THE DESIGN OF AN INSULIN PUMP – CONCEPT OF CLOSING THE LOOP

Hubert J. Hawłas, Krzysztof Lewenstein

Abstract:

This paper explains what insulin pump is and outlines basic requirements for such device. The material presented in this paper is an attempt to collect actual knowledge about closed loop insulin delivery systems. From scientific point of view we are going to propose the closed loop insulin-dispensing device with control built on the base of predictive neural network system. The blocks of such systems are listed, and main problems to overcome are defined.

Keywords: *insulin pump, diabetes, artificial pancreas.*

1. Introduction

An insulin pump is a device used for continuous dosage of insulin at a selected rate. An ordinary insulin pump is automatic drug-dispensing device that works in open loop mode. This means it exactly follows programmed drug dispending instructions with no any feedback form the patient body. Even with such easy job to do this device significantly facilitates treatment and improves the lives of diabetic patients.

In conventional insulin therapy [1], two types of insulin are needed: long-term and short-term insulin. Long-term type is used for daily insulin demand. Short-term type is fast acting insulin that is needed to reduce postprandial blood glucose (BG) level and its dose mainly depends on carbohydrates contents in meals.
An insulin pump uses only short-term insulin, which is distributed evenly during the day, so it works on a long-term basis (called basal), and a dose to counteract food (called bolus) that works on a short-term basis.

This small mechatronics device makes the life of patients more normal. It is important especially in the case of children. Unfortunately, insulin pumps are not easily affordable because of their price, as high as several monthly incomes of an average family in Poland. There is no manufacturer of such pumps in Poland, which is one of the reasons of their high price. Starting production in Poland would lower the price and make the device more affordable, which is one of the reasons why we started our design.

2. Ordinary insulin pumps

There are three types of such devices (a) hospital insulin pump, (b) personal insulin pump, (c) implantable insulin pump. This paper regards insulin pump of personal type, which is an iPod-size unit. The whole unit and each of its blocks must fulfil clinical, technical and user requirements

Treatment requires that the person be connected to the insulin pump for nearly 24 hours a day, 7 days a week. Thus patient carries the pump with himself/herself mostly all the time and the pump acts almost like a part of his/her body. This indicates the importance of a well-thought out design.

Insulin pump is compact mechatronics device, which may be split into functional blocks as show in Fig. 1. The link between the human body and the insulin pump is The Infusion Set. It consists of a needle or cannula and thin tubing connected to a reservoir for insulin (Cartridge).

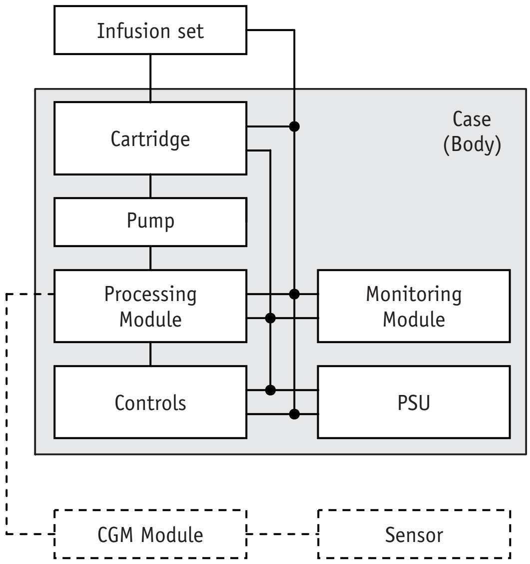

Fig. 1. Functional diagram of an insulin pump.

The Pump Module controlled by Processing Module doses a precise amount of medicine through Infusion Set into the patient's body. There are also other blocks, as Control Module that let user to communicate with device, or Power Supply Unit (PSU), which controls battery level and provides power to whole units. The Monitoring Module may be a function of the Processing Module instead of being a device by itself. It has to monitor proper work of all blocks of the pump. It must detect any malfunction of the whole unit and also has to inform the user about it, e.g. about a disconnected infusion set.

Blocks in dashed line are external and optional part of the insulin pump. These modules are planned in a version with closed-loop operation. The Continuous Glucose Monitoring (CGM) Module and a Sensor are devices for measuring level of blood glucose. Our plan is that the glucose sensor would allow creating a closed loop control of insulin dosage making the insulin pump work almost like an artificial pancreas.

2.1. Basic requirements.

Giving priority to the functional specifications is mandatory requirement for reliable and safe operation. The device must have a monitoring system that ensures safe operation in case of hardware failure or improper usage. Not only electrical and mechanical components have to be reliable but working algorithm has to be safe, too. Some other requirements are: miniaturization, energy-efficient design or basal range, duration and frequency, or types (shape) of bolus.

2.2. Patient wish list

Some users would like to have some extra features/functions in their pumps [2] amongst them the remote control is mentioned often. Pumps are quite often hidden under clothing, so using a remote control would help to take a bolus or check an alarm when in public. Remote control in the form of a hand watch is a solution suggested by some of them.

