Feedback Control in Anaesthesia

A dissertation submitted to the
SWISS FEDERAL INSTITUTE OF TECHNOLOGY
ZURICH

for the degree of
Doctor of Technical Sciences

presented by
Marco Paolo Derighetti
Dipl. El.-Ing. ETHZ
born 25 Dezember 1967
citizen of Dongio (TI)

accepted on the recommendation of
Prof. Dr. A. H. Glattfelder, examiner
Prof. Dr. P. Niederer, co-examiner
Prof. Dr. A. M. Zbinden, co-examiner

1999
Preface

The research presented in this thesis was conducted at the Institute of Automatic Control, Swiss Federal Institute of Technology Zürich (ETH), under the supervision of Prof. A. H. Glattfelder. My "second office" was at the Institute of Anaesthesiology and Intensive Care, Insel Hospital, Berne. The medical part of the research was conducted under the direction of Prof. A. M. Zbinden. I want to express my gratitude to both supervisors for always believing in this project, and for giving me precious hints and making suggestion and comments which contributed to a successful ending of this project.

I am also greatly indebted to Prof. P. Niederer for consenting to act as co-referee of this thesis.

The financial support partially provided by the Swiss National Science Foundation and by Drägerwerke AG, Lübeck, Germany, is also gratefully acknowledged.

Certainly I must thank Selim Hacisalihzade, who pioneered the co-operation between ETH and the hospital, and successfully supervised first diploma and semester theses.

My gratitude goes to all my colleagues at the Institute of Automatic Control (short IfA) and the Institute of Anaesthesiology and Intensive Care (short IfAI), who helped me directly or indirectly whilst I was carrying out this work.

As to the IfA, I would especially like to thank the biomedical group (Christian Frei and Andrea Gentilini) for their collaboration, and Jacques Chapuis, with whom I had the privilege of sharing an office since 1992 and who contributed to this work in countless and very fruitful discussions.

As to the IfAI, I would explicitly like to thank Peter Feigenwinter and Daniel Leibundgut for their precious technical support, as well as the entire medical staff (especially Dr. Michele Curatolo, Dr. Martin Luginbühl, Dr. Luc Mayer, Dr. Jürg Schäublin, Dr. Thomas Schneider and Dr. Steen Petersen-Felix) who always were ready to explain to me the medical concepts and to solve the medical part of the project (defining, realising and analysing all clinical studies with patients).

Many thanks go also to the supporting staff of the Institute of Automatic Control. Their unbureaucratic approach to needs of any kind contributed much to the success of this work. I deeply regret that I cannot personally thank Hannes Wichser for his precious technical
support at the Institute.

Infinite thanks go to my parents, who gave me the opportunity and the support to tackle this important goal of my life, as well as to my sister and brothers, who have always believed in my goals.

Finally a very special "thanks" goes to my wife, Michela: "Questa montagna era ripida, tortuosa e difficile ma grazie al tuo aiuto, alla tua pazienza e ai tuoi dolcissimi incoraggiamenti siamo arrivati in cima. Il panorama bellissimo, mozzafiato. Che facciamo, ci fermiamo? No! altre sfide, altre cime, altri panorami ci aspettano, e non vedo l'ora di affrontarli insieme a te. Grazie di cuore!"

Marco Derighetti
Zürich, March 1999
Summary

The evolution of online monitoring of the patient's physiological parameters in the last twenty years has contributed to increase the number of complex surgical operations. As a consequence the role of the anaesthetist has become more complex and he must deal with a higher number of control actions. Feedback control may reduce his work load and consequently increase the safety of the patient. Feedback control in anaesthesia was subject to many investigations in the past, but none led to practical implementation in the clinical routine. Therefore, all control tasks of the anaesthetist are still performed manually. The main questions to answer during this work were to determine if automatic feedback control can be applied with an acceptable performance in routine cases, if it is possible to apply different kinds of control techniques and finally, which controller performs best in this biomedical field. We considered the feedback control of inhaled and exhaled gas concentrations, which are routinely measured online, and of the mean arterial pressure (MAP). This variable can be influenced by the anaesthetic gas concentration in the human body. The system to be controlled is composed of a breathing circuit and the relevant part of the patient’s body (represented by the pharmacokinetics and pharmacodynamics) and the necessary actuators and sensors. Although some previous investigations were available in the mathematical modeling of some subsystems (especially for the pharmacokinetics), there were many open question about the dynamical behaviour of the system to be controlled. In addition, there is a high individual parameter variability and a lack of measurable variables (especially of body internal values), which must be considered in the modeling and control phase.

The present work describes the results of different feedback control techniques applied to anaesthesia. The first part shortly introduces the reader to the purposes of anaesthesia and describes the structure and the characteristics of an anaesthesia control system. In the second part, the mathematical modeling of the system to be controlled is described in detail. The third part describes the implemented controllers. Three design techniques are used: one experience based technique (fuzzy logic control) and two model based techniques (state feedback control, and model predictive control). A systematic design procedure (specifications, modeling, design, simulations, pilot studies and standard clinical studies) has been used.

While the model based strategies will systematically use quantitative information in form of mathematical models, the experience based model use qualitative information mainly coming from experts knowledge. These different sources often lead to different implementation time scales: the experience based controller can normally be implemented faster than the model based one (which needs a long modeling phase). In contrast, the quantitative information
available in mathematical models allows algebraic or numerical optimisation (which is not possible using experience based controllers) and efficient pretuning in simulation.

Good results were achieved with fuzzy logic control algorithms. This technique has proven to be useful, fast and efficient by translating the manual control strategies and experience into an automatic control algorithm. Especially efficient was the realization of decision based functionalities. However, with fuzzy logic control the tuning phase was very long and inefficient if a substantial improvement of the control performance was required. The computational effort of fuzzy logic controllers depends on the implementation type: low computer power but high memory requirements are needed if the nonlinear function derived from a fuzzy rule engine is memorized as a static input output table; vice versa high computer power and low memory are required if the rule engine is evaluated in real time.

This work showed that, with a considerable model effort, it is possible to efficiently use a linear model based control algorithm even for the variability of patients and the complexity of the system. For technical reasons, the comparison of the two model based techniques could not be done with identical functional specifications (no output constraints were implemented for MPC). Therefore, additional work is necessary to make definitive assertions. Nevertheless, these methods have shown to produce similar results. The main differences can be located in the design, which is rather simpler for MPC and on the computational effort which is clearly lower for state feedback control. MPC implicitly covers all particular functionalities (such as input and output constrains, tracking of particular trajectories, time dependent weightings in the performance index, etc.), while state feedback control needs additional design efforts for each of these functionalities.

These first results have shown that automatic control in anaesthesia under routine conditions is feasible.
Zusammenfassung


Diese Arbeit ist ein Beitrag zur Untersuchung der Möglichkeiten, diese Regelaufgaben weitgehend zu automatisieren und in der Klinik anzuwenden. Folgende Fragestellungen waren zu beantworten: Können bekannte Regelungsalgorithmen in diesem Anwendungsgebiet erfolgreich eingesetzt werden? Wenn ja, welche regelungstechnische Verfahren können angewendet werden und mit welchem Erfolg?


Diese ersten Ergebnisse haben gezeigt, dass automatisierte Regelung in der Anästhesie unter routinemässigen Bedingungen realisierbar ist.
Contents

Preface i

Summary iii

Zusammenfassung v

I Introduction 1
1.1 The operating theater 3
1.2 Main actions of the anaesthetist 4
  1.2.1 Depth of anaesthesia 4
  1.2.2 Used drugs 5
  1.2.3 Measurements and observations 6
1.3 Description of the anaesthesia system 7
1.4 The anaesthesia control system 7
1.5 Implementation steps 8
1.6 Previous work 11
  1.6.1 Project phases 12

II Modeling 15

2 The patient model 21
  2.1 Physical phenomena 21
  2.2 The compartment model of the uptake of inhalation anaesthetic gas 22
  2.2.1 The model for distribution of anaesthetics 22
2.2.2 The circulation model ........................................ 25
2.2.3 The pharmacodynamics ..................................... 25
2.2.4 The combined nonlinear model ........................................ 25
2.3 Multiple gas model ........................................... 27
  2.3.1 Second gas effect ........................................... 28
2.4 Linearization ................................................... 28
  2.4.1 Performance of the linearized system ...................... 30
  2.4.2 Sensitivity of the linearized system ...................... 35
2.5 Model reduction ............................................... 35
2.6 Parameter set of the patient ...................................... 37
  2.6.1 Conventional parameter set .................................. 40
  2.6.2 From the conventional to the consolidated parameter set ........... 42
  2.6.3 Gas dependency of parameters .............................. 44
2.7 Model validation and identification .................................. 44
  2.7.1 Validation .................................................. 44

3 The breathing system ........................................... 47
  3.1 Description of the system ...................................... 48
  3.2 Ideal gas laws .................................................. 49
  3.3 Model elements .................................................. 50
    3.3.1 General compartment ...................................... 50
    3.3.2 Model implementation .................................... 53
    3.3.3 Model of a Tube .......................................... 54
    3.3.4 The T-piece ............................................... 55
    3.3.5 The manual ventilation bag ................................ 56
    3.3.6 The Pump ................................................ 56
    3.3.7 The CO₂ Absorber ........................................ 56
    3.3.8 The Lung ................................................ 57
    3.3.9 Convective transport and diffusion ...................... 61
  3.4 Overall model of the breathing system ...................... 62
3.5 Validation of the nonlinear model ............................................. 66
3.6 Model for control ................................................................. 66
3.7 Parameter set of the breathing system ...................................... 71
3.8 Validation ................................................................. 72

4 Model of surgical stimulation .................................................. 75
4.1 Physiology ................................................................. 76
  4.1.1 The neuronal reaction ...................................................... 77
  4.1.2 The humoral reaction ...................................................... 77
4.2 Compartment modeling ...................................................... 77
  4.2.1 The model for the humoral reaction .................................. 77
  4.2.2 The model for the neuronal reaction ................................ 79
4.3 Validation of the model ...................................................... 81
4.4 Reduced model ................................................................. 82
  4.4.1 Description ................................................................. 82
  4.4.2 Linearization ............................................................... 83
  4.4.3 Validation ................................................................. 86
4.5 Outlook ................................................................. 86

5 Model integration, benchmark signals and typical parameter values  89
5.1 Model integration ............................................................... 89
  5.1.1 Benchmark MAP disturbance signals ................................ 92

III Control Algorithms ................................................................. 95
6 Fuzzy-control ......................................................................... 99
  6.1 Short introduction on fuzzy control ....................................... 99
    6.1.1 Fuzzy sets and fuzzification .......................................... 99
    6.1.2 Definition of rules: the fuzzy inference machine ............... 100
    6.1.3 From fuzzy to crisp: defuzzification ................................ 100
    6.1.4 Mathematical interpretation .......................................... 100
6.1.5 Application field of fuzzy logic ........................................ 102
6.1.6 Fuzzy logic control ..................................................... 102
6.2 Fuzzy logic control in anaesthesia ...................................... 104
6.3 Control of the inspiratory anaesthesia gas concentration .......... 105
  6.3.1 Results ............................................................... 106
6.4 Fuzzy logic control of the inspiratory $O_2$ concentration .......... 106
  6.4.1 Control structure .................................................. 109
  6.4.2 Results ............................................................... 114
6.5 Fuzzy logic control of the endtidal anaesthesia gas concentration .... 116
  6.5.1 Controller structure ............................................... 116
  6.5.2 Results ............................................................... 121
6.6 Fuzzy logic control of mechanical ventilation during anaesthesia .... 123
  6.6.1 Problem description ................................................. 123
  6.6.2 The control scheme ................................................ 124
  6.6.3 First step: setting the $MV$ ...................................... 125
  6.6.4 Second step: splitting of $MV$ in to $V_T$ and $f_R$ ................. 127
  6.6.5 Tuning and test phase ............................................. 130
  6.6.6 Results ............................................................... 131
6.7 Concluding observation about fuzzy logic in control ................ 133

7 State feedback control .................................................... 135
  7.1 General Structure of an observer based ............................ 135
  7.1.1 The observer ...................................................... 136
  7.1.2 The state feedback controller .................................... 137
  7.1.3 Trajectory tracking ............................................... 137
  7.2 State feedback control with additional integral action .......... 139
  7.3 Linear quadratic Gaussian controllers and loop transfer recovery .... 140
  7.4 Control algorithm and tuning parameters .......................... 141
  7.5 Structure realization ................................................ 142
    7.5.1 Synchronization ................................................ 143
Contents

7.5.2 Signal filtering ........................................ 144
7.5.3 Artifacts Handling ....................................... 145
7.5.4 Implementation ........................................ 147
7.6 Control of the inspired anaesthesia concentration .......... 148
7.7 Control of the endtidal anaesthesia concentration .......... 150
  7.7.1 Clinical test validation ................................ 150
7.8 Control of Mean Arterial Pressure .......................... 155
  7.8.1 Override control ....................................... 157
  7.8.2 Controller settings and simulations ...................... 157
  7.8.3 Clinical test validation ................................ 158
7.9 Concluding remarks ....................................... 160

8 MPC-control .............................................. 163
  8.1 Introduction ............................................. 163
  8.2 Basics of MPC ........................................... 164
  8.3 Models .................................................. 166
  8.4 Performance index ....................................... 166
  8.5 Constraints .............................................. 167
  8.6 Observer, Filter .......................................... 168
  8.7 Disturbance rejection and steady state error compensation 168
  8.8 Tuning and implementation of the MPC ..................... 169
    8.8.1 Implementation problems for the feed forward path 170
  8.9 MPC of the inspired anaesthesia gas concentration .......... 170
  8.10 MPC of the endtidal anaesthesia gas concentration ........ 171
  8.11 MPC of the MAP ......................................... 174
  8.12 Clinical test validation ................................ 177
  8.13 Concluding remarks .................................... 177

9 Conclusions ............................................... 183

A Systems of units ........................................... 187
B Parameter set

B.1 Patient related parameters ........................................ 189
B.2 Gas related parameters ............................................. 189
  B.2.1 Halothane ..................................................... 189
  B.2.2 Isoflurane .................................................... 190
  B.2.3 Desflurane .................................................... 190
  B.2.4 Enflurane ...................................................... 190
  B.2.5 Sevoflurane ................................................... 191
  B.2.6 \( N_2O \) ......................................................... 191

C Linearization of the model of the patient: nonlinearity measures  193
  C.1 Simulation results ............................................... 193

Bibliography .......................................................... 197

Curriculum vitae ..................................................... 205
Part I

Introduction
Leer - Vide - Empty
The patient was lying on the surgery bed and was prepared for the chirurgical operation, all instruments were sterilized and the surgeon was ready to begin with his assistant and the surgery specialized nurse. The anaesthetist was observing the heart rate and the breath pressures of the patient. “Cut in 3 Minutes” says the surgeon. “All right”, answered the anaesthetist. He was thinking about the actual patient situation, the breathing frequency and the tidal volume were well set on the breathing machine, 3 minutes were just enough to increase the anesthetic depth of the patient on increasing the amount of anesthetic gas inhaled by the patient.

This imaginary situation in a surgery room shows only some elements and the main role distribution during a surgical operation. There are mainly two physicians: the surgeon and the anaesthetist. The surgeon is responsible for the surgical operation, the anaesthetist must guarantee that the patient:

1. is insensitive to pain,
2. his cardiovascular and other vital functions are stable (homeostasis),
3. has muscle relaxation,
4. does not remember any situation (amnesia).

In the last twenty years the number of different complex surgical operations increased. This was only possible with a better online monitoring of the patient’s physiological parameters. Furthermore the role of the anaesthetist has become more and more complex and indispensable to maintain the patients vital functions. In normal situations the anaesthetist role consists of reactions to some changes in measurements. In stress situations the anaesthetist must deal with routine assessments and at the same time must solve complex problems quickly. The automatisation of some routine actions of the anaesthetist can reduce his work load and consequently increase the safety of the patient, particularly during stress situations.

Today only a small number of values are automatically controlled through closed loop algorithms. A strong cooperation was build up between the Automatic Control Laboratory of the ETH Zürich (Prof. A. H. Glattfelder) and the Institute of Anaesthesiology and Intensive Care of the University Hospital in Bern (Prof. A. M. Zbinden). The main aims of this project are:

1. The automatisation of some routine activities of the anaesthetist in order to allow him better patient care especially during stress or special situations.
2. The patient should receive the optimal amount of drugs based on scientific knowledge.
3. To increase the understanding of anaesthesia mechanisms and time behaviour.
4. To apply and develop recent control algorithms in this specific field.
The focus is placed not only on the control algorithms but also on the modeling, a safe implementation and a thorough testing phase. The implementation is done recursively by using a model of system response, until all systems are ready to be applied in a pilot study with patients. After further tuning the regulator will then be applied in standard clinical studies. The project will implement only “working prototypes”. These prototypes need specially trained anaesthetists and are of course far away from commercial solutions.

1.2 Main actions of the anaesthetist

The anaesthetist is responsible for the safety of the vital functions of the patient before, during and after surgery. To do this it is necessary to:

1. monitor patient condition,
2. estimate the situation, by applying previous experiences and knowledge from the literature,
3. define necessary actions to maintain vital functions of the patient and achieve a good anaesthesia depth time profile. Monitoring is an important role of the anaesthetist in the operating theater. Good monitoring include the following actions:
   • an attentive observation of the patient during a critical phase, where often physiological safeguarding mechanisms are reduced or even canceled by a drug or drug combinations.
   • an attentive observation of all events and manipulations in the operating room.

1.2.1 Depth of anaesthesia

During general anaesthesia the anaesthetist must keep the anaesthesia depth at a desired level. The depth of anaesthesia is a functional state of the central nervous system resulting from stimulation by surgical stimuli and inhibitions of the cerebral activity through anaesthetic agents ([1, 2, 3]). The depth and type of anaesthesia depends on the actuation degree of following conditions:

• **Hypnosis** is the loss of consciousness
• **Amnesia** is the inhibition of conscious feeling (so called awareness) and remembering (so called recall) of pain
• **Analgesia** is the inhibition of the perception of pain stimuli.
• **Muscle relaxation** can be measured, e.g. by electrical stimulation, and is important for intubation and for some types of surgery.
1.2 Main actions of the anaesthetist

It is obvious that it is not easy and maybe also not correct to express depth of anaesthesia by a single value. Numerous possible observations and measurements exist to estimate anaesthesia depth, each giving a different kind and quality of information, e.g. (from [2]):

- **Intra operative Mean Arterial Pressure (MAP) behaviour:** changes on MAP can reflect the actual anaesthesia state of a patient: an increase could be caused from a surgical stimulation and could demand an increasing amount of anaesthesia drug to keep the patient in a good depth of anaesthesia. Unfortunately MAP is not only influenced by pain but also by other pathologies (like blood loss, dehydration, etc.) and drug concentrations (like isoflurane, etc.).

- **Intra operative heart rate behaviour:** Heart rate may be increased by pain. In contrast to blood pressure it may be increased by some volatile anaesthetics (isoflurane) and it may also rise with dehydration.

- **Electroencephalogram (EEG):** EEG represents the cortical electrical activity as a sum of excitatory and inhibitory activities that are controlled by the sub cortical thalamic center. The EEG activity reflect changes of cerebral perfusion and exchange activities. Processed EEG seems to be adequate to measure anaesthesia depth.

- **Evoked potential (EP):** From the EEG signal it is possible to extract some signal that can be interpreted as a evoked response (so called evoked potential) of a given sensoric, auditory or acoustic stimulation. The transfer function between the source (the given stimulus) and the target (the neuronal generator of the EEG reaction) can be used to check the path of the stimulus signal. This method seems to have produced good results on correlation with the effect site concentration of the drug.

Surgical stimulations cause hemodynamic reactions that generally increase MAP. This means that the variation of MAP can be used to estimate the analgesia of the patient. Because the anaesthetist knows exactly the amount and types of delivered drugs and their pharmacodynamic effects, he can roughly estimate the actual depth of anaesthesia of the patient.

1.2.2 Used drugs

In this section we will describe the main characteristics of the drug we will use in the anaesthesia control system. We will limit our operating range to inhaled anaesthesia agents and specially (although we will take into account possible future changes) we will concentrate on the use of isoflurane and nitrous oxide.

Inhaled anaesthesia agents have now been in clinical use for 150 years, following the introduction of di-ethyl ether by W.E. Clarke and Crawford Long in 1842, and subsequent public demonstration by Morton in 1846 (survey see [4, 5, 1]). The introduction of ether rapidly improved surgery techniques (it was no more necessary to hold the patient with violent physical methods). It was followed by the introduction of new substances like chloroform and at the beginning of the 19th nitrous oxide. This last substance was probably already
used before from Paracelsus, but was mainly known till then for its exhilarating effects. After the introduction of nitrous oxide by the dentists a fast evolution and intensive research began on the field of inhaled anaesthesia substances. The first products (like cyclopropane) were effective but flammable (sometimes also explosive!). The first clinically useful fluorinated anaesthesia was found on 1951 with halothane. Although representing a major advance, halothane was associated with a number of undesirable side effects. These included mainly myocardial depression and cardiac arrhythmias. The next major advance came with the synthesis of enflurane in 1963 and isoflurane in 1965. Both are superior to halothane in terms of molecular stability and effects on myocardial function and cardiac rhythm. Enflurane, easier to synthesize, was introduced into clinical practice in 1972, isoflurane only on 1981. In 1971 sevoflurane was first described, but due to concerns about possible toxicity of breakdown products, the release into clinical practice was delayed in the United States. After that only in the 90th new inhalatory anaesthetic agents came out in clinical useful form: 1993 with desflurane and in the last years with xenon.

The standard measure of potency for inhalatory anaesthetics is the MAC (Minimum Alveolar Concentration) and is defined as the minimum alveolar concentration of an anaesthetic that prevents movement in response to skin incision in 50% of patients [6].

Isoflurane is an inhalational anaesthetic of intermediate potency. A progressive obtundation of consciousness and sensory perception occurs with increasing concentrations of isoflurane. The MAC varies with age and is 1.28 [vol%], for 20-30 years old patients and at 1.15 [vol%], for 30-50 years old patients.

The anaesthetic effect of nitrous oxide is additive to that of volatile anaesthetics. Nitrous oxide is the least potent of the currently used anaesthetics, with a MAC of 104 [vol%]. Nonetheless, certain characteristics make it an attractive anesthetic, including low blood and tissue solubilities, analgesic effects at subanaesthetic concentrations, few clinically significant cardiovascular effects and minimal toxicity.

1.2.3 Measurements and observations

The anaesthetist uses many informations to accomplish his role: the measured and monitored values, the setting parameters of the breathing system, the amount of submitted drugs, the main actions of the surgeon and other directly observed characteristics of the patients and of the actual situation in the operation room. Considering the patient together with the breathing and monitoring system as a general plant we can divide the anaesthetists informations in measured and unmeasured inputs and outputs (see figure 1.1). We can observe that there is only a reduced amount of measured informations. This limitation must be considered. This work will only treat a reduced number of control loops. Other activities will not be considered here and are to be performed normally by the anaesthetist.
1.3 Description of the anaesthesia system

The anaesthesia system we used (see figure 1.2) is composed of a breathing system with fresh gas setting unit, some measurement equipment and a controller (implemented on a personal computer). The breathing system ensures artificial breath movement with a given breathing frequency ($f_B$) and tidal volume ($V_T$, volume of gas inflowing in the lung during a breath movement) while respecting pressure limits ($P_{max}$, $P_{plate}$) and time relations ($K_{T ITE}$, $K_{T IPT I}$). The system is a closed circuit that will reuse the patient’s expired gas. The expired $CO_2$ will be absorbed and will not be reused by the patient. The patient’s gas consumptions are compensated by inflowing fresh gas. This fresh gas is also used to change the gas composition in the breathing system. Fresh gas composition and breath parameters can be set by the controller, which receives some measurements through standard patient monitoring systems.

1.4 The anaesthesia control system

The aim of an anaesthesia control system is the automatisation of some control tasks of the anaesthetist in normal situation. To avoid dangerous situations, the anaesthetist should always have a clear overview of the state of the automated processes. As we mentioned above there is only a limited amount of measurements available for the system. It is therefore important to monitor the available informations to the anaesthetist in order to illustrate the actual information level of the automated system. Moreover to increase safety, the controller must be permanently checked by a unit on the next hierarchical level (which we will call supervisor). The supervisor will perform consistency checks on the inputs and outputs of the controller, decide which kind of configuration (controller, parameter set) should be activated and strongly interacts with the anaesthetist. Figure 1.3 illustrates the hierarchical structure.
of the anaesthesia control system and the interactions of elements in the operating room. The surgery system (composed by the patient, the surgeon staff and the technical equipment) provides a big amount of informations that will be partially received by the anaesthetist and by the measurement equipment of the anaesthesia control system. These measurements will be filtered and checked by the supervisor and delivered to the active controller, which will propose some control variables. These will be checked by the supervisor and finally delivered through actuators to the surgery system. As illustrated on the figure, the anaesthesia control system will relieve a limited number of control actions and can at any time be switched off by the anaesthetist.

