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REVIEW ARTICLE

A review of personalized blood glucose prediction strategies for T1DM patients

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Abstract

This paper presents a methodological review of models for predicting blood glucose (BG) concentration, risks and BG events. The surveyed models are classified into three categories, and they are presented in summary tables containing the most relevant data regarding the experimental setup for fitting and testing each model as well as the input signals and the performance metrics. Each category exhibits trends that are presented and discussed. This document aims to be a compact guide to determine the modeling options that are currently being exploited for personalized BG prediction.

KEYWORDS

artificial pancreas, blood glucose prediction, data-driven BG prediction models, hybrid BG prediction models, physiological BG prediction models, predictive models

1 | INTRODUCTION

Diabetes is a chronic disease characterized by the body's inability to produce enough insulin or insulin at all. According to the International Diabetes Federation (IDF), in 2015, there were 415 million people with diabetes in the world, making diabetes one of the largest global health emergencies of the 21st century. Diabetes can be classified in three main groups: Type 1 diabetes mellitus (T1D), Type 2 diabetes (T2D), and gestational diabetes. Particularly, T1D is caused by an autoimmune attack on β-cells. People with T1D highly rely on external insulin in order to control their blood glucose (BG) levels. As stated in,[1] the number of people who develop type 1 diabetes is increasing for reasons still unclear; apparent reasons include changes in environmental risk factors and/or viral infections. The aforementioned motivated several efforts in therapeutic solutions, including the most ambitious one: the artificial pancreas (AP). This automated system is intended to manage BG and reduce T1D risks like, hypo/hyperglycemia, which are life-threatening situations for the patient.

Although the AP endeavor is rapidly expanding its achievements, including an increasing number of relatively successful *in vivo* trials, there are still many limitations. These limitations include the accuracy of the sensors, the delay of insulin action when infused into subcutaneous (SC) tissue, the delay in glucose level estimation by the continuous glucose monitoring (CGM) system when measuring interstitial fluid, and the lack of models that include physical activity and emotional factors, among other limitations. Therefore, to use AP properly in common clinical practices, key challenges must be addressed. For example, some recent studies focused on overnight control and short-term BG prediction for pump shut-off or alarm setting and management.

For studying models designed to identify patients, BG prediction and control validation are necessary steps when determining the best approach for insulin dosage automation and optimization using CGM systems. In the past few years, many researchers from several disciplines have contributed to closing gaps in the AP endeavor,[2–10] which has resulted in advances in glucose sensing technologies with increased accuracy,[11–13] the commercial availability of several insulin pumps[14,15] and even fully operating AP prototypes.[16] A fully automated AP system must accurately calculate and administer the right amount of insulin, minimize hypoglycemic events, generate alerts,[17] detect and cope with several types of faults, be able to adapt to changing conditions, such as fasting, food intake, and exercise, and should be simple and adjustable for various clinical practices.[18] However, one of the main obstacles for achieving a fully automated and

reliable AP is the lack of BG prediction models that are reliable enough to model the variance of a diabetic patient's physiology.[19] A fully reliable model should not only be able to mimic the patient's physiology but also cope with external disturbances, such as noise, exercise, unannounced meals,[20] and stress, among other factors.

Since the introduction of CGM devices, several short-time glucose prediction methods have been proposed in the literature, including the popular time series models that use only the CGM signal as an input.[21,22] Nevertheless, glucose concentration is sensitive to the quantity of ingested carbohydrates, insulin administration, physical activity, stress, and the influence of pathologies other than diabetes. Therefore, there is much interest in determining the limitations and improvements that need to be addressed for these models to be accurate.

One of the most recent reviews of modeling in an AP context is the review by Cobelli et al.,[23] which focused on physiological models, an analysis of CGM time series signals, and recent developments in model predictive control (MPC) as a strategy for closing the gap in BG control. By classifying models as knowledge-driven BG models and empirical BG models,[24] presents the existing glucose–insulin dynamic models dating from the 1960s with a detailed analysis of knowledge-based glucose–insulin dynamics models, models of meal absorption dynamics, and models of exercise effects. On the other hand,[25] dedicates a section to synthetize some of the principal characteristics and performance metrics of 12 data-based approaches for glucose prediction using autoregressive (AR) models with time varying parameters and other machine learning methods. However, the increasing popularity of machine learning algorithms and their expanding applications in BG prediction[26] require an updated review to establish the current trends in modeling strategies, not only for the next generation of controllers of APs[27] but also for other applications that are still in the early stages of development, such as personalized decision systems and BG event alarms based on short-term predictions.

Revisiting the control applications, the strategies for modeling diabetic patients are used either for *in silico* testing of controllers or for algorithms that include a patient's internal model in predicting the outcome of the control action at a given time, for example, BG concentration, $BG(t)$, from a BG set point, $BG_{SP}(t)$ (see Figure 1). Specifically, the control methods that allow an internal model of the patient to be included are feedforward-feedback control, H∞ control, robust control, and MPC.[28] *In silico* testing of controllers is usually carried out using tools such as the Uva/Padova Type I Diabetes Simulator[29] or the simulation environment presented in,[30] which are constantly being updated to include new features that decrease the intra- or inter-patient variability. According to,[18] *in silico* validation models must include a model for glucose kinetics and insulin action on one side and insulin kinetics on another. The models should also include a meal absorption dynamics model and a sensor error model that represents the time delays and measurement deviations that are common in CGM systems. In addition, the models can include an exercise model or models representing other phenomena, such as the dawn phenomenon. However, there is not currently a consensus about how to include physical activity and other intra-patient variability sources in the glucose kinetics models. Turning now to the controller's internal model of the patient (i.e. when the control strategy includes an internal BG prediction), the most popular control approaches according to the review in[28] are linear and nonlinear MPC and feedforward-feedback control. However, the most recent publications that are addressed in that review are from 2008, which is one of the key reasons for writing this review.

In regard to the importance of the individualization of the patient model, some patients exhibit large variations in their BG signals during the day, especially after a meal or physical activity. Others experience a blood sugar increase before, during, or after anxious moments. As mentioned in,[31] there are secondary factors that tend to raise or lower BG levels, and some of those factors depend on lifestyle. The factors that tend to increase BG levels include caffeine and fatty food intake, growth and weight gain, illnesses or infections, the Somogyi phenomenon, steroids and other medications, surgery, and traveling. Factors that lower BG levels include aging, intense periods of concentration, specific climate conditions, high altitude, and even some medications. Additionally, some factors can produce unpredictable glycemic excursions, such as consuming alcohol, impaired digestion, menstruation, and menopause, among other factors.

In addition to the daytime food- and exercise-related variability, T1D patients can exhibit large variations in their BG signals during sleep, hormonal fluctuations, or heart rate variations,[32] among many other factors. Therefore, personalized glycemic prediction strategies have become necessary

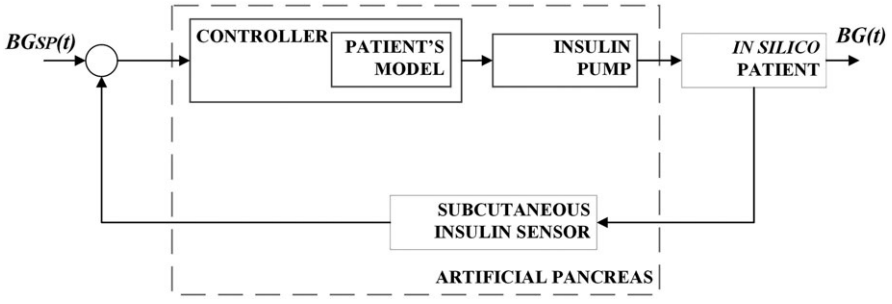

FIGURE 1 Schematic of closed-loop control for AP with an internal model controller

for BG control because it is neither safe nor accurate to use models with generalized parameters that do not reflect the dynamic behavior of the patient during the day. Because using personal parameters such as the correction factor, insulin-to-carbohydrates ratio, and physical characteristics such as the patient's weight[33] enhances the ability of models to accurately capture a single patient's dynamics, there has been increasing interest in personalizing BG prediction models involved in type I diabetes monitoring and treatment,[34,35] by including physical activity data and information concerning lifestyle and the emotional status of the patient.[36]

