# Pharmacokinetic and pharmacodynamic modeling of neuromuscular blocking agents for educational simulation

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*Award date:*
1995

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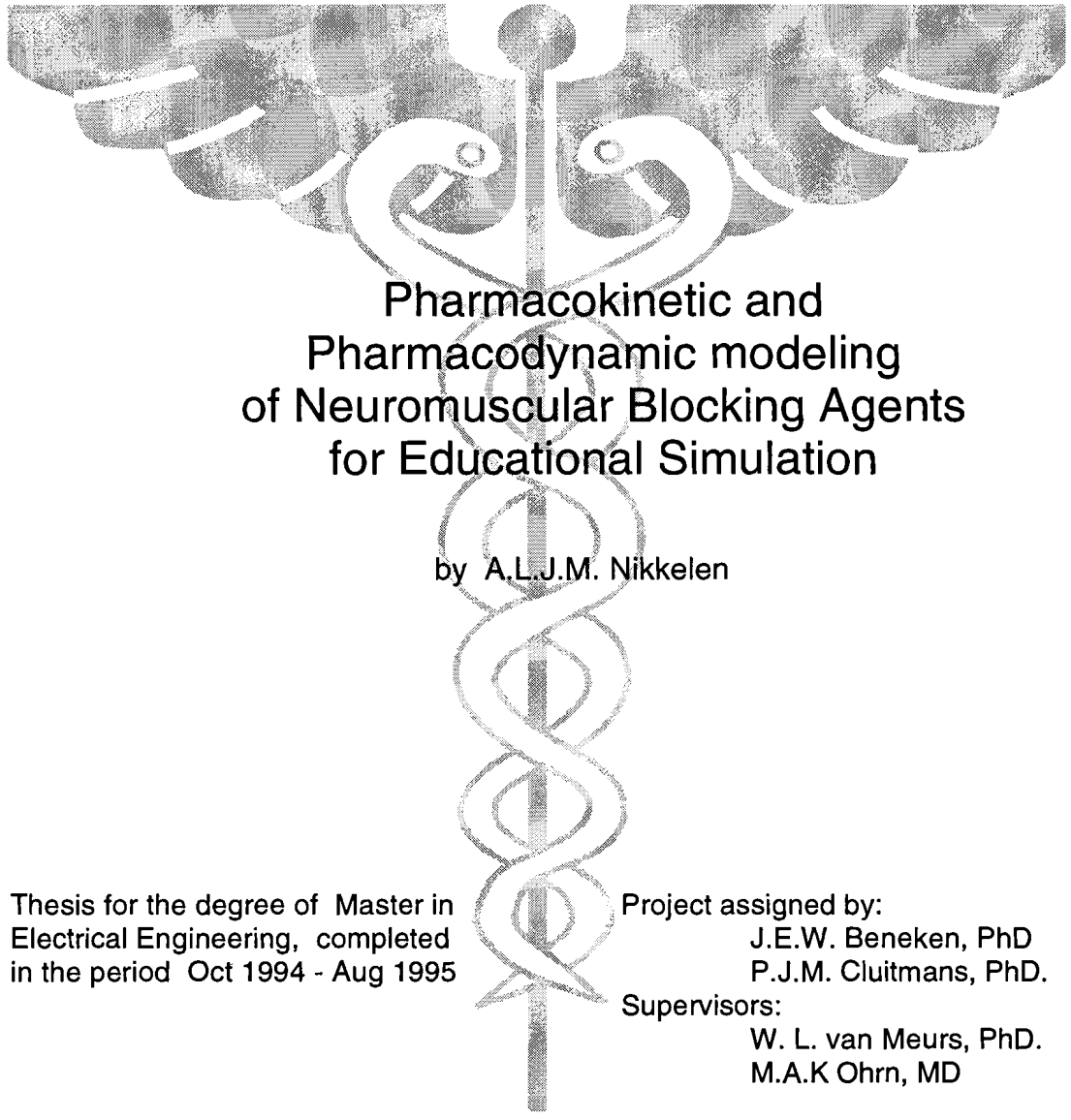

# Pharmacokinetic and Pharmacodynamic modeling of Neuromuscular Blocking Agents for Educational Simulation

by A.L.J.M. Nikkelen

Thesis for the degree of Master in Electrical Engineering, completed in the period Oct 1994 - Aug 1995

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# Abstract

This thesis describes part of the development of an interactive computer based Part Task Trainer (PTT) for assisting Intensive Care Unit (ICU) nursing staff in learning safe administration of the neuromuscular blocking agent (NMB-agent) Atracurium and monitoring of neuromuscular blockade by peripheral nerve stimulation. The main goal of the study was to derive and integrate into the PTT a pharmacokinetic and pharmacodynamic model to simulate the effects of the NMB-agent Atracurium. The specific research objectives are described in chapter 1.

Chapter 2 presents the principles of physiology and pharmacology, necessary for the mathematical modeling of NMB-agents.

The models for simultaneous modeling of pharmacokinetics and pharmacodynamics that can be found in the literature have disadvantages when used for educational simulations. These traditional models were reformulated (chapter 3) to eliminate redundant information, reducing the number of model parameters from 8 to 3, thereby optimizing the calculation efficiency. The parameters of the reformulated model are derived from literature data concerning the NMB-agent Atracurium. Preliminary results from taking the parameter reduction approach even further were presented in the form of an abstract co-authored by the author of this thesis at the first conference on "Simulators in Anesthesia Education" in Rochester, NY. The abstract is appended to this report (Appendix A).

Traditional pharmacodynamic models for Single Twitch, Train-of-Four, and a previously developed empirical model for Tetanic Stimulation are presented. A new empirical model for Post Tetanic Count was derived, based on the principle of an increased sensitivity to peripheral nerve stimulation after Tetanic Stimulation. This model was shown to reflect clinical data.

The interactive nature of computer based learning can put extra constraints on a Central Processing Unit (CPU) that is already handling text, graphics, etc., hence the need for an appropriate modeling approach and efficient numerical integration method. The specific requirements for interactive simulation of pharmacokinetics in the ICU-PTT were formulated (chapter 4). A method based on the discretization of the continuous state transition equation was shown to meet all the requirements.

The presented pharmacological model and the selected numerical integration method were successfully integrated in the ICU-PTT. The model response was

evaluated by an expert and the initial parameters of the model were slightly adjusted to generate the desired response (chapter 5).

Traditionally, compartment models are used to explain pharmacokinetic principles. However, the didactic disadvantages of compartment models are associated to their mathematical representation. To overcome this disadvantage a more intuitive hydraulic analogue was developed in chapter 6 and shown to be mathematically equivalent to the compartment model. This hydraulic analogue was used during a morning conference to anesthesia residents.

# Table of Contents

# 1 Introduction

Interactive computer based training devices and simulators were first introduced for the training of pilots. Nowadays, these educational tools have found their way into many other fields where risks are high and errors are expensive. An example of a recently developed medical educational tool is the Human Patient Simulator, developed by the Florida Anesthesia Computer and Engineering Team (FACET) of the University of Florida Department of Anesthesiology. This thesis describes part of the development of a related medical educational tool: a Part Task Trainer (PTT) for assisting Intensive Care Unit (ICU) nursing staff in learning safe administration of the neuromuscular blocking agent (NMB-agent) Atracurium and the monitoring of neuromuscular blockade by peripheral nerve stimulation.

The main goal of the study was to derive and integrate a pharmacological model to simulate the effects of NMB-agents. Making the PTT model driven greatly enhances the interactivity of the PTT by allowing the learner to use a great variety of dosing schemes and observe the resulting effects. Although the main focus of the PTT is on the NMB-agent Atracurium, the research in this thesis is presented in such a way that it can be used for other model driven educational tools as well.

Basic knowledge of the integrated principles of physiology and pharmacology is essential for the proper modeling of NMB-agents, and will be introduced in the report. A literature search was performed to explore the traditional pharmacological models for NMB-agents. These traditional models were reformulated to eliminate redundant information, and to reduce the number of parameters. Requirements for interactive pharmacokinetic simulations were formulated, and modeling approaches and numerical simulation methods were evaluated in terms of these requirements. The integration of the retrieved models in the PTT, and the model parameter adjustments and validation will be described. The mathematical equivalency between pharmacokinetic models and their hydraulic and electric analogues was investigated. Learning objectives and a second model driven educational application in the area of pharmacokinetics and pharmacodynamics, based on the hydraulic analogue, will be discussed.

# 2 Principles of Anesthesia, Pharmacology, and Neuromuscular Blockade

Suppression of pain was not systematically studied until the need for surgical treatment of disease arose. Operations had been performed over the centuries but always for the superficial malady - a fracture, amputation, *cataract* extraction, *trephination* of the skull, or removal of *bladder calculus*. To these ends, the anesthetic properties of hypnosis and trance, pressure over *peripheral* nerves and blood vessels, application of cold, alcohol intoxication, or ingestion of *herbal concoctions* were used. More recently the inhalation of vapors became an alternative approach.

The *gastrointestinal* tract long remained the only avenue for medical therapy, but with techniques of anesthetic administration more or less divided into schools, the choice now lies among *inhalation*, *intravenous*, or regional techniques, or combinations thereof. This introductory chapter presents the pharmacological principles of intravenous anesthetics with a special focus on neuromuscular blocking agents. The italic printed words in this chapter refer to the glossary of medical terms, in the back of this thesis.

## *2.1 Principles of Pharmacology and Anesthesia*

The *therapeutic* objective of anesthesia is to maintain adequate drug concentrations at the desired sites of action to produce desired effects and to avoid undesirable side effects or *toxicity*. For general anesthesia desired effects incorporate *analgesia* (insensitivity to pain), *amnesia* (loss of memory), unconsciousness and relaxation of *skeletal muscles*. General anesthesia affects the entire body and is pharmacologically caused by a combination of drugs given intravenously and/or by inhalation.

The empirical approach to drug administration consists of adjusting an initial dose in an amount and rate in accordance with the clinical response of an individual patient. The ability of anesthesiologists to make these adjustments before administering a chosen dose has often been termed "the art of anesthesia", reflecting the important skill of establishing individualized dose-response relationships. Essential for the appropriate administration of drugs to humans is basic knowledge of the integrated principles of *physiology*, *pathophysiology* and *pharmacology*. Principles of pharmacology are normally subdivided into two classes: *Pharmacodynamic* principles and *pharmacokinetic* principles, described in a general way in the following sections.

### 2.1.1 Clinical Pharmacodynamics

Simply stated, pharmacodynamics describe what effect a drug has on the body. In the strict pharmacological sense pharmacodynamics describe the relationship between the effector site *plasma* drug concentration and the pharmacological effect. However, in clinical terms, pharmacodynamics reflect the drug effect compared to the dose of drug administered. Clinical pharmacodynamics may be divided into three general areas, 1) **transduction of biologic signals**, 2) **biologic variability** and 3) **clinical evaluation of drug effects**.

- **Transduction of Biologic Signals:** Many clinically important drugs act on *excitable* cell membrane proteins such as receptors, ion channels, and ion pumps to initiate their clinical effect. Stimulation of excitable cell membranes result in activation or inhibition of chemical cascades that lead swiftly to clinical effects.

- **Biologic Variability:** Individual variation in pharmacological effect to an identical dose of administered drug occurs as a result of differences in pharmacodynamic sensitivity.

- **Clinical Evaluation of Drug Effects:** Methods of evaluating drug effects clinically include dose-response curves, 50 percent effective dose ($ED_{50}$ ) 50 percent lethal dose ($LD_{50}$ ) and therapeutic index.
  Dose-response curves depict the relationship between the administered dose and the resulting maximal pharmacological effect. This yields a time independent relationship. The actual shape of the dose-response curves is determined by the choice of scales for the two axes. The effect scale is generally normalized to a percentage of the maximum effect. Logarithmic transformation of dosage is frequently used, because it permits display of a wide range of doses. Dose-response curves are characterized by the parameters potency, efficacy, and slope (figure 2-1.)
  In the scientific literature some confusion exists about the definition of Effective Dose. One way to define the $ED_{50}$ is the dose of drug required to produce a specific effect in 50 percent of individuals. Another definition states that $ED_{50}$ is the amount of drug necessary to produce 50% of a specified maximum effect. The Lethal Dose ($LD_{50}$) is defined as the dose of a drug that produces death in 50 percent of the individuals. The ratio between $LD_{50}$ and $ED_{50}$ ($LD_{50}/ED_{50}$) is defined as the therapeutic index of a drug, (ED50

according to the first definition). The higher the therapeutic index of a drug, the safer it is for clinical administration.

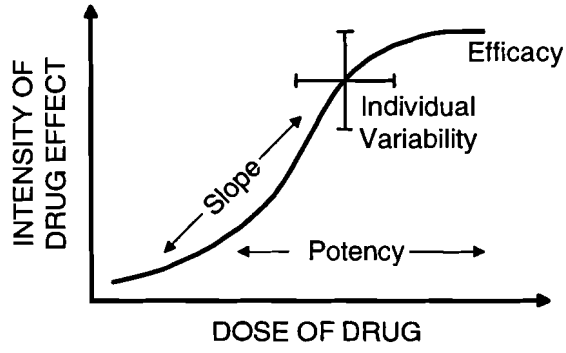


**Fig. 2-1.** Dose-response curves are characterized by differences in potency, slope, efficacy, and individual variability of these parameters.

The parameters that describe the clinical pharmacodynamics (potency, efficacy and slope) depend not only on pharmacodynamics in the strict pharmacological sense, but also on the time dependent aspects of drug transport and elimination. We will use the following interpretation for pharmacodynamics in the remainder of this thesis.

**Pharmaco*dynamics*** describe the relationship between the (target) effector site plasma drug concentration and the pharmacological effect.

### 2.1.2 Pharmacokinetics

Simply stated, pharmacokinetics describe what the body does to a drug. In the strict pharmacological sense, pharmacokinetics is the quantitative study of the absorption, distribution, *metabolism*, and elimination of chemicals in the body and the way in which these phenomena affect drug concentrations.

The mathematical complexity that has developed in pharmacokinetics to reflect the phases of drug absorption, distribution, and elimination has prevented many clinicians from developing a thorough understanding of this science. However, as anesthesiologists develop a higher level of understanding of the principles of pharmacokinetics, the dose-response relationships of anesthetic drugs can be more accurately predicted in normal or pathological states. These

pharmacokinetic principles can be applied to the great majority of intravenous anesthetic drugs.

- **Absorption of Drugs:** The process by which drugs are delivered to the plasma in their pharmacologically active form is called absorption and involves several physical processes, including route of administration, ionization, transport across membranes, and protein binding. Each of these processes contributes to the amount of active drug ultimately reaching local *tissue* plasma. The rate of absorption influences the time course of drug effect and is an important consideration in determining drug dosage.

- **Drug Distribution:** Most drugs, before producing an effect, must circulate through the bloodstream to get to the site of action in their pharmacologically active forms. Distribution refers to the reversible transfer of drug from one location to another and involves movement across lipid membranes and capillary walls as well as between active and inactive binding sites in different tissues of the body. The initial distribution is determined by the physicochemical characteristics of the drug, as well as by cardiac output and regional blood flow to various organs. Drugs are rapidly distributed to heart, brain, kidney, liver and other extensively perfused organs. Less rapid distribution into muscle and still slower distribution into fat will occur because these organs receive a smaller fraction of the cardiac output. Drugs may achieve a higher concentration in peripheral tissues than in blood because of tissue binding and dissolution in fat.

- **Drug Elimination:** Elimination (or clearance) is a general term for all irreversible processes that are involved with the removal of drugs in their active form, from the body. Major processes include metabolism (biotransformation), renal clearance (through the kidneys), hepatobiliary clearance (through the liver), and *pulmonary* excretion (through the lungs). Minor routes of elimination are *saliva*, sweat, breast milk, and tears. The most important form of elimination concerning pharmacokinetics is metabolism. The rate of metabolism of most drugs is determined by the concentration of drug at the site of metabolism.

Absorption, distribution, and metabolism (and other forms of elimination), all influence the time course of plasma drug concentration at different sites. These pharmacokinetic aspects can often be described mathematically. Most pharmacokinetic models use the concept of pharmacokinetic compartments

within the body. The aggregate of the compartments include all tissues necessary to simulate the time aspects.

## *2.2 Physiology of Neuromuscular Transmission and Blockade*

The principal use of neuromuscular blocking drugs is to provide skeletal muscle relaxation for optimal surgical working conditions. Relaxation of skeletal muscles requires some form of ventilatory support generally accomplished by *intubation* of the *trachea*. Intubation is also facilitated by neuromuscular blocking drugs. The principal pharmacological action of neuromuscular blocking drugs is to interrupt transmission of nerve impulses at the neuromuscular junction. On the basis of distinct electrophysiologic differences in their mechanism and duration of action, these drugs can be classified as *depolarizing* neuromuscular blocking drugs and *nondepolarizing* neuromuscular blocking drugs which are further subdivided as to their duration of action. Clinically, the degree of neuromuscular blockade can be evaluated by monitoring the skeletal muscle responses evoked by an electrical stimulus from a peripheral nerve stimulator. Other indicators of neuromuscular blockade include grip strength, ability to sustain head lift, vital capacity measurement, and negative *inspiratory* force.

The physiology of neuromuscular blockade is discussed in detail in the next three sections, providing necessary background knowledge for the development of the computer based model driven training devices which are presented in the remainder of this thesis.

### 2.2.1 Neuromuscular Junction

Neuromuscular junctions transmit and receive chemical messages. The junction consists of a prejunctional motor nerve ending separated from a highly folded postjunctional membrane of the skeletal muscle fiber by a synaptic cleft that is 20 to 30 nm wide and filled with extracellular fluid (figure 2-2.). Acetylcholine (Ach) in motor nerve endings is synthesized by the acetylation of choline under the control of the enzyme cholineacetylase. The acetylcholine is stored in synaptic vesicles in motor nerve endings and is released into the synaptic cleft as packets (quanta) if a nerve impulse arrives. Each quantum contains at least 1000 molecules of acetylcholine.

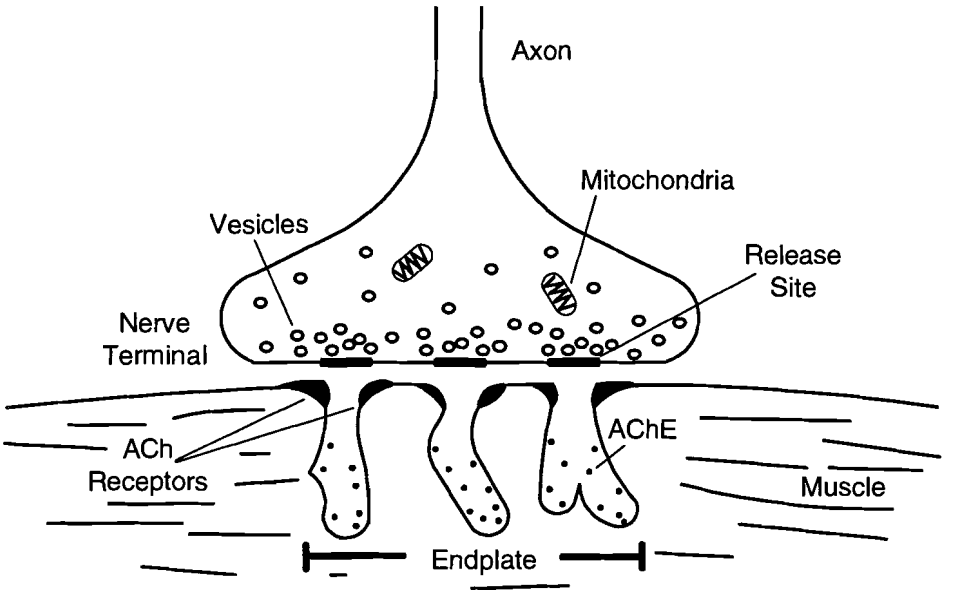


**Fig. 2-2.** Schematic depiction of the neuromuscular junction. Acetylcholine (ACh), synthesized from choline and acetylcoenzyme A (acetylCoA), is transported in coated vesicles (V) that are moved to the release sites. The Acetylcholine is released from the vesicles into the synaptic cleft in response to nerve impulses. [Stoelting, R.K., 1991]

The postjunctional membrane contains receptors that are created by the muscle cells. The muscle cells make a series of protein subunits and assemble them into cylinders. These are inserted into the membrane and held rigidly in place in such a way that each cylinder crosses from one side of the muscle cell membrane to the other (figure 2-3.). Normally these are closed, but if acetylcholine reacts with specific sites on the extracellular portion, then the proteins undergo a change in conformation that opens the cylinder to form a channel that allows ions to move along their concentration gradients. When the channel is open, sodium and calcium flow from the outside of the cell to the inside, and potassium flows from the inside to the outside. The net current is depolarizing and creates the endplate potential that stimulates the muscle to contract.

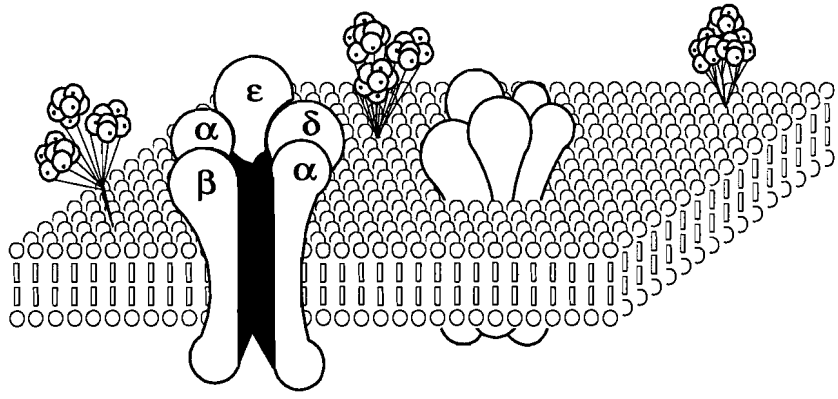


**Fig. 2-3.** Sketch of the postjunctional membrane. The two structures in the center represent receptors. Each member of the pair is made of five subunits arranged in a circle around a channel. The balloon like structures at the periphery represent acetylcholinesterase.

