AI BASED DIABETES PREDICTION SYSTEM

Abstract

Background: Artificial intelligence (AI) methods in combination with the latest technologies, including medical devices, mobile computing, and sensor technologies, have the potential to enable the creation and delivery of better management services to deal with chronic diseases. One of the most lethal and prevalent chronic diseases is diabetes mellitus, which is characterized by dysfunction of glucose homeostasis.

Objective: To review recent efforts to use AI techniques to assist in the management of diabetes, along with the associated challenges.

Methods: We conducted a review of the literature using PubMed and related bibliographic resources. Analyses of the literature from 2010 to 2018 yielded 1849 pertinent articles, of which we selected 141 for detailed review.

Results: We propose a functional taxonomy for diabetes management and AI. We also performed a detailed analysis of each subject category using related key outcomes. This approach revealed that the experiments and studies reviewed yielded encouraging results.

Conclusions: We obtained evidence of an acceleration of research activity aimed at developing AI-powered tools for prediction and prevention of complications associated with diabetes. Our results indicate that AI methods are being progressively established as suitable for use in clinical daily practice, as well as for the self-management of diabetes. Consequently, these methods provide powerful tools for improving patients' quality of life.

Introduction

Diabetes mellitus refers collectively to a group of diseases resulting from dysfunction of the glucose regulatory system . Hyper glycaemia, the hallmark of diabetes, is the primary consequence of this dysregulation. Chronic hyperglycaemia in diabetes is associated with long-term complications involving tissue damage and organ failure, which can decrease life expectancy and even cause death. The International Diabetes Federation estimates that, by 2017, diabetes affected 425 million people worldwide, of whom 4 million people died in the same year. These figures are expected to increase dramatically in the coming decades, placing a rising burden on health care systems.

Most diabetes can be categorized into three subgroups: type 1 diabetes (T1D), type 2 diabetes (T2D), and gestational diabetes (GDM). Over the long term, T2D patients become resistant to the normal effects of insulin and gradually lose their capacity to produce enough of this hormone. A wide range of therapeutic options are available for patients with T2D. At the early stages of disease, they commonly receive medications that improve insulin secretion or insulin absorption, but eventually they must receive external doses of insulin. On the other hand, T1D patients have severe impairments in insulin production, and must use external insulin exclusively to manage their blood glucose (BG). Treatment of T1D requires consistent doses of insulin through multiple daily injection (MDI) or continuous subcutaneous insulin infusion (CSII) using a pump. GDM is treated similarly to T2D, but only occurs during pregnancy due to the interaction between insulin and hormones released by the placenta.

Artificial Intelligence Techniques

Defining the concept of AI, computational intelligence, or machine intelligence is not a trivial undertaking. In this paper, we refer to AI as a branch of computer science that aims to create

systems or methods that analyze information and allow the handling of complexity in a wide range of applications (in this case, diabetes management). Although the application of AI algorithms involves highly technical and specialized knowledge, this has not prevented AI from becoming an essential part of the technology industry and making contributions to major advances within the field. This section will provide a short overview of several well-known computational intelligence paradigms. For a more in depth discussion of various intelligent algorithms, theoretical results, and applications, the reader is referred to the work by Nilsson. In this study, we categorized methodologies with respect to the objective sought: to explore and discover information, to learn using information, or to extract conclusions from information.

Learning from Knowledge

Acquisition of knowledge is a key requirement of solutions intended to exhibit intelligent behaviour. Because learning is an effective way to introduce such knowledge, most AI studies to date have employed learning techniques. The primary aim of learning from knowledge is to allow computers to learn automatically without human intervention or assistance. This process could involve any method that includes some inductive component, ranging from a simple Kaman filter to a complex convolutional neural network. No method is inherently better than any other; each is more or less well-suited 5 to different scenarios, e.g., a softer learning curve, faster execution, or more flexible solutions. Furthermore, the performances of various methods are closely related to the quality and quantity of data: when more information is gathered, and less noise is present in the data, better solutions can be obtained. The most important families of techniques are artificial neural networks (ANNs), support vector machines (SVMs), random forest (RF), evolutionary algorithms (EAs), deep learning (DL), Naïve Bayes (NB), decision trees (DTs), and regression algorithms (RAs)

