

Recent Advances in Modeling and Prediction of Blood Glucose in Type 1 Diabetes

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Abstract

Accurate prediction and control of blood glucose levels are essential for the management of type 1 diabetes, where patients rely on exogenous insulin and are vulnerable to both hypoglycemia and hyperglycemia. The widespread adoption of continuous glucose monitoring systems, insulin pumps, and wearable devices has generated large volumes of physiological and behavioral data, creating new opportunities for computational modeling and intelligent decision support. This review surveys recent advances in glucose prediction and control models, with a primary focus on type 1 diabetes. We examine three major classes of approaches: mechanistic models based on physiological principles, data-driven machine learning methods, and hybrid or biology-informed frameworks that integrate mechanistic knowledge with learning-based techniques. We also discuss the growing role of multimodal data, deep learning architectures, and reinforcement learning for automated insulin dosing and adaptive control in artificial pancreas systems. Despite significant progress, important challenges remain, including handling noisy and heterogeneous data, improving predictive reliability and uncertainty quantification, and enabling real-time deployment on resource-constrained medical devices. Emerging strategies such as edge computing, efficient model design, and hardware–algorithm co-optimization may help bridge this gap. Continued progress will require interdisciplinary collaboration, standardized evaluation on public datasets, and rigorous clinical validation to translate emerging modeling approaches into practical tools that improve patient outcomes.

Introduction

Diabetes mellitus (DM) is a complex metabolic disorder characterized by chronic hyperglycemia, a condition marked by persistently elevated glucose levels in the bloodstream.¹ Hyperglycemia may arise from impaired insulin secretion, reduced insulin sensitivity, or a combination of both, leading to type 1 diabetes or type 2 diabetes. Type 1 and type 2 diabetes differ in their underlying causes and treatment strategies.²

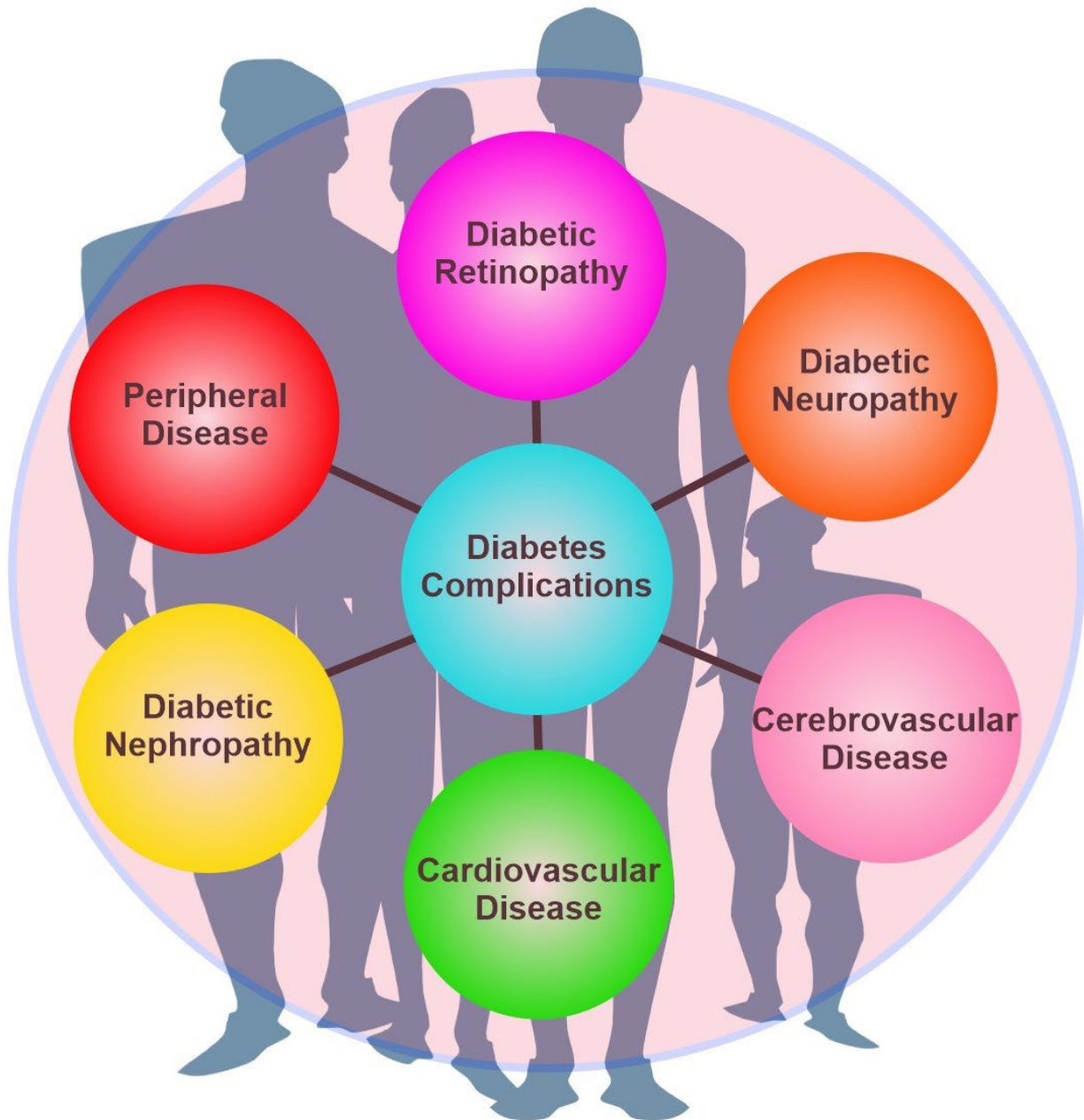
Type 1 diabetes (T1D) is an autoimmune disease characterized by the destruction of pancreatic β -cells, leading to an absolute deficiency of insulin. As a result, individuals with T1D require lifelong insulin therapy, delivered through multiple daily injections or insulin pumps, to maintain glucose control. In contrast, type 2 diabetes (T2D) is primarily associated with insulin resistance combined with a progressive decline in β -cell function. T2D is strongly influenced by genetic predisposition, lifestyle factors such as diet and physical inactivity, and metabolic conditions including obesity. Treatment for T2D typically begins with lifestyle interventions and oral