This paper contains a summary of the relevant features of the most recent and most relevant studies that were developed and published in the field of predicting BG levels or BG events, including internal models for control applications. This article will present, discuss, and summarize the state of the art of modeling strategies in the context of AP projects from the past five years. The remainder of this paper is organized as follows: Section 2 presents a description of the methodology that was designed to select the surveyed papers and extract and present relevant information. Section 3 is dedicated to the classification of prediction models and the relevant features of each surveyed study in summary tables. The same section includes a summary for control-oriented prediction models because closing the loop is the main goal for current studies related to AP research. Then, in Section 4, the key aspects of the results are presented, including model classification, prediction horizon (PH), model outcomes, the use of additional input signals, and performance metrics. Finally, Section 5 contains concluding remarks.

2 | METHODS

Because of the increasing number of studies in the field of BG control and monitoring, including state-of-the-art reviews, development of new control strategies, and glycemic prediction algorithms, the scope of this methodological review is limited to publications found between 2010 and April 2016. The specific search criteria were patient identification for BG prediction, BG prediction models, and control-oriented prediction models. Figure 2 presents a flowchart of the methodology followed for this review. We started with an initial record search using keywords related to BG prediction, and only the papers that met the inclusion criteria were considered in the next stage. This first screening stage was completed by taking into account the relevance of the model, which meant determining whether the model was indeed used

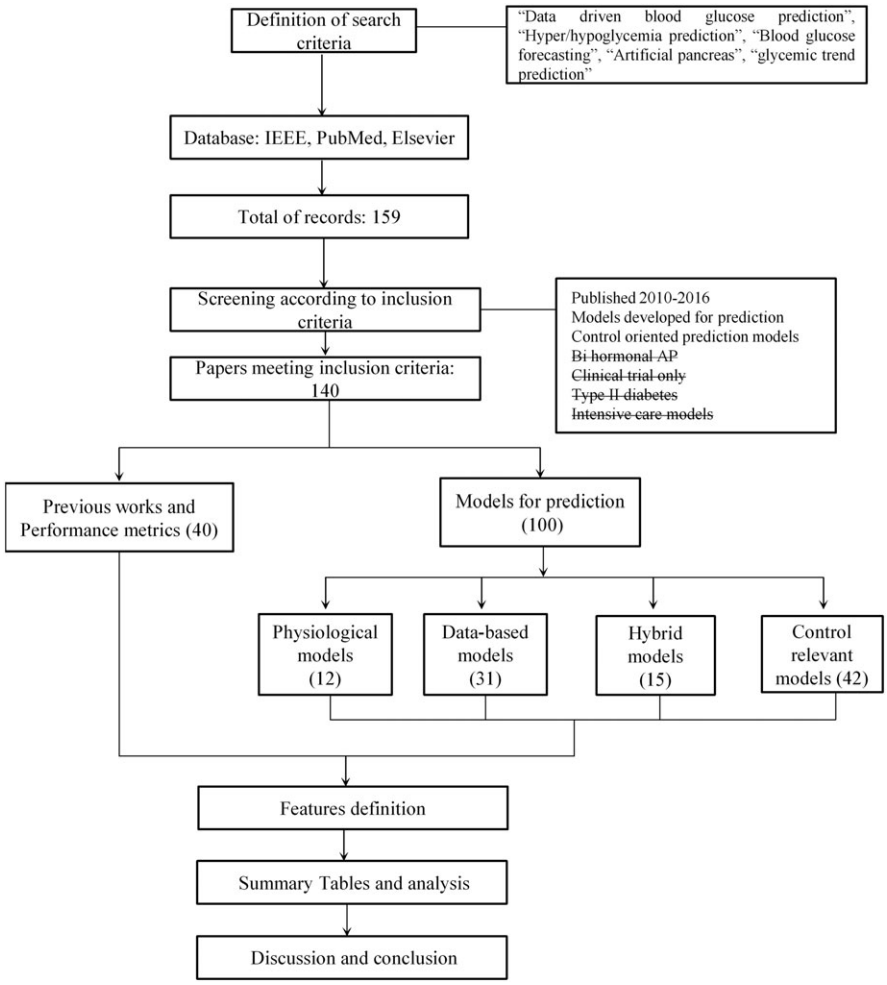

FIGURE 2 Flowchart of review methodology

for prediction of future outcomes and whether that prediction was evaluated using the standard or new BG-specific metrics. Therefore, studies using models only for patient identification or generation of virtual patients were excluded. Additionally, with the aim of including control-oriented prediction models, the initial search included insulin delivery control strategies with prediction capability. However, only studies with control strategies that had an internal model for prediction of future outcomes were included. Black box control schemes such as proportional-integral-derivative controller (PID), run-to-run, or rule-based models were excluded in the first screening. Additionally, because this review is based on a single hormone AP concept, studies that examined multiple hormones were excluded. Likewise, papers presenting only results from clinical studies in which there were no details about the prediction models were excluded, as were intensive care patient models and type II diabetes approaches, which fall outside the scope of this review. After the screening, 140 papers were included in this review, including previous reviews, model performance metrics proposals, and predictive models. The predictive models have been classified into four different categories: physiological models, data-driven models, hybrid models, and control-relevant models.

Physiological models require a previous understanding of insulin and glucose metabolism. They are useful for performing simulations of BG metabolism in the form of compartmental models and for studying the physiological processes that are involved in glucose regulation. Figure 3a is a block diagram representation of the model structure that is common for this approach in which the prediction of BG concentration, BG events, or risks are the result of using complementary sub-models, including those of SC insulin absorption, carbohydrate digestion and absorption, insulin action, and glucose kinetics.[37] Usually, the inputs of these

