Adaptive basal insulin recommender system based on Kalman filter for type 1 diabetes

F. Torrent-Fontbona[a,*]

[a] *eXiT research group, Institute of Informatics and Applications, University of Girona, Campus Montilivi, Edifici P4, 17071 Girona, Catalunya*

Abstract

Type 1 diabetes mellitus is a chronic disease that requires those affected to self-administer insulin to control their blood glucose level. However, the estimation of the correct insulin dosage is not easy due to the complexity of glucose metabolism, which usually leads to blood glucose levels far from the optimal. This paper presents an adaptive and personalised basal insulin recommender system based on Kalman filter theory that can be used with or without continuous glucose monitoring systems. The proposed approach is tested with the UVa/PADOVA simulator with eleven virtual adult subjects. It has been tested in combination with two different bolus calculators, and the performance achieved has been compared with that obtained with the default basal doses of the simulator, which can be assumed as optimal. The achieved results demonstrate that the proposed system rapidly converges to the optimal basal dose, and it can be used with adaptive bolus calculators without the risk of instability.

Keywords: Diabetes, basal recommender system, Kalman filter, patient empowerment

1. Introduction

Type 1 Diabetes Mellitus (T1DM) is a chronic metabolic disease characterised by the autoimmune destruction of the beta cells of the endocrine pancreas that are responsible for controlling Blood Glucose (BG) levels through the secretion of insulin. There are no global statistics about the number of people suffering from T1DM (World Health Organization, 2016), but the American Diabetes Association estimates that there are approximately 1.25 million American children and adults with T1DM, and according to the International Diabetes Federation, Europe has approximately 140,000 children with T1DM and has the highest incidence rates, with 21,600 new cases of T1DM every year (International Diabetes Federation, 2015).

People living with T1DM need to control their BG level in order to avoid it being too high and suffering hyperglycaemia[1] events, or too low and suffering hypoglycaemia[2] events. Therefore,

*Corresponding author

Email address: ferran.torrent@udg.edu (F. Torrent-Fontbona)

URL: http://eia.udg.es/~ftorrent/ (F. Torrent-Fontbona)

[1] Hyperglycaemia can cause, in the long term, micro-vascular complications such as retinopathy, nephropathy and neuropathy, and macro-vascular complications such as coronary heart disease, stroke and peripheral vascular disease.

[2] Hypoglycaemia may result in clumsiness, trouble talking, loss of consciousness, seizures, or death.

people with T1DM have to periodically check their BG using a Continuous Glucose Monitor (CGM) or with capillary BG measurements, i.e. by drawing blood from the fingertips in order to measure the glucose concentration. Usually, two types of insulin are used to regulate the BG - a fast acting insulin also called bolus insulin, and a slow acting insulin called basal insulin. While bolus insulin is used to metabolise the ingested carbohydrates from food, basal insulin is used to metabolise the liver's continuous secretion of glucose. Therefore, bolus doses are usually calculated considering the current BG and the quantity of carbohydrates to ingest, while basal doses are calculated analysing BG behaviour over a particular period of time, e.g. a month.

The estimation of the insulin needed is usually done following very simple rules, mainly based on empirical experience, that barely catches the complexity of the glucose metabolism and, consequently, fail to optimise the insulin therapy. Consequently, there are Bolus Calculators (BC) on the market (Garg et al., 2008; Sussman et al., 2012) that help people to calculate the appropriate bolus dose. However, basal doses are usually agreed upon by patients and their endocrinologist.

This paper explains a novel methodology based on Kalman filter to automatically adjust basal insulin. The proposed method takes advantage of the use of CGM. Nevertheless, a variation of the algorithm that does not require the use of CGM is also presented. The methodology is tested in combination with a traditional BC and with an adaptive BC based on Case-Based Reasoning (CBR) presented in the previous work (Torrent-Fontbona et al., 2017). The system is tested with ten virtual adults and an average adult using the UVa/PADOVA T1DM simulator. The results show that the proposed algorithm is capable of achieving optimal values in a few iterations, even without the use of CGM.

This paper is organised as follows: first, some background information regarding insulin dosage calculation is presented with support of the related literature; second, the basal recommender system is described; third, the experimentation and the results are explained; finally, the paper ends with the achieved conclusions.

2. Background and related work

Basal-bolus therapy consists of administering basal and bolus insulin to metabolise and control BG. The market offers BC software tools which usually incorporate glucose meters (Sussman et al., 2012) or personal digital assistants (Garg et al., 2008), etc., to help people to calculate the appropriate bolus dosage. BCs usually rely on a mathematical formulation similar to Equation (1) (Brown, 2015; Herrero et al., 2015a) to calculate the bolus dose B, where CHO (in g) is the amount of carbohydrates in the meal, G_c (in mg/dl) is the blood glucose level, G_{sp} (in mg/dl) is the target blood glucose level, ISF (in mg/dl) is the insulin sensitivity factor, ICR (in g) is the insulin to carbohydrates ratio and IOB is the remaining active insulin (insulin on board).

$$B = \frac{CHO}{ICR} + \frac{G_c - G_{sp}}{ISF} - IOB \tag{1}$$

Despite BCs having been proved useful in terms of improving glycaemic self-control (Lepore et al., 2012; Shashaj et al., 2008; Gross et al., 2003), they are still far from achieving optimal glycaemic control, usually because of the difficulty of setting their parameters (ICR and ISF) and regularly adjusting them according to changes in insulin requirements.