In this work we will focus on the controller part: we will analyze different solution approaches to similar problems trying to find out the advantages and disadvantages of each technique. We did not neglect the implementation of the supervisor, but we only implemented a basic functionality (simple signal filtering and essential visualization of the actually registered measurements and of the actual settings of the controller variables). To overcome this deficiency, during the test phase, a second anaesthetist provides the necessary supervisory functionality. This guarantees the usual level of safety for the patient and excludes any risk due to controller failure. The procedure has been accepted by the local ethics committee.

1.5 Implementation steps

The implementation process of a controller in the anaesthesia control system is done by the usual engineering steps:
1.5 Implementation steps

Figure 1.3: General structure of an anaesthesia control system

1. **Problem description, specifications**: In this first phase, information about the plant and the already used control techniques are collected. Then, specification on the closed loop performance must be defined. In this application field, physiological mechanisms influencing the value to be controlled as well experience based manual control techniques of the anaesthetist must be understood. Moreover, the admitted operating range of the controller must be defined (e.g. the patient's risk class, dangerous pathologic conditions, type of surgery, type of anaesthesia technique, etc.).

2. **Modeling of the plant**: The model of a plant is necessary for different reasons. First, it allows to reduce the amount of control experiments with real patients needed during the tuning phase; second, it allows the implementation of model based controllers which try to systematically use these additional informations. In this work we shall use various modeling techniques, from first principle models (based on physical and physiological phenomena descriptions) to black-box models (based on a optimized approximation of measured input/output data of the given plant).

3. **Model validation**: During this phase the implemented models are validated through measurements. The main goal of the validation is to achieve similar, but not necessarily identical, dynamical behaviour. The model and parameter set used in simulation will be considered the *nominal point*. This point represents a set of model in the parameter space with slightly different parameter values but similar dynamical behaviour (we will call this set *working region*). This region represents the possible parameter variation of the plant due to the big variability between patients and the complexity of the used breathing system. The goal of the validation will therefore be to check if the measured behaviour corresponds to a point into the working region represented by the nominal point.

4. **Controller design and implementation**: In this phase the structure and the parameters of the controller are designed. Depending on the information level about the
system reached with the preceding phases, different control techniques will result in better performance than others to solve the formulated problem.

5. **Controller validation:** The implemented controller will be tested. First tests are done in simulation using mathematical models of the plant. Robustness is tested using different parameter settings in the patients group considered (e.g., weights between 40 and 120 [kg]). In a second step, first tests (so called *pilot studies*) are done on the anaesthesia control system with real patients under surgery conditions. These experiments have to be approved by the local ethical committee. Patients have to be informed and have to give their written consent. After first successful implementation of the controller, the parameters are iteratively tuned to the desired behaviour (tuning phase).

6. **System test:** During the last phase, serial tests (so called *clinical studies*) are done with the final controller version. Because a statistical evaluation will be done at the end, no further changes in the controller structure and parameter are allowed during this phase.

Each implementation phase presents interesting complex aspects:

1. **Physiologic mechanisms:** The basic mechanisms of the effects of anaesthetic drugs on the human body are not completely understood for all agents.

2. **Experience based knowledge:** Anaesthetists' experience based knowledge is not easy to extract and understand. Often decisions are taken intuitively: the anaesthetist evaluate mostly unconsciously measurable and unmeasurable informations about the system.

3. **Model variability:** Each patient has different characteristics and therefore is described with a different parameter set. The individual parameters are not easy to be identified in the normally short surgery time. Some important parameters can also change during the surgery.

4. **Controller design:** The controller design is not obvious. This is mainly due to model uncertainty and to nonlinearities on the plant.

5. **Testing:** Practical testing on real patients must be reduced to a minimum. Another problem is the fact that under clinical conditions the set point profile is mainly given by the actual patients condition and can not be set arbitrarily.

6. **Supervision:** The realization of a supervision block requires the solution of many different complex problems, which often are strongly correlated e.g.:

   - Intelligent alarming: involves e.g. fast and efficient alarming of all possible critical situations.
   - Man machine interface: the operator should at each time have an overview of the actual situation (including alarm messages) and must be able to change any setting in a efficient and intuitive way.
1.6 Previous work

- Artifact handling: All known system disturbances due to artifacts must be detected and reported. In addition, possible erroneous and dangerous reactions of the anaesthesia control system must be avoided.

7. Cost constraints: As in all application fields, the anaesthesia control system must have a simple structure, minimizing the number of different components (e.g. sensors, valves, pumps, etc.) in order to reduce costs.

Such an anaesthesia control system is therefore a complex system.

1.6 Previous work

We found more than 100 publications about closed loop control in anaesthesia ([7, 8, 9] gives a limited overview). Many publications originate from 1947 to 1970 (see overview in [7]). The first main impulse was given in the early 70s with the introduction of the physiologically based compartment models of uptake and action of anaesthesia drugs (e.g. [10, 11]). Many controller techniques were applied but till the 1980, only a few were tested under clinical conditions. In these years all attempts to find a unique indicator for anaesthesia depth failed. The 80s were mainly characterized by the introduction of more powerful computers. This was reflected by a huge number of publications of adaptive control algorithms in anaesthesia based principally in simulation results or in animal experiments ([12, 13, 14, 15, 16, 17, 18, 19, 20, 21]). In the last 10 years many other attempts were made with adaptive control algorithms often combined with the latest control techniques like fuzzy control and neuronal network ([22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36]). Many of these controllers were validated with clinical studies. Although the main number of publications, the realization of standard medical equipment is on the beginning ([37]). An anaesthesia control system must be reliable, transparent to the user and must be applicable in clinical routine environment. The anaesthetist must trust the system but always have a good overview of the actual situation. The system we used clinically was composed by standard equipment, with the addition of a screen and some actuators. The anaesthetist can at any time switch immediately off the automatic control and continue with the usual actuators.

Most of the models used for the implementation and validation of the control algorithms were simple compositions of pure time delays with first or second order linear transfer functions; this is especially the case when adaptive control or multiple model approaches were implemented. In this work we will always use non adaptive control techniques. The parameters of the controller are only dependent of known operating conditions. Big changes of operating conditions will in the future lead to a gain scheduling in the controller algorithm.

While before the 80s the main goal of the scientific community was to control depth of anaesthesia with different indicators as EEG, MAP or estimation of anaesthetic partial pressure in the brain, more selective automatisation purposes were chosen. Thereafter most work successfully controlled MAP with either intravenous or inhaled drugs separately. Only in the 90s combined drug delivery was analyzed. To minimize the time constant for the
uptake of inhaled agents, high fresh gas flows or even open breathing system have to be used.

1.6.1 Project phases

Our project began on 1991 with one diploma ([38]) and one semester thesis ([39]) with the control of Mean Arterial Pressure (MAP) with isoflurane using high constant fresh gas flows and 100 % oxygen concentration. The applied fuzzy controller was tested under clinical conditions and resulted to be equivalent to human manual control ([40, 41, 42]). The simple controller structure (see figure 1.4) was then gradually expanded to a multi variable control structure. The next step consisted in expanding the functionality of the controller to allow the use in normal clinical conditions. To improve the dynamic behaviour of the system while minimizing the consumption of costly anesthetic gases the controller constantly has to adjust the following three variables: the isoflurane concentration in the fresh gas flow, the oxygen and the nitrous oxide fresh gas flows (see figure 1.5). The controller was designed as a cascade (where the external controller is setting the set point of the internal one) to improve safety in case of a failure and to allow decoupling of the dynamics of the patient and of the breathing system ([43, 44]). The controller showed interesting preliminary results ([45]) but was not tested in a series of clinical studies, because further improvements were needed at low fresh gas flow conditions. After these first experiences a new controller structure was developed (see figure 1.6). The new control system was expanded with the control of the endtidal CO$_2$ concentration and the internal loop of figure 1.5 was decoupled in a controller of the inspired oxygen concentration and an anaesthesia gas controller. The anaesthesia gas controller can have different configurations (see figure 1.7):

1. **MAP controller**: it directly calculates the anaesthesia gas in the fresh gas flow from the actual MAP set and measured value, the measured inspired and endtidal concentrations.

2. **Endtidal anaesthetic gas controller**: it directly calculates the anaesthetic gas concentration in the fresh gas flow from the actual endtidal anaesthetic gas concentration set and measured value and the measured inspired concentrations.

Figure 1.4: First realization of the control of MAP
Figure 1.5: Realization of a multi variable control of MAP

Figure 1.6: Anaesthesia control system in the actual implementation form

3. **Inspired anaesthetic gas controller**: it directly calculates the anaesthetic gas concentration in the fresh gas flow from the actual inspired anaesthetic gas concentration set and measured value, and the measured endtidal concentrations.

4. **Cascade structure**: A MAP or an endtidal anaesthetic gas controller will define an inspired anaesthetic gas set value that will be controlled by an internal loop.

All controller parameters depend also on the actual fresh gas flow and some breathing parameters. This structure allows flexible switching between operating points and controller structures.

The main goals of this work were to extend the functionality of the earlier works (resulting in the new structure of figure 1.6) and to compare different control techniques. The comparison
Figure 1.7: Different realized variants of control of the anaesthesia gas concentration.

does not only consider control performance but all implementation steps: from the problem description and know-how collection, through the modeling phase to the testing phase. A limited number of control techniques were used for the comparison. Non adaptive controllers will be compared: experience based control (represented mainly by fuzzy and some PID controllers) and model based controllers (from state feedback to predictive control techniques). All implemented controllers were clinically tested, but considering the long times needed for clinical tests, their performance has not yet been statistically proved. Therefore, we will mainly present their step responses or disturbance rejections on single real examples and compare them, where possible, with the expected simulation results.
Part II
Modeling
Leer - Vide - Empty
In general, there exist many ways to build a mathematical model of the input/output dynamical behaviour of a physical system. These different methods are characterized by the different usage of information about the system. There exist two main kinds of information:

1. *Measurements of input/output data*

2. *Equations of the physical principles the system is based on*

The modeling method using only input/output data is called direct empirical modeling, it is mainly based on numerical minimization of the error between measured and simulated outputs. On the other side first principle models (also called *fundamental models*) are built using exclusively mathematical descriptions of physical principles the system is based on (see figure 1.8). Of course there exist a large number of methods in between these two extrema.

![Diagram](image_url)

*Figure 1.8: Modeling methods depend on the type of information about the system*

Another degree of freedom is of course the complexity. Depending on the future use of the mathematical model and the amount of information about the system, it is convenient to use simplified model structures.

Mainly two strategies are used to model biomedical systems and related components:
• The top-down strategy (from physiological models, to minimal compartment models).

• The bottom-up strategy (from input/output identification to compartment models).

With the top-down strategy one considers the physical and biochemical processes influencing a system and tries to describe it in a mathematical way [46]. Due to uncertainty, lack of information and variability of the problem, in the second step one will try to reduce the system to its relevant components. The aim of these methods is to describe the system with parameters, which are physiologically measurable or easily estimable. This kind of description allows the computation of parameter sensitivity and the extrapolation of possible parameter variability among a defined population. The robustness and performance of a control strategy over a population can then be determined. Unfortunately, biomedical processes are often not completely understood and also when they are, parameter identification is very hard to accomplish with sufficient precision because of the lack of measurements (especially of body internal values like concentrations, volumes, etc.). Moreover, a very high time, structure or individual parameter variability makes the task of physiological modeling a hard job to do.

It was frequently observed that a very complex system has a quasi linear behaviour around some working points, or that the order and the nonlinearity can be extremely reduced. Reducing a physiological system in such a way that the behaviour around a working point is described is not always possible without enormous effort. If we consider that biomedical system also have a structure uncertainty, due to lack of process understandings, it will be difficult to reduce the model appropriately. In these cases the bottom-up strategy can be a better solution to describe the system. These techniques consist of a black-box identification of the system on the first step. The identification makes no assumption of model structure but assumes it is linear. A first estimate of the apparent order of the system can be introduced. In the second step, parameters of a minimal compartment system will be identified. The system takes some information of the structure from the complex physiological model, but their parameters are not physiological. Much works have been done on the analysis of the possible structure of such systems and their parameter identification [47, 48, 49].

The system we are considering can be split in three main elements:

1. The patient model: (the pharmacokinetic and the hemodynamic effects of anaesthetic gas)

2. The breathing system: (extracorporeal)

3. The hemodynamic effects of surgical stimulation

The first element describes the gas exchange between gas and blood in the lung, their distribution dynamic (pharmacokinetic) and effect dynamic (pharmacodynamic) in the human body. The second element is the artificial breathing system. It is composed by actuators and mechanical devices ensuring artificial breathing. The third element is a description of the hemodynamic effects of surgical stimulation which is a main disturbance on the control loop.
In this part all these elements will be accurately described and modeled. All model descriptions start with a short introduction into the main physical and physiological phenomena. After that, a first principle model representing all main mechanisms involved will be presented. The often complex nonlinear model is then reduced and/or linearized. The resulting simplified model is therefore based on physical assumptions but can be corrected with measurement data (where it is possible).

The idea is to achieve the simplest possible model structure maintaining the necessary links to physiologic/physical parameters of the system.
Chapter 2

The patient model

In this chapter the modeling of the uptake and distribution (so called pharmacokinetics) and the various effects of some concentration levels of various gases in the human body (so called pharmacodynamics) will be described. All main gases involved in breathing during surgery will be considered: $O_2$, $CO_2$, $N_2O$ and anaesthetic gas (isoflurane, halothane, enfurane, desflurane). The remaining gases ($N_2$, $Ar$, $Ne$, ...) will be neglected and considered as unmeasured disturbances. All gases are inhaled through the breathing system and therefore are inhaled through the lung by the patient. The inhaled (or inspiratory) gas concentration in the lung together with some breathing parameters are the inputs of the model. The chapter will first shortly describe the main physiological mechanisms involved with the different gases, then a compartment model structure is presented for the pharmacokinetics and pharmacodynamics of anaesthetic gases. Short results of the validation of the model are then presented. The nonlinear model will then be analyzed and reduced to a usable form for control purposes.

2.1 Physical phenomena

In this chapter we are interested in the mathematical description of mass transport phenomena. Gases are transported by blood flow, by airflow and by active and/or passive diffusion from blood to tissue and from blood to the alveolar gas part. Blood flow will distribute the substances and exchange it (always through diffusion phenomena) with the tissue part of the body. In the breathing circuit (including the gas part of the lungs), mass transport could be successfully modeled through compartment modeling [11, 48, 50]: the mass transport path is divided into subsystems. Each subsystem (called compartment) is in our case modeled as a “perfectly stirred tank”. Depending on the purpose of the modeling, a different compartment subdivision and structure can be chosen. Generally a reduced number of compartments will loose the possibility of physiological interpretation of compartments parameter, but will gain in identifiability [47].
2.2 The compartment model of the uptake of inhalation anaesthetic gas

In this section we first reintroduce the model of [11]. It consists of two parts - one for the uptake and distribution of drugs and one for the circulation of the blood flows. To describe the drug distribution in the body, a compartment model is established (left part of figure 2.2). The circulation model (right part of figure 2.2) is utilized to describe the hemodynamics. Pharmacodynamic laws are postulated to link the two models. For the derivation of that model the following assumptions have been made [11]:

1. The model can be realized with a finite number of compartments.
2. Ventilation and blood flow can be described as nonpulsatile phenomena since equilibration times are large compared to cardiac and respiratory cycles.
3. Transportation times can be neglected for similar reasons.
4. Ventilation is kept constant.
5. There is no other way of exchange between different compartments than transport by the blood.
6. Equilibration within a compartment is instantaneous.
7. The inhalation agent is not metabolized.
8. There is no adaptation to the anaesthetic agent (no change on the characteristic of the pharmacodynamic due to customization).

Assumptions 1, 2, 5 and 6 are common assumptions when deriving pharmacokinetic models [51, 52, 53]. Assumption 7 is justified because isoflurane is only marginally metabolized (0.2-1%) [54]. Mapleson showed in [55] that an arterial pool compartment accounts well for the transportation delay which justifies assumption 3. Finally, assumption 4 is justified since ventilation is indeed usually kept constant. If ventilation is used to control arterial CO₂ concentration, a switching of the parameter set is necessary. During control, the ventilation will only change significantly (for modeling) during set point changes.

2.2.1 The model for distribution of anaesthetics

The uptake and distribution model (left part of figure 2.2) describes the pharmacokinetics of the anaesthetic agent. It consists of 12 different compartments (see table 2.1). Each compartment represent organs or groups of organs with similar properties concerning pharmacokinetics, pharmacodynamics as well as haemodynamics. The compartments 1 to 9 are referred to as normal compartments. Two compartments model the arterial and venous blood pool, respectively, and one compartment models the lung.

All of the normal compartments have the same structure (figure 2.1). They are modeled as consisting of a tissue and a blood part. Both tissue and blood part are assumed to have the
2.2 The compartment model of the uptake of inhalation anaesthetic gas

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>myocard (heart muscle)</td>
</tr>
<tr>
<td>2</td>
<td>brain gray matter</td>
</tr>
<tr>
<td>3</td>
<td>brain white matter</td>
</tr>
<tr>
<td>4</td>
<td>well perfused organs</td>
</tr>
<tr>
<td>5</td>
<td>poorly perfused organs</td>
</tr>
<tr>
<td>6</td>
<td>splanchnicus (stomach, intestine)</td>
</tr>
<tr>
<td>7</td>
<td>skeletal muscle</td>
</tr>
<tr>
<td>8</td>
<td>fat</td>
</tr>
<tr>
<td>9</td>
<td>skin shunt</td>
</tr>
<tr>
<td>L</td>
<td>lung</td>
</tr>
<tr>
<td>A</td>
<td>arterial system</td>
</tr>
<tr>
<td>V</td>
<td>venous system</td>
</tr>
</tbody>
</table>

Table 2.1: List of the different compartments.

Figure 2.1: The model for a normal tissue compartment consists of a blood part and a tissue part with volumes $V_{i,b}$ and $V_{i,t}$, respectively. Each part has different solubility $\lambda_b$ and $\lambda_t$ but (by assumption) the same partial pressure $p_i(t)$ of the anaesthetic.

The same anaesthetic partial pressure $p_i$ but different solubilities in tissue and blood. Anaesthetics enter the compartment with blood and partial pressure $p_A$ and they leave the compartment with the venous blood and partial pressure $p_i$. This description leads to the following equation for the evolution of partial pressure of the anaesthetic in the compartment:

$$\dot{p_i}(t) = K_i \lambda_b q_i(t) [p_A(t) - p_i(t)]$$  \hspace{1cm} (2.1)

$$K_i = \frac{1}{\lambda_b V_{i,b} + \lambda_t V_{i,t}}$$  \hspace{1cm} (2.2)

The three extra compartments ($L$, $A$ and $V$) have a slightly different structure. The lung compartment depends in addition to the blood and tissue volumes on the functional residual capacity ($V_o$, it is the volume of gas remaining in the lung after normal expiration). This is due to the gas exchange between blood and gas in the lung. Not all the blood flowing through the lung is subject to the gas exchange. For this reason the venous blood flow is split in two parts: the first represents the effective blood flow subject to the gas exchange and the second goes directly from the veins to the arteries (this part is called lung shunt. It will be expressed with the fraction parameter $l_s$. Its typical value is 3 %). This leads to the
The patient model

Equation:

\[
\dot{p}_L(t) = KL\lambda bp_L(t) [p_V(t) - p_L(t)] + q_{A\text{ir}}(t) [p_{A\text{ir}}(t) - p_V(t)] \quad (2.3)
\]

\[
KL = \frac{1}{\lambda_b V_{L,b} + \lambda_L V_{L,t} + V_a} \quad (2.4)
\]

\[
q_L(t) = CO(t) (1 - ls) \quad (2.5)
\]

where \(q_{A\text{ir}}\) denotes the minute volume and \(p_{A\text{ir}}\) denotes the anaesthetic gas concentration (partial pressure) of the inhaled air.

Figure 2.2: Compartment model of pharmacokinetic and pharmacodynamic of anaesthetic gas.

Arterial and venous compartments differ from the normal compartments in the balance equations in so far as their flows entering and leaving the compartments comes or goes from or to different compartments (see outgoing and incoming arrows of the respective compartments in the left block scheme of figure 2.2). The equations are:

\[
\dot{p}_A(t) = K_A\lambda_b CO(t) [p_V ls + p_L(1 - ls) - p_A(t)] \quad (2.6)
\]

\[
K_A = \frac{1}{\lambda_b V_{A,b} + \lambda_A V_{A,t}} \quad (2.7)
\]

\[
\dot{p}_V(t) = KV\lambda_b \left[ \sum_{i=1}^{9} q_i(t)p_i(t) - CO(t)p_V(t) \right] \quad (2.8)
\]

\[
KV = \frac{1}{\lambda_b V_{V,b} + \lambda_V V_{V,t}} \quad (2.9)
\]
2.2.2 The circulation model

The circulation model describes the blood flow (right part of figure 2.2). The heart produces a certain amount of average blood outflow (cardiac output denoted by \( CO \)). The total \( CO \) is distributed to the various normal compartments. Each of these compartments exhibits a certain conductance \( g_i \). Given \( CO \) and \( g_i \), the mean arterial blood pressure \( MAP \) is given analogously to Ohm's law by

\[
MAP = \frac{CO}{\sum_{i=1}^{9} g_i}
\]  

(2.10)

Both blood and pressure dynamics for all compartments are considered stationary, that is all dynamic effects are neglected.

