Accepted Manuscript

A simple method for recommending specialized specifications for diabetes monitoring

Luis Omar Avila , Marcelo Luis Errecalde

PII: S0957-4174(17)30626-7
DOI: [10.1016/j.eswa.2017.09.019](https://doi.org/10.1016/j.eswa.2017.09.019)
Reference: ESWA 11540

To appear in: *Expert Systems With Applications*

Received date: 2 March 2017
Revised date: 15 August 2017
Accepted date: 9 September 2017

Please cite this article as: Luis Omar Avila , Marcelo Luis Errecalde , A simple method for recommending specialized specifications for diabetes monitoring, *Expert Systems With Applications* (2017), doi: [10.1016/j.eswa.2017.09.019](https://doi.org/10.1016/j.eswa.2017.09.019)

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Highlights

- Glycemic behavior in healthy individuals is used as a monitoring specification.
- The specification is customized to each diabetic patient.
- Decision trees characterized subjects with different glycemic behaviors.
- Insulin treated patients show larger glycemic variability than healthy subjects.

A simple method for recommending specialized specifications for diabetes monitoring

Luis Omar Avila¹ and Marcelo Luis Errecalde²

¹Corresponding author: Luis Omar Avila

Laboratorio de Investigación y Desarrollo en Inteligencia Computacional, Universidad Nacional de San Luis, Av. Ejército de los Andes 950 - 1º Piso, D5700HHW San Luis, Argentina.

Phone: +54-266-4420823

Email: loavila@unsl.edu.ar

Orcid ID: [0000-0003-0321-068X](https://orcid.org/0000-0003-0321-068X)

²Marcelo Luis Errecalde

Laboratorio de Investigación y Desarrollo en Inteligencia Computacional, Universidad Nacional de San Luis, Av. Ejército de los Andes 950 - 1º Piso, D5700HHW San Luis, Argentina.

Phone: +54-266-4420823

Email: merreca@unsl.edu.ar

Abstract

Under glycemic variability, a characterization of the desired blood glucose (BG) behavior is needed to assess if a given artificial pancreas (AP) respects its specification. The specification is an essential element to detect any deviation from an adequate insulin policy. Specializing the monitoring specification is therefore of utmost importance as existing guidelines for diabetes management are general and do not take into account how the personal factors and lifestyle affect the glycemic behavior. Surely, recommending personalized monitoring specifications may provide flexible and appropriate treatment goals to be attained by diabetic patients in order to account for their actual treatment needs. In this work, we use machine learning models to characterize glycemic behavior in synthetic healthy individuals. To account for the day-by-day fluctuation in BG levels, we use a stochastic process superimposed on a deterministic model of the glucose-insulin dynamics. The obtained characterization of the glycemic behavior in healthy individuals is then used as the target class to predict, and thus recommend, personalized monitoring specifications to diabetic patients. Results show that the approach stands as a feasible strategy to recommending appropriate and realistic monitoring goals for diabetic patients based on healthy individuals who share a similar glycemic behavior. Eventually, the incorporation of a recommender approach on an intelligent monitoring system for the AP will allow on-line adaptation of the treatment requirements for each patient.

Keywords: cold-start recommendation, glycemic control, monitoring specification, machine learning.

1. Introduction

By maintaining blood glucose (BG) profiles close to normoglycemia, diabetic patients can avoid or mitigate serious complications, including heart and kidney disease, blindness, strokes and more. With the latest developments around the artificial pancreas (AP) and numerous connected diabetes management devices, real-time glycemic monitoring becomes of paramount importance. Besides providing insight into the quality of the regulatory process, monitoring devices can also improve the care of patients treated with intensive insulin therapies or critical patients in hospital wards (Russell, 2008). When the BG levels under external control are sufficiently close to the established targets, then, diabetes treatment goals are satisfied while minimizing the risk of hypoglycemia. However, there still remains a lack of understanding of what actually stands for satisfactory glycemic control. Most glycemia monitoring guidelines typically aim at strictly maintain BG levels in the normoglycemia range, i.e. commonly levels between 70 and 140 [mg/dl]. Eventually, glycemic monitoring studies rely on authoritative bodies for the delineation of insulin therapies for diabetes treatment (Mazze et al., 2008). However, this is not always beneficial to all patients at all times. Even though guidelines have the potential to lower the mean of BG profiles as a whole, due to the risk of hypoglycemia the how and for whom these therapies are safe and effective remain quite elusive (Bellazzi & Abu-Hanna, 2009; Chase & Shaw, 2007). Briefly, two patients having the same age, weight and gender may experience different glycemic behavior according to their lifestyle (physical exercise, the level of stress, etc.). At this point, we may wonder whether glycemic behavior should be evaluated according to general guidelines or using a specialized specification of the desired glycemic behavior for a given patient. In such a case, the next question would be how a specification is defined.

Future intelligent monitoring devices may recommend appropriate and realistic monitoring goals based on the common knowledge of groups of patients who share similar characteristics. However, a current limitation in the development of intelligent monitoring devices is BG assessment is still based on thresholds, fixed limits or crisp boundaries between what would be considered “normal” and “abnormal”. When the value of a measured BG level is above or below a stiff bound or limit, as observed in Fig. 1, the patient is considered to be in an anomalous state. Nevertheless, glycemic profiles in both diabetic and healthy individuals do constantly exhibit a greater or less fluctuating behavior which results inconsistent with fixed limits. It has been proven that any monitoring strategy designed around the same standard patients will paradoxically lead to undesired scenarios, such as episodes of hypoglycemia (Lacherade, Jacqueminet, & Preiser, 2009). This

emphasizes the need of a complementary shift in the way we grasp the idea of satisfactory glycemic control. The ultimate goal of any diabetes treatment is not to tightly maintain the BG levels between the limits but mimicking the natural metabolic regulatory mechanism presented in healthy individuals (Ali & Padhi, 2011). This is significant since BG levels in non-diabetic individuals can also present significant fluctuations. It was reported that most of the general population without a diagnosis of diabetes, can reach glucose concentrations that exceeded acceptable levels (Borg et al., 2010). Thus, by first characterizing the glycemic behavior in healthy individuals we may boost the development of intelligent monitoring strategies for evaluating the effectiveness of glycemic control.

***** Figure 1 *****

The main challenge in defining monitoring goals is how to personalize the specifications for different diabetic patients under real-life conditions. This problem may be outlined as one of a recommender system. By implementing recommender systems, different users receive support on the basis of their explicit and implicit preferences, the preferences of other users, and a number of relevant attributes (Nguyen, Denos, & Berrut, 2007). Personalized recommendations involve knowledge discovery techniques to describe different user profiles according to their behavior and preferences. Today, the rise of social media has encouraged the development of recommender systems for diabetes management. Recent studies on recommender systems for diabetes treatment have focused on the issue of incorporating monitoring elements such as BG tracking (Chomutare, Tatara, Arsand, & Hartvigsen, 2013), providing food recommendations based on the user's nutrition requirements and preferences (Suksom, Buranarach, & Thein, 2010), physical activity advice in individuals susceptible to developing diabetes (Sparling, Howard, Dunstan, & Neville, 2015), and so on. Moreover, communities of online patients offer unique opportunities to store large amounts of medical data, while allowing transparent communication across the members. In this context, a number of works have addressed the issue of sharing patient experience using patient-reported outcomes, finding other patients like them matched on clinical characteristics, and learning from the reports of others (van der Eijk et al., 2013; Wicks et al., 2010; Wicks, Vaughan, Massagli, & Heywood, 2011). Online communities have the potential to provide an environment to recommend diabetes treatments and evaluate their consequences. In such a case, any approach will require of

improving data selection and patient matching schemes and a technology that supports autonomy (Weitzman, Adida, Kelemen, Mandl, & Lourenco, 2011).