### 2.2.2 Neuromuscular Transmission

The resting transmembrane potential of approximately -90 mV across nerve and skeletal muscle membranes is maintained by the equal distribution of potassium (K+) and sodium (Na+) ions across the membrane.

The neuromuscular transmission starts in the nerve ending. A nerve action potential initiates a calcium flux into the nerve ending and causes the vesicles to migrate to the surface of the nerve. The vesicles discharge their acetylcholine into the synaptic cleft and receptors in the endplate of the muscle respond to the acetylcholine by opening channels allowing ions to move across the muscle membrane. This movement of ions causes a decline in the transmembrane potential to -40 mV (depolarizing) that triggers the adjacent muscle membrane into initiating a *contraction*. The acetylcholine detached from the receptor reacts with an enzyme, acetylcholinesterase, present in the cleft, and is destroyed.

### 2.2.3 Neuromuscular Blockade

Depolarizing neuromuscular blocking drugs act on the receptors in the endplate of the muscle to mimic the effect of acetylcholine and cause prolonged depolarization of the endplate. Non-depolarizing neuromuscular blocking drugs also act on the endplate receptors, but they prevent acetylcholine from reacting with the postjunctional receptors and hence prevent depolarization. The result is a competition between acetylcholine and the neuromuscular blocking drug, which means that the channel blockade depends on the relative concentrations

of the chemicals and their comparative affinities for the receptor. Hence the important role of effector site concentrations in both pharmaco*kinetics* and pharmaco*dynamics*. Note that two molecules of acetylcholine are required to open an ion channel, while a single molecule of *antagonist* is adequate to prevent the effect.

Another group of drugs affecting the neuromuscular transmission inhibits acetylcholinesterase and accordingly delays the hydrolysis of acetylcholine. The prolonged presence of acetylcholine antagonizes the effects of nondepolarizing neuromuscular blocking drugs by competing with the neuromuscular blocking drugs for the available receptors. Therefore this group of drugs is referred to as reversal agents.

# 3 Simultaneous Modeling of Pharmacokinetics and Pharmacodynamics for Muscle Relaxants; Application to Atracurium

Traditionally, pharmaco*kinetic* models are derived to fit the time profile of plasma drug mass, and pharmaco*dynamic* models are derived to fit effect data as function of an effector site drug mass. Several models are derived for simultaneous modeling of pharmacokinetics and pharmacodynamics, see for example Sheiner,et al. 1979. The disadvantages of these traditional models, when used for educational simulation, are [Van Meurs, W.L., Nikkelen, E., Good, M.L., 1995-2]

- The mathematical descriptions contain a large number of dependent parameters which make programming of patient variability difficult.
- The parameters have physiologic meaning, but do not directly relate to dose or effect.
- The combined effect of pharmacokinetics and pharmacodynamics on, for example, onset is difficult to understand.

This chapter discusses the model of Sheiner et al. and reformulates it to reflect concentrations and to reduce the number of parameters (which facilitates adjusting the model response to reflect patient variability) and to optimize calculation efficiency. The objective of these modifications is to adapt the model to educational simulations. The last section of this chapter shows how the parameters of the model can be adjusted to fit the pharmacological response to Atracurium.

## *3.1 Traditional Compartment Pharmacokinetics*

In traditional two compartment models, illustrated in fig 3-1, the first or central compartment represents the highly perfused tissues like the brain, kidneys, liver, lungs, and heart. The peripheral compartment reflects other tissues that store significant amounts of drugs, like muscles and fat. For most drugs the pharmacological effects are not parallel to the concentrations in either the central or the peripheral compartment, therefore, a hypothetical effect compartment is often modeled as an additional compartment linked to the plasma compartment by a first-order process. However, this compartment receives negligible actual mass of drug (illustrated by the dotted lines in figure 3.1), and its time constant

does not enter into the pharmacokinetic solution for the mass of drug in the body [Sheiner, L.B., Stanski, D.R., Vozeh, S., et al. 1979]

Administered drugs enter the central compartment directly and are distributed to the peripheral and effect compartment. The rate constants $k_{ij}$ determine the velocity of drug transport from compartment i to j. Elimination is often assumed to occur only from the central compartment, and $k_{10}$ reflects the elimination rate constant.

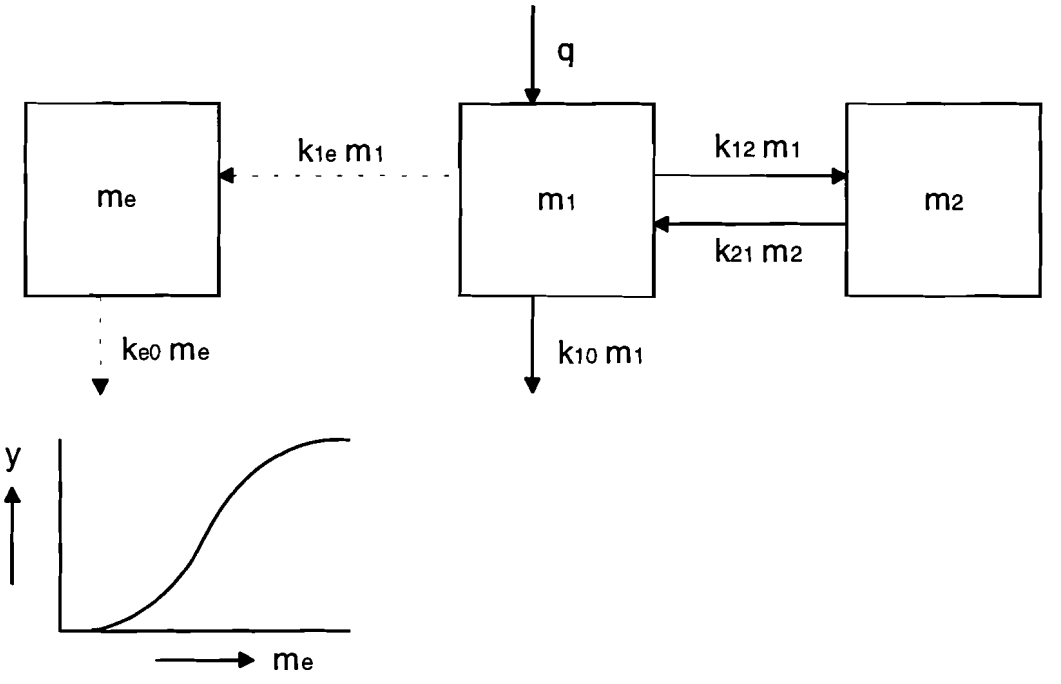


**Fig.3-1.** A traditional pharmacokinetic compartment model and a Hill-type pharmacodynamic relationship. The variables $m_1$, $m_2$ and $m_e$ reflect the amount of drug in the central, peripheral and effector compartment, respectively. [Sheiner, L.B., Stanski, D.R., Vozeh, S., et al. 1979].

Mathematically, two compartment pharmacokinetics models are usually described by the change of compartment drug mass over time, using the differential equations (3.1a) and (3.1b) (e.g. [Jaklitsch, R.R., Westenskow, D.R., 1990] ). The change of compartment drug mass over time is a summation of the total amount of drug coming into the compartment by infusion and distribution and the total amount of drug removed from the compartment by clearance and distribution, indicated by a minus sign. The input variable of the system is the amount of intravenously induced drug per unit of time, indicated by q(t).

$$\frac{dm_1(t)}{dt} = -[k_{10} + k_{12}]m_1(t) + k_{21}m_2(t) + q(t) \quad \textbf{(3.1a)}$$

$$\frac{dm_2(t)}{dt} = k_{12}m_1(t) - k_{21}m_2(t) \quad \textbf{(3.1b)}$$

$$\frac{dm_e(t)}{dt} = k_{1e}m_1(t) - k_{e0}m_e(t) \quad \textbf{(3.1c)}$$

The drug concentrations in the three compartments can be written as a function of the drug mass $m_i$, equation (3.2), where $V_1$ , $V_2$ and $V_e$ are the volumes of distribution of the central , peripheral and effect compartment respectively .

$$c_1(t) = \frac{m_1(t)}{V_1} \qquad c_2(t) = \frac{m_2(t)}{V_2} \qquad c_e(t) = \frac{m_e(t)}{V_e} \quad \textbf{(3.2)}$$

Clearance or distribution of drugs from compartment *i* to compartment *j* is given by the product of a rate constant $k_{ij}$ times the drug mass $m_i$ in compartment i, and can be rewritten with equations (3.2) to $Cl=k_{ij}.V_i.c_i$ (Cl=clearance). Including clearance from the central compartment eight different parameters describe this compartment model: $k_{10}$, $k_{12}$, $k_{21}$, $k_{1e}$, $k_{e0}$, $V_1$, $V_2$ and $V_e$. However, parameter interdependency can be derived from the assumption that distribution of drugs into body tissues is a linear, concentration driven process. Consider the net intercompartment mass flow rate $F_m$, which is the subtraction of the two distribution flow rates, indicated in fig. 3-1 by the two intercompartment arrows, equation (3.3).

$$F_m(t) = F_{12}(t) - F_{21}(t) = k_{12}m_1(t) - k_{21}m_2(t) \quad \textbf{(3.3)}$$

For a concentration driven process, the net intercompartment mass flow rate $F_m(t)$ is proportional to the concentration gradient between the central and peripheral compartments, equation (3.4). Were $\alpha$ is the proportionality constant.

$$F_m(t) = \alpha.[c_1(t) - c_2(t)] \quad \textbf{(3.4)}$$

After substitution of equation 3.2 in equation 3.3, expression 3.5 results:

$$k_{12}V_1c_1(t) - k_{21}V_2c_2(t) = \alpha.[c_1(t) - c_2(t)] \quad \textbf{(3.5)}$$

Equation (3.5) is valid for every moment in time and therefore for any possible combination of $c_1(t)$ and $c_2(t)$, e.g. immediately after an injection, the central compartment concentration is non zero while the concentration in the peripheral compartment is still zero. Equation 3.6 gives the interdependency among the parameters $k_{12}$, $k_{21}$, $V_1$,$V_2$,

$$k_{12}\,V_1 \;=\; \alpha \;=\; k_{21}\,V_2 \qquad \Rightarrow \qquad k_{12}\,V_1 \;=\; k_{21}\,V_2 \tag{3.6}$$

The combination of equations 3.1, 3.2 and 3.6 result in the following differential equations for the compartment concentrations $C_1$, $C_2$ and $C_e$ , 3.7a,b,c

$$\frac{dc_1(t)}{dt} \;=\; -\left[k_{10}+k_{12}\right]c_1(t) \;+\; k_{12}\,c_2(t) \;+\; \frac{q(t)}{V_1} \tag{3.7a}$$

$$\frac{dc_2(t)}{dt} \;=\; k_{21}\left[c_1(t) \;-\; c_2(t)\right] \tag{3.7b}$$

$$\frac{dc_e(t)}{dt} \;=\; k_{1e}\frac{V_1}{V_e}\,c_1(t) \;-\; k_{e0}\,c_e(t) \tag{3.7c}$$

To derive further parameter interdependency, we consider a special case of the model of figure 3.1, were the effect compartment reflects the Interstitial Space in the Muscle (ISM). The ISM drug concentration can be modeled by a limited flow model, equation 3.8 [Nigrovic, V., Banoud, M., 1993].

$$\frac{d}{dt}[\mathrm{MR}]_{\mathrm{ISM},t} = \frac{\mathrm{flow}.[\mathrm{MR}]_{\mathrm{Pl},t} - \mathrm{flow}.[\mathrm{MR}]_{\mathrm{ISM},t}}{V_{\mathrm{ISM}}} \tag{3.8}$$

with $[MR]_{Pl,t}$= Plasma Concentration = $C_1(t)$
$[MR]_{ISM,t}$= ISM Drug Concentration = $C_e(t)$
flow= Plasma flow, 1.82-2.62 $ml.min^{-1}.(100g)^{-1}$
$V_{ISM}$= Volume of the Interstitial Space, 12-18 $ml.(100g)^{-1}$ = $V_e$

Rewriting equation 3.8 in terms of effect and central compartment concentrations results in equation 3.9,

$$\frac{d\,c_e(t)}{dt} = \frac{flow}{V_e}\left[c_1(t) - c_e(t)\right] \qquad \textbf{(3.9)}$$

Equation 3.9 and equation 3.7c both describe the time response of the effect compartment concentration, which gives the relationship between $k_{1e}$, $k_{e0}$, $V_1$ and $V_e$, equation 3.10a.

$$k_{e0} = k_{1e}\frac{V_1}{V_e} = \frac{flow}{V_{ISM}} \qquad \textbf{(3.10a)}$$

The range of "flow" and "$V_{ISM}$" is limited, resulting in a limited range for $k_{e0}$, as shown by equation 3.10b [Nigrovic, V., Banoud, M., 1993]

$$0.1 \leq \frac{flow}{V_{ISM}} \leq 0.22 \qquad \textbf{(3.10b)}$$

The simultaneous solution of equations 3.7a,b and 3.9 gives the time responses of the central compartment drug concentration and the effector site drug concentration. Figure 3.2 illustrates an example of the time responses to a unit bolus injection.

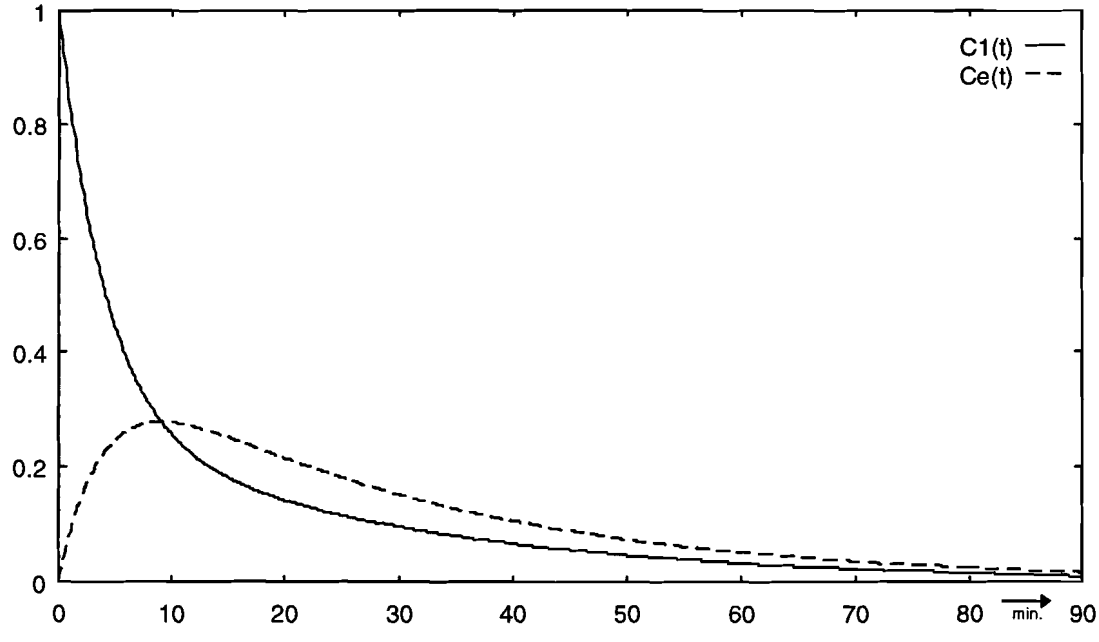


**Fig. 3-2:** Time responses of the normalized plasma drug concentration $c_1(t)$ and the normalized effector site drug concentration $c_e(t)$, after the administration of a bolus injection.

## *3.2 A Pharmacokinetic Model by Eigenvalue Decomposition*

Validation of pharmacokinetic models can only be done through clinical measurements of blood plasma drug concentration because measurement of the (hypothetical) effector site drug concentrations is impossible. Traditional pharmacokinetic models simulate the time response of plasma drug concentration and effector site drug concentration simultaneously (see figure 3.2). However, to simulate clinical effects as a function of the amount of administered drugs, only the effector site drug concentration has to be known to the pharmaco*dynamic* model. This section describes a pharmacokinetic model for the simulation of the effector site drug concentrations only, and the determination of its parameters based on clinical measurements.

The relationship between the effect compartment concentration and the administered amount of drugs is given by the transfer function $H_e(s)=C_e(s)/q(s)$, and can be derived from the Laplace transformation of equation 3.7a,bc.

$$H_e(s) = \frac{k_{e0}}{s+k_{e0}} H_1(s) = \frac{1}{V_1}\left(\frac{k_{e0}}{s+k_{e0}}\right)\left(\frac{s+k_{21}}{s^2+(k_{10}+k_{12}+k_{21})s+k_{21}k_{10}}\right) \qquad \textbf{(3.11a)}$$

To determine the (real, distinct) Eigenvalues, equation 3.11a can be rewritten as equation 3.11b

$$H_e(s) = \frac{X}{s+a} + \frac{Y}{s+b} + \frac{Z}{s+c} \qquad \textbf{(3.11b)}$$

with the following transformation between the rate constants $k_{ij}$ and Volume $V_1$ on one hand and the Eigenvalues -a,-b,-c and amplitudes X,Y,Z on the other.

$$ab = k_{10}\,k_{21}, \qquad a+b = k_{12}+k_{10}+k_{21}, \qquad c = k_{e0} \qquad \textbf{(3.12a)}$$

$$X = -Y - Z, \quad Y = \frac{c\,(k_{21}-b)}{V_1\,(a-b)(c-b)}, \qquad Z = \frac{c\,(c-k_{21})}{V_1\,(a-c)(c-b)} \qquad \textbf{(3.12b)}$$

A state variable representation is used for the numerical simulation of the transfer function $H_e(s)$. A state variable representation describes the change of the state variables over time as a function of the momentary values of the state variables $\underline{x}(t)$ and the subsequent input u(t). For a SISO (single input single output) linear time-invariant system we can write the following equation,

$$\frac{d\underline{x}(t)}{dt} = \mathbf{A}\,\underline{x}(t) + \underline{b}\,u(t) \qquad \textbf{(3.13a)}$$

$$y(t) = \underline{c}^T\,\underline{x}(t) \qquad \textbf{(3.13b)}$$

Where y(t) is the output of the system and A, b and c are parameter matrices. The matrices A, $\underline{b}$ and $\underline{c}$ can be easily derived from the transfer function $H_e(s)$ of equation 3.11b:

$$\mathbf{A} = \begin{bmatrix} -a & 0 & 0 \\ 0 & -b & 0 \\ 0 & 0 & -c \end{bmatrix}, \qquad \underline{b} = \begin{bmatrix} 1 \\ 1 \\ 1 \end{bmatrix}, \qquad \underline{c}^T = \begin{bmatrix} (-Y-Z) & Y & Z \end{bmatrix} \qquad \textbf{(3.13c)}$$

The pharmacokinetic parameters of the above state variable representation can be derived from the rate constants $k_{10}$, $k_{21}$, $k_{12}$ and $k_{e0}$ and Volume $V_1$. However, values for the rate constants $k_{ij}$ and volume $V_1$ are not always given directly and have to be found by an alternative method. For example, the clinically obtained time response of the blood plasma drug concentration can often be approximated by a sum of exponentials. Equation 3.14 shows this model for second order kinetics [Nigrovic, V., Banoud, M., 1993].

$$c_1(t) = \frac{dose}{V_1}\left( A e^{-at} + B e^{-bt} \right) \qquad \textbf{(3.14)}$$

Fitting this model to the clinical data results in values for the parameters a, b, A, B and $V_1$. To simulate the time response of equation 3.14 with the time response of the central compartment, the Laplace Transformation of equation 3.14 must be equal to the Laplace transformation of equation 3.7a, resulting in equation 3.15a and equation 3.15b respectively.

$$H_1(s) = L^{-1}[\,c_1(t)\,] = \frac{1}{V_1}\left(\frac{A}{s+a} + \frac{B}{s+b}\right) \qquad \textbf{(3.15a)}$$

$$H_1(s) = \frac{C_1(s)}{q(s)} = \frac{1}{V_1}\left(\frac{s+k_{21}}{s^2 + (k_{10}+k_{12}+k_{21})s + k_{21}k_{10}}\right) \qquad \textbf{(3.15b)}$$

Combining equations 3.15a and 3.15b gives the parameter transformations necessary to obtain the rate constants $k_{10}$, $k_{12}$ and $k_{21}$ in terms of the clinically determined parameters a, b, A and B, equations 3.16 a,b,c,d

$$k_{21} = Ab + Ba \tag{3.16a}$$

$$ab = k_{10}\, k_{21} \tag{3.16b}$$

$$a + b = k_{12} + k_{10} + k_{21} \tag{3.16c}$$

$$A + B = 1 \tag{3.16d}$$

The parameters A, B, a, b and $V_1$ are often given by the literature. Equation 3.16a,b,c then allows the computation of $k_{21}$, $k_{21}$ and $k_{10}$,. Subsequently, X, Y and Z can be calculated with equations 3.12a,b. The parameter $k_{e0}$ is arbitrary within the range given by equation 3.10b and is used to "fine-tune" the simultaneous pharmacokinetic and pharmacodynamic model. When for a specific drug the parameter $k_{e0}$ turns out to be equal to the parameter $k_{21}$ then pole-zero cancellation occurs in the equation for $H_e(s)$ (equation 3.11a). Furthermore, with equation 3.7a,b an expression can be found for $H_2(s)=C_2(s)/q(s)$:

$$H_2(s) = \frac{k_{21}}{s+k_{21}} H_1(s) = \frac{1}{V_1}\left(\frac{k_{21}}{s^2 + (k_{10}+k_{12}+k_{21})s + k_{21}k_{10}}\right) = H_e(s)\Big|_{k_{e0}=k_{21}} \tag{3.17a}$$

