Closed-loop Artificial Pancreas Development: A Review

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***Abstract* - Diabetes is a widespread disease, suffered by millions, including children. Treatment of diabetes type 1 and sometimes even type 2, entails multiple blood glucose checks and insulin injections per day, and can thus be extremely exhausting, especially for very young children. Open-loop systems of insulin delivery, insulin pumps, used today commercially, require human interaction which can lead to low blood glucose control due to human mistakes. Fully automated closed-loop systems of artificial pancreas, as one-hormone as well as dual-hormone systems, are being developed. This paper is the literature survey of the latest research on the automated closed-loop artificial pancreas. The objective of this paper is to explore the development of devices and techniques to facilitate the daily life of diabetic patients with emphasis on the latest research on the topic. From so-called pens to open-loop systems of insulin pumps, closed-loop systems with user interaction - hybrid closed-loop, to the latest fully automatized closed-loop – artificial pancreas. In total 300 articles are reviewed from which 150 articles are retained for the literature survey and 50 are analysed in this literature review.**

Keywords – artificial pancreas, bionic pancreas, close-loop, prediction-based algorithm, detection-based algorithm

I. INTRODUCTION

Diabetes is one of the most prevalent diseases of today. Even children as young as 2 months can suffer from it. According to the WHO [1] more than 422 million people suffer from diabetes, of which 9 million suffer from type 1. In type 1 diabetes (T1D), a patient usually suffers from congenital flaws that prevent them from producing hormones that regulate blood glucose. Type 2 diabetes patients (T2D) produce those hormones, but their function in the body is diminished.

Currently, patients with diabetes are treated with either: 1. multiple daily blood glucose measurements and insulin injections, which can be very unpleasant, especially for young children (as well as for their parents and caregivers), or 2. continuous subcutaneous blood glucose measurements and insulin infusion delivered via an insulin pump. Various open-loop insulin pumps available in the market are programmable to deliver the required amount of insulin. However, all of them require user intervention. A fully automated closed-loop insulin infusion system that can deliver appropriate amounts of insulin to patients without any manual interference is being developed. Dual-hormone systems, insulin with glucagon, or pramlintide are also being developed. The closed-loop system contains three main components: continuous glucose monitoring (CGM), an intelligent controller, and an insulin pump.

In the last 20 years, several prediction-based and detection-based algorithms for insulin attenuation/suspension, as well as dual-hormone systems, have been proposed in the literature, with the aim of preventing or mitigating hyperglycaemia (high blood glucose level) and hypoglycaemia (low blood glucose level).

However, for artificial pancreas construction, there is a basic terminology to be comprehended:

- Basal insulin stabilizes blood glucose levels when a patient is in a fasting state, especially during periods of sleep. Patients that use conventional methods – needles or pens to inject insulin into the body, usually take basal insulin before sleep. Patients that use insulin pumps, either open-loop or hybrid close-loop, are administered basal insulin automatically, in small doses throughout the day.
- Bolus is a dose of insulin taken to handle a rise in blood glucose that happens after eating, especially peroral carbohydrate intake.
- Insulin on board (IOB) is defined as the amount of administered insulin that is still active in the body.
- Insulin pump is a system that consists of an insulin tank, pump controller, and in the latest systems that are on the market – a communications system with CGM via Bluetooth.
- CGM is the system that measures the level of blood glucose, usually in 5 minutes periods, and in some latest commercial systems it sends information to the pump controller via Bluetooth. In older systems, that are still in use, blood glucose level monitoring is done via NFC (near-field communication) and mobile phone applications.
- Open-loop systems consist of CGM and insulin pumps that are not interconnected, there is no communication between the two of them and the pump is completely user-controlled.
- The closed-loop system contains three main components: CGM, insulin pump, and intelligent controller that regulate insulin delivery.

Table I. Blood glucose target values

	healthy	diabetic
fasting (before a meal, during the night, …)	4–6 mmol/L 70–110 mg/dL	4–7 mmol/L 70–130 mg/dL
2h post-prandial (after meal)	<7,8 mmol/L < 140 mg/dL	<10 mmol/L <180 mg/dL

Information about the crucial parameter for close-loop artificial/bionic pancreas construction, target blood glucose levels for diabetic persons, compared with levels of a healthy non-diabetic person, is shown in table I.

