Hypoglycaemia prediction models with auto explanation

VIRGINIE FELIZARDO¹, DIOGO MACHADO², NUNO GARCIA¹, NUNO POMBO¹, AND PEDRO BRANDÃO²

virginie@it.ubi.pt, dmachado@dcc.fc.up.pt, {ngarcia,ngpombo}@di.ubi.pt, pbrandao@dcc.fc.up.pt
Instituto de Telecomunicações
¹Universidade da Beira Interior
²Universidade do Porto

ABSTRACT

World-wide statistics show a considerable growth of the occurrence of different types of Diabetes Mellitus, posing diverse challenges at many levels for public health policies. Some of these challenges may be addressed by means of computerised systems which may pave the way to provide practitioners with insight on their patient’s conditions anywhere and at anytime, but also to empower Diabetes patients as managers of their health. These systems for disease management come in many shapes and sizes, being the most promising trends the ones that involve expert systems that comprise specialised knowledge, use predictive models, feature engineering and reasoning.

This study presents the state-of-the-art on reasoning and prediction models related with either blood glucose level or hypoglycaemia events. The main findings revealed are that there is room for improvement on predictive models, namely to enhance its accuracy and ability to forecast future events into a wider time frame. On the other hand, reasoning models are understudied and its usage in Diabetes management is reduced. We discuss an architecture that combines a predictive model and a reasoning system, with the objective of alerting of impending occurrences and interpret the current situation to accurately advise the diabetic user.

INDEX TERMS

AI, eHealth, Expert-Systems, Data-mining, Prediction models, Diabetes Mellitus

I. INTRODUCTION

DIABETES is a chronic disease that in 2019 affected approximately 463 million adults around the world (International Diabetes Federation, 2019). Despite all the efforts to stale the growth of this disease, the number of people with diabetes is continuously increasing and it is estimated to reach 700 million in 2045 (International Diabetes Federation, 2019). Alongside these numbers there is the economic impact. Diabetes is reported to have caused expenditures of 727 billion USD dollars in 2017 (International Diabetes Federation, 2019). These facts challenge for innovative solutions capable not only mitigating the origin of new cases, but also providing sustainable medical practices for those already affected by diabetes. Diabetes is characterised by high levels of glucose in the blood, caused by the person’s pancreas only producing little or no insulin. If glycaemic values are not controlled, diabetes can seriously decrease the quality of life. In the worst cases, this disease leads to blindness, amputation or heart problems. There are different types of diabetes where type 2 and type 1 are the most common. Each type of diabetes has a specific treatment associated. Given the diabetic’s inability to produce insulin, a strict regime and periodic or even continuous verification of glycaemic values is recommended. This regime evolves and adapts each time the diabetic consults a doctor. In these appointments, the medical expert evaluates the evolution of the glycaemic values, among other relevant annotated information, and personalises the current regime, to the diabetic’s needs. This process is not optimal since it requires the availability of a medical expert to receive the person, evaluate the data and refine the treatment. Real-time events such as hyperglycaemia (when concentration of Blood Glucose (BG) is high) or hypoglycaemia (when BG is low)¹, require immediate action which poses a possible problem in the absence of expert knowledge.

Research has tried to provide support directly to the

¹These thresholds may vary according to the patient’s characteristics: before/meal, age, disease development and others. Usually hypoglycaemia is a BG below 70 mg/dL (3.9 mmol/L) and hyperglycaemia a BG higher than 170 mg/dL (9.4 mmol/L) after a meal (NICE UK, 2020a; NICE UK, 2020b).
patient, embedding this knowledge at the patient side. Predictive models have been increasingly adopted to cope with hypoglycaemia events. The objective is to empower patients before an event occurs and thus to support them on the decision-making required to mitigate or to avoid the subsequent symptoms. However, in current research, the reasons for the hypoglycaemia to occur are not addressed. Reasoning about why a hypoglycaemia will occur, may help avoid it and educate the patient on a better control. This last point concerns the area of expert systems for health.

The objective of predictive algorithms can be divided into three purposes: improving the health care of the population, increasing patient experience, and adding value to health care. A predictive algorithm can be applied to some challenging healthcare scenarios such as: promoting self-management by status interpretation and health education, individual change detection, future event prediction or assisting medical decision-making. Predictive algorithms are based on various techniques, including data mining, statistical, modelling and artificial intelligence. For developing these models different pre-processing techniques, various feature extraction techniques and classifiers are applied.

This approach attempts to glance the future. Considering the user’s past data, it trains specialised models to foresee the consequences of the user’s current actions. Doing so, these systems create a window of opportunity for the user to avoid possible unwanted occurrences. Therefore, the discovery of patterns associated with future events in combination with feature engineering to understand which features allow reasoning about this field is crucial development for diabetes management.

Reasoning systems, are a part of computer science that given a goal attempts to make logical inferences automatically (Hayes-Roth, Waterman and Lenat, 1984; Wos et al., 1984). In the case of diabetes management, these systems can be viewed as a medical support tool. Diabetes management is a complex task that requires not only expert knowledge, but also experience. There are multiple factors that influence glycaemic values, and often these factors vary from person to person. With this in mind, many projects try to specialise in a particular aspect of diabetes management, insulin calculation being the most popular. In general, reasoning systems, applied to diabetes, seek to advise and assist their users as an expert would.

In this article we will first describe what is the current state of the art for hypoglycaemia prediction models and reasoning approaches for diabetes management. We will then discuss the shortcomings of the current methodologies. After which we will argue that both techniques need to be improved and coupled to provide the diabetic patient with a good support for diabetes management.

II. METHODOLOGY

In this work, the authors searched and reviewed the state of the art of both prediction and reasoning models applied to diabetes. The models focus on different subjects, as a consequence, search parameters differ, although the search engines used were the same. The authors used the ScienceDirect, IEEE Xplore, ACM Digital Library, SCOPUS and PubMed databases to retrieve relevant peer-reviewed publications.

This study aims to provide an up-to-date state-of-the-art on data-based or hybrid models applied to predict either blood glucose levels or hypoglycaemia events by means of data collected from patients with diabetes.

We searched titles and abstracts using: “hypoglycaemia prediction” OR “hypoglycaemia detection” OR “blood glucose prediction” OR “blood glucose estimation” OR “hypoglycaemia estimation” OR “blood glucose detection”, for the databases ScienceDirect, IEEE Xplore, SCOPUS and PubMed; and (hypoglycaemia OR “blood glucose”) AND (prediction OR detection OR estimation), for ACM Digital Library. We used the US version of hypoglycaemia for searching as it provides more results. In this paper we use the UK version to conform to UK English². The inclusion criteria were: real data from participants; collected on clinical or daily living contexts; with at least one of these data categories, comprising BG levels (from Continuous Glucose Monitoring (CGM) or Self-Monitoring Blood Glucose (SMBG)), insulin, meal, or exercise information. Information from the selected publications was extracted taken into account the following characteristics:

- Study Information: This defines the study’s citation and year of publication;
- Data: This defines the type of diabetes, sample (number of participants, age range or average age and gender distribution) and source (collected, clinical trial, EHR or dataset);
- Prediction: This defines the application where the algorithm is being exploited. It can be short or mid-term predictions, nocturnal, postprandial or other;
- Algorithms: This defines the different approaches used to train the model;
- Input: This was defined to assess the inputs used to develop the algorithm. This includes BG, meal, insulin, exercise or others.

After a search and an eligibility review, 33 studies were included for data extraction and qualitative synthesis.

The reasoning models that fit our criteria are expert-systems with the ability to support patients on the decision-making. In this case, the authors did not filter works considering implementation platform or published date. For the reasoning models, we searched titles and abstracts considering the keywords: “expert-system diabetes” OR “expert system diabetes” OR “reasoning diabetes”. A careful review of all the titles and abstracts associated with this search was performed. To filter out non-pertinent studies the following inclusion criteria were applied: original studies, studies directed for management of diabetes type I containing user advice. We have obtained 50 results related to expert

²We added hypoglycemia to this article’s keywords.
systems and diabetes management in the initial search. From these we have considered 19 to fit our inclusion criteria. Information from the selected publications was extracted taken into account the following characteristics:

- **Algorithm:** This defines the different methods used by the given approach;
- **Input:** The input required by the given approach in order to function correctly;
- **Output:** Defines the application’s feedback to the users. It can be insulin recommendations, glycaemia read recommendations, generic recommendations or treatment recommendations.