The transfer function $H_2(s)$ is identical to the transfer function $H_e(s)$ for $k_{e0} = k_{21}$, therefore $c_e(t)$ can be replaced by $c_2(t)$. The corresponding parameter matrices for the second order pharmacokinetic model becomes,

$$\mathbf{A} = \begin{bmatrix} -a & 0 \\ 0 & -b \end{bmatrix}, \qquad \underline{\mathbf{b}} = \begin{bmatrix} 1 \\ 1 \end{bmatrix}, \quad \underline{\mathbf{c}}^T = \begin{bmatrix} -Y & Y \end{bmatrix} \tag{3.17b}$$

The time solution for the effector site drug concentration after administering a single unit bolus is then given by equation 3.17c

$$c_2(t) = Y\left(e^{-bt} - e^{-at}\right) \tag{3.17c}$$

### *3.3 Pharmacokinetic Parameters for Atracurium*

This section derives the parameters of the pharmacokinetic model described by equation 3.13 to reflect the response of the neuromuscular blocking agent Atracurium. The literature provides the parameters A, B, a, b and $V_1$, which are obtained by measurement of blood plasma drug concentrations after administering a bolus injection of Atracurium [Nigrovic, V., Banoud, M., 1993]. Using equation 3.16, 3.12 and 3.10 the parameters can be derived for the model presented in equation 3.13,

$$\left.\begin{aligned} &A = 0.718 \\ &B = 0.282 \\ &a = 0.2501\,(\text{min}^{-1}) \\ &b = 0.0362\,(\text{min}^{-1}) \\ &V_1 = 0.07\,(\text{liters/kg}) \\ &0.1 \le \frac{\text{flow}}{V_{ISM}} \le 0.2\,(\text{min}^{-1}) \end{aligned}\right\} \Rightarrow \left\{\begin{aligned} &k_{21} = 0.097 \approx 0.1\,(\text{min}^{-1}) \\ &k_{10} = 0.094 \approx 0.1\,(\text{min}^{-1}) \\ &k_{12} = 0.096 \approx 0.1\,(\text{min}^{-1}) \\ &0.1 \le k_{e0} \le 0.2\,(\text{min}^{-1}) \\ &V_1 = 0.07\,(\text{liters/kg}) \end{aligned}\right.$$

The pharmacokinetic parameters of Atracurium for the state variable model of equation 3.13 then become,

$$a = 0.2501\,(\text{min}^{-1}),\quad b = 0.0362\,(\text{min}^{-1}),\quad c = 0.1\,(\text{min}^{-1}),\quad X = -0.45,\quad Y = 0.45,\quad Z = 0$$

As mentioned before, the relationship $k_{e0} = k_{21}$ (for Atracurium) results in a second order pharmacokinetic model of Atracurium. The corresponding parameter matrices for Atracurium then become,

$$\mathbf{A} = \begin{bmatrix} -0.2501 & 0 \\ 0 & -0.0362 \end{bmatrix}, \qquad \underline{\mathbf{b}} = \begin{bmatrix} 1 \\ 1 \end{bmatrix}, \qquad \underline{\mathbf{c}}^T = \begin{bmatrix} -0.45 & 0.45 \end{bmatrix}$$

This three parameter (a, b, $V_1$) pharmacokinetic model for Atracurium, replaces the general eight parameter model represented by equation 3.1 and 3.2. This parameter reduction greatly facilitates adjusting the model responses according to individual variability.

## 3.4 Pharmacodynamics

Traditional pharmacodynamics use Hill-type sigmoidal curves to relate the intensity of pharmacological effect to the concentration of drug in body fluid, equation 3.18 [Sheiner, L.B., Stanski, D.R., Vozeh, S., et al. 1979]

$$E = \frac{[c_e(t)]^{\gamma}}{[c_e(t)]^{\gamma} + [EC_{50}^{e}]^{\gamma}} \qquad (3.18)$$

where $c_e(t)$ is the effector site drug concentration, and E is the intensity of pharmacological effect expressed as a fraction of the maximum effect. $EC_e(50)$ is a constant equal to the value of $c_e(t)$ at 50% effect, and $\gamma$ is a parameter that reflects the sigmoidicity in the relationship between the concentration $c_e(t)$ and the effect E. Neuromuscular function is monitored by evaluating the response (twitch height) of a muscle to electrical stimulation of a peripheral motor nerve, e.g. response of the adductor pollicis muscle after stimulation of the ulnar nerve. After administration of a muscle relaxant, the twitch height decreases reflecting the degree of neuromuscular blockade. In this context, the pharmacodynamic effect is defined as twitch height depression. The twitch height depression depends on the used (electrical) stimulus mode; Single Twitch, Train of Four, Tetanic Stimulus or Post Tetanic Count.

### 3.4.1 Single Twitch

With the peripheral nerve stimulator in the single-twitch mode (figure 3.3), single electrical stimuli are applied to a peripheral motor nerve at frequencies ranging from 0.1 Hz to 1 Hz. The muscle response to single twitch stimulation depends on the frequency of stimuli delivery. If the rate of delivery is increased to more than 0.15 Hz, the evoked response will gradually decrease and settle at lower level. Therefore, usually a frequency of 0.1 Hz is used for single-twitch stimulation. The twitch height depression y after a single-twitch stimulation is given by equation 3.19.

$$y^{ST}(t) = \frac{[c_2(t)]^{\gamma}}{[c_2(t)]^{\gamma} + [EC_{50}^{ST}]^{\gamma}} \qquad (3.19)$$

Where $c_2(t)=c_e(t)$ is the effector site drug concentration.

In the clinical environment, twitch height rather than twitch height depression is evaluated. The expression for twitch height is given by equation 3.20,

$$Y^{ST}(t) = 1 - y^{ST}(t) = 1 - \frac{[c_2(t)]^{\gamma}}{[c_2(t)]^{\gamma} + [EC_{50}^{ST}]^{\gamma}} = \frac{1}{1 + \left[\frac{c_2(t)}{EC_{50}^{ST}}\right]^{\gamma}} \qquad \textbf{(3.20)}$$

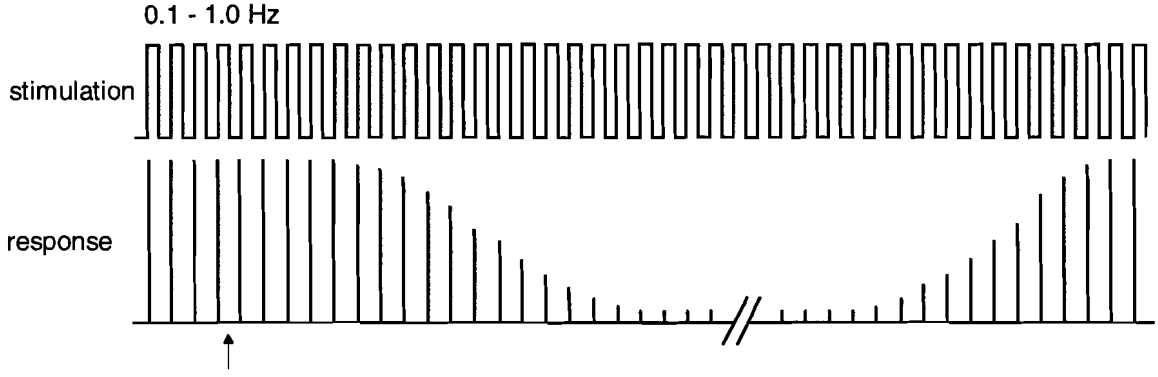


**Fig. 3-3** Single Twitch stimulation and response after a bolus of a non-depolarizing NMB agent. The arrow indicates the time of administration of the bolus, and the response curve illustrates the onset and recovery of the resulting effect (twitch height depression).

### 3.4.2 Train-of-Four

In train-of-four (TOF) stimulation (figure 3.4), four electrical stimuli are given at a rate of 2 Hz. When applied continuously, each train of stimuli is repeated every 10 to 12 seconds.

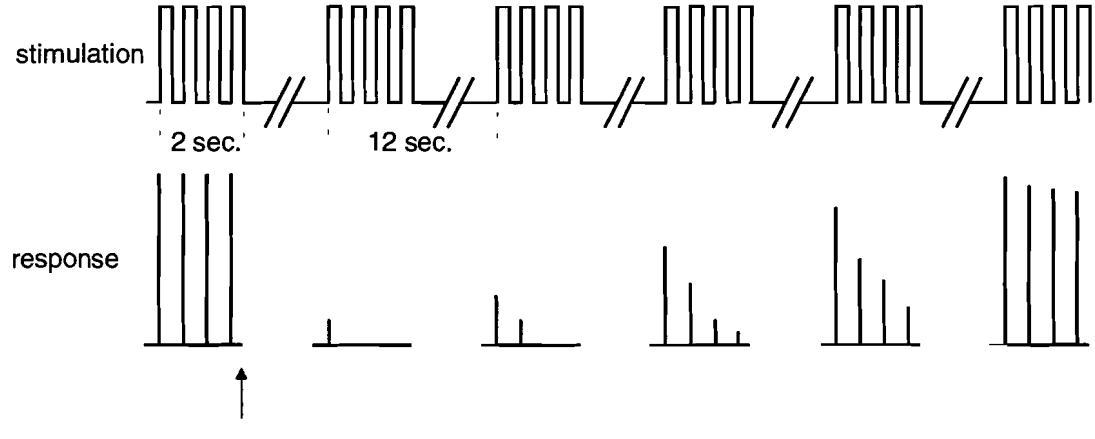


**Fig. 3-4** Train-of-Four stimulation and typical response patterns for different levels of blockade to a bolus injection of a non-depolarizing NMB agent.

Each stimulus in the train causes the muscle to contract. The fade in twitch response that is observed when using non-depolarizing drugs, provides the basis for evaluation of the level of blockade. The train-of-four fade is defined by equation 3.21

$$\theta = 100\left(\frac{Y_4^{TOF}}{Y_1^{TOF}}\right) \qquad \textbf{(3.21)}$$

where $Y_1$ and $Y_4$ represent the amplitudes of the first and the fourth twitches respectively. The twitch height of the first TOF twitch ($Y_1$) is identical to the twitch height following single twitch stimulus,

$$Y_1^{TOF}(t) = Y^{ST}(t) \qquad \textbf{(3.22)}$$

To evaluate the twitch fade, the twitch height of the fourth twitch could be modeled separately, however, an empirically determined relationship between the train of four twitch height responses was found in the scientific literature [Jaklitsch, R.R., Westenskow, D.R., 1990]:

$$Y_{i+1} = Y_i^2 \quad , \quad i = 1,2,3 \qquad \textbf{(3.23a)}$$

For later use we rewrite this relation in terms of twitch height related to the twitch height of the first TOF,

$$Y_i^{TOF} = \left(Y^{ST}\right)^{2^{i-1}} \qquad \textbf{(3.23b)}$$

### 3.4.3 Tetanic Stimulation

Tetanic Stimulation consists of relatively high frequency electrical stimuli (30-100 Hz) applied for several seconds. The most commonly used pattern in clinical practice is 50 Hz stimulation applied for 5 seconds (figure 3.5). During a nondepolarizing block, the response to Tetanic Stimulation fades dependent of the degree of neuromuscular blockade. Tetanic Stimulation is followed by a post-tetanic increase in twitch tension for a period of about 60 seconds.
Because Tetanic Stimulation is very painful, it is not used on unanesthezed patients, and for this reason the tetanic fade is not used for monitoring twitch height depression, but only to incidentally evaluate a high level of neuromuscular

blockade. Furthermore, Tetanic Stimulation is mostly used in combination with Post Tetanic Count (PTC), which will be discussed in detail in section 3.4.4

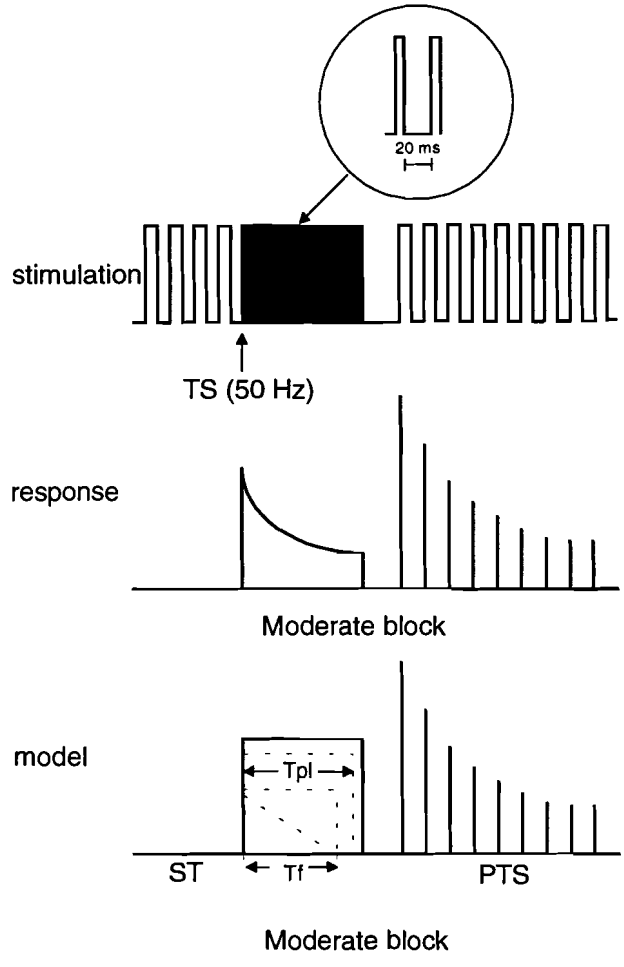


**Fig. 3-5:** Tetanic simulation, response and the empirical model for non-depolarizing NMB drugs (see equations 3.25 and 3.26).

Because Tetanic stimuli are not used to evaluate the degree of neuromuscular blockade, only an empirical model is used based on expert data. According to that data, it is sufficient for the empirical model to indicate if a fade in the response to tetanic stimulation occurs. Therefore the initial twitch height of the response to tetanic stimulation is chosen identical to the twitch height response to single twitch stimulation, equation 3.24.

$$Y^{TS} = Y^{ST} \qquad \textbf{(3.24)}$$

As shown in figure 3-5, the empirical model consists of a twitch height, a plateau time ($T_{pl}$) to indicate the response time without fade, and a fade time ($T_f$) to indicate the duration of the fade. A fade in the response to tetanic stimulus

occurs if the initial twitch height is less then 25% of the maximum, and the plateau time is then zero. If the initial twitch height is greater than 25%, the fade time is zero, and the plateau time is equal to the length of the stimulus. The amplitude and the duration of the fade provide no additional information. The equations 3.25 and 3.26 give the plateau time and the fade time as a function of the initial twitch height.

$$T_{pl} = \begin{cases} 0\,\text{sec} & \text{for} \quad Y^{TS} < 0.25 \\ T_{stimulus} & \text{for} \quad Y^{TS} \geq 0.25 \end{cases} \tag{3.25}$$

$$T_{f} = \begin{cases} 1\,\text{sec} & \text{for} \quad Y_t^{TS} < 0.25 \\ 0\,\text{sec} & \text{for} \quad Y_t^{TS} \geq 0.25 \end{cases} \tag{3.26}$$

### 3.4.4 Post Tetanic Count

Injection of a sufficient dose of neuromuscular blocking drugs results in total blockade in response to TOF and single-twitch stimulation, so the degree of blockade can no longer be determined by these methods. However, it is possible to quantify intense neuromuscular blockade of the peripheral muscles by applying tetanic stimulation and observing the post-tetanic response to single-twitch stimulation (given at 1 Hz, starting 3 seconds after the end of tetanic stimulation). Before the first response to ST or TOF stimulation reappears the intense neuromuscular blockade dissipates and the first response to post-tetanic stimulation (PTS) occurs. More responses to post-tetanic stimulation appear as the dissipation proceeds, figure 3.6

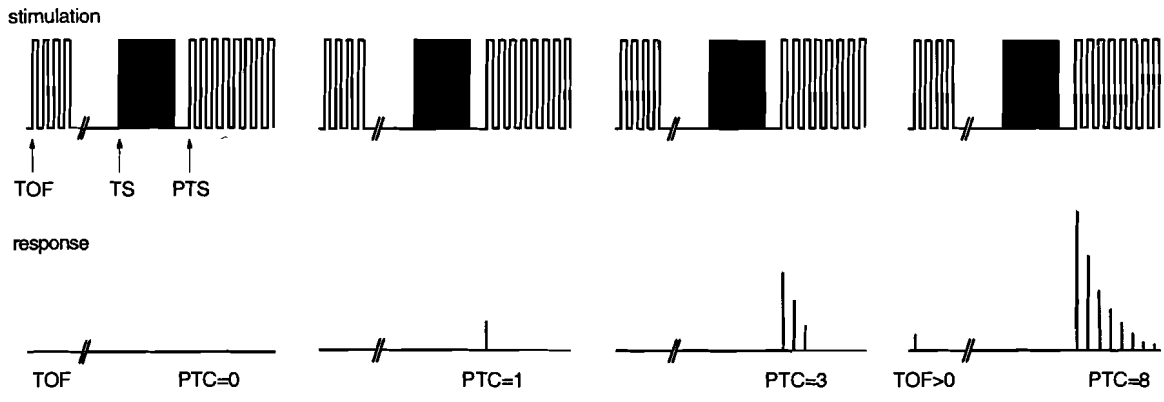


**Fig. 3-6** TOF and Post Tetanic stimulation and response for decreasing levels of non-depolarizing blockade. Note that the first response to TOF occurs when the Post Tetanic Count is equal to 8 (PTC=8).

For a given neuromuscular blocking drug, the elapsed time until return of the first ST or TOF response is related to the number of post-tetanic twitches, also known as Post Tetanic Count (PTC) , figure 3.7

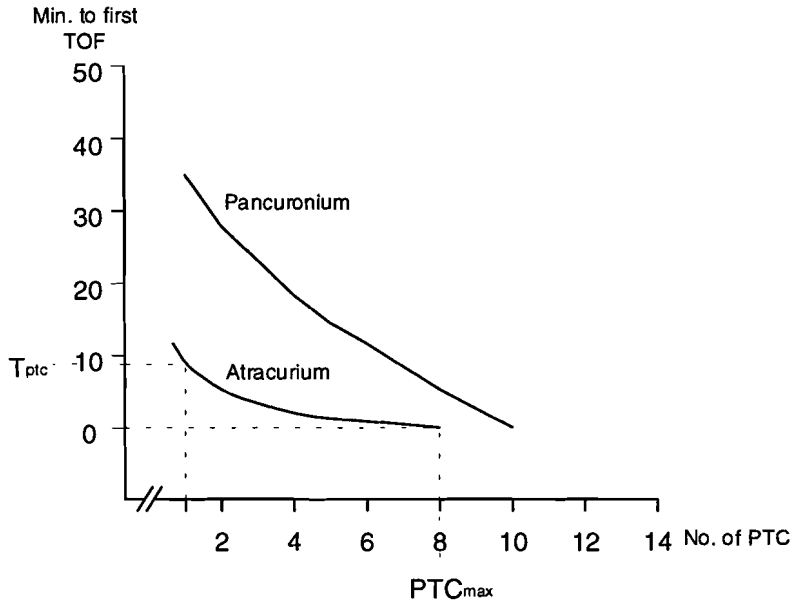


**Fig. 3-7:** Typical curves for the relationship between PTC and Time to First TOF, [Miller, R.D., 1990]

The response to post-tetanic twitch stimulation (PTS) depends primarily on the degree of neuromuscular blockade. It also depends on the frequency and duration of tetanic stimulation, the length of time between the end of tetanic stimulation and the first post-tetanic stimulus, and the frequency of single-twitch stimulation. To facilitate PTC modeling, these parameters are kept constant.
No mathematical model relating effector compartment concentration and Post Tetanic Count could be found in the literature. The remainder of this section describes the derivation of such a model.
The following assumptions were made:

- First, it is assumed that twitch responses are detectable when their twitch height response is equal or larger than a predefined *threshold*; this was selected to be 5% of maximum twitch height.
- Second, the Post Tetanic increase in twitch tension is modeled with changes in pharmacodynamics only.
- Third, it is assumed that Post Tetanic Count is only used after the administration of a drug dose which was sufficient to produce total block to ST and TOF stimulation.

The first and second assumption allow to model Post Tetanic Stimulation (PTS) as a change in drug sensitivity based on a shifted $EC_{50}$ , as compared to the $EC_{50}$ of ST and TOF stimulation, (figure 3.8).

