

Pharmacokinetic- and pharmacodynamic-based infusion

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5.1: Introduction

Intravenous agents have gained considerable popularity in recent years, particularly with the advent of short-acting non-cumulative drugs such as propofol. Nevertheless, compared with the administration of inhalational anaesthetic drugs, achieving and maintaining the desired effect-site concentration with intravenous drugs are more difficult. For the inhalational drugs, the inspired and end-tidal concentration can be measured on line and non-invasively, thereby enabling the anaesthetist to correlate concentration with clinical effect, as shown in Fig. 5.1.

inhalational anaesthetics

VAPOR (vol%) → Inspired concentration → End tidal concentration → drug effect
(“MAC” on line)

Intravenous anaesthetics

Dose (mg/kg) → ?????????? → ?????????????? → drug effect
(plasma and effect-site concentration not on line)

Fig.: 5.1: Possibilities of measuring pharmacokinetic-dynamic relation in clinical practice when using intravenous anaesthetics compared with inhalational anaesthetics. MAC means minimum alveolar concentration.

In contrast, intravenous drugs are generally delivered on a dose per kilogram of body weight basis by manually controlled infusion pumps. Hereby, on line measurements of plasma or effect-site concentration of an intravenous drug is not possible today. Thanks to the development of short-acting drugs and advanced computer technology, and to better knowledge about patients' dedicated pharmacokinetics and dynamics, it has been possible to develop accurate, computer-controlled, intravenous drug delivery systems for clinical use.

These devices enable the clinician to continuously control the drug concentration in the plasma or at the effect-site, and to administer anaesthetics according to their pharmacokinetic profile without performing the mental gymnastics required to calculate the compartmental drug concentration on the basis of polyexponential functions, as explained in Chapter 3. Instead of measuring the plasma or effect-site concentration (what is impossible in vivo), the computer-controlled infusion device predicts the drug concentration, thereby allowing the anaesthetist to dose intravenous drugs to a target plasma or effect-site concentration instead of on the basis of dose per kilogram of body weight (1, 2).

Computer-controlled infusion pumps can only be used optimally when three elements have been carefully worked out. First, the model that controls the pump has to work accurately. Second, the pharmacokinetic parameter set of a particular drug provided to the computer model should match the pharmacokinetics of the patient. Third, the pharmacodynamics of the administered drug should be well defined to enable the anaesthetist to attain the plasma concentration needed for the required effect (2). These necessities will be explained in this chapter.

5.2: Principles of target-controlled infusion

Various synonyms for the term computer-controlled infusion are found in the literature: computer-assisted continuous infusion (CACI), computer-controlled infusion pumps (CCIP), target-controlled infusion (TCI). In this thesis, the term target-controlled infusion is used.

TCI systems deliver variable infusion schemes based on a complex mathematical solution to the pharmacokinetic model. Patient factors such as weight and age are entered into the system together with a “target” plasma or effect-site concentration. The control software then calculates and delivers a rapid infusion designed to achieve this target concentration as quick as possible without “overshoot”, followed by a computer-controlled constantly adjusting infusion regimen calculated to maintain the target concentration. A new target concentration can be selected at any time. If a higher target concentration is chosen, the system will deliver an additional rapid infusion. If a lower concentration is chosen, the control software will stop the infusion until it has calculated that the new target concentration has been achieved, after which the system will control the infusion rate to maintain the new target concentration, as illustrated in Fig. 5.2. This method is analogous to the use of a calibrated vaporizer. When

using TCI, the anesthesiologist selects a target concentration of intravenous agent just as he would select an inspired or end tidal concentration of volatile agent. The target concentration has to be adjusted according to the patient's response to surgery (3). There are two different approaches to achieve a required target concentration: open and closed loop infusion. Open loop TCI means that the clinician set the target concentration on the infusion device. In closed-loop infusion, a feed-back system steered by a computer is used to control the target concentration.

