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Intelligent Data-Driven Model for Diabetes Diurnal Patterns Analysis

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***Abstract*— In type 1 diabetes, diurnal activity routines are influential factors in insulin dose calculations. Bolus advisors have been developed to more accurately suggest doses of meal-related insulin based on carbohydrate intake, according to pre-set insulin to carbohydrate levels and insulin sensitivity factors. These parameters can be varied according to the time of day and their optimal setting relies on identifying the daily time periods of routines accurately. The main issues with reporting and adjustments of daily activity routines are the reliance on self-reporting which is prone to inaccuracy and within bolus calculators, the keeping of default settings for daily time periods, such as within insulin pumps, glucose meters, and mobile applications. Moreover, daily routines are subject to change over periods of time which could go unnoticed. Hence, forgetting to change the daily time periods in the bolus calculator could contribute to sub-optimal self-management. In this paper, these issues are addressed by proposing a data-driven model for identification of diabetes diurnal patterns based on self-monitoring data. The model uses time-series clustering to achieve a meaningful separation of the patterns which is then used to identify the daily time periods and to advise of any time changes required. Further improvements in bolus advisor settings are proposed to include week/weekend or even modifiable daily time settings. The proposed model provides a quick, granular, more accurate, and personalized daily time setting profile while providing a more contextual perspective to glycemic pattern identification to both patients and clinicians.**

***Index Terms*— K-means clustering, bolus advisor, diurnal patterns, glycemic patterns, diabetes**

I. Introduction

People with type 1 diabetes are recommended to follow a multiple daily dose insulin regimen utilizing insulin pens or insulin pumps. People with diabetes determine the amount of insulin manually or using bolus advisors. An insulin bolus advisor (BA) is a decision support tool incorporated in many commercial insulin pumps, a few glucose meters, and more recently some APPs to aid with calculating the required units of meal-related insulin for injection [1], [2]. Users manually input the amount of carbohydrate (CHO) they are about to consume and the device advises a dose of insulin. Studies have reported the usage of a BA is associated with improvements in diabetes control as measured by glycated hemoglobin (HbA1c levels) [2], [3], [4], [5]. Each bolus advisor relies on its settings for advising the amount of insulin [6], and so improvements in glycemic control are reliant on the accuracy of the setup [7]. The settings in a BA involve the number of time-blocks, periods of time-blocks, insulin sensitivity factor (ISF), insulin to carbohydrate ratio (ICR) and blood glucose (BG) target range. In some BAs, the setting up process begins by first choosing the number of time-blocks (TB) in a day. The length of each time-block is specified by choosing the start and end time appropriately. As illustrated in Table I. In other BAs, the number of time blocks and their periods are preset and unmodifiable, thus limiting personalization.

TABLE I
Example bolus advisor time-block settings. Each time-block defines ISF, ICR and BG target range.

Time Blocks		Target range		ICR		ISF	
Start	End	Lower (mmol/L)	Upper (mmol/L)	Insulin (U)	CHO (g)	Insulin (U)	BG (mmol/L)
00:00	05:29	5	9	1	10	1	3
05:30	10:59	4	7	2	10	1	3
11:00	16:59	4	7	3	10	2	3
17:00	21:29	4	7	2.5	10	1	3
21:30	23:59	5	9	1.5	10	1	3

The ICR determines the required units of insulin for the specified amount of CHO. Whereas the ISF is used for correcting an out of range blood glucose (BG) reading, the glucose targets are preprandial glucose levels defined as a reference for the insulin correction calculation. Default settings are often an ICR of 1 unit of insulin per 10 grams of CHO, an ISF of 1 unit of insulin per 3 mmol/L of glucose, and a blood glucose of target range of 4 mmol/L to 7 mmol/L. However, any of these parameters and TBs may need to be altered on an individual basis to achieve optimal glycemic control. The following equation is a typical bolus insulin calculation formula, although manufacturers may also include other factors (e.g. psychological states).

$$bolus\ insulin = meal\ insulin + correction\ insulin \quad (1)$$

$$bolus\ insulin = \frac{CHO}{ICR} + \frac{Current\ BG - Target\ BG}{ISF} \quad (2)$$

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Due to the change in physiological and lifestyle states of people with diabetes, the use of a BA for optimal benefit requires attention and close review on a regular basis. Also, trust in the BA is an important factor in patients' engagement with it [8]. If the settings are set correctly, the BA can perform as a helpful tool for insulin administration; otherwise, if the settings are inaccurate, the advice given will be sub-optimal and lead to more episodes of low blood glucose (hypoglycaemia) and high blood glucose (hyperglycaemia).

The fundamental component of BA settings is the time-blocks. If the time-blocks are not personalized and modified based on the diurnal activities of the patient, the remaining settings of the BA cannot be tuned for optimal usage. A study of 24 individuals using pumps reported that most BAs were set on incorrect settings for patients [9]. To be practical, BAs are constrained in terms of the number of settings and typically have the same set of time-block based settings applied for every day of the week. This is a limiting factor in personalizing the BA for the day to day variations of daily routines that exist in real life. Additionally to the baseline settings, users would be expected to make their own adjustments for factors such as periods of exercise, stress or illness.

