Using Grammatical Evolution to Generate Short-Term Blood Glucose Prediction models

Iván Contreras[1], **Arthur Bertachi**[1,2], **Lyvia Biagi**[1,2], **Silvia Oviedo**[1] **Josep Vehí**[1,3]
[1] Institut d'Informatica i Aplicacions. Universitat de Girona, Spain
[2] Federal University of Technology – Paraná (UTFPR), Guarapuava, Brazil
[3] Centro de Investigación Biomédica en Red de Diabetes y
Enfermedades Metabólicas Asociadas (CIBERDEM), Spain
ivancontrerasfd@gmail.com

Abstract

Blood glucose levels prediction provides the possibility to issue early warnings related to ineffective or poor treatments. Advance notifications of adverse glycemic events can provide sufficient time windows to issue appropriate responses and adjust the therapy. Consequently, patients could avoid hyperglycemia and hypoglycemia conditions which would improve overall health, safety, and the quality of life of insulin dependent patients. This report concerns to the application of a search-based algorithm to generate models able to capture the dynamics of the blood glucose at a personalized patient level. The grammar-based feature generation allows to build complex empirical models using the data gathered by a sensor augmented therapy, a fitness band and a basic knowledge of T1D dynamics. Final model solutions provide blood glucose levels estimations using prediction horizons of 30, 60 and 90 minutes.

1 Introduction

The human body requires that blood glucose (BG) levels are maintained in a narrow range, approximately in the range of 70 to 110 mg/dl. BG levels are affected by a large number of exogenous factors and, therefore, the pancreas is required to regulate these levels by releasing the insulin and glucagon hormones that are secreted by β-cells and α-cells, respectively. Type 1 diabetes (T1D) is the consequence of an autoimmune attack on β-cells that significantly impairs insulin production. Thus, individuals with T1D fully rely on external insulin to manage their BG.

The increasing interest in the improvement of the management of this disease and its comorbidities is accompanied by several research efforts focused on therapeutic solutions for T1D. One of the most challenging efforts is placed in the artificial pancreas (AP) field. AP refers to an automated system that combine a glucose sensor, a closed-loop control algorithm, and an insulin infusion device which are all engaged together to manage BG and reduce T1D adverse events. AP has promoted the emergence of increasing research in prediction engines [Cobelli *et al.*, 2011] and its role. Additionally, it has boosted the commercialization and recent technological advances of continuous glucose monitoring sensors (CGM). Thus, the popularization of CGM sensors has led to more robust and portable devices which has stimulated the availability of semi-continuous BG measurements which in turn are frequently used as data source for predictive modeling in diabetes.

It is well-known in clinical practice that is complex to achieve a tight glycemic control specially since certain patients exhibit large variations in their BG signals. There are plenty of factors that influence the blood glucose dynamics and thereby influence glycemic control response. Some of the factors strongly affecting the glucose metabolism are the exercise or physical activity, weather conditions, dietary disturbances, physical conditions, psychological status of patients ([Brusko *et al.*, 2005; Fuchsjäger-Mayrl *et al.*, 2002; Mianowska *et al.*, 2011]) together endogenous processes, such as circadian cycles [Hinshaw *et al.*, 2013], menstrual periods and pregnancies in women ([Evers *et al.*, 2004; Cramer, 1942]) and other diseases. These varied factors are often complex to identify, and therefore the prediction of BG values using personalized models is specially important in these scenarios [I. *et al.*, 2016]. Customized models can capture lifestyle factors which influence the physiologic response of a patient to its carbohydrate intake and insulin dosage. Thus, the wide range of variability in the glucose dynamics of T1D patients makes the generation of predictive models a challenging and crucial task.

On the one hand, the treatment of diabetes is conditioned by a high inter-patient variability which leads to a lack of general models to respond to the particularities of patients. On the other hand, intra-patient variability makes it complex to generalize models for the glucose response of a singular patient. The variability points at personalized and dynamic glucose models as one of the best options to implements features to deal with the treatments variability. At present, intelligent algorithms are obtaining a substantial success applying data driven methods to support advanced analytics and providing individualized medical aid to patients suffering with diabetes. The incremental repositories of data together with the improved performance of intelligent methodologies to handle and process this information have led to the development of tools and applications that enhance the effective management of diabetes [Contreras and Vehi, 2018]. This report propose the implementation of customizable models for patients using