This has led researchers to develop new methods that automatically adjust BC parameters such as those of (Herrero et al., 2015a,b; Torrent-Fontbona et al., 2017) which then recommend

an accurate dosage. However, these methods require an optimised basal insulin to achieve good results.

In this regard, (Torrent-Fontbona et al., 2017) propose a method that uses physical activity, time of day and meal size to define the cases of a CBR system. The method models the changes in terms of ICR and ISF according to physical activity, time of day and meal size throughout a set of cases, to then estimate the value of ICR and ISF under a new situation. Once the ICR and ISF are calculated, the method recommends a bolus dose using Equation (1). Cases are updated according to the blood glucose values after a bolus recommendation in order to recursively adjust the modelling of the ICR and ISF. This paper presents a basal insulin recommender system and analyses its performance in combination with (Torrent-Fontbona et al., 2017) and in combination with a standard bolus calculator with fixed ICR and ISF.

Basal insulin is usually adjusted by the endocrinologist in agreement with the patient with T1DM. Usually, clinicians start with the rule of 50% bolus and 50% basal insulin (Brown, 2015). Therefore, when they have a new patient, they make an estimation of the Total Daily Dose (TDD) of insulin that she may need, and then they set the basal insulin and the parameters (ICR and ISF) used to calculate bolus doses depending on carbohydrate intake and BG. After this initialisation, the clinician and the patient adjust the basal dose according to the BG behaviour in the periodic meetings they have (e.g. monthly).

Despite the fact that basal insulin adjustment has been traditionally left to an endocrinologist, the literature presents methods with the objective of automatically adjusting basal insulin. For example, (Herrero et al., 2017) propose the combination of CBR and a run-to-run algorithm, to calculate the appropriate basal dosage. The authors use CBR to retrieve a past basal dosage for a given context, and they use the run-to-run algorithm to iteratively adjust the basal dosage for each context. Conversely, this paper proposes to iteratively adjust the Kalman filter model, which then guarantees the best linear estimation and prediction of the needed insulin. Therefore, the proposed methodology does not assume that there are clear identifiable contexts for which the required basal dosage is different. Despite this it could be easily extended to a table of models, each of which is applicable to a particular context.

The authors in (Palerm et al., 2008) also propose a run-to-run algorithm to iteratively adjust the basal dosage using six capillary glucose measurements per day and (Toffanin et al., 2017) propose to use a run-to-run algorithm to adapt basal dosage during the night and insulin-to-carbohydrate ratio during the day, using a CGM. We also take advantage of the use of CGM and basal dosage is estimated daily, but we also propose a variation of the method to avoid the need for CGM.

Artificial pancreas has led to important research on developing algorithms to control insulin infusion, such as the methods reviewed in (Doyle et al., 2014). However, these methods cannot be compared to the presented approach since it aims to help people with T1DM with a basal-bolus therapy using a pump or multiple daily injections, instead of an artificial pancreas system.

Artificial intelligence has been also used to aid people with T1DM beyond the recommendation of basal insulin. In this regard, CBR has proved to be a powerful tool in terms of providing bolus recommendations for T1DM (Brown, 2015; Herrero et al., 2015a,b; Torrent-Fontbona et al., 2017). These works exploit the capacity of CBR to describe the solution space throughout a set of past experiences in order to learn from them, and recommend a bolus dose for each new situation. The authors in (Marling et al., 2008) propose a case-based decision support system to detect complications in people with TD1M on insulin pump therapy, and then recommend therapeutic adjustments stored in the case base.

Fuzzy logic has been also used to develop models of subjects' physiology, and provide bolus

recommendations relying on these fuzzy logic models. For example, (Liu et al., 2013) presents a fuzzy logic model of glucose behaviour according to the size of the meal. This fuzzy model is updated using new information regarding meals and BG values, and it is used to provide bolus recommendations.

Artificial intelligence has been also used to predict BG and possible hypoglycaemia and hyperglycaemia events. Various researchers have opted for using CGM data to train machine learning models. In this regard, (Mo et al., 2013; Pappada et al., 2008) propose the use of artificial neural networks to predict hypoglycaemia; (Plis et al., 2014) proposes the use of a generic physiological model of BG dynamics to generate informative features for a support vector regression model to predict BG levels; (Sudharsan et al., 2015) analyses the performance of random forests, K-nearest neighbour, support vector machine and nave Bayes to predict hypoglycaemia for type 2 diabetes. They conclude that random forests and support vector machine outperform the other two methods. The authors in (Oviedo et al., 2016) present a deep review of BG prediction strategies for T1DM.

3. Basal recommender system

This paper presents an adaptive and personalised basal insulin recommender system based on Kalman filter theory (Grewal, 2011). The methodology is depicted in Figure 1. This consists of predicting the TDD and then updating its value according to Kalman filter theory, and using the measured TDD (the sum of basal and bolus doses) which is provided by the user. The predicted TDD is used to recommend a basal dose for the user. In parallel, the method updates the bolus/basal proportion and the covariance of the process noise which are parameters used for updating the TDD.

The remainder of the section explains the different parts of the system.

3.1. Kalman filter modelling

Kalman filter is a recursive estimator used to infer parameters of interest from indirect, inaccurate and uncertain observations. It consists of a two-step method which firstly predicts the one-step ahead state (the value of the parameters of interest) and then updates the prediction given a new observation of the state (new measurements of the parameters).

Assuming that state x_n is governed by a system control sequence u_n and the corresponding system noise w_n, the system state equation is formalised as follows:

$$x_{n+1} = A \cdot x_n + B \cdot (u_n + w_n) \tag{2}$$

where A is the state transition model and B is the control-input model.

