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Diabetes management through artificial intelligence and gamification

Blood glucose prediction models and mHealth design considerations

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Abbreviations

AI *Artificial intelligence*

(A)NN *(Artificial) neural network*

AR *Autoregressive (model)*

AR(I)MA *Autoregressive (integrated) moving average (model)*

ARX *Autoregressive (model) with exogenous inputs*

BGL *Blood glucose level*

CGM *Continuous glucose monitoring*

CM *Compartmental model*

DBN *Dynamic Bayesian network*

e-Health *Healthcare practice supported by electronic processes and communication*

ENN *Elman neural network*

HCP *Health care professional*

HMM *Hidden Markov model*

mHealth *Healthcare practice supported by mobile devices*

MLP *Multilayer perceptron*

NARX *Nonlinear autoregressive (model) with exogenous inputs*

RBFN *Radial basis function network*

RF *Random forest*

RMSE *Root-mean-square error*

RNN *Recurrent neural network*

SVM *Support vector machine*

SVR *Support vector regression*

Chapter 1

Introduction

Diabetes mellitus is a major, global, and increasing problem. The most common method for insulin-dependent (type 1) diabetes management is through monitoring the blood glucose level (BGL), using fingerprick blood tests taken several times a day, and adjusting insulin doses based on these readings. For a dynamic, nonlinear, and complex condition such as diabetes, this can be far from satisfactory. Factors such as insulin type and dose, diet, stress, exercise, illness, or insufficient sleep all have significant influences on the BGLs. Management may be compromised through lack of data and, for some patients, an inability to interpret data adequately [1].

However, it has been shown that, through a better monitoring of BGLs and appropriate patient-specific empowerment, lifestyle behavior of diabetics can be positively influenced and the associated and costly diabetes complications significantly reduced. In this perspective, this Graduation Project will aim at highlighting main diabetes management issues, reviewing state-of-the-art blood glucose prediction methods, and proposing patient empowerment through the use of artificial intelligence (AI) algorithms, and gamification in a mHealth/e-health context.

In this introduction chapter, we will shortly describe the diabetes condition and complications, enumerate factors controlling blood glucose dynamics, underline the need for empowerment of diabetic patients and main motivations of this Graduation Project. Then, after having restated the core problem, a roadmap of the work will be introduced.

1.1 The diabetes condition

Pathophysiology

Diabetes is a condition that occurs when the insulin–glucose–glucagon regulatory mechanism is affected. Normally, plasma glucose levels are maintained within a narrow range through the antagonistic and combined action of the two pancreatic hormones, i.e. the insulin and the glucagon, produced by Beta and Alpha cells of the islets of Langerhans, respectively.

In normal individuals, high blood glucose levels (BGLs) induce the release of insulin, which enables its target cells to take up glucose. In low-glucose conditions, glucagon induces the breakdown of glycogen into glucose. In opposition, in diabetic individuals, this synchronized mechanism is disrupted, which results in persistent too high blood glucose levels, known as *hyperglycemia*. Besides, in many cases - that will be further detailed - diabetic patients also strive to avoid too low BGLs or *hypoglycemia*.

A general overview of the glucose homeostasis mechanism under normal and diabetic condition is illustrated in Figure 6.1 (Annexes).

Based on pathophysiology, two types of diabetes can be distinguished :

1. In *type 1* diabetes (T1D), formerly called juvenile-onset or insulin-dependent diabetes, there is almost complete destruction of beta cells. More specifically, in individuals with a genetic predisposition, an unidentified trigger initiates an abnormal immune response and the development of autoantibodies directed against beta cells. The alpha cells are present in normal numbers but their function is impaired. T1D, being a complex genetic and autoimmune disorder, can not be prevented or cured, but it can be effectively treated with external supplies of insulin and managed through BGLs control [2, 3].

2. In *type 2* diabetes (T2D), formerly called adult-onset or non-insulin-dependent diabetes, the major islet pathology relates to amyloid deposition[1]. Beta-cell numbers are probably reduced by 25% to 30% and this reduction is progressive. Alpha-cell numbers may actually be increased and glucagon responses to hypoglycemia in type 2 diabetes are thought to remain intact [3, 4].

Note that T1D, the most severe kind, accounts for 5–10% of the total cases of diabetes worldwide. T1D has been historically, and continues to be, the most common type of diabetes in children (especially in Europe) and adolescents, although T2D is increasingly diagnosed in youth [5].

[1] Islet amyloid polypeptide (IAPP; amylin), the major component of islet amyloid, is co-secreted with insulin from beta-cells. In type 2 diabetes, this peptide aggregates to form amyloid fibrils that are toxic to beta-cells [4]

A global, major, and increasing challenge

In 2013, about 382 million people had diabetes worldwide. Today, this number is estimated to be 415 million or, in other words, 1 in 11 adults, with equal rates in both women and men. According to the International Diabetes Federation (IDF) - the umbrella organization for 200 diabetes associations in more than 160 countries - the number of people with diabetes is even expected to rise to 592 million by 2035 [6] (Figure 1.1).

Besides, IDF also claims that diabetes at least doubles a person's risk of early death [7]. From 2012 to 2015, diabetes is estimated to have resulted in 1.5 to 5.0 million deaths per year, which represents about 1 death every 6 seconds.

Furthermore, the global economic cost of diabetes in 2015 is estimated to be 600 billion €, meaning that 12% of global health expenditure is spent on diabetes [8].

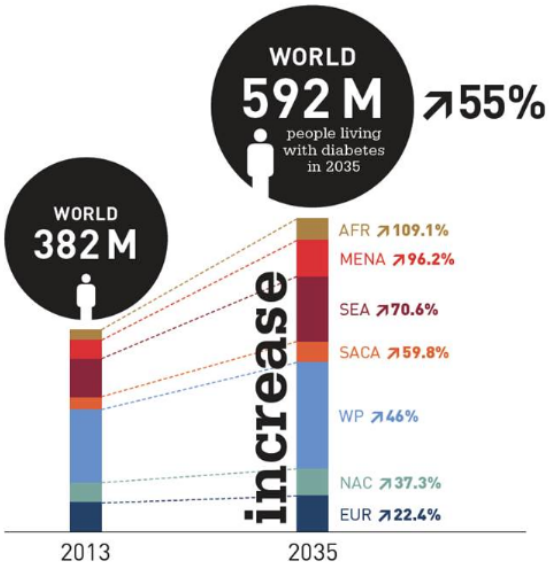


Figure 1.1: *IDF Diabetes projections [7]. Note that three quarters of people with diabetes live in low and middle income countries [8]. Legend : AFR ; Africa. MENA: Middle East and North Africa. SEA : South-East Asia. SACA : South and Central America. WP: Western Pacific. NAC : North America and Caribbean. EUR : Europa.*

1.2 The need for BG monitoring and prediction

The major concern associated with diabetes is its multietiological (i.e. multifactorial) and systemic nature. Chronicity of hyperglycemia and/or hypoglycemia can result in multiple micro- and macrovascular damages, leading to several systemic complications [9].

Hyperglycemia, left untreated, can lead to several long-term complications. Amongst others, we can enumerate neuropathy (i.e. nerve damage, that can lead to diabetic foot disorders including severe infections, and may require amputation), nephropathy (kidney failure), retinopathy (i.e. bloods vessels of the retina are damaged and can lead to blindness), as well as cardiovascular diseases such as heart attacks and strokes [10].

Furthermore, if blood sugar rises high enough or for a prolonged period of time, it can lead to two emergency conditions, i.e. diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar syndrome (HHS), which can both lead to life-threatening dehydration and a coma [11].

In the same manner, *hypoglycemia* - of which immediate symptoms are amongst others weakness, shaking, sweating, neurological disorders - can increase significantly the risk of cardiovascular diseases and lead to coma or death in the most severe cases, if not treated in time.

Moreover, it should be noted that hypoglycemia affects all aspects of life for the person with type 1 diabetes, including employment, social interactions, driving, sport and leisure activities, and sleep [12]. Nocturnal hypoglycemic events, of which extra physical activity and alcohol consumption, or the improper take of long-effect medication are common causes, are particularly undesirable.

However, there is huge evidence that good BG control helps to delay or prevent these serious long-term complications [13]. Still, achieving and maintaining good BG control[2] remains a difficult task, especially for T1D patients.

There is therefore a real need for developing accurate blood glucose monitoring and prediction systems. Indeed, being able to accurately predict impending hyper or hypoglycemia would give patients time to intervene and prevent these BG excursions, improving overall health, safety, and quality of life. Such predictions would enable or facilitate numerous potential applications of benefit to T1D patients, including [14] :

1. Alerts warning of immediately impending problems;
2. Individual, tailored recommendations of interventions to prevent problems;
3. "What if" analysis to project the effects of different lifestyle choices and treatment options.

[2]Ideally, one should maintain the blood glucose within the normal range (70 – 120 mg/dL). Lower glucose levels (< 50mg/dL) is said to be *Hypoglycemia*, higher glucose levels (> 200 mg/dL) is said to be *Hyperglycemia*.

1.3 The difficulty in BG prediction

Since decades, there has been a growing interest in BG prediction. However, the artificial pancreas - which aims to substitute endocrine functionality of a healthy pancreas - is a technology that is still in development. The main reason is that diabetes is a nonlinear, multifactorial and dynamic condition, subject to huge intra- and inter-patient variability. Blood glucose prediction is therefore a very complex problem.

This difficulty can be illustrated based on personal experience of Adam Brown [15], type 1 diabetic patient since 13 years. Following conversations with experts, and scientific research, Adam enumerated a non-exhaustive list of 22 factors that can affect blood glucose, separated into five areas : Food ; Medication ; Activity ; Biological and Environmental factors, represented in Figure 1.2 hereafter. For the sake of completeness and scientific accuracy, we describe here factors whose effects have been well documented in the literature, together with their references when needed.

1. Food factors

Carbohydrates Of all the three sources of energy from food (carbohydrates, protein, and fat), carbohydrates affect blood glucose the most. Accurately counting carbs is very difficult, and getting the number wrong can dramatically affect blood glucose. The type of carbohydrate also matters – higher glycemic index carbs tend to spike blood glucose more rapidly.

Fat Fatty foods tend to make people with diabetes more insulin resistant, meaning more insulin is often needed to cover the same amount of food relative to a similar meal without the fat [16].

Protein Though protein typically has little effect on blood glucose, a protein-only meal, in the absence of insulin, can raise blood glucose [17, 18].

Cafeine Many studies have suggested that caffeine increases insulin resistance and stimulates the release of adrenaline [19].

Alcohol Normally, the liver releases glucose to maintain blood sugar levels. But when alcohol is consumed, the liver is busy breaking the alcohol down, and it reduces its output of glucose into the bloodstream. This can lead to a increase of insulin sensitivity and a drop in blood sugar levels if the alcohol was consumed on an empty stomach. However, alcoholic drinks with carbohydraterich mixers (e.g., orange juice) can also raise blood sugar [20].

2. Medication factors

Medication dose The dose of medication (pills or insulin injections) directly impacts blood glucose – in most cases (but not always), taking a higher dose of a diabetes medication means a greater blood glucose-lowering effect.

Medication timing In addition to dose, medication timing can also be critical. For instance, taking rapid-acting insulin (Humalog, Novolog, Apidra) 20 minutes before a

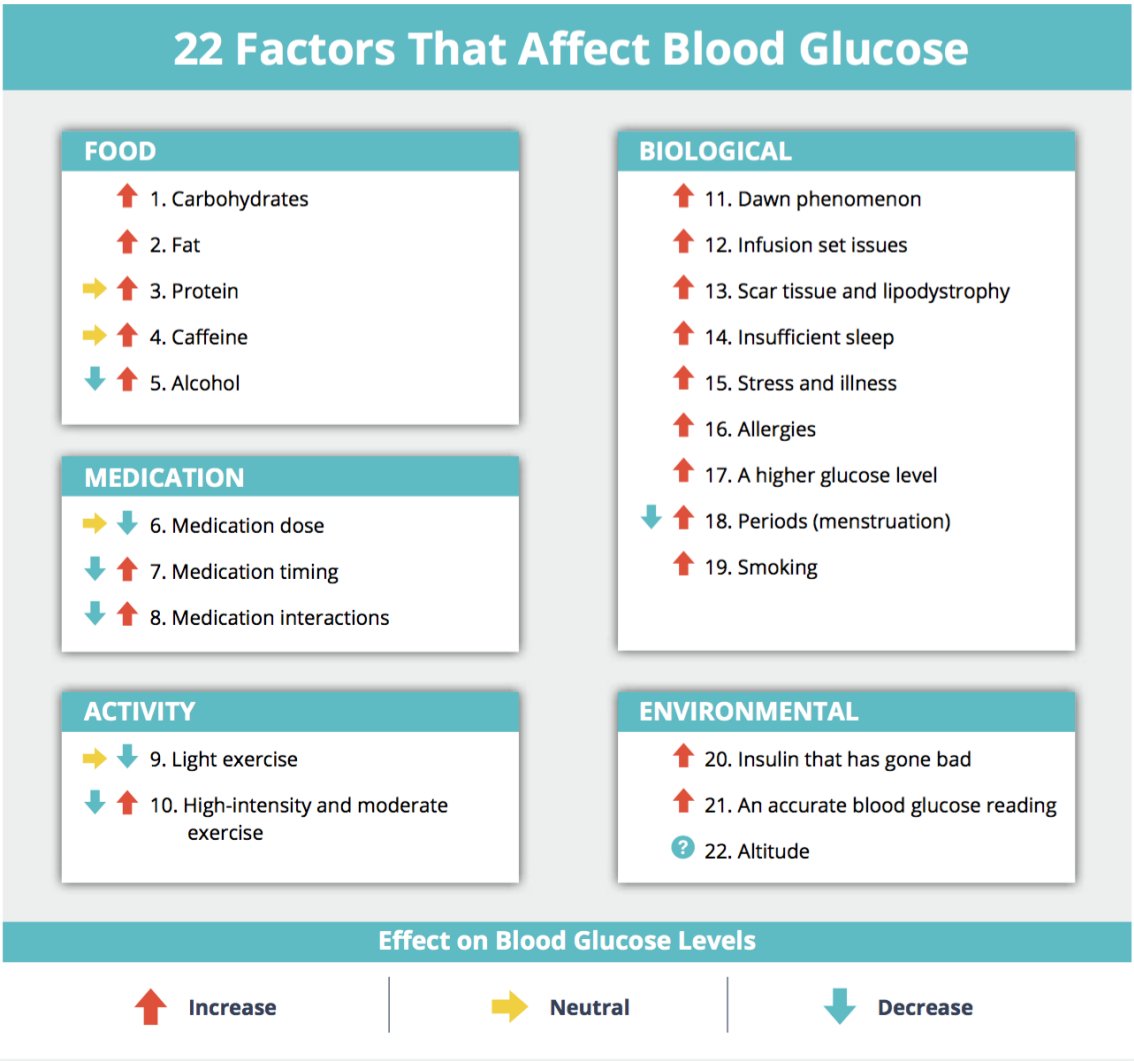


Figure 1.2: *Arrows show the general effect these factors have on Adam Brown's blood glucose (a sideways arrow indicates a neutral effect), but emphasize that not every individual will respond in the same way (and even within the same person, there may be differences from day-to-day or over time).Certain factors may also apply more to type 1 vs. type 2 diabetes (or the other way around).*

meal is ideal for Adam Brown - it leads to a lower spike in glucose vs. taking it at the start of the meal or after the meal has concluded. The timing of many type 2 diabetes medications matters a lot – some can consistently be taken at any time of day (e.g., Januvia, Victoza), while others are most optimally taken at meals (e.g., metformin).

Medication interactions Non-diabetes medications can interfere with your diabetes medications and blood glucose. Diabetic patients need to consult the information included in both diabetes and non-diabetes medications.

3. Activity factors

High intensity and moderate exercise Exercise is often positioned as something that always lowers blood glucose; however, high-intensity exercise, such as sprinting or weight lifting, can sometimes raise blood glucose. This stems from the adrenaline response, which tells the body to release stored glucose [21].

4. Biological factors

Dawn phenomenon The "dawn phenomenon" occurs in people with and without diabetes. The term refers to the body's daily production of hormones around 4:00-5:00 AM. During this time, the body makes less insulin and produces more glucagon, which raises blood glucose [22].

Infusion set issues Infusion sets are not as well understood as we would like, and a huge number of factors can lead to higher glucose levels: air bubbles in the tubing, an occluded cannula, an infected site, or even the location of the set. Adam Brown finds that his glucose always tends to run higher on the third day of wearing an infusion set [23].

Insufficient sleep Many studies have found that not getting enough sleep leads to worse diabetes control, insulin resistance, weight gain, and increased food intake [24, 25, 26]. In Adam's experience, he needs nearly 25% more insulin on days following less than seven hours of sleep. In addition, he observed his glucose was 21% more variable.

Stress and illness Stress and illness can cause the body to release epinephrine (adrenaline), glucagon, growth hormone, and cortisol. As a result, more glucose is released from the liver (glucagon, adrenaline) and the body can become less sensitive to insulin (growth hormone, cortisol). In some cases, people are much more insulin sensitive right before getting sick and can tend to run low blood sugars [27, 28].

A higher glucose level Hyperglycemia can lead to a state known as "glucotoxicity," which can actually increase insulin resistance [29, 30].

Smoking Some studies suggest that smoking can increase insulin resistance, and people with diabetes who smoke are more likely than nonsmokers to have trouble with insulin dosing and managing their diabetes. Smokers also have higher risks for serious complications [31].

5. Environmental factors

Insulin that has gone bad According to the product labels from all three U.S. insulin manufacturers, it is recommended that insulin be stored in a refrigerator at approximately 4°C to 14°C. Exposing insulin to direct sunlight or leaving it in the car on a hot day can definitively alter insulin efficiency. In addition, accuracy may be limited due to strip manufacturing variances, strip storage, and aging [32].

Errors in measurement They may also be due to patient factors such as improper coding, incorrect hand washing, altered hematocrit, or naturally occurring interfering substances. As an example, for a meter that needs a tiny 0.3 microliter blood sample, a speck of glucose on the finger with the weight of a dust particle can increase the reading by 300 $[mg/dl]$! Wash properly his hands before using finger-prick device is crucial [32].

1.4 The need for patient empowerment

1.4.1 Importance of lifestyle behaviour

According to [33] and [34], there is an increasing recognition that lifestyle behaviours account for a substantial ($> 40\%$) portion of premature mortality and also play a determinant role in diabetes, in both types 1 and 2. Lifestyle and health-related behaviours include physical activity, nutrition, alcohol consumption, sleeping, socialization, and smoking. Unfortunately, poor health behaviours and habits appear to be easily acquired but difficult to eliminate. Perhaps even more challenging is the fact that once developed, good habits and behaviours are difficult to maintain long term. How can we keep patients engaged ?

1.4.2 Patient-centred approach

The serious and chronic nature of diabetes, the complexity of its management, and the multiple daily self-care decisions that diabetes requires mean that being adherent to a predetermined care program is generally not adequate over the course of a person's life with diabetes. This is particularly true when the self-management plan has been designed to fit patients' diabetes, but has not been tailored to fit their priorities, goals, resources, culture, and lifestyle. Furthermore, there is considerable evidence that health interventions tailored to individuals are more effective that generic ones, and that timely feedback plays an important role in changing and sustaining behavior [33].

To manage diabetes successfully, patients must be able to set goals and make frequent daily decisions that are both effective and fit their values and lifestyles, while taking into account multiple physiological and personal psychosocial factors. That is the main issue *patient empowerment*, which aims to help patients discover and develop the inherent capacity to be responsible for one's own life (thus, closely related to "diabetes education"), should deal with [35, 36].

1.4.3 Empowerment scale

Empowerment efficiency is not easy to measure. However, [37] provides a scale for that purpose. According to that study, empowerment can be sub-scaled into 3 mains aspects :

1. *Managing the Psychosocial Aspects of Diabetes:* this subscale assesses the patients' perceived ability to obtain social support, manage stress, be self-motivating, and make diabetes-related decisions that are "right for me."

2. *Assessing Dissatisfaction and Readiness to Change:* this scale assesses patients' perceived ability to identify aspects of caring for diabetes that they are dissatisfied with and their ability to determine when they are ready to change their diabetes self-management plan.

3. *Setting and Achieving Diabetes Goals:* this scale assesses patients' perceived ability to set realistic goals and reach them by overcoming the barriers to achieving their goals.

It has been shown that individuals with greater diabetes empowerment have greater knowledge about diabetes, have healthier diets, are more physically active, are more adherent to their medication treatment plans, and test their blood sugar more frequently compared to individuals with lower diabetes empowerment [38, 39].

1.5 Empowerment through gamification

The best way to empower a diabetic patient is a personal face-to-face coaching [33], day after day, ideally in close collaboration with physicians, dietitians, nurses and other diabetes health care professionals. However, such solution is not an economically feasible method for helping people to improve and manage their health behaviours.

In view of the empowerment scale we just described (especially concerning items 1. and 3.), another and hopeful way for keeping patients motivated appears suitable : the gamification. This concept, which can be defined as *the use of game mechanics and experience design to digitally engage and motivate people to achieve their goals in non-game contexts* [40], has become a trending topic in many fields. Amongst others, gamification attempts to improve user/customer engagement, organizational productivity, education, communication or physical exercise. A review of research on gamification shows that majority of studies on it have found positive and hopeful results [41].

As a valuable example, let us mention the case of the *Bant* app. The researchers of the Centre for Global eHealth Innovation and of the University Health Network of Toronto have shown that by combining the use of an mHealth app with gamification as an incentive, a substantial increase is achieved in the frequency with which adolescents with type 1 diabetes carry out a control [42]. To encourage the use of the application

by the diabetic adolescents, the developers had introduced a reward algorithm. The app produced a code to download songs, games and other applications free from the Apple iTunes store if the boy or girl maintained a good practice in measuring glucose in the blood throughout the day. Furthermore, it was also checked whether the adolescent shared the results of tests with their parents and doctors.

The participants' daily measurement of glucose in the blood increased by 50% in comparison with previous routines, with an average of eight rewards per head. Moreover, 88% of patients said that they felt satisfied with the app and that they would continue to use this system for controlling glycaemia.

Finally, as more and more people own mobile phones and in view of the success of gaming apps, designing Mobile Health (*mHealth*) apps with gamification elements seems, in my opinion, a promising way to empower diabetic patients. This concept will be further detailed in Chapter 4.

1.6 Summary and roadmap

Throughout this Introduction chapter, we made several observations :

1. Diabetes is a condition that occurs when the insulin–glucagon regulatory mechanism is affected, leading to uncontrolled and undesirable hyperglycemia and hypoglycemia events.
2. Chronicity of hyperglycemia and/or hypoglycemia can result in multiple micro- and macrovascular damages, leading to several systemic complications [9], which can, left untreated, be life-threatening.
3. Diabetes is a major, global and increasing problem. The number of people with diabetes is estimated to be 415 million today and expected to rise to 592 million by 2035 [6].
4. Type 1 diabetes, the more severe kind, can not be prevented or cured but can be effectively treated with external supplies of insulin and through BG control.
5. Diabetes is a nonlinear, multifactorial and dynamic condition, subject to huge intra- and inter-patient variability. Blood glucose prediction is therefore a very complex problem.
6. Lifestyle and health-related behaviours - including exercise, diet, alcohol consumption, smoking, sleeping and socialization - play an important role in diabetes management [33, 34].
7. It has been shown that individuals with greater diabetes empowerment have greater knowledge about diabetes, healthier diets, are more physically active, more adherent to their medication treatment plans, and test their blood sugar more frequently compared to individuals with lower diabetes empowerment [38, 39]. However, personal face-to-face coaching is costly and hard to scale.

7. A review of research on gamification - which can be defined as *"the use of game mechanics and experience design to digitally engage and motivate people to achieve their goals in non-game contexts"* [40] - has shown that majority of related studies have found positive results [41].

8. It has been shown in [42] that by combining the use of an mHealth app with gamification as an incentive, a substantial increase is achieved in the frequency with which adolescents with type 1 diabetes carry out BG control.

In view of these observations which highlight the importance of blood glucose control and empowerment in the diabetes management process, we are now able to set clear and meaningful objectives of the further work to carry out. With the utimate goal of suggesting an innovative design of mHealth app for the self-management of diabetes, including a BG prediction tool and taking advantage of gamification mechanics, I decided to organize my master's thesis into the followings chapters :

Chapter 2 : *State of the art (SOA) in glucose prediction.*
In this chapter, SOA methods in glucose prediction - relying on physiological models, machine learning or time-series analysis - will be described, reviewed and discussed.

Chapter 3 : *Design of a dynamic neural network : `NARX`*
In the continuity of Chapter 2, we will propose the design and implementation of a blood glucose prediction model with MATLAB Neural Network Toolbox, known as `NARX` or *nonlinear autoregressive network with exogenous inputs*.

Chapter 4 : *Empowerment through mHealth gamification.*
Based on best design principles, successful mHealth apps and key ingredients of gamification, we will discuss the design of an innovative mobile application for diabetic patients.

Chapter 5 : *Case study : `Eglé`.*
In this chapter, in the light of previous observations, we will study the case of `Eglé` - `https://beta.egle.be/` - a web application dedicated to diabetic patient empowerment and which makes use of artificial intelligence and user-centred design.

Chapter 6 : *Conclusion.*
In a last point, we will try to incorporate in a synthetic way the main results and compare them with the initial objectives. This final chapter will also present limitations and prospects for the continuation of the work undertaken.

Chapter 2

State of the art in glucose prediction

Several studies aiming at the prediction of glucose in diabetic patients have been presented in the literature. In this chapter, we will distinguish the reported methods into three major groups :

- *The first one includes mathematical models that simulate the underlying physiology of the glucose-insulin regulatory system. Indeed, compartmental models, which are a class of linear dynamic models, have been widely used for studying various aspects of normal physiology and the pathophysiology of diabetes.*

- *The second group, based on time-series analysis, provides methods that can be used to exploit recent history of glucose measures and identify systematic patterns - such as trends and seasonalities - as well as methods for time-series modelling and prediction.*

- *On the other hand, the third group takes advantage of machine learning - a sub-field of Artificial Intelligence - and offers data-driven models which are able to capture complex, hidden relationships and predict blood glucose levels, based only on existing input-output data.*

In what follows, relying on relevant literature, the three introduced approaches will be further described, reviewed and discussed. For each approach, we will rigorously present the most popular models and, for the sake of completeness, provide mathematical background and underlying concepts. However, note that a concise summary can be found in Section 2.6 , page 33.

2.1 Physiological models

Since the 1960s, a huge number of mathematical models have been used to describe glucose–insulin dynamics. These models are in the form of ordinary differential, partial differential, delay differential and integro-differential equations. However, reviewing all of these methods is not the main goal of this section, that's why we will focus on most popular ones.

According to a paper published by Bergman in 2002 [43], more than 500 studies are related to the minimal model. Hence it appears consistent to start with this latter to give the reader an insight into physiological modelling.

Besides, beause the minimal model only describes a small part of the glucose-insulin dynamics, we will also present some other phenomenological studies, including exogenous insulin absorption, carbohydrates absorption and exercice-induced glycogenolysis models[1].

2.1.1 Bergman's minimal model

Bergman and colleagues proposed a three-compartment minimal model (illustrated in Figure 2.1 to analyse the glucose disappearance and insulin sensitivity during an intravenous glucose tolerance test. Compartments I, X, and G represent plasma insulin $[\mu U/ml]$, remote insulin $[\mu U/ml]$, and plasma glucose $[mg/dl]$ concentrations, respectively.

The model as written assumes that all the necessary insulin is infused exogenously $(u1)$, thereby modeling the insulin-dependent diabetic patient. A portion of the infused insulin enters into the remote compartment, X, from the circulatory system, I. The remote insulin (X) actively takes part in promoting the uptake of plasma glucose (G) into the hepatic and extrahepatic tissues.

The Bergman minimal model is given mathematically by [45] :

$$\begin{cases} \dfrac{dI}{dt} = -nI(t) + p_4 u_1(t) \\ I(0) = I_b = \dfrac{p_4}{n} u_{1b} \end{cases} \tag{2.1}$$

$$\begin{cases} \dfrac{dX}{dt} = -p_2 X(t) + p_3[I(t) - I_b] \\ x(0) = 0 \end{cases} \tag{2.2}$$

$$\begin{cases} \dfrac{dG}{dt} = -p_1 G(t) - X(t)G(t) + p_1 G_b + \dfrac{u_2(t)}{Vol_G} \\ G(0) = G_b \end{cases} \tag{2.3}$$

Here, I_b and G_b are the basal plasma insulin and glucose concentrations, respectively. The exogenous insulin infusion rate to maintain I_b is represented by u_{1b} $[mU/min]$. The rate constant n represents clearance of plasma insulin. The rates of appearance of insulin in, and disappearance of remote insulin from, the remote insulin compartment

[1] Note that this part of the section will highly be inspired from the research paper [44].

are governed by the parameters p_3 and p_2, respectively. Dietary absorption or external infusion of glucose is indicated by $u2(t)$, and the glucose distribution space is indicated by Vol_G. Parameter p_1 represents the rate at which glucose is removed from the plasma space independent of the influence of insulin. Glucose uptake under the influence of insulin is governed by the term $X(t)G(t)$.

Note that parameter values for the minimal model obtained from Bergman et al. can easily be found in the literature.

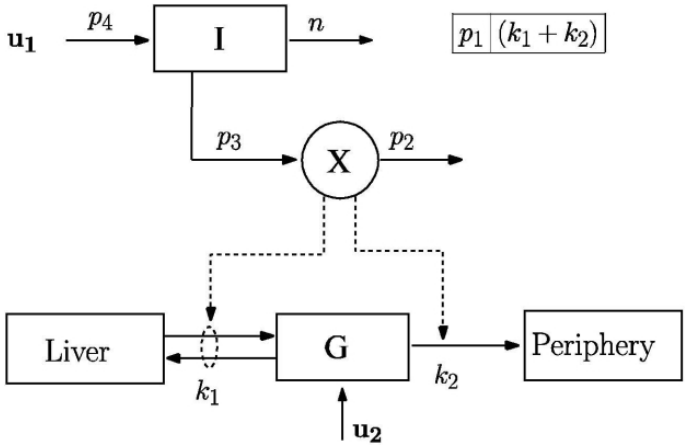


Figure 2.1: *Bergman minimal model of insuline and glucose dynamics, adapted from Bergman and colleagues.*

Extensions

However, some authors indicated that while the minimal model has minimal number of constants and has been indisputably useful in physiological research, it has many drawbacks [43]. That is why a lot of variant versions and extensions have been considered by different authors, as illustrated in Figure 2.2. Some examples include, albeit non-exhaustively, the work of Derouich and Boutayeb, that introduced parameters related to physical exercise [46], the dynamical (aggregated delay differential) model of De Gaetano and Arino [47], or the glucose kinetics model of Cobelli and Tomaseth [48].

