Status of creation of hardware-software complex of automatic control of the insulin delivery

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Abstract. The article discusses issues related to the prospects for the implementation of the idea of creating a hardware-software complex for automated regulation of insulin delivery. Today, there are drugs that allow people to live relatively comfortable even with the most serious types of diabetes. The main difficulty of insulin therapy is the need for consistency (at any time, day or night) of carrying out the control and regulation of the drug infusion into the patient's body. Unfortunately, not all patients are able to perform it properly. The ideal solution could be a system that performs all these actions automatically without the participation of the patient. Therefore, the implementation of the idea of creating a hardware-software system for automatic regulation of insulin delivery using the program-adaptive control scheme is relevant. The article forms the general requirements for an approach capable of providing safe medical care for people with type 1 diabetes. There are requirements for the hardware-software complexes of automatic regulation of insulin delivery must correspond are formulated. Also the block diagram is presented.

1. Introduction

Today there are more than 34 million people in the world suffering from insulin-dependent diabetes mellitus (type 1 diabetes). More than 1 million patients live in Russia. More than 10 thousand in Tatarstan. According to the Diabetes Institute "Endocrinological Research Center" of the Ministry of Health of the Russian Federation, this figure increases annually by 6% [1].

The most physiological method of administering insulin for diabetics is the insulin pump (insulin pump). However, the delivery of insulin is manually controlled by the patient himself, and it is almost impossible to achieve perfect compensation. There is the following situation according to the research on diabetes mellitus compensation in adolescents [2]: only 13% of patients are fully compensated (stable maintenance of blood glucose level, as close as possible to normal values), 16% are in a subcompensation state (intermediate state between compensation and decompensation). The overwhelming number of patients - 71% - are decompensated (a condition in which the blood sugar level is not amenable to correction with drugs, as a result of which serious lesions of many systems and organs of the patient develop).

One of the temporary solutions to this problem is to create a system that simulates the algorithm of a healthy pancreas. This system should be based on data on the level of blood sugar...
and physiological features of a particular patient, automatically calculate the required dose of insulin and inject it into the patient’s body. At the same time it makes sense to design and develop such the comprehensive automated system for collecting, storing, processing information and adaptive management.

Separately, we note that an artificial intelligence (AI) block. This block can be included in such an ambient system, but due to the lack of stable and safe AI samples, we still offer purposefully and deliberately limited to AI and software-adaptive control (“intelligent” unit).

Let’s formulate the requirements for the system and its possibility of hardware-software complex for the automatic regulation of insulin delivery in particular.

2. Requirements for the system of hardware-software complexes for automatic regulation of insulin delivery

We formulate the basic requirements for the system:

(1) Minimum risk for the patient, provided by relying on modern standardized and optimized algorithms for specialized medical care for diabetics.

(2) Convenience of targeted use (preservation of the patients state of compensation for an arbitrarily long period of time while observing and fulfilling a certain list of requirements).

(3) Availability (this means the acquiring or receiving by quota, that is, if the personal hardware-software complex for automatic regulation of insulin delivery is too expensive or too difficult to manufacture, then it will become practically useless and the binding system will be idle without need).

(4) The possibility of interfacing with modern devices of communication (mobile devices, computers, etc.).

(5) The ability to provide viewing and collecting data on the patient’s condition (patients) directly from the patient’s personal device and remotely. It should be noted the need to ensure high reliability and efficiency of such data, which can be achieved using appropriate models, methods and approaches [3],[4],[5].

(6) Availability of the necessary interfaces for viewing the collected data and the possibility of their on-line processing, analysis and provision of the processing results to interested persons who have the appropriate permission for this with the use of modern computing tools [6],[7],[8]

(7) Ensuring the required level of information security [9].

In general a huge number of current existing automated systems for collecting, storing and processing information corresponds to these requirements. But the medical specificity of the problem under consideration introduces its own characteristics in the design and development of such system in the design and development of an automated feed control software insulin (especially its interfaces to the ambient system).

