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"ADAPTIVE IDENTIFICATION AND NONLINEAR OPTIMAL CONTROL FOR GLUCOSE REGULATION IN TYPE 1 DIABETIC PATIENTS"

by

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T H E S I S

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ADAPTIVE IDENTIFICATION AND NONLINEAR OPTIMAL CONTROL FOR GLUCOSE REGULATION IN TYPE 1 DIABETIC PATIENTS

Los Miembros del Jurado de Examen de Grado aprueban la **Tesis de Doctorado en Ciencias de Ingeniería Eléctrica Opción en Sistemas de Control de Angel Eduardo Villafuerte Nuñez.**

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First and foremost, I would like to thank God Almighty for giving me the strength, knowledge, ability and opportunity to undertake this research study and to persevere and complete it satisfactorily. Without his blessings, this achievement would not have been possible.

Abstract

This thesis reports an adaptive identification scheme applied to uncertain and disturbed nonlinear systems. The adaptive identifier parameters are adapted on-line using a recursive least-squares algorithm. As an important characteristic of the adaptive identifier is that it can be proposed in the state dependent coefficient factorization form, which could be used for control purposes. Another important contribution is a robust optimal tracking nonlinear control, which can be synthesized for state dependent coefficient factorization systems. The optimal control scheme is related to finding a control law, such that a performance criterion is minimized. This criterion is usually formulated as a cost functional, which is a function of state and control variables. As a theoretical contribution, formal proofs are developed to show the convergence in the adaptive identifier and the optimal control.

The adaptive identification and optimal tracking control effectiveness is validated via simulation. Both schemes are applied for the type 1 diabetes treatment using the Bergman minimal model and the Cobelli model. The principal aim is to regulate the blood glucose levels in type 1 diabetic patients, where the dynamical behavior for different patients is difficult to model since each one has particular biological characteristics, different eating and healthy habits, age and weight, among other aspects. The optimal control versatility is demonstrated by the generation of continuous and discontinuous control signals, with the aim to be used in continuous and discontinuous insulin pumps, which are used in the current type 1 diabetes treatments. To validate the adaptive identification and the optimal control schemes, is used a specialized simulator approved by the food and drug administration in USA.

Resumen

Esta Tesis propone un esquema de identificación adaptativa aplicado a sistemas no lineales inciertos y perturbados. Los parámetros del identificador adaptativo se adaptan en línea utilizando algoritmo de mínimos cuadrados recursivos. Como una característica importante del identificador adaptativo es que puede proponerse en la forma de factorización de coeficientes dependientes del estado, que podría usarse con fines de control. Otra contribución importante es un control no lineal de seguimiento óptimo robusto, que se puede sintetizar para sistemas en su forma de factorización de coeficientes dependientes del estado. El esquema de control óptimo está relacionado con la búsqueda de una ley de control, de modo que se minimice un criterio de rendimiento. Este criterio generalmente se formula como un funcional de costo, que esta en función de las variables de estado y control. Como contribución teórica, se desarrollan pruebas formales para mostrar la convergencia en el identificador adaptativo y el control óptimo.

La identificación adaptativa y la efectividad del control óptimo de seguimiento se validan mediante simulación. Ambos esquemas se aplican para el tratamiento de diabetes tipo 1 usando el modelo mínimo Bergman y el modelo Cobelli. El objetivo principal es regular los niveles de glucosa en sangre en pacientes diabéticos tipo 1, donde el comportamiento dinámico de diferentes pacientes es difícil de modelar ya que cada uno tiene características biológicas particulares, hábitos alimentarios y saludables diferentes, edad y peso, entre otros aspectos. La versatilidad de control óptimo se demuestra mediante la generación de señales de control continuas y discontinuas, con el objetivo de ser utilizadas en bombas de insulina continuas y discontinuas, que se utilizan en los tratamientos actuales de diabetes tipo 1. Para validar la identificación adaptativa y el esquemas de control óptimo, se utiliza un simulador especializado aprobado por la administración de alimentos y medicamentos en USA.

Palabras clave: Sistemas no linelaes, Identificación adaptiva, Control óptimo no lineal, Modelo glucos-insulina, Diabetes tipo 1, Simulador T1DMS.

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Abbreviations

SDCF State Dependent Coefficients Factorization.

HJB Hamilton-Jacobi-Bellman.

SDRE State Dependent Riccati Equation.

T1DM Type 1 Diabetes Mellitus.

MDII Multiple Daily Insulin Injections.

CSII Continuous Subcutaneous Insulin Injections.

CGM Continuous Glucose Monitoring.

CGM International Diabetes Federation.

WHO World Health Organization.

PID Proportional-Integral-Derivative.

MPC Model Predictive Control.

MPILC Model Predictive Iterative Learning Control.

T1DMS Type 1 Diabetes Mellitus Metabolic Simulator.

FDA Food and Drug Administration.

SGUUB Semiglobally Uniformly Ultimately Bounded.

RLS Recursive Least-Squares.

LMS Least Mean-Squares.

NLMS Normalized Least Mean-Squares.

BeMM Bergman Minimal Model.

MCPS Medical Cyber-Physical System.

AP Artificial Pancreas. acreT2DMType 2 Diabetes Mellitus.

IVGTT Intra-Venous Glucose Tolerance Test.

OGTT Oral Glucose Tolerance Test.

EHC Euglycemic Hyperinsulinemic Clamp

EGP Endogenous Glucose Production.

PXM Pulse-Width Modulation.

FPGA Field Programmable Gate Array.

Nomenclature

G	glucose.
I	insulin.
R_a	appearance rate.
EGP	endogenous glucose production.
U	glucose utilization.
S	insulin secretion.
D	insulin degradation.
G_p	plasma glucose.
G_t	tissue glucose.
E	renal glucose excretion.
U_{ii}	use of independent insulin.
U_{id}	dependent insulin utilization.
V_G	glucose distribution volume.
k_1 and k_2	constant parameters.
I_p	plasma insulin.
I_L	liver insulin.
V_I	volume of insulin distribution.
m_1 to m_4	model parameters.
I_{po}	portal vein insulin.
I_d	delayed insulin.
k_{p1}	model parameter.
k_{p2}	efficacy of hepatic glucose.
k_{p3}	parameter that governs the amplitude of insulin action in the liver.
k_i	delay between the insulin signal and the insulin action.
Q_{sto}	amount of glucose in the stomach.
Q_{sto1}	solid phase of glucose in the stomach.
Q_{sto2}	liquid phase of glucose in the stomach.
Q_{gut}	mass of glucose in the intestine.
k_{gri}	grinding speed.
f	fraction of intestinal absorption.

BW	body weight.
D	bolus of glucose.
d_G	amount of carbohydrate intake.
A_G	bioavailability of carbohydrates.
T_{maxI}	maximum time of insulin absorption.
T_{maxG}	maximum time of the appearance of glucose.
k_{empt}	gastric emptying speed constant.
b	model parameter.
k_{max} and k_{min}	model parameters.
V_{m0} and V_{mx}	model parameters.
k_{m0} and k_{mx}	model parameters.
p_{2u}	insulin speed constant over peripheral glucose.
γ	constant rate of transfer between the portal vein and the liver.
K	responsiveness of the pancreas to the rate of glucose exchange.
$\bar{\alpha}$	delay time between the glucose signal and insulin secretion.
$\bar{\beta}$	pancreatic response capacity to glucose.
k_{e1}	glomerular filtration rate.
k_{e2}	renal glucose threshold.
k_d	degradation constant.
k_{a1} and k_{a2}	absorption constants.
$\mathcal{X}$	state variables system vector.
x	identifier states vector.
x_a	augmented vector of the controlled system.
θ	identifier parameters.
ε	identification error.
e	control tracking error.
q	integral term.
w	regressor vector.
g and Ψ	design parameters for the identifier model.
Φ	covariance matrix.
V	Lyapunov function.
u	control input.

List of publications

Conference Papers

Angel E. Villafuerte, F. Ornelas-Tellez, J. J. Rico-Melgoza, and Edgar N. Sanchez, "Adaptive polynomial identification and optimal tracking control for polynomial systems", XVI Congreso Latinoamericano de Control Automático (CLCA), Cancún Quintana Roo, México, Oct 2014. Published in the congress memories.

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Angel E. Villafuerte-Nuez, Febe Jocabed Zavala-Mendoza, Fernando Ornelas-Tellez and J. Jesús Rico-Melgoza, "Adaptive reduced-order identifier applied to the glucose-insulin nonlinear system" International Autumn Meeting on Power, Electronics and Computing (ROPEC), Ixtapa, Mexico, Nov. 2016. IEEE.

Fernando Ornelas-Tellez and Angel Villafuerte, "Adaptive Polynomial Identification and Optimal Tracking Control for Nonlinear Systems", Proceedings of the Conference on Control and its Applications (SIAM). Paris, France, July 2015, pp. 259-265. eISBN: 978-1-61197-407-2

Febe Jocabed Zavala-Mendoza, Angel E. Villafuerte-Nuez, Fernando Ornelas-Tellez and J. Jesús Rico-Melgoza, "Identificación y control de un sistema glucosa-insulina para el tratamiento de pacientes diabéticos tipo 1", Congreso Nacional de Control Automático (CNCA), Monterrey, Nuevo León, Oct. 2017.

Journal Papers

Angel E. Villafuerte-Nuez, Febe Jocabed Zavala-Mendoza, Fernando Ornelas-Tellez and J. J. Rico-Melgoza, "Adaptive polynomial identification: application to the glucose-insulin system", International Journal of Adaptive Control and Signal Processing, Jhon Wiley and Sons Ltd, ISSN 1099-1115 (under review)

Febe Jocabed Zavala-Mendoza, Angel E. Villafuerte-Nuez, Fernando Ornelas-Tellez and J. J. Rico-Melgoza, "Identificación polinomial y control óptimo no lineal para la regulación de glucosa en pacientes diabéticos tipo 1", Revista del IEEE América Latina, ISSN 1548-0992. (under review)

Chapter 1

Introduction

Nonlinear systems usually present complex and often unpredictable behaviours in different natural phenomena. The nonlinear systems are present in different areas of everyday life, e.g., engineering, industrial process, economic data, biology and life sciences, medicine and health care. It is difficult to have general modeling methods due to the variety of nonlinear systems, which are generally subject to uncertainties and disturbances. Therefore, it is convenient to use alternative methodologies for modeling, such as systems identification, which is the estimation of dynamic system models from observed data, among other methodologies. Once an adequate system identification is achieved, it is necessary synthesize effective controllers that satisfy the design needs. A specific area in biological systems is focused for the application of the adaptive identification and the optimal nonlinear control strategies, which is the type 1 diabetes treatment. Diabetes is a serious, chronic disease that occurs either when the pancreas does not produce enough insulin (a hormone that regulates blood sugar, or glucose), or when the body cannot effectively use the insulin it produces. Diabetes is an important public health problem, one of four priority noncommunicable diseases targeted for action by world leaders. Both the number of cases and the prevalence of diabetes have been steadily increasing over the past few decades. Globally, an estimated 422 million adults were living with diabetes in 2014, compared to 108 million in 1980. The global prevalence (age-standardized) of diabetes has nearly doubled since 1980, rising from 4.7% to 8.5% in the adult population. This reflects an increase in associated risk

factors such as being overweight or obese. Over the past decade, diabetes prevalence has risen faster in low- and middle-income countries than in high-income countries. Diabetes caused 1.5 million deaths in 2012. Higher than optimal blood glucose caused an additional 2.2 million deaths, by increasing the risks of cardiovascular and other diseases. Forty three percent of these 3.7 million deaths occur before the age of 70 years. The percentage of deaths attributable to high blood glucose or diabetes that occurs prior to age 70 is higher in low- and middle-income countries than in high-income countries [WHO].

Diabetes is on the rise, no longer a disease of predominantly rich nations, the prevalence of diabetes is steadily increasing everywhere, most markedly in the world's middle-income countries. Unfortunately, in many settings the lack of effective policies to create supportive environments for healthy lifestyles and the lack of access to quality health care means that the prevention and treatment of diabetes, particularly for people of modest means, are not being pursued. When diabetes is uncontrolled, it has dire consequences for health and well-being. In addition, diabetes and its complications impact harshly on the finances of individuals and their families, and the economies of nations. Therefore, the design of an adaptive identification and a robust optimal control scheme capable to close the loop between the continuous glucose monitoring and the insulin pumps can provide a solution to the blood glucose regulation problem in type 1 diabetic patients, allowing the automation in the treatment with the aim that people with the disease live a life as close as possible as a healthy person. This chapter presents an introduction of the identification and control problem applied nonlinear systems as well as the objectives, the contributions and the application of this thesis.

1.1 Nonlinear systems identification

For linear systems, there exist well-structured theory, methodologies and algorithms for their respective modeling and control. For the case of nonlinear systems, the situation is more complex. In this sense, the identification method is only as good as the model it utilizes depending of the inputs and outputs of the system that can be measured. In literature exist different methods, which are used to identify nonlinear systems [Now02, Nel],

such as polynomial identifiers [MS87, Fun92], neural and polynomial networks [NI06], etc. These identifier methods propose nonlinear models whose structures are based on parameters to be determined. If the parameters are linear respect to the model structure, the identification may be carried out using linear parameter estimation methods, even though the model is nonlinear in the system state variables. When parameters present uncertainties, and unexpected disturbances affect the system dynamics, then it is convenient to use an adaptive identification, which allows adapt the parameters to the changes in the system behavior. Therefore, the adaptive identification is an adequate technique for obtaining the optimal identifier parameter values due to that minimizes the error between the simulated results and the experimental data [OTV15, VOTRM15]. Different techniques are used to obtain the identification scheme that allow an approximation among the simulations of the proposed model and the experimental data, however, these methods are not necessarily computationally efficient and could not guarantee convergence [Nel13].

Two schemes are common in the field of system identification: *a)* A black-box methodology, where only the data of the relationships between the input and output are known, which should serve to determine an identifier model; *b)* a grey-box methodology, where a priori knowledge of the system (e.g. system order, structure, variables relationships, etc.) can be used to propose an identifier model. The last methodology is applied in this thesis because of there exist a previous knowledge of the nonlinear system studied here. In this sense, adaptive identifiers are used to determine accurate model structures, which describe the behavior of a nonlinear system; however, in practice it is convenient to develop efficient procedures that allow to approximate the complex nonlinear systems through generating suitable identifier structures, considering that the most important characteristics are taken into account in the modeling process [SOH04].

In the literature exist different methods, which are used to identify nonlinear systems [Now02, Nel], such as polynomial identifiers [MS87, Fun92], neural and polynomial networks [NI06], etc. Because of that, there exist different areas where the identification process is used to obtain models to describe the essential behaviours of nonlinear systems, e.g. in biochemical networks [MBVS05], electrical engineering [FNG12], biomedical process [DJS$^+$07], etc. Various nonlinear systems can be modelled by polynomial structures and

are used as identifiers models, which is the case of the glucose-insulin system. Due to the glucose-insulin system behaviours are very slow with soft curves, i.e., its dynamics are represented in hours, in this thesis is proposed an adaptive identification scheme which consists to develop a polynomial identifier model whose parameters are linear regarding to the model structure. The identifier parameters are adapted on-line using a recursive least-squares algorithm (RLSA) due to has faster convergence rate than least mean-square (LMS) and normalized least mean square (NLMS) algorithms with better robustness to noises, unpredictable situations and better tracking capability, which allows an adequate identification of the nonlinear systems, specifically the glucose insulin system. The polynomial structure is selected due to their approximating capabilities, relatively simple structure, easy to implement, and with the capacity to adjust its parameters (polynomial's coefficients) on-line. One of the most important advantages of polynomial models is that they allow a state dependent coefficient factorization (SDCF) representation, whose feature can be used to design nonlinear feedback controllers.

1.2 Optimal nonlinear control

Classical control system design is generally a trial-and-error process in which various methods of analysis are used iteratively to determine the design parameters of an acceptable system. Acceptable performance is generally defined in terms of time and frequency domain criteria such as rise time, settling time, peak overshoot, gain and phase margin, and bandwidth. Radically different performance criteria must be satisfied, however, by the complex, multiple-input, multiple-output systems required to meet the demands of modern technology. For example, the design of a spacecraft attitude control system that minimizes fuel expenditure is not amenable to solution by classical methods. A new and direct approach to the synthesis of these complex systems, called optimal control theory, has been made feasible by the development of the digital computer.

The objective of optimal control theory is to determine the control signals that will cause a process to satisfy the physical constraints and at the same time minimize (or maximize) some performance criterion. In optimal nonlinear control, one deals with the

determination of a stabilizing control law for a given system in a manner such that a performance criterion is minimized, which is a function of the state variables and the control inputs. Optimal control laws benefit from adequate stability margins, and the fact that they minimize a meaningful cost functional ensures that control effort is not wasted [FK96]. Indeed, optimal control theory is introduced in [SJK12, FK08] as a synthesis tool to guarantee stability margins, which are basic robustness properties that a control system must possess [SJK12, AM07]. Optimality is thus a discriminating measure to select a control law with desirable properties among a set of stabilizing control laws [FK96]. In [FK08, LG95, LG94], the robust optimal control approach is presented to deal with disturbances and uncertainties in the system, and in [GKM06, SM12, Ebi13, Roj13] for systems in the discrete-time framework, meanwhile optimal techniques based on model predictive control are presented in [ZLC08, ZCC10, ANT14, Din13]. Optimal control can be solved by using the maximum principle of Pontryagin (a necessary condition) [Pon87] and the method of dynamic programming developed by Bellman [BBBB95].

The latter leads to a nonlinear partial differential equation named the Hamilton-Jacobi-Bellman (HJB) equation (a sufficient condition), whose solution provides state feedback controllers and optimal trajectories from every initial condition [SJK12, PND99]. The application of this equation is well-established in solving the optimal control problem for linear systems, where its formulation results in the differential Riccati equation [AM07]. However, solving the HJB equation is rather complicated for general nonlinear systems [SJK12, FK08].

Different control strategies have been proposed to provide nonlinear feedback controllers, including the state-dependent Riccati equation (SDRE) approach, which is well-known and has become popular over the last decade [CDM96b, Erd01, Erd01, BLT07b, Cim08]. This control approach provides an effective algorithm for synthesizing nonlinear feedback controllers. In [Pea62], a linear time and state-dependent approximation is proposed to optimize a nonlinear system with respect to a quadratic performance index by considering an instantaneously linear stationary system. A suboptimal solution to the nonlinear quadratic regulator and tracking with infinite final time is investigated in [WC75],

for which the nonlinear system is represented by an instantaneous linearization and then solves the optimal control.

A comprehensive survey on the SDRE scheme is presented in [Cim08], which describes the approach as an effective methodology for synthesizing nonlinear controllers, observers and filters. In [BP10] a numerical optimal control approach is established for polynomial nonlinear systems based on the sum of squares. In essence, the SDRE technique is a systematic way of synthesizing nonlinear feedback controllers, which mimic the controller synthesis as done for the linear case [BLT07b]. In addition, SDRE has been an effective applied control technique in the control of an artificial human pancreas [PR97], the regulation of the growth of thin films in a high-pressure chemical vapor deposition reactor [TAZ98, KBTB02], satellite and spacecraft control and estimation [Erd01, Puk13, HHR98b], robotics [EA01] and a magnetic levitation ball [EA99]. Other systems that can be represented by in state-dependent coefficient factorization are polynomial systems, mechanical systems [Bog04, ZAPP05] and electrical machines (inductions motor, induction generators). In [MC98] the SDRE approach has been applied to unstable non-minimum phase systems. An analysis for the stability region of the SDRE controllers is given in [CC09]. Recent results [Erd01, KBTB02] have reported the success of the SDRE control technique in the synthesis of feedback controllers for real-time implementation. Indeed, the SDRE approach can be used for systems such as complex networks that may contain multiple nodes [LC05], possibly competing or collaborating to achieve system wide goals, if a state-dependent coefficient factorization of the complex network can be accomplished. Interestingly, the SDRE approach has advantages with respect to other control techniques (such as feedback linearization [Isi13] and backstepping [Kha96b]), since non-robust cancellations and possible zero divisions are avoided [SJK12, Erd01]; moreover, the nonlinear SDRE technique has a larger domain over the state space than the Taylor linearization [CDM96b, Erd01]. Furthermore, this control technique allows the incorporation of physical intuition characteristics when the control scheme is synthesized, such that a specified performance for the system is imposed by properly tuning the weighting matrices in the cost functional [Erd01]. Note that although, as mentioned above, there already exist many important results on optimal control based on the SDRE to achieve stabilization for nonlinear systems, the optimal track-

ing for nonlinear systems has been seldom analyzed [CB04, Udw08]. In spite of that, for different control applications, it is required that the output of the system tracks a desired trajectory. Due to the adaptive identification scheme develops polynomial identifier models which can be represented in the SDCF form, the optimal nonlinear control allows to synthesize controllers for that kind of systems [OTRRC13, OTV15]. The principal aim of the optimal nonlinear control is to minimize a meaningful cost functional, which is a function of the state variables and the control inputs. In the particular application presented in this thesis, this feature allows to determine an adequate insulin dose. The type 1 diabetes treatment demands an adequate regulation of the blood glucose into safety levels, this problem can be solved using the property of the nonlinear optimal control to track constant or slowly time-varying references.

1.3 Modeling and control applied to biomedical systems

There exist different areas where the optimal control can be applied, but one of the most interesting areas is the biological systems, which can be represented by nonlinear models and affected by different disturbances. Therefore, it is important synthesize adequate control strategies capable to deal with the complexity of the different biological systems. The optimal nonlinear control is an excellent option to determine control signals that satisfy the physical constraints in the biological systems and at the same time minimize (or maximize) some performance criterion. In the last decades have existed an important attention in some biological systems, specifically in the glucose-insulin system due to it is used to treat the type 1 diabetes disease. The principal aim to study this particular biological system is to develop an adequate control system capable to determine the optimal insulin signal to maintain the glucose in safe levels. It could represent an opportunity for type 1 diabetic patients to recover a normal life. The importance of solving this problem is due to the diabetes is a chronic disease that occurs when the pancreas is no longer able to make insulin, or when the body cannot make good use of the insulin it produces. Insulin is a hormone made by the pancreas, that acts like a key to let glucose from the food we eat pass from the blood stream into the cells in the body to produce energy. All carbohydrate

foods are broken down into glucose in the blood. Insulin helps glucose get into the cells. Not being able to produce insulin or use it effectively leads to raised glucose levels in the blood (known as hyperglycaemia). Over the long-term high glucose levels are associated with damage to the body and failure of various organs and tissues. There are two major types of diabetes: type 1 and type 2 [FMD].

Type 1 Diabetes Mellitus (T1DM) used to be called juvenile-onset diabetes. It is usually caused by an auto-immune reaction where the bodys defence system attacks the cells that produce insulin. The reason this occurs is not fully understood. People with type 1 diabetes produce very little or no insulin. The disease may affect people of any age, but usually develops in children or young adults. People with this form of diabetes need injections of insulin every day in order to control the levels of glucose in their blood. If people with type 1 diabetes do not have access to insulin, they will die. In Mexico the 2016 National Health and Nutrition Survey (ENSANUT Encuesta Nacional de Salud y Nutrición) explored the status of several chronic diseases [FMD]. Among them, diabetes cases in the Mexican population over 15 years old. It was found that diabetes prevalence in the country went from 9.2% in 2012 to 9.4% in 2016, based on a previous diagnosis of the disease. On this population:

- At least 10 million people are diagnosed with this disease.
- 542,000 children live with type 1 diabetes.
- 78,000 children develop type 1 diabetes each year.

The current insulin therapy for T1DM patients is based on discrete blood glucose measurements and Multiple Daily Insulin Injections (MDII) or a Continuous Subcutaneous Insulin Infusion (CSII). The use of sensors and CSII pumps systems in an open-loop combination has resulted in better clinical outcomes than conventional MDII therapy [Klo05]. Therefore, automatic regulation of a patient's blood glucose level requires a minimum of three components, namely, a continuous blood glucose sensor, a controller that matches blood glucose level with an appropriate insulin delivery rate, and an infusion pump to deliver the insulin to the subject. Figure 1.1 shows a schematic closed-loop system that

combines a glucose sensor, a control algorithm, and an insulin infusion device, which could be called as artificial pancreas.

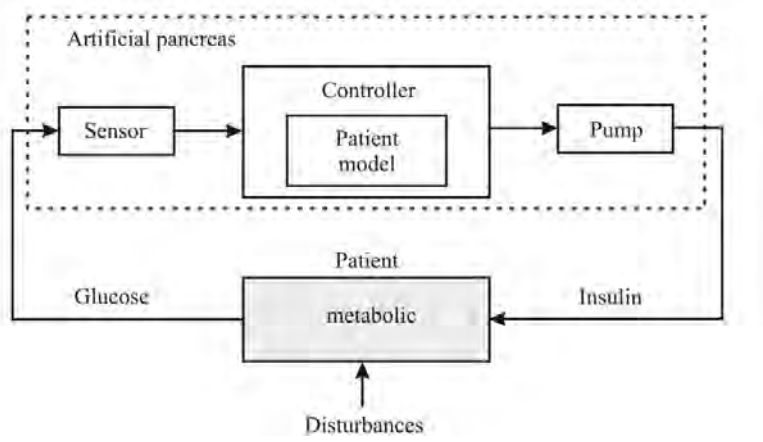


Figure 1.1: Schematic of glucose management with an artificial pancreas.

The principal control algorithm's aim in the artificial pancreas is to determine the needed amount of insulin to maintain blood glucose levels within the desired range, preventing hypoglycemia, minimizing the need for patient intervention in the therapy and giving higher flexibility for patients in daily life (e.g. meal times and quantities, physical activity, stress, among others). Given the inability of current therapies to achieve satisfactory glycemic control, the development of continuous glucose monitoring (CGM) sensors and the increasing use of CSII pumps, the development of an optimal nonlinear control technique is viewed as a promising solution in the automatic control of the glucose level in T1DM problem, due to this technique determines the control signals that will cause a process (glucose-insulin system) to satisfy the physical constrains and at the same time minimize or maximize a chosen performance criterion (optimal insulin dosage) [Kir12]. Optimal control laws benefit from adequate stability margins, and the fact that they minimize a meaningful cost functional ensures that control effort is not wasted [FK96]. Indeed, optimal control theory is introduced in [SJK12, FK08] as a synthesis tool to guarantee stability margins, which are basic robustness properties that a control system must possess [SJK12, AM07]. Optimality is thus a discriminating measure to select a control law with desirable properties

among a set of stabilizing control laws [FK96]. In [FK08, LG95, LG94], the robust optimal control approach is presented to deal with disturbances and uncertainties in the system, and in [GKM06, SM12, Ebi13, Roj13] for systems in the discrete-time framework, meanwhile optimal techniques based on model predictive control are presented in [ZLC08, ZCC10].

The formulation of optimal control problem requires a mathematical description or model (glucose-insulin system) of the process to be controlled (generally in state variable form), a specification of the performance index, and a statement of boundary conditions and the physical constraints on the states and/or controls. In this thesis the optimal control technique is developed considering that systems are usually uncertain and exposed to disturbances, characteristics that the glucose-insulin system presents. The development of an optimal control scheme capable of maintaining the glucose in normal levels over extended periods of time could improve the quality of life for diabetic patients. Therefore, this thesis presents an adaptive identifier for modeling the glucose-insulin dynamics and an optimal nonlinear control scheme capable to deal with disturbances and determine the needed insulin dosage to maintain the blood glucose in the safety levels.

1.4 Research motivation

In Mexico the diabetes is one of the most serious health problems of our time. In addition to its significant mortality rate (is the leading cause of death in the country), the direct healthcare costs of diabetes are around 8,835 millions [IDF], and its related complications range from 2.5% to 15% of annual healthcare budgets worldwide [WHO]. Therefore, from quality of life and economic perspectives, it is very important for diabetic patients to regulate their blood glucose level tightly, keeping it within the acceptable range of 70-180 mg/dL [ADA05], by using insulin therapy. Optimal nonlinear control techniques allow to achieving the desired glycemic control in T1DM by delivering optimal doses of insulin, resulting in less long-term medical complications, as well as avoiding hypoglycemic and hyperglycemic incidents. The development of a closed-loop control algorithm has been a continuously growing research topic for more than four decades. Different clinical and simulation studies have demonstrated the feasibility of such an automated system, where

several classical and advanced control algorithms have been tested as possible candidates to close the control loop [Beq12, Beq05, CF07, EYCW09, TXH08, CDMS+09]. However, a closed-loop system is not yet commercially available, and automatic blood glucose regulation in T1DM is still a challenging problem in biomedical engineering and optimal controllers development.

Glucose regulation in T1DM includes several sources of errors and uncertainties that convert the design of a control algorithm into a very complex task. The principal problem to solve is the complexity of the insulin-glucose system which includes the presence of nonlinearities, patient-specific parameters and disturbances (lifestyle, stress, cardiovascular diseases, physical activities and special diets). An adequate adaptive identifier and optimal nonlinear control algorithm must be capable of handling these physiological challenges while still providing acceptable performance, increasing the quality lifestyle of the type 1 diabetic patients.

1.5 Review of control algorithms applied in type 1 diabetes

A method for optimal continuous insulin therapy for diabetes patients has been sought since the early 1970's. The principal aim is to develop control algorithms for type 1 diabetic patients which automatically connect continuous glucose monitoring and insulin injection, without patient intervention. Black-box model and grey-box model based control strategies have been developed and their performances are evaluated, with a focus on their feasibility of implementation in a real-life situation. In conclusion, a satisfactory control strategy has not yet been proposed, mainly because most control algorithms rely on continuous blood glucose measurement which is not yet available. Therefore, research on blood glucose control needs to concentrate on patient modeling and control optimization under realistic patient-oriented conditions.

At the moment, T1DM patients face the daily challenge of manually controlling their blood glucose concentration as shown in Figure 1.2. After measuring their blood glucose concentration e.g. with a test strip, they have to determine the appropriate size of the insulin bolus and inject it subcutaneously with an insulin pen or pump.

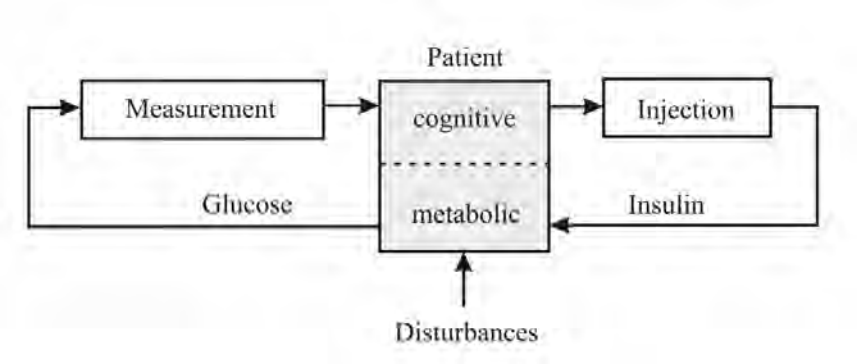


Figure 1.2: Schematic of current glucose management process: the patient appears once as the metabolic system to be controlled and again as the controller itself.

Thus, in the resulting control loop, the patient appears twice: once as the glucose metabolic system which has to be controlled and again as the controller itself (cognitive system). In the decision-making process, external disturbances and internal system changes have to be taken into account. Since it is difficult to take all effects into consideration, the control method is often accompanied by hypo- or hyperglycemic events. On the one hand, a low blood glucose concentration (<60 mg/dl) may induce an acute medical condition, such as sudden loss of consciousness or even coma, which can be fatal. On the other hand, a high blood glucose concentration (>180 mg/dl) may not be immediately life-threatening but can lead to severe secondary disorders, such as diabetic nephropathy (kidney disease or damage), neuropathy (general diseases or malfunctions of the nerves) and retinopathy (eye disease).

To avoid patients having to determine each insulin dose manually, and to limit the large variation in blood glucose concentration, an efficient control algorithm needs to be developed. The basic idea is to calculate the required insulin dose using a control algorithm based on continuous glucose measurements. For this, a mathematical patient model may support the computation of an appropriate insulin injection. Then, the precise insulin dose is automatically administered via a pump that continuously delivers insulin. This section describes a review of different control algorithms developed with the aim to close the loop for blood glucose control in type 1 diabetic patients.