medications that improve insulin sensitivity or insulin secretion, and may eventually require insulin therapy in advanced stages. The disease develops progressively through multifactorial mechanisms that are not yet fully understood and manifests in diverse clinical presentations.^{3,4} Sustained elevation of blood glucose and the associated disruptions in carbohydrate, lipid, and protein metabolism have widespread adverse effects on multiple organ systems.⁵ As a result, diabetes can lead to severe clinical outcomes affecting the eyes, kidneys, heart, nerves, and brain (Figure 1). Because many of these complications are closely linked to prolonged hyperglycemia or dangerous hypoglycemia, maintaining glucose levels within a safe range is a central goal of diabetes management. However, glucose regulation in humans is influenced by numerous interacting factors, including meal composition and timing, insulin dosing and absorption variability, physical activity, stress, hormonal fluctuations, illness, and circadian rhythms. In addition, inter- and intra-subject variability, sensor noise, and delays in glucose measurement further complicate the accurate assessment and prediction of glucose dynamics.

Accurate monitoring and prediction of glucose dynamics are therefore essential for clinical decisionmaking.⁶ The development of continuous glucose monitoring (CGM) systems has significantly transformed diabetes care by enabling frequent, minimally invasive measurement of interstitial glucose levels.⁷ Compared with traditional finger-stick measurements, CGM provides high-frequency time-series data that capture short-term glucose variability and long-term trends. In addition, insulin pumps have enabled more precise and programmable insulin delivery, paving the way for closed-loop and artificial pancreas systems. These technological advances have created unprecedented opportunities to develop computational models for glucose prediction and control. However, the increasing availability of high-frequency physiological data also introduces new challenges. CGM measurements are often noisy, subject to calibration errors, and influenced by physiological delays between blood and interstitial glucose. In addition, glucose dynamics depend on numerous factors, including meals, physical activity, stress, and inter-individual variability, making accurate prediction difficult. Effective integration of heterogeneous data sources and extracting clinically actionable insights remain open problems. To address these challenges, a wide range of computational approaches has been proposed, broadly including mechanistic models based on physiological principles, data-driven machine learning models, and hybrid approaches that combine both paradigms. Mechanistic models, providing an abstract compartmental representation of the human body, often formulated as systems of ordinary differential equations, provide interpretability and physiological consistency but may suffer from parameter uncertainty and limited adaptability to the nonlinear biological dynamics. In contrast, purely data-driven models can capture complex patterns from large datasets but may lack interpretability and robustness outside the training distribution. More recently, hybrid modeling approaches combining these two, for example, scientific machine learning methods, have emerged to bridge this gap by embedding physiological knowledge into machine learning frameworks.⁸