Our aim is to explore the feasibility of recommending personalized glycemic specifications to be used as benchmarks to be attained in insulin treatments. However, a well-known problem when implementing recommender system is the cold-start scenario. Cold-start scenarios are situations in which no information is a priori handled about a new user. However, this problem is usually alleviated by exploiting patient accessible information so as to automatically associate an initial guess or cold-start behavior to a given individual. Such data only include information that is readily available and can be effortlessly collected. However, as it is not possible to determine the incidence of external factors and unobservable states, then unknown information must be regarded as variability and uncertainty. Regarding diabetes, it is known that exercise and smoking cessation programs are always beneficial; however, it is not completely possible to quantify such benefits on the glycemic behavior.

In this work, we use machine learning tools to characterize glycemic behavior in daily BG profiles of synthetic healthy and diabetic individuals. To account for the day-by-day fluctuations, glycemic variability (GV) and other uncertain factors (such as psychological stress, physical activity, etc.) are estimated by implementing a stochastic model superimposed on an otherwise deterministic model of the glucose-insulin dynamics. This ensures a cohort of healthy and diabetic individuals that accounts sufficiently well for the observed inter and intra patient variability. Our ultimate goal is to use glycemic behavior in healthy individuals as a benchmark to continuously evaluate BG levels in diabetic patients. In this sense, specifying the expected glycemic behavior in synthetic healthy individuals has the potential to establishing more sensitive means of evaluating BG control. Because of the cold-start scenario, no metabolic information is a priori available to early recommend a personalized specification to each patient. Fortunately, by only considering the patient age and weight we managed to bridge the gap between previously characterized healthy individuals and new diabetic users. At this point, we can provide a cold-start recommendation to insulin-treated patients, based on the assumed metabolic similarity to previously characterized healthy individuals. To provide an enhanced monitoring specification once enough glycemic information has been collected, a decision tree (DT) model was trained on the basis of glycemic attributes extracted from BG profiles of healthy patients. The obtained model is used to predict the target (healthy) class to which each diabetic patient belongs. Finally, the DT predictions are compared to

the initial cold-start setting to decide whether a more appropriate monitoring specification should be prescribed to the diabetic patient.

The article is structured as follows. Section 2 describes the stochastic glucose-insulin model used to describe the fluctuating BG patterns in healthy and diabetic patients. Section 3 introduces a DT classifier trained using a set of glycemia relevant features aiming to portray different aspects of GV in healthy patients. In Section 4, the DT is used to recommend a specialized monitoring specification to different diabetic patients. Finally, in Section 5 some remarks and future works are discussed.

2. In-silico glyceimic models

The expected magnitude of glyceimic fluctuations in healthy individuals under real-life conditions is used as a specification for the more detailed assessment of glyceimic control in diabetic individuals. Studies as the one performed in (Borg et al., 2010) confirm that considerable variability of glucose levels exists even among individuals who do not experience diabetes symptoms. BG profiles in both healthy and insulin synthetic patients were obtained via an Ito's diffusion process superimposed on a deterministic model describing the glucose-insulin dynamics (Acikgoz & Diwekar, 2010). This allows us performing more realistic simulations of normal metabolic conditions while capturing a heterogeneous cohort of in-silico individuals that accounts sufficiently well for the observed inter and intra variability.

2.1 Healthy individuals

The Dalla Man simulation model of the glucose-insulin system (Dalla Man, Rizza, & Cobelli, 2007) is used as the basis to describe the deterministic component of the glyceimic dynamics. This model is made up of glucose and insulin subsystems linked by the control of glucose on insulin secretion and by insulin on glucose utilization as well as endogenous production. Together these, there are other organs which also have an effect on the glucose flow in the body, e.g. the brain and the kidneys. Two main variables describe the glucose behavior, where $G_p(t)$ represents the glucose masses in plasma and rapidly equilibrating tissues, while $G_t(t)$ is the glucose masses in slowly equilibrating tissues. Both are defined by the equations

$$\frac{dG_p(t)}{dt} = EGP(t) + Ra(t) - Uii(t) - E(t) - k_1 G_p(t) + k_2 G_t(t) \quad (1)$$

$$\frac{dG_t(t)}{dt} = -Uid(t) + k_1 G_p(t) - k_2 G_t(t) \quad (2)$$

where $EGP(t)$ accounts for the glucose production by the liver, $Ra(t)$ is the glucose rate of appearance in plasma coming from the gastro-intestinal tract-compartment, $E(t)$ is the renal excretion, Uii and Uid are the insulin-independent and insulin-dependent glucose utilizations respectively. Glucose masses interact with each other through the rate parameters k_1 and k_2 . Plasma glucose concentration, i.e. the glucose concentration that tells the insulin level to be infused (either endogenous or exogenous) is given by

$$G(t) = \frac{G_p}{V_G} \quad (3)$$

where V_G is the distribution volume of glucose. For all the simulations hereafter we kept the protocol of carbohydrate intake given in Table 1.

Table 1 Carbohydrate intake protocol

Carbohydrate content (g)	47	16	63	31	63	31
Meal times (h)	3.00	5.00	7.30	11.00	14.30	17.00

The insulin kinetic subsystem is described in a similar way, here $I_p(t)$ to represent the insulin masses in plasma, and $I_l(t)$ the insulin masses in the liver. So the insulin subsystem controlled by following differential equations

$$\frac{dI_l(t)}{dt} = -(m_1 + m_3(t))I_l(t) + m_2 I_p(t) + S(t) \quad (4)$$

$$\frac{dI_p(t)}{dt} = -(m_2 + m_4)I_p(t) + m_1 I_l(t) \quad (5)$$

where we have several rate parameters m_i and the insulin secretion $S(t)$ from the pancreas to the liver, which in turn depends on other equations describing insulin secretion into the plasma. The variable for the plasma insulin concentration is given by

$$I(t) = \frac{I_p}{V_I} \quad (6)$$

where V_I is the distribution volume of insulin. All the parameters values and initial or basal states, as well as a full description of the model, can be found in the original work in (Dalla Man, Rizza, et al., 2007).