### III. MODELS AND SYSTEMS FOR GLYCAEMIA PREDICTION

The majority of models described in this section aim to predict glycaemic values. The accuracy and time frame varies depending on the predictive model. Some of these works (Botwey et al., 2014; Fox et al., 2018; Mhaskar, Pereverzyev and Walt, 2017; Plis et al., 2014; Zarkogianni, K. et al., 2015) predict, classify and label glycaemic values. Others aim to predict hypoglycaemia events (Bertachi et al., 2018; D. Dave et al., 2020; Jensen et al., 2019; Reddy et al., 2019; Vehí et al., 2019).

BG prediction is the estimation of future BG values based on present and past inputs. For this, several approaches have been proposed by the scientific community: physiological models, data-based approaches, and a combination of both, the hybrid models (Hidalgo et al., 2017).

In the physiological model, the overall BG dynamic is usually characterised into: meal dynamics (Dalla Man, Rizza and Cobelli, 2007; Hovorka et al., 2004), insulin dynamics (Duke, 2010; Wilinska et al., 2005), exercise model (Vehí et al., 2019) and glucose dynamics (Duke, 2010; Lehmann and Deutsch, 1992; Tarín et al., 2005). These models require previous knowledge to set the physiological constants (Hidalgo et al., 2017; Novara et al., 2016).

The data-based models are in general more accurate (Novara et al., 2016). These models have been proposed using pattern recognition techniques and experimental data. However, there may be exceptions as shown in Mirshekarian et al. (2017).

The major challenge for the predictive models is related to the variable impact that the collected variables have on the glycaemia value. The effects of insulin intake, meals, physical activity and other events in glucose dynamics are different for every person (inter-subject variability) and even in the same person there are changes over time (intra-subject variability) (Faccioli et al., 2018). According to this, the models for BG can be categorised into two groups: individual-based models trained on an individual’s specific data, and population-based models trained on pooled data from many people expecting they will generalise well enough to allow them to be used in previously unseen individuals.

Despite the efforts in this area, no specific method provides total reliable event predictions, thus an increasing number of approaches have been proposed for inputs and techniques fusion in the hope to represent spatial and temporal input–output dependencies. The availability of personal devices and wearable devices allowed the data collection of several individual inputs provided by the user. Among them, we find CGM systems, smartphones, smartwatches, wristbands, among others. It allows the collection of real data on clinical or free-living context. Some studies have used simulated data (from virtual patients) using BG software simulators AIDA\(^3\) and UVAPadova\(^4\). CGM systems usually measure BG levels at a fixed instant time, e.g., every 3 or 5 minutes, as such, the majority of studies work with time-series approaches. Past reviews (Felizardo et al., 2021; Oviedo et al., 2017; Woldaregay et al., 2019) in this subject show that uni-variate approaches are commonly used predicting the future BG only based on past BG data. But these reviews also show that studies started to combine different data such as therapies, meal, exercise, and contextual information. Different datasets were used but few are accessibile, e.g., OhioT1DM (Marling and R. C. Bunescu, 2018) and DirectNet datasets\(^5\). There are several approaches for the predictive task, including Artificial Neural Networks (ANN), supervised learning, statistics or probabilistic models, auto-regressive models, evolutionary models, adaptive filter models, deep learning, hybrid, and ensemble. Table 1 shows some information about each study: year of publication, data information and prediction model. Most studies between 2014 and 2020 used ANN based models, deep learning, and ensemble models. Table 2 shows detailed information about the prediction model, inputs category and prediction outcome of ANN based models. ANN approaches are used due to its great capacity to model the various non-linear and non-stationary glucose dynamics. Several approaches of ANN are addressed, including extreme learning machine (ELM), jump neural networks (JNN), multi-layer perception (MLP), recurrent neural network (RNN), and self-organising map (SOM). As an emerging theory, ELM presents a better generalisation performance, a faster learning speed, a good performance in regression applications and in large datasets or multi-class application. According to Mirshekarian et al. (2017), ANN approaches, with gradient-based learning methods and back propagation, are difficult to train due to vanishing gradients, a problem that is often compounded by small datasets. So, some approaches start to use Long Short Term Memory (LSTM) units, which are not affected by the vanishing gradient problem, embedded into Deep Learning (DL) frameworks they can capture the complex dynamics system, particularly, when it is difficult to derive the mathematical expressions of the system. Table 2 show detailed information about the prediction model, inputs category and prediction outcome of DL based models.

Despite the good results and potentialities of ANN based and DL based approaches, some authors continue to use

---

\(3\) AIDA http://www.2aida.org/

\(4\) UVAPadova https://tegvirginia.com/software/t1dms/.

\(5\) DirectNet https://public.jaeb.org/datasets/diabetes.
### Table 1. Studies information, year, data and prediction model.

| Study                        | DM Type | Sample | Data Source                      | Prediction model | Category | Approach          |
|------------------------------|---------|--------|----------------------------------|------------------|----------|-------------------|
| Botwey et al. (2014)         | T1DM    | 25 participants, 17–70 years     | Collected (daily living) | Ensemble | (c)ARX+RNN+data fusion |
| Pla et al. (2014)            | T1DM    | 5 participants                   | Collected         | Ensemble | SVM+ARIMA          |
| E-I Georga et al. (2015)     | T1DM    | 15 participants                  | METABO dataset (daily living) | ANN     | KELM               |
| Zarkogianni, K. et al. (2015)| T1DM    | 10 participants, 42 years (7M/3F) | METABO dataset (daily living) | ANN     | SOM                |
| E-I Georga et al. (2015)     | T1DM    | 15 participants                  | METABO dataset (daily living) | Ensemble | Genetic Programming+RF |
| Zecchin et al. (2016)        | T1DM    | 15 participants                  | DIAvisor dataset (clinical context) | ANN     | JNN                |
| Mirshaharian et al. (2017)   | T1DM    | 10 participants                  | Collected         | Deep Learning (DL) | RNN using LSTM |
| Bhaskar, Povccczyov and Walt (2017) | T1DM    | 25 participants, <18 years         | DRENet dataset (clinical context) | DL      | Deep Network       |
| Ben Ali et al. (2018)        | T1DM    | 12 participants                  | Collected (daily living) | ANN     | ANN                |
| Fox et al. (2018)            | T1DM    | 40 participants                  | Collected (daily living) | ANN     | Sequential polynomial multi-output RNN |
| Bertachi et al. (2018)       | T1DM    | 6 participants, 40–60 years (3M/2F) | OhioT1DM dataset (daily living) | ANN     | ANN                |
| Hamdi et al. (2018)          | T1DM    | 12 participants                  | Collected (daily living) | Ensemble | SVR-Differential evolution |
| He et al. (2019)             | T1D/T1D | 112 participants, >55 years (40 M/5F) | Collected         | Ensemble | Sparse-group lasso based RNN |
| Li et al. (2019)             | T1DM    | 10 participants, 47 years and 6, 40–60 years (2M/4F) | ARCOID (both context) and OhioT1DM dataset (daily living) | DL      | dilated convolutional ANN |
| Aliberti et al. (2019)       | T1DM    | 451 participants, 8–25 years and >25 years (55F) | Clinical trial | DL      | LSTM network       |
| Dong et al. (2019)           | T1D/T1D | 80 participants                  | Collected         | Ensemble | Clustering based pre-process RNN |
| Chen, Tao and Wang (2019)    | T1DM    | 5 participants                   | DRENet dataset (clinical context) | ANN     | kernel ELM         |
| Reddy et al. (2019)          | T1DM    | 55 participants, 35 ≥ 6 years (18F/32M) | Collected (controlled exercise environment) | Supervised Learning (SL) | Random Forest (RF) |
| Jensen et al. (2019)         | T1DM    | 463 participants                 | Clinical trial (daily living) | SL      | linear discriminant function |
| De Rosa, Yacoub and Attini (2019) | T1D/T1D | 11 participants                  | Collected and OhioT1DM dataset (daily living) | DL      | pLSVM              |
| W. Wang, Tong and Yu (2020)  | T1D/T1D | 56 participants                  | RTGDM dataset (daily living) | Ensemble | VMD+improved PSO+LSTM |
| Alessandro Aliberti et al. (2020) | T1D    | 6 participants, 40–60 years (2M/4F) | OhioT1DM dataset (daily living) | DL      | LSTM ANN           |
| Allam et al. (2020)          | T1DM    | 12 participants, <18 years         | DRENet dataset (clinical context) | ANN     | MLP                |
| Mohrbi et al. (2020)         | T1DM    | 50 participants                  | Collected (daily living) | DL      | LSTM RNN           |
| Paron et al. (2020)          | T1DM    | 6 participants, 40–60 years (3M/4F) | OhioT1DM dataset (daily living) | Ensemble | Shallow ANN + Dropout |
| Gu, Dong and Prisciacc a (2020)| T1D    | 34 participants and 6 participants, 40–60 years (3M/4F) | Collected and OhioT1DM dataset (daily living) | DL      | LSTM+Neutral physiological encoder |
| Nemati et al. (2020)         | T1DM    | 6 participants, 40–60 years (2M/4F) | OhioT1DM dataset (daily living) | Ensemble | MLP+LSTM+PLSR        |
| Montazer et al. (2020)       | T1DM    | 18 participants                  | Collected (clinical context) | Ensemble | Global Seasonal Model (fuzzy approach) |
| Cappon et al. (2020)         | T1DM    | 6 participants, 40–60 years (2M/4F) | OhioT1DM dataset (daily living) | DL      | bidirectional LSTM |
| Contador et al. (2020)       | T1DM    | 10 participants                  | Collected (daily living) | Ensemble | Genetic programming+clustering |
| Veit et al. (2019)           | T1DM    | 10 participants, 41 years (6F/4M) | Collected and OhioT1DM dataset (daily living) | SL      | ANN and SVR        |
| D. Dave et al. (2020)        | T1DM    | 112 participants, 1–21 years (30F/82M) | Collected (daily living) | SL      | RF                |
| Kriventsov, Lindsey and Hayman (2020) | T1D    | 1200 participants and 6 participants, 40–60 years (2M/4F) | Collected (daily living) and OhioT1DM dataset (daily living) | Ensemble | boosted Tree+SVR       |
supervised learning (SL) approaches. Random Forest (RF) and Support vector machine (SVM) are commonly used for glucose concentration prediction (D. Dave et al., 2020; Reddy et al., 2019; Vehi et al., 2019). RF presents some advantages useful for this kind of predictions: reduce overfitting, flexible to both classification and regression problems and works well with both categorical and numeric attributes. SVMs also present interesting advantages for this task, e.g., the reliability of Support Vector Recursion (SVR) for predictions (Hamdi et al., 2018). Table 2 shows detailed information about the prediction model, inputs category and prediction outcome of SL-based models. Nevertheless, every prediction algorithm has its own advantages. So, sometimes it is necessary to combine different prediction methods to cover the disadvantages. Table 2 shows detailed information about the prediction model, inputs category and prediction outcome of ensemble approaches. In this category we find different approaches of ensembles. In order to address the complexity of factors affecting glucose response some studies (Contador et al., 2020; Dong et al., 2019; Montaser et al., 2020) used clustering associated with other kind of models to better characterise scenarios with similar responses. Other studies used regression models and auto-regressive models (Auto-regressive model with output correction (cARX) or Auto-Regressive Integrated Moving Average (ARIMA)) in combination with other models (Botwey et al., 2014; Fox et al., 2018; He et al., 2019; Montaser et al., 2020; Plis et al., 2014). He et al. (2019) used a sparse group lasso to mine the underlying causal features. Eleni I. Georga et al. (2015), Kriventsov, Lindsey and Hayeri (2020) and Pavan et al. (2020) used ensembles based on decision trees because this kind of ensemble handles higher dimensional data very well (Bagging Tree, Boosting Tree or RF). W. Wang, Tong and Yu (2020) used variational mode decomposition (VMD) to reduce non-stationarity of BG time series and the Particle Swarm Optimization (PSO) algorithm is used to optimise these LSTM parameters. Nemat et al. (2020) applied a stacked regression to enhance the performance of BG prediction. This technique uses predictions from several models (MLP, LSTM and Partial Least Squares Regression (PLSR)) as features to train a new model based on PLSR.

