Towards individualised anaesthesia: A comparison between target-controlled infusion and closed-loop control

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Abstract

Individualised healthcare is the future of medicine, due to the so called inter-patient variability. The inter-patient variability involves differences in the drug response between different patients. The effect of a drug can usually be divided into pharmacokinetics (PK) and pharmacodynamics (PD). One way to individualise anaesthesia, may be to automate it using closed-loop control systems.

This thesis focused on comparing a commonly used method to calculate the dosage of propofol for anaesthesia, target-controlled infusion (TCI), with closed-loop control using a proportional-integral-derivative (PID) controller. The TCI method was implemented with quadratic programming in two ways: one to calculate the optimal propofol dosage for a reference patient, and the other to calculate an optimal propofol dosage for all patients in the patient set. The patient model set is based on a model developed by Eleveld et al, which is a PKPD model using six different covariates to cover a broad population.

The two TCI methods and the closed-loop control method were simulated on the same set of 100 patients, and the results were compared. The results show that the range of resulting depth of hypnosis after stabilisation for all patients in the set was smaller for closed-loop control than it was for the both TCI-methods. Furthermore, the simulation of closed-loop control resulted in all patients being within the desired interval, whereof the majority reached the desired depth of hypnosis. This indicates the high potential of closed-loop controlled anaesthesia in the future, and a more individualised healthcare.

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Acronyms

BIS	Bispectral index
DOH	Depth of hypnosis
EEG	Electroencephalogram
PD	Pharmacodynamics
PID	Proportional-integral-derivative
PK	Pharmacokinetics
QP	Quadratic programming
TCI	Target-controlled infusion
ZOH	Zero-order hold

1

Introduction

1.1 Background

Anaesthesia

Anaesthesia means "loss of sensation" and there are several types, where one of the most common is general anaesthesia. This is mostly used during surgeries and in intensive care units when the procedure could cause the patient too much pain. General anaesthesia, here on referred to as anaesthesia, is a state of controlled unconsciousness, meaning that the patient is medically induced to unconsciousness in a safe and reversible way. The patient should have no recollection of any events that occur during the procedure and be unable to process any information of the environment [*NHS* 2023].

Anaesthesia can be divided into hypnosis, analgesia, and neuromuscular blockade [Barash, 2009]. The main part is hypnosis, which is the temporary loss of consciousness and memory and is induced by a hypnotic drug. Propofol is a commonly used hypnotic drug and is the drug considered in this thesis. A temporary loss of memory is important due to the rare, but highly undesirable, risk of a patient awakening and feeling pain during the procedure. Apart from physical pain, the awakening may also cause the patient psychological trauma [Kim et al., 2021]. Analgesia involves giving the patient loss of sensation, which is done by analgesic drugs, such as the opioid remifentanil, affecting the nervous system. Neuromuscular blockade is a state of muscle relaxation.

An anaesthetic episode can be divided into three phases, which are the induction, maintenance, and emergence phases [Soltesz, 2013]. The induction phase is where the patient is brought to unconsciousness. This is usually done by giving a bolus dose of the chosen drug or drugs, meaning an injection of a certain dose over a short period of time. The bolus dose is often followed by a constant rate of infusion until the depth of hypnosis (DOH) has stabilised at a desired level. The induction phase is desirable to be short to minimise discomfort for the patient as well as to be resource efficient. The DOH is then continuously adjusted during the maintenance phase while the surgery takes place. The DOH will vary during the surgery,

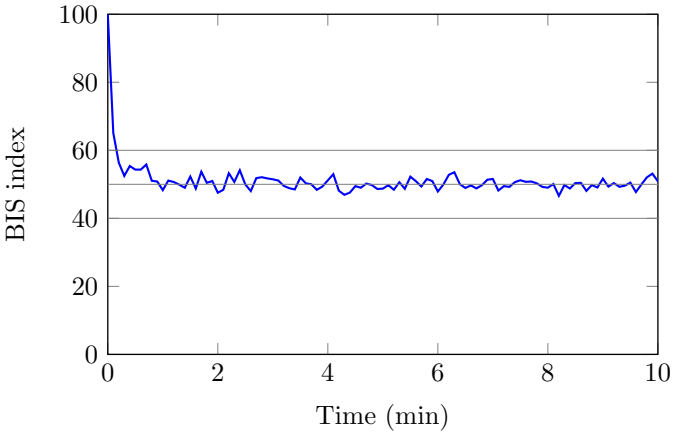


Figure 1.1 BIS value over time (blue) for a patient infused with propofol, with a desired BIS value of 50. The target BIS value for surgery is within the interval of 40 to 60.

especially when surgical disturbances occur, and must be counteracted manually by the anaesthesiologist since the disturbance is immeasurable. After the surgery is complete, the drug infusions are terminated, and the patient is brought back to consciousness, which is the emergence phase.

Depth of Hypnosis and the Bispectral Index

One commonly used index to estimate the depth of hypnosis (DOH) is the bispectral index (BIS). A sensor with four electrodes is placed on the forehead of the patient to measure and collect electroencephalogram (EEG) data [Kissin, 2000]. The EEG data is divided into different epochs using bispectral analysis and the Fourier transform of each epoch is computed. This gives a dimensionless number, which is referred to as BIS. The BIS values ranges from 100 to 0, where 100 represents full consciousness and 0 represents an iso-electric EEG, meaning there is no brain activity [Mathur et al., 2023].

A BIS value in the interval of 40 to 60 is considered appropriate for many surgical procedures, with a desired or reference value of 50. A BIS value over 60 increases the risk of anaesthesia awareness, meaning recall of sensory perceptions which can lead to anxiety and post-traumatic stress disorders [Avidan et al., 2008]. A BIS value below 40 may cause a longer emergence phase, which may lead to side effects such as nausea when the patient wakes up. The BIS of a simulated example of induction and maintenance phase is shown in Figure 1.1.

Inter-patient variability

When patients undergo anaesthesia, they will obtain different depths of hypnosis even though they have been injected with the same drug dose. This is due to the so

called inter-patient variability, which means that patients will response differently to the same drug dose, and thereby receive different depths of hypnosis.

How a patient will react to a drug depends on numerous factors, both environmental and genetic. Propofol is the anaesthetic drug considered in this thesis, which is a drug with numerous factors that have been found to influence the responses to the drug. These factors include both factors that are easy to measure, such as body weight and height, and factors that are more or less immeasurable such as the overall condition of the patient. This also includes the patient's ratio between different tissues such as fat and muscle, since different tissues equilibrate at different rates [Przybyłowski et al., 2015]. When deciding an appropriate dosage, these factors have to be considered in order to better predict how the patient will response and thereby obtaining a safer drug administration.

1.2 Aim of the Thesis

The aim of this thesis is to provide further insight on whether closed-loop controlled anaesthesia could be a good replacement for the commonly used method, target controlled infusion (TCI). Implementing closed-loop control could potentially further individualise anaesthesia, and thereby be safer for the patient.

In this thesis, three different methods to calculate the propofol dosage are implemented, where two of them are different approaches to the TCI method and the third uses closed-loop control. The first approach of the TCI method is done to investigate the patients' drug responses when the patients are given a dosage based on a specific patient. The second approach is done to be on the safe side, meaning that the dosage is calculated based on all patients where none of them should be obtain a BIS value below the appropriate interval.

The dosage calculated for each method is simulated on the same patient data set, and the resulting BIS values are compared in aspect of spread in drug response between the different patients as well as how long the induction phase is.

2

PKPD modeling

2.1 PKPD model structure

Pharmacology is the science of how drugs interact with biological systems, where pharmacokinetics (PK) and pharmacodynamics (PD) are two major disciplines. Pharmacokinetics is used to describe the absorption, distribution, metabolism, and excretion of a drug [Atkinson, 2009]. Pharmacodynamics is used to describe the biological effects that result from the interaction between drugs and biological systems [Lalonde, 2009]. Simplified, pharmacokinetics is *"what the body does to the drug"* and pharmacodynamics is *"what the drug does to the body"*.