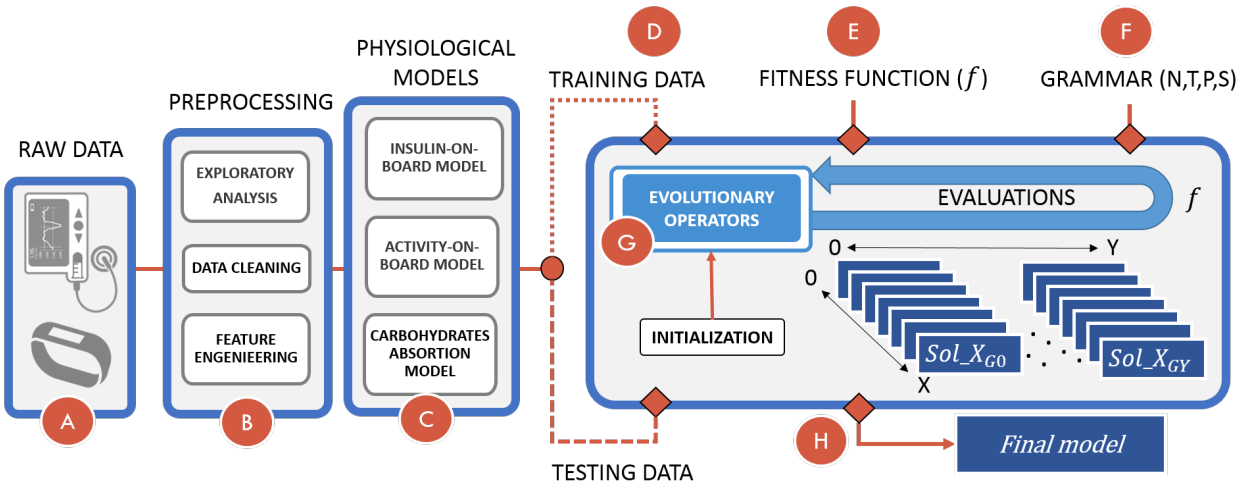

Figure 1: Schematic representation of the method implemented to generate prediction models for blood glucose values

an evolutionary computation approach. The article focuses on the critical problem of anticipating BG levels in a short-term (30 to 90 min). The proposal involves a prediction tool based on the grammatical evolution method which introduces multiple features with the aim of dealing with unforeseen changes.

2 Related Work

BG prediction models can be classified into three different subsets: physiological models, data-driven models, and hybrid models. First, physiological models are usually generated by the experts with wide knowledge and comprehension of insulin, glucose metabolism and other parameters. Second, data-driven models completely relies on BG measurements and other data inputs. These type of models are typically based on artificial intelligence techniques such as genetic algorithms, robust filters, fuzzy logic, case reasoning, auto-regressive models, reinforcement learning, random forests, support vector regression, and artificial neural networks models. Finally, an alternative architecture involves a combination of the two previous approaches. These models are commonly used in a pre-processing stage, and the preprocessed inputs enter a data driven model. These type of models are commonly known as hybrid models and some recent approaches were examined in previous studies [Balakrishnan *et al.*, 2013; Estrada *et al.*, 2010; Zecchin *et al.*, 2014]. We redirect interested readers to a more comprehensive review of prediction BG models in [Oviedo *et al.*, 2016].

Previous studies using grammatical evolution (GE) to estimate BG values include the studies [Hidalgo *et al.*, 2014; 2017] in which a novel customization of BG models for five virtual patient using GE was first proposed. The incorporation of medical knowledge into the grammar led to the implementation of an expression for glucose that considered the previous BG values, carbohydrate intake, and insulin administration. This involved exploring four different grammars and five fitness functions and evaluated all the grammars and functions with respect to all the patients in terms of average error as a performance metric. The results indicated that it is feasible to evolve useful models that consider BG readings, meals, and insulin dose information to model BG values. Later, authors extended the findings by including three additional virtual patients and using the root mean squared error (RMSE) as the fitness function. The authors tested the clinical significance of the results with an error grid analysis (EGA) by means of Clarke error grid (CEG) and Parkes error grid (PEG). Other previous studies tested the feasibility of GE prediction systems based on time series of BG levels [Contreras and Vehi, 2016; Contreras *et al.*, 2017]. These studies extended the fore-mentioned research to investigate the utility of a novel and complementary approach by using symbolic regression through GE to evolve personalized BG predictive models that incorporate physiological models as part of the inputs. These models included the glucose absorption rate and the insulin on board model.