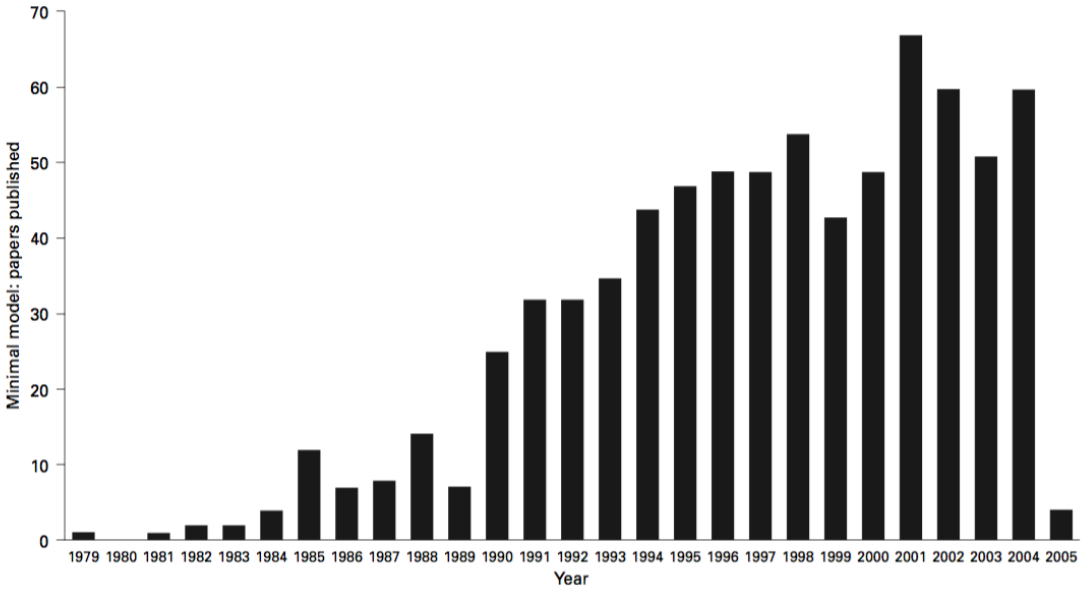


Figure 2.2: *Studies using or studying the minimal model from 1979 to April 2005, estimated from the PubMed Citation Index, according to [49].*

2.1.2 The insulin model

The input to a typical insulin physiological model is the exogenous insulin flow, $I_{ex}(t)$, while the output is the plasma insulin concentration I_p. According to the compartmental modelling approach [50], the concentration - time evolution of plasma insulin I_p $[uU/ml]$, hepatic insulin I_h and interstitial insulin I_i after a subcutaneous injection can be described as follows :

$$\dot{I}_p = \frac{I_{ex}(t)}{V_d} - k_1 I_p(t) + k_2 I_h(t) + k_3 I_i(t) \tag{2.4}$$

where V_d is the plasma insulin distribution volume, and k_1, k_2, k_3 are the rate constants of plasma, hepatic and interstitial insulin elimination, respectively.

The absorption of subcutaneously injected insulin is described by the pharmacokinetic model proposed in [51]. This model describes the diffusion of insulin through the subcutaneous depot, the molecular dissociation of insulin (hexameric/dimeric) and the absorption of insulin into the bloodstream by the following nonlinear partial differential equations :

$$\frac{\partial c_d(t,r)}{\partial t} = P\left(c_h(t,r) - Q c_d(t,r)^3\right) - B_d c_d(t,r) + D\nabla^2 c_d(t,r) \tag{2.5}$$

$$\frac{\partial c_h(t,r)}{\partial t} = -P\left(c_h(t,r) - Q c_d(t,r)^3\right) + \kappa c_b(t,r)(c_{h,max} - c_h(t,r)) + D\nabla^2 c_h(t,r) \tag{2.6}$$

$$\frac{\partial c_b(t,r)}{\partial t} = -\kappa c_b(t,r)(c_{h,max} - c_h(t,r)) + d_b D \nabla^2 c_h(t,r) \tag{2.7}$$

where c_h, c_d, c_b are the hexameric, dimeric and bound insulin concentrations in the subcutaneous tissue, respectively, D is the diffusion constant, d_b is a non-dimensional factor that reduces the diffusion effect, P is the dimeric-to-hexameric association rate, Q is the corresponding equilibrium constant, κ is the proportional factor of disengagement of hexameric insulin from the bound state, $c_{h,max}$ is the maximum concentration of hexameric insulin and B_d is the absorption rate constant. The bound state in this model is a virtual state introduced to model the dynamics of long-acting insulin analogues e.g. Glargine.

As can be observed from these equations, the diffusion process of insulin in the subcutaneous tissue is considered to be isotropic i.e. homogeneous and with rotational symmetry with respect to the origin (injection site). Additionally, it is assumed that only the dimeric form of insulin can be absorbed into the plasma with a rate proportional to its concentration. Hence, the exogenous insulin flow $[U/min]$ into the bloodstream is given by:

$$I_{ex}(t) = B_d \int_{V_{sc}} c_d(t,r) dV \tag{2.8}$$

where V_{sc} is the complete subcutaneous volume.

This model allows the description of all insulin formulations through the adequate selection of the parameters $Q, D, B_d, k, c_{h,max}$ and d_b.

2.1.3 The meal model

The model by [52] is used to describe the ingestion and absorption of carbohydrates intake. This model describes the rate of appearance of glucose in plasma on the assumption that the rate of gastric emptying is a trapezoidal function and that the intestinal glucose absorption follows first order linear kinetics.

The amount of glucose in the gut, q_{gut}, after the ingestion of a meal containing D grams of glucose equivalent carbohydrates is defined as :

$$\dot{q}_{gut}(t) = -k_{abs} q_{gut}(t) + G_{empt}(t, D) \tag{2.9}$$

where k_{abs} is the rate constant of intestinal absorption and G_{empt} $[mg/min]$ is the gastric emptying function. The function G_{empt} is described by:

$$G_{empt} = \begin{cases} V_{max}/T_{asc} & \text{if } t < T_{asc} \\ V_{max} & \text{if } T_{asc} < t \leq T_{asc} + T_{max} \\ V_{max} - (V_{max}/T_{des})(t - T_{asc} - T_{max}) & \text{if } T_{asc} + T_{max} < t \leq T_{asc} + T_{des} \\ 0 & \text{otherwise} \end{cases} \tag{2.10}$$

where

$$T_{max} = \frac{2D - V_{max}(T_{asc} + T_{des})}{2V_{max}} \tag{2.11}$$

corresponds to the duration of the period for which the gastric emptying function is constant and maximum (V_{max}), and T_{asc}, T_{des} are the duration of rising up and dropping periods of G_{empt}, respectively. Then, the rate of appearance of glucose in plasma $[mg/min]$ is given as:

$$R_a(t) = k_{abs} q_{gut}(t) \tag{2.12}$$

The values for the model parameters can be derived from [52] and are assumed to be patient-independent.

2.1.4 The exercise model

The study of Roy & Parker [21] describes in detail the dynamics of glycogenolysis and derives the exercise-induced changes on glucose – insulin metabolism as follows:

$$\dot{G}_{prod} = a_1 PV0_2^{max}(t) - a_2 G_{prod}(t) \tag{2.13}$$

$$\dot{G}_{up} = a_3 PV0_2^{max}(t) - a_4 G_{up}(t) \tag{2.14}$$

$$\dot{I}_e = a_5 PV0_2^{max}(t) - a_6 I_e(t) \tag{2.15}$$

where G_{prod} and G_{up} represent the rates $[mg/min]$ of hepatic glucose production (glycogenolysis) and glucose uptake induced by exercise, respectively, while the I_e $[uU/ml.min]$ denotes the rate of insulin removal from the circulatory system during and after exercise. As shown in above equations, the exercise intensity is quantified by the percentage of the maximum oxygen consumption $PV0_2^{max}$. According to [44], this term can be calculated as follows :

$$PV0_2^{max} = \frac{V0_2}{V0_2^{max}} = \frac{3.5MET}{V0_2^{max}} \tag{2.16}$$

where MET is the *Metabolic Equivalent of Task* - a physiological measure expressing the energy cost of physical activities [2] - while $V0_2^{max}$ is the maximal oxygen uptake and depends on patient's age, gender and physical status. This parameter value can be derived from reference tables.

[2] MET is defined as the ratio of metabolic rate (and therefore the rate of energy consumption) during a specific physical activity to a reference metabolic rate, set by convention to 3.5 $ml * O_2 * kg^{-1} * min^{-1}$ or equivalently:

$$1 \text{ MET } \equiv 1\frac{\text{kcal}}{\text{kg} * h} \equiv 4.184\frac{\text{kJ}}{\text{kg} * h} \tag{2.17}$$

[53]

2.1.5 Discussion

Compartmental models of the glucoregulatory system are composed of sub-models that describe the main processes affecting glucose metabolism in diabetic patients and offer powerful tools for understanding and predicting physiological processes. However, as highlighted by the number of equations we derived throughout this section, the glucose-insulin system is inherently highly complex.[44] Because physiological models contain a large number of parameters that are usually difficult to be identified and tuned to a specific patient, it potentially reduces their practical applicability. These algorithms are generally representative of an average subject under specific conditions and may not provide good performance results for a specific patient [54].

Based on these observations, in recent years the attention moved from the prediction models based on the compartmental models to the data-driven predictive models. Indeed, these latter are able to capture hidden, complex relationships and provide prediction of the future BG level using available information about the current and past blood glucose evolution and/or external perturbations, such as meals, insulin injections or exercise. This new generation of prediction algorithms are mainly realized by time-series analysis and machine learning methods [55].

2.2 Time series analysis

Recently, continuous glucose monitoring (CGM) technology has significantly modified the way glucose levels are monitored in patients with type 1 diabetes, allowing an increase in the number of readings from, for example, 3 to 4 spot measurements per day to a continuous (every 1 or 5 minutes typically) glucose signal [56]. Although such a technology also presents some disadvantages (expensiveness, required daily calibration, "lag time"), the large amount of data obtained by CGM sensors greatly stimulated the development of several applications. According to Bremer and Gough (1999) [57], the autocorrelation analysis of CGM time series made clear that glucose dynamics have a detectable structure and, thus, the glucose can be predicted by exploiting its recent history. Since that work, several studies have considered autoregressive (AR) prediction models based - mostly - on CGM data. In addition, several multivariate time series models have been developed that are enhanced with external information regarding insulin, food and physical activity. [44]

AR and ARIMA, being the two most popular and basic time series models for glucose prediction, will be briefly described in what follows.

2.2.1 Auto-regressive

An autoregressive model is when a value from a time series is regressed on previous values from that same time series. The order of an autoregression is the number of immediately preceding values in the series that are used to predict the value at the present time. The glucose time series can be described locally by an auto-regressive model of

first-order (AR(1)), corresponding to the following time-domain difference equation [58]:

$$y_i = ay_{i-1} + \epsilon_i \tag{2.18}$$

In this above equation , $i = 1, 2, ...n$ denotes the order of glucose samples collected till the n-th sampling time t_n and ϵ_i is a random white noise process with zero mean and variance equal to σ^2.

The prediction strategy is as follows. Let θ denote the vector of the parameters of the model employed to describe the glucose time-series, i.e., $\theta = (a, \sigma^2)$. At each sampling time t_n, a new value of θ is first determined by fitting the model against past glucose data y_n, y_{n-1}, y_{n-2},... by weighted linear least squares (WLS). WLS with weight w_i and residuals r_i can be expressed as :

$$r_i = \hat{y}_i(a, \sigma^2) - y_i \tag{2.19}$$

$$\hat{A} = \arg\min_{A} \sum_{i=1}^{n} w_i r_i^2 \tag{2.20}$$

Once θ is determined, the model is used to calculate the prediction of glucose level T steps ahead, i.e., $\hat{\theta}_{n+T}$. The value $\hat{\theta}_{n+T}$ is calculated iteratively for $i = n+1, n+2, \ldots, n+T$.

In determining the model parameters θ at a given time, all the past data $y_n, y_{n-1}, ..., y_1$ participate, with different relative weights w_i . A typical choice is to employ exponential weighting, i.e., μ^k is the weight of the sample taken k instants before the actual sampling time i.e., taken at time t_{n-k} with $k = 0, 1, \ldots, n-1$.

μ, taken in the range (0,1), acts as a forgetting factor [58]. If a forgetting factor is not used (which is equivalent to letting $\mu = 1$), glucose samples collected tens of hours, if not days, before the actual sampling time would influence prediction. This could lead to a possible deterioration of the algorithm capability to promptly track changes in the signal, in particular those due to perturbations, e.g., meals.

Note that from an algorithmic point of view, recursive least squares (RLS) implementations are possible in order to estimate the unknown model parameters θ in a computationally efficient manner.

2.2.2 ARIMA modelling

As we just have seen, the stochastic *Auto Regressive* model is extremely useful in the representation of certain practically occurring series . In this model, the current value of the process is expressed as a linear aggregate of previous values of the process. Another kind of model is the *Moving Average* model which depends on the previous deviations. To achieve greater flexibility in fitting of actual time series, it is advantageous to include both AutoRegressive and Moving Average terms in the model. ARIMA models are the

most general class of models for forecasting a time series which can be stationarized by transformations such as differencing and logging. [59]

Given a time series of data X_t where t is an integer index and the X_t are real numbers, an ARIMA model is given by [60]:

$$\left(1 - \sum_{i=1}^{p} \phi_i L^i\right) (1 - L)^d X_t = \left(1 + \sum_{i=1}^{q} \theta_i L^i\right) \varepsilon_t \tag{2.21}$$

or more concisely by :

$$\varphi(L) X_t = \theta(L) \varepsilon_t \tag{2.22}$$

where :

- L is the lag (or *backshift*) operator - defined such as $LX_t = X_{t-1}$ for all $t > 1$
- The α_i are the parameters of the autoregressive part of the model
- The θ_i are the parameters of the moving average part
- The ε_t are error terms, generally assumed to be independent, identically distributed variables sampled from a normal distribution with zero mean.
- p is the order of the autoregressive part. That is the number of unknown terms that multiply the signal at past times (as many past times as p)
- d is the degree of first differencing involved, i.e. the number of times time-series need to be differenced in order to obtain a stationary one. The optimal order of differencing is often the differencing at which the standard deviation is minimum.
- q is the order of the moving average part, i.e. the number of unknown terms that multiply tge forecast errors at past times (as many past times as q)

The fine tuning consists of adding lags of the differenced series and/or lags of the forecast errors to the prediction equation. Values of parameters p, d, q can be easily estimated based on the autocorrelation (ACF) and partial autocorrelation functions (PACF).

Coefficients of model parameters can be determined by Maximum likelihood estimation. A comprehensive modelling approach to obtain the best fit is given by the *Box-Jenkins* method [61].

2.2.3 Discussion

Auto-regressive models - though they do not require a lot of patient information - can give excellent predictive results. As a recent example (2014), by preprocessing CGM data with Kalman filter and using adaptive auto-regressive model, the authors of [62] managed to obtain RMSE of 0.282 $[mmol/l]$ and efficiently detect hypoglycemia events for 30-min -ahead prediction.

However, in view of the inherent complexity of blood glucose dynamics, a question naturally arises. Could linear time-series models reflect well the non-linear relationship

between therapeutically valuable input factors (BG measurements, meals, insulin injections, physical activities, etc.) and future glucose evolution, or some other models could perform better ? Motivated by this question and the potential portability from patient to patient, a variety of non-linear regression models and machine learning methods have been recently studied to address the problem of the blood glucose prediction in a new light.[55]

2.3 Machine learning methods

As - just - highlighted in the last section, the fact that the relationship between input variables (i.e. medication, diet, physical activity, stress etc.) and glucose levels is nonlinear, dynamic, interactive and patient-specific, motivates the application of machine learning methods, such as support vector regression, Gaussian processes, extended Kalman filters or artificial neural networks (ANN).

A lot of different types of neural networks have been considered in modelling the blood glucose metabolism, such as multilayer perceptron (MLP) [63], radial basis function (RBF) [64], wavelet networks [65], and recurrent neural networks (RNN) [66].

As illustrative examples and because neural networks have been extensively used according to literature reviews, we'll briefly describe the essence of two techniques based on ANN : the multilayer perceptron (MLP) and Elman recurrent networks.

2.3.1 Neural networks : background

Neural networks are composed of simple elements operating in parallel. These elements are inspired by biological nervous systems. As in nature, the connections between elements largely determine the network function. A neural network can be trained to perform a particular function by adjusting the values of the connections (weights) between elements [67, 68].

Typically, neural networks are adjusted, or trained, so that a particular input leads to a specific target output. The Figure 2.3 illustrates such a situation. Here, the network is adjusted, based on a comparison of the output and the target, until the network output matches the target. Many such input/target pairs are needed to train a network.

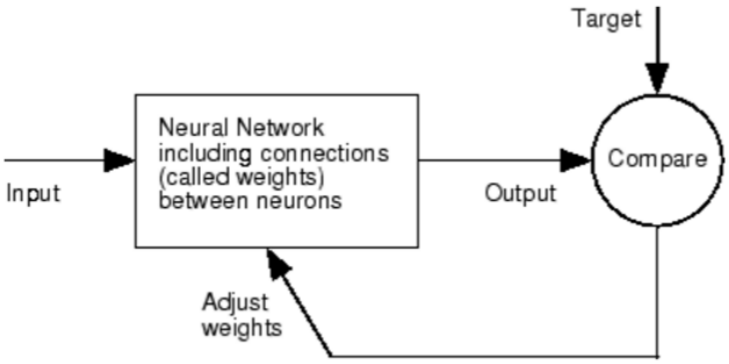


Figure 2.3: *A schematic representation of a neural network [67]*

Neural networks have been trained to perform complex functions in various fields, including pattern recognition, identification, classification, speech, vision, and control systems. Neural networks can also be trained to solve problems that are difficult for conventional computers or human beings. In the context of glucose prediction, an additional interesting feature of NNs is that they can easily combine exogenous information from different sources such as CGM, meals, insulin or physical activity.

2.3.2 Multi-layer perceptron

An MLP is a network of simple neurons called *perceptrons*. The perceptron computes a single output from multiple real-valued inputs by forming a linear combination according to its input weights and then possibly putting the output through some nonlinear activation function. Mathematically this can be written [69] as :

$$y = \varphi(\sum_{i=1}^{n} w_i x_i + b) = \varphi(\mathbf{w}^T \mathbf{x} + b) \tag{2.23}$$

where $\mathbf{w}$ denotes the vector of weights, $\mathbf{x}$ is the vector of inputs, b is the bias and φ is the activation function.

A single perceptron is not very useful because of its limited mapping ability. It can can, however, be used as building block of a larger, much more practical structure : the multilayer perceptron (MLP). A typical MLP network consists of a set of source nodes forming the input layer, one or more hidden layers of computation nodes, and an output layer of nodes. The input signal propagates through the network layer-by-layer. The nodes are connected by weights and output signals which are a function of the sum of the inputs to the node modified by a simple nonlinear transfer - or activation - function Φ. It is the superposition of many simple nonlinear transfer functions that enables the multilayer perceptron to approximate extremely non-linear functions. If the transfer function was linear then the multiperceptron would only be able to model linear functions.

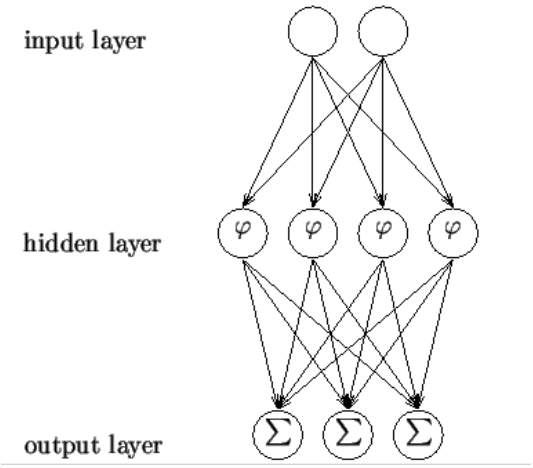


Figure 2.4

The signal-flow of such a network with one hidden layer is shown in Figure 2.4 taken from [70].

The computations performed by such a feedforward network with a single hidden layer with nonlinear activation functions and a linear output layer can be written mathematically [69] as :

$$\mathbf{y} = \mathbf{f}(\mathbf{x}) = \mathbf{B}\boldsymbol{\varphi}(\mathbf{A}\mathbf{x} + \mathbf{a}) + \mathbf{b} \tag{2.24}$$

where $\mathbf{x}$ is a vector of inputs and $\mathbf{y}$ a vector of outputs. $\mathbf{A}$ is the matrix of weights of the first layer, $\mathbf{a}$ is the bias vector of the first layer. $\mathbf{B}$ and $\mathbf{b}$ are, respectively, the weight matrix and the bias vector of the second layer. The function $\boldsymbol{\varphi}$ denotes an elementwise nonlinearity. The generalisation of the model to more hidden layers is obvious.

Activation functions

Due to their easily computed derivative, commonly used transfer functions are described [71] by :

$$\varphi(v_i) = \tanh(v_i) \quad \text{and} \quad \varphi(v_i) = (1 + e^{-v_i})^{-1} \tag{2.25}$$

These functions are both sigmoids. The former is a hyperbolic tangent which ranges from -1 to 1, and the latter, the logistic function, is similar in shape but ranges from 0 to 1. Here y_i is the output of the ith node (neuron) and v_i is the weighted sum of the input synapses. More specialized activation functions include radial basis functions which are used in another class of supervised neural network models.

Learning

By selecting a suitable set of connecting weights and transfer functions, it has been shown that a multilayer perceptron can approximate any smooth, measurable function between the input and output vectors [72]. The MLP has the ability to learn values of weights through training, during a supervised procedure. This process requires a set of training data; which consists of a series of input and associated output vectors. During training, the output from the MLP for a given input vector, may not equal to the desired output. An error signal is defined as the difference between the desired and actual output. The learning process uses the magnitude of this error signal to determine to what degree the weight in the network should be adjusted so that the overall error of the MLP is reduced. The most popular way to carry out this learning process is using the well-known *backpropagation* algorithm, a generalization of the least mean squares technique.

2.3.3 Elman recurrent network

Recurrent networks

Recurrent neural networks (RNN) are different from feedforward network architecture in the sense that there is at least one feedback loop. The presence of feedback loop has a profound impact on the learning capability of the network. Furthermore, these feedback loops involve the use of particular branches composed of unit delay elements that result in nonlinear dynamical behaviour by virtue of the nonlinear nature of neurons. Contrary to feedforward networks, recurrent networks can be sensitive, and be adapted to past inputs.

Elman RNN architecture

Elman has proposed a partially RNN, where the feedforward connections are modifiable and the recurrent connections are fixed. It occupies a set of context nodes to store the internal states. The connections are mainly feedforward but also include a set of carefully chosen feedback connections that allow the network to remember cues from the recent past. The input layer is divided into two parts that are the true input units and the context units that hold a copy of the activations of the hidden units from the previous time step. As the feedback connections are fixed, backpropagation can be used for training of the feedforward connections.

The structure of the Elman NN (ENN) is illustrated in Figure 2.5 where z^{-1} is a unit delay.

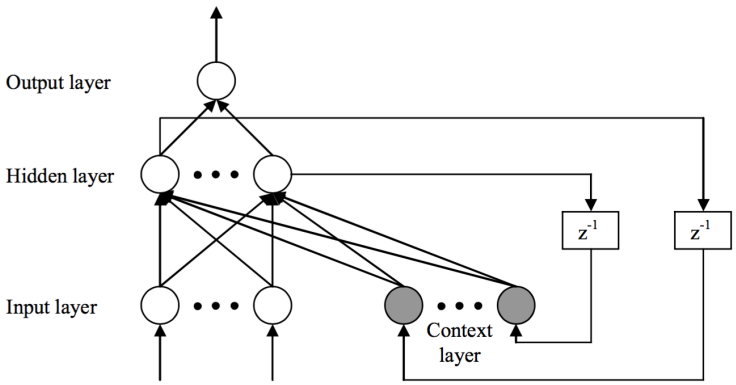


Figure 4. Architectural graph of Elman neural network

Figure 2.5: *It is easy to observe that the Elman network consists of four layers: input layer, hidden layer, context layer, and output layer. There are adjustable weights connecting each two adjacent layers. Generally, it can be considered as a special type of feedforward NN with additional memory neurons and local feedback.*

The Elman network has *tansig* neurons in its hidden (recurrent) layer - i.e. with hyperbolic tangent sigmoid transfer function, and *purelin* neurons - i.e. with linear transfer function - in its output layer. This combination is special in that two-layer networks with these transfer functions can approximate any function (with a finite number of discontinuities) with arbitrary accuracy. The only requirement is that the hidden layer must have enough neurons. These activation function are illustrated in Figure 2.6, taken from [73].

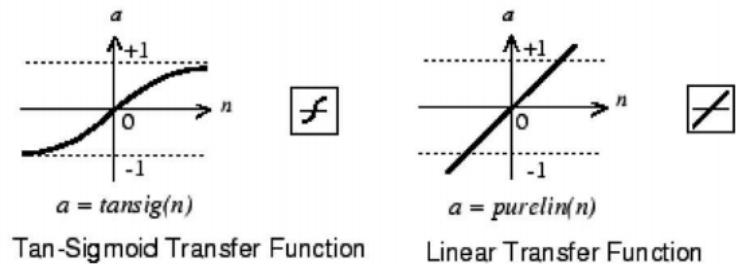


Figure 2.6

Finally, the outputs of the Elman Recurrent Neural Network at each time step can be calculated, in the context of bloog glucose prediction, as follows [63] :

$$a_j(k) = tansig(X_i \cdot IW_{ij} + a_j(k-1)LW_{ij}) \tag{2.26}$$

$$BGL = pureline(a_j(k) \cdot V_j) \tag{2.27}$$

where :

- X_i is the input
- IW_{ij} are the weights of the input layer
- $a_j(k)$ is the output of the hidden layer
- LW_{ij} are the weights of the context layer
- V_j are the weights of the output layer
- BGL is the predicted blood glucose level

Elman RNN vs MLP networks

Among the several NN architectures found in the literature, recurrent NNs (RNNs) involving dynamic elements and internal feedback connections have been considered as more suitable for modelling and control of non-linear systems than feedforward networks, such as MLP networks [74].

In the specific context of blood glucose prediction it also has been shown that, for an identical construction (number of neurons, number of layers, type of activation functions, training algorithm) Elman RNN give better results than MLP networks [63].

2.3.4 Hybrid approach

In a last subsection, it also should be noted that many predictors based on Machine Learning use compartmental models (CM) to enrich the input and enhance their model.

Support vector regression (SVR) and CMs

In the paper [44] from 2011, compartmental models were used to simulate (i) the ingestion and absorption of carbohydrates (the Meal Model), (ii) the absorption and the pharmacodynamics of subcutaneously administered insulin (the Insulin Model) as well as (iii) the impact of exercise on glucose - insulin metabolism (the Exercise Model). In addition, support vector machines for regression (SVR) were employed to provide individualized glucose predictions. More recently (2014), a similar solution was described in [75]. It also uses a generic physiological model of blood glucose dynamics to generate informative features for a SVR model that is trained on patient-specific data. This model outperformed diabetes experts at predicting blood glucose levels and could be used to anticipate almost a quarter of hypoglycemic events 30 minutes in advance.

As the support vector regression model has been extensively used in the context of BG prediction, it appears meaningful to briefly describe its underlying mathematical background.

The basic idea of SVR models can be described as follows. Supposing that there are training data $(x_l, y_l), \ldots (x_i, y_i), \ldots (x_n, y_n)$, where x_i parameters are input patterns and y_i parameters are the associated output values, the goal of SVR is to map the data x into a higher-dimensional feature space via a nonlinear mapping and perform a linear regression in this feature space [76] :

$$f(x) = w^T \phi(x) + b \tag{2.28}$$

where $\phi(x)$ is the feature and w and b are coefficients of SVR.

The optimal coefficients can be determined by solving the following minimization problem [77, 76]:

$$\min \frac{1}{2} \sum_{i,j=1}^{n} (a_i^\star - a_i)^T K(x_i, x_j)(a_j^\star - a_j) - \sum_{i=1}^{n} [a_i^\star (y_i - \epsilon) - a_i (y_i + \epsilon)] \tag{2.29}$$

$$\text{subject to} : \begin{cases} \sum_{i=1}^{n} (a_i - a_i^\star) = 0 \\ a_i, a_i^\star \in [0, C] \end{cases} \tag{2.30}$$

where $K(x_i, x_j) = \phi(x_i)^T \phi(x_j)$ is the kernel function and C is the regularization parameter. There are some kernel functions such as linear kernel, polynomial kernel, and gauss kernel. They are inner products in a very high dimensional space (or infinite dimensional space) but can be computed efficiently by the *kernel trick*[3] even without knowing $\phi(x)$. According to Karush-Kuhn-Tucker [77] the coefficients $a_i, a_i^\star, b$ can be obtained, and the regression function can be defined as :

$$f(x) = \sum_{i=1}^{n} (a_i - a_i^\star) K(x_i, x) + b \tag{2.31}$$

Recurrent NN and CMs

In 2006, Mougiakakou et al. [79] proposed a hybrid system based on the combination of a compartmental model (CM) and a recurrent neural network (RNN) for blood glucose prediction. Data from a Type 1 diabetes patient, stored in a database, have been used as input to the hybrid system. The data contained information about measured blood glucose levels (without CGM device), insulin intake, and description of food intake, along with the corresponding time. The data were passed to three separate CMs, which produce estimations about (i) the effect of Short Acting (SA) insulin intake on blood insulin concentration, (ii) the effect of Intermediate Acting (IA) insulin intake on blood insulin concentration, and (iii) the effect of carbohydrate intake on blood glucose absorption from the gut. The outputs of the three CMs were then passed to the RNN in order to predict subsequent blood glucose levels, and led to promising results.

[3]The kernel trick avoids the explicit mapping that is needed to get linear learning algorithms to learn a nonlinear function or decision boundary. For all $\mathbf{x}$ and $\mathbf{x}'$ in the input space $\mathcal{X}$, certain functions $k(\mathbf{x}, \mathbf{x}'$ can be expressed as an inner product in another space $\mathcal{V}$. The function $k \colon \mathcal{X} \times \mathcal{X} \to \mathbb{R}$ is often referred to as a kernel or a kernel function. [78]

2.4 Adaptive-weighted-average framework

As mentioned throughout the section, a lot of specific data-driven methods have been used for BG prediction, including time series analysis, regression prediction, artificial neural networks and support vector machine. Every prediction algorithm has its own advantages and disadvantages, i.e. it uses some specific aspects of information but ignores some other useful aspects. Therefore, the use of only one particular method for BG prediction can give one-sided results.

Given this observation, the authors of [76] recently proposed a novel framework with the idea of combining various prediction methods such that their disadvantages are minimized and advantages are maximized. In this framework, an adaptive weight was given for each algorithm, where one algorithm's weight was inversely proportional to the sum of its squared prediction errors. In general, this framework can be applied to combine any BG prediction algorithm.

In this context, the combined BG prediction $\hat{y}$ can be written as follows:

$$\hat{y}(k) = \sum_{i=1}^{n} w_i(k)\hat{y}_i(k) \tag{2.32}$$

$$w_i(k) = \frac{\frac{1}{S_i(k)}}{\sum_{j=1}^{n} \frac{1}{S_j(k)}} \tag{2.33}$$

where $w_i(k)$,$S_i(k)$ correspond respectively to the time-varying weight normalized weight and sum of squared prediction errors for the i-th considered algorithm at time k.

