A Study of Methods for Predicting and Controlling Blood Glucose in Diabetic Patients

Shuya Liu, Ruizhuo Song, and Xiang Lu

***Abstract*—With the development of society and the improvement of people's living standard, diabetes has gradually become one of the world public health problems that endangers human life safety and affects the development of global economy. Type 1 diabetes is a chronic metabolic disorder that prevents the pancreas from producing insulin and requires lifelong treatment with daily insulin injections to prevent high blood sugar. The lack of insulin leads to the continuous high level of blood sugar in patients. The most important thing for patients is to monitor blood sugar changes and control blood sugar within the normal range. In this paper, a systematic literature search is carried out to study these two aspects, and key information such as the learning model adopted in the literature, the main results, the development of relevant technologies, and the limitations are summarized. From the perspective of glucose-insulin prediction model, due to the complex structure of physiological model, many parameters are difficult to identify, most of the modeling methods are data-driven. There is a great room for improvement in the research on how to mine and utilize existing models to effectively establish accurate glucose prediction models for different objects. From the perspective of control theory, after insulin injection, there is a certain delay in the reduction of blood glucose concentration, and the onset time is different depending on the injection site. The rapid development of deep learning and the increase in available data offer the possibility of addressing these challenges in the near future. When designing closed-loop glucose algorithms, we consider using a variety of approaches to establish a personalized glucose control algorithm for each diabetic patient.**

***Index Terms*—Blood glucose prediction, data-driven, artificial pancreas, control algorithm**

I. INTRODUCTION

Diabetes mellitus is a chronic disease caused mainly by abnormal blood glucose (BG) levels due to disorders of glucose metabolism, which may be above or below the normal range: 70–140 mg/dL [1]. There are three main types: firstly, type 1 diabetes mellitus (T1DM) due to the lack of pancreas to produce adequate amounts of insulin; secondly, type 2 diabetes mellitus (T2DM) due to insulin resistance and relative insulin deficiency; and also gestational diabetes mellitus (GDM) in which the placenta produces high levels of hormones that impair the action of insulin during pregnancy [2]. According to the International Diabetes Federation (IDF), the number of adults with diabetes has reached 537 million worldwide in 2021, and the number of diabetes cases is expected to increase to 783 million by 2025. Diabetes is responsible for nearly one trillion dollars in healthcare expenditures worldwide, and approximately 6.7 million people died from diabetes or diabetes complications in 2021. This number is expected to reach 578 million by 2030 and 700 million by 2045. Diabetes treatment aims to maintain blood glucose levels within normal limits [3]. Otherwise, people with diabetes may face a higher risk of complications, including vascular damage, cardiovascular disease, kidney damage, coma, and even death [4]. Fortunately, complications are very rare in patients who manage their blood glucose levels effectively [5]. China, which has the largest number of diabetic patients in the world, faces enormous challenges in preventing and controlling diabetes. Thus, it is important to research and develop advanced treatment techniques suitable for diabetic patients. The proposed artificial pancreas (AP) brings a whole new way of thinking for intensive insulin therapy. The artificial pancreas secretes insulin through an electronic device instead of the human pancreas. It does not require user participation in control and can control insulin infusion according to blood glucose levels through a fully closed-loop control strategy to mimic the insulin secretion pattern of the normal human pancreas, thus achieving automatic real-time regulation of blood glucose levels. The device can output insulin in real-time through the changes of the patient's blood glucose to keep the patient's blood glucose level under normal control. For type 1 diabetic patients, the artificial pancreas can provide more accurate control of their blood glucose, reduce human error intervention, and effectively improve the treatment effect of diabetes. The artificial pancreas consists of three main components: continuous glucose monitiring system (CGMS), control algorithm, and insulin pump. The working principle of the artificial pancreas is: Firstly, the patient's blood glucose is monitored in real-time by the blood glucose monitoring system, then the insulin output rate is calculated according to the current monitored blood glucose value and the closed-loop control algorithm, and finally the insulin is outputted by the insulin pump to control the patient's blood glucose. Its advantages not only liberate patients from the daily supervision of blood glucose, but also avoid the occurrence of high and low blood glucose events caused by human operation faults. The most important thing for patients with diabetes, whose blood glucose is constantly high due to insulin deficiency, is to monitor the changes in blood glucose and control it within the normal range.

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Shuya Liu, Ruizhuo Song, and Xiang Lu are with School of Automation and Electrical Engineering, University of Science and Technology Beijing, Beijing 100083, China (e-mail: m202120653@xs.ustb.edu.cn; ruizhuosong@ustb.edu.cn; g20208660@xs.ustb.edu.cn).

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II. Blood Glucose Prediction

The dynamic characteristics of human blood glucose-insulin interactions are a more complex biochemical reaction, and it is difficult for mathematical models to accurately describe the dynamic characteristics between them. But more and more scientists and research scholars have done a lot of research works in this area, which has led to a good development of blood glucose models, and to a certain extent has promoted the development of high and low blood glucose alarms, blood glucose prediction, and artificial pancreatic closed-loop control systems. Blood glucose prediction can not only help patients to regulate blood glucose, but also avoid the occurrence of hyperglycemia and hypoglycemia [6]. Prediction models are divided into three main categories: physiological model, data-driven model, and hybrid model, as shown in Fig. 1.

