Control Engineering Methods for Blood Glucose Levels Regulation

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Abstract: In this article, we review recently proposed, advanced methods, for the control of blood glucose levels, in patients with type 1 diabetes. The proposed methods are based on various techniques, such as predictive control, filters, and machine learning. Results have shown that the artificial pancreas may control blood glucose levels better than conservative insulin administration, while avoiding the risk of hypoglycemia or hyperglycemia. The most commonly used methods for controlling blood glucose levels are giving good results, while methods based on machine learning algorithms also offer promising performance. Nevertheless, there are numerous challenges in designing algorithms for the artificial pancreas, which need to be considered. The aim of this research is to provide an overview of the latest achievements in this research field, find the best solutions and, ultimately, improve them in the future.

Keywords: Artificial pancreas; continuous glucose monitoring; model predictive control; sliding mode control; Kalman filters; machine learning; neural networks; type 1 diabetes

1 Introduction

In the last few decades, the number of people suffering from diabetes has constantly increased. According to the latest information, about 422 million people worldwide have diabetes, while 1.5 million deaths are directly attributed to diabetes each year [1]. Diabetes is a chronic autoimmune disease that occurs when the pancreas produces little or no insulin, as in type 1 diabetes (T1D), or when the body produces insulin but cannot use it effectively, as in type 2 diabetes (T2D). This disease destroys pancreatic β-cells, which are responsible for the production of the insulin peptide hormone, which regulates blood glucose (BG) levels.

Although T2D makes up 90-95% of cases, our focus will be on T1D, which is also known as juvenile diabetes or insulin-dependent diabetes.

Due to the lack of internal insulin production, patients with T1D need treatment with exogenous insulin, which is necessary for their survival. However, it should be taken into account that external administration of insulin also has its risks. In case of hypoglycemia, the patient’s BG level is below 3.9 mmol/l (70 mg/dl), which can lead to a potential loss of consciousness, seizures, coma, or death. On the other hand, we have elevated BG levels or hyperglycemia, where the patient’s BG level is greater than 11.1 mmol/l (200 mg/dl). This can lead to serious damage to the patient's body system and long-term complications such as neuropathies, nephropathy, or cardiovascular disease [2].

The artificial pancreas (AP) is a closed-loop glucose controller that provides automatic delivery of insulin. It consists of a continuous subcutaneous insulin infusion (CSII) pump which communicates with the continuous glucose monitoring (CGM) system that measures the BG levels, to automatically deliver insulin when needed [3]. After calculating the required amount of insulin, the pump releases and delivers an appropriate dose to the patient’s body using a specific control algorithm.

The results showed that the AP may control the BG levels and reduce the risk of hypoglycemia better than the conservative insulin administration compared with conventional insulin therapy (open-loop control) [4]. Even though the recently proposed methods give good results, there are many challenges in designing algorithms that need to be considered. Glucose metabolic disorders can occur under the influence of various factors such as changes in diet, circadian rhythm, stress, alcohol consumption, unannounced physical exercise, menstrual cycle, chronic metabolic variations, or insulin sensitivity [5]. Also, there are additional factors such as urgent time requirements, unknown analytical relationships between custom parameters and measured values, and security issues, which present additional challenges for the development of the algorithms [6].

After a brief introduction of T1D and AP, in Section II we present a review of control methods based on model predictive control, Bayesian optimization, sliding mode control, proportional integral derivative control, linear parameter varying, iterative learning control, active disturbance rejection control, robust fixed point transformations, disturbance observer, terminal synergetic, state feedback linearization, and bioinspired AP. In Section III is given a brief review of a method for the identification of parameters, while in Section IV we review methods based on kernel and Kalman filters. In Section V we present a review of novel approaches based on machine learning such as unsupervised and supervised learning, clustering, artificial neural networks, and bioinspired reinforcement learning. Finally, we conclude with Section VI.

2 Approaches Based on Control Methods

In this Section, we present recently proposed methods for controlling and regulating BG levels, but also for preventing large delays in insulin absorption. One of the most commonly used methods is model predictive control, which is used to handle meal announcements [7], control BG levels, limit insulin infusion rates, and improve its delivery through the prediction horizon. The sliding mode control approach is a common method used for handling insulin stabilization, regulating glycaemia, and improving glucose regulation. A proportional integral derivative model-based approach that relies on physiological models that consider the operation of metabolism is also commonly used. Other approaches include Bayesian optimization, linear parameter varying, iterative learning control, robust fixed point transformations, active disturbance control, disturbance observer, terminal synergetic, state feedback linearization, and bioinspired AP.

2.1 Model Predictive Control Approach

Most of the proposed methods, which have been tested in clinical studies, are based on the linear model predictive control (MPC). MPC has shown that it is able to stabilize BG levels, but also to improve the bolus calculator for more efficient meal management [8-10]. Currently, used calculators depend on the correction between BG levels and insulin intakes. The reason is that a linear relationship between the size of the announced meal and the insulin bolus should be assumed [11].

While Chakrabarty et al. [12] used an observer-based MPC algorithm with the novel event-triggered communication (ETC) method for reducing sensor-controller transmissions, Cairoli et al. [3] improved MPC with a signal temporal logic (STL) method using the Hovorka compartment ordinary differential equation (ODE) model (Fig. 1). The STL was able to provide safe BG pathways allowing soft constraints, even during meal disturbances, while avoiding hypoglycemia and hyperglycemia.