By adding an Ito's process to the model, glycemic behavior can be represented in the following form

$$d\mathbf{x} = \mathbf{a}(\mathbf{x})dt + \mathbf{B}(\mathbf{x})(u dt + \sigma d\omega) \quad (7)$$

where $\omega \in \mathbb{R}^1$ and σ denote a diffusion process and its scaling parameter respectively. The expression $\mathbf{a}(\mathbf{x})$ describes the system dynamics, $\mathbf{B}(\mathbf{x})$ is the input-gain matrix and $u(t)$ is the input signal. GV is obtained by adding noise to the term in Eq. (1) that describe the glucose mass in plasma

$$dGp = (EGP(t) + Ra(t) - U_{it} - E(t) - k_1 Gp(t) + k_2 Gt(t))dt + \sigma d\omega \quad (8)$$

In Fig. 2, diverse implementations of the glucose stochastic process in healthy individuals are obtained for different scales of BG fluctuations. To simulate an increase in the GV, the noise scale parameter is progressively augmented from $\sigma = 0.10$ (blue) to 0.25 (green) and 0.50 (red), while all the remaining parameters are maintained. Notice that as the σ parameter grows also the number and magnitude of sudden highs and lows in BG levels do, which represents different individuals experiencing different metabolic behavior.

*** Figure 2 ***

2.2 Diabetic patients

Ordinary type 1 diabetes therapies consist in insulin protocols searching for normoglycemia. External insulin can be administrated either by control algorithms which deliver insulin continuously, this is continuous subcutaneous insulin infusion (CSII) or by regular and multiple daily injections (MDI). We will evaluate the performance of both types of treatments in patients with type 1 diabetes, according to their effectiveness to mimic the expected glycemic behavior in healthy individuals. Usually, MDI treatment results in poor maintenance of glycemia and excessive variations in BG levels, due to the inefficacy of intermittent BG control.

Even though the Dalla Man simulation model describes the glucose-insulin dynamics in a healthy individual, it can as well be used to simulate a diabetes scenario by annulling the natural insulin secretion by the pancreas. In order to simulate a type 1 diabetic individual the insulin secretion module, represented by $S(t)$ in Eq. (4), is substituted by a subcutaneous insulin infusion module. Besides some steady-state constraints and parameters in the diabetes model are different than those in the normal model. In order to account for the higher basal glucose presented in individuals with impaired glucose tolerance, certain parameters are changed in order to increase the endogenous glucose production. But since the simulated diabetic individual is assumed in good control, all the other parameters are kept at values of the normal individual (Dalla Man, Raimondo, Rizza, & Cobelli, 2007). The model for the subcutaneous insulin kinetics is described as follows

$$\frac{dI_{sc1}(t)}{dt} = -(k_d + k_{a1}(t))I_{sc1}(t) + IIR(t) \quad (9)$$

$$\frac{dI_{sc2}(t)}{dt} = k_d I_{sc1}(t) - k_{a2} I_{sc2}(t) \quad (10)$$

where $I_{sc1}(t)$ is the amount of nonmonomeric insulin in the subcutaneous space, $I_{sc2}(t)$ is the amount of monomeric insulin in the subcutaneous space and $IIR(t)$ is the exogenous insulin infusion rate. k_d and k_{a1} and k_{a2} are the rate constants for insulin dissociation and absorption, respectively.

For CSII the simple proportional-integral-derivative (PID) controller proposed in (Steil, Rebrin, Darwin, Hariri, & Saad, 2006) is implemented. The insulin infusion rate is

$$IIR(t) = PID(t) = P(t) + I(t) + D(t) \quad (11)$$

where each term is defined as

$$P(t) = K_P [G_{sen}(t) - G_{tar}(t)]$$

$$I(t) = \frac{K_P}{T_I} \int_0^t [G_{sen}(t) - G_{tar}(t)]$$

$$D(t) = K_P T_D \frac{dG_{sen}(t)}{dt} \quad (12)$$

here $G_{tar}(t)$ is the glucose target and $G_{sen}(t)$ is the glucose sensor signal. Parameter values of the PID controller are: $K_P = 0.032$ [pmol/kg/min per mg/dl], $T_D = 66$ [min], and $T_I = 450$ [min].

For the MDI insulin infusion case, it is also possible to use the model of subcutaneous insulin kinetics as follows

$$IIR(t) = \sum_{j=1}^{N_{meals}} D_j^{ins} \delta(t - t_j) + IIR_b \quad (13)$$

where N_{meal} is the number of meals, t_j is the time of meal occurrence, D_j^{ins} is the exogenous insulin dose injected subcutaneously at t_j , and IIR_b is the basal insulin infusion rate. We followed a protocol with three subcutaneous insulin boluses: 3 U of insulin injected at 8 a.m., 4.5 U of insulin at 12 a.m., 4.5 U of insulin at 8 p.m. It is assumed that the basal insulin infusion rate is equal to 1 [pmol/kg/min] and only short-acting insulin is administrated. Based on the MDI treatment, the insulin bolus is given as an impulse on a time t_j before the meal intake.

3. Recommending specifications

3.1 Early recommendations

To start, we labeled individuals by simply considering their age-to-weight ratio and the GV magnitude of BG according to simulation parameters. The age-to-weight ratio corresponds to the average age of individuals according to their bodyweight, where the bodyweight is thought to increase with age. It has been proven a positive relationship between age and BG (Derosa et al., 2009) due to a reduction in the insulin secretion by beta-cells and glucose extraction in the liver in

elderly people. Even if this may seem trivial since it is not possible to differentiate between the metabolism of an obese child -with poor eating habits- or a thin adult -who is aware of meals and exercises-, the evident disparity between those glycemic behaviors will be associated to different amounts of BG fluctuations. Hence, even if the obese child and the thin adult may initially belong to close bodyweight classes, the former is expected to undergo larger amounts of GV. This is also concurrent with different lifestyles, in particular in relation to different nutritional habits. In Fig. 3 it is shown in which manner the bodyweight affects the BG level, where the variability parameter has been set to $\sigma = 0$ for a better appreciation. Since we are only adjusting this parameter, the image explains the importance of considering the individual weight when prescribing personalized monitoring specifications, since the acceptable range for satisfactory diabetes control may change.

*** Figure 3 ***

In turn, the magnitude of glycemic profiles was augmented according to increments in the simulation parameter σ in Eq. (8). By using a stochastic process we ensured the group of synthetic individuals belonging to the same class will experience similar but not equal glycemic behavior. We can as well include other unknown sources of uncertainty that are responsible for the degree of glycemic fluctuations, such as psychological stress, physical activity, diet, stress, etc. Consequently, given that different individuals with the same age and weight may experience different levels of GV according to their lifestyle, they should not be recommended the same specification in order to evaluate glycemic control.

BG profiles obtained through the healthy, CSII and MDI models were a priori divided into five groups according to increasing bodyweights [30, 50, 70, 90, 110] kg in order to compress a large number of key demographic and metabolic parameters. To add some glycemic fluctuations within each group, different degrees of GV were attained by incrementing the noise scale factor of the stochastic process from $\sigma = 0.1$ (Low GV) to 0.25 (Medium GV) and 0.5 (High GV). Therefore, for each category healthy, CSII and MDI, we collected a sufficiently large data set of 750 24hs BG profiles with different levels of BG fluctuations. In Fig. 4 it is possible to see how a given BG profile from a 50kg diabetic patient who experience medium GV can overlap the BG profile from a 70kg patient but who experiences a low level of GV. This emphasizes the fact that an individual with an

expected magnitude of glycemic fluctuations according to initial information –given a particular cold-start setting- may, in turn, undergo increased levels of GV under real-life conditions.

