Clarke and Parkes Error Grid Analysis of Diabetic Glucose Models obtained with Evolutionary Computation

J. Ignacio Hidalgo*
hidalgo@ucm.es

J. Manuel Colmenar *
jmcolmenar@ajz.ucm.es

Jose L. Risco-Martín*
jlrisco@ucm.es

Esther Maqueda
Endocrinology and Nutrition S.
Hospital Virgen de la Salud,
Toledo (Spain)
esthermaq@gmail.com

Marta Botella
Endocrinology and Nutrition S.
Hospital U. Príncipe Asturias,
Alcalá de Henares (Spain)
marta.botella@salud.madrid.org

Jose-Antonio Rubio
Endocrinology and Nutrition S.
Hospital U. Príncipe Asturias,
Alcalá de Henares (Spain)
joseantonio.rubio@salud.madrid.org

Alfredo Cuesta-Infante*
acuestai@ucm.es

Juan Lanchares*
julandan@ucm.es

Oscar Garnica*
ogarnica@ucm.es

*Adaptive and Bioinspired Systems Group (ABSys)
Facultad de Informática
Universidad Complutense de Madrid (Spain)

ABSTRACT

Diabetes mellitus is a disease that affects to hundreds of millions of people worldwide. Maintaining a good control of the disease is critical to avoid severe long-term complications. In recent years, a lot of research has been made to improve the quality of life of the diabetic patient, especially in the automation of glucose level control. One of the main problems that arises in the (semi) automatic control of diabetes, is to obtain a model that explains the behavior of blood glucose levels with insulin, food intakes and other external factors, fitting the characteristics of each individual or patient. Recently, Grammatical Evolution (GE), has been proposed to solve this lack of models. A proposal based on GE was able to obtain customized models of five in-silico patient data with a mean percentage average error of 13.69 %, modeling well also both hyper and hypoglycemic situations. In this paper we have extended the study of Error Grid Analysis (EGA) to prediction models in up to 8 in-silico patients. EGA is commonly used in Endocrinology to test the clinical significance of differences between measurements and real value of blood glucose, but has not been used before as a metric in obtention of glycemia models.

Categories and Subject Descriptors

I.2.8 [**Artificial Intelligence**]: Problem Solving, Control Methods, and Search—*Heuristic methods*; G.1.6 [**Numerical Analysis**]: Optimization—*Global optimization*

Keywords

Grammatical Evolution, Modeling, Diabetes

GECCO'14, July 12–16, 2014, Vancouver, BC, Canada.

http://dx.doi.org/10.1145/2598394.2609856 .

1. INTRODUCTION AND MOTIVATION

Diabetes mellitus is a disease affecting more than 366 million people worldwide. According to the World Health Organization (WHO, http://www.who.int) those figures are expected to double by 2030, so in some forums, diabetes is considered the epidemic of the XXI Century. Many factors influence the appearance of the disease, but all diabetics suffer a defect in either the secretion or in the action of insulin, which is essential for the control of blood glucose levels. The result is that cells does not assimilate sugar and, as a consequence, there is a rise in blood glucose levels, or hyperglycemia. According to the American Diabetes Association (ADA, http://www.diabetes.org/) we can distinguish four types of diabetes:

- Type 1 Diabetes (T1DM): cells do not produce insulin because of an autoimmune process. T1 diabetics needs to inject insulin or wear an insulin pump to control glucose levels.
- Type 2 Diabetes (T2DM): results from insulin resistance, where cells fail to use insulin properly, sometimes combined with an absolute insulin deficiency.
- Gestational Diabetes: appears in the gestation period in one out of ten pregnant women. Pregnancy is a change in the body's metabolism, since the fetus uses the mother's energy for food, oxygen and others. This causes a decrease in the secretion of insulin from the mother. Some T2 diabetics can control the illness only with exercise, pills or a combination of them.
- Other Types: such as problems on β -cells, genetic defects affecting insulin action, induced by drugs, genetic syndromes, etc.

It is important to maintain a good glycemic control to prevent the acute complications specific to diabetes (diabetic ketoacidosis and hypoglycemia, defined as blood glucose value lower than $70mg/dl$). Multiple studies have also demonstrated that good glycemic control prevents chronic complications (mainly nephropathy, retinopathy and microangiopathy).

Diabetic retinopathy, for instance is a leading cause of blindness in the world and visual disturbances in patients between 25 and 74 years old. regarding diabetic nephropathy, the percentage of patients who develop kidney failure has decreased significantly in recent years due to improved metabolic control, more aggressive treatment of hypertension and the use of drugs that inhibit the renin-angiotensin system: This means a reduction in the number of patients who have to be subjected to dialysis and / or kidney transplantation. In T1DM cohort of DCCT[1] / EDIC[2], less than 2 % (10 of 711) of patients treated with intensive therapy developed renal failure.

Regarding neuropathy, approximately 50 % of diabetic patients develop neuropathy. This leads to increased morbidity, including infections, ulcers and amputations. Diabetic patients are also at increased risk for cardiovascular disease (myocardial infarction, angina, silent ischemia). The coronary risk of a diabetic patient is similar to that of a person who has previously had a heart attack. The EDIC study showed that intensive therapy was able to reduce cardiovascular morbidity and mortality.