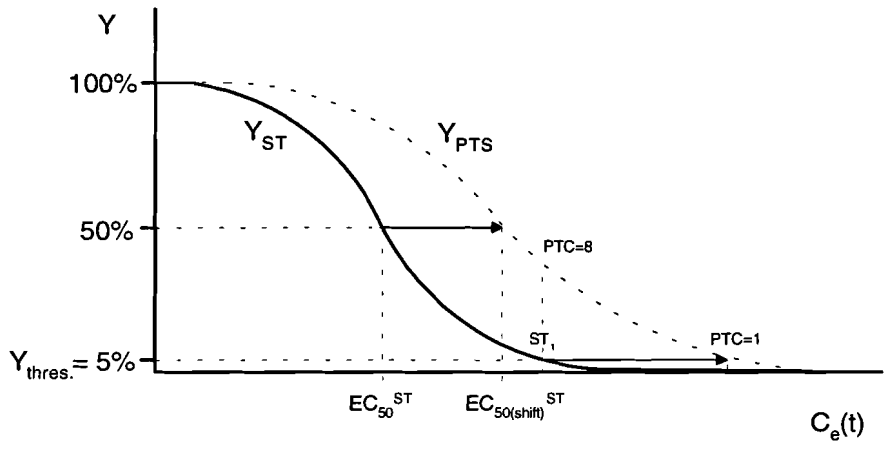


**Fig.3-8:** PTS simulation based on a shift in sensitivity, which can be reflected by a shifted $EC_{50}^{ST}$

The third assumption guarantees that the first twitch response to ST or TOF stimulation always occurs after Tmax (figure 3.9), therefore the PTC at Tmax is smaller then or equal to $PTC_{max}$, as illustrated in figure 3.6. The third assumption also allows the effector concentration time dependency to be approximated by the following equation,

$$c_2(t)_{t>T_{max}} \approx \text{Dose}.Q.e^{(-bt)} \qquad \textbf{(3.27)}$$

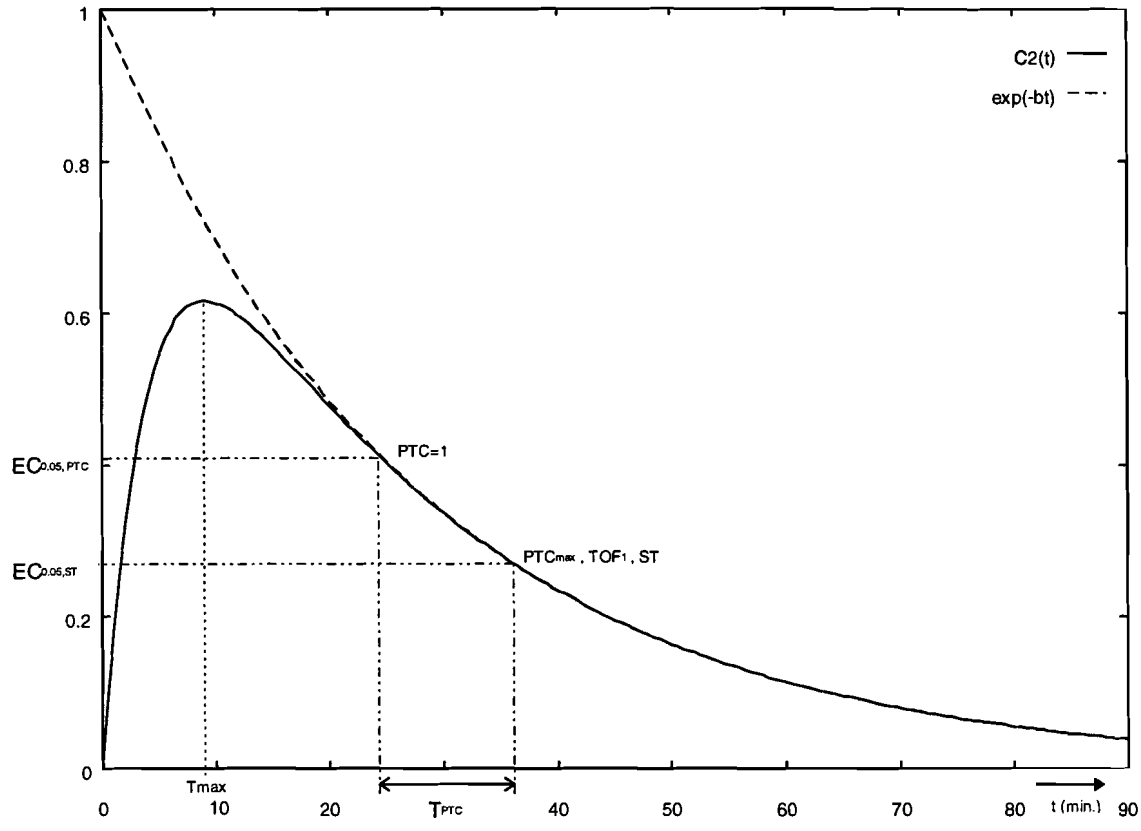


**Fig. 3-9:** Illustration of the concentration approximation, on which the PTC modeling is based.

The first detectable ST or TOF response appears when the twitch is larger then the *threshold* $Y_{thres}$, which again is taken to be 5%. The corresponding drug concentration in the **effect** compartment is then given by $EC_{05}^{ST}$. The first PTC>0 appears when the response to Post Tetanic Stimulation (= shifted Single Twitch response) is greater than the predefined threshold, consequently resulting in the effect compartment concentration $EC_{05}^{PTC}$. By using equation 3.27 for the effector site concentration, an expression can be found for $EC_{05}^{PTC}$ as a function of $EC_{05}^{ST}$, equation 3.28a. The time period $T_{PTC}$ is indicated in figure 3.9.

$$EC_{05}^{PTC} = e^{bT_{PTC}} . EC_{05}^{ST} \qquad \textbf{(3.28a)}$$

Based on the assumption of a shift in sensitivity, the relationship between the threshold concentration $EC_{05}$ and the 50% effect concentration $EC_{50}$ is the same for ST, TOF and PTC, and can be derived from equation 3.20.

$$EC_{50} = 19^{-\frac{1}{\gamma}} . EC_{05} \qquad \textbf{(3.28b)}$$

The expression for the shifted $EC_{50}^{ST}$ for PTC results from the substitution of equation 3.28b in 3.28a, when the same gamma value ($\gamma$) is used for both stimulus modes, equation 3.28c

$$EC_{50}^{PTC} = e^{bT_{PTC}}.EC_{50}^{ST} \qquad \textbf{(3.28c)}$$

The pharmacodynamic description for the twitch height of the first response to post tetanic stimulation then becomes equal to equation 3.29

$$Y_1^{PTC}(t) = \frac{1}{1+\left[\frac{c_2(t)}{EC_{50}^{PTC}}\right]^{\gamma}} = \frac{1}{1+\left[\frac{c_2(t)}{e^{bT_{PTC}}.EC_{50}^{ST}}\right]^{\gamma}} \qquad \textbf{(3.29)}$$

To model the PTS twitch fade, we use a similar expression for the PTS twitch fade as for the TOF fade. For PTS we also have to consider the PTC value when the first TOF twitch occurs, therefore an extra drug dependent constant $\delta$ is necessary. The expression for the PTS twitch fade is then given by equation 3.30a,

$$Y_i^{PTC} = \left(Y_1^{PTC}\right)^{\delta^{(i-1)}} \qquad \textbf{(3.30a)}$$

To derive a value for the exponent $\delta$, we rewrite equation 3.30a as follows,

$$\delta = \left(\frac{\ln\left(Y_i^{PTC}\right)}{\ln\left(Y_1^{PTC}\right)}\right)^{\left(\frac{1}{i-1}\right)} \qquad \textbf{(3.30b)}$$

To determine $\delta$ we have to consider the following steps,

- The first twitch response to **TOF** (=$TOF_1$) occurs when the $i^{th}$ number ($PTC_{max}$) of PTC appears. The effector site drug concentration for that situation is given by equation 3.31

$$c_2(t)_{TOFI}^{\gamma} = \left(\frac{Y_{Thres.}}{1-Y_{Thres.}}\right)EC_{50}^{ST\gamma} \qquad \textbf{(3.31)}$$

- The twitch height of the first response to PTS results from the substitution of that concentration in the pharmacodynamic relationship for PTC, equation 3.29,

$$Y_1^{PTC}(t_{TOF_1}) = \frac{1}{1+\left(\frac{1}{Y_{Thres.}}-1\right)e^{-\gamma\, bT_{PTC}}} \qquad \textbf{(3.32)}$$

- The $i^{th}$ response to PTS (=$PTC_{max}$) appears at approximately the same time as when the first response to TOF stimulation occurs, hence the twitch height of that response, $Y_{PTCMAX}$, equals the threshold twitch height $Y_{thres}$ at that time,

$$Y_{i=PTC_{max}}^{PTC} = Y_{thres.} \qquad \textbf{(3.33)}$$

- The detection threshold for the first twitch responses is 5%, $Y_{thres} = 0.05$

Now the values can be determined for $Y_1^{PTC}$, $Y_i^{PTC}$ and i=$PTC_{max}$ , and the substitution of these values into equation 3.30b, gives the drug dependent PTC exponent $\delta$.

## *3.5 Pharmacodynamic Parameters for Atracurium*

The literature gives values for gamma and for the dose that produces 50% effect ($ED_{50}$). The time at which maximal effect occurs is called $t_{max}$, and at that time the two compartment concentrations are equal ($c_1(t_{max}) = c_2(t_{max})$ see figure 3.2 and equation 3.7b). The relationship between the **effect** compartment concentration for 50% effect and $ED_{50}$ is given by equation 3.34,

$$EC_{50} = c_2(t_{max}) = c_1(t_{max}) = \frac{ED_{50}}{V_1}\left(Ae^{-a\,t_{max}} + Be^{-b\,t_{max}}\right) \qquad \textbf{(3.34)}$$

where $V_1$, A, B, a and b are the pharmacokinetic parameters discussed in section 3.3.

By taking the derivative of equation 3.17c, the following expression for $t_{max}$ can be found,

$$t_{max} = \frac{1}{b-a} \ln\left(\frac{b}{a}\right) \qquad \textbf{(3.35)}$$

$ED_{50}$ and $\gamma$ are given in the literature, [Jaklitsch, R.R., Westenskow, D.R., 1990],

$ED_{50}$ = 0.12 mg/kg
$\gamma$ = 4.4

and with the pharmacokinetic parameters of section 3.3 this results in

$t_{max}$ = 9.04 min.
$EC_{50}$ = 0.48 mg/l

From figure 3.5 we find the PTC constants for Atracurium

$PTC_{max}$=8
$T_{PTC}$=10 min.

resulting in the PTC exponent $\delta$

$\delta$ = 1.096

# 4 Numerical Methods for Interactive Simulation of Linear Systems

We have seen earlier that computer based learning and teaching tools gain in realism and interactivity by using model driven feedback to the user, for example, in the form of animation's or graphs. The interactive nature of the simulations, and the sometimes required "faster-than-real-time" capabilities, can put extra constraints on the CPU that is already handling text, graphics, etc., hence the need for an efficient numerical simulation of the mathematical models. In this chapter we will discuss the requirements for interactive simulation of pharmacokinetics, and select a numerical simulation method that meets these requirements.

## *4.1 Requirements for Interactive Pharmacokinetic Simulation*

For interactive training devices, inputs are generated by the user, e.g. administering a bolus or infusion, and model output samples are generated only when the user requests them, e.g. twitch height measurement in the Intensive Care Unit Part Task Trainer (ICU-PTT) for neuromuscular blockade. The time interval between two user generated inputs is called $T_i$, and the time interval between two model output requests $T_o$. The calculation interval $T_c$ is the time interval between two subsequent model iterations. The different sample intervals are illustrated in figure 4.1.

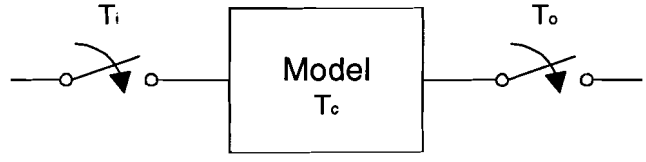


**Fig. 4-1:** Overview of the different sample periods for the simulation

The sample intervals $T_i$, $T_o$ and $T_c$ can be derived from the following simulation requirements:

- **Accurate response**: To reflect reality as close as possible, the simulation error should be small.
- **Smoothness of response**: The simulation step size must be small enough to give the impression of a continuous response, both in time and amplitude. In

this context we will not consider the use of signal reconstruction algorithms other than interpolation.

- **Asynchronous input and output**: To allow the user to generate input and request output at every moment in time, the calculation step size should be transparent to the user, and not result in any noticeable time delay in the response.
- **Efficiency / Complexity:** To make real time and especially "fast forward" modes possible, the calculation time for one iteration, is limited by the available CPU time.

The following sections discuss several modeling approaches and numerical simulation techniques in view of the mentioned requirements.

## *4.2 Non-iterative Simulation based on the Superposition Principle*

Pharmacologically, only two inputs have to be considered: a bolus injection and a stepwise change in infusion rate. Assuming that a bolus injection can be simulated by an impulse input $\delta(t)$, and a change in infusion rate by a step input $U(t)$, the class of possible inputs can be described by equation 4.1.

$$u(t) \in \begin{cases} u_b(t) = U_m.\delta\,(t - t_m) \\ u_i(t) = U_n.U(t - t_n) \end{cases} \qquad \textbf{(4.1)}$$

where $U_m$ and $U_n$ are the magnitudes and $t_m$ and $t_n$ the administration times of the boluses and infusions respectively. Applying the superposition principle for linear systems to pharmacokinetics, we can state that if the pharmacokinetic response (any compartment concentration of interest) to a single bolus or infusion is known, then the pharmacokinetic response to repetitive boluses and changes of the infusion rate is the summation of the separate responses. Let the pharmacokinetic response to a single unit bolus be given by $h_b(t)$, and to a single unit infusion by $h_i(t)$ then the pharmacokinetic response y(t) can be described by equation 4.2.

$$y(t) = \sum_k U_{m_k}.h_b(t - t_{m_k}) + \sum_l U_{n_l}.h_i(t - t_{n_l}) \qquad \textbf{(4.2)}$$

In the case of two compartment pharmacokinetics, the time responses of the peripheral compartment concentration to a unit bolus, $h_b(t)$, and an unit infusion, $h_i(t)$, are described by equations 4.3a and 4.3b (see chapter 3, equation 3.17c)

$$h_b(t) = Y( e^{-bt} - e^{-at} ) \quad , \quad h_b(0) = 0 \qquad \textbf{(4.3a)}$$

$$h_i(t) = ( Ae^{-at} + Be^{-bt} + C ) \quad , \quad h_i(0) = 0 \qquad \textbf{(4.3b)}$$

Using the superposition method to simulate the pharmacokinetic equations, results in a precise response. Nevertheless, the efficiency of the method decreases linearly with the number of repetitive inputs. Moreover, the complexity and memory requirements of this method increase with the number of possible repetitive inputs.

For these reasons we recommend the use of this method only if there is a known, low upper limit on the number of repetitive inputs. This is certainly not the case for the 8 hour shift simulated in the ICU-PTT, therefore we investigate another modeling approach and two different methods for its numerical simulation.

## *4.3 Iterative Simulation based on a State Variable Representation*

The state variable representation was introduced in section 3.2. For a single input single output (SISO) linear, time-invariant system we can write the following state and output equations,

$$\frac{d\underline{x}(t)}{dt} = \mathbf{A}\,\underline{x}(t) + \underline{b}\,u(t) \qquad \textbf{(4.4a)}$$

$$y(t) = \underline{c}^T\,\underline{x}(t) \qquad \textbf{(4.4b)}$$

where y(t) is the output of the system, A, b and c are parameter matrices, and u(t) is the input class defined in the previous section.

Using the state variable representation for the simulation solves the problem of handling several repetitive inputs. Its complexity is independent of the number of possible repetitive inputs. However, to solve the state variable equations a discrete integration method has to be selected.

### 4.3.1 Euler Integration

To simulate the evolution of the state variable $\underline{\mathbf{x}}$ over time, the state variable equation 4.4a can be discretized based on a numerical approximation of the time derivative, equation 4.5.

$$\frac{d\,\underline{\mathbf{x}}(t)}{dt} \cong \frac{\underline{\mathbf{x}}(t+T_d)-\underline{\mathbf{x}}(t)}{T_d} \qquad \textbf{(4.5)}$$

To distinguish the discrete approximation from the exact solution, the following notations are used: $\underline{\mathbf{x}}_k^{Td}$ to reflect the discrete approximation and $\underline{\mathbf{x}}(t_k)$ for the exact solution at time $t_k=kT_d$. Rewriting equation 4.5 with these notations results in the well known Euler forward equation:

$$\underline{\mathbf{x}}_{k+1}^{T_d} = \underline{\mathbf{x}}_k^{T_d} + T_d.\dot{\underline{\mathbf{x}}}_k^{T_d} \qquad \textbf{(4.6)}$$

Applying the Euler Forward equation to the state variable representation of equation 4.4 results in the following discrete iterative state variable representation.

$$\underline{\mathbf{x}}_{k+1}^{T_d} = (\mathbf{I}+T_d.\mathbf{A}).\underline{\mathbf{x}}_k^{T_d} + T_d.\underline{\mathbf{b}}\,u(t_k) \qquad \textbf{(4.7a)}$$

$$y_k^{T_d} = \underline{\mathbf{c}}^T\,\underline{\mathbf{x}}_k^{T_d} \qquad \textbf{(4.7b)}$$

Considering the input class defined by equation 4.1, the time derivative for the impulse inputs is assumed to be infinity. Therefore, the discrete state variable representation of equation 4.7 cannot handle the impulse inputs through the input variable u(t). For simulation purposes, the impulse inputs have to be added directly to the state variable, before calculating the next state (equation 4.8):

$$\underline{\mathbf{x}}_k^{T_d} = \underline{\mathbf{x}}_k^{T_d} + \underline{\mathbf{b}}\,u_b(t_k) \qquad \textbf{(4.8)}$$

The step inputs can be included normally, through the input variable. The sample interval $T_d=T_c$ has a definite influence on precision, smoothness of the response, and the efficiency of the Euler method. The discretization error, equation 4.9, which occurs by using the Euler method, can be avoided if an analytic solution of equation 4.4a exists.

$$\underline{e}_k^{T_d} = \underline{x}(t_k) - \underline{x}_k^{T_d} \quad (4.9)$$

The next section discusses a precise integration method based on an analytic solution for the linear, time-invariant system represented by equation 4.4a.

### 4.3.2 Integration based on the State Transition Equations

The first part of this section is a brief overview of an analytic solution of equation 4.4a described by Kuo [Kuo, B.C., 1980]. Subsequently, the equations for that solution are discretized for iterative numerical integration. By maintaining the integration interval $T_c$ as a variable, asynchronous inputs and outputs can be simulated. We will show that if the user is only interested in the momentary value of the system response, then the calculation interval $T_c$ can be changed accordingly to the elapsed time between the last input or output and the new input or output.

For a linear time-invariant system, an analytic continuous time solution of the state equation 4.4a can be written as follows,

$$\underline{x}(t) = \phi(t-t_0)\,\underline{x}(t_0) + \int_{t_0}^{t} \phi(t-\tau)\underline{b}\,u_i(\tau)\,d\tau \quad (4.10)$$

where $\phi(t\text{-}t_0)$ is the transition matrix; the nxn matrix which satisfies the homogeneous state equation:

$$\frac{d\phi(t-t_0)}{dt} = \mathbf{A}.\phi(t-t_0) \quad (4.11)$$

The following expression for $\phi(t\text{-}t_0)$ can be derived:

$$\phi(t-t_0) = e^{\mathbf{A}(t-t_0)} = \sum_{k=0}^{\infty} \frac{\mathbf{A}^k (t-t_0)^k}{k!} \quad (4.12)$$

The state transition matrix can also be computed by the inverse Laplace transform:

$$\phi(t) = L^{-1}[(s\mathbf{I}-\mathbf{A})^{-1}] \quad (4.13)$$

The solution (4.10) of the state equation is also referred to as the *state transition equation* [Kuo, B.C., 1980].

By assuming that the input signal $u_i(t)$ is constant over the calculation interval $T_c$, the state transition equation can be used to describe the transition of the states between two successive sample instants $kT_c \le t \le (k+1)T_c$. Substitution of $t_0=kT_c=t_k$ and $t=(k+1)T_c=t_{k+1}$ in the state equation 4.10, results in the *discrete state transition equation* (4.14) [Kuo, B.C., 1980]:

$$\underline{\mathbf{x}}[t_{k+1}] = \phi[T_c]\,\underline{\mathbf{x}}(t_k) + \theta[T_c]\,u_i(t_k) \qquad \textbf{(4.14)}$$

with

$$\theta[T_c] = \int_{kT_c}^{(k+1)T_c} \phi[t_{k+1} - \tau]\,\underline{\mathbf{b}}\,d\tau \qquad \textbf{(4.15)}$$

It should be noted that the solution $\underline{\mathbf{x}}(t_{k+1})$ in equation (4.14) represents the exact values of $\underline{\mathbf{x}}(t)$ for any sample time $t=t_{k+1}$. Therefore, the discretization error equals zero. The discretized state representation of two compartment pharmacokinetics (4.4a,b) can then be described by equations 4.16a,b,c:

Bolus administration: $$\underline{\mathbf{x}}[t_k] = \underline{\mathbf{x}}[t_k] + u_b(t_k) \qquad \textbf{(4.16a)}$$

Output equation: $$y[t_k] = \underline{\mathbf{c}}^{T_s}\,\underline{\mathbf{x}}[t_k] \qquad \textbf{(4.16b)}$$

State transition: $$\underline{\mathbf{x}}[t_{k+1}] = \phi[T_c]\,\underline{\mathbf{x}}[t_k] + \theta[T_c]\,u_i(t_k) \qquad \textbf{(4.16c)}$$

For the parameter matrices for Atracurium, derived in the previous chapter, the state transition matrix becomes:

$$\phi(T_c) = e^{AT_c} = \begin{bmatrix} e^{aT_c} & 0 \\ 0 & e^{bT_c} \end{bmatrix}$$

and

$$\theta[T_c] = \int_{kT_c}^{(k+1)T_c} \phi[t_{k+1} - \tau]\,\underline{\mathbf{b}}\,d\tau = \begin{bmatrix} \frac{1}{a}\left(e^{aT_c} - 1\right) \\ \\ \frac{1}{b}\left(e^{bT_c} - 1\right) \end{bmatrix}$$

### 4.3.3 The State Transition Method in terms of the simulation requirements

We will now consider the calculation interval $T_c$ , the input sample period $T_i$ and the output sample period $T_o$ (figure 4.1) with respect to the requirements formulated in section 4.1.

- **Accurate response**
  Because no discretization error occurs for the state transition method an accurate response for the simulations is guaranteed independently of the calculation interval $T_c$. Hence, the possibility of variable calculation intervals to optimize the efficiency.

