Journal for Health Sciences, Volume 13, Issue 1 (2023), pp. 5–14.
https://doi.org/10.32967/etk.2023.009

FULLY AUTOMATED INSULIN DELIVERY: ARTIFICIAL PANCREAS

LÁSZLÓ BARKAI

Institute of Theoretical Health Sciences, Faculty of Health Sciences,
University of Miskolc;
University Children's Hospital, Faculty of Medicine,
PJ Safarik University, Kosice
e-mail: barkail@t-online.hu

Summary: Despite the increasing use of new treatment options, the glycaemic control of most diabetes patients is not satisfactory. However, a clear advantage is documented in the subpopulation of patients applying advanced technologies. Nevertheless, there is a need to improve the replacement of islet function and to check the achievement of treatment goals in individuals with diabetes. Aiming to fulfil these requirements, new technologies need to attain. Parallel development of insulin pumps and continuous glucose monitoring devices lead to automated insulin delivery systems. The future development goal is to achieve systems not dependent on user inputs, e.g. the fully closed loop system (artificial pancreas). The biggest barriers are the non-physiological insulin delivery and glucose monitoring subcutaneous/interstitial) of the systems used currently, therefore further research will establish the long-term benefits of emerging technologies in the care of diabetes individuals.

Keywords: *artificial pancreas, closed loop system, diabetes*

INTRODUCTION

The cure for diabetes has not been solved until today, which is why different methods have been investigated that seek to completely replace the endocrine function of the pancreas, and thereby aim to cure the disease. During diabetes, the islet cell apparatus of the pancreas − the islets of Langerhans − is completely destroyed. Three alternatives are currently available to replace the function: 1) transplantation (of the whole pancreas or pancreatic islet cells), 2) the use of beta cells that can be produced from stem cells, and 3) the use of an artificial pancreas. This paper deals with the research direction of the artificial pancreas.

In recent years, thanks to the development of information technology, the replacement of islet cell function has become a realistic possibility. The portable insulin pump (CSII: continuous subcutaneous insulin infusion) and the instantaneous glucose monitoring (rtCGM: real-time continuous glucose monitor) have been available in clinical practice for a long time, which form the technological basis of research and development. Using the traditional insulin pump and glucose monitoring together provides an open feedback system (OLS: open loop system), which, however, cannot ensure complete normoglycaemia. One of the most significant barriers to ensuring a normal blood glucose level is hypoglycemia, the

most common side effect of insulin treatment, which limits the success of the treatment. In the course of developments over the past few years, two new functions have been developed with the available tools to avoid hypoglycemia: suspension of insulin infusion in case of low glucose level (LGS: low glucose suspend) and predictive suspension of insulin infusion anticipating the upcoming low glucose level (PLGS: predictive low glucose suspend). Despite all this, it is still not possible to ensure long-term normoglycaemia in the majority of patients. Hypoglycemia cannot be avoided in many cases and the fear of it significantly worsens the quality of life of patients, therefore the research and development of the artificial pancreas (AP: artificial pancreas, or CLS: closed loop system) is also of fundamental importance from a clinical point of view.

The artificial pancreas is a system that can adjust the administration of insulin to the glucose level. The prototypes that could only be used in hospital conditions were developed in the 70s, ("biostator") however, portable systems have also appeared in the last decade, and they have recently been licensed for clinical use in the USA. Today's artificial pancreas consists of a portable insulin pump (CSII) communicating with a subcutaneous interstitial glucose sensor (CGM) and an algorithm that analyses the results and regulates insulin administration. The sensor continuously sends information about the interstitial glucose level to the algorithm, which, based on this, gives instructions to the pump for the necessary insulin infusion *(Figure 1)*. The components of the AP are reviewed below.