Another feature/function that users of the insulin pumps would like to have is the possibility of scanning meal for contents of carbohydrates leading to the automatic insulin dosage. Unfortunately, this feature/function looks sci-fi idea, however, we can create a user-edited library with meals and their contents of carbohydrates and knowing approximate body response to insulin and carbohydrates than calculate the insulin bolus.

3. Closing the loop

Just an ordinary insulin pump is a "dumb machine" that does exactly what its wearer says. But we can imagine device that will automatically choose appropriate dose of medicine to correct BG level. In this case we could treat it as an artificial pancreas. But term artificial pancreas popularly used for such devices may be seemed not fully adequate even if we are interested in glycemic control only. There are more functions of pancreas and glycemic control is more complex. The real healthy pancreas produces amylin (IAPP) and glucagons (GCG) along with insulin (INS) to stabilize BG level. Action of glucagon is opposite to that of insulin, which instructs liver cells to take in glucose from blood. Effect of amylin is to slow down rate at which glucose appears in blood, by slowing down digestion. Use of synthetic amylin that is called symlin in treatment of diabetics type 1 may reduce amount of needed insulin even by 50% [3]. Furthermore there are many other factors affecting natural physiological glucose level control, for example neural signals.

The function of closed-loop BG level control system based solely on insulin delivery is closer to just eta-Cell working itself than the whole pancreas. Idea of such device is shown in Fig. 2.

A healthy pancreas begins secreting insulin when a person smells or thinks about food [4], but its artificial counterpart does it when senses that BG level is rising. The consequence of this approach is that we will be always a step behind the right glucose level, but even if we only manage to reduce events of hyper and hypoglycemia it be a success.

The problem is complex but preliminary tests shows that this kind of treatment improves diabetes control [5]. A closed-loop insulin delivery system consists of a three blocks, which are: (i) IDD Insulin Dispensing Device, (ii) CGM Continuous Glucose Monitoring, (iii) Algorithm.

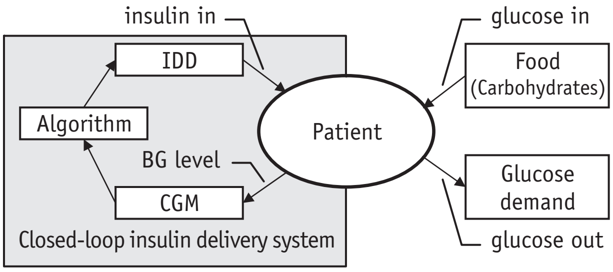

Fig. 2. The closed-loop insulin delivery system diagram.

3.1. Insulin Dispensing Device

Insulin Dispensing Device (IDD) dose insulin into patients' blood. It may be a standard insulin pump that is described in sections above. There are no technical problems to overcome with the insulin pump itself, but there is an issue about subcutaneous insulin delivery, which causes delays in absorption.

3.2. Continuous Glucose Monitoring

CGM that stands for Continuous Glucose Monitoring is responsible for continuous measuring BG levels, however it may deliver results with short intervals instead of continuous reading. Most of the glucose sensors are placed in the tissue just beneath the skin (minimal invasion sensor) and they measure glucose level not in the blood but in the interstitial fluid and there are some consequences of this approach.

First and foremost is that, there is a lag time between change of glucose level in blood and in interstitial fluid. This is not a significant problem when glucose level is not changing rapidly, but it becomes significant after meals when such situation occurs. For example delay for the microdialysis sensor is 7.1 ± 5.5 min. [6] or for the subcutaneous glucose sensor the half-time response was estimated to be 4.0 ± 1.0 min. [7]. But some users report that they experience delay between 10.15 min. This imposes that in case of rapid changes of BG level the event of hyperglycemia or hypoglycemia may be read as euglycemia.

Second fact is that CGM has to be calibrated with traditional BG measurement, so there is a need for use both CGM system and from time to time use of traditional glucose meter.

Next problem with sensors is that their accuracy drops when measuring low BG levels. "CGM sensors experienced periods of transient loss of sensitivity, particularly during hypoglycemia, identified as sensor readings holding steady at a very low glucose value" [8].

Another point to improve glucose sensor is to make it non-invasive or implantable for long term, because patients are not satisfied with inserting another needle type device in their body. This shows that sensor design needs improvement.

3.3. Algorithm

Algorithm is a link between IDD and CGM. An idea is that it will take measurement of BG from CGM and will respond with an appropriate insulin dosing instructions for IDD. Unfortunately, this is not a trivial task.

The basal and bolus amount and timing needs to be set basing on BG level, but as mentioned before there is a lag time between the insulin delivery and moment when it reaches blood system and starts working, plus another lag time between change of BG level and response from CGM sensor. Algorithm has to cope with these lags. that's the main problem to overcome. Some of the researchers suggest step back from fully automated closed-loop insulin delivery to the hybrid approach with manual insulin delivery before meal. The result shows that it improves postprandial glycemic excursions [9].

There are two main concepts for glycemic control in the treatment of type 1 diabetes: the Proportional-Integral-Derivative (PID) system and the Model Predictive Control (MPC) system [10].

PID system is known from the industrial sector and it utilizes formula that calculates the insulin dose by proportional, integral and derivative parts of glucose error signal, where error signal is difference between actual and desired BG level.

