Continuous glucose monitoring systems in the service of artificial pancreas

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***Abstract*—Diabetes mellitus is a chronic disease causing several side effects. The basis of conventional diabetes management is the blood glucose detection with glucometers. Another approach is the continuous glucose monitoring (CGM) that can be the solution for individual and optimal management of diabetes because it is less painful and inconvenient. Although there are several challenges with CGM which must be solved there are proofs of the usability and justification of using CGM systems. In this paper, we gave a short review of the basics, goals and methods of CGM systems.**

Keywords: Continuous glucose monitoring; Glucose sensors; Analysis methods; Analysis from body fluids.

I. INTRODUCTION

Diabetes mellitus (DM) is a malfunction in the regulatory system of human glucose metabolism which is connected to the incorrect operation of insulin system. [1]. These days, about 347 million people have DM in the world [2]. Their number is growing from year by year, not just because of the formation of the illness, but also due to the better understanding of the disease and because of the definition of DM is extending [3]. Due to its frightening increase, the World Health Organization (WHO) warns that diabetes could be the "disease of the future" as diabetic population is predicted to be doubled from 2000 to 2030 [4], and according to the WHO's projections, diabetes will be the 7th leading cause of death in 2030 [5].

The normal blood glucose (BG) level is between 70-110 mg/dl. Because of this narrow range, the smallest error in the control of BG level could lead to the dysfunction of the energy household, carbohydrate toleration etc. If the untreated condition persists for a long time, the side effects of DM (like neuropathy, cardiovascular diseases, etc.) make the condition of the patient more dangerous [1]. Diabetes is currently incurable, but treatable. The mode of treatment depends on the type of DM (Type 1 DM (T1DM), Type 2 DM, gestational or other) and the condition of the patient (age, sex, activity, sicknesses, etc.). From the treatment viewpoint, there are two ways: medical or engineering option. Despite the fact that the development of medical treatments are continuous and there are progress in the final cure of diabetes, like pancreatic islet transplantation [6-7], better understanding of insulin mechanism [8] or experimental drugs to increase the beta cell proliferation [9], these methods have increased risk (like immune answer, rejection, allergy, etc.) or – because of its experimental nature – they are not conclusive solutions yet. From engineering point of view, the best solution for treating DM is the artificial pancreas (AP). To realize the AP, three subunits are needed: *(i)* an insulin pump (IP), which contain the control electronics and the insulin, *(ii)* a continuous glucose monitoring system, which is measuring and forwarding the BG or interstitial glucose (IG) level and *(iii)* control algorithms which are realized by the insulin pump and accomplish the BG level [10].

In conservative therapy, the primary tool for the measuring of BG level is the blood glucose meters which are widely available in the market. It has several advantages and disadvantages, but the main problem is that it cannot give continuous data and also the painful finger pricking repeatedly a day.

In contrast to this, continuous glucose monitoring (CGM) gives an alternative to conservative BG measuring, however it has several drawbacks too, which will be reviewed in detail in this study.

The rest of the paper is organized as follows. First, we give an overview of continuous glucose monitoring systems. Second, we study the models which are used to model the CGMs, then a survey will be given about the methods and possibilities in the area of CGMs. Finally, we give an overview of the available tools on the market and last but not least some concluding remarks.

II. CONTINUOUS GLUCOSE MONITORING AND ITS USAGE

Continuous glucose monitoring is an essential element in the modern DM treatment [10]. As CGMs can be used as an individual tool or additional tools, the needed subunits can be divided as follows:

A. if CGM is used in itself then typically the system contains three subunits: *(i)* sensor, which is measuring the glucose from blood, interstitial fluid (ISF) or else, *(ii)* data forwarding unit, which can be wired or wireless and *(iii)* data processing and displaying unit [11].

B. if CGM is used with insulin pump, then two subunits are needed: *(i)* sensor, *(ii)* data forwarding unit, which can be wired or wireless [10].

