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FRACTIONAL-ORDER MODEL REFERENCE ADAPTIVE CONTROL WITH APPLICATION TO ANESTHESIA

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P R E S E N T A :

NAVARRO GUERRERO GERARDO

TUTOR PRINCIPAL:

DR. YU TANG XU, FACULTAD DE INGENIERÍA

COMITÉ TUTOR:

DR. GERARDO RENÉ ESPINOSA PÉREZ, FACULTAD DE INGENIERÍA

DR. JAIME ALBERTO MORENO PÉREZ, INSTITUTO DE INGENIERÍA

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JURADO ASIGNADO:

Presidente:	DR. JAIME ALBERTO MORENO PÉREZ
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1 $^{er.}$ Suplente:	DR. ARTEAGA PÉREZ MARCO ANTONIO
2 $^{do.}$ Suplente:	DR. MARCOS ANGEL GONZALEZ OLVERA

Lugar o lugares donde se realizó la tesis:

CIUDAD UNIVERSITARIA, UNAM

TUTOR DE TESIS

DR. YU TANG XU

FIRMA

RESUMEN

El Cálculo fraccional ha ganado una atención significativa en la ciencia y la ingeniería y es un campo emergente en la ingeniería de control. Esta rama de las matemáticas estudia las derivadas e integrales de orden arbitrario y se ha demostrado que el uso de operadores de orden fraccional en sistemas dinámicos y diseño de controladores podría mejorar el modelado y la flexibilidad y robustez de los controladores. El diseño de controladores basados en modelos de orden fraccional han ganado un rápido desarrollo impulsado por el creciente número de investigaciones sobre la estabilidad de los sistemas de orden fraccional. Entre esto, la investigación de controladores adaptables ha sido un tema activo de investigación.

Este trabajo está dedicado al diseño de controladores adaptables, específicamente, el enfoque de control adaptable con modelo referencia. En primer lugar, mejoramos resultados previos sobre el esquema de control adaptatable con modelo de referencia de orden fraccional al proponer una extensión del Lema de Barbalat. Esta extensión nos permite realizar un análisis de estabilidad completo del esquema adaptable basado en el método directo de Lyapunov y concluir la convergencia del error a cero. Además, aplicamos este análisis para diseñar un esquema de control adaptable con modelo de referencia en lazo cerrado de orden fraccional y, como resultado complementario, extendimos dos esquemas de identificación para sistemas de orden fraccional basados en el análisis de Lyapunov.

Como caso de estudio, abordamos el problema de control de anestesia. Propusimos un modelo simple de orden fraccional para representar la respuesta entrada-salida del modelo PK/PD de un paciente. Este modelo propuesto supera muchas dificultades, por ejemplo, parámetros desconocidos, falta de medición de estado, variabilidad inter e intrapaciente y retardo variable, que se encuentra al diseñar controladores basados en el modelo PK/PD. En base a este modelo simple aplicamos los esquemas adaptables diseñados. Los resultados se ilustran a través de simulaciones usando 30 pacientes virtuales, que muestran que los esquemas de adaptables de orden fraccional diseñados son robustos contra la variabilidad inter e intrapaciente, el retraso de tiempo variable, las perturbaciones y el ruido. Por lo tanto, proponemos una solución novedosa y simple para el control de la anestesia utilizando un enfoque adaptable de orden fraccional.

ABSTRACT

Fractional Calculus has gained significant attention in science and engineering and is an emergent field in control engineering. This branch of mathematics studies the derivatives and integrals of arbitrary order and has been shown that the use of fractional-order operators in dynamical systems and control design could improve the modeling and the flexibility and robustness of the controllers. The controller designs based on fractional-order models have gained a rapid development impulsed by the growing number of research on the stability of fractional-order systems. Among this, the research of fractional-order adaptive controllers has been an active topic of research.

This work is devoted to the design of adaptive controllers, specifically, the model reference adaptive control approach. First, we improve previous results on the fractional-order model reference adaptive control scheme by proposing an extension of the Barbalat's Lemma. This extension allows us to realize a full stability analysis of the adaptive scheme based on the Lyapunov's direct method and concluding the convergence of the error to zero. Moreover, we apply this analysis to design a fractional-order closed-loop model reference adaptive control scheme, and as a complementary result, we extend two identification schemes for fractional-order systems based on Lyapunov's analysis.

As a study case, we deal with the problem of control of anesthesia. We proposed a simple fractional-order model to represent the input-output behaviour of the PK/PD model of a patient. This proposed model gets around many difficulties, for example, unknown parameters, lack of state measurement, inter and intra-patient variability, and variable time-delay, encountered in controller designs based on the PK/PD model. Based on this simple model we apply the adaptive schemes designed. The results are illustrated via simulations using 30 virtual patients, showing that the fractional-order adaptive schemes designed are robust against inter and intra-patient variability, variable time-delay, perturbations, and noise. Therefore, proposing a novel and straightforward solution for the control of anesthesia using a fractional-order adaptive approach.

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Contents

List of Figures

Chapter 1

Introduction

The introduction of fractional-order operators (integrals and derivatives of non-integer-order) in the identification and control fields has gained considerable attention during the last years. The nature of many complex systems can be more accurately modeled using fractional differential equations (Freed and Diethelm 2007, Tejado *et al.* 2014). In that sense, the systems to be controlled can now be described not only using integer-order differential equations but using fractional differential equations as well.

In recent years fractional calculus has been a growing field of research in science and engineering (Oldham and Spanier 2002, Podlubny 1999a, Ortigueira 2011). In fact, in many scientific areas are currently paying attention to fractional calculus concepts and we can see its application in viscoelasticity and damping, diffusion and wave propagation, electromagnetism, chaos and fractals, heat transfer, biology, electronics, signal processing, robotics, system identification, traffic systems, genetic algorithms, modelling and identification, telecommunications, chemistry, physics, control systems, economy and finance (Machado *et al.* 2010, Barbosa and Machado 2011, Bassingthwaighte *et al.* 1994, Magin 2006, West *et al.* 2003, Ionescu *et al.* 2013, Mainardi 2010, Hartley *et al.* 1995, Vinagre *et al.* 2003, Lo 1991).

Fractional calculus is the field of mathematical analysis which deals with the study and application of integrals and derivatives of arbitrary order. Since the second half of the twentieth century, many scientific studies have shown the importance of fractional derivatives and fractional differential equations as well as its applications in science and engineering (see *e.g.*, (Podlubny 1999a, Kilbas *et al.* 2006) and the references therein). And the related mathematical theory is relatively well established (Kilbas *et al.* 2006, Miller and

Ross 1993, Ortigueira 2011, Petráš 2011, Podlubny 1999a, Padula and Visioli 2015).

Taking fractional operators dynamics into account may be useful in modeling any system that possesses memory and/or hereditary properties (Podlubny 1999a). Given rise to fractional-order models (FOMs) that are a mathematical representation of physical systems using fractional differential equations. Moreover, since fractional calculus is a generalization of conventional calculus, it is expected that fractional models will provide a more accurate description of the dynamics of physical systems than those based on classical differential equations (Monje *et al.* 2010).

Control is an interdisciplinary branch of engineering and mathematics dealing with the design, identification, and analysis that deals with the modification of dynamic systems to obtain the desired behavior given in terms of a set of specifications or a reference model. To achieve the desired behavior, a designed controller measure the system variables and response, compares it to the desired behavior, computes corrective actions based on the specifications or the reference model, and produce the control action to obtain the desired changes.

To modify the dynamics of a system or a process, we need a model of the system, a tool for its analysis, ways to specify the required behavior, methods to design the controller, and techniques to implement them. The standard tools to model, and analyze dynamic systems and control algorithms are mainly based on integrals and derivatives. Therefore, one could think that extending the definition of integrals and derivatives to a non-integer order could lead to a more robust and flexibles controllers.

Fractional calculus has been found especially useful in system theory and automatic control, where fractional differential equations are used to obtain more accurate models of dynamic systems, develop new control strategies and enhance the characteristics of control loops.

The controller designs based on FOMs have gained rapid development impulsed by the growing number of research on the stability of fractional-order systems (Li *et al.* 2010, Diethelm 2010, Li and Zhang 2011, Aguila-Camacho *et al.* 2014, Padula and Visioli 2015).

The integer-order control schemes can be extended to their non-integer counterparts. For example, fractional sliding mode control with fractional-order sliding surface dynamics, model reference adaptive control using fractional-order adaptive laws. The opportunities for extensions of existing integer-order controls are almost endless.

Lyapunov's theory has been a cornerstone in the study of the stability of nonlinear systems and especially for adaptive systems. Since the publication of an extension of the Lyapunov´s method for fractional-order systems (Li *et al.* 2010), the study and design of fractional adaptive controllers has been grown (Duarte-Mermoud and Aguila-Camacho 2011, Aguila-Camacho and Duarte-Mermoud 2013, Duarte-Mermoud *et al.* 2015, Chen *et al.* 2016, Navarro-Guerrero and Tang 2017a).

Besides the Lyapunov's method, there is another approach used to analyze the stability of fractional-order adaptive systems. This approach uses a transformation of the error model of the adaptive system to a continuous frequency distributed model. With this transformation, the system becomes an integer-order model, and they use the well-known tools for analyzing the stability (Shi *et al.* 2014, Wei *et al.* 2014, Chen *et al.* 2016).

In the results presented in (Duarte-Mermoud *et al.* 2015, Aguila-Camacho and Duarte-Mermoud 2017, Fernandez-Anaya *et al.* 2017) the analysis presented proves stability in the Lyapunov sense for FOMRAC schemes. However, no conclusion about the convergence of the error has made from this analysis for the lack of a tool to prove the converse in the fractional order case. In the integer-order case, it is used the Barbalat's Lemma and his corollaries to conclude the convergence to zero. This Lemma is not applicable (or is very difficult like it is shown in (**?**)) in the fractional-order case because it required the knowledge that the integer-order integral of the quadratic error is bounded, which is unknown in the fractional-order case.

Recently it has been proposed a class of adaptive controller with a closed-loop model reference for integer-order systems (Gibson *et al.* 2015). The main characteristic of this class of adaptive controllers is the inclusion of a feedback gain in the reference model. Besides no state measurement is needed, this scheme also gives an improved transient response. Moreover, an extension of this particular adaptive scheme is presented in this work.

In medical practice, the application of general anesthesia plays a significant role in the patient's well-being, through the administration of a combination of drugs that act to provide adequate hypnosis (unconsciousness and amnesia to avoid traumatic recalls), paralysis or muscle relaxation (to attain immobility, an absence of reflexes, and proper operating conditions), and analgesia (pain relief). This process is accomplished by an anesthesiologist who must continuously observe and adjust the rates and overall amounts of anesthetic agents delivered to the patient, preserving the stability of the autonomic, cardiovascular, respiratory, and thermoregulatory systems (Brown *et al.* 2010).

Even though it has been a subject of intense research in the last decades, the process of anesthesia is a complicated process and still is not well understood, resulting in a challenging control problem (Dumont *et al.* 2009, Ionescu *et al.* 2013, Nascu *et al.* 2015).

Moreover, in drug delivery systems, the controller has to tackle issues such as inter- and intra-patient variability, multivariable characteristics, variable time delays, dynamics dependent on the hypnotic agent, model variability, and stability issues (Absalom *et al.* 2011, Bailey and Haddad 2005, Silva *et al.* 2015). The current state of the art in the understanding of consciousness and the mechanisms of anesthetic-induced loss of consciousness is limited. Consciousness is very subjective and ethereal that it is difficult to model. At present, the models available, are such as the mean field models of drug action (Absalom *et al.* 2011), which describe the phenomena presented in the electroencephalogram (EEG) associated with different brain states (Silva *et al.* 2015).

There have been many attempts to automatize this process, and the expectations of the application of closed-loop control to drug delivery is that will assist anesthesiologists to improve the safety of the patient by avoiding excessive over-dosages and under-dosages in their patients (Lemos *et al.* 2014), minimizing side effects and the risk of awareness and overdosing during anesthesia. Optimizing the delivery of anesthetics could lead the way for personalized health care, where the individual patient characteristics are taken into account for optimal and flexible drug administration. The first step towards an automated anesthesia process is to derive a mathematical model that adequately describes the system (or the experimental data), avoiding the very complex models that may contain too many parameters that cannot be determined or estimated independently, mainly due to the lack of measurements and adequate sensors.

Commonly, the mathematical model used to study the depth of anesthesia is a PK/PD (pharmacokinetic/pharmacodynamic) model, with a third-order linear PK model, and a PD model consisting of a first-order linear transfer function (which represents the time-lag between the drug infusion and the observed response) and a static nonlinearity (Wiener structure) (Bailey and Haddad 2005). Despite its plausibility accepted by biomedical and control community, being a physiologically based empirical model it presents many difficulties for controller designs, namely, a large number of uncertain parameters due to significant variability among different individuals, time delay, lack of state measurements and nonlinearity. The limited amount of real-time data and the poor excitation properties of the input signals constitute further challenges making the identification of an individualized model on-line very difficult. Many attempts to simplify this model have been made: PK/PD model structures with some fixed parameters (Coppens *et al.* 2011, Bibian *et al.* 2006), first-order plus time-delay models with an output nonlinearity (Hahn *et al.* 2012, Wang *et al.* 2003), piece-wise linear models (Lin *et al.* 2004). A simplified model for the effect of both propofol and remifentanil including an output nonlinearity (Silva *et al.* 2010), and low-complexity control-oriented models have been proposed in the literature (Hahn *et al.* 2012). One notable different approach was the recent introduction of fractional PK models (Dokoumetzidis and Macheras 2009, Copot *et al.* 2013).

The control of anesthesia has been an active subject of research for the past decades and many control schemes have been developed, such as PID (Heusden *et al.* 2013), robust control (Dumont *et al.* 2009), predictive control (Ionescu *et al.* 2008), adaptive (Haddad *et al.* 2003a, Nino *et al.* 2009) and intelligent (Haddad *et al.* 2011) among others.

The implementation of such controllers is based on the assumption that the state values are available from the system measurements and that we have a clear and measurable output with not much noise influence. However, in reality, the measured output may be noisy, and the system measurements do not produce this information directly. Instead, the state information needs to be inferred from the available output measurements. All of these challenges bring us the need of using estimation techniques that can estimate the state of each patient and adjust them based on the dynamics of each patient and deal with the system constraints (Chang *et al.* 2015).

This work is devoted to the design of adaptive controllers, specifically, the model reference adaptive control approach. First, we improve previous results on the fractional-order model reference adaptive control scheme by proposing an extension of the Barbalat's Lemma. This extension allows us to realize a full stability analysis of the adaptive scheme based on the Lyapunov's direct method and concluding the convergence of the error to zero. Moreover, we apply this analysis to design a fractional-order closed-loop model reference adaptive control scheme, and as a complementary result, we extend two identification schemes for fractional-order systems based on Lyapunov's analysis.

As a study case, we deal with the problem of control of anesthesia. Based on the recent paradigm of modeling in physiology and biology using fractional calculus and knowing that the response of the PK/PD model of anesthesia has an S-shape response, we proposed three simple fractional-order models to represent the input-output behavior of the PK/PD model. These proposed models gets around many difficulties, for example, unknown parameters, lack of state measurement, inter and intra-patient variability, and variable time-delay, encountered in controller designs based on the PK/PD model. Based on these simple models we apply the adaptive schemes designed. The results are illustrated via simulations using 30 virtual patients, showing that the fractional-order adaptive schemes designed are robust against inter and intra-patient variability, variable time-delay, perturbations, and noise. Therefore, proposing a novel and straightforward solution for the control of anesthesia using a fractional-order adaptive approach.

1.1 State of the art

In (Sokolov *et al.* 2002) is stated that fractional-order calculus was restricted to the field of mathematics until the last decade of the twentieth century when it became popular among physicists and engineers as a powerful way to describe the dynamics of a variety of complex physical phenomena.

Fractional calculus has attracted many interests in recent years, and numerous physical real-world phenomena and process have been modeled effectively with fractional-order dynamics. And there are a growing number of fractional calculus applications in different areas (Hilfer 2000, Kilbas *et al.* 2006, Koeller 1984, Magin 2010, Podlubny 1999a).

Fractional calculus is considered as an emergent branch of applied mathematics with many applications in the fields of physics and engineering using fractional differential equations to model the dynamics of different processes, but also introduce more efficient modeling in fields as signal processing or control theory (see, (Tenreiro Machado *et al.* 2011, Caponetto *et al.* 2010, Klafter *et al.* 2011, Monje *et al.* 2009, Chen *et al.* 2013, Ortigueira 2011, Sabatier *et al.* 2007, Machado 2002)).

The fractional differential equations capture nonlocal relations in space and time with power-law memory kernels, due to this fact, fractional differentials and integrals provide more accurate models of systems with memory or anomalous behavior that are difficult to grasp with integer-order operators. Few examples of how many authors have demonstrated the application of fractional calculus can be seen in: electrochemistry (Ichise *et al.* 1971), thermal systems and heat conduction (Battaglia *et al.* 2001), viscoelastic materials (Adolfsson *et al.* 2005), fractal electrical networks (Petráš 2002), neural dynamics (Lundstrom *et al.* 2008, Kaslik and Sivasundaram 2012) and many others areas.

Many researchers have extensively studied the problem of fractional-order dynamical systems, some relevant and interesting results were proposed in the existing literature (see (Hadi *et al.* 2012, Sabatier *et al.* 2015, Zhang *et al.* 2015) and references therein).

The main reason for using the integer-order models was the absence of analytical methods to solve fractional differential equations. At present, there are many methods for approximation of fractional derivatives and integrals (Vinagre *et al.* 2000, Machado 2001, Chen *et al.* 2009).

Stability theory plays a crucial role in the study of dynamical systems and is essential for both scientists and engineers. The stability theory of fractional-order systems has been investigated extensively in recent years, and numerous papers have been published for the case of fractional-order linear system (Matignon 1996, Tavazoei and Haeri 2009, Li and Zhang 2011). However, the stability of fractional-order nonlinear systems has not been studied intensively as the case of the linear systems.

The Lyapunov's method for stability analysis for integer-order nonlinear systems has been extended to fractional-order systems (Li *et al.* 2010). Also, a quadratic Lyapunov function for the Caputo fractional derivative has been constructed and applied in many stability analysis of fractional-order systems (Aguila-Camacho *et al.* 2014, Duarte-Mermoud *et al.* 2015). In (Li *et al.* 2009, Li *et al.* 2010), Li and coworkers proposed the definition of Mittag-Leffler stability, the generalized Mittag-Leffler stability theory and analyzed the stability of fractional nonautonomous systems. By using a Lyapunov-like function, the fractional differential inequalities and comparison method, (Zhang *et al.* 2011) obtained some sufficient conditions on asymptotical stability for the nonlinear fractional differential system with Caputo derivative. Other studies on the stability of nonlinear systems can be seen in (Wen *et al.* 2008, Hadi *et al.* 2012).

Barbalat's lemma has been a well-known and useful tool to deduce asymptotic stability of nonlinear uncertain and time-varying systems with integer-order (like adaptive systems). Due to some different properties between fractional-order derivatives and integer-order derivatives, it is not easy (but is possible) to use Barbalat's lemma in fractional-order systems. There has been some extension of this lemma proposed in the literature, including the one proposed in this thesis (Gallegos *et al.* 2015, Navarro-Guerrero and Tang 2017b, Zhang and Liu 2017).

However, the majority of this results just considered the fractional-order α lying in $\alpha \in (0, 1)$, with only a few results on the stability problem of fractional-order nonlinear systems when $\alpha \in (1, 2)$, some results can be found in (Zhang *et al.* 2015, Guo and Ma 2016)

An increasing interest in issues related to fractional dynamical systems oriented towards the area of control theory can be observed in the literature.

Existing studies have shown that the best fractional-order controller can outperform the best integer-order controller. It has also been put into consideration why to consider fractional-order control even when integer-order control works comparatively well (Monje *et al.* 2008).

One of the early attempts to apply fractional-order derivative to systems control can be found in (Manabe 1961, Axtell and Bise 1990).

The fractional-order PID (FOPID) controller was introduced by Podlubny in (Podlubny *et al.* 1997, Podlubny 1999b) and some results suggest that FOPID controllers offer superior performance compared to conventional PID controllers (Čech and Schlegel 2006, Monje *et al.* 2008, Xue *et al.* 2006).

Many different control schemes has been designed using fractional-order operators, for instance, CRONE control (Oustaloup *et al.* 1993), fractional lead-lag compensator (Raynaud 2000), sliding mode control (Zhang and Yang 2012), and fractional optimal control (Djennoune and Bettayeb 2013). In these applications, fractional differentiation is used to model phenomena that exhibit nonstandard dynamical behavior, with a long memory or hereditary effects (Herrmann 2011, Sun *et al.* 2011).

Fractional adaptive control combines fractional-order operators and systems with various adaptive control laws resulting in a variety of fractional-order adaptive control techniques.

Numerous adaptive control strategies have been generalized using fractional operators. The paper (Vinagre *et al.* 2002) was the first proposing the inclusion of fractional operators in Model Reference Adaptive Control (MRAC) schemes but without analytical support. Many works have been published regarding the fractional-order MRAC schemes (see for example (Ladaci *et al.* 2006, Suarez *et al.* 2008, Ma *et al.* 2009, YaLi and RuiKun 2010, Sawai *et al.* 2012, Aguila-Camacho and Duarte-Mermoud 2013)) but also in some other adaptive schemes (Ladaci *et al.* 2008, Charef *et al.* 2013). Some researchers have reported advantages of using fractional operators in MRAC schemes such as better management of noise (Ladaci *et al.* 2008), better behavior under disturbances (Ladaci *et al.* 2006, Suarez *et al.* 2008, Aguila-Camacho and Duarte-Mermoud 2013) and improvements in transient responses (Vinagre *et al.* 2002, Aguila-Camacho and Duarte-Mermoud 2013), among others. Indirect fractional-order direct model reference adaptive control has been reported in (Chen *et al.* 2016), and combined fractional-order direct model reference adaptive control has also been reported (Aguila-Camacho and Duarte-Mermoud 2017).

In (Hemmerling *et al.* 2010, Neckebroek *et al.* 2013) throughout clinical experiments the authors shown that the administration of anesthesia via a PID control has significant improvements in comparison with the standard manual administration.

Many control schemes have been designed for anesthesia control like PID control (Kenny and Mantzaridis 1999, Morley *et al.* 2000, Sakai *et al.* 2000, Absalom *et al.* 2002, Liu *et al.* 2006, Puri *et al.* 2007), adaptive controllers (Mortier *et al.* 1998, Haddad *et al.* 2003b, Haddad *et al.* 2006), predictive controllers (Ionescu *et al.* 2008, Nino *et al.* 2009, Furutani *et al.* 2010), sliding mode control (Castro *et al.* 2008), and neural networks (Haddad *et al.* 2007, Haddad *et al.* 2011).

1.2 Motivation

The motivations for this work arise from the pending work left in the master thesis of the author. In this previous work, it was proposed a simple integer-order non-linear model for the representation of the input-output response of the PK/PD model of anesthesia. It was designed as an adaptive MRAC scheme based on the proposed model to control the PK/PD model. We obtain a good performance result taking into account that this proposed scheme does not need a priori knowledge of the parameters nor state measurement. However, this model does not take into account the time-lag between the drug infusion and the response of the patient, and when we add this time-lag to the proposed adaptive scheme, we obtain and oscillatory response, which is not recommended for the process.

So we look for alternatives to compensate this time-lag in the adaptive scheme. Moreover, after reviewing different methods and technics, we pursued the use of fractional calculus, because we obtain promising results in the previous test and it represents a novel approach to attack this problem. In the development of this work, we identify the niches or missing parts in the theory, like the lack of an extension of Barbalat's lemma to conclude the convergence of the tracking error in adaptive schemes. From there we developed our contributions in fractional-order adaptive control and applied those results to the control of anesthesia, thus presenting a simple, robust and novel approach to attack this problem.

1.3 Contributions

We can categorize the contributions of this thesis in general and specific contributions.

- The general contributions are in the area of fractional-order adaptive control.

  The first contribution is an extension of the Barbalat lemma for fractional-order systems. With this proposed lemma we conclude the convergence of the tracking error to zero in a fractional MRAC scheme with state feedback (which was a missing part of the results previously published).

  Furthermore, we extend the closed-loop model reference adaptive control scheme for fractional-order systems.

- The specific contribution is the application of the general contributions to the problem control of anesthesia.

  In control of anesthesia, there is a great variety of controller designed for this problem, and we offer a simple and novel solution using a fractional adaptive approach.

  First, we propose a fractional-order model to represent the input-output behavior of the PK/PD model of anesthesia. Then based on this model a fractional-order MRAC scheme is designed.

Parts of this thesis are published in (Navarro-Guerrero and Tang 2015, Navarro-Guerrero and Tang 2017a, Navarro-Guerrero and Tang 2017b, Navarro-Guerrero and Tang 2018a, Navarro-Guerrero and Tang 2018b).

1.4 Outline

This thesis is organized as follows:

In Chapter 2 the reader is introduced to the basic concepts of fractional calculus used in fractional-order systems and control.

Chapter 3 is devoted to fractional-order Lyapunov theory, introducing the basic concepts and theorem for the application of the fractional-order Lyapunov direct method. An extension of the Barbalat´s Lemma for fractional-order systems also is introduced.

The topic of Chapter 4 is the fractional-order model reference adaptive control scheme. Here we use the extension of the Barbalat's Lemma proposed to complement the previous results reported in the literature in FOMRAC with state feedback. Moreover, we extend the closed-loop model reference adaptive control scheme for fractional-order systems. Also, we extend identification schemes with and without state measurement for the fractional-order system.

In Chapter 5, we present our case of study, control of anesthesia. It is present the concepts of general anesthesia, and the modeling and control challenges. Moreover, is proposed simple fractional-order models to represent the input-output behavior of the PK/PD model of anesthesia.

Chapter 6 presents the simulation results of applying the result of Chapter 4 and the models proposed in Chapter 5 to the case of study, the control of anesthesia using 30 virtual patients models.

In Chapter 7 we draw some conclusions on the results of this work, discussing the advantages and disadvantages of the use of fractional calculus concepts to modeling and control physical phenomena and process. Also, we propose some lines of investigation for future work.

Chapter 2

Fractional-Order Systems

Fractional-order systems are mathematical representations of physical systems represented by integro-differential equations involving fractional-order operators. Fractional calculus is the generalization of the classical operations of derivation and integration to non-integer order.

In this chapter are presented the basic definitions of fractional calculus, fractional-order dynamic systems, and control.

2.1 Fractional calculus

One of the very powerful mathematical modeling and analysis techniques at our disposition is calculus and differential equations. The underlying mathematical basis of almost all science and engineering disciplines has essentially been integer-order calculus.

Fractional calculus is a mathematical branch that studies the derivatives and integrals of non-integer order (also called differintegrals or integro-differential operators). The history of fractional calculus started almost at the same time when classical calculus was established. It was first mentioned in Leibniz's letter to l'Hôpital in 1695, where the idea of semi-derivatives was suggested. With the passing of time, fractional calculus was built on formal foundations by many renowned mathematicians, like Abel, Euler, Fourier, Grünwald, Heaviside, Liouville, Riemann, among others. A detailed history of the development of fractional calculus and his contributors can be found in (Oldham and Spanier 2002, Machado and Kiryakova 2017).

Nowadays, fractional calculus has a wide area of applications, for instance bioengineering

(Magin 2006), physics (Hilfer 2000), chaos theory (Petráš 2011), viscoelasticity (Mainardi 2010), and many others (see e.g. (Sabatier *et al.* 2007)).

In the next Section, the definitions and properties of the fractional-order operators are briefly summarized.

2.1.1 Definitions

The integro-differential operator is define as

$$
{}_{t_0}D_t^{\alpha} = \begin{cases} \dfrac{d^{\alpha}}{dt^{\alpha}}, & \alpha > 0, \\ 1 & \alpha = 0, \\ \displaystyle\int_{t_0}^{t} (d\tau)^{\alpha} & \alpha < 0. \end{cases} \tag{2.1}
$$

where t_0 and t are the bounds of the operation and $\alpha \in R$

There are various definitions of the fractional derivatives. This problem arises from the lack of a unique concept explaining the geometrical and physical sense of the fractional operations. So the physical or other model considered in various scientific fields leads to different types of fractional order derivatives. For example, the more abstract mathematical studies usually use the Riemann-Liouville definition, and the applied studies concerned with physics or control theory mostly use the definition of Caputo or that of Grünwald-Letnikov which is more adequate in the numerical calculations (Butkovskii *et al.* 2013). Other definitions like Oldham and Spanier, Miller and Ross, Weyl, Fourier, Cauchy, Abel, Nishimoto among others exist. A review of the existing definitions of the fractional operator can be consulted in (Capelas and Machado 2014).

The notion of fractional-order integral of order $\alpha > 0 \in \mathbb{R}$ is a natural consequence of Cauchy's formula for repeated integrals, which reduces the computation of the primitive corresponding to the n-fold integral of a function $f(t)$ to a simple convolution (Podlubny 1999a).

Next, we present the most common definitions of the fractional integral and fractional derivative (Kilbas *et al.* 2006).

Definition 2.1. *The Riemann-Liouville integral (or, fractional integral) with fractional-order*

$\alpha \in \mathcal{R}_+$ of a function $f(t)$ is defined by

$$ {}_{t_0}D_t^{-\alpha} f(t) = {}_{t_0} I_t^{\alpha} f(t) = \frac{1}{\Gamma(\alpha)} \int_{t_0}^{t} \frac{f(\tau)}{(t-\tau)^{1-\alpha}} d\tau, \tag{2.2} $$

where $t = t_0$ is the initial time and

$$ \Gamma(\alpha) = \int_0^{\infty} t^{\alpha-1} e^{-t} dt, \tag{2.3} $$

is the Euler's gamma function.

In integer-order calculus, the factorial plays an essential role, and the Gamma function has the same importance in the fractional-order calculus.

Definition 2.2. *The Riemann-Liouville derivative with fractional-order $\alpha \in \mathcal{R}_+$ of a function $f(t)$ is defined by*

$$ {}_{t_0}D_t^{\alpha} f(t) = \frac{d^m}{dt^m} {}_{t_0}I_t^{m-\alpha} = \frac{1}{\Gamma(m-\alpha)} \frac{d^m}{dt^m} \int_{t_0}^{t} (t-\tau)^{m-\alpha-1} f(\tau) d\tau, \tag{2.4} $$

where $m - 1 < \alpha < m \in \mathbb{Z}_+$.

Definition 2.3. *The Caputo derivative with fractional-order $\alpha \in \mathcal{R}_+$ of a function $f(t)$ is defined by*

$$ {}_{t_0}D_t^{\alpha} f(t) = {}_{t_0} I_t^{n-\alpha} \frac{d^n}{dt^n} = \frac{1}{\Gamma(n-\alpha)} \int_{t_0}^{t} \frac{f^{(n)}(\tau)}{(t-\tau)^{\alpha-n+1}} d\tau, \tag{2.5} $$

where $n - 1 < \alpha < n \in \mathbb{Z}_+$.

One of the advantages of Caputo derivative, which is a modification of the Riemann–Liouville definition, is that the initial conditions for fractional differential equations take the same form as those for integer-order differentiation, which has a well-understood physical meaning.

It is important noticed that, unlike the integer-order differentiation, fractional-order differentiation is a nonlocal operation (the past values of the function are needed) that is defined over an interval $[t_0, t]$.

As we can observe from the previous definitions, in the time domain, the fractional-order derivative and integral are defined by a convolution operation. From (2.2) we have

$$ {}_{t_0}I_t^{\alpha} = \Phi_\alpha(t) * f(t) = \int_{t_0}^{t} \Phi_\alpha(t) f(t-\tau) d\tau, \quad \alpha \in \mathcal{R}_+, \tag{2.6} $$

with

$$\Phi_\alpha(t) = \frac{t^{\alpha-1}}{\Gamma(\alpha)}, \quad \alpha \in \mathcal{R}_+. \tag{2.7}$$

Therefore, we can view the fractional-order operators as a convolution between two functions.

The memory effect of these operators, shown by the convolution integral, reveal the unlimited memory of these operators, ideal for modeling hereditary and memory properties in physical systems and materials.

The exponential function is another essential tool in the theory of integer-order differential equations, and the generalization of this function, so-called Mittag-Leffler function, plays an essential role in the theory of fractional differential equations.

The Mittag-Leffler of one and two-parameters are given by

$$E_\alpha = \sum_{k=0}^{\infty} \frac{z^k}{\Gamma(k\alpha+1)}, \tag{2.8}$$

$$E_{\alpha,\beta} = \sum_{k=0}^{\infty} \frac{z^k}{\Gamma(k\alpha+\beta)}, \tag{2.9}$$

where $\alpha > 0$, $\beta > 0$ and $z \in \mathbb{C}$. For $\beta = 1$ in (2.9), we have $E_\alpha(z) = E_{\alpha,1}(z)$. Also $E_{1,1} = e^x$.

The main properties of fractional derivatives and integrals can be summarized as follows (Petráš 2011):

Property 2.1. *If f(t) is an analytical function of t, then its fractional derivative ${}_0D_t^\alpha$ is an analytical function of t, α.*

Property 2.2. *For $\alpha = n$, where n is integer, the operation ${}_0D_t^\alpha$ gives the same result as classical differentiation of integer-order n*

Property 2.3. *For $\alpha = 0$ the operation ${}_0D_t^\alpha$ is the identity operator:*

$${}_0D_t^\alpha = f(t).$$

Property 2.4. *Fractional differentiation and fractional integration are linear operations:*

$${}_{t_0}D_t^\alpha(\lambda f(t) + \mu g(t)) = \lambda {}_{t_0}D_t^\alpha f(t) + \mu {}_{t_0}D_t^\alpha g(t).$$

Property 2.5. *The additive index law (semigroup property)*

$$ {}_0D_t^{\alpha}\,{}_0D_t^{\beta}f(t) =_0 D_t^{\beta}\,{}_0D_t^{\alpha}f(t) =_0 D_t^{\alpha+\beta}f(t), $$

holds under some reasonable constraints on the function $f(t)$. The fractional-order derivative commutes with integer-order derivative

$$ \frac{d^n}{dt^n}({}_{t_0}D_t^{\alpha}f(t)) =_{t_0} D_t^{\alpha}\left(\frac{d^n f(t)}{dt^n}\right) =_{t_0} D_t^{\alpha+n}f(t), $$

under the condition $t = t_0$ we have $f^{(k)}(t_0) = 0$, with $k = 0, 1, 2, ..., n-1$). The relationship above says the operators $\frac{d^n}{dt^n}$ and ${}_{t_0}D_t^{\alpha}$ commute.

Property 2.6. *The Leibniz's rule for fractional differentiation is given as*

$$ {}_{t_0}D_t^{\alpha}(\phi(t)f(t)) = \sum_{k=0}^{\infty}\begin{pmatrix}\alpha\\ k\end{pmatrix}\phi^{(k)}(t)_{t_0}D_t^{\alpha-k}f(t), $$

if $\phi(t)$ and $f(t)$ and all their derivatives are continuous in the interval $[a, t]$.

Property 2.7. *(Tarasov 2008) Newton-Leibniz formula generalization*

$$ {}_{t_0}I_t^{\alpha}\,{}_{t_0}D_t^{\alpha}f(x) = f(t) - f(t_0). \tag{2.10} $$

where ${}_{t_0}D_t^{\alpha}$ is represented for the Caputo derivative and ${}_{t_0}I_t^{\alpha}$ for the Riemann-Liouville integral.

Some other important properties of the fractional derivatives and integrals can be found in several works such as (Magin 2006, Monje *et al.* 2010, Oldham and Spanier 2002, Podlubny 1999a, Kilbas *et al.* 2006, Padula and Visioli 2015).

2.1.2 Laplace transform

The Laplace transform is a practical and useful technique to solve differential equations which frequently arise in applied science and engineering problems. This technique converts linear differential equations to linear algebraic equations which can be solved easily.

The Laplace transform of a function of time $f(t)$ is defined by

$$ \mathcal{L}\{f(t)\} = F(s) = \int_0^{\infty} e^{-st}f(t)dt, \tag{2.11} $$

with $f(t) = 0$ for $t < 0$.

In the following, some important transformations for fractional-order operators are presented:

- Laplace transform of the Riemann-Liouville integral

$$\mathcal{L}\{{}_0I_t^{\alpha}\} = s^{-\alpha}F(s), \quad \alpha \geq 0 \tag{2.12}$$

- Laplace transform of the Riemann-Liouville derivative

$$\mathcal{L}\{{}_0D_t^{\alpha}\} = s^{\alpha}F(s) - \sum_{k=0}^{m-1} s^k [{}_0D_t^{\alpha-k-1} f(t)]|_{t=0}, \tag{2.13}$$

  where $m-1 < \alpha \leq m$, $m \in \mathbb{N}$, $\alpha > 0$ and ${}_0D_t^{\alpha-k-1}f(0)$ is the initial value of order $\alpha - k - 1$ of the function $f(t)$ for $k = 0, 1, 2, ...m-1$.

