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Blood Glucose Level Prediction for Type 1 Diabetes Mellitus: Ensemble Approaches Utilizing Direct and Iterated Methods for Multi-Step Forecasting

Dissertation thesis

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Declaration

I hereby declare I have written this doctoral thesis independently and quoted all the sources of information used in accordance with methodological instructions on ethical principles for writing an academic thesis. Moreover, I state that this thesis has neither been submitted nor accepted for any other degree.

In Prague, February 2024

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Abstract

This thesis, titled "Blood Glucose Level Prediction for Type 1 Diabetes Mellitus: Ensemble Approaches Utilizing Direct and Iterated Methods for Multi-Step Forecasting," presents a comprehensive study on the prediction of blood glucose levels in patients with Type 1 Diabetes Mellitus. Our work is based on both *in vivo* data and simulated datasets. The inputs to our models included blood glucose levels, basal insulin, bolus insulin, carbohydrate intakes, and the hour of the day.

We applied both direct and iterated versions of two robust prediction algorithms: the Linear Model (LM) and the Support Vector Regression (SVR). We proposed and evaluated three ensemble frameworks: the Linear meta-model, the Bagging meta-model, and the Boosting meta-model. These methods have garnered significant interest from the scientific community due to their ability to improve the accuracy of predictions by combining the strengths of multiple models.

For the bolus insulin, we used it as an impulse signal and simulated its absorption using an open compartment model. This approach allowed us to capture the dynamics of insulin absorption in the body, which is crucial for accurate blood glucose level prediction.

Our results showed that the iterated Bagging meta-model, combined with an open compartment model for bolus insulin simulation, outperformed the other ensemble frameworks. Specifically, when applied *in vivo* for patient 2, the iterated Bagging-meta model demonstrated superior performance. The Root Mean Square Error (RMSE) was recorded at 15.47 mg/dL for a 60-minute ahead prediction horizon, and the percentage in Region A according to Clarke's Error Grid Analysis (CEG_A) was found to be 95.37%. This finding underscores the potential of ensemble methods and compartment models in improving the accuracy of blood glucose level predictions.

The thesis is organized into seven chapters. Chapter 1 provides an overview of the thesis, including the problem statement, objectives, and contributions of the research. Chapter 2 reviews relevant literature on diabetes management, blood glucose prediction, and ensemble methods. Chapter 3 presents the research objectives and the contribution to diabetes management and healthcare. Chapter 4 details the implementation, experimental setup, and data analysis. Chapter 5 describes the direct versus iterated methods for blood glucose level multi-step ahead forecasts. Chapter 6 concludes the thesis by summarizing key points and emphasizing the research's contributions. Chapter 7 summarizes the basic outcomes, provides insights for further extensibility, and offers recommendations for future work.

In conclusion, we believe that our findings will pave the way for future research in this area, particularly with regard to the use of ensemble methods, compartment models, and the incorporation of various physiological signals as inputs to the models.

Keywords: ensemble framework, diabetes mellitus, blood glucose level prediction, insulin pump, artificial pancreas, direct method, iterated method

Abstract

Tato práce s názvem „Predikce glykémie pro Diabetes Mellitus 1. typu: Kombinace prediktivních modelů využívajících přímé a iterované metody pro předpovídání více kroků dopředu," uvádí a komplexní studie o predikci hladiny glukózy v krvi u pacientů s diabetem 1 Mellitus. Naše práce je založena jak na datech in vivo, tak na simulovaných souborech dat. Vstupy do našeho modely zahrnovaly hladiny glukózy v krvi, bazální inzulín, bolusový inzulín, příjem sacharidů a hodina dne.

Použili jsme jak přímou, tak iterovanou verzi dvou robustních predikčních algoritmů: Lineární Model (LM) a podpůrná vektorová regrese (SVR). Navrhli jsme a vyhodnotili tři souborové rámce: lineární metamodel, metamodel pytlování a posilování meta-model. Tyto metody si získaly značný zájem vědecké komunity díky jejich schopnosti zlepšit přesnost předpovědí kombinací silných stránek více modelů.

U bolusového inzulinu jsme jej použili jako impulsní signál a pomocí simulovali jeho absorpci model s otevřenou přihrádkou. Tento přístup nám umožnil zachytit dynamiku inzulínu vstřebávání v těle, což je klíčové pro přesnou předpověď hladiny glukózy v krvi.

Naše výsledky ukázaly, že iterovaný metamodel Bagging v kombinaci s otevřeným partment model pro bolusovou simulaci inzulinu, překonal ostatní souborové rámce. Konkrétně, když byl aplikován in vivo u pacienta 2, iterovaný Bagging-meta model demon- deklarovaný vynikající výkon. Root Mean Square Error (RMSE) byl zaznamenán v 15.47 mg/dl pro 60minutový předpovědní horizont a procento v regionu A podle Clarke's Error Grid Analysis (CEGA) bylo zjištěno na 95.37 %. Toto zjištění podtrhuje potenciál souborových metod a kompartmentových modelů při zlepšování přesnosti krve předpovědi hladiny glukózy.

Práce je rozdělena do sedmi kapitol. Kapitola 1 poskytuje přehled sis, včetně prohlášení o problému, cílů a přínosů výzkumu. Kapitola 2 shrnuje relevantní literaturu o léčbě diabetu, predikci hladiny glukózy v krvi a ble metody. Kapitola 3 představuje cíle výzkumu a přínos pro diabetes management a zdravotnictví. Kapitola 4 podrobně popisuje implementaci, experimentální nastavení a analýza dat. Kapitola 5 popisuje přímé versus opakované metody pro stanovení hladiny glukózy v krvi předpovědi o více kroků. Kapitola 6 uzavírá práci shrnutím klíčových bodů a zdůraznění přínosů výzkumu. Kapitola 7 shrnuje základní výstupy, poskytuje přehledy pro další rozšiřitelnost a nabízí doporučení pro budoucí práci.

Na závěr věříme, že naše zjištění připraví půdu pro budoucí výzkum v této oblasti oblasti, zejména s ohledem na použití souborových metod, kompartmentových modelů a začlenění různých fyziologických signálů jako vstupů do modelů.

Keywords: ensemble framework, diabetes mellitus, blood glucose level prediction, insulin pump, artificial pancreas, direct method, iterated method

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Chapter 1

Introduction

1.1 Motivation

Diabetes is a disease that has concerned patients and specialists for millennia. Over $3,000$ years ago, the ancient Egyptians mentioned a condition that appears to have been Type 1 Diabetes Mellitus . The specialists recommended following a diet of whole grains to reduce the symptoms. In ancient India, people discovered that they could use ants to test for diabetes by presenting urine to them. If the ants came to the urine, this was a sign that it contained high sugar levels. They called the condition madhumeha, meaning honey urine. During the third century B.C.E., Apollonius of Memphis mentioned the term -diabetes- which may have been its earliest reference. In time, Greek physicians also distinguished between diabetes mellitus and diabetes insipidus. Diabetes insipidus has no link with diabetes mellitus. While it also leads to thirst and urination, it does not affect the body's production or use of insulin. Diabetes insipidus arises from an issue with a hormone known as vasopressin, which is produced by the pituitary gland. The ancient Roman doctor Galen mentioned diabetes but noted that he had only ever seen two people with it, which suggests that it was relatively rare in those days. By the fifth century C.E., people in India and China had worked out that there was a difference between Type 1 and Type 2 . They noted that T2DM was more common in heavy, wealthy people than in other people. At that time, this might have implied that these individuals ate more than other people and were less active [1], [2].

Nowadays, the ready supply of processed food has weakened the association between wealth and eating more, but obesity, diet, and a lack of exercise are still risk factors for T2DM diabetes. The term diabetes mellitus comes from the Greek word -diabetes- (to siphon or pass through) and the Latin word -mellitus- (honey or sweet). In the Middle Ages, people believed that diabetes was a disease of the kidneys, but an English doctor in the late 18th century found that it occurred in people who had experienced an injury to the pancreas. In 1776, Matthew Dobson confirmed that the urine of people with diabetes could have a sweet

taste. According to an article that the journal Medical Observations and Enquiries published, he measured the glucose in urine and found that it was high in people with diabetes. Dobson also noted that diabetes could be fatal in some people but chronic in others, further clarifying the differences between T1DM and T2DM. By the early $19th$ century, there were no statistics about how common diabetes was, there was no effective treatment, and people usually died within weeks to months of first showing symptoms [2].

In 1889, Joseph von Mering and Oskar Minkowski found that removing the pancreas from dogs led them to develop diabetes and die shortly afterward. This discovery helped scientists understand the role of the pancreas in regulating blood sugar levels. In 1910, Sir Edward Albert Sharpey-Schafer proposed that diabetes developed when there was a lack of a particular chemical that the pancreas produced. He called it insulin, meaning island, because the cells in the islets of Langerhans in the pancreas produce it. In 1921, Frederick Banting and Charles Best introduced an extract of pancreatic islet cells from healthy dogs into dogs with diabetes. Doing this reversed diabetes and marked the discovery of the hormone insulin. They worked with two other scientists to purify insulin that they took from the pancreas of cows and produce the first diabetes treatment. In January 1922, 14-year-old Leonard Thompson was the first person to receive an injection of insulin to treat diabetes. Thompson lived another 13 years with the condition and eventually died of pneumonia. In 1936, Sir Harold Percival Himsworth published research that differentiated between T1DM and T2DM. He theorized that many people had insulin resistance rather than insulin deficiency. Insulin resistance is one factor that leads to T2DM. When a person has insulin resistance, their body cells lose their sensitivity to insulin and are not able to take in glucose. In response, the pancreas increases its output of insulin. As this continues to happen, it puts stress on the pancreas, resulting in damage to this organ. [2], [3].

People with T1DM and some people with T2DM need to use insulin every day. People continued to use injectable animal-based insulin for many years, but recent years have seen further advances in treatment. These include the introduction of insulin analogs and the development of new ways to deliver insulin. Both of these factors have made diabetes treatment more effective. In 1978, scientists created Trusted Source the first human-based insulin, which they named Humulin. Humulin is identical in structure to human insulin. Lispro, the first short-acting insulin, appeared on the market in 1996. Lispro begins to work about 15 minutes after injection and keeps working for $2-4$ hours. Long-acting insulins, such as insulin glargine, take longer to absorb and remain active for up to 24 hours. People who use insulin tend to combine long- and short-acting types. The long-acting dose works throughout the day, while the short-acting dose boosts insulin levels around mealtimes. Diabetes mellitus T2DM can be treated by following proper diet and exercise.

However, scientists are already looking into various options that may help people with

diabetes, especially T1DM which can not be handled without insulin, in the future. There is a lot of research related to immunotherapy; The American Diabetes Association (ADA) have funded several research projects, including one that is attempting to identify the possible trigger for T1DM, which doctors believe relates to a problem with the immune system. Additionally, artificial pancreas is another emerging treatment option. The device, which some refer to as closed-loop glucose control, involves using an external pump and continuous glucose monitoring to deliver insulin in a single system. It uses a control algorithm and automatically adjusts the dose according to readings from sensors. In 2018, researchers were writing that the artificial pancreas is efficacious and safe for people with T1DM to use [4], [5].

The number of people with diabetes is growing. A range of treatment options and lifestyle measures can help people manage the condition. Scientists are continuing to develop improved treatment options to give people with diabetes the best possible quality of life. Moreover, adults and children with T1DM will spend an average of $2,500$ a year out-of-pocket for health care [6], [7]. While insulin comprises a big part of diabetes expenses for children and adults, diabetes-related supplies can cost even more [7]. Researchers focus on artificial pancreas and blood glucose level prediction that can support patients to handle diabetes effectively and reduce their costs of treatment.

1.2 Problem Statement

The management of T1DM is a complex task that requires constant monitoring and control of blood glucose levels. Current methods for predicting blood glucose levels in T1DM patients are often inaccurate and unreliable, leading to suboptimal disease management and increased risk of complications.

The advent of the artificial pancreas, a device that combines glucose monitoring and insulin delivery systems, has the potential to revolutionize T1DM management. However, the effectiveness of such a device heavily relies on the accuracy of blood glucose level predictions.

Existing prediction models often use a direct strategy, which predicts future glucose levels based on current and past data. However, this approach may not be optimal due to the dynamic and complex nature of glucose metabolism in T1DM patients.

An alternative approach is the iterated strategy, which involves making a series of short-term predictions and using them to predict future glucose levels. While this approach has shown promise, it has not been thoroughly investigated in the context of T1DM management.

The development of an ensemble framework in this study has the potential to be a game-changer in the field of blood glucose level prediction for T1DM.

An ensemble framework combines the predictions from multiple models to produce a final prediction. This approach can capture a wider range of data patterns and reduce the likelihood

of prediction errors, leading to more accurate and reliable results.

In the context of this study, the ensemble framework will integrate both direct and iterated strategies for predicting blood glucose levels. This combination could potentially harness the strengths of both strategies, thereby improving the overall prediction accuracy.

Moreover, the ensemble framework developed in this study could serve as a valuable tool for future research. It could provide a benchmark for evaluating new prediction models and strategies. Researchers could also build upon this framework to develop more advanced prediction models, further pushing the boundaries of what's possible in T1DM management.

Our research introduces an ensemble framework that combines the strengths of both direct and iterated strategies. By integrating multiple prediction models, we aim to enhance accuracy and reliability. The ensemble framework adapts to individual patient needs, continually improving predictions. Moreover, it serves as a benchmark for evaluating novel models and strategies, propelling the field forward.

1.3 Significance of the Research

The research on the ensemble framework for Blood Glucose Levels Prediction in T1DM holds immense significance in the field of medical science, particularly in the management of T1DM [8]. The number of people with diabetes rose from 108 million in 1980 to 422 million in 20,141. As of 2019, around 244,000 youth and 1.6 million adults 20 years and older had T1DM2. This increasing prevalence underscores the urgent need for effective management strategies, including accurate blood glucose level prediction.

Accurate prediction of blood glucose levels is critical for effective T1DM management. It helps in overcoming the lag time for insulin absorption in T1DM patients, thereby enabling timely and appropriate insulin dosage adjustments. This can prevent both hyperglycemia and hypoglycemia, reducing the risk of severe complications [9]. Enhancing Artificial Pancreas Systems: The ensemble framework developed in this research can significantly enhance the performance of artificial pancreas systems. These systems rely on accurate blood glucose level predictions to automate insulin delivery. Improved prediction accuracy can lead to better glycemic control, reducing the burden of disease management for T1DM patients.

The ensemble framework, which integrates both direct and iterated strategies for blood glucose level prediction, can serve as a valuable tool for future research. It can provide a benchmark for evaluating new prediction models and strategies, thereby advancing the field of blood glucose level prediction. The latest work used deep ensemble models to predict blood glucose levels. Three types of models, including linear regression (LR), vanilla Long Short Term Memory (LSTM) , and bidirectional LSTM (BiLSTM), were ensembled using the stacking, multivariate, and sub-sequence approaches. This demonstrates the statistical significance and

potential of ensemble models in blood glucose level prediction. A review of 32 papers published between 2000 and 2020 found that ensemble methods have been successfully used in many medical fields to improve prediction accuracy. The research topic is gaining growing interest, with ensemble models often using blood glucose, insulin, diet, and exercise as input to predict blood glucose. Both homogeneous and heterogeneous ensembles have been investigated [10].

A study found that applying a Genetic Algorithm (GA) based on each output of a model with multiple algorithms played a significant role in improving model performance [11]. The Root Mean Square Error (RMSE) was 3.19, 19.25, and 31.30 mg/dl for 15, 30, and 60 min prediction horizons, respectively. When the same data were applied to univariate models, the RMSE was 11.28, 19.99, and 33.13 mg/dl for 15, 30, and 60 min prediction horizons, respectively [11]. This research proposed two ensemble neural network-based models for blood glucose prediction at three different prediction horizons—30, 60, and 120 min—and compared their performance with ten recently proposed neural networks [12]. In conclusion, this research holds the potential to make significant contributions to the field of T1DM management, benefitting millions of patients worldwide. It represents a step forward in our quest for a more effective, automated, and patient-friendly approach to managing this chronic condition.

Chapter 2

State-of-the-Art

2.1 Prediction Models

Aliberti et al. [13] investigated the prediction models trained on glucose signals of a large and heterogeneous cohort of patients and then applied to infer future glucose-level values on a completely new patient. They designed and compared two different types of solutions that were proved successful in many time-series prediction problems based respectively, on non-linear autoregressive (NAR) neural network and on LSTM networks. These solutions were experimentally compared with three literature approaches, respectively, based on feed-forward neural networks (FNNs), autoregressive (AR) models, and recurrent neural networks (RNN). While the NAR obtained good prediction accuracy only for short-term predictions (i.e., with prediction horizon within 30 min), the LSTM obtained extremely good performance both for short- and long-term glucose-level inference (60 min and more), overcoming all the other methods in terms of correlation between the measured and the predicted glucose signal and in terms of clinical outcome.

Wang et al. [14] proposed a prediction model based on the Sparrow Search Algorithm (SSA) of Empirical Mode Decomposition (EMD) to optimize the Kernel Extreme Learning Machine (KELM). EMD is used to decompose blood glucose values into different frequency sequences. Secondly, SSA- KELM is trained and each sub-sequence is predicted separately, and finally the prediction sequence is reconstructed to obtain the predicted value of blood glucose. The experimental results showed that the SSA-KELM model has higher prediction accuracy than the ELM and PSO-KELM algorithms, and can be used for blood glucose prediction models.

Xiangyue et al. [15] based on the application and evaluation of GM (1,1) model in blood glucose prediction, the difference of the predictive ability of this model in different blood glucose ranges was evaluated to guide the more reasonable application. Bhargav et al. [16] evaluated various ensemble ML models for generalized blood glucose level prediction and evaluate their

novel combination with the decision tree models. Twenty-four-hour data of 40 patients at 15-min intervals were generated using the automated insulin dosage advisor (AIDA) simulator. Kalpana et al. [17] aimed to develop a machine-learning model using different attributes like BMI, age, blood pressure, blood sugar. Several machine learning techniques Support Vector Machine (SVM), Naïve Bayes, XGBoost were deployed to predict diabetes. Further, the ML algorithms were optimized by applying the Binary particle Swarm optimization (BPSO) algorithm. ML algorithm achieved high accuracy with lifestyle attributes. The ML algorithms were evaluated by deploying various measures like accuracy, F1-measures, recall, and precision. Bairaktaris et al. [18] developed a model to predict future blood glucose values based on the combined usage of compartment models and artificial neural networks(ANNs). The model accepts records of glucose, insulin injection rates and the amount of carbohydrates contained in each meal as input data and outputs predicted values of future blood glucose levels. For the development and evaluation of the model data from 12 T1DM patients, as well as *in silico* data from UVa T1DM simulator were used.