Exploration and Discovery of Knowledge

The discovery of knowledge revolves around the exploration and creation of algorithms for retrieving potential information from databases, commonly referred to as knowledge discovery in databases (KDD). The primary objective of KDD is identification of valid, potentially useful, and understandable information. KDD involves evaluation and interpretation of patterns and models for making decisions about what does and does not constitute knowledge, i.e., distinguishing between data that are useful and those that are (in the context of interest) useless. Therefore, KDD requires broad and deep knowledge about the area of study.

The overall KDD process may be characterized into six steps in the CRISP-DM model business understanding, data understanding, data preparation, data modelling, evaluation of the model, and deployment. The application of data mining modelling is the most technical stage of the process. Techniques for data mining have taken much of their inspiration from learning algorithms and statistics, although the two types of approaches have different objectives. The most important data mining tasks involve detection of anomalies, identification of dependencies between variables, regression, clustering, and classification. Examples of representative techniques are k means, k-nearest neighbour (KNN) algorithm, and hierarchical clustering (HC).

Reasoning from Knowledge

In this discourse, the idea of reasoning from knowledge denotes the creation of precise and effective ways to generate inferences in more precise and robust ways. Thus, reasoning from knowledge involves the use of logical techniques such as deduction and induction to generate conclusions from the available knowledge. The primary objective of systems that implement reasoning mechanisms is to perform tasks at a human-expert level in a narrow, specialized manner

within the domain of interest. Such systems commonly apply heuristics to guide reasoning and reduce the search space of possible solutions.

These systems are based on three main components. First, a knowledge acquisition system is used to gather and collect inferences that can be used for further development. In this context, such a system is used to extract new rules and gather information. Second, a knowledge base, characterized by rules and information, is used for problem solving. Important aspects here include relations, conditions, recommendations, directives, and strategies. Finally, the inference engine links the knowledge base with the gathered information. Overall, this process facilitates reasoning, whereby the system becomes able to facilitate the realization of the anticipated solution. It is possible for a system structured on this basis to transfer expert knowledge directly to the knowledge base. This, in turn, helps to build new solutions based on previous cases, or to deal with ambiguous concepts and uncertainty. Representatives of these tasks include rule-based reasoning (RBR), case-based reasoning (CBR) and fuzzy logic (FL).

Methods

A review of the literature was conducted using the PubMed database. The selection of this bibliographic system as the primary data source was motivated by the sharp increase in the number of articles in the database and the strong link between these articles and the healthcare sector. PubMed has been validated as a reliable tool for retrieving information on medical research and clinical applications. Only English-language documents published between 2010 and 2018 were considered.

Results

Main Findings Ultimately, 141 papers were included in the review. The potential of AI to enable diabetes solutions has been investigated in the context of multiple critical management issues. In this section, we use the following proposed diabetes management categories to summarize the latest contributions, the state of the art, and the results described in the reviewed articles:

- Blood glucose control strategies

- Blood glucose prediction

- Detection of adverse glycaemic events

- Insulin bolus calculators and advisory systems

- Risk and patient personalization

- Detection of meals, exercise and faults

- Lifestyle and daily-life support in diabetes management

Blood Glucose Control Strategies

Development of the AP has been intensively pursued over the past decade. An AP consists of an automated system that mimics islet physiology, including a glucose sensor, a closed-loop control algorithm, and an insulin infusion device. The ultimate goal of an AP system is to improve overall diabetes management and reduce the frequency of life threatening events associated with T1D. The algorithms used by the AP to calculate insulin dosage have been intensively investigated, either using data from diabetic patients or computer simulated patients, commonly named virtual patients (VP). The major candidate algorithms are derived from traditional control engineering theory;

however, AI has become more established over the past few years, and could ultimately provide better candidates to meet the challenges of an AP. Although AI and control engineering have converged to some extent as the two fields incrementally exchange methods, here we will focus on studies dealing with closed-loop algorithms based on AI techniques. We direct interested readers to a recent comprehensive review on AP systems.