*** Figure 4 ***

3.2 Learning the healthy classes

Later, a machine learning model was trained to automatically learn glycemic attributes in healthy individuals with different age-to-weight ratios and experiencing low, medium or high GV. According to this, each class was labeled based on the individual bodyweight and the amount of GV (for example 30L was the label for the class 30kg and low GV). In this manner, each class represents the glycemic behavior that is expected to be achieved by diabetic patients given the initial parameters. By learning how BG behaves in different healthy individuals with different lifestyles we should be able to predict specialized monitoring specifications to diabetic patients. Each of these specifications will be used as the monitoring reference or “golden truth” to evaluate whether the glycemic control performed respects its expected performance. To train the model, we represented daily BG profiles as a vector of attributes. In this sense, many studies have considered GV patterns in context of its direction, periodicity, and amplitude, and have besides proposed new tools and metrics as well (Czerwoniuk, Fendler, Walenciak, & Mlynarski, 2011; Fritzsche, Kohnert, Heinke, Vogt, & Salzsieder, 2011; Marling, Shubrook, Vernier, Wiley, & Schwartz, 2011). The GV magnitude (Low, Medium or High) appears in the vector as the target value or class to be evaluated. Remaining elements in the vector, given as training examples, were chosen to represent diverse aspects of the glycemic behavior.

A total of twelve domain dependent metrics set up the complete list of features used in the experiments: standard deviation (SD), mean (MA), range (RA), kurtosis (KUR), integral via trapezoidal method (TRPZ), distance traveled (DT), area under the curve high (AUC_H), area under the curve low (AUC_L), percentage spent above the target range (%_HIGH), percentage spent below the target range (%_LOW), continuous overall net glycemic action (CONGA) and mean amplitude of glycemic excursions (MAGE). The premise here is that there is no one measure that covers all aspects of glycemic control, and hence a multifaceted approach must be considered.

Some of these attributes are themselves metrics used to estimate the amount of GV. For example, MAGE computes the mean distance between the local minima and maxima of a BG profile (Baghurst, 2011). MAGE includes only large oscillations and does not reflect the rate of change of BG values. It is weakly associated with hypoglycemia and inherently biased towards hyperglycemia. DT accounts for the sum of the distances between each pair of consecutive BG data points, hence the greater the DT the greater the variability (Hermanides et al., 2010). It does not directly calculate frequency or amplitude of excursions, instead it captures overall variability. CONGA is calculated on the basis of the standard deviation of the differences between consecutive BG values (McDonnell, Donath, Vidmar, Werther, & Cameron, 2005). This measure is based on the premise that normoglycemia inherently allows for little glycemic variation, hence higher CONGA values reflect increased glycemic excursions consistent with less stable BG control. In turn, %_HIGH and %_LOW are a measure of the frequency and extent of readings of high and low BG levels, respectively, based on the hyper and hypoglycemia section of the glycemic risk range. Briefly, they measure the time spent outside the normal range.

Other attributes employed are numeric attributes generally used in signal processing applications. Between them, RA computes the interval between the maximum and minimum values and therefore gives an idea of the dispersion of the glycemic data. In turn, KUR gives the degree of concentration of the BG values around the central zone. TRPZ works by approximating the region under the BG curve as a trapezoid and calculating its area. Finally, AUC_H and AUC_L are defined as the region between the BG curve and a horizontal line corresponding to the maximum or minimum BG level measured for on the day, respectively.

A Decision Tree (DT) classifier was trained to learn the extended set of features aiming to portray different aspects of GV in healthy patients. DTs are diagrams that purport to show the range of possible outcomes and subsequent decisions after initial information. The objective is to use input data to form subgroups of the study population, healthy individuals in this case, which are homogenous with regards to the class variable of interest GV level. We decided to use DTs models since they allow for explicit representation of decision rules. This facilitates the interpretation of any decision and allows explaining why that is the best alternative given existing information. All the training data sets containing the twelve attributes and the class for the Healthy category were input to the open source data analytics platform KNIME, a machine learning toolkit that facilitates the rapid development and evaluation of classifiers via a library of machine learning algorithms.

The DT model for healthy individuals was trained and tested using 10-fold cross validation, where nine folds are used for training, and the other is used to test.

To improve the performance of the DT classifier we removed redundant and/or irrelevant attributes from the dataset. In the feature subset selection problem, a learning algorithm is faced with the problem of selecting some subset of features upon which to focus its attention, while ignoring the rest. The workflow in Fig. 5 shows the data flow for a wrapper feature elimination strategy, where the implementation starts with all attributes and successively removes one (Kohavi & John, 1997). In the wrapper approach, the feature subset selection algorithm exists as a wrapper around a learning model. The selection algorithm conducts a search for a good subset using the learner itself as part of the function evaluating feature subsets. Thus, the idea behind the wrapper approach is simple. The learning algorithm is run on the dataset, usually partitioned into internal training and holdout sets, with different groups of features removed from the data. The wrapper method iteratively removes the feature that has the lowest influence on classification accuracy. The feature subset with the highest evaluation is chosen as the final set on which to run the induction algorithm. The resulting classifier is then evaluated on an independent test set that was not used during the search. Since the typical goal of supervised learning algorithms is to maximize classification accuracy on an unseen test set, we have adopted this as our goal in guiding the feature subset selection.

*** Figure 5 ***

Table 2 shows how the features were grouped by the wrapper method and the resulting average error magnitude for predictions. Even when others set of features led to a null prediction error, using 8 or more features, we finally decided to use only a group of five features {DT %_HIGH %_LOW CONGA MAGE} since they are themselves measures of GV. Remaining features are numeric transformations commonly used in signal processing applications, regardless of the source of the signal, and may take us away from a precise portrayal of glycemic behavior.

Table 2 Selected features for error minimization. Left: errors for different groups of features. Right: selected group of features

Error	N° of feature s	Selected features
0,221	1	MAGE
0,109	2	MAGE, DT
0,096	3	MAGE, DT, SD
0,075	4	MAGE, DT, %_LOW, %_HIGH
0,021	5	MAGE, DT, %_HIGH, %_LOW, CONGA
0,03	6	MAGE, DT, %_HIGH, %_LOW, SD, CONGA
0,015	7	MAGE, DT, %_HIGH, %_LOW, CONGA, SD, AUC_H
0	8	MAGE, DT, %_HIGH, %_LOW, CONGA, SD, AUC_H, KUR
0	9	MAGE, DT, %_HIGH, %_LOW, CONGA, SD, AUC_H, KUR, AUC_L
0	10	MAGE, DT, %_HIGH, %_LOW, CONGA, SD, AUC_H, KUR, AUC_L, RA
0	11	MAGE, DT, %_HIGH, %_LOW, CONGA, SD, AUC_H, AUC_L, TRPZ, KUR, RA
0	12	MAGE, DT, %_HIGH, %_LOW, CONGA, SD, AUC_H, KUR, AUC_L, RA, TRPZ, MA

Based on the selected features, the obtained tree is comprised of 14 nodes and 28 leaves and its graph is displayed in Fig. 6. Information gain was used as a quality measure to select the test attribute at each node in the tree. Hence, the attribute with the highest information gain was chosen as the test attribute for the current node. Such approach minimizes the expected number of tests needed to classify a profile and guarantees that a simple tree is found. More precisely, information gain is based on the decrease in entropy after the dataset is split on an attribute.