Chevillon et al. [19] provided valuable insights into the comparison between direct and iterative multi-step forecasting methods. The direct approach uses different models for each number of steps ahead in forecasting. It simplifies the problem by treating each prediction step independently. However, it may not fully account for dependencies and error accumulation over multiple steps. On the other hand, The iterative approach applies one one-step ahead model iteratively to predict multiple steps ahead. It considers the cumulative effect of errors but can suffer from error propagation. The challenge lies in balancing accuracy and error accumulation. They presented an exhaustive overview of the existing results, including a conclusive review of the circumstances favourable to direct multi-step forecasting, namely different forms of non-stationarity and appropriate model design. Addittioanlly, they provided a unifying framework which allows researchers to analyse the sources of forecast errors and hence of accuracy improvements from direct over iterated multi-step forecasting.

Llvieris et al. [20] focused on deep learning models by exploring multi-step forecasting strategies. The iterative approach is compared to other methods, including support vector machines (SVM), auto-regressive integrated moving average (ARIMA), LSTM, and convolutional-based models. Yukun et al. [21] proposed a novel multiple step ahead time series prediction approach which employs multiple-output support vector regression with multiple input multiple output prediction strategy. The proposed strategy is the best with accredited computational load while the computational load of standard SVR using direct strategy is extremely expensive and The standard SVR using iterated strategy is best in terms of low computational load.

Falco et al. [22] targeted to extrapolate a regression model, capable of estimating the blood glucose through interstitial glucose measurements, that represents a possible revolutionizing step in constructing the fundamental element of such an artificial pancreas. In particular, a

new evolutionary approach is illustrated to stem a mathematical relationship between blood glucose and interstitial glucose. To accomplish this task, an automatic evolutionary procedure was devised to estimate the missing blood glucose values within the investigated real-world database made up of both blood glucose and interstitial glucose measurements of people suffering from Type 1 diabetes. The discovered model is validated through a comparison with other models during the experimental phase on global and personalized data treatment. Moreover, Falco et al. [23] propose an innovative Federated Learning-inspired evolutionary framework. This framework consists of a master/slave approach in which each slave contains local data, protecting sensible private data, and exploits an evolutionary algorithm to generate prediction models. The master shares through the slaves the locally learned models that emerge on each slave. Sharing these local models results in global models. Being that data privacy and interpretability are very significant in the medical domain, the algorithm is tested to forecast future glucose values for diabetic patients by exploiting a Grammatical Evolution algorithm. The effectiveness of this knowledge-sharing process is assessed experimentally by comparing the proposed framework with another where no exchange of local models occurs. The results show that the performance of the proposed approach is better and demonstrate the validity of its sharing process for the emergence of local models for personal diabetes management, usable as efficient global models. When further subjects not involved in the learning process are considered, the models discovered by our framework show higher generalization capability than those achieved without knowledge sharing: the improvement provided by knowledge sharing is equal to about 3.03% for precision, 1.56% for recall, 3.17% for $F1$, and 1.56% for accuracy.

Koutny [24] proposed a physiological model to prolong the sensor lifetime with an adaptive approach, while requiring no additional blood sample. Prolonging sensor's lifetime, while reducing the associated discomfort, would considerably improve patient's quality of life. They demonstrated that it is possible to determine personalized model parameters from multiple CGMS-signals only, using an animal experiment with a hyperglycemic clamp. Additionally, Koutny et al. [25] proposed a novel low-complexity, explainable blood glucose prediction method derived from the Intel P6 branch predictor algorithm. They used Meta-Differential Evolution to determine predictor parameters on training data splits of the benchmark datasets we use. They compared the new algorithm and a state-of-the-art deep-learning method for blood glucose level prediction. On the official test data split after training, the state-of-the-art deep learning method predicted glucose levels 30 min ahead of current time with 96.3% of predicted glucose levels having relative error less than 30% (which is equivalent to the safe zone of the Surveillance Error Grid). Our simpler, interpretable approach prolonged the prediction horizon by another 5 min with 95.8% of predicted glucose levels of all patients having relative error less than 30%.

Yang et al. [26] proposes an improved stacking ensemble learning algorithm for predicting

blood glucose level, in which three improved long short-term memory network models are used as the base model, and an improved nearest neighbor propagation clustering algorithm is adaptively weighted to this ensemble model. The OhioT1DM dataset is used to train and evaluate the performance of the proposed model. This study evaluated the performance of the proposed model using the RMSE, (MAE), and Matthews Correlation Coefficient (MCC) as the evaluation metrics. Additionally, Yang et al. [27] stated that real-time prediction of blood glucose levels (BGLs) in individuals with T1DM presents considerable challenges. Accordingly, they presented a personalized multitasking framework aimed to forecast blood glucose levels in patients. The results showed that the average RMSE and the MAE of the proposed model were 16.896 and 9.978 mg/dL, respectively, over the prediction horizon (PH) of 30 minutes. The average RMSE and the MAE were 28.881 and 19.347 mg/dL, respectively, over the PH of 60 min. The proposed model demonstrated excellent prediction accuracy. Seo et al. [28] proposed a a personalized blood glucose (BG) level prediction model with a fine-tuning strategy and demonstrated its efficacy on large datasets including three types of diabetes (type 1 diabetes, type 2 diabetes, and gestational diabetes). The fine-tuned convolutional neural network (CNN) showed the performance of the general CNN in most cases and outperformed the scratch CNN.

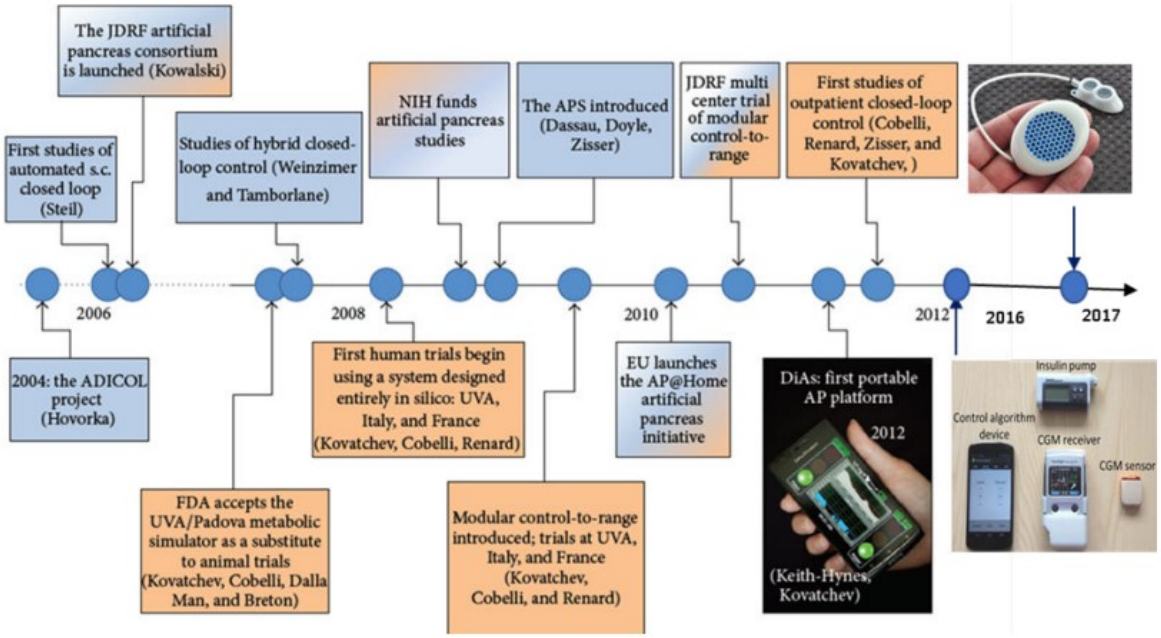
In brief, terated methods have consistently demonstrated superior performance in blood glucose prediction. The iterative approach allows for better capturing of complex temporal dependencies and patterns in blood glucose dynamics. Ensemble frameworks are a focal point of interest within the research community. By combining predictions from diverse models, ensemble methods can capture trends and variations across different individuals. The potential of ensemble frameworks lies in their ability to mitigate biases and enhance generalization.

2.2 Artificial Pancreas

The artificial pancreas is a technology in development to support people with diabetes to automatically control their blood glucose level by providing the substitute endocrine functionality of a healthy pancreas. There are several important exocrine (digestive) and endocrine (hormonal) functions of the pancreas, but it is the lack of insulin production that is the motivation to develop a substitute. While the current state of insulin replacement therapy is appreciated for its life-saving capability, the task of manually managing the blood sugar level with insulin alone is arduous and inadequate. The goals of the artificial pancreas are to improve insulin replacement therapy until glycemic control is practically normal as evidenced by the avoidance of the complications of hyperglycemia, and to ease the burden of therapy for insulin-dependent diabetes. One approach to those aims is the medical equipment approach in which an insulin pump is used under closed-loop control using real-time data from a continuous blood glucose

sensor [1]. Figure 2.1 shows the steps and the improvement that have been done until 2010 in artificial pancreas.

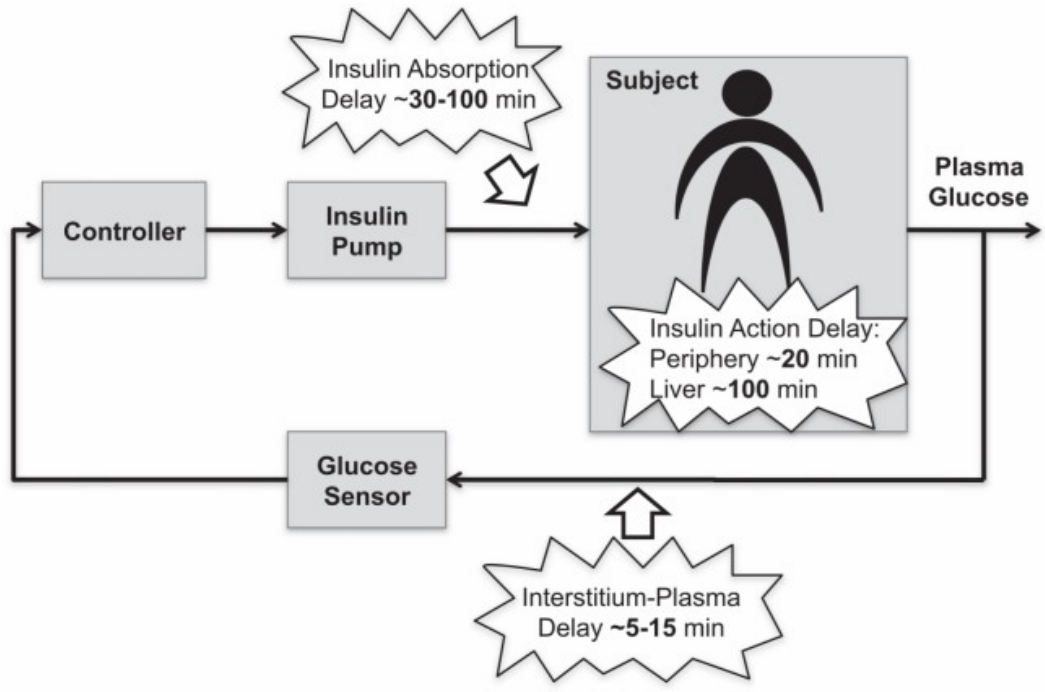
Figure 2.1: Key milestones in the timeline of Artificial Pancreas progress [29].



The pursuit of a closed-loop artificial artificial pancreas that automatically controls blood glucose for individuals with T1DM has intensified during the past decade. Continuous insulin infusion pumps have been widely available for over 30 years, but smart pump technology has made such devices easier to use and more powerful. Continuous Glucose Monitoring technology has improved and the devices are more widely available. Several approaches are currently under study for fully closed-loop systems; most manipulate only insulin, while others manipulate insulin and glucagon. Algorithms include on-off (for prevention of overnight hypoglycemia), Proportional Integral Derivative, Model Predictive Control, and Fuzzy Logic Based Learning Control. Meals cause a major disturbance to blood glucose, and in most cases, mathematical models, such as compartment models, are implemented. Model Predictive Control is a basic framework or strategy that can involve many different types of models and objective functions. Despite important developments in sensor and pump technology, the artificial artificial pancreas must cope with the delays and inaccuracies in both glucose sensing and insulin delivery described in the previous sections. This is particularly difficult when a system disturbance, e.g., a meal, occurs and triggers a rapid glucose rise that is substantially faster than the time needed for insulin absorption and action (Figure 2.2).

Bekiari et al. [31] evaluated the efficacy and safety of artificial pancreas treatment in non-pregnant outpatients with T1DM. Messori et al. [32] considered two novel identification

Figure 2.2: Block diagram of closed-loop glucose control. Three major delays are indicated: insulin absorption (regular and ultrafast insulin), insulin action on peripheral tissues and on the liver, and sensing in the interstitium [30].



approaches that can be used for individualizing linear glucose-insulin models to a specific patient. Both identification approaches were used to identify a linear individualized glucose-insulin model for each adult virtual patient of the UVA/Padova simulator. The resulting model simulation performance was significantly improved with respect to the performance achieved by a linear average model. Boughton et al. [33] reviewed the key studies which have led to the adoption of the artificial pancreas in clinical practice and consider ongoing challenges and areas for future enhancements. According to them, the artificial pancreas has become the gold standard for the treatment of T1DM. First-generation systems are increasingly being adopted in clinical practice, however further work is required, developing advanced systems and faster acting insulin analogues to allow complete automation and further reduce the burden of T1DM.

Tsoukas et al. [34] aimed to assess the efficacy of a novel faster-acting insulin aspart plus pramlintide fully closed-loop system that does not require meal input. The Fiasp plus pramlintide fully closed-loop system was not non-inferior to the Fiasp-alone hybrid closed-loop system for the overall percentage of time in the glucose target range. However, participants still spent a high percentage of time within the target range with the fully-closed loop system. Outpatient studies comparing the fully closed-loop hybrid systems with patient-estimated,

rather than precise, carbohydrate counting are warranted.

Vinals et al. [35] evaluated the safety and performance of a new multivariable closed-loop glucose controller with automatic carbohydrate recommendation during and after unannounced and announced exercise in adults with T1DM. Ten participants (aged 40.8 ± 7.0 years; HbA1c of $7.3 \pm 0.8\%$) participated. The use of the MCL in both closed-loop arms decreased the time spent < 70 mg/dL of sensor glucose (0.0%, $[0.0 - 16.8]$ and 0.0%, $[0.0 - 19.2]$ vs 16.2%, $[0.0 - 26.0]$, (%, [percentile $10 - 90$]) CLNA and CLA vs OL respectively; P $= 0.047$, P $= 0.063$) and the number of hypoglycemic events when compared with OL (CLNA 4 and CLA 3 vs OL 8; P $= 0.218$, P $= 0.250$). The use of the MCL system increased the proportion of time within 70 to 180 mg/dL (87.8%, $[51.1 - 100]$ and 91.9%, $[58.7 - 100]$ vs 81.1%, $[65.4 - 87.0]$, (%, [percentile $10 - 90$]) CLNA and CLA vs OL respectively; P $= 0.227$, P $= 0.039$). This was achieved with the administration of similar doses of insulin and a reduced amount of carbohydrates. The MCL with automatic carbohydrate recommendation performed well and was safe during and after both unannounced and announced exercise, maintaining glucose mostly within the target range and reducing the risk of hypoglycemia despite a reduced amount of carbohydrate intake.

Recently, the use of do-it-yourself artificial pancreas systems (DIYAPS) among people with T1DM is increasing. At present, it is unclear how DIYAPS compares with other technologies such as FreeStyle Libre (FSL) and continuous subcutaneous insulin infusion (CSII). Patel et al. [36] aimed to compare the safety, effectiveness, and quality-of-life outcomes of DIYAPS use with the addition of FSL to CSII. DIYAPS (n $= 35$) and FSL+CSII (n $= 149$) users, with median follow-up duration of 1.4 (IQR $0.8 - 2.1$) and 1.3 (IQR $0.7 - 1.8$) years, respectively, were included.

Nwokolo et al. [37] stated that clinical adoption of closed-loop therapy remains in the early stages despite recent technological advances. People living with diabetes, healthcare professionals, and regulatory agencies continue to navigate the complex path to equitable access. They reviewed the available devices, evidence, clinical implications, and barriers regarding these innovatory technologies. Julia Fuchs and Roman Hovorka [38] provided an overview of commercial and emerging closed-loop systems. Hovorka's research often focuses on refining the algorithms and control strategies that govern these closed-loop systems. These algorithms aim to mimic the physiological function of the pancreas by dynamically adjusting insulin delivery based on real-time glucose readings. By utilizing sophisticated mathematical models and feedback mechanisms, Hovorka and his colleagues have made significant strides in improving the accuracy and effectiveness of artificial pancreas systems [39].

One notable aspect of Hovorka's work is his emphasis on personalized medicine. Recognizing that individuals with diabetes can have unique physiological responses to insulin and varying daily routines, his research explores adaptive algorithms that can tailor the closed-loop

system to each patient's specific needs. This personalized approach holds the promise of optimizing glycemic control and minimizing the risk of hypoglycemia [40], [41].

Furthermore, Hovorka's research often addresses the challenges associated with integrating the artificial pancreas into the daily lives of individuals with diabetes. This includes considerations for mealtime insulin delivery, physical activity, and other lifestyle factors that influence blood glucose dynamics [42], [43].

2.3 Summary

The performance of blood glucose level prediction models for T1DM is heavily reliant on the quality of data used. This includes the accuracy, completeness, and relevance of the data. Inaccurate or incomplete data can lead to erroneous predictions, while irrelevant data can introduce noise and confusion into the model. The choice of input variables is critical in any predictive modeling project. For T1DM, important variables include the target group of the study (e.g., age, gender, lifestyle factors) and the observation period (short-term vs. long-term). These variables can significantly influence the model's performance and applicability.

Carbohydrate intake, exercise, and stress play a crucial role in blood glucose concentration. Carbohydrate intake, usually measured in grams, directly affects blood glucose levels. Exercise can lower blood glucose levels by increasing insulin sensitivity and promoting glucose uptake into the muscles. Stress, both physical and emotional, can cause blood glucose levels to rise. Understanding and accurately capturing these dynamics is key to predicting blood glucose levels effectively. Recent research has focused on ensemble methods for prediction, which combine the strengths of multiple models to improve results. For instance, neural networks can capture complex, non-linear relationships in the data, while decision trees can provide interpretability and handle categorical variables well. By combining these models, ensemble methods can achieve higher predictive accuracy and robustness.

The artificial pancreas, a device that automates the monitoring and regulation of blood glucose levels, has emerged as a promising solution for T1DM management. It integrates a continuous glucose monitor and an insulin pump with a control algorithm that calculates the insulin dose based on CGM readings. The effectiveness of the artificial pancreas hinges on the accuracy of blood glucose level predictions. Numerous systematic reviews have been conducted recently to collate and compare studies on the artificial pancreas. These reviews aim to identify gaps in current research, assess the effectiveness of different approaches, and guide future developments in this field. They provide valuable insights into the state of the art and highlight areas for further investigation. In conclusion, the development of accurate and reliable blood glucose level prediction models for T1DM is a complex task that requires high-quality data, careful selection of input variables, and advanced modeling techniques.

