# NEW METHODS FOR COMPUTER BASED BLOOD GLUCOSE LEVEL PREDICTION

Ph.D. Thesis

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# List of Abbreviations

| | |
|---|---|
| ARNN | Autoregressive Artificial Neural Network |
| BGL | Blood Glucose Level |
| CC | Correlation Coefficient |
| CGMS | Continuous Glucose Monitoring System |
| CH | Carbohydrates |
| Cmax | Maximum insulin concentration in plasma |
| DDE | Delay Differential Equations |
| DIAS | Diabetes Advisory System |
| DM | Diabetes Mellitus |
| EGA | Error Grid Analysis |
| EM | Expectation Maximization |
| FNN | Feed-forward Artificial Neural Network |
| GA | Genetic Algorithms |
| GI | Glycemic Index |
| MAE | Mean Absolute Error |
| MIRDC | Pannon University, Medical Informatics Research and Development Centre |
| MLP | Multilayer Perceptron |
| MSPE | Mean Squared Prediction Error |
| NN | Artificial Neural Network |
| RMSE | Root Mean Square Error |
| RNN | Recurrent Artificial Neural Network |
| T1DM | Type 1 Diabetes Mellitus |
| T2DM | Type 2 Diabetes Mellitus |
| Teff | Effective half-lives |
| Tmax | Maximal absorption time |
| Weka | Waikato Environment for Knowledge Analysis |

# Statement of Original Authorship

The work contained in this thesis has not been previously submitted to meet requirements for an award at this or any other higher education institution. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made.

Signature: 

Date: **September 24, 2020**

# Kivonat

Jelen dolgozatban a vércukorszint-modellezés területén végzett tudományos kutatásomat ismertetem, az annak eredményeként megalkotott új módszereket, valamint a már meglévő modelleken végzett továbbfejlesztési javaslatokat, melyek célja a cukorbetegek vércukorszintjének pontosabb előrejelzése.

Kísérleti adatok segítségével bemutattam, hogy az egyéni vércukorszint-válaszgörbe alakulása a korábbi ismert válaszreakciók és egy-egy étkezés összetétele alapján milyen mértékben reprodukálható, jósolható. Megmutattam, hogy ezek a válaszreakciók jellegzetesek mind az egyén, mind az étkezés típusa szempontjából. Ezek alapján kidolgoztam egy válaszfüggvény-alapú, rövid távú vércukorszint-előrejelzési módszert, és megmutattam, hogy a válasz klaszterek alapján történő jellemzéssel javítható a válaszreakció-alapú előrejelzés megbízhatósága.

Munkám során emellett továbbfejlesztettem egy életmód-tanácsadó szakértői rendszerbe integrált vércukorszint-előrejelző modellt, a bázis inzulinok hatásának pontosabb modellezésére. Ehhez egy olyan korrekciós eljárást dolgoztam ki, melynek alapja az, hogy a korábbi megközelítésben használt egyetlen nagyobb bázisinzulin-adag helyett kisebb bólusinzulin-adagok sorozata kerül felhasználásra. Kísérleti eredményekkel igazoltam, hogy a javasolt módszer több javulást hozott az éjszakai előrejelzések esetében és az ébredési vércukorszint-becslés pontosságán is.

Egy új, tápanyag-felszívódási modellre épülő módszert dolgoztam ki vércukorszint-előrejelző mesterséges neurális hálózatok tanításához. Ennek újszerűségét az adja, hogy a gyakran használt megoldással ellentétben a nyers szénhidrát értékek helyett a glükózfelszívódási modell által kiszámított görbét használom a tanítási bemenetként. Pontosabban, a felszívódási görbe numerikus jellemzőit, az alkalmazott inzulin dózisokkal és a mért vércukorszint értékekkel együtt. Az új modell előrejelzési pontossága minden olyan eddig közölt, akár modell, akár neurális háló alapú eredményt felülmúl, mellyel a javasolt módszer közvetlenül összehasonlítható.

# Abstract

In this dissertation, the results of my research done in the field of blood sugar modeling are presented. I have introduced new methods and developed upgrades for existing models in order to predict blood sugar levels of diabetic patients more accurately.

I examined to what extent the individual blood glucose response curve could be reproduced and predicted based on previously recorded responses and diet logs. I have shown such responses are characteristic to both the individual and the type of meal consumed. I developed a short-term blood glucose prediction method based on the response function, and have shown that characterization based on response clusters can improve the reliability of response-based prediction.

I upgraded a blood glucose prediction model, integrated into a lifestyle counseling expert system, to model the effect of basal insulins more precisely. I introduced a correction procedure that is based on using a series of smaller bolus insulin doses instead of a single larger base insulin dose. I demonstrated by experimental results that the predictions of the proposed method produced better results for the night periods and also improved the prediction accuracy of wake-up blood glucose.

I have developed a new method for blood glucose prediction by training artificial neural networks based on a nutrient absorption model. The novelty of my model is that the curve calculated by the glucose absorption model is used as the training input of the neural network, instead of raw carbohydrate values. More precisely, I used the numerical characteristics of the absorption curve, the applied insulin doses and the measured blood glucose values. The predictive accuracy of the new model exceeds all previously reported results, whether model or neural network, with which the proposed method can be directly compared.

# Astratto

In questa dissertazione vengono presentati i risultati della mia ricerca svolta nel campo della modellazione della glicemia. Ho introdotto nuovi metodi e sviluppato aggiornamenti per i modelli esistenti al fine di prevedere i livelli di zucchero nel sangue dei pazienti diabetici in modo più accurato.

Ho esaminato in che misura la curva di risposta della glicemia individuale poteva essere riprodotta e prevista sulla base delle risposte registrate in precedenza e dei registri dietetici. Ho dimostrato che tali risposte sono caratteristiche sia dell'individuo che del tipo di pasto consumato. Ho sviluppato un metodo di previsione della glicemia a breve termine basato sulla funzione di risposta e ho dimostrato che la caratterizzazione basata su cluster di risposta può migliorare l'affidabilità della previsione basata sulla risposta.

Ho aggiornato un modello di previsione della glicemia, integrato in un sistema esperto di consulenza sullo stile di vita, per modellare l'effetto delle insuline basali in modo più preciso. Ho introdotto una procedura di correzione basata sull'utilizzo di una serie di dosi di insulina in bolo più piccole invece di una singola dose di insulina base più grande. Ho dimostrato con risultati sperimentali che le previsioni del metodo proposto hanno prodotto risultati migliori per i periodi notturni e hanno anche migliorato l'accuratezza della previsione del glucosio nel sangue al risveglio.

Ho sviluppato un nuovo metodo per la previsione della glicemia allenando reti neurali artificiali basate su un modello di assorbimento dei nutrienti. La novità del mio modello è che la curva calcolata dal modello di assorbimento del glucosio viene utilizzata come input di allenamento della rete neurale, invece dei valori dei carboidrati grezzi. Più precisamente, ho utilizzato le caratteristiche numeriche della curva di assorbimento, le dosi di insulina applicate e i valori di glicemia misurati. L'accuratezza predittiva del nuovo modello supera tutti i risultati precedentemente riportati, sia di modello che di rete neurale, con i quali il metodo proposto può essere direttamente confrontato.

# Chapter 1: Introduction

The body balances BGL in the blood through a complex, coordinated regulatory mechanism in which insulin, the hormone produced in the beta cells of the Langerhans Islands, plays a key role. Insulin regulates the uptake of glucose by cells in the body. With the exception of the brain, all the cells in the body need sufficient and effective insulin to absorb glucose, the main energy source, from the blood. In addition, insulin is the main regulating hormone for the body's overall metabolism, both carbohydrate, fat, and protein. When there is not enough insulin in the body or if for some reason it is unable to work, the BGL is raised.

Diabetes mellitus (DM) is a widespread chronic metabolic disorder in which cells of the body are unable to take up glucose from the blood in sufficient volume, resulting in abnormally high blood glucose levels (BGL). The cause of this phenomenon is the absolute or relative lack of insulin. Accordingly, we can speak of type 1 or type 2 diabetes mellitus (T1DM or T2DM). The two types are significantly different in etiological (causal) terms. In T1DM, due to autoimmune disease, insulin production is virtually eliminated and must be replaced externally. In the case of T2DM, there is limited insulin production and/or increased insulin resistance, consequently, cells have limited ability to absorb circulating glucose. All T1DM and some T2DM patients use external insulin, most often in the form of subcutaneous injections, typically one injection for each main meal, and all DM patients must take special care of their diet to prevent overly low BGL (hypoglycemia), which can lead to an emergency, as well as overly high BGL (hyperglycemia), which may cause severe complications if it is sustained for a long time. In practice, this means that the patients on external insulin must estimate their insulin needs such that it matches their daily meals—for which they can rely on some general medical guidelines, frequent fingertip BGL measurements, and their personal experience.

The dissertation is structured as follows.

In chapter 2, background and related work are overviewed.

In chapter 3, a meal log based BGL prediction method is proposed. The results of two experiments are used to validate solely meal log based BGL prediction, without using mathematical models. The meal-wise responses characterized with three numerical parameters and the characteristics of the postprandial blood glucose response curves for meals and persons were examined.

In chapter 4, a new method for modeling long-acting (basal) insulin absorption is presented. The new method improves the accuracy of the BGL prediction model. The proposed method simulates the absorption of basal insulin as a series of smaller insulin doses according to four alternative 'dosing profiles', such that the original time interval is divided into shorter subintervals with lower Maximal absorption times (Tmax). This approach is in contrast with the original approach of using a single big dose of bolus insulin.

In chapter 5, a neural network based prediction method is presented. The model uses a new training method for a neural network in which an absorption model is applied that uses the nutrient contents of meals. The numerical characteristics of the computed absorption curve are fed to the neural network as training inputs along with the applied insulin doses and BGL evolution measured by a Continuous Glucose Monitoring (CGM) system. For comparison, another version of the training in which raw carbohydrate values are used as dietary inputs has also been implemented.

# Chapter 2: Background and previous work

This chapter provides a brief overview of glucose/insulin control processes in the human body, blood glucose level (BGL) measurement methods, and relevant earlier results achieved at the Medical Informatics Research and Development Centre (MIRDC). Specific background overviews will also be presented later in the relevant chapters.

## 2.1 GLUCOSE AND INSULIN CONTROL IN THE HUMAN BODY

Though the new scientific results presented in this thesis are in the field of informatics and it was not an objective of my work to improve or change the referenced, validated absorption and BGL regulation models, in this section I give a short overview of the underlying physiological processes for a better understanding of the problem domain.

Glucose is a source of energy for the cells that the body provides primarily from the carbohydrates it ingests. In physiological cases, the body tries to regulate glucose levels within a relatively narrow range (glucose homeostasis) through regulatory mechanisms. Increased blood glucose levels in the pancreas after a meal are sensed by β-cells in the so-called Langerhans Islands (in addition, there are many distributed sensors ranging from the taste buds to parts of the intestinal tract).

Upon sensing glucose levels, β-cells, on the one hand, deliver their "ready" insulin molecules into the bloodstream (rapid response) and begin to produce additional insulin molecules (slow response). In the case of long-term glucose surplus, the number of working β-cells increases, in part by increasing their life cycle, or according to other assumptions, by increasing their number [1]–[3].

The regulation (lowering) of BGL at the cellular level is achieved by the action of insulin hormone, which allows cells to take up glucose from the blood through the cell membrane, thereby reducing BGL. Insulin achieves glucose uptake by opening the cell membrane glucose uptake pathways. Most cells import glucose by

a process of facilitative diffusion mediated by members of the Glut family of membrane transport proteins. Human Glut family stand of 14 glut proteins and they include transporters for substrates other than glucose, including fructose, myoinositol, and urate. Gluts 1-4 have specific roles in cellular and whole body glucose homeostasis

GLUT1, the erythrocyte glucose transporter is the first GLUT isoform identified, and it is expressed at highest levels in the endothelial of barrier tissues such as blood vessels and the blood-brain barrier [4]. GLUT2 is found mainly in liver, pancreatic β-cells, intestine, kidney and hepatocytes [5]. GLUT3 is the major neuronal glucose transporter, and the brain highly relies on GLUT3 beside GLUT1 [6]. GLUT4 is the insulin-regulated glucose transporter found in adipose tissues, heart muscles, and skeletal muscles and it is responsible for insulin-regulated glucose disposal [4]. *Figure 1* shows how insulin achieves glucose uptake by opening glucose uptake channels in the cell membrane through GLUT4 an insulin-regulated glucose transporter.

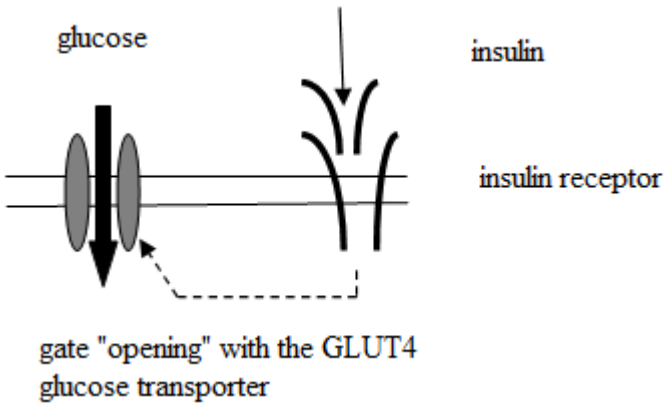


*Figure 1. Changes in the glucose permeability of cell walls. Symbolically, insulin through the cell membrane insulin receptor opens the "cellular gate" for the influx of glucose molecules through an activated glucose transporter [7].*

When blood glucose levels fall (e.g. due to physical activity), pancreas's α-cells produce the hormone glucagon, which in the liver converts to glucose and then circulates in the blood to increase the amount of glucose. *Figure 2* illustrates a

simplified process of blood glucose control (glucose homeostasis, the dynamic stability of the internal environment)[7].

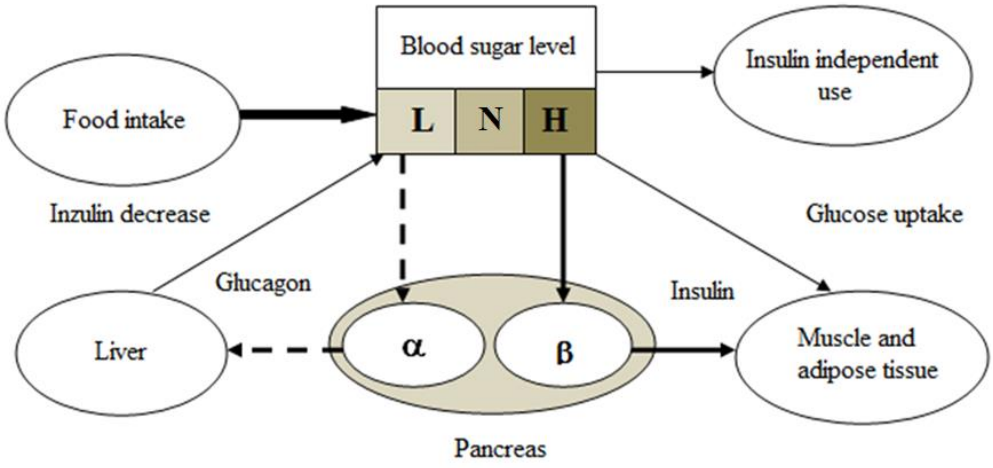


*Figure 2. Schematic and qualitative flow chart of global blood glucose control (L: low, N: normal, H: high BGL)[7].*

The control system maintains the BGL between 4.0 to 5.9 mmol/l when fasting and under 7.8 mm/l 2 hours after meal.

## 2.2 DIABETES MELLITUS AND ITS MANAGEMENT

Experiments have shown that under normal physiological conditions, shortly after nutrition (2 minutes), the first, pulsed phase of insulin secretion begins, which stops after 10–15 min, when the second phase of insulin secretion starts. Experimental studies have also shown that in the case of T2DM, an early sign of abnormal function is a lack of first-phase. This phenomenon has been explained by the fact that during the pre-diabetic state, an increased insulin resistance develops (i.e., an abnormal amount of insulin is required for a normal biological response). As a result, β-cells are slowly “depleted” and this results in the disappearance of the first phase[8].

When the glucose control system is unable to maintain a state called homeostasis, pharmacological regulation may also be required beside nutritional restrictions and lifestyle development to manage the new situation. It is common that taking one medicine alone is not enough to achieve adequate BGL, in which

case it may be necessary to take more than one medicine at the same time, and it may be necessary to supplement the treatment with insulin therapy to keep the BGL in appropriate range. Insulin types are detailed in subsection 2.2.1.

Target ranges of BGL may differ depending on age, duration of diabetes, the type of used medication. Table 1 provides general guidance. An individual target set by a healthcare team is the one that patient should aim for.

*Table 1. Recommended target blood glucose level ranges for type 2 and type 1 diabetic.*

| DM Type | Before meal | 2 hours after a meal |
|---|---|---|
| Type 2 diabetes | 4 to 7 mmol/l | under 8.5 mmol/l |
| Type 1 diabetes | 4 to 7 mmol/l | 5 to 9 mmol/l |

In the case of T2DM, persistently improper nutrition and obesity are largely responsible for the development of the disease. It follows that prevention can also be achieved primarily through proper lifestyle/nutrition and physical activity. There are restrictions/recommendations on both food intake and physical activity for patients with T2DM. The regulatory task is to optimize food intake, limit/personalize carbohydrate intake in both quantity and quality. Carbohydrate-containing foods differ in their effects on blood glucose concentrations as the same carbohydrate content but a lower glycemic index (GI) intake will produce lower glucose concentration. In other words, the GI shows the BGL raising effect of a certain food, ranging from 0 (for water) to 140 (for glucose itself) [9].

The primary clinical objective is to keep the mean blood glucose level within the specified limits. In clinical practice, HbA1c levels are used to characterize/monitor mean blood glucose levels, which are monitored by measurements every three months on average. HbA1c, or glycated hemoglobin, is a form of hemoglobin found in red blood cells that stains blood red, in which it binds glucose to hemoglobin. The ratio of glucose-bound (glycosylated) hemoglobin to total hemoglobin (expressed as a percentage) is an important laboratory parameter in the treatment of diabetes. It can be used to determine the patient's average BGL over the past three months. The goal of diabetes treatment is to keep HbA1c below

6.5% so that long-term complications of diabetes should not occur until later or not at all.