- **Smoothness of response**
  In the ICU part task trainer (discussed in chapter 5) the model driven feedback to the user has two different modes. In the first mode the user makes a request for only the momentary value of the system response. In the second mode, the "DISPLAY-MODE" , the user is interested in the system response over a period of time. To evaluate system characteristics, output samples have to be generated at small regular time intervals $T_o$ so that the overall output response has a smooth appearance. Which means that the maximal changes in response over one sample period must be small enough so that no visible discretization occurs in the response. If the output sample period $T_o$ is chosen 10-15 times smaller than the fastest time constant of the system, then the maximum change per sample period is limited. The calculation interval $T_c$ has to be smaller or equal to the output sample period. This results in the following upper limit for the calculation interval $T_c$ in the DISPLAY- MODE

$$T_c \leq T_o = \frac{\tau_{fast}}{10} \qquad (4.17)$$

- **Asynchronous input and output**
  In the "DISPLAY-MODE", input can be taken into account at sample times only. Therefore, the sample period should be small enough that no noticeable time delay between the simulated response and the realistic response occurs, when the user generates an input. Also, distinguishing between repetitive inputs within one sample period is not possible, consequently the sample period must be small enough to allow addition of repetitive inputs which are administered in one sample period. The previously defined limit for the

calculation interval $T_c$ for a smooth response is also suitable for the asynchronous input requirements.

$$T_c \leq T_o = \frac{\tau_{fast}}{10}$$

- **Efficiency / complexity**

  For real time simulations , "faster than real time" simulations and simulations in a multi-tasking environment, there is only a specific amount of time available to calculate the requested output response. Here we discuss the example of simulating the model response for a total time period of $T_o$ in a (much smaller) available CPU time, $T_{CPU}$

  The necessary number of model iterations (k) to simulate a total time period $T_o$ , is given by equation 4.18a. Where $T_c$ is the calculation interval.

$$k = \frac{T_o}{T_c} \qquad \textbf{(4.18a)}$$

If calculating one model iteration takes N clock cycles then the necessary time to calculate that one iteration is given by equation 4.18b. Where $f_c$ is the clock frequency of the CPU.

$$T_k = \frac{N}{f_c} \qquad \textbf{(4.18b)}$$

Then the total time to calculate k iterations is equal to equation 4.18c

$$k.T_k = \frac{T_o.N}{f_c\ T_c} \qquad \textbf{(4.18c)}$$

This total calculation time has to be smaller then the available CPU time ($T_{CPU}$), resulting in equation 4.18d

$$\frac{T_o.N}{f_c\ T_c} \leq T_{CPU} \qquad \textbf{(4.18d)}$$

Rewriting equation 4.18d results in a lower limit for the calculation interval $T_c$, equation 4.18e. The upper limit for the calculation interval was already given by equation 4.17.

$$\frac{T_o.N}{T_{cpu}.f_c} \leq T_c\,(\text{sec.}) \leq \frac{\tau_{fast}}{10} \qquad \textbf{(4.18e)}$$

For example, when the model response has to be calculated for 8 hours with an algorithm that takes 1000 clock cycles per iteration, and the available time for these calculation is 1 second with a clock frequency of 33 MHz, then the calculation interval must be larger or equal to 0.9 seconds. (Results from substitution of $T_o$=28800 sec., N=1000, $T_{CPU}$=1 sec. and $f_c=33x10^6$ , in equation 4.18e)

The efficiency of implementation (N) was experimentally determined for three different algorithms based on the state transition equations. The first algorithm assumed a constant calculation interval $T_c$, resulting in a constant state transition matrix which had to be calculated only once. The second algorithm included the possibility for variable calculation intervals $T_c$ and calculated the new state transition matrix for every iteration. The third algorithm also included possible variations in the calculation interval $T_c$, but tested every iteration if the calculation interval was changed. The different simulations were carried out with a 486 DX2 60 MHz computer ($f_c$=60 MHz ) and the results are listed below, table 4.1.

**Table 4.1:** Experimental determination of the efficiency of implementation by measuring the number of clock cycles per iteration (N) for three different algorithms (which are explained in the text). The used computer was a 486 DX2 with a clock frequency of 60 MHz . The calculation interval $T_c$ was not changed during all three simulations: $T_c$=1 sec.

| | $k.T_k$ (for k=1M iterations) | $N (=T_k.f_c)$ |
|---|---|---|
| Algorithm 1 | 7.80 sec. | 468 |
| Algorithm 2 | 24.38 sec. | 1463 |
| Algorithm 3 | 8.18 sec. | 491 |

Table 4.1 shows that algorithm 1 is the optimal algorithm based on the efficiency of implementation (N). However, the disadvantage of algorithm 1 is that it does not allow changes in the calculation interval $T_c$, one of the most desirable features of the state transition method, necessary for asynchronous

inputs and outputs. In algorithm 2 and 3 changes in calculation interval are allowed and for those two algorithms algorithm 3 is the most efficient one. Note that the reported efficiency of implementation N for algorithm 3, is the number of clock cycles obtained with a constant calculation interval $T_c$. If the calculation interval changes between two iterations then the state transition matrices have to be recalculated, resulting in one iteration with an increased number of clock cycles, comparable with the number of clock cycles per iteration of algorithm 2.

## *4.4 Conclusions and Algorithm for State Variable Interactive Pharmacokinetic Simulation*

The purpose of this chapter is to find the most suitable method for interactive pharmacokinetic simulation based on the requirements of section 4.1. The most important advantages of the state variable over the conventional transfer function method is the capability to handle repetitive asynchronous inputs. Some other advantages are that the state variable formulation is natural and convenient for computer simulations, it allows an unified representation for single variable and multi-variable systems and the state variable method can be applied to certain types of nonlinear and time-varying systems.

For solving the state variable representation for linear, time-invariant systems such as the pharmacokinetic model, the use of the state transition equations is preferred over the Euler integration because the latter introduces a discretization error. Three different algorithms were tested for simulations with the state transition equations, and the most efficient algorithm for interactive pharmacokinetic simulations is given below, in pseudo-code.

**if** (DISPLAYMODE) **then** SamplePeriod = $T_o$ **else** SamplePeriod = **MIN** ( | t -$T_i$ | , | t -$T_o$ | );

**function** PK_model (SamplePeriod)

**{**

$T_s^{new}$ = SamplePeriod;

**if** ($T_s^{new}$ <> $T_s^{old}$) **then**

**{**

$T_s^{old} = T_s^{new}$ ;

$$\phi\,(T_s^{new}) \;=\; \begin{bmatrix} e^{a\,T_s^{new}} & 0 \\ 0 & e^{b\,T_s^{new}} \end{bmatrix};$$

$$\theta\;[T_s^{new}] \;=\; \begin{bmatrix} \frac{1}{a}\left(e^{a\,T_s^{new}} - 1\right) \\ \\ \frac{1}{b}\left(e^{b\,T_s^{new}} - 1\right) \end{bmatrix};$$

**};**

$\underline{x}[t_k] = \underline{x}[t_k] + u_b(t_k)$ ;

$y[t_k] = \underline{c}^T\,\underline{x}[t_k]$ ;

$\underline{x}[t_{k+1}] = \phi\,[T_s^{new}]\,\underline{x}[t_k] + \theta\,[T_s^{new}]\,u_i(t_k)$ ;

**};**

# 5 Integration of the pharmacological models in a Part Task Trainer

In this chapter we will discuss the development of an interactive Part Task Trainer (PTT) for Intensive Care Units (ICU). The *Main Goal* for the ICU-PTT is to assist ICU nursing staff in learning safe administration of Atracurium and monitoring of neuromuscular blockade by peripheral nerve stimulation. The learning objectives and the configuration for the ICU-PTT are discussed in the next section. Thereafter, we will describe the integration of the previously derived pharmacological model and its validation.

## *5.1 Learning Objectives and the configuration of the Part Task Trainer*

The specific clinical learning objectives to be achieved in the ICU-PTT, are the following [Ohrn, M.A.K., 1995]:

- Understand why the ulnar nerve is the preferred site for peripheral nerve stimulation to monitor depth of neuromuscular blockade.
- Select reasons why different monitoring modes are required for certain clinical situations.
- Select correct dosing of Atracurium for bolus and infusion in an intubated, mechanically ventilated, patient.
- Titrate appropriate infusion rates based on the patient's response to peripheral nerve stimulation and clinical signs.
- Understand why neuromuscular blocking agents do not provide analgesia and amnesia.
- Select appropriate anxiolytics or analgesics to administer concomitantly with neuromuscular blockade.
- Identify at least two reasons why it is undesirable to overdose patients with neuromuscular blocking agents.

To support learning the monitoring of neuromuscular blockade by peripheral nerve stimulation, the ICU-PTT will interface with a mechanical arm: TWITCHER (figure 5.1). The pharmacological response of the TWITCHER arm is calculated with a mathematical pharmacological model of Atracurium (discussed in chapter 3) for simulations in real time and accelerated time. The total running time of the training program is approximately 25 minutes. In the scope of this report only the modeling part of the ICU-PTT is discussed.

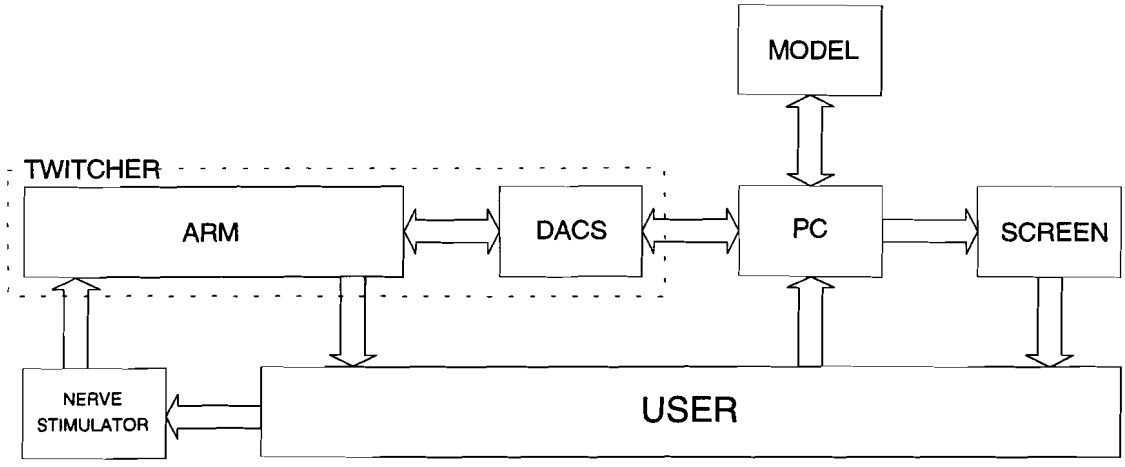


**Fig. 5-1:** Block diagram of the Intensive Care Unit Part Task Trainer. The TWITCHER consists of a mannequin arm with a mobile ( "twitching" ) thumb, controlled by a DACS board (Data Acquisition and Control System). The peripheral nerve stimulator is a device that stimulates the nerves leading to skeletal muscles with an electric current. Several stimuli patterns are available like Single Twitch, Train of Four (TOF), Tetanus Stimulation and Post Tetanic Stimulation. An IBM personal computer uses a RS232 serial port for communication with the DACS board. The PC also calculates the model response and handles the screen output and part of the user input. The user selected nerve stimulation pattern is detected by the DACS board and is then sent to the PC.

## *5.2 Integration of the Pharmacokinetic-pharmacodynamic Model in the ICU-PTT*

The ICU-PTT windows-based interactive user interface was developed using the authoring tool "ICON Author (Aim-Tech)" in combination with in-house developed software. To establish communication between the different modules of the ICU-PTT, several protocols were defined. This section describes the protocol for the interface between the Icon Author program and the pharmacological model, written in the program language C (see Appendix B).

**Protocol for Icon Author/Drug Model Interface**

This protocol describes the functions for the dynamic link library (DLL) in Icon Author that contains the pharmacokinetic and pharmacodynamic model for neuromuscular blocking drugs.

```
int far pascal Init (char far *patname);
```

This function initializes the model by reading the file *patname* for patient parameters. It returns 1 if the initialization was successful, and 0 if it failed.

**`void far pascal Set_Infusion(int drugid, long itime, double rate);`**

This function sets the current infusion rate for drug *drugid*. The time at which the rate change took place is indicated by *itime* in seconds after the "Init" call. The infusion rate is passed in *rate* with the dimensions mg/kg/min. Internally this function calculates the pharmacokinetic part of the model up until *itime*, then the current infusion rate is changed. There is no return value.

**`void far pascal Set_Bolus(int drugid, long itime, double amount);`**

This function gives a bolus of drug drugid at time *itime*. The amount is passed through the parameter *amount* with the dimensions mg/kg. Internally this function calculates the pharmacokinetic part of the model up until *itime*, then adds the amount *amount*. Currently the only drug-ID accepted is 0 representing Atracurium. There is no return value.

**`void far pascal Get_TwitchHeight(long itime, int type, int far *data);`**

This function calculates the pharmacokinetic part of the model up until *itime*, then calculates the pharamcodynamic part of the model and returns the twitch data (format depends on stimulus type *type*) at time *itime* in the array *data*. There is no return value.

The *type* parameter can be expanded to include other stimulus modes. The function only calculates the response to the selected stimulus pattern. The following stimulus types and one dimensional data arrays are defined:

| Stimulus type | data |
|---|---|
| 1: single twitch | data[0]: one twitch height value |
| 3: tetanic stimulus | data[0]: single twitch height, data[1]: plateau time (msec), data[2]: fade time (msec) |
| 4: TOF | data[0-3]: 4 twitch heights |
| 8: PTC | data[0-7]: 8 twitch heights (max for Atracurium) |

*Note: For PTC this specification can be expanded if a particular drug causes another maximum number of twitch responses, by either adding a new type , or by expanding the data array.*

```
void far pascal Get_Concentration(int drugid, long itime,
     int far *data);
```

This function calculates the pharmacokinetic part of the model up until *itime* and returns the concentration of drug *drugid* in *data* at time *itime*. The units are µg/l. Two concentrations are returned in *data* (central compartment data[0] and peripheral compartment data[1]). There is no return value.

```
void far pascal DeInit(void);
```

This function performs deinitialization and is called when the model is not needed anymore. There is no return value.

## *5.3 Model Validation*

Validation of the pharmacological model was done separately from the ICU-PTT. For that purpose a graphical interface was programmed to display the simulated compartment concentrations and corresponding twitch height responses as a function of time. The model validation was performed by a clinical expert. The evaluated features of the model were Onset Time (OT), 25% Recovery Time (RT25) and 95% Recovery Time (RT95). The Onset Time is defined as the time after a bolus injection or infusion until 100% twitch height depression occurs (0% twitch height), the 25% Recovery Time is the time after drug administration until the point where the first twitch height is again 25% of the initial baseline. The 95% Recovery Time is the time until the first twitch height is restored to 95% of the baseline.

### 5.3.1 Validation of Bolus Response for ST and TOF Stimulation

The model response to a bolus injection was compared to the data provided by the manufacturer of Atracurium. Table 5.1 reflects the validation features OT, RT25 and RT95 for the simulated pharmacological responses to an intubation dose of 0.4 mg/kg and to an intubation dose of 0.5 mg/kg. The typical values for OT, RT25 and RT95 for these intubating dosages provided by the manufacturer, are also given in the table. The first row of table 5.1 shows the model response with the initial set of model parameters derived from the ones found in the literature (see chapter 3). The second and third row of table 5.1 show the model responses for subsequent adjustments of the model parameters that were made

in cooperation with the expert. For the parameter adjustments the ratio between the pharmacokinetic parameters a and b was kept constant and the pharmacodynamic parameter $\gamma$ was kept at a constant value of 4.5 [Nigrovic, V., Banoud, M., 1993]. The pharmacodynamic parameter $EC_{50}$ was derived from the clinical parameter $ED_{50}$, using equation 3.34

***Table 5.1:*** *Simulated pharmacological response after administration of an intubating dose of 0.4 and 0.5 mg/kg Atracurium. The evaluated features of the model were Onset Time (OT), 25% Recovery Time (RT25) and 95% Recovery Time (RT95). The first value for each feature corresponds to the 0.4 mg/kg dose, the second value to the 0.5 mk/kg dose. The typical values for OT, RT25 and RT95 are given by the manufacturer of Atracurium (detached box below the table). The first row reflects the model response based on the parameters found in the literature, the second and third row are model responses with subsequent parameter adjustments, which are discussed in the text.*

| | a ($min.^{-1}$) | b ($min.^{-1}$) | ED50 (mg/kg) | OT (min.) | RT25 (min.) | RT95 (min.) |
|---|---|---|---|---|---|---|
| 1 | 0.250 | 0.0362 | 0.23 | 2.3-1.7 | 40-46 | 64-71 |
| 2 | 0.210 | 0.0300 | 0.23 | 3-2 | 48-55 | 78 |
| 3 | 0.210 | 0.0300 | 0.33 | 5-3 | 38-45 | 71-78 |
| | | | | 5-3 | 35-45 | >60 |

Initially only the pharmacokinetic parameters a, b were changed (to keep the clinical parameters $ED_{50}$ and $ED_{95}$ equal to their typical value). The resulting model response (second row in table 5.1) featured a large increase in 25% recovery time. Therefore, the pharmacodynamic parameter $ED_{50}$ (and $ED_{95}$ as a consequence of a constant $\gamma$) was subsequently adjusted until the evaluated features were acceptable, i.e. within the range of the typical values as provided by the manufacturer of Atracurium (third row in table 5.1).

### 5.3.2 Verification of an Infusion Response for ST and TOF Stimulation

According to the data provided by the manufacturer, an infusion rate of 5 to 9 µg/kg/min should be adequate to maintain continuous twitch height depression in the range of 89% to 99%. An infusion rate of 5 µg/kg/min applied to the tuned model resulted in a twitch height depression of 89% and using a twitch detection threshold of 5% (see chapter 3), resulted in one detectable TOF twitch.

### 5.3.3 Validation of Bolus and Infusion PTC Response

Validation of the model generated PTC for several bolus dosages and an infusion rate, was done by comparing the model output to literature data. The administered bolus dosages and the infusion rate produced total neuromuscular blockade to TOF stimulation. The evaluated feature was the time period $T_{PTC}$, which is the time difference between PTC=1 and the first response to TOF stimulation. Table 5.2 reflects the validation features for the different bolus injections and the infusion rate. The first bolus dosage was chosen relatively small (0.44 mg/kg), the second an average intubation dose (0.5 mg/kg) and the third a relative overdose (0.6 mg/kg). The infusion rate was chosen 9 µg/kg/min. The typical values for the evaluated features were obtained from the literature (see chapter 3, figure 3.7).

***Table 5.2:*** *The evaluated features of the model generated PTC for the administration of three bolus dosages of Atracurium: 0.44 mg/kg, 0.5 mg/kg and 0.6 mg/kg and for an infusion rate of 9 µg/kg/min. The typical values are given in the last row and are dose independent.*

| | $t_{PTC=1}$ | $t_{TOF1}$ | $T_{PTC}=t_{TOF1}-t_{PTC=1}$ |
|---|---|---|---|
| 0.44 mg/kg | 10:50 min. | 25:20 min. | 14:30 min. |
| 0.50 mg/kg | 18:38 min. | 29:44 min. | 11:06 min. |
| 0.60 mg/kg | 25:34 min. | 35:51 min. | 10:17 min. |
| 9 µg/kg/min | 37:00 min. | 50:46 min. | 13:46 min. |
| Typical | - | - | 10 min. |

The time between PTC=8 and the first response to TOF stimulation was negligible (in the order of seconds) for all inputs. The typical curve for the relationship between the number of PTC and the time left to the first response to TOF was given in chapter 3 (figure 3.7). A range of tolerance for that relationship due to patient variability can be found in the literature [Miller, R.D., 1990], which results in a range for $T_{PTC}$ of 5 to 15 min. Therefore, the features of the model generated PTC for the different bolus dosages and the infusion rate are acceptable.

# 6 Hydraulic and Electrical Analogues for Muscle Relaxant Pharmacokinetics and Pharmacodynamics

Compartment models are often used, to explain pharmacokinetic principles. However, didactic disadvantages of compartment models are associated to their mathematical representation [Bradley, J.R., Fayle, R.J.S., Harmsworth, N.J., et al. 1979]. To overcome this didactic disadvantage, we elaborate on a more intuitive hydraulic representation to illustrate compartment pharmacokinetics [Saidman, L.J., Eger, E.I., 1966]. For a hydraulic representation to depict the features of two compartment pharmacokinetics, it should be equivalent to the classic mathematical descriptions. In this chapter we demonstrate this equivalence.

We also introduce an electrical analogue. Electrical analogues have been developed in the past [Hull, C.J., McLeod, K., 1976] but, for the purpose of physical realization, embody nonlinear active components (operational amplifiers). The intended use of the electrical analogue presented in this section is for computer simulation only, and it consists of linear passive components like resistors and capacitors.

