INESC-ID Technical Report

A Physiological Model for Human Patients subject to Anaesthesia

Tiago Jorge
INESC-ID
Bolsa de Integração na Investigação BII/1018/2008 of FCT

December 9, 2009
Acknowledgements

This report has been produced in the framework of grant BII/1018/2008, supported by FCT, Portugal. The work was produced at INESC-ID under the supervision of Professor J. Miranda Lemos.

We thank Professor C. Peskin for a suggestion concerning the modelling of heart rate.
## Contents

1 Introduction .......................... 3  
2 Basic structure of the cardiovascular system  .... 4  
3 Compliance and resistive vessels  .... 5  
4 The cardiovascular model .... 6  
   4.1 Systemic and pulmonary circulations  .......... 6  
   4.2 The heart  .................................... 7  
      4.2.1 The ventricles  .......................... 7  
      4.2.2 Variable heart rate  ...................... 9  
      4.2.3 Heart valves  ............................ 9  
   4.3 MAP detection  ............................. 9  
   4.4 MAP-remifentanil interaction .................. 10  
5 The neuromuscular blockade and depth of anaesthesia models ...... 11  
   5.1 Neuromuscular Blockade model .................. 11  
   5.2 Depth of Anaesthesia model .................... 12  
6 Results ................................ 14  
7 Conclusions ............................ 17  
A Appendix: Model parameter values .................. 18
1 Introduction

The purpose of this report is to present a physiological model for use in the simulation of a human patient under the effect of anesthesia. To that effect, the interaction between cardiovascular state indicators (i.e. the mean arterial pressure, MAP) and the effect concentration of the analgesic remifentanil in the patient’s body are also modelled. The importance of these models is considerable given current research in the field of computer-controlled drug delivery to patients undergoing surgical procedures [1] [2].

The basis of the model presented closely follows the work of Frank C. Hoppendsdeadt and Charles S. Peskin [3] in what concerns the cardiovascular system. This is coupled with a pharmacokinetic/pharmacodynamic model for anesthetic drugs [4].

Outline The remainder of this report is organized as follows. First we present the concepts required to understand the components of the cardiovascular model. Following this, the various parts of the cardiovascular model are described and its main characteristics explained. Afterwards, a brief explanation of the previously developed models for patient’s neuromuscular blockade level and depth of anaesthesia is presented. Simulation results that show model behaviour under various conditions are presented in the 6 section. Finally, section 7 gives the conclusions of this report.
2 Basic structure of the cardiovascular system

The model of the cardiovascular system used follows [3] with some adaptations. The human cardiovascular system, represented in figure 1, is responsible for the transport of blood throughout the body. The cardiovascular system, henceforth called circulation system or simply circulation, can be seen as two similar structures that complement each other, forming together a closed loop.

The first is the systemic circulation, responsible for distributing blood to the body tissues where the oxygen ($O_2$) it carries is absorbed and carbon-dioxide ($CO_2$) produced by those tissues is picked up. The complementary structure is the pulmonary circulation, responsible for carrying blood through the lungs, where the blood stream releases the $CO_2$ it had picked up and receives more $O_2$ for distribution.

![Figure 1: Schematic representation of the blood circulation](image)

The systemic circulation starts at the left side of the heart, where blood is pumped by the left ventricle into the systemic arteries, ultimately towards the systemic capilarities. After passing through the systemic capilarities, blood returns to the right side of the heart by means of the systemic veins. Similarly, in the pulmonary circulation blood is pumped from the right ventricle into the pulmonary arteries, passing through the pulmonary capilarities where the gas exchanges occur, and finally returning to the left side of the heart to begin a new cycle.

In order to build this model, we first need to introduce the notions of compliance and resistive vessels.
3 Compliance and resistive vessels

Consider a simple blood vessel, like the one depicted in figure 2, with volume $V$, influx $Q_1$, outflux $Q_2$ and $P_1$ and $P_2$ the pressures at both ends of the vessel. Assuming that blood is an incompressible fluid, if we consider a fixed vessel volume (i.e. a rigid, inelastic vessel) we have $Q_i = Q_o = Q$ and thus the pressure at the outflux end, $P_2$, will be lower than the pressure at the influx end, $P_1$. Specifically, we have

$$Q = \frac{P_1 - P_2}{R} \quad (1)$$

where $R$ is the resistance of the vessel.