1.5.1 Control algorithms applied to T1DM treatment

Different techniques have been applied for diabetes closed-loop control. These schemes range from the classical PID control scheme [DMRRC07, KBDMC09, Pal11, SPR04, PDZ+09], the model predictive control (MPC) [KBDMC09, MFT+09, PBB+09], MPILC (A combination of iterative learning control and MPC) [WDDI10]. In [BFC+09, EKRN+10, CDMS+09] continuous subcutaneous insulin infusion is used with an approach based on MPC; however there is no formal demonstration for stability [CDMS+09, PDP01, PD01]. All those control schemes are exhaustive reviewed in [CDMS+09, PDP01, PD01], where advantages and disadvantages for each one of them are explained. In Table 1.1 are summarized the most important control strategies, which are based on different internal models that represent glucose-insulin dynamics in T1DM patients [Sor85, HCC+04a, LSW+13]. In Table 1.5.1 the control performance evaluation is summarized including blood glucose

Table 1.1: Overview of reviewed control algorithms classifying them using the input, output and model type.

Publication	Control algorithm							
	Control strategy	Internal model	Input Gluc(t)	Output IIR(t)	Manual input	Sampling time	Glucose target	Adaptation
Black-box model-based control strategies								
Steil (2006)	PID	–	s.c.	s.c.	–	5 min (CGMS), 20 min BG i.v.	120 mg/dl	√
Dalla Man (2007)	PID	–	s.c.	s.c.	–	continuous	130 mg/dl	–
Gantt (2007)	Adaptive PI	–	s.c.	s.c.	–		81 mg/dl	√
Marchetti (2008)	ext. PID	–	filt.	s.c.	Switch time	5 min	80 mg/dl	√
Palerm (2008)	Run-to-run	–	i.v.	s.c.	–	5 times/day	80 mg/dl	√
Grey-box model-based control strategies								
Parker (1999)	Linear MPC With Kalman filter	Sorensen and Lehman	i.v.	i.v.	*D*, ?	5 min		–
Lynch (2001)	Linear MPC With Kalman filter	*minimal model*, Lehman/Fisher	s.c.	i.v.	?	5 min	81.3 mg/dl	–
Gillis (2007)	Linear MPC With Kalman filter	*minimal model*, Part. Hovorka	s.c.	s.c.	*D*	5 min	80 mg/dl	√
Magni (2007)	Linear MPC	Red. Dalla Man	s.c.	s.c.	*BW*, *D*	30 min	112 mg/dl	√
Magni (2008)	Nonlinear MPC	Dalla Man	s.c.	s.c.	*BW*, *D*	30 min	135 mg/dl	–
Hovorka (2004)	Nonlinear MPC (self-adapting)	Hovorka	i.v.	s.c.	–	15 min	6 mmol/L, Time-variant	√
Marchetti (2008)	Feedforward-feedback Control strategy	ext. Hovorka	i.v.	s.c.	*D*	5 min	Time-variant	√

settling time and possible future control adaptations for performance improvement. In the first column is presented the author, the publication year of the paper, and the applied control strategy. The control algorithms are divided into black-box and grey-box model-

Table 1.2: Overview of reviewed control algorithms classifying them using the control evaluation.

Publication	Control evaluation				
	Meal	*In silico*	*In vivo*	Settling time	Future adaptation
Black-box model-based control strategies					
Steil (2006)	40–90 g	–	10 type 1		More robust for noise, faster settling time
Dalla Man (2007)	45–70 g, adaptive	Dalla Man	–		Discrete measurement, robust noise response
Gantt (2007)	3–33 mg	mod. *minimal model*	–		Response to meal uptake more aggressively
Marchetti (2008)	60 g	ext. Hovorka	–		Automatic control switch-off, s.c. glucose measurement
Palerm (2008)	Not given	ext. Hovorka	–		Continuous time-dependent insulin infusion
Grey-box model-based control strategies					
Parker (1999)	50 g	yes, Model unknown	–	Approx. 3 h	s.c. glucose measurement Possibly s.c. insulin infusion
Lynch (2001)	50 g	Sorensen	–	Approx. 3 h	s.c. glucose measurement More aggressively performance
Gillis (2007)	50 g	Hovorka +noise, Historical data	Advisory mode	approx. 6 h	Reduction of BG undershoot
Magni (2007)	45–80 g	Dalla Man (full)	–	Approx. 6 h	s.c. glucose measurement
Magni (2008)	45–85 g	Dalla Man	–	Unclear	s.c. glucose measurement
Hovorka (2004)	–	Evaluation Algorithm	10 type 1	–	Meal response s.c. glucose measurement
Marchetti (2008)	60 g ± 50 %	ext. Hovorka	–	min. 5 h	s.c. glucose measurement

based strategies. With regards to the evaluation of the controller, a distinction is made between *in silico* and *in vivo* tests. Table 1.5.1 includes information whether or not the control behavior was evaluated with respect to ingestion response, which is simply called a *meal*, and to the quantity of glucose ingested. Most of the reviewed control algorithms assume continuous intravenous (i.v.) glucose measurement. However, because no adequate sensor device is available, the algorithms have not yet been applied in clinical studies for closed-loop diabetic insulin therapy. For those algorithms addressing adequate sensor devices, the step from *in silico* to *in vivo* application did not appear sufficiently safe for the patient. Therefore, the performance of the controllers was generally evaluated by application on simulation platforms only [KBDMC09, CWH04]. Some of the analysed algorithms were tested as closed-loop systems in clinical trials [KBDMC09, CWH04].

The challenge of mimicking the natural closed-loop behavior with state-of-the-art diabetes therapy devices are the large time delays induced by subcutaneous (s.c.) glucose measurements and the effect of subcutaneously injected insulin on glucose metabolism. Because the response of black-box model-based control algorithms to disturbances is slowed

down, a rapid increase in blood glucose cannot be prevented in reasonable time by applying a common PID control algorithm. This control strategy can only be used for initial closed-loop trials. To stabilize blood glucose concentration at normoglycemia, advanced control algorithms are preferred, such as MPC or feedforward-feedback control. These grey-box model-based strategies include information on the patient's glucose metabolism and, thus, may prevent critical events, depending on the accuracy of the internal model.

Due to control simplification and reduced patient penetration, insulin is generally used as the sole system input (cf. Table 1.1) and the counter hormone glucagon is ignored as an actuating variable. As insulin is responsible for a decrease in glucose concentration, the controller has to be designed with a slow dynamic behavior in order to avoid hypoglycemic events. This requirement is valid for single-input control algorithm, but is even more important for black-box model-based control strategies than for gray-box model-based ones. Especially the internal patient models in the latter control strategy are modified by supplementary external information such as the patient's body weight. Impending glucose ingestion must be announced in order to adapt the calculations of insulin dose to reduce hyperglycemia and impede hypoglycemic events.

Table 1.1 shows that almost all grey-box model-based control strategies require supplementary patient information (manual input), which increases the manual effort but improves the control performance. In contrast, the black-box model-based control strategies do not need extra patient information. Several external and internal disturbances change the behavior of the diabetic patient:

- Glucose ingestion and physical activity have a considerable impact on the patient's blood glucose concentration. According to patient models summarized in Table 1.1, glucose uptake through the gastro-intestinal tract is assumed to be well understood. In contrast, the influence of physical activity on glucose metabolism is not yet fully elucidated and is generally ignored [DB02, Bre08, DMBC09, Nag06].

- Diurnal variation of insulin sensitivity of the glucose-consuming cells affects the essential amount of plasma insulin. This behavior depends, for example, on eating and sleeping times [DMRC07].

Thus, a patient's specific insulin demand depends on external disturbances and intracorporeal metabolic changes, and differs between individuals. Some of the reviewed control algorithms are able to adapt to the individual patient and minor system changes as indicated with a check in Table 1.1. Especially black-box model-based control strategies have the advantage that they do not require specific patient information for satisfactory control performance. Grey-box model-based algorithms are able to control blood glucose concentration in a tighter way, by adapting the internal model to the patient's individual behavior with the information provided.

Their performance is based on specifying the time and size of the meal. Black-box control algorithms have a simple structure, do not require detailed information about the patient's internal behavior, and are easily designed. However, their performance is not optimal due to large time delays, and system changes such as alterations in insulin sensitivity are typically not accounted. In contrast, as model-based control algorithms predict the plant behavior they may prevent critical events from occurring. As their response depends on the accuracy of the internal model, control performance degradation is caused by model-induced system simplification and neglected adaptation to the individuals patient's metabolism.

In a more specific comparative, in [PJvzMB98] is employed the neural network approach to predict the time course of the blood glucose level. The data used for predicting blood glucose were measured only in one diabetic patient over almost 6 months and consisted of the times and dosages of insulin injections, the times and amounts of food intake, and the times and durations of exercise. Blood glucose levels were measured only a few times a day. This model is used in [EJ05] where the modeling and simulation of type 1 diabetes mellitus is based on an artificial neural network approach. The methodology builds upon an existing rich database on the progression of type 1 diabetes for a group of diabetic patients. The model was found to perform well at estimating the next glucose level over time without control. A neural controller that mimics the pancreas secretion of insulin into the body was also developed. This controller is of the two term type: one stage is responsible for short-term and the other for mid-term insulin delivery. In [MRDM$^+$09] a feedback control of glucose concentration in type 1 diabetic patients using subcutaneous insulin delivery and subcutaneous continuous glucose monitoring is considered. A recently

developed in silico model of glucose metabolism is employed to generate virtual patients on which control algorithms can be validated against interindividual variability. An in silico trial consisting of 100 patients is used to assess the performances of a linear output feedback and a nonlinear state-feedback model predictive controller, designed on the basis of the in silico model. Finally, in [LAS$^+$12] an inverse optimal neural control for trajectory tracking is applied to glycemic control of type 1 diabetes mellitus patients. The proposed control law calculates the adequate insulin delivery rate in order to prevent hyperglycemia and hypoglycemia levels in T1DM patients. Two models are used: (1) a nonlinear compartmental model in order to obtain type 1 diabetes mellitus virtual patient behavior, and (2) a neural model obtained from an on-line neural identifier, which uses a recurrent neural network, trained with the extended Kalman filter (EKF); the last one allows the applicability of an inverse optimal neural controller. The proposed algorithm is tuned to track a desired trajectory; this trajectory reproduces the glucose absorption of a healthy person. This last comparative present different techniques based on artificial intelligence, neural networks, model predictive control and inverse optimal neural control, all of them with the aim to obtain an adequate blood glucose regulation in type 1 diabetic patients based on the development of models to represent the dynamics of the glucose-insulin system in type 1 diabetes, and the use of different mathematical models proposed by Sorensen [Sor85] and Hovorka [HCE$^+$08].

However, synthesizing a control law for these models is complicated due to the complexity associated with measurements, and uncertainty of the related parameters [HCC$^+$04a], because of that it is necessary to develop an adaptive identifier scheme capable to represent the glucose-insulin dynamics in T1DM patients, dealing with the complexity of the human system and the internal and external disturbances. Once developed an adequate adaptive identifier, the glucose-insulin control problem can be formulated within the framework of optimal control theory [VOTRM15, AP$^+$11, KKGB11, QFGF11], which allows an optimal blood glucose regulation optimizing the resources under certain physical specifications.

A previous work related to the topic of this thesis is presented in [Men17], where a reduced-order adaptive identifier and optimal control scheme are applied to regulate the glucose level in type 1 diabetic patients. The adaptation of the identifier parameters is

based on a recursive least squares algorithm. Then, a robust optimal controller design is presented which supports the representation of state dependent coefficients, the proposed optimal controller is applied to the proposed identifier model. The validation of the identifier and the control is done through type 1 diabetes mellitus software (T1DMS) simulator and simulations in *Wolfram Mathematica*® and *MATLAB*®.

Some important differences between the previous work and this thesis are: *a)* theoretical contributions (formal proofs) about the adaptive identifier and optimal control convergence are presented in this thesis, *b)* continuous and discontinuous optimal control signals are developed to be used in the different insulin pumps used in the T1DM treatments, *c)* the validation of the proposed adaptive identifier, which is based on the Cobelli model, and the robust optimal tracking nonlinear control scheme is presented using the T1DMS software. It is important to highlight that the T1DMS software is based on the Cobelli model and is approved by the FDA in USA to validate control techniques focused in the type 1 diabetes treatment.

1.6 Hypothesis

The design of an adaptive identification scheme and a robust optimal control scheme for uncertain and disturbed nonlinear systems, can provide a solution to glucose regulation in type 1 diabetic patients. An adequate adaptive identification of the glucose-insulin behavior allows to deal with the different disturbances that affect the glucose dynamics in a type 1 diabetic patient (factors as eating and healthy habits, age, weight, among others), due to allows the minimization of the identification error by the use of a RLSA to adapt on-line the parameters in the adaptive identifier, achieving an adequate identification of the dynamical glucose behavior in the type 1 diabetic patients. The optimal tracking nonlinear control ensures an optimal regulation into the desired reference level by the minimization of a cost functional that provides the needed dose of insulin. This contribution allows people with type 1 diabetes to live a life as close as possible to that of a healthy person.

1.7 Research objectives

The main objective of the thesis is to develop an adaptive identification scheme applied to uncertain and disturbed nonlinear systems, and a robust optimal nonlinear control scheme applied to the developed adaptive identifier models, whose principal application is the glucose regulation in type 1 diabetic patients.

1.7.1 Specific objectives

- To develop an adaptive identifier scheme to model uncertain and disturbed nonlinear system dynamics by the use of an identification algorithm based on a recursive least squares to adapt the identifier parameters.
- To develop a robust optimal nonlinear control scheme with the aim to be applied in the developed adaptive identifier models, capable to reject disturbances and achieving a trajectory tracking of the system output toward the desired reference.
- To apply the adaptive identification scheme to nonlinear mathematical models that represent the physiological glucose-insulin dynamics in type 1 virtual diabetic patients.
- To apply the robust optimal tracking nonlinear control scheme in the developed adaptive identifier models with the aim to determine the continuous optimal amount of insulin needed to regulate the blood glucose in type 1 diabetic virtual patients.
- To develop discontinuous (periodic) control signals by the use of a discretization strategy applied to the continuous control signal obtained by the robust optimal control scheme.
- To validate the adaptive identifier and control scheme using (T1DMS) software which is accepted by the food and drug administration (FDA) as a substitute for pre-clinical studies.

1.8 Thesis contributions

The specific contributions of the proposed research are:

- The development of an adaptive identification scheme used to model unknown and disturbed nonlinear systems, which adapts its parameters on-line using a recursive least squares algorithm. The convergence of the adaptive identifier is presented in a formal proof.
- A robust optimal tracking control scheme for SDCF nonlinear systems capable to reject disturbances that affect the system. A formal proof of the robust optimal tracking nonlinear control scheme is presented.
- The developed robust optimal tracking nonlinear control scheme, which is applied to the different proposed adaptive identifier models, is capable to determine the required insulin dose to regulate the blood glucose in type 1 diabetic patients toward the desired reference (constant or variable).
- An optimal nonlinear control scheme capable to be used in continuous and discontinuous insulin pumps.
- The adaptive identifier and optimal nonlinear control scheme validation by using the T1DMS used to simulate real-life conditions in type 1 diabetic patients.

1.9 Thesis outline

The reminder of this thesis is organized into 5 Chapters. A brief overview of each one of these Chapters is given below:

Chapter 2 describes the identification background, which is the basis to develop the adaptive identifier. A formal proof is presented to demonstrate its convergence. The adaptive identifier model is proposed with the aim to identify disturbed and uncertain nonlinear system dynamics. Finally, an application example is showed with some simulation results.

Chapter 3 presents the robust optimal tracking nonlinear control development, a formal to demonstrate its convergence and an example of the optimal control scheme application. The control scheme shows capabilities to reject disturbances and achieve a trajectory tracking of the system output toward the desired reference. The control scheme

is applied to the adaptive identifier proposed in Chapter 2. The results are shown at the end of this Chapter.

Chapter 4 details the modeling and control of the glucose-insulin system proposed by Cobelli, which is accepted by the FDA to simulate the glucose-insulin dynamics in type 1 diabetic patients. The adaptive identifier and the optimal nonlinear control scheme are applied under certain specifications such as: different disturbances, different virtual patients, different regulation levels(constant and variables) and control signals to continuous and discontinuous insulin pumps. A reduced-order identifier is presented to demonstrate the effectiveness of the proposed adaptive identification scheme. The adaptive identification and the optimal nonlinear control schemes are validated using the T1DMS software, which is accepted by FDA.

Chapter 5 provides general conclusions on the work done, and summarizes the major scientific contributions of the thesis. The chapter ends by highlighting the directions of future work.

The thesis structure is summarized in Figure 1.3.

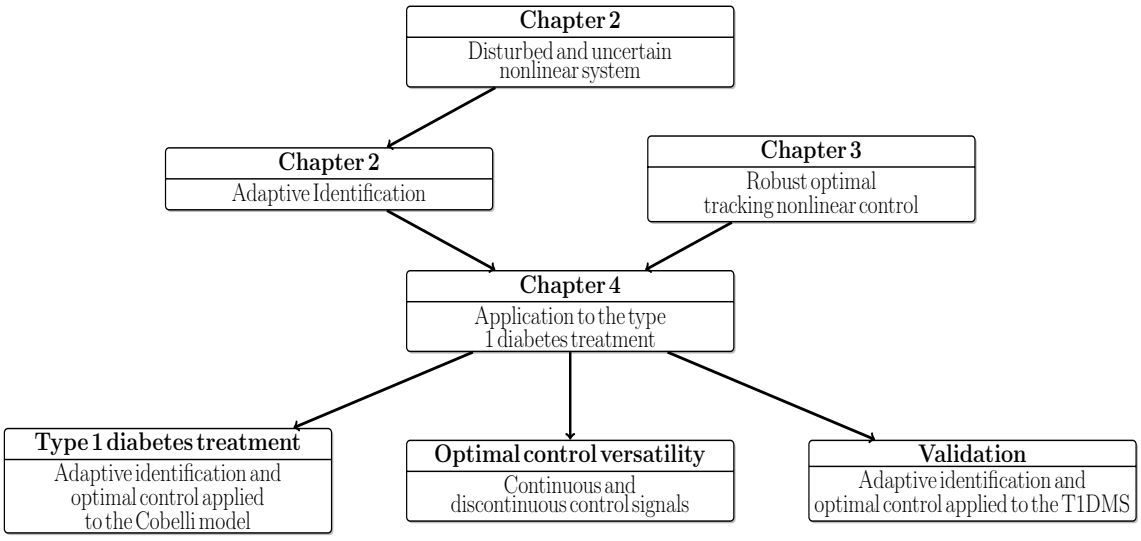


Figure 1.3: Thesis outline.

Chapter 2

Adaptive Identification

System identification is an important issue in many areas. It deals with characterizing an unknown system using measurements of the system's input and output. Although the linear system model has been widely used in system theory for many years, many real-life systems are actually nonlinear and it is important to consider nonlinear system identification. Adaptive identification algorithms are particularly interesting being considered in the area of nonlinear system identification. A major problem in the identification of nonlinear system is to deal with disturbances. Adaptive identification is used to model nonlinear dynamics adapting on-line the parameters in an identifier structure. This chapter briefly describes useful results on adaptive identification of nonlinear systems, Lyapunov theory, required in future chapters, for the optimal control problem solution. Section 2.2 gives the mathematical preliminaries about nonlinear systems and Lyapunov stability. Section 2.3 presents the adaptive identifier and its formal convergence proof. Section 2.4 shows an application example and its results. Finally, Section 2.5 presents the chapter summary.

2.1 Mathematical preliminaries

This chapter presents important mathematical preliminaries, required in future chapters.

2.1.1 Nonlinear autonomous systems

Consider the autonomous nonlinear system

$$\dot{x} = f(x) \tag{2.1}$$

where $f : D \to \mathbb{R}^n$ is a locally Lipschitz map from a domain $D \subset \mathbb{R}^n$ into $\mathbb{R}^n$. Suppose $\bar{x} \in D$ is an equilibrium point of (2.1); that is

$$f(\bar{x}) = 0.$$

The principal aim is to characterize and study stability of $\bar{x}$. For convenience, all definitions and theorems are stated for the case where the equilibrium point is at the origin of $\mathbb{R}^n$; that is, $\bar{x} = 0$. There is no loss of generality in doing so because any equilibrium point can be shifted to the origin via a change of variables. Suppose $\bar{x} \neq 0$, and consider the change of variables $y = x - \bar{x}$. The derivative of y is given by

$$\dot{y} = \dot{x} = f(x) = f(y - \bar{x}) = g(y), \qquad \textit{where} \;\; g(0) = 0.$$

In the new variable y, the system has equilibrium at the origin. Therefore, without loss of generality, we shall always assume that $f(x)$ satisfies $f(0) = 0$, and study stability at the origin $x = 0$.

Definition 2.1.1. *[GHLZ13]. The equilibrium point $x = 0$ of (2.1) is*

- *stable if, for each $\epsilon > 0$, there is $\delta = \delta(\epsilon) > 0$ such that*

$$\|x(0)\| < \delta \Rightarrow \|x(t)\| < \epsilon, \qquad \forall\ t \geq 0$$

- *unstable if not stable*

- *asymptotically stable if it is stable and δ can be chosen such that*

$$\|x(0)\| < \delta \Rightarrow \lim_{t \to \infty} x(t) = 0.$$

2.1.2 Lyapunov stability

Stability theory plays a central role in systems theory and engineering. There are different kinds of stability problems that arise in the study of dynamical systems. Stability of equilibrium points is usually characterized in the sense of Lyapunov, a Russian mathematician and engineer who laid the foundation of the theory which now carries his name. An equilibrium point is stable if all solutions starting at nearby points stay nearby; otherwise, it is unstable. It is asymptotically stable if all solutions starting at nearby points not only stay nearby, but also tend to the equilibrium point as time approaches infinity.

Lyapunov stability theorems give sufficient conditions for stability and asymptotic stability, among other stability proofs. In 1892, Lyapunov showed that energy-based functions or other mathematical functions could be used to determine stability of an equilibrium point [Kha96a]. Let $V(x) : D \to \mathbb{R}$ be a continuously differentiable function defined in a domain $D \subset \mathbb{R}^n$ that contains the origin. V is positive definite if $V(x) > 0,\ \forall x \in D$, if $V(x) < 0,\ \forall x \in D$ is negative definite, if $V(x) \geq 0,\ \forall x \in D$ is positive semidefinite, and if $V(x) \leq 0,\ \forall x \in D$ is negative semidefinite. The derivative of V along the trajectories of (2.1), denoted by $\dot{V}(x)$, is given by

$$\dot{V}(x) = \sum_{i=1}^{n} \frac{\partial V}{\partial x_i}\dot{x}_i = \sum_{i=1}^{n} \frac{\partial V}{\partial x_i} f_i(x).$$

The derivative of V along the trajectories of a system is dependent on the system's equation. Hence, $\dot{V}(x)$ will be different for different systems. If $\phi(t, x)$ is the solution of (2.1) that starts at initial state x_0 at time $t = 0$, then

$$\dot{V}(x) = \frac{d}{dt} V(\phi(t, x))\bigg|_{t=0}.$$

Therefore, if $\dot{V}(x)$ is negative, V will decrease along the solution of (2.1). The Lyapunov's stability theorem is presented as follows.

Theorem 2.1.1. *[Kha96a]. Let $x = 0$ be an equilibrium point for (2.1) and $D \subset \mathbb{R}^n$ be a domain containing $x = 0$. Let $V : D \to \mathbb{R}$ be a continuously differentiable function, such that*

$$V(0) = 0 \quad and \quad V(x) > 0 \quad in \quad D - \{0\} \tag{2.2}$$

and

$$\dot{V}(x) \leq 0 \quad in \quad D - \{0\}. \tag{2.3}$$

Then, $x = 0$ is stable. Moreover, if

$$\dot{V}(x) < 0 \quad in \quad D - \{0\} \tag{2.4}$$

then $x = 0$ is asymptotically stable.

In summary, the Lyapunov's theorem establishes that: *a)* if $V(x,t)$ is locally positive definite and $\dot{V}(x,t) \leq 0$ locally in x and for all t, then the origin of the system is locally stable, *b)* if $V(x,t)$ is locally positive definite and decrescent, and $\dot{V}(x,t) \leq 0$ locally in x and for all t, then the origin of the system is uniformly locally stable, *c)* if $V(x,t)$ is locally positive definite and decrescent, and $-\dot{V}(x,t) \leq 0$ is locally positive definite, then the origin of the system is uniformly locally asymptotically stable, and *d)* if $V(x,t)$ is positive definite and decrescent, and $-\dot{V}(x,t)$ is positive definite, then the origin of the system is globally uniformly asymptotically stable.

A class of scalar functions $V(x)$ for which sign definiteness can be easily checked is the class of functions of the quadratic form

$$V(x) = x^T P x = \sum_{i=1}^{n} \sum_{j=1}^{n} p_{ij} x_i x_j$$

where P is a real symmetric matrix ($P = P^T$). In this case, $V(x)$ is positive definite (positive semidefinite) if and only if all the eigenvalues of P are positive (nonnegative), which is true if and only if all the leading principal minors of P are positive (all principal minors[1] of P are nonnegative). If $V(x) = x^T P x$ is positive definite (positive semidefinite), we say that the matrix P is positive definite (positive semidefinite) and write $P > 0$ ($P \geq 0$).

[1] A minor of a matrix A is the determinant of some smaller square matrix, cut down from A by removing one or more of its rows or columns. Minors obtained by removing just one row and one column from square matrices (first minors) are required for calculating matrix cofactors, which in turn are useful for computing both the determinant and inverse of square matrices.

2.1.3 Stability definitions

Consider the disturbed and uncertain nonlinear system, whose dynamical behaviour is given by

$$\begin{aligned} \dot{\mathcal{X}} &= \mathcal{F}(\mathcal{X}, u, t) + \bar{\Gamma} \\ \mathcal{Y} &= \mathcal{C}\mathcal{X} \end{aligned} \tag{2.5}$$

where $\mathcal{X} \in \mathbb{R}^n$ is the system state, $u \in \mathbb{R}^m$ is the system input, $\mathcal{Y} \in \mathbb{R}^p$ is the system output; $\mathcal{F}$ and $\mathcal{C}$ are unknown (or partially known) smooth vector fields of appropriate dimensions. $\bar{\Gamma}$ is an unknown and bounded disturbance term representing uncertainties and/or unmodelled dynamics. Therefore, an adaptive polynomial identifier is proposed to obtain the dynamical behaviour of the system (2.5), which is assumed to be observable such that the identification process can be carried out.

Definition 2.1.2. *[Kha96b]. The system* (2.5) *is said to be forced or to have input. In contrast, the system described by an equation without explicit presence of an input u, that is* (2.1)*, is said to be unforced. It can be obtained after selecting the input u as a feedback function of the state*

$$u = \mu(x). \tag{2.6}$$

Such substitution eliminates u:

$$\dot{x} = f(x, \mu(x), t) + \bar{\Gamma} \tag{2.7}$$

and yields an unforced system (2.7).

Definition 2.1.3. *[GHLZ13]. The solution of* (2.5) *and* (2.7) *is semiglobally uniformly ultimately bounded (SGUUB), if for any Ω, a compact subset of $\mathbb{R}^n$, and all $x(t_0) = x_0 \in \Omega$, there exist a $\epsilon > 0$ and a time $T(\epsilon, x)$ such that $||x(t)|| < \epsilon$ for all $t > t_0 + T$.*

In other words, the solution of (2.5) is said to be SGUUB if, for any a priori given bounded set Ω and any a priori given (arbitrarily small) set Ω_0, which contains (0,0) as an interior point, there exists a control (2.6) such that every trajectory of the closed loop system starting from Ω enters the set $\Omega_0 = \{x(t) | ||x(t)|| < \epsilon\}$ in a finite time and remains in it thereafter.

Lemma 2.1.2. *[GW02]. Suppose that there exists a C^1 continuous and positive definite Lyapunov function $V(x)$ satisfying*

$$\gamma_1(||x||) \leq V(x) \leq \gamma_2(||x||), \tag{2.8}$$

such that

$$\dot{V}(x) \leq -c_1 V(x) + c_2 \tag{2.9}$$

where $\gamma_1,\ \gamma_2 : \mathbb{R}^n$ are class K_∞ functions[2] and $c_1,\ c_2$ are positive constants, then the solution x is SGUUB.

In nonlinear systems, observability is an important characteristic when the system modeling is required. A system is said to be observable if, for any possible sequence of state and control vectors, the current state can be determined in finite time using only the outputs, i.e., one can determine the behavior of the entire system from the system's outputs. A system is not observable, if the current values of some of its state variables cannot be determined through output sensors. This implies that their value is unknown to the controller. A formal observability definition is presented as follows.

Definition 2.1.4. *[HS72]. The system described by* (2.5) *is said to be completely observable in Ω_0 on the time interval $[t_0, t_1]$ if there exists a one-to-one correspondence between the set Ω_0 of initial states and the set of trajectories of the observed output $y(t)$ for $t \in [t_0, t_1]$. Now if the observability map H is one-to-one from Ω_0 to $H(\Omega_0)$, then by the data $\mathcal{Z}$, the initial state $x(t_0)$ of the system can be uniquely determined. Hence, according to the above definition of observability, the system is completely observable.*

The nonlinear map is represented by $\mathcal{Z} = H(x(t_0))$ and H is the observability mapping of the system. The univalence of map H from Ω_0 to $H(\Omega_0)$ is only a sufficient condition of observability for nonlinear continuous-time systems. The reason is that the vector $\mathcal{Z}$ shown before does not represent the whole trajectory $y(t)$, $t \in [t_0, t_1]$.

[2] A continuous function $\alpha : [0, a) \to [0, \infty)$ is said to belong to class K_∞ if it belongs to class K, it is s.t. $a = \infty$ and it is s.t. $\lim_{r\to\infty} \alpha(r) = \infty$

2.2 Adaptive identifier

In order to identify a supposed real system (2.5), an adaptive identifier model is proposed as

$$\begin{aligned} \dot{x} &= f(x)\theta + Bu + \Gamma(\theta) \\ y &= C\,x \end{aligned} \tag{2.10}$$

where $x \in \mathbb{R}^n$ is the state vector, $u \in \mathbb{R}^m$ is the control input, $y \in \mathbb{R}^p$ is the system output, C is the output matrix and θ is the identifier parameters vector, which is adapted on-line to ensure that the identifier converges toward the system (2.5). $\Gamma(\theta)$ represents possible additional (constant or slowly time-varying) parameters of the identifier. In this sense, different polynomial basis for $f(x)\theta$ can be used to approximate the vector field $\mathcal{F}$ in (2.5), such as Chebyshev [MS87], Legendre polynomials [Fun92], etc. In addition to this, there are different nonlinear systems with a natural polynomial structure [CDM96a, BLHG11, BEG$^+$03, GS97]. It is worth mentioning that function $f(x)$ is proposed to be linear with respect to the entries of vector θ. In the identification process, the parameters θ are adapted on-line using an adaptation algorithm based on a recursive least-squares (RLS) algorithm.

2.2.1 Convergence analysis of the adaptive identifier using RLS

An adequate approximation of the original system is obtained if some characteristics as essential dynamics are preserved and if the error between the adaptive identifier and the original system is minimized. To achieve that, an adaptive identifier (2.10) is proposed to approximate an uncertain and disturbed nonlinear system (2.5). The identifier parameters are adapted using a RLSA, which minimizes the identification error. The identification process is shown in Figure 2.1.

For analysis purpose, it is assumed that there exists an ideal unknown parameters vector θ^* in the adaptive identifier (2.10), whose dynamics can be described by

$$\dot{\theta}^* = 0. \tag{2.11}$$

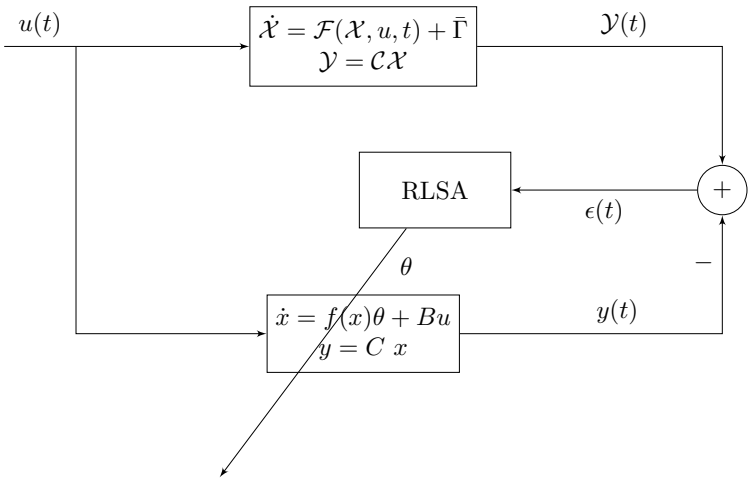


Figure 2.1: Convergence between the proposed adaptive identifier and the real nonlinear system using RLS.