## *6.1 Mathematical Equivalence between Two Compartment Pharmacokinetic Models and Hydraulic and Electrical Analogues*

To demonstrate the mathematical equivalence between the analogues and the two compartment model, a two step proof is given in the following sections. First, the equations for the analogues are shown to fit the same generic state variable representation as for compartment models, equation 6.1, with corresponding vector and matrix dimensions. (Equation 6.1a and 6.1b and the corresponding matrices A,b and c are derived from equations 3.1a and 3.1b).

$$\frac{d\underline{x}(t)}{dt} = \mathbf{A}\,\underline{x}(t) + \underline{b}\,u(t) \qquad \textbf{(6.1a)}$$

$$\underline{y}(t) = \mathbf{c}^T\,\underline{x}(t) \qquad \textbf{(6.1b)}$$

with

$$\underline{x} = \underline{m} \quad , \quad u = q \quad , \quad \underline{y} = \underline{c}$$

where m is the amount of drug, q the administered dose and c the drug concentration.

and

$$A = \begin{bmatrix} -(k_{10}+k_{12}) & k_{21} \\ k_{12} & -k_{21} \end{bmatrix}, \quad \underline{b} = \begin{bmatrix} 1 \\ 0 \end{bmatrix}, \quad C = \begin{bmatrix} \frac{1}{V_1} & 0 \\ 0 & \frac{1}{V_2} \end{bmatrix}$$

Second, a bijective translation is derived between the independent parameter sets of the analogues and the independent parameter set of the compartment model. If a bijective translation exists, each analogue has one (and only one) corresponding set of parameters for the compartment model. If both steps can be completed for both analogues, all three state variable representations are interchangeable using the appropriate parameter translations

### 6.1.1 Hydraulic Representation of Two Compartment Pharmacokinetics

The hydraulic analogue [Saidman, L.J., Eger, E.I., 1966], consists of reservoirs instead of compartments, figure 6-1, where liquid volume represents drug mass. Choosing the liquid height to reflect the compartment drug concentrations [Hughes, M.A., Glass, P.S.A., Jacobs, J.R., 1992] yields a nice illustration of pharmacokinetics [Jansen, J.A., 1977] in a manner which may be more readily understood [Eger, E.I. 1974]. This section will show that making the cross sectional areas of the reservoirs in the hydraulic system equivalent to the volumes of the compartment model, results in a analogue where drug concentrations are reflected by liquid height in the reservoirs.

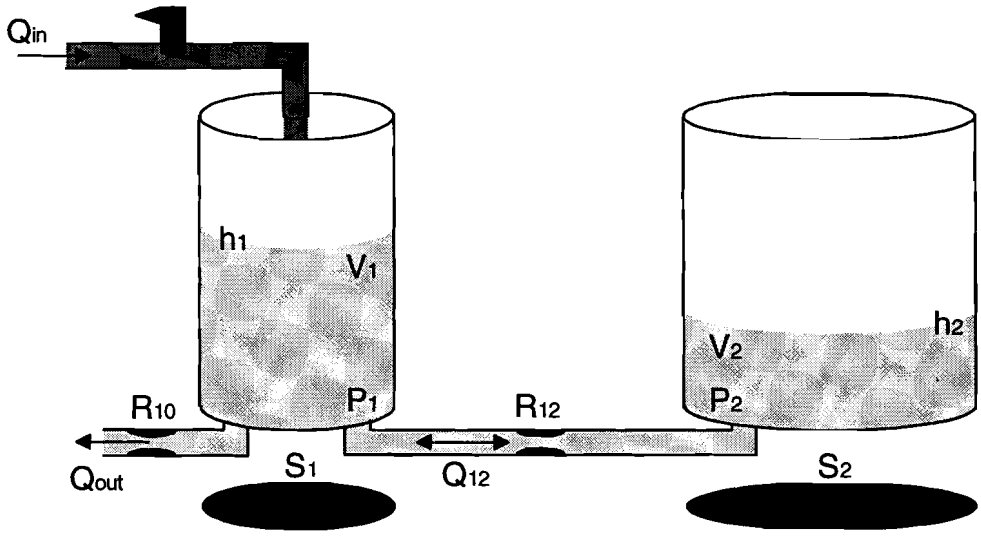


**Fig.6-1.** Hydraulic representation of two compartment pharmacokinetics (The elements will be introduced in the main text)

System state equations describe the change of the state variables (liquid volume) over time as a function of the state variables and subsequent inputs. This behavior is governed by the system parameters. For the hydraulic system, the change of liquid volume in the reservoirs over time is equal to the summation of all incoming and outgoing liquid flow rates $Q_k$. Positive flow rates contribute to the total liquid volume in the reservoirs, whereas negative flow rates decrease the total liquid volume, indicated with a minus sign, equation 6.2:

$$\frac{dV_i(t)}{dt} = \sum_k Q_k(t) \quad \Rightarrow \quad \begin{cases} \frac{dV_1(t)}{dt} = Q_{in}(t) - Q_{10}(t) - Q_{12}(t) \\ \frac{dV_2(t)}{dt} = Q_{12}(t) \end{cases} \qquad \textbf{(6.2)}$$

To complete the state equations, expressions in terms of liquid volume must be found for the intercompartment flow rate $Q_{12}$ through the hydraulic resistor $R_{12}$, and for the clearance flow rate $Q_{10}$. The liquid flow rate through a hydraulic resistor depends on the pressure gradient across the resistor and the resistance value. Furthermore, the liquid pressures can be written in terms of liquid volume $V_i(t)$, the surface area $S_i$, liquid density $\rho$, and the gravitational acceleration *g*. For the two flow rates $Q_{12}$ and $Q_{10}$ this results in the following expressions, equations 6.3a and 6.3b.

$$Q_{12}(t) = \frac{p_1(t) - p_2(t)}{R_{12}} = \rho g \frac{\left(\frac{V_1(t)}{S_1} - \frac{V_2(t)}{S_2}\right)}{R_{12}} \qquad \textbf{(6.3a)}$$

$$Q_{10}(t) = \frac{p_1(t)}{R_{10}} = \rho g \frac{V_1(t)}{R_{10} S_1} \qquad \textbf{(6.3b)}$$

By substitution of expressions 6.3a and 6.3b in equations 6.2, the hydraulic state equations are found, equations (6.4a) and (6.4b)

$$\frac{dV_1(t)}{dt} = -\left[\frac{\rho g}{R_{10} S_1} + \frac{\rho g}{R_{12} S_1}\right] V_1(t) + \frac{\rho g}{R_{12} S_2} V_2(t) + Q_{in}(t) \qquad \textbf{(6.4a)}$$

$$\frac{dV_2(t)}{dt} = \frac{\rho g}{R_{12} S_1} V_1(t) - \frac{\rho g}{R_{12} S_2} V_2(t) \qquad \textbf{(6.4b)}$$

The liquid heights in the reservoirs as a function of the liquid volume are described by equations (6.5a) and (6.5b).

$$h_1(t) = V_1(t) \frac{1}{S_1} \qquad \textbf{(6.5a)}$$

$$h_2(t) = V_2(t) \frac{1}{S_2} \qquad \textbf{(6.5b)}$$

Rewriting the hydraulic state equations in the general form of equations (6.1a) and (6.1b) facilitates comparison of the hydraulic state equations with the traditional compartment state equations. To rewrite the hydraulic state equations (6.4a) - (6.5b) in the format of equations (6.1a) and (6.1b) the following matrix and vector substitutions are required.

$\underline{x} = \underline{V}$ , $u = Q_{in}$ , $\underline{y} = \underline{h}$

$$A = \rho g \cdot \begin{bmatrix} -\left(\frac{1}{R_{10} S_1} + \frac{1}{R_{12} S_1}\right) & \frac{1}{R_{12} S_2} \\ \frac{1}{R_{12} S_1} & -\frac{1}{R_{12} S_2} \end{bmatrix}, \quad b = \begin{bmatrix} 1 \\ 0 \end{bmatrix}, \quad C = \begin{bmatrix} \frac{1}{S_1} & 0 \\ 0 & \frac{1}{S_2} \end{bmatrix}$$

The liquid density ρ and gravitational acceleration *g* are physical characteristics of the hydraulic model. However, the hydraulic analogue is developed for educational purposes and the liquid density and gravitational acceleration are simply constants necessary to convert compartment models into hydraulic models. Therefore, they can be integrated in the hydraulic resistors as a constant common factor .

Step two in demonstrating equivalency between the hydraulic analogue and the compartment model involves finding a bijective translation of the different parameter sets. The parameter translation can be determined by comparing the parameter matrices A, b and C of the general state equations for both systems. Both systems support the same b vector and comparing the C matrices shows the required equivalence between the compartment volumes V and the cross

sectional areas of the reservoirs S, in order to obtain a conversion of compartment drug concentrations to liquid heights in the hydraulic analogue.

Using the equivalence between the compartment volumes V and the cross sectional areas S, when comparing the two different A matrices, results in a relationship between the hydraulic resistors $R_{10}$, $R_{12}$ and the compartment parameters $k_{10}$, $k_{12}$, $k_{21}$, $V_1$, $V_2$, equation 6.6a and 6.6b.

$$\frac{\rho g}{R_{10}} = \frac{1}{k_{10} V_1} \qquad \textbf{(6.6a)}$$

$$\frac{\rho g}{R_{12}} = \frac{1}{k_{12} V_1} = \frac{1}{k_{21} V_2} \qquad \textbf{(6.6b)}$$

Because of the parameter interdependency $k_{12}V_1=k_{21}V_2$ , expressions 6.6a and 6.6b become a bijective translation between $k_{10}$ , $k_{12}$ and $k_{21}$ on one hand and $R_{10}$ and $R_{12}$ on the other. This completes the proof of equivalence between the hydraulic analogue and the two compartment model.

### 6.1.2 Electrical Representation of Two Compartment Pharmacokinetics

Hull and McLeod developed an electrical analogue to predict plasma drug concentrations and physically realized this circuit [Hull, C.J., McLeod, K., 1976]. The electrical model discussed in this section is developed for computer simulation of compartment pharmacokinetics only, not for physical realization, and therefore has a reduced complexity as compared to the Hull-McLeod analogue. In the electrical model, illustrated in figure 6-2, the capacitor charges reflect drug mass. Before using the electrical analogue in computer based pharmacokinetic simulations, equivalence between the electric circuit and the compartment model must be demonstrated. This section will show that making the capacities in the electric circuit equivalent to the compartment volumes of the compartment model, results in a electrical analogue where the drug concentrations are reflected by the capacitor voltages.

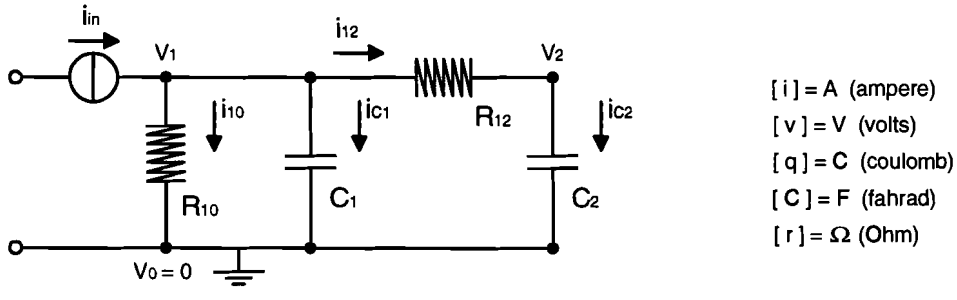


**Fig.6-2.** Electrical analogue

As for the hydraulic analogue, the proof is obtained in two steps, first the general state equations of the electric circuit are determined and compared with those of the compartment pharmacokinetics. Then a bijective transformation between the parameter sets of the electrical and the compartment model is derived.

The system state equations describe the change of the state variables (capacitor charge) over time as a function of the state variables, and the subsequent inputs (current $I_{in}$ reflecting a bolus or infusion). The dynamic behavior is governed by the system parameters. For the electric circuit, the change of capacitor charge over time is equal to the summation of all electric currents at node $V_i$ (Kirchoff's law of current). Positive circuit currents contribute to the total charge on the capacitor, whereas negative electric currents decrease the total charge on the capacitor, indicated by a minus sign, equation 6.7a and 6.7b.

$$\text{node } v_1: \quad i_{c_1}(t) = i_{in}(t) - i_{10}(t) - i_{12}(t) \qquad \textbf{(6.7a)}$$

$$\text{node } v_2: \quad i_{c_2}(t) = i_{12}(t) \qquad \textbf{(6.7b)}$$

To determine the state equation, expressions in terms of the electric charge on the capacitors and the input must be found for all circuit currents in equations 6.7a and 6.7b. For the capacitor currents $i_c(t)$ the relation between the capacitor charge $q_c(t)$ and capacitor current $i_c(t)$ is given by equation 6.8a and 6.8b.

$$i_{c_1}(t) = \dot{q}_{c_1}(t) = i_{in}(t) - i_{10}(t) - i_{12}(t) \qquad \textbf{(6.8a)}$$

$$i_{c_2}(t) = \dot{q}_{c_2}(t) = i_{12}(t) \qquad \textbf{(6.8b)}$$

The currents through the resistors depend on the voltage gradient across the resistors and the resistance value. The following expressions result from applying Kirchoff's law of voltage to each loop in the circuit, equation 6.9a and 6.9b.

$$v_{c_1}(t) = v_{10}(t) = R_{10}\, i_{10}(t) \qquad \textbf{(6.9b)}$$

$$v_{12}(t) = v_{c_1}(t) - v_{c_2}(t) = R_{12}\, i_{12}(t) \qquad \textbf{(6.9b)}$$

Furthermore, the capacitor voltages can be written in terms of capacitor charges and capacities, equation 6.10a and 6.10b:

$$v_{c_1}(t) = q_{c_1}(t)\frac{1}{C_1} \quad \textbf{(6.10a)}$$

$$v_{c_2}(t) = q_{c_2}(t)\frac{1}{C_2} \quad \textbf{(6.10b)}$$

For the two resistor currents $i_{10}(t)$ and $i_{12}(t)$ this results in the following expressions, equations (6.11a) and (6.11b):

$$i_{10}(t) = \frac{v_{c_1}(t)}{R_{10}} = \frac{q_{c_1}(t)}{R_{10}.C_1} \quad \textbf{(6.11a)}$$

$$i_{12}(t) = \frac{\left(\frac{q_{c_1}(t)}{C_1} - \frac{q_{c_2}(t)}{C_2}\right)}{R_{12}} \quad \textbf{(6.11b)}$$

Substitution of equations 6.11a and 6.11b in equation 6.8a and 6.8b, results in the electrical state equations, equations (6.12a) and (6.12b):

$$\frac{dq_{c1}(t)}{dt} = -q_{c1}(t)\left[\frac{1}{R_{10}C_1} + \frac{1}{R_{12}C_1}\right] + q_{c2}(t)\frac{1}{R_{12}C_2} + i_{in}(t) \quad \textbf{(6.12a)}$$

$$\frac{dq_{c2}(t)}{dt} = q_{c1}(t)\frac{1}{R_{12}C_1} - q_{c2}(t)\frac{1}{R_{12}C_2} \quad \textbf{(6.12b)}$$

To write the electrical state equations (6.12a) - (6.12b) in the general form of equations (6.1a) - (6.1b) the following matrix and vector conversion is required.

$\underline{x} = \underline{q_c}$ , $u = i_{in}(t)$ , $\underline{y} = \underline{v_c}$

$$A = \begin{bmatrix} -\left(\frac{1}{R_{10}C_1} + \frac{1}{R_{12}C_1}\right) & \frac{1}{R_{12}C_2} \\ \frac{1}{R_{12}C_1} & -\frac{1}{R_{12}C_2} \end{bmatrix}, \quad b = \begin{bmatrix} 1 \\ 0 \end{bmatrix}, \quad C = \begin{bmatrix} \frac{1}{C_1} & 0 \\ 0 & \frac{1}{C_2} \end{bmatrix}$$

Step two in demonstrating equivalence between the electrical analogue and the compartment model involves finding a bijective translation of the different parameter sets. The parameter translation can be determined by comparing the parameter matrices A, b, and C of the general state equations for both systems.

Both systems support the same b vector and comparing the C matrices shows the required equivalence between the compartment volumes $V_i$ and the capacity values $C_i$, in order to obtain a conversion of compartment drug concentration to capacitor voltage in the electrical analogue.

Using the equivalence between the compartment volumes $V_i$ and the capacity values $C_i$, when comparing the A matrices, results in a relationship between the electric resistors $R_{12}$, $R_{10}$ and the compartment parameters $k_{10}$, $k_{12}$, $k_{21}$, $V_1$ and $V_2$ ,equation 6.13a and 6.13b.

$$R_{10} = \frac{1}{k_{10} V_1} \qquad \textbf{(6.13a)}$$

$$R_{12} = \frac{1}{k_{12} V_1} = \frac{1}{k_{21} V_2} \qquad \textbf{(6.13b)}$$

Because of the parameter interdependency $k_{12}V_1=k_{21}V_2$, expression 6.15 becomes a bijective translation between $k_{10}$ , $k_{12}$ and $k_{21}$ on one hand and $R_{10}$ and $R_{21}$ on the other. This completes the proof of equivalence between the electrical and the two compartment model.

## *6.2 A Pharmacology Teaching Tool based on a Model Driven Hydraulic Analogue*

In the previous sections an intuitive representation of two compartment pharmaco*kinetics*, using a hydraulic analogue was introduced. We demonstrated that this more intuitive model is equivalent to the traditional mathematical description. Outlined below are several pharmacological learning objectives that are difficult to attain with mathematical two compartment models, but that are easily demonstrated with a hydraulic analogue:

- **Differences between bolus and infusion**
- **Priming principle**
- **Effect of overdosing**
- **Inter patient variability**
- **Different stimulation patterns**

Before discussing these learning objectives in detail, we first introduce an intuitive representation of pharmaco*dynamics*, elaborating on the hydraulic analogue.

### 6.2.1 Gauge Principle for Hydraulic Model Pharmacodynamics

As shown before, the liquid heights in the reservoirs of the hydraulic analogue reflect the compartment drug concentrations. Besides this more intuitive representation of pharmacokinetics, the hydraulic analogue can also be used to demonstrate the difference between clinically observable versus clinically unobservable drug concentrations.

Clinically, neither one of the drug concentrations is measured. An indicator for the drug concentration in the peripheral compartment is the twitch height depression. It can be shown that the whole system is only observable for a limited range of peripheral compartment concentrations [Van Meurs, W.L., Ohrn, M.A.K., 1995-1]. However, the hydraulic analogue can display the peripheral drug concentration for every moment in time. The hydraulic analogue can be adapted to show the clinically detectable drug effects simply by adding a scaled gauge on the peripheral reservoir, as illustrated in figure 6.4. Peripheral drug concentrations that do not result in a change of clinical effect correspond to liquid heights in the peripheral reservoir below the lower margin of the gauge. Drug concentrations in the peripheral compartment that cause a noticeable change in clinical effects match with liquid levels that are visible through the

gauge, and the magnitude of that effect corresponds to the marked scale on the gauge. Peripheral drug concentrations that cause the maximal detectable effect (100% twitch height depression) correspond to liquid levels beyond the upper margin of the gauge.

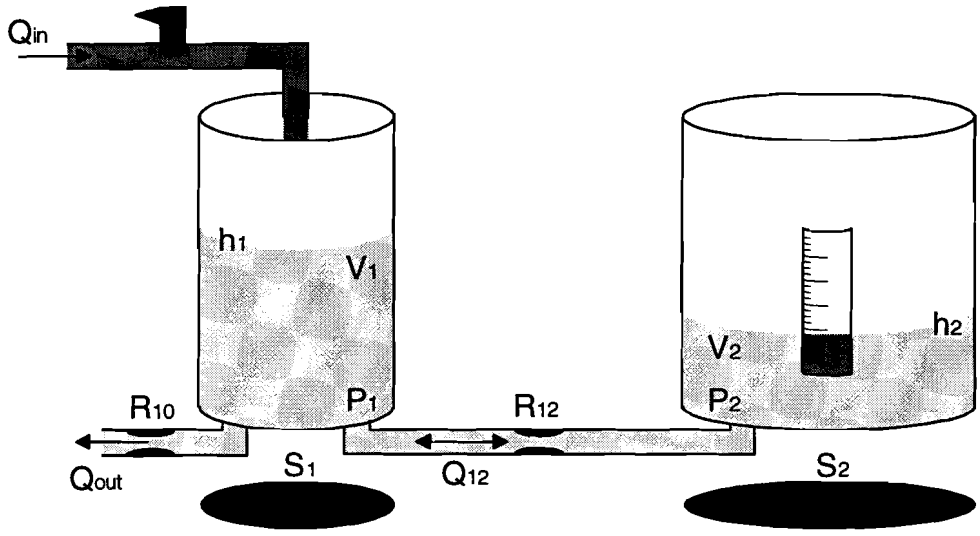


**Fig. 6-4.** Hydraulic Analogue with gauge to reflect simultaneous pharmacokinetic and pharmacodynamic principles.

### 6.2.2 Implementation of a model driven animation

The hydraulic analogue was mainly developed to facilitate teaching of pharmacokinetic and pharmacodynamic principles in a more intuitive way rather than through the complicated mathematical equations. For optimal use of the hydraulic representation, interactive aspects are included, resulting in a model driven teaching tool, illustrating the complex pharmacological learning objectives listed in the beginning of this section.

- **Differences between bolus and infusion:**
  After a bolus injection a maximal clinical effect will occur after a relatively short period of time. Thereafter, the clinical effect will decrease slowly because of drug metabolism in the body. With an infusion, the onset of the clinical effect takes more time than with a bolus, and instead of reaching a peak for a short period of time, the effect will reach a maximum effect at a later time and stabilize at that effect until the infusion is discontinued. Thereafter, the clinical effect will again decrease because of drug metabolism in the body, but not as fast as after a bolus injection.

- **Priming principle**
  The priming principle is based on the fact that for a small bolus of drug, no clinically significant effect will occur. With neuromuscular blockers, a patient will receive a very small bolus 2-5 minutes before induction. This small bolus shortens the onset time to clinically significant blockade. By using the hydraulic analogue it is easy to illustrate what happens *in vivo*. The priming dose elevates the drug concentration in the peripheral resevoir to just below the lower margin of the gauge. When the subsequent intubation dose is given, the clinical effect will occur much more rapidly because the liquid height will rise in the visible range of the gauge almost instantaneously.

- **Effect of overdosing**
  Most drugs have an optimal range of plasma concentrations. For neuromuscular blocking agents this range corresponds to an effector compartment concentration that allows for a detectable clinical response. When too much neuromuscular blocking agent is given, eventually the response is maximal and no subsequent change will occur. This can be illustrated in the hydraulic model with liquid heights beyond the upper margin of the gauge.

