Doctoral Thesis

Modelling and control in anaesthesia from design to validation

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Modelling and Control in Anaesthesia
– From Design to Validation –

A dissertation submitted to the
Swiss Federal Institute of Technology Zurich

for the degree of
Doctor of Technical Sciences

presented by
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Patient safety and cost reduction as a cause of minimized drug consumption and shortened post-operative recovery phases are part of the main issues to motivate automation in anaesthesia. The anaesthetist has four main objectives while maintaining anaesthesia, these are to provide hypnosis, analgesia, skeletal muscle relaxation and artificial ventilation. For all objectives a solution to automate these routine tasks is described including the clinical tests on patients undergoing general anaesthesia for elective surgery.

A first focus is on the development of a framework for the design of closed-loop controllers. This includes a modelling framework based on a physiologically based model. With the same model structure the patient’s reaction to different anaesthetic drugs can be estimated, which allows to design artefact and robust controllers. A crucial part in introducing any automatic system is the appropriate testing of the system prior to the application in the actual environment. Therefore, a simulation tool was developed, which allows strict closed-loop testing and moreover, allows the involved anaesthetist to “train” on the system.

A second focus are the descriptions of the single controllers for the main four objectives, which includes many details on the specific implementation. All controllers were tested during pilot studies and with one exception also tested during a clinical study. The results are described in detail. The clinical studies are partially designed to compare the performance of the controllers to the performance of an anaesthetist. The results suggest that the automatic system outperforms the anaesthetist and indications are found that patient safety may be improved.
Zusammenfassung


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In the following chapter a short overview of anaesthesia is given describing the main forms and the relevant aspects related to the thesis. The potential of automatic control in anaesthesia motivates the presented work and the development cycle of the controllers indicates the considered scope of automation. A brief introduction of the control platform and work previously presented by authors from inside the research group allows to define the starting point of this thesis.
1.1 Anaesthesia

The word anaesthesia originates from the Greek word “aesthesia”, which means ability to sense and the prefix “a” (or “an” in the presence of a vocal) for negation. Therefore, it means no ability to sense or a state of being unable to feel anything.

Anaesthetists care for the patients health and well being long before and long after the surgical procedures. They assess the patients conditions and decide on the type of anaesthesia the patients should receive; since the patients health state will greatly influence the anaesthesia procedures and techniques. They consult the surgical team, provide pain relieve and support the patients life functions during the operation. They supervise the patients recovery and when necessary provide pain control. The different anaesthesia types as stated in [105] are summarized below.

**General anaesthesia**

General anaesthesia is the most “invasive” of all anaesthesia types as the patients are rendered unconscious such that the patient does not recall any of the surgical procedures. Typically the administered anaesthetics suppress spontaneous breathing and therefore the patient needs artificial ventilation. The anaesthetist monitors and maintains the vital functions of the patient by administering different anaesthetics. For some surgical procedures the skeletal muscles of the patient are relaxed to improve surgical conditions.

**Local or regional anaesthesia**

Local or regional anaesthesia is often used for surgical procedures, where only a well defined operating region is necessary. The patient is awake and breathes spontaneously. The patient’s body usually tolerates better local or regional than general anaesthesia and as far less anaesthetics are administered the patient’s recovery is faster and less critical.

**Monitored anaesthesia care**

During regional anaesthesia the patient is sedated (e.g. for eye surgery) and additional unforeseen complications (apnea, surgical conditions) may request the induction of general anaesthesia. The patient is continuously monitored.

In the following, only aspects of general anaesthesia are described, as the other anaesthesia types are not considered in this project. The main intraoperative objectives of the anaesthetist
during general anaesthesia is to provide

(i) hypnosis
(ii) analgesia
(iii) skeletal muscle relaxation

and last but not least to maintain the

(iv) vital functions

Hypnosis describes a state of anaesthesia which is not only related to unconsciousness of the patient but also to the disability of the patient to recall (amnesia). The disability to recall is particularly important as an awakening patient, who is intubated and ventilated artificially, might feel pain and be aware of the surgical procedures but cannot “communicate” this to the clinical staff. This awareness can be a traumatic experience, which is much feared by the patients as well as the anaesthetists. Until recently no direct measure of hypnosis was available and often arterial blood pressure was used as an indirect indicator. In 1996 an EEG derived parameter (bispectral index (BIS), Aspect Medical Systems) was introduced, which correlates with the hypnotic component of anaesthetic state [59]. More recently a few promising monitors were released but they have not yet established a significant market share. Hypnosis is provided by administration of hypnotic agents, which are either volatile (e.g. isoflurane) or intravenously administered (e.g. propofol).

Analgesia describes the disability of the patient to perceive pain. Surgical procedures are painful and pain stimulates the patient. Different patient reactions to surgical stimulation are observed, from rapid haemodynamic changes to awakening. Analgesia is provided by administration of analgesics (opioids). Therefore, a stable analgesia state is partially responsible for a stable hypnosis and vice versa. It is important to have a “balance” between hypnosis and analgesia. There does not exist a direct measure of pain. Clinically arterial blood pressure is often used as an indirect indicator.

Relaxing skeletal muscles is standard practice during induction of anaesthesia to facilitate tracheal intubation. Many surgical procedures request skeletal muscle relaxation to improve surgical conditions or to reduce surgical risks caused by movements of the patients. Relaxation is provided by administration of neuromuscular blocking agents and can be assessed by the muscular response to electrical nerve stimuli. Measurement devices have been available and clinically established for several years.

Vital functions are monitored throughout anaesthesia. Haemodynamic stability is maintained by administration of anaesthetics and/or replacement of blood volume by isotonic solutions or
less often by blood transfusions. As spontaneous breathing is suppressed by several anaesthetics the patient is ventilated artificially to ensure sufficient blood oxygenation and carbon dioxide elimination.

1.2 Motivation

The anaesthetist’s tasks are most of the time of routine nature. However, critical incidents occur in the operating theatre as in any other safety critical procedure. The anaesthetist needs to be prepared for such critical incidents to minimize occurrence and subsequent negative effect for the patient. Moreover, recent developments of short acting drugs ask for persistent monitoring of the corresponding effect, which automatic control concepts are able to provide.

The potential for automation is therefore in reducing the workload of the anaesthetist’s routine tasks such that increased supervision of the critical signs is possible. So far, the supervision of critical signs cannot be accomplished by a circuitry or a computer system [91]. Moreover, automated systems have the advantage of not being subject to distraction or to fatigue, thus they maintain the same vigilance level throughout the surgical procedure. Continuous supervision of certain patient parameters\(^1\) by a computer system in combination with increased possibilities of supervision by the anaesthetist should obviously reduce critical incidents and therefore reduce patient risk. Other patient benefits are improved outcome (faster recovery, less side effects) due to improved stability of the controlled parameters.

Ever rising costs in health care encourage considerations concerning economic aspects. Reducing costs by minimizing drug consumption is often discussed but so far the impact is comparatively low. Such studies [164] show only a moderate potential to reduce cost compared to the general costs of a surgical procedure. The increasing number of open positions for anaesthetists may require solutions along the line of an “autopilot” to free resources for tasks, which require an anaesthetist.

A more scientific motivation is the use of closed-loop controllers to study interactions between different drugs [102, 113, 117] by tightly maintaining two or more target effects. The degree of drug interaction of different drugs can be quantified by assessing the differences in drug consumption.

Many authors describe closed-loop control in anaesthesia. Until now, most of the systems are still under development [162] and have not passed the testing phase. It should be remembered that it takes considerable time for a technique to mature into routine usage [91]. Therefore, the development of closed-loop control systems for anaesthesia needs also to focus on increasing the clinical applicability.

\(^1\) Generally, in clinical practice the term parameter (or patient parameter) is used for “time varying” measurements.
1.3 Automation

The application of closed-loop control strategies in a clinical environment raises many interesting questions. The process, i.e. the patient, is generally a stable but highly variable system where algorithms perform sufficiently well. Patient condition, surgical procedures or mismanagement in anaesthesia may lead the process to highly unstable reactions, i.e. critical incidents. Automatic systems may help in avoiding these situations and may help in supporting the anaesthetist during these critical phases. It is therefore important that critical phases are detected and the appropriate reactions triggered.

![Development cycle of a controller in the anaesthesia project showing the main iterations.](image)

The anaesthetist uses the measured patient parameters to adjust the administration of anaesthetics or ventilation parameters and acts therefore as a human controller. In this thesis several single input single output control loops are discussed and automatic controllers are implemented. The evolution of the controllers all followed a specific scheme, represented in the development cycle in Figure 1.1. The development phases are shortly discussed in Section 1.3.1. The development of automatic controllers for anaesthesia is an iterative process and only the main iteration loops are discussed in Section 1.3.2.
1.3.1 Development Phases

Specification

Defining specifications well ahead of the actual development phase is important for the success of many projects. Process specifications are related to drug selection (drug action, constraints on administration) and to possible disturbances (noise, patient conditions, clinical procedures). From experience made in this research project defining specifications related to the desired control performance is more difficult. Many difficulties arose from misunderstanding between the involved professions, which only were resolved after many discussions. Bases for the discussions were often simulations, which obviously resulted from development phases well ahead of the actual specification phase. Nevertheless, the performance criteria are crucial for the clinical acceptance and therefore they were updated all along the development cycle. The main point, which increased user confidence in the automated system, was that a controller should imitate the behaviour of the anaesthetist and many ideas evolved to support this intuitive requirement.

The aim was to develop a research prototype where the operators are very attentive to the performance of the controller.

Modelling

A main phase of the development is the mathematic modelling of the reaction of the patient to input changes (anaesthetics, ventilation parameters, disturbances). In pharmacology different models are in common use [165] and a main objective was to develop a modelling framework, which could be applied to many different anaesthetics and different effects. Automatic control concepts based on a mathematic model of the process show many advantages concerning robustness and possible artefact handling procedures. Well established design procedures can be applied.

Controller design

An important but not necessarily time consuming phase was the design of the actual controllers. In general, standard design techniques were used. Important features were added to meet the specification of the “imitated” anaesthetist, safety strategies in case of measurement artefacts, failures or faults were implemented. Moreover, signal characteristics were analysed and appropriate filters were designed.
1.3. Automation

Implementation

The actual implementation of the control algorithms was carried out on an existing automatic control platform. The earlier developed system described in [46] was used (see also Section 1.4.2 for a short summary).

Testing

For in-depth testing of the control algorithms a hardware-in-the-loop (HIL) simulator (Section 2.3) was developed. This simulation environment allows the actual control hardware to be active in a simulated process environment. This testing strategy pointed out major faults in the implementation of the controller well before a clinical trial. Moreover, it uncovered inconsistencies concerning input and output devices of the actual real-time platform. This resulted in a higher reliability of the system. Furthermore, the anaesthetist was able to get used to the actual system in a training environment. Many control actions were analysed and corrections in the control design as well as in the implementation were carried out. Many safety features cannot be tested on a patient due to ethical reasons, critical incidents cannot be forced for patients safety. With the HIL simulator these safety features were tested before the clinical tests. During the following clinical tests most safety features were activated at least once and all safety strategies proved to be appropriate.

Pilot study

For the pilot study and the following clinical study the protocol was approved by the cantonal ethical committee. Patients were informed prior to surgery and written informed consent was obtained.

During pilot studies the functionality, the dynamic response of the controller to set-point variations as well as disturbance rejection were tested in a clinical setting. Many insights were gained and the controller design was adapted accordingly.

Clinical study

As a general rule, during clinical studies the actual implementation of the controller was not changed. Enhanced experience with the controller in the operating theatre often resulted in insights on how the controller design might be improved. However, only if a patient could be at risk then the implementation had to be changed. Changes to improve dynamic behaviour of the controller were not allowed. The main reason is the consistency of the recorded data for
the final statistical evaluation of the controller. Most clinical studies are designed to compare the behaviour of the controller to the behaviour of an anaesthetist.

1.3.2 Development Cycle

The process of developing the controllers follows the described phases. It is not a sequential but an iterative process. The main iteration loops are shown in Figure 1.1. Appropriate testing plays an important role in the development cycle as the pilot study is not used to verify the implementation and hence the corresponding iteration is not necessary. This is important as every pilot study needs planning, ethical committee and patient approval and medical staff to be carried out. Moreover, there is no or only moderate gain in functionality by such an iteration. A main source of evidence to improve the performance of the controller is the pilot study. Gained evidence results often in adjusting either the controller design, the model or even the specification. The development then restarts at the corresponding point in the developing cycle. Generally, the time needed to implement the changes and to retrace the phases reduces with each loop performed. The development phases end with a satisfying solution, which is then used in the clinical study. Obviously, some unexpected problem may occur and then the iteration process restarts at any possible point of the development cycle as indicated.

1.4 Previous Work

1.4.1 Literature

Since the first steps in automating anaesthesia [11] back in 1949 not only anaesthesia has changed considerably. Many new anaesthetics were introduced which have much less side effects for the patient. Drug characteristics have changed to decrease onset and recovery time of anaesthetic effects. Anaesthesia machines have changed significantly, the newest generation to be released on the market is able to provide for the functionality needed for closed-loop control and first controllers are already implemented. In parallel, technology has never stopped in introducing more powerful possibilities to implement automatic controllers. Today computers allow efficient handling of sophisticated control algorithms, including supervisory and safety functions; the limit is beyond the current need.

Many authors describe closed-loop control in anaesthesia and good review articles are [91, 162]. In each of the following chapters, which is concerned with the control of a specific patient parameter, an overview of the known contributions is presented. The emphasis is on studies conducted with patients, whereas simulations and animal studies are mainly not considered.
1.4.2 Basis Provided by the Research Group

First steps in automation of anaesthesia were undertaken more than ten years ago establishing the collaboration between the Department of Anaesthesiology of the University Hospital in Berne and the Automatic Control Laboratory of the ETH in Zurich. Regular exchanges with Dräger Medizintechnik AG, Lübeck, Germany, a market leader in respiratory and anaesthesia systems, have provided a focus towards industrial needs. First concepts to control arterial blood pressure [97, 188], inspired [34] and mechanical ventilation [137] were based on fuzzy systems. The model based concepts were first used in the late nineties to control expired anaesthetic gas concentration [37, 46, 151] and subsequently further model based control loops were developed [46, 55, 56].

Established control loops

The following list provides an overview of the main controllers, which are the bases for the following developments. Further information can be found in [37, 46, 53].

Artificial ventilation

The main focus of that controller was to regulate artificial ventilation by adjusting minute ventilation according to the expired carbon dioxide fraction [37]. A fuzzy based control approach was used and a clinical study was conducted on 30 patients comparing the performance of an anaesthetist with the performance of the controller [137]. The controller performed at least as good as the anaesthetist.

Anaesthetic gas concentration

The endtidal (i.e. end- inspiratory) anaesthetic gas concentration is controlled by adjusting the vaporizer setting [46]. The vaporizer setting influences the anaesthetic gas concentration in the fresh gas flow of the ventilating system. The anaesthetic gas used is isoflurane. A model based approach was established and tested successfully in a clinical study of 22 patients [151]. No further improvement of the functionality of the controller is planned.

Mean arterial pressure (Version 1)

This controller regulates invasive mean arterial pressure (MAP) by using anaesthetic gas. It is implemented with an override structure to handle constraints on the endtidal concentrations [46]. A model based approach was established and the controller was validated in a clinical study of 20 patients. To control MAP with an hypnotic has turned obsolete after the BIS was introduced. The override structure is an important safety feature as overdosing is prevented. With this controller sophisticated artefact detection and fault tolerant control concepts are introduced.
**Bispectral Index**

The Bispectral Index (BIS) as an indicator of the hypnotic state is used to adjust the anaesthetic gas concentration (isoflurane) [53, 55]. The controller has a cascade structure consisting of the outer control loop for BIS, which provides the reference value for the inner control loop for endtidal gas concentration. The cascade structure divides the control objective into two separate problems, which corresponds to the separation of the pharmacokinetics and the pharmacodynamics. An internal model control (IMC) structure was chosen for both the inner and outer control loop. This approach was tested on five patients in a pilot study. As the performance did not meet the clinical requirements no clinical study followed.

**Mean Arterial Pressure (Version 2)**

As a consequence to the introduction of the bispectral index, the mean arterial pressure (MAP) is used as an indirect measure of the analgesic state. Therefore, the controller in [53, 56] regulates the invasive MAP (iMAP) by administering the opioid alfentanil. A model predictive control approach is implemented where two targets, the iMAP and the predicted alfentanil plasma concentration, are used. This reduces the risk of over- or underdosing the opioid which results in a trade-off between the targeted values. The controller was validated in a clinical study of nine patients.

**Platform**

As mentioned earlier, the system on which the actual controllers were implemented has been designed and extended over several years with many significant contributions from different colleagues; the basis of the controller platform is described in [46].

Figure 1.2: Schematic representation of the set-up used in the operating theatre, consisting of patient, sensors, actuators, the actual controller platform with the main components (host and target computer) as well as the anaesthetist who is operating the device.

In Figure 1.2 the set-up of the controller platform in a clinical environment is represented. The controller platform consists of a target and a host computer. The target is a VME-board PowerPC using the real-time operating system XO.2, which has been developed at the Institute of...
Robotics of the ETH Zurich [20, 21]. The host is a standard personal computer running under Windows NT. The man machine interface (MMI) is programmed using the gadgets framework of Oberon System 3 [43, 63, 127]. The target reads from the sensors (S) and drives the actuators (A) every five seconds. The sensor signals are all received via a device specific RS232 link. The actuators are driven either via a RS232 link or an analogue output. The sampling period is not time critical concerning computational resources.

In Figure 1.3 the actual anaesthesia machine (Cicero EM, Dräger Medizintechnik GmbH, Lübeck, Germany) with the additional controller platform is shown. Information from most sensors and some actuators are collected and displayed on one screen, the patient monitor (PM8060, Dräger). An additional electronically driven gas dosing system is installed in parallel to the standard system. It consists of an anaesthetic gas vaporizer driven by an external servo-motor and three mass flow controllers (Bronkhorst Hi-Tech, Ruurlo, Netherlands) for oxygen, nitrous oxide and air. For safety reasons, an emergency switch is integrated to enable the anaesthetist to switch back from the electronic actuator to the manual gas dosing system.

Many more sensors and actuators have been added to the system in recent years, which are mentioned in the corresponding chapters. Moreover, several alterations to the software structure has been made to allow several control loops to work in parallel both on the actual target as well as on the host computer.

Figure 1.3 gives also an impression of the atmosphere in the operating theatre. The anaesthesia machine, syringe pumps, ventilator and monitors are connected to the patient. Only a small part of the patient is accessible for the anaesthetist.

1.5 Scope

Previous work conducted in the research group influenced directly the work presented in this thesis. The project adhered to the development cycle shown in Figure 1.1.

The first overview from the previous work undertaken by the research group shows that all but one of the main four objectives of the anaesthetist have been investigated and first solutions have been found. A second look, however, raises some more problems to be solved. The BIS controller was tested on five patients during pilot studies only. The controller had difficulties in fulfilling the clinical requirements and therefore considerable changes were necessary. Both MAP controllers were validated in a clinical study, but a major disadvantage of the controllers is that they use the invasive arterial blood pressure measure as the controlled variable. So far, the health state and the type of surgery of the considered patients does not necessary require an invasive blood pressure measurement and therefore the controller will not be applied in clinical practice. A controller using a non-invasive blood pressure measurement is therefore necessary.

\(^2\text{http://www.xo2.org}\)
The successful fuzzy based controller for artificial ventilation ($CO_2$) has not been transferred from the original PC-MSDOS platform to the current one. Instead of simply re-implementing it, a model based approach is pursued to improve artefact handling and correspond to the general model based approach.
The goal was to automate not only one task of the main four objectives of the anaesthetist as presented by many authors but to automate all four tasks. They should be running on the same platform at the same time, thus the routine work load of the anaesthetist is considerably reduced and observation and supervision can be increased.

A main objective is to create a common framework for future work in anaesthesia projects which can be applied to a broad range control objectives. Therefore, models should be based on the same assumptions and follow the same identification procedures. Model based approaches showed good performance in a clinical environment not only concerning set-point performance but also as a possibility to handle measurement artefacts and therefore, a standard model based controller design is suggested.

As mentioned above rigorous testing increases patient safety, speeds up clinical testing and saves resources, therefore a “strict” testing environment was developed to validate the implementation before the system is brought to the operating room. The simulation environment can be used for training the anaesthetist on the control platform and therefore the functionality and operability can be tested in advance.

In Chapter 2 the methods and concepts used throughout the development cycle of the different controllers are described. It includes the description of the testing environment. In the following four chapters these concepts were applied to design controllers for the main objectives of the anaesthetist. Chapter 3 describes the objective of skeletal muscle relaxation, Chapter 4 the objective of analgesia, Chapter 5 the objective of hypnosis and Chapter 6 the objective of artificial ventilation. In Chapter 7 first results of combined controllers are presented. Finally, Chapter 8 draws conclusions from the obtained results and highlights the main achievements.
The sciences do not try to explain, they hardly even try to interpret, they mainly make models. By a model is meant a mathematical construct which, with the addition of certain verbal interpretations, describes observed phenomena. The justification of such a mathematical construct is solely and precisely that it is expected to work.

— John von Neumann

Chapter 2

Concepts and Methods

This chapter summarizes the main methods and concepts applied in modelling, controller design and testing in simulations as well as in clinical environments. These methods were used to develop the controllers described in the following chapters and underwent a development process themselves. Only the end-product is described here. Where necessary the main points of interest of the development process are described in the corresponding chapters. The sequence of the following descriptions correspond to the development cycle of Chapter 1. The methods and concepts are viewed as general procedures to develop automatic control systems in anaesthesia. In Section 2.1 the modelling concepts are described, which includes an approximate validation of the model on the basis of non-compartmental analysis. Section 2.2 concentrates on the design of controllers and Section 2.3 describes the simulation environment used to test the controllers prior to clinical studies. Finally, Section 2.4.2 describes the study set-up to validate the controllers in clinical practice, which includes some measures used to assess the performance of the system.
2.1 Modelling in Anaesthesia

2.1.1 Introduction

When modelling biological systems for drug distribution several methods are common and all have their significance. In [165] a good overview of pharmacokinetic and pharmacodynamic models is given. Pharmacokinetics (PK) means the dynamic process of drug distribution in the body and pharmacodynamics (PD) means the description of the effect of the drug on the body. The three main forms are empirical, compartmental and physiological models and all share many characteristics of the other representations [165].

Empirical models are black box models and relate input and output by an analytical expression, such as the sums of exponentials. Compartmental models are formulated on the basis of the minimal number of compartments that adequately fits observed data. Physiologically based models are the most realistic representation of drug kinetics, because the parameters relate directly to physiology, to anatomy and to biochemistry.

Obviously all forms are “empirical” and the above definitions indicate towards the specific approach of formulating the model rather than to the resulting model. All formulations end up with a set of ordinary differential equations describing the specific drug characteristics. The main two forms used in anaesthesia are compartmental and physiological models.

2.1.2 Compartmental Models

Compartmental models are subdivided into simple, catenary and mamillary models, where the simple model can be viewed as a special case of the other two model types. The peripheral compartments of the mamillary model are arranged around a central compartment. All peripheral compartments are only linked via micro rate constants to the central compartment. The compartments of the catenary model are on the other hand arranged in a chain. The most common structure is the mamillary model.

Mamillary compartmental models are widely used to describe the pharmacokinetics and pharmacodynamics of intravenously administered drugs. A typical structure is shown in Figure 2.1. The pharmacokinetics is described by one central compartment (compartment 1 in Figure 2.1) and one or more peripheral compartments (2), which are linked to the central compartment. Drug distribution is described by the micro rate constants \( k_{ij} \) and by the elimination time constant \( k_{10} \). The pharmacodynamics are described by an additional dynamic compartment, the effect site compartment (E) and a static dose-effect nonlinearity (fractional \( E_{\text{max}} \) model). An introduction to PK and PD modelling with clinically relevant examples can be found in [33] and more detailed insights are provided in [48, 58, 71, 165]. The identification of the PKPD...
(i) The pharmacokinetics are identified on the basis of input output data sequences. A drug bolus is administered and the time course is measured by taking blood samples. The infusion time of the bolus is generally neglected and therefore the response can be viewed as an approximation of an impulse response. As the “blood” or better the “plasma” compartment the central compartment (compartment 1) is used. Depending on the characteristics of the drug one or more peripheral compartments are added.

Typically, the concentration on the central compartment versus the drug effect shows a time lag. In pharmacology this is often referred as “hysteresis”, because a plot showing drug concentration after a bolus versus drug effect looks similar to a hysteresis. Moreover, the peripheral compartments are used to describe the characteristic time course of plasma concentration in the central compartment. Generally, the time course of drug effect will therefore differ from the time course in any of the compartments.

(ii) To describe this time lag an effect site compartment (compartment E in Figure 2.1) is added to the pharmacokinetic model. The effect site concentration is not directly linked to the type of effect of interest (most drugs show more than one effect) but to the “site” of effect and is only used to account for the time lag between drug concentration and drug effect [103]. A standard fractional sigmoid $E_{\text{max}}$ model is added relating concentration at the effect site to drug effect [48].

The advantage of these models is that with relative few parameters a good estimation of effect time course can be made. However, no “body to model” compartment relation can be assigned and the models are only designed to describe the elimination and not the initial transport and distribution of the drug. For example, in [185] a five compartment mamillary model was identified to estimate anaesthetic gas concentrations up to several days after the administration.
Moreover, instantaneous mixing in the central compartment is assumed, i.e. the model uses an initial condition corresponding to the bolus instead of an actually administered bolus infusion, which is in principle a rapid infusion over a short time (15-30 seconds). Therefore, the time course is assumed to start at the peak concentration in the plasma compartment and the time course to this peak concentration is not considered. Obviously, good results can be therefore only expected where the elimination is slow in comparison to the initial distribution of the drug. The blood circulation is the transport mechanism of the drug and introduces an additional time lag typically of a few minutes [180] until the drug concentration peaks in the arterial blood. For modern, short acting drugs such as mivacurium and remifentanil, where the elimination time is similar to the distribution time, poor results are to be expected. The elimination half-life $T_{1/2}$ for mivacurium is less than 3 minutes [26, 120] and for remifentanil less than 10 minutes [60].

When using a model for control purposes it is important to capture the fast initial dynamics of the pharmacokinetics rather than the slow elimination, which can be viewed as a near-static disturbance to the closed-loop system. It is therefore important that the model is sufficiently descriptive during the initial distribution phase of the drug.

A different method is to use physiologically based models, which take into account blood circulation as the transport mechanism of the drug and therefore gives better insight into the first crucial minutes of drug distribution. In anaesthesia physiologically based models are rarely used for intravenously administered drugs, they are more often used for volatile anaesthetics.

### 2.1.3 Physiologically Based Models

Physiologically based modelling is widely used in drug development. In [29] a good overview of physiologically based pharmacokinetic models is given. The advantage of physiologically based models are that they provide a better description of the time course of drug distribution in the body.

Physiological models are subdivided into flow based and recirculatory based models [165].

The first subgroup concentrates on the distribution of the drug into different organs or organ groups and consists therefore of many body compartments. Drug distribution, storage and elimination is described by tissue size, vascular perfusion and binding or partitioning of drug between blood and tissue components. The parameters correspond to actual physiological and anatomical measures and alterations may be predicted by changing the appropriate parameters [58]. The principles of a flow based model is used to derive a model for closed-loop control purposes.

The second subgroup consists of a lumped body compartment and is used to describe general indicators of drug characteristics. Essentially, the body is considered as a dynamic control system with a positive feedback arrangement [165]. Thus the drug disposition is described by repetitive circulations. The principles of recirculatory based models allow a validation of the
physiologically based models. The same validation is generally used for mamillary compartmental models and therefore a direct comparison can be made.

In [93] the following statement summarizes the advantage of physiologically based pharmacokinetic and pharmacodynamic (PBPKPD) modelling:

*Physiologically based pharmacokinetic modelling offers the opportunity to introduce an appropriate pharmacodynamic model (PD) and to allow the PD model to interact with the physiologically based pharmacokinetic model via physiologic (homoeostatic) control mechanisms. This would be particularly useful for drugs that influence cardiac output and regional blood flows which, in turn, can affect drug distribution and elimination.*

Even if the drug does not affect cardiac output and regional blood flow itself, changes in cardiac output and regional blood flow nevertheless affect drug distribution and elimination. Thus, some advantages of flow based models in drug development correspond to the requirements in closed-loop control. The main advantage concerning the latter is the detailed description of the initial distribution of the drug providing crucial information for the controller. As mentioned above this is important mainly when applying short acting drugs where elimination and distribution have similar time characteristics. However, a “highly” variable cardiac output will probably lead to “wave” type variations in the drug distribution process. The body will act as a low-pass filter and in average it will have therefore a moderate influence. More persistent changes in cardiac output will lead to near-static disturbances, which can be handled by the integral action of the controller.

During the past years several attempts by the research group to control different parameters in anaesthesia were undertaken using physiologically based pharmacokinetic and pharmacodynamic models [37, 46] and using mamillary compartmental models [53]. Furthermore, attempts were made to control skeletal muscle relaxation with a mamillary compartmental model published in the literature [84]. In pilot studies the latter showed considerable deviations from simulations in closed-loop dynamics and problems in robustness and noise sensitivity (see Chapter 3). Moreover, an overall model concept applicable for different anaesthetic drugs with different characteristics was aimed at and therefore the following principles described in Section 2.1.4 were used to derive sufficiently descriptive physiologically based compartmental models for control purposes, based on [37, 46, 156, 189]. New concepts are introduced for tuning the pharmacokinetics and pharmacodynamics.

2.1.4 Physiologically Based Pharmacokinetics

In Figure 2.2 the model structure is shown. The model consists of an arterial and a venous blood pool and several organ compartments. The fractions $q_i$ of total cardiac output $q$ flowing through each compartment depend upon the compartmental resistance and upon the arterial pressure. By assuming constant cardiac output and constant mean arterial pressure $q$, can be calculated...
according to [46]. The intra and inter patient variability is influenced by many parameters including time varying cardiac output [80, 169].

![Physiologically based pharmacokinetic model](image)

Initially, the cardiac output was assumed constant for simplicity. The obtained models reproduced the main characteristics and the robust controller design made it not necessary to introduce a time varying cardiac output and therefore no further investigations were carried out along this line. Intravenously administered drugs are infused into the venous blood pool with the infusion rate \( i_R \), which is a common infusion site described in the literature [12]. Other authors subdivide the venous compartment into a pre- and post-injection pool [165] or inject the drug into the lung compartment [13] instead. Uptake and elimination of volatile anaesthetics are described by an adapted lung. For details the reader is referred to [46]. Each organ compartment is further subdivided into a local blood pool and the respective organ tissue Figure 2.3. The apparent volume of the compartment in Figure 2.3 depends therefore on the blood volume \( V_{ib} \) and the tissue volume \( V_{it} \), which are known from [46], as well as the ability of the tissue to bind the drug. From [165] the apparent volume of drug distribution of compartment \( i \) is described by

\[
V_i = V_{ib} + \frac{\lambda_{it}}{\lambda_{ib}} V_{it}
\]

where \( \lambda_{it} \) and \( \lambda_{ib} \) describe the free fraction of drug in tissue and in blood for the corresponding compartments. Often the tissue/blood partition coefficient \( \lambda_i = \lambda_{it} / \lambda_{ib} \) is substituted. Furthermore, the rate of elimination (or metabolism) is described by \( \kappa_i \). Instant equilibration between blood and tissue concentrations is assumed and therefore the concentration of the specific drug in each compartment \( c_i(t) \) (Figure 2.3) is described by the standard approach of Equation (2.2),

\[
\frac{V_i}{q_i} \frac{dc_i(t)}{dt} = c_{in}(t) - c_i(t) - \frac{\kappa_i V_i}{q_i} c_i(t)
\]

where \( c_{in}(t) \) is the drug concentration in the blood entering the compartment and \( V_i \) is the volume of the compartment which eliminates or metabolizes the drug. This is generally assumed
2.1. Modelling in Anaesthesia

Figure 2.3: Schematic representation of a compartment divided into a blood and a tissue part with corresponding volumes \( V_{i,b} \) and \( V_{i,t} \) and coefficients \( \lambda_{i,b} \) and \( \lambda_{i,t} \) describing the free fraction of drug. Blood flow through the compartment is \( q_i \), incoming drug concentration is \( c_{in} \) and compartmental drug concentration is \( c_i \). Elimination is described by \( \kappa_i \).

to be only the blood part of the compartment, i.e \( V = V_{i,b} \). It is common to assume instant equilibration. At least for highly perfused organs the capillary system provides a large surface where the diffusion process takes place. Generally, this process is considerably faster than the time constants related to drug distribution and elimination. Therefore, all parallel compartments \( i \in \{1, 2, \ldots, 9\} \) can be modelled by Equation (2.3).

\[
\frac{V_i}{q_i} \frac{dc_i(t)}{dt} = c_A(t) - c_i(t) - \kappa_i \frac{V_{i,b}}{q_i} c_i(t)
\]  

(2.3)

Analogously, \( c_L(t), c_A(t) \) and \( c_V(t) \) are described by Equations (2.4), (2.5) and (2.6) respectively.

\[
\frac{V_L}{q_L} \frac{dc_L(t)}{dt} = c_V(t) - c_L(t) - \kappa_L \frac{V_{L,b}}{q_L} c_L(t)
\]  

(2.4)

\[
\frac{V_A}{q_A} \frac{dc_A(t)}{dt} = ls \cdot c_V(t) + (1 - ls) \cdot c_L(t) - c_A(t) - \kappa_A \frac{V_{A,b}}{q_A} c_A(t)
\]  

(2.5)

\[
\frac{V_V}{q_V} \frac{dc_V(t)}{dt} = \sum_{i=1}^{9} \frac{q_i}{q_V} \cdot c_i(t) - c_V(t) - \kappa_V \frac{V_{V,b}}{q_V} c_V(t) + \frac{1}{q_V} i_R(t)
\]  

(2.6)

The model parameters can be classified as drug specific and drug independent (i.e. physiologically based). Physiological parameters obviously cannot be used to “tune” the model to individual characteristics of a drug. Therefore, in order to obtain close resemblance of the model output to experimental concentration data, the partition coefficients \( \lambda_i \) and the elimination rates \( \kappa_i \) are empirically adjusted.
Short comparison between mamillary compartmental and physiologically based pharmacokinetic models

By lumping the lung, venous and arterial compartments of the physiologically based model a mamillary compartmental model structure is obtained. The lumped compartment corresponds to the central compartment with nine additional peripheral compartments arranged around it. Drug infusion is similarly located, but the physiologically based model provides a more realistic description of the initial distribution. Meaning that the time course until concentration peaks in the compartment related to blood samples (i.e. arterial or central compartment respectively) is described by a higher order model. A more in detail description of the distribution and elimination of the drug is indicated by the nine peripheral compartments. An important difference is that generally mamillary models assume central elimination and the physiologically based model assumes elimination where it physiologically occurs. Meaning that the $k_i$ of the above equations are zero if the drug is not eliminated and non zero if the drug is eliminated from the corresponding compartment. For several intravenously administered drugs the elimination will not or only partially take place in the venous, lung and arterial compartment. Therefore, the elimination from peripheral compartments should be dominant. In [44] it is indicated that the assumption of central elimination must be flawed when applying it for several specific drugs and moreover, in [85] it is tried to use also peripheral elimination to overcome problems when modelling short acting drugs. Mamillary models where the elimination time constant is large compared to the distribution will describe the elimination appropriately as homogenous distribution can be assumed. Therefore, the advantage of the physiologically based model is that the elimination can be adapted to the specific drug characteristics.

In [44] it is also stated that in pharmacokinetic studies approximately the first two minutes after bolus administration are masked and that the following time course would show superposed oscillations instead of a smooth decay. These oscillations are caused by the drug transport mechanism, which is the blood circulation. Each compartment has different transport characteristics (depending on the perfusion) and therefore, the different time lags introduced result in different drug “waves” reaching the sampling compartment until a certain level of homogeneity is reached. Both the physiologically based and the mamillary compartmental models do not account for this mixing phenomena caused by different transport delays.

Pharmacokinetic tuning

The physiologically based pharmacokinetic model consists of parameters derived from the haemodynamic model, which are therefore drug independent, namely all blood flows ($q_i$) and volumes ($V_i$, $V_{i,b}$, $V_{i,c}$). Furthermore, it consists of drug dependent parameters, namely tissue/blood partition coefficients ($\lambda_i$) and elimination constants ($\kappa_i$). The drug independent parameters are known from [46] and therefore 24 “dependent” parameters (two - $\kappa_i$ and $\lambda_i$ - for each compartment) are available to tune the model and to fit the drug specific properties.
This seems a lot in comparison to a mamillary compartmental model, which for two or three compartments requires four or six parameters to be identified (see Table 2.1 in Section 2.5). Moreover, these models normally - but not always [85] - assume no peripheral elimination, which is an intrinsic parameter reduction. The following considerations are used to reduce the 24 free parameters of the physiologically based model considerably.

In a first step the characteristics of “elimination” of each drug is investigated. A better term is “inactivation” as mainly the drug molecules are metabolized and the metabolites are inactive concerning a specific pharmacological effect. Metabolism either takes place in the liver (hepatic metabolism) or in blood plasma by hydrolysis. Thereafter the metabolites are eliminated by the kidneys (renal clearance). In the literature the inactivation is described by elimination time constants. For example, the inactivation of mivacurium takes place in the blood [68, 105] and therefore all elimination constants must be the same \( \kappa_i = \kappa \) for all compartments. Alfentanil is inactivated by hepatic metabolism [105] only and therefore all \( \kappa_i = 0 \) except for the compartment, which includes the liver (i.e. \( \kappa_4 \neq 0 \)). In both examples twelve parameters are reduced to one and this will be the case for most drugs. The remaining parameter can be approximated by using the elimination half-life \( T_{1/2} \) or the mean residence time \( MRT \) described in the literature. Both \( T_{1/2} \) and \( MRT \) can be derived from non-compartmental investigations (see [58]) and are related by Equation (2.7).

\[
T_{1/2} = \ln(2) \cdot MRT \tag{2.7}
\]

**CASE A: Simultaneous elimination from all compartments**

Assuming steady state conditions and all \( \kappa \) equal, i.e simultaneous elimination from all compartments \((\kappa_i = \kappa)\), then \( \kappa \) can be approximately derived directly with \( T_{1/2} \) or \( MRT \).

\[
\kappa = \frac{\ln(2)}{T_{1/2}} = \frac{1}{MRT} \tag{2.8}
\]

**CASE B: Elimination from a single compartment only**

When elimination takes place in one compartment only, \( \kappa \) needs to be adjusted according to the following procedure. Assume that \( \tilde{\kappa} \) is the elimination rate if all compartments would participate in eliminating the drug and is therefore derived according to Equation (2.8) and \( \kappa_e \) is the actual elimination rate of the one compartment participating in elimination. If the same total elimination has to be achieved even though only one compartment participates then \( \kappa_e \) needs to be significantly larger than \( \tilde{\kappa} \). The main additional factor influencing elimination is the perfusion of the involved compartment, i.e. it depends on the actual volume \( V_e \) and actual flow \( q_e \). Therefore, the ratio between total flow (cardiac output) \( q \) and flow through the specific compartment \( q_e \) as well as the ratio between the summed up volumes of all compartments \( V \) and the volume of the specific compartment \( V_e \) has to influence \( \kappa_e \). Accordingly, the following approximation is used.

\[
\kappa_e \approx \tilde{\kappa} \cdot \frac{V}{V_e} \cdot \frac{q}{q_e} \tag{2.9}
\]
As
\[ \frac{V_e}{V} = \frac{V_{e,b} + \lambda_e V_{e,t}}{\sum_i (V_{i,b} + \lambda_i V_{i,t})} \]  

(2.10)
is dependent on \( \lambda_i \) the corresponding \( \kappa_e \) can only be derived after tuning of \( \lambda_i \).

In a second step the ability of the tissue to bind the specific drug is investigated. The arterial, venous and the skin shunt compartment exist of only the blood part of the compartment, therefore \( \lambda_A = \lambda_V = \lambda_0 = 0 \). For further parameter reduction different approaches can be used.

(i) Literature provides clues when different tissue concentrations in response to a drug bolus are maximal. This information can be directly used to tune the compartments response by shifting \( \lambda_i \) correspondingly.

(ii) For some drugs, but in particular for volatile anaesthetics the solubility constants can be found in the literature, which correspond directly to the tissue/blood partition coefficients \( \lambda_i \).

(iii) A pragmatic possibility is to assign a relative binding coefficient \( l_i \) for each compartment. For example, if the tissue part of fat can bind double the amount of drug molecules than the muscle compartment, then \( l_b = 2 \cdot l_7 \). Thus a relation \( \lambda_i = l_i \cdot \lambda \) for all \( i \) compartments can be derived, where \( \lambda \) is a single parameter left to tune the required behaviour. From tissue/blood partition coefficients published in the literature clues to derive these relation coefficients \( l_i \) can be found.

(iv) Similar, but even more simplified, is to assign all \( \lambda_i \) to the same value, i.e. \( \lambda_i = \lambda \), and tune \( \lambda \) to achieve the required behaviour.

Approach (i) relies on accurate data from the literature, which are normally derived by scaling up an animal (rat) to a human model (e.g. [14]). The necessary data can only be found in the literature for a few drugs.

Approach (ii) was previously used for volatile anaesthetics (e.g. [46]).