Three main AI methodologies have been established as control techniques in recent years: FL, ANNs, and reinforcement learning (RL). Most alternatives to control engineering algorithms are based on FL. Controllers apply FL theory to imitate the lines of reasoning of diabetes caregivers. Thus, the primary benefit of FL over classic control engineering is the ability to deal with nonlinearities and uncertainties. However fuzzy systems have not yet been proven to clearly outperform well-tuned classical approaches

MD-Logic was developed by authors who sought to individualize glycaemic control using a fuzzy controller. Two feasibility studies were conducted in cohorts of seven T1D patients to introduce the methodology and test the viability of the controller. Subsequently, a randomized crossover trial was conducted in 12 T1D patients. The results suggested that the fuzzy method could improve nocturnal BG control without increasing the risk of hypoglycaemia. Following these successful feasibility studies, the authors performed a randomized crossover study of 56 young patients over 3 days. The results confirmed a reduced rate of nocturnal hypoglycaemia and superior glycaemic control in comparison with insulin pump treatment. In a home-based randomized trial of 15 T1D patients , the authors compared the fuzzy AP and sensor-augmented pump over 4 nights; the results confirmed the feasibility, safety, and efficiency of their approach in a home setting.

 A later extended study of 24 T1D patients during 6 weeks of nocturnal control demonstrated the safety and effectiveness of long-term use of a FL based controller. In a recent clinical trial evaluating remote patient monitoring of the FL controller, the AP was tested in 75 T1D patients for 4 consecutive nights. The results demonstrated safe and efficient glycaemic control. Further studies will evaluate the MD-Logic controller implemented in Misnamed 690G.

Other research groups have also investigated the application of FL to BG control. For example, Maspeth et al. reported a FL controller designed to personalize glycaemic control. They tested it in 30 virtual patients on the UVA/PADOVA T1D simulator. Next, to demonstrate the feasibility of their approach, they conducted a pilot study in 12 T1D patients. In a later study, they proposed stressing a fuzzy controller with highfat meals and exercise, and tested this approach in a trial with 10 T1D patients. The results revealed deficits in their previous approach and ultimately led to improvements in the FL controller.

Blood Glucose Prediction The ability to anticipate BG excursions could provide early warnings regarding ineffective or poor treatments. Thus, information collected from new technologies for diabetes management, such as the CGM devices, could lead to real-time predictions of future glucose levels. Prediction of BG levels is challenging due to the number of physiological factors involved, such as delays associated with absorption of food and insulin, and the lag associated to measurements in the interstitial tissue. Errors of the CGM also increase the difficulty of predicting BG values (approximately 9% of the mean absolute relative difference for the best sensors).

 We outline the features of each study using key information, including prediction horizon (PH) in minutes, objective population criteria, number of participants in the cohort, mean number of monitored days per patient, mean number of monitored hours per day, existence of monitoring during the overnight period, type of monitoring technology, and information about physical activity

(PA). Finally, we highlight the main AI methods applied in the studies, the bibliographic reference, and the year of publication. AI for BG prediction has been addressed in as many as 13 parallel lines of research. Most of these studies focused on T1D because of the inherent utility of AI in this condition and the availability of high frequency data collected from patients using a CGM device. The results of our review reveal the range of PHs explored, from 5 to 180 minutes. Short-term predictions were the most frequently explored: 38 out of 49 studies (76%) used PHs below 60 minutes. ANN approaches were the most widely applied methodology, but other machine learning methodologies such as RF, SVM or RAs are being adopted with increasing frequency.