3 Materials and methods

Figure 1 shows a schematic representation of the overall methodology proposed in this study. Initially, we collect the experimental datasets (A). Here we use the Ohio dataset [Marling and Bunescu, 2018] which consists on information from a CSII-CGM therapy and the data from a fitness tracker band. Next, data was subjected to a preprocessed stage (B) where we perform an exploratory analysis and a data cleaning tasks. Next, we perform a feature engineering phase (C), which encompasses tasks to provide additional value to the dataset. The most representative transformations involve the implementation of the following physiological models (D):

- The insulin on board (IOB): the insulin that remains active within the body [Wilinska *et al.*, 2005]:

$$\begin{aligned} \frac{dC_1(t)}{dt} &= u(t) - K_{dia}C_1(t) \\ \frac{dC_2(t)}{dt} &= K_{dia}(C_1(t) - C_2(t)) \\ IOB(t) &= C_1(t) + C_2(t) \end{aligned} \tag{1}$$

  where the compartments C_1 and C_2 have initial values set as 0, *u(t)* is the insulin dose, and K_{dia} is a constant related to the duration of insulin action (hs) set as 0.013.

- The glucose absorption rate RA(t) (mg/min): carbohydrate intake of the patient. [Hovorka *et al.*, 2004]:

$$RA(t) = \frac{C_{in}\, C_{bio}\, t\, e^{(-t/t_{max,G})}}{t^2_{\max,G}} \quad (2)$$

where C_{in} is the amount of carbohydrates digested, C_{bio} is the carbohydrate bioavailability, and $t_{max,G}$ (min) denotes the time of the maximum appearance rate of glucose in the glucose compartment.

- The activity on board (AOB): model based on the total steps of an individual [Ozaslan *et al.*, 2017].

$$AOB(t) = steps(t)e^{(-k_s t)} \quad (3)$$

where steps(t) is the total number of steps performed at time instant t and k_s is a constant related to the duration of the effects of physical activity set as 0.0115.

After pre-processing stages the dataset will provide crucial information to the system training and subsequent validation of the method (D). The system requires the definition of a problem specific function (E), which evaluates the solutions, and a customized grammar (F), which defines the structure of the generated solutions. Solutions will be iteratively combined to create new and better solutions aiming to incrementally improve the quality of solutions and reach a final solution that minimizes the fitness function satisfactorily (G). Once a final solution is generated (H), the prediction model is evaluated using data from the remaining data base information. Next, we describe the complete methodology setup in detail.

3.1 Grammatical Evolution Approach

The grammatical evolution (GE) method is a type of search-based algorithm designed to evolve computer programs or expressions defined by a context free grammar, usually defined in Backus normal form (BNF notation). Using the context free grammar, GE performs a genotype-phenotype mapping process which decodes bit strings to generate programs in an arbitrary language. GE methodology involves two main design phases. On the one hand, the generation of the context free grammar which is in charge of defining the effective search space of the problem. On the other hand, the search process of the solution, that is, the expression derived from the grammar which states what should be done. Furthermore, the separate approach for the search and solution spaces can lead to the generation of complex phenotypes, as all genetic operators are applied to the genotype. The GE method thus becomes an attractive method thanks to its flexibility, closely associated with the high degree of modularity provided by a well-structured grammar.

The context-free evolutionary grammars is a set of derivation rules expressed in the form:

$$[\text{non-terminal}] \rightarrow \{\text{production}_1 \mid ... \mid \text{production}_N\}$$

Each rule is composed by two key elements, a non-terminal at the left-hand-side {symbol}, and a definition of the non-terminal at the right-hand-side {productions}. Each definition involves one or more alternatives that are split by the character "|". Each of the alternatives, known as productions, are composed of a sequence of terminals and non-terminals. These definitions indicate that a non-terminal can be substituted for any of the productions listed. The quality of the generated solutions depends directly on this structure. The context free grammar proposed here combines insulin, carbohydrates, BG values and physical activity. Furthermore, we have also considered the circadian rhythm of T1D patients and the reliance of generated models from the time. A grammar is represented by a 4-Tuple N, T, P, S, N being the non-terminal set, T is the terminal set, P the Production rules for the assignment of elements on N and T. And finally, a start symbol S which should appear in N. Next we present an excerpt of the defined grammar:

[Body] $\rightarrow$ (**[Term][Op][Body]**) | **[Term][Op][Body]** |
(**[Term]**) | **[Term]**
[Term] $\rightarrow$ $getG$(**[PrevIni]**, **[Cte]**, **[Op]**, **[Preop]**, **[Exp]**) |
$getRa$(**[PrevIni]**, **[Cte]**, **[Op]**, **[Preop]**, **[Exp]**) |
$getIOB$(**[PrevIni]**, **[Cte][Op]**, **[Preop]**, **[Exp]**) |
$getAOB$(**[PrevIni]**, **[Cte][Op]**, **[Preop]**, **[Exp]**) |
$getCircadian$(**[OpB]**, **[Cte]**, **[Cte]**, **[Cte]**) |
[Preop] $\rightarrow$ $sqrt$ | sin | log | pow | exp | **[Preop][Preop]** | λ
[Op] $\rightarrow$ **[OpA]** | **[OpB]**
[PrevIni] $\rightarrow$ 0 | 1 | 2 | 3 | 4 | 5 | 6 |7 | 8 | 9
[OpA] $\rightarrow$ + | −
[OpB] $\rightarrow$ / | ∗

Where λ defines the empty set which does not contain any terminals. This grammar is designed to constraint the search space of solutions by using functions that operate the historical values of the input signals (insulin, carbohydrates, and BG). Additionally, they can be biased by a sinusoidal function to account for the circadian variations of the patients' physiology. Summarizing, the generated solutions are combinations of five expressions, namely (**[G]**, [$\boldsymbol{Ra}$], [$\boldsymbol{IOB}$], [$\boldsymbol{AOB}$], and **[Circadian]**).

As other evolutionary techniques, the goodness of the fit achieved by the generated prediction models not only relies in a grammar definition, but also requires the definition of an objective. Through this objective, GE measures the value of each solution of the population and guides the methodology towards a final solution. The definition of this objective is managed by the so-called fitness function which is the other key factor of the GE methodologies. In this paper we use the root mean square error (RMSE), see Equation (4), with the aim to train the predictor according to the aim of the present challenge. However, there are multiple possibilities to define a fitness function in this approach, including fitness functions considering the clinical assessment of the predictions. We have used two of these metrics to assess the results, the glucose specific RMSE (gRMSE) proposed by [Del Favero *et al.*,

Table 1: General parameters of the GE implementation and its operators

Parameters	Value	Parameters	Value
Population size	200	Tournament size	2
Generations	500	Max. Wraps	0
Crossover prob.	0.90	Codon length	256
Mutation prob.	0.03	Chromosome length	100

Table 2: Mean values of the RMSE, gRMSE and Clarke error grid zones for the 6 patients (PH=30, 60 and 90 minutes)

Patient_{PH}	gRMSE	RMSE	CEG_A	CEG_B	CEG_C	CEG_D	CEG_E
$P(559)_{30}$	25.11	20.98	88.6	10.5	0.0	0.8	0.0
$P(563)_{30}$	22.60	19.36	91.6	7.7	0.0	0.6	0.0
$P(570)_{30}$	23.92	19.55	93.2	6.4	0.0	0.3	0.0
$P(575)_{30}$	30.10	24.49	82.4	14.3	0.0	3.2	0.0
$P(588)_{30}$	23.18	20.45	89.5	10.4	0.0	0.1	0.0
$P(591)_{30}$	24.08	22.28	76.9	19.6	0.0	3.4	0.0
Average_{30}	24.83	21.19	87.1	11.5	0.0	1.4	0.0
$P(559)_{60}$	35.19	32.47	74.6	23.0	0.3	2.1	0.0
$P(563)_{60}$	28.43	27.52	75.5	23.3	0.1	1.1	0.0
$P(570)_{60}$	29.17	26.45	83.2	15.6	0.1	1.1	0.0
$P(575)_{60}$	32.77	35.29	63.0	32.5	0.5	3.8	0.0
$P(588)_{60}$	34.78	31.53	74.6	24.3	0.1	0.8	0.1
$P(591)_{60}$	33.97	34.77	68.0	29.3	0.2	2.3	0.1
Average_{60}	32.39	31.34	73.1	24.7	0.2	1.9	0.0
$P(559)_{90}$	45.90	39.81	64.7	31.3	0.6	3.4	0.0
$P(563)_{90}$	37.49	34.22	71.8	26.6	0.0	1.6	0.0
$P(570)_{90}$	34.81	31.27	81.3	17.9	0.0	0.8	0.0
$P(575)_{90}$	41.32	39.78	59.4	33.7	0.3	6.6	0.0
$P(588)_{90}$	40.06	36.85	71.8	26.3	1.1	0.8	0.0
$P(591)_{90}$	41.76	35.63	58.5	35.7	0.3	5.4	0.0
Average_{90}	40.23	36.26	67.9	28.6	0.4	3.1	0.0