- **Inter patient variability**
  Not all patients will respond identically to given drug doses. Sensitive patients may react faster and more extensively to an average dose, while others require relatively high doses for a minimal clinical effect. This variability is mainly caused by differences in volume of distribution among patients [Gravenstein, J.S., 1995]. Illustrating this phenomenon with the hydraulic analogue can easily be accomplished through different cross sectional areas for the reservoirs. With the same amount of drug in the reservoirs, the liquid levels will change depending on the cross sectional areas. The clinical effect will rise or fall accordingly.

- **Different stimulation patterns**
  To monitor the degree of neuromuscular blockade, the peripheral nerve is stimulated with a specific electrical pattern. The amplitude of response of the peripheral muscle depends on the stimulus pattern, as discussed in chapter 3. Illustrating these different responses with the hydraulic analogue can be achieved by extending or compressing the gauge.

# 7 Conclusions and Perspectives

A pharmacokinetic and pharmacodynamic model for educational simulation of the effects of the neuromuscular blocking agent Atracurium was derived. By making parameter interdependencies explicit, and by defining a model for the effector site drug concentration only, the number of parameters of the traditional pharmacokinetic model was reduced from 8 to 3. The derivation of these parameters from measured data was described. Preliminary results from taking this parameter reduction approach even further were presented in the form of an abstract co-authored by the author of this thesis at the first conference on "Simulators in Anesthesia Education" in Rochester, NY (Appendix A). This approach will be investigated in the continuation of this project.

Traditional pharmacodynamic models for Single Twitch, Train-of-Four, and a previously developed empirical model for Tetanic Stimulation were discussed. A new empirical model for Post Tetanic Count was derived based on the principle of an increased sensitivity to peripheral nerve stimulation after Tetanic Stimulation. This model was shown to reflect clinical data. This approach could be extended by reducing the assumptions on the time aspects of the stimulus pattern.

Requirements for interactive pharmacokinetic simulation were formulated and an optimal modeling approach (state variable) and numerical simulation method (discretization of the state transition equation) in terms of these requirements were found. Comparative simulations confirmed the efficiency of the chosen integration method.

The presented pharmacological model and the selected numerical integration method were successfully integrated in an educational tool for assisting Intensive Care Unit (ICU) nursing staff in learning safe administration of the neuromuscular blocking agent (NMB-agent) Atracurium and the monitoring of neuromuscular blockade by peripheral nerve stimulation. The model response was evaluated by an expert and the initial parameters of the model were slightly adjusted to generate the desired response.

The mathematical equivalency between pharmacokinetic models and their hydraulic and electric analogues was proven. Learning objectives and a second model driven educational application in the area of pharmacokinetics and pharmacodynamics, based on the hydraulic analogue, were presented. This hydraulic analogue was used during a morning conference to anesthesia residents. A full paper concerning the hydraulic analogue is currently in preparation.

# GLOSSARY OF MEDICAL TERMS:

(source: Anderson, K.N., Anderson, L.E., 1990 )

**adductor** a muscle that acts to draw a part toward the axis or midline of the body.

**agonist** [Gk *agon* struggle], **1.** a contracting muscle whose contractionis opposed by another muscle (an antagonist). **2.** a drug or other substance having a specific affinity that produces a predictable response.

**amnesia** [Gk *a, mnemonic* not memory], a loss of memory caused by brain damage or by serve emotional trauma.

**analgesia** [Gk *a, algos* not pain], a lack of pain without loss of consciousness.

**antagonist** [Gk *antagonisma* struggle], **1.** one who contends with or is opposed to another. **2.** (in physiology) any agent, such as a drug or muscle, that exerts an opposite action to that of another or competes for the same receptor sites.

**bladder** **1.** a membranous sac serving as a receptacle for secretions. **2.** the urinary bladder.

**calculus** [L, little stone], an abnormal stone formed in body tissues by an accumulation of mineral salts.

**cataract** [Gk *katarrhakies* waterfall], an abnormal progressive condition of the lens of the eye, characterized by loss of transparency.

**concoction** [L *con* + *coquere* to cook], a remedy prepared from a mixture of two or more drugs or substances that have been heated.

**contractility,** (in cardiology) the force of a heart contraction when preload and afterload are constant.

**contraction** [L *con* + *trahere* to draw], **1.** a reduction in size, especially of muscle fibers. **2.** an abnormal shrinkage.

**depolarization** [L *de* + Gk *polos* pilot], the reduction of a membrane potential to a less negative value.

**excitability** [L *excitare* to arouse], the property of a cell that enables it to react to irritation or stimulation, such as the reaction of a nerve or myocardial cell to an adequate stimulus.

**gastrointestinal (GI)** [Gk *gaster* + L *intestinum* intestine], of or pertaining to the organs of the GI tract, from mouth to anus.

**inspiratory** [L *in* within, *spirare* to breathe], of or pertaining to inspiration.

**intravenous (IV)** [L *intra* + *vena* vein], of or pertaining to the inside of a vein, as of a thrombus or an injection, infusion, or catheter.

**intubation** [L *in* within, *tubus* tube, *atio* process], passage of a tube into a body aperture, specifically the insertion of a breathing tube through the mouth or nose or into the trachea to ensure a patent airway for the delivery of an anesthetic gas or oxygen.

**lymph** [L *lympha* water], a thin opalescent fluid orginating in many organs and tissues of the body that is circulated through the lymphatic vessels and filtered by the lymph nodes. Lymph enters the bloodstream at the junction of the internal jugular and subclavian viens. It contains chyle, a few erythrocytes, and variable numbers of leukocytes, most of which are lymphocytes. It is otherwise similar to plasma.

**metabolism** [Gk *metabole* change, *ismos* process], the aggregate of all chemical processes that take place in living organisms, resulting in growth, generation of energy, elimination of wastes, and other bodily functions as they relate to the distribution of nutrients in the blood after digestion. Elimination example: many anesthetic drugs are lipophilic substances that are not easily excreted in the aqueous urine, their removal from the body must be preceded by metabolism to render them hydrophilic (water soluble). These hydrophilic substances may subsequently be excreted in the urine. Therefore, metabolism usually leads to inactivation of drugs.

**muscle relaxant,** a chemotherapeutic agent that reduces the contractility of muscle fibers.

**noxious** [L *noxa* harmfull], harmfull, injurious, or detrimental to health.

**pathophysiology** [Gk *pathos* disease, *physis* nature, *logos* science], the study of the biologic and physical manifestations of disease as they correlate with the underlying abnormalities and physiologic distrubances.

# GLOSSARY OF MEDICAL TERMS:

(source: Anderson, K.N., Anderson, L.E., 1990 )

**peripheral** [Gk *periphereia* circumference], of or pertaining to the outside, surface, or surrounding area of an organ or other structure.

**pharmacodynamics** [Gk *pharmakon* drug, *dynamis* power], the study of how a drug acts on a living organism, including the pharmacologic response observed relative to the concentration of the drug at an active site in the organism.

**pharmacokinetics** [Gk *pharmakon* + *kinesis* motion], (in pharmacology) the study of the action of drugs within the body, including the routes and mechanisms of absorption and excretion, the rate at which a drug's action begins and the duration of the effect, the biotransformation of the substance in the body, and the effects and routes of excretion of the metabolites of the drug.

**pharmacology** [Gk *pharmakon* + *logos* science], the study of the preparation, properties, uses, and actions of drugs.

**physiology** [Gk *physikos* natural, *logos* science], **1.** the study of the processes and function of the human body. **2.** the study of the physical and chemical processes involved in the functioning of living organisms and their component parts.

**plasma** [Gk, something formed], the watery, colorless, fluid portion of the lymph and the blood in which the leukocytes, erythrocytes, and platelets are suspended. It contains no cells and is made up of water, electrolytes, proteins, glucose, fats, bilirubin, and gases. It is essential for carrying the cellular elements of the blood through the circulation, transporting nutrients, maintaining the acid-base balance of the body, and transporting wastes from the tissues.

**pulmonary** [L *pulmoneus* relating to the lungs], of or pertaining to the lungs or the respitory system.

**respiratory** [L *re* out, *spirare* to breathe], of or pertaining to respiration.

**respiratory system.** See **respiratory tract.**

**respiratory tract,** the complex of organs and structures that performs the pulmonary ventilation of the body and the exchange of oxygen and carbon dioxide between the ambient air and the blood circulation through the lungs. It also warms the air passing into the body and assists in the speech function by providing air for the larynx and the vocal cords.

**saliva** [L, spittle], the clear , viscous fluid secreted by the salivary and mucous glands in the mouth.

**skeletal muscle** See **striated muscle**

**striated muscle** [L *stria* + *musculus* muscle], muscle tissue, including all the skeletal muscles, that appears microscopically to consist of striped myofibrils. Muscle contraction occurs when an electrochemical impulse crosses the myoneural junction, causing the thin filaments to shorten.

**therapeutic** [Gk *therapeuein* to treat], **1.** beneficial. **2.** pertaining to a treatment.

**tissue** [Fr *tissu* fabric], a collection of similar cells that act together in the performance of a particular function.

**toxicity** [Gk *toxikon*], **1.** the degree to which something is poisonous. **2.** a condition that results from exposure to a toxin or to toxic amounts of a substance that does not cuase adverse effects in smaller amounts.

**trachea** [Gk *tracheia* rough artery], a nearly cylindric tube in the neck, composed of cartilage and membrane, that conveys air to the lungs.

## References:


Aa, J.J. van der, : Intelligent alarms in anesthesia: a real time expert system application. Diss. Technische Universiteit Eindhoven, 1990.

Anderson, Kenneth N. and Anderson, Lois E.: Mosby's pocket dictionary of Medicine, Nursing, & Allied Health. The C.V. Mosby Company, St. Louis, 1990.

Bradley, J.R., Fayle, R.J.S., Harmsworth, N.J., Kayani J.A., Lockett W.I., Montgomery S.C., Short A.H., Trimble I.M.G & Wilson C.G.: Student-constructed hydraulic and mechanical models foe learning fundamentals of pharmacokinetics. Proceedings of the B.P.S., 17th-20th July, 1979

Donati, F., PhD, MD, FRCP(C), Varin, F., PhD, Ducharme, J., Msc, Gill, S.S., MB, FFARCS, Theoret, Y., PhD, and Bevan, D.R., MB, MRCP, FFARCS; Pharmacokinetics and Pharmacodynamics of Atracurium obtained with arterial and venous blood samples., *Clin. Pharmacol. Ther*, May 1991

Eger, Edmond I.: Anesthetic uptake and Action. The Williams&Wilkins Company, Baltimore, Maryland, 1974.

Faculteit der Wiskunde en Informatica (F.W.I.)., Syllabus bij het college Inleiding Numerieke methoden., Technische Universiteit Eindhoven, 1991

Gibaldi, Milo., and Perrier, Donald.: Pharmacokinetics. second edition, revised and expanded, Marcel Dekker, inc., New York and Basel, 1982.

Gravenstein, J.S.; Personal communication, Jan. 1995

Hughes, Michael A., Glass, Peter S.A., Jacobs, James R.: Context-sensitive Half-time in multicompartment Pharmacokinetic Models for Intravenous Anesthetic Drugs. *Anesthesiology* 76: 334-341, 1992.

Hull, C.J. and McLeod, K.: Pharmacokinetic analysis using electrical analogue. *Br. J. Anaesth.* (1976), 48, 677.

Jaklitsch, Roman R., and Westenskow, Dwayne R.: A simulation of neuromuscular function and heart rate during induction maintance, and reversal of neuromuscular blockade. *J. Clin. Monit.*, Vol. 6 (1990) p. 24-38.

Jansen, J.A.; A simple simulator as an aid to teaching of pharmacokinetics. *Acta. Pharmac. Tox.*, Suppl. 55., 1977

Kuo, Benjamin C. : Digital Control Systems. Holt, Rinehart and Winston, inc, New York, 1980, p163-172.

Miller, Ronald D. : Anesthesia. 3rd Edition (Volume I and Volume II) Churchill Livingstone Inc., New York, 1990.

Nigrovic, Vladimir., Banoud, Mark.: Onset of the Nondepolarizing Neuromuscular Block in Humans: Quantitive Aspects. *Anesthesiology* 76;85-91, 1993

## References:


Papper, E.M., and Kitz, Richard J.: Uptake and Distribution of Anesthetic Agents. McGraw-Hill Book Company, inc, New York, 1963.

Parker, C.J.R. and Hunter, J.M: Dependence of the neuromuscular blocking effect of atracurium upon its disposition., British Journal of Anesthesia: 1992; **68**: 555-561

Ohrn, M.A.K.; Personal communication, March 1995.

Saidman, Lawrence J., Eger, Edmond I.: The effect of Thiopental Metabolism on Duration of Anesthesia., *Anesthesiology*, Mar.-Apr., 1966

Shafer, Steven L., and Stanski, Donald R.: Improving the Clinical Utility of Anesthetic Drug Pharmacokinetics, editorial views., *Anesthesiology* 76: 327-330, 1992

Sheiner, Lewis B., Stanski, Donald R., Vozeh, Samuel, Miller, Ronald D., Ham, Jay.: Simultaneous modeling of pharmacokinetics and pharmacodynamics:
Application to d-tubocurarine., *Clin. Pharmacol. Ther.*: 358-371 March 1979.

Stoelting, Robert K. : Pharmacology & Physiology in Anesthetic Practice. 2nd Edition J.B. Lippincott Company, Philadelphia, 1991.

Van Meurs, W.L. PhD, Ohrn, M.A.K. MD; Observability of system state variables as a means to evaluate monitoring techniques. Accepted for presentation at the 17th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, Montreal, Canada, September 20-23 1995.

Van Meurs, W.L. PhD, Nikkelen, E. BSEE, Good, M.L. MD, Ohrn, M.A.K. MD; Pharmacokinetic and Pharmacodynamic modeling with a reduced parameter set. Simulators in Anesthesia, University of Rochester, Department of Anesthesiology, Rochester, New York, May 12-14, 1995, p7

Ward, S. and Wright, D.: Combined Pharmacokinetic and Pharmacodynamic study of a single bolus does of Atracurium., *Br. J. Anaesth.* 1983, **55**, 35S

Weatherley, B.C., Williams, S.G., Neill, E.A.M.: Pharmacokinetics, Pharmacodynamics and Dose-Response relationships of Atracurium administered i.v.; *Br. J. Anaesth.* 1983, **55**, 39S

# Appendix A:

## Pharmacokinetic and Pharmacodynamic Modelling with a Reduced Parameter Set

**Willem L. van Meurs, PhD, Eric Nikkelen, BSEE, Michael L. Good, MD, Maria AK Öhrn, MD**
**Department of Anesthesiology, College of Medicine, University of Florida**
Simulators in Anesthesia, University of Rochester, Department of Anesthesiology, Rochester, New York, May 12-14, 1995, p7

**Introduction** Traditional, two-compartment pharmacokinetics are described by five parameters in one of two ways: either by the volumes of distribution of the two compartments and three elimination rates, or by two exponential time constants and three amplitudes. Pharmaco*dynamics* are described as having a Hill-type sigmoid relationship between the effector compartment concentration and the clinical effect. This relationship typically is characterized by two parameters: the concentration at 50% clinical effect and the parameter indicating the slope ("steepness") of the response. The disadvantages of these traditional descriptions when used for educational simulation are: 1) The mathematical descriptions contain a large number of dependent parameters; 2) the parameters have physiologic meaning, but do not directly relate to dose or effect; and 3) the combined effect of pharmacokinetics and pharmacodynamics on, for example, onset is difficult to understand. We present an integrated model that has none of these three limitations. Our model is mathematically equivalent to the traditional two compartment pharmacokinetic model, and results from only a minor simplification to the traditional pharmacodynamic model.

**Methods** In the clinical setting, the time aspects of pharmacokinetics are fully characterized by the effector compartment concentration changes in response to a bolus (impulse response). Because of the linear nature of the pharmacokinetics, the response keeps its temporal characteristics for different bolus dosages. We normalize the concentration response to the input dose (Figure 1). Additional boluses and infusions can be applied to the model by simulation of a discrete approximation of a state variable representation. The two parameters of the state variable representation are derived from the two parameters: $\mathbf{T_{max}}$, and **duration** (Figure 1). The sigmoid pharmacodynamic relationship is approximated by a **drug activation** (Figure 2). The parameters of this relationship are the minimum dose that is required to get an effect, $\mathbf{ED_{min}}$, and the dose above which the effect at $\mathbf{T_{max}}$ no longer increases with an increasing dose, $\mathbf{ED_{max}}$. The drug activation, with the dimension of the drug dose, is then multiplied with an **effector gain** to provide one or more effects.

# Appendix A:

## Pharmacokinetic and Pharmacodynamic Modelling with a Reduced Parameter Set

**Willem L. van Meurs, PhD, Eric Nikkelen, BSEE, Michael L. Good, MD, Maria AK Öhrn, MD**
**Department of Anesthesiology, College of Medicine, University of Florida**
Simulators in Anesthesia, University of Rochester, Department of Anesthesiology, Rochester, New York, May 12-14, 1995, p7

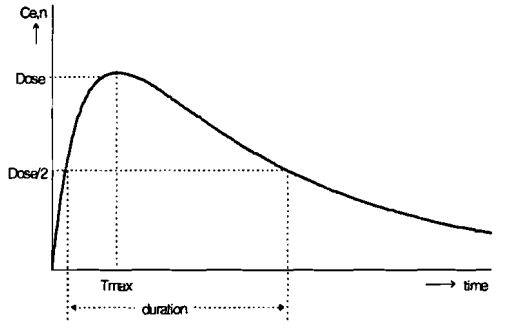


Figure 1 Normalized effector compartment concentration ($C_{e,n}$) after a bolus.

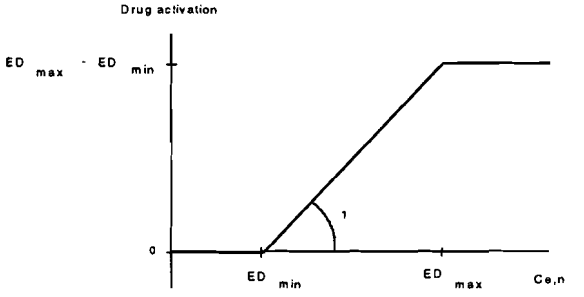


Figure 2 Drug activation as a function of normalized concentration ($C_{e,n}$).

**Results** We used the described model to simulate the effect of atracurium on neuromuscular blockade. The results, that will be presented at the meeting, compare favorably to the literature. Clinicians can easily modify the model parameters, $\mathbf{T_{max}}$ , **duration**, $\mathbf{Ed_{min}}$ , $\mathbf{ED_{max}}$ , and the **effector gain**, with a high predictability of the effects on the drug response.