In this review, we survey recent advances in glucose prediction and control models, with an emphasis on mechanistic modeling, data-driven methods, and emerging hybrid approaches. Although many of the discussed methods are broadly applicable, we primarily focus on type 1 diabetes, where accurate glucose prediction and automated insulin delivery play a central role in daily disease management. We discuss the strengths and limitations of different modeling paradigms, highlight key challenges in clinical deployment, and outline future research directions toward more reliable and physiologically consistent prediction and control systems.

Figure 1. Diabetes and the Associated Complications



Associated complications include cardiovascular and cerebrovascular complications, nerve damage (Neuropathy), kidney disease (Nephropathy), eye diseases (Retinopathy).

Mechanistic Modeling of Diabetic Glucose-Insulin Dynamics

Mechanistic models of type 1 diabetes describe glucose–insulin dynamics using compartmental formulations that provide a biologically motivated but simplified representation of physiological processes. In these models, major body components and pathways—such as plasma glucose, interstitial glucose, insulin in plasma and subcutaneous tissue, the gastrointestinal tract, liver, and peripheral tissues—are represented as interconnected pools or compartments that exchange mass according to governing kinetic laws. This abstraction enables the prediction of system responses

to perturbations such as meals, insulin delivery, and physical activity while maintaining a level of physiological interpretability. Importantly, because these models explicitly represent physiological processes and control inputs, they provide a natural foundation for designing and evaluating glucose control strategies, including closed-loop insulin delivery and artificial pancreas systems. We have summarized the popular mechanistic models in Table 1.

The foundation of physiological glucose prediction can be traced to the Bergman Minimal Model¹⁷ (Figure 2), which employed a parsimonious set of ordinary differential equations to characterize glucose–insulin interactions and estimate insulin sensitivity. While its simplicity facilitated analytical insight, the absence of anatomical structure limited its applicability to continuous prediction and control. To overcome this limitation, Sorensen¹⁸ proposed a comprehensive whole-body model with multiple organ compartments, including liver, muscle, and brain. Although this model contains a more comprehensive set of physiological parameters, the resulting high-dimensional parameter space led to difficult parameter identification and individual personalization for real-time use. Driven by the need to balance physiological meaningfulness with computational tractability in artificial pancreas applications, models with moderate complexity were subsequently developed. The Hovorka model¹⁹ and the UVA/Padova simulator²⁰ explicitly represent subcutaneous insulin absorption and gastrointestinal glucose transport, enabling short-term prediction and closed-loop control. The latter was further extended by Dalla Man et al.²¹ to incorporate glucagon dynamics and more than 30 state variables, and has since become the FDA-accepted *in silico* standard for pre-clinical evaluation (Figure 2). In addition to model structure, accurate glucose prediction depends on capturing the nonlinear delays and stacking effects associated with insulin delivery, as demonstrated by Wilinska et al.²² These phenomena underscore the sensitivity of ODE-based models to physiological processes that are not explicitly represented.

