

CENTERIS - International Conference on ENTERprise Information Systems / ProjMAN - International Conference on Project MANagement / HCist - International Conference on Health and Social Care Information Systems and Technologies

Towards Optimal Glycemic Control: A Case-Based Reasoning System for Predicting Postprandial Glucose

Débora Amorim^a, Carlos Abreu^{a,b,*}, Francisco Miranda^{a,b,c,d}

^aADiT-Lab, Instituto Politécnico de Viana do Castelo, Rua Escola Industrial e Comercial de Nun'Álvares, 4900-347 Viana do Castelo, Portugal

^bInstituto Politécnico de Viana do Castelo, Rua Escola Industrial e Comercial de Nun'Álvares, 4900-347 Viana do Castelo, Portugal

^cCenter for Research and Development in Mathematics and Applications (CIDMA), Department of Mathematics, University of Aveiro, 3810-193 Aveiro, Portugal

^dproMetheus, Instituto Politécnico de Viana do Castelo, Rua Escola Industrial e Comercial de Nun'Álvares, 4900-347 Viana do Castelo, Portugal

Abstract

Managing type 1 diabetes presents a daily challenge for patients. Advanced technologies have emerged to simplify disease management and support patients and caregivers. Notably, dosing prandial insulin remains a complex and error-prone task. This study introduces a case-based reasoning system to predict postprandial blood glucose by considering several attributes that influence glycemic metabolism. The case-based reasoning system leverages the knowledge of historical cases to forecast blood glucose levels and use it to optimize insulin bolus calculation. The proposed approach holds promise for enhancing glycemic control, offering patients a more accurate and personalized insulin regimen.

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Peer-review under responsibility of the scientific committee of the CENTERIS - International Conference on ENTERprise Information Systems / ProjMAN - International Conference on Project MANagement / HCist - International Conference on Health and Social Care Information Systems and Technologies

Keywords: Case-based Reasoning; Type 1 Diabetes; Bolus Insulin; Artificial Intelligence; Personalized Medicine.

* Corresponding author.

E-mail address: cabreu@estg.ipv.pt

1. Introduction

Patients with diabetes, particularly those who are insulin-dependent, face the daily challenge of managing an exhausting disease. Numerous technologies and applications have emerged to simplify management and provide support to patients and caregivers [1]. One of the most complex and error-prone tasks in type 1 diabetes (T1D) is dosing prandial insulin, where advanced bolus calculators and decision support systems have been developed, integrating artificial intelligence to determine the optimal insulin dose for each patient at every meal [2, 3, 4, 5]. However, despite these advancements, no system has yet met the necessary safety standards for integration into an artificial pancreas due to the intricacies of glucose metabolism. Therefore, addressing this issue remains of utmost importance.

In this study, we propose a case-based reasoning (CBR) system to predict postprandial glycemia by considering various attributes that can influence blood glucose (BG) regulation. Furthermore, the system aims to forecast blood glucose peaks based on the most similar previous situation. By obtaining a postprandial glycemia value from the CBR system that closely approximates the actual value, this data can be used to accurately calculate the insulin bolus and incorporated into a patient recommendation system, as described in [6].

The next section will address other works available in the literature that use CBR to achieve the optimal bolus every meal. Then, the CBR system developed will be presented, including all the steps and respective algorithms. After that, a detailed explanation will be provided on how the output of the CBR system will be used to obtain the accurate dose of bolus insulin. This work ends with the discussion and conclusion sections, where the potential of the system and how it should be used to improve patients' quality of life, as well as the study's limitations, are explained.

2. Related Work

In related works, various authors have employed CBR with the overarching aim of optimizing insulin bolus dosages. Herrero et al. introduced a novel algorithm by integrating Run-To-Run and CBR methodologies to aid patients in dosing bolus insulin [7]. Their CBR system utilizes five entry parameters, including BG levels and carbohydrate (CHO) intake, to predict the appropriate insulin-to-carbohydrate ratio (ICR) and insulin sensitivity factor (ISF) tailored to individual patients. Subsequently, they compute the optimal bolus insulin dose based on these parameters, subject to validation through postprandial glycemic analysis.

