MEDINFO 2010
C. Safran et al. (Eds.)
IOS Press, 2010

doi:10.3233/978-1-60750-588-4-1150

Temporal Clustering for Blood Glucose Analysis in the ICU: Identification of Groups of Patients with Different Risk Profile

Lucia Sacchi[a], Giuseppe D'Ancona[b], Federico Bertuzzi[c], Riccardo Bellazzi[a]

[a] *Computer Engineering and Systems Science Department, University of Pavia, Pavia, Italy*
[b] *Department of CT surgery, Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT) Palermo, Italy*
[c] *S.S.D. Diabetologia, Niguarda Cà Granda Hospital, Milano, Italy*

Abstract

Blood Glucose (BG) analysis and control in critically ill patients became an important research challenge in the last few years. Despite the big improvements that have been achieved both in research and in clinical practice, there are still many aspects that need to be elucidated. A first step towards a better comprehension of the phenomena underlying BG dynamics is represented by the study of retrospectively collected data. In this paper we propose an analysis of blood glucose time series through a combined temporal clustering and standard statistical analysis approach. The ultimate goal of the analysis is the identification of groups of patients showing different BG dynamics and evaluate their risk profiles, which is a very important issue in the Intensive Care Units. The method is applied to a set of patients treated at the Mediterranean Institute for Transplantation and Advanced Specialized Therapies in Palermo, Italy. We show that it is possible to identify two groups based on the initial blood glucose trends, and that the two groups significantly differ in terms of their future BG behaviour.

Keywords:

Blood glucose analysis, Temporal data mining, Clustering, Intensive care units.

Introduction

Blood Glucose (BG) analysis in critically ill patients has become a crucial issue over the last few years [1,2]. Recent studies have demonstrated that a tight glycaemic control in Intensive Care Units (ICUs) causes a significant reduction in mortality and in the development of post-operative morbidities in surgical ICU patients [3-5]. The use of standardized protocols is leading to better patients' outcomes, so that many tools have been proposed to improve the compliance of ICU departments to current guidelines [6]. Several "ad hoc" glucose variability indexes have been proposed in the literature to evaluate and compare the quality of BG control algorithms among patients [7-9]. Although a lot of progresses have been achieved in this field, many aspects of BG control in ICU patients still have to be deeply understood and there is certainly room for large improvement.

A first step towards a better comprehension of the phenomena underlying BG dynamics is represented by the analysis of retrospectively collected data resorting to statistical and data mining methods. In particular, since BG monitoring data are naturally collected over time, an interesting application is to study such data by exploiting Temporal Data Mining techniques. This can be useful for example to detect different risk profiles in the patients and to plan different therapies for different groups. To this end, temporal clustering techniques are particularly suitable to identify groups of patients showing similarities in glycaemic profiles. However, since ICU patients are usually characterized by severe conditions, the collected time series are often very noisy and irregular. Moreover, they are characterized by uneven sampling time and missing data. To tackle these problems, many researchers are starting to move towards methods that resort to a qualitative and abstract representation of temporal profiles, which are often based on the Temporal Abstraction (TA) technique [10-12].

In this paper we present a combined analysis through TA-based clustering [13] and classical statistical methods applied to ICU patients who underwent cardiovascular surgery at the Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT) in Palermo, Italy. We show that it is possible to identify two risk groups based on the initial blood glucose trends, and that the two groups significantly differ on some important aspects of their future behavior.

The paper is structured as follows: in the Methods Section we describe the algorithms and analysis approach we used; in the Results Section we introduce the ISMETT ICU data set and we show the results obtained on the patients. The results are further commented in the Discussion Section. In the last Section we draw some final conclusions.

Methods

The analysis approach we adopted in this work is mainly characterized by three methodological issues. The first part of the

analysis deals with the extraction of a suitable representation of BG time series through Temporal Abstractions. Such representation serves as a preparation for the second step, which is temporal clustering. The third phase deals with knowledge extraction from clustering results. The aim of this last phase is to find significantly different groups of patients, focusing in particular on the risk of hypo and hyper-glycaemic events during ICU stay. The different analysis steps are described in the following sections.