Firstly, we will present a sketch of the structural diagram of such a system of complexes (figure 1). There is the following notation in figure 1:

- CQS - communication and query server;
- \( P_1, ..., P_N \) - patients with insulin-dependent diabetes mellitus (type 1 diabetes);
- \( PCD_1, ..., PCD_{i}, ..., PCD_N \) - a personal compensation device, that is, ensuring stable maintenance of the level of glucose in the blood, which corresponds most to the normal values for a particular patient;
- \( M_1, ..., M_R \) - medical workers who, either remotely or in direct personal contact with the patient, monitor and possibly change the settings of the onions of one or several patients;
3. Hardware-software complex for automatic regulation of insulin delivery

Specify requirements for PCD.

(1) the subsystem should be executed from blocks with clearly defined functionality;
(2) each unit of the subsystem must have the ability to function autonomously;
(3) component parts of the blocks should be produced in series;
(4) the component parts must be of domestic production;
(5) all components of the units must be obtained state certificates for the possibility of their use for medical purposes.

We will offer one of the layout options for the PCD. The hardware-software complex of automatic regulation of insulin delivery could be consist of three main blocks:

(1) a sensor measuring the patient’s blood glucose level;
(2) an insulin pump that provides continuous administration of the drug subcutaneously through a catheter;
(3) an intelligent block linking all components into a single closed loop system.

The intelligent block noted in the third item of the list should receive data from the sensor, calculate the required dose (it takes from account the physiological data of the particular patient entered into it) and generate the control signal for the insulin pump to administer the calculated dose. The first two components - the sensor and the insulin pump - are usually serial standard medical products, and there are freely sold or provided to diabetics in the Russian Federation, which ensures that requirements one and two of the above list are met. There is a problem associated with the design and development of an "intelligent" unit, such a unit is called the "Artificial Pancreas System" (APS). The hardware part of the intelligent unit can be assembled from standard components based on a microcomputer and a radio card transmitting a radio signal. The "intelligent" block is understood only as a software-adaptive control scheme, which does not allow for the provision of an intelligent control scheme. We present a block diagram of the hardware-software complex of automatic regulation of the supply of insulin (PCD), figure 2.

Let us briefly explain the figure 2 - a term that has not previously been encountered in the article, and arrows marked with numbers:

- communication and control device - a mobile device of the patient, either a health worker or a researcher with the ability to access the Internet; it uses wireless networks, Bluetooth data transmission channels, which is equipped with an interface to the APS for control (which also provides for the analysis of the patients state over time, any reports related to the data collected on the patient’s condition and on the functioning of the APS) to its directly and with the insulin pump indirectly through the APS; a personal computer can also act as such a device which can additionally allow using the interface to the APS via a twisted pair wired network;
- arrow 1) - the ability of the patient through the communication and control device to obtain the necessary permissible and secure access to the APS through one of the available communication channels with him;
- arrow 2) - the ability of the patient through the interface of an insulin pump to influence its mode of operation and change it to any other;
- arrow 3) - the possibility of a direct connection of the patient to the APS for service purposes in case of he has the appropriate qualifications and admission in exceptional cases;
• arrow 4) - shows the physical process of measuring the patient’s blood sugar level by the sensor;
• arrow 5) - shows the process of transmitting information about the level of sugar in the patient’s blood received by the sensor in the APS;
• arrow 6) - shows the ability of the APS to connect to the Internet or some other computer network. The modules and blocks for ensuring the required level of information security of the PCD should be introduced into the APS software;
• arrow 7) - indicates the presence of a physical channel for the exchange of data and commands between the ICG and the communication and control device;
• arrow 8) - indicates the presence of a physical channel for the exchange of data and commands between the ICH and the insulin pump.

4. The Open Artificial Pancreas System project
Which implementations of APS exist today in the world? In fact, the only platform that allows you to create an APS is a project OpenAPS. OpenAPS is an open and transparent effort to make safe and effective basic Artificial Pancreas System (APS) technology widely available to more quickly improve and save as many lives as possible and reduce the burden of Type 1 diabetes. The community has created a safety-focused reference design and a reference implementation of an overnight closed loop APS system that uses CGM sensors estimate of blood glucose (BG) to automatically adjust basal insulin levels, in order to keep BG levels inside a safe range overnight and between meals. OpenAPS uses term – temporal insulin injection rates (temporary basal or basal).

OpenAPS is a simplified Artificial Pancreas System (APS) designed to automatically adjust an insulin pumps basal insulin delivery to keep blood glucose (BG) in a safe range overnight and between meals. It does this by communicating with an insulin pump to obtain details of all recent insulin dosing (basal and boluses), by communicating with a Continuous Glucose Monitor (CGM) to obtain current and recent BG estimates, and by issuing commands to the insulin pump to adjust temporary basal rates as needed. It follows the same basic diabetes math that a person would do to calculate a needed adjustment to their BG but its automated and precise in its measurements.