As an example, the above-mentioned framework was used in [76] to combine the Auto Regressive (AR) model, Extreme Learning Machine (ELM)[4], and Support Vector Regression (SVR) because these three methods are very popular for BG prediction.

The new algorithm was compared with these three prediction algorithms on the continuous glucose monitoring system (CGMS) readings of 10 type 1 diabetes mellitus patients; the CGMS readings of each patient included 860 CGMS data points. For each patient, the algorithms were evaluated in terms of RMSE, relative error, and Clarke error-grid analysis. Of the 40 evaluations, the new adaptive-weighted algorithm achieved the best prediction performance in 37 (92.5%). The authors concluded that the proposed framework, being universal and robust to variations, should be used in BG prediction.

Despite the great accuracy it offers, such a method is computationally intensive and may be not suitable in a e-health/mHealth context.

[4]Extreme learning machines are feedforward neural networks with a single layer of hidden nodes, where the weights connecting inputs to hidden nodes are randomly assigned and never updated. These weights between hidden nodes and outputs are learned in a single step, which essentially amounts to learning a linear model. [80]

2.5 Performance : discussion

In recent years, and with the ultimate purpose of improving everyday life of diabetics patients, a large number of physiological and data-driven methods have been proposed to help patients control their blood sugar. Throughout this section we have briefly described a lot of these models, but reviewing all of them would be out of scope for this research.

However - as suggested in the Introduction chapter - if we had to develop a BG prediction tool in a e-health/mHealth context, which approach should we choose ? Based on the literature, are we able to compare them in terms of accuracy ? Which criteria do we have to take into account in our analysis ?

2.5.1 Assessment metric

In order to be able to analyze and compare the prediction algorithms, proper assessment metrics that could help to understand advantages or disadvantages of the considered algorithms are needed. In the case of the blood glucose prediction, there is a large number - making direct comparisons difficult - of assessment metrics adopted in the literature, including Clarke error grid analysis (EGA), mean relative absolute deviation percentage (RAD), root mean square error (RMSE), continuous glucose-error grid analysis (CG-EGA), J index, and the prediction-error grid analysis (PRED-EGA) [55].

2.5.2 Data

Not only the assessment metric is important but also what data are compared. If the assessment results are even provided in terms of the same metric, their comparison is not so straightforward due to a possible difference in data sources and references.

- **Virtual vs real subject** : In the vast majority of the existing literature on the blood glucose prediction techniques one can find the performance assessment results on simulated clinical data, so-called virtual subjects. In this case, the assessment results can only serve as the proof of concept of the constructed predictors but cannot be used to quantify the clinical acceptability of the algorithms since the simulated data do not usually provide the realistic models of the blood glucose evolution.

- **Measuring devices** : Fingerpricks - often regarded as cumbersome and uncomfortable by patients - only provide information about a single point in time, so it is difficult to discern trends in decline of rises in blood glucose levels. In opposition, continuous glucose monitoring (CGM) systems measure blood glucose levels semi-continuously (every 5-minutes or every minute), providing much more valuable data to prediction algorithms and therefore a better accuracy. Besides, we should note that, even from one CGM device to another, small differences in accuracy can be observed [81].

- **Subcutaneous vs blood glucose** : Even if the assessment of the algorithms is performed on real data, in most models the reference is taken as the glucose value given by CGM system, which is the subcutaneous blood glucose. However, management of diabetes is defined in terms of blood (but not subcutaneous) glucose and therefore a more honest assessment of the constructed predictors is a comparison with respect to the blood glucose obtained by a glucose meter.

- **Inter-patient variability**: As previously mentioned, there clearly exists inter-patient variability in diabetes. The factors that affect inter-patient variability include sex, age, weight, hormonal changes, stress, illness, and activity levels. As a consequence, patients can have low or high glucose variability, of which standard deviation and mean amplitude of glycemic excursions are common measures. High glucose variability tends to increase the complexity of a model and decrease its accuracy. Hence, it appears logical to assume performance of modelling algorithms also varies from one patient to another, underlining the need for large patient dataset.

- **Inputs variables**: Some methods described in the literature made use of richer multivariate inputs (including, as examples, physical activity or heart rate variability[82]) but it does not necessarily means that other prediction algorithms are less efficient.

2.5.3 Comparison

As highlighted by previous subsections, direct comparison of the different approaches is not an easy task and requires to take into account certain criteria. Nevertheless, in this subsection we will introduce some relevant observations found in the literature.

Physiological[5] models describe the underlying physiological process (production, distribution, and degradation of glucose and insulin) by compartments, each of which is associated with several differential equations, forming thus a compartmental submodel . Although the inherent nonlinearity of the glucose–insulin interaction has been recognised in these models, their application in predictive control is limited by two factors: they are not patient-specific and contain a high number of system parameters making such models hard to map to low-dimensional data and to validate [83, 44, 84, 54].

Time-series analysis by auto-regressive (AR) models show yet more promising results, especially in [85], where the prediction error was on average, in terms of RMSE, less than 3.6 $[mg/dl]$ for a 30-min prediction. The model was evaluated for three different datasets, each utilizing a different CGM device, and the patient cohorts included both type I and type II diabetes. However, these results were achieved by filtering the CGM signal in both training and test data using a non-causal filter, removing the high frequency components.[86]

[5]Sometimes also referred to as "*phenomenological*" models

Besides, recurrent neural network (RNN) models have been shown to be serious competitor in [87]. In this paper, the RNN model was compared against an AR and an ARX (i.e. auto-regressive with exogenous inputs) model on a 30 patient dataset, retrieved from the Padova simulation model. Here, the NN clearly outperformed the competing models with an average RMSE of 4.9 $[mg/dl]$ versus 29 $[mg/dl]$ (AR) and 26 $[mg/dl]$ (ARX) for the 45-min prediction. In opposition, it was noted [88, 89] that NN-based models not necessarily outperform simple time-series models such as low-order AR models...

In recent years, hybrid machine learning approaches have also been considered and include, e.g., support vector regression (SVR) [90] and random forests (RF) [91] combined with compartmental models. Both techniques were evaluated on the same dataset of 27 type 1 patient records from free-living conditions collected within the METABO project [92]. The recorded insulin injections as well as the meal intakes were fed into compartment models to provide estimated profiles of plasma insulin and glucose rate of appearance. Besides, physical activity, estimated from a body monitoring system, and the time of the day were also added as input variables. The reported RMSE of the SVR for these predictions horizons was 6.0 $[mg/dl]$ whereas the RF method managed slightly worse; 8.2 $[mg/dl]$ for a 30-min ahead prediction horizon [86].

In addition, another SVR model, also informed by a physiological model and trained on patient specific data, has outperformed ARIMA and diabetes experts at predicting blood glucose levels, thus demonstrating the utility of physiological modelling in machine learning models for blood glucose level prediction [14].

According to the authors of [76], every prediction algorithm has its own advantages and disadvantages, i.e. it uses some specific aspects of information but ignores some other useful aspects. Given this observation and as described in section 2.4, they proposed a novel framework with the idea of combining various prediction methods such that their disadvantages are minimized and advantages are maximized. Note that this idea is also studied in [86]. As an example, the framework was used to combine the AR, ELM, and SVR models, three very popular methods for BG prediction. The new algorithm was compared with these three prediction algorithms on the continuous glucose monitoring system (CGMS) readings of 10 type 1 diabetes mellitus patients. Of the 40 evaluations, the new adaptive-weighted algorithm achieved the best prediction performance in 37 (92.5%).

2.6 Summary

1. **Physiological models** of the glucoregulatory system are composed of compartmental sub-models, each of which is associated with several differential equations that describe the main processes affecting glucose metabolism in diabetic patients and offer powerful tools for understanding and predicting physiological processes. Some examples include, though not-exhaustively :

   - The well-established *Bergman's Minimal Model*, suggested as a means to estimate insulin sensitivity from an intravenous glucose tolerance test
   - The *Meal Model*, used to simulate the ingestion and absorption of carbohydrates
   - The *Insulin Model*, used to simulate the absorption and pharmacokinetics of subcutaneously administered insulin
   - The *Exercise Model*, used to simulate the impact of exercise on glucose-insulin metabolism (e.g. glycogenolysis)

   However, their practical applicability is limited by two factors: they are not patient-specific and contain a high number of system parameters that are usually difficult to be identified and validated. [83, 44, 84, 54].

2. **Time-series analysis** provides methods that can be used to identify systematic patterns in time series data - such as trends and seasonalities - as well as methods for time series modelling and prediction. According to [57], the autocorrelation analysis of CGM time series made clear that glucose dynamics have a detectable structure and, thus, the glucose can be predicted by exploiting its recent history. Some popular methods include, though not-exhaustively :

   - The autoregressive (AR) model
   - The autoregressive integrated moving average ($ARIMA$) model
   - The autoregressive with exogenous inputs (ARX) model
   - The autoregressive–moving-average with exogenous inputs ($ARMAX$) model

3. However, in view of the inherent complexity of BG dynamics naturally arises the question whether linear time-series models could reflect well the non-linear relationship between therapeutically valuable input factors (BG measurements, meals, insulin injections, physical activities, etc.) and future glucose evolution, or some other models could perform better [55]. Motivated by this question, a variety of **Machine Learning methods** have been developed to address the problem of the blood glucose prediction - that can be considered as a nonlinear regression problem with a time component - in a new light. Some popular methods include, though not-exhaustively :

   - Artifical neural networks (*MLP*, *RNN*, *RBF*,...)
   - Support vector regression (SVR)
   - Random forests (RF)
   - Gaussian processes

3b. It also should be noted that, in recent years, many Machine Learning predictors adopted an "***hybrid*** *approach*", i.e. made use of compartmental models (CM) to enrich the input and enhance their model.

4. Due to the large number of papers dealing with blood glucose prediction, the diversity of methodologies and the contradictory results, there is no clear evidence that Machine Learning methods outperform Time-series analysis approach.

5. In the **adaptive-weighted-average** framework, it is assumed that every prediction algorithm (e.g. related to Machine Learning or Time-Series analysis) has its own advantages and disadvantages, i.e. it uses some specific aspects of information but ignores some other useful aspects. Given this observation, the authors of [76] proposed a novel framework with the idea of combining various prediction methods such that one algorithm's adaptive weight was inversely proportional to the sum of its squared prediction errors. Despite the great accuracy it offers, such a method is computationally intensive and may be not suitable in a e-health/mHealth context.

6. **Performance assessment** is not an easy task. In order to be able to analyze and compare the prediction algorithms, proper assessment metrics are needed. In the case of blood glucose prediction, there exist many different performance measures (*RMSE, EGA, RAD, CG-EGA, PRED-EGA*). Not only the assessment metric is important but also what data are compared. Data can differ by their sources (e.g. real vs. virtual subjects) and references (e.g. measuring device).

Chapter 3

Design of a dynamic neural network : NARX

As mentioned in the last section, the powerfulness of autoregressive models has been shown more than once in previous work. However, some authors claim such linear models are not the best to cope with non-linearity of blood glucose time series.

On the other hand, neural networks are very efficient when applied to non-linear problems whose solutions require knowledge which is difficult to specify. Still, it also has been found that neural networks encounter difficulty in modelling seasonal patterns in time series, mainly due to high observation frequency and long-term dependencies which are hard to "learn" with gradient-descent algorithm. [93, 94]

It is obvious that both approaches have their own advantages and disadvantages. Is there a way, without adopting the excellent but computationally expensive adaptive-average-weighted framework we discussed earlier, to combine autoregressive models with neural networks ? Though not very popular so far in the context of blood glucose prediction, the non-linear autoregressive model with exogenous inputs, aka NARX, seems to meet our expectations and will be the object of this chapter.

More specifically, in this chapter, we will propose an implementation of NARX with Matlab *Neural Network Toolbox. First, this dynamical recurrent neural network will be briefly introduced and mathematically described. Then, we will detail and discuss our design, from the collection of blood glucose time series, to the training of the NARX model, to the analysis of its predictive performance.*

3.1 Introduction

3.1.1 Dynamic neural network

`NARX` is said to be a *dynamic network*, i.e. that contains delays and that operate on a sequence of inputs. Such networks are more and more used for nonlinear filtering and prediction. Because they have memory, dynamic networks are generally more powerful than static networks - although somewhat more difficult to train - and can be trained to learn sequential or time-varying patterns.

This has applications in such disparate areas as prediction in financial markets (e.g. predict the future value of a stock), fault detection , speech recognition, and even genetics. These dynamic predictive models are important for analysis, simulation, monitoring and control of a variety of systems, including manufacturing systems, chemical processes, robotics and aerospace systems.

3.1.2 Recurrent neural network

Dynamic neural networks can be divided into two categories : those that have only feedforward connections, and those that have feedback, or recurrent, connections. *Recurrent* dynamic networks typically have a longer response than feedforward dynamic networks, which appears useful to learn long-term dependencies and make multi-step-ahead predictions. The `NARX`, or *nonlinear autoregressive network with exogenous inputs*, is a recurrent dynamic network, with feedback connections enclosing several layers of the network.

3.1.3 Mathematical definition

The defining equation for the `NARX` model is :

$$y(t) = F(y(t-1), y(t-2), ..., y(t-n_y), u(t-1), u(t-2), ..., u(t-n_u)) + \epsilon_t \qquad (3.1)$$

where the next value of the dependent output signal $y(t)$ is regressed on previous values of the output signal and previous values of an independent (exogenous) input signal $u(t)$. Besides, F referred to some nonlinear function, implemented here by a multilayer perceptron, while ϵ_t is the error term, sometimes called noise.

Architecture

Each layer in a `NARX` model is made up of the following parts:

- Set of weight matrices that come into that layer (which can connect from other layers or from external inputs) ;
- Associated weight function rule used to combine the weight matrix with its input (typically standard matrix multiplication)
- Associated tapped delay line ;

- Bias vector ;
- Net input function rule that is used to combine the outputs of the various weight functions with the bias to produce the net input (normally a summing junction);
- Transfer function;

The standard `NARX` architecture is illustrated in Figure 3.1.

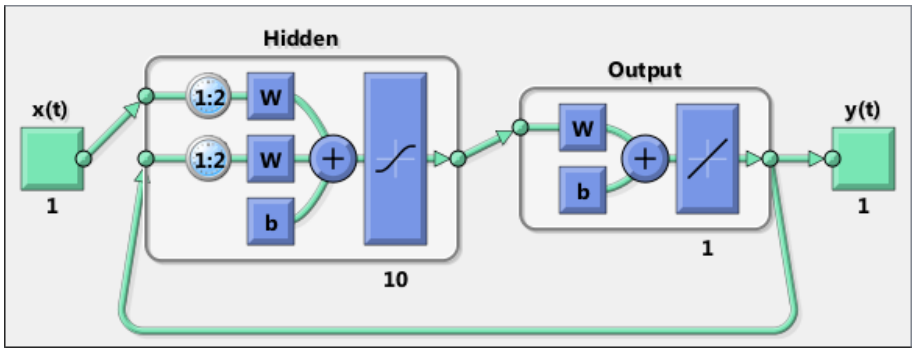


Figure 3.1: *The standard `NARX` is a two-layer network, with a sigmoid transfer function in the hidden layer and a linear transfer function in the output layer. This network also uses tapped delay lines to store previous values of the $x(t) = u(t)$ and $y(t)$ sequences. Note that the output of the `NARX` network, $y(t)$, is fed back to the input of the network (through delays), since $y(t)$ is a function of $y(t-1), y(t-2), ..., y(t-d)$. However, for efficient training this feedback loop can be opened, as we'll see later. This Figure is taken from [95].*

The general prediction equations for computing the next value of time series $y(t+1)$, with past observations $u(t), u(t-1), \ldots, u(t-d_u)$ and the past outputs $y(t), y(t-1), \ldots, y(t-d_y)$ as inputs may be written in the form [96] :

$$y(t+1) = F_o \cdot \left[b_o + \sum_{h=1}^{N} w_{ho} \cdot F_h \left(b_h + \sum_{i=0}^{d_u} w_{ih} u(t-i) + \sum_{j=0}^{d_y} w_{jh} y(t-j) \right) \right] \tag{3.2}$$

where :

- b_h and b_o refer to bias vectors of hidden and output layers
- $w_{ih,jh}$, and $w_h o$ are weights associated, respectively, to hidden and output layers
- F_h and F_o, refer to transfer functions of hidden and output layers.

  In our case, as F is approximated using a multilayer perceptron (cfr section 2.3.2), $F_u = tansig$ (hyperbolic tangent sigmoid function) and $F_o = purelin$ (linear transfer function).
- d_u, d_y, are respectively input and output delays

3.2 Methods

3.2.1 Data generation : AIDA

AIDA is a mathematical model and freeware diabetes simulator. The AIDA compartmental model takes into consideration a number of factors: carbohydrate intake (amount in grams and time), insulin (type, amount, and time), kidney function, and insulin sensitivity. Using these variables, a compartmental model of the various interactions within the body is described by a series of equations to build a picture of BGL fluctuations over a 24-hour period in time steps of 0.25 hours. It assumes a patient is unable to produce endogenous insulin, as is the case with Type-1 diabetics[1].

For the reason that I was not able to find accurate clinical data, I decided to use generated data (times-series) from AIDA simulator to build the neural network developed in this section.

3.2.2 Data collection

Fourteen days of data were produced from AIDA (single patient, Case Study 2) in which a day commenced at midnight (00:00) and terminated at midnight the following day. Each day contained the following events :

- 3 meals and 3 'snacks'
- 2 short-acting insulin doses (administered before the meals),
- 2 long-acting insulin doses (administered before and after meals).

Original inputs - in AIDA GUI - are illustrated in Figure 3.2, while the corresponding BGL output with a 15 minute frequency, is illustrated in Figure 3.3.

Meals:	Breakfast:	Snack:	Lunch:	Snack:	Supper:	Snack:
Time (hhmm): 24 hr clock	0730	1000	1200	1600	1900	2200
Carbohydrate (grams):	30	20	50	20	40	20

Insulin Injections:					
Preparations:	Time (hhmm): 24 hr clock	0700	1130	1830	2300
Actrapid SHORT ACTING	Dose (units):	6	4	3	0
Lentard MC INTERMEDIATE & LONG ACTING	Dose (units):	0	4	0	6

Figure 3.2

[1]For more information on AIDA, readers should consult the website `http://www.2aida.org/` or see the separate paper in this special issue [97].

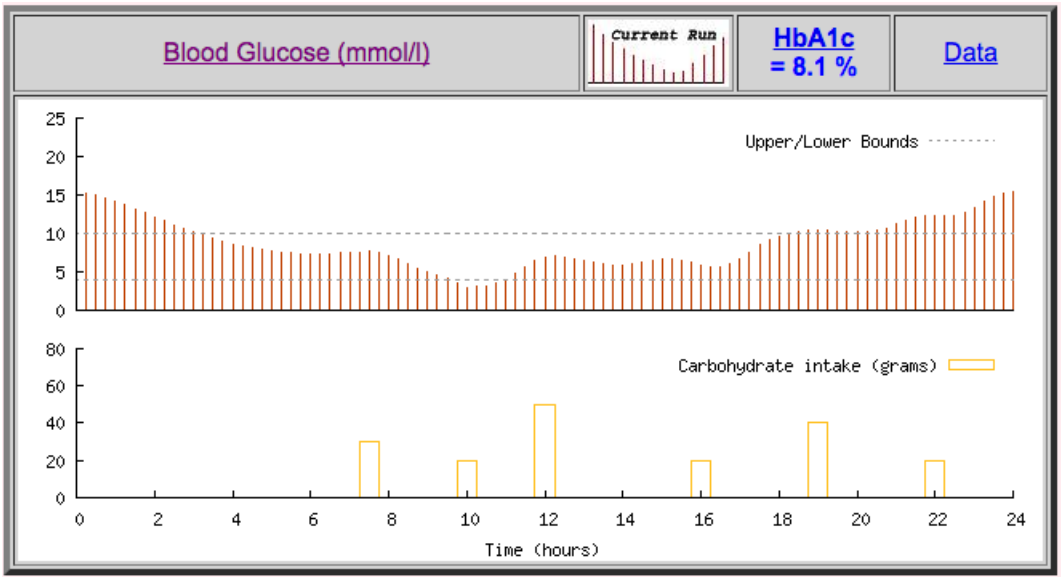


Figure 3.3

From one simulation to another we changed quite arbitrarily the values of the inputs : initial timings $[min] \pm t_i \in [0; 60]$; initial carbohydrates intakes $[grams] \pm c_i \in [0; 10]$; insulin doses $[units] \pm d_i \in [-2; 2]$. Note that the only periods where the insulin and carbohydrate vectors had a non zero value were around meal times, when insulin is required and carbohydrates are consumed.

Finally, the way we feed our dynamic network can be schematized as follows :

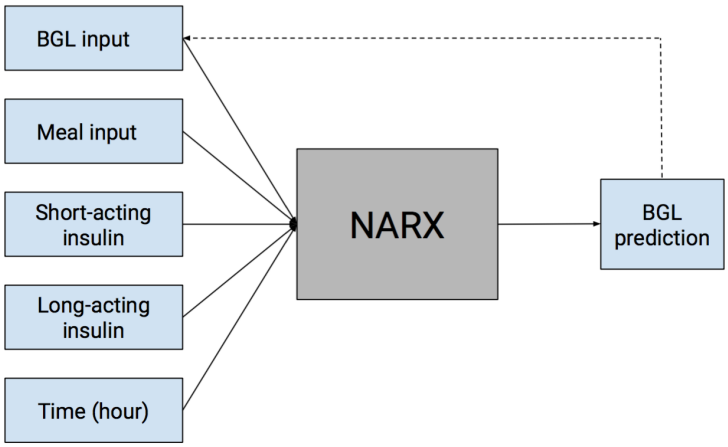


Figure 3.4

3.2.3 Data pre-processing

In this work, all inputs vectors (that encompass time, BGL, short-action insulin, long-action insulin and carbohydrates variables) were normalized. In this way, we observed the learning algorithm converges faster.

Furthermore, because we generated data with quite arbitrary parameters and in order to obtain consistent and smoother transitions between BGL measures from one day to another (00:00), we decided to smooth the BGL target vector by using a moving average filter of small span.

3.2.4 Network creation

As said in the beginning of the section, we did use *Neural Network Time Series Tool* of MATLAB in order to build the `NARX` network. This latter was built using `narxnet` function, and, as illustrated in Figure 3.1, is a recurrent network with the default tangent-sigmoid transfer function in the hidden layer and linear transfer function in the output layer. This network has two inputs. One is an external input, and the other is a feedback connection from the network output. For each of these inputs, there is a tapped delay line to store previous values.

Increasing the number of neurons and the number of delays requires more computation, and has a tendency to overfit the data, but allows the network to solve more complicated problems. Similarly, more layers require more computation, but their use might also result in the network solving complex problems more efficiently. In our case, optimal delays and numbers of neurons in the hidden layer were found by trial and error and based on multiple performance analysis tools. Results will be introduced in Subsection 3.3.

3.2.5 Data preparation

When training a network containing tapped delay lines, it is necessary to fill the delays with initial values of the inputs and outputs of the network. There is a toolbox command that facilitates this process : `preparets`. This function has three input arguments : the network, the input sequence and the target sequence. The function returns the initial conditions that are needed to fill the tapped delay lines in the network, and modified input and target sequences, where the initial conditions have been removed.

3.2.6 Data division

When training multilayer networks, the general practice is to first divide the data into three subsets. The first subset is the training set, which is used for computing the gradient and updating the network weights and biases.

The second subset is the validation set. The error on the validation set is monitored during the training process. The validation error normally decreases during the initial phase of training, as does the training set error. However, when the network begins to

overfit the data, the error on the validation set typically begins to rise. The network weights and biases are saved at the minimum of the validation set error. [98]

The test set error is not used during training, but it is used to compare different models. It is also useful to plot the test set error during the training process. If the error on the test set reaches a minimum at a significantly different iteration number than the validation set error, this might indicate a poor division of the data set.

In view of what has just been said, the input vectors and target vectors were randomly divided, with `dividerand` function, into three sets as follows :

- 70% were used for training.
- 15% were used to validate that the network is generalizing and to stop training before overfitting.
- The last 15% were used as a completely independent test of network generalization.

3.2.7 Network training

For learning purposes, a dynamic back-propagation algorithm is required to compute the gradients, which is more computationally intensive than static back-propagation and takes more time. In addition, the error surfaces for dynamic networks can be more complex than those for static networks. Training is more likely to be trapped in local minima [99].

However, because the true output is available during the training of the network, we can use a **series-parallel architecture** [100], in which the true output is used instead of feeding back the estimated output, as shown in Figure 3.5. This has two advantages. The first is that the input to the feedforward network is more accurate. The second is that the resulting network has a purely feedforward architecture, and static backpropagation can be used for training.

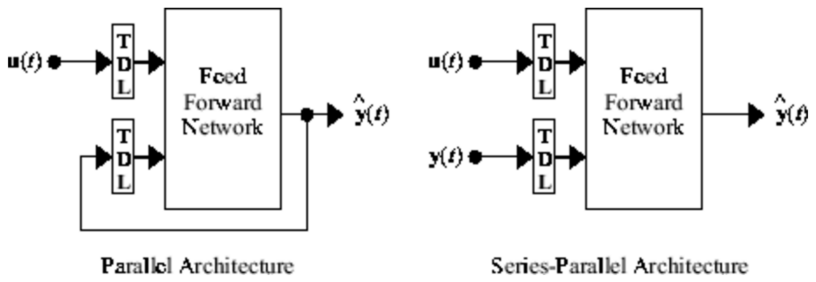


Figure 3.5: [95]

3.2.8 Learning algorithm

However, the training process has some difficulties. One is related to the number of parameters, which refers to how many connections or weights are contained in network.

Usually, this number is large and there is a real danger of "overtraining" the data and producing a false fit which does not lead to better forecasts. A solution is penalizing the parameter increase [99, 101]. This fact motivates the use of an algorithm including the regularization technique, which involves modifying the performance function for reducing parameters value. Practically, the typical performance function used in training, MSE, is replaced by a new one, MSE_{reg}, as follows :

$$MSE = \frac{1}{N}\sum_{i=1}^{N}(e_i)^2 = \frac{1}{N}\sum_{i=1}^{N}(t_i - \hat{y}_i)^2 \tag{3.3}$$

$$MSW = \frac{1}{n}\sum_{j=1}^{n} {w_j}^2 \tag{3.4}$$

$$MSE_{reg} = \alpha MSE + (1-\alpha)MSW \tag{3.5}$$

where t_i is the target and α is the performance ratio. The new performance function causes the network to have smaller weights and biases, and in this way forces the network response to be smoother and less likely to overfit.

The network training function that updates the weight and bias values according to Levenberg-Marquardt[2] optimization was modified to include the regularization technique. It minimizes a combination of squared errors and weights and, then determines the correct combination so as to produce a network which generalizes well. The process is called **Bayesian regularization** and is also implemented in MATLAB Neural Net Toolbox.

3.3 Results

Performance analysis suggested that our optimal parameters are the following ones :

- **Training algorithm** : Bayesian Regularization
- **Hidden layer size** : 6
- **Number of delays** : 12

And were validated based on :

- Autocorrelation errors analysis
- Cross-correlation errors analysis
- Regression analysis
- Root mean square error
- Computational work

[2]Note that in function approximation problems, for networks that contain up to a few hundred weights, the simple Levenberg-Marquardt algorithm will have the fastest convergence. However, as the number of weights in the network increases, the advantage of this algorithm decreases.

3.3.1 Error autocorrelation

The coefficient of correlation between two values in a time series is called the *autocorrelation* function (ACF). For example the ACF for a time series y_t is given by: $Corr(y_t, y_{t-k})$, with k the time gap being considered, also called the *lag*. A lag 1 autocorrelation (i.e., $k = 1$ in the above) is the correlation between values that are one time period apart. More generally, a lag k autocorrelation is the correlation between values that are k time periods apart.

Hence, the *error* autocorrelation function can be described as a way to measure how the prediction errors are linearly related in time. For a perfect prediction model, there should only be one nonzero value of the autocorrelation function - corresponding to the mean square error - and it should occur at zero lag. This would mean that the prediction errors were completely uncorrelated with each other (white noise). If there was significant correlation in the prediction errors, then it should be possible to improve the prediction perhaps by increasing the number of delays in the tapped delay lines.

In our case, the correlations, except for the one at zero lag, fall approximately within the 95% confidence limits around zero. Based on this result, we can conclude that the errors follow a white noise process, reinforcing the idea that the model seems to be adequate. Note that if we change the initial weights and biases of the network, it may produce another network after retraining.

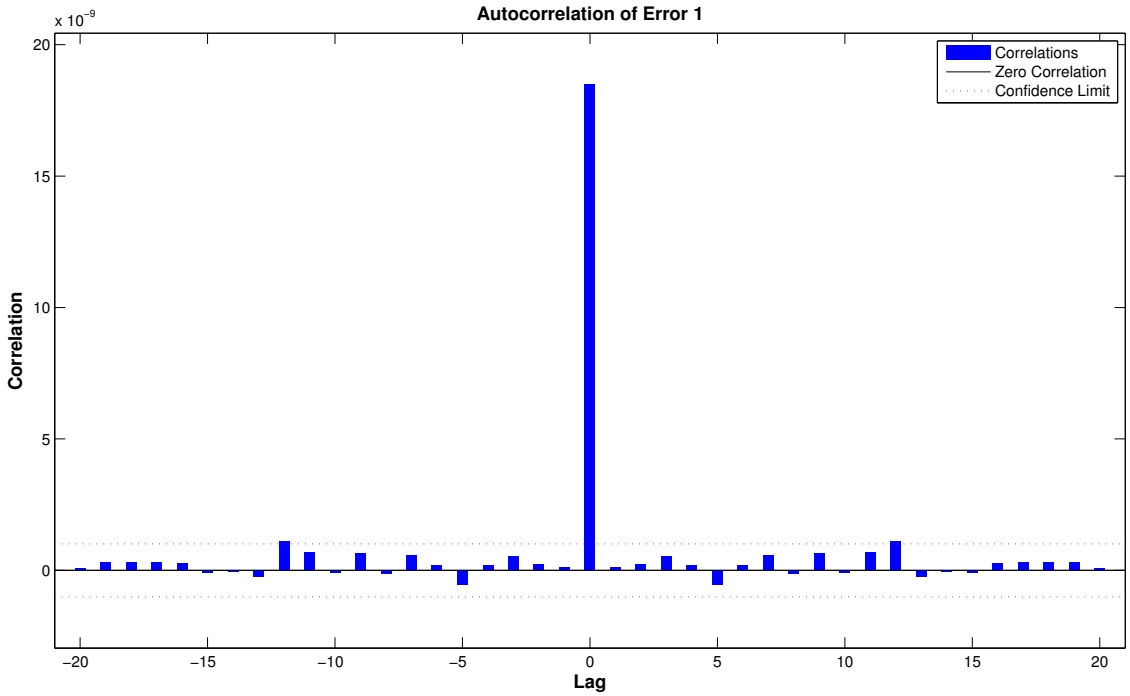


Figure 3.6: *Error autocorrelation*

3.3.2 Input-error cross-correlation

This input-error cross-correlation function illustrates how the errors are correlated with the input sequence $x(t)$. For a perfect prediction model, all of the correlations should be zero. If the input is correlated with the error, then it should be possible to improve the prediction, perhaps by increasing the number of delays in the tapped delay lines. In this case, all of the correlations fall within the confidence bounds around zero.