Knowledge-based Temporal Abstractions

Knowledge-based Temporal Abstractions (TAs) were first introduced in [14]; they are a formalism that allows to move from a time-point to an interval-based representation of time series data. Such technique provides a description of a (set of) time series through sequences of temporal intervals corresponding to relevant qualitative patterns detected in their time courses. Following the model proposed in [15,16], TAs can be classified into two main categories, depending on the input and output data that are provided. *Basic* TAs are used to transform time-stamped data into a sequence of intervals, while *Complex* TAs are used to abstract intervals into other intervals applying suitable temporal operators [17]. In this paper we will mainly refer to Basic temporal abstractions, that we herein exploit to extract Increasing, Decreasing and Stationary trend patterns from blood glucose time series.

The algorithms that are used to detect TAs are known as TA mechanisms. We herein use a segmentation-and-labeling methodology to extract trends from the raw blood glucose time series. Time series are first processed through a stepwise linear segmentation and then a label is assigned to each segment on the base of its slope. For time series segmentation we use a bottom-up approach [18] suitably designed to deal with unevenly sampled and missing data. Once segments are extracted, the following step is to assign a label to each of them according to the slope of the segment itself. In this work we use a purely data-driven labeling approach, where a two-tailed t-test is performed on the slope parameter of the linear regression used for segment definition. A significance level α is established for the test, and the labeling criterion is the following:

- if |p-value|$\leq\alpha$ AND slope>0 then label = *Increasing*
- if |p-value|$\leq\alpha$ AND slope<0 then label = *Decreasing*
- if |p-value|>α then label = *Steady*

An alternative solution to the labeling issue is the knowledge based definition of a minimum slope threshold to which the segment slope value is compared.

As a result of this first analysis step, BG time series are represented by a qualitative label (or abstract pattern) made up of a set of consecutive basic trend TAs.

Temporal Clustering

The second analysis step concerns the application of a novel method to cluster time series data according to their qualitative behavior [13,19]. This method is called TA-clustering and, although designed to deal with gene expression data, well adapts to any time series with irregular sampling time. The TA-clustering technique is a generalization of template-based clustering [20] and it is based on a qualitative representation of profiles derived exploiting trend TAs (as described in the previous section). One of the most relevant features of TA-clustering is that it is based on a multi-level strategy that works on qualitative labels. In particular, we originally defined three abstraction levels for time series representation, that reflect different label aggregation. As a starting point we take the label deriving from the segmentation-and-labeling step; we will call this label the L_2-level label, since it represents the intermediate level from which the other two are then derived. L_1-level labels are obtained by removing all the *Steady* elements from L_2 labels and re-aggregating consecutive equal labels when needed. L_3-level labels are low-level abstractions obtained by assigning to each time interval of the original time series the corresponding qualitative label (consecutive labels can be duplicated in such representation). An example of the multi-level labeling system is depicted in Figure 1.

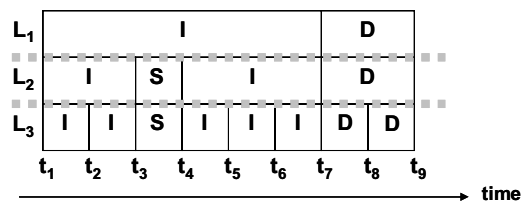

*Figure 1 – Example of the multi-level labeling scheme used for temporal clustering. Herein **I** stands for Increasing, **D** for Decreasing and **S** for Steady. At the bottom of the picture the time line is reported.*

Considering the high heterogeneity in sampling time, number of measurements and length of stay characterizing critically ill patients, in this work we will only refer to the most abstracted levels (L_1 and L_2).

Once the abstracted labels are created, the aggregation procedure for the two top levels is straightforward: time series with the same label are grouped into the same cluster. For L_3 labels a distance function is instead defined to group together time series that show similar qualitative behavior [13].

Evaluation and Comparison of Patients' Risk profiles

Relying on clustering results it is often possible to identify patients groups and to evaluate the clinical profiles of the members of such groups on the base of interesting characteristics. As regards BG monitoring, an interesting index to assess a patient's condition is to evaluate his/her risk of experiencing hyper or hypo-glycaemic episodes during the ICU stay.

To this end, for each patient we compute the risk profile following the indications proposed in [8]. In particular, for any BG measurement (*bg*) expressed in mg/dl, the risk function(*r(bg)*) is defined as follows:

$$r(bg) = 10 \times \left\{1.509 \times \left[(\ln(bg))^{1.084} - 5.381\right]\right\}^2 \quad (1)$$

Exploiting equation (1) it is possible to derive a risk time series for each patient. From this time series the average risk can then be calculated on a specific time window as required by the analysis purposes. We will exploit such solution on the groups of patients extracted through clustering. As we will show in the next section, comparisons between groups are performed towards standard statistical methods.