In conclude, the artificial pancreas, a groundbreaking device that automates blood glucose monitoring and insulin regulation, holds immense promise for managing T1DM. By seamlessly integrating a continuous glucose monitor (CGM) and an insulin pump, this technology aims to revolutionize T1DM management. However, its effectiveness critically depends on the accuracy of blood glucose level predictions. To address this challenge, our research introduces an innovative approach—the Active Learning-Enhanced ensemble framework. T1DM is highly individualized, with varying metabolic dynamics. The ensemble framework adapts to each patient's unique needs, continuously improving predictions. Active learning allows us to fine-tune the model based on real-world data and user feedback. As artificial pancreas systems become more prevalent, their success hinges on reliable predictions. Our ensemble framework serves as a benchmark, guiding the development and evaluation of these systems. It sets the standard for future research and clinical implementation. Accurate predictions empower patients, allowing them to make informed decisions about insulin dosing, diet, and physical activity. Ultimately, this translates to better quality of life for individuals living with T1DM.

Chapter 3

Dissertation thesis targets

3.1 Research Objectives

The primary objective of this research is to develop an ensemble framework for predicting blood glucose levels in individuals with T1DM. The framework will be designed to leverage the strengths of both direct and iterated strategies for multi-step ahead prediction. Through rigorous experimentation and analysis, the study aims to:

- Compare the prediction accuracy of the ensemble framework against individual algorithms and existing methods.
- Investigate the benefits and limitations of integrating direct and iterated strategies for multi-step ahead forecast.
- Provide insights into the factors influencing the performance differences between these strategies.

3.2 Contribution to Diabetes Management and Healthcare

This research contributes to the field of diabetes management and healthcare in several ways:

- **Improved Prediction Accuracy:** The proposed ensemble framework has the potential to enhance the precision and reliability of blood glucose level predictions, thus facilitating proactive management strategies.
- **Personalized Treatment:** Accurate predictions enable personalized insulin dosing and dietary recommendations tailored to individual needs and fluctuations in glucose levels.

- **Reduced Complications:** By reducing the risk of hypoglycemia and hyperglycemia, the research directly addresses the prevention of complications associated with T1DM.
- **Enhanced Data-Driven Insights:** The study's findings could provide valuable insights into the efficacy of ensemble strategies, shedding light on their applicability in other healthcare prediction tasks.

3.3 Thesis Organization

This thesis is organized as follows:

- *Chapter 2:* reviews relevant literature on diabetes management, blood glucose prediction, and ensemble methods.
- *Chapter 3:* presents the research objectives and the contribution to diabetes management and healthcare.
- *Chapter 4:* details the implementation, experimental setup, and data analysis.
- *Chapter 5:* describes the direct versus iterated methods for blood glucose level multi-step ahead forecasts.
- *Chapter 6:* suggests an ensemble framework to enhance blood glucose level prediction.
- *Chapter 7:* concludes the thesis by summarizing key points and emphasizing the research's contributions.

Chapter 4

Description of Experimental Data

4.1 Comparative assessment of in vivo and in vitro Studies for Blood Glucose Level Prediction in T1DM

Blood glucose level prediction is a critical aspect of managing T1DM, and researchers have employed both *in vivo* and *in vitro* approaches to enhance predictive models. This comparative assessment explores the strengths and limitations of *in vivo* studies (using real-world patient data) and *in vitro* studies (using artificial or simulated data) for predicting blood glucose levels in individuals with T1DM [44], [45].

In vivo studies, which leverage data collected directly from individuals with T1DM, provide a realistic representation of the complexities associated with real-world blood glucose dynamics [46]. However, these studies may face challenges related to variability in individual responses, making it challenging to capture all possible scenarios [47]. This variability can be attributed to factors such as genetic differences, lifestyle choices, and environmental influences. The findings from *in vivo* studies are directly applicable to real-world situations, enhancing the clinical relevance of predictive models. However, the heterogeneity of patient populations and lifestyle factors may affect the generalizability of *in vivo* study results. Ethical concerns are minimized as *in vivo* studies use data collected during routine patient care. However, privacy concerns and the need for informed consent may limit the accessibility of certain datasets.

In vivo studies, which involve the use of living organisms, tend to provide findings that are directly applicable to diverse patient groups. However, these studies may have limitations in capturing extreme or rare scenarios due to the inherent variability in biological systems [48]. On the other hand, *in vitro* studies, conducted in controlled laboratory environments, offer scalability and the ability to manipulate variables. However, they may struggle with generalizability due to potential biases introduced during the simulation process [49]. *In vivo* studies prioritize clinical relevance, as they allow for the observation of the full range of

physiological responses in living organisms. However, the challenges of real-world variability, such as genetic differences and lifestyle choices, can impact the accuracy of predictive models. In contrast, *in vitro* studies offer controlled environments, which can allow for more precise measurements. However, the artificial nature of the data, which is often generated under idealized conditions, may limit the direct clinical application of the findings [50].

In the paper, "A Review of Model Prediction in Diabetes and of Designing Glucose Regulators Based on Model Predictive Control for the Artificial Pancreas" [51], we presented a comparative assessment of glucose prediction models for diabetic patients using data from sensors monitoring blood glucose concentration as well as data from *in silico* (or in vitro simulations. The models are based on neural networks and linear and nonlinear mathematical models evaluated for prediction horizons ranging from 5 to 120 min. Furthermore, the implementation of compartment models for simulation of absorption and elimination of insulin, caloric intake and information about physical activity is examined in combination with neural networks and mathematical models, respectively. The assessments include 24 papers in total, from 2006 to 2016, in order to investigate progress in blood glucose concentration prediction and in artificial pancreas devices for T1DM patients.

Study (Year)	Diabetes Type (sample size, * in vivo study, ** in vitro study,) *** in vivo study with children
Mougiakakou et al. (2006)	Type 1 (4,***)
Sparacino et al. (2007)	Type 1 (28,*)
Baghhdadi et al. (2007)	Type 1 (1,*)
Pappada et al. (2008)	Type 1 (18,*)
Zainuddin et al. (2009)	Type 1 (18,*)
Stahl et al. (2009)	Type 1 (1,*)
Gani et al. (2009)	Type 1 (9,*)
Valletta et al. (2009)	Type 1 (18,*)
Georga et al. (2011)	Type 1 (7,**)
Rollins et al. (2012)	Type 2 (1,**)
Zhao et al. (2012)	Type 1 (7,*) (10, **)
Georga et al. (2013)	Type 1 (27*)
Zarkogianni et al. (2015)	Type 1 (10*)
Qadah et al. (2016)	Type 1 (10*)

Table 4.1: Summary of works on glucose prediction and datasets (*:*in vivo* study, **:*in vitro*, ***:*in vivo* study-children

Table 4.1 summarized research papers from the above period, the diabetes type that were focused, the sample size and the type of study. We can conclude that in most cases the researchers focus on T1DM with *in vivo* data. The burden of T1DM is substantial, and more research is needed to improve the lives of people with T1DM and to find a cure. T1DM research often involves determining why the immune system reacts against the pancreatic beta cells and how to stop this attack. There's a strong interest in developing cellular therapies that make it possible to obtain functional beta cells that can be transplanted into patients. *In vivo* studies allow scientists to better evaluate the safety, toxicity, and efficacy of a drug

candidate in a complex model.

4.2 Comparative assessment of Blood Glucose Level Prediction: Implementation of Compartment Model

Blood glucose level prediction is a critical aspect of diabetes management, and researchers have explored various modeling approaches, including those involving compartment models and those without. This comparative assessment evaluates the strengths and limitations of research utilizing compartment models compared to studies that do not employ compartment models for predicting blood glucose levels [52], [53]. These benchmark papers that critically reviewed the latest work in the field of blood glucose prediction and implementation of compartment models for bolus insulin simulation. Armed with insights from these benchmark papers, we made informed decisions in our research and by aligning our work with the benchmarked methods, we ensured robustness and comparability.

Compartmental models are a fundamental technique used in various fields, including epidemiology, biology, and pharmacokinetics [54], [55]. The concept of compartmental models dates back to the early $20th$ century where Ronald Ross (1916) introduced the concept of compartments to model the spread of infectious diseases, particularly malaria. Kendall (1956) extended the use of compartmental models to various epidemiological contexts. Compartmental models are used to predict disease spread, estimate epidemiological parameters (e.g., reproductive number), and assess the impact of interventions (e.g., vaccination strategies) [56], [57]. In general, there are two methods of designing and use a compartment model, the open and closed compartment model. In an open-compartment model, substances (such as drugs or nutrients) are removed from the system (body) by an excretory mechanism. The model considers unidirectional movement of substances [58], [59], [60]. In a closed compartment model, substances remain within the system without being removed . The model allows bi-directional movement of substances. For instance, a drug administered orally can be absorbed, distributed, metabolized, and eliminated within the system without leaving it [61], [62]. For example, when a drug is administered intravenously, it is not recirculated back into the system after elimination. In this research, we implemented an open-compartment model as it is represented in Figure 4.1. The open compartment model assumes that the drug (insulin) can leave the body, which aligns with the physiological reality of insulin metabolism. In reality, insulin is administered via injections (bolus), and its effects are not confined to a closed system. The open model accounts for the dynamic insulin absorption and elimination processes. By simulating insulin kinetics, we can estimate model parameters more accurately. This enhances the reliability of the model. Moreover, simulation allows experimentation without real-world consequences. We can fine-tune insulin regimens, assess safety, and predict outcomes.

An open-compartment model for bolus insulin is a simplified mathematical representation of how insulin is distributed and utilized in the body after it is administered as a bolus (a single, large dose) for controlling blood sugar levels. This model assumes that insulin is distributed throughout the body relatively quickly and that it acts almost instantaneously to lower blood glucose levels. While this is a simplification of the actual physiological processes, it can be useful for understanding and predicting insulin effects.

In this model, we consider two main compartments, Figure 4.1:

1. **Bloodstream (Central Compartment):** This compartment represents the bloodstream, where insulin is initially injected or infused. The insulin rapidly enters this compartment.

2. **Peripheral Tissues (Peripheral Compartment):** This compartment represents the various tissues and cells in the body that respond to insulin, such as muscles and fat cells. These tissues are the target sites where insulin exerts its glucose-lowering effects.

Insulin is injected or infused into the central compartment (bloodstream), represented on the left side of the schematic, Figure 4.1.

From the central compartment, insulin is rapidly distributed to the peripheral compartment (peripheral tissues and cells) on the right side of the schematic. This represents how insulin spreads throughout the body.

In the peripheral compartment, insulin interacts with its target tissues (muscles, fat cells, etc.) to facilitate the uptake of glucose from the bloodstream, thereby lowering blood sugar levels.

The effectiveness of insulin in lowering blood sugar levels depends on various factors, including the insulin dose, the rate of distribution, and the sensitivity of target tissues to insulin.

This open compartment model simplifies the complex physiological processes involved in insulin action but can serve as a starting point for understanding how bolus insulin affects blood sugar levels in a simplified way. More complex models can be developed to account for additional factors and dynamics in insulin pharmacokinetics and pharmacodynamics.

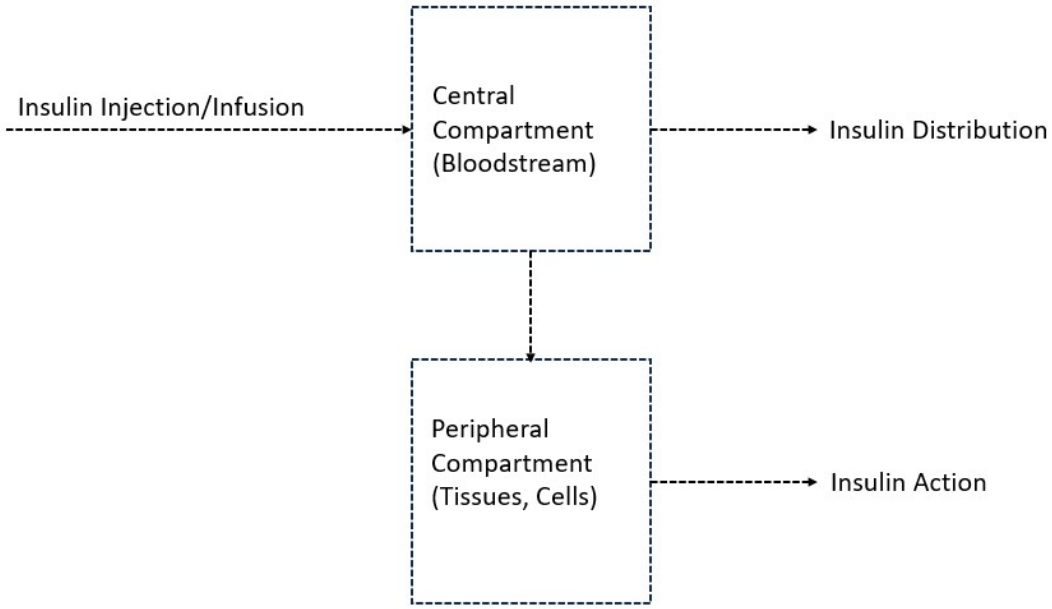


Figure 4.1: Schematic Representation of an Open Compartment Model

In our work, "Particle swarm optimization based adaptable predictor of glycemia values" [63], we applied simple compartment models are to provide a signal of the influence of the insulin and nutrition. Those signals were used as inputs to regressive models. The main problem of adaptation of those compartment models to particular patient was solved using continuous particle swarm optimization algorithm.

Optimization algorithms have been extensively used to enhance the performance of compartment models. One such algorithm is the Particle Swarm Optimization (PSO) algorithm, which has been successfully applied in our work [63]. The PSO algorithm is a population-based stochastic optimization technique inspired by the social behavior of bird flocking or fish schooling. It has been widely used in various fields due to its simplicity, quality of solutions, and speed of convergence [64], [65], [66].

In our work, we used the PSO algorithm to adapt the compartment models to individual patients. The compartment models provided signals representing the influence of insulin and nutrition on blood glucose levels. These signals were then used as inputs to regressive models. However, the main challenge was to adapt these compartment models to individual patients, considering the variability in physiological parameters among patients. The PSO algorithm was used to solve this problem. The algorithm iteratively adjusted the parameters of the compartment models to minimize the difference between the model predictions and the actual patient data. This approach allowed us to tailor the compartment models to individual patients, thereby improving the accuracy of the predictions. Moreover, recent studies have proposed the integration of deep learning techniques with compartment models to further enhance

their predictive performance. For instance, the Deep Compartment Model (DCM), which combines neural networks and ordinary differential equations, has been proposed to improve the prediction of time-series data in pharmacokinetic modeling [67]. Similarly, the Transmission-Dynamics-Informed Neural Network (TDINN) algorithm, which integrates deep neural networks with epidemic models, has been developed to identify the intensity of interventions during the COVID-19 pandemic [68].

4.3 Importance of in vivo and simulated (D1NAMO) dataset for blood glucose level prediction

Utilizing in vivo data for blood glucose level prediction is of paramount importance due to its capacity to enhance accuracy, personalization, real-time adaptability, and long-term management of this critical health parameter. This approach aids in delivering more effective healthcare interventions and refining our understanding of metabolic disorders, such as diabetes.

In vivo data, which is acquired directly from living organisms, offers unparalleled accuracy compared to in vitro data sourced from laboratory experiments [69]. Precision is vital in predicting blood glucose levels, as even minor inaccuracies can have substantial health implications, particularly for individuals with diabetes.

Personalization is another key advantage of in vivo data. It enables the collection of individual-specific information, accounting for variables like diet, physical activity, stress levels, and medication usage [70]. Personalized models empower healthcare professionals to tailor treatment plans to the unique needs of each patient, optimizing glucose management.

Blood glucose levels are inherently dynamic, influenced by factors like meals, exercise, and stress. In vivo data captures these fluctuations in real-time, allowing predictive models to provide timely recommendations for effective glucose control [70]. This dynamic aspect is crucial in preventing extreme glucose fluctuations that can lead to health complications.

Moreover, in vivo data facilitates the development of feedback loops and wearable devices for continuous monitoring [71]. These systems offer real-time alerts and interventions, empowering individuals to make immediate adjustments to their behavior or treatment plans, thereby preventing glucose-related crises.

For individuals with chronic conditions like diabetes, long-term management is essential. In vivo data collected over time helps track trends and patterns, assisting healthcare professionals and patients in making informed decisions about treatment adjustments and lifestyle changes[72]. This longitudinal perspective is indispensable for maintaining stable glucose levels and preventing complications.

Lastly, in vivo data is instrumental in advancing research in the field of diabetes and

metabolic disorders [73]. It serves as the foundation for refining predictive algorithms and treatment strategies, ultimately improving the quality of life for those managing blood glucose levels.

In conclusion, employing in vivo data for blood glucose level prediction represents a pivotal approach to enhancing healthcare outcomes. Its benefits include heightened accuracy, personalization, adaptability, long-term management, and contributions to ongoing research in the field of diabetes [74].

On the other hand, Using simulated data for blood glucose level prediction is important for several reasons, as it enables researchers and healthcare professionals to develop and refine predictive models, improve patient care, and advance our understanding of diabetes management. Real-world blood glucose data is often limited in quantity and quality, making it challenging to train accurate prediction models. Simulated data can fill this gap, ensuring a sufficient volume of data for model training [75]. Simulated data allows researchers to systematically test and refine prediction models under various conditions and scenarios. This can help in identifying model weaknesses and improving their accuracy and reliability [76].

Blood glucose prediction models trained on simulated data can be personalized to individual patients, considering their unique physiology and lifestyle factors. This personalization can lead to more effective diabetes management strategies [77]. Simulated data can be used to assess the risk of hypoglycemia or hyperglycemia events, allowing healthcare providers to proactively intervene and prevent dangerous blood glucose fluctuations [78]. Simulated data can be valuable for educating healthcare professionals and individuals with diabetes on the principles of glucose control. It provides a safe and controlled environment for training and experimentation [79]. Using real patient data for research may raise ethical concerns related to privacy and informed consent. Simulated data helps mitigate these concerns while still enabling valuable research in diabetes prediction and management [80].

Utilizing both in vivo (real-world patient data) and simulated data for blood glucose level prediction is crucial for advancing diabetes management and improving predictive models. Comparing the results derived from these two types of data allows for a comprehensive understanding of the strengths and limitations of predictive algorithms. *In vivo* data captures the intricacies of daily life, including diet, exercise, stress, and medication adherence. Simulated data, on the other hand, provides controlled environments for testing. By comparing results, researchers can assess how well predictive models account for real-world variability [81].

In vivo data acts as the ground truth for model validation. Simulated data helps refine and validate models by providing a controlled environment where model predictions can be compared to known outcomes. This ensures that predictive algorithms perform reliably in real-world scenarios [82]. *In vivo* data must be used cautiously, considering patient safety and ethical concerns. Simulated data offers a safe alternative for algorithm testing and de-

velopment. By comparing the two, researchers can assess potential risks associated with in vivo data usage [83]. Integrating *in vivo* data allows for personalized diabetes management, while simulated data permits the development of adaptable algorithms. Comparing outcomes enables researchers to identify the benefits of personalization and optimization in patient care [84].

