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Wearable Continuous Glucose Monitoring Sensors: A Revolution in Diabetes Treatment

Giacomo Cappon, Giada Acciaroli, Martina Vettoretti, Andrea Facchinetti 
and Giovanni Sparacino * 

Department of Information Engineering, University of Padova, Padova 35100, Italy; cappongi@dei.unipd.it (G.C.); acciarol@dei.unipd.it (G.A.); vettore1@dei.unipd.it (M.V.); facchine@dei.unipd.it (A.F.)

* Correspondence: gianni@dei.unipd.it; Tel.: +39-049-827-7741

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Abstract: Worldwide, the number of people affected by diabetes is rapidly increasing due to aging populations and sedentary lifestyles, with the prospect of exceeding 500 million cases in 2030, resulting in one of the most challenging socio-health emergencies of the third millennium. Daily management of diabetes by patients relies on the capability of correctly measuring glucose concentration levels in the blood by using suitable sensors. In recent years, glucose monitoring has been revolutionized by the development of Continuous Glucose Monitoring (CGM) sensors, wearable non/minimally-invasive devices that measure glucose concentration by exploiting different physical principles, e.g., glucose-oxidase, fluorescence, or skin dielectric properties, and provide real-time measurements every 1–5 min. CGM opened new challenges in different disciplines, e.g., medicine, physics, electronics, chemistry, ergonomics, data/signal processing, and software development to mention but a few. This paper first makes an overview of wearable CGM sensor technologies, covering both commercial devices and research prototypes. Then, the role of CGM in the actual evolution of decision support systems for diabetes therapy is discussed. Finally, the paper presents new possible horizons for wearable CGM sensor applications and perspectives in terms of big data analytics for personalized and proactive medicine.

Keywords: decision support; big data analytics; personalized medicine; proactive medicine; sensor calibration

1. Introduction

Diabetes is a chronic metabolic disorder resulting from defects of insulin secretion and/or action. Type 1 diabetes (T1D) is characterized by a lack of insulin secretion by the pancreas and can be treated by exogenous administration of insulin, while Type 2 diabetes (T2D), whose onset is often facilitated by bad daily habits, e.g., physical inactivity and unhealthy diet, is characterized by an inefficiency in the action of insulin [1]. In diabetic people, concentration of blood glucose (BG) tends to exceed the safe range, resulting in hyperglycemic events that, in the long term, can lead to serious damage such as retinopathy and cardiovascular disease, or in hypoglycemic events due to exogenous insulin administration, that can be dangerous in the short term, e.g., they can cause coma or even death [2].

Diabetes numbers are impressive. According to the last report provided by the World Health Organization, the number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014, which means that about 8.5% of adults aged 18 years and older had diabetes, with the prospective of exceeding 500 million cases in 2030 [3]. Of note is that 10% of diabetic cases are T1D [4], a pathology treated through exogenous insulin administrations which requires careful management because of the risk of inducing harmful hypoglycemic events.

Diabetes requires 24/7 management, which mainly consists of diet, physical exercise and drug/insulin therapy [1,5,6]. Almost all of these actions, especially the dosing of drug/insulin, rely on the capability of correctly measuring the BG concentration levels by using suitable sensors.

Monitoring BG is not straightforward. Monitoring BG at home has become possible only in the late 1970s, when self-monitoring BG (SMBG) meters started to be marketed [7]. SMBG systems are portable devices that allow for the measuring of BG concentration, usually 3–4 times per day, on a drop of capillary blood by means of the oxidation of glucose to gluconolactone catalyzed by glucose oxidase [8]. A representative SMBG timeseries (collected by One Touch Ultra 2 (LifeScan Inc., Milpitas, CA, USA) is displayed in Figure 1. It is apparent that SMBG, due to insufficient sampling frequency, cannot reveal all critical episodes occurring in daily life, e.g., hypoglycemia and severe hyperglycemia during day 2. In recent years, BG monitoring has been revolutionized by the development of Continuous Glucose Monitoring (CGM) sensors, wearable non/minimally-invasive devices that measure glucose concentration almost continuously (1–5 min sampling period) for several consecutive days/weeks mitigating the need of the SMBG and greatly increasing the information on BG fluctuations [9–11]. Figure 1 shows hypo- and hyperglycemic episodes, detected by CGM (continuous line shows the BG profile monitored by Dexcom G4 Platinum (Dexcom Inc., San Diego, CA, USA sensor). The first wearable CGM sensor prototype was introduced in 1999 [12] and, since then, devices have evolved rapidly (see [13] for review). Today, CGM devices embed several features that can empower the ability of making decisions concerning therapeutic actions, e.g., snack to counterbalance hypoglycemia, drug or physical exercise to deal with hyperglycemia. For example, modern CGM devices can visualize in real-time the current BG and trend and generate acoustic and visual alerts for hypo/ hyperglycemia.