2.2.3 The pharmacodynamics

Pharmacodynamics describe the effects of drugs. Effects of the anaesthetic agent on the compartment conductivity and the cardiac output are known and are modeled as affine functions of partial pressure of the anaesthetic in the compartment (see equations 2.11, 2.12).

\[
g_i = g_{i,0}(1 + b_i p_i) \quad (2.11)
\]

\[
CO = CO_0(1 + a_1 p_1 + a_2 p_2 + a_{AP_A}) \quad (2.12)
\]

2.2.4 The combined nonlinear model

The resulting nonlinear model can be written on following form:

\[
\dot{p}(t) = f(p(t), u(t))
\]

\[
MAP(t) = h(p(t), u(t)) \quad (2.13)
\]

where the state vector \( p(t) \) describes the partial pressure of the anaesthetic gas in every compartment; the input is the concentration of anaesthetic gas in the inspired air and mean arterial pressure \( MAP \) is the output of the system. Utilizing equations (2.1) to (2.12), we
get the different components of the function \( f \) as:

\[
\dot{p}_i = k_i g_i,0 CO_i (1 + a_1 p_1 + a_2 p_2 + a_{AP_i}) (p_A - p_i) \frac{(1 + b_i p_i)}{\sum_{j=1}^{9} g_{j,0}(1 + b_j p_j)} \tag{2.14}
\]

\[
\dot{p}_L = k_L \{ \lambda_b (1 - l s) CO_0 (1 + a_1 p_1 + a_2 p_2 + a_{AP_i}) (p_V - p_L) + q_{Air} (p_{Air} - p_L) \} \tag{2.15}
\]

\[
\dot{p}_A = k_A CO_0 (1 + a_1 p_1 + a_2 p_2 + a_{AP_i}) [p_V l s + p_L (1 - l s) - p_A] \tag{2.16}
\]

\[
\dot{p}_V = k_V CO_0 (1 + a_1 p_1 + a_2 p_2 + a_{AP_i}) \left[ \frac{\sum_{i=1}^{9} g_{i,0}(1 + b_i p_i)p_i}{\sum_{j=1}^{9} g_{j,0}(1 + b_j p_j)} - p_V \right] \tag{2.17}
\]

\[
MAP = CO_0 \frac{(1 + a_1 p_1 + a_2 p_2 + a_{AP_i})}{\sum_{j=1}^{9} g_{j,0}(1 + b_j p_j)} \tag{2.18}
\]

This kind of representation will be used for linearization and all nonlinearities can be easily observed. Writing these equations in a compact way we obtain:

\[
\dot{p}_i = k_i Q_i (p_A - p_i) \tag{2.19}
\]

\[
\dot{p}_L = k_L \{ \lambda_b (1 - l s) CO (p_V - p_L) + q_{Air} (p_{Air} - p_L) \} \tag{2.20}
\]

\[
\dot{p}_A = k_A CO [p_V l s + p_L (1 - l s) - p_A] \tag{2.21}
\]

\[
\dot{p}_V = k_V CO \left[ \frac{\sum_{i=1}^{9} g_{i,0}(1 + b_i p_i)}{\sum_{j=1}^{9} g_j} - p_V \right] \tag{2.22}
\]

\[
MAP = \frac{CO}{\sum_{j=1}^{9} g_j} \tag{2.23}
\]

\[
Q_i = MAP \ g_i \tag{2.24}
\]

where \( Q_i \) is the blood flow going through the \( i \)-th normal compartment. An interesting property of this system can be seen by writing equations 2.19 to 2.24 in matrix form (this
property will also been observed later on, after linearization):

\[ \dot{p} = A(p) p + B u \]  

\[ A = \begin{bmatrix} -k_1 Q_1 & 0 & 0 & k_1 Q_1 & 0 \\ \vdots & \ddots & \vdots & \vdots & \vdots \\ 0 & \ldots & -k_9 Q_9 & 0 & k_9 Q_9 & 0 \\ 0 & \ldots & 0 & -k_L (q_L + q_{Air}) & 0 & k_L q_L \\ k_V Q_1 & \ldots & k_V Q_1 & 0 & 0 & -k_V CO \end{bmatrix} \]  

\[ B = \begin{bmatrix} 0 & 0 \\ \vdots & \vdots \\ \frac{k_L q_{Air}}{2} & \frac{k_L q_{Air}}{2} \\ 0 & 0 \\ 0 & 0 \end{bmatrix} \]  

\[ \lambda_6 CO (1 - l_s) \]  

\( A(p) \) describes a nonlinear compartment system with state dependent transfer coefficients ([56]). The system is not autonomous due to the connection of the lung compartment. The entry \( a_{ij}(p) \) is the fractional transfer coefficient for the compartment system; it describes the flow from compartment \( j \) to compartment \( i \). The only considered mass transfer to the outside, by neglecting the very low metabolic activity in all compartments, is the transfer through the lung. The volume of each compartment is approximatively constant:

\[ a_{ij}(p) = \sum_{i=1}^{n} a_{ij}(p) \quad \forall \, j \neq j_L \]  

where \( j_L \) is the index of the lung compartment. In this compartment an additional term \(-k_L q_{Air}\) is added to relation 2.29. With equation 2.25 the main compartment structure (a combination of closed catenary system and mammillary system) of the pharmacokinetics is conserved. The nonlinearities due to the pharmacodynamics with the circulatory system, is mainly expressed in \( Q \) and \( CO \). This model obviously requires the determination of many parameters. However, there is no need to identify all of them from experimental input/output data alone. Some parameters (e.g. blood volumes) are known from anatomy, other parameters (e.g. solubility) can be found in anesthesia literature, and only a few have to be determined individually. The parameter set will be discussed later in section 2.6.

### 2.3 Multiple gas model

The model described above can be used for all main anaesthesia gases. The definition of the respective parameters is described in section 2.6. In our work some investigations were
made for the modeling in cases of the combination of anaesthesia gases. Specifically, the mixing between \( N_2O \) and another anaesthesia gas was implemented. The model was extended with the same pharmacokinetic equations (from 2.1 to 2.8) for \( N_2O \). The pharmacodynamic equations were extended with the affine to \( N_2O \) concentration (\( p_{i,N_2O} \)):

\[
g_i = g_{i,0}(1 + b_ip_i + b_{i,N_2O}p_i,N_2O) \quad (2.30)
\]

\[
CO = CO_0(1 + a_1p_1 + a_2p_2 + a_Ap_A + a_4p_1,N_2O + a_5p_2,N_2O + a_6p_A,N_2O) \quad (2.31)
\]

As one can notice, the model extension assumes an additive effect using two different gases simultaneously.

### 2.3.1 Second gas effect

It has been observed, that using multiple anaesthesia gas mixtures (especially with \( N_2O \)) the transport of anaesthesia gas from the lung to the blood is influenced by concentration changes of gases that are used in high concentrations [57]. In our case \( N_2O \), can act as carrier for the other anaesthesia gases lowing the equilibrium time. This effect was modeled by increasing the effective air flow \( q_{Air} \) (so called ventilation) in the differential equation of the lung compartment (eq. 2.3) by an affine factor (\( K_{q_{Air}} \)) depending on the gas concentration mixture in the lung gas and in the veins:

\[
\dot{q}_{Air} = q_{Air} \left[ 1 + K_{q_{Air}}(p_{Air}, p_{Air,N_2O}, P_{V,N_2O}) \right] \quad (2.32)
\]

For the usual operating point with \( p_{Air,N_2O} = 70 \text{ [vol\%]} \) and \( p_{Air,O_2} = 30 \text{ [vol\%]} \), \( K_{q_{Air}} \) was set to 0.235 and was set independent from \( p_{V,N_2O} \) (value set from experimental data, see [58]).

### 2.4 Linearization

For controller design it is preferable to use a linear model obtained by linearization around a nominal operating point. Usually, operating points are steady state conditions of the system:

\[
\dot{p} = 0 \quad \rightarrow \quad f(p, u) = 0 \quad (2.33)
\]

In this system there exist three main types of steady state conditions:

\[
\bar{p}_1 = \bar{p} \quad | \quad \begin{cases} CO = 0 \\ p_{Air} = p_L \end{cases} \quad (2.34)
\]

\[
\bar{p}_2 = \bar{p} \quad | \quad p_i = p_A = p_V = p_L = p_{Air} \quad \forall \ i \quad (2.35)
\]

\[
\bar{p}_3 = \bar{p} \quad | \quad \begin{cases} p_i = - \frac{1}{b_i} \quad \forall \ i \\ p_A = p_V = p_L = p_{Air} \quad \forall \ i \end{cases} \quad (2.36)
\]
The first steady state condition ($p_1$), assumes that Cardiac Output ($CO$) is equal to zero. This condition is therefore ignored since a blood circulation is necessary for vital functionality of human body.

The second steady state condition ($p_2$), assumes that all body compartments have the same partial pressure. In this case, the total mass exchange of anaesthesia drug between each compartment is equal to zero. This condition will hardly be reached in reality since there are very slow compartments in the body. However the very slow dynamic parts can be neglected for control purposes, (e.g. considering those dynamics as a disturbance). Excluding leakages on the system parameter changes does not affect the steady state value. The third steady state condition ($p_3$), occurs if in all normal compartments the conductivity is equal to zero. All organs will not be perfused anymore and therefore, no change of the concentration is possible. Like the first steady state, it is a purely theoretical steady state that cannot occur in reality (or better not to happen!). The anaesthetic agent we are considering has different effects in different compartments but leads mainly to vasodilatation and therefore cannot reach this dangerous steady state. It is important not to spend too much time considering the reachability of pathologic steady states with this compartment model. Such kinds of pathologic states mostly require the modeling of other nonlinear effects (e.g. leaving the linear range of the Michaelis Menten kinetics, other internal feedback mechanisms). Because our operating region does not require such a high modeling precision, these kinds of nonlinearities were neglected. Therefore, the second steady state condition is selected as reference point for the linearization. In the following it will be abbreviated as working point.

The Jacobi linearization over a working point $\mathbf{p}, \mathbf{u}$ is defined as:

$$
\delta \mathbf{p}(t) = \frac{\partial f}{\partial \mathbf{p}} \delta \mathbf{p}(t) + \frac{\partial f}{\partial \mathbf{u}} \delta \mathbf{u}(t)
$$

$$
\delta MAP(t) = \frac{\partial h}{\partial \mathbf{p}} \delta \mathbf{p}(t) + \frac{\partial h}{\partial \mathbf{u}} \delta \mathbf{u}(t)
$$

or:

$$
\delta \mathbf{p}(t) = A \delta \mathbf{p}(t) + B \delta \mathbf{u}(t)
$$

$$
\delta MAP(t) = C \delta \mathbf{p}(t) + D \delta \mathbf{u}(t)
$$

where $\delta \mathbf{p}(t)$ and $\delta MAP$ express the difference of the actual value to the quasi steady state value at the working point:

$$
\delta \mathbf{p}(t) = \mathbf{p}(t) - \mathbf{p}
$$

$$
\delta MAP(t) = MAP(t) - MAP
$$

All variables providing an overline are constant values calculated at the given working point $\mathbf{p}, \mathbf{u}$. For example:

$$
CO = C O_0 (1 + a_1 \overline{p_1} + a_2 \overline{p_2} + a_A \overline{p_A})
$$
The linearization over the second steady state $p_2$ gives following matrices:

$$A = \begin{bmatrix}
-k_1\bar{Q}_1 & 0 & \cdots & 0 \\
0 & \cdots & \cdots & 0 \\
0 & \cdots & \cdots & 0 \\
-k_9\bar{Q}_9 & 0 & \cdots & 0 \\
-k_L(\bar{q}_L) & 0 & \cdots & 0 \\
-k_L\bar{q}_L & 0 & \cdots & 0 \\
k_A\bar{C\bar{O}} & -k_A\bar{C\bar{O}} & \cdots & -k_A\bar{C\bar{O}} \\
k_L\bar{q}_L & 0 & \cdots & 0 \\
-k_V\bar{C\bar{O}} & 0 & \cdots & 0 \\
k_V\bar{q}_L & 0 & \cdots & 0 \\
k_V\bar{q}_L & 0 & \cdots & 0 \\
k_V\bar{q}_L & 0 & \cdots & 0 \\
k_V\bar{q}_L & 0 & \cdots & 0 \\
k_V\bar{q}_L & 0 & \cdots & 0 \\
\end{bmatrix}$$

$$B = \begin{bmatrix}
0 & 0 \\
\vdots & \vdots \\
0 & 0 \\
-k_L\bar{q}_{\text{Air}} & -k_L\bar{p}_{\text{Air}} \\
0 & 0 \\
0 & 0 \\
0 & 0 \\
\end{bmatrix}$$

$$C = \begin{bmatrix}
\bar{m}_1 - \bar{n}_1 \\
\bar{m}_2 - \bar{n}_2 \\
\bar{m}_3 - \bar{n}_3 \\
\vdots \\
\bar{m}_9 - \bar{n}_9 \\
0 \\
0 \\
\end{bmatrix}$$

$$D = 0$$

with the abbreviated constants:

$$\bar{m}_i = \frac{CO_{\text{O}_2} a_i}{\sum_{j=1}^{9} \bar{g}_j}$$

$$\bar{n}_i = -\frac{CO_{g_{i,3}} \bar{b}_i}{\left[\sum_{j=1}^{9} \bar{g}_j\right]^2}$$

$$\bar{q}_L = \lambda_b\bar{C\bar{O}}(1-\ell s)$$

After linearization some questions are to be answered:

1. How good is the linearized model?
2. How many models are necessary to cover the whole working region?
3. How sensitive is the dynamic behaviour to parameter changes?
4. Is it possible to reduce the model?
5. Is this model usable for parameter identification and for control?

To answer these questions, some further analysis of the system is necessary.

### 2.4.1 Performance of the linearized system

The answer to the first question can be given in many different ways: the performance of the model can be given in comparison with the nonlinear system or with some measurements.
2.4 Linearization

Time and frequency responses

Let us first of all compare the nonlinear system (2.25) (which can be assumed to be an exact model of a possible patient body behaviour) with its Jacobian linearization (2.38). A comparison between simulation with real measured input signals shows optically good results (2.3), but due to the property of nonlinear systems, does not guarantee a good behaviour in all situations. The graphic shows the comparison between three different models resulting from linearization around different working points. The best fit is achieved when the mean inspiratory value is around the respective working point used for linearization (by inspection of figure 2.3). Comparing the Bode diagrams of the resulting systems after linearization around different working points we observe differences in the low frequency gain and after 150 degrees phase shift (see figure 2.4). Due to the gain factor $-1$ we obtain a supplementary gain shift of $180^\circ$.

![Simulation of linearized and nonlinear model](image-url)

Figure 2.3: The first three figures represents the output signal with a comparison between linearizations around different working points ($p_{air} = [0.1 \ 0.5 \ 1] [\text{vol\%}]$ from top to down) and the nonlinear system. The last figure show the used measured input signal of the system (inspiratory anaesthesia gas concentration).

Nonlinearity measure

There are systems with nonlinearities that have no significant influence in the I/O behavior. To estimate this influence, it possible to define a nonlinearity measure of the I/O behaviour.
Figure 2.4: Comparison between Bode diagrams computed from three linearizations around different working of the nonlinear system: \( p_{\text{air}} = [0.1(-) 0.5(-.) 1.0(\ldots)] \). Their respective static gain factors are approx.: \( K_{\text{Gain}} = [34 26 15] \). The +180° phase is given by the negative gain factor of the transfer function.

between a nonlinear system and a set of linear one. We will apply the definition proposed in [59], [60] and [61]:

The nonlinearity measure \( \theta_N^U \) of a BIBO-stable, causal I/O-system \( N : U_a \rightarrow (Y) \) for input signals \( u \in U \subseteq U_a \) is defined by the nonnegative number

\[
\theta_N^U = \inf_{G \in G} \sup_{u \in U} \frac{||G[u] - N[u]||_Y}{||N[u]||_Y}
\]

with \( G : U_a \rightarrow Y \) being a linear I/O-operator, \( ||.||_Y \) a norm in \( Y \), \( ||.||_{U_a} \) a norm in \( U_a \), and \( U \) being the set of inputs considered.

The “size” of the nonlinearity of an I/O-system is thus defined as the normalized largest difference between the output of the nonlinear system \( N \) and a linear system \( G \) measured by the Norm \( ||.||_Y \) in \( Y \). The nonlinearity measure of (2.47) is the result of the minimization over a given set of linear approximations \( G \) of this calculated “size”. We will use this function to evaluate the linearized model around and outside its working point. On comparing the performance of different linearized model realizations (with different \( \bar{p} \)) we will try to find out if model switching is necessary to cover the whole working region.

Figure 2.3 shows by inspection that the best nonlinearity measure is achieved with the model linearized around the mean value of the input. The best computation of the nonlinearity
measure will be to find a representative set of input vectors $U$. Since the results will be highly dependent on the working region we will restrict $U$ to a suitable set (as in [59, 60]):

$$u(t) = A_0 + A \sin(\omega t)$$  (2.48)

This will lead to a frequency response measurement on the nonlinear system. The norm operator will be defined as:

$$\|y\|_{VT} = \sqrt{\frac{1}{T} \int_0^T (y(t) - y_0)^2 dt}$$  (2.49)

where the amplitude $A$, the offset $A_0$ and frequency $\omega$ are taken from the sets:

$$A \in \mathcal{A} = \{A \in \mathbb{R}^+ | 0 \leq A \leq A_{\text{max}} \}$$  (2.50)

$$A_0 \in \mathcal{A}_0 = \{A_0 \in \mathbb{R}^+ | 0 \leq A_0 \leq A_{0,\text{max}} \}$$  (2.51)

$$\omega \in \Omega = \{\omega \in \mathbb{R}^+ | 0 \leq \omega \leq \omega_{\text{max}} \}$$  (2.52)

This specific set of inputs (called $U_k$) is thus parameterized by $A$, $A_0$ and $\omega$. To avoid infinite norm values for $T \to \infty$, the zero order trend ($y_0$) of the value is subtracted. Applied to our model, this allows us to compare input signals with different mean working point values. We will call $G_{pk} \in \mathcal{G}$ the linearized model at working point $k$. $\Theta_N(u, G_{pk})$ is the resulting simplified nonlinearity value for a given input signal $u \in U_k$ and model $G_{pk} \in \mathcal{G}$ for the nonlinear model $\mathcal{N}$:

$$\Theta_N(u, G_{pk}) = \lim_{T \to \infty} \frac{\|G_{pk}[u] - N[u]\|_{VT}}{\|N[u]\|_{VT}}$$  (2.53)

In our simulations, for computational reasons we have only considered the following discrete set:

$$G_{pk} \in \{G_{P_{0.1}}, G_{P_{0.5}}, G_{P_{1.0}}\}$$  (2.54)

$$A_0 \in \{0.1, 0.5, 1.0\}$$  (2.55)

$$A \in \{0.1, 0.2, 0.5, 1.0\}$$  (2.56)

$$\omega \in \{0.001, 0.01, 0.1, 1.0\}$$  (2.57)

$A_0$ represents the offset value between 0.1 and 1.0 [vol%], this values covers the usual mean concentration range. The variations from the mean concentration is expressed through the amplitude value $A$, the usual changes are located between 0.1/0.2 [vol%] (for low changes) and 1.0 [vol%] (for big changes). The choice of the frequency bandwidth depends on the control bandwidth. The fraction between the total blood volume and the cardiac output (CO, the amount of blood flowing from the hearth to the arteries) gives us an approximation of the blood mixing time constant:

$$T_{\text{mix}} = \frac{V}{CO} = \frac{0.08 W_{kg}}{0.2 W_{kg}^{3/4}} = 0.4 W_{kg}^{1/4} = \begin{cases} 0.8 \text{ [min]} & \text{for } W_{Kg} = 32 \text{ [kg]} \\ 1.2 \text{ [min]} & \text{for } W_{Kg} = 81 \text{ [kg]} \end{cases}$$  (2.58)
where \( W_{Kg} \) is the body weight in kg. The relation between \( V \), \( CO \) and \( W_{Kg} \) was taken from [62]. A reasonable bandwidth of the model due to this transport time constant (around 1 minute) is therefore:

\[
\omega \leq \frac{2\pi}{T_{me} / 10} \leq 1.0 \ [\text{rad/sec}]
\]  

(2.59)

Since no negative inputs are allowed there are only 96 from 144 possible combinations. In the appendix C complete simulation results are presented in table format. If we compute:

\[
\Theta_N^k = \inf_{G_{\delta \omega}} \sup_{u \in U} \Theta_N(u, G_{P_k})
\]  

(2.60)

we found that \( G_{P0.5} \) is the best linearized model representing the nonlinear system, but if we analyze the single values we will observe that the differences between models mainly depends on the mean working region expressed by \( A_0 \).

<table>
<thead>
<tr>
<th>( G_{P_k} )</th>
<th>( A_0 )</th>
<th>( A_0 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0e-01</td>
<td>5.0e-01</td>
<td>1.00e+02</td>
</tr>
<tr>
<td>5.0e-01</td>
<td>1.97e+00</td>
<td>1.99e+01</td>
</tr>
<tr>
<td>1.00e+02</td>
<td>3.76e+01</td>
<td>4.51e+00</td>
</tr>
<tr>
<td>inf_{G_{\delta \omega}}</td>
<td>( G_{P0.1} )</td>
<td>( G_{P0.5} )</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>( G_{P_k} )</th>
<th>( A_0 )</th>
<th>( A_0 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0e-01</td>
<td>5.34e+02</td>
<td>5.21e+03</td>
</tr>
<tr>
<td>5.0e-01</td>
<td>7.11e+01</td>
<td>1.15e+03</td>
</tr>
<tr>
<td>1.04e+03</td>
<td>5.29e+02</td>
<td>1.79e+02</td>
</tr>
<tr>
<td>inf_{G_{\delta \omega}}</td>
<td>( G_{P0.1} )</td>
<td>( G_{P0.5} )</td>
</tr>
</tbody>
</table>

Table 2.2: Role of frequency and of the working point for the performance of the linearization. The table shows the nonlinearity measure obtained from equation 2.53. In the last row the best model of three for a defined offset \( A_0 \) is indicated.

As expected, for low amplitudes and frequency the best value is always obtained with the model linearized at that point. The nonlinearity value increases quickly with increased amplitudes on the inputs: this means that the nonlinearity of the system is rather high. In table 2.2 the nonlinearity values of signals with same amplitude \( A \) and frequency \( \omega \) obtained with different \( G_{P_k} \) are compared. The comparison shows that for small frequencies and amplitudes, the reduction in the nominal point is considerably better (first table on table 2.2). On the other side very close results were obtained on high frequencies (second table on table 2.2).
2.5 Model reduction

In conclusion, as expected the nominal linear plant results to be the best model to approximate the nonlinear system. However considering the similarity between models error on input signals of high frequencies there is not a big need of model switching during control if the signals remains mainly within a band of ±0.4 vol%. The gain factor variation error (uncertainty) is sufficiently suppressed by using a well tuned regulator with integral action. The low frequency gain error (see figure 2.4) can be easily compensated with an integral control part in closed loop control.

2.4.2 Sensitivity of the linearized system

By defining parameter set bounds $B_{NL}$ of the physiological parameters describing the nonlinear system, it is possible to derive the parameter set bound of the linearized system $B_L$. Unfortunately linearization is a nonlinear transformation. This will imply that the resulting $B_L$ will not be necessarily a closed set. A sensitivity analysis will therefore lead to a conservative solution because some combination of parameter changes that will be analyzed could be physiologically non realistic. Due to the complexity of the problem, we will therefore not focus this work on parameter sensitivity.

It is interesting to observe that [55, 63] have shown that in order to match a model adequately to a patient, standard values can be used for the distribution of body mass, cardiac output between tissues and organs and for the tissue/gas partition coefficients, but that it is necessary to know total body mass, alveolar ventilation, cardiac output and perhaps blood/gas partition coefficient in the individual patient: e.g. the model of a patient of 120 kg weight is approximatively 2 times slower than the model of a 60 kg patient. In our model we will set individually the weight and the respiratory parameters. The cardiac output can be estimated by the weight dependent Brodys relation ([62]).

2.5 Model reduction

This section describes a possible model reduction strategy for the pharmacokinetic and pharmacodynamic model of anaesthesia gas. This model will be used as a single input, multiple output (SIMO) model where $MAP$, $P_t$ and $P_e$ are the measured values. The goal of this part is to find a single reduced model for all three measurements. The first part of this section will give some motivations and the model reduction strategy. The second part will illustrate the characteristics of the reduced system.

The main goal of modeling was to find mathematical models that allow the implementation of model based controllers. Not all physically motivated models (derived from first principles) will be suitable for closed loop control: the system has to be reduced to its minimal realization (see [64]). This means that all states of the considered system must be controllable and observable. In our case the linearized system satisfies the controllability and observability conditions for all states (see quantitative results in chapter 5). But not all states have the same influence on the input/output behaviour. For control purposes, we are not interested in
weakly observable and controllable states: due to system uncertainty, such subsystems will be in any case hard to distinguish from disturbances and very difficult to control.