A different approach was used in [8], where the authors developed a CBR system to directly determine the optimized insulin dose. This personalized bolus calculator incorporates temporal sequences into its CBR phases to consider preceding events comprehensively. The insulin dosage proposed by the system is further evaluated through postprandial glycemic monitoring.

Fontbona and López presented PepperRec, a CBR system, that also focused on bolus insulin recommendations [9]. Their system used several input parameters that affect glucose metabolism to obtain the corrected ICR value, based on past situations. Later, the authors published another study in which they added the maintenance phase in their CBR system, which is relevant to refining the database of cases [10].

All the works mentioned tested their bolus recommendation systems through the UVa-Padova Type 1 Diabetes Simulator. On the whole, the results make clear that the application of the AI technique, CBR, has the potential to improve glycemic results for insulin-dependent patients.

After reviewing the literature, we decided to define the CBR input parameters with more detail, ensuring that the main factors that interfere with glycemic metabolism were included. To do so in a distinctive way, we assigned well-defined criteria to fields such as physical activity, patient weight, and time of the day. The approach presented in this work implies sophisticated algorithms for the different phases of the CBR, especially to find the most similar case, applying adaptive weights to the different categories that compose a case.

3. Proposed CBR System

A CBR system utilizes knowledge from similar past situations to tackle new problems. In developing the CBR system, we followed the 4-phase cyclic model introduced by Aamodt and Plaza [11]. These sequential phases, also known as the 4Rs, involve the Retrieval of cases or identifying more similar cases from the case database, Reusing

prior knowledge to solve the current problem, Revising the solution presented based on the result, and Retaining the current case if it is deemed useful in resolving future situations. In this section, we will detail how the cases will be constructed and the algorithms created for each phase.

3.1. The query case

The construction of a new case (query case) involves gathering and combining attributes (inputs). Only after going through the 4R phases of the CBR does the case become complete, including the solution found (outputs). In our proposed system, we have considered twelve attributes that have been identified in the literature as having an impact on glycemia regulation. These attributes are depicted in Figure 1.