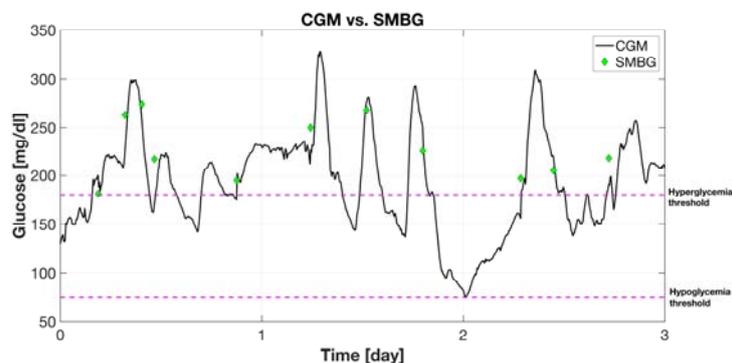


Figure 1. Representative blood glucose (BG) monitoring for three days obtained with self-monitoring BG (SMBG) (green diamonds) and with Continuous Glucose Monitoring (CGM) (black solid line) for three days. Horizontal dashed lines evidence hyperglycemic and hypoglycemic thresholds (180 mg/dL and 70 mg/dL respectively).

Wearable CGM sensors present a potential revolution in diabetes treatment. Development of CGM technologies and applications stimulates the scientific research in different areas, ranging from medicine to physics, electronics and chemistry. As a consequence, a new interdisciplinary scientific community has been established, with its own annual reference meetings (among the most popular, we mention the *Annual Diabetes Technology Meeting* and the *International Conference on Advanced Technologies & Treatments for Diabetes*) and journals (among the most popular we cite *Diabetes Technology & Therapeutics* and *Journal of Diabetes Science & Technology*). Present challenges in medical research include, for instance, the assessment of the clinical benefits brought by CGM sensors in diabetes management. From the technological point of view, examples of research activities include the exploration of principles alternative to glucose-oxidase, such as fluorescence and skin dielectric properties [14], ergonomics [15], data/signal processing [16], and software development [17] to mention a few. The aim of this paper is to provide an overview of the current status of CGM sensors and to discuss future scenarios of diabetic therapy and the technologies, hardware and software. We clarify

from the very beginning that our review of the literature will be not exhaustive. Rather, among the published studies of potential interest for the *Electronics* readership, we will focus on those that, according to our experience as investigators active in this specific research field, have received the most attention from the above-mentioned diabetes technology community.

The paper is organized as follows. In Section 2, an overview of wearable CGM sensor technologies is presented, covering both commercial-grade level devices and research emerging prototypes. Section 3 focuses on the role of CGM in the actual evolution of the decision support systems for diabetes therapy, from both the patient and physician point of view. Section 4 presents the possible future scenarios, mainly related to a recent tendency of manufacturers to produce low-cost devices to target a broader population, e.g., including obese and elderly, and perspectives in terms of big data analytics for personalized and proactive medicine. Finally, some conclusions are drawn in Section 5.

2. CGM Sensor Technologies

In recent years, various glucose-sensing mechanisms for non-invasive, or at least minimally invasive, CGM have been tested [18–26], in an attempt to match all fundamental requirements for an extended in vivo use, e.g., sensitivity, specificity, linearity within biological relevant range, biocompatibility, and lifetime [13]. Among all the proposed techniques, i.e., electrochemical, optical, and piezoelectric, the one that is today exploited by most of the commercialized CGM systems is the glucose-oxidase electrochemical principle [8]. The devices based on this principle employ a minimally-invasive needle sensor, usually inserted in the subcutaneous tissue, in the abdomen or on the arm (see Figure 2a), which measures an electrical current signal generated by the glucose-oxidase reaction. This signal is proportional to the glucose concentration available in the interstitial fluid, which is then converted into a glucose concentration by a calibration procedure usually performed twice a day.



Figure 2. Examples of minimally-invasive CGM systems based on electrochemical sensing technique: (a) A patient wearing a sensor (taken from [27]); (b) Medtronic Enlite sensor with dedicated inserter device (taken from [28]); (c) Dexcom G5 Mobile with Share technology (taken from [29]); (d) Abbott FreeStyle Navigator II. (taken from [30]).