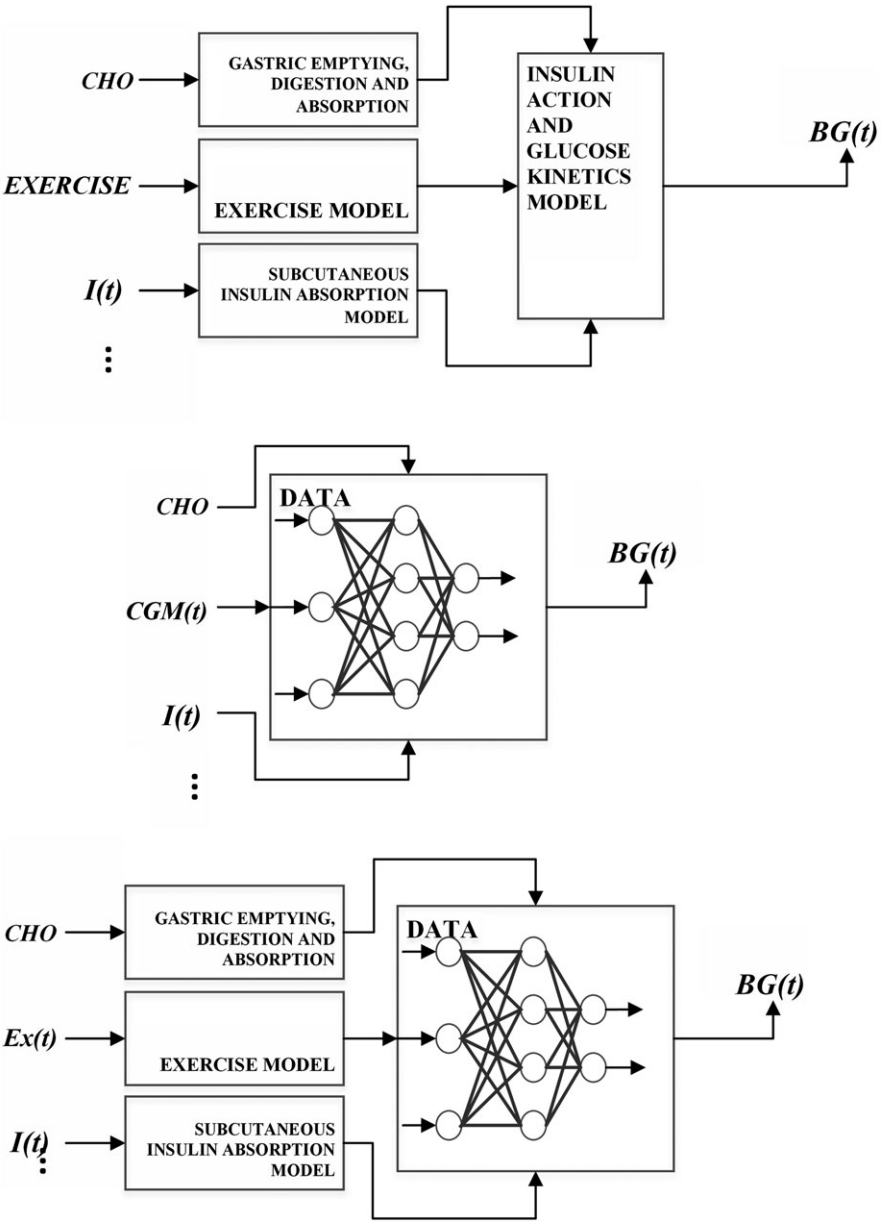

FIGURE 3 Block diagram representation of BG prediction models

approaches include estimation of carbohydrate intake, external insulin therapy, and, in some cases, other variables related primarily to physical activity. One major drawback of this approach is that this type of model contains several physiological parameters that need to be set prior to their use to make BG predictions. These parameters can be adjusted using identification techniques, machine learning techniques, or population values. There are some minimized versions of these models, but obtaining a satisfying model with a good generalization capability is difficult because they usually contain several variables and parameters that are difficult to adjust.

In contrast, non-physiological models, which are also known as data-based/driven models, fully rely on CGM data and, sometimes, additional signals to model a patient's physiological response without involving physiological variables (see Figure 3b). Neural networks (NN) and AR models are common examples of this type of approach. An alternative scheme is a physiological model for glucose digestion and absorption, a second model for insulin absorption, and a third model for exercise. These models are used in a pre-processing stage, as depicted in Figure 3c. Models of this type are commonly known as hybrid models because they partially rely on physiological models and require the identification and setting of some physiological parameters. Finally, the prediction models used in internal-model control algorithms can use any of the prior alternatives and have been included in the review because of their importance in AP research. Thus, a specific category was created for them.

Once the model categories were established, the information contained in the previous review, along with information from different surveyed papers, led to the establishment of a set of features that sum up the different approaches for predicting future BG outcomes. Below, there is a short description of each one of the features presented in all the summary tables in this paper:

- Reference: Presents the first author family name, the reference number, and the year of publication of the study.
- Model type: Refers to the name of the model as mentioned in the referenced paper. If the model is a new proposal with no specific name, then it was labeled in the table as 'New Model'.
- PH: Refers to the future time in which the predicted glucose concentration is determined by the model. When the PH was not explicit in the referenced work, a dash (—) appears in the box.
- Software/language: Refers to the software or programming language in which the prediction model was coded. When this feature was not explicit in the referenced work, a dash (—) appears in the box.
- Patient data: This feature states whether clinical studies or simulated data were used for developing or testing/validating the prediction models. The US Food and Drug Administration (FDA) has accepted *in silico* modeling as a nonclinical assessment tool for models and controllers using a theoretical human model of insulin and glucose metabolism, which made it easier to fit models and design controllers in a less expensive manner.
- #Patients: The number of virtual or real patients whose data were used for identifying and assessing the prediction model.
- #Days/# hours: The number of days or hours of simulated or real data that were used for identifying and assessing the prediction model.
- Monitoring devices: The brand and model of the devices that were utilized in each study to collect BG in time and other input signals.
- Inputs: Check marks indicate that CGM data, insulin therapy, carbohydrate content estimation (CHO), and additional inputs such as physical activity level or sleep, were used as inputs for the prediction model.
- Performance metrics: Measure of the model's predictive power. These metrics were different for classifiers and for regression models. Predictive power is normally assessed using metrics computed from a holdout set or using k-fold cross-validation.

After the data were distributed among these features, the summaries were analyzed, and the prediction modeling trends are presented at the end of each section. It is important to acknowledge that the summaries and the conclusions drawn out of these are limited to be observations of the surveyed works and that they do not constitute a statistical analysis, because the total of surveyed works in each category does not allow doing such analysis. The inferred trends are then, observations from a tabulation of the total of entries in each category. In addition, it is necessary to be aware of the fact that some authors have been very active in the surveyed period for this review, and thus, a given author and collaborators might have more than one entry in the summary tables. Therefore, the interpretation of the figures given at the end of each section must be done carefully, taking into account a possible bias in the percentage distribution.

3 | RESULTS

This section focuses on the characteristics of the four model categories. Each category is summarized in a table that references the surveyed studies. Additionally, the percentage distribution of modeling strategies is presented at the end of each category.

3.1 | Physiological prediction models

The purpose of this section is to review the most recent studies that involved the use of physiological models,

TABLE 1 Physiological prediction model approaches

Reference	Model type for insulin action and glucose kinetics	Prediction horizon	Software/ Language	Patient real data	# Patients	#Days or # hs	Monitoring devices	Inputs				Performance metrics
								CGM/Blood glucose data	Insulin therapy	CHO	Other inputs	
Balakrishnan, 2014[50]	Extended Bergman´s minimal model	-	Matlab	✓	34	-	Continuous glucose monitoring sensors (CGMS)	✓	✓	✓	RPE	Coefficient of determination R^2
Bock, 2015[51]	Therapy parameter based model (TPM)	15-165 min	Matlab/ Simulink	✓	10 virtual 12 real	4 days for virtual 10 days for real	Accu-Chek	✓	✓	✓	-	MAD (Mean absolute difference) coefficient of determination R^2 EGA
Cheng, 2010[52]	DDEs model	-	Matlab	✓	4	1 day	-	✓	✓	✓	-	Sum of squared errors
Cheng, 2010[53]	Modified delay differential equations (DDEs) model	-	Matlab	✓	56	1 day	-	✓	✓	✓	-	Sum of squared errors
Duun, 2013[54]	Extended minimal model	10 min	-	✓	4	4 days	YSI2300 STAT plus	✓	✓	✓	-	Autocorrelation function (ACF) likelihood-ratio tests
Laguna, 2014[55]	Hovorka	300 min	Matlab	✓	12	4 times, 5 hs each time	YSI 2300 STAT plus glucose analyzer	✓	✓	✓	-	Envelope width, Number of glucose measurements included inside the predicted glucose envelope, mean absolute relative difference
Wu, 2011[56]	New model	-	-	✓	3	-	Accu-chek inform II	✓	✓	✓	-	Sum of the square error (SSE)
Calm, 2011[57]	Hovorka	400 min	C++ Builder	×	1	6 hs	-	✓	✓	✓	-	-
De Pereda, 2012[58]	Hovorka	300 min	Matlab	×	1	5hs	-	✓	✓	✓	-	Envelope area vs montecarlo simulations
Eberle, 2012[34]	Bergman	-	-	×	-	-	-	✓	✓	✓	-	-
Fang, 2015[59]	Modified Cobelli's model	-	-	×	30	1 day	-	✓	✓	✓	-	RMSE
Laguna, 2014[60]	Hovorka	300 min	Matlab	×	15	3 days	-	✓	✓	✓	-	Envelope width, Number of glucose measurements included inside the predicted glucose envelope, mean absolute relative difference (MARD)