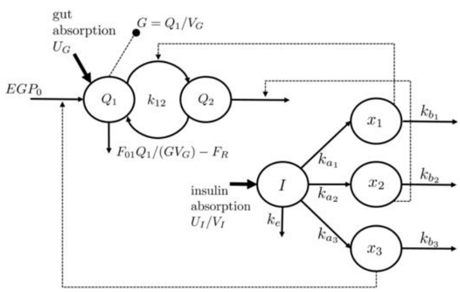

Figure 1

Scheme of the applied Hovorka compartment ODE model [3]

A recursive subspace-based empirical modeling algorithm based on the predictor-based subspace identification (PBSID) method was presented by Rashid et al. [13] to determine the linear dynamic model, while CGM measurements were used to determine the appropriate values for the plasma insulin concentration (PIC) bounds and risk indexes. The proposed method provided a stable, time-varying, and individualized state-space model for predicting CGM measurements, while keeping BG levels within the safe range, without meal announcement.

Boiroux et al. [14] presented the identified physiological model for describing the glucose-insulin dynamics for the nonlinear MPC (NMPC), where virtual patients were generated using the Hovorka model, as well as its parameter distributions, to test the identification procedure (Fig. 2). The results showed that the proposed method has the potential to be used in NMPC algorithms.

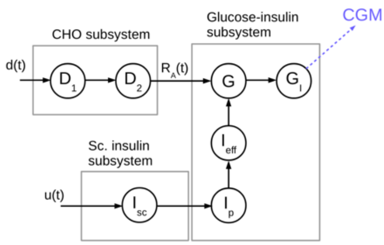

Figure 2
The proposed MPV model [14]

On the other hand, Embaby et al. [15] proposed a novel adaptive NMPC (AMPC) approach, consisting of a Cobelli model, a fuzzy logic controller (FLC), a feedforward neural network (FFNN), and an adaptation method, for BG levels regulation. The FLC was used to compute the amount of insulin infusion and maintain BG levels in a normal range, while the genetic algorithm was used to solve FLC optimization problems and improve search performance. The FFNN was used as the NMPC to manage the insulin delay between the time of injection and its interaction, while the adaptation method was used to adjust the compensation of the proposed system for physiological differences between patients. The results indicated that the time of increase in BG levels was in the normal range, causing less hyperglycemia.

To update the real-time control penalty parameters for a zone MPC (ZMPC) method, Shi et al. [16] applied a dynamic cost function. The proposed method gave a good performance for announced moderate meal-bolus, unannounced meals, and physical exercises, and improved BG levels, while the rate of insulin delivery was within a safe range, without the risks of hypoglycemia.

Chakrabarty et al. [17] implemented an embedded ZMPC method, using the fast adaptive memetic algorithm (FAMA) and the fast alternating direction method of multipliers (FADMM) algorithm to solve convex constraints of the linear MPC method. The generated closed-loop data were used to select the optimization algorithm and the appropriate setting parameters. The proposed method was able to maintain BG regulation and it was compatible with other embedded systems.

Abuin et al. [18] improved the robustness of a time-varying pulsatile ZMPC (pZMPC) with the linear time-invariant (LTI) method, by adding a circadian insulin sensitivity (S_I) scheme. The performance of the time-varying pZMPC was compared with respect to the linear time-invariant pZMPC-LTI, with the models configured with low and high S_I. The pZMPC-h achieved better performance during high S_I intervals by improving the analyzed metrics, while during the period of low S_I it produced hyperglycemic events.

Hajizadeh et al. [19] integrated a multivariable AP (mAP) method with a controller performance monitoring, assessment, and modification (CPMAM) system to analyze closed-loop behavior, modify MPC parameters, and automate insulin delivery systems during different meal amounts and exercise times (Fig. 3). The CPMAM system was proposed for the adaptive learning MPC (AL-MPC) and then applied in the mAP system for real-time estimation using various key performance indexes (KPIs). The control of BG levels was improved without the risk of hypoglycemia.

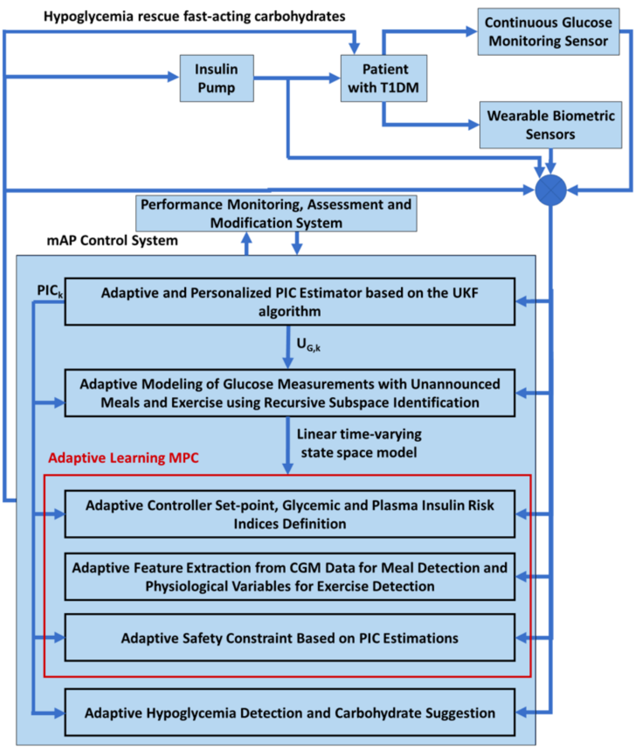

Figure 3

The proposed mAP method with integrated CPMAM system [19]

Reenberg et al. [20] presented a linear MPC-based algorithm for critically ill patients in an intensive care unit (ICU). The proposed algorithm is based on a stochastic continuous-discrete state-space model and represents a model of multi-input single-output (MISO) transfer function. To demonstrate the performance of the closed-loop algorithm, the Bergman minimal model (BMM), the Hovorka ICU Model, and the Chase ICU Model were used. Additional measurement delays, which are associated with glucose-sensing or enteral nutrition, have made it difficult to achieve strict glycemic control, which increases the risk of hypoglycemia.