Approach (iii) relies on a rough approximation of a relative drug binding coefficient. For some drugs (e.g. alfentanil) the tissue/blood partition coefficient can be found from measurements in animals [12]. The animal data can be used to estimate the relation coefficients between compartments. Moreover, the tissue/blood partition coefficient varies only moderately [42] and the main factor for variation of the time constants will be the volume of the compartment. Clearly approach (iv) will not be sufficiently descriptive for drug development purposes where the distribution is essential. However, for control purposes where only the effect site compartment is essential this may be sufficient.

An important fact has to be considered concerning the method used to tune the model. In mamillary compartmental modelling pharmacokinetic behaviour is typically reproduced by either two or three compartments depending on the anaesthetic, which leads to a characteristic
Figure 2.4: Characteristic time course of arterial concentration (logarithmic) for two (dash-dotted line) and three compartment (solid line) models reproduced with the physiologically based pharmacokinetic model.

Figure 2.4: Characteristic time course of arterial concentration (logarithmic) for two (dash-dotted line) and three compartment (solid line) models reproduced with the physiologically based pharmacokinetic model.

In Figure 2.4 a semi-logarithmic plot of the time course of concentration for a two and a three compartment model is shown, which were simulated by using the physiologically based model. Typically, a two compartmental time course (dash-dotted line) shows two distinct slopes: A first, steep slope is associated with the distribution phase and a second, less steep slope with the elimination phase. Correspondingly, a three compartment model shows three characteristic slopes (solid line), which are associated with a fast and a slow distribution phase and an elimination phase respectively. When using the fourth method described earlier, only a two compartment model can be reproduced, which is sufficient for mivacurium. On the contrary, for alfentanil normally a three compartmental model is used and therefore the third approach is appropriate.

Approaches (i) and (ii) use measured data to identify the partition coefficient of each compartment, whereas approaches (iii) and (iv) tune one parameter such that a published input output data set is reproduced. From pharmacokinetic pharmacodynamic investigations [84, 135, 145] either time to peak effect or time to peak effect site concentrations are known. By using one of the body compartments as “effect site” (for example the muscle compartment for neuromuscular blocking agents) $\lambda$ is tuned such that the concentration peaks at the same time as known from the literature. In Figure 2.5 the time shift caused by different $\lambda$ can be seen: increasing $\lambda$ causes the concentration to peak later.
2.1.5 Pharmacodynamics

In mamillary compartmental pharmacodynamic modelling an effect site compartment is added to the pharmacokinetics to describe the dose effect relation with a standard fractional sigmoid $E_{max}$ model (Figure 2.1). As already mentioned above the physiologically based pharmacokinetic model incorporates directly the “effect site compartment” (also suggested by [93]), which was introduced in the pharmacokinetic model for better tuning.

\[
E = E_{max} \left( \frac{C_E^\gamma}{C_E^\gamma + EC_{50}^\gamma} \right)
\]  

(2.11)

Therefore, the pharmacodynamic part consists only of a fractional sigmoid $E_{max}$ model given in Equation (2.11), where $E$ is the effect, $C_E$ is the effect site concentration, $EC_{50}$ is the effect site concentration to achieve 50% effect and $\gamma$ describes the steepness (often also referred as the degree of nonlinearity) of the dose-effect relation.

The pharmacodynamic model very strongly depends on the effect of interest. For the models for mivacurium and isoflurane the effects are directly measurable and the PD parameters $EC_{50}$ and $\gamma$ can either be derived from input output data sequences or taken from the literature. For further details refer to the corresponding chapters.
2.1.6 Validation using Non-Compartmental Analysis

The principles of recirculatory models and the application of the concept of moments in statistics allows the calculation of the main pharmacokinetic parameters [165]. This non-compartmental analysis - see [58, 131, 165] for further details - was used to verify the derived models by comparing the results with the literature. However, it is not possible to use non-compartmental analysis to verify models for volatile agents, as volatile anaesthetics are not significantly eliminated by body clearance, but by exhalation only.

The main parameters are clearance $CI$, i.e. the amount of drug which is eliminated from the body and the apparent volume of distribution at steady state $V_{dss}$, i.e. a relation between drug concentration of blood or plasma to the amount of drug in the body. For drugs, which are bound significantly in either vascular or extravascular space, the volume of distribution changes and can exceed the real volume of distribution significantly. The real volume of distribution [58] cannot exceed total body water ($\lesssim 58\%$ of bodyweight).

Clearance

Clearance $CI$ as described in [58] can be calculated as:

$$CI = \frac{D}{\int_0^\infty C \, dt}$$

(2.12)

where $D$ is the drug dose administered intravenously and $\int_0^\infty C \, dt$ is the zero moment of plasma drug concentration (area under curve).

In practice two methods can be used. When applying a drug bolus the simulation or the measurement sequence is stopped after the concentration decay of the drug has reached terminal elimination phase at $t = \hat{t}$ and $C(t = \hat{t}) = \hat{C}$ and the zero moment is approximated by

$$\int_0^\infty C \, dt = \int_0^{\hat{t}} C \, dt + \frac{\ln(10) \cdot \hat{C}}{|\beta|}$$

(2.13)

where $\beta$ is the slope of the logarithmic concentration versus time during terminal elimination phase. When applying a constant infusion $i_{R_{ss}}$ until steady state conditions are reached, then the clearance can be derived from

$$CI = \frac{i_{R_{ss}}}{C_{ss}}$$

(2.14)

where $C_{ss}$ is the steady state concentration of the drug in plasma or blood.
Apparent volume of distribution at steady state

Steady state distribution volume $V_{dss}$ as described in [58] can be derived from:

$$V_{dss} = D \frac{\int_{0}^{\infty} t \, C \, dt}{(\int_{0}^{\infty} C \, dt)^2} \quad (2.15)$$

Where $\int_{0}^{\infty} t \, C \, dt$ is the first moment of plasma drug concentration (area under the first moment curve). The same procedure as in Equation (2.13) is used to approximate the zero and the first moment. The first moment approximation is:

$$\int_{0}^{\infty} t \, C \, dt = \int_{0}^{\tilde{t}} t \, C \, dt + \frac{\ln(10) \cdot \tilde{t} \cdot \tilde{C}}{|\beta|} + \frac{\ln(10)^2 \cdot \tilde{C}}{|\beta|^2} \quad (2.16)$$

The apparent volume of distribution can also be calculated by summing up all compartmental volumes [165].

$$V_{dss} = \sum_i V_i \quad (2.17)$$

Both clearance $Cl$ and volume of distribution $V_{dss}$ are independent of the model structure and both are important properties to describe the pharmacokinetic properties of a drug. In particular the reciprocal form of Equation 2.14 is

$$\frac{1}{Cl} = \frac{C_{ss}}{i_{Rss}} \quad (2.18)$$

and describes the open-loop gain of the process. Furthermore, both values can be easily derived by simulations (or by blood samples) and can be compared to published values.

### 2.2 Controller Design

In the following sections only an overview of the design procedures used is given as the controllers have different requirements, different signal characteristics and different constraints. However, the same basic concepts were applied.

#### 2.2.1 Model Based Approach

Different control strategies can be applied and many approaches have been published. The observed patient variability is considerable and therefore classical PID techniques may be limited.
The main applications related to PID control and automation of anaesthesia [2, 98, 106] state that the performance would be improved by using a more sophisticated approach. Adaptive controllers have the disadvantage of restricted stability properties. A totally different approach is to use rule based methods, such as fuzzy system or neuronal networks, which have been successfully applied [87, 130, 137]. The initial success of these systems fades as many tests are needed to settle the control parameters and artefact handling is not straightforward.

Model based approaches on the other hand are widely applicable and the main advantages meet the requirements of a clinical environment.

The advantages of model based controllers are:

- increased performance and robustness
- well known design rules, which can be often directly applied by using mathematical software packages such as MATLAB® (The MathWorks, Inc.).
- in spite of a high process variability a satisfying control performance can be achieved.
- less sensitive to noise than standard PID controllers.
- artefact detection and handling can be supported.

In Figure 2.6 the generally used control structure is shown. It is an observer based state feedback controller augmented with an additional integral action. Generally, by applying the principles of the linear quadratic regulator (LQR) problem [5, 124] the parameters for both the controller state feedback ($k$ and $k_j$) as well as the output injection ($h$) are derived. The design procedures are given below. Standard anti windup structures are used to prevent integral overflow in case the controller output ($u$) is constrained. Artefacts are handled by switching between the actual measured ($y$) and the observed ($\hat{y}$) value in case invalid measurements are detected. Artefacts can be a single invalid measurement or a sequence of several measurements. Procedures to detect invalid measurements are described later in the corresponding chapters. The conditions related to $k_{aw}$ and the exact discrete implementation is given in Appendix A.2.
Figure 2.6: Model based controller with state feedback coefficients $k$, integral action $k_I$, observer $P$, output injection $h$ with additional anti windup structure ($k_{aw}$) and switch for artefact handling.

**Linear quadratic regulator design**

Let’s assume any general linear time invariant (LTI) system described by:

$$\dot{x}(t) = A x(t) + B u(t)$$

$$y(t) = C x(t) + D u(t)$$

For the LTI models used $D$ is generally zero and it is therefore not further considered.

If the above system is controllable and observable then the formulation of the LQR problem is:

$$\min_{u(t)} \int_0^\infty \left\{ x^T(t) Q x(t) + u^T(t) R u(t) \right\} dt$$

s.t. $$\dot{x}(t) = A x(t) + B u(t)$$

where the state cost is described by $Q$ and the input cost by $R$. The solution to this problem is a constant state feedback with

$$u(t) = -K x(t)$$

where $K$ is derived by solving the corresponding algebraic Riccati equation [155]. The resulting parameters are optimal with respect to the cost function formulated above.
To simultaneously derive the control parameters for the LTI model $A$, $B$, $C$ and $D$ augmented with an additional integral action as shown in Figure 2.6. The LQR system matrices need to be reformulated by setting:

$$A = \begin{bmatrix} 0 & -C \\ 0 & A \end{bmatrix} \quad B = \begin{bmatrix} 0 \\ B \end{bmatrix} \quad C = \begin{bmatrix} \Gamma & C \end{bmatrix}$$

(2.24)

where $\Gamma$ is a tuning parameter related to the integral action. To preserve the conditions of observability and controllability the LTI model $A$, $B$, $C$ and $D$ is not allowed to have a zero in the origin, $\Gamma \neq 0$ and $\Gamma$ has to differ from the eigenvalues of $A$ [64].

The cost matrices are then set to:

$$Q = C^TQ C \quad R = R$$

(2.25)

and the parameters of the integral action and the state feedback are:

$$k_I = \mathcal{K}(1) \quad k = \mathcal{K}(2 : n)$$

(2.26)

where $n$ is the order of $A$.

Note that in case of a single input single output system the integral action can be directly derived by:

$$|k_I| = \frac{\Gamma}{\sqrt{R}}$$

(2.27)

A feed forward term $f$ can be derived by:

$$f = \left[ C (B \mathcal{K} - A)^{-1} B \right]^{-1}$$

(2.28)

which corresponds to the inverse of the static gain of the system $A$, $B$ and $C$. Therefore, the total static loop gain is one.

Similarly to derive the output injection parameter $h$ the LQR problem is formulated by setting:

$$\mathcal{A} = A^T \quad B = C^T$$

(2.29)

$$Q = \rho B B^T \quad R = R$$

The tuning parameters are $\rho$ and $R$. The output injection $h$ is given by:

$$h = \mathcal{K}^T$$

(2.30)

The Separation Theorem allows the individual tuning of the state feedback $k$ and the output injection $h$ [5]. This controller structure is often referred as linear quadratic gaussian control, as it combines optimal state feedback (LQR) and optimal state estimation of the process. The process noise is usually assumed to be an uncorrelated zero-mean Gaussian stochastic process [155].
2.2.2 Cascade Structure

Typically, cascade control structures can be used when there are several measured signals and only one manipulated variable [8]. By using an additional measurement the controller can be tuned tighter for systems with time lags and long time constants. The additional measurement is generally chosen such that its response to the manipulated variable is faster than the response of the controlled variable. Cascade controllers are designed by nesting two or more control loops as shown in Figure 2.7. The outer control loop uses the controlled variable $y_1$ and the corresponding reference $y_1,\text{ref}$ as the inputs to the controller $C_1$ which generates the reference $y_2,\text{ref}$ for the inner control loop. With the second measurement $y_2$ controller $C_2$ generates the manipulated variable $u$.

![Figure 2.7: Cascade controller structure. Outer cascade with controller $C_1$ and inner cascade with controller $C_2$.](image)

The concept of using a cascade controller structure was introduced in [55] to control bispectral index ($BIS$). In the case of volatile anaesthetics the endtidal gas concentration can be measured, therefore providing a good estimation of the pharmacokinetics. The $BIS$, which is used to describe the effect of the drug (pharmacodynamics), has a high noise level of stochastic nature and intra and inter patient variability is significant. A cascade controller as shown in Figure 2.7 matches the two-levelled model structure and splits the comparably well known pharmacokinetics from the uncertain and variable pharmacodynamics. Additionally, different safety strategies can be applied to the different control loops, which are matched to the different signal and model characteristics. The cascade structure is an adequate solution in different situations. For example non-measurable pharmacokinetics can be estimated, where the estimation is fed back instead of a measurement. Measurable pharmacodynamics can then adjust the target of the estimation to achieve the desired effect. This was previously used in [163].

Other reasons to use a cascade controller can be signal characteristics. For regulating neuromuscular blockade generally a measurement is used which has no clinical relevance. Clinically only a very coarse measurement is used, which is not directly applicable for closed-loop purposes. To overcome this dilemma a cascade controller was introduced combining both measurements. Further details are described in Chapter 3.
2.2.3 Improving Clinical Applicability

Many concepts developed to automate anaesthesia were either tested in simulations or on animals. Only relatively few concepts were actually tested on humans and the majority were studies to provide feasibility rather than to conduct a clinical study. Generally, clinical studies require a higher degree of automation of the system to handle incidents introduced by standard clinical practice. The incidents are mainly caused by disconnections of a sensor or an actuator. There are several reasons for these disconnections. The following list gives a few examples.

- Measurement or actuator lines are shortly disconnected to "untangle" the connections to the patient.
- The infusion is interrupted to refill a syringe of an infusion pump.
- Disconnections are necessary in case the patient is turned or re-positioned.

Many possible incidents have to be analysed concerning the effect on a control system. Appropriate procedures to handle these incidents need to be implemented. The aim is to provide sufficient autonomy of the system that an anaesthetist can pursue clinical tasks without having to inactivate the controller.

A major interest is therefore not only the controller design, but to improve applicability by incorporating safety features such as output constraint handling (override structures), feedforward terms to speed up system behaviour, artefact handling or special handling procedures such as during periods where an empty syringe is refilled or exchanged. For details the reader is referred to the corresponding chapters.

2.2.4 Closed-loop Bandwidth

The closed-loop bandwidth is a performance indicator of feedback systems. A large bandwidth generally correlates with a fast system response since higher frequency components are considered. Whereas a small bandwidth correlates with a slow system response, which is generally more robust [155]. Where possible the closed-loop bandwidth is given to illustrate the systems performance. Furthermore, it nicely verifies the controller design in case several control loops interact, such as in a cascade arrangement.

2.2.5 Discrete Implementation

The discrete implementation of the integrators of the model (observer) as well as of the controller are based on standard approximations described in the literature [39, 45]. Of importance
are the anti windup feedback structure and the resulting conditions for the coefficient \( k_{\text{aw}} \). Its structure and further details are described in Appendix A.2. The sampling period \( T_s \) is five seconds, which corresponds to the update rate of the measurements.

### 2.3 Hardware-in-the-loop Simulation

#### 2.3.1 Introduction

Before entering the operating theatre a thorough testing of the whole system is necessary for this safety critical application. The tests have to validate the controller design, its implementation and the communication between the different input and output devices. Furthermore, the handling of the platform as applied in clinical practice has to be verified. A short summary can be found in [157] and further details concerning the implementation are described in [152].

For this purpose a testing environment has to satisfy following requirements:

- simulate the behaviour of a patient undergoing general anaesthesia according to the actuator signals
- the different communication interfaces need to be included in the tests
- real-time simulation to imitate clinical application
- ability to propagate events\(^1\), which are triggered from outside the control loop and imitate clinical incidents or characteristics

Note that the hardware and the software of the control system has to correspond exactly to the set-up which is used during the clinical studies. These requirements lead to the implementation of a hardware-in-the-loop (HIL) simulator. A HIL simulation is based on a simulated process operated by the real control hardware [70].

A strong interest was to use a system which was well known instead of introducing a new system, based on new software and/or hardware components. This led to adapting the existing system and using the same software and hardware components. A short description of the controller and simulator platforms and the concepts of this specific simulation environment are presented in the following.

\(^1\)Events are described in detail in Section 2.3.2
2.3.2 Definitions

Hardware-in-the-loop (HIL) simulation has gained importance in different fields of automatic control [70, 133, 134, 136]. Many applications of HIL simulations can be found in automotive, aerospace, process and also maritime engineering and often they are also used for educational purposes (e.g. flight simulators). A good definition is given in [70] where HIL simulation is also set in perspective to other simulation regimes. However, for this specific use a variation of this definition is used.

Hardware-in-the-loop simulation

In [70] hardware-in-the-loop simulation is classified as a real-time simulation. This means that the actual signal flow between controller and process has the same time characteristics. Furthermore, the following definition for hardware-in-the-loop simulation is given.

*The simulated process can be operated with the real control hardware.*

The simulated process is defined as follows.

*The simulated process replaces either fully or partially the controlled process consisting of actuators, physical processes and sensors.*

In Figure 2.8 this is visualized. In the specific case all components described, meaning the actuator (A), the physical process (P) and the sensor (S), are replaced by the simulated process.

Events

The process has to be modelled well enough to ensure proper simulation. However, some process characteristics are intentionally not considered in the process simulation because of irregular or rare occurrence, such as signal failures, faults or noise. Moreover, noise is often not considered as filters are supposed to work sufficiently well.

It is still important to test the behaviour of the controllers including these special process characteristics. Not all characteristics can be classified as faults (see [15] for further details). Sensor subsystems perform self-calibration automatically and this leads to measurement artefacts, which are not a result of a fault or a failure. Hence a new class of an event is defined.

*An event is a process characteristic which is (partially or entirely) not considered in the process simulation.*
Figure 2.8: Real system versus hardware-in-the-loop simulation environment. System set-up with controller (C), actuator (A), process (P) and sensor (S) for the real and the simulated process respectively.

In Figure 2.9 this is visualized. Events (E) are triggered from outside the control loop and are introduced at one of the replaced elements (Actuator (A), Process (P), Sensor(S)). The generation of an event may be either a dynamic model itself, a boolean to activate specific states or a sequence of both. The effect of the event propagating through the control loop can be analysed. Note: The notion event is used here differently compared to timed discrete event processes [121], where a sequence of events is used to describe the actual process.

The simulated process as described above is therefore extended by a second layer describing the process characteristics captured by events. All known process characteristics can be either modelled in the physical process (P) or added by an event (E). The following list provides an overview of possible events considered. This is not a complete or finalized list, new events are added constantly.

- Measurement noise
- Measurement failure or fault
- Actuator failure
- Sensor calibration
- Surgical stimulation (pain reaction)
- Pulmonary embolism (see Section 6.5)
- Mismatch between patient model and controller model (intra and inter patient variability)
- Peak inspiratory airway pressure reaches constraint
2.3. Hardware-in-the-loop Simulation

2.3.3 The HIL Simulator Platform

Hardware

In Figure 2.10 the hardware set-up of the HIL simulator is shown. The actual control hardware is part of the environment and consists of a host (PC, WinNT, Oberon System 3) and a target (PowerPC, XO/2) computer. For both the controller platform and the simulator platform the host is mainly used for the interaction between control system and anaesthetist or between the simulator system and the trainer respectively via a man machine interface (MMI) and for data storage. The MMI is programmed using the gadgets framework of Oberon System 3 [43, 63, 127]. The target computers run with the real time operating system XO/2 [20, 21]. On the target of the controller platform the control algorithm and supervisor functions are implemented (see [46] for further details). On the simulator platform the derived models (see

![Figure 2.9: Hardware-in-the-loop set-up with the extension to generate events (E) including controller (C), actuator (A), process (P) and sensor (S).](image)

![Figure 2.10: Set-up of the HIL simulator consisting of the two independent platforms for the controller and for the simulator. The controller is operated by the anaesthetist, the simulator by a trainer.](image)
Section 2.1.3) are implemented to reproduce the patient behaviour. To test also the robustness of the control algorithm the patient model used in the simulator can be de-tuned in comparison to the model used in the controller (event). All events are started (triggered) by the trainer. An implementation of an automatic test sequence is possible, but has not been considered so far.

Software architecture

The simulator platform is set-up with the same software components as the controller platform. Figure 2.11 shows the software architecture of both controller and simulator platforms for host and target computers. Both system architectures are the same and therefore many components were copied with minor alterations. The hard real-time tasks implemented on the controller and on the simulator platform are not synchronized as in reality the peripheral devices (actuators and sensors) are also not synchronized. The only difference between the controller and the simulator target architecture is that in the latter the controller layer is missing and that the supervisor layer is replaced by an event layer. The event layer is necessary as some events either have a dynamic time response (e.g. dynamic model of painful stimulation) or have a finite horizon (e.g. auto-calibration of sensor subsystems). The target computers generate every five seconds (period of the task) a new actuator setting or sensor signal respectively. In each period the inputs are read first, the control algorithm or the mathematical model respectively produces a new output which is then sent to the other platform. The input devices are “threads”, which provide the last valid value independent of the actual time point of measurement. As a
safety feature the measurement consists of two values: The actual value of measurement and the time-stamp of the measurement. The receiving controller platform can use this additional information for the validity check of the measurements.

### 2.4 Clinical Evaluation

The general aims for the clinician and for the control engineer are somewhat different. For the anaesthetist the aim is to investigate a clinically relevant hypothesis, whereas for the control engineer it is to prove the developed concepts and to evolve a clinically applicable control system. Therefore, evaluation consists of two phases.

#### 2.4.1 Pilot Study Design

The aim of the pilot study is to check the proper functioning of the control algorithms and the operability in a clinical environment. The tuning of the control parameters and the additional handling procedures are finalized. The experience gained during the pilot study increases the maturity of the control system and therefore reduces potential “down-time” during the clinical study.

As patient variability is high several patients are needed to validate the implemented concepts. Often good parameter settings were found within two or three patients, but the validation of the handling procedures and additional add-on functions needed considerably more tests, as their activation cannot be predicted. From our experience most situations will appear at least once in a series of twelve clinical tests.

#### 2.4.2 Clinical Study Design

The beginning of the clinical study marks the end of the main work of the control engineer. The clinical study is designed to evaluate the controller concerning a clinical relevant hypothesis. Key questions are related to patient safety and patient benefit. Where possible a comparison between the performance of an anaesthetist and the performance of the closed-loop control system is targeted. For future clinical acceptance a relevant advantage for the automatic system over the anaesthetist is necessary.

Up to 20 or more patients are enrolled for the clinical study. Patients are preoperatively classified into standard physical status classification provided by the American Society of Anesthesiologists (ASA I to V) [105]. This classification provides information on the health conditions
of the enrolled patients. Mainly patients classified ASA I to III are considered in this evaluation. So far mainly patients undergoing elective neuro-, orthopaedic, plastic, gynaecologic or visceral surgery are considered. No patients undergoing cardiac surgery and no critically ill, children or elderly patients are considered.

The standard anaesthesia team responsible for the patient during surgery is reinforced with at least one additional research anaesthetist. Mostly a control engineer was present as well. The clinical study was conducted following a predefined protocol. Critical situations lead to an immediate abortion of the clinical study. No such critical situation caused by the automatic control system occurred throughout the different clinical evaluations.

In clinical studies where the performance of the system is compared to the performance of an anaesthetist, the patients are randomly assigned to an automatic control group (AC) or a manual control group (MC). The clinical study provides further evidence of the functionality and the validation of the automatic control system.

2.4.3 Performance Assessment

Different performance parameters for the assessment of safety and patient benefit are under discussion [140], but are not analysed in detail in this thesis. Depending on a hypothesis different performance parameters are used to corroborate or abandon it. For computer controlled infusion pumps (target controlled infusion) - strictly open-loop systems - different performance parameters were suggested in [168] and subsequently also used for closed-loop systems [1, 2, 163]. However, these performance parameters strongly depend on the chosen set-point and by using median values the actual performance is “embellished”. Other performance measures for volatile anaesthetics based on mean values were used in [88, 169, 170] to validate model predictions. Overshoot and response time were used in [137, 175] to assess dynamic performance of closed-loop systems. For brevity only a restricted amount of parameters are considered, which are not set-point dependent.

Static performance parameters

Static performance is expressed by the average absolute deviation (AAD) from set-point, given in Equation (2.31) and the mean error (ME) from set-point is given in Equation (2.32).

The $AAD_j$ for each patient $j$ is calculated as

$$AAD_j = \frac{1}{n_j} \sum_{i=1}^{n_j} |m_j(i) - r_j(i)|$$  \hspace{1cm} (2.31)
where \( n_j \) is the total amount of measurements of patient \( j \), \( m_j(i) \) is the measurement at time step \( i \) and \( r_j(i) \) is the reference at time step \( i \). The AAD for all \( j \) patients is expressed as mean and standard deviation (SD).

The \( ME_j \) for each patient \( j \) is calculated as

\[
ME_j = \frac{1}{n_j} \sum_{i=1}^{n_j} (m_j(i) - r_j(i))
\]

(2.32)

The \( ME \) for all \( j \) patients is expressed as mean and SD.

The AAD is a measure of accuracy and the \( ME \) a measure of bias. Additionally, as an intuitively understandable measure the percentage of measurements in a range of \( \pm \varpi \% \) of set-point (\( R_{\varpi \%} \)) is given in Equation (2.33). Several \( \varpi \), specific for the control objective may be chosen.

The \( \varpi \% \) range is calculated as

\[
R_{\varpi \%} = \frac{\sum_j \sum_{i=1}^{n_j} N_j(i)}{\sum_j n_j}
\]

(2.33)

with

\[
N_j(i) = \begin{cases} 
1 & \text{forall } i \text{ with } |m_j(i) - r_j(i)| \leq \frac{\varpi}{100} \cdot r_j(i) \\
0 & \text{else}
\end{cases}
\]

**Dynamic performance parameters**

Set-point changes are rarely relevant in clinical routine and therefore most of the controllers presented in the following are not statistically evaluated concerning any dynamic performance parameters.

Nevertheless, where applicable dynamic performance is assessed by overshoot \( OS \) after set-point change and by rise time \( RT \) (time from 10\% to 90\% of set-point change). Both parameters are good indicators of disturbance suppression performance of the control loop which is clinically much more relevant than set-point responses. Depending on the length of surgery several set-point changes are performed, typically between two to ten. All dynamic performance parameters are expressed as mean and standard deviation (SD) over all patients.
2.5 Discussion

Modelling

The starting point is a higher order physiological pharmacokinetic model compared to mamillary compartmental pharmacokinetic models for the specific drugs (Table 2.1).

Physiologically based models are tuned to satisfy the drug specific properties. They are tuned by adjusting the elimination constants according to the elimination half-life of the specific drug and by determining the partition coefficients according to one of four specific approaches. The derived models can be validated by comparing \( V_{dss} \) and \( Cl \), which are independent of model structure. Under these circumstances it was concluded that an appropriate physiological pharmacokinetic model can be identified. Where necessary, the parameters of a fractional sigmoid \( E_{max} \) model were then adjusted using pharmacodynamic data after bolus application.

Table 2.1: Comparison of free (drug dependent) model parameters for mamillary compartmental and physiologically based PKPD models.

<table>
<thead>
<tr>
<th>Model type</th>
<th>PK</th>
<th>PD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>mamillary compartmental, 2 compartments</td>
<td>4</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>mamillary compartmental, 3 compartments</td>
<td>6</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>mamillary compartmental, 5 compartments</td>
<td>10</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>physiologically based, 12 compartments</td>
<td>24</td>
<td>2</td>
<td>26</td>
</tr>
<tr>
<td>physiologically based, 12 compartments\textsuperscript{1}</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

\textsuperscript{1} reduced parameters due to parameter reduction procedures

In Table 2.1 the number of free parameters for mamillary compartmental and physiologically based pharmacokinetic and pharmacodynamic models are summarized. Clearly the initial number of free parameters for physiologically based models is much higher. However, often evident assumptions reduce the number of free parameters significantly. Moreover, mamillary compartmental models normally only consider central elimination, which is a similar assumption as the assumption made to reduce the physiologically based model. A mamillary compartmental model assuming peripheral elimination can be found in [85].

Mamillary compartmental models consist of two or more pharmacokinetic compartments, the effect site compartment and the fractional \( E_{max} \) model. The described physiologically based model consists of the 12 pharmacokinetic compartments, where one of them is a designated effect site compartment, and the fractional \( E_{max} \) model. Therefore, the difference in the number of pharmacodynamic (PD) parameters is that for the mamillary compartmental model the additional effect site compartment is described by an additional parameter \( k_{e0} \).

On the contrary to [37], where an actual model reduction was successfully performed, only a
2.5. Discussion 43

Parameter reduction was attempted here. The advantage of the parameter reduction procedure is that the physiological character of the model is not changed, i.e. physiological parameters are preserved and can be adjusted where necessary. In addition, the model structure is the same for all drugs, independent of the importance of a compartment for the specific drug.

As mentioned earlier, the physiologically based model describes more accurately the initial distribution of the drug. It is therefore necessary to discuss the importance of the initial distribution in a closed-loop perspective. The time constant of the initial distribution can be associated with the short time constants (or with the high frequency components). In Figure 2.12 the Nyquist plot of the closed-loop system is shown, where the solid line represents a system where the physiologically based model is used and the dash-dotted line represents a system where a corresponding mamillary compartmental model is used. In both cases the same standard PI controller was used. It can be clearly seen that the phase margin for the system with the physiologically based model is significantly lower than for the system with the mamillary compartmental model. The lower the phase margin the less damped will be the closed-loop

![Figure 2.12: Nyquist plot of closed-loop systems using mamillary compartmental and a physiologically based model respectively.](image-url)
performance. The gain margin in both cases is not critical. The restricting factors are therefore the high frequency components. By using the physiologically based model these are more appropriately considered in the control design. On the other hand a control design based on the mamillary model is "ignorant" concerning the high frequency components and therefore poor performance caused by inaccurate control design has to be expected. This means also that more pilot trials are needed to fine tune the controller.

This is probably one of the reasons for the poor performance observed during a first attempt to regulate skeletal muscle relaxation with a mamillary compartmental model found in the literature [84]. After that, the corresponding physiologically based model was used instead, and from the beginning the performance was highly satisfying.

Controller design

The high inter and intra patient variability requests a robust control design. Moreover, the artefact prone and partially high noise level disturbed measurements request special handling and filtering procedures. The model based design provides for robustness and for artefact handling concepts as well as less sensitivity to noise. Moreover, standard design procedures (LQR) are well established and simplify the development procedure.

A special interest is in increasing the clinical applicability of the automatic control system. Clinical routine introduces situations which have to be handled by special "add-on" features to allow the automatic control system to be active without interruption. The design of these features are based on the imitation of clinical anaesthesia practice.

HIL Simulation

The hardware-in-the-loop simulation environment has proven to be a powerful tool to test and verify the applicability and the functionality of the controller platform. Many software problems were identified before initial testing of the controller on patients. Moreover, the involved anaesthetists were introduced to the functionality of the controller platform during "training sessions". Many additional features to improve the behaviour of the controller were brought up during discussions while performing those training sessions. The simulation environment proved to be a very effective tool not only in the development phase but in the identification of incidents caused by clinical situations\(^2\), which could be "replayed" in real time.

\(^2\)No critical incidents for the patients were caused by applying these controllers, however some unexpected clinical procedures caused the controller to react differently from what was expected.
Clinical evaluation

The clinical evaluation first in pilot studies and later in clinical investigations proves the applicability of the designed control system in a clinical setting. The statistical analysis of the performance parameters is important for the investigated clinical hypothesis, but is also an indicator for the maturity of the tested system. No clinical study can be conducted if the used equipment has not reached clinical applicability. Major interruptions are not allowed and therefore the system needs to be robust to situations caused by clinical routine. Furthermore, the performance parameters show the quality of the control performance over a wide range of patients. For brevity, only few performance parameters are presented, a more detailed analysis can be found in the forthcoming medical publications.
Chapter 3

Regulating Skeletal Muscle Relaxation

Measuring skeletal muscle relaxation has been well established and electronically driven syringe pumps provide the basis for an automated system. Muscle relaxing drugs, which are more generally known as neuromuscular blocking drugs, have only a moderate influence on analgesia state and depth of hypnosis. Therefore, regulating skeletal muscle relaxation has been the ideal application in anaesthesia to prove concepts and conduct studies in a clinical environment. Several research groups have been active in the last 15 years but no commercially available system has evolved. This may be the result of a moderate clinical and patient benefit, which does not justify the higher costs of development, purchase and training of the anaesthetist to introduce such a device. Moreover, the automatic systems proposed so far use a different measurement than the anaesthetist in standard clinical practice which has several unacceptable drawbacks. In the following the specific model for the neuromuscular blocking drug is derived and then, a controller using the same measurement as previously used by other research groups is described. Subsequently, a new concept is presented, which allows to evolve this research controller to a controller appropriate for clinical practice.
3.1 Introduction

To facilitate intubation during induction patients are generally totally relaxed. By relaxing the patient the risk of injuring the vocal cords is reduced. Depending on the type of surgery different levels of relaxation are maintained thereafter to ease surgical conditions. Muscle relaxation is affected by neuromuscular blocking drugs. For intubation a rapid onset of neuromuscular block is requested and therefore a multiple $ED95$ dose\(^1\) is administered to ensure total block in a short time. The administered dose depends on the drug used, it generally ranges between two to four $ED95$. To maintain requested levels of relaxation either repetitive boli are administered or a continuous infusion (for short acting drugs only) of a neuromuscular blocking drug is administered.

The advantage of infusing short acting drugs is that at the end of surgery the neuromuscular block reverses spontaneously in a short time which is necessary for the patient to be extubated. For long acting neuromuscular blocking drugs an active reversal of the block by administering an antagonist is mandatory, else extubation might be delayed. In clinical routine delays are a cost factor, because of the prolonged surgical schedule. Continuous infusion of short acting drugs allows more accurate maintenance of neuromuscular block and thus reduces overdosing and speeds up recovery. Using an automatic control system to maintain skeletal muscle relaxation increases the accuracy of the desired block and minimizes the administered drug at the same time. Furthermore, more appropriate levels of relaxation corresponding to the clinical requirement can be targeted as the observation interval is considerably reduced.

3.1.1 Neuromuscular Blocking Drugs and their Mechanism of Action

Neuromuscular blocking drugs block the transmission of nerve signals at the neuromuscular junction. In Figure 3.1 the neuromuscular junction is shown. A nerve stimulation increases the electrical potential at the presynaptic terminal membrane, which releases acetylcholine (ACh) from a reservoir. The ACh molecules diffuse across the synaptic cleft and bind to specific receptors at the motor endplate of the muscle fibre. Bound receptors open ion channels generating the endplate potential, which causes the muscle to contract. Acetylcholine (ACh) is rapidly hydrolyzed by an ACh specific enzyme (acetylcholinesterase) causing the ion channels to close which repolarizes the endplate.

Two types of neuromuscular blocking drugs are used. Depolarizing neuromuscular blocking drugs are able to bind likewise to the ACh receptors. Similarly the ion channels are opened but the neuromuscular blocking drug is not hydrolyzed by acetylcholinesterase. The molecules diffuse away and are hydrolyzed by a different enzyme (pseudocholinesterase) in the plasma. Therefore, the depolarization of the endplate is prolonged in comparison to ACh. The most

\(^1\) The $ED95$ dose is the effective dose (population average) required to achieve 95% of total effect.
3.1. Introduction

Figure 3.1: Schematic representation of the neuromuscular junction.

A common depolarizing neuromuscular blocking drug is succinylcholine, which is mainly used for intubation as the onset is rapid and the duration of action is short. Succinylcholine has many side-effects, which are not further described.

On the other hand non-depolarizing neuromuscular blocking drugs are able to bind to the ACh receptors, but are not able to open the ion channels and therefore no endplate potential is developed. With the exception of mivacurium, all non-depolarizing drugs (such as atracurium, vecuronium, pancuronium and rocuronium) are not hydrolyzed by a specific enzyme. Therefore, the reversal of action depends on the relative slow process of redistribution, metabolism and excretion. Mivacurium, like succinylcholine, is hydrolyzed by pseudocholinesterase into inactive metabolites and has therefore a short duration of action.

3.1.2 Measurement Procedures

In clinical practice the degree of muscle relaxation (or the level of neuromuscular block) is measured by assessing responses to peripheral nerve stimulations (typically on the ulnar nerve). For brevity, only the relevant stimulation and measurement method is described, which is the standard measurement procedure. The usual method to assess degree of relaxation is based on a train-of-four (TOF) stimulation [105] and the respective measurement of response (Figure 3.2). A series of four stimulations in an interval of 500 ms, each 0.2 ms long, is applied. The stimulation current is normally “supramaximal”. After start of anaesthesia, i.e. the patient is already unconscious, but before administration of the neuromuscular blocking drug
Figure 3.2: The train-of-four nerve stimulation (front) and the corresponding evoked muscular response (back).

The measurement current is assessed. Single stimulation twitches are applied with increasing current until no increasing response is detected. The supramaximal current is defined as a 10% higher current than the detected current during this process. However, it may not exceed 70 mA for the specific monitor used. This procedure is commonly referred to as calibration as additionally a reference response is defined, which is used to relate the following measurements with. In clinical practice usually only the number of twitch responses, either assessed by the anaesthetist directly by visual or tactile observation or by a measuring device, is used. Commonly this measurement is referred as TOF-Count or simply count. For better reading the abbreviation TC is used. The measuring device is based either on measuring the evoked force (mechanomyography), the evoked acceleration (acceleromyography) or the evoked action potential of the muscles (electromyography) [171]. For most kinds of surgeries one or two twitch responses define a sufficient level of muscle relaxation. In clinical research and in pharmacokinetic and pharmacodynamic studies in particular [172, 173] the TC measurement is not sufficiently precise. Therefore, the more exact measurement of $T1\%$ is used, which is defined as

$$T1\% = 100 \frac{a_1}{a_{1,\text{ref}}} \quad (3.1)$$

where $a_1$ is the response of the first twitch and $a_{1,\text{ref}}$ is the reference twitch assigned during calibration of the measurement system. Neuromuscular block is defined as $100 - T1\%$. An approximation relating $T1\%$ to $TC$ is given in [78], where it is stated that 8%, 20%, 33% and 44% correspond to one, two, three and four twitch responses ($TC$) respectively.

A third measurement, which is referred as TOF% is defined as

$$TOF\% = 100 \frac{a_4}{a_1} \quad (3.2)$$

where $a_4$ is the response of the fourth evoked response. The fading of the consecutive twitch
3.1. Introduction

Responses correlates to the ability of the synaptic cleft to re-polarize. In clinical routine this measurement is sometimes used as an indicator for extubation. A TOF% greater than 50% to 70% is necessary as it indicates safe return of muscle power [123]. Other publications [23, 79] target a TOF% ratio larger than 70%-90%.

For control purposes only the T1% measurement is sufficiently descriptive and smooth, but is not generally used in clinical practice. TOF-Count on the other hand is clinically used, but is clearly insufficient for control purposes because of the large quantization intervals. Moreover, at the beginning of the measurement procedure the T1% measurement drifts significantly [99]. This phenomenon is well known but its origin is still unknown. However, good clinical research practice [172, 173] suggests that after start of anaesthesia but prior to administering neuromuscular blocking drugs this base line drift is stabilized, which may take ten to twenty or even more minutes. During this period of stabilizing the base line drift in T1%, the airway of the patient is not secured and the anaesthetist has to manually ventilate the patient. This clearly increases the risk for the patient and it prolongs the time between induction and actual start of surgery, which is intolerable in clinical practice.

The measurement device used to assess T1% and TC is based on electromyography (Datex Ohmeda, AS3 monitor with NMT module). The degree of relaxation is assessed every 20 seconds.

3.1.3 Previous Work and State of the Art

Automatic feedback control of skeletal muscle relaxation has been addressed by several research groups, mainly because syringe pumps can be easily controlled by computer systems and more importantly a direct and reliable measure of effect is available. All authors except one [35] use the T1% measure to control muscle relaxation. Performance is generally assessed in relation to neuromuscular block instead of degree of relaxation (T1%) because the performance parameters depend on the selected set-point: A set-point of 90% block yields “nicer” results than with the corresponding set-point of 10 T1%. Different drugs, different control strategies and different models are used. A summary of publications is listed in Table 3.1; publications are sorted by year of publication and their different characteristics are stated.

For all drugs a wide variety of control strategies can be found ranging from on-off controllers to model based and adaptive controllers. It is notable that all publications concerning mivacurium use controllers which are based on a mathematical model.

Many controllers exist for the neuromuscular blocking drug atracurium, which is a drug of intermediate duration (T1/2 = 20 minutes [178]) and is often used in clinical practice. Over

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2 In some countries it is standard practice to intubate the patient without administration of any neuromuscular blocking drug. This technique is rarely used by the involved anaesthetists.
Table 3.1: Summary of publications concerning automatic control of muscle relaxation.