Recent studies suggest that HbA1c alone does not characterize the condition of a T2DM patient, as a correct diagnosis and therapy also requires information about BGL variability. According to the research results, the therapy should keep not only the average BGL, but also the glucose variance value low [10].

### 2.2.1 Insulin types

There are two major types of insulin products, fast acting insulins (bolus) and long basal insulin. Bolus insulin is specifically taken at meal times to keep blood glucose levels under control following a meal. Bolus insulin needs to act quickly; it is also known as short acting insulin or rapid acting insulin. According to current practice, insulin dependent diabetic patients use basal insulin injections typically once a day, to maintain a basic, continuous insulin level for the whole day (which is important especially during the night and the wake-up period), and bolus injections 3-4 times a day. Since the role of basal insulin is to keep blood glucose levels at consistent levels during periods of fasting, basal insulin need to act over a relatively long period of time. The goal of subcutaneous insulin therapy is to imitate both the normal prandial insulin secretion and the basal insulin levels as close as possible. An idealized insulin dosing regimen can be seen in *Figure 3*.

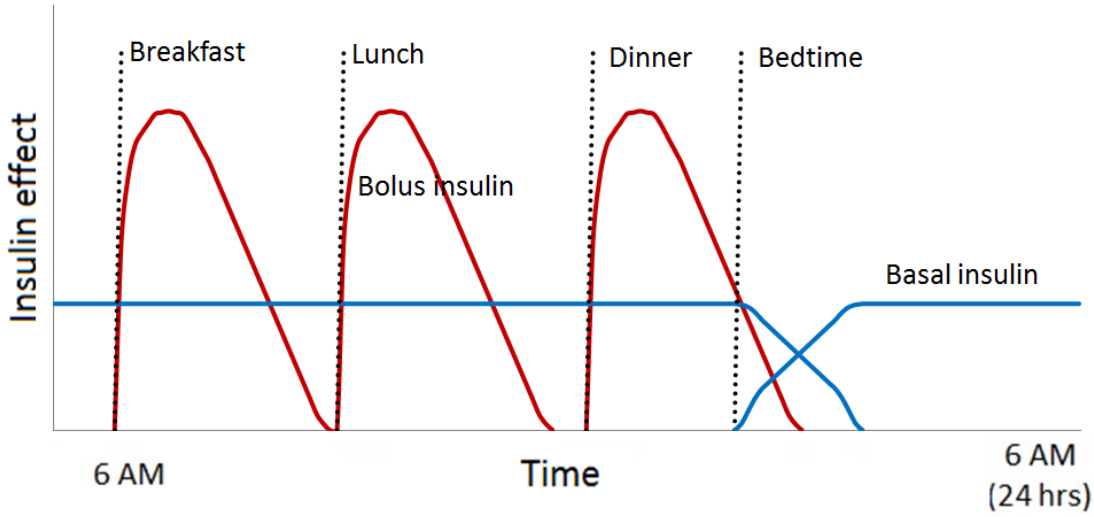


*Figure 3. Effect of insulin administration. The red curve shows an idealized theoretical approximation of the effect of the once-daily basal insulin that has ~ 24-hour duration of*

*action. Rapidly acting bolus insulins are used as prandial insulins that the patient administers at meal time (green curve).*

## 2.3 GLUCOSE MEASUREMENT

The BGL is the concentration of glucose present in the blood of humans. Glucose is a simple sugar and approximately 4 grams of glucose is present in the blood of a 70-kilogram human at all times [11]. The international standard way of measuring blood glucose levels is in terms of the molar concentration, measured in mmol/l (millimoles per liter). The BGL measurement usually contains single or continuous values. The single point BGL values are measured by ordinary fingertip blood glucose meters, while the continuous BGL values are measured by Continuous Glucose Monitoring (CGM) systems (Figure 4). These latter devices measure tissue glucose level every 2 or 5 minutes, which results in a little time-shift compared to the fingertip blood glucose meter in terms of the current BGL value.

CGM sensors are not as accurate as fingertip blood glucose meters. Studies comparing CGM versus fingertip blood glucose meters demonstrated that CGM is affected by a distortion due to diffusion processes and by time-varying systematic under/overestimations due to calibrations and sensor drifts [12].

The CGMS is calibrated with the ordinary BGL meter's value frequently, but still has worst case errors in the range of 3-4 mmol/l [13] compared to the 1 mmol/l [14] maximal error of the ordinary meter.


*Figure 4. Ordinary fingertip blood glucose meter (left) and glucose monitoring with Continuous Glucose Monitoring device (right).*

The exact BGL can be measured from blood taken intravenously in a laboratory (an invasive procedure) and the accuracy of blood glucose measuring devices is measured relative to this value.

It is important to note that since there were no intravenously BGL measurements in the clinical studies used for evaluation throughout the thesis, my goal was generally to predict the BGL value measured by a CGM calibrated from a fingertip device. This approach is in line with the methods widely accepted in the research community of outpatient diabetes care. Therefore, throughout the work when I write about BGL, I really mean the values measured by CGM.

## 2.4 MATHEMATICAL MODELS

The BGL related metabolism can be divided into two parts. One of them is the main glucose control process including insulin absorption and the reaction mechanism to the changing blood glucose level. This part is matched with the other subsystem including nutrient uptake and glucose absorption.

### 2.4.1 Glucose absorption models

There are many methods for modeling nutrient absorption proposed in the literature [15], the most well-known of which is the one used in the Diabetes Advisory System (DIAS) [16]. DIAS uses a one-compartment (stomach) absorption model, without considering the effect of the glycemic index of the various carbohydrates contained in the meal, nor the fiber and other nutrient content. In contrast, the two-compartment model due to Arleth et al. that I chose for glucose absorption modeling has a separate compartment for the intestine and it can model the timing of the absorption processes, such as the breakdown of starch to monosaccharide, in finer detail [17]. The structure of the model is shown in Figure 5. It should be noted that the real processes of the metabolism are naturally far more complicated.

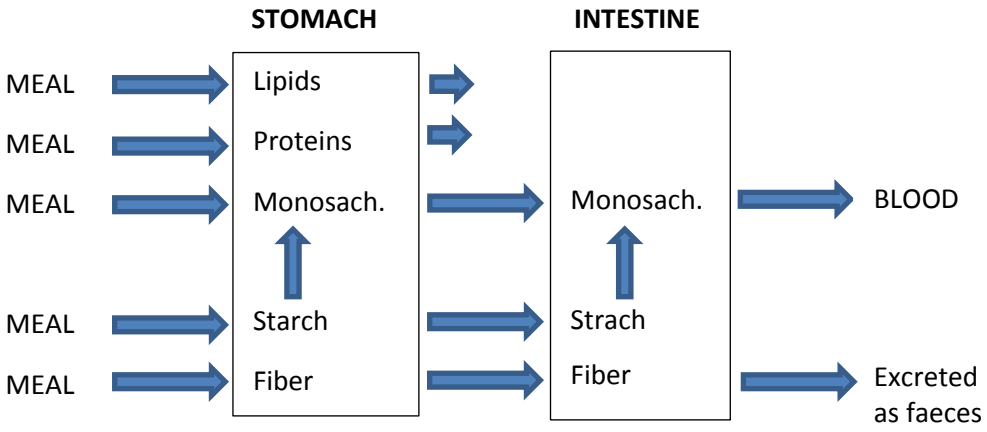


*Figure 5. Structure of the two-compartment glucose absorption model. Arrows show the transport and absorption (transformation) of the nutrients in the two compartments. In the first compartment, processing takes place in the stomach and in the second compartment, in the intestine. Adopted from* [18].

The Arleth model takes the consumed quantities of lipids, proteins, dietary fibers, monosaccharides and starch as inputs. An important feature of the model is the support of a Glycemic Index (GI) parameter that can be attached to a meal item or ingredient, by which it is possible to model 'mixed' meals. Modern dietary databases are expected to contain GI information for each ingredient containing carbohydrates, so a meal can be modeled as a 'glycemic mix'.

The main input parameters of the model, shown in Figure 5, are the amounts of protein, fat, fiber, monosaccharide and starch consumed. The algorithm uses the simple material balance equations described in equations (1-5), shown in the same order as the food itself progresses. The exact values for the constants used in the equations are detailed in [18].

$$\mathrm{sProteins}(t_{i+1}) = \mathrm{sProteins}(t_i) + \Delta\mathrm{mProteins}(t_i) - \Delta\mathrm{eProteins}(t_i) \quad (1)$$

$$\mathrm{sLipids}(t_{i+1}) = \mathrm{sLipids}(t_i) + \Delta\mathrm{mLipids}(t_i) - \Delta\mathrm{eLipids}(t_i) \quad (2)$$

$$\mathrm{Fibres}(t_{i+1}) = \mathrm{sFibres}(t_i) + \Delta\mathrm{mFibres}(t_i) - \Delta\mathrm{eFibres}(t_i) \quad (3)$$

$$\mathrm{Monosac}(t_{i+1}) = \mathrm{sMonosac}(t_i) + \Delta\mathrm{mMonosac}(t_i) * \mathrm{CHOAvail} - \Delta\mathrm{eMonosac}(t_i) + \sum_{\mathrm{GI}} \Delta\mathrm{sStarch}_{\mathrm{GI}}(t_i) \quad (4)$$

$$\mathrm{sStarch_{GI}}(t_{i+1}) = \mathrm{sStarch_{GI}}(t_i) + \Delta\mathrm{mStarch_{GI}}(t_i) * \mathrm{CHOAvail} - \Delta\mathrm{eStarch_{GI}}(t_i) - \Delta\mathrm{sStarch_{GI}}(t_i) \quad (5)$$

Equations (1-5) refer to the gastric compartment, taking the present material amount ('s' prefix), the food consumed ('m' prefix) and the amount injected from stomach into the intestine ('e' prefix) into account. The $\mathrm{CHOAvail}$ constant represents the uptake rate of stomach monosaccharide and starch from the food consumed and is set to 0.76 [18]. The breakdown of starch to monosaccharide is represented by $\Delta\mathrm{sStarch_{GI}}(t_i)$ in the equation (4). Further description of the model is given in reference [18].

### 2.4.2 Glucose control and insulin absorption system

The other important part of the combined model is the glucose control system that calculates the insulin evolution. A great overview about these methods is presented in [19]. Many of these algorithms are based on the original Minimal Model [20], which is a stable base of BGL estimation, but lacks in parameter set and model complexity, resulting in weaker prediction force. Other, more sophisticated methods include integro-differential [21], partial differential [22] and delay differential equations [23], often validated on a 'virtual patient' [24]–[26]. A common feature of these models is that they have been developed for inpatient care, where it is possible to measure several personal physiological model parameters. In general, more complex BGL regulation models describe the metabolism better, but are very hard to personalize for outpatients for whom invasive clinical measurements are not available. At the same time, even the most sophisticated models cannot account for such factors as the mental state.

Model personalization means to find the BGL model parameters individually for each patient. If the clinical measurement option is not viable, we can also use a historical lifestyle log with corresponding CGM data to estimate the parameter set (via a machine learning method), but only if the number of parameters is low i.e. the model is not very complex. This was a basic consideration behind the previous BGL model personalization efforts of the Medical Informatics Research and Development Centre (MIRDC).

The simple model used in the earlier work at the MIRDC was created by P. Palumbo et al. [23], [27] and is based on Delay Differential Equations (DDE). The main equations of the model are as follows.

$$\frac{dG}{dt} = -K_{xgi}G(t)I(t) + \frac{T_{GH}}{V_G} \tag{6}$$

$$\frac{dI}{dt} = -K_{xi}I(t) + \frac{T_{iGmax}}{V_I} f\big(G(t-\tau_G)\big) + \frac{1}{V_I t_{max,I}} S_2(t) \tag{7}$$

$$\frac{dS_2}{dt} = \frac{1}{t_{max,I}} S_1(t) - \frac{1}{t_{max,I}} S_2(t) \tag{8}$$

$$\frac{dS_1}{dt} = -\frac{1}{t_{max,I}} S_1(t) - u(t) \tag{9}$$

The above equations describe insulin transfer between $S_1$ and $S_2$ subcutaneous insulin depots (8,9), insulin (I) absorption into blood (7) and the role of insulin in blood glucose level (G) control (6) Function $u(t)$ describes the subcutaneous insulin input, while the $f\big(G(t-\tau_G)\big)$ function used in equation (7) represents the endogenous insulin production equation (10) The parameters of the model are also shown in *Table 2* with a more detailed description.

$$f(G) = \frac{\left(\frac{G}{G^*}\right)^{\gamma}}{1 + \left(\frac{G}{G^*}\right)^{\gamma}} \tag{10}$$

*Table 2. Glucose control model parameters in the Palumbo model (kgBW = weight in kilograms)* [23].

| Name | Description | Unit |
|---|---|---|
| $K_{xgi}$ | Rate of glucose uptake by insulin-dependent tissues | $1/(min * pM)$ |
| $T_{GH}$ | Net balance between hepatic glucose output and insulin-independent zero-order glucose uptake by brain | $mmol/(min * kgBW)$ |

| | | |
|---|---|---|
| $V_G$ | Apparent distribution volume for glucose | $L/kgBW$ |
| $K_{xi}$ | Apparent 1st order disappearance rate constant for insulin | $1/min$ |
| $T_{iGmax}$ | Maximal rate of second-phase insulin release | $pmol/(min * kgBW)$ |
| $V_i$ | Apparent distribution volume for insulin | $L/kgBW$ |
| $\tau_G$ | Apparent delay with which the pancreas varies secondary insulin release in response to varying plasma glucose concentrations | $min$ |
| $t_{max,I}$ | Time-to-maximum insulin absorption | $min$ |
| $G^*$ | The glycaemia at which the insulin release is half of its maximal rate | $mmol/l$ |
| $\gamma$ | The progressivity with which the pancreas reacts to circulating glucose concentrations | $-$ |

In our previous work [28], we implemented an outpatient blood glucose prediction model by combining the Arleth and Palumbo models described above. The combination was achieved by changing the equation (6). As a result (11), the new equation contains the monosaccharide absorption through intestine wall (ΔaMonosac(t)) calculated by the glucose absorption model.

$$\frac{dG}{dt} = -K_{xgi} * G(t) * I(t) + \frac{T_{GH}}{V_G} + \Delta aMonosac(t) \quad (11)$$

## 2.5 ASSESSMENT OF PREDICTION MODEL ERRORS

In the field of model based BGL prediction, the prediction time frame, also referred to as 'horizon', typically lasts for 15 to 240 minutes and the prediction is usually started after a meal and insulin administration event. From the clinical point

of view, the practical goal of the prediction is to estimate the patient's glycemia between two main meals of the day, so 15-minute predictions have limited applicability (though they can be used to assess model performance). The unit used for RMSE is either mmol/l or mg/dl; in this dissertation I'll use only mmol/l for consistency.

There are several assessment methods and figures of merit used routinely in the literature to measure and analyze the strength and weakness of prediction models. The figures of merit include Mean Absolute Error (MAE), Correlation Coefficient (CC), the Root Mean Square Error (RMSE), and the ratio of acceptable error i.e. the percentile of the cases when the prediction error remained under 1 mmol /l or 3 mmol /l (margin of error of the measurement devices).

The MAE is the absolute difference between the predicted and the measured BGL values at all time instances for which a BGL measurement is available over a prediction time frame. MAE can be calculated with the following equation:

$$MAE = \frac{\sum_{i=1}^{n} | (x_i - y_i) |}{n} \tag{12}$$

where $x_i$ is the measured glucose value at the time instant $t_i$, $y_i$ is the predicted BGL at the same time instant, and $n$ is the total number of blood glucose measurements in each dataset.

The RMSE is a quadratic score that also measures the average magnitude of the error. It is the square root of the average of squared differences between prediction and actual measured values. RMSE can be obtained by using the following formula:

$$RMSE = \sqrt{\frac{\sum_{i=1}^{n}(x_i - y_i)^2}{n}} \tag{13}$$

The CC value statistically shows the strength of the relationship between the relative movements of actual measurement and the prediction. The values range between -1.0 and 1.0. A correlation of -1.0 shows a perfect negative correlation, while a correlation of 1.0 shows a perfect positive correlation. A correlation of 0.0 shows no linear relationship.

Besides MAE and RMSE, the clinical reliability of BGL predictions is often evaluated with Clarke's Error Grid Analysis (EGA) [29]. The Clarke error grid approach is used to assess the clinical significance of differences between the predicted values and the blood glucose reference measurements. The method uses a Cartesian diagram, in which the predicted values are displayed on the y-axis, whereas the values from the reference method are displayed on the x-axis. EGA classifies predictions into 5 classes A-B-C-D-E with respect to the clinical outcome of an insulin dosing based on the predicted BGL. The worst scenarios (Classes D and E) is an overly high BGL prediction when the actual BGL of the patient is in the < 4 mmol/l range, because relying on such a prediction may lead to hypoglycemia, an emergency situation. Thus, the same absolute numerical error may be classified into various classes depending on the real BGL range and the sign of the error. A predicted value is termed 'clinically acceptable' if it is classified into either the A or B EGA class. For a graphical representation of the EGA regions, see Figure 6. CG-EGA is a variation of the EGA grid in which the 'accurate' domain is roughly equivalent to the EGA 'clinically acceptable' classification [30].