- Laplace transform of the Caputo derivative

$$\mathcal{L}\{{}_0D_t^{\alpha}\} = s^{\alpha}F(s) - \sum_{k=0}^{m-1} s^{\alpha-k-1} [{}_0D_t^{\alpha-k-1} f(t)]|_{t=0}, \tag{2.14}$$

  where $m-1 < \alpha \leq m$, $m \in \mathbb{N}$, $\alpha > 0$ and ${}_0D_t^{k}f(0)$ is the initial value of order k of the function $f(t)$ for $k = 0, 1, 2, ...m-1$.

It can be noticed that for null initial conditions the Laplace transform of the Riemann-Liouville derivative and the Caputo derivative give the same result.

Despite the complexity of fractional operators in the time domain, in the frequency domain, they have a straightforward form. Under null initial conditions, the Laplace transform becomes,

$$\mathcal{L}\{{}_0D_t^{\alpha}\} = s^{\alpha}F(s), \tag{2.15}$$

and it can be seen that this is a natural generalization for a non-integer order operators.

In the literature (Gorenflo and Minardi 1997, Herrmann 2011, Kilbas *et al.* 2006, Petráš 2011) it can be found in more detail the facts and properties of this transformation applied to the fractional operators.

2.1.3 Numerical evaluation

Due to the complexity of analytic solutions, or even numerical solutions to fractional differential equations (which are a recursive process that, in theory, requires an infinite amount of memory), approximations based on the so-called short memory principle (Podlubny 1999a) are often used. A review of existing continuous and discrete time approximations of fractional operators are given in (Vinagre *et al.* 2000). More recently, methods for analog implementation of fractional-order systems and controllers were proposed in (Dorčák *et al.* 2012). Digital approximations of fractional operators usually rely on power series expansion or continued fraction expansion of corresponding generating functions (Chen *et al.* 2009), and other methods based on discretization have been proposed (Machado 2001).

For example, one common approach to implement the fractional operators in simulations and practical applications is through the use of an integer-order transfer function whose behavior approximates the fractional operator $C(s) = s^{\alpha}$.

The Oustaloup's method (Oustaloup 1991) is one of the available methods to implement this approximation, which use a distribution of N poles y N zeros of the form

$$C(s) = C_0 \prod_{n=1}^{N} \frac{1 + s/\omega_{zn}}{1 + s/\omega_{pn}}$$

where $r \in \mathbb{R}$, $\omega_{zn} = \omega_b \left(\frac{\omega_h}{\omega_b}\right)^{\frac{r+N+0.5(1-\alpha)}{2N+1}}$, $\omega_{pn} = \omega_h \left(\frac{\omega_h}{\omega_b}\right)^{\frac{r+N+0.5(1-\alpha)}{2N+1}}$ and $C_0 = \left(\frac{\omega_h}{\omega_b}\right)^{-\frac{\alpha}{2}} \prod_{k=-N}^{N} \frac{\omega_{pn}}{\omega_{zp}}$, the poles and zeros are distributed inside a frequency interval $[\omega_b, \omega_h]$.

In (Petráš (2011) and there references therein) we can find an explanation of the different methods to approximate the fractional operator, in the time domain and frequency domain.

To perform the simulations, we will use the Matlab toolbox for fractional control NINTEGER v.2.3 developed by D. Valério[]. In this toolbox are implemented various numerical approximations for the fractional-order operators that are explained in detail in (Valério and Sá da Costa 2005).

The available approximations in this toolbox for the operator in continuous-time are briefly summarized next:

- Crone (First generation Crone with n zeros and n poles)
- Carlson (Approximation with n zeros and n poles)
- Matsuda (Approximation with n zeros and n poles)
- Cfehigh (Approximation based on the expansion of continuous fractions of $(1+s)^{\alpha}$, with n zeros and n poles)

- Cfelow (Approximation based on the expansion of continuous fractions of $(1+1/s)^{\alpha}$, with n zeros and n poles)

To implement these approximations, we need to choose four options, the approximation, the associated expansion (MacLaurin, continuous fraction expansion), the order n of the approximation and the bandwidth $[\omega_b, \omega_h]$.

The quality of the simulations is related to the approximation used and his associated parameters. In this work, we will use the Crone approximation with the MacLaurin series expansion, n=10 and a bandwidth [0.001 1000]. This approximation was chosen to make a trade-off between the quality of the simulation and the computing time.

2.2 Fractional-order systems

The Caputo derivative provides an alternative to the Riemann-Liouville derivative. This derivative, thanks to its properties, is a useful tool to describe physical phenomena (Ortigueira 2011). One of the main drawbacks of the Riemann-Liouville derivative is that they lead to differential equations whose initial conditions are expressed in terms of fractional derivatives, as seen in (2.13). Fractional initial conditions have no clear physical interpretation. Unlike the Riemann-Liouville derivative, the Caputo derivative leads to differential equations whose initial conditions are expressed as integer-order derivatives (thus having a clear physical meaning) as seen in (2.14). In general, when we work with dynamic systems, it is usual that we deal with causal functions of t. Therefore through this work the initial time of the fractional operators ${}_{t_0}D_t^{\alpha}$ and ${}_{t_0}I_t^{\alpha}$ it is supposed $t_0 = 0$. In this section, all the fractional differential equations are represented by the Caputo derivative.

2.2.1 Fractional-order LTI systems: transfer function representation

The conventional input-output transfer function approach for integer-order systems can be extended to the fractional-order case. For LTI systems defined by a fractional-order ordinary differential equation, the Laplace transform can be used to obtain a fractional-order transfer function representation of the system.

Consider the following SISO fractional system described by the fractional-order differential equation:

$$\sum_{k=0}^{n} a_{k0} D_t^{\alpha_k} y(t) = \sum_{k=0}^{n} b_{k0} D_t^{\beta_k} u(t), \tag{2.16}$$

where $u(t)$ is the input, $y(t)$ is the output, $\alpha_k, \beta_k \in \mathbb{R}_+$, $a_k, b_k \in \mathbb{R}$.

Applying the Laplace transform and under null initial conditions, independently from the adopted definition of the fractional operator, the transfer function of the fractional-order differential equation (2.16) is

$$G(s) = \frac{Y(s)}{U(s)} = \frac{\sum_{k=0}^{n} b_k s^{\beta_k}}{\sum_{k=0}^{n} a_k s^{\alpha_k}} = \frac{b_m s^{\beta_m} + b_{m-1} s^{\beta_{m-1}} + \cdots + b_m s^{\beta_0}}{a_n s^{\alpha_n} + a_{n-1} s^{\alpha_{n-1}} + \cdots + a s^{\alpha_0}} \tag{2.17}$$

In general, a fractional transfer function is the ratio of two fractional polynomials.

The characteristic polynomial of the fractional system (2.17) has the form

$$P(s) = a_n s^{\alpha_n} + a_{n-1} s^{\alpha_{n-1}} + \cdots + a_0 s^{\alpha_0}. \tag{2.18}$$

The polynomial (2.18) is a multivalued function whose domain is a Riemann surface. In the general case, this surface has an infinite number of sheets, and the fractional polynomial (2.18) has an infinite number of roots. Only a finite number of these roots will be on the main sheet of the Riemann surface and which determine the dynamic behavior (Monje *et al.* 2010).

The LTI systems can be classified as follows

$$\text{LTI Systems} \begin{cases} \text{Non-integer} & \begin{cases} \text{Commensurate} & \begin{cases} \text{Rational} \\ \text{Irrational} \end{cases} \\ \text{Non-commensurate} \end{cases} \\ \text{Integer} \end{cases}$$

taking this into account the fractional transfer function (2.17) is defined as (Monje *et al.* 2010):

- Commensurate order if

$$\begin{aligned} \alpha_i &= i\alpha,\ i = 0, 1, ..., n, \\ \beta_k &= k\alpha,\ k = 0, 1, 2, ..., m, \end{aligned} \tag{2.19}$$

  where $\alpha, \beta > 0$ are real numbers.

- Rational order if it is a commensurate order and $\alpha = \frac{1}{q}$, where q is a positive integer.

- Non-commensurate order if (2.19) does not hold.

As we can see later, the systems of commensurate-order enable a straightforward generalization of the well-known results for integer-order LTI systems.

The transfer function of a fractional-order system of commensurate order can be written in the form

$$G(s) = \frac{b_m s^{m\alpha} + b_{m-1} s^{(m-1)\alpha} + \cdots + b_0}{a_n s^{n\alpha} + a_{n-1} s^{(n-1)\alpha} + \cdots + a_0}. \tag{2.20}$$

Substituting $\lambda = s^\alpha$ in (2.20), we obtain the associated natural order transfer function

$$G(\lambda) = \frac{b_m \lambda^m + b_{m-1} \lambda^{m-1} + \cdots + b_0}{a_n \lambda^n + a_{n-1} \lambda^{n-1} + \cdots + a_0} \tag{2.21}$$

The poles of the commensurate transfer function (2.21) are located on the first sheet of the Riemann surface.

2.2.2 Fractional-order LTI systems: state space representation

A useful representation for systems of fractional-order differential equations is the state space representation. This representation is a generalization of the state space equations of the integer-order system theory.

Consider the state-space representation of a fractional-order LTI system given by

$$\begin{aligned} {}_0D_t^\alpha x(t) =& Ax + Bu \\ y =& Cx, \end{aligned} \tag{2.22}$$

where $\alpha = [\alpha_1, \alpha_2, \cdots, \alpha_n]$, $u \in \mathbb{R}^m$ is the input vector, $x \in \mathbb{R}^n$ is the state vector, $y \in \mathbb{R}^p$ is the output vector, $A \in \mathbb{R}^{n\times n}$ is the state matrix, $B \in \mathbb{R}^{n\times m}$ is the input matrix, $C \in \mathbb{R}^{p\times n}$ is the output matrix.

Given the nonlocality and infinite order of the fractional operations, the description of the state of such systems must take into consideration not only the values of the, generally speaking, infinite set of the system variables at a particular time instant, but also the system history. The initial condition of a fractional-order system is a time-varying function called initialization term (Hartley and Lorenzo 2002), for the time being, these questions remain open, and the states and dynamics of the fractional systems are analyzed mostly by their approximation with the use of the dynamic systems of a finite integer-order (**?**). Therefore, the state of such systems is called "pseudo-state" (Trigeassou *et al.* 2012). For simplicity in this work, we call this vector a state throughout the remainder work only for simplification purposes, and we will suppose null initial conditions.

The above fractional-order state space representation can be simplified in the particular case when $\alpha = [\alpha, \alpha, \cdots, \alpha]$, a commensurate order system.

Next, we will show the solution of a commensurate LTI fractional-order system with constant coeficients.

Consider the system

$$\begin{aligned} {}_0D_t^{\alpha} x(t) =& Ax + Bu, \\ y =& Cx, \end{aligned} \tag{2.23}$$

where $\alpha = [\alpha, \alpha, \cdots, \alpha]$, $u \in \mathbb{R}^m$ is the input vector, $x \in \mathbb{R}^n$ is the state vector, $y \in \mathbb{R}^p$ is the output vector, $A \in \mathbb{R}^{n\times n}$ is the state matrix, $B \in \mathbb{R}^{n\times m}$ is the input matrix, $C \in \mathbb{R}^{p\times n}$ is the output matrix, and initial condition $x(0) = x_0$.

Lets introduce the two parameter Mittag-Leffler function for a matrix, defined by

$$E_{\alpha,\beta}(Az) = \sum_{k=0}^{\infty} \frac{(Az)^k}{\Gamma(\alpha k + \beta)},\ \alpha > 0,\ \beta > 0,\ z \in \mathbb{C}. \tag{2.24}$$

This system, in general, can be solved using the inverse Laplace transform, just as in the integer-order case. From system (2.23) we have

$$x(t) = \mathcal{L}^{-1}\{X(s)\} = \mathcal{L}^{-1}\{(s^{\alpha}I - A)^{-1}BU(s) + (s^{\alpha}I - A)^{-1}s^{\alpha-1}x(0)\}. \tag{2.25}$$

Defining

$$\hat{\Phi} = \mathcal{L}^{-1}\{(s^{\alpha}I - A)^{-1}\},\ t \geq 0. \tag{2.26}$$

$$\Phi = \mathcal{L}^{-1}\{(s^{\alpha}I - A)^{-1}s^{\alpha-1}\},\ t \geq 0 \tag{2.27}$$

Then

$$x(t) = \Phi x(0) + \hat{\Phi} * [Bu(t)] = \Phi x(0) + \int_0^t \hat{\Phi}(t-\tau)Bu(\tau)d\tau. \tag{2.28}$$

As can be seen in (2.28), $\Phi(t)$ is the matrix usually known as the state transition matrix. Following a procedure similar to that used for linear systems of integer-order, the form of the state transition matrix can be determined. For that purpose the following expression will be used: ${}_0D_t^{\alpha}x(t) = Ax$ with $x(0) = 0$. Taking into account the use of the Caputo derivative, the solution can be expressed as

$$x(t) = \left(\sum_{k=0}^{\infty} \frac{A^k t^{\alpha k}}{\Gamma(1+\alpha k)}\right) x_0 = E_{\alpha,\beta}(At^{\alpha})x_0 = \Phi x_0. \tag{2.29}$$

Is clear that the Mittag–Leffler function here performs the same role as that performed by the exponential function for the integer-order systems. The well known exponential matrix, e^{At} is just a particular case of the generalized exponential matrix, $E_{\alpha,1}(At^{\alpha})$, which can be called Mittag–Leffler matrix function.

As in the case of the state-space representation of integer-order, three canonical representations can be proposed, which are similar to the classical ones (controllable canonical form, observable canonical form and modal canonical form) (Caponetto *et al.* 2010).

2.3 Stability

In this section, we briefly explain the fundamentals and previous considerations to understand the stability of fractional-order systems.

The known stability methods for integer-order systems differ from those that have been proposed for fractional-order systems. The conditions under which linear time-invariant fractional-order systems are stable were studied in (Matignon 1996).

To understand the dynamic behavior and stability properties of the system (2.22) is necessary to analyze the eigenvalues of the system matrix A. For integer-order linear system theory ($\alpha = 1$), the eigenvalues of the matrix A are studied in the complex Laplace $s-plane$. The stability boundary in the $s-plane$ is the imaginary axis, any poles lying to the left of the imaginary axis represent a stable time response, while the poles lying to the right of the imaginary axis represent an unstable time response.

For commensurate fractional-order systems, the eigenvalues of the matrix A must now be evaluated in what would appear to be the $s^{\alpha} - plane$. Rather than dealing with the fractional power of s, the analysis is simplified if a change of variables is used. It is defined $\omega = s^{\alpha}$, and then the eigenvalue analysis will be performed in the new complex $\omega - plane$, which is a mapping of the $s - plane$ (Podlubny 1999a, Li and Zhang 2011).

It is necessary to map the $s - plane$, along with the time-domain function properties associated with each point, into the complex $\omega - plane$. To simplify the discussion, we will limit the order of the fractional operator to $\alpha \in (0, 1)$.

This section is based on Chapter 2 of (Monje *et al.* 2010) and the example to illustrate the concepts is taken from there.

In general, the study of the stability of fractional-order systems can be carried out by studying the solutions of the integrodifferential equations that characterize them. An alternative way is the study of the transfer function of the system (2.16).

The characteristic polynomial (also called pseudo-characteristic polynomial) of the transfer function (2.17)

$$P(s) = a_n s^{\alpha_n} + a_{n-1} s^{\alpha_{n-1}} + \cdots + a_0 s^{\alpha_0}, \tag{2.30}$$

with α_i, is a multi-valued function of complex variable s, whose domain is a Riemann surface (Podlubny 1999a) of a number of sheets which is finite only in the case of $\forall i$, $\alpha_i \in \mathbb{Q}_+$, being the principal sheet defined by $-\pi < arg(s) < \pi$. This equation has an infinite number of roots, among which only a finite number of roots will be on the main sheet of the Riemann surface. In the case of $\alpha_i \in \mathbb{Q}_+$, that is, $\alpha = \frac{1}{q}$. where q is a positive integer, the q sheets of the Riemann surface are determined by

$$s = |s|e^{j\phi}, \ (2k+1)\pi < \phi < (2k+3)\pi, \quad k = -1, 0, \cdots q-2. \tag{2.31}$$

Where the case $k = -1$ corresponds to the main sheet. For the mapping $\omega = s^{\alpha}$, these sheets become the region of the plane ω defined by

$$\omega = |s|e^{j\theta}, \ \alpha(2k+1)\pi < \theta < \alpha(2k+3)\pi. \tag{2.32}$$

All of the well-known control techniques concerning eigenvalues, or poles, can be used in the $\omega - plane$ (Hartley and Lorenzo 2002).

To illustrate the previous concepts is presented an example for the case of $\omega = s^{1/3}$. The Riemann surface that represents the transformation $\omega = s^{1/3}$ is shown in Figure 2.1 and the regions of stability on the complex plane ω are presented in Figure 4.3.

These three sheets correspond to:

$$k = \begin{cases} -1, & -\pi < arg(s) < \pi, \text{ (the principal sheet)} \\ 0, & \pi < arg(s) < 3\pi, \text{ (sheet 2)} \\ 1, & 3\pi < arg(s) < 5\pi, \text{ (sheet 3)} \end{cases}$$

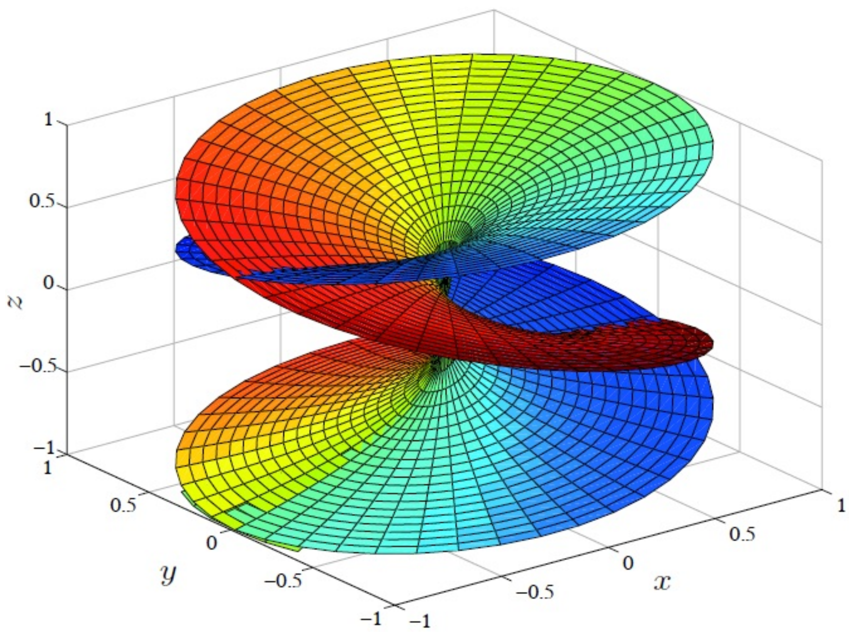


Figure 2.1: Riemann surface for $s^{1/3}$.

The roots laying in the secondary sheets of the Riemann surface are related to solutions that are always monotonically decreasing functions (they go to zero without oscillations when $t \to \infty$). Only the roots that are on the main sheet of the Riemann surface are responsible for a different dynamics, for example, damped oscillations, oscillations of constant amplitude, oscillations of increasing amplitude with monotonic growth. The roots which are in the principal sheet are called *structural roots* or *relevant roots* (Matignon 1996, Podlubny 1999a). A more elaborate description of this topic can be seen in (Podlubny 1999a, Kilbas *et al.* 2006, Petráš 2011, Sabatier *et al.* 2015).

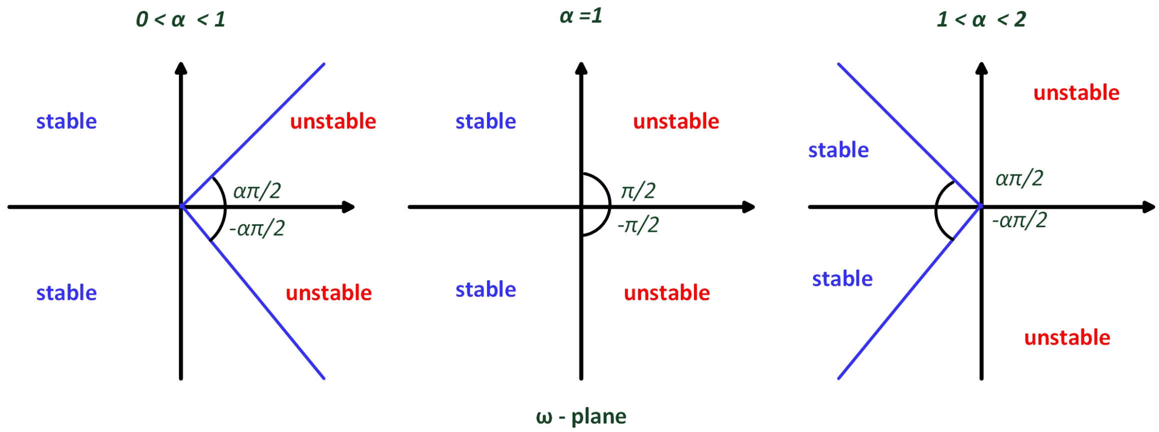


Figure 2.2: Stability regions of the $\omega - plain$.

2.3.1 Stability of fractional-order LTI systems

It is known from the stability theory that an LTI system is stable if the roots of the characteristic polynomial are negative or have negative real parts if they are complex conjugate. It means that they are located on the left half of the complex plane. In the fractional-order LTI case, the stability is different from the integer one. An interesting notion is that a stable fractional system may have roots in the right half of complex plane (see Fig. 4.3). It has been shown that system (2.17) is stable if the following condition is satisfied.

Theorem 2.1. *(Matignon 1996) A commensurate-order system described by a rational transfer function*

$$G(\lambda) = \frac{Q(\lambda)}{P(\lambda)}, \tag{2.33}$$

where $\lambda = s^{\alpha}$, $\alpha \in \mathbb{R}_{+}$, $0 < \alpha < 2$, *is stable if and only if*

$$|arg(\lambda_i)| > \alpha\frac{\pi}{2}, \tag{2.34}$$

with $\forall\lambda_i \in \mathbb{C}$ *being the* $i - th$ *root of* $P(\lambda) = 0$.

For $\alpha = 1$ this is the classical theorem of pole location in the complex plane, that is, P has no pole in the closed half plane of the first Riemann sheet.

Theorem 2.2. *(Matignon 1998) The commensurate system (2.23) is stable if the following condition is satisfied (also if the triplet A, B, C is minimal)*

$$|arg(eig(A))| > \alpha\frac{\pi}{2}, \tag{2.35}$$

where $0 < \alpha < 2$ and $eig(A)$ represent the eigenvalues of the matrix A.

The frequency response approach applies directly to fractional-order systems as long as the primary roots are used in evaluating the individual fractional elements. Likewise, the root locus approach, Nyquist and Bode plots can be applied directly to fractional-order systems as long as they are performed in the $\omega - plane$.

2.3.2 Stability of fractional-order nonlinear systems

Stability of the fractional-order nonlinear system is very complex and is different from the fractional-order linear systems. The main difference is that for a nonlinear system it is necessary to investigate steady states having two types: equilibrium point and limit cycle. Nonlinear systems may have several equilibrium points, and there are many definitions of stability (asymptotic, global, orbital).

Based on Caputo derivative, a fractional-order system can be described as

$$ {}_{t_0}D_t^{\alpha} x(t) = f(x,t), \tag{2.36} $$

with initial conditions $x(t_0)$, where $\alpha \in (0,1)$, $f : \Omega \times \mathbb{R}_+ \to \mathbb{R}^n$ is piecewise continuous in t and locally Lipschitz in x on $\Omega \times \mathbb{R}_+$, and $\Omega \in \mathbb{R}^n$ is a domain that contains the origin $x = 0$.

As mentioned in (Matignon 1996), exponential stability cannot be used to characterize the asymptotic stability of fractional-order systems. A new definition was introduced

Definition 2.4. *(Oustaloup et al. 2008) The trajectory $x(t) = 0$ of the system (2.36) is $t^{-\alpha}$ asymptotically stable if there is a possible real α so that: $\forall \parallel x(t) \parallel$ with $t \leq t_0$, $\exists N(x(t))$, such that $\forall t \geq t_0$, $\parallel x(t) \parallel \leq N t^{-\alpha}$.*

The fact that the components of $x(t)$ slowly decay towards zero following $t^{-\alpha}$ leads to fractional systems sometimes called long memory systems. Power law stability $t^{-\alpha}$ in a particular case of the Mittag-Leffler stability (Li et al. 2008) which will be defined in the next chapter.

The next Theorem presented in (Tavazoei and Haeri 2008) can be seen as an extension of the Lyapunov's indirect method.

Theorem 2.3. *The equilibrium points x_{e_i} of the fractional-order commensurate system (2.36) are asymptotically stable if all eigenvalues λ_i with $i = 1, 2, .., n$, of the Jacobian matrix $J = \frac{\partial f}{\partial x}$,* *where* $f = [f_1, f_2, ..., f_n]^T$*, evaluated at the equilibrium* x_{e_i}*, satisfy the condition*

$$|arg(eig(J))| = |arg(\lambda_i)| > \alpha\frac{\pi}{2}, \quad i = 1, 2, ..., n. \tag{2.37}$$

One of the most used tools to study the stability of nonlinear systems is the Lyapunov's direct method, whose extension for fractional-order systems will be treated in the next chapter.

2.3.3 Controllability and observability

The study of the observability and controllability of the fractional dynamical systems are two important issues for many applied problems. It is well known that the problem of controllability of dynamical systems is widely used in analysis and the design of control system. Any system is said to be controllable if every state corresponding to this process can be affected or controlled in finite time by some controller. Observability is a measure of how well internal states of a system can be inferred by knowledge of is external outputs.

There are few works reporting the study of observability and controllability of fractional linear systems (see, for example, (Bettayeb and Djennoune 2008, Chen *et al.* 2006, Sabatier *et al.* 2012)).

Definition 2.5. *The system (2.23) is observable on an interval* $[t_0, t_1]$ *if*

$$y(t) = Cx(t) = 0 \quad t \in [t_0, t_1],$$

implies

$$x(t) = 0 \quad t \in [t_0, t_1].$$

Theorem 2.4. *(Observability criterion)(Monje et al. 2010) The system given by (2.23) is observable if and only if the matrix* O *defined by*

$$O = \begin{bmatrix} C \\ CA \\ CA^2 \\ \vdots \\ CA^{n-1} \end{bmatrix}, \tag{2.38}$$

called the observability matrix, is full-rank.

The observability condition for commensurate-order LTI systems coincides with the well-known one for integer-order LTI systems.

The observability property can also be studied through the observability Grammian matrix.

Theorem 2.5. *(Balachandran et al. 2013) The observed linear system (2.23) is observable on* $[t_0, t_1]$ *if and only if the observability Grammian matrix*

$$W = \int_{t_0}^{t_1} E_\alpha(A^T(t-t_0)^\alpha)C^T C E_\alpha(A^T(t-t_0)^\alpha)dt, \tag{2.39}$$

is positive definite.

Definition 2.6. *The system (2.23) is controllable on* $[t_0, t_1]$ *if for every pair of vectors* x_0*,* $x_1 \in \mathcal{R}^n$*, there is a control* $u(t) \in L^2([t_0, t_1], \mathcal{R}^m)$ *such that the solution* $x(t)$ *of (2.22) which satisfies*

$$x(t_0) = x_0,$$

$$x(t_1) = x_1.$$

We say that u *steers the system form* x_0 *to* x_1 *during the interval* $[t_0, t_1]$.

Lemma 2.1. *The system (2.23) is controllable on* $[t_0, t_1]$ *if and only if for each vector* $x_1 \in \mathcal{R}^n$ *there is a control* $u(t) \in L^2([t_0, t_1], \mathcal{R}^m)$ *which steers* x_0 *to* x_1 *during* $[t_0, t_1]$.

Theorem 2.6. *(Controllability criterion)(Monje et al. 2010) The system given by (2.23) is controllable if and only if the matrix* C *defined by*

$$C = [B, AB, A^2B, \cdots, A^{n-1}B], \tag{2.40}$$

denoted as controllability matrix, is full-rank.

This controllability condition (2.40) for a commensurate order system is the same as the well known for integer-order systems.

The controllability property also can be studied through the controllability Grammian matrix.

Theorem 2.7. *(Balachandran et al. 2013) The linear control system (2.23) is controllable on* $[t_0, t_1]$ *if and only if the controllability Grammian matrix*

$$M = \int_{t_0}^{t_1} (t_1-\tau)^{(\alpha-1)} E_{\alpha,\alpha}(A(t_1-\tau)^\alpha)BB^T \times E_{\alpha,\alpha}(A^T(t_1-\tau)^\alpha) \tag{2.41}$$

is positive definite, for some $t_1 > t_0$.

2.4 Fractional-order control

The fractional controllers are defined by irrational continuous transfer functions, in the Laplace domain. Therefore, when analyzing fractional systems, we usually adopt continuous or discrete integer-order approximations of fractional-order operators.

The fact that the integer-order dynamic models are more used is probably due to the absence of analytical solution methods for fractional differential equations. For example, PID controllers, which have been dominating industrial controllers, have been modified using the notion of a fractional-order integrator and differentiator. It has been shown that two extra degrees of freedom from the use of a fractional-order integrator and differentiator make it possible to improve the performance of traditional PID controllers (Podlubny *et al.* 1997) further. Also, the plant to be controlled can also be modeled as a dynamic system described by a fractional differential equation.

In theory, control systems can include both the fractional-order dynamic system or plant to be controlled and the fractional-order controller. However, in control engineering, it is a common practice to consider only the fractional-order controller, because the plant model may have already been obtained as an integer-order model. In most cases, the objective is to apply fractional-order control to improve system control performance.

In the last decades, fractional systems start to get significant attention in engineering, physics, biology, economics, control among others fields, due to the new possibilities which fractional calculus brings into the modeling of complex phenomena and their richer dynamics and flexibility (Bassingthwaighte *et al.* 1994, Herrmann 2011, Ortigueira 2011).

In control engineering, this tool has been employed for a great variety of controller designs. For example, the fractional-order $PI^{\lambda}D^{\delta}$ controller was proposed in (Podlubny 1999b) as a generalization of the PID controller with integrator of real order λ and differentiator of real order δ. There are many other modification of the fractional $PI^{\lambda}D^{\delta}$ controller, like CRONE control (Oustaloup *et al.* 1993), fractional lead-lag compensator (Raynaud 2000). Also we can see applied to advance control schemes like sliding mode control (Zhang and Yang 2012), fractional adaptive control (Vinagre *et al.* 2002, Duarte-Mermoud and Aguila-Camacho 2011, Shi *et al.* 2014, Wei *et al.* 2014, Chen *et al.* 2016, Wei *et al.* 2015, Wei *et al.* 2016, Wei *et al.* 2015, Aguila-Camacho and Duarte-Mermoud 2016) and fractional optimal control (Djennoune and Bettayeb 2013). In these applications, fractional differentiation is used to model phenomena that exhibit non-standard dynamical behavior, with a long memory or hereditary effects (Herrmann 2011, Sun *et al.* 2011).

Another important research topic that has helped to the development of fractional control is the stability of fractional systems (Li *et al.* 2010, Diethelm 2010, Li and Zhang 2011, Aguila-Camacho *et al.* 2014, Padula and Visioli 2015) that has been growing over the past decades.

Chapter 3

Lyapunov Theory for Fractional-order Systems

For nonlinear systems, Lyapunov's direct method provides a way to analyze the stability of a system without explicitly solving the differential equations. The method generalizes the idea which shows that the system is stable if there is a Lyapunov function for the system. This method is one of the most useful tools to analyze the stability of adaptive systems, make him essential in the study of these systems.

In this Chapter the basic concepts of the Lyapunov direct method for fractional-order systems are presented.

3.1 Preliminaries

One of the classical analysis techniques, which is still widely used in the analysis of stability and stabilization problems is the Lyapunov method. Many problems have been approached by restricting the search of a candidate functions to quadratic polynomials of the state variables, this makes the problem tractable and can often result in linear matrix inequalities that can be solved easily. However, if the quadratic Lyapunov candidate cannot be found, it is not possible to say that the system is unstable as there might be other nonlinear function that proves the stability of the system. The choice of the Lyapunov candidate function for such cases is very elusive and in general, depends on the intuition of the designer.

The Lyapunov candidate function in a sense gives the energy of a system qualitatively.

If the first derivative of a Lyapunov function is less than zero, then it implies that the system is a dissipative one and would lose energy in a finite time, hence proving that it is stable. However, we can consider the fractional-order derivative of the Lyapunov function, and this would indicate the rate at which the dissipation of energy is occurring in the system. Then the dissipation is not constrained to only an exponential decay and can follow a generalized power law curve. This type of slow dissipation may be desirable in many applications, adding an extra degree of flexibility.

The Lyapunov direct method is a sufficient condition to show the stability of nonlinear systems, which means the system may still be stable, even if one cannot find a Lyapunov function candidate to conclude the system stability.

In this section, we give the basics definitions needed for the Lyapunov direct method (also called Lyapunov´s first method).

Definition 3.1. *A continuos function* $\varphi : [0, r] \mapsto \mathbb{R}_+$ *(or a continuous funtion* $\varphi : [0, \infty] \mapsto \mathbf{B}_+$*) is said to belong to class* $\mathcal{K}$ *if*

1. $\varphi(0) = 0$
2. φ *is strictly increasing on* $[0, r]$ *(or on* $[0, \infty]$*).*

Definition 3.2. *A continuos function* $\varphi : [0, \infty] \mapsto \mathbb{R}_+$ *is said to belong to class* $\mathcal{KR}$ *if*

1. $\varphi(0) = 0$
2. φ *is strictly increasing on* $[0, \infty]$
3. $lim_{r\to\infty}\varphi(r) = \infty$

Definition 3.3. *A function* $V(t, x) : \mathbb{R}_+ \times \mathcal{B}(r) \mapsto \mathbb{R}$ *with* $V(t, 0) = 0\ \forall t \in \mathbb{R}_+$ *is* ***positive definite*** *if there exist a continuous function* $\varphi \in \mathcal{K}$ *such that* $V(t, x) \geq \varphi(|x|)\ \forall t \in \mathbb{R}_+$, $x \in \mathcal{B}(r)$ *and some* $r > 0$. $V(t, x)$ *is called negative definite if* $-V(t, x)$ *is positive definite.*

Definition 3.4. *A function* $V(t, x) : \mathbb{R}_+ \times \mathcal{B}(r) \mapsto \mathbb{R}$ *with* $V(t, 0) = 0\ \forall t \in \mathbb{R}_+$ *is said to be* ***positive (negative) semidefinite*** *if* $V(t, x) \geq 0$ *(*$V(t, x) \leq 0$*) for all* $r \in \mathbb{R}_+$ *and* $x \in \mathcal{B}(r)$ *for some* $r > 0$.

Definition 3.5. *A function* $V(t, x) : \mathbb{R}_+ \times \mathcal{B}(r) \mapsto \mathbb{R}$ *with* $V(t, 0) = 0\ \forall t \in \mathbb{R}_+$ *is said to be* ***decrescent*** *if there exist* $\varphi \in \mathcal{K}$ *such that* $|V(t, x)| \leq \varphi(|x|)\ \forall t \geq 0$ *and* $\forall x \in \mathcal{B}(r)$ *for some* $r > 0$.

Definition 3.6. *A function $V(t,x) : \mathbb{R}_+ \times \mathbb{R}^n \mapsto \mathbb{R}$ with $V(t,0) = 0$ $\forall t \in \mathbb{R}_+$ is said to be* ***radially unbounded*** *if there exist $\varphi \in \mathcal{KR}$ such that $V(t,x) \geq \varphi(|x|)$ for all $x \in \mathbb{R}^n$ and $t \in \mathbb{R}_+$*

Other important concepts are the positive realness (PR) and strictly positive realness (SPR). According to (Ladaci *et al.* 2007, Ladaci *et al.* 2009) this concepts for integer-order systems are valid for fractional-order commensurate systems with $\alpha \in (0,1)$.