Summing up, in recent years, it has been shown that a strict glycemic control in critically ill patients improves performance and reduces medical costs [1] [14]. Unfortunately glucose levels control is a demanding and difficult task for both patients and their families. To keep good levels of blood glucose, the patient must perform regular measurements (which involves at least one puncture in each measure), insulin dose estimation, carbohydrates estimation, analyze all this information somehow and to have some capacity of prediction to know what level of glucose would have if ingested a certain amount of food or injected with a quantity of an insulin of a certain kind. In fact, the objective is to avoid not only long periods of hyperglycemia (glucose levels $\geq 120mg/dl$) but also episodes of severe hypoglycemia (glucose levels $\leq 40mg/dl$) that can lead to patient death.

One of the higher barriers for fully automatic insulin administration is the lack of individualized models of glucose levels. Recently, the application of evolutionary computation for obtaining customized models of patients, has been proposed [10]. Unlike previous approaches, that obtain averaged models, the proposal of Hidalgo et al. uses Grammatical Evolution (GE) to obtain individualized models. [10] and [11] outlined preliminary and promising results with 5 in-silico patients.

The aim of this paper is twofold. First, we would like to share the explained proposal with the audience of the MedGec Workshop, in order to receive the feedback of an expert community. Second, we have extended the work in [10] in several ways:

- We have obtained validated models for three new in-silico patients. The objective is to test the robustness of the evolutionary approach, using more variety of patients and including at least one with hypoglycemia.
- We have analyzed experimental results in terms of Error Grid Analysis (EGA) for the eight in-silico patients. EGA is commonly used in Endocrinology to test the clinical significance of differences between measurements and real value of blood glucose. We present here EGAs performed with two approaches: Clarke [3] and Parkes [17] error grids.
- We propose to apply EGA analysis in the generation and optimization of prediction models.

[1]Diabetes Control and Complications Trial

[2]Epidemiology of Diabetes Interventions and Complications

The rest of the paper is organized as follows. Section 2 gives a brief description of the related work in glycaemia models. Section 3 explains how to obtain individualized models by means of Grammatical Evolution. Section 4 presents the experimental setup, giving detailed information of the data. Section 4 also remembers the basis of EGA under both approaches, Clarke and Parkes. In Section 5 we present the experimental analysis and discussion. We conclude the paper and propose future work on Section 6.

2. RELATED WORK

Our ultimate goal is to provide a tool that allows patients to improve glucose control. As we have mentioned, glucose level control is a hard task, because patients need to perform blood glucose regular measurements, develop some ability to estimate carbohydrates units or rations, incorporate some knowledge about their personal bodies or feelings, and eventually make an insulin dose estimation. Thus, a diabetic patient needs to mentally construct the abstract model of his glucose levels and apply a kind-of algorithm to decide the insulin to be injected with each meal or at some times between two meals. One of the main problems in the automation of blood glucose levels control is the lack of reliable models in response to both insulin and the other various factors involved. We can find in the literature some approaches that provide models for the average case [21][2]. However, it is well known that each patient has a different metabolism, insulin resistance, and other features. Unfortunately, there are hardly few approaches adapted to the particularities of each patient. Other important aspect that we should have in mind is the delay between insulin administration and the appearance of insulin in the blood stream with the use of subcutaneous (SC) insulin. This delay time limits the achievable control performance on subcutaneous administration of insulin.

Most of the models in the literature apply classical modeling techniques, resulting in linear equations defined profiles, or models with a limited set of inputs [4]. There are other interesting approximations, for instance, Heusden et al. [21] proposed to use personalized information of the patient, easily accesible by the specialist or the automatic system. They construct robust models looking for improving the behavior on mismatches between estimated and real data. However, this approach is only useful with linear models and can not incorporate other important factors such as exercise or stress that clearly affect glycemias.

Apart from the mentioned works, we can find in the literature other proposals that use control models. Next, we classify them in three categories:

- **Solutions by commercial companies:** *Glucofacts Deluxe* by *Bayern*, *CoPilot Health Management System* by *Abbot*, and *MenaDiab* by *Menarini* are only some of them. Those approaches were designed to facilitate the control of diabetes. The main problem is that they work only for specific glucometers. Some of them provide also insulin recommendations, although the way the model is obtained is not available.
- **Models used in artificial pancreas systems or closed loop control models:** artificial pancreas systems are closed loop control systems trying to emulate the action of a pancreas [5] [20] . They are based on the assumption that it is possible to reach a good control with approximate models, provided that the model is related to the control objective [9][18]. The main risk is hypoglycemia as a result of excessive insulin administration and due to the lack of accurate individualized models. We can find also Autoregressive models (AR) [8][19] and protocols to improve the reliability of the models [7][5] [15].

- **Other personalized control approaches:** [12][6][13] are proposals following the clinical practice. Treatment for subjects with T1DM uses rates of basal insulin delivery, insulin to carbohydrate ratios (CHO) and individual correction factors, typically from observations of the specialist. Those models are often inaccurate, since clinical data in T1DM are not extensive enough to identify the exact models [7].

Evolutionary computation has a high potential to incorporate to the model factors that are difficult to quantify, in other words to collect system dynamics, allowing us to obtain individualized models since they are able to provide a solution for each set of data on a single patient.