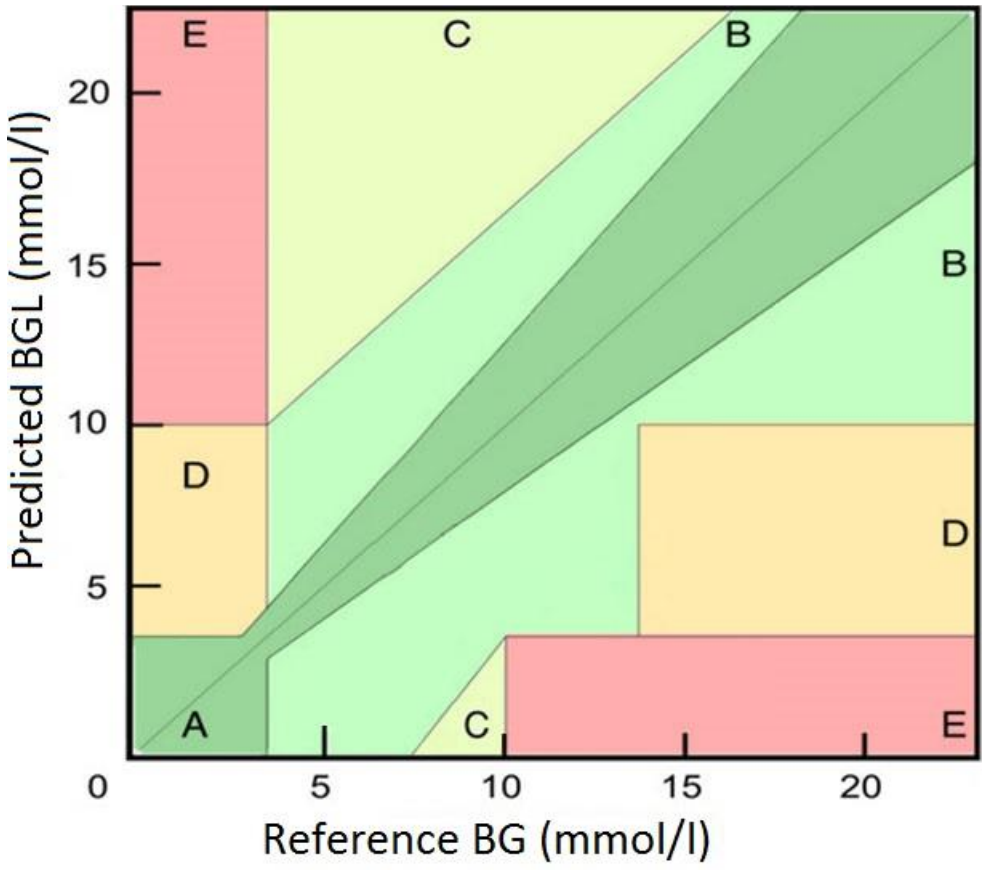

*Figure 6. Clarke Error grid analysis. A: clinically accurate prediction, smaller than 20% error, B: error still resulting clinically acceptable decision, C: possibility of hypo- or hyper-glycemia, D: sector of dangerous errors, E: resulting in opposite decision, endangers the life of the patient Adapted from* [29].

## 2.6 THE LAVINIA LIFESTYLE MIRROR APPLICATION

Diabetes is strongly linked with overweight and bad nutrition, the results of improper lifestyle. Lifestyle, however, is very hard to change, and since it is not expected that all patients endangered by, or already having diabetes could receive daily dietary advice from expert dietitians, there is a great need for personalized dietary advice and lifestyle support on mobile devices. A mobile application that provides instant feedback on the logged nutrition, physical activity and medication of a patient can effectively assist in learning the lifestyle related do's and don'ts for a diabetic or pre-diabetic person.

Advances in mobile technology make it now possible to keep reliable lifestyle logs including nutrition. Such logs can be a basis for smart services like BGL prediction for millions of diabetic patients in their daily life. It has been shown that patients can benefit from mobile Ambient Assisted Living [31] services for diabetes management [32].

The Lavinia Lifestyle Mirror is an Android application supported by a dietary expert system backend, developed at the MIRDC [33], [34]. Screens of Lavinia application's different modules can be seen in Figure 7. The main screen in Figure 7.A. shows the consumed meals on a given day and the aggregated nutritional values of all meals. In Figure 7.B the input data and the BGL values predicted by the integrated prediction model can be seen. Figure 7.C displays a chart of energy nutrient contents of the consumed meals.

An advantage of Lavinia over other mobile apps for DM management and lifestyle logging on the market is its support for instant numerical evaluation and visual feedback (see e.g. Fig. 7.B).

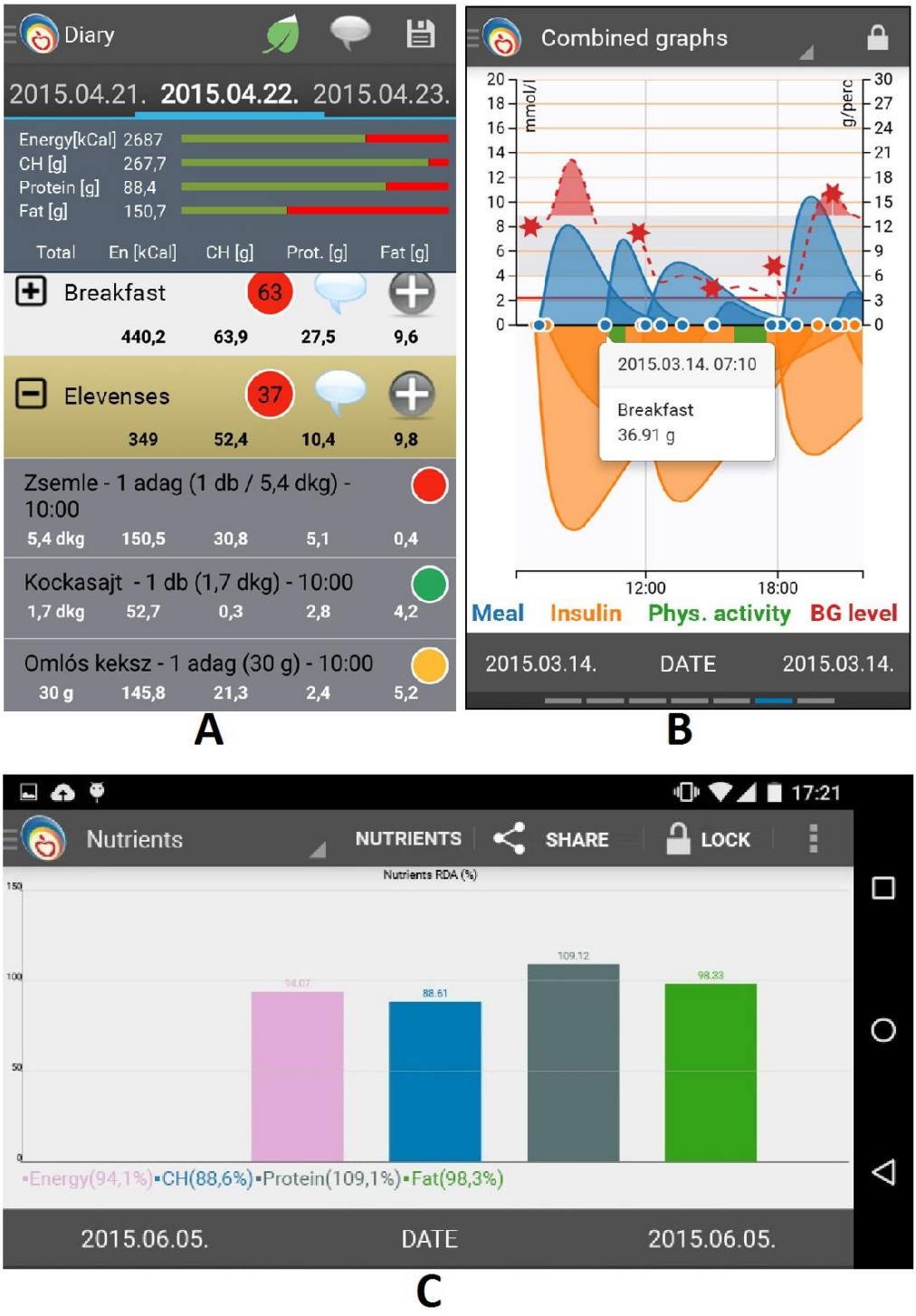


*Figure 7. Panels of the Lavinia lifestyle application. A: Daily dietary log summary ('Zsemle': bread, 'Kockasajt': cream cheese, 'Omlós keksz': biscuits are items of the meal). B. The computed absorption curves for insulin (orange) and meals' carbohydrates (blue). The stars show the results of logged fingertip BGL measurements. BGL prediction is shown as a dashed red line. C. chart of nutrient contents of consumed meals (adopted from* [35], [36]*).*

Figure 8 illustrates the traditional paper based lifestyle logging method. An obvious advantage of the digital method is the possibility of data processing by giving a response based on automated numerical analysis immediately. This cannot be done with a paper dietary. In the digital solution, the patient receives immediate feedback on the food entry and the patient has a better understanding of the relationships between diet and BGL development, thereby a better understanding of lifestyle as a motivating effect.

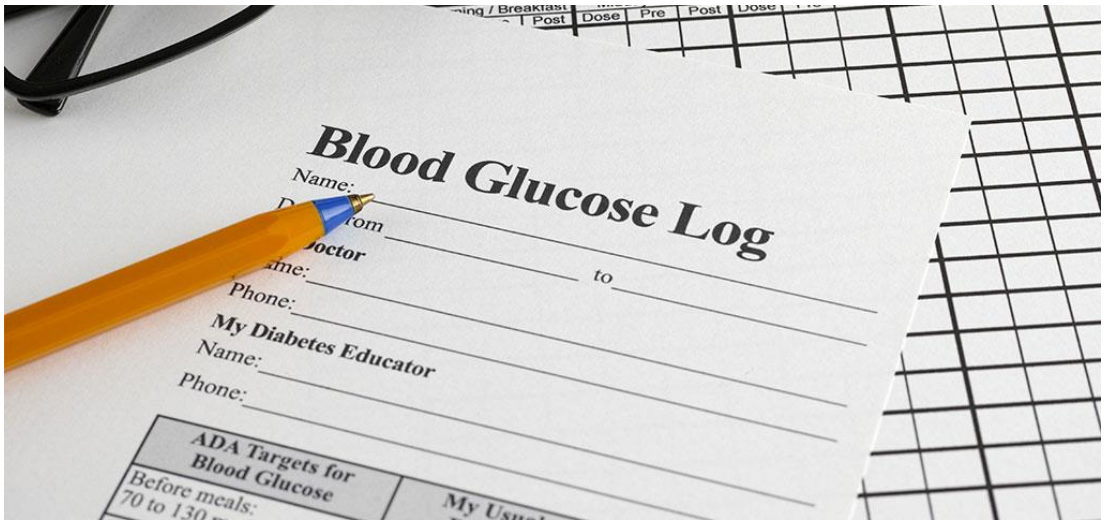


*Figure 8. Sample of paper based diabetic diary*

## 2.7 CLINICAL TRIALS

In my research I worked with datasets collected in the following trials.

### 2.7.1 The HK4 clinical trial

The clinical study was performed at the Cardiac Rehabilitation Institute of the Military Hospital, Balatonfüred, Hungary. The study was designed to simulate the real circumstances of the planned lifestyle counseling application. It started on 2014.09.17. For data entry Nexus 4 smartphone and Nexus 7 tablet, with the Lavinia application pre-installed was used. The patients were under continuous medical and dietary supervision and an informed consent was obtained from the patients as a prerequisite to enter the trial. The study protocol was approved 18 October 2013 by

the institutional ethical committee of the Military Hospital, Budapest, Hungary, chaired by Dr. László Kovács, under the submission number II/20-265-2013. The protocol was designed and implemented in compliance with the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects.

The continuous BGL measurement data was provided by the Guardian Real-Time and iPro Continuous Glucose Monitoring Systems (CGMS) by Medtronic Company [37]. The summary of the trial:

- 22 T2DM patients (15 men and 7 women)
- Age: 41-84, median 66.7
- Tracking days per patient: 3-25, median 18, 369 in total
- Meals logged per patient: 16-202, median 87.5, 1884 in total
- Insulin administration events logged per patient: 8-102, median 69, 1397 in total
- BGL values logged per patient
    - Single value 18-112, median 55, 1307 in total
    - CGM 556-3285, median 1533, 31995 in total

### 2.7.2 The HK5 clinical trial

The clinical study was performed at the Cardiac Rehabilitation Institute of the Military Hospital, Balatonfüred, Hungary. The study included insulin-dependent T1DM and T2DM patients taking part in 3-week rehabilitation courses between April and August 2019, with daily activities similar to everyday life. The CGM system used was the Medtrum's S7 EasySense CGM System [38], which registered subcutaneous glucose values every 2 minutes.

- 8 T2DM patients (3 men and 5 women)
- Age 48-70, median 60.5
- Tracking days 11-23, median 18.5, 142 in total
- Meals 39-109, median 86, 640 in total
- Insulin 44-92, median 72.5, 562 in total
- BGL values

- CGM 5346-14558, median 6607, 66238 in total

### 2.7.3 Data availability

The detailed, anonymized data sets used for the research presented in this dissertation are available at request from the author. Other data related to the clinical trial may be released upon application to the institutional Ethical Committee of the Military Hospital, which can be contacted at Magyar Honvédség Egészségügyi Központ Intézményi és Regionális Kutatásetikai Bizottsága, Róbert Károly körút 44, 1134 Budapest, Hungary.

## 2.8 PROBLEM STATEMENT

My main objective is to predict BGL for the purpose of an educational and lifestyle management aid for DM patients. Characterizing and diagnosing the patient's current condition is not an objective of the work. The input for the predictions is limited to the data available from the clinical trials: fingertip BGL, CGM data, insulin log and detailed dietary log. The support for other factors influencing BGL like physical activity, stress and state of mind is left for future research.

The predictions should be applicable for DM patients, especially those on external insulin, by providing BGL predictions based on their dietary and insulin administration log. If the prediction is reliable and the method is integrated into a lifestyle management application like Lavinia, the patients could be warned of hypo/hyperglycemia in time to reconsider their insulin dosage or planned meal. It should be emphasized that in contrast to artificial pancreas research, my aim is not to give a recommendation for insulin dosing, I provide only a prediction—either as an educational aid or as a tool to test ‘what-if’ scenarios.

## 2.9 OVERVIEW OF THE CHAPTERS

Chapter 3 investigates the feasibility of providing BGL prediction for two hours period after meals based on a dietary log and a calibration measurement without using insulin information. The goal is to Develop an ‘impulse response’ type

prediction method by clustering patients upon the characteristic of postprandial glucose response profiles and using the calculated average BGL response for clusters to predict the glucose evolution of patients belonging to the clusters. If the new method produces accurate results, it can be applicable to support or replace the mathematical models in case of insulin independent patients.

The goal of the work presented in Chapter 4 was to adjust the mathematical model described in subsection 2.4 to support basal insulin in order to provide more accurate short term blood glucose prediction. The basic idea is to simulate the absorption of basal insulin as a series of smaller insulin doses according to four alternative 'dosing profiles', instead of using a single big dose of bolus insulin.

The objective of Chapter 5 was to develop a method for BGL prediction based on the baseline BGL, the insulin dosing and a dietary log using artificial neural network, without any mathematical BGL regulation model. As a novelty compared to other published neural-based BGL prediction results, the glucose absorption curve of the meal computed using the Arleth glucose absorption model (subsection 2.4.1) will provide the input training data for the neural network.

# Chapter 3: Examination of blood glucose response curves and diet relationship in a small scale study

One of the advanced Lavinia services is the log based short term BGL prediction. For this task, our research group previously developed a method [28] that uses the combination of two state-of-the-art models reflecting the real process happening in the body. However, since this method runs mathematical models for the digestion and blood glucose control system, it is not feasible in pre-diabetes because the endogenous insulin production, an important input of the model, is hard to estimate. Pre-diabetes is a "pre-diagnosis" of diabetes which is characterized by an elevated BGL. Thus, the motivation of my work was to find an alternative way for personalized and log-based BGL prediction. The idea is based on the fact that the postprandial glucose profiles depend on meal's absorption characteristics [39]. We therefore try to find the typical responses to characteristic meals and try to predict the BGL responses using a personalized training sample, recorded via a CGM device. If the response proves characteristic to the individual person and the meal type, this could be used as a starting point in short term postprandial blood glucose prediction.

## 3.1 METHODS

First I performed a *pre-study* with 6 healthy volunteers members of the MIRDC [2 female, 4 male, age 29.5 ± 8.5 years, body mass index 24.5 ± 5.4 kg/m2]. The study took place in June 2015 and the protocol involved 6 days with CGM measurement, with 3 days of standardized diet with 5 meals per day, and 3 days normal meals according to the individual eating habits. The 'standardized diet' means that the participants had the same breakfast, lunch, dinner and the 2 snacks for each day at the same time, designed by a dietitian expert. Meals were designed according to daily energy needs. There was a lower (2000 kcal) and a higher (2500

kcal) energy need group. The participants used the Lavinia dietary mirror application to log their meals. I characterized the postprandial glucose response profile with the following three numeric parameters (*Figure 9*):

- the time to peak of BGL after a meal, in minutes
- the BGL difference between the start and the peak in mmol/l
- elapsed time to complete the BGL curve, in minute. The curve is considered complete when the BGL stops dropping.

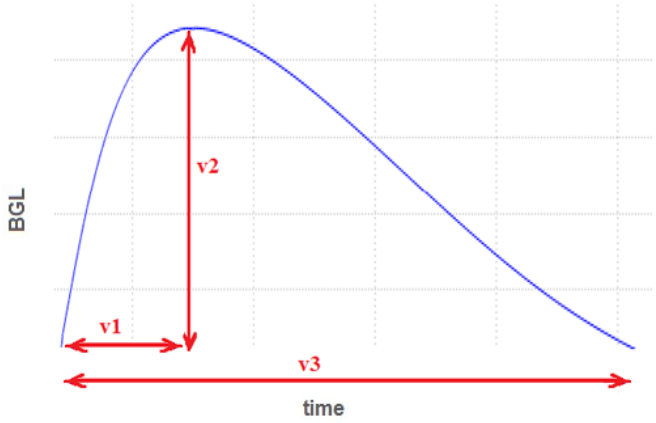


*Figure 9. BGL response curve characterization by V1, V2 and V3 numeric parameters.*

I linked these 3 parameters to the carbohydrate content and the glycemic composition of the meals [9] for each investigated subject, thus setting up an 'impulse response' type method to predict the glucose concentration evolution for two hours after the meals. The characteristics and variability of the responses among the meal types and patients were also analyzed. 2 persons (P02, P06) were excluded due to incomplete or unreliable data. The results showed that 3 of the 4 persons with acceptable data had a rather characteristic (personal) BGL response to the meal, so the idea of relying solely on the dietary log for qualitative predictions is promising. *Figure 10* shows the BGL responses of breakfasts in the standard meal days for the 6 healthy volunteers.