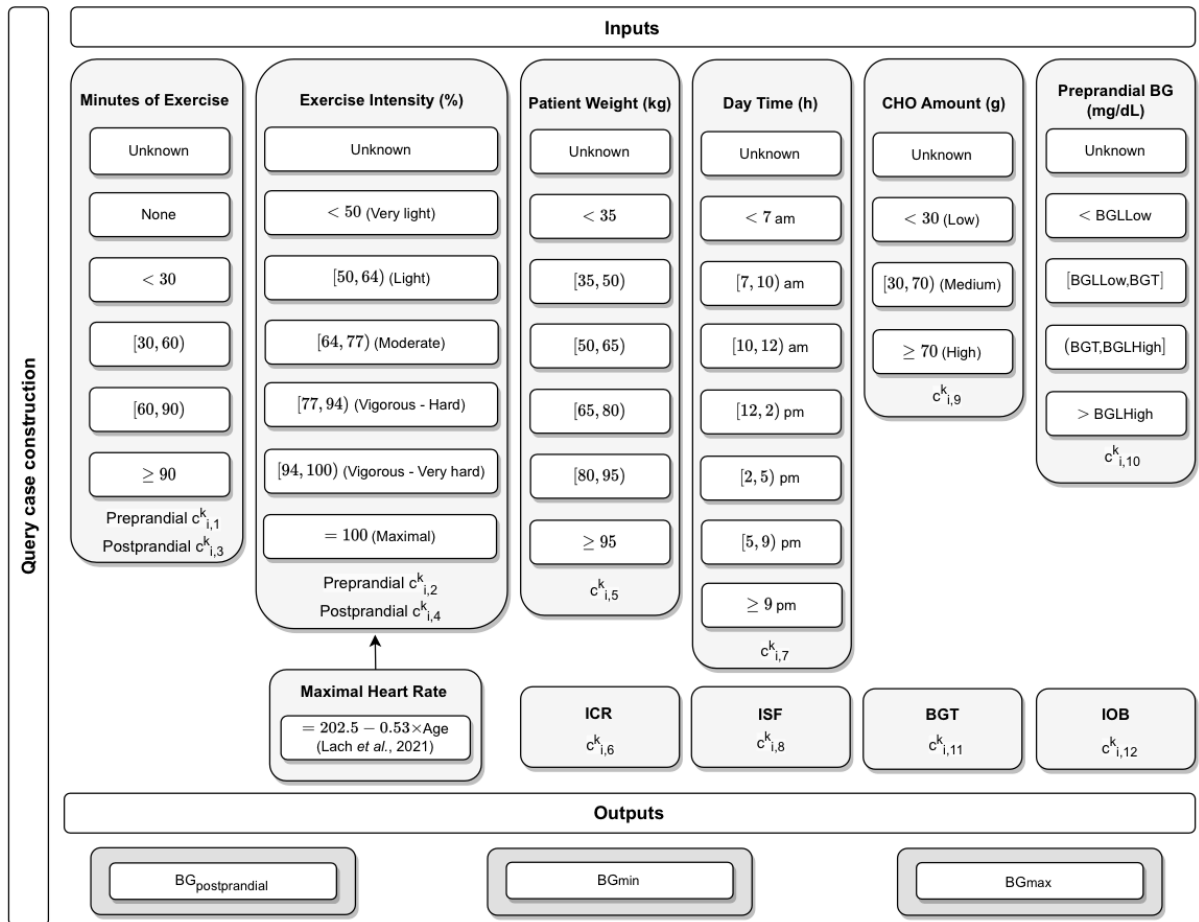


Fig. 1. Representative schema of the attributes included in a case. The input parameters are indicated at the top and the outcomes of the case at the bottom. A designation of the type " $c^k_{i,j}$ " was assigned to each retrieved case, where i is the number of the case, j is the attribute of the case and k is the class of the case. CHO stands for carbohydrates, BGLLow and BGLHigh are the blood glucose lower and upper limits, respectively, BGT is the blood glucose target, IOB is the insulin-on-board, BG_{postprandial} is the expected BG level 1-2h after the meal, BG_{min} and BG_{max} are the minimum and maximum BG value expected, respectively.

Regarding physical activity, we take into account two parameters: exercise duration and intensity. Both parameters are divided into ranges [12] that need to be selected for inclusion in the new case. Exercise intensity can be determined by the patient based on their perception or, for more accurate measurements, by monitoring heart rate during exercise.

In that case, it is necessary to know the patient's maximal heart rate (HR_{max}) which mainly relates to age. According to Lash et al. [13] the HR_{max} is given by Equation 1:

$$HR_{max} = 202.5 - 0.53 \times Age \quad (1)$$

Physical activity, therefore, contributes to the new case through these two parameters, and it can be either pre or postprandial. Consequently, a new case will have a total of four inputs related to this aspect. The patient's carbohydrate (CHO) intake is crucial for estimating postprandial glycemia and must be incorporated into the case by selecting one of the options [9] presented in Figure 1. Additionally, considering the time of day adds further precision to the case, taking into account the patient's routines in terms of meals, sleep, and physical activity. Patient-specific characteristics such as weight, ICR, and ISF are also essential inputs. By combining preprandial blood glucose levels with the insulin on board (IOB), which represents the active insulin from the previous bolus, the case becomes comprehensive. All the parameters must be normalized for the correct construction of the case. The normalized function is given by the following equations (Weighted Euclidean distance):

$$n(\Psi) = (\Psi - \min\{q_j, c_{1,j}^k, \dots, c_{n_k,j}^k\}) (\max\{q_j, c_{1,j}^k, \dots, c_{n_k,j}^k\} - \min\{q_j, c_{1,j}^k, \dots, c_{n_k,j}^k\}) \quad (2)$$

$$\Psi = q_j, c_{i,j}^k \quad (3)$$

where q_j is the query case value of the j^{th} attribute, $c_{i,j}^k$ is the value of the retrieved case number i , $i = 1, \dots, n_k$, with attribute j , $j = 1, \dots, 12$, of the k class ($k \in \{1, \dots, 47040\}$), and n_k is the case number in k class.