2012] and the Clarke error grid [Clarke *et al.*, 1987].

$$RMSE = \sqrt{\frac{1}{N}\sum_{t=1}^{N}(BG(t) - \hat{BG}(t))^2} \qquad (4)$$

The operators implemented in this GE approach are the modulo operator as a mapping operator, the classic crossover by a single point, the integer flip mutation, the selection by tournament and the elitism. Candidate solutions to a the problem were randomly initialized. The related parameters are defined in Table 1.

4 Results

Table 2 summarizes the results of all patients and approaches involved in this study. The results include values for gRMSE, RMSE and percentages by zone from the Clarke error grid. In addition, Figure **??** shows the predictions performed during the first day of the testing data for patients 563 and 575.

5 Discussion And Conclusions

This paper has described a methodology based on grammatical evolution (GE) to generate individualized and customized models for BG dynamics. The approach method relies on the generation of a set of rules that determine the search space of solutions for a search-based algorithm. We have implemented a hybrid model using GE and insulin on board, activity on board and glucose rate of absorption models to predict BG values 30, 60 and, 90 minutes ahead. The experimental results with PH=30 minutes of are promising since they reflects a fitted representation of hyper and hypoglycemic events and an satisfactory RMSE values. Regarding the Clarke error grid, the 30, 60 and 90 minutes GE approaches achieved that more than 98%, 97% and 96% respectively of the prediction results fell inside regions A and B for the test data, which implies that the prediction was safe from a therapeutic point of view. Predictive models for patients 559, 575 and 591 obtain the worst results in all the approaches, while models for patients 563, 570 and 588 achieve the best results in that order. Future work involves further improving the performance and safety of predictions by generating sets of models based on the determination of individual specific dynamics, lifestyle, and other factors.

Advantages of GE over other techniques such as linear regression, neural networks or support vector machines are the flexibility, the modularity and the extensive exploratory power of the method which provides ample room for improvement. The integration of tools with the potential to provide timely warning of poor or ineffective insulin treatment, which could lead to adverse glycaemic events, is of major relevance for open and closed loop applications. Continuous short-term predictions of BG levels are plausible, but challenging due to variability, delays in insulin and food absorption, and delayed BG measurements. Methods that appropriately address such delays and variabilities are likely to provide accurate forecasts which would promote numerous potential applications of benefit to T1D patients. These systems would involve features such as, warning alerts of immediately impending problems, automatic recommendations to prevent BG excursions or fail detection in pumps or sensors.