Definition 3.7. *The $m \times m$ transfer function matrix $G(s)$ is called strictly positive real* ***(SPR)*** *if*

1. *All elements of $G(s)$ are analytic in $\mathbb{R} \geq 0$.*
2. *$G(s)$ is real for real s.*
3. *$G(s) + G^{T*}(s)$ for $\mathbb{R} \geq 0$ and finite s.*

A nonlinear fractional-order system can be described as (Podlubny 1999b)

$$ {}_{t_0}D_t^{\alpha} x(t) = f(x,t), \tag{3.1}$$

with initial conditions $x(t_0)$, where D denotes the Caputo fractional operator, $\alpha \in (0,1)$, $f : \Omega \times \mathbb{R}_+ \to \mathbb{R}^n$ is piecewise continuous in t and locally Lipschitz in x on $\Omega \times \mathbb{R}_+$, and $\Omega \in \mathbb{R}^n$ is a domain that contains the origin $x = 0$.

When $\alpha \in (0,1)$, the fractional-order system (3.1) has the same equilibrium points as the integer-order system $\dot{x} = f(t,x)$ (Li *et al.* 2010).

Definition 3.8. *(Li et al. 2009) The constant x_0 is an equilibrium point of Caputo fractional dynamical system (3.1), if and only if $f(t,x_0) = 0$.*

Theorem 3.1. *(Existence and uniqueness Theorem (Podlubny 1999b)) Let $f(t,x)$ be a real-valued continuous function, defined in the domain G, satisfying the Lipschitz condition with respect to x, i.e.*

$$|f(t,x_1)| - f(t,x_2)| \leq l|x_1 - x_2|,$$

where l is a positive constant, such that

$$|f(t,x) \leq M \leq \infty \;\; \forall (t,x) \in G.$$

Let also

$$K \geq \frac{Mh^{\sigma_n - \sigma_1 + 1}}{\Gamma(1+\sigma_n}$$

Then there exists in a region $R(h, K)$ *a unique and continuous solution* $y(t)$ *of the following initial-value problem,*

$$ {}_{t_0}D_t^{\sigma_k} x(t) = f(t, x) \tag{3.2}$$

$$[{}_{t_0}D_t^{\sigma_k} x(t)]_{t=0} = b_k, \quad k = 1, 2, ..., n, \tag{3.3}$$

where

$$ {}_{t_0}D_t^{\sigma_k} \equiv_{t_0} D_t^{\alpha_k} \; {}_{t_0}D_t^{\alpha_{k-1}} ... {}_{t_0}D_t^{\alpha_1};$$

$$ {}_{t_0}D_t^{\sigma_{k-1}} \equiv_{t_0} D_t^{\alpha_{k-1}} \; {}_{t_0}D_t^{\alpha_{k-2}} ... {}_{t_0}D_t^{\alpha_1};$$

$$\sigma_k = \sum_{j=1}^{k} \alpha_j \quad (k = 1, 2, ...n);$$

$$0 < \alpha < 1, \quad (j = 1, 2, ...n);$$

Then if $f(t, x)$ is locally bounded and is locally Lipschitz in x implies the existence and uniqueness of the solution to the Caputo fractional-order system (3.1).

Lemma 3.1. *(Li et al. 2009) For the real-valued continuous* $f(t, x)$ *in (3.1), we have* $\|_{t_0} D_t^{\alpha} f(x,t) \| \leq_{t_0} D_t^{-\alpha} \| f(x,t) \|$*, where* $\alpha \geq 0$ *and* $\| \cdot \|$ *denotes and arbitrary norm.*

Theorem 3.2. *(Li et al. 2010) If* $x = 0$ *is an equilibrium point of the system (3.1),* f *is Lipschitz on* x *with Lipschitz constant* l *and is piecewise continuous with respect to* t*, then the solution of (3.1) satisfies*

$$\| x(t) \| \leq \| x(t_0) \| E_{\alpha}(l(t-t_0)^{\alpha}), \tag{3.4}$$

where $\alpha \in (0, 1)$.

Lemma 3.2. *(Fractional comparison principle (Li et al. 2010)) Let* ${}_{t_0}D_t^{\alpha} x(t) \geq_{t_0} D_t^{\alpha} y(t)$*,* $\alpha \in (0, 1)$*, and* $x(t_0) = y(t_0)$*. Then* $x(t) \geq y(t)$*.*

3.2 Mittag-Leffler stability

Mittag-Leffler stability is a more general type of stability, whose decay is represented by a Mittag-Leffler function, which has as special cases the t^{α} stability and exponential stability (Li *et al.* 2009, Yua *et al.* 2013).

Definition 3.9. *(Mittag-Leffler stability (Li et al. 2009)) The solution of (3.1) is said to be Mittag-Leffler stable if*

$$\parallel x \parallel \leq m[x(t_0)]E_\alpha(-\lambda(t-t_0)^\alpha)^b, \tag{3.5}$$

where t_0 is the initial time, $\alpha \in (0,1)$, $\lambda > 0$, $b > 0$, $m(0) = 0$, $m(x) \geq 0$, and $m(x)$ is locally lipschitz on $x \in \mathbb{B} \in \mathbb{R}^n$ with Lipschitz constant m_0

It is worth noticing that Mittag-Leffler stability implies asymptotic stability.

3.3 Extension of the Lyapunov direct method

The idea behind the Lyapunov direct method is to search for a Lyapunov candidate function for a given nonlinear system, and if such function exists, the system is stable.

The Lyapunov direct method is a sufficient condition, so if we cannot find a Lyapunov candidate function to conclude the system stability, the system may still be stable, and it cannot conclude that the system is unstable.

Next, an extension of the Lyapunov direct method for fractional-order systems is presented.

Theorem 3.3. *(Fractional-order extension of Lyapunov direct method (Li et al. 2010)) Let $x = 0$ be an equilibrium point for the fractional-order system (3.1) and $\mathbb{D} \subset \mathbb{R}^n$ be a domain containing the origin. Let $V(t, x(t)) : [0, \infty) \times \mathbb{D} \to \mathbb{R}$ be a continuously differentiable function and locally Lipschitz with respect to x such that*

$$\gamma_1 \parallel x \parallel \leq V(t, x(t)) \leq \gamma_2 \parallel x \parallel^{ab} \tag{3.6}$$

$${}_{t_0}D_t^\alpha V(t, x(t)) \leq -\gamma_3 \parallel x \parallel^{ab} \tag{3.7}$$

where $t \geq 0$, $x \in \mathbb{D}$, $\alpha \in (0,1)$, γ_1, γ_2, γ_3, a and b are arbitrary positive constants. Then $x = 0$ is Mittag-Leffler stable. If the assumptions hold globally on $\mathbb{R}^n$, then $x = 0$ is globally Mittag-Leffler stable.

The idea of this fractional-order extension Lyapunov theorem is that the stability condition is derived by constructing a positive definite function V and calculating the fractional derivative of the function V.

Next is present a version of Theorem 3.3, that is useful for the analysis of adaptive systems, especially when ${}_{t_0}D_t^{\alpha}V(x,t)$ is negative semidefinite.

Theorem 3.4. *(Duarte-Mermoud et al. 2015) Let $x = 0$ be an equilibrium point for the non autonomous fractional-order system (3.1). Let us assume that there exists a continuous function $V(x,t)$ such that*

- *$V(x,t)$ is positive definite.*
- *${}_{t_0}D_t^{\alpha}(x,t)$, with $\alpha \in (0,1]$, is negative semidefinite.*

Then the origin of system (3.1) is Lyapunov stable. Furthermore, if $V(x(t),t)$ is decrescent, then the origin of system (3.1) is Lyapunov uniformly stable.

One of the most used Lyapunov candidate functions to analyze the stability of integer-order system are the quadratic functions. However, in the fractional case, the use of these functions are not immediate, since evaluating the fractional derivative of the Lyapunov candidate function, in general, involves the evaluation of infinite sums, which include higher order integrals and derivatives of the states of the fractional system, which is not an easy task (Aguila-Camacho *et al.* 2014).

Next, we present some inequalities that facilitate the use of quadratic Lyapunov candidate functions in the analysis of stability of fractional-order system using Lyapunov's direct method.

Lemma 3.3. *(Duarte-Mermoud et al. 2015) Let $x(t) \in \mathbb{R}^n$ be a vector of differentiable functions. Then, for any time instant $t \geq t_0$, the following relationship holds*

$$\frac{1}{2}\ {}_{t_0}D_t^{\alpha}(x^T(t)Px(t)) \leq x^T(t)P_{t_0}D_t^{\alpha}x(t) \tag{3.8}$$

where $P \in \mathbb{R}^{nxn}$ is a constant, square, symmetric and positive definite matrix.

Lemma 3.4. *(Duarte-Mermoud et al. 2015) Let $A(t) \in \mathbb{R}^n$ be a time varying differentiable matrix. Then, for any time instant $t \geq t_0$, the following relationship holds*

$${}_{t_0}D_t^{\alpha}[tr(A^T(t)PA(t))] \leqslant 2tr(A^T(t)_{t_0}PD_t^{\alpha}A(t)),\ \forall \alpha \in (0,1] \tag{3.9}$$

A more extense review on fractional-order Lyapunov theory can be consulted in (Gallegos and Duarte-Mermoud 2016b, Gallegos and Duarte-Mermoud 2016a).

3.4 Extension of the Barbalat Lemma

The stability of fractional nonlinear systems and time-varying can be studied using the extension of the Lyapunov direct method for fractional systems. Using this technique is usually a difficult task, since finding a Lyapunov function for the fractional case is more complicated than in the integer-order case. Also, when a candidate function of Lyapunov is found, in most cases (especially in adaptive control), the derivative is only semi-definite negative, which assures the stability of the system but not the convergence of the states of the system (or the error of the system).

For the integer-order systems, the Barbalat lemma and some of its corollaries are used to conclude the convergence of a function to zero based on some conditions of the integer-order integral of the function. However, in fractional systems, it is usually more complicated to establish conditions on the integer integral of the function, and it can be challenging to use these tools.

In the literature has been proposed some extensions of the Barbalat lemma, a preliminary version of the extension proposed in this work was published in (Navarro-Guerrero and Tang 2015), and a version with an improve proof was published in (Navarro-Guerrero and Tang 2017b). This extension of the Barbalat lemma is very useful to conclude the convergence of the error in fractional-order adaptive systems.

Next, this extension is presented.

Lemma 3.5. *Let $f : \mathbb{R} \to \mathbb{R}_+$ be a function uniformly continuous, and ${}_{t_0}I_t^{\alpha}$ given by the Riemann-Liouville integral with $\alpha \in (0,1)$.*

If $\lim\limits_{t\to\infty} {}_{t_0}I_t^{\alpha} f(t)$ exists and is finite, then $f(t) \to 0$, as $t \to \infty$.

Proof. By contradiction, assume that $f(t)$ does not go to zero as $t \to \infty$. Then exist $\epsilon > 0$, an increasing time sequence $\{t_i\}_{i\in N_+}$, with $t_1 > 0$, $t_{i+1} = t_i + T_i$ for some $T_i > 0$ and a $T > 0$ such that $\forall t_i > T$, $f(t_i) \geq \epsilon$. As $f(t)$ is uniformly continuous there exists $\delta > 0$ such that

$f(t) > \epsilon/2,\ \forall\, t \in [t_i, t_i+\delta]$. Now consider the Riemann-Liouville fractional integral

$$\begin{aligned}
\Gamma(\alpha)_{t_0}I_t^\alpha f(t) &= \int_{t_0}^{t} \frac{f(\tau)}{(t-\tau)^{1-\alpha}}d\tau \\
&= \int_{t_0}^{t-1} \frac{f(\tau)}{(t-\tau)^{1-\alpha}}d\tau + \int_{t-1}^{t} \frac{f(\tau)}{(t-\tau)^{1-\alpha}}d\tau \\
&\geq \int_{t_0}^{t-1} \frac{f(\tau)}{(t-\tau)^{1-\alpha}}d\tau \\
&\geq \int_{t_0}^{t-1} \frac{f(\tau)}{t_i^{1-\alpha}}d\tau \\
&\geq \frac{\epsilon\delta}{2}\sum_{i=1}^{N}\frac{1}{t_i^{1-\alpha}},
\end{aligned} \tag{3.10}$$

where $N = max\{i | t_i \leq t-1\}$. Define $S_N = \sum_{i=1}^{N}\frac{1}{t_i^{1-\alpha}}$ then

$$\begin{aligned}
S_N &= \sum_{i=1}^{N}\frac{1}{t_i^{1-\alpha}} \\
&= \frac{1}{t_1^{1-\alpha}}\left\{1 + \frac{1}{(1+\frac{T_1}{t_1})^{1-\alpha}} + \frac{1}{(1+\frac{T_1+T_2}{t_1})^{1-\alpha}} + ... + \frac{1}{(1+\frac{\sum_{j=1}^{N}T_j}{t_1})^{1-\alpha}}\right\}.
\end{aligned} \tag{3.11}$$

Let's consider first the case $T_i < \infty,\ \forall i \in N_+$. In this case, let $T_{max} = \max_{i\in N_+}\{T_i\}$ and $t_1 > \max\{T_{max},\ T\}$. Then

$$1 + \frac{\sum_{j=1}^{n}T_j}{t_1} \leq 1 + n\frac{T_{max}}{t_1} < 1+n,\ \forall n \in N_+. \tag{3.12}$$

Therefore

$$(1 + \frac{\sum_{j=1}^{n}T_j}{t_1})^{1-\alpha} \leq (1 + \frac{\sum_{j=1}^{n}T_j}{t_1}) < 1+n,\ \forall n \in N_+. \tag{3.13}$$

This implies that

$$S_N > \frac{1}{t_1^{1-\alpha}}\left\{1 + \frac{1}{1+1} + ... + \frac{1}{1+N}\right\} \to \infty, \quad N \to \infty. \tag{3.14}$$

This together with (3.10) implies that $\lim\limits_{t\to\infty} {}_{t_0}I_t^\alpha f(t)$ is unbounded, which is a contradiction.

For the case $T_i \to \infty$ as $i \to \infty$, it implies that $f(t_i) \to 0$ as $i \to \infty$, which is again a contradiction. □

Chapter 4

Fractional-order Model Reference Adaptive Control

Adaptive control consists in adapting in real time the controller's parameters in response to the plant variations to ensure stability and constant performance. Since its apparition half a century ago, adaptive control maintains interest in the automatic control community with a significant number of papers and many publications of specialized books every year.

In model reference adaptive control the desired performance of the closed-loop system is expressed in terms of a reference model, that describe the desired input-output properties, and the parameters of the controller are adjusted based on the error between the reference model output and the output of the system.

In this chapter, is presented the methodology based on the Lyapunov direct method for the design of fractional-order model reference adaptive control (FOMRAC) schemes.

4.1 Model reference adaptive control

The adaptive control techniques were developed during the 1960s (Whitaker 1959, Osborn *et al.* 1961). These developments did not catch the attention because at the time there was not very much knowledge on stability analysis of controllers with nonstationary parameters, and modern methods of stability analysis that had been developed by Lyapunov at the start of the 19th century were not broadly known. After the initial problems with adaptive control techniques of the 1960s, stability analysis has become a center point in new developments related to adaptive control.

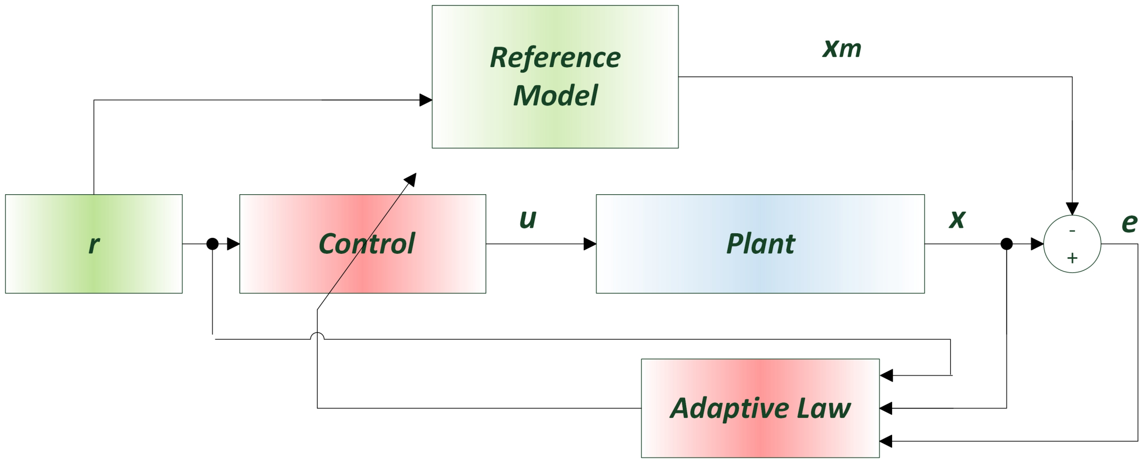


Figure 4.1: Direct MRAC scheme

New tools and techniques have been used or developed explicitly for rigorous stability analysis and the finally led to successful proofs of stability, mainly based on the Lyapunov approach.

The standard adaptive control methodology is the MRAC (Fig. 4.1) approach that, as its name states, the plant follows the behavior of a reference model which represent the desired performance.

Consider the LTI system

$$\dot{x}(t) = Ax(t) + Bu(t), \tag{4.1}$$

$$y(t) = Cx(t). \tag{4.2}$$

and the reference model

$$\dot{x}_m(t) = A_m x_m(t) + B_m r(t), \tag{4.3}$$

$$y_m(t) = C_m x_m(t). \tag{4.4}$$

The control signals that feed the plant is a linear combination of the state variables

$$u(t) = \sum k_{xi} x_i(t) + \sum k_{ui} r_i(t) = K_x x(t) + K_u r(t). \tag{4.5}$$

If the plant parameters were fully known, one could compute the corresponding controller gains that would force the plant to asymptotically behave exactly as the reference model, or

$$x(t) \to x_m(t), \tag{4.6}$$

and

$$y(t) \to y_m(t). \tag{4.7}$$

When the plant parameters are not known, one could think of the use of adaptive gains. The idea is that the plant is fed a control signal that is a linear combination of the model states through some gains. If all gains are correct, the entire plant state vector will follow the model reference exactly. However, if not all gains are correct, the plant does not exactly behave such as the model reference, and its measured output differs from the output of the model reference. The resulting tracking error is given by

$$e(t) = x_m(t) - x(t), \tag{4.8}$$

and can be monitored and used to generate the adaptive gains. Then the basic idea of adaptation is the following: assume that one component of the control signal (4.5) that is fed to the plant is coming from the variable x_i through the gain k_{xi}. If the gain is not perfectly correct, this component contributes to the tracking error, and therefore, the tracking error and the component x_i are correlated. This correlation is used to generate the adaptive gain

$$\dot{k}_{xi}(t) = \gamma_{xi} e(t) x_i \tag{4.9}$$

$$\dot{k}_{ui}(t) = \gamma_{ui} e(t) r_i \tag{4.10}$$

where γ_{*i} is the adaptation gain, a parameter that affects the rate of adaptation. The adaptation continues until, under appropriate conditions, the correlation diminishes and ultimately vanishes, and therefore, the gain derivative tends to zero, and the gain itself is supposed to go to a constant value. In vectorial form,

$$\dot{K}_x(t) = \sum \gamma_{xi} e(t) x_i = e(t) x^T(t) \Gamma_x, \tag{4.11}$$

$$\dot{K}_u(t) = \sum \gamma_{ui} e(t) r_i = e(t) r^T(t) \Gamma_u, \tag{4.12}$$

$$u(t) = K_x(t)x(t) + K_u r(t) \tag{4.13}$$

This basic approach was able to generate the first rigorous proof of stability that showed that not only the tracking error but even the entire state error asymptotically vanishes. This result implied that the plant behavior would asymptotically reproduce the stable model behavior and would ultimately achieve the desired performance represented by the ideal model reference. In particular, the Lyapunov stability technique revealed the prior conditions that had to be satisfied to guarantee stability and allowed getting rigorous proofs of stability of the adaptive control system.

In practice only a nominal model of the real-world plant is usually available for the control design and, furthermore, plant parameters may vary under various operational and environmental conditions. Therefore, adaptive control methodologies seemed to be the natural solution for these problems.

4.2 Fractional-order model reference adaptive control

Here we present the extension of the state-feedback MRAC for fractional-order systems previously reported in (Duarte-Mermoud *et al.* 2015). This result only concludes the boundedness of the closed-loop signals and the tracking error, but not the convergence of the tracking error.

In the following Theorem, we complement those results by applying the extension of the Barbalat's Lemma proposed (Lemma 3.5) and conclude the convergence of the tracking error to zero.

Theorem 4.1. *Consider the fractional-order system given by*

$$ {}_0D_t^{\alpha} x(t) = Ax + Bu, \quad x \in \mathbb{R}^n, \quad 0 < \alpha < 1, \tag{4.14}$$

where $A \in \mathbb{R}^{nxn}$, $B \in \mathbb{R}^{nxq}$ are unknown constant matrices, and the reference model

$$ {}_0D_t^{\alpha} x_m(t) = A_m x_m + B_m r, \tag{4.15}$$

where $A_m \in \mathbb{R}^{nxn}$ is Hurwitz, $B_m \in \mathbb{R}^{nxq}$ are design matrices, and $r \in \mathbb{R}^q$ is a bounded reference input vector, and the adaptive control law

$$u = -K(t)x + L(t)r, \tag{4.16}$$

where $K(t)$ and $L(t)$ are the estimates of the true parameters $K^* \in \mathbb{R}^{qxn}$, $L^*\mathbb{R}^{qxq}$ such that $A - BK^* = A_m$ and $BL^* = B_m$. And the adaptive laws

$${}_0D_t^{\alpha}\Phi(t) = -\gamma\Psi^T Pe, \tag{4.17}$$

where $P = P^T > 0$, and $\gamma > 0$ is the adaptation gain. Then all signals in the closed-loop system given by (4.14), (4.15), (4.16) and (4.17) are bounded $\forall t \leq 0$. Furthermore, the tracking error $e \to 0$ when $t \to \infty$.

Proof. Consider the tracking error $e = x - x_m$, and the error dynamics given by

$${}_0D_t^{\alpha}e = A_m e + \Psi^T\Phi \tag{4.18}$$

where $\Psi^T = [x \;\; r]$, $\Phi = [\Theta - \Theta_m] = \tilde{\Theta}$, $\Theta^T = [A - BK(t) \;\; BL(t)]$, $\Theta_m^T = [A_m \;\; B_m]$.

Consider the following Lyapunov candidate function

$$V(e, \Phi) = \frac{1}{2}\gamma e^T Pe + \frac{1}{2}\Phi^T\Phi. \tag{4.19}$$

Applying the Caputo derivative and Lemma 3.3 and substituting the error dynamics we have

$${}_0D_t^{\alpha}V(e, \Phi) \leq \gamma e^T[A_m^T P + PA_m]e + \gamma e^T P\Psi^T\Phi + \Phi_0^T D_t^{\alpha}\Phi,$$

since A_m is Hurwitz, there exists a matrix $Q = Q^T > 0$ such that $A_m^T P + PA_m = -Q$, then

$${}_0D_t^{\alpha}V(e, \Phi) \leq -\gamma e^T Qe + \gamma e^T P\Psi^T\Phi + \Phi_0^T D_t^{\alpha}\Phi, \tag{4.20}$$

we choose the update laws such that

$$\gamma e^T P\Psi^T\Phi + \Phi_0^T D_t^{\alpha}\Phi = 0, \tag{4.21}$$

then we have

$${}_0D_t^{\alpha}\Phi = -\gamma\Psi^T Pe. \tag{4.22}$$

Using the adaptive laws given by (4.22), then

$$ {}_0D_t^\alpha V(e,\Phi) \leq -\gamma e^T Q e \tag{4.23} $$

where $\gamma > 0$ is the adaptation gain. Since ${}_0D_t^\alpha V$ is negative semidefinite, from Theorem 3.4 the stability of the closed-loop can be concluded. So all the signals in the closed-loop are bounded.

Applying the fractional integral and Property 2.7

$$ {}_0I_t^\alpha e^T Q e \leq \frac{V(0)}{\gamma} \tag{4.24} $$

Then the integral (4.24) exist, and by Lemma 3.5 it concludes that the tracking error converge to zero when $t \to \infty$. □

4.2.1 Ilustrative example

In order to show the control scheme designed in Theorem 4.1 we carried out one simulation with following model reference

$$ \begin{aligned} D^{0.5}x_m(t) =& \begin{bmatrix} 0 & 1 \\ -10 & -5 \end{bmatrix} x_m + \begin{bmatrix} 0 \\ 2 \end{bmatrix} r, \\ y_m(t) =& [1 \;\; 0] x_m(t), \end{aligned} \tag{4.25} $$

and the plant

$$ \begin{aligned} D^{0.5}x(t) =& \begin{bmatrix} 0 & 1 \\ -6 & -7 \end{bmatrix} x + \begin{bmatrix} 0 \\ 8 \end{bmatrix} u, \\ y(t) =& [1 \;\; 0] x(t), \end{aligned} \tag{4.26} $$

with the update laws given by (4.17) with, $\gamma = 10$.

Fig. 4.2 shown the output of the reference model, the output of the adaptive system, the tracking error, and the controller parameters.

It can be observed that the scheme met the control objective and the tracking error $e \to 0$ when $t \to \infty$.

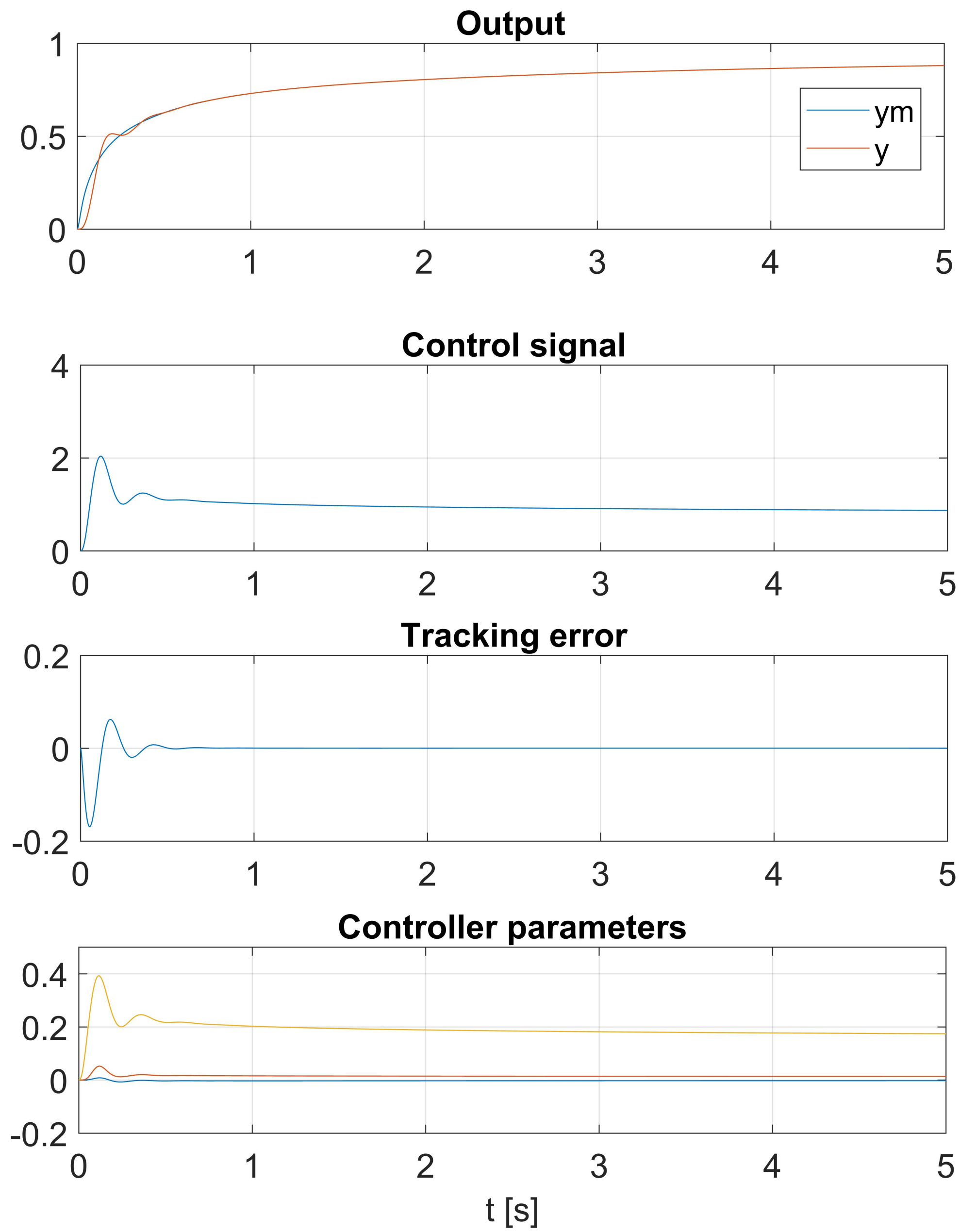


Figure 4.2: Simulations results of the FOMRAC scheme

4.3 Fractional-order closed-loop model reference adaptive control

One recent approach in adaptive control that improve transient behavior by using a closed-loop architecture for reference models is presented in (Gibson *et al.* 2013, Gibson *et al.* 2015). In this approach, the focus is adaptive systems with output-feedback where it is shown that such closed-loop reference models can lead to a separation principle based adaptive controller which is simpler to implement compared to the classical ones based on observers or filtered signals. The simplification comes with the use of the reference model states in the construction of the regressor and not the classic approach where the regressor is constructed from filtered plant inputs and outputs.

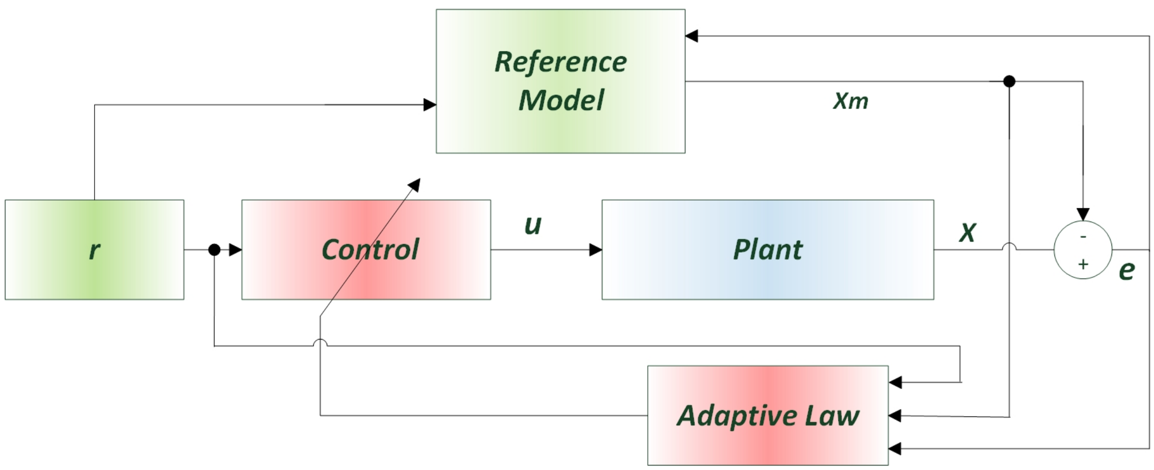


Figure 4.3: FOCMRAC scheme.

Next, the generalization of this scheme, denoted, fractional-order closed-loop model reference adaptive control (FOCMRAC) is presented. As far as the author's knowledge, this extension was not reported in literature until (Navarro-Guerrero and Tang 2017a).

Consider the fractional-order system given by

$$\begin{aligned} {}_0D_t^{\alpha}x(t) =& Ax(t) - B\Lambda u(t) \\ z(t) =& C^T x(t) \end{aligned} \tag{4.27}$$

where $x \in R^n$, $n \leq 2$, $u \in R$, and $z \in R$. A and Λ are unknown, B y C are known and only z is available for measurement.

The control objective is to design a control signal u such that x follow the state x_m of the reference model given by

$$\begin{aligned} {}_0D_t^{\alpha} x_m(t) =& A_m x_m(t) - Br(t) - L(z - z_m) \\ z_m(t) =& C^T x_m(t) \end{aligned} \tag{4.28}$$

where $r \in R$ is the reference signal and L is a feedback gain to be design.

The following assumptions are made:

- 1) The product $C^T B$ is full rank.
- 2) The pair A_m, C^T is observable.
- 3) The system in (4.27) is minimum phase.
- 4) There exist $\Theta^* \in R^{nx1}$ such that $A + B\Lambda\Theta^{*T} = A_m$ and $K^* \in R$ such that $\Lambda K^{*T} = I$ (*matching conditions*).
- 5) Λ is diagonal with positive elements.
- 6) The uncertain matching parameter Θ^*, and the input uncertainty matrix Λ have *a priori* a upper bounds.

$$\bar{\theta}^* \triangleq sup\|\Theta^*\| \quad y \quad \bar{\lambda} \triangleq sup\|\Lambda\| \tag{4.29}$$

Next, some results needed for the design and analysis of the control scheme are presented. The proofs can be found in (Gibson *et al.* 2015).

Lemma 4.1. *For the SISO case the system (4.27) satisfying the suppositions 1-3, there exist a L_s such that*

$$C^T(sI - A_m - L_s C^T)^{-1} B = \frac{a}{s + \rho} \tag{4.30}$$

where $\rho > 0$ is an arbitrary parameter and $a = C^T B$.

Lemma 4.2. *If L_s is chosen as (4.30) and $M \triangleq C^T B$, the SISO transfer function $M^T C^T (sI - A_m - L_s C^T)^{-1} B$ is SPR. Therefore, there exists $P = P^T > 0$ and $Q_s = Q_s^T > 0$ such that*

$$\begin{aligned} (A_m + L_s C^T)^T P + P(A_m + L_s C^T) =& -Q_s \\ PB =& CM \end{aligned} \tag{4.31}$$

Lemma 4.3. *Choosing $L = L_s - \rho B M^T$ where L_s is defined by (4.30) and is arbitrary, $\rho > 0$, the transfer function $M^T C^T (sI - A_m - LC^T)^{-1} B$ is SPR and satisfies*

$$\begin{aligned}(A_m + LC^T)^T P + P(A_m + LC^T) =& - Q \\ Q \triangleq& Q_s + 2\rho C M M^T C^T\end{aligned} \tag{4.32}$$

where P y Q_s are defined in (4.31) and $M = C^T B$.

Assuming that L is choose using the above lemmas, in the following theorem the adaptive scheme is formulated.

Theorem 4.2. *Consider the fractional-order system given by (4.27) satisfying assumptions 1-6 and the closed-loop model reference given by (4.28) and the control law*

$$u(t) = \Theta^T(t) x_m + K^T(t) r(t) \tag{4.33}$$

with adaptive laws

$$\begin{aligned}{}_0D_t^\alpha \Theta =& - \Gamma x_m e_y^T \\ {}_0D_t^\alpha K =& - \Gamma r(t) e_y^T\end{aligned} \tag{4.34}$$

where $e_y = C^T e$, $\Gamma > 0$. Then all the signals in the closed-loop system given by (4.27), (4.28), (4.33) and (4.34) are bounded $\forall t \geq 0$. Futhermore, the tracking error $e \to 0$ when $t \to \infty$.

Proof. From (4.27) , (4.28) and (4.33) the dynamic of the error $e = x - x_m$ is given by

$$\begin{aligned}{}_0D_t^\alpha e =& (A_m + LC^T)e + B\Lambda(\tilde{\Theta}^T x_m + \tilde{K}^T r) \\ e_y =& C^T e\end{aligned} \tag{4.35}$$

Consider the Lyapunov candidate function

$$V = \frac{1}{2} e^T P e + \frac{1}{2} tr\left(\frac{\tilde{\Theta}^T P \tilde{\Theta}}{\Gamma}\right) + \frac{1}{2} tr\left(\frac{\tilde{K}^T P \tilde{K}}{\Gamma}\right) \tag{4.36}$$

taking the Caputo derivative and applying lemma 3.3 and 3.4

$${}_0D_t^\alpha V \leq e^T P {}_0D_t^\alpha e + tr\left(\frac{\tilde{\Theta}^T P {}_0D_t^\alpha \tilde{\Theta}}{\Gamma}\right) + tr\left(\frac{\tilde{K}^T P {}_0D_t^\alpha \tilde{K}}{\Gamma}\right) \tag{4.37}$$

substitute (4.35), (4.31) and (4.32) we have

$$\begin{aligned} {}_0D_t^\alpha V \leq & -e^TQe + e^TPB\tilde{\Theta}^T x_m + e^TPB\tilde{K}^T r + \\ & + tr\left(\frac{\tilde{\Theta}^T P_0 D_t^\alpha \tilde{\Theta}}{\Gamma}\right) + tr\left(\frac{\tilde{K}^T P_0 D_t^\alpha \tilde{K}}{\Gamma}\right) \end{aligned} \tag{4.38}$$

using the properties of the operator $tr(*)$ and the fact that $e_y = C^T x$ and taking the adaptation laws as (4.34) we have

$${}_0D_t^\alpha V \leq -e^TQe \tag{4.39}$$

Given that $\gamma > 0$ and ${}_0D_t^\alpha V$ is negative semidefinite, From Theorem 3.4 It can be concluded the stability of the closed-loop system. Applying the fractional integral and property 2.7 to (4.39), we have

$${}_0I_t^\alpha e^TQe \leq V(0) \tag{4.40}$$

Then the fractional integral (4.40) exits, and by lemma 3.5 it concludes that the tracking error $e \to 0$ where $t \to \infty$.