3. METHODOLOGY

Figure 1 shows the proposed scheme for model induction and optimization. The scheme is based on a data set of patients with T1DM and, the result of the process are validated models of glucose. In this process, we use Grammatical Evolution (GE) to obtain a mathematical expression, which describes how glycemia varies as a function of a set of parameters. Input data set should include several observable factors that can be collected by the patient or recorded by monitoring systems. The actual level of glycaemia depends on several factors with different degrees of importance. Here, it is well known that the most important are glucose level, carbohydrate intakes and insulin injections. These are the parameters that our models do take into account to predict the future glucose level.

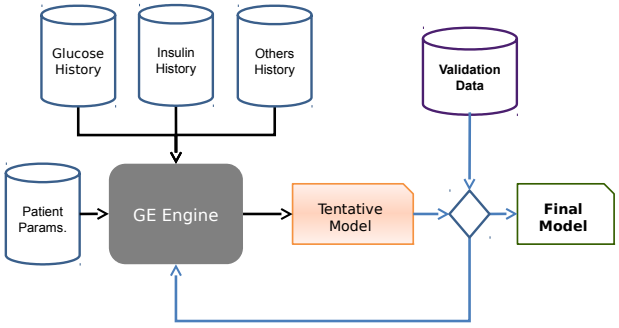


Figure 1: Model generation and optimization.

3.1 Problem description

Le us suppose that the patient is using two types of insulin, IS (Short term insulin) and IL (Long term insulin). We have registered the set of measures explained below. Given a set of measures

$$GL = \{gl_0, gl_1, \cdots, gl_n\}$$

of the glucose level of a patient, and knowing that gl_i was measured at time t_i. Given a set of intakes

$$CH = \{ch_0, ch_1, \cdots, ch_n\}$$

of carbohydrates units of a patient, and knowing that ch_i was eaten at time t_i. Given a set of injections of insulin of type S

$$IS = \{is_0, is_1, \cdots, is_n\}$$

and knowing that is_i was injected at time t_i. Given a set of injections of insulin of type L

$$IL = \{il_0, il_1, \cdots, il_n\}$$

and knowing that il_i was injected at time t_i. The problem of modeling the glucose blood level of a patient, in its simplified form, can be formulated as follows: Find an expression of estimated glucose values, denoted as $\widehat{GL}$

$$\widehat{GL}(k+1) = f(\widehat{GL}, CH, IS, IL), 0 \leq k \leq N \quad (1)$$

which minimizes the fitness function F, which tries to close the gap between real and estimated glucose values:

$$F = \sum_{i=0}^{n} \sqrt{(GL(i) - \widehat{GL}(i))^2}$$

Where $\widehat{GL}$ corresponds to previous estimated glucose values, CH corresponds to previously ingested carbohydrates and IS and IL correspond to previously injected insulin for both types, short and long effect. It should be noted that the model will provide estimated glucose values, denoted as $\widehat{GL}$. Hence, for each time step, estimated glucose is obtained by using previous estimated glucose values and actual carbohydrates and insulin units. Therefore, the dataset should provide input values for the variables in our glucose model proposal. Table 1 shows a reduced version of a data set for one of the in-silico patients under study.

k	GL	CH	IS	IL
...	...	...	...	...
30	170.88974	0	0	0
31	171.55425	0	0	0
32	172.27976	0	3	12
33	173.05923	30	0	0
34	174.09018	0	0	0
...	...	...	...	...
40	237.54628	0	0	0
41	247.25104	20	0	0
42	250.72465	0	0	0
43	251.90543	0	0	0
...	...	...	...	...

Table 1: Portion of a 24-hours dataset for a in-silico patien (Joy Wilson).

In this way, the GE engine should be able to decide how F looks like. However, in order to guide the search of the evolutionary process, we do need a grammar that will both limit the search space and represent the behavior of the blood glucose level. Next, we detail the grammars that we studied in this work.

3.2 BNF Grammars for Modeling Glucose

Unlike traditional GAs, GE evolves a genetic code that determines the production process of this solution. The code translation process is determined by grammars represented as Backus Naur Forms (BNF) which is a notation for expressing context-free grammars. In brief, a BNF specification is a set of derivation rules, expressed in the form:

```
<symbol> ::= <expression>
```

The rules are composed of sequences of terminals and non terminals. Symbols that appear at the left are non-terminals while terminals never appear on a left side. In this case we can affirm that `<symbol>` is a non terminal and, although this is not a complete BNF specification, we can affirm also that `<expression>` will be also a non-terminal since those are always enclosed between the pair <>. So, in this case the non-terminal `<symbol>` will be replaced (indicated by `::=`) by an expression. The rest of the grammar must indicate the different possibilities.

A grammar is represented by the 4-Tuple {N, T, P, S}, being N the non-terminal set, T is the terminal set, P the production rules for the assignment of elements on N and T, and S is a start symbol which should appear in N. The options within a production rule are separated by a "|" symbol. For more details on the mapping process we refer the reader to [10] from where this last paragraph was borrowed.