Pharmacokinetics

The drugs are not evenly distributed throughout the body after injection. For the case of propofol, the pharmacokinetics is traditionally modelled by using a PK three-compartment model [Sahinovic et al., 2018]. The concentration of the central compartment, compartment 1 in Figure 2.1, represents the blood plasma concentration. The other two compartments, compartment 2 and 3, model the tissue that equilibrate rapidly (muscle and other well-perfused tissue) and slowly (mainly fat), respectively. The distribution and redistribution to and from the central compartment are described with the drug transfer rate constants k_{ij}, going from compartment i to j. The drug is injected intravenously, meaning that it is added to compartment 1, and is represented by u. The constant k_{10} is the elimination rate constant from compartment 1.

The drug concentration, C, in each compartment can be described by the following state-space model:

$$\dot{c} = A_{PK}c + B_{PK}u, \tag{2.1a}$$

$$A_{PK} = \begin{bmatrix} -(k_{10}+k_{12}+k_{13}) & k_{21} & k_{31} \\ k_{12} & -k_{21} & 0 \\ k_{13} & 0 & -k_{31} \end{bmatrix}, \tag{2.1b}$$

$$B_{PK} = \frac{1}{V_1}\begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix}, \tag{2.1c}$$

where V_1 is the volume of compartment 1.

Pharmacodynamics

There is a delay in the drug effect between the blood plasma and effect site, which in the case of propofol is the cerebellar cortex in the brain, which is modelled by the pharmacodynamics. The fourth compartment, effect site, in Figure 2.1 represents this time lag and the pharmacodynamics of the drug. The constant k_{e0} is both the drug transfer rate from the central compartment to the effect site, and the elimination rate from the effect site. The state-space representation of the effect site concentration is the following:

$$\dot{C}_e = k_{e0}(C_1 - C_e), \tag{2.2}$$

where C_1 is the drug concentration in the central compartment (compartment 1) and C_e is the drug concentration in the effect site [Soltesz, 2013].

The effect site concentration is related to the drug effect with a non-linear Hill function, the sigmoidal E_{max} model:

$$E = E_0 + \frac{E_{max} \cdot C_e^{\gamma}}{C_{e50}^{\gamma} + C_e^{\gamma}}, \ \gamma \geq 1. \tag{2.3}$$

E_0 is the baseline estimate in the absence of the drug, E_{max} is the maximal effect of a drug, C_e is the drug concentration, C_{e50} is the drug concentration associated with half of the maximal effect, and γ is the Hill coefficient [Salahudeen and Nishtala, 2017]. The Hill coefficient is a measure of how steep the response curve is. It is used to describe the cooperativity of binding in a molecular interaction, where a value larger than 1 indicates positive cooperativity.

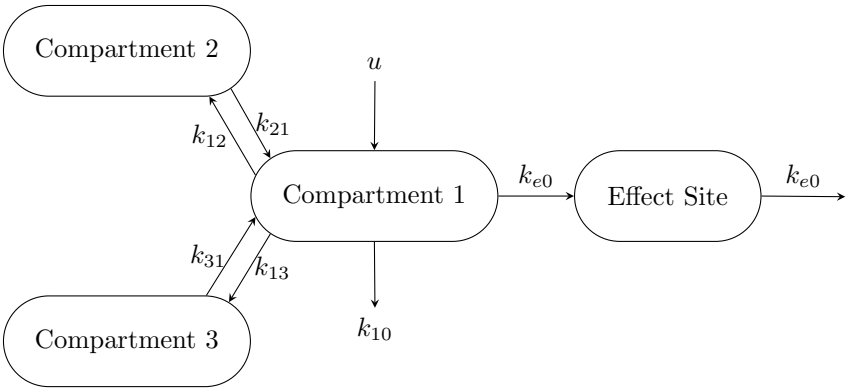


Figure 2.1 A three-compartment PK model where compartment 1, the central compartment, represents the blood, compartment 2 represents muscle and other well-perfused tissue that equilibrate rapidly, and compartment 3 represents tissue that equilibrate slowly, such as fat. u is the injected drug dose, k_{ij} is the drug transfer rates from compartment i to j and k_{10} is the elimination rate constant from compartment 1. The PD compartment, effect site, has a drug transfer rate k_{e0} from compartment 1, and this constant is also the elimination rate. The effect site concentration, C_e, is measured in the effect site compartment and is related to the drug effect with a non-linear Hill function.

2.2 The Eleveld PKPD model

When using systems that rely on pharmacokinetic-pharmacodynamic (PKPD) models, clinicians must be aware of the demographic support of the models they utilise since they are most reliable when used in patients with similar characteristics to those of the study population. In the PKPD model developed by [Eleveld et al., 2018], later referred to as the Eleveld model, data from 30 previously published studies was used. It is preferable to use covariates, i.e. variables that is considered to potentially influence the result, in order to find a model that describe the population well. The Elevel model uses six different covariates, which are age, post-menstrual age (PMA), weight, height, sex and whether there is an absence or presence of concomitant anaesthetic drugs.

Equations 2.4a - 2.4o describe the PK part of the Eleveld model and the PD part is described by Equations 2.4p - 2.4t. In the equations, the reference patient (marked by subscript ref) is a male, 35 years old, weighs 70 kg and is 1.7 metres tall. The parameters $\theta_1 - \theta_{18}$ and $\theta_{PD1} - \theta_{PD9}$ are estimated model parameters, and $\eta_1 - \eta_6$ and $\eta_{PD1} - \eta_{PD3}$ are random variables that represent the inter-patient variability that cannot be explained by covariates. All of these parameter values can be found in the original publication of [Eleveld et al., 2018].

$$f_{\text{aging}}(x) = \exp\left(x(\text{AGE} - \text{AGE}_{\text{ref}})\right) \tag{2.4a}$$

$$f_{\text{sigmoid}}(x, E50, \lambda) = \frac{x^{\lambda}}{x^{\lambda} + E50^{\lambda}} \tag{2.4b}$$

$$f_{\text{central}}(x) = f_{\text{sigmoid}}(x, \theta_{12}, 1) \tag{2.4c}$$

$$f_{\text{CLmat}} = f_{\text{sigmoid}}(\text{PMA}, \theta_8, \theta_9) \tag{2.4d}$$

$$f_{\text{Q3mat}} = f_{\text{sigmoid}}(\text{AGE} + 40_{\text{weeks}}, \theta_{14}, 1) \tag{2.4e}$$

$$f_{\text{opi}}(x) = \begin{cases} 1, & \text{absence of opiates} \\ \exp\left(x \cdot \text{AGE}\right), & \text{presence of opiates} \end{cases} \tag{2.4f}$$

$$f_{\text{Al-Sallami}} = \begin{cases} \left(0.88 + \frac{0.12}{1+(\text{AGE}/13.4)^{-12.7}}\right)\left(\frac{9270 \cdot \text{WGT}}{6680+216\text{BMI}}\right), & \text{males} \\ \left(1.11 + \frac{-0.89}{1+(\text{AGE}/7.1)^{-1.1}}\right)\left(\frac{9270 \cdot \text{WGT}}{8780+244\text{BMI}}\right), & \text{females} \end{cases} \tag{2.4g}$$

$$V_{1,\text{arterial}}(\text{L}) = \theta_1 \frac{f_{\text{central}}(\text{WGT})}{f_{\text{central}}(\text{WGT}_{\text{ref}})} \cdot \exp\left(\eta_1\right) \tag{2.4h}$$

$$V_{1,\text{venous}}(\text{L}) = V_{1,\text{arterial}}\left(1 + \theta_{17}(1 - f_{\text{central}}(\text{WGT}))\right) \tag{2.4i}$$

$$V_2(\text{L}) = \theta_2 \frac{\text{WGT}}{\text{WGT}_{\text{ref}}} f_{\text{ageing}}(\theta_{10}) \cdot \exp\left(\eta_2\right) \tag{2.4j}$$

$$V_3(\text{L}) = \theta_3 \frac{f_{\text{Al-Sallami}}}{f_{\text{Al-Sallami, ref}}} f_{\text{opi}}(\theta_{13}) \cdot \exp\left(\eta_3\right) \tag{2.4k}$$

$$CL(\text{L/min}) = \begin{Bmatrix} \theta_4, & \text{male} \\ \theta_{14}, & \text{female} \end{Bmatrix} \left(\frac{\text{WGT}}{\text{WGT}_{\text{ref}}}\right)^{0.75} \frac{f_{\text{CLmat}}}{f_{\text{CLmat, ref}}} f_{\text{opi}}(\theta_{11}) \cdot \exp\left(\eta_4\right) \tag{2.4l}$$