In our case, the input-error cross-correlations fall approximately within the 95% confidence limits around zero, so the model, again, seems to be adequate.

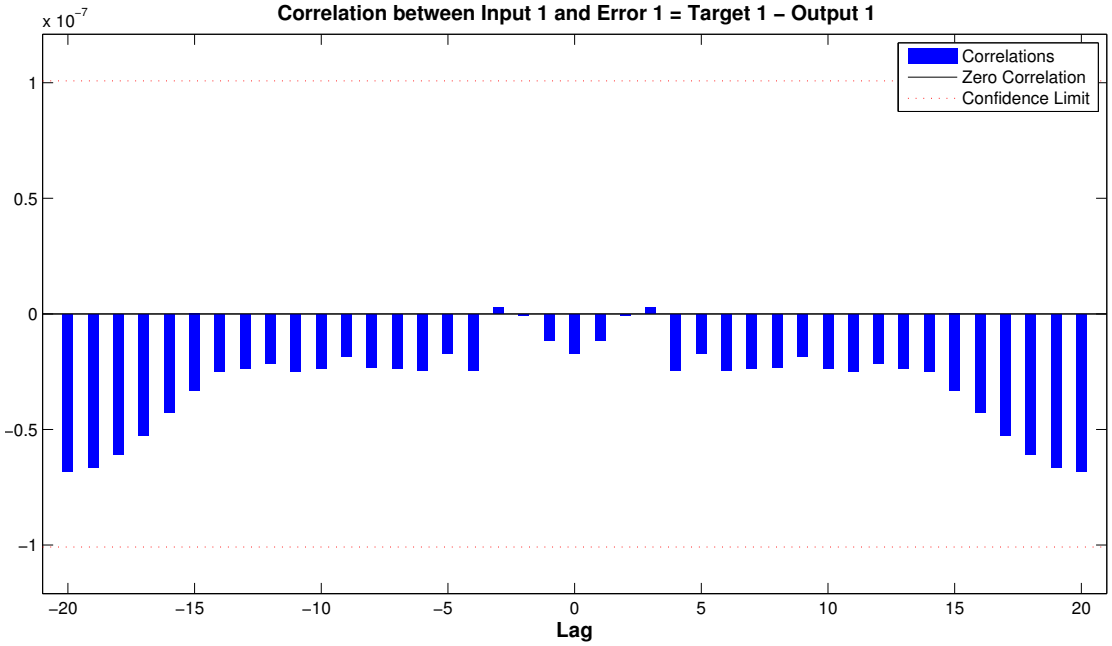


Figure 3.7: *Input-error cross-correlation*

3.3.3 Regression analysis

Regression analysis is a common tool used to validate the network performance. The regression plots (see Figure 6.2 in Annexes) display the network outputs with respect to targets for training, and test sets[3]. For a perfect fit, the data should fall along a 45 degree line, where the network outputs are equal to the targets. The solid line represents the best fit linear regression line between outputs and targets. The R value (Pearson correlation coefficient) is an indication of the relationship between the outputs and targets. If R = 1, this indicates that there is an exact linear relationship between outputs and targets. If R is close to zero, then there is no linear relationship between outputs and targets.

$$R = \frac{\sum_{i=1}^{n}(t_i - \bar{t})(y_i - \bar{y})}{\sqrt{\sum_{i=1}^{n}(t_i - \bar{t})^2}\sqrt{\sum_{i=1}^{n}(y_i - \bar{y})^2}}$$

In our case, the fit is excellent for all data sets, with R values in each case ≈ 0.999.

[3]Note that no validation set is required with Bayesian regularization

3.3.4 Root mean square error

The root-mean-square deviation (RMSD) or root-mean-square error (RMSE) is a frequently used measure of the differences between values predicted by a model and the values actually observed. It represents the sample standard deviation of the differences between predicted values and observed values. Performed over out-sample data (test set), it is a good measure of accuracy and predictive power of a model, for a particular variable.

$$\mathrm{RMSE} = \sqrt{\frac{\sum_{i=1}^{n}(t_i - y_i)^2}{n}}$$

In our case, $RMSE = 0.0602$ $[mmol/L]$, which is very low, knowing that normal BG range varies from 5 to 9 $[mmol/L]$, and hence tends to confirm our model is accurate.

3.3.5 Response

The times-series response of our model, i.e. the output $y(t)$, is illustrated in Figure 3.8. Again, though we observe the blood glucose levels vary a lot from one day to another (14 days of measure = 1358 time-steps of 15 min on the x-axis), the network almost perfectly reproduces the target distribution.

Note that random data division is also represented, except the validation set. That's because in the specific case of Bayesian regularization, the learning algorithm does not consider the validation data set to be separated from the training data set; it uses all the data to efficiently prevent our model from overfitting.

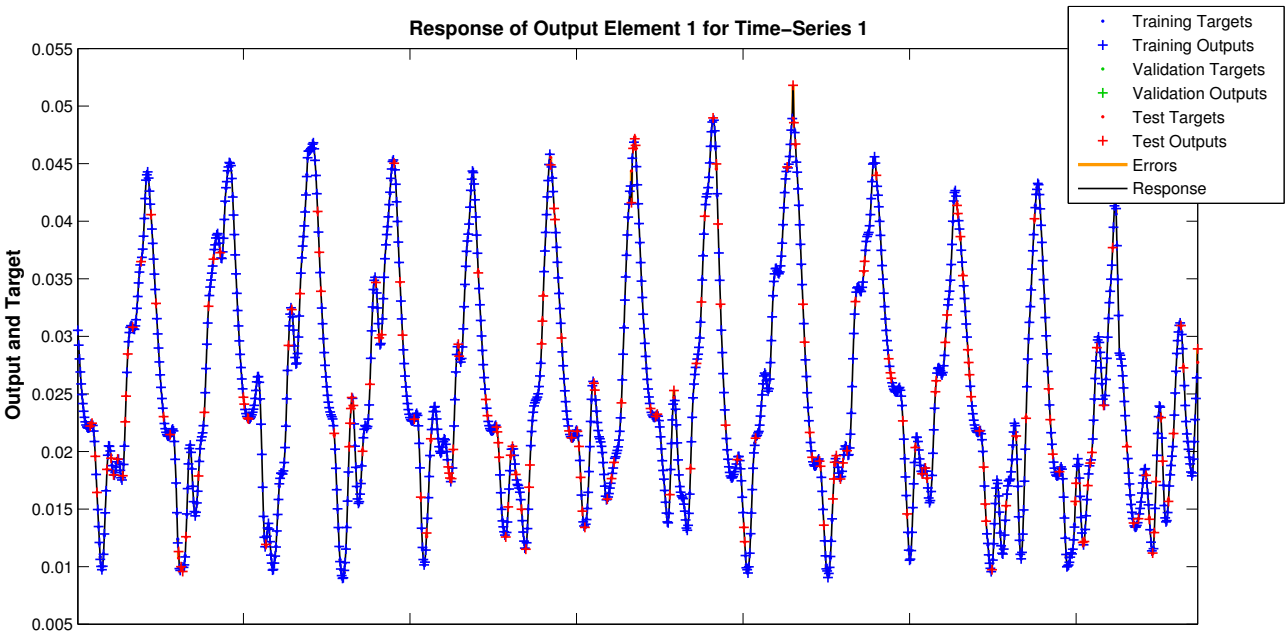


Figure 3.8

3.4 Multi-step prediction

As discussed earlier (Subsection 3.2.7) all of the training is done in open loop, also called series-parallel architecture. When the feedback loop is open on the `NARX` network, it is performing a one-step-ahead prediction. It is predicting the next value of $y(t)$ from previous values of $y(t)$ and $x(t)$. With the feedback loop closed, it can be used to perform multi-step-ahead predictions. This is because predictions of $y(t)$ will be used in place of actual future values of $y(t)$.

In this subsection, we'll analyse performance of `NARX` in blood glucose levels prediction for time windows of different size (prediction horizons) N, i.e. : 15, 30, 45, 60, 75, 90 $[min]$ corresponding respectively to 1-,2-,3-,4-,5- and 6-steps-ahead predictions. The Figure 3.9 and equations 3.6, 3.7, 3.8 describe the metrics we used for multi-step prediction performance analysis.

Results are given in Tables 3.1, 3.2, 3.3 and illustrated in Figure 3.10 for 2-steps and 3-steps predictions. Other Figures (1-,4-,5-steps predictions) can be found in Annexes.

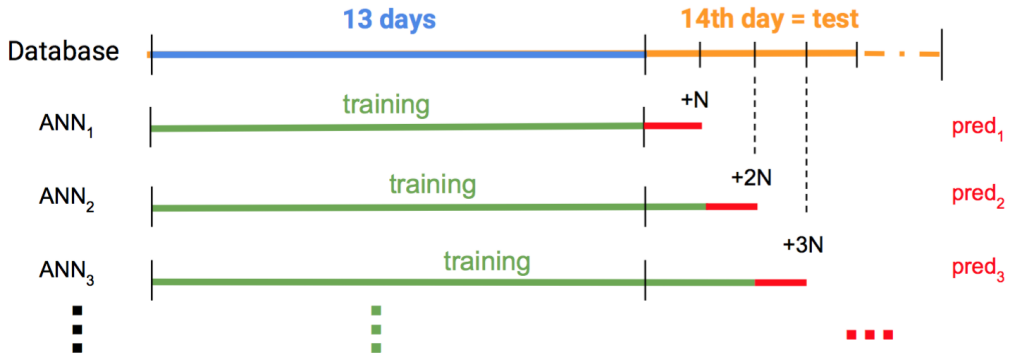


Figure 3.9: *For each N, and for each interval of time K of the 14th-day (i.e. the test set) a ANN (`NARX`) network was built - with the parameters we discussed previously - and a prediction performed.*

For $N \in 1, 2, 3, 4, 5, 6$:

$$\begin{aligned} K &= \lfloor 97/N \rfloor \\ L &= 97 - \text{mod}(97, N) \end{aligned} \tag{3.6}$$

$$\begin{aligned} \overline{RMSE_N} &= \frac{1}{K} \sum_{k=1}^{K} RMSE_N \\ &= \frac{1}{K} \sum_{k=1}^{K} \sqrt{\frac{\sum_{i=1}^{N} (t_i - y_i)^2}{n}} \end{aligned} \tag{3.7}$$

$$
\begin{aligned}
RMSE^{\star}_{tot} &= RMSE(\mathbf{y} = \sum_{k=1}^{K} pred_k, \mathbf{t}) \\
&= \sqrt{\frac{\sum_{i=1}^{L}(t_i - y_i)^2}{n}}
\end{aligned}
\tag{3.8}
$$

Table 3.1: $\overline{RMSE_N}$ $[mmol/L]$

	15 min	30 min	45 min	60 min	75 min	90 min
Original prediction	0.016	0.069	0.139	0.239	0.630	0.749
Smoothed prediction	0.016	0.069	0.141	0.254	0.646	0.793

As we can observe, $\overline{RMSE_N}$ values remain quite low (in view of the BGL range one must control) until 4-steps-ahead (60 min) prediction. Values of original prediction tend to be lower than smoothed ones when N increases, but these small differences are not significant.

Table 3.2: $RMSE^{\star}_{tot}$ $[mmol/L]$

	15 min	30 min	45 min	60 min	75 min	90 min
Original prediction	0.026	0.101	0.204	0.307	0.987	1.062
Smoothed prediction	0.151	0.154	0.165	0.278	0.722	0.801

As we can observe, $RMSE *_t ot$ values remain quite low (in view of the BGL range one must control) until 4-steps-ahead (60 min) prediction. Values are bigger than $\overline{RMSE_N}$ corresponding values. Values of original prediction tends to be lower than smoothed ones for $N = 1$ (15 min) and $N = 2$ (30 min) but when $N \geq 3$, smoothed prediction give better results.

Table 3.3: $Max\ errors$ $[mmol/L]$

	15 min	30 min	45 min	60 min	75 min	90 min
Original prediction	0.185	0.555	1.349	1.375	4.128	5.124
Smoothed prediction	0.763	0.637	0.642	1.095	1.985	3.169

As we can observe, maximal errors values remain quite low (in view of the BGL range one must control) until 3-steps-ahead (45 min) prediction. Error values of original prediction tends to be lower than smoothed ones for $N = 1$ (15 min) and $N = 2$ (30 min) but when $N \geq 3$, smoothed prediction give better results.

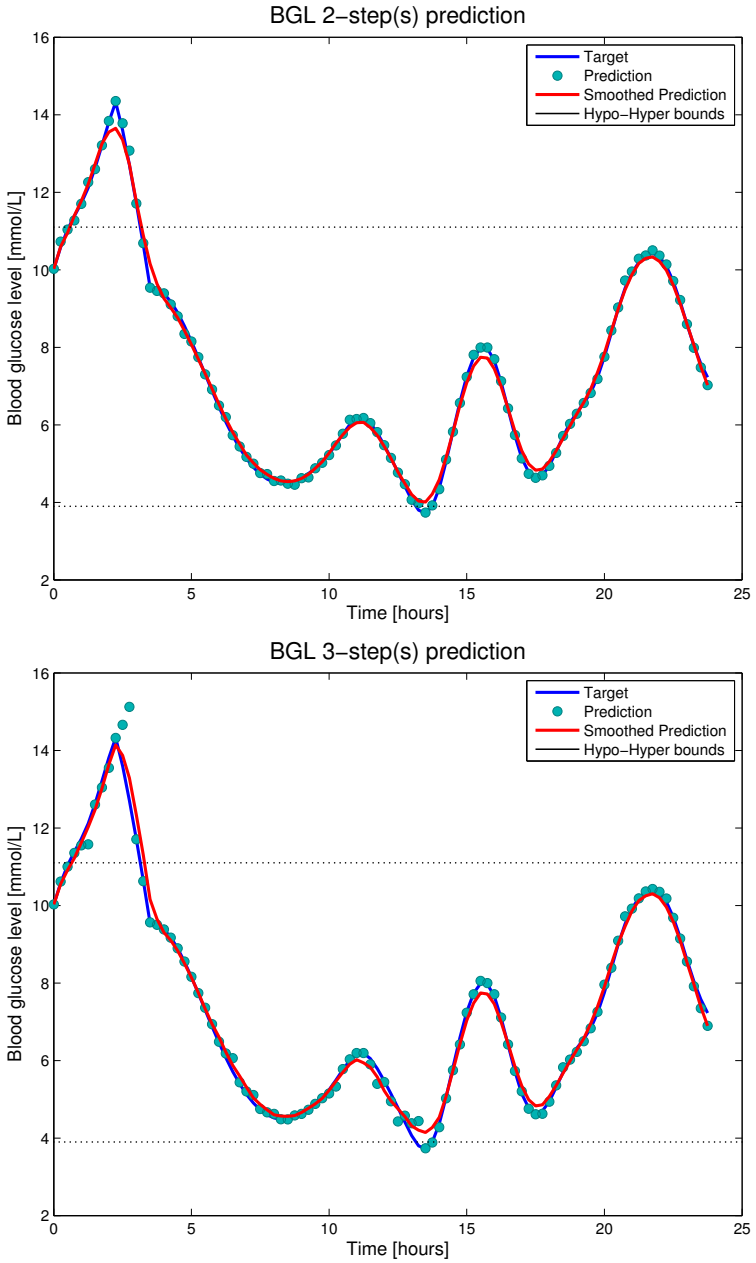


Figure 3.10: *As we can observe, 30 min and 45 min predictions and target values are highly correlated ($R \approx 99\%$). Events of hyperglycemia and hypoglycemia seem to be well detected. Given these results, although it should be validated on clinical data, we conclude our* `NARX` *model is accurate enough and suitable for BGL control of diabetic patients.*

3.5 Discussion

Our designed `NARX`, with RMSE of $0,069$ $[mmol/l]$, $0,139$ $[mmol/l]$ and $0,239$ $[mmol/l]$ respectively for 30−, 45− and 60−min-ahead predictions[4], shows results that are similar (if not better) to those of state-of-the-art algorithms we discussed earlier.

Nevertheless, as we mentioned in section 2.5 we have to keep in mind that direct comparisons are not very relevant, due to methodology differences.

3.5.1 Limitations

AIDA

- **Limited but useful :** in our work and as explained in section 3.2.1, data were simulated with AIDA. However, the authors make clear the limitations of this model. There are many warnings that it should not be used to make predictions for real-life patients' BGLs or to make changes to insulin regimens [1, 54] .

  Despite this limitation, there is still a great value in its capabilities as an educational tool for diabetic patients to manage their condition and in providing simulated data for research purposes. Overall, research projects making use of AIDA have been identified in Australia, Italy, South Korea, the United Kingdom, and the United States. The review in [102] highlights a variety of these projects that have benefited from the free availability of the AIDA diabetes software simulator.

- **Virtual vs real subject :** as highlighted in section 2.5.2, since simulated data do not usually provide realistic enough models of the blood glucose evolution, our results can only serve as a proof of concept of the constructed predictor but cannot be used to quantify its clinical acceptability.

- **Individual variability.** Using more than one virtual patient would have been more relevant to assess the validity of the prediction accuracy of our model. This would allow for interindividual variability to be analysed. On the other hand, we believe that a neural network should be specific to an individual's physiology, and that having trained our `NARX` on more than one patient's BGL data would have been inadequate and would have reduced accuracy.

- **Alternative :** There seems to exist a more valuable diabetes simulator : `Padova` (University of Virginia). Indeed, according to [103], the Food and Drug Administration (FDA) accepted this type 1 diabetes mellitus (T1DM) simulator, equipped with 100 in silico adults, 100 adolescents, and 100 children, as a substitute for preclinical trials for certain insulin treatments, including closed-loop algorithms.

[4]Note that US units for blood glucose levels are $[mg/dl]$ and not $[mmol/l]$, giving us RMSE of 1.24 $[mg/dl]$, $2,50$ $[mg/dl]$ and $4,30$ $[mg/dl]$ respectively for 30−, 45− and 60−min-ahead predictions

Pre-processing

As said earlier, all inputs vectors were normalized as a preprocessing step. In this way, we observed the algorithm converges faster. Furthermore, because we collected quite arbitrarily data and in order to obtain physiologically consistent transitions between BGL measures from one day to another (00:00), we used a moving average filter as a low-pass filter on all the target BGL signal. This is illustated in Figure 3.11.

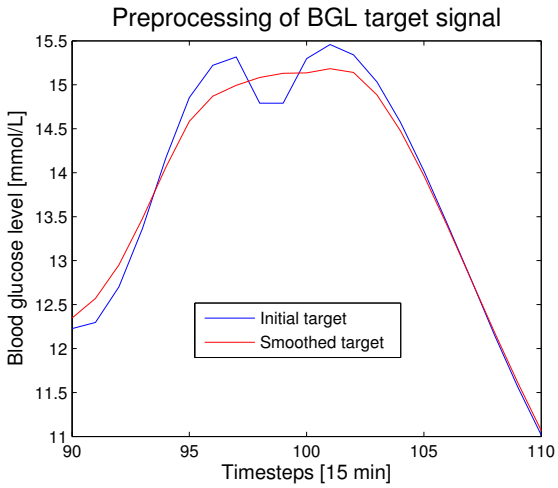


Figure 3.11

However, this pre-processing could have facilitated the modelling not only on inter-day transition BGL measures. A better alternative would have been to apply this filter only locally.

3.5.2 Comparative examples

As we just explained, making relevant performance comparisons is not an easy task. Despite this observation, we give here three illustrative examples : two whose data sources are similar to ours, and another using a similar `NARX` model.

Similar data sources

In [86, 87], a recurrent neural network (RNN) and auto regressive models AR and ARX were trained based on a 30 patient dataset, retrieved from the Padova simulation model. The authors obtained RMSE of 0.27 $[mmol/l]$[5] versus 1.60 $[mmol/l]$ (AR) and 1.44 $[mmol/l]$ (ARX) for the 45-min prediction, while for the same prediction horizon, our `NARX` gave us a RMSE of $\approx 0,14$ $[mmol/l]$.

[5]Note that we converted the original units. $[mg/dl]$ $\times 0.0555 = [mmol/l]$ and $[mmol/l]$ $\times 18.0182 = [mg/dl]$

On the other hand, in [1], the authors claimed having obtained a $RMSE_{5day}$ of $\approx 0.15[mmol/L]$ for BGL predictions of up to 1 hour with an Elman recurrent neural network, also trained from AIDA-simulated data. However, the way the authors calculated their $RMSE$ is quite ambiguous. It appears that their $RMSE_{5day}$ "up to 1 hour" :

- Is the average performance of the four individuals ANNs of different prediction legnths (15, 30, 45, 60 minutes) and;
- Is calculated over five nocturnal (limited) periods (i.e. 18:00 until 6:30 the following day)

In our case, if we average our 15-, 30-, 45-, 60-minutes-ahead RMSE prediction errors, we would obtain $RMSE = 0,115\ [mmol/l]$.

Similar algorithm

In [94] a `NARX` network was built from a samples set of 800 cases, 500 of them being selected for training. Each day was splitted into six measurement points (glucose meter) : ahead/after breakfast, before/after lunch, before/after dinner. The measurement points were further categorized into three intervals: morning, afternoon, and evening. The time of glucose measurement, insulin injection, food intake, stress and exercise were added to each measurement at each time of data recording. A three level scale (low=1, medium=2, and maximum=3) was assigned for stress and exercise.

The performance of the NN was tested on 17 patient's records, each one covers a continuous period of 31 days. The authors calculated an average RMSE of $\approx 0,8$ and $\approx 1,25\ [mmol/l]$ for 20-min and 40-min-predictions respectively.

3.5.3 Ways of improvement

- **Clinical data**, on several patients, are of course crucial to scientifically validate our model.
- **Network inputs :** it is obvious that the more richer is the inputs set of a neural network, the more accurate could be its predictions. Some examples of inputs capable of enhance predictive performance could be, according to the litterature, the following :
  - The use of SOA compartmental models, which of Meal, Insulin and Exercise models discussed in section 2.1 are good examples. Indeed, hybrid machine learning approaches have been shown to be powerful (cfr. section 2.5.3). Note that the Exercise model requires the use of an activity monitor, e.g. the *SenseWear* armband [44].
  - Recently, it has been found that the information of the complex dynamic/pattern of heart rate variability (HRV) could improve the accuracy of hypoglycemia detection [82].

- Besides, there is evidence that others factors such as sleep and stress [15] also account for - smaller but - significant parts in blood glucose evolution. If we were are able to quantify such factors accurately and in an unobtrusive way (SOA sensors ?), it certainly could improve prediction models.

- **Online learning.** In our multistep prediction analysis, several `NARX` were built throughout the test day, for every prediction horizon. Ideally and as the patient's physiology is constantly changing, small adjustments should be made to the weights of the network every time new data is acquired (i.e. every time step). An online (or real-time) learning algorithm should be considered, however, such a network design was beyond the scope of our initial study.

- **Extension to another measuring device.** Note that in our case, simulated data aim at corresponding to continuous glucose monitoring (CGM) measures, providing glucose readings every 15 minutes. However, although it was also out of scope of this project, the constructed predictor can be adapted to simpler glucometers, which provide glucose readings only four or five a day (finger-prick samples). In paper [104] and [94], the authors built neural networks (respectively Elman reccurent NN and `NARX`) with small-size training sets and obtained, albeit obviously less accurate, interesting results.

  As a suggestion, our model could be adapted for small-size training set by defining the target as a weighted combination between a validated compartmental model (e.g. `Padova` simulator) and real measures. This is illustrated in Figure 3.12, where the target BGL was refined by taking into account new measures and using a moving average filter.

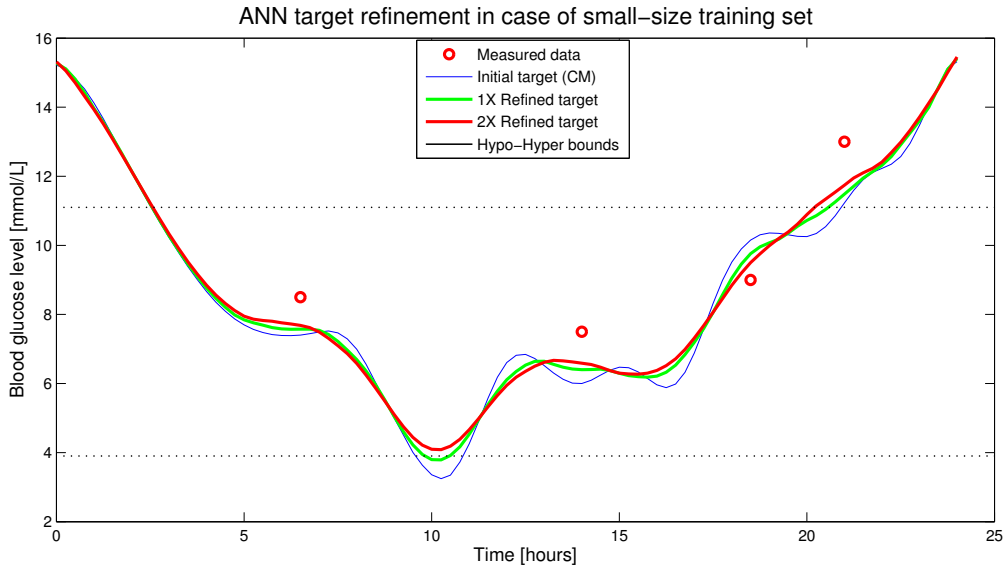


Figure 3.12

In an alternative and simpler manner, compartmentals models could provide inputs to our NARX. Note that a similar, hybrid approach is adopted in [79].

- **Performance metrics :**

  - In addition of RMSE, the Clarke Error Grid Analysis (EGA), accepted as one of the "gold standards" for determining the accuracy of blood glucose meters, could have been chosen as another relevant performance metrics.
  - The main purpose of blood glucose prediction being the detection of hypo- and hyper-glycemia events, perhaps our regression problem could have been turned into a classification problem. In this field, relevant metrics would have been *sensitivity* (true positive rate) and *specificity* (true negative rate).

3.6 Summary

1. On the one hand, auto regressive models are very efficient in modelling seasonal patterns in times series, although such linear algorithms are not the best to cope with non-linearity of blood glucose measurements. On the other hand, recurrent neural networks are very powerful when applied to non-linear regression problems. Still, they encounter difficulty to learn long-term dependencies.

2. NARX, or *nonlinear autoregressive network with exogenous inputs*, are dynamic recurrent neural networks which attempt to combine both approaches, exploiting efficiently history of measurements and taking advantage of the multilayer perceptron architecture.

3. In this chapter, we designed and implemented a NARX network with MATLAB Neural Net Toolbox. Our model had the following characteristics :

   - Data were collected from the freeware diabetes simulator AIDA.
   - Training was performed with :
     i. Series-parallel architecture, allowing us to use the static *backpropagation* algorithm;
     ii. Bayesian regularization learning, preventing the model from overfitting.
   - Optimal performance was found with 6 hidden neurons and delays of 12 time steps.
   - Autocorrelation errors, cross-correlation errors, root mean squared errors (RMSE) and regression analysis were performed to validate the model.

4. Multi-step ahead predictions were performed for 15-, 30-, 45-, 60-, 75-, and 90-minutes prediction lengths on independent test sets. It should be noted that direct performance comparisons in terms of $RMSE$ are not very relevant, due to large methodology differences in the literature. However, our NARX model showed very promising results (e.g. $RMSE_{30min} \approx 0,07$ $[mmol/l]$) comparable to state-of-the-art methods we discussed earlier.

Chapter 4

Empowerment through mHealth gamification

In recent years, mobile applications have become a key driver of mobile Health (mHealth) deployment, especially as a complementary way for self-monitoring. It is foreseen that the market of mHealth app users will reach 2 billion by 2017 [105].

According to Research2Guidance's annual survey, 76 % of mobile health app publishers see diabetes as the therapeutic area with the highest business potential for mobile health. In 2013 only 1.2 % of people with diabetes who own a smartphone or tablet used apps to manage their condition, the latest report found. Research2Guidance is predicting that will increase to 7.8 % in 2018 [106]

Besides, as said earlier, there is evidence that gamifying disease management can help children, adolescents, and adults with diabetes to better cope with their lifelong condition. Gamification and social in-game components are means to keep motivate players/patients and positively change their behaviour and lifestyle.

In this chapter, we will describe best mHealth design principles and key ingredients of gamification, based on literature. Besides, we will review and discuss some successful mHealth apps on the Market. In a last section, in the light of previous observations, we will propose a new design of mobile application : `DiaBeast`.

4.1 The gamification trend

In recent years, gamification, which can be defined as the application of game-design elements and game principles in non-game contexts, has become a trending topic in many fields (see Figure 4.2). Among other examples, gamification attempts to improve user/-customer engagement, organizational productivity, education, communication or physical exercise. Gamification market is growing fast and is expected to worth approximately $5.5 billion in 2018 [107](see Figure 4.3). As illustrated in Figure 4.3, the popular interest in gamification is also reflected in an academic context : the number of papers published on gamification particularly increased from 2010 to 2013 [41].

In their recent report on the mobile gamification, BI Intelligence suggests that the success of gamification represents the fusion of four trends: the explosion of social media usage, the mobile revolution, the rise of big data, and the emergence of wearable computing [108].

Although individual and contextual differences exist, a review of research on the topic has shown that a majority of studies on gamification have found positive effects from gamification [41].