A. Physiological Model

Before physiological models can be used to model the metabolism of insulin and glucose, some knowledge of insulin and glucose is required. The physiological models use chamber models to simulate blood glucose metabolism, thereby enabling the understanding and control of the physiological processes of glucose. Figure 2 below shows a schematic diagram of a physiological model in which blood glucose concentration, glucose events, or risk are predicted using a complement of submodels including subcutaneous insulin uptake, carbohydrate digestion and absorption, and insulin action [7]. The biggest hole in these methods is that there are multiple physiological parameters in the model that can be adjusted, and it is these parameters that are applied to make glycemic predictions. This generally includes estimation of carbohydrate intake, external insulin therapy, and several other variables related to physical activity. These parameters can be adjusted by recognition techniques, machine learning techniques, or overall values. Although some models are minimalist, it is difficult to identify a specific model because the models often contain variables and parameters that are not easily identified and adjusted. According to their complexity, they can be divided into two types: The first type of model is called minimal model, which allows glucose metabolism with insulin by simple formulas and identifiable parameters and requires only the most basic identifiable parameters and nonlinear equations; the second type is called the maximal or integrated model, which contains all the knowledge of the physiological system and can simulate or reproduce the metabolism of a diabetic patient. Thus, it can be experimentally evaluated for control and treatment. However, some studies do not have clear guidelines on how to choose the appropriate method and appropriate model by comparing the postprandial insulin effect with the differences in glucose kinetic models, such as insulin sensitivity, basal insulin, and uncertainty in dietary intake. Over the last few decades, several scholars have used experimental data on glucose production and utilization, insulin, and dietary absorption to model insulin action and glucose kinetics. Many of these are partitioned models, where some of these processes cannot be directly metricized, and they appear to be inaccessible to the system. In this way, the inaccessible parts are represented by several interconnected compartments. Currently, the most popular physiological models in insulin action and glucose kinetic systems are the Dalla-Man model, the Bergman minimal model, and the Hovorka model. The following are a

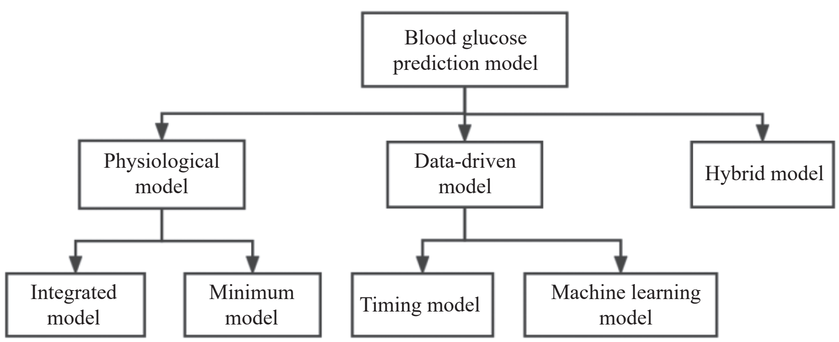

Figure 1 Classification of blood glucose prediction methods.

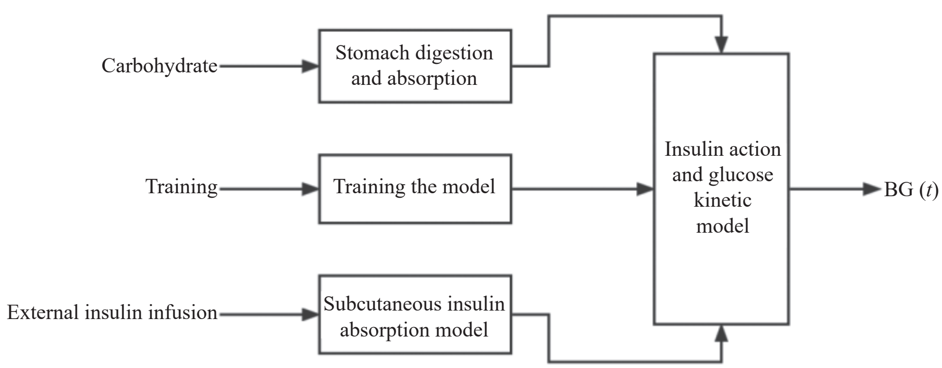

Figure 2 Schematic diagram of the physiological model.

few commonly used physiological models that have been experimented by a large number of scholars and physicians and have proven their validity. More precisely, the Dalla-Man model consists of a glucose and an insulin subsystem, which is achieved by regulating the use of glucose and the insulin produced in the body. The difference is that the minimal model uses a three-compartment model that further characterizes plasma insulin concentration, distal insulin, and plasma glucose to obtain Bergman's nonlinear minimal model extended response states, evaluates the observability of state and external inputs, and identifies the model [8]. Based on this model, an improved model of exercise, diet, and insulin intervention mechanisms was proposed and was good in explaining glucose kinetics [9]. For most of the estimated parameters, the individualized point estimates and their confidence intervals were found to be within the physiological range of the modeling. The Hovorka model uses two compartments to represent the dynamic process of glucose separately and considers insulin action separately from its final effect on blood glucose. These input variables incorporate factors external to insulin as well as nutrient levels over time. Laguna et al. [10] proposed a new approach to identification based on Hovorka interval analysis, in which variability and model imprecision are represented by the interval model as parameter uncertainty. The postprandial response, uncertainty due to physiological variability, input error, insulin input rate, and nutrient composition in the diet were all predicted better using the interval model for multi-objective optimization [11]. Monotonicity analysis of the model states and parameters was performed by considering uncertainties under all parameters and initial conditions.