With the controllability and the observability gramians \(G_c\) resp. \(G_o\):

\[
G_c = \int_0^\infty e^{At}BB^Te^{At^T} \, dt
\]

(2.61)

\[
G_o = \int_0^\infty e^{At}C^TCe^{At^T} \, dt
\]

(2.62)

(2.63)

it is possible to define separately some degree of controllability or observability, but it is not possible to give accurate indications of the dominance of system states in the input/output behaviour. [65] proposed a balanced realization of the system where \(\hat{G}_c = \hat{G}_o = \Sigma\). The balanced realization is obtained by a state space transformation \(T\) such that \(\hat{x} = Tx\). Assuming an asymptotic stable system \(G(\hat{A}, \hat{B}, \hat{C}, \hat{D})\), the balanced realization \(G(\hat{A}, \hat{B}, \hat{C}, \hat{D})\) will be:

\[
G = \begin{bmatrix}
\hat{A} & \hat{B} \\
\hat{C} & \hat{D}
\end{bmatrix} = \begin{bmatrix}
T\hat{A}T^{-1} & TB \\
CT^{-1} & D
\end{bmatrix}
\]

(2.64)

\(T\) will be chosen in order that \(G_c = G_o = \Sigma\) where:

\[
\Sigma = \text{diag}(\sigma_1, \sigma_2, \ldots, \sigma_n)
\]

(2.65)

\(\sigma_1 \geq \sigma_2 \geq \cdots \geq \sigma_n\) are called the \textit{Hankel singular values} (for more details see [66]). With this form controllability and observability of each state are identical and therefore strongly related to each other. The singular values decomposition of the Gramians allows to identify the weakly controllable (and observable) states. The truncation of these states will lead to a reduced balanced asymptotically stable system ([65]). Mathematically, the following theorem will hold (equivalent to theorem 7.3 of [66]):

\textit{Suppose} \(G(s) \in \mathcal{RH}_\infty\) \textit{and}

\[
G(s) = \begin{bmatrix}
A_{11} & A_{12} & B_1 \\
A_{21} & A_{22} & B_2 \\
C_1 & C_2 & D
\end{bmatrix}
\]

is a balanced realization with Gramian \(\Sigma = \text{diag}(\Sigma_1, \Sigma_2)\)

\[
\Sigma_1 = \text{diag}(\sigma_1I_{s_1}, \sigma_2I_{s_2}, \ldots, \sigma_rI_{s_r})
\]

(2.68)

\[
\Sigma_2 = \text{diag}(\sigma_{r+1}I_{sr+1}, \sigma_{r+2}I_{sr+2}, \ldots, \sigma_NI_{s_N})
\]

(2.69)

and

\[
\sigma_1 \geq \sigma_2 \geq \cdots \geq \sigma_r \geq \sigma_{r+1} \geq \sigma_{r+2} \geq \cdots \sigma_N
\]

(2.70)

where \(\sigma_i\) has multiplicity \(s_i\) \(i = 1, 2, \ldots, N\) and \(s_1 + s_2 + \cdots + s_N = n\). Then the truncated system

\[
G_r(s) = \begin{bmatrix}
A_{11} & B_1 \\
C_1 & D
\end{bmatrix}
\]

(2.71)
2.6 Parameter set of the patient

is balanced and asymptotically stable. Furthermore

\[ ||G(s) - G_r(s)||_\infty \leq 2(\sigma_{r+1} + \sigma_{r+2} + \cdots + \sigma_N) \]  

(2.72)

and the bounds are achieved if \( r = N - 1 \), i.e.,

\[ ||G(s) - G_r(s)||_\infty = 2\sigma_N. \]  

(2.73)

The resulting Hankel singular values of the pharmacokinetic and pharmacodynamic model of anaesthesia gases can be divided in two main groups:

| \( \sigma_1 \) | \( \sigma_2 \) | \( \sigma_3 \) | \( \sigma_4 \) | \( \sigma_5 \) |
| 1.03 \times 10^1 | 2.65 \times 10^0 | 4.73 \times 10^{-1} | 3.81 \times 10^{-1} | 2.40 \times 10^{-2} |

| \( \sigma_6 \) | \( \sigma_7 \) | \( \sigma_8 \) | \( \sigma_9 \) | \( \sigma_{10} \) | \( \sigma_{11} \) | \( \sigma_{12} \) |
| 6.26 \times 10^{-3} | 1.81 \times 10^{-3} | 5.49 \times 10^{-5} | 8.61 \times 10^{-6} | 1.16 \times 10^{-6} | 2.06 \times 10^{-7} | 3.32 \times 10^{-8} |

Observe that the error bound calculated from (2.72) decreases in a logarithmic way in function of the number of states considered (see figure 2.5). To achieve an error less than 1%, a system of order 5 must be considered, for an error less than 3% a system of order 3 is needed. It may be interesting to note that the full system goes to a 180° phase shift and has therefore a relative degree of 2. The Bode diagram of figure 2.6 shows a comparison between different reduction degrees. A reduction to order 2 will reproduce the plant only to a frequency of 0.2 [rad/sec] around the 90 degree of phase shift. This bandwidth does not cover the requested band (see equation 2.59). Systems of higher order will have a useful bandwidth to 7 [rad/sec] and a phase shift clearly below the 90 degrees which is within the expectations. The bandwidth behaviour from 3th to 5th order systems is sufficient and does not need any optimizations through frequency weighted balanced model reduction methods ([67]) since it does not have any additional particular need on the frequency band behaviour. Another interesting analysis of the system can be done through the observation of the pole/zero locations of the system. All poles and zeros are on the LHS of the real axis (see figure 2.7 first line). It is interesting to observe that 7 poles and 7 zeros are very close together. This will lead to an intuitive reduction to at least order 5. The reduction by balanced truncation confirms this intuitive result and shows that the system can even be reduced to order 3 without loss of the main pole and zero symmetry (see figure 2.7) If we consider again the reasonable bandwidth of equation 2.59 due to transport effects in blood circuit and all aspect described above, a model reduction from third to fifth degree can be applied.

2.6 Parameter set of the patient

The nonlinear model of the pharmacokinetics and pharmacodynamics of anaesthesia gases in the human body described in chapter 2 is characterized by the parameters described in table 2.3 (we will call this parameter set as the consolidated parameter set).
Figure 2.5: Error bounds in percentage from the maximal error bound value ($r = 1$).

<table>
<thead>
<tr>
<th>parameter</th>
<th>description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\lambda_i$</td>
<td>gas solubility in the $i$th compartment</td>
</tr>
<tr>
<td>$\lambda_b$</td>
<td>gas solubility in blood</td>
</tr>
<tr>
<td>$V_{i,b}$</td>
<td>Volume of blood part of the $i$th compartment</td>
</tr>
<tr>
<td>$V_{i,t}$</td>
<td>Volume of tissue part of the $i$th compartment</td>
</tr>
<tr>
<td>$g_i$</td>
<td>conductivity of the $i$th compartment</td>
</tr>
<tr>
<td>$b_i$</td>
<td>Factor describing affinity of conductivity of the $i$th compartment to anaesthesiagas concentration in the compartment $p_i$</td>
</tr>
<tr>
<td>$I_s$</td>
<td>Lung shunt</td>
</tr>
<tr>
<td>$a_1, a_2, a_A$</td>
<td>Factor describing affinity of cardiac output of the first (resp. the second or the arterial compartment) to anaesthesiagas concentration $p_1$ (resp. $p_2$ or $p_A$)</td>
</tr>
<tr>
<td>$CO_0$</td>
<td>Cardiac output without any anaesthesiagas</td>
</tr>
<tr>
<td>$V_a$</td>
<td>Functional residual capacity</td>
</tr>
</tbody>
</table>

Table 2.3: Setting parameters of the model of the pharmacokinetic and pharmacodynamic of anaesthesia gases in the human body described in chapter 2
2.6 Parameter set of the patient

Figure 2.6: Comparison of the bode diagrams of the linearized model of order 12 (-) and the balanced truncations of order 2 (-), 3 (-), 4 and 5 (both not distinguishable from the unreduced model).

Figure 2.7: Zeroes (o) and poles (x) of the linearized system (first line), from the reduced system by balanced truncation to order 2 (second line), 3 (third line), 4 (fourth line) and 5 (fifth line). All poles and zeroes have no imaginary part, they are shifted for representation reasons.

All parameters have a direct physiological meaning but unfortunately most of them can not be found in the literature or are not intuitive for the anaesthetist. In addition there is no decoupling between parameters describing the patients physiological characteristics and parameters describing anaesthesia characteristics. To define the parameter value appropriately, we will start from a conventional parameter set (see figure 2.8) allowing:
• an explicit use of statistics found in the literature,

• a stronger decoupling between patient dependent and anaesthesiagas dependent parameters,

• a more intuitive approach for setting a wide range of different parameter sets describing different patient groups,

• a coherent setting of the parameters (avoiding contradictory settings). This means that the parameter number is equal to the degree of freedom.

Figure 2.8: Data from the literature, measurements or from the anaesthetic experience can be easily expressed in values of the conventional parameter set. From this set, mathematical relations allow to define the parameter values of consolidated model used for simulation.

In this section we will describe this conventional parameter set and the mathematical relations with the consolidated parameter set.

2.6.1 Conventional parameter set

This parameter set can be divided into three group of parameters. The first group (including $\lambda_i$ and $\lambda_o$) are strictly parameters describing gas properties mainly independent from body characteristics. The second group (including $l$, $W_kg$, $K_{ub}$, $K_{ut}$, $K_{tissue,i}$, $K_{blood,i}$, $K_{flow,i}$, $CO_2$, $MAP_{init}$) is composed by parameters that describes physiological characteristics of the body. This part represents the parameter description of the pharmacokinetics. Some of them can be measured, the others are expressed in typical distribution factors (how many parts of the whole is this attribute belonging to this compartment), that can be easily modified to describe pathologic cases. The third part, composed by $\Delta MAP_{test}$, $P_{test}$, $\Delta_{flow,i}$, $\hat{a}_1$, $\hat{a}_2$ and $\hat{a}_A$, describe the pharmacodynamic effects of anaesthesia gas in the body. This description is done mainly through data extracted from the body saturated with a test concentration $P_{test}$ of anaesthesia gas. Motivated by the affine relations describing pharmacodynamics (see
2.6 Parameter set of the patient

<table>
<thead>
<tr>
<th>parameter</th>
<th>description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\lambda_i$</td>
<td>Gas solubility in the $i$th compartment</td>
</tr>
<tr>
<td>$\lambda_0$</td>
<td>Gas solubility in blood</td>
</tr>
<tr>
<td>$l_s$</td>
<td>Lung shunt</td>
</tr>
<tr>
<td>$V_a$</td>
<td>Functional residual capacity</td>
</tr>
<tr>
<td>$W_{kg}$</td>
<td>Body weight in [kg]</td>
</tr>
<tr>
<td>$K_{wb}$</td>
<td>Relation between blood volume and $W_{kg}$</td>
</tr>
<tr>
<td>$K_{wt}$</td>
<td>Relation between tissue volume and $W_{kg}$</td>
</tr>
<tr>
<td>$K_{tissue,i}$</td>
<td>Part of body tissue volume belonging to the $i$th compartment</td>
</tr>
<tr>
<td>$K_{blood,i}$</td>
<td>Percentage of body blood volume belonging to the $i$th compartment</td>
</tr>
<tr>
<td>$CO_0$</td>
<td>Cardiac output without any anaesthesiagas</td>
</tr>
<tr>
<td>$MAP_0$</td>
<td>MAP concentration without anaesthesiagas in the body</td>
</tr>
<tr>
<td>$p_{test}$</td>
<td>Test anaesthesiagas concentration</td>
</tr>
<tr>
<td>$\Delta MAP_{test}$</td>
<td>Change of $MAP_0$ with $p_{test}$ anaesthesiagas concentration saturated in all tissues of the body.</td>
</tr>
<tr>
<td>$K_{flow,i}$</td>
<td>Part of $CO_0$ flowing through the $i$th compartment, if no anaesthesiagas is in the body</td>
</tr>
<tr>
<td>$\Delta_{flow,i}$</td>
<td>Percentage of flow rate change in the $i$th compartment with $p_{test}$ anaesthesiagas concentration in the body in respect to the case described with $K_{flow,i}$</td>
</tr>
<tr>
<td>$\hat{a}_1$, $\hat{a}_2$, $\hat{a}_A$</td>
<td>Weights describing affinity of cardiac output of the first (resp. the second or the arterial compartment) to anaesthesiagas concentration $p_1$ (resp. $p_2$ or $p_A$)</td>
</tr>
</tbody>
</table>

Table 2.4: Alternative setting parameters of the model of the pharmacokinetic and pharmacodynamic of anaesthesiagas in the human body described in chapter 2
equations 2.11 and 2.12), a linear interpolation will be done to find the original parameter settings \((a_i, b_i)\). \(\Delta MAP_{test}\) and \(\Delta flow_{i}\) describe the changes on \(MAP\) and blood flows on the body during the test phase, because relative data are mostly used in the literature to describe pharmacodynamic.

### 2.6.2 From the conventional to the consolidated parameter set

In this section we will describe the mathematical relations allowing to find the values of the consolidated parameter set from the conventional parameter set.

**Setting the initial cardiac output \((CO_0)\)**

If not set manually, \(CO_0\) is given by Brodys relation (see [62]):

\[
CO_0 = 0.2 \ W_{kg}^{3/2} \ [l/min]
\]  

(2.74)

**Determination of compartments volumes**

The different blood and tissue volumes are calculated from the assumed proportionality to the body weight and their distribution weights \((K_{tissue,i} \text{ and } K_{blood,i})\):

\[
V_{i,t} = \frac{K_{tissue,i}}{g} (K_{wt} \ W_{kg}) \sum_{i=1}^{K_{tissue,i}} \]

\[
V_{i,b} = \frac{K_{blood,i}}{g} (K_{wb} \ W_{kg}) \sum_{i=1}^{K_{blood,i}}
\]

(2.75)

(2.76)

Normally \(K_{wb}\) is set to 0.07 liter per kg body weight, while 0.75 will be used for \(K_{wt}\). It is to be observed that \(K_{tissue,i}\) and \(K_{blood,i}\) are not percentages but distribution weights. This is equivalent to percentages if the sum of all factors is 100 (or 1 depending of the scaling). This was done because data in the literature are often referenced to a normed compartment: assertion like "compartment 1 is 2 times bigger than one" can then be more easily translated into numbers.

**Determination of conductivity related parameters**

From the affine relation of equation 2.11, \(g_{i,0}\) and \(b_i\) are the necessary parameters to determine the conductivity. The alternative parameter set describe the blood flow distributions when
\[ p_i = 0 \forall i \text{ and when } p_i = p_{\text{test}} \forall i. \] From this data it is possible to derive \( g_{i,0} \) and \( g_{i,p_{\text{test}}} \), and therefore \( b_i \) from equation 2.11:

\[
b_i = \frac{g_{i,p_{\text{test}}} - 1}{p_{\text{test}}}
\]

(2.77)

To find all conductivities, it is first necessary to convert the blood flow distribution factors of table 2.4 into flows \( q_i \). To define blood flows through the different compartments without any anaesthesia \( p_i = 0 \), the same procedure as in equations 2.75 and 2.76 was used:

\[
q_i(0) = CO_0 \frac{K_{\text{flow},i}}{\sum_{i=1}^{9} K_{\text{flow},i}}
\]

(2.78)

In the literature it is possible to find the average changing of blood flow in some compartments saturated with a test concentration \( p_{\text{test}} \) of anaesthesiagas. The effective blood flow with \( p_i = p_{\text{test}} \) in the \( i \)th compartment can then be written as:

\[
q_i(p_{\text{test}}) = CO_0 \left( \frac{K_{\text{flow},i}}{\sum_{i=1}^{9} K_{\text{flow},i}} \right) \left( 1 + \Delta_{\text{flow},i} \right)
\]

(2.79)

The sum of these blood flows gives the cardiac output if the body is saturated with \( p_{\text{test}} \) gas concentration:

\[
CO_{\text{test}} = \sum_{i=1}^{9} q_i(p_{\text{test}})
\]

(2.80)

With

\[
MAP_{\text{test}} = MAP_0 (1 + \Delta MAP_{\text{test}})
\]

(2.81)

The total conductivities can be defined from equation 2.10:

\[
g_{\text{tot},0} = \frac{CO_0}{MAP_0} = \sum_{i=1}^{9} g_{i,0}
\]

(2.82)

\[
g_{\text{tot},p_{\text{test}}} = \frac{CO_{\text{test}}}{MAP_{\text{test}}} = \sum_{i=1}^{9} g_{i,p_{\text{test}}}
\]

(2.83)

And finally, the conductivities can be written as:

\[
g_{i,0} = g_{\text{tot},0} \frac{K_{\text{flow},i}}{\sum_{i=1}^{9} K_{\text{flow},i}}
\]

(2.84)

\[
g_{i,p_{\text{test}}} = g_{\text{tot},p_{\text{test}}} \frac{q_i(p_{\text{test}})}{CO_{\text{test}}}
\]

(2.85)
Affinity to the CO

$a_1$, $a_2$ and $a_A$ are factors describing affinity of cardiac output to the anaesthesia gas concentrations. From experimental data, it is possible to determine (approximatively) changes on the cardiac output in relations with anaesthesiagas concentrations. The physiological sources of influence are not exactly known. With the alternative data set, instead of giving absolute values of these pharmacodynamic parameters, relative values (weights) are expected. The CO changes, explicable through affinity described in equation 2.12, are distributed proportionally to the weights given with $a_1$, $a_2$ and $a_A$:

$$\text{CO} = \frac{1}{a_1 + a_2 + a_A} \left(1 + a_1 p_1 + a_2 p_2 + a_A p_A \right)$$ (2.86)

2.6.3 Gas dependency of parameters

As mentioned, the conventional parameter set allows the decoupling of the patient’s body characteristics from parameter correlated with the anaesthesiagas. Parameter sets for 6 gases (halothane, isoflurane, desflurane, enfurane, sevoflurane, $N_2O$) are defined in appendix B.2

2.7 Model validation and identification

2.7.1 Validation

The nonlinear model was validated by a medical PhD thesis (see [58]). There, a very thorough bibliographic research was done in order to find as much statistical data as possible for the physiological parameters of the nonlinear model (see table 2.4). The obtained parameters were validated on the consulted literature. To validate the performance of the model arterial blood probes were collected in regular time intervals during long operations. The measured inspired concentration was used as input of our nonlinear model and the expected arterial concentration was simulated. Figure 2.9 shows a representative result of such a comparison. We observe that the dynamic behaviour seems well reproduced through the model. Only after a large inspired anaesthesia gas step and after more than 3 hours a larger low frequency error appears. It can be easily compensated by the integral action of the controller.
Figure 2.9: Comparison between measured and simulated isoflurane arterial isoflurane concentration.
Chapter 3

The breathing system

Most of the breathing systems used for anaesthesia are in form of semi-closed circuits. In these circuits, the $CO_2$ of a part of the expired gases is eliminated. This part of gas is reused after an enrichment of new anaesthetic gases (including oxygen, of course). The exceeding gas is blown off the circuit. The amount of the exceeding gas depends on the fresh gas flow and the construction of the system. Such engines are characterized by time periodic structural changes, due to changing valve configurations, and the nonlinear periodic behaviour of a pump, which determines the breathing flows and pressures. Furthermore, we will see that some elements of the system, such as the manual breathing bag, the $CO_2$ absorber and patient’s lung are nonlinear and determine the dynamic behaviour of the plant. In this section we will begin with a technical description of the breathing system used. After that a first principles model (see figure 1.8) will be derived in order to understand and simulate the very complex behaviour of the system. This model is constructed as a set of independent dynamical subsystems. After a detailed validation of all single elements, this strategy would allow the construction of any possible breathing system configuration and allow an estimate of the possible dynamical behaviour. However such a complex model structure is not suitable for automatic control and must be linearized and reduced. Unfortunately the system is characterized by different valves which cause some periodical and state dependent structure switches. These structural switches would force the building of linearized models for each structure configuration and make the goal of model reduction very hard to attain. On the other hand the control bandwidth extends to $\omega = 1 \text{ [rad/sec]}$ and needs only good models up to $\omega = 10 \text{ [rad/sec]}$. For this reason we decided to implement a trivial model, where the parameters are identified from measurement (if there are available) or from simulation (to cover the whole operational space). Considering the high and complex dependence of the parameter values of the simplified system from the respiratory set parameters, such a strategy saves time and reduces measurement effort.
3.1 Description of the system

Figure 3.1 shows the structure of the breathing system used (Drägerwerk AG, Cicero). The system is characterized by time periodic structural changes due to a cyclic valve switching and periodic pump cylinder movement. During the inspiratory phase the gas flows from the pump unit through the inspiratory pipe path into the patient's lung. The excess valve ($V_2$) and the fresh gas path valve ($V_1$) are closed. After the inspiratory pause, $V_2$ is opened (begin of the expiratory phase). The expiratory phase can be divided into five different valve configurations. Depending on the pressure measurement and the time elapsed, some configurations will not appear during a breathing cycle. During the first moment (approximately 160 ms) lung gas will flow into the manual ventilation bag. After that, the pump begins to move in order to fill the pump cylinder. This piston backward movement is done within 1.22 sec. A switch to a new configuration is made if $V_2$ is opened while the pump piston is moving. $V_2$ is opened at least during 80 ms (180 ms before the end of expiratory phase time), but will open as soon as the pressure at pump output increases during 250 ms. At the end $V_2$ is closed, $V_1$ is open and the pump has finished its movement. The scheme on table 3.1 shows the different configurations during the respiratory cycle. There exist two possible sequences on configuration switching (see table 3.1). Crucial is the opening time point of $V_2$. 
3.2 Ideal gas laws

For our model we will neglect the influence of attractive force between molecules and of the volume of the gas molecule themselves and therefore we will use the ideal gas equation (see 3.1) instead of the Van der Waals’s equation.

\[ PV = NRT \quad (3.1) \]

Where \( N \) is the mole fraction of a gas. The mole fraction can also be written as the fraction between the gas mass \( m \) and the mole mass \( m^* \), (see 3.2).

\[ N = \frac{m}{m^*} \quad (3.2) \]

Since we are modeling a system with a gas mixture we have to apply Dalton’s law: The total pressure of a gas mixture can be divided among the partial pressures of the components in the mixture in proportion to the mole fraction of each gas (at same volume and temperature condition) (3.4).

\[ P = \sum_i p_i \quad (3.3) \]
\[ N = \sum_i N_i \quad (3.4) \]
It is to be observed that the total pressure of the mixture is not proportional to the total mass but is linearly dependent to the masses of each gas component (3.5).

\[ P = \sum_i \frac{m_i}{m_i^*} \frac{RT}{V} \]  

Another important law was formulated by William Henry (1774-1836): At constant temperature, any gas physically dissolves in a liquid in proportion to its partial pressure, although the solubility coefficient decreases with increasing temperature and differs from one gas to another. Of course this law applies only to physical solution and ignores any amount of gas that may chemically combine, as CO\(_2\) combines with an alkaline solution or as O\(_2\) combines with hemoglobin.

3.3 Model elements

The model of the breathing system is a model of a gas pipe going through different elements (figure 3.2). This gas pipe can be divided into following units of different types:

<table>
<thead>
<tr>
<th>Elementary units</th>
<th>Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tube</td>
<td>Tu(_i)</td>
<td>Tube</td>
</tr>
<tr>
<td>T-piece</td>
<td>T(_i)</td>
<td>T-pieces</td>
</tr>
<tr>
<td>Bag</td>
<td>B</td>
<td>Manual ventilation bag</td>
</tr>
<tr>
<td>Pump</td>
<td>P</td>
<td>Pump</td>
</tr>
<tr>
<td>Outlet</td>
<td>OUT</td>
<td>Outlet</td>
</tr>
<tr>
<td>Absorber</td>
<td>A</td>
<td>Absorber</td>
</tr>
<tr>
<td>Fresh gas</td>
<td>FF</td>
<td>Fresh gas source connection</td>
</tr>
<tr>
<td>Lung</td>
<td>L</td>
<td>Lung and connection with Patient</td>
</tr>
</tbody>
</table>

We are interested in the partial pressure of each gas component in each system segment. If we consider each segment as an ideal compartment, we are interested in the incoming and outgoing amount of gas from and to the compartment. Each section type has its own dynamic behaviour due to its specific functionality, but all sections are based on the same gas laws.

3.3.1 General compartment

Let us define a general compartment with \( n \) connections (see figure 3.3). Gas exchange between elements is only possible through these connection points. Gas is exchanged only if a pressure difference exists which generates a flow. No exchange through diffusion is assumed. Gas mixing in the compartment is considered ideal (fast and uniform). The relation between flows and pressure difference is assumed to be linear (see equation (3.6), \( F_i \) is the gas flow...
3.3 Model elements

Figure 3.2: Block diagram of the breathing system. Equal block types have an equivalent dynamic behaviour.