Blood glucose levels for a diabetic patient:

4 – 7 mmol/L (70 – 130 mg/dL): euglycemia (normal level of blood glucose)

3 – 5 mmol/L (55 – 90 mg/dL): hypoglycaemia (low level of blood glucose)

< 2 mmol/L (40 mg/dL): life-threatening hypoglycaemia

7 – 15 mmol/L (130 – 270 mg/dL): hyperglycaemia (high level of blood glucose)

> 16 mmol/L (300 mg/dL): life-threatening hyperglycaemia

II. TECHNICAL BACKGROUND

Open-loop system of insulin delivery, insulin pumps used today commercially, require human interaction which can lead to low blood glucose control due to human mistakes.

Both single-hormone systems (delivering insulin only) and dual-hormone systems (delivering insulin and glucagon or another hormone) are being pursued clinically. The addition of glucagon has the potential to further alleviate the risk of hypoglycaemia but increases the system's complexity with separate drug reservoirs, infusion sets, and algorithms. From a patient perspective, the ideal closed-loop system requires minimal user interaction, device burden, and inconvenience while achieving optimal glucose control.

Fully closed-loop systems that detect and automatically dose insulin for meals have been attempted, but glucose control is compromised because of delays in the absorption of subcutaneous rapid-acting insulin analogue. Therefore, most closed-loop systems adopt a hybrid approach, requiring manual administration of insulin boluses for meals.

Closed-loop control overnight reduced time in hypoglycaemia and increased time in the target glucose range.

The efficacy and safety of closed-loop glucose control in the outpatient setting have been demonstrated in multiple studies using different closed-loop prototypes and in meta-analysis.

III. LITERATURE REVIEW

During the research, it has been found that diabetes and closed-loop artificial/bionic pancreas topic is very popular in the last 20 years, and there are many scientific papers on different research aspects. From about 300 papers retrieved from different scientific sites, such as Research Gate, Google Scholar, IEEE, Journal of Diabetes Science and Technology, and PubMed/Medline, around 150 met the inclusion criteria, technical aspect of closed-loop, and 50 of them are included in this literature review. A lot of papers explore the medical aspects and clinical research of available systems, so they are excluded from further review.

The function of basal insulin is successfully incorporated into artificial pancreas systems that are already in use, so papers that treat basal insulin control are excluded. CGM/pump communication papers are excluded, due to CGM and its communication with the pump are also successfully incorporated into commercially available systems.

Papers relating to mobile phone applications for monitoring and blood glucose regulation are also excluded, since research aim isn't mobile application.

Bolus insulin is the aspect that is hardest to automate, so the focus was placed on works that relate to algorithms to incorporate different factors that influence blood glucose dynamics. The majority of the technical papers treat the prediction of blood glucose dynamics.

Blood glucose is unpredictable. Each person is different and special, and there are a huge number of factors that influence blood glucose levels. Type of meal (number of carbohydrates, but also proteins and fats in a meal), physical activity (level and type), stress, hormonal fluctuation (during puberty, menstrual cycle, pregnancy, childbirth, menopause…), illness, high body temperature, sleep deprivation …. Everything mentioned above should be incorporated into artificial/bionic pancreas that emulates functions of the healthy human pancreas. But, human organisms, and every and each organ, are very complex systems that are almost impossible to emulate by mechanical means.

Children are the most delicate and unpredictable of all patients. Their bodies demand higher doses of insulin, which leads to a greater risk of low blood glucose hours after meals. So young children and their caregivers face many different obstacles. The majority of the research is for adult patients, and just a small number of research are led for the youngest diabetes patients. Papers [5], [9], [11], [14], [15], [27], [29] from the reference list address the use of the pump in the youngest population and their effects.

Teenagers with diabetes, on the other hand, provide another subset of challenges. Papers [10], [11], [15], [27],

[29] also includes teenagers and adolescent in their research.

All other papers consider only adult diabetic patients.

Only one paper [2] presents research on pregnant diabetes patients' blood glucose control.