B. Data-Driven

The data-driven model relies only on continuous glucose monitor (CGM) data and requires additional signals to model the patient's physiological response when physiological parameters are not included, as shown in the schematic diagram in Fig. 3. The most common examples of this approach are neural network (NN) and augmented reality (AR) model, with alternatives being physiological models of glucose digestion and absorption, a second model of insulin absorption, and a third model of exercise. Data-driven modeling refers to a model that uses historical data from diabetic patients to identify blood glucose and predict future blood glucose values from blood glucose data, insulin input values, dietary inputs, and other variables that may affect changes in blood glucose [12, 13]. Since the data-driven approach does not require much complex physiological knowledge, blood glucose prediction models can be built in a shorter period of time and can be modeled using only collected historical data, while being easy to operate and implement. Therefore, data-driven approach is used in many times when modeling patients. The accumulation of a large number of patient histories has laid the foundation for the introduction of machine learning and its application in the treatment of diabetes. The ability of machine learning to solve complex tasks under dynamic conditions and knowledge will help it to be better applied to diabetes research. Deep learning is a promising machine learning method with promising applications in high dimensional data [13]. With the development of deep learning techniques in the field of image recognition and speech recognition, breakthroughs have been made [14, 15]. Similarly, deep learning has been used to good effect in blood glucose prediction [16]. Zhu et al. [17] proposed a convolutional neural network (CNN) model to predict blood glucose levels over a 30 min period, which also incorporates CGM, food intake, and insulin regulation. Li et al. [18] used a deep learning framework for long short term memory (LSTM) to predict the overall trend of future changes in BG levels. Since the support of such models is based on machine learning, there are many current prediction methods such as: time series models, regularized learning, robust filters, random forest (RF), fuzzy logic models, Kalman filters, Gaussian mixture models (GMMs), reinforcement learning, support vector models, and artificial neural network (ANN) models. Several representative models are described below.

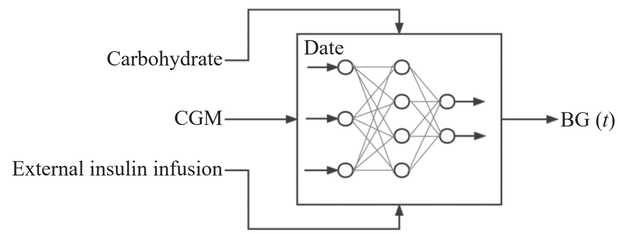

Figure 3 Block diagram of data-driven principle.

a. Artificial Neural Network

An artificial neural network is a computational model consisting of different processing units, i.e., neurons, and being connected by scaling of weights. Network topologies can take many forms, but can generally be classified as recurrent/feedback networks (Hopfield networks and Kohonen's self-organizing mapping (SOM)) and feedforward networks. Recursive or feedback network topologies contain at least one feedback loop [19]. Feedforward networks containing connections between neurons that have only one direction (forward) from pre to post are the most commonly used topology. These two network topologies have been successfully applied to model and predict blood glucose in type 1 diabetic patients. Recurrent or feedback networks have been used in blood glucose prediction: It includes self-organizing mappings, autoregressive neural networks, and recurrent neural networks. Allam et al. [20] trained two feedback loops through a complete multilevel network using a real-time recursive algorithm forced by a teacher. Pérez-Gandía et al. [21] compared and analyzed four types of modeling for blood glucose dynamics machine learning techniques: Feedforward neural networks (FNNs) are trained by backward propagation algorithms, self-organizing mapping is implemented by vector quantization, and neuro-fuzzy networks are implemented with wavelets as the initiating function as well as linear regression models (LRMs). Pappada et al. [22] and Pappada and Cameron [23] trained autoregressive neural networks by means of the extended Kalman filter algorithm to train autoregressive neural networks, called neural network autoregressive external input. In terms of feedforward networks, Ahmed and Serener [24], Zarkogianni et al. [25], and Mhaskar et al. [26] used the back-propagation Levenberg-Marquardt optimization training algorithm to develop data from CGM to propose feedforward neural networks. Georga et al. [27] developed a seven-layer neuro-fuzzy neural network with wavelets as the activation function and Gaussian function as the affiliation function, and used a gradient based adaptive learning rate for training. Daskalaki et al. [28] and Alanis et al. [29] proposed a time lag forward neural network which is trained by the back-propagation gradient descent algorithm to store the previous data values into the network. Ruiz-Velázquez et al. [30] proposed a function approximation using diffusion polynomials on data defined stream forms, a semi-supervised deep learning neural network. Campbell and Ying [31] investigated the applicability of extreme learning machines (ELMs), especially online sequential extreme learning machine and online sequential extreme learning machine-kernel in the training of single hidden layer feedforward neural networks. Recursive or feedback networks, including recurrent neural networks, autoregressive neural networks, and self-organizing mappings, have been used in blood glucose prediction. For example, Allam et al. [20] used a fully connected multilevel network to train two feedback loops using a real-time recursive algorithm forced by the teacher. In addition to this, Pérez-Gandía et al. [21] compared and analyzed four machine learning techniques for modeling blood glucose dynamics: Neuro-fuzzy networks and linear regression models are based on wavelets as activation functions, SOM is implemented by vector quantization, and feedforward neural networks are trained by back-propagation algorithms.

b. Support Vector Machines (SVMs), Kernel Function, and Gaussian Process Regression