The automated bolus advisor control and usability study (ABACUS), a controlled randomized trial study, showed that more frequent adjustments of the settings positively contributed to glycemic outcomes [10]. Also, continuous adjustments improved the consistency of the usage of BAs. However, manual analysis of the large amounts of self-monitoring blood glucose (SMBG) data to identify time-blocks and their corresponding settings is time-consuming and cumbersome. Usually, the applied changes are a reactive intervention at times where glycemic control is more challenging than normal. Furthermore, among diabetes complications is progressive vessel dysfunction, which contributes towards accelerating physical ageing and over time is influential on diurnal physical activities [11]. Hence, automatically tracking patients' diurnal patterns over time is of considerable importance in achieving optimal glycemic control, thus reduced risk of complications.

Previous studies have utilized a case-based reasoning technique to provide adaptability and personalization of BAs [12], [13], [14] [15]. The advised bolus is calculated based on previously observed measures. This is achieved by defining a similarity measure to identify a close match to the currently inquired insulin dose by comparison to historical data. The results were tested in a simulation and later as a mobile application to evaluate acceptance by users. As of any case-based reasoning system, it requires a huge database of many variant cases and maintenance otherwise its performance is lessened [16]. A neural network (NN) approach is proposed for the personalization of the BAs in [17]. In the NN approach, continuous glucose monitoring (CGM) and pump data are used alongside individuals' information such as weight, glucose rate of change, and insulin sensitivity to determine the amount of injected insulin for a meal. The method was examined in an in-silico experiment under a single meal, single day, and noise free scenario. In another study [18], various machine learning techniques are utilized in bolus correction factor calculation. The study was limited to reducing the postprandial hypoglycemia occurrences. However, in these proposed methods for BAs, there is no evidence to show a benefit in comparison to current BAs.

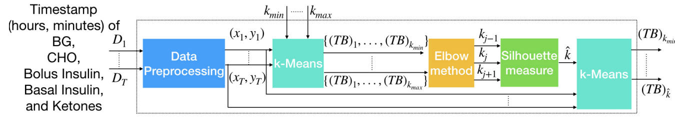


Fig. 1. The proposed model to identify diurnal patterns from timestamps of the measurement events of routinely collected data in diabetes including: the data preprocessing, K-means clustering, fitness measurements, and the optimal suggested number of time-blocks

In this paper, an intelligent data-driven technique is proposed that enables the clustering of the diurnal activities of people with type 1 diabetes to suggest the number and periods of time-blocks for BA settings automatically. The automated aspect of the technique reduces the burden on both clinicians and patients in terms of effort and time to analyze and understand diurnal patterns for correct setting of time-blocks within BAs. In addition, the proposed approach will allow personalization of the BA settings in real-time based on data. This to our knowledge is the first attempt at providing real-time recommended settings of BAs that corresponds to a patient's diurnal patterns automatically.

II. Methodology

Patient daily measurement records such as BG, CHO, bolus insulin, basal insulin, and ketones are used as inputs to the system. Only the timestamps of the measurement events are extracted and then transformed to be features. Therefore, the methodology adopted in the analysis in this paper corresponds to that of an unsupervised machine learning problem of univariate time series data which produces clusters in daily time (hours and minutes), as illustrated in Table II. The proposed model is depicted in Fig. 1

TABLE II
An example of the univariate time series data of a person with type 1 diabetes. These data are recorded throughout a day as an event at a certain timestamp. Only the glucose measurements are measured using a glucose meter and the rest of the data are manually entered by the participant. Albeit usually using a user interface on their BG meter.

Record No	Hour	Minutes	Result	Type
1	0	11	6.3 mmol/L	Glucose
2	0	11	40.0 g	Carbs
3	0	11	4 U	Bolus Insulin
4	10	27	15.5 mmol/L	Glucose
5	10	27	3.0 U	Bolus Insulin
6	14	18	7.4 mmol/L	Glucose

A. Dataset

The data is the timestamp of a combination of everyday measurements of BG, CHO, bolus insulin, basal insulin and ketones. Data from 70 anonymized participants with type 1 diabetes enrolled in the DAFNEplus pilot trial (IRAS 208842) alongside their meter's BA settings were collected. The participants utilized an Accu-Chek Aviva Expert glucose meter for data recording and bolus advice. The data recorded in the glucose meter were used to produce an electronic logbook. The proposed algorithm generated the equivalent BA time-block settings for each logbook. For the application validation of the experiment only two weeks of data was used to match current clinical practice. For the other parts, exploring beyond current limitations, a month of data was used.

B. Data preprocessing

Pre-processing is an important aspect of the proposed technique to transform the time series data accurately and efficiently. The time series data processed by the algorithm is only the timestamp at which a measurement event has occurred. For modeling and inference of timestamp data, a transformation is needed to be able to apply the common linear methods. Time has a circular characteristic. Also, the order of the time is arbitrary, for example, 00:00 can be represented as 24:00. Also, 24:00 and 01:00 are adjacent. It is important to note that someone can have a bedtime of 01:00 which means their natural day overlaps to the next calendar day. This can be a problem when the utilized methods require mathematical operations such as mean. For example, if an event occurs at 12 am and then again at 2 am, the arithmetic mean of these events (regardless of the day of the event) is $\frac{24+2}{2} = 13$ rather than 1 (01:00 AM), which on a circular clock (see Fig. 3a) has a different direction. In here the clock (i.e. a circle) starts at 0 ($\theta = 0°$) and moves clockwise direction on a circle to equally represent 24 hours ($\theta = 360°$).