$$Q_{2,\text{arterial}}(\text{L/min}) = \theta_5 \left(V_2/V_{2,\text{ref}}\right)^{0.75} \left(1 + \theta_{16}(1 - f_{\text{Q3mat}})\right) \cdot \exp\left(\eta_5\right) \tag{2.4m}$$

$$Q_{2,\text{venous}}(\text{L/min}) = Q_{2,\text{arterial}} \cdot \theta_{18} \tag{2.4n}$$

$$Q_3(\text{L/min}) = \theta_6 \left(V_3/V_{3,\text{ref}}\right)^{0.75} \frac{f_{\text{Q3mat}}}{f_{\text{Q3mat, ref}}} \cdot \exp\left(\eta_6\right) \tag{2.4o}$$

$$C_{e50}(\text{g L}^{-1}) = \theta_{PD1} \cdot f_{\text{aging}} \cdot \exp\left(\eta_{PD1}\right) \tag{2.4p}$$

$$k_{e50}(1/\text{min}) = \begin{Bmatrix} \theta_{PD2}, & \text{arterial PK} \\ \theta_{PD8}, & \text{venous PK} \end{Bmatrix} \cdot \frac{\text{WGT}}{\text{WGT}_{\text{ref}}}^{-0.25} \cdot \exp\left(\eta_{PD2}\right) \tag{2.4q}$$

$$\text{BIS}_{\text{baseline}} = \theta_{PD3} \tag{2.4r}$$

$$\gamma = \begin{cases} \theta_{PD4}, & \text{for } C_e \leq C_{e50} \\ \theta_{PD9}, & \text{for } C_e > C_{e50} \end{cases} \tag{2.4s}$$

$$\text{BIS} = \text{BIS}_{\text{baseline}} \cdot \frac{C_{e50}^{\gamma}}{C_{e50}^{\gamma} + C_e^{\gamma}} + \theta_{PD5} \cdot \varepsilon \cdot \exp\left(\eta_{PD3}\right) \tag{2.4t}$$

3

Control of anaesthesia

This chapter explains two methods that can be used to control anaesthesia.

1. Target-controlled infusion (TCI), a technique to administer intravenous anaesthetics by entering a target concentration and various parameters to a computer, which calculates a dose based on the desired concentration.

2. Closed-loop control, a system where the BIS is continuously measured and used to adjust the dosage with a controller.

3.1 Target-controlled infusion

Target-controlled infusion (TCI) is an open-loop feed-forward technique commonly used to administer intravenous anaesthetics. Various parameters such as age, gender and weight are entered to a computer along with a desired target effect site concentration. The computer calculates the amount of drug that is required to achieve the target concentration by using a PKPD model [Van Poucke et al., 2004].

TCI as a QP problem

Quadratic programming (QP) is a method where a quadratic function is minimised subject to linear constraints [Yagi et al., 2023]. The TCI technique can be written as a QP problem.

Let $\boldsymbol{x}$ be the system states with x_1, x_2 and x_3 being concentrations in the three different PK compartments and x_4 being the effect site concentration. By actuating the system using zero-order hold (ZOH), meaning that the signal is converted from continuous to discrete time, the dynamics can be described as:

$$\boldsymbol{x}(k+1) = \Phi\boldsymbol{x}(k) + \Gamma u(k), \tag{3.1}$$

where Φ is the discrete version of the matrix A_{PK} in Equation 2.1b and Γ is the discrete version of the column vector B_{PK} in Equation 2.1c. $\boldsymbol{x}(0) = \boldsymbol{x}_0 = 0$ assuming

that the concentration of the drug is zero when the infusion starts. All elements of Γ are zero, except for the first element being $\gamma_1 > 0$.

The pharmacodynamics (PD) can be described by a linear first-order model with the following continuous-time transfer function:

$$X_4(s) = \frac{1}{sT_e + 1} X_1(s), \tag{3.2}$$

where $x_1 = C_1$ is the drug concentration in the plasma and $x_4 = C_e$ is the drug concentration in the effect site. The time-constant T_e determines the effect-site dynamics.

By introducing x_4 as a state variable, Equation 3.2 can be written as:

$$\dot{x}_4 = -\frac{1}{T_e} x_4 + \frac{1}{T_e} x_1, \tag{3.3}$$

which can be represented by the continuous-time state-space matrices:

$$\begin{bmatrix} A_{PD} & B_{PD} \\ C_{PD} & D_{PD} \end{bmatrix} = \begin{bmatrix} -\frac{1}{T_e} & \frac{1}{T_e} \\ 1 & 0 \end{bmatrix}. \tag{3.4}$$

The combined dynamics for PK and effect-site PD can be written as:

$$A_{PKPD} = \begin{bmatrix} A_{PK} & \mathbf{0}_{3\times 1} \\ \frac{1}{T_e} \quad 0_{1\times 2} & -\frac{1}{T_e} \end{bmatrix}, \tag{3.5a}$$

$$B_{PKPD} = \begin{bmatrix} B_{PK} \\ 0 \end{bmatrix}. \tag{3.5b}$$

The desired effect site drug concentration is the reference $\boldsymbol{r}$,

$$\boldsymbol{r} = \begin{bmatrix} r(1) & \dots & r(N) \end{bmatrix}^\top, \tag{3.6}$$

and we are in search of a drug infusion rate $\boldsymbol{u}$,

$$\boldsymbol{u} = \begin{bmatrix} u(1) & \dots & u(N) \end{bmatrix}^\top, \tag{3.7}$$

that minimises the quadratic cost J', which is calculated based on the effect site drug concentration x_4,

$$J' = \left(\sum_{k=1}^{N} (x_4(k) - r(k))^2 \right), \tag{3.8}$$

where $N > 0$ is the prediction horizon.

The concentration in each compartment i can be described by:

$$\boldsymbol{\chi}_i = \begin{bmatrix} x_i(1) & \dots & x_i(N) \end{bmatrix}^\top. \tag{3.9}$$

Equation 3.8 combined with Equation 3.9, gives the following expression for the cost:

$$J' = (\boldsymbol{\chi}_4 - \boldsymbol{r})^\top D(\boldsymbol{\chi}_4 - \boldsymbol{r}) = \boldsymbol{\chi}_4^\top D\boldsymbol{\chi}_4 - 2\boldsymbol{r}^\top D\boldsymbol{\chi}_4 + \boldsymbol{r}^\top D\boldsymbol{r}, \tag{3.10}$$

where

$$D = \text{diag}(\begin{bmatrix} 1 & \dots & 1 \end{bmatrix}). \tag{3.11}$$

Equation 3.1 can be rewritten as

$$\begin{aligned} \boldsymbol{x}(1) &= \Phi\boldsymbol{x}_0 + \Gamma u(1), \\ \boldsymbol{x}(2) &= \Phi^2\boldsymbol{x}_0 + \Phi\Gamma u(1) + \Gamma u(2), \\ &\vdots \\ \boldsymbol{x}(N) &= \Phi^N\boldsymbol{x}_0 + \Phi^{N-1}\Gamma u(1) + \dots + \Gamma u(N). \end{aligned} \tag{3.12}$$

$\boldsymbol{\chi}_4$ can then be expressed as an explicit function of $\boldsymbol{u}$

$$\begin{aligned} \boldsymbol{\chi}_4(1) &= \Phi_4^1\boldsymbol{x}_0 + \Phi_4^0\Gamma u(1), \\ \boldsymbol{\chi}_4(2) &= \Phi_4^2\boldsymbol{x}_0 + \Phi_4^1\Gamma u(1) + \Phi_4^0\Gamma u(2), \\ &\vdots \\ \boldsymbol{\chi}_4(N) &= \Phi_4^N\boldsymbol{x}_0 + \Phi_4^{N-1}\Gamma u(1) + \dots + \Phi_4^0\Gamma u(N), \end{aligned} \tag{3.13}$$

which can be rewritten as

$$\boldsymbol{\chi}_4 = \underbrace{\begin{bmatrix} \Phi_4^1 \\ \vdots \\ \Phi_4^N \end{bmatrix}}_{E_4} \boldsymbol{x_0} + \underbrace{\begin{bmatrix} \Phi_4^0\Gamma & & & \\ \Phi_4^1\Gamma & \Phi_4^0\Gamma & & \\ \vdots & \vdots & \ddots & \\ \Phi_4^{N-1}\Gamma & \Phi_4^{N-2}\Gamma & \dots & \Phi_4^0\Gamma \end{bmatrix}}_{F_4} \boldsymbol{u}, \tag{3.14}$$

where E_4 and F_4 can be recursively computed from $\boldsymbol{x}_0$, Φ, and Γ using Equation 3.13.