The following figure 3 shows the appearance of the assembled APS system, which is placed on a patient with type 1 diabetes.

Figure 3. The system of closed-loop control in diabetes type 1 diabetes mellitus (T1DM). Components of the OpenAPS system (installation example on a volunteer tester): 1 - insulin pump, 2 - blood glucose measurement sensor, 3 - monitoring device (APS - microcomputer).
5. APS operation algorithm

It is accepted to consider biological systems as stochastic nonlinear systems with multi-compartmental interactions [11]. The same applies to the system of regulation blood glucose concentrations (BG). There are 2 main classes of mathematical models designed to predict the value of BG and control it [12]:

- empirical (based on evidence);
- based on physiological and pathophysiological principles (theoretical models). In the openAPS project, a simple and reasonably safe empirical model is used to predict BG. But the developers themselves openAPS report that the model in the future may be replaced by another.

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If we turn to the consideration of the essence of the algorithm for the automatic regulation of the blood sugar level in a patient with diabetes mellitus, which is used in OpenAPS, we will be able to see an empirical algorithm that includes several interconnected blocks:[13]

- Basic overnight operation (oref0)
- Adjusting for unexpected BG deviation
- Bolus snooze
- oref1 and supermicroboluses

5.1. Basic overnight operation (oref0)

OpenAPS uses past information about bolus and temporal insulin injection rates in conjunction with DIA (Duration of Insulin Action), also OpenAPS uses published so-called pump IOB curves to calculate current net IOB (pure insulin on board or active in the body). The value of DIA usually ranges from 2 to 8 hours, most often it is about 3 hours, the appearance of the IOB is shown in figure 4, it shows how the IOB is modified for different values of DIA (from 2 to 8 hours)[14]. For the calculation of intermediate values IOB use analytical formulas. Then, if no bolus was entered, OpenAPS can use the current glucose reading from the CGM to calculate a possible BG estimate as follows:

\[ \text{currentBG} - (\text{ISF} \times \text{IOB}) = \text{possibleBG} \]  \hspace{1cm} (1)

Where in (1) ISF – Insulin sensitivity factor.

If the current BG is below the configured threshold (30mg/dl below the target range), OpenAPS enters the low glucose mode and continues to issue 30 minute time bases equal to zero until the BG starts to grow. Otherwise, OpenAPS determines whether a possible BG level is predicted above or below the target range, noting the rapid rise or fall in blood glucose levels based on data from the CGM. He further adheres to the following steps:

- if BG is rising but eventual BG is below target, cancel any temp basals.
- if BG is falling and eventual BG is above target, cancel any temp basals.
- if eventual BG is above target:
  - calculate 30min temp required to get eventual BG down to target
  - if required temp is > existing basal, issue the new high temp basal
- else, if BG is below target:
  - calculate 30min temp required to get projected BG up to target
  - if required temp is < existing basal, issue the new low temp basal
• if >30min required, extend zero temp to 30m

The maximum temp basal rate is set on the pump, but for safety purposes OpenAPS will set a lower maximum temp basal rate if necessary, as the minimum of:

• The pumps maximum temp basal rate
• 3x the maximum daily scheduled basal rate
• 4x the current scheduled basal rate

This helps ensure that the patient will always be able to recover from any excessive insulin simply by eating fast-acting carbs.

5.2. Adjusting for unexpected BG deviation

The above algorithm is sufficient for a simple and safe implementation of OpenAPS. But, as practice has shown, in some cases it is very useful to take into account the deviation of the rate of increase (decrease) of the observed level of BG from the rate of change of BG calculated on the basis of insulin activity.