*** Figure 6 ***

4. Predicting specifications

Eventually, the recommender system would work as follows. First, a new diabetic user would parameterize the glycemic monitor by setting the age-to-weight parameter and a GV magnitude according to its lifestyle. According to this information, the monitor would recommend an initial specification based on the glycemic behavior characterization of an analogous healthy individual. Since this initial specification may not represent the real BG fluctuating trends for that user, a new and more detailed evaluation of the patient glycemic behavior should be later carried out. In the

case a new specification should be recommended to the patient, it will be based a characterization of its own BG profiles (Avila & Martínez, 2014). Such profiles are obtained by employing a subcutaneous glycemic sensor, considering that the patient metabolism is stabilized at the moment of the measures. If the new specification differs from the initial, it means that both the age-to-weight and GV parameter were not enough to describe BG fluctuations of the diabetic patient. Notice this process might be repeated as the age or weight grow, new insulin therapies, new diets, pregnancy or clinical advisory.

To account firstly for the cold-start scenario, in which no precise information is a priori handled about the glycemic behavior for a given individual, diabetic patients were a priori labeled based on their age-to-weight ratio and an expected GV magnitude. This is because patients can either mitigate or exacerbate BG fluctuations according to their own lifestyle. For example, low fluctuations could be achieved by controlling the diet, maintaining the level of physical activity, maintaining the proper weight, etc. The cold-start setting will assist the monitor to beforehand recommend specifications based on the assumed metabolic similarity between diabetic and healthy individuals who share the same age-to-weight ratio and GV level. Nonetheless, due to the lack of glycemic information it is not possible to guarantee whether an early recommendation will result appropriate for the considered patient.

After a period of time in which enough information about the BG behavior of the patient was collected using a sensor, the set of GV attributes is computed. To achieve that, the five attributes are computed along patient representative 24hs BG profiles and the resulting vector is used as training input to the DT predictor. Based on this characterization, patients will be classified according to their effectiveness to mimic metabolic conditions in an analogous healthy individual, i.e. patients with the same age-to-weight ratio and GV level. If the case this patient be predicted to belong to another healthy class, it will be thus recommended a more suitable monitoring specification. In order to make the approach feasible, BG readings should only contain sensor data measured when the patient presented stabilized metabolic conditions, so that the resulting prediction will truly represent the expected glycemic behavior for that patient. The resulting monitoring specification will be onwards used to detect any deviation from the expected glycemic behavior.

4.1 Cold-Start Prediction Accuracy

In Fig. 7 and Fig. 8 we can observe the confusion matrices with the DT predictions obtained for the CSII and MDI cases of insulin treatments respectively. Each column of the matrix represents the instances in the current class (age-to-weight ratio and GV level according to the cold-start setting for a diabetic patient) whereas each row represents the instances in the predicted class according to an analogous healthy individual. Remember that the bodyweight increases according to the age progression, from children with 30kg to elderly with 110kg. All correct guesses are located in the diagonal and they correspond to those cases in which the cold-start setting matched the DT prediction. In other words, they represent the cases in which the initial specification, based only on the patient age and weight and an expected GV magnitude according to its lifestyle, was enough to properly characterize its glycemic behavior. In such a case, the diabetic patient presented a metabolic behavior accordingly to its analogous healthy individual.

Notably, we obtained up to 66% prediction error for the CSII case and approximately 85% prediction error when implementing the MDI insulin treatment. Low errors in the CSII treatment were expected, as insulin continuously administrated throughout the day causes fewer sudden highs and lows in BG levels. Notice that for the CSII most of the patients were correctly predicted according to their age-to-weight ratio, but failed to be classified in terms of the amount of GV. More precisely, for given age-to-weight and noise scale parameters, BG levels in a diabetic patient will frequently show larger fluctuations than levels found in the analogous healthy individual. For example from 50 profiles a priori labeled as 30L (children with 30kg and low variability) only 15 were correctly predicted, 31 were predicted to show higher GV levels, while 4 were predicted to fall in the next age-weight ratio. Notice that in both cases, a number of the diabetic individuals predicted to experience a GV according to the healthy class 110H, actually may belong to a non-defined upper class with larger glycemic fluctuations. This situation is further accentuated in the MDI case where only 1 profile was correctly predicted. Most of the diabetic patients were predicted to belong to an upper age-to-weight class. Notice also the major dispersion of instances along the diagonal on the MDI case in Fig. 8 against the CSII treatment in Fig. 7, since regular injections are prone to cause sudden highs and lows in BG levels.

*** Figure 7 ***

***** Figure 8 *****

In Fig. 9 and Fig. 10 it is shown the results for the precision and recall performance metrics. In this study performance metrics are related to the capability of the cold-start setting to predict fluctuations in the BG levels for a given patient. Briefly, high precision means that the DT model returned substantially more relevant results than irrelevant ones, while high recall means that the DT returned most of the relevant results. It is remarkable how the performance to predict the patient glycemic behavior decreases when the MDI type of insulin treatment is compared to the CSII case, as a consequence of administrating more irregular insulin boluses. In other words, given a case of age-to-weight class, a patient using a discontinuous insulin treatment will experience more BG fluctuations and this will make it harder to correctly identify the underlying glycemic behavior.

***** Figure 9 ********** Figure 10 *****

In a second experiment, see Figs. 11 and 12, we decided to train a DT to predict a new specification based only on the age-to-weight ratio leaving out different degrees of GV. A great number of the a priori labeled examples of glycemic profiles in diabetic patients were predicted to experience the same metabolic patterns than elder healthy individuals. In the confusion matrix for the MDI case for example, from 150 diabetic patients controlled with insulin injections only the half of them were predicted to belong to its a priori labeled class.

***** Figure 11 ********** Figure 12 *****

4.2 Recommending specifications

Specializing the monitoring specification is of utmost importance since existing guidelines for diabetes management are general and do not take into account the fact that physical factors and lifestyle affect the behavior of BG levels. Therefore, once the monitor collects enough information about the glycemic behavior of a given diabetic patient, a more appropriate specification will be recommended. Based on this characterization, patients will be later monitored to detect any deviation from the expected glycemic behavior.