<table>
<thead>
<tr>
<th>Publication</th>
<th>Model</th>
<th>Controller</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MC</td>
<td>PB NN</td>
<td>PID</td>
</tr>
<tr>
<td>[6]</td>
<td>-</td>
<td>-</td>
<td>✓</td>
</tr>
<tr>
<td>[36]</td>
<td>-</td>
<td>-</td>
<td>✓&lt;sup&gt;5&lt;/sup&gt; - -    - -   ✓&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>[19, 166]</td>
<td>✓</td>
<td>-</td>
<td>✓    - ✓    - ✓  -    -</td>
</tr>
<tr>
<td>[179]</td>
<td>-</td>
<td>-</td>
<td>✓    - -    - ✓    -</td>
</tr>
<tr>
<td>[176]</td>
<td>-</td>
<td>-</td>
<td>✓&lt;sup&gt;5&lt;/sup&gt; - -    - ✓    -</td>
</tr>
<tr>
<td>Sev&lt;sup&gt;6&lt;/sup&gt;</td>
<td>✓</td>
<td>-</td>
<td>✓ -    - ✓    - ✓    ✓&lt;sup&gt;1,3&lt;/sup&gt;</td>
</tr>
<tr>
<td>[112]</td>
<td>-</td>
<td>-</td>
<td>✓    - -    - ✓    -</td>
</tr>
<tr>
<td>[7]</td>
<td>-</td>
<td>✓</td>
<td>✓    - -    - ✓    -</td>
</tr>
<tr>
<td>[95]</td>
<td>✓</td>
<td>-</td>
<td>✓    - ✓    - ✓    -</td>
</tr>
<tr>
<td>[41, 96, 130]</td>
<td>-</td>
<td>-</td>
<td>✓&lt;sup&gt;7&lt;/sup&gt; ✓&lt;sup&gt;7&lt;/sup&gt; ✓ - -    - ✓    -</td>
</tr>
<tr>
<td>[76]</td>
<td>✓</td>
<td>-</td>
<td>✓ -    ✓&lt;sup&gt;7&lt;/sup&gt; ✓&lt;sup&gt;7&lt;/sup&gt; ✓ - -    - ✓    -</td>
</tr>
<tr>
<td>[98]</td>
<td>-</td>
<td>✓</td>
<td>✓    - -    - ✓    -</td>
</tr>
<tr>
<td>[52, 86]</td>
<td>-</td>
<td>✓</td>
<td>✓ -    ✓ -    - ✓    -</td>
</tr>
<tr>
<td>[154]</td>
<td>✓</td>
<td>-</td>
<td>✓    - -    - ✓    -</td>
</tr>
<tr>
<td>[35]</td>
<td>-</td>
<td>✓</td>
<td>✓ -    ✓ -    - ✓    -</td>
</tr>
</tbody>
</table>

Abbreviations: MC, mamillary compartmental model; PB, physiologically based model; NN, models derived by neuronal networks; PID, PID control techniques; MB, model based control techniques; FU, fuzzy control; AD, adaptive control algorithms; A, atracurium; M, mivacurium.

Footnotes: 1 vecuronium; 2 pancuronium; 3 rocuronium; 4 regulates TC; 5 on-off controller; 6 several publications from the same authors with similar set-up [40, 73, 74, 100, 114, 115, 116, 117, 141]; 7 fuzzy logic is used for model adaptation.

20% of conducted anaesthesia use atracurium [10].

As mentioned before, all publications but one use T1% to control skeletal muscle relaxation and even though first attempts were made nearly 20 years ago, no control system has evolved, which is applicable in clinical routine.

In [35] a simple controller (probably on the basis of PID) is used to maintain skeletal muscle relaxation for 48 hours in one patient in the intensive care unit. The patient received rocuronium, a drug with an intermediate duration (T<sub>1/2</sub> = 69 minutes [4]) and the control objective was to maintain TC between 0 and 2. This publication does not give any details of the controller. It is a “case report” and it focuses on the decreasing infusion requirement of rocuronium over a long time period.
3.1.4 Problem Formulation

A controller for skeletal muscle relaxation has not been investigated so far in our research group and it is therefore necessary for the overall aim to automate the main four tasks of the anaesthetists. Only few approaches to regulate skeletal muscle relaxation with mivacurium have been presented. The short duration of action is ideal for continuous administration but introduces also more difficulties concerning modelling and control. In a first step a “standard” T1% controller is designed and in a second step the goal is to improve clinical applicability by introducing new concepts.

3.2 The Mivacurium Model

Mivacurium is a short acting, non-depolarizing neuromuscular blocking drug [135]. It is metabolized by pseudocholinesterase (i.e. plasmacholinesterase) [105] and the metabolites are pharmacologically inactive. The liver eliminates the metabolites. For the case of neuromuscular blocking drugs the pharmacodynamic information can be easily found in the literature as corresponding studies can rely on a directly measurable effect. Mivacurium consists of three isomers - \textit{trans-trans}, \textit{cis-trans}, \textit{cis-cis} - with different fractions, different clearance rates and different potencies [26, 31, 68]. In Table 3.2, which is reproduced from [26], these characteristics are summarized. Instead of clearance rates the elimination half-life $T_1/2$ is given, as this is used later for the tuning of the model. The \textit{cis-cis} isomer has clearly the lowest clearance rate, i.e the highest elimination half-life, but has the lowest fraction and the lowest potency. The other two isomers (\textit{trans-trans} and \textit{cis-trans}) have similar characteristics. For the tuning of the model a weighted average of the characteristic parameters is used where only the two active isomers are considered. An average elimination half-life can be derived by $0.4 \cdot 1.8 + 0.6 \cdot 1.9 = 1.86 \text{ min}$, yielding $\kappa = \frac{m(2)}{T_{1/2}} = 0.37 \text{ min}^{-1}$. Similar values for $T_{1/2}$ (2-3 minutes) can be found in [68], and in [120] where age dependent $T_{1/2}$ are given.

<table>
<thead>
<tr>
<th>Isomer</th>
<th>Relative fraction</th>
<th>Relative potency</th>
<th>$T_1/2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>trans-trans</td>
<td>52-62%</td>
<td>1</td>
<td>1.9 min</td>
</tr>
<tr>
<td>cis-trans</td>
<td>34-40%</td>
<td>1</td>
<td>1.8 min</td>
</tr>
<tr>
<td>cis-cis</td>
<td>4-8%</td>
<td>1/10</td>
<td>52.9 min</td>
</tr>
</tbody>
</table>
3.2.1 Pharmacokinetic Tuning

As mentioned before mivacurium is hydrolyzed by pseudocholinesterase into inactive metabolites in the blood. Therefore, all $\kappa_i$ are equal ($\kappa = \kappa_i$). However, it is only metabolized in the blood part of the compartment and therefore $\kappa$ is scaled with $V_i h$. The parameters $\kappa$ can be derived from the average elimination half-life $T_{1/2}$, which is known from above.

The documented mamillary compartmental models of mivacurium generally consist of two compartments [85, 119]. From the conclusion in Section 2.1.3 it is sufficient to use approach (iv) to tune the pharmacokinetic model. The same tissue/blood coefficients are therefore assumed ($\lambda_i = \lambda$).

The onset time of effect, i.e. time to maximal block after an administration of a specific bolus, is used to tune $\lambda$. The onset time corresponds to the time at which the concentration at the effect site peaks after a bolus. In contrast to standard procedures on pharmacokinetic modelling, where the plasma concentration time course is used to identify the model, this approach allows directly to tune the concentration time course in the effect compartment. For a given volume and perfusion of the compartment the partition coefficient $\lambda$ determines the time of peak effect after a bolus dose. Therefore, the onset time is used to empirically determine $\lambda$. It appears obvious that the effect of neuromuscular blocking drugs is correlated to the concentration time course in the muscle compartment. From [135] bolus dependent onset times are known, which are population averages derived from input output data sequences. In other publications [31, 68] similar values can be found. For a bolus of 0.15 mg/kg bodyweight the onset time is 3.3 minutes. Therefore, $\lambda$ was adjusted until the correct onset time was obtained for the muscle compartment in simulations ($\lambda = 0.3$).

3.2.2 Pharmacodynamic Tuning

The specific $E_{max}$ model for mivacurium is derived from Equation (2.11) and is described by Equation (3.3),

$$T1\% = 100 \left( 1 - \frac{C_T}{C_T^* + EC_{50}^*} \right)$$ (3.3)

where $C_T$ - the mivacurium concentration in the muscle compartment - is used as the effect site concentration.

Additional model independent descriptors of pharmacokinetics and pharmacodynamics are the different recovery times, i.e. the elapsed time before the block has returned to 25% ($T_{25}$) or to 95% ($T_{95}$) after bolus administration. A wide selection of recovery times (10%, 25%, 75%, 90%, 95%) can be found in the literature [31, 68, 69, 120, 135]. It is sufficient to focus on data from [31, 135], as the values from all sources correlate well.
Recovery times (population average) from total block to recovery of twitch response can be used to tune the PD parameters $\gamma$ and $EC_{50}$ in simulations. As an example the time course of neuromuscular relaxation $T1\%$ compared to the pharmacodynamic descriptors onset and recovery time is shown in Figure 3.3. The resulting $\gamma$ and $EC_{50}$ are 7.5 and 100 ng/ml, respectively.

Figure 3.3: Simulation of the time course of neuromuscular relaxation after a bolus administration of 0.15 mg per kg bodyweight mivacurium (solid line) compared with the onset and recovery time published in [31, 135].

The simulation in Figure 3.3 shows a time lag of approximately two minutes, which corresponds to the pharmacodynamic effect observed. This is caused by the $E_{max}$ model as the sensitivity for low drug concentrations is marginal. The concentration time course of Figure 2.5 shows a smaller time lag.

3.2.3 Validation by Non-compartmental Analysis

The assumption of equal $\lambda_i$ values for mivacurium yielded a volume of distribution at steady state ($V_{dss}$) of 224 ml/kg or 318 ml/kg depending on the way it was calculated. This corresponds to the notion that mivacurium is distributed in the extracellular water and is in close agreement with the published $V_{dss}$ values. In Table 3.3 the published values for the steady state volume of distribution and the clearance are summarized and the derived values for the physiologically based model are added.

Some publications consider only the active isomers (the method of consideration is not specified in detail). Other publications state the values for the three isomers each and therefore, for comparison only the two active isomers were considered, weighted by their occurrence,
Table 3.3: Summary of the published pharmacokinetic parameters of mivacurium in comparison to the same parameters derived from simulations of the physiologically based model.

<table>
<thead>
<tr>
<th>Pub.</th>
<th>$V_{dss} \ [\text{ml/kg}]$</th>
<th>$Cl \ [\text{ml/kg-min]}$</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>[31]</td>
<td>112</td>
<td>70.4</td>
<td>1</td>
</tr>
<tr>
<td>[89]</td>
<td>235</td>
<td>88.8</td>
<td>2, 3</td>
</tr>
<tr>
<td>[65]</td>
<td>251</td>
<td>86.4</td>
<td>2, 4</td>
</tr>
<tr>
<td>[82]</td>
<td>51</td>
<td>39.1</td>
<td>2, 5</td>
</tr>
<tr>
<td>[82]</td>
<td>146</td>
<td>71.5</td>
<td>2, 6</td>
</tr>
<tr>
<td>[85]</td>
<td>53</td>
<td>25.7</td>
<td>2, 3</td>
</tr>
<tr>
<td>[119]</td>
<td>156</td>
<td>41.2</td>
<td>2</td>
</tr>
<tr>
<td>[138]</td>
<td>67</td>
<td>40</td>
<td>1</td>
</tr>
<tr>
<td>[120]</td>
<td>242</td>
<td>68.2</td>
<td>2, 3, 7</td>
</tr>
<tr>
<td>[120]</td>
<td>488</td>
<td>93.4</td>
<td>2, 3, 8</td>
</tr>
<tr>
<td>this model</td>
<td>268</td>
<td>25.8</td>
<td>9</td>
</tr>
<tr>
<td>model</td>
<td>350</td>
<td>25.8</td>
<td>10</td>
</tr>
</tbody>
</table>

1 Only the two active isomers considered. 2 Weighted average over the two active isomers. 3 $V_{dss} = (T_{1/2} \cdot Cl) / \ln(2)$. 4 Data only of healthy patients. 5 Data derived from intensive blood sampling. 6 Data derived from limited blood sampling. 7 Data of young adults. 8 Data of elderly people. 9 $V_{dss}$ derived by Equation (2.15). 10 $V_{dss}$ derived by Equation (2.17).

i.e 60% trans-trans and 40% cis-trans. As the main model parameters are within the range of published values, further tuning of the model was not attempted.

The mismatch between the two methods to calculate $V_{dss}$ results from a relative large $\kappa$ value. With the following equation this can be visualized:

$$\tau \frac{dc_{t}(t)}{dt} = \frac{q_{t}}{q_{t} + \kappa \overline{V}} c_{A}(t) - c_{t}(t) \quad (3.4)$$

Equation (3.4) is directly derived from Equation (2.3) with

$$\tau = \frac{V_{t}}{q_{t} + \kappa \overline{V}} \quad (3.5)$$

The two methods to derive the apparent volume of distribution at steady state (Equations (2.15) and (2.17)) have an important difference. While Equation (2.17) is a pure “static” calculation, the derivation in Equation (2.15) is based on a dynamic simulation, i.e. depends on the characteristic time constants of the system. Equation (3.5) visualizes that the time constant $\tau$ of the compartment is altered by $\kappa$. Hence, for large $\kappa$ values the characteristic time constant $\tau$ is reduced. From the result in Table 3.3 the volume of distribution is reduced for the dynamic
derivation (Equation (2.15)) indicating that by reducing $\tau$ the steady state distribution volume is reduced as well.

This hypothesis cannot be strictly proven, but by analogy to mamillary compartmental pharmacokinetic models this can be plausibly explained. A compartmental concentration of a mamillary compartmental model consisting of two compartments as shown in Figure 2.1 is described for example by:

$$\frac{dc_2(t)}{dt} = k_{12} \frac{V_1}{V_2} c_1(t) - k_{21} c_2(t)$$

(3.6)

Equation (3.7) is derived by transformation analogously to Equation (3.4)

$$\tau \frac{dc_2(t)}{dt} = \frac{k_{12}}{k_{21}} \frac{V_1}{V_2} c_1(t) - c_2(t)$$

(3.7)

with $\tau = \frac{1}{k_{21}}$. The apparent volume of distribution at steady state $V_{dss}$ for a two compartment model [58] is $V_{dss} = (1 + \frac{k_{12}}{k_{21}})$ and substituting $k_{21}$ yields

$$V_{dss} = V_1 (1 + k_{12} \tau)$$

(3.8)

Hence by reducing $\tau$ the volume of distribution is reduced. Obviously, the comparison has to be handled with care as the mamillary compartmental model has a different structure compared to the physiologically based model. However, the expected direction of change is verified.

On the contrary, Equation (2.17) does not depend on $\kappa$ at all. For mivacurium, where $\kappa$ is relatively large and elimination takes place in all compartments, this effect is significant. Alfentanil in contrast to mivacurium has a relative small $\kappa$ and affects only one compartment and therefore the mismatch is expected to be much smaller, see Section 4.2.3 for details.

### 3.2.4 Comparison of the $E_{max}$ Model Parameters

The derived $\gamma$ and $EC_{50}$ of the physiologically based model do not differ significantly from values given in the literature. Only few pharmacokinetic pharmacodynamic models exist [84, 100, 138] and the available information is summarized in Table 3.4. In [100] a mamillary compartmental model is used for closed-loop control and in [84, 138] difficulties in modelling mivacurium behaviour is reported. Both publications try to circumvent these problems by introducing altered structures of the mamillary compartmental model. In [84] a peripheral link of the effect site instead of a central link is suggested and in [138] an additional compartment between central and effect site compartment is used (interstitial compartment). Therefore, in both cases an additional compartment is situated between the central and the effect compartment.

The $EC_{50}$ value is similar for all models as it corresponds to a constant infusion rate achieving steady state effect of 50%. On the contrary, the steepness of the $E_{max}$ model described by $\gamma$
Table 3.4: Summary of the published $E_{\text{max}}$ model parameters of mivacurium.

<table>
<thead>
<tr>
<th>Pub.</th>
<th>$\gamma$</th>
<th>$EC_{50}$ [ng/ml]</th>
<th>$\eta_{\gamma}$</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>[100]</td>
<td>3.5</td>
<td>100</td>
<td></td>
<td>derived from data recorded on children central link mamillary compartmental model</td>
</tr>
<tr>
<td>[138]</td>
<td>7.7</td>
<td>93</td>
<td></td>
<td>central link mamillary compartmental model</td>
</tr>
<tr>
<td></td>
<td>4.0</td>
<td>100</td>
<td></td>
<td>additional interstitial compartment between central and effect compartment</td>
</tr>
<tr>
<td>[84]</td>
<td>18.1</td>
<td>57</td>
<td></td>
<td>central link mamillary compartmental model</td>
</tr>
<tr>
<td></td>
<td>4.1</td>
<td>130</td>
<td></td>
<td>peripheral link mamillary compartmental model</td>
</tr>
<tr>
<td>this model</td>
<td>7.5</td>
<td>100</td>
<td></td>
<td>physiologically based model</td>
</tr>
</tbody>
</table>

varies considerably, which may explain the observed difficulties by other authors. Especially the central link model in [84] reports an exceptionally high $\gamma$ value, which would lead to an on-off characteristic of mivacurium rather than a gradually changing dose-effect relation.

3.3 Controller Design

In Section 3.3.1 a $T1\%$ controller for mivacurium is developed, which corresponds to controllers described in the literature. Its clinical applicability is a major obstacle and this is improved by introducing a cascade controller. The inner loop of the cascade is the $T1\%$ controller. The outer loop of the cascade produces the reference value of the inner loop by using $TC$ as the controlled parameter. The TOF-Count controller is described in Section 3.3.2.

3.3.1 $T1\%$ Controller

In Figure 3.4 the controller for regulating $T1\%$ is shown. The model of the patient response consists of a linear process $P$ corresponding to the pharmacokinetics and the non-linear dose-effect relation corresponding to the pharmacodynamics ($E_{\text{max}}$ model). Due to the non-linear dose-effect relation the controller is compensated to attain approximately unity gain by using the inverse function of the dose-effect relation. For the inverse function a parameter set of a standard patient is assumed. Using this “effect-dose” relationship the nonlinear pharmacodynamics is compensated and the value of $C_7$ can be approximated ($C_7_{\text{APP}}$). The $E_{\text{max}}$ model has a considerable variance. Even though extreme outliers are observed an uncertainty range of $\pm 25\%$ on $\gamma$ and on $EC_{50}$ covers most cases. By linearizing the standard and the extreme $E_{\text{max}}$ models in a typical operating point (i.e. 10 $T1\%$) a gain variation between 0.54 and 1.76 in relation to the standard model is observed. By compensating the dose effect relation with the
3.3. Controller Design

The resulting controller is linear with an additional integral action to reduce steady state errors and it is designed according to Section 2.2. In Figure 3.4 the integral action is shown simplified, a more detailed description is given later in Figure 3.6. The standard implementation described in Appendix A.2 with coefficient $k_{I,1}$ and anti windup feedback $k_{aw,1}$ is used. The anti windup coefficient is set to the dead beat condition.

The tuning parameters to derive the control parameters are:

$$Q = 1, \quad R = 0.3 \quad \text{and} \quad \Gamma = -6.75. \quad (3.9)$$

The tuning parameters to derive the output injection to the observer are:

$$\rho = 1, \quad \text{and} \quad R = 10. \quad (3.10)$$

The explicit parameters are given in Table B.1 in Appendix B.

**Noise sensitivity introduced by inverted nonlinearity**

By using the inversion of the $E_{max}$ model an approximately linear plant behaviour is generated, which allows linear design methods to be used. However, the inversion may introduce noise sensitivity. The $T1\%$ measurement has an intrinsic noise level which depends upon measurement procedures, measurement conditions and signal quantization. In Figure 3.5 two $E_{max}$ models with different degrees of nonlinearity $\gamma$ are shown. The effect site concentration is
normalized to the corresponding $EC_{50}$ value. The $E_{\text{max}}$ model of $PD1$ corresponds to the physiologically based model derived above and $PD2$ corresponds to the model used in [100] for closed-loop control. Again the typical operating point of $10\ T1\%$ is assumed. A hypothetical noise range corresponding to $\Delta T1\%$ would be translated by the inversion to a concentration range of $\Delta C1$ and $\Delta C2$ for $PD1$ and $PD2$ respectively. Thus the higher $\gamma$ is, the lower is the noise amplification by the compensation. This is especially important in an operating range below $10\ T1\%$, where a small variation in $T1\%$ causes a large variation on the approximated effect site concentration $C_{T\text{APP}}$.

![Figure 3.5: Noise sensitivity of the $E_{\text{max}}$ model for different $\gamma$ where the effect site concentration is normalized to $EC_{50}$ ($C_e/EC_{50}$), $\Delta T1\%$ is the usual operating region of the controller and $\Delta C1$ and $\Delta C2$ are the corresponding concentration ranges for a steep ($PD1$) and a flat ($PD2$) model respectively.](image)

**Anti windup, bumpless transfer and syringe refill strategy**

In Figure 3.6 the enhanced anti windup structure is shown. For operating state transition (man/ctrl) from manual ($i_R = i_{R\text{MAN}}$) to automatic control ($i_{R\text{AUTO}} = -k\bar{x} + i$) a standard bumpless transfer structure is used. The infusion rate is limited to the possible range ($0 = i_{R\text{MIN}} \leq i_R \leq i_{R\text{MAX}} \leq 1200\ \text{ml/h}$). Regularly during surgery the syringe of the infusion pump needs refilling. This typically requires 1 to 2 minutes. Switching back to manual and setting the infusion rate to zero during this period would reduce the integral action leading to an infusion rate of zero from where the controller output has to run up after switching back to automatic control. This produces a deficit of administered drug which leads to a significant overshoot in $T1\%$. Hence an additional switch (syringe change on/off) is inserted after the anti windup structure. Then the integral action is not reset but stays near its previous value (the integral action is tuned comparatively slow). Also the input $i_R$ to the patient and the observer is now zero. Therefore, the state variables $\dot{x}$ will decay and therefore the contribution $-k\bar{x}$ to $i_R$.
will decrease. Thus the output $i_{RAUTO}$ of the controller will increase. After the syringe change switch is put to off again, the increase in $i_{RAUTO}$ partially compensates the deficit in drug delivery during the syringe change. In control systems integral windup is generally avoided, as it tends to result in overshoot. In this specific case it is advantageous.

![Figure 3.6: Anti windup structure with additional switch for syringe change.](image)

### 3.3.2 TOF-Count Controller

In Figure 3.7 the structure of the TOF-Count controller is shown. Controller $C2$ corresponds to the $T1\%$ controller described in Section 3.3.1. Controller $C1$ makes use of the second measure the TOF-Count ($TC$), to adjust the reference ($T1\%_{REF}$) of the inner cascade. The TOF-Count is available in the train-of-four measurement procedure. It is coarse measure in the range between 0 and 4 and is regularly assessed during clinical routine. It is appropriate to refer to a $TC$ region as a whole range of $T1\%$ will provide the same $TC$ measurement. The signal characteristic and the clinical requirements lead to the structure of $C1$ shown in Figure 3.8. It is an integral controller ($I$) with an additional feed forward term ($f$). The feed forward term speeds up the

![Figure 3.7: Cascade structure of the neuromuscular block controller.](image)
system response after set-point changes. The $T1\%$ range corresponding to the clinical relevant levels of relaxation, i.e. one or two $TC$, is approximately $10T1\%$. The feed forward term is set to $5 \frac{T1\%}{TC}$ to provide half of the necessary “distance” to the next region. The integral action is tuned such that it “searches” for the $T1\%_{REF}$ by allowing the inner cascade to track the reference with a relative small deviation only. The allowed change is $1T1\%$ per minute.

Figure 3.8: Structure of controller $C1$ (outer cascade) with feed-forward $f$, integral action $I$, anti windup feedback $k_{I.2}$, additional input for the correction term $corr$ and the indication of variable constraints on $T1\%_{REF}$.

Due to the characteristic of $TC$, large deviations between $T1\%_{REF}$ and $T1\%$ may cause $T1\%_{REF}$ to move out of the corresponding $TC_{REF}$ region and lead to oscillatory behaviour. Moreover, the variability concerning the relation between $TC$ and $T1\%$ is considerable. The problem is visualized in Figure 3.9 for step change from one to two $TC$. Part A shows the reaction of the controller without the correction term. The feed-forward term causes a sudden change and the integral action further increases $T1\%_{REF}$ linearly. Only after $T1\%$ reaches two $TC$, $T1\%_{REF}$ is not further increased but kept constant. As shown in Part A the $T1\%_{REF}$ set by the outer control loop may produce a higher $TC$ and only after $T1\%$ enters the next region ($3 \ TC$) the integral action reduces $T1\%_{REF}$. Different methods to correct the behaviour can be considered. For example as soon as $T1\%$ enters the desired $TC$ region that specific $T1\%$ replaces the $T1\%_{REF}$ found by the outer cascade. Another possibility could be to use algorithms to detect the actual switching points between the regions and to use this information to calculate an appropriate $T1\%_{REF}$. From experience, population average values vary considerably and are not appropriate to derive $T1\%_{REF}$. Moreover, measurement drift, intraoperatively temperature and perfusion changes influence the relation considerably. Therefore, an approach by using a correction term is used in combination with a scheme to detect the actual switching points between the $TC$ regions.

The following correction term is added to the input of the integral action, with $\Delta = T1\% - T1\%_{REF}$. 

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure38.png}
\caption{Structure of controller $C1$ (outer cascade) with feed-forward $f$, integral action $I$, anti windup feedback $k_{I.2}$, additional input for the correction term $corr$ and the indication of variable constraints on $T1\%_{REF}$.}
\end{figure}
3.3. Controller Design

![T1% TC Graph](image)

Figure 3.9: Expected reaction of the controller without (A) and with (B) correction term in the outer cascade of the controller. Measured TC are shown in varying T1% ranges to emphasize that the distribution is not linear.

The expected behaviour is shown in Part B of Figure 3.9. As soon as the controller reaches the desired TC region the integral action changes direction, thus reference and measurement drift towards each other.

Additionally, the detection scheme adjusts the constraints on T1%REF by using a weighted average of the last eight T1% measurements, which caused a change in either direction between neighbouring TC regions (e.g. from 1 to 2 or from 2 to 1 TC). As long as no detection was made the corresponding constraint for T1% is not active. The detection algorithm is further described in Appendix B.2. By detecting the T1% which correlates to the switching point between two TC regions the controller receives information, which can be used to minimize drug consumption. In any case the correction term increases moderately T1%REF until the detected limit is reached. In case the switching point changes intraoperatively and therefore the detected limit allows the inner cascade not to trigger a TC change to the next higher region the corresponding limit is relaxed occasionally. Hence, the controller continuously searches for the minimal infusion rate required to maintain the desired TC region. To ensure that the controller C1 provides a T1%REF that is close to the switching point, the lower limit on T1%REF is set to the arithmetic mean of the upper and lower switching points of the specific region. A specific example and further explanations can be found in Section 3.5.2 (Figures 3.18 and 3.19).

The parameters of the controller are summarized in Appendix B.
The first clinical studies documented a huge difference between patients in the recovery characteristics of neuromuscular block. After administration of the same bolus dose with some patients the first twitch response returned after less than 10 minutes and with other patients only after 45 minutes. This depends strongly on the plasma cholinesterase concentration \([118]\) in the blood. The higher the concentration the faster is the elimination (i.e. inactivation) of mivacurium and hence the higher is the mivacurium consumption to maintain a specific level of relaxation. In \([50]\) it is stated that patients who took longer to recover from the bolus dose showed a subsequent reduction in dose requirements of mivacurium. To capture the variability a second parameter set for the \(T1\%\) controller tuned to a “slower” responding patient is implemented and if necessary can be switched to. So far it was not necessary to adjust the dynamics of the outer controller as it is already tuned to a slow response. Whether the slower tuned controller is used is related to the time of first twitch recovery. For a bolus of 0.3 \(mg\) mivacurium per kg bodyweight the switch-over threshold is 30 minutes.

### 3.3.3 Closed-loop Bandwidth

The closed-loop bandwidth of the inner cascade was derived by investigating the linear system only, i.e. without considering any pharmacodynamic relation or its corresponding inversion. This simplification does not change the system dynamics. Therefore, the closed-loop bandwidth of the inner cascade is 0.49 rad/min, resulting in a settling time of approximately 2 minutes.

The \(TC\) signal is used to “correct” the \(T1\%_{REF}\) by using an integral action and a detection scheme as described earlier. The part introducing a dynamic is only the integral action and therefore the detection scheme was neglected to derive the overall closed-loop bandwidth. Furthermore, a linear approximation was used to relate the effect site concentration \(C_7\) to \(TC\). By using

\[
\tilde{TC} = -\frac{C_7}{12.5} + 12
\]  

the range between 100 \(ng/ml\) to 150 \(ng/ml\), which corresponds to a range between 40 and 5 \(T1\%\) for a standard patient, is translated to a “continuous” range between 4 and 0 \(TC\). The continuous value is denoted with \(\tilde{TC}\). The derived overall closed-loop bandwidth is 0.06 rad/min and a settling time of approximately 16 minutes. Therefore, the inner loop is about eight times faster than the outer loop. This is in accordance to the design criteria, where the inner loop has to follow its reference with a small deviation only.

### 3.3.4 Artefact Handling Procedures

Several incidents may cause invalid or corrupted measurements. Measurement procedures may be stopped because an electrode is disconnected. Clinical handling of the measurement arm
may cause faulty detection of the evoked response. The observed results are often four twitch responses even though a relaxation degree of one or two twitches is maintained. As a specific \( TC \) is always related to a range of \( T1\% \) it is rare to have rapid changes of more than one \( TC \) from one to the next measurement. An exception of this rule occurs in case the corresponding \( T1\% \) range is very narrow, for example one or two \( T1\% \). Generally, the \( T1\% \) range for three \( TC \) is narrow and therefore direct changes from 2 to 4 \( TC \) are observed. Therefore, changes from zero and one \( TC \) to four \( TC \) is considered as faulty and both measurements (\( TC \) and \( T1\% \)) are considered as invalid. This rule is abbreviated as \( \delta \) in the following table, where \( \delta \) is true in case the measurement is valid.

Measurements are pronounced valid if the following conditions are fulfilled.

<table>
<thead>
<tr>
<th>Param.</th>
<th>min</th>
<th>max</th>
<th>( et ) [sec.]</th>
<th>( \delta )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( T1% )</td>
<td>0</td>
<td>130</td>
<td>(&lt;60)</td>
<td>TRUE</td>
</tr>
<tr>
<td>( TC )</td>
<td>0</td>
<td>4</td>
<td>(&lt;60)</td>
<td>TRUE</td>
</tr>
</tbody>
</table>

The elapsed time since measurement is described by parameter \( et \). In case the measurement is not updated for \( et \) seconds the measurement is invalid. In this specific case a new measurement is obtained only every 20 seconds, which means that the system allows one sampling instant to be missed before any action is taken. The \( T1\% \) may exceed 100%. Especially shortly after calibration of the supramaximal stimulation current at the beginning of anaesthesia this can be observed. The administration of anaesthetics may cause a change in measurement conditions (peripheral perfusion changes) which elevates the evoked response.

In case a measurement is detected as invalid, the last valid measurement is used instead. The anaesthetist is provided with the time since the last valid measurement was obtained and decides if the controller needs to be inactivated. For safety reasons the controller is not inactivated automatically, as this could be missed by the anaesthetist and may lead to critical situations for both the patient and the anaesthetist. In case of the administration of neuromuscular blocking drugs the worst case scenario is overdosing. This may lead to a prolonged block after surgery, but has no other implications. Therefore, a warning is issued and the anaesthetist has to decide on the further proceedings.

### 3.4 HIL Simulation

Testing of the system was carried out according to the descriptions in Section 2.3. After successful testing the controller was tested in a clinical setting. No HIL simulation results are shown here as the functionality of the controller and the additional add-on functions can be documented by the clinical tests.
3.5 Results

3.5.1 T1% Controller

In Figure 3.10 the recording of a typical clinical study is shown. The upper plot displays the reference and the measured $T1\%$ values. Additional markers indicate skin incisions (start of actual surgery). In this specific case a first small cut was made by the surgeons for laparoscopy. After minimal invasive surgery had not been sufficient a second larger cut followed (laparotomy). At the beginning the measurement is “stabilized” for more than ten minutes (stabilization phase) where a baseline drift in the measurement can be clearly seen. Generally a base line drift up

![Graph 1](image1)

![Graph 2](image2)

Figure 3.10: Clinical test regulating $T1\%$. Top: reference (dash-dotted, $T1\%_{REF}$) and measured $T1\%$ (solid). Bottom: infusion rate (solid, $i_R$).
to 20% or more can be observed in the first 10 to 20 minutes after induction before the signal stabilizes [172]. After signal stabilization follows the re-calibration of the supramaximal stimulation. This can be seen by the abrupt return of $T1\%$ to 100%. The administration of the bolus of mivacurium achieves a total block for intubation. At 58 minutes the controller was switched on. After 211 minutes the syringe was refilled and due to the compensation effect the time course of $T1\%$ is not visibly affected.

After approximately 170 minutes the visual character of the measurement as well as of the infusion rate changes. The character change suggests that some state of the patient changed which influenced the measurement procedure. Most likely this change is related to haemodynamic or perfusion changes. It is notable that the characteristics of the signal changed shortly after the second skin incision. Laparoscopy and standard surgery have different influences on the state of the patient. Pain level is different, which may cause an haemodynamic effect and result in the administration of more opioids. Opioids again influence the haemodynamic state and hence the influence is sustained. The base-line drift of the measurement at the beginning of anaesthesia might be related to haemodynamic or perfusion changes caused by the administration of anaesthetics. This is supported by [122] where it is stated that duration of anaesthesia influences the level of paralysis.

The $T1\%$ measurement is sensitive to disturbances caused by surgical procedures, such as repositioning of the patient. For example just after the second skin incision at about 155 minutes several sharp peaks can be seen on $T1\%$. These were caused by an additional surgeon trying to get comfortable at the operating table and thereby moving the patient’s arm used for measurements.

**Syringe refill strategy**

Figures 3.11 and 3.12 visualize the advantage of the enhanced anti windup procedures described above in case an empty syringe needs to be refilled or exchanged. In the top plots the measured $TC$, in the middle plot the reference (dash-dotted) and the measured (solid) $T1\%$ and in the bottom plot the infusion rate (solid) and the alarm flag (dotted) from the pump are shown. The pump issues a warning for many incidents. Among others a warning is announced in case a syringe is about to be empty. Furthermore, an open syringe “lock” of the infusion pump releases a warning. The pump state is requested every 5 seconds by the control system, which includes the alarm flag. Hence the activated alarm flag while the infusion rate is zero indicates the time where the pump was manipulated. The patient in Figure 3.11 is heavier than the patient in Figure 3.12, which results in the lower infusion rate of the latter. Both patients show normal behaviour concerning mivacurium requirements to maintain the target level of relaxation. In Figure 3.11 the additional syringe change procedures were not yet implemented. Even though the alarm flag only shows up for a short period during the time where the infusion rate is zero the infusion rate is kept far longer at zero as the actual measurement has not drifted away yet. This drift follows with a significant time delay, and as the period of no infusion was
prolonged the missing amount of neuromuscular blocking drug is significant. Moreover, the integral action has lost all information gained in the period before the refill of the syringe and therefore, the controller starts from scratch, which prolongs the effect even further. Not only the measured $T1\%$ is pushed from the reference, even the measured $TC$ shows a significant change indicating that the degree of relaxation has really shifted considerably. In Figure 3.12 the same plot is shown during a clinical trial where the additional refill procedures are implemented. The alarm flag shows up shortly before the infusion rate is zero, indicating that the pump is nearly empty. It shows up again while pump is manipulated, which can be compared to the time in Figure 3.11. Instead of loosing all information the controller compensates partially the missing neuromuscular blocking drug. The measured $T1\%$ and $TC$ are not disturbed.

Figure 3.11: Syringe change without special handling procedures. Top: $TC$, Middle: reference (dash-dotted, $T1\%_{REF}$) and measurement (solid) $T1\%$, Bottom: infusion rate (solid, $i_R$) and alarm flag returned by the pump (dotted).
3.5. Results

3.5.2 TOF-Count Controller

Overview

In Figure 3.13 a recording of a clinical test for the TOF-Count controller is shown. Just before 60 minutes the inner cascade ($T1\%$ controller) is switched on and at 100 minutes into the operation the outer cascade (TOF-Count controller) is activated as well. Even though the outer cascade reduces the reference $T1\%$ only moderately (approximately $-2T1\%$) the effect on the $TC$ is significant. Before the outer cascade is activated $TC$ varies between 2 and 4, after activation the $TC$ measurements are generally on target with some measurements below and

![Graph showing TC, T1%, and infusion rate over time](image)

Figure 3.12: Syringe change with special handling procedures. Top: $TC$, Middle: reference (dash-dotted, $T1\%_{\text{REF}}$) and measurement (solid) $T1\%$, Bottom: infusion rate (solid, $i_R$) and alarm flag returned by the pump (dotted).
above target. At 196 minutes the syringe was changed (refilled). The performance achieved during several set-point changes (to one and two $TC$) is good. Set-point changes to three $TC$ show that the controller has difficulties in finding an appropriate $T1\%_{\text{REF}}$. This is caused by an unexpected narrow $T1\%$ range corresponding to three $TC$. This is visualized in Figure 3.14 where $T1\%$ is plotted against the percentage of measured $TC$ for a specific $T1\%$. Black bars represent $0$, light grey $1$, grey $2$, dark grey $3$ and pale grey $4$ $TC$ respectively. Additionally, the total number of measurements for a specific $T1\%$ is shown in black dots. The $T1\%$ range that corresponds to $3$ $TC$ is very narrow; moreover there is no $T1\%$ which exclusively showed $3$ twitch responses. This obviously makes it difficult for the outer control loop to find a stable $T1\%_{\text{REF}}$. The narrow $T1\%$ range is partially a result of the physiology of the synaptic cleft. As previously mentioned, fading correlates to the ability of the synaptic cleft to re-polarize. The
time between the stimulations is equal and the first and second stimulation produce “standard” conditions for the dynamic process of re-polarization of the neuromuscular junction. The following third and fourth stimulation have the same “initial” conditions and therefore the evoked responses are practically equal. The result is the observed narrow and inconsistent range for three $TC$. A target of three $TC$ is clinically not used, which supports the fact that it is not relevant or not a consistent measure.

This is further supported by Figure 3.15, which shows the pooled data recorded during nine pilot studies of the TOF-Count controller. Two separate measurements were taken from different hands using two Datex AS3 monitors equipped with the NMT module. The measurement used for control was not base-line stabilized, whereas the measurement used as a reference was base-line stabilized before administration of the initial bolus (i.e. in compliance with good clinical research practice [172, 173]). Measurements were assessed every 20 seconds on both hands and in Figure 3.15 both recorded measurements are compared. In case both $TC$ measurements are independent of any stimulation condition such as stimulation current, hand temperature, perfusion differences and base-line stabilization, both measurements would be equal, i.e. only bars on the diagonal $(0, 0), (1, 1), (2, 2), (3, 3), (4, 4)$ are expected. Incidentally, Figure 3.15 shows the highest peaks on the diagonal. However, there are significant amount of measurements, which show differing results. It is noticeable that there is a tendency of higher reference measurements compared to the measurements used by the controller. This is probably caused by the fact that re-calibration of the supramaximal stimulation on the reference hand might shift the detection sensitivity. Furthermore, comparatively few measurements for three $TC$ but more for neighbouring combinations $(2, 4), (4, 2), \ldots$ are observed. This result has to be viewed with caution as the amount of observed measurements over the whole range is not distributed uniformly.
Figure 3.15: TC measurements of the reference hand TC(ref) versus TC measurements of the controller hand TC(ctrl).

No overdosing while maintaining total relaxation

A recording of a further patient is shown in Figure 3.16 where the T1% controller is switched on after 36 minutes and the TC controller is activated after 63 minutes. Both the inner and the outer cascade stay active until surgical procedures are nearly completed at 176 minutes. The set-point change after 85 minutes from one to two TC had not settled to near steady state before surgical procedures requested total relaxation of the patient. The patient was undergoing abdominal laparoscopy and during insertion of the device the patient needs to be well relaxed to reduce the risk of injuring any internal organs. The surgeons were instructed to announce insertion sufficiently early such that the controller was able to reach total relaxation. The elapsed time from set-point change to total relaxation is 5 minutes. The controller maintained total relaxation with a practically constant infusion rate i_R.

Further interesting information can be seen in Figure 3.17, which is a part of Figure 3.16, where the patient was totally relaxed. Additionally to the sensor used by the controller, the reference measurement, i.e. the measurement which was baseline stabilized, is shown. As mentioned before, the controller produces a practically constant infusion rate to maintain total relaxation. This is proven by the reference measurement T1%(ref), which does not show a total relaxation, but a single twitch response with a low T1% value. The reference measurement T1%(ref) is
3.5. Results

![Graphs showing TC, T1%, and infusion rate over time](image)

NMB T28B0300, Bodyweight = 49 kg

**Figure 3.16:** Recording of a pilot study. Top: reference (dash-dotted, \( TC_{REF} \)) and measured \( TC \) (solid); Middle: reference (dash-dotted, \( T1\%_{REF} \)) and measured \( T1\% \) (solid); Bottom: infusion rate (solid, \( i_R \)).

practically constant over the time where \( TC_{REF} \) is zero, indicating that the infusion rate set by the controller maintains the level of relaxation without overdosing, which ensures a minimal recovery time. This is supported by the fact that after the controller was inactivated the recovery of both sensor signals started at approximately the same time (180 minutes).