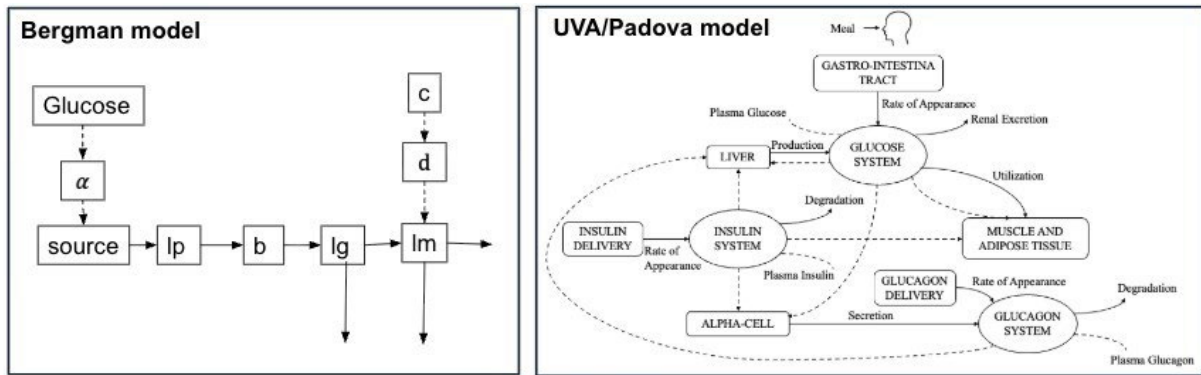
Apart from the major role meals play in glucose variation, physical activity represents another important source of glucose changes, especially in patients with type 1 diabetes, as it substantially alters insulin sensitivity and glucose utilization. To account for this effect, several extensions have been proposed to incorporate exercise physiology into ODE frameworks. In particular, Roy and Parker²³ extended the Bergman minimal model by introducing free fatty acid (FFA) dynamics, providing a mechanistic description of exercise-induced modulation of insulin action during sustained activity. Young et al.²⁴ designed an exercise-aware digital-twin–based decision support system (exDSS) that personalizes treatment recommendations for different types of exercise and significantly improves time-in-range while reducing hypoglycemia compared with both standard clinical guidelines and no intervention in largescale free-living simulations of individuals with type 1 diabetes. Deichmann et al.¹¹ develop and validate a personalized glucose–insulin model that explicitly incorporates the physiological effects of physical activity—such as insulin-independent glucose uptake, glycogen depletion, and prolonged changes in insulin sensitivity—enabling accurate simulation of real-world scenarios and *in-silico* evaluation of individualized treatment strategies for people with type 1 diabetes.

Table 1: Summary of Popular Digital Twin Methods in Reconstructing Glucose-Insulin Dynamics in Type 1 Diabetes (PA: Physical Activity.)

Article	Model Name	Method	Required Data
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Cappon et al. ⁹	Bergman minimal model + multi-module extension	MCMC	CGM glucose, meals, insulin
Colmegna et al. ¹⁰	UVa/Padova T1D model	MAP	CGM glucose, meals, insulin
Deichmann et al. ¹¹	Physiological model + activity module	Least squares	Glucose, meals, insulin, accelerometer
Goodwin et al. ¹²	Low-order transfer function model	Parameter optimization	Glucose, meals, insulin
Haidar et al. ¹³	Custom physiological model	MCMC	Plasma glucose, plasma insulin
Hughes et al. ¹⁴	Physiological model + residual model	Least squares + deconvolution	Glucose, meals, insulin
Visentin et al. ¹⁵	UVa/Padova T1D model	MAP	Plasma glucose, plasma insulin
Young et al. ¹⁶	Virtual population model (Resalat)	Similar trajectory matching	Glucose, meals, insulin, heart rate

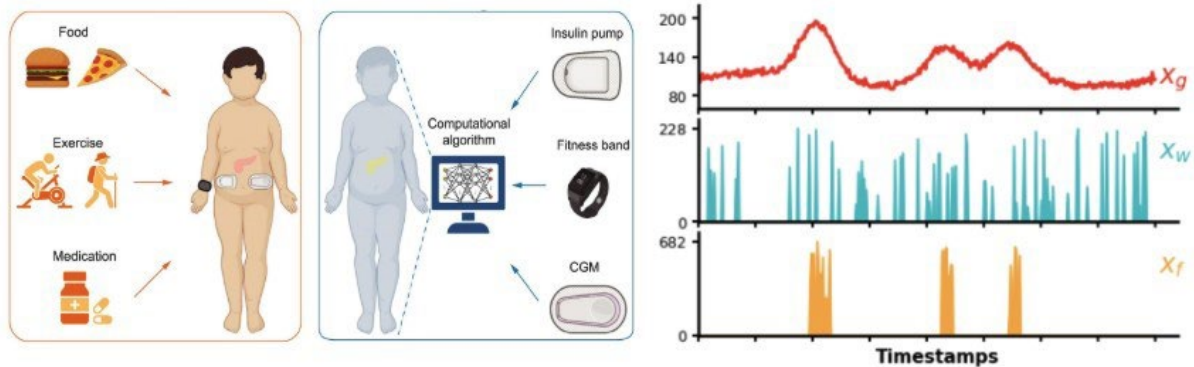
Figure 2. Glucose Prediction Models



Multimodal data for diabetic patients in the real world

Multimodal data for diabetic patients in the digital world

Visualization of multimodal data



(Top) Two examples of compartment models capturing the glucose-insulin dynamics. (Left, Bergeman model¹⁷; Right: UVA/Padova simulator²⁰). (Bottom) Demonstration of how to use multimodal data to build a digital twin of DM patients.