whether they were classical models or new modeling proposals that aimed to predict BG in type I diabetes patients. Physiological models can be divided into two types according to their complexity. The first type of models is the so-called minimal models, which are capable of capturing crucial processes of glucose metabolism and insulin action with few equations and identifiable parameters. The second type is maximal or comprehensive models, which comprise all the available knowledge of the physiological system and are capable of simulating or reproducing a diabetic patient's metabolic response, which allows *in silico* experiments to assess controllers and treatments.[23] So far, there has been no specific guidance on the selection of a given model for a given approach. However, some studies can help with this selection because they compare postprandial insulin action and glucose kinetics models in terms of patient variability, for example, insulin sensitivity, basal insulin, and uncertainty in food intake estimation.[38,24]

In recent decades, several authors have proposed models of insulin action and glucose kinetics using experimental data to measure glucose production, glucose utilization, and insulin and meal absorption. Many of those models are compartmental models, which describe the processes that occur in the inaccessible portions of the system because these processes are not directly measurable. Therefore, the inaccessible portion of a system is represented by a number of interconnected compartments.[39] The most popular proposals regarding physiological models of insulin action and the glucose kinetics system are the Dalla Man Model,[40] Hovorka model,[41] and Bergman minimal model.[42] The different models allow for the estimation of variables, such as SC insulin absorption, gastric emptying, carbohydrate digestion and absorption, insulin kinetics, and glucose metabolism. More specifically, the Dalla Man model is composed of one glucose and one insulin subsystem linked by the control of insulin in glucose utilization and endogenous production. In contrast, the Bergman minimal model uses a three-compartment model to represent the concentrations of plasma insulin I (mU mL^{-1}), remote insulin X (min^{-1}), and plasma glucose G (mg dL^{-1}). Finally, the Hovorka model uses two compartments representing the kinetics of glucose and regards each insulin action with its final effect on BG separately. For these models, the input variables include factors from external insulin therapy and nutritional content over time. Table 1 presents a summary of the most recent studies related to the use of physiological models for BG prediction purposes.

This review shows that for the prediction approaches using physiological models, the Bergman and Hovorka models are widely used. Other types of physiological models (see Table 2), including new proposals, account for 33.3% of the total. Finally, Dalla Man model is widely used for *in silico* testing of prediction models and controllers, thanks to the UVa-Padova simulator based on it. Nevertheless, because this review takes into account only works for BG prediction, only one work was surveyed.

TABLE 2 Percentage distribution for physiological models

Physiological model	Percentage
Hovorka	33.3%
Bergman/modified	25%
Dalla Man/modified	8.3%
Others	33.3%

3.2 | Data-driven models

This section presents the latest studies on BG non-physiological prediction models that use the information contained in CGM data, insulin therapy data, food content data, and a few other inputs. Because these models are often supported by machine learning techniques, there are several approaches for the predictive task, including time series models, genetic algorithm models, grammatical evolution models, robust filters, fuzzy logic models, rule based models, multi-model approaches, Gaussian mixture models (GMM), regularized learning, reinforcement learning, random forest, Kalman filters, support vector models, and artificial NN (ANN) models, among others. Models generating hypoglycemia/hyperglycemia alerts based on a prediction of glucose concentration are useful as well and are included in this section. It is worth mentioning that only predictive data-driven models are included because there is a large number of descriptive data-driven models.

Despite the fact that many models for forecasting glucose concentration use several inputs, some works suggest that ingested carbohydrate information, along with injected insulin information might be redundant,[43] which is why some recent developments use the CGM signal as the only input. Other studies state that the use of additional inputs makes the prediction task harder because formalizing these inputs in mathematical terms and extracting useful signals from them is not easy.[44]

For the data-driven models, there is not a single technique that can be identified as the most popular model as can be seen in Table 3. The trend in the data-driven approach shows that researchers are still experimenting with a vast pool of machine learning techniques. Therefore, there are still many research opportunities in this field because of the constantly increasing possibilities for mixing techniques to enhance prediction capability and accuracy. The previous statement is supported by the fact that the mixed technique approaches and the use of other techniques account for 31% and 28% of the total studies, respectively (see Table 4). Time-series modelling approaches based on AR and autoregressive with moving average (ARMA) models determine future glucose concentration as a linear function of previous glucose measurements only. Other approaches consider additional inputs, such as insulin in plasma or meal information through exogenous signals (ARX-ARMAX).

TABLE 3 Summary of data-driven models for BG prediction

Author	Model type	Prediction horizon	Software/ Language	Patient real data	# Patients	#Days or # hs	Monitoring Devices	Inputs				Performance Metrics
								CGM/Blood glucose data	Insulin therapy	CHO	Other inputs	
Buckingham, 2010[61]	Modified linear prediction alarm+ kalman filtering+ adaptive hybrid infinite impulse response (HIIR) filte+ statistical prediction+ numerical logical algorithm	35 min	-	✓	40	10 nights	FreeStyle navigator	✓	×	×	-	Percent of predicted hypoglycemic events
Dassau, 2010[62]	Linear prediction algorithm, statistical prediction algorithm, kalman filter algorithm, hybrid impulse response filter, and numerical logical algorithm	35, 45, 55 min	-	✓	46	24 hs	Abbott free style navigator	✓	×	×	-	Percent of predicted hypoglycemic events
Efendic, 2014[63]	GMM	10-30 min	-	✓	12	7 days	FreeStyle navigatorTM by Abbott Diabetes Care, Alameda, CA; Guardian® REAL-Time by Medtronic MiniMed, Northridge, CA; and DexComTM Seven® Plus by DexCom, San Diego, CA	✓	✓	✓	-	Correct and incorrect prediction rates
Fernández, 2012[64]	ANN	-	Simulink	✓	20	30 days	Medtronic minimed guardian	✓	✓	✓	Exercise level :0 for low, 1 for moderate, 2 for strong	Sum of squared errors (glucose-prediction)
Fong, 2013[65]	Fuzzy lattice reasoning	-	Weka	✓	1	-	-	✓	✓	×	-	accuracy of the model, Kappa statistics, and the normalized gain ratio in rule generation
Fong, 2013[49]	Very fast decision tree (VFDT), ANN (perceptron), incrementally optimized very fast decision tree (iOVFDT)	Several hours	java	✓	70	Several months	-	✓	✓	✓	Event exercise: typical, more than usual, less than usual	Accuracy test (total number of correctly classified instances/the total number of instances available for a particular patient) Receiver operating characteristic Sensitivity, specificity

(Continues)