In Figure 3.16 and in Figure 3.17 the effect of an artefact can be seen. After 108 minutes, just before the start of surgical procedures the \( TC \) measurement is consistently at zero and a single measurement at four \( TC \) is observed. This is probably caused by the patient being positioned for surgery and therefore manipulations were carried out, which disturbed the measurement. Not only the \( TC \) measurement was corrupted, but also the \( T1\% \) measurement. This can be seen more accurately in Figure 3.17. The controller reacted immediately by temporarily increasing
Figure 3.17: Detail of Figure 3.16. Top: reference (dashed, $T1\%_{\text{REF}}$) and $T1\%$ measurement of the controller hand (solid, $T1\%_{\text{ctrl}}$) and of the reference (dash-dotted, $T1\%_{\text{ref}}$) hand; Bottom: infusion rate (solid, $i_R$).

The infusion rate. Subsequently, the artefact detection was adjusted according to Section 3.3.4.

Minimizing drug requirement

A recording of another patient is shown in Figure 3.18. This is an nice example where the controller minimizes drug consumption. This female patient underwent also abdominal surgery. At the beginning the mivacurium requirement is relative high, whereas towards the end it is low. After 100 minutes the infusion rate is more than 20 ml/h and at the end of surgery it is only above 6 ml/h. As mentioned before the inactivation of mivacurium depends upon the plasma
3.5. Results

Patient T28E0300, Bodyweight = 64 kg

Figure 3.18: Recording of a clinical study. Top: reference (dash-dotted, $TC_{\text{REF}}$) and measured $TC$ (solid); Middle: reference (dash-dotted, $T1\%_{\text{REF}}$) and measured $T1\%$ (solid); Bottom: infusion rate (solid, $i_R$).

Cholinesterase "activity", i.e. the available plasma cholinesterase. This is supported by the analysis of two blood probes, one taken at induction of anaesthesia and one after surgery was terminated. According to the analytical laboratory the normal range of plasmacholinesterase for this healthy female patient is 2000 - 6700 units/litre. In the beginning the plasmacholinesterase concentration was 5794 units/litre and after surgery it was only 2118 units/litre. Generally, a decrease of available plasmacholinesterase is observed, which results in lower mivacurium requirements.

Further information is gained in Figure 3.19 which is a part of the recording of Figure 3.18. Additionally, in the lower plot the variable constraints of $T1\%_{\text{REF}}$ are shown. The correction
term increases slowly $T1\%_{\text{REF}}$ until the upper constraint $T1\%_{\text{UP}}$ is reached at 210 minutes. Since $T1\%$ is sufficiently long in the range of the upper constraint, which should correspond with the switching point between the neighbouring $TC$ regions, but without any detection of the higher $TC$ value $T1\%_{\text{UP}}$ is relaxed and the correction term is free to increase $T1\%_{\text{REF}}$ further. After 222 minutes the higher $TC$ region is detected and therefore the upper constraint is re-initialized. The same procedure occurs again shortly after. This guarantees that both the dosing regime of mivacurium and the recovery from neuromuscular block are minimized.

![Figure 3.19](image)

**Figure 3.19:** Part of recording of Figure 3.18. Top: reference (dash-dotted, $TC_{\text{REF}}$) and measured $TC$ (solid), the reference is shifted by minus 0.1 for better visualization; Bottom: reference (dotted, $T1\%_{\text{REF}}$), measured $T1\%$ (solid) and the upper (dash-dotted, $T1\%_{\text{UP}}$) and lower (dashed, $T1\%_{\text{DN}}$) detected constraints of $T1\%_{\text{REF}}$. 

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**Figure 3.19:** Part of recording of Figure 3.18. Top: reference (dash-dotted, $TC_{\text{REF}}$) and measured $TC$ (solid), the reference is shifted by minus 0.1 for better visualization; Bottom: reference (dotted, $T1\%_{\text{REF}}$), measured $T1\%$ (solid) and the upper (dash-dotted, $T1\%_{\text{UP}}$) and lower (dashed, $T1\%_{\text{DN}}$) detected constraints of $T1\%_{\text{REF}}$. 

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**Figure 3.19:** Part of recording of Figure 3.18. Top: reference (dash-dotted, $TC_{\text{REF}}$) and measured $TC$ (solid), the reference is shifted by minus 0.1 for better visualization; Bottom: reference (dotted, $T1\%_{\text{REF}}$), measured $T1\%$ (solid) and the upper (dash-dotted, $T1\%_{\text{UP}}$) and lower (dashed, $T1\%_{\text{DN}}$) detected constraints of $T1\%_{\text{REF}}$.
3.5. Results

3.5.3 Performance Assessment

T1% controller

Fifteen patients (ASA class I and II) were enrolled undergoing general anaesthesia, two patients had to be excluded from the statistical analysis due to sensor problems and two more because the hand temperature dropped below 32°C. According to good clinical research practice [172, 173] a low hand temperature influences the measurement procedures. Accumulated time of closed-loop control of the remaining eleven patients was 29.6 hours.

The static performance parameters are summarized in Table 3.5.

Table 3.5: Static performance parameters of the clinical study using the T1% controller.

<table>
<thead>
<tr>
<th>Param. [unit]</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAD [T1%]</td>
<td>1.85</td>
<td>0.89</td>
</tr>
<tr>
<td>ME [T1%]</td>
<td>-0.28</td>
<td>0.30</td>
</tr>
<tr>
<td>R10% [%]</td>
<td>51.2</td>
<td>18.9</td>
</tr>
<tr>
<td>R20% [%]</td>
<td>72.9</td>
<td>18.6</td>
</tr>
<tr>
<td>R30% [%]</td>
<td>83.1</td>
<td>14.6</td>
</tr>
</tbody>
</table>

Note that the set-point was set at 10 T1% and therefore ranges of ±10%, 20% and 30% relative to T1%REF correspond to ±1, 2 and 3 T1% respectively. The standard deviation indicates that considerable variability of the signal is observed. This has to be handled with care as the R10%, R20% and R30% ranges are narrow at the operating point. Most publications change from a T1% to a neuromuscular block measurement for the statistical analysis, i.e. from 10 T1% to 90% block. This leads to a changed reference and similar results can be expressed in ±1%, 2% and 5% ranges. The R1%, R2% and R5% values are 45%, 71% and 91% respectively.

Additionally, the inter and intra patient variability of the infusion rate was analysed. The mean infusion rate of mivacurium during closed-loop control was 6.97 µg/min per kg body-weight and the inter patient range of the observed infusion rates was 3.87 µg/kg/min to 10.20 µg/kg/min. To compare inter patient variability the total time of closed-loop control was divided into segments of 30 minutes and an inter segmental ratio R for each patient j according to Equation (3.13) was derived

\[ R(j) = \frac{\max \left[ \bar{s}_R(j) \right] - \min \left[ \bar{s}_R(j) \right]}{\bar{i}_R(j)} \]  

(3.13)

where \( \bar{s}_R(j) \) is the vector containing all mean segmental infusion rates and \( \bar{i}_R(j) \) is the overall mean infusion rate of patient j. Intra patient variability derived by the inter segmental ratio R showed a mean of 0.31 and a range between 0.12 to 0.56 over all patients.
TOF-Count controller

The clinical study is currently under way. No statistical results are available yet.

3.6 Discussion

In comparison to mamillary compartmental PKPD models [84, 100], which entirely neglect the contribution of circulatory phenomena on drug distribution, the physiologically based PKPD model accounts for the initial phase of drug distribution (< 2 minutes after bolus administration). Modelling the distribution is obviously essential for closed-loop control purposes of mivacurium. The benefit of the enhanced modified anti windup structure is apparent as the temporary suspended infusion rate \((i_R)\) is compensated immediately after restart, thus the controlled variable \(T1\%\) varies only moderately. The measurement of \(T1\%\) is prone to movement artefacts caused by passive position changes of the patient’s hand used for measurements. No large inter patient variability of the dynamic performance was observed. However, large differences of inter patient and intra patient consumption of mivacurium were observed. This difference resulted in a static or slowly varying offset on the mean infusion rate, which was handled well by the integral action. Haemodynamic and perfusion changes may influence the measurement conditions.

For control purposes a sufficiently descriptive model for mivacurium was developed. The designed \(T1\%\) controller showed excellent results in clinical trials and the control structure allows handling of most clinical incidents (artefacts, faulty signals, syringe change). However, the duration to stabilize the \(T1\%\) is not tolerable in clinical practice as securing the airway has to be postponed accordingly in the unconscious patient.

Regulating \(TC\) with an underlying \(T1\%\) controller solved two main problems. Firstly, the anaesthetist is confronted with a measurement \((TC)\), which is used in clinical practice and secondly, the base line stabilization phase is not necessary as the outer cascade compensates this by adjusting the reference of the inner cascade automatically.

Controlling \(TC\) has proved to be possible and the accurate set-points \((T1\%_\text{REF})\) were found by the controller in the outer loop. Furthermore, controlling zero \(TC\) maintains a constant infusion rate without overdosing the patient. Even for long periods of more than an hour this performed well. The detection scheme to limit \(T1\%_\text{REF}\) allowed to minimize drug consumption.

The generally narrow and inconsistent \(T1\%\) range for three \(TC\) indicates that it does not provide consistent information of the level of neuromuscular block. The recorded data suggests that a train-of-three measurement would have no significant loss of information compared to the standard train-of-four measurement.
Performance assessment shows good results in set-point tracking and disturbance rejection. Similar performance results for mivacurium and other neuromuscular blocking drugs can be found in [74] even though they used a set-point of $5T1\%$ for mivacurium and $10T1\%$ for all the other drugs. Generally, a set-point furthest away from 50% effect is easier to track as the sigmoid form of the pharmacodynamics allows for a larger concentration variation to achieve the same $T1\%$ [7]. The lower set-point for mivacurium used in [74] indicates that the controller was not able to perform equally well with the short acting drug as with the drugs of intermediate duration of action. As the controller presented here was able to maintain a set-point at $10T1\%$ without any difficulty it may be concluded that the controller is superior to the controller presented in [74].

The observed variability between patients and within a patient is considerable. The clinical study with the $T1\%$ controller was carried out initially to show an interaction between blood $pH$ on the infusion requirements of mivacurium. Therefore, endtidal $CO_2$ was varied between 28 $mmHg$ (hyperventilation) and 42 $mmHg$ (hypoventilation) by using the controller described in Chapter 6. With the number of studied patients no significant interaction could be shown.

Furthermore, the observed variability within a patient suggests that closed-loop control is a necessity when using mivacurium for surgery where skeletal muscle relaxation is crucial. This is further supported by [10], where the usage of mivacurium in clinical routine is compared to other drugs. Mivacurium is rarely used for surgery where maintenance of paralysis is standard practice and more often used for surgery where paralysis is not necessarily maintained. This allows the indirect conclusion that maintaining skeletal muscle relaxation with mivacurium due to the short acting characteristics increases workload to the point where it becomes cumbersome for the anaesthetist. Only an automatic control system can reduce this workload.
Regulating analgesia is the most demanding control task because no direct and continuous measure is available yet. No true endpoint can be assessed, its definition is subject to ongoing discussions. In this chapter concepts are described which allow to imitate the current clinical practice concerning opioid administration, and it is not attempted to define a new measure.

First the concepts of pain perception and the resulting patient response is described. Then the derivation of the physiologically based model and the controller design are presented. The controller makes use of a simple algorithm to detect “pain” and to use this information to influence the dynamic response of the controller. Simulation results are used to support the developed concepts and the results of two pilot studies further validate the controller.
4.1 Introduction

4.1.1 Opioids and their Mechanism of Action

The basic building block of the nervous system are neurons, which are responsible for the transmission of information - including pain - in the body [51]. The neurons consist of three main parts, the receptor zone, the axon and the nerve endings. Information of a disturbance is captured in the receptor zone and triggered by either an electrical, a chemical or a mechanical stimulus. If the threshold of excitation is reached by the stimulus an action potential or nerve impulse is generated and conducted along the axon to the nerve endings or synaptic knob at the central nervous system (CNS). There the transmission is chemical and the disturbance is further evaluated. Opioids bind to specific receptors throughout the CNS and other tissues [105]. The main four receptors are the \( \mu \), \( \kappa \), \( \delta \) and the \( \sigma \) receptors, which have different clinical effect when an opioid binds. The same opioid may act as an agonist or antagonist of a clinical effect on different receptors. Opioids are most effective in the central nervous system and inhibit the presynaptic and postsynaptic response to excitatory transmitters (e.g. acetylcholine) from nociceptive neurons (i.e. nociceptors or pain receptors) [105]. Similar to the action of a neuromuscular blocking agent at the synaptic cleft between effector neuron and muscle (Chapter 3), the activated receptors alter the potassium and calcium ion conductance and are able to "block" the transmission of the disturbance.

The fast onset of opioids is related to the high lipid solubility which allows fast passage across the blood-brain barrier. The brain (and the CNS) is the main site of action of opioids.

Different opioids are used in different clinical situations. Intraoperatively mainly fentanyl, alfentanil, sufentanil and remifentanil are used, where the order reflects decreasing duration of action. Except remifentanil, which is hydrolyzed by nonspecific esterase in blood and tissue, the biotransformation of opioids depend upon the liver and their high hepatic extraction ratio causes their clearance to be dependent upon liver blood flow [105]. The metabolites are inactive and are eliminated by renal extraction.

4.1.2 Measurement Procedures

There is so far no direct measure for the state of analgesia of the patient. However, stimuli, which are perceived as pain, cause reactions of the autonomous nervous system. This is often referred as stress response. Both the neuronal and humoral reaction influence the patient in manifold ways. The main effect used in anaesthesia as an indirect measure of pain is the cardiovascular response. The cardiovascular response is observed in hypertension (increased blood pressure), which is caused by increased cardiac output, increased heart rate (tachycardia) and/or increased systemic vascular resistance [105]. Cardiac output is not routinely measured
on all patients, whereas arterial blood pressure and heart rate are.

Depending on the health state of the patient and type of surgical procedures arterial blood pressure is either measured invasively or non-invasively. The automatic non-invasive measurement of patient monitors are based on oscillometry. A cuff is inflated and the monitors measure the pressure at which the pulse oscillation amplitudes change [105] and from which the systolic, mean and diastolic pressures can be derived. Non-invasive or intermittent measurements are typically obtained every two to five minutes intraoperatively. The invasive measurement is based on placing a high pressure tubing through a catheter directly into an artery. The tubing is connected to a pressure transducer. The invasive or intra-arterial blood pressure provides beat-to-beat measurements and is considered the “gold” standard [105]. In the following mainly the invasive (iMAP) and non-invasive (MAP) mean arterial blood pressure are considered. Further blood pressure measurement procedures are known, but are not relevant in this context.

Heart rate (HR) is obtained at least via two different measurement procedures. The electrocardiogram (ECG) and the pulse oximeter directly provide the heart rate. Both measurements are routinely available. In case the invasive blood pressure measurement is applied, then even a third measurement of the heart rate is available.

### 4.1.3 Previous Work and State of the Art

Controlling depth of analgesia raises many questions. Firstly, there is no direct possibility to assess “pain” in an unconscious patient. Secondly, opioids do not generally influence the haemodynamic state of the patient, since they have a suppressing influence only in the presence of noxious stimuli. Patients undergoing general anaesthesia who are not stimulated painfully will therefore show no or only a moderate reaction to changes of opioid levels. During anaesthesia the “pain” level cannot be measured and therefore it is difficult to assess the required opioid level. The intraoperatively used opioids usually depress spontaneous breathing, which is critical towards the end of surgery as overdosing may cause unwanted prolongation of anaesthesia. With the exception of remifentanil, which is ultra-short acting and has an elimination half-life of a few minutes, the opioids have an elimination half-life of more than an hour. The ultra-short acting characteristic of remifentanil has a clinical disadvantage. An interrupted infusion of only a minute may cause the patient to feel pain and therefore, it is used often in combination with a second opioid, such as fentanyl, which provides a base level of analgesia and remifentanil is adjusted to suppress the faster variations of the effect caused by surgical stimuli. Alfentanil, on the contrary is short acting with an elimination half-life of about 100 minutes (see Section 4.2.1 for further details) and can be used either for consecutive administration of bolus or for continuous infusion.

In Table 4.1 an overview of publications is given. It reflects the situation that only in [53, 56]
Table 4.1: Summary of publications concerning automatic control of analgesia.

<table>
<thead>
<tr>
<th>Publication</th>
<th>Model</th>
<th>Controller</th>
<th>Controlled parameter</th>
<th>Controller output</th>
</tr>
</thead>
<tbody>
<tr>
<td>[187]¹</td>
<td>✓</td>
<td>- ✓ - ✓ ✓</td>
<td>$iMAP / q$</td>
<td>phenylephrine</td>
</tr>
<tr>
<td>[142]</td>
<td>✓</td>
<td>- ✓ - ✓ ✓</td>
<td>$EEG$</td>
<td>alfentanil</td>
</tr>
<tr>
<td>[81]²</td>
<td>✓</td>
<td>- ✓ - ✓ ✓</td>
<td>$iMAP$</td>
<td>nitroprusside</td>
</tr>
<tr>
<td>[53, 56]</td>
<td>✓</td>
<td>- ✓ - ✓ ✓</td>
<td>$iMAP / C_p$</td>
<td>alfentanil</td>
</tr>
<tr>
<td>This model</td>
<td>✓</td>
<td>- ✓ - ✓ ✓</td>
<td>$MAP / HR$</td>
<td>alfentanil</td>
</tr>
</tbody>
</table>

Abbreviations: PID, PID control techniques; MB, model based control techniques; FU, fuzzy based controllers; AD, adaptive control algorithms; $iMAP$, invasive mean arterial pressure; $MAP$, non-invasive mean arterial pressure; $EEG$, median EEG frequency; $q$, cardiac output; $C_p$, predicted alfentanil plasma concentration; $HR$, heart rate.

Footnotes: ¹ Not pain but vasoconstriction regulation. Tested on dogs in a laboratory setting. ² Not pain but intraoperative $MAP$ regulation during cardio pulmonary bypass.

Control of analgesia is considered. The focus of the other studies is on appropriate perfusion of the organs, which is a hypothetical anaesthesia endpoint, and not on the suppression of haemodynamic changes caused by a painful stimulus.

In [187] a model predictive controller (MPC) is used to influence the vascular resistance and therefore influences haemodynamic parameters. The controller was tested on animals only in a laboratory setting and no pain stimuli were present.

In [142] closed-loop administration of alfentanil is described on the basis of a median frequency of the electroencephalogram (EEG). This study does not address adequate analgesia as true endpoint. The feasibility to maintain an EEG derived parameter with an opioid results from the EEG depressant effect of the opioid. As mentioned above opioids act on different receptors and exhibit a variety of different effects which are not necessarily connected to the suppression of stress response.

In [81] a MPC framework is used to infuse sodium nitroprusside, a vasodilator and thus again the haemodynamic parameters can be influenced. The controller was used on two patients undergoing cardiac surgery during the phase of cardiopulmonary bypass, i.e. the patient’s heart is not perfused with blood.

Alfentanil was used in [53, 56] to regulate mean arterial blood pressure in a multiple input multiple output MPC framework, where not only $iMAP$ but also the predicted alfentanil plasma concentration was used to derive the infusion rate. The controller was able to relax the condition of set-point maintenance of $iMAP$ to avoid over- and underdosing. This is so far the most relevant contribution in targeting analgesia via haemodynamic parameters.

In [9] alfentanil was administered using a target control infusion concept, i.e. open-loop con-
4.2. The Alfentanil Model

trol. The target concentration was adjusted by the anaesthetist according to haemodynamic state changes (systolic blood pressure and heart rate).

4.1.4 Problem Formulation

Invasive blood pressure measurement is not routinely used on every patient undergoing elective surgery. The clinical indications for using an invasive measurement depend on the health state and on the type of operation. The patients considered during the clinical studies so far have been “healthy” (ASA classification I-III) in the sense of cardiac and pulmonary diseases. No critical ill patients have been considered and therefore, a main clinical indication for an invasive measurement is not given. Under research conditions an invasive measurement can be used, but this does not reflect clinical practice. Thus, a main goal of the controller to be designed is to use a non-invasive blood pressure measurement as an input signal to control analgesia.

The non-invasive measurement is obtained with a period typically of 5 minutes, but can be reduced to 2 minutes without any major implication for the patient or the measurement device. Haemodynamic changes, however, are more rapid and are most probably missed when using a sampling time of 2 or 5 minutes. Therefore, rapid changes are captured by the continuously available heart rate, which is measured by at least two sensors.

Similar to [53, 56] different constraints have to be considered to prevent over- and underdosing.

To summarize, the suggested controller shall use a non-invasive blood pressure measurement in combination with continuous heart rate measurement to adjust the administration of the opioid alfentanil.

4.2 The Alfentanil Model

Alfentanil is a synthetic opioid which undergoes extensive hepatic metabolism and clearance [77]. The metabolites are pharmacologically not active. A relative high lipid solubility (but considerably lower than the lipid solubility of fentanyl) allows a rapid onset of action [160]. A high lipid solubility of the drug is related to a high ability of the drug to cross the blood brain barrier and penetrate into nerve cells. It also increases elimination time significantly because the tissue acts as a reservoir.

\(^2\)At least for surgeries with a short duration.
4.2.1 Pharmacokinetic Tuning

The liver is part of the “well perfused” organ group of the physiologically based pharmacokinetic model (Section 2.1.4). Therefore, elimination is restricted to the compartment with subscript 4. All elimination constants $\kappa_i$ are zero except $\kappa_4 \neq 0$. As the elimination is reduced to one compartment only $\kappa_4$ is derived analogously to Equation (2.9) and by using Equation (2.7) yields

$$\kappa_4 = \frac{\ln(2)}{\frac{V_4}{q} \cdot \frac{T_{1/2}}{V}}$$

(4.1)

where $V$ is the total volume of all compartments and can be set equal to $V_{dss}$. Several publications report a similar terminal elimination half-life between 94...118 minutes [17, 18, 27, 145, 147], and $T_{1/2} = 111$ minutes was used in the model. The cardiac output and the flow through the specific compartment $q_4$ are known. The compartmental volume $V_4$ and the total volume depend on the tuning factor $\lambda$, which is set such that the concentration peaks in simulations at a specific time after bolus administration.

Generally, mamillary compartmental pharmacokinetic models of alfentanil consist of three compartments. Therefore, approach (iii) to tune $\lambda$ is considered (Chapter 2.1.4). From [12] the steady state tissue/blood partition coefficients of alfentanil in rats are known for different organs and tissue. From the absolute values the following relations for the different compartments ($\lambda_i = l_i \cdot \lambda$) are approximated and listed in Table 4.2. Note that for three compartments (V, A, 9) no such relation is required, as they do consist of a blood part only.

<table>
<thead>
<tr>
<th>Compartment</th>
<th>V</th>
<th>L</th>
<th>A</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>$l_i$</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>6</td>
<td>1</td>
<td>6</td>
<td>-</td>
</tr>
</tbody>
</table>

This approximation allows the model to be tuned by one parameter $\lambda$. Only few pharmacodynamic studies were conducted for alfentanil as there is no obvious measure of analgesia state. There are studies concerning the effect of respiratory depression [16, 101] or an EEG quantitation of narcotic effect [144, 145]. In the specific case of alfentanil normally an effect site compartment is added. The corresponding equilibration time constant $k_{e0}$ (micro rate constant) is derived by statistical analysis of input-output data sets and accounts for the time lag (“hysteresis”) only. No fractional sigmoid $E_{max}$ model is identified. Such pharmacokinetic pharmacodynamic models are used in freely available target controlled infusion systems (TCI), such as STANPUMP3 or RUGLOOP4. Both TCI systems are at present not clinically approved and are therefore only of research interest. Nevertheless, the time course in the central and in

3freely available by Steven Shafer, http://anesthesia.stanford.edu/pkpd
4Demed, Belgium, http://www.demed.be
the effect site compartments are well described. The central compartment is often viewed as the plasma compartment and therefore has to correspond with the arterial compartment of the physiologically based model. Analogously, the effect site for pain perception is the brain (grey matter, compartment 2) and therefore $C_2$ is chosen as the effect site concentration.

The tuning parameter $\lambda$ is empirically adjusted such that effect compartment concentration time course corresponds to the time course in the models described in [94, 145]. In Figure 4.1 a simulation of the time course of concentration in the central/arterial compartment (top plot) and of the effect site compartment (lower plot) are shown. The bolus is $10 \, \mu g$ per kg bodyweight administered in 7.5 seconds. The results of the physiologically based model with $\lambda = 0.1$ are shown by solid lines, the results of the mamillary compartmental model described by [145] and [94] are shown by dashed-dotted and dashed lines respectively. For both the central/arterial

![Figure 4.1](image_url)

**Figure 4.1:** Concentration time course in the central/arterial and the effect site compartments; comparing the physiologically based pharmacokinetic pharmacodynamic model with the models in [94, 145].
and the effect site concentrations the physiologically based model shows similar time course compared to the models in [145] and [94].

### 4.2.2 Pharmacodynamic Tuning

As there is no direct measurement of the state of analgesia available, no measurable effect can be used to derive an $E_{max}$ model for alfentanil. In [53, 56] a simple relation is given, which relates effect site variations and $MAP$. The model predictive control algorithm used in [53, 56] requires a linear model and hence a linear relationship was assumed with $k = -0.081$ mmHg/(ng/ml). This gain was derived from linearizing an approximate $E_{max}$ model suggested by anaesthetists. For control design and testing purposes the same relation was used.

As mentioned above, opioids do have only a haemodynamic influence in the presence of painful stimuli. This means in case $MAP$ is elevated because of stress response, opioids will in most situations decrease $MAP$. In Figure 4.2 this is visualized. A surgical stimulation leads to a stress response ($SR$) that generates an elevation of $MAP$ ($\Delta MAP$). The effect site concentration ($C_2$) results in a factor ($Sup$) which attenuates stress response, i.e. $\Delta MAP = Sup \cdot SR$ where $0 \leq Sup \leq 1$. Finally, the actually measured $MAP$ is therefore the sum of the elevation caused by a painful stimuli $\Delta MAP$ and the mean arterial pressure of the non-stimulated patient $\overline{MAP}$.

![Figure 4.2: Simplified visualization of the pharmacodynamic effect of an opioid.](image)

Figure 4.2: Simplified visualization of the pharmacodynamic effect of an opioid. The effect site concentration is $C_2$ and $Sup$ is a attenuation factor for a specific effect site concentration ($0 \leq Sup \leq 1$), $SR$ is a “hypothetical” stress response in the absence of opioids, $\Delta MAP$ is the deviation caused by surgical stimuli, $\overline{MAP}$ is the mean arterial pressure of the non-stimulated patient and $MAP$ is the mean arterial pressure.

Obviously, by administering a high opioid dose the influence of $SR$ can be attenuated. Clinically a high alfentanil dose is not desired as its elimination time constant may introduce a prolonged respiratory depressant effect at the end of surgery. Hence, the ideal control objective is to control $\Delta MAP$ and simultaneously minimize the respiratory depressant effect. This
4.3. Controller Design

is not possible as $\Delta MAP$ and the respiratory depressant effect cannot be measured directly. Nevertheless, both objectives have to be considered in a controller design.

4.2.3 Validation by Non-compartmental Analysis

In Table 4.3 the characteristic pharmacokinetic parameters are summarized from the literature and the results from simulations with the physiologically based pharmacokinetic model are added. The results of the physiologically based pharmacokinetic model are in agreement with published data.

Table 4.3: Summary of the published pharmacokinetic parameters of alfentanil in comparison to the same parameters derived from simulations of the physiologically based model.

<table>
<thead>
<tr>
<th>Pub.</th>
<th>$V_{dss}$ [ml/kg]</th>
<th>$Cl$ [ml/(kg·min)]</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>[18]</td>
<td>386</td>
<td>3.4</td>
<td>11 patients</td>
</tr>
<tr>
<td>[17]</td>
<td>860</td>
<td>6.4</td>
<td>11 patients</td>
</tr>
<tr>
<td>[27]</td>
<td>1030</td>
<td>8.3</td>
<td>5 female patients only</td>
</tr>
<tr>
<td>[147]</td>
<td>470</td>
<td>4.2</td>
<td>more than 50 patients</td>
</tr>
<tr>
<td>[145]</td>
<td>319</td>
<td>2.8</td>
<td>17 male patients</td>
</tr>
<tr>
<td>[94]</td>
<td>432</td>
<td>5.1</td>
<td>45 patients</td>
</tr>
<tr>
<td>this model</td>
<td>305</td>
<td>5.0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>306</td>
<td>5.0</td>
<td>2</td>
</tr>
</tbody>
</table>

$V_{dss}$ derived by Equation (2.15). $V_{dss}$ derived by Equation (2.17).

The clearance $Cl$ is within the range of published data and the steady state volume of distribution $V_{dss}$ is just on the lower side. This could be caused by the different partition coefficients, especially by the large fat compartment which has a high ability to bind alfentanil. The tissue parts of the compartments therefore can hold a higher amount of drug, thus reducing the necessary volume of distribution.

As predicted in Section 3.2.3 the mismatch between the methods to calculate $V_{dss}$ is negligible.

4.3 Controller Design

Essentially a modified cascade structure (Figure 2.7) is used. In Figure 4.3 the inner control loop $C_2$ is replaced by a system for target controlled infusion (TCI). The TCI system drives
Chapter 4. Regulating Analgesia

The infusion rate is maintained to maintain an estimated effect site concentration. Note that the TCI system has no feedback from the patient. The outer control loop \( C_1 \) takes non-invasive mean arterial pressure (MAP) and heart rate (HR) into account to adjust the target concentration \( C_{2\text{REF}} \) of the TCI system. As indicated by the dash-dotted line the heart rate is not a controlled variable, it is used only to trigger the appropriate control action.

The TCI system is described first because it has specific functions, which explain the design of the outer control loop. It is described in Section 4.3.1. The outer control loop is described in Section 4.3.2.

4.3.1 System for Target Controlled Infusion

The advantage of using a TCI system as the inner cascade is that in case a measurement fails it still provides an infusion rate. In the specific case of the MAP the TCI system is independent of receiving regular measurements. This is important as several minutes pass - maybe even in irregular intervals - before a new measurement is available. Therefore, new target set-points can be provided by the outer loop whenever it is possible.

This resembles clinical practice. The only routinely used TCI system is the one to administer the hypnotic drug propofol. The anaesthetist adjusts the target concentration according to clinical signs (e.g. BIS). The anaesthetist acts as a controller for that objective and assesses depth of hypnosis in “irregular” intervals (depending upon work load). On the basis of the past and current measurements and observations the target concentration is adjusted.

In Figure 4.4 the TCI system is shown. It is an observer based (\( \hat{P} \)) state feedback (\( -k \)) structure with additional integral action (\( I \)) and feed forward term (\( f_2 \)). The observer is used to estimate the target concentration \( C_{2\text{OBS}} \). As \( C_2 \) cannot be measured online, no output injection is used. The anti windup structure is not shown. The implementation of the integral action and the anti windup structure is standard and described in Appendix A.2. The standard design procedures described in Section 2.2 are used with:

\[
Q = 1, \quad R = 0.01 \quad \text{and} \quad \Gamma = -0.51.
\]  

The feed forward term \( f_2 \) is derived according to Equation 2.28. The explicit parameters are given in Table C.1 in Appendix C.
4.3. Controller Design

The discussion in Section 4.2.2 concerning the pharmacodynamic model indicates that the ideal patient parameter to control - the elevation caused by surgical stimulation $\Delta MAP$ - is not available (see Figure 4.2). Using the $MAP$ as the controlled variable introduces the difficulty of set-point selection. In case the set-point is set lower than $\overline{MAP}$, which is the $MAP$ of the non-stimulated patient, the controller will increase the target concentration continuously. In case the set-point is set higher than $\overline{MAP}$ the target concentration is continuously reduced.

The pharmacokinetic and pharmacodynamic characteristics impose several additional requirements. For alfentanil, the large difference between the relatively short onset time (a few minutes) compared to the slow elimination (more than 100 minutes) requires different dynamic behaviour of the controller concerning onset and elimination. To prevent prolonged respiratory depression it is especially important that the controller stops alfentanil infusion immediately in case the measurement is below set-point. Furthermore, clinical routine indicates that there is a separation between operating modes. Namely, while $MAP$ varies moderately near the set-point no or only small adjustments are necessary. However, the haemodynamic response to surgical procedures may cause large positive deviations from set-point which require fast responses of the controller.

In Figure 4.5 the structure is shown. The sample and hold ($S\&H$) element on $MAP$ indicates that the non-invasive measurement has a different sampling interval to the rest of the system. This sampling interval of $MAP$ is 2 minutes. Further details are given in Section 4.3.6. The integral action has a “split range” characteristic\(^5\) to account for the asymmetric requirement

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\(^5\)This terminology is used here even though it is traditionally used for systems where more than one actuator is responsible for different directions of action [8].
Figure 4.5: Controller structure of the outer cascade on the basis of an integral action with two different parameters $k_{111}$ and $k_{112}$. The feed forward term $f_1$ is only activated if “pain” is detected, the detection algorithm is a function of heart rate $HR$ and additional safety conditions indicated by the logic block $L$. The parameters $ΔC_2$ and $C_{2\text{MAN}}$ are set by the anaesthetist. The sample and hold block $S\&H$ indicates a different sampling interval.

mentioned above. For $MAP \geq MAP_{\text{REF}}$ the branch with parameter $k_{111}$ is active and for $MAP < MAP_{\text{REF}}$ the branch with $k_{112}$ is active. Parameter $k_{112}$ is considerably larger than $k_{111}$, which means that the reference concentration $C_{2\text{AUTO}}$ derived by the controller is considerably faster decreased than increased. A fast decrease means that the infusion rate resulting from the TCI system will be reduced to zero. No anti windup structure is shown, the implemented structure corresponds to the descriptions in Appendix A.2. While the outer cascade is not active the anaesthetist sets $C_{2\text{MAN}}$ manually. In case the anaesthetist has predictive knowledge of the surgical procedures or is unsatisfied with analgesia state $ΔC_2$ allows to increase the target concentration manually. This is especially important shortly before skin incision. The anaesthetist generally is able to predict the time point, which indicates the start of surgical procedures. The anaesthetist then administers additional opioids just before skin incision to prevent stress response. Analogously by setting $ΔC_2$ the system administers more opioids. The last important feature of the controller is the possibility to react fast in the presence of a strong pain response. Let us first assume it is possible to detect pain as indicated in Figure 4.5. The pain detection algorithm is based on simple analysis of the heart rate and is described in Section 4.3.5. Then it makes sense to use this information and react by increasing $C_{2\text{AUTO}}$. Generally, haemodynamic stress response results in both an increase of $HR$ and $MAP$. The $HR$ is measured continuously and therefore the detection of “pain” is immediate compared to the intermittent measurement of $MAP$. Theoretically it would be possible to allow the control reaction only on the basis of the detection of pain. Some critical clinical situations do not allow this. For example in patients developing a state of shock - caused by a sudden blood loss or
an allergic reaction - blood pressure drops sharply and the heart rate speeds up, which would lead to a false reaction. Therefore, it is important that the control algorithm only reacts after the next measurement was received and if $MAP > MAP_{REF}$, this is implemented in the logic block L.

The explicit parameters are given in Table C.1 in Appendix C.

### 4.3.3 Closed-loop Bandwidth

The closed-loop bandwidth of the TCI system is $3.1\ rad/min$. This relatively large bandwidth can be achieved as there is no measurement involved. The overall closed-loop bandwidth is approximately $0.05\ rad/min$ for the upper branch and $0.4\ rad/min$ for the lower branch of the split range controller. This resembles the slower and faster system response required in case $MAP \geq MAP_{REF}$ or $MAP < MAP_{REF}$ respectively.

### 4.3.4 Artefact Handling Procedures

**Mean arterial pressure**

Generally, the non-invasive mean arterial pressure measurement is robust, meaning that outliers are rare. Therefore a simple approach is used, which compares diastolic ($DIA$), mean ($MAP$) and systolic ($SYS$) arterial pressure. All three values are obtained from the same sampling. If the following conditions hold, then the corresponding $MAP$ is pronounced valid.

- Condition 1 $0 < DIA < MAP < SYS < 300$
- Condition 2 $20 < (SYS - DIA) < 100$
- Condition 3 $et < Sampling\ interval$

Parameter $et$ is the elapsed time in seconds since the sensor obtained the last measurement. In case the measurement is pronounced invalid the last valid measurement is used and the anaesthetist is informed with a warning containing $et$. For information on the sampling interval see Section 4.3.6.

**Heart rate**

As mentioned above the heart rate is routinely measured with two independent sensors (pulse oximetry and electrocardiography). This redundancy allows effective artefact rejection. Essentially, both measurements are checked to comply with the range of validity ($30 < HR < 180$).
If both are valid then the one closer to its mean is chosen. The mean is derived from the last 29 received values (sampling period is 5 seconds). In case both measurements are invalid the system issues a warning. If the measurement is invalid, no pain detection is possible.

4.3.5 Pain Detection

Pain detection is based on the \( \text{HR} \) exceeding a variable threshold. The threshold \( t_s \) is calculated as \( t_s = (1 + p) \cdot P_{90\%} \), where \( P_{90\%} \) is the 90\% percentile (i.e. the value that is greater than 90\% of all values in a vector) and \( p \) is a tuning parameter.

Obviously, two parameters influence \( P_{90\%} \), the length of the vector and the tuning parameter \( p \), which were empirically tuned by applying this simple detection scheme on experimental data records. The length of the data set corresponds to the last 29 measurements and \( p \) was set to 0.05. Figure 4.6 shows a typical data trace of a volunteer study conducted in a previous project [53]. Isoflurane and alfentanil were used and the effect on different clinical parameters was investigated. The advantage of the data is that defined experimental stimuli were applied and marked in the data record. It is therefore possible to validate the detection algorithm.

Figure 4.6 shows the performance of the detection algorithm. The top plot shows the \( i\text{MAP} \), \( \text{HR} \) and \( \text{BIS} \) and the markers to indicate the time point of different stimuli. Several stimulations show no response on any of the parameters (e.g. sound). Major reactions on \( \text{HR} \) and \( \text{MAP} \) are caused by the intubation at 49 minutes, a hand in ice water after 101 minutes and a painful electrical stimuli after 114 minutes. With the two latter stimuli also clear reactions on the \( \text{BIS} \) are observed, where the later reaches nearly a \( \text{BIS} \) of 100. Additionally, the last response shows also a peak in endtidal isoflurane concentration (lower plot) indicating that the volunteer was awake and trying to breathe spontaneously. Mainly the opioid level was low which explains these reactions. After that the opioid level was increased and the responses caused by different stimuli are less accentuated. The algorithm detected the three large responses correctly. Later two more detections are observed, which also can be related to stress response. A few responses were not detected as a result of hardly any reaction on \( \text{HR} \) (e.g. after 71 minutes). It has to be noted that this detection algorithm is not intended to detect pain accurately. It is used to identify painful periods, which allows the controller to react faster if necessary. The actual \( \text{MAP} \) measurement is used to define the reaction. Therefore, even if pain is detected a low \( \text{MAP} \) will cause the controller not to infuse more opioids. On the other hand, if no pain is detected the controller will still increase the target concentration in case \( \text{MAP} \) is high.
4.3. Controller Design

Figure 4.6: Validation of the pain detection algorithm. Top: invasive mean arterial pressure (solid, iMAP), heart rate (dotted, HR) and bispectral index (dots, BIS). Markers to indicate different stimuli (intubation ▼, hand in ice water □, sound ◦, trapezoidal squeeze ◤, electrical stimulus △) and the detection of pain ◊. Bottom: endtidal isoflurane concentration (solid, FeISO) and alfentanil effect site concentration (dash-dotted, C･ALF).

4.3.6 Variable Sampling Intervals and the Implications for Future Control Structures

The controller described above uses a sampling interval of two minutes. In clinical practice this is a short interval for several reasons. The sensor device has to inflate the cuff and thereafter to decrease the cuff pressure to detect and derive systolic, mean and diastolic arterial pressure. This typically takes approximately 30 seconds. Furthermore, the applied pressure can lead to injuries, especially when it is applied over longer periods. In clinical routine the anaesthetist adapts the sampling interval according to the need. Hence, shortly before and after intubation or potentially painful surgical procedures the interval is set to 2 minutes and during “calm” phases
the interval is set to 5 minutes. While using the 5 minutes interval the anaesthetist might decide to trigger an additional measurement in between to verify some other haemodynamic parameter (e.g. heart rate). The potential risk for injury is therefore reduced.

The control structure described above is independent of the sampling interval of MAP. The TCI system as mentioned above uses strictly the last provided value. The only critical element is the integrator of the controller in the outer control loop. For this purpose the discrete integrator is operated with the standard five seconds sampling period. Thus, the controller receives every five seconds a new measurement, which happens to be updated only every two minutes. Therefore, the implemented system accepts also a variable update interval. The only issue to be considered is the tuning of the parameters $k_{I_{11}}$ and $k_{I_{12}}$ of the integral action. The control parameter $k_{I_{12}}$ is not designed on the basis to achieve a desired dynamic response. It is tuned such that the infusion rate is lowered rapidly to zero as soon as MAP is below set-point. This is due to the relative high time constant related to the elimination of alfentanil from the body. Therefore, this parameter is not critical concerning the update interval. On the other hand $k_{I_{11}}$ is strongly dependent on the update rate of the blood pressure measurement. The TCI system has approximately a settling time of 2 minutes to achieve a higher target concentration. This means that for the outer control loop the system can be approximated as a pure time delay, where the time delay $T_d$ is the update interval of the blood pressure measurement. To reach satisfying stability margins $k_{I_{11}}$ has to be proportional to $\frac{1}{T_d}$.