The observations of the state are defined as

$$\hat{y}_n = H \cdot x_n + v_n \tag{3}$$

where y_n is the observed state, H is the observation model, and v_k is the observation noise.

The prediction of the future state is formalised as Equations (4) and (5), where $\hat{x}_{n+1|n}$ is the predicted TDD for time $n+1$, $\hat{x}_{n|n}$ is the estimated TDD for time n conditioned to the measurements until n, and K_n is the Kalman gain.

$$\hat{x}_{n+1|n} = A \cdot \hat{x}_{n|n} + B \cdot u_n \tag{4}$$

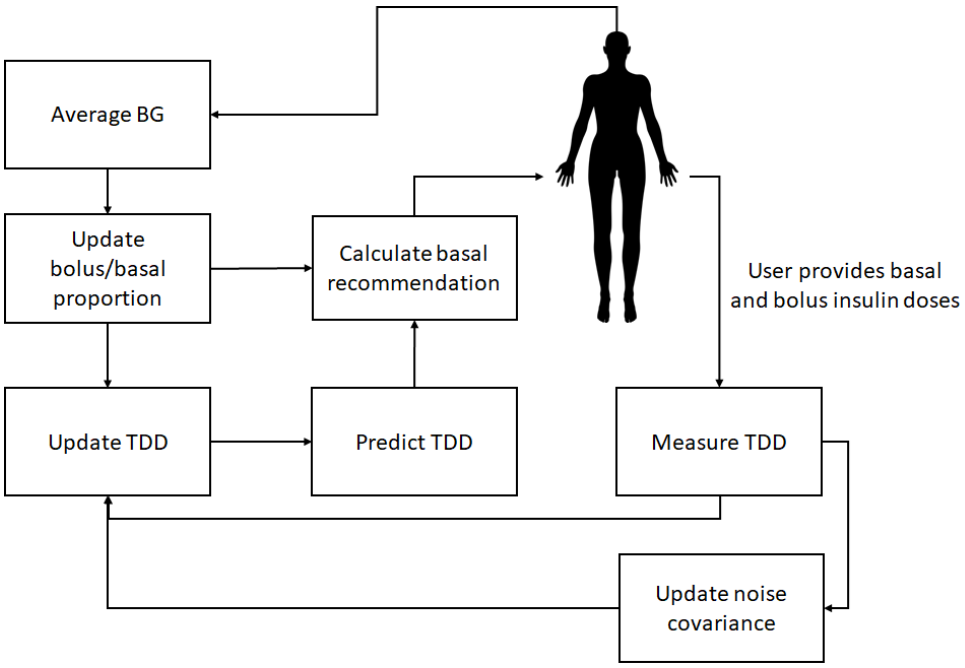

Figure 1: Adaptive and personalised basal insulin recommender system.

$$\hat{x}_{n|n} = \hat{x}_{n|n-1} + K_n \left(y_n - \hat{x}_{n|n-1}\right) \tag{5}$$

The Kalman gain is formalised according to Equation (6), where R_n denotes the observation noise covariance at the nth time and $P_{n|n-1}$ and $P_{n|n}$ are formalised according to Equations (7) and (8) and denote the covariance of prediction error of $\hat{x}_{n|n-1}$ and its update. Q_n denotes the known covariance of the process noise at the nth time.

$$K_n = A \cdot P_{n|n-1} \cdot H^T \cdot \left(H \cdot P_{n|n-1} \cdot H^T + R_n\right) \tag{6}$$

$$P_{n|n-1} = A \cdot P_{n-1|n-1} \cdot A^T + Q_{n-1} \tag{7}$$

$$P_{n|n} = (I - K_n \cdot H) \cdot P_{n|n-1} \tag{8}$$

If w_n and v_n are Gaussian white noise ($w_n \backsim N(0, Q)$ and $v_n \backsim N(0, R)$), the Kalman filter minimises the mean square error of the estimated parameters. If the noise is not Gaussian, given the mean and the standard deviation of the noise, the Kalman filter is the best linear estimator (Grewal, 2011).

The standard Kalman filter works well if there is exact *a priori* knowledge of the system structure (A, B and H), as well as the statistical properties, which are mainly the covariances of the process and observation noise (Q and R).

3.2. Process and observation model

In order to achieve a good performance, the structure of the system has to be known *a priori*. In the proposed modelling, if we consider that the state variable x_n describes the TDD, and the control variable u_n denotes the daily bolus dose, then Equation (4) predicts the TDD for day $n+1$ ($\hat{x}_{n+1|n}$), given the estimation of the TDD on day n ($\hat{x}_{n|n}$) and the amount of bolus insulin administered on day n. Since u_n is the amount of bolus insulin infused on day n and it is known, we can assume $B = 1$. According to this, A models the amount of basal insulin in the prediction of the TDD for the next day, and it models it as a portion of the TDD of the current day.

Clinicians usually initialise basal insulin as half of the estimated TDD, i.e. $A = \frac{1}{2}$. However, they periodically adjust it according to the BG behaviour. This paper proposes to iteratively adjust A according to the average BG level according to Equation (9), where A_k is the estimated transition model at the kth iteration of the algorithm, α is the learning rate, μ_G is the average BG (e.g. average of CGM readings) since the last update of A, and G_{sp} is the glucose set point, i.e. the target average BG.

$$A_{k+1} = A_k + \alpha \frac{\mu_G - G_{sp}}{G_{sp}} \tag{9}$$

Note that the average of CGM values can be defined as $\mu_G = \frac{1}{M} \sum_{m=t-M}^{t} G_m$, where G_m is the mth BG measurement, M is the number of BG samples used, and t denotes the time when A_{k+1} is estimated. Nevertheless, it can be iteratively calculated as

$$\mu_{G_m} = \frac{m-1}{m} \mu_{G_{m-1}} + \frac{1}{m} G_m \tag{10}$$

where m is the number of BG samples, μ_{G_m} is the mth update of μ_G and G_m is the mth BG sample, i.e. the new BG reading.