Results

Data Set Description

In this study we considered a group of 596 ICU patients treated by the Mediterranean Institute for Transplantation and Advanced Specialized Therapies in Palermo, Italy, from August 2006 to February 2008. The patients belonging to our sample underwent various types of cardiac surgery, as reported in Table 1. For 11 patients the information related to the type of intervention was not available.

Table 1 – Type of surgery and number of patients in our data set

Type of surgery	Number of patients
Single valve	216
Multiple valves	47
Aortic surgery	16
Ventricular surgery	24
Bypass	180
Bypass and Valve	78
Transplantation	15
Minor cardiac surgery	9

A set of 22 parameters was monitored over time for all the patients during the ICU stay. In this study we will consider blood glucose time series. BG was monitored for all the patients by means of BG fingerstick and venous measurements. The median of ICU stay was of 3 days (minimum: 1 day, maximum 31 days), with an average number of 14 measures per patient and an average inter-measurement time of 3.7 hours.

Data Analysis

Considering the median length of stay and the fact that patients staying at the ICU for 3 or more days usually show the most critical illness conditions, in our analysis we chose to take into account the first 3 monitoring days. As a first analysis step we performed TA-clustering using L_1 and L_2-level labels. The result of this step was a set of 14 L_1 clusters, that we further joined to form two macro-groups based on the initial trend of the glucose monitored values (*Increasing* and *Decreasing*)

In particular, we identified 300 patients starting with an initial increasing trend and 286 patients starting with a decreasing glucose trend. Figures 2 and 3 represent the two clusters with the average profile of the initial trend.

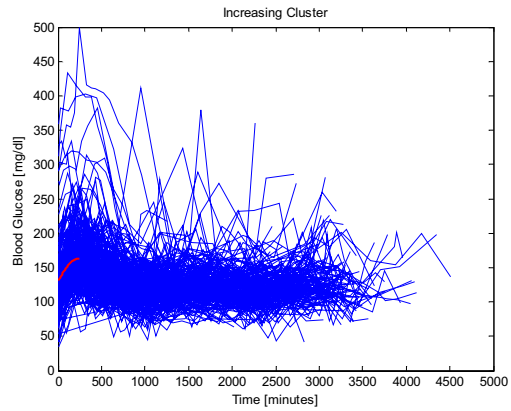

Figure 2 – Cluster of patients with an initial increasing trend

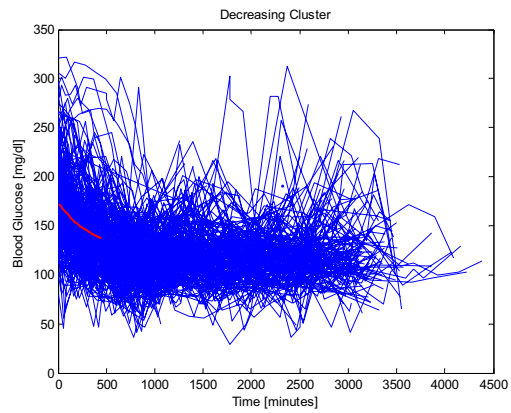

Figure 3 – Cluster of patients with an initial decreasing trend

The median time span of the initial increasing interval was found to be 4.03 hours, with an interquartile range of [1.9 - 8.4] hours. The median duration of the initial decrease was found to be 14.4 hours, with interquartile range [7.98–21.15] hours. The two medians are significantly different ($p << 0.01$). The duration of the increasing trend is significantly shorter than the duration of the decreasing BG trend ($p << 0.01$).

We also found a significant difference ($p < 0.05$) between the initial BG values in the two groups. Rather interestingly, the higher BG basal value is associated to the decreasing group, as it can be noticed by the boxplot in Figure 4.

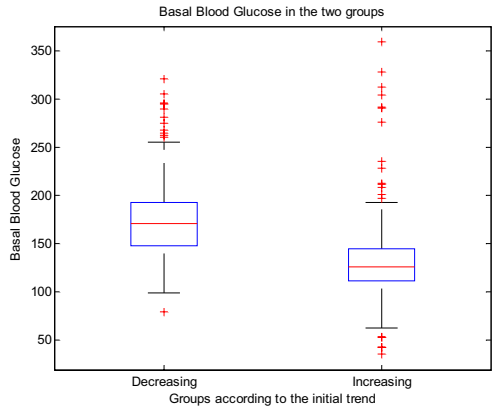

Figure 4 – Boxplot of the distributions of the basal BG value in the two groups

As a next analysis step, we have subdivided the BG time series for each patient into two periods to evaluate the patients' risk profiles. The first period was set to finish at the end of the initial trend (i.e. the increasing or decreasing period), while the second period was defined by the remaining monitoring time.