For example, in the upper plot in Fig.13 we show the BG profiles of the MDI treated patient who belongs to the class 90kg with Low GV (blue line): a) against its analogous healthy individual given the cold-start setting (red line) and b) against the predicted healthy class 110kg and Low GV (green line). It is easy to see how the BG levels for that patient are closer to the new recommended specification than the one given the cold-start scenario. To quantify the difference we used the root-mean-square error (RMSE), which is a frequently used measure of the differences between values predicted by a model or an estimator and the values actually observed. The RMSE value between the real glycemic behavior and that assumed by the recommender is given as

$$RMSE = \sqrt{\sum \frac{(y_{pred} - y_{obs})^2}{N}} \quad (14)$$

and is equal to $RMSE = 2.76$ for the cold-start class and decreases to $RMSE = 1.80$ for the predicted one.

This result on a feasible strategy to recommending appropriate and realistic monitoring goals based on healthy individuals who share similar glycemic behavior. As the specification represents the expected glycemic behavior for a patient, any deviation from the one recommended will be an indicator of an anomalous metabolic state, either by a misadjusting on the diet, the amount of insulin infused, etc. The result is also noticeable in the plot below, where the BG profile of a CSII treated patient is compared against its analogous healthy individual: a) given the cold-start setting (50kg with High GV) and gives a value $RMSE = 11.34$ and b) given the predicted class (70kg and Medium GV) which gives a value $RMSE = 8.26$. In this scenario, the patient experiments a fewer number of BG fluctuations (blue line) than expected according to the cold-start setting (red line). What is more, lower BG trends were also expected according to the initial specification which does

not match patient data. This is the advantage of using a stochastic model, where GV is modeled as an endogenous and unknown metabolic process which differs for each patient.

*** Figure 13 ***

4.3 An intelligent APp monitor

The development of an AP is an active and encouraging field of research, and even though the idea of an autonomous device has existed for decades, its commercial viability is quite recent (Dassau, Lowe, Barr, Atlas, & Phillip, 2012). The incorporation of machine learning techniques into the formulation of monitoring systems for the AP makes it possible to work with a continuous data stream in real time, which allows the on-line adaptation of the corresponding specification (Avila and Martínez, 2014b). What is more, there exists the possibility for old users of updating their reference specification online and adapting it to the actual treatment needs of each individual.

The potential benefits from mobile technology have transformed our life at the same pace as the acquisition of smartphones is increasing worldwide (Cobelli et al., 2012; Kovatchev et al., 2013). Notably, smartphone ownerships are fully connected to the digital world while on the go and they exhibit greater variation based on age, income and educational attainment. Noticeably, the magnitude, diversity and complexity of new information services applied to diabetes require of new architectures, techniques, algorithms and data analysis to handle patient reports so as to extract the hidden patterns and knowledge of data (Harper, 2014). In consequence, diabetes treatment can benefit from research on data mining techniques on heterogeneous and distributed data collections (Chittaranjan, Blom, & Gatica-Perez, 2013). Even the so-called Internet of Things (IoT) has focused attention on the necessity to incorporate in the diabetes *ecosystem* (Heintzman, 2016; Renard, Cobelli, Zisser, & Kovatchev, 2013) data from connected portable devices and new media technologies.

In such a context, computing the specification of the expected glycemic behavior for diabetic patients allows the design of an affordable, practical and safe mobile application to monitor the AP, let's name it the APp monitor. In Fig. 14 we show a possible scheme to recommend specifications to a new APp monitor user. While the basic functions and parameters for setting the cold start

monitoring specification will probably reside on the APp monitor, global functions such as the required to customize the specification will reside in the cloud. Therefore, in the ecosystem of diabetic patients (Kovatchev et al., 2013) the distributed collective knowledge (different behaviors) can be shared. To achieve this, we can think of a data exchange scheme so that the collective knowledge can be exploited by every new agent that is incorporated into the APp monitor user community. Likewise, this knowledge can be used by old users with outdated recommendations to improve their own monitoring specifications according to change on bodyweight, diet, pregnancy and more. In order to achieve this data exchange scheme, it is possible to think of a client-server architecture, where the server processes and generates the collective knowledge about the monitoring policy, which is available to be requested by any client belonging to the community and at any time. In this sense, the benefits of a global designed component may also include the ability to alert family members or emergency services if BG levels exceed their specification or assisting patients and clinicians in decision making.

*** Figure 14 ***

5. Concluding remarks

Despite a clear physiologic rationale in the glycemic control, monitoring guidelines are still debated. Adaptable and personalized tools may help to achieve more attainable and safer protocols to administrate insulin. However, as most metrics emphasize the quality of glycemic control based on presetted and inflexible boundaries, they prevent clinicians to make decisions based on the current patient state and its preferences. In this work, we describe a novel approach to using the glycemic behavior on synthetic healthy individuals as a monitoring specification to assess BG control in diabetic patients. Eventually, a glycemic specification based on healthy individuals would result in a more realistic manner of monitoring diabetic patients than using fixed limits or thresholds. What is more, a specification of the glycemic behavior would provide contextual reassurance for implementing personalized therapies in order to enhance glycemic control.

To validate the approach, we implemented a stochastic glucose-insulin model to reproduce the fluctuating BG levels found in healthy and diabetic individuals. The use of a stochastic model facilitates a data set of synthetic individuals that accounts sufficiently well for the BG intra and inter

variability. Nevertheless, even though a large cohort of patients showing different glycemic attributes was obtained, stochastic simulations may differ from glycemic behavior under real-life conditions. To enhance the proposed method and to obtain statistically significant results, real glycemic data should be incorporated so as to include additional hormonal parameters which are significant in the GV patterns.

Because of the difficulty of interpreting numerous effects describing the fluctuating phenomenon in BG profiles, the use of GV as a parameter is discouraged in clinical practice. Machine learning methods and Decision Trees in particular, provide an accessible and helpful method for characterizing glycemic related attributes. We introduced a wrapper feature elimination strategy that iteratively removes the attributes that have the lowest influence on the classification accuracy. Results pinpoint that those attributes specially designed to quantify GV resulted the best to characterize BG fluctuations. Nevertheless, as it is not completely clear how these attributes correlate each other, further analysis may include an exhaustive analysis of other metrics so as to improve the characterization of the GV. What is more, despite DTs models allow for explicit representation of decision rules in a recommender system, comparing among other predictive methods, such as naïve Bayes or SVM, may also improve the method to make recommendations.

As the main contribution, this work proposes the use of the glycemic behavior of healthy individuals as a specification to monitor GV in diabetic patients. This solves the problem of defining an appropriate criterion to quantify BG excursions in the relative terms of setpoints or boundaries. Experiments show that an insulin treated patient will frequently experience larger BG fluctuations than an analogous healthy individual having the same age and bodyweight. In consequence, defining monitoring specifications based on an assumed cold-start glycemic behavior may lead to poor BG control. On the other hand, even though a setpoint may have the potential to lower the overall mean in glycemic profiles, excessive penalization of large BG values may increase the risk of hypoglycemia in insulin-treated patients.

Once refined and validated, our aim is to include this method into an intelligent monitoring system to provide a personalized glycemic specification as a routine assessment of overall glycemic control. Later we will integrate the results obtained on a mobile portable monitor to take advantage in the use of connected devices and user's information. In the future, in a connected community of diabetic patients the collective knowledge will be shared and used to recommend more attainable diabetes treatment goals.