□

4.3.1 Ilustrative example

We carried out one simulation to illustrate the scheme design in Theorem 4.1, with following model reference

$$\begin{aligned} D^{0.5}x_m(t) =& \begin{bmatrix} 0 & 1 \\ -10 & -5 \end{bmatrix} x_m(t) + \begin{bmatrix} 0 \\ 2 \end{bmatrix} r(r) + \begin{bmatrix} -10 \\ -2 \end{bmatrix} (y - y_m), \\ y_m(t) =& [1 \;\; 0] x_m(t), \end{aligned} \tag{4.41}$$

and the plant

$$\begin{aligned} D^{0.5}x(t) =& \begin{bmatrix} 0 & 1 \\ -6 & -7 \end{bmatrix} x(t) + \begin{bmatrix} 0 \\ 8 \end{bmatrix} u(t), \\ y(t) =& [1 \;\; 0] x(t), \end{aligned} \tag{4.42}$$

with the update laws given by (4.34) with, $\gamma = 10$.

Fig. 4.4 shown the output of the reference model, the output of the adaptive system, the tracking error, and the controller parameters.

It can be observed that the scheme met the control objective and the tracking error $e \to 0$ when $t \to \infty$.

4.4 Fractional-order parameter identifier with state feedback

Another important technique in adaptive systems is parameters estimation. In this section, we extend a parameter estimator with state measurement for fractional-order systems using the Lyapunov direct method.

Consider the plant given by

$$
{}_0D_t^{\alpha} x = A_p x + B_p u, \tag{4.43}
$$

where $x \in \mathbb{R}^n$ and $u \in \mathbb{R}^r$ are available for measurement, $A_p \in \mathbb{R}^{n\times n}$, $B_p \in \mathbb{R}^{n\times r}$ are unknown, A_p is stable, and u is bounded.

Consider the model

$$
{}_0D_t^{\alpha} \hat{x} = \hat{A}_p \hat{x} + \hat{B}_p u, \tag{4.44}
$$

where $\hat{A}_p(t)$, $\hat{B}_p(t)$ are the estimates of A_p, B_p, and $\hat{x}(t)$ is the estimate of the vextor $x(t)$.

Theorem 4.3. *Consider the system (4.43), the model (4.44) and the adaptive laws*

$$
\begin{aligned}
{}_0D_t^{\alpha} \hat{A}_p &= \gamma_1 \epsilon \hat{x}^T, \\
{}_0D_t^{\alpha} \hat{B}_p &= \gamma_2 \epsilon u^T,
\end{aligned} \tag{4.45}
$$

where γ_1, $\gamma_2 > 0$ are the adaptive gains, $\hat{A}_p(t)$, $\hat{B}_p(t)$ are the estimates of the parameters of (4.43) and the identification error is given by $\epsilon = x - \hat{x}$. Then the identification error $\epsilon \to 0$ as $t \to \infty$. Futhermore if the vector $[x^T, u^T]$ is of persistent exitation, then $\hat{A}_p \to A_p$ and $\hat{B}_p \to B_p$.

Proof. From (4.43) and (4.44) the identification error is given by

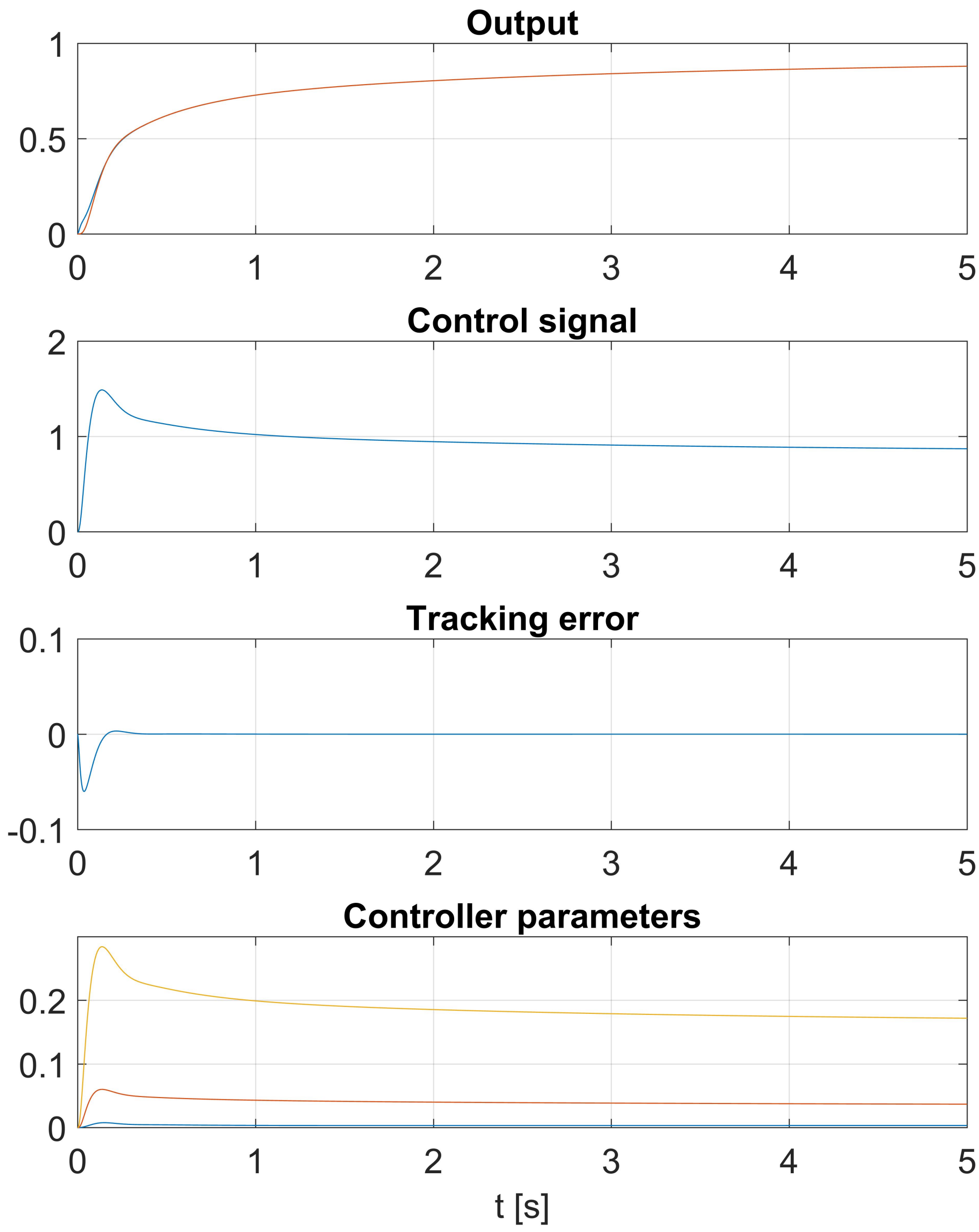


Figure 4.4: Simulations results of the FOCMRAC scheme

$$ {}_0D_t^{\alpha}\epsilon = A_p\epsilon - \tilde{A}_p\hat{x} - \tilde{B}_p u, \tag{4.46} $$

where $\tilde{A}_p - A_p$ and $\tilde{B}_p - B_p$.

Consider the Lyapunov candidate function

$$ V(\epsilon, \tilde{A}_p, \tilde{B}_p) = \frac{1}{2}\epsilon^T P\epsilon + \frac{1}{2}tr\left(\frac{\tilde{A}_p^T P\tilde{A}_p}{\gamma_1}\right) + \frac{1}{2}tr\left(\frac{\tilde{B}_p^T P\tilde{B}_p}{\gamma_2}\right), \tag{4.47} $$

where $tr(*)$ denotes the trace operator, γ_1, $\gamma_2 > 0$ are constants and $P = P^T > 0$ is chosen as the solution of the Lyapunov equation

$$ PA_p + A_p^T = -Q. \tag{4.48} $$

Taking the Caputo derivative (4.47) and applying the Lemmas 3.3 and 3.4 we have

$$ {}_0D_t^{\alpha}V \leq \epsilon^T P {}_0D_t^{\alpha}\epsilon + tr\left(\frac{\tilde{A}_p^T P {}_0D_t^{\alpha}\tilde{A}_p}{\gamma_1}\right) + \frac{1}{2}tr\left(\frac{\tilde{B}_p^T P {}_0D_t^{\alpha}\tilde{B}_p}{\gamma_2}\right), \tag{4.49} $$

substituting (4.46) we have □

$$ {}_0D_t^{\alpha}V \leq -\epsilon^T[PA_p + A_p^T P]\epsilon - \epsilon^T P\hat{A}_p\hat{x} - \epsilon^T P\hat{B}_p u + tr\left(\frac{\tilde{A}_p^T P {}_0D_t^{\alpha}\tilde{A}_p}{\gamma_1}\right) + \frac{1}{2}tr\left(\frac{\tilde{B}_p^T P {}_0D_t^{\alpha}\tilde{B}_p}{\gamma_2}\right), \tag{4.50} $$

using the $tr(*)$ operator properties we known that

$$ \begin{aligned} \epsilon^T P\hat{A}_p\hat{x} &= tr(\hat{A}_p^T P\epsilon\hat{x}^T) \\ \epsilon^T P\hat{B}_p u &= tr(\hat{B}_p^T P\epsilon u^T) \end{aligned} \tag{4.51} $$

substituting (4.51) in (4.50) we have

$$ {}_0D_t^{\alpha}V \leq -\epsilon Q\epsilon + tr\left(-\hat{A}_p^T P\epsilon\hat{x}^T + \frac{\tilde{A}_p^T P {}_0D_t^{\alpha}\tilde{A}_p}{\gamma_1}\right) + tr\left(-\hat{B}_p^T P\epsilon u^T + \frac{\tilde{B}_p^T P {}_0D_t^{\alpha}\tilde{B}_p}{\gamma_2}\right), \tag{4.52} $$

from (4.52) we need that the last two right-hand terms equal to zero, then choosing

$$ \begin{aligned} {}_0D_t^{\alpha}\tilde{A}_p &= {}_0D_t^{\alpha}\hat{A}_p = \gamma_1\epsilon\hat{x}^T, \\ {}_0D_t^{\alpha}\tilde{A}_p &= {}_0D_t^{\alpha}\hat{B}_p = \gamma_2\epsilon u^T, \end{aligned} \tag{4.53} $$

we have

$$ {}_0D_t^{\alpha} V \leq -\epsilon Q \epsilon \tag{4.54} $$

Since (4.54) is negative semidefinite from Theorem 3.4 the stability of the closed-loop system can be concluded.

Applying the Riemann-Liouville integral on both sides of the inequality (4.54) and Property 2.7 we have

$$ I^{\alpha} e^T Q e \leq V(0). \tag{4.55} $$

Then the integral (4.55) exist and by Lemma 3.5 it concludes that the identification error $e \to 0$ when $t \to \infty$.

4.4.1 Ilustrative example

To illustrate the identification scheme of Theorem 4.3 we carried out one simulation.

Consider the plant given by

$$ \begin{aligned} {}_0D_t^{0.8} x(t) &= \begin{bmatrix} -4 & 1 \\ -6 & 0 \end{bmatrix} x + \begin{bmatrix} 1 \\ 3 \end{bmatrix} u, \\ y(t) &= [1 \quad 0] x(t), \end{aligned} \tag{4.56} $$

and the update laws given by (4.45) with, $\gamma_1 = 50, \gamma_2 = 1$, and $u = 5sin(2.5t) + 6sin(5t)$.

Figure 4.5 shown the states of the plant, the states estimated and the errors. Figure 4.6 shown the parameters estimated, we can observe that the estimated parameters converge to the parameters of the plant.

4.5 Fractional-order parameter identifier without state feedback

The next identification scheme is an extension for fractional-order systems of the scheme presented in (Ioannou and Sun 1996). This identification scheme does not need state measurement and only used information of the input and output to construct the identifier. This

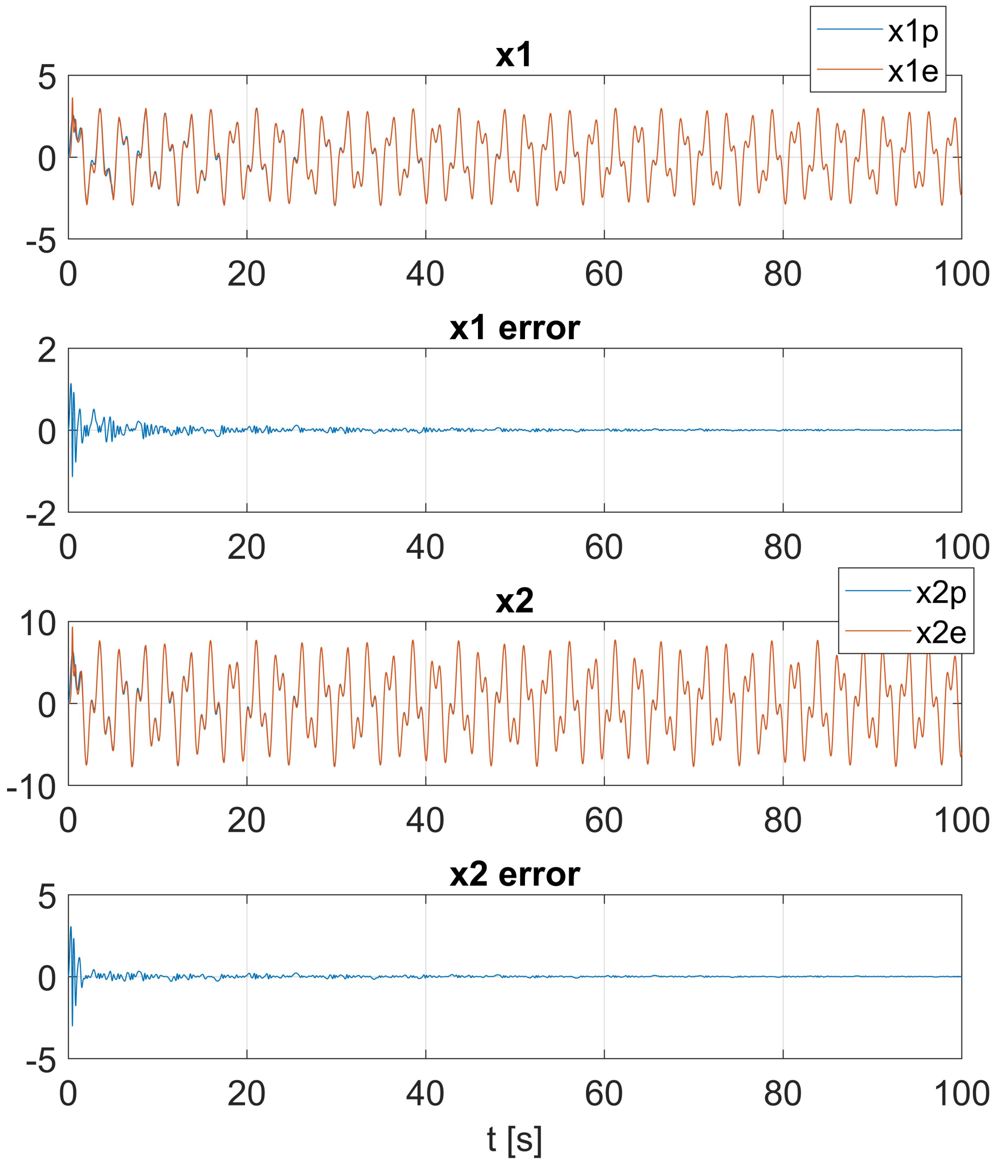


Figure 4.5: Identification scheme with state measurement, states and states error, where p and e indicates plant and estimate, respectively.

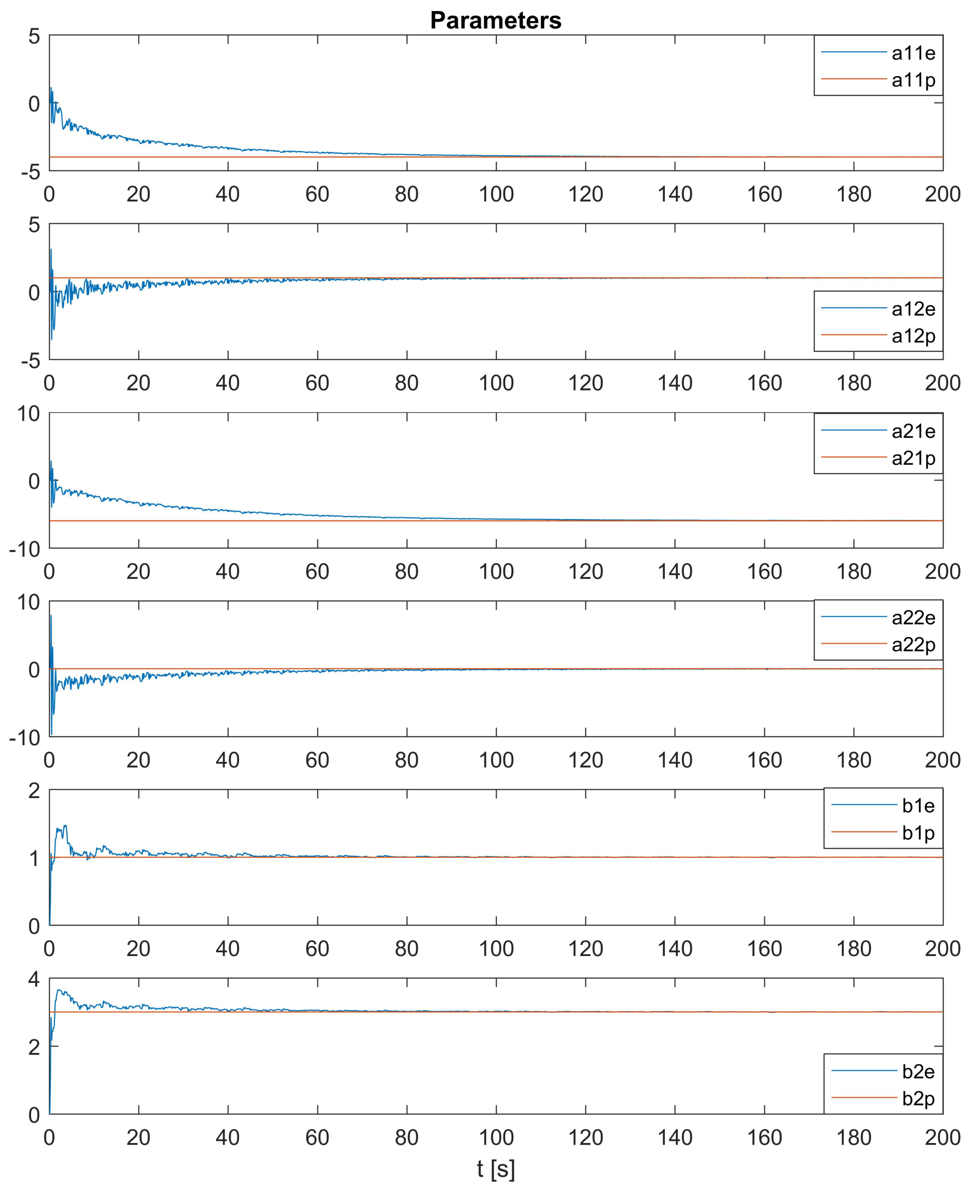


Figure 4.6: Identification scheme with state measurement, parameters estimates, where p and e indicates plant and estimate, respectively.

scheme will be used in our case of study, to shown that the fractional model proposed in the next section capture the behavior of the PK/PD model.

Consider the fractional-order commensurate SISO system

$$\begin{aligned} {}_0D_t^{\alpha} x =& Ax + Bu, \\ z =& C^T x, \end{aligned} \tag{4.57}$$

where $x \in R^n$, $n \leq 2$ and only y, u are available for measurement. The system (4.57) can be written as

$$z = \frac{B(\lambda)}{A(\lambda)} u = C^T (\lambda I - A)^{-1} B u, \tag{4.58}$$

where $\lambda = s^{\alpha}$ and α is the commensurate order with $0 < \alpha < 1$, and $A(\lambda), B(\lambda)$ are in the form

$$\begin{aligned} A(\lambda) =& \lambda^n + a_{n-1}\lambda^{n-1} + \cdots + a_1\lambda + a_0, \\ B(\lambda) =& b_m\lambda^m + b_{m-1}\lambda^{m-1} + \ldots b_1\lambda b_0, \end{aligned} \tag{4.59}$$

where the constants a_i, b_i for $i = 0, 1, 2, \ldots, n-1$ are the system parameters, $n \leq 2$ and $m \leq 1$. Now consider the linear parameterization of (4.58)

$$z = W(\lambda)\theta^{*T}\psi \tag{4.60}$$

where θ^{*T} is the parameter vector, ψ is the regressor that contains the filtered measurable signals u, y, $W(\lambda)$ is a proper stable transfer function.

$$\theta^* = [b_m, b_{m-1}, \ldots, b_0, a_{n-1}, a_{n-2}, \ldots, a_0]^T, \tag{4.61}$$

$$z = \frac{1}{\Lambda(\lambda)} y = \frac{\lambda^n}{\Lambda(\lambda)} y, \tag{4.62}$$

$$\phi = \left[\frac{\beta_{n-1}^T(\lambda)}{\Lambda(\lambda)} u, -\frac{\beta_{n-1}^T(\lambda)}{\Lambda(\lambda)} y \right], \tag{4.63}$$

$$\Lambda(\lambda) = \lambda^n + \eta_{n-1}\lambda^{n-1} + \eta_{n-2}\lambda^{n-2} + \cdots + \eta_0 \tag{4.64}$$

$$= \lambda^n + \eta^T \beta_{n-1}(\lambda). \tag{4.65}$$

With the parameterization (4.60) the signals z and ψ can be generated only with the information of u and y.

Because θ^* is a constant vector, we can write (4.60) in the form $z = W(\lambda)L(\lambda)\theta^{*T}\phi$, where $\phi = L^{-1}(\lambda)\psi$.

And $L(s)$ is chosen so that $L^{-1}(\lambda)$ is a proper stable transfer function and $W(\lambda)L(\lambda)$ is a proper SPR transfer function.

A state-space representation of the parameterization (4.60) is given by

$$\begin{aligned} {}_0D_t^{\alpha}\phi_1 &= \Lambda_c\phi_1 + lu, \\ {}_0D_t^{\alpha}\phi_2 &= \Lambda_c\phi_2 + ly, \\ z &= y + \beta_{n-1}^T\phi_2 = \theta^{*T}\phi \end{aligned} \tag{4.66}$$

where

$$\Lambda_c = \begin{bmatrix} -\eta_{n-1} & -\eta_{n-2} & \dots & -\eta_0 \\ 1 & 0 & \dots & 0 \\ \vdots & \ddots & & \vdots \\ 0 & \dots & 1 & 0 \end{bmatrix}, \ l = \begin{bmatrix} 1 \\ 0 \\ \vdots \\ 0 \end{bmatrix}, \tag{4.67}$$

because $\Lambda(\lambda) = det(\lambda I - \Lambda_c)$ and $\Lambda(\lambda)$ is stable, it follows that Λ_c is a stable matrix.

The state-space model (4.66) has the same input-output response as (4.57) and (4.58), provided that all state initial condition are $x_0 = 0$, $\phi_1 = \phi_2 = 0$.

Now the identification scheme is formulated by the following theorem.

Theorem 4.4. *Consider the system (4.57), the linear parameterization (4.60) and the the matrices A_c, B_c and C_c associate with the state-space system $W(\lambda)L(\lambda) = C_c^T(\lambda I - A_c)^{-1}B_c$, and the adaptive law*

$$ {}_0D_t^{\alpha}\hat{\theta} = \Gamma\epsilon\phi \tag{4.68}$$

where $\Gamma > 0$ is the adaptation gain and $\hat{\theta}$ are the estimates θ^* in (4.60) and the identification error is given by $e = z - \hat{z}$ and $\epsilon = C_c e$. Then the identification error $\epsilon \to 0$ as $t \to 0$.

Proof. The dynamics of the identification error is given by

$$ {}_0D_t^{\alpha} e = A_c e - B_c \tilde{\theta}\phi, \tag{4.69}$$

where the parameter error is defined as $\tilde{\theta} = \hat{\theta} - \theta^*$.

Consider the following Lyapunov candidate function

$$ V(\tilde{\theta}, e) = \frac{1}{2} e^T P_c e + \frac{1}{2}\tilde{\theta}^T \Gamma^{-1} \tilde{\theta}. \tag{4.70}$$

where $\Gamma = \Gamma^T > 0$ is a constant matrix and $P_c = P_c^T > 0$ satisfies the algebraic equation

$$ \begin{aligned} P_c A_c + A_c^T P_c &= -Q, \\ P_c B_c &= C_c. \end{aligned} \tag{4.71}$$

and applying the Caputo derivative to (4.70)

$$ \begin{aligned} {}_0D_t^{\alpha} V \leq & e^T P_c {}_0D_t^{\alpha} e + \tilde{\theta}^T \Gamma^{-1} {}_0D_t^{\alpha} \tilde{\theta} \\ \leq & e^T [P_c A_c + A_c^T P_c] e - e^T P_c B_c \tilde{\theta}\phi + \tilde{\theta}^T \Gamma^{-1} {}_0D_t^{\alpha} \tilde{\theta} \\ \leq & - e^T Q e - e^T P_c B_c \tilde{\theta}\phi + \tilde{\theta}^T \Gamma^{-1} {}_0D_t^{\alpha} \tilde{\theta} \end{aligned} \tag{4.72}$$

From (4.72) we need that

$$ - e^T P_c B_c \tilde{\theta}\phi + \tilde{\theta}^T \Gamma^{-1} {}_0D_t^{\alpha} \tilde{\theta} = 0, \tag{4.73}$$

from (4.71) we have $P_c B_c = C_c$ which implies that $e^T P_c B_c = \epsilon$, then (4.73) can be written as

$$ - \tilde{\theta}^T \phi \epsilon + \tilde{\theta}^T \Gamma^{-1} {}_0D_t^{\alpha} \tilde{\theta} = 0. \tag{4.74}$$

which leads to (4.68).

Let the adaptation law be given in (4.68), then

$$ {}_0D_t^{\alpha} V \leq -e^T Q e. \tag{4.75}$$

Since (4.75) is negative semidefinite from Theorem 3.4 the stability of the closed-loop system can be concluded.

Applying the Riemann-Liouville integral on both sides of the inequality (4.75) and Property 2.7 we have

$$I^{\alpha} e^T Q e \leq V(0). \tag{4.76}$$

Then the integral (4.76) exist and by Lemma 3.5 it concludes that the identification error $e \to 0$ when $t \to \infty$.

□

4.5.1 Ilustrative example

To illustrate the identification scheme of Theorem 4.4 we carried out one simulation.

$$\begin{aligned} D^{0.8}x(t) =& \begin{bmatrix} -4 & 1 \\ -6 & 0 \end{bmatrix} x + \begin{bmatrix} 1 \\ 3 \end{bmatrix} u, \\ y(t) =& [1 \;\; 0] x(t), \end{aligned} \tag{4.77}$$

with $\Lambda_c = \begin{bmatrix} -5 & -6 \\ 1 & 0 \end{bmatrix}$ and the update laws given by (4.68) with, $\Gamma = 10$ and $u = 5sin(2.5t) + 6sin(5t)$.

Figure 4.7 shown the output of the plant, the output estimated and the error. Figure 4.8 shown the parameters estimated, we can observe that the estimated parameters converge to the parameters of the plant with small oscillations around the real values, which is translated in a small identification error.

This is an example of the how the numerical approximation used affects the results of the simulations. This particular identification scheme is more demanding, computational-wise because it uses the filtered input and output signals to construct the regressor. The simulation uses 10 fractional integrators, using the crone approximation, with $n = 10$ and a bandwidth [0.01 100].

In the Figures 4.9-4.10 is shown the same simulation using the Matsuda approximation with $n = 50$ and a bandwidth [0.0001 10000]. We can observe that the overall performance improves, we obtain signals with fewer oscillations.

So we need to choose the numerical approximation that gives us the best result in the particular case studied.

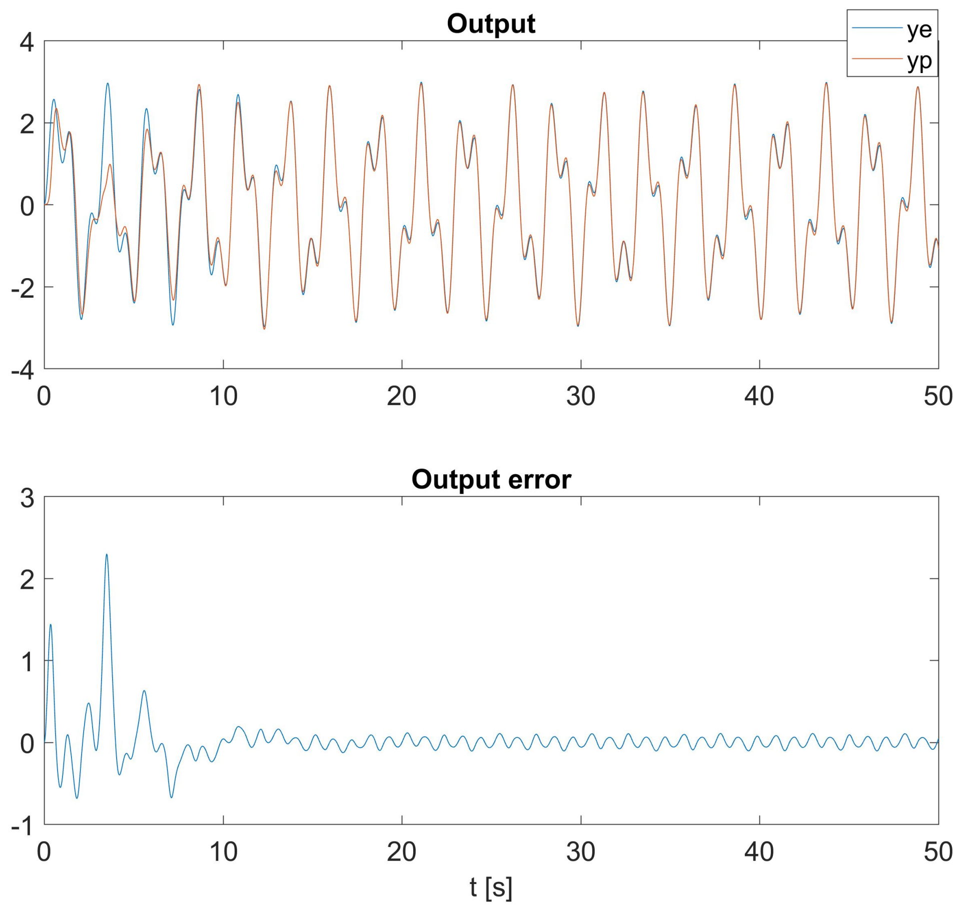


Figure 4.7: Identification scheme without state measurement, output and output error using the Crone approximation

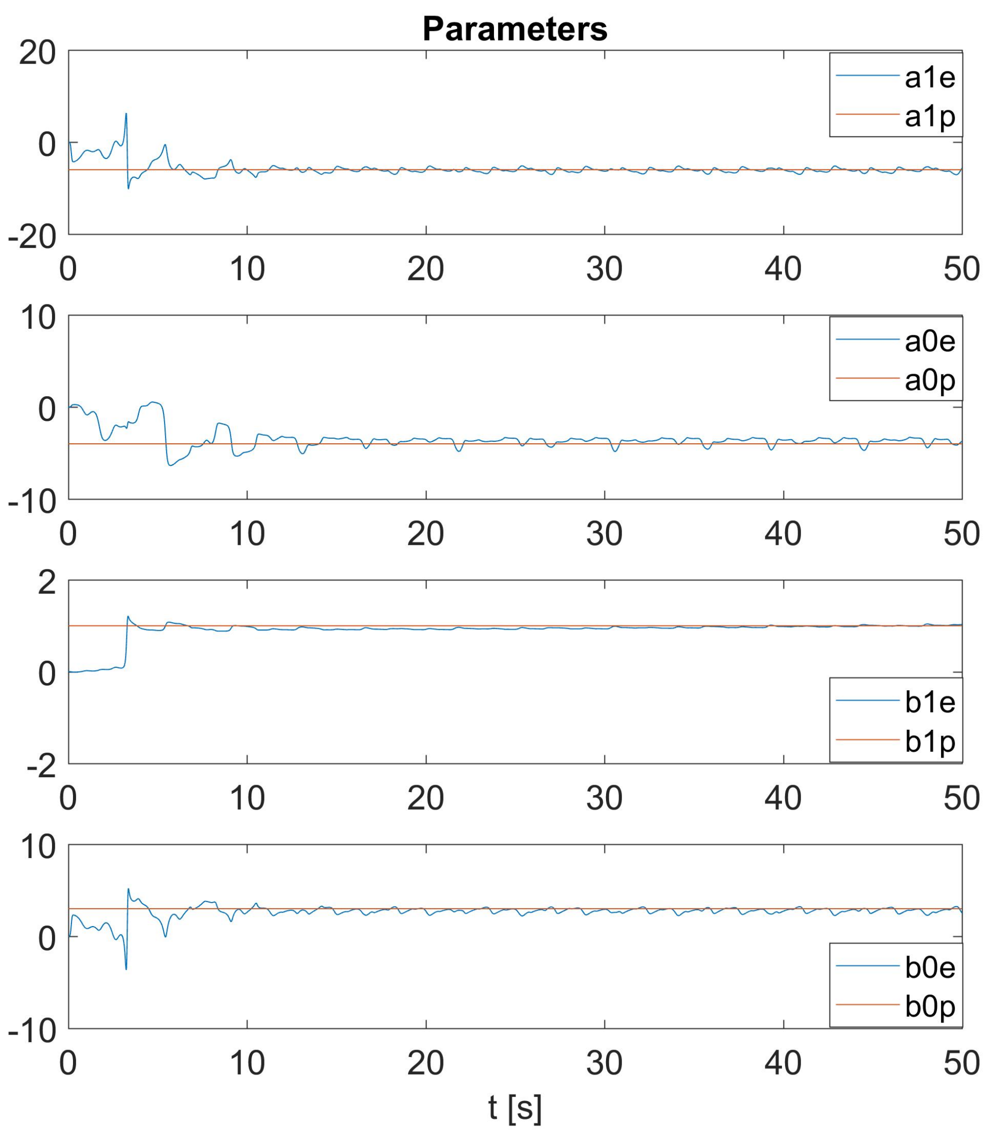


Figure 4.8: Identification scheme without state measurement, parameters estimates using the Crone approximation

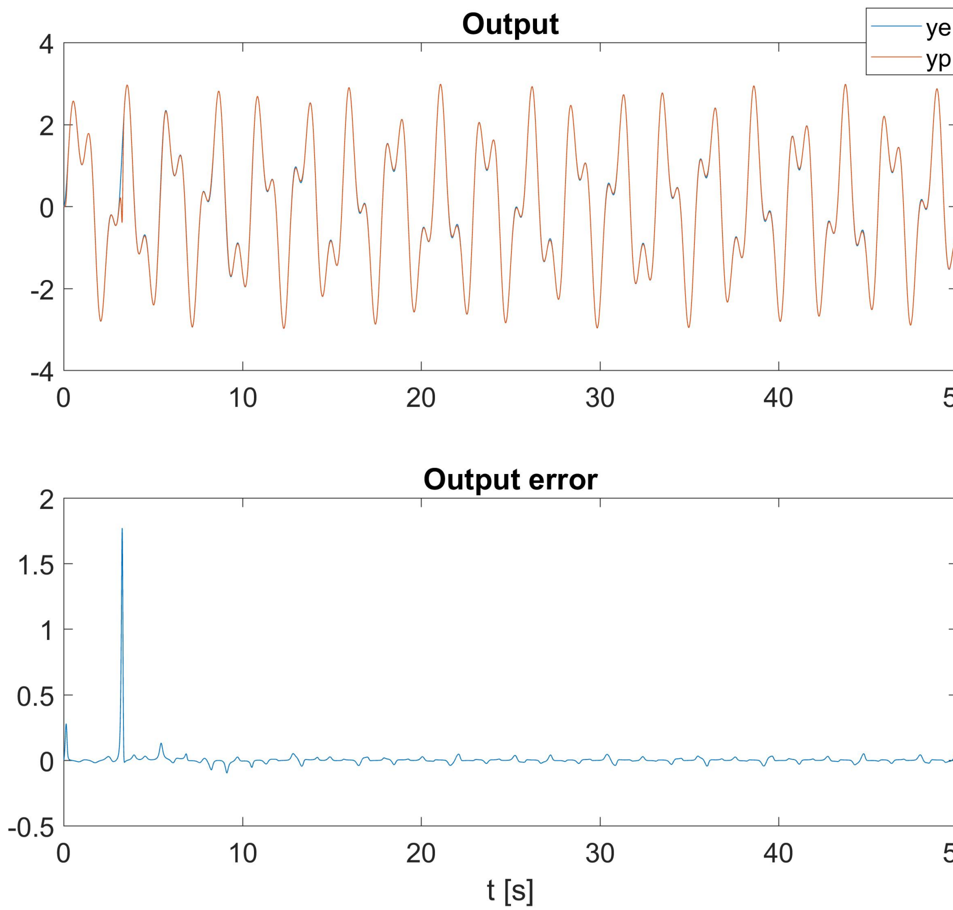


Figure 4.9: Identification scheme without state measurement, parameters estimates using the Matsuda approximation