Hence, the dynamics behaviour of system (2.5) without modelling error, is given as

$$\dot{\mathcal{X}}_i^* = -a_i\mathcal{X}_i^* + \theta_i^{*T} w^*(\mathcal{X}^*), \qquad \mathcal{X}_i^*(0) = \mathcal{X}_i^{*0} \tag{2.12}$$

$$\mathcal{Y}_i^* = C\mathcal{X}_i^* \tag{2.13}$$

where $\mathcal{X}_i^*$ is the ideal state vector, w^* is an ideal state vector of optimal polynomial functions, a_i are constant parameters and $\mathcal{Y}_i$ is the output system.

There exist different adaptive algorithms to obtain the parameter values that approximate the identifier dynamics into the dynamics of the nonlinear system. In a comparative study of adaptive algorithms [IA15], Islam concludes that the RLS algorithm has faster convergence rate than LMS and NLMS algorithms, with better robustness to noises, unpredictable situations, and better tracking capability. Therefore, for the adaptation on-line of the parameters θ in the proposed identifier model (2.10), an RLS algorithm is applied, which provides an efficient computational technique, which minimizes the identification error [BKM$^+$86, Hay04], given as

$$\varepsilon = x - \mathcal{X}. \tag{2.14}$$

For the use of the RLS algorithm in the identification process, it is assumed that (2.11) is affected by zero mean white Gaussian noises of spectral intensities $\Psi \in \mathbb{R}^{2n\times 2n}$ and $g \in \mathbb{R}$, respectively.

Then, the RLS algorithm is presented as follows

$$\begin{aligned} \dot{\theta} &= -g\,\Phi\,w\,C\varepsilon \\ \dot{\Phi} &= \Psi - g\,\Phi\,w\,w^T\Phi, \qquad \Psi,\ g>0 \end{aligned} \tag{2.15}$$

where the identification error depends on the difference between real system output and identifier output $C\varepsilon$ [SB11]. Assuming that $w = f_i(x)$ represents the i-th row of $f(x)$ in the adaptive identifier (2.10) which corresponds to the base structure used to approximate the dynamics in (2.5), Ψ and g are design parameters used in the identifier process and their values guarantee the convergence of the identification error. Φ is a covariance matrix used as adaptation gain in the θ updating law. $\Phi(0)$ is a symmetric positive definite matrix and its initial condition is $\Phi(0) > 0$, whereas the initial condition for θ is arbitrary. $\Phi(0)$ is usually chosen to reflect the confidence in the initial estimate of $\theta(0)$. In general selecting a large value for $\Phi(0)$ is recommended. It is worth remarking that the adaptation law (2.15) is implemented for each system state variable.

The following lemma, presented in [RC12], is useful in the adaptive identifier convergence proof presented in this work.

Lemma 2.2.1. *System* (2.12) *can be presented as*

$$\dot{\xi}_i = -a_i\xi_i + w*, \qquad \xi_i(0) = 0 \tag{2.16}$$

$$\mathcal{X}_i^* = \theta_i^{*T}\xi_i + e^{-a_i t}\mathcal{X}_i^{*0}. \tag{2.17}$$

Proof. Solving (2.12), we obtain

$$\mathcal{X}_i^* = e^{-a_i t}\mathcal{X}_i^0 + \int_{t_0}^{t} e^{-a_i(t-\tau)}\theta_i^{*T}w^*(\mathcal{X}(\tau))d\tau. \tag{2.18}$$

Then solving (2.16), results in

$$\xi_i = \int_{t_0}^{t} e^{-a_i(t-\tau)}w^*(\mathcal{X}(\tau))d\tau \tag{2.19}$$

and replacing (2.19) in (2.17), we obtain

$$\mathcal{X}_i^* = e^{-a_i t}\mathcal{X}_i^0 + \int_{t_0}^{t} e^{-a_i(t-\tau)}\theta_i^{*T}w^*(\mathcal{X}(\tau))d\tau. \tag{2.20}$$

Therefore, the solution of (2.12), as developed in (2.18), is equal to the right hand side of (2.17). This concludes the proof. □

Hence, one of the main contributions of this thesis related to the identifier convergence is established as the following theorem.

Theorem 2.2.2. *Consider that system* (2.5) *is observable. Then, the proposed adaptive identifier* (2.10)*, whose parameters* θ *are adapted on-line by the adaptive law* (2.15)*, identifies the unknown and disturbed nonlinear system* (2.5)*, and guarantee that the identification error* (2.14) *is SGUUB.*

Proof. Using *Lemma* 2.2.1, the dynamical system described by (2.5), is represented by its ideal identifier as

$$\mathcal{X}_i^* = \theta_i^{*T}\xi_i + e_{iCI} \qquad\qquad i = 1, 2, ..., n, \tag{2.21}$$

where $e_{iCI} = e^{-a_i t}\mathcal{X}_i^{*0}$ is an exponentially decaying term, which appears if the system is in a nonzero initial state. By replacing the unknown parameters vector θ_i^* in (2.21) by its estimate θ_i, the following identification model is proposed

$$x_i = \theta_i^T\xi_i - e_{iID} \qquad\qquad i = 1, 2, ..., n, \tag{2.22}$$

where e_{iID} represents a bounded approximation error. Then, the identification error (2.14) becomes

$$\begin{aligned} \varepsilon_i &= \theta_i^T\xi_i - \theta_i^{*T}\xi_i - e_{iCI} - e_{iID} \\ &= \phi_i^T\xi_i - e_{iCI} - e_{iID}, \qquad\qquad \phi_i = \theta_i^T - \theta_i^{*T} \end{aligned} \tag{2.23}$$

where ϕ_i is the parameter estimation error. Then, consider the Lyapunov candidate function

$$V = \frac{1}{2}\sum_{i=1}^{n}\left(\phi_i^T\Phi_i\phi_i + \varepsilon_i^T\varepsilon_i + \int_{t_0}^{\infty} e_{iCI}^2(\tau)d\tau\right). \tag{2.24}$$

Considering (2.15) and (2.23), the time derivative of V in (2.24) is expressed as

$$\begin{aligned} \dot{V} &= \frac{1}{2}\sum_{i=1}^{n}\left(\dot{\phi}_i^T\Phi_i\phi_i + \phi_i^T\dot{\Phi}_i\phi_i + \phi_i^T\Phi_i\dot{\phi}_i + \dot{\varepsilon}_i^T\varepsilon_i + \varepsilon_i^T\dot{\varepsilon}_i - e_{iCI}^2\right) \\ &= \frac{1}{2}\sum_{i=1}^{n}\left([-g_i\Phi_i\xi_i C\varepsilon_i]^T\Phi_i\phi_i + \phi_i^T[\Psi - g_i\Phi_i\xi_i\xi_i^T\Phi_i]\phi_i + \phi_i^T\Phi_i[-g_i\Phi_i\xi_i C\varepsilon_i]\right. \end{aligned}$$

$$
\begin{aligned}
&+[-g_i\xi_i^T\Phi_i\xi_iC\varepsilon_i - a_i\phi_i^T\xi_i + \phi_i^Tw - \dot{e}_{iCI} - \dot{e}_{iID}]^T\varepsilon_i \\
&+\varepsilon_i^T[-g_i\xi_i^T\Phi_i\xi_iC\varepsilon_i - a_i\phi_i^T\xi_i + \phi_i^Tw - \dot{e}_{iCI} - \dot{e}_{iID}] - e_{iCI}^2\Big) \\
= \;& \frac{1}{2}\sum_{i=1}^{n}\Big(- 2g_i\phi_i^T\Phi_i^T\Phi_i\xi_iC\varepsilon_i - \phi_i^T[g_i\Phi_i\xi_i\xi_i^T\Phi_i - \Psi]\phi_i - 2g_i\varepsilon_i^T\xi_i^T\Phi_i\xi_iC\varepsilon_i - 2a_i\varepsilon_i^T\phi_i^T\xi_i \\
&+2\varepsilon_i^T\phi_i^Tw - 2\varepsilon_i^T[\dot{e}_{iCI} + \dot{e}_{iID}] - e_{iCI}^2\Big) \\
= \;& \sum_{i=1}^{n}\Big(- \frac{1}{2}\phi_i^T[g_i\Phi_i\xi_i\xi_i^T\Phi_i - \Psi]\phi_i - \varepsilon_i^T\left[g_i\xi_i^T\Phi_i\xi_iC\right]\varepsilon_i - \varepsilon_i^T[g_iC^T\xi_i^T\Phi_i^T\Phi_i - w^T + a_i\xi_i^T]\phi_i \\
&-\varepsilon_i^T[\dot{e}_{iCI} + \dot{e}_{iID}] - \frac{1}{2}e_{iCI}^2\Big) \\
\leq \;& -\frac{1}{2}||\phi_i||^2||g_i\Phi_i\xi_i\xi_i^T\Phi_i - \Psi|| - ||\varepsilon_i||^2||g_i\xi_i^T\Phi_i\xi_iC|| - ||\varepsilon_i||\;||g_iC^T\xi_i^T\Phi_i^T\Phi_i - w^T + a_i\xi_i^T||\;||\phi_i|| \\
&-||\varepsilon_i||\;||\dot{e}_{iCI} + \dot{e}_{iID}|| - \frac{1}{2}||e_{iCI}||^2 \\
\leq \;& -\frac{1}{2}||\phi_i||^2||g_i\Phi_i\xi_i\xi_i^T\Phi_i - \Psi|| - ||\varepsilon_i||\Big(||g_i\xi_i^T\Phi_i\xi_iC||\;||\varepsilon_i|| + ||g_iC^T\xi_i^T\Phi_i^T\Phi_i||\;||\phi_i|| \\
&-||w^T||\;||\phi_i|| + ||a_i\xi_i^T||\;||\phi_i|| + ||\dot{e}_{iCI} + \dot{e}_{iID}||\Big) - \frac{1}{2}||e_{iCI}||^2
\end{aligned}
$$

the term $||g_i\Phi_i\xi_i\xi_i^T\Phi_i - \Psi||$ is > 0 due to in (2.15), the RLSA established that $\Psi > 0$ and $g > 0$. Generally, they are selected with large values, which ensures that the term be positive. Then, we obtain that $\dot{V} < 0$ for

$$
||\varepsilon_i|| \geq \frac{||w^T||\;||\phi_i|| - ||g_iC^T\xi_i^T\Phi_i^T\Phi_i||\;||\phi_i|| - ||a_i\xi_i^T||\;||\phi_i|| - ||\dot{e}_{iCI} + \dot{e}_{iID}||}{||g_i\xi_i^T\Phi_i\xi_iC||}. \tag{2.25}
$$

Therefore, the time derivative of V is negative definite when the condition (2.25) is fulfilled; then any trajectory moves in the direction of decreasing V. Consequently, the function V will continue decreasing until the trajectory enters to a small region fo which (2.25) is not fulfilled and stays there for all future time. Then, it is concluded that the identification error (2.14) is SGUUB. □

2.3 Adaptive identification applied to a nonlinear system

This subsection presents an example of the adaptive identification scheme application. The principal aim is to demonstrate its effectiveness modeling the dynamics in a nonlinear system. The nonlinear system used in this application, which for identification purposes is considered to be unknown, is described as follows.

2.3.1 Bergman minimal model

The Bergman Minimal Model (BeMM) is composed of two separate parts: one describing the dynamics of the glucose uptake after the external stimulus, regarding the insulin concentration as a known forcing function; the other describing the dynamics of the pancreatic insulin release in response to the glucose stimulus, with the glucose concentration regarded as a known forcing function. This model is only used to simulate the glucose-insulin dynamics, which are described as [BIBC79a]

$$\dot{G} = -p_1 G - XG + p_1 G_b + D \tag{2.26}$$

$$\dot{X} = -p_2 X + p_3 (I - I_b) \tag{2.27}$$

$$\dot{I} = -\eta (I - I_b) + \gamma (G - h) t \tag{2.28}$$

where G, X and I are plasma glucose concentration, the insulin influence on glucose concentration reduction, and insulin concentration in plasma, respectively. Insulin-independent glucose-utilization rate is represented by p_1, p_2 is the rate of decrease of the tissue glucose uptake ability, p_3 is the insulin-dependent increase of the glucose uptake ability and $D = \frac{D_G \, A_G \, t \, e^{-t/T_{maxI}}}{V_G \, T_{maxG}^2}$ is the disturbance caused by the meal [HCC$^+$04b], where D_G is the meal carbohydrate load, A_G is the carbohydrate bioavailability, T_{maxI} is the time-to-maximum insulin absorption, T_{maxG} is the time-of-maximum appearance rate of glucose in the accessible glucose compartment and V_G is the glucose distribution space. The term $\gamma(G - h)t$ represents the pancreatic insulin secretion after a meal intake at $t = 0$. The threshold value of glucose above which the pancreatic β-cells release insulin is represented by h and γ is the rate of the pancreatic β-cells' release of insulin after the glucose injection.

2.3.2 Adaptive identification for the BeMM

Since system (2.26)–(2.28) has a polynomial structure, we use such feature to directly synthesize the adaptable identifier. It is assumed that the actual system parameters are unknown and that the measurements of the blood glucose level (G) are available. Then,

the adaptive identifier is proposed as

$$\dot{x}_1 = \theta_1 x_1 - x_2 x_1 + \theta_2 \tag{2.29}$$

$$\dot{x}_2 = \theta_3 x_2 + \theta_4 x_3 + \theta_5 \tag{2.30}$$

$$\dot{x}_3 = \theta_6 x_3 + \theta_7 \tag{2.31}$$

where the state vector $x = [x_1\ x_2\ x_3]^T$ identifies to the actual state vector $\mathcal{X} = [G\ X\ I]^T$. System (2.29)–(2.31) can be presented in a SDCF as in (3.16)–(3.17), with $A(x,\theta) = \begin{bmatrix} \theta_1 & -x_1 & 0 \\ 0 & \theta_2 & \theta_4 \\ 0 & 0 & \theta_6 \end{bmatrix}$, $B = \begin{bmatrix} 0,\ 0,\ 1 \end{bmatrix}^T$, $C = \begin{bmatrix} 1 & 0 & 0 \end{bmatrix}$, and $\Gamma(\theta) = \begin{bmatrix} \theta_2,\ \theta_5,\ \theta_7 \end{bmatrix}^T$, where

$\theta = [\theta_1\ \theta_2\ \theta_3\ \theta_4\ \theta_5\ \theta_6\ \theta_7]^T$ are the parameters to be identified by the RLS algorithm. Based on the assumption that only the glucose measurement is available, the identification error used to identify all the parameters θ in (2.29)–(2.31) is $\varepsilon = x_1 - G$. It is worth remarking that the system (2.26)–(2.28) is an uncertain and disturbed nonlinear one, representing the glucose-insulin biological behavior, which depends on various factors as eating and healthy habits, age, weight, etc. Therefore, it is convenient to develop a robust modeling scheme, as the presented in (2.29)–(2.31), which is adequately adapted to the actual system changes and admits an SDCF representation, which a posteriori will be used for control purposes. The effectiveness of the proposed adaptive identifier strategy is illustrated via simulation. For the adaptive identification process, the significant terms of the basis w in (2.15) are given as $w_1 = [x_2\ 1]^T$, $w_2 = [x_3\ x_4\ 1]^T$ and $w_3 = [x_4\ 1]^T$, which allow an efficient adaptive identification process. The identifier parameters to ensure the identification convergence are $\Psi_1 = diag\{0.1,\ 1000\}$, $\Psi_2 = diag\{0.0001,\ 0.0001,\ 0.0001\}$, $\Psi_3 = diag\{1,\ 10000\}$ and $g_1 = 10$, $g_2 = 900000$ and $g_3 = 10000$. The parameters to simulate the glucose-insulin dynamics are presented in Table 2.1 [KS08].

Figure 2.2 shows the adaptive identification for the basal glucose response, corresponding to the BeMM variable G (continuous red line), which is identified by the adaptive identifier variable x_1 (dashed blue line).

Table 2.1: BeMM parameters used to simulate glucose-insulin dynamics.

Parameter	Value	Units
G_b	105	mg/dl
I_b	85	$\mu U/ml$
$G(0)$	126	mg/dl
$I(0)$	102	$\mu U/ml$
$X(0)$	0	$1/min$
p_1	0.1076	$1/min$
p_2	0.0192	$1/min$
p_3	5.1×10^{-6}	$ml/\mu U min^2$
η	0.2867	$1/min$
T_{maxG}	7	min
T_{maxI}	16	min
D_G	130	mg
V_G	12.85	dl
A_G	0.79	$Adimensional$
γ	0	$\mu U/ml\ min^{-2}(mg/dl)^{-1}$
h	80	mg/dl

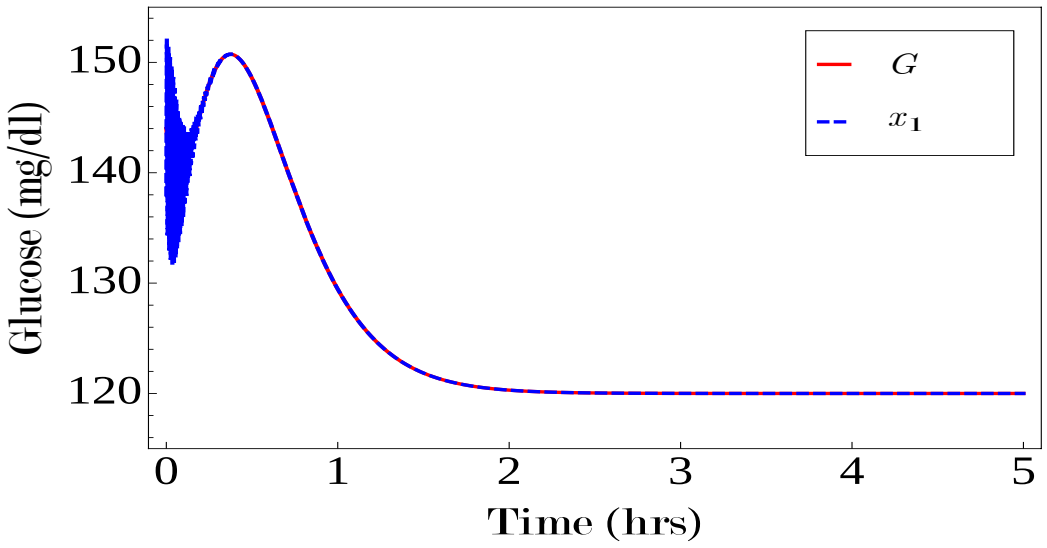


Figure 2.2: Adaptive identification of the glucose signal in the BeMM.

In Figure 2.2 can be appreciated oscillations at the beginning of the simulation due to the minimization of the identification error by the use of the RLSA to adapt online the identifier parameters and achieve an adequate identification of the BeMM glucose variable behaviour. Figure 2.3 shows the identification error Ge between the BeMM variable (G) and its corresponding identifier variable x_1. At the beginning of the simulation can be appreciated that the error is high, this is due to the oscillations presented in the identification process. It is important to highlight that the convergence speed can be improved by tuning the parameters Ψ and g. Their values were chosen to demonstrate a slow convergence process between G and x_1. In addition, it can be seen that the identification error is minimized (tending to zero).

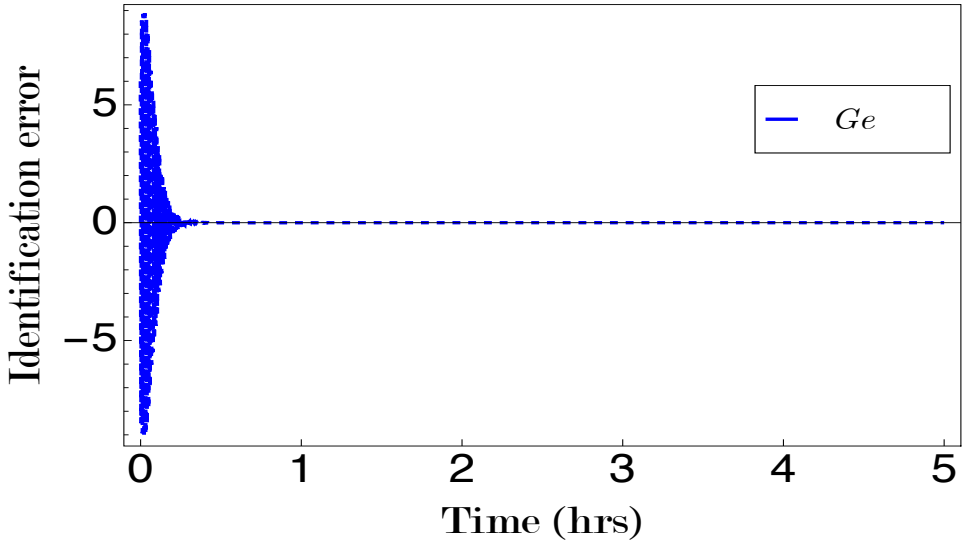


Figure 2.3: Glucose identification error.

Figure 2.4 shows the identification of the effect of active insulin response, corresponding to the minimal model X (continuous red line), by means of the proposed identifier x_2 (dashed blue line). The adaptive identification is carried out for each variable of the proposed identifier. In the case of the variable x_2, values of Ψ and g are selected to obtain a faster convergence and less oscillations.

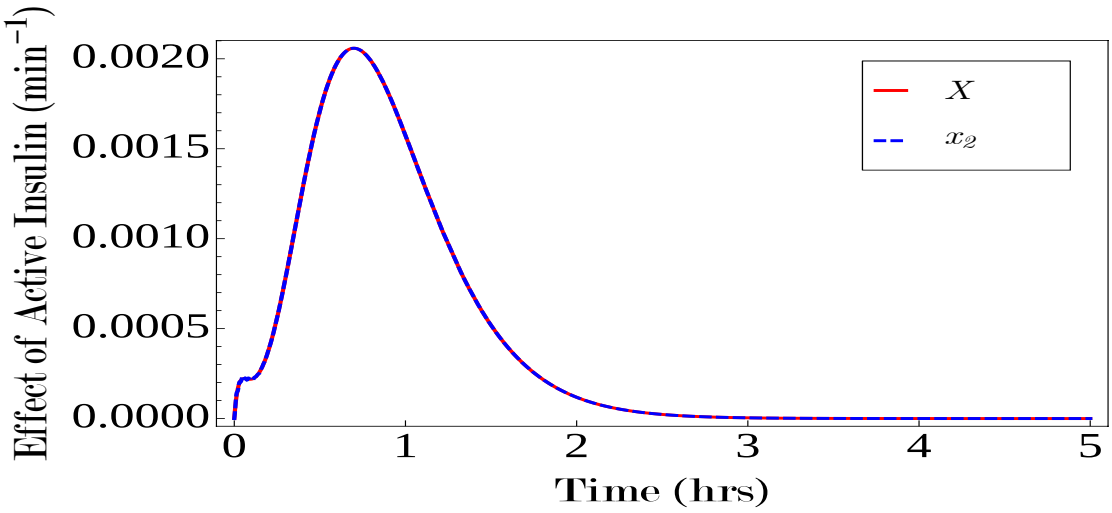


Figure 2.4: Adaptive identification of the effect of active insulin signal in the BeMM.

Figure 2.5 shows the identification error Xe between the BeMM variable X and its corresponding identifier variable x_2. In this case the parameters Ψ and g were chosen to demonstrate a faster convergence between both variables. Due to the selected values of the parameters Ψ and g in the identification process, a faster convergence can be appreciated.

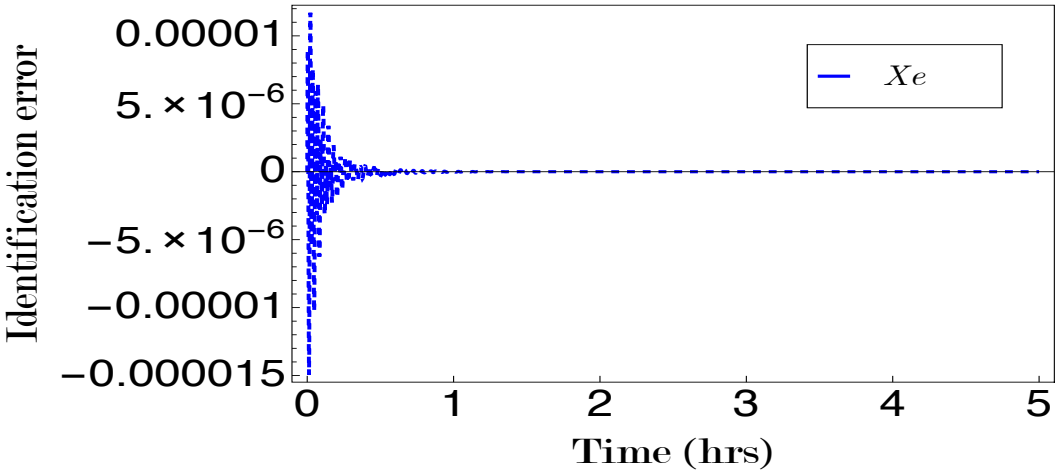


Figure 2.5: Effect of active insulin identification error.

Figure 2.6 shows the adaptive identification of the basal insulin response, corresponding to the BeMM variable I (continuous red line), by means of the proposed identifier x_3 (dashed blue line). At the beginning of the simulation, small oscillations can be appreciated due to the selected values of the parameters Ψ and g in the identification process.

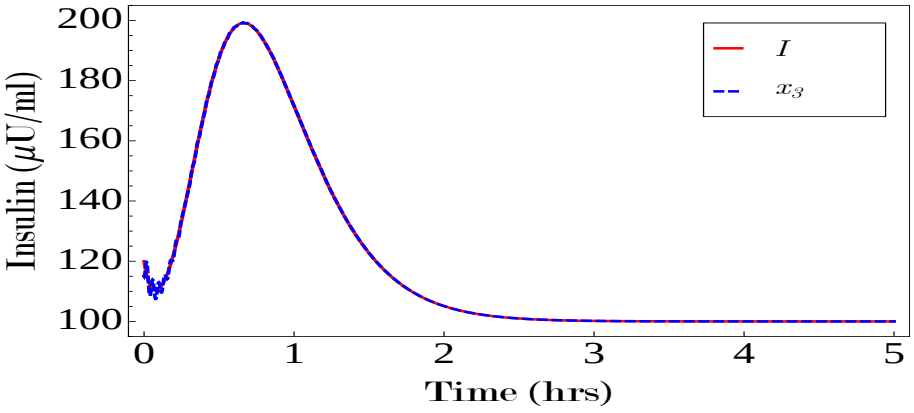


Figure 2.6: Adaptive identification of the insulin signal in the BeMM.

Figure 2.7 shows the insulin identification error Ie between the BeMM variable I and its corresponding identifier variable x_3. It can be appreciated that the convergence error is minimized by the use of the RLSA and tends to zero.

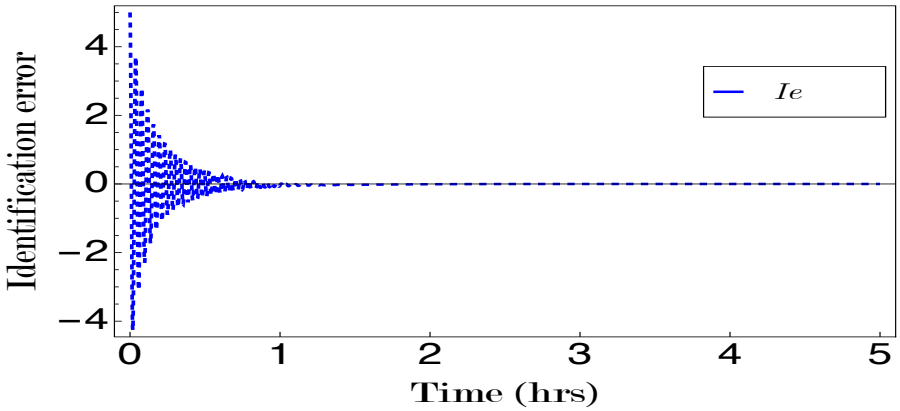


Figure 2.7: Insulin identification error.

2.4 Adaptive reduced-order identification

Over the last years, investigators have attempted to develop several methodologies to reduce the order in nonlinear systems [DHR97, EH99, HTD99]. These methods work exceedingly well when the dynamics of the system can be considered to be linear. Researchers have in recent years looked into the creation of black box models which use only input and output data to create a model which can be used to predict system behavior. Many such methods, a majority of which are based on the seminal work done by Kalman [K$^+$60], are used in the structural dynamics community to build linear state-space equations and to predict system parameters [Jua94, JP85]. Recently similar methods have been used to build linear state-space aerodynamics models as well [TKJD01, Cov04]. Although these system realization methods produce a compact model which relies only on input and output data, the input/output mapping produced by such methods is linear. In [ADWT06], a nonlinear system identification methodology is presented which is used to identify a set of low dimensional, nonlinear, first order ordinary differential equations. The coefficients of the terms in the ordinary differential equations are found using a simple least squares method.

The description of a dynamic system can be obtained from mathematical models (described by differential or difference equations) or experimental results. Based on a priory knowledge about the system, the differences between the high-order model dynamics and the reduced-order model can be taken into account as disturbances or dynamics rapidly disappear, which can be handled using adaptive identification methodologies. In any case, the model reduction procedures might be flexible enough to let the user indicate the essential behaviours that need to be captured for his/her application [ADWT06]. In the order reduction process, the dynamics of a system model M of high order n is approximated by a model M_r of order $r < n$. Assume that (2.5) is a supposedly real, uncertain and disturbed non linear system with a complete-order and $\mathcal{X} \in \mathbb{R}^n$, then a reduce-order model is proposed as

$$\dot{x} = f(x)\theta + Bu + \Gamma(\theta) \tag{2.32}$$

$$y = C\ x \tag{2.33}$$

where $x \in \mathbb{R}^r$, with $r < n$, the control input is $u \in \mathbb{R}^j$ with $j < m$, the system output is

$y \in \mathbb{R}^q$ with $q < p$, the output matrix is C, and θ is the identifier parameters vector.

The quality of the approximation is usually evaluated by looking at the model reduction error, that is, the signal obtained as the difference between the outputs of the original system and the outputs of the reduced-order model, driven by the same excitation signal, as is shown in Figure 2.8.

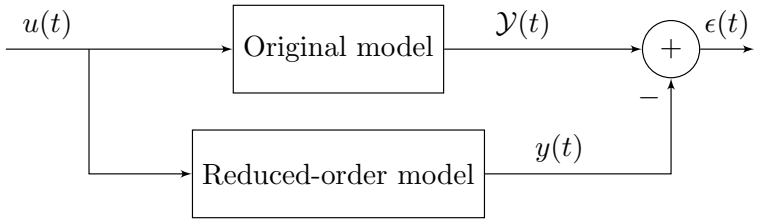


Figure 2.8: Model order reduction that preserves the input-output behaviour.

Model order reduction is a branch of systems and control theory which studies properties of dynamical systems in application for reducing their complexity, while preserving their input-output behavior. To ensure an adequate approximation of the original system is needed to preserve some system's properties, essential dynamics, stability, and controllability. Therefore, the adaptation algorithm must be efficient to identify the original system dynamics minimizing the error between the outputs of the original system and the outputs of the reduced-order model, as shown in Figure 2.9.

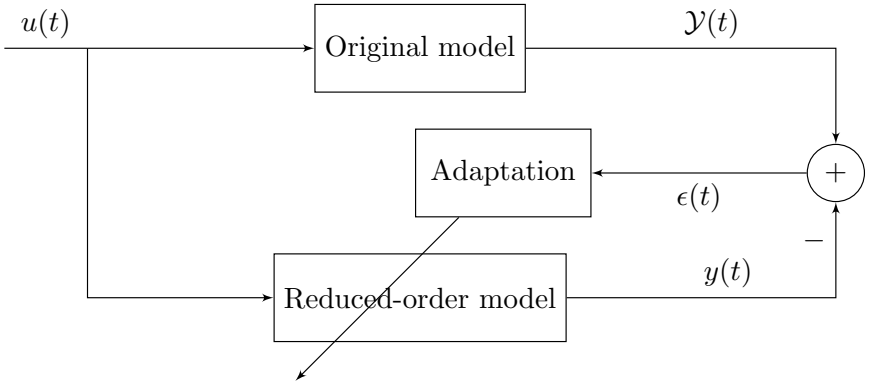


Figure 2.9: Model order reduction with adaptive identification.