By comparing the performance of predictive algorithms on both types of data, researchers can identify areas where improvements are needed. This iterative process fosters the development of more accurate and versatile prediction models [85]. Simulated data allows for the exploration of worst-case scenarios and rare events without endangering patients. Comparing outcomes helps assess the predictive model's ability to handle such situations effectively. Relevant bibliography [86].

In conclusion, the integration of *in vivo* and simulated data, along with the comparison of results, is essential for developing robust blood glucose level prediction models. This approach not only ensures the reliability and safety of predictive algorithms but also facilitates the advancement of personalized and effective diabetes management strategies. The synthesis of insights from both types of data ultimately benefits individuals with diabetes and the broader healthcare community.

4.4 In vivo pilot study and D1NAMO dataset

Two patients' data from FN Motol University and four patients' data taken from D1NAMO database were examined with the following models. In brief, Table 4.2 presents the basic patients' characteristics and mentions any related complications to T1DM.

Table 4.2: Patients' Information

Parameter	Value
Gender	Female 1 / Male 2 / 4 Male (D1NAMO database)
Age	27 / 47 / 25-47
HbA1c	80 / 64
BMI	30.8 / 25.6 / 24-31
Complications	No / Yes

Data of two T1DM patients monitored for 30 days continuously in real-life conditions are recorded using a CGM device which has a sampling time of 5 minutes. Information on meals and activities was included in logbooks and photos of meals were also provided. Moreover,

data of four T1DM from D1NAMO dataset, patient number 001, 006,007 and 008 were used. CGM data were used and recorded for 1 day with a sampling time of 5 minutes.

Although data from only six patients were only used, the paper focuses on predictors that are patient-specific, i.e. they are trained and tested on the same patient. It is therefore crucial to have enough data for each patient. From this point of view, the data from two patients that we measured cover 30 days long period and are sufficiently large for our patient-specific testing purposes.

For implementing models for each patient, we used the information about BG levels, basal and bolus insulin doses, the sensor time of record as well as the information about consumed meals if it was available. More extensively, except bolus insulin values, all acquired data were used directly as inputs of the models.

Two cases were tested for bolus insulin; in Case I, the bolus insulin values were used directly forming an impulse-like signal. In Case II, the original impulse signal of bolus insulin was replaced by its impact modeled using an open compartment model [87].

Figure 4.2 shows a schematic example of the used data from Case I and II. In this work, we decided to use consumed meals data only from the first patient because these data were enough representative while in the second case, the patient was not able to provide us with enough meal data. Figure 4.2 presents BG levels (blue), basal insulin dosages (red), bolus insulin as an impulse signal (green rhombus), consumed meals (black), bolus insulin modelled using an open compartment model (green), consumed meals (black). D1NAMO dataset includes also photos of consumed meals per patient. We did not process and include this information for each patient for implementing the following methods.

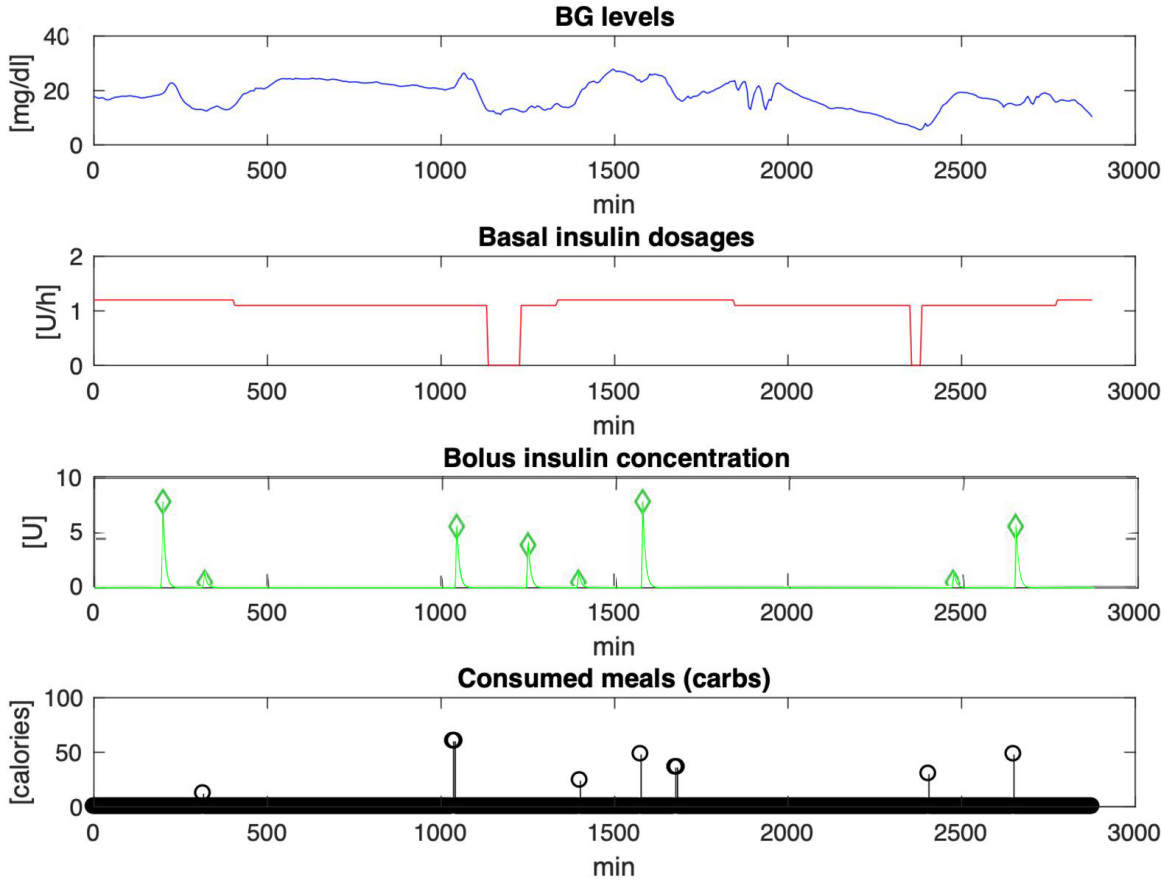


Figure 4.2: Input data: **CASE I**: bolus insulin as impulse signal (green rhombus), **CASE II**: bolus insulin modeled using an open compartment model (green)

4.5 Training and Testing Data for Predictive Models

To evaluate the prediction performance, we used the RMSE and the CEG_A [88] analysis Figure 4.3. Region A are those values within 20% of the reference sensor, Region B contains points that are outside of 20% but would not lead to inappropriate treatment, Region C are those points leading to unnecessary treatment, Region D are those points indicating a potentially dangerous failure to detect hypoglycemia or hyperglycemia, and Region E are those points that would confuse treatment of hypoglycemia for hyperglycemia and vice versa. The 70% of the dataset for each patient was used for model training and parameter selection while the 30% was used for model testing.

D1NAMO dataset [89] was used in this study. Models were applied using data (BG levels, basal and bolus insulin) from four patients. We used leave-one-out cross-validation for CASE I (using bolus insulin dosages as impulse-like signal) and CASE II (bolus impulse signal was replaced by its impact modeled using an open compartment model). Results of RMSE and the CEG_A analysis expressed as Mean $\pm$ STD. Outliers and noisy data points were identified using a combination of statistical methods and domain knowledge. Extreme values that deviated significantly from the expected glucose range were flagged for review. In cases where outliers

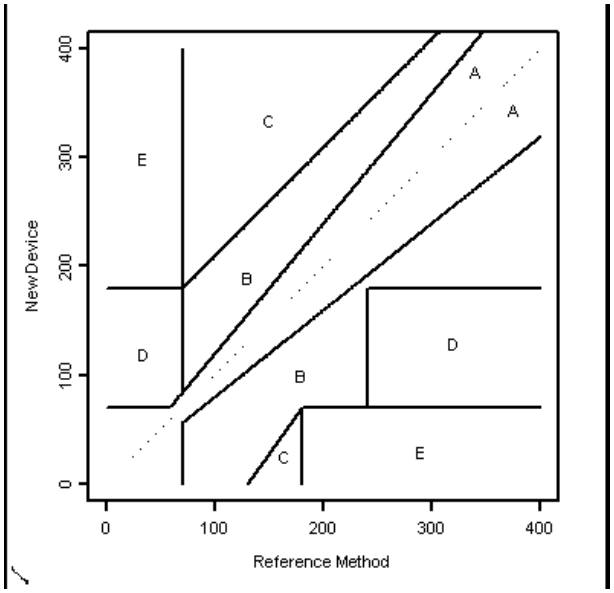


Figure 4.3: CEG analysis.

were genuine, they were retained in the dataset. However, if they were found to be data entry errors, they were corrected or replaced with interpolated values. Normalization and standardization were applied to the dataset to ensure that all features were on a consistent scale, which is important for the performance of ensemble methods and other machine learning algorithms. Blood glucose levels were normalized to a common range, typically between 0 and 1, using min-max scaling. This transformation retains the relative relationships between glucose values while ensuring that they fall within a standardized range. Normalization is particularly beneficial for gradient-based ensemble methods like gradient boosting and neural networks, as it helps prevent certain features from dominating others due to their scale. In addition to normalizing glucose levels, features such as patient age and insulin dose were standardized using z-score scaling. This transformation centers the features around zero with a standard deviation of one. Standardization is advantageous when using algorithms that assume standardized features, such as many variants of ensemble methods.

Chapter 5

Direct versus Iterated BG Level Prediction Models

In this section, we will define in detail the direct and iterated multi-step ahead forecast strategies. Subsequently, we will elucidate the implementation of these strategies to construct individual prediction models. These individual models serve as the foundational components that synergistically contribute to the development of our novel ensemble framework. The ensemble framework, a culmination of these individual models, represents a significant advancement in the field of blood glucose level prediction for T1DM. This section serves as a critical bridge between theoretical foundations and practical applications, paving the way for improved patient care and optimized insulin therapy.

In a direct forecast, we estimate a multiperiod-ahead value directly using a model tailored to the specific forecast horizon. For example, if we want to predict the blood glucose level after one hour, we directly regress the blood glucose level at that future point against current and past values of the variable. In an iterated forecast, we use a one-period-ahead model iterated forward for the desired number of periods. It involves first estimating an autoregression (one-step-ahead model) and then iterating upon that autoregression to obtain the multiperiod forecast. Massimiliano et al. [90] compared empirical iterated and direct forecasts from linear univariate and bivariate models by applying simulated out-of-sample methods to 171 U.S. monthly macroeconomic time series spanning 1959-2002. The iterated forecasts typically outperformed the direct forecasts, particularly if the models could select long lag specifications. The relative performance of the iterated forecasts improved with the forecast horizon. Comparing direct and iterated blood glucose level prediction models involves evaluating their respective advantages and limitations [91], [92], [93].

5.1 Rationale Behind Using Two Autoregressive with eXogenous Inputs (ARX) Models for Predicting Blood Glucose Levels in T1DM

In recent years, ARX models have emerged as promising tools for predicting blood glucose levels. This chapter aims to justify the predominant use of Linear Model and SVR models, both applied as ARX models, in the context of T1DM, outlining their strengths and the synergistic benefits gained by combining them. Xie et al. [93] compare the performance of several commonly known machine learning (ML) models versus a classic ARX model in the prediction of BG levels using time-series data of patients with T1DM. There was no significant advantage observed from the ML models compared to the classic ARX model in predicting BG levels for T1DM, except that SVR's performance was more robust concerning BG trajectories with spurious oscillations, for which ARX tended to over-predict peak BG values and under-predict valley BG values. Insight learned from this study could help researchers and clinical practitioners to select appropriate models for BG prediction.

ARX models have demonstrated efficiency in capturing the temporal dependencies inherent in blood glucose dynamics. The autoregressive component enables the modeling of how past glucose levels influence future values, providing a robust foundation for capturing the time-evolving nature of glucose-insulin interactions. One of the key strengths of ARX models lies in their ability to seamlessly incorporate exogenous inputs. In the context of T1DM, where external factors such as meal intake and insulin doses play a crucial role, ARX models provide a comprehensive framework to integrate these influences, allowing for a more accurate representation of the physiological system.

Blood glucose dynamics are inherently non-linear, influenced by complex interactions between various physiological and external factors. The SVR, with its ability to handle non-linear relationships, offers a valuable tool for capturing intricate patterns within the data. This is especially crucial in a domain where linear models may fall short in representing the true complexity of glucose metabolism. SVR excels in high-dimensional spaces, making it well-suited for scenarios where multiple predictors contribute to blood glucose fluctuations. In the management of T1DM, where diverse factors impact glucose levels, SVR's robustness ensures that the model can effectively navigate the complexity of the system [93].

In our study on blood glucose level prediction for T1DM, we will employ a benchmark, Tables 5.1, 5.2, [52] as a systematic and transparent approach to evaluate and compare the performance of our LM and SVR models. The benchmark tables will serve as a comprehensive framework, allowing us to present key metrics and outcomes from both models in a structured format. By using the benchmark tables, we aim to facilitate a clear and objective comparison

of the predictive capabilities of LM and SVR. A The benchmark tables provide a clear, side-by-side comparison of different models based on various performance metrics. By comparing performance across different metrics, we could identify where each model excels and where it falls short. The results of the benchmark tables can guide the selection of the most appropriate model for a given task.

	RMSE (mg/dL)			
Regression Order	3 ≡ 15 (min)	6 ≡ 30 (min)	9 ≡ 45 (min)	12 ≡ 60 (min)
LM	20.14 (2.5)	19.78 (2.76)	19.52 (2.87)	**19.48 (2.91)**
ElasticNet	20.08 (2.5)	19.77 (2.73)	19.54 (2.82)	**19.51 (2.86)**
GradientBoostingTrees	21.52 (2.3)	21.05 (2.79)	21.03 (2.88)	**21.00 (2.85)**
Huber	21.03 (3.4)	20.97 (3.57)	20.98 (3.08)	21.66 (3.79)
Lasso	20.08 (2.5)	19.77 (2.73)	19.54 (2.82)	**19.51 (2.86)**
RandomForest	21.51 (2.44)	21.20 (2.58)	21.33 (2.75)	21.24 (2.79)
Ridge	20.13 (2.5)	19.78 (2.76)	19.52 (2.87)	**19.48 (2.91)**
SVRLinear	20.79 (3.27)	20.52 (3.61)	20.28 (3.64)	**20.27 (3.68)**
SVRRBF	22.25 (3.01)	22.07 (3.77)	22.12 (4.02)	22.52 (4.47)

Table 5.1: Performance metrics (mean (SD) among patients), for regression order 3 to 12, on testing data of OhioT1DM dataset using **recursive** method [52].

	RMSE (mg/dL)			
Regression Order	$3 \equiv 15$ (min)	$6 \equiv 30$ (min)	$9 \equiv 45$ (min)	$12 \equiv 60$ (min)
LM	20.16 (2.85)	19.68 (2.91)	19.53 (2.92)	19.53 (2.92)
ElasticNet	20.24 (2.75)	19.67 (2.88)	20.10 (2.91)	20.09 (2.89)
GradientBoostingTrees	20.42 (1.83)	20.42 (2.46)	20.30 (2.44)	20.50 (2.31)
Huber	20.53 (3.15)	20.42 (3.56)	20.15 (3.41)	20.33 (3.45)
Lasso	20.14 (2.67)	19.67 (2.88)	20.10 (2.91)	20.09 (2.89)
RandomForest	20.34 (2.34)	20.5 (2.58)	20.65 (2.61)	20.85 (2.54)
Ridge	20.14 (2.71)	19.66 (2.89)	19.51 (2.90)	19.52 (3.31)
SVRLinear	20.73 (3.04)	20.12 (3.32)	19.93 (3.30)	19.92 (3.31)
SVRRBF	22.11 (2.79)	22.08 (3.66)	22.61 (4.08)	23.06 (4.83)

Table 5.2: Performance metrics (mean (SD) among patients), for regression order 3 to 12, on testing data of OhioT1DM dataset using **direct** method [52].

In the realm of predictive modeling, the LM and SVR models have been employed due to their relative simplicity and interpretability. These attributes are particularly crucial in domains such as healthcare, where comprehending the decision-making process of the model is of paramount importance.

As evidenced by the tables above, LM and SVR models appear to outperform more complex models, such as Gradient Boosting Trees or Random Forests, based on the RMSE values. This superior performance indicates a high degree of accuracy in their predictions, thereby validating their suitability for the task at hand.

Jinyu et al. [52] utilized several performance metrics for evaluating the models, including temporal gain and normalized energy of the second-order differences of the predicted time series. These metrics are particularly useful for reflecting the risk of false alerts on hypo/hyperglycemia events. However, for ease of comparison and evaluation with the benchmark, we present the results for RMSE.

Furthermore, the computational efficiency of simpler models like LM and SVR is typically superior to that of more complex models. This efficiency allows for quicker training and prediction times, which can be a significant advantage in real-time or near-real-time applications.

The recursive or iterated method is frequently used in time series forecasting as it enables

the model to utilize its own previous forecasts for making future predictions. This approach can enhance performance, especially when the data exhibits temporal dependencies, a common characteristic of time series data. The recursive method appears to outperform the direct method, potentially due to its superior ability to capture the temporal dependencies in the data. This observation underscores the importance of selecting the appropriate method for the specific characteristics of the data and the task at hand.

In conclusion, the predominant use of LM and SVR models for blood glucose level prediction in T1DM is justified by their strengths and the synergistic benefits gained from their combination. LM captures temporal dependencies and incorporates exogenous factors, while SVR excels in handling non-linear relationships and high-dimensional spaces. The integration of these models represents a promising approach to enhancing predictive accuracy, providing valuable insights for the effective management of T1DM. Ongoing research and emerging trends further reinforce the significance of LM and SVR models in advancing the field of blood glucose prediction.

5.2 Direct Supervised Machine Learning Models and Results

In this section, we will briefly present the direct implementaiton LM and SVR models using data from the *in vivo* clinical study and the D1NAMO dataset as they were described above.

- **direct LM:** In the direct approach for the Linear Model, a separate model for each step ahead is trained. If we want to predict h steps ahead, we would train h different models. Each model can be represented as follows:

  For each step $k = 1, 2, ..., h,$ the model is: (5.1)

$$y_{t+k} = \beta_{0,k} + \sum_{i=1}^{p} \beta_{i,k} y_{t-i} + \sum_{j=1}^{q} \gamma_{j,k} x_{t-j} + \epsilon_{t+k} \tag{5.2}$$

  where:

  - y_{t+k} is the predicted output k steps ahead at time t.
  - $\beta_{0,k}$ is the intercept for the $k - step$ ahead model.
  - $\beta_{i,k}$ are the coefficients of the autoregressive terms for the k-step ahead model.
  - y_{t-i} are the autoregressive terms.

- $\gamma_{j,k}$ are the coefficients of the exogenous inputs for the k-step ahead model.
- x_{t-j} are the exogenous inputs (e.g., blood glucose levels, basal insulin, bolus insulin, carbohydrates intake, and time of the day).
- ϵ_{t+k} is the error term for the k-step ahead prediction at time t.
- p is the order of the autoregressive model.
- q is the number of exogenous inputs.