Detection of Adverse Glycaemic Events:

 As with BG prediction, glycaemic episode detection encompasses a set of tools that deal with the complexity of effective BG control. However, in this section we will not address glucose values, but instead focus on the appearance of hyperglycaemic or hypoglycaemic events. These tools enable us to detect the occurrence of glycaemic episodes and give us the opportunity to respond promptly to their effects. In contrast to the previous section, 15 most of the reviewed studies on this topic focus on detecting hyperglycaemia or hypoglycaemia in situations when it is not possible to effectively monitor BG. Therefore, most of these studies deal with real-time approaches rather than predictions of future events. We summarize the studies dealing with detection of BG excursions in Table 3. Each scenario is represented by the following features: PH in minutes, objective population criteria, number of participants in the cohort, mean number of monitored days per patient, mean number of monitored hours per day, type of monitoring technology, existence of monitoring during the overnight period, and inclusion of exercise or physical activity information.

 Finally, we highlight the main AI methods applied in each study, the bibliographic reference, and the year of publication. The results revealed that nine of the 14 studies (64%) reported real-time detection systems, and 10 of these studies (93%) were specifically focused on T1D. Table 3 shows that over six of the approaches that exclusively addressed T1D (60%) gathered data from CGM sensors, whereas the remainder used a electroencephalogram (EEG) or self-monitoring blood glucose (SMBG) measurements. Studies focusing on T1D were performed with fewer than 15 patients, whereas studies of T2D included larger cohorts. Sensitivity and specificity were the most common outcomes used to assess the quality of approaches to glycaemic detection.

Although this section contains fewer papers than the one on BG prediction, we identified more than 10 research groups contributing to this topic. In particular, researchers at the Centre for Health Technologies (Faculty of Engineering and Information

 Insulin Bolus Calculators and Advisory Systems:

 The most common insulin therapies for diabetics, continuous subcutaneous insulin infusion (CSII) and multiple daily insulin injections (MDI), operate according to similar principles [79]. Both utilize basal insulin (injection of long-acting basal insulin and infusion at a constant basal rate, respectively) and bolus insulin (injection of quick-acting bolus insulin and meal boluses, respectively) to cover meals or snacks. The calculation of correct insulin doses and the estimation of the amount of CHO is a regular task in the daily life of many insulin-dependent patients. Bolus advisors are based on previous insulin doses, BG measurements, planned CHO estimates, and other patient-specific parameters, including insulin-to-CHO ratio and insulin sensitivity.

 Manually calculating bolus doses and counting CHOs can be complex and challenging because individuals must consider multiple parameters to achieve satisfactory glucose control, and miscalculation of these values may result in persistent glycaemic episodes. To support CHO

estimation and determination of insulin doses by patients, tools for providing bolus advice and CHO estimates are increasingly being adopted. These tools seek to increase the accuracy of mealtime and correction boluses. AI has been used to provide sets of tools to improve the accuracy of CHO estimates and to calculate the optimal insulin bolus for the ingested meal We identified several studies that applied AI to systems aimed at supporting patient decisions by issuing advice regarding meals, exercise, or medication.

Research groups at the Imperial College London performed an extensive study of an insulin bolus calculator based on CBR methodology [80–84]. Their approach, which manages various dynamically optimized diabetes scenarios, was proven in a clinical trial (NCT02053051) to be a safe decision support tool. Additionally, this approach was demonstrated to improve glycaemic control in diabetes management when it was combined with an AP system [84]. A similar approach was presented recently by another group [85], which also proposed an insulin bolus calculator based on CBR but in contrast to other bolus calculators, it used a novel temporal retrieval algorithm.

The Centre for Biomedical Engineering Research at the University of Bern (ARTORG) performed several important and extensive studies [86–90] investigating the Go-cart system, which provides dietary advice to diabetic patients based on automatic CHO counting. Their approach is based on the use of computer vision techniques, such as feature extraction and SVM, and pilot studies show it to be an excellent assistive tool. We have also found several studies that validated their approach using the UVA/Pad ova patient simulator.