In [CW$^+$00], a quadratic reduction method which uses the Krylov subspace generated from linearized analysis and the result is a reduced order model with a quadratic nonlinearity. In [TKMK89], an adaptive update law, which counteracts the effects of unknown parameters, is shown to be robust to the unmodeled dynamics. In the presence of unmodeled dynamics, the regulation property is preserved in a stability region. The size of the region is estimated using bounds that not only prove robustness, but also allow a comparison between adaptive and nonadaptive nonlinear controls.

In this thesis a reduced-order modeling to approximate the essential behaviours of an uncertain and disturbed nonlinear system is proposed, with the aim to develop adaptive reduced-order identifiers with fewer parameters to be adapted than the complete-order identifiers. The reduced-order modeling allows a faster convergence, lower dimension, and some variables can be considered as disturbances. The reduced-order modeling will be used in Chapter 4 with the aim to demonstrate the effectiveness of the adaptive identification scheme.

2.5 Summary

An adaptive identification scheme based on a RLS algorithm to adapt on-line its parameters is proposed. The RLSA minimizes the identification error between the nonlinear system and the proposed adaptive identifier and its effectiveness is verified via simulation. The proposed adaptive identifier model can be presented in SDCF, so it can be used in control purposes in the following chapter. Complementing the adaptive identification scheme, a theoretical contribution is developed and is presented as a formal proof to validate the adaptive identifier convergence. The application shows that an adequate adaptive identifier model is proposed to approximate the BeMM dynamics. The adaptation algorithm is capable to achieve a complete identification of the minimal model dynamics using only the glucose signal G to adapt the parameters θ in the identifier model under the assumption that there is only available the measurements of the plasma glucose concentration. Comparing with some related works, in [HCL$^+$05] a model that uses two time-varying patient specific parameters for glucose effectiveness and insulin sensitivity is developed. This method is

used for the identification of patient specific parameters. In [DMRC07] a simulation model of the glucose-insulin system is presented. The simulation model is for normal humans and describes the physiological events that occur after a meal. Model parameters were set to fit the mean data of a large normal subject database that underwent a triple tracer meal protocol which provided quasi-model-independent estimates of major glucose and insulin fluxes. Those works present the identification of specific parameters for specific patients and scenarios. Contrary to the obtained results in this chapter, the identification is carried out adapting the parameters of the developed adaptive identifier with the aim to mimic the behavior of the BeMM variables, i.e., the identifier process identifies behaviours adapting the parameters in the proposed identifier model, which allows the identification for different patients in different scenarios. Finally, an introduction about the reduced-order identification is presented with the aim to be applied in the proposed adaptive identification scheme.

Chapter 3

Robust Optimal Nonlinear Control

The optimal control of nonlinear systems is a topic of great practical interest, especially with regard to the development of control laws that minimize or maximize a performance cost. Over the past four decades, a considerable amount of research has been concentrated in analysis and stability problems that arise from constraints imposed on control. The majority of techniques have focused on the stability analysis applying the Lyapunov theory. The Hamilton-Jacobi theory and the maximum principle of Pontryagin have been given to solve the optimization problems and find optimal control laws. This chapter presents the optimal control theory and the developed nonlinear optimal control strategy. Section 3.2 presents the theory needed to develop a optimal nonlinear controller. Section 3.3 shows the basic definitions and theory about nonlinear control stabilization, which is the basis to understand the optimal tracking control. In Section 3.4 the robust optimal tracking control for disturbed nonlinear systems is developed. As a theoretical contribution and as a complement, a formal proof about the optimal tracking control convergence is presented. The application of the optimal control scheme is applied to the adaptive identifier previously developed in Section 2.4. Finally, in Section 3.5 the chapter is summarized.

3.1 Optimal nonlinear control theory

The formulation of an optimal control problem requires: *a)* a mathematical description (or model) of the process to be controlled. A nontrivial part of any control prob-

lem is modeling the process. The objective is to obtain the mathematical description that adequately predicts the response of the physical system to all anticipated inputs, *b)* the specification of a performance criterion. In order to evaluate the performance of a system quantitatively, the designer selects a performance measure. An optimal control is defined as one that minimizes (or maximizes) the performance measure. In certain cases the problem statement may clearly indicate what to select for a performance measure, whereas in other problems the selection is a subjective matter. For example, the time can be the performance measure to be minimized, or use a small expenditure of control energy. The designer may be required to try several performance measures before selecting one that yields what he considers to be optimal performance.

Optimal control methodology can be generalized if physical constraints are considered. More specifically, the optimal control is related to finding a control law for a given system such that a performance criterion is minimized. This criterion is usually formulated as a cost functional, which is a function of state and control variables. The optimal control problem can be solved using Pontryagin's maximum principle (a necessary condition) [Pon87], and the method of dynamic programming developed by Bellman [BD62, Bel57], which can leads to a nonlinear partial differential equation called the HJB equation (a sufficient condition). For the optimal control methodology, the proposed modeling developed in Chapter 2 is used.

3.1.1 Performance measures

The optimal control problem is to find a control $u^* \in U$ which causes the system (2.5) to follow a trajectory x^* that minimizes the performance measure [Kir12]

$$J(x,t) = h(x(t_f), t_f) + \int_{t_0}^{t_f} g(x(t), u(t), t)dt. \tag{3.1}$$

The specific selection of a performance measure can be described as:

- **Terminal control problem**. To minimize the deviation of the final state of a system from a desired value $r(t_f)$. A possible performance measure is

$$J(x,t) = \sum_{i=1}^{n} \left[x_i(t_f) - r_i(t_f)\right]^2. \tag{3.2}$$

Since positive and negative deviations are equally undesirable, the error is squared. Absolute values could also be used, but the quadratic form in (3.2) is easier to handle mathematically.

- **Minimum-control-effort problem**. To transfer a system from an arbitrary initial state x_0 to a specified target set S, with a minimum expenditure of control effort. That depends upon the particular physical application; therefore, the performance measure may assume various forms.

$$J(x,t) = \int_{t_0}^{t_f} \left[u^T(t)Ru(t)\right] dt \tag{3.3}$$

where R is a real symmetric positive definite weighting matrix. The elements of R may be functions of time if it is desired to vary the weighing on control-effort expenditure during the interval $[t_0, t_f]$.

- **Stabilization problem**. Consider the system (2.5). Let the matrices $Q(t)$ and $R(t)$ have continuous entries, be symmetric, and be nonnegative and positive definite, respectively. Define the performance index as

$$J(x,t) = \int_{t_0}^{t_f} \left[x(t)^T Q(t)x(t) + u^T Ru\right] dt. \tag{3.4}$$

and the stabilization problem as the task of finding an optimal control $u^*(t)$ for $t \geq 0$, minimizing J and the associated optimum performeance index $J^*(x(t_0), t_0)$.

- **Tracking problem**. To maintain the system state $x(t)$ as close as possible to the desired reference $r(t)$ in the interval $[t_0, t_f]$. Note $r(t)$ can be selected as a time-varying signal. The performance measure is selected as

$$J(x,t) = \int_{t_0}^{t_f} \left[x(t) - r(t)\right]^T Q(t) \left[x(t) - r(t)\right] dt. \tag{3.5}$$

$Q(t)$ is a real symmetric $n \times n$ matrix that is positive semi-definite for al $t \in [t_0, t_f]$. The elements of the matrix Q are selected to weight the relative importance of the different components of the state vector and to normalize the numerical values of the deviations. If control energy is to be conserved, the following modified performance is used

$$J(x,t) = \int_{t_0}^{t_f} \{\left[x(t) - r(t)\right]^T Q(t) \left[x(t) - r(t)\right] + u^T Ru\} dt \tag{3.6}$$

where $R(t)$ is a real symmetric positive definite $m \times m$ matrix for all $t \in [t_0, t_f]$. It may be specially important that the states be close to their desired values at the final time. In this case, the performance measure is

$$J(x,t) = [x(t) - r(t)]^T H [x(t) - r(t)] + \int_{t_0}^{t_f} \{[x(t) - r(t)]^T Q(t) [x(t) - r(t)] + u^T R u\} dt \tag{3.7}$$

where H is a real symmetric positive semi-definite $n \times n$ matrix.

- **Regulation problem**. A regulation problem is a special case of a tracking problem, which results when the desired reference $r(t)$ value is constant $r(t) = c$ for all $t \in [t_0, t_f]$, where c is a constant or piece-wise constant signal.

Once the performance measure for a system has been selected, the next task is to determine a control function that minimizes this criterion.

3.1.2 The optimal control law

Two methods of accomplishing the minimization are the minimum principle of Pontryagin, and the method of dynamic programming developed by Bellman. The optimal control law is defined as

$$u^*(t) = k(x,t) \tag{3.8}$$

as being as closed-loop or feedback optimal control. The functional relationship k is called the optimal control law, or the optimal policy. The control law specifies how to generate the control value at time t from the state value at time t. The presence of t as an argument of k indicates that the optimal control law may be time-varying.

3.1.3 The Hamilton-Jacobi-Bellman equation

In this subsection, we present a method of obtaining the closed-loop optimal control, using the principle of optimality and the HJB equation. The optimal feedback control of a linear system is a subject which has been extensively studied [AM07]. If the cost functional is quadratic in the state and control, and it is assumed a full state knowledge, then the

optimal control is a linear state feedback law where the control gains are obtained by solving a differential/algebraic Riccati equation. The success of this linear quadratic regulator problem is due to the successful development of robust and efficient algorithms for solving the Riccati equation. However, if the system is described by nonlinear dynamics, then the optimal state feedback law is given in terms of the solution to the Hamilton-Jacobi-Bellman equation [Kir12]. The HJB equation provides the solution to the optimal control problem for general nonlinear systems; however, it is in most cases difficult to solve analytically.

To define the HJB equation, first we need to state Bellman's principle of optimality [Bel57]. It simply states that any portion of the optimal trajectory is optimal. Alternatively, the optimal control has the property that no matter what the previous control signal have been, the remaining decision must constitute an optimal control signal. Considering the nonlinear system (2.5)–(2.6) and the performance index

$$J(x(t_0), t_0) = \int_{t_0}^{t_f} l(x, u, t)dt. \tag{3.9}$$

where l represents a function of x, u, t. The control law is a function of the state variables, leading to closed-loop optimal control. This is important from the practical point of view in implementation of the optimal control. Let us define a scalar function $J^*(x^*(t), t)$ as the minimum value of the performance index J for an initial state $x^*(t)$ at time t, which is defined as,

$$J^*(x^*(t), t) = \int_{t_0}^{t_f} l(x^*(\tau), u^*(\tau), \tau)d\tau \tag{3.10}$$

where $J^*(x^*(t), t)$ is the value of the performance index when evaluated along the optimal trajectory starting at $x(t)$. Here, we use the principle of optimality in saying that the trajectory from t to t_f is optimal. The Hamiltonian definition is

$$\mathcal{H} = V(x, u, t) + \left(\frac{\partial V^*(x^*, t)}{\partial x^*}\right)^T f(x, u, t). \tag{3.11}$$

The interest is to find $V(x(t_0), t_0)$ as a function of $x(t_0)$ and t_0. Therefore, the Hamilton-Jacobi equation is defined as

$$\frac{\partial V^*(x^*, t)}{\partial t} + \mathcal{H}\left(x^*, \frac{\partial V^*(x^*, t)}{\partial x^*}, u^*, t\right) = 0 \qquad \forall\ t \in [t_0, t_f) \tag{3.12}$$

with boundary condition from as

$$V^*(x^*(t_f), t_f) = 0 \tag{3.13}$$

Since (3.13) is the continuous-time analog of Bellman's recurrence equations in dynamic programming [Bel57], it is also called the Hamilton-Jacobi-Bellman equation and is

$$V_t^* + \mathcal{H}(x^*, V_x^*, u^*, t) = 0. \tag{3.14}$$

In general, (3.14) is a nonlinear partial differential equation in V^*, which can be solved for V^*. Once V^* is known, its gradient V_x^* can be calculated and the optimal control $u^*(t)$ is obtained as

$$\left(\frac{\partial \mathcal{H}}{\partial u}\right)_* = 0 \rightarrow u^*(t) = k(x^*, V_x^*, t). \tag{3.15}$$

The HJB partial differential equation solves the optimal control problem for every initial condition all at once. In this sense it is a global approach, and provides a closed-loop (state-feedback) formula for the optimal control action. Unfortunately, most of the systems are nonlinear and obtaining the solution to the optimal nonlinear control is complicated since solving the HJB partial differential equation is required, which rarely has solution for the nonlinear case. However, there is a solution for the HJB equation, developed for a specific nonlinear system class named state dependent coefficient factorized systems. Recently, an optimal control scheme for state-dependent coefficient factorized nonlinear systems has been proposed based on the state dependent Riccati equation approach which is a systematic way for synthesizing nonlinear feedback controllers, and mimic the controller synthesis as done for the linear case. This method also possesses many of the capabilities of other nonlinear design methods as; stability, optimality, real-time implementability, and inherent robustness with respect to parametric uncertainties and unmodeled dynamics, as well as disturbance rejection.

3.1.4 State-dependent coefficient factorized nonlinear systems

One of the most important characteristics of considering in a polynomial structure, specifically for $f(x)\theta$, is that this function always admits the state-dependent coefficient

factorization as $f(x)\theta = A(x,\theta)\,x$[1]. Then, system (2.10)–(2.11) can be rewritten as

$$\dot{x} = A(x,\theta)\,x + Bu + \Gamma(\theta) \tag{3.16}$$

$$y = C\,x \tag{3.17}$$

where the state-dependent factorizations must be determined such that controllability and observability properties for system (3.16)–(3.17) are fulfilled and will be used in Chapter 3 for control purposes [BLT07a, OTRRC14, HHR98a].

As established in [Cim08, Clo97], the assumptions $f(0) = 0$ and $f(\cdot) \in C^1$ guarantee that the factorization as described in (3.16)–(3.17) can be carried out. This salient feature is used to obtain an analytical solution for the optimal control via the Riccati equation. In order to obtain well-defined control schemes, appropriate factorization for these representations should be determined such that controllability and observability properties are fulfilled for system (3.16)–(3.17). For notation facility the term θ is omitted in $A(x,\theta)$.

In [BLT07b, HHR98b], the generalization of the rank test for the state-dependent controllability matrix of system (3.16) is defined as

$$rank\{\mathcal{C}(x)\} = n \forall x \tag{3.18}$$

where

$$\mathcal{C}(x) = [B(x) \quad A(x)B(x)\cdots A^{n-1}(x)B(x)]$$

whereas weak controllability for system (1) is characterized at each x in terms of the span dimension for the smallest nonsingular and involutive distribution $\Delta_C(x)$, as established in [BLT07b, Isi95]. Here the weak controllability test is summarized for the sake of completeness as follows:

1. Let the control matrix be described as $B(x) = [b_1,\ b_2 \cdots b_m]$ and $\Delta_0 = span\{B(x)\} = span(b_i),\ 1 \leq i \leq m$.

2. Let $\Delta_1 = \Delta_0 + [f(x),\ b_i] + [b_j,\ b_i],\ 1 \leq j \leq m$ where $[f(x),\ b]$ is the Lie bracket defined as $[f(x),\ b] = (\partial b/\partial x)f(x) - (\partial b/\partial x)b(x)$, notation + indicates the sum of spans.

[1]For instance, the polynomial scalar system $\dot{x} = -x + x^3$ can be presented as $\dot{x} = a(x)x$, with $a(x) = (x^2 - 1)$.

3. Let $\Delta_k = \Delta_{k+1} + [f(x),\ d_j] + [b_d\ d_j],\ 1 \leq i \leq m,\ 1 \leq j \leq m$, where d_j is a basis for Δ_{k-1}.

4. The test terminates when $\Delta_{k+1} = \Delta_k$. A system is weakly controllable if $rank\{\Delta_C\} = rank\Delta_k = n \forall x$.

The state-dependent observability matrix is defined as [BLT07b]

$$\mathcal{O}(x) = \begin{bmatrix} C(x) \\ C(x)A(x) \\ \vdots \\ C(x)A^{n-1}(x) \end{bmatrix}. \tag{3.19}$$

Hence, by considering that a system is weakly controllable, factorization $A(x)x$ must be determined such that $C(x)$ has full rank and then state-dependent controllability is fulfilled. Similar analysis must be done to determine state-dependent observability, or to use duality between controllability and observability [Isi95, HK77].

3.1.5 Stabilization for SDCF nonlinear systems

Before developing the optimal tracking scheme, the optimal stabilization solution for SDCF nonlinear systems is established, in which a controller is synthesized in order to achieve that the state of the system converges to zero in an optimal sense.

Theorem 3.1.1. *[OTRRC14]. Assume that system* (3.16) *is state-dependent controllable and state-dependent observable. Then the control law*

$$u^* = -R^{-1}B^T(x)P(x)x \tag{3.20}$$

is a state feedback optimal control law for system (3.16)*, which ensures asymptotic stability of the closed-loop system, and minimizes the associated cost functional*

$$J = \frac{1}{2}\int_0^\infty (x^T Q x + u^T R u)dt \tag{3.21}$$

where Q and R are symmetric and positive definite matrices, and $P(x)$ in (3.20) *is the solution of the SDRE*

$$\dot{P} = -Q + P(x)B(x)R^{-1}B^T(x)P(x) - A^T(x)P(x) - P(x)A(x) \tag{3.22}$$

with boundary condition $P(\infty) = 0$.

From the proof of Theorem 3.1.1, it is worth noting, once the system is described as (3.16)–(3.17), the solution of the HJB equation is possible, since it is related to the solution of the state-dependent Riccati equation (3.22). It turns out that the proposed state-dependent factorization may be understood as linear time-varying systems, for which the solution of the optimal control through the Riccati equation is analyzed in detail in [AM07] and in [KS72b]. Matrix Q in (3.21) is a matrix weighting the performance of the state vector x, meanwhile R is a matrix weighting the control effort expenditure; hence these matrices are used to establish a trade-off between state performance and control effort [Kir70]. If more importance is given to the system state performance, one can select a higher value for Q or reduce R. If one is more interested in saving control energy, it is suggested a lower value for Q is selected or R is increased [AM07, AF13]. Particularly in [Bry75], the entries of these matrices are selected such that physical constraints for states and control signals are included in the control scheme. Note that in [OTRRC14] does not consider disturbances exciting the dynamics of the system.

3.2 Robust optimal tracking control for nonlinear systems

Based on the stabilization theory In order to synthesize the optimal controller, we will use the salient feature of the state-dependent representation for (3.16)–(3.17) to obtain, via the Riccati equation, an analytical solution for the robust optimal tracking control, for which the output of the system is required to track a desired trajectory as close as possible in an optimal sense and with minimum control effort expenditure [AM90, AF66]. In order to introduce the trajectory tracking, the tracking error is defined as

$$\begin{aligned} e &= r - y \\ &= r - C\,x \end{aligned} \tag{3.23}$$

where r is the desired reference to be tracked by the system output y.

Considering that the disturbance term $\Gamma(\theta)$ is affecting system (3.16), an integral term of the tracking error e is included such that this disturbance is rejected and the

robustness of the controller is proved. The integral term is defined as

$$\dot{q} = -e \tag{3.24}$$

where $q \in \mathbb{R}^p$ is a vector of integrators for a system with p outputs. Then, an augmented system, which includes the integrator, can be established as

$$\begin{aligned} \dot{x}_a &= \begin{bmatrix} \dot{q} \\ \dot{x} \end{bmatrix} \\ &= \begin{bmatrix} -e \\ A(x)x + Bu + \Gamma \end{bmatrix} \\ &= \begin{bmatrix} Cx - r \\ A(x)x + Bu + \Gamma \end{bmatrix}. \end{aligned} \tag{3.25}$$

with $x_a = [q^T,\ x^T]^T$. The dependence of parameter θ in all functions is omitted for simplicity of notation. System (3.25) can be rewritten as

$$\dot{x}_a = A_a(x_a)\, x_a + B_a u + D_a \tag{3.26}$$

$$y_a = C_a x_a \tag{3.27}$$

where $A_a(x_a) = \begin{bmatrix} 0 & C \\ 0 & A(x) \end{bmatrix}$, $B_a = \begin{bmatrix} 0 \\ B \end{bmatrix}$, $C_a = \begin{bmatrix} 0 & C \end{bmatrix}$ and $D_a = \begin{bmatrix} -r \\ \Gamma \end{bmatrix}$. For system (3.26), let us consider the problem of minimizing the cost functional

$$J = \frac{1}{2}\int_{t_0}^{\infty} \left(q^T\, Q_I\, q + e^T\, Q\, e + u^T\, R\, u\right) dt \tag{3.28}$$

where Q_I is a parameter weighting the integrator performance, which can be considered as the integrator gain, Q is a matrix weighting the time evolution of the error, meanwhile R is a matrix weighting the control effort expenditure. These matrices are used to establish a trade-off between state performance and control effort [Kir70].

The robust optimal tracking solution, which is one of the main contributions of this work, is established as the following theorem.

Theorem 3.2.1. *Assume that system* (3.16)-(3.17) *is state-dependent controllable and state-dependent observable. Then the robust optimal control law*

$$u^*(x_a) = -R^{-1}B_a^T\ (P(x_a)\, x_a - z(x_a)) \tag{3.29}$$

ensures trajectory tracking for the system along a desired trajectory r, where $P(x_a)$ is the solution to the symmetric matrix differential equation

$$\dot{P}(x_a) = -Q_a + P(x_a)\, B_a\, R^{-1}\, B_a^T P(x_a) - A_a^T(x_a)\, P(x_a) - P(x_a)\, A(x_a) \quad (3.30)$$

and $z(x_a)$ is the solution to the vector differential equation

$$\dot{z}(x_a) = -\left[A_a(x_a) - B_a\, R^{-1} B_a^T\, P(x_a)\right]^T z(x_a) + P D_a - r^T Q C_a \quad (3.31)$$

with boundary conditions $P(\infty) = 0$ and $z(\infty) = 0$, respectively. Control law (3.29) *is optimal in the sense that it minimizes the cost functional* (3.28)*, which has an optimal value function given as*

$$J^* = \frac{1}{2} x_a^T(t_0)\, P(t_0)\, x_a(t_0) - z^T(t_0)\, x_a(t_0) + \varphi(t_0) \quad (3.32)$$

where φ is the solution to the scalar differentiable function

$$\dot{\varphi} = -\frac{1}{2} r^T Q r + z^T D_a + \frac{1}{2} z^T(x_a)\, B_a\, R^{-1}\, B_a^T\, z \quad (3.33)$$

with $\varphi(\infty) = 0$.

Proof. Hereafter, $P(x_a)$ in (3.30) will be written as P only to simplify notation, however, P is always a state-dependent matrix on x_a; the same can be said for $z(x_a)$ in (3.31), i.e., for simplicity vector $z(x_a)$ will be written as z. In order to determine the conditions for which the optimal control law (3.29) stabilizes the system (3.26) along a desired trajectory and at same time minimizes (3.28), let us rewrite (3.28) as

$$\begin{aligned}
J &= \frac{1}{2}\int_{t_0}^{\infty} \left(q^T\, Q_I\, q + e^T\, Q\, e + u^T\, R\, u\right) dt \\
&= \frac{1}{2}\int_{t_0}^{\infty} \left(q^T Q_I q + (r - C_a x_a)^T Q (r - C_a x_a) + u^T R u\right) dt \\
&= \frac{1}{2}\int_{t_0}^{\infty} \left(x_a^T \begin{bmatrix} Q_I & 0 \\ 0 & C_a^T Q C_a \end{bmatrix} x_a + u^T\, R\, u \right) dt + \frac{1}{2}\int_{t_0}^{\infty} \left(r^T Q r - 2 r^T Q C_a x_a\right) dt \\
&= \frac{1}{2}\int_{t_0}^{\infty} \left(x_a^T Q_a x_a + u^T\, R\, u\right) dt + \frac{1}{2}\int_{t_0}^{\infty} \left(r^T Q r - 2 r^T Q C_a x_a\right) dt \qquad (3.34)
\end{aligned}$$

with $Q_a = \begin{bmatrix} Q_I & 0 \\ 0 & C_a^T Q C_a \end{bmatrix}$. Hence, the Hamiltonian is established as

$$\begin{aligned} \mathcal{H}(x_a, u, t) &= \frac{1}{2} x_a^T Q_a \, x_a + \frac{1}{2} u^T R \, u + \frac{1}{2} \left(r^T Q r - 2 r^T Q C_a x_a \right) \\ &\quad + \frac{\partial V(x_a, t)}{\partial x_a}^T \Big[A_a(x_a) \, x_a + B_a \, u + D_a \Big] \end{aligned} \tag{3.35}$$

where $V(x_a, t)$ is the optimal value function. The Hamiltonian is used to determine the control law u by applying the maximum principle condition

$$\frac{\partial \mathcal{H}(x_a, u)}{\partial u} = R \, u + B_a^T \, \frac{\partial V(x_a, t)}{\partial x_a} = 0.$$

Then the optimal control law results in

$$u^*(x_a) = -R^{-1}(t) \, B_a^T \, \frac{\partial V(x_a, t)}{\partial x_a}. \tag{3.36}$$

For the optimal control solution, based on (3.35) and (3.36), the following HJB equation must be satisfied [Kir70]:

$$\begin{aligned} 0 &= \frac{\partial V(x_a, t)}{\partial t} + \mathcal{H}(x_a, u^*, t) \\ &= \frac{\partial V(x_a, t)}{\partial t} + \frac{1}{2} x_a^T Q_a \, x_a + \frac{1}{2} u^{*T} \, R \, u^* + \frac{1}{2} \left(r^T Q r - 2 r^T Q C_a x_a \right) \\ &\quad + \frac{\partial V(x_a, t)}{\partial x_a}^T \left[A_a(x_a) \, x_a + B_a \, u^* + D_a \right] \\ &= \frac{\partial V(x_a, t)}{\partial t} + \frac{1}{2} x_a^T Q_a x_a + \frac{1}{2} r^T Q \, r - r^T Q \, C_a \, x_a - \frac{1}{2} \frac{\partial V(x_a, t)}{\partial x_a}^T B_a \\ &\quad \times R^{-1} \, B_a^T \, \frac{\partial V(x_a, t)}{\partial x_a} + \frac{\partial V(x_a, t)}{\partial x_a}^T A_a(x_a) \, x_a + \frac{\partial V(x_a, t)}{\partial x_a}^T D_a. \end{aligned}$$

One way of solving (3.37) for $V(x_a, t)$ is to guess a solution such that (3.37) is satisfied [Kir70]; hence, $V(x_a, t)$ is proposed as

$$V(x_a, t) = \frac{1}{2} x_a^T P \, x_a - z^T x_a + \varphi, \quad P = P^T > 0. \tag{3.37}$$

Thus $\dfrac{\partial V(x_a, t)}{\partial t} = \dfrac{1}{2} x_a^T \dot{P} \, x_a - \dot{z}^T x_a + \dot{\varphi}$ and $\dfrac{\partial V(x_a, t)}{\partial x_a} = P \, x_a - z.$

Hence, the HJB equation becomes

$$\begin{aligned} 0 &= \frac{1}{2}x_a^T\,\dot{P}\,x_a - \dot{z}^T x_a + \dot{\varphi} + \frac{1}{2}x_a^T Q_a x_a - \frac{1}{2}\left(P\,x_a - z\right)^T B_a\,R^{-1}\,B_a^T\,\left(P\,x_a - z\right) \\ &\quad + \left(P\,x_a - z\right)^T A_a(x_a)\,x_a + (Px_a - z)^T D_a + \frac{1}{2}r^T\,Q\,r - r^T\,Q\,C_a\,x_a \\ &= \frac{1}{2}x_a^T\left[\dot{P} + Q_a - PB_aR^{-1}B_a^TP + A_a^T(x_a)P + P\,A_a(x_a)\right]x_a \\ &\quad -\frac{1}{2}z^T\,B_a\,R^{-1}\,B_a^T\,z + \frac{1}{2}r^TQr - z^TD_a + \dot{\varphi} \\ &\quad -\left[\dot{z}^T + z^T\left(A_a(x_a) - B_a\,R^{-1}\,B_a^T\,P\right) - PD_a + r^TQC_a\right]x_a. \end{aligned} \tag{3.38}$$

From (3.38), differential equations (3.30), (3.31) and (3.33) are derived. Equation (3.30) is also named the state-dependent differential Riccati equation (SDDRE). Mimicking the linear optimal control results [AM90, AF66, KEB62], the controllability and observability assumptions for (3.16) guarantee that the solution for the SDDRE (3.30) exists [BLT07a], is unique and its solution is a positive definite matrix. Once satisfied the HJB equation by using the proposed function $V(x,t)$, the optimal controller (3.29) is directly obtained from (3.36) with (3.37). The trajectory tracking convergence can be analyzed in two steps. Firstly, we consider the closed-loop system (3.26) with (3.29) as

$$\dot{x}_a = \left[A_a(x_a) - B_a\,R^{-1}\,B_a^T\,P\right]\,x_a + B_a\,R^{-1}\,B_a^T\,z_a + D_a \tag{3.39}$$

which is composed of a dynamical (nominal) system plus the forcing functions z_a (which depends on the reference r) and D_a. Note that by using the proposed adaptive identifier (2.10)–(2.11), disturbance D_a is known. At this point, the stability of the nominal system $\dot{x} = \left[A_a(x_a) - B_a\,R^{-1}\,B_a^T\,P\right]x_a$ can be investigated as follows. Assuming controllability and observability for system (3.26) and output (3.27), there exists a differentiable, symmetric and positive definite matrix P as a solution of (3.30). Considering the positive definite and radially unbounded candidate Lyapunov function $W = x_a^T\,P\,x_a$ and taking the time derivative for W along the nominal system, it results in

$$\begin{aligned} \dot{W} &= x_a^T\dot{P}\,x_a + x_a^TP\,\dot{x_a} + \dot{x_a}^T P\,x_a \\ &= x_a^T\dot{P}\,x_a + x_a^T\left[P\,A_a(x_a) + A_a^T(x_a)\,P - 2\,P\,B_a\,R^{-1}B_a^T\,P\right]x_a. \end{aligned} \tag{3.40}$$

From (3.30) $PA_a(x_a) + A_a^T(x_a)\,P = -\dot{P} - Q_a + P\,B_a R^{-1} B_a^T\,P$ then (3.40) becomes

$$\begin{aligned} \dot{W} &= x_a^T \dot{P} x_a + x_a^T \big[-\dot{P} - Q_a - PB_a\,R^{-1} B_a^T P \big] x_a \\ &= -x_a^T \big[Q_a + PB_a\,R^{-1} B_a^T P \big]\, x_a. \end{aligned} \tag{3.41}$$

Therefore, $\dot{W}$ is negative semidefinite. Since the pair $(A(x), C)$ is observable, and by LaSalle's theorem, asymptotic stability for the nominal system is ensured [Kha96a]; hence $\lim_{t\to\infty} x_a = 0$ (or $\lim_{t\to\infty} \dot{x}_a = 0$), and thus $\lim_{t\to\infty} \dot{q} = e = 0$, and therefore $y = r$.

Secondly, by being the entries of D_a either constants or piece-wise constant bounded inputs signals, it is known that these signals does not affect the asymptotic stability of (3.39) [KS72a], therefore $\lim_{t\to\infty} \dot{q} = e = 0$ and thus $y = r$.