By further imitating the anaesthetist the described system can be further enhanced. The detection of pain should automatically trigger the sensor device, which reduces the necessity of having a two minute sampling interval. On the current system this is not yet possible, but it is planned for the future.

### 4.4 Results

In this section some results presented are derived in simulations. So far the controller was only tested on two patients and therefore it is necessary to document some of the implemented functions by simulations.

#### 4.4.1 Simulations

**Simple model for stress response**

During anaesthesia the haemodynamic response changes according the surgical stimulation. To test the system it is therefore necessary to model the patient's stress response. The stress response model is implemented on the event layer in the simulation environment (see Sec-
The simple model used can be associated with a periodically occurring single painful stimuli and the corresponding neuronal and humoral reaction described by [46]. In Figure 4.7 the resulting offset $\Delta MAP$ on the simulated mean arterial pressure is visualized.

The $HR$ response is modelled analogously. The difference is that the $HR$ is updated every 5 seconds, whereas the $MAP$ is only updated every 2 minutes.

![Figure 4.7: Modelled stress response. The parameter $\Delta MAP$ is a time varying offset on $MAP$ and $t0$ is the activation time.](image)

**HIL Simulation**

A simulation result is given in Figure 4.8. The TCI system is activated after 19 minutes, which results in a bolus like administration at the beginning of the recording. At 22 minutes the $MAP$ controller is activated. The periodical stress response model introduces a quasi periodic response of the system. In the second plot the markers (+) indicate where pain is detected but the controller waits until a new measurement is received before the feed forward term $f_1$ is activated as indicated by the markers (V) in the top plot. Only where $f_1$ is active the infusion rate changes rapidly as indicated by the same markers (V) in the bottom plot.

**Simulation with $MAP$ emulation**

Figure 4.9 shows the data record of a test where $MAP$ is emulated, meaning that instead of generating a $MAP$ measurement in the HIL simulator environment the actual blood pressure cuff was fixed on a $MAP$ emulator device. The cuff is inflated and the emulator generates the physical pressure waves which are needed for the measurement procedure. The emulator imitates therefore the patients arm. This device is used to test and calibrate medical equipment as it produces reproducible measurements. In the perspective of closed-loop control it does not provide the functionality needed for testing. It was used to verify the data acquisition and
Figure 4.8: Record of a simulation. Top: non-invasive arterial pressure (solid, $MAP$) and its reference (dash-dotted, $MAP_{REF}$), the markers $\nabla$ indicate where the feed forward term $f_1$ is activated; Second: heart rate (solid, $HR$), the markers $+$ indicate where pain is detected; Third: reference (dash-dotted, $C_{2REF}$) and observed effect site concentration (solid, $C_{2OBS}$); Bottom: infusion rate (solid, $i_R$), the markers $\nabla$ indicate the effect of the feed forward term $f_1$ on the infusion rate.

Data processing rather than to verify the controller. The $MAP$ changes are manually set on the device and therefore no patient reaction can be simulated, i.e. the controller operates in closed-loop mode but the loop is not closed as the patient is missing. Furthermore, no $HR$ signal is available and therefore the feed forward term $f_1$ cannot be activated.

Nevertheless, the simulation illustrates the split range structure of the controller. The two integral actions are differently tuned for increasing and decreasing target concentrations (Figure 4.5).
At 64 minutes the \( MAP \) measurement is increased and the controller reacts by linearly increasing \( C_{2\text{REF}} \) because the error signal \( MAP_{\text{REF}} - MAP \) is constant. At 70 minutes the measurement returns to the previous level and therefore the \( C_{2\text{REF}} \) is approximately constant. At 84 minutes \( MAP \) is reduced and the controller reacts analogously by reducing \( C_{2\text{REF}} \) linearly and after 85.5 minutes the \( MAP_{\text{REF}} \) is adjusted to stabilize \( C_{2\text{REF}} \). The relative changes of \( C_{2\text{REF}} \) in both directions are approximately equal, but the time it takes to reduce compared to the time to increase the same change is about four times shorter. The result is that the infusion rate is switched off as soon as the measurement drops below the reference. Note that for the currently used controller the tuning difference is by a factor of eight.
4.4.2 Pilot Study

Overview

In Figure 4.10 the recording of a clinical test is shown. The TCI system is first activated and the manually set reference of 50 ng/ml is targeted, which is not a high dose for surgery. At 44 minutes the controller is switched on and as the blood pressure is stable, no large changes are observed. The anaesthetist predicted skin cut and therefore increased the target concentration $C_{2}\text{REF}$ by activating $\Delta C_2$ at 55 minutes. Two minutes later skin cut occurred and the haemo-
dynamic response can be seen on $MAP$ and $HR$. Pain was not detected as the variation on $HR$ was not high enough. Several times the detection algorithm detected pain as indicated by the black bars in the top plot. The detections $p_1$, $p_2$ and $p_3$ can be associated with the clinical procedure. Shortly before skin incision the patient is covered up and the operating area is sterilized. The sterilant used is generally cold and the patient shows a clear response to the stimulation as indicated by $p_1$. This patient underwent decompressive spinal surgery and at 66 minutes the surgeon has reached the nucleus which causes the pressure on the nerve and therefore the pain. This is the most painful part of the operation. The detection is therefore correct as indicated by $p_2$. Shortly after $MAP$ drops below the set-point and the controller immediately reduces the infusion rate. After 84 minutes the controller is switched off and the TCI system is activated. This marks the beginning of skin closure and the near end of surgery. The reference for the TCI system was set to zero. At 99 minutes the patient was turned on his back. The positioning is typically a strong stimulation as the tube, which secures the patient’s airway can slightly dislocate. This is again detected by the algorithm as indicated by $p_3$. For both $p_1$ and $p_2$ the $f_1$ is activated, but the reaction of the controller is moderate because the error signal $MAP - MAP_{REF}$ is small.

To prevent the controller from detecting the same stimulation multiple times, the detection is suspended for three minutes as indicated by the corresponding bars in the top plot.

**Feed forward action**

In Figure 4.11 the part of a different pilot study where the controller is active is shown. Only a moderate haemodynamic reaction to skin incision is visible. At 74 minutes the most painful period of the operation starts. Again several times pain is detected as indicated by the black bars. This data trace shows nicely the different responses where the feed forward term $f_1$ is not activated and where it is activated. At 74 minutes the next recorded $MAP$ measurement after pain detection $p_4$ is nearly on target and therefore $f_1$ has practically no influence. The measurement received another two minutes later shows a clear increase, but the detection was inactivated and therefore $f_1$ is also not activated.

The pain detection $p_5$ on the other hand shows also a larger increase in $MAP$ and therefore the influence of $f_1$ on $C_{2\text{REF}}$ and on $i_R$ can be clearly seen. The pain detection $p_6$ at 90 minutes shows that even though the $f_1$ is active but as the following $MAP$ measurement is not larger than its reference, $C_{2\text{REF}}$ is not changed.

**Pain detection algorithm**

In Figure 4.12 the same part of the clinical study as in Figure 4.11 is shown. Here only the heart rate along with the 10% and the 90% percentile of the last 29 $HR$ measurements and the
detection threshold derived by $1.05 \cdot P_{90\%}$ is shown.

It illustrates the effectiveness of the detection algorithm presented in Section 4.3.5. Before the painful part of the operation starts the heart rate variability is low as indicated by the narrow $P_{10\%}$ to $P_{90\%}$ range. The advantage of using $P_{90\%}$ to derive the threshold instead of the standard deviation is that the $P_{90\%}$ is always a value in the range of the actual $HR$ whereas the standard deviation may tend to zero for a $HR$ signal with almost no variation. After 74 minutes the most painful part starts and the same pain detections as in Figure 4.11 are indicated. During this phase the the $P_{10\%}$ to $P_{90\%}$ range is considerably broader. After surgery is terminated the
4.5. Discussion

The modelling framework described in Chapter 2 is used to derive a physiologically based pharmacokinetic model. The input output characteristic is tuned to correspond to published mamillary compartmental models. The derived model is validated by non-compartmental analysis and the results are in good agreement with the published pharmacokinetic indicators. As mentioned earlier, physiologically based models describe better the initial distribution phase of drugs where distribution and elimination time constants are similar. Alfentanil does not exhibit this characteristic. Nevertheless, it shows that the presented modelling framework can be applied for many different drugs with different characteristics. Furthermore, the control structure directly related to the model is the TCI system, which uses only an estimate and no measurement.

The controller design is able to handle intermittent MAP measurements and is prepared to handle different sampling intervals. Furthermore, it provides the necessary functionality for clinical routine by adapting the closed-loop response in case pain is detected.
Pain detection has to be viewed with care as actually the haemodynamic response to pain is assessed and not pain perception or state of analgesia. Nevertheless, the so far closest indicators of the state of analgesia are used to control the infusion of an opioid. It is therefore appropriate to refer to it as regulation of analgesia. The pain detection algorithm is appropriate as long as it is used in combination with the actual MAP controller.

Two pilot studies were conducted on patients undergoing decompressive neurosurgery, which means that the actual time of surgery is about 30 minutes and mainly two well defined surgical stimuli can be observed (skin incision and the painful phase of surgery). To further validate the concepts longer studies with many and more intensely painful periods are necessary.
The model used for regulating hypnosis is taken from previous work [37, 46] which provides the basis for the derived model concept presented in Chapter 2. Some model alterations were necessary which are commented in the following. Furthermore, previous control concepts [37, 46, 53] are amalgamated and adapted to meet the clinical requirements and to increase the clinical applicability of the controller. The clinical study concerned a comparison of a manually controlled group and an automatic controlled group. The comparison is presented and shortly discussed.

5.1 Introduction

During general anaesthesia the patient receives anaesthetic agents to ensure unconsciousness and amnesia. This part of anaesthesia is often referred to as depth of hypnosis or depth of anaesthesia. To avoid confusion with the main focus of this thesis of controlling different tasks in anaesthesia only the term “depth of hypnosis” is used.

The patient is very strongly stimulated by surgical procedures, which obviously causes pain
response. A patient feeling pain may arouse during surgery. It is clearly one main task of the anaesthetist to provide sufficient anaesthetic drug to ensure that the patient does not awake during surgery. Moreover, the patient must not recall any incident, which may cause significant psychological stress. Luckily, such critical incidents are very rare in clinical practice. Besides administering anaesthetics to ensure hypnosis, the anaesthetist has to administer opioids to suppress pain perception and therefore, the patient will be less easily aroused (see Chapter 4). Incidentally, opioids have also an hypnotic effect and hypnotic agents have an analgesic effect. An appropriate balance of both agents provides an adequate anaesthesia. It is assumed that in parallel a corresponding level of analgesia is maintained either by manual or by automatic opioid administration.

5.1.1 Anaesthetics and their Mechanism of Action

Different volatile and non-volatile anaesthetic agents are known and widely used. The choice of a particular agent largely depends on type of operation, side effects, availability and price of the specific drug. Propofol as the main non-volatile anaesthetic is often used for induction and may then also be used to maintain anaesthesia. Generally, volatile or inhalational anaesthetics such as isoflurane are less expensive and are often used to maintain anaesthesia. The anaesthetic used is isoflurane and in the following only the drug specific physiology of this substance is considered.

The mechanism of action of inhalational anaesthetics is still obscure. It is generally assumed that the effect depends upon attainment of a therapeutic tissue concentration in the brain [105]. Several theories exist and for further details the reader is referred to appropriate literature. Uptake of the anaesthetic is by the pulmonary blood circulation. It enters rapidly into the blood circulation and subsequently into the brain. Metabolism of isoflurane is insignificant and therefore the anaesthetic leaves the body dominantly by exhalation. Different tissue groups have a different affinity to anaesthetics depending on solubility and blood flow. The brain as a well perfused organ is with the first to take up the drug and the moderate solubility and the small volume limit the drug capacity. Therefore, the brain is also fast to get rid of the drug. On the other hand, fat tissue has a low perfusion, large volume and a high solubility and therefore, it is very slow in taking up the drug as well as getting rid of it. Traces of isoflurane can be detected in the exhaled air for several days after an operation [185].

5.1.2 Measurement Procedures

Measuring depth of hypnosis is often disputed and no final answer can be made. However, many research groups and companies [59, 90, 92, 126, 146, 161, 167, 174, 184] are searching for the best parameters, but only the bispectral index (BIS) monitor developed by Aspect Medical Systems (Newton, Massachusetts) has gained significance in clinical practice so far.
5.1. Introduction

The BIS is derived from the electroencephalogram (EEG) by bispectral analysis. It is reported to relate to the hypnotic component of the anaesthetic state [59]. A BIS value of 100 represents an awake state and a BIS value of 0 represents an isoelectric signal. A BIS between 40 and 60 is generally accepted as appropriate during most surgical procedures. The signal nature (EEG) and the spectral analysis cause a high intrinsic (stochastic) noise level, which can easily reach up to ±10 BIS points. Moreover, the signal is prone to artefacts, caused by electro cautery and by general clinical handling of the patient (electrode disconnection).

Along with the actual BIS measurement the sensor provides a signal quality index (SQI) which is related to the reliability of the BIS measurement.

5.1.3 Previous Work and State of the Art

Recently, controlling depth of hypnosis has gained popularity mainly because a reliable measure is available and is clinically established. In Table 5.1 the main references are summarized.

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Abbreviations: MC, mamillary compartmental model; PB, physiologically based models; NN, models derived by neuronal networks; PID, PID control techniques; MB, model based control techniques; FU, fuzzy control; AD, adaptive control algorithms; P, propofol; I, isoflurane.

Footnotes: ¹ spectral EEG values; ² used an index derived from auditory evoked potentials; ³ used the controller in advisory mode on three patients only; ⁴ propofol/alfentanil mixture.

Most research groups concentrate on administering the intravenous agent propofol, as the technical requirements are less demanding. In general two concepts are applied. Either standard PID controllers or more sophisticated model based and adaptive approaches are used. To our knowledge, only mamillary compartmental models have been used so far.
In [106] a PID controller to infuse isoflurane directly into the inspiratory limb of the respiratory system (circle absorber system) was used. The controller was not considered to be sophisticated by the authors. So far no commercially available monitor for depth of anaesthesia other than the BIS has been used for closed-loop control [162], some authors [75, 90] have used “home-made” indicators. In [90] the system was not used in closed-loop mode but in advisory mode. This means that the control system suggested an infusion rate of propofol, which the anaesthetist could accept or not.

The development of the described controller for hypnosis is strongly influenced by previous work of our research group. In [37] a physiologically based model for endtidal anaesthetic gas concentration was adapted from [156, 189] and subsequently refined in [46]. Moreover, the model was extended to capture different pharmacodynamic effects, mainly the mean arterial blood pressure (MAP). In [37, 46] controllers were developed on the basis of the physiologically based model to regulate MAP, which seemed sensible as at that time no reliable measurement of hypnosis was available. The controller used an observer based state feedback approach and included override structures to handle lower and upper limits on the endtidal anaesthetic measurement [54]. Since the different EEG derived parameters - such as bispectral index (BIS) [59, 146] or auditory evoked potentials (AEP) [49, 92] - have shown reasonable correlation with the state of hypnosis and have been used in clinical routine blood pressure is more often related to stress response than to depth of hypnosis. The obvious step therefore is to control hypnosis by a hypnotic anaesthetic drug. First attempts were presented in [53], which used a mamillary compartmental model [185], i.e. describing the pharmacokinetics of isoflurane added by the description of the pharmacodynamics of isoflurane by BIS. The controller in [54, 55] used has a cascade control structure (Figure 5.1), where the outer cascade (controller C1) regulates the BIS by regulating an endtidal anaesthetic gas concentration of the inner control loop (controller C2). Both controllers for the inner and outer cascade were designed on the method of internal model control (IMC) [104]. The IMC structure implies that the poles

![Figure 5.1: Simplified cascade control structure. Controller C1 represents the actual BIS controller, C2 controls endtidal isoflurane concentration.](image)
and zeros of the plant are cancelled and therefore the performance to disturbances may be poor [8]. The controller was tested during pilot studies, but showed unsatisfactory results, especially concerning fast BIS changes and therefore no clinical study was carried out.

The controllers in [46, 54, 55] used the isoflurane concentration at the vaporizer as the manipulated variable. As the dynamics of the respiratory circuit varies considerably with the fresh gas flow set by the anaesthetist, the model and the controller parameters are adapted accordingly. The parameters are adapted to preset values (gain scheduling). Hence this is not a feedback adaptive controller in a classical sense.

5.1.4 Problem Formulation

The main goal was to increase applicability of the existing BIS controller [54, 55] by meeting clinical requirements. This existing controller did not react sufficiently fast during potentially critically phases of high BIS. Low-flow anaesthesia (i.e. 1 litre/min fresh gas flow) is a clinical requirement as drug consumption is minimized although it introduces also a relative slow system response. To achieve an acceptable performance the controller in [54, 55] was operated with 3 litre/min fresh gas flow, which provides a faster dynamic response. Furthermore, the dynamic reaction of the controller was slowed down by the constraints on the endtidal reference of the inner control loop. During the clinical application the upper constraint was increased such that a minimal dynamic response could be guaranteed but the important constraint to prevent overdosing was essentially inactivated. In [3] first steps in redesigning the controller were made with the physiologically based pharmacokinetic model. The cascade control structure was inherited from [55], but the controller of the inner cascade was re-replaced by the endtidal controller developed in [37, 46]. In [151] that endtidal controller was tested in a clinical study where good results were observed. It already incorporated the main functionality to meet the clinical requirements.
5.2 The Isoflurane Model

5.2.1 Pharmacokinetic Tuning

The pharmacokinetic model for endtidal isoflurane concentration originated from [37] with refinements described in [46]. Therefore, only the main aspects are described and the reader is referred to the above mentioned literature for further details.

Instead of concentrations the preferred term for volatile anaesthetics is fraction, but it will be used correspondingly.

Elimination of isoflurane is mainly through pulmonary excretion [67], meaning that the only way to reduce isoflurane in the body is by exhalation. Therefore, all $\kappa_i$ are zero.

The blood/tissue partition coefficients $\lambda_i$ are found in the literature (see [37] and references therein).

5.2.2 Pharmacodynamic Tuning

The effect site for isoflurane is the brain compartment (grey matter, subscript 2). As patient variability is high the $E_{max}$ model for $BIS$ identified in [53] was used with $EC_{50} = 0.75 \text{ vol}\%$ and $\gamma = 1.6$. The specific $E_{max}$ model is described by the following equation.

$$BIS = 100 \left( 1 - \frac{C_2}{C_2 + EC_{50}} \right)$$ (5.1)

The parameter $C_2$ describes the isoflurane concentration in the brain.

The PD model was used for the design and testing of the controllers. To capture patient variability the model was varied considerably ($0.5 < \gamma < 3.0$ and $0.3 < EC_{50} < 1.5$).

5.3 Controller Design

As a result of the following considerations the control structure was defined. Figure 5.2 shows a recording during a clinical test of the mean arterial pressure controller developed in [46]. The measured endtidal anaesthetic gas concentration $F_{E_{ISO}}$ and the estimated brain concentration $F_{b_{ISO}}$ of the observer is compared to the inverted and scaled $BIS$ measurements. The controller
was inactivated at about 150 minutes. Thereafter, the observer provided no estimation of $F_{BISO}$. Note that the $BIS$ was not regulated during this study; it was only recorded and the anaesthetist had no access to the $BIS$ measurements. The corrupted $BIS$ at the beginning of the recording is a consequence of the blinding of the measurement. A poorly attached electrode was not noticed for a considerable amount of time. Figure 5.2 reproduces well the clinical notion that the endtidal anaesthetic concentration is an indicator for depth of hypnosis. Therefore, it makes sense to adjust the endtidal gas concentration such that a $BIS$ target is achieved.

For this reason a cascade control structure is used as shown in Figure 5.1, where the outer cascade $C1$ provides the reference endtidal gas concentration ($F_{EREF}$) for the inner cascade $C2$. The cascade control structure allows to separate the control task, i.e. in essence the inner cascade regulates the pharmacokinetics and the outer cascade regulates the pharmacodynamics.

A main clinical requirement is a fast reacting controller. In case the patient’s state changes abruptly the controller has to react fast for two reasons. Firstly, the patient enters a potentially critical situation. Secondly, the respiratory system delays the administration of anaesthetic gas.

This is visualized in Figure 5.3, which shows the schematic setup of the system. The respiratory system or circle system has an air volume of approximately 6 litres and causes a significant time lag depending on the selected fresh gas flow (FF). While maintaining anaesthesia a low fresh gas flow of 1 litre per minute is desired to reduce anaesthetic gas consumption. It is therefore especially important that the respiratory system is filled with isoflurane as fast as possible. This is considered in the design of the inner cascade.
Figure 5.3: Schematic representation of the closed-loop system with patient, sensors, control hardware, actuators and the respiratory system.

5.3.1 Inner Cascade

The structure of the inner cascade is adapted from [46]. The inner cascade is shown in Figure 5.4, it receives its reference value $F_{\text{REF}}$ from the outer cascade (Section 5.3.2).

A main feature is the override structure of the controller allowing output constraint handling of the endtidal anaesthetics gas concentration. It was already introduced in [37] and extended in [46] for a controller regulating mean arterial pressure ($MAP$) with isoflurane. The main controller there was a $MAP$ controller and the two override controllers were endtidal isoflurane controllers. Here the main controller is also an endtidal isoflurane controller. By activating the upper override controllers toxic endtidal concentrations cannot be reached and therefore overdosing is not possible. Furthermore, the controller will always provide a minimal endtidal concentration by activating the lower override controller to avoid shallow levels of unconsciousness, which could result in arousal in case the level of surgical stimulation is changed abruptly. The minimal and maximal endtidal reference concentrations are set by the anaesthetist.

A second important feature is the feed-forward term $f$ of the main endtidal controller, which was already introduced by [46] in the endtidal isoflurane controller. It is mandatory, as fast $BIS$ changes caused by an arousal request a fast reaction of the controller as described earlier.
Figure 5.4: The detailed structure of controller C2 (inner control loop).
The main endtidal controller has an observer based state feedback structure with additional integral action to reduce steady state errors. The main endtidal controller is tuned such that a moderate overshoot occurs [25, 46]. This is advantageous as the concentration related to the BIS is not directly the endtidal concentration but the brain concentration. In other words the overshoot in endtidal concentration allows for a faster asymptotic equilibration of the brain concentration. The respiratory system dynamics depends on fresh gas flow, tidal volume and respiratory frequency and therefore the model coefficients of the observer and the controller are adapted accordingly (gain scheduling). For the main endtidal controller the same design procedures as described in [46] were used, i.e for the state feedback the tuning parameters are

\[ Q = 1 \quad R = 0.05 \quad \Gamma = 3 \quad (5.2) \]

and for the output injection they are

\[ R = \begin{bmatrix} 1 & 0 \\ 0 & 0.1 \end{bmatrix} \quad p = 100 \quad (5.3) \]

and finally the feed-forward term \( f \) is designed according to Equation (2.28).

The controllers in the override structure are PI controllers. The override controllers are not used for set-point changes and therefore no feed-forward term is needed. Moreover, the consumption of isoflurane of the patient will not vary considerably at a constant operating point and therefore the main dynamic factor is the respiratory system. In [46] a first order model for the respiratory system is suggested. The PI controllers are adapted corresponding to the changing dynamics of the respiratory system as described above. The idea is to have approximately equal response dynamics of the respiratory system independently of the fresh gas flow \( FF \). By increasing \( FF \) the dynamic response speeds up. The relation is assumed to be linear. Therefore, the controller needs to be slowed down by the same factor, i.e \( k_p = k_{p,0}/FF \) and \( k_i \) is not changed.

In Figure 5.4 the anti windup structure is not shown. All integral actions are equipped by anti windup feedback to prevent “windup”. Standard override controllers tend to follow the output of the main controller closely. The feed-forward term of the main endtidal controller introduces fast changes on the vaporizer, which could be restricted by standard override structures. Therefore, the override controllers need to be inactivated as long as the actual endtidal measurement is sufficiently far away from the corresponding limits (\( F_{\text{M AX}} \) and \( F_{\text{M IN}} \)).

This is achieved by additional switches. As an example Figure 5.5 shows the complete anti windup structure of the upper override controller. As long as \( F_{\text{M AX}}-F_{\text{ISO}} > 0.1 \text{ vol\%} \) (or \( F_{\text{ISO}}-F_{\text{M IN}} > 0.1 \text{ vol\%} \) for the lower override controller) the output of the override controller \( F_{\text{V HIGH}} \) (or \( F_{\text{V LOW}} \)) is not allowed to follow \( F_{\text{ISO}} \). It is forced to the corresponding upper (\( F_{\text{V MAX}} \)) (or lower (\( F_{\text{V M IN}} \)) isoflurane constraint. In Section 5.4 this is visualized in simulations.
5.3. Controller Design

5.3.2 Outer Cascade

The feed-forward term of the inner cascade increases noise sensitivity considerably. Therefore, a special filter is used on the BIS measurement, which detects large deviations from the mean ($BIS > BIS_{mean} + 15$) over the last three minutes or BIS measurements higher than 70. In both cases the actual BIS measurement is used for control instead of the mean BIS value. Hence a large error on the outer controller leads to a moderate change of $Fv_{REF}$, but $f$ amplifies the change and the controller reacts by fully opening the vaporizer. In Appendix D.2 the program code of the filter is given.

In general, the outer cascade is only able to adjust the inner set-point with moderate dynamics. The nonlinear (sigmoid) relation between effect site concentration ($C_2$) and effect ($BIS$) is prone to a high patient inter and intra variability. In [53, 55] $\gamma$ varies between 0.79 and 5 (the mean is 1.6) and $EC_{50}$ varies between 0.49 and 1.09 (mean 0.74). This makes it difficult to design a tightly tuned controller. This is visualized in Figure 5.6 where the average and extreme models are shown.

During surgery a BIS range between 40 and 60 is targeted. A shift in $EC_{50}$ primarily affects the steady state administration of anaesthetic gas and can be handled by an integral action. A change in $\gamma$ directly affects the loop gain and therefore, a tightly tuned controller will be sensitive to such changes. Therefore, only a “slow” PI controller was implemented to adjust the endtidal isoflurane set-point, which is sufficiently robust to the expected changes in $\gamma$. The derived control parameters are given in Table D.1 in Appendix D.

5.3.3 Closed-loop Bandwidth

The relative dynamic response of the different controllers can be assessed by comparing the closed-loop bandwidth of the different controllers. To guarantee proper functioning of the cascade and the override structure the relation of the different bandwidths need to be as follows
Figure 5.6: Variability of the pharmacodynamic model published in [53, 55].

\[
BW_{\text{override}} > BW_{\text{main}} > BW_{\text{overall}} \tag{5.4}
\]

where \(BW_{\text{override}}\) is the bandwidth of the override controllers, \(BW_{\text{main}}\) is the bandwidth of the main endtidal controller and \(BW_{\text{overall}}\) is the bandwidth of the overall cascade control system.

In accordance with [46] the closed-loop bandwidth of the main endtidal controller is \(1 \text{ rad/min}\). The closed-loop bandwidth of the override controllers is \(2.8 \text{ rad/min}\) and the closed-loop bandwidth of the cascaded controllers is approximately \(0.5 \text{ rad/min}\). The above described requirement is therefore met.

### 5.3.4 Artefact Handling Procedures

Artefact handling procedures are adapted from [55], where both the reference value of the inner cascade and the vaporizer setting drifted to preset “safety” values in case the corresponding measurement was detected as invalid. The IMC structure in [55] did not allow to use an observed value to replace an actual measurement.

The \(BIS\) measurement is significantly corrupted by noise, artefacts and poor signal quality caused by loosened electrodes. As there is no observation of the \(BIS\) measurement available, the same safety concept as in [55] was applied. In case the \(BIS\) measurement is invalid the endtidal reference drifts slowly to a predefined value. As soon as a valid measurement is observed the outer cascade is reactivated.
The inspired and the expired anaesthetic concentration measurements are corrupted by artefacts. Disconnected sampling tubes or sensor calibration may cause the measurement to fall temporarily to zero. Intraoperatively this makes no sense as the concentrations cannot drop suddenly. The controller described above uses a classic observer to predict endtidal and inspired isoflurane concentrations. Therefore, in case these measurements are detected to be invalid the controller uses the estimates instead (Figure 5.4).

The following detection criteria for $BIS$ and $F_{1iso}$ and $F_{eiso}$ were applied.

<table>
<thead>
<tr>
<th>Param. [Unit]</th>
<th>min</th>
<th>max</th>
<th>et [Sec.]</th>
<th>SQI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$BIS$</td>
<td>0</td>
<td>100</td>
<td>-</td>
<td>$&gt;30$</td>
</tr>
<tr>
<td>$F_{1iso}$ [vol%]</td>
<td>$&gt;0$</td>
<td>5</td>
<td>15</td>
<td>-</td>
</tr>
<tr>
<td>$F_{eiso}$ [vol%]</td>
<td>$&gt;0$</td>
<td>5</td>
<td>15</td>
<td>-</td>
</tr>
</tbody>
</table>

The parameter $et$ is the elapsed time since measurement, i.e. in case the measurement is not updated for $et$ seconds the measurement is invalid. Every five seconds the control task requests the updated measurements from the patient monitors. In rare cases the real-time task misses the reply of the patient monitor in order to ensure that every five seconds a new actuator setting is generated. Therefore, the measurement is only declared as invalid if the measurement is older than two sampling instances. The $SQI$ is the signal quality index provided by the $BIS$ monitor. The threshold of $30$ is provided by the manufacturer.

After checking for validity the $BIS$ is filtered according to the descriptions in Section 5.3.1 and Appendix D.2. No additional filter is used for $F_{1iso}$ and $F_{eiso}$. 

5.4 HIL Simulation

In Figure 5.7 a step response of the main endtidal controller is shown. The endtidal concentration $F_{\text{EISO}}$ slightly overshoots the reference such that the brain concentration $F_{\text{BISO}}$ reaches a new steady state as fast as possible.

![Figure 5.7: Recording of a simulation. Endtidal isoflurane (solid, $F_{\text{EISO}}$), endtidal isoflurane reference (dashed, $F_{\text{ERE}}$) and predicted brain concentration (dash-dotted, $F_{\text{BISO}}$).](image)

The simulation in Figure 5.8 shows the inactivated override controllers in case the measurement is far away from the corresponding constraint. The arrows in the top plot indicate where the actual $BIS$ is disturbed by a step like load to illustrate the characteristics imposed by the override structure. At the beginning both override controllers are inactivated and therefore their outputs are forced beyond the actual constraint. Fast reactions of the main controller such as the one after 25 minutes are not restricted as the override controllers are masked. Only during the third large disturbance at 45 minutes the endtidal measurement $F_{\text{EISO}}$ approaches the upper constraint $F_{\text{EMAX}}$ and therefore the upper override controller is activated. It immediately reduces the vaporizer setting $F_{\text{VISO}}$ and the constraint is not violated. The output of the endtidal controller follows the vaporizer setting as its anti windup structure is active. This is indicated by the arrow in the bottom plot.

In Figure 5.9 a detail of the same simulation as in Figure 5.8 is shown without the structure to mask the override structure. The advantage of the masking function can be seen on the endtidal values and the vaporizer setting. The result is that for the system with the masking structure the vaporizer setting is allowed to fully open whereas for the system without it is not. The vaporizer setting by the main endtidal controller in the lower left plot tries to act fast on the large disturbance but is restricted by the too closely following value derived by the upper endtidal override controller. Essentially the performance the controller is able to achieve in this configuration is related to the override controllers rather than to the main endtidal controller.
Figure 5.8: Recording of a simulation. Top: measured (solid, $BIS_{\text{RAW}}$) and reference (dash-dotted, $BIS_{\text{REF}}$) BIS values; Middle: endtidal isoflurane (solid, $F_{e\text{ISO}}$), endtidal isoflurane reference (dash-dotted, $F_{e\text{REF}}$) and corresponding minimal and maximal constraints (dashed, $F_{e\text{MIN}}$ and $F_{e\text{MAX}}$); Bottom: controller output derived by the main endtidal controller (dash-dotted, $F_{V\text{BIS}}$) and by the lower and upper override controllers (dashed, $F_{V\text{LOW}}$ and $F_{V\text{HIGH}}$) as well as the minimal and maximal isoflurane setting (dotted, $F_{V\text{MIN}}$ and $F_{V\text{MAX}}$) and the selected vaporizing setting is $F_{V\text{ISO}}$ (solid).

This leads to a slower change of the endtidal isoflurane setting and hence to a lower disturbance rejection on the BIS. For the system without the masking structure the time until the reference is reached is 9.0 minutes whereas for the system with the masking structure it is 6.7 minutes.
Figure 5.9: Recording of simulations without (left column) and with (right column) the masking structure of the override controllers. Top: measured (solid, $BIS_{RAW}$) and reference (dash-dotted, $BIS_{REF}$) BIS values; Middle: endtidal isoflurane (solid, $F_{\text{iso}}$), endtidal isoflurane reference (dash-dotted, $F_{\text{ref}}$) and corresponding minimal and maximal constraints (dashed, $F_{M\text{IN}}$ and $F_{M\text{AX}}$); Bottom: controller output derived by the main endtidal controller (dash-dotted, $F_{V\text{BIS}}$) and by the lower and upper override controllers (dashed, $F_{V\text{LOW}}$ and $F_{V\text{HIGH}}$) as well as the minimal and maximal isoflurane setting (dotted, $F_{V\text{MIN}}$ and $F_{V\text{MAX}}$) and the selected vaporizing setting is $F_{V\text{ISO}}$ (solid).
5.5 Results

5.5.1 Overview of the Clinical Tests

Figure 5.10 shows the recording of a clinical test where the anaesthetist controlled \( BIS \) manually by adjusting the vaporizer setting \( F_{VISO} \). The patient was enrolled for elective decompressive surgery. The anaesthetist adjusted \( F_{VISO} \) only moderately and therefore, the response was slow. Skin incision, a comparatively well defined surgical stimulus, caused a significant reac-

![Graph showing the recording of a clinical test.](image-url)
tion of the BIS. After skin incision BIS dropped below the target value and only after fresh gas flow (FF) was reduced from 3 l/min to 1 l/min the BIS recovered. At the beginning of skin closure fresh gas flow returned to 3 l/min and BIS_{REF} was changed to 60 to prepare emergence of anaesthesia.

Coincidentally, the same patient as in Figure 5.10 had to undergo additional surgery about 10 days later, as the first operation was not entirely successful and willingly enrolled for a second time. The result of the second operation is shown in Figure 5.11. This time the BIS was automatically controlled. The considerable noise level on the BIS measurement can be clearly seen, which results in a highly variable vaporizer setting F_{VISO}. Due to the filter characteristic

![Figure 5.11: Recording of a clinical test. Top: measured (dots, BIS_{RAW}), filtered (solid BIS_{FILT}) and reference (dashed, BIS_{REF}) BIS values; Bottom: vaporizer setting (solid, F_{VISO}), endtidal isoflurane concentration (dash-dotted, F_{EISO}) and fresh gas flow (dotted, FF).]
of the respiratory system the endtidal isoflurane concentration $F_{EISO}$ changed only moderately. The controller was switched on at 45 minutes. It reached set-point in less than 10 minutes. Skin incision caused a moderate reaction of the patient. After 105 minutes fresh gas flow was reduced from 3 l/min to 1 l/min. Gain scheduling compensated the dynamic behaviour by increasing the average $F_{VISO}$ as less anaesthetic gas would otherwise reach the patient. At about 135 minutes the $BIS$ showed a strong reaction. This was caused by a painful surgical stimulation while the surgeon removed the part of the nucleus missed during the first surgery. The controller reacted by fully opening the vaporizer for several minutes to counteract the arousal reaction on the $BIS$. After removal of the nucleus the surgeon started closing the skin. This coincided with $FF$ set to 3 l/min and $BIS_{REF}$ set to 60. Skin closure was presumably less painful than the removal of the nucleus. As a result of the lower stimulation level $BIS$ dropped rapidly below target. The new set-point was reached faster and maintained more accurately by the control system than by the anaesthetist in Figure 5.10.

**Influence of the $BIS$ filter and the feed forward term**

As mentioned earlier the $BIS$ filter (Appendix D.2) was especially designed to reduce considerably the transmission of noise but at the same time to preserve a fast reaction to sudden changes to $BIS$. The feed forward term $f$ can partially compensate for the low pass characteristic of the respiratory system where $f$ initially amplifies small changes in $F_{EREF}$ provided by the outer control loop. However, sufficient noise attenuation is necessary to reduce the variability of the controller output. Figure 5.12 shows a part of a clinical test where the influence of the filter is apparent. It has a different time axis and the quality of the $BIS$ is comparable to the previous figure. The $BIS$ of the patient reacts to skin incision and filtered $BIS$ value ($BIS_{FILT}$) follows slowly. Therefore the vaporizer opens moderately ($F_{VISO}$). Shortly after, the $BIS$ rises even further and the filter detects a too large deviation and therefore passes through the actual measurement instead of the mean of the measurement over the last three minutes, thus the controller reacts by fully opening the vaporizer ($F_{VISO}$). As the $BIS$ value returns within the detection limit after the next few measurements the filter returns to the state before detection and control resumes from the previous $F_{VISO}$. If the measurements would not have returned to the detection limit within the next few measurements then the filter would have been re-initialized from the higher level.

The feed forward term $f$ introduces a rather nervous controller output compared to the previously described controller in [53]. However, this is not critical as the respiratory system acts as a low pass filter. The endtidal gas concentrations are smooth as shown in Figure 5.11.
Artefact handling

In Figure 5.12 three artefact periods for the endtidal isoflurane concentration ($F_{eISO}$) can be seen. The detection allows the controller to switch automatically to the observed value instead. Hence the performance of the controller is not disturbed.

In Figure 5.13 the artefact handling in case of invalid BIS measurements is shown. During several periods no valid BIS measurement is received as the SQI of the device dropped below 30. This is indicated by the arrows and the interrupted line of $BIS_{FILT}$ in the top plot. During these periods the preset safety reference $F_{eman}$ is activated and the actual endtidal reference
Figure 5.13: Artefact handling during a clinical test. Top: measured (dots, \(BIS_{\text{RAW}}\)), filtered (solid \(BIS_{\text{FILT}}\)) and reference (dashed, \(BIS_{\text{REF}}\)) \(BIS\) values; Bottom: reference (dash-dotted, \(F_{\text{REF}}\)), manually set reference (solid, \(F_{\text{MAN}}\)) endtidal isoflurane concentration (dotted, \(F_{\text{ISO}}\)).

The value \(F_{\text{REF}}\) drifts towards \(F_{\text{MAN}}\) over several minutes. The manual endtidal reference \(F_{\text{MAN}}\) is set at 0.8 vol\%. Related to the \(BIS\) reference which is generally achieved with far less isoflurane this seems rather high. Relative large changes on the vaporizer \(F_{\text{ISO}}\) are the result. It is nevertheless on the safe side and therefore, it was not modified by the anaesthetist. Furthermore, in relation to the effect these periods where \(F_{\text{ISO}}\) is increased are not long enough to affect the \(BIS\) considerably.

Activation of \(F_{\text{MAN}}\) is indicated by \(F_{\text{MAN}}\) appearing in the lower plot and the corresponding first order low pass reaction of \(F_{\text{REF}}\) can be clearly seen. As soon as valid \(BIS\) measurements return, the actual reference is obtained from the outer control loop.
Influence of the override controllers

Figure 5.14 shows a detail of a clinical study where the patient needed only a low endtidal isoflurane concentration \( F_{\text{ISO}} \) to achieve the requested target \( BIS_{\text{REF}} \). Even though the \( BIS \) values are clearly below target, the lower override controller ensures that a minimal endtidal concentration \( F_{\text{MIN}} \) is maintained instead. Hence the actual control of \( F_{\text{ISO}} \) is taken over by the lower override controller and the \( BIS \) controller is inactivated. As anaesthesia seemed well balanced the anaesthetist decided to reduce \( F_{\text{MIN}} \) from 0.4 vol\% to 0.3 vol\% at about 168 minutes. The controller follows the new set-point and a significantly lower \( F_{\text{ISO}} \) steady state is found. The \( BIS \) reference is still not reached.

Figure 5.14: Part of a recording of a clinical test. Top: measured (dots, \( BIS_{\text{RAW}} \)), filtered (solid \( BIS_{\text{FILT}} \)) and reference (dashed, \( BIS_{\text{REF}} \)) \( BIS \) values; Centre: endtidal isoflurane concentration (solid, \( F_{\text{ISO}} \)) and lower isoflurane concentration limit (dash-dotted, \( F_{\text{MIN}} \)); Bottom: vaporizer setting (solid, \( F_{\text{ISO}} \)).
5.5.2 Performance Assessment

In the clinical study results of manually controlled (MC) versus automatically controlled (AC) patients were compared. For this purpose two distinct phases were defined while maintaining anaesthesia and compared between the two groups. The skin incision phase (sip) consisted of the period 5 minutes before and 5 minutes after skin incision and low flow phase (lfp) spanned the total period where \( FF \) was 1 l/min.

In total 23 patients (ASA class I or II) scheduled for decompressive spinal surgery were randomized into an automatic (AC) or manual (MC) control group. Two patients had to be excluded from the statistical analysis as the lfp was too short and one patient was excluded because the lower override structure was activated (see Figure 5.14) and therefore inactivated the BIS control.

Accumulated time of closed-loop control was 17.7 hours (including the 3 patients which were excluded from statistical analysis). No incident occurred where the controller had to be inactivated for safety reasons.