Data-Driven Glucose Prediction in Diabetes

Generally, blood glucose dynamics exhibit strong temporal correlation; many data-driven forecasting models hence predict future glucose levels by exploiting statistical dependencies in historical blood glucose (BG) time-series data, oftentimes the CGM data. Typically, these machine learning models take the past glucose within a time period, called the sampling horizon, and predict the glucose for another time period ahead in the future. This future time period is called the prediction horizon (PH), which typically ranges from 15 minutes to 2 hours. Early work by Sparacino et al.²⁵ demonstrated that simple machine learning-style time-series models, including adaptive autoregressive and polynomial predictors trained on continuous glucose monitoring data, can forecast near-future glucose levels in individuals with type 1 diabetes and anticipate hypoglycemic events about 20–25 minutes in advance. Yang et al.²⁶ developed adaptive-order ARIMA forecasting to address non-stationarity and improve the robustness of hypoglycemia alarms under changing conditions. Yu et al.²⁷ developed computationally efficient, sparsity-based adaptive kernel filtering algorithms for real-time glucose prediction from continuous glucose monitoring data, enabling accurate modeling of nonlinear and time-varying glycemic dynamics while reducing computational cost and maintaining robustness to measurement noise in both in-silico and clinical evaluations.

Recent advances in deep learning have enabled the development of more sophisticated models for glucose prediction in diabetes. Convolutional neural networks (CNNs) have been used to automatically extract local temporal patterns and reduce noise in physiological signals, while recurrent neural networks (RNNs), particularly long short-term memory (LSTM) networks, are well-suited for modeling temporal dependencies and long-range dynamics in glucose time-series data. These architectures have improved the ability of predictive models to capture nonlinear relationships and complex temporal behavior in continuous glucose monitoring data. Perez-Gandia et al.²⁸ proposed an artificial neural network-based method for online glucose prediction using recent continuous glucose monitoring data, demonstrating improved accuracy over autoregressive models while maintaining acceptable prediction delays across multiple prediction horizons (15–45 minutes). Mirshekarian et al.²⁹ investigated LSTM models with attention, showing that modeling longer temporal dependencies can improve forecasts, while also highlighting that performance gains can be sensitive to data characteristics and evaluation strategy. In addition, robustness and uncertainty became central themes because glucose-only predictors lack cross-modal redundancy to correct sensor artifacts. Martinsson et al.³⁰ proposed an end-to-end recurrent neural network (RNN) model for predicting blood glucose levels up to one hour ahead using only glucose history, achieving competitive performance on a public dataset while also estimating predictive uncertainty by modeling the output as a Gaussian distribution to aid interpretation and decision-making. More recent work prioritizes generalization and data efficiency. For example, Dave et al.³¹ evaluated predictive alerts under patient level and time-based validation and emphasized sustained event definitions to reduce false alarms. Deng et al.³² introduced transfer learning and data augmentation to improve patient-specific forecasting under limited data. Finally, benchmarking efforts have clarified the capability boundary of glucose-only models by contrasting univariate and richer-input settings,³³ while newer architectures reflect the broader shift toward attention/Transformer-style sequence modeling.³⁴ Overall, these studies suggest that glucose-only models provide reliable and easily deployable baselines for short-term prediction, but their performance is inherently limited when sudden glucose fluctuations are driven by unobserved factors such as meals, exercise, or stress.