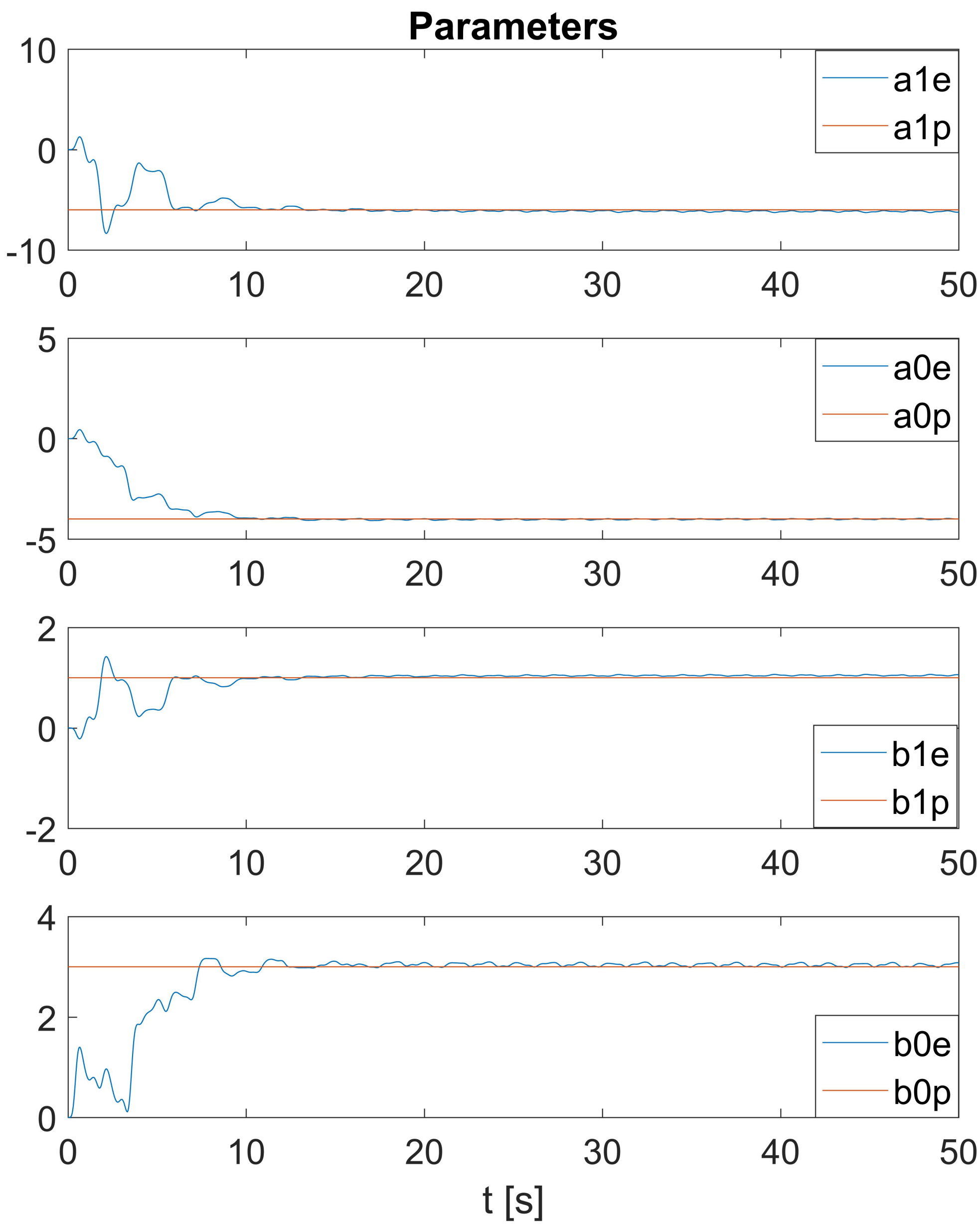


Figure 4.10: Identification scheme without state measurement, parameters estimates using the Matsuda approximation

4.6 Observer for fractional-order systems

The reconstruction of system states from its inputs and outputs has received a great deal of attention recently. In (Hartley and Lorenzo 2002, Doye *et al.* 2009) studied the fractional-order Luenberger observer and observer-based controller design, and in (Wei *et al.* 2015) present the design for a fractional-order adaptive observer.

Just as it is in integer-order system theory, it is important to create observers, or vector estimators, for fractional-order systems. This result has been previously reported in the literature (Hartley and Lorenzo 2002), but for completeness, we present this results because this observer can be used in conjunction with the FOMRAC with state feedback when the states are not available for measurement.

The fractional-order state estimator (Luenberger type observer) has the form

$$\begin{aligned} {}_0D_t^\alpha \hat{x}(t) =& A\hat{x} + Bu(t) - L(y(t) - \hat{y}(t)), \\ \hat{y}(t) =& C\hat{x}(t). \end{aligned} \tag{4.78}$$

The error $e(t)$ is defined as the difference between the real system output $x(t)$, and the estimated observer output $\hat{x}(t)$.

$$e(t) = x(t) - \hat{x}(t). \tag{4.79}$$

The observer error gain L is determined to force the error between the two plant vectors to go to zero. The dynamics of the error is obtained applying the fractional derivative to (4.79),

$${}_0D_t^\alpha e(t) = {}_0D_t^\alpha x(t) - {}_0D_t^\alpha \hat{x}(t). \tag{4.80}$$

Substituting the system equations from Equations (4.14) and (4.78) yields

$${}_0D_t^\alpha e(t) = [Ax + Bu(t)] - [A\hat{x} + Bu(t) - L(y(t) - \hat{y}(t))]. \tag{4.81}$$

Now replacing the measured system outputs, $y(t)$ and $\hat{y}(t)$ with the vector variables using (4.14) and (4.78), yields

$${}_0D_t^\alpha e(t) = [Ax + Bu(t)] - [A\hat{x} + Bu(t) - L(Cx(t) - C\hat{x}(t))]. \tag{4.82}$$

Replacing $e(t) = x(t) - \hat{x}(t)$, and combing terms, gives

$$ {}_0D_t^{\alpha} e(t) = (A - LC)e(t). \tag{4.83}$$

The matrix L is determined to force the observer error to zero by placing the eigenvalues of $A - LC$ in a stable region of the $w - plane$ using standard methods.

4.6.1 Ilustrative example

We carried out one simulation to illustrate the fractional-order observer.

Consider the plant

$$\begin{aligned} D^{0.5}x(t) =& \begin{bmatrix} 0 & 1 \\ -10 & -5 \end{bmatrix} x + \begin{bmatrix} 0 \\ 2 \end{bmatrix} u, \\ y(t) =& [1 \quad 0]x(t), \end{aligned} \tag{4.84}$$

with the matrix $(A - LC) = \begin{bmatrix} 5 & 1 \\ -15 & -5 \end{bmatrix}$ and $u = 5sin(2t)$.

Fig. 4.11 shown states of the plant, the states estimates and the evolution of the states error. We can observe that $\hat{x} \to x$ and $e \to 0$.

4.7 Fractional-Order Adaptive Observer

An adaptive observer can be built using the fractional-order Luenberger observer and a parameters identifier. In this case, the objective is to estimate both, the states and the parameters of the system.

Using the fractional-order Luenberger observer (4.78) and the parameter identifier given by Theorem 4.4 we construct an adaptive observer. To illustrate this observer we carrie a simulation with the plant given by

$$\begin{aligned} D^{0.7}x(t) =& \begin{bmatrix} a_1 & 1 \\ a_2 & 0 \end{bmatrix} x + \begin{bmatrix} b_1 \\ b_2 \end{bmatrix} u, \\ y(t) =& [1 \quad 0]x(t), \end{aligned} \tag{4.85}$$

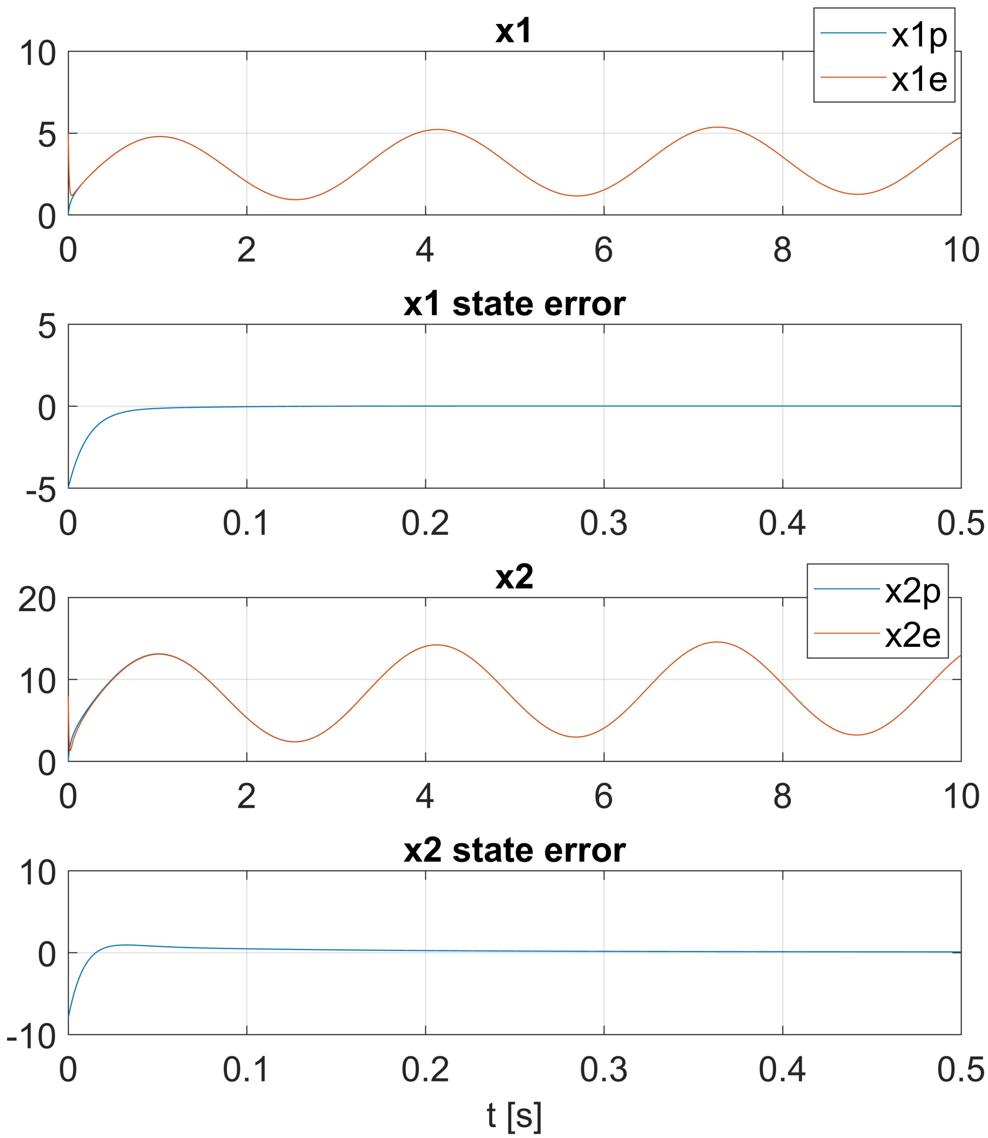


Figure 4.11: States estimates and identification error.

where a_1, a_2, b_1, b_2 are the unknown parameters and u, y are the only signals available for measurement.

From Section 4.6 the observer is given by

$$\begin{aligned} D^{0.7}\hat{x}(t) =& \begin{bmatrix} \hat{a}_1 & 1 \\ \hat{a}_2 & 0 \end{bmatrix} \hat{x} + \begin{bmatrix} \hat{b}_1 \\ \hat{b}_2 \end{bmatrix} u, + \begin{bmatrix} l_1 \\ l_2 \end{bmatrix} (y - \hat{y}), \\ y(t) =& [1 \quad 0]\hat{x}, \end{aligned} \tag{4.86}$$

where $\hat{a}_1$, $\hat{a}_2$, $\hat{b}_1$, $\hat{b}_2$ are the parameters estimates, and $\hat{x}$, $\hat{y}$ are the states and output estimates of (4.85).

The parameter identifier can be built using the results of Theorem 4.4 and is given by

$$\Lambda(\lambda) = (s+5)(s+6) = s^2 + 11s + 30, \tag{4.87}$$

and the vector $\phi = [\phi_1^T, \phi_2^T]$ is generating by

$$D^{0.7}\phi_1 = \begin{bmatrix} -11 & -30 \\ 1 & 0 \end{bmatrix} \begin{bmatrix} \phi_{11} \\ \phi_{12} \end{bmatrix} + \begin{bmatrix} 1 \\ 0 \end{bmatrix} u, \tag{4.88}$$

$$D^{0.7}\phi_2 = \begin{bmatrix} -11 & -30 \\ 1 & 0 \end{bmatrix} \begin{bmatrix} \phi_{21} \\ \phi_{22} \end{bmatrix} + \begin{bmatrix} -1 \\ 0 \end{bmatrix} y, \tag{4.89}$$

and the signals

$$z = y + 11\phi_{21} + 30\phi_{22}, \tag{4.90}$$

$$\hat{z} = \hat{b}_1\phi_{12} + \hat{b}_2\phi_{12} + \hat{a}_1\phi_{21} + \hat{a}_2\phi_{22}, \tag{4.91}$$

$$e = z - \hat{z} \tag{4.92}$$

and the adaptive laws are given by

$$\begin{aligned} D^{0.7}\hat{b}_1 =& \gamma_1 e\phi_{11}, \\ D^{0.7}\hat{b}_2 =& \gamma_1 e\phi_{12}, \end{aligned} \tag{4.93}$$

$$\begin{aligned} D^{0.7}\hat{a}_1 =& \gamma_1 e\phi_{21}, \\ D^{0.7}\hat{a}_2 =& \gamma_1 e\phi_{22}, \end{aligned} \tag{4.94}$$

The real values of the plant parameters are $a_1^* = -4$, $a_2^* = -6$, $b_1^* = 2$, $b_2^* = 3$. The simulation is carried out with $_1 = 2$, $l_2 = 11$, $\gamma_1 = 1$, $\gamma_2 = 0.5$.

In Fig. 4.12 shown the estimates of the states and in Fig. 4.13 is shown the parameters estimates. We can observe that $e \to 0$ as $t \to \infty$ and $\hat{a} \to a^*$, $\hat{b} \to b^*$.

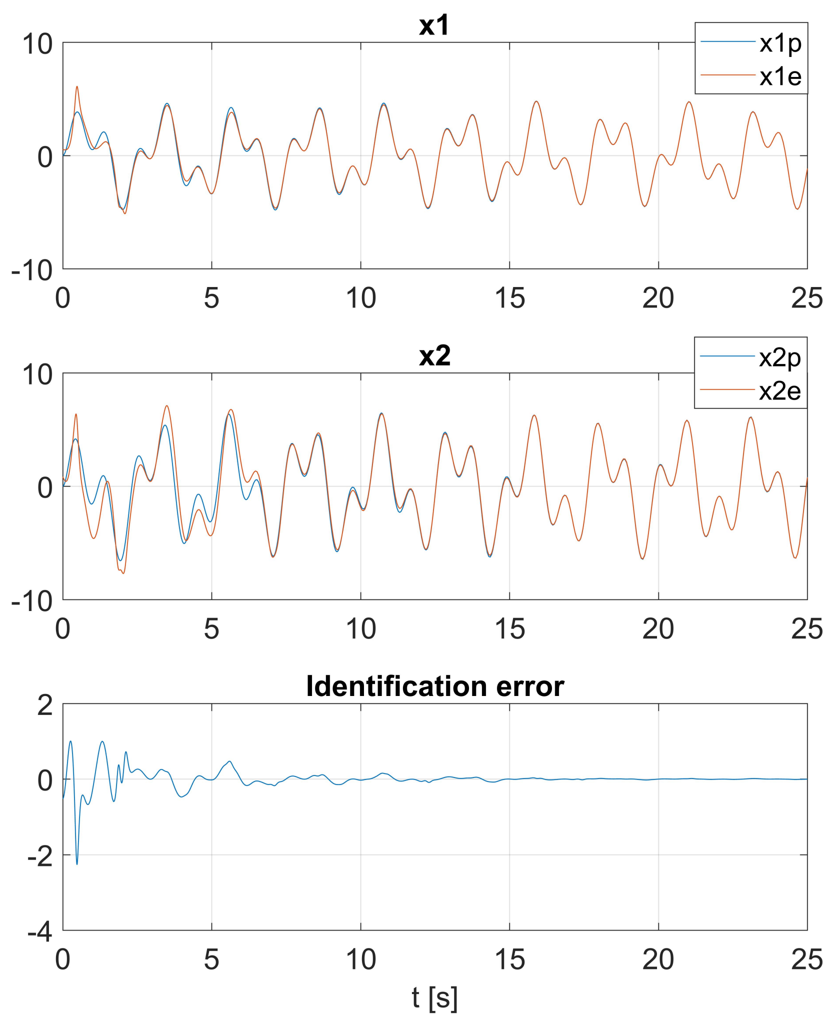


Figure 4.12: States estimates and identification error.

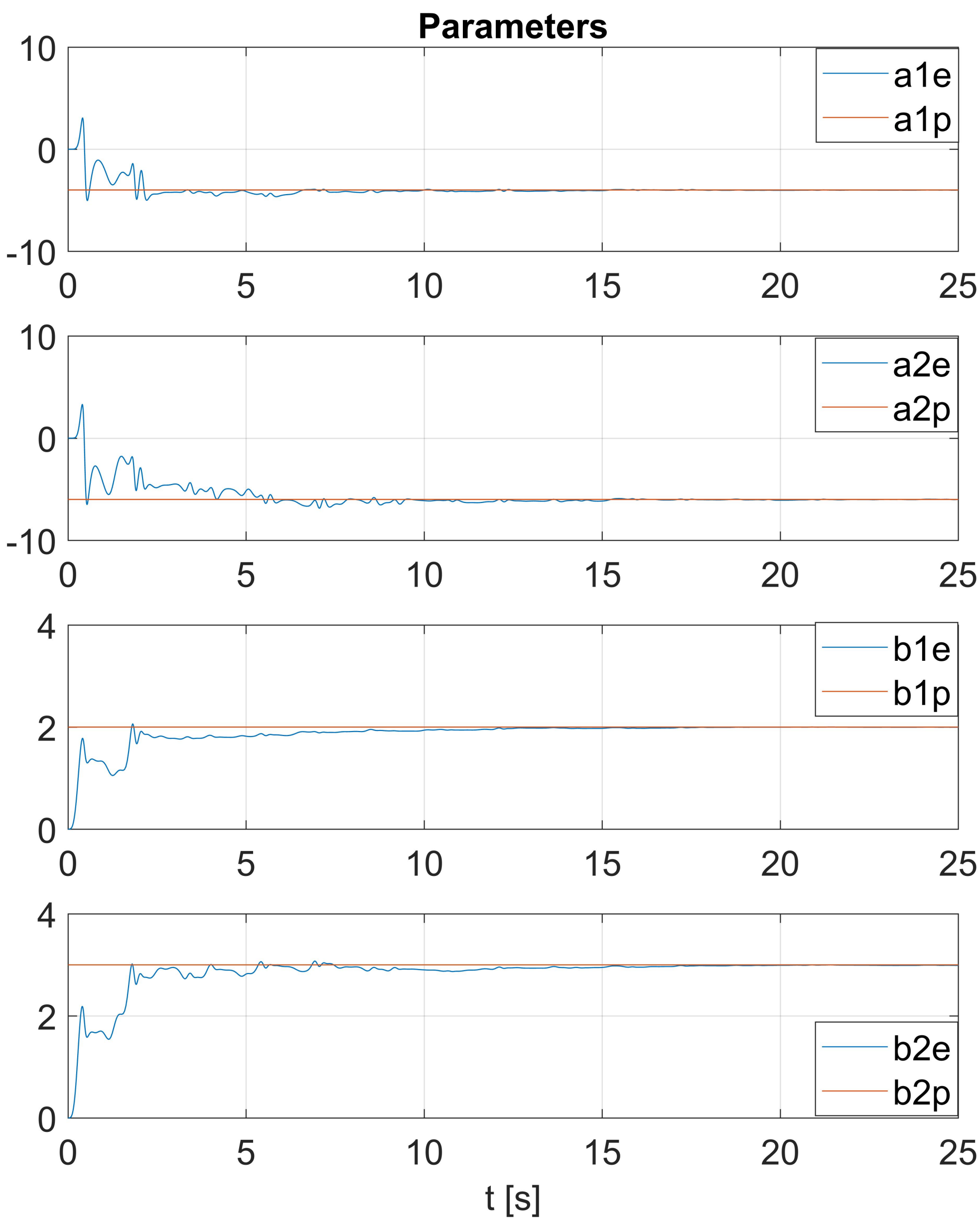


Figure 4.13: Parameters estimates.

Chapter 5

Anesthesia Control

In medical practice, the application of general anesthesia plays a significant role in the patient's well-being, this is achieved through the administration of a combination of drugs that act to provide adequate hypnosis (unconsciousness and amnesia to avoid traumatic recalls), paralysis or muscle relaxation (to attain immobility, an absence of reflexes, and proper operating conditions), and analgesia (pain relief). This process is accomplished by an anesthesiologist who must continuously observe and adjust the rates and overall amounts of anesthetic agents delivered to the patient, preserving the stability of the autonomic, cardiovascular, respiratory, and thermoregulatory systems.

The concepts of the general anesthesia, the modeling, and the control challenges are presented in this Chapter. Moreover, is proposed simple fractional-order models to represent the input-output behavior of the PK/PD model of anesthesia.

5.1 General anesthesia

The effects of drugs on patients in the operating room vary with drug dosage, from patient to patient, and with time. Different doses of drugs result in different concentrations in various tissues, producing a range of therapeutic and sometimes undesirable responses. Responses depend on drug pharmacokinetics (time curse of drug concentration in the body) and drug pharmacodynamics (the relationship between drug concentration and drug effect). These processes may be influenced by factors including pre-existing disease, age, and genetic variability. Patient responses to drugs may also dynamically altered by factors such as temperature, pH, circulating ion and protein concentration, levels of endogenous signaling molecules, and coadministration of the drug in the operating room environment (Brown *et al.* 2010).

General anesthesia consists of providing the patient with a reversible state of loss of consciousness (hypnosis), analgesia and muscle relaxation.

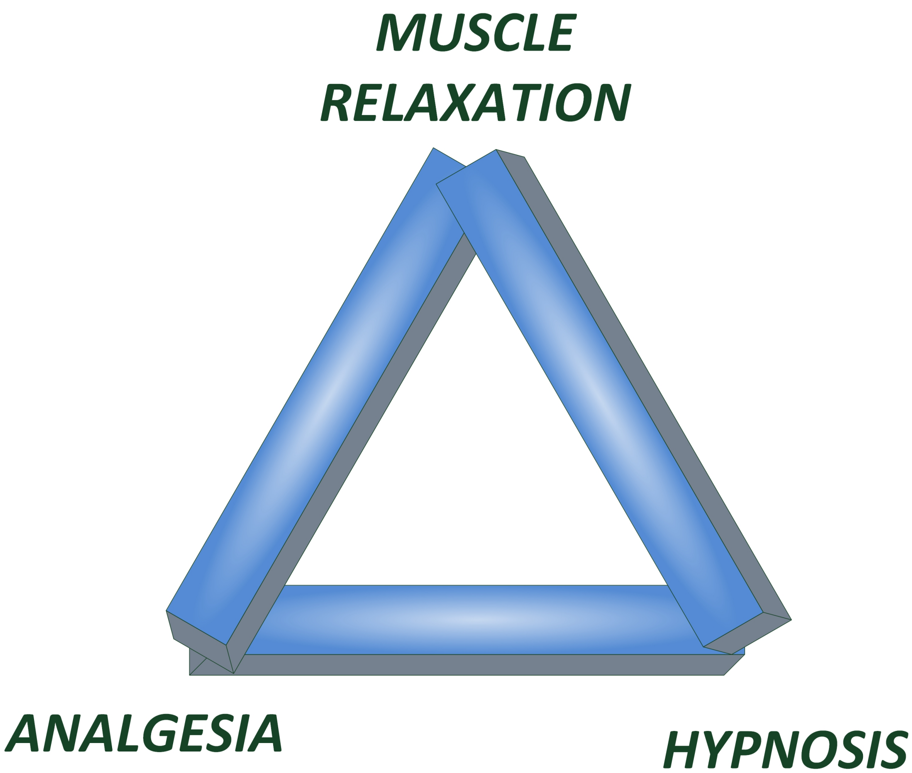


Figure 5.1: General anesthesia components

The purpose of general anesthesia is to allow the patient to be operated without pain, by administering anesthetic drugs intravenously or inhaled, providing maximum safety, comfort and vigilance during the surgical act. The description of the general process with its variables is shown in Figure 5.2. As can be seen, the variables that can be manipulated are the anesthetics, relaxants, and serums, the disturbances in the system are signals that can occur at any time, such as surgical stimulation, and blood loss. The output variables are divided into measurable and non-measurable, and the main interest in the control of anesthesia is focused on the non-measurable variables: hypnosis, analgesia, and muscle relaxation.

In practice, an anesthesiologist has to observe and control a large number of hemodynamic

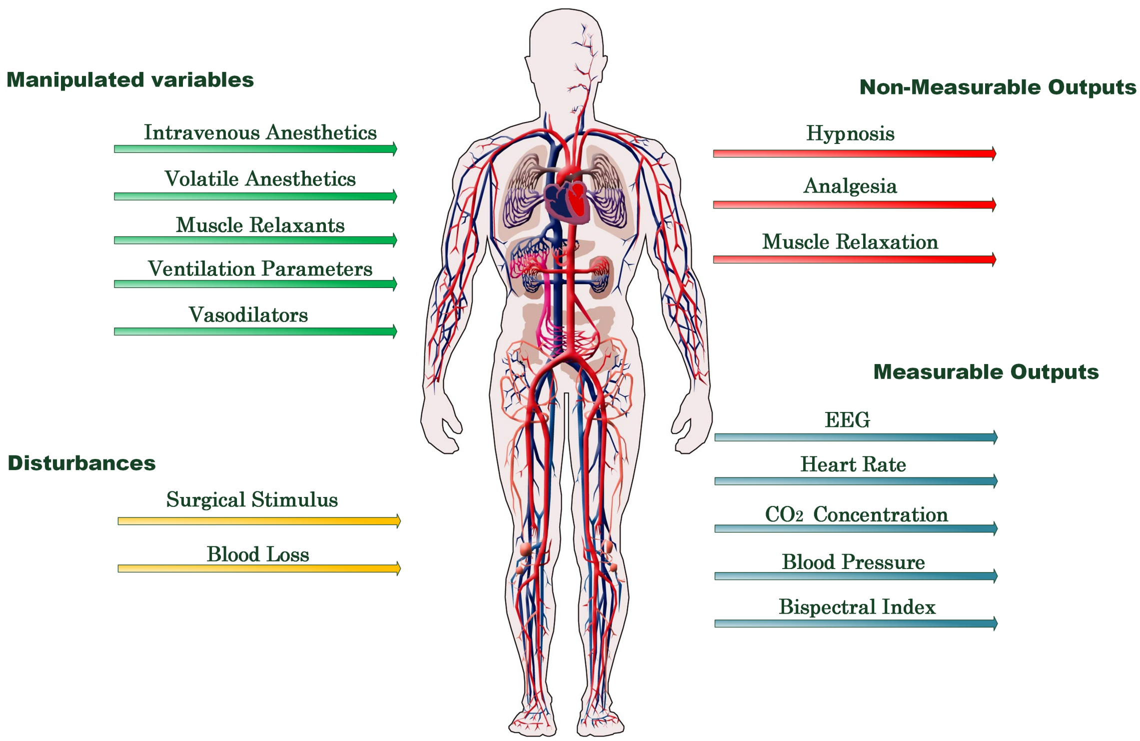


Figure 5.2: Input-Output variables in anesthesia

and respiratory variables as well as clinical signs that indicate the state of hypnosis and analgesia.

Most of the drugs used do not only operate on the desired effect but alter other aspects, for example, the effects of the anesthetic drug propofol not only affect the level of hypnosis but also increase the level of analgesia. The same behavior has the drug remifentanil whose main objective is to increase the level of analgesia but as a side effect also increases the level of hypnosis. Due to this cross effect between these drugs the anesthesiologist must adjust the desired level of hypnosis and analgesia with different amounts of both drugs. From the point of view of control engineering, this problem is a problem of multiple inputs and multiple outputs.

In the daily work routine, the anesthesiologist calculates the amount of the necessary drug with the help of dose regimes given by the supplier of the drug, which in most cases are based on the patient's body weight.

General anesthesia produces reversible behavioral and physiological phenomena (unconsciousness, amnesia, analgesia) with the stability of the cardiovascular, respiratory and thermoregulatory systems. Also generates distinct patterns in the electroencephalogram (EEG), the most frequent being the progressive increase in the activity of low frequency and high amplitude as the level of anesthesia deepens (Brown *et al.* 2010).

Recovery from general anesthesia is a passive process that depends on the number of drugs administered, its places of action, potency, pharmacokinetics, the physiological characteristics of the patient and the type and duration of the surgery (Brown *et al.* 2010).

General anesthesia is divided into three phases (Kellicker 2010):

- Induction phase: consists of administering drugs that cause the loss of consciousness. Anesthetics are administered through an intravenous or gas within the lungs.
- Maintenance phase: drugs are administered continuously to maintain a stable therapeutic status.
- Emerging or recovery phase: this is the last phase. The drugs are stopped being administered to slowly reverse the effects of the anesthesia and allow the patient to wake up.

For a more detail description of the process of general anesthesia, the reader is referred to (Bailey and Haddad 2005, Brown *et al.* 2010, V.V. 2011).

5.2 Pharmacokinetic/Pharmacodynamic model

The PK/PD models most frequently used for Propofol (hypnotic drug) are the fourth-order compartmental model (Fig. 5.3) (Schnider *et al.* 1998, Marsh *et al.* 1991). These models, developed, tested, and validated on a wide range of real patient data are often used in the literature for control of anesthesia (Beck 2015).

In this paper we use the model presented in (Schnider *et al.* 1998) given by

$$\dot{x}(t) = \begin{bmatrix} -(a_{11}+a_{21}+a_{31}) & a_{12} & a_{13} \\ a_{21} & -a_{12} & 0 \\ a_{31} & 0 & -a_{13} \end{bmatrix} x(t) + \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix} u(t), \tag{5.1}$$

where x_1 represents the concentration of the drug in the central compartment (intravascular blood), x_2 y x_3 represent the concentration of the drug in the peripheral compartments, a_{12},

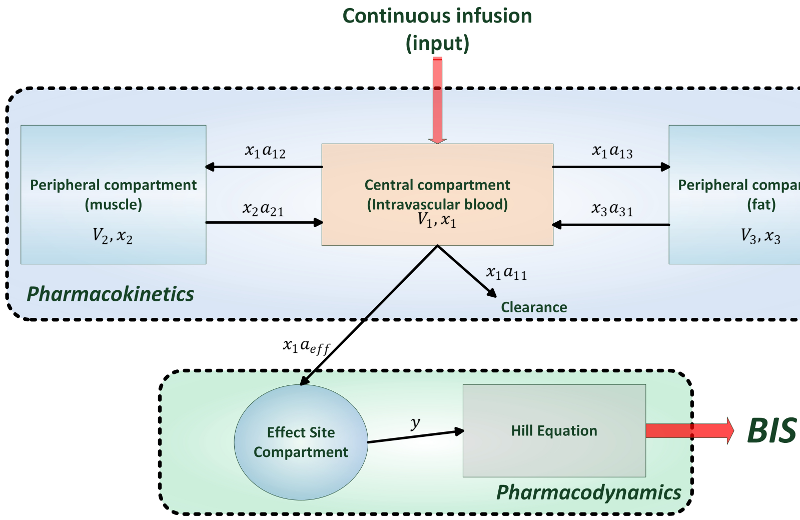


Figure 5.3: PK/PD model.

a_{13}, a_{21}, a_{31} are positive constants representing the flow between compartments, a_{11} is the elimination rate of the drug through metabolism and $u(t)[mg/min]$ is the rate of infusion of anesthetic (propofol) in the central compartment, and a_{ij} are in $[min^{-1}]$ and x_i are in $[mg]$.

An additional compartment, namely, the effect compartment, is introduced to represent the time-delay between the observed effect and the plasma concentration. The effect compartment model links the plasma concentration (concentration in the central compartment) to the effect concentration with a first order differential equation

$$\dot{y}(t) = a_{eff}(x_1(t) - y(t)), \quad y(0) = x_1(0), \quad t \geq 0, \tag{5.2}$$

where a_{eff} is the time constant, $x_1(t)$ is the concentration in the central compartment defined in (5.1) and $y(t)$ is the concentration of the effect compartment.

The pharmacokinetic parameters can be obtained through the following equations (Schnider *et al.* 1998):

$$
\begin{aligned}
V_1 &= 4.27[l] \\
V_2 &= 18.9 - 0.391(age - 53)[l] \\
V_3 &= 2.38[l] \\
C_{11} &= 1.89 + 0 - 0456(weight - 77) - 0.06681(ibm - 59) \\
&\quad +0.0264(height - 177)[l/min] \\
C_{12} &= 1.29 - 0.024(age - 53)[l/min] \\
C_{13} &= 0.836[l/min]
\end{aligned}
$$

$$
\begin{aligned}
a_{11} &= \frac{C_{11}}{V_1}[min^{-1}];\ a_{12} = \frac{C_{12}}{V_1}[min^{-1}];\ a_{13} = \frac{C_{13}}{V_1}[min^{-1}] \\
a_{21} &= \frac{C_{21}}{V_2}[min^{-1}];\ a_{31} = \frac{C_{13}}{V_3}[min^{-1}] \\
a_{eff} &= 0.456[min^{-1}] \\
lbm_m &= 1.1 \cdot weight - 128 \cdot \frac{weight^2}{height^2} \\
lbm_f &= 1.07 \cdot weight - 148 \cdot \frac{weight^2}{height^2}
\end{aligned}
$$

As we can observe in the previous equations, the PK parameters depend on the biometrical characteristic of the patient.

The bispectral index (BIS) is a signal derived from the electroencephalogram (EEG) used to assess the level of consciousness in anesthesia. A BIS value of 0 equals a flat line in the EEG while a BIS value of 100 is the expected value of a fully conscious adult patient, $60 - 70$ and $40 - 60$ range represent light and moderate hypnotic conditions (Fig. 5.4), respectively. The target value during surgery is 50, giving us a gap between 40 and 60 to guarantee adequate sedation (Fig. 5.5).

The BIS can be related to the concentration of the effect compartment by the nonlinear static function, termed Hill equation (Bailey and Haddad 2005):

$$
z = BIS(y) = E_0 - E_{max}\frac{y^{\gamma}(t)}{y^{\gamma}(t) + EC_{50}^{\gamma}}, \tag{5.3}
$$

where E_0 denotes the base value (awaken state) and by convention typically is given the value of 100, E_{max} is the maximum effect achieved by drug infusion, EC_{50} is the drug concentration to half maximal effect and represents the patient's sensibility to the drug, and γ determines the degree of nonlinearity of the function.