Exercise has proven to be a particularly difficult-to-control metabolic disturbance. Exercise increases muscle demand for glucose and can increase insulin sensitivity for hours later. Given the long-time delays of insulin action, stopping insulin delivery for a rapidly falling glucose is unlikely to prevent hypoglycaemia. Much work has been done to detect exercise through the use of heart rate alone, but it alone isn't enough. Additional signals that detect physical activity faster than CGM alone, may improve blood glucose control and reduce exercise-related hypoglycaemia. In papers [16], [18], [25], the research was based on the inclusion of the detection of physical activity into the algorithm to perform corrections of insulin dosage.

One challenge of managing diabetes without significant hypoglycaemia relates to the wide fluctuation in insulin requirements to maintain euglycemia, between people and for the same person from day to day and in different situations. A second challenge is the time delay between subcutaneous insulin injection and insulin action to lower blood glucose levels, which can extend to more than an hour. As a result, it is exceedingly difficult for an individual to accurately predict how much insulin is needed in any particular situation, often resulting in hypoglycaemia or hyperglycaemia.

The majority of the research uses prediction-based algorithms. The most used are MPC (Model Predictive Control) and PID (Proportional-Integral-Derivative). Papers [2], [6], [7], [9], [17], [27], [31], [32] research closed-loop systems using the MPC algorithm, and papers [8], [17], [21], [24], [27] PID. Some of the papers use Machine Learning, Deep Learning, and Artificial Neural Networks [14], [15], [16], [18], [26], [32], [33], [37], [39] for decisions on insulin administrated.

Around 80% of the papers are about one-hormone pumps, while some, like[5], [10], [11], [13], [34], [40] test bi-hormonal cases, two separate pumps, and controllers. Also, the majority of the research is on hybrid close-loop systems that include user intervention in some way [2], [3], [7], [9], [16], [18], [19]. Almost all reviewed papers are about T1D, and just a few include T2D patients [22], [25], [35]. The reason is that T1D patients' bodies don't produce insulin (and some other hormones), so they are condemned to multiple injections day and night, unlike T2D patients whose body produces insulin in a certain amount and the need for a pump isn't that substantial. Even though, some scientists are considering constructing insulin pumps for T2D [22], [35].

All testing that is done in-silco is done using the UVa/Padova diabetes simulator.

As previously mentioned, the biggest challenge is blood glucose regulation around mealtime due to slow digestion and absorption of food (conversion to blood glucose), and on the other hand slow effect of injected insulin. In a healthy human body, a healthy pancreas starts insulin production and secretion at the moment a person starts a meal. In everyday life, diabetic patients, both T1D and T2D that use insulin for blood glucose regulation, calculate the number of carbohydrates to be eaten, calculate the responding bolus insulin dose, and inject it, via the conventional method – pens, or enter the number of insulin units into pump controller. How to detect or predict meals, how to detect or estimate the size of meals, number of carbohydrates consumed, and similar questions are discussed in papers [2], [3], [4], [6], [7], [16], [28], [30], [31], [32], [38].

In further literature review, the aim was to find researches that use artificial neural networks (ANN) for bolus insulin regulation, or for detecting some irregular events that affect blood glucose level like stress, physical activity, illness, life phases with hormonal changes, etc. There is a small number of papers that treat the topic of bolus and/or meal detection/prediction using ANN [14], [15], [16] and [37]. Similar is for physical activity using ANN [16], [18]. No research is done in a case of some irregular events like stress, illness, or hormonal changes during pregnancy, puberty, etc.

A Convolutional Neural Network (CNN) and a Long Short-Term Memory Recurrent Neural Network (LSTM RNN) are used in research [14] for blood glucose forecasting of 10 virtual paediatric patients. ReLu activation function was used for both training models. The models were implemented and trained on Google Colab using libraries Keras and TensorFlow. Both models take as input a 3×30 matrix of values, corresponding to the last 30 min of the 3 feature values. Dynamic range quantization, in *.tflite* format, is used for performing regression tasks on Rasperry, and the full integer quantization, *uint8*, for DevBoard. Results of the research showed that LSTM model achieves the best numeric and clinical accuracy when tested in the *.tflite* format, whereas the CNN achieves the best clinical accuracy in *uint8*. The models achieved numerical accuracy comparable to those reported in the literature for adult patients.