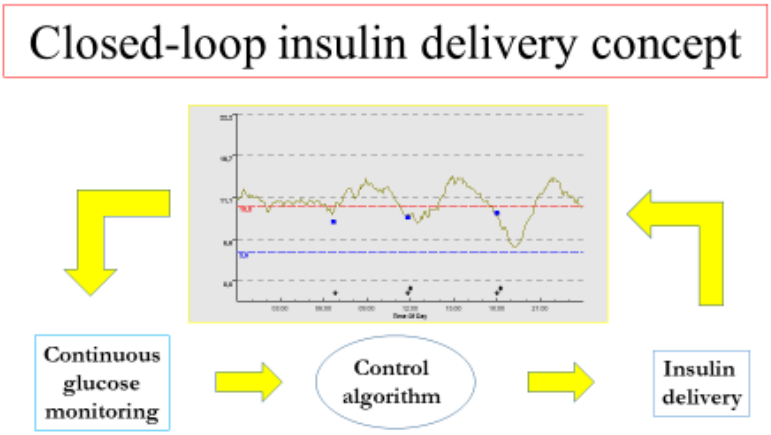

Figure 1. *Artificial pancreas*

Insulin pump

An insulin pump contains an insulin reservoir, a graphical interface, a battery, and mechanical and hardware components for injecting insulin into the subcutaneous tissue. Nowadays, many companies offer functional products that can be used to automatically administer insulin to the patient. In contrast to the traditional injection practice, the number of people choosing an insulin pump has been steadily increasing

lately. Their number is currently estimated at more than one million worldwide [1]. Insulin pumps can be divided into two main categories: catheter and patch versions. Traditional catheter-based pumps include devices from Animas, Medtronic, and Roche that connect a metal or plastic cannula placed under the skin to the pump's insulin reservoir. In contrast, the Omnipod patch system does not require a wire, the insulin reservoir is fixed above the injection point. In both cases, it is recommended to change the cannula every 3-6 days. The results of a recent comprehensive study showed no significant difference in HbA1c values between individual manufacturers and types [2]. In the 2000s, traditional catheter pumps were more common, but thanks to numerous technological innovations, the popularity of patch pumps is increasing nowadays [3].

Most advanced technologies leading to fully automated insulin delivery systems integrate the three main components of the AP into one device. Such an important milestone was the combined use of the CGM system and insulin pump, which allowed an algorithm to stop basal insulin administration in the event of hypoglycemia. An improved function of this can interrupt the insulin administration before the blood sugar drop occurs (this is available from the 640G series by Medtronic) [4]. It is an innovation that Medtronic's MiniMed 670G system can operate partially autonomously by continuously adjusting the basal insulin, which can be achieved using the "proportional-integral-derivative" (PID) control algorithm mentioned in more detail later [5]. In contrast to the seven-day operating time of CGM systems, the cannulas of insulin pumps must be changed every 3-6 days. Therefore, it is particularly important to develop cannulas that can be used to increase the service life and require fewer replacements. No significant difference was found between the currently used stainless steel and Teflon cannula in terms of inflammatory processes and lifespan. It is important to examine whether the additional cost of Teflon is associated with a significant increase in service life [6].

Sensor

The use of CGM systems is becoming more and more widespread, given that their cost implications are significantly lower than those of classic fingerprick measurements [7]. Their advantage over classic measurements is that they provide continuous feedback on the patient's glucose level, which, due to the continuous information, is a significant help in adjusting therapy. In addition, it helps patients to achieve both the glycemic goals set and the desired HbA1c level with the help of closer glycemic control. However, it must be emphasised that the sensor measures interstitial glucose levels and the blood glucose concentration is calculated from these data. The use of CGM is beneficial for all patients with diabetes regardless of the use of an insulin pump. In 2018, several clinical studies were also carried out, which proved that the use of such a system is helpful in all age groups and types of diseases [8]. By increasing the frequency of measurement, the patient can better adjust his/her treatment, and other important statistical information for the patient can be obtained. CGM systems consist of three main units: sensor, transmitter and

receiver. Depending on the technology, the sensor and the transmitter can be placed in the same device, they do not need to form separate units. There are solutions based on different measuring principles for the implementation of CGM systems. In most cases, the structure is attached to the patient's abdomen, where it is connected to the subcutaneous layer of the skin through a thin catheter. The most commonly used measurement method is based on the glucose oxidase enzyme, which can be used to estimate the patient's blood sugar level through changes in the electrical properties of the sensor. The enzyme catalyzes the conversion of glucose into gluconic acid, and an electric charge is indirectly created in the reaction. The estimated glucose concentration can be calculated from the magnitude of the charge created in the electrode with appropriate analogue and digital signal processing.