The feature extraction and feature selection are crucial techniques to obtain good and optimised prediction algorithms and to understand the effects of some inputs in the predictions in order to later try to reason about these effects. The meals content of individual diets and how carbohydrates affect BG is one of the basis of diabetes treatment. Proper exercise plays an important role in BG control and reduces the risk of cardiovascular events. Reasoning is targeted inference where experts, the conclusions obtained by these methods, can be even be used to better understand the user’s needs, and adapt the user’s current diabetes’ monitoring plan.

Expert knowledge is an ever-increasing necessity. In various areas such as engineering, finance, science and medicine, experts are a fundamental piece. As our base knowledge increases, the necessary expertise to handle this knowledge also increases. In some cases, teams of experts are needed to handle and work with a particular system. Expert knowledge is therefore an uttermost valuable asset. With today’s demand of experts, it is unreasonable to expect an expert to be perpetually available. Nonetheless, certain occurrences require the continuous attention of an expert.

Expert systems are automatic consulting systems (Akerkar and Sajja, 2010) that attempt to emulate an expert’s decision-making (Todd and Group, 1992). Expert systems have been implemented in numerous areas from agriculture (Elsharif and Abu-Naser, 2019; Al-Qumboz, Mohammed and Abu-Naser, 2019) to computer security (Lunt and Jagannathan, 1988) and health (McAndrew et al., 1996; Velicer and Prochaska, 1999). In the scope of diabetes, expert-systems have been, for a long time, a useful tool to interpret data and retrieve information. For instance, the SESAM-DIABETE project, an interactive educational expert-system capable of providing personalised advice and therapeutic recommendations for insulin diabetic patients was available in 1989 (Levy, Ferrand and Chirat, 1989). Table 4 shows details about different studies: the used algorithm, the required input, and the output.

Generally, expert-systems related to diabetes focus on bolus adjustments. These systems, evaluate the user’s data, trace the user’s profile, calculate and recommend insulin dosage adjustments (Ambrosiadou, Alevizos and Ziakas, 1993; Ambrosiadou, Goulis and Pappas, 1996; Cosenza,
Projects like the DIABETES (Ambrosiadou, Goulis and Pappas, 1996) system can even explain, to users, the therapeutic recommendations given. The treatment recommendations made by the system were evaluated against the recommendations of an expert. The results showed that in 22% of the cases there was a full disagreement; 31% of the cases had one parameter in disagreement and finally, in 47% of the cases the medical expert fully confirmed the expert system’s conclusions. The authors explain that in some cases, a conclusion that has resulted in a total disagreement may not be wrong, in some cases the system suggests a correct, but more complex route that diverges from the more direct expert’s approach. Other expert-system approaches, related to diabetes, can also advise basal rate adjustments (Reinke, Price and Galley, 2011) and advise changes to meal and insulin administration scheduling (Lehmann, T. Deutsch et al., 1994).

Less frequent, there are approaches that aid users to better their glycaemic management, giving general advice, which is usually abstract or related to meal, exercise and glucose value test guidelines (Angelides, 2013). Advising in the diabetes context is a complex task, since it will influence the user’s health. Possibly, because of this, most approaches avoid specifying what the user should do, instead, the application will show the user general best practices as advice (Al-Ghamdi et al., 2011; Hashemi, 2012; Mbogho, J. Dave and Makhubele, 2013; McCausland et al., 1999). The project 4 Diabetes Support System (Marling, Wiley et al., 2011) tries a different approach. This system is a case-based approach to diabetes self-management. In this project several problems related to diabetes are identified and defined as cases. Cases are constituted by an identified problem, a determined solution to the problem and a verification of the problem’s resolution. This case is then translated to logical rules. The created rules identify the problem, apply the determined solution and verify its success. In order to update and evolve this system, the impact of the solution is verified. If the known solution does not solve the identified problem or if a better solution is uncovered, then it is possible to reach the case and update its parameters to translates the new, better, solution. In this manner, it is possible to advise diabetics with a good level of confidence. This project was developed during seven years and had three clinical research studies (Marling, Wiley et al., 2011). The project MyDiabetes (Machado et al., 2017)\(^6\) is a mobile application that contains an expert-system. This system did not follow a case-based approach, instead, the authors translated existing medical rules and guidelines to logical rules, that compose the expert-system. This approach takes advantage of the records introduced by the user in the mobile application, to evaluate the user’s state and advise accordingly. Although there are important contributions made by the different presented projects, there is a lack of results on the impact these systems have on glycaemic control.