2.1. The Early Age of Glucose-Oxidase CGM Sensors

The first prototypes of CGM systems based on this principle were proposed in the late 1990s [12] but biocompatibility problems often led to commercially unsuccessful products. The first generation of commercial CGM systems became available for personal use only a few years later, starting in 2005. The first three successfully commercialized products were the Medtronic Guardian (Medtronic Minimed, Northridge, CA, USA), the Dexcom Seven Plus (Dexcom, San Diego, CA, USA) and the Abbott Navigator (Abbott Diabetes Care, Alameda, CA, USA). Accuracy of these systems is commonly computed by comparing the CGM sensor output with a reference BG measurement acquired with highly accurate laboratory instruments, i.e., Yellow Spring Instrument Inc. (YSI, Yellow Springs, OH, USA) instruments. An example of a dataset provided to assess accuracy of a sensor is reported in Figure 3. Of note is that high frequency YSI references (one every 15 min in the

picture) can be collected only in a hospital setting. Although different metrics have been proposed in the literature to quantify accuracy of CGM sensors, e.g., mean absolute difference (MAD), mean absolute relative difference (MARD), and Clarke error grid analysis [31], for sake of simplicity in the remainder of this paper we will make reference only to MARD, which is the most popular accuracy index used in recent literature. From a number of datasets like that of Figure 3, it is trivial to estimate the MARD, which, for instance, was 15.8% for the Medtronic Guardian [32], 16.7% for the Dexcom Seven Plus [33], and 12.8% for the Abbott Navigator [34], for a mean lifetime of 4–5 days. As for any other medical device, accuracy represents one of the most important requirements, since critical (and possibly harmful for the patient) therapeutic decisions and actions, like insulin dosing, are based on BG readings. At the end of the past decade, accuracy values of commercial grade CGM sensors were still significantly worse than those of SMBG systems (that have a MARD between 5% and 10%), making therefore CGM sensors still unsafe for taking therapeutic decisions. Thus, in the past 10 years, CGM companies concentrated a big effort in developing improved, more accurate, sensor systems.

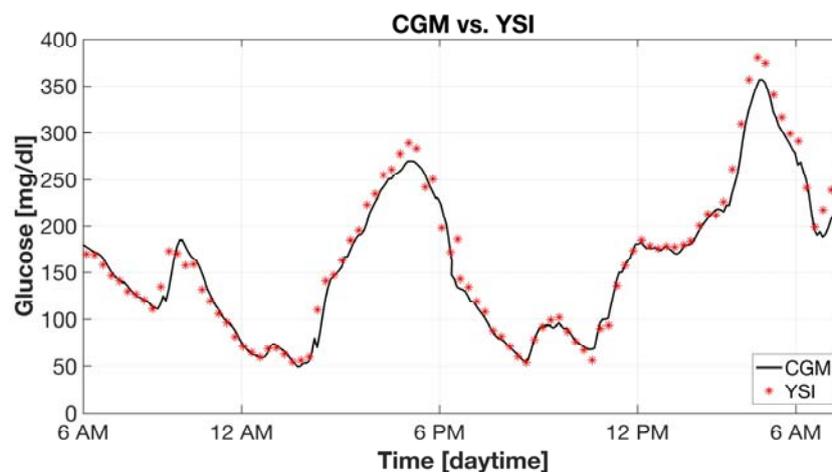


Figure 3. Example of YSI measurements (red stars) versus Dexcom G4 Platinum CGM (black solid line) measurements, collected during a monitoring of a T1D patient made for about 1 day within a hospital. By using YSI data as ground truth, accuracy of the sensor can be quantified e.g., by computing the mean absolute relative difference (MARD) as the average of the ratio between the absolute difference between the CGM measurement and the YSI over the YSI.

2.2. State-Of-Art Glucose-Oxidase Sensors

In 2011, Medtronic launched the new Enlite sensor (see Figure 2b), which received the CE approval in 2011 and the FDA approval in 2013, providing users with a more accurate and comfortable sensor. Indeed, with respect to the previous first generation device, the Enlite sensor shows significant clinical and human factors improvements. The electrode layout was redesigned to face inflammatory response effects, the size of the sensor decreased, the wear time was extended from 3 to 6 days, and the inserter device became more user-friendly. All these changes improved usability and accuracy, reaching 13.6% MARD [35]. In 2016, the same company proposed a new and more accurate sensor, the Guardian Sensor 3 [36], which has been recently FDA approved to be used in the Minimed 670 G hybrid closed loop system [37].