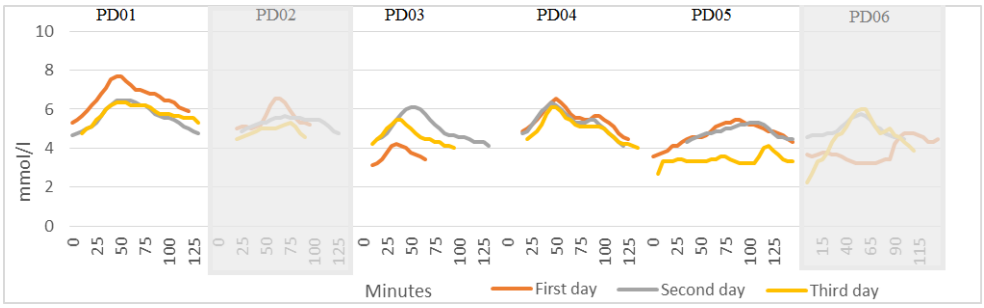


*Figure 10. BGL response curves of the first 3 day's breakfast for the 6 healthy volunteers. The curves show 2 hours BGL evolution measured by CGM. Zero minute is the moment of breakfast. PD02 and PD06 (shaded) were excluded because of unreliable data.*

Based on these findings, I extended and validated the method on a larger sample. The larger sample was drawn from the HK4 clinical study involving 22 patients with CGM for duration of 6 days. These participants were in general not so fully committed as those of the pre-study, so the collected data was less reliable. The participants had a standardized menu with personal deviations and they used the Lavinia application to log their meals. A Guardian Real-Time CGM by Medtronic Company [37] was used for monitoring blood glucose concentration. I had three initial study hypotheses that I wished to validate:

1. The post-prandial responses to standardized meals show a typical, reproducible, but personal BGL curve
2. Characterizing the patients based on response clusters improves the reliability of the response-based prediction
3. Post-prandial glucose profile in the whole response set depends on meal's dietary characteristics, e.g. fiber, fat, liquid intake

After the data collection phase, I performed a rigorous data cleaning process that included the identification and removal of possibly erroneous log records such as those with obviously incorrect timing. I also removed meal logs with insufficient or incorrect CGM data. The data cleaning process resulted in the exclusion of 7 patients. The Input data contained 439 breakfasts for 22 patients. Only 122 breakfasts for 20 patients had CGM. 79 breakfasts for 19 patients satisfied for 30 g CH ±20% (excluding those with too much deviation). After excluding visible

measurement errors and artifacts due to uncontrolled parameters (physical activity, incorrect timing, bad logs) 44 breakfasts for 15 patients remained.

I performed k-means meal-wise clustering on the whole record set with respect to the three numeric parameters, and also on the remaining meal logs and analyzed the characteristic differences among the clusters. I used the Waikato Environment for Knowledge Analysis (Weka) [40] framework for clustering. In Weka I chose the Expectation Maximization (EM) clustering algorithm that relies on maximizing the likelihood to find the statistical parameters of the underlying sub-populations in the dataset. EM parameterizes the k-means cluster so that the quality of the grouping is as good as possible, i.e. values of the mixture log likelihood to be the best. I used the default parameter set for the expectation maximization clustering algorithm.

## 3.2 RESULTS

The clustering on 282 meals separated the meal records into 3 distinct clusters for the breakfast, lunch and dinner *Figure 11*, suggesting that the meal type has a stronger influence on the BGL response than other factors. I therefore focused on the breakfasts only, assuming that it is the breakfast that is the least influenced by other meals.

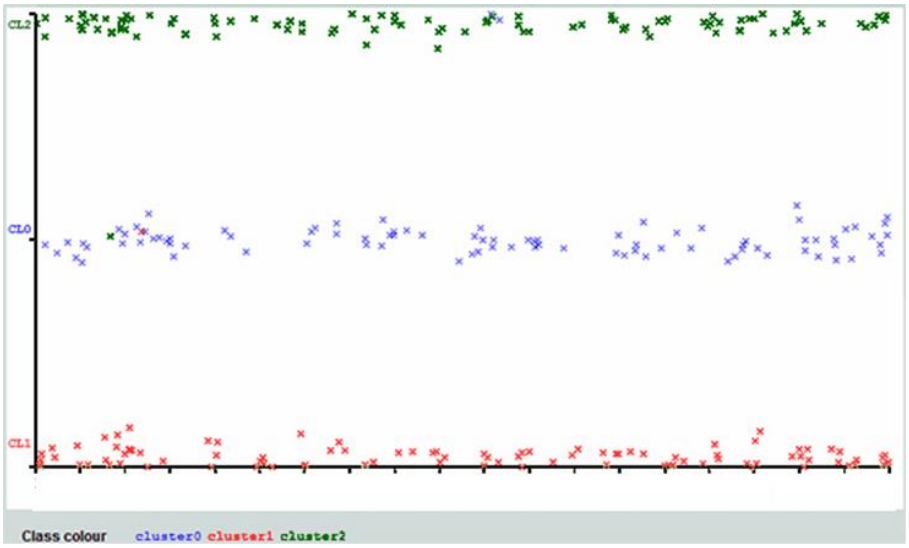


*Figure 11. 282 meals for 20 patients form 3 clusters with respect to V1-V3 parameters Cluster0 – lunch, Cluster1 – breakfast, Cluster2 – dinner.*

In the followings, I used the 44 breakfast responses of the 15 patients of the cleaned data set. Further clustering of breakfasts resulted in 3 distinct clusters, the ‘symmetrical’, 'flat top’ and ‘steep rising’ shaped curves for Cluster0, Cluster1 and Cluster2 respectively as it is shown in *Figure 12*. 18 responses (41%) were grouped in Cluster0, 12 responses (27%) in Cluster1 and Cluster2 included 14 responses (32%). The averaged response curves of the three clusters are shown in Figure 12. By a simple visual inspection, Cluster0 is described as ‘symmetrical’, Cluster1 ‘flat top’ and Cluster2 ‘steep rising’.

An important result was that only 2 persons’ responses belonged to multiple clusters, all other patients were found cluster dependent, which supports the idea that patients can be characterized by clusters.

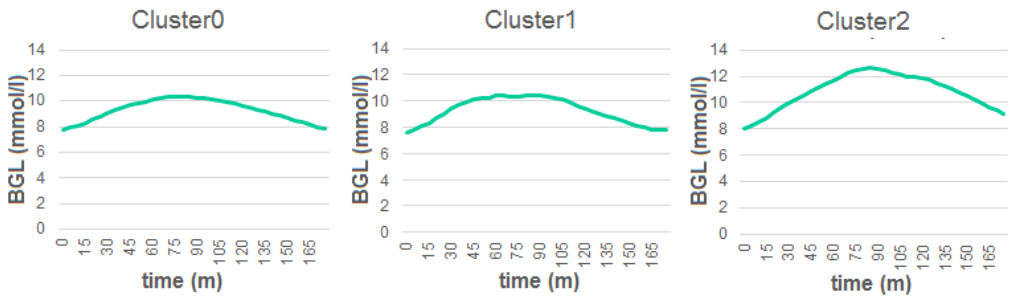


*Figure 12. Representation of the response curves for the 3 clusters calculated as the average of the postprandial blood glucose response curves of the patients in that cluster.*

In order to check the predicting power of the clusters, I computed the total absolute error of the averaged curves compared to the CGM data, first using for each patient the averaged curve of all responses, then the cluster specific curve. The cluster specific curve calculated by the average of all patients responses belong to the given cluster. MAE with a global response was 1.242 mmol/l which decreased to 1.146 mmol/l when using the response of the patient’s cluster. The improvement was 7.7% ($p<001$). The cluster-wise results are shown in Table 3.

*Table 3. Total absolute error and MAE of BGL prediction with and without clustering and the improvement. p-values show the significance level of the paired sample t-test.*

| Cluster | No. of Patients (measurements) | Global response (mmol/l) | | Cluster response (mmol/l) | | % improvement |
|---|---|---|---|---|---|---|
| | | Total abs. error | MAE | Total abs. error | MAE | |
| Cluster0 | 6 (648) | 672 | 1.037 | 625 | 0.964 | **7%** p<0.01 |
| Cluster1 | 5 (396) | 580 | 1.465 | 575 | 1.451 | **1%** p<0.01 |
| Cluster2 | 2 (432) | 582 | 1.347 | 493 | 1.140 | **15%** p<0.01 |

To examine whether the clusters different from each other, and to quantify the difference between them I compared the prediction of blood glucose levels of the patient group in one cluster with the prediction of the impulse response function of another cluster. The difference between prediction using own cluster response and other cluster response based prediction support the uniqueness of the response functions. The results can be seen in Table 4.

*Table 4. MAE (mmol/l) of BGL prediction with own cluster response and with other cluster response. The first data row shows MAE of predicting BGL of patients in Cluster0 using the average response of Clusters in the column headers, same for the second and third data row. Bold values are MAE values using response of own cluster for prediction.*

| Clusters | Cluster0 | Cluster1 | Cluster2 |
|---|---|---|---|
| Cluster0 | **0.964** | 1.022 | 1.376 |
| Cluster1 | 1.460 | **1.451** | 1.672 |
| Cluster2 | 1.546 | 1.534 | **1.140** |

In order to check the third hypothesis i.e. the response's dependence on the meal composition, I also performed Paired t-tests on 19 standard breakfasts compared to 19 'modified' breakfasts. I expected that a larger portion of the same meal would produce the same curve length with a higher peak, and that another

meal with the same CH content but with higher glycemic index would produce a shorter length with the same area under the curve. However, the test results did not show a significant difference ($p>0.1$).

## 3.3 DISCUSSION AND CONCLUSION

If there were more data per patient and we could assign typical trajectory curves to meal parameters and person customizable, these curves could be used to roughly estimate the postprandial blood glucose response. At present, insulin has not been addressed, assuming that there is no external insulin for example in the case of prediabetes patients or that the dose is always approximately the same. This would be the applicability of the method.

As the results show, most patients in the study can be clearly classified in a specific cluster based on their meal response characteristics, and this supports the hypothesis that the post-prandial responses to standardized meals show a typical, reproducible, but personal BGL curve. The reduction of the absolute error of the BGL prediction achieved by using patient clusters shows that the patient characterization based on response clusters improves the reliability of the response-based prediction. However, the meal responses of standard breakfasts compared to modified breakfasts did not show a significant difference, so I could not verify the third hypothesis. The cause for this may lie in uncontrolled factors such as stress and physical activity, but most of all, the small data set. The results are promising, but further work and possibly trials with more subjects are needed to integrate a clustering-based BGL prediction service into mobile lifestyle services.

# Chapter 4: Basal insulin management for blood glucose prediction modeling

## 4.1 BACKGROUND

The mathematical models commonly used for BGL prediction support the specification of short acting insulin dosing via a maximum value and the time-to-maximum value. Though the real action of insulin is far more complex, this method is satisfactory for modeling bolus insulin correctly, but not basal insulin, making the models applicable only for inpatient care scenarios. The effect of the basal insulin is usually simulated as a single injection of bolus insulin, with a slowly rising absorption curve and a very high maximum absorption value. However, in reality, the pharmaco-dynamic profile of bolus insulin level differs fundamentally from that of long lasting insulins. An adjustment to the traditional model is required to properly handle basal insulin in order to reach more accurate results. Based on our previous results in this field [28], [41], [42], the core idea of my work is that by substituting the single big dose of insulin with a series of several smaller bolus insulin doses we can better simulate the steady curve of insulin presence in the blood similar to the curve defined by the medicine manufacturers, and thus we can decrease the error of the prediction.

Currently available state-of-the-art mathematical models for blood glucose level prediction have been developed for intensive care departments, and thus they do not support basal insulins. Such basal insulins are, however, widely used by masses of diabetic outpatients typically once a day that produce a steady insulin level for the whole day, and fast-acting or bolus injections for every meal in order to control their blood glucose. Therefore, if we want to apply the prediction models in outpatient care, the current models need some adjustment. In this chapter I, present a new method for handling basal insulin absorption is presented in order to improve the accuracy of blood glucose level prediction. I propose a method that simulates the absorption of basal insulin as a series of smaller insulin doses

according to four alternative ‘dosing profiles’, such the original time interval is divided into shorter subintervals with lowers Tmax. This approach is in contrast with the original approach of using a single big dose of bolus insulin.

## 4.2 RELATED WORK

Although currently available basal insulins fail to fully imitate the physiological basal insulin secretion, their characteristic shows a gentle rise and fall compared to intermediate–acting insulins [43], [44]. In order to duplicate the endogenous insulin secretion affording more flexible treatment with fewer hypoglycemia episodes. In a related study, basal insulin demonstrated great improvements in glycemic control and reduced nocturnal hypoglycemia, as well as reduced weight and lowered mealtime insulin doses [45]. Bolli et al. [46] and Chapman et al. [47] have shown in their works that Glargine (GL) and Detemir insulins prolong subcutaneous absorption by altering amino acid structure (GL) or adding fatty acylated side chains (Detemir). However, in [48] it was shown that there are differences in the pharmacokinetic and pharmaco-dynamic properties of Detemir and Glargine insulins.

As the problem of how insulin absorption can be modeled in BGL prediction is a complex task, many different approaches are used. In [49]–[52] the authors focus on short term prediction, where only the 15-30 minutes after a meal is considered. In such cases, however, the effect of bolus insulin is so much greater than that of basal insulin, that the latter is usually excluded from the prediction process. However, in real life, not only these short time intervals are crucial for diabetics: how their BGL fluctuates throughout the rest of the day is just as important.

Some prediction methods concern patients that require no direct insulin intake in their medications [53]. Others use only BGL history as input and exclude the effect of factors like insulin injection or meal intake [51], [54], [55]. Such an approach, however, assumes accurate insulin doses and nutrition in a strict daily regime, and patients whose metabolism reacts almost identically to that of “healthy” ones [56].

The task was to adjust the mathematical model to support basal insulin. The original model simulated the basal insulin effect as bolus insulin. Before the correction, I acknowledge the abnormal handling of insulin or I excluded the basal insulin from inputs. Both excluding basal insulin or running the calculation with it led to rising in the prediction error

To my best knowledge, there was no other method or result published in literature about support basal insulin in BGL prediction models.

## 4.3 MATERIALS AND METHODS

In the previous work at MIRDC with the Palumbo model, we observed abnormal basal insulin handling by the used insulin absorption model, which was one of the most important inputs of our prediction model (see Section 2.4.2). The model simulated the basal insulin as a big amount of bolus insulin with a slowly rising curve and a very high maximum value. However in reality the basal insulin level reaches a proper level in a very short time and the effect lasts for a long time. So, an adjustment is required for dealing with basal insulin to reach more precise results.

In the new method proposed, I model the basal insulin in a more accurate way by using a series of smaller insulin doses, instead of one big dose, dividing the original time interval into short subintervals with low Tmax.

To demonstrate the idea, the top left curve in Figure 13 represents basal insulin absorption according to information from medicine manufacturers. The top right curve shows how the model simulates a 50-unit basal insulin before the proposed correction. The curve at the bottom shows the correction method i.e. smaller doses with appropriate overlap can simulate the required flat curve.

Different insulin level curves published by researchers[57]–[59]. However, manufacturers publish a simplified curve in their own materials. In my study, I examined how much more accurate a prediction can be made by approximating the real situation with such a simplified basal insulin curve instead of the simply starched rapid absorption curve used in our previous model.

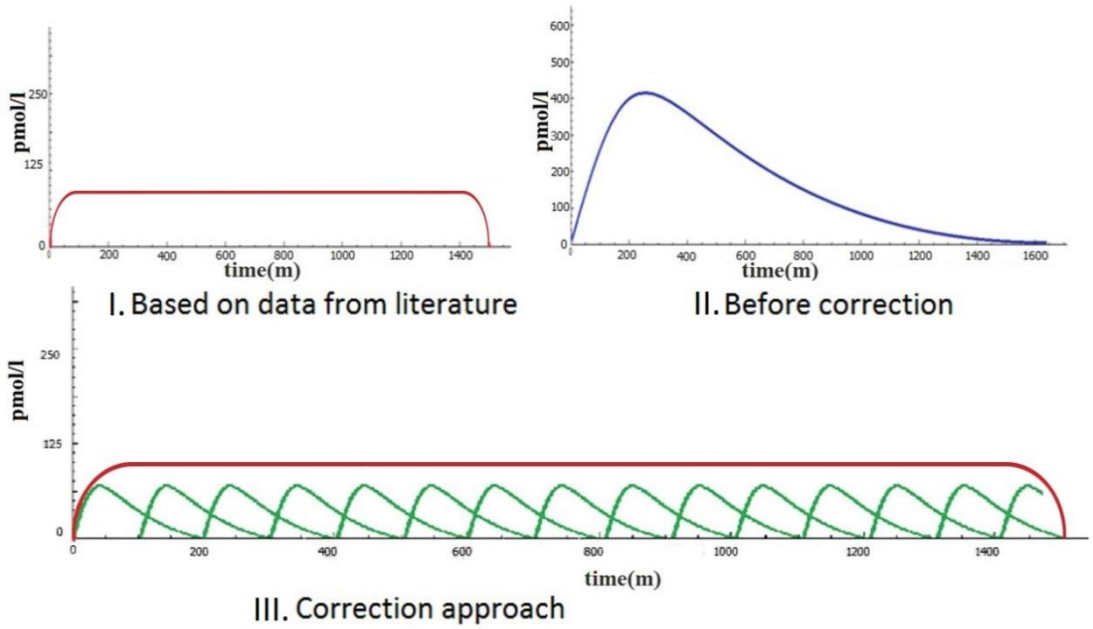


*Figure 13. The core idea of the basal insulin management method. I. Represents the idealized approximation model curve used in this study. II. Shows the curve used in our previous published studies for depicting the long lasting insulin effect simple by stretching for 24 hours the short acting insulin curve. III. Series of small bolus insulin doses (Green curves) simulate the flat curve of a basal insulin (red curve).*

The insulin absorption model developed by Palumbo et al. expect only two parameters to specify the insulin dose, the two parameters are Tmax and dose amount. I only need to specify those two parameters. I can't determine the shape of the absorption curve; it's calculated by the insulin absorption model.

In order to find a suitable number of sub-doses, I designed four ad-hoc 'dosing profiles', ranging from very few (6-7) to several (130-150) doses, and I run the tests for each of them. According to the product sheets, there are differences in duration of action, rising and falling characteristics among long-acting and intermediate-acting insulin products [60].

I determined the parameters of the profiles to form a kind of series from many small doses to fewer larger doses. I can get the flat curve more accurately if I use a lot of doses and that means more computational capacity but still may not really affect the accuracy of the model.

Of course, the ideal solution would probably be to somehow the model be able to simulate the presence of insulin continuously, but the model is not capable of that and I did not want to change the model as it is a validated model, I just use the model. Therefore, a finite number of discrete administrations required to simulating basal insulin.

