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A review of biosensor technology and algorithms for glucose monitoring

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ABSTRACT

Diabetes mellitus (DM) has become a serious illness in the whole world. Until now, there is no effective cure for patients with DM. It is well known that the glucose level is one key factor to determine the progress of DM. It is also an important reference to carry out the accurate and timely treatment for patients with DM. In this article, the related biosensors technology that can be utilized to identify and predict glucose level are reviewed in detail, including the algorithms that can help to achieve numerical value of glucose level. Firstly, the biosensor technology based on the physiological fluids are illustrated, including blood, sweat, interstitial fluid, ocular fluid, and other available fluids. Secondly, the algorithms for achieving numerical value of glucose level are investigated, including the physiological model-based method and the machine learning-based method. Finally, the future development trend and challenges of glucose level monitoring are given and the conclusions are drawn.

Contents

1. Introduction

Diabetes mellitus (DM) is one kind of incurable disease, which is due to the insufficiency or insensitivity of insulin in the human body.[1] According to the report of world health organization, there are about 422 million people living with DM, and 1.6 million deaths are directly caused each year.[2] Most of these patients are with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). Many of patients with DM have the form of T2DM.[3] To implement appropriate treatment, the glucose level of patients is the most important dependent metric.[4] However, its numerical value is affected by many factors, such as meal, exercise, weather, sleep, etc. It is always a huge challenge to achieve accurate and stable glucose level estimation or prediction. With the development of various sensing technologies and algorithms, many available methods have been studied to achieve this objective.[5] In this article, the related works in this field are reviewed and illustrated to provide the direct reference for researchers.

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Traditionally, the glucose sensing device mainly consists of the glucose sensor, which is usually based on the electrochemical method. At present, the blood is still the widely utilized fluid for analyzing the glucose level.[6] A small volume of blood sample (<1 μL) is required to implement analysis of glucose level, which is usually obtained by the "finger-pricking" collection method. However, this method is inconvenient and may lead to the low compliance of patients. The alternative manners of glucose monitoring have been studied for a long time. The continuous glucose monitoring (CGM) and the flash glucose monitoring (FGM) are two typical manners. The first CGM system was proposed in 1999, and it has undergone several revolutions.[7] By utilizing the CGM devices, patients can obtain real time glucose monitoring results. In contrast, the FGM could obtain the near real time glucose level. It could be regarded as a hybrid way of self-monitoring of glucose and CGM, which provides an economical alternative to CGM.[8] In addition, the non-invasive sensing methods have drawn much attention from the academia area.[9] And these methods usually utilize other fluids instead of blood, such as sweat, interstitial fluid, ocular fluid, and urine.[10] The developments of biosensor technology and data transmission have promoted the wide application of glucose monitoring in many ways.

After the raw data collected by sensors, it needs appropriate algorithms to process these data for achieving the glucose level estimation. In this field, different types of algorithms have been comprehensively studied.[11,12] Two typical methods are based on the physiological models and the data-driven models.[13,14] Not only the glucose level can be realized immediately by using these algorithms, but also the trend prediction is also available for the practical application. To improve the monitoring accuracy, some additional information should be considered, such as meal absorption and physical exercise.[15] The studies on short-term and long-term prediction horizons have both been implemented,[16,17] which are making the clinical application being available. The related algorithms for analyzing the raw sensing data of glucose have provided many feasible ways for implementing reasonable treatment for patients with DM. In addition, some algorithms on data anomaly detection, data recovery have been studied, which can help to enhance the monitoring result of the objective.[18,19] The hybrid method is also helpful for improving the monitoring results.[20] The development of related algorithms provides different feasible ways for implementing appropriate applications.

With the help of available glucose monitoring results, many clinical treatments can be implemented to prevent harm for patients with DM. One typical application is to monitor the CGM with appropriate sensing devices and algorithms.[21,22] CGM can provide the changing information of glucose level during a day or several days. These data can be utilized for the retrospective analysis, which is an important progress for the treatment of DM patients.[23] At present, the automatic insulin delivery pump can be realized with the intelligent CGM system.[24] In the past, the lifetime of sensors in CGM was a barrier for the wide application due to the large cost for calibration, inconvenience and discomfort.[25] The emerging wireless devices provide a feasible way to promote the application. For example, smart phones can be used for analyzing CGM data and offering the information for taking drugs.[26] The related biosensor technology and algorithms for glucose monitoring have provided such valuable information for many clinical applications.

This review mainly focuses on the related biosensor technology and algorithms that can achieve glucose monitoring. In Section 2, the biosensor technology for glucose monitoring is illustrated, including the available fluids of human body and sensors. In Section 3, two kinds of typical algorithms are provided, including the physiological model-based method and the data-driven methods. In Section 4, the future developments of glucose monitoring in these two directions are provided. In Section 5, the conclusions of this article are drawn.

2. Biosensor technology for glucose monitoring

Biosensor technology has been paid much attention to help achieve glucose monitoring. Sensors are used to analyze different physiological fluids, which mainly include blood, sweat, interstitial fluid, ocular fluid, and urine. By using appropriate sensors, the typical monitoring results of these physiological fluids are illustrated in Table 1. The representative biosensor technology will be reviewed in the following subsections.