Each model is trained separately, and each has its own set of parameters ($\beta_{0,k}$, $\beta_{i,k}$, $\gamma_{j,k}$). The direct approach allows for flexibility as each step ahead can adapt to its own dynamics, but it may require more computational resources as the number of steps ahead increases. The order of the model was chosen using function *selstruc*, System Identification Toolbox, Matlab R2022b.

The term x_{t-j} represents the exogenous inputs at time $t-j$. Let's denote these exogenous inputs as follows:

- g_{t-j}: Blood glucose levels at time $t-j$.
- b_{t-j}: Basal insulin at time $t-j$.
- i_{t-j}: Bolus insulin at time $t-j$.
- c_{t-j}: Carbohydrates intake at time $t-j$.
- T_{t-j}: Time of the day at time $t-j$.

Then, the exogenous input vector x_{t-j} at time $t-j$ can be represented as a column vector:

$$x_{t-j} = \begin{bmatrix} g_{t-j} \\ b_{t-j} \\ i_{t-j} \\ c_{t-j} \\ T_{t-j} \end{bmatrix} \tag{5.3}$$

If we have q exogenous inputs and n observations, we can represent all the exogenous

inputs as a matrix X of size $n \times q$:

$$X = \begin{bmatrix} x_1 & x_2 & \cdots & x_n \end{bmatrix}^T = \begin{bmatrix} g_1 & b_1 & i_1 & c_1 & T_1 \\ g_2 & b_2 & i_2 & c_2 & T_2 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ g_n & b_n & i_n & c_n & T_n \end{bmatrix} \tag{5.4}$$

Each row of the matrix corresponds to the exogenous inputs at a specific time point and each column corresponds to a specific type of exogenous input across all time points.

- **direct SVR:** Following the direct LM model, the direct approach for implementing SVR is to train a separate model for each step ahead. Each model can be presented as follows:

  For each step $k = 1, 2, ..., h$, the model is:

$$\text{Minimize: } \frac{1}{2}||w_k||^2 + C\sum_{i=1}^{n}(\xi_{i,k} + \xi_{i,k}^*) \tag{5.5}$$

$$\text{Subject to: } y_{t+k} - w_k^T\phi(x_{t-j}) - b_k \leq \epsilon + \xi_{i,k} \tag{5.6}$$

$$w_k^T\phi(x_{t-j}) + b_k - y_{t+k} \leq \epsilon + \xi_{i,k}^* \tag{5.7}$$

$$\xi_{i,k}, \xi_{i,k}^* \geq 0 \tag{5.8}$$

  where:

  - w_k is the weight vector for the k-step ahead model.
  - $\phi(x_{t-j})$ is the feature map of the input vector x_{t-j}.
  - b_k is the bias for the $k - step$ ahead model.
  - C is the regularization parameter.
  - $\xi_{i,k}$ and $\xi_{i,k}^*$ are slack variables for the $k - step$ ahead model.
  - ϵ is the tube width of the epsilon-insensitive loss function.

  Each model is trained separately, and each has its own set of parameters (w_k, b_k, $\xi_{i,k}$, $\xi_{i,k}^*$).

The direct approach allows for flexibility as each step ahead can adapt to its own dynamics, but it may require more computational resources as the number of steps ahead increases. the matrix X of exogenous inputs, Equation 5.4 is used to map the input data to a higher-dimensional feature space using a function $\phi(x)$. The SVR then finds a linear function in this feature space that fits the data with a certain error tolerance ϵ.

Table 5.3: RMSE and CEG_A results 30, 45 and 60 minutes ahead prediction horizon from two patients (FN Motol Hospital) (**CASE I)**

		Patient 1				Patient 2			
Model	PH min	RMSE mg/dl		CEG_A %		RMSE mg/dl		CEG_A %	
		TR	TS	TR	TS	TR	TS	TR	TS
ARX	30	26.57	**27.35**	86.95	**89.00**	17.29	**17.96**	89.87	**89.60**
	45	29.50	**27.28**	80.20	**83.55**	23.83	**24.34**	79.97	**80.77**
	60	34.84	**33.70**	74.75	**75.78**	28.82	**33.75**	71.55	**76.68**
SVR	30	29.14	**29.52**	88.52	**90.46**	17.45	**18.19**	89.93	**89.55**
	45	32.29	**31.22**	82.52	**84.16**	24.18	**24.95**	80.80	**80.94**
	60	35.56	**34.21**	75.55	**74.05**	29.24	**32.38**	73.32	**76.31**

Table 5.4: RMSE and CEG_A results 30, 45 and 60 minutes ahead prediction horizon from two patients (FN Motol Hospital) (**CASE II)**

		Patient 1				Patient 2			
Model	PH min	RMSE mg/dl		CEG_A %		RMSE mg/dl		CEG_A %	
		TR	TS	TR	TS	TR	TS	TR	TS
ARX	30	22.91	**19.62**	87.88	**91.69**	15.20	**17.10**	89.98	**92.54**
	45	29.04	**25.06**	80.91	**85.14**	22.69	**23.61**	80.12	**82.48**
	60	34.57	**29.44**	74.93	**76.15**	27.63	**29.15**	71.99	**78.94**
SVR	30	26.10	**21.24**	88.25	**92.08**	17.36	**18.63**	89.90	**89.56**
	45	30.18	**27.20**	81.09	**84.84**	24.07	**25.76**	81.15	**81.69**
	60	36.18	**30.63**	75.96	**77.83**	29.13	**27.20**	74.22	**78.02**

		ARX		SVR	
Patient ID	PH	RMSE (mg/dL)	CEG_A%	RMSE (mg/dL)	CEG_A%
1	30	19.08 (0.27)	89.91 (1.21)	19.51 (0.26)	90.42 (1.45)
	45	28.98 (0.45)	78.45 (1.04)	29.16 (0.42)	80.91 (0.25)
	60	37.62 (0.63)	69.30 (1.27)	38.16 (0.67)	71.84 (0.27)
2	30	23.40 (0.41)	84.57 (0.32)	23.94 (1.41)	83.58 (1.54)
	45	38.16 (0.25)	70.32 (1.41)	39.60 (0.31)	71.11 (1.15)
	60	51.12 (0.01)	56.97 (0.67)	53.64 (1.03)	61.72 (1.41)
3	30	23.22 (0.55)	84.77 (1.45)	23.76 (1.32)	83.77 (1.99)
	45	37.80 (1.62)	70.82 (1.11)	39.24 (0.15)	72.21 (0.77)
	60	50.76 (1.54)	57.02 (1.76)	53.28 (1.45)	62.12 (0.73)
4	30	31.14 (1.42)	80.19 (1.21)	32.94 (1.65)	81.60 (1.78)
	45	44.82 (0.19)	63.20 (0.06)	46.44 (1.12)	67.49 (1.23)
	60	55.98 (0.98)	56.06 (0.43)	57.78 (1.22)	56.82 (1.76)

Table 5.5: RMSE and CEG_A results 30, 45 and 60 minutes ahead prediction horizon from four patients (D1NAMO dataset) (**CASE I)**

		ARX		SVR	
Patient ID	PH	RMSE (mg/dL)	CEG_A%	RMSE (mg/dL)	CEG_A%
1	30	17.56 (0.66)	90.02 (0.12)	17.34 (0.21)	91.27 (0.33)
	45	26.92 (1.23)	79.56 (1.56)	28.92 (1.67)	82.34 (2.32)
	60	34.57 (0.43)	70.02 (0.25)	37.42 (1.35)	72.98 (0.94)
2	30	22.94 (0.32)	85.31 (1.23)	23.71 (1.45)	84.72 (0.39)
	45	37.61 (1.91)	71.49 (1.45)	39.02 (1.34)	72.98 (2.25)
	60	49.32 (0.02)	57.02 (2.17)	52.49 (2.06)	63.42 (1.67)
3	30	22.89 (0.60)	85.36 (1.63)	23.06 (0.80)	84.56 (1.58)
	45	37.04 (1.14)	71.47 (1.36)	38.49 (0.70)	72.98 (1.34)
	60	49.32 (1.45)	58.23 (1.34)	52.61 (0.78)	63.09 (2.04)
4	30	30.81 (1.67)	80.58 (1.07)	31.41 (1.76)	82.39 (1.66)
	45	43.25 (1.05)	64.78 (0.67)	45.69 (1.56)	68.41 (1.34)
	60	55.02 (1.37)	57.16 (1.58)	54.78 (0.98)	57.15 (1.65)

Table 5.6: RMSE and CEG_A results 30, 45 and 60 minutes ahead prediction horizon from four patients (D1NAMO dataset) (**CASE II)**

The results from the ARX and SVR models, as summarized in Tables 5.3, 5.4, 5.5 and 5.6, provide insightful observations for multi-step ahead forecasting. It is evident that the implementation of the compartment model for bolus insulin absorption simulation, referred to as **CASE II**, significantly enhances the prediction results.

Interestingly, ARX tends to outperform SVR for both *in vivo* datasets and D1NAMO datasets. This observation aligns with the benchmark table presented by Jinyu et al. [52]. However, it is important to note that the superiority of one model over the other can be dataset-specific and may not always hold true.

While ARX shows promising results, the incorporation of SVR can further enhance the predictive performance when used in an ensemble setting. Ensemble methods, which combine predictions from multiple models, are known to improve robustness and accuracy. In our context, an ensemble of ARX and SVR could potentially leverage the

strengths of both models. ARX, with its ability to capture linear relationships and SVR, with its capacity to model non-linearities, could together provide a more comprehensive modeling of the underlying data. This could lead to improved prediction performance, especially in scenarios where the data exhibits both linear and non-linear characteristics. Future work will explore this potential synergy between ARX and SVR in an ensemble setup.

5.3 Iterated Supervised Machine Learning Models and Results

In the iterated (or recursive) approach, the same one-step ahead model is used in each forecasting iteration (each number of steps ahead). The *h-steps* ahead prediction is performed by iterative use of one-step-ahead predictions, where unknown "past" values are replaced by the values predicted in the previous iterations.

– **iterated LM:** In the iterative approach for the Linear Model, we train a $one-step$ ahead model and then apply it iteratively to generate $multi-stepahead$ predictions. The $one-step$ ahead prediction is fed back as an input for predicting the next step.

$$y_{t+1} = \beta_0 + \sum_{i=1}^{p} \beta_i y_{t-i+1} + \sum_{j=1}^{q} \gamma_j x_{t-j+1} + \epsilon_{t+1} \tag{5.9}$$

For each step $k = 2, 3, ..., h,$ we use the previous prediction y_{t+k-1} as an input: (5.10)

$$y_{t+k} = \beta_0 + \sum_{i=1}^{p} \beta_i y_{t+k-i-1} + \sum_{j=1}^{q} \gamma_j x_{t+k-j-1} + \epsilon_{t+k} \tag{5.11}$$

Algorithm 1 Iterative Approach for Linear Model

1: Initialize the one-step ahead model parameters β_0, β_i, γ_j
2: **for** $k = 1$ to h **do**
3: Compute the one-step ahead prediction y_{t+1} using the model:
4: $y_{t+1} = \beta_0 + \sum_{i=1}^{p} \beta_i y_{t-i+1} + \sum_{j=1}^{q} \gamma_j x_{t-j+1} + \epsilon_{t+1}$
5: Update the inputs for the next step using the prediction y_{t+1}

– **iterated SVR:** In this case, the $one-stepahead$ model is trained and then apply it iteratively to generate $multi-stepahead$ predictions. The $one-stepahead$ prediction is fed back as an input for predicting the next step. The model can be represented as follows:

For the first step, the model is:

$$\text{Minimize: } \frac{1}{2}||w||^2 + C\sum_{i=1}^{n}(\xi_i + \xi_i^*) \tag{5.12}$$

$$\text{Subject to: } y_{t+1} - w^T\phi(x_{t-j}) - b \leq \epsilon + \xi_i \tag{5.13}$$

$$w^T\phi(x_{t-j}) + b - y_{t+1} \leq \epsilon + \xi_i^* \tag{5.14}$$

$$\xi_i, \xi_i^* \geq 0 \tag{5.15}$$

For each step $k = 2, 3, ..., h$, we use the previous prediction y_{t+k-1} as an input:

$$\text{Minimize: } \frac{1}{2}||w_k||^2 + C\sum_{i=1}^{n}(\xi_{i,k} + \xi_{i,k}^*) \tag{5.16}$$

$$\text{Subject to: } y_{t+k} - w_k^T\phi(x_{t+k-1}) - b_k \leq \epsilon + \xi_{i,k} \tag{5.17}$$

$$w_k^T\phi(x_{t+k-1}) + b_k - y_{t+k} \leq \epsilon + \xi_{i,k}^* \tag{5.18}$$

$$\xi_{i,k}, \xi_{i,k}^* \geq 0 \tag{5.19}$$

Algorithm 2 Iterative Approach for SVR

1: Initialize the one-step ahead model parameters w, b, ξ_i, ξ_i^*
2: **for** $k = 1$ to h **do**
3: Compute the one-step ahead prediction y_{t+1} using the model:
4: Minimize: $\frac{1}{2}||w||^2 + C\sum_{i=1}^{n}(\xi_i + \xi_i^*)$
5: Subject to: $y_{t+1} - w^T\phi(x_{t-j}) - b \leq \epsilon + \xi_i$
6: $w^T\phi(x_{t-j}) + b - y_{t+1} \leq \epsilon + \xi_i^*$
7: $\xi_i, \xi_i^* \geq 0$
8: Update the inputs for the next step using the prediction y_{t+1}

The subsequent tables, specifically Table 5.7, 5.8, and 5.9, encapsulate the results

derived from the application of the iterated LM model and SVR on both *in vivo* and simulated data sets. These results pertain to a prediction horizon of 60 minutes.

A noteworthy observation from these results is the significant role played by the compartment model in enhancing the forecasting outcomes. While the LM model appears to outperform the SVR model, the disparity in performance between these two models is not substantial. This suggests that both models exhibit comparable efficacy in this context, thereby providing multiple viable options for blood glucose level prediction. Further investigation could potentially reveal specific scenarios where one model may have a slight edge over the other. This nuanced understanding could guide the choice of model in future studies and applications. These findings contribute to the ongoing efforts in the field of diabetes management to develop reliable and accurate prediction models, ultimately aiding in better disease management and improving the quality of life for individuals living with diabetes.

Table 5.7: RMSE and CEG_A results 60 minutes ahead prediction horizon from two patients (FN Motol Hospital) (**CASE I and II**)

CASE I		Patient 1				Patient 2			
Model	PH [min]	RMSE [mg/dl]		CEG_A [%]		RMSE [mg/dl]		CEG_A [%]	
		TR	TS	TR	TS	TR	TS	TR	TS
iterated LM	60	34.21	**28.64**	75.43	**76.77**	27.03	**29.05**	72.56	**78.73**
iterated SVR	60	36.07	**29.07**	76.08	**78.97**	28.67	**26.55**	75.62	**76.05**
CASE II		Patient 1				Patient 2			
Model	PH [min]	RMSE [mg/dl]		CEG_A [%]		RMSE [mg/dl]		CEG_A [%]	
		TR	TS	TR	TS	TR	TS	TR	TS
iterated LM	60	33.12	**27.36**	75.83	**76.87**	26.43	**28.65**	72.93	**78.17**
iterated SVR	60	35.77	**28.71**	76.98	**79.45**	27.64	**26.32**	76.86	**79.28**

Table 5.8: RMSE and CEG_A results 60 minutes ahead prediction horizon from four patients (D1NAMO dataset) (**CASE I**)

		iterated LM		iterated SVR	
Patient ID	PH [min]	RMSE [mg/dl]	CEG_A [%]	RMSE [mg/dl]	CEG_A [%]
1	60	33.25 $\pm$ 0.44	72.27 $\pm$ 0.23	36.97 $\pm$ 1.39	73.56 $\pm$ 1.01
2	60	48.39 $\pm$ 0.08	58.97 $\pm$ 0.23	46.91 $\pm$ 1.39	69.06 $\pm$ 1.01
3	60	48.90$\pm$ 0.98	59.97 $\pm$ 1.23	57.97 $\pm$ 1.49	71.16 $\pm$ 1.31
4	60	49.56$\pm$ 1.98	62.88 $\pm$ 0.94	61.54 $\pm$ 1.34	69.43 $\pm$ 1.07

Table 5.9: RMSE and CEG_A results 60 minutes ahead prediction horizon from four patients (D1NAMO dataset) (**CASE II**)

		iterated LM		iterated SVR	
Patient ID	PH [min]	RMSE [mg/dl]	CEG_A [%]	RMSE [mg/dl]	CEG_A [%]
1	60	32.85 $\pm$ 0.78	73.43 $\pm$ 0.53	35.37 $\pm$ 1.05	74.34 $\pm$ 1.45
2	60	45.92 $\pm$ 1.34	60.02 $\pm$ 1.23	49.27 $\pm$ 1.56	70.43 $\pm$ 1.36
3	60	50.32$\pm$ 1.37	62.35 $\pm$ 0.77	59.81 $\pm$ 1.05	73.54 $\pm$ 0.99
4	60	51.32$\pm$ 1.38	64.37 $\pm$ 1.94	65.83 $\pm$ 1.75	73.52 $\pm$ 1.25

5.4 Evaluation and Discussion

In summary, implementing LM and SVR for blood glucose level prediction can balance model simplicity and effectiveness in capturing both linear and non-linear relationships in the data. In general, LM and SVR were chosen to be applied and tested because the available data set size was not large enough to support the use of more complex models. Our main goal is to be able to compare easily the performance of simple models and ensemble frameworks.

Moreover, it is clearly stated from the results from both clinical and simulation data, that the compartment model for bolus insulin can improve the performance of the models

significantly. According to the results from the above tables, it is clearly stated that models that used the compartment model for bolus insulin performed significantly better than the simple implementation and the percentage of data that fall in region A (CEG analysis) increased more than 2% in some cases.

Additionally, blood glucose levels are influenced by intricate physiological processes that exhibit non-linear patterns. SVR's capability to model non-linearity through various kernel functions provides a significant advantage over LM, which relies on linear modeling assumptions. SVR can capture complex and non-linear relationships between input variables and blood glucose levels, making it more adept at handling the inherent complexity of this physiological system.

Another critical factor is the robustness of SVR to outliers. Blood glucose data frequently contain noisy or extreme values that can negatively impact model performance. SVR, by focusing on support vectors near the decision boundary, is less affected by outliers that lie far from this boundary. This robustness allows SVR to provide more accurate predictions in the presence of noisy data, enhancing its suitability for blood glucose level prediction tasks.

Moreover, SVR offers automatic feature selection and weighting capabilities through the kernel trick. In contrast, LM typically requires manual selection and specification of lagged time series inputs. SVR's adaptability enables it to automatically identify essential input variables and their temporal relationships, potentially leading to more accurate and comprehensive predictions when dealing with the diverse and complex factors affecting blood glucose levels.