For a clearer understanding, some details need to be described about Tmax. Cmax: maximum insulin concentration in plasma and Tmax: Time to Cmax. Usually, Tmax is only used in case of bolus insulins, with the fact that Tmax also exists for basal insulins, but it is not interesting for my work, rather what is important is the Effective half-lives (Teff) of basal insulins, which is the half time of acting period. As described above, the Insulin absorption model does not support basal insulin, so it also treats a basal insulin input as a bolus, thus interpreting Teff as Tmax. The correction method Insulin sub doses defined in insulin profiles are a special derivation of bolus insulin so that they have Tmax calculated from the base insulin Teff. Both Tmax and Teff measured are in minute.

Table 5 shows how I modeled (Number of doses, new Dose amount and new Tmax for the series insulin doses), in the four profiles separately, the five basal insulin products that appeared in the patient logs.

*Table 5. The parameter set of the four tested insulin profiles for the five relevant basal insulin products. Teff: Effective half-lives of basal insulin in column headers. Columns data contain the determined Tmax in minute for insulin sub dose defined in the given insulin profile. Dose amount indicate the percentage of the basal insulin dose.*

| **Insulins** | **Lantus** | **Levemir** | **Humulin N** | **Insulatard** | **Insuman Basal** |
|---|---|---|---|---|---|
| **Teff (minute)** | 750 | 420 | 390 | 300 | 300 |
| **1. profile (6 doses) Dose amount =16.67%** | 100 | 70 | 65 | 50 | 50 |
| **2. profile (20 doses) Dose amount 5%** | 37 | 21 | 20 | 15 | 15 |
| **3. profile (40 doses) Dose amount 2.5%** | 19 | 10 | 10 | 7 | 7 |
| **4. profile (150 doses) Dose amount 0.67%** | 5 | 3 | 3 | 2 | 2 |

Figure 14 shows a graphical comparison of Profile 1 and Profile 2.

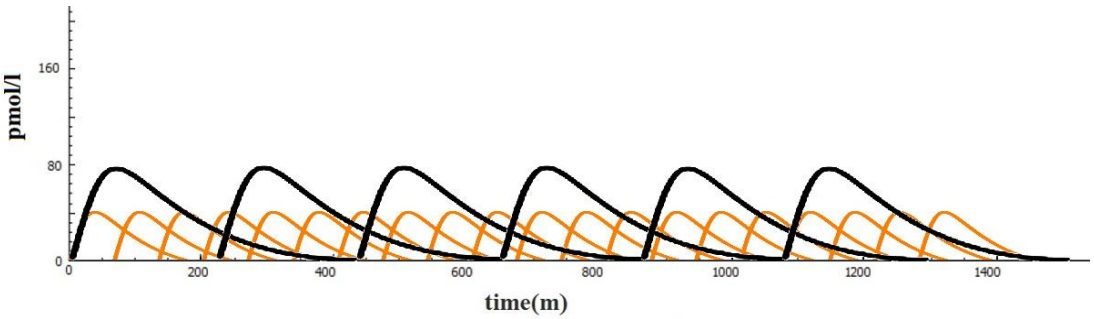


*Figure 14. Comparison of Profile 1 (Black curves) and profile 2 (Orange curves). One basal insulin dose with 36 unit dose amount simulated with 6 doses (6 unit/dose) for profile 1 and with 20 doses (1,8 unit/dose) for profile 2.*

## 4.4 DATA SETS

The input data consisted of 18 anonymized datasets of the HK4 clinical trial from 16 T2DM patients (7 female and 9 male) as shown in Table 6, each dataset containing at least 3 days CGM records (ca. 25000 CGM records in total). Patient 04 and Patient 12 had two data sets. The average age of the patients is 70±8 years (Mean ± Standard Deviation) with an average weight of 90±18 kg. The data set contained 340 meal logs and 280 insulin injection records. In addition to the CGM values, I also had access to fingertip BGL records, measured with an ordinary fingertip blood glucose meter. The study was performed as part of a 21-day rehabilitation treatment with no stress in the patients' everyday life and the patients were asked to refrain from excessive physical activity during the trial.

*Table 6. Patient characteristics.*

| ID | Gender | Height [cm] | Weight [kg] | Age | Data days | Insulin | Agent per unit (pmol) |
|---|---|---|---|---|---|---|---|
| P01 | male | 165 | 85 | 63 | 16 | Lantus | 5773 |
| P02 | male | 172 | 96 | 73 | 17 | Levemir | 5915 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| P03 | male | 176 | 98 | 79 | 20 | Humulin N | 6026 |
| P04 | male | 185 | 95 | 67 | 21 | Lantus | 5773 |
| P06 | female | 170 | 80 | 65 | 19 | Levemir | 5915 |
| P07 | male | 176 | 103 | 85 | 11 | Lantus | 5773 |
| P09 | male | 169 | 80 | 75 | 12 | Insulatard | 6026 |
| P10 | female | 165 | 101 | 76 | 21 | Humalog Mix50 | 6026 |
| P11 | female | 156 | 105 | 75 | 18 | Levemir | 5915 |
| P12 | male | 172 | 73 | 58 | 17 | Lantus | 5773 |
| P14 | male | 153 | 90 | 68 | 13 | Humalog Mix25 | 6026 |
| P15 | female | 156 | 88 | 79 | 19 | Insulatard | 6026 |
| P16 | female | 165 | 74 | 61 | 20 | Lantus | 5773 |
| P17 | male | 163 | 100 | 65 | 20 | Levemir | 5915 |
| P18 | female | 165 | 84 | 76 | 19 | Insulatard | 6026 |
| P19 | female | 157 | 87 | 61 | 20 | Lantus | 5773 |

## 4.5 RESULTS

I tested the corrected model against the original setup (i.e. a large dose of a single bolus insulin for a basal insulin administration) in four configurations:

- 180-minute predictions, on the whole time period and night-time taken separately, for each data set
- Wake-up BGL prediction
- EGA evaluation

### *4.5.1* Results for the 180-minute predictions

I applied the original model and the corrected model to predict short term (180 minutes) blood glucose levels with various basal insulin profiles and computed the average absolute error of the prediction using the CGM records of the clinical study running the prediction model on all the 18 datasets.

In order to find the best profile, I first ran this test without separating the day-time from the night-time. As Table 7 shows, Profile 1 with relatively few doses

proved the best with respect to the improvement in the average absolute error. The original model produced 4.41 mmol/l average absolute error, while the corrected model produced 3.79 mmol/l average absolute error, thus the achieved improvement is 0.62 mmol/l.

*Table 7. Average improvement, Biggest improvement and Worse results data for each insulin profile by using the correction method compared to the original model. p-values show the significance level of the paired sample t-test.*

| | **Profile 1** | **Profile 2** | **Profile 3** | **Profile 4** |
|---|---|---|---|---|
| Average improvement (mmol/l) | 0.62<br>p<0.01 | 0.46<br>P<0.05 | 0.47<br>P=0.01 | 0.58<br>p<0.01 |
| Biggest improvement (mmol/l) | 2.37 | 2.35 | 2.32 | 2.35 |
| No. of data sets with worse results | 3 | 4 | 5 | 3 |

On *Figure 15*, can be seen how the prediction error distribution varies with using 4 insulin profiles. Running the corrected model with insulin Profile 1 for produced errors with smaller Mean and small Standard Deviation compared to the rest 3 insulin profiles.

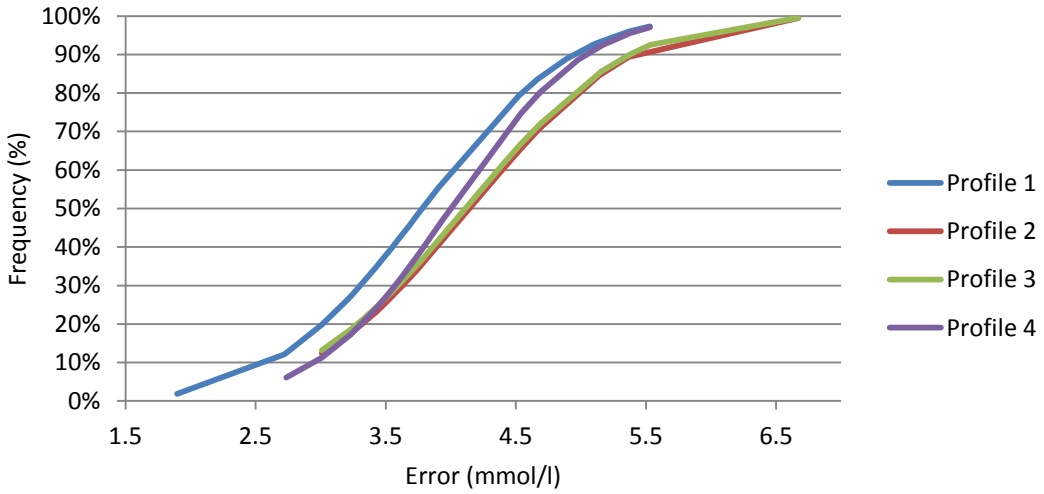


*Figure 15. Normal cumulative prediction error distribution for the different 4 insulin profiles. Mean and Standard Deviation were (3.782, 0.908), (4.145, 0.980), (4.112, 0.986) and (3.998, 0.814) for Profile 1, Profile 2, Profile 3 and Profile 4 respectively.*

I also performed a paired t-test of the errors before correction and after correction. As Table 8 shows, the new method produced significantly better predictions except in two cases, where it still gave better prediction, but the differences were not significant.

*Table 8. Paired t-test result for prediction errors of the original method and new method.*

| Dataset | No. of measurements | p |
|---|---|---|
| P01 | 1524 | < 0.01 |
| P02 | 1456 | 0.093 |
| P03 | 1562 | < 0.01 |
| P04.1 | 1724 | < 0.01 |
| P04.2 | 1491 | < 0.01 |
| P06 | 947 | < 0.01 |
| P07 | 1477 | < 0.01 |
| P09 | 1440 | < 0.01 |
| P10 | 1534 | < 0.01 |
| P11 | 1674 | < 0.01 |
| P12.1 | 590 | < 0.01 |
| P12.2 | 1589 | < 0.01 |
| P14 | 1445 | < 0.05 |
| P15 | 433 | < 0.01 |
| P16 | 1444 | 0.11 |
| P17 | 1695 | < 0.01 |
| P18 | 1473 | < 0.01 |
| P19 | 1487 | < 0.01 |

Since the night periods bear a specific significance with respect to basal insulins, I divided the 24 hours of the day into two parts, the night-time from 22’00 to 5’59 the next and the day-time from 6’00 to 21’59. During the night, patients are fasting, while during day-time bolus insulin injections and meals are also present. Using Profile 1, I repeated the test. For the night the average absolute error reduced from 5.01 mmol/l to 4.33 mmol/l (improvement is 0.69 mmol/l), and in day-time the average absolute error decreased from 4.13 mmol/l to 3.54 mmol/l (improvement is 0.59 mmol/l).

### *4.5.2* Wake-up BGL prediction

Since there are no bolus insulin doses during the night time, I can expect a remarkable improvement in the prediction accuracy in the wake-up (fasting) BGL before the first meal and the first insulin injection. It is also an important question from the clinical point of view whether I can reliably predict the fasting BGL because it can affect the insulin administration regime. For this reason, I performed a paired t-test on the 83 morning samples of the 16 patients. The test showed that there are significant improvements in the prediction error between the original model's prediction and the new model's prediction ($p < 0.01$). The difference of the average absolute error between the original and the corrected model is 1.02 mmol/l.

### *4.5.3* EGA evaluation

The EGA evaluation for all patient datasets showed that the percentage of prediction falling in the A or B (clinically acceptable) regions increased from 75% (18739 predictions) to 81% (20238 predictions) by applying the corrected model (6% improvement). As an example, Figure 16 below demonstrates on one of the datasets that the errors were effectively translated into a "clinically safer" domain i.e. closer to the area of the A region.

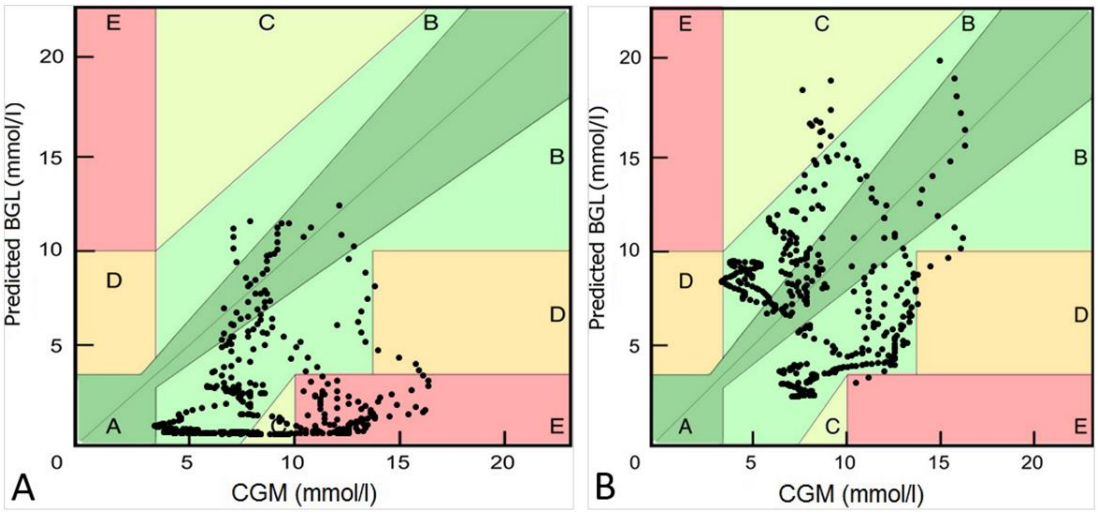


*Figure 16. Clark error grid. The result of a P15 patient's dataset. A: Before correction (left). B: After correction (right).*

## 4.6 DISCUSSION

It is hard to relate my work to previous results because to my best knowledge no research has so far been published in the exact field of modeling basal insulin modeling in blood glucose prediction based on mathematical models.

The tests were designed to investigate all important aspects of the BGL prediction, with an emphasis on the applicability for clinical decision support. The results were quite in line with my expectations, showing an improvement in all investigated areas:

- The short-time 180-minute predictions produced more improvement during the night, which can be explained by the fact that due to the missing meals and bolus insulin administration, an improved prediction of the action of the basal insulin has more effect on the overall prediction error.
- The wake-up BGL has a specific clinical importance. The application of the model correction resulted in a relatively small, but statistically significant improvement (1.02 mmol/l) in the average absolute error.
- In terms of the EGA assessment, 6% more of the predictions fall into the A or B regions. This shows that by the application of the correction, the errors were effectively translated into the “clinically safer” domains (see Figure 16).

A known limitation of my approach is due to the fact that the insulin producers do not publish the exact action profile of the insulin products, the only suggestion being that the insulin has a ‘fast’ time to maximum and a nearly constant, flat top for the specified duration, usually 24 hours. Thus my method that implements a perfectly flat-top plateau is just an approximation of the real action. The fact that I got the worst prediction results specifically in the case of Lantus and Levemir insulins may be due to a significant deviation of these insulins’ actual profile from the ‘ideal’ flat-top profile that I tried to approximate.

Nevertheless, my approximation can be assumed still better and closer to reality than the single-dose approach. Since the prediction errors decreased

considerably and statistically significantly, I can regard the above assumption clinically proven.

A definite limitation of the proposed method stems from the mathematical model being capable to tackle only nutrition and insulin administration, but not the two other influential factors of emotional, social or cognitive stress, and physical activity—though these factors are well known to have a profound and long-lasting effect on the BGL of diabetics [61]. Though our clinical setting excluded the presence of stress and physical activity from the current clinical study, in a practical application outside the rehabilitation clinic such factors must be accounted for.

## 4.7 SUMMARY

In summary, I presented the results in the modeling of basal insulin regimes for outpatient diabetes lifestyle support. The improvement over the traditional modeling method, combined with the expected improvement from the planned management of other factors like stress, insulin sensitivity and physical activity, could make a personalized prediction model more efficient and reliable as a module of a lifestyle support mobile application for outpatient healthcare.

# Chapter 5: Blood glucose prediction using artificial intelligence

## 5.1 INTRODUCTION

Due to the significance of the problem, the characteristics of BGL evolution have been researched extensively in healthy and DM persons in the past decades, and BGL was found to be influenced by physical activity [62], stress [63], mental state, and most of all, nutrition. In order to model the effect of nutrition, i.e. the effect of absorbed carbohydrates entering the circulation, on the BGL regulation system, several hundred mathematical models of various complexity have been proposed [64]. As stated in Chapter 2, complex models with many parameters can generally simulate the human metabolism better than simple models with few parameters, but they are increasingly harder to 'personalize' for a real DM outpatient, due to the significant personal (natural) variations in the model parameters.

In an earlier study we applied genetic algorithms (GA) and other methods to find the personalized parameter set using a simple but quite model for BGL regulation. The training input to the model was a detailed nutrition and medication log of a clinical trial, complemented with frequent BGL readings from a Continuous Glucose Monitor (CGM) device. Stress and excessive physical activity were avoided by the patients during the trial. The glucose intake profiles of the consumed meals were computed with an absorption model that could also handle the effect of other nutrients like dietary fiber and the glycemic mix of the logged items. We applied evolutionary parameter search and diurnal parameter profiles during model training [28], [65] and the previous chapter described my results in applying a special representation of basal insulins [66] to decrease the errors of the model. The results were promising, especially compared to published results of similar trained or untrained models for outpatient care.

In this chapter, I propose a 'gray-box' approach by keeping only the simple absorption model and not using any BGL regulation model at all. Instead, I predict

the patients' reactions to the computed glycemic load using an Artificial Neural Network (NN) that is trained by the past meals and corresponding BGL measurements of the patient. Compared to similar work on NN based BGL prediction, the novelty of my approach lies in the use of an absorption model output instead of raw carbohydrate values, for the training. My hypothesis is that the integration of 'some' a priori domain-specific knowledge in the training process will counter-balance the limited number and variety of meal samples available for NN training, which will in turn improve the prediction.

## 5.2 BACKGROUND

Artificial neural networks are computational tools with a structure resembling biological neural networks, often used to learn the behavior of systems that are generally too complex for accurate modeling and identification. To yield a practically usable prediction model, the NN must be provided with a sufficient amount of training data—in our case meal/insulin log and BGL records. Key parameters of an NN are the number of hidden neural layers, the activation function used in the neurons, the number and interpretation of the inputs and outputs as well as several other algorithmic parameters of the training process [67].