If, on the other hand, we consider an elastic vessel that presents no resistance to the flow of blood, like the one depicted in figure 3, then the pressure at both ends of the vessel will be the same ($P_1 = P_2 = P$) and the volume of the vessel will be a function of its pressure. We will consider a linear relationship between $P$ and $V$,

$$V = V_d + CP \quad (2)$$

where $V_d$ is the volume of the blood vessel at zero pressure, called dead volume. Furthermore, since the vessel is elastic its volume changes depending on how much blood flows in and out of it, meaning that

$$\frac{dV}{dt} = Q_1 - Q_2 \quad (3)$$

Note that equation (3) can be seen as a particular form of the mass conservation law.

Vessels that follow equation (1) are called resistive vessels, whereas those that follow equation 2 are called compliance vessels.

Throughout the description of the model, the units used are liters [L] for volumes, liters/second [L s$^{-1}$] for blood flux, milligrams of mercury [mmHg] for pressures, liters/milligram of mercury [L mmHg$^{-1}$] for compliances and milligrams of mercury/blood flux unit [mmHg (L/s)$^{-1}$] for resistances.

![Figure 2: Generic fluid vessel](image2)

![Figure 3: Representation of a compliance vessel](image3)
4 The cardiovascular model

The cardiovascular model comprises the systemic and pulmonary circulations, the heart, the way mean arterial pressure (MAP) is computed and the interaction between MAP and the analgesic drug remifentanil. Figure 4 [3] shows a schematic of the system model whose elements are now detailed.

Figure 4: Schematic of the cardiovascular system [3].

A table containing values for the parameters of the cardiovascular model can be found in Appendix A. Most of these parameters are taken from [3].

4.1 Systemic and pulmonary circulations

Human arteries and veins in the systemic and pulmonary circulations are flexible blood vessels whose volume increases to accommodate for an increase in blood pressure, and decreases when blood pressure drops. Thus, the arteries and veins of both the systemic and pulmonary circulation will be modeled as compliance vessels. In defining these equations, we will use subscripts that represent the vessel we are referring to: $sa$ – systemic arteries; $sv$ – systemic veins; $pa$ – pulmonary arteries; $pv$ – pulmonary veins. Additionally, the subscript $p$ will refer to the pulmonary circulation while $s$ will refer to the systemic circulation.

The equations for these vessels are the ones that relate pressure with volume, reading

$$V_{sa} = (V_d)_{sa} + C_{sa}P_{sa}$$

$$V_{sv} = (V_d)_{sv} + C_{sv}P_{sv}$$

$$V_{pa} = (V_d)_{pa} + C_{pa}P_{pa}$$

$$V_{pv} = (V_d)_{pv} + C_{pv}P_{pv}$$

and those that relate the rate of change in the volume with the in/out flux of the vessel, namely

$$\frac{dV_{sa}}{dt} = Q_{Ao} - Q_S - (Q_L)_{sa}$$

$$\frac{dV_{sv}}{dt} = Q_S - Q_{Tr} - (Q_L)_{sv}$$

$$\frac{dV_{pa}}{dt} = Q_{pa} - Q_P - (Q_L)_{pa}$$

$$\frac{dV_{pv}}{dt} = Q_P - Q_{Mi} - (Q_L)_{pv}.$$
The last term in equations (8 – 11), \((Q_L)_i\) \((i = sa, sv, pa, pv)\), corresponds to a blood loss flux that allows to simulate a loss of blood occurring at any given moment in the simulation. If \((Q_L)_i > 0\), then the patient is losing blood, e.g. a constant blood loss along an entire operation, or an accidental cut of an artery in the middle of the operation. On the other hand, if \((Q_L)_i < 0\), then the patient is receiving blood, e.g. from a blood transfusion. Typically, the last situation is less relevant than the first, which occurs more often, but the model is prepared to handle both.

Systemic and pulmonary tissues, where \(CO_2/O_2\) gas exchanges occur, present a very significative drop in blood pressure. In a typical adult human, blood leaves the left heart into the systemic arteries with a mean pressure of around 100 \(mmHg\), that drops to around 2 \(mmHg\) at the systemic veins. Afterwards, blood is pumped by the right heart, achieves a mean pressure of 15 \(mmHg\) at the pulmonary arteries, and drops to 5 \(mmHg\) after leaving the lung tissues, at the pulmonary veins. For this reason, we model the systemic and pulmonary tissues as resistive vessels, yielding

\[
Q_S = \frac{P_{sa} - P_{sv}}{R_S} \quad (12)
\]

\[
Q_P = \frac{P_{pa} - P_{pv}}{R_P} \quad (13)
\]

where \(Q_S\) and \(Q_P\) represent the value of instantaneous blood flux through the systemic and pulmonary tissues, and \(R_S\) and \(R_P\) the corresponding tissue resistances.

