COMPUTER METHODS AND PROGRAMS IN BIOMEDICINE 134 (2016) 179–186

journal homepage: www.intl.elsevierhealth.com/journals/cmpb

Prediction of nocturnal hypoglycemia by an aggregation of previously known prediction approaches: proof of concept for clinical application

Pavlo Tkachenko [a,*], *Galyna Kriukova* [a], *Marharyta Aleksandrova* [b,c], *Oleg Chertov* [b], *Eric Renard* [d,e], *Sergei V. Pereverzyev* [a]

[a] *Johann Radon Institute for Computational and Applied Mathematics (RICAM), Austrian Academy of Sciences, Altenbergerstrasse 69, 4040 Linz, Austria*
[b] *National Technical University of Ukraine "Kyiv Polytechnic Institute", Kyiv, Ukraine*
[c] *Université de Lorraine—LORIA, Vandoeuvre les Nancy, France*
[d] *Department of Endocrinology, Diabetes, Nutrition, and CIC INSERM 1411, Montpellier University Hospital, Montpellier, France*
[e] *Institute of Functional Genomics, UMR CNRS 5203/INSERM U1191, University of Montpellier, Montpellier, France*

A R T I C L E I N F O

Article history:
Received 23 February 2016
Received in revised form
6 June 2016
Accepted 1 July 2016

Keywords:
Prediction of nocturnal hypoglycemia
Type 1 diabetes
Aggregation
Last before bed measurement
LBGI

A B S T R A C T

Background and Objective: Nocturnal hypoglycemia (NH) is common in patients with insulin-treated diabetes. Despite the risk associated with NH, there are only a few methods aiming at the prediction of such events based on intermittent blood glucose monitoring data and none has been validated for clinical use. Here we propose a method of combining several predictors into a new one that will perform at the level of the best involved one, or even outperform all individual candidates.
Methods: The idea of the method is to use a recently developed strategy for aggregating ranking algorithms. The method has been calibrated and tested on data extracted from clinical trials, performed in the European FP7-funded project DIAdvisor. Then we have tested the proposed approach on other datasets to show the portability of the method. This feature of the method allows its simple implementation in the form of a diabetic smartphone app.
Results: On the considered datasets the proposed approach exhibits good performance in terms of sensitivity, specificity and predictive values. Moreover, the resulting predictor automatically performs at the level of the best involved method or even outperforms it.
Conclusion: We propose a strategy for a combination of NH predictors that leads to a method exhibiting a reliable performance and the potential for everyday use by any patient who performs self-monitoring of blood glucose.

1. Introduction

According to a report of a Workgroup of the American Diabetes Association and the Endocrine Society [1] hypoglycemia is defined as blood glucose (BG) level less than 70 mg/dL. Nocturnal hypoglycemia (NH) is the most feared type of hypoglycemia in patients with diabetes treated by insulin. Due to its time of occurrence, it is usually asymptomatic [2,3] but has negative impact on patients' health. NH problem is less

* *Corresponding author.* Johann Radon Institute for Computational and Applied Mathematics (RICAM), Austrian Academy of Sciences, Altenbergerstrasse 69, 4040 Linz, Austria. Fax: +43 732 2468 5212.
E-mail address: pavlo.tkachenko@oeaw.ac.at (P. Tkachenko).
http://dx.doi.org/10.1016/j.cmpb.2016.07.003
0169-2607/

worrisome for patients equipped with Continuous Glucose Monitors (CGM), especially when they are combined with other sensors that can be used for detecting NH, such as electrocardiogram (ECG) sensors [4] or electroencephalogram (EEG) sensors [5]. But such systems are still not widely spread. For example, only about 2–3% of insulin-treated patients use CGM systems because of their high market price, frequent annoying false alarms and the lag behind actual glucose measures which impairs patients' trust.

On the other hand, intermittent monitoring performed from finger sticks remains the most widely used blood glucose monitoring method (BGM). The main advantage of this method is that it provides fairly accurate results of BG concentration. Additionally, this type of BGM is marketed at very low prices compared to noninvasive systems or CGM. Therefore, it is attractive to develop a method for predicting NH that uses only limited discrete information on blood glucose level during daytime hours.

In the literature, there are several techniques that, in principle, can be employed for this purpose. The first attempt in predicting NH from daily finger sticks measurements of capillary blood was done by Whincup and Milner [6] in 1987. They proposed a classification method which uses only one before-bed measurement for the prediction. However, this method has been criticized, for example by Davies [7], because of its poor performance on other datasets.