Sun et al. [21] proposed a novel event-triggered MPC (ET-MPC) algorithm for personal insulin dosing to regulate BG levels and reduce computational requirements during unannounced meals and physical activity, performed according to pre-established criteria. The proposed method proved to be robust to a CGM data deficiency and signal loss, providing personalized assessment, while maintaining BG levels in a safe range without risk of hypoglycemia.

2.2 Bayesian Optimization Approach

A method based on the multivariate Bayesian optimization (BO) approach and the dynamic parameter selection module for solving the parameter adaptation problem was presented by Shi et al. [6]. The dynamic parameter selection module was used to determine the parameters, while the BO-based optimization module was used to automatically adjust the selected parameter and to optimize an unknown cost function, as is shown in Fig. 4. The efficiency and robustness of the proposed algorithm was verified in two scenarios. In the first case, the rate of insulin delivery was improved, while BG levels were reduced to the euglycemic range. In the second case, the algorithm was able to improve the duration of insulin delivery. Therefore, the proposed method may properly adjust the parameters to achieve their regulation, without the risk of hypoglycemia.

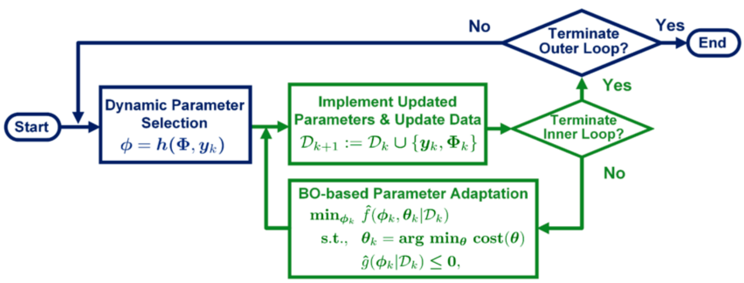

Figure 4

The proposed method based on the dynamic parameter selection module (blue) and the optimization module (green) [6]

2.3 Sliding Mode Control Approach

Beneyto et al. [22] applied an insulin-only controller using fast-acting carbohydrates (CHO) for the recommender system to improve the regulation of BG levels caused by unannounced physical activity. The proposed method consists of a proportional–derivative (PD) controller with insulin feedback (IFB) and a safety auxiliary feedback element (SAFE) layer, as shown in Fig. 5. The SAFE layer consists of insulin on board (IOB) constraints, a sliding mode reference conditioning (SMRC) block, and a low-pass first-order filter, while the CHO controller is based on a predictive quantified PD controller. Comparison of the original insulin-only controller and the combined insulin CHO recommender system showed that the novel combined system may reduce daily episodes of hypoglycemia and increase the rate of insulin delivery within acceptable limits.

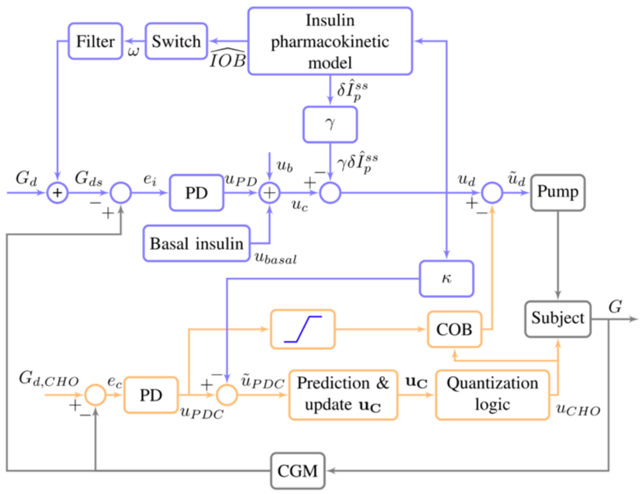

Figure 5

The proposed insulin-only controller (blue) with the CHO controller (orange) [22]

Moscardö et al. [23] used the SMRC method to improve the coordinated configuration (CC) control structure with IOB limitation for coordinated BG control levels (Fig. 6). A comparison of CC and CC-SMRC control structures was made based on meals, snacks, and exercise scenarios. Although the results of the proposed method were better during the exercise periods, than during the meals, in the most demanding exercise scenario, insulin delivery levels were not sufficient to prevent hypoglycemia.

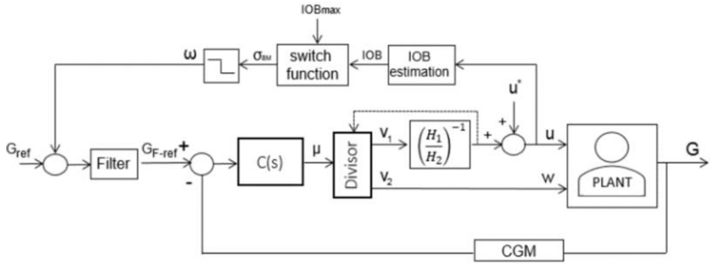

Figure 6
The proposed method based on the CC-SMRC controller [23]

Leyva et al. [24] presented methods based on the positive sliding mode control (SMC) and the control Lyapunov function (CLF), where the cascade structure of the physiological model was used to improve the rate and stabilize BG levels, while the compartmental mathematical model was used to reproduce glucose metabolism, and insulin and glucagon dynamics. Although both methods managed to solve the problem of stabilization, the CLF gave better results by improving the convergence rate and generating a continuous signal that prevented the accumulation of insulin.

A finite-time synergistic control approach based on a gain-scheduled Luenberger observer (GSLO) was presented by Alam et al. [25] to establish a closed-loop insulin delivery system (Fig. 7). A finite-time back-stepping SMC strategy was used to regulate glycemia, while the CLF law was systematically achieved in a recursive procedure. The intravenous glucose tolerance test (IVGTT) model (BMM), was considered to design a nonlinear control algorithm. The robustness of the system was achieved despite external disturbances, while postprandial hyperglycemia and hypoglycemia were suspended.