Support vector machines have been widely used in pattern recognition and identification, classification or categorization, and regression and prediction [31]. Support vector regression (SVR) is one of the most widely used SVMs in blood glucose prediction and modeling. In this context, Reymann et al. [32] investigated the feasibility of using SVR mobile platform for blood glucose prediction using radial basis function as a kernel. In addition, Li and Fernando [33] attempted to use the collected patient data to obtain similarities between patients, thus using the smartphone of SVR to collect data to develop personalized blood glucose prediction models. Georga et al. [34] proposed predictors based on SVR for random forests and extended the ReliefF algorithm for multi-class scenarios, investigating the potential performance improvements of using feature ranking algorithms. Naumova et al. developed a new approach to fully adaptive regularization learning (FARL) using meta-learning to select kernels and positive regular parameters from a rule-based learning algorithm for kernels [35]. Gaussian process regression is a very practical non-parametric regression tool that has been widely used in vital sign "early warning systems", disease prediction, patient physiological monitoring, biomarker detection in microarray gene expression data, etc. Tomczak investigated the application of classification-based inputs in blood glucose prediction [36]. Applications were investigated. The inputs include data, time, code, and the level of blood glucose. Classification codes were used to describe measures of insulin dose, dietary intake, exercise, and preprandial glucose measurement, and the classification inputs were analyzed.

c. Random Forest

Stochastic decision forest is an integrated learning method that uses decision trees for classification and regression to generate patterns of classes or predicted averages. In this context, Xao et al. [37] evaluated the performance improvement obtained by using a combined approach of feature importance score and sequence backward selection (SBS) algorithm in integrated learning to select the optimal feature representation for prediction of blood glucose based on random forest regression and support vector regression techniques. In addition, Georga et al. [38] used a random forest regression approach to predict BG from a dataset that consisted of plasma insulin concentration, subcutaneous glucose distribution, digestion and absorption of dietary glucose, and daily energy expenditure.

C. Hybrid Model

Hybrid models are used in the preprocessing phase, as shown in Fig. 4. Since these models depend to some extent on the physiological model, and certain physiological parameters

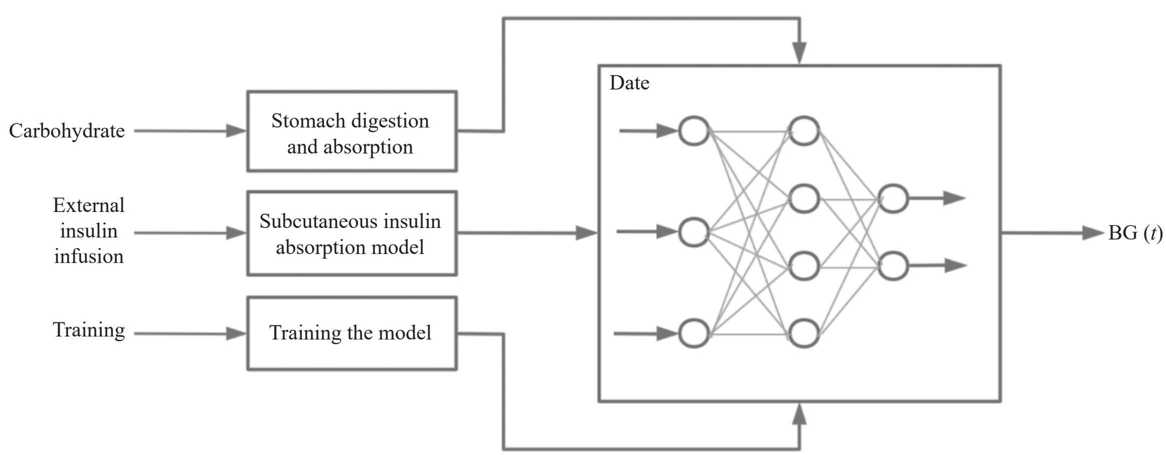

Figure 4 Hybrid model schematic block diagram.

must be identified and set. Finally, any of the previous options can be used for the predictive model of the internal model control algorithm and are therefore referred to as hybrid models.

Solutions that mix physiological and data-driven models are usually based on modules of physiological models that can represent the relationship between learning inputs and future outcomes either through classes (qualitative approach) or through actual blood glucose continuum values (quantitative approach). The general physiological models are dietary models and insulin uptake models. The most commonly used approach to model diet/glucose uptake is the Dalla-Man diet model, followed by the Lehmann and Deutsch model. Whenever information about insulin therapy is used as input, the most commonly used model is the Berger model, followed by the Dalla-Man model. Finally, different types of NNs are the most common method for predicting future blood glucose. The hybrid contains three or more methods in preprocessing, feature extraction, and learning to improve performance. Most of the current blood glucose prediction models combine various machine learning techniques with physiological models. In support vector regression, Plis et al. [39] combined support vector regression with physiological models, which generated informative input features to train SVR models. In addition, Georga et al. [40] combined support vector regression and chamber models to quantify the effects of postprandial intestinal glucose absorption, subcutaneous insulin absorption, and exercise on the dynamics of insulin. Also, many researchers have combined artificial neural networks with other methods. Zecchin et al. [41] combined artificial neural networks with physiological models to combine information from food with CGM data. A jump neural network based on a physiological model of food and CGM data input was studied [42, 43], and the results were compared with a previously studied ANN [41]. Contreras et al. [44] studied a hybrid model using an algorithm for genetic programming, as well as a physiological model. Self-organizing mapping techniques have also been used in physiological and hybrid models. Zarkogianni et al. [45] used a physiological model to simulate the dynamic process of subcutaneous insulin and aspiration of glucose from the intestine into the bloodstream into a self-organizing mapping. Jankovic et al. [46] proposed an online adjustable glucose prediction model with adaptive with both prediction and correction layers. The prediction layer consists of an artificial neural network and an autoregressive model with exogenous inputs (ARX), which incorporates external inputs for estimation. Subsequently, the output is further refined by an extreme value learning machine in the correction layer.