2.1. Glucose monitoring in blood

To diagnose and manage patients with DM, glucose monitoring in blood is one of the most important standards.[32] The basic principle of glucose sensing is to catalyze the oxidation of β-D-glucose by the immobilized glucose oxidase (GOx), and the molecular oxygen is utilized to generate gluconic acid and hydrogen peroxide.[33] The flavin adenine dinucleotide (FAD) is transformed to $FADH_2$, as given by.

$$\text{Glucose} + \text{GOx}-\text{FAD}^{+} \rightarrow \text{Glucolactone} + \text{GOx}-\text{FADH}_2. \quad (1)$$

The hydrogen peroxides are formatted by the cofactor that is produced by reacting with oxygen, as given by.

$$\text{GOx}-\text{FADH}_2 + O_2 \rightarrow \text{GOx}-\text{FAD} + H_2O_2. \quad (2)$$

By using the platinum anode, the catalytic is able to oxidize the hydrogen peroxide. The number of electron transfers can be identified by electrode. The electron flow is used to analyze the number of glucose molecules in blood.[34]

$$H_2O_2 \rightarrow 2H^{+} + O_2 + 2e. \quad (3)$$

To achieve electrochemical sensing of glucose, the available methods include the oxygen consumption measurement, and the hydrogen peroxide measurement. Pyrroquinolinequinone (PQQ) is utilized as a cofactor to identify the quinoprotein glucose-1-dehydrogenase (GDH).

$$\text{Glucose} + \text{PQQ}(\text{ox}) \rightarrow \text{gluconolactone} + \text{PQQ}(\text{red}). \quad (4)$$

Then, NADH is generated by using GDH and nicotinamide-adenine dinucleotide (NAD), which is the major electron acceptor. Finally, NAD^{+} receives two electrons and the hydrogen ion and NADH is electrochemically oxidized.

$$\text{Glucose} + \text{NAD}^{+} \rightarrow \text{gluconolactone} + \text{NADH}, \text{NADH} \rightarrow \text{NAD}^{+} + \text{H}^{+} + 2e. \quad (5)$$

Based on the aforementioned principles, the first generation of glucose sensing device is designed by Clark and Lyons in 1962.[35] The glucose concentration is realized in the manner of indirect quantification. The first measurement process is that a thin layer of GOx enzyme is placed on a platinum electrode. Meanwhile, the semipermeable dialysis membrane is utilized to assist placement. However, the measurement results of this method are easily influenced by other electroactive species in blood, including urea and ascorbic acid.[36] In addition, the

Table 1
Summary of glucose monitoring by different physiological fluids.

Index	Physiological fluid	Glucose concentrations of patients with DM
1	Blood	2–40 mM[27]
2	Sweat	0.01–1 mM[28]
3	Interstitial fluid	1.99–22.2 mM[29]
4	Ocular fluid	0.5–5 mM[30]
5	Urine	>5.55 mM[31]

platinum electrode is expensive, which is not suitable for the clinical utilization.

In the 1980s, the second generation of glucose sensing device was proposed, which could improve the insufficiency caused by oxygen.[37] Instead of oxygen, the synthetic electron readbox mediator is used. In this way, the disposable enzyme electrode strip is realized, which promote the emerging of the pocket-size blood glucose meter.[38] In the strip, the working electrode has complex compositions, including an electron-shuttle redox mediator, glucose oxidase, stabilizer, etc. These techniques help lead to the self-monitored glucose management, a.k.a. the "finger-pricking" method, as shown in Fig. 1.

At present, the "finger-pricking" method is still widely utilized for the health management of patients with DM.[10] In Fig. 1, the sample blood is obtained from a finger by pricking and analyzed by the test-strip and a glucose meter.[39,40] The disadvantages of this method include pain, inconvenience, and time constraints. Especially, for assessing glucose level, it needs to implement "finger-pricking" at multiple intervals in a day.[31] The typical monitoring steps include the glucose after meal, exercise, and insulin dosing.[41] However, this method cannot identify the periods of hypoglycaemia and hyperglycaemia that are outside of the sampling time. To solve this problem, the implantable sensors that can be utilized with insulin pumps. In this way, the instant insulin dosing can be realized.[42] The implantable sensors are mainly used to achieve the CGM.

The CGM was firstly proposed by Albisser et al. in the 1970s, which was based on the artificial pancreas.[43] During the monitoring, the blood is removed to an external benchtop analyzer, which is also connected with the insulin pump. However, the artificial pancreas is not portable. Based on this device, the third generation of glucose sensing device was designed. In the 1990s, Medtronic Minimed Inc. (Sylmar, CA, USA) released the commercial glucose monitor sensor.[36] For the practical application, the real-time glucose monitoring results cannot be obtained by this sensor. Until now, the glucose monitoring in blood is still studied widely. For the health management and treatment of patients with DM, the monitoring results are the most important references. Meanwhile, other available sensing technologies have been paid much attention, e.g., by analyzing sweat, interstitial fluid, ocular fluid, urine, etc.

2.2. Glucose monitoring in sweat

The biological function of sweat is for thermoregulation. The biological information contained in sweat has been studied by using appropriate sensors for diagnostic purpose. The disease markers in sweat can be utilized, including potassium, calcium, sodium, and glucose.[44] In addition, the advantage of using sweat is that it can be continuously accessed with non-invasive manner. For example, the iontophoresis can be utilized to stimulate the production of sweat on-demand.[45]

The study in[28] has revealed the glucose level of different people. For the healthy people, the glucose monitoring in sweat is between 0.06 and 0.11 mM. In contrast, for patients with DM, the corresponding value is between 0.01 and 1 mM. A representative study in this field is how to design sweat-sensing patches that consider sweat production, measurement technique for analyte concentrations, and transmission manner to a smartphone.[46]

Recently, the non-invasive and continuous sensing device that can detect analytes in sweat has been studied in.[47,48] Stick-on flexible sensors[47] and multi-analyte eyeglasses[48] are two typical sensing techniques. The latter manner is easy to be utilized in the daily life and the details are given in Fig. 2.