Moreover, α is a design parameter that can be the same for everybody, and G_{sp} is easier to set than A for any clinician or patient since it is the desired average blood glucose. It is usually the mid-point of the glycaemic target range.

On the other hand, H denotes the observation model. Since x_n is the true TDD and y_n is the measured TDD, we can assume $H = 1$.

3.3. Iterative estimation of Q

As stated previously, a precise estimation of the noises covariance is needed. However, in practice, this is difficult to estimate, especially with regard to process noise, since we are often not able to completely understand the mechanism of noise. For example, in the case of the TDD, its variability is caused by several different factors that are very difficult to model.

On the other hand, the observation noise is easy to model since it depends on the accuracy of the insulin infusion mechanism, e.g. a pump. Therefore, its covariance $\mathrm{cov}(v) = R$ can be assumed to be known.

This paper proposes an iterative estimation of the covariance of the process noise (Q). The proposed method is based on (Feng et al., 2014) and considers that the covariance of a random variable can be approximated as follows

$$cov_{n+1}(\zeta) = \frac{1}{n+1} \sum_{i=1}^{n+1} \zeta_i^2 - \left(\frac{1}{n+1} \sum_{i=1}^{n+1} \zeta_i \right)^2 \tag{11}$$

Therefore, as $n \to \infty$ then, $(cov_n(\zeta) - cov(\zeta)) \to 0$.

Developing Equation (11), we obtain

$$cov_{n+1}(\zeta) = \frac{n}{n+1} cov_n(\zeta) + \frac{1}{n+1}\zeta_{n+1}^2 - \left(\frac{n}{n+1}\mu_n + \frac{1}{n+1}\zeta_{n+1}\right)^2 \tag{12}$$

Then, if we define variables ζ_n and V_n as follows

$$\zeta_n = \left(H^T H\right)^{-1} H^T y_n - A\left(H^T H\right)^{-1} H^T y_{n-1} \tag{13}$$

$$V_n = \left(H^T H\right)^{-1} H^T v_n - A\left(H^T C\right)^{-1} H^T v_{n-1} \tag{14}$$

we can state

$$\zeta_k = B \cdot w_{k-1} + V_k \tag{15}$$

Therefore, as (Feng et al., 2014) states, we can estimate Q at the nth time as follows

$$\hat{Q}_n = \text{cov}(B \cdot w_{n-1}) = \text{cov}(\zeta_n) - \text{var}(V_n) \tag{16}$$

where $\text{cov}(\zeta_n)$ can be obtained by taking consecutive samples of y_n and using Equations (12) and (13). Moreover, if we consider that two consecutive samples of v are independent, then the covariance of V_n can be calculated *a priori* using $\text{cov}(v)$ according to Equation (17).

$$\text{cov}(V_n) = \text{cov}\left(\left(H^T H\right)^{-1} H^T \cdot v\right) + A\left(H^T H\right)^{-1} H^T \text{cov}\left(A\left(H^T H\right)^{-1} H^T \cdot v\right) \tag{17}$$

Considering that $B = 1$, $H = 1$ and A is a scalar, then

$$\text{cov}(V_n) = \left(1 + A^2\right) R \tag{18}$$

3.4. Complete algorithm

The proposed algorithm consists of using Kalman filter theory for estimating the next day's TDD and, based on this, setting the basal insulin dose. However, this requires *a priori* knowledge of the system's structure and its statistical properties. As this section has explained, most of this information is known but, in practice, the transition model and the process noise covariances are difficult to determine *a priori*, and may be different for each T1DM patient. Therefore, the complete algorithm consists of a Kalman filter that predicts the TDD of the next day and two methods that iteratively estimate the personalised transition model A and the process noise covariance Q. The process noise covariance is estimated every time we have a TDD sample, i.e. once per day. On the other hand, to update A, it is necessary to measure the BG average. Therefore, this paper suggests the need to do this every several days in order to let the BG average reach the stability point for a given A, e.g. once per week.

Algorithm 1 shows an implementation of the proposed method assuming $H = 1$ and $B = 1$. Step 11 shows the update step of the Kalman filter, and step 12 shows the prediction of the next day's TDD. Then, step 14 calculates the basal dose recommendation for the next day.

The proposed system assumes that bolus insulin is a given information. Therefore, this algorithm can be used in combination with bolus recommender systems and even adaptive bolus recommender systems such as that detailed in (Torrent-Fontbona et al., 2017).