D. Problems Faced by Blood Glucose Prediction Models

The data-driven trend shows that a large number of researchers are still experimenting with techniques such as machine learning. At the same time, a single method does not satisfy our requirements of prediction results, and the increasing combination of different methods to improve the accuracy and possibility of predictive power opens up new ideas for future research. Any successful prediction algorithm should take into account the patient's control parameters (blood glucose, insulin, diet, exercise, etc.) as well as the patient's non-control parameters (stress, infection, medications, etc.). In addition, any relevant contextual information, such as internal and intra-variability of patient lifestyle changes, time of day (day and night), etc., needs to be considered. Future investigators will have to take into account longer prediction ranges (providing more corresponding time), reasonable clinical precision, time delays in improving CGM, and long-term clinical trials using actual patients with large numbers of subjects. In addition to this, regions of hypoglycemia, normoglycemia, and hyperglycemia should be given appropriate weights and penalties. For errors in some regions, predictors should be given appropriate weights and penalties to improve prediction accuracy. An appropriate estimation of the relationship between dietary intake and physical exertion must also be considered during the integration of machine learning. Stress and infection have a significant impact on blood glucose dynamics and prediction effectiveness. For this purpose, it is necessary to monitor subjects and test and evaluate the impact of lifestyle or physiological (infection) changes on prediction performance. In addition, the impact of various CGM devices on the quantitative performance and time lag of the prediction algorithm should be explored.

III. Current Status of Research on Glycemic Control and Evaluation

The artificial pancreas has received increasingly widespread attention as one of the most researched treatments for diabetes. The artificial pancreas consists of three main components: a continuous glucose monitor, a control algorithm, and an insulin pump. Many control strategies have also been proposed in the course of research, and the continuous glucose monitor is a key component of the artificial pancreas, and it follows the improvement of sensor technology and the rapid development of computer technology that continuous glucose monitoring of patients has become possible. The blood glucose monitoring system monitors the patient's blood glucose in real-time, and the control algorithm determines the final amount of insulin to be injected into the body to control the patient's blood glucose values within the normal range. The principle of the control system to control the body's blood glucose is shown in Fig. 5.

In previous in-depth exploration of the physiological model of human glucose-insulin metabolism, the blood glucose model has become more and more accurate, and more advanced control algorithms were applied to the field of blood glucose control, and the block diagram of the closed-loop control system is shown in Fig. 6. However, the human blood glucose regulation process is nonlinear, and then considering the safety, reliability, and stability of the control system, many automatic control algorithms are applied to the actual blood glucose control and achieve good results, in which proportional-integral-derivative (PID) control algorithm was first used for blood glucose control, and then such as the improved PID algorithms [47, 48], neural network control [49], fuzzy logic control [50, 51], model predictive control

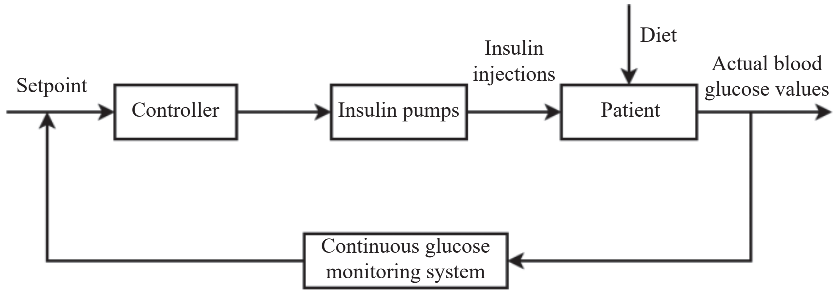

Figure 5 Principle of control system of human blood glucose.

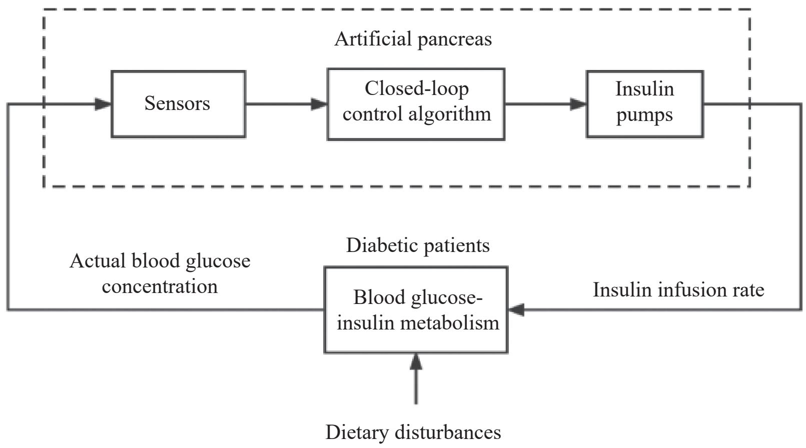

Figure 6 Block diagram of closed-loop control system.