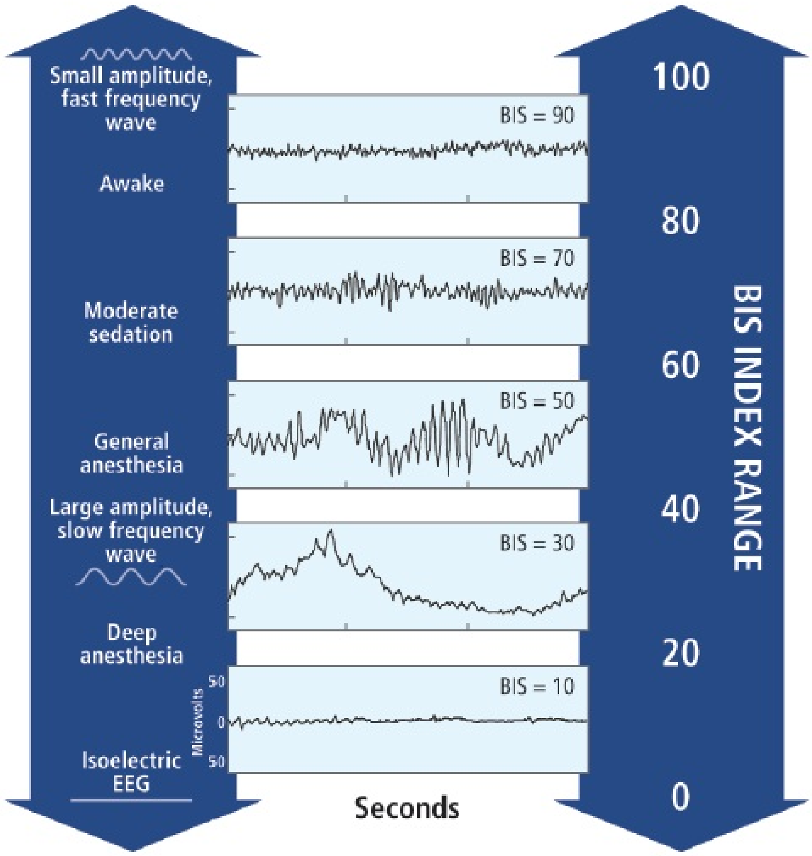


Figure 5.4: The BIS Index is scaled to correlate with important clinical end points during administration of anesthetic agent (Kelley 2010).

The model of anesthesia, from physical considerations, describes a non-negative system, that is, the state trajectories remain non-negative for non-negative initial conditions and a non-negative control input, which must be taken into account for controller designs.

One of the significant challenges in the control of anesthesia is the variability among patients. This variability can occur as a result of patient physiology (age, gender, disease), variations in PK processes (rate of absorption, distribution, metabolism, and elimination), and differences in PD (sensitivity of receptor) (Shafer *et al.* 2010). Also, in the medical practice, no state of this model is available for measurement, only the output (BIS) is measurable for feedback.

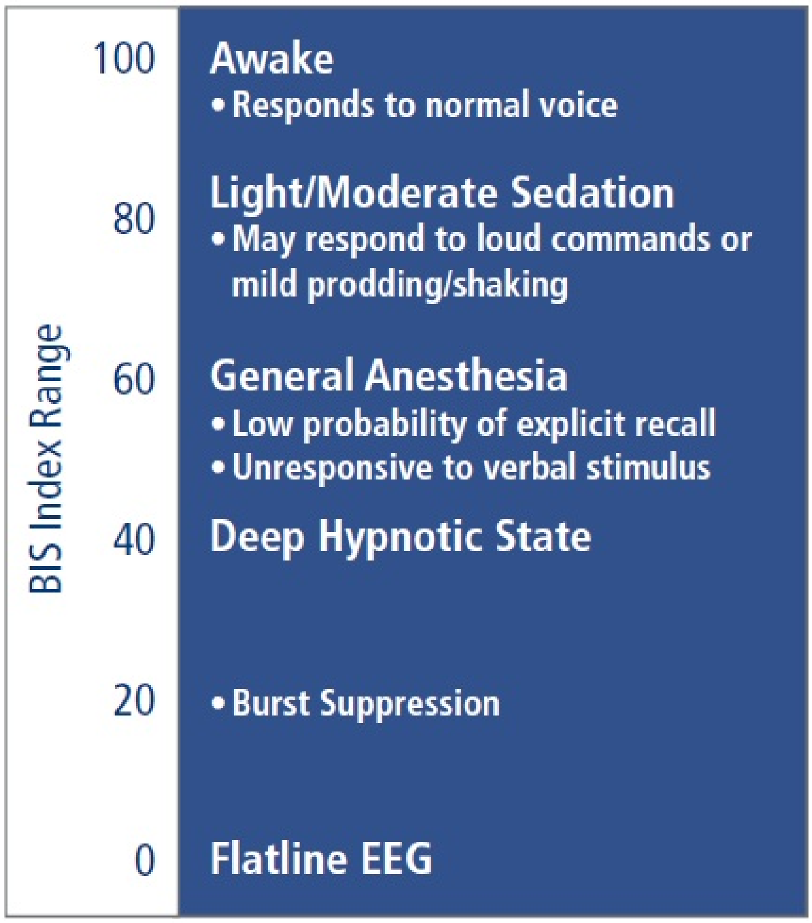


Figure 5.5: BIS Index Range (Kelley 2010).

5.3 Anesthesia control

The problem of control of drug administration in anesthesia has been studied since the 1950s (Bickford 1950). Since then it has been clear that the control of anesthesia has many challenges, such as multivariate features (Petersen-Felix *et al.* 1995), different dynamics dependent on the drug and place of administration (Curatolo *et al.* 1996, Struys *et al.* 2003), stability problems (Asbury 1997) and performance of the control algorithm (Mainland *et al.* 2000, Ting *et al.* 2004).

Given the complex nature and uncertainty of the process, it is not surprising that reliable models for control of drug administration are not available.

Because the level of system uncertainty, fixed and robust gain controllers can unnecessarily sacrifice system performance, while adaptive controls can tolerate much higher levels of uncertainty and improve performance (Ioannou and Sun 1996).

The interaction between a drug and the body is divided into two phases: pharmacokinetics (PK) and pharmacodynamics (PD). Pharmacokinetics described what the body does the drug while the pharmacodynamics described what drug does to the body (Schnider *et al.* 1998). Regarding the level of anesthesia or hypnosis (loss of consciousness), the body's response to the administration of a hypnotic or anesthetic drug is commonly modeled as a Wiener model of higher order, that is, a linear part corresponding to the pharmacokinetics, and a static non-linearity corresponding to the pharmacodynamics (Bailey and Haddad 2005).

The concentration of the drug in the human body is not measurable online and also the level of hypnosis is not measurable, so it is necessary to have a surrogate measurement as variable to be controlled.

The bispectral index (BIS) has been tested and validated as a measurement of the hypnotic component of anesthesia and has been used in multiple studies as a variable to be controlled.

In surgery, the level of hypnosis should be brought to a therapeutic value between 40 - 60 in a few minutes and kept there. High values of the bispectral index correspond to a low level of hypnosis, and the possibility of being aware during the surgical procedure (Myles *et al.* 2004). Values below 40 are undesirable because they are correlated with postoperative complications and with an increase in the mortality rate after one year (Monk *et al.* 2005).

The application of a closed-loop system of drug administration is complex and require a

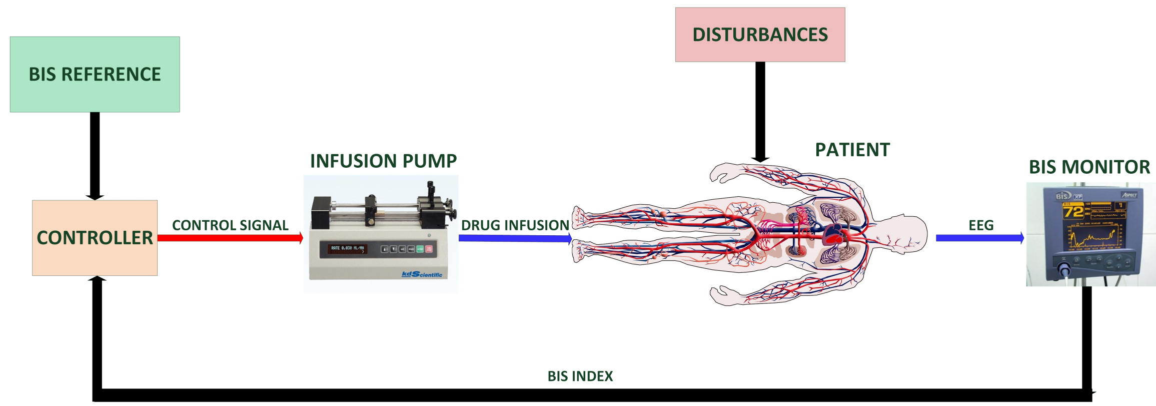


Figure 5.6: Control of anesthesia implementation.

balance between all his basic components (O'Hara *et al.* 1992):

- A variable to be controlled representative of the desired therapeutic effect
- A clinically relevant reference value for this variable
- An actuator (in this case, an infusion pump)
- One system (the patient)
- An accurate, stable and robust control algorithm

In (Huang *et al.* 1999) and (Kenny and Mantzaridis 1999) it was proved that the anesthetic propofol has properties that make it appropriate for anesthesia control. Many research studies have been carried out using the anesthetic propofol as input to the system and the bispectral index as a substitute measure of the level of hypnosis. In (Kenny and Mantzaridis 1999, Morley *et al.* 2000, Sakai *et al.* 2000, Absalom *et al.* 2002, Liu *et al.* 2006, Puri *et al.* 2007) were considered fixed-gain controllers, mostly PID. Adaptive controllers were developed in (Mortier *et al.* 1998, Haddad *et al.* 2003b, Haddad *et al.* 2006). To deal with delays in the system, predictive controllers were used in (Ionescu *et al.* 2008, Nino *et al.* 2009, Furutani *et al.* 2010). Also has been used sliding mode control in (Castro *et al.* 2008) and control based on neural networks in (Haddad *et al.* 2007, Haddad *et al.* 2011). As the best of the knowledge of the author, there has not been published any previous studies using a fractional control to the problem of control of anesthesia.

5.4 Challenges

Achieving the appropriate drug effect at any time during surgery, and after surgery is an essential objective in anesthesia. The main drugs used to induce general anesthesia are the hypnotics, analgesics and muscle relaxants, which are given to ensure unconsciousness, to provide analgesia and suppress the hemodynamic response, and to suppress reflex movements, respectively. The dose of each drug is titrated against the individual patient's response to achieve the intraoperative therapeutic goals. The patient should lose consciousness rapidly after induction, the level of analgesia should follow the level of surgical stimulation closely, and at the end of the operation, the drug effect should dissipate so that the patient wakes up, has no residual muscle relaxation, and is pain-free. Unfortunately, at the end of a surgical procedure, the desired intraoperative drug effects are viewed as side effects, for example, excessive sedation and respiratory depression.

From a pharmacology perspective, anesthesia is concerned with controlling the time course of drug effect. The drug effect is dependent on the site and rate of input of the drug, the distribution of the drug within the body, the elimination of the drug from the body, and the sensitivity of the patient to the drug. Innumerable anatomic, physiologic, and chemical factors influence these processes. If we knew quantitatively all of the factors affecting the distribution, elimination, and sensitivity to a drug in an individual patient, we could predict the time course of the drug effect exactly. However, we only know a few of all the aspects of the dose-response relationship.

Drug responses in humans are the results of integrated effects, including signal amplification and dampening mechanisms at a cellular, tissue, and physiological systems level, and the pharmacodynamic responses can be therapeutic, toxic, or lethal.

In anesthesiology, it is easy to observe that response to the same drug dose vary widely among patients. Part of the process of delivering anesthesia is titrating drug dose to provide optimal therapy for a specific patient, mainly when the drug has significant toxicities. At the same time, the anesthesiologist must know dosing ranges that are appropriate for large populations of patients, to provide dosing guidelines.

The classical PK/PD models are coarse abstractions of a real distribution and elimination process. Still, these models describe the measured and observed concentrations. They exist another more complex type of models called physiologically based models (Upton and

Ludbrook 2005), with these models it is possible to have more information available, for example, the influence of changes in cardiac output and organ blood flow on the time course of the concentration in the blood and various organs and tissues. Unfortunately, the development of such accurate models is expensive and can only be performed in animals. Furthermore, this accurate models, are complex that have too many variables and parameters to be useful in the development of controllers.

All these difficulties make the process of control of anesthesia a very challenging problem. The potential benefits of a closed-loop anesthesia delivery are: more consistent drug administration, less inter and intra-patient variability, less over and under-dosage, faster control action to unexpected arousal (perturbation rejection), smaller quantities of drug usage, faster recovery of the patient, better hemodynamic control and less hypotension during induction of anesthesia, is what keeps the interest in the control community to design reliable control schemes. Moreover, this problem is still considered an open problem.

5.5 Models for control of anesthesia

Even though it has been a subject of intense research in the last decades, anesthesia is a complicated and not well-understood process, resulting in a challenging control problem. The current state of the art understanding the unconsciousness and the mechanisms of drug-induced unconsciousness is limited, therefore is very challenging translated these little-known mechanisms to an accurate mathematical model. At present, the models available and most used are the mean field models of drug action(Absalom *et al.* 2011) such as the PK/PD model, which describe the different brain states associated with the electroencephalogram (EEG).

The crucial step towards the control of anesthesia is to derive an adequate mathematical model that describes the process. Is essential to find a good balance between the complex models that may contain too many parameters that cannot be identified to the lack of appropriate measurements and sensors, and the over-simplified model that might not capture the system dynamics. Overall we should identify the objective of the model, be prediction or control, or both, and choose the right model structure for that objective.

Another challenge is the identification of a model from clinical data, is has been shown (Silva *et al.* 2014) that the information available in the operating room (infusion rate of the drug and BIS index usually) is insufficient to identify a full-order PK/PD model. The excitation in the input signal is not sufficiently frequency rich and is not able to excite all the modes in the model because this input cannot be selected freely, additionally, this model has a Wiener structure. Therefore the task of identifying an individualized model online is very challenging.

Linear and nonlinear reduced-order models structures have been proposed to improve the identifiability and the control synthesis of the anesthesia process.

One of the main characteristics of the models used for identification and control of anesthesia are in some level simplified models, for example, models with fixed parameters in the PK or PD parts (linear or nonlinear), linearizations or order reduction.

In (Lin *et al.* 2004) the authors present a piece-wise linear model, with which they use different LTI models to represent different phases of the process, for example, one model for the induction phase and other for the maintenance phase. Then they synthesized a controller for each phase, similar to gain scheduling schemes.

In (Sartori *et al.* 2005) is proposed a standard PK/PD model where the authors assume that only the PD parameters are responsible for the inter-patient variability, and use an extended PK model and linearized the model and identify the PD parameters and via a Kalman filter.

A first-order plus time-delay is proposed in (Bibian *et al.* 2006), here the PK parameters are fixed, the Hill curve is linearized around an operating point, and the PD parameters are calculated using a standard least square estimation.

In (Alonso *et al.* 2009) is presented a reduced-order model obtained using model reduction technics. This model is an affine model with only four parameters and takes advantage of the redundancy shown in the PK model, that is, the adjacent poles and zeros.

In (Silva *et al.* 2010) is proposed a MISO Wiener model for the pharmacokinetics and pharmacodynamics of propofol and remifentanil. This model uses a PK part with a reduced number of parameters (with a combination of three fixed parameters and one unknown), for the hypnotic drug and other for the analgesic. Also, a combine Hill equation (with a reduced number of parameters) that combine the effect of both drug in the level of unconsciousness.

In (Navarro-Guerrero 2013) based on the cancellation of adjacent poles and zeros presented in the PK part of the PK/PD model, we propose a nonlinear first-order model with a linear parameterization of two parameters. This model has the advantage that represents the input-output behavior of the PK/PD model, and do not rely on linearization by the inversion of the nonlinearity and state measurement, but do not take into account the time-delay in the PD part.

Every proposed model has his particulars advantages and disadvantage (which can be seen in detail in his respective reference), but all these papers show us the necessity to develop a simple model for identification and control synthesis to circumvent the difficulties of using the PK/PD model with a Wiener structure.

Moreover, the majority of the control schemes based on the proposed models relied on the inversion of the non-linearity and supposed that the states are available for measurement, However, in practice the parameters of the non-linearity are unknown, and the states are not measurable online, thus adding more uncertainty in the control schemes presented.

5.6 New modeling paradigm: Fractional calculus

Some researchers had proposed the necessity for a fractal view of physiology that explicitly takes into account the complexity of the living matter and its dynamics. Complexity in this context incorporates the recent advances in physiology concerned with the applications of the concepts from fractal geometry, fractal statistics, and nonlinear dynamics, to the formation of a new kind of understanding within the life sciences.

The complexity of the human body and the characterization of that complexity through fractal measures and their dynamics involve the use of fractional calculus. Not only anatomical structures are fractal (Grizzi and Chiriva-Internati 2005), such as the convoluted surface of the brain, the lining of the bowel, neural networks, and placenta, but the output of dynamical physiologic networks are fractal as well (Bassingthwaighte *et al.* 1994).

The time series for the inter-beat intervals of the heart, inter-breath intervals, and inter-stride intervals have all been shown to be fractal or multifractal statistical phenomena. Consequently, the fractal dimension turns out to be a significantly better indicator of organismic functions in health and disease than the traditional average measures, such as heart rate, breathing rate, and stride rate. The observation that human physiology is primarily fractal was first made in the 1980s (Bassingthwaighte *et al.* 1994).

Control of physiologic variables is one of the goals of medicine, in particular, understanding and controlling physiological networks to ensure their proper operation.

Therefore it seems reasonable that one novel strategy for modeling the dynamics and control of complex physiologic phenomena is through the application of the fractional calculus (West 2009).

The fractional calculus has been used to model the interdependence, organization, and concinnity of complex phenomena ranging from the vestibule-oculomotor system, to the electrical impedance of biological tissue to the biomechanical behavior of physiologic organs (see, for example, Magin (2006) for a review of these applications).

In (Podlubny 1999a) the author's comment that if reality has the dynamics of a fractional-differential equation, then attempting to control it with integer-order feedback leads to extremely slow convergence, if not divergence, of the network output. On the other hand, fractional-order feedback, with the indices appropriately chosen, leads to rapid convergence of output to the desired signal.

In (West 2009) is suggested that from the point of view of fractal physiology the blood flow and ventilation are delivered in a fractal manner in both space and time in a healthy body.

A fundamental mechanism in the absorption of a drug in the human body is the process of diffusion. In (Copot *et al.* 2014) the authors present the relation between the diffusion process and fractional-order models. Also, the introduction of fractional-order pharmacokinetic models (Dokoumetzidis and Macheras 2009, Verotta 2010, Popović *et al.* 2011, Copot *et al.* 2013) that represent the experimental data more precise way, thanks to the $t^{-\alpha}$ decay of the fractional operators, and with this open a new line of investigation on the area of drug delivery systems.

In (Magin 2006, Dokoumetzidis and Macheras 2009, Copot *et al.* 2014) it is suggested that biological systems (like in pharmacology and bioengineering) could be represented with a fractional-order model with a more simple structure compared with his integer-order counterpart, simplifying the control design by using a less complex model.

So we can see that fractional calculus can offer us a new point of view to understand certain physical phenomena, especially those who from the point of view of integer-order systems seems too complex.

5.7 Proposed model

Under a process where exists a great uncertainty between individuals (inter-patient variability) and in the same individual (intra-patient variability), to have a deterministic model valid is challenging (in practice almost impossible or too complex to be useful). So if we could have a model for a single patient, this model is only valid for a period because of the changes in the physiological variables during surgery, which imply a change in the parameters of the model, hence the need for update the model online. Therefore, it would be convenient to have a generic model that has the ability of capture a wide range of dynamics (in this case the range characterized for the inter-patient variability) and adapted online to individualize the model for each patient.

Based on these facts a simple FOMs are considered. Three fractional commensurate order models to represent the input-output behavior of the Wiener system (5.1-5.3) are proposed:

$$G_1(\lambda) = \frac{b_0}{\lambda + a_0}, \tag{5.4}$$

$$G_2(\lambda) = \frac{b_1\lambda + b_0}{\lambda^2 + a_1\lambda + a_0}, \tag{5.5}$$

$$G_3(\lambda) = \frac{b_2\lambda^2 + b_1\lambda + b_0}{\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0}, \tag{5.6}$$

where $\lambda = s^{\alpha}$, s is the complex variable and α the commensurate order, with $0 < \alpha < 1$. a_1, a_0 and b_0 are the model parameters.

These models structures we can see them as phenomenological models (or some kind black-box model), namely, models that can capture the input-output dynamics of the patient's models, but with the disadvantage of the loss of physical meaning of the model parameters.

It has been shown in (Gonzalez-Olvera *et al.* 2015) that there exist a set of parameters (depending on the respective structure) with which the fractional-order model can capture the response of a particular patient's model. However, with the use of adaptive control we aim to control a large set of patients with one controller, so we do not need to identify a specific set of parameters for the FOM for a given patient, we only need a model structure capable of capture the overall response.

It is known that the particular response of a PK/PD model has an S-shape response, and in (Isaksson and Graebe 1999, Tavakoli-Kakhki *et al.* 2010) have shown that simple structures like those proposed can capture this type of response.

Chapter 6

Simulations

In this Chapter, the numerical simulations are presented, the FOMRAC and FOCMRAC schemes designed in the previous Chapter are implemented in 30 virtual patients. The simulations test the robustness of the control schemes against the intra-patient variability, inter-patient variability, disturbance, noise, and time-delay.

6.1 Identification

To assess the variability among patients, 30 patient models (taken from different studies, patients 1-10 (Mendonça *et al.* 2012), patients 11-20 (Ionescu *et al.* 2008), patients 21-30 (Heusden *et al.* 2013)) are used to emphasize the variability among the population. Fig. 6.1 shows the response of these models to a step input. Table 6.1 shows the pharmacodynamic and the biometric characteristics of the 30 patients.

As can be observed in Table 6.1 the parameters of the PK/PD models have significant variations, depending on age, weight, height, and gender, making a considerable variation in the step response.

To verify the ability of the proposed FOMs to capture the dynamics of the PK/PD model, a simulation is carried out with the three structures proposed.

We use a nominal patient to carry out this simulation, in Figure 6.2 is shown the identification scheme, and in Figure 6.3 the simulation results, output, and the identification error. We can observe that the three fractional-order structures proposed can capture the step response of the PK/PD model. In Fig. 6.4 is shown the identification error and the evolution

Tabla 6.1: Patient's pharmacodynamic parameters and biometric features

Patient	Age	Height	Weight	Gender	EC_{50}	γ
1	56	160	88	F	13.94	2.0321
2	48	158	52	F	13.88	1.0133
3	51	165	55	F	20	2.0196
4	56	160	65	F	20	1.8930
5	64	146	60	F	14.85	1.0702
6	59	159	110	F	20	2.6169
7	45	155	58	F	3.35	0.9172
8	51	163	55	F	12.17	1.8645
9	32	172	56	F	16.91	1.4517
10	68	160	64	F	15.52	0.9334
11	40	163	54	F	6.33	2.24
12	36	163	50	F	6.76	4.29
13	28	164	60	M	4.93	2.46
14	43	163	59	F	12.10	2.42
15	37	187	75	M	8.02	2.10
16	38	174	80	F	6.56	4.12
17	41	170	70	F	6.15	6.89
18	37	167	58	F	13.70	1.65
19	42	179	78	M	4.82	1.85
20	34	172	58	F	4.95	1.84
21	15	180.5	71	M	3.95	1.74
22	7	132	25.1	M	4.24	1.90
23	10	139	41.1	F	3.83	2.17
24	8	128	22	F	5.77	1.56
25	10	138	33.6	M	3.88	1.89
26	16	154.9	52.5	F	8.80	1.49
27	8	130	25.3	M	5.44	1.52
28	15	169	48	M	3.85	1.88
29	13	151	65	M	3.45	1.58
30	7	121	24	M	3.64	1.59

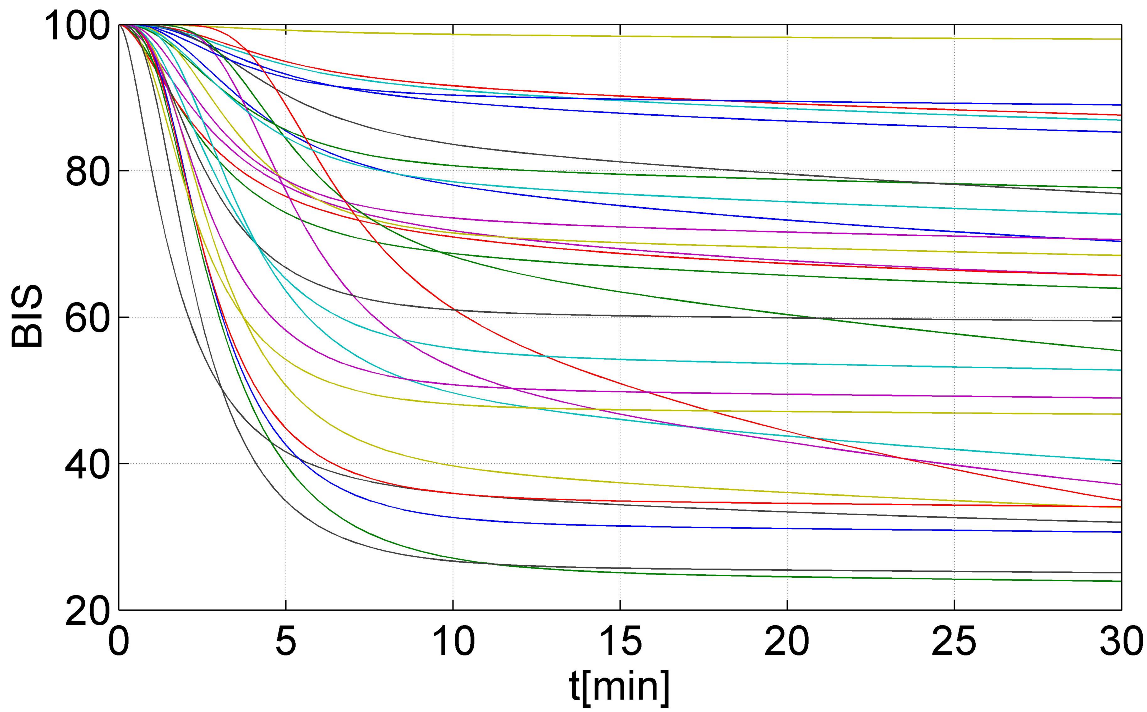


Figure 6.1: Patient's response to a step input.

of the model's parameters.

It can be seen that the input-output behavior of the PK/PD model is well captured by the model structures proposed.

It is worth noting that the objective of this study is the design of an adaptive control scheme, not to modeling a particular system, and for adaptive control, in general, only is needed a model structure. So with the identification scheme and the simulation presented is shown that the proposed models can capture the input-output behavior of the presented example.

6.2 Control

In this section, it is illustrated via simulations the effectiveness of the adaptive schemes designed in the previous Chapters (Figure 6.5). It is worth noticing that in the simulations the plants (patients) are represented by the Wiener system (PK/PD model), the fractional-order models proposed only are used to design and analyze the control schemes.

Table 6.2 shows the values of the design parameters of the control schemes implemented.

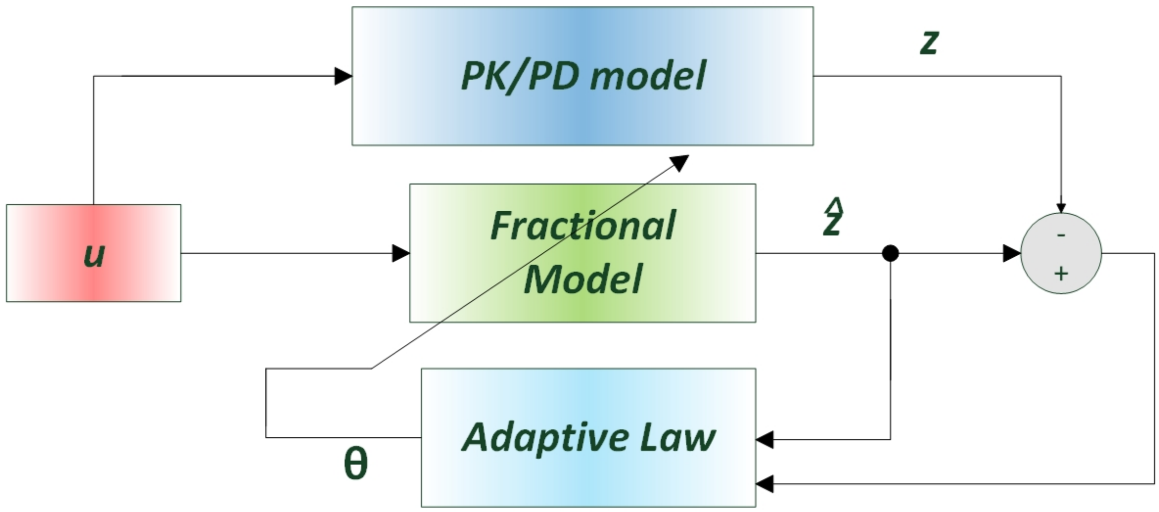


Figure 6.2: Identification scheme

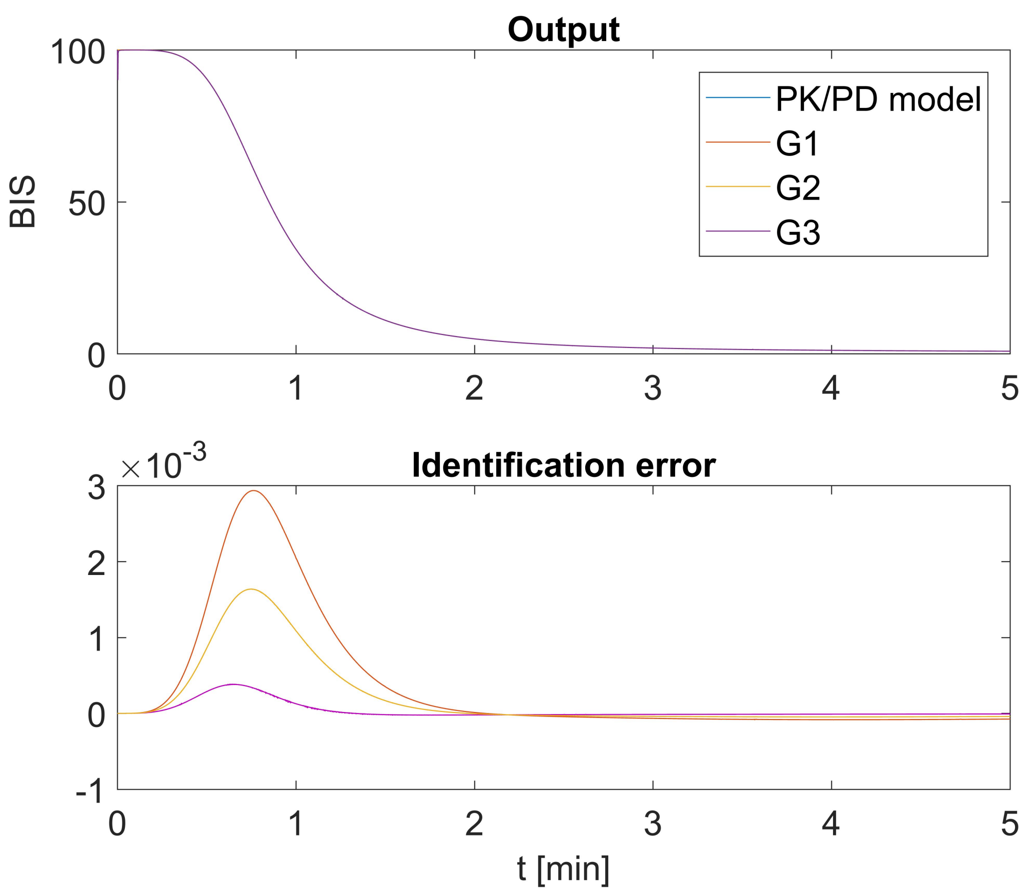


Figure 6.3: Identification, BIS output of the PK/PD model and the proposed FOMs.

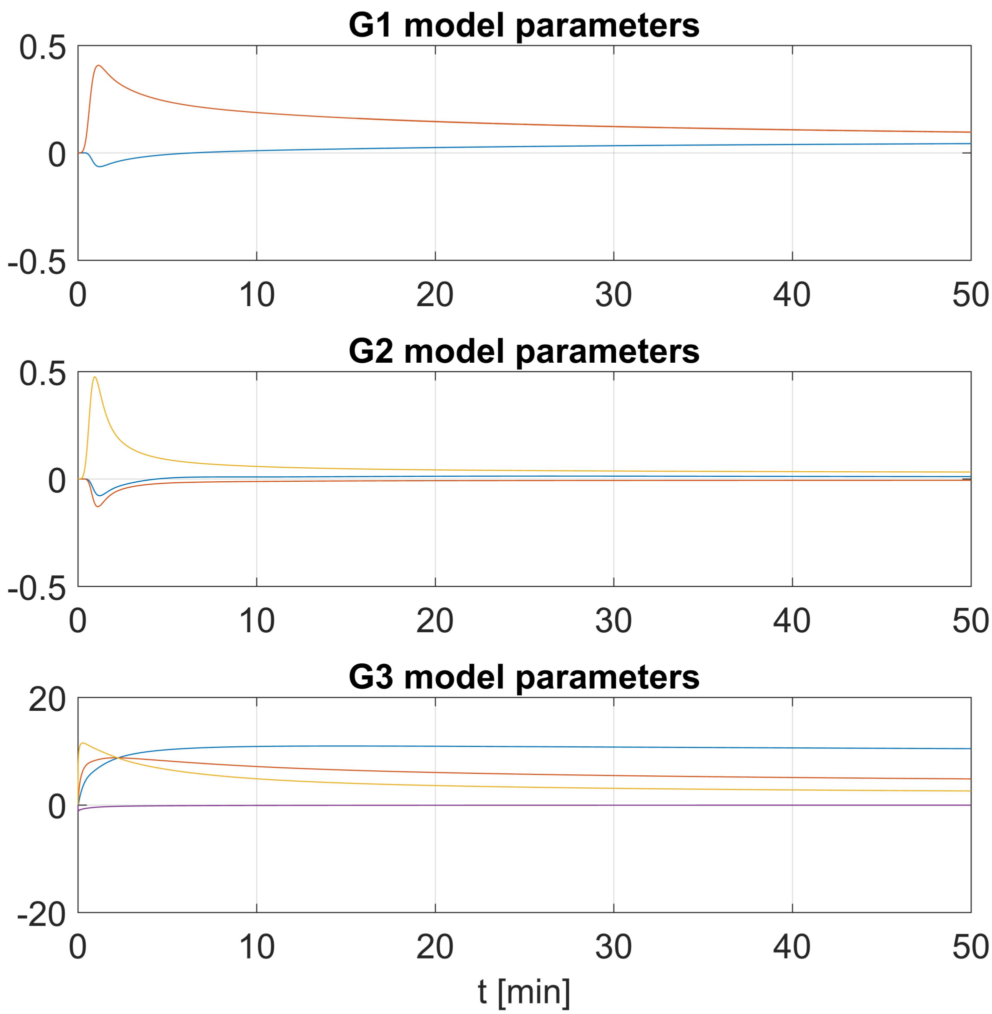
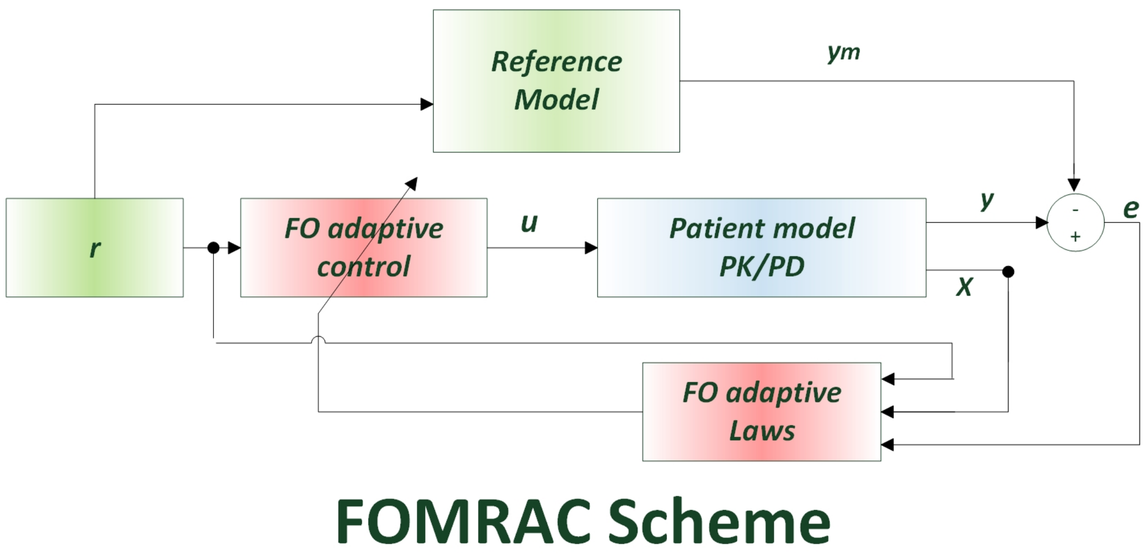


Figure 6.4: Identification, model parameters.