The optimal value function J^* for (3.28) is calculated as

$$\begin{aligned} J^* &= \frac{1}{2}\int_{t_0}^{\infty} \left(x_a^T Q_a x_a + u^{*T}\,R\,u^* \right) dt + \frac{1}{2}\int_{t_0}^{\infty} \left(r^T Q r - 2 r^T Q C_a x_a \right) dt \\ &= \frac{1}{2}\int_{t_0}^{\infty} x_a^T \big[Q_a + P\,B_a\,R^{-1} B_a^T\,P \big] x_a\,dt + \frac{1}{2}\int_{t_0}^{\infty} z^T B_a R^{-1} B_a^T\,z\,dt \\ &\quad - \int_{t_0}^{\infty} \left(z^T B_a\,R^{-1} B_a^T P + r^T Q C_a \right)\, x_a\,dt + \frac{1}{2}\int_{t_0}^{\infty} r^T Q\,r\,dt. \end{aligned} \tag{3.42}$$

From (3.30), the following relation can be obtained: $Q_a + P\,B_a\,R^{-1} B_a^T\,P = -\dot{P} + 2\,P\,B_a\,R^{-1} B_a^T\,P - A_a^T(x_a)\,P - P\,A_a(x_a)$ then (3.42) results in

$$\begin{aligned} J^* &= \frac{1}{2}\int_{t_0}^{\infty} x_a^T \big[-\dot{P} + 2\,P\,B_a\,R^{-1} B_a^T\,P - A_a^T(x_a)\,P - P\,A_a(x_a) \big] x_a\,dt \\ &\quad - \int_{t_0}^{\infty} \left(z^T B_a R^{-1}\,B_a^T P + r^T Q C_a \right) x_a\,dt + \int_{t_0}^{\infty} z^T B_a\,R^{-1} B_a^T\,z\,dt + \int_{t_0}^{\infty} -\left[\dot{\varphi} - z^T D_a \right]\,dt \\ &= -\frac{1}{2} x_a^T P\,x_a \Big|_{t_0}^{\infty} + z^T x_a \Big|_{t_0}^{\infty} - \varphi \Big|_{t_0}^{\infty} \\ &= -\frac{1}{2} x_a^T(\infty)\,P(\infty)\,x_a(\infty) + \frac{1}{2} x_a^T(t_0)\,P(t_0)\,x_a(t_0) + z^T(\infty)\,x_a(\infty) - z^T(t_0)\,x_a(t_0) \\ &\quad -\varphi(\infty) + \varphi(t_0). \end{aligned}$$

Considering the boundary conditions for $P(\infty)$, $z(\infty)$ and $\varphi(\infty)$, optimal value function (3.32) follows. □

3.2.1 Robust optimal tracking control applied to the BeMM

The proposed identifier system (2.29)–(2.31) applied to the minimal model (2.26)–(2.28) is presented in a SDCF, used in the optimal nonlinear control scheme. The output

of the minimal model is only the blood glucose level, then it requires to add only one integrator; hence, the augmented system becomes

$$\begin{aligned} \dot{x}_a &= \begin{bmatrix} -e \\ A(x,\theta)x + Bu + \Gamma \end{bmatrix} \\ &= \begin{bmatrix} x_1 - r \\ A(x,\theta)x + Bu + \Gamma \end{bmatrix} \end{aligned} \tag{3.43}$$

with $x_a = [q \;\; x]^T = [q \;\; x_1 \;\; x_2 \;\; x_3]^T$, which can be rewritten as

$$\dot{x}_a = A_a\left(x_a, \theta\right) x_a + B_a u + \Gamma_a \tag{3.44}$$

and

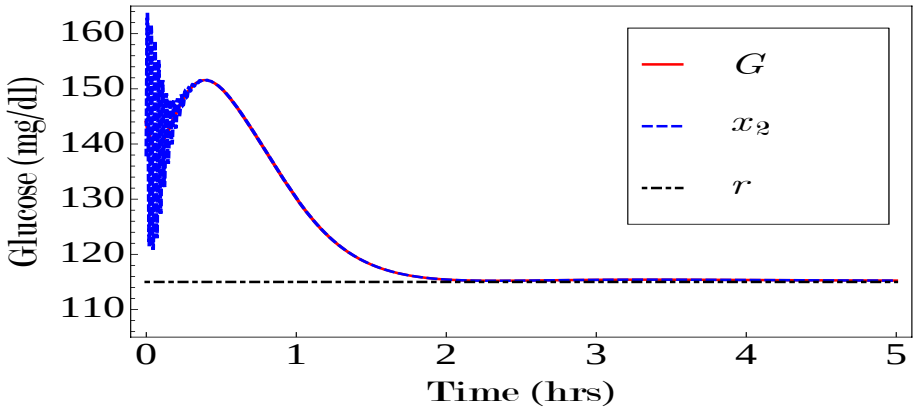
$$y = C_a x_a \tag{3.45}$$

where $A_a\left(x_a, \theta\right) = \begin{bmatrix} 0 & 1 & 0 & 0 \\ 0 & \theta_1 & -x_1 & 0 \\ 0 & 0 & \theta_2 & \theta_4 \\ 0 & 0 & 0 & \theta_6 \end{bmatrix}$, $B_a = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 1 \end{bmatrix}$, $C_a = \begin{bmatrix} 0 & 1 & 0 & 0 \end{bmatrix}$ and $\Gamma_a = \begin{bmatrix} -r \;\; \theta_2 \;\; \theta_5 \;\; \theta_7 \end{bmatrix}^T$. Parameter r is the reference value for the glucose level, and the cost functional to be minimized is (3.28). For the augmented system, the robust optimal controller is given by (3.29).

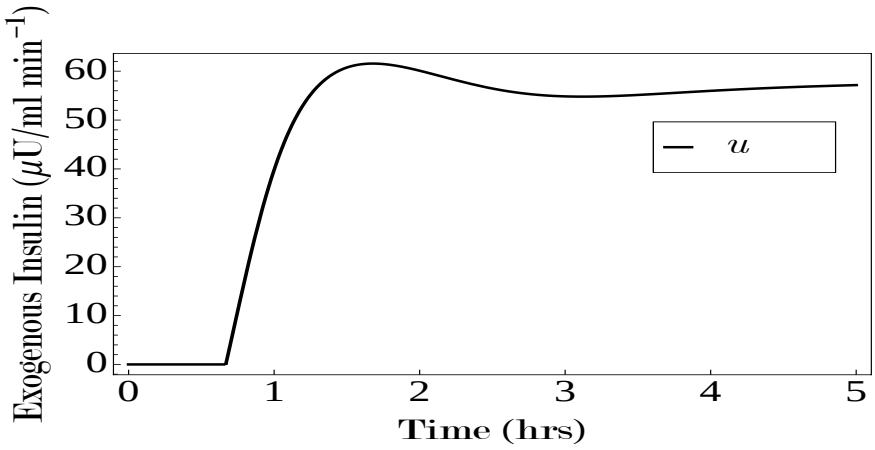
Simulation results

Once the adaptive identifier has converged, the optimal control law is applied, this is at time $t \geq 40\ min$ ($0.66\ hrs$). The parameters for the robust optimal tracking controller, which determine the speed convergence of the error in the control law, are $Q_I = 0.06$, $Q = 10$ and $R = 1$. These parameter values are selected such that an adequate performance of the control system is achieved. Fig. 3.1(a) shows the glucose level regulation with a reference level $r = 115\ mg/dl$. Fig. 3.1(b) shows the control signal that represents the required level of exogenous insulin to maintain the blood glucose on the reference level for a type 1 diabetic patient fed with 50 grams of carbohydrates. At the beginning of the simulation can be appreciated oscillations, which are generated in the identification process. The convergence

speed and the size of the oscillations depend on the selected parameters values g and Ψ in (2.15). In this case the values were chosen to show a slow convergence speed and large oscillations. Once the variable x_1 from the adaptive identifier converges to the dynamical behaviour of the BeMM glucose variable G, the optimal tracking nonlinear control is applied.



(a) ***Glucose regulation at reference level*** r.

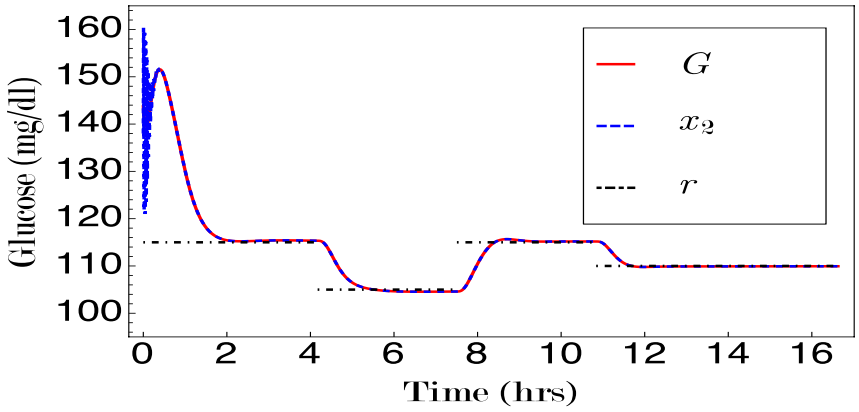


(b) ***Control signal*** u.

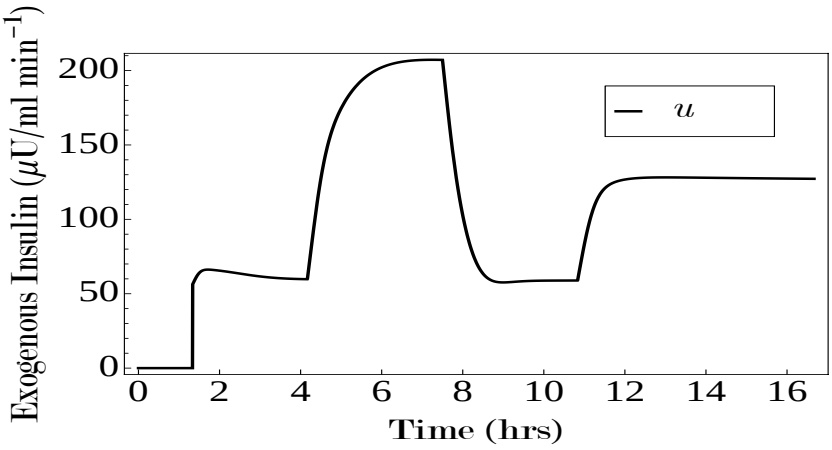
Figure 3.1: Adaptive identification and optimal tracking control applied to the BeMM.

Finally, Fig. 3.2(a) illustrates the capabilities of the optimal control scheme for regulating the glucose level to different reference values at different intervals of time, i.e., for $t < 250\ min(4.16\ hrs)$ the reference level is $r = 115\ mg/dl$. In the same way, for

250 $min(4.16\ hrs) \leq t < 450\ min(7.5\ hrs)$ the reference level is $r = 100\ mg/dl$, for $450\ min(7.5\ hrs) \leq t < 650\ min(10.83\ hrs)$ the reference level is $r = 120\ mg/dl$ and the last time interval is $t \geq 650\ min(10.83\ hrs)$ with reference level $r = 110\ mg/dl$ and Fig. 3.2(b) shows the control signal to maintain the glucose at reference levels above r.



(a) ***Glucose regulation at different reference levels*** r.

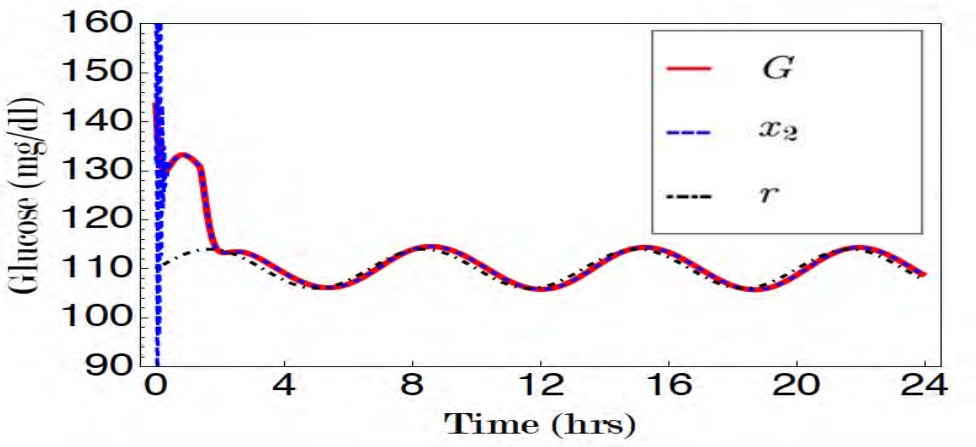


(b) ***Control signal*** u ***to regulate the glucose level at different reference levels*** r.

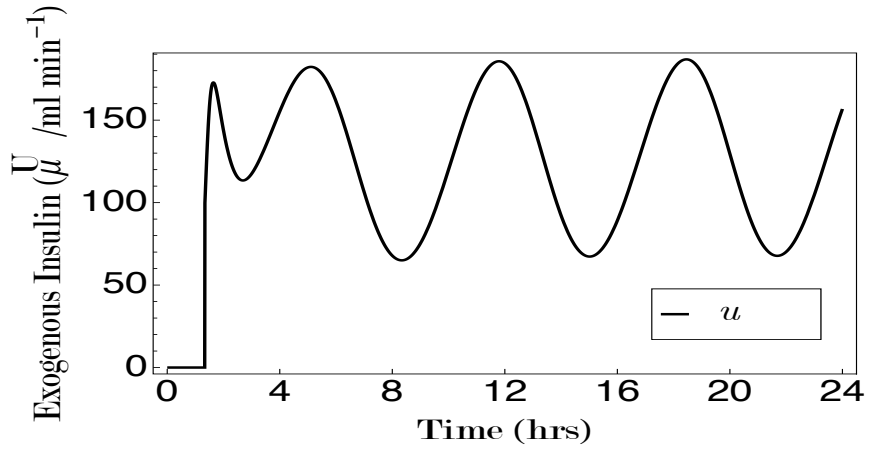
Figure 3.2: Adaptive identification and optimal tracking control applied to the BeMM at different reference levels r.

The proposed optimal tracking nonlinear control scheme has the advantage to track variable references. In Fig. 3.3(a) is shown the regulation of the blood glucose into a variable reference. At the beginning of the simulation are some oscillations that repre-

sent the adaptive identifier convergence, and once the convergence is achieved, the optimal control is applied to track the variable reference. Fig. 3.3(b) shows the control signal u that represents the exogenous insulin dose to maintain the glucose level into the variable reference level r.



(a) ***Glucose regulation for a variable reference level*** r.



(b) ***Control signal*** u ***to regulate the glucose level into a variable reference level*** r.

Figure 3.3: Adaptive identification and optimal tracking control applied to the BeMM for a variable reference level r.

In the simulation results it is shown that by adding an integrator term to the proposed optimal control law, one can deal with possible disturbances affecting the identifier, resulting in a robust optimal tracking control scheme. As an application, the simulation

results show that the proposed optimal controller can regulate the glucose level for an assumed uncertain type 1 diabetic patient. The proposed identification and control schemes have advantages, such as: they can work with disturbances affecting the system, and an appropriate identifier model can be obtained for control purposes.

In Table 1.1 are summarized the most important control strategies, which are based on different internal models that represent glucose-insulin dynamics in T1DM patients. Some of them use the BeMM as a mathematical model to develop different control strategies, e.g., in [LB01] a constrained state space model predictive controller, designed based on the BeMM, was implemented on a 19 state simulation model of a type 1 diabetic patient. In [GRG07] a control algorithm is presented for feedback control of glucose levels in type 1 diabetic patients using the BeMM. A simple asymmetric PI controller is presented where controller parameters vary depending on the sign of the current error value. In comparison with the optimal nonlinear control scheme proposed in this thesis, the results obtained in [LB01, GRG07] show oscillations on the established reference, reaching values under 60 mg/dl which could be dangerous for the patient. The results presented in this thesis show a soft regulation reaching the established reference level (without oscillations) regardless of whether the reference is variable.

3.3 Summary

This chapter has presented a robust optimal control scheme, which achieve trajectory tracking for uncertain and disturbed nonlinear system, minimizing a meaningful cost functional. A formal proof is resented as a theoretical contribution to validate the optimal tracking control convergence. The applicability of the proposed method is illustrated via simulation. The adaptive identifier model proposed in Chapter 2 used to model the BeMM dynamics delivers appropriate identifier structure which is used in the optimal nonlinear control process. The proposed adaptive identifier is presented in the SDCF form to approximate uncertainties in the glucose-insulin nonlinear system, and by adding an integrator term to the proposed optimal control law, we can deal with possible disturbances affecting the identifier (different eating and healthy habits, age, weight, among other aspects) resulting

in a robust optimal tracking control scheme. Both schemes are successfully applied with the aim to regulate the blood glucose level in type 1 diabetic patients using the BeMM model, where the dynamical behavior for different patients is difficult to model. Both schemes are applied with the aim to be included in type 1 diabetic treatments, where the patients only have access to measure the blood glucose concentration as an indicator to be used in the classic control process to regulate the blood glucose into the safety levels. In this thesis is analysed only the regulation problem due to is pretended that the patient reach a constant reference level regulation of the blood glucose concentration which could be changed depending the patients needs and the medical instructions. Some experiments have been done to track variable references but they are not highlighted in this thesis due to the blood glucose regulation in type 1 diabetic patients is solved using constant reference levels at different times. Some studies show that trajectories tracking establishing restrictions as the time when the patient has to be fed among other restrictions and that restrictions are pretended to be avoided by using glucose regulation for constant reference levels.

In next chapter the adaptive identification and the optimal control scheme are applied in virtual type 1 diabetic patients using the T1DM software to validate both schemes.

Chapter 4

Modeling and Control of the Glucose-Insulin System for Type 1 Diabetes

This chapter presents the application of the adaptive identification and the optimal tracking control scheme focused on the type 1 diabetes treatment. In the previous chapters, the adaptive identification and the optimal nonlinear control scheme were applied to the Bergman minimal model, which was used only as an example to simulate the glucose insulin dynamics in type 1 diabetic patients. In this chapter, the adaptive identification and the optimal nonlinear control scheme will be applied to the Cobelli model, whose principal advantage and difference compared with the Bergman minimal model is that the Cobelli model was used in the development of the T1DMS software, which is approved by the FDA and is used to validate the control strategies for type 1 diabetes treatments. Section 4.2 describes the mathematical models used to simulate the glucose-insulin dynamics in type 1 diabetic patients. In Section 4.3 the adaptive identification scheme is applied to the Cobelli system used to simulate the glucose-insulin in healthy people. Section 4.4 shows the adaptive identification and the optimal tracking control scheme which are applied to the Cobelli system used to represent the glucose insulin dynamics in type 1 diabetic patients. The simulation resluts are presented in Section 4.5, where continuous and discontinuous

control signals are developed for constant and variable reference levels, different scenarios and different virtual patients. A reduced-order identifier is proposed in Section 4.6 and is validated using the T1DMS software. Finally, a general summary of the chapter is presented in Section 4.7.

4.1 Glucose-insulin mathematical models used to simulate type 1 diabetes disease

Approximately 10 million people in Mexico have diabetes, among which about 5% have type 1 diabetes [FMD], an auto-immune disease that destroys a person's pancreas' ability to release insulin. Type 1 diabetics depend on everyday insulin infusion or injection to maintain their glucose level within the acceptable range where too much insulin can cause life-threatening hypoglycemia (extremely low glucose level) and too little insulin can cause nerve-damaging hyperglycemia (high glucose level) [MKOP$^+$17]. Unfortunately, meal carbohydrates are a major disturbance to one's blood glucose level, and therefore every type 1 diabetic patient faces a life-long control challenge: the patient has to carefully control the blood glucose injecting exogenous insulin doses for every meal so that post-meal hyperglycemia is effectively controlled without risking hypoglycemia. In recent years, CGM technology has become more popular, which drives a whole class of Medical Cyber-Physical System (MCPS), most notably the artificial pancreas (AP), that aims to facilitate glucose management for type 1 diabetics. At the AP system's core are a CGM sensor, a wearable insulin pump for continuous and discontinuous infusion, and algorithms that control the insulin infusion and boluses [CRK11]. Reliably predicting meals is difficult in real-life situations, thus all AP systems depend on certain kinds of meal declaration/detection mechanisms. Meal detection is a safety critical problem, where an incorrectly identified meal may trigger the system to either deliver too much insulin unnecessarily or deliver too little insulin, both of which have harmful (if not deadly) consequences. Currently, most type 1 diabetics who use CGM sensors and wearable insulin pumps manually input the time and estimated carbohydrates count of each meal into the device, which then calculates a suggested insulin dose. Unfortunately, self-reported meal information is inherently

unreliable [DBBD08]. Thus, more dependable meal detection methods are necessary to ensure patient safety. whereby, it is important developing adaptive identifiers capable to identify the glucose-insulin dynamics regardless of gender, age, diet and lifestyle, and developing control algorithms that allow an optimal regulation with the capabilities to deal with different disturbances, achieving the adequate blood glucose regulation into safety levels.

The literature dealing with mathematical modelling for diabetes is abundant. During the last decades, a variety of models have been devoted to different aspects of diabetes, including glucose and insulin dynamics, management and complications prevention, cost and cost-effectiveness of strategies and epidemiology of diabetes in general. Over the years, researchers modelled the behavior of the glucose-insulin system in diabetic patients by applying either an empirical approach [FZJ$^+$06, FPD$^+$09] or the more attractive compartment modelling technique based on mass balance equations which results in first-principles models, as described in [CF07, CC08].

The glucose-insulin system offers one of the clearest and simplest examples of homeostatic control in the organism. The level of glucose in blood needs to be kept within a narrow range. Since it represents the main energy source, for brain tissue, abnormally low glucose concentrations give rise to anxiety, tremors, aggressiveness, obfuscation, coma, and eventually death. On the other hand, excessive plasma glucose concentrations produce microvascular damages (notably in the retina and kidney) and neural damages, leading among others to blindness and chronic renal insufficiency. The way the body controls glycemia seems deceptively simple. Essentially a single hormone (insulin) is secreted by the β-cells of the pancreas in response to rising glucose concentrations (hyperglycemia). Insulin effects include increasing peripheral tissue glucose uptake (mainly by the muscle and fat tissues) and decreasing spontaneous glucose output by the liver. When insulin secretion by the pancreas is insufficient or absent, due to (autoimmune) destruction of β-cells, the clinical picture of T1DM results. A number of hormones contribute to rescuing the organism from hypoglycemia (adrenalin, glucagon, growth hormone, cortisol, etc.): however, since in clinical practice the situation of interest is normally inappropriately high glycemia, concentrating attention on the response to hyperglycemia by insulin seems justified, at least as a first modeling approach. We may therefore consider, as a first approximation, a simplified

system in which a single metabolite (glucose) is controlled by a single hormone (insulin). This system will have to maintain glycemia in the absence of food intake, and will have to suppress hyperglycemia rapidly after meals, without incurring in dangerous hypoglycemias. Therefore, the glucose-insulin system could be viewed, at least approximately, as a feedback control with a controller (the pancreas) and multiple effectors (muscle, liver, fat tissue).

First-principle models of glucose physiology broadly fall into two categories: maximal models and minimal models [CDMS$^+$09]. This section introduces a minimal model and an FDA-accepted maximal model, which are used in in-silico evaluations in this thesis.

4.1.1 Mathematical models

Short term modeling concerns the glucose-insulin dynamics after an external perturbation such as a glucose bolus injection (intra-venous glucose tolerance test, IVGTT), an oral glucose consumption (oral glucose tolerance test, OGTT) or continuous glucose and insulin infusions like the Euglycemic Hyperinsulinemic Clamp (EHC), within a relatively short time period of a few hours. These clinical experiments, and the mathematical models aimed at their interpretations, have generated much interest in the last decades since they offered the possibility to estimate a set of key markers of T1DM development. Besides generally allowing a more accurate knowledge of the regulatory mechanisms underlying glucose-insulin homeostasis, short term mathematical models may be fruitfully linked to clinical protocols in order to compute the insulin sensitivity of a given subject. The common denominator of these models is the fact that they are top-down compartmental models, representing the observable features of glucose-insulin homeostasis without detailing the molecular events leading to such features. The IVGTT is a clinical experiment where a glucose bolus is rapidly injected intra-venously into a subject. Glucose and insulin samples are acquired in the following three hours, during which glycemia and insulinemia return to their basal values. The glucose injection is modelled as an instantaneous change in the plasma glucose concentration. In healthy subjects the glucose induced pancreatic response of insulin release consists of two contributions: a first phase release, which is a quick response to a sudden change in glycemia, and a second phase release, which occurs some ten minutes after the bolus injection. The first phase is usually modelled as an instantaneous

change in the plasma insulin concentration. The second phase is described by the model equations, and the difference among the many existing mathematical models are evaluated by their ability to capture correctly the observed dynamics.

Minimal model

Minimal model use only a few compartments to model the physiology, and they have a simple structure that is convenient for linearization and control design [GPZ$^+$07]. The early linear models of the glucose-insulin homeostasis, which have been validated by means of an IVGTT, date back to Bolie [BOL61] and Ackerman's research group [EA64, AGRM65] in the sixties. However, the most famous and still greatly widespread model used in clinical assessments, such as the estimate of the insulin sensitivity index, is the so-called Bergman Minimal Model, proposed by Bergman and collaborators in the late seventies [BIBC79b]. For a historical review see [Ber97, Ber03]. The BeMM is composed of two separate parts: one describing the dynamics of the glucose uptake after the external stimulus, regarding the insulin concentration as a known forcing function; the other describing the dynamics of the pancreatic insulin release in response to the glucose stimulus, with the glucose concentration regarded as a known forcing function.

The model equations for the glucose dynamics are (2.26)–(2.28), which were used in Chapter 2 as an example of a nonlinear system used to propose an optimal identifier capable to identify the glucose-insulin dynamics. The BeMM is a two-compartment model: the first equation refers to the plasma glucose concentration in plasma G(mg/dl), the second refers to a remote compartment for the insulin. The physiological assumption is that the insulin-dependent glucose uptake does not directly depend on the plasma insulin concentration $I(\mu\text{U}\ /\text{ml})$, but on the insulin concentration in the remote compartment, through the auxiliary function $X(\text{min}^{-1})$, whose dynamics depends on the plasma insulinemia.

The insulin kinetics of the BeMM is thus necessarily associated to the IVGTT procedure, since the initial experimental time plays a crucial role in assessing the insulin secretion rate. Therefore the model cannot be used for other purposes, such as a multi bolus experiment, or during glucose infusions. The integrated glucose-insulin system is illustrated by the compartment model in Figure 4.1 [DGA00]. The BeMM is presented in (2.26)–(2.28),

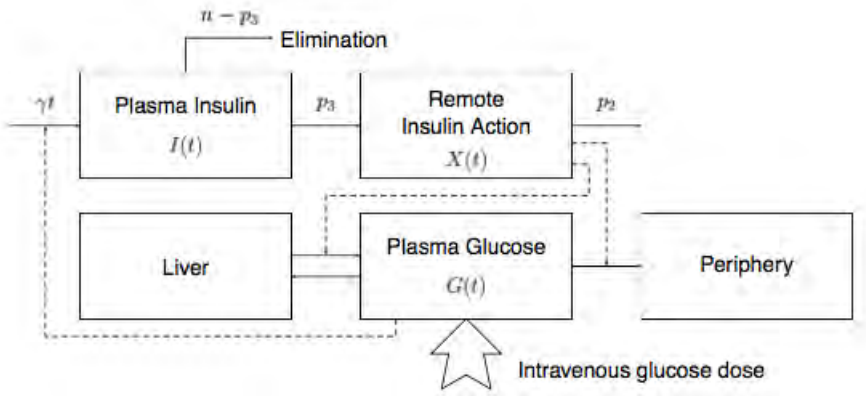


Figure 4.1: BeMM describing the glucose and insulin kinetics in an IVGTT study.

where the parameter h (mg/dl) is the threshold value of glucose above which the pancreatic β-cells release insulin. The term γ (μU/ml min^{-2}(mg/dl)$^{-1}$) is the rate of the pancreatic β-cells' release of insulin after the glucose injection and with glucose concentration above h. The control input u represents the exogenous insulin infusion rate, and U is the units of insulin needed to regulate the glucose into the desired level. Data from a normal glucose tolerant individual is shown in Figure 4.2 [PB86].

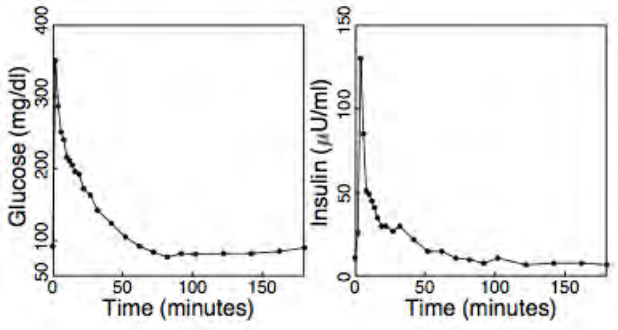


Figure 4.2: Glucose-insulin concentrations in plasma frequently sampled over 180 minutes after an intravenous glucose injection given to a normal glucose tolerant individual.

The model parameters usually are estimated by a recursive least squares estimation technique, where the parameters in G and X are estimated using insulin as a forcing function and then the parameters in I are estimated using glucose as a forcing function.

Maximal model

Maximal models use compartmental submodels to describe the dynamics of glucose and insulin in the human body. These models are mostly used for simulation purposes.

One of the most used maximal model is the Cobelli model, which includes insulin subsystem, the meal glucose absorption, and the glucose kinetics. Extensive details of the model, including the modeling rationale and meanings of the variables and parameters, can be found in a series of publications [MRDM$^+$09, DMRC07, MML$^+$14, KBDMC09]. In the Cobelli model, the glucose-insulin system is represented by a model with 6 subsystems, which include 14 equations that describe the relation between plasma concentrations (glucose G and insulin I), glucose fluxes (rate of appearance R_a, endogenous glucose production EGP, utilization U, renal extraction E), and insulin fluxes (secretion S, and degradation D) [MRM$^+$09]. Figure 4.3 describes the interactions between the different components belonging to the system [MRC07].

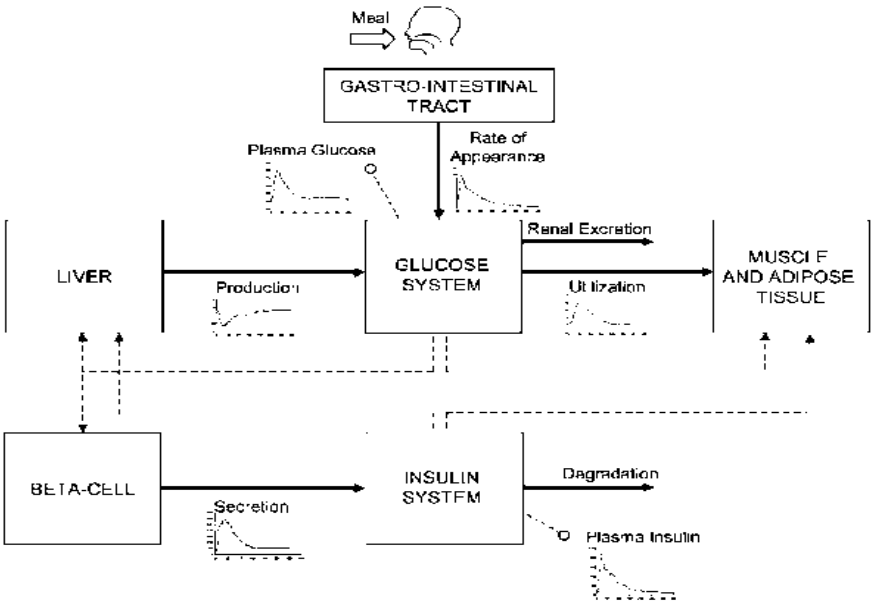


Figure 4.3: Interaction scheme between the different components of the glucose-insulin system.

The dynamical behavior for each subsystem in the Cobelli model is summarized in Appendix A, through equations (A.1)–(A.14).

4.2 Adaptive identification applied to the Cobelli system used to model the glucose-insulin dynamics in healthy persons

In order to apply the adaptive identification scheme, the meal glucose-insulin model is summarized in Figure 4.4. The current system (A.1)–(A.14) is considered to be an uncertain and a disturbed nonlinear one, representing the glucose-insulin dynamical behavior in the human body, which depends on various factors as eating and healthy habits, age, weight, etc.; therefore, it is convenient to deal with those uncertainties and disturbances by applying an adaptive identifier. It is assumed that the glucose-insulin system and its parameters are unknown, and only the measurements of the plasma glucose concentration G are available to be used in the adaptive identification process as shown in Figure 4.5.