4.2 The heart

The heart model comprises the ventricles and the heart valves.

4.2.1 The ventricles

To complete the description of the model we need to specify how the heart pumps blood into the systemic and pulmonary arteries. Our simple approach consists in “ignoring” that the left and right auricles exist (i.e. consider that they are simply an extension of the pulmonary and systemic veins, respectively), and model both ventricles as compliance compartments, with a time-varying compliance. Thus, for the heart we write the equations that pertain to the left (LV) and right (RV) ventricles,

\[
V_{LV} = (V_d)_{LV} + C_{LV}(t)P_{LV} \quad (14)
\]

\[
\frac{dV_{LV}}{dt} = Q_{Mi} - Q_{Ao} \quad (15)
\]

\[
V_{RV} = (V_d)_{RV} + C_{RV}(t)P_{RV} \cdot \quad (16)
\]

\[
\frac{dV_{RV}}{dt} = Q_{Tr} - Q_{Pu} \quad (17)
\]

where \(Q_{Mi}, Q_{Ao}, Q_{Tr}\) and \(Q_{Pu}\) correspond to the flow of blood through the mitral, aortic, tricuspid and pulmonary heart valves.

The time-varying compliances of the ventricles are implemented by a periodic function such that, during systole the function decreases to a fixed low value, and during diastole it increases up to a different fixed value. Furthermore, since the systolic phase of a heartbeat lasts typically less than the diastolic phase, the absolute value of the rate at which the compliance function decreases in systole will be higher than the absolute value of the rate at which it increases during diastole. For the purposes of the model considered, the same function will be used for both ventricles, with different parameter values in each one. This function is given by
Figure 5: A possible qualitative plot of the ventricle time varying-compliance function, taken from [3]

\[
C(t) = \begin{cases} 
  C_D \left( \frac{C_S}{C_D} \right)^{1 - \exp \left( -t/\tau_S \right) / \tau_D}, & 0 \leq t \leq T_S, \\
  C_S \left( \frac{C_D}{C_S} \right)^{1 - \exp \left( -\left( T - T_S \right)/\tau_D \right) / \tau_D}, & T_S \leq t \leq T, 
\end{cases}
\]  

(18)

where the first term of the equation corresponds to the systolic period of the heartbeat, while the second pertains to the diastolic period. Parameter \( T \) is the duration of a heartbeat (both systole and diastole), \( T_S \) is the duration of systole in a heartbeat, and \( \tau_S \) and \( \tau_D \) are used as time constants to control the speed at which the ventricle compliance decreases from \( C_D \) to \( C_S \) (during systole) or increases from \( C_S \) to \( C_D \) (during diastole), respectively. The plot of this function is given in figure 6.

Note that, although the function plot resembles the one depicted in figure 5, they are clearly not the same. However, it still allows us to achieve the expected results, and will thus be used in the model.

Figure 6: Plot of the ventricular compliance function along time, using \( C_D = 0.0146 \) and \( C_S = 0.00003 \).
4.2.2 Variable heart rate

Equation (18) gives the value of the time-varying compliance if the duration of a heart beat is $T$. In order to change the speed at which the simulated heart is pumping blood, a possible approach might be to change the value of all the parameters of equation (18) that are time-related, i.e. $T$, $T_S$, $\tau_D$ and $\tau_S$.

However, a much simpler approach consists of manipulating the speed at which the compliance function sees time changing. In other words, equation (18) can be fed with time values that do not directly correspond to the simulation time itself, but rather to a modified version of the simulation time, $t_{\text{heart}}$. A situation in which a patient’s heart rate increases can thus be simulated by making $t_{\text{heart}}$ grow faster than $t$, the simulation time. When the modified time, $t_{\text{heart}}$, is growing at the same rate as the simulation time, $t$, that means the patient’s heart beat duration is at it’s normal value, $T_{\text{normal}}$.

This can be translated into an expression for the rate of growth of $t_{\text{normal}}$ that reads

$$\frac{dt_{\text{heart}}}{dt} = \frac{T_{\text{normal}}}{T_{\text{patient}}}$$

where $T_{\text{normal}}$ is the patient’s average heart beat duration and $T_{\text{patient}}$ is the desired value for the (instantaneous) heart beat duration. Equation (19) states that when $T_{\text{patient}}$ increases (i.e. lower heart rate), $t_{\text{heart}}$ grows at a slower pace, effectively slowing down the ventricular compliance computation when seen from the point of view of the simulation time. The opposite effect occurs when $T_{\text{patient}}$ decreases (i.e. higher heart rate).