# Appendix B: C-code of the ICU-PTT model interface

```
/*=========================================================================*/
//ICUMODEL.h: Version 1.0
//Header file associated to ICUMODEL.C
//Eric, 05/03/95
/*=========================================================================*/
// PROTOTYPES OF FUNCTIONS THAT CAN BE CALLED FROM OTHER
// FILES
/*-------------------------------------------------------------------------*/
// Main Library functions according to Drug model interface specifications

int far pascal Init(char far *patname, char far *drugsset, int drugid);
/*-------------------------------------------------------------------------
 * This function initializes the model by reading the file "patname" for
 * patient parameters. The initialization is done for the drug given by
 * "drugid". It returns 1 if the initialization was successful,
 * and 0 if it failed
 *-------------------------------------------------------------------------*/

void far pascal Set_Infusion(long itime, double rate);
/*-------------------------------------------------------------------------
 * This function sets the current infusion rate for the current drug. The time
 * that the rate change took place is indicated by "itime" and is in [seconds]
 * after the Init call. The infusion rate is passed in "rate", and is in
 * [mg/kg/min]. Internally this function recalculates the model up until
 * "itime", then the current infusion rate is changed.
 * There is no return value.
 *-------------------------------------------------------------------------*/

void far pascal Set_Bolus(long itime, double amount);
/*-------------------------------------------------------------------------
 * his function gives a bolus for the current drug at time "itime". The amount
 * is stored in "amount" and the unit is [mg/kg]. Internally this function
 * recalcultates the model until "itime", and then adds the "amount" amount.
 * There is no return value.
 *-------------------------------------------------------------------------*/

void far pascal Get_Concentration(long itime, int far *data);
/*-------------------------------------------------------------------------
 * This function calculates and returns the concentration for the current drug
 * in "data" at time "itime". The units are [ug/l]. Two concentrations are
 * returned in "data" (central compartment "data[0]" and peripheral compartment
 * "data[1]".
 * There is no return value.
 *-------------------------------------------------------------------------*/

void far pascal Get_TwitchHeight(long itime, int type, int far *data);
/*-------------------------------------------------------------------------
 * This function returns the twitch data (format depends on stimulus tupe) at
 * time "itime" in the array "data".
 * There is no return value.
 * The reasoning behind the "type" parameter is: It can be expanded to include
 * other stimulus modes and just the stimulus modes that are used in a
 * particular trainer can be obtained.
 * STIMULUS TYPE:
 * 1 = Single Twitch, 3 = Tetanic Stimulus, 4 = Train Of Four, 8 = Post Tetanic Count
 *-------------------------------------------------------------------------*/
```

# Appendix B: C-code of the ICU-PTT model interface

```
void far pascal DeInit(void);
/*-----------------------------------------------------------------------------------------------------------------------
 * This function performs deinitialization and is called when the model is not
 * needed anymore.
 * There is no return value.
 *-----------------------------------------------------------------------------------------------------------------------*/

/*=======================================================================================*/
// Extra Library function for feedback purposes and future applications
/*=======================================================================================*/
void far pascal Set_DescriptorsPKPD(int drugid);
/*-----------------------------------------------------------------------------------------------------------------------
 * This function initializes the pharmacokinetic and pharmacodynamic
 * parameters for drug "drugid".
 * There is no return value.
 *-----------------------------------------------------------------------------------------------------------------------*/

void far pascal Set_Weight(double Weight);
/*-----------------------------------------------------------------------------------------------------------------------
 * This function sets the patient's body weight in [kg] and can be usefull when
 * infuences of body weight are included in the model later on.
 * There is no return value.
 *-----------------------------------------------------------------------------------------------------------------------*/

void far pascal Set_SamplePeriod(long SamplePeriod);
/*-----------------------------------------------------------------------------------------------------------------------
 * This function redefines the time between two sample in [seconds] and can be
 * used to optimize the used discretization method.
 * There is no return value.
 *-----------------------------------------------------------------------------------------------------------------------*/

void far pascal Set_SampleTime(long SampleTime);
/*-----------------------------------------------------------------------------------------------------------------------
 * This function defines the initial sample time in [seconds] and can be used
 * to reinitialize the model for multiple runs.
 * There is no return value.
 *-----------------------------------------------------------------------------------------------------------------------*/

void far pascal Set_Concentration(long C1, long C2);
/*-----------------------------------------------------------------------------------------------------------------------
 * This function defines the initial compartment concetrations in [ug/l] and
 * can be used to preset the model for different patients.
 * There is no return value.
 *-----------------------------------------------------------------------------------------------------------------------*/

double far pascal GetVolume (int Compartment);
/*-----------------------------------------------------------------------------------------------------------------------
 * This function calculates the volume of distribution in [liters] of
 * copartment "Compartment". This function can be used to scale the vessels
 * in the hydraulic model drive animation.
 *-----------------------------------------------------------------------------------------------------------------------*/
```

# Appendix B: C-code of the ICU-PTT model interface

```
/*=========================================================================*/
//ICUMODEL.C: Version 1.0      State Transition Implementation
//Eric, 07/29/95
/*=========================================================================*/
//INCLUDES
/*-------------------------------------------------------------------------*/
#include <windows.h>
#include <stdio.h>
#include <math.h>
#include <string.h>
#include <stdlib.h>
#include "icumodel.h"

/*=========================================================================*/
//LOCAL TYPE DEFINITIONS
/*-------------------------------------------------------------------------*/
enum STIMULUS{ST, TOF, SUST, PTC};        //Set of possible Nerve Stimuli

typedef struct                  //structure to store the necessary PK and PD parameters
        {
         int drugid;            //drug identification number
         double weight;         //patient body weight in [kg]

         float a;               //[1/min]=>[1/sec]
         float b;               //[1/min]=>[1/sec]
         float A;               //ratio, A+B=1
         float B;               //ratio, A+B=1
         float Q;               //dependent of previous four parameters
         float V1;              //central compartment Volume in [liter/kg]

         float EC50;            // [ug/kg], peripheral concentration for 50% effect
         float GAMMA;           // [-], sigmoidal constant
         float DELTA;           // [1/min], constant for Post Tetanic Count calculations
         float TRESHOLD;        //threshold to detect twitches
         float T_PTC;           // Ttime between first PTC and first TOF response
         float MAX_PTC;         //Maximum  number of Post Tetenic Count for Atracurium
         float SUST_Gain;       //gain for "SUST" twitch height compared with "ST"

         }PKPDSET;


typedef struct                  //structure to store and read state model data
        {
        long SamplePeriod;      //time between two samples
        long SampleTime;        //relative time of sample
        double bolus;           //drug concentration for bolus injection in [ug/kg]
        double q;               //infusion rate in [ug/kg/min]
        double x1;              //state variable 1
        double x2;              //state variable 2
        double c1;              //concentration of the central compartment in [ug/l]
        double c2;              //concentration of the peripheral compartment in [ug/l]
        float TwitchHeight[10];   //ratio of the twitch height, max. of 10 twitches

        }SAMPLE;
```

# Appendix B: C-code of the ICU-PTT model interface

```
/*=============================================================================*/
//INTERNAL FUNCTION HEADERS
/*-----------------------------------------------------------------------------*/
void Pharmacokinetics(long NewSamplePeriod);
/*-----------------------------------------------------------------------------
 * This function calculates the model state transistion equations per
 * SamplePeriod in [seconds], and checks if the NewSamplePeriod is different
 * from the Old sampleperiod.
 * There is no return value.
 *-----------------------------------------------------------------------------*/

void Pharmacodynamics(enum STIMULUS stimulus);
/*-----------------------------------------------------------------------------
 * This function calculates the percentage blockade and the resulting first
 * twitch height for the stimulus type "stimulus".
 * There is no return value.
 *-----------------------------------------------------------------------------*/

void TwitchFade(enum STIMULUS stimulus);
/*-----------------------------------------------------------------------------
 * This function calculates the height of the twitches in case fade occurs
 * between different twitches, which depends on the stimulus type "stimulus".
 * There is no return value.
 *-----------------------------------------------------------------------------*/

void Update(long NewTime);
/*-----------------------------------------------------------------------------
 * This function recalculates the model state equations until time "NewTime"
 * which is in [seconds].
 * There is no return value.
*-----------------------------------------------------------------------------*/

/*=============================================================================*/
//GLOBAL VARIABLES
/*-----------------------------------------------------------------------------*/
//Model calculations always from these two structures

SAMPLE sample;              //information for the model input and output
PKPDSET PKPDset;            //storage of drug dependent pharmacologic descriptors

/*=============================================================================*/
//DEFINITION OF THE FUNCTIONS THAT CAN BE CALLED FROM OUTSIDE THIS FILE
/*-----------------------------------------------------------------------------*/
int far pascal Init(char far *patname, char far *drugsset, int drugid)
{/* ACCEPTS:  "drugid", integer with drug identification number: Atracurium=0
  *           "*patname", character string with initialization file name
  * RETURNS:  1 if succesfull else 0.
  * USAGE:    see header file
  * AUHTOR:   Eric Nikkelen
  * DATE:     01/95
  */

  char *p;
  char buff[100];
  FILE *fp;
  float ED50;           //[mg/kg], clinical dose for 50% twitch height
  float ED95;           //[mg/kg], clinical dose for 5% twitch height
```

## Appendix B: C-code of the ICU-PTT model interface

```
float Tm;                    // [min], time of maximal peripheral concentration
fp=fopen(drugsset,"r");

if(!fp) return(0);

fgets(buff, 100, fp);
p=strtok(buff,": ;");

while((!(atoi(p)==drugid))&&(!feof(fp)))
        {
         fgets(buff, 100, fp);
         p=strtok(buff,": ;");
        };//end-while

if(!(feof(fp)))
        {
         p=strtok(NULL,"; = :");
         (ED50)=atof(p);

         p=strtok(NULL,"; = :");
         (ED95)=atof(p);

         p=strtok(NULL,"; = :");
         (PKPDset.a)=atof(p);

         p=strtok(NULL,"; = :");
         (PKPDset.b)=atof(p);

         p=strtok(NULL,"; = :");
         (PKPDset.A)=atof(p);

         p=strtok(NULL,"; = :");
         (PKPDset.B)=atof(p);

         p=strtok(NULL,"; = :");
         (PKPDset.V1)=atof(p);

         p=strtok(NULL,"; = :");
         (PKPDset.T_PTC)=atof(p);

         p=strtok(NULL,"; = :");
         (PKPDset.MAX_PTC)=atof(p);

         p=strtok(NULL,"; = :");
         (PKPDset.SUST_Gain)=atof(p);

         p=strtok(NULL,"; = :");
         (PKPDset.TRESHOLD)=atof(p);

         //Tm is the time when C2 is maximal, typical Tm=10 minutes
         Tm=(log(PKPDset.b/PKPDset.a)/(PKPDset.b-PKPDset.a));

         PKPDset.EC50=(ED50/PKPDset.V1)*(PKPDset.A*exp(-PKPDset.a*Tm)+
         PKPDset.B*exp(-PKPDset.b*Tm));
         PKPDset.GAMMA=(log(19)/log(ED95/ED50));   //in the order of 4.5

         //Delta is the exponent for the PTC fade function
```

```
        PKPDset.DELTA= pow( (log(0.05))/ (log(1/(1+19*(exp(-PKPDset.b*PKPDset.T_PTC*
        PKPDset.GAMMA))))), (pow((PKPDset.MAX_PTC-1), -1)) );
        PKPDset.Q=((PKPDset.A*PKPDset.b+PKPDset.B*PKPDset.a)/(PKPDset.a-
        PKPDset.b));

        Set_DescriptorsPKPD(0);      //drugid=0 is Atracurium
        Set_Weight(70.0);            //default body weight: 70.0 kg
        Set_SamplePeriod(0);         //default sample period: 0 secondes !
        Set_SampleTime(0);           //default start time 00:00:00
        Set_Bolus(0,0);              //default no input
        Set_Infusion(0,0);           //default no input
        Set_Concentration(0,0);      //default no input

        fclose(fp);

        return(1);

 }//end-if
 else
 {
  fclose(fp);
  return(0);
 };//end-else

};//end-Init
/*-------------------------------------------------------------------------------------------------------------------------------------------*/

void far pascal Set_Infusion(long itime, double rate)
{/* ACCEPTS:  "itime", time in [second] that the infusion is given
  *           "rate", infusion rate in [mg/kg/min]
  * RETURNS:  none.
  * USAGE:    see header file
  * AUHTOR:   Eric Nikkelen
  * DATE:     01/95
  */

 Update(itime);          //Update model to infusion injection time "itime"

 if(rate>0)
 {
  sample.q=((1000*rate)/60);//"rate"=infusionrate in mg/kg/min !!!
 }//end-if
 else sample.q=0;

};//end-Set_Infusion
/*-------------------------------------------------------------------------------------------------------------------------------------------*/

void far pascal Set_Bolus(long itime, double amount)
{/* ACCEPTS:  "itime", time in [second] that the bolus is given
  *           "amount", amount of drugs in [mg/kg]
  * RETURNS:  none.
  * USAGE:    see header file
  * AUHTOR:   Eric Nikkelen
  * DATE:     01/95
  */

 Update(itime);                  //Update model to time "itime"
```

```
 if(amount>=0)
 {
 sample.bolus=1000*amount;    //model calulation are in [ug/kg]!!!
 };//end-if

};//end-Set_Bolus
/*-----------------------------------------------------------------------------------------------------------------------------------*/

void far pascal Get_Concentration(long itime, int far *data)
{/* ACCEPTS:  "itime", time in [second] to read the concentration
  *           "*data", integer array to store the concentration values
  * RETURNS:  none.
  * USAGE:    see header file
  * AUHTOR:   Eric Nikkelen
  * DATE:     01/95
  */

 Update(itime);

 data[0]=(int)(sample.c1);              //data[0]=central compartment concentration
 data[1]=(int)(sample.c2);              //data[1]=peripheral compartment concentration

};//end-Get_Concentration
/*-----------------------------------------------------------------------------------------------------------------------------------*/

void far pascal Get_TwitchHeight(long itime, int type, int far *data)
{/* ACCEPTS:  "itime", time in [second] to read the twitch heights
  *           "type", stimulus type
  *           "*data", integer array to store the twitch heights
  * RETURNS:  none.
  * USAGE:    see header file
  * AUHTOR:   Eric Nikkelen
  * DATE:     01/95
  */

 //Local Variables
 enum STIMULUS StimulusType;
 int ForCount;

 Update(itime);          //Update model to time "itime"

 switch(type)            //conversion of "type" integer to different stimulus types
 {
  case 1: StimulusType=ST;     break;  //ST=Single Twitch
  case 3: StimulusType=SUST;break;     //SUST=Sustained Tetanus
  case 4: StimulusType=TOF; break;     //TOF=Train Of Four
  case 8: StimulusType=PTC; break;     //PTC=Post Tetanic Count
  default: type=0; break;
 };

 Pharmacodynamics(StimulusType);     //Calculation of the first twitch height
 TwitchFade(StimulusType);

 //Convertion of twitch heights
 for(ForCount=0; ForCount<type; ForCount++)
         data[ForCount]=(int)(sample.TwitchHeight[ForCount]*1000);
```

```
};//end-Get_TwitchHeight
/*-----------------------------------------------------------------------------------------------------------------------------------------*/

void far pascal DeInit(void)
{/* ACCEPTS:  none.
 * RETURNS:  none.
 * USAGE:    see header file
 * AUHTOR:   Eric Nikkelen
 * DATE:     01/95
 */

        // NOT USED

};//end-DeInit
/*-----------------------------------------------------------------------------------------------------------------------------------------*/

void far pascal Set_DescriptorsPKPD(int drugid)
{/* ACCEPTS:  "drugid", integer with drug identification number: Atracurium=0
 * RETURNS:  none.
 * USAGE:    see header file
 * AUHTOR:   Eric Nikkelen
 * DATE:     07/95
 */

 (PKPDset.drugid)=drugid;       //Atracurium's drug ID number is 0

 PKPDset.T_PTC*=60;             //dimensions of T_PTC in [seconds]
 PKPDset.EC50*=1000;            //dimensions of EC50 are [mug/ml]
 PKPDset.a/=60;                 //resolution 1 sec. therefore dimensions [1/sec]
 PKPDset.b/=60;       //resolution 1 sec. therefore dimensions [1/sec]

};//end-Set_DescriptorsPKPD
/*-----------------------------------------------------------------------------------------------------------------------------------------*/

void far pascal Set_Weight(double Weight)
{/* ACCEPTS:  "Weight", the patient's body weight in [kg]
 * RETURNS:  none.
 * USAGE:    see header file
 * AUHTOR:   Eric Nikkelen
 * DATE:     01/95
 */

 PKPDset.weight=Weight;

};//end-Set_Weight
/*-----------------------------------------------------------------------------------------------------------------------------------------*/

void far pascal Set_SamplePeriod(long SamplePeriod)
{/* ACCEPTS:  "SamplePeriod", the time between to samples in [seconds]
 * RETURNS:  none.
 * USAGE:    see header file
 * AUHTOR:   Eric Nikkelen
 * DATE:     01/95
 */

 sample.SamplePeriod=SamplePeriod;
```

```
};//end-Set_SamplePeriod
/*-----------------------------------------------------------------------------------------------------------------------------------*/

void far pascal Set_SampleTime(long SampleTime)
{/* ACCEPTS:   "SampleTime", the initial sample time in [seconds]
  * RETURNS:  none.
  * USAGE:    see header file
  * AUHTOR:   Eric Nikkelen
  * DATE:     05/95
  */

 sample.SampleTime=SampleTime;

};//end-Set_SampleTime
/*-----------------------------------------------------------------------------------------------------------------------------------*/

void far pascal Set_Concentration(long C1, long C2)
{/* ACCEPTS:   "C1","C2" the initial compartment concetrations in [ug/l]
  * RETURNS:  none.
  * USAGE:    see header file
  * AUHTOR:   Eric Nikkelen
  * DATE:     07/95
  */

 float A=PKPDset.A;
 float B=PKPDset.B;
 float Q=PKPDset.Q;

 sample.x1=((C1*Q-B*C2)/(Q*(A+B)));
 sample.x2=((C2*A+Q*C1)/(Q*(A+B)));

};//end-Set_Concentration
/*-----------------------------------------------------------------------------------------------------------------------------------*/

double far pascal Get_Volume (int Compartment)
{/* ACCEPTS:   "Compartment", the compartment for which the volume must becalculated
  * RETURNS:  The volume of distribution in [liters]
  * USAGE:    see header file
  * AUHTOR:   Eric Nikkelen
  * DATE:     07/95
  */

 double V1,V2;

 float A=PKPDset.A;
 float B=PKPDset.B;
 float a=PKPDset.a;
 float b=PKPDset.b;

 float k21;

 k21=A*b+B*a;
 V1=(PKPDset.V1)*(PKPDset.weight);
 V2=((a+b-((a*b)/k21)-k21)/k21)*V1;
 return ((Compartment==1)? V1 : V2 );

};//end-Get_Volume
```

# Appendix B: C-code of the ICU-PTT model interface

```
/*=============================================================================*/
//DEFINITION OF INTERNAL FUNCTIONS
/*-----------------------------------------------------------------------------*/

void Pharmacokinetics(long NewSamplePeriod)
{/* ACCEPTS:  none.
  * RETURNS:  none.
  * USAGE:    see header file
  * AUHTOR:   Eric Nikkelen
  * DATE:     01/95
  */

  //Local variables
  static SAMPLE NextSample;          //To store the values for the next sample
  static double PHI[3], THETA[3];
  long Tc_Old=sample.SamplePeriod;
  long Tc_New=NewSamplePeriod;

  if (!(Tc_New==Tc_Old))
        {
         Set_SamplePeriod(Tc_New);

         PHI[1]=exp(-(PKPDset.a*Tc_New));
         PHI[2]=exp(-(PKPDset.b*Tc_New));
         THETA[1]=((1-PHI[1])/PKPDset.a);
         THETA[2]=((1-PHI[2])/PKPDset.b);

   }; //end-if

  if (sample.bolus)
        {
         //A bolus injection increases C1 without delay
         sample.x1+=(sample.bolus/PKPDset.V1);
         sample.x2+=(sample.bolus/PKPDset.V1);
         sample.bolus=0;
   };//end-if

  (NextSample.x1)=PHI[1]*(sample.x1)+THETA[1]*(sample.q/PKPDset.V1);
  (NextSample.x2)=PHI[2]*(sample.x2)+THETA[2]*(sample.q/PKPDset.V1);

  sample.c1=(PKPDset.A)*(sample.x1)+(PKPDset.B)*(sample.x2);
  sample.c2=(PKPDset.Q)*(sample.x2-sample.x1);

  //Update variables
  sample.SampleTime+=Tc_New;
  sample.x1=NextSample.x1;
  sample.x2=NextSample.x2;

};//end-Pharmacokinetics
/*-----------------------------------------------------------------------------*/
void Pharmacodynamics(enum STIMULUS stimulus)
{/* ACCEPTS:   "stimulus", is the type of nerve stimulus
  * RETURNS:  none.
  * USAGE:    see header file
  * AUHTOR:   Eric Nikkelen
  * DATE:     01/95
  */
```

## Appendix B: C-code of the ICU-PTT model interface

```
//Local variables
float Yt, C2, GAMMA, EC50;          //Sigmoidal function between Yt and C2

C2=(sample.c2);
GAMMA=(PKPDset.GAMMA);
EC50=(PKPDset.EC50);

switch(stimulus)
        {
         case(PTC):
        //The EC50 of PTC is modelled as a shift of the EC50 of TOF
        Yt =( (pow(C2,GAMMA))/
        (pow(C2,GAMMA)+(exp(PKPDset.b*(PKPDset.T_PTC)*GAMMA)*pow((EC50),GAMMA))
        ) );
        break;

        default:
        //Amplitude of Single Twitches and First Pulse of Train of Four are equal
                Yt=(  (pow(C2,GAMMA)) /( pow(C2,GAMMA)+pow(EC50,GAMMA) ) );
                break;

        };//end of switch(stimulus)

sample.TwitchHeight[0]=1-Yt;

};//end-Pharmacodynamics
/*-----------------------------------------------------------------------------------------------------------------------*/

void TwitchFade(enum STIMULUS stimulus)
{/* ACCEPTS:  "stimulus", is the type of nerve stimulus
 * RETURNS:  none.
 * USAGE:    see header file
 * AUHTOR:   Eric Nikkelen
 * DATE:     01/95
 */

 //Local Variables
 float SUST_PlateauTime;     //Time of Plateau duration
 int SUST_SlopeTime;         //Time of Slope decay duration
 float Yi,Yt;                //twitch heights for the different pulses in one train
 int i;                      //counter for loops

 Yt=sample.TwitchHeight[0];  //Calculated hieght of first twitch

 switch(stimulus)
        {
         case (ST):
                //For Single Twitch all twitches have equal height and NO fade
                for(i=0; i<PKPDset.MAX_PTC; i++)
                        sample.TwitchHeight[i]= (Yt>=PKPDset.TRESHOLD)? Yt : 0;
                break;

         case (TOF):
           //For TOF twitches are related to eachother with a power function
                for(i=1; i<=4; i++)
                        {
                         Yi=( pow( Yt,(pow(2,(i-1))) ) );
```

```
                        sample.TwitchHeight[i-1]= (Yi>=PKPDset.TRESHOLD)? Yi : 0;
                        };
    break;

        case (SUST):
                //Sustained Tetani can be modelled as a gained Single Twitch
                if(Yt<=0.25)
                        {
                        SUST_SlopeTime=1;
                        SUST_PlateauTime=0;
                        }
                else
                        {
                        SUST_PlateauTime=(((Yt-0.25)*100/20)+1);
                        SUST_SlopeTime=0;
                        };

                sample.TwitchHeight[0]=Yt;
                sample.TwitchHeight[1]=SUST_PlateauTime;
                sample.TwitchHeight[2]=SUST_SlopeTime;
                break;

                case (PTC):
                //The number of PTC twitches is related to the time of the first
                //TOF twitch, therefore an extra scaling exponent "delta" is required
                for(i=1; i<=PKPDset.MAX_PTC; i++)
                        {
                        Yi=PKPDset.SUST_Gain*pow(Yt,( pow(PKPDset.DELTA,(i-1)) ) );
                        sample.TwitchHeight[i-1]=
                        (Yi>=(PKPDset.SUST_Gain*PKPDset.TRESHOLD))? Yi : 0;
                        };//end for
                break;
   }; //end of switch(stimulus)

};//end-TwitchFade
/*-------------------------------------------------------------------------------------------------------------------------------------------*/

void Update(long NewTime)
{/* ACCEPTS:  "NewTime", time in [seconds] to which the model must be updated
  * RETURNS:  none.
  * USAGE:    see header file
  * AUHTOR:   Eric Nikkelen
  * DATE:     01/95
  */

 if ((NewTime-sample.SampleTime)>0) Pharmacokinetics(NewTime-sample.SampleTime);

};//end-Update
/*-------------------------------------------------------------------------------------------------------------------------------------------*/
```