To calculate this deviation, OpenAPS first calculates BGI (BG Impact), which is simply the current insulin activity (the first derivative of IOB) multiplied by insulin sensitivity:

\[
BGI = \frac{d(IOB)}{dt} \cdot \text{sens} \tag{2}
\]

For simplicity, this BGI, (2), will be called calculated, \(BGI_{IOB}\). At the same time, BGI is expressed in units (mg/dl/5min), that is, in its essence it represents the amount by which the level of BG is supposed to increase or decrease. Remarkably, the fact that the BGI can be directly compared with the change in the BG for the last 5 minutes, 15 minutes or 30 minutes (based on indications from the CGM, which are taken at intervals of 5 minutes). Thus, we can talk about the second BGI calculated on the basis of the readings of the CGM, we will designate it as \(BGI_{CGM}(t)\), where \(t\) is the time interval for which this indicator is calculated.
To calculate this actual deviation, OpenAPS compares the deviation of BG for 15 minutes (obtained on the basis of the readings of the CGM) with the predicted BGI. It then applies this deviation as an adjustment to a possible BG forecast. This is based on the simple assumption that if BG rises or falls more than expected during the last 15 minutes, this trend is likely to continue for the next 15-30 minutes, and the predicted deviation is approximately the same as that observed in the last 15 minutes.

The above BGI calculation is also used in OpenAPS enhanced implementations to allow high basal to continue working if BG falls slower than expected (less than $\frac{1}{2}$ from BGI), and similarly for setting a low basal if BG grows slower than expected or falls faster than expected.

5.3. Bolus snooze
In practice the issuing of low basals which counteract the reception of a bolus or prebolus when eating (when the level of BG has not yet begun to rise) should be avoided. To do this the OpenAPS algorithm uses a Bolus snooze, when the user enters a bolus. OpenAPS starts to act again only if BG falls below the threshold for suspending low glucose or rises more than expected or does not fall after a meal or starts falling faster than expected.

The bolus snooze is currently implemented by tracking bolus IOB (with an accelerated decay based on half the users normal DIA) separately from net IOB, and re-adding the BG impact of the bolus IOB (plus a small multiple) when deciding whether to set a low temporary basal. If the resulting BG is higher than the BG target, then OpenAPS will not set a low temporary basal, even if the eventual BG (based solely on net IOB) is much lower than target.

Most insulin pumps do not calculate net IOB and use only the bolus IOB (from the pump’s bolus calculator), so additional precautions have been taken to OpenAPS to help the patient not manually insert an excess bolus, following the bolus calculator. This is achieved by setting the "maximum IOB", which instructs OpenAPS never to set high basal.

5.4. oref1 and supermicroboluses
Community have developed an extension of the oref0 - AMA(Advanced Meal Assist) algorithm, which they are calling oref1. Function AMA provides a highly adaptable algorithm for safely dosing insulin after meals, despite widely varying meal types, and the high variance in digestion speed between individuals. Of course AMA has some limitations, but it shows it’s effectiveness. The notable difference between the oref0 and oref1 algorithms is that oref1 makes use of small supermicroboluses (SMB) of insulin at mealtimes to more quickly (but safely) administer the insulin required to respond to blood sugar rises due to carb absorption.

The microboluses administered by oref1 are called super because they use a miniature version of the super bolus technique to safely dose mealtime insulin more rapidly. This SMB technique involves first setting a temp basal rate of zero (0) U/hr, of sufficient duration to ensure that BG levels will return to a safe range with no further action even if carb absorption slows suddenly or stops completely. As with oref0, the oref1 algorithm continuously recalculates the insulin required every 5 minutes based on CGM data and previous dosing, which means that oref1 will continually issue new supermicroboluses every 5 minutes, increasing or reducing their size as needed as long as CGM data indicates that blood glucose levels are rising (or not falling) relative to what would be expected from insulin alone. If BG levels start falling, there is generally already a long zero temp basal running, which means that excess IOB is quickly reduced as needed, until BG levels stabilize and more insulin is warranted.

6. Using machine learning methods
Nowadays machine learning methods are widespread, there are works [15],[16],[17],[18] that report some successes in the application of artificial neural networks (ANN) to accurately predict the patients’s BG with type 1 diabetes using a ANN.
For this Intermediate and final data of the OpenAPS system can be used to train a ANN. In the future, such a trained network can be integrated into an OpenAPS for predicting BG. It can adapting to the peculiarities of a particular patient with diabetes. The last one is extremely difficult to implement with the use of analytical models, since it requires a constant change in the analytical mathematical model. You can train the network on not diabetic patients’ data if you can find them or pay for their services.