Dexcom launched the new G4 Platinum CGM sensor in 2012, after receiving CE Mark in June and FDA approval in October of the same year. The new Dexcom G4 Platinum system, which lasts for seven days, employs a completely redesigned smaller transmitter and several sensor improvements that allowed enhancing accuracy to 13% MARD [38]. In 2014, algorithmic changes in the Dexcom G4 Platinum sensor further enhanced accuracy decreasing MARD to 9% [39]. In addition to accuracy improvements, Dexcom pushed to render their new products more effective and user-friendly by embedding the G4 Platinum sensor with the Share technology (2015) [40]. The Share technology

allows secure wireless connection via Bluetooth Low Energy between a patient's receiver and an app on the patient's smartphone and up to five designated recipients. In the same direction, in 2015, Dexcom launched the G5 Mobile CGM system (see Figure 2c) that allows direct wireless communication to a smartphone without the need to have a dedicated receiver [15].

Abbott launched the FreeStyle Navigator II CGM system (see Figure 2d) in 2011 in some European countries. The new sensor, which lasts for five days, shows a completely redesigned receiver, a smaller transmitter, a slightly smaller and redesigned sensor that allowed reducing warm-up time from 10 to 1 h [41].

Table 1 summarizes the characteristics in term of performance, features and requirements of the currently commercialized CGM systems.

Table 1. Summary of the currently commercialized CGM sensor systems performance, features and requirements.

Company	Sensor System	Accuracy (MARD)	Features	Requirements
Dexcom	G4 Platinum	13% [38], updated to 9% [39] in 2014	7-day lifetime, trend arrows, rate-of-change alerts, hyper and hypo alarms, remote monitoring (Share technology from 2015)	Calibration recommended at least every 12 h, approved only as adjunctive device
	G5 Mobile	9% [39]	7-day lifetime, trend arrows, rate-of-change alerts, hyper and hypo alarms, remote monitoring, direct wireless communication with smart devices (up to 5 devices)	Calibration recommended at least every 12 h
Medtronic	Enlite Sensor	13.6% [35]	6-day lifetime, trend arrows, rate-of-change alerts, hyper and hypo alarms, direct integration with Medtronic insulin pumps	Calibration recommended at least every 12 h, approved only as adjunctive device
	Guardian Sensor 3	10.6% in the abdomen, 9.1% in the arm [36]	7-day lifetime, trend arrows, rate-of-change alerts, hyper and hypo alarms, direct integration with Medtronic insulin pumps	Calibration recommended at least every 12 h, approved only as adjunctive device
Abbott	Navigator II	14.5% [41]	5-day lifetime, trend arrows, rate-of-change alerts, hyper and hypo alarms	Calibration recommended 2, 10, 24, and 72 h after sensor insertion, approved only in some European countries as adjunctive device
	FreeStyle Libre	11.4% [42]	14-day lifetime, trend arrows, communication with a smart device	To read glucose values the sensor needs to be scanned with the receiver or the smartphone, not FDA approved yet
Senseonics	Eversense	11.4% [43]	90-day lifetime, trend arrows, rate-of-change alerts, hyper and hypo alarms, communication with a smart device	The sensor needs to be inserted and removed in doctor's office, approved as adjunctive device in Europe only

2.3. Clinical Impact of CGM Sensors

The growing interest in the development of new sensor technologies and features for CGM systems is well supported by several clinical studies confirming the benefits of the use of CGM systems for

diabetes management [44]. From a clinical point of view, the use of real-time CGM showed meaningful improvements in glycated hemoglobin (HbA1c) [45] and a reduction of hypoglycemic events [46]. Moreover, the use of CGM sensors was demonstrated to improve quality of life [47], e.g., by reducing fear of hypoglycemia [48], and resulted in being cost-effective in long-term projections [45]. Although all these benefits have been extensively proven, there are still many other factors that influence patient and clinician confidence in the use of CGM, such as accuracy, reliability, usability, duration of sensor life, and calibration requirements [49]. Many factors, such as delays, drifts, compression artifacts and calibration errors can impact the CGM sensor accuracy leading to dangerous and inappropriate treatment decisions, e.g., injecting too much insulin rising hypoglycemic events. For this reason, next generation CGM systems are expected to address all these issues in the coming years, both from a hardware point of view, e.g., device design, and a software perspective, e.g., algorithms development.