CGMs have many advantages as well as disadvantages. These disadvantages stem, on the one hand, from the lack of education of sensor users, as they may not use the device as prescribed. On the other hand, they represent a challenge from the point of view of engineering design. Due to technological limitations, the data of sensor measurements are available every five minutes on average, i.e. a sampling time of five minutes can be expected in the case of automated algorithms, which greatly complicates the design of a continuous regulator [9, 10].

The control algorithms used within the framework of AP require that the measurement data be available at appropriate intervals, which is currently possible primarily by using a CGM system. The control algorithms evaluate the incoming CGM data according to a given methodology, based on which the amount of insulin to be administered is determined. In practice, this means that if there is a discrepancy between the measured blood sugar level and the prescribed blood sugar level, an error signal is generated, and the amount of insulin to be administered is calculated concerning the level of the error signal.

Since insulin pumps use fast-acting insulin analogues (insulin aspart, lispro or glulisine among the active ingredients available in Hungary), control algorithms are expected to allow for the reaction dynamics and reaction kinetics of these preparations, which is usually the area of model creation and application. From the point of view of CGM, however, this means that reliable data must be available quickly enough so that the error signal generation and the amount to be administered can be calculated by the given algorithm. In daily practice, the availability of five-minute blood glucose measurement data is suitable for the design of "quasi-continuous" and discrete (sampled) algorithms.

In connection with the AP concept, several CGM systems have been tested in clinical conditions in recent years, which without exception were based on glucose oxidase enzyme technologies. In the vast majority of recent clinical trials, devices from three manufacturers were used: Medtronic's Enlite sensor, Dexcom's G series (mainly G4, G5 and G6) and Abbott's Freestyle Navigator II system. Currently, the Dexcom G6 is one of the most advanced CGMS systems available on the market. The biggest innovations of the sensor in terms of the AP concept are the ten-day wearing time, new data access options, smartphone display, and the use of factory settings. The latter allows patients to use the sensor without fingerprick calibration

after the sensor has been placed, which can perform measurements of adequate quality even without a reference value [11].

One of the most widely used versions of the Dexcom G series is the G4, which has also been successfully used in many AP-related clinical surveys (e.g. nighttime blood sugar control, as well as various distractions, stress, and physical activity) [12, 13]. It is worth mentioning that implantable CGM sensors have also appeared in recent years, of which Senseonics' Eversense sensor recently received FDA approval. This can be implanted for 90 days [14].

Algorithm

The third important component of AP is the control algorithm, which enables automated insulin administration. Since insulin pumps are currently mainly used for the treatment of T1DM patients, most of the control algorithms were also developed to automate this treatment. The main expectation of the AP is to keep the patient's blood glucose level in the normoglycemic range (3.6–6.0 mmol/l) despite the disturbing effects (food intake, exercise, etc.) so that only minimal intervention is required by the patient. Furthermore, the main criterion is that dangerously low blood sugar levels, which could endanger the patient, can be avoided in an automated way using the AP.