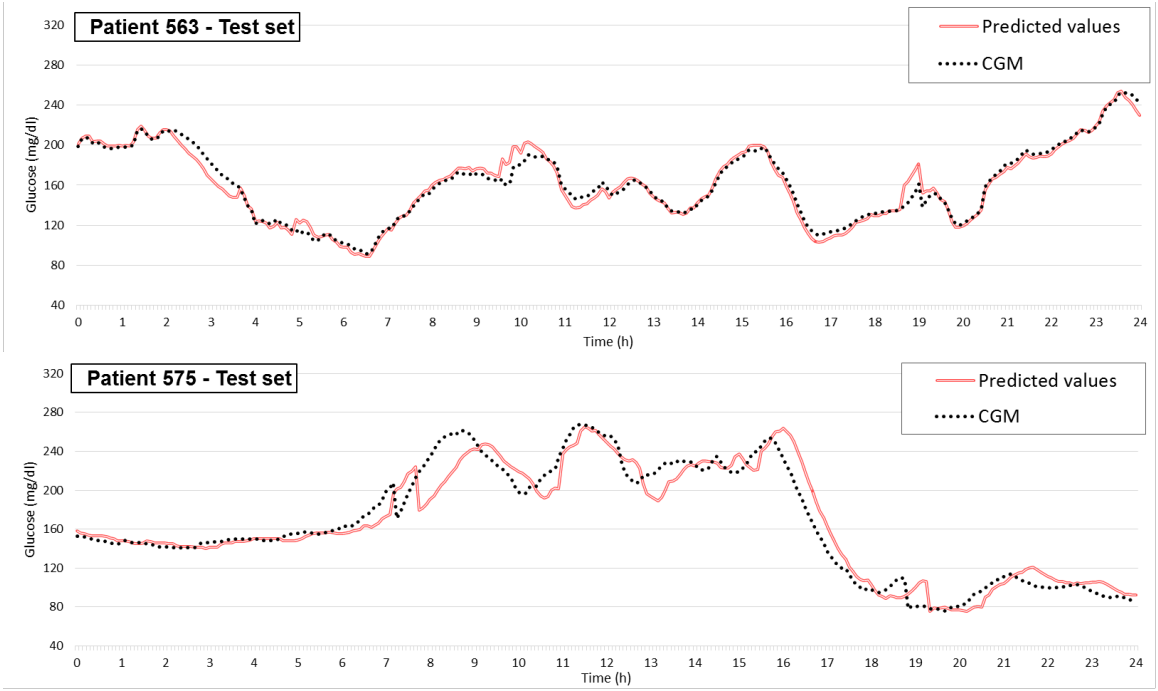

Figure 2: Comparison between CGM readings and predictions (PH=30) performed during the first 24-h of the test data of patients 563 (patient with the best average RMSE values) and 575 (patient with the worst average RMSE values).

Funding

This work has been partially funded by the Spanish Government through contracts DPI2016-78831-C2-2-R, ES-2014-068289 and by the National Counsel of Technological and Scientific Development, CNPq - Brazil (202050/2015-7 and 207688/2014-1).

References

[Balakrishnan *et al.*, 2013] NP. Balakrishnan, L. Samavedham, and GP. Rangaiah. Personalized Hybrid Models for Exercise, Meal, and Insulin Interventions in Type 1 Diabetic Children and Adolescents. *Industrial & Engineering Chemistry Research*, 52(36):13020–13033, sep 2013.

[Brusko *et al.*, 2005] TM. Brusko, CH. Wasserfall, MJ. Clare-Salzler, DA. Schatz, and MA. Atkinson. Functional defects and the influence of age on the frequency of cd4+ cd25+ t-cells in type 1 diabetes. *Diabetes*, 54(5):1407–1414, 2005.

[Clarke *et al.*, 1987] WL. Clarke, D. Cox, LA. Gonder-Frederick, W. Carter, and SL. Pohl. Evaluating Clinical Accuracy of Systems for Self-Monitoring of Blood Glucose. *Diabetes Care*, 10(5):622–628, 1987.

[Cobelli *et al.*, 2011] Claudio Cobelli, Eric Renard, and Boris Kovatchev. Artificial pancreas: Past, present, future. *Diabetes*, 60(11):2672–2682, 2011.

[Contreras and Vehi, 2016] I. Contreras and J. Vehi. Mid-term prediction of blood glucose from continuous glucose sensors, meal information and administered insulin. In *XIV Mediterranean Conference on Medical and Biological Engineering and Computing 2016*, pages 1137–1143. Springer, 2016.

[Contreras and Vehi, 2018] I. Contreras and J. Vehi. Artificial intelligence for diabetes management and decision support: Literature review. *J Med Internet Res*, 20(5):e10775, May 2018.

[Contreras *et al.*, 2017] I. Contreras, S. Oviedo, M. Vettoretti, R. Visentin, and J. Vehi. Personalized blood glucose prediction: A hybrid approach using grammatical evolution and physiological models. *PLOS ONE*, 12(11):1–16, 11 2017.

[Cramer, 1942] HI. Cramer. The influence of menstruation on carbohydrate tolerance in diabetes mellitus. *Can Med Assoc J*, 47(1):51–55, 1942.

[Del Favero *et al.*, 2012] S. Del Del Favero, A. Facchinetti, and C. Cobelli. A glucose-specific metric to assess predictors and identify models. *IEEE Transactions on Biomedical Engineering*, 59(5):1281–1290, 2012.

