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# Analysis of an individualized physiologically based model for anesthesia control

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**Abstract:** This paper presents a physiologically based, patient-specific, compartmental model for volatile anesthesia, consisting of a multiple blood and tissue compartmental model, adjusted to the weight, height, sex and age of the patient. The predicted hypnotic effect measured by the Bispectral Index is linked to the arterial anesthetic concentration by an effect site compartment and the Hill-Equation. To gain an in-depth understanding about the influence of individual patient variables and characteristics, the pharmacokinetic and pharmacodynamic variables are analyzed for application of the model in future model predictive control. In this study the pharmacodynamic variables are identified to have a higher influence on the modeling output and are therefore more important to be identified accurately. The initial sensitivity of the patient is calculated based on default physiological variables and updated during the course of anesthesia as a function of the obtained measurement of the Bispectral Index.

*Keywords:* Compartmental model, anesthesia, volatile anesthetics, pharmacokinetics, inter-patient variability, intra-patient variability, pharmacodynamics

## 1. INTRODUCTION & MOTIVATION

The modeling and control of anesthesia is believed to benefit the safety of the patient undergoing surgery and provide anesthetists and researchers with valuable insights. It is expected that high-fidelity modeling and optimized control could (i) pave the way for personalized health care, taking into account the individual patient characteristics for optimal and flexible drug infusion rates, (ii) provide the anesthetist with more time to focus on critical issues, and (iii) improve the safety of the patient by minimizing side-effects (Hemmerling, 2009). One of the challenges for control and modeling of anesthesia remains the high inter- and intra-patient variability. This paper addresses a way to cope with the variability by including individual patient variables in the mathematical description of the pharmacokinetics (PK) and pharmacodynamics (PD). The remaining uncertainty that can not be captured in the model is addressed by estimating the sensitivity of the individual patient during the course of anesthesia, where average values are used as an initial guess.

Anesthetists use the minimum alveolar concentration (MAC) defined as the concentration that is required to prevent movement in response to surgical incision in 50 % of the patients as a guideline. Usually 1.3 MAC of the volatile anesthetic is administered during anesthesia to assure sufficient anesthesia in 90% of the patients (Miller et al., 2010). The resulting cumulative probability curve for the entire population is shown in Fig. 1.

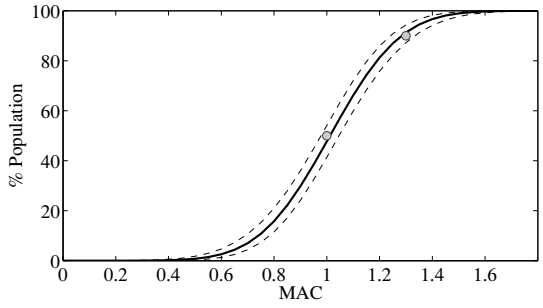


Fig. 1. Population distribution of MAC to assure sufficient hypnosis with 95% confidence interval. The dots represent 1 MAC for 50% of the patients and 1.3 MAC for 90% of the population.

Fig. 1 highlights the challenge to identify the individual patient's sensitivity and anesthetic state to avoid awareness or overdosing during anesthesia. Studies by Brunner et al. (1994) investigated the correlation of MAC with patient characteristics or analgesics administered during anesthesia, e.g. elderly patients are more sensitive to anesthetics and MAC is decreased with age (Mapleson, 1996). The consideration of all patient specific variables in the mathematical the PK-PD model might still not allow to capture the remaining uncertainty and a control strategy

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based on this model might not be safe for the patient if used in a model predictive controller.
Hence, in this paper a PK-PD model is presented and its variables are analyzed with respect to uncertainty on the hypnotic depth measured by the Bispectral Index (BIS).

## 2. PHYSIOLOGICALLY BASED PATIENT MODEL

In this section a physiologically based model for the distribution and effect of volatile anesthetic drugs is presented. The PK model is based on the model previously published in Krieger et al. (2011).

### *2.1 Pharmacokinetic anesthesia patient model*

The proposed physiologically based compartmental model for volatile anesthetics (Fig. 2) is based on Egers' compartmental model for volatile anesthesia (Eger, 1974), the vessel rich group (VRG), the muscle group (M) and the adipose tissue (F). Each compartment is further subdivided into an ideally mixed lumped blood and ideally mixed lumped tissue part (Fig. 3), applied for multiple compartment models and different drugs by Bischoff (1986). The volumes of the blood and tissue parts are individually adjusted to the weight, height, sex and age of the patient (Krieger et al., 2011). A list of all variables is given in Appendix A.