In the literature, we can find examples of the adaptation of many control methods to AP. The most promising directions include model predictive control (MPC), fuzzy logic control (FL), classical proportional-integral-derivative control (PID) and the use of robust control solutions [15]. All control algorithms are based on the fact that before we intervene in the process, we must first know the characteristic to be controlled at a given moment. In the case of AP, this is the patient's blood glucose level, the value of which is provided by the CGM system based on the measured tissue glucose value. From the difference between the measured value and the target value we want to achieve, we can create a so-called error signal. Individual algorithms are distinguished by the form in which this error signal is taken into account and possibly what other information is required to determine the intervention (insulin dose). Algorithms must meet certain qualitative and quantitative requirements. A qualitative requirement is to keep the blood sugar level in the appropriate range, while a quantitative criterion is the dose of insulin administered.

The first AP control algorithms were based on PID, because they are simple, which is why they are used most often in industrial applications to this day. This algorithm works in such a manner that it examines the blood sugar level coming from the CGM and the desired blood sugar level at each moment, which, when compared, forms an error signal proportional to the magnitude of the error. The algorithm also considers the value of the previous error signals (its integral) as well as the slope of the error change (derivative). Based on these, the algorithm produces the appropriate insulin dosage. It can be said about the control algorithm that its implementation is simple, but it is sensitive to all kinds of unprogrammed conditions. With this regulation, promising results could be achieved during the application of AP [16, 17].

Today, MPC is the most advanced and widespread AP control technique, but this method is very sensitive to changes in the patient's internal properties (e.g. ageing processes), as well as to differences between patients and external disturbances. MPC is a model-based approach that uses prediction, that is, estimates future blood glucose levels based on available information and the amount of insulin currently administered. This means that, based on a mathematical model (cost function) and other information, the regulator determines the amount of insulin that needs to be administered to meet the regulatory goals over time. The cost function describes the actual control goals, such as the amount of insulin used, the variability of blood sugar levels, etc [18].

Fuzzy logic control methods (FL) can also be found in the literature in connection with AP, but the clinical examination of these methods has only become timely in the last few years [19]. There are also attempts to use the recently fashionable machine learning algorithms, but the use of these methods is still in a very experimental stage [20].

In recent years, modern robust regulations regarding the AP concept have also appeared. The goal of these regulations is to eliminate deterministic disturbances that arise from physiological variations, as well as food intake as a disturbance affecting blood sugar levels. In other words, modern robust regulations aim to provide general security guarantees during AP operation. As a result, the given robust regulation may be able to minimise the disturbing effects resulting from parameter variability, food intake and possibly other effects [21−25]. These methods enable uniform handling of the already mentioned parameter variabilities and unfavourable mathematical properties and significantly simplify the controller design, as well as have favourable properties to minimise disturbing effects.

The approaches described above can be applied to systems based on insulin delivery (single-hormone AP). In addition, there are also dual hormone-based regulators, which not only administer insulin but also glucagon working as the so-called bionic systems (bihormonal AP). A major advantage of dual hormone regulators over the traditional AP concept is that they can handle external disturbances more effectively, such as larger, unpredicted food intake and vigorous exercise. This conceptually different new approach is gaining ground among AP researchers, and clinical trials have also provided promising results. However, some studies did not show a significant difference compared to the traditional method in certain age groups, and it should also be taken into account that the practical application of this method is also more complicated due to the double hormone handling [26, 27].

Clinical applicability

During the development of AP and control algorithms, an important aspect is their testing in clinical practice. Encouraging results have been obtained in numerous clinical trials in recent years. The AP that only administers insulin was tested for the first time in hospital conditions. These studies have demonstrated safety and efficacy for nocturnal blood glucose control and hypoglycemia. Later, the tests were also performed outside the hospital, and the safety and effectiveness proved to be

adequate. However, contradictory results were obtained, as some authors were able to demonstrate an improvement in the duration of the blood glucose value within the target range, while others could not prove this, only a reduction in the rate of hypoglycemia.