(MPC) [52], model iterative learning control (ILC) [53], and other control algorithms arose. But these algorithms also have some other problems that require us to continuously improve and refine the algorithm design [54].

A. Common Blood Glucose Closed-Loop Control Algorithms

a. Blood Glucose PID Control Algorithm

Proportional-integral-derivative control algorithm has a long history of development, and its model structure is simple and robust, and is now widely used in various fields. The flow chart of its action is shown in Fig. 7. When the PID control algorithm is used for blood glucose control, there is no need to construct another insulin-glucose model of the patient; the PID algorithm treats the insulin injection rate as a weighted sum of the three components, the proportional, integral, and differential terms, and the PID uses the three components shown in Eq. (1) to simulate the process of insulin secretion in a normal human [55].

$$\mathrm{IIR} = K_{\mathrm{P}}(G-r) + K_{\mathrm{I}}\int(G-r) + K_{\mathrm{d}}\frac{\partial G}{\partial t} \tag{1}$$

where IIR denotes the calculated insulin infusion rate, K_{p}, K_{I}, and K_{d} are the parameters of controller proportional, integral, and differential yet to be determined, G is the measured glucose, and r is the target glucose, respectively. $K_{\mathrm{p}}(G-r)$ represents the difference between the actual output glucose value and the set target value for the required fraction of insulin injections; while $K_{\mathrm{d}}\frac{\partial G}{\partial t}$ is related to the rate of glucose change and can perform rapid regulation of insulin secretion. Due to the complexity of human blood glucose changes, a single PID parameter cannot adapt to the blood glucose changes caused by various external factors such as exercise and diet, so the setting of controller parameters becomes a major difficulty in the design process of PID control algorithm, which may have a certain impact on the algorithm control effect [56]. Current research based on PID control parameter adjustment has used neural networks, fuzzy control, or greedy algorithms to dynamically change the PID parameters to adapt to the complex blood glucose changes in the human body. The advantage of PID for blood glucose

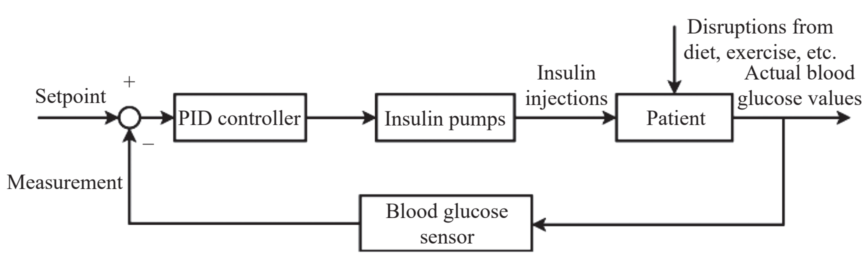

Figure 7 Flow chart of PID action.

control is that it is based on no model and even if there is no model of blood glucose dynamics in diabetic patients, the appropriate controller parameters can be set by means of parameter rectification. And disturbances such as feeding and exercise can be considered as perturbations. Steil et al. [57] considered PID control algorithms for AP systems applying insulin feedback to prevent controller-induced hypoglycemia in an inpatient clinical trial. Garg et al. [58] conducted a safe and effective study of an AP control system for home application of PID that automatically increases, decreases, and pauses insulin delivery in response to continuous glucose monitoring.

b. Neural Network Control Algorithm

Neural network, also known as artificial neural network, is a simulation system that mimics the structure and function of biological neural networks, making it as capable of learning and discriminating as the human brain, in order to accomplish the processing of various information. Artificial neural network consists of many parallel adjustable weight neurons, which can find the intrinsic laws of these data from existing data, and is suitable for dealing with some problems with complex intrinsic relationships with nonlinear characteristics, or suitable for exploring the patterns of data. And the insulin action process is a nonlinear and strongly perturbed dynamic process, so that the neural network is suitable for closed-loop glucose control [59]. Figure 8 below shows the block diagram of its algorithm, in which TDI stands for time delay isogram. The disadvantage of neural network control is that a large amount of a priori data are required to accurately summarize the patterns. And in reality, patients often need to face the interference of external factors such as irregular eating and movement. Therefore, the selection and processing of a priori data has a large impact on the control effect. And due to the strong time lag characteristic of the glucose-insulin system, it is easy to over-inject insulin and cause hypoglycemia to the patient, thus posing a threat to the patient's life safety, so neural network algorithms are often used in combination with other algorithms.

c. Blood Glucose Fuzzy Control Algorithm

Fuzzy control is an intelligent control technique based on fuzzy set theory, fuzzy logic reasoning, and fuzzy linguistic variables. The algorithm works by coding expert's or operator's experience into fuzzy rules and fuzzifying the real-time data collected by sensors and later as fuzzy rules for input to enable fuzzy reasoning and adding its output values to the actuators to achieve control over the control target. The transformation performed is represented by Z in the principle block diagram of blood glucose fuzzy control, as shown in Fig. 9. Atlas et al. applied fuzzy logic control to a clinical object and achieved better control results [60].

d. Model Predictive Control Algorithm

MPC is an advanced control algorithm that operates on the principle of predicting the system's future dynamic behavior. This is achieved by using predictive models such as the