2.4. Technological Trends and Challenges for the Next Generation of CGM Sensors

From a hardware point of view, the size and lifetime of a CGM system represent critical factors in device development. In general, among a series of equally performing devices, the smallest and more long-lasting product often has the greatest appeal and success. It is reasonable to extend this general concept to CGM devices, expecting that next generation CGM systems will be small, easy to wear, and possibly guarantee longer duration. Many companies are currently working to match these fundamental requirements by employing different strategies. In August 2015, Dexcom announced the agreement with the Life Science team at Google (Google Inc., Mountain View, CA, USA) to develop jointly a series of next generation CGM products designed to be smaller, cheaper, and lasting for 10–14 consecutive days [50]. On the other hand, in 2014 Abbott already launched in Europe the Freestyle Libre flash glucose monitoring system, which can be worn for 14 consecutive days (showing glucose levels when scanned by the user) with an accuracy of 11.4% MARD [49].

While research is still improving the development of new technologies for miniaturization of electrochemical biosensors [51], alternative approaches based on optical sensing became much more appealing in recent years. Indeed, many limits associated with electrochemical sensors, e.g., the dependence of sensor sensitivity and stability on the enzyme used and interference with active agents (acetaminophen, ascorbate) [52], can be overcome by optical sensing technologies. Several optical detection methods have been proposed in the literature, both for noninvasive detection, e.g., near infrared detection and Raman spectroscopy, and for implanted systems, which are instead fluorescence-based sensors [18,26]. This last category of optical sensing technique has been recently successfully applied by Senseonics (Senseonics, Inc., Germantown, MD, USA) to develop a fully implanted CGM system [22,53], the Eversense sensor, which provides real-time glucose measurements through the external coupled transmitter for an expected lifetime of six months [54]. Currently, the Eversense CGM is approved to be used in European countries only (CE mark received in 2016) with a lifetime of 90 days and an accuracy of 11.4% MARD [55]. While biocompatibility and patient acceptance of the new fully implanted technology remain key issues, lifetime and ease of use are the fundamental strengths of this approach.

Beyond the requirements just discussed in terms of sensor lifetime, size, and user acceptability, which can be achieved mostly by hardware adjustments, next generation CGM systems need to address several other requirements through software updates. Currently available CGM systems already incorporate smart features, such as alerts and alarms generation in case of hypoglycemic or hyperglycemic events, incorporation of glucose trend information, detection of sensor faults and artifacts [55,56]. Next generation systems certainly need to incorporate these features and to deal with data management and integration into external devices, e.g., smartphone apps or dedicated cloud platforms.

Another crucial aspect that needs to be considered to improve the ease of use of next generation sensors is calibration requirement. Most commercially available CGM sensors need to be calibrated to convert the raw measurements (e.g., electrical current or optical intensity) to glucose values, usually

twice per day, requiring the collection of one or more SMBGs to use as a ground truth [56]. In order to facilitate the use of CGM technology, next generation systems need to be less calibration dependent. On the other hand, sensor accuracy needs to be maintained despite the reduction of calibration requirements. The Freestyle Libre Flash glucose monitoring system [42] is currently the only available glucose sensor which is factory calibrated and does not require additional in vivo calibrations; it lasts for two consecutive weeks, but it presents the limit of not providing many on-line features such as glucose trends and alarms. Conversely, in terms of accuracy and smart features incorporation, the Dexcom G5 Mobile CGM system is currently the leading product. With a 9% MARD, it is the first and only CGM system that can be used to make daily diabetes treatment decisions without finger pricking [57,58]. However, it still requires finger pricks for in vivo calibration, although some recent studies showed promising results towards a calibration-free scenario [59,60].

Research improvements in CGM technologies and recent industrial trends suggest that sophisticated next generation CGM systems will be next to appear in the market. There is confidence that future products will be more accurate, smaller, less painful and obtrusive, long lasting, easier to use and more user friendly both in terms of calibration requirements and incorporation of smart features for more efficient data management.

3. The Role of CGM in Decision Support Tools

The standard therapy for T1D consists of multiple daily injections of insulin finalized to keep BG concentration in the normal safety range of 70–180 mg/dL, this was already highlighted in Figure 1. Each insulin bolus injection is administered usually at meal time and its amount is tuned according to diet, physical activity and level of BG measured by SMBG. This approach is very demanding and it greatly affects the quality of life of T1D patients that are required to perform, for their whole life, a huge number of tasks, e.g., to effectively control the BG concentration fluctuation due to a meal, patients are required to measure preprandial BG, to inject insulin boluses to counterbalance prandial hyperglycemia and eventually to repeat the procedure until the BG level gets in the safety range. In fact, it can be calculated that, on average, a T1D can have to do a number of actions that can exceed 500,000 in an entire lifetime.