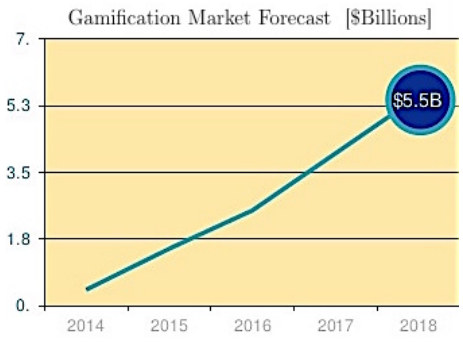


Figure 4.1: *Spending on gamification is expected to grow by 67% year over year and reach $5.5B in 2018. Source : Markets and Markets, M2 Research*

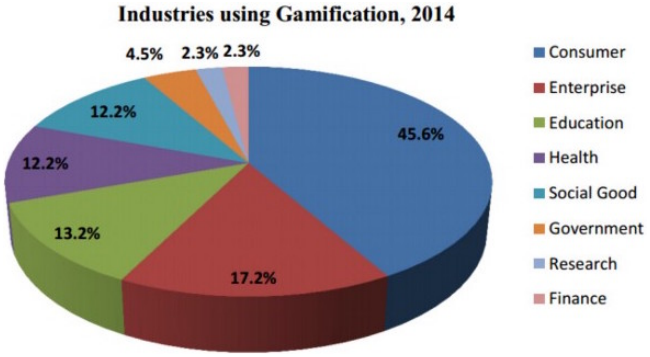


Figure 4.2: *In recent years, gamification has become a trending topic in many fields. Key industries such as enterprise, healthcare and education are showing great promise [109].*

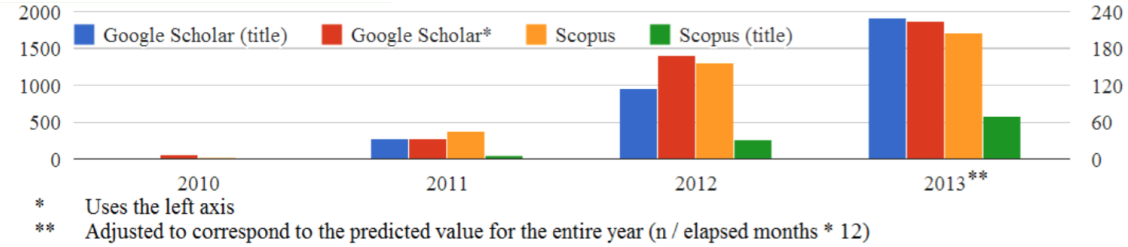


Figure 4.3: *The popular interest in gamification is also reflected in an academic context : the number of papers published on gamification was especially growing between 2011 and 2013 [41].*

4.2 Best mHealth design practices

Despite the high business potential in mHealth market, currently diabetes apps are not meeting the expectations of app publishers, healthcare professionals and diabetic patients. The acceptance rate and usage of diabetes apps within the target group is low. As said earlier, in 2013, only 1,2% of the diabetics with a capable device use a diabetes app. The main reason is that the majority of today's 1.100 diabetes apps do not meet best practice standards [106].

In this subsection, based on well-established reviews and papers from the literature, we will attempt to point out the best design practices for diabetes app and key ingredients of gamification.

4.2.1 Diabetes apps : 7 design standards

According to the *Diabetes App Market Report 2014* by Research 2 Guidance, a mobile applications market analysis firm, there exists 7 best practice elements a diabetes app should take care of. By applying the following design principles, mobile apps would come closer to leverage the potential they have in better supporting diabetes management [110] :

1. **Personalization** : A successful diabetes app should allow the user to choose how data is displayed, how and what information is transmitted to third parties (such as friends, family, social networks, physicians), what metrics are being measured and what are the reference levels for these metrics, taking into account various lifestyle factors. In addidition, based on the data generated by users, diabetes apps should provide customized feedback and actions to improve behavior.

2. **Feedback** : Successful diabetes apps should include a social dimension and create a supportive network (family, friends, health care professionals) to provide coaching and real-time feedback on users progress, in order to sustain behavioral change.

3. **Feature coverage** : A good diabetes app should include all the tools and features that are needed for successfully keeping diabetes under control. Amongst others, it should include tools for tracking insulin, carbohydrate, weight, activity and trend charts.

4. **Integration and interoperability** : Diabetes apps should be designed in a way that allows users to input and access their data through multiple devices from various sources. Ideally, diabetes apps should be integrated with external devices, sensors, databases and other apps, which help users achieve better control of critical health parameters in the management of diabetes (such as BGL, blood pressure, cholesterol), support the necessary lifestyle changes (weight, exercise, nutrition) and provide new ways for connecting patients with their physicians (electronic health records).

5. **Motivational system** : A good diabetes app should include a well-designed motivational system, which engages users, provides incentives for constant use and ultimately leads to behavior change. Best practice apps make full use of gamification elements.

6. **Ease of data input** : The usage should be effortless. Diabetes apps should fit seamlessly into users' lives and routines, making the input of data as easy as possible without requiring too much effort from the users. Solutions should automatically transmit their glucose readings, for instance, from the blood glucose monitor to the mobile device.

7. **Design and user experience** : The aesthetic dimension plays a very important part in keeping users engaged and motivated and, at the same time, it can constitute a powerful differentiation element. Just like with any other app, the design and initial visual impression determines the entire user experience and can definitely determine whether a diabetes app is successful or not. In addition, accessibility should be taken into account for people experiencing disabilities.

Figure 4.4 gives an overview of those best practice dimensions and current status of diabetes apps, according to Research2Guidance.

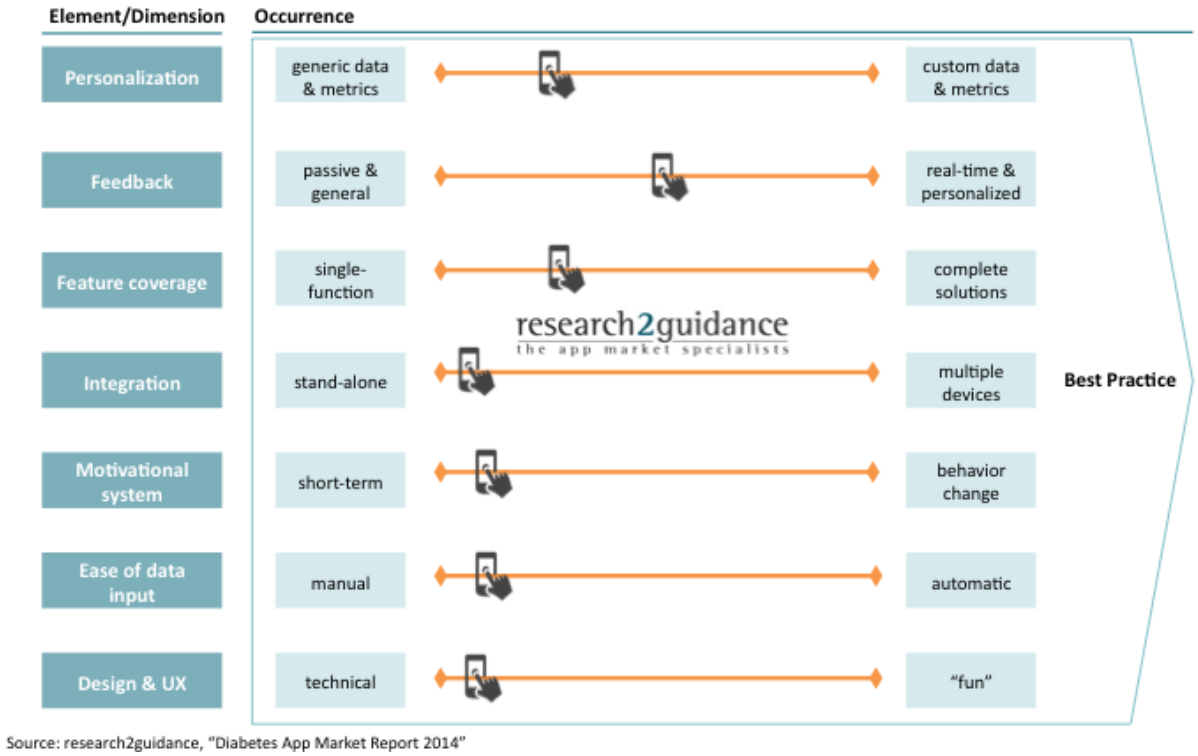


Figure 4.4: Source : [110]

4.2.2 Motivational system : 6 key ingredients

In [111], the author, editorial member of JMIR Serious Games - a journal devoted to research and opinion around gamification - provides a behavioral science view on gamification and health behaviour change. Based on a review of popular gamification taxonomies ([112, 113, 114]), the author identified 6 gamification persuasive strategies that can be enumerated as follows :

1. Clear goals and challenges setting
2. Constant feedback on performance
3. Reinforcement through rewards (not punishments)
4. Progress monitoring and comparison with self and others
5. Social connectivity
6. Fun and playfulness

According to [111], these core ingredients are complementary and indissociable. If we take away some of them, we loose the persuasive capacity of gamification. These strategies, which are the broad principles that make gamification addictive, can be implemented with several tactics, as detailed in the next subsection.

4.2.3 Gamification mechanics : 6 successful tactics

In [115], the authors, researchers at the University of Toronto and members of the Centre for Global eHealth Innovation, define and explain the design considerations around gamification mechanics, together with successful mHealth apps. Essentially based on their work, we are able to list six efficient gamification tactics :

1. **Badges** or trophies are used to identify and reward individual achievements [113]. Zichermann and Cunningham suggest that badges should not be patronizing in their descriptions, such as being over-congratulatory, or by rewarding rote tasks. In addition, badges should be appropriate to the goals of the application. For example, mHealth users should not be rewarded for poor behavior or failing to meet objectives as they are defined by the application. A dashboard should provide a summary of all badges obtained.

   Example : *Fitocracy* is a robust mHealth fitness tracker application that uses badges and which enables users to visualize their performance, and contextualize their personal progress with that of their peers [116]. Ranging from completing a set number of bench presses or pull-ups, from running, to squats, even to the use of the social features of the application, users can achieve “badges” by completing the task described, and refer back to them through their “achievements” dashboard. The achievements are colorful and engaging with different images on each achievement, and there are a sufficient number of badges available to incentivize continued use in motivating the user to attempt to earn them all. This is illustrated in Figure 4.5.

2. **Leaderboards** dynamically rank individual user progress and achievements as compared to their peers. Leaderboards can represent to a user their position relative to others, providing them a sense of how well they are using the application as compared to their peers [117].

   Example : *RunKeeper* is a global positioning system (GPS)-enabled fitness manager application that enables users to initiate and track a number of different activities, set fitness goals, and take on custom challenges as recommended by the application [118]. The application has a very simple, yet engaging leaderboard that can optionally be synced with the user's social network, either through Facebook or via their personal email contacts list. This is illustrated in Figure 4.6.

3. **Points and levels** are implemented to inform the user of their level of familiarity, and reward continued expertise and knowledge using the system [113]. This metaphor for user experience is important to driving social user engagement, as new and potential users are more likely to engage with more experienced users, as evidenced through their point and level values [119]. It is advised that application user experience be reflected through a progressively nonlinear and increasingly more difficult point and leveling system, with ranking or insignia to document progress benchmarks [113]. Progress bars are also a very common feature of points and levels, because user can see how many points they have attained along a continuum, and how many more points they need to acquire to achieve the next level, thus motivating their continued use, especially when they can see they are on the verge of attaining a new level or benchmark.

   Example : *Mango Health* is a medication and nutritional supplement manager application that enables users to input their medications and set reminders for their drug regimen [120]. Users earn points for inputting their medications and taking them regularly and on time. As users accrue points, they "level-up" and, the higher their level, the greater chance they have of winning prizes. This feature is illustrated in Figure 4.7.

4. **Challenges and quests** may keep users motivated to continue using to continue using an application, especially where these challenges validate their understanding of the goals of the application [113]. Challenges and quests are effective methods to drive other gamification mechanics. For example, they can be nested within badges, assigned point values for a leveling system, or quantified to sort users on a leaderboard.

   Example : *mySugr* is a diabetes management application that enables users to manually input blood glucose readings, indicate their mood through a number of creative and descriptive icons, record their dietary habits, provide nutrition facts, and take pictures of their food for ease of recall [121]. Completing daily challenges contribute to a dashboard progress bar that, when full, "tames" their *mySugr* "diabetes monster", a daily avatar that effectively provides feedback to the user regarding whether they have taken adequate steps in managing their diabetes

for the day. Challenges are regularly updated to provide the user sufficient options to keep them motivated to use the application. This is illustrated in Figure 4.8.

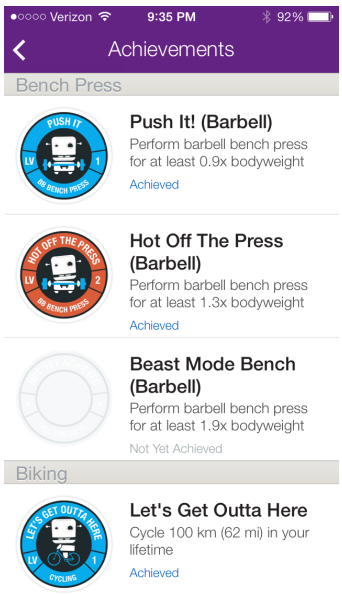


Figure 4.5: *Badges (achievements) - Fitocracy [116]*

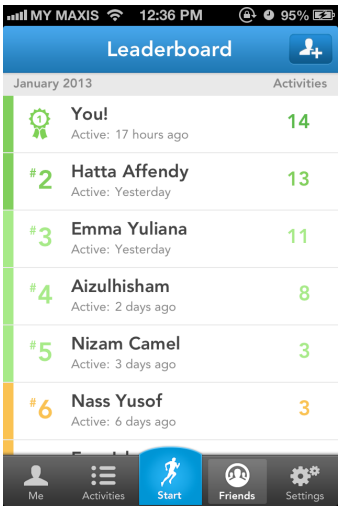


Figure 4.6: *Leaderboard - Runkeeper [118]*

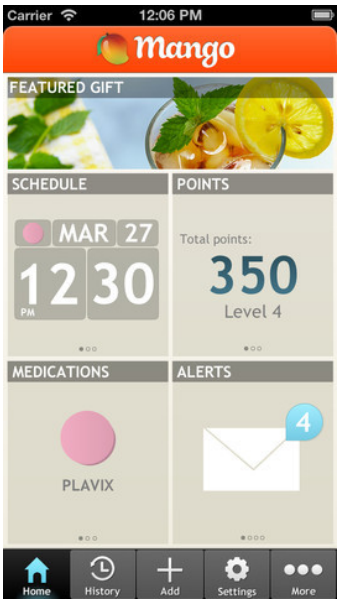


Figure 4.7: *Points and levelling system - Mango Health [120]*

5. **Social engagement loops and onboarding.**

   The development of interactive social networks online has enabled people with diabetes to create supportive online communities and share information about their experiences of living with diabetes [122]. These online communities act as a catalyst in the learning process of the person with diabetes, accelerating behaviour change and adopting of new habits. [123] There is evidence that the integration of social media platforms, such as Facebook and Twitter, have the capacity to motivate continued user compliance [124, 125].

   Implementing social media interface facilitates *social engagement loops* in two notable ways. First, users may wish to share personal data and achievements from their application so as to build social capital with other peers using the same application, as well as to garner support from these peers [126]. Furthermore, these loops mediate *onboarding*, whereby new users are brought into the system via invites from existing users, with new users being further compelled by other implemented gamification mechanics and the inherent benefits they gain by using social media. In turn, these new users may invite peers from their respective social networks to join and participate, thus perpetuating this social engagement loop [113].

   Example : *Diabetic Connect*, the largest community of diabetes patients on the

Web, aims at empowering people living with diabetes through sharing experiences and creating a community of support. With *Diabetic Connect* mobile, it is possible to follow discussions while on the go, ask questions and add comments to interesting posts. It is also defined as a place to discuss treatments, start conversations, and learn from others [127]. This feature is illustrated in Figure 4.9.

6. **Avatars** are unique representations for a player. They usually represent a customizable picture to represent the player in many visual ways across a website, and can be as simple as a Facebook profile picture. Games that use Avatars show a high emotional attachment between the player and the game. As the users customize their avatar, they create a bond, the avatar becomes an extension of themselves [128].

   According to Michael Fergusson, CEO and founder of Ayogo - a company that uses game psychology to design social games and apps to engage, educate and empower patients with chronic conditions - healthcare game designers are often neglecting the human aspects and avatars are personal elements which is missing for engaging people [129].

   Example : The application *Avafeed* uses a virtual avatar and gaming to help make choosing healthier food options easier among children [130]. Note that *mySugr Junior* adopted the same strategy [121]. This is illustrated in Figure 4.10.

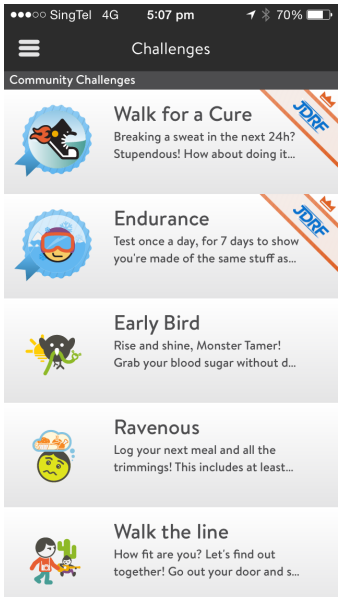


Figure 4.8: *Challenges - MySugr [121]*

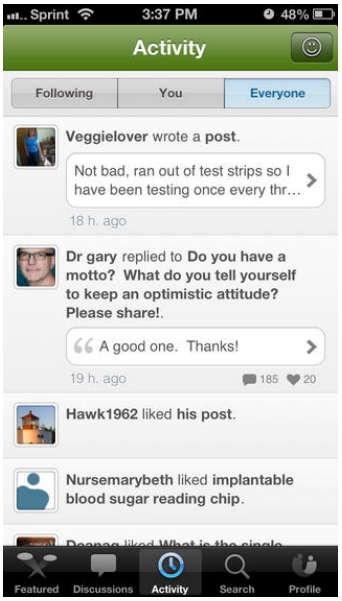


Figure 4.9: *Social engagement - Diabetic Connect [127]*

Figure 4.10: *Avatar (for children) - Avafeed [130]*

4.2.4 Gamification efficacy : 3 validated mHealth apps

Bant

Bant is a gamified diabetes management application, that is able to capture data from the user's blood glucose meter over Bluetooth automatically [131]. To encourage the use of the application by the diabetic adolescents, the developers had introduced a reward algorithm. The app produced a code to download songs, games and other applications free from the Apple iTunes store if the patient maintained a good practice in measuring glucose in the blood throughout the day. Furthermore, it was also checked whether the adolescent shared the results of tests with their parents and doctors.

Although it cannot be shown the improvement was solely attributable to gamification, a pilot of *Bant* with 20 adolescent children with type 1 diabetes showed nearly a 50% increase in the frequency of their daily measurements in comparison with previous routines. In addition, 88% of patients said that they felt satisfied with the app and that they would continue to use this system for controlling glycaemia. Exit interviews indicated that the reward system was motivating to the participants [42, 115].

mySugr

According to a recent *mySugr* usability engineering study with 20 type-1 diabetes participants, 95 percent (n = 19) were still actively using the application after 1 month, 90 percent (n = 18) after 2 months, and 85 percent (n = 17) after 3 months' use [132, 115]. Although it has yet to be seen whether this application has the capacity to incentivize adherence over a longer period of time, the preliminary usability study data are promising. Note that *mySugr* is FDA (Food and Drug Administration) cleared [133].

SuperBetter

SuperBetter is available as both a computer-based and iPhone application. The gamified system takes a holistic health approach in aiming to address physical, emotional, mental, and social health through the completion of a series of challenges [134]. The system was developed by McGonigal and contains applications of the examples discussed in her book [135]. Users are asked to provide their reason for using *SuperBetter*, and given options such as "depression" or "anxiety", for which the system presents a series of quests, each of which the user can specify they completed by clicking an affirmative link with the text "I DID THIS!"

SuperBetter, which utilizes most of the mechanics outlined in this section, is validated in two clinical studies:

1. A randomized controlled study conducted by the University of Pennsylvania found that playing *SuperBetter* for 30 days significantly reduces symptoms of depression and anxiety, and increases optimism, social support, and player's belief in their own ability to succeed and achieve their goals. They also found that *SuperBetter* users were significantly happier and more satisfied with their lives [136].

2. A clinical trial funded by the National Institutes of Health and conducted at Ohio State University Wexner Medical Center and Cincinnati Children's Hospital found that using *SuperBetter* improves mood, decreases anxiety and suffering, and strengthens family relationships during rehabilitation and recovery [137].

4.3 Market analysis : Most popular diabetes apps

It was found in [138] that there are no clear differences in ratings between paid and free apps, although more expensive apps tended to have poorer ratings. In this section, based on iTunes store, Android PlayStore ratings and [139] we will review the top 8 free apps for diabetic patients, in view of the best design practices we just discussed.

For each of the top 8 free apps, and for each of the design criteria, we will give a rate on a scale from 0 (i.e. the app did not include the corresponding feature) to 3 (i.e. the app fulfilled the "best design" expectations). More specifically, our analysis and ratings focused on the followings 7 criteria :

1. Personalization

    - Possibility to choose the metrics ($[mmol/l]$ or $[mg/dl]$) and reference bounds
    - Customizable data display
    - Possibility to choose how much information to share, with whom and when
    - Tailored (user, lifestyle) feedback

2. Social dimension

    - Possibilty to find answers and support from others ("friends", "followers") in diabetic community
    - Possibility to easily share information (SMS, mails) with family (especially important when the patient is a child), health care providers, physician

3. Feature coverage

    - Blood glucose tracking
    - Diet tracking
    - Exercise tracking
    - Insulin dose estimator
    - Customizable (medication) alarms and reminders
    - Blood pressure, sleep, mood, heart rate tracking
    - Blood glucose levels prediction (detection and prevention of hypo-, hyperglycaemia events)

4. Integration and interoperability

    - Supported on multiple devices from various sources (Android, iOS, PC, Macintosh, Web, ...)

- Shareable electronic health records (with health care providers, physicians)
- Compatible with sensors, blood glucose measuring devices, insulin pumps and other related apps (e.g. iOS Health)

5. Motivational system (gamification)

   - Feedback on performance
   - Goals and challenges
   - Progress monitoring (points, levels, leaderboards, badges)
   - Fun and playfulness (avatar, quests, ...)
   - Virtual vs tangible rewards

6. Ease of data input

   - Automatic transmission of glucose readings from the glucose monitor to the mobile device
   - Food and exercise database
   - Food barcode scanner
   - Compatibility with sensors (e.g. exercise, heart rate, podometer) and automatic transmission

7. Design and user experience (although quite subjective)

   - Aesthetic dimension
   - Usability, ergonomics
   - Accessibility (for people who experience disabilities)

In addition, noticeable strength(s) and weakness(es) were also reported for each app. Results are synthesized in Table 4.1.

According to our analysis, we are able to make several important observations :

i) No app is perfect, but all apps are somehow complementary in their features. As examples, *Diabetic Connect* is the only app dealing efficiently with the social dimension (despite the abundant and supportive literature [124, 125, 123, 122, 140, 141]) *Glooko*, being compatible with various devices, offers the best interoperability, while *mySugr* benefits from a great motivational system.

ii) Although chronic hyperglycemia and hypoglycemia can lead to severe complications (e.g. retina damage, kidney, neurological, cardiovascular) that may be life-threatening, none of the 8 most popular free apps offers a BGL prediction tool.

iii) Most of the apps do not propose any gamified motivational system. In addition, although the pilot study [42] suggests tangible rewards are an efficient way to enhance patients motivation, no app offers such a feature.

Table 4.1

Top 8 free diabetes apps								
Criteria	*BG Monitor Diabetes*	*BlueLoop*	*Diabetes in Check*	*Diabetic Connect*	*Glooko*	*Glucose Buddy*	*mySugr*	*On Track Diabetes*
Market ratings	4.5	4.25	4	4.5	4	4.25	4.75	4
Personalization	1	1	1	1	1	1	2	2
Social dimension	0	1	1	3	0	1	0	0
Feature coverage	2	2	2	0	2	2	2	2
Integr. & Interop.	1	2	1	2	3	2	2	1
Motivational sys.	0	0	1	1	0	0	3	0
Data input (ease)	2	1	2	1	3	2	2	1
Design & UX	3	2	3	2	2	3	3	3
Strength(s)	*Photo log of meals, tags*	*Text messages btwn Family/HCPs*	*Food barcode scanner, Daily tips, Meal planner*	*Ability to find large support*	*Syncs with numerous devices, web platform*	*Sync with web platform, forum, reminders*	*Fun, Sync with 1 glucose reader, Hba1c estimator, Mood tracker, Photo log*	*Simplicity, usability, design*
Weakness(es)	*(*)*	*(*)*	*(*) + Bugs*	*(*) + Weak feature coverage*	*(*) + Paying online subscription*	*(*)*	*No (short-term) BGL prediction*	*(*)*

(*) = The app does not include a BGL prediction tool, nor (motivational) gamification mechanics.

4.4 Towards the design of *DiaBeast*

Based on best design practices we have listed so far, and observations we made from the app market analysis, we briefly suggest in this section the design of a diabetes app which aims to gather all the successful mHealth and gamification ingredients we discussed previously.

This app would include six tools :

1. Dashboard ;
2. Health tracker ;
3. Challenges ;
4. My DiaBeast ;
5. Community ;
6. and Rewards,

whose features are shortly described in Figure 4.11. Further details will be provided in the following subsections.

Figure 4.11

4.4.1 Health tracker

This tool, which is directly related to three of our seven considered design criteria (i.e. feature coverage, integration and interoperability, ease of data input) is of utmost importance.

1. **Ease of data input.** Many diabetes apps are limited in that they require manual entry of blood glucose data [142, 106] meals and activities, which requires significant patient effort and time commitment. However, there exists interesting alternatives to address this issue :

   (a) Bluetooth adapters allow the user to wirelessly transfer its glucose readings from glucose meters to both iPhone and Android devices. As an example, *Glooko* developed the *MeterSync Blue* (see Figure 4.12), compatible with more than 30 FDA cleared glucose meters. Note that *Bant* and *mySugr* apps - that we also introduced earlier - opted for similar (although less compatible) technologies.

Figure 4.12: *MeterSync Blue by Glooko. Taken from [143]*

   (b) The *SenseWear® Pro* (see Figure 4.13) is a wearable armband developed by *BodyMedia* to enable automatic monitoring of physical activity (energy consumption, steps counter), heart rate and sleep efficiency. It employs a multisensory array composed of a 3-axis accelerometer, a near-body ambient temperature sensor, a skin temperature sensor, a heat flux sensor, a sensor for galvanic skin response and ECG electrodes worn on the arm and shoulder. Because there is evidence that exercise, sleep [24, 25, 26] and heart rate [144, 145] are variables closely related to blood glucose evolution (e.g. it

affects carbohydrates metabolism, glucose intolerance, insulin resistance), it appears suitable to track them, in an unobtrusive and non-invasive way. Such variables, provided as inputs, are able to significantly enrich our Machine Learning `NARX` model, as suggested in [82].

Moreover, in [146], it has been shown that the approach of multisensor technology (*SenseWear® Pro Armband*) with integrated data analysis can provide satisfying estimates of plasma glucose concentration in diabetes without requiring continuous blood glucose measures.

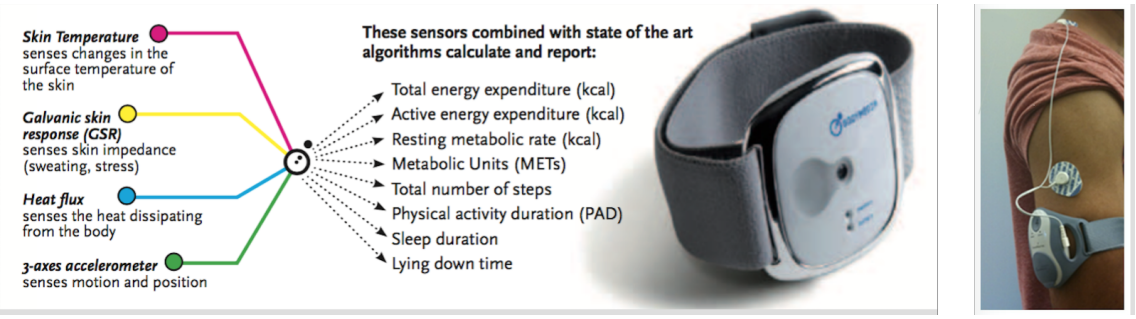


Figure 4.13: *Left : the SenseWear® Pro Armband employs four physiological sensors. Combined with machine learning methods, the system is able to calculate in real-time (amongst others) physical activity duration, energy expenditure, sleep duration. Right : The armband can easily be coupled with ECG electrodes and capture heart rate. The figure is adapted from [147, 148].*

(c) Besides, inspired by apps such as *Diabetes in Check* and *Fooducate*, the "ideal" app should provide a food barcode scanner as well as a large database of food graded products and physical activities in order to facilitate manual entries.

2. **Feature coverage**

(a) As mentioned earlier, chronic hyperglycaemia and hypoglycaemia can lead to severe complications such as retina, kidney, neurological or cardiovascular damage that may be life-threatening if left untreated. Hence, we consider the app should offer a blood glucose levels **prediction tool**, allowing the user to efficiently detect and avoid such undesirable events. As described throughout Chapter 2, there exist several algorithms for that purpose. As an example, we suggest here the deployment of the promising `NARX` model we designed and implemented in MATLAB in Chapter 3. To that end, there exist two ways :

i. Recode our `NARX` model in Java, C, C++ (Android) or Objective-C (iOS). Note that MATLAB CODER^{TM} is an add-on product that generates readable and portable C and C++ code from MATLAB code. Nevertheless, this tool supports a limited range of toolboxes of which *Neural Net* unfortunately is unfortunately not part.

ii. Deploy our MATLAB code as a web service that the mobile application would call. The add-on products MATLAB *Builder JA* and MATLAB

Builder NE allow to convert MATLAB code to standalone Java components or to .NET assemblies respectively. We can then implement a web service in Java or .NET depending on our preference, and call the deployed component in a more scalable way [149, 150].

(b) Another major limitation of many apps is that they do not use inputted data to help patients determine their daily insulin doses. Most often the patient has to rely on hand calculations based on insulin-to-carbohydrate ratios provided by health care professionals [142]. Such calculations are not straightforward and have to integrate expected carbohydrate intake, measured blood glucose levels, past insulin doses for postprandial ("mealtime", "short-action") doses, and ideally take into account individual lifestyle behaviour (e.g. planned exercise) for basal ("long-action") doses. In addition, the use of a smartphone - an object not typically associated with medical care - may offer a discrete way to determine dosage in social situations like mealtimes. **Automated insulin dose calculations** are thus a desirable feature in diabetes mobile apps.

On the other hand, according to [151], the majority of existing insulin dose calculator apps provide no protection against, and may actively contribute to, incorrect or inappropriate dose recommendations that put users at risk of both catastrophic overdose and more subtle harms resulting from suboptimal glucose control. Hence there is a need for an accurate modelling of glucose-insulin dynamics, which could - again - be offered (although it would necessitate further development beyond the scope of our work) by adapting complex models such as our `NARX` network.

(c) Other features should include meals and activities planner (possible sync with Google Calendar), healthy recommendations (e.g. healthy recipes, from the large database) and customizable reminders.

3. **Integration and interoperability**

(a) As discussed earlier, diabetes apps should be designed in a way that allows users to input and access their data through multiple devices from various sources : e.g. iOS, Android devices, tablets, smartphones, computers. This can be achieved through *Responsive Web Design* (RWD), which aimed at allowing desktop webpages to be viewed in response to the size of the device one is viewing with [152]. Typically, a site designed with RWD adapts the layout to the viewing environment by using fluid, proportion-based grids, flexible images, and *CSS3* media queries.

(b) A basic and indispensable feature required in a diabetes app is the possibility to export *electronic health records* in order to efficiently connect patients with their physicians and share data.

(c) Finally, the app should be compatible with external devices such as sensors (already discussed in last subsection), and others apps, e.g. the iOS Health app.

Features are synthesized in Figure 4.14, here below.