3.2. Retrieve

Our proposal for the first CBR phase solution involves finding the similarity between the query case and the retrieved cases, following the algorithm outlined below. Retrieve the case C_i^k (i^{th} retrieved case of class k) if

$$sim(Q, C_j^k) = 1 - \left(\sum_{\substack{j=1 \\ q_j, c_{i,j}^k \neq unknown}}^{12} W_j (n(q_j) - n(c_{i,j}^k))^2 + \sum_{\substack{j=1 \\ q_j = unknown \vee c_{i,j}^k = unknown}}^{12} W_j \cdot \mathbb{1}_A(q_j, c_{i,j}^k) \right) \quad (4)$$

for a choose $\Lambda \in [0, 1]$, and where Q is the query case (new problem), $n(q_j)$ and $n(c_{i,j}^k)$ are the normalized j^{th} attribute (as indicated for each attribute in Figure 1) of query case (q_j) and retrieved case C_i^k ($c_{i,j}^k$), respectively, and $\mathbb{1}_A(q_j, c_{i,j}^k)$ is the characteristic (indicator) function, where $A = \{(q_j, c_{i,j}^k) : q_j \neq c_{i,j}^k, i = 1, \dots, n_k\}$. The W_j are the weights for each j^{th} attribute obtained taking into account the influence on postprandial glycemia of the error that can be caused in each attribute. Note that $W_j \in [0, 1]$ and $\sum_{j=1}^{12} W_j = 1$. Therefore, to calculate these weights we use the following relationship:

$$|BG_{postprandial} - BGT| = |B_j - B_{j,estimated}| \cdot ISF \text{ for } j = 1, \dots, 12 \quad (5)$$

where B_j is the correct bolus given by Equation 16 and $B_{estimated}$ is given by the same equation but influenced by an error committed in the j^{th} attribute. We have

$$W_1 = \dots = W_7 = \frac{CHO \cdot ISF}{\xi \cdot ICR^2} \quad (6)$$

$$W_8 = \frac{|BG_{preprandial} - BGT|}{\xi \cdot ISF} \quad (7)$$

$$W_9 = \frac{ISF}{\xi \cdot ICR'} \quad (8)$$

$$W_{10} = W_{11} = W_{12} = \frac{1}{\xi} \quad (9)$$

$$\xi = 3 + \frac{(7 \times CHO + ICR) \cdot ISF^2 + |BG_{preprandial} - BGT| \cdot ICR^2}{ISF \cdot ICR^2} \quad (10)$$

If $BG_{preprandial}$ are known, then we consider all attributes with the same weight, i.e., $W_1 = \dots = W_{12} = 1/12$.
If there are no cases that verify these conditions, the BG forecast is not carried out.

3.3. Reuse

The next step encompasses reusing the solutions derived from similarity, and for this purpose, we put forth two hypotheses: i) using the weighted mean of the BG_η , $\eta \in \{postprandial, min, max\}$, of the retrieved cases or ii) using multivariate linear regression of the BG_η of the retrieved cases based on their similarity to the query case.

i)

$$BG_\eta^Q = \left(\sum_{i=1}^l (sim(Q, C_i^k) + f_i^k) \right)^{-1} \times \sum_{i=1}^l (sim(Q, C_i^k) + f_i^k) BG_\eta^{C_i^k} \quad (11)$$

where l is the number of retrieved cases (i.e., $sim(Q, C_i^k) \geq \lambda$, $i = 1, \dots, l$), f_i^k is the relative frequency with which the case C_i^k has been used in the past in relation to the total times that all cases C_i^k , $i = 1, \dots, l$, have been used. BG_η^Q is the BG_η of the query case, and $BG_\eta^{C_i^k}$ is the BG_η corresponding to retrieve case C_i^k .

ii)

$$BG_\eta^Q = \sum_{j=1}^{12} \alpha_j (f_j^k)_\eta \cdot q_j, \text{ with condition } \min C_{i,j}^k \leq q_j \leq \max C_{i,j}^k \quad (12)$$

where $\alpha_j (f_j^k)_\eta$ are the linear regression coefficients determined by the least squares method with weights f_j^k (relative frequency with which the j^{th} attribute of class k has been used in the past in relation to the total cases that have at least one k class attribute). This linear regression should only be used if the coefficient of determination $R^2 > \lambda$ for λ sufficiently large in the range $[0, 1]$.