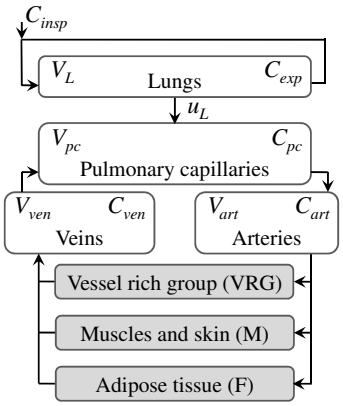


Fig. 2. Structure of the physiologically based patient model

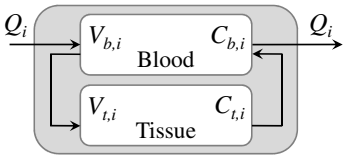


Fig. 3. Structure of one body compartment applied

A flow-limited formulation of the compartments is implemented. This implies that the mass transfer of drug to tissue is restricted by the perfusion of the compartment. This approximation is not fundamental to the physiological pharmacokinetic approach, but commonly used due to the lack of sufficient physiological information of e.g. membrane permeabilities, diffusion coefficients and tissue surfaces (Bischoff, 1986). Adapted from Zwart et al. (1972) an arterial and a venous blood pool as well as a blood pool for the pulmonary capillaries are added to the physiologically based model. No inter-tissue diffusion e.g. from the VRG to the adipose tissue is assumed Zwart et al. (1972). This implies that mass exchange only occurs through the blood vessels. The transport time and the pulsatile character of the blood flow and the ventilation are neglected, because the equilibration times are large compared to cardiac and respiratory cycle (Zwart et al., 1972). All fluxes leaving a compartment are assumed to be in equilibrium with the compartment. This results in equilibrium between the arterial blood leaving the lungs, alveolar gas, and lung tissue.
In the three body compartments the partition coefficients $\lambda_i$ relate the concentrations in the tissue $C_{t,i}$ to the concentrations in the blood $C_{b,i}$ at equilibrium. The driving force of the anesthetic uptake by the tissue $u_{t,i}$ in each compartment is the difference of the concentration in tissue at equilibrium for the given concentration in the blood $C_{b,i}$ and the actual concentration in the tissue $C_{t,i}$ (Enderle et al., 2005).

$$u_{t,i} = Q_i(\lambda_i C_{b,i} - C_{t,i}) \tag{1}$$

The perfusion of the compartment is denoted with $Q_i$. Applying (1) to the anesthetic uptake in the tissues, the mass balances for the blood and tissue sub-compartment of each group result in

$$V_{b,i}\frac{dC_{b,i}}{dt} = Q_i(C_{art} - C_{b,i}) - u_{t,i} \tag{2}$$

$$V_{t,i}\frac{dC_{t,i}}{dt} = u_{t,i} \tag{3}$$

where $C_{art}$ is the concentration in the arterial blood (Fig. 2). The blood and tissue volumes depend on the patient's body volume $V$ and blood volume $V_B$.

$$V_{b,i} = r_{V_B,i} \cdot V_B \tag{4}$$

$$V_{t,i} = r_{V,i} \cdot V \tag{5}$$

The parameter $r_{V_B,i}$ refers to the ratio of the total blood volume in compartment $i$ and $r_{V,i}$ to the ratio of total body volume respectively. The perfusion of compartment $i$ is given as a ratio of the cardiac output $r_{CO,i}$.

$$Q_i = r_{CO,i} \cdot Q_{CO} \tag{6}$$

The uptake of anesthetic in the lungs is determined by two factors, the ventilation and the perfusion. The ventilation is related to the gas exchange in the lungs, described by the dead space in the lungs and the minute ventilation ($f_R V_T$) set through the anesthetic machine. The fluxes of gas and blood in the lungs are shown in Fig. 4.

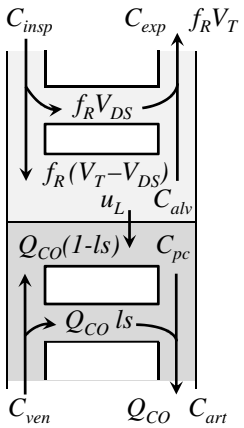


Fig. 4. Detailed blood and gas fluxes in the lungs

The inspired concentration $C_{insp}$ of the volatile anesthetic agent is set by the anesthetic machine. The concentration