A limitation regular expert systems have is their static nature. The rules and knowledge integrated in the expert system are not dynamic and can only be changed after a software update. Considering the learning abilities of data-mining and machine-learning, these systems, if integrated within an expert system could give it the opportunity to adapt and better the knowledge contained in it. The “4 diabetes project” (Marling, Wiley et al., 2011) has two branches dedicated to the use of data-mining for prediction. During the project’s second study, a common diabetes problem was addressed, glycaemic variability. This blood control problem is linked to hypoglycaemia unawareness and to oxidative stress which leads to long-term diabetic complications. The system can identify twelve types of glycaemic variability, using multiple different rules. It was not possible to create a generic rule capable of identifying this problem. The authors refer that there are numerous metrics for glycaemic variability characterisation, but there is no consensus on a technique to be used in clinical practice. Still, for physicians, the identification of this problem becomes trivial when in the presence of a BG plot. In order to reach a global method for identification of glycaemic variability, the authors decided to apply machine learning. To create a system capable of recognising glycaemic variability, the authors considered the quantifiable aspects of this problem. The metric chosen to quantify the glycaemic variability was the Mean Amplitude of Glycaemic Excursion (MAGE). This metric captures the distance between the local maximum and minimum of a BG plot. Considering this metric insufficient, the authors devised two other metrics: the distance travelled and the excursion frequency. Distance travelled captures the overall daily fluctuations, and excursion frequency counts the number of significant glucose deviations in a day. Two physicians, also authors in this work, classified BG plots as excessively variable or not, based on their expert knowledge. The same plots were also scored by MAGE and the two other metrics. The classifications obtained for 218 BG plots were then used to train multiple machine learning algorithms. Among the tested algorithms, the naive Bayes classifier used was able to match 85% of the physicians’ ratings.

The “4 Diabetes Support System” also addressed glycaemic value prediction. To achieve this goal, SVR was used. The choice of SVR is bound to its ability of incorporating contextual features, without the assumption of feature independence. The results obtained showed that SVR is capable of achieving better results than a baseline model that uses the present BG as the prediction for future values.

These prediction systems’ results, if integrated in an expert-system, could be used to prevent future occurrences, but also as input data. For the expert system, knowing that certain occurrences are reasonably believed to happen, can be even more meaningful than simple data. In the case of the referred systems, the expert-system would be able to obtain data about glycaemic variability, and a projection of future glycaemic

---

\(^6\)MyDiabetes https://mydiabetes.dcc.fc.up.pt/ (in Portuguese).
values. With this information, the system could be pro-active and better advise the user. Additionally, the system could use this information to refine variables such as insulin sensitivity or carbohydrate ratios.

V. DISCUSSION

The field of prediction models and reasoning applied to diabetes is rich and varied in approaches. Considering the described research, in general, most options tend to focus on aiding, or solving a particular diabetes related issue. Only a few, such as the 4diabetes project attempt to include different modules that encompass different diabetes related issues. The prediction models approaches contribute to identify the features that affect the patterns associated with risk of future events.

A. PREDICTION MODELS

Prediction models have made significant progress in transforming available data and clinical information into valuable new knowledge allowing new patterns discovery and what-if scenarios definition. These new findings can give some reasoning about the effects of concurrent actions. The distribution of inputs presented in the tables of the different approaches shows that several papers combined features from different types of input. However, there are some studies that use BG alone due to inter-subject variability in variables. Therefore, we highlight some studies that use different sources for feature and contextual information integration. Features based on BG in the last 30 minutes is clear to have a PH of 30 and 60 minutes (Alfian et al., 2020; E I Georgia et al., 2015; Eleni I. Georgia et al., 2015). The contribution of other features, like meal, insulin or exercise, are lower but not insignificant (Eleni I. Georga et al., 2015).

Traditional standalone expert-systems for diabetes management. Few studies (Marling, Wiley et al., 2011; Reddy et al., 2019) address reasoning or explanations about predictions results. This is crucial to understand how other features like insulin, meal and exercise influence the BG dynamics and their effects on prediction models. From selected studies, Reddy et al. (2019) present a rule for recommendation during aerobic exercise, which they identified after the prediction during physical exercise. This recommendation consists of: if the glucose is below 180 at the beginning of the physical exercise and the heart rate above 120 during the exercise, there is risk of hypoglycaemia. We will discuss reasoning and its importance in the next section.

B. REASONING APPROACHES

Recent approaches to this topic utilise data-mining and machine learning algorithms, more autonomous and dynamic to create modules that can then be used to advise diabetic patients. These approaches are usually specialised, attempting to tackle specific diabetes related issues. Regarding the approaches presented previously, they focus on two topics: bolus adjustments (Ambrosiadou, Alevizos and Ziakas, 1993; Ambrosiadou, Goulis and Pappas, 1996; Cosenza, 2012; El Fathi et al., 2020; Fortwaengler et al., 2013; Lehmann, T. Deutsch et al., 1994; Rudi and Celler, 2006) and glycaemic advice (Angelides, 2013; Al-Ghamdi et al., 2011; Hashemi, 2012; Mbogho, J. Dave and Makhubele, 2013; McCausland et al., 1999) for better glycaemic control. Most do not have concrete evaluations of the impact of their approach. Nonetheless, the ones that disclose their results, prove that these systems have a positive impact on the user’s diabetes management.

The “4 diabetes project” (Marling, R. Bunescu et al., 2012; Marling, Wiley et al., 2011), in contrast, possesses reasoning models and prediction models. The system is composed of a case-based reasoning system for glycaemic control and depending on what PH (30 or 60 minutes) is aimed for. For one patient the combination of features is the same for the two PH (CGM, insulin and reported meals). In Alfian et al. (2020) the contribution of time domain features shows potentialities for predictions. Also, the use of time of day includes some novel features highly connected to glucose dynamics (Eleni I. Georgia et al., 2015). However, in He et al. (2019), the results show that meal and insulin intake and time provide more dominant causal correlations than sleep and exercise on BG inference. In Jensen et al. (2019) the feature subset with the highest results is reached using four features: slope of linear regression and minimum value of the evening (9–12 pm) before the event, minimum values of the three nights before the event and body mass index at baseline. Based on selection methods, D. Dave et al. (2020) show the importance of contextual features such as hour and day when observation was made. Few studies (Marling, Wiley et al., 2011; Reddy et al., 2019) address reasoning or explanations about predictions results. This is crucial to understand how other features like insulin, meal and exercise influence the BG dynamics and their effects on prediction models. From selected studies, Reddy et al. (2019) present a rule for recommendation during aerobic exercise, which they identified after the prediction during physical exercise. This recommendation consists of: if the glucose is below 180 at the beginning of the physical exercise and the heart rate above 120 during the exercise, there is risk of hypoglycaemia. We will discuss reasoning and its importance in the next section.
therapeutic adjustments, a glycaemic variability classifier, and a blood-glucose prediction component. The different modules were not tested as a unit. Marling, R. Bunescu et al. (2012) report accuracy levels of 77.5% in a first test, and 97.9% in a second test, for the case-based system. The glycaemic variability classifier, the best classifier, also evaluated in two tests, obtained a 93.8% accuracy. Finally, the prediction model, being a work-in-progress, was only described, not mentioning practical results. Nonetheless, as the authors convey, this module, once available, could be valuable to take preventative actions.

Reasoning modules can be accurate and beneficial to detect and act on particular occurrences. Despite this, diabetes management consists of more than singular occurrences. The authors believe that, in order to help diabetic patients to better manage their diabetes, it is necessary to combine both reasoning and prediction in a more complete approach.

C. IMPROVE AND COMBINE APPROACHES

In our view, what is needed is the combination of glycaemia prediction and explaining the potential reason for the prediction of a dangerous event.

While managing diabetes, diabetic patients should avoid episodes of hypoglycaemia or hyperglycaemia. Hyperglycaemia episodes on the long term can damage the nerves, blood vessels, tissues, and even organs. Hypoglycaemia is significantly more dangerous on the short-term. Reaching this glycaemic state, in severe cases, can lead to loss of consciousness, seizures and ultimately to death. Given its severity, it is important to not only predict hypoglycaemic episodes, but also to understand the actions that led to this consequence. Uncovering the causes of hypoglycaemia for a given user, can be the first step to educate and ultimately change the user’s routine for the better. To achieve this, the authors propose combining a predictive module with a reasoning module.

Our current reasoning component is a rule-based system, in Prolog, composed of logical rules, obtained from medical protocols and guidelines. The current system has access to the MyDiabetes app’s database and, after each new record, evaluates the user’s current situation. If it concludes that the user requires guidance, it sends an advice through the mobile app as a notification, indicating the recommended medical approach for the current occurrence.

Our current prediction component, for hypoglycemia events, uses discrete information fusion and a predictive model consensus. This component uses as data the glucose levels, the insulin therapy, meals, exercises, and other information related to time-dependent information, for example, the record’s date and time, the type of meal, and the glucose level variability, considering the previous records. Predictive models are trained and tested using machine learning. The consensus decision of the predictive models is given in a personalised way to the patient, indicating the risk of a hypoglycemic event that may occur within the next 24 hours (window).