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>( AAD ) [mmHg]</td>
<td>6.84 3.61</td>
<td>3.93 1.15</td>
<td>0.017*</td>
</tr>
<tr>
<td>( ME ) [mmHg]</td>
<td>-1.87 13.80</td>
<td>-0.26 2.57</td>
<td>0.363</td>
</tr>
<tr>
<td>( R_{10%} ) [%]</td>
<td>42.9 24.3</td>
<td>68.8 15.1</td>
<td>0.006*</td>
</tr>
<tr>
<td>( R_{20%} ) [%]</td>
<td>77.9 26.3</td>
<td>93.2 7.3</td>
<td>0.053</td>
</tr>
</tbody>
</table>

**Table 5.2: Static performance parameters of the skin incision phase (sip).**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>( AAD ) [mmHg]</td>
<td>6.22 2.59</td>
<td>4.25 0.83</td>
<td>0.022*</td>
</tr>
<tr>
<td>( ME ) [mmHg]</td>
<td>-2.58 10.38</td>
<td>-0.68 2.31</td>
<td>0.178</td>
</tr>
<tr>
<td>( R_{10%} ) [%]</td>
<td>45.5 20.7</td>
<td>64.2 12.1</td>
<td>0.013*</td>
</tr>
<tr>
<td>( R_{20%} ) [%]</td>
<td>86.2 18.1</td>
<td>93.1 4.8</td>
<td>0.137</td>
</tr>
</tbody>
</table>

**Table 5.3: Static performance parameters of the low flow phase (lfp).**

The static performance parameters are summarized in Tables 5.2 and 5.3 for sip and lfp respectively. The performance parameters with a statistically significant difference between the two groups (Student’s t-test, \( p \leq 0.05 \)) are marked with an asterisk (*). The statistical significance is mainly not reached because of the high variability in the manual control group. The 10% range corresponds to a BIS range between 45 and 55 and the 20% range corresponds to...
a range between 40 and 60. All performance parameters are in favour of the automatic control system.

**Reduced patient risk**

In this specific case it is important to show that the patient benefit is related to reducing patient risk. It is difficult to define an appropriate measure as patient risk depends on many factors. Nevertheless, phases with high *BIS* measures indicate an arousal reaction of the patient and have to be avoided. Potentially risky phases are defined as *BIS* phases above 60 for at least one minute of duration. Therefore, several patient risk parameters (*PRP*) are defined. The *PRP*\(_n\) is the total amount of *PRP* incidents and the accumulated time in minutes of these phases is *PRP*\(_t\). Furthermore, *PRP*\(_r\) is the ratio of *PRP*\(_t\) to total time of anaesthesia. The parameter *PRP*\(_r\) is presented in mean and standard deviation (SD). In Table 5.4 the patient risk parameters are shown.

<table>
<thead>
<tr>
<th>Param.</th>
<th>[unit]</th>
<th>MC</th>
<th>AC</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>PRP</em>(_n)</td>
<td>[ ]</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td><em>PRP</em>(_t)</td>
<td>[min.]</td>
<td>97.1</td>
<td>8.3</td>
</tr>
<tr>
<td><em>PRP</em>(_r)</td>
<td>[%]</td>
<td>9.6 (17.5)</td>
<td>1.1 (2.8)</td>
</tr>
</tbody>
</table>

The variation of the manually controlled group is too large to prove any significance, larger groups would be necessary to do so.

### 5.6 Discussion

In contrast to other control loops described in this thesis the controller for *BIS* was built up from a previously developed model and considerable parts of previously developed controllers. Important changes and adaptation were necessary to provide the requested functionality.

The high noise level on the *BIS* measurement required special filter procedures to detect a possible arousal. Not detecting an arousal is critical and therefore the filter was designed to react rather too often. The measurements will be preferably below rather than above target, which leads partially to the negative bias found in the performance parameter *ME*. However, this is exactly the same preference the anaesthetist has in clinical routine.

The override structure and the feed-forward term are important for the usefulness of the control system and to minimize patient risk in the operating theatre. Artefact handling for both the
The inner and outer control loop proved to be adequate.

The performance parameters presented here and many more favour automatic control. Both the AAD and the $R_{10\%}$ for both intraoperative periods show a significant advantage. This suggests that the controller outperforms the anaesthetist.

In some experiments of the clinical study the inner cascade showed on-off behaviour caused by windup of the integral action. Data analysis showed that it resulted from false anti windup gain settings. Essentially, for both the inner and outer integral action the corresponding anti windup structure was inactivated. This is the reason for the apparently wrong anti windup parameters given in Table D.1 in Appendix D. During the clinical study this was not allowed to be changed for consistency of the recorded data. Therefore, an even higher level of significance is expected for future clinical studies.

The automatic control system reduced phases of increased BIS levels compared to the anaesthetist performing the same task. (The potentially risky periods are considerably shorter). The considerably shorter periods of elevated BIS are partially the result of the feed-forward term $f$, which causes a fast reaction with high impact to lower the BIS as soon as possible. The anaesthetists on the other hand tended to observe the evolution of the BIS longer before reacting by increasing the vaporizer setting.

The results achieved in this study oppose the finding in [106], where no clinical advantage between a closed-loop and a manually controlled group could be shown. The results presented here suggest that the closed-loop system is advantageous concerning set-point precision as well as patient safety. Note that in [106] BIS was controlled by infusing liquid isoflurane directly into the breathing circuit with an infusion pump and the authors state that their standard PID controller had potential for improvement.
The oxygen and the carbon dioxide exchange and the underlying transport of gases are based on nonlinear phenomena which motivate a different modelling approach. Significant simplifications lead to a model with three compartments that has many characteristics in common with the model framework described in Chapter 2. The controller is designed to manage different clinical situations. Endtidal carbon dioxide is used as the controlled variable which in clinical routine is used to detect pulmonary embolism. By controlling endtidal carbon dioxide the detection shifts to the manipulated variable (minute ventilation) instead. This is supported by simulation results. Finally, clinical results are shown and compared to a fuzzy based controller developed previously by our research group.
6.1 Introduction

6.1.1 Physiology and Measurement Procedures

The respiratory sensors (chemoreceptors) respond primarily to changes in blood $pH$ which is directly related to the carbon dioxide tension. The corresponding respiratory centres in the medulla stimulate the respiratory rhythm.

Many anaesthetic agents depress spontaneous breathing [16, 105] and therefore the patient needs to be ventilated artificially to ensure vital functions. The main issue is to sufficiently supply the organs with oxygen ($O_2$) and to eliminate the carbon dioxide ($CO_2$) produced by the metabolism of the body.

The blood takes up oxygen in the lungs. Oxygen content depends mainly on blood haemoglobin ($Hb$) to which oxygen molecules bind ($O_2 + Hb \rightleftharpoons HbO_2$), only few percent of total oxygen is dissolved [110, 182]. Increasing oxygen blood gas tensions allows haemoglobin to bind more oxygen. Below 50 mmHg bound oxygen increases rapidly, but above that bound oxygen increases only moderately resulting in a sigmoid $O_2$ dissociation curve. Several parameters such as $H^+$ ion concentration ($pH$ value), carbon dioxide tension or temperature influence the affinity of haemoglobin to bind oxygen. The effect of carbon dioxide tension on oxygen dissociation is known as the Bohr effect. Artificial ventilation during general anaesthesia is conducted with sufficiently oxygen enriched air. As long as the patient has no pulmonary disease arterial oxygen saturation will be close to 100%. Adequacy of ventilation is fundamentally described by measuring arterial $CO_2$ tension ($PaCO_2$) and $pH$ [182]. In clinical routine they are not measured. Generally, endtidal $CO_2$ partial pressure is measured and related to arterial $CO_2$ tension.

Tension is synonymous with partial pressure. It is typically used for gases dissolved in a liquid such as blood [111]. Here, tension is used for a gas dissolved in blood and partial pressure is used for a gas in a gas mixture. Both are measured in mmHg and they share the same main symbol $P$. To distinguish tension from partial pressure the second symbol is lower case or capital respectively, i.e. $PaO_2$ is the arterial oxygen tension and $P_{ACO_2}$ is the alveolar partial pressure. Furthermore, expired partial pressure is denoted with a capital $E$ and end-expired (i.e. endtidal) partial pressure is denoted with $E'$.

Carbon dioxide is carried in three forms: dissolved, as bicarbonate ($CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$) and in combination with proteins as carbamino compounds (carbamino-haemoglobin) [182]. The carbon dioxide dissociation curve is much more linear than the oxygen dissociation curve and it depends on the level of oxygenation. Deoxygenated blood has a higher affinity to bind carbon dioxide, which is known as the Haldane effect. In arterial blood 90% of carbon dioxide content is in bicarbonate form, whereas in venous blood only 60% is in bicarbonate form and up to 30% is bound to reduced haemoglobin.
Blood circulation transports oxygen enriched blood (arterial) from the lungs to the site of consumption and returns with carbon dioxide enriched (venous) blood. Venous blood perfuses the alveoli and the gradient between venous carbon dioxide tension and alveolar carbon dioxide partial pressure allows $CO_2$ to diffuse through the alveolar wall. Similarly, oxygen diffuses the other way.

Inspired air has a very low $CO_2$ and a high $O_2$ content compared to the $CO_2$ and $O_2$ content in the lungs. With each inspiration-expiration cycle, where carbon dioxide “free” air is mixed with enriched air, $CO_2$ is eliminated from and $O_2$ is supplied to the lungs. The respiratory volume only partially takes part in exchanging oxygen and carbon dioxide. The air in the conducting airway (trachea for example) does not take part in gas exchange and is exhaled unchanged. Therefore, the total air volume of respiration (tidal volume, $V_t$) consists of dead space volume ($V_D$) and alveolar volume ($V_A$).

Typically, carbon dioxide is measured with a side-stream capnometer (capnograph), which continuously draws breathing air into a sample cell. Carbon dioxide is determined by comparing infrared light absorption in the sample cell with a chamber free of $CO_2$ [105]. After start of expiration the $CO_2$ content in the sample cell increases rapidly and typically reaches a plateau before abruptly falling to zero\(^1\) during inspiration. The plateau or endtidal partial pressure ($P_{Et}CO_2$) corresponds to the alveolar gas tension ($P_{ACO_2}$) and is used to determine adequate ventilation.

Artificial ventilation during general anaesthesia is of different nature compared to artificial ventilation used with intensive care patients. In the latter spontaneous breathing may be suppressed only partially and therefore, artificial ventilation is only used to support spontaneous breathing. The different ventilation modes are summarized in [62, 105, 111, 148]. During general anaesthesia where spontaneous breathing is suppressed almost without exception, intermittent positive pressure ventilation (IPPV) is applied [111]. During inspiration airway pressure is intermittently raised above ambient pressure to allow a predefined gas volume to flow into the respiratory system. During expiration the airway pressure falls to ambient and expiration is then passive. Expiration may be impeded by the application of positive end-expiratory pressure (PEEP), i.e. the end-expiratory pressure does not drop quite to ambient pressure. This opens previously closed alveoli and thus will reduce airway resistance [111]. The main ventilation parameters influencing transport of oxygen to and carbon dioxide from the lungs are respiratory frequency ($f_R$) and tidal volume ($V_t$).

### 6.1.2 Previous Work and State of the Art

The main contributions concerning closed-loop control in ventilation for general anaesthesia are summarized in Table 6.1.

\(^1\)For ambient dry air at sea level the $CO_2$ partial pressure is 0.23 mmHg which is less than the signal accuracy.
Table 6.1: Summary of publications concerning automatic control of mechanical ventilation.

<table>
<thead>
<tr>
<th>Publication</th>
<th>Model</th>
<th>Controller Parameter</th>
<th>Controller Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>[47]</td>
<td></td>
<td>$CO_2$</td>
<td>$P_{in}sp$</td>
</tr>
<tr>
<td>[66]</td>
<td></td>
<td>$MMV$ $f_R$</td>
<td></td>
</tr>
<tr>
<td>[32]$^1$</td>
<td></td>
<td>$pH^2$ $V_t$</td>
<td></td>
</tr>
<tr>
<td>[186]$^1$</td>
<td>$^3$</td>
<td>$O_2$ $P_{O_2}$</td>
<td></td>
</tr>
<tr>
<td>[128, 129]$^1$</td>
<td></td>
<td>$CO_2$ $MV$</td>
<td></td>
</tr>
<tr>
<td>[137]</td>
<td></td>
<td>$CO_2$ $f_R$, $V_t$</td>
<td></td>
</tr>
<tr>
<td>[177]</td>
<td>$^5$</td>
<td>$CO_2$ $f_R$</td>
<td></td>
</tr>
</tbody>
</table>

**This, [159] $^4$**: $CO_2$ $f_R$, $V_t$

Abbreviations: PID, PID control techniques; MB, model based control techniques; FU, fuzzy based controllers; AD, adaptive control algorithms; $CO_2$, endtidal $CO_2$; MMV, mandatory minute ventilation; $O_2$, oxygen saturation; $P_{in}sp$, inspired airway pressure; $f_R$, respiratory frequency; $V_t$, tidal volume; $P_{O_2}$, inspired oxygen fraction; $MV$, minute ventilation.

Footnotes: $^1$ tested on animals only; $^2$ blood $pH$ was measured with an intra-arterial sensor; $^3$ model is a first order low pass filter with additional time delay; $^4$ physiologically based model; $^5$ linear autoregressive moving average model, volunteers were awake and instructed to follow the respiratory rhythm dictated by the controller.

Reviews of publications can be found in [24, 183], where also simulation and animal studies are included. Important contributions such as [38, 83, 109] and many others concern automatic ventilation for intensive care patients and are not included here because of the different control objective. Only a few studies were conducted on humans, whereas several studies were conducted on animals. Some important contributions related to animal studies are added to Table 6.1. The first reports of closed-loop control of mechanical ventilation date back to the late fifties and subsequently different patient parameters were controlled using different controller outputs. The fact that relatively few clinical studies were conducted results from a moderate need in the operating theatre and an assumed higher risk for the patient. Changing operating conditions, measurement artefacts or disconnections of the respiratory system are common in a clinical setting, which have to be handled by the feedback control system. The implementation of such a non-sensitive controller implies an increased complexity and thus a higher implementation and testing effort.

In [37, 137] a fuzzy based closed-loop controller was developed and successfully applied in a clinical study. The clinical study compared the performance of the controller to the performance of an anaesthetist concentrating on maintaining exact endtidal carbon dioxide concentrations. These results and the experience gained during the clinical study were important for the development of the controller described in this thesis.
6.1.3 Problem Formulation

The earlier developed fuzzy controller showed satisfying performance in clinical practice but concepts of artefact handling were not considered. The goal was to design and implement a model based controller in the sense defined in Chapter 2, which can be used in clinical routine.

6.2 The $CO_2$ Model

The model described in this section originates from [57]. It is derived from [30]. The main aspects and alterations to the model are described.

6.2.1 The Model Structure

The structure of the model is shown in Figure 6.1. It consists of three compartments: the brain, the tissue and the lung compartment. Two separate ordinary differential equations (ODE) describe the behaviour of oxygen and carbon dioxide in each compartment, i.e six ODE in total. The three ODE for oxygen are linked via nonlinear characteristics to the three ODE for carbon dioxide and vice versa ($O_2$ and $CO_2$ dissociation). Significant assumptions were made to simplify the nonlinear model which are described below.

The arterial blood tension $P_a$ is approximately equal to the partial pressure in the lung compartment, i.e. the alveolar partial pressure $P_A$, and the mixed venous blood tension is derived by the brain $P_b$ and the tissue $P_t$ compartment tensions.

The input to the system is derived from minute ventilation ($MV$), which is

$$MV = f_R \cdot V_t$$

(6.1)

where $f_R$ is the respiratory frequency and $V_t$ the tidal volume. The $V_t$ consists of the alveolar volume $V_A$ and the physiologic dead space volume $V_D$, i.e $V_t = V_A + V_D$. The physiologic dead space consists of the anatomic dead space (e.g. trachea) and the alveolar dead space (i.e. the part of the alveoli which is not perfused). The alveolar ventilation $\dot{V}_A$, i.e. the air volume which takes part in the $O_2/CO_2$ exchange over a minute\(^2\), is therefore

$$\dot{V}_A = (V_t - V_D) \cdot f_R$$

(6.2)

Dead space can be affected by several factors, such as age, type of ventilation or posture [105]. However, the effect does hardly change over time.

\(^2\)The medical terminology is $\dot{V}_A$. To prevent confusion with the derivative $\dot{V}_A$ is used instead.
6.2.2 Assumptions and Simplifications

Constant oxygen saturation

During artificial ventilation the patient is supplied with sufficient oxygen and therefore, the uptake of $O_2$ can be assumed to be continuous and more or less independent of actual minute ventilation. This is supported by the nonlinear characteristic of the oxygen dissociation (Figure 6.2), where the distinct operating areas for the arterial and venous blood are indicated. Even though different factors [105] influence oxygen binding - including $CO_2$ tension - the clinical arterial “operating area” for oxygen saturation is close to 100% and does not change overtime significantly due to the saturating effect of the dissociation curve. On the other hand the venous “operating area” of oxygen saturation is influenced by the different factors. Especially, the blood $pH$ which is related to $CO_2$ tension will shift the behaviour accordingly (Bohr effect). This leads to the relevant objective of the controller, namely to maintain a predefined target of expired $CO_2$ and therefore to maintain a stable blood $pH$. As described earlier, this is the same objective as the respiratory control centres use to stimulate breathing. The venous operating area is related to an approximately 25% lower haemoglobin saturation than the corresponding arterial operating area [111], which leads to the tilting of the operating area. By assuming constant operating points for arterial and venous oxygen saturation the dynamic model for $O_2$ is
6.2. The CO₂ Model

Figure 6.2: Qualitative behaviour of the haemoglobin-\(O_2\) dissociation curve for decreased (dotted line), normal (solid line) and increased (dash-dotted line) \(CO_2\) blood tension respectively.

simplified to a constant. Therefore, only a dynamic \(CO_2\) model is considered necessary, where the input of the model is alveolar ventilation (\(\dot{V}_A\)) and the output is alveolar carbon dioxide partial pressure (\(P_{\dot{A}CO_2}\)).

In Figure 6.3 the assumption of a constant oxygenation is illustrated by a clinical recording of several hours. Before intubation the patient receives 100% oxygen to breathe to ensure that sufficient oxygen is available during intubation. After intubation the oxygen in the breathing air is reduced to a level which provides for a high oxygenation.

**Immediate \(O_2/CO_2\) exchange**

Oxygen (\(O_2\)) enriched air flows into the lungs where oxygen is taken up by the alveoli and exchanged with carbon dioxide (\(CO_2\)). This exchange mechanism is relatively fast - typically much faster than a breathing cycle - in comparison to the slow \(CO_2\) and \(O_2\) distribution, \(O_2\)
absorption and $CO_2$ production in the body. Therefore, the gas volume is not modelled. The $CO_2$ elimination is then directly proportional to the alveolar ventilation, i.e.

$$CO_2 \sim \dot{V}_A \cdot P_a$$

This allows to describe the elimination independently of the breathing cycle.

**Linear dependance of oxygen on the $CO_2$ dissociation**

Analogously to the oxygen dissociation the carbon dioxide dissociation has a sigmoid characteristic but it is much more linear. Furthermore, oxygen has also an effect on the $CO_2$ dissociation (Haldane-Effect) [105, 182]. The previous assumption of constant oxygenation allows to define two distinct operating points for the venous and the arterial blood. Therefore, the nonlinear $CO_2$ dissociation curve can be linearized.

**Constant cardiac output**

The model described by [30] uses a time varying cardiac output. In [61, 181] the cardiac output $q$ is described by

$$q = q_0 + q_a(SO_2) + q_b(P_{aCO_2})$$

where $q_0$ is the cardiac output at rest and $q_a$ and $q_b$ are addends depending on oxygen saturation $SO_2$ and arterial carbon dioxide tension $P_{aCO_2}$ respectively. The latter two terms vary considerably for abnormal $SO_2$ and $P_{aCO_2}$ levels only, but are negligible under normal conditions.
Moreover, cardiac output of patients under general anaesthesia is affected more significantly by anaesthetic drugs and surgical stimuli, as the feedback control strategy allows compensation. A specific example on drug dependency of cardiac output can be seen in Section 6.6.1, Figure 6.9.

**Constant arterial/alveolar to endtidal CO₂ gradient**

As mentioned earlier, the true end-point to control artificial ventilation is $P_{aCO₂}$, which can be approximated by $P_{ACO₂}$. However, during clinical routine only $P_{ECO₂}$ is measured continuously. Normally, alveolar $CO₂$ tension is virtually identical to arterial $CO₂$ tension [105] and the alveolar to endtidal gradient$^3$ is less than 8 mmHg [182], which is caused by dilution of the alveolar with $CO₂$-free gas (alveolar dead space). Typically, this gradient is approximately constant and an initial guess can be used in the model. The difference might be even greater in critical ill patients. This suggests that the control of ventilation cannot be based on endtidal $CO₂$ concentration alone. During clinical practice the gradient can be easily determined by blood gas analysis and can be used to update the initial guess. This procedure is also used by the anaesthetists during manual control, as they correct the target endtidal $CO₂$ concentration accordingly. Several factors may change the arterial to endtidal gradient intraoperatively, such as positioning of the patient, which introduces a constant offset [149]. During the clinical studies the determination of the gradient was not used to “correct” the measurement even though it would have been possible. Moreover, the anaesthetist adjusted $P_{EREF}$ accordingly.

### 6.2.3 Model Equations

Equations (6.5), (6.6) and (6.7) describe the model for the $CO₂$ partial pressure in the alveoli (subscript A) and the $CO₂$ tension in the brain (b) and the tissue (t). For simplicity, it is represented here in the continuous form.

\[
\begin{align*}
\dot{P}_A & = n_{11} \cdot P_A + n_{12} \cdot P_b + n_{13} \cdot P_t + n_{14} - P_A \cdot \frac{\dot{V}_A}{V_A} \\
\dot{P}_b & = n_{21} \cdot P_A + n_{22} \cdot P_b + n_{23} \cdot P_t + n_{24} \\
\dot{P}_t & = n_{31} \cdot P_A + n_{32} \cdot P_b + n_{33} \cdot P_t + n_{34}
\end{align*}
\]

The parameter $V_A$ is the alveolar gas volume and the coefficients $n_{ij}$ ($\forall i,j \in \{1,2,3\}$) depend on cardiac output $q$, lung shunt $ls$, fraction of $q$ flowing through the tissue compartment $z$, the respective compartment volumes $V_i$ and the linearisation of the $CO₂$ dissociation curve $(m_{(i)}, n_{(i)})$. The model is bi-linear meaning that the driving input is not a function of a constant only but also of the state variable $P_A$. This can be seen in Equation 6.5. The parameters $n_{ij}$ are given below.

---

$^3$Here “gradient” is the usual medical terminology to describe a static difference or offset!
The coefficients \( n_{i4} (\forall i \in \{2, 3\}) \) additionally depend on the corresponding metabolic production of \( CO_2 \) in the body compartments described by the constants \( M_b \) and \( M_t \). The coefficient \( K \) is a proportionality constant relating partial pressure to the corresponding gas fraction. As mentioned above the arterial tension \( P_aCO_2 \) and the partial pressure in the lungs \( P_{ACO_2} \) correspond and give an approximation of the endtidal \( CO_2 \) partial pressure which can be measured easily during the operation. Details on the parameters can be found in Table E.1 in Appendix E.

The corresponding steady state values are \( P_{Ass} = 40.10 \text{ mmHg} \), \( P_{bss} = 52.67 \text{ mmHg} \) and \( P_{tss} = 44.46 \text{ mmHg} \).
6.2.4 Verification

The model cannot be verified by non-compartmental analysis as there is no specified “drug” input. However, responses on endtidal $CO_2$ partial pressure to changes of alveolar ventilation can be measured and compared to corresponding simulations of arterial $CO_2$ tension. The dynamic behaviour can be compared as the arterial $CO_2$ should only differ by a constant value (the arterial to endtidal gradient, $a - E'$ gradient) which varies between patients. A typical comparison is shown in Figure 6.4, where the offset between the simulated $P_{aCO_2}$ and the measured $P_{ECO_2}$ can be clearly seen. The general dynamic trend is reproduced. However, the initial reaction of the model is faster than that of the patient. This indicates that the gas transport and exchange is too simplified in the model. Only a higher order model can describe this more accurately.

6.3 Controller Design

The controller consists of a state feedback $k$, the observer feedback $h$, an additional integral term with coefficient $k_I$ and an anti windup configuration with coefficient $k_{aw}$. The output of the controller $\dot{V}_A$ is translated into $f_B$ and $V_t$, which takes place in block $J$. The algorithm used in block $J$ is described in Section 6.4.3. The bi-linearity is taken into account by a nonlinear input function $N$ of the observer $P$ (see Figure 6.5).
The nonlinear function is the bi-linear term of Equation (6.9), i.e.

\[ u = -P_A \frac{\dot{V}_A}{V_A} \]  

which leads to a linear observer.

Note that the measured and the observed values have to be corrected by the arterial to endtidal gradient where necessary. This is indicated by \( \nabla \) in the figure.

In this specific case the controller was designed by pole placement instead of the LQR approach. The system is augmented with an additional integral action (i.e. \( A \) and \( B \), Equation (2.24)) and are set to

\[ [-10.3 - 0.14 - 0.51 - 0.69] \]  

and for the observer system \( (A,C) \) the poles are set to

\[ [-13.8 - 6.0 - 0.68] \]  

The explicit control parameters can be found in Appendix E.

The closed-loop bandwidth is 0.63 rad/min.
6.4 Considerations Concerning Implementation

6.4.1 Artefact Handling Procedures

The main artefacts on the endtidal \( CO_2 \) measurement occur when the measurement line to the side stream capnograph is disconnected or the sensor device automatically recalibrates. In both cases the measurement falls to or below zero.

Artefact handling is indicated in Figure 6.5. If invalid measurements are detected the controller uses the endtidal concentration estimated by the model \( (P_{\text{et}}^{\text{OBS}}) \) instead of the actual measurement. During artefact periods the anaesthetist is alerted by a corresponding warning on the man machine interface. The warning includes the displaying of the elapsed time since the last valid measurement was received. Notification of prolonged periods indicate faulty measurement procedures.

The following detection criteria for \( P_{\text{et}}^{\text{CO}_2} \) are applied.

<table>
<thead>
<tr>
<th>Param. ( [\text{Unit}] )</th>
<th>( \text{min} )</th>
<th>( \text{max} )</th>
<th>( \text{et} ) [sec.]</th>
</tr>
</thead>
<tbody>
<tr>
<td>( P_{\text{et}}^{\text{CO}_2} ) [mmHg]</td>
<td>20</td>
<td>60</td>
<td>15</td>
</tr>
</tbody>
</table>

The parameter \( \text{et} \) is again the elapsed time since measurement and it indicates when a measurement is rejected as invalid.

After checking for validity of the \( P_{\text{et}}^{\text{CO}_2} \) measurement, it is filtered according to the descriptions in Section 6.4.2. The effectiveness of the artefact handling procedure is documented in Section 6.6.1.

6.4.2 Median Filter

A median filter was used to smooth the output of the controller due to measurement noise. During the first study a fast reaction of the controller to changes of \( P_{\text{et}}^{\text{CO}_2} \) was observed including some rapid changes caused by surgical disturbances. For example a surgeon leaning on the chest of the patient causes a distinctly higher measurement value than the previous measurements as the patient expires more air due to the pressure on the chest. The measured \( CO_2 \) value is filtered by a simple median filter to prevent the controller from reacting too aggressively upon these disturbances. A median filter using the seven last measured values proved to be satisfying. In Figure 6.6 the effect of the filter can be seen from the record of a clinical trial. The dash dotted line in both the upper and the lower plot is the reference value, the solid line in the upper plot is the unfiltered and in the bottom plot the filtered measurement. After 150 minutes the noise level is increased due to the surgeon closing the skin cut, which is in this
patient in the lower chest area. The manipulation caused the patient to expire irregular bursts of additional air. The start of the skin closure was captured by a time stamp in the recorded data set.

Figure 6.6: Increased noise level on the raw measurement due to surgical disturbances (top) and comparison to the filtered signal (bottom). Top: reference (dash-dotted, $P_{E\text{REF}}$) and filtered (solid, $P_{E\text{FILT}}$) $CO_2$ partial pressure; Bottom: reference (dash-dotted, $P_{E\text{REF}}$) and measured (solid, $P_{E\text{CO}_2}$) $CO_2$ partial pressure.
6.4.3 Algorithm to Split $MV$ in $f_R$ and $V_t$

The actual manipulated variable derived by the controller is $\dot{V}_A$. As it is directly related to $MV$ (Equations (6.1) and (6.2)) by

$$MV = \dot{V}_A + V_D \cdot f_R$$  \hspace{1cm} (6.23)

and therefore, $MV$ is used for simplicity. The manipulated variables implemented on the respiratory system are the respiratory frequency ($f_R$) and the tidal volume ($V_t$), with $MV = f_R \cdot V_t$. A change in minute ventilation may be achieved by changing either $f_R$ or $V_t$ or both. Anaesthetists tend to keep the respiratory frequency at about 10 per minute and adjust the tidal volume to regulate the expired CO$_2$. However, for large changes they prefer to change $f_R$ as well, because increasing $V_t$ causes the respiratory pressure to increase. For this reason a special algorithm was implemented (block $J$ in Figure 6.5).

**Basic principles**

The following requirements need to be met by the splitting algorithm:

- Appropriate imitation of the usual practice. Small changes in $MV$ are achieved by adjusting the tidal volume and only large changes by adjusting both tidal volume and respiratory frequency.

- Possibility to adapt online to patient variability. Different patients may have a different “ideal” combination of $f_R$ and $V_t$ due to differences in physiology and healthiness of the lungs. Moreover, surgical conditions (one lung ventilation) may require to target a different ideal combination intraoperatively.

- The algorithm needs to be “stable” meaning that it provides a solution closest to the “ideal” combination. This is important as different combinations of $f_R$ and $V_t$ are able to achieve the same $MV$. A close to optimal solution is desired and not an extreme combination (e.g. $f_R = f_{R_{\text{min}}}$ and $V_t = V_{t_{\text{max}}}$) or “wandering” solutions.

In [37, 137] the splitting of $MV$ was achieved by a fuzzy engine which was based on ten rules. The fuzzy engine covered an appropriate reaction in case of high inspiratory pressure (see the following section for further details) but it was not able to adapt to patient variability.

In order to accommodate all requirements a new approach was developed. It minimizes the quadratic cost function
\begin{equation}
\min_i \left\{ \varphi \left[ (f_{R_{\text{dd}}} + i) - \bar{f}_R \right]^2 + \psi \left[ \frac{MV}{(f_{R_{\text{dd}}} + i)} - \bar{V}_t \right]^2 + \varphi \right\} \tag{6.24}
\end{equation}

The requested \( MV \) is provided by the controller output and \( f_{R_{\text{dd}}} \) is the respiratory frequency of the last sampling instance. The parameter \( i \) is a cardinal number between \(-n...+n\) where \( n \) is the maximally allowed change of \( f_R \) between two subsequent sampling instances. It proved sufficient to choose \( n = 1 \). This means that the respiratory frequency changes between each step by a maximum of one and the minimization only has to compare the results for the three possible new values of \( f_R \). The parameters \( \varphi \) and \( \psi \) are used to normalize the functions to the maximum range of possible values. Furthermore, \( \varphi \) is a penalty term which is only non-zero if either \( f_R \) or \( V_t \) hits the corresponding upper or lower limit. This ensures that a requested \( MV \) is really translated under this special condition. The exact formulation is given in Appendix E.2. By inspection the combination \([f_R(i), V_t(i)]\), with \( V_t(i) = \frac{MV}{f_R(i)} \), closest to \( f_R \) and \( V_t \) will minimize Equation (6.24). By setting \( \bar{f}_R \) and \( \bar{V}_t \) the anaesthetist can shift the operating area of the algorithm and adapt to the patient variability. The quadratic form ensures that the closest combination is chosen. As \( f_R \) is quantized to 1 \( \text{min}^{-1} \) and \( V_t \) to 0.01 litre, small changes in \( MV \) are preferably implemented by changing \( V_t \) as a variation of \( f_R \) would lead to larger cost values in Equation (6.24). Larger changes will affect both \( f_R \) and \( V_t \). In principle this behaviour can be changed by additionally setting a weight on \( \varphi \) or \( \psi \). However, in the clinical test this has not been proved necessary.

Hence all requirements are met and in Figure 6.7 the result of the splitting algorithm is shown. This is the data record of a clinical trial, where the upper plot shows \( MV \) and the lower plot shows the resulting \( f_R \) and \( V_t \).

Between 25 and 65 minutes the respiratory frequency is rarely changed as the requested \( MV \) could be achieved by only adapting \( V_t \). After that several set-point changes (see also the results in Section 6.6.1) require large changes of \( MV \) and therefore both \( V_t \) and \( f_R \) are changed.

### 6.4.4 Automatic Handling of High Inspiratory Pressure

By increasing \( V_t \) the peak inspiratory pressure (\( PIP \)) will rise. This \( PIP \) is allowed to reach only a certain threshold \( PIP_{\text{max}} \), as a baro trauma may occur and the patient may be seriously injured. Moreover, the respiratory system has a safety limit, which is set by the anaesthetist. If the safety limit is hit, the desired \( MV \) cannot be set by the respiratory system. Therefore, when reaching \( PIP_{\text{max}} \) the control system increases \( f_R \) and thus decreases \( V_t \) automatically. This is achieved directly with Equation (6.24) by forcing \( i = 1 \). The maximum allowed peak inspiratory pressure coincides with the safety limit set on the respiratory system.
6.5 HIL Simulation of Pulmonary Air Embolism

Pulmonary air embolism is a critical incident during various operations, mainly during surgery on cervical spine or structures in the posterior fossa carried out in the sitting position [33]. A significant amount of air enters the venous circulation and reaches via the heart the pulmonary vessels, where it obstructs the blood circulation and hinders pulmonary gas exchange. The result is that the total amount of alveoli active in gas exchange is reduced. Typically, the result is a drop in endtidal \( CO_2 \) and a slow recovery while air is cleared from the body and more and more alveoli are perfused again. The endtidal \( CO_2 \) measurement is the simplest method to diagnose air embolism intraoperatively [111]. By using it as the controlled variable the
characteristic time course observed during an air embolism is changed, which makes it difficult to detect the incident by standard methods. Therefore, closed-loop control of endtidal $CO_2$ is often criticized by clinicians.

A naive approach to modelling a pulmonary embolism would be to increase dead space ventilation, i.e. by increasing $V_D$ in Equation (6.2). However, this does not show the typical endtidal $CO_2$ response as endtidal $CO_2$ increases due to reduced alveolar ventilation.

More appropriate is to model a reduced cardiac output ($q$) reaching the alveoli (see Equations (6.8) to (6.19)). In [28] a “balloon” of a pulmonary catheter was inflated to simulate

![Simulation of an air embolism](image)

**Figure 6.8**: Simulation of a pulmonary embolism during open-loop (up to 60 minutes) and closed-loop control (from 60 minutes onward). Top: reference (dash-dotted, $PE'REF$) and simulated (solid, $PE'CO_2$) endtidal $CO_2$; Bottom: minute ventilation (solid, $MV$).
6.6 Results

6.6.1 Overview of the Clinical Tests

The implemented controller was tested in clinical trials and used during a clinical study. In Figure 6.9 a typical result is shown. Step changes are performed to evaluate the behaviour of the controller. During clinical practice the set-point of endtidal \( CO_2 \) is rarely changed. Exceptions are neurosurgical patients [149], where hyperventilation is often used to reduce intracranial pressure. The arterial \( CO_2 \) tension correlates inversely with cerebral arterial resistance and by hyper-ventilating the patient resistance increases and therefore bleeding is reduced.

The endtidal \( CO_2 \) measurement follows its reference nicely. The effect of the splitting algorithm on the manipulated variables \( f_R \) and \( V_t \) can be seen clearly from about 25 minutes onwards, where the respiratory frequency is not changed for more than 40 minutes due to the stable phase of the operation before actual surgery starts at 80 minutes. After about 120 minutes a bolus of ephedrin was administered to counteract a hypotensive patient condition. The strong reaction on the blood pressure can be seen clearly. This leads also to an increase of \( CO_2 \) due to the temporary increased cardiac output, the controller reacted by increasing both \( f_R \) and \( V_t \). Both reference tracking and disturbance rejection are more than satisfactory. The increased noise level after 150 minutes (see also Figure 6.6 for a detail of the recording) introduced by the surgeon closing the skin towards the end of the operation was handled well.
In the following selected clinical tests are presented which document the effectiveness of the main implemented functions.

**Artefact handling**

In Figure 6.10 a further example is shown. Again the controller performs well with set-point changes and disturbance rejection. After about 280 minutes a pneumatic tourniquet on a lower extremity is deflated. A tourniquet blocks blood circulation in an extremity - in this specific
Figure 6.10: Data record of a clinical trial. Top: measured (solid, $P_{\text{E}CO_2}$) and reference (dash-dotted, $P_{\text{E}REF}$) endtidal $CO_2$ tension; Middle: tidal volume $V_t$; Bottom: respiratory frequency $f_R$.

case the left leg - to eliminate intraoperative bleeding and thereby provide better operative conditions [150]. After deflation of the tourniquet $CO_2$ enriched blood of that leg enters suddenly the blood circulation, resulting in a large $P_{\text{E}CO_2}$ peak. The controller reacts immediately by increasing minute ventilation.

Figure 6.11 shows a detail from Figure 6.10. During the period between 242 and 244 minutes the anaesthetist decided to listen to the lungs of the patient and therefore ventilated the patient with an “ambu” bag. During this period the disconnected respiratory system provided no valid measurement of $CO_2$ and therefore, the observed value was used instead. This can be seen in the deviation between $P_{\text{E}CO_2}$ and the actually used value in the controller $P_{\text{E}CTRL}$. The controller output, i.e. minute ventilation was not changed. After reconnection of the respiratory
system valid measurements returned and an increased CO₂ level was detected. The controller reacted by increasing minute ventilation MV to eliminate excess CO₂ within two minutes.

Figure 6.12 shows a detail of a different data record. Towards the end of this operation the absorbent exhausted (at 265 minutes) and carbon dioxide was not eliminated sufficiently from the respiratory system, leading to the patient re-breathing carbon dioxide. The controller reacts by increasing the minute ventilation significantly and is able to maintain the requested target. Similar to the case of the pulmonary embolism endtidal CO₂ can be used to detect the exhausted absorbent. Again the indicator is shifted to the change of minute ventilation in the closed-loop system. In this specific case there are additional indicators, namely the continuously measured CO₂ partial pressure of the capnograph does not return to zero and shows increasing tendency during inspiration. After the absorbent was replaced (280 minute) the minute ventilation returned to normal.

Generally, artefact handling during clinical application showed good performance. All incidents were handled safely by the controller. Furthermore, some incidents were detected earlier by using the closed-loop controller than they would have been noticed by the anaesthetist in manual mode. In one case the cuff of the endotracheal tube leaked and the controller reduced
6.6. Results

Figure 6.12: Detail of data record of a clinical trial. Measured (solid, $P_{E\,CO_2}$) and reference (dotted, $P_{E\,REF}$) endtidal $CO_2$ partial pressure, minute ventilation (dash-dotted, $MV$).

$MV$ ventilation significantly as the measurement dropped rapidly. The alarm of the monitor concerning low minute ventilation was triggered earlier than any other alarm. The patient was not harmed as the cuff was replaced immediately. This again shows that by using closed-loop control, incidents are not necessarily avoided. However, other and additional clinical signs can be used to identify problems early and may help to reduce risks for the patient.

High inspiratory airway pressure

Figure 6.13 shows a clinical test where during active closed-loop control the peak airway pressure $PIP$ reaches the preset limit. After 150 minutes a pneumatic tourniquet is deflated and therefore $P_{E\,CO_2}$ peaks shortly after. As the controller was implementing already a high minute ventilation, the additional increase especially of $V_t$ caused the inspiratory airway pressure to reach the preset safety limit. The controller acted by increasing $f_R$ and thus reducing $V_t$. The
Figure 6.13: Data record of a clinical test. Top: measured (solid, $P_{E'CO2}$) and reference (dash-dotted, $P_{E'REF}$) endtidal CO$_2$ partial pressure; Middle: tidal volume (solid, $V_t$, scaled by 10) and respiratory frequency (dash-dotted, $f_R$); Bottom: peak inspiratory airway pressure (solid, PIP) and upper PIP limit (dashed, $PIP_{max}$).

Further this recording shows an interesting fact when the set-point changes from a low to a high reference. During hypoventilation ($P_{E'REF}$ 28 mmHg) the minute ventilation is high to eliminate sufficient CO$_2$. Therefore, the airway pressure is relatively high and most parts of the lungs and of the alveoli are opened. During transition from hypoventilation to hyperventilation ($P_{E'REF}$ 42 mmHg) the controller reduces MV to the minimum allowed (time between 171 and 179 minutes) and therefore reduces also PIP considerably. A large fraction of the lung is
not ventilated during this time and therefore, lung perfusion is not regular, gas mixing is not uniform and $P_{\text{v} \text{CO}_2}$ is inconsistent. Furthermore, when finally reaching the new set-point the controller increases $MV$ and therefore opens previously inactivated parts of the lungs with a relative high $CO_2$ content, thereby increasing $P_{\text{v} \text{CO}_2}$ even more. This results in the relatively large overshoot after 180 minutes for this specific step change.

