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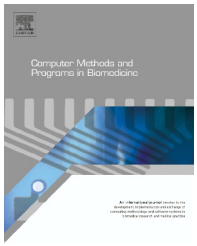

Local identifiability and sensitivity analysis of neuromuscular blockade and depth of hypnosis models

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ABSTRACT

This paper addresses the local identifiability and sensitivity properties of two classes of Wiener models for the neuromuscular blockade and depth of hypnosis, when drug dose profiles like the ones commonly administered in the clinical practice are used as model inputs. The local parameter identifiability was assessed based on the singular value decomposition of the normalized sensitivity matrix. For the given input signal excitation, the results show an over-parameterization of the standard pharmacokinetic/pharmacodynamic models. The same identifiability assessment was performed on recently proposed minimally parameterized parsimonious models for both the neuromuscular blockade and the depth of hypnosis. The results show that the majority of the model parameters are identifiable from the available input–output data. This indicates that any identification strategy based on the minimally parameterized parsimonious Wiener models for the neuromuscular blockade and for the depth of hypnosis is likely to be more successful than if standard models are used.

Abbreviations: BIS, bispectral index; DoH, depth of hypnosis; EEG, electroencephalogram; MPP, minimally parameterized parsimonious; NMB, neuromuscular blockade; PD, pharmacodynamics; PEM, prediction error method; PK, pharmacokinetics; TOF, train-of-four.

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1. Introduction

This paper addresses the local identifiability and sensitivity properties of two classes of Wiener models for the neuromuscular blockade and the depth of hypnosis of patients subject to general anesthesia.

1.1. *General anesthesia*

General anesthesia is a reversible drug-induced state in which the patient's muscle relaxation, analgesia and hypnosis are guaranteed [1].

The degree of muscle relaxation can be measured from the electromyography evoked at the hand of the patient by electrical stimulation of the *adductor pollicis* muscle to supramaximal train-of-four (TOF) stimulation of the ulnar nerve. In this paper, the measurement of the neuromuscular blockade (NMB) was chosen as the first single response from a TOF stimulation calibrated by a reference twitch [2]. Consequently, the quantification of the NMB is normalized between 0% (total paralysis) and 100% (full muscular activity).

Analgesics aim to provide pain relief. At present, a quantitative and reliable index for the direct measurement of pain in patients has not yet been widely accepted and validated. Hypnotics control the level of unconsciousness and must guarantee absence of recall of intra operative events after surgery. Since most of the hypnotics and analgesics interact, the effect of the administration analgesics in the depth of hypnosis (DoH) modeling is usually taken into account. Several univariate parameters computed using the raw data from the electroencephalogram (EEG) are used to assess the DoH. The bispectral index (BIS) [3] is the most commonly used index by anesthesiologists and researchers in the field to infer the patients' DoH. The BIS ranges from 0, equivalent to a flat line EEG, to 100 (or 97.7 depending on the software version implemented in the BIS monitor), equivalent to a fully awake state. After the induction of a general anesthesia, the BIS should lay between 40 and 65 [4].

1.2. *Background*

From an engineering point of view, a patient under anesthesia may be envisaged as a black box from which the only accessible measurements are the amount of drugs that are administered (the system inputs), and the physiological responses that are monitored (the system outputs). It is too seldom that intermediate variables such as drug concentrations in different parts of the body are measured. Consequently, in order to predict the physiological responses or unobserved concentrations that result from different inputs or external perturbations [5], mathematical models of the effect of drugs have to be built. A major bottleneck of the accuracy of these predictions is the estimation of the model parameters from the measured signals. The possibility to uniquely recover the unknown parameters from input–output data is denoted identifiability. *A priori* global identifiability of linear systems has been extensively studied [6]. However, the systems describing the effect of drugs in the human body are usually nonlinear. Therefore, issues like identifiability of those models and the convergence of the estimates have few general answers [7].

Even though being important for display, warning, decision analysis and outcome comparison [8], a significant use of the models describing the effect of drugs in the human body is to design closed-loop controllers. When identifying systems operating in closed-loop, two important aspects need to be jointly considered [9]: the excitatory properties of the controlled input signals and the model structure. This follows since it is known that a more complicated model with more parameters puts higher requirements on the inputs than do simple models with few parameters [10]. In the case of drug delivery in anesthesia, the drug dose profiles (input signals) have to follow standard administration protocols, and cannot be arbitrarily selected for best identification experiments or probing excitation [8]. In intravenous anesthesia the common practice is to administer a bolus dose (that approximates an impulse from the mathematical point of view) at the beginning of the surgery, followed by a sequence of steps of different amplitudes depending on the patients' needs. Given this poorly exciting profile of the (open-loop and closed-loop) input signals in this application, the choice of the model structure is crucial to guarantee model identifiability.

By looking at the properties of the normalized sensitivity matrix [11], the sensitivity and identifiability properties of the model at a given point in the parameter space can be studied together with the excitatory properties of the input signals. Hence, what is here at stake is the combined effect of the input signal excitation and the number of parameters to be identified in the models.

This identifiability issue was implicitly mentioned in [12], where the authors acknowledge that the main identification challenge lies in that the input–output data is not informative enough to robustly distinguish between two parameters in the standard pharmacokinetic/pharmacodynamic (PK/PD) model used to describe the effect of the hypnotic propofol in anesthesia. Some studies have been recently carried out to explicitly assess the identifiability properties of the standard PK/PD models describing the effect of drugs in anesthesia. Regarding the NMB, the results of a model sensitivity analysis in [13] show that half of the parameters in the standard PK/PD model for the muscle relaxant atracurium are potentially unidentifiable. In the paper, this information is useful to modify the weights of a Bayesian cost function for the identification of the model parameters. This approach was further extended in [14] to the standard DoH model, using data from sedation cases. The conclusions of the local parameter identifiability assessment in [14] are that the standard PK model is not fully identifiable, which suggests the use of other, simpler, models.

Minimally parameterized parsimonious (MPP) models for these two components of anesthesia were recently proposed [15,16], and no identifiability study on those models has been carried out yet.

1.3. *Contributions and paper structure*

The first contribution of this paper is to investigate the sensitivity with respect to the model parameters of both the standard PK/PD and the MPP Wiener models for the NMB and