By combining Equation 3.14 and 3.10, and removing the terms independent of $\boldsymbol{u}$, we obtain

$$J(\boldsymbol{u}) = \frac{1}{2}\boldsymbol{u}^\top \underbrace{F_4^\top DF_4}_{H}\boldsymbol{u} + \boldsymbol{x}_0^\top \underbrace{E_4^\top DF_4}_{\boldsymbol{f}_0^\top}\boldsymbol{u} - \underbrace{\boldsymbol{r}^\top DF_4}_{\boldsymbol{f}_1^\top}\boldsymbol{u}, \tag{3.15}$$

which can be rewritten as

$$J(\boldsymbol{u}) = \frac{1}{2}\boldsymbol{u}^\top H\boldsymbol{u} + \boldsymbol{f}^\top \boldsymbol{u}, \tag{3.16}$$

where

$$\boldsymbol{f} = \boldsymbol{f}_0\boldsymbol{x}_0 - \boldsymbol{f}_1. \tag{3.17}$$

When implementing this, $\boldsymbol{f}_0$, $\boldsymbol{f}_1$ and H can be pre-computed since it is a linear time-invariant (LTI) system. All that has to be done in each iteration is to update $\boldsymbol{f}$ using Equation 3.17 to update the cost function in Equation 3.16

In order for the patient to not get a too high effect site concentration, it needs to be limited. This can be done by introducing an upper bound $C_{e,\max}$, which is the concentration corresponding to a BIS value of 40. The constraint on the effect site concentration x_4 can be expressed as

$$F_4\boldsymbol{u} \preccurlyeq \boldsymbol{C}_{e,\max} - E_4\boldsymbol{x}_0. \tag{3.18}$$

Since the infusion pump only can add drug and not retract it, it yields that $u \geq 0$, which can be expressed as

$$-I_N\boldsymbol{u} \preccurlyeq \boldsymbol{0}_N, \tag{3.19}$$

where

$$I_N = \text{diag}(\begin{bmatrix}1 & \dots & 1\end{bmatrix}). \tag{3.20}$$

Combining the two constraints, the following joint linear constraint can be formulated

$$\underbrace{\begin{bmatrix}-I_N \\ F_4\end{bmatrix}}_{A}\boldsymbol{u} \preccurlyeq \underbrace{\begin{bmatrix}\boldsymbol{0}_N \\ \boldsymbol{C}_{e,\max} - E_4\boldsymbol{x}_0\end{bmatrix}}_{\boldsymbol{b}}. \tag{3.21}$$

The calculated matrices for H, $\boldsymbol{f}^\top$, A and $\boldsymbol{b}$ can be inserted in the Matlab function *quadprog* which returns the wanted vector $\boldsymbol{u}$ containing the dosage.

This can also be done for m patients simultaneously. If H_k and $\boldsymbol{f}_k^\top$ define the objective for patient k, the joint objective is defined by

$$H = \sum_{k=1}^{m} w_k H_k, \tag{3.22a}$$

$$\boldsymbol{f}^\top = \sum_{k=1}^{m} w_k \boldsymbol{f}_k^\top, \tag{3.22b}$$

where w_k is the relative weight for each patient, and the sum of all weights are 1. A_k and $\boldsymbol{b}_k$ define the constraints for patient k. Constraints can be stacked, giving the following equations

$$A = \begin{bmatrix}A_1^\top & \dots & A_m^\top\end{bmatrix}^\top, \tag{3.23a}$$

$$\boldsymbol{b} = \begin{bmatrix}\boldsymbol{b}_1^\top & \dots & \mathbf{b}_m^\top\end{bmatrix}^\top. \tag{3.23b}$$

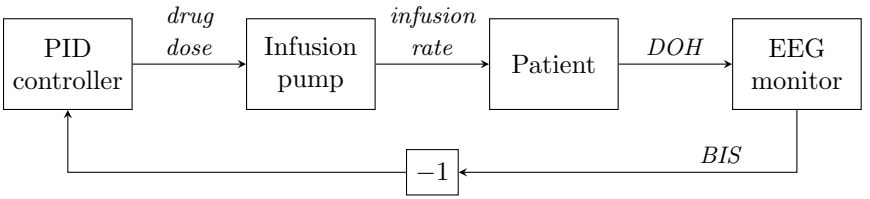


Figure 3.1 A schematic overview of closed-loop control for anaesthesia, with a PID controller that calculates the drug dose based on a reference patient, an infusion pump that inject the drug to the patient, whom is in a certain depth of hypnotic which is measured by an EEG monitor, and the calculated BIS is sent to the PID controller for adjustment of the dosage.

These matrices, H, $\boldsymbol{f}^\top$, A and $\boldsymbol{b}$, can then be inserted in the Matlab function *quadprog* which will return a vector $\boldsymbol{u}$ that satisfies the constraints for the m patients.

3.2 Closed-loop control

Closed-loop control, or feedback control, is a control system that continuously monitors the output or performance of a system and adjusts the input or control signal accordingly to maintain a desired or target value. It involves a feedback loop where the output of the system is compared to a reference or set-point value, and the difference between the two, known as the error signal, is used to generate the control action [Sharma, 2011].

Closed-loop control of anaesthesia means that the dosing of the drug, in this case propofol, is based on feedback from an estimate of the depth of hypnosis. The electroencephalogram (EEG) of the patient is continuously measured, and a controller calculates an appropriate infusion rate of the drug depending on the current EEG measurement and calculated BIS. A schematic view of a closed-loop control system for anaesthesia is shown in Figure 3.1.

The controller considered in this thesis is a proportional-integral-derivative (PID) controller. The PID controller is considered to be the most classical option when choosing a control method for control of anaesthesia, due to its accuracy, stability and tuning flexibility [Padula et al., 2017]. The ideal form of a PID controller can be written as:

$$G(s) = K_p\left(1 + \frac{1}{T_i s} + T_d s\right), \tag{3.24}$$

where K_p is the controller gain, T_i is the integrator parameter, and T_d is the derivative parameter. When using a controller with a derivative part a filter is needed. The filter is inserted before the PID controller and had the following expression:

$$F(s) = \frac{1}{T_f^2 s^2 + 2\zeta T_f s + s}, \tag{3.25}$$

where T_f is the filter time constant and ζ is a dimensionless dampening constant.

The values used in this thesis were $K_p = 1.04$ mg/kg/min, $T_i = 314$ s, $T_d = 65.1$ s, $T_f = 15.3$ s and $\zeta = 0.71$ and were taken from [Gonzalez-Cava et al., 2021]. To mimic measurement noise, white noise with samples drawn from the normal distribution $\mathcal{N}(0,9)$ (taken from [Soltesz, 2013]), is added to the BIS signal before it is sent to the PID controller as feedback.

4

Method

This thesis focuses on investigating how three different methods for computing the dosage of propofol are affected by the inter-patient variability. The results are evaluated and compared. In order to be able to do an accurate comparison, the same simulated 100 patients, here on referred to as set of patients, are used in the simulations of the three methods. The simulations are set to 20 minutes in order to see how the patients react to the propofol dosage over time.

The three different methods for computing the dosage of propofol are listed below, and the terms in parenthesis will be used as abbreviations. Two of the methods are different approaches of TCI, where the first is done to fit a specific patient, meaning that this patient should obtain the desired BIS index of 50, and it is investigated how well other patients response to the same dosage. The second TCI method takes all patients in consideration when the dosage is computed, which is done to investigate how well it can optimise the dosage while fulfilling the limitation of no patient obtaining a BIS index below 40.