To transform the data the pair (x,y) defined by $x^2 + y^2 = 1$ is used for representation. Although it is denoted as a pair, x and y are not bi-variate on a plane. Therefore, these points are strictly located on the circumference of the circle defined by $x^2 + y^2 = 1$.

x and y are therefore calculated as such: $x = r\,cos(\theta)$ and $y = r\,sin(\theta)$ where r is the distance from the origin and θ is the angle. If the point is on the circumference of a unit circle, then it can be simplified as: $x = cos(\theta)$ and $y = sin(\theta)$. The θ is calculated for timestamp measured in hours as follows:

$$\theta = \frac{2\pi}{24}(hours + \frac{minutes}{60}) \tag{3}$$

It would be naturally incorrect to consider the change of calendar day as a discontinuous event. For example, the day finishes at 24:00 and it is equally the start of the next day at 00:00. This periodicity possesses the property of continuity that exists in the cyclic data. In sine and cosine, the end of a period is the beginning of a new period. This is the benefit of using trigonometric sine and cosine predictors for cyclic data. Additionally, the sine and cosine are orthogonal. The orthogonality can be expressed as the lack of correlation between the two functions. In the analysis, it is necessary to avoid a high correlation among the predictor features.

After the pre-processing, the common linear methods can be applied to the transformed data. Hence, clustering can be used to identify meaningful diurnal patterns based on measuring patterns of the data recorded.

C. Clustering for diurnal patterns

The trigonometrically transformed timestamps of the measurement events of each participant are used individually to cluster their day to explore their daily patterns. Among the clustering techniques, K-means is the most popular and it is widely used in practical applications [19]. The K-means is highly efficient and scalable which is desirable for time-series data. The K-means algorithm takes k as an input parameter and starts with k randomly selected centers in the data [20]. The K-means clusters the data into groups through the process of iterative update of the cluster centers, see Procedure K-means(D, k) in Algorithm 1.

Let D be the entire data set for an individual and $D = (d_1, d_2, ..d_t..., d_T)$ where d_t is the transformed timestamp of the event (i.e. d_t is the pair of (x_t, y_t) calculated in the preprocessing) for t-th measurement carried out by the participant. The K-means clustering method is used to find the time-block intervals by solving for the following problem.

$$\min_{(TB)_1,(TB)_2,...,(TB)_k} \sum_{i}^{K} \sum_{d_t \in (TB)_i} ||d_t - E(d_t)||^2 \tag{4}$$

where $(TB)_k$ is the k-th time-block; k is the number of clusters; $(TB)_1 \cup (TB)_2 \cup ... \cup (TB)_k = D = (d_1, d_2, ..., d_T)$ and $(TB)p \cap (TB)q = \varnothing$; $||\ \ ||^2$ is $l2$ norm of a vector and E is expectation over T measurement events. K-Means requires the number of clusters to be specified. Usually the performance of the clustering is evaluated using measures such as the Akaike information criterion (AIC), Bayesian information criterion (BIC), Calinski-Harabasz (CH), Davies-Bouldin (DB), Deviance information criterion (DIC), and sum of the squared error (SSE). These measures resulted in various methods to select the optimal number of clusters. Such as split and merge [19], elbow method [21], and silhouette method [22]. Considering the range for the possible number of clusters in our application is always low ($\leq$ 24, i.e. at most a cluster per hour), it is therefore entirely feasible to run the K-means exhaustively to obtain measures of fitness for the given clusters. Then, numbers of the K selected is based on the measured fitness. In this paper, these measures of fitness are silhouette (mean ratio of intra-clusters) [21] and elbow methods (mean sum of the squared distance) [22] which are combined in a step-wise approach to produce the optimal number of time-blocks.

The K-means is first used to produce a set of clusters in the range of 3 to 24 per participant. That is the day is divided into k^* periods varying in length, $k^* = (k_3, k_4, ..., k_{24})$. The elbow method is then deployed to measure the fitness of each cluster k_i , $3 \leq\ i \leq 24$.

In the elbow method the mean sum of the squared distances diminish as extra clusters are added. Therefore, the optimal number of clusters can be determined by the highest decrease in the gradient of the sums. This optimal number of clusters is the suggested number of time-blocks. However, the elbow method suffers at times to clearly identify the optimal number of clusters (i.e. not having a clear elbow point). In this paper, we combine the elbow method with the silhouette measure to overcome this limitation. The optimal number of clusters, k_j, selected in the elbow method, k_{j-1} and k_{j+1} is used as a guide for calculation of silhouette values to generate the optimal number of time-blocks. For example, if the suggested number of time-blocks from the elbow method is four, the silhouette measures for three, four, and five clusters are calculated. Then, the number of clusters with the highest silhouette value is chosen as the optimal number of clusters ($\widehat{k}$) for the diurnal patterns of the participant, thus the optimal number of time-blocks. The clusters generated by K-means with $\widehat{k}$ as the parameter are the start-time and end-time of the various time-blocks during a single day for an individual.