A potassium sensor and a lactate are both installed on the nose-bridge pads, and they can interface with the electronic backbone of the arm. Bluetooth is used to transmit the sensing data to a smartphone. At present, the lactate and potassium ions in sweat can be sensed for a few hours by using the eyeglasses. The authors in this work[48] have verified that the eyeglasses can provide glucose concentrations by changing the lactate sensor for the glucose sensitive device.

In addition, another sensing device for glucose monitoring in sweat is designed in,[49] which is integrated with a Bluetooth-enabled wristband. Multiple sensing units are utilized in this design to solve the problems when a single sensing unit is used to analyze the complex elements in sweat. Experimental results in this study show that the minimum volume of sweat for effective analysis is 10 μL. Some soft materials that are suitable for analyzing sweat have been investigated in.[50] An objective of using soft materials is to realize comfortable wearing when the sensing device is utilized. The contact of electrodes with skin can also be avoided. The most function of these soft materials is that they can absorb and retain sweat for effective analysis.

Although some valuable works have been implemented in this field, a challenge for analyzing sweat is that the related markers contained in sweat may change significantly in different individuals. For basal and exercising states, these markers also show the large difference. For example, when the individual is in the excising state, the range of pH values can fluctuate from 4.0 to 6.8.[51] It is a similar phenomenon for monitoring other markers contained in sweat, which brings challenges for chemical-sensing or biosensing techniques to implement diagnosis. In addition, two challenges in this field have been analyzed in.[52] The first is how to prepare sensors from scratch from basic chemicals. The other is that sensors have high electrical impedance, which brings difficulty for designing electronics.

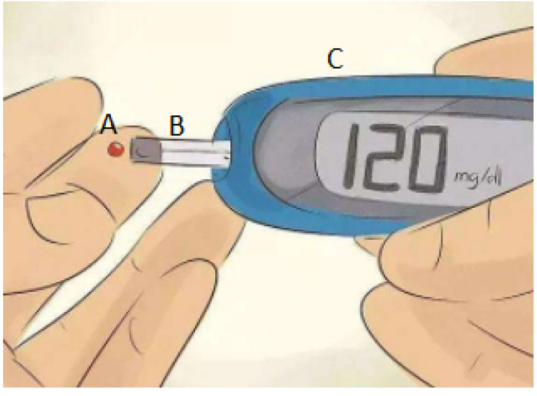

Fig. 1. The glucose monitoring by the "finger-pricking" method. A. Blood; B. Test-strip; C. Glucose meter.

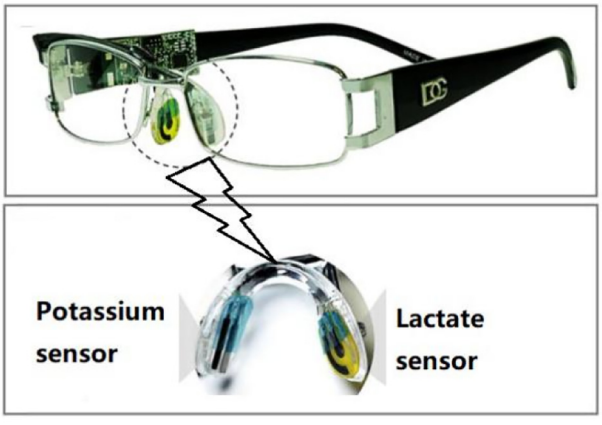

Fig. 2. The biosensor technology based on the eyeglasses.

2.3. Glucose monitoring in interstitial fluid

Similar to the monitoring manner in sweat, the glucose monitoring in interstitial fluid is also able to realize non-invasively. A number of biomarkers are contained in the interstitial fluid, which can be used to achieve clinical diagnostics.[53] In the area of glucose monitoring, research efforts have been implemented for the non-invasive sensing, which is able to provide valuable information regarding the glucose level of patients with DM. The related methods that implement glucose monitoring via the skin are reviewed comprehensively in,[54] e.g., the biosensor technology based on optical detection, ultrasound, heat or thermal emission, etc.

A typical method for implementing glucose monitoring in interstitial fluid is to utilize the sensor based on microneedle array.[55] The schematic of prototype device is shown in Fig. 3, which consists of the sensing part and microneedle array. The sensing part is a 3-electrode amperometric sensor, and the hydrogen peroxide product of the enzymatic oxidation of glucose is directly detected. in the microneedle array, there are approximate 200 silicon microneedles with the area of 6 × 6 mm. Every microneedle is about 300 μm in length and the lumen is 50 × 50 μm. Therefore, it can be seen that this kind of glucose sensing unit is in very small size.

To carry out continuous glucose sensing, the GlucoWatch based on monitoring in the interstitial fluid is designed.[56] In the GlucoWatch, the interstitial fluid is analyzed by the reverse iontophoresis technique. The pH range of the monitored glucose level can be 7.2–7.4.[53] The GlucoWatch promotes the development of glucose monitoring. However, it needs to implement the periodic recalibration and the main method is based on pricking, which brings the problem of cost increase for calibration and patient care.[57] In addition, it takes long time for warm up and it is uncomfortable with skin rash. In 2008, the GlucoWatch was removed from the market. Another glucose monitoring device in this field is BioRadioTransmitter, which is mainly utilized in the artificial pancreas.[58] It is mainly comprised of three components, including a capacitor, radio transmitter and receiver. The capacitor is used to sense the glucose by discharging the radio signal. Then, this signal is received and amplified by the radio receiver. Finally, the change of in transmission frequency can be utilized to achieve the glucose concentration.