Tight glycemic control (TGC) is a protocol to keep the patient's glycemic parameters in a narrow range. This protocol is widely used in case of diabetes or if the patient recovery is better with it [13, 18, 20]. Both *A.* and

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B. cases appropriate for TGC realization. CGM used to implement TGC protocol could be important especially in critically ill patients, childhood diabetes or pregnancy [18, 22, 27] although CGM not lived up to expectations in pregnancy [23].

A. CGM usage as an individual tool

In those situations when the continuous monitoring of BG level is indicated (for example to keep the BG level in a given range, or to avoid hypo- or hyperglycemia), but there is no need to control the glucose level with insulin, the CGM was demonstrated to be a solution. Typically these situations include monitoring in intensive care units (ICU), patients who are in pre-diabetic stage, in the case of chronic alcoholism [12-15]. There are studies which showed that the glucose level monitoring in ICU reduced the mortality and morbidity [16] and BG level is correlated with the recovery after stress (typically after surgical intervention) [17]. Significant part of the realization is the consensus in CGM protocol usage with caregivers [18].

B. CGM usage as an additional tool

The main indication to use insulin pump is when the patient has T1DM [19], e.g. there is no internal insulin production [1] and has an active lifestyle. Usually in this case the CGM system is a subunit of some kind of AP system which can be realized with IP. Because the insulin pump can handle, display and also process the data, no other subunit is needed [20].

A recent step forward in CGM use was given by the FDA approval of AP from 2012 [21].

It is likely that the frontier of CGM will expand due to the new challenges (like dual-hormone control), but to our knowledge, all available automated BG control methods are based only on the blood sugar level. It is possible that the CGM method will be supplemented with the continuous monitoring of insulin, glucagon or both.

The fully automated AP is just a future promise now, but it can be stated that without CGMs, it is impossible.

C. Advantages and disadvantages of CGM and a comparison with traditional tools

Although it has clear advantages, the CGM technique has disadvantages too.

Without exception, the available devices are capable for BG monitoring, realize real-time CGM (RT-CGM), follow the patient records etc. These data and capability allows the identification of postprandial hyperglycemia, blood glucose variability, hypoglycemia, unexpected hypoglycemia, and glucose trends [24].

CGM and RT-CGM is beneficial for those who meet the following requirements: hypoglycemia unawareness, constantly high and/or elevated HbA1c (which is a stable form of glycohemoglobin), undue or/and high glucose variability, required BG check from fingerstick testing more than 10 times a day or dislike this method (which is frequent in children's case), rapid rise and fall of BG, inability to reach the glycemic goals, need for glycemic profile (it is beneficial in professional athletes), and some other cases [25].

There are various types of CGM sensors and the disadvantages of these depend on the applied methods to evaluate the BG level. It is generally established that the main problems of CGM sensors – independently from the measuring methods – are decalibration, inaccuracy, high sensitivity to noise and disturbances, possibility of infection and/or inflammation (in invasive cases), the time delay between the measured glucose level and the core glucose level (near liver circulation) [11].

The disadvantages are different depending on the sensor type. In minimally invasive and implanted sensors the infections pose a real threat and patients using subcutaneous sensors always need to be aware of it [26-30].

An illustration of the benefits and drawbacks of CGMs compared with traditional BG meter is given in Table I.

TABLE I. COMPARISON OF CGMS WITH BG METER

CGMs	Traditional BG meters
Continuous BG data Better TGC realization Possible to identify BG trends More expensive Disturbance, noise sensitiveness Bigger time delays Sensor needs permanent attention More chance to infections Calibration required	Cost effective Painful Better accuracy Smaller time delays More chance to inflammation Worse TGC realization and BG trend identification Less BG data

III. METHODS TO MEASURE THE BG LEVEL

A. Summary of the currently used BG detection methods

There are many detection techniques which are based on devices that can measure the BG level directly or indirectly. The measuring methods can be divided to three types depending on the degree of invasiveness: *(i)* invasive, *(ii)* minimal invasive, *(iii)* non-invasive [20]. In several cases, there are overlap between the different detection methods and used tools. For example, the enzymatic type sensors can be applied in invasive and non-invasive cases too and depends on what was the compartment and/or body-fluid from where the sample originated [26].

Table II summarizes the sources of measurements and grouping by invasiveness.