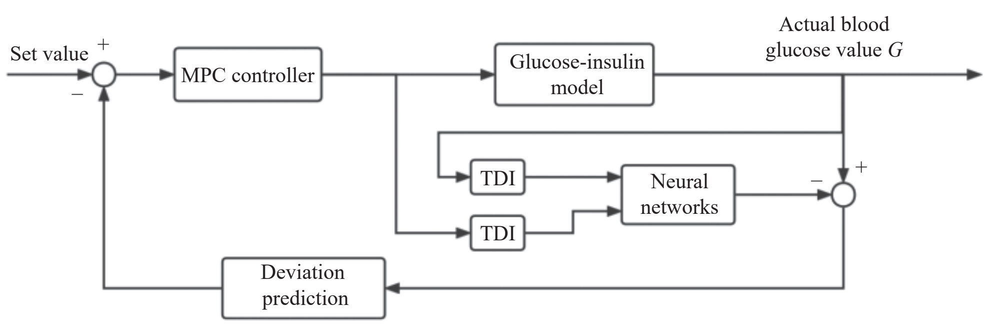

Figure 8 Schematic diagram of a blood glucose control system based on neural network prediction.

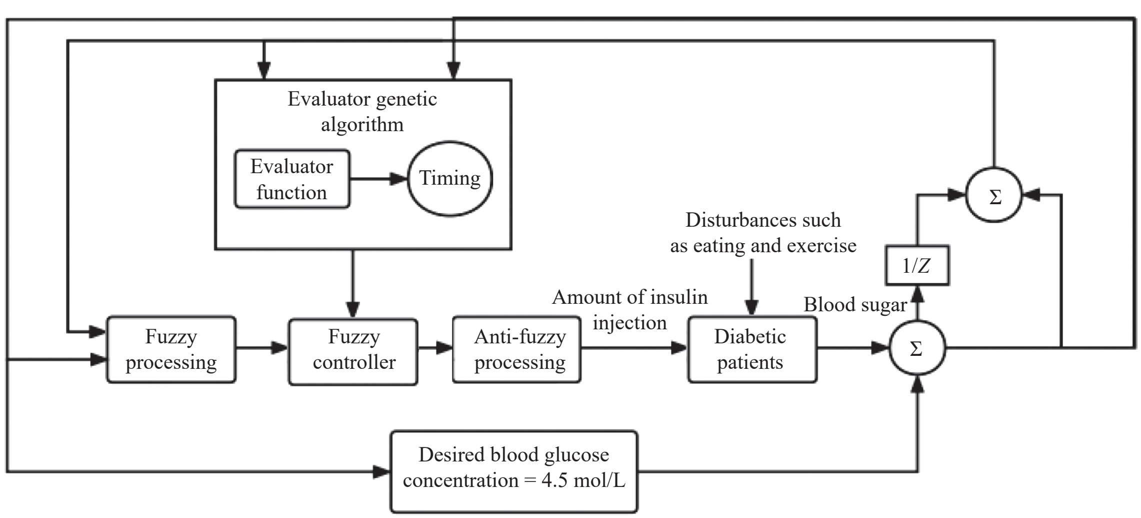

Figure 9 Block diagram of blood glucose fuzzy control principle.

impulse response model, step response model, or the controlled autoregressive integrated sliding average model. Based on these predictions, MPC solves for the optimal control sequence at the current moment by rolling the corresponding cost function and constraints. The objective is to apply the current control sequence in a way that minimizes the deviation between the controlled variables and the desired trajectory [61]. It is characterized by the fact that the first element of the optimal sequence obtained from each solution is used on the controlled object, and the above steps are repeated at the next sampling time, and so on continuously for rolling optimization. MPC is a rather complex control algorithm, and its control flow is shown in Fig. 10. Grosman et al. [62] proposed the zone-MPC control model by changing the original objective function into an interval objective. Both linear model predictive control (LMPC) [63, 64] and nonlinear model predictive control (NMPC) [65, 66] have been considered. Most of these algorithms are designed for insulin-only single-hormone, and therefore they cannot effectively handle hypoglycemic events in different situations. The proposed algorithm for dual hormone (insulin and glucagon) control provides a new idea for future studies. In this algorithm, glucagon is the counter-regulatory hormone of insulin, which raises blood glucose. There are greater advantages in terms of safe and tight glycemic control, for example during exercise or insulin over-delivery [67]. Therefore, researchers are now working on a dual hormone system to control both insulin and glucagon [68, 69]. Moscardó et al. [70] developed a dual hormone control algorithm based on proportional differential control. Boiroux et al. [71] aimed to prevent hypoglycemic events caused by insulin over-delivery by employing an linear matrix predictive control algorithm, which was based on several different transfer function models.

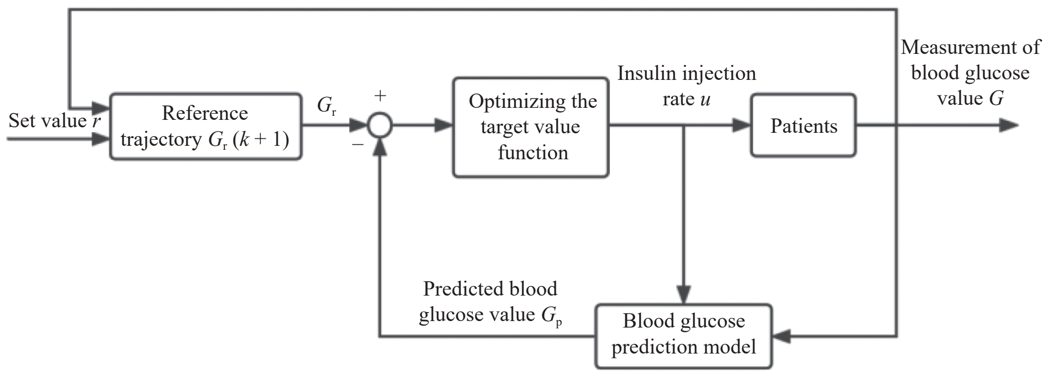

Figure 10 Block diagram of MPC role.