At present, the typical models of Dexcom and Abbott are the G6 CGM System and the FreeStyle Libre Starter Pack, respectively. These products show the great intelligence on glucose monitoring. For example, G6 provides the function of customizable alerts and alarms. Another advantage is that these products do not need to be calibrated. In addition, Medtronic provides two types of CGM systems, which are Guardian™ Connect and iPRO™2. The Guardian™ Connect could offer the information where glucose levels are heading. And the iPRO™2 could be used the personalize therapy adjustments. The commercial product has been widely utilized for glucose monitoring,[25,59] as shown in Fig. 4. The main advantage of the Abbott is that the sensor does not need to be recalibrated for 14 days. And the interval for each glucose sensing can be realized in 1 s.

The implantable sensors are also available for glucose monitoring by analyzing the glucose contained in the interstitial fluid. For example, the Eversense sensor developed by Senseonics is one type of implantable sensors.[60] The actual size of the Eversense sensor is only 3.5 mm × 18.3 mm, and it could provide the long-time CGM, as the 180-day trial implementation.[61] These advantages provide the continuous and stable glucose monitoring, which may bring many benefits for clinical treatment of diabetes mellitus.

Some new sensing techniques in this field are under development, e.g., the sensors based on impedance spectroscopy and optical transducers. The development of glucose monitoring in the interstitial fluid is promising for the future clinical diagnosis and health management. Especially, some sensing devices and systems have been used in the practical application. The key problem is to design the advanced sensors that do not need to be calibrated with working time as long as possible. Meanwhile, the sensing accuracy and stability are required to be used for clinical application.

2.4. Glucose monitoring in ocular fluid

Blind is a serious complication caused by DM. A usual medical examination is to check the fundus of eyes. The biological remarks in the ocular fluid (also known as the aqueous humour) include glucose, hormones, lipids, proteins, etc. If these remarks can be analyzed correctly, they can provide valuable information for health management of patients with DM.[62] Until now, many researches have been carried out to study the non-invasive and CGM.

The smart-contact lens that integrates an electrochemical battery-operated enzymatic glucose sensor was designed by Google[X] lab and Novartis in 2014.[63] The enzyme GOx is utilized as the sensing component and the corresponding microchip is deployed between two layers of the smart-contact lens, as shown in Fig. 5. In this sensor, the glucose level in the ocular fluid is achieved by the redox reaction, which is generated by the hydrogen peroxide at the electrode.[64] For glucose monitoring data transmission, the sensor relays technique is used.

Another typical technique is to design the sensor based on screen-printed structure, which is installed on the polymeric substrate of the lens.[65] The glucose level can be obtained by analyzing the current signal that can be measured in the oxidation and reduction of the reaction. The study in[66] reveals that, compared with the glucose level in blood, the achieved result is 10 times smaller. And there is also a lag time of about 10 min. In addition, this lens has the rapid response time as small as 20 s and the reproducibility is relatively good. However, it does not belong to the category of non-invasive and continuous glucose-monitoring.

There are some disadvantages when the ocular fluid is utilized for glucose sensing of patients with DM. In general, the sensor signal is transmitted by the wireless manner, which is influenced by the blinking of eyes. The battery is usually embedded in the sensing lens. However, the external power is required to achieve wireless transmission efficiently. In addition, the monitored glucose level is easily affected by the tear fluid. And the technique based on the electrochemical sensing method may generate corrosive hydrogen peroxide, which can bring interference for the glucose level assessment in the ocular fluid.

To overcome these problems, some innovative techniques are being studied. For solving the power dependence problem, the optical

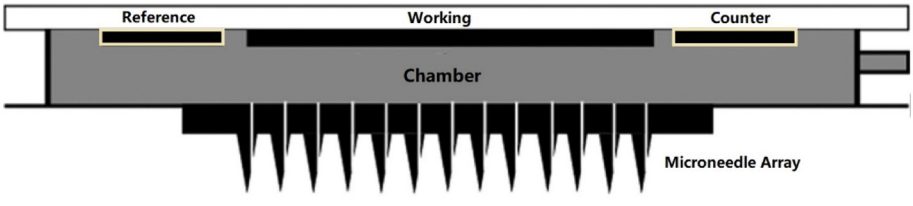

Fig. 3. Schematic of glucose monitoring based on the microneedle array in the interstitial fluid.

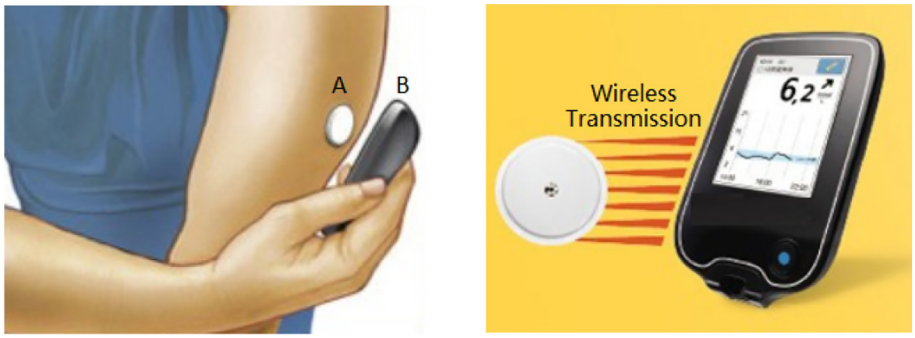

Fig. 4. The glucose monitoring in the interstitial fluid. (**a**) Typical continuous glucose monitoring; (b) Wireless transmission of monitoring data; A. Sensor; B. Glucose monitoring meter.

chemical sensor is a potential resolution.[67] In the new sensing material, the surface-enhanced Ramen scattering can be used to detect the glucose.[68] This technique is a typically non-invasive sensing method. With the development of new sensing methods and effort of researchers, it is expected to realize more accurate and stable results of glucose sensing results in this field.