“Model Predictive Control (MPC) systems are highly adaptive methods that utilize mathematical models based on observations of biological behaviour patterns using system identification…” [10]. MPC is also referred as receding horizon control. An idea of algorithm is to solve finite horizon optimal control problem in a current state and over a fixed future interval. For calculation it takes into account current state as an initial state and also future constrains. It applies controls only for next sampling time and again recalculates controls.

In effect it provides a solution for each sampling time instead of single solution for all points along the timeline. This allows for parameter optimisation while algorithm is running. “In sillico study effectively highlighted the fact that MPC systems improved glucose regulation over classical PID systems in limiting the oscillation of glucose levels.” [10]

“The application of further mathematical models, such as fuzzy control and artificial neural networks, are also promising, but are largely clinically untested.” [10]

We have some experience in using neural networks of different kind for computer aided of the medical (cardiological) diagnosis and, what's more important, for prediction individual insulin dosing for diabetics patient [11].

As mentioned before, BG level depends on many factors thus it may be worth to take into account some other parameters than BG level itself. For example, we know that body glucose demand depends (somehow) on physical activity. Physical activity itself is hard to measure, however blood pressure, heart rate and body temperature are easily measurable, and they give some information about physical activity.

Neural network control is suitable for control of BG level because it can be highly individualised and trained when running. Neural networks can be tuned to person's metabolism and typical day activity by continuous body monitoring.

4. Conclusion

All requirements specified above will make possible to design an insulin pump with all necessary functions. We hope that this work will result in working out a model of an insulin pump and control algorithm that fully or semi automatically will choose an insulin dose.

The concept of closed loop insulin delivery system is promising treatment method for persons with diabetes because it has to reduce chronic complication of diabetes mellitus potentially. But before technology will be available to utilization there is a place for improvement in stability and accuracy of CGM sensors. Problems and limitations with delayed action and BG sensing due to subcutaneous insulin delivery/glucose sensing also needs to be overcome.

There is a need for reliable and safe control algorithm for a device working in closed-loop mode. We need to trace improvement of CGMs and work done to the closed-loop systems. We believe that our work on control algorithm with artificial neural network will bring new information to overall design of such medical device.

We have already started consultations with medical specialists to meet medical requirements of an insulin pump. From the scientific point of view, our design will enable us to inter-compare typical insulin treatments to meet individual requirements using a closed loop insulin control based on a glucose sensor and a neural network system.

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References

[1] Tatoń J., “*Cukrzyca wymagająca wstrzyknięć insuliny Poradnik dla pacjentów*”, 1st ed. Warszawa: Wydawnictwo Lekarskie PZWL, 1998, p. 424 and f. (in Polish)
[2] Your Insulin Pump Proposals, *www.diabeteshealth.com/read/2007/12/13/5586.html*
[3] Symlin Word Wide Web, *www.symlin.com*
[4] Friedrich M.J., “Artificial Pancreas May Soon Be a Reality”, *JAMA*, vol. 301, issue 15, Apr. 2009, pp. 1525-1527.
[5] Hovorka R., Chassin L.J., Wilinska M.E., Canonico V., Akwi J.A., Federici M.O., Massi-Benedetti M., Hutzli I., Zaugg C., Kaufmann H., Both M., Vering T., Schaller H.C., Schaupp L., Bodenlenz M., Pieber T.R., „Closing the loop: the adicol experience”, *Diabetes Technol. Ther.*, vol. 6, issue 3, 2004, pp. 307-318.
[6] Wentholt I.M., Vollebregt M.A., Hart A.A., Hoekstra J.B., DeVries J.H., “Comparison of a Needle-Type and a Microdialysis Continuous Glucose Monitor in Type 1 Diabetic Patients”, *Diabetes Care*, vol. 28, issue 12, December 2005, pp. 2871-2876.
[7] Steil G.M., Rebrin K., Mastrototaro J., Bernaba B., Saad M.F., “Diabetes Technology & Therapeutics”, vol. 5, issue 1, January 2003, pp. 27-31.

[8] Kovatchev B., Anderson S., Heinemann L., Clarke W., "Comparison of the Numerical and Clinical Accuracy of Four Continuous Glucose Monitors", *Diabetes Care*, vol. 31, issue 6, June 2008, pp. 1160-1164.
[9] Weinzimer S.A., Steil G.M., Swan K.L., Dziura J., Kurtz N., Tamborlane W.V., "Fully Automated Closed-Loop Insulin Delivery Versus Semiautomated Hybrid Control in Pediatric Patients With Type 1 Diabetes Using an Artificial Pancreas", May 2008, vol. 31, pp. 934-939.
[10] El Youssef J., Castle J., Ward W., "A Review of Closed-Loop Algorithms for Glycemic Control in the Treatment of Type 1 Diabetes", *Algorithms*, vol. 2, issue 1, 2009, pp. 518-532.
[11] Lewenstein K., Czerwińska D., „Prediction of Twenty four hour insuline doses and glycaemia profiles in a neural network based system", *Pol. J. of Med. Phys. and Eng.*, vol. 5, issue 1, 1999, pp. 21-33.