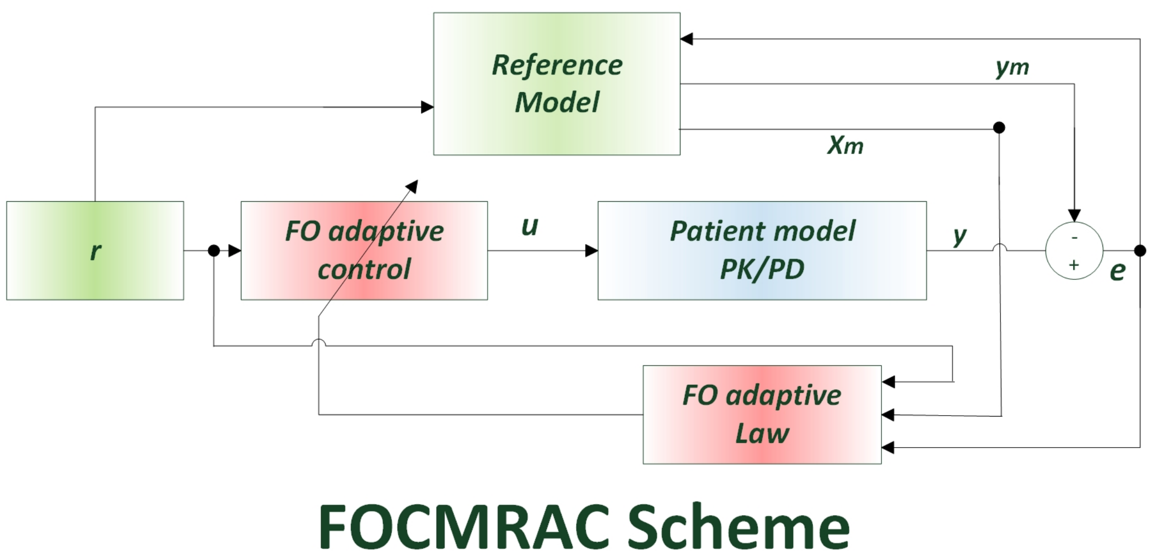


Figure 6.5: FOMRAC and FOCMRAC schemes implemented.

Tabla 6.2: Tuning parameters

Control with 30 patients			
1st order FOMRAC	1st order FOCMRAC	2nd order FOCMRAC	3rd order FOCMRAC
$\alpha = 0.005$	$\alpha = 0.05$	$\alpha = 0.005$	$\alpha = 0.1$
$\gamma = 0.0008$	$\gamma = 0.005$	$\gamma = 0.05$	$\gamma = 0.05$
	$L = -30$	$L_1 = -10$	$L_1 = -10$
		$L_2 = -2$	$L_2 = -0.5$
			$L_3 = -1$
Control with perturbations			
1st order FOMRAC	1st order FOCMRAC	2nd order FOCMRAC	3rd order FOCMRAC
$\alpha = 0.005$	$\alpha = 0.05$	$\alpha = 0.005$	$\alpha = 0.005$
$\gamma = 0.0008$	$\gamma = 0.0008$	$\gamma = 0.001$	$\gamma = 0.0008$
	$L = -0.1$	$L_1 = -0.5$	$L_1 = 0.5$
		$L_2 = -0.1$	$L_2 = -0.5$
			$L_3 = -0.05$
Time-delay robustness			
1st order FOMRAC	1st order FOCMRAC	2nd order FOCMRAC	3rd order FOCMRAC
$\alpha = 0.005$	$\alpha = 0.05$	$\alpha = 0.005$	$\alpha = 0.1$
$\gamma = 0.0008$	$\gamma = 0.005$	$\gamma = 0.01$	$\gamma = 0.01$
	$L = -25$	$L_1 = -10$	$L_1 = -10$
		$L_2 = -2$	$L_2 = -0.5$
			$L_3 = -1$

These values were chosen to make a trade-off between speed of convergence and transient performance.

The simulations are done with the PK/PD model of anesthesia given by (5.1-5.3), the objective is to take the patient to the level of $BIS = 50$.

6.2.1 Inter-patient robustness

The inter-patient variability denotes the variation of the mathematical models among the individuals. Every patient has his specific model.

The simulations were done using the 30 virtual patients applied to four different control schemes. In the case of the FOMRAC scheme we only use a controller based on the model (5.4), because the states are not measurable, and for the other two models are needed for feedback, it could be implemented using an observer, but also the parameters are unknown. So to use this scheme with the models (5.5 - 5.6) we would need to implement a parameter identifier and a state observer, this configuration is too complex and computational-wise very demanding, thus defeating the premise of using a simple control scheme.

For the case of the FOCMRAC scheme is implemented with the three models proposed applied to the 30 virtual patients.

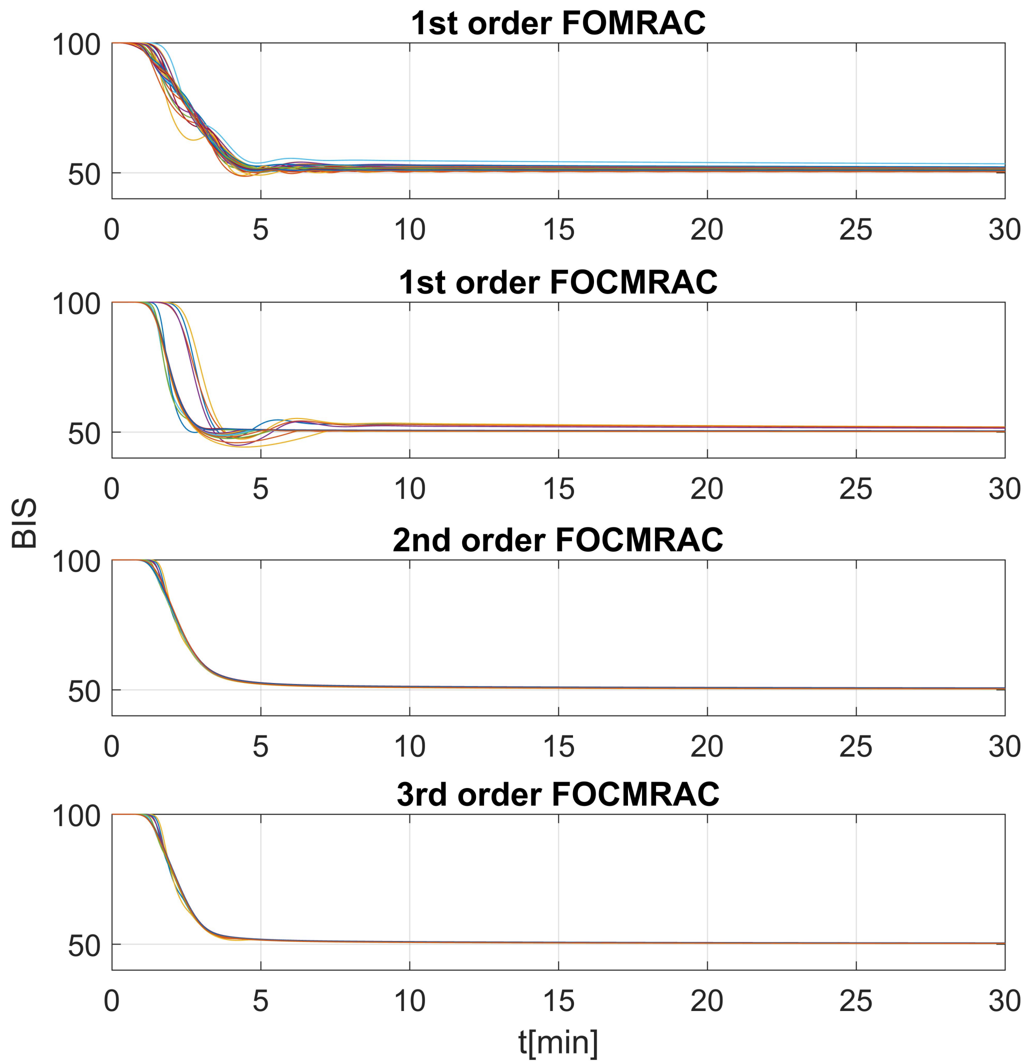


Figure 6.6: BIS output of the 30 virtual patients with the FOMRAC and FOCMRAC schemes

Figure 6.6 shows the response of the 30 virtual patients with the four control schemes. We can observe that all scheme meet the control objective, take all the patients to $BIS = 50$. It can be seen that the controllers based on the second and third-order structure have better performance in comparison with the controllers based on the first-order structure.

Figure 6.7 show the control input of the four controllers implemented and it can be seen a similar behavior between the controllers.

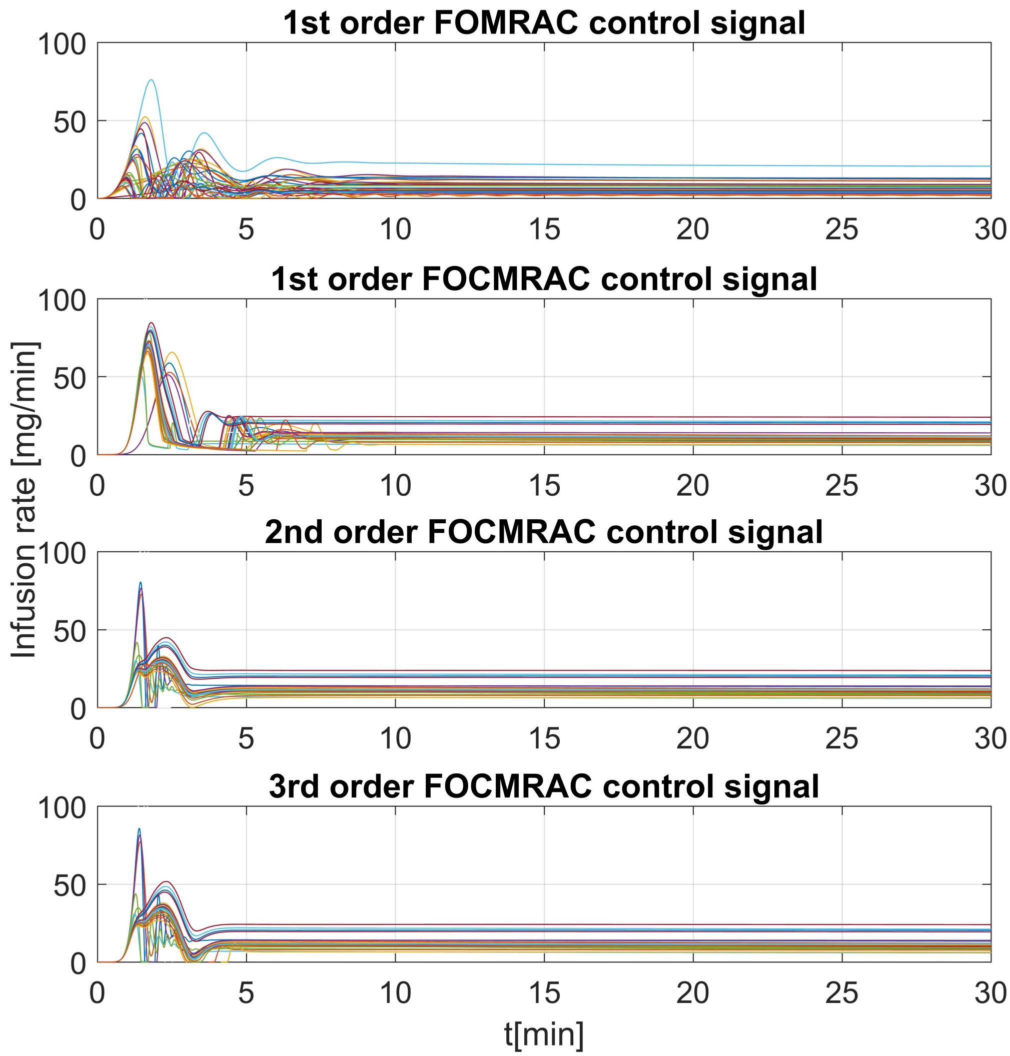


Figure 6.7: Control-input of the FOMRAC and FOCMRAC schemes with the 30 virtual patients

In Figure 6.8 is shown the tracking errors, the error of the FOMRAC scheme have more oscillations in the induction phase and higher convergence time.

In Figures 6.9-6.12 are shown the evolution of the controller parameters.

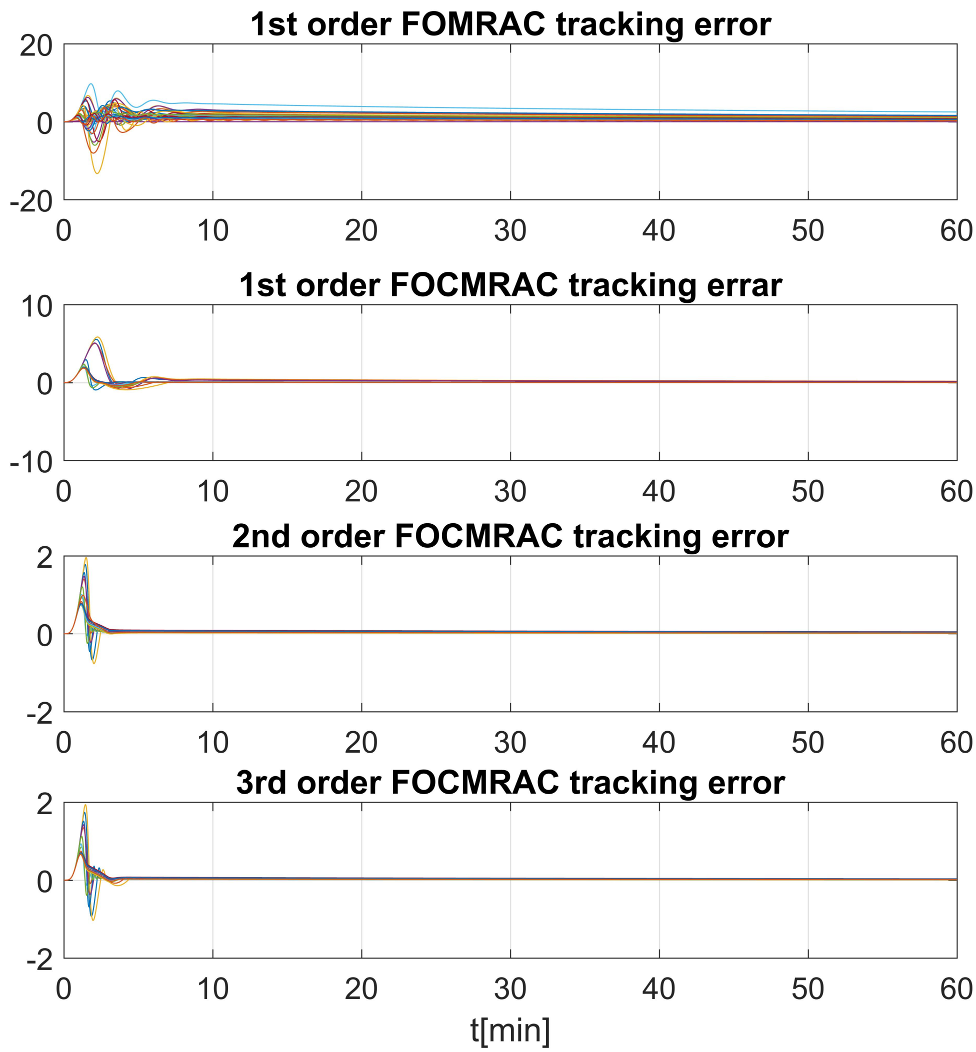


Figure 6.8: Tracking error of the FOMRAC and FOCMRAC schemes with the 30 virtual patients

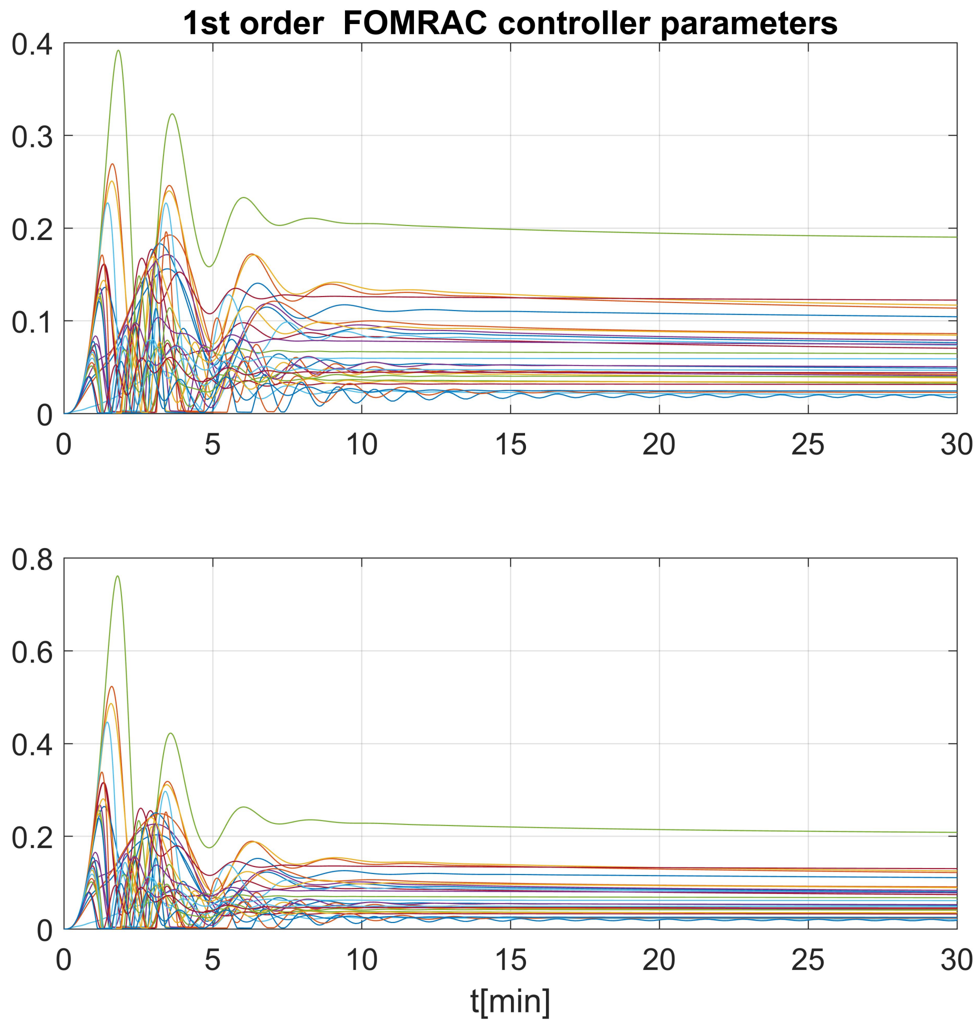


Figure 6.9: Controller parameters of the FOMRAC scheme using the 1st order structure

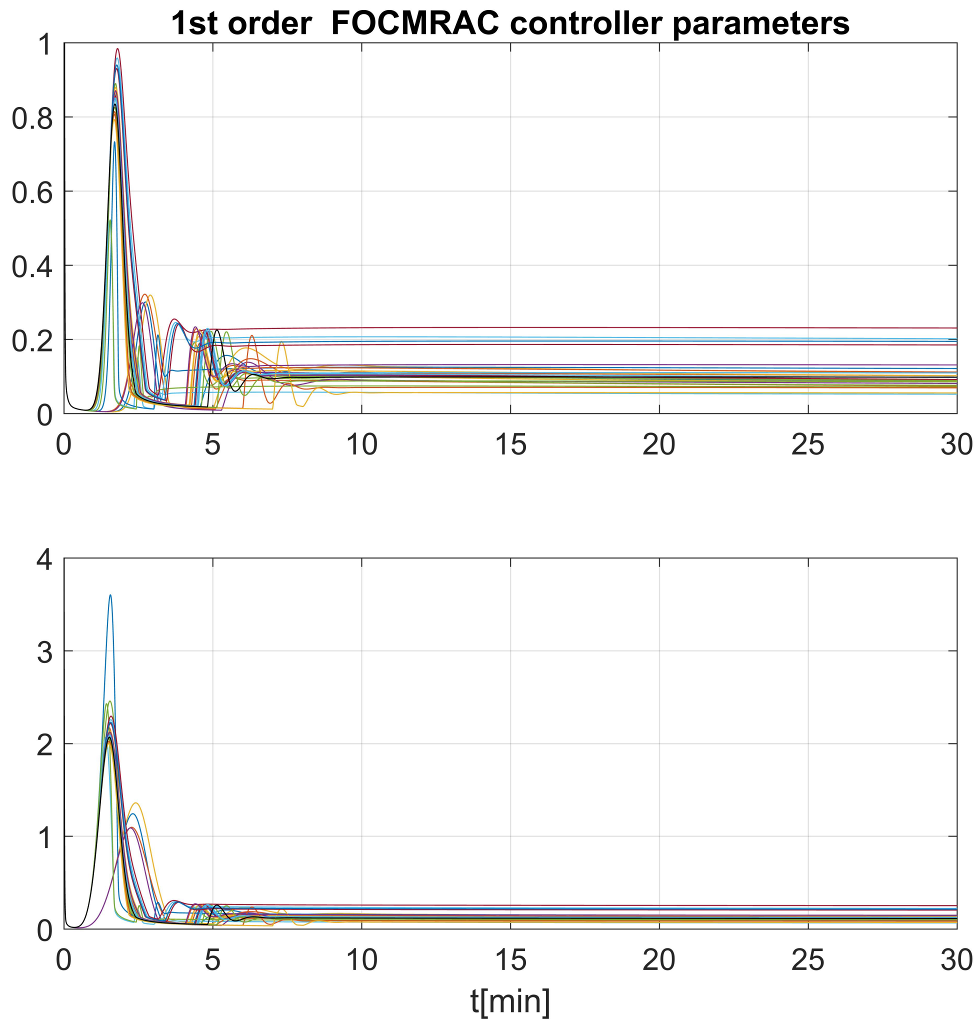


Figure 6.10: Controller parameters of the FCOMRAC scheme using the 1st order structure

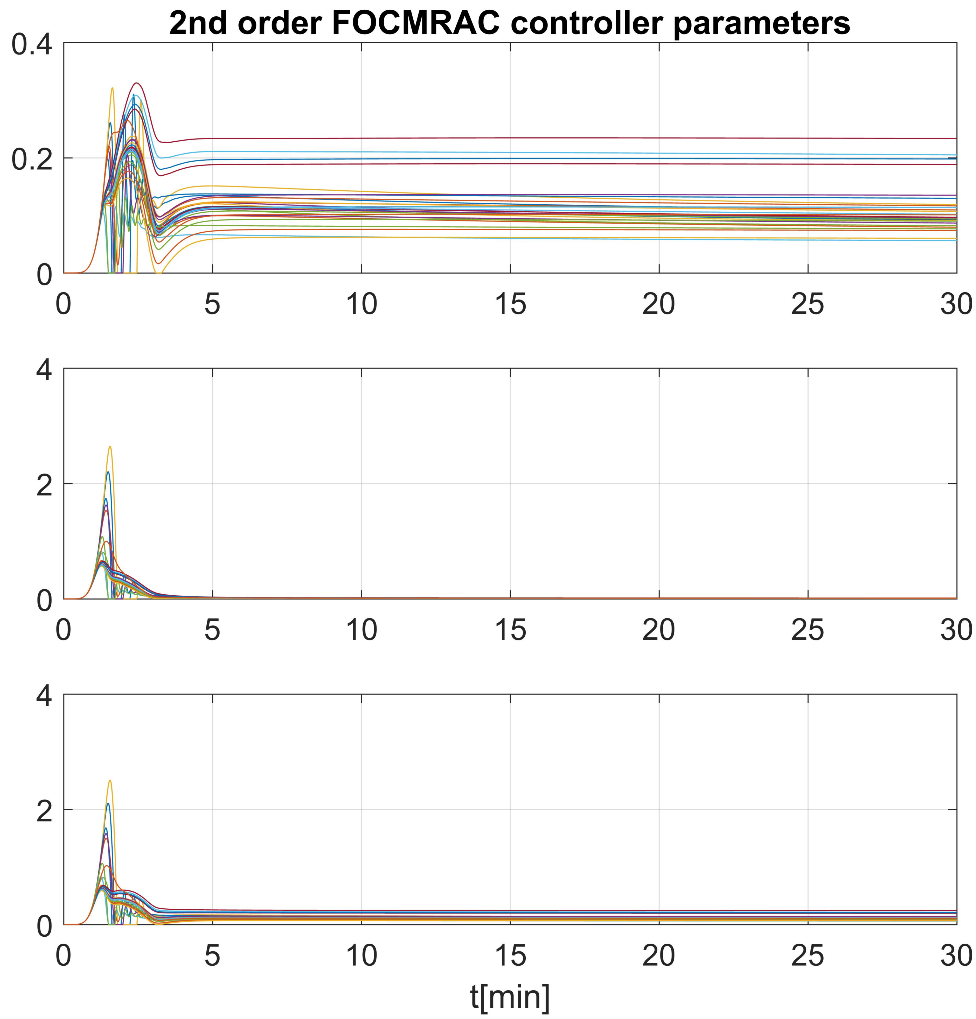


Figure 6.11: Controller parameters of the FOCMRAC scheme using the 2nd order structure

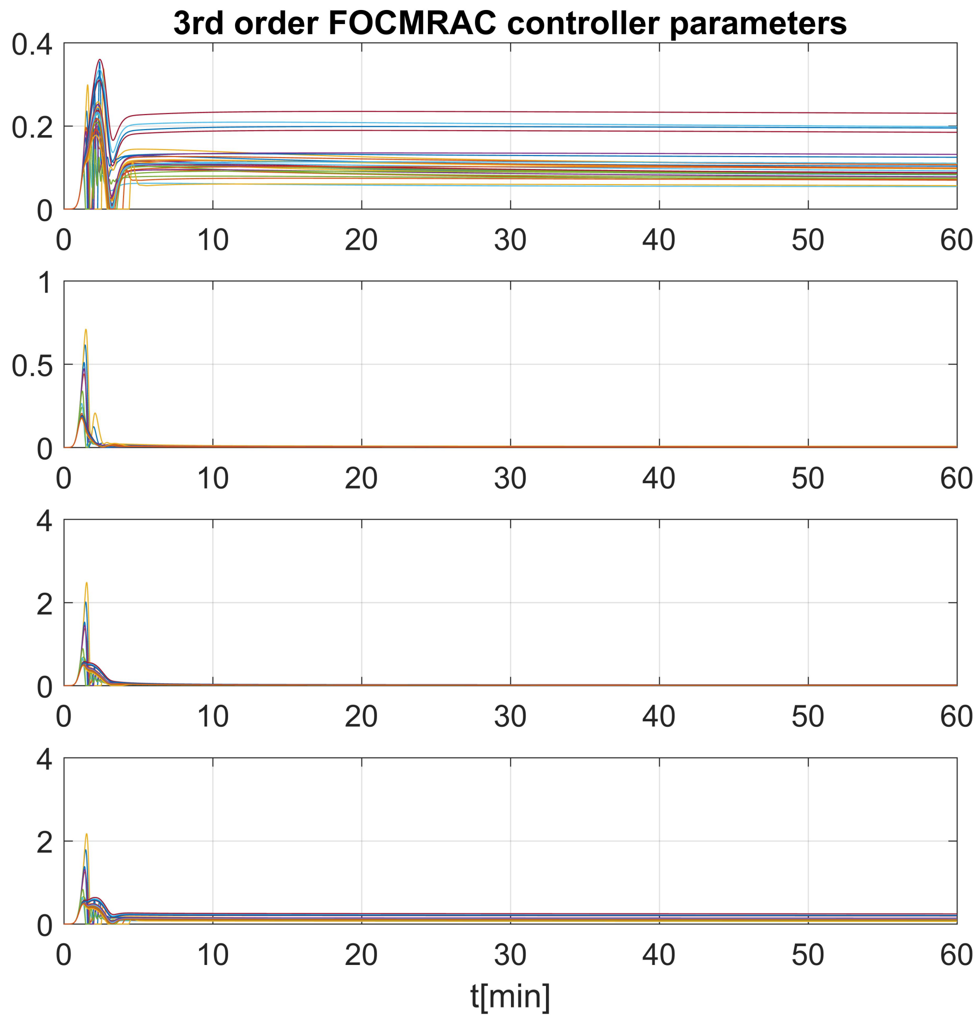


Figure 6.12: Controller parameters of the FOCMRAC scheme using the 3rd order structure

6.2.2 Perturbations and noise robustness

During the maintenance phase is essential that the controller be capable of rejecting disturbances occurred during surgery.

The second simulation illustrates the robustness of the control scheme to perturbations and noisy measurements, specifically, to those perturbations that affect the value of the BIS index in the patients. These perturbations occur because of, for example, intubation of the patient, painful stimuli or blood loss. In Fig. 6.13 shows the artificial disturbance signal. Fig. 6.14 shows the BIS response of the patient 1 with the four control schemes. Notice that the controllers are capable of compensating these perturbations and noise, although the undershoots in the responses are accentuated for the value of the adaptive gain and the lack of negative control. In Fig. 6.15 it is shown the tracking error.

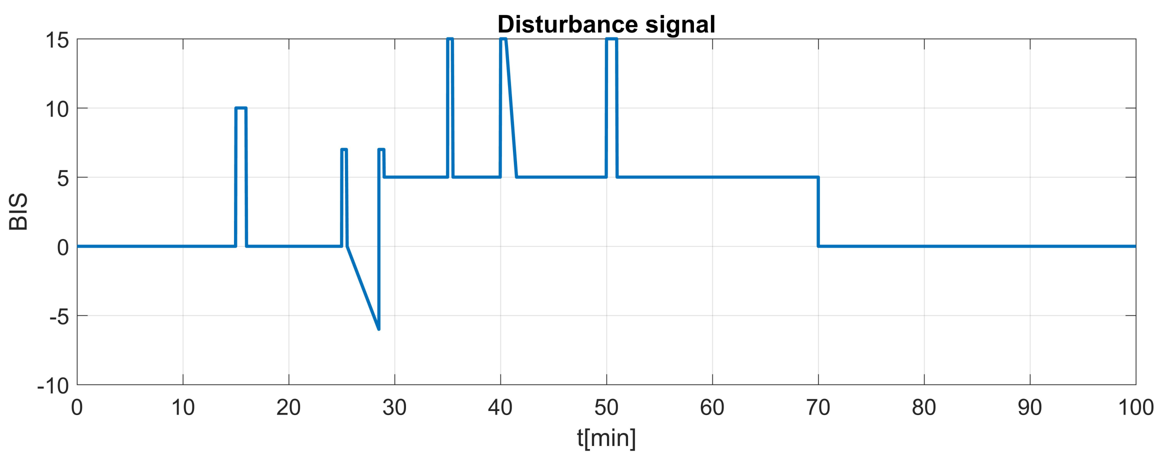


Figure 6.13: Artificial disturbance signal

6.2.3 Time-delay robustness

The simulation illustrates the robustness of the control scheme to the time-delay, represented by the parameter a_{eff} in the effect compartment (5.2) of the PD part of the PK/PD model. In Fig. 6.16 it is shown the step response of patient 1 for different values of a_{eff}.

Figures (6.17-6.20) shows the BIS output, control input and tracking error of patient 1 with different time-delays, from 0 - 8 minutes, approximately. It can be observed that despite the change of the time-delay, the four adaptive controllers are capable of compensating the delay variation, thanks to the memory effect of the fractional operators.

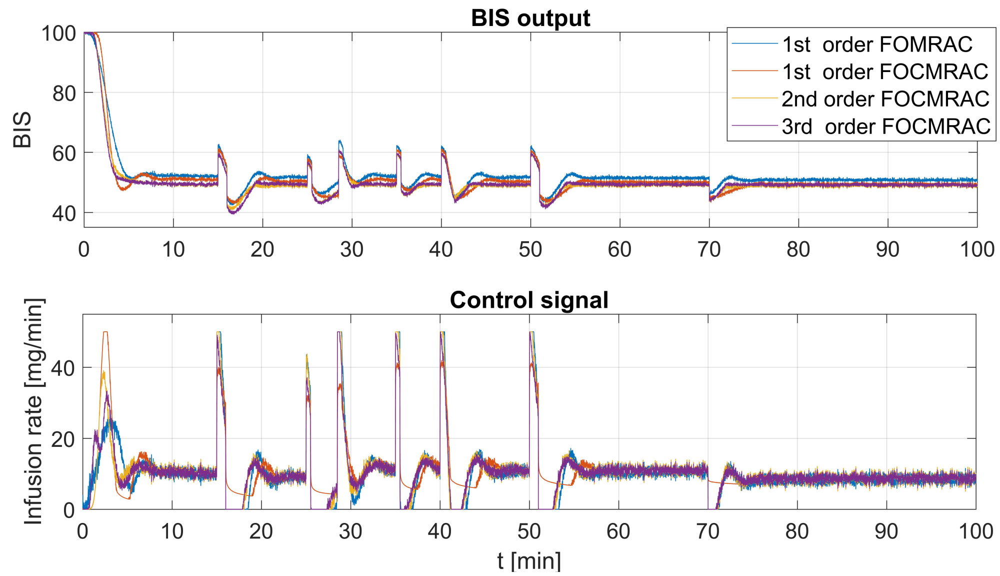


Figure 6.14: BIS response under disturbances and noisy measuremens

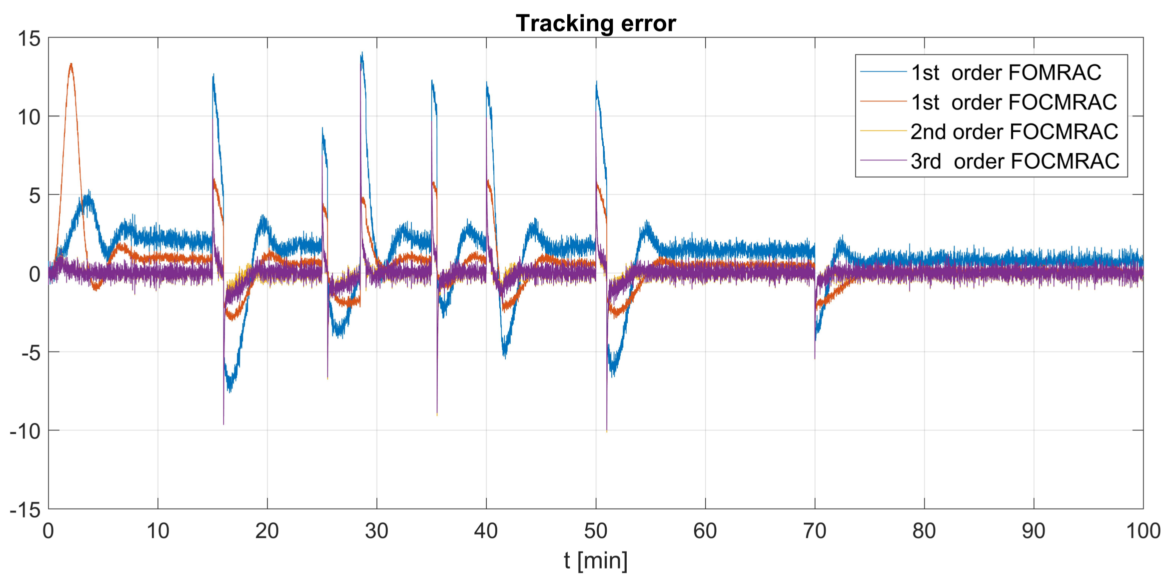


Figure 6.15: Tracking error of the adaptive schemes under disturbances and noisy measuremens

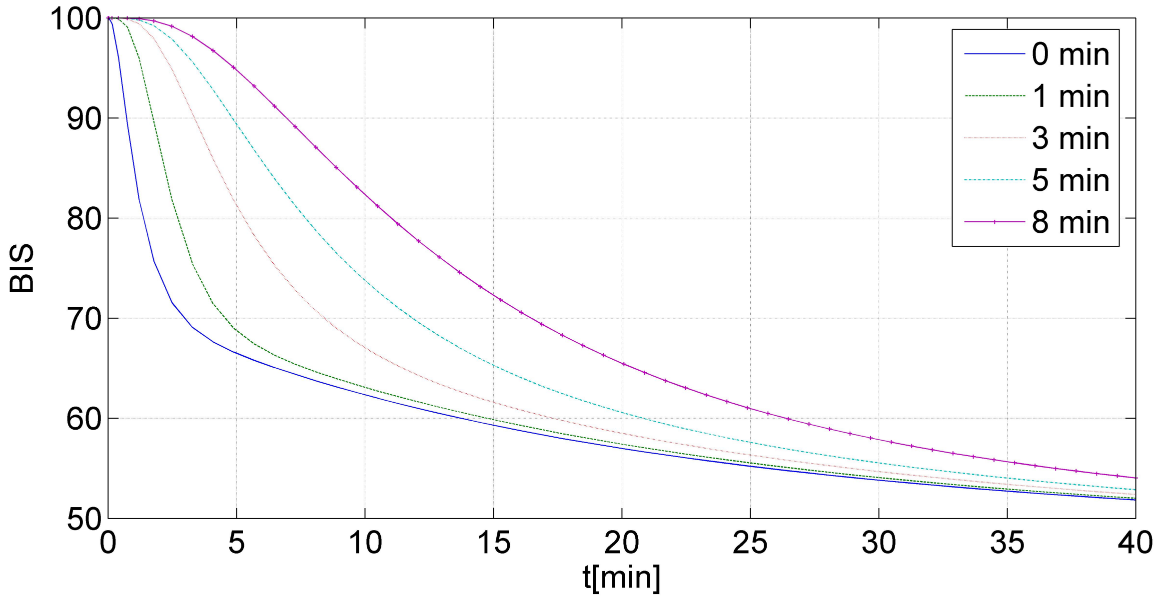


Figure 6.16: Patient response under different values of e_{eff} in the PK/PD model

6.2.4 Comparison between fractional-order and integer-order MRAC schemes

In the last simulation, we make a comparison between the fractional-order MRAC schemes and his counterpart of integer-order applied to patient 1.