2.5. Other sensing techniques for glucose monitoring

Some fluids of the human body can also be utilized to realize glucose monitoring. For example, the study in[31] reveals that the glucose level in the urine is in the range of 2.78–5.55 mM, which can be as a reference to carry out health management of patients with DM. Although urine is easily collected and analyzed, this technique cannot be realized in the continuous manner due to the intermittent nature of urine.

Saliva is another available fluid that can be used for glucose monitoring. Similar to the urine, it is easy to collect saliva in the non-invasive manner. Gupta et al.[69] have demonstrated that the glucose level of healthy people is in the range of 0.23–0.38 mM. In contrast, for the patients with DM, the glucose level in in the range of 0.55–1.77 mM. It is believed that there is a connection between saliva and blood in term of glucose level. However, it is hard to discover the exact relationship, which limits its application.

The biological remarks produced by breath can also be utilized for glucose monitoring. Instead of sensing glucose, the monitoring of acetone concentrations provides an alternative method.[70] In addition, the study in[71] also reveal that methyl nitrite and ethanol can also be used for the patients with DM. Usually, it is easy to sense breath with the wearable sensor. However, the main disadvantage is that it is easily inferenced by the external air.

3. Algorithms for glucose monitoring

To obtain the numerical value of glucose concentration, the raw electrical signal of glucose sensing or the alternative biological remark needs to be processed by appropriate algorithms. The typical algorithms include the physiological model-based method and the machine learning-based method. The related developments in these areas will be illustrated in this subsection. And other available methods will also be introduced.

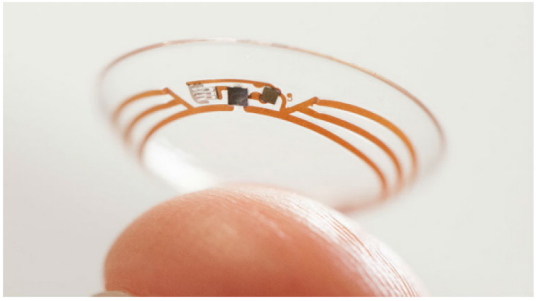

Fig. 5. Diagram of the smart-contact lens for glucose monitoring in ocular fluid.

3.1. Physiological model-based algorithms

The physiological model of human body is complex, and it is relevant to many factors (e.g., male, age, weight, meal, external environment, etc.). If the glucose monitoring can be realized by the physiological model, it can bring benefits for treating and managing patients with DM. A typical study was the UVA-PADOVA T1D Simulator formulated in 2008.[72] The related content is shown in Fig. 6.

In this study, glucose, insulin and glucagon dynamics are considered together. To sense glucose accurately, a subsystem in the model is established, which is comprised of a 2-compartment model. In the first compartment, the independence on insulin takes place, representing plasma and rapidly equilibrating tissues. On the other hand, the dependence on insulin takes place in the second compartment, representing slowly equilibrating tissues. In the model, the glucose kinetics is defined by

$$\begin{cases} \dot{G}_P = EGP - U_{ii} - k_1 \cdot G_p(t) + k_2 \cdot G_t(t) & G_p(0) = G_{pb} \\ \dot{G}_t = -U_{id}(t) + k_1 \cdot G_p(t) - k_2 \cdot G_t(t) & G_t(0) = G_{pb}\frac{k_1}{k_2} \end{cases}, \tag{6}$$

where $G_p(t)$ indicates the amount of glucose in the plasma, $G_t(t)$ refers to the amount of glucose in the tissue, k_1 and k_2 are the rate parameters.

Let U_{id} denote the insulin-dependent utilization and it can be described by

$$U_{id}(t) = \frac{[V_{m0} + V_{mx} \cdot X(t)] \cdot G_t(t)}{K_{m0} + G_t(t)}, \tag{7}$$

$$\dot{X}(T) = -p_{2U} \cdot X(t) + p_{2U} \cdot [I(t) - I_b] \quad X(0) = 0, \tag{8}$$

where $X(t)$ denotes the insulin action on glucose, V_{m0}, V_{mx}, K_{m0}, and p_{2u} are rate parameters.

The endogenous glucose production model is defined by

$$EGP(t) = k_{p1} - k_{p2} \cdot G_p(t) - k_{p3} \cdot X^L(t), \tag{9}$$

$$\dot{I}_l(t) = -k_i \cdot [I_l(t) - I(t)] \quad \dot{I}_l(0) = I_b, \tag{10}$$

$$\dot{X}L(t) = -k_i \cdot \left[X^L(t) - I_l(t)\right] \quad X^L(t) = I_b, \tag{11}$$

where $G_p(t)$ indicates the amount of glucose in the plasma compartment, $X^L(t)$ refers to the delayed insulin action, k_i, k_{p1}, k_{p2}, and k_{p3} are rate parameters.