![Block diagram of the breathing system](image)

Figure 3.3: General compartment for the modeling of the respiratory cycle. The arrows defines the positive flow direction. Flows can also be negative.

coming from the i-th neighbor element, $P_{ni}$ is the pressure of this element and $R$ is the resistance of the i-th connection).

$$F_i = \frac{P_{ni} - P}{R_i} \quad (3.6)$$

The flow amount of any single gas component ($m$ is the number of gas component in a gas mixture) is assumed to be proportional to the gas composition of the source compartment (see eq. (3.7), $i = 1 \cdots n$, $j = 1 \cdots m$). One can observe that this is not equivalent to the difference of the respective partial pressure.

$$F_{ij} = \begin{cases} F_i \frac{P_j}{P} & \text{if } F_i < 0 \\ F_i \frac{P_{ni}}{P_{ni}} & \text{if } F_i \geq 0 \end{cases} \quad (3.7)$$
The mass balance differential equation (3.8) is the sum of all incoming flows multiplied by their densities.

\[
\dot{m} = \sum_{i=1}^{n} \rho_i F_i \quad (3.8)
\]

Flow density decreases almost linearly from the source compartment to the target. The mean values between source and target density can be a good approximation of flow density (3.11). But since changes in gas concentrations and pressures does not affect the density value significantly, it is possible to assume a constant value. This simplifies the differential equation significantly, without affecting simulation results seriously.

\[
\rho_i = \sum_{j=0}^{m_j} \frac{m_j}{RT} P_{pj} \approx \frac{\bar{m}^*}{RT} P_{pi} = \bar{\rho}_i \quad (3.9)
\]

\[
P_{pi} = \frac{P_{in} + P}{2} = P \pm 1\% \quad (3.10)
\]

If we differentiate the ideal gas equation and insert the mass balance equation, we obtain a bilinear differential equation for the PV product (3.14).

\[
\frac{d}{dt} PV = \frac{\dot{m}}{\bar{m}^*} \sum_{i=1}^{n} \bar{\rho}_i F_i \quad (3.12)
\]

\[
= \frac{RT}{\bar{m}} \sum_{i=1}^{n} \bar{m}^* \frac{P}{RT} P_{pi} F_i \quad (3.13)
\]

\[
= P \rho \sum_{i=1}^{n} F_i \quad (3.14)
\]

Finally we obtain a general description of the compartments:

\[
\dot{P} V + P \dot{V} = P \rho \sum_{i=1}^{n} \frac{P_{in} - P}{R_i} \quad (3.15)
\]

Assuming (3.10) we can easily obtain the equivalent equation of partial pressures:

\[
\dot{P}_j V + P_j \dot{V} = P \rho \sum_{i=1}^{n} F_{ij} \quad (3.16)
\]

Defining the concentration \(c_j\) as the fraction between partial and total gas pressure one can define following relations:

\[
c_j = \frac{P_j}{P} \quad \Rightarrow \quad \dot{P}_j = \dot{c}_j P + \dot{P} c_j \quad (3.17)
\]
Using (3.17) in (3.16) we obtain:

\[ \dot{c}_j \frac{P}{P_p} = \frac{1}{V} \sum_{i=1}^{n} F_{ij} - c_j \left[ \frac{\dot{P}}{P_p} + \frac{P}{P_p} \frac{\dot{V}}{V} \right] \]  

(3.18)

Assuming the effective total pressure \( P \) and the pressure at the mean density \( P_p \) (see eq. 3.11) to be approximatively equal:

\[ \frac{P}{P_p} \approx 1 \]  

(3.19)

and using (3.6) and (3.15) we finally obtain:

\[ \dot{c}_j = \frac{1}{V} \left[ \sum_{i=1}^{n} F_{ij} - F_i \dot{c}_j \right] \]  

(3.20)

This equation can also be found by defining as the partial volume \( V_j \), the amount of fictive volume of density \( \bar{p} \) occupied by a specific gas. From (3.11) it is possible to assume that this volume is proportional to its concentration:

\[ V_j = \frac{P_j}{P} V \]  

(3.21)

this means that:

\[ c_j = \frac{P_j}{P} \approx \frac{V_j}{V} \]  

(3.22)

By differentiation of (3.21) we obtain a balance equation of incoming and outgoing moles of a certain gases under the mentioned simplifying assumptions:

\[ \dot{V}_j = \sum_{i=1}^{n} F_{ij} \]  

(3.23)

Finally the differentiation of (3.22) gives:

\[ \dot{c}_j = \frac{\dot{V}_j}{V} - \frac{\dot{V}_j}{V^2} V_j \]  

(3.24)

which leads to the same equation of (3.20). The assumption of (3.22) has been often used in literature and we show it to be equivalent to starting from the general gas laws and using the simplifying assumptions (3.10), (3.11) and (3.19)).

### 3.3.2 Model implementation

Resuming the general model description, the following steps must be implemented in a simulation environment (such as ACSL\(^1\) or MATLAB/SIMULINK\(^2\)) to correctly realize a single model element:

\(^1\)ACSL (Advanced Continuous Simulation Language) is a trademark of Mitchell and Gauthier Associates (MGA), Inc., Concord MA 01742, USA

\(^2\)MATLAB and SIMULINK are trademarks of The Math Works, Inc., Natick, Massachusetts 01760, USA
1. Determine the total flow amount incoming/outgoing from a compartment \( F_i \) (see equation 3.6)

2. Determine the partial flow amount incoming/outgoing from a compartment \( F_{ij} \) (see equation 3.7)

3. Solve the differential equation (3.15) and find \( P \) and \( V \);

4. Solve the differential equations (3.20). To not over determine the system, only \( m - 1 \) equation have to be solved, \( c_m \) can then be found from:

\[
\sum_{j=1}^{m} c_j = 1
\]  

(3.25)

With exception of the source blocks (fresh gas and outlet) all block units follow the equations (3.15), (3.16) or (3.20). The only differences are the definition of \( V \), \( P \) and the number of connections. Table 3.3 will resume these differences. In the next sections we will explain the characteristic behaviour of each compartment. \( V_0 \) is the volume of the chamber at atmospheric conditions. In many compartments at the working point the volume of the chamber \( (V) \) is affine to the relative pressure (see equations 3.26 and 3.27). The relative pressure \( (\Delta P) \) is the difference of the external \( (P_{out} \), usually the atmospheric pressure) to the internal pressure \( (P) \).

\[
V = \Delta P C + V_0
\]  

(3.26)

\[
\Delta P = P_{out} - P
\]  

(3.27)

The factor \( C \) is usually called compliance. In reality \( C \) is often nonlinearly dependent of \( P \), but in our case it can be linearized around the working point.

### 3.3.3 Model of a Tube

A tube is the connection piece between different compartments. Its length is on a range between 7.5 and 150 cm. Its principal characteristics are:

<table>
<thead>
<tr>
<th>Unit</th>
<th>Number of Connections</th>
<th>Volume</th>
<th>Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tube</td>
<td>2</td>
<td>( V_0 + C \ P(t) )</td>
<td>( P(t) )</td>
</tr>
<tr>
<td>T-piece</td>
<td>3</td>
<td>( V_0 )</td>
<td>( P(t) )</td>
</tr>
<tr>
<td>Bag</td>
<td>1</td>
<td>( V(P) )</td>
<td>( P(t) )</td>
</tr>
<tr>
<td>Pump</td>
<td>1</td>
<td>( V(t) )</td>
<td>( P(t) )</td>
</tr>
<tr>
<td>Absorber</td>
<td>3</td>
<td>( V_0 + C \ P(t) )</td>
<td>( P(t) )</td>
</tr>
<tr>
<td>Lung ( \geq 5 )</td>
<td></td>
<td>( V_0 + C \ P(t) )</td>
<td>( P(t) )</td>
</tr>
</tbody>
</table>

Table 3.3: Comparison between different block units of the respiratory system.
1. A very small compliance

2. Long pipes have some time delays

A more precise model is described by an infinity of identical tube segments. To reduce the order of the system let us consider only segments of 7.5 cm of length. Solving equation (3.15) by introducing (3.26) gives the dynamic behaviour of this unit:

\[
\dot{P} = \frac{P_p}{V_0 + C (2P - P_{atm})} \sum_{i=1}^{2} \frac{P_{in_i} - P}{R_i}
\]  

(3.28)

A good approximation gives finally:

\[
\dot{P} = \frac{P}{V_0 + C P} \sum_{i=1}^{2} \frac{P_{in_i} - P}{R_i}
\]  

(3.29)

Since 60 mbar pressure variation corresponds to maximal 6 % variation in time constant, which is within tolerance, we can consider a tube unit as a first order linear System (eq. 3.30).

\[
\dot{P} = K_{tub} \sum_{i=1}^{2} \frac{P_{in_i} - P}{R_i}
\]  

(3.30)

\[
K_{tub} = \frac{P}{V_0 + C P}
\]  

(3.31)

\[K_{tub}\] is often approximated with the inverse of compliance in the literature (e.g. [50]), this is only true if \(V_0 \ll CP\). In this case:

\[V_0 = 2 \pi 0.75^2 7.5 \text{ cm}^3\]  

(3.32)

\[= 26.5 \text{ cm}^3\]

\[CP = 5 10^{-5} 10^6\]  

(3.33)

\[= 50 \text{ cm}^3\]

\[K_{tub} = 1.315 10^5\]  

(3.34)

### 3.3.4 The T-piece

This element has a very low compliance (almost zero) and a very fast dynamic on pressure assessment. It can be interpreted as a tube with three connections without compliance (3.35)

\[
\dot{P} = \frac{P_2}{V_0} \sum_{i=1}^{3} \frac{P_{in_i} - P}{R_i}
\]  

(3.35)
3.3.5 The manual ventilation bag

This is a flexible bag which is used by the anaesthetist in case of manual ventilation: high fresh gas flow will then inflate the bag and the tidal volume will be pushed by the anaesthetist into the patient’s lung by pressing periodically on the bag. The bag has therefore a variable volume. The volume depends non-linearly on the pressure difference between inside and outside. The nonlinearity increases monotonically with the pressure and is smooth. It can be approximated by a polynomial (see 3.36).

\[ V(P) = \sum_{i=1}^{n} a_i P^n \quad (3.36) \]

The coefficients of the polynomial was identified by least square fit from measured data of a specific experiment (see section 3.7).

\[ \frac{dV}{dt} = \frac{dV}{dP} \frac{dP}{dt} = \frac{dV}{dP} \dot{P} \quad (3.37) \]

Inserting (3.36) and (3.37) into the general equation (3.15) and solving for \( \dot{P} \) we obtain:

\[ \dot{P} = \frac{P_\rho}{V + \frac{dV}{dP} P} \frac{P_{m1} - P}{R_1} \quad (3.38) \]

3.3.6 The Pump

The pump is an element with time varying controlled volume with a single connection to the inspiratory cycle (this means that \( V(t) \) and \( \dot{V}(t) \) are known). During inspiration the volume of the chamber decreases linearly with time, while it increases linearly during the second expiratory phase (see 3.1). From equation (3.15) we obtain:

\[ \dot{P} = \frac{P_\rho}{V} \frac{P_{m1} - P}{R_1} - P \frac{\dot{V}}{V} \quad (3.39) \]

3.3.7 The \( CO_2 \) Absorber

This element eliminates from the circuit a specific gas (\( CO_2 \)) with a given rate. In all other aspects it behaves like a tube element. The differential equation (3.40) shows this additive term which represents a supplementary outlet. \( P_{CO_2} \) is the \( CO_2 \) partial pressure in the absorber and \( K_{abs} \) the absorber time constant.

\[ \dot{P} = K_A \left( \frac{P_{m1} - P}{R_1} + \frac{P_{m2} - P}{R_2} \right) - K_{abs} P_{CO_2} \quad (3.40) \]

\( K_A \) is derived from equation (3.31).
3.3 Model elements

3.3.8 The Lung

The dynamics of respiration can be found in almost all physiology manuals (survey [68]). In this section we will introduce the most important concept related to the volume and pressure dynamics necessary for our modeling purpose (for more details see the survey [68]).

Physiology of the respiratory tract

The respiratory tract can be divided into 2 main zones:

- **The upper respiratory tract** is composed by nose, pharynx and larynx
- **The lower respiratory tract** from the trachea to the alveoli

The first one is not of interest to us because it is bridged by the intubation. For our purposes it is therefore composed basically by a tube with low compliance characteristics. The lower respiratory tract commences with the trachea (diameter ≈ 2.5 cm) which divides into the two main bronchi, one to each lung. There exist another 23 layers of subdivisions before the alveoli are reached. The first 16 subdivision layers are conducting airways. This means that there will be no gas exchange. The first 11 layers are supported by cartilage and therefore characterized by a low compliance. The 12th to the 16th divisions are called bronchioles and, lacking cartilage, have a higher compliance. The last 6 divisions are composed by the respiratory bronchioles (there is some gas exchange activity due to some alveoli) and the alveolar ducts with the main respiratory zone composed by the alveoli. We therefore divide the lung into 4 compartments having an increasing compliance value (see figure 3.4).

Lung volumes

The volume of air moving in and out of the lung is called the **tidal volume** ($V_T$, at rest it is about 500 ml). The remaining extra volume that can be inhaled voluntarily after a normal inspiration is called the **inspiratory reserve volume** (IRV, about 3 liters). Reversely at the end of a normal expiration, the volume amount that can be exhaled is the **expiratory reserve volume** (ERV, about 1.4 liters). The remaining volume that cannot be expelled from the lung is called the **residual volume** (RV). The **functional residual capacity** (FRC) is the sum of ERV and RC and is the volume of gas remaining in the lung after normal expiration (about 2.5 liters). Finally the total amount of gas that can be shifted in and out of the lung is called **vital capacity** (VT) and the maximal volume of gas on the lung is called the **total lung capacity** (TLC). These classical volume definitions are schematically illustrated in figure 3.5.

For our model the most important values are the FRC and $V_T$. These two volumes are relevant for mechanical ventilation.
Figure 3.4: Schematic representation of the lung compartments. $V_{h,0}$ is the functional residual capacity in [ml] and $C_h$ is the compliance value in [ml/mbar].
Respiratory mechanism during anesthesia and mechanical ventilation

An interesting review of the effect of general anaesthesia on the mechanism of the respiratory system can be found in [69]. After induction of drug induced muscle paralysis the loss of muscle tone changes the dynamics of the respiratory lung system. In completely paralyzed normal subjects the chest wall is deformed primarily by the influence of gravity. Therefore no action of respiratory muscles will be expected. In [69] the following changes in the standard respiratory values were observed during general anaesthesia:

- A reduction of approximatively 18% in FRC in respect to the awake value. The decrease depends on weight, height and age of the patient and seems not to be dependent on the amount of anaesthetic gas.

- A decrease of about 20% in the compliance value.

\[ 0.120 \leq C_{\text{awake}} \leq 0.190 \quad \Rightarrow \quad 0.085 \leq C_{\text{anesthetized}} \leq 0.150 \]

- An increase of the pulmonary resistance of about 40%. Tissue resistances are probably not directly affected by anaesthetic agents. This change can be motivated by:

  - changes in the airway diameters;
  - changes of the physical properties of the inspired gas mixture: densities and viscosities of common anaesthetic gases and vapors differ greatly from those of air and oxygen (see table 3.4).

The relative contribution from each of the possible mechanism controlling airway resistance remains unclear.
### Table 3.4: Density and viscosity of different gas mixtures

<table>
<thead>
<tr>
<th>Mixture</th>
<th>Density [g/liter]</th>
<th>Kinematic viscosity relative to air</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>1.13</td>
<td>1.00</td>
</tr>
<tr>
<td>Oxygen</td>
<td>1.26</td>
<td>1.01</td>
</tr>
<tr>
<td>Nitrogen</td>
<td>1.10</td>
<td>1.01</td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td>1.73</td>
<td>0.52</td>
</tr>
<tr>
<td>Halothane vapor</td>
<td>7.76</td>
<td>n.a.</td>
</tr>
<tr>
<td>Isoflurane vapor</td>
<td>7.25</td>
<td>n.a.</td>
</tr>
<tr>
<td>70% N&lt;sub&gt;2&lt;/sub&gt;O, 30% O&lt;sub&gt;2&lt;/sub&gt;</td>
<td>1.59</td>
<td>0.63</td>
</tr>
</tbody>
</table>

#### Modeling

The model is composed of three compartments without gas exchange, which behave like a tube element and one compartment with additional terms describing gas exchange flows. Since we will focus our attention on the respiratory system, gas exchange is modeled as constant flow amounts. This is sufficient to model the respiratory dynamic considering the slow dynamic changes on the O<sub>2</sub> consumption and CO<sub>2</sub> production. The incoming CO<sub>2</sub> and the outgoing O<sub>2</sub> flows are the most important terms of the mass balance between lung and blood.

\[
\dot{P}_{l1} = K_{l1} \left( F_{in1} - \frac{P_{l1} - P_{l2}}{R_{l1}} \right) \tag{3.41}
\]

\[
\dot{P}_{l2} = K_{l2} \left( \frac{P_{l1} - P_{l2}}{R_{l2}} - \frac{P_{l2} - P_{l3}}{R_{l2}} \right) \tag{3.42}
\]

\[
\dot{P}_{l3} = K_{l3} \left( \frac{P_{l2} - P_{l3}}{R_{l3}} - \frac{P_{l3} - P_{l4}}{R_{l3}} \right) \tag{3.43}
\]

\[
\dot{P}_{l1} = K_{l4} \left( \frac{P_{l3} - P_{l4}}{R_{l4}} - F_{out4} \right) \tag{3.44}
\]

\[
F_{out4} = F_{O2} + F_{N2O} + F_{CO2} + F_{gas} + F_{others} \tag{3.45}
\]

\(K_{l1}\) derived from (3.31) where \(V_0\) is the Volume of the considered part of lung, \(C\) is the presumed compliance under general anaesthesia and \(P\) the atmospheric pressure \(P_{at}\). \(K_{l1}\) in the first three compartment will be considered constant for reasons of the low volume changes and fast dynamic. The factor \(K_{l4}\) for the alveolar compartment is also assumed to be constant because:

\(V_0 \approx 2'500\ [cm^3] \ll 20'000\ [cm^3] \approx CP\)

\(R_{l1}\) are the flow resistance factors, \(F_{in}\) (see equations 3.41 and 3.46) is the total incoming and outgoing flow amount to and from the lung system and \(F_{out}\) the flow balance of the gas exchange between lung and blood. All flows can change their sign during simulation.

\[
F_{in1} = \frac{P_0 - P_{l1}}{R_{0l1}} \tag{3.46}
\]
3.3 Model elements

3.3.9 Convective transport and diffusion

The relative velocity of the mass through the pipe can be calculated by the flow amount $F$, and the radius of the pipe $r$:

$$v = \frac{F}{\pi r^2} \quad (3.47)$$

There exist different flow movements during a breathing cycle:

- **Fresh gas flow**: it is constant and varies from 0.5 to 10 litre/min. The velocity into the fresh gas pipe ($r = 0.5\,\text{cm}$ and $FF = [0.5\ldots10] \,\text{litre/min}$) is between 0.1 and 2 $m/\text{sec}$

- **Inspiration**: during inspiration the tidal volume $V_T$ must be pumped to the lung in

$$T_i = \frac{K_{T_i}T_i}{K_{T_i}T_i + 1} \, f_R \, (1 - K_{T_i}T_i) \quad (3.48)$$

minutes. For typical time partitioning values of $K_{T_i}T_i = 1 : 2$ and $K_{T_i}T_i = 10\%$ and a range of $V_T = [0.6 \ldots 1.2]$ and of $f_R = [6 \ldots 12]$ we will obtain a flow range between 12 and 48 litre/min. With the normal operating pipes ($r = 1\,\text{cm}$) this corresponds to a velocity range between 0.63 and 2.54 $m/\text{sec}$.

- **Expiration**: During this phase all kind of flow will be active but the most important mass flows are the first expiration phase and the filling time of the pump piston (which is fast: 1.22 sec). Both produces flow movement above 2 $m/\text{sec}$.

Although we must deal with continuously changing flow values, we will consider all flows as turbulent. This is certainly correct for the most important mass flows and is partially confirmed by the measurements of figure 3.3.9 showing the transport and diffusion phenomena measured on standard anaesthesia tubes (diameter 2 cm, total length 240 cm) during step changes of $O_2$ concentrations for different constant flows. On the other side we will consider a linear relation (and not a quadratic relation, which is normally used for turbulent flow) between the relative velocity $v$ and the pressure difference due to friction phenomena (see equation 3.6). This simplified assumption can be motivated by measurements which confirmed this relation. Note that flows are around the critical Reynolds number (transition from laminar to turbulent flow). Further investigations with better measurement equipment are necessary to confirm these assumptions.

In conclusion, we must deal with some unmodelled phenomena (like diffusion) that smoothes the ideal plug flow behaviour of pipes. Ideal plug flow transportation can only be modeled with an infinite segmentation tube in elementary elements described in section 3.3.3. By finite segmentation we approximate the tube in a series of mixing chambers. This segmentation will result in a approximative modeling of the existing diffusion.
Figure 3.6: Step changes of $O_2$ concentrations on standard anaesthesia tubes. The upper graphs show 4 measured step changes with constant flow (from top to bottom: 10, 5, 1 and 0.5 litre/min). The solid lines are the input signal, the dashed lines are the measured concentration at the output of the tube. The dotted lines are the expected signals in case of plug flows (pure time delay).

### 3.4 Overall model of the breathing system

Putting together all elements as in figure 3.1, we will obtain a very complex system. Valves can be modeled by varying the resistance values between two elements. A change of valves value can be modeled in two ways: as discrete event system which involves a hard dynamic structure switch or inserting some fast dynamics in the change of resistance value. The second method can smoothen the switching problem but the switching dynamics will have to be fast in respect to the system dynamics. In such cases, numerical simulation problems are to be expected.

The overall model will take into account two different phenomena: the settling of pressure and flows due to the pump movement and the composition of the gas mixture. Considering the tube element, we can easily find the settling time of pressure (and therefore of the flow).

\[
T_{tub} = \left( \frac{K_{tub}}{R_{tub}} \right)^{-1} = 7.610^{-6} \text{ [sec]}
\]
Figure 3.7: Stiffness reduction of the dynamical system. For fast elements (tubes and T-connections) $\dot{P} = 0$ is assumed and the algebraic equation problem is solved.

As expected, it is a very fast process on elements with low compliance. Considering the worst case (using the highest flow rate of 60 [litre/min]) we can find the transport delay time for gas concentrations:

$$T_{\text{tub2}} = \left(\frac{F_{\text{max}}}{V_0}\right)^{-1}$$

$$= 26.5 \times 10^{-3} \text{ [sec]}$$

(3.50)

The big difference between (3.49) and (3.50) leads to simulation problem (stiffness). To reduce the stiffness of this problem formulation, we can assume instantaneous setting of pressure in elements with low compliance (see figure 3.4).

This involves an algebraic equation problem:

$$\dot{P} = 0$$

$$\Downarrow$$

$$P = \frac{\sum_{n=1}^{n} P_{m_i}}{n}$$

(3.51)

For the partial pressures the system is therefore divided in dynamic elements and static ones (behaving like resistors). The static elements build a resistor network connected to a number of sources. To solve all algebraic equations (concerning tube and T-pieces), classical network theory ([70]) was applied, using following equivalence relations:

$$\text{pressure} \triangleq \text{voltage} \quad \text{flow} \triangleq \text{current}$$

(3.52)
One can define n-nodes in the block scheme of the respiratory system (figure 3.2). Each network node represents the pressure (equivalent to a voltage) in a given compartment. Let us define the following nodes vector:

\[ V_n = [TU_1\ TU_2\ TU_3\ TU_4\ TU_5\ TU_6\ TU_7\ TU_8\ TU_9\ T1\ T2\ T3\ T4\ T5\ A1\ A2\ B\ F\ P\ V2OUT\ L1] \]

We can now define the vector of known border nodes ("pressure sources"), these nodes are represented by all passive dynamic elements:

\[ K_u = [A1\ A2\ L1\ V2OUT\ B] \] (3.53)

Flow sources are active nodes that are dependent from internal (static) nodes. In our configuration the vector of active nodes is represented by the pump and the fresh gas flow source:

\[ K_i = [F\ P] \] (3.54)

The value of active nodes is derived from the pressure difference with the neighbor compartment \( K_{ci} \)

\[ K_{ci} = [TU_9\ TU_7] \] (3.55)

All remaining nodes will be defined as \( K_c \). The following resistances will represent valves:

\[ K_{ri} = \begin{bmatrix} RTU8T1 \\ RT2V2OUT \\ RTU1T1 \\ RTU4T2 \end{bmatrix} \] (3.56)

where \( RXY \) is the airway resistance between the element \( X \) and \( Y \).

According to [70] the Master resistance matrix \( R \) describes the connection between all nodes of the circuit. \( R(i, j) = R(j, i) \) will be set to the resistance value between node \( i \) and \( j \). If no connection exists, \( R(i, j) \) and \( R(j, i) \) will be set to zero (instead of \( \infty \)). This exception does not allow "short circuits" between elements. If two nodes are temporally not connected (e.g. valve), a very high resistance value will be set \( (R(i, j) = 10^{20}) \). The master resistance matrix is determined automatically through a MATLAB function using \( K_u, K_i, K_c, K_{ci} \) and all existing resistance values. The undetermined admittance matrix (also UAM, see [70]) is defined in the following way:

\[ UAM(i, j) = -\frac{1}{R(i, j)} \quad \forall \ i \neq j \] (3.57)

\[ UAM(i, i) = -\sum_{j=1}^{n} R(i, j) \quad \forall \ i \] (3.58)

The pressure vector (3.59) is composed of three parts:

\( P_t \): Pressures of tubes and t-pieces. Dimension: \([m \times 1]\).
3.4 Overall model of the breathing system

$P_u$ Pressures of compartment with some dynamics (the manual ventilation bag, the lungs, the CO$_2$ absorber) and such a compartment, which behaves like an ideal pressure source (outlet). Dimension: $[z \times 1]$.