4.2.3 Heart valves

Blood coming from the left auricle enters the left ventricle through the mitral valve, while blood flowing from the right auricle to the right ventricle passes the tricuspid valve. Furthermore, blood leaving the left and right ventricles passes through the aortic and pulmonary valve, respectively. In order to simulate the presence of these valves we will only consider the model of a perfect valve, i.e. blood will flow through a valve in one direction only. If downstream blood pressure is higher than upstream blood pressure, then the valve will stay closed, and there will be no blood flux through that valve.

Then, blood flux through the heart’s mitral, tricuspid, aortic and pulmonary valves can be described as

$$Q_{Mi} = \begin{cases} \frac{P_{pv} - P_{LV}}{R_{Mi}}, & P_{pv} > P_{LV}, \\ 0, & P_{pv} < P_{LV}, \end{cases}$$

$$Q_{Tr} = \begin{cases} \frac{P_{sv} - P_{RV}}{R_{Tr}}, & P_{sv} > P_{RV}, \\ 0, & P_{sv} < P_{RV}, \end{cases}$$

$$Q_{Ao} = \begin{cases} \frac{P_{LV} - P_{sa}}{R_{Ao}}, & P_{LV} > P_{sa}, \\ 0, & P_{LV} < P_{sa}, \end{cases}$$

$$Q_{Pu} = \begin{cases} \frac{P_{RV} - P_{pa}}{R_{Pu}}, & P_{RV} > P_{pa}, \\ 0, & P_{RV} < P_{pa}, \end{cases}$$

respectively, where $R_{Mi}$, $R_{Tr}$, $R_{Ao}$ and $R_{Pu}$ are the valve resistances to the flow of blood, which are typically chosen with a very small value.

4.3 MAP detection

Defined as the average arterial pressure during a single cardiac cycle, the mean arterial pressure (MAP) is an important indicator of the patient’s state. At normal resting heart
rates, the value of MAP can be estimated as

\[ MAP = P_D + \frac{1}{3}(P_S - P_D) \]  

(24)

where \( P_D \) and \( P_S \) are the diastolic and systolic pressures, respectively.

In order to obtain the value of MAP in this way, it is necessary to first detect the value of the systolic and diastolic pressures, which are the maxima and minima of the systemic arterial pressure (\( P_{sa} \)). Thus, a maximum/minimum detection block was developed. In general terms, the block outputs the value of MAP as computed by (24), where \( P_D \) and \( P_S \) correspond to the most recently detected values of the minimum and maximum of the systemic arterial pressure, respectively. The value of \( P_D \) is held constant until the next local minimum of \( P_{sa} \), when it is updated. The same happens with \( P_S \), in what pertains to the local maximum of \( P_{sa} \).

As such, the value of MAP will remain constant between a local maximum and the next local minimum of \( P_{sa} \) (or vice-versa), and will instantaneously change when the new maximum/minimum is computed. In order to prevent this abrupt change in the value of MAP, the signal is passed through a first-order filter

\[ H(s) = \frac{1}{1 + s\tau} \]  

(25)

where \( \tau = 1 \text{s} \). It is necessary to point out that this solution does not produce a perfect MAP signal, but the results are satisfactory.

### 4.4 MAP-remifentanil interaction

Recent studies suggest that the relation between the effect-site concentration of remifentanil (\( c_{\text{remi}}^{\text{remi}}, [\mu g mL^{-1}] \)), a commonly used analgesic in surgical procedures, and MAP can be modelled as being linear. The slope of the dependence is taken to be \(-176.2 \text{ mmHg} (\mu g/mL)^{-1}\). This means that an increase in the value of \( c_{\text{remi}}^{\text{remi}} \) causes a decrease in the value of MAP.

In this model, MAP is obtained directly from the values of the systemic arterial pressure, which in turn is obtained from equation (4). In that equation, only \( (V_d)_{sa} \) and \( C_{sa} \) are model parameters that can be manipulated. Thus, in order to simulate the effect of the concentration of remifentanil on MAP, we will induce a change in the value of the compliance of the vessel. More specifically, when \( c_{\text{remi}}^{\text{remi}} \) increases, the value of the compliance of the systemic arteries will also increase, thereby making the value of systemic blood pressure, and thus MAP, decrease.

It will be assumed that the systolic and diastolic compliance values for the heart’s ventricles do not change with the value of \( c_{\text{remi}}^{\text{remi}} \). On the other hand, it will be assumed that the compliance values of the remaining four compliance vessels will change with the value of \( c_{\text{remi}}^{\text{remi}} \), and that the measure by which they change is a percentage of their base values (i.e. when \( c_{\text{remi}}^{\text{remi}} = 0 \)).

