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Controller design for neuromuscular blockade level tracking based on optimal control

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ABSTRACT

The contribution of this paper is to present and compare two state-feedback design methods for the automatic control of the Neuromuscular Blockade Level (NMB) based on optimal control. For this purpose a parsimoniously parameterized model is used to describe the patient's response to a muscle relaxant. Due to clinical restrictions the controller action begins when the patient recovers after an initial drug *bolus*. The NMB control problem, typically consisting of tracking a constant NMB reference level, can be associated with an optimal control problem (OCP) with a positivity constraint in the input signal. Due to the complexity associated with the introduction of a positivity constraint in the input, approximate solutions to this OCP will be found in this paper using two methods. In the first method, the optimal control problem is relaxed into a Semi-Definite Program (SDP) using a change of variables, whereas in the second method the OCP is approximated by an infinite horizon constrained Linear Quadratic Regulator (LQR) problem. These two controllers are compared with a classical PI controller in simulation. The PI exhibits a slightly worse performance in terms of the control magnitude but it was not optimized taking this magnitude into account. The simulation results show that the SDP relaxation and the saturated LQR methods lead to the same controller gains and therefore the same trajectory tracking using parameters from a patient's database, thus encouraging its application and validation in clinical trials. Although the performance of the proposed controllers can be compared in terms of how they work when applied to the patient's database models, the two proposed methods cannot be compared from an optimal control theoretical point of view because they correspond to the solution of two different relaxations of the original control problem using two different functions of merit.

1. Introduction

State feedback has been widely used to solve a variety of control problems over the last years, including the automatic control of the drug dosing during general anesthesia (Mendonça, Magalhães, Lago, & Esteves, 2004). The aim of this paper is to present and analyze the performance of two state feedback control laws for the administration of a muscle relaxant in order to achieve a desired muscle inactivity (neuromuscular blockade). At the beginning of the surgery a *bolus* of muscle relaxant is administered to the patient to facilitate the intubation; after this initial phase the administration of muscle relaxants is maintained to enable the remaining surgical procedures. The effect of the muscle relaxants is measured by the neuromuscular blockade (NMB) level. This level is assessed by applying a supramaximal train-of-four (TOF) stimulus of the *adductor pollicis* muscle of the patient's hand and can be registered by electromyography (EMG), mechanomyography (MMG) or acceleromyography (AMG) (McGranth & Hunter, 2006). The NMB level then corresponds to the first response calibrated by a reference twitch and varies between 100% (full muscle activity) and 0% (full paralysis). According to general clinical practice, the desired NMB level during general surgery is 10%.

As shown in Fig. 1, the NMB can be modeled by a pharmacokinetic/ pharmacodynamic (PK/PD) model (Weatherley, Williams, & Neil, 1983). This is a physiological model that explains the effect of the muscle relaxant in the patient. The first block relates the drug amount, $u(t)$, with the plasmatic concentration $c_p(t)$, through the pharmacokinetic model. The pharmacodynamic model relates the plasmatic concentration with the effect concentration, $c_e(t)$, by means of a linear equation, and this is in turn related with the NMB level by a static nonlinearity, known as Hill's equation, Weatherley et al. (1983). This model involves a total of eight patient-dependent parameters which may be difficult to estimate.

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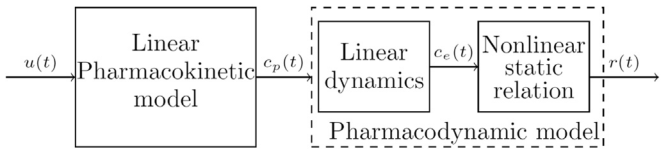

Fig. 1. PK/PD model diagram scheme.

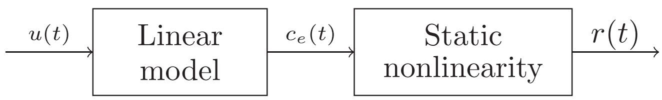

Fig. 2. PP model diagram scheme.

In this paper an alternative model will be used as basis for the design of our control strategies. This model has been introduced in Silva, Wigren, and Mendonça (2012) to overcome the drawback related to the high number of parameters of the PK/PD model. The main advantage of this new model is that it involves a much lower number of patient dependent parameters while keeping an adequate modeling accuracy for control design (Silva et al., 2014). For this reason this model is known as parsimoniously parameterized (PP), as shown in Silva et al. (2012).

The PP model is not a physiological model and does not have a PK/PD structure. However it maintains a Wiener structure with the Hill's equation as nonlinear part, Fig. 2. The PP model has recently been successfully used for the design of some automatic control schemes for drug delivery (Almeida, Mendonça, & Rocha, 2011; Silva, PAz, Wigren, & Mendonça, 2015).