e. Iterative Learning Control Algorithm for Blood Glucose

Based on the simple principle that individuals seek satisfactory indicators to achieve desired behaviors in repetitive processes, these scholars have successfully endowed industrial robots with the capability to perform trajectory tracking tasks with high speed and accuracy. These robots, featuring strongly coupled nonlinear multivariate characteristics, are now extensively utilized in robotics and other fields. Its desired control performance is achieved by continuously learning from past experience control performance, i.e., using past information to redesign and improve the control signal. Diabetic patients are generally required to have a regular diet, while hormone levels are periodic, the dynamic model then has a certain degree of repetitiveness and can be used with iterative learning control algorithms. Wang et al. first applied a model predictive control algorithm combined with iterative learning control algorithm to an artificial pancreas . Also, to achieve stable control of the closed-loop system and suppression of disturbances, a Kalman filter-based forgetting factor-based iterative learning control rate was proposed [72].

f. Research in Other Areas

The performance of closed-loop AP control algorithms is influenced by clinical parameters, and the study of the effectiveness and robustness of the error of closed-loop algorithms in ensuring the safety and efficiency of AP systems is essential and a direction for future development. Incremona et al. [73] introduced an integral error term into the cost function to overcome the static error introduced by the MPC algorithm. Turksoy et al. [74] applied a novel food mass calculation strategy to an adaptive multivariate AP system and designed one that can effectively prevent postprandial hyperglycemia without the need of manual meal addition notification. Hajizadeh et al. [75] developed an adaptive glucose model based on CGM data, physiological information based control estimated mean arterial pressure control, and wearable physiological measurements that can effectively address perturbations from unannounced meals and physical activity. Meanwhile, a PID control combined with an expansive state observer was proposed as an alternative to adaptive glucose based models within the framework of the active disturbance rejection control (ADRC) approach [76], which has proven its effectiveness in various industrial applications [77–79]. Reenberg et al. [80] used maximum likelihood estimation (MLE) for a dual hormone AP system to discriminate model parameters, switching nonlinear model predictive control algorithms were investigated, and a simpler model was used to extend the glucose regulation model. Cai et al. [81] proposed an event-triggered mechanism to address the asymmetric risk of hyperglycemia and hypoglycemia using an adaptive interference suppression technique, while introducing glucose and velocity for each hormone infusion dependent parameter adaptive feedback control.

B. Problems Facing Closed-Loop Glucose Control

The artificial pancreas has strong specificity, and the current algorithm of closed-loop control of blood glucose still has some difficult problems to solve. From the perspective of control theory, there is a certain delay in the reduction of blood glucose concentration after insulin injection, while the onset of effect time is different for different injection sites, and blood glucose-insulin metabolism is a time lag system. From the perspective of glucose-insulin prediction model, due to the complex structure of physiological model, more parameters are difficult to identify, now mostly use data-driven approach to modeling. There is much room for research enhancement on how to tap into the existing models and efficiently build accurate glucose prediction models for different subjects. The current blood glucose closed-loop control algorithm mainly weakens the characteristics of diabetic patients themselves and builds their unified model, which is more robust, but the control accuracy for individuals is not high; furthermore, it builds a personalized model to achieve precise control for individuals, but the cost of building the model is high. In summary, when designing the blood glucose closed-loop algorithm, one should consider using multiple deep learning algorithms, modern control methods, etc. to suggest a personalized blood glucose control algorithm for each diabetic patient.

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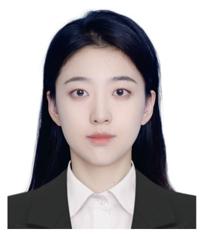
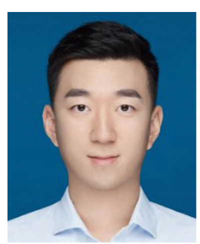


Shuya Liu is currently pursuing the ME degree at University of Science and Technology Beijing, China. Her research interests include blood glucose prediction, control in diabetes mellitus, neural networks, and machine learning.

Ruizhuo Song received the PhD degree in control theory and control engineering from Northeastern University, Shenyang, China, in 2012. From 2013 to 2014, she was a visiting scholar at Department of Electrical Engineering, University of Texas at Arlington, Arlington, TX, USA. From January 2018 to February 2018, she was a visiting scholar at Department of Electrical, Computer, and Biomedical Engineering, University of Rhode Island, Kingston, RI, USA. She was a postdoctoral fellow at University of Science and Technology Beijing, Beijing, China, in 2012. She is currently a professor at School of Automation and Electrical Engineering, University of Science and Technology Beijing, China. She has authored or coauthored more than 100 journals and conference articles and coauthored 3 monographs. Her current research interests include intelligent perception and computing, optimal decision-making, and gaming for virtual/real complex systems, and the results are applied to human body signal measurement and control, target positioning and recognition, energy internet, etc.



Xiang Lu is currently pursuing the ME degree at University of Science and Technology Beijing, China. His research interests include deep learning, blood glucose prediction, and blood glucose control.