Algorithm 1 Pseudo code of the proposed algorithm for diurnal patterns

Initialize Elbow[]
Initialize k_{min}, k_{max}
Initialize $D = \{d_1, d_2 ..., d_T\} = \{(x_1, y_1), (x_2, y_2), ...(x_T, y_T)\}$
procedure K-MEANS(D, k)
  Randomly initialize cluster means: $\mu_1, \mu_2, ..., \mu_k$
  repeat
    for each i **do**
      $c^{(i)} := \arg\min_j ||d^{(i)} - \mu_{(j)}||$
    for each j **do**
      $\mu_j := \frac{\sum_{i=1}^{m} \{c^{(i)}=j\} d^{(i)}}{\sum_{i=1}^{m} \{c^{(i)}=j\}}$
  until convergence
for i in k_{min} to k_{max} **do**
  Perform K-means clustering on D data, K-means(D, k_i)
  Elbow.append(mean sum of squared distance of k_i clusters)

Using elbow method find suggested number of clusters k_j at elbow point
Select $\widehat{k}$ where:
the Silhouette measure is the highest, Max-Silhouette(k_{j-1}, k_j, k_{j+1})
Find the time-blocks as, $(TB) =$ K-means$(D, \widehat{k})$

III. APPLICATION VALIDATION

The ground truth of the time-blocks was not available to confirm the results of the algorithm in the BA application. Therefore, the validation process was carried out by recruited experts on real data from participants in the DAFNEplus pilot trial.

A. Experts

Twelve expert clinicians from the DAFNEplus pilot trial centers were recruited to validate the algorithm. The experts included three dietitians, four specialist consultant physicians and five diabetes specialist nurses. The experts are current practising clinicians in their centers and have years of experience in diabetes care.

B. Experiment

The experiment was conducted as a Turing test [23]. The experts were blind to the source of the time-block settings. Each expert responded to 25 generated cases (12 participant, and 13 algorithms). The cases were randomly chosen to avoid any bias and produced a unique combination of cases for each clinician. Experts were posed with the question:"*Are the time blocks optimal for the participant; clinically, would you change any of them?*". Then, they responded with agreement or disagreement on each case of the survey. If the clinician disagreed with the presented time-block settings, they were asked to suggest one.

C. Statistical analysis

The response of the experiment was agreement or disagreement with the presented time-blocks. For this binary outcome, logistic regression is utilized for the analysis. Each case could have been assessed multiple times by different experts and each expert responded to 25 cases assigned to them. Therefore, to account for these correlations in the response, a generalized estimating equation (GEE) logistic regression was carried out. In GEE logistic regression of a binary outcome, empirical evidence shows a nonlinear link function is appropriate. Hence, the nonlinear S-shaped logistic response function is employed. This also enables the determination of an odds of agreement. O_R is the odds ratio that expresses the increased chance of success by an increase of one unit in the predictor. Therefore, the family distribution for GEE is binomial due to the binary outcome variable and *logit* is the link function.

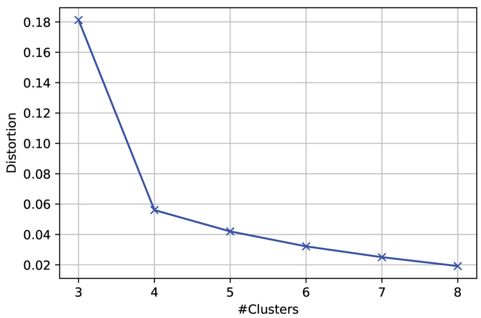
IV. RESULTS

K-Means clustering was used to group the daily data of participants. The grouping of data produced the time-blocks setting. The algorithm proceeded to cluster the data into between three to eight distinctive groups. This range was chosen based on the settings of the Accu-Chek Expert meter to produce comparable results. The anonymized data of the users were processed to develop the algorithm as explained in part C of the methodology section above.

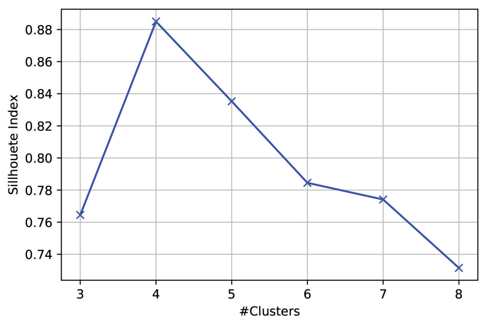
The algorithm was utilized to search for the periods and the number of time-blocks in the diary. Fig. 2 shows the coefficients for silhouette and elbow methods of the suggested clusters for one participant, as an example. We considered the highest decrease in gradient (first derivative) of the distance in the elbow method as a guide for the number of clusters. Using this process, the threshold distortion difference in the elbow method was usually < 0.025. The suggested gradient point (e.g. four clusters) alongside one less and one more cluster (e.g. three or five clusters) were the suggested number of clusters which were assessed by the silhouette method. The highest silhouette coefficient among the suggested number of clusters in the elbow method was the chosen number of clusters.

Fig.2a shows the elbow of the distortion graph is significant at the fourth cluster. Also, it can be confirmed using the highest silhouette index as shown in Fig.2b. Therefore, four is the ideal number of clusters for the presented diary.