$P_i$ Pressures of compartment which behaves like ideal flow sources (the pump, the fresh gas flow). Dimension $[s \times 1]$.

$$P = \begin{bmatrix} P_r \\ P_u \\ P_i \end{bmatrix}$$  \hspace{1cm} (3.59)

From $UAM$ it is easy to find a so called transfer function matrix $TUAM$ such that:

$$P = TUAM \cdot \begin{bmatrix} P_{\text{const}} \\ P_{\text{init}} \\ P_{\text{init}} \end{bmatrix}$$  \hspace{1cm} (3.60)

$$= \begin{bmatrix} 0 & T_{12} \\ 0 & I_1 \\ 0 & 0 \end{bmatrix} \begin{bmatrix} 0 \\ P_{\text{const}} \\ P_{\text{init}} \end{bmatrix}$$  \hspace{1cm} (3.61)

$$= \begin{bmatrix} 0 & T_{12} \\ 0 & I_1 \\ 0 & 0 \end{bmatrix} \begin{bmatrix} 0 \\ P_{\text{const}} \\ P_{\text{init}} \end{bmatrix}$$  \hspace{1cm} (3.62)

where $I_1 [z \times z]$ and $I_2 [s \times s]$ are unity matrices, and $T_{12} [m \times z]$ and $T_{23} [m \times z]$ are transition matrices which satisfy (from equation 3.60):

$$p_c = T_{12} P_u + T_{13} P_i$$  \hspace{1cm} (3.63)

The pressure of flow source compartments depend on the pressure of neighbor compartments:

$$P_i = T^* P_c + R^* q$$  \hspace{1cm} (3.64)

$T^* ([s \times m])$ defines the neighbor compartment pressure, $R^* ([s \times s])$ is the resistance between flow source and neighbor compartment and $q ([s \times 1])$ is the vector of flow values. After some computation we finally find the relation between the inputs (pressure and flow compartments) and output (the desired pressure of the passive elements):

$$P_c = A^* P_u + B^* q$$  \hspace{1cm} (3.65)

$$A^* = (I - T_{13} T)^{-1} T_{12}$$  \hspace{1cm} (3.66)

$$B^* = (I - T_{13} T)^{-1} T_{13} R^*$$  \hspace{1cm} (3.67)

$A^* ([m \times z])$ and $B^* ([m \times s])$ are constant by a specific valve configuration. A valve can be described with a tube-piece with time variable resistance (low if open, very high if closed). Valve closing and opening procedure can be approximated with first/second order changes of the resistance (to avoid stiff problems).
3.5 Validation of the nonlinear model

To validate the nonlinear model, pressure and concentration transients were measured on a mechanical lung model without gas exchange which was connected to the breathing machine. Figure 3.8 shows the flow from and to the manual ventilation bag. The differences between the curves are mainly motivated by the not exactly known switching strategy of the valves. Figure 3.9 shows step responses at PT5 (the ordinary place where inspired and expired gas concentrations are measured) after a concentration step on the fresh gas flow. Six different operating modes of the breathing system were measured and simulated. Considering the complicated switching scheme and the number of nonlinear elements in the system, the model implemented reflects the principal dynamic behaviour of the real plant. The remaining differences between simulated and measured values can be attributed to the effect of the ventilation bag which was not fully considered in the simulation.

![Figure 3.8: Comparison between measured and simulated flows from and to the manual ventilation bag (F_{T_4-H}). On the left: FF = 1 [liter/min], V_T = 0.6 [liter] and f_R = 12 [1/min]; on the right: FF = 20 [liter/min], V_T = 0.6 [liter] and f_R = 12 [1/min]](image)

3.6 Model for control

The model described in the last section was very useful to describe the most important phenomena about flow and concentration changes on the whole breathing circuit. However it is too complex to be used for the implementation of model based controllers. The structure switches given by the valves (time and state dependent!) do not allow the linearization and the reduction strategy adopted for the model of section 2.

It would be possible to linearize the model between each structure switch and to obtain a number of linear systems that will be activated periodically during a breathing cycle. Inten-
3.6 Model for control

Figure 3.9: Comparison between measured and simulated concentration at block T5 (concentration just outside the lung of the patient). On the left: $FF = 1 \text{ [liter/min]}, V_T = 0.6 \text{ [liter]}$ and $f_R = 12 \text{ [1/min]}$; on the right: $FF = 20 \text{ [liter/min]}, V_T = 0.6 \text{ [liter]}$ and $f_R = 12 \text{ [1/min]}$.

...seive effort would then be necessary to produce the correct switching times and, especially if some reduction was done, correct context switching (where the actual states must be set in the new model structure).

However, the relation between the fresh gas concentrations and the inspiratory and endtidal concentration are the only information needed by the controller. Our model implemented in the last section delivers much more information than necessary. However he can be used to analyze new breathing subsystem configurations by simulation. It can be also used to “validate” reduced order models without resorting extensive measurements.

In this section we will present a simplified model of the inspiratory and endtidal concentration behaviour in the breathing system.

The system will be approximated by two blocks representing the breathing machine and the lung respectively (see figure 3.11). The mass flow inflowing in the first block is composed of the anaesthesia gas flowing in the fresh gas ($F_i = P_f F_{ff}$) and the reused anaesthesia gas coming from the expiration ($F_e = P_e AMV$). The inspired anaesthesia gas flow $F_i = P_i AMV$ together with some exceeding anaesthesia gas are flowing out from the first block ($F_{out}$). The second block represents the gas part of the lung. Inspiratory and expiratory anaesthesia flows describe the breathing movement, while the gas exchange between the blood part and the gas part of the lung is described through $F_{ven}$ for the gas flow from the venous compartment and $F_{art}$ for the flow to the arterial compartment. The transportation time from the lung to the breathing machine ($T_e$) and vice versa ($T_i$) as well for the fresh gas flow ($T_{ff}$) to the breathing machine are modeled as approximations of time delays $e^{-sT}$. A low order time delay approximation was used for these blocks. There are different alternatives:
Figure 3.10: Comparison between three different pure delay approximation in time and frequency domain: the modified Padé (-) approximation, the truncated Taylor (-) approximation and the chosen solution (-). In the first graph the ideal delayed step is represented with a solid line.

- All pass filters (Padé and other variants, [71, 72, 73]):

\[
G(s) = \frac{\sum_{j=0}^{n} (-1)^j a_j (sT_i)^j}{\sum_{j=0}^{n} a_j (sT_i)^j} \quad (3.68)
\]

- Truncated Taylor expansion [71]:

\[
G(s) = \frac{1}{\sum_{j=0}^{n} (sT_i)^{n-j} (n-j)!} \quad (3.69)
\]

- and a modification of the truncated Taylor expansion of order two to avoid overshoot:

\[
G(s) = \frac{1}{(1 + sT_i/2)^2} = \frac{1}{1 + sT_i + s^2 T_i^2 / 4} \quad (3.70)
\]

Because mass flow transportation through pipes is submitted to diffusion and other smoothing phenomena (see section 3.3.9) this approximation will rather reflect the reality. Because of the low frequency character of the signal passing through the time delays \( T_i \) and \( T_e \), no large differences between the methods were observed. However, due to the non minimum phase realization of the all pass filters, and the overshooting of the truncated Taylor approximation the third solution was preferred (comparison see figure 3.6). This choice was motivated in order to avoid the effect of the short but intense inverse response reaction due
to the non minimum phase characteristic in the closed loop. Time delays could not be decoupled from the plant because they appear in a closed loop structure (this concerns $T_i$ and $T_e$).

Both blocks of the system are of first order and characterized as an ideal stirred gas tank. In the block of the breathing machine, the relations between the input and output flows of the block and the input and output of the tank strongly depend on the setting parameters of the breathing machine (see table 3.5). Depending on the breathing parameters, a part of

<table>
<thead>
<tr>
<th>value</th>
<th>description</th>
<th>range</th>
</tr>
</thead>
<tbody>
<tr>
<td>$FF$</td>
<td>Fresh gas flow [liter/min]</td>
<td>0.5 to 20</td>
</tr>
<tr>
<td>$f_R$</td>
<td>Breath frequency [1/min]</td>
<td>6 to 60</td>
</tr>
<tr>
<td>$V_T$</td>
<td>Tidal volume [liter]</td>
<td>0.05 to 1.4</td>
</tr>
<tr>
<td>$T_iT_e$</td>
<td>Fraction between duration of inspiratory and expiratory phase</td>
<td>1:3 to 2:1</td>
</tr>
<tr>
<td>$T_i$</td>
<td>Fraction between duration of inspiratory movement and pause</td>
<td>0 to 60 %</td>
</tr>
<tr>
<td>$PEEP$</td>
<td>Endtidal pressure [mbar]</td>
<td>0 or 3 to 20</td>
</tr>
</tbody>
</table>

Table 3.5: Typical setting parameter of a breathing machine.

the fresh gas flow $1 - K - \beta$ will go directly to the outlet (see figure 3.12):

$$K_\beta(FF, V_T, f_R, K_T T_e) = \min(AMV, \max(0, \frac{K_T T_e}{1 + K_T T_e} \frac{FF}{f_R} - V_T)) \quad (3.71)$$

Another part $1 - K_\gamma$ will short-circuit the tank and flow directly into the lung. So the amount of anaesthesia gas coming from the fresh gas will be:

$$F_{fresh} = F_{ff} \ K_\beta \ K_\gamma \quad (3.72)$$

The stirred tank will be ventilated by a total flow amount of $AMV$. Therefore the reused gas flow will be:

$$F_{reused} = \begin{cases} AMV - F_{ff} \ K_\beta & AMV > F_{ff} \ K_\beta \\ 0 & AMV \leq F_{ff} \ K_\beta \end{cases} \quad (3.73)$$

$$K_{alpha} = \frac{F_{reused}}{AMV} \quad (3.74)$$

The volume of the tank represents the effective volume of the breathing system directly influencing the composition of the inspired gas. To resume, the following parameters are set to describe the model:
<table>
<thead>
<tr>
<th>variable</th>
<th>description</th>
<th>value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_a$</td>
<td>Reused gas amount from AMV</td>
<td></td>
</tr>
<tr>
<td>$K_\beta$</td>
<td>Used gas amount from fresh gas</td>
<td></td>
</tr>
<tr>
<td>$K_\gamma$</td>
<td>Part of gas amount described by $K_\beta$ that will be mixed in the virtual gas tank</td>
<td></td>
</tr>
<tr>
<td>$K_s$</td>
<td>Part of gas amount that will not be mixed in the lung and flows directly into the end tidal path</td>
<td></td>
</tr>
<tr>
<td>$V_0$</td>
<td>Volume of the virtual gas tank representing the breathing machine</td>
<td></td>
</tr>
<tr>
<td>$V_L$</td>
<td>Gas volume of the lung taking active part in the gas exchanges</td>
<td></td>
</tr>
</tbody>
</table>

The three parameters $K_\gamma$, $K_s$ and $V_0$ are to be identified by the measured or simulated data for all possible breathing parameter sets. Investigation showed that these parameters are sensitive to the actual operating condition of the system. A first approximation is given by:

$$K_\gamma(FF) = \begin{cases} 
0 & FF < 1 \\
-\frac{1}{3} + \frac{1}{3} FF & 1 \leq FF < 4 \\
1 & FF \geq 4 
\end{cases}$$  \hspace{1cm} (3.75)

$$K_s(FF) = 0.3$$  \hspace{1cm} (3.76)

$$V_0(FF) = \begin{cases} 
2.0 - 0.4 FF & FF < 4 \\
0.4 & FF \geq 4 
\end{cases}$$  \hspace{1cm} (3.77)

$$F_{out}$$

Figure 3.11: Mass flow diagram of a simple model structure of the breathing and lung system. $T_{ff}, T_i, T_e$ are time delays approximations, the other blocks represent ideal stirred tanks.

The lung will also be strongly simplified to a first order system (see figure 3.12): it will be approximated as a stirred tank with two input flows and two output flows generated by
3.7 Parameter set of the breathing system

In this section we will illustrate values (see table 3.6) of the parameter used for the validation of the complex, nonlinear model of the breathing system. The breathing system was connected to a lung simulator without gas exchange. The lung simulator was composed by a flexible bag. To simulate the compliance, the bag was pressed by some springs. The volume of the bag was between 0.5 and 1.5 litres. The total volume in the lung model was reduced to this value.

The pressure to volume relation of the manual ventilation bag was approximated with fol-
3 The breathing system

<table>
<thead>
<tr>
<th>Element</th>
<th>$R$</th>
<th>$V_0$</th>
<th>$C$</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tube (1 to 4)</td>
<td>0.1</td>
<td>750</td>
<td>$5.10^{-4}$</td>
<td></td>
</tr>
<tr>
<td>Tube (5 to 8)</td>
<td>0.1</td>
<td>75</td>
<td>$5.10^{-5}$</td>
<td></td>
</tr>
<tr>
<td>Ventilation bag</td>
<td>0.1</td>
<td>-</td>
<td>-</td>
<td>$a=10^5$</td>
</tr>
<tr>
<td>Pump</td>
<td>0.1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$CO_2$ Absorber</td>
<td>0.1</td>
<td>1500</td>
<td>$1.10^{-3}$</td>
<td>$K_{abs} = 0.95$</td>
</tr>
<tr>
<td>Lung</td>
<td>$R_{01}$</td>
<td>1.0</td>
<td>$V_{01}$</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>$R_{12}$</td>
<td>0.33</td>
<td>$V_{12}$</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>$R_{23}$</td>
<td>0.3</td>
<td>$V_{23}$</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>$R_{34}$</td>
<td>0.8</td>
<td>$V_{34}$</td>
<td>800</td>
</tr>
</tbody>
</table>

Table 3.6: Overview of the parameter values of the elements of the breathing system used for validation

The following polynomial:

$$V(P) = \sum_{i=0}^{5} a_i P^i$$  \hspace{1cm} (3.79)

with:

$$a = 10^5 \begin{bmatrix} 1.2599 & -2.8958 & 2.1298 & -0.4901 & 0.0139 & 0.0014 \end{bmatrix}$$  \hspace{1cm} (3.80)

The values of $a$ were identified with a least square fit from measured data. The resulting approximation is within the band of measured trajectories (see figure 3.13). This approximation and its derivative in respect to $P$ will be used in equation (3.38). The derivative value is monotonously decreasing until 5 mbar. Some simulation problems could appear on the region around 5 mbar, where the derivative in respect to $P$ is very low.

### 3.8 Validation

The same measurement equipment described in section 3.5 was used to test the simulation results. The response to a step in the anaesthesia fresh gas concentration was measured on the element T5 (see figure 3.14). T5 is the usual measurement point for the inspiratory and expiratory concentration. A lung simulator without any anaesthesia gas uptake was used instead of a patient. The flows $F_{ecn}$ and $F_{art}$ were consequently set to zero. The manual breathing bag was pressed out just before the step. During low and minimal flow the bag is
an important part of volume of the virtual stirred tank $V_O$. During the initial filling time of the bag the system will have a faster time constant, these unmodelled effects cause some error in simulation especially with low flow (upper two graphics of figure 3.14). The comparison between measurements and simulations shows that this simplified model assumption gives good results in the operating conditions covered by measurements.
Figure 3.14: Comparison between simulated and measured step responses of a anaesthesia concentration change in the fresh gas flow.
Chapter 4

Effect of surgical stimulation on mean arterial pressure

One of the main objectives in our anaesthesia control system is to keep mean arterial blood pressure within certain bounds. For the regulation of MAP it is necessary to investigate the sources of influences on the value of MAP. In control engineering there exist two main types of input signals: manipulated variables and disturbances. The manipulated variables are all the inputs of the plant that can be set by the controller, while disturbances can not. Knowledge on disturbances is therefore very important for control, because they can only be compensated indirectly through the manipulated variables. In our case the main disturbance signal is the surgical stimulation, the manipulated variable is the anaesthesia fresh gas flow (see figure 4). Both, $G_g(s)$ and $G_d(s)$, act additively on the basic mean arterial pressure $MAP_0$. $G_g(s)$ and $G_d(s)$ are only slightly influenced by their respective operating conditions (74). Beneath these two factors there exist other disturbance sources such as infusion drugs, blood loss, etc. Each disturbance acts differently to the $MAP$. Infusion drugs can for example have a strong influence on the effect of surgical stimulations ($G_d(s)$). In this work we will limit the analysis to the two main influence factors. For an extension of the anaesthesia control system to combined inhalation and infusion anaesthesia techniques, a more complete analysis of these interactions will be necessary.

In this section we propose a physiological approach to model the effects of surgical stimulation on MAP (presented in 75). Since no exact measurements of these stimuli are possible, we qualitatively validate the model by assuming excitation by a temporally well defined pulse stimulus (e.g. intubation) and we compare MAP reactions to our model.

In the past years much work has been done to understand and model pain perception (76, 77), trying to find a relationship between drug infusion and pain perception during and after the infusion. The effect of these standardized painful stimuli to physiological reactions was only qualitatively described. The main objective of these investigations was to find optimal strategies of drug administration in critical care. Knowledge of the dynamics of physiological reactions to surgical stimulations was not the main interest. Note that we purposely avoid the term pain and use surgical stimulation instead, when speaking about haemodynamic
Figure 4.1: *Possible influence factors on mean arterial pressure (MAP).* The dashed line represents the influence of the actual operating condition on the dynamic of the respective $G_i(s)$. Other influence factors can be e.g. drug combinations, temperature, haemorrhage, dehydration, ...

reaction. We feel that this distinction should be made because haemodynamic reactions also occur in patients getting adequate anesthesia with no pain perception [74].

4.1 Physiology

Surgical stimulations cause similar haemodynamic reactions as do painful stimulations in the awake state [74]. A stimulus propagates through the autonomous nervous system from the origin of the stimulation to the spinal nerves. Then, the processed signal will be transmitted to the brain followed by a stimulation of the sympathetic system. The sympathetic nervous system can be considered as an emergency mechanism usually activated under conditions of stress, infection, haemorrhage and of course pain. Such stimulation prepares the body for critical situations. It leads to physiological reactions such as pupil widening, increase of heart rate and blood pressure (leading to better blood flow in the main organs) and contraction of skin vessels (to decrease blood loss in case of injury). Generally speaking, the human body is being prepared for fight or flight. The sympathetic nervous system evokes a neuronal and humoral reaction (compare figure 4.2) that causes specific reactions of effector cells [1]. For the purpose of haemodynamic modeling we are only interested in those reactions which are haemodynamically important (such as changes in peripheral resistance and cardiac output (CO)). This is the reason why we limit our attention to the two substances epinephrine (adrenaline) and norepinephrine (noradrenaline) [78].
4.2 Compartment modeling

4.1.1 The neuronal reaction

The neuronal reaction is a relatively fast mechanism. The stimulation propagates through the sympathetic system to the sympathetic nerve endings where norepinephrine is released into the synaptic cleft (the space between the nerve endings and the effector cells). The amount of released norepinephrine is influenced by the epinephrine concentration detected by adrenergic receptors at the presynaptic nerve endings. As soon as the neuronal reaction is terminated, there is a rapid decrease of norepinephrine in the sympathetic cleft due to a very fast absorption of epinephrine by the nerve ending. About 90% of released norepinephrine is reabsorbed by the nerve ending [79].

4.1.2 The humoral reaction

The humoral reaction consists of an increase of epinephrine and norepinephrine release from the adrenal medulla. These hormones are discharged into the blood stream and exert their effects when they are carried to the effector cells.

4.2 Compartment modeling

In this section we will propose a compartment model describing the pharmacokinetic and pharmacodynamic of the production, distribution, and of the haemodynamic effects of epinephrine and norepinephrine.

4.2.1 The model for the humoral reaction

As mentioned above, surgical stimulation causes mainly two different reactions, a humoral and a neuronal reaction.

For the humoral reaction epinephrine and norepinephrine produced in the adrenal medulla are released into the circulatory system. It is intuitive to model these pharmacokinetics with the same compartments as were used to model the distribution of anesthetic drugs (see chapter 2), therefore the model has been extended with another 24 compartments. In contrast to volatile anesthetic agents, epinephrine and norepinephrine are rapidly inactivated through specialized enzymes which is modeled by a Michaelis-Menten equation [80]. The dynamic equation is then similar to equation (2.1) but with an additional clearance term ($A_n$).
Figure 4.2: Qualitative description of the physiology of how surgical stimulation influences MAP. A stimulus propagates through the autonomous nervous system from the origin of the stimulation to the spinal nerves. The processed signal will then be transmitted to the brain followed by a stimulation of the sympathetic system. The sympathetic nervous system evokes a neuronal and humoral reaction which causes specific reactions of effector cells. The haemodynamic reactions of importance are changes in peripheral resistance and cardiac output (CO). Due to the different dimension of the transport medium the humoral reaction is much slower than the neuronal one.
4.2 Compartment modeling

\[ \dot{n}_i(t) = \frac{q_i(t)}{V_{i,b}} [n_A(t) - n_i(t)] - A_n \]  \hspace{1cm} (4.1)

\[ A_n = \frac{V_n n_i}{k_n + n_i} \]  \hspace{1cm} (4.2)

Here \( n_i \) denotes the norepinephrine concentration in the \( i \)-th compartment, \( n_A \) denotes the norepinephrine concentration in the arterial compartment, and \( V_n \) and \( k_n \) are the constants governing the Michaelis-Menten-dynamic. Similar equations hold for the epinephrine concentration \( e \).

### 4.2.2 The model for the neuronal reaction

For the neuronal reaction the stimulation signal is transmitted by the release of norepinephrine into the synaptic cleft. The amount of receptors stimulated at the effector cells is proportional to the amount of norepinephrine present in the cleft. The release of norepinephrine \( (P_c) \) is dependent on the presynaptic stimulation of adrenergic receptors \( (\beta_2) \) reached by the epinephrine in the blood. The stimulation of these receptors is further assumed to be proportional to the epinephrine concentration. There exist several regulation mechanisms preventing high norepinephrine concentrations in the synaptic cleft. On one hand norepinephrine is reabsorbed by the synapse itself at a high rate, on the other hand norepinephrine release is inhibited by high concentration in the cleft. The change of the concentration in a cleft \( (c) \) is determined by the release rate and an absorption rate \( A_c \) (see equation (4.3)). The release rate depends on the synaptic stimulation \( u_s \) which is assumed to be an affine function of the epinephrine concentration in the blood of the compartment \( e_i \) (see equation (4.4)). The norepinephrine absorption is assumed to be limited by a Michaelis-Menten dynamic (see equation (4.5)).

\[ \dot{c} = P_c - A_c \]  \hspace{1cm} (4.3)

\[ P_c = u_s [1 + K(e_i)] \]  \hspace{1cm} (4.4)

\[ A_c = \frac{c V_c}{c + k_c} \]  \hspace{1cm} (4.5)

Since the two interesting effects of sympathetic stimulation are changes in CO and peripheral resistance \( (\frac{1}{r_h}) \), it is intuitive to extend the pharmacodynamic equations (2.11) and (2.12) with epinephrine and norepinephrine dependent terms as follows

\[ g_i = g_{i,0} (1 + b_i p_i + \gamma e_i + \delta_i n_i + \varepsilon_i c_i) \]  \hspace{1cm} (4.6)

\[ CO = CO_0 (1 + \alpha_1 p_1 + \alpha_2 p_2 + \alpha_3 p_4 + \alpha_4 e_1 + \alpha_5 n_1 + \alpha_6 c_1) \]

where CO is assumed to be only influenced by the humoral and neuronal reaction in the heart.
Figure 4.3: Block diagram of the model for MAP as a function of volatile anesthetic partial pressures and surgical stimulations. The two structures on the left show the model for the distribution of anesthetics (upper structure) and the circulation model (bottom). The other two central structures represent the distribution of epinephrine (right) and norepinephrine (left) released in the adrenal medulla during humoral reaction to surgical stimulation. The structure on the right describes the compartments for norepinephrine concentration in the synaptic clefts of each compartment and epinephrine concentration of the compartments. The following index convention was used for the compartments: (1) myocard, (2) brain gray matter, (3) brain white matter, (4) well perfused organs, (5) poorly perfused organs, (6) splanchnicus, (7) skeletal muscle, (8) fat, (9) skin shunt, (L) lung, (A) arterial system, (V) venous system.
4.3 Validation of the model

A major difficulty in the development of this physiologically motivated model was to find the appropriate values for the parameters introduced. Although qualitative descriptions of the facts discussed here can be found in the literature [1, 78], almost no quantitative information could be found. With these limitations we first manually tuned the parameters so that the response of the model matched responses measured during operations (figure 4.4). The dashed line corresponds to the assumed stimulation caused by intubation (the intubation took around 15 seconds and a decreasing stimulation is assumed to remain after intubation). The dotted lines correspond to actual MAP responses of 5 patients. The solid line is the output of our model to the assumed stimulation profile (dashed).