References

- Acikgoz, U., & Diwekar, U. M. (2010). Blood glucose regulation with stochastic optimal control for insulin-dependent diabetic patients. *Chemical Engineering Science*, 65(3), 1227–1236.
- Ali, S., & Padhi, R. (2011). Optimal blood glucose regulation of diabetic patients using single network adaptive critics. *Optimal Control Applications and Methods*, 32(2), 196–214.
- Avila, L., & Martínez, E. (2014). Behavior monitoring under uncertainty using Bayesian surprise and optimal action selection. *Expert Systems with Applications*, 41(14), 6327–6345.
- Baghurst, P. A. (2011). Calculating the Mean Amplitude of Glycemic Excursion from Continuous Glucose Monitoring Data: An Automated Algorithm. *Diabetes Technology & Therapeutics*, 13(3), 296–302.
- Bellazzi, R., & Abu-Hanna, A. (2009). Data mining technologies for blood glucose and diabetes management. *Journal of Diabetes Science and Technology*, 3(3), 603–612.
- Borg, R., Kuenen, J. C., Carstensen, B., Zheng, H., Nathan, D. M., Heine, R. J., ... Group, A. S. (2010). Real-life glycaemic profiles in non-diabetic individuals with low fasting glucose and normal HbA1c: the A1C-Derived Average Glucose (ADAG) study. *Diabetologia*, 53(8), 1608–1611.
- Chase, J. G., & Shaw, G. M. (2007). Is there more to glycaemic control than meets the eye? *Critical Care*, 11(4), 1.
- Chittaranjan, G., Blom, J., & Gatica-Perez, D. (2013). Mining large-scale smartphone data for individuality studies. *Individual and Ubiquitous Computing*, 17(3), 433–450.
- Chomutare, T., Tataru, N., Arsand, E., & Hartvigsen, G. (2013). Designing a diabetes mobile application with social network. In *Health Informatics: Digital Health Service Delivery* (pp. 58–64).
- Cobelli, C., Renard, E., Kovatchev, B. P., Keith-Hynes, P., Ben, B. N., Place, J., ... Bruttomesso, D. (2012). Pilot studies of wearable outpatient artificial pancreas in type 1 diabetes. *Diabetes Care*, 35(9), e65.
- Czerwoniuk, D., Fendler, W., Walenciak, L., & Mlynarski, W. (2011). GlyCulator: a glycemic variability calculation tool for continuous glucose monitoring data. *Journal of Diabetes Science and Technology*, 5(2), 447–451.
- Dalla Man, C., Raimondo, D. M., Rizza, R. A., & Cobelli, C. (2007). GIM, simulation software of meal glucose—insulin model. *Journal of Diabetes Science and Technology*, 1(3), 323–330.
- Dalla Man, C., Rizza, R. A., & Cobelli, C. (2007). Meal simulation model of the glucose-insulin system. *IEEE Transactions on Biomedical Engineering*, 54(10), 1740–1749.
- Dassau, E., Lowe, C., Barr, C., Atlas, E., & Phillip, M. (2012). Closing the loop. *International Journal of Clinical Practice*, 66(s175), 20–29.
- Derosa, G., Salvadeo, S. A., Mereu, R., D'Angelo, A., Ciccarelli, L., Piccinni, M. N., ... Tinelli, C. (2009). Continuous glucose monitoring system in free-living healthy individuals: results from a pilot study. *Diabetes Technology & Therapeutics*, 11(3), 159–169.
- Fritzsche, G., Kohnert, K.-D., Heinke, P., Vogt, L., & Salzsieder, E. (2011). The use of a computer program to calculate the mean amplitude of glycemic excursions. *Diabetes Technology & Therapeutics*, 13(3), 319–325.
- Güemes, M., Rahman, S. A., & Hussain, K. (2016). What is a normal blood glucose? *Archives of Disease in Childhood*, 101(6), 569–574.
- Harper, E. (2014). Can big data transform electronic health records into learning health systems? In *Nursing Informatics* (pp. 470–475).
- Heintzman, N. D. (2016). A Digital Ecosystem of Diabetes Data and Technology Services, Systems, and Tools Enabled by Wearables, Sensors, and Apps. *Journal of Diabetes Science and Technology*, 10(1), 35–41.
- Hermanides, J., Vriesendorp, T. M., Bosman, R. J., Zandstra, D. F., Hoekstra, J. B., & DeVries, J. H. (2010). Glucose variability is associated with intensive care unit mortality*. *Critical Care Medicine*, 38(3), 838–842.
- Kohavi, R., & John, G. H. (1997). Wrappers for feature subset selection. *Artificial Intelligence*, 97(1), 273–324.
- Kovatchev, B. P., Renard, E., Cobelli, C., Zisser, H. C., Keith-Hynes, P., Anderson, S. M., ... Farret, A. (2013). Feasibility of outpatient fully integrated closed-loop control first studies of wearable artificial pancreas. *Diabetes Care*, 36(7), 1851–1858.

- Lacherade, J.-C., Jacqueminet, S., & Preiser, J.-C. (2009). An overview of hypoglycemia in the critically ill. *Journal of Diabetes Science and Technology*, 3(6), 1242–1249.
- Marling, C. R., Shubrook, J. H., Vernier, S. J., Wiley, M. T., & Schwartz, F. L. (2011). Characterizing Blood Glucose Variability Using New Metrics with Continuous Glucose Monitoring Data. *Journal of Diabetes Science and Technology*, 5(4), 871–878.
- Mazze, R. S., Strock, E., Wesley, D., Borgman, S., Morgan, B., Bergenstal, R., & Cuddihy, R. (2008). Characterizing glucose exposure for individuals with normal glucose tolerance using continuous glucose monitoring and ambulatory glucose profile analysis. *Diabetes Technology & Therapeutics*, 10(3), 149–159.
- McDonnell, C. M., Donath, S. M., Vidmar, S. I., Werther, G. A., & Cameron, F. J. (2005). A Novel Approach to Continuous Glucose Analysis Utilizing Glycemic Variation. *Diabetes Technology & Therapeutics*, 7(2), 253–263.
- Nguyen, A.-T., Denos, N., & Berrut, C. (2007). Improving new user recommendations with rule-based induction on cold user data. In *Proceedings of the 2007 ACM conference on Recommender systems* (pp. 121–128). ACM.
- Renard, E., Cobelli, C., Zisser, H. C., & Kovatchev, B. P. (2013). Artificial Pancreas Goes Outpatient: A New Diabetes Ecosystem. *Journal of Diabetes Science and Technology*, 7(6), 1411–1415.
- Russell, S. J. (2008). Continuous glucose monitoring awaits its “killer app.” *Journal of Diabetes Science and Technology*, 2(3), 490–494.
- Sparling, P., Howard, B., Dunstan, D., & Neville, O. (2015). Recommendations for physical activity in older adults. *BMJ: British Medical Journal*, 350, 1–5.
- Steil, G. M., Rebrin, K., Darwin, C., Hariri, F., & Saad, M. F. (2006). Feasibility of automating insulin delivery for the treatment of type 1 diabetes. *Diabetes*, 55(12), 3344–3350.
- Suksom, N., Buranarach, M., & Thein, Y. M. (2010). A Knowledge-based Framework for Development of Individualized Food Recommender System. In *Proc. of the 5th Int. Conf. on Knowledge, Information and Creativity Support Systems*.
- van der Eijk, M., Faber, M. J., Aarts, J. W., Kremer, J. A., Munneke, M., & Bloem, B. R. (2013). Using Online Health Communities to Deliver Patient-Centered Care to People With Chronic Conditions. *Journal of Medical Internet Research*, 15(6), e115.
- Weitzman, E. R., Adida, B., Kelemen, S., Mandl, K. D., & Lourenco, J. L. (2011). Sharing Data for Public Health Research by Members of an International Online Diabetes Social Network. *PLoS ONE*, 6(4), e19256.
- Wicks, P., Massagli, M., Frost, J., Brownstein, C., Okun, S., Vaughan, T., ... Heywood, J. (2010). Sharing Health Data for Better Outcomes on PatientsLikeMe. *Journal of Medical Internet Research*, 12(2), e19.
- Wicks, P., Vaughan, T. E., Massagli, M. P., & Heywood, J. (2011). Accelerated clinical discovery using self-reported patient data collected online and a patient-matching algorithm. *Nat Biotech*, 29(5), 411–414.