Here shows the composition of the data that can be used to train the ANN. These data are proposed to be obtained from the OpenAPS logs:

- ISFs – Insulin sensitivity factor measurement vector
- CRs – Carb Ratio measurement vector
- IOBs – Units of Insulin on Board measurement vector
- COBs – Units of Carbs on Board measurement vector
- BGs – Blood Glucose measurement vector
- BR – Basal Rate (set for every half hour) measurement vector

There are fast insulins applied in insulin pumps, the action time of which usually does not exceed 5 hours. The activity curves are used to determine the current activity of the insulin administered. For example, as shown in the following figure 4. The sampling step is 5 minutes and the retrospective window is 5 hours.

Thus, as an example, in table 1 we can consider the following data sets for learning ANN for one epoch. Here, as you can see, the size of the flashback window is 300 minutes, and the step is 5 minutes. The values in this example correspond to the actual data obtained when one of the volunteers with type 1 diabetes was using openaps. Zero values correspond to the fact that during this five-minute period there was no consumption of carbohydrates. A network trained in this way must provide a BG forecast for a period of up to 4 hours.

| t  | BG   | ISF  | CR   | COB  | IOB  | BR   |
|----|------|------|------|------|------|------|
| T+5·0 | 208  | 46.800 | 5.762 | 0    | 5.93 | 0.708 |
| T+5·1 | 204  | 46.800 | 5.762 | 0    | 5.94 | 0.708 |
| T+5·2 | 202  | 46.800 | 5.762 | 23   | 5.94 | 0.708 |
| T+5·3 | 198  | 46.800 | 5.762 | 0    | 5.98 | 0.708 |
|     |     |      |      |      |      |      |
| T+5·i | 92   | 47.284 | 5.324 | 0    | 4.12 | 0.844 |
| T+5·(i+1) | 96   | 47.284 | 5.324 | 0    | 4.6  | 0.844 |
|     |     |      |      |      |      |      |
| T+5·58 | 130  | 47.101 | 5.426 | 0    | 5.01 | 0.719 |
| T+5·59 | 126  | 47.101 | 5.426 | 14   | 4.98 | 0.719 |
| T+5·60 | 120  | 47.101 | 5.426 | 0    | 4.91 | 0.719 |

Will consider the ANN, figure 5. As you can see offered, the network consists of one input layer and one computational layer. Here the value of the BG(i+1) on the next step is used to verify the correctness of the network training. That is a comparison of the value of BG(i+1) with the predicted set in 5 minutes of the value of BG occurs. Thus, the learning process during
one epoch occurs on all data sets, which are shown in Table 1. In the course of preliminary studies, it was determined that the number of computational layer neurons should be about 102 pieces in order to make BG prediction possible. The predicted by the network level of BG in the i-th step is compared with the given level of BG in the (i+1)-th step. Thus, learning for one epoch is \( \frac{T}{5mn} \) cycles. In this case the ratio is 60. The sample for training is equivalent in size to the sample for at least two weeks. A training sample of this size can be obtained by analyzing the microcomputer’s OpenAPS log files. Conveniently, OpenAPS works in a closed loop and keeps logs, day and night. This makes it possible to judge that the data from the training sample meet the conditions for sufficient coverage and relevance.

In order to get a BG change forecast for the next hours you need apply to the trained network the following algorithm (figure 6):

1. to submit to the network input the last obtained values of BG, ISF, CR, COB, IOB, BR;
2. perform 12, 24 or 48 cycles, respectively, calculating the value of BG(i) using the already trained network. In this case, the predicted values of BG(+5min) each time you need to submit to the input of the network, in the next cycle;
3. Build a BG forecast graph for an hour, two, or four hours, respectively.

The value of COB on subsequent iterations of the calculation of BG(i) is zero. It is assumed that the patient does not eat during the period of making forecast. If you are planning to eat food you should assign the amount of COB(i) to the amount of carbohydrates absorbed from the accepted food.

Figure 5. Schematic view of the proposed of artificial neural network at the training stage.

Figure 6. Schematic view of the proposed of artificial neural network at the stage of use to predict the future levels of BG.

7. Conclusion
The article consistently states the following: the problem of treating type 1 diabetes has been voiced; a modern approach for the treatment of type 1 diabetes has been considered; modification for the marked approach for the treatment of type 1 diabetes mellitus has been proposed; as a modification, it is proposed to use a specially trained network in predicting the level of BG in ballast diabetes mellitus; the structure of the network, the algorithm of its learning and use has been proposed.
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