In Figure (6.21) and Figure (6.22) shown the adaptive schemes based on the first order model, we can see that the controller of integer-order have an oscillatory response and in particular the MRAC scheme become unstable.

Figure (6.23) show the schemes CMRAC schemes based on the second order model, we can observe that the integer-order controller have a constant oscillatory response around the reference level.

In Figure (6.24) is illustrated the response of the CMRAC schemes based in the third order model, we can observe that the integer-order controller have a damped oscillatory response around the reference level but with a much larger control input.

These simulations show that a complex process like control of anesthesia can be controlled and met the control objective using simple fractional-order models, which is not possible with the same simple models and controllers of integer-order.

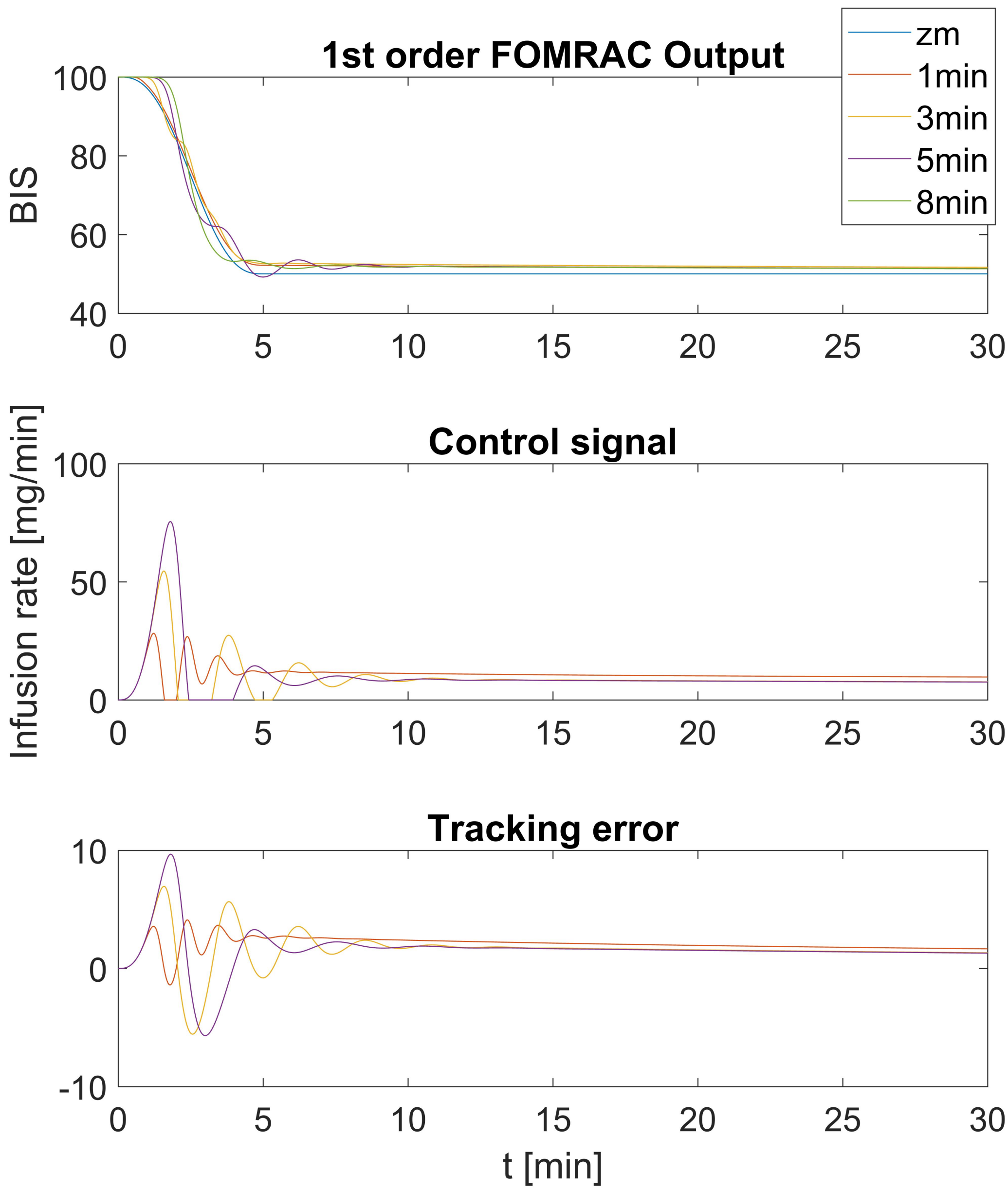


Figure 6.17: BIS response of patient 1 with different time-delays using the 1st order FOMRAC scheme.

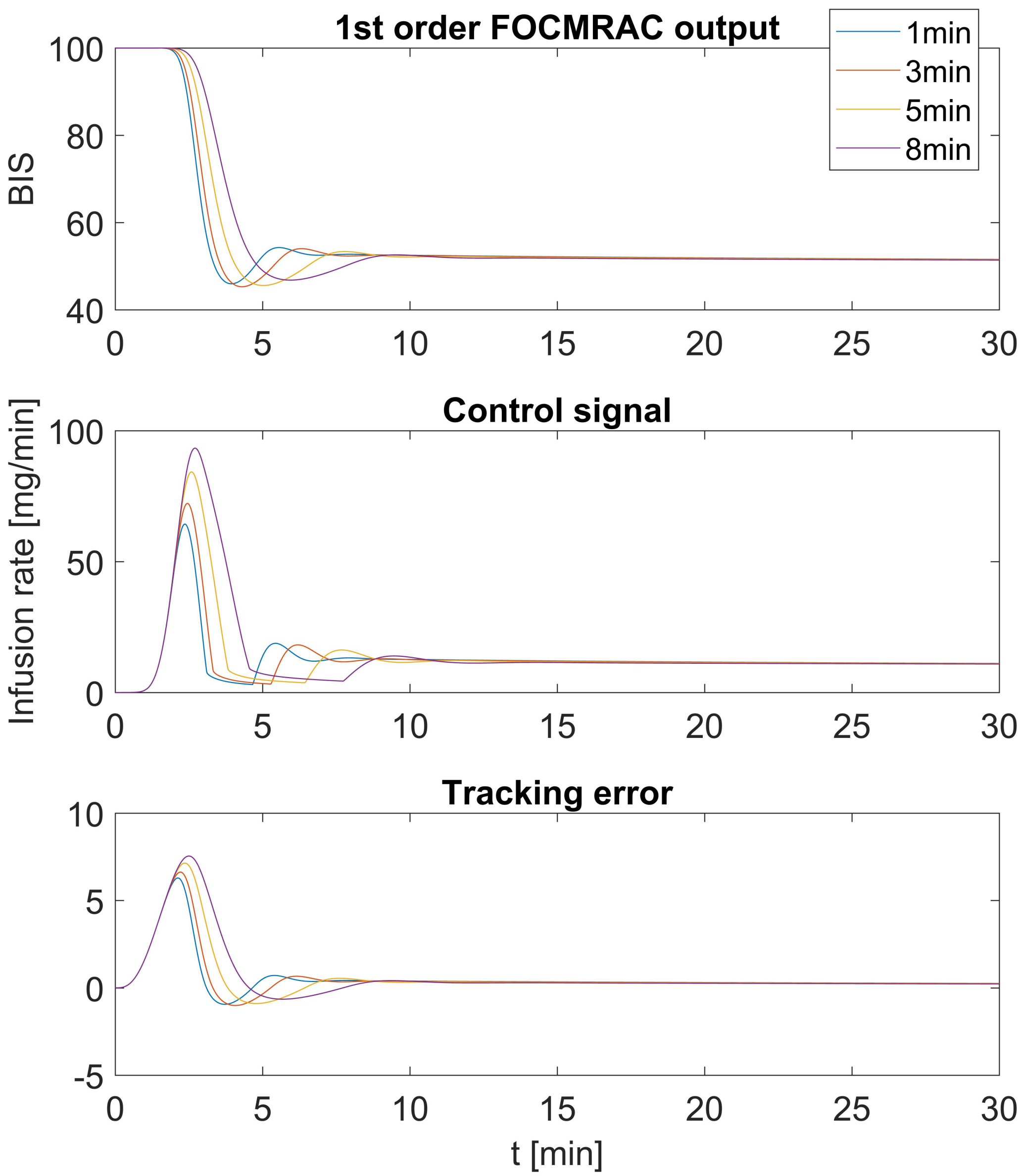


Figure 6.18: BIS response of patient 1 with different time-delays using the 1st order FOCMRAC scheme.

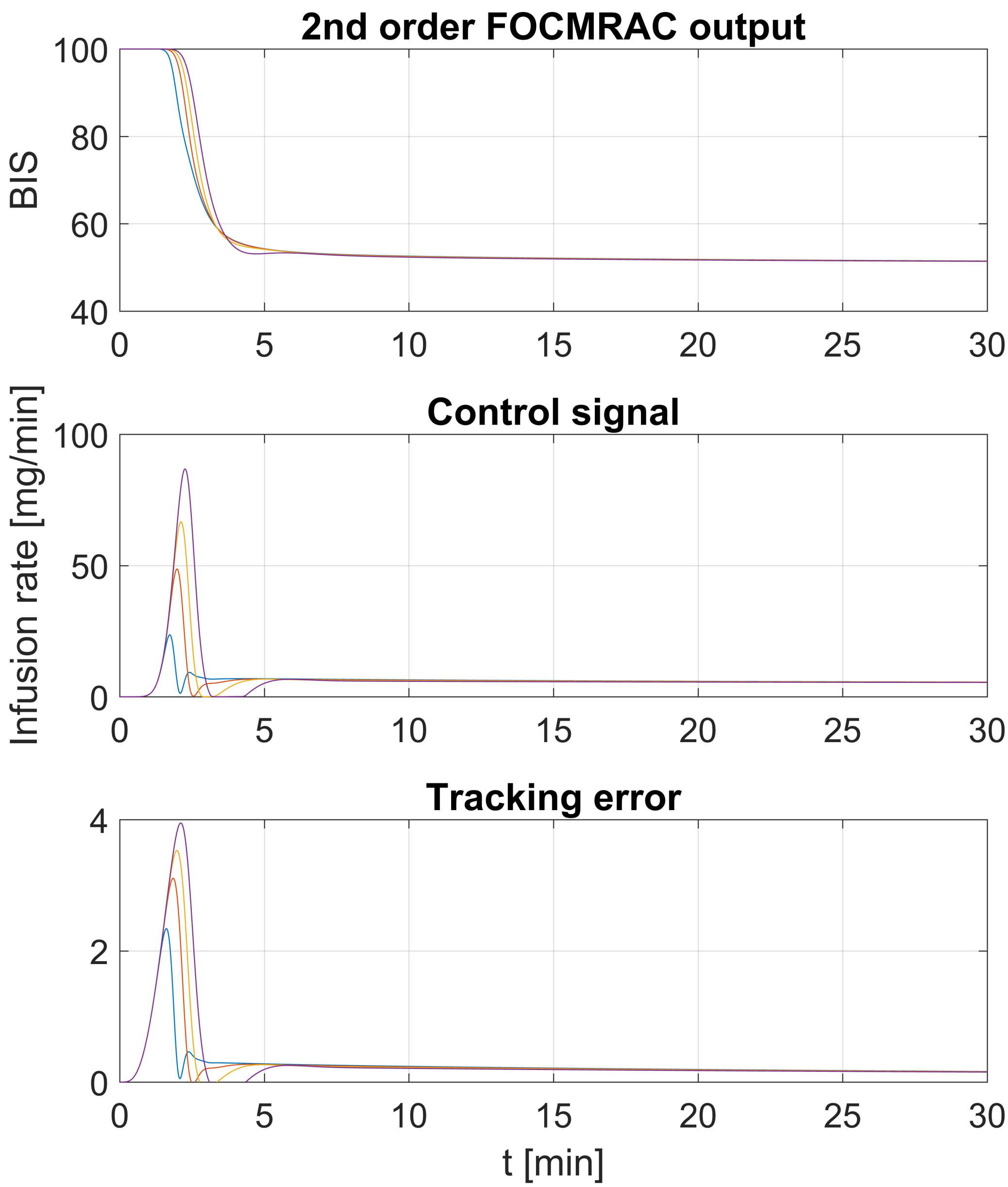


Figure 6.19: BIS response of patient 1 with different time-delays using the 2nd order FOCM-RAC scheme.

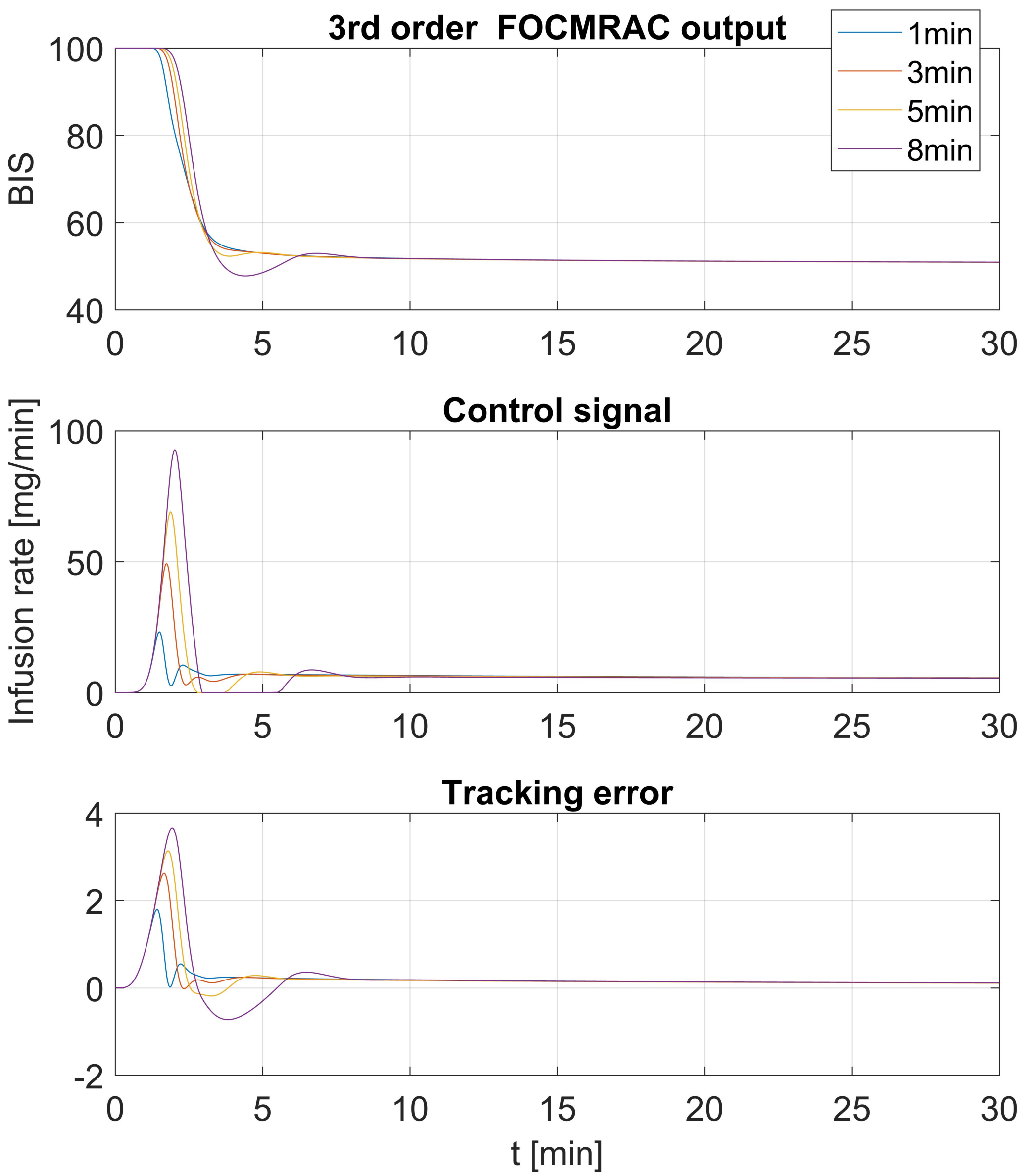


Figure 6.20: BIS response of patient 1 with different time-delays using the 3rd order FOCM-RAC scheme.

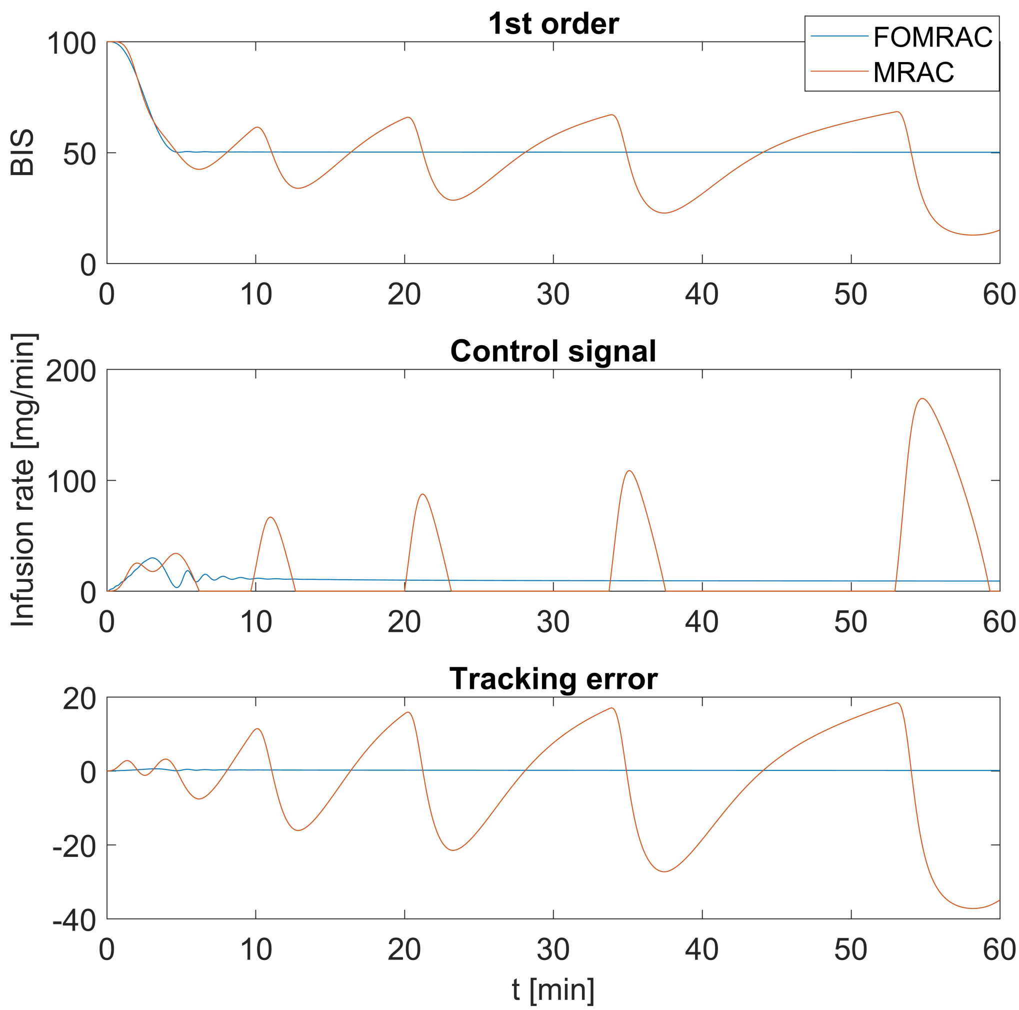


Figure 6.21: Comparison between 1st order FOMRAC and MRAC, BIS output, control signal and tracking error.

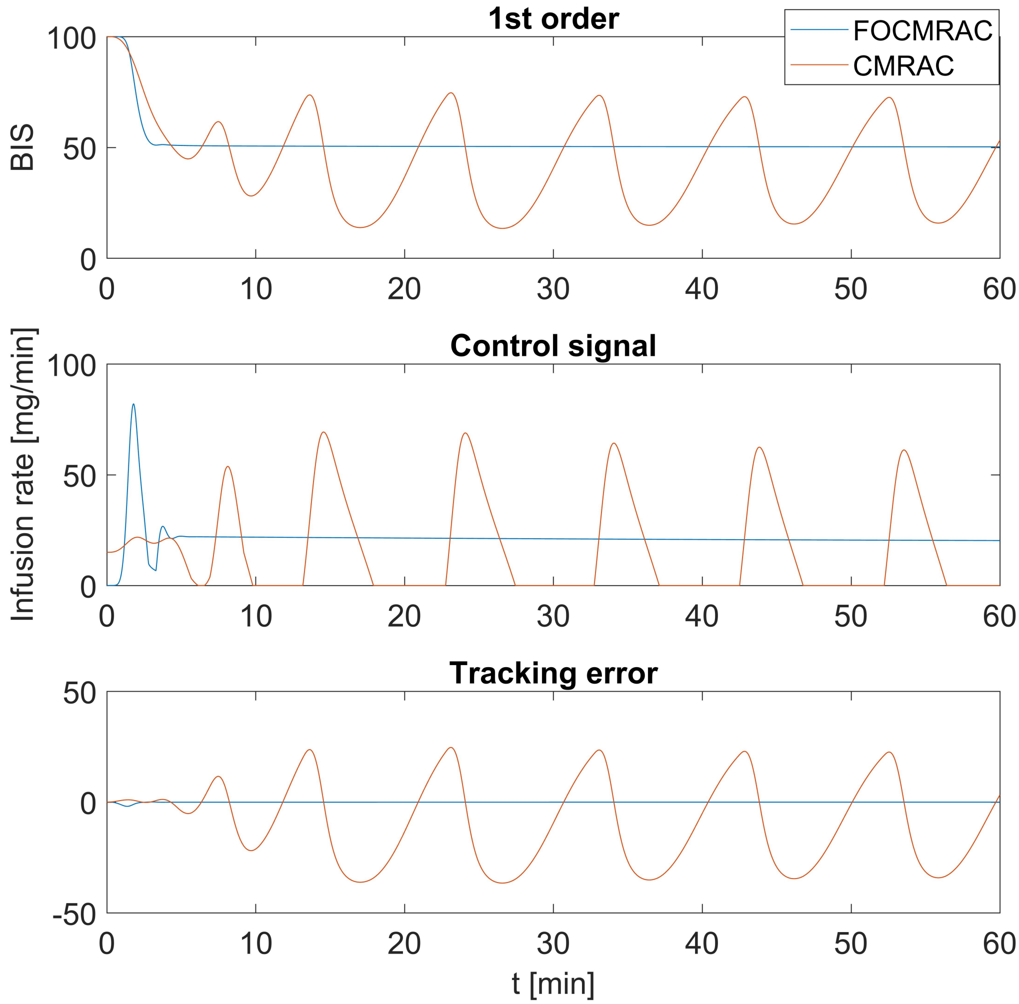


Figure 6.22: Comparison between 1st order FOCMRAC and CMRAC, BIS output, control signal and tracking error.

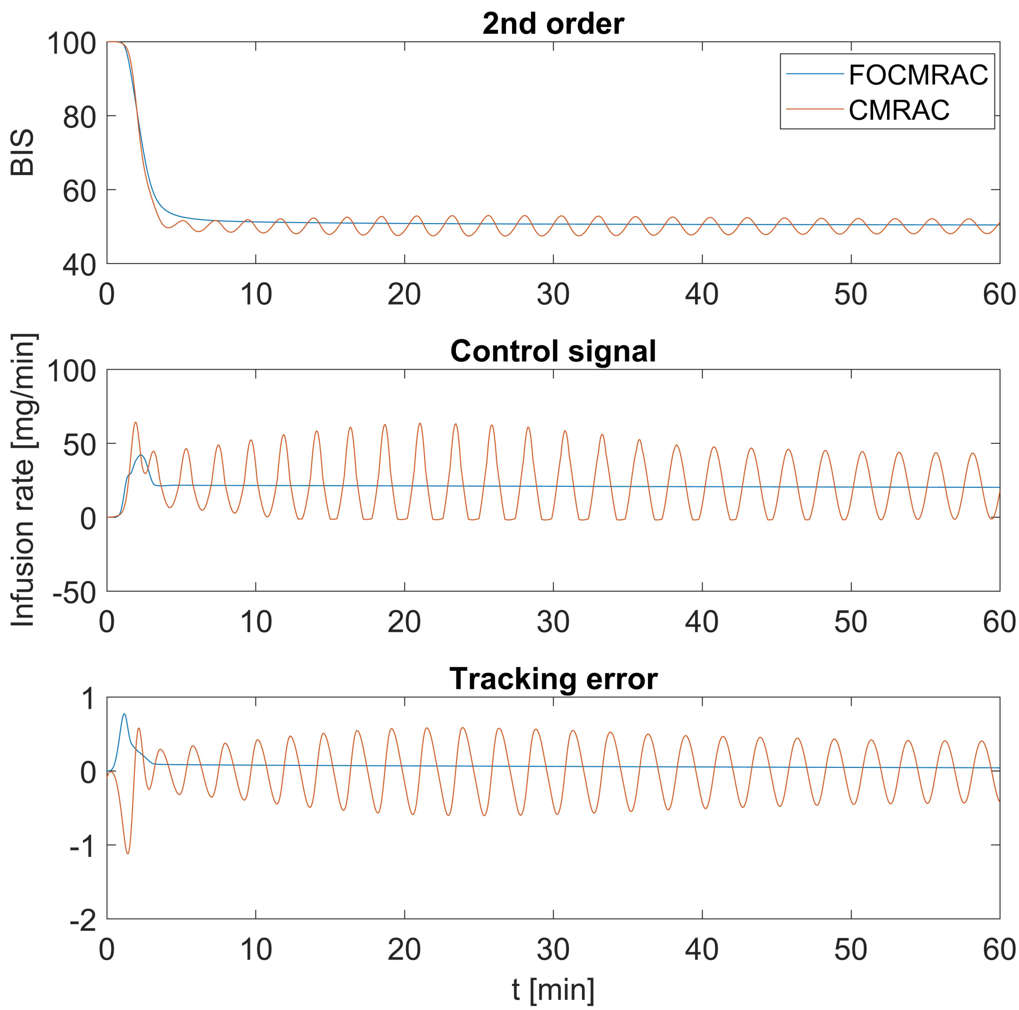


Figure 6.23: Comparison between 2nd order FOCMRAC and CMRAC, BIS output, control signal and tracking error.

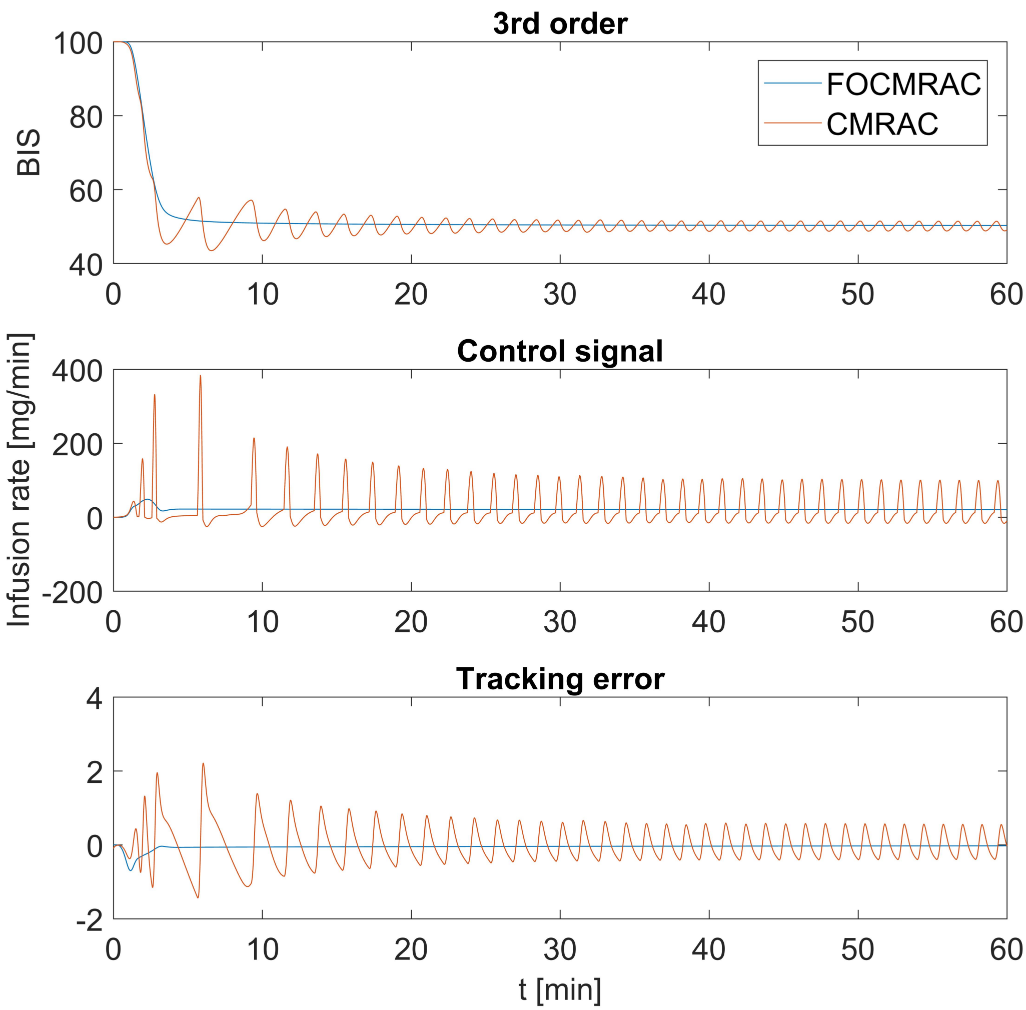


Figure 6.24: Comparison between 3rd order FOCMRAC and CMRAC, BIS output, control signal and tracking error.

Chapter 7

Conclusions

he application of fractional calculus can have a considerable impact on everyday life, namely, in technology, social and health issues. Therefore, significant challenges are still posed to the scientific community that motivates researchers to explore new features of fractional systems.

In the current state of the art of fractional-order modeling, there is a significant gap and disadvantages with respect to the integer-order modeling that prevents to become widely used. Mainly is the lack of a clear physical interpretation, there exist a geometrical (Podlubny 2002, Tarasov 2016), and probabilistic (Machado 2009) interpretation. However, these interpretation are not intuitive and are difficult to grasp which make more controversial the use of fractional calculus to model physical phenomena. Furthermore, these interpretations are not widely accepted, therefore there is no consensus in the community on this essential topic.

For example, suppose that we have an integer-order differential equation that describes the velocity of some object Z, this equation is well understood, and we know the physical interpretations of integral and derivative of that expression, namely, position and acceleration, respectively. Now assume that we find (empirically for example) a fractional-order model that describe more accurate and precise the velocity of the object Z. Then, will arise some question, for example: a variable of a fractional-order equation could represent the velocity of that object?, Which integral or derivative (integer or fractional-order) we need to apply to obtain the position and acceleration of the object?, This mathematical representation is equivalent to his integer-order counterpart?, and ultimately, Are mathematical models with fractional differential equations consistent with the laws of physics?. This fundamental questions and the lack of clear answers is what prevents the widespread use of fractional calculus in the modeling of physical phenomena. However, this controversial concepts could lead to new directions of research.

On the other hand, view this approach as a mathematical tool has shown in the literature in diverse areas and fields an excellent improvement over his integer-order counterpart. In modeling (view as an empirical or black-box model) showing the better fit of experimental data with a more simple structure. Also, in control theory, showing more flexibility in the controller's design and improve performance, opening a vast opportunity for research in this areas.

he utility of the Lyapunov theory to study the stability in many areas of mathematics and engineering is manifest. However, many issues remain controversial in fractional-order systems, for example, What is the state of a fractional-order system? Can a Lyapunov function be defined for variables which are not the state of the system? Are fractional-order systems dynamic ones?, Do Lyapunov stability concepts apply?.

Which is an indicator that the state of development of the Lyapunov theory for fractional-order systems is not fully developed and there is much more work to be done.

In the case of control of anesthesia, we deal with a process that is not fully understand, and with the current integer-order model paradigm, dominated for the PK/PD approach, despite his plausibility and the acceptance of the biomedical and control community, present a significant challenge not only by the nature of the processes (unknown parameters, unknown time delay, states not available for measurement, positivity and poor excitation in the control input) but also by the model structure (Wiener structure). The recent developments in biology and physiology with a focus on fractal dynamics (Bassingthwaighte *et al.* 1994, Magin 2010, West 2010), pharmacology (Dokoumetzidis and Macheras 2009, Verotta 2010, Popović *et al.* 2011, Copot *et al.* 2014) and anesthesia (Chevalier *et al.* 2013, Copot *et al.* 2013), using fractional calculus shown a new paradigm in the understanding and modeling of the physical phenomena in this areas. This new paradigm suggests that the complex phenomena (including anesthesia) can be modeled more precise, accurate and with a simple structure with fractional-order tools.

In this thesis, we present some general and specific contributions. The general contribution is regarded to fractional-order adaptive control, here we proposed an extension of the

Barbalat's lemma which allows us to conclude the convergence of the error to zero in the adaptive schemes designed. We complete the stability proof of the FOMRAC with state feedback applying the extension of the Barbalat's lemma. Moreover, we extended the fractional-order closed-loop MRAC and an identification scheme with output-feedback for fractional-order systems.

Concerning specific results, it was proposed fractional-order models to represent the input-output behavior of the PK/PD model of anesthesia, showing his effectiveness through the identification scheme designed. Moreover, it can be seen that a simple fractional-order structure can capture the response of the patient, which is represented by a nonlinear model (Wiener model) by his integer-order counterpart. The disadvantage is that the proposed fractional models have no physical interpretation and only can be seen as an empirical (phenomenological) model.

Based on this fractional models proposed it was designed a fractional-order MRAC to control the PK/PD model of anesthesia, showing through simulations that these controllers meet the control objectives. Moreover, these schemes are robust again inter and intra-patient variability, time delay, parameter uncertainty, perturbation, and noise.

These results represent a different and novel approach to attack the problem of control of anesthesia, which still is an open problem and an active topic of research.

Future Work

For the short term, we can gather in one place all the results regarding the fractional-order model reference adaptive control. Namely, direct FOMRAC with and without state measurement, indirect FOMRAC, adaptive observers and adaptive identifiers, to locate the missing theory in this area and make contributions.

For the long-term, there are many opportunities of research in a wide range of areas involving the application of fractional calculus, for example, a personal area of interest is the modeling and understanding of the physiology using concepts of fractional calculus and the control of biomedical systems in general.

In control of anesthesia, it is also an active area of research because the challenges involved and the possible benefits of the automatization of this process, and we could deepen the research on this topic using fractional-order control.

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