Srinivasan et al. of proposed the use of a set of insulin delivery profiles optimized by a PSO to find the optimal open- and closed-loop profiles for various meal compositions. More recently, another study presented an approach based on ANN to optimize bolus calculation by patients using CGM. The results revealed that it was better at reducing the blood glucose 17 risk index value than other approaches. Finally, Lee et al. proposed an advisory treatment system that provides insulin, meal, and exercise recommendations. Their study, which compared RBR and KNN algorithms, concluded that the KNN algorithm was best suited to this approach. Technology, Sydney, Australia) have published five studies on this topic over the last 7 years.

Risk and Patient Stratification*:*

Most commercially available tools and protocols for managing diabetes are based on general models of the diabetic population or involve subsets of patients defined by simple cauterization features and easily identifiable characteristics. However, the daily lives of diabetic patients are determined by a wide range of management scenarios that are not represented in these general models. Insulin-dependent patients must manage a highly complex process to maintain suitable levels of BG. Treatment of diabetes is governed by diverse factors, implying high intra- and integration variability.

Exercise, nutrition disturbances, age, and cardiovascular complications are just some of the long list of factors that can dramatically impact quality of life and undermine medication adherence even when patients follow their treatment regimen strictly. Such patient variability severely limits the use of general models, which cannot capture the specific physiological behaviours of individuals. Thus, an important step toward better risk detection and intervention is personalization of the system. Over the past decade, major research efforts have been devoted to developing management tools capable of stratifying patients in different segments of the population.

Risk assessment and patient stratification methods are important to improving the management of diabetes, and therefore the overall health outcomes of diabetic patients, and consequently have

attracted a greater share of attention from the medical community. This category gathers all reviewed papers that systematically identified individual patients and their risk factors to manage and coordinate their care based on specific conditions and on evidence-based guidelines. Table 4 outlines the type of stratification together with the specific challenge. Main characteristics, such as number of years, cohort, and objective population, are also included. Finally, the table defines the AI methodology applied, bibliographic reference, and year of publication

Detection of meals , exercise, and faults:

Because people with both types of diabetes need support to successfully manage their disease, solutions with higher accuracy that require less user interaction are associated with higher-quality diabetes treatments. Tools or algorithms capable of early detection of critical events affecting glycaemic control, such as exercise, a meal, or an infusion set failure, are critical for systematic automation of both closed-loop and open-loop systems. Insulin-dependent patients monitoring their glucose with CGM devices use BG measurements to calculate insulin infusion rates. Consequently, failure of these devices can lead to episodes of hyperglycaemia or hypoglycaemia.

Leal et al. proposed an approach using SVM to detect correct and incorrect measurements in real-time CGM. They tested their system on 23 critically ill patients, and obtained promising results in patients with sepsis or septic shock. The same objective was pursued in the work performed by Turk soy et al. who used a KNN algorithm for the diagnosis of faults 19 and the data from 51 patients to validate the performance of their approach. For the detection of inaccurate measurements by glucose meters, another study developed a SVM algorithm to minimize the effect of haematocrit on glucose measurement, and tested their method on 400 BG samples.

Physical activity offers multiple benefits for diabetic patients, but also complicates the management of diabetes, especially in T1D patients. Some of the factors affecting BG dynamics during exercise include the intensity, duration, and type of exercise, insulin on board, and the carbohydrate absorption rate. Tools and systems focused on automated detection of exercise could improve the accuracy of treatments. Turk soy et al. [116] also proposed the use of a KNN classification algorithm to automatically detect exercise type and intensity in an AP system. They tested their approach in five T1D patients, and reported a sensitivity of 98.37%. Similarly, Jacobs et al.proposed a regression model to automatically detect physical exercise in patients carrying an accelerometer and a heart rate sensor. The system was assessed in 13 T1D patients, yielding a sensitivity of 97.2% and a specificity of 99.5%. Meal detection is important in AP systems that do not permit manual meal announcements and as a safety system for patients who may forget to enter meal information manually.