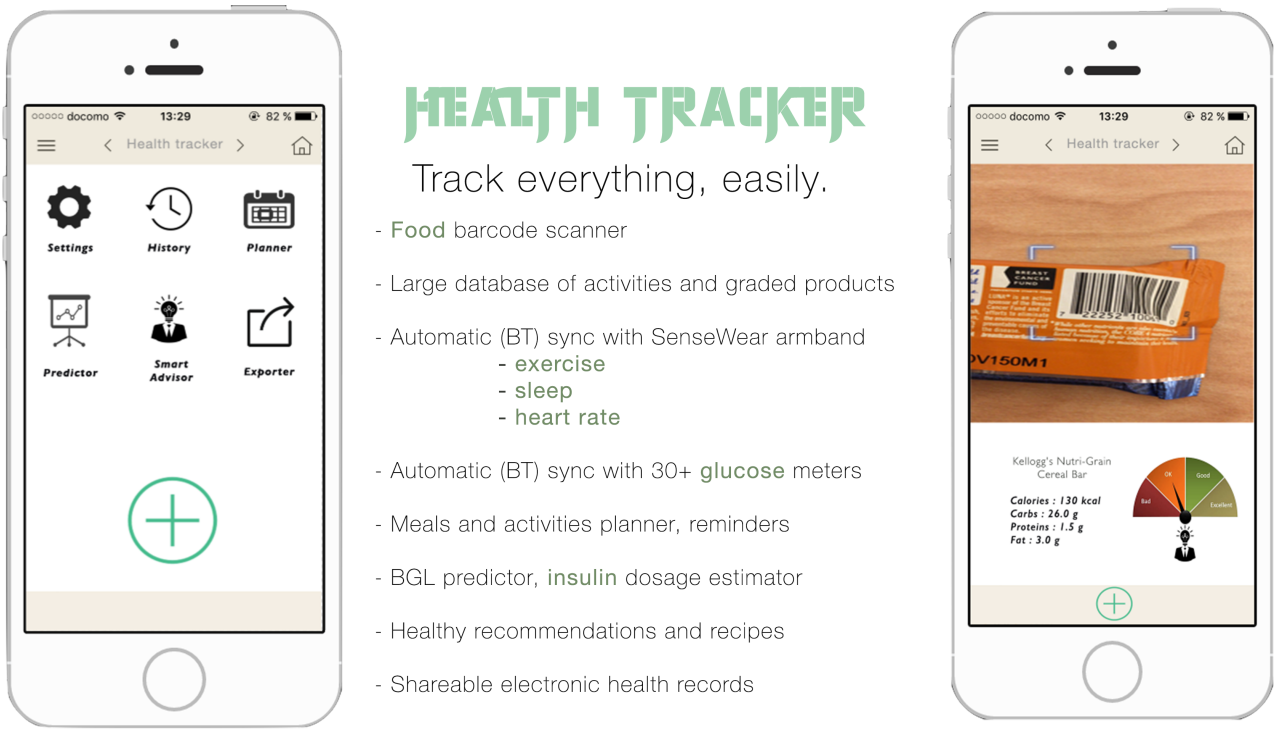


Figure 4.14

4.4.2 Motivational system

As stated earlier, the design of a motivational system is of great importance to enhance patient compliance. There is evidence that the use of gamification can keep users engaged, of which some very interesting examples in mHealth include *SupperBetter*, *Bant*, and *mySugr*, as seen in Section 4.2.4.

On "My Diabeast" (see Figure 4.16) and "Challenges" (see Figure 4.15) screens of which main purposes are, respectively, to allow the user to monitor their progress and motivate him to excel, our design focused on the combination of successful gamification mechanics (the social dimension being considered separately) and incorporates :

1. Customizable avatar (an anonymous "beast" able to evolve, or any profile picture)
2. Levelling system and points.
   (a) In our case, we suggest the use of five progress bars, related to :
      i. Blood glucose control
         ↪ *Proper recording of readings, glycemia variability, hypo/hyper events*
      ii. Perservance

↪ *App usage frequency, compliance*

iii. Weight loss objective

iv. Physical activity

v. Diet

(b) Points, closely linked to rewards, are represented if the form of virtual money, and are mainly earned by completing specific actions : the "Challenges".

(c) Note that personal goals and difficulty should be set in agreement with patient's physician.

3. Challenges may include, amongst others :

   (a) Avoiding any hypo- or hyper-glycaemia event 3 days in a row ;

   (b) Properly recording BG readings 3 days in a row ;

   (c) Eating "healthy" 5 meals in a row ;

   (d) Running a total distance of 10 kilometers ;

   (e) Using the app 3 days in a row ;

   (f) Complete a 10-question quiz on diabetes (self-management education) ;

4. Badges (as well as virtual money) are earned for each completed challenge

5. Inspired from the pilot study [42] and feedback I received during my visit in Keio University (Tokyo), concrete rewards should be afforded with users accumulated points (virtual money). Although it should necessitate further investigation beyond the scope of this work, such rewards may include, for instance :

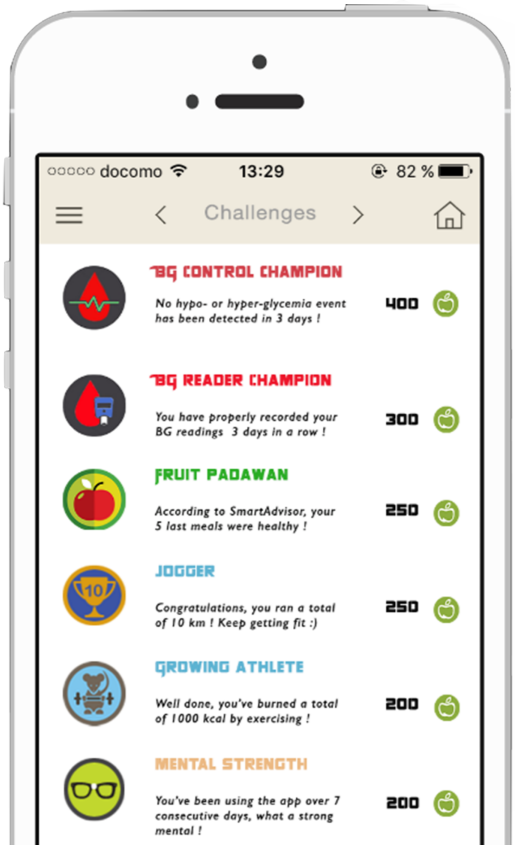
   (a) iTunes gift card

   (b) Facebook game credits

   (c) All kinds of discounts on sport products (e.g. sportswear, facilities)

   (d) Gifts from family and friends ("sponsorship deal")

Figure 4.15



CHALLENGES

Challenge yourself !

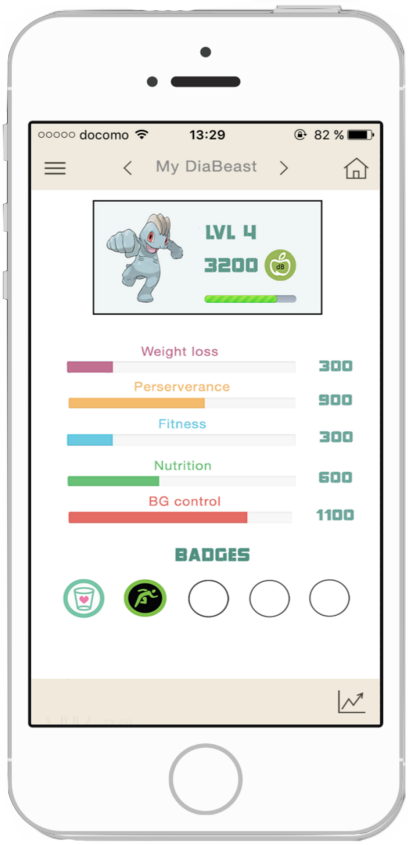
Meet our challenges and earn more

- Put your body and your mind to the test
- Gain experience and evolve ur Diabeast

REWARDS

Get what you deserved !

- Convert your into sthg you like



MY DIABEAST

Monitor your progress

- Watch your DiaBeast evolution in terms of
  - Weight loss
  - Perseverance
  - Fitness
  - Nutrition
  - Blood glucose control
- Look at the badges you earned until yet
- See daily, weekly and monthly charts

Figure 4.16

4.4.3 Community

As stated previously, online communities act as a catalyst in the learning process of the person with diabetes, accelerating behaviour change and adopting of new habits. [123] Interactive social networks online enables people with diabetes to get support and share information and questions about their experiences of living with diabetes [122]. There is evidence that the integration of social media platforms, such as Facebook and Twitter, have the capacity to motivate continued user compliance [124, 125].

Therefore, inspired from *Diabetic Connect*, it appears of utmost importance to incorporate a "Community" platform in our design, as illustrated in Figure 4.17.

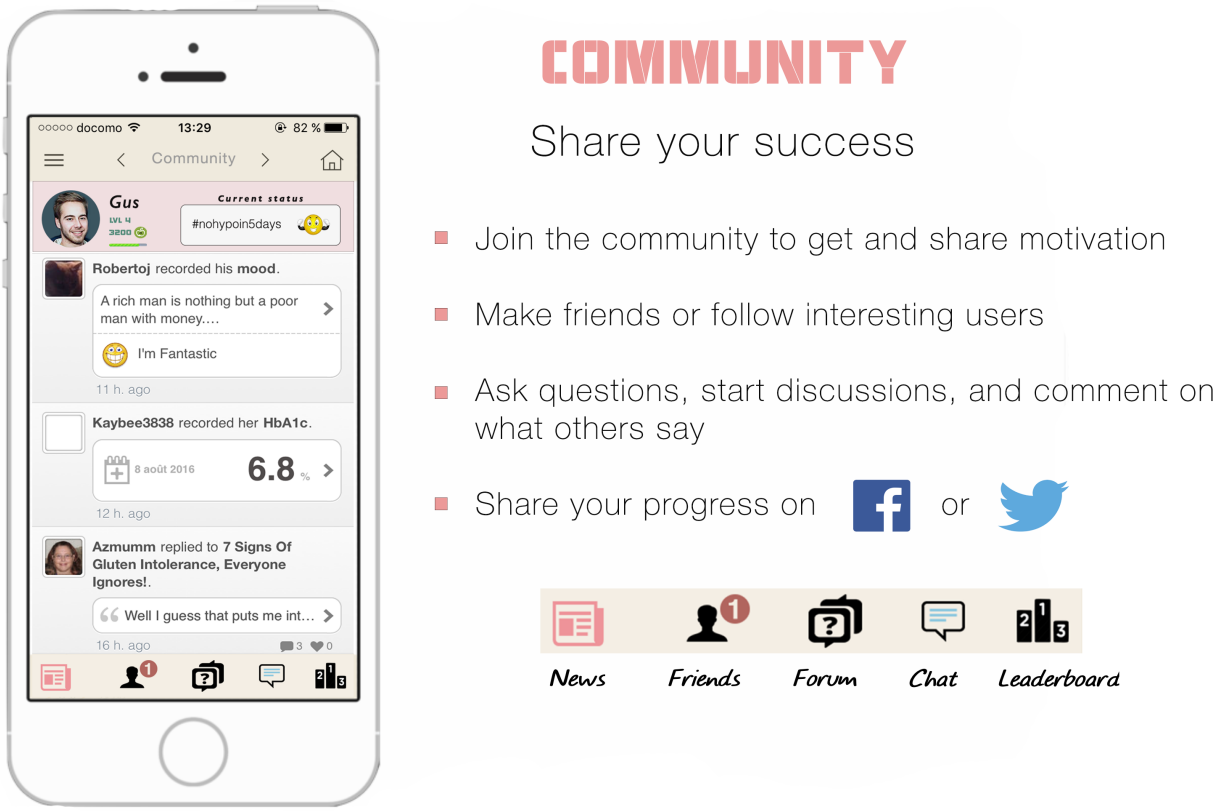


Figure 4.17

4.4.4 Dashboard

Great feature coverage is often correlated with poorer usability. The purpose of this tool is to combine, synthesize and display important information from other tools in a concise and clear way. Although aesthetics can certainly be improved, Figure 4.18 illustrates how this tool should like in my opinion, including :

- Daily summary of activities (exercise, meals, blood glucose trends)

- Possibility to add new entries
- Notifications from other tools (community, challenges, tips, ...)
- Current status of the avatar (points and level)
- Prediction on blood glucose evolution, in order to avoid hypoglycaemia and hyperglycaemia events.

Figure 4.18

4.5 Discussion : limitations

Because we adopted a mostly qualitative and illustrative approach throughout this chapter, some limitations need to be discussed.

1. Note that adopting gamification (being a "hype") may be a risky undertaking but has merit when used in the right way, under the right circumstances. According to [111], core ingredients we enumerated in section 4.2 are complementary and indissociable. If we take away some of them, we loose the persuasive capacity of gamification.

2. In section 4.2, some design principles may slightly overlap in their implementation. That's why we only used 7 design criteria in our analysis in section 4.3.

3. Note that there is no standardized methodology for rating mHealth applications qualitatively, particularly as regards their Design & UX. Even if Table 4.1 is based on well-defined criteria, some ratings may appear a bit subjective, depending mainly on users comments, ratings and my observations.

4. In section 4.4, based on best design practices, and observations we made from our app market analysis, we proposed a diabetes app design which aims to gather all the successful ingredients we discussed so far. However, we do not pretend our solution is unique and flawless, but essentially illustrative of interesting concepts. In addition, further investigation should be performed, e.g. :

   (a) Further personalization. Note that our design, incoporating a lot of gamification mechanics and focusing on hypoglycemia avoidance, seems more suitable to manage insulin-dependent diabetes (type 1) of teenagers and young adults. However, we could further personalize and adapt the design based on user profile (age, user frequency, gender, preferences), and diabetes type.

   (b) Create a poll, meet diabetic patients and health care professionals and get their feedback to validate our approach;

   (c) Contact brands, organizations or any person likely to help us shape our "Concrete Rewards" service. Note that the idea of concrete rewards is inspired from my visit to Keio University in Tokyo - where this topic was closely related to another student's master thesis - as well as from the pilot study [42]. A more realistic alternative could be seeking for a sponsorship from family members and friends.

   (d) Develop a system to detect and avoid cheating. This could be achieved by analysing (automatically) relevance of input data and progress, and setting personal health objectives in agreement with the physician.

   (e) Deploy our MATLAB implementation of the BG predictive `NARX` model to the Web;

4.6 Summary

1. It is foreseen that the market of mHealth app users will reach 2 billion by 2017 [105]. 76 % of mobile health app publishers see diabetes as the therapeutic area with the highest business potential for mobile health.

2. In 2013 only 1.2 % of people with diabetes who own a smartphone or tablet used apps to manage their condition. Research2Guidance is predicting that will increase to 7.8 % in 2018 [106]

3. The acceptance rate and usage of diabetes apps within the target group is low. The main reason is that the majority of today's 1.100 diabetes apps do not meet best practice standards [106].

4. Best practice standards can be distinguished into 7 criteria [111, 115, 106, 113] :

   (a) Personalization
   (b) Social dimension
   (c) Feature coverage
   (d) Integration and interoperability
   (e) Motivational system (gamification)
   (f) Ease of data input
   (g) Design and user experience

5. In section 4.3, we reviewed the top 8 free apps for diabetic patients. According to our analysis, we made several important observations :

   (a) No app is perfect, but all apps are somehow complementary in their features. As examples, *Diabetic Connect* is the only app dealing efficiently with the social dimension (despite the abundant and supportive literature [124, 125, 123, 122, 140, 141]) *Glooko*, being compatible with various devices, offers the best interoperability, while *mySugr* benefits from a great motivational system.

   (b) Although chronic hyperglycemia and hypoglycemia can lead to severe complications (e.g. kidney, neurological, cardiovascular, retina damage), none of the 8 most popular free apps offers a BGL prediction tool.

   (c) Most of the apps do not propose any gamified motivational system. In addition, although the pilot study [42] suggests tangible rewards are an efficient way to enhance patients motivation, no app offers such a feature.

6. Although individual and contextual differences exist, a review of research on the topic shows that a majority of studies on gamification find positive effects from gamification [41].

7. In mHealth, the design of a motivational system is of great importance to enhance patient compliance. There is evidence that the use of gamification can keep users engaged, of which some very interesting examples in mHealth include *SupperBetter*, *Bant*, and *mySugr*, as seen in Section 4.2.4.

8. Adopting gamification (being a "hype") may be a risky undertaking when misused. According to [111], core ingredients we enumerated in section 4.2 are complementary and indissociable.

9. Gamification mechanics - that implement key ingredients - include badges, leaderboards, points and levels, challenges and quests, social engagement loops, rewards and avatars.

10. In section 4.4, based on best design practices and observations we made throughout the chapter, we propose the design of a diabetes app (*DiaBeast*) with aim to gather all the successful ingredients we have discussed.

Chapter 5

Case study : Eglé

Composed of experts in artificial intelligence, software engineering, public health and social sciences, the Eglé team has for mission to support patient empowerment through the development of a scalable platform of multimedia tools, designed to improve medical care and foster communication between the patient, the family and health professionals.

Though still in development, the Eglé platform comprises a structured set of medical knowledge; a communication tool allowing the patient or relatives to receive and send data; a personalized system for monitoring the patient's health on a daily basis; and a dedicated area for information exchange and communication between health professionals [153].

Because Eglé, making use of artificial intelligence and user-centred design, is closely linked to my master's thesis, it appears meaningful to dedicate a chapter to shortly describe the architecture, algorithms and user interface of the platform, and discuss it in light of previous observations.

5.1 Summary of Eglé Project Goal

Eglé project aims at the development and evaluation of a new intelligent information and management system by and for patients living with chronic disease. The entire project, still under development, will be validated on two specific diseases for which patient information to the care team can significantly improve treatment : Alzheimer and Diabetes (adult and pediatric). In this chapter, we will only consider this latter.

Eglé addresses this challenge by developing a dedicated and scalable Web platform that aims to automate intelligent processing, aggregation and distribution of digital content from large volumes of multi-format data that make up the medical record. The design of this system is based on the merge of known expert medical knowledge and trustworthy recommendations of associations of patients with the patient's medical data, whether acquired by the medical team or by the patient himself.

This smartly structured and annotated information is filtered and presented to the patient through an intuitive interface, whose originality lies in the comprehensiveness of the proposed approach: the integration of patient organizations and medical team in to a unique platform for a two-way communication. The ultimate goal of this information exchange platform, through the presentation of personalized data, is to empower the patient throughout his treatment.

5.2 Architecture

Note : Most of the following section (figures and content) is adapted and inspired from the annual report [154] and from my test of the (beta) app available on `https://beta.egle.be/`

5.2.1 Technology identification and selection

The desire to offer a platform that does not require installing any software and use on smartphone or tablet has largely guided Eglé design choices.

Chosen technologies consist of a *full stack* environment (concerning both the client side and server) that is MEAN.JS (composed of Node.JS, MongoDB, Angular.JS). The programming language is from stem to stern JavaScript and HTML5 for the user interface, while Python is mainly used for the artificial intelligent module. It should be noted that MEAN.JS is a relatively recent technology (less than 5 years), but has gained notoriety and a very important community, one of the most active in the field of web application development. This choice facilitated and accelerated the development of the platform.

The second design choice concerns the video chat feature. For the same reasons of accessibility (no plugin to be installed by the user, use of smartphone / tablet etc.), the choice fell on the WebRTC (Web Real-Time Communications) technology, which can be set

up very quickly by using free servers. However, given the sensitivity of the information submitted, one server is deployed in `HealthCompass` infrastructure so that no information is channeled through non-controlled servers. The implementation of this server was more complex, but properly achieved, based on an "open source" implementation.

One of the chosen development strategies is to widely disseminate the source code in a "viral" way, particularly through associations of diabetics to reach and educate as many actors as possible and ensure sustainability of the product. The code is available on *GitHub* directory of UCL[1] and the prototype is online via the address: `https://beta.egle.be/`.

Note that the role management and access permissions to the data required the implementation of a complete ACL (access control list) model, allowing the management of permissions for each feature of the platform. This model, illustrated in Figure 5.1, also allows management of the choice of specialized interfaces.

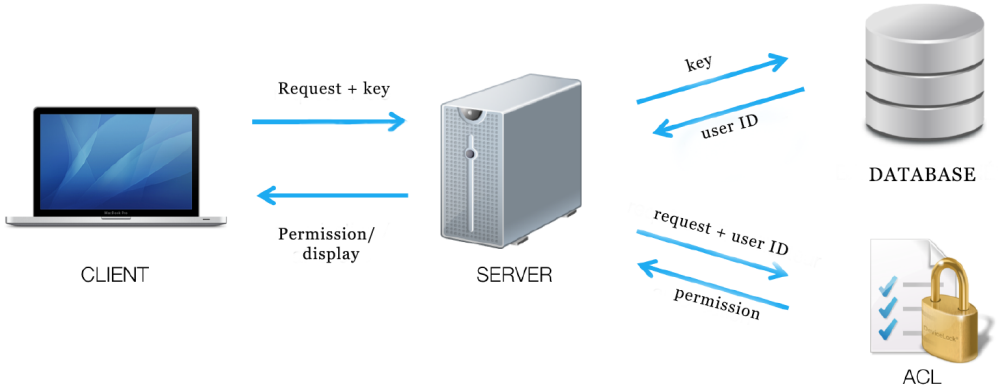


Figure 5.1: Overview of request (query) processing, including an ACL model

5.2.2 Personalized user interface

The main objective of this work package is the development of the portal and services "front-end" for access, management and data exchange between patients and health care professionals. Particular attention is paid to "man-machine" interface to facilitate the best use of the developed tools. Access to information, the adding of medical data or the communication between patient and physican should be as intuitive as possible for both parties. To achieve this level of interaction, the platform aims at customizing, automatically, the user interface based on the context of the pathology and the user profile (e.g. age and user frequency).

[1] `https://github.com/uclouvain/egle`

Cards or widgets

The home page is a dashboard in the form of customizable "cards" or widgets. We can list two types of cards : the *input cards*, allowing to timely obtain information from the user, and *display cards* which allow the user to view the data. These gadgets can be ignored and/or disabled at any time in two ways: directly on the card header or through the parameters page.

Some cards offer a "Add" or "Target" button on their header, that will bring the user on a specific (depending on the card category) page to record new health entries, or set personal health goals, respectively.

The following cards have been implemented :

1. *To do list* (Figure 5.2) : is a card placed in the top of the dashboard, which facilitates daily recording of patients data. For each interaction with the server, the system checks whether if patients' daily data (i.e. glycaemia, meals, insulin) have been properly recorded by the user. In case of missing information, the widget notifies the logged user and allows him to easily and directly complete the missing entry.

2. *Frequent Contacts* : automatic generation of the closest contacts.

3. *Meals* (Figure 5.3) : monitoring of diet, generates daily, weekly and monthly charts, as well as short feedbacks if needed.

4. *Glycaemia* (Figure 5.4) : monitoring of glucose levels in the form of a "standard day" graph. The standard day graph is defined as the regular recurrence in 24-hour cycles from one BG measure to another.

5. *Insulin* (Figure 5.6) : monitoring of injected insulin doses, generates daily, weekly and monthly charts.

6. *Weight*: monitoring the patient's weight, generates a graph of the evolution of patient entries against patient's set goals.

7. *Sport*: monitoring of physical activity, generates a chart based on patient's entries and patient's set goals.

8. *What are you up to?* : card asking the user to specify (in 2 "clicks") the activity he is about to do (activities that could have an impact on the management of his illness).

9. *What did you-have for breakfast / lunch / dinner?* : card asking the user to quickly (in 2 "clicks") describe his meals.

10. *How much do you weight?* : card asking the user to record his current weight.

11. *How did you travel today ?* (Figure 5.7) : card asking the user to record his daily means of transport (car, bike, walking, ...)

It should be noted that the dashboard has been implemented in agreement with strict rules of generic design, enabling any developer to easily create and configure a new card.

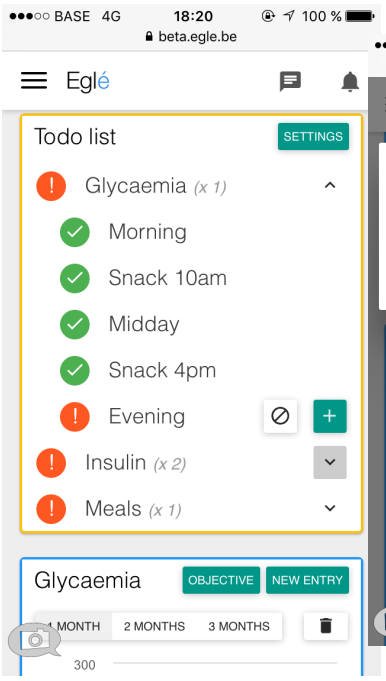


Figure 5.2

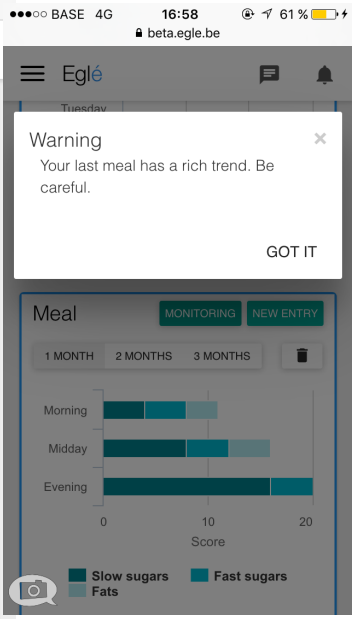


Figure 5.3

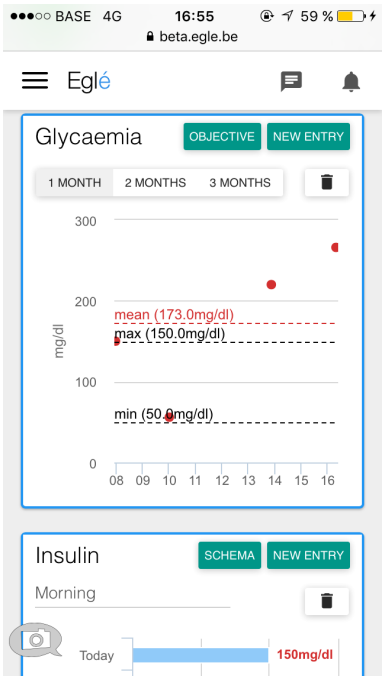


Figure 5.4

Agenda

A planning tool for organizing events (meetings, appointment with the doctor, reminders, ...) of the user has been implemented.

Avatar

An automatic icon avatar-generator based on the first letter of the user name and a user selected color was introduced. This mechanism was created to replace the avatar-picture system already in place and which, on the advice of the legal team, was very likely to be rejected by ethics and privacy committees (protection of the name and the picture of the user-patient).

Discussion tool

A deferred or real-time discussion tool ("chat" or videos calls) has been developed, inspired from the aesthetics of popular video call tools (p. ex. *FaceTime*, *Skype*), and includes all common features : non-intrusive call notifications; display of call duration;

call history, missed calls etc. In addition, communication security is ensured through a token authentication system.

Besides, this tool includes a *Relationship Manager*. In the manner of a social network (e.g. *Facebook*), the *Relationship Manager* allows the user to add contacts with whom the logged user can interact. A logged physician is able to consult patient's medical data and treatment goals only if a relationship exists between them.

This tool is illustrated in Figure 5.5 here below.

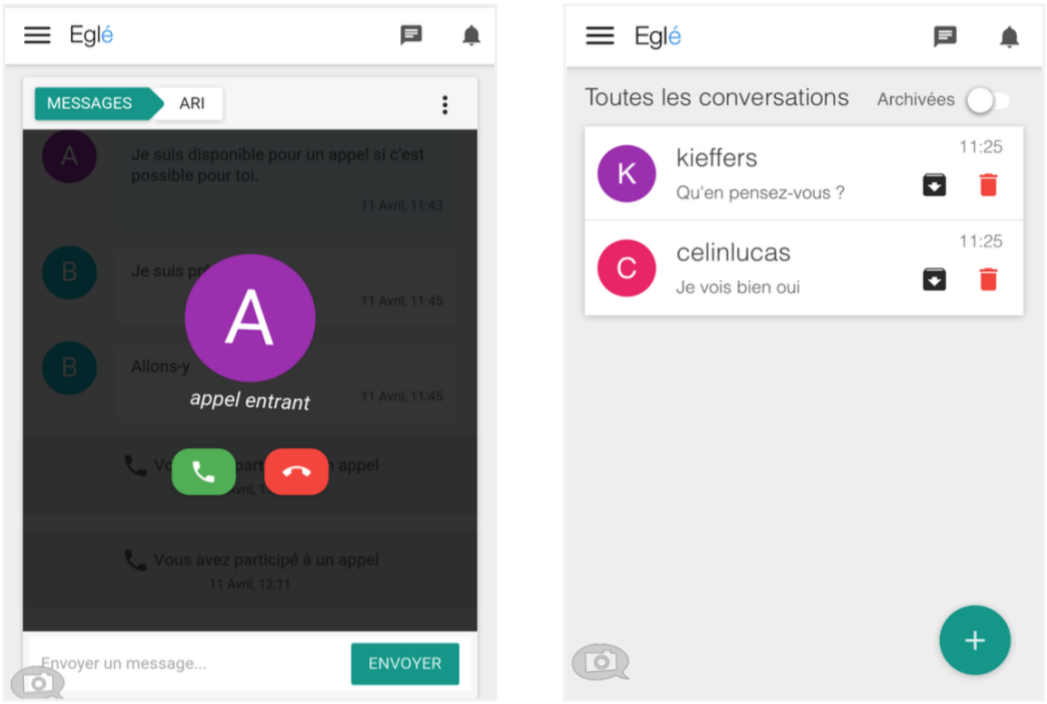


Figure 5.5

Tips & Tricks

This tool allows to gather in one place short suggestions to the patient. These notes can be selected from a general database or be selected according to the patient's health or environment, or according to previously recorded tracking information. Following the needs expressed by patients during usability testing, these tips are grouped in 12 categories :

1. Diabetes monitoring
2. Glucagon
3. Glucagon injection
4. Blood glucose measurement
5. Insulin : estimation of the dose

6. Insulin : injection and absorption
7. Insulin : the different types
8. Needles
9. The glycated hemoglobin (HbA1c)
10. Complications
11. Eating habits
12. Travel

Each official web resources used for writing these tips were cited with possible access by hypertext links. Other resources include the master's thesis of Carette Pascale, education nurse in the service of Dr. Vandeleene - as well as the "*Clinical Diabetology*" book written by Prof. Martin Buysschaert, diabetologist at Saint-Luc Cliniques.

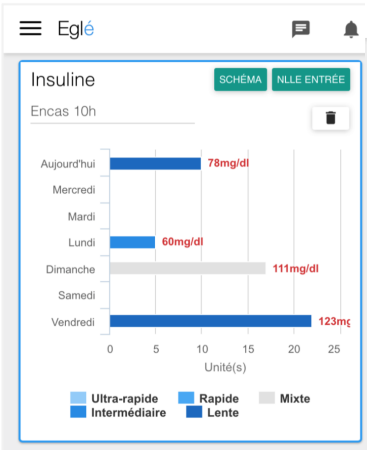


Figure 5.6

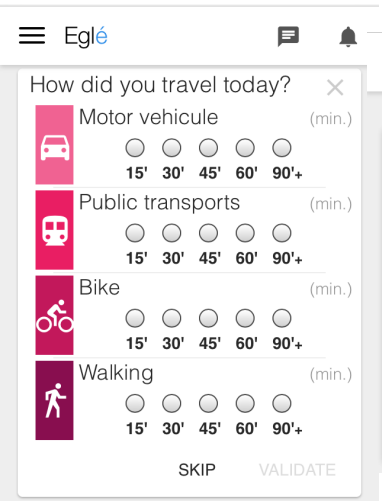


Figure 5.7

Figure 5.8

Responsive Web Design

All the user interface has been implemented following a "*responsive web design*" methodology so that the application can adapt to any screen (tablet, smartphone, desktop, etc.) without requiring any additional development.