The parameters finally chosen are physiologically realistic and the concentration levels obtained from our model during stimulation correspond to values that can be found in the literature [81, 82].
4.4 Reduced model

It is evident that this first model of the MAP disturbance due to surgical stimulation cannot be used as a model for disturbance rejection during control. The model is of too high order, has too many unknown parameters, is nonlinear and is coupled with the pharmacokinetic and pharmacodynamic model of anaesthetic gases. Furthermore, the dynamic of surgical stimuli is more a composition of approx. 3 time constants than the result of a complex nonlinear model (see figure 4.4). In this section we will find a reduced model with clear relation to the more complex model presented above.

4.4.1 Description

Mainly three different compartments can be defined (see figure 4.5):

1. The mean humoral epinephrine blood concentration ($e$),
2. The mean neuronal norepinephrine concentration in the synaptic cleft ($c$),
3. The mean humoral norepinephrine blood concentration ($n$).

The epinephrine compartment can be described with one input representing the release from the adrenal medulla and one output given by the clearance ($C_e$) due to the rapid inactivation through enzymes. Because there is a basic epinephrine concentration in the blood, it is assumed that the Michaelis-Menten equation (4.2) can be linearized at a mean working point:

$$\dot{e} = -C_e e + P_e$$  \hspace{1cm} (4.7)

The epinephrine production $P_e$ is assumed to be proportional to the actual surgical stimulation:

$$P_e = K_{pe} u_s$$  \hspace{1cm} (4.8)

The same kind of structure can be assumed for the humoral epinephrine compartment. In addition there is a significant epinephrine exchange with the surgical cleft (term with $K_{cn}$ and $K_{nc}$) due to diffusion phenomena (named spillover effect):

$$\dot{n} = -C_n n + K_{cn} c - K_{nc} n + P_n$$  \hspace{1cm} (4.9)

$$P_n = K_{pn} u_s$$  \hspace{1cm} (4.10)

The only nonlinearity on this model describes the very complex release mechanism of norepinephrine in the cleft:

$$P_c = u_s [1 + \Delta P_c]$$  \hspace{1cm} (4.11)

$$\Delta P_c = K_\beta e - K_\alpha f(c)$$  \hspace{1cm} (4.12)

$$f(c) = \begin{cases} 
0 & 0 \leq c \leq c_{min} \\
(c - c_{min}) & c > c_{min}
\end{cases}$$  \hspace{1cm} (4.13)
4.4 Reduced model

The release is amplified ($K_p$) by the epinephrine concentration in the blood plasma (through $\beta_2$ receptors) and inhibited affine to the cleft concentration itself. The inhibition is only acting from a minimal concentration $c_{\text{min}}$. The compartment dynamic of epinephrine concentration in the cleft is therefore characterized by the release ($P_c$) and absorption ($A_c$) of epinephrine from the presynapsis in the cleft and by the spillover effect (term with $K_{en}$ and $K_{nc}$). As on the other compartment, the Michaelis-Menten kinetic was linearized at a mean working point.

$$\dot{c} = -A_c - K_{en} c + K_{nc} n + P_c \quad (4.14)$$

![Figure 4.5: Simplified nonlinear model of hormonal production and concentration due to surgical stimulation.](image)

4.4.2 Linearization

The differential equation for $c$ (4.14) is nonlinear due to the release mechanism 4.11. The most problematic nonlinearity 4.11 is composed by two linear regions. Equation 4.14 can therefore be split into two continuous nonlinear differential equations:
4 Model of surgical stimulation

\[
\dot{c} = \begin{cases} 
\begin{bmatrix} 0 & K_{nc} \ - (K_{cn} + K_{\alpha}) \end{bmatrix} \begin{bmatrix} e \\ n \\ c \end{bmatrix} + K_{\beta} u_{s} (e - K_{\alpha} u_{s} (c - c_{\min})) & 0 \leq c \leq c_{\min} \\
\begin{bmatrix} 0 & K_{nc} \ - (K_{cn} + K_{\alpha}) \end{bmatrix} \begin{bmatrix} e \\ n \\ c \end{bmatrix} + K_{\beta} u_{s} e & c > c_{\min}
\end{cases}
\]

(4.15)

The resulting linearization with respect to \( e, n \) and \( c \) at the working points \( \bar{e}, \bar{n} \) and \( \bar{c} \) is:

\[
\delta \dot{c} = \begin{cases} 
\begin{bmatrix} K_{\beta} \ u_{s} & K_{nc} \ - (K_{cn} + K_{\alpha}) \end{bmatrix} \begin{bmatrix} \delta e \\ \delta n \\ \delta c \end{bmatrix} & 0 \leq c \leq c_{\min} \\
\begin{bmatrix} K_{\beta} \ u_{s} & K_{nc} \ - (K_{cn} + K_{\alpha} + K_{\alpha} \ u_{s}) \end{bmatrix} \begin{bmatrix} \delta e \\ \delta n \\ \delta c \end{bmatrix} & c > c_{\min}
\end{cases}
\]

(4.16)

with

\[
e(t) = \bar{e} + \delta e(t) \quad n(t) = \bar{n} + \delta n(t) \quad c(t) = \bar{c} + \delta c(t)
\]

(4.17)

The haemodynamic effects described with equations 4.6 and 4.7 will be simplified through the use of the same concentration values on all compartments:

\[
e_{i} = e \quad c_{i} = c \quad n_{i} = n \quad \forall i
\]

(4.18)

The next step is to decouple the effect of humoral and neuronal reaction to MAP from the effect coming from the anaesthetic gas. In other words the nonlinear output equation:

\[
MAP = \frac{CO_{0} \ (1 + \alpha_{1} p_{1} + \alpha_{2} p_{2} + \alpha_{3} p_{A} + \alpha_{4} e + \alpha_{5} n + \alpha_{6} c)}{\sum_{i=1}^{9} g_{i,0} \ (1 + b_{i} p_{i} + \gamma e_{i} + \delta n_{i} + \varepsilon c_{i})}
\]

(4.19)

should be split into:

\[
MAP = \overline{MAP}(\bar{p}, \bar{e}, \bar{n}, \bar{c}) + \delta MAP_{g} + \delta MAP_{d}(\delta e, \delta n, \delta c)
\]

(4.20)

where \( \overline{MAP} \) is the MAP value at working point \( \bar{p}, \bar{e}, \bar{n} \) and \( \bar{c} \); \( \delta MAP_{g} \) is the haemodynamic effect of anaesthetic gas concentration (see equation 2.38) and \( \delta MAP_{d} \) is the haemodynamic effect of surgical stimulation. In section 2.4.1 we have shown that the nonlinearity of this function is basically neglectable in respect to the dynamic behaviour of the system. For this reason we approximated this equation through linearisation.
Definition of a working point for the MAP:

Given $\bar{p} = p_i \ \forall \ i$ as reference level of anaesthetic gas in the body's compartments and $\bar{e}, \bar{n}, \bar{c}$ as the reference levels of catecholamine concentrations due to a constant surgical stimulation, we obtain:

$$\Delta CO = (\alpha_1 + \alpha_2 + \alpha_3) \bar{p}$$

$$\Delta \bar{g}_i = b_i \bar{p} \tag{4.21}$$

such that:

$$\overline{MAP} = \frac{CO_0 (1 + \Delta CO + \alpha_4 \bar{e} + \alpha_5 \bar{n} + \alpha_6 \bar{c})}{\sum_{i=1}^{g} g_{i,0} (1 + \Delta \bar{g}_i + \gamma_i \bar{e} + \delta_i \bar{n} + \varepsilon_i \bar{c})} \tag{4.22}$$

Linearization with respect to $e, n$ and $c$ at $\bar{e}, \bar{n}, \bar{c}$ and $\bar{p}$.

Equation 4.19 can be linearized to:

$$\delta MAP_d(e, n, c) = C_d^T x_d \tag{4.23}$$

$$\begin{bmatrix}
\frac{CO_0 \alpha_4}{G} - \frac{\Delta CO \sum_{i=1}^{g} g_{i,0} \gamma_i}{G^2} \\
\frac{CO_0 \alpha_5}{G} - \frac{\Delta CO \sum_{i=1}^{g} g_{i,0} \delta_i}{G^2} \\
\frac{CO_0 \alpha_6}{G} - \frac{\Delta CO \sum_{i=1}^{g} g_{i,0} \varepsilon_i}{G^2}
\end{bmatrix}^T = \begin{bmatrix}
\delta e \\
\delta n \\
\delta c
\end{bmatrix} \tag{4.24}$$

$$\Delta CO = CO_0 (1 + \Delta CO + \alpha_4 \bar{e} + \alpha_5 \bar{n} + \alpha_6 \bar{c}) \tag{4.25}$$

$$\Delta G = \sum_{i=1}^{g} g_{i,0} (1 + \Delta \bar{g}_i + \gamma_i \bar{e} + \delta_i \bar{n} + \varepsilon_i \bar{c}) \tag{4.26}$$

Where all overlined variables are the respective steady state values of the linearization work-
ing point. The state space description of the resulting linear MAP disturbance model is:

\[ \dot{x}_d = A_d x_d + B_d u_s \]  
(4.27)

\[ \delta MAP_d = C_d x_d \]  
(4.28)

\[
A_d = \begin{bmatrix}
-C_e & 0 & 0 \\
0 & -K_{nc} - C_n & K_{cn} \\
K \bar{u}_s & K_{nc} & -(K_{cn} + K \alpha(1 + \kappa \bar{u}_s))
\end{bmatrix}
\]  
(4.29)

\[
B_d = \begin{bmatrix}
K_p_c \\
K_p_n \\
A_c - \kappa K \alpha(c - c_{min})
\end{bmatrix}
\]  
(4.30)

where

\[ \kappa = \begin{cases}
0 & 0 \leq c \leq c_{min} \\
1 & c > c_{min}
\end{cases} \]

\[ x_d = \begin{bmatrix}
\delta c \\
\delta n \\
\delta c
\end{bmatrix} \]  
(4.31)

### 4.4.3 Validation

To validate this reduced model, we have to analyze the difference between the first implementation, the nonlinear reduced order model and the linear model of the third order. Figure 4.6 shows the MAP responses to the same stimulation of figure 4.4 caused by an intubation. All four simulations show similar dynamic behaviour. Following interesting points can be focused:

- The difference between the two linear models due to the nonlinearity of equation 4.13 are very similar. This similarity depends on the value of \( c_{min} \). There is no need for online parameter switching.
- The nonlinear reduced model is very well approximated by the linearized model.
- The nonlinear complex model is smoother in the fast dynamics. This is mainly due to the additional modeling of the mass transportation time constants through the venous and arterial pools.

### 4.5 Outlook

These modeling approaches are only first implementations of mechanisms that are difficult to measure. For a fair validation of our assumptions, a considerable effort is still necessary. It is not asserted that norepinephrine and epinephrine are the only main substances involved in haemodynamic reactions due to surgical stimulations.
Disturbance rejection is one of the main objectives during control of depth of anesthesia. Unfortunately these disturbances are not directly measurable. A better knowledge of the disturbance source signal (e.g. the surgical stimulation) and of the disturbance dynamics (e.g. the haemodynamic effects of surgical stimulation) can help to increase the detection and suppression performance during filtering of measurement signals. This is especially important using an observer-based control algorithm: a good separation of the disturbance signals from the plant outputs allow a better observer state correction due to parameter variations. Therefore a good characterization of disturbance dynamics in respect to the plant dynamics is necessary to evaluate the performance of different control algorithms.
Chapter 5

Model integration, benchmark signals and typical parameter values

In this section we will join the three model presented in the last sections and define some benchmark signals and models for test, evaluation and comparison of different model based controllers.

5.1 Model integration

Figure 5.1 shows graphically the connections between the model of the breathing system (section 3), the model of the pharmacokinetic and pharmacodynamic of the delivery of anaesthesia gases (section 2) and the model of haemodynamic reactions to surgical stimulations (section 4). Following linear model realizations will be defined:

- \( \{A_p, B_p, C_p, D_p\} \)
  Represents the reduced linear model of the pharmacokinetic and pharmacodynamic of the delivery of anaesthesia gases. The order depends on the reduction degree. The input of the model is the inspiratory anaesthesia concentration, the output are the effect on MAP \( (\Delta MAP_g) \) and the venous isoflurane partial pressure \( (p_V) \), which are needed to define the anaesthesia mass flow through the lung. As a benchmark, the coefficients for a reduced system of fifth order are given. The main parameter values using isoflurane as anaesthesia gas are:

\[
W_{Kg} = 70 \text{ [kg]} \quad FF = 1 \text{ [liter/min]} \quad (5.1)
\]
\[
f_R = 6 \text{ [1/min]} \quad V_T = 1.2 \text{ [liter]} \quad (5.2)
\]
Figure 5.1: Conjunction of the different implemented models: the model of the breathing system (section 3), the model of the pharmacokinetic and pharmacodynamic of the delivery of anaesthesia gases (section 2) and the model of haemodynamic reactions to surgical stimulations (section 4). The linear system description of each block are given through the indicated \( \{A, B, C, D\} \) matrices; \( P_i \) and \( P_e \) are the inspired respectively the endtidal anaesthesia gas concentrations; \( p_v \) is the venous anaesthesia gas partial pressure.

\[
A_p = \begin{bmatrix}
-0.0973 & -0.0694 & 0.2338 & -0.0106 & -0.0184 \\
-0.0694 & -0.0661 & 0.3816 & -0.0140 & -0.0246 \\
-0.2338 & -0.3818 & -2.0969 & 0.4611 & 0.6585 \\
-0.0121 & -0.0164 & -0.4777 & -0.0128 & -0.0234 \\
-0.0204 & -0.0280 & -0.6835 & -0.0236 & -0.0438 \\
\end{bmatrix}
\] (5.3)

\[
B_p = \begin{bmatrix}
1.1868 \\
0.5648 \\
1.3418 \\
0.0757 \\
0.1276 \\
\end{bmatrix}
\] (5.4)

\[
C_p = \begin{bmatrix}
-1.1855 & -0.5645 & 1.3391 & -0.0653 & -0.1124 \\
0.0565 & 0.0171 & -0.0857 & 0.0383 & 0.0602 \\
\end{bmatrix}
\] (5.5)

\[
D_p = \begin{bmatrix}
0 \\
0 \\
\end{bmatrix}
\] (5.6)
\section*{5.1 Model integration}

\begin{itemize}
  \item \{\(A_r, B_r, C_r, D_r\}\}
  
  Represents the simplified model of the breathing system. The model is of 8th order due to three second order time delay approximations and two main compartments. The model has two inputs, the anaesthesia gas concentration in the fresh gas flow (\(P_{f_{\text{ff}}}\)) and in the venous body compartment (\(P_{v_{\text{c}}}\)), and two outputs, the inspired (\(P_i\)) and expired (\(P_e\)) anaesthesia gas concentrations. For the same working points as described in 5.2 we obtain:

  \[
  A_r = \begin{bmatrix}
  -32.000 & -256.000 & 0 & 0 & 0 & 0.8611 & 0 & 2.2222 \\
  1.0000 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
  0 & 496.2462 & -4.7077 & 0 & 0 & 0 & 0 & 0 \\
  0 & 76.8000 & 0.7000 & -32.000 & -256.000 & 0 & 0 & 0 \\
  0 & 0 & 0 & 1.0000 & 0 & 0 & 0 & 0 \\
  0 & 0 & 0 & 0 & 992.0000 & -3.8750 & 0 & 0 \\
  0 & 0 & 0 & 0 & 0 & -8.0000 & -16.0000 & 0 \\
  0 & 0 & 0 & 0 & 0 & 0 & 1.0000 & 0
  \end{bmatrix}
  \]  

  \[
  B_r = \begin{bmatrix}
  0 & 0 \\
  0 & 0 \\
  0 & 0 \\
  0 & 0 \\
  0 & 0 \\
  0 & 0 \\
  1.0000 & 0 \\
  0 & 0
  \end{bmatrix}
  \]  

  \[
  C_r = \begin{bmatrix}
  0 & 256.0000 & 0 & 0 & 0 & 0 & 0 & 0 \\
  0 & 76.8000 & 0.7000 & 0 & 0 & 0 & 0 & 0
  \end{bmatrix}
  \]  

  \[
  D_r = \begin{bmatrix}
  0 & 0 \\
  0 & 0
  \end{bmatrix}
  \]  

  \item \{\(A_w, B_w, C_w, D_w\}\}
  
  These matrices represent the model of the hemodynamic reactions to surgical stimulations. The model has one input, the surgical disturbance signal (\(w\)) and one output, the effect on the MAP (\(\Delta MAP_d\)). Following benchmark values are used:

  \[
  A_w = \begin{bmatrix}
  -1.2714 & 0 & 0 \\
  0.4114 & -3.0000 & 0.5000 \\
  0 & 0.5000 & -0.5571
  \end{bmatrix}
  \]  

  \[
  B_w = \begin{bmatrix}
  24.4898 \\
  87.9241 \\
  15.3061
  \end{bmatrix}
  \]  

  \[
  C_w = \begin{bmatrix}
  2.9035 & 0.1936 & 0.1563
  \end{bmatrix}
  \]  

  \[
  D_w = \begin{bmatrix}
  0
  \end{bmatrix}
  \]

  \item \{\(A_{rp}, B_{rp}, C_{rp}, D_{rp}\}\}
  
  These matrices represents the conjunction of the breathing system and the model of the patient shown on figure 5.1.
5 Model integration, benchmark signals and typical parameter values

Figure 5.2: Benchmark signal of the MAP disturbance signal derived from the model of the haemodynamic effect of surgical stimulations.

- \{A_{rpu}, B_{rpu}, C_{rpu}, D_{rpu}\}

These matrices represents the conjunction of all three models.

In the following chapter we will refer to these matrices. The simulation for the model based controllers, if not mentioned differently, were done with the given parameter sets and matrices.

5.1.1 Benchmark MAP disturbance signals

The control of MAP is basically a disturbance rejection problem. Set point variations are very infrequently applied. To evaluate disturbance rejection properties of a controller two different benchmark MAP disturbance signals were defined. The first is based on the model implemented in section 4. The chosen surgical disturbance is a piecewise constant function representing the main different stimulation intensities during surgery (see figure 5.2). The intensive cut and opening phase is represented with a high and 12 minutes long rectangular pulse. After that, during the main surgery phase (approx. 50 minutes long), a constant stimulation is admitted with an exemplary peak of especially intensive but short surgical stimulation. The closing and stitching phase is 25 minutes long and less intensive than the initial phase. The second disturbance profile (see figure 5.3) is derived from real measurements during a surgery. The signal contains all unmodeled disturbances: the measurement noise, artifacts and the effect of surgical stimulations. To generate this signal, the basic MAP of the patient (MAP_{init}) and the effect of the inhaled anaesthesia gas was subtracted after open loop simulation with the nonlinear model of section 2.
Figure 5.3: Benchmark signal of the MAP disturbance signal derived from measurements during surgery (third graphic). The estimated MAP basic level and the estimated effect of isoflurane (second graphic) has been subtracted from the measured MAP (first graphic). The high peaks on time points 170, 280, 380 and 475 are produced by measurement artifacts due to blood sample extractions.
Part III

Control Algorithms
Leer - Vide - Empty
The aim of this part is to report the experience made while applying different controller algorithms for the implementation of an anaesthesia control system. Since there were not much quantitative experience on feedback control in anaesthesia, we first tried simple controller methods. More advanced methods such as adaptive algorithms and neuronal fuzzy techniques may be used at a later time.

In this part we will present three different design techniques. The first one is the implementation of controller structures using fuzzy logic (chapter 6). This kind of controllers is experience based: the setting and tuning of the controllers are based on the experience made during manual control or during the last test of the control algorithms. Of course the first tuning phase can also be done in simulation, but it remains mainly a heuristic implementation approach. The other two techniques are model based: state feedback control (chapter 7) and model predictive control (MPC for short, chapter 8). Both explicitly use mathematical model descriptions of the plant (using differential equations) to compute the control action. Because of the long testing phases, the fast evolution of anaesthesia techniques and the necessity to implement other controllers than for the MAP, it was not always possible to apply different controller techniques for identical requirements and operating conditions. In addition, statistic test results need a large amount of clinical tests, which we have not been always possible to finish during this time period. Nevertheless the similarity of the problem formulation allows a comparison of the different approaches. The comparison will be done mainly looking at the implementation effort needed to obtain the desired behaviour and the effort needed for the enhancement of the controllers operating range.
6.1 Short introduction on fuzzy control

In this section we shortly introduce the concepts of fuzzy logic and fuzzy logic control. For more detailed introductions see [83, 84, 85].

6.1.1 Fuzzy sets and fuzzification

The notion of fuzzy sets were first introduced by Zadeh in 1965. In traditional (or crisp) sets the belonging of a given element to a set can be expressed by a binary crisp value. This means that the element can belong or not to the given set. In fuzzy logic the belonging of an element to a set is expressed by a value between 0 and 1. This value is called the membership or fuzzy set value. The function that describes the degree of belonging to a fuzzy set of an element depending on his characteristics (expressed in crisp number) is called membership function. Let us give an example: the set of big people ($\Omega$) can be defined in many ways (let $h$ be the height in cm of a person):

1. Binary logic:

\[
\begin{align*}
h \in \Omega & \iff \{h \mid h \geq 180\} \\
& (6.1)
\end{align*}
\]

2. Fuzzy logic:

\[
\begin{align*}
h \in \Omega \land h \in U \\
& (6.2)
\end{align*}
\]

$U$ is called the universe of discourse and is defined as the set of all considered heights. The membership function $\mu_\Omega$ is defined as:

\[
\mu_\Omega(h) = \begin{cases} 
0 & \text{if } h \leq 175 \\
\frac{h-175}{10} & \text{if } 175 < h < 185 \\
1 & \text{if } h \geq 185
\end{cases} \\
& (6.3)
\]
The first definition of big people divide the humanity into two parts, people that are big and people that are not. A fuzzy logic definition allows to define degrees of belonging: a person with 180 cm of height is big but belongs only with a membership of 0.5 to this set. The operation (e.g. $\mu_D(h)$) that permits to define a fuzzy set value (e.g. big) from a crisp value (e.g. $h$ value), is named fuzzyfication.

### 6.1.2 Definition of rules: the fuzzy inference machine

As in the given example fuzzy logic reflects often human thinking logic. Linguistic rules like:

- If a person is big, heavy and sporting then the person is not fat
- If a person is big, heavy and sedentary then the person is fat

left hand side (LHF) right hand side (RHF)

can be formulated as fuzzy logic operations. The operation that finds a new fuzzy set (membership to fat) from a set of rules (e.g. 1 or 2) depending on different fuzzy sets (e.g. big, heavy, sporting and sedentary), is named fuzzy inference machine. This operation is depending on the meaning of the operators (e.g. and, or, not) used on the linguistic rules. In our case, we will apply the min composition for the and and the max composition for the or operator in the LHS of the formulated rules. This method will take the minimal membership of the RHS sets tied up by the and logical operator to define the resulting shape of the LHS set (e.g. fat). After this step one needs to know how to combine these fuzzy variables resulting from a set of rules. To combine the different rules, all shapes are put together choosing the maximum value at each point. The result of the inference machine is a new fuzzy set. This fuzzy set summarizes the amount of information given by the crisp characteristics of an element (e.g. big, heavy, sporting and sedentary) and the formulated rules. This makes the fuzzy set a powerful mathematical description of linguistic rules.

### 6.1.3 From fuzzy to crisp: defuzzification

The last step (so called defuzzification) will return a crisp value from this resulting fuzzy set. Among the different defuzzification methods the center of gravity function was used in our application. The following weighted mean value $\bar{u}$ of the fuzzy set $\mu_f(u)$:

$$\bar{u} = \frac{1}{u_{\text{max}} - u_{\text{min}}} \int_{u_{\text{min}}}^{u_{\text{max}}} \mu_f \, du$$  \hspace{1cm} (6.4)

At the beginning the choice was given because it was the most used method. The experience with this particular technique it has proven to be robust and near to the linguistic rules formulated by the anaesthetists.

### 6.1.4 Mathematical interpretation

With the three steps (see figure 6.1):
6.1 Short introduction on fuzzy control

1. Fuzzification
2. Fuzzy inference
3. Defuzzification

It is possible to define a nonlinear static relation $J$ (example in figure 6.2) between an input vector of values $v_{in}$ and an output vector $v_{out}$.

![Figure 6.1: Structure of fuzzy evaluation of rules and tuning parameters.](image)

This nonlinear function is described by:

1. The membership functions of the input and output values $\mu_i$
2. The rules
3. The inference engine algorithm
4. The defuzzification method

In spite of the high number of tuning parameters (see figure 6.1), fuzzy logic has shown to be powerful especially for the implementation of static relationships based on human experience (and consequently often formulated as linguistic rules).

