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Principal component analysis in combination with case-based reasoning for detecting therapeutically correct and incorrect measurements in continuous glucose monitoring systems

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ABSTRACT

This paper introduces a data-driven methodology for detecting therapeutically correct and incorrect measurements in continuous glucose monitoring systems (CGMSs) in an intensive care unit (ICU). The data collected from 22 patients in an ICU with insulin therapy were obtained following the protocol established in the ICU. Measurements were classified using principal component analysis (PCA) in combination with case-based reasoning (CBR), where a PCA model was built to extract features that were used as inputs of the CBR system. CBR was trained to recognize patterns and classify these data. Experimental results showed that this methodology is a potential tool to distinguish between therapeutically correct and incorrect measurements from a CGMS, using the information provided by the monitor itself, and incorporating variables about the patient's clinical condition.

1. Introduction

Continuous glucose monitoring systems (CGMSs) are devices that provide detailed information about glucose variability in the interstitial fluid on a continuous basis: direction, magnitude, duration, and frequency of hypo- or hyperglycemia [1]. This information permits to identify glucose trends throughout the day. Over the past decade, there has been unprecedented technological progress in the development of CGMSs. CGMSs in combination with insulin pumps and control algorithms have fuelled research in the development of the so-called "artificial pancreas".

Nowadays the need to manage glycemia in critically ill patients has been the focus of multiple studies. In intensive care units (ICUs), blood glucose (BG) monitoring is performed intermittently using different bedside BG meters. CGMSs would allow a better control of glycemia in critically ill patients allowing the staff to anticipate episodes of hyper- and hypoglycemia. The potential benefits of the use of the CGMS would be avoiding multiple blood draws from the patient. Other benefits of using the CGMS would be a reduction in the workload of nurses and a reduction in the risk of accidental puncture.

Although the CGMS could be clinically useful in the ICU, it is not sufficiently accurate and reliable at present to be used for therapeutic decisions. The lack of accuracy and reliability has been an important limiting factor for insulin delivery automation, and for clinical use. For this reason, none of the CGMS available has been approved by the regulatory agencies as a replacement for traditional self-monitoring of blood glucose (SMBG). Thus, improvement of the accuracy and reliability of these devices is essential.

Previous studies have been developed to improve accuracy and reliability in CGMS. To improve the accuracy, new algorithms considering blood-to-interstitial glucose dynamics have been developed and implemented [2–6]. However, accuracy is not as big an issue as reliability and error detection [7]. Reliability is one of the main requirements for a CGMS and in order to improve it, detection of abrupt faults and malfunctions must be included in

Abbreviations: ABG, arterial blood glucose; APACHE, acute physiology and chronic health evaluation; CBR, case-based reasoning; CGMS, continuous glucose monitoring system; CII, infusion of intravenous insulin; ICU, intensive care unit; PCA, principal component analysis; RTCGMS, REAL-Time Continuous Glucose Monitoring System; SOFA, sequential organ failure assessment.

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Table 1
Baseline characteristics, primary conditions and outcomes of all patients included in this work.

Variable	Overall
Number (%)	22 (100)
Type of critically ill patient (medical/surgical/trauma)	7/11/4 (31.8/50.0/18.2)
Age (years)	62.0 (55.5–74.0)
Sex (female/%)	11/50
Body mass index (kg/m^2)	29.5 (28.0–32.8)
Previous known diabetes (yes/%)	12/54.5
Stay in ICU (days)	21.0 (14.3–33.5)
Stay in the hospital (days)	35.0 (27.5–54.0)
ICU mortality (yes/%)	7/31.8
Hospital mortality (yes/%)	8/36.4
SOFA[a]	8.5 (6.0–10.0)
APACHE II[a]	20.0 (15.0–21.8)
Sepsis[a] (yes/%)	18/81.8
Mechanical ventilation (yes/%)	22/100.0
Nutrition (enteral/parenteral)	14/8

Data are median values. Numbers in parentheses indicated the interquartile range (Q1–Q3, respectively).

[a] These values correspond to the initial condition of the patient.

CGMSs. A limited number of works about fault detection methods for CGMSs have been published [8–13]. For this reason, significant progress needs to be made in CGMS fault detection. Moreover, and according to the idea proposed in [14], this work proposes the use of monitoring techniques and abnormal situation management in CGMS fault detection, in the same way that these techniques are often used in different applications [15].

In order to make clinical decisions, the main goal of this work was to develop a data-driven methodology for detecting therapeutically correct (TC) and therapeutically incorrect (TI) measurements made by a CGMS. Measurements were classified using statistical methods (principal component analysis, PCA) in combination with expert systems (case-based reasoning, CBR). PCA was used to extract features (the *Q*-statistic and the scores). Then, the *Q*-statistic and the scores obtained from PCA together with the septic status of the patient have been proposed as descriptors for the CBR methodology. CBR was applied to recognize patterns and classify measurements made by a CGMS. The CBR considers two different procedures of the *z*-Nearest Neighbours (*z*-NN) to classify measurements: one of them based just on the *z*-NN two-steps distance criterion (based solely on PCA features) (CBR-2SR), and the other based on the *z*-NN two-steps distance criterion and the similarity of the septic status between cases (CBR-3SR).