Our goal is to connect both components. The predictive model receives data from users and detects possible future hypoglycaemia occurrences. Then it supplies this information to the reasoning system that, knowing that a hypoglycaemia will occur, searches the user’s data for possible motives for this occurrence. The motives can be simple daily actions such as exercise or incorrect insulin intake, or connected to deeper patterns related to the day of the week and the user’s routine, that culminates in a hypoglycaemic occurrence.

We aim to develop this approach in the MyDiabetes smartphone application. Using a mobile application not only facilitates the access to the user’s data, but also provides a convenient mean to alert and advice the user.

The first steps will involve adapting the prediction work done to run on a mobile platform. The proposed architecture is shown in Fig. 1. The offline trained model would run online on the smartphone, in the machine learning system. Based on the input data it will predict potential hypoglycaemias and inform the reasoning system. The reasoning system, based on the available data, will warn the user providing advice and a possible reason for the hypoglycaemia. The current reasoning engine (Machado et al., 2017) is to be tuned to use the more relevant variables for explaining the future hypoglycaemia result.

VI. CONCLUSION

In this article we reviewed the work being done for glycaemia prediction and for reasoning in diabetes management for patients. As discussed, there is still a need to improve the predictions, to make them more useful within pragmatic horizon times and accuracy. Regarding reasoning systems they are still lacking in its usage for diabetes management.

Our focus is on type I diabetics, as there is more information being collected by these patients than type II, and they are in need of a more permanent advising. Type I disease management has several decisions to be taken along the day, whereas for type II this decision taking is less stringent.

7 Under review for publication and patent being submitted.
In some cases diabetics type II are treated with type I methodologies, namely when the disease control deteriorates. In those cases, the proposed approach can also be applied to them.

We briefly propose an approach to incorporate prediction and reasoning, to provide a more whole counselling to patients. They would be able to, using their regular smartphone, receive warnings regarding future episodes and explanations with possible reasons that lead to those events. This future work aims to not only interconnect both approaches but also to improve the predictions and the accuracy of the reasoning in the provided advice.

References

Akerkar, R. and P. Sajja (2010). Knowledge-Based Systems. Jones & Bartlett Learning. ISBN: 9781449612948.

Alfian, Ganjar et al. (2020). ‘Blood glucose prediction model for type 1 diabetes based on artificial neural network with time-domain features’ In: Biocybernetics and Biomedical Engineering 40.4, pp. 1586–1599. ISSN: 02085216. DOI: 10.1016/j.bbe.2020.10.004.

Aliberti, A et al. (2019). ‘A Multi-Patient Data-Driven Approach to Blood Glucose Prediction’. In: IEEE Access 7, pp. 69311–69325. DOI: 10.1109/ACCESS.2019.2919184.

Aliberti, Alessandro et al. (2020). ‘Data driven patient-specialized neural networks for blood glucose prediction’. In: 2020 IEEE International Conference on Multimedia and Expo Workshops, ICMEW 2020, pp. 1–6. DOI: 10.1109/ICMEW46912.2020.9105950.

Ambrosiadou, B. V., M. Alevizos and G. Ziakas (1993). ‘Decision support in diabetes management for optimal glycaemic control by insulin administration’. In: Proceedings of IEEE Systems Man and Cybernetics Conference - SMC. Vol. 5, 391–396 vol.5. DOI: 10.1109/ICSMC.1993.390883.

Ambrosiadou, B. V., D. G. Goulis and C. Pappas (1996). ‘Clinical evaluation of the DIABETES expert system for decision support by multiple regimen insulin dose adjustment’. In: Computer Methods and Programs in Biomedicine 49.1, pp. 105–115. ISBN: 01692607. DOI: 10.1016/0169-2607(95)01711-9.

Angelides, Kimon J (July 2013). Method and Device for Personalized Interactive Monitoring for Diabetes. US Patent App. 13/793,208.

Ben Ali, Jaouther et al. (2018). ‘Continuous blood glucose level prediction of Type 1 Diabetes based on Artificial Neural Network’. In: Biocybernetics and Biomedical Engineering 38.4, pp. 828–840. ISSN: 02085216. DOI: 10.1016/j.bbe.2018.06.005.

Bertachi, Arthur et al. (2018). ‘Prediction of blood glucose levels and nocturnal hypoglycemia using physiological models and artificial neural networks’. In: KHD® IJCAI, pp. 85–90.

Botway, Ransford Henry et al. (2014). ‘Multi-model data fusion to improve an early warning system for hypoglycemia events’. In: 2014 36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBC 2014, pp. 4843–4846. ISSN: 1557-170X. DOI: 10.1109/EMBC.2014.6944708.

Cappon, Giacomo et al. (2020). ‘A personalized and interpretable deep learning based approach to predict blood glucose concentration in type 1 diabetes’. In: CEUR Workshop Proceedings 2675, pp. 75–79. ISSN: 16130073.

Chen, Xiaoyu, Jianyong Tuo and Youqing Wang (2019). ‘A prediction method for blood glucose based on grey wolf optimization evolving kernel extreme learning machine’. In: Chinese Control Conference, CCC 2019-July, pp. 3000–3005. ISSN: 21612927. DOI: 10.23919/ChiCC.2019.8866210.

Contador, Sergio et al. (2020). ‘Profiled glucose forecasting using genetic programming and clustering’. In: Proceedings of the ACM Symposium on Applied Computing, pp. 529–536. DOI: 10.1145/3341105.3374003.

Cosenza, Bartolomeo (2012). ‘Off-line control of the post-prandial glycemia in type 1 diabetes patients by a fuzzy logic decision support’. In: Expert Systems with Applications 39.12, pp. 10693–10699. ISSN: 0957-4174. DOI: 10.1016/j.eswa.2012.02.198.

Dalla Man, Chiara, Robert A Rizza and Claudio Cobelli (2007). ‘Meal Simulation of Glucose-Insulin System’. In: IEEE Transactions on Biomedical Engineering 54.10, pp. 1–33.

Dave, Darpit et al. (2020). ‘Feature-Based Machine Learning Model for Real-Time Hypoglycemia Prediction’. In: Journal of Diabetes Science and Technology. DOI: 10.1177/1933296820922622.

De Bois, Maxime, Mounim A El Yacoubi and Mehdi Ammi (2019). ‘Prediction-coherent LSTM-based recurrent neural network for safer glucose predictions in diabetic people’. In: International Conference on Neural Information Processing, pp. 510–521. DOI: 10.1007/978-3-030-36718-3_43.

Dong, Y et al. (2019). ‘Clu-RNN: A New RNN Based Approach to Diabetic Blood Glucose Prediction’. In: 2019 IEEE 7th International Conference on Bioinformatics and Computational Biology (ICBCB), pp. 50–55. DOI: 10.1109/ICBCB.2019.8854670.

Duke, David L (2010). ‘Intelligent diabetes assistant: A telemedicine system for modeling and managing blood glucose’. PhD thesis. Carnegie Mellon University. ISBN: 9788112412280.

El Fathi, A. et al. (2020). ‘A Model-Based Insulin Dose Optimization Algorithm for People with Type 1 Diabetes on Multiple Daily Injections Therapy’. In: IEEE Transactions on Biomedical Engineering, pp. 1–1. DOI: 10.1109/TBME.2020.3023555.

Elsharif, Abeer A and Sammy S Abu-Naser (2019). ‘An Expert System for Diagnosing Sugarcane Diseases’. In: International Journal of Academic Engineering Research (IJEAR) 3.3, pp. 19–27.

Faccioli, S et al. (2018). ‘Black-box Model Identification of Physical Activity in Type-1 Diabetes Patients’. In:
2018 40th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), pp. 3910–3913. doi: 10.1109/EMBC.2018.8513378.

Felixardo, Virginie et al. (2021). ‘Data-based algorithms and models using diabetics real data for blood glucose and hypoglycaemia prediction – A systematic literature review’. In: Artificial Intelligence in Medicine 118. DOI: 10.1016/j.artmed.2021.102120.

Fortwaengler, K. et al. (2013). ‘PDB37 - Lower Short-Term Health Care Cost with the Accu-Chek Aviva Expert System in Multiple Daily Insulin Injection (MDI) Treated Diabetes Patients - Learnings from the Automated Bolus Advisor Control and Usability Study (ABACUS)’. In: Value in Health 16.7. ISPOR 16th Annual European Congress and 4th Latin America Conference Research Abstracts, A437. ISSN: 1098-3015. DOI: 10.1016/j.jval.2013.08.658.