Because of the high number of tuning parameters, the task of systematic optimisation, in respect to a given objective function, remains extremely difficult. Some adaptive algorithms with different techniques were implemented to avoid this important disadvantage ([86, 87, 88, 89]). Almost all techniques are based on training phases.
6.1.5 Application field of fuzzy logic

At the beginning of the 80’s fuzzy logic was applied on almost all possible applications that needed such experience based nonlinear static relation, e.g.:

- Decision based systems
- Image processing
- Control Applications

6.1.6 Fuzzy logic control

The first European industrial application of fuzzy logic in a closed loop was implemented in 1974 (source from [84]). A steam generator was successfully controlled. The main motivation of applying fuzzy logic for control purposes was the translation of experience based manual actions into an automatic closed loop circuit.

The application of fuzzy logic in control loops can be realized in different ways, depending on whether a static nonlinear relation is needed in the algorithm. In our case we will use two different structures (see figure 6.3):

The first structure will use fuzzy logic directly in the closed loop to calculate the control value. The fuzzy system is composed of a dynamic preparation block and the fuzzy engine (6.1.6). The dynamic block prepares the crisp inputs for the fuzzy engine. The inputs can dynamically depend on the error, the measured values and the control value. Thus almost all possible linear dynamic elements (such as Kalman filters, observers, integrators, etc.) can
6.1 Short introduction on fuzzy control

Figure 6.3: Used structures of fuzzy logic in control loops.

Figure 6.4: The fuzzy system is composed by a dynamic block and the fuzzy engine. The dynamic block prepares the input for the fuzzy part. The fuzzy engine is a static nonlinear transfer function.

To implement a fuzzy controller, following implementation steps are necessary:

1. Formulation of linguistic rules and
2. Definition of inputs and outputs and their membership functions (together with the experts).
3. Definition of the controller structure to implement the results of step 1. and 2. on the computer.
4. Validation of the controller. The controller will be tested first through simulations (if any mathematical model of the plant is available), then in pilot studies. The parameters of the controller will be tuned in order to increase the performance.
Experience has shown that with a good structure definition, control behaviour equivalent to manual manual control is possible with a little implementation effort. However, a systematic tuning procedure to increase performance, has not yet been realized. Some results have been shown for adaptive or self-learning algorithms, sometimes using combinations of neuronal net theory and fuzzy logic [33, 32]. In our work we will not implement any of these self-tuning techniques for three main reasons: first, in the operating room there is not enough time to train the controller to the patient's individual dynamic response; second, a large effort is necessary to guarantee stability (in term of number of experiments needed and automatic supervisory functions), and third such an investigation requires long experience in non adaptive fuzzy control in this particular area. Some successful first results can be found in the literature ([24, 27, 32, 30]). These first results are encouraging, but are still far from routine applications in the field of biomedical critical care.

6.2 Fuzzy logic control in anaesthesia

The first idea of using fuzzy control algorithm in anaesthesia is to translate the experience of the anaesthetist in an automatic closed loop control. The main questions are if the controller can deal with a reduced amount of information for a wide application range and if this experience can be implemented correctly through fuzzy control. During two diploma theses [38, 43] and a semester thesis [39] a fuzzy controller of the MAP with isoflurane was successfully implemented (see [90]). The evaluation of clinical tests showed that the implemented fuzzy controller has an equivalent performance than manual control by anaesthetists [42]. The controller was realized with the structure type 1 (see 6.3), and a constant fresh gas flow of 3 l/min was used on the breathing system. For simulation, the following black-box model has been identified from measurements of step responses:

$$\Delta MAP = G(s) \frac{e^{-sT_{t1}}}{1+sT_{t1}} + \frac{e^{-sT_{t2}}}{1+sT_{t2}}$$

$$G(s) = K \left( A_1 \frac{e^{-sT_{t1}}}{1+sT_{t1}} + A_2 \frac{e^{-sT_{t2}}}{1+sT_{t2}} \right)$$

$$K \approx -10.3 \text{ [mmHg/vol%]}$$
$$A_1 \approx 0.30 \quad T_{t1} \approx 24 \text{ [s]} \quad T_1 \approx 100 \text{ [s]}$$
$$A_2 \approx 0.70 \quad T_{t2} \approx 100 \text{ [s]} \quad T_2 \approx 165 \text{ [s]}$$

The controller was tested and tuned in simulation and during 5 clinical studies. After that, MAP control was evaluated during skin incision on 32 different patient: 16 patients were tested with the fuzzy controller and 16 with manual control. The fuzzy control behaviour was evaluated as satisfactory in all episodes and not statistically different from manual control. The involved anaesthetists tried to be better than the automatic system. After this encouraging implementation, we tried to implement a fuzzy controller with a larger operating range and more automatisation.

In normal clinical conditions, 3 l/min fresh gas flow is considered as high and is mainly used when rapid changes in the gas concentrations are needed or if re-breathing is not demanded
6.3 Control of the inspiratory anaesthesia gas concentration

(e.g. during induction where $N_2$ must be flushed from the body). Under these conditions, the gas composition in the fresh gas is quickly transmitted to the patient. We can write ($P_i$ is the inspiratory concentration of gas type $i$, $P_f$ is the concentration of the fresh gas):

$$P_i \approx P_f$$ \hspace{1cm} (6.7)

and the settling time is below 30-40 sec.

To increase flexibility, any possible fresh gas flow should be used during control, from high flow (max. 10 l/min), through low flow (approx. 1 l/min), to minimal flow (min. 0.5 l/min). To achieve this operating range, a cascade structure was first implemented.

Because of the high re-breathing rate during low or minimal fresh gas flows, the gas concentrations of this flow are not equal to the inspiratory concentrations. The steady state relation between actuated and inspiratory composition of gas ($K_f$) is highly dependent on the mass balance of the gas exchange in the lungs, the respiratory parameters and the leakage. We can write:

$$P_i \approx K_f P_f \hspace{1cm} K_f \neq 1$$ \hspace{1cm} (6.8)

and the settling time slow (from 2-3 minutes to approx. 20 minutes). For this reason control of inspiratory $O_2$ had to be added to the control system (see section 6.4).

In the following sections a short description of the implemented controllers is given. We will begin with the control of the inspiratory anaesthesia gas and $O_2$ concentration. After that, the control of the endtidal anaesthesia will be described, which is widely used in the operating room. Finally, a description of the control of mechanical ventilation during anaesthesia will be given as an example of how fuzzy logic can be applied for other purposes.

### 6.3 Control of the inspiratory anaesthesia gas concentration

The control of the inspiratory anaesthesia gas concentration was first solved by a fuzzy controller with three inputs:

1. $e_{insp}$: the error between inspiratory set value ($SetP_{insp}$) and the measured value ($P_{insp}$)
2. $i e_{insp}$: the integral of this error ($i e_{insp}$) as input of the fuzzy inference engine.
3. $Flow$: the amount of fresh gas flow

The analysis of the transfer function of this controller showed a good correspondence with the following nonlinear PI-controller algorithm:

$$u_{gas}(k) = SetP_{insp}(k) + \frac{K_p}{Flow(k)} e_{insp}(k) + \frac{K_I}{Flow(k)} i e_{insp}(k)$$ \hspace{1cm} (6.9)
with:

\[ K_P = 2.5 \quad K_I = 0.16 \]  \hfill (6.10)

For high flows the time constants is very fast so that no control at all is needed (open loop) to set the inspiratory concentration. In addition the constant sampling time of 10 second is too large with respect to system's response: large \( K_P \) values for high fresh gas flows would therefore result in an unstable behaviour. It this case the Parameter \( K_P \) and \( K_I \) could be even set to zero (overshooting problems can then be avoided).

### 6.3.1 Results

This controller showed a good performance in clinical tests (resume of results see [91]). The controller was applied in all phases of artificial breathing, this means also in induction and emergence phases.

The controller was applied in a clinical study with 30 ASA I-II patients. Two groups were studied. In the first group of 15 patients (called standard group) the routine anesthesia method of the department was used (1.2-1.3 litre/min fresh gas flow). In the other group (called fuzzy group) feedback control of inspired isoflurane and oxygen was used. During surgery, if possible minimal flow anaesthesia (fresh gas flow equal 0.5 litre/min) was applied. The study was approved by the local Ethics Committee and written informed consent was obtained from all patients. Patients were allocated randomly to each of the two groups on an alternate basis. Feedback control was applied in all phases: induction, intubation, surgery, extubation. The controller achieved and maintained the desired inspired concentration of isoflurane during minimal flow anaesthesia very accurately (see figure 6.5): relevant overshoot resp. undershoot was not observed and the desired concentration (± 1 vol%) was maintained for 94 % of the time (see table 6.1). Details about material methods and results are described in [91].

### 6.4 Fuzzy logic control of the inspiratory \( O_2 \) concentration

If low and minimal flow anaesthesia technique are used, then all relevant inspiratory concentrations need to be controlled. Under such low fresh gas flow amounts, the high rebreathing rate, system leakages and the gas exchange in the lung have a large influence on the needed composition in the fresh gas. This also concerns the amount of inspiratory \( O_2 \) concentration (\( P_{O_2} \)). The response of \( O_2 \) concentration during minimal flows is extremely slow: with \( \text{Flow} = 0.5 \, [l/min] \) the step response shows a time delay between 30 and 40 seconds (with a sampling time of \( T_s = 10 \, [sec] \)). If we consider the breathing system on minimal flow condition as an ideal stirred gas tank with two inputs:
Figure 6.5: Controller behaviour during all phases of artificial breathing. During induction and emergence, high fresh gas flows where used. During main surgery phases, minimal flow anaesthesia was applied.
Table 6.1: Description of the control of inspired isoflurane concentration during the phase of minimal flow. \( n = \) Number of increases \((N_1)\) and decreases \((n_2)\) of isoflurane concentrations and of phases during which isoflurane concentration was not changed \((n_3)\), which were included in the analysis. The first four variables describe the ability on the feedback system to achieve the desired isoflurane concentration, whereas the last one describes the ability to maintain the desired concentration, beginning 2 min after achieving the desired concentration (more details on [91]).

<table>
<thead>
<tr>
<th>description</th>
<th>value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rise time to 100% ( (n_1 = 26) )</td>
<td>( 700 ) ((540-850))</td>
</tr>
<tr>
<td>Overshoot after increasing ( (n_1 = 26) )</td>
<td>( 0.1 ) ((0.1-0.2))</td>
</tr>
<tr>
<td>Decrease time ( (n_2 = 17) )</td>
<td>( 660 ) ((360-1130))</td>
</tr>
<tr>
<td>Undershoot after decreasing ( (n_1 = 17))</td>
<td>( 0.1 ) ((0.1-0.2))</td>
</tr>
<tr>
<td>Histogram of the control error ( (n_3 = 36))</td>
<td>-0.2 vol% (3%)</td>
</tr>
<tr>
<td></td>
<td>±0.1 vol% (94%)</td>
</tr>
<tr>
<td></td>
<td>+0.2 vol% (3%)</td>
</tr>
<tr>
<td></td>
<td>&gt;0.3 vol% (0%)</td>
</tr>
</tbody>
</table>

\[
F_{in_f} : \quad \text{the fresh gas inflowing in the cycle with } O_2 \text{ partial pressure } P_{O_2}
\]
\[
F_{in_{CO_2}} : \quad \text{the rejected } CO_2 \text{ flow in the lung}
\]

and two outputs:

\[
F_{out_{O_2}} : \quad \text{the } O_2 \text{ absorption flow amount in the lung}
\]
\[
F_{out} : \quad \text{the outflow}
\]

Assuming:

\[
F_{out_{O_2}} = F_{in_{CO_2}} \quad (6.11)
\]
\[
F_{out} = F_{in_f} \quad (6.12)
\]

results in the following mathematical model for the \( O_2 \) concentration in the tank with a typical volume \( V_{tank} = 4l \):

\[
\dot{x}_{O_2} = \frac{1}{V_{tank}} \{ P_{O_2} F_{in_f} - F_{out_{O_2}} \} \quad (6.13)
\]

The estimated metabolic \( O_2 \) consumption of a patient can be expressed as:

\[
F_{out_{O_2}} = 0.01 \, W_{kg}^{0.75} l/min \quad (6.14)
\]
With:

\[ 0 \leq P_{O_2}F_{inj} \leq 0.5 \ \text{l/min} \quad (6.15) \]

\[ 0 < P_{O_2}F_{inj} < 0.5 \ \text{l/min} \quad (6.16) \]

we obtain a minimal time constant of:

\[ T = \frac{6}{0.5 - 0.01W_{kg}^{0.75}} \ \text{min} \quad (6.17) \]

If we consider weights \( W_{kg} \) from 45 to 125 kg, we will have time constants from 12 to 32 minutes! The controller was tuned for a nominal point of 70 Kg, but it was set in order to work appropriately for the whole weight range.

The following specifications were set for the implementation of the controller:

- The controller should work with any fresh gas flow \( Flow \)
- The controller should reach the desired value \( SetP_{O_2} \)
- \( Flow \) should be as long as possible in minimal flow range
- A stronger reaction of the controller is expected for positive errors \( (P_{O_2} \) lower than \( SetP_{O_2} \) \) than for negative errors. An asymmetric and therefore nonlinear structure of the controller is needed.
- If the previous asymmetry is not sufficient and the error is larger than \( \epsilon_{O_2\text{max}} \) then the controller should provide a short \( O_2 \) flush (switching to high flow, 10 l/min, for about 4 seconds). \( \epsilon_{O_2\text{max}} \) is to be set point dependent:

\[ \epsilon_{O_2\text{max}} > 5 \left\{ 1 + \frac{SetP_{O_2} - 30}{70} \right\} \quad (6.18) \]

This means that for example given a desired \( O_2 \) inspired concentration of 30 vol%, a flushing process must be provided while the measured concentration is below 25 vol% (see figure 6.6).

- If the previous action is still not sufficient and \( P_{O_2} \) is lower than 23 vol%, then \( O_2 \) flushing must be hold until this limit is attained (emergency action).

### 6.4.1 Control structure

After testing several alternatives (mainly on clinical pilot studies) we decided to use a fuzzy rule base for the parameter determination of a PID controller with feed forward path and explicit nonlinearities (see figure 6.7). The structure is therefore basically composed of three main components:
The PID controller

The fuzzy block

Some explicit nonlinearities: $G$, $\alpha$, and $H$

Figure 6.7: Structure of the controller for the inspiratory $O_2$ concentration.

The PID controller

The classical weighted sum of the $O_2$ error $e_{O_2}$, a limited integral of the error $ie_{O_2}$ (with trivial anti reset windup) and a strongly filtered differentiation of the error $de_{O_2}$ are used:

$$e_{O_2}(k) = \alpha(SetP_{O_2}(k)) [SetP_{O_2}(k) - P_{O_2}(k)]$$

$$ie_{O_2}(k) = \begin{cases} ie_{O_2}(k-1) + e_{O_2}(k) & ||ie_{O_2}|| \leq 0.75 \\ 0.75 & ie_{O_2} > 0.75 \\ -0.75 & ie_{O_2} < 0.75 \end{cases}$$

$$de_{O_2}(k) = e_{O_2}(k) - e_{O_2}(k - 24) \quad (6.19)$$
The error is calculated as usual with an additional correction factor \( \alpha \). This correction factor will be explained later on. The integral is reset after each flow change. \( deO_2 \) is defined as the difference between the actual and the 4 minutes past value of the error: this big time difference has low pass character and is motivated by the very slow time constants. This corresponds to the actual procedures of the anaesthetists. In general such a simple numerical differentiation is susceptible to noise. However in this special case the measurement noise level is low enough to still give meaningful results. Because it is mainly used in low and minimal flow, the differentiation does not depend on the fresh gas flow \( Flow \). The output value of the controller \( \Delta uO_2 \):

\[
\Delta uO_2 = K_P eO_2 + K_I iO_2 + K_D dO_2
\]

is a percentage of change in respect to the given feed forward \( O_2 \) flow value \( F_{fO_2} \) and the fresh gas flow \( Flow \). The exact relation between \( \Delta uO_2 \), \( F_{fO_2} \) and \( Flow \) will be explained below, describing the nonlinearity \( H \).

The fuzzy block

The fuzzy block determines the PID control parameters \( K_P \), \( K_I \) and \( K_D \) from the \( O_2 \) error \( eO_2 \) and the set fresh gas flow \( Flow \). It provides for a sliding parameter change (gain scheduling). The following strategy was implemented (see figures 6.8, 6.9 for the input respectively output membership functions and figure 6.10 for the defined rule base):

- If the error is big, use basically only a strong P-controller
- If the error is small, use the highest values for \( K_I \) and \( K_D \), and a normal \( K_P \)
- For increasing flows, decrease the control action and act as open loop control.
- If the error is medium and it decreases fast, then activate \( K_D \) to slow down the decrease and avoid over- and undershooting.

The Membership functions for \( eO_2 \) are characterized by an asymmetry of the 2 extreme values (\( pb \) and \( nb \)). This asymmetry can be mainly motivated by the request of asymmetric behaviour of the controller in respect to the sign of the error. The 2 central values (\( med \) and \( ze \)) cover the error region around zero. \( med \) covers a larger left side because it is used to activate \( K_D \) on time to avoid fast decreases of \( O_2 \) (which is also a condition). Using the center of gravity method for defuzzification allows the use of non overlapping output membership functions. This visualization of the functions allows a more transparent individual weighting. Note that the same final result could be attained with overlapping output membership functions.

Explicit nonlinearities: \( \mathcal{G} \), \( \alpha \), and \( H \)

Fuzzy logic control is an elegant way to describe nonlinearities, but it is not always convenient to integrate predefined nonlinearities in a fuzzy rule base. The danger of such integrations
Figure 6.8: Input membership functions for the control of the inspiratory $O_2$.

Figure 6.9: Output membership functions for the control of the inspiratory $O_2$. 
6.4 Fuzzy logic control of the inspiratory $O_2$ concentration

<table>
<thead>
<tr>
<th>INPUTS</th>
<th>OUTPUTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>$e_{O2}$</td>
<td>Flow</td>
</tr>
<tr>
<td>Kp</td>
<td>$K_d$</td>
</tr>
<tr>
<td>nb</td>
<td>sml</td>
</tr>
<tr>
<td>pb</td>
<td>sml</td>
</tr>
<tr>
<td>med</td>
<td>sml</td>
</tr>
<tr>
<td>ze</td>
<td>sml</td>
</tr>
<tr>
<td>pb</td>
<td>sml</td>
</tr>
<tr>
<td>-</td>
<td>big</td>
</tr>
</tbody>
</table>

Figure 6.10: Fuzzy rule base of the fuzzy block for the determination of the parameter of the PID part of the controller of the inspiratory $O_2$.

is to build contradictory and complicated fuzzy rule bases that are very difficult to tune adequately. This is why we decided, after several failed attempts, to construct a more complex control structure with all known nonlinearities defined outside the PID and the fuzzy block:

1. $G$: **feed forward value**: The feed forward value is calculated from the actual fresh gas flow $Flow$ and the desired $O_2$ concentration:

   $P_{f_{O2}} = G(Flow, SetPo_2) = \begin{cases} \frac{1}{2} [4 SetPo_2 + (2 SetPo_2 - 200)(Flow - 0.5) + 300] & Flow \leq 2 \\ SetPo_2, Flow & Flow > 2 \end{cases}$

   (6.21)

   The three dimensional static nonlinearity of equation 6.21 (see figure 6.11) represents an estimation of the basic set value of the $O_2$ flow. It is the result of a linear interpolation between the following points:

   - For flow $\geq 2$ l/min no strong oxygen control is necessary, so the concentration of the fresh gas flow can be set equal to the desired inspiratory concentration
   - At minimal flow and $SetPo_2 = 30$ vol%, a $O_2$ fresh gas flow of 0.3 l/min is generally a good setting.

2. $\alpha$: **correction factor of the error**: In equations 6.19 the $O_2$ error was corrected by a factor $\alpha$:

   $\alpha(SetP_{insp}) = 1 - \frac{0.5}{10} (SetP_{O2} - 30)$

   (6.22)

   This factor is interpolated between the two extrema: $\alpha = 1$ if the set value is 30 vol% and $\alpha = 0.5$ if it is 100 vol%. This is because on minimal flow, the settling times of the two extreme working points are different by a factor of approximatively 2: therefore the errors of higher set points should be weighted by a half for the same controller (this is a kind of nonlinear gain compensation).
3. \( \mathcal{H}: \) Output value: The output value is defined as follow:

\[
F_{O_2} = \mathcal{H}(F_{ffo_2}, \Delta u_{O_2}, Flow) = F_{ffo_2} + \Delta u_{O_2} \begin{cases} 
F_{ffo_2} & \Delta u_{O_2} < 0 \\
Flow - F_{ffo_2} & \Delta u_{O_2} \geq 0
\end{cases}
\]

(6.23)

In this way the output is scaled in such a way that the universe of discourse of \( \Delta u_{O_2} \) is \( \in [-100 100] \) with zero equal to the unmodified feed forward value.

![Graphical overview of equation 6.21.](image)

Figure 6.11: Graphical overview of equation 6.21.

### 6.4.2 Results

The controller was applied at the same time as the controller of the inspired anaesthesia gas concentration of section 6.3. Figure 6.12 shows a typical behaviour of the oxygen controller in all phases of anaesthesia. During induction and emergence a high fresh gas flow (between 8 and 10 [litre/min]) of 100% of oxygen were used. After intubation, fresh gas flow was set to 4 [litre/min] for 15 [min]. Flow was then reduced to 1.2-1.3 [litre/min] in the standard group and 0.5 [litre/min] in the fuzzy group. To prevent accumulation of non-anaesthesia gases, when the cumulative inspired concentration of oxygen and nitrous oxide and isoflurane was lower than 85 vol\%, fresh gas flow was increased manually to 8 [litre/min] until a total concentration of 97 vol\% was achieved (see figure 6.12 fresh gas pulses on minute 54, 114...
6.4 Fuzzy logic control of the inspiratory $O_2$ concentration

and 195). A typical transition phase from 4 to 0.4 [litre/min] fresh gas flow can be observed at minute 33. A short $O_2$ flush (switching to high flow, 10 l/min, for about 4 seconds) was necessary around minute 46 where $P_{O_2}$ reached 26 [vol%].

![Graph of Set and measured inspired oxygen concentration](image1)

![Graph of Total and oxygen fresh gas flow](image2)

Figure 6.12: Controller behaviour during all phases of artificial breathing. During induction and emergence high fresh gas flows were used. During main surgery phases, minimal flow anaesthesia was applied.

During the study a comparison between a standard, manually controlled group of patients, and a fuzzy controlled group was done. The control of inspiratory concentration of the fuzzy group was more precise than the standard group (see 6.2), in spite of the lower fresh gas flow delivered. The fuzzy controller was therefore able to satisfy the requested performances (More details about material methods and results are described on [91]).

The structure of resulting controller is composed of a PID based algorithm, explicit nonlinearities and a fuzzy engine part. The design strategy was to decouple crisp knowledge about nonlinearities from fuzzy based nonlinearities. The resulting controller meets its specifications, however its structure is now quite complex. It will be interesting to try to simplify it in a future phase.
Table 6.2: Control of inspired oxygen ($O_2$) concentration in the two groups during the maintenance phase (between $t = 34$ [min] and $t = 232$ [min] in figure 6.12). The duration of episodes during which the concentration was between 28 and 32 [vol%] are expressed as percentage of duration of the maintenance phase. Median (25-75 percentiles) values are presented.

6.5  Fuzzy logic control of the endtidal anaesthesia gas concentration

The endtidal concentration is used by the anaesthetist to estimate the amount of inhaled anaesthesia drug in the body of the patient. The control of this output variable is therefore an efficient way to set and maintain the effect of the applied drug. The controller structure will be of the second type (see figure 6.3).

6.5.1 Controller structure

The controller is in cascade with the inspiratory anaesthesia controller of section 6.3 (see figure 6.13). The endtidal controller essentially consists of a PID controller with feed forward path and a fuzzy engine setting the PID parameter depending from the actual error $e_{rEndt}$

![Figure 6.13: Cascade structure of the fuzzy controller of the endtidal concentration with the inspiratory PID controller. $P_i$ and $P_e$ are the measured anaesthesia gas concentrations (inspired, resp. endtidal); $r_i$ and $r_e$ are their respective reference values.](image)
6.5 Fuzzy logic control of the endtidal anaesthesia gas concentration

and fresh gas flow rate $Flow$ (see figure 6.14). The transfer function of the used PID controller is:

$$