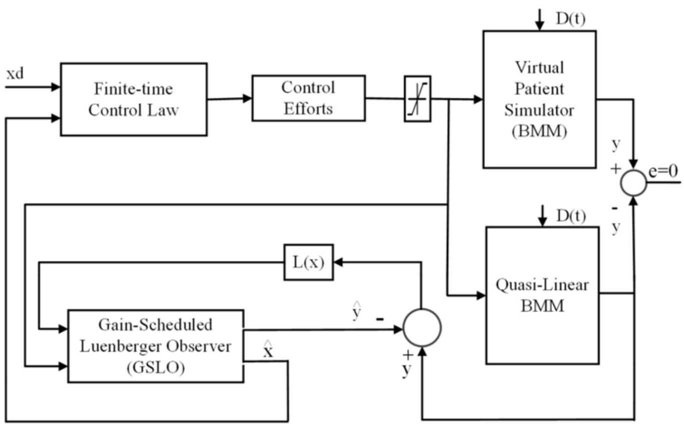

Figure 7
The proposed closed-loop control system based on the GSLO [25]

2.4 Proportional Integral Derivative Control Approach

Kushner et al. [26] presented a novel non-deterministic data-driven model with a proportional integral derivative (PID) based closed-loop system to predict patient reaction to the proposed system while maintaining BG levels control. The proposed model was able to efficiently adjust key controller parameters and improve BG levels control. To reduce insulin absorption delay, Barnes and Jones [27] applied the continuous intraperitoneal insulin infusion (CIPII) method based on the PID controller. The IMC-PID controller based on the internal model control (IMC) tuning method was introduced, which employs an inverter to realize the PID controller feedback. The time delay was adjusted using a first-order with time delay (FOPTD) model, along with a Pade approximation. The proposed controller was able to successfully control the oscillations of BG levels.

A novel PID control-based method, consisting of an adaptive weighted PID (AWPID) controller and a look-ahead PID with retrospective estimation error correction (LAPID-REC), was presented by Alshalalfah et al. [28] to prevent large delays incurred in insulin action and glucose sensitivity. In the AWPID approach, the proportional gain of the PID controller was rated based on the short-term CGM history, while in the LAPID-REC approach prospective estimates of future measurements were used to calculate the control action with retrospective estimation error correction. The safety and performance of standard PID control were improved, while the LAPID-REC approach showed high performance over existing techniques, especially under sensor noise, counteracting the long delays that occur in CGM and insulin action.

2.5 Linear Parameter Systems Approach

Eigner et al. [29] presented an advanced controller design method for a physiological model, using a theorem based on the linear parameter varying (LPV) and linear matrix inequality (LMI), which was applied on a modified version of the minimal model. The resulting controller used a state feedback type control rule due to the applicable LPV-LMI conditions.

Conversely, Colmegna et al. [30] extended the IOB safety loop method with an inner switched LPV (SLPV) controller and an outer sliding-mode safety layer (SAFE), to limit the controller’s action, during multiple meals and exercises. A mode selection algorithm was added to combine the hyperglycemia detection module with heart rate (HR) data for automatically adjusted controller settings (Fig. 8). The proposed method was able to effectively reduce the risk of hypoglycemia during the moderate exercise scenario.

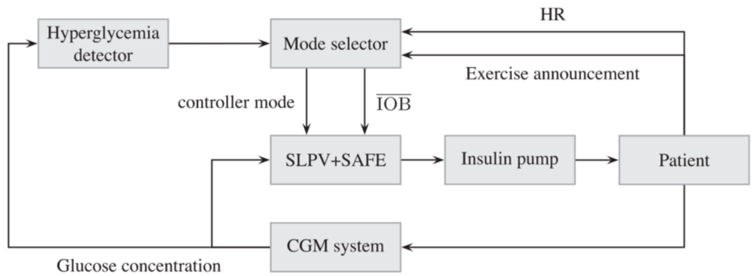

Figure 8
The extended method based on the SLPV and SAFE [30]

2.6 Iterative Learning Control Approach

Modifications of the Dalla Man metabolic model were proposed by Cescon et al. [31] by adding a long-acting insulin absorption model to facilitate validation of the control strategy for the multiple daily injections (MDI) therapy. A once-a-day iterative learning control (ILC) based dosing method was proposed to provide basal insulin delivery. Fig. 9 presents the proposed model of subcutaneous insulin absorption, with the amount of injected rapid-acting and long-acting. In the case of fasting, meal and meal with induced insulin resistance, the ILC performed better than the open-loop dose, by providing an appropriate amount of basal insulin.

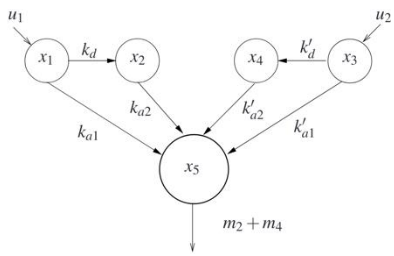

Figure 9
The proposed model of subcutaneous insulin absorption [31]

Cescon et al. [32] also proposed the ILC algorithm for the delivery of long-acting (basal) and rapid-acting (bolus) insulin, for patients following the MDI therapy (Fig. 10). The ILC updates basal therapy consisting of one long-acting insulin injection per day, while by updating the mealtime-specific insulin-to-carbohydrate ratio, the run-to-run (R2R) controller adjust meal bolus therapy. The results showed that the proposed method can provide robustness against random variations, resistance to protocol deviations while improving glycemic regulation over time.