The remainder of this paper is organized as follows: Section 2 describes the clinical experimental setup used for data capture, and the transformation of the CGMS fault detection problem into a bi-classification problem. Furthermore, the feature extraction using PCA and the methodology for detecting TC and TI measurements by applying CBR are also outlined. Finally, Section 3 is reported and Section 4 is presented.

2. Materials and methods

2.1. Information collection

The clinical experimental setup was obtained from a prospective observational study in an intensive care unit (ICU). The research reported in this manuscript was performed using data from 22 patients admitted to an 18-bed mixed ICU at the Doctor Josep Trueta Hospital (Girona, Spain) (acute physiology and chronic health evaluation (APACHE) II score, 20.0 [range, 15.0–21.8]; sequential organ failure assessment (SOFA) score, 8.5 [range, 6.0–10.0]). The characteristics of the patients are given in Table 1. The overall results of the study were presented in [16]. This study followed the protocol approved by the Ethics Committee of the Doctor Josep Trueta Hospital. All of the patients gave informed consent, either signed by them if they were conscious or signed by family members in cases of unconscious patients.

The data set was gathered from patients who presented with hyperglycemia and needed intravenous insulin therapy on admission to the ICU. This data set contains information provided by the Guardian® REAL-Time Continuous Glucose Monitoring System (RTCGMS) (Medtronic, Northridge, CA) and variables about the patient's clinical condition.

Arterial BG (***ABG***) readings were used as the gold standard to classify the data set on TC and TI measurements. ***ABG*** was measured using the whole BG concentration reported by the HemoCue® 201 DM (HemoCue AB, Ängelholm, Sweden). Quality control checks were performed using liquid controls recommended by HemoCue® instructions. The ABG samples were obtained following the glycemic control protocol established in the ICU [16]. According to this protocol, when a patient showed high glycemic instability (hyper- and hypoglycemia), ***ABG*** samples were taken every 30 min. Then, if glycemic values were stabilized, ***ABG*** measurements were spaced to every one, two, three, and until every 4 h. If the patient's nutritional intake was stopped for any reason, the glycemic control testing was performed more frequently, even during euglycemia. Additional ***ABG*** measurements were used for RTCGMS calibration. After the third day, the ***ABG*** data were downloaded to a computer using HemoCue® 201 DM 3.1 software.

The RTCGMS provided the following measurements: the electrical signal (*Isig*, measured in nanoamperes) and the glucose estimation in the interstitial fluid (G_{RTCGMS}, measured in mg/dL). Patients were monitored for 72 h using the RTCGMS (MiniMed reference CSS72). This device consists of a disposable subcutaneous needle-type sensor and an external monitor. The sensor is an amperometric system that uses glucose oxidase, which generates an electrical signal (*Isig*) proportional to the glucose concentration in the interstitial fluid (G_{RTCGMS}) [17]. The sensor measures *Isig* every 10 s and records the mean values at 5-min intervals. The sensor estimates G_{RTCGMS} at 5-min intervals. The RTCGMS was placed in the subcutaneous tissue of the upper leg of each patient. Following a 2-h initialization period, the first *ABG* measurement was used for RTCGMS calibration. These calibrations were performed according to the RTCGMS manufacturer's instructions (three to four per day). RTCGMS readings were not used to modify insulin therapy. After the third day, the RTCGMS data were downloaded to a computer using Medtronic Carelink Pro version 2.0B software.

Variables about the patient's clinical condition corresponding to the dose of continuous infusion of intravenous insulin (CII or ***Insulin***), the axillary body temperature (***Temperature***) and the septic status (***Sepsis***) of the patient were recorded. ***ABG*** samples were used by the nurses to administer insulin therapy, according to the protocol established by the ICU. A CII was started once the patient had ***ABG*** values above 150 mg/dL to maintain the ***ABG*** between 120 and 160 mg/dL. Short-acting insulin (Actrapid, Novo Nordisk, Bagsværd, Denmark) diluted in 0.9% saline was used. Intravenous insulin therapy was stopped when the ***ABG*** was below 110 mg/dL. ***Insulin*** was recorded at the same time as ***ABG***.

Temperature was measured at 30-min intervals with electronic thermometers (Thermoval Basic, Hartmann®, Germany). Under continuous glucose monitoring, ***Sepsis*** of the patient was recorded every 24 h by the patient's medical team. The patient's medical team gave the diagnostic about the septic status of the patient based on the definitions of The American College of Chest Physicians and Society of Critical Care Medicine Consensus Conference Committee [18]. The patient's medical team gave a presumptive diagnosis considering the patient's medical history and the results of laboratory tests such as leucocytosis, C-reactive protein (PCR) and procalcitonin (PCT). Furthermore, cardiogenic, haemorrhagic,