Fox, Ian et al. (2018). ‘Deep multi-output forecasting learning to accurately predict blood glucose trajectories’. In: Proceedings of the ACM SIGKDD International Conference on Knowledge Discovery and Data Mining, pp. 1387–1395. DOI: 10.1145/3219819.3220102. arXiv: 1806.05357.

Georga, Eleni I. et al. (2015). ‘Online prediction of glucose concentration in type 1 diabetes using extreme learning machines’. In: 2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), pp. 3262–3265. DOI: 10.1109/EMBC.2015.7319088.

Georga, Eleni I. et al. (2015). ‘Evaluation of short-term predictors of glucose concentration in type 1 diabetes combining feature ranking with regression models’. In: Medical and Biological Engineering and Computing 53.12, pp. 1305–1318. ISSN: 17410444. DOI: 10.1007/s11517-015-1263-1.

Al-Ghamdi, Dr Abdullah Al-Malaise et al. (2011). ‘An expert system of determining diabetes treatment based on cloud computing platforms’. In: IJCSIT International Journal of Computer Science and Information Technologies 2.5.

Gu, Kang, Ruoqi Dang and Temiloluwa Prioleau (2020). ‘Neural Physiological Model: A Simple Module for Blood Glucose Prediction’. In: Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS 2020-July, pp. 5476–5481. ISSN: 1557170X. DOI: 10.1109/EMBC44109.2020.9176004.

Hamdi, Takoua et al. (2018). ‘Accurate prediction of continuous blood glucose based on support vector regression and differential evolution algorithm’. In: Biocybernetics and Biomedical Engineering 38.2, pp. 362–372. ISSN: 02085216. DOI: 10.1016/j.bbe.2018.02.005.

Hashemi, Baran (2012). ‘An Approach for Recommendations in Self Management of Diabetes based on Expert System’. In: International Journal of Computer Applications 53.14, pp. 975–8887. ISSN: 09758887. DOI: 10.5120/68487-2431.

Hayes-Roth, F., D. Waterman and D. Lenat (Jan. 1984). Building expert systems. Addison-Wesley Longman Publishing Co.

He, M et al. (2019). ‘CausalBG: Causal Recurrent Neural Network for the Blood Glucose Inference with IoT Platform’. In: IEEE Internet of Things Journal, p. 1. DOI: 10.1109/JIOT.2019.2946693.

Hidalgo, J. Ignacio et al. (2017). ‘Data Based Prediction of Blood Glucose Concentrations Using Evolutionary Methods’. In: Journal of Medical Systems 41.9. ISSN: 1573689X. DOI: 10.1007/s10916-017-0788-2.

Hovorka, Roman et al. (2004). ‘Non-linear model predictive control of glucose concentration in subjects with type 1 diabetes’. In: Physiological Measurement. DOI: 10.1088/0967-3334/25/4/010.

International Diabetes Federation (2019). IDF Diabetes Atlas. 9th edn. Brussels. Available at: https://www.diabetesatlas.org, Accessed 2021-06. Belgium.

Jensen, Morten H. et al. (2019). ‘Prediction of Nocturnal Hypoglycaemia From Continuous Glucose Monitoring Data in People With Type 1 Diabetes: A Proof-of-Concept Study’. In: Journal of Diabetes Science and Technology 14.2, pp. 250–256. ISSN: 19322968. DOI: 10.1177/1932296819868727.

Kriventsov, Stan, Alexander Lindsey and Amir Hayeri (2020). ‘The diabits app for smartphone assisted predictive monitoring of glycemia in patients with diabetes: Retrospective observational study’. In: JMIR Diabetes 5.3, pp. 1–14. ISSN: 23714379. DOI: 10.2196/18660.

Lehmann, E.D. and T Deutsch (1992). ‘A physiological model of glucose-insulin interaction in type 1 diabetes mellitus’. In: Journal of Biomedical Engineering 14, pp. 235–242.

Lehmann, E.D., T. Deutsch et al. (1994). ‘Combining rule-based reasoning and mathematical modelling in diabetes care’. In: Artificial Intelligence in Medicine 6.2, pp. 137–160. ISSN: 0933-3657. DOI: 10.1016/0933-3657(94)90042-6.

Levy, M., P. Ferrand and V. Chirat (Oct. 1989). ‘SESAM-DIABETE, an expert system for insulin-requiring diabetic patient education’. In: Computers and biomedical research, an international journal 22.5, pp. 442–453. ISSN: 0010-4809. DOI: 10.1016/0010-4809(89)90037-2.

Li, K et al. (2019). ‘GluNet: A Deep Learning Framework For Accurate Glucose Forecasting’. In: IEEE Journal of Biomedical and Health Informatics, p. 1. DOI: 10.1109/JBHI.2019.2931842.

Lunt, Teresa F and R Jagannathan (1988). ‘A prototype real-time intrusion-detection expert system.’ In: IEEE Symposium on Security and Privacy. Vol. 59. Oakland, CA, USA.

Machado, D. et al. (July 2017). ‘Managing Diabetes: counselling supported by user data in a mobile platform’. In: RuleML+RR: International Joint Conference on Rules and Reasoning. Vol. 1875.
Marling, Cindy, Razvan Bunescu et al. (2012). ‘System Overview: The 4 Diabetes Support System’. In: Workshop Proceedings of the Twentieth International Conference on Case-Based Reasoning, pp. 81–86.

Marling, Cindy and Razvan C Bunescu (2018). ‘The OhioT1DM dataset for blood glucose level prediction’. In: KHD@ IJCAI.

Marling, Cindy, Matthew Wiley et al. (2011). ‘The 4 diabetes support system: A case study in CBR research and development’. In: Lecture Notes in Computer Science (including subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics) 6880 LNAI, pp. 137–150. ISSN: 03029743. DOI: 10.1007/978-3-642-23291-6_12.

Mbogho, Audrey, Joel Dave and Kulani Makhubele (2013). ‘Diabetes advisor—a medical expert system for diabetes management’. In: International Conference on e-Infrastructure and e-Services for Developing Countries. Springer, pp. 140–144. DOI: 10.1007/978-3-319-08368-1_16.

McAndrew, Peter D. et al. (May 1996). Expert system for providing interactive assistance in solving problems such as health care management. US Patent 5,517,405.

McCausland, L. et al. (1999). ‘An adaptive expert system for blood glucose control in type 1 diabetes mellitus’. In: Proceedings of the First Joint BMES/EMBS Conference. 1999 IEEE Engineering in Medicine and Biology 21st Annual Conference and the 1999 Annual Fall Meeting of the Biomedical Engineering Society (Cat. N. Vol. 2. 1209. DOI: 10.1109/IEMBS.1999.804375.

Mhaskar, Hrushikesh N., Sergei V. Pereverzyev and Maria Reddy, Ravi et al. (2019). ‘Prediction of Hypoglycemia During Aerobic Exercise in Adults With Type 1 Diabetes’. In: Journal of Diabetes Science and Technology 13.5, pp. 919–927. ISSN: 19322968. DOI: 10.1177 / 1932296818823792.

Reinke, Robert E., John F. Price and Paul J. Galley (May 2011). Diabetes health management systems and methods. US Patent App. 12/622,520.

Rudi, Rudi and Branko G Celler (2006). ‘Design and implementation of expert telemedicine system for diabetes management at home’. In: 2006 International Conference on Biomedical and Pharmaceutical Engineering. IEEE, pp. 595–599. DOI: 10.1109/ICBPE.2006.348664.

Tarín, C et al. (2005). ‘Comprehensive Pharmacokinetic Model of Insulin Glargine and Other Insulin Formulations’. In: IEEE Transactions on Biomedical Engineering 52.12, pp. 1994–2005.

Todd, B.S. and Oxford University Computing Laboratory. Programming Research Group (1992). An Introduction to Expert Systems. An Introduction to Expert Systems n.º 95. Oxford University Computing Laboratory, Programming Research Group. ISBN: 9780902928732.

Velicer, Wayne F and James O Prochaska (1999). ‘An expert system intervention for smoking cessation’. In: Patient education and counseling 36.2, pp. 119–129.

Wang, Wenbo, Meng Tong and Min Yu (2020). ‘Blood Glucose Prediction with VMD and LSTM Optimized by Improved Particle Swarm Optimization’. In: IEEE Access 8, pp. 217908–217916. ISSN: 21693536. DOI: 10.1109/ACCESS.2020.3041355.
Wilinska, Małgorzata E. et al. (2005). ‘Insulin kinetics in type-1 diabetes: Continuous and bolus delivery of rapid acting insulin’. In: IEEE Transactions on Biomedical Engineering. ISSN: 00189294. DOI: 10.1109/TBME.2004.839639.