Some researchers have examined the applicability of AP in the case of T2DM in hospital conditions and the results have proven to be promising [28]. Other studies have examined the effectiveness of the regulations in the case of exercise of varying intensity and unpredicted, large amounts of food intake, with favourable results [29, 30]. During the testing of the bionic AP, the first results in terms of safety and efficiency were promising, and the results of the subsequent tests also confirmed the previous data. In a recent study, better blood sugar control and a lower rate of hypoglycemia could be achieved with the use of bihormonal AP than with the use of an insulin-only AP or a traditional insulin pump. However, the few available studies are not yet sufficient to determine whether the currently used bionic AP has clear benefits. Further longer-term clinical studies are necessary to establish this.

Several difficulties arise during the development of the artificial pancreas. One is the latency between blood glucose and interstitial glucose levels, which delays the adaptation of insulin administration. The other is the late onset of action of the meal insulin and the still too long duration of action, which causes the postprandial blood sugar rise to be significant, and the increased risk of late hypoglycemia after a meal. Another difficulty is monitoring and avoiding the metabolic effects of unplanned physical activity. In the case of bionic AP, the instability of glucagon preparations is also a difficulty, which makes it necessary to replace the hormone daily. But last but not least, the non-physiologic route of insulin administration (subcutaneous tissue vs. portal vein) and glucose measurement (interstitial vs. intravascular compartments) are prominent challenges needed to be overcome in the future [31].

In summary, intensive research and development regarding the treatment and care of diabetes have been going on for decades. Currently, the development of the artificial pancreas is already in the shorter term with the possibility of clinical application promises. Although diabetes is still an essentially incurable disease, with the automation of insulin administration methods developed over the years, AP can be an attractive option for many patients. Clinical trials conducted in recent years have proven the success of the developments, however, many difficulties and barriers still need to be overcome for AP to become a widely used and fully automated method for people with diabetes.

REFERENCES

[1] Nimri, R., Dassau, E., Segall, T., Muller, I., Bratina, N., Kordonouri, O. et al.: Adjusting insulin doses in patients with type 1 diabetes who use insulin pump and continuous glucose monitoring: Variations among countries and physicians. *Diabetes Obes. Metab.*, 2018, 20 (10), pp. 2458−2466. https://doi.org/10.1111/dom.13408

[2] Leelarathna, L., Roberts, S. A., Hindle, A., Markakis, K., Alam, T., Chapman, A, et al.: Comparison of different insulin pump makes under routine care conditions in adults with Type 1 diabetes. *Diabet. Med.*, 2017, 34 (10), pp. 1372−1379, https://doi.org/10.1111/dme.13412.

[3] Karges, B., Schwandt, A., Heidtmann, B., Kordonouri, O., Binder, E., Schierloch, U. et al.: Association of insulin pump therapy vs. insulin injection therapy with severe hypoglycemia, ketoacidosis, and glycemic control among children, adolescents, and young adults with type 1 diabetes. *JAMA*, 2017, 318 (14), pp. 1358−1366, https://doi.org/10.1001/jama.2017.13994.

[4] Abraham, M. B., Nicholas, J. A., Smith, G. J., Fairchild, J. M., King, B. R., Ambler, G. R. et al.: Reduction in hypoglycemia with the predictive low-glucose management system: A long-term randomized controlled trial in adolescents with type 1 diabetes. *Diabetes Care*, 2018, 41 (2), pp. 303−310. https://doi.org/10.2337/dc17-1604

[5] Messer, L. H., Forlenza, G. P., Sherr, J. L., Wadwa, R. P., Buckingham, B. A., Weinzimer, S. A. et al.: Optimizing hybrid closed-loop therapy in adolescents and emerging adults using the MiniMed 670G System. *Diabetes Care*, 2018, 41 (4), pp. 789−796, https://doi.org/10.2337/dc17-1682.

[6] Hauzenberger, J. R., Münzker, J., Kotzbeck, P., Asslaber, M., Bubalo, V., Joseph, J. I. et al.: Systematic in vivo evaluation of the time-dependent inflammatory response to steel and Teflon insulin infusion catheters. *Scientific Reports*, 2018, 8 (1), p. 1132, https://doi.org/10.1038/s41598-017-18790-0.