For each patient we computed the time series of the risks, and we calculated the average risk index on the two periods. We compared the average risk distributions for the second period in the two clusters, and we obtained a significant result ($p << 0.01$), being the decreasing group less risky. Besides the average risk index we also evaluated the standard deviation of BG measurements in the second period and compared it in the two groups. Also in this case the result showed a significant difference (p-value<<0.01) with higher values for the Increasing group. In particular the median value for standard deviations in the Increasing group was of 25.03, while for the Decreasing group it was 20.6.

To better evaluate the instability scenario that clearly characterizes the patients belonging to the Increasing group, we also analyzed the insulin intake in our set of patients with the goal of comparing the two groups. In particular, we compared the medians of the standard deviation of the insulin intakes after the initial trend in the two groups. The result is significant (p-value <<0.01), with a lower value for the Decreasing group. The median value of the insulin intake standard deviation for the Increasing group was found to be 1.24, while for the Decreasing patients it was found to be 0.95.

A further analysis also revealed that the duration of the increasing period is significantly positively correlated with the risk in the second period and that the duration of the decreasing period is negatively correlated with the risk in the second period ($p < 0.05$).

To better elucidate if the difference between the two groups is due to some clinical reasons not related to BG control, we performed an additional analysis to check the frequency of the surgery type and risk factors (comorbidities) in the two groups of patients. We didn't find clinically interesting differences in the distribution of clinical interventions; however, we found that in the Decreasing group there are significantly more Diabetes mellitus patients (76 vs 52, $p < 0.05$) while in the Increasing group there are more Valvular Heart Disease patients (148 vs 193 $p<0.05$)

Finally, we analyzed the distributions of clinical morbidities of the two groups, that showed significant differences only concerning Bleeding (Decreasing 15, Increasing 26, $p<0.01$) and the need of an Intra Aortic Balloon Pump (Decreasing 15, Increasing 3, $p<<0.01$).

Discussion

In the previous section we have shown that it is possible to divide ICU patients into two groups related to the initial BG trend and that these groups show significant differences in their risk profiles and in insulin treatment.

In particular, we have demonstrated that the basal BG values are significantly higher in the Decreasing group. This can be motivated by analyzing the post-operative patient management. Each patient gets an insulin drip starting immediately after surgery until they start to eat. If an high basal glycaemic level is observed, it is immediately treated to return to normal values, thus originating a decrease in BG time series. Higher basal glycaemic values lead thus to a more aggressive treatment in BG control at least in the first period.

Similarly, the resulting shorter duration of the increasing trend is clinically motivated by the fact that an increase in BG is often considered as an alarm. The procedures to go back to a normoglycaemic pattern are performed quite quickly in order to stop the increase and to avoid severe complications.

Broader glycaemic oscillations and higher average risk indexes were also found for the Increasing patients. This was coupled to an higher variability in the associated insulin therapy for such group, highlighting a clear relationship between the glycaemic temporal patterns and the clinical management of the patients.

Trying to further characterize the two groups of patients on the base of their clinical characteristics, we also compared the frequencies of surgery type and risk factors in the two samples. The aim of this analysis was to verify whether the group characterized by the higher instability and risk index (the Increasing group) was made up of patients who underwent major surgeries or characterized by important risk factors. However, our tests resulted in almost no significant differences into the distributions of surgeries and comorbidities among patients. Also the number of diabetic patients, that are usually characterized by a more aggressive insulin therapy and were thus expected to fall into the decreasing group, was only slightly higher in such group. The same conclusion can be drawn if we observe the distribution of the morbidities in our two samples. Besides the increase of the risk index and in the incidence of bleeding, the patients of the Increasing group don't show major morbidities if compared to the Decreasing group.

We might thus conclude that, at least in the clinical center under study, an increase of BG after surgery is a useful marker of

metabolic instability and of a critical evolution of the patient's condition which requires more frequent intervention of the health care providers. A further step of the analysis will be to include in the study also the other parameters that are monitored during the ICU stay.