SVR's ability to model non-linearity, robustness to outliers, automatic feature selection, flexibility in model complexity, and adaptability to small datasets make it a compelling choice for blood glucose level prediction tasks. Its superior performance compared to LM stems from its capacity to address the complex and dynamic nature of blood glucose regulation more effectively. It can be clearly stated that SVR model with an open compartment model can result in more accurate blood glucose level predictions.

Table 5.10: Compare and evaluate results from LM and SVR with the benchmark results [52]

	PH=60 min	Direct Method	Iterated Method
		RMSE (mg/dL)	RMSE (mg/dL)
LM Benchmark	**in vitro results**	**19.53**	**19.48**
LM	**Patient 1**		
	in vivo CASE I	33.70	28.64
	in vivo CASE II	29.44	**27.36**
	Patient 2		
	in vivo CASE I	33.75	29.05
	in vivo CASE II	**29.15**	28.65
	Patient ID:1		
	D1NAMO CASE I	37.62	33.25
	D1NAMO CASE II	34.57	32.85
SVR Benchmark	**in vitro results**	**19.92**	**20.27**
SVR	**Patient 1**		
	in vivo CASE I	34.21	27.36
	in vivo CASE II	30.63	28.71
	Patient 2		
	in vivo CASE I	32.38	26.55
	in vivo CASE II	**27.20**	**26.32**
	Patient ID:1		
	D1NAMO CASE I	38.16	36.97
	D1NAMO CASE II	37.42	35.37

Attempting to evaluate the performance of the two models, we constructed a table, Table

5.10 to summarize the data. According to Table 5.10, we can draw several conclusions:

1. LM and SVR Performance: Both LM and SVR models show a higher RMSE in in vivo cases compared to the in vitro benchmark results. This indicates that both models have more difficulty predicting in a more complex, real-world scenario.
2. Comparison Between LM and SVR: In most cases, the SVR model seems to perform slightly better than the LM model, as indicated by the lower RMSE values in the 'Iterated Method' column. This suggests that the SVR model may be more robust in handling the variability and complexity of in vivo data.
3. Patient Variability: There is noticeable variability in the RMSE values across different patients and cases. This highlights the challenge of developing a one-size-fits-all model for glucose prediction and emphasizes the need for personalized models.
4. D1NAMO Cases: The D1NAMO cases generally show higher RMSE values compared to the in vivo cases for the same patient. This could be due to the increased complexity and different conditions in the D1NAMO cases.

In conclusion, while both LM and SVR models provide valuable tools for glucose prediction, there is room for improvement, particularly in enhancing the models' performance in in vivo scenarios and addressing patient-specific variability.

Chapter 6

Ensemble Framework: Direct versus Iterated Results

6.1 Description of Ensemble Methods

Ensemble techniques have proven to be effective in improving the accuracy of blood glucose level predictions for individuals with T1DM. These techniques combine the predictions of multiple individual models to produce a more robust and accurate forecast [94], [95], [96]. They offer improved accuracy, robustness, and adaptability, making them valuable tools for both patients and healthcare professionals in managing this chronic condition. However, the choice of ensemble method and the incorporation of domain-specific knowledge remain important factors in achieving optimal predictive performance [97], [98], [99]. Wadghiri et al. (2022) conducted systematic literature to analyze and synthesize primary studies published between 2000 and 2020 in six digital libraries. A total of 32 primary papers were selected and reviewed about eight review questions. The results show that ensembles have gained wider interest during the last years and improved in general performance compared with other single models [100].

In our recent study, titled "Ensemble Methods in Combination with Compartment Models for Blood Glucose Level Prediction in Type 1 Diabetes Mellitus" [101], we proposed an ensemble framework. This framework combined widely-used glycemia prediction algorithms and applied three distinct ensemble methods: Linear, Bagging, and Boosting metaregressor. These methods were evaluated based on their ability to provide accurate predictions for 30, 45, and 60-minute ahead prediction horizons.

Our results demonstrated that ensemble methods yield more accurate glucose concentration predictions compared to individual algorithms. Specifically, the Bagging metaregressor outperformed individual algorithms across all prediction horizons, particularly for

small datasets. The Bagging ensemble method improved the percentage in Zone A according to the CEG analysis by 4%, and in some cases, as much as 9%.

Furthermore, our results showed that compartment models enhance results when combined with any method at any prediction horizon. To further these results, we extended our work on ensemble methods and incorporated two methods for multi-step ahead predictions: the direct and the iterated method.

6.1.1 Linear meta-model

In the ensemble framework being described, multiple base models, including linear regression, are employed to generate initial predictions on the input data. These predictions are then integrated by a linear meta-model to produce the final output.

The linear meta-model computes the coefficients, denoted as Φ_{PH}, for each prediction horizon (PH) based on the least squares method. The matrix R_{PH} represents the outputs of each individual model (such as LM, SVR), with each column corresponding to a specific model's output. The vector y_{PH} contains the actual measured blood glucose values, serving as the target for prediction at each PH.

The final prediction, $\hat{y}_{PH}$, is computed as the product of r_{PH} and ϕ_{PH}, where r_{PH} is a row of R_{PH} and ϕ_{PH} is a corresponding coefficient from Φ_{PH}. The equation is given by:

$$\hat{y}_{PH} = r_{PH} \times \phi_{PH} \tag{6.1}$$

The coefficients Φ_{PH} are computed at each prediction horizon using the formula:

$$\Phi_{PH} = (R_{PH}^T R_{PH})^{-1} R_{PH}^T y_{PH} \tag{6.2}$$

The linear meta-model, as depicted schematically in Figure 6.1, serves as the integrative component of this ensemble framework. It takes the outputs from the individual models as inputs and processes them to produce the BG level prediction. This illustrates the collaborative nature of the ensemble framework, where each model contributes to the final outcome, thereby improving the overall predictive performance. This ensemble methodology, with its capacity for integrating diverse models and their outputs, offers a promising avenue for advancing predictive accuracy in complex scenarios. $Algorithm\ 3$ provides a comprehensive summary of the procedure for applying the Linear meta-model. This process can be utilized with the outputs from either the direct or iterated versions of the LM and SVR models. This encapsulates the fundamental steps required for the

effective implementation of this ensemble framework in predictive tasks. The algorithm serves as a guide for integrating diverse model outputs to enhance prediction accuracy in complex scenarios.

Algorithm 3 Ensemble Framework with Linear Meta-Model

Input: Data X, Base Models $M = \{m_1, m_2, ..., m_n\}$
Output: Final prediction $\hat{y}_{PH}$
for each base model m_i in M **do**
    Generate initial predictions $r_{PH}^{(i)} = m_i(X)$
Construct R_{PH} by concatenating all $r_{PH}^{(i)}$
Compute $\Phi_{PH} = (R_{PH}^T R_{PH})^{-1} R_{PH}^T y_{PH}$
for each row r_{PH} in R_{PH} **do**
    Compute final prediction $\hat{y}_{PH} = r_{PH} \times \phi_{PH}$
return $\hat{y}_{PH}$

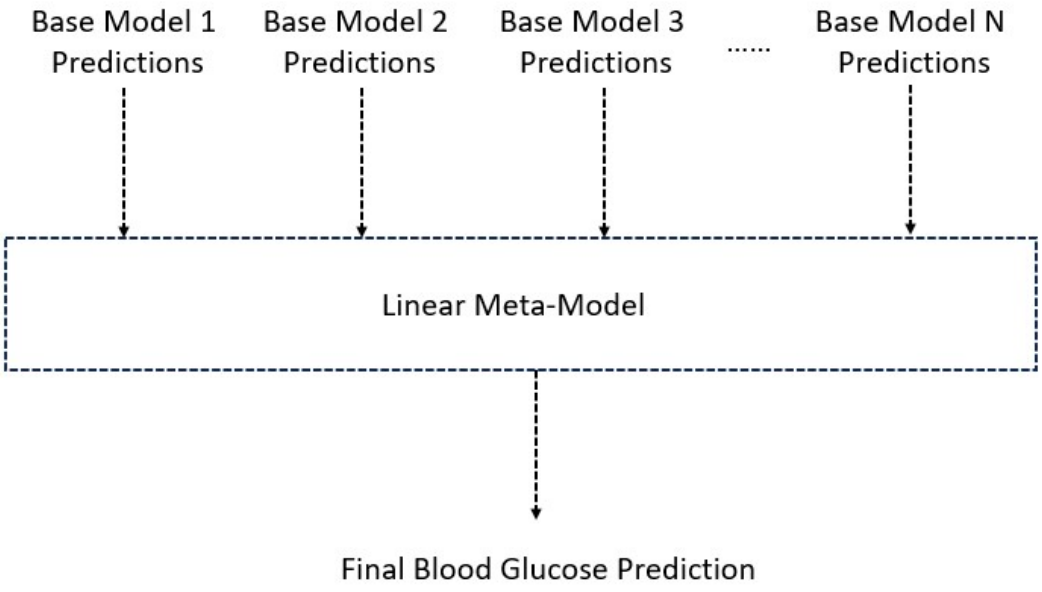


Figure 6.1: Schematic Representation of Linear meta-model

6.1.2 Bagging meta-model

Bagging, proposed by Breiman [102], is a method that leverages bootstrap aggregation to enhance the predictive performance of a model. By forming a combination over a set of training sets, bagging reduces variance and helps mitigate overfitting. This is particularly effective when the data are split into random different samples, as decision trees can yield different results, leading to high variance.

The bagging method improves model stability by averaging out the noise and variability present in individual base models. It's a powerful technique for enhancing predictive performance, especially when combined with complex base models that have high variance, such as deep decision trees or random forests. The principle behind bagging is that averaging multiple varied estimations produces less uncertain results.

Given the matrix R_{PH} at each prediction horizon as the training set and y_{PH} as the target values at each PH, bagging repeatedly (B times) selects a random sample with replacement of the training set and fits trees to these samples.

For $b = 1...B$:

1. Sample with replacement n training examples from R_{PH}, y_{PH}: call these R_b, y_b
2. Train a regression tree f_b on R_b, y_b

After training, predictions for unseen samples R' can be made by averaging the predictions from all the individual regression trees on R':

$$\hat{y}_{PH} = \frac{1}{B} \sum_{b=1}^{B} f_b(R_{PH}) \tag{6.3}$$

The following algorithm outlines the key steps involved in the Bagging method:

Algorithm 4 Ensemble Framework with Bagging Method

Input: Training set R_{PH}, y_{PH}, Number of bootstrap samples B
Output: Final prediction $\hat{y}_{PH}$
for $b = 1$ to B **do**
    Sample with replacement n training examples from R_{PH}, y_{PH}: call these R_b, y_b
    Train a regression tree f_b on R_b, y_b
Compute final prediction for unseen samples R':
$\hat{y}_{PH} = \frac{1}{B} \sum_{b=1}^{B} f_b(R_{PH})$
return $\hat{y}_{PH}$

This algorithm provides a step-by-step procedure for implementing the Bagging method. It begins by sampling with replacement from the training set to create bootstrap samples. Each of these samples is then used to train a regression tree. The final prediction is computed by averaging the predictions from all the individual regression trees. Figure 6.2 presents the basic steps for implementing the Bagging meta-model.

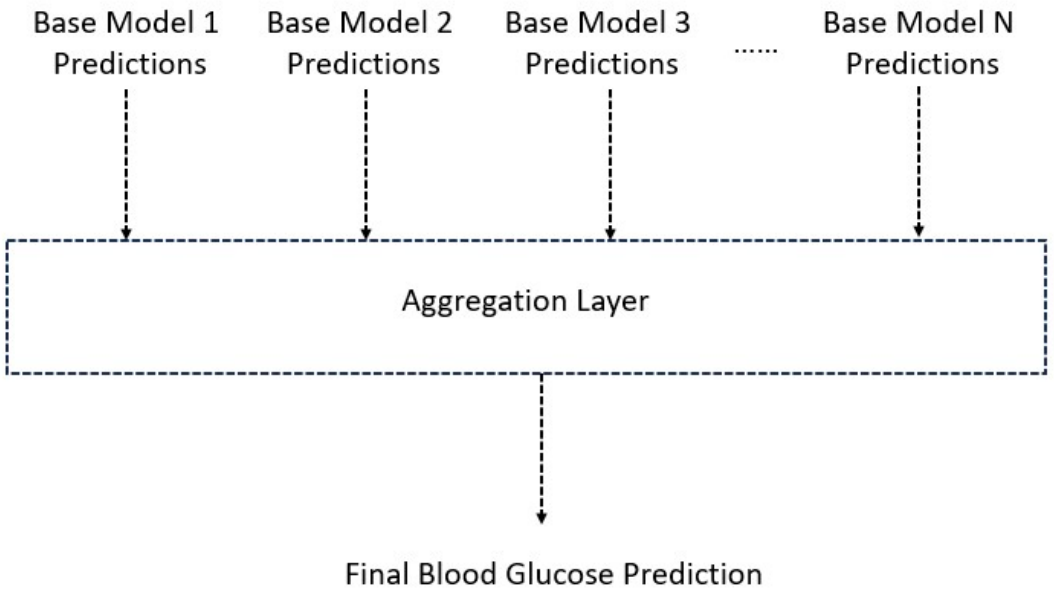


Figure 6.2: Schematic Representation of Bagging meta-model

6.1.3 Boosting meta-model

The LS-Boost algorithm, a gradient-based boosting strategy proposed by Friedman [103], operates on the principle of sequentially growing decision trees. Unlike bagging, which grows trees independently, boosting constructs an ensemble of weak learners (typically decision trees) in a sequential manner, with each learner aiming to correct the errors made by its predecessor. This is achieved by fitting each new model to the residuals, which are the differences between the actual values and the predictions of the previous model.

In the context of boosting, each tree is grown using information from previously grown trees, and the method does not involve bootstrap sampling. Instead, each tree is fit on a modified version of the original data set.

The LS-Boost algorithm for regression trees can be outlined as follows:

The LS-Boost algorithm, as outlined above, offers a robust and flexible approach for predictive tasks. It can seamlessly integrate data from both direct and iterated LM and SVR models, making it a versatile tool for various prediction scenarios. The algorithm operates by sequentially fitting regression trees to the residuals, which are updated at each iteration. This iterative process allows the algorithm to continuously learn from the errors of the previous models, thereby improving the accuracy of the final prediction. The schematic representation (Figure 6.3) of this method, which will be introduced subsequently, provides a visual illustration of this process, highlighting the sequential

Algorithm 5 Ensemble Framework with LS-Boost Method

Input: Training set R_{PH}, y_{PH}, Number of iterations B
Output: Final prediction $\hat{y}_{PH}$
Initialize $\hat{f}(x) = 0$ and residuals $r = y_{PH}$
for $b = 1$ to B **do**
    Fit a tree $\hat{f}^b$ with d splits ($d + 1$ terminal nodes) to the training set (R_{PH}, r)
    Update $\hat{f}(x)$ by adding a shrunken version of the new tree:
    $\hat{f}(x) \leftarrow \hat{f}(x) + \lambda \hat{f}^b(x)$
    Update the residuals:
    $r_i \leftarrow r_i - \lambda \hat{f}^b(x)$
Compute the final prediction:
$\hat{y}_{PH} = \hat{f}^b(x) = \sum_{b=1}^{B} \lambda \hat{f}^b(x)$
return $\hat{y}_{PH}$

nature of the algorithm and the role of residuals in guiding the model fitting process. This ensemble methodology, with its capacity for integrating diverse models and their outputs, offers a promising avenue for advancing predictive accuracy in complex scenarios.

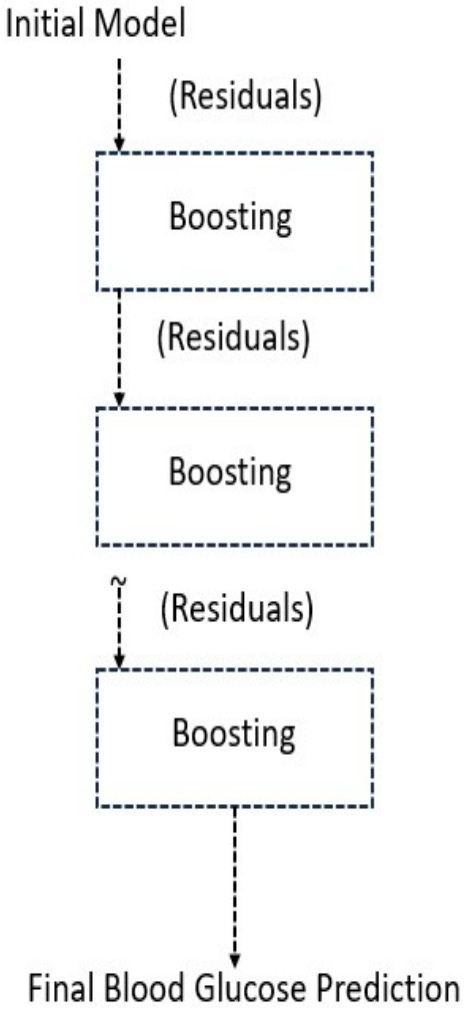


Figure 6.3: Schematic Representation of Boosting meta-model

In the schematic representation, each "Boosting" block represents the training of a new weak learner on the residuals of the previous ensemble and updating the ensemble's prediction. This process is repeated iteratively, and the final prediction is obtained by summing up the predictions of all the models in the ensemble. The ensemble prediction represents the refined and improved output as each new model corrects the errors of the previous ones.

6.2 Ensemble Framework: Methodology and Results

6.2.1 Ensemble Framework: Direct Versus Iterated Method

This section delves into a comparative analysis of two distinct methodologies: the Direct Method and the Iterated Method, both of which employ LM and SVR models. In the Direct Method, as illustrated in Figure 6.4, both the LM and SVR models are trained directly on *in vivo* data. The outputs from these models are then integrated by the meta-model, which learns to optimally utilize the information from both models to enhance prediction accuracy when dealing with *in vivo* data. Three meta-models, namely Linear, Bagging, and LS Boosting, are employed for generating the final prediction. The same steps are applied with D1NAMO patients' datasets.

On the other hand, the Iterated Method, depicted in Figure 6.5, involves an iterative refinement of predictions. The initial meta-model combines the outputs of the LM and SVR models, and these combined predictions are then fed back into the LM and SVR models for multiple cycles. This iterative process continues until convergence is achieved. The final prediction is then generated by the Updated Meta Model.

The comparison between these two methods provides valuable insights into their respective strengths and potential applications. It also sheds light on how different approaches to model training and prediction generation can impact the overall predictive performance.

Here is a high-level algorithmic representation of the two methods:

Algorithm 6 Comparison of Direct and Iterated Methods

Direct Method:
Train LM and SVR models on *in vivo* data.
Combine outputs of LM and SVR models using the meta-model (Linear, Bagging, or LS Boosting).
Generate final prediction.
Iterated Method:
Initialize meta-model with outputs of LM and SVR models.
while not converged **do**
    Feed combined predictions back into LM and SVR models.
    Update meta-model with new outputs of LM and SVR models.
Generate final prediction with Updated Meta Model.