3.1. Bolus Calculator

A first simple tool devised to provide decision support to T1D patients is the so-called bolus calculator [61], a software that implements a simple formula for computing the amount of insulin to inject subcutaneously which is expected to compensate for carbohydrates intakes. The formula for calculating the recommended dose of insulin, B (U) is:

$$B = \frac{CHO}{CR} + \frac{G_C - G_T}{CF} - IOB, \quad (1)$$

where the carbohydrate-to-insulin ratio (CR) (g/U), which specifies the number of grams of carbohydrate covered by each unit of insulin, and the correction factor (CF) (mg/dL/U), which represents the drop in BG level caused by each unit of insulin, are two patient specific parameters usually tuned up by physician with empirical laws and trial-and-error procedures [62], CHO (g) is the estimated amount of carbohydrates in the meal, G_C (mg/dL) is the current BG level, G_T (mg/dL) is the target BG level and IOB (U) is an estimate of the amount of insulin previously injected in the body not been assimilated yet.

Numerous studies [63] showed how the bolus calculator improved BG control and quality of life reducing the risk for hypo/hyperglycemic events. In particular, it resulted useful in diabetes management [64], given that, for most people, accurate bolus dose calculation can be either difficult, imprecise [65] or time consuming. Nevertheless, bolus calculator implementing (1) is far from being optimal, firstly because it depends on the patients' skill of correctly estimating CHO intakes (inaccuracy of ± 20 g significantly affects postprandial glycaemia in children [66]), secondly, because the parameters

CR and CF may vary during the day according to physiological factors such as circadian rhythms, physical activity, hormone cycles or alcohol consumption, and thirdly, because the formula does not exploit the dynamic information (e.g., trend) available nowadays by CGM sensors.

3.2. Technological Solutions to Improve Bolus Calculators

As far as the first weak point of present bolus calculators is concerned, much effort is presently being made to develop tools able to automatically assess CHO content in a patient's diet. In particular, the growing availability of mobile phones, together with their increasing hardware performance, led researchers to develop mobile applications (apps) that use phones' features such as their camera, the constant internet connection and even their microphone. For example, Rhyner et al. [67] proposed GoCARB: A mobile-phone based system designed to estimate CHO which runs on Android, implements computer vision techniques and automatically provides the nutritional contents from photos of plated meals. In Bally et al. [68], encouraging results of a randomized pilot study evaluating the performance of GoCARB in 20 adults with T1D have been presented.

A very different approach is represented by the VoiceDiab expert system [69], an app that combines a nutrient database with software for automatic speech recognition in which patients describe vocally the meal they are planning to eat and they receive back information about the recommended amount of insulin to inject. In [69], VoiceDiab has been evaluated in a crossover randomized controlled study made in 12 T1D adults, showing promising results.

3.3. Use of CGM Information to Improve Bolus Calculators

As stated at the end of Par. 3.1, there is a need to make the bolus calculator formulation more "dynamic" in order to adapt to the patients' lifestyles. In Herrero et al. [70], an approach to automatically adjust CR and CF exploiting the CGM measurements is presented. The method is based on a run-to-run (R2R) control technique, i.e., an iterative procedure in which the values of CR and CF are updated daily according to a performance metric, e.g., the distance between the minimum postprandial glucose concentration and the patient's target BG. The proposed method has been evaluated in-silico over a population of 10 adults and 10 adolescents using a simulation approach [71]. Results showed a statistically significant improvement of all glycemic metrics.

Another work by Herrero et al. [17] tried to integrate R2R with case-based reasoning (CBR), i.e., an artificial intelligence technique that solves new problems by applying solutions learned from solving similar problems in the past. Using the same approach as in [70], they assessed the method in-silico obtaining a significant decrease of the time spent outside the safety range.

All of the above cited methods rely on (1) calculation of the recommended insulin bolus to inject, taking into account only a single BG measurement. Intuitively, this is suboptimal given that one can exploit the CGM measurements to obtain more information on the patients' status. Present CGM systems, such as the Dexcom G5 Mobile or the Senseonics Eversense system, provide users with the so-called rate-of-change (ROC) arrows (see Figures 2c and 4), i.e., a graphical indication of the current direction and velocity of changing glucose. It is natural to think of improving the bolus calculators' outcomes by modulating the recommended insulin dosage according to the patient's current ROC. In [72], a rule was proposed to empirically adjusting in Equation (1) the current G_C according to ROC, in order to suitably alter the total amount of insulin to inject, while in [73], the whole meal dose was modulated according to ROC by a fixed percentage.