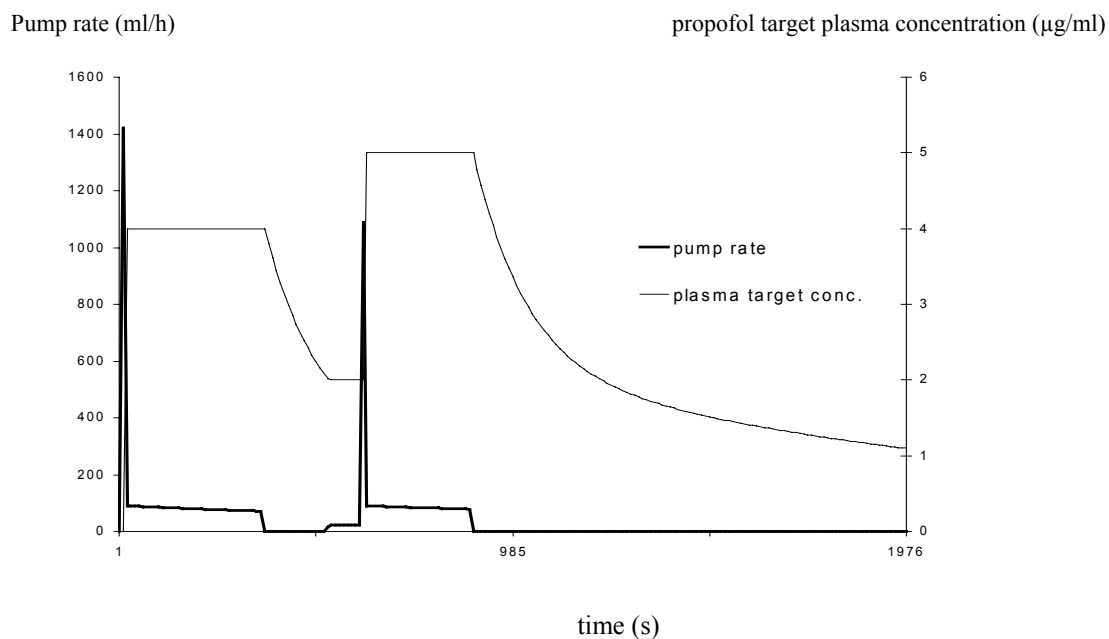


Fig. 5.2: Target controlled infusion of propofol. An initial bolus at maximum pump rate is administered to achieve the target concentration of 4 $\mu\text{g/ml}$. Thereafter, the pump rate decreases exponentially to maintain the desired target concentration. After 400 s, the target concentration is decreased to 2 $\mu\text{g/ml}$. The infusion stops till the lower concentration is reached and restart at a lower level. After 600 s, the target concentration is increased to 5 $\mu\text{g/ml}$. The infusion controller will deliver another bolus to reach the higher concentration and will maintain this at a higher level. At 870 s, the infusion is stopped.

5.3: The history of TCI

Given a fully parameterized linear, time-invariant, two-or three-compartment pharmacokinetic model (see Chapter 3), several approaches can determine the infusion rates required as a function of time to achieve the target drug concentration specified as a function of time. The concept of TCI originated in the pioneering work of Kruger-Thiemer (4), when he derived the equations specifying the intravenous infusion-rate profile required theoretically to reach and maintain a constant, specified plasma concentration of a drug whose

pharmacokinetic properties could be described by a linear, multicompartment model. For a two-compartment model, this regimen would later become known as the BET infusion scheme (5,6) (see Chapter 4). In 1981, Schwilden et al. (7) expanded the existing concept and incorporated it into the first computer-controlled infusion system, called CATIA. The BET infusion scheme is now just one of the several algorithms that are used to effect pharmacokinetic model-driven infusion of anaesthetic drugs through automated drug delivery systems. All of these algorithms are derived by manipulating a pharmacokinetic model, expressed as either a polyexponential equation or compartmental models described earlier (see Chapter 2), to calculate the infusion rates required to obtain the theoretically desired plasma or effect-site concentration. Since the development of the BET scheme, groups working in many different countries have reported on the use of these systems in their pharmacological research. In this thesis, three systems were used to steer and simulate constant drug concentrations during sedation and anaesthesia with propofol:

- STANPUMP ®, a computer program that can be installed on a personal computer using DOS as Operating System. It is developed by Dr. Steven Shafer at Stanford University and available on the internet: <http://pkpd.icon.palo-alto.med.va.gov/> . This system is able to steer a syringe pump with an RS 232 interface for controlling a constant concentration in the plasma or the effect-site compartment. (available since 4/9/1996)
- RUGLOOP ®, a computer program that is developed by Ir. Tom De smet and Dr. Michel Struys at the University Hospital in Gent. It is developed for steering TCI in the Windows 95/NT environment and is also able to collect and manage simultaneously patient haemodynamic, respiratory and cerebral data, when connected with a Datex AS/3 and a Aspect A-1000 monitor, respectively. This program is also available on the internet: <http://pkpd.icon.palo-alto.med.va.gov/> , thanks to the cooperation of Dr. Steven Shafer. (available since 27/1/98)
- DIPRIFUSOR ®, a system based on an Atari 1040ST microcomputer which is connected to an Graseby 3400 syringe pump via an RS 232 connector. This system was developed by White and Kenny (8) and for our clinical work we used a prototype of the device. Recently, this device has been commercialized and is available for controlling plasma concentrations of Diprivan ® (propofol; Zeneca Ltd, UK). (commercialized in Belgium since 20/4/1998)