[7] Murphy, H. R., Feig, D. S., Sanchez, J. J., de Portu, S., Sale, A.: CONCEPTT Collaborative Group: Modelling potential cost savings from use of real-time continuous glucose monitoring in pregnant women with Type 1 diabetes. *Diabet. Med*., June 2019, https://doi.org/10.1111/dme.14046.

[8] Heinemann, L., Fleming, G. A., Petrie, J. R., Holl, R. W., Bergenstal, R. M., Peters, A. L.: Insulin pump risks and benefits: A clinical appraisal of pump safety standards, adverse event reporting, and research needs: A joint statement of the European Association for the Study of Diabetes and the American Diabetes Association Diabetes Technology Working Group. *Diabetes Care*, 2015, 38 (4), pp. 716−722, https://doi:10.2337/dc15-0168.

[9] Klonoff, D. C., Ahn, D., Drincic, A.: Continuous glucose monitoring: A review of the technology and clinical use. *Diabetes Res. Clin. Pract*., 2017, 133, pp. 178−192, https://doi:10.1016/j.diabres.2017.08.005.

[10] Eigner G.y, Kovács L.: Realization methods of continuous glucose monitoring systems. Buletinul stiintific al universitatii politehnica din timisoara romania seria automatica si calculatorae 2014, 59 (73), pp. 175−182.

[11] *Dexcom G6, continuous glucose monitoring system*. User guide, 2018. https://s3-us-west-2.amazonaws.com/dexcompdf/G6-CGM-Users-Guide.pdf

[12] Bequette, B. W., Cameron, F., Buckingham, B. A., Maahs, D. M., Lum, J.: Overnight hypoglycemia and hyperglycemia mitigation for individuals with type 1 diabetes: How risks can be reduced. *IEEE Control Systems*, 2018, 38 (1), pp. 125−134, https://doi:10.1109/MCS.2017.2767119.

[13] Turksoy, K., Littlejohn, E., Cinar, A.: Multimodule, multivariable artificial pancreas for patients with type 1 diabetes: Regulating glucose concentration under challenging conditions. *IEEE Control Systems*, 2018, 38 (1), pp. 105−124, https://doi:10.1109/MCS.2017.2766326.

[14] Christiansen, M. P., Klaff, L. J., Brazg, R., Carlson, G., Tweden, K. S.: A prospective multicenter evaluation of the accuracy of a novel implanted continuous glucose sensor: PRECISE II. *Diabetes Technol. Ther*., 2018, 20 (3), pp. 197−206, https://doi.org/10.1089/dia.2017.0142.

[15] Peyser, T., Dassau, E., Breton, M., Skyler, J. S.: The artificial pancreas: Current status and future prospects in the management of diabetes. *Ann N Y Acad. Sci*., 2014, 1311, pp. 102−123, https://doi:10.1111/nyas.12431.

[16] Kamath, S.: Model-based simulation for Type I diabetic patients. *Asian Am. J. Chem*., 2013, 1, pp. 11−19.

[17] Bondia, J., Romero-Vivo, S., Ricarte, B., Diez, J. L.: Insulin estimation and prediction: A review of the estimation and prediction of subcutaneous insulin pharmacokinetics in closed-loop glucose control. *IEEE Control Systems*, 2018, 38 (1), pp. 47−66, https://doi:10.1109/MCS.2017.2766312.

[18] Pinsker, J. E., Laguna Sanz, A. J., Lee, J. B., Church, M. M., Andre, C., Lindsey, L. E. et al.: Evaluation of an artificial pancreas with enhanced model predictive control and a glucose prediction Trust index with unannounced exercise. *Diabetes Technol. Ther*., 2018, 20 (7), pp. 455−464. https://doi:10.1089/dia.2018.0031

[19] Kong, J. D., Kumar, S. S., Palumbo, P.: DDE Models of the glucose-insulin system: A useful tool for the artificial pancreas. In: Delitala, M., Ajmone Marsan. G, (eds.): Managing Complexity, Reducing Perplexity. Springer Proceedings in Mathematics & Statistics. Springer International Publishing, 2014, pp. 109−117.