1. **Dose based on a reference patient (Reference patient).** The dosage is computed to be optimal for a reference patient (see Section 4.1) to reach a BIS index of 50, while restricting the effect site concentration to not get higher than the concentration corresponding to a BIS value of 40. To evaluate how this dosage curve affects a variety of patients, we simulate two different data sets of patients with the obtained dose.

2. **Dose based on all patients in the model set (Multi-patient).** A single dosage is computed to be optimal for all patients in the data set, while restricting the effect site concentration so none of the patients reach a BIS value below 40.

3. **Dose based on closed-loop control (Closed-loop).** A PID regulator and closed-loop feedback is used to calculate an individual dosage for each patient in the data set. The current BIS is measured and used with negative feedback. White noise is added to the BIS signal.

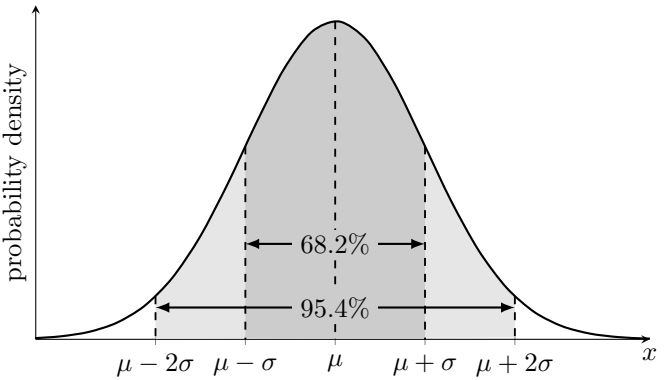


Figure 4.1 Visualisation of the normal distribution with 1 and 2 standard deviations σ from the mean μ.

4.1 Patient model set

All patients used in the simulations are 35 year old males, that are 1.7 metres tall and weigh 70 kg, meaning that the covariates in the Eleveld model (Section 2.2) are the same for all patients. The patient with all parameters η in Equations 2.4a-2.4t put to zero is referred to as *reference patient*. To create a data set of several patients, the values for η are drawn from each parameter's normal distribution.

In order to prevent outliers, meaning a patient with large positive or negative values of η, from affecting the result too much, the drawing from the normal distributions are limited to be within $\mathcal{N}(0,\sigma)$. The standard deviation σ for each η, along with the mean for each PKPD parameter are presented in Table 4.1. Since the standard normal distribution is symmetric, this means that approximately 68.2% of the possible values of each η is included in $\mathcal{N}(0,\sigma)$.

To investigate how much outliers can affect the resulting effect site concentration, and thereby the BIS, the calculation for dose based on the reference patient was simulated on both the set of patients described above as well as on an additional set of patients. For this set, the choosing from the normal distributions are limited to be within $\mathcal{N}(0,2\sigma)$, covering approximately 95.4% of the possible values for each η. Figure 4.1 shows the visualisation of a normal distribution with 1 and 2 standard deviations marked out.

This thesis considers nine variables from the Eleveld model that affect the inter-patient variability, which are η_{1-6} and $\eta_{PD1-PD3}$ described in Section 2.2. These variables affect one PKPD parameter each, and the parameters are the three compartment volumes V_1, V_2 and V_3, the clearances CL from the central compartment, Q_2 and Q_3 from compartment 2 and 3, the effect site compartment concentration associated with 50% drug effect C_{e0}, the rate constant between the central and effect compartment k_{e0} and the residual error for the BIS value. Table 4.1 shows the parameters, their mean value as well as the standard deviation.

Table 4.1 The mean and standard deviation for the nine parameters which are affected by the variables η.

Parameter	mean	σ
V_1 [L]	6.28	0.78
V_2 [L]	25.50	0.75
V_3 [L]	272.89	0.77
CL [L/min]	1.79	0.51
Q_2 [L/min]	1.91	0.59
Q_3 [L/min]	1.11	0.46
C_{e50} [g/L]	3.08	0.49
k_{e0} [1/min]	0.14	0.84
Residual error for BIS	8.03	0.48

4.2 Dose based on a reference patient

To calculate a dose based on a reference patient means that the dosage should result in the desired value of BIS, in this case 50, for this specific patient. What's interesting is to investigate how well the same dosage works on other patients, i.e. how they respond to the dosage and many of them obtain a BIS value within the desired interval.

The model parameters for the reference patient described in Section 4.1 were calculated using Equations 2.4a-2.4t from the Eleveld model, with all values of η set to zero. Then, two data sets of patients were created. The first one had values of η drawn from $\mathcal{N}(0,\sigma)$, and the second from $\mathcal{N}(0,2\sigma)$, as described in Section 4.1.

The Matlab function *quadprog* with parameters for input obtained as described in Section 3.1, was used to get the control signal $\mathbf{u}$, i.e. the propofol dosage, needed for the reference patient to reach a BIS value of 50 without going below 40 due to the constraint put on the effect site concentration.

The control-signal $\mathbf{u}$ was then used when simulating the patient response for each patient in the two data sets using the Matlab function *lsim*. The simulation resulted in the effect site concentrations over time, giving the BIS values at each time point using Equation 2.4t. To investigate how the patients' values of BIS are affected in the long run, the BIS values in steady state is of interest.

4.3 Dose based on all patients in model set

To consider all patients in the data set when calculating the dosage means that the constraints are applied to all patients, which should be safer in the aspect of no patient going below the desired BIS interval. This is done to see whether this results in more patients obtaining a BIS value within the desired interval.

The Matlab function *quadprog* was used with input obtained from all patients in the patient data set as described in Equations 3.22 and 3.23 to obtain the control-signal **u**. This control-signal, i.e. the dosage of propofol, should in theory result in all patients reaching a BIS value of 50, with no patient getting a BIS value below 40 due to the constraint put on the effect site concentration.

The simulation and calculation of the resulting BIS index for each patient were then done as in Section 4.2.

4.4 Dose based on closed-loop control

In theory, calculating the dose individually for each patient with a closed-loop system should result in all patients obtaining the desired value of BIS. Apart from investigating the resulting BIS values with white noise added to it, it is also interesting to see whether this method would result in an induction phase of other length than for the two TCI-methods.

A closed-loop system with a PID-regulator as shown in Figure 3.1, including filter and additive white noise drawn from $\mathcal{N}(0,9)$, was implemented in Simulink using equations and parameter values described in 3.2.

The system was given a reference BIS value of 50, and the feedback signal was the current BIS value, which was calculated from the effect-site concentration with the added noise.

The system was simulated on each patient in the patient data set with their corresponding infusion rate.

5

Results

The results are presented in four different sections. One each for the different methods for computing a propofol dosage described in Section 4.2-4.4. Finally, we present a comparison for the three methods.

5.1 Dose based on a reference patient

Figure 5.2 shows the BIS values over time for the patients with the variables η drawn from the normal distributions $\mathcal{N}(0, \sigma)$ and $\mathcal{N}(0, 2\sigma)$, respectively, as well as the propofol dosage given to all patients during the simulation. The two subfigures for the BIS values include, for each time point, the median, the interval for 50% of the patients with limits being the 25^{th} and 75^{th} percentiles as well as the interval containing the BIS values for all patients. This is included to give an overview of all the obtained BIS values.

After stabilisation, the values for BIS varied among the simulated patients. As can be seen in both Figure 5.2 a and b, the reference patient reached a BIS value of 50 after the induction phase. The induction phase lasted for approximately 2 minutes for the reference patient, and closer to 3 minutes for the patients in the data set.

Figure 5.1 shows two histograms for the BIS values for all patients after 20 minutes of simulation, one for each set of patients. Figure 5.7 contains a box-plot for the two sets of patients showing the BIS values for each set of patients after 20 minutes of simulation.

The 0^{th}, 25^{th}, 50^{th}, 75^{th} and 100^{th} percentiles of obtained BIS values after 20 minutes of simulation are presented in Table 5.1. The difference between the patient with lowest and highest BIS, i.e. the difference between the 0^{th} and the 100^{th} percentiles, were 43 for the first patient set and 69 for the second. For the first patient set, 13% of the patients were below a BIS value of 40 and 13% were above 60, meaning that 74% of the patients were within the appropriate interval of 40-60 described in Section 1.2. For the second patient set, 14% of the patients were below a BIS value of 40 and 32% were above 60, meaning that 54% of the patients were within the interval of 40-60.