The first artificial neural model was set up in 1943 by Warren McCulloch and Walter Pitts. Due to the shortcomings of the first models, interest in this field of study was significantly reduced during the initial period. In 1986, David Rumelhart, Geoffrey Hinton, and Ronald Williams published the operation and efficiency of a backpropagation algorithm. Research and use of artificial neural networks has been revived, based on the results achieved in the 1980s, and the error-propagation algorithm has been successfully applied in many systems today. The science of artificial neural networks is still evolving and new research results are regularly published [67], [68].

Artificial neural networks are generally successful in solving problems that conventional algorithmic methods cannot, or only with great difficulties, due to the problem complexity or to the lack of precise knowledge. Artificial neural networks

are capable of generalizing and applying information of the problem. The resulting solution is generally incomplete but sufficiently precise.

Artificial neural networks consist of processing units connected by controlled, weighted links. The processing units are similar to biological neurons, which is why they are referred to as artificial neurons. The structure of biological neurons is shown in Figure 17 and the structure of artificial neurons in Figure 18. The artificial neuron generates its current output value from its input values using the activation function applied to the sum of the weighted values of the inputs.

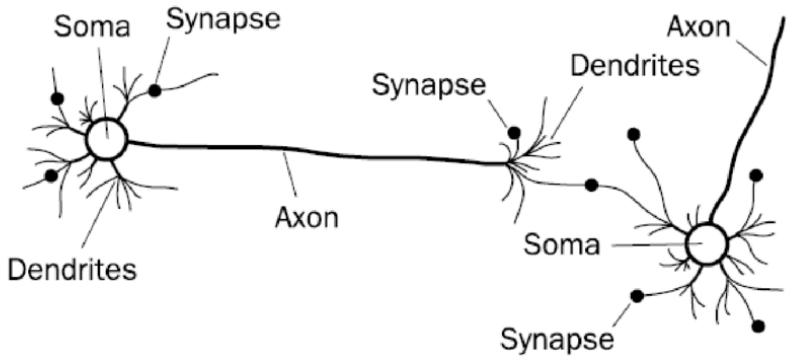


*Figure 17. Structure of the biological neuron.*

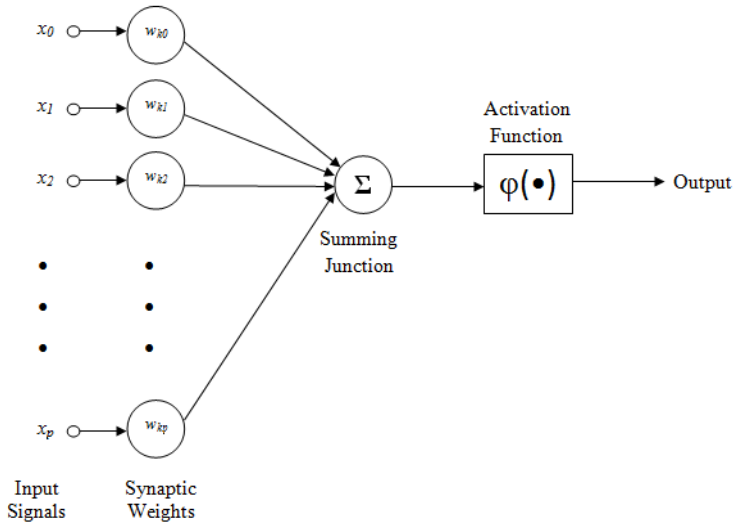


*Figure 18. Structure of the artificial neuron.*

The activation function decides, whether a neuron should be activated or not by calculating the weighted sum and further adding bias with it. There are a number of common activation functions in use with neural networks. Sign is the most

commonly used and simplest one of them. The activation function is expected to return about 1 ("active") for "correct" input, and 0 (-1 in case of some activation functions) "inactive" for “incorrect” input. The Sign activation function described by equation (14).

$$f(x) = \begin{cases} +1, & x > 0 \\ 0, & x = 0 \\ -1, & x \leq 0 \end{cases} \tag{14}$$

Artificial neural networks are mostly layered, with each layer consisting of artificial neurons. In general, there is a connection among all the neurons in the adjacent layers, while there is no connection between the non-adjacent layers. The input of each neuron is the output value of the neurons of the previous layer. The input of the first layer is provided by the input of the network, which is called the input layer. The output of the last layer of the network provides the result provided by the network. This last layer is called the highlight layer, and this term is used throughout the dissertation. The layers between the input and output layers (in some literature, however, including the output layer) are referred to as hidden layers.

The most common NN structures are as follows.

- Feed-forward NN (FNN): The first and simplest type, used for known inputs and given outputs, that minimizes errors by changing the weighting of the input values.
- Recurrent NN (RNN): A more complex structure having an infinite dynamic response due to hidden layers with directed feedback connections. The information passes through a loop so when the neuron provides an output, it can take into account the response to previous inputs.
- Autoregressive NN (ARNN): Such NN’s model current values of a series as a function of past values and have a finite dynamic response.

## 5.3 AN OVERVIEW OF ARTIFICIAL NEURAL NETWORKS USED FOR BGL PREDICTION

The studies published in the literature can be characterized by the application area (real outpatients vs. simulated data), the number of patients, the model inputs (CGM or fingertip BGL log, diet, insulin dosing, physical activity, symptoms, etc.), the length of the training data set and the NN structure.

One of the first works to propose NN for BGL prediction was due to Sandham et al. in 1998 who used two T1DM patients' data sets of 10 days each [69]. The training input consisted of insulin, diet (meaning CH quantity), exercise, BGL and an 'X' vector that included parameters such as stress and illness. The FNN had a hidden layer of 95 neurons and the output layer represented the predicted BGL values and used a linear activation function. The input data consisted of 122 events in 20 days, out of which 97 were used for training and the rest for evaluation. As a result, they found that most of the predictions were very close to the measured values (difference of 1.5mmol/l or less).

Later, especially in the last decade, several results were published in this field, due to the significance of the problem. Here I give an overview of only 10 recent studies that I selected as most relevant to my work. For a more comprehensive review, see [70].

Some authors use no dietary log for the prediction, only the past CGM or fingertip BGL data of the patient [71]–[74]. It should be noted that such an approach assumes that the patient has a very stable daily schedule with similar or controlled meals every day—an assumption that usually does not hold for real patients. The most recent of these is due to Ali et al., who used fingertip BGL data recorded from 13 T1DM patients. The prediction horizons were 15, 30, 45, and 60 minutes, and the resulting RMSE values 0.36, 0.4, 0.45l and 0.5 mmol/l, respectively [71]. Two years earlier, the work of Frandes et al. was very similar as they monitored 17 T1DM patients for 4 to 7 days in free-living conditions, with slightly less accurate results (30-min: 0.1, 60-min: 0.2, and 90-min: 1.2 mmol/l) [72]. Zarkogianni et al. had 6 patients monitored for 7 to 15 days and trained a special adaptive neuro-fuzzy inference system with wavelet activation functions that

integrated both NN and fuzzy logic principles. They validated the model according to EGA. For the 30-minute horizon, 94% of the predicted values were in the A class, which fell to 72% for the 60-minute horizon [74]. As for the earlier results, Daskalaki et al. compared the performance of a NN model to that of an autoregressive model with or without external insulin input, using a simulator for validation with 30 virtual patients. The NN provided more accurate results compared to other models for the 45-min horizon with an RMSE of only 0.3 mmol/l versus 1.6 mmol/l and 1.4 mmol/l for the autoregressive models [73].

The more typical approach is to use the CH content of the meal consumed and the bolus insulin dose administered before the meal as inputs for the prediction, thus supporting a more realistic application scenario [75]–[81]. The latest of these results is that of Li et al., who could use a very long training sample of 1 to 3 months from 10 real and 10 simulated patients. The results for the real patients are impressive (30-min 1.17, 60-min 1.85 mmol/l RMSE) [80]. Mirshekarian et al. had worse results (30-min 1.19, 60-min 2.11 mmol/l RMSE), but their training sample contained only 400 records collected from 10 T1DM patients [81]. Jankovic et al. focused on the effect of physical activity on BGL evolution in their study involving 6 T1DM patients and using a hybrid NN they tried to predict post-exercise BGL based on training with pre-exercise data [78]. Mathiyazhagan & Schechter monitored only 2 patients with CGM but for a longer period (over 8 weeks each). The inputs contained exercise type and duration as well as the time of day. Instead of RMSE, they published MAE error for the 30-min (1.7 mmol/l), 60-min ( 3.2 mmol/l) and 120-min (5.7 mmol/l) horizons [79]. An earlier result is due to Pappada et al. with the highest reported number of real patients (27) and many kinds of inputs including emotions in a carefully designed and elaborate clinical trial. The performance of the model was validated on 10 patients not included in the model training set, so the objective was slightly different from mine i.e. personalized prediction model research. An RMSE of 2.44 mmol/l was found on the 75-min horizon [75].

The closest approach to mine is perhaps that of Zecchin et al., who first proposed a predictor based ‘jump’ NN, trained with CH and CGM data form 10

patients, resulting in an RMSE of 0.9 mmol/l on the 30-min horizon [77]. In 2016 the authors tested their jump NN for 20 T1DM patients, with 4 different model versions with respect to the input: (1) CGM only, (2) CGM and insulin dosing, (3) CGM and CH, (4) CGM, insulin and CH. The MAE error was 0.79 mmol/l in scenario (1), 0.8 mmol/l in scenario (2), 0.75 mmol/l in scenario (3) and 0.78 mmol/l in scenario (4), all for the 30-min horizon, showing that meal intake improved prediction accuracy more than insulin information [76].

As a summary, Table 9 shows a compact reference for the main parameters of the above prediction models and the results achieved.

*Table 9. Recent studies on NN based BGL prediction. CH means the total CH content of the meal consumed. All CGM data is recorded every 5 minutes. All RMSE and MAE results are in mmol/l. NDA: no data available, h: hours, d: days, m: months, sim: simulated, acc.: accurate.*

| First Author (Year) | NN Type | Inputs | No. patients or data sets | Length of a single data set | Validation Approach (Train./Valid.) | Results (RMSE/EGA/CG-EGA) for each horizon |
|---|---|---|---|---|---|---|
| Li (2019) | Convolutional RNN | CGM, insulin, CH | 10 sim., 10 real | Sim.: 360 d Real: 6 m | 50/50% | RMSE Sim.: 30-min: 0.5, 60-min: 1.05; Real: 30-min: 1.17, 60-min: 1.85 |
| Ali (2018) | FNN | CGM only | 12 real | 14 d | 70/30% | 15-min: 0.36, 30-min: 0.41, 45-min: 0.45, 60-min: 0.5 |
| Mirshekarian (2017) | RNN | CGM, insulin, CH quantity | 10 real | 400 measurements | 50/50% | 30-min: 1.19, 60-min: 2.11 |
| Jankovic (2016) | ARNN vs. RNN | CGM, insulin, CH, physical activity | 6 real | CGM: 48 h before and 35 h after exercise | Pre-exercise for training, post-exercise for evaluation | 15-min: 0.47, 30-min: 0.98, 45-min: 1.35 |
| Frandes (2016) | ARNN | CGM only | 17 real | 4-7 d | NDA | 30-min: 0.13, 60-min: 0.24, 90-min: 1.23 |
| Zecchin (2014, 2016) | Jump NN | CGM, CH | 20 real | 2-3 d | 10 for training, the other 10 for validation | 30-min: 0.92 |
| Zarkogianni (2014, 2015) | adaptive neuro-fuzzy inference system | CGM, BGL change, physical activity | 10 real | 6 d | 10-fold cross-validation | 30-min: 0.74, 60-min: 1.26, 120-min: 2.08, CG-EGA acc. in hypo-glycemic range: 60-min: 73.3%, 120-min: 33.7% |
| Mathiyazhagan (2014) | Adaptive network-based fuzzy inference system | CGM, insulin, CH | 2 real | 56 d | Both patients: 6 pieces of 2-hour CGM records for training. | MAE: 30-min; 1.72, 60-min: 3.16, 120-min: 5.71 |
| Daskalaki (2012) | ARNN | CGM, insulin | 30 sim. | 8 d | 50/50% | 30-min:0.2, 45-min: 0.3; CG-EGA acc.: 89% (93% in hypoglycemic range) |
| Pappada (2011) | FNN | CGM, insulin, CH, emotions, symptoms | 27 real | 115 CGM h for training, 39 h for validation (calculated) | 17 for training, the other 10 for validation | 75-min: 2.43; EGA 'A/B' 92.3%, 'A': 62.3% |
| Sandham (1998) | RNN | fingertip BGL, insulin, CH, illness, stress, pregnancy | 2 real | 10 d (122 total BGL records) | 97 events/25 events | MAE: 1.5 |

I can conclude the literature survey stating that, concerning the nutrition information as training input, none of the published prediction models used other

than raw CH content of the meal to my best knowledge. This is the point that I try to improve in this work.

## 5.4 METHODS

My concrete goal is to predict the short term BGL evolution for insulin-dependent DM patients using the following input:

- Baseline (starting) BGL
- Insulin dosing administered by the patient
- Detailed dietary log

I used the two-compartment glucose absorption model developed by Arleth et al.. The model uses the simple material balance equations describing the progress of the food through the stomach and the intestine. The timing constants of the equations are described in 2.4.1 subsection. By using the model I make the assumption that the absorption system in DM patients can be regarded as operating normally and independently from the malfunction of the BGL regulation system.

That the dynamics of glucose uptake/absorption in the blood is indeed significantly dependent on GI and the presence of low-CH ingredients like fiber as well, is shown in the example below. Here I used the Arleth model to compute the theoretical glucose load curves of two meals similar in total CH content but different in composition (Table 10), and measured the CGM response for the same patient in the clinical trial (Figure 19).

*Table 10. Components of two meals and their nutritional values.*

| Meal ID | Food | CH (gr) | Lipids (gr) | Protein (gr) | GI index | Fiber (gr) |
|---|---|---|---|---|---|---|
| 6615 | Ham | 0.16 | 2.84 | 9.04 | 0 | 0 |
| | Light margarine | 0 | 2.5 | 0 | 0 | 0.06 |
| | Mineral water | 0 | 0 | 0 | 0 | 0 |
| | Bread roll | 30.78 | 0.38 | 5.08 | 75 | 1.78 |
| 6618 | Mineral water | 0 | 0 | 0 | 0 | 0 |
| | Ham | 0.4 | 7.1 | 22.6 | 0 | 0 |
| | Green pepper | 2.7 | 0.27 | 1.08 | 0 | 2.03 |
| | Tomato | 4.6 | 0.23 | 1.15 | 0 | 1.99 |
| | Bread | 39.86 | 1.27 | 6.54 | 66 | 11.6 |
| | Cold cuts of turkey | 0.05 | 3.75 | 10.3 | 0 | 0 |

As Figure 19 shows, though the 6618 meal contains 54% more CH, its model-computed absorption peak is lower and the shape of the curve is wider than that of 6615, due to its composition. The CGM-measured BGL responses verify this phenomenon.

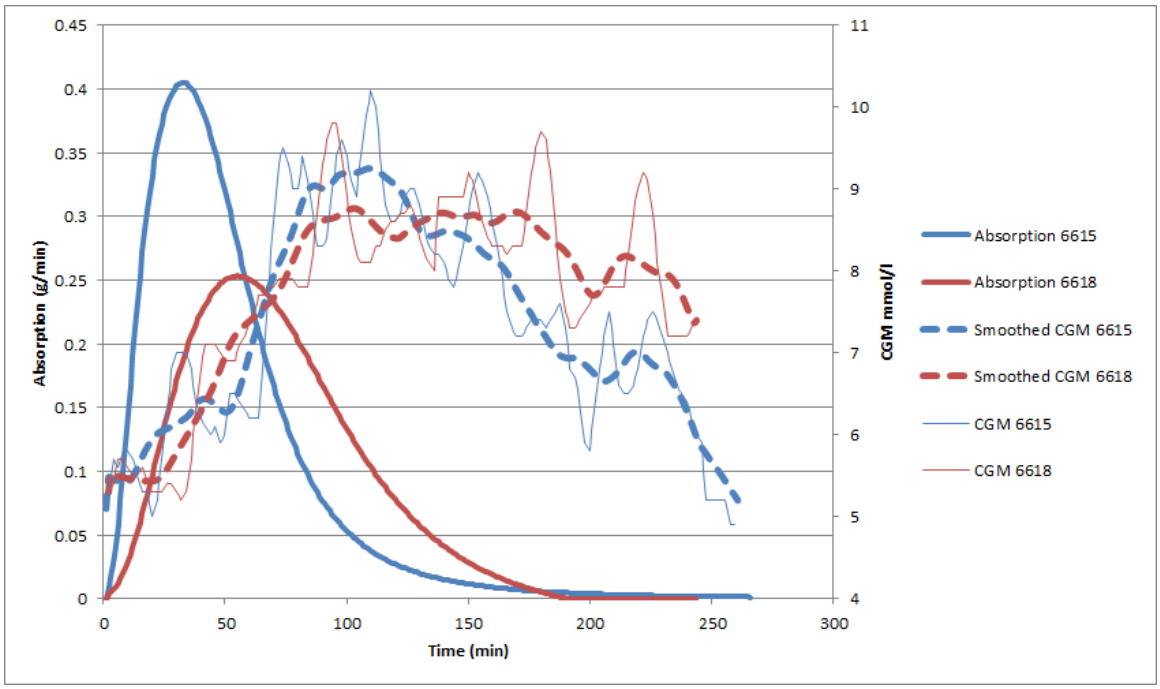


*Figure 19. Glucose absorption in the blood computed by the Arleth model of two alternative meals (solid thick blue and red curves) and the measured CGM values (thin blue and red curves) for a patient of the clinical trial. For clarity, dashed lines show the smoothed version of the CGM. The smoothing*

*formula stand of average calculation of 15 previous and 15 next value for each value.*

### 5.4.1 Training data and model training

I have chosen the Multilayer Perceptron (MLP) FNN using sign activation function for its simplicity. To prepare the inputs for the training, I first used the Lavinia application and the MenuGene dietary expert database [36] to find the lipid, protein, dietary fiber, monosaccharide and starch quantity of every logged meal, and run the Arleth model to compute its glucose absorption curve. In the next step, I 'quantified' the shape of the computed absorption curve with the following 3 numerical parameters (Figure 20).