The problem of tracking a desired NMB level by means of automatic controllers for the administration of muscle relaxants has been widely addressed in the literature, see for instance (Almeida et al., 2011) and the references therein. However, the optimal control techniques presented here have not been used for solving the tracking problem, which is an important gap in the literature given the optimal nature of the tracking problem. One of the major difficulties preventing the use of optimal control techniques is the positivity constraint in the control input, which corresponds to the amount of drug to be administered, since it is obviously impossible to extract the drug from the blood vessels after its administration, and, also, because in many cases an antidote is not available. Positive control systems, also called non-negative control systems, have been widely studied in the literature but optimal control of positive systems has not been used to address the NMB tracking problem, to the best of our knowledge. For an earlier account of the properties of positive systems see Luenberger (1979) and for a comprehensive summary of the research on non-negative systems up to 2010 see Haddad, Chellaboina, and Hui (2010).

In this paper we focus on the feedback control of a positive linear system with a static nonlinearity at the output. Our approach is to formulate an Optimal Control Problem (OCP) in order to design a controller that tracks a desired NMB level. This has the advantage of enabling a penalty for the excessive use of drug. An OCP problem with non-negative input and state constraints is in general hard to solve. Reference Goebel and Subbotin (2007) proposes a technique based on duality for Linear Quadratic Regulator (LQR) problems with constrained input but it assumes that the origin is in the interior of the allowable set for the control inputs, which is not the case for positive systems. In Beauthier and Winkin (2010) LQ optimal control of positive linear systems is studied. The optimal control is obtained through the solution of a Hamiltonian two point boundary value problem and it is time dependent instead of a state feedback solution. Furthermore, for the continuous time example presented in the paper the solution has to be obtained by numerical integration of the equations. A more recent paper on constrained LQR problems (Burachik, Kaya, & Majeed, 2014) proposes to solve the dual problem of the LQR but it yields again a controller that is time dependent that must be computed by a numerical algorithm. An alternative technique for positive linear systems yielding a state feedback controller is derived in Roszak and Davison (2008) where a clamping controller with an integral term of the tracking error is proposed. Although this is an extremely interesting technique leading to a state feedback solution for positive linear systems, it does not correspond to the solution of an optimal control problem. Furthermore, the integral term may suffer from the well-known phenomenon of windup, which should be avoided for a drug delivery control problem.

There are three important objectives of the work in this paper that are different from the approaches presented in the literature:

- the system has a static nonlinearity at the output,
- integral terms in the controller will be avoided because of possible windup,
- the solution that is sought is a feedback controller instead of a time dependent control law.

Due to the stated objectives and the added complexity associated with the introduction of a positivity constraint in the input, we consider two different approximations to the solution of an OCP. In the first approximation, the tracking problem is formulated as a suitable finite horizon OCP, which is then relaxed into a semi-definite program (SDP) by replacing the original variables by their moments up to a certain order in the same line of what is done in Lasserre (2009) and Lasserre, Henrion, Prieur, and Trélat (2008). The optimal values of the moments can then be computed by semi-definite programming solvers (Grant & Boyd; Lofberg, 2013; Sturm, 2013) and the gains of the state-feedback control law are then computed based on these values. Although the obtained control law is only an approximation of the optimal solution, this approach has the advantage of easily coping with state and input constraints. The second approximation consists of a reformulation of the OCP as an infinite horizon LQR problem with constraints following the ideas presented in Bellman (1954) and Doná, Seron, Mayne, and Goodwin (2002). The approximate solution consists of imposing a saturation to the optimal feedback control obtained *via* the solution of the algebraic Riccati equation associated with the unconstrained LQR problem. As shown in Doná et al. (2002) for the discrete-time case, the saturated control law can be optimal for the constrained problem only under certain special conditions, and therefore such a solution is in general only an approximation to the optimal. Since this method yields an approximate solution of the associated finite horizon problem while yielding time independent instead of time dependent gains, it leads to a clear advantage for real-time implementation. These two proposed methods will be compared to a classical PI in the section on simulation results.

This paper is organized as follows. Section 2 presents the NMB model used to design the control law and to simulate the patient's response. Section 3 is dedicated to the design of the state-feedback control laws, and Section 4 presents the main simulation results. Finally, the conclusions are presented in Section 5.

2. Neuromuscular blockade model

The PP model for the patient's NMB level response to the administration of the muscle relaxant *rocuronium* is presented in this section. This model will be used to design the feedback control laws as well as to simulate the patient's response.

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