Table 3. *(Continued)*

Author	Model type	Prediction horizon	Software/ Language	Patient real data	# Patients	#Days or # hs	Monitoring Devices	Inputs				Performance Metrics
								CGM/Blood glucose data	Insulin therapy	CHO	Other inputs	
Gani, 2011[66]	AR	30 min	Matlab	✓	34	5 to 56 days	iSense Guardian Dexcom	✓	×	×	-	RMSE
Henry, 2014[67]	Autoregressive model with output correction – cARX, and a recurrent neural network – RNN	15,30, 45 min	-	✓	23	Training 5.30±1.40 days Evaluation 4.83±1.80 days	Medtronic MiniMed	✓	×	×	-	RMSE, Time lag, Correlation coefficient
Kirchsteiger, 2011[68]	MISO transfer function	-	-	✓	15	3 days	-	✓	✓	✓	-	-
Lu, 2010[43]	AR	Up to 50 min	Matlab	✓	9	5 days	iSense CGM system	✓	×	×	-	RMSE
Lu, 2011[69]	ARX	10, 20 min	Matlab	✓	27	6 days	iSense CGM system	✓	×	×	-	RMSE
Naumova, 2012[70]	Meta learning approach	20,40, 60, 75 min	Matlab	✓	90	3 to 10 days	Abbott's Freestyle Navigator and Dexcom®SEVEN R PLUS	✓	×	×	-	Clarke Error Grid Analysis, Prediction Error Grid Analysis (PRED-EGA)
Novara, 2015[71]	ARIMAX	30 min	Matlab	✓	5	10 days	Medtronic-MiniMed continuous glucose monitoring systems	✓	×	×	-	Fit value
Pérez, 2010[72,73]	ANN	15,30,45 min	Matlab/ Weka	✓	9 6	72 hours/week over four weeks 72 hs	Medtronic Guardian Abbott Navigator	✓	✓	✓	-	RMSE Clarke error grid analysis Relative difference mean value Prediction delay TG Correlation coefficient
Shanthi, 2012[74]	feed forward back propagation NN	30,45, 60 min	Matlab	✓	-	-	Medtronic Minimed Guardian	✓	×	×	-	Mean Squared Error (MSE)
Shi, 2015[75]	Linear model	-	-	✓	1	60 days	Johnson ONETOUCH UltraVue Blood Glucose Meter	✓	×	×	-	MSE
Stahl, 2012[76]	Multiple merged predictors	40 min	-	✓	12	3 days	-	✓	×	×	-	Clarke grid analysis Root mean square error (RMSE)
Turksoy, 2013[77]	ARMAX	30 min	Matlab	✓	14	48 to 60 hs	Medtronic Continuous Glucose Monitor SenseWear Pro3	✓	×	×	Energy expenditure and galvanic skin response	Sum of squares of the glucose prediction error (SSGPE) RMSE Sensitivity False Alarm Ratio (FAR)
Wang, 2014[48]	Time-varying State-space model	30 min	Matlab	✓	30 Virtual 5 real	1 day	MiniMed Continuous Glucose Monitor model MMT-7102	✓	✓	✓	-	Coefficient of determination R2 relative absolute difference RAD TG time gain J index ESOD

(Continues)

Table 3. *(Continued)*

Author	Model type	Prediction horizon	Software/ Language	Patient real data	# Patients	#Days or # hs	Monitoring Devices	Inputs				Performance Metrics
								CGM/Blood glucose data	Insulin therapy	CHO	Other inputs	
Wang, 2013[78]	AR model + extreme learning machine + support vector regression	15, 30, 45 min	Matlab	✓	10	-	-	✓	×	×	-	Root-mean-square error, relative error, Clarke error-grid analysis, and J index
Zarkogianni, 2014[79]	Neuro-fuzzy model with wavelet activation functions	30,45,60 min	Matlab	✓	6	10.83 ± 3.86 days	Guardian Real-Time CGM system SenseWear Armband	✓	×	×	Energy expenditure	Root-mean-squared error (RMSE) and correlation coefficient (CC), Error Grid Analysis (EGA) and the MARD mean absolute relative difference
Zarkogianni, 2015[80]	Feedforward neural network (FNN) / a self-organizing map (SOM)/ a neuro-fuzzy network with wavelets as ctivation functions (WFNN)/ linear regression model (LRM)	30,60,120 min	Matlab	✓	10	10.70 ± 4.69 days	Medtronic Minimed Inc. SenseWear Armband	✓	×	×	Energy expenditure	Continuous glucose-error grid analysis RMSE correlation coefficient (CC) mean absolute relative difference (MARD)
Zhang, 2015[81]	Nonlinear stochastic model	-	-	✓	4	72hours	Medtronic Minimed CGM system	✓	×	×	-	Free energy
Zhao, 2012[82]	Latent variable	15,30,45,60 min	Matlab	✓	7 real	1 day	DexCom 7 PlusTM	✓	×	×	-	RMSE CG-EGA mean absolute deviation (MAD)
Eljil, 2013[83]	Time Series Data Mining (TSDM) + classification trees	30 min	Weka	✓	10	-	Medtronic Minimed	✓	×	×	-	Sensitivity, specificity, accuracy, youden's index
Harsh, 2013[46]	Time-varying autoregressive and exogenous model	30 min	Matlab	×	30	1 day	-	✓	✓	✓	-	FIT Relative Absolute Difference (RAD) coefficient of determination R2
Hidalgo, 2014[84]	Grammatical Evolution	-	Java	×	5	24 hs	-	✓	✓	✓	-	Mean absolute deviation MAD, RMSE, average error, maximum error.
Mo, 2013[85]	Extreme learning machine (ELM) +regularized LM	10, 20, 30 min	-	-	-	-	-	✓	×	×	-	RMSE, Sensitivity, specificity, ROC curve
Peng, 2014[86]	ARX	30 min	Matlab	×	10	2 days	-	✓	×	×	-	FIT value
Zhao, 2015[87]	ARX	30- 60 min	-	×	30	6 days	-	✓	✓	✓	-	Root-Mean-Square Error Rate Error Grid Analysis (R-EGA) TimeLag Sensitivity and specificity

TABLE 4 Percentage distribution of data-driven models

Data-driven model	Percentage
AR/ARMA	6.45%
ARX/ARMAX	16.13%
ANN	16.13%
Multi-model/mixed techniques	32.26%
Others	29.03%

3.3 | Hybrid models

This section is devoted to presenting the latest studies that use both data-driven and physiological models to construct a predictor of BG values or hypo/hyperglycemia risk. The scheme for a mixed physiological and data-driven model is usually a module based on a physiological model followed by a data-driven model that learns the relationship between inputs and future outcomes, which could be expressed either by means of classes (qualitative approach) or by means of the actual BG continuous values (quantitative approach). The physiological models are frequently meal models and insulin absorption models, such as the ones addressed in Table 1. The reason hybrid models have a separate section in this review is that they rely on the premise that inclusion of meal information, meal announcement, or insulin absorption through physiological models enrichens the overall prediction accuracy of the model. Table 5 presents a summary of the latest hybrid BG prediction models.

For the hybrid model prediction approaches included in this review, the most popular alternative for modeling meal/glucose absorption is the Dalla Man meal model, followed by the Lehmann and Deutsch model. However, whenever information about insulin therapy was used as an input, the most popular model for insulin kinetics was Berger's model, followed by the Dalla Man. Finally, NN in its many forms is the most commonly used option for predicting future BG outcomes. Table 6 presents the percentage distribution of models for hybrid approaches.

In regard to model inputs, two clear trends have been identified. First, the majority of the referenced works included in the summary table use both meal models and insulin models to preprocess the carbohydrate content estimation and insulin therapy inputs. In general, hybrid BG prediction models always use information on carbohydrate content, whereas these models do not always consider insulin therapy as a mandatory input. In this study, 78.5% of the surveyed studies used an insulin kinetics model to incorporate this input into the data-driven model.

3.4 | Control-oriented prediction models

This section presents the latest studies regarding internal models used in controllers, that is, control strategies that involve a plant model for prediction purposes. The fact that these internal models anticipate future outcomes and critical situations makes them suitable for being included in this review. These internal models hold the same classification used in the previous sections. This type of control scheme is called a grey-box-model-based control and includes feedforward-feedback control, H_∞ control, robust control, and MPC.[28] Unfortunately, most of the studies that use internal models do not show the performance metrics for the internal model but rather focus on the performance evaluation in terms of the control action, which was not of particular interest in the case of this paper (see Table 7). Because of safety and practical constraints inherent to controller testing, most of the studies that met the inclusion criteria are *in silico* applications.