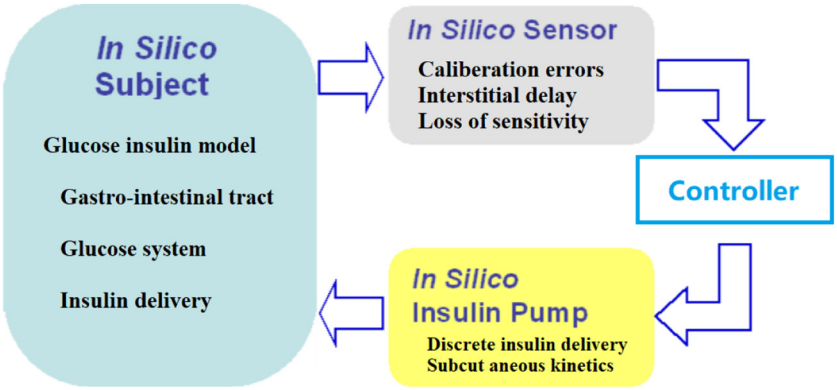

Fig. 6. Main components of the UVA-PADOVA T1D Simulator.

In 2013, the UVA-PADOVA T1D Simulator was improved in several aspects.[73] The glucose, insulin kinetics, and gastro-intestinal are same with those in the model proposed in 2008. The updated components in this new model include liver, muscle, and adipose tissue. And glucagon kinetics, alpha cell and delivery are added to the new model. A 1-compartment linear model is used to describe the glucagon kinetics, as given by

$$\dot{H}(t) = -n \cdot H(t) + SR_H(t) \quad H(0) = H_b, \tag{12}$$

where $H(t)$ refers to the plasma hormone concentration, $SRH(t)$ denotes the glucagon secretion, and n is the clearance rate.

Two components are considered to describe the glucagon secretion, as given by

$$SR_H(t) = SR_H^s(t) + SR_H^d(t), \tag{13}$$

$$\dot{S}R_H^s(t) = \begin{cases} -\rho \cdot \left[\mathrm{SR_H^s(t)} - \max\left(\sigma_2 \cdot [\mathrm{G}_{th} - \mathrm{G(t)}] + \mathrm{SR_H^b}, 0\right)\right] if \mathrm{G(t)} \geq \mathrm{G_b} \\ -\rho \cdot \left[\mathrm{SR_H^s(t)} - \max\left(\dfrac{\sigma \cdot [\mathrm{G}_{th} - \mathrm{G(t)}]}{\mathrm{I(t)} + 1} + \mathrm{SR_H^b}, 0\right)\right] f \mathrm{G(t)} < \mathrm{G_b} \end{cases}, \tag{14}$$

where $G(t)$ indicates the plasma glucose, $I(t)$ denotes the plasma insulin concentration, σ and σ_2 are the alpha-cell responsivity to glucose level, $1/\rho$ refers to the delay.

The glucose rate of change in the second part can be expressed by

$$SR_H^d = \delta \cdot \max\left(-\frac{dG(t)}{dt}, 0\right), \tag{15}$$

where $dG(t)/dt$ indicates the plasma glucose, and δ refers to the alpha-cell responsivity to glucose rate of change.

In 2018, the UVA-PADOVA T1D Simulator was further improved and applied to a realistic scenario.[74] In this study, the errors that affect CGM and self-monitoring of blood glucose are considered. By utilizing the clinical T1D data, the "dawn" phenomenon is incorporated. In addition, the insulin dosing is also updated with the fast-acting insulin analogs. The inhaled insulin pharmacokinetics and the intradermal are also considered. By the aforementioned improvement, this method makes large progress for the clinical application.

In 2019, the physiological model was utilized to achieve long-term glucose forecasting.[75] The proposed algorithm is mainly based on the compartmental composite model of glucose–insulin dynamics. This model utilizes the deconvolution technique, which is able to achieve the CGM. Moreover, the meal absorption information is used as the input of model for improving the forecasting accuracy. This algorithm has been applied to 10 patients with DM. And its effectiveness of clinical application is verified to a large degree.

3.2. Data-driven algorithms

The physiological model takes the biological nature of human body into account. If it is formulated correctly enough, the accurate and stable prediction of glucose level can be achieved. However, human nature is very complex and influenced by many factors. Different people may have their own nature. It is hardly to formulate a uniform model. In contrast, the data-driven algorithms that based on the available data have attracted much attention in the academic and clinical areas. Some efforts have been carried out to realize the prediction of glucose level, especially with the development of machine learning.[76] The typical works in this field are summarized in Table 2.

In,[77] the authors firstly design a real-time signal-enhancement model. To further enhance its effectiveness of clinical application, the distortion between the real glucose level and sensing value is considered. To be specific, a linear regression model is utilized to compensate this distortion, which is implemented in a regularized deconvolution procedure. The linear regression model can be updated under the condition of suitable self-monitoring blood glucose references. Simulation experiments verify the robustness of the proposed method. In addition, experiments implemented on real data also prove that the proposed method can effectively enhance the accuracy of the blood glucose level by utilizing the proposed method.

To address the accuracy and precision issues of CGM, Facchinetti et al.[78] propose a prediction method that is mainly based on the autoregressive model. The first order AR(1) of the model is used to

Table 2
Summary of glucose monitoring based on data-driven methods.