5.4: Predictive models of patients drug concentrations to control propofol TCI

In clinical practice nowadays, it is impossible to measure individual plasma concentrations of propofol during anaesthesia or sedation. Therefore, prediction of the patient's plasma or even effect-site concentration by using a pharmacokinetic-dynamic model with appropriate parameter set is required.

5.4.1: The model to be controlled

As explained in chapter 3, the pharmacokinetic and dynamic behaviour of a drug has been described by compartmental models, which are based on the mathematical characterization of the plasma drug concentration against time. In these models, volume of distribution and micro rate constants (e.g. for a three compartmental model, V_1 , k_{10} , k_{12} , k_{21} , k_{13} , k_{31}) are used to predict an infusion rate pattern suitable for establishing and maintaining the target concentration as it is varied by the operator. If the site of action of the drug, as with propofol, is remote from the arterial circulation, a further rate constant may be necessary (k_{e0}) to predict the transfer of drug to the effect site.

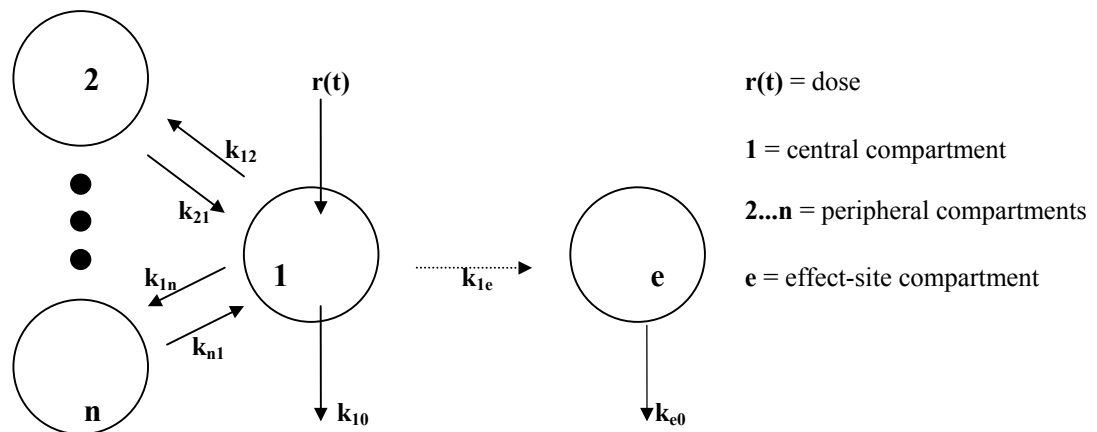


Fig. 1: n-compartmental model with effect-site compartment

Intravenous drugs are delivered directly into the central compartment or plasma compartment. As said, the effect-compartment drug concentration equilibrates with the central compartment drug concentration at a rate determined by k_{e0} . For semantic purposes, the effect compartment is not regarded per se as one of the n-1 peripheral compartments of the n-compartment model.

To approach target controlled infusion techniques using tractable mathematical techniques, two major assumptions about the dose-concentration relationships in the compartmental model are required, i.e. linearity and time invariance (stationarity). Simply put, linearity of the dose-concentration relationship, also called superposition, implies that if the concentration profile in any compartment resulting from $r(t) = a(t)$ is $x(t)$ and that resulting from $r(t) = b(t)$ is $y(t)$ then $r(t) = a(t) + b(t)$ will yield $x(t) + y(t)$. Time invariance implies that the constants ($V_1, k_{10}, k_{12}, \text{etc.}$) are truly constant and do not vary across time (i.e., during administration of the infusion).