Security

In regard to information security, a collaboration with Prof. Alain Ninane - Safety Manager of UCL Information System - has been initiated. A highly secured and privacy-compliant server is used in `Eglé` Project. Besides, only open-source and free license (MIT license) libraries were used during development.

5.3 Artificial intelligent module

NB : *most of this subsection (figures and content), aiming at being an exhaustive description, is highly based on the report [154], and Aurelien Vermeir's work.*

The AI part of the application is composed of two sub-modules :

1. **Intelligent assistant sub-module** : after several types of interactions "multiple choice"; a *case-based* algorithm will identify the concern of the patient and offer him advice from an *ontology*[2] developed as part of the application. This ontology, which is a structured knowledge base, will also be a source of information accessible to the patient.

2. **Objective sub-module** : an intelligent system accompanying (by identifying "positive" and "negative" trends) the patient in achieving personal goals established with the doctor. Some typical goals relate to :

   - Blood glucose monitoring
   - Weight (as illustrated in Figure 5.9)
   - Diet
   - Physical activity
   - Medication

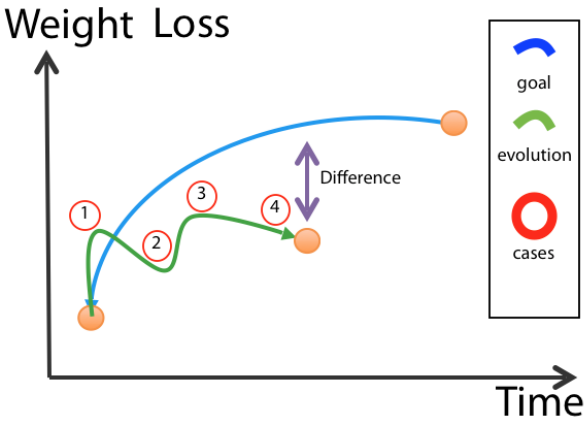


Figure 5.9

Because it is more closely related to our work, we will focus on the Objective sub-module. The goal of this sub-module is to support the patient in the realization of its

[2]In computer science an ontology is a formal naming and definition of the types, properties, and interrelationships of the entities that really or fundamentally exist for a particular domain of discourse. Medicine, for example, has produced large, standardized, structured vocabularies such as `SNOMED`.

own measurable objectives, through intelligent notifications, while preventing undesirable scenarios. Those objectives do not have any specific end date or timing. Thus, supporting the patient's efforts revolves around daily analysis of his data, and undertaking actions that help him to converge towards his desired goal value. Two models have been implemented by Aurelien Vermeir. The first one uses a Perceptron to coach the patient when a bad situation, objective-wise, arises. The second one predicts such situation in the future, and warns him, using a dynamic Bayesian network (DBN).

5.3.1 A reactive module for patient empowerment

The first reactive part strives to analyse the recent short-term behaviour of the patient, by detecting trends that could prevent him from attaining or maintaining its objectives. First, the patient is given the possibility to define glycaemia level limits (low and high), weekly total time of physical exercise as well as daily objective on its diet. While glycaemia has a double limit (Figure 5.10), weekly exercise as well as diet have goal values (Figure 5.11) (regarding diet, he is expected to maintain an average consumption of slow sugar, fast sugar and fat).

For each objective, a safety zone is created, where user will never receive any notification. Safe zone is designed around single limit objective, or between dual limits.

Then, as the patient encodes data, if the last value is out of the "safe zone", his recent behaviour will be analysed.

Figure 5.10

Figure 5.11

5.3.2 From data to shapes

In the healthcare field, simplicity and readability of models is critical. Therefore, Aurelien opted for a transformation of data from granular numbers to discrete shapes (see Fig. 5.12). The last encoded variables as are supplemented with the patient history of the last weeks. As an ultimate goal, the algorithm will interpolate those data in a curve, and analyse its tail. This could be done through the use of a *cubic hermit spline*. In this case, an interpolation function locally defined by polynomials of the 3rd degree has been chosen, building a continuous curve given the patient encoded dataset.

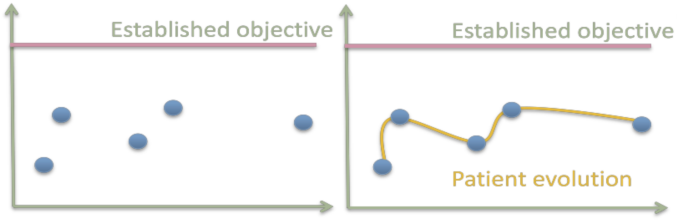


Figure 5.12

Then, to observe the behaviour of the user, Aurelien analyses the derivatives of the tail of the curve. Empirically, he uses finite difference method to derive at the first and second order and study the slope and convexity. Each sign variation marks a new segment, qualified by a shape, given derivative values. This is illustrated in Figure 5.13.

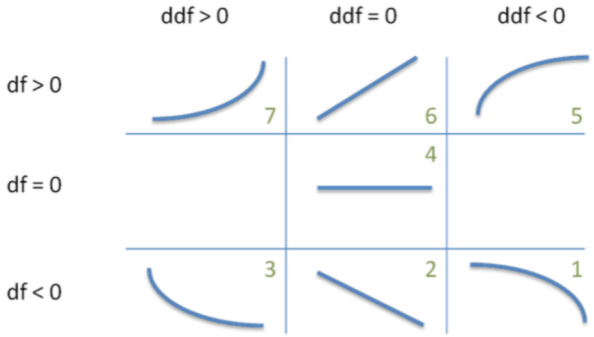


Figure 5.13

Finally, the dataset will be converted into a sequence of shapes that is saved in the user data history (Fig. 5.14).

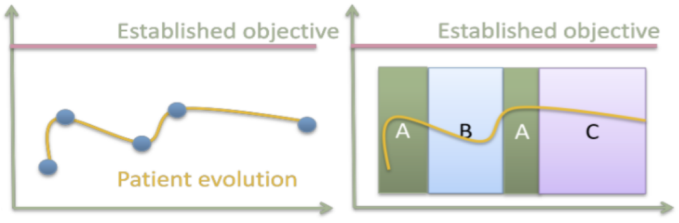


Figure 5.14

The case of glycaemia

In the case of blood glucose, variations (which occur with respect to the meal timings e.g.) should not be regarded as behavioral changes. Aurelien Vermeir opted for a normalisation of patient glycaemia, using a polynomial fit on patient history. When new

glycemia data is encoded, a longer history is taken into account, applied in a 24-hours graph, and polynomial curve fitting algorithm is run. Recent history is then normalised using the polynom. If the patient does not change any habit, a straight line would be obtained. If it is not the case, normalized data are extracted for the next step.

5.3.3 From shapes to case-based scenarii

Given the goal of supporting the user when it is most needed, actions are undertaken when the user typically tilts from a behavior to another. To detect this, "*scenarii*" where built, i.e. sequences of shapes that describe, among others, a *good* or a *bad* evolution :

- *Good scenario* : A series of 3 shapes having positive slope and convexity.
- *Bad scenario* : A series of 3 shapes having negative slope and convexity.
- *Hope scenario* : Appears when, with two *bad* shapes, we observe a positive concavity on the third one.
- *Caution scenario* : Appears when, with two *positive* shapes, we observe a negative concavity on the third one.
- *Neutral scenario* : Appears when slope is nearly flat for 3 or more curves.

5.3.4 Selecting the best action with Perceptron

Perceptron

For each of the possible scenarii (e.g. *bad* diet) specific actions are implemented. When a scenario is observed, an action is undertaken. Basic ones are notifications congratulating, exhorting, warning or supporting the patient accordingly.

Knowing which action has the more impact on the user depends on many unobserved parameters. Therefore, Aurelien opted for a trial-and-errors methodology, using a linear classifier called a *perceptron*, whose architecture is illustrated in Figure 5.15.

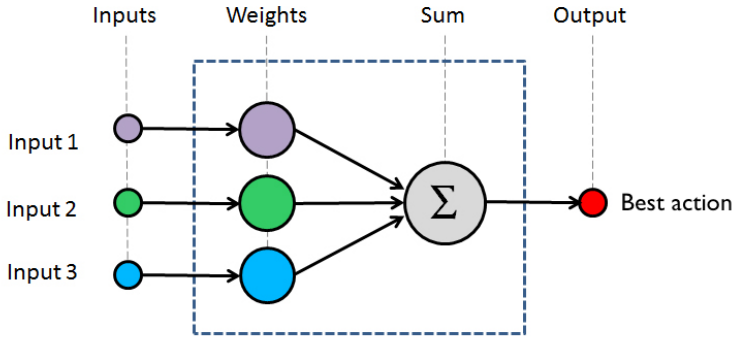


Figure 5.15: [155]

By providing features as input values (let f be the features vector), such as all the observed scenarii (binary value) and others parameters such as the age, frequency of use and the weight of the user, a simple classification is made to determine which action y suits the best, given the weights of the features w_y for each action. In other words, the action y with the highest score wins :

$$g = \arg\max_y w_y f(x) \tag{5.1}$$

The perceptron communicates it to the server, which undertakes its execution.

More specifically, the implemented perceptron takes as features:

- The binary occurrences of bad scenarii (glycaemia, diet and physical exercise)
- The rigor of the user ("*Does he forget to encode data?*")
- The age of the user (when provided)

Current actions are :

- Exhorting notifications
- Detailed notification (why, giving data about his objective)
- Email
- Proposal of scheduling reminders (work in progress)

The perceptron has been implemented in Object-Oriented Python. It consists of a single class, loading the weights of a specific user producing scores based on the received features and outputting the action that obtained the highest score through the "classify" function.

Learning

As explained in the implementation, reinforced learning has been implemented and is one of the major perceptron advantages. Each time an action is advised, a "watcher" is created for the user. It will assess the success of the undertaken action, detecting possible failures :

- If a good scenario happened, it should be reproduced on the next time period. Otherwise, it is a failure.
- If a bad scenario happened, it should not be reproduced on the next time period (the next day or week, depending on the variable). Otherwise, it is a failure.
- In case of failure, the learning is triggered, lowering the scores of the features that induced the action, and increasing the others. We do not know the correct action, hence the convergence to optimal weights will be slower, but the algorithm remains efficient nonetheless.

Also, learning from a user benefits to others since new users received the weights of the most successful setups (having less failures) of existing users.

5.3.5 A predictive model for patient empowerment : DBN

The goal of this model is to deliver the patient notifications about avoidable negative situations. By analysing recent behaviour of the patient, Aurelien computes the probabilities of bad scenarii (for example, a bad glycaemia that could happen on the next day) and warn him beforehand through meaningful notifications.

The implemented model takes into account the impact of glycaemia and diet or patient's past, as well as his rigour in data encoding (not forgetting to input 3 glycaemia and meals per day), on the glycaemia and diet behaviour in the future. The calibration is per-patient and the model updates itself through supervised learning.

Simple hidden Markov Model (HMM)

By aligning the observations of scenarii through time, we can form a *Markov Chain*. Thus, we build a reasoning that replicates the states (scenarii) of the user: bad glycemia, bad diet, lack of physical exercise, etc. Those states are bound by transition probabilities, specifying how the state of the patient evolves over time; in other words it can be translated as "*how likely will it be that a "bad glycemia" will happen when a "bad glycemia" happened the day before.*

Also, each state can be complemented by additional evidences that sharpens the predictions, such as: "*is the patient up to date with his data encoding?*", "*did he go through a "caution" scenario recently?*" "*did he go through a "hope" scenario recently?*".

Evidences R_t (e.g. "rigour") are always observed variables. Their effects on the random variable are translated by the emission probability $P(R_t|BG_t)$. Emissions probabilities tell us the probability of the evidence given each underlying state (bad glycaemia, or not).

The model is illustrated in Figure 5.16.

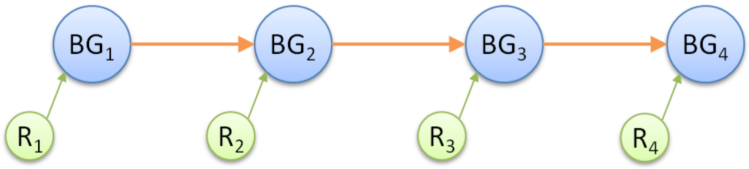


Figure 5.16

Then, according to Fig 5.16, Bayes chain rule and under Markov assumption we can write :

$$P(BG_t) = \sum_{X_{t-1}} P(BG_t|BG_{t-1})P(BG_{t-1}) \tag{5.2}$$

and if we incorporate evidences :

$$P(BG_t) = \sum_{X_{t-1}} P(BG_t|BG_{t-1})P(BG_{t-1}|R_{t-1})P(BG_{t-1}) \tag{5.3}$$

Dynamic Bayesian Network (DBN)

The main objective of this model is to track the probabilities of bad scenarii given what happened before, scenarii-wise and evidence-wise. Tracking multiple types of scenarii requires a dynamic Bayesian network that analyses evolution of several variables over time. Here, bad glycaemia and bad diets are both considered. As time goes by, whether the patient risks having a bad glycaemia on the next day depends on its glycaemia of the current day and its past (if not observed), and on its diet behaviour of the current day and its past (if not observed). Those probabilities are also supplemented with the rigour of the patient as evidence. The DBN model is illustrated in Figure 5.17.

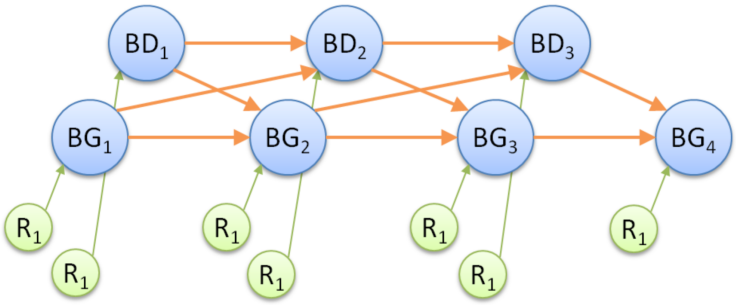


Figure 5.17

This model can be viewed as a simple Bayesian network, though evolving through time following the dynamics explained earlier. It enables to take into account the interdependences of the random variables which lead to interesting effects.

For example, depending on the calibrated probabilities, a patient that encoded his last glycaemia two days ago (no bad scenarii detected), but underwent into two bad scenarii about diet could receive a notification about the risk of having a bad glycaemia on the next day. Or if the patient has no bad scenarii recently, but starts to forget some encodings, he could be warned about bad diet risks, if such experience happened to him in the past.

As an illustrated example, on Figure 5.18, we have a scenario where bad glycaemia and bad diet happened respectively on day 1 and 2 (red circles), while user was only rigorous until the day 1. While he forgot to encode data for diet on day 1 and glycaemia on day 2 (blue circles), the model still computes a probability.

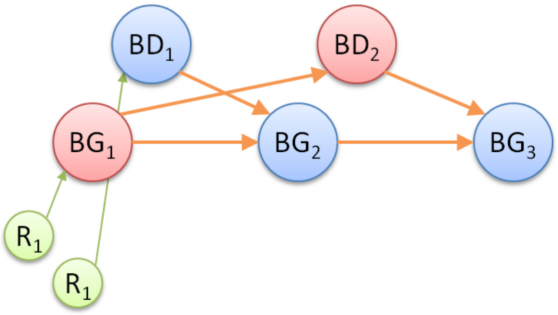


Figure 5.18

In that case, given the transition of glycaemia from day 1 to day 3, and the impact of the bad diet of the second day, we could compute a critically high probability of bad glycaemia on the third day (higher than 50%), which would trigger a notification, warning the user about it, at the very end of the second day.

Implementation

This algorithm has been coded in `Python`, using Object-Oriented programming. The module is called once a day, and is given the data whether a bad glycaemia or diet has been observed, or not, as well as information about user rigor. After loading the probabilities related to the day before, it overrides them with observations if applicable and updates variables. Then, the prediction function uses those data (BG, BD, R), along with the fixed transition and emission probabilities to "step forward" and compute the probabilities of bad scenarii for the next day. It returns those numbers as outputs.

Also, the DBN can be told to "learn". It will reset all its probabilities, loop through the unlearned-yet history and do a supervised learning routine based on a frequency approach. For example, if during a day, a bad diet was observed, but bad glycaemia, and on the next day, only a bad glycaemia was observed, it will increment $\hat{P}(BG_t|BD_{t-1}, BG_{t-1})$. After all the loops, this value will be divided by the amount of occurrences of the (BD_{t-1}, BG_{t-1}) pattern, to estimate the new probability.

5.4 Discussion

5.4.1 mHealth design criteria

In this subsection, based on the criteria we listed in Section 4.3, we'll analyse `Eglé` 's design choices and discuss them in the light of best known practices.

1. **Personalization.** During the development of `Eglé` platform, an emphasis has been put in personalization. Indeed, the platform aims at customizing, automatically, the user interface based on the context of the pathology and the user profile (e.g.

user frequency) with intelligently placed cards in the Dashboard. In addition, at any time, the user has the possibility to disable the display of some widgets/cards.

Besides, although this tool is not yet validated (by a daily usage) and will be discussed in the next subsection, the AI module has the purpose of giving tailored, patient-specific messages and feedback to the user.

2. **Social dimension.** As illustrated in Figure 5.5, the discussion tool allow users to "chat" and make video calls. This latter feature is particularly of interest for improving communication between health care providers and patients. Nevertheless, in my opinion, given the success of the mHealth app *Diabetic Connect* and according to abundant literature on social media benefits ([123, 122, 140, 141]), the social dimension could be further investigated and developed in `Eglé` platform. As examples of additional features, the tool could also include forums, status (e.g. current mood), trend topics, news, allowing the entire diabetic community to share information and get support from each other.

3. **Feature coverage.** The tools implemented in `Eglé` to monitor diabetes include :

   (a) Blood glucose tracker
   (b) Meals tracker
   (c) Physical activity tracker
   (d) Insulin tracker
   (e) Agenda
   (f) Intelligent tracking of health behaviour changes
   (g) Tips and tricks (self-management education tool)

   For each health tracker, the platform offers intuitive and aesthetic trends graphs or charts. Although ease of data input is fast and easy, range of values is quite limited. Concerning food, meals can only be described by three 1-to-5 scales (fat, slow sugars, fast sugars) while physical activities are quantified by two 1-to-5 scales (duration, intensity). In my opinion, this tool could easily be improved by incorporating food and sports databases.

   Besides, even though the platform does not offer a blood glucose prediction model, it provides a supportive and intelligent tool able to track and prevent the patient from undesirable health behaviour changes (e.g. Bad control over glycemia). However, this tool, using artificial intelligence (perceptron and dynamic bayesian network) has not yet been used and validated by test patients, and will be further discussed in the next subsection.

   In a last point, the platform offers a self-management education and information tool ("Tips & Tricks") with hypertext links to the corresponding web resources. There is evidence that diabetes education [156] enhances patients compliance, which makes of "Tips & Tricks" a great and noticeable feature, often overlooked in other apps.

4. **Integration and interoperability.** A great feature of `Eglé` is the integration of patient organizations and medical teams into a unique platform, allowing an efficient two-way communication. If a relationship exists between them, a logged physician is able to directly consult patient's medical data and treatment goals on the platform.

   Furthermore, a responsive web design (RWD) approach has been adopted during the development, allowing users to access the application from any device (smartphones, tablets, e-readers, laptops) supporting a web-browser, no matter the screen-size or resolution.

5. **Motivational system.** As just mentioned, the platform provides a supportive and intelligent tool able to track and prevent the patient from undesirable health behaviour changes. When such a event is predicted or detected (e.g. Bad diet), an action is undertaken. Nevertheless, the range of implemented actions is quite limited so far and includes :

   (a) Exhorting notifications/mails
   (b) Detailed notification (why, giving data about his objective)
   (c) Proposal of scheduling reminders

   Besides, short feedbacks are also provided to the user when recorded meals seem unhealthy. Finally, except the social feature and short personalized feedbacks, no gamification ingredient has been adopted in the platform. In my opinion and in agreement with [110], the motivational system could be enhanced by incorporating successful gamification mechanics such as challenges, points, rewards, in the same manner as *Bant* or *mySugr* did.

6. **Ease of data input** The "*To Do List*" card appears very useful and allows the user to never forget to encode daily health data. Meals, physical activities, insulin, blood glucose levels and other health variables are really easily and quickly encoded.

   However it should be noticed, as said earlier, that description of meals and exercise are pretty limited. Several successful alternatives, reducing manual data entry errors, exist on the mHealth market : graded food products and sports database (e.g. *BG Monitor Diabetes*), food barcode scanner (e.g. *Diabetes in Check*), wireless (bluetooth) sync with blood glucose meters (e.g. *Glooko*).

7. **Design and user experience** Although this criterion remains quite subjective, in my opinion the platform offers a sleek and aesthetic design. The user interface is user-friendly and provides intuitive features. Charts and graphs, being clear and relevant, allow the patients to monitor their progress. In addition, interface and on/off buttons colors have been chosen to suit users experiencing visual disabilities, such as colorblind people.

   On the other hand, and this is the downside of web responsive design, the platform is not entirely optimised for smartphones. As an example, whereas the "long scrolling"

is a Web design trend, it appears a bit tedious on a smartphone, especially when the user wants to switch from the first dashboard widget to the last one.

5.4.2 Objective module (AI) : the Perceptron

In this subsection, we attempt to enumerate strengths, weaknesses and suggest ways of improvement of the adopted Perceptron approach. However, we should note that the project is still under development. Furthermore, several following observations are personal and mostly based on my own knowledge.

1. Strengths :

   - *Scalability :* The model is scalable, i.e. it can support a large range of variables and objectives, displaying dual limit or single limit variables, and encompassing various periods: daily data, weekly data and monthly data.
   - *Convergence :* If the data can be classified in a linear fashion, and if inputs are reasonably simple, it will theoretically always converge to efficient decisions in a finite number of steps and learn quite fast.
   - *Learning :* New users can benefit from the weights of successful setups (showing the fewest failures) of existing users, speeding up their own weights convergence process.

2. Weaknesses :

   - *Polyfit :* What about the polyfit, while it performs well with individuals displaying a regular behaviour, it can be impossible to fit a curve in the most heterogeneous cases. The issue arises especially when week-end habits differ a lot from working days.
   - *Blood glucose trends :* In the specific case of glycaemia, inaccuracy in blood glucose trends prediction is very undesirable. Indeed, let us remind that one ultimate goal of diabetes management consists in preventing the patient from hyperglycaemia and hypoglycaemia events, which can lead to severe complications in the long term. As diabetes is a nonlinear, dynamic and multifactorial disease, subject to huge intra-patient variability, a polynomial curve fitting (*polyfit*) applied in a 24 hours graph and only based on glycaemia history can not, in my opinion, be accurate enough. Blood glucose prediction requires the use of state-of-the-art methods and to take various factors into account (e.g. meals, insulin, exercise,...).
   - *Learning :* In my opinion, there exists some inconsistency in learning process. Each time an action is advised, a "watcher" assessed the success of the undertaken action, detecting possible failures:
     i. Currently implemented actions include exhorting notifications, mails or proposal of scheduling reminders.
     ii. If a bad scenario happened, the action should not be reproduced on the next time period. Otherwise, it is a failure.

iii. If a good scenario happened, the action should be reproduced on the next time period. Otherwise, it is a failure.

iv. In case of failure, the weights of the features that induced the action are lowered, while others weights (actions) are increased.

The controversy question is, on what basis can we affirm that an action, as simple as a notification, has exerted the good/bad influence on the - just - detected health behaviour change ? Is, such a learning, relevant according to behavioural science ? How could we validate such a reasoning ?

- *Validation :* The perceptron algorithm has not yet been tested on a large population of patients
- *Linear separability :* The perceptron convergence theorem states that : "*For any finite set of linearly separable labeled examples, the Perceptron Learning algorithm will halt after a finite number of iterations*" [157]. How can we assess that data, in our case, are **linearly** separable ?

3. Ways of improvement (suggestions)

- *Polyfit* : Implement a more complex and well-grounded blood glucose model (cfr. Chapter 2 and Chapter 3)
- *Linear separability* : In the case where we keep the classification approach, implementing a multilayer perceptron could be a good alternative to deal with non linearly separable problems.
- Given the *limited range of undertaken actions* and the unknown speed of convergence (which can appear repellent to the user), does our case really needs such a classification algorithm ? In my opinion, relevant actions (considering simple messages or notifications) could be undertaken based mainly on good sense and predetermined values (e.g. taking into consideration user age, app usage frequency). Besides, current implemented actions seem not, in my opinion, sufficient to induce positive health behaviour changes. According to me, a more advanced motivational system should rely on *gamification*.

5.4.3 The dynamic Bayesian network

Based on [158], [159] and [154], we can enumerate strengths, weaknesses and suggest ways of improvement of the adopted dynamic Bayesian approach.

1. Strengths

- Bayesian networks can readily *handle incomplete data sets*.
- Can efficiently *learn* (probabilities) about (unknwown) *causal relationships*.
- *Combine domain knowledge and data* : Bayesian networks readily facilitate use of prior knowledge. Prior knowledge is relatively straightforward to incorportate, by constructing “causal” edges between any two factors that are believed to be correlated. Weight of the directed edges can be easily updated based on new data.

- *Avoid over fitting* : Bayesian methods provide an efficient method for preventing the over fitting of data, a preprocessing step is thus not required. In addition, contradictions do not need to be removed from the data, the method being robust to "outliers".

2. Weaknesses

   - *Trade-off accuracy/speed:* A trade-off must be made between personalization of calibration, amount of random variables, and speed of convergence. Indeed:
     i. If probabilities are patient-specific, volume of data will be low, implying that the model will take a long time before having a reliable predictive power on patient's health behaviour. However, having the same probabilities for all users would lead to many prediction errors.
     ii. Exploring a previously unknown network requires to calculate the probability of any branch of the network. This process of network discovery is an NP-hard task which might either be too costly to perform (exponential time complexity), or impossible given the number and combination of variables [158].
   - *Requires reliable prior knowledge :* Either an excessively optimistic or pessimistic expectation of the quality of prior beliefs will distort the entire network and invalidate the results.
   - *Amount of random variables :* So far, although blood glucose metabolism depends on many more factors, only two random variables ("Bad diet", "Bad Glycaemia") are considered in the implemented network. However, this part is still under development.

3. Ways of improvements (suggestions)

   - *Trade-off speed/accuracy :* segmenting patients in categories (given habits and/or age), and calibrate probabilities per category, may improve convergence speed. In addition, adding services in order to collect more observed evidences (e.g. medication, sleep, heart rate) supplementing the random variables, or consider richer (not just "Bad" or "Good" event) random variables could enhance the predictive power of the model.
   - In my opinion, the dynamic Bayesian network should be replaced by a *well-grounded blood glucose prediction model.* Many state-of-the-art models I presented in Chapter 2 and Chapter 3 (`NARX`) offer the ability to model complex and hidden non-linear relationships, without requiring any prior knowledge. Even in the case of small training data set, machine learning methods are able to provide reliable predictions, especially by enriching their inputs with compartmental (physiological) models.

5.5 Summary tables

In this summary section, based on mHealth best design practices and succesful ingredients described throughout this work, we synthesized in a table strengths, weaknesses and improvement suggestions of `Eglé` general design (Figure 5.20). In the same manner, we focused our analysis on the - artificial intelligent - Objective module (Figure 5.19).

However, it should be noted that the project is still under development. Only tools accessible in the beta version[3] were analyzed in our study[4]. Furthermore, there exists no standardized methodology for evaluating mHealth applications, some observations may thus - even though built from well-defined criteria (See Chapter 4) - appear quite subjective.

Objective module (AI)			
	Strengths	**Weaknesses**	**Suggestions of improvements**
Perceptron	- Scalability - Guaranteed convergence if data set = linearly separable - News users can benefit from learning of existing users	- Polyfit is not powerful enough, especially for modeling BG levels - How can we assess that data = linearly separable ? - Not yet tested by patients - Limited range of undertaken actions (e.g. exhorting messages)	- Implement a well-grounded blood glucose prediction model - Use a more advanced motivational system relying on gamification. - Group patients by categories - Enrich the data set : additional discriminant variables (e.g. medication, sleep) and physiological (CM) models.
Dynamic Bayesian network (DBN)	- Handles incomplete data sets - Learns about unknown causal relationships - Takes advantage of prior knowledge - Avoids overfitting	- Important trade-off between accuracy (lack of data, the problem being patient-specific) and speed of convergence - Exploring a unknown network = NP-hard task - Requires reliable prior knowledge ! - So far, network = only 2 variables	

Figure 5.19

[3] `https://beta.egle.be/`

[4] Some tools not yet fully implemented, such as ontology-based advices, were thus excluded from our analysis.

mHealth design			
	Strengths	**Weaknesses**	**Suggestions of improvements**
Personalization	- Intelligently placed and customizable widgets - Tailored notifications (AI)	- cfr. Perceptron	- Possibility to change reference metrics - More advanced avatar - cfr. Perceptron
Social dimension	- Chat and video calls - Relationship between patients and physicians	- Could be further developed	- Forums, news, status, etc. Example : *Diabetic Connect*
Feature coverage	- Includes all basic health trackers, great charts/graphs - Tips and tricks - Tracking of undesirable health behavior changes (AI)	- Food and exercise trackers are limited - cfr. DBN	- Incorporate food and exercise database - cfr. DBN
Integration and interoperability	- Patient and physician can easily share medical data - Responsive Web Design		- Support external devices, sensors (e.g. *SenseWear* armband) - Integrate others apps (e.g. iOS Health, Google Calendar...)
Motivational system	- Tailored notifications (AI) and short feedbacks (e.g. meals)	- cfr. Perceptron	- Gamification Example : *mySugr*
Ease of data input	- « To do List » - Easy and quick data encoding	- Manual entries - Limited description of health data (e.g. meals, exercise)	- Food and exercise database - Food barcode scanner - Wireless sync with glucose meters (e.g. *Glooko*)
Design and UX	- Sleek and aesthetic - User-friendly, intuitive features - Clear and relevant graphs/ charts (progress monitoring) - Accessibility (colorblind users)	- Long scrolling on smartphones	
Others	- Generic design (widgets) - Uses open-source and free-license libraries - Security, privacy		

Figure 5.20

Chapter 6

Conclusion

In this final chapter, we will try to incorporate in a synthetic way the main results and observations we made throughout this Graduation Project, and compare them with the initial objectives. This chapter also aims to present limitations and prospects for the continuation of the work undertaken.