Algorithm 1 Basal recommender system algorithm

Initialisation: $A = \frac{1}{2}$, $Q = 1$, $basal = 0$

Require: G_{sp}, average BG, sample sequence $\{y_n\}$ of TDD, sample sequence $\{u_n\}$ of daily bolus, R

for each day n **do**
  if end of week **then**
    Update A according to Equation (9)
  end if
  $y_n \leftarrow basal + u_n$
  $\text{cov}(V_n) \leftarrow \left(1 + A^2\right) R$
  $\zeta_n \leftarrow y_n - A \cdot y_{n-1}$
  Calculate $\text{cov}(\zeta)$ using Equation (12)
  $Q \leftarrow \text{cov}(\zeta) - \text{cov}(V_n)$
  $K \leftarrow \frac{P}{P+R}$
  $x \leftarrow x + K \cdot (y_n - x)$
  $x \leftarrow A \cdot x + u_n$
  $P \leftarrow A^2 P + Q$
  $basal \leftarrow A \cdot x$
end for

3.5. Proposal for non-CGM users

The proposed approach takes advantage of the increasing use of CGM. However, there are still T1DM patients who rely on capillary BG measurements. In order to avoid the use of CGM, Equation (9) could be relaxed as follows

$$A_{k+1} = A_k + \mu \frac{\frac{1}{M} \sum_{i=t-M}^{t} FG_i - FG_{sp}}{FG_{sp}} \tag{19}$$

where FG_i is the ith fasting glucose measurement, and FG_{sp} is the target fasting glucose level. Fasting glucose can be measured every morning before breakfast or before each meal. Therefore, this does not involve extra capillary BG measurements than for calculating bolus doses.

4. Results and discussion

The basal recommender system has been tested using the UVa/PADOVA T1DM simulator with eleven (ten plus the average subject) virtual adult subjects, which are supposed to represent the variability found amongst real adults with T1DM (Visentin et al., 2014; Kovatchev et al., 2009). The UVa/PADOVA T1DM simulator is the only T1DM simulator approved by the United States Food and Drug Administration as an alternative to animal testing of T1DM control strategies. The simulator consists of a model of glucose-insulin dynamics during a meal; a model of glucose kinetics in hypoglycaemia which allows insulin utilization to increase at low glucose levels; and a model of glucagon kinetics, secretion and action that mimics endogenous glucose production at low glucose levels. The glucose dynamics of the simulator reproduces the distribution of insulin correction factors, and the glucose fluctuations in T1DM observed during meal challenges and in hypoglycaemia (Visentin et al., 2014; Kovatchev et al., 2009). The simulator is described in more detail in (Visentin et al., 2014).

The proposed system has been tested using a BC with constant parameters and the CBR-based BC presented in (Torrent-Fontbona et al., 2017). The performance of the basal recommender system has been compared to that achieved with a constant basal dosage. The constant

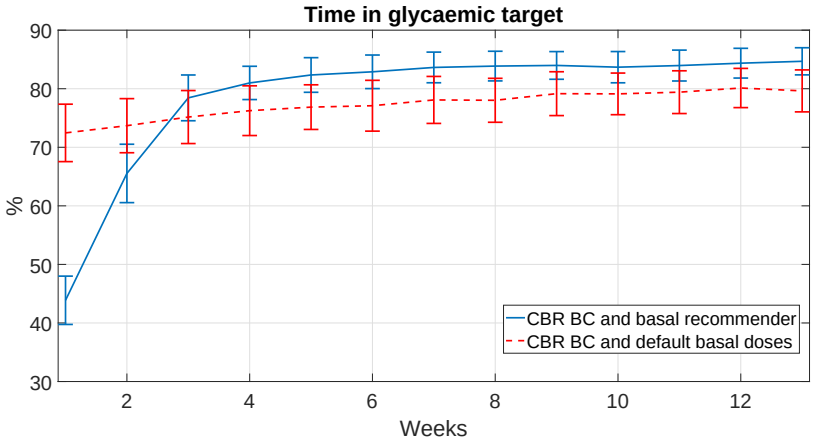

Figure 2: Average between the eleven virtual subjects of the mean and standard deviation of the proportion of time in the target glycaemic range using the proposed basal recommender system or the default basal dosage in combination with a CBR-based bolus calculator.

BC parameters and basal dose were the ones provided by the default insulin therapy of the simulator, and they can be considered as optimal or nearly optimal. The simulator has been modified to simulate lifestyle changes according to (Herrero et al., 2017) to incorporate intra-day variability and impact of physical activity on BG behaviour.

The conducted experimentation consists of 20 simulation of 90 days. The results are analysed in terms of time (average and standard deviation) in the target glycaemic range which is the proportion of time when BG is within a healthy range.

4.1. Results with CGM

Figure 2 shows the average and standard deviation of the time in the target glycaemic range throughout the 90-day simulations. It displays the mean values between all virtual subjects of the average and standard deviation of the proportion of time in the target glycaemic range throughout the 20 simulations. It shows how the average increases along the 90 days (about 13 weeks) and how the combination of the CBR BC and basal recommender outperforms the CBR BC with the default basal doses.

The basal recommender system combined with the CBR BC achieves about 5% more time in the target range than the default basal combined with the CBR BC, meaning that the adaptability of the basal recommender system is capable of achieving a better adjustment.

Moreover, the standard deviation decreases along the 90 days when both systems are used. In particular, the standard deviation decreases from more than 4% to 2.5% approximately, when the basal recommender and the CBR BC are used, and from 5% to 3.5% approximately, when the CBR BC is used with the default basal doses.