The relationship between drug input, $r(t)$, into the central compartment (e.g., intravenous injection or infusion) and the resulting central compartment drug concentration in linear, time invariant n-compartment mamillary models is :

$$c_1(t) = r(t) * \text{udf}_1(t) \quad (\text{formula 5.1})$$

where $\text{udf}_1(t)$ is the unit disposition function for the central compartment and $*$ denotes the mathematical operation of convolution. Convolution integral mathematics are used in more sophisticated applications to establish the input-response relation. The convolution integral approach also arises directly from the superposition principle but applied at the infinitesimal scale (9). If $\text{udf}_1(t)$ is known, $c_1(t)$ resulting from any $r(t)$ can be predicted unambiguously by convolving $r(t)$ with $\text{udf}_1(t)$. Reference to a “pharmacokinetic simulation” implies some form of $r(t) * \text{udf}_1(t)$.

For a n-compartment model, $\text{udf}_1(t)$ is an n-exponential function of the form:

$$\text{udf}_1(t) = A_1 e^{-a_1 t} + A_2 e^{-a_2 t} + \dots + A_n e^{-a_n t} \quad (\text{formula 5.2})$$

This is the equivalent of the BET scheme, as described previously (see Chapter 4). A n-exponential $\text{udf}_1(t)$ implies a n-compartment model, and vice versa. Likewise, formulae are readily available to compute values for the central compartment volume and rate constants of the compartment model from the A_i 's and a_i 's of $\text{udf}_1(t)$, and vice versa (10). In one form or another, a fully parameterized $\text{udf}_1(t)$ is the ultimate product of any complete pharmacokinetic study.

If pharmacodynamic data are also available for the drug of interest so that a value has been defined for k_{e0} , there exists a $n + 1$ exponential-unit disposition function, $udf_e(t)$, for the effect compartment of the form :

$$udf_e(t) = B_1 e^{-a_1 t} + B_2 e^{-a_2 t} + \dots + B_n e^{-a_n t} + \left[\sum_{i=1}^n B_i \right] \cdot e^{-k_{e0} t} \quad (\text{formula 5.3})$$

with $B_i = -Ak_{e0} / (\alpha_i - k_{e0})$, which characterizes completely the relation between drug input into the central compartment and the resulting effect-compartment drug concentration (11, 12), such that

$$c_e(t) = r(t)^* \cdot udf_e(t) \quad (\text{formula 5.4})$$

5.4.2: Choosing the correct pharmacokinetic-dynamic parameters

5.4.2.1: Pharmacokinetic parameters

The pharmacokinetic parameters of the compartmental model necessary to calculate the TCI algorithm are the central volume of distribution (V_1) and the intercompartmental micro-rate constants (k_{10} , k_{12} , k_{21} , k_{13} , k_{31}). As explained in chapter 3, these parameters are derived from population pharmacokinetic studies. With the use of sophisticated software programs such as NONMEM[®], available from Sheiner at the WWW (<http://pkpd.icon.palo-alto.med.va.gov/>), it is possible to calculate the pharmacokinetic model and parameter set for a specific drug.

Investigators who have assessed the accuracy of TCI of propofol report inevitable variation of achieved concentrations in plasma around the targeted concentration (13). Possible sources of variability arise during estimation of the pharmacokinetic parameters and during use of the model for TCI. For example, variance among the parameters of a polyexponential function fitted to a single set of concentration-time data (14). In addition, there is pharmacokinetic variation among the subjects who constitute the sample selected for derivation of the averaged parameter set. Often, for cost consideration, the number of subjects in the sample is small, casting doubt as to whether the sample can be assumed to represent the population adequately. Furthermore, patients receiving TCI do not necessarily belong to the same population from whom the original pharmacokinetic model was derived, and the effect of the surgical procedure can result in pharmacokinetic variability within each patient (15). All of these factors can lead to bias and inaccuracy of the concentrations achieved during TCI.

Several calculation and statistical methods are used to describe the accuracy of a specific parameter set (13):

- percentage *prediction error of the predicted concentration* in plasma :

$$PE = (\text{measured} - \text{predicted} / \text{predicted}) \cdot 100 \quad (\text{formula 5.6})$$

PE is an indication of the bias of the achieved concentrations, and the absolute value PE ($|PE|$) is a measure of the precision (inaccuracy).

- *Median absolute prediction error*, indicating the inaccuracy of TCI in the i-th subject:

$$MDAPE_i = \text{median} \{ |PE|_{ij}, j = 1, \dots, N_i \} \quad (\text{formula 5.7})$$

whereby N_i is the number of values $|PE|$ obtained for the i-th subject.

