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Modelling of BIS-Index Dynamics for Total Intravenous Anesthesia Simulation in Matlab-Simulink ⋆

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Abstract:
The anesthesiologic technique, where substances are injected intravenously, is known as total intravenous anesthesia (TIVA). The anesthesiologist's task is to carefully assess the depth of anesthesia (DoA) and adjusts the injection of intravenous anesthetic agents accordingly. In the paper, we present a framework for studying DoA dynamics within the Matlab-Simulink environment. DoA can be indirectly measured by bispectral index (BIS index), which is calculated from appropriate electroencephalographic (EEG) signals, and is assumed to be influenced primarily by inflow of propofol. The 3-compartmental model is presented and the 4th (virtual) compartment dealing with the effect-site model is introduced. Next, the pharmacodynamic model structure is presented and the BIS-index effect output is formulated. The relevant parameters based on patient's age, weight, height and gender are established. The model is verified by comparing the simulation results to the data obtained during an actual target-controlled anesthetic application of intravenously administered propofol (total duration approx. 70 minutes).
The data were recorded by an Orchestra Base Primea infusion workstation and a Lidco monitor. The data parser and the model developed in the Matlab-Simulink environment provide a basis for further refining the dynamic model and for development and validation of closed-loop control approaches for DoA. The presented model allows conducting simulations and tests of various scenarios of propofol administration within the Matlab-Simulink environment with the goal of a deeper insight into the mechanisms of DoA dynamics. This will lead to better administration methods that will benefit the patient, relieve the workload and allow the anesthesiologist to focus on the critical aspects of the procedure.

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Keywords: Target-Controlled Infusion; Propofol; BIS index; Depth of Anesthesia; Matlab-Simulink Environment;

1. INTRODUCTION

When performing a general anesthesia (GA), it is necessary to use substances, which enable deep unconsciousness, analgesia, amnesia and muscle relaxation. A proper introduction of anesthetic agents is essential when performing a diagnostic procedure or a surgery. GA and the related activities in the human body are dynamically very complex processes. The processes involve various pharmacokinetic and pharmacodynamic mechanisms, which have not been fully studied yet.

During the GA, the anesthesiologist needs to monitor the patients vital functions and maintain the functions of vital organs. To achieve adequate GA, substances are introduced in different manners into the patients body. In clinical practice, the most commonly used methods are the intravenous induction of an anesthetic agent, i.e., injection of the anesthetic into a vein, and inhalation induction of anesthesia, whereby the patient inhales the substance from the breathing mixture. The anesthesiologic technique, where substances are injected intravenously, is known as total intravenous anesthesia (TIVA).

The goal of the anesthesiologist is to maintain the appropriate depth of anesthesia (DoA) by adjusting the dosage of anesthetic. Clearly, the pharmacokinetics and pharmacodynamics of the anesthetic agent and the type of procedure must be taken into account. Too deep anesthesia is manifested with a drop in blood pressure level and heart

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rate frequency as well as slow post-operative awakening of the patient from GA. On the other hand, inadequate depth of anesthesia results in the activation of sympathetic nerves, or in the most unlikely event with the patient awakening, which must be avoided at all costs. In modern clinical practice, the DoA is determined by assessing the relevant clinical signs (iris, sweating, movements), by interpreting hemodynamic measurements (see Potočnik et al. (2011)) and by estimating the DoA from EEG signals. The latter is made possible by several established measurement systems, e.g. BIS index, Narcotrend, Scale Entropy and Response Entropy.

Bispectral (BIS) index is a non-invasive measurement method. A BIS monitor is connected to electrodes on the patients head and the bispectral index is calculated from the measured EEG signals. The value represents the DoA. The BIS monitor provides a single dimensionless number, which ranges from 0 (equivalent to EEG silence) to 100. A BIS value between 40 and 60 indicates an appropriate level for GA, whereas a value below 40 is appropriate for long-term sedation due to head injuries. The reference can thus be set to the applicable value; the manner and speed of approaching the reference value depend on the specific characteristics of the procedure and the pharmacokinetics and pharmacodynamics of the substance in the patient's body.