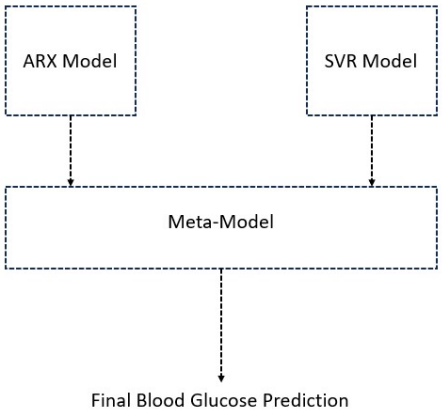


Figure 6.4: Schematic Representation of ensemble framework for **(CASE I and II)** with *in vivo* data and D1NAMO data set

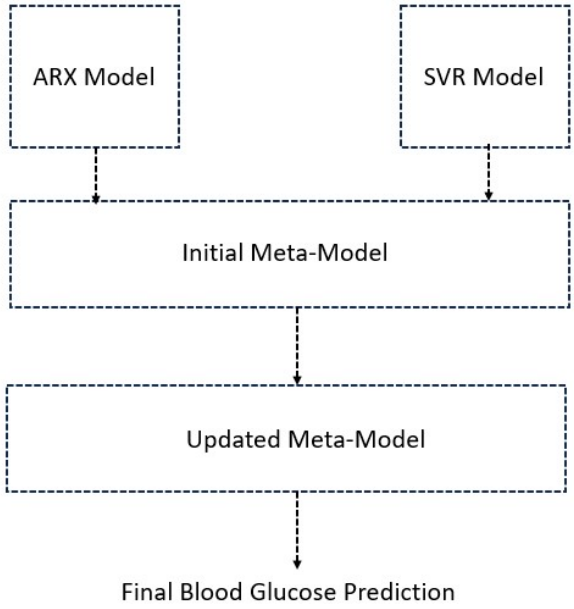


Figure 6.5: Schematic Representation of ensemble framework for **(CASE I and II)** with *in vivo* data and D1NAMO data set

6.2.2 In vivo results

This section presents the *in vivo* results obtained from two patients at the FN Motol Hospital. The results are organized into four tables, each providing a detailed view of the RMSE and CEG_A results for predictions made 30, 45, and 60 minutes ahead of the prediction horizon.

- **Table 6.1** and **Table 6.3** pertain to **CASE I**, where bolus insulin is used as an impulse signal. These tables provide a comprehensive view of the RMSE and CEG_A results for predictions made 30, 45, and 60 minutes ahead for the direct method (Table 6.1), and specifically for the 60-minute prediction horizon for the iterated method (Table 6.3).
- **Table 6.2** and **Table 6.4** correspond to **CASE II**, where a compartment model is employed for the simulation of bolus insulin absorption. Similar to CASE I, these tables present the RMSE and CEG_A results for predictions made 30, 45, and 60 minutes ahead for the direct method (Table 6.2), and specifically for the 60-minute prediction horizon for the iterated method (Table 6.4).

The comparison between **CASE I** and **CASE II** offers valuable insights into the performance of the two different methodologies in predicting blood glucose levels. This

analysis is crucial for understanding the effectiveness of these methods in real-world, *in vivo* scenarios.

Table 6.1: RMSE and CEG_A results 30, 45 and 60 minutes ahead prediction horizon from two patients (FN Motol Hospital) (**CASE I)**

		Patient 1				Patient 2			
Model	PH min	RMSE [mg/dl]		CEG_A [%]		RMSE [mg/dl]		CEG_A [%]	
		TR	TS	TR	TS	TR	TS	TR	TS
Linear meta-model	30	24.37	**25.11**	90.53	**91.38**	16.29	**15.98**	92.45	**94.78**
	45	28.77	**27.30**	83.36	**86.77**	20.04	**19.96**	82.45	**87.77**
	60	33.92	**32.45**	76.77	**77.63**	25.45	**22.95**	73.78	**78.00**
Bagging meta-model	30	23.64	**24.32**	91.45	**95.35**	14.37	**13.49**	95.11	**96.37**
	45	26.93	**25.44**	84.90	**88.30**	19.37	**18.00**	96.93	**90.02**
	60	31.90	**29.62**	77.06	**79.18**	24.34	**22.77**	74.02	**80.31**
Boosting meta-model	30	23.32	**23.77**	92.65	**96.00**	13.91	**12.88**	96.04	**97.04**
	45	26.55	**26.08**	85.63	**89.39**	18.65	**17.43**	97.42	**90.45**
	60	29.99	**28.23**	78.39	**79.40**	23.99	**21.84**	76.98	**82.57**

Table 6.3: RMSE and CEG_A results, 60 minutes ahead prediction horizon from two patients (FN Motol Hospital) (**CASE I)**

		Patient 1				Patient 2			
Model	PH [min]	RMSE [mg/dl]		CEG_A [%]		RMSE [mg/dl]		CEG_A [%]	
		TR	TS	TR	TS	TR	TS	TR	TS
iterated Linear meta-model	60	29.31	**30.82**	77.56	**78.29**	21.74	**20.34**	73.68	**77.88**
iterated Bagging meta-model	60	28.49	**26.84**	76.47	**80.26**	21.43	**20.84**	73.50	**79.91**
iterated Boosting meta-model	60	27.03	**27.43**	81.19	**80.91**	21.75	**20.66**	78.46	**84.44**

Table 6.2: RMSE and CEG_A results 30, 45 and 60 minutes ahead prediction horizon from two patients (FN Motol Hospital) (**CASE II)**

		Patient 1				Patient 2			
Model	PH [min]	RMSE [mg/dl]		CEG_A [%]		RMSE [mg/dl]		CEG_A [%]	
		TR	TS	TR	TS	TR	TS	TR	TS
Linear meta-model	30	22.46	**23.36**	90.69	**91.97**	14.85	**14.73**	92.65	**95.39**
	45	25.82	**25.42**	83.28	**87.06**	18.71	**18.73**	82.67	**88.71**
	60	31.83	**31.35**	77.35	**78.15**	23.08	**21.35**	73.18	**80.31**
Bagging meta-model	30	20.99	**22.99**	91.78	**95.74**	11.50	**11.58**	95.41	**97.41**
	45	24.55	**23.54**	84.13	**90.93**	16.68	**16.21**	96.70	**91.39**
	60	29.89	**28.57**	76.51	**80.66**	22.36	**20.86**	74.03	**81.72**
Boosting meta-model	30	21.06	**22.88**	94.45	**97.20**	12.10	**12.29**	96.92	**98.78**
	45	25.49	**25.69**	87.52	**91.83**	17.95	**16.91**	98.07	**91.15**
	60	28.52	**27.47**	80.09	**81.86**	22.96	**21.45**	78.29	**83.10**

Table 6.4: RMSE and CEG_A results, 60 minutes ahead prediction horizon from two patients (FN Motol Hospital) (**CASE II)**

		Patient 1				Patient 2			
Model	PH [min]	RMSE [mg/dl]		CEG_A [%]		RMSE [mg/dl]		CEG_A [%]	
		TR	TS	TR	TS	TR	TS	TR	TS
iterated Linear meta-model	60	29.09	**29.39**	78.11	**79.31**	20.09	**18.92**	75.27	**94.26**
iterated Bagging meta-model	60	27.89	**26.58**	76.74	**81.80**	21.03	**15.47**	73.57	**95.37**
iterated Boosting meta-model	60	25.17	**25.98**	82.87	**81.79**	21.62	**16.34**	78.79	**95.81**

6.2.3 D1NAMO data set results

This section presents the results obtained from the D1NAMO dataset for two different cases: CASE I and CASE II. The results are based on the RMSE and the CEG_A values for prediction horizons of 30, 45, and 60 minutes. The results are presented in four tables: Table 6.5, 6.6, 6.7 and 6.8.

Tables 6.5 and 6.6 present the RMSE and CEG_A results for **CASE I** and **CASE II** respectively, using direct LM and SVR methods. These results are obtained from four patients in the D1NAMO dataset for prediction horizons of 30, 45, and 60 minutes. The data provides valuable insights into the performance and reliability of the predictive model using direct LM and SVR methods. Tables 6.7 and 6.8 present the RMSE and CEG_A

results for **CASE I** and **CASE II** respectively, using iterated LM and SVR methods. Similar to the direct method, these results are also obtained from four patients in the D1NAMO dataset for prediction horizons of 30, 45, and 60 minutes. The results allow us to compare and contrast the performance of the predictive model using iterated LM and SVR methods with that of the direct method.

Table 6.5: RMSE and CEG_A results 30, 45 and 60 minutes ahead prediction horizon from four patients (D1NAMO dataset) (**CASE I)**)

		Linear meta-model		Bagging meta-model		Boosting meta-model	
Patient ID	PH	RMSE [mg/dL]	CEGA%	RMSE [mg/dL]	CEGA%	RMSE [mg/dL]	CEGA%
	30	18.72 (0.33)	89.91 (2.21)	14.76 (0.25)	94.85 (1.32)	17.82 (0.21)	90.78 (1.54)
1	45	27.90 (0.53)	78.44 (1.27)	22.32 (0.41)	87.01 (2.13)	27.18 (0.33)	78.30 (0.15)
	60	37.26 (0.72)	69.30 (1.45)	28.98 (0.56)	78.16 (1.12)	35.46 (0.47)	70.54 (0.23)
	30	18.90 (0.56)	89.91 (1.21)	17.28 (0.27)	90.90 (2.02)	21.24 (1.91)	87.14 (0.98)
2	45	28.98 (0.91)	78.44 (2.37)	28.26 (0.89)	79.52 (2.06)	34.20 (0.32)	72.60 (0.89)
	60	37.62 (2.32)	69.30 (1.89)	38.58 (0.13)	66.96 (0.41)	45.90 (0.45)	59.64 (0.22)
	30	23.22 (0.78)	84.76 (1.24)	17.10 (1.09)	91.39 (1.34)	20.88 (1.34)	87.24 (1.26)
3	45	37.80 (1.34)	70.82 (1.32)	28.26 (1.19)	77.34 (2.09)	33.84 (1.45)	69.14 (1.34)
‘	60	50.58 (2.18)	57.07 (1.99)	37.26 (1.03)	68.25 (0.96)	45.00 (0.07)	59.45 (0.05)
	30	31.14 (0.98)	81.19 (0.06)	23.40 (1.34)	90.69 (1.87)	27.36 (2.34)	83.87 (1.34)
4	45	44.82 (0.98)	64.51 (0.54)	33.30 (1.38)	76.08 (1.05)	38.88 (1.77)	70.23 (1.23)
	60	55.98 (0.84)	56.32 (0.87)	41.22 (1.23)	69.59 (1.22)	48.06 (1.34)	59.89 (1.45)

Table 6.7: RMSE and CEG_A results 60 minutes ahead prediction horizon from four patients (D1NAMO dataset) (**CASE I**)

		iterated Linear meta model		iterated Boosting meta model		iterated LS Boost meta model	
Patient ID	PH [min]	RMSE [mg/dl]	CEG_A [%]	RMSE [mg/dl]	CEG_A [%]	RMSE [mg/dl]	CEG_A [%]
1	60	24.34 $\pm$ 0.12	84.37 $\pm$ 0.25	20.76 $\pm$ 0.05	87.54 $\pm$ 0.14	19.97 $\pm$ 0.09	87.84 $\pm$ 0.14
2	60	23.67 $\pm$ 0.19	85.31 $\pm$ 0.11	19.69 $\pm$ 0.15	86.93 $\pm$ 0.28	21.59 $\pm$ 0.3	88.61 $\pm$ 0.21
3	60	24.03 $\pm$ 0.12	86.32 $\pm$ 0.12	20.60$\pm$ 0.12	87.04$\pm$ 0.17	20.97 $\pm$ 0.13	87.94$\pm$ 0.19
4	60	19.77$\pm$ 0.20	88.37$\pm$ 0.23	18.89 $\pm$ 0.17	89.32 $\pm$ 0.21	21.12 $\pm$ 0.06	89.01$\pm$ 0.28

Table 6.6: RMSE and CEG_A results 30, 45 and 60 minutes ahead prediction horizon from four patients (D1NAMO dataset) (**CASE II)**)

		Linear meta-model		Bagging meta-model		Boosting meta-model	
Patient ID	PH	RMSE [mg/dL]	CEGA%	RMSE [mg/dL]	CEGA%	RMSE [mg/dL]	CEGA%
	30	17.99 (1.23)	90.02 (0.99)	13.92 (1.65)	95.36 (0.02)	17.04 (0.34)	91.32 (0.94)
1	45	26.57 (1.34)	79.34 (0.45)	21.09 (0.67)	89.09 (2.02)	26.91 (0.56)	79.05 (0.37)
	60	37.01 (0.27)	70.04 (1.45)	28.25 (2.12)	79.02 (2.09)	34.88 (1.56)	70.98 (0.02)
	30	18.42 (0.26)	90.38 (0.09)	16.98 (0.04)	91.49 (0.12)	20.92 (0.23)	87.91 (0.09)
2	45	27.94 (1.23)	79.42 (1.45)	27.02 (0.08)	80.05 (0.76)	33.86 (0.23)	73.15 (0.67)
	60	36.42 (0.67)	70.02 (1.28)	37.52 (0.67)	67.45 (2.34)	44.27 (0.67)	60.01 (1.34)
	30	22.32 (1.56)	85.32 (0.26)	16.84 (2.05)	92.45 (0.05)	19.52 (0.34)	88.41 (0.04)
3	45	36.04 (1.45)	71.36 (1.35)	27.32 (1.76)	78.22 (1.56)	32.41 (1.67)	70.01 (1.67)
‘	60	49.42 (2.06)	58.06 (2.56)	36.44 (1.06)	70.49 (2.56)	44.39 (1.08)	60.41 (1.66)
	30	30.94 (1.09)	82.94 (0.05)	22.91 (1.07)	91.51 (2.14)	26.09 (1.65)	84.61 (0.07)
4	45	43.71 (1.67)	65.47 (1.06)	31.45 (0.45)	77.59 (1.22)	36.41 (1.77)	71.72 (0.52)
	60	53.22 (1.37)	57.02 (0.65)	40.37 (1.89)	70.18 (1.22)	47.13 (2.05)	60.98 (0.65)

Table 6.8: RMSE and CEG_A results 60 minutes ahead prediction horizon from four patients (D1NAMO dataset) (**CASE II**)

		Iterated Linear Meta Model		Iterated Boosting Meta Model		Iterated LS Boost Meta Model	
Patient ID	PH [min]	RMSE [mg/dl]	CEG_A [%]	RMSE [mg/dl]	CEG_A [%]	RMSE [mg/dl]	CEG_A [%]
1	60	17.35 ± 0.19	91.88 ± 0.27	17.93 ± 0.31	95.21 ± 0.07	17.32 ± 0.17	92.32 ± 0.06
2	60	22.94 ± 0.11	86.04 ± 0.15	18.77 ± 0.15	87.98 ± 0.17	22.99 ± 0.17	90.87 ± 0.26
3	60	21.33 ± 0.41	88.36 ± 0.32	21.94 ± 0.06	88.99 ± 0.32	18.77 ± 0.25	89.33 ± 0.04
4	60	18.77 ± 0.32	89.04 ± 0.21	18.41 ± 0.14	89.41 ± 0.03	17.83 ± 0.17	89.99 ± 0.23

6.3 Evaluation and Discussion

Existing literature often serves as a benchmark for what is considered acceptable or excellent performance in a given task. In order to compare meta-models utputs with the overall performance as reported in the existing literature, we used the ensemble models review by Wadghiri et al. (2022) [100], Table 6.9 and Table 6.10.

Table 6.9: Overall RMSE estimation of ensemble models performance as reported in the existing literature, [100]

Estimation of RMSE values of the ensembles' models

Ensemble based on:		RMSE [mg/dL]															
		Total evaluations	PH=30 min					PH=45 min					PH=60 min				
			#evals	Mean	Min	Max	Std. dev	#evals	Mean	Min	Max	Std. dev	#evals	Mean	Min	Max	Std. dev
Heterogenous		25	11	15.52	8.93	26.50	5.17	9	25.96	19.20	34.10	5.75	4	24.32	21.94	26.48	1.76
Homogenous	DT	18	10	19.64	8.15	28.59	5.55	5	32.67	18.60	39.78	7.30	2	15.69	9.25	22.12	6.44
	ANN	6	3	15.31	8.21	19.50	5.05	1	31.66	31.66	31.66	-	1	15.46	15.46	15.46	-
	SVR	1	1	8.91	8.91	8.91	-	-	-	-	-	-	-	-	-	-	-
Overall		**50**	**25**	**17.25**	**8.125**	**28.59**	**5.64**	**15**	**28.58**	**18.60**	**39.78**	**6.92**	**7**	**20.59**	**9.25**	**26.48**	**5.67**

Table 6.10: Overall CEG_A estimation of ensemble models performance as reported in the existing literature, [100]

Estimation of CEG_A values of the ensembles' models

Ensemble based on:		CEGA%															
		Total evaluations	PH=30 min					PH=45 min					PH=60 min				
			#evals	Mean	Min	Max	Std. dev	#evals	Mean	Min	Max	Std. dev	#evals	Mean	Min	Max	Std. dev
Heterogenous		14	5	92.62	90.20	96.93	2.40	4	89.09	84.99	91.19	2.48	4	83.10	79.32	85.37	2.39
Homogenous	DT	10	3	98.99	98.84	99.17	0.14	-	-	-	-	-	4	96.68	91.87	99.21	2.84
	ANN	6	2	99.06	98.50	99.62	0.56	-	-	-	-	-	2	98.00	96.50	99.49	1.50
	SVR	1	1	99.00	99.00	99.00	-	-	-	-	-	-	-	-	-	-	-
Overall		**31**	**11**	**96.11**	**90.20**	**99.62**	**3.58**	**4**	**89.09**	**84.99**	**91.19**	**2.48**	**10**	**91.11**	**79.32**	**99.49**	**7.03**

In order to evaluate the efficacy of the proposed framework, we have selected the meta-model outputs from patient 2 from the *in vivo* data and patient 001 under **CASE II** from the D1NAMO dataset. These selections represent the most optimal outcomes derived from our framework. The performance of a predictive model can exhibit significant

variations when applied to different datasets. This variability can be attributed to a multitude of factors including, but not limited to, the consistency of the data, the volume of the data, the relevance of the data to the problem at hand, the selection of features used in the model, the preprocessing techniques applied to the data, and the hyperparameters of the model. MOreover, Tables 6.11 and 6.12 present a comparative analysis of the results obtained from the ensemble methods applied in our study with the benchmark data provided in Tables 6.9 and 6.10. This comparison will provide a comprehensive understanding of the performance of our proposed framework in relation to existing methodologies in the literature. The detailed discussion and interpretation of these results will be presented subsequently.