The concrete form of f_{GL}, f_{CH}, f_{IS} and f_{IL} will be determined by GE engine with the help of a grammar. Figure 2 shows our first and most generic tested grammar. The three terms <exprgluc>, <exprch> and <exprins> correspond to f_{GL}, f_{CH} and f_{IN}, respectively, being f_{IN} a function of f_{IS} and f_{IL}. All of them are expressions that could use prefix operands like those in rule V, variables for each of one the terms, or combinations of them through operators in rule VII.

```
N = {func, expr, op, pre-op, dig, num, var}
T = { +,-,*,/, sin, cos, abs, exp, 0, 1, 2, 3, 4, 5, 6,
     7, 8, 9, 0, glucprev, chprev, insprev}
S =  {func}
P={I, II ,III ,IV ,V ,VI ,VII}

I <func> ::= glucprev <op> <expr>

II <var> ::= glucprev
        |chprev
        |insprev

III <expr> ::= <expr> <op> <expr>
|<pre-op> (<expr>)
|<var>

IV <op> ::= + | -| / | *

V <pre-op>::=sin|cos|abs|exp

VI <dig>::=0|1|2|3|4|5|6|7|8|9

VII <num>::=<dig>.<dig>|<dig>
```

Figure 2: First grammar (generic attempt).

The grammar in Figure 3 incorporates some knowledge of the problem, since we know that glucose levels rise when the patient eats and decrease when some insulin is injected into the blood flow. The general model will be approximated with expressions similar to (2), where any previous values of glucose, carbohydrates and insulin may be used. Hence, in this grammar carbohydrates are always added, while insulin values are always subtracted, as shown in rule I.

$$\widehat{GL}(k+1) = f_{gl}(\widehat{GL}(k-m)) + f_{ch}(CH(k-m)) - \\ -f_{in}(IS(k-m), IL(k-m)), 0 \leq m \leq k \qquad (2)$$

3.3 Genetic Parameters

As with genetic programming, GE can use any search algorithm able to operate on integer or binary strings. We have selected a simple GA with single-point crossover and point mutation. Population initialization is made by randomly generating fixed integer strings. Table 2 shows the rest of the genetic and GE parameters (see [16] for more information on GE)

4. EXPERIMENTAL SETUP

In this section we describe the characteristics of the eight in-silico patients we deal with, as well as the configuration of each set of experiments. As we have explained, we predict a future value of the level of glucose in the patient's blood depending on, at least, the glucose level, the carbohydrates ingested and the insulin injected. Hence we need to consider those values in our datasets.

```
N = {func, exprgluc, gluc, exprch, varch, exprins, varins
     , op, preop, idx, cte, dgt}
T = { +,-,*,/, sin, cos, tan, exp, 0, 1, 2, 3, 4, 5, 6,
     7, 8, 9, 0, GL, CH, IS, IL, K}
S = {func}
P = {I, II ,III ,IV ,V ,VI ,VII, VIII, IX, X, XI, XII}

I    <func> ::= <exprgluc> + <exprch> - <exprins>

II   <exprgluc> ::= <preop> (<gluc>)
        |(<cte> <op> <gluc>)
        |<gluc>

III  <gluc> ::= #{GL[k_<idx>]}|#{K}

IV   <exprch> ::= <exprch> <op> <exprch>
        |<preop> (<exprch>)
        |<varch>

V    <varch> ::= #{CH[k_<idx>]}|#{K}|<cte>

VI   <exprins> ::= <exprins> <op> <exprins>
        |<preop> (<exprins>)
        |<varins>

VII  <varins> ::= #{IS[k_<idx>]}|#{IL[k_<idx>]}|#{K}
        |<cte>

VIII <op> ::=+|-|/|*
IX   <preop>::=sin|cos|tan|exp
X    <idx> ::= <dgt><dgt>
XI   <cte> ::= <dgt><dgt>.<dgt><dgt>
XII  <dgt>::=0|1|2|3|4|5|6|7|8|9
```

Figure 3: Grammar including knowledge of the problem: carbohydrates are added and insulin units are subtracted from glucose values.

Parameter	Value
Population size	100
Generations	2500
Crossover probability	0.6
Mutation probability	0.2
Tournament size	2
Max. wraps	3
Codon size	256
Chromosome length	100

Table 2: Parameters for GE experiments.

In the target in-silico patients, data were obtained with the AIDA simulator (www2aida.org). More precisely, our data series represent measures taken each 15 minutes along the day. Table 1 shows an example of the dataset of one of the in-silico patients, named Joy Wilson . For each time step, represented in one line of the table, k is the actual time, GL is the actual glucose level, CH is the carbohydrates units ingested, IS is the short effect insulin injected and IL is the long effect insulin injected. We work with a set of in-silico patients obtained with AIDA simulator. The website of the simulator offers several characterized patients from which we selected eight of them. We have included here a more varied selection in order to better analyze the quality of the GE solutions. The glucose values for each patient were obtained by introducing different carbohydrates and insulin values and then running the simulator. The description of each one of the patients can be found on the website,

but we replicate them here for the sake of clarity. The patients are the following:

Joy Wilson . This woman is on three injections of short and/or intermediate acting insulin each day, with a split-evening dose. She wants to start a family, but consistently has had quite high blood glucose levels in the early afternoon.