Conclusion

In this paper we have presented a temporal data mining approach to the problem of analyzing blood glucose monitoring time series in ICU patients. In particular, we have applied a TA-based clustering technique to identify groups of patients showing similarities in their glycaemic profiles. We have been able to identify two macro-groups of patients characterized by a different initial trend in BG, namely Increasing and Decreasing trends. Such groups were found to significantly differ on some important characteristics, and in particular we found that the patients showing an initial increase in BG have an higher future BG risk and higher future oscillations. Moreover, the risk in the second period results to be correlated with the duration of the initial trend. These promising results lead us to conclude that evaluating the initial BG trend can be predictive of the future behavior of the patients' risk profile.

This paper showed that temporal data mining is a useful tool to better understand the data collected in routine clinic and to provide health care providers with useful advice and caveats.

References

[1] Finfer S, Heritier S; NICE Study Management Committee and SUGAR Study Executive Committee. The NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) Study: statistical analysis plan. Crit Care Resusc. 2009 Mar;11(1):46-57.

[2] Merz TM, Finfer S. Pro/con debate: Is intensive insulin therapy targeting tight blood glucose control of benefit in critically ill patients? Crit Care. 2008;12(2):212. Epub 2008 Apr 25

[3] Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in the critically ill patients. N Engl J Med. 2001 Nov 8;345(19):1359-67.

[4] Finney SJ, Zekveld C, Elia A, Evans TW. Glucose control and mortality in critically ill patients. JAMA. 2003 Oct 15;290(15):2041-7.

[5] Van den Berghe G, Wouters PJ, Bouillon R, Weekers F, Verwaest C, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P. Outcome benefit of intensive insulin therapy in the critically ill: Insulin dose versus glycemic control. Crit Care Med. 2003 Feb;31(2):359-66.

[6] Morris AH, et al. A replicable method for blood glucose control in critically Ill patients. Crit Care Med. 2008 Jun;36(6):1787-95.

[7] Kovatchev BP, Otto E, Cox D, Gonder-Frederick L, Clarke W. Evaluation of a new measure of blood glucose variability in diabetes. Diabetes Care. 2006 Nov;29(11):2433-8.

[8] Kovatchev BP, Clarke WL, Breton M, Brayman K, McCall A. Quantifying temporal glucose variability in diabetes via continuous glucose monitoring: mathematical methods and clinical application. Diabetes Technol Ther. 2005 Dec;7(6):849-62

[9] Vogelzang M, van der Horst IC, Nijsten MW. Hyperglycaemic index as a tool to assess glucose control: a retrospective study. Crit Care. 2004 Jun;8(3):R122-7.

[10]Stacey M, McGregor C. Temporal abstraction in intelligent clinical data analysis: a survey. Artif Intell Med 2007;39:1—24.

[11]Moskovitch R, ShaharY. Medical temporal-knowledge discovery via Temporal Abstraction. To be published in Proc. of AMIA 2009 annual symposium.

[12]Verduijn M, Sacchi L, Peek N, Bellazzi R, de Jonge E, de Mol BA. Temporal abstraction for feature extraction: a comparative case study in prediction from intensive care monitoring data. Artif Intell Med. 2007 Sep;41(1):1-12.

[13]Sacchi L, Bellazzi R, Larizza C, Magni P, Curk T, Petrovic U, Zupan B. TA-clustering: cluster analysis of gene expression profiles through Temporal Abstractions. Int J Med Inform. 2005 Aug;74(7-8):505-17.

[14]Shahar Y. A framework for knowledge-based temporal abstraction. Art Int 1997;90:79–133.

[15]Bellazzi R, Larizza C, Riva A. Temporal abstractions for interpreting diabetic patients monitoring data. Intel. Data Anal. 1998;2:97–122.

[16]Sacchi L, Larizza C, Magni P, Bellazzi R. Precedence Temporal Networks to represent temporal relationships in gene expression data. J Biomed Inform. 2007 Dec;40(6):761-74.

[17]Allen JF. Towards a general theory of action and time. Art Int 1984;23:123–54.

[18]Keogh E, Chu S, Hart D, Pazzani M. Segmenting time series: a survey and novel approach. In: Data mining in time series databases. World Scientific Publishing Company, 2004;1–22.

[19]Magni P, Ferrazzi F, Sacchi L, Bellazzi R. TimeClust: a clustering tool for gene expression time series. Bioinformatics. 2008 Feb 1;24(3):430-2.

[20]Lagreid A, Hvidsten TR, Midelfart H, Komorowski J, Sandvik AK. Predicting gene ontology biological process from temporal gene expression patterns. Genome Res. 2003 May;13(5):965-79.

Address for correspondence

Lucia Sacchi: lucia.sacchi@unipv.it