By trial-and-error it was determined that, in order to achieve the linear model between \( c_{\text{remi}}^{\text{remi}} \) and MAP, the relation between compliance values and \( c_{\text{remi}}^{\text{remi}} \) need only be a linear one. The equations that relate the latter two are as follows

\[ \begin{align*}
C_{sa} &= C_{sa0}(1 + K_{cc}c_{\text{remi}}^{\text{remi}}) \\
C_{sv} &= C_{sv0}(1 + K_{cc}c_{\text{remi}}^{\text{remi}}) \\
C_{pa} &= C_{pa0}(1 + K_{cc}c_{\text{remi}}^{\text{remi}}) \\
C_{pv} &= C_{pv0}(1 + K_{cc}c_{\text{remi}}^{\text{remi}})
\end{align*} \]  

(26)-(29)

where \( C_{i0} (i = sa, sv, pa, pv) \) are the compliance values at zero effect-site concentration and the model parameter \( K_{cc} \) was obtained by trial-and-error.
5 The neuromuscular blockade and depth of anaesthesia models

The Neuromuscular Blockade (NMB) and Depth of Anaesthesia (DoA) models allow the computation of the patient’s level of areflexia and anaesthesia, respectively. Both are based on compartmental models, a class of models that is widely used in the study of clinical pharmacology [5]. In this model, the drugs used for anaesthesia, analgesia and areflexia purposes are propofol, remifentanil and atracurium, respectively.


5.1 Neuromuscular Blockade model

The dynamic response of the neuromuscular blockade induced by a bolus (i.e., a sudden infusion performed with a syringe) of atracurium may be modeled as shown in figure 7 by a pharmacokinetic/pharmacodynamic (PK/PD) model that has a Wiener structure [6].

The pharmacokinetic part (figure 7, block 1) is a compartmental model that relates the drug infusion rate \( u(t) \) with the plasma concentration \( c_p(t) \). It is assumed to be linear and with two plasma compartments (central and peripheral) that communicate with each other.

The pharmacodynamic part (figure 7, blocks 2, 3 and 4), relates the plasma concentration \( c_p(t) \) to the level of neuromuscular blockade (normalized between 0 and 100, with 0 corresponding to full paralysis and 100 to normal muscular activity), \( r(t) \) [%]. This involves the effect compartment and a nonlinearity described by the Hill equation.

The equations of the neuromuscular blockade model are as follows: the pharmacokinetic model, which is assumed to be linear and with two plasma compartments (central and peripheral) that communicate with each other, is described by the following linear system of state equations

\[
\begin{align*}
\dot{x}_1(t) &= -\lambda_1 x_1(t) + a_1 u(t) \\
\dot{x}_2(t) &= -\lambda_2 x_2(t) + a_2 u(t) \\
c_p(t) &= \sum_{i=1}^2 x_i(t)
\end{align*}
\]

and relates the drug infusion rate \( u(t) \) [\( \mu g kg^{-1} s^{-1} \)] with the plasma concentration \( c_p(t) \) [\( \mu g mL^{-1} \)], where \( x_i \) (\( i = 1, 2 \)) are state variables (implicitly defined by 32) and \( a_i \) [\( kg mL^{-1} \)], \( \lambda_i \) [\( s^{-1} \)] (\( i = 1, 2 \)) are patient dependent parameters.

A linear second order model, described by the cascade of two first order systems, written as

\[
\begin{align*}
\dot{c}(t) &= -\lambda c(t) + \lambda c_p(t) \\
\dot{c}_e(t) &= -\frac{1}{\tau} c_e(t) + \frac{1}{\tau} c(t)
\end{align*}
\]

relates \( c_p(t) \) with the concentration in the effect compartment, \( c_e(t) \) [\( \mu g mL^{-1} \)]. Here, \( c(t) \) is an intermediate variable and \( \lambda \) [\( s^{-1} \)], \( \tau \) [\( s \)] are patient dependent parameters. It is remarked that standard models developed for atracurium [6] do not consider the block 3. As shown in [7], the inclusion of the extra delay associated to \( \tau \) allows a better replication of the observed experimental responses.
Finally the pharmacodynamic effect, that relates $c_p(t)$ to the induced pharmacodynamic response, $r(t) \ [%\]$, is modeled by the Hill equation \[6\],

$$r(t) = \frac{100 C_{50}^γ}{C_{50}^γ + c(t)}$$ \ (35)

where the parameters $C_{50} \ [μg \text{ mL}^{-1}]$ and $γ$ (dimensionless) are also patient-dependent.