Index	Authors	Algorithms
1	Guerra et al.[77]	Linear regressor
2	Facchinetti et al.[78]	Autoregressive model
3	Yang et al.[79]	Autoregressive integrated moving average model
4	Cameron et al.[80]	Kalman-filter-based method
5	Zhao et al.[81]	Latent-variable based statistical method
6	Yu et al.[82]	Sparse Kernel filtering algorithm
7	Georga E. A., et al.[83] Hamdi et al.[84]	Support vector machine
8	Sudharsan et al.[85]	Support vector machine and random forest
9	Li et al.[86]	Echo state networks embedded with incremental learning
10	Pappada M. S., et al.[87] Zecchin et al.[88] Ali et al.[89]	Neural network
11	Zecchin et al.[90]	Jump neural network
12	Li et al.[91]	Deep learning
13	Aliberti et al.[92]	Long short-memory network
14	Li et al.[93]	Convolutional recurrent neural network

predict glucose. In addition, the denoising and enhancement are two important parts in the named "smart sensor", which can realize prediction of CGM. The real data of 24 T1DM patients are utilized to evaluate the proposed method. Experimental results show that this relatively method can achieve accurate and precise prediction results. The more valuable point is that this method is a relatively simple method. It has the advantages of implementing the real-time glucose continuous monitoring.

The time-varying non-stationarity of CGM data is considered when the prediction of blood glucose levels is implemented in.[79] To solve this problem, an autoregressive integrated moving average (ARIMA) model is utilized. In the proposed prediction framework, the adaptive identification algorithm is used to estimate the orders of ARIMA model. Meanwhile, the corresponding parameters are determined by employing the least square estimation and the Akaike information criterion. To evaluate the performance of the proposed method, the CGM data of patients with daily living conditions are used to carry out experiments. Results show that it can provide valuable information for avoiding hyperglycemia or hypoglycemia.

In the clinical application, it is important to realize the insulin pump off with the help of glucose monitoring, especially for preventing nocturnal hypoglycemia. In,[80] Kalman filter is utilized to achieve this objective, which has the feature of dealing with noise. Therefore, the probability of sensor data change due to noise can be solved effectively. In this study, Kalman filter can realize the glucose prediction at 1 min intervals. The requirement is that the new sensor data should be obtained 5 min intervals. For evaluating the practical feasibility, a total of 16 subjects are studied and 15 subjects are analyzed in detail. Most of the studied objectives can reach the satisficed results and it is meaningful for preventing nocturnal hypoglycemia to some degree.

To avoid the undesirable glucose concentrations of patients with T1DM, the glucose dynamics affected by insulin infusion rates and meal carbohydrate are studied in.[81] A latent variable-based statistical method is proposed to achieve the prediction of future glucose, which has the empirical and linear dynamic features. During the prediction process, the historical glucose data are utilized by the statistical model. This method is compared with two conventional models, including the autoregressive model and the autoregressive with exogenous input model. And the real data of seven patients with T1DM are utilized for evaluating the proposed method. Experimental results show that it can achieve the best prediction results of larger horizons (≥30 mins).

When glucose monitoring is applied in clinical application, the computational requirement for online and real-time scenario is relatively high. To mitigate this constraint, the adaptive kernel filtering algorithms are proposed in.[82] The predictive performance of this method is achieved by using the sparsification criterion, which is mainly based on the information theory. In this way, the complexity of kernel filters can be reduced to a large degree without the adversely deteriorating. The other advantage of this method is that it considers the abnormal values of CGM. The sparsification-based real-time model can be updated with the adaptive feature. Experimental results show that the time-varying and the nonlinear dynamics of glucose levels can be addressed effectively.

The above works are mainly based on the basic methods of data-driven methods. To be worth noting, machine learning methods have been well developed. A typical method is to utilized support vector machine for achieving glucose prediction. In,[83] the method based on support vector machine to predict glucose concentration is proposed, which considers application for patients with T1D. The meal-derived influence is addressed and the energy expenditure is taken into account. In,[84] the continuous glucose prediction is studied with support vector machine. Its parameters are optimized by the differential evolution algorithm. For the duration of 60 min, the root mean square error of glucose prediction can be as small as 12.95 mg/dL.

Glucose prediction for patients with T2D is studied in,[85] which employs support vector machine and random forest. The main objective is to avoid the problem of hypoglycemia. And several machine learning methods are comprehensively investigated, including support vector machine, random forest, K-nearest neighbor, and naïve Bayes. By cross-validating the model with different data sets, results show that support vector machine and random forest can realize the best prediction performance. And the accuracy of glucose prediction is over 90%. In further, the sparse self-monitored blood glucose data are used to implement prediction, which verify that the problem of hypoglycemia can be addressed effectively. By using the medication information, the false positive prediction results are reduced to large degree.

To solve the chaotic properties contained in the glucose monitoring data, the method based on echo state networks is proposed in.[86] The innovation of this study includes two perspectives. The first is to propose a new method based on the combination of echo state networks and incremental learning. By partial optimization of parameters, the suitable network structure is determined, which is the basic foundation to achieve accurate prediction. The other innovation is that the feedback mechanism is used. In this way, the relationship of different predictions can be excavated adequately. The proposed method is evaluated on ten patients with T1D. Compared with three conventional methods, it can realize better prediction results.

In the domain of machine learning methods, neural network and its variants have been paid much attention. To assess glucose concentration for patients with DM, a feed-forward neural network model is used to realize the real-time prediction in.[87] The CGM values, metered glucose values, insulin dosing, lifestyle, nutrition, and emotion are taken as the input of neural network. The effectiveness of the proposed method is evaluated in 10 patients. In,[88] the combination of neural network and first-order polynomial extrapolation algorithm is studied for short-time glucose prediction, which can incorporate meal information well. It is verified by using 20 simulation datasets and 9 real CGM datasets. In,[89] only the CGM data are taken as the input of neural network to achieve glucose prediction. The accuracy is assessed by root mean square error and mean absolute percentage error. Experimental results show that the proposed method can reach very small error values, which encourages for the clinical application.