6.6.2 Performance Assessment

Statistical analysis

Fifteen patients (ASA class I and II) scheduled for elective surgery were enrolled in the study. Accumulated time of closed-loop control was 41.8 hours. No incident occurred where the controller had to be switched off for safety reasons.

Note: This clinical study was carried out together with the clinical study regulating skeletal muscle relaxation. Patients and accumulated time of operation are not equal. Some patients were excluded from the statistical analysis for skeletal muscle relaxation as some clinical conditions were not satisfied over the whole period.

The static performance parameters are summarized in Table 6.2.

<table>
<thead>
<tr>
<th>Param. [unit]</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>$AAD$ [mmHg]</td>
<td>0.37</td>
<td>0.13</td>
</tr>
<tr>
<td>$ME$ [mmHg]</td>
<td>0.01</td>
<td>0.07</td>
</tr>
<tr>
<td>$R_{1%}$ [%]</td>
<td>68.1</td>
<td>8.8</td>
</tr>
<tr>
<td>$R_{10%}$ [%]</td>
<td>99.9</td>
<td>0.4</td>
</tr>
</tbody>
</table>

A 1% range ($R_{1\%}$) corresponds to approximately $\pm 0.4 \text{mmHg}$ and a 10% range ($R_{10\%}$) to $\pm 4 \text{mmHg}$.

The dynamic performance parameters are summarized in Table 6.3.

The rise time ($RT$) for $+14 \text{mmHg}$ is considerably larger than for the $-14 \text{mmHg}$ step change. This is due to the fact that the lower limit on $MV$ is reached for the $+14 \text{mmHg}$ change whereas the upper limit is not reached for the $-14 \text{mmHg}$ set-point change. The overshoot ($OS$) is larger for the $+14 \text{mmHg}$ step change due to the previously described fact of the larger lung fraction which is not ventilated (Section 6.6.1).
Comparison fuzzy versus model based controller

In Figure 6.14 a visual comparison between the model based controller described and the previously used fuzzy controller [37, 137] is shown. The two upper plots show a reference change from 35 mmHg to 42 mmHg handled by the model based controller, the bottom two plots show the same reference change handled by the fuzzy controller. The top and the third plot show the reference CO$_2$ value (dash dotted line) and the measured CO$_2$ value (solid line). The second and the bottom plot show the tidal volume (dashed line) and the respiratory frequency (dash dotted line). The model based controller used measurements in mmHg, and the values are therefore quantized to 1 mmHg. The fuzzy controller used measurements in % volume. The latter data was translated into mmHg and therefore shows a different quantization. The faster response of the model based controller can be seen. The model based controller settles in less than 4 minutes, the fuzzy controller in about 7 minutes. The splitting algorithm of the model based controller shows the desired performance. From the level of quantization results a minimal overshoot of 1 mmHg for the model based controller. It is not precise to talk about overshoot in the traditional sense, as the slow compartments takes more time to reach new steady state conditions and therefore, the required minute ventilation is adjusted, but only after an error between reference and measurement is detected. The fuzzy controller shows the same behaviour, but as the dynamic response is slower and in combination with a slightly lower quantization level this effect is reduced.

For all static performance parameters and for OS the comparison of fuzzy to model based control shows no significance. However, rise time $RT$ is significantly faster$^4$ for the 7 mmHg step changes. For the positive and negative set-point changes the $RT$ values of the fuzzy controller are 313 (90) seconds and 355 (127) seconds respectively. No 14 mmHg step changes were conducted with the fuzzy controller.

\begin{table}[h]
\centering
\caption{Dynamic closed-loop performance parameters (mean (SD)).}
\begin{tabular}{lll}
\hline
\textbf{$\Delta$ [mmHg]} & \textbf{$RT$ [sec.]} & \textbf{$OS$ [mmHg]} \\
\hline
+7 & 144 (17) & 1.3 (0.8) \\
-7 & 177 (36) & -1.0 (0.0) \\
+14 & 311 (85) & 2.7 (1.1) \\
-14 & 215 (18) & -1.3 (0.5) \\
\hline
\end{tabular}
\end{table}

\footnote{$^4$Student’s t-test (p \leq 0.001)}
6.7 Discussion

The clinical study was initially designed to proof that there is an interaction of blood pH on the degree of skeletal muscle relaxation. Therefore, large step changes (14 mmHg) had to be carried out. Nevertheless, the results could be compared to the previous study [37, 137], which was able to show that closed-loop control is at least as good as manual control. The controller described in this section did not show any significant differences concerning set-point precision, however, for set-point changes the model based controller outperformed the fuzzy controller.
Assuming that the $CO_2$ target is not changed during the operation the venous oxygen operating point was considered constant. This is one of the assumptions made to simplify the model. During the clinical trials the $CO_2$ set-point was often changed considerably to assess the performance of the controller and to identify possible interactions with other anaesthetic drugs (see Section 6.6). Therefore, the above assumption was violated significantly. However, the controller design is sufficiently robust to permit these modelling assumptions.

Obviously, the model is not strictly validated as the verification is based on a few input output data sequences. Furthermore, it indicates that the high frequency components are not accurately reproduced (see Section 6.2.4). However, the main error is the static offset associated with the arterial to endtidal gradient. Setting the arterial to endtidal $CO_2$ gradient to zero seems not to be disadvantageous as the anaesthetist adjusted instead the set-point where necessary. The blood gas analysis showed similar results compared to the literature [182]. (The mean gradient was 5.8 mmHg, standard deviation 3.4 mmHg). The dynamic differences are obviously not significant in this perspective.

From the start the controller showed good performance in a clinical environment and the control parameters were not changed during the pilot studies. This is especially remarkable as [37, 137] used 20 patients to settle on the final tuning of their fuzzy controller. Nevertheless, several additions to the control structure (artefact handling) and signal processing (median filter) were made to improve the overall performance.

Typical small incidents such as temporary disconnection of the breathing system introduced by the clinical environment were handled well, leading to an improved clinical applicability.

The HIL simulations concerning the detection of the pulmonary embolism show that other parameters can be used instead of $P_{E\text{CO}_2}$. The question whether the clinician will accept another measure instead cannot be answered here. Close bounds on the minute ventilation can be used to detect many potentially critical incidents sufficiently early. Furthermore, the detection of pulmonary embolism has to be addressed and a safety strategy implemented to prevent an automatic system from a false reaction. The minimum requirement is a detection scheme and an issuing of a warning, asking the anaesthetist to continue artificial ventilation manually. The next step would be an override scheme which automatically limits the minute ventilation to a safety bound.
Chapter 7

Integrated Control

The main goal of this project is to design working prototypes of the main four control objectives and to integrate them on the same system. This chapter demonstrates that the first steps in integrating multiple single input single output controllers has been achieved. Some results where two controllers are active simultaneously are shown.

7.1 Introduction

Regulating more than one patient parameter introduces requirements concerning the controller platform. More than one controller will be active at the same time and therefore the system needs to incorporate them all. Moreover, some signals and settings are used by several control loops and therefore these interconnections need to be handled. For example the respiratory frequency is a manipulated variable of the $CO_2$ controller and at the same time it is a parameter in the model of the endtidal isoflurane controller. Furthermore, all necessary input output devices and an appropriate man-machine-interface are necessary to operate the controller platform in the operating theatre.
7.1.1 Interactions

The main concern when operating multiple controllers simultaneously is that interactions can cause instability. For this reason the main interactions between the different control loops are shortly described.

(i) It is suspected that the pH value of the blood may influence the effectiveness of mivacu- rium. The pH level depends on the carbon dioxide tension and therefore by changing the ventilation parameters the neuromuscular block may be influenced.

(ii) Endtidal carbon dioxide is mainly influenced by haemodynamic changes, positioning and surgical procedures. An example shown in Section 6.6 illustrates the temporary effect of an ephedrine bolus and the temporary effect of deflating a pneumatic tourniquet.

(iii) Endtidal isoflurane is influenced by the uptake of isoflurane by the patient and by the respiratory parameters which change the dynamics of uptake.

(iv) The bispectral index is influenced by hypnotic drugs and also by opioids. The effect of opioids on BIS is related with their potential to suppress a surgical stimulus.

(v) As the control objective in [37, 46] proves, the hypnotic isoflurane can be used to regulate MAP.

(vi) Clinical situations may influence MAP. A typical case is the hypovolemic patient where a considerably lower MAP is observed.

Interaction (i) was investigated in a clinical study. Data records of this study are shown later in Section 7.2.1. No significant interaction was observed and no stability problems were observed.

The critical haemodynamic changes which cause interaction (ii) are of temporary nature. The controller is designed to sufficiently suppress these disturbances.

To test the CO₂ controller large step changes were performed which changes the dynamics of uptake of a volatile anaesthetic. Generally, in clinical practice such step changes are rare and the adjustment of the respiratory parameters is moderate. Therefore, the interaction (iii) is probably not critical.

Interactions (iv) and (v) are the most critical. It is an ongoing discussion how the corresponding drugs should be administered. Nevertheless, by increasing opioid level and therefore suppressing stress response the BIS level and mainly its variability may be reduced. The used opioid has a relative fast onset but a long offset, i.e. fast and therefore critical reactions on the BIS caused by alfentanil are always in the safe direction. The influence of isoflurane on MAP is more direct. Increasing isoflurane concentrations generally decrease MAP. The controller reacts with higher isoflurane concentrations in case the BIS increases, which can be related to an awakening reaction of the patient. This reaction is mainly caused by a surgical stimulation and the following stress response. Again both controllers act in the same direction and therefore
it is less critical than if they were reacting in opposite directions. Nevertheless, it is necessary to guarantee upper and lower limits on both of the administered drugs. Furthermore, this is a safety issue in relation with interaction (vi). Increasing levels of hypovolemia introduces a slow varying drift-like disturbance which causes the MAP to decrease over time and therefore the administration of alfentanil is reduced. This has to be handled by the anaesthetist with care as a low opioid level may influence the hypnotic state considerably.

Patient benefit is possibly related to maintaining all patient parameters in a narrow range. This hypothesis can be associated with the anaesthetist’s way of managing anaesthetics, fluids and artificial ventilation. Furthermore, the anaesthetist is able to handle all these interactions in most cases without any major difficulties. By imitating the anaesthetist it is therefore hoped to manage the critical interactions analogously.

7.1.2 Previous Work and State of the Art

Not many clinical investigations used more than one parameter for automatic control purposes and to our knowledge only animal studies were conducted.

In [139] halothane is used to control mean arterial pressure and a measure of EEG frequency (spectral edge frequency). The system is based on an on/off controller to administer the volatile anaesthetic and a “coordinator” is used to force the system states as near as possible to reference values since only one drug input is used. The system was tested on one dog.

In [187] sodium nitroprusside and dopamine are used to control mean arterial blood pressure and cardiac output. Nitroprusside allows precise titration of MAP and dopamine is used in the treatment of shock to support blood pressure and cardiac output [105]. They used a multiple model adaptive and predictive control framework. This multiple input and a multiple output system was validated on six mongrel dogs. In this case no true anaesthetic endpoint is maintained. Both cardiac output and mean arterial pressure are forced to some reference value. Set-point changes are carried out to verify the concept.

In [125] also sodium nitroprusside and dopamine are used to control mean arterial blood pressure and cardiac output. The concepts are similar to [187] and the system was tested several times on three mongrel dogs.
7.2 Results

The main combination so far is the simultaneous management of skeletal muscle relaxation and artificial ventilation. Additionally, one pilot study was conducted with the simultaneous administration of isoflurane and alfentanil.

7.2.1 Simultaneous Regulation of Skeletal Muscle Relaxation and Artificial Ventilation

In Figure 7.1 an early study in the clinical investigations is shown. The endtidal $CO_2$ controller is active for more than six hours and the $Ti%$ controller is active for more than five hours. Several large disturbances as indicated on the top plot were observed. It is not clear where these disturbances originate from, but they cannot be related to the $CO_2$ step changes carried out. In later studies as shown in Figure 7.2 these disturbances were rarely observed. The most plausible origin is therefore the inappropriate attachment of the stimulation and the measurement electrodes, which improved from each test to the next. In the second example shown the controllers are simultaneously active for more than three hours.

The clinical hypothesis was to prove an interaction between blood $pH$ and the effect of mivacurium. Blood $pH$ is influenced by the arterial $CO_2$ tension which can be changed by altering the endtidal concentration. To increase the effect large $CO_2$ step changes were made, but over all recordings no statistically significant interaction could be observed. The disturbances seen in the early studies (Figure 7.1) cannot be related to the large $CO_2$ step changes.

7.2.2 Simultaneous Regulation of Hypnosis and Analgesia

So far only one pilot study was carried with the simultaneous objectives of maintaining a desired endtidal isoflurane set-point and a desired mean arterial set-point. Its data record is shown in Figure 7.3. Both controllers were active for about 40 minutes. The details of the reaction of the $MAP$ controller is described in Section 4.4.2. This is the first step to investigate the necessity of an interaction model between both drugs. For this purpose endtidal isoflurane is kept constant rather than the $BIS$. The first impression when comparing the infusion rate of alfentanil $i_R$ and the recording of the $BIS$ leads to the conclusion that both are somehow related. However, there is more to consider. The pain detection is indicated by the black bars in the third plot and the changes of $BIS$ as well as of $MAP$ are a result of painful surgical procedures. Therefore, $i_R$ and $BIS$ increase simultaneously. In any case, further investigations are necessary.
7.2. Results

Patient T16E0200, Bodyweight = 81 kg

Figure 7.1: Recording of clinical test where skeletal muscle relaxation and artificial ventilation are controlled simultaneously. Top: $T1\%$ (solid) and $T1\%_{REF}$ (dashed-dotted); Second: infusion rate $i_R$; Third: endtidal $CO_2$ partial pressure (solid, $P_{E\,CO_2}$) and its reference (dash-dotted, $P_{E\,REF}$); Bottom: minute ventilation (solid, $MV$).
Figure 7.2: Recording of clinical test where skeletal muscle relaxation and artificial ventilation are controlled simultaneously. Top: $T1\%$ (solid) and $T1\%_{\text{REF}}$ (dashed-dotted); Second: infusion rate $i_R$; Third: endtidal $CO_2$ partial pressure (solid, $P_{E\text{CO}_2}$) and its reference (dash-dotted, $P_{E\text{CO}_2}_{\text{REF}}$); Bottom: minute ventilation (solid, $MV$).
7.2. Results

Figure 7.3: Recording of clinical test where endtidal isoflurane and alfentanil are controlled simultaneously. Top: non-invasive arterial pressure (solid, MAP) and its reference (dashed-dotted, MAPREF); Second: infusion rate (iR); Third: bispectral index (BIS) and pain detection (bars (dots), Pain); Fourth: endtidal isoflurane concentration (solid, FEISO) and its reference (dash-dotted, FEREF); Bottom: vaporizer setting (solid, FvISO).
7.3 Discussion

The promising results shown in this chapter illustrate the possibilities of automatic control in anaesthesia. First of all, these supportive systems can facilitate the routine tasks of the anaesthetist. So far only one patient parameter was automatically regulated in humans and this does not significantly reduce workload. By attempting to maintain all four main objectives this will change, thus the anaesthetist is able to pursue more supervisory and more demanding tasks.

By maintaining the main patient parameters in a narrow range the hypothesis of a patient benefit can be investigated and compared to standard clinical practice. This also minimizes drug requirement and prevents overdosing.

The clinical investigations in the near future will show if a more general approach is necessary for the interaction between isoflurane and alfentanil. Further studies are necessary to validate the concepts.
Chapter 8

Conclusion

8.1 Main Contributions

Modelling

Modelling biological system has been investigated by many authors and different concepts are published. Physiologically based models try to imitate drug distribution based on assumptions concerning drug binding, blood flow to the different body compartments and their respective volumes. These assumptions can be based on measurements, which are partially major invasive procedures. Often only data derived from animal experiments are available and therefore the human model parameters are generated by scaling the corresponding animal model. Mamillary compartmental models on the other hand are based on input output data sequences and only a few parameters are identified to reproduce a specific time course. The synthesis of the advantages of both model concepts allows to describe a drug specific input output behaviour. The novelty of the tuning concept described is that parameters of the physiologically based model that are difficult to attain are used to tune the model to the time characteristics of the drug. The derived model is sufficiently descriptive for closed-loop control purposes.
Controller design

The design of the controllers is divided into two levels. A standard design method provides standard functionality and add-on functions are needed to increase clinical applicability. The add-on functions are mainly designed by imitating the anaesthetist.

All controllers were designed to handle most common artefacts such as generated by standard routine handling of the patient and of sensor and actuator devices. This means that for example a sample line is allowed to be temporarily disconnected without any implications for the control action in case the anaesthetist has a clinical indication to do so. This increases clinical applicability. Many specific examples are shown throughout this thesis.

Hardware-in-the-loop simulation

The development of the HIL simulation environment allows a strict validation of the implemented controllers. Not only the implementation of the algorithms but also the input output communication drivers can be tested, which increases the stability and availability of the control platform. Furthermore, the involved research anaesthetists can be trained on the actual control platform. Many clinical requirements were clarified during such “training sessions” and the corresponding add-functions were validated in real-time simulations.

Regulating skeletal muscle relaxation

To maintain target levels of skeletal muscle relaxation a clinically applicable controller was developed in several steps. In a first step a controller was developed which is comparable to the controllers described in the literature. Good results were achieved with this model based control design. It was used in a clinical study where a considerable intra and inter patient variability was observed. This suggests that supportive automatic control during mivacurium relaxation is a necessity.

The applicability of this first controller in clinical routine is questionable. The measurement signal is not standard clinical practice and moreover the time from induction of anaesthesia to intubation is prolonged, thus patient risk is increased. Therefore, in a second step the first controller was extended with an outer cascade, which clearly enhances clinical applicability, as a standard measure is used (TOF-Count) and the patient can be intubated directly after induction of anaesthesia. This is the first known approach of controlling skeletal muscle relaxation with a short acting neuromuscular blocking drug by maintaining TOF-Count instead of $T1\%$. 
8.1. Main Contributions

Regulating hypnosis

The basis of the controller design is provided by previous work of the research group. The main advancement is based on the combination of the best parts of the previous controllers. The new controller meets the main clinical requirements concerning the dynamic response. The clinical study showed that not only the performance concerning set-point precision but also patient safety and therefore benefit is superior to an anaesthetist performing the same task.

Regulating analgesia

The first controller using a non-invasive MAP measurement is presented. It is prepared to operate with different sampling intervals. Furthermore, it uses the continuously available HR to adapt the system response in case a painful period is detected. The first pilot studies were carried out which show promising results. An improvement to enhance the system is suggested, namely that the pain detection can additionally trigger the MAP sampling procedure.

Regulating artificial ventilation

The model based approach along with special algorithms imitates the anaesthetist when adjusting the respiratory parameters. A new quadratic cost function to select $f_R$ and $V_t$ was introduced and successfully tested. Thus, the anaesthetist can intraoperatively change the behaviour of the controller according to the patients health and type of operation. The clinical study concentrated on set-point precision and set-point changes. The model based controller outperforms the previously used fuzzy controller, which already showed a better performance than an anaesthetist performing the same task.

Integrated control

This is the first report where more than one anaesthetic relevant effect is automatically controlled.

A clinical study was performed where the controller for artificial ventilation and skeletal muscle relaxation were active simultaneously. This clinical study showed that there is no need to investigate further the corresponding interaction, as it has no implications on the stability of the controllers.

So far one pilot study was conducted where isoflurane and alfentanil were simultaneously administered. No strong interactions were observed indicating that there is no strong adverse effect on the control performance. However, further tests are necessary.
Patient safety

Patient safety is a primary concern and a special emphasis of this work was on introducing reliable and applicable control systems that fit well into clinical routine. Incidentally the clinical study of the BIS controller showed a reduced amount and length of potentially critical incidents compared to a manually controlled group. By considering all clinical investigations so far more than 80 patients were investigated where at least one controller was active. This resulted in an estimated 200 hours of anaesthesia where the developed system supported the anaesthetist. All controllers tested showed a good control performance and were easy to handle in a clinical environment.

8.2 Outlook

The main task of automating the main four objectives of the anaesthetist is concluded in the sense that for all four a good solution has been found and has been tested in a clinical environment. A clinical study with the enhanced controller for skeletal muscle relaxation is currently conducted.

So far the analgesia controller has been only tested during pilot studies. Further studies are required to validate the concepts before the clinical study of all controllers combined regulating the four main tasks can commence.

Benefit can be defined in different outcome parameters such as patient well being after surgery, reduced awareness, reduced drug consumption, faster wake up and recovery and many more. From the obtained results with the single control loops only a moderate benefit for the patient is observed. Mainly because it is difficult to define a measure for patient benefit in this context. Furthermore, the observed variance is high and hence large clinical investigations are necessary to prove a statistical significant.

A major impact will have parameters describing patient safety. Adverse incidents cannot be "simulated" during clinical routine, they have to happen! But for both the control system and for the anaesthetist the prevention of such potentially critical phases is of main interest. Again to show a significantly increased patient safety a large clinical study needs to be conducted incorporating many different clinics and several hundred patients.

The patients recruited so far were all scheduled for elective surgery. No critical ill patients were considered. By increasing the patient range the variability of the patient behaviour will most probably increase. This has to be further investigated and where necessary appropriate methods have to be introduced.

The clinical applicability of the control systems is a major factor, the controllers described in
this thesis clearly go beyond the mere proof-of-concept. Nevertheless, more clinical tests need to be conducted before the system can be released for a multi-centre study. The system needs a development level where it can be operated by the standard clinical staff with no additional help from the researchers.

The recent years have shown an increased research and development activity concerning good measures of hypnosis and analgesia. Several commercially available monitors for hypnosis have been introduced. Furthermore, newly released anaesthesia workplaces are equipped with all the necessary devices used for closed-loop operation and the first commercially available endtidal anaesthetic gas controller is announced. This opens up possibilities for automation in clinical anaesthesia on a broad scale in the near future.
## Appendix A

### Concepts and Methods

### A.1 List of Used Parameters

Table A.1: Description of all parameters, including values and references where appropriate.

<table>
<thead>
<tr>
<th>Param.</th>
<th>Description</th>
<th>Value</th>
<th>Unit</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_{ij}$</td>
<td>micro rate constants</td>
<td></td>
<td>$min^{-1}$</td>
<td>-</td>
</tr>
<tr>
<td>$i_R$</td>
<td>infusion rate</td>
<td></td>
<td>$ml/h$</td>
<td>-</td>
</tr>
</tbody>
</table>

**Mamillary compartmental PKPD model**

| $i_R$           | infusion rate                         |       | $ml/h$ | -    |
| $c_i$           | concentration of compartment $i$      |       | -      | -    |
| ($\forall i \in \{1, 2, \ldots, 9, A, L, V\}$, Figure 2.2) | | |
| $l_s$           | lung shunt                            | 10    | %      | [46] |
| $BW$            | body weight of the patient            |       | kg     |      |

continued on next page
<table>
<thead>
<tr>
<th>Param.</th>
<th>Description</th>
<th>Value</th>
<th>Unit</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
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<td>$q$</td>
<td>cardiac output</td>
<td>$\frac{1}{5} BW^{3/4}$</td>
<td>l/min</td>
<td>[22]</td>
</tr>
<tr>
<td>$q_A$</td>
<td>blood flow through arterial compartment</td>
<td>$q$</td>
<td>l/min</td>
<td>[46]</td>
</tr>
<tr>
<td>$q_L$</td>
<td>blood flow through lung compartment</td>
<td>$(1 - ts)q$</td>
<td>l/min</td>
<td>[46]</td>
</tr>
<tr>
<td>$q_V$</td>
<td>blood flow through venous compartment</td>
<td>$q$</td>
<td>l/min</td>
<td>[46]</td>
</tr>
<tr>
<td>$q_1$</td>
<td>blood flow through myocardium</td>
<td>0.05$q$</td>
<td>l/min</td>
<td>[46]</td>
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<tr>
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<td>blood flow through brain grey matter</td>
<td>0.115$q$</td>
<td>l/min</td>
<td>[46]</td>
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<tr>
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<td>0.035$q$</td>
<td>l/min</td>
<td>[46]</td>
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<td>l/min</td>
<td>[46]</td>
</tr>
<tr>
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<td>blood flow through poorly perfused organs</td>
<td>0.025$q$</td>
<td>l/min</td>
<td>[46]</td>
</tr>
<tr>
<td>$q_6$</td>
<td>blood flow through stomach and intestine</td>
<td>0.235$q$</td>
<td>l/min</td>
<td>[46]</td>
</tr>
<tr>
<td>$q_7$</td>
<td>blood flow through skeletal muscles</td>
<td>0.185$q$</td>
<td>l/min</td>
<td>[46]</td>
</tr>
<tr>
<td>$q_8$</td>
<td>blood flow through fat compartment</td>
<td>0.025$q$</td>
<td>l/min</td>
<td>[46]</td>
</tr>
<tr>
<td>$q_9$</td>
<td>blood flow of skin shunt</td>
<td>0.08$q$</td>
<td>l/min</td>
<td>[46]</td>
</tr>
<tr>
<td>$V_i$</td>
<td>volume of compartment $i$</td>
<td>$\iota$</td>
<td>l</td>
<td>(2.1)</td>
</tr>
<tr>
<td>$V_{i,b}$</td>
<td>volume of blood part of compartment $i$</td>
<td></td>
<td></td>
<td>[46]</td>
</tr>
<tr>
<td>$V_{i,t}$</td>
<td>volume of tissue part of compartment $i$</td>
<td></td>
<td></td>
<td>[46]</td>
</tr>
<tr>
<td>$\lambda_{i,b}$</td>
<td>free fraction of drug in the blood part of compartment $i$ ($\forall i \in {1, 2, \ldots, 9, A, L, V}$)</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>$\lambda_{i,t}$</td>
<td>free fraction of drug in the tissue part of compartment $i$ ($\forall i \in {1, 2, \ldots, 9, A, L, V}$)</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>$X_i$</td>
<td>tissue/blood partition coefficient of compartment $i$ ($\forall i \in {1, 2, \ldots, 9, A, L, V}$)</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>$\kappa_i$</td>
<td>elimination rate constant ($\forall i \in {1, 2, \ldots, 9, A, L, V}$)</td>
<td>$min^{-1}$</td>
<td></td>
<td>(2.8)</td>
</tr>
<tr>
<td>$E$</td>
<td>unspecific effect</td>
<td></td>
<td></td>
<td>(2.11)</td>
</tr>
<tr>
<td>$E_{max}$</td>
<td>maximal possible effect</td>
<td></td>
<td></td>
<td>(2.11)</td>
</tr>
<tr>
<td>$C_e$</td>
<td>effect site compartment concentration</td>
<td></td>
<td></td>
<td>(2.11)</td>
</tr>
<tr>
<td>$EC_{50}$</td>
<td>effect site concentration to achieve 50% effect</td>
<td></td>
<td></td>
<td>(2.11)</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>degree of nonlinearity of the $E_{max}$ model (steepness)</td>
<td></td>
<td></td>
<td>-</td>
</tr>
</tbody>
</table>

*continued on next page*
### Table A.1: continued

<table>
<thead>
<tr>
<th>Param.</th>
<th>Description</th>
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<th>Unit</th>
<th>Ref.</th>
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<tr>
<td><strong>Non-compartmental analysis</strong></td>
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<td></td>
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<tr>
<td>$T_{1/2}$</td>
<td>elimination half-life</td>
<td></td>
<td>min</td>
<td>(2.7)</td>
</tr>
<tr>
<td>MRT</td>
<td>mean drug residence time in the body</td>
<td></td>
<td>min</td>
<td>(2.7)</td>
</tr>
<tr>
<td>$Cl$</td>
<td>clearance</td>
<td>$l/min$</td>
<td>(2.12)</td>
<td></td>
</tr>
<tr>
<td>$V_{dss}$</td>
<td>steady state distribution volume</td>
<td>$l$</td>
<td>(2.15)</td>
<td></td>
</tr>
<tr>
<td><strong>LQR problem formulation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$A$</td>
<td>system matrix A used to formulate the LQR problem</td>
<td></td>
<td>(2.19)</td>
<td></td>
</tr>
<tr>
<td>$B$</td>
<td>system matrix B used to formulate the LQR problem</td>
<td></td>
<td>(2.19)</td>
<td></td>
</tr>
<tr>
<td>$C$</td>
<td>system matrix C used to formulate the LQR problem</td>
<td></td>
<td>(2.20)</td>
<td></td>
</tr>
<tr>
<td>$D$</td>
<td>system matrix D used to formulate the LQR problem</td>
<td></td>
<td>(2.20)</td>
<td></td>
</tr>
<tr>
<td>$Q$</td>
<td>weight matrix used to formulate the LQR problem</td>
<td></td>
<td>(2.21)</td>
<td></td>
</tr>
<tr>
<td>$R$</td>
<td>weight matrix used to formulate the LQR problem</td>
<td></td>
<td>(2.21)</td>
<td></td>
</tr>
<tr>
<td><strong>Tuning parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$Q$</td>
<td>tuning parameter to derive $Q$</td>
<td></td>
<td>(2.25),(2.29)</td>
<td></td>
</tr>
<tr>
<td>$R$</td>
<td>tuning parameter to derive $R$</td>
<td></td>
<td>(2.25),(2.29)</td>
<td></td>
</tr>
<tr>
<td>$\Gamma$</td>
<td>tuning parameter to derive $k_f$</td>
<td></td>
<td>(2.27)</td>
<td></td>
</tr>
<tr>
<td>$\rho$</td>
<td>tuning parameter to derive $Q$</td>
<td></td>
<td>(2.29)</td>
<td></td>
</tr>
<tr>
<td><strong>Control parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$k_I$</td>
<td>integral control action</td>
<td>$[u]_{min}$</td>
<td>(2.26)</td>
<td></td>
</tr>
<tr>
<td>$k_i$</td>
<td>control feedback of state $i$</td>
<td>$[u]_{[x]}$</td>
<td>(2.26)</td>
<td></td>
</tr>
<tr>
<td>$f$</td>
<td>feed forward control action</td>
<td>$[u]_{[x]}$</td>
<td>(2.28)</td>
<td></td>
</tr>
<tr>
<td>$k$</td>
<td>state feedback vector</td>
<td>$[l]_{[x]}$</td>
<td>(2.15)</td>
<td></td>
</tr>
<tr>
<td>$h_i$</td>
<td>output injection of state $i$</td>
<td>$[u]_{[r]}$</td>
<td>(2.30)</td>
<td></td>
</tr>
<tr>
<td>$h$</td>
<td>output injection vector</td>
<td>$[r]_{[r]}$</td>
<td>(2.30)</td>
<td></td>
</tr>
<tr>
<td>$k_{aw}$</td>
<td>anti windup feedback constant</td>
<td>$l_{min}$</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>$T's$</td>
<td>sampling period</td>
<td>5/60</td>
<td>min</td>
<td>-</td>
</tr>
</tbody>
</table>

*continued on next page*
# Tissue and Blood Volume

The tissue and blood volumes are derived according to [46].

The blood volume of compartment \( i \) is:

\[
V_{i,b} = 0.08 \frac{kg}{BW} \cdot \mathcal{P}_{i,b}
\]  
(A.1)

The tissue volume of compartment \( i \) is:

\[
V_{i,t} = 0.9 \frac{kg}{BW} \cdot \mathcal{P}_{i,t}
\]  
(A.2)

where \( \mathcal{P}_{i,b} \) and \( \mathcal{P}_{i,t} \) are summarized in the following table.

<table>
<thead>
<tr>
<th>Comp. ( i )</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>L</th>
<th>A</th>
<th>V</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \mathcal{P}_{i,b} [%] )</td>
<td>2.7</td>
<td>6.8</td>
<td>1.9</td>
<td>16.1</td>
<td>2.1</td>
<td>17.9</td>
<td>7.5</td>
<td>2.9</td>
<td>7.3</td>
<td>6.8</td>
<td>17.6</td>
<td>10.4</td>
</tr>
<tr>
<td>( \mathcal{P}_{i,t} [%] )</td>
<td>0.5</td>
<td>0.9</td>
<td>1.7</td>
<td>0.6</td>
<td>10.7</td>
<td>6.7</td>
<td>56.9</td>
<td>21.0</td>
<td>0.0</td>
<td>1.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>
A.2 Implementation of the Integral Action with Anti Windup Feedback

For the discrete implementation of the integral action two standard approximations were used. In general, Euler’s method [39] was used with the anti windup feedback connected to the time shift element $z^{-1}$ (Figure A.1). The derived conditions for the anti windup feedback coefficient are then independent of the sampling time. Dead beat condition is reached for $k_{aw} = 1$, instability is reached at $k_{aw} = 2$.

A more accurate approximation was used in the case of regulating skeletal muscle relaxation because of the larger measurement period of 20 seconds instead of the usual 5 seconds. (The period of the controller algorithm was kept at 5 seconds, but the algorithm received only every 20 second a new measurement.) Tustin’s method uses a trapezoidal integration [45], the implementation is shown in Figure A.2. The conditions for the anti windup feedback conditions are the same as above.

Figure A.1: Implementation of an integral action with anti windup feedback (Euler’s method).

Figure A.2: Implementation of an integral action with anti windup feedback (Tustin’s method).
## Appendix B

### Regulating Skeletal Muscle Relaxation

#### B.1 List of Used Parameters

Table B.1: Description of all parameters, including values and references where appropriate.

<table>
<thead>
<tr>
<th>Param.</th>
<th>Description</th>
<th>Value</th>
<th>Unit</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inputs and outputs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$a_1$</td>
<td>absolute value of first twitch</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>$a_{1,\text{ref}}$</td>
<td>absolute value of first twitch used to reference the following measurements</td>
<td></td>
<td></td>
<td>(3.1)</td>
</tr>
<tr>
<td>$a_4$</td>
<td>absolute value of fourth twitch</td>
<td></td>
<td></td>
<td>(3.1)</td>
</tr>
<tr>
<td>$T1%$</td>
<td>relative depression of first twitch</td>
<td></td>
<td>%</td>
<td>(3.2)</td>
</tr>
<tr>
<td>$T1%_{\text{REF}}$</td>
<td>reference/target $T1%$</td>
<td></td>
<td>%</td>
<td>(3.1)</td>
</tr>
<tr>
<td>$TC$</td>
<td>TOF-Count, number of twitch responses</td>
<td></td>
<td></td>
<td>-</td>
</tr>
</tbody>
</table>

*continued on next page*
Table B.1: continued

<table>
<thead>
<tr>
<th>Param.</th>
<th>Description</th>
<th>Value</th>
<th>Unit</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCref</td>
<td>reference/target TC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOF%</td>
<td>ratio of the fourth to the first twitch</td>
<td>%</td>
<td></td>
<td>(3.2)</td>
</tr>
<tr>
<td>$i_R$</td>
<td>infusion rate</td>
<td>ml/h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$i_{R_{AUTO}}$</td>
<td>infusion rate calculated by the controller</td>
<td>ml/h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$i_{R_{MAN}}$</td>
<td>manual infusion rate set by the anaesthetian</td>
<td>ml/h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$i_{R_{MAX}}$</td>
<td>maximal infusion rate set by the anaesthetian $0.2 \frac{mg}{kg} \cdot BW$ administered in 30 seconds</td>
<td>12 · BW</td>
<td>ml/h</td>
<td></td>
</tr>
<tr>
<td>$i_{R_{MIN}}$</td>
<td>minimal infusion rate</td>
<td>0 ml/h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$i_{R_{change}}$</td>
<td>infusion rate during syringe change</td>
<td>0 ml/h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physiologically based PKPD model</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\kappa$</td>
<td>elimination rate constants $\kappa_i = \kappa \forall i$</td>
<td>0.37</td>
<td>min$^{-1}$</td>
<td></td>
</tr>
<tr>
<td>$\lambda$</td>
<td>partition coefficient $\lambda_i = \lambda \forall i$</td>
<td>0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\gamma$</td>
<td>degree of nonlinearity</td>
<td>7.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$EC_{50}$</td>
<td>effect compartment concentration to achieve 50% of maximal effect</td>
<td>100</td>
<td>ng/ml</td>
<td></td>
</tr>
<tr>
<td>$C_7$</td>
<td>effect site concentration (= $C_e$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_7_{REF}$</td>
<td>reference effect site concentration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_7_{OBS}$</td>
<td>observed effect site concentration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_7_{APP}$</td>
<td>approximated effect site concentration derived from the inverted dose effect relation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Note that generally the infusion rate implemented on the syringe pump ($i_R$) is in $\frac{ng}{min}$ whereas the infusion rate derived by the controller ($i_{R_{c}}$) is in $\frac{mg}{h}$. Therefore, $i_R = \frac{10^6}{120} \cdot i_{R_{c}}$. In the following the units associated with the controller and the observer are based on $i_{R_{c}}$!</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$f$</td>
<td>feed-forward of outer control loop</td>
<td>5.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$k_{I1}$</td>
<td>integral control action, outer loop</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$k_{aw,1}$</td>
<td>anti windup feedback coefficient for the outer control loop</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$corr$</td>
<td>correction term</td>
<td></td>
<td></td>
<td>(3.11)</td>
</tr>
<tr>
<td>$k_{I2}$</td>
<td>integral control action, inner loop</td>
<td>12.3</td>
<td></td>
<td></td>
</tr>
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</table>

continued on next page
### Table B.1: continued

<table>
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<th>Value</th>
<th>Unit</th>
<th>Ref.</th>
</tr>
</thead>
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<td>$k_{aw,2}$</td>
<td>anti windup feedback coefficient for inner cascade controller</td>
<td>1</td>
<td>$\frac{1}{\text{min}}$</td>
<td></td>
</tr>
<tr>
<td>$k_A$</td>
<td>state feedback coefficient</td>
<td>0.8</td>
<td>ml/min</td>
<td></td>
</tr>
<tr>
<td>$k_L$</td>
<td>state feedback coefficient</td>
<td>0.4</td>
<td>ml/min</td>
<td></td>
</tr>
<tr>
<td>$k_V$</td>
<td>state feedback coefficient</td>
<td>0.4</td>
<td>ml/min</td>
<td></td>
</tr>
<tr>
<td>$k_1$</td>
<td>state feedback coefficient</td>
<td>0.1</td>
<td>ml/min</td>
<td></td>
</tr>
<tr>
<td>$k_2$</td>
<td>state feedback coefficient</td>
<td>0.2</td>
<td>ml/min</td>
<td></td>
</tr>
<tr>
<td>$k_3$</td>
<td>state feedback coefficient</td>
<td>0.1</td>
<td>ml/min</td>
<td></td>
</tr>
<tr>
<td>$k_4$</td>
<td>state feedback coefficient</td>
<td>0.4</td>
<td>ml/min</td>
<td></td>
</tr>
<tr>
<td>$k_5$</td>
<td>state feedback coefficient</td>
<td>0.1</td>
<td>ml/min</td>
<td></td>
</tr>
<tr>
<td>$k_6$</td>
<td>state feedback coefficient</td>
<td>0.7</td>
<td>ml/min</td>
<td></td>
</tr>
<tr>
<td>$k_7$</td>
<td>state feedback coefficient</td>
<td>37.6</td>
<td>ml/min</td>
<td></td>
</tr>
<tr>
<td>$k_8$</td>
<td>state feedback coefficient</td>
<td>0.1</td>
<td>ml/min</td>
<td></td>
</tr>
<tr>
<td>$k_9$</td>
<td>state feedback coefficient</td>
<td>0.2</td>
<td>ml/min</td>
<td></td>
</tr>
</tbody>
</table>

#### Output injection parameters

<table>
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<th>Description</th>
<th>Value</th>
<th>Unit</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$h_A$</td>
<td>output injection coefficient</td>
<td>0.1</td>
<td>ng/ml</td>
<td></td>
</tr>
<tr>
<td>$h_L$</td>
<td>output injection coefficient</td>
<td>0.2</td>
<td>ng/ml</td>
<td></td>
</tr>
<tr>
<td>$h_V$</td>
<td>output injection coefficient</td>
<td>0.2</td>
<td>ng/ml</td>
<td></td>
</tr>
<tr>
<td>$h_1$</td>
<td>output injection coefficient</td>
<td>0.06</td>
<td>ng/ml</td>
<td></td>
</tr>
<tr>
<td>$h_2$</td>
<td>output injection coefficient</td>
<td>0.06</td>
<td>ng/ml</td>
<td></td>
</tr>
<tr>
<td>$h_3$</td>
<td>output injection coefficient</td>
<td>0.04</td>
<td>ng/ml</td>
<td></td>
</tr>
<tr>
<td>$h_4$</td>
<td>output injection coefficient</td>
<td>0.06</td>
<td>ng/ml</td>
<td></td>
</tr>
<tr>
<td>$h_5$</td>
<td>output injection coefficient</td>
<td>0.007</td>
<td>ng/ml</td>
<td></td>
</tr>
<tr>
<td>$h_6$</td>
<td>output injection coefficient</td>
<td>0.04</td>
<td>ng/ml</td>
<td></td>
</tr>
<tr>
<td>$h_7$</td>
<td>output injection coefficient</td>
<td>0.004</td>
<td>ng/ml</td>
<td></td>
</tr>
<tr>
<td>$h_8$</td>
<td>output injection coefficient</td>
<td>0.06</td>
<td>ng/ml</td>
<td></td>
</tr>
<tr>
<td>$h_9$</td>
<td>output injection coefficient</td>
<td>0.2</td>
<td>ng/ml</td>
<td></td>
</tr>
</tbody>
</table>
B.2 Algorithm to Detect TOF-Count Ranges

The following sequence describes the detection algorithm used to derive the constraints on \( T1\%_{\text{REF}} \). Further comments and details on the different steps are given.

General Overview

*Step 0:* Use artefact handling and detection procedures to “clean” the measurements. Proceed to Step 1.