Figures

Figure captions

Fig. 1: BG profiles for diabetic patients and bounds for satisfactory glycemic control

Fig. 2: Implementations of the glucose stochastic process of a healthy subject using different scales of variability, $\sigma = 0.10$ (blue), 0.25 (green) and 0.50 (red)

Fig. 3: BG profiles for different bodyweights, the darker the heavier

Fig. 4: BG profiles for overlapping age-to-weight classes

Fig. 5: Wrapper feature elimination strategy

Fig. 6: Decision Tree graph for the selected features

Fig. 7: Confusion matrix for CSII according to age-to-weight ratio and GV level

Fig. 8: Confusion matrix for MDI according to age-to-weight ratio and GV level

Fig. 9: Precision and recall for the col-start setting in the CSII case

Fig. 10: Precision and recall for the col-start setting in the MDI case

Fig. 11: Confusion matrix for CSII according to age-to-weight ratio

Fig. 12: Confusion matrix for MDI according to age-to-weight ratio

Fig. 13: BG data in blue, initial specification in red, predicted specification in green

Fig. 14: Workflow for recommending specialized specifications

Fig. 1

Fig. 2

Fig. 3

Fig. 4

Fig. 5

Fig. 6

			diabetic														
			children			adolescent			youth			adult			elderly		
			30L	30M	30H	50L	50M	50H	70L	70M	70H	90L	90M	90H	110L	110M	110H
health	children	30L	15	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		30M	19	19	0	0	0	0	0	0	0	0	0	0	0	0	0
		30H	12	17	16	0	0	0	0	0	0	0	0	0	0	0	0
	adolesc	50L	4	11	17	20	0	0	0	0	0	0	0	0	0	0	0
		50M	0	3	10	14	17	0	0	0	0	0	0	0	0	0	0
		50H	0	0	5	11	14	14	0	0	0	0	0	0	0	0	0
	youth	70L	0	0	2	4	11	16	19	1	0	0	0	0	0	0	0
		70M	0	0	0	0	6	12	13	15	1	0	0	0	0	0	0
		70H	0	0	0	1	2	5	11	18	14	0	0	0	0	0	0
	adult	90L	0	0	0	0	0	1	5	11	19	19	1	0	0	0	0
		90M	0	0	0	0	0	2	2	4	10	17	16	0	0	0	0
		90H	0	0	0	0	0	0	1	3	10	19	14	1	0	0	0
	elderly	110L	0	0	0	0	0	0	0	1	4	9	20	21	2	1	1
		110M	0	0	0	0	0	0	0	0	0	5	11	17	19	2	2
		110H	0	0	0	0	0	0	0	2	0	0	5	11	29	47	47

Fig. 7

			diabetic														
			children			adolescent			youth			adult			elderly		
			30L	30M	30H	50L	50M	50H	70L	70M	70H	90L	90M	90H	110L	110M	110H
health	children	30L	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		30M	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0
		30H	12	5	0	0	0	0	0	0	0	0	0	0	0	0	0
	adolesc	50L	15	11	7	0	0	0	0	0	0	0	0	0	0	0	0
		50M	11	18	7	5	0	0	0	0	0	0	0	0	0	0	0
		50H	4	13	18	15	5	2	0	0	0	0	0	0	0	0	0
	youth	70L	1	2	14	17	11	9	1	0	0	0	0	0	0	0	0
		70M	1	0	3	8	19	16	7	1	0	0	0	0	0	0	0
		70H	0	0	0	4	13	13	18	5	2	0	0	0	0	0	0
	adult	90L	0	0	1	1	1	7	13	13	9	1	0	0	0	0	0
		90M	0	0	0	0	1	2	7	18	20	6	1	0	0	0	0
		90H	0	0	0	0	0	1	3	9	12	11	4	3	1	0	0
	elderly	110L	0	0	0	0	0	0	0	3	4	13	14	11	3	1	0
		110M	0	0	0	0	0	0	1	1	1	14	25	23	10	9	2
		110H	0	0	0	0	0	0	0	2	5	6	13	36	40	48	48

Fig. 8

	children			adolescent			youth			adult			elderly		
	30L	30M	30H	50L	50M	50H	70L	70M	70H	90L	90M	90H	110L	110M	110H
precision	1	0.50	0.35	0.38	0.38	0.31	0.35	0.31	0.27	0.33	0.31	0.29	0.36	0.35	0.50
recall	0.3	0.38	0.32	0.40	0.34	0.28	0.38	0.30	0.28	0.38	0.32	0.28	0.42	0.38	0.94

Fig. 9

	children			adolescent			youth			adult			elderly		
	30L	30M	30H	50L	50M	50H	70L	70M	70H	90L	90M	90H	110L	110M	110H
precision	1	0.2	0	0	0	0.03	0.01	0.01	0.03	0.02	0.01	0.06	0.06	0.10	0.40
recall	0.02	0.02	0	0	0	0.04	0.02	0.02	0.04	0.02	0.02	0.06	0.06	0.18	0.96

Fig. 10

			diabetic				
			age to weight				
			30	50	70	90	110
health	age to weight	30	98	0	0	0	0
		50	50	91	0	0	0
		70	2	58	92	2	0
		90	0	1	56	95	2
		110	0	0	2	53	148

Fig. 11

			diabetic				
			age to weight				
			30	50	70	90	110
health	age to weight	30	73	0	0	0	0
		50	75	67	0	0	0
		70	2	64	77	3	1
		90	0	18	58	69	3
		110	0	1	15	78	146

Fig. 12

Fig. 13

Fig. 14