- *Median prediction error* reflects the bias of TCI in the i-th subject:

$$MDPE_i = \text{median} \{ PE_{ij}, j = 1, \dots, N_i \} \quad (\text{formula 5.8})$$

- *Divergence* is a measure of how the resulting drug concentrations in a subject are affected by time. It is defined as the slope of the linear regression equation of $|PE|$ against time and is expressed in units of percentage divergence per hour. A positive value indicates progressive widening of the gap between predicted and measured concentrations, whereas a negative value reveals that the measured concentrations converge on the predicted values.

- *Wobble* is another index of the time-related changes in performance and measures the intrasubject variability in performance errors. In the i-th subject the percentage of wobble is calculated as follows:

$$\text{wobble}_i = \text{median} \{ |PE_{ij} - MDPE_i|, j = 1, \dots, N_i \} \quad (\text{formula 5.9})$$

For propofol, the anaesthetic drug used in our computer-controlled infusion systems, five major pharmacokinetic sets are calculated. The five models are: Gepts (16), Shafer (15), Kirkpatrick (17), Cockshott (18) and Tackley (19). Vuyck et al. (2) evaluated the performance of the five sets of pharmacokinetic parameters and concluded that all sets except those of the Kirkpatrick model resulted in an equally clinically acceptable, although not optimal, performance. With all pharmacokinetic parameter sets, the measured concentrations of propofol exceed the predicted concentrations. The measured-predicted difference in propofol concentration increases with increasing target concentration. Coetzee et al. (20) did some similar tests and found that the parameter sets provided by Marsh et al. (22) (these parameters

are derived from the Gepts model but extended to a paediatric population) and Tackley et al. (21) proved adequate with acceptable prediction errors, ‘divergence’ and ‘wobble’. They proved that TCI worked well in clinical practice and that the selection of a particular pharmacokinetic parameter set did not appear to make a difference. It is always recommended, if possible, to use a locally derived parameter set, due to population characteristics. Therefore, we used the Gepts and Marsh parameter sets in our clinical work. These sets have been used by various investigators, even in long neurosurgical and cardiac cases, and have a provenly acceptable clinical performance for propofol (23, 24). The numerical value of the Marsh set is shown in table 5.1:

parameter	value
V_1	0.228 L / kg
k_{10}	0.119 min^{-1}
k_{12}	0.112 min^{-1}
k_{21}	0.055 min^{-1}
k_{13}	0.0419 min^{-1}
k_{31}	0.0033 min^{-1}

Table 5.1: Pharmacokinetic parameter set for propofol derived by Marsh et al. (from ref 22).h

In the study of Coetzee et al (20), the prediction errors and within subject indices of TCI performance for the Marsh parameter set were:

PE (mean arterial sample value) = - 0.9 %	MDPE (%) = -7.0
PE (mean arterial sample value) = 23.1 %	MDAPE (%) = 18.2
PE (mean venous sample value) = - 19.9 %	Divergence (%/h) = 6.5
PE (mean venous sample value) = 31.6 %	Wobble (%) = 10.0

For propofol, it has been shown that a mean variation of measured plasma concentrations of 20 - 30 % greater or lesser than targeted concentrations can occur (25).

5.4.2.2: Estimation of k_{e0}

As explained in chapter 3.3.3.2, the relationship between the plasma and effect-site concentration of propofol is characterized by a time constant k_{e0} , which reflects the hysteresis between changes in plasma concentration and corresponding changes in drug effect. For propofol, the site of effect is the brain and drug effect can be quantified by EEG, as said in chapter 2.

For propofol, few data are found in the literature. In 1986, Schüttler et al.(26), calculated a $k_{e0} = 0.25 \text{ min}^{-1}$. This value was found using median frequency, a processed EEG variable. Median frequency has now been proved not being a good variable for measuring the effects of propofol. This value was used in most of our clinical trials, except the closed-loop.

Billard et al. (27) compared three different EEG variables (delta power, spectral edge 95% and BIS, version 1.1) for modelling k_{e0} for propofol. They found that the estimates of k_{e0} were significantly higher for delta power (mean, 0.27 min^{-1}) than those for SEF 95% (mean, 0.21 min^{-1}) and BIS (mean, 0.20 min^{-1}). This is the first available peer-reviewed value derived from an acceptable population. This value was used in our closed-loop research and was also used for the simulations depicted in this thesis.