The preceding summary identifies a clear trend in the control-oriented BG prediction models. The vast majority of the models are data driven, followed by physiological prediction models and finally hybrid approaches. Nevertheless, taking into account only the studies validated by clinical data, the studies are rather evenly distributed among physiological and data-driven approaches (see Table 8).

4 | DISCUSSION

This section is dedicated to the trends that were observed in the surveyed studies regarding the types of prediction models, PH, types of outcomes that are considered most useful, and the use of physical activity input signals. Finally, a description of the most common performance features for the assessment of the models is presented.

4.1 | Types of prediction models

There is wide variety of modeling options to predict future BG values. This paper classified the prediction models into three categories: physiological models, data-driven models, and hybrid models. The first type of modeling was the typical approach that was developed a few years ago. However, because physiological models are somewhat time-consuming and require previous knowledge to set the physiological constants, scientific efforts are currently concentrated in exploring innovative and less time-consuming models by taking advantage of the always growing machine learning modeling options. Hybrid models make use of the simplest physiological models to process meal information and insulin therapy information and then fit data-driven models to future BG outcomes. Finally, data-driven models completely rely on some non-physiological formulations to characterize the relationship between current and past CGM values and future BG outcomes.

4.2 | Prediction horizon

Because of the inherent delays with SC insulin infusion action and glucose sensing, it is desirable to find a reasonable compromise between the accuracy of the prediction model and its prediction capability. The vast majority of the studies

TABLE 5 Summary of hybrid BG prediction models

Author	Model Type	Prediction Horizon	Software/ Language	Patient Real data	# Patients	#Days or # hs	Monitoring Devices	Inputs				Performance Metrics Insulin therapy
								CGM/Blood Glucose data	Insulin therapy	CHO	Other Inputs	
Balakrishnan, 2012[35]	Hovorka's meal absorption model + subcutaneous insulin absorption kinetics model +Time series models	-	Matlab	✓	12	2 visits 7 hs/visit	-	✓	✓	✓	RPE	Fit value
Balakrishnan, 2013[88]	Berger's insulin kinetics model+ Hovorka's meal absorption model +NN	-	Matlab	✓	34	2 days	-	✓	✓	✓	RPE	MSE, R^2
Bunescu,2013[89]	Modified Lehmann and Deutsch glucose absorption model +SVR	30, 60 min	Java	✓	5	3 months	Medtronic Enlite CGM	✓	✓	✓	-	RMSE
Castillo, 2010[90]	Dalla Man glucose absorption model + Verdonk, insulin rate of appearance + Autoregressive eXogenous (ARX) model	45 min	-	✓	15	3 days	Abbott Free Style Navigator	✓	✓	✓	-	FIT value Error Grid Analysis
Castillo, 2010[91]	Dalla Man meal model+ Verdonk plasma insulin model + ARX	45 min	-	✓	15	76 hs	Abbott Free Style Navigator	✓	✓	✓	-	FIT value continuous glucose - error grid analysis (CG-EGA)
Cescon, 2015[92]	Dalla Man glucose absoption model + Dalla Man insulin absorption model + Subspace-based linear multi-step predictors	30 min, 60 min, 90 min, 120 min	Matlab	✓	14	3 days	Abbott Freestyle NavigatorTM	✓	✓	✓	-	Prediction error standard deviation Clarke error grid analysis Absolute difference Relative difference
Georga, 2010[93]	Lehmann and Deutsch glucose absorption model + Tarin insulin model+ exercise model+ SVR	15,30,60,120 min	-	✓	3	5 patient 1 11 patient 2 13 patient 3	Guardian Real-Time CGM system SenseWear Armband	✓	✓	✓	MET (Metabolic Equivalent of Task) , heat flux (hf) , skin temperature	RMSE, correlation coefficient, continuous glucose error grid analysis (CGEGA)
Georga, 2012[94]	Tarin´s plasma insulin concentration model + Lehmann's glucose rate of appearance model +random forests	15,30,60,120 min	-	✓	27	5-22 days	Guardian Real-Time CGM system SenseWear Armband	✓	✓	✓	Instantaneous energy expenditure (Kcal)	RMSE, correlation coefficient, Clark error grid analysis (CEGA)
Georga, 2013[95,96]	Lehmann and Deutsch glucose absorption model +Cobelli insulin model+SVR	15,30,60,120 min	-	✓	27	5-22 days	Guardian Real-Time CGM SenseWear Armband	✓	✓	✓	Instantaneous energy expenditure EE	RMSE, correlation coefficient, % of successful hypo and hyperglycemic predictions, continuous glucose error grid analysis (CGEGA)
Zarkogianni, 2013[97]	Dalla Man glucose absoption model + Dalla Man insulin absorption model+ Self Organizing Maps (SOM)	30, 60 min	-	✓	12	10 days	-	✓	✓	✓	-	Root-mean-squared error (RMSE) and correlation coefficient (CC), Continuous Glucose Error Grid Analysis (CG-EGA)
Zecchin, 2011[98]	Linear Prediction Algorithm +NN+ Dalla Man glucose absoption model	30 min	Matlab	✓	1 real 5 virtual	1 real 5 virtual	Freestyle navigator	✓	×	✓	-	RMSE, Time Gain, Clinical Usefulness J

(Continues)

Table 5. *(Continued)*

Author	Model Type	Prediction Horizon	Software/ Language	Patient Real data	# Patients	#Days or # hs	Monitoring Devices	Inputs			Performance Metrics Insulin therapy
								CGM/Blood Glucose data	Insulin therapy	CHO	Other Inputs	
Zecchin, 2012[21]	Linear Prediction Algorithm +NN (with meal announcement) + Dalla Man glucose absorption model	30 min	Matlab	✓	20 virtual 15 real	11 virtual 15 real	Abbott Navigator	✓	×	✓	-	RMSE, Time Gain, Energy of the second differences ESOD, J index
Zecchin,2014[99]	Dalla Man glucose absorption model + Jump NN	30 min	Matlab	✓	10	2-3 days	Dexcom Seven Plus CGM sensor	✓	×	✓	-	RMSE, Time Gain, Energy of the second differences
Alma, 2011[100]	Lehmann and Deutsch glucose absorption model + Berger plasma insulin concentration +Neural Network AutoRegresive External input	-	Matlab	×	1	5 days	Paradigm Real-time Continuous Glucose Monitoring System	✓	✓	✓	-	Identification error

TABLE 6 Percentage distribution of model types for hybrid prediction modeling approaches.

Meal absorption models	Percentage
Dalla Man	50%
Lehmann and Deutsch/Modified	35.7%
Hovorka	14.3%
Insulin kinetics models	Percentage
Berger	27.2%
Dalla Man	18.1%
Tarín	18.1%
Verdonk	18.1%
Cobelli	9.1%
Data-driven models	Percentage
Neural Networks	43%
Support vector regression	21.4%
Time series model	21.4%
Other models	14.2%

in this paper explicitly use the PH in their mathematical presentation of the model fitting and evaluation process. Generally speaking, an increase in the PH leads to a deterioration in the accuracy of the prediction for a given model. Nevertheless, the inclusion of meal information, physical activity, other input signals, and changing the model structure also affect the accuracy of a particular PH. Therefore, performance metrics should be understood as a function of PH, and the individual, clinician, or decision system must select the PH/accuracy relationship that best meets the patient's needs. In the reviewed studies, a PH range of 15–120 min is usually explored, and a 30 min PH is the most common value.