Table 5.1 The 0^{th}, 25^{th}, 50^{th}, 75^{th} and 100^{th} percentiles for the BIS value after 20 minutes of simulation with a dosage calculated based on a reference patient. The simulation was done for the two sets of patients, where the variables η had been drawn from the normal distributions $\mathcal{N}(0,\sigma)$ and $\mathcal{N}(0,2\sigma)$, respectively.

	min	25^{th}	50^{th}	75^{th}	max
$\mathcal{N}(0,\sigma)$	31.2	42.6	50.3	57.3	73.8
$\mathcal{N}(0,2\sigma)$	17.2	44.0	56.8	65.8	86.5

5.2 Dose based on all patients in model set

Figure 5.4 shows the BIS values over time for the patients in the patient set used in the simulation and the propofol dosage given to all patients during the simulation. Figure 5.3 shows a histogram for the BIS values for all patients after 20 minutes of simulation.

The 0^{th}, 25^{th}, 50^{th}, 75^{th} and 100^{th} percentiles after 20 minutes of simulation are presented in Table 5.1. The difference between the patient with lowest and highest BIS were 48. 2% of the patients were below a BIS value of 40 and 62% were above 60, meaning that 36% of the patients were within the appropriate interval of 40-60.

Table 5.2 The 0^{th}, 25^{th}, 50^{th}, 75^{th} and 100^{th} percentiles for the BIS value after 20 minutes of simulation with the dosage calculated based on all patients in the model set.

min	25^{th}	50^{th}	75^{th}	max
37.3	52.8	63.8	73.4	85.5

5.3 Dose based on closed-loop control

Figure 5.6 shows the BIS values over time for the patients in the patient set used in the simulation. As can be seen in the figure, the induction phase lasts for approximately 2 minutes.

Figure 5.5 shows a histogram for the BIS values for all patients after 20 minutes of simulation. The 0^{th}, 25^{th}, 50^{th}, 75^{th} and 100^{th} percentiles after 20 minutes of simulation are presented in Table 5.1. The difference between the patient with lowest and highest BIS was 9. As can be seen in both 5.6 and 5.5, all of the simulated patients have a BIS value within the appropriate interval of 40-60 described in Section 1.2 with the exception of a few patients briefly going below 40 during the induction phase.

Table 5.3 The 0^{th}, 25^{th}, 50^{th}, 75^{th} and 100^{th} percentiles for the BIS values after 20 minutes of simulation when the dosage is calculated by using a measured BIS as feedback in closed-loop control.

min	25^{th}	50^{th}	75^{th}	max
45.7	49.1	50.0	50.9	54.4

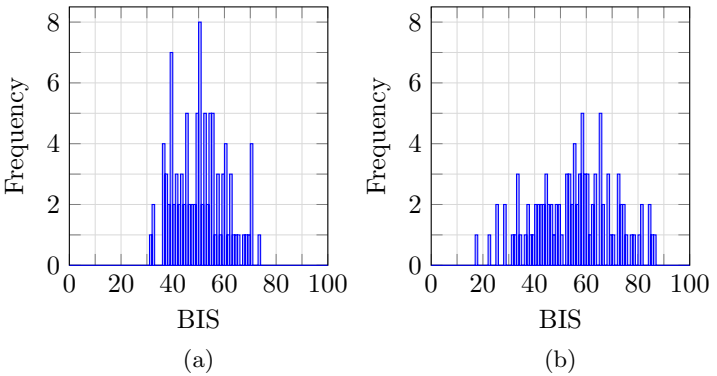
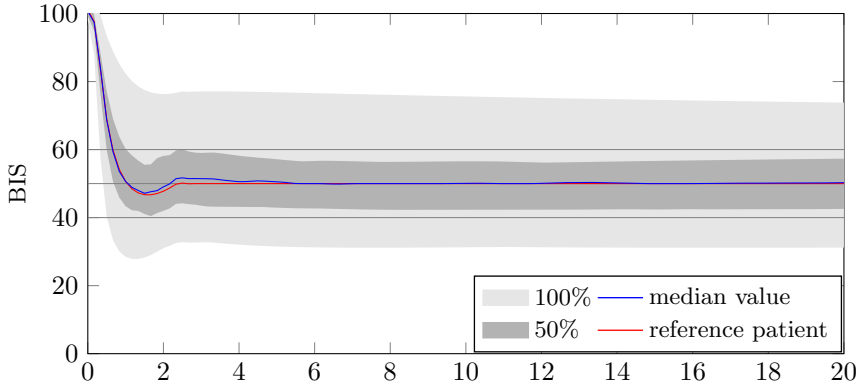


Figure 5.1 Histogram of the BIS values after 20 minutes of simulation for the method where the dosage is calculated based on a reference patient. The same dosage is given to 100 simulated patients from the Eleveld model with the values of η drawn from a normal distribution $\mathcal{N}(0,\sigma)$ in (a) and from $\mathcal{N}(0,2\sigma)$ in (b).

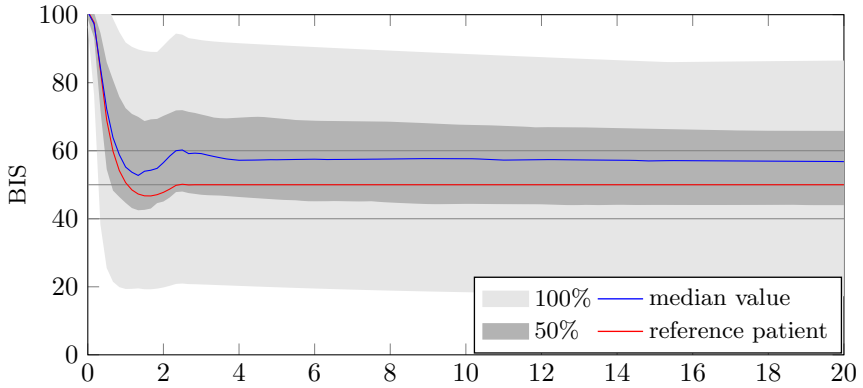
5.4 Comparison

Figure 5.8 shows a box-plot of the BIS values after 20 minutes of simulation for the three different methods of calculating the dosage of propofol. As can be seen in the figure, only the closed-loop calculated dosage satisfies in BIS values during the maintenance phase to be within the interval of 40 to 60 for all patients.

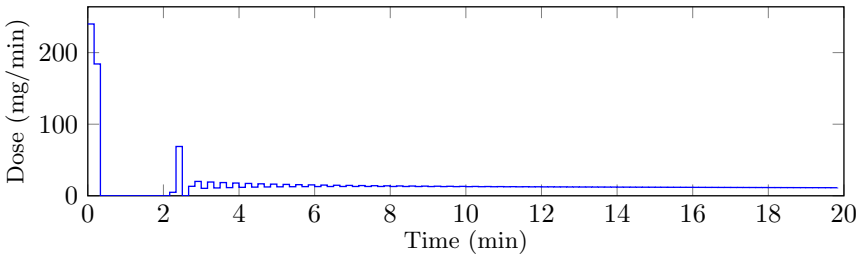
During the induction phase, the TCI-method for reference patient resulted in approximately 25% of the patients obtaining a BIS value below 40, the multi-patient TCI-method resulted in no patients going below 40 and closed-loop resulted in a few patients briefly going below 40.



(a) Simulated BIS with values of η drawn from $\mathcal{N}(0, \sigma)$



(b) Simulated BIS with values of η drawn from $\mathcal{N}(0, 2\sigma)$



(c) Dosage used for both simulations

Figure 5.2 BIS values and the propofol dosage over time for the method where the dosage is calculated based on a reference patient. The same dosage (c) is given to 100 simulated patients from the Eleveld model with the values of η drawn from a normal distribution $\mathcal{N}(0, \sigma)$, shown in (a) and from $\mathcal{N}(0, 2\sigma)$ in (b). The upper plot includes the intervals for 100% and 50% of the simulated patients as well as curves for the reference patient and the median value.