5.5: Open loop target controlled infusion : controlling the plasma or the effect-site compartment

5.5.1: Plasma- or central-compartment control

The BET algorithm for designing infusion regimen, as described previously in this thesis (chapter 4), consists of a bolus to load the central compartment to the desired concentration and a zero-order continuous infusion to replace drug elimination from the central compartment by clearance mechanisms superimposed on n-1 exponentially declining continuous infusions to replace drug transferred (distributed) out of the central compartment into the n-1 peripheral-compartments. This result was achieved by mathematically

deconvolving $udf_1(t)$ from the desired central compartment concentration profile, using formula 5.1 :

$$r(t) = udf_1(t)^{*^{-1}} \cdot c_{1_d} \quad (\text{formula 5.9})$$

where $*^{-1}$ denotes deconvolution (cf. formula 5.1) and a constant concentration of c_{1_d} is the desired outcome, meaning the target concentration set by the anaesthetist. This formula results in the following algorithm :

$$r(t) = c_{1_d} V_1 \delta(t) + c_{1_d} V_1 k_{10} u(t) + \sum_{i=2}^n c_{1_d} V_1 k_{1i} e^{-k_{1i} t} \quad (\text{formula 5.10})$$

where $\delta(t)$ denotes an instantaneous unit of a bolus injection and $u(t)$ denotes a constant rate infusion, which is required to achieve instantaneously and maintain a central compartment drug concentration of c_{1_d} , assuming an initial concentration of 0.

Formula 5.10 is the optimal generalized equation for the BET scheme, but represents a continuous-value, continuous time equation. As it is impossible to prescribe infusion rates of unlimited precision (e.g. 67.76391...ml/h) that change from one value to the next as a continuous function of time rather than at discrete intervals. The implication is that a BET-type infusion scheme cannot be implemented directly using realistic electromechanical infusion techniques. It is necessary to implement some supplemental software for discretizing the BET scheme. This can be done in different ways (11, 21), using statistical analysing techniques.

b) Effect-site compartment control

Effect-site compartment modelling is motivated by the observed dissociation between measured plasma drug concentrations and concurrently measured indexes of drug effect (e.g. processed EEG). This was explained in Chapter 3. Ultimately, the groups at Duke University (30) and Stanford University (31) developed computer algorithms for steering and controlling

the effect-site concentration. For mathematical reasons, it is not possible to derive a BET-type dosing equation for controlling the effect-site concentration, so there is no option here to attempt discrete implementation of an analytical infusion profile. Once again, however, a piecewise-continuous algorithm is derived from Jacobs et al. (30) by exploiting the linearity of the model (see Fig. 5.1), but with a result that is much more complex than can be used for the central compartment control technique. The basic correlation between plasma and effect-site concentration is shown in formula 5.11.

$$C_e(t) = C_p(t) \cdot (k_{e0} \cdot e^{-k_{e0} t}) \quad (\text{formula 5.11})$$

whereby $C_e(t)$ is the effect-site concentration at time t , $C_p(t)$ is the plasma concentration at time t and k_{e0} is the time constant expressing the blood-brain barrier equilibration time.

The algorithm steering the effect-site controlled TCI infusion is much more difficult than the basic relation expressed in formula 5.11. It is not the object of this thesis to explain the very difficult computer algorithms that steer the effect-site concentration. These details can be found in the original references (30, 31). We applied the Stanford algorithm, by using Stanpump® to steer our infusion pump in clinical practice.

Few data are available to compare the central with the effect-site compartmental steering method. Wakeling et al. (32) compared the two steering systems and confirmed both the accuracy and utility of the previously derived pharmacokinetic-dynamic coupling for propofol infusion. Compared with targeting plasma concentrations, targeting an effect-site concentration of 5.4 µg/ml significantly shortens the time to loss of consciousness without adverse cardiovascular effects. The difference between targeting the plasma versus effect-site concentration is shown in Fig. 2.