Woldaregay, Ashenafi Zebene et al. (2019). Data-driven modeling and prediction of blood glucose dynamics: Machine learning applications in type 1 diabetes. DOI: 10.1016/j.artmed.2019.07.007.

Wos, Larry et al. (1984). Automated Reasoning: Introduction and Applications. Prentice Hall Professional Technical Reference. ISBN: 0130544469.

Zarkogianni, K. et al. (2015). ‘Comparative assessment of glucose prediction models for patients with type 1 diabetes mellitus applying sensors for glucose and physical activity monitoring’. In: Medical and Biological Engineering and Computing 53:12, pp. 1333–1343. ISSN: 17410444. DOI: 10.1007/s11517-015-1320-9.

Zecchin, Chiara et al. (2016). ‘How much is short-term glucose prediction in type 1 diabetes improved by adding insulin delivery and meal content information to CGM data? A proof-of-concept study’. In: Journal of Diabetes Science and Technology 10:3, pp. 1149–1160. ISSN: 19322968. DOI: 10.1177/1932296816654161.

NUNO M. GARCIA holds a PhD in Computer Science Engineering from the Universidade da Beira Interior (UBI, Covilhã, Portugal) (2008) and is a 5-year B.Sc. in Mathematics / Informatics (Hons.) also from UBI (1999-2004). He was an entrepreneur (1988-2004), member of the Research Team at Siemens SA (2004-2007) and Nokia Siemens SA (2007-2008), and Head of Research at PLUX SA (2008-2010). Currently, serving as Vice Dean of the Faculty of Engineering at UBI (2018-), he is an Associate Professor with Habilitation at the Computer Science Department at UBI (2010) and Invited Associate Professor at the Universidade Lusófona de Humanidades e Tecnologias (Lisbon, Portugal, 2010-). He was the founder and is a researcher of the Assisted Living Computing and Telecommunications Laboratory (ALLab, 2010), a research group within the Instituto de Telecomunicações at UBI. He was also co-founder and is Chair of the Executive Council of the BSAFE LAB — Law enforcement, Justice and Public Safety Research and Technology Transfer Laboratory, a multidisciplinary research laboratory in UBI (2015). His main interests include Next-Generation Networks, predictive algorithms for healthcare and well-being, distributed and cooperative algorithms, and the battle for a Free and Open Internet.

NUNO POMBO is an Assistant Professor at University of Beira Interior (UBI), Covilhã, Portugal. His current research interests include: information systems (with special focus on clinical decision support systems), data fusion, artificial intelligence, and software. He is the coordinator of the Assisted Living Computing and Telecommunication Laboratory (ALLab) at UBI. He is also member of BSAFE Lab, and Instituto de Telecomunicações — IT at UBI.

PEDRO BRANDÃO is an assistant professor at the Computer Science Department of the School of Sciences in the University of Porto. He obtained his Ph.D. degree at the Computer Laboratory, University of Cambridge under the topic of Body Sensor Networks. The PhD was supported by a scholarship from the Fundação para a Ciência e Tecnologia of Portugal. I did my diploma and M.Sc. (ECE) at the Engineering School of the University of Porto. He has worked in Research at IT-Aveiro, PT Inovação (now Altice Labs), INESC-Porto, LIACC and since 2007 in IT-Porto. During this time he worked in identity management, communication networks, middleware development and currently on ad-hoc wireless networks for sensors/actuators and protocols for these networks; medical informatics and mHealth; and network security. He has participated in several national and international projects (DAIDALOS, Future Cities, Future Health, VR2Market, NanoSTIMA, etc.); where in some there was development of prototypes (app for diabetes management, health kiosk, ad-hoc network for smartphones).
Table 2. Algorithms, inputs and prediction outcome.

| Approach         | Study                              | Algorithm                                                                 | Inputs | Predict. Outcome |
|------------------|------------------------------------|---------------------------------------------------------------------------|--------|------------------|
|                  |                                    |                                                                           | BG     | I                | CHO/M | PA | P |                      |                      |                  |
| ANN-Based        | E I Giorgia et al. (2015)           | ELM, kernel ELM, online sequential ELM and online sequential ELM kernels. | x      | x                | x      |    |    | Short term           |                      |                  |
|                  | Zakharenko, K. et al. (2019)        | Neural fuzzy network (seven layers) using a gradient-based algorithm with an adaptive learning rate; activation function: tanh; membership function: Gaussian function. | x      |                  |        |    |    | Short term           |                      |                  |
|                  | Zechin et al. (2010)                | JNN that is a feedforward neural network with inputs directly connected to both the first hidden layer and the output layer. | x      | x                |        |    |    | Nocturnal             |                      |                  |
|                  | Zechin et al. (2010)                | JNN that is a feedforward neural network with inputs directly connected to both the first hidden layer and the output layer. | x      |                  |        |    |    | Nocturnal             |                      |                  |
|                  | Bai, Xu et al. (2019)               | ANN using algorithm: Least-squares-Quadratic. Input activation function: tanh; output activation function: linear function. | x      |                  |        |    |    | Short term           |                      |                  |
|                  | Bellaske et al. (2019)              | Eight-layer network using a hyperbolic tangent as hidden layer activation model and linear function as output layer activation, the training algorithm used was Levenberg-Marquardt. | x      |                  |        |    |    | Short term           |                      |                  |
|                  | Bellaske et al. (2019)              | Eight-layer network using a hyperbolic tangent as hidden layer activation model and linear function as output layer activation, the training algorithm used was Levenberg-Marquardt. | x      |                  |        |    |    | Short term           |                      |                  |
|                  | Chao, Tao and Y. Wang (2019)        | Kernel ELM combined with gray wolf optimization                          | x      |                  |        |    |    | Short term           |                      |                  |
|                  | Alireza et al. (2020)               | MLP using a grid search algorithm to select the first two parameters: two-hidden layer network with 100 neurons each; activation function: rectified linear unit (ReLU); weight optimization: Adam. | x      |                  |        |    |    | Short term           |                      |                  |
|                  | Vito et al. (2018)                  | ANN-based model with adaptive synthetic sampling algorithm; 6-hour window. | x      | x                | x      |    |    | Nocturnal             |                      |                  |
|                  | Minshakoum et al. (2017)            | RNN architecture that uses a single LSTM layer in the hidden layer, with 5 nodes. | x      | x                | x      |    |    | Short term           |                      |                  |
|                  | Mickey, Peterson and Wahl (2017)    | Semi-supervised deep learning model network with a judge predicted based on the function approximation on data defined manifolds, using diffusion polynomials. | x      |                  |        |    |    | Short term           |                      |                  |
|                  | Li et al. (2019)                    | GENet architecture, based on tree-layer related convolutional neural network. For the first three layers, the hidden units are set to 32, while the top two layers have 64 neurons. The sliding window with a size of 16 time-steps. | x      | x                |        |    |    | Short term           |                      |                  |
|                  | Abisemiri et al. (2019)             | LSTM network consisted of a layer of 30 LSTM units and a single output layer, with a number of units equal to the future glucose samples that need to be predicted. | x      |                  |        |    |    | Short term           |                      |                  |
|                  | Dr. Bos, Koval and Aamer (2009)     | Predictive-regression LSTM RNN consists of a single hidden layer of 128 LSTM units, two-output architecture and its associated MSE loss function. The coherence factor of 2 has been optimized through grid search to ensure a good trade-off between the accuracy of the predictions and the accuracy of the predicted variations. | x      |                  |        |    |    | Short term           |                      |                  |
|                  | Alessandro Albini et al. (2020)     | The structure consists of 30 inputs, a layer composed of 30 cells and an output layer. The Adaptive Moment Estimation (Adam) was used as optimization algorithm obtained the optimal number of 2000 iterations, and the learning rate 0.001. | x      |                  |        |    |    | Short term           |                      |                  |
|                  | Modibelo et al. (2020)              | Population-based LSTM using a sliding window using 20-minute steps of BG values as input in batches of 64 windows. A Bayesian optimization implemented in SigOpt was used to efficiently explore a predefined bounded hyperparameter space for LSTMs, drop-out level of the MLP layer, and historical window size. Networks are optimized by the Rectified Adam (RAdam) gradient descent method. | x      |                  |        |    |    | Short term           |                      |                  |
|                  | Liu, Meng and Pichakarn (2020)      | Modular Hysterical network (MHN), which can combine with any downstream neural network model and trained end-to-end. NPE was combined with LSTM, gated recurrent unit and BNN. | x      |                  |        |    |    | Short term           |                      |                  |
|                  | Uppin et al. (2020)                 | Intermittent LSTM architecture, this consists of a four-layer neural network; a bidirectional LSTM input layer composed of 128 cells having a look back of 15 minutes (i.e. 3 samples); two LSTM layers respectively composed of 64 and 32 cells, and a fully connected layer consisting of a single neuron computing the BG level prediction. | x      |                  |        |    |    | Short term           |                      |                  |
| DL-Based         | Reddy et al. (2018)                 | RF                                                                         | x      |                  |        |    |    | Short-term during exercise protocol |                      |                  |
|                  | Sinha et al. (2018)                 | LSTM                                                                      | x      | x                |        |    |    | Multi-modal          |                      |                  |
|                  | Yale et al. (2018)                  | SVM                                                                       | x      | x                | x      |    |    | Postprandial         |                      |                  |
|                  | Dh Div et al. (2018)                | RF                                                                         | x      |                  |        |    |    | Short term           |                      |                  |
| SL-Based         | Botrychek et al. (2020)             | Sequential model with output correction and an RNN in combination with data-fusion techniques based on Dempster-Shafer evidential theory (DST), genetic algorithm (GA) and genetic programming (GP). | x      |                  |        |    |    | Short term           |                      |                  |
| Ensemble-Based   | Botrychek et al. (2020)             | Sequential model with output correction and an RNN in combination with data-fusion techniques based on Dempster-Shafer evidential theory (DST), genetic algorithm (GA) and genetic programming (GP). | x      |                  |        |    |    | Short term           |                      |                  |
|                  | Pain et al. (2014)                  | SVM using Physiological parameters + ARIMA (Exogenous variables)           | x      |                  |        |    |    | Short term           |                      |                  |
|                  | Reddy et al. (2013)                 | Gaussian Process and Random Forest                                         | x      |                  |        |    |    | Short term           |                      |                  |
|                  | Reddy et al. (2018)                 | Support Vector Regression based on Disturbance evolution                    | x      |                  |        |    |    | Short term           |                      |                  |
|                  | Wang et al. (2019)                  | Gaussian processes-based RNN                                                | x      |                  |        |    |    | Short term           |                      |                  |
|                  | He et al. (2019)                    | Sparse group-lent-based RNN                                                 | x      | x                |        |    |    | Short term           |                      |                  |
|                  | W. Wang, T. Yu and Y. Xu (2019)     | Variational mode decompositions- improved Particle swarm optimization + LSTM | x      |                  |        |    |    | Short term           |                      |                  |
|                  | Nishikawa et al. (2019)             | Multivariate perspective + LSTM; Fittal train square regression             | x      |                  |        |    |    | Short term           |                      |                  |
|                  | Risch et al. (2015)                 | Stroke neural network and an other regression model (KNN, SVM, a Bayesian optimization procedures returns the best method to train the ensemble of trees (i.e., Bagging or Boosting). | x      |                  |        |    |    | Short term           |                      |                  |
|                  | Cunietti et al. (2019)              | Genetic Programming/evolving (EP/GPE)                                       | x      |                  |        |    |    | Meta-Medication      |                      |                  |
|                  | Kreuztobler, Lindsey and Hazen (2020) | gradient boosted decision trees and Support Vector Machine (SVM) regression | x      |                  |        |    |    | Short term           |                      |                  |
|                  | Mielczarek et al. (2019)            | Multiagent Artificial Intelligence Modeling Average including Exogenous variables (SARIMA); local model is built for each cluster (Fuzzy C-Means). Box-Jenkins methodology is used to identify a seasonal model for each set. | x      |                  |        |    |    | Postprandial         |                      |                  |