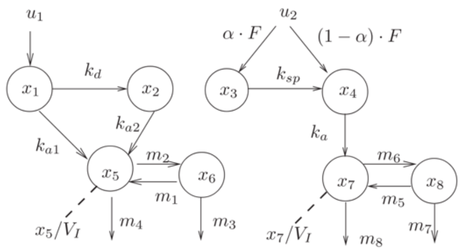

Figure 10
The proposed compartment model of insulin subsystem [32]

2.7 Robust Fixed Point Transformations Approach

To create a robust and adaptive control approach for BG levels control, Kovács et al. [33] presented a novel robust fixed point transformation (RFPT) based controller approach which consists of the two delay blocks corresponding to the cycle time of the digital controller (Fig. 11). Although the proposed method constantly absorbed external glucose concentration, it was able to interfere with the negative effect of inherent model uncertainties and measurement disturbances, while reducing the risk of hyperglycemia and hypoglycemia.

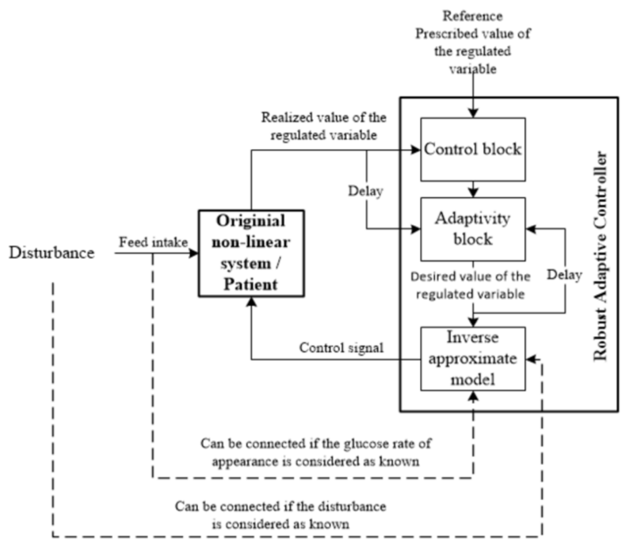

Figure 11
Scheme of the proposed RFPT method [33]

2.8 Active Disturbance Rejection Control Approach

Cai et al. [34] proposed an active disturbance rejection control (ADRC) method by adding IOB and insulin delivery constraints to ensure the safety of the control algorithm. The controller consists of the ADRC module (composed of tracking differentiator, extended state observer (ESO) and nonlinear feedback) and the constraints module (composed of the IOB, non-negative and maximum input constraints). The proposed method was able to achieve satisfactory performance of BG regulation and insulin delivery rate without the risk of hypoglycemia.

2.9 Disturbance Observer Approach

Sanz et al. [35] used disturbance observer (DOB) to estimate the effect of unannounced meals, and feedforward compensator for the insulin pharmacokinetics, to control postprandial BG levels of patients. The results showed that the DOB may successfully estimate and counteract the effect of meals and the sudden drops in BG levels while avoiding hypoglycemia. For unannounced meals with high CHO content, a median time-in-range was 80% with large intra-subject variability, while for announced meals the median time-in-range was increased up to 88%, even considering severe bolus mismatch and CHO counting errors.

2.10 Terminal Synergetic and Feedback Linearization Controller Approaches

Babar et al. [36] extended BMM (EBMM) with the nonlinear terminal synergetic controller (TSC) and the state feedback linearization based controller (SFC), while the Lyapunov theory was used to provide asymptotic stability of the proposed controllers. White noise was added to the EBMM, and then the performance of each controller was evaluated to check their ability to withstand disturbance. Compared to other controllers, the TSC gave the best results with about zero steady-state error, lesser settling, convergence time, with acceptable overdrafts.

2.11 Bioinspired AP Approach

A bi-hormonal bioinspired AP (BiAP) controller was extended with a novel hybrid hormonal-insulin sensitivity glucose (InSiG) by Güemes et al. [37], to determine insulin and glucagon doses with the coordinated bi-hormonal BiAP controller, and to determine the desired S_I from CGM with a standard PD (sPD) controller. After comparing the InSiG controller and the coordinated bi-hormonal BiAP controller, the results showed that the InSiG controller was able to improve BG levels control while maintaining within the target range without the risk of hypoglycemia.

Although, the proposed controller was able to reduce the delivered dose of insulin and significantly reduce the glucagon dose, the relationship between the magnitude of nervous system stimulation and the S_I dynamics remained unknown.

3 Approaches Based on Sensitivity Analysis

Staal et al. [38] investigated methods to improve recognition and estimation of the most appropriate model parameters to reduce the parameters of critical models. The identification of nonlinear state-space model parameters was also investigated. The nonlinear observability rank condition (NORC) was used for structural, while sensitivity analysis and the Fisher information matrix (FIM) were used for practical identifications. A simplified model, derived from CGM, scarce self-monitoring of BG (SMBG), meal and insulin data, showed to be useful for the AP applications.

4 Approaches Based on Filters

In this Section, we review recently proposed methods based on extended Kalman and kernel filtering algorithms for detecting unannounced meals or missed meal announcements, real-time insulin pump faults detection, insulin infusion rate regulation, and BG levels control.

4.1 Extended Kernel Filter

To improve computational efficiency in online glucose prediction, Yu et al. [39] extended an adaptive kernel filter (KRLS) algorithm with the sparsification criteria. The KRLS algorithm was combined with the approximate linear dependency (ALD) and the surprise criterion (SC) to design an online sparse ALD-KRLS and SC-KRLS algorithms. The proposed online adaptive method proved to be insensitive to abnormal or inaccurate CGM measurements and it was adaptable to prediction models. Thus, it could effectively reduce the computational load and regulate the time delay in the nonlinear dynamics of glucose.