*Step 1:* Check if the TC measurement has changed by \( \pm 1 \). If this is true then proceed to Step 2, else proceed to Step 3.

*Step 2:* Shift the data structure corresponding to the switching points detected between the two neighbouring regions such that the oldest is lost and store the current \( T1\% \) along with the current time in the data structure. Proceed to Step 3.

*Step 3:* Depending on the TC reference get \( T1\%_{\text{up}} \) an \( T1\%_{\text{dn}} \) which are the detected switching points to the neighbouring regions, e.g. for 2 TC this means \( T1\%_{\text{dn}} \) is the highest \( T1\% \) which presumably produces 1 TC and \( T1\%_{\text{up}} \) is the lowest \( T1\% \) which presumably produces 3 TC. Proceed to Step 4.

*Step 4:* Derive the actual constraints \( T1\%_{\text{DN}} \) and \( T1\%_{\text{UP}} \) which are used in the control algorithm. They depend upon the following conditions.

For \( T1\%_{\text{DN}} \) these are:

- If the corresponding \( T1\%_{\text{up}} \) has been detected and the constraint does **not** have to be relaxed than set \( T1\%_{\text{DN}} = (T1\%_{\text{up}} + T1\%_{\text{dn}})/2 \). (This ensures that the controller finds a \( T1\%_{\text{REF}} \) which is in the upper half of the corresponding region. Hence, the infusion requirement is lower.)

- If the corresponding \( T1\%_{\text{up}} \) has **not** been detected and the constraint does **not** have to be relaxed than set \( T1\%_{\text{DN}} = T1\%_{\text{dn}} \).

- If the corresponding \( T1\%_{\text{up}} \) has been detected and the constraint does have to be relaxed than set \( T1\%_{\text{DN}} = (T1\%_{\text{up}} + T1\%_{\text{dn}})/3 \).

- If the corresponding \( T1\%_{\text{up}} \) has **not** been detected and the constraint does have to be relaxed than set \( T1\%_{\text{DN}} = T1\%_{\text{dn}}/2 \).

For \( T1\%_{\text{UP}} \) these are:

- If the constraint does **not** have to be relaxed than set \( T1\%_{\text{UP}} = T1\%_{\text{up}} \).

- If the constraint does have to be relaxed than set \( T1\%_{\text{UP}} = T1\%_{\text{up}} + (T1\%_{\text{dn}} + T1\%_{\text{dn}})/3 \).

Proceed to Step 5.
Step 5: Apply the constraints $T1\%_{UP}$ and $T1\%_{DN}$ in the control algorithm and restart this sequence at the next sampling instance.

**Comments on Step 2**

For Step 2 the following *Oberon* program code was used. It is the procedure related to the switching point between one and two TC (*Calcswl2*). The other switching points are derived analogously.

```
PROCEDURE Calcswl2(tl, now:REAL); (*tl is the current measurement*)
VAR jj:INTEGER; (*now is the current time*)
BEGIN
  FOR jj := 0 TO maxj-1 DO
    swl2[jj] := swl2[jj+1];
    twl2[jj] := twl2[jj+1];
  END;
  swl2[maxj] := tl;
  twl2[maxj] := now;
  s2 := WMean(swl2, twl2, now); (*derivates a weighted mean*)
END Calcswl2;
```

A weighted mean of the last nine detected $T1\%$ measurements is used. The corresponding program code is given below. The weight derived depends on the corresponding elapsed time since detection. The parameter *Filterdt* is 3600, which corresponds to the last hour and *Filterst* is 400 and is an offset to calculate the weight factor.

```
PROCEDURE WMean(s, t, now:ARRAY OF REAL):REAL;
VAR jj:INTEGER;
  ss, tt, tmp:REAL;
BEGIN
  tt := 0;
  ss := 0;
  FOR jj := 0 TO maxj DO
    IF t[jj] < 0 THEN
      tmp := 0;
    ELSE
      tmp := Filterst + Filterdt - (now - t[jj]);
    END;
    IF tmp < Filterst THEN tmp := 0; END;
    tmp := tmp / 1000;
  END;
END WMean;
```
SS := ss + s[jj] * tmp;

END;

IF tt <= 0 THEN
    SS := -1;
ELSE
    SS := ss / tt;
END;
RETURN SS;
END WMean;

Comments on Step 4

If constraint $T1_{xy}$ did not change and $|T1_{xy} - T1_{ref}| < 0.1$ for the last 3 minutes then the condition to relax constraint $T1_{xy}$ is given.
Appendix C

Regulating Analgesia

C.1 List of Used Parameters

Table C.1: Description of all parameters, including values and references where appropriate.

<table>
<thead>
<tr>
<th>Param.</th>
<th>Description</th>
<th>Value</th>
<th>Unit</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inputs and outputs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$MAP$</td>
<td>non-invasively (i.e. intermittently) measured mean arterial pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$MAP_{REF}$</td>
<td>reference $MAP$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$DIA$</td>
<td>diastolic arterial pressure (intermittent)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$SYS$</td>
<td>systolic arterial pressure (intermittent)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$HR$</td>
<td>Heart rate (measured either by ECG or oximetry)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*continued on next page*
### Table C.1: continued

<table>
<thead>
<tr>
<th>Param.</th>
<th>Description</th>
<th>Value</th>
<th>Unit</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$iMAP$</td>
<td>invasively measured mean arterial pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$i_R$</td>
<td>infusion rate</td>
<td></td>
<td>$ml/h$</td>
<td>-</td>
</tr>
<tr>
<td>$T_d$</td>
<td>update interval of the blood pressure measurement</td>
<td>2</td>
<td>$min$</td>
<td>-</td>
</tr>
</tbody>
</table>

### Physiologically based PKPD model

| $\kappa_4$ | elimination rate constants | 0.73 | $min^{-1}$ | (4.1) |
| $\lambda$ | partition coefficient used for tuning | 0.3 | | |
| $\lambda_i$ | partition coefficient for compartment $i$ with $\lambda_i = l_i \lambda$ | | | |
| $l_i$ | relation between partition coefficients $\lambda_i = l_i \lambda$, see Table 4.2. | | | |
| $k$ | parameter of linear pharmacokinetic relation | -0.081 | $minHg$ | [53] |
| $C_{2}$ | effect site concentration ($= C_e$) | | $ng/ml$ | |
| $C_{2ref}$ | reference effect site concentration | | $ng/ml$ | |
| $C_{2obs}$ | observed effect site concentration | | $ng/ml$ | |
| $C_{2man}$ | manually set effect site concentration | | $ng/ml$ | |
| $C_{2auto}$ | effect site concentration derived by controller | | $ng/ml$ | |
| $\Delta C_2$ | offset of $C_{2ref}$ for manual adjustment | | $ng/ml$ | |

### Control parameters (outer cascade)

| $f_1$ | feed-forward of outer control loop | 20 | $ng/ml$ | $MAP$ |
| $k_{I11}$ | integral control action for $MAP - MAP_{REF} \geq 0$, outer loop, $k_{I11} = \frac{T_d}{l_1}$ | 0.5 | $ng/ml$ | $MAP_{min}$ |
| $k_{I12}$ | integral control action for $MAP - MAP_{REF} < 0$, outer loop | 4 | $ng/ml$ | $MAP_{min}$ |
| $k_{aw,1}$ | anti windup feedback coefficient for the outer loop | 1 | | $min$ |

### Parameters of the TCI system (inner cascade)

Note that generally the infusion rate implemented on the syringe pump ($i_R$) is in $\frac{ml}{h}$ where as the infusion rate derived by the controller ($i_{Ru}$) is in $\frac{ng}{min}$. Therefore, $i_R = \frac{10^6}{120} \cdot i_{Ru}$. In the following the units associated with the controller and the observer are based on $i_{Ru}$!

| $f_2$ | feed-forward of inner loop | 10 | $\frac{ml}{min}$ | |

*continued on next page*
### Table C.1: continued

<table>
<thead>
<tr>
<th>Param.</th>
<th>Description</th>
<th>Value</th>
<th>Unit</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_{I2}$</td>
<td>integral control action, inner loop</td>
<td>5.1</td>
<td>ml/s</td>
<td></td>
</tr>
<tr>
<td>$k_{aw,2}$</td>
<td>anti windup feedback coefficient of the inner loop</td>
<td>1</td>
<td>1/min</td>
<td></td>
</tr>
<tr>
<td>$k_A$</td>
<td>state feedback coefficient</td>
<td>2.01</td>
<td>ml</td>
<td></td>
</tr>
<tr>
<td>$k_L$</td>
<td>state feedback coefficient</td>
<td>0.96</td>
<td>ml</td>
<td></td>
</tr>
<tr>
<td>$k_V$</td>
<td>state feedback coefficient</td>
<td>1.01</td>
<td>ml</td>
<td></td>
</tr>
<tr>
<td>$k_1$</td>
<td>state feedback coefficient</td>
<td>0.16</td>
<td>ml</td>
<td></td>
</tr>
<tr>
<td>$k_2$</td>
<td>state feedback coefficient</td>
<td>6.80</td>
<td>ml</td>
<td></td>
</tr>
<tr>
<td>$k_3$</td>
<td>state feedback coefficient</td>
<td>0.13</td>
<td>ml</td>
<td></td>
</tr>
<tr>
<td>$k_4$</td>
<td>state feedback coefficient</td>
<td>0.66</td>
<td>ml</td>
<td></td>
</tr>
<tr>
<td>$k_5$</td>
<td>state feedback coefficient</td>
<td>0.12</td>
<td>ml</td>
<td></td>
</tr>
<tr>
<td>$k_6$</td>
<td>state feedback coefficient</td>
<td>1.02</td>
<td>ml</td>
<td></td>
</tr>
<tr>
<td>$k_7$</td>
<td>state feedback coefficient</td>
<td>0.83</td>
<td>ml</td>
<td></td>
</tr>
<tr>
<td>$k_8$</td>
<td>state feedback coefficient</td>
<td>0.12</td>
<td>ml</td>
<td></td>
</tr>
<tr>
<td>$k_9$</td>
<td>state feedback coefficient</td>
<td>0.27</td>
<td>ml</td>
<td></td>
</tr>
</tbody>
</table>
## Appendix D

Regulating Hypnosis

### D.1 List of Used Parameters

Table D.1: Description of all parameters, including values and references where appropriate.

<table>
<thead>
<tr>
<th>Param.</th>
<th>Description</th>
<th>Value</th>
<th>Unit</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$F_{\text{ISO}}$</td>
<td>isoflurane fraction setting of the vaporizer</td>
<td></td>
<td>vol%</td>
<td>-</td>
</tr>
<tr>
<td>$F_{\text{MAX}}$</td>
<td>maximal isoflurane fraction setting of the vaporizer</td>
<td>5</td>
<td>vol%</td>
<td>-</td>
</tr>
<tr>
<td>$F_{\text{MIN}}$</td>
<td>minimal isoflurane fraction setting of the vaporizer</td>
<td>0</td>
<td>vol%</td>
<td>-</td>
</tr>
<tr>
<td>$F_{\text{BIS}}$</td>
<td>isoflurane setting derived by the outer control loop</td>
<td></td>
<td>vol%</td>
<td>-</td>
</tr>
</tbody>
</table>

*continued on next page*
Table D.1: continued

<table>
<thead>
<tr>
<th>Param.</th>
<th>Description</th>
<th>Value</th>
<th>Unit</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$F_{Y\text{HIGH}}$</td>
<td>isoflurane setting derived by the over-</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>ride controller using $F_{\text{emax}}$</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>as reference</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>$F_{Y\text{LOW}}$</td>
<td>isoflurane setting derived by the over-</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>ride controller using $F_{\text{emin}}$</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>as reference</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>$F_{\text{ISO}}$</td>
<td>inspired isoflurane fraction</td>
<td></td>
<td>vol%</td>
<td>-</td>
</tr>
<tr>
<td>$F_{\text{EISO}}$</td>
<td>endtidal isoflurane fraction</td>
<td></td>
<td>vol%</td>
<td>-</td>
</tr>
<tr>
<td>$F_{\text{OBS}}$</td>
<td>observed inspired isoflurane fraction</td>
<td></td>
<td>vol%</td>
<td>-</td>
</tr>
<tr>
<td>$F_{\text{OBS}}$</td>
<td>observed endtidal isoflurane fraction</td>
<td></td>
<td>vol%</td>
<td>-</td>
</tr>
<tr>
<td>$F_{\text{MAX}}$</td>
<td>maximal endtidal isoflurane fraction</td>
<td>≈ 1.4</td>
<td>vol%</td>
<td>-</td>
</tr>
<tr>
<td>$F_{\text{REF}}$</td>
<td>reference endtidal isoflurane fraction</td>
<td></td>
<td>vol%</td>
<td>-</td>
</tr>
<tr>
<td>$F_{\text{MAN}}$</td>
<td>reference endtidal isoflurane fraction</td>
<td></td>
<td>vol%</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>during endtidal control only</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>$F_{\text{MIN}}$</td>
<td>minimal endtidal isoflurane fraction</td>
<td>≈ 0.4</td>
<td>vol%</td>
<td>-</td>
</tr>
<tr>
<td>$F_{\text{ISO}}$</td>
<td>estimated brain isoflurane fraction</td>
<td></td>
<td>vol%</td>
<td>-</td>
</tr>
<tr>
<td>$B_{\text{IS}}$</td>
<td>bispectral index measurement</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>$B_{\text{ISREF}}$</td>
<td>bispectral index reference</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>$B_{\text{ISRAW}}$</td>
<td>raw data of $B_{\text{IS}}$ measurement</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>$B_{\text{ISFILT}}$</td>
<td>filtered $B_{\text{IS}}$ measurement</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>$F_{F}$</td>
<td>fresh gas flow</td>
<td></td>
<td>l/min</td>
<td>-</td>
</tr>
</tbody>
</table>

Physiologically based PKPD model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
<th>Unit</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\kappa_i$</td>
<td>elimination rate constants $\forall i$</td>
<td>0</td>
<td>min$^{-1}$</td>
<td>-</td>
</tr>
<tr>
<td>$\lambda_A$</td>
<td>tissue/blood partition coefficient of</td>
<td>1.46</td>
<td></td>
<td>[46]</td>
</tr>
<tr>
<td></td>
<td>compartment A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\lambda_L$</td>
<td>tissue/blood partition coefficient of</td>
<td>2.40</td>
<td></td>
<td>[46]</td>
</tr>
<tr>
<td></td>
<td>compartment L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\lambda_V$</td>
<td>tissue/blood partition coefficient of</td>
<td>0</td>
<td></td>
<td>[46]</td>
</tr>
<tr>
<td></td>
<td>compartment V</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\lambda_1$</td>
<td>tissue/blood partition coefficient of</td>
<td>1.60</td>
<td></td>
<td>[46]</td>
</tr>
<tr>
<td></td>
<td>compartment 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\lambda_2$</td>
<td>tissue/blood partition coefficient of</td>
<td>1.60</td>
<td></td>
<td>[46]</td>
</tr>
<tr>
<td></td>
<td>compartment 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\lambda_3$</td>
<td>tissue/blood partition coefficient of</td>
<td>1.60</td>
<td></td>
<td>[46]</td>
</tr>
<tr>
<td></td>
<td>compartment 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\lambda_4$</td>
<td>tissue/blood partition coefficient of</td>
<td>1.30</td>
<td></td>
<td>[46]</td>
</tr>
<tr>
<td></td>
<td>compartment 4</td>
<td></td>
<td></td>
<td></td>
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</tbody>
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continued on next page
### Table D.1: continued

<table>
<thead>
<tr>
<th>Param.</th>
<th>Description</th>
<th>Value</th>
<th>Unit</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\lambda_5$</td>
<td>tissue/blood partition coefficient of compartment 5</td>
<td>2.40</td>
<td></td>
<td>[46]</td>
</tr>
<tr>
<td>$\lambda_6$</td>
<td>tissue/blood partition coefficient of compartment 6</td>
<td>1.90</td>
<td></td>
<td>[46]</td>
</tr>
<tr>
<td>$\lambda_7$</td>
<td>tissue/blood partition coefficient of compartment 7</td>
<td>4.40</td>
<td></td>
<td>[46]</td>
</tr>
<tr>
<td>$\lambda_8$</td>
<td>tissue/blood partition coefficient of compartment 8</td>
<td>64.00</td>
<td></td>
<td>[46]</td>
</tr>
<tr>
<td>$\lambda_9$</td>
<td>tissue/blood partition coefficient of compartment 9</td>
<td>0</td>
<td></td>
<td>[46]</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>degree of nonlinearity</td>
<td>1.6</td>
<td></td>
<td>[53]</td>
</tr>
<tr>
<td>$EC_{50}$</td>
<td>effect compartment concentration to achieve 50% of maximal effect</td>
<td>0.75 vol%</td>
<td></td>
<td>[53]</td>
</tr>
<tr>
<td>$C_{2e}$</td>
<td>effect site concentration (= $C_{2e}$)</td>
<td></td>
<td>vol%</td>
<td></td>
</tr>
</tbody>
</table>

#### Control parameters (outer cascade)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
<th>Unit</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_{p,1}$</td>
<td>proportional control action of the outer cascade</td>
<td>2</td>
<td>vol%</td>
<td>BIS</td>
</tr>
<tr>
<td>$k_{I,1}$</td>
<td>integral control action of the outer cascade</td>
<td>1</td>
<td>vol%</td>
<td>BIS/min</td>
</tr>
<tr>
<td>$k_{aw,1}$</td>
<td>anti windup feedback coefficient for the outer cascade</td>
<td>1/560</td>
<td>1/min</td>
<td></td>
</tr>
</tbody>
</table>

#### Control parameters (override endtidal controllers)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
<th>Unit</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_{p,o}$</td>
<td>proportional control action override controllers</td>
<td>16.6/FF</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>$k_{I,o}$</td>
<td>integral control action override controllers</td>
<td>7.1818</td>
<td>1/min</td>
<td></td>
</tr>
<tr>
<td>$k_{aw,o}$</td>
<td>anti windup feedback coefficient of the override controllers</td>
<td>1.25</td>
<td>1/min</td>
<td></td>
</tr>
</tbody>
</table>

#### Control parameters (main endtidal controller)

Note that the coefficients of the respiratory system are declared with subscript $R$. For further information see [46].

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
<th>Unit</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_{I,2}$</td>
<td>integral control action of the main endtidal controller</td>
<td>7.1818</td>
<td>1/min</td>
<td>[46]</td>
</tr>
<tr>
<td>$k_{aw,2}$</td>
<td>anti windup feedback coefficient for main endtidal controller</td>
<td>1/560</td>
<td>1/min</td>
<td></td>
</tr>
<tr>
<td>$f$</td>
<td>feed-forward coefficient</td>
<td>11.0558</td>
<td>1</td>
<td>[46]</td>
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continued on next page
Table D.1: continued

<table>
<thead>
<tr>
<th>Param.</th>
<th>Description</th>
<th>Value</th>
<th>Unit</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_R$</td>
<td>state feedback coefficient</td>
<td>1.6806</td>
<td>1</td>
<td>[46]</td>
</tr>
<tr>
<td>$k_1$</td>
<td>state feedback coefficient</td>
<td>0.1872</td>
<td>1</td>
<td>[46]</td>
</tr>
<tr>
<td>$k_2$</td>
<td>state feedback coefficient</td>
<td>0.2705</td>
<td>1</td>
<td>[46]</td>
</tr>
<tr>
<td>$k_3$</td>
<td>state feedback coefficient</td>
<td>0.2077</td>
<td>1</td>
<td>[46]</td>
</tr>
<tr>
<td>$k_4$</td>
<td>state feedback coefficient</td>
<td>0.3292</td>
<td>1</td>
<td>[46]</td>
</tr>
<tr>
<td>$k_5$</td>
<td>state feedback coefficient</td>
<td>0.0571</td>
<td>1</td>
<td>[46]</td>
</tr>
<tr>
<td>$k_6$</td>
<td>state feedback coefficient</td>
<td>0.6282</td>
<td>1</td>
<td>[46]</td>
</tr>
<tr>
<td>$k_7$</td>
<td>state feedback coefficient</td>
<td>0.1653</td>
<td>1</td>
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<tr>
<td>$k_8$</td>
<td>state feedback coefficient</td>
<td>0.0050</td>
<td>1</td>
<td>[46]</td>
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<tr>
<td>$k_9$</td>
<td>state feedback coefficient</td>
<td>0.1557</td>
<td>1</td>
<td>[46]</td>
</tr>
<tr>
<td>$k_L$</td>
<td>state feedback coefficient</td>
<td>0.9957</td>
<td>1</td>
<td>[46]</td>
</tr>
<tr>
<td>$k_A$</td>
<td>state feedback coefficient</td>
<td>0.1860</td>
<td>1</td>
<td>[46]</td>
</tr>
<tr>
<td>$k_V$</td>
<td>state feedback coefficient</td>
<td>0.1861</td>
<td>1</td>
<td>[46]</td>
</tr>
</tbody>
</table>

**Output injection parameters**

Note that according to [46] the observer uses both $F_{1iso}$ and $F_{eiso}$ for output injection, where $h_{ij}$ is the output injection of $F_{1iso}$ and $h_{ej}$ is the output injection of $F_{eiso}$ respectively.

<table>
<thead>
<tr>
<th>$h_{iB}$</th>
<th>$F_{1iso}$</th>
<th>1.5190</th>
<th>1/min</th>
<th>[46]</th>
</tr>
</thead>
<tbody>
<tr>
<td>$h_{i1}$</td>
<td>$F_{1iso}$</td>
<td>0.0002</td>
<td>1/min</td>
<td>[46]</td>
</tr>
<tr>
<td>$h_{i2}$</td>
<td>$F_{1iso}$</td>
<td>0.0003</td>
<td>1/min</td>
<td>[46]</td>
</tr>
<tr>
<td>$h_{i3}$</td>
<td>$F_{1iso}$</td>
<td>-0.0003</td>
<td>1/min</td>
<td>[46]</td>
</tr>
<tr>
<td>$h_{i4}$</td>
<td>$F_{1iso}$</td>
<td>0.0013</td>
<td>1/min</td>
<td>[46]</td>
</tr>
<tr>
<td>$h_{i5}$</td>
<td>$F_{1iso}$</td>
<td>-0.0001</td>
<td>1/min</td>
<td>[46]</td>
</tr>
<tr>
<td>$h_{i6}$</td>
<td>$F_{1iso}$</td>
<td>-0.0003</td>
<td>1/min</td>
<td>[46]</td>
</tr>
<tr>
<td>$h_{i7}$</td>
<td>$F_{1iso}$</td>
<td>-0.0001</td>
<td>1/min</td>
<td>[46]</td>
</tr>
<tr>
<td>$h_{i8}$</td>
<td>$F_{1iso}$</td>
<td>0</td>
<td>1/min</td>
<td>[46]</td>
</tr>
<tr>
<td>$h_{i9}$</td>
<td>$F_{1iso}$</td>
<td>0.0013</td>
<td>1/min</td>
<td>[46]</td>
</tr>
<tr>
<td>$h_{iL}$</td>
<td>$F_{1iso}$</td>
<td>0.0789</td>
<td>1/min</td>
<td>[46]</td>
</tr>
<tr>
<td>$h_{iA}$</td>
<td>$F_{1iso}$</td>
<td>0.0263</td>
<td>1/min</td>
<td>[46]</td>
</tr>
<tr>
<td>$h_{iV}$</td>
<td>$F_{1iso}$</td>
<td>0.0263</td>
<td>1/min</td>
<td>[46]</td>
</tr>
<tr>
<td>$h_{eR}$</td>
<td>$F_{eiso}$</td>
<td>7.9898</td>
<td>1/min</td>
<td>[46]</td>
</tr>
<tr>
<td>$h_{e1}$</td>
<td>$F_{eiso}$</td>
<td>0.0178</td>
<td>1/min</td>
<td>[46]</td>
</tr>
<tr>
<td>$h_{e2}$</td>
<td>$F_{eiso}$</td>
<td>0.0197</td>
<td>1/min</td>
<td>[46]</td>
</tr>
<tr>
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<td>$F_{eiso}$</td>
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<td>1/min</td>
<td>[46]</td>
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<tr>
<td>$h_{e4}$</td>
<td>$F_{eiso}$</td>
<td>0.0300</td>
<td>1/min</td>
<td>[46]</td>
</tr>
<tr>
<td>$h_{e5}$</td>
<td>$F_{eiso}$</td>
<td>0.0008</td>
<td>1/min</td>
<td>[46]</td>
</tr>
<tr>
<td>$h_{e6}$</td>
<td>$F_{eiso}$</td>
<td>0.0081</td>
<td>1/min</td>
<td>[46]</td>
</tr>
<tr>
<td>$h_{e7}$</td>
<td>$F_{eiso}$</td>
<td>0.0007</td>
<td>1/min</td>
<td>[46]</td>
</tr>
</tbody>
</table>

*continued on next page*
Table D.1: continued

<table>
<thead>
<tr>
<th>Param.</th>
<th>Description</th>
<th>Value</th>
<th>Unit</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$h_{e8}$</td>
<td>$F_{\text{FeSO}}$</td>
<td>0</td>
<td>1/min</td>
<td>46</td>
</tr>
<tr>
<td>$h_{e9}$</td>
<td>$F_{\text{FeSO}}$</td>
<td>0.0293</td>
<td>1/min</td>
<td>46</td>
</tr>
<tr>
<td>$h_{eL}$</td>
<td>$F_{\text{FeSO}}$</td>
<td>0.4658</td>
<td>1/min</td>
<td>46</td>
</tr>
<tr>
<td>$h_{vA}$</td>
<td>$F_{\text{FeSO}}$</td>
<td>0.1812</td>
<td>1/min</td>
<td>46</td>
</tr>
<tr>
<td>$h_{vV}$</td>
<td>$F_{\text{FeSO}}$</td>
<td>0.0103</td>
<td>1/min</td>
<td>46</td>
</tr>
</tbody>
</table>

**Patient risk parameters (PRP)**

- $PRP_n$: total amount of PRP incidents (see Table 5.4)
- $PRP_t$: accumulated time of PRP incidents (see Table 5.4)
- $PRP_r$: ratio of $PRP_t$ to total time of anaesthesia (see Table 5.4)
D.2 BIS Filter

The following Oberon code describes the filter used in the BIS controller. In case fast BIS changes are detected the new BIS value is used to start a second mean filter. In case the increased BIS is not detected for three consecutive measurements then the previous mean filter is re-established. The mean filter covers the measurements of the last three minutes.

PROCEDURE BISFilter(bis,sqi:REAL);
BEGIN
  IF (sqi>30) & (bis>=0) & (bis<=100) THEN
    bisold:=bis;
  ELSE
    bisold:=bisold; (*else use old BIS instead*)
  END;

  IF ((MEAN1+15)<bisold) OR ((MEAN1-35)>bisold) OR (bisold>=70) THEN
    CONSTR:= TRUE; (*limit is violated*)
  ELSE
    CONSTR:= FALSE; (*limit is acceptable*)
  END;

  IF CONSTR=TRUE THEN
    IF FIRST=TRUE THEN
      FIRST:= FALSE;
      FREEZE:= TRUE;
      FOR j:=0 TO maxj DO
        FILTER2[j]:= bisold;
      END;
    ELSE
      FOR j:=maxj TO 1 BY -1 DO
        FILTER2[j]:= FILTER2[j-1]; (*shift and*)
      END;
      FILTER2[0]:= bisold; (*add current BIS value*)
    END;
  ELSE
    FOR j:=0 TO maxj DO
      FILTER2[j]:= 0; (*Set second mean filter to zero*)
    END;
    FIRST:= TRUE;
  END;
END;
D.2. BIS Filter

FREEZE := FALSE;
END;

IF FREEZE THEN (*This memorizes the first mean filter*)
  INC(FREEZECNT);
ELSE (*else the first filter is used*)
  FOR j := maxj TO 1 BY -1 DO
    FILTER1[j] := FILTER1[j-1];
  END;
  FILTER1[0] := bisold;
  FREEZECNT := 0;
END;

IF FREEZECNT >= 3 THEN (*In case in three consecutive *)
  FILTER1 := FILTER2; (*BIS measurements the limit *)
  FREEZE := FALSE; (*was violated, then use the *)
  FREEZECNT := 0; (*second filter as new first *)
  END; (*filter *)

MEAN1 := Mean(FILTER1); (*Calculate mean of filter one*)
MEAN2 := Mean(FILTER2); (*Calculate mean of filter two*)

IF FREEZE THEN (*In case limit is violated then*)
  BISF := MEAN2; (*use the 2nd mean as BIS value*)
ELSE
  BISF := MEAN1; (*use the 1st mean as BIS value*)
END;
END BISFilter;
# E.1 List of Used Parameters

Table E.1: Description of all parameters, including values and references where appropriate.

<table>
<thead>
<tr>
<th>Param.</th>
<th>Description</th>
<th>Value</th>
<th>Unit</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inputs and outputs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$pH$</td>
<td>logarithm of the inverse $H^+$ ion</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$V_t$</td>
<td>tidal volume</td>
<td>$l$</td>
<td>-</td>
<td>[111]</td>
</tr>
<tr>
<td>$V_D$</td>
<td>dead space volume</td>
<td>0.15</td>
<td>$l$</td>
<td>[111]</td>
</tr>
<tr>
<td>$V_A$</td>
<td>alveolar ventilation</td>
<td>$l/min$</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$\dot{V}_{Ass}$</td>
<td>steady state $\dot{V}_A$</td>
<td>4.95</td>
<td>$l/min$</td>
<td>[57]</td>
</tr>
<tr>
<td>$f_R$</td>
<td>respiratory frequency</td>
<td>$min^{-1}$</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$MV$</td>
<td>minute ventilation</td>
<td>$l/min$</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*continued on next page*
### Table E.1: continued

<table>
<thead>
<tr>
<th>Param.</th>
<th>Description</th>
<th>Value</th>
<th>Unit</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S_{O_2}$</td>
<td>oxygen saturation</td>
<td>%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$P_{aCO_2}$</td>
<td>arterial $CO_2$ tension</td>
<td>mmHg</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$P_{vCO_2}$</td>
<td>venous $CO_2$ tension</td>
<td>mmHg</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$P_{ACO_2}$</td>
<td>alveolar $CO_2$ partial pressure</td>
<td>mmHg</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$P_{ECO_2}$</td>
<td>endtidal $CO_2$ partial pressure</td>
<td>mmHg</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$P_{EOBS}$</td>
<td>observed endtidal $CO_2$ partial pressure</td>
<td>mmHg</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$P_{EREF}$</td>
<td>reference endtidal $CO_2$ partial pressure</td>
<td>mmHg</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$P_{EFILT}$</td>
<td>filtered endtidal $CO_2$ partial pressure</td>
<td>mmHg</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$P_{ECTRL}$</td>
<td>endtidal $CO_2$ partial pressure used as the input of the controller</td>
<td>mmHg</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PEEP</td>
<td>positive end-expiratory pressure</td>
<td>mmHg</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$P_{insp}$</td>
<td>inspired airway pressure</td>
<td>mmHg</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$PIP$</td>
<td>peak inspired airway pressure</td>
<td>mmHg</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$PIP_{max}$</td>
<td>maximal peak inspired airway pressure</td>
<td>mmHg</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$P_{aO_2}$</td>
<td>inspired oxygen fraction</td>
<td>%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Physiologically based PK model**

| $P_A$ | alveolar $CO_2$ partial pressure | mmHg  | -    |
| $P_a$ | arterial $CO_2$ tension          | mmHg  | -    |
| $P_b$ | brain $CO_2$ tension             | mmHg  | -    |
| $P_t$ | tissue $CO_2$ tension            | mmHg  | -    |
| $P_{Ass}$ | steady state $P_A$               | 40.10 | mmHg | [57] |
| $P_{bss}$ | steady state $P_b$               | 52.67 | mmHg | [57] |
| $P_{tss}$ | steady state $P_t$               | 44.46 | mmHg | [57] |
| $V_A$  | average alveolar volume           | l     | [57] |
| $V_b$  | average brain volume              | l     | [57] |
| $V_t$  | average tissue volume             | l     | [57] |
| $t_s$  | lung shunt                        | %     | [30] |
| $q$    | cardiac output                    | l/min | [57] |
| $z$    | fraction of $q$ flowing through tissue compartment | %     | [57] |
| $K$    | proportionality coefficient       | 863   | mmHg  | [182] |

$P_{ACO_2} = K \cdot F_{ACO_2}$, where $F_{ACO_2}$ is the fractional concentration of $CO_2$ in the alveoli.

*continued on next page*
Table E.1: continued

<table>
<thead>
<tr>
<th>Param.</th>
<th>Description</th>
<th>Value</th>
<th>Unit</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$M_b$</td>
<td>metabolic $CO_2$ production in the brain compartment</td>
<td>0.058</td>
<td>$\frac{l}{\text{min}}$</td>
<td>[57]</td>
</tr>
<tr>
<td>$M_t$</td>
<td>metabolic $CO_2$ production in the tissue compartment</td>
<td>0.172</td>
<td>$\frac{l}{\text{min}}$</td>
<td>[57]</td>
</tr>
<tr>
<td>$m_a$</td>
<td>parameter of the linearisation of the $CO_2$ dissociation curve, arterial operating point</td>
<td>5.43\times10^{-3}</td>
<td>mmHg</td>
<td>[57]</td>
</tr>
<tr>
<td>$m_v$</td>
<td>parameter of the linearisation of the $CO_2$ dissociation curve, venous operating point</td>
<td>4.98\times10^{-3}</td>
<td>mmHg</td>
<td>[57]</td>
</tr>
<tr>
<td>$n_a$</td>
<td>parameter of the linearisation of the $CO_2$ dissociation curve, arterial operating point</td>
<td>0.26</td>
<td>1</td>
<td>[57]</td>
</tr>
<tr>
<td>$n_v$</td>
<td>parameter of the linearisation of the $CO_2$ dissociation curve, venous operating point</td>
<td>0.29</td>
<td>1</td>
<td>[57]</td>
</tr>
<tr>
<td>$n_{11}$</td>
<td>model coefficient</td>
<td>-7.030</td>
<td>$min^{-1}$</td>
<td>(6.8)</td>
</tr>
<tr>
<td>$n_{12}$</td>
<td>model coefficient</td>
<td>0.858</td>
<td>$min^{-1}$</td>
<td>(6.9)</td>
</tr>
<tr>
<td>$n_{13}$</td>
<td>model coefficient</td>
<td>5.582</td>
<td>$min^{-1}$</td>
<td>(6.10)</td>
</tr>
<tr>
<td>$n_{14}$</td>
<td>model coefficient</td>
<td>34.686</td>
<td>$\frac{mmHg}{min}$</td>
<td>(6.11)</td>
</tr>
<tr>
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<td>model coefficient</td>
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<td>$min^{-1}$</td>
<td>(6.12)</td>
</tr>
<tr>
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<td>model coefficient</td>
<td>-0.860</td>
<td>$min^{-1}$</td>
<td>(6.13)</td>
</tr>
<tr>
<td>$n_{23}$</td>
<td>model coefficient</td>
<td>0.018</td>
<td>$min^{-1}$</td>
<td>(6.14)</td>
</tr>
<tr>
<td>$n_{24}$</td>
<td>model coefficient</td>
<td>8.383</td>
<td>$\frac{mmHg}{min}$</td>
<td>(6.15)</td>
</tr>
<tr>
<td>$n_{31}$</td>
<td>model coefficient</td>
<td>0.139</td>
<td>$min^{-1}$</td>
<td>(6.16)</td>
</tr>
<tr>
<td>$n_{32}$</td>
<td>model coefficient</td>
<td>4.172\times10^{-4}</td>
<td>$min^{-1}$</td>
<td>(6.17)</td>
</tr>
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<td>$n_{33}$</td>
<td>model coefficient</td>
<td>-0.128</td>
<td>$min^{-1}$</td>
<td>(6.18)</td>
</tr>
<tr>
<td>$n_{34}$</td>
<td>model coefficient</td>
<td>0.215</td>
<td>$\frac{mmHg}{min}$</td>
<td>(6.19)</td>
</tr>
</tbody>
</table>

**Control parameters**

| $k_I$  | integral control action | -0.4438 | $\frac{t}{mmHg\cdot min^2}$ | - |
| $k_1$  | control feedback of state 1 | 0.0898 | $\frac{mmHg}{min}$ | - |
| $k_2$  | control feedback of state 2 | 0.0499 | $\frac{mmHg}{min}$ | - |
| $k_3$  | control feedback of state 3 | 0.1109 | $\frac{mmHg}{min}$ | - |
| $h_1$  | observer feedback of state 1 | 9.9911 | $min^{-1}$ | - |
| $h_2$  | observer feedback of state 2 | 11.4702 | $min^{-1}$ | - |
| $h_3$  | observer feedback of state 3 | 10.7220 | $min^{-1}$ | - |

*continued on next page*
Table E.1: continued

<table>
<thead>
<tr>
<th>Param.</th>
<th>Description</th>
<th>Value</th>
<th>Unit</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$f_{\text{aw}}$</td>
<td>anti windup feedback constant</td>
<td>1</td>
<td>$min^{-1}$</td>
<td>-</td>
</tr>
</tbody>
</table>

### Limits of respiratory parameters

<table>
<thead>
<tr>
<th>Param.</th>
<th>Description</th>
<th>Value</th>
<th>Unit</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$f_{R_{\text{max}}}$</td>
<td>maximal $f_R$</td>
<td>20</td>
<td>$min^{-1}$</td>
<td>-</td>
</tr>
<tr>
<td>$f_{R_{\text{min}}}$</td>
<td>minimal $f_R$</td>
<td>6</td>
<td>$min^{-1}$</td>
<td>-</td>
</tr>
<tr>
<td>$V_{t_{\text{max}}}$</td>
<td>maximal $V_t$</td>
<td>1.4</td>
<td>$l$</td>
<td>-</td>
</tr>
<tr>
<td>$V_{t_{\text{min}}}$</td>
<td>minimal $V_t$</td>
<td>$\begin{cases} \text{min. } 0.35 \text{ or} \ \text{BW.5ml/kg} \end{cases}$</td>
<td>$l$</td>
<td>-</td>
</tr>
</tbody>
</table>

### Splitting algorithm

<table>
<thead>
<tr>
<th>Param.</th>
<th>Description</th>
<th>Value</th>
<th>Unit</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\tilde{f}_R$</td>
<td>optimal $f_R$</td>
<td></td>
<td>$min^{-1}$</td>
<td>-</td>
</tr>
<tr>
<td>$\tilde{V}_t$</td>
<td>optimal $V_t$</td>
<td></td>
<td>$l$</td>
<td>-</td>
</tr>
<tr>
<td>$f_{R_{\text{old}}}$</td>
<td>$f_R$ implemented at the last sampling instance</td>
<td></td>
<td>$min^{-1}$</td>
<td>-</td>
</tr>
<tr>
<td>$\varphi$</td>
<td>normalizing and weighting factor (for $f_R$)</td>
<td></td>
<td>$min^2$</td>
<td>-</td>
</tr>
<tr>
<td>$\psi$</td>
<td>normalizing and weighting factor (for $V_t$)</td>
<td></td>
<td>$l^{-2}$</td>
<td>-</td>
</tr>
<tr>
<td>$\varphi$</td>
<td>penalty term (see Section E.2)</td>
<td></td>
<td>1</td>
<td>(E.1)</td>
</tr>
</tbody>
</table>

(E.1)
E.2 Formulation of Penalty Term $\varphi$

The penalty term $\varphi$ in Equation (6.24) is needed to ensure that the required $MV$ is really translated to a valid $[f_R(i), V_t(i)]$ combination.

In case either or both of $f_R(x)$ and $V_t(x)$ of the derived combination $[f_R(x), V_t(x)]$ hits a limit (e.g. $V_t(x) > V_{t\text{max}}$) than the combination needs to be reformulated as $[f_R(x), V_{t\text{max}}]$, which obviously corresponds to less than the required $MV$. This new combination may have a lower cost in Equation (6.24) than a combination meeting the required $MV$. Hence, only the reduced $MV$ would be implemented. This is especially important on the lower limits $[f_{R\text{min}}, V_{t\text{min}}]$. Generally the ideal combinations $[f_{R}, V_t]$ set by the anaesthetist are not distributed symmetrically between the limits but far closer to the lower limits. This means also that the lower limits are reached more often during clinical application.

To derive the solution to Equation (6.24) the following steps are pursued.

1. Derive the possible combinations $f_R$ and $V_t$ for the requested $MV$ by using $f_R(i) = f_{R\text{old}} + i$ and $V_t(i) = \frac{MV}{f_{R\text{old}} + i}$ for all possible $i (i \in \{-1, 0, 1\})$.

2. If of the produced combinations $[f_R(i), V_t(i)]$ any value is beyond its limit ($f_R(i) \notin \{f_{R\text{min}}, ..., f_{R\text{max}}\}$ and $V_t(i) \notin \{V_{t\text{min}}, ..., V_{t\text{max}}\}$) then constrain it accordingly.

3. Derive the penalty term $\varphi$ (Equation (E.1)).

4. Derive the cost of each combination $[f_R(i), V_t(i)]$ by using Equation (6.24).

5. Choose the combination $[f_R(i), V_t(i)]$ with the lowest cost.

The penalty term is

$$\varphi = \frac{5 \cdot 10^3}{MV_{norm}^2} \cdot \left(\overline{MV} - MV\right)^2$$  \hspace{1cm} (E.1)

where $\overline{MV}$ is the constraint $MV$ and $MV_{norm}$ is used to normalize the equation ($MV_{norm} = 7 l/min$). In case the combination hits no limits than $\varphi$ is zero.


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