Bevier, M.W. Percival, L. Jovanovic, and F.J. Doyle. Artificial pancreatic betta-cell protocol for enhanced model identification. *Diabetes*, pages A105–A106, 2009.

[13] G. M. Steil, C. C. Palerm, N. Kurtz, G. Voskanyan, A. Roy, S. Paz, and F. R. Kandeel. The effect of insulin feedback on closed loop glucose control. *J Clin Endocrinol Metab*, 96:1402–1408, 2011.

[14] Michel Gevers. Identification for control: From the early achievements to the revival of experiment design*. *European Journal of Control*, 11(4):335 – 352, 2005.

[15] J. C. Cortés, Almudena Sánchez-Sánchez, Francisco-José Santonja, and Rafael J. Villanueva. Non-parametric probabilistic forecasting of academic performance in spanish high school using an epidemiological modelling approach. *Appl. Math. Comput.*, 221:648–661, 2013.

[16] M. A. Tanner and W. H. Wong. From EM to Data Augmentation: The Emergence of MCMC Bayesian Computation in the 1980s. *ArXiv e-prints*, April 2011.

[17] Mohit Yadav, Pankaj Malhotra, Lovekesh Vig, K. Sriram, and Gautam Shroff. ODE - augmented training improves anomaly detection in sensor data from machines. *CoRR*, abs/1605.01534, 2016.

[18] José Manuel Velasco, Oscar Garnica, Juan Lanchares, Marta Botella, and José Ignacio Hidalgo. Combining data augmentation, edas and grammatical evolution for blood glucose forecasting. *Memetic Comput.*, 10(3):267–277, 2018.

[19] R.N. Bergman, Y.Z. Ider, C.R. Bowden, and C Cobelli. Quantitative estimation of insulin sensitivity. *The American journal of physiology*, 236:E667–77, 07 1979.

[20] Anirban Roy and Robert S. Parker. Dynamic modeling of exercise effects on plasma glucose and insulin levels. *Journal of Diabetes Science and Technology*, 1(3):338–347, 2007. PMID: 19885088.

[21] MATLAB. *version 7.10.0 (R2010a)*. The MathWorks Inc., Natick, Massachusetts, 2010.

[22] Jiquan Wang, Mingxin Zhang, Okan K. Ersoy, Kexin Sun, and Yusheng Bi. An improved real-coded genetic algorithm using the heuristical normal distribution and direction-based crossover. *Comput. Intell. Neurosci.*, 2019:4243853:1–4243853:17, 2019.

[23] K. Valarmathi, D. Devaraj, and T.K. Radhakrishnan. Real-coded genetic algorithm for system identification and controller tuning. *Applied Mathematical Modelling*, 33(8):3392–3401, 2009.

[24] W.L. Clarke, D. Cox, L.A. Gonder Frederick, W. Carter, and S.L. Pohl. Evaluating clinical accuracy of systems for self-monitoring of blood glucose. *Diabetes Care*, 10(5):622–628, September 1987.

[25] Andreas Pfützner, David C. Klonoff, Scott Pardo, and Joan L. Parkes. Technical aspects of the parkes error grid. *Journal of Diabetes Science and Technology*, 7(5):1275–1281, 2013. PMID: 24124954.

[26] J L Parkes, S L Slatin, S Pardo, and B H Ginsberg. A new consensus error grid to evaluate the clinical significance of inaccuracies in the measurement of blood glucose. *Diabetes Care*, 23(8):1143–1148, 2000.

[27] Nina Jendrike, Annette Baumstark, Ulrike Kamecke, Cornelia Haug, and Guido Freckmann. Iso 15197: 2013 evaluation of a blood glucose monitoring system's measurement accuracy. *Journal of Diabetes Science and Technology*, 11(6):1275–1276, 2017. PMID: 28849677.

[28] Yoshua Bengio and Yves Grandvalet. No unbiased estimator of the variance of k-fold cross-validation. *J. Mach. Learn. Res.*, 5:1089–1105, December 2004.