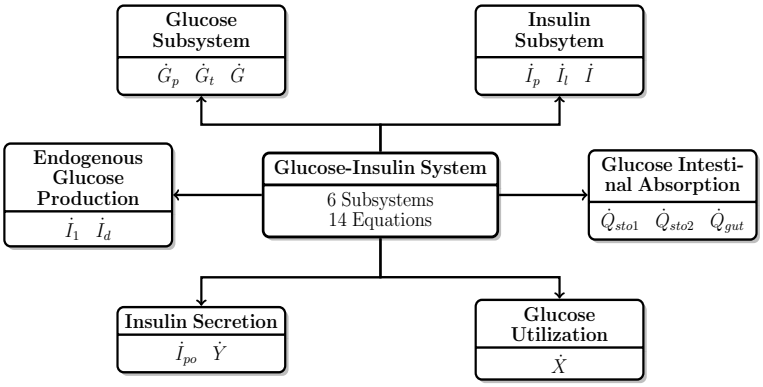


Figure 4.4: Cobelli glucose-insulin subsystems summarized in differential equations.

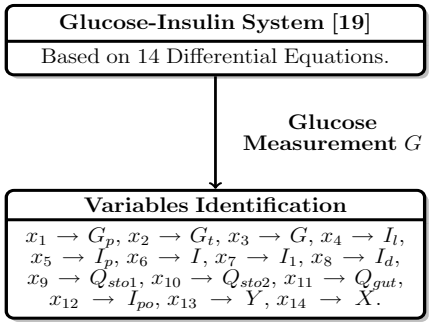


Figure 4.5: Adaptive identification and variables convergence.

This Section proposes an adaptive identifier presented in SDCF for an adequate approximation of the Cobelli model dynamics. The adaptive identifier process minimizes the identification error using the adaptation algorithm (2.15) to adapt its parameters on-line.

The adaptive identifier to approximate the dynamics of the glucose-insulin model (A.1)–(A.14) is proposed as

$$
\begin{aligned}
\dot{x}_1 &= \theta_1 + \theta_2 x_1 + \theta_3 x_3 + \theta_4 x_8 + \theta_5 x_{12} + \theta_6 x_{11} \\
\dot{x}_2 &= \theta_7 x_1 + \theta_8 x_2 + \theta_9 + \theta_{10} x_2 x_{14} + \theta_{11} x_8 + \theta_{12} x_{10} \\
\dot{x}_3 &= \theta_{13} + \theta_{14} x_2 x_3 + \theta_{15} x_2 + \theta_{16} x_7 x_8 + \theta_{17} x_1 x_{12} + \theta_{18} x_{11} \\
\dot{x}_4 &= \theta_{19} + \theta_{20} x_4 + \theta_{21} x_5 + \theta_{22} x_{12} + \theta_{23} x_4 x_{12} + \theta_{24} x_8 \\
\dot{x}_5 &= \theta_{25} x_4 + \theta_{26} x_5 \\
\dot{x}_6 &= \theta_{27} x_4 + \theta_{28} x_5 + \theta_{29} x_6 + \theta_{30} + \theta_{31} x_8 \\
\dot{x}_7 &= \theta_{32} x_5 + \theta_{33} x_7 + \theta_{34} \\
\dot{x}_8 &= \theta_{35} x_7 + \theta_{36} x_8 \\
\dot{x}_9 &= \theta_{37} x_9 + \theta_{38} d \\
\dot{x}_{10} &= \theta_{39} x_9 + \theta_{40} x_{10} \\
\dot{x}_{11} &= \theta_{41} x_{10} + \theta_{42} x_{11} \\
\dot{x}_{12} &= \theta_{43} + \theta_{44} x_1 + \theta_{45} x_3 + \theta_{46} x_8 + \theta_{47} x_{11} + \theta_{48} x_{12} + x_{13} \\
\dot{x}_{13} &= \theta_{49} + \theta_{50} x_3 + \theta_{51} x_{13} \\
\dot{x}_{14} &= \theta_{52} + \theta_{53} x_5 + \theta_{54} x_{14}
\end{aligned}
\tag{4.1}
$$

where $\theta = [\theta_1, \theta_2, \theta_3 \ldots \theta_{52},\ \theta_{53},\ \theta_{54}]^T$ are the parameters to be determined, $x = [x_1\ \ldots x_{14}]^T$ is the state vector, which identifies the glucose-insulin variables in the Cobelli model $\mathcal{X} = [G_p\ Gt\ G\ I_l\ I_p\ I\ I_1\ I_d\ Q_{sto1}\ Q_{sto2}\ Q_{gut}\ I_{po}\ Y\ X]^T$. Based only on the plasma glucose concentration measurement, the identification error $\varepsilon = x_3 - G$ is used to adapt the parameters θ in (4.1) through the RLSA given in (2.15). Different structures, different orders and relation between the variables can be proposed to design the identifier model, the developed one in this section allows the adequate identification of the Cobelli system.

4.2.1 Adaptive identifier performance

The performance effectiveness of the adaptive identification scheme applied to the Cobelli model is shown as follows. The parameters θ in the proposed identifier are adapted using the RLSA. The convergence speed and the oscillations are determined by the values of the parameters Ψ and g in (2.15). The parameters used to simulate the glucose-insulin dynamics in a healthy person are shown in Table 4.1 [MRC07]. The initial conditions for the identifier are given with a difference of 10 % with respect to the initial conditions of the glucose-insulin model.

Table 4.1: Cobelli system parameters for a healthy person.

Parameter	Value	Unit	Parameter	Value	Unit
d_G	78000	mg	A_G	0.8	dimensionless
V_G	1.88	dl	T_{maxG}	1	min
T_{maxI}	1.3	min	G_{pb}	172.5	mg/kg
G_{tb}	130.29	mg/kg	G_b	91.48	mg/l
I_{lb}	4.54	$pmol/kg$	I_{pb}	1.2745	$pmol/kg$
I_b	25.49	$pmol/l$	I_{pob}	3.084	$pmol/kg$
$G_p(0)$	172.5	mg/kg	$G_t(0)$	130.29	mg/kg
$G(0)$	91.48	mg/dl	$I_l(0)$	4.086	$pmol/kg$
$I_p(0)$	1.143	$pmol/kg$	$I_1(0)$	22.94	$pmol/l$
$I_d(0)$	24	$pmol/l$	$I(0)$	25.4	$pmol/l$
$Q_{sto1}(0)$	0	mg	$Q_{gut}(0)$	0	mg
$Q_{sto2}(0)$	0	mg	$I_{po}(0)$	2.775	$pmol/kg$
$Y(0)$	0	$pmol/kg$	$X(0)$	0	$pmol/kg$

For the identification process, the bases w and the parameters Ψ, as well as g used for the RLSA are presented in Table 4.2, Table 4.3, Table 4.4 respectively, which are selected to achieve an adequate on-line adaptation of the parameters θ in (4.1).

Table 4.2: Bases w used in the proposed adaptive identifier.

$w_1 = [1 \;\; x_1 \;\; x_3 \;\; x_8 \;\; x_{12} \;\; x_{11}]^T$	$w_2 = [x_1 \;\; x_2 \;\; 1 \;\; x_2x_{14} \;\; x_8 \;\; x_{10}]^T$
$w_3 = [1 \;\; x_2x_3 \;\; x_2 \;\; x_7x_8 \;\; x_1x_{12} \;\; x_{11}]^T$	$w_4 = [1 \;\; x_4 \;\; x_5 \;\; x_{12} \;\; x_4x_{12} \;\; x_8]^T$
$w_5 = [x_4 \;\; x_5]^T$	$w_6 = [x_4 \;\; x_5 \;\; x_6 \;\; 1 \;\; x_8]^T$
$w_7 = [x_5 \;\; x_7 \;\; 1]^T$	$w_8 = [x_7 \;\; x_8]^T$
$w_9 = [x_9 \;\; d]^T$	$w_{10} = [x_9 \;\; x_{10}]^T$
$w_{11} = [x_{10} \;\; x_{11}]^T$	$w_{12} = [1 \;\; x_1 \;\; x_3 \;\; x_8 \;\; x_{11} \;\; x_{12}]^T$
$w_{13} = [1 \;\; x_3 \;\; x_{13}]^T$	$w_{14} = [1 \;\; x_5 \;\; x_{14}]^T$

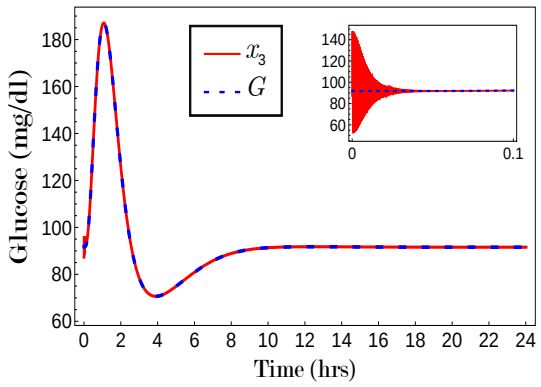
Table 4.3: Parameters Ψ used in the proposed adaptive identifier.

$\Psi_1 = diag\{0.005,\ \ 0.005,\ \ 0.005,\ \ 0.005,\ \ 0.005,\ \ 0.005\}$
$\Psi_2 = diag\{5\times10^{-8},\ 5\times10^{-8},\ 5\times10^{-8},\ 5\times10^{-8},\ 5\times10^{-8},\ 5\times10^{-8},\ 5\times10^{-8}\}$
$\Psi_3 = diag\{0.05,\ \ 0.05,\ \ 0.05,\ \ 0.05,\ \ 0.05,\ \ 0.05\}$
$\Psi_4 = diag\{5,\ \ 5,\ \ 5,\ \ 5,\ \ 5,\ \ 5,\ \ 5\}$
$\Psi_5 = diag\{5,\ \ 5\}$
$\Psi_6 = diag\{5,\ \ 5,\ \ 5,\ \ 5,\ \ 5,\ \ 5\}$
$\Psi_7 = diag\{5,\ \ 5,\ \ 5\}$
$\Psi_8 = diag\{5,\ \ 5\}$
$\Psi_9 = diag\{5,\ \ 5\}$
$\Psi_{10} = diag\{5,\ \ 5\}$
$\Psi_{11} = diag\{5,\ \ 5\}$
$\Psi_{12} = diag\{0.0005,\ \ 0.0005,\ \ 0.0005,\ \ 0.0005,\ \ 0.0005,\ \ 0.0005\}$
$\Psi_{13} = diag\{0.0005,\ \ 0.0005,\ \ 0.0005\}$
$\Psi_{14} = diag\{0.0005,\ \ 0.0005,\ \ 0.0005\}$

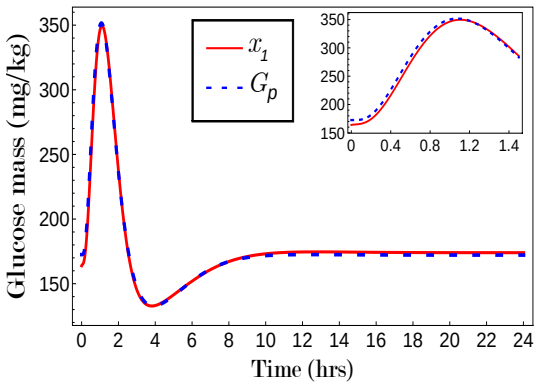
Table 4.4: Parameters g used in the proposed adaptive identifier.

$g_1 = 1\times10^6$	$g_2 = 5\times10^7$	$g_3 = 0.0088$	$g_4 = 1\times10^5$
$g_5 = 1\times10^6$	$g_6 = 1\times10^6$	$g_7 = 1\times10^6$	$g_8 = 1\times10^6$
$g_9 = 1\times10^6$	$g_{10} = 1\times10^6$	$g_{11} = 1\times10^6$	$g_{12} = 1\times10^6$
$g_{13} = 1\times10^6$	$g_{14} = 1\times10^6$		

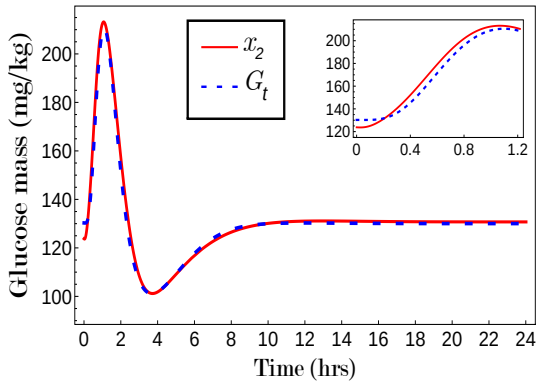
In the simulation results, Figure 4.6 shows the adaptive identification scheme applied to the glucose-insulin system in a healthy person. Figure 4.6(a) shows the convergence between the glucose signal G from the glucose-insulin model (A.3) and its corresponding variable x_3 from the proposed identifier. From all the identifier's variables only the glucose signal measurement is available to be used in the RLSA to minimize the convergence error. Figure 4.6(b) displays the convergence between the glucose mass in plasma G_p and its corresponding identification variable x_1. In Figure 4.6(c) shows the convergence between the glucose mass in tissues G_t and its corresponding variable x_2. In Figure 4.6(d) shows the convergence between the insulin mass in liver I_l and its corresponding variable x_4. In a similar way Figure 4.7 and Figure 4.8 show the convergence between the adaptive identifier variables and the glucose-insulin system. From Figure 4.6(e) to Figure 4.8(b) are represented the remainder variables; in the same figures, a little square with zoom is shown to appreciate the convergence between the variables.



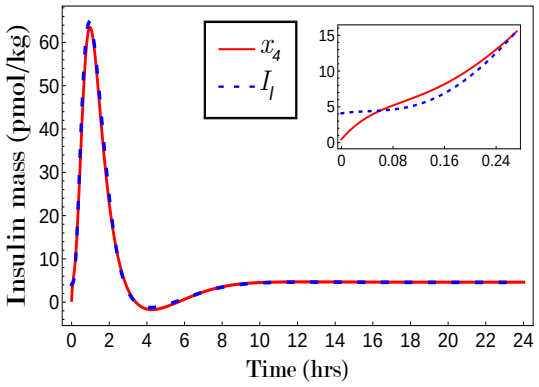
(a) ***Identification and convergence of the plasma glucose concentration*** G.



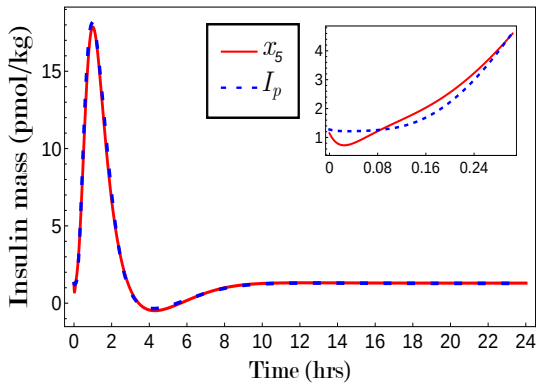
(b) ***Identification and convergence of the glucose mass in plasma*** G_p.



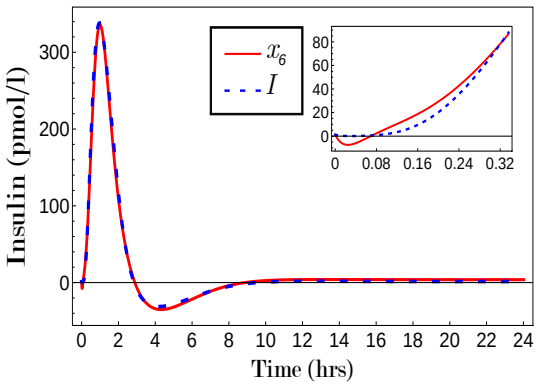
(c) ***Identification and convergence of the glucose mass in tissues*** G_t.



(d) ***Identification and convergence of the insulin mass in liver*** I_l

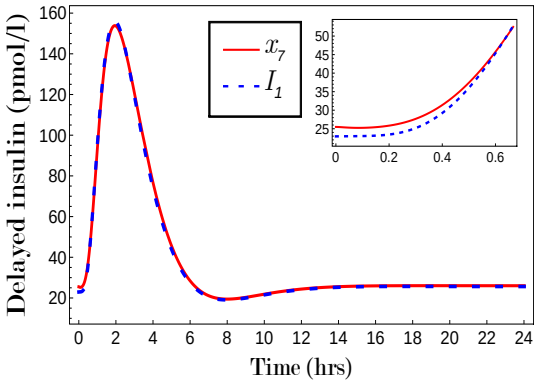


(e) ***Identification and convergence of the insulin mass in plasma*** I_p.

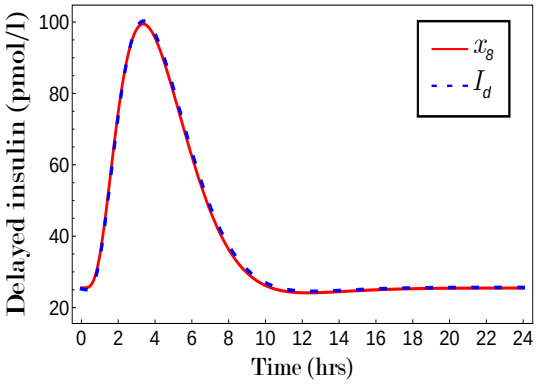


(f) ***Identification and convergence of the plasma insulin concentration*** I.

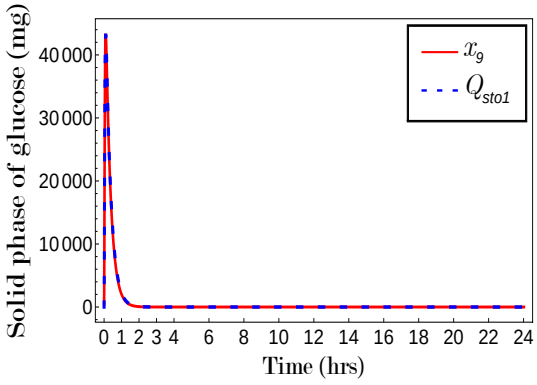
Figure 4.6: Adaptive identification scheme applied to the Cobelli system in a healthy person. Identification of the variables G, G_p, G_t, I_l, I_p and I.



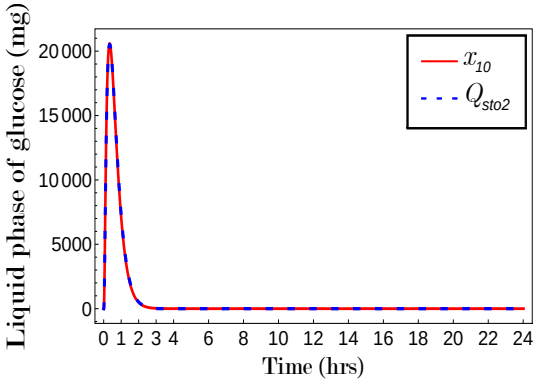
(a) ***Identification and convergence of the delayed insulin signal*** I_1.



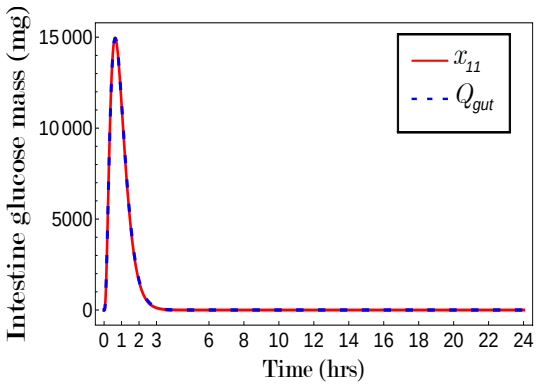
(b) ***Identification and convergence of the delayed insulin signal*** I_d.



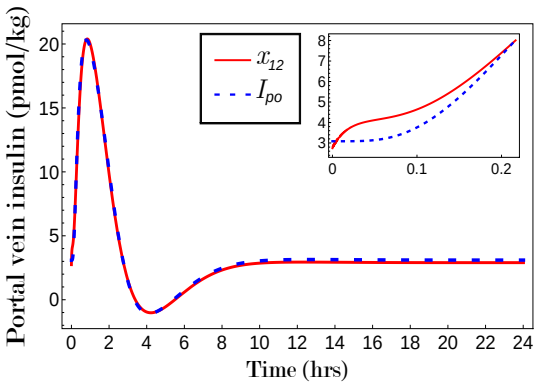
(c) ***Identification and convergence of the solid phase of the glucose in the stomach*** Q_{sto1}.



(d) ***Identification and convergence of the liquid phase of the glucose in the stomach*** Q_{sto2}.

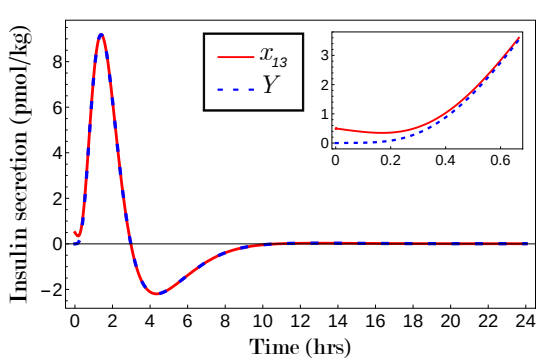


(e) ***Identification and convergence of the glucose mass in the intestine*** Q_{gut}.

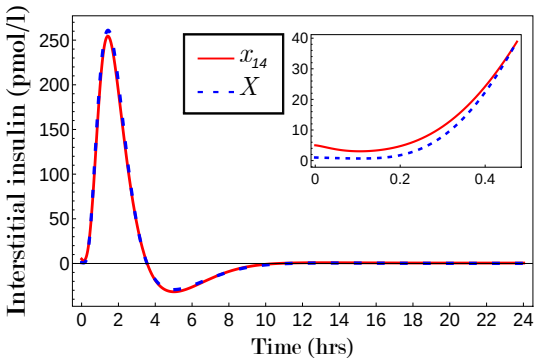


(f) ***Identification and convergence of the insulin in the portal vein*** I_{po}.

Figure 4.7: Adaptive identification scheme applied to the Cobelli system in a healthy person. Identification of the variables I_1, I_d, Q_{sto1}, Q_{sto2}, Q_{gut} and I_{po}.



(a) ***Identification and convergence of the insulin secretion*** Y***.***



(b) ***Identification and convergence of the insulin in the interstitial fluid*** X***.***

Figure 4.8: Adaptive identification scheme applied to the Cobelli system in a healthy person. Identification of the variables Y and X.

This section presented the adaptive identification scheme applied to the Cobelli system which is used to model the glucose-insulin in a healthy person with the aim to demonstrate the adaptive identifier effectiveness. The simulation results showed an adequate convergence between the adaptive identifier variables and the Cobelli system variables, i.e., the dynamical behavior is identified for every variable of the Cobelli's model. This Section is the basis to introduce the reader to the adaptive identification and optimal control applied to type 1 diabetes. Next Section will show the differences between the Cobelli model used to simulate the glucose-insulin dynamics in a healthy person and the modified Cobelli model used to simulate the glucose-insulin dynamics in type 1 diabetic patients. The last model is used to evaluate different control schemes in the T1DM treatments.

4.3 Adaptive identification and optimal nonlinear control applied to the Cobelli system used to model the glucose-insulin dynamics in type 1 diabetic patients

In type 1 diabetic patients, insulin is usually administered by subcutaneous injection, when the pancreas produces little or no insulin. Insulin is needed to allow glucose to enter cells to produce energy. Then, to represent the glucose-insulin dynamics in a type

1 diabetic person, the Cobelli system is adapted to represent the insulin subcutaneous injection with two compartments, S_1 and S_2 (pmol/kg) (which is a variation of the model (A.1)–(A.14) described in [MRC07])

$$\dot{S}_1 = -(k_{a1} + k_d)S_1 + u \tag{4.2}$$

$$\dot{S}_2 = k_d S_1 - k_{a2} S_2 \tag{4.3}$$

where S_1 represents polymeric insulin and S_2 monomeric insulin in the subcutaneous tissue, u (pmol/kg/min) represents injected insulin flow, k_d is called degradation constant, k_{a1} and k_{a2} are absorption constants. The parameters used to simulate the glucose-insulin dynamics in a type 1 diabetic person are shown in Table 4.5 [MRM$^+$09].

Table 4.5: Cobelli system parameters for a type 1 diabetic person.

Parameter	Value	Unit	Parameter	Value	Unit
d_G	60000	mg	A_G	0.78	$dimensionless$
V_G	1.8	dl	T_{maxG}	0.89	min
T_{maxI}	2.5	min	G_{pb}	102.5	mg/kg
G_{tb}	98.29	mg/kg	G_{mb}	55	mg/l
I_{lb}	4.45	$pmol/kg$	I_{pb}	1.2745	$pmol/kg$
I_{1b}	25.49	$pmol/l$	I_{db}	3.084	$pmol/kg$
$G_p(0)$	90	mg/kg	$G_t(0)$	130.29	mg/kg
$G_m(0)$	50	mg/dl	$I_l(0)$	5.8	$pmol/kg$
$I_p(0)$	5	$pmol/kg$	$I_1(0)$	24	$pmol/l$
$I_d(0)$	24	$pmol/l$	$X(0)$	0	$pmol/kg$
$S_1(0)$	0	$pmol/kg$	$S_2(0)$	0	$pmol/kg$
k_{a1}	0.52	$dimensionless$	k_{a2}	0.077	$dimensionless$
k_d	0.0162	$dimensionless$			

4.3.1 Adaptive identifier

Due to this adaptation, the Cobelli model is the basis on which the UVa/Padova T1DMS has been developed [MRDM$^+$09, DMRC07, KBDMC09]. At the present time, this model is an FDA-accepted substitute for pre-clinical trials and evaluating certain control algorithms [MML$^+$14]. This Section proposes an adaptive identifier, which is based in the Cobelli's model, and a robust nonlinear optimal tracking control scheme to regulate the blood glucose levels in type 1 diabetic patients.

The adaptive polynomial identifier to approximate the glucose-insulin dynamics in type 1 diabetic patients using the adapted Cobelli model [MRM$^+$09] is proposed with the following structure

$$\begin{aligned}
\dot{x}_1 &= \theta_1 x_1 + \theta_2 x_2 x_3 \\
\dot{x}_2 &= \theta_3 x_2 + \theta_4 x_3 \\
\dot{x}_3 &= \theta_5 x_2 + \theta_6 x_3 + \theta_7 x_7 + \theta_8 x_8 \\
\dot{x}_4 &= \theta_9 x_3 + \theta_{10} x_4 \\
\dot{x}_5 &= \theta_{11} x_4 + \theta_{12} x_5 \\
\dot{x}_6 &= \theta_{13} x_3 + \theta_{14} x_6 + \theta_{15} \\
\dot{x}_7 &= \theta_{16} x_7 + u \\
\dot{x}_8 &= \theta_{17} x_7 + \theta_{18} x_8
\end{aligned} \tag{4.4}$$

where $\theta = [\theta_1 \dots \theta_{18}]^T$ are the parameters to be determined by the recursive least-squares algorithm, $x = [x_1 \ \dots x_8]^T$ is the state vector, which identifies the glucose-insulin variables $\mathcal{X} = [G_p \ G_M \ I_l \ I_p \ I_d \ X \ S_1 \ S_2]^T$. Based only on the plasma glucose concentration measurement, the identification error $\varepsilon = x_2 - G_M$ is used to adapt the parameters θ in (4.4) through the RLSA given in (2.15). The difference between (4.1) and (4.4) is that the last one is used to represent the glucose-insulin dynamics in type 1 diabetic patients and the first one is used to model the dynamics of the glucose-insulin system in healthy people.

4.3.2 Robust optimal tracking control

In order to synthesize the optimal controller and based on the structure of the adaptive identifier (4.4), the salient feature of the state-dependent representation in the proposed adaptive identifier is used to obtain the solution to the robust optimal tracking control. The output of the system is required to track a desired trajectory as close as possible in an optimal sense and with minimum control effort expenditure [AM90, AF66]. Since the output of the adapted Cobelli model is only the blood glucose level, then it is required to add only one integrator; hence, the augmented system becomes into (3.43), with $x_a = [q \ x]^T = [q \ x_1 \ x_2 \ x_3 \ x_4 \ x_5 \ x_6 \ x_7 \ x_8]^T$, which can be rewritten as (3.44)–(3.45),

with

$$A_a(x_a,\theta)=\begin{bmatrix} 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \theta_1 & 0 & \theta_2 x_2 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \theta_3 & \theta_4 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \theta_5 & \theta_6 & 0 & 0 & 0 & \theta_7 & \theta_8 \\ 0 & 0 & 0 & \theta_9 & \theta_{10} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \theta_{11} & \theta_{12} & 0 & 0 & 0 \\ 0 & 0 & 0 & \theta_{13} & 0 & 0 & \theta_{14} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \theta_{16} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \theta_{17} & \theta_{18} \end{bmatrix}, B_a=\begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}^T,$$

$C_a = \begin{bmatrix} 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$ and $\Gamma_a = \begin{bmatrix} -r & G_m & 0 & 0 & 0 & 0 & \theta_{15} & 0 & 0 \end{bmatrix}^T$.
Parameter r is the reference value for the glucose level, G_m is the blood glucose measurement, and the cost functional to be minimized is (3.28). For the augmented system, the robust optimal controller is given by (3.29).

4.4 Simulation results

The performance effectiveness of the adaptive identifier and the optimal tracking control scheme, which are applied to the adapted Cobelli system used to represent the glucose-insulin dynamics in a type 1 diabetic patient, is shown in this subsection.

For the identification process, the bases w and the parameters Ψ, as well as g used for the RLSA are presented in Table 4.6, which are selected to achieve an adequate on-line adaptation of the parameters θ in (4.4).

4.4.1 Adaptive identification and optimal control for continuous insulin pumps and constant reference

The following figures show the simulation results of the adaptive identification process applied to the adapted Cobelli system used to represent the glucose-insulin dynamics in type 1 diabetic patients. The adaptive identification and optimal control of the glucose

Table 4.6: Parameters used in the adapted Cobelli system identification process.

$w_1 = [x_1\ x_2 x_3]^T$	$\Psi_1 = diag\{0.05, 0.05, 0.05\}$	$g_1 = 1 \times 10^5$
$w_2 = [x_2\ x_3]^T$	$\Psi_2 = diag\{0.0005, 0.0005\}$	$g_2 = 1 \times 10^6$
$w_3 = [x_2\ x_3\ x_7\ x_8]^T$	$\Psi_3 = diag\{0.05, 0.05, 0.05, 0.05\}$	$g_3 = 5 \times 10^6$
$w_4 = [x_3\ x_4]^T$	$\Psi_4 = diag\{0.005, 0.005\}$	$g_4 = 1 \times 10^6$
$w_5 = [x_4\ x_5]^T$	$\Psi_5 = diag\{5, 5\}$	$g_5 = 1 \times 10^4$
$w_6 = [x_3\ x_4\ 1]^T$	$\Psi_6 = diag\{0.005, 0.005, 0.005\}$	$g_6 = 5 \times 10^4$
$w_7 = [x_7]^T$	$\Psi_7 = diag\{0.0005\}$	$g_7 = 1 \times 10^6$
$w_8 = [x_8\ x_9]^T$	$\Psi_8 = diag\{0.0005, 0.0005\}$	$g_8 = 5 \times 10^6$

dynamical behavior for type 1 diabetic disease is carried out into the following scenario:

Scenario 1 consists in a one day feed scheme for an adolescent virtual patient, where the first intake is at 07:00 hrs with 30 grams of carbohydrates, the second intake is at 09:00 hrs with 50 grams of carbohydrates, the third intake is at 13:00 hrs with 70 grams of carbohydrates, the fourth intake is at 18:00 hrs with 50 grams of carbohydrates, and the fifth intake is at 21:00 hrs with 30 grams of carbohydrates. Figure 4.9 shows the simulation results obtained in the application of the adaptive identifier and the robust optimal control scheme. Once the identifier (continuous red line) converges to the glucose signal G (dashed blue line), the optimal tracking control is applied. In this simulation the control signal is applied at 02:00 hrs and is programmed to regulate the blood glucose signal to the reference $r = 110$ mg/dl.