3.4. Revise

After reusing the obtained solution, the process of revision is crucial to the quality and refinement of the cases' database. This involves the utilization of blood glucose levels measured by the continuous glucose meter ($BG_\eta^{observed}$). Therefore, the revision algorithm is defined as follows:

$$BG_\eta^{revised} = \kappa \cdot BG_\eta^Q + (1 - \kappa) BG_\eta^{observed} \quad (13)$$

where $\kappa = ff^k(BG_\eta^Q) \in [0, 1]$ is the learning rate, i.e., the relative frequency with which BG_η^Q has been observed in the past considering cases of class k .

This learning rate is incorporated to smooth changes since they could be influenced by noisy measurements of the CGM, giving sufficient importance to the values of BG often obtained in the class k .

3.5. Retain

Once the solution has been revised, the next step is to determine whether the case should be stored and specify the conditions for doing so. The metric established for that is defined by the expressions below. Since patient characteristics continually change, the priority is to retain the new problem Q removing the case that verifies the following:

$$C_{max}^k = \operatorname{argmax}_{C \in \{C_1^k, \dots, C_1^k\}} (\operatorname{sim}(Q, C) - f_i^k), \quad (14)$$

if

$$\operatorname{sim}(Q, C_{max}^k) \geq Y, \text{ for a choose } Y \in [0,1]. \quad (15)$$

Otherwise, only retain Q .

4. Bolus Optimization

To achieve the central objective of maximizing the accuracy of the insulin bolus for each patient at every meal, we introduced an optimization factor, K . The standard method for calculating the insulin bolus is given by Equation 16.

$$B = \frac{CHO}{ICT} + \frac{BG_{preprandial} - BGT}{ISF} - IOB \quad (16)$$

The optimized bolus is then calculated by adding the K factor to the standard equation, thereby compensating for errors arising from the ICR and CHO estimates:

$$B = \frac{CHO}{ICT} + \frac{BG_{preprandial} - BGT}{ISF} + K - IOB \quad (17)$$

The CBR system outputs, specifically the postprandial BG prediction and the identification of maximum and minimum peaks play a crucial role in obtaining an accurate K value. Using the predicted value of postprandial BG, the K is obtained through Equation 18 [14].

$$K = \frac{W(BG_{postprandial} - BGT)}{\alpha(ICR_{estimated} + ICR_{error})}, \quad (18)$$

where W is the patient weight, $BG_{postprandial}$ is the BG level measured 1-2 hours after the meal, α represents the relation between ICR and ISF (given by: $W \times (ISF/ICR)$), $ICR_{estimated}$ is determined by the physician and ICR_{error} is the error associated to the estimation, calculated through Equation 19.

$$ICR_{error} = - \frac{W \times ICR_{estimated} \times (BG_{postprandial} - BGT)}{\alpha \times (CHO_{estimated} + CHO_{error}) + W(BG_{preprandial} - BGT)}, \quad (19)$$

where $CHO_{estimated} + CHO_{error}$ implies the knowledge of actual CHO intake.

Furthermore, utilizing the forecasted maximum and minimum BG values, the factor K can be calculated through the application of Equations 20, 21, and 22 [14], in accordance with the anticipated glycemic behavior. It is important to note that BG values are expected to fall within the range of [70-180 mg/dL] [15]. Therefore, if the prediction generated by the CBR system for a patient shows a maximum BG exceeding 180 mg/dL and a minimum BG exceeding 70 mg/dL, which represents a hyperglycemia event, K is determined by the Equations 20 and 21:

$$K = \frac{W(BG_{max} - BGLHigh)}{\gamma \times \alpha(ICR_{estimated} + ICR_{error})}, \quad (20)$$

where $BGLHigh$ is the BG upper limit and γ is an adjustment coefficient applied to compensate for the difference in the amplitude of the displacements that occur at the maximum and minimum points of BG when a glycemic curve undergoes translation. Equation 20 should be employed when the difference between BG_{max} and $BGLHigh$ is less than

or equal to the difference between BG_{min} and $BGLLow$. Conversely, if the opposite is true, the calculation of K should consider the difference between BG_{min} and $BGLLow$, as per Equation 21.