Fig.1 presents a classification based on the detection method [11, 20].

Electrochemical methods

The glucose detection methods based on electrochemical reactions are possible with different strategies. It can measure the used oxygen by the reactions, the quantity of nascente hydrogen-peroxyd or the rate of the electron transfer [32]. The last method can be divided into enzymatic or non-enzymatic methods, but it is true for all of them that the measured signal is the amperometric signal [11].

TABLE II. THE MOST COMMON METHODS TO MEASURING GLUCOSE LEVEL

Body fluids	Measuring options		
	Invasive	Minimal invasive	Non-invasive
Blood	Intravenous catheter; implant	BG meter (via finger pricking)	Optical based devices; Other
Interstitial fluid	Implant	Subcutaneous sensor	Not usual, but possible
Urine	-	-	In vitro analyzers
Eyewater	-	-	In vitro analyzers; Surface electrode (in contact lens)

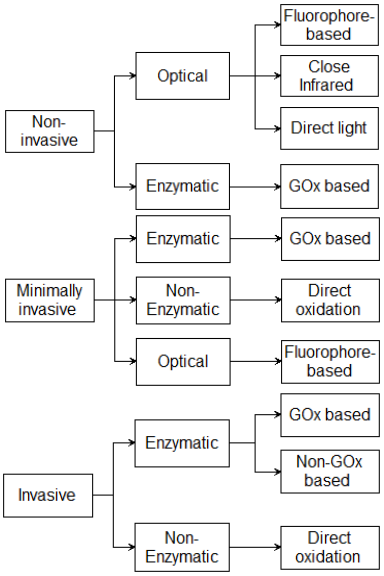

Figure 1. Detection technologies (GOx – Glucose-Oxidase enzyme) [11, 20]

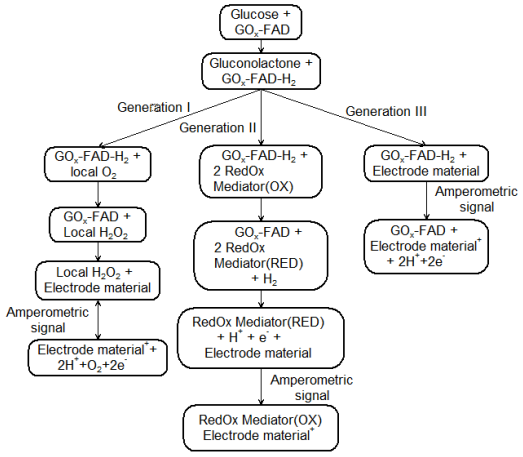

Figure 2. Amperometric glucose detection method with enzymatic reaction [31]

The glucose level detection based on enzymatic reaction is one of the most common and stable technique which can be grouped by the used enzymes [35]. The oldest well working method uses the reaction catalized by the glucose oxidase (GOx) enzyme (glucose oxidation to gluconolactone). The GOx based sensor family can be divided into three generations and their reaction products are presented in Fig. 2 [31]. These reactions are used by most available subcutaneous sensors combined with IP [26].

Enzymatic, but not GOx based methods are known as well [35]; here the principle is similar to GOx based methods. Amperometric, but not enzymatic reactions are based on the direct redox reaction between the sensor material and the local environment (i.e. Ag/Ag+ electrode direct e- transfer with extracellular matrix). This direction of sensor development is progressing rapidly, because it has several advantages against enzymatic methods, like accuracy, glucose sensitivity, lower disturbance sensitivity (from temperature, local chemical household, etc.), lower manufacturing costs etc. [33-34].

Optical methods

There are several optical methods which allow the measurement of the quantity of glucose from body fluids although not all of that is appropriate to continuous glucose monitoring [36]. Fig. 3 summarizes the available methods.