Howard Kistler . This 45 year old man was diagnosed as having diabetes at the age of 14. He is currently on a regimen of combined short and/or intermediate acting insulin preparations four times per day. As you can see from his home monitoring blood glucose measurements, he tends to higher blood glucose values overnight but has a low blood glucose in the mid-morning.

Steven Jones . This man is a relatively newly diagnosed insulin-dependent (type 1) diabetic patient. He has had problems maintaining his blood glucose profile on two and more recently three injections per day; so currently he is controlled on four injections per day. He tends to quite high blood glucose levels in the middle of the day, despite not eating excessively.

Elizabeth Whittaker . It has taken a lot of effort to stabilize this girl's blood glucose profile. However, she still often goes hypoglycemic in the middle of the day, especially between breakfast and lunch. She is on a slightly unusual regimen taking a short acting insulin preparation three times per day, with an intermediate acting preparation twice a day – at lunchtime and before bed.

Lizzy Laurence . This overweight 58 year old insulin-dependent (type 1) diabetic patient has had major problems losing weight. She is quite sensitive to insulin. In addition, she smokes and is at great risk of suffering a heart attack or stroke.

Mohammed Abdullah . This man often wakes with 'sweats' and feeling profoundly unwell in the middle of the night. However, his blood sugars are quite respectable when he gets up at 7:30 AM. In such a situation he needs to measure his blood glucose when he wakes in the middle of the night, feeling unwell. Clearly injecting so much insulin before he goes to bed isn't a good idea. Try adjusting his bedtime insulin and see if you can stop him going 'hypo'.

David Robins . This 18 year old insulin-dependent patient has just left home for the first time to go to the University. He isn't a very good cook and hasn't been taking good care of himself. He feels pretty awful most mornings and even going to bed early hasn't helped. He tends to quite low blood sugars in the morning, at times being at risk of going 'hypo'. See if you can adjust his insulin regimen so that his blood sugars don't run quite so low in the morning.

Hugh Allibaster . This 35 year old insulin-dependent diabetic man recently switched to using an insulin pen, injecting three 'shots' of short-acting insulin before breakfast, lunch, and dinner, while taking a single dose of long-acting insulin before going to bed. However, he hasn't quite gotten full control of his blood sugars, still tending towards high blood glucose levels overnight. How might you improve his control, through adjusting his existing insulin doses?

4.1 Error Grid Analysis

The Clarke error grid approach is used to assess the clinical significance of differences between the glucose measurement technique under test and the venous blood glucose reference measurements. The method was presented in 1986 by Clarke et al. [3] and uses a cartesian diagram to represent the values of the prediction versus the reference (actual) values. For example, if a value of 118 is predicted for a point where the real value is 90, this will be represented by the point (90, 118) in the XY cartesian graphic. In this way the diagonal, i.e. $Y = X$, represents the perfect measure, the points below and above the line indicate, respectively, overestimation and underestimation of the actual values. What is interesting in this graphic is that the XY graph is divided into a grid of zones depending on the severity of the misprediction, which is the reason of the Error Grid name. Clarke differentiated five zones in the graph (A to E), with the following meanings:

- Zone A: represents the glucose values that deviate from the reference values by 20 % or less and those that are in the hypoglycemic range (<70 mg/dl), not only the predicted value but also the reference value. Those values are clinically exact and acceptable and thus the clinical treatment will be correct.
- Zone B: represents the glucose values that deviate from the reference values by more than 20 %. In this zone we are close to unacceptable errors but the clinical treatment has a high probability of being correct. The values that fall within zone B are also clinically acceptable.
- Zones C-E: The values included in those areas are potentially dangerous, since the measure or prediction is far from being acceptable and the indicated treatment will be different from the correct. There is a high possibility of making clinically significant mistakes for values within this zones.

In 2000 Parkes et al. [17] revisited the definition of the zone and constructed a set of new error grids by using the expertise of a large panel of clinicians. They constructed new grids, differentiating for T1DM and T2DM patients. The followed method was to ask a total of 100 experts of diabetes to assign any error a category form A to E as in the Clarke error grid.

Currently, in the field of endocrinology there is not a general consensus for evaluating errors in the measurement of blood glucose for diabetics, so we use here both EGs to analyze the results.

5. EXPERIMENTAL RESULTS

Starting with the models of the eight in-silico patients, we have taken their validation data and we have obtained the Clarke and Parkes Error Grids.

Figures 4 to 11 show the experimental results on validation data and the corresponding Error Grid Analysis. Each figure is composed by four graphics. Starting from the left Figures (a) show the glucose values obtained with the best grammar-objective combination of the training phase for each patient. The actual glucose curve of the patient (in blue), the glucose value generated with the best solution of this combination (in red) and the glucose value generated with the average of the 30 solutions (in yellow) are displayed in the figure. The next two figures (b) and (c) represent the Clarke EGA for the best solution and for the average of the 30 solutions. Finally subfigures (d) show the Parkes EGA of each Patient on the validation phase.

For each patient, we have calculated the percentage that the average error of each simulation run represents in the range of the patient glucose values. The experimental results shows the quality of the models. In terms of the accuracy of the model, predicted values has an average error of 12.83 %. This results are in consonance with those presented in [10]. Once again, minimizing the average error objective does not obtain the best average results, for some of the patients.