- p1: time elapsed to the peak of the curve [minute]
- p2: time elapsed to 50% of the peak of the curve [minute]
- p3: rate of absorption at the maximum of the curve [g/minute]

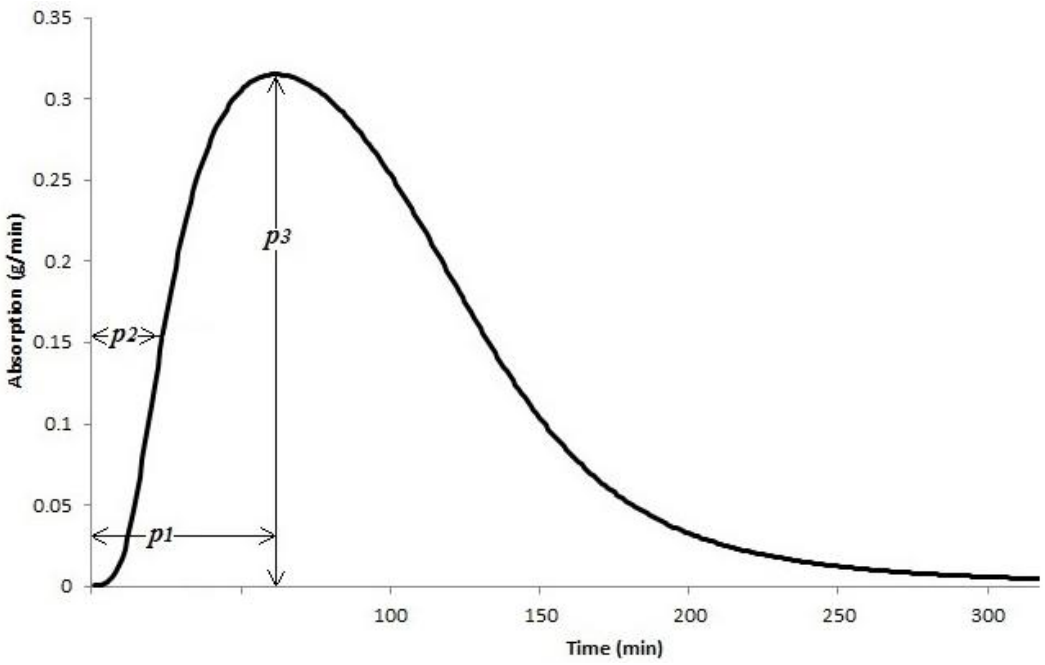


*Figure 20. Meal absorption curve represented by numerical parameters. p1: time elapsed to the peak of the curve [minute], p2: time elapsed to 50% of the peak of the curve [minute], p3: rate of absorption at the maximum of the curve [g/minute]*

The rest two parameters of the training input vector were selected as follows.

- p4: insulin amount [pmol/1000]

- p5: baseline BGL [mmol/l]

### 5.4.2 FNN training and evaluation

The FNN used in the training had 5 inputs (see above) and 30 to 120 outputs depending on the desired prediction horizon. As the CGM device used in the trial took a measurement every 2 minutes, 30 outputs were used for the 1-hour, 60 outputs for the 2-hour, 90 outputs for the 3-hour and 120 outputs for the 4-hour long predictions. For the training regime, I used the Quasi-Newton method [82]. The most important algorithmic parameters of the training were determined empirically to achieve the best results; as a result, the number of hidden layers was set to 20, the maximum number of iteration cycles to 118 and the error threshold to 10E-16, meaning that in most cases the iteration limit served as the stop condition. Using more hidden layers or more iteration cycles was found to result in over-training, and hence worse predictions.

I have not tried other network topologies as others [83], [84] have already successfully applied it to such a task. Of course, training other types of NNs could be a further research line.

To verify my original hypothesis that the use of an absorption model could be beneficial for the accuracy of the FNN model, I also trained the same FNN with the raw nutrient values of the meals, i.e. without using the absorption model. In this version, I used the following 5 training inputs:

- p1: CH (g)
- p2: Lipids (g)
- p3: Fiber (g)
- p4: insulin amount [pmol/1000]
- p5: baseline BGL [mmol/l]

In order to distinguish the two versions, I use FNN-ABS for the absorption model-based version and FNN-NUT for the version using raw nutrient quantities.

Though, to my best knowledge, all the NN-based BGL prediction methods proposed in the literature use raw (if any) CH values and none uses GI, a sub-version of FNN-NUT has also been implemented in which the p3 parameter was replaced

with the ‘summary GI’ of the logged meal. This was computed as the average of the GI’s of the meal’s ingredients weighed by the ingredients’ quantity.

When comparing the performance of the FNN-ABS to the FNN-NUT, I used the paired sample T-test to check for significant differences [85]. Since it can be argued that the ‘predictability’ of patients may differ.

The following figures of merit were used in the evaluation.

- MAE
- RMSE
- Percent of predicted values in the ‘clinically acceptable’ EGA classes A and B

The predictions were evaluated on the 1, 2 and 3-hour horizons.

### 5.4.3 Data used for training and validation

8 volunteers had participated in the clinical study when the data set was finalized. The data sets were examined concerning the accuracy and completeness of the CGM and lifestyle log data. As a result, 3 patients were excluded from the study due to their lack of cooperation resulting in incomplete lifestyle logs. In total, 84 days of CGM data and lifestyle logs were available, containing 365 meals and 391 insulin injections. Table 11 shows a summary of the data available for the study.

*Table 11. Properties of the datasets used for the study.*

| Patient ID | P01 | P02 | P03 | P04 | P05 | Total |
|---|---|---|---|---|---|---|
| Gender | Female | Female | Male | Female | Male | - |
| Age | 52 | 49 | 33 | 18 | 23 | - |
| Height | 169 | 175 | 160 | 183 | 197 | - |
| Weight | 77 | 133 | 50 | 97 | 82 | - |
| Log length (days) | 24 | 23 | 15 | 12 | 10 | 84 |
| # meals | 97 | 109 | 75 | 39 | 45 | 365 |
| Breakfast | 20 | 23 | 15 | 10 | 7 | 75 |
| Lunch | 22 | 23 | 14 | 11 | 9 | 79 |
| Dinner | 19 | 23 | 13 | 11 | 9 | 75 |
| Other | 36 | 40 | 33 | 7 | 20 | 136 |
| # insulin | 87 | 92 | 107 | 58 | 47 | 391 |
| # CGM | 5,523 | 14,558 | 5,420 | 7,692 | 2,311 | 35,504 |

records

In the next step, I excluded meals that had no corresponding pre-meal insulin dosing information in the log and those whose total CH content was less than 5 g. I also excluded a meal if the time to the patient's next meal was less than my minimal prediction horizon, one hour. After this process, a total of 167 meals were left that I could use in the study. Table 12 shows the patient-wise distribution of the meals used for training (2/3) and validation (1/3). The number of meals shows the state after data cleaning. Many meals omitted due to a lack of insulin/CGM or insufficient time interval between the current meal and the next meal.

*Table 12. Number of monitoring days and meals used for FNN training and validation, for each patient. # days: Duration of dietary, # meals: number of meals used for training, # meals: number of meals used for validation.*

| Patient | # days | # meals (training) | # meals (validation) | # all meals |
|---|---|---|---|---|
| P01 | 23 | 19 | 10 | 29 |
| P02 | 22 | 28 | 15 | 43 |
| P03 | 14 | 17 | 9 | 26 |
| P04 | 11 | 22 | 12 | 34 |
| P05 | 15 | 22 | 13 | 35 |
| SUM | 85 | 108 | 59 | 167 |

### 5.4.4 Ethical considerations

The study protocol was approved on 9 April 2018 by the National Institute of Pharmacy and Nutrition (OGYÉI), Budapest, Hungary, chaired by Péter Bunyitai, under the submission number OGYÉI/4778/2018. The protocol was designed and implemented in compliance with the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects.

### 5.4.5 Data processing tools

Mongodb database technology was used for storing the dietary and insulin logs [86]. For calculating the ingredient quantity and the GI values from the dietary logs as required by the absorption model, the Lavinia application and the MenuGene dietary expert database was used [33].

The absorption model was implemented according to the original paper due to Arleth [17], in the form of a custom desktop application for BGL modeling [28].

The FNN used for the study was the OpenNN library, a feed-forward, MLP network implemented as a C++ open-source library [87].

Microsoft Excel 2013 was used for statistical analysis and visualization.

## 5.5 RESULTS

Table 13-Table 15 show the results achieved by the FNN-ABS, FNN-NUT and FNN-NUT-GI training methods.

*Table 13. Results of the FNN-ABS method for the five patients (best results in bold). All RMSE and MAE results are in mmol/l.*

| Patient | Figure of merit | 1 hour | 2 hours | 3 hours |
|---|---|---|---|---|
| P01 | MAE | 1.651 | 2.095 | 3.070 |
| | RMSE | 1.908 | 2.426 | 3.568 |
| | EGA acceptable | 86.39% | 94.86% | 87.28% |
| P02 | MAE | 0.768 | 1.208 | 1.504 |
| | RMSE | 0.887 | 1.434 | 1.721 |
| | EGA acceptable | 97.84% | 98.53% | 98.81% |
| P03 | MAE | 1.060 | 1.900 | 2.147 |
| | RMSE | 1.237 | 2.283 | 2.484 |
| | EGA acceptable | 95.56% | 99.81% | 95.06% |
| P04 | MAE | 0.477 | 0.961 | 1.349 |
| | RMSE | **0.540** | **1.126** | **1.571** |
| | EGA acceptable | 100.00% | 100.00% | 98.89% |
| P05 | MAE | 1.047 | 1.582 | 1.660 |
| | RMSE | 1.236 | 1.825 | 1.976 |
| | EGA acceptable | 99.97% | 97.31% | 97.61% |
| All datasets | | | | |
| All datasets | MAE | 0.965 | 1.550 | 1.870 |
| | RMSE | 1.120 | 1.755 | 2.176 |
| | EGA acceptable | 96.46% | 98.13% | 96.03% |

*Table 14. Results of FNN-NUT method for the five patients (best results in bold). All RMSE and MAE results are in mmol/l.*

| Patient | Criteria | 1 hour | 2 hours | 3 hours |
|---|---|---|---|---|
| P01 | MAE | 1.450 | 2.633 | 2.795 |
| | RMSE | 2.096 | 3.402 | 3.838 |
| | EGA acceptable | 93.33% | 91.00% | 89.00% |
| P02 | MAE | 1.421 | 1.548 | 1.628 |
| | RMSE | 1.647 | 1.996 | 2.019 |
| | EGA acceptable | 97.56% | 98.78% | 99.04% |
| P03 | MAE | 2.245 | 2.550 | 2.617 |
| | RMSE | 3.214 | 3.641 | 3.398 |
| | EGA acceptable | 82.96% | 82.78% | 81.48% |
| P04 | MAE | 1.032 | 1.623 | 1.501 |
| | RMSE | **1.293** | **1.967** | **1.906** |
| | EGA acceptable | 100.00% | 100.00% | 98.98% |
| P05 | MAE | 1.146 | 1.969 | 1.965 |
| | RMSE | 1.312 | 2.248 | 2.336 |
| | EGA acceptable | 99.23% | 97.18% | 92.39% |
| All datasets | | | | |
| All datasets | MAE | 1.412 | 2.054 | 2.025 |
| | RMSE | 1.816 | 2.535 | 2.585 |
| | EGA acceptable | 95.48% | 94.92% | 93.18% |

*Table 15. Results of FNN-NUT-GI method for the five patients (best results in bold). All RMSE and MAE results are in mmol/l.*

| Patient | Figure of merit | 1-hour | 2-hour | 3-hour |
|---|---|---|---|---|
| P01 | MAE | 1.430 | 2.346 | 2.736 |
| | RMSE | 2.006 | 2.982 | 3.738 |
| | EGA acceptable | 90.21% | 92.00% | 88.00% |
| P02 | MAE | 1.084 | 1.524 | 1.598 |
| | RMSE | 1.456 | 1.812 | 2.004 |
| | EGA | 97.68% | 98.78% | 99.34% |

| | | | | |
|---|---|---|---|---|
| | acceptable | | | |
| P03 | MAE | 1.885 | 2.240 | 2.478 |
| | RMSE | 2.684 | 3.211 | 3.418 |
| | EGA acceptable | 87.36% | 86.29% | 83.38% |
| P04 | MAE | 0.973 | 1.572 | 1.481 |
| | RMSE | 1.232 | 1.843 | 1.736 |
| | EGA acceptable | 99.46% | 100.00% | 99.13% |
| P05 | MAE | 1.132 | 1.753 | 1.912 |
| | RMSE | 1.341 | 2.203 | 2.273 |
| | EGA acceptable | 98.17% | 98.36% | 94.16% |
| All datasets | | | | |
| All datasets | MAE | 1.253 | 1.932 | 1.971 |
| | RMSE | 1.666 | 2.316 | 2.518 |
| | EGA acceptable | 95.31% | 95.88% | 93.80% |

### 5.5.1 Comparison of FNN-NUT/FNN-NUT-GI to FNN-ABS

I found that the FNN-NUT performed worse on all horizons and with all figures of merit, though the difference was not always statistically significant. Table 16 shows the average gain of the prediction accuracy as a percentage, in favor of FNN-ABS. The bar charts in Figure 21 and Figure 22 shows the comparison of FNN-NUT and FNN-ABS model versions prediction accuracy for all three prediction horizons (1,2 and 3 hours. MAE and RMSE evaluation in Figure 21 and EGA evaluation in Figure 22.

*Table 16. Prediction accuracy gain of FNN-ABS over FNN-NUT. P-values show the significance level of the paired sample T-test.*

| Figure of merit | 1 hour | 2 hour | 3 hour | ALL horizons together |
|---|---|---|---|---|
| MAE | 31.69%<br>p<0.01 | 24.56%<br>p<0.01 | 7.65%<br>p>0.05 | **18.26%** |
| RMSE | 38.35%<br>p<0.01 | 30.76%<br>p<0.01 | 15.81%<br>p>0.5 | **24.60%** |
| EGA A/B | 1.02%<br>p>0.05 | 3.28%<br>p=0.017 | 2.97%<br>p>0.05 | **2.22%** |

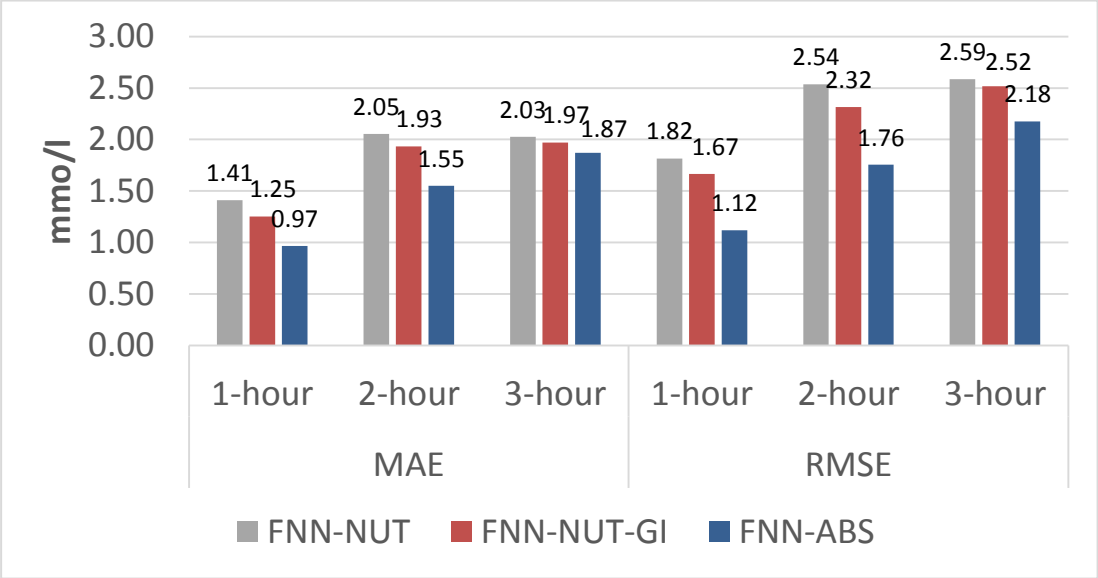


*Figure 21. FNN-NUT, FNN-NUT-GI and FNN-ABS model error comparison by MAE and RMSE in all three prediction horizons. Gray columns represent the FNN-NUT, red columns for FNN-NUT-GI and the blue columns for FNN-ABS training method.*

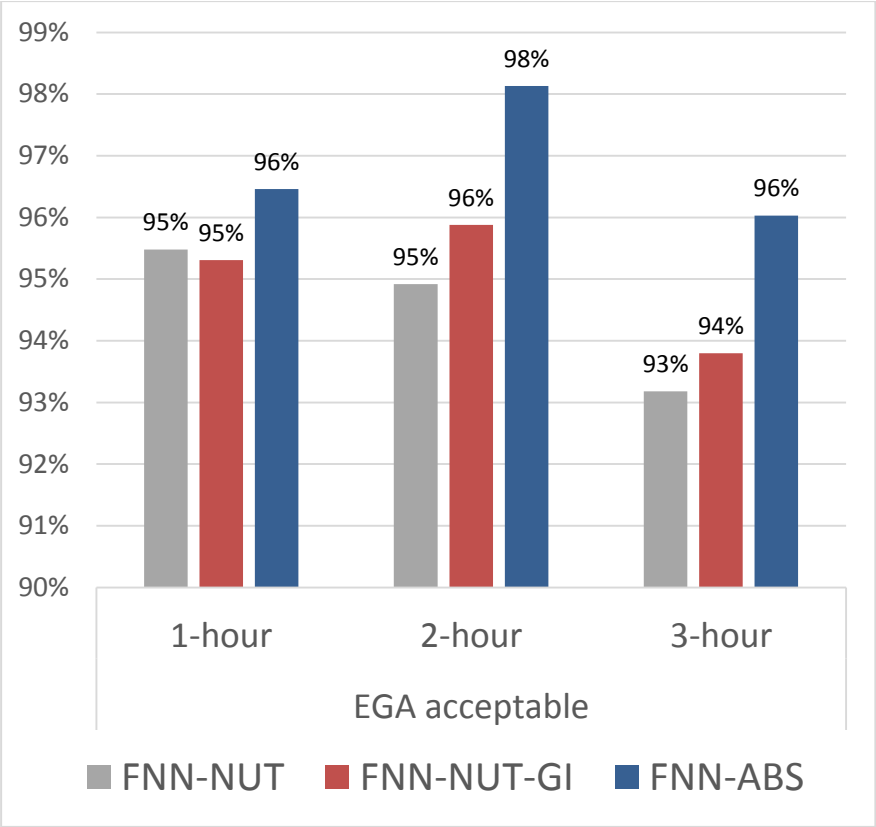


*Figure 22. Clarck Error Grid evaluation comparison for 1, 2 and 3 hours prediction horizons. Gray columns represent the FNN-NUT, red columns for FNN-NUT-GI and the blue columns for FNN-ABS training method.*

For qualitative visual comparison, Figure 23 shows the first 60 minutes of the BGL measured by the CGM and predicted by the two methods, belonging to a typical meal of the P03 patient.