Based on the work in,[88] Zecchin et al.[90] propose a kind of jump neural network to achieve glucose prediction of patients with T1D. The named jump neural network means that a feed-forward neural network that utilizes both the first hidden layer and the output layer. This kind of structure can deal with both linear and non-linear dynamics feature of the glucose data. The hidden neurons in the method are utilized to describe the non-linear feature between the input and the target. And the output neurons are used to describe the linear feature between the input and the target. In addition, the CGM data and the ingested carbohydrates information are both considered in the method. This method is trained by 10 datasets and tested by another 10 datasets, and results proves that it has excellent performance.

The deep learning method is also utilized to achieve glucose prediction.[91] The method is comprised of four components, which are data pre-processing, label transform/label, multi-layers of convolutional neural network, and the post-processing. The historical data of patients are mined adequately to help realize better prediction, which include glucose measurements, insulin dose, meal information, etc. Comprehensive evaluation experiments are implemented to assess the proposed method. To be specific, the in-silico is used as the evaluation platform, which include both the adult and the adolescent subjects. Compared with the traditional neural network and other algorithms, this method can obtain significant improvement.

The recently developed long short-term memory is studied for glucose monitoring in.[92] The prediction model is trained by utilizing the heterogeneous cohort data of patients. Then, it is applied to infer the glucose level of new patients. During the study, the non-linear autoregressive neural network and long short-term memory are both designed, which have been verified the successful application in many prediction problems. These two methods are both compared with the

existing feed-forward neural network, autoregressive model, and recurrent neural network. Experimental results show that the non-linear autoregressive neural network can achieve good prediction results for short-time prediction. In comparison, the long short-term memory can obtain excellent performance for both short-time and long-time prediction, which are 60 min and more.

In the direction of neural network methods, the newest study is based on convolutional recurrent neural network.[93] In fact, this method belongs to the category of deep learning, as the previous work in.[91] The advantages of convolutional neural network and recurrent neural network are mined and modified to achieve better accuracy of glucose prediction. Four benchmark methods are compared with the proposed method to verify its effectiveness, including support vector regression, the autoregressive model, the latent variable model, and neural network. Especially, the proposed method can be implemented on an Android mobile phone. The glucose prediction time can be as small as 6 ms, which provides a feasible application for many patients with DM.

To summarize the aforementioned studies based on data-driven methods, the glucose prediction can be realized in relatively high accuracy and stability. Some influences on the prediction results have been considered. However, there is still a long distance between the research and clinical application. The main reason is that the biological mechanism of human body is very complex. People have different life styles (e.g., meal, weight, and exercise), which have significant influence on the glucose change. It is difficult to realize a standard prediction method for different people. In addition, it is valuable to combine the biological model (e.g., physiological model) and data-driven methods to achieve glucose prediction, which may bring practical value for the clinical application.

4. Future developments and challenges of glucose monitoring

Until now, many valuable studies have been carried out in the field of glucose monitoring. The achieved results are making the practical application closer and closer. However, there are still some research topics that needs to be paid attention. In this section, three development trends and the related problems are summarized, which are based on the newest research achievement.

(1) There are some key problems that need to be solved with the emerging developments of new monitoring techniques. A typical method is the rapidly developed wearable sensors that can sense glucose monitoring in the pain-free way.[94,95] Though it is relatively convenient for patients with DM, the concerns include portability, comfort, time efficiency, power consumption, etc. There are also other challenges for attracting users, including but not limit to recalibration, time, and power efficiency. In general, there is a tradeoff between high performance requirements and the limited source of wearable sensors. This research direction is promising for the volume patients with DM, which needs to be paid much attention.

(2) Many efforts have been made from all over the world to promote the application of CGM. In 2016, the United States Food and Drug Administration approved that CGM can be utilized for the independent medical decision.[96] In 2017, the international consensus on the utilization of CGM was achieved by the Advanced Technologies & Treatments for Diabetes Congress.[97] In 2019, the Working Group on CGM was created by the International Federation of Clinical Chemistry and Laboratory Medicine.[98] However, it is lack of the reference measurement procedure and the compartment method to implement glucose level monitoring in the interstitial fluid.[99] CGM still needs to define its performance criteria, which should consider clinical targets for diabetes therapy.

(3) The monitoring results of glucose level may be unbelievable. When sensors are used in the practical application, the sensing data may become anomalous or fault. If these data cannot be detected timely, the wrong decision making may be implemented. For example, the real-time fault detection for glucose monitoring has been considered, which is mainly based on multivariable statistical monitoring methods.[100] Due the complex biological feature of human body, it usually needs to utilize the combined methods to achieve accurate and stable detection results. Therefore, some efforts are required to implement the anomalous or fault detection for different patients with DM.

5. Conclusions

With the development of biosensor technology and algorithms, more and more methods are available for glucose monitoring of patients with DM. These methods are providing feasible ways for giving reasonable suggestions to carry out treatment. Except the sensing technique based on blood, other fluids of human body are becoming available source for achieving glucose level estimation and prediction. The rapid development of algorithms for analyzing glucose contained in different fluids make the practical application closer and closer. In addition, the new materials and wearable sensors have provided other feasible ways for glucose monitoring. However, there is still a large gap between the existing research and the clinical application. Some key techniques need to be addressed, which have drawn much attention from the academic and industrial field.

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