Regarding the Error Grid Analysis, as seen in the figures, the EGA is quite good for all the in-silico patients. In the case of Clarke EG, more than 95 % of the data were found into Zone A. For Parkes EG the results are even a little bit higher. Results for patient David Robins and patient Hugh Allibaster are especially important since predict hypoglycemic values. For the first, the prediction in terms of Clarke EGA are bad. Although very close to A zone, we

found several values on dangerous zones. On the other hand, results on Hugh Allibaster shows a very good prediction on low glucose values. This clearly confirms the necessity to adapt the grammars to specific cases, including other factors or allowing a small biasing in the search. This will be one of the focus of the future work.

In general, we have found that data near hypoglycemic zones are more likely to be mispredicted by our models. Hence, we will study two approaches: on the one hand, we will incorporate the EG in the object function of the optimization; on the other hand, we will study a multi-objective approach where one objective will be to fit all the data values into the A zone in both EGs.

6. CONCLUSIONS

In this paper we extend previous works were Gramatical Evolution is applied to obtain individual models of blood glucose levels in humans. Here, we present validation data for three new in-silico patients, tackling a total number of eight in-silico patients, which were taken from the AIDA simulator. Experimental results confirm that Evolutionary Computation can solve problems for a higher variety of in-silico patients and also for patients with dangerous values of glucose, i.e. hypoglycemic values.

There is still a lot of work to do, the main focus of our research is to apply the method explained in this paper to real patients. This step necessarily implies the adaptation and customization of grammars, a higher study of the fitness function and landscapes. In addition, we will consider the multiobjective optimization with both average and maximum error objective and EGAs. We will also consider to integrate fuzzy regression into the GP process.

7. REFERENCES

[1] International surviving sepsis campaign guidelines committee: Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock. *Crit Care Med*, 36:296–327, 2008.

[2] A. American-Diabetes-Association. Standards of medical care in diabetes 2010. *Diabetes Care*, 33(S1):11–61, 2010.

[3] G.-F. L. C. W. P. S. Clarke WL1, Cox D. Evaluating clinical accuracy of systems for self-monitoring of blood glucose. *Diabetes Care*, 10(5):622–628, 1987.

[4] C. Cobelli, C. Dalla Man, G. Sparacino, L. Magni, G. De Nicolao, and B. Kovatchev. Diabetes: Models, signals, and control. *Biomedical Engineering, IEEE Reviews in*, 2:54 –96, 2009.

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

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

[7] D. A. Finan, C. C. Palerm, F. J. Doyle, D. E. Seborg, H. Zisser, W. C. Bevier, and L. Jovanovic. Effect of input excitation on the quality of empirical dynamic models for type 1 diabetes. *AIChE Journal*, 55(5):1135–1146, 2009.

[8] A. Gani, A. Gribok, Y. Lu, W. Ward, R. Vigersky, and J. Reifman. Universal glucose models for predicting subcutaneous glucose concentration in humans. *Information Technology in Biomedicine, IEEE Transactions on*, 14(1):157 –165, jan. 2010.

[9] M. Gevers. Identification for control: From the early achievements to the revival of experiment design. In *44th IEEE Conference on Decision and Control, 2005 and 2005 European Control Conference. CDC-ECC '05*, page 12, dec. 2005.

[10] J. I. Hidalgo, J. M. Colmenar, J. L. Risco-Martin, A. Cuesta-Infante, E. Maqueda, M. Botella, and J. A. Rubio. Modeling glycemia in humans by means of grammatical evolution. *Applied Soft Computing*, (0):–, 2013.

[11] J. I. Hidalgo, E. Maqueda, J. L. Risco-Martín, A. Cuesta-Infante, J. M. Colmenar, and J. Nobel. glucmodel: A monitoring and modeling system for chronic diseases applied to diabetes. *Journal of Biomedical Informatics*, (0):–, 2014.

[12] R. Hovorka, J. M. Allen, D. Elleri, L. J. Chassin, J. Harris, D. Xing, C. Kollman, T. Hovorka, A. M. F. Larsen, M. Nodale, A. D. Palma, M. E. Wilinska, C. L. Acerini, and D. 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.

[13] B. Kovatchev, C. Cobelli, E. Renard, S. Anderson, M. Breton, S. Patek, W. Clarke, D. Bruttomesso, A. Maran, S. Costa, A. Avogaro, C. D. Man, A. Facchinetti, L. Magni, G. D. 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.

[14] J. Krinsley and R. Jones. Cost analysis of intensive glycemic control in critically ill adult patients. *Chest*, 129:644–650, 2006.

[15] H. Lee and B. Bequette. A closed-loop artificial pancreas based on model predictive control: Human-friendly identification and automatic meal disturbance rejection. *Biomedical Signal Processing and Control*, 4(4):347 – 354, 2009. Special Issue on Biomedical Systems, Signals and Control Extended Selected papers from the IFAC World Congress, Seoul, July 2008.

[16] M. O'Neill and C. Ryan. *Grammatical Evolution: Evolutionary Automatic Programming in an Arbitrary Language*. Kluwer Academic Publishers, 2003.