Then a diabetes advisory system (DIAS) based on causal probabilistic network was proposed in Ref. [8] as a tool to identify periods of unrecognized NH. However, in five of the six patients in whom NH was predicted by DIAS for four consecutive nights, the tests [8] confirmed hypoglycemia on only one of the nights.

Another method, which aims at the prediction of severe hypoglycemia, and can be potentially also used for prediction of NH, is based on the low blood glucose index (LBGI) [9,10]. However, from the definition of the LBGI it follows that hypoglycemia cannot be predicted when a patient did not have low BG-measurements during daytime and was affected by a NH during sleep hours. At the same time, some of such NH cases can be caught by the classifiers of Whincup and Milner [6]. This hints at the idea of combining several NH predictors such that they would complement each other.

In the current study we present a general approach based upon combining known NH predictors that automatically works at the level of the best involved predictor, and may even outperform all of them. Our approach requires solving a low-dimensional system of linear equations, and can potentially be implemented in on-line mode. The approach has been realized in the form of an app for Android smartphones, tested on clinical datasets and exhibited a secure level of predictive accuracy.

2. Materials and methods

In what follows we are going to describe a constructive approach to combining forecasts from various models or sources. The proposed approach has been recently advocated in Ref. [11] in the context of ranking, which is relatively a new problem of machine learning. Note that the use of ranking framework is natural for NH prediction, because, for example, Accu-Chek Connect [12] suggests the use of LBGI values for ranking NH risks into 4 categories: minimal, low, moderate and high.

Then similar to Ref. [8], the appearance of NH can be represented by a stochastic model operating in a discrete space of a finite number of NH risk levels y. For example, the value $y = 1, 0.5, -0.5, -1$ may mean respectively high, moderate, low and minimal NH risk levels.

2.1. NH prediction as a ranking problem

Let $x = (x^1, x^2, x^3, \ldots, x^l) \in \mathbb{R}^l$ be a vector of daily BG measurements, where, for instance, x^l is the last before-bed (LBB) measurement that is used as input in NH predictors [6,7]. Then as in Ref. [8] the relation between x and the value y for the night succeeding the day with BG measurements x is specified using conditional probabillity $\rho(y|x)$ of y given x.

As is explained in the Introduction section, we deliberately restrict ourselves to stochastic models including only two parameters: y and x. Then let $\rho(x)$ be a marginal probability distribution for the remaining model variable x.

In spite of the assumption of a stochastic relationship between x and y, we are interested in synthesizing a deterministic predictor p that will assign NH risk levels $p(x)$ to the night succeeding the day with BG measurements, forming vector x. Note that the value $p(x)$ can also be used to predict whether or not NH appears.

For given true NH risk levels y and y', which correspond to daily BG measurements x and x', the value:

$$(y - y' - (p(x) - p(x')))^2$$

is interpreted by a standard assessment methodology of machine learning [13,14] as the loss of the predictor p in its risk ranking. Then the quality of a predictor p can be measured by the expected misranking error

$$\varepsilon(p) = \int\int (y - y' - (p(x) - p(x')))^2 \, d\rho(y'|x') d\rho(y|x) d\rho(x') d\rho(x),$$

and it is natural to minimize this in the space $L_{2,\rho}$ of all functions $p(x)$, which are square-integrable with respect to the marginal dictribution $\rho(x)$.

It is known [13,14] that one of the expected error minimizers can be written as:

$$p_\rho(x) = \int y d\rho(y|x) - \int\int y d\rho(y|x) d\rho(x),$$

but this ideal predictor cannot be used in practice, because neither the conditional probability $\rho(y|x)$ nor the marginal distribution $\rho(x)$ is known.

On the other hand, we can access clinical records of diabetic patients, which contain the historical data, such as daily BG measurements $x_j = (x_j^1, x_j^2, \ldots, x_j^l)$, $j = 1, 2, \ldots, n$ collected within n different days, and retrospectively estimated NH risk levels y_j for the corresponding succeeding nights. In the simple situation, which we will deal with later on in this paper, the real case of NH in the night after the day j is coded as $y_j = 1$, while the night without NH corresponds to $y_j = -1$.

The set of pairs $Z_n = \{(x_j, y_j), j = 1, 2, \ldots, n\}$ will appear further under the name of training set.