4.2 Extended Kalman Filter

Fushimi et al. [40] proposed the integration of the automatic switching signal generator (SSG) into the automatic regulation of glucose (ARG) algorithm and an advanced version of the switched linear quadratic Gaussian (SLQG) controller, to regulate the basal insulin infusion rate. The SSG module, based on the KF, was used to generate a filtered version of BG levels. Despite the large delay in selecting the post-meal controller mode, the proposed algorithm had efficiency of 83.3% in terms of meal detection, it was able to regulate the basal insulin infusion rate and generate insulin feedback during unannounced meals, without significantly increasing the risk of hypoglycemia or hyperglycemia.

A novel kernel function for the Gaussian process was proposed by Ortmann et al. [2] by improving the existing MPC controller and solving the problem of noise in measurements during unannounced meals. The unscented KF was used to assess the condition, extract data, and change S_I. The extracted data were processed using a Gaussian filter to predict future effects, while the MPC optimized the received data to calculate the volume of insulin injections, as shown in Fig. 12. The collected training data became insensitive to noise after the application of the Gaussian process, making the controller insensitive to unannounced meals.

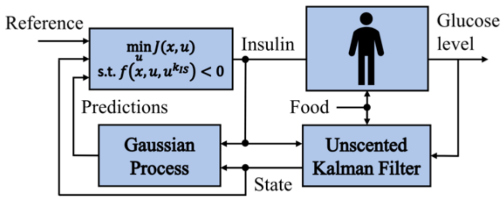

Figure 12

The proposed method based on the unscented KF, Gaussian process, and MPC [2]

To present a novel adaptive model-based algorithm for detecting unannounced meals, Fathi et al. [41] used a linear KF to compute the evaluation of BG measurements, applying the statistical generalized likelihood ratio test under the null hypothesis, to estimate the impact of an unannounced meal on BG levels. The proposed algorithm managed to successfully detect unannounced moderate meals 96.29% of the time, without false positives.

Boiroux et al. [42] presented a model for nonlinear estimation of the maximum probability of estimated parameters, where the state covariance matrix and its gradient were calculated using explicit Runge-Kutta schemes, while the method implementation was verified by using a numerical example for nonlinear parameter estimation.

On the other hand, Kovács et al. [43] applied advanced LPV, linear matrix inequality (LMI), tensor product (TP) model transformation, and extended KF (EKF) control methods, to guarantee strong safety control of BG levels. An extension of the minimal model was applied to simulate the glucose-insulin dynamics and glucose and insulin absorption. The control structure of the TP model was combined with LMI based optimization and LPV control (TP-LMI-LPV controller), EKF, and D/A converter (Fig. 13). The proposed controller was able to intervene effectively during the process and provide appropriate control actions, thus satisfy predefined requirements while avoiding hypoglycemia.

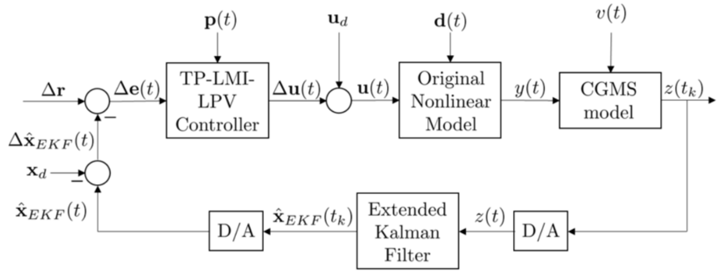

Figure 13

Scheme of the proposed method with the TP-LMI-LPV controller and mixed EKF [43]

Kovács et al. [44] also introduced the dual EKF (DEKF) framework to estimate the state variables and model parameters at the same time by utilizing the discrete LPV methodology. A nonlinear model was applied to the quasi-LPV (qLPV) model (derived from the nonlinear Cambridge T1DM model) to map the noise effects that occurred during the application of the CGM system. The results showed that the proposed method was able to estimate state variables with good accuracy.

Meneghetti et al. [45] proposed a method for real-time insulin pump fault detection and missed meal announcements to improve the safety of the AP system architecture. The proposed method consists of an offline model and a predictor module, and an online prediction and alert module, as shown in Fig. 14. The confounding factor introduced by meals was tested to detect insulin pump faults ability. The proposed method was able to improve patient feedback, providing various alarms and effectively preventing pump malfunctioning due to user errors, without causing hyperglycemic events.

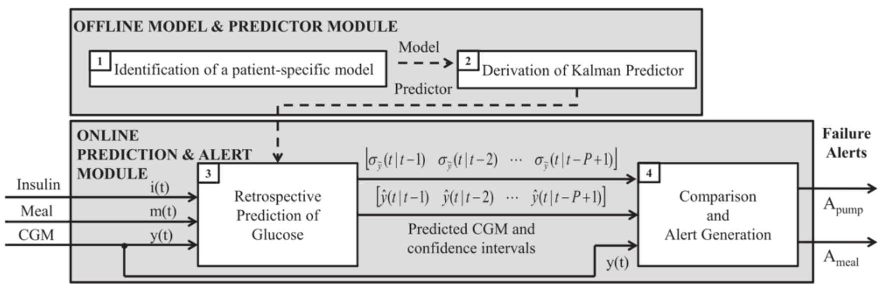

Figure 14

The proposed fault detection method [45]

Sala-Mira et al. [46] compared the LPV dual KF, the LPV joint KF, and the nonlinear sliding mode observer (NSMO), to evaluate the effect of observer structure on estimation performance. Observers were composed of the Hovorka and Identifiable Virtual Patient (IVP) models, which represents a compromise between the Bergman and Hovorka model in terms of structural complexity and accuracy. Analysis of variance (ANOVA) and multiple comparisons were used to assess the individual factors. Based on PIC and rate of appearance, the results showed that proportions of variance were low for each factor, indicating a small difference between observer structures.