It is important to note that a major difficulty when modeling this system is patient variability. Typical values of the different parameters entering the model fall into the ranges shown in the table below \[2\].

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Min</th>
<th>Max</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>$a_1$</td>
<td>0.0029</td>
<td>0.0581</td>
<td>$kg \text{ mL}^{-1}$</td>
</tr>
<tr>
<td>$a_2$</td>
<td>0.0031</td>
<td>0.0083</td>
<td>$kg \text{ mL}^{-1}$</td>
</tr>
<tr>
<td>$λ_1$</td>
<td>0.14</td>
<td>0.45</td>
<td>$s^{-1}$</td>
</tr>
<tr>
<td>$λ_2$</td>
<td>0.026</td>
<td>0.46</td>
<td>$s^{-1}$</td>
</tr>
<tr>
<td>$λ$</td>
<td>0.081</td>
<td>0.64</td>
<td>$s^{-1}$</td>
</tr>
<tr>
<td>$C_{50}$</td>
<td>0.59</td>
<td>0.72</td>
<td>$μg \text{ mL}^{-1}$</td>
</tr>
<tr>
<td>$γ$</td>
<td>2.8</td>
<td>6.2</td>
<td>dimensionless</td>
</tr>
<tr>
<td>$τ$</td>
<td>25.2</td>
<td>840</td>
<td>$s$</td>
</tr>
</tbody>
</table>

### 5.2 Depth of Anaesthesia model

The DoA model resembles the NMB model in that it can also be modeled by a PK/PD model similar to the one presented in figure 7. However, this model takes into account the interaction between *remifentanil* and *propofol*, which is assumed to occur only on the last block (Hill equation). The value for the effect-site concentration of *remifentanil* $c_{\text{remi}}$ is given as an input to the model, i.e. the PK/PD dynamics of *remifentanil* are not modeled. The output of the model is a measure of the depth of anaesthesia of the patient, via the bispectral index (BIS) method. This is relevant because different DoA measure methods may lead to different models. The BIS signal ranges from 0% to 100%, with 0% corresponding to fully anesthetized and 100% to a fully awake state.

The equations of the depth of anaesthesia model are as follows: the pharmacokinetic model, which is assumed to be linear and with three plasma compartments that communicate with each other, is described by the following linear system of state equations

$$\dot{x}_1(t) = -k_{10}x_1 - k_{12}x_1 - k_{13}x_1 + k_{21}x_2 + k_{31}x_3 + u^{\text{prop}}(t)$$ \(36\)

$$\dot{x}_2(t) = k_{12}x_1 - k_{21}x_2$$ \(37\)

$$\dot{x}_3(t) = k_{13}x_1 - k_{31}x_3$$ \(38\)

$$c^{\text{prop}}_p(t) = \frac{x_1(t)}{1000v_1}$$ \(39\)

and relates the drug infusion rate $u^{\text{prop}}(t) \ [μg \text{ s}^{-1}]$ with the plasma concentration $c^{\text{prop}}_p(t) \ [μg \text{ mL}^{-1}]$, where $x_i \ (i = 1, 2, 3) \ [μg]$ are state variables, $k_{ij} \ [s^{-1}]$ are transfer coefficients taken from \[8\] and $v_1 \ [L]$ is the volume of compartment one, all of which are patient-dependent parameters. Parameter $v_1$ can be computed as

$$v_1 = \text{weight} \times v_c$$ \(40\)

where $\text{weight} \ [Kg]$ is the patient’s weight and $v_c \ [L/Kg]$ represents the typical volume of compartment one per patient unit weight.

A linear first order model written as

$$c^{\text{prop}}_e(t) = -k_{e0}c^{\text{prop}}_e(t) + k_{e0}c^{\text{prop}}_p(t)$$ \(41\)
relates $c_{prop}^{e}(t)$ with the concentration in the effect compartment, $c_{prop}^{e}(t)$ [$\mu g mL^{-1}$]. Unlike in the NMB model, block 3 (figure 7) is not modeled.