[20] Mhaskar, H. N., Pereverzyev, S. V., van der Walt, M. D.: A deep learning approach to diabetic blood glucose prediction. *Front Appl. Math. Stat*., 2017, 3 (14), pp. 1−11, https://doi:10.3389/fams.2017.00014.

[21] Kovács, L.: A robust fixed point transformation-based approach for type 1 diabetes control. *Nonlinear Dynamics*, 2017, 89 (4), pp. 2481−2493.

[22] Kovács, L.: Linear parameter varying (LPV) based robust control of type-I diabetes driven for real patient data. Knowledge-Based Systems 2017, 122, pp. 199−213, https://doi:10.1016/j.knosys.2017.02.008.

[23] Colmegna, P., Sánchez-Peña, R. S., Gondhalekar, R.: Linear parameter-varying model to design control laws for an artificial pancreas. *Biomed. Signal Process. Control*, 2018, 40, pp. 204−213, https://doi:10.1016/j.bspc.2017.09.021.

[24] Szalay, P., Eigner, G., Kovács, L. A.: Linear matrix inequality-based robust controller design for type-1 diabetes model. *IFAC Proceedings Volumes*, 2014, 47 (3), pp. 9247−9252, https://doi:10.3182/20140824-6-ZA-1003.02451.

[25] Galambos, P., Kuti, J., Baranyi, P.: On the Tensor Product based qLPV modeling of bio-inspired dynamic processes. In: *2013 IEEE 17th International Conference on Intelligent Engineering Systems (INES)*, 2013, pp. 79−84, https://doi:10.1109/INES.2013.6632787.

[26] Gingras, V., Rabasa-Lhoret, R., Messier, V., Ladouceur, M., Legault, L., Haidar, A.: Efficacy of dual-hormone artificial pancreas to alleviate the carbohydrate- counting burden of type 1 diabetes: A randomized crossover trial. *Diabetes Metab*., 2016, 42 (1), pp. 47−54. https://doi:10.1016/j.diabet.2015.05.001

[27] Bally, L., Thabit, H., Hartnell, S., Andereggen, E., Ruan, Y., Wilinska, M. E. et al.: Closed-loop insulin delivery for glycemic control in noncritical care. *N. Engl. J. Med*., 2018, 379 (6), pp. 547−556. https://doi:10.1056/NEJMoa1805233

[28] Thabit, H., Hartnell, S., Allen, J. M., Lake, A., Wilinska, M. E., Ruan, Y. et al.: Closed-loop insulin delivery in inpatients with type 2 diabetes: A randomised, parallel-group trial. *Lancet Diabetes Endocrinol*., 2017, 5 (2), pp. 117−124, https://doi:10.1016/S2213-8587(16)30280-7.

[29] Breton, M. D., Cherñavvsky, D. R., Forlenza, G. P., DeBoer, M. D., Robic, J., Wadwa, R. P. et al.: Closed-loop control during intense prolonged outdoor exercise in adolescents with type 1 diabetes: The artificial pancreas Ski study. *Diabetes Care*, 2017, 40 (12), pp. 1644−1650, https://doi:10.2337/dc17-0883.

[30] Forlenza, G. P., Cameron, F. M., Ly, T. T., Lam, D., Howsmon, D. P., Baysal, N. et al.: Fully closed-loop multiple model probabilistic predictive controller artificial pancreas performance in adolescents and adults in a supervised hotel setting. *Diabetes Technol. Ther*., 2018, 20 (5), pp. 335−343. https://doi:10.1089/dia.2017.0424

[31] Kovács, L., Eigner, Gy., Siket, M., Barkai, L.: Control of diabetes mellitus by advanced robust control solution. *IEEE Access*, 2019, 7, pp. 125609−125622. https://doi.org/10.1109/ACCESS.2019.2938267