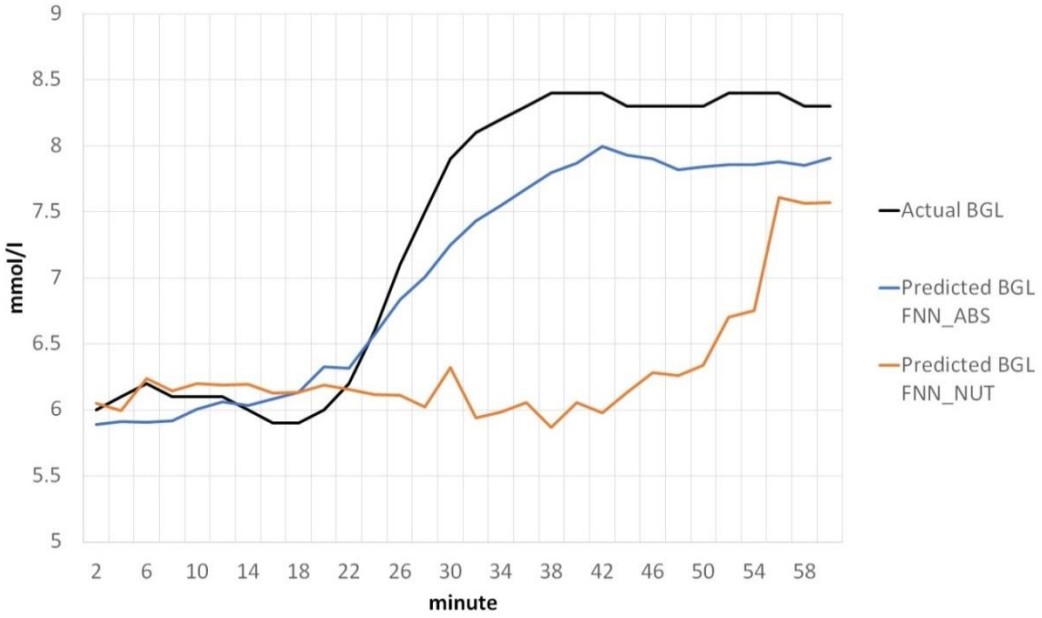


*Figure 23. A typical meal's measured BGL (black line) and predicted (FNN-ABS: blue, FNN-NUT: orange) BGL values of the P03 patient for one hour*

## 5.6 DISCUSSION

Tables 13-15 show that there are considerable differences among the 5 patients concerning the accuracy of the predictions. This may be partly due to the quality of the input data or even more to the length of the training sample: P02 and P04 had much more samples than P01 and P03, and performed ca. 30% better. A NN is naturally expected to produce a better model if a longer training sequence is available. However, results for P05 were much worse than those for P04 despite the nearly same number of their logged meals. This may be due to fundamental differences in the 'predictability' of humans: my model missed several factors that are hard to quantify, but which are known to influence BGL, such as emotions, and it can be stipulated that those patients for whom the impact of such factors is relatively stronger are harder to predict.

Personal variations in predictability naturally call for a larger number of patients to validate a prediction approach. As Table 9 shows, this number varies between 2 to 37 in the reported studies. These numbers are relatively low compared to other clinical research fields, which is explained by the difficulties

associated with the acquisition of high quality dietary and especially CGM data from volunteers in a properly managed clinical trial.

The superior performance of the ABS over the NUT method, shown in Table 16, verified my startup hypothesis that additional domain knowledge formulated in an absorption model will improve the predictability of a complex system such as the human absorption system combined with the BGL regulation system. This conclusion may seem to contradict the results of Zecchin et al., who did not find much difference with respect to whether CH data was included in the training scenario [76]—however, they did not use an absorption model, only 'raw' CH values.

Table 16 also shows that in general, while the accuracy of both methods decreases naturally for longer horizons, the performance advantage of the ABS method over the NUT also decreases (RMSE 1-hour: 38.35%, 2-hour: 30.76%, 3-hour: 15.81%, for MAE 31.69%, 24.56%, 7.65%, respectively). This phenomenon may be explained by the accumulation of 'noise' i.e. error due to not modeled factors, in the prediction error as time passes by. As the BGL curve becomes harder to explain by the absorption model, the ABS method loses its power over the simpler NUT method. EGA errors do not follow this rule as the differences are very small (1 to 3%) and not significant, but we should not forget that during training, an FNN always tries to minimize the difference between the measured and predicted values, which in my case was the MAE error and not the best EGA classification.

### 5.6.1 Comparison to related work

First, we can compare my new results with our own earlier results using a state-of-the-art BGL regulation model, the parameters of which were trained (personalized) with various methods of optimization [65]. That study used a similar clinical protocol, the same dietary database, and it was supervised by the same medical team as this trial. The RMSE result with the best algorithmic setup was 1.62 mmol/l, considerably worse than the 1.12 mmol/l of the FNN-ABS, proving that in our previous study the possibly over-simplified BGL model itself was a limitation.

When numerically comparing my results with those of other studies, we should not forget that for a fair comparison, the various methods should be run on the same data sets which are not always available for sharing, due to restrictions of the clinical trials. In my specific case, I could not use dietary log data from other trials anyway, because my method uses fiber, lipid, GI etc. values which are not included in other trials and which can only be computed from a culture-specific dietary expert database. That being said, I can state that my new result (1.12 mmol/l) is very promising compared to the 60-min, outpatient and CH-insulin based RMSE results of my literature survey, (Li: 1.85, Mirshekarian: 2.11, Mathiyazhagan: 3.16 mmol/l). Though there are far better results than this as well on the 45/60-min horizon (cf. Ali: 0.5, Frandes: 0.24, Daskalaki: 0.3 on 45-min, Zarkogianni: 1.26), but these models do not consider the (possibly hectic) CH input of the patient, so I feel that a direct comparison is not fair. Another point that I must bear in mind is that CGM-only predictors require a continuous CGM data input even when the model is already trained, which is not possible for a large part of the DM outpatient community for financial reasons.

Published RMSE results of simulated datasets are considerably better than my results [73], [80]. However, BGL is influenced by such factors as the mental state, emotions, sudden movement and environmental changes etc., which form an inherent part of an outpatient's daily life, but which even sophisticated simulators cannot consider. However, the effect of these factors appears as a 'noise' imposed on the real-life measured BGL curve, which makes the accuracy of predictions for real patients worse than those validated on simulators (see these differences in e.g. [80]). Also, simulators cannot account for the significant variances in the personal parameters of the metabolism. Therefore, the direct comparison of simulator vs. real patients' results would naturally be biased in favor of the simulators.

There are only a few published RMSE results for the 120-min and no results for the 180-min horizons, making it hard to evaluate my results (1.75 mmol/l and 2.75 mmol/l, respectively). For 120 minutes, Mathiyazhagan reported 5.71 mmol/l using CH input and Zarkogianni 2.08 mmol/l, better than my result, but without CH input. As a summary, Figure 24 shows a graphical comparison chart of the results.

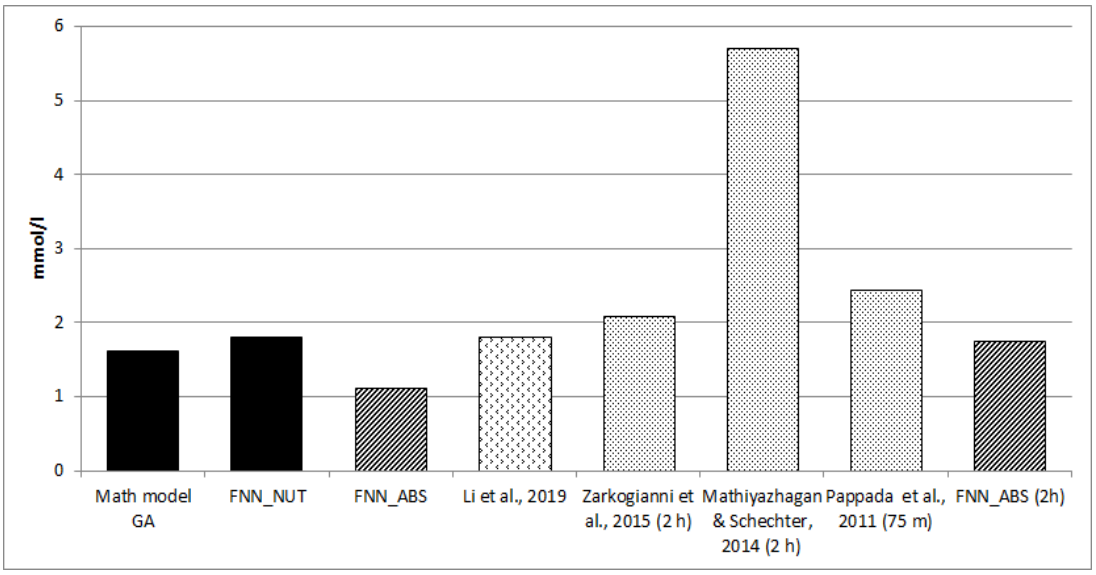


*Figure 24. Prediction results compared with results from other studies. Math model GA: our earlier method using the BGL control model. Other studies are identified by the author and year.*

As for the EGA evaluation, though CG-EGA classes are not exactly comparable to EGA classes, my 96.46% result on the 60-min horizon for the 'clinically acceptable' classes compares very favorably to Pappada's 92.3% (75-min, EGA), Daskalaki's 89% (93% in the hypoglycemic range, 45-min, CG-EGA), and Zarkogianni's 73.3% (60-min, CG-EGA). It also a strength of my model that the EGA accuracy does not decrease significantly on the 120-min and 180-min horizons.

## 5.7 CONCLUSION AND FUTURE WORK

The dissertation presented a new outpatient BGL predicting method that is based on the application of an absorption model to generate training input for a neural network. For the successful training of the network, a good quality dietary and insulin log as well as the CGMS data is needed for a period of ca. one week. The trained model uses only a startup (fingertip) BGL, and the dietary and insulin log for a 60- to 180-minute prediction, therefore it is applicable in practice for outpatients without continuous access to a CGMS device. The RMSE and EGA accuracy of the prediction (60-min: 1.12 mmol/l, 96.46% clinically acceptable) is better than those published results to which my method is directly comparable, and it also surpasses our previous results using personalized BGL control models. The study also showed that the application of the absorption model has significantly decreased the RMSE

prediction error at least on the 60- and 120-minute horizons compared to a CH-only version, so the integration of dietary science has indeed contributed to the success of the model.

Future research in this field must include, most of all, new trials with more patients to verify these promising results. On a larger sample, the inclusion of insulin types (basal vs. bolus insulin), the physical activity, and the presence of emotional or mental stress as training inputs are also expected to improve the accuracy of the prediction—if these factors could be monitored in a reliable way.

# Acknowledgments

I would like to express my sincere gratitude to my supervisors Dr. István Vassányi and Dr. István Kósa who supported my studies and research in the last years. Without them this thesis, too, would not have been completed or written. One simply could not wish for better or friendlier supervisors.

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Expressing thankfulness will never be enough for me towards my family, especially my mother Galawezh, my wife Bakhcha, my sister Tavga and my brother Ranj who encouraged and supported me all the way.

Finally, I would like to say special thanks for the work and guidance of those who contributed to my dissertation.

# Theses

**Thesis 1.** *Characterizing the relationships between diet and BGL response in a small scale study (Chapter 3)*

1.1. I examined experimentally the extent to which the individual blood glucose response curve could be reproduced based on previously recorded response and diet logs. I showed that the response is characteristic to the individual and the type of meal as the post-prandial responses to standardized meals in patients with type 2 diabetes show a typical, reproducible, but personal BGL curve.

1.2. I proposed a short-term blood glucose prediction method based on the nutrition log alone, without the use of mathematical models. I defined the key parameters of CGM responses to meals and performed a clustering of the responses based on the parameters. I used the averaged response of the cluster to predict the individual responses of patients belonging to the cluster. I have proved that according to the source data recorded in the trial, the patient characterization based on response clusters improves the reliability of the response-based prediction.

Related publications: [88], [89]

**Thesis 2.** *Basal insulin management for blood glucose prediction modeling (Chapter 4)*

2.1. I designed a parameterization method for a blood glucose prediction model to more accurately model the effect of basal insulins. The method is based on using a series of smaller bolus insulin doses instead of one big basal insulin dose. I showed that the short-time 180-minute predictions produced more improvement during the night, which can be explained by the fact that due to the missing meals and bolus insulin administration, an improved prediction of the action of the basal insulin has more effect on the overall prediction errors.

2.2. Since the morning fasting blood glucose has special clinical significance, I have investigated whether the method proposed in 2.1 improves the wake-

up BGL prediction. It showed that the application of the correction resulted in a relatively small but statistically significant improvement in the mean absolute error.

2.3. I have experimentally demonstrated that by using the correction the prediction errors were effectively translated into the "clinically safer" EGA domains. I showed that in terms of the EGA assessment, 6% more of the predictions fall into the A or B regions.

Related publications: [66], [90], [91]

**Thesis 3.** *Blood glucose prediction using artificial intelligence (Chapter 5)*

3.1. I have developed a new method for blood glucose prediction by training artificial neural networks based on a nutrient absorption model. I used the numerical characteristics of the calculated absorption curve as the training input of the artificial neural network beside the insulin doses and the evolution of blood glucose measured by the CGM system. I showed experimentally that using the output of the absorption model to train the neural network significantly improves the accuracy of the model compared to traditional training methods based on raw CH. The accuracy is superior to all results reported so far to which the proposed method is directly comparable, regardless of whether they use a mathematical model or a neural network.

3.2. For comparison, I have implemented two another versions of the artificial neural network training method. In the first version (FNN_NUT) raw carbohydrate, fat, and fiber nutrient intake values provide the input as usual in the literature. The second version (FNN-NUT-GI) is subversion of FNN-NUT where instead of fiber input data I used the 'weighted summary GI' of the logged meal. I showed that the FNN-NUT-GI method using weighted GI achieved significantly better results than the FNN-NUT version using raw CH and fiber values, which supports the applicability of using GI as a new idea in blood glucose level prediction.

Related publications: [92]

# Applicability of new scientific results

The new methods proposed can be used primarily to support the lifestyle management of diabetics, specifically outpatients in need of insulin treatment. The importance of the results is supported by the large number of diabetics (estimated at 1-1.5 million in Hungary). Due to the limited number of clinical trials executed, and their complexity (omitting factors such as physical activity, stress, and state of consciousness), the methods developed could only use dietary log, insulin doses, and previously measured blood glucose levels as inputs. This causes that the reliability of the prediction is also limited. Yet, it can already be used in its current form directly, as the personalized prediction model can run on a mobile device (by having low computational resource requirements), by integrating it into a mobile lifestyle support application for short-term prediction of blood glucose levels. Providing immediate feedback is possible based on the values calculated by the model, allowing dietary recommendations to be made for users through which they can learn the right lifestyle. This not only useful in slowing down the progression of their disease, but can even lead to reverse it. As the presented Lavinia lifestyle mirror application developed at the University of Pannonia currently supports only general (non-personalized), mathematical model-based prediction, the result achieved can be implemented to enhance its capabilities.

# Summary

The dissertation briefly reviewed the diabetes mellitus, glucose and insulin control processes in the human body and highlighted the importance of the field of decision support systems for diabetes. I then gave a brief description of the mathematical models used in my work. A combination of a glucose absorption model and insulin-glucose control algorithm was implemented to perform BGL prediction.

I proposed a response-based prediction method for supporting insulin independent pre-diabetes and normal people. I tested the method on 22 patient's data from a clinical trial. The results showed that i) most patients in the study can be clearly classified in a specific cluster based on their meal response characteristics and ii) the absolute error of the BGL prediction decreased due to the application of patient clusters showing that the patient characterization based on response clusters improves the reliability of the response-based prediction. However, the meal responses of standard breakfasts compared to modified breakfasts did not show a significant difference.

The pharmaco-dynamic profile of bolus insulins is fundamentally different from that of basal insulins, which resulted in significant BGL prediction errors in our previous work, especially at the night periods. To overcome this problem, I proposed to simulate a constant insulin presence curve in the blood with a series of several smaller bolus insulin doses instead of a single high dose of insulin, in order to approximate the curve defined by drug manufacturers, and thus reduce the error of the prediction. I have experimentally demonstrated that using the correction, the 180-minute predictions with the original BGL model can produce more accurate results over the night. 30-50% of the next meal time prediction errors were within 3 mmol/l. For wake-up BGL prediction the correction resulted in an improvement of 1.02 mmol/l (MAE). In terms of EGA evaluation, 6% more predictions fall in the clinically acceptable regions 'A' or 'B'. This shows that by applying the correction, the errors were effectively translated into "clinically safer" ranges.

Finally, I proposed a new FNN based method for BGL prediction. The neural network is trained with CGM records and three features describing the estimated meal absorption curve, in addition to meal insulin bolus amount and the startup pre-prandial glucose levels. The trained model predicts the BGL evolution for 60-180 minutes using only one startup BGL, Insulin amount and the meal absorption curve. The RMSE of the prediction was 1.12 mmol/l, lower than any directly comparable result published in the literature, and EGA evaluation showed that 96.46% of the predicted values could be regarded as clinically acceptable. These results are also remarkable compared with our previous results using personalized BGL control models. The performance comparison between the absorption curve input and raw data input models also prove successfulness of the absorption model version as it decreased the prediction error.

As a future work, FNN_ABS should be evaluated on a larger number of patients with longer dietary log and CGM periods. NN's input parameters normalization could bring more improvement, therefore it is worth for further investigation and research.

Beside the proposed basal insulin correction method, the mathematical prediction model needs to be supplemented with other factors like physical activity, insulin sensitivity and stress, the latter being currently under research at MIRDC. The most important aspect is the integration of the improved methods.

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