In their research [15] authors use offline Reinforcement Learning (RL) algorithms: batch constrained deep Q-learning (BCQ), conservative Q-learning (CQL) and twin delayed deep deterministic policy gradient with behavioural cloning (TD3-BC) for nine virtual diabetes patients, with UVa/Padova simulator, and compares results with PID controller's. Performance was evaluated by monitoring blood glucose levels over a simulated 10-day test period and aggregating the results over three test seeds per training seed. Offline RL algorithms had better results in time in the healthy glucose range (6.4±1.1)%, meal estimation, even in case of irregular meal patterns. The work showed that offline RL conduce more effective and safer insulin dosing from smaller samples of data comparing with the current standard of glucose control algorithms.

In [16] authors described a deep reinforcement learning algorithm they developed using a T1DM dataset, data from wearable devices, with aim to automate insulin dosing. They built patient-specific computational models using systems biology informed neural networks (SBINN) with the Roy-Parker model, to mimic the glucose-insulin dynamics by simultaneously considering patient-specific carbohydrate intake and physical exercise intensity. Dataset that is used contained 8-week continuous glucose monitoring, insulin, physiological sensor, and self-reported life-event data for 12 patients. According to the authors conclusion model not only correctly predicts the hidden states that cannot be measured with current diabetes technology, but also accurately infers patient-specific parameters, different daily routine of physical activities and insulin injection, governing the patient-specific Roy Parker model by reconstructing all states of interest.

The study [18] investigates the classification of different types of acute psychological stress (APS) and physical activity (PA) via physiological variables measured by a wristband device. Random convolutional kernel transformation is used to extract a large number of feature maps from the bio signals measured by a wristband device (blood volume pulse, galvanic skin response, skin temperature, and 3D accelerometer signals). Three different feature selection techniques (principal component analysis, partial least squares–discriminant analysis (PLS-DA), and sequential forward selection) as well as four approaches for addressing imbalanced sizes of classes (up sampling, down sampling, adaptive synthetic sampling (ADASYN), and weighted training) are evaluated for maximizing detection and classification accuracy. A LSTM RNN model is trained to estimate PA (sedentary state, treadmill run, stationary bike) and APS (non-stress, emotional anxiety stress, mental stress) from wristband signals. The balanced accuracy scores for various combinations of data balancing and feature selection techniques range between 96.82% and 99.99%. The combination of PLS–DA for feature selection and ADASYN for data balancing provide the best overall performance.

A LSTM NN is used in [37] for glucose forecasting, to predict blood glucose levels up to 60 minutes in advance, using continuous glucose measurements and insulin data collected from 175 people with T1D. Authors introduce the glucose variability impact index (GVII) and the glucose prediction consistency index (GPCI) to assess the accuracy of prediction algorithms. The inputs to the model are glucose prediction up to 60 minutes, and glucose and insulin on board (IOB) 3 hours values. Activation function used is ReLu. During the network training phase, the mean-square-error (MSE) loss function was minimized and multiple passes over the entire training set were done. Weights were updated using batches of 64 training sequences. The model was compared with several naïve approaches for estimating glucose and with alternative machine learning algorithms. The LSTM had highest accuracy and best GVII and GPCI.

Research of a machine learning model developed for probabilistic prediction of hypoglycaemia is explained in the paper [39]. The model is developed for 30- and 60-minute time horizons, based on CGM datasets and obtained from 112 patients over a range of 90 days. The model predicted hypoglycaemia with >91% sensitivity while maintaining a specificity of >90%. Two approaches were considered for prediction: Logistic Regression (LR) and Random Forests (RF). Classifiers based on Decision Trees, Gradient Boosting, and Support Vector Machines were developed. From the aforementioned research, it is concluded that 30 minutes time horizon is sufficient for the results.

IV. CONCLUSION

Bolus insulin isn't completely regulated so far. A very limited amount of research has been done on children, and adolescents, as well as the effects of pregnancy and exercise. An even smaller amount of research exists for dual hormone pumps specifically. Recent researches on ML, DL and ANN algorithms show better results in blood glucose regulation, more secure, accurate and precise, than PID and MPC algorithms already used in commercially available systems. Further research should be directed to bolus insulin regulation, and dual hormone pumps, and specifically include children and adolescents in their sample. The system in use should work efficiently even in periods of frequent blood glucose variations due to hormonal changes, like growing up, puberty, pregnancy, breastfeeding, virus/bacterial diseases, stress, etc. The system should also adapt to varying carbohydrate intake. It is of uttermost importance to get a model with high degrees of both precision and accuracy.

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