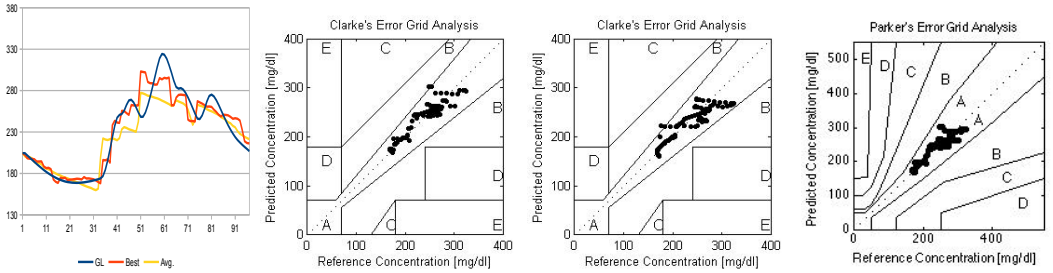
[17] P. S. G. B. Parkes JL, Slatin SL. A new consensus error grid to evaluate the clinical significance of inaccuracies in the measurement of blood glucose. *Diabetes Care*, 23(8):1143–1148., 2000.

[18] D. E. Rivera and S. V. Gaikwad. Systematic techniques for determining modelling requirements for siso and mimo feedback control. *Journal of Process Control*, 5(4):213 – 224, 1995. IFAC Symposium: Advanced Control of Chemical Processes.

[19] G. Sparacino, F. Zanderigo, S. Corazza, A. Maran, A. Facchinetti, and C. Cobelli. Glucose concentration can be predicted ahead in time from continuous glucose monitoring sensor time-series. *Biomedical Engineering, IEEE Transactions on*, 54(5):931 –937, may 2007.

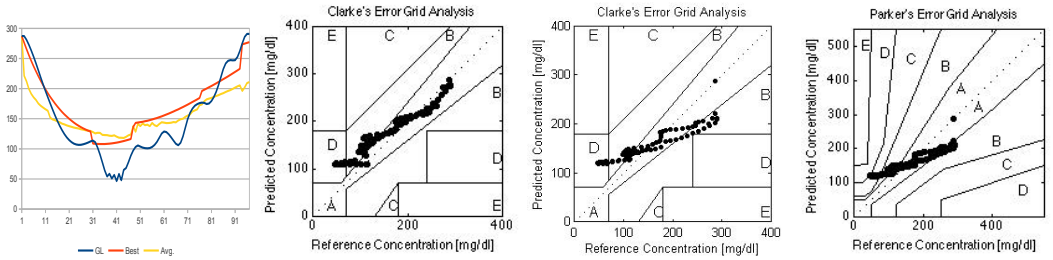
[20] G. M. Steil, C. C. Palerm, N. Kurtz, G. Voskanyan, A. Roy, S. Paz, and F. R. Kandeel. The effect of insulin feedback on closed loop glucose control. *J Clin Endocrinol Metab*, 96:1402–1408, 2011.

[21] K. van Heusden, E. Dassau, H. Zisser, D. Seborg, and F. Doyle. Control-relevant models for glucose control using a priori patient characteristics. *IEEE Transactions on Biomedical Engineering*, 59(7):1839 –1849, july 2012.



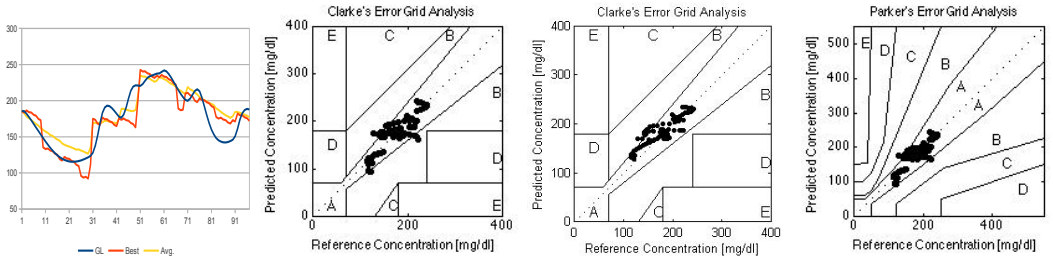
(a) Validation (b) Clarke EGA of the best (c) Clarke EGA of the Avg. (d) Parkes EGA of the best

Figure 4: Results and EGA for Joy Wilson



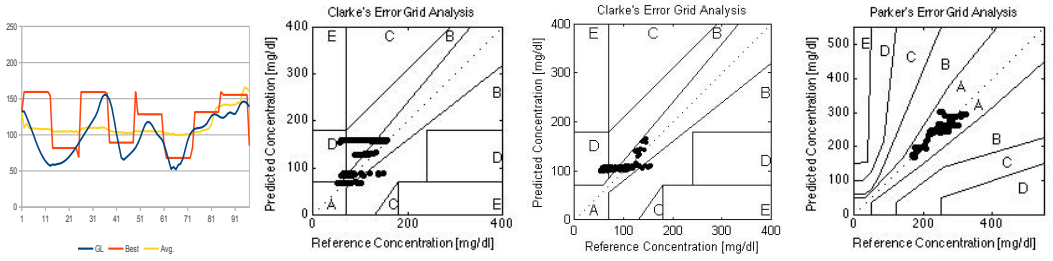
(a) Validation (b) Clarke EGA of the best (c) Clarke EGA of the Avg. (d) Parkes EGA of the best