Turk soy et al.have also investigated the development of a meal detection system based on analysis of CGM signals using an unscented Kaman filter and a fuzzy system to estimate the carbohydrates content. Their approach was validated in silicon in 30 T1D patients using the UVA/Pad ova simulator, which revealed a sensitivity of 91.3% and an error of 23.1% in CHO estimation, and vivo using data from 11 T1D patients, which revealed a sensitivity of 93.5% for meals and 68.0% for snacks.

Lifestyle and Daily-Life Support in Diabetes Management:

- Recently, Everett et al. presented a DSS using machine learning to promote adherence to physical activity and weight reduction. Authors validated the system with 55 patients with prediabetes. Previously, Yom-Tov et al.proposed a DSS based on a RL algorithm that automatically sends messages to patients who are following a personalized plan for physical exercise. The approach was validated in 27 sedentary T2D patients. Daily-life support

systems using AI tools for GDM were also investigated. A weight management proposal was presented in the Media Class system.

- The system, which is based on the application of a natural language processing (NLP) algorithm, was validated during the postpartum visits of 600 GDM patients. Ringlet also investigated tools for GDM patients. They proposed a mobile application based on an Augmented telemedicine DSS as a tool for helping GDM patients. Later, they presented a platform to remotely evaluate patients using a classifier based on a clustering algorithm and a DT learning algorithm. The system was evaluated in 90 GDM patients. The results showed a reduction in the time by clinicians to patients and in facet-face visits per patient. Six other studies have proposed alternatives to the manual creation of patient care workflows. The studies offer support for the design and deployment of diabetes management protocols, as well as ways to continuously improve patient tracking throughout the entire process. Cleveringetal . presented a system aimed at decreasing cardiovascular risk of T2D patients by optimizing patient care workflows. The authors validated their system by administering questionnaires to 3391 T2D patients. Miller et alludes a machine learning approach to extract information from drug prescriptions from electronic health record (EHR) data and identify factors associated with patient care flow deviations. Another DSS with care flow tools was presented in the work of Alotaibi et al.

- This system focuses on the management of T2D patients using advanced features, such as computerized alerts and reminders. It was tested in 20 T2D patients for 6 months, and resulted in reduced HbA1c levels and improved diabetes awareness. Fernandez-Plataea . proposed using data mining methods to enable the dynamic design of care protocols, but highlighted the need for mechanisms to reduce the Spaghetti Effect and make DSSs usable by experts. Contreras et al. developed a diabetes management system to integrate a series of AI models and tools with an engine to manage diabetes patient care flows. Finally, Suh et al. proposed a dynamic care 21 flow system that applied data clustering together with rule mining techniques to prioritize required user tasks. Other tools have been p Lifestyle management is a fundamental aspect of diabetes care.

- Sedentary living, stress, non-adherence to medication, lack of regular medical examinations, and bad habits can lead to discontinuation of treatment for patients with diabetes. From the time of diagnosis, patients are required to optimize their lifestyles to manage complications and other comorbid conditions, with the overall goal of enhancing their own care. Current technologies and data warehouses enable solutions that model data and make quality decisions based upon them. Decision support systems (DSSs) consist of tools focused on helping patients or doctors to manage diabetes therapies. These systems usually have monitoring features that facilitate systematic recording of information about diet, PA, medication, glucose measurements, etc., and combine it with tools to support both Furthermore, tools have been developed to analyses clinical appointments, medication, and therapy adherence. For example, a machine learning approach to examine medication adherence thresholds and risk of hospitalization was implemented.

- The system implemented in promotes patient empowerment and adherence to therapy based on the automatic generation of feedback messages. Greaves et al. proposed a clinical DSS that issues medication interaction alerts based on clusters with similar management recommendations. A fuzzy approach was also presented by EghbaliZarch et al. to address the problem of medication selection in T2D patients. Finally, NutraSweet al. proposed a machine learning algorithm to predict missed clinical appointments and help patients continue regular doctor visits . patients and clinicians, with the overall goal of enhancing therapeutic outcomes.