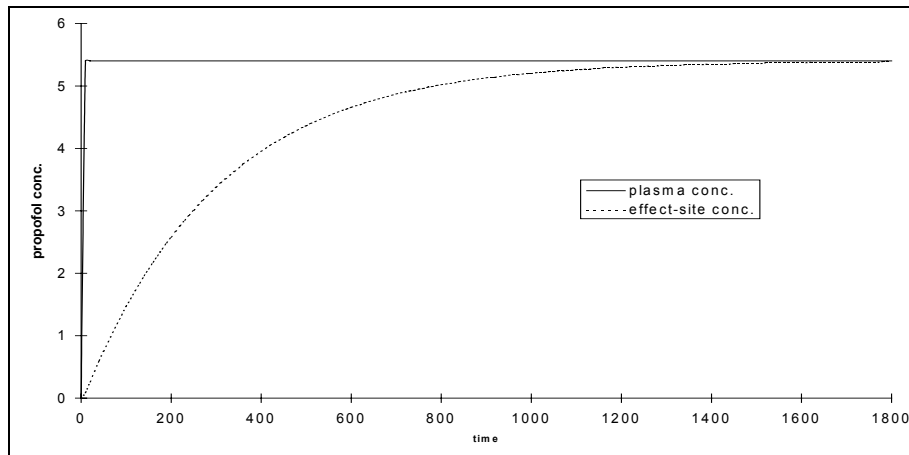


Fig. 2A : propofol plasma compartment-controlled infusion. Propofol plasma target concentration: 5.4 µg/ml. (male, 70 kg body weight, 167 cm height, 45 years old) : Time for intercompartmental equilibration, ± 1600 s.

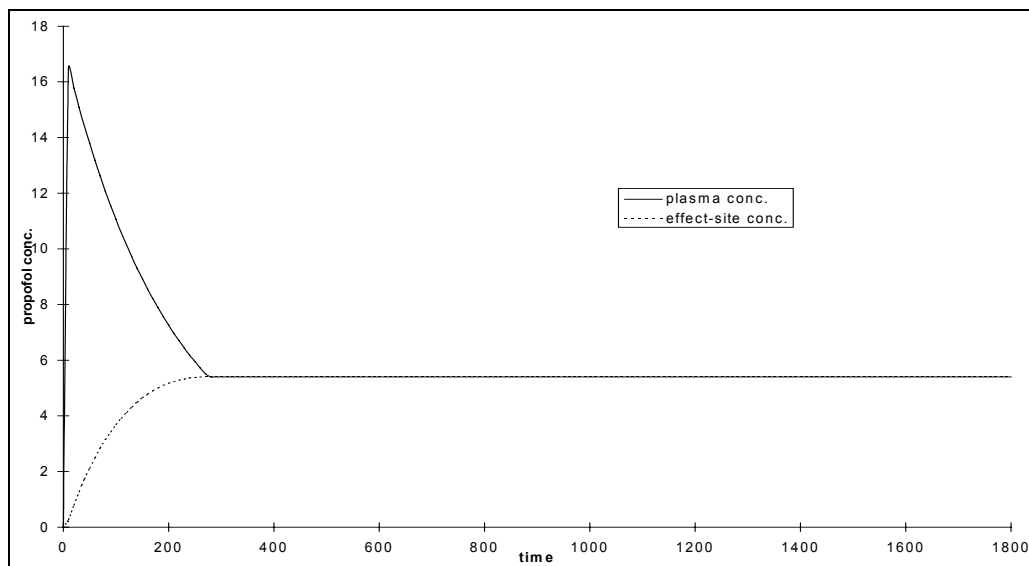


Fig. 2B : propofol effect compartment-controlled infusion. Propofol effect-site target concentration: 5.4 µg/ml. (male, 70 kg body weight, 167 cm height, 45 years old) : Time for intercompartmental equilibration, ± 220 s.

5.6. Closed-loop feed-back control systems

5.6.1: Introduction and principles

In the previously mentioned control systems, the target concentrations (plasma or effect-site) was set by the operator (the anaesthetist). The anaesthetist makes a decision to maintain or change the desired target concentration after having evaluated the patient's variables (haemodynamic, respiratory, cerebral, etc). This is called "open-loop" control. When the

desired target concentration is adapted by the computer after having evaluated the patient's variables, this is called "closed-loop feed-back" control. In closed-loop, the anaesthetist only enters the desired variables to maintain, for example a mean arterial blood pressure of 60 mmHg or a bispectral index of 50.

In our work, we have developed a closed-loop feed-back system for propofol, so this chapter is only intended to serve as a theoretical background. "Automated control theory" is an engineering speciality on its own and we do not intend to explain all the different control systems and methods here. Furthermore, the closed loop module of RUGLOOP®, containing the closed loop algorithm, is currently under the process of patent generation. Therefore, the details can only be disclosed in the near future.

A number of basic components are needed to develop a satisfactory closed-loop control system :

- 1) the controlled variable (or any derived variable reflecting the original one as closely as possible);
- 2) the set-point for this variable (= the chosen target value specified by the user);
- 3) a controller to steer the actuator (in this case the infusion pump driving the propofol administration), comprising
 - a) an algorithm to translate a measured value for the variable to a particular action for the actuator in order to approach the target value,
 - b) a user interface to set the target value and other settings as required;
- 4) the control actuator;
- 5) a system, in this case a patient, described by a relevant model.