Chapter 1 aimed at setting the scene and introduce the roadmap of the subsequent work. In this part, we observed that diabetes mellitus is a major, global and increasing problem. Such a condition can lead to undesirable hyperglycemia or hypoglycemia events, of which chronicity can result in multiple micro- and macrovascular damages, leading to several systemic and sometimes life-threatening complications. There is therefore a need, in the diabetes management process, to accurately predict and control blood glucose levels, especially for type 1 diabetes which can not be prevented or cured but only treated with external supplies of insulin. Despite this underlined need, blood glucose prediction remains a very complex problem due tue the nonlinear, multifactorial, dynamic aspcects of the condition, which, in addition, is subject to huge intra- and inter-patient variability.

Besides, we know that lifestyle and health-related behaviours - including for examples exercise, diet, alcohol consumption, smoking, sleeping and socialization - play an important role in diabetes management [33, 34]. To manage diabetes successfully, patients must be able to set goals and make frequent daily decisions that are both effective and fit their values and lifestyles, while taking into account multiple physiological and personal psychosocial factors. That are the main issues *patient empowerment*, whose ultimate goal is to help patients discover and develop their inherent capacity to be responsible for their own life, should deal with [35, 36].

The best way to empower a diabetic patient is a personal face-to-face coaching [33], day after day, ideally in close collaboration with physicians, dietitians, nurses and other diabetes health care professionals. However, such a solution is not an economically feasible method. In view of the empowerment scale we described, another and hopeful way for keeping patients motivated appears suitable : the gamification, which can be defined as *the use of game mechanics and experience design to digitally engage and motivate people to achieve their goals in non-game contexts* [40]. A review of research on

gamification shows that majority of studies on it have found positive results [41]. As a valuable example, it has been shown in [42] that by combining the use of an mHealth app with gamification as an incentive, a substantial increase is achieved in the frequency with which adolescents with type 1 diabetes carry out BG control.

All these observations highlight the importance of blood glucose control and empowerment in the diabetes management process. In view of this, I therefore decided to focus my Graduation Project on an innovative design of mHealth app for the self-management of diabetes, including a blood glucose prediction tool and taking advantage of gamification mechanics.

Chapter 2 Within this context, it appeared meaningful to dedicate a chapter to describe, review and discuss state-of-the-art blood glucose prediction methods. In this chapter, we distinguished the reported methods into three major groups : physiological models; machine learning methods; and time-series analysis.

Physiological models of the glucoregulatory system are composed of compartmental sub-models, each of which is associated with several differential equations that describe the main processes affecting glucose metabolism in diabetic patients and offer powerful tools for understanding and predicting physiological processes. However, their practical applicability is limited by two factors: they are not patient-specific and contain a high number of system parameters that are usually difficult to be identified and validated. [83, 44, 84, 54].

Time-series analysis provides methods that can be used to identify systematic patterns in time series data - such as trends and seasonalities - as well as methods for time series modelling and prediction. According to [57], the autocorrelation analysis of CGM time series made clear that glucose dynamics have a detectable structure and, thus, the glucose can be predicted by exploiting its recent history. Some popular methods include, though not exhaustively, the autoregressive AR, ARIMA, ARX or ARMA models.

However, in view of the inherent complexity of BG dynamics naturally arises the question whether linear time-series models could reflect well the non-linear relationship between therapeutically valuable input factors (BG measurements, meals, insulin injections, physical activities, etc.) and future glucose evolution, or some other models could perform better [55]. Motivated by this question, a variety of *Machine Learning* methods have been developed to address the problem of the blood glucose prediction - that can be considered as a nonlinear regression problem with a time component - in a new light. Some popular methods include, though not exhaustively : artifical neural networks (MLP, RNN, RBF); support vector regression (SVR); random forests (RF); Gaussian processes. Besides, it also should be noted that, in recent years, many Machine Learning predictors adopted an "hybrid approach", i.e. made use of compartmental models (CM) to enrich the input and enhance their model.

Due to the large number of papers dealing with blood glucose prediction, the diversity of methodologies and the contradictory results, there is no clear evidence that *Machine Learning* methods outperform *Time-series* analysis approach. Furthermore, we should note that performance assessment is not an easy task. In order to be able to analyze and

compare the prediction algorithms, proper assessment metrics are needed. In the case of blood glucose prediction, there exist many different performance measures (RMSE, EGA, RAD, CG-EGA, PRED-EGA). Not only the assessment metric is important but also what data are compared. Data can differ by their sources (e.g. real vs. virtual subjects) and references (e.g. measuring device).

Chapter 3 In the continuity of Chapter 2, we proposed the design and implementation of a blood glucose prediction model with MATLAB Neural Network Toolbox, known as `NARX` or *nonlinear autoregressive network with exogenous inputs*.

Indeed, on the one hand, autoregressive models are very efficient in modelling seasonal patterns in times series, although such linear algorithms are not the best to cope with non-linearity of blood glucose measurements. On the other hand, recurrent neural networks are very powerful when applied to non-linear regression problems. Still, they encounter difficulty to learn long-term dependencies. Because `NARX` seem to combine both approaches, exploiting efficiently history of measurements and taking advantage of the multilayer perceptron architecture, we assumed such dynamic recurrent neural networks are suitable in our case.

Our implemented model had the following characteristics :

- Data were collected from the freeware diabetes simulator AIDA.
- Training was performed with :
  (a) Series-parallel architecture (and thus static backpropagation algorithm) ;
  (b) Bayesian regularization learning, preventing the model from overfitting.
- The optimal performance was found with 6 hidden neurons and delays of 12 time steps.

Autocorrelation errors, cross-correlation errors, root mean squared errors (RMSE) and regression analysis were performed to validate the model. Multi-step ahead predictions were realized for 15-, 30-, 45-, 60-, 75-, and 90-minutes prediction lengths on independent test sets. It should be noted that direct performance comparisons in terms of RMSE with other approaches are not very relevant, due to large methodology differences in the literature.

However, our `NARX` model, although it should be validated on clinical data, showed very promising results (e.g. $RMSE_{30min} \approx 0,07$ $[mmol/l]$) comparable to best state-of-the-art methods we discussed in Chapter 2.

Chapter 4 As highlighted by Chapter 1, there is evidence that gamifying disease management can help children, adolescents, and adults with diabetes to better cope with their lifelong condition. Gamification and social in-game components are means to keep motivate patients and positively change their behaviour and lifestyle.

Besides, 76 % of mobile health app publishers see diabetes as the therapeutic area with the highest business potential for mobile health. It is foreseen that the market of

mHealth app users will reach 2 billion by 2017 [105]. However, the current low acceptance rate and usage of diabetes apps is explained by the fact that the majority of today's 1.100 diabetes apps do not meet best practice standards [106].

Within this context, we decided to dedicate Chapter 4 to describe best mHealth design principles and gamification key ingredients, review and discuss some successful mHealth apps and, in a last section, suggest a new design of mobile application : *DiaBeast*.

Best practice standards can be distinguished into 7 criteria [111, 115, 106, 113] : (a) Personalization; (b) Social dimension; (c) Feature coverage ;(d) Integration and interoperability; (e) Motivational system (gamification); (f) Ease of data input; and (g) Design and user experience.

In section 4.3, we reviewed the top 8 free apps for diabetic patients. According to our analysis, we made several important observations :

1. No app is perfect, but all apps are somehow complementary in their features. As examples, *Diabetic Connect* is the only app dealing efficiently with the social dimension (despite the abundant and supportive literature [124, 125, 123, 122, 140, 141]) *Glooko*, being compatible with various devices, offers the best interoperability, while *mySugr* benefits from a great motivational system.

2. Although chronic hyperglycemia and hypoglycemia can lead to severe complications (e.g. kidney, neurological, cardiovascular, retina damage) and may be life-threatening, none of the 8 most popular free apps offers a BGL prediction tool.

3. Most of the apps do not propose any gamified motivational system. In addition, although the pilot study [42] suggests tangible rewards are an efficient way to enhance patients motivation, no app offers such a feature.

Finally, in section 4.4, based on these observations, established design criteria and previous findings, we have proposed the design of a diabetes app (*DiaBeast*) with aim to gather all the successful ingredients we had discussed so far. In this design, an emphasis has been put on gamification mechanics (i.e. it should include badges; leaderboards; points and levels; challenges and quests; social engagement loops; concrete rewards, avatar) as well as on efficient health tracking (blood glucose prediction tool, insulin dosage estimator, food barcode scanner, wearable physical activity sensor, wireless (Bluetooth) sync of BG readings, etc.).

Chapter 5 Because the e-health/mHealth web application `Eglé`, making use of artificial intelligence and user-centred design, is closely linked to my master's thesis, it also appeared meaningful to dedicate a chapter to shortly describe the architecture, algorithms and user interface of the platform, and discuss it in light of previous observations.

Composed of experts in artificial intelligence, software engineering, public health and social sciences, the `Eglé` team has for mission to support patient empowerment through the development of a scalable platform of multimedia tools, designed to improve medical care and foster communication between the patient, the family and health professionals. Though still in development, the `Eglé` platform comprises a structured set of medical

knowledge; a communication tool allowing the patient or relatives to receive and send data; a personalized system for monitoring the patient's health on a daily basis; and a dedicated area for information exchange and communication between health professionals.

Based on mHealth best design practices and successful ingredients described throughout this work, we synthesized in a table strengths, weaknesses and improvement suggestions of `Eglé` general design (Figure 5.20). In the same manner, we focused our analysis on the artificial intelligent Objective module (Figure 5.19). Only tools accessible in the beta version (`https://beta.egle.be/`) were analyzed in our study. It should be noted that there exists no standardized methodology for evaluating mHealth applications, some observations may thus - even though built from well-defined criteria (cfr. Chapter 4) - appear quite subjective. Amongst others, some suggestions of improvement included the integration of a well-grounded blood glucose prediction model, such as the `NARX` we developed, as well as the enhancement of the motivational system through the use of gamification principles. Therefore, our approaches tend to be, in some way, complementary.

Limitations and further work : even though we think we have quite successfully achieved our initial objectives, our Graduation Project is obviously subject to some limitations. More precisely, further work should or could include :

1. *Validate* the `NARX` on clinical data
2. *Enrich* the `NARX` inputs : it is obvious that the more rich is the inputs set of a neural network, the more accurate could be its predictions. Some examples of inputs capable of enhance predictive performance could be, according to the litterature, the following :
   (a) The use of SOA compartmental models, which of Meal, Insulin and Exercise models discussed in Section 2.1 are good examples. Indeed, hybrid machine learning approaches have been shown to be powerful (cfr Section 2.5.3, e.g. [79]), and are able, especially in the case of small training set (i.e. non-continuous glucose monitoring), to significantly enhance the predictive power of a model.
   (b) The observation of more health-related variables. Amongst others, there is evidence that heart rate variability [82] and insufficient sleep [24, 25, 26] are significantly related to/affect the blood glucose. Note that such variables could be tracked, in a non invasive and unobtrusive way, by wearing sensors. As suggested in Section 4.4.1, such a device could be the *SenseWear® Pro Armband*. Furthermore, it has been shown that the approach of multisensor technology with integrated data analysis can provide satisfying estimates of plasma glucose concentration in diabetes [146], without necessitating continuous blood glucose measures.
3. *Online learning* : in our multistep prediction analysis, for every prediction horizon throughout the test day, a `NARX` was built. This is kind of "online learning".

However, as the patient's physiology is constantly changing, small adjustments should ideally be made to the weights of the network every time new data is acquired (i.e. every time step). An advanced online learning algorithm should thus be considered. Note that, in view of the quite fast convergence of `NARX`, this does not seem to be an important issue.

4. `NARX` *Web deployment* : further work should also focus on the deployment of our MATLAB code as a web service that the mobile application would call. The add-on products MATLAB *Builder JA* and MATLAB *Builder NE* allow to convert MATLAB code to standalone Java components or to .NET assemblies respectively. We could then implement a web service in Java or .NET depending on our preference, and call the deployed component in a more scalable way [149, 150].

5. *Validate* the design of *DiaBeast* : we do not pretend our solution is unique and flawless, but essentially illustrative of interesting concepts. As an example of improvement, our design could be further personalized (e.g. less/more gamification mechanics) and adapted based on user profile (e.g. age, usage frequency, gender) and diabetes type. Further investigation should be performed, e.g. : create a poll, meet diabetic patients or related organizations, health care professionals, and get their feedback to validate our approach.

6. *Concrete rewards* : in a future work, we should also contact brands, organizations or any person likely to help us shape our "Concrete Rewards" service. Note that the idea of concrete rewards was inspired from my visit to Keio University in Tokyo, where this topic was closely related to another student's master thesis, as well as from the pilot study on *Bant* [42]. A more realistic alternative could be seeking for a sponsorship from family members and friends. Moreover, such a service should require the development of an "anti-cheat" system. This could be achieved by analysing (automatically) relevance of input data and progress, and setting patient's personal health objectives in agreement with the physician.

Finally, I hope this Graduation Project, highlighting the main diabetes management issues, underlining the importance of blood glucose prediction and motivational systems, may inspire and encourage the development of innovative mHealth/e-health applications dedicated to diabetes self-management and empowerment, such as the `Eglé` platform.

The subject of this Master's thesis, combining mHealth design, biomedical engineering, and - above all - including a social dimension, was of utmost interest for me. Therefore, I also hope that, whoever my readers may be, they get even half as much pleasure from reading my work as I did from writing it.

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Annexes

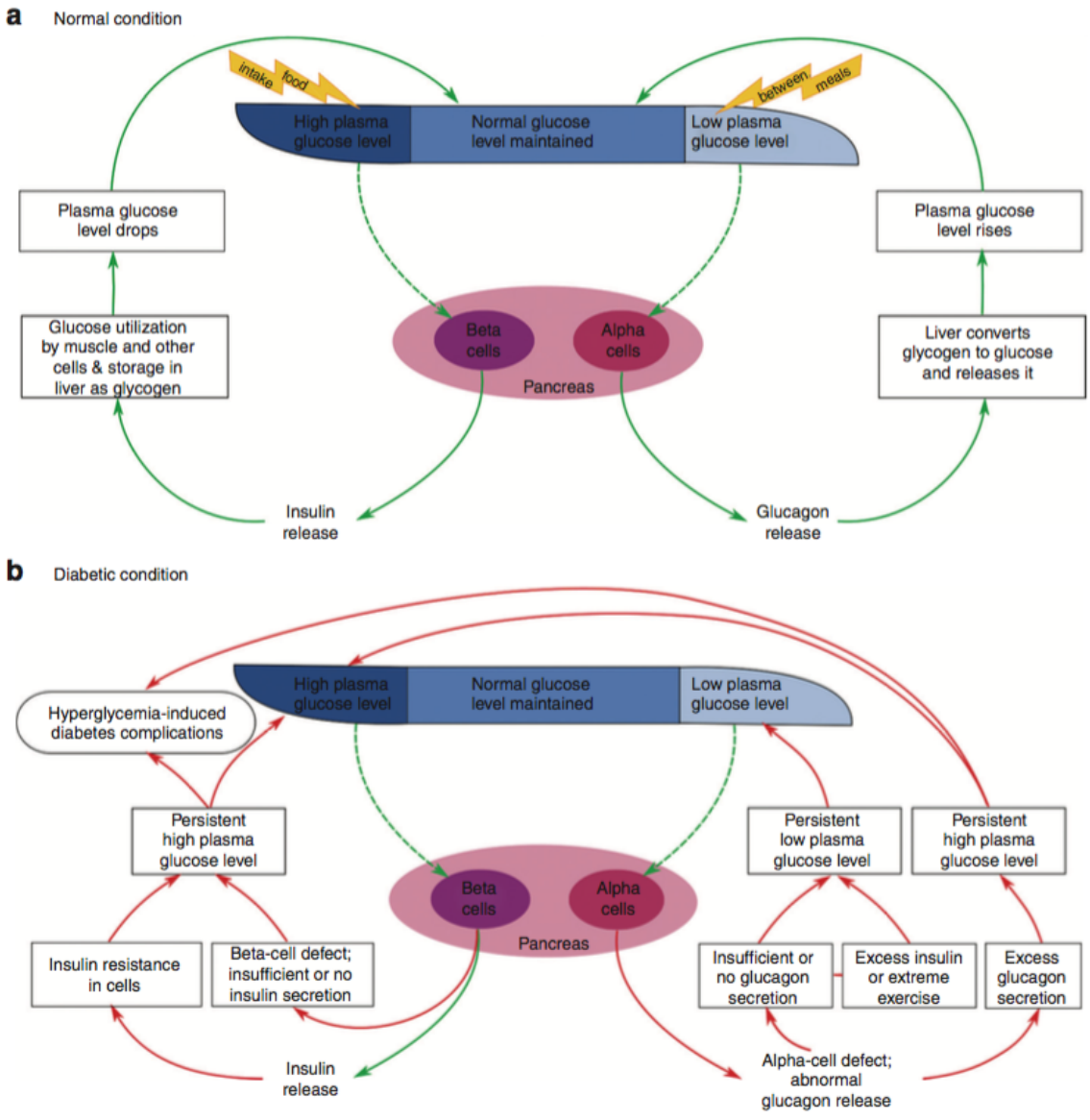

Figure 6.1: *General overview of the glucose homeostasis mechanism under normal and diabetic condition. Taken from [9]*

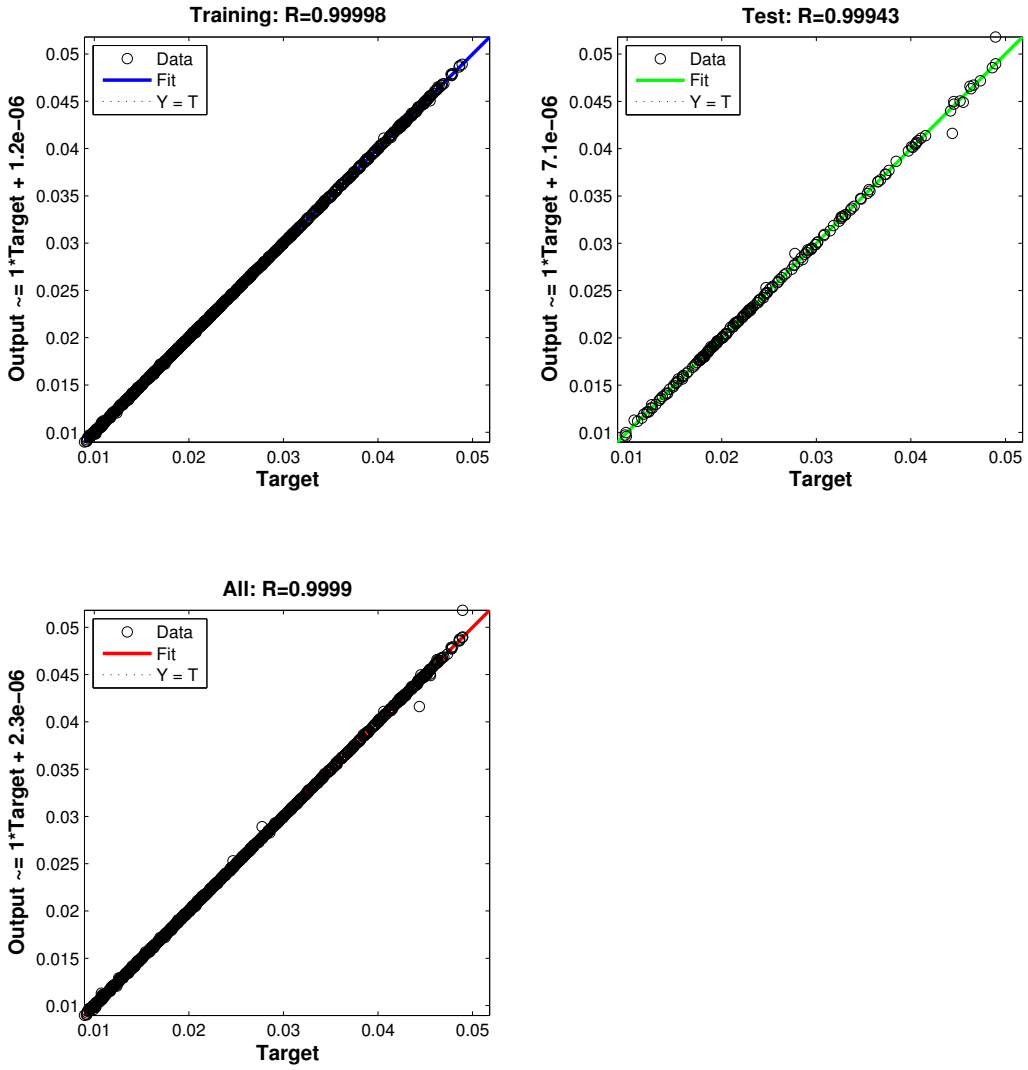

Figure 6.2: *Regression analysis of the* `NARX` *response. In our case, the fit is excellent for all data sets, with* R *values in each case of* 0.999. *See Section 3.3.3 for further details.*

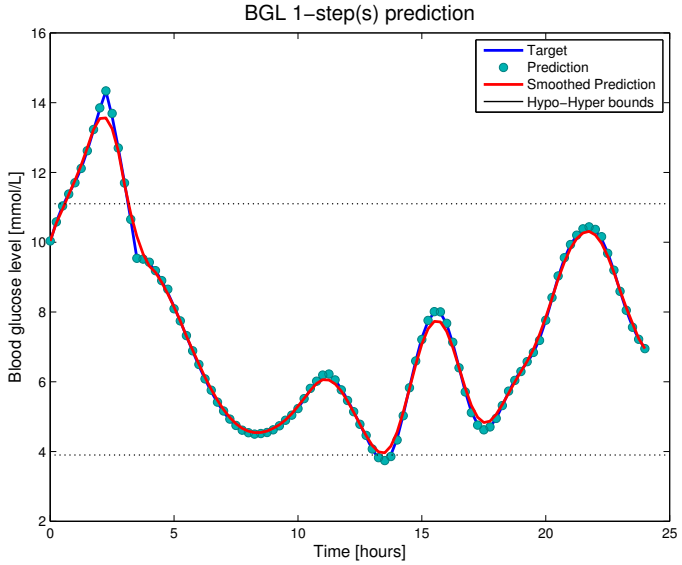

Figure 6.3: *As we can observe, 15 min predictions and target values are highly correlated ($R \approx 99\%$). Events of hyperglycemia and hypoglycemia seem to be well detected. Given these results, although it should be validated on clinical data, we conclude our* `NARX` *model is accurate enough and suitable for BGL control of diabetic patients. See Section 3.4 for further details.*

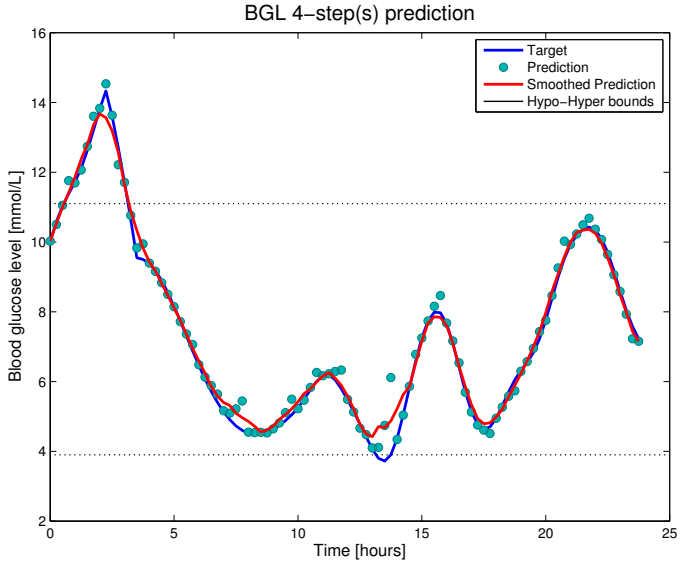

Figure 6.4: *As we can observe, 60 min predictions and target values are well correlated ($R \approx 97\%$), although less accurate than for smaller prediction lengths. Events of hyperglycemia and hypoglycemia seem to be well detected. Given these results, although it should be validated on clinical data, we conclude our* `NARX` *model is accurate enough and suitable for BGL control of diabetic patients. See Section 3.4 for further details.*

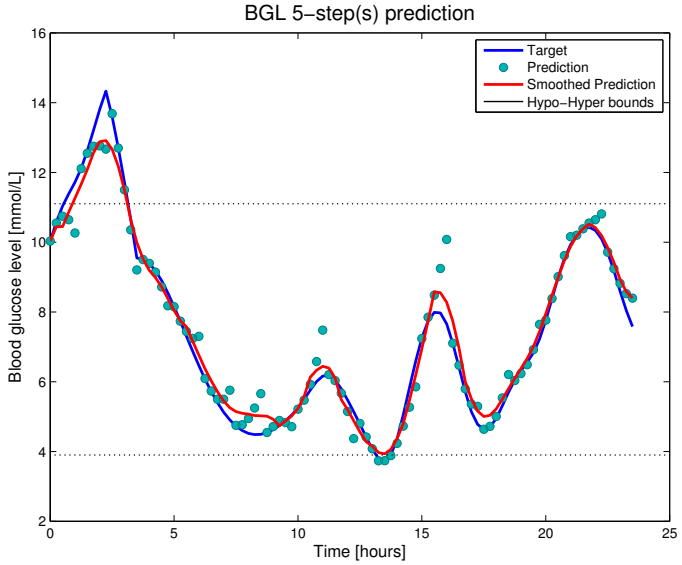

Figure 6.5: *As we can observe, 75 min predictions and target values are quite well correlated, although less accurate than for smaller prediction lengths. Events of hyperglycemia and hypoglycemia seem to be well detected. Given these results, although it should be validated on clinical data, we conclude our* ***NARX*** *model is accurate enough and suitable for BGL control of diabetic patients. See Section 3.4 for further details.*

```
%% ==== Multi-steps prediction of blood glucose levels === %%
% - Author : Guillaume Gustin
% - Note : The built model is a NARX,
%          implemented with the Neural Network Toolbox
%% ========================================================= %%

close all; clear all; nntraintool('close');

%% LOAD THE DATABASE, i.e. :
% Formatted, preprocessed, simulated (AIDA) times-series
% 14 days of  : - glycaemia (time, value) = NARX target
%               - meals (time, carbohydrates)
%               - insulin (time, dose, type)

[target_DB,inputs_DB,normDB] = load_DB();
pred = [];


%% PARAMETERS
delay = 12;
hiddenLayerSize = 6;
N = 4;
```

```
modu = mod(97,N);
nwindow = 97:-N:N;

% For each different moment of the day (time window)
for k = nwindow

%% DATA DIVISION
% Note : "online-learning-like"
% We remove (k-N) last elements of the TS
inputs = inputs_DB(1:end-k+N,:);
target = target_DB(1:end-k+N);

% -- Time-series objects --
X = tonndata(inputs,false,false);
T = tonndata(target,false,false);

% -- Training data --
% On the modified TS, we don't use N last elements during training
inputSeries  = X(1:end-N);
targetSeries = T(1:end-N);

% -- Test data --
% During the test, N last inputs are available (but target values won't !)
% targetSeriesVal will only be used to compute RMSE (validation)
inputSeriesVal  = X(end-N+1:end);
targetSeriesVal = T(end-N+1:end);

%%  NETWORK CREATION
trainFcn = 'trainbr';  % Bayesian Regularization
inputDelays = 1:delay;
feedbackDelays = 1:delay;
net = narxnet(inputDelays,feedbackDelays,hiddenLayerSize,'open',trainFcn);

%% DATA Subdivision (for building the ANN)
net.divideFcn = 'dividerand';
net.divideParam.trainRatio = 70/100;
net.divideParam.valRatio = 15/100;
net.divideParam.testRatio = 15/100;


%% TRAINING
```

```
[x,xi,ai,t] = preparets(net,X,{},T);
net.trainParam.showWindow=0;
[net,tr] = train(net,x,t,xi,ai);
y = net(x,xi,ai);

%% MULTI-STEP PRED

%[Shifted inputs, Initial input delay states, Initial layer delay
   states]
[Xs1,Xio,Aio] = preparets(net,inputSeries(1:end-delay),{},targetSeries
   (1:end-delay));

% Estimate initial parameters of closeloop network
[Y1,Xfo,Afo] = net(Xs1,Xio,Aio);
[netc,Xic,Aic] = closeloop(net,Xfo,Afo);

% Predict based only on new inputs (feedback is an estimation)
[yPred,Xfc,Afc] = netc(inputSeriesVal,Xic,Aic);

% Append N-step predictions for one entire day ("moving window")
yp = cell2mat(yPred).*normDB(6);
pred = [pred yp];

end


%% PERFORMANCE ANALYSIS

yb = target_DB(end-(96+delay):end-delay-modu).*normDB(6);
RMSE = sqrt(mean((yb - pred').^2));
RMSE_smooth = sqrt(mean((yb - smooth(pred,6)).^2));
max_error = max(abs(yb-pred'));
max_error_smooth = max(abs(yb-smooth(pred,6)));

correl = corr(yb,pred') ;
correl_smooth = corr(yb,smooth(pred));

for i=1:N:length(yb)
    a = yb(i:i+N-1);
    b = pred(i:i+N-1)';
    MSE(i) = mse(a,b);
    rmse(i) = sqrt(mean((a-b).^2));
    rmse_smooth(i) = sqrt(mean((a-smooth(b)).^2));
```

```
105 end
106
107 % Retrieve zeros values Matlab strangely added
108 k = find(rmse);
109 RMSE_c = mean(rmse(k));
110 RMSE_c_smooth = mean(rmse_smooth(k));
111
112
113
114 %% PLOTS
115 time = inputs_DB(:,1).*normDB(1);
116 time = time(end-96:end-modu);
117
118 bounds = [3.9,11.1];
119 figure;
120 plot(time,yb,'LineWidth',2); hold on;
121 plot(time,pred,'o','Color','m','MarkerEdgeColor',[0 .5 .5],'
       MarkerFaceColor',[0 .7 .7]); hold on;
122 plot(time,smooth(pred)','Color','r','LineWidth',2); hold on;
123 plot(0:0.2:25,bounds(1),'-','Color','k','LineWidth',1); hold on;
124 plot(0:0.2:25,bounds(2),'-','Color','k','LineWidth',1);
125 legend('Target','Prediction','Smoothed Prediction','Hypo-Hyper bounds'
       )
126 x = [0.7 0.3];
127 y = [0.4 0.5];
128 str = {'RMSE : ' num2str(RMSE),' ','RMSE 2 :' num2str(RMSE_smooth)}
129 title(['BGL ' num2str(N) '-step(s) prediction'],'FontSize', 15)
130 xlabel('Time [hours]','FontSize', 12) % x-axis label
131 ylabel('Blood glucose level [mmol/L]','FontSize', 12) % y-axis label
132
133
134 %% SAVE RESULTS
135
136 % % Plot
137 % filename = ['RESULTS/' num2str(N) 'step_predC'];
138 % saveas(gcf,filename,'epsc')
139 %
140 % % RMSE and max errors
141 % results =[N, 0; RMSE, max_error ; RMSE_smooth, max_error_smooth ;
       RMSE_c , RMSE_c_smooth]
142 % filename_r = ['RESULTS/' num2str(N) 'steps_RMSEC'];
143 % dlmwrite(filename_r,results,'delimiter', '\t');
```

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