Finally, the model for the interaction between $c_{prop}^{e}(t)$ and $c_{remi}^{e}$ to obtain the measure of DoA, $BIS(t)$ [%], is taken from [9] and generalizes the Hill equation used for the NMB model (equation (35)), reading

$$U_{prop}(t) = \frac{c_{prop}^{e}(t)}{C_{prop50}^{BIS}}$$  \hspace{1cm} (42)

$$U_{remi}(t) = \frac{c_{remi}^{e}(t)}{C_{remi50}^{BIS}}$$  \hspace{1cm} (43)

$$\theta(t) = \frac{U_{prop}(t)}{U_{prop}(t)+U_{remi}(t)}$$  \hspace{1cm} (44)

$$U_{50}(\theta) = 1 - \beta \theta(t) + \beta \theta^2(t)$$  \hspace{1cm} (45)

$$BIS(t) = BIS_0 \left(1 - \frac{[U_{prop}(t)+U_{remi}(t)]}{1+[(U_{prop}(t)+U_{remi}(t))/U_{50}(\theta)]^\gamma}\right)$$  \hspace{1cm} (46)

where $C_{prop50}^{BIS}$ and $C_{remi50}^{BIS}$ [$\mu g mL^{-1}$] (propofol and remifentanil concentrations at half the maximal effect, i.e. $BIS = 50\%$), $\beta$ (dimensionless), $\gamma$ (dimensionless) and $BIS_0$ (the value of BIS at zero concentrations) are patient-dependent parameters.
Simulation results using the developed model are presented. All simulations were carried out using the Simulink® toolbox from MATLAB®.

Figure 8 holds a portion of a typical signal for the systemic arterial pressure. There are many differences between this signal and a real pressure signal taken from a patient, but it is nonetheless a reasonable approximation.

Figure 9 represents a basic result in what regards the ability to specify the patient’s heart beat duration. In this example, the patient’s heart beat instantaneously drops from 80 beats per minute down to 65 beats per minute (i.e., the heart beat duration increases). Both the decrease in the rate of growth of the time seen by the heart ($t_{\text{heart}}$) and speed of the left ventricle compliance plot are clearly visible. Furthermore, due to the lower heart beat rate the systemic arterial pressure also tends to drop.

Figure 9: Systemic arterial pressure and MAP signals with a sudden decrease in patient’s heart rate at $t = 15$ seconds, from 80 beats/minute to 65 beats/minute.
Situations might occur during surgical procedures that might lead to the situation depicted in figure 10. In this example, the effect of a blood loss of the systemic arteries is simulated. A steady decline in the value of the systemic arterial pressure is visible.

Figure 10: Systemic arterial pressure and MAP signals with the start of blood loss (250mL/minute) in the systemic arteries occurring at 15 seconds.

To induce a state of loss of conscience on the patient, propofol is used. During most lengthy surgical procedures, analgesic drugs like remifentanil are needed to relieve the patient of any noxious stimuli ("pain") that might be caused by the surgery. Figure 11 exemplifies the effect of the usage of both these drugs on the patient’s depth of anaesthesia, over nearly 5 hours.

Figure 11: Simulation results for the infusion of propofol and remifentanil for inducing anaesthesia over a period of approximately 4 hours and 45 minutes.
The simulation result indicates that it is possible to keep the patient in a steady anesthetized state for a long period of time by choosing the correct infusion rates.

Regarding the neuromuscular blockade level of the patient, figure 12 represents a simulation run where the patient is injected with an initial bolus of $500 \mu g Kg^{-1}$ at $t = 0$ seconds. This is sufficient to keep the level of neuromuscular blockade at close to 0% for approximately 30 minutes.

![Atracurium infusion rate](image1)

![Neuromuscular blockade](image2)

Figure 12: Simulation results for the infusion of atracurium for inducing neuromuscular blockade on a patient.

Figure 13 presents the result for the interaction of remifentanil with MAP. Unfortunately, at this stage it was discovered that the cardiovascular model has a severe conditioning problem and, as such, can present very poor simulation results, as is clearly visible in figure 13.

![MAP](image3)

![Effect−site concentration of remifentanil](image4)

Figure 13: Simulation results for the effect-site concentration of remifentanil on the mean arterial pressure. The unstable nature of the MAP signal stems from the fact that the cardiovascular model is badly conditioned.
7 Conclusions

In theory, the implemented model should allow for a simulation of a patient’s physiological reactions while under the effect of anaesthesia, e.g. during a surgical procedure. The model is ready to accommodate different scenarios, such as blood loss or the varying of the patient’s heart rate and produces a signal of the patient’s systemic arterial pressure ($P_{sa}$) that resembles a real signal. The effect of anaesthetic, analgesic and areflexia-related drugs is also modelled.

However, whereas the depth of anaesthesia and neuromuscular blockade models present no difficulties when simulated, the same is not true for the cardiovascular model, which is badly conditioned.