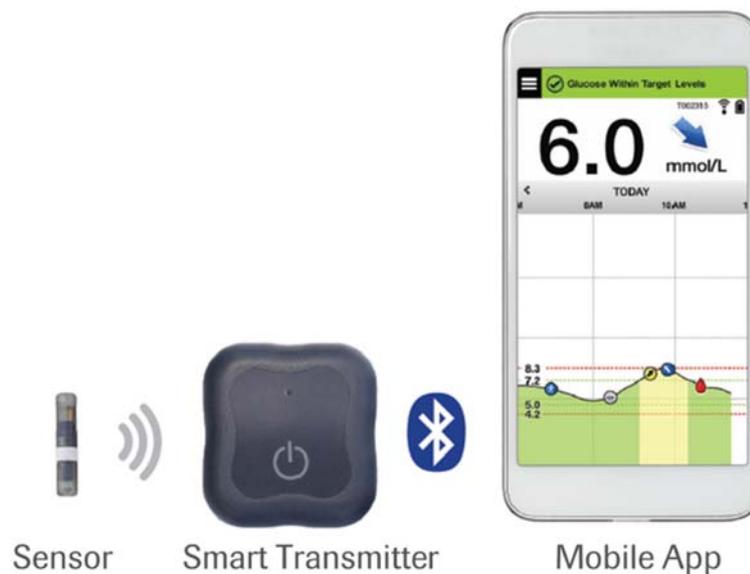


Figure 4. Example of implantable CGM system based on optical sensing technique, the Senseonics Eversense continuous glucose monitoring system (taken from [74]).

3.4. Future Challenges

Bolus calculators are useful tools that are able to support diabetic patients in their therapy management. Availability of ever increasing amount of CGM data at the individual and population level offers new perspectives to develop new decision support tools able to fit each patient's diet, behavior and therapy. Following this rationale, a "smarter" bolus calculator can be designed to understand patients' characteristics, providing clinicians with even more useful information. In this context, big data analysis can be exploited to discover daily or weekly patterns, whether patients perform better than others and even clusterize each subject into different categories according to their outcomes. For example, a possible advantage of having "clusters" of patients instead of a single one is the possibility of using not only that subject information for the insulin bolus calculation, but also the whole cluster information, that, containing much more data, makes it possible to deploy powerful deep learning techniques.

4. Present Diffusion of CGM Sensors and Future Horizons for Extending Their Field of Use

4.1. Diffusion of CGM Sensors in the Diabetic Population

Use of CGM sensor is recognized to be not only clinically beneficial for T1D glycaemic control [75,76], but also cost-effective in the long term [77,78], despite the fact that only 10% of T1D patients are currently using this technology [79]. CGM use is even less widespread among people with T2D. At the present time, the major barriers to CGM diffusion can be attributed to the cost (around 3000–4000 dollars per year for current-generation devices) and, in many countries, lack of reimbursement by medical insurances and government [80,81], a bottleneck which is strongly related to the absence of regulatory approval of CGM use for making treatment decisions. Indeed, because of accuracy problems, for several years CGM devices have been approved only for the so-called adjunctive use i.e., before making treatment decisions a patient was supposed to collect also SMBG measurements in order to confirm CGM readings.

However, in recent years the situation started changing: The accuracy of CGM sensors has been improved a lot [37,39,41] and some CGM devices have been approved to be used nonadjunctively, i.e., without confirmatory SMBG, both in Europe (approval of Abbott Navigator II, Abbott Freestyle Libre Flash and Dexcom G5 Mobile between 2014 and 2015) and the United States (approval of the

Dexcom G5 Mobile in 2016 [59]). Importantly, in March 2017 Medicare announced criteria for Dexcom G5 Mobile reimbursement to all T1D and T2D people on intensive insulin therapy (i.e., basal-bolus insulin regimens) [82]. These important achievements will contribute to considerably increasing the number of CGM users in the coming years.

4.2. Extending the Market of CGM Sensors: New Populations

Certainly, people with T1D are those who can benefit more from CGM use, however they represent only 5–10% of diabetics. Leading companies in CGM manufacturing are working on developing new products to target a much wider market, e.g., including T2D, which affect 90–95% of diabetics [83], and gestational diabetes, present in 3% to 9% of pregnant women [84] with an increasing trend [85]. These products are supposed to be smaller, less expensive and factory-calibrated at the compromise of lower accuracy, which is not such a stringent requirement for these categories, since they do not require frequent adjustments of their insulin doses according to the real-time use of glucose measurements.