Fig. 3a shows the histogram of the data in a circular plot. The red lines divide the graph by the algorithm's selected time-blocks. In this example, the graph shows that the data have four clear peaks at around 7, 12, 16 and 22. The algorithm has clustered these peaks with nearing data points into a separate cluster. Also, this can be observed in Fig. 3b. The figure shows a histogram of the blood glucose tests in a bar chart. Similarly, the red lines split the time blocks. The peaks and

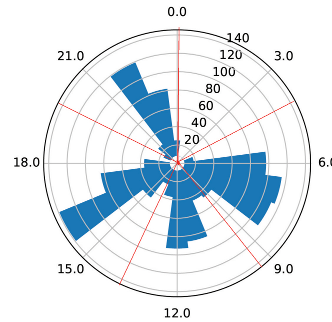


(a) Average distortion

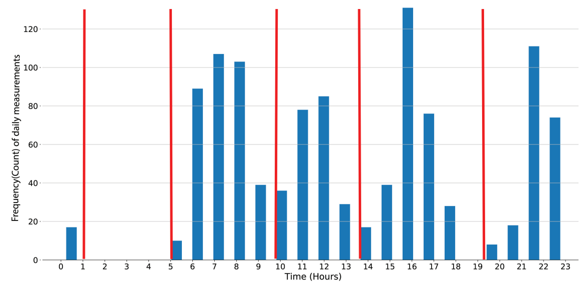


(b) Average Silhouette index

Fig. 2. An example of internal index measures to evaluate the suitable number of clusters using fitness measures of elbow method and silhouette method. Illustrative plots for test case #1. a) Average distortion in the elbow method resulted from addition of each cluster to the model; b) Average silhouette index of each cluster using the silhouette method.



(a) The circular histogram



(b) The bar chart histogram

Fig. 3. The histogram of a diary. The red lines represent the time separation between time-blocks. Illustrative plot for test case #2. a) The circular histogram of the measurement events on a clock that starts at 0 hours (zero degrees) to 24 hours (360 degrees); b) The bar chart histogram of the frequency of the daily measurement events in an hourly basis for a nominal day.

the surrounding data form a bell-like curve in each time-block that can represent a separate pattern in different periods of the day. Furthermore, the daily routine of the patient ends at past midnight around 1 am of the next day. Hence, the algorithm suggests the end of the day be at 01:00 rather than 00:00.

A. Application validation

The validation process was carried out to determine whether the proposed automated method can substitute the current time and labor intensive practice that people with diabetes or their diabetes healthcare professional need to undertake manually. A Turing test was conducted to validate the suggested time-blocks. The result of the survey is presented in Table III. The expert respondents agreed with the algorithm's generated time-blocks 39.1% of the time and 36.1% with the participant generated ones. The percentage of agreement on the algorithm generated time blocks was 3% higher than the participant generated time-blocks. The logistic regression analysis shows that the algorithm's results were agreed with more by ~ 0.18 compared to the participant time-blocks. However, the p-value is higher than 0.05 which suggests the algorithm is similar in performance to the clinicians. This can be investigated by analyzing the odds of the agreements. The odds ratio is calculated as follows:

$$O_R = exp(0.18) = 1.197$$

Therefore, experts were $\sim$ 1.2 times as more likely to agree with the algorithm's suggested time-blocks (confidence interval of [0.69 - 2.07]). However, the confidence interval of the odds ratio includes one which suggests a similar odds of agreement between the algorithm and participant time-blocks. Therefore, the generalization that the algorithm outperforms the participants generated time-blocks is inconclusive. Nonetheless, the analysis of the results shows that the algorithm suggestion is as good as the participants time-blocks suggestions. Additionally, the agreement with the proposed algorithm was 3% higher.

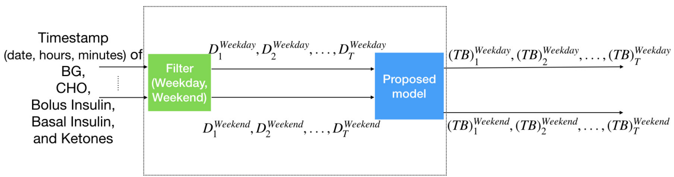
TABLE III
OVERALL AGREEMENT RESULTS FROM THE TIME-BLOCK SURVEY FOR TURING TEST

Source	True	False	Total
Algorithm	61 (39.1%)	89	156
Participants	52 (36.1%)	92	144
Total	113	187	300

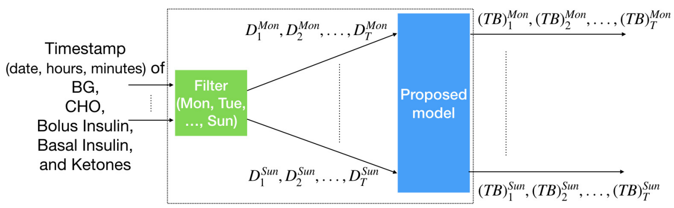
B. Beyond current limitations

The bolus advisor enabled BG meter used, allows only a single set of time-block based settings for every day of the week. This is a limiting factor towards personalization of the BA. Also, this can impact glycemic control greatly if the day to day routine of the participant is variable.

Incorrect time-block settings can lead to incorrect insulin doses. The current workaround for a person with diabetes is to actively remember that their BA settings are not suitable for that day's activity or situation, and manually adjust the dose accordingly. Our proposed method is a viable solution to automate more personalized and suitable settings based on patients' measured patterns. A filtering is added to the proposed model in Fig. 1 that can be used to accommodate the changing nature of day to day activities. In this paper day to day and weekday to weekend personalization patterns for people with type 1 diabetes are analyzed, see Fig. 4. The onward experiments are based on a period of one month of the collected data.