4.3 | Model outcomes

Predicting future BG concentration is the most popular approach when using predictive models, as demonstrated by the review presented in this paper. Nevertheless, there are some proposals that, instead of adapting a regression model, adapt classifiers to detect life-threatening conditions and facilitate decision making for both patients and physicians. For example, if there is a future outcome that lies beyond the established normal ranges, a pre-established recommendation could be followed. This approach means that an effective therapy could be established without an explicit BG estimation, and a more direct determination of key features and the class in which they fall could be used instead. These key features could be based directly on therapy doses and timing, nutritional content of food, exercise-related variables, and CGM signals or pre-defined event features. These events include food intake, hypoglycemia episodes, insulin dosage, and exercise, among others. The previous proposal raises the question: Should a model learn to predict future continuous values (regression problem) of BG or should it learn to map inputs to pre-established classes (classification

TABLE 7 Summary of internal models for control

Author	Model Type	Prediction Horizon	Platform	Patient Real data	# Patients	#Days or # hs	Monitoring Devices	Inputs				Performance Metrics Insulin therapy
								CGM/Blood Glucose data	Insulin therapy	CHO	Other Inputs	
Boiroux, 2012[101] **Schmidt, 2013**[102]	ARIMAX model	10 hours	Matlab/ Labview	✓	12	2 nights	-	✓	✓	✓	-	-
Cameron, 2012[103]	Multiple model predictor	1-5 hs	Matlab	✓	19	1 day	-	✓	✓	✓	Sleep announcement	mean error, root mean squared error (RMSE), and confidence level agreement
Capel, 2014[33]	Predictive rule-based algorithm (pRBA)	30 min	-	✓	10	12 hs	Paradigm REAL-Time	✓	✓	✓	-	Clarke error grid analysis
Fernandez, 2012[64]	ANN	-	Simulink	✓	20	30 days	Medtronic Minimed Guardian	✓	✓	✓	Exercise level : 0 for low, 1 for moderate, 2 for strong	RMSE Correlation coefficient
Gondhalekar, 2014[104]	ARX	45 min	-	✓	1	1 day	Dexcom G4 Platinum	✓	×	×	-	-
Herrero, 2012[105]	Pedersen	20 min	-	✓	12	24 hs	-	✓	✓	✓	-	-
Hovorka, 2014[106]	Hovorka	-	Florence closed-loop system	✓	16	6 weeks	FreeStyle Navigator	✓	✓	✓	-	
Leelarathna, 2014[107]	Hovorka	-	Florence closed-loop system	✓	17	16 days	FreeStyle Navigator	✓	✓	✓	-	-
Ly, 2014[108]	Minimal model	30 min	-	✓	12	6 days	Dexcom G4 Platinum	✓	✓	✓	-	-
Molenaar, 2010[109]	Autoregressive model	45 min	-	✓	2	1 day	-	✓	✓	✓	-	-
Quemerais, 2014[110]	Hovorka	3 hs	-	✓	12	2 days	DexCom G4	✓	✓	✓	-	-
Thabit, 2014[111,112]	Hovorka	-	-	✓	24	4 weeks	-	-	✓	✓	✓	-
Thabit, 2015[113]	Hovorka	-	-	✓	40	4 weeks	FreeStyle Navigator	✓	✓	✓	-	
Turksoy, 2014[114]	Constrained weighted recursive least squares	30 min	-	✓	30	3 days	Freestyle Navigator OmniPod Insulin Management System	✓	×	×	Energy expenditure (EE) and galvanic skin response (GSR)	-
Cameron, 2011[115]	Data driven linear model	300 min	-	×	9	36 hs	-	×	✓	✓	-	RMSE value

(Continues)

Table 7. *(Continued)*

Author	Model Type	Prediction Horizon	Platform	Patient Real data	# Patients	#Days or # hs	Monitoring Devices	Inputs				Performance Metrics Insulin therapy
								CGM/Blood Glucose data	Insulin therapy	CHO	Other Inputs	
Campetelli, 2013[116]	Adaptive predictive controller	60 min	Matlab	×	1	1 day	-	✓	✓	×	-	Control Variability Grid Analysis
Colmegna, 2015[117]	Transfer function model	-	Matlab	×	10	-	-	✓	×	×	-	-
Cormerais, 2013[118]	Modified minimal model	-	Matlab	×	10	1 day	-	✓	✓	×	-	Squared Error
De Paula, 2015[119,120]	Lehmann and Deutsch	-	-	×	-	-	-	✓	✓	✓	-	-
Eren, 2009[121]	ARMA Model	30 min	-	×	1	2 days	-	✓	×	×	-	normalized prediction error criterion
Gallardo, 2013[122]	Bergman Minimal Model, Sorensen Model	-	-	×	6	1 day	-	✓	✓	✓	-	-
Ghorbani, 2014[123]	Fractional order model	120 -150-180 min	-	×	1	4 days	-	✓	✓	✓	-	Average Glycemic Risk Index
Heusden, 2012[124]	discrete 3rd order control-relevant model	100 min	-	×	10	72 hs	-	✓	×	×	-	Fit value
Ilka, 2015[125]	Bergman minimal model	-	-	×	1	4 days	-	✓	✓	✓	-	RMSE
Lee, 2014[126]	a priori control relevant model	40 min	-	×	10	7 hours	-	✓	✓	✓	-	Square Sum of the state estimation Errors (SSE)
Lee, 2013[127]	discrete 3rd order control-relevant model	180-360 min	-	×	10	31 hs	-	✓	×	×	-	-
Leon , 2015[128]	ARX model	250 min	Labview	×	10	1 day	-	✓	✓	✓	-	-
Leon, 2012[129]	ANN	-	Matlab	×	2	4-5 days	Paradigm Real-time Continuous Glucose Monitoring System	✓	✓	✓	-	Tracking performance Tracking error
Liu, 2014[130,131]	Autoregressive exogenous input (NARX) neural network (NN) model	-	-	×	2	3 days	-	✓	×	✓	Heart rate HR (bpm)	-
Messori, 2015[132]	Linear model	1-3 h	-	×	100	-	-	✓	✓	✓	-	Prediction Mean Squared Error (PMSE)
Mythreyi, 2014[133]	Sorenson's model	100 min	Matlab	×	30	24 hs	Medtronic MiniMeds Guardian RT subcutaneous sensor	✓	✓	✓	-	-
Patek, 2012[134]	Dalla man	-	-	×	100	22 h	-	✓	✓	✓	-	-
Percival, 2011[135]	First-order-plus-time-delay-with-integrator transfer function models	6h	-	×	10	30 days	-	✓	✓	✓	-	FIT metric
Quiroz, 2010[136]	ARX model	-	Matlab	×	15	-	-	✓	✓	✓	Glucose and lactate	-

(Continues)

Table 7. *(Continued)*

Author	Model Type	Prediction Horizon	Platform	Patient Real data	# Patients	#Days or # hs	Monitoring Devices	Inputs: CGM/Blood Glucose data	Inputs: Insulin therapy	Inputs: CHO	Inputs: Other Inputs	Performance Metrics Insulin therapy
Semizer, 2012[137]	State space model- hovorka model- NN-nonlinear autoregressive moving average	100 min, 100 min, -, -	Matlab	×	1	2 days	-	✓	✓	✓	-	-
Soru, 2012[138]	Linear model	-	-	×	100	24 hs	-	✓	✓	✓	-	Sum of squares of differences.
Yan, 2013[139]	Time series predictor	30 min	-	×	10	7 days	-	✓	✓	×	-	HypoPer(%) HyperPer(%) SafePer(%) Mean BG
Zarkogianni, 2011[140]	Dalla Man glucose absorption model + Dalla Man insulin absorption model +RNN	30 min	Matlab	×	10	7 days	-	✓	✓	✓	-	RMSE Correlation coefficient continuous error grid analysis

problem)? Those classes could include normal and abnormal BG ranges or hypo/hyperglycemia risk, for example. From a clinical perspective, by having a continuous predicted BG value, the physician's decision support systems would be able to guide decisions according to past experience and observations of a patient's lifestyle, eating habits, and health/physical conditions that might affect both the diabetes manifestations and therapy response. Even if the model belongs to an automatic decision support system, the BG values could be accessed for further analysis. Conversely, a classification-based approach would map the input information directly to output classes, which would make it a less transparent model for guiding decisions. Nevertheless, from an engineering perspective, it is rather difficult to state whether one approach would be more or less demanding because different classification/regression techniques imply different costs in terms of computing effort, accuracy, and data management, among other factors. The accuracy of each approach is defined in a different way according to the data available. For example, in the classification approach, the accuracy depends on the total amount of correctly classified data and the total amount of available data, whereas the accuracy in a continuous BG predictor depends on the differences between the values predicted by the model and the actual values that are observed. Table 9 presents the percentage distribution of the type of outcomes over the total number of studies presented in the summary tables from previous sections, excluding the control-oriented models. Because the model outcome does not directly reflect the regression/classification approach, the percentage distributions for these two features are included in the same table.