$$K = \frac{W(BG_{min} - BGLLow)}{\gamma \times \alpha(ICR_{estimated} + ICR_{error})}, \quad (21)$$

where $BGLLow$ is the BG lower limit. In cases where the maximum BG peak remains below the 180 mg/dL threshold and BG_{min} stays under 70 mg/dL, predicting a hypoglycemic event, K is given by:

$$K = \frac{\gamma \times W(BGLLow - BG_{min})}{\alpha(ICR_{estimated} + ICR_{error})}. \quad (22)$$

5. Discussion

CBR is an artificial intelligence method that allows for making informed decisions about future scenarios based on similar situations from the past. This quality makes it widely applicable in the medical field. The proposed *CBR* system takes into consideration a series of crucial parameters for accurately dosing prandial insulin. All these inputs contribute to selecting the most similar cases, each assigned different weights calculated in specific ways to enhance the retrieval process. The *CBR* outputs play a vital role in determining the suitable correction factor for each situation. By predicting BG values, the system can anticipate potential undesirable glycemic fluctuations and optimize the insulin bolus using Equation 17.

To ensure that the correction factor adequately addresses errors in the *ICR* estimate, it is imperative to determine the corresponding error using Equation 19. Additionally, an existing system in the literature, known as *PepperRec*, utilizes a *CBR* approach to ascertain the corrected *ICR*, which could potentially complement the proposed system. Additionally, beyond the outlined phases, future work could involve implementing a database maintenance process. This process would help retain the most relevant cases while eliminating redundant or unnecessary ones, thus improving the system's responsiveness and refining its performance.

When integrated into a patient recommendation system as described in [6], this *CBR* system has the potential to significantly enhance insulin bolus calculation accuracy. This can grant patients greater autonomy, which is especially important for those who struggle with precise insulin dosing due to challenges in estimating *CHO* or understanding how physical activity affects blood glucose levels, among other factors.

Although a robust system has been developed with algorithms for each phase of the *CBR* cycle based on the literature, the model must undergo validation using real cases before practical application. The correction factor K has already been tested using historical patient data, utilizing the *UVA/Padova* simulator for *T1D*. Cases of hyperglycemia due to carbohydrate estimation errors were considered [16]. In these preliminary tests, it was observed that K has the potential to enhance glycemic control. However, it is believed that the use of *CBR* for the forecast of BG can produce better results, as these values take into account the patient's context at that specific moment.

6. Conclusions

Our study addresses a critical aspect of *T1D* management by proposing a *CBR* system to predict postprandial glycemia with the final goal of optimizing bolus insulin. The proposed approach details the *CBR* phases algorithms, highlighting the method developed to retrieve similar cases, considering different weights for each attribute of the new case. The output of the *CBR* is crucial for accurately calculating the optimization factor K , as the forecasted BG values consider the patient's context at that specific moment. This factor will be included in the bolus calculation, compensating errors in *CHO* and *ICR* estimations. The preliminary success of factor K underscores the potential for improved glycemic outcomes. However, validating our model with real-world cases will be pivotal to its practical application. By granting patients greater autonomy and precision in insulin dosing, this approach could highly impact the lives of individuals with *T1D*, paving the way for more effective and personalized diabetes management strategies.

Acknowledgements

This work is a result of the project TECH – Technology, Environment, Creativity and Health, supported by Norte Portugal Regional Operational Program (NORTE 2020), under the PORTUGAL 2020 Partnership Agreement, through the European Regional Development Fund (ERDF), Norte-01-0145-FEDER-000043. F. Miranda was also supported by the Portuguese Foundation for Science and Technology (FCT – Fundação para a Ciência e a Tecnologia), through CIDMA – Center for Research and Development in Mathematics and Applications, within project UIDB/04106/2020 with DOI identifier <https://doi.org/10.54499/UIDB/04106/2020>.

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