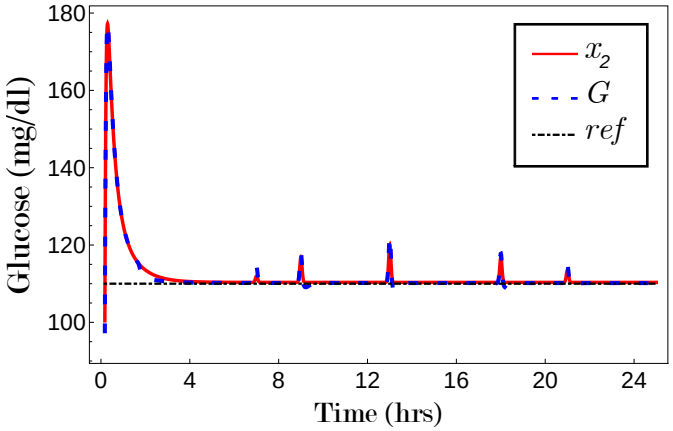


Figure 4.9: Adaptive identification and optimal tracking control applied to the adapted Cobelli system. The blood glucose regulation is carried out to a constant reference level $r = 110$ mg/dl. Every peak represents the time when the patient was fed.

Once the reference level is achieved, the optimal control maintains the blood glucose value in that reference even the patient is fed, rejecting the possible disturbances that could alter the glucose level in the patient. At the times when the patient is fed, it could appreciate that the control scheme maintains the blood glucose into a threshold of ± 10 mg/dl over the reference, avoiding possible hyperglycemia cases. Figure 4.10 depicts the control signal u for a continuous infusion insulin pump, and represents the continuous exogenous infusion of insulin to maintain the glucose level to the required reference level $r = 110$ mg/dl. At the moment when the patient is fed, the rate of insulin infusion increase, allowing to reject the disturbances caused by different food quantities.

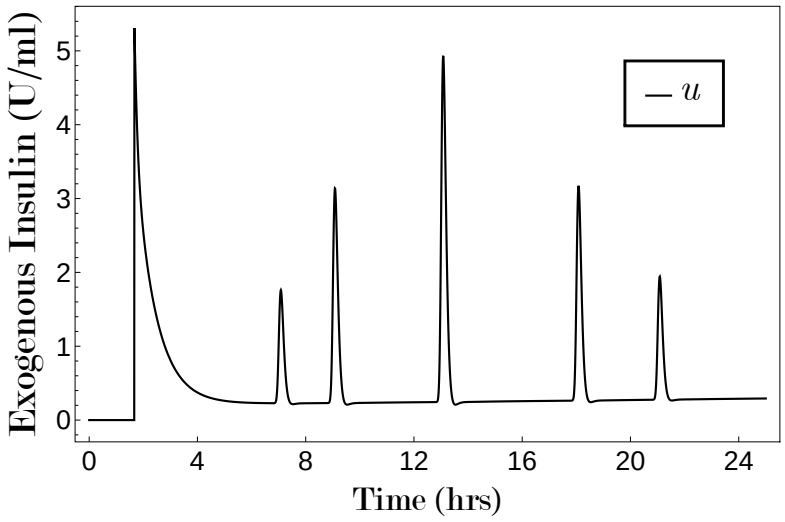


Figure 4.10: Control signal u that represents the continuous exogenous insulin needed to regulate the glucose at the constant reference level $r = 110$ mg/dl.

The bolus dose for food coverage is prescribed as an insulin to carbohydrate ratio. The insulin to carbohydrate ratio represents how many grams of carbohydrate are covered or disposed of by 1 unit of insulin. Generally, one unit of insulin will dispose of 12-18 grams of carbohydrate. This range can vary depending on an individual's sensitivity to insulin and the insulin sensitivity can vary according to the time of day, from person to person, and is affected by physical activity and stress [FMD]. Based on the above, Figure 4.10 shows the control signal needed to regulate the blood glucose in a type 1 diabetic patient under scenario 1, where to regulate the first intake (30 grams of carbohydrates) an exogenous dose of 2

insulin units is calculated, in the second intake (50 grams of carbohydrates) an exogenous dose of 3 insulin units is calculated , and for the third intake (70 grams of carbohydrates) an exogenous dose of 5 insulin units is calculated. The simulation results confirms that the control signal matches with the insulin units needed to regulate each intake in the type 1 diabetic patient, i.e., to regulate an intake from 30 grams of carbohydrates an average dose of 2 units of insulin is needed, to regulate an intake from 50 grams of carbohydrates an average dose of 3 units of insulin is needed, and to regulate an intake from 70 grams of carbohydrates an average dose of 5 units of insulin is needed. The simulation results shows that the signal u determines the insulin infusion needed to regulate the glucose into the desired reference.

4.4.2 Adaptive identification and optimal control for discontinuous insulin pumps and constant reference

There exist different types of insulin pumps (continuous and discontinuous), so it is necessary that the control algorithm can be used for both of them. In this subsection is shown an adaptation from the proposed optimal control scheme to be used in discontinuous insulin pumps. The simplest way to generate a PWM signal is the intersective method, which requires only a sawtooth or a triangle waveform and a comparator as shown in Figure 4.11.

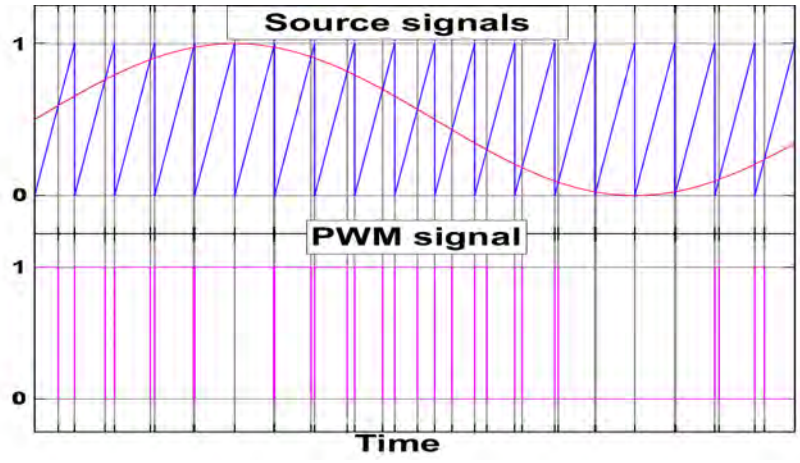


Figure 4.11: Intersective PWM.

When the value of the reference signal (the red sine wave) is more than the modulation waveform (blue), the PWM signal (magenta) is in the high state, otherwise it is in the low state [SKSP14]. The intersective method is applied to the continuous control signal u calculated by the optimal control algorithm. In this sense, the continuous control signal u is converted to a discontinuous signal with different pulse width, depending on the continuous control signal dynamics, i.e., if the continuous control signal u exceeds the amplitude of a proposed triangular signal, the PWM signal is in the high state, otherwise it is in the low state.

Figure 4.12 shows the simulation results obtained in the application of the PWM in the continuous control signal u obtained by the optimal control scheme. The established reference is $r = 110$ mg/dl; once the reference level is achieved, the optimal control maintains the blood glucose value in that reference using the control signal u_{PWM}, even when the patient is fed and rejecting the possible disturbances that could alter the glucose level in the patient. The regulated glucose signal G shows oscillations around the reference signal due to the nature of the control signal u_{PWM}. As in the previous case (continuous control signal u), at the times when the patient is fed, it can be observed that the control scheme maintains the blood glucose in an average threshold of ± 10 mg/dl over the reference, avoiding possible hyperglycemia cases.

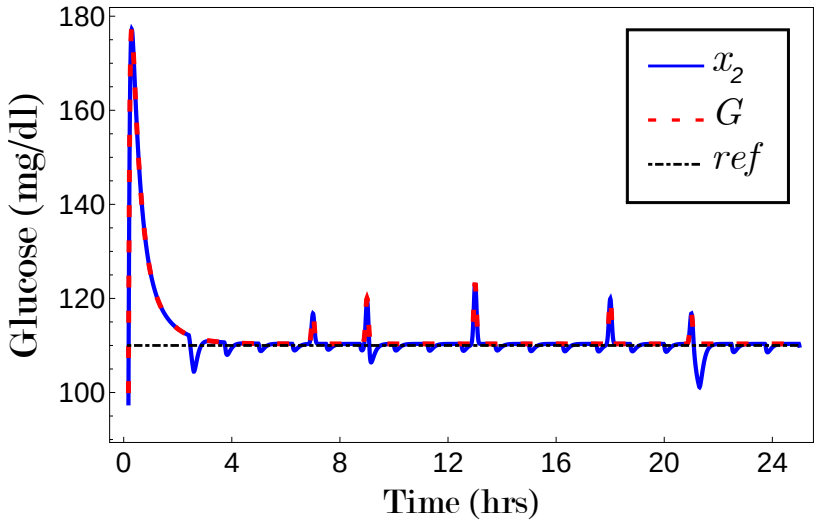


Figure 4.12: Constant blood glucose regulation using a discontinuous control signal u_{PWM}.

The control signal u_{PWM} is shown in Figure 4.13, which represents the exogenous discontinuous insulin doses needed to regulate de glucose level to the required reference $r = 110$ mg/dl. The discontinuous control signal shows multiple insulin infusions at different times determined by the switching frequency and the pulse width is determined by the value of the control signal u in the moment when the PWM is in a high state. Both signals are compared showing how the control signal u_{PWM} changes its pulse width depending if the continuous control signal behaviour u exceeds or doesn't exceed the established PWM amplitude. At the moment when the patient is fed, the rate of insulin infusion increase, allowing to reject the disturbances caused by food.

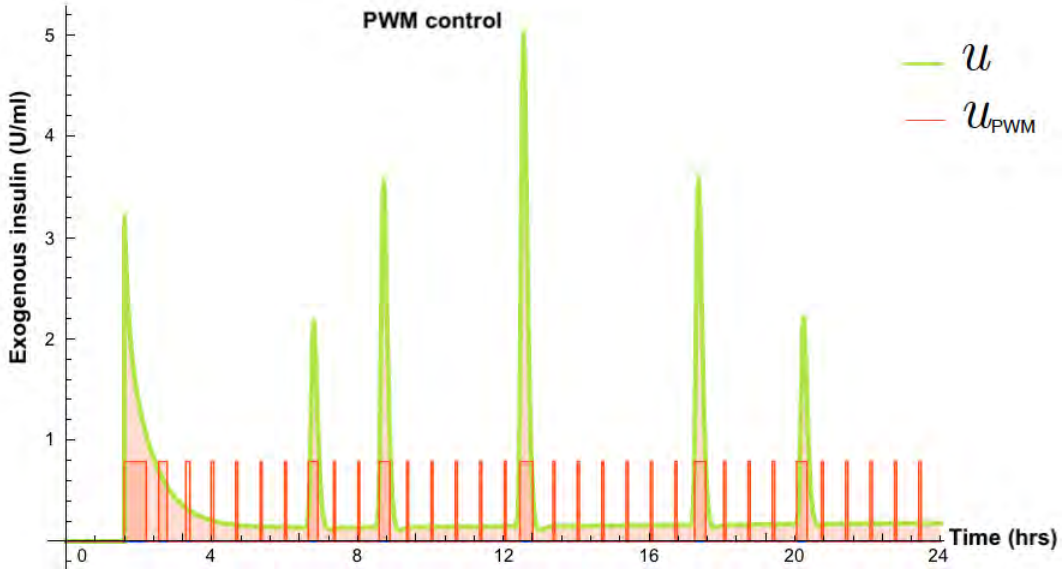


Figure 4.13: Control signal that represents the discontinuous exogenous insulin needed to regulate the glucose at the reference $r = 110$ mg/dl.

4.4.3 Adaptive identification and optimal control for continuous insulin pumps and variable references

The adaptive identification and optimal control of the glucose dynamical behavior for type 1 diabetic disease is carried out into the following scenario:

Scenario 2 consists of a one day feed scheme for an adult virtual patient, where the first intake is at 07:00 hrs with 15 grams of carbohydrates, the second intake is at

09:00 hrs with 30 grams of carbohydrates, the third intake is at 13:00 hrs with 50 grams of carbohydrates, the fourth intake is at 18:00 hrs with 30 grams of carbohydrates, and the fifth intake is at 21:00 hrs with 15 grams of carbohydrates. Figure 4.14 illustrates the capabilities of the optimal control scheme for regulating the glucose level to different reference values (r) at different intervals of time (t), i.e., for $t < 9$ hrs the reference level is $r = 150$ mg/dl, and in the same way, for $9 \leq t < 24$ hrs the reference level is $r = 110$ mg/dl.

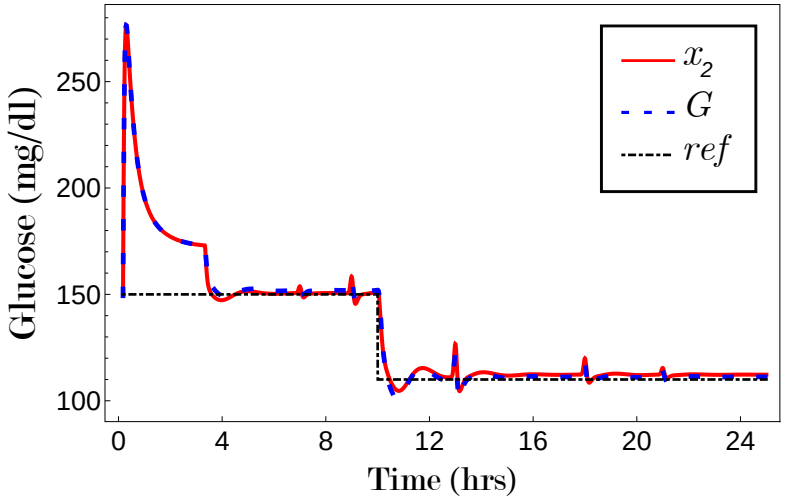


Figure 4.14: Adaptive identification and optimal tracking control applied to the adapted Cobelli system. The blood glucose regulation is carried out to different reference levels $r = 150$ and $r = 110$ mg/dl.

Figure 4.15 shows the exogenous continuous insulin dose needed to regulate de glucose level to the required references $r = 150$ mg/dl and $r = 110$ mg/dl. The control signal u shows different insulin dosage which depends of the required level to regulate the blood glucose. To regulate the glucose into the level $r = 150$ a continuous insulin infusion of 1 U/ml is needed. When the patient is fed, the optimal control determines a bigger insulin dose to maintain the glucose into the established level as is shown at 7 and 9 hrs. If the level reference change to a lower value, is needed more insulin dosage as is appreciated at 12 hrs when the reference level change from $r = 150$ mg/dl to $r = 110$ mg/dl, i.e., to maintain the glucose into the level $r = 110$ mg/dl is needed a continuous dosage of 2 U/ml and if the patient is fed, the needed insulin dose is incremented. As in the previous results (control

for constant reference), to regulate an intake from 15 grams of carbohydrates is needed an average dose of 1 unit of insulin, to regulate an intake from 30 grams of carbohydrates is needed an average dose of 2 units of insulin, and to regulate an intake from 50 grams of carbohydrates is needed an average dose of 3 units of insulin.

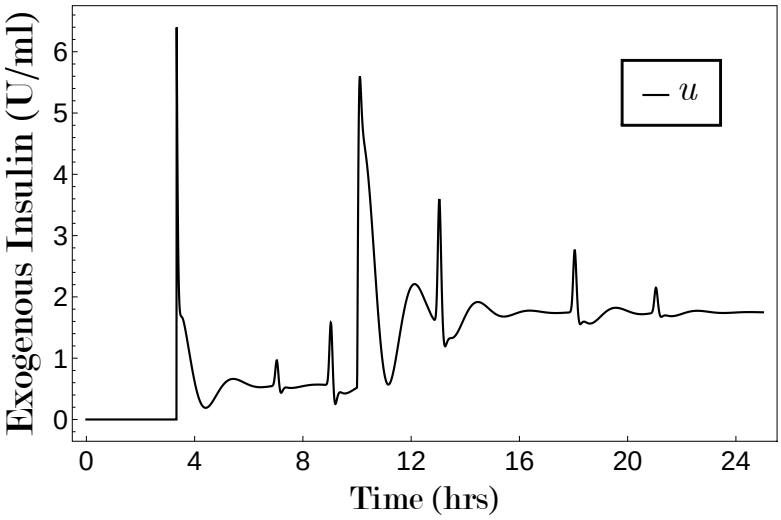


Figure 4.15: Control signal u that represents the continuous exogenous insulin needed to regulate the glucose at different reference levels r.

4.4.4 Adaptive identification and optimal control for discontinuous insulin pumps and variable references

In Figure 4.16 is shown the simulation results obtained in the application of the PWM in the continuous control signal u for different reference levels r. The first established reference level is $r = 150$ mg/dl, and once the reference level is achieved, the optimal control maintains the blood glucose value in that reference using the control signal u_{PWM}, even the patient is fed and rejecting the possible disturbances that could alter the glucose level in the patient. As in the previous case (PWM control for constant reference), the regulated glucose signal G shows oscillations around the reference signals r. The control signal u_{PWM} maintains the oscillations into a threshold of ± 10 mg/dl.

Figure 4.17 shows the control signal u_{PWM} for variable reference levels r, representing the exogenous discontinuous insulin doses needed to regulate de glucose level into

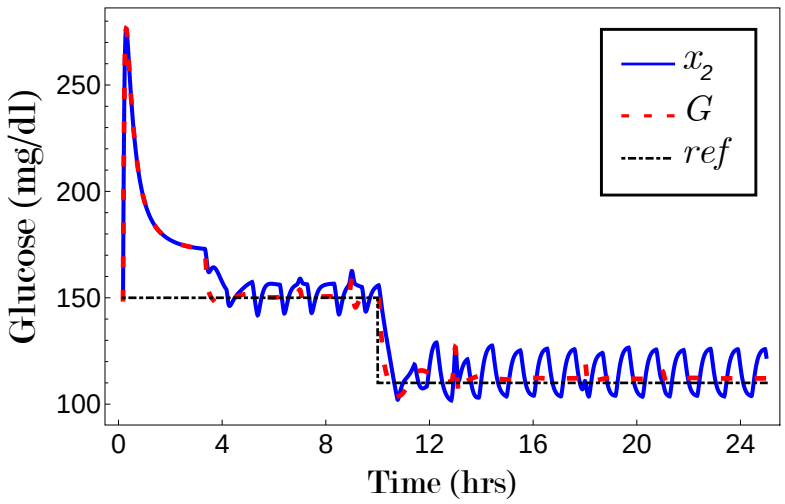


Figure 4.16: Glucose regulation at different reference levels using the control signal u_{PWM}.

the required reference $r = 110$ mg/dl and $r = 150$ mg/dl.

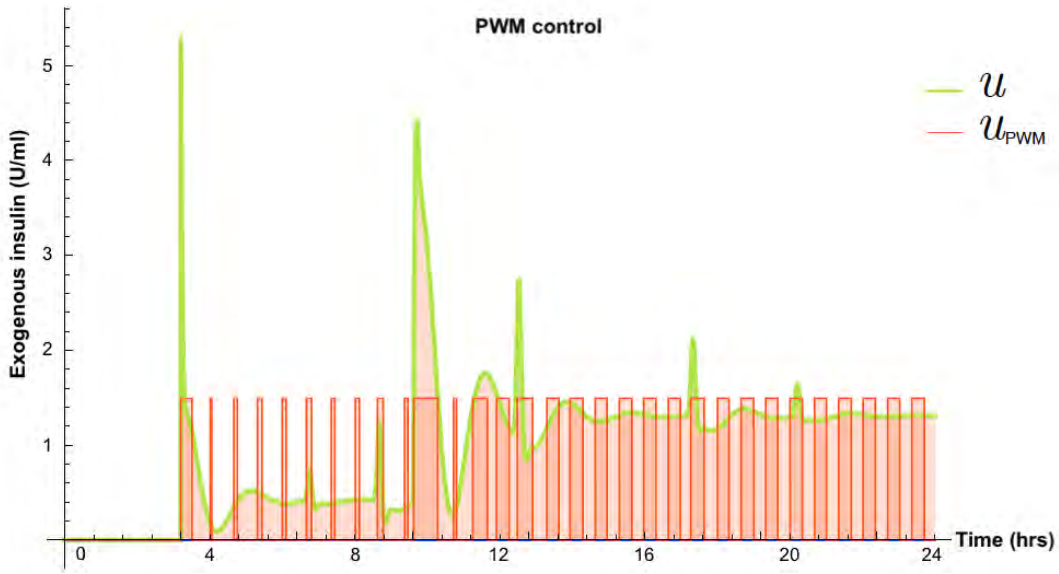


Figure 4.17: Control signal u_{PWM} to achieve different regulation levels $r = 150$ and 110 mg/dl.

The discontinuous control signal shows multiple insulin infusions at different times determined by the switching frequency and the pulse width is determined by the value of the control signal u in the moment when the PWM is in a high state. Both signals are compared showing how the control signal u_{PWM} changes its pulse width depending if the continuous

control signal behaviour u exceeds or doesn't exceed the established PWM amplitude. At the moment when the patient is fed, the rate of insulin infusion increase, allowing to reject the disturbances. Considering the application of rapid-acting insulin, which has a initial acting time at 5 minutes after being injected, insulin pump cartridges can be used for continuous and discontinuous pumps. Each cartridge contains 1.5 ml of insulin equivalent to 150 units of insulin with an average use of 28 days [FMD].

4.5 Adaptive identifier and optimal nonlinear control validation: application to the T1DMS software

4.5.1 T1DMS software

The T1DMS [Gro] is a computer model of the human metabolic system based on the glucose-insulin dynamics in human subjects, which is described in [MRC07, DMCC06]. The T1DMS technology provides realistic computer simulation of clinical trials using an in silico population of 300 subjects with parameters derived from triple tracer metabolic studies that reflect the human metabolism found with type 1 diabetes mellitus. It has been validated against actual clinical data and is accepted by the FDA as a substitute for pre-clinical trials in the testing of certain control strategies for T1DM. In Figure 4.18 is shown the software platform in MATLAB® based on files and structures to describe simulation scenarios, hardware (insulin-pumps and glucose sensors), the control algorithm, and the parameters of the human metabolic models.

4.5.2 Adaptive identifier

The Cobelli system [MRDM$^+$09] used to model the glucose dynamics in type 1 diabetic patients is considered to be an uncertain and a disturbed nonlinear one. In the previous section the Cobelli model was approximated by an adaptive identifier, therefore, the proposed identifier will be applied, in this section, to the T1DMS software. The Cobelli system structure and dynamics were only used to proposed the adaptive identifier model in the previous section, which is capable to approximate the dynamics of the Cobelli system.

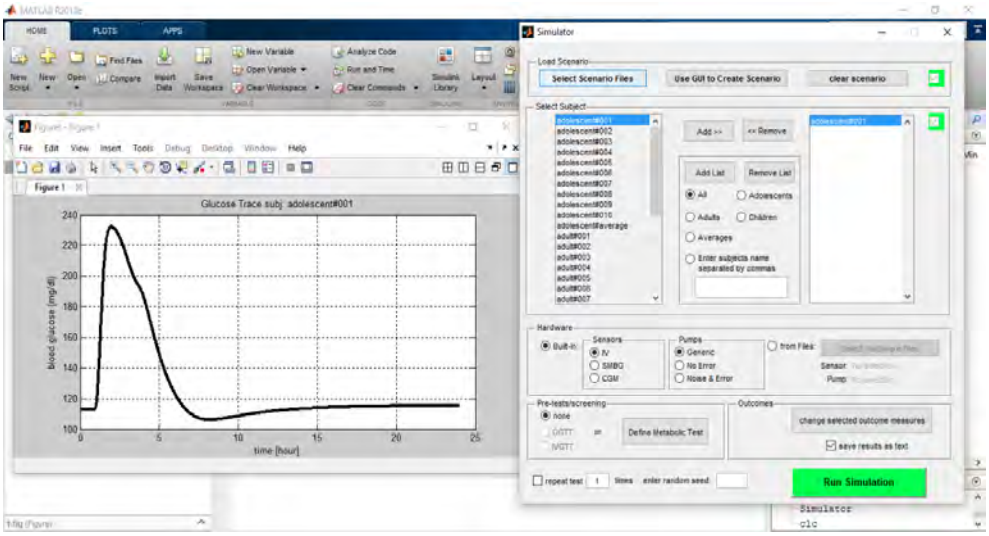


Figure 4.18: T1DMS software.

The adaptive identifier model is presented through (4.4), where the identification error, which is used to adapt its parameters θ, is given by $\varepsilon = x_1 - G$ and G is the signal glucose delivered by the T1DMS software.

4.5.3 Optimal control applied to the adaptive identifier

Exploiting the characteristics of the proposed SDCF adaptive identifier (4.4), a state-feedback robust optimal tracking controller (3.29)–(3.31), based on SDCF, is synthesized with the aim to validate and determine the needed insulin to regulate the glucose level in the T1DMS software. The performance effectiveness of the adaptive identifier model and the control scheme which are applied to T1DMS software is shown via simulation. For the identification process, the parameters Ψ and g, are selected with the aim that allow an adequate on-line adaptation of the parameters θ in (4.4), and are presented in Table 4.6. In this case the optimal control algorithm is programmed in the T1DMS testing platform as is shown in Figure 4.19. In Figure 4.20 is shown the proposed optimal nonlinear controller, which is programmed in the orange block (control law Simulink block).

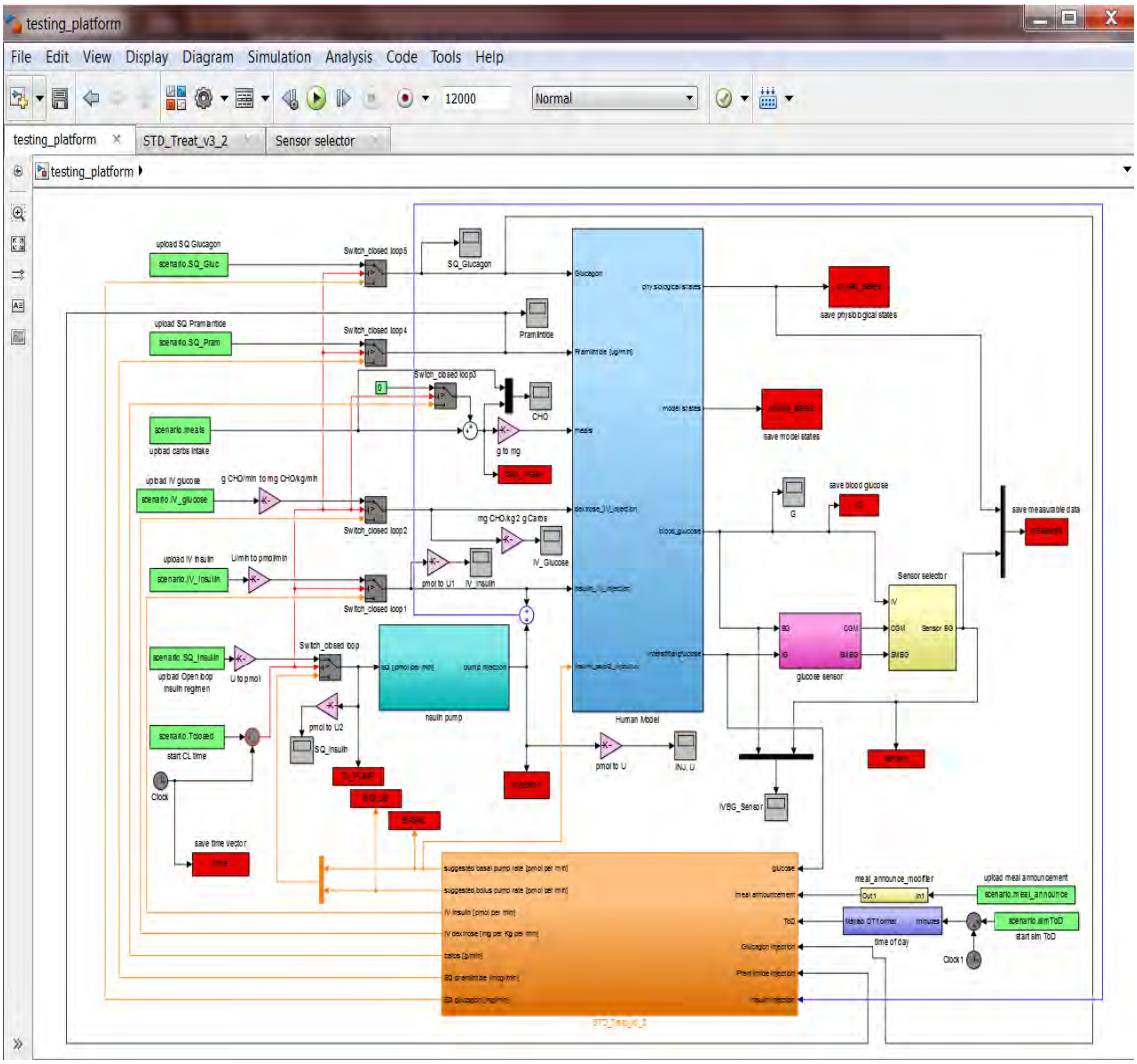


Figure 4.19: T1DMS testing platform.

4.5.4 Validation results

Based in the software T1DMS, the identification and control of the glucose-insulin dynamical behavior for an adolescent with type 1 diabetic disease is carried out into two scenarios: **Scenario 3** shows a 50 grams of carbohydrates which are administrated at the time 2, 8 and 16 hours in a simulation of 24 hours. The following figure shows the results where the adaptive identification process and the optimal control scheme are applied to regulate the glucose level.

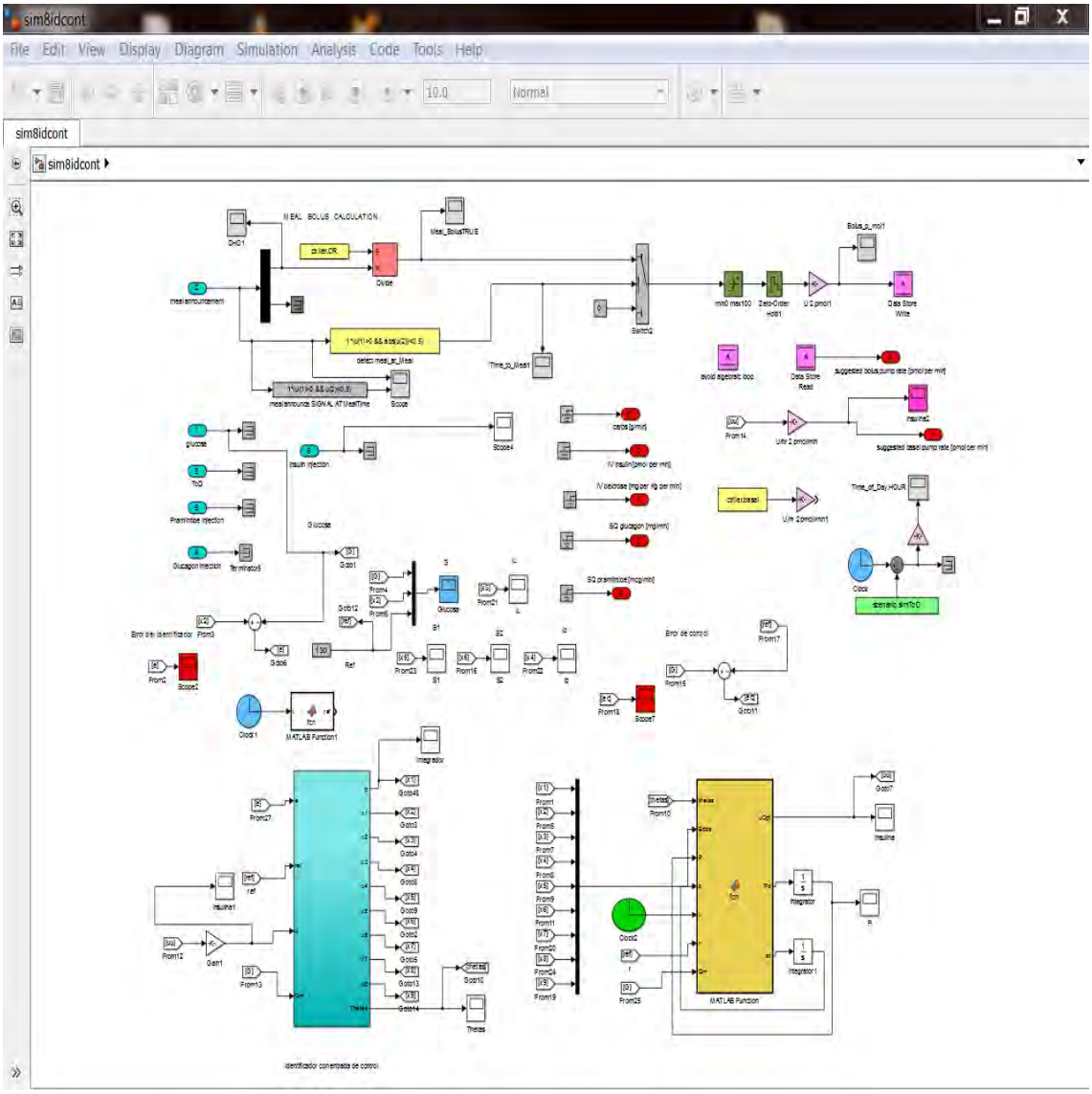


Figure 4.20: Optimal nonlinear control programmed in the T1DMS testing platform.