(a) Weekdays vs. weekend proposed model



(b) Days of the week proposed model

Fig. 4. Addition of filtering into the pre-processing of the proposed model to facilitate beyond current practices and overcome the limitations for personalizing the BAs. a) Weekday vs weekend model where data are filtered to accommodate change of routine between weekdays and weekends; b) Days of the week proposed model where each day of the week is personalized for its specific routine patterns.

1) Weekdays vs Weekend: One approach to provide this flexibility is to accommodate different routines by allowing different settings between for example work days (Monday to Friday) and weekends (Saturday and Sunday). Therefore, a modification to the algorithm was applied to carry out the experiment.

The modified algorithm is a multi-step operation. First, the filter categorizes the data to weekdays and weekends. Then, Algorithm 1 processes each category to identify diurnal patterns accordingly. This is illustrated in Fig. 4a.

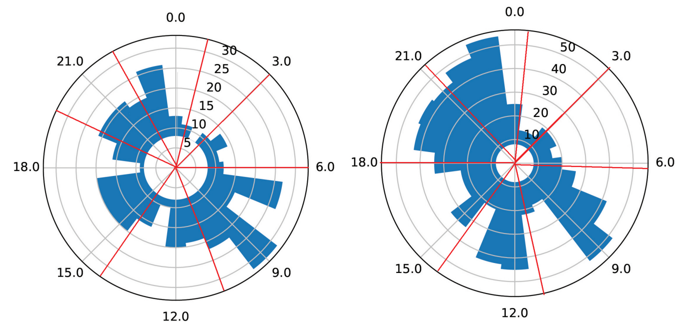
An example of weekend versus weekday of the identified time-block settings by the modified algorithm is presented in Table IV. The example shows that a 3.5 hours accumulative time difference arises between weekdays and weekends time-blocks; such a significant time-difference would be missed otherwise, leading to incorrect BA settings and therefore incorrect insulin doses. For example, if the ICR of TB2 is 2 U:10 g but the ICR of TB3 is 1 U: 10 g, then if the person uses the weekday setting for the weekend for an injection at 10 am (on weekdays, 10 am is in TB2), the person would inject twice the insulin dose needed, which is clinically significant and may be harmful.

Also, the result of the algorithm is shown in Fig. 5. Looking at the histogram of the graphs, the frequency of data in the morning time-block (TB2) is similar during the week and the weekend, with a slight delay in the start of the morning on the weekends. However, the rest of the day, the frequency of data

TABLE IV
AN EXAMPLE OF TIME-BLOCKS BASED ON WEEKDAYS VS WEEKEND FOR TEST SUBJECT #3

	TB1	TB2	TB3	TB4	TB5	TB6	Silhouette index
Weekends	03:00	06:00	10:00	14:00	19:00	22:00	0.741
Weekdays	03:00	06:30	11:00	14:30	18:00	21:30	0.756

is much lower relative to the TB2 and there is a slight variation in the start and end of the time-blocks between weekday and the weekend. These are more apparent in TB3 and TB5. For the afternoon time-block (TB4), the weekend has a longer span and relatively more activity in comparison to the weekdays.



(a) Weekends pattern (b) Weekdays pattern

Fig. 5. An example of the circular histogram of the weekdays and weekends of a diary. The red lines show the separation hours of the time-blocks suggested by the proposed algorithm for test case #3. a) Weekends measurement patterns; b) Weekdays measurement patterns.

2) Days of the week: Another approach to provide a more personalized BA, is to allow different settings for different days of the week. Similar to the weekday vs weekends' experiment, a modified algorithm was utilized to cluster the diary data into time-blocks.

This is a multi-step operation. First, the filter categorizes the data into days of the week. Then, processes each day to identify diurnal patterns accordingly. The suggested time-blocks of the algorithm is shown in Table V. The participant for one example exhibits a different routine based on their logbook data. The different days of the week can have a different number of time-blocks and starting hours.

Fig. 6 shows the circular histogram of the days of the week. Considering the measuring patterns, the week appears similar in its relative frequency of measurements between TBs on each day of the week with the exception of Tuesday (Tue) and Wednesday (Wed). Especially in the peak hours of those

TABLE V
AN EXAMPLE OF TIME-BLOCKS BASED ON DIFFERENT DAYS OF THE WEEK FOR TEST CASE #4

Day	TB1	TB2	TB3	TB4	TB5	Silhouette index
Mon	05:00	10:00	12:00	15:00	20:00	0.930
Tue	05:00	07:00	12:00	16:00	21:00	0.949
Wed	——	07:00	12:00	16:00	20:00	0.950
Thu	05:00	10:00	12:00	16:00	21:00	0.978
Fri	05:00	10:00	12:00	16:00	20:00	0.986
Sat	05:00	10:00	12:00	17:00	21:00	0.980
Sun	05:00	09:00	12:00	16:00	21:00	0.981

days (i.e. 5, 10, 12, and 18). However, by looking at the relative frequency of measurements between TBs, Tuesdays show a less active morning routine and more active afternoons. Whereas Wednesdays show a less active midday period.