For example, as anticipated in Section 2, in 2014 Abbott launched in Europe the Freestyle Libre Flash, a 14-day factory-calibrated sensor [42], considerably less expensive than other commercial CGM systems despite maintaining good sensor accuracy (11.4% MARD), which is becoming very popular among T2D individuals [86]. In 2015, Dexcom and Verily Life Sciences announced the start of a collaboration for developing a series of be miniaturized, factory-calibrated and low-cost CGM products to target not only T2D and gestational diabetes, but also prediabetics and obese subjects [50]. Similarly, in 2016 Medtronic and Qualcomm Life, Inc. announced a new collaboration to jointly develop a future generation of single-use and inexpensive CGM sensors for T2D [87].

Other emerging companies, like Glucovation [88] and Nemaura Medical Inc. (Leics, UK) [89], are also working on novel low-cost CGM products, devised not only for diabetics but also for non-diabetics as part of wellness, fitness or weight-reduction programs, which are expecting to enter the market by the end of 2017.

4.3. Integration of CGM Data with other Data Sources: Towards Big Data Analytics for Precision and Proactive Medicine

Modern commercial CGM sensors can transfer data directly to smartphones, which act as a substitute for traditional CGM receivers [40,90]. The availability of smartphone- and internet-connected CGM sensors together with the extension of their use to a larger population will allow the creation of large databases in which CGM data are integrated with different data sources. For example, CGM data can be merged with information provided by other medical devices (e.g., SMBG monitors, insulin pumps and insulin pens) and mHealth apps [91–94] used in diabetes management.

The integration of other data sources like clinical registries, electronic health records, prescription registries, and quality of life and health surveys [95] will provide important clinical, psychosocial and economic contextualization to CGM data. CGM data can also be combined with variables and signals collected by other wearable sensors, not specific for use in diabetes, like smart-watches [96,97] monitoring subject mobility, smart clothes measuring biometrics and activity [98,99] or miniaturized sensors for other biomarkers based on tears, saliva, sweat and breath analysis [100].

In addition, the connection of CGM to smartphones equipped with GPS connectivity allows the geo-referencing of data collected by these devices. This will provide information on the context of CGM measurement, potentially driving to a better understanding of diabetes and the environmental factors that can influence its onset/course [101,102].

The integration of CGM data with a variety of data sources will contribute to generating a digital ecosystem of diabetes that can be used to improve our understanding of the disease and, in particular, design data-driven strategies for personalized diabetes therapy and prevention. For instance, taking advantage of patients' integrated data, dashboards to identify diabetic patients with poor glycaemic control and high risk of developing diabetes-related complications can be designed, e.g., by implementation of pattern recognition techniques and risk models [103]. Rich individual-level

data will also allow the development of precision medicine applications, like personalized decision support systems and telemedicine services, with the aim of tailoring the patient's therapy around his personal needs. Furthermore, the extension of CGM technology beyond the diabetic population will enable the development of software solutions for proactive medicine, like systems to determine subjects at risk of developing diabetes based on prediction models for diabetes onset [98]. This will allow health care agencies to devise targeted prevention plans with considerable saving of money and resources.

Of course, the development of precision and proactive medicine applications requires the collection of a large amount of individual-level data. Their processing by machine learning, datamining, and big data analytics [101,104], however, is sensitive to the reliability of data sources [101,104]. In fact, among the "V" properties of big data [105], that indicated as veracity refers to the uncertain nature of data collected in large volumes with limited control of the quality. Although veracity is expected to affect effectiveness of healthcare applications, there is still limited knowledge on its possible impact in the setting of interest for the present paper and proper investigation will be needed in the next future.

5. Conclusions

It is widely accepted that wearable CGM sensors and their application will revolutionize the treatment of diabetes, one of the most challenging socio-health emergencies of the third millennium. This paper reported an overview of present CGM hardware technologies and of the decision support systems which, implemented in software applications, can render them of great impact in the daily life of patients. A perspective on possible future developments has also been proposed, mainly related to the recent tendency of CGM manufacturers to invest in the development of low-cost devices, a trend that, by enlarging the market to new populations such as obese and pre-diabetic people, can open completely new scenarios and opportunities, for both industry and clinical/scientific research. In fact, massive CGM data acquisition by low cost devices and exploitation of other data sources (originating from e.g., electronic health record, sensors of physical activity, geolocalization, etc.) will likely be essential in developing new data-driven strategies for personalized, preventive and proactive diabetes management.

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