Notes: This table shows the algorithm and inputs (blood glucose (BG), insulin (I), meal information (CHO/M), Exercise information (E) and features from physiological models (P)) used to perform the predictions.
Table 3. Feature selection techniques.

| Study | Technique | Feature selected | Improvements |
|-------|-----------|------------------|--------------|
| Plis et al. (2014) | SVR using physiological features and other using also ARIMA features. | Physiological features and ARIMA features | Performance |
| E I Georga et al. (2015) | Different combination of inputs: 1) glucose concentration within the last 30 minutes, 2) with meal-derived glucose rate, total glucose, plasma insulin concentration, and 3) with energy expenditure. | Case 3: all features | Performance |
| Eleni I. Georga et al. (2015) | Random forest and RReliefF are used to rank the 46 candidate features. | 20 features: CGM data, glucose rate after meal, plasma insulin concentration, energy expenditure and time of the day. | Feature importance/Performance |
| Zarkogianni, K. et al. (2015) | Different combination of inputs: 1) glucose concentration and glucose change; and 2) with energy expenditure. | Case 2: all features | Performance |
| Zecchin et al. (2015) | Different combination of inputs: 1) CGM, 2) CGM and insulin, 3) CGM and CHO and 4) CGM, insulin and CHO | Postprandial prediction: case 4 and Nocturnal prediction: case 2 | Performance/Target importance |
| He et al. (2019) | 10 physiological features and CHO, insulin, energy expenditure and sleep quality score. Causal feature learning using sparse group lasso. | Food, insulin and time features provide more dominant causal correlations than those of sleep and exercise. | Feature importance/Performance |
| Jensen et al. (2019) | forward selection to select features from 32 candidate features | Slope of linear regression and minimum value the evening (9-12 pm) before the event, minimum value the first, second, or third night before the event and body mass index at baseline. | Feature importance/Performance |
| Allian et al. (2020) | MLP using last 30 minutes BG or with addition of time domain features | last 30 minutes BG and time domain features | Performance |
| Pavan et al. (2020) | CGM readings, CGM slope and IOB and additional features selected with ReliefF: first order differences, at several time lags, of CGM, IOB, COB, sleepwork period, skin temperature and acceleration data. | CGM readings and additional features selected with ReliefF. | Feature importance/Performance |
| Cappon et al. (2020) | generated the power set, dynamic risk; insulin; correction boluses; CHO, physical activity | Personalised feature set | Personalised features/Performance |

Notes: The features in the table are: carbohydrate ingestion (CHO), insulin on board (IOB), carbohydrates on board (COB)

Table 4. Reasoning approaches.

| Study | Algorithm | Input | Output |
|-------|-----------|-------|--------|
| Ambrosiadou, Alevizos and Zaiakos (1993) and Ambrosiadou, Goulis and Pappas (1996) | Rule-based | BG, administrated insulin (type/quantity), hyper/hypo episodes, sleep | insulin recommendations, glycaemia read recommendations |
| Cosenza (2012) | Fuzzy-based | carbohydrates, proteins, lipids, preprandial glycaemia, insulin | insulin recommendations |
| Fortweinler et al. (2013) | undisclosed | carbohydrates | insulin recommendations |
| Lehmann, T. Deutsch et al. (1996) | Rule-based reasoning and mathematical modelling | clinical data, BG data, insulin data, special event data, nutritional data | insulin recommendations |
| El Fathi et al. (2020) | Maximum-a-posteriori method | insulin basal dose Units (U), Insulin bolus dose Units (U), Amount of carbohydrates in consumed meal (g), Sensor glucose mmol/L, Optimal basal insulin dose Units (U), Optimal carbohydrate ratio g/U, Basal insulin sensitivity mmol/L/U, Time-to-peak of insulin action min, Carbohydrate sensitivity mmol/L, Time-to-peak of carbohydrate absorption min, Duration effect of insulin basal dose min, Transfer-rate constant between plasma and interstitial glucose | Insulin doses recommendations |
| Rudi and Celler (2006) | Rule-based | glycaemic values, Insulin, Exercise | Insulin recommendations, Generic recommendations |
| Al-Ghamdi et al. (2011) | Undisclosed, cloud-computing | age, gender, weight, diabetes type, glycaemic values, HbA1c | Generic recommendations |
| McCauland et al. (1999) | Rule-based, Fuzzy-based | current BG level, anticipated food intake, exercise level, prescribed insulin dosage | Generic recommendations |
| Hashemi (2012) | Rule-based | hypoglycaemic symptoms, hyperglycaemic symptoms, diabetes type, fasting glycaemia, postprandial (2h), random glycaemia, HbA1c | Generic recommendations |
| Mbogho, J. Duve and Malkanbule (2013) | Rule-based | diabetes related questions | Generic recommendations |
| Marling, Wiley et al. (2011) | Case-based | daily BG, life-event data, insulin | Treatment recommendations |
| Machado et al. (2017) | Rule-based | Glycaemic values, insulin, carbohydrates, exercise, HbA1c, weight, cholesterol, blood pressure, disease events | Treatment recommendations, general recommendations |