Recall that due to limitations of current approaches, the patient has to actively apply a corrective percentage to accommodate his/her change of routines between days. This can adversely affect their glycemic control. We can examine such effects by the provided context from the algorithm's recommended time-blocks. For this diary, the presented time-blocks for Tuesdays and Wednesdays are very different from other days of the week. By a closer look at the diary, it can be observed that the person with diabetes manages his/her BG levels relatively well in the hours of TB2 and TB3 in days other than Tues and Weds. However, Tues and Weds seem to be more challenging for the participant with many out of range BGs. This indicates a possible change in the routine e.g. less activity on those days. Possibly, different settings for Tues and Weds would be suitable to accommodate the change in the routine. As illustrated, such details and context are provided in seconds using the proposed model. This can be presented to participants as a recommendation to clarify their routine based on their data and encourage them to review the diary in such a context.

V. Discussion

The proposed model in this paper applies a clustering technique to detect diurnal patterns in the time series data of the participants. The timestamps of the daily measurements of BG, CHO, bolus insulin, basal insulin and ketones were extracted and transformed. Orthogonal and periodic trigonometric predictors in terms of sine and cosine were adopted to transform the univariate time series data. Then, K-means clustering was utilized to recognize the diurnal patterns and suggest the numbers and periods of time-block settings of the BA. The developed method aids to eliminate the error-prone self-reporting practice and automate the suggestions based on the real-time change detected in the daily routines. Up to date and accurate BA settings are crucial in maximizing the benefits of a BA as a decision support tool.

The results of the proposed method were compared to the participants' suggested time-blocks. Blinding the source of a time-block, the participant-generated time-blocks acted as the control group in the conducted survey. Furthermore, the cases were allocated randomly. This enabled investigation of a higher number of unique cases (Overall 300 cases, 51 unique cases compared to 25 otherwise).

Our proposed intelligent system of routinely collected data has similar accuracy to an expert that can automatically process vast amounts of individual data to efficiently adjust TBs in real-time. These prompt adjustments can contribute to the accuracy of the underlying settings and therefore improved utilization of the BAs, which is known to improve glycemic control [10].

A. Underlying context of glycemic patterns

The data-driven suggested time-blocks can help to provide more context to the diabetes data. Diurnal patterns can provide clues and drive the conversation to specific actions that influence the glycemic management. For participants, clinical appointments are limited and time constrained. Maximizing available contexts to the collected data is time and cost saving. Manual analysis and pattern finding of a large amount of data to suggest the BA settings is challenging and time-consuming. In the conducted survey, it was expected to take the experts about an hour to analyze the time blocks of 25 examples. This was to assess two weeks data on an organized diary. However, many experts feedback said that it required a longer time. For some respondents, it took about three hours to complete. Therefore, it accentuates the need for an automatic system to aid with decision making.

Additionally, the presented method enables daily routines to be tracked. A study showed that temporal and chronic factors of diabetes are associated with altered diurnal rest-activity rhythmicity [11]. The proposed method has the potential to facilitate a thorough and reliable analysis of changes in the daily activity of people with diabetes. Therefore, empowering participants with an insight into their complex and variable daily routine to use the suggestions as a guide to adapt TB settings promptly.

Furthermore, our proposed model only uses the timestamp; therefore, including other data events such as exercise and circadian rhythms would help the algorithm to divide the day even more appropriately, especially when the data are closely dispersed naturally. Recording of such data events can also contribute to improved contextual information.

B. Do experts agree?

The expert respondents to the survey agreed about 36% of the time with the participants time blocks and 39% with the proposed algorithm's suggestions. The analysis of the odds of agreement showed a slight favorability in choosing the algorithm. Nonetheless, in both cases of participant and algorithm generated time-blocks, the agreement is relatively lower than expected. This is potentially an indication of variation in the approach. The respondents to the survey were asked to present their suggestions of the time-block settings if they did not agree with the presented ones. Observing the expert time-block suggestions, one hypothesis for the variation and low agreement is that the discrepancy stems from the fact that participants daily routines can change from one day of the week to the other. More importantly, one generic time-block setting cannot include all the variations in the diurnal patterns. The expert respondents had different approaches in assessing each case. In some cases, a change in the ratios was accounted as a trigger for a new time-block whereas in other cases, it was the BG testing pattern. Additionally, glycemic control at different times of the day can influence the decision. By looking at a diary through these approaches, it could result in different settings. If it is the BG, the problematic hours (frequent hyperglycaemia, or hypoglycaemia) are a possible time-block. If it is based on glycemic patterns, the change in the patterns during the day is the separating criteria. Certainly, a change in ratios necessitates a change in time-blocks. Experts' clinical experience seems to have resulted

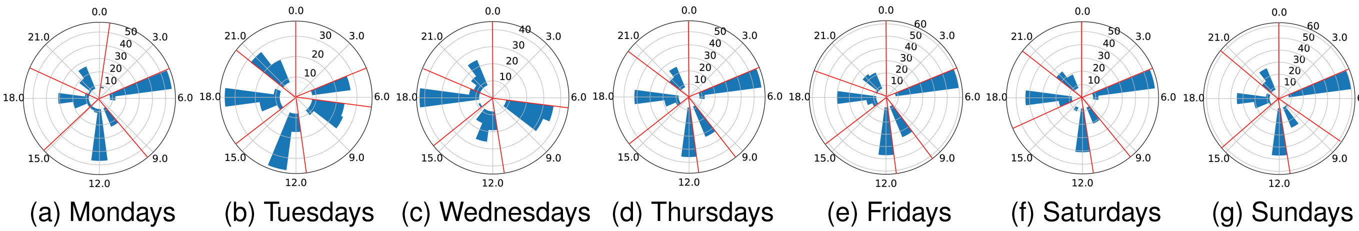


Fig. 6. Daily cyclic histogram of the diary from test case #4 over one month. The red lines split the time periods based on the suggested time-blocks for each day of the week.

in a practical approach to the problem of finding the diurnal patterns and possibly a subjective one. Participants with a more routine lifestyle are more likely to spot a more generic pattern in their diary. However, a more variable routine can pose a challenge and varying decision depending on the approach.