5 Machine Learning Algorithms

In this Section, we review recently proposed Machine Learning methods [47] for automatic insulin infusion, insulin pump failure detection, physical activity prediction, overnight glycemic control quality prediction, online prediction of BG levels and its stability, gradient problems, but also to improve prediction accuracy and robustness of previous methods. The proposed methods are based on unsupervised and supervised learning, clustering, artificial neural networks, and bioinspired reinforcement learning.

5.1 Algorithms Based on Unsupervised Learning

An unsupervised model-free approach based on data-driven techniques for anomaly detection was presented by Meneghetti et al. [48] to detect insulin pump malfunction. Machine learning (ML) methods for detecting anomalies, using local outlier factor (LOF), connectivity-based outlier factor (COF), and isolation forest (iF/iForest), were applied to the extracted set of features. To overcome correlations between time-closed samples, the for time series data (4TSD) procedure was applied to LOF and COF. The optimal parameter configuration for LOF and iForest was able to provide satisfactory detection performance while maintaining high accuracy. After comparison with the traditional multivariate control chart (MCC) method, the results showed that COF outperformed other methods, while LOF and iForest offered comparable performance. Despite the good performance, iForest has been shown to be prone to errors and instabilities.

5.2 Algorithms Based on Supervised Learning

Güemes et al. [49] proposed a novel data-driven method for predicting the overnight quality of glycemic control, by analyzing a small data set from CGM measurements, meal intake, and insulin bolus. To classify the overnight quality of glycemic control, binary classification algorithms such as random forest classifier (RFC), artificial neural networks (ANN), support vector machine (SVM), linear logistic regression (LLR), and extended tree classifier (ETC) were used. The proposed method was able to predict overnight BG levels within the target range with reasonable accuracy of 0.7. However, a larger data set is needed to fully validate the proposed method.

The solution based on supervised ML, to predict future BG levels, was proposed by Eigner et al. [50]. To prove the concept, TensorFlow and Keras frameworks were used with the AIDA diabetes simulator for data generation. The results showed that the proposed method gives an accurate prediction of BG levels within acceptable limits, with overall accuracy of 0.879, taking into account that the accuracy of predicting normal BG levels should be improved.

Dénes-Fazakas et al. [51] applied synthetic data generated by an extended open-source version of the Jacobs T1DM simulator, which employs the Cambridge model and contains an embedded physical activity sub-model. To predict the presence of physical activity, a logistic regression, AdaBoost classifier, decision tree classifier, Gaussian naive Bayes, the k-nearest neighbor classifier (k-NN), SVM, RFC, and multilayer perceptron networks (MLP) were used, and then trained classifiers were applied to all feature vectors of the test data set. Decision tree, k-NN, and RFC gave the best results, with overall accuracy of 0.91, 0.95 and 0.98. Other models may be also suitable, but they need additional mechanisms to avoid false positives.

5.3 Algorithms Based on Clustering

Montaser et al. [52] proposed a seasonal autoregressive integrated moving average (SARIMAX) model, an extended version of the non-seasonal ARIMAX model, and examined the possibility of preprocessing original CGM measurements to obtain sets of similar glycemic profiles (clusters) to identify a seasonal model of postprandial periods. Using the fuzzy c-means (FCM) clustering method, the number of sets and corresponding features of the BG profile was obtained in the modeling step, while the Box-Jenkins methodology was used to identify the seasonal model for each cluster set. The results showed that using online BG predictions through a global seasonal model may reduce the risk of hypoglycemia or hyperglycemia.

A data-driven approach for determining the final set of daily CGM profiles (motifs) was presented by Lobo et al. [53] so that almost every generated daily profile could be matched with one of the motifs from the final set. A training data set was used to identify candidate motif sets, while a validation data set was used to select the final set. The results showed that robustness was successfully established while matching with representative daily CGM profiles in the test data set was 99.0%.

5.4 Algorithms Based on Artificial Neural Networks

Aliberti et al. [54] applied a nonlinear autoregressive (NAR) neural network and long short-term memory (LSTM) on BG signals, to improve prediction accuracy and robustness of previous methods (Fig. 15). NAR was used to solve BG stability problems, while LSTM was used to explode and disappear the gradient, as well as to maintain long-term information over time.

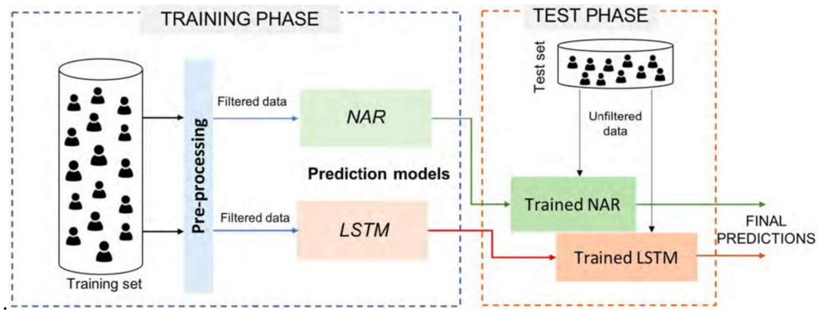

Figure 15
The proposed solution with applied NAR and LSTM methods [54]

Compared to the recurrent neural networks (RNNs), the LSTM was more resistant to the exploding and vanishing gradient problems. The NAR model gave good prediction accuracy only for a short-term period (30-minute prediction horizon), while the LSTM exhibited very good performance for predicting both short-term and long-term BG levels (60 minute prediction horizon).

Li et al. [55] proposed a convolutional RNN (CRNN) method that consists of a multilayer convolutional neural network (CNN), a RNN layer with LSTM cells, and fully connected layers, to predict BG levels. The CNN was used to extract features or patterns of the multidimensional time series, while a modified RNN was used to analyze the previous sequential data and predict BG levels. The results showed that the proposed method was able to predict BG levels with high accuracy.