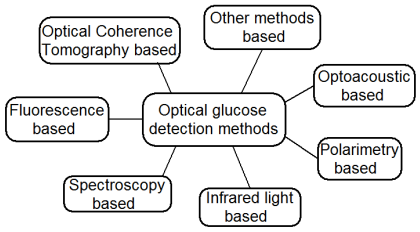

Figure 3. Optical based glucose measuring methods

Infrared light (IR) based methods work on the idea that the change of glucose concentration changes the absorption of IR light in the human tissues. The difference between these approaches lies in the used wavelength. Mid-IR cannot pass through the skin, therefore it is used mostly in vitro. In contrast, the Near-IR (NIR) can be used as in vivo method, because the NIR light can penetrate the stratum corneum amongst to the subcutaneous tissues [20]. The idea of Thermal-IR method is that modulated irradiated energy (a kind of IR light) heats the tissue, which increases the temperature and the local circulation (the blood vessels expand). Hence, the changing of the local glucose level correlates with the refractive and reflective coefficients of the tissue. Because the circulation becomes more active, the level of glucose is increasing. With an indirect way, the amount of glucose is detectible from this phenomenon [11].

Spectroscopy methods (in extended sense, the IR based methods belongs here too) are based on the changing of the transmitted light during the interaction with the substrate. Raman spectroscopy uses the inelastic Raman-scattering of monochromatic light which depends on the energy states of molecules (rotational, vibrational, or other). When the incident monochromatic light interact with the substrate, different lines appear in the spectrum

which are symmetric, but weaker than the original light. Here it is needed to investigate the Raman-effect of the glucose molecules when they interact with the used light. Because every molecule has different image in the spectrum, this method is suitable for distinguish the different molecules too [11]. Occlusion spectroscopy uses the pulsatile arterial blood flow. It is suitable solution for measuring the general state (quantity and quality) of blood because it can measure the property of blood particles, like red blood cells (RBC). Investigating the scatter pattern of RBC aggregation at the site the glucose concentration can be evaluated [40]. The principle of scattering spectroscopy is the same as occlusion spectroscopy. The scattering (from refraction and reflection) of tissues depend on the particles which procreate the tissue. The quantity of the glucose in the tissue (solid material or body fluids) correlates with the scattering properties of the tissue; hence, the glucose amount becomes measurable [20].

The *optoacoustic* (or photoacoustic) method can be classified as spectroscopy methods although the measured signal is basically different from the other spectroscopy methods. The point of this approach is based on the focused irradiated light absorbing in the tissues which causes local heating. Due to the increasing temperature, the tissue suffers thermal expansion. This expansion generates an ultrasound pulse which can be measured. As the concentration of glucose is correlated with the thermal properties of the tissue, the glucose concentration can be evaluated [42].

Optical coherence tomography (OCT) is based on the low coherence interferometry. The reason why this method is suitable for glucose detection is the fact that the OCT is very sensitive for the changing refractivity of the sample. The presence of glucose molecules affects the refractive indices of the tissue; thus, the amount of glucose is measurable by indirect way. Chromoscopy principle is the same as OCT, but it is based on the transmitted and scattering light [11].

Polarimetry based methods use linearly polarized light passed through on the optically active sample and rotating the light plane of polarization. Only the asymmetric molecules have the ability of optical rotation so this is a limitation of this method. The rotation of light depends on several factors, including the glucose concentration of the sample [20].

Fluorescence based methods are not so many, but they are different based on the source of fluorescence. The point of this phenomenon is the light emission by an optically active material after the irradiation of light was ended. One of the first approaches used the dextran labeled by fluorescein as the source of the emission. In this case, the receptor is the concanavalin A (conA) protein to which the glucose and dextran can bind (these two molecules are competitive agonists here). The emitted light is increasing when the dextran is not connected to conA. Another approach is the using the fluorescence resonance energy transfer (FRET) to measure the glucose concentration. The essence of this method is the energy transfer between to fluorophore molecule if they are closer than the Förster-radius (the maximum distance while the energy transport exists). These two are the basic methods, but further ones can be found in the literature [20, 39].

There are other methods to measure the BG level. One of these approaches is the microwave based method [37]. Another technic is based on radio frequency [38].

Other methods

There is no consensus about the classification of the following methods what are presented from the literature.

Sonophoresis utilizes that low-ultrasound increases the permeability of skin what makes easier to add drugs or measuring glucose through the stratum corneum [41].