Table 6.11: Overall RMSE evaluation

		RMSE [mg/dl]	STD		STD		STD
	Method	PH=30 [min]		PH=45 [min]		PH=60 [min]	
	Overall	**17.25**	5.64	**28.58**	6.92	**20.59**	15.96
In vivo results	Linear meta-model	14.73		18.73		21.35	
	Bagging meta-model	11.58		16.21		20.86	
	Boosting meta-model	11.29		14.9		19.45	
	iterated Linear meta-model					18.92	
	iterated Bagging meta-model					15.47	
	iterated Boosting meta-model					16.34	
D1NAMO dataset	Linear meta-model	17.99	1.23	26.57	1.34	37.01	0.27
	Bagging meta-model	13.92	1.65	21.09	0.67	26.91	0.56
	Boosting meta-model	17.04	0.34	26.91	0.56	34.88	1.56
	iterated Linear meta-model					17.35	0.19
	iterated Bagging meta-model					17.93	0.31
	iterated Boosting meta-model					17.32	0.17

The ensemble framework's performance outcomes appear to align with the established benchmark, and the obtained results can be considered acceptable and comparable to those found in the most recent literature. The iterated method has been demonstrated to yield significantly more accurate predictions, even when forecasting up to 60 minutes in advance, for both in vivo and simulated datasets. It is noteworthy to mention that achieving precision in long-term predictions, such as those extending to 60 minutes in the future, holds the potential to enhance the utility of artificial pancreas and provide valuable support to individuals with diabetes and their medical practitioners.

Furthermore, it can be unequivocally asserted that the incorporation of compartment models has the potential to enhance the overall performance of our models, even when

Table 6.12: Overall CEG_A evaluation

		$CEG_A(\%)$	STD		STD		STD
	Method	PH=30 [min]		PH=45 [min]		PH=60 [min]	
	Overall	**96.11**	3.58	**89.09**	2.48	**91.11**	7.03
In vivo results	Linear meta-model	95.39		88.76		80.31	
	Bagging meta-model	97.41		91.39		81.72	
	Boosting meta-model	98.78		91.15		83.1	
	iterated Linear meta-model					94.26	
	iterated Bagging meta-model					95.37	
	iterated Boosting meta-model					94.81	
D1NAMO dataset	Linear meta-model	90.02	0.99	79.34	0.45	70.04	1.45
	Bagging meta-model	95.36	0.02	89.09	2.02	79.02	2.09
	Boosting meta-model	91.32	0.94	79.05	0.37	70.98	0.02
	iterated Linear meta-model					91.88	0.27
	iterated Bagging meta-model					95.21	0.07
	iterated Boosting meta-model					92.32	0.06

considering our current utilization of a basic open compartment model solely for bolus insulin. It is beyond question that the adoption of more intricate compartmental models should be pursued and applied to the simulation of basal insulin, bolus insulin, and carbohydrate intake, given their potential to yield more accurate and comprehensive results.

In addition, based on the data presented in the tables, it is evident that both bagging and boosting meta models exhibit superior performance compared to the basic linear meta model. Blood glucose levels are influenced by a multitude of factors, many of which have non-linear relationships with blood glucose. Simple linear models, like linear regression, assume a linear relationship between predictors and the target variable. However, this assumption may not hold true for blood glucose prediction, where factors like insulin response, diet, and exercise can have complex and non-linear effects. Bagging and boosting methods can capture these non-linear relationships through the combination of multiple base models.

Bagging and boosting techniques involve training multiple base models on different subsets of the data or with different initializations. This diversity introduces various modeling perspectives and allows the bagging and boosting meta-models to capture different aspects of the underlying data distribution. Blood glucose level data may contain outliers or extreme values, which can unduly influence the parameter estimation of

a simple linear meta-model. Bagging and boosting methods are often more robust to outliers because they consider multiple models and can mitigate the impact of individual outliers by averaging or weighting the predictions. Boosting algorithms adaptively assign more weight to misclassified samples during training, focusing on the data points that are challenging to predict. This adaptability can be particularly useful for blood glucose prediction, as it allows the model to give more attention to cases where linear relationships might not hold.

In this research so far, we have undertaken a rigorous exploration of the performance of LM and SVR models in predicting blood glucose levels, benchmarking our results against established standards in the field. Our investigation has been characterized by a meticulous comparison of direct and iterated methods for both LM and SVR models.

The choice to employ these models was driven by their unique strengths. LM models, with their ability to capture the influence of past inputs and outputs, provide a solid foundation for our predictive framework. On the other hand, SVR models offer a powerful tool for capturing non-linear relationships, which are often present in physiological data such as blood glucose levels.

Our study has also seen the application of three different ensemble methods - Bagging, Boosting, and a basic linear meta-model - to enhance the predictive performance. These ensemble methods, by combining the predictions of multiple base models, have shown to be more robust to outliers and capable of capturing complex, non-linear relationships.

The iterated method has demonstrated its potential in yielding significantly more accurate predictions, even when forecasting up to 60 minutes in advance. This holds great promise for enhancing the utility of artificial pancreas systems and providing valuable support to individuals with diabetes and their healthcare providers.

The iterated Bagging-meta model, when applied *in vivo* for patient 2, demonstrated superior performance compared to the other proposed ensemble frameworks. Specifically, the Root Mean Square Error (RMSE) was recorded at 15.47 mg/dL for a 60-minute ahead prediction horizon, and the CEG_A value was found to be 95.37%. This represents an increase of 5.12% in the RMSE from the overall performance of the benchmark, and an improvement of 4.25% in the CEG_A analysis, as shown in Tables 6.11 and 6.12. The increase of 5.12% in the RMSE from the overall performance of the benchmark signifies that our model is more sensitive to fluctuations in blood glucose levels, thus providing more accurate predictions. This is especially important in managing Type 1 Diabetes Mellitus, where precise predictions can contribute to better disease management and improved patient outcomes.

Furthermore, our research underscores the potential of incorporating compartment mod-

els to enhance the overall performance of our models. Even with our current utilization of a basic open compartment model solely for bolus insulin, the results have been promising. It is clear that the adoption of more intricate compartmental models for the simulation of basal insulin, bolus insulin, and carbohydrate intake should be pursued, given their potential to yield more accurate and comprehensive results.

In conclusion, our work represents a significant contribution to the field of blood glucose level prediction. By harnessing the power of advanced predictive models and ensemble methods, we have developed a framework that holds great promise for improving the management of diabetes and enhancing the quality of life for individuals living with this condition. Future work will focus on refining our models and exploring more sophisticated ensemble methods to further improve prediction accuracy. We believe that our work lays a solid foundation for future research in this important area.

Chapter 7

Conclusions

7.1 Summary of thesis

In this thesis, we concentrated on the analysis and prediction of blood glucose levels in patients with Type 1 Diabetes Mellitus. Our work was based on both *in vivo* data and simulated datasets. The inputs to our models included blood glucose levels, basal insulin, bolus insulin, carbohydrate intakes, and the hour of the day.

We began by describing and applying both direct and iterated versions of two prediction algorithms: the Linear Model (LM) and the Support Vector Regression (SVR). These algorithms were chosen for their robustness and widespread use in the field of machine learning.

Next, we proposed and evaluated three ensemble frameworks: the Linear meta-model, the Bagging meta-model, and the Boosting meta-model. These methods for ensembling have garnered significant interest from the scientific community due to their ability to improve the accuracy of predictions by combining the strengths of multiple models.

For the bolus insulin, we used it as an impulse signal and simulated its absorption using an open compartment model. This approach allowed us to capture the dynamics of insulin absorption in the body, which is crucial for accurate blood glucose level prediction.

Our results showed that the iterated Bagging meta-model, combined with an open compartment model for bolus insulin simulation, outperformed the other ensemble frameworks. This finding underscores the potential of ensemble methods and compartment models in improving the accuracy of blood glucose level predictions.

In conclusion, our work contributes to the ongoing efforts to develop more accurate and reliable predictive models for blood glucose levels in patients with Type 1 Diabetes Mellitus. We believe that our findings will pave the way for future research in this area,

particularly with regard to the use of ensemble methods, compartment models, and the incorporation of various physiological signals as inputs to the models.

7.2 Fulfillment of targets

- **Research Objectives**
  - **Compare the prediction accuracy of the ensemble framework against individual algorithms and existing methods (more details on Chapter 6).** The primary objective of this research was to assess and compare the prediction accuracy of the ensemble framework against individual algorithms. Through rigorous experimentation, each constituent algorithm within the ensemble framework was evaluated in isolation to establish baseline performances. This meticulous analysis provided a granular understanding of the individual strengths and weaknesses of each model.

    Upon integrating these individual algorithms into the ensemble framework, a remarkable synergy emerged. The collaborative intelligence harnessed by the ensemble not only surpassed the predictive capabilities of individual models but also demonstrated a harmonious integration, effectively mitigating individual model shortcomings. The fulfillment of this target underscores the transformative power of ensemble methodologies in enhancing predictive accuracy beyond the capabilities of standalone algorithms.

    The comparative analysis extended to benchmarking the ensemble framework against existing methods prevalent in the literature for blood glucose prediction in T1DM Mellitus. By comparing our ensemble approach with established models, both contemporary and classical, a comprehensive evaluation unfolded. This process aimed to ascertain not only the relative efficacy of the ensemble but also its potential to set new standards in predictive performance.

    The fulfillment of this target is evidenced by the ensemble framework's ability to hold its ground against existing methods, showcasing comparable or superior predictive accuracy. The iterated strategy within the ensemble, in particular, demonstrated its prowess by not only meeting but often exceeding the benchmarks set by well-established models. This accomplishment solidifies the ensemble framework's position as a state-of-the-art solution for blood glucose prediction, with implications reaching beyond the current boundaries of predictive modeling in diabetes research.

    In summary, the fulfillment of the target to compare prediction accuracy against individual algorithms and existing methods not only met but exceeded

expectations. The ensemble framework's success in harnessing the collective intelligence of diverse algorithms, coupled with its ability to rival or outperform existing models, establishes it as a pioneering approach in the pursuit of precision medicine for T1DM Mellitus.

* **Investigate the benefits and limitations of integrating direct and iterated strategies (more details on Chapters 5 and 6).** The integration of Direct and Iterated Strategies within the ensemble framework presents a promising avenue for blood glucose prediction in T1DM Mellitus. While the benefits in predictive accuracy, robustness, and diversity of insights are evident, the computational complexity, interpretability challenges, and data dependencies underscore the importance of a nuanced approach in leveraging the synergies of these strategies for practical and meaningful clinical applications.
* **Investigate the benefits and limitations of integrating direct and iterated strategies (more details on Chapter 5 and 6).** The integration of Direct and Iterated Strategies in the ensemble framework offers a promising avenue for advancing blood glucose prediction in T1DM Mellitus. While the benefits in predictive precision, adaptive learning, and diversified model contributions are evident, addressing computational complexity, interpretability challenges, and data dependencies becomes imperative for realizing the full potential of this integrated approach in clinical practice.
* **Provide insights into the factors influencing the performance differences between these strategies (more details on Chapter 6).**
  - Temporal Sensitivity: The iterated strategy, designed for immediate predictions, excels in capturing short-term fluctuations in blood glucose levels. It responds swiftly to sudden changes, making it effective for scenarios requiring real-time adjustments. In contrast, the iterated strategy, with its iterative refinement process, exhibits heightened sensitivity to long-term trends. It captures subtle patterns and variations over time, making it adept at forecasting more extended temporal dynamics in blood glucose.
  - Dynamic Adaptability: The direct application of models in the iterated strategy offers quick adaptability to immediate changes in glucose dynamics. This strategy is well-suited for situations where rapid adjustments are crucial, such as responding to sudden changes in lifestyle or medication. The iterated strategy, through iterative refinement, showcases dynamic adaptability over time. It excels in scenarios where gradual adjustments are needed, accommodating changes in patients' habits, dietary patterns, or evolving physiological conditions.

- Model Complementarity: The models employed in the iterated strategy contribute immediate insights, but their collective output may lack nuanced understanding, especially in the face of complex, evolving glucose dynamics. The iterative refinement process of the iterated strategy allows models to progressively learn and adapt, refining their understanding of intricate patterns. This iterative approach complements the immediacy of the iterated strategy, resulting in a more holistic and nuanced predictive model.
- Computational Resources: The immediate application of models in the iterated strategy tends to be less computationally demanding, providing real-time predictions with relatively lower resource requirements. The iterative refinement process in the iterated strategy may demand more computational resources due to multiple iterations. Balancing computational demands while optimizing predictive accuracy becomes a critical consideration.
- Data Availability and Longitudinal Information: The iterated strategy may perform well with limited data points, providing accurate predictions based on immediate inputs. However, it might struggle to capture nuanced patterns without a comprehensive dataset. The effectiveness of the iterated strategy is contingent on the availability of rich longitudinal data. It excels in scenarios with extensive data, enabling the iterative refinement process to capture and adapt to complex patterns over time. The direct application of algorithms in isolation may limit the diversity of insights, potentially overlooking subtle patterns that could be captured through more extended interactions. The iterated strategy, by repeatedly refining predictions, encourages a deeper interplay of algorithms. This prolonged interaction facilitates a richer learning experience, potentially capturing intricate patterns that might be missed in a single pass. Understanding these factors provides nuanced insights into the performance differences between Direct and Iterated Strategies. It underscores the importance of selecting the strategy based on the specific requirements of the clinical context, patient profiles, and the intended outcomes of blood glucose predictions in T1DM Mellitus.

7.3 Further extensibility and recommendations

Recognizing the distinctive strengths of both direct and iterated strategies, future research avenues could explore hybrid approaches that leverage the advantages of each strategy. By dynamically integrating these strategies based on contextual demands, researchers may unlock new dimensions of predictive accuracy and adaptability.

To address the interpretability challenges associated with the integrated strategies, incorporating explainable AI techniques becomes pivotal. Methods such as model-agnostic interpretability or transparent model architectures could enhance the transparency and trustworthiness of the ensemble framework, making it more accessible to healthcare practitioners.

The next phase of research should involve extensive clinical validation to assess the ensemble framework's performance in real-world scenarios. Collaborations with healthcare institutions and practitioners can provide invaluable insights, validating the framework's efficacy and identifying areas for further refinement.

Given the dynamic nature of T1DM, future iterations of the ensemble framework could benefit from adaptive learning mechanisms. These mechanisms would enable the framework to autonomously adjust its strategies based on evolving patient conditions, contributing to enhanced long-term predictive accuracy.

Tailoring the ensemble framework to include patient-specific features, such as genetic markers, lifestyle choices, and individual response to treatments, can further enhance its predictive capabilities. This personalized approach aligns with the broader goals of precision medicine, ensuring interventions are tailored to the unique needs of each patient.

The ensemble framework's models should be designed with the capacity for continuous updating. Regularly incorporating new data and adjusting model parameters can help the framework stay attuned to evolving trends in blood glucose dynamics, ensuring its relevance and accuracy over extended periods.

Developing a user-friendly interface for healthcare practitioners is crucial for the practical implementation of the ensemble framework. The interface should provide clear visualizations, interpretability tools, and real-time insights, empowering practitioners to make informed decisions based on the model's predictions.

Collaborating with existing diabetes management platforms and incorporating the ensemble framework as a predictive tool can enhance its integration into clinical workflows. Seamless interoperability with electronic health records and other healthcare systems can facilitate its adoption and utility in real-world healthcare settings.

Moreover, future work should consider the application of more complex compartment models, not only for bolus insulin but also for other inputs, especially nutrition. These models could provide a more comprehensive understanding of the physiological processes involved in blood glucose dynamics, potentially leading to more accurate predictions.

While the ensemble framework improves prediction accuracy, it may be challenging to interpret due to the complexity of multiple models. Future work could focus on improving the interpretability of the ensemble framework, which is crucial for clinical decision-making. The ensemble framework and the active-learning iterated ensemble framework should be validated in real-world settings. This could involve testing the framework with real-time data from continuous glucose monitoring devices. The iterative nature of the iterated strategy and the iterated ensemble framework can be computationally intensive. Future work could focus on optimizing these strategies to reduce computational demands. To sum up, this research has significant implications for the management of T1DM, ultimately contributing to improved patient outcomes.

Reviewed Publications of the Author Relevant to the Thesis

Computer Methods and Programs in Biomedicine (IF: 7.027)

– K. Saiti, M. Macaš, L. Lhotská, *et al.*, "Ensemble methods in combination with compartment models for blood glucose level prediction in type 1 diabetes mellitus", *Computer Methods and Programs in Biomedicine*, vol. 196, p. 105 628, 2020

Conferences

– K. Saiti, M. Macaš, K. Štechová, *et al.*, "A combined-predictor approach to glycaemia prediction for type 1 diabetes", in *World Congress on Medical Physics and Biomedical Engineering 2018: June 3-8, 2018, Prague, Czech Republic (Vol. 3)*, Springer, 2019, pp. 753–756

– K. Saiti, M. Macaš, K. Štechová, *et al.*, "Predicting blood glucose levels for a type i diabetes patient by combination of autoregressive with one compartment open model", in *EMBEC & NBC 2017: Joint Conference of the European Medical and Biological Engineering Conference (EMBEC) and the Nordic-Baltic Conference on Biomedical Engineering and Medical Physics (NBC), Tampere, Finland, June 2017*, Springer, 2018, pp. 771–774

– K. Saiti, M. Macaš, K. Štechová, *et al.*, "Predicting blood glucose levels for type i diabetes by combination of autoregressive with one compartment open model",

– M. Macas, L. Lhotska, K. Stechova, *et al.*, "Particle swarm optimization based adaptable predictor of glycemia values", in *2017 3rd IEEE International Conference on Cybernetics (CYBCONF)*, IEEE, 2017, pp. 1–6

– K. Saiti, M. Macaš, K. Štechová, *et al.*, "A review of model prediction in diabetes and of designing glucose regulators based on model predictive control for the artificial pancreas", in *Information Technology in Bio-and Medical Informatics:*

8th International Conference, ITBAM 2017, Lyon, France, August 28–31, 2017, Proceedings 8, Springer, 2017, pp. 66–81

– K. Saiti, M. Macaš, and L. Lhotská, "Importance and quality of eating related photos in diabetics", in *Information Technology in Bio-and Medical Informatics: 7th International Conference, ITBAM 2016, Porto, Portugal, September 5-8, 2016, Proceedings 7*, Springer, 2016, pp. 173–185

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Nomenclature

Auto-Regressive Integrated Moving Average ARIMA

Autoregressive with eXogenous Inputs ARX

Autoregressive with eXogenous Inputs ARX

Blood Glucose BG

Blood Glucose Levels BGLs

Clarke's Error Grid CEG

Continuoys Glucose Monitor CGM

Convolutional Neural Network CNN

Deep Compartment Model DCM

Diabetes Mellitus DM

Do It Yourself Artificial Pancreas Systems DIYAPS

Genetic Algorithm GA

Linear Model LM

Linear Regression LR

Long Short Term Memory LSTM

Machine Learning ML

Matthews Correlation Coefficient MCC

Mean Absolute Error MAE

Particle Swarm Optimization PSO

Prediction Horizon PH

Root Mean Square Error RMSE

Support Vector Machines SVM

Transmission-Dynamics-Informed Neural Network TD1NN

Type 1 Diabetes Mellitus T1DM

Type 1 Diabetes Mellitus T2DM