To predict BG levels, Zhu et al. [56] proposed a novel deep learning framework with the edge inference on a microcontroller unit (MCU) embedded in a low-power system, by using CGM measurements and the RNN that builds on LSTM (Fig. 16). Collected data from wearable devices were uploaded to the server. Then, a well-trained deep neural network (DNN) was embedded in the MCU and further implemented in wearable devices to help in decision making. The proposed framework was agnostic to the types of neural networks employed and learning targets, and it showed a good BG prediction performance. Therefore, it could be applied for the realization of various tasks on wearable devices, such as event detection (e.g. meals, exercise, illness, errors) and glucose regulation.

A novel deep reinforcement learning (RL) model for optimizing single-hormone (insulin) and dual-hormone (insulin and glucagon) delivery was presented by Zhu et al. [57].

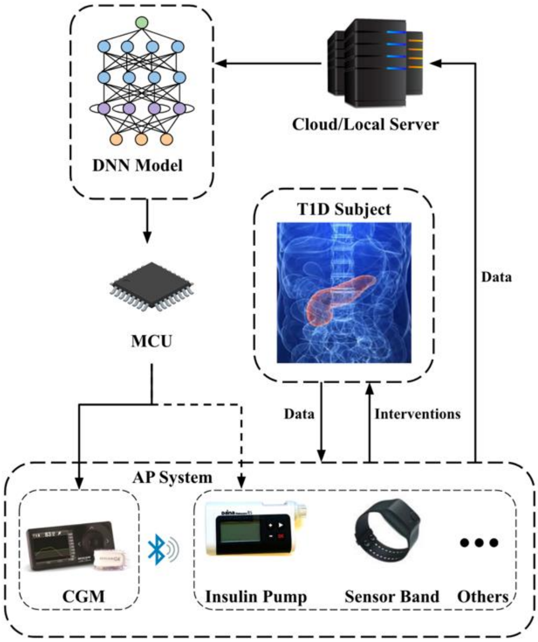

Figure 16
The system architecture of the proposed DNN-based method [56]

Dilated RNNs were applied to the structure of double deep Q-network (DQNs), to develop personalized models through a two-step framework that involves transfer learning (Fig. 17). Proposed methods gave good control of BG levels with a significant reduction in hypoglycemia making the use of deep RL a sustainable approach to closed-loop BG control, with the best TIR score of 93%.

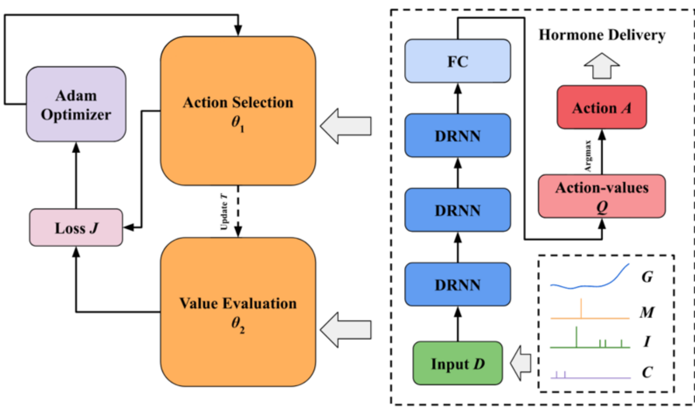

Figure 17
Scheme of the proposed double DQN method [57]

5.5 Bioinspired Reinforcement Learning

A novel AI-based bioinspired RL approach for automated insulin infusion was proposed by Lee et al. [58], to maintain BG levels and robustness of the CGM sensor. The layer-wise relevance propagation (LRP) method was used to analyze input-output relevance and define the rate of insulin infusion. The proposed LRP method was able to provide information about insulin distribution, making the decision step by step, without distinguishing between basal and bolus insulin, which is similar to the principle of human β-cells. A trained policy could automatically maintain fasting BG levels after unannounced meal intake without a prediction model, automatically respond and regulate postprandial glucose, provide robustness with respect to CGM sensor noise, achieve a mean BG level in the normal range of 89.56%, and without the risks of hypoglycemia.

Conclusions

In this work, we reviewed various recently proposed methods, based on predictive control, sensitivity analysis, filters and machine learning algorithms, intended for regulating insulin delivery and controlling BG levels in patients with T1D. The control approaches included control methods based on model predictive control, Bayesian optimization, sliding mode control, proportional integral derivative control, linear parameter varying, iterative learning control, active disturbance rejection control, robust fixed point transformation, disturbance observer, terminal synergetic controller, state feedback linearization based controller and bi-hormonal bioinspired AP. Combining common control methods has shown good results in controlling BG levels while maintaining a safe range. The proposed methods based on the Kalman filter, combined with different control methods, gave good results in state variables and model parameters estimation.

Other successful approaches included methods that are based on machine learning techniques, such as, unsupervised and supervised learning, clustering, artificial neural networks and bioinspired reinforcement learning. The Long Short-term Memory has shown very good performance for predicting short-term and long-term BG levels, while combining with recurrent neural networks could predict BG levels with high accuracy. Novel, deep reinforcement machine learning algorithms, promise improved performance for larger experimental datasets, with the support of powerful hardware platforms. Clustering methods gave good results in predictive modeling, decision support, and automated systems, while bioinspired reinforcement learning was able to provide insulin distribution information, automated postprandial regulation, sensor robustness, and fully automate BG levels control for unannounced meals. For the case of insulin infusion, bioinspired reinforcement learning made the decisions step by step, without distinguishing between basal and bolus insulin, similar to the principle of the human β-cells.

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