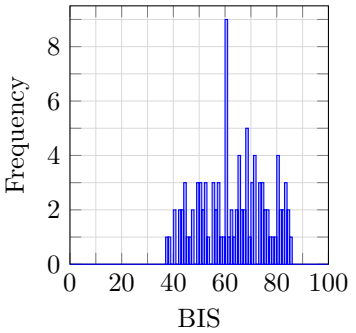


Figure 5.3 The same dosage is given to 100 simulated patients from the Eleveld model with the values of η drawn from a normal distribution $\mathcal{N}(0, \sigma)$. The dosage is calculated so all patients obtain a drug response that fulfils the constraints as described in the method in Section 4.3. The histogram shows the BIS values after 20 minutes of simulation.

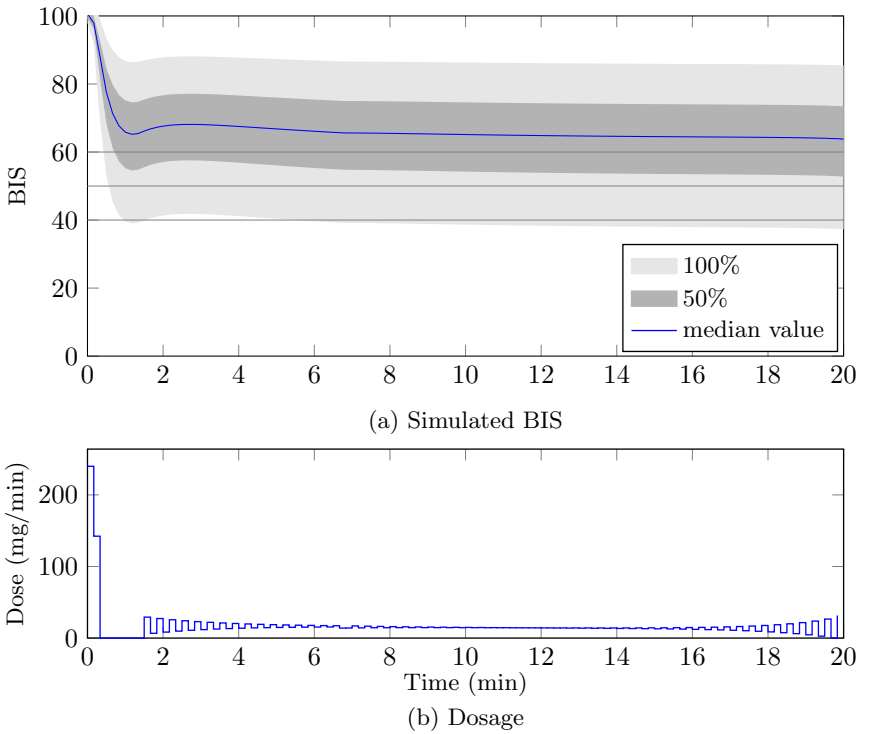


Figure 5.4 The same dosage is given to 100 simulated patients from the Eleveld model with the values of η drawn from a normal distribution $\mathcal{N}(0, \sigma)$. The dosage is calculated so all patients obtain a drug response that fulfils the constraints as described in the method in Section 4.3. The upper plot (a) shows BIS values over time, including the intervals for 100% and 50% of the simulated patients as well as a curve for the median value. The lower plot (b) shows the propofol dosage given to all patients during the simulation.

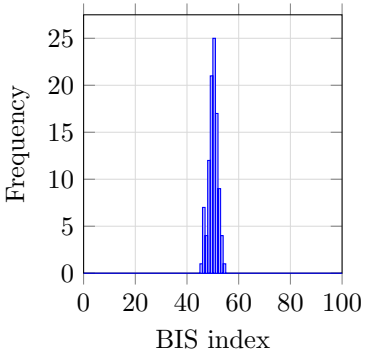
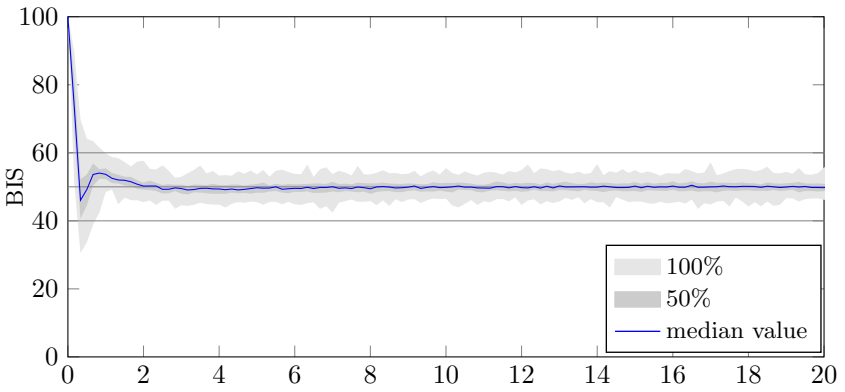
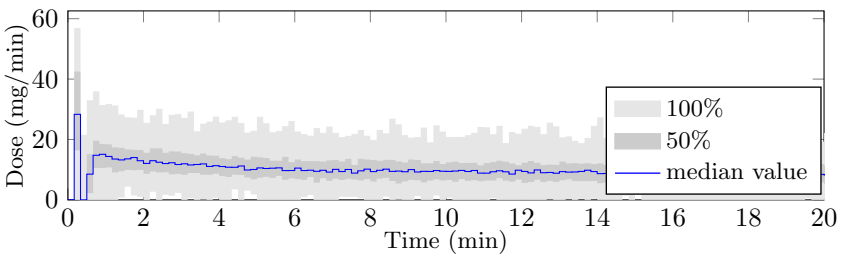


Figure 5.5 The dosage is calculated with a closed-loop system for each patient individually as described in Section 4.4. The data set of patients is simulated from the Eleveld model with the values of η drawn from a normal distribution $\mathcal{N}(0,\sigma)$. The histogram shows the BIS values after 20 minutes of simulation.



(a) Simulated BIS



(b) Dosage

Figure 5.6 BIS values over time for 100 simulated patients from the Eleveld model with the values of η drawn from a normal distribution $\mathcal{N}(0,\sigma)$. The propofol dosage is calculated individually for each patient by using the current BIS value as feedback in a closed-loop control system, as described in Section 4.4. White noise drawn from the normal distribution $\mathcal{N}(0,9)$ is added to the BIS signal. The plot shows BIS values over time, including the intervals for 100% and 50% of the simulated patients as well as a curve for the median value.

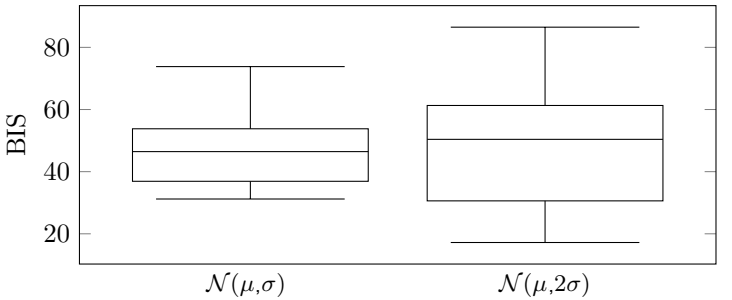


Figure 5.7 Box plot illustrating the distribution of BIS values after 20 minutes of simulation of the TCI-method for reference patient for two different data sets of patients, as described in Section 4.2. The left represents the patient data set with all values of η drawn from $\mathcal{N}(0,\sigma)$, and the right with all values of η drawn from $\mathcal{N}(0,2\sigma)$.

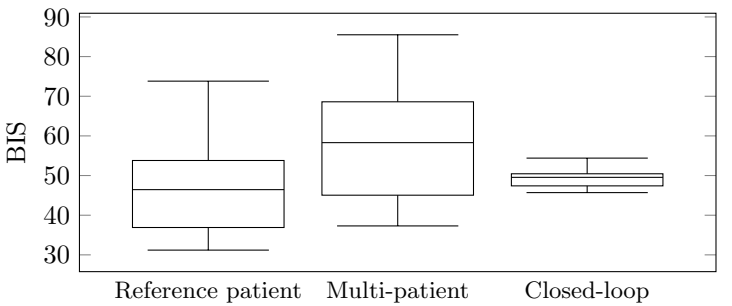


Figure 5.8 Box plot showing the BIS values after 20 minutes for all patients with the dosage calculated with the three different methods: dose based on a reference patient, on all patients in model set and on closed-loop control.