Table 2: Multi-Modality Data for Diabetic Patients

Dataset	Age Group	Dx	Modalities	Coverage
DINAMO ³⁵	Adults to Older Adults	T1D+Healthy	CGM; Insulin; ECG; Food logs; Meal images	4–6 d
AZT1D ³⁶	Adults to Older Adults	1D	CGM; Insulin (Bolus/Auto); AID system data; Meal logs	6–8 w
OhioT1DM ³⁷	Adults to Older Adults	1D	CGM; Insulin; Physiological (HR/GSR); Meal info	8 w

Abbreviations: Dx = diagnosis; T1D/T2D = type 1/2 diabetes; ECG = electrocardiogram; HR = heart rate; GSR = galvanic skin response; AID = automated insulin delivery; w = weeks; d = days

Although many successful models have been developed to predict glucose levels using single-modality data—most commonly the patient’s historical glucose trajectory—such approaches are inherently limited by the restricted information available from a single source. Glucose regulation is influenced by multiple interacting factors rather than a single physiological variable, and is strongly affected by exogenous inputs such as physical activity, medication, dietary intake, and psychological or physiological stress. Recent advances in wearable and mobile health technologies have expanded glucose monitoring beyond glucose measurements alone. Real-time observation of relevant factors is now possible, including food intake patterns inferred from meal logs or images, insulin administration recorded by insulin pumps, and physical activity measured using fitness trackers and other wearable sensors (Figure 2 Bottom). To facilitate the development and benchmarking of glucose prediction algorithms, several publicly available datasets have been released in recent years. In addition to continuous glucose monitoring (CGM), these datasets may incorporate insulin dosing records, meal annotations, physiological signals from wearable devices, and other contextual information, enabling the study of multimodal and personalized prediction approaches. Table 2 summarizes representative publicly available datasets that are either widely used in the literature or provide richer multimodal data suitable for emerging machine learning and hybrid modeling methods.

Recent multimodality model development has increasingly focused on incorporating the aforementioned physiological knowledge. Zhu et al.³⁸ develop the hybrid CNN-LSTM model for glucose prediction, in which CNN layers are employed as powerful feature extractors to assist in noise reduction in modalities, and the LSTM layers are employed to capture temporal dependencies among heterogeneous signals. Following this architectural paradigm, Haleem et al.³⁹ employed a purely data-driven multimodal architecture based on stacked CNN and BiLSTM layers with attention mechanisms to implicitly learn complex non-linear mappings between structured multimodal inputs, such as CGM signals and health records, and future glucose levels, without relying on predefined mechanistic constraints. Similarly, Singh et al.⁴⁰ emphasized the extraction of statistical patterns over physiological explainability upon these architectural foundations. Neumann et al.⁴¹ suggested that this architecture alone is not enough for free-living conditions and proposed a transfer learning approach to address the issue of individual differences during exercise. Going beyond the conventional LSTM architecture and training approach, Farahmand et al.⁴² recently proposed a Transformer-based model (AttenGlucO), which utilizes the attention mechanism to achieve a higher level of predictive power than the existing RNN-based models, especially when the prediction period is longer. However, most existing

multimodal glucose prediction models remain purely data-driven and face challenges in integrating unstructured dietary information. To address this limitation, Wolber et al.⁴³ utilized multimodal large language models (MLLM) to convert food images into structured nutritional data, making it easier to incorporate dietary data into glucose prediction models.

Biology-Informed Machine Learning Glucose Prediction

Purely data-driven (black-box) models often achieve high predictive precision but lack physiological interpretability and generalizability. Conversely, purely physiological (white-box) models are limited by simplifying assumptions and the difficulty of parameter identification due to significant inter- and intra-subject variability. Hence, hybrid (grey-box) modeling approaches, also referred to as biology-informed machine learning models,⁴⁴⁻⁴⁹ have emerged to combine the interpretability of physiological models with the flexibility of data-driven methods for improved blood glucose (BG) prediction. Hybrid modeling strategies enhance BG prediction by integrating heterogeneous paradigms at various stages of the modeling pipeline, including data preprocessing, feature construction, and predictive learning. In practice, a substantial body of research combines physiological compartmental models with machine learning algorithms to leverage both mechanistic insights and data-driven flexibility. Early work demonstrated that physiological models can serve as structured intermediates for learning-based predictors. For instance, Plis et al.⁵⁰ proposed a hybrid approach that uses a physiological model to generate features for a patient-specific Support Vector Regression predictor, achieving glucose forecasts that outperform clinical experts and enabling the anticipation of a substantial fraction of hypoglycemic events about 30 minutes in advance, with most false alarms occurring in near-hypoglycemic ranges. Similarly, Georga et al.⁵¹ have proposed hybrid approaches for glucose prediction in type 1 diabetes that combine compartmental physiological models of insulin absorption, meal intake, and exercise with support vector regression (SVR). These methods, evaluated using free-living data, show that incorporating physiological and behavioral variables improves prediction accuracy and enables clinically acceptable forecasts of glucose dynamics.