Figure 3 shows the average and standard deviation of the proportion of time in the target glycaemic range throughout the 90-day simulations using the default BC with the proposed basal recommender system or the default basal dosage. According to this, the average increases along the 90 days when the basal recommender system is used in combination with the default BC. After 4 weeks, the time on target becomes similar to that achieved using the default basal, which

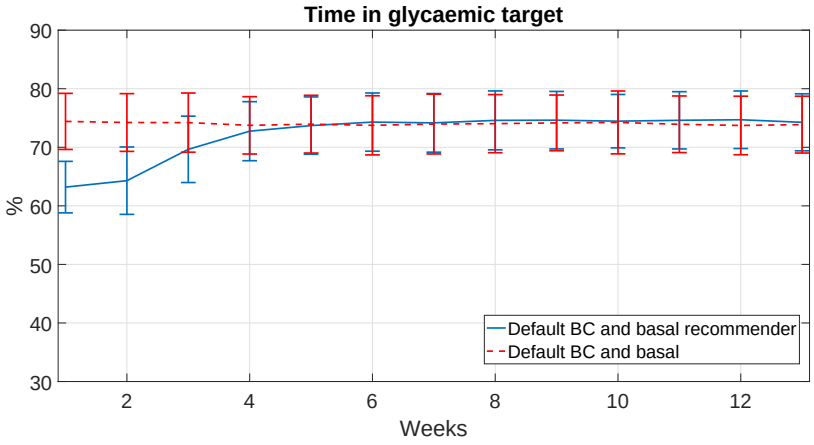

Figure 3: Average between the eleven virtual subjects of the mean and standard deviation of the proportion of time in the target glycaemic range using the proposed basal recommender system or the default basal dosage in combination with the default bolus calculator.

is considered optimal. Therefore, the proposed basal recommender system reaches optimality after 3 iterations.

In contrast with the results achieved using the CBR BC, the standard deviation is not reduced using the default BC, with or without the basal recommender system, since its values oscillate between 4% and 5% approximately.

Figure 4 shows the average and standard deviation of the time in the target glycaemic range for each subject after an initialisation of six weeks using the default BC and basal, or using the default BC with the basal recommender system, or using a CBR-based BC with the default basal, or using a CBR-based BC and the basal recommender system. The figure shows that the combination of the CBR-based BC and the basal recommender system outperforms all the other methods. On average, the combination of the CBR-based BC and the basal recommender system achieves 83.87 ± 1.35 percent of time on target, while the CBR BC with default basal doses obtains 78.92 ± 2.90, the default BC with the basal recommender system 74.44 ± 3.64, and the default BC and basal doses 76.63 ± 4.37.

Moreover, when comparing the use of the basal recommender system and the default basal doses with the default BC, the differences are only significant[3] for subjects 2 and 10, for which the performance of the basal recommender system is better than the constant basal dose. Therefore, the results are similar for both methods, meaning that the basal recommender system is capable of estimating the optimal dosage. On the other hand, when the basal recommender system is used with the CBR-based BC, the performance is significantly better for all subjects compared to that achieved with the CBR BC and the default basal doses, because these are optimal in combination with the default BC.

4.2. Results without CGM

Figure 5 shows the results of the proposed basal recommender system modified for non-CGM users as explained in Section 3.5. The achieved time in the target glycaemic range is

[3]Significant according to Wilcoxon tests.

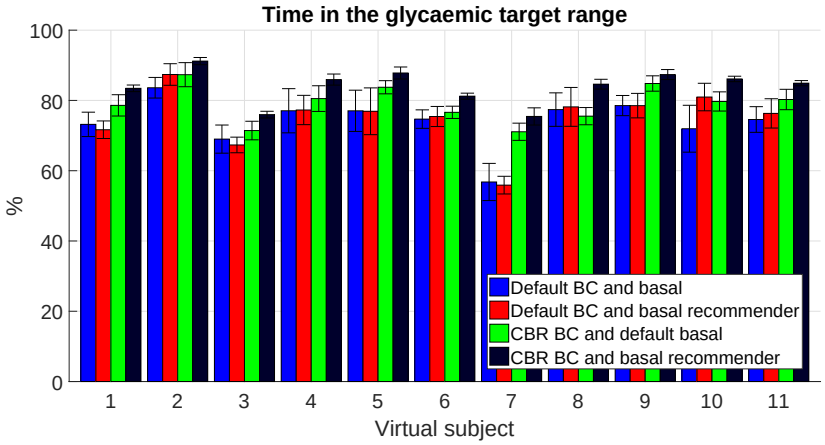

Figure 4: Average and standard deviation of the proportion of time in the glycaemic target range using the default bolus calculator and basal doses, the default bolus calculator with the basal recommender system, a CBR-based bolus calculator with the default basal doses and a CBR-based bolus calculator with the basal recommender system.

compared with that achieved with a constant BC and basal dose. The results show that the proposed methodology is capable of achieving similar results, meaning that the basal recommender methodology is, in general, capable of approximately achieving the optimal basal dose. In particular, there are not significant differences between the time in the target glycaemic range for all subjects, except for subject 7, for which the proposed method demonstrate worse results, and subjects 2 and 10, for whom the proposed methodology obtains better results.

4.3. Discussion

The proposed basal recommender system is capable of accurately estimating the optimal basal dose for all virtual subjects since it achieves similar results to the default basal doses (assumed as optimal) of the simulator when the default BC is also used.

On the other hand, the stability and convergence demonstrated in Figure 2, and the fact that the basal recommender system achieves better results than the default basal doses when it is combined with the CBR BC, means that it can be easily used with other adaptive BC available on the market or described in the literature.

The fast convergence of the algorithm shown in Figures 2 and 3 makes the algorithm very attractive for people with T1DM and for endocrinologists, since its use can speed up the adjustment of the insulin therapy, especially for new patients with T1DM. Moreover, the capacity of adjusting the algorithm to avoid the need of CGM while maintaining the good results, also makes it very attractive for people with T1DM and health insurance companies since it does not require the purchase of CGM which may represent between €1000 and €6000 per person/per year.