TABLE 8 Percentage distribution of control-oriented models.

Control-oriented model	Overall percentage	Validated with clinical data (39.4% of the overall)
Physiological model	36.8%	53.3%
Data-driven model	55.2%	46.6%
Hybrid model	7.9%	0%

4.4 | Other signals

Some studies included additional input signals related to physical activity. In most of these cases, those signals were acquired using commercial physical activity monitors. For this review, the Sense wear band Pro3 was the most popular solution for acquiring data on skin temperature, heat-flux, and galvanic skin response and to estimate the energy expenditure (EE), which happens to be the most common additional input. Nevertheless, EE is highly dependent on the type of physical activity, and accurately determining EE is

TABLE 9 Distribution of model outcomes.

		Blood glucose	Risk/event
Approach	Regression	87%	6%
	Classification	0%	7%

still a major challenge. The possible under/over-estimation of EE naturally affects the overall accuracy of the BG prediction.

Other additional signals that are currently being added to the prediction approaches are heart rate, rate of perceived exertion (RPE), and sleep. In conclusion, the number of studies that include additional signals is low and does not cover the full range of possible inputs that have been demonstrated to be related to BG levels, such as emotional state and some illnesses.

4.5 | Performance metrics

The assessment of the prediction capability of the BG prediction models is a key factor because most of the model fitting processes are based on accepting the model once certain performance metrics are met. Those performance metrics represent the quality of the model prediction to a great extent and its general capability. The most popular performance metrics are always defined in terms of the error. Sum of squared errors (SSE) is a very common choice as well as mean squared error (MSE). Nevertheless, as stated in,[45] this metric does not treat errors differently for hypoglycemic events (which are more threatening) and hyperglycemic events, which is why some innovative metrics such as glucose-specific MSE (gMSE) have been proposed recently. This proposal adds some extra penalties whenever the error is potentially more dangerous from a clinical point of view, which is similar to Clark's error grid (CEG) methodology, and makes the predictive model more accurate in potentially harmful situations. CEG was used whenever the accuracy of the model was presented in a clinical perspective. According to this assessment method, each pair that coordinated the predicted value with its corresponding observed value fell into one of the five zones, and each zone had a fixed qualitative clinical accuracy significance. The continuous glucose error grid analysis (CG-EGA) is a variation of the CEG that accounted for the CGM data as opposed to BG data points at specific times.

Additionally, in recent studies, relative absolute difference (RAD) and coefficient of determination (CoD) are often calculated and reported as standard metrics. RAD computes the normalized absolute error between the measurement and prediction with respect to the measured value.[46] In contrast, the CoD reports the proportion of variation of the outcomes explained by the model. Another widely accepted metric is fit index, which represents the accuracy of the data fit, but it is used as a prediction assessment metric in the same manner.

Other performance metrics include temporal gain (TG), which is the average time gained for early detection of a hypo/hyperglycemia event predicted by the model. J index provides a measure of the 'clinical usefulness' or effective usability of the predicted glucose profile. This metric was defined in terms of the ratio of regularity of the predicted glucose profile and the temporal gain.[47] Finally, energy of the second order difference (ESOD) denotes the normalized sum of the squared second-order differences of predicted time series.[48]

For classification approaches, the most popular metrics are receiver operating curve (ROC), sensitivity, specificity, precision, accuracy, and Kappa statistics. Some studies, such as,[49] present an extensive analysis of a classifier for a clinical decision support system in terms of those metrics.

5 | CONCLUSION AND FUTURE WORK

This review presents the most recent works in BG prediction using different kinds of models, inputs signals, and performance metrics. These works are highly relevant to the AP development and improvement, because BG predictions are fundamental to perform a reliable control, but also to help physicians and patients to make better decisions regarding insulin therapy and life style. During the past few years, there has been a sustained increase in the number of studies involving AP prototypes using innovative closed-loop strategies that address key aspects of the general problem, for example, safety, intra-patient variability, and exercise, among other factors. The increasing interest in improving the closed-loop control has been reflected in the increased number of prediction model proposals. Although the control task is the strongest motivation for improving prediction models, improving models in terms of accuracy, properly estimating the effect of mixed meals, emotions, and exercise could also help enhance the current insulin therapies to take advantage of BG prediction. For example, programming hypo/hyperglycemic event alarms based on a more accurate prediction could facilitate better management of the disease in the short-term and make the predictive models more reliable for both clinicians and patients using CGM.

The observations made in this review indicate the lack of model strategies that include exercise and emotions effects for determining future glucose values and associated risks. Those factors are a daily reality for diabetic patients; therefore, it is very important to address them in future works to provide suitable closed-loop solutions. Intuitively, the use of additional inputs concerning exercise and emotions would lead to better predictions, although some findings suggest that their use should be carefully studied, in order to add meaningful information that indeed enrichens the models. Because physical activity monitoring devices and sensors are actively being upgraded, the inclusion of exercise related signals in future modeling strategies constitutes a very important research opportunity.

As far as the patient data is concerned, despite the exploration of machine learning techniques, many proposals lack clinical evidence because they are validated only with *in silico* data. Before a certain prediction technique is adopted as a control-oriented model, it must be validated using real

patient data from different scenarios. Therefore, future works, especially the ones introducing new machine learning techniques should be constructed and validated using clinical data. In this regard, although there are many new proposals for BG prediction, specifically data-driven models, most of the surveyed studies in control applications that used real patient data rely on physiological models or widely explored data-driven techniques such as NN. One reason for this is the low availability of public access clinical data, which constitutes a challenge for many researchers that do not have the resources to conduct clinical trials.

The review process allowed us to determine that the most popular outcome for the reviewed models was the continuous BG value, whereas the risks of hypo/hyperglycemia and other events were included in fewer approaches. This trend might exist because the majority of the critical decisions regarding therapy still rely on the estimated BG value. Likewise, in addition to the current trend in research focusing on closing the loop, performance comparisons between different BG or risk/event prediction techniques should be conducted at a larger scale. These comparisons should be made by several research groups and should use the same data from real patients, including additional factors such as physical activity and stress. Because all the comparisons are limited to the specific conditions of each author's data and software, there is no meaningful way to perform a comparative analysis to establish which proposals were the most effective in terms of accuracy.

Finally, among the surveyed works, there is a clear trend for model individualization because it allows adaptation of the model features and their relevancy on the prediction in terms of the particular physiology and lifestyle of the patient and obtaining predictions that are more accurate. Another essential challenge that demands substantial effort is the improvement of the PH without compromising the right level of accuracy, as well as the inclusion of meal and exercise detection and dynamic adaptation to the patient behavior and physiological changes.

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