Reverse iontophoresis uses electrical current with low intensity between two electrodes on the surface of the skin causing the changing of the local chemical household because of the ions flow to the electrodes. The consequence is that small amount of fluids from interstitial space leak out the pores that is enough to measure with another method (like GOx based) [44]. Skin blister suction utilizes the power of vacuum to create an inside fluid vesicle near the surface of the skin whereon the ISF are collecting. Then this fluid can be analyzed, externally [47].

Microporation utilizes focused, low powered laser beam to create micropores on the skin through the ISF that can be collected by vacuum or pressure. From this fluid, the glucose concentration can be detected [47]. The last four methods are collectively known as Transdermal Methods (TM) [11].

Microdyalisis uses ex-vivo sensor to analyze the blood or ISF glucose concentration. It is based on the conventional dyalisis techniques [20]. Impedance spectroscopy uses alternating current which is traverse through the tissues and this current can be detected. Because the local concentration of glucose changes the electric properties of tissues the amount of glucose is measurable [45]. Electromagnetic glucose detection is based on the phenomena that the electromagnetic permittivity of the tissue is influenced by the local glucose concentration. The presence of glucose is well visible in the electromagnetic spectrum [46]. Microneedle arrays are good alternative because they are less painful and minimal invasive. The microneedles on the carrier surface create microtunnels. Through these ISF and blood can be collected but also drugs (like insulin) can be delivered. To our knowledge, this technique is not used as lab-on-a-chip approach yet [48].

Several disturbances interfere with the detection of glucose quantity. The fact is that every method has weaknesses which can distort the measurements as it clear from the referred literature. Broadly speaking, the main disturbance sources are the following: molecules with the same optical, electrical, physiological and other physical properties like the glucose, the physical properties of the investigated tissues, environmental effects (like temperature, light contamination, electric and magnetic field, etc.).

B. *The used body materials to detect the glucose level*

Several body fluids and samples are proper to establish the glucose level of the body. Naturally the most relevant is blood through the glucose transport to the large part of the cells. Almost every mentioned method is suitable for that. The oldest indicator of DM is the urine. In DM, the amount of sugar is increasing because of the higher glucose secretion of the kidneys. The testing of urine for glucose is the part of standard laboratory test nowadays [51].

Other approach is the glucose detection from saliva possible for example by enzymatic way. This method is appropriate to differentiate the healthy and DM persons [52].

Glucose detection from eyewater is another possibility as well. Detection with wearable contact lens with enzymatic detection is a suitable painless solution [53]. Moreover, BG level can be evaluated from breathing too. However, this process is able to detect only high glucose level [49].

C. *Equality of data from different methods*

Because of the difference between the glucose measuring methods the gathered data are different. Comparing the measured BG level with different devices (based on different methods) making the measurements accurate and comparable the Continuous (Clarke type) and Consensus (Parke type) Error Grid methods [50] are used.

IV. Goals of In-Silico Modelling

In these days the using of in-silico simulation and modelling in medical field is not questionable. The CGM modelling is a proper important field inside the DM modelling. The accuracy of simulation of human systems is eligible only if every subpart of the whole model is eligible. There are several challenging tasks in this field and there are no adequate solutions for these yet. The most important two of these are the following:

- The dynamics of the patients are similar, but different from many aspects: depends on the signals (food, increasing glucose BG level, brain commands through the nervous system, etc.), actuators (hormones, dynamics of intestine system, etc.), time-lag (from different compartments because of absorption, diffusion, active transport, etc.) and other aspects [1, 20].
- The structure and identification of CGM models mostly depends on the methods of the glucose measuring and data processing applied [54-57].

V. Summary

Lot of methods are available to detect the amount of glucose from human samples and several methods are appropriate to realize continuous glucose monitoring. The devices available on the market are using the mentioned methods to realize the CGM systems often in a combined way (than multi-sensors), but there are several problems which must be solved to further development (accuracy, data equality from different methods, modelling questions, etc.). The CGM approaches are involving continuously and the trends show that the CGM system is expected to become more integrated to the AP concept [58].

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