The proposed basal recommender system is the first approach based on the use of the Kalman filter, which is the best linear estimator. The literature presents only a few algorithms for basal insulin recommendation, and they rely on run-to-run algorithms such as (Palerm et al., 2008; Toffanin et al., 2017; Herrero et al., 2017). The variations in terms of the run-to-run algorithms mainly depend on whether the system proposes the use of CGM or a sequence of capillary BG measurements. The approach proposed in this paper relies on the use of CGM, but the paper also presents an adaptation of the algorithm for non-CGM users.

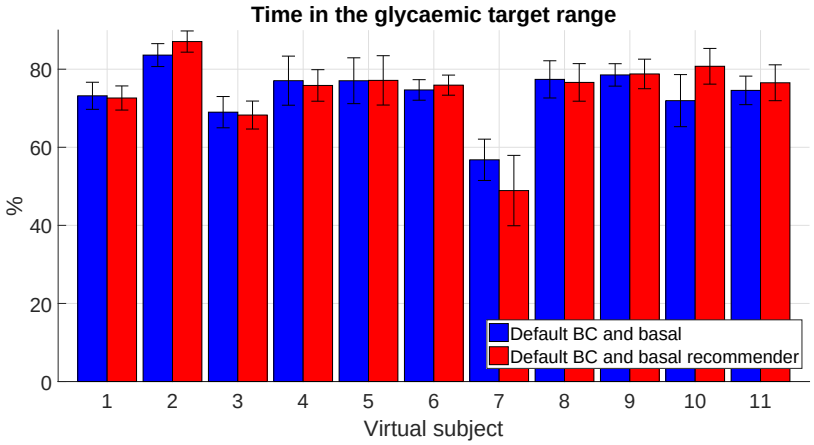

Figure 5: Proportion of time in the glycaemic target range using a bolus calculator with constant parameters and constant basal dose, and the bolus calculator with the basal recommender system without using CGM.

Basal dosage may change due to change in routine or changes in the patient's metabolism. If these changes are faster than the convergence time of the presented methodology, then it may fail to recommend appropriate basal doses. Furthermore, the proposed system does not consider external factors beyond bolus insulin such as menstrual cycle, physical activity or stress that may change the needed basal dose. Thus, a system considering these factors and modelling basal changes on them may outperform the basal recommender presented in this paper. Unfortunately, there are not sufficient clinical studies to model the impact of such factors. On the other hand, (Herrero et al., 2017) proposes representing this variability throughout a case base of representative scenarios with a particular basal dosage for each case. This procedure may overcome this limitations of the presented basal recommender system.

5. Conclusion

This paper presents a system based on Kalman filter theory aimed at recommending adaptive and personalised basal doses for people with type 1 diabetes mellitus. The proposed system can be used with or without a continuous glucose monitoring system. The system has been tested with the UVa/PADOVA type 1 diabetes simulator, demonstrating its capacity to recommend optimal basal doses. Moreover, the system can be easily used in combination with adaptive bolus calculators available on the market or noted in the literature, that help patients to optimise their bolus doses. Finally, the presented system can be very useful for people with type 1 diabetes and their endocrinologists since its use can speed up the adjustment of the basal dosage.

In terms of future research, the system should be tested in a real environment with real patients with type 1 diabetes in order to analyse the performance of the proposed approach out of the the limitations of the UVA/PADOVA T1DM simulator.

Acknowledgment

This project has received funding from the grant of the University of Girona 2016-2018 (MPCUdG2016) and the European Union Horizon 2020 research and innovation programme un-

der grant agreement No. 689810, www.pepper.eu.com/, PEPPER. The work has been developed with the support of the research group SITES awarded with distinction by the Generalitat de Catalunya (SGR 2014-2016).

Members of the PEPPER Group are as follows: project leader: C. Martin; project management team: D. Brown, F. Torrent-Fontbona, P. Herrero Vinas, L. Nita, J. Masoud, J.M. Fernández-Real, B. López; co-investigators: A. Aldea, D. Duce, M. Fernández-Balsells, P. Gay, P. Georgiou, R. Harrison, B. Innocenti, Y.Leal, N. Oliver, R. Petite, M. Reddy, C. Roman, J. Shapley, M. Waite and M. Wos.

6. References

Brown, D. (2015). *Temporal case-based reasoning for insulin decision support*. Ph.D. thesis Oxford Brookes University.

Doyle, F. J., Huyett, L. M., Lee, J. B., Zisser, H. C., & Dassau, E. (2014). Closed-loop artificial pancreas systems: engineering the algorithms. *Diabetes care*, *37*, 1191–7.

Feng, B., Fu, M., Ma, H., Xia, Y., & Wang, B. (2014). Kalman filter with recursive covariance estimation-Sequentially estimating process noise covariance. *IEEE Transactions on Industrial Electronics*, *61*, 6253–6263.

Garg, S. K., Bookout, T. R., McFann, K. K., Kelly, W. C., Beatson, C., Ellis, S. L., Gutin, R. S., & Gottlieb, P. A. (2008). Improved Glycemic Control in Intensively Treated Adult Subjects with Type 1 Diabetes Using Insulin Guidance Software. *Diabetes Technology & Therapeutics*, *10*, 369–375.

Grewal, M. S. (2011). Kalman Filtering. In *International Encyclopedia of Statistical Science* (pp. 705–708). Berlin, Heidelberg: Springer Berlin Heidelberg.