Recently, deep learning has also been incorporated into hybrid models, enabling more flexible representations of nonlinear glucose dynamics while retaining physiological interpretability. Mougiakakou et al.⁵² utilized compartmental models to estimate the impact of food intake and injected insulin on glucose dynamics, integrating these estimates with historical BG measurements to train an artificial neural network. This framework was later extended using recurrent neural networks coupled with multiple compartmental subsystems capturing short-acting insulin, intermediate-acting insulin, and carbohydrate absorption dynamics.⁵³ Related efforts by Zecchin et al.⁵⁴ leveraged physiological modeling of meal effects to augment CGM-driven neural predictors and subsequently explored jump neural network formulations informed by meal-related physiological inputs. By embedding the loss of residue terms in ordinary differential equations, Deng et al.⁵⁵ developed a patient-specific insulin dosing framework that combines systems biology-informed neural networks to model glucose-insulin dynamics with deep reinforcement learning to automate insulin delivery, explicitly accounting for meal intake and physical activity using wearable-device data to improve next-generation artificial pancreas control. Hybridization has also been investigated beyond conventional feature-based learning. Briegel et al.⁵⁶ proposed a nonlinear state-space formulation combining compartmental glucose dynamics with neural network components to model individual BG trajectories, while Contreras et al.⁵⁷ introduced a personalized framework integrating physiological modeling with grammatical evolution-based genetic programming. More recent developments emphasize not

only predictive accuracy but also physiological coherence; for example, the H2NCM framework proposed by Zou et al.⁵⁸ incorporates a ranking-based causal loss to enforce physiological consistency alongside data-driven learning.

Conclusion

Despite substantial progress, several challenges remain, including handling noisy and heterogeneous data, improving predictive reliability, quantifying uncertainty, and enabling real-time control in closed-loop systems. A comprehensive understanding of existing modeling strategies, their assumptions, and their limitations is therefore essential. Mechanistic models, data-driven approaches, and hybrid frameworks each offer distinct advantages, yet none alone fully addresses the complexity of glucose regulation in free-living conditions. Mechanistic models provide physiological interpretability and a principled basis for treatment design and in-silico evaluation, but often require careful parameterization and may struggle to capture inter- and intra-subject variability. Data-driven models, particularly those based on deep learning, have demonstrated strong predictive performance but may suffer from limited generalizability, reduced interpretability, and sensitivity to data quality. Hybrid and biology-informed approaches represent a promising direction by combining physiological structure with flexible learning models, although their clinical validation and deployment remain ongoing challenges.

While multimodal data provide unprecedented opportunities for personalized prediction, effectively integrating heterogeneous data streams to assist the recommendation and dosage of treatment remains difficult,

but it is necessary to address this in order to help control the glucose volatility for diabetic patients. In parallel, reinforcement learning has emerged as a promising paradigm for automated insulin dosing and adaptive glucose control,^{55,59} as it enables treatment policies to be optimized through interaction with patient-specific models or simulators. Continued advances in safe and sample-efficient reinforcement learning may play a key role in the development of next-generation artificial pancreas systems moving toward diagnosis and treatment.

Future Directions

The growing use of deep learning models for glucose prediction and control also introduces significant computational demands. Modern architectures such as recurrent neural networks, transformers, and reinforcement learning-based controllers often require substantial memory and energy consumption,⁶⁰ which limits their direct deployment on resource-constrained devices such as continuous glucose monitoring, insulin pumps, or other embedded controllers. This gap between algorithmic capability and hardware feasibility has motivated increasing interest in edge computing and hardware-aware modeling strategies. Techniques such as model compression, pruning, quantization, and knowledge distillation could be explored to reduce computational overhead while preserving predictive performance. Continued advances in edge computing and efficient model design will be essential to enable the safe and practical deployment of next-generation intelligent diabetes management systems.

In summary, glucose prediction and control in diabetes remain active and rapidly evolving research areas at the intersection of physiology, control theory, and machine learning. Continued progress will depend on interdisciplinary collaboration, standardized benchmarking on public datasets, rigorous clinical validation, and advances in computational infrastructure to ensure that emerging modeling approaches translate into practical tools that improve patient outcomes.

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