6

Discussion

In this thesis, three different methods to calculate the propofol dosage were implemented. The thesis aimed to provide further insight on whether closed-loop controlled anaesthesia could be a good replacement for the commonly used method, target controlled infusion (TCI).

When comparing the results from the three different methods, it is clear to say that closed-loop control results in a significantly smaller range of BIS values for all patients, and all patients are within the desired interval of 40-60 during the maintenance phase and the induction phase is shorter.

For the first TCI-method, where the propofol dosage is calculated to be optimal for a reference patient with no inter-patient variability included, approximately three quarters of the patients were within the desired interval of a BIS value of 40 to 60. However, the variables for the inter-patient variability were limited to be drawn from the normal distribution $\mathcal{N}(0, \sigma)$. This means that approximately 68.2% of the possible values for each variable were included in the simulations of the patients. In the patient model used in this thesis, nine covariates for inter-patient variability from the Eleveld model were included. Nine values, each drawn from a separate normal distribution $\mathcal{N}(0, \sigma)$, means that only approximately 3.2% of the theoretical possible patients were included when 100 patients were randomly chosen to be included in the set of patients. For the second set of patients, where the nine covariates were drawn from the normal distributions $\mathcal{N}(0, 2\sigma)$, approximately 65.5% of the theoretical possible patients were possible to be chosen. Therefore, it is more representative of the reality to use a larger span of the normal distributions. The resulting BIS values for this second set of patients were considerably worse compared to the first set, since only 54% of the patients had a BIS value within the desired interval after stabilisation compared to 74% for the first set.

As described in Section 1.1, the interval of 40-60 is considered appropriate due to the eventual consequences if a patients obtains a BIS value below 40 or over 60. In particular a BIS value over 60, which was the case for 13% and 32% of the patients in the two data sets, could lead to the patient gaining awareness during the surgery.

In the second TCI-method, where all patients of the data set are considered when the propofol dosage is calculated, the interval of the resulting BIS index got slightly wider than for the first method as the difference between lowest and highest value of BIS was 48 compared to the difference being 43 for the first method. However, the most significant difference between the two methods is the median value and number of patients that reached a BIS value within the desired interval. The first TCI method had a median value of 50.3, while for the second TCI method the median value were 63.8, meaning that more than half of the patients were not sufficiently anaesthetised. Only 36% of the patients were within the desired interval of a BIS value of 40-60. This method was supposed to result in no patients obtaining a BIS value lower than 40. However, after 20 minutes there is 2% below, where the lowest is 37.3. The constraints were based on the effect site concentration, meaning that the patients going below 40 most likely is due to the computational transition from effect site concentration to BIS.

In the third method, when a closed-loop system with a PID controller were implemented to calculate the dosage, none of the patients were outside the interval of a BIS value of 40 to 60 after stabilisation, even though noise was added. After 20 minutes of simulation, the difference between the lowest and highest value of BIS was approximately 9, which is significantly lower than for the two TCI-methods. During the induction phase, a few patients go below 40 for a short period of time. This is most likely due to the added noise, and it can be seen that the system quickly adapt so they get closer to 50.

All three methods have their advantages and disadvantages. The first TCI-method works perfectly for the patient the dosage was calculated to be optimal for. However, the results show that new patients have a high risk of falling outside the appropriate range, and it is not possible to predict whether they are going to obtain a BIS value that is too low or too high. The second TCI-method is better in the aspect that no patient gets too deeply sedated, but the majority received a BIS value above 60. This is due to the constraints considered when calculating the dosage, i.e. the patient with the greatest drug response will limit the dosage.

Thus, TCI is not very reliable when used by itself. However, in practice an anaesthetist will monitor the patient and can adjust the dosage when the patient shows signs of being too heavily or lightly sedated. The anaesthetist can also adjust the dosage before surgical stimuli occur. This is an advantage since when surgical stimuli occur, the patient will need a larger dose to stay at the same depth of hypnosis. When the anaesthetist counteract by adjusting the dosage the risk of the patient gaining awareness is lowered. TCI is also a cheap and considerably easy method to implement.

The equipment and implementation needed for closed-loop controlled anaesthesia is expensive. Also, due to it being a medical technique, there is a lot of regulatory aspects that need to be considered. It is a long process with research, simulations, clinical trials and more before it potentially could be a commonly used technique. However, if the implementation is successful, closed-loop controlled anaesthesia

could have several advantages. The dosage would be more precise and individualised, which means that both the induction and the emergence phases could be shorter, and the risk of getting side effects such as nausea during the emergence phase would thereby be reduced. Shorter time under anaesthesia would also lead to faster patient recovery and reduced healthcare cost. Closed-loop could also lead to more efficient use of anaesthetic drugs, including propofol. Propofol can be considered a rather expensive drug, especially in the aspects of the large amounts needed during longer surgical procedures. The patient safety could be enhanced since drug-related errors caused by the human factor could be prevented.

6.1 Limitations

This project has, as all studies do, its limitations. One limitation is the relatively small set of patients used. In order for the implemented method to be able to calculate a dosage for all patients combined, a limit of 100 patients was needed due to the power of the computer used. It is also important to keep in mind that the patients used had the same gender, age, height and weight as the reference patient used in the Eleveld model, meaning that using a completely different patient could give different results even though the model was developed to work on a broad population. Also, the limiting of the values of η to be drawn from $\mathcal{N}(\mu,\sigma)$ and $\mathcal{N}(\mu,2\sigma)$, means that not all theoretical possible patients are included.

6.2 Future work

The result from this thesis suggests that closed-loop controlled anaesthesia could be a safer and more individualised method than the traditionally used TCI. One way to investigate this further is to include a larger and broader population in the simulations, both by the mean of not limiting the drawing the values of η from the standard deviations as well as using patients of different gender, age, height and weight.

Another way to continue this work is to do simulations with a control system which includes infusion of an analgesic drug, since anaesthetics and analgesics often are combined. It is also important to investigate how closed-loop would handle surgical stimuli.

As of all medical equipment, there is a lot of regulatory aspects. This means that a lot of research and simulations have to be done to ensure the safety, before the method could be tested on actual patients.

7

Conclusion

This thesis aimed to provide further insight on closed-loop controlled anaesthesia and whether it could be a possible method to individualise anaesthesia. The results from the simulations done in this project show that closed-loop controlled anaesthesia result in all patients stabilising within the desired interval due to precise and individualised dosage, and the difference between largest and smallest value of BIS was significantly smaller than for the two TCI-methods. This is due to the closed-loop system being able to handle the differences in drug response between different patients better thanks to the adjustment based on the feedback. Closed-loop controlled anaesthesia could potentially result in safer anaesthesia due to the individualised dosage, it could lead to more efficient use of resources and shorten the time for the induction and maintenance phases, leading to less side effects.

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Title and subtitle

Towards individualised anaesthesia: A comparison between target-controlled infusion and closed-loop control

Abstract

Individualised healthcare is the future of medicine, due to the so called inter-patient variability. The inter-patient variability involves differences in the drug response between different patients. The effect of a drug can usually be divided into pharmacokinetics (PK) and pharmacodynamics (PD). One way to individualise anaesthesia, may be to automate it using closed-loop control systems.

This thesis focused on comparing a commonly used method to calculate the dosage of propofol for anaesthesia, target-controlled infusion (TCI), with closedloop control using a proportional-integral-derivative (PID) controller. The TCI method was implemented with quadratic programming in two ways: one to calculate the optimal propofol dosage for a reference patient, and the other to calculate an optimal propofol dosage for all patients in the patient set. The patient model set is based on a model developed by Eleveld et al, which is a PKPD model using six different covariates to cover a broad population.

The two TCI methods and the closed-loop control method were simulated on the same set of 100 patients, and the results were compared. The results show that the range of resulting depth of hypnosis after stabilisation for all patients in the set was smaller for closed-loop control than it was for the both TCI-methods. Furthermore, the simulation of closed-loop control resulted in all patients being within the desired interval, whereof the majority reached the desired depth of hypnosis. This indicates the high potential of closed-loop controlled anaesthesia in the future, and a more individualised healthcare.

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