In Figure 4.21 is shown the glucose regulation into a reference level $r = 120$ mg/dl. **Scenario 4** shows a 50, 30, and 30 grams of carbohydrates which are administrated at the time 2, 7 and 18 hours, respectively. The simulation is focused in an adult type 1 diabetic patient with a 24 hours duration. In this scenario, the glucose regulation is carried out for a variable reference $r = 140$ mg/dl for $t < 12$ hours and $r = 120$ mg/dl for $t \geq 12$ hours.

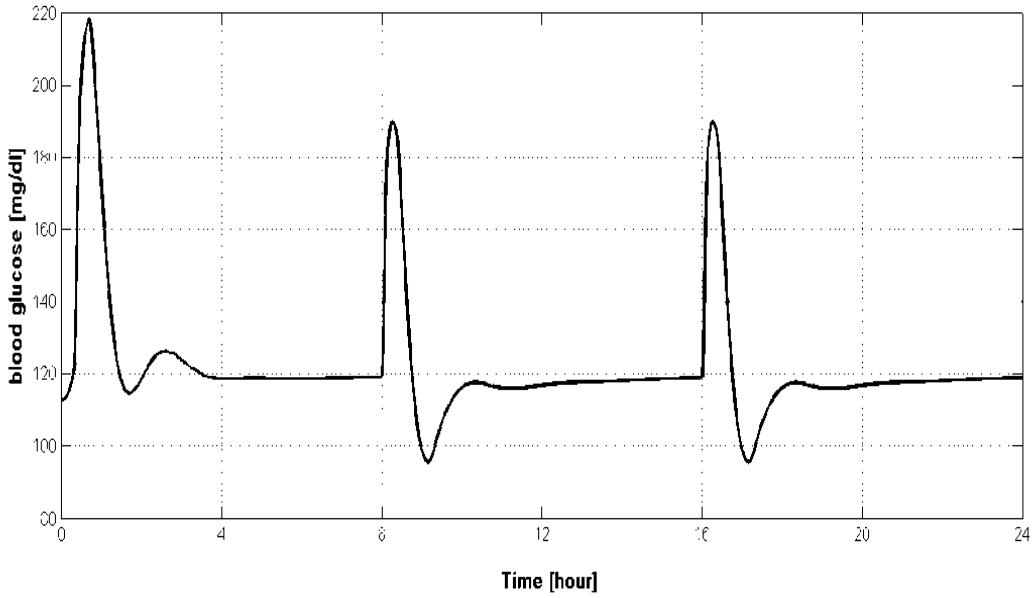


Figure 4.21: Glucose regulation into a reference level $r = 120$ mg/dl applying the adaptive identifier and the optimal nonlinear control in the T1DMS.

The simulation result is shown in Figure 4.22.

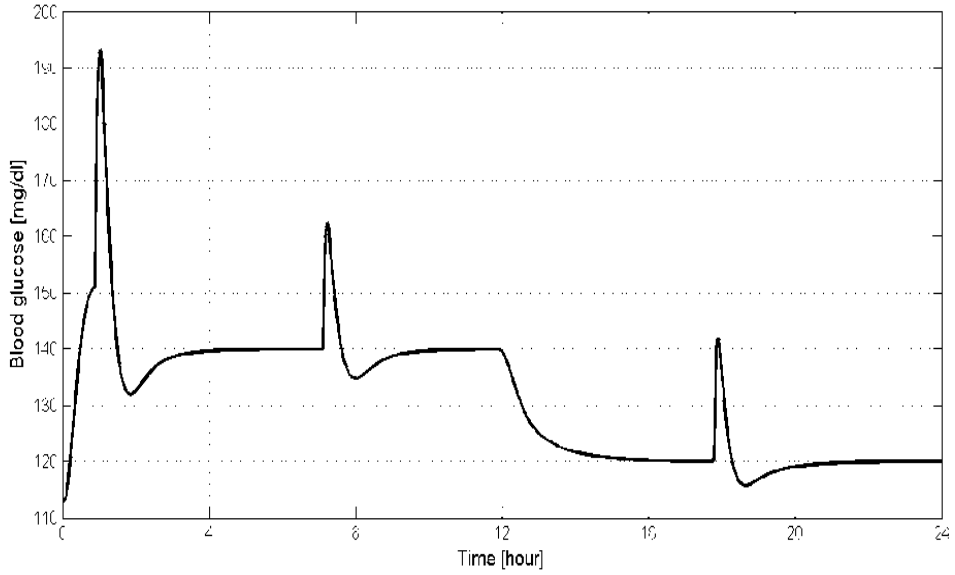


Figure 4.22: Glucose regulation into a variable reference for an adult type 1 diabetic patient.

The simulation results show an adequate regulation for constant and variable references. The adaptive identifier and the optimal tracking nonlinear control scheme are capable to deal with the different disturbances (factors as eating and healthy habits, age, weight, etc.), which affect the type 1 diabetic patients.

In the reviewed literature exist different works focused on the type 1 diabetes control, some of them are evaluated using the T1DMS software e.g., in [KBDMC09] and [mag]. In a general conclusion, the MPC (proposed in the reviewed works) produces a better regulation than PID, limiting glucose oscillation significantly with the disadvantage that the best implementations is reached for individual tuning. Those works present an adequate regulation compared with the behavior of a healthy person, however, an adequate behaviour identification is not achieved just as there is no tracking of trajectories. In comparison with the results presented in this work, the adaptive identification and the optimal tracking nonlinear control of the glucose-insulin system is achieved regardless the different disturbances that affect the glucose dynamics in a type 1 diabetic patient (factors as eating and healthy habits, age, weight, among others).

4.6 Adaptive reduced-order identifier and optimal nonlinear control validation: application to the T1DMS software

4.6.1 Adaptive reduced-order identifier

The Cobelli system [MRDM$^+$09] used to model the glucose dynamics in type 1 diabetic patients is considered to be an uncertain and a disturbed nonlinear one with order n and can be approximated by a reduced-order adaptive identifier. The glucose-insulin dynamics in type 1 diabetic patients depend on various factors as eating and healthy habits, age, weight, etc.; therefore, it is convenient to deal with those uncertainties and disturbances by applying an adequate adaptive identification and optimal control scheme. Therefore, in this Section, the Cobelli system structure and dynamics are only used to proposed a reduced-order identifier model, which is capable to approximate the essential dynamics of the Cobelli system used to model the glucose-insulin dynamics in type 1 diabetic patients.

The adaptive reduced-order identification proposed to model the glucose-insulin dynamics in the Cobelli system is proposed as follows

$$\begin{aligned}
\dot{x}_1 &= \theta_1 + \theta_2 x_1 x_3 + \theta_3 x_3 \\
\dot{x}_2 &= \theta_4 x_2 + \theta_5 x_3 \\
\dot{x}_3 &= \theta_6 x_2 + \theta_7 x_3 + \theta_8 x_4 + \theta_9 x_5 \\
\dot{x}_4 &= \theta_{10} x_4 + u \\
\dot{x}_5 &= \theta_{11} x_4 + \theta_{12} x_5
\end{aligned} \tag{4.5}$$

where $\theta = [\theta_1 \dots \theta_{12}]^T$ are the parameters to be adapted on-line by the RLSA (2.15), $x = [x_1 \dots x_5]^T$ is the state vector which identifies the glucose-insulin variables $\mathcal{X} = [G\ I_l\ I_p\ S_1\ S_2]^T$ in the Cobelli system. The identification error which is used to adapt the parameters θ in (4.5) is given by $\varepsilon = x_1 - G$.

4.6.2 Optimal control applied to the adaptive reduced-order identifier

Exploiting the characteristics of the proposed SDCF adaptive reduced-order identifier (4.5), a state-feedback robust optimal tracking controller (3.29)–(3.31), based on SDCF, is synthesized with the aim to determine the insulin for regulating the glucose level in the identifier (4.5) and hence the glucose level in the T1DMS software. The process of the identification and control methodology is shown in Figure 4.23.

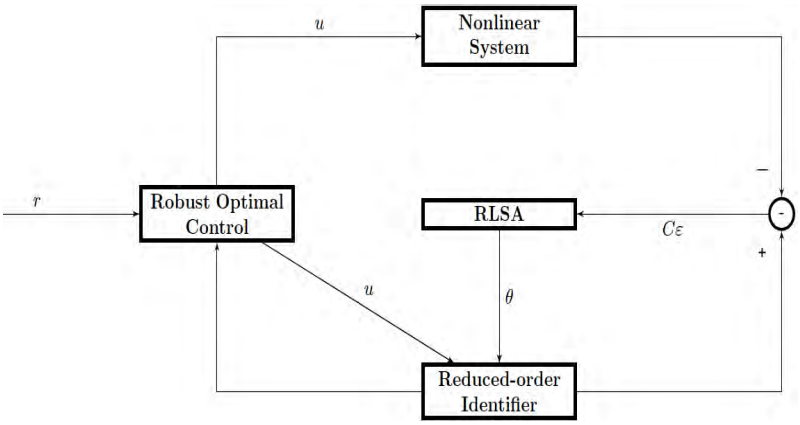


Figure 4.23: Reduced-order identification and optimal control scheme.

The performance effectiveness of the reduced-order identifier model and the control scheme which are applied to T1DMS software is shown via simulation. The validation results are presented in Appendix B.

4.7 Summary

This chapter has presented the application of the adaptive identification and the robust optimal tracking control scheme for disturbed and uncertain nonlinear systems. First, the adaptive identification is applied to the Cobelli system used to model the glucose-insulin dynamics in a healthy person. Secondly, to introduce the robust optimal tracking control scheme, an adaptive identifier is proposed to model the Cobelli system which is adapted to represent the dynamics in type 1 diabetic patients. The proposed adaptive identifier is presented in a SDCF with the aim to synthesis a nonlinear optimal controller to regulate the glucose in type 1 diabetes patients. With the purpose of proposing a versatile control scheme, continuous and discontinuous control signals are developed with the aim to be used in the different types of insulin pumps that currently exist in the market. The robustness of the control scheme presented robustness against the disturbances proposed in the different scenarios for two different virtual patients, achieving an adequate regulation regardless of whether the regulation is required in constant or variable reference levels. Thirdly, to demonstrate the effectiveness of the adaptive identification scheme, a reduced-order identifier is proposed, which uses the RLSA to adapt on-line its parameters based on the assumption that only the blood glucose concentration G is available to be measured, which is obtained from T1DMS simulator. The adaptive reduced-order identifier model is used for control purposes in type 1 diabetic treatments which are based on different scenarios and virtual patients. Some advantages that presents the proposed adaptive reduced-order identification are: *a)* lower dimension, *b)* some of the variables that are presented in the Cobelli model are considered as disturbances allowing an order reduction in the proposed identifier system, *c)* fewer parameters to be determined. All these characteristics make the adaptive reduced-order identifier computationally more efficient.

Chapter 5

Final remarks and future research work

5.1 General conclusions

System identification is about building mathematical models of dynamical nonlinear systems based on observed input-output data. The difficulty with nonlinear systems is that a unified model structure is generally not possible. This means that besides requiring a priori information about the order of the system, a priori knowledge about the model structure is also required. There may be special classes of nonlinear models where the model structure is linear in the unknown parameters. In this case, the identification may be done using linear parameter estimation methods even though the model is nonlinear in the system variables.

This thesis proposed adaptive identifiers (for the BeMM and the Cobelli model) to approximate the dynamical behavior of unknown nonlinear systems. The proposed adaptive identifiers are presented in the SDCF form, and whose structure is linear in the unknown parameters θ. The adaptive identifiers uses a RLSA for the on-line adaptation of its parameters such that the identification error is minimized. The following benefits of the proposed identification scheme can be mentioned: *a)* the identifier serves to on-line approximate uncertain and disturbed nonlinear system, using a RLSA to adapt the identifier parame-

ters, and *b)* the effectiveness of the proposed adaptive identification methodology have been successfully validated via computer simulations. This thesis also presents a reduced-order adaptive identification scheme used to approximate the essential dynamical behaviours of uncertain and disturbed nonlinear systems. The proposed reduced-order identifier algorithm minimizes the identification error between the real nonlinear system dynamics and the proposed reduced-order identifier model, using the developed RLSA in the adaptation process.

An optimal nonlinear control scheme is developed for SDCF nonlinear systems. In this thesis the optimal control is developed with the aim to reject disturbances that affect the system and track the desired references, minimizing a meaningful cost functional. As a theoretical contribution, formal convergence proofs are presented for both schemes, the adaptive identification and the optimal tracking nonlinear control.

The principal application of the adaptive identifier and the optimal nonlinear control is focused on the type 1 diabetes treatment. The adaptive identifiers are proposed for two different mathematical models (BeMM and Cobelli models), which represent the blood-glucose dynamics in type 1 diabetic patients. The simulation results, for both models, show an adequate identification of the principal glucose-insulin dynamics. The importance to use de Cobelli model is that the T1DMS software is based in this model and is used to validate different control techniques focused on the type 1 diabetes treatment. All the adaptive identifier models are used for control purposes in type 1 diabetic treatments, under the assumption that only the blood glucose measurement is considered to be available for adapting the parameters in the adaptive identification process., i.e., the type 1 diabetic patients only have access to measure the blood glucose concentration as an indicator to be used in the control process. A reduced-order adaptive identification scheme is presented with the aim to demonstrate the versatility and efficacy of the proposed adaptive identification scheme. The reduced-order identifier presents lower dimension and different structure compared with the Cobelli system, where some variables are considered as disturbances allowing the reduction in the proposed identifier model, resulting in fewer parameters to be determined. All these characteristics make the reduced-order identifier computationally more efficient.

Once the adaptive identifiers are developed, the optimal nonlinear control scheme is applied in different virtual patients under 6 different scenarios. By adding an integrator term to the proposed optimal control law, we can deal with possible disturbances affecting the identifier (factors as eating and healthy habits, age, weight, etc.), resulting in a robust optimal tracking control scheme. To validate the efficacy of the control scheme, the simulation results show that the regulation of the plasma glucose concentration can be achieved for different established reference levels. Also the control signal is converted from a continuous dosage to a discontinuous dosage applying a PWM intersective method. This is an important contribution because the optimal control algorithm can be used for continuous and discontinuous insulin pumps.

With the proposed identifier and control schemes it is possible to obtain an appropriate identifier model to use for control purposes and deal with disturbances and uncertainties that affect the system which in this case are uncertain type 1 diabetic virtual patients. The proposed adaptive identification and robust optimal tracking control schemes are developed with the aim to be applied in the type 1 diabetes treatment. The adaptive identification and the optimal nonlinear control schemes are validated using the T1DMS software, which is approved by the FDA. As a conclusion both schemes showed an adequate behavior and promising results.

5.2 Future work

Work is progressing in the implementation of the proposed methodology in real diabetic patients under the assumption that the proposed identifier and control schemes could improve the style life in type 1 diabetic patients allowing them to live as a normal person. Departing from the adaptive identification and the optimal nonlinear control scheme proposed in this work, new proposals for future research work are proposed below:

1. Implementation

- Include a continuous glucose meter (invasive or non invasive) to obtain real glucose

measurements and use them in the adaptive identification and optimal nonlinear control process.

- Use a Field Programmable Gate Array (FPGA) to program the optimal nonlinear control law.
- Include continuous and discontinuous insulin pumps to verify if the control signals generated by the optimal control scheme are the needed by the insulin pumps to deliver the adequate insulin dose in the glucose regulation process.
- Develop a prototype which includes all the previous elements (continuous glucose meter, the control law programmed in a FPGA and an insulin pump) to close the control loop and be used in a type 1 diabetic person.

2. Trials

- Determine the adequate protocols to use the prototype in type 1 diabetic patients.
- Work with some health sectors in the application the protocols and the validation of the prototype.

Appendix A

Cobelli glucose-insulin system

The T1DMS software emulated meal challenges and included a population of 300 in silico subjects (100 adults, 100 adolescents, 100 children). Each virtual subject was represented by a model parameter vector, which was randomly extracted from an appropriate joint parameter distribution. The T1DMS has been successfully used by 32 research groups in academia, as well as by companies active in the field of T1DM; simulation results were presented by 63 publications in peer-reviewed journals. The UVA/PADOVA T1DMS was accepted to FDA in 2013 and is used to test and validate control strategies developed for the type 1 diabetes treatment. This important simulator is based on the Cobelli model and due to this model is used in the adaptive identifier process proposed in this thesis.

The dynamical behavior for each subsystem in the Cobelli model, which represents the glucose-insulin dynamics in the human body is summarized as follows.

Glucose Subsystem

Three differential equations are used to describe the glucose dynamics as

$$\dot{G}_p = EGP + Ra - U_{ii} - E - k_1 G_p + k_2 G_t \tag{A.1}$$

$$\dot{G}_t = -U_{id} + k_1 G_p - k_2 G_t \tag{A.2}$$

$$\dot{G} = \frac{\dot{G}_p}{V_G} \tag{A.3}$$

where G is the plasma glucose concentration, G_p and G_t are glucose masses in plasma and rapidly equilibrating tissues, and in slowly equilibrating tissues, respectively, EGP is

the endogenous glucose production, Ra is the glucose rate of appearance in plasma, E is renal excretion, U_{ii} and U_{id} are assumed constant and describe the insulin-independent and insulin-dependent glucose utilizations, respectively. V_G is the distribution volume of glucose, and k_1 and k_2 are constant parameters.

Insulin Subsystem

Three differential equations are used to describe the insulin subsystem, where the insulin flows S, coming from the subcutaneous compartments, enters the bloodstream and is degradated in the liver and in the periphery. The subsystem is described as

$$\dot{I}_l = -(m_1 + m_3)I_l + m_2 I_p + S \tag{A.4}$$

$$\dot{I}_p = -(m_2 + m_4)I_p + m_1 I_l \tag{A.5}$$

$$\dot{I} = \frac{\dot{I}_p}{V_I} \tag{A.6}$$

where I is the plasma insulin concentration, I_p and I_l are insulin masses in plasma and in liver, respectively. Term S denotes the insulin secretion, V_I is the distribution volume of insulin and m_1, m_2, m_3 and m_4 are model parameters.

Endogenous Glucose Production

The function description of EGP in terms of glucose and insulin signals comes from the liver, where glucose reserve exists (glycogen). EGP is inhibited by high levels of glucose and insulin as

$$EGP = k_{p1} - k_{p2}G_p - k_{p3}I_d - k_{p4}I_{po}$$

where I_{po} is the amount of insulin in the portal vein and I_d is a delayed insulin signal, represented as

$$\dot{I}_1 = -k_i(I_1 - I) \tag{A.7}$$

$$\dot{I}_d = -k_i(I_d - I_1) \tag{A.8}$$

for which k_{p1} is the extrapolated EGP at zero glucose and insulin, k_{p2} is the liver glucose effectiveness, k_{p3} is the parameter governing amplitude of insulin action on the liver, k_{p4}

is the parameter governing amplitude of portal insulin action on the liver and k_i is the rate parameter accounting for delay between insulin signal and insulin action. EGP is also constrained to be non-negative.

Glucose Intestinal Absorption

A three-compartment model describes the glucose transit through the stomach and intestine by assuming the stomach is represented by two compartments (one for solid and one for triturated phase), while a single compartment is used to describe the gut. The subsystem is described by

$$\begin{aligned} \dot{Q}_{sto1} &= -k_{gri}Q_{sto1} + d && \text{(A.9)} \\ \dot{Q}_{sto2} &= -k_{empt}Q_{sto2} + k_{gri}Q_{sto1} && \text{(A.10)} \\ \dot{Q}_{gut} &= -k_{abs}Q_{gut} + k_{empt}Q_{sto2} && \text{(A.11)} \\ Q_{sto} &= Q_{sto1} + Q_{sto2} \\ Ra &= \frac{f k_{abs} Q_{gut}}{BW} \end{aligned}$$

where Q_{sto} is the amount of glucose in the stomach (solid, Q_{sto1} and liquid phase Q_{sto2}), Q_{gut} is the glucose mass in the intestine, k_{gri} is the rate of grinding and k_{abs} is the rate constant of intestinal absorption, f is the fraction of intestinal absorption which actually appears in plasma, BW is the body weight, and Ra is the appearance rate of glucose in plasma. Term d is the amount of ingested glucose that represents the disturbance caused by the meal intake [HCC$^+$04a], which is given as

$$d = \frac{d_G\, A_G\, t\, e^{-t/T_{maxI}}}{V_G\, T_{maxG}^2}$$

where d_G is the amount of carbohydrates intake, A_G is the carbohydrate bioavailability, T_{maxI} is the time-to-maximum insulin absorption, T_{maxG} is the time-of-maximum appearance rate of glucose in the accessible glucose compartment and V_G is the glucose distribution space. k_{empt} is the rate constant of gastric emptying, which is a nonlinear function of Q_{sto} described as

$$k_{empt} = k_{max} + \frac{k_{max} - k_{min}}{2}\{\tanh[\alpha(Q_{sto} - bd)] - \tanh[\beta(Q_{sto} - nd)]\}$$

where

$$\alpha = \frac{5}{2d(1-b)}, \qquad \beta = \frac{5}{2dn}$$

with b, n, k_{max} and k_{min} as model parameters.

Glucose Utilization (U)

Glucose utilization is made up of two components: *1)* the insulin-independent utilization U_{ii}, which takes place in the first compartment and represents the glucose uptake by the brain and erythrocytes, and *2)* the insulin-dependent component utilization U_{id}, which takes place in the remote compartment and depends nonlinearly from glucose in the tissues. The total glucose utilization U is thus

$$U = U_{ii} + U_{id}$$

where U_{ii} is assumed constant as

$$U_{ii} = F_{cns}$$

while U_{id} is represented by

$$U_{id} = \frac{V_m G_t}{k_m + Gt}$$

where V_m and K_m are assumed to be linearly dependent from a remote insulin X as

$$\begin{aligned} V_m &= V_{m0} + V_{mx} X \\ K_m &= k_{m0} + k_{mx} X \end{aligned}$$

which depends from insulinemia in the following way:

$$\dot{X} = -p_{2u} X + p_{2u}(I - I_b) \tag{A.12}$$

where V_{m0}, V_{mx}, k_{m0} and k_{mx} are model parameters, I is plasma insulin, and p_{2u} is the rate constant of insulin action on the peripheral glucose utilization.

Insulin Secretion (S)

The model used to describe pancreatic insulin secretion is the proposed in [TBC$^+$01, BCT$^+$01], given as

$$\begin{aligned}
\dot{I}_{po} &= -\gamma I_{po} + S_{po} && \text{(A.13)}\\
\dot{Y} &= \begin{cases} -\alpha[Y - \beta(G-h)] & \text{if } \beta(G-h) \geq -S_b \\ -\alpha Y - \alpha S_b & \text{if } \beta(G-h) < -S_b \end{cases} && \text{(A.14)}\\
S_{po} &= \begin{cases} Y + K\dot{G} + S_b & \text{for } \dot{G} > 0 \\ Y + S_b & \text{for } \dot{G} \leq 0 \end{cases} \\
S &= \gamma I_{po}
\end{aligned}$$

where term S_{po} is the insulin secretion in the portal vein, S_b is the basal insulin secretion, γ is the transfer rate constant between portal vein and liver, K is the pancreatic responsivity to the glucose rate of change, α is the delay between glucose signal and insulin secretion, β is the pancreatic responsivity to glucose, h is the threshold level of glucose above, which the β-cells initiate to produce new insulin, and Y is the difference between the basal insulin secretion and the threshold glucose level.

Glucose Renal Excretion (E)

Glucose excretion by the kidney occurs when plasma glucose exceeds a certain threshold, which can be modeled by a linear relationship with plasma glucose as

$$E = \begin{cases} k_{e1}(G_p - k_{e2}) & \text{if } G_p > k_{e2} \\ 0 & \text{if } G \leq k_{e2} \end{cases}$$

where k_{e1} is the glomerular filtration rate and k_{e2} is the renal threshold of glucose. The complete glucose-insulin model is given by system (A.1)–(A.14).

Appendix B

Adaptive reduced-order and optimal nonlinear control validation results

For the identification process, the parameters Ψ and g, are selected with the aim that allow an adequate on-line adaptation of the parameters θ in (4.5), as shown in Table B.1.

Table B.1: Parameters used in the identification process applied to T1DMS software.

$\Psi_1 = diag\{5000, 5000, 5000\}$	$g_1 = 4.5 \times 10^5$
$\Psi_2 = diag\{5, 5\}$	$g_2 = 1 \times 10^3$
$\Psi_3 = diag\{0.5, 0.5, 0.5, 0.5\}$	$g_3 = 50 \times 10^3$
$\Psi_4 = diag\{50\}$	$g_4 = 1 \times 10^4$
$\Psi_5 = diag\{5, 5\}$	$g_5 = 1 \times 10^4$

Based in the software T1DMS, the identification and control of the glucose-insulin dynamical behavior for an adult with type 1 diabetic disease is carried out into two scenarios:

Scenario 5 shows a 50 grams of carbohydrates which are administrated during the first 2 hours of the simulation. The following figures show the results where the adaptive identification process and the optimal control scheme are applied to regulate the glucose level. In Figure B.1 is shown the convergence between the glucose concentration (dashed

line) obtained from the T1DMS simulator, and its corresponding identification variable (solid line). The Figure shows a zoom where it is appreciated the identifier and control convergence. Figure B.2 depicts the control signal u which represents the exogenous insulin needed to regulate de glucose level to the required reference $r = 130$ mg/dl.

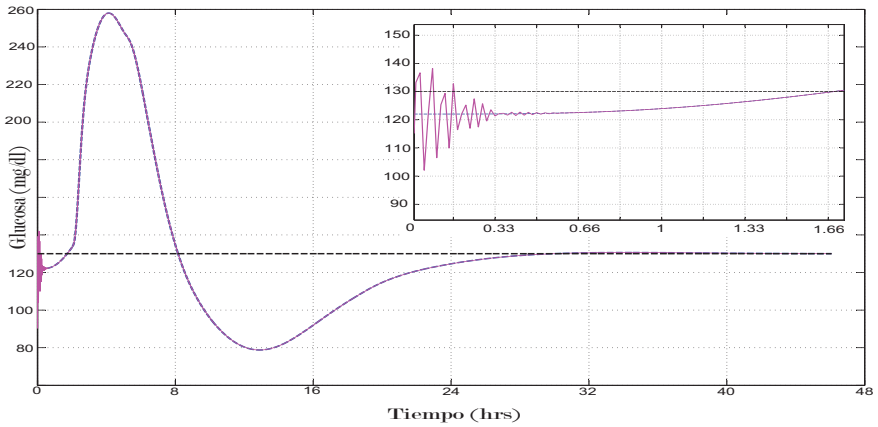


Figure B.1: Adaptive identification and control scheme applied to a virtual patient under the third scenario using the T1DMS simulator.

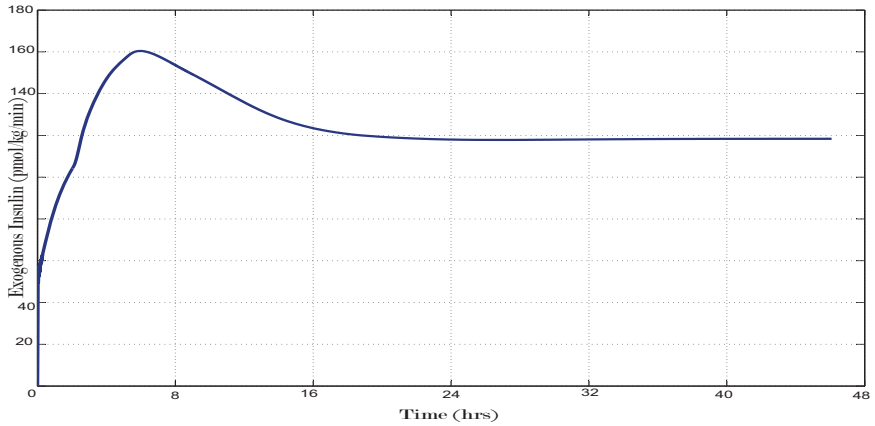


Figure B.2: Control signal u applied to the T1DMS simulator to regulate the glucose level in type 1 diabetic patients under the third scenario.

Scenario 6 shows a 50 grams of carbohydrates which are administrated during the first 2 hours of the simulation, then, 30 grams of carbohydrates are administrated at 48 hours of the simulation. Based on the glucose signal, which is acquired from the T1DMS,

the identification process and the control of the level glucose is performed. The convergence is appreciated in the zoom of the Figure B.3. In Figure B.3 shows the convergence between the glucose concentration (dashed line) obtained from the T1DMS simulator, and its corresponding identification variable (solid line), which is regulated to $r = 130$ mg/dl. Figure B.4 depicts the control signal u which represents the exogenous insulin needed to regulate de glucose level to the required reference.

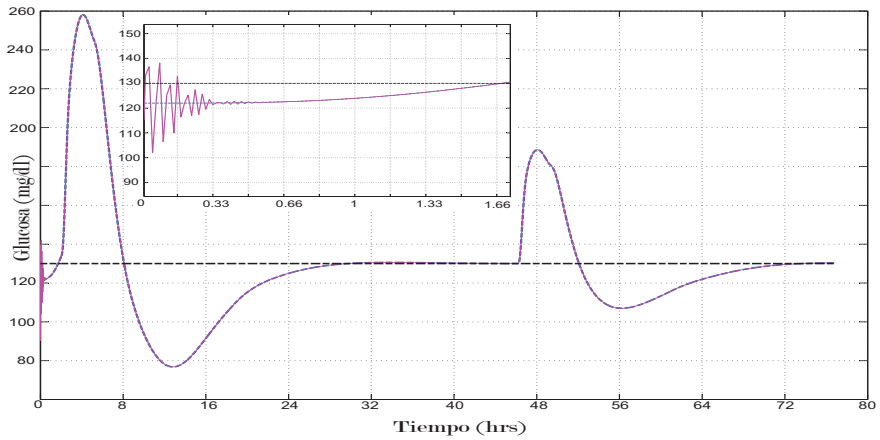


Figure B.3: Adaptive identification and control scheme applied to a virtual patient under the fourth scenario using the T1DMS simulator.

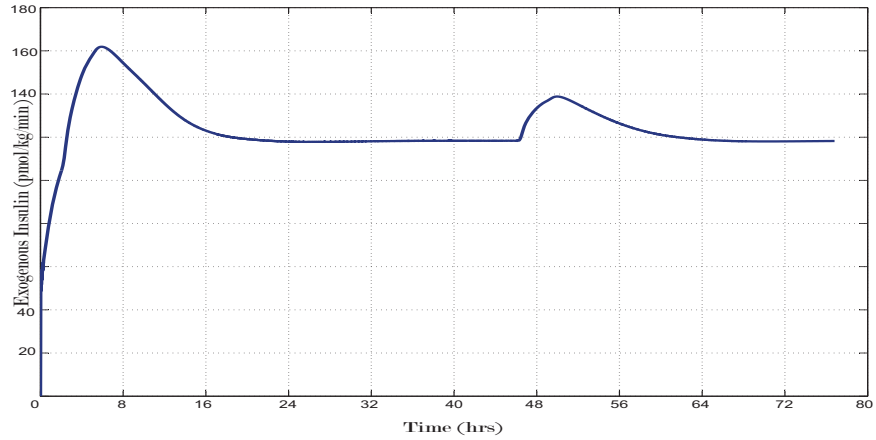


Figure B.4: Control signal u applied to the T1DMS simulator to regulate the glucose level in type 1 diabetic patients under the fourth scenario.

The results show the effectiveness performance of the proposed adaptive identification and optimal tracking control scheme. For both scenarios, the identifier converged, and the regulation were achieved applying the control scheme, i.e, the identifier and control methodologies are robust against the disturbances that could be present in the subject (healthy habits, age, weight, etc.). In this particular case the regulation was achieved to $r = 130$ mg/dl for an adult person.

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