Figure 5: Results and EGA for Howard Kistler



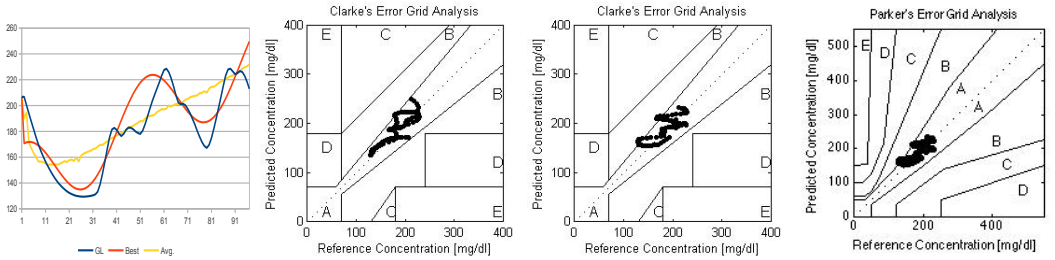
(a) Validation (b) Clarke EGA of the best (c) Clarke EGA of the Avg. (d) Parkes EGA of the best

Figure 6: Results and EGA for Steven Jones



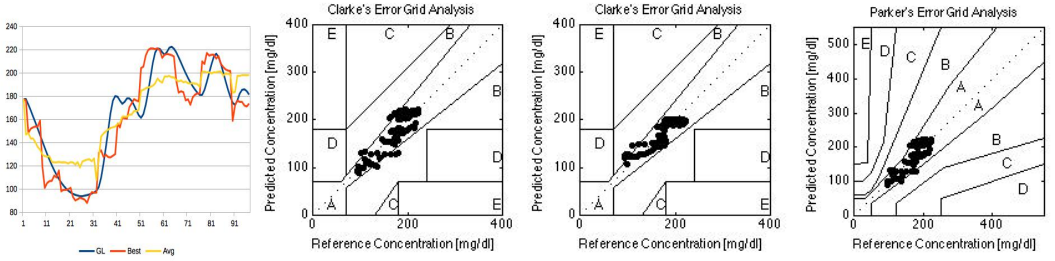
(a) Validation (b) Clarke EGA of the best (c) Clarke EGA of the Avg. (d) Parkes EGA of the best

Figure 7: Results and EGA for Elizabeth Whittaker



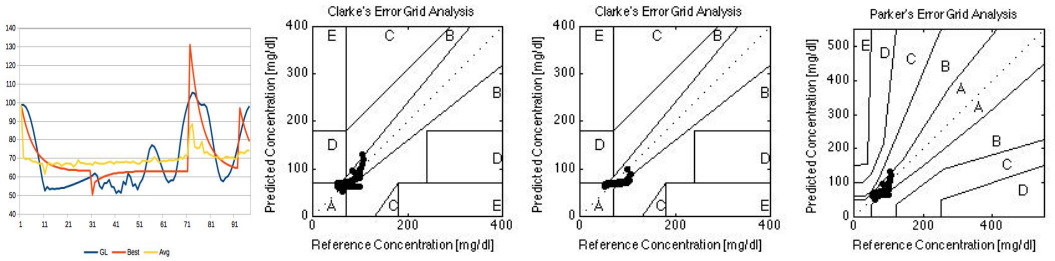
(a) Validation (b) Clarke EGA of the best (c) Clarke EGA of the Avg. (d) Parkes EGA of the best

Figure 8: Results and EGA for Lizzy Laurence



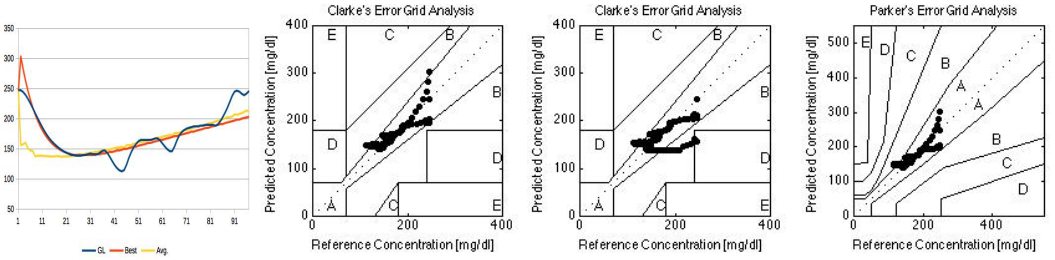
(a) Validation (b) Clarke EGA of the best (c) Clarke EGA of the Avg. (d) Parkes EGA of the best

Figure 9: Results and EGA for Mohammed Abdullah



(a) Validation (b) Clarke EGA of the best (c) Clarke EGA of the Avg. (d) Parkes EGA of the best

Figure 10: Results and EGA for David Robins



(a) Validation (b) Clarke EGA of the best (c) Clarke EGA of the Avg. (d) Parkes EGA of the best

Figure 11: Results and EGA for Hugh Allibaster