[Estrada *et al.*, 2010] GC. Estrada, H. Kirchsteiger, and R. Eric. Innovative Approach for Online Prediction of Blood Glucose Profile in Type 1 Diabetes Patients. pages 2015–2020, 2010.

[Evers *et al.*, 2004] I. Evers, H. De Valk, and G. Visser. Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the netherlands. *Bmj*, 328(7445):915, 2004.

[Fuchsjäger-Mayrl *et al.*, 2002] G. Fuchsjäger-Mayrl, J. Pleiner, GF. Wiesinger, A. Sieder, M. Quittan,

MJ. Nuhr, C. Francesconi, HP. Seit, M. Francesconi, L. Schmetterer, et al. Exercise training improves vascular endothelial function in patients with type 1 diabetes. *Diabetes care*, 25(10):1795–1801, 2002.

[Hidalgo *et al.*, 2014] JI. Hidalgo, JM. Colmenar, JL. Risco-Martin, A. Cuesta-Infante, E. Maqueda, M. Botella, and JA. Rubio. Modeling glycemia in humans by means of Grammatical Evolution. *Applied Soft Computing*, 20:40–53, jul 2014.

[Hidalgo *et al.*, 2017] JI. Hidalgo, JM. Colmenar, G. Kronberger, SM. Winkler, O. Garnica, and J. Lanchares. Data based prediction of blood glucose concentrations using evolutionary methods. *Journal of Medical Systems*, 41(9):142, Aug 2017.

[Hinshaw *et al.*, 2013] L. Hinshaw, C. Dalla Man, DK. Nandy, A. Saad, AE. Bharucha, JA. Levine, RA. Rizza, R. Basu, RE. Carter, C. Cobelli, YC. Kudva, and A. Basu. Diurnal pattern of insulin action in type 1 diabetes: implications for a closed-loop system. *Diabetes*, 62(7):2223–9, jul 2013.

[Hovorka *et al.*, 2004] R. Hovorka, V. Canonico, LJ. Chassin, U. Haueter, M. Massi-Benedetti, MO. Federici, TR. Pieber, HC. Schaller, L. Schaupp, T. Vering, and ME. Wilinska. Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes. *Physiological measurement*, 25(4):905–920, aug 2004.

[I. *et al.*, 2016] Contreras I., Quirós C., Giménez M., Conget I., and Vehi J. Profiling intra-patient type i diabetes behaviors. *Computer Methods and Programs in Biomedicine*, 136:131 – 141, 2016.

[Marling and Bunescu, 2018] C. Marling and R. Bunescu. The OhioT1DM dataset for blood glucose level prediction. In *The 3rd International Workshop on Knowledge Discovery in Healthcare Data*, Stockholm, Sweden, July 2018. CEUR proceedings in press, available at http://smarthealth.cs.ohio.edu/bglp/OhioT1DM-dataset-paper.pdf.

[Mianowska *et al.*, 2011] B. Mianowska, W. Fendler, A. Szadkowska, A. Baranowska, E. Grzelak-Agaciak, J. Sadon, H. Keenan, and W. Mlynarski. Hba1c levels in schoolchildren with type 1 diabetes are seasonally variable and dependent on weather conditions. *Diabetologia*, 54(4):749–756, 2011.

[Oviedo *et al.*, 2016] S. Oviedo, J. Vehí, R. Calm, and J. Armengol. A review of personalized blood glucose prediction strategies for t1dm patients. *International Journal for Numerical Methods in Biomedical Engineering*, pages e02833–n/a, 2016.

[Ozaslan *et al.*, 2017] B. Ozaslan, S. Patek, and M. Breton. Quantifying the effect of antecedent physical activity on prandial glucose control in type 1 diabetes: Defining exercise on board. In *ATTD 2017, Paris , France*, pages A24–A25, Feb 2017.

[Wilinska *et al.*, 2005] ME. Wilinska, LJ. Chassin, HC. Schaller, L. Schaupp, TR. Pieber, and R. Hovorka. Insulin kinetics in type-I diabetes: continuous and bolus delivery of rapid acting insulin. *IEEE Transactions on Biomedical Engineering*, 52(1):3–12, jan 2005.

[Zecchin *et al.*, 2014] C. Zecchin, A. Facchinetti, G. Sparacino, and C. Cobelli. Jump neural network for online short-time prediction of blood glucose from continuous monitoring sensors and meal information. *Computer Methods and Programs in Biomedicine*, 113(1):144–152, 2014.