Table 1 (appendix A) contains the values used for each of the parameters in the cardiovascular section of the model. The values of parameters pertaining to the cardiovascular model were taken from [3].
### Appendix: Model parameter values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{normal}$</td>
<td>Standard duration of a heartbeat</td>
<td>0.75</td>
<td>s</td>
</tr>
<tr>
<td>$T_S$</td>
<td>Duration of systole in a standard heartbeat</td>
<td>0.3</td>
<td>s</td>
</tr>
<tr>
<td>$V_0$</td>
<td>Initial blood volume inside compliance vessels</td>
<td>5</td>
<td>L</td>
</tr>
<tr>
<td>$(V_d)_{sa}$</td>
<td>Systemic arteries dead-volume</td>
<td>0.825</td>
<td>L</td>
</tr>
<tr>
<td>$(V_d)_{sv}$</td>
<td>Systemic veins dead-volume</td>
<td>0</td>
<td>L</td>
</tr>
<tr>
<td>$(V_d)_{pa}$</td>
<td>Pulmonary arteries dead-volume</td>
<td>0.0382</td>
<td>L</td>
</tr>
<tr>
<td>$(V_d)_{pv}$</td>
<td>Pulmonary veins dead-volume</td>
<td>0</td>
<td>L</td>
</tr>
<tr>
<td>$(V_d)_{LV}$</td>
<td>Left ventricle dead-volume</td>
<td>0.027</td>
<td>L</td>
</tr>
<tr>
<td>$(V_d)_{RV}$</td>
<td>Right ventricle dead-volume</td>
<td>0.027</td>
<td>L</td>
</tr>
<tr>
<td>$C_{sa0}$</td>
<td>Compliance of the systemic arteries (when $c_{remi} = 0$)</td>
<td>0.00105</td>
<td>L/mmHg</td>
</tr>
<tr>
<td>$C_{sv0}$</td>
<td>Compliance of the systemic veins (when $c_{remi} = 0$)</td>
<td>1.75</td>
<td>L/mmHg</td>
</tr>
<tr>
<td>$C_{pa0}$</td>
<td>Compliance of the pulmonary arteries (when $c_{remi} = 0$)</td>
<td>0.00350</td>
<td>L/mmHg</td>
</tr>
<tr>
<td>$C_{pv0}$</td>
<td>Compliance of the pulmonary veins (when $c_{remi} = 0$)</td>
<td>0.08</td>
<td>L/mmHg</td>
</tr>
<tr>
<td>$(C_{LV})_D$</td>
<td>Diastolic compliance of the left ventricle</td>
<td>0.0146</td>
<td>L/mmHg</td>
</tr>
<tr>
<td>$(C_{LV})_S$</td>
<td>Systolic compliance of the left ventricle</td>
<td>0.00003</td>
<td>L/mmHg</td>
</tr>
<tr>
<td>$(C_{RV})_D$</td>
<td>Diastolic compliance of the right ventricle</td>
<td>0.0365</td>
<td>L/mmHg</td>
</tr>
<tr>
<td>$(C_{RV})_S$</td>
<td>Systolic compliance of the right ventricle</td>
<td>0.0002</td>
<td>L/mmHg</td>
</tr>
<tr>
<td>$\tau_D$</td>
<td>Ventricular diastolic compliance time constant</td>
<td>0.45</td>
<td>s</td>
</tr>
<tr>
<td>$\tau_S$</td>
<td>Ventricular systolic compliance time constant</td>
<td>0.15</td>
<td>s</td>
</tr>
<tr>
<td>$R_S$</td>
<td>Systemic resistance</td>
<td>1071.6</td>
<td>mmHg/(L/s)</td>
</tr>
<tr>
<td>$R_P$</td>
<td>Pulmonary resistance</td>
<td>107.4</td>
<td>mmHg/(L/s)</td>
</tr>
<tr>
<td>$R_{mi}$</td>
<td>Mitral valve resistance</td>
<td>0.6</td>
<td>mmHg/(L/s)</td>
</tr>
<tr>
<td>$R_{ao}$</td>
<td>Aortic valve resistance</td>
<td>0.6</td>
<td>mmHg/(L/s)</td>
</tr>
<tr>
<td>$R_{tr}$</td>
<td>Tricuspid valve resistance</td>
<td>0.6</td>
<td>mmHg/(L/s)</td>
</tr>
<tr>
<td>$R_{pu}$</td>
<td>Pulmonary valve resistance</td>
<td>0.6</td>
<td>mmHg/(L/s)</td>
</tr>
<tr>
<td>$K_{cc}$</td>
<td>Linear gain of the $c_{remi}/$compliance relation</td>
<td>2.58</td>
<td>mL/µg</td>
</tr>
</tbody>
</table>

Table 1: Parameters in the cardiovascular section of the model and respective values.
References