5.6.2: The controlled variable

Various parameters for monitoring the effect of propofol, like the median frequency of the EEG (33) or auditory evoked potentials (34) (see chapter 2), have been applied successfully as controlled variables. Recently, bispectral analysis, a new quantitative EEG analysing technique, has been proved to be accurate for measuring drug effect during anaesthesia (see

chapter 2). Therefore, we used the BIS as controlled variable in our closed-loop feed-back system for propofol administration.

5.6.3: The set-point

The set-point is the value for the controlled variable which the controller uses as its target. This target is specified by the anaesthetist and will be approached as closely as possible during the maintenance of anaesthesia; therefore an adequate individual set point for each controlled variable is very important for the accuracy of the closed-loop system (35). In our system, the set-points for the variable to be controlled are offered to the anaesthetist as the values measured after induction, in a quiet state before intubation. These set-points can be changed according to clinical needs during the course of the surgical procedure.

5.6.4: The controller

5.6.4.1: Theoretical background

There are many examples of automatically controlled devices, based on different levels of control (33, 34, 36). Most of these applications use a general PID (= proportional - integral - derivative) controller, which is widely employed in the operation of modern electronic and mechanical equipment. The required infusion rate of a drug is calculated by a straightforward mathematical formula based on the difference between the measured value (= the controlled value) and the chosen “target” value set by the user. PID controllers are essentially “ignorant”, i.e., without knowledge of the drug metabolism and the realized (potentially dangerous) concentration values. Without fine tuning for the specific situation these general controllers can be slow to establish control and can be dangerous to use because of possible oscillations. Fine tuning of a PID controller is difficult in this particular setting because the human body is very complex. This may lead to several clinical difficulties due to the complex pharmacological behaviour of the products used, interindividual pharmacological variability and patient’s reactions to external surgical stimuli.

The model-based controller may be a better alternative. Here, the administration of drugs in response to clinical effect (surgical manipulations) is based on knowledge of the fate of the drug and its effect in the human body, concentrated in a mathematical model. Several different parametric and non-parametric pharmacokinetic-dynamic (PK-PD) models have

been described in the literature as basic predetermined models for anaesthesia applications (see chapter 3).

Today, it is possible to steer the PK part and different target-controlled infusion systems (TCI) based on a PK-PD model are used in clinical practice, as already described previously in this thesis (see Chapter 3).

The application of PK-PD models to the selection of a dosage regimen for an individual patient usually assumes population mean values of the model parameters. Due to great interindividual variability, this method is difficult to use in clinical practise. The PK-PD models can be partially compensated for patient variability in pharmacological behaviour by using variables such as age and weight. The PK part of the model can be derived from individual measurements of plasma concentrations. The reduced influence of interindividual variability in these advanced models can be considered as lying in the (difficult to measure) PD part of the model (37). Trying to estimate the relationship between the effect and plasma concentration may improve the accuracy of the model for the specific patient.

The solution to this problem may be to use a model-based adaptive controller which compares the predicted values of the control signal (e.g. BIS) against the actual values of the control signal, and modifies the model parameters accordingly (35).

5.6.4.2: Specific use of the PK-PD model

In our system, we used the PK-PD model described by Sheiner et al. (38), who combined a multicompartimental PK model and the well-known Hill equilibration curve to describe the behaviour of d-tubocurarine.

As mentioned before, TCI technology was used to reduce the overall order of the system to be controlled. We have set up our system such that the closed-loop part of our controller calculates a target concentration for a TCI system that will steer for this concentration by calculating the corresponding infusion regimen. The idea behind using a TCI system in this way is that the input-output complexity can be reduced.

In other words, if we are able to steer the plasma or effect-site concentration immediately instead of the pump rate with our controller, we do not have to keep in mind the third-order behaviour of the anaesthetic in the body, as the TCI system compensates for this. This results in a much faster control than any PID controlling the infusion rate. Also, this provides an easy way of quickly checking the controller's actions, as a particular plasma or effect-site concentration of the drug can be related easily to a certain effect. Moreover, for clinical use

the controller can be forbidden to go beyond certain dangerous concentrations. In our project, we used the open-loop module from RUGLOOP ® as the PK TCI program. This TCI program is able to steer both plasma and effect-site concentration. As in the Sheiner model (38), effect-site compartment modelling was applied to connect the PK part with the PD part. For the modelling of the PD part, the sigmoid Emax-model was used (see chapter 3).

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