There are various approaches to modelling the effect of propofol described in literature. For these purpose, a number of pharmacokinetic and pharmacodynamic models have been developed, e.g. Marsh et al. (1991), Schnider et al. (1998, 1999), Kataria et al. (1994), Scüttler and Ihmsen (2000), Kenny and White (1990) etc. The models of propofol effect typically define the basic structure of the dynamic system, whereas the parameters depend on the individual patient's characteristics, such as weight, height, age, gender etc., as well as the patient's individual sensitivity to propofol and his ability to excrete propofol.

Certain infusion pumps enable target controlled infusion (TCI), where the pump sets the proper flow of the medication with regard to the model. Various pharmacokinetic models can be employed for this purpose. However, the models often do not reflect the real dynamics, which also depends on individual sensitivity of the patients to the substance, which is typically not considered. Since TCI procedures are based on open-loop induction, they often can not ensure optimal performance, especially when dealing with a particular patient's considerable discrepancy from the mean-population models.

In the paper, we present a framework for studying DoA dynamics within the Matlab-Simulink environment. DoA can be indirectly measured by BIS-index (calculated from appropriate EEG signals). It is assumed DoA is primarily influenced by inflow of propofol, which is set by the infusion pump. The paper is organized as follows. First, we introduce the modelling approach to pharmacokinetics and pharmacodynamics of propofol. The 3-compartmental model is presented. The 4th (virtual) compartment dealing with the effect-site model is introduced. Next, the pharmacodynamic model structure is presented and the BIS-index effect output is formulated. The relevant parameters based on patient's age, weight, height and gender are established. In section 4, the model is verified by comparing the simulation results to the data obtained during an actual anesthetic application of intravenously administered propofol (total duration approx. 70 minutes). In the end, we give some concluding remarks.

2. MODELLING THE PHARMACOKINETICS AND PHARMACODYNAMICS OF PROPOFOL

2.1 The 3-compartmental model

The pharmacokinetics of the derived model is based on the Schnider model (see Schnider et al. (1998) and Schnider et al. (1999)). A similar approach for treating the pharmacokinetics of propofol has been described in Karer (2016). However, in that implementation, the Marsh pharmacokinetic model (see Marsh et al. (1991)) has been used. Furthermore, BIS-index output has not been measured nor treated.

A well-established 3-compartmental model structure, as shown in Figure 1 is used as the basis for dynamic relations.

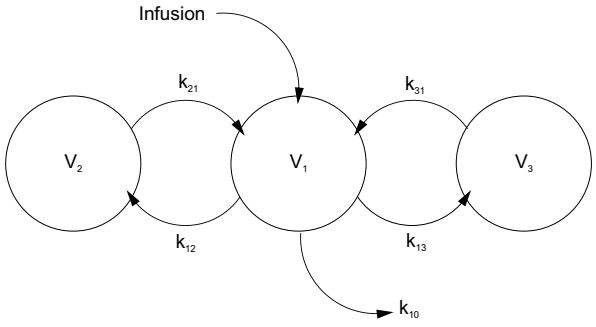

Fig. 1. The pharmacokinetics of the 3-compartmental model.

The 3-compartmental model can be described as follows:

- The drug (namely *propofol*) is injected intravenously into the central compartment (V_1), representing the blood (or plasma) in the body - contained primarily in the arteries and veins and the directly influenced tissues and organs, such as brain, heart, liver, kidney etc.
- The second compartment (V_2) represents the group of tissues that are indirectly affected by the amount of drug in the central compartment, i.e., mainly the muscles. The exchange of the drug with the central compartment is denoted by k_{12} and k_{21}.
- The third compartment (V_3) represents the group of tissues that can store a certain amount of drug, but the exchange with the central compartment is rather slow, i.e., mainly the fat. However, the amount of drug in these tissues influences the amount of the drug in the central compartment in the long run. The exchange of the drug with the central compartment is denoted by k_{13} and k_{31}.
- The drug is eliminated from the body with a rate denoted by k_{10}.

The internal dynamics of the model can be formulated using eqs. (1), (2), and (3).

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