Gross, T. M., Kayne, D., King, A., Rother, C., & Juth, S. (2003). A Bolus Calculator Is an Effective Means of Controlling Postprandial Glycemia in Patients on Insulin Pump Therapy. *Diabetes Technology & Therapeutics*, *5*, 365–369.

Herrero, P., Pesl, P., Bondia, J., Reddy, M., Oliver, N., Georgiou, P., & Toumazou, C. (2015a). Method for automatic adjustment of an insulin bolus calculator: In silico robustness evaluation under intra-day variability. *Computer Methods and Programs in Biomedicine*, *119*, 1–8.

Herrero, P., Pesl, P., Reddy, M., Oliver, N., Georgiou, P., & Member, S. (2015b). Advanced Insulin Bolus Advisor based on Run-To-Run Control and Case-Based Reasoning. *IEEE Journal of Biomedical and Health Informatics*, *19*, 1087–1096.

Herrero, P., Pesl, P., Reddy, M., Oliver, N., & Pantelis, G. (2017). Automatic adjustment of basal insulin infusion rates in type 1 diabetes using run-to-run control and case based reasoning. In *Proceedings of the 2nd International Workshop on Artificial Intelligence for Diabetes* (pp. 2–8). Vienna.

International Diabetes Federation (2015). *2015 Diabetes Atlas*. Technical Report International Diabetes Federation.

Kovatchev, B. P., Breton, M., Dalla Man, C., & Cobelli, C. (2009). In Silico Preclinical Trials: A Proof of Concept in Closed-Loop Control of Type 1 Diabetes. *Journal of Diabetes Science and Technology*, *3*, 44–55.

Lepore, G., Dodesini, A., Nosari, I., Scaranna, C., Corsi, A., & Trevisan, R. (2012). Bolus calculator improves long-term metabolic control and reduces glucose variability in pump-treated patients with Type 1 diabetes. *Nutrition, Metabolism and Cardiovascular Diseases*, *22*, e15–e16.

Liu, S.-W., Huang, H.-P., Lin, C.-H., & Chien, I.-L. (2013). Fuzzy-Logic-Based Supervisor of Insulin Bolus Delivery for Patients with Type 1 Diabetes Mellitus. *Industrial & Engineering Chemistry Research*, *52*, 1678–1690.

Marling, C., Shubrook, J., & Schwartz, F. (2008). Case-Based Decision Support for Patients with Type 1 Diabetes on Insulin Pump Therapy. In *Advances in Case-Based Reasoning* (pp. 325–339). Berlin, Heidelberg: Springer Berlin Heidelberg.

Mo, X., Wang, Y., & Wu, X. (2013). Hypoglycemia prediction using extreme learning machine (ELM) and regularized ELM. In *2013 25th Chinese Control and Decision Conference (CCDC)* (pp. 4405–4409). IEEE.

Oviedo, S., Vehí, J., Calm, R., & Armengol, J. (2016). A REVIEW OF PERSONALIZED BLOOD GLUCOSE PREDICTION STRATEGIES FOR T1DM PATIENTS. *International Journal for Numerical Methods in Biomedical Engineering*, *02833*, e02833.

Palerm, C. C., Zisser, H., Jovanovič, L., & Doyle, F. J. (2008). A run-to-run control strategy to adjust basal insulin infusion rates in type 1 diabetes. *Journal of Process Control*, *18*, 258–265.

Pappada, S. M., Cameron, B. D., & Rosman, P. M. (2008). Development of a Neural Network for Prediction of Glucose Concentration in Type 1 Diabetes Patients. *Journal of Diabetes Science and Technology*, *2*, 792–801.

Plis, K., Bunescu, R., Marling, C., Shubrook, J., & Schwartz, F. (2014). A machine learning approach to predicting blood glucose levels for diabetes management. *Modern Intelligence for Health Analytics. Papers from the AAAI-14*, .

Shashaj, B., Busetto, E., & Sulli, N. (2008). Benefits of a bolus calculator in pre- and postprandial glycaemic control and

meal flexibility of paediatric patients using continuous subcutaneous insulin infusion (CSII). *Diabetic Medicine*, *25*, 1036–1042.

Sudharsan, B., Peeples, M., & Shomali, M. (2015). Hypoglycemia Prediction Using Machine Learning Models for Patients With Type 2 Diabetes. *Journal of Diabetes Science and Technology*, *9*, 86–90.

Sussman, A., Taylor, E. J., Patel, M., Ward, J., Alva, S., Lawrence, A., & Ng, R. (2012). Performance of a Glucose Meter with a Built-in Automated Bolus Calculator versus Manual Bolus Calculation in Insulin-Using Subjects. *Journal of Diabetes Science and Technology*, *6*, 339–344.

Toffanin, C., Visentin, R., Messori, M., Di Palma, F., Magni, L., & Cobelli, C. (2017). Towards a Run-to-Run Adaptive Artificial Pancreas: In Silico Results. *IEEE Transactions on Biomedical Engineering*, *PP*, 1–1.

Torrent-Fontbona, F., Lopez, B., & Pozo-Alonso, A. (2017). A CBR-based bolus recommender system for type 1 diabetes. In *Proceedings of the 2nd International Workshop on Artificial Intelligence for Diabetes* (pp. 9–14). Vienna.

Visentin, R., Dalla Man, C., Kovatchev, B., & Cobelli, C. (2014). The University of Virginia/Padova Type 1 Diabetes Simulator Matches the Glucose Traces of a Clinical Trial. *Diabetes Technology & Therapeutics*, *16*, 428–434.

World Health Organization (2016). *Global Report on Diabetes*. Technical Report World Health Organization.