C. Standardized vs weekday settings

In some cases, a person with diabetes might be recommended to replicate glycemic control of their better days of the week i.e. *”whatever you do on Tuesday and Wednesday, do on the other days”*. This can potentially be from the limited generic settings of the BA that suits certain days of the week and not the others. Such recommendations indicate the need for more flexibility in settings options. Additionally, the time and resources of the clinicians are limited. The manual personalization of the BA to more granular settings requires higher engagement and analysis, which is time-consuming. The proposed method can process a diary with longer periods of time and produce personalized daily time-blocks in a matter of seconds.

This especially applies to the difference between the daily routines of the weekdays and weekends. In pumps, this can be accounted for to a certain degree by having different basal insulin profiles. For those on pen therapy, different amounts of background insulin (e.g., because more or less active at weekends) can be utilized. Alternatively, the exercise settings can be set to reduce the dose (e.g. -33%) to account for the change in the ratio. These adjustments require active participation and judgment of the person with diabetes for every insulin injection. Many people with diabetes do not have the knowledge or confidence to change their BA settings. These drawbacks contribute to limiting the uptake of BAs as an assisting tool for dose calculation. However, utilizing the proposed method can automate the process by days, or weekdays and weekends to suggest more suitable time-block settings.

D. Participant awareness vs data

From the clustered data, many participants’ natural day overlaps with the early hours (e.g. 2 am) of the next day. This is rarely observed in the participant time-block settings. It can be seen in the data that people with diabetes make glycemic decisions that relate to their last time-block of the day in the early hours of the next day. Hence, the algorithm usually includes these data points to the last time-block setting of the day. In many cases presented in the survey, the respondent agreed with this overlap. However, this does not seem to be applied in practice. One explanation can be because most of the time-blocks are set in consultation with the participant that might overlook those early hours of the day. This high precision is one of the benefits of using a clustering technique for identifying the time-blocks that can be translated into practice in the clinics to reflect the findings.

E. Other methods and related works

As shown in the Fig. 3b, the divided time blocks of glucose data represent a combination of bell curves which suggests a mixture of Gaussian models. Hence, we tested this hypothesis; in many cases, the Gaussian mixture model clustering produced identical results to K-means. However, this model-based clustering has a scalability issue and its performance suffered when the clusters are close to each other.

To our knowledge, the presented method is the first to attempt a data-driven model to automate the process of identifying diurnal patterns for recommending and tracking time-block settings of BAs in diabetes. The closest work to partially improve BAs was presented in the case-based reasoning models. However, these studies are mostly limited to continuous glucose monitoring. Whereas the proposed method applies to any diabetes data irrespective of the type (e.g. glucose, CHO, insulin or a combination of the three). Also, the previous studies attempt a new approach to the bolus advisor which is not evident to provide any benefits over current bolus advisors. From the patient perspective, it is a ‘black box’ that relies on previous cases to suggest an insulin dose. Hence, the focus is on the insulin patterns rather than diurnal patterns that can define patients daily routine. This does not provide context and the ability to use the settings to review patterns of glycemic control.

We have used real world data with a panel of experts to validate our presented model. In-silico can potentially be used in the future to run simulated results for our proposed method. Recently Visentine et al. [24] have proposed intra-day variability for in-silico to partially improve on the engineered environment and lack of real-world variations that exist in real patients and their behavior in decision making. Additionally, other researchers have shown that optimized BA settings in commercially available BAs lead to improved glycaemic control [3], [4], [10]. Our method is applicable to such BAs and can provide as good advice as an expert clinician.

Furthermore, our proposed model can be applied to continuous glucose monitoring data without any modification when other modalities are recorded. In CGM, BG timestamps are uniformly spaced and driven by the sensor rather than the participant's patterns, thus clustering would only be on the other recorded data such as carbs, basal insulin, bolus insulin, and ketone timestamps.

Deep learning has increasingly been applied to the analysis of medical data [25], [26]. In [27], we adopted deep learning for HbA1c prediction in type 1 diabetes. Future work could consider a deep learning approach to exploit our proposed method in this paper for improved personalization.

VI. Conclusion

The proposed K-means based model improves the accuracy of time-block settings, provides context to data and as it is an automated process dramatically reduces the reviewing time and potentially improves the engagement and adherence to the BA. Furthermore, it could be implemented in pumps, glucose meters, glucose sensors and APPs to provide an auto adjustment. We believe the evaluation method utilized in the study should be the standard for any developed work related to bolus advisors. Reported works on the developed bolus advisors have tended to be based on simulators/in-silico experiments; and the testing of the efficacy of these advisors with people with diabetes rely on the degree of their glycemic control and acceptance of the recommended bolus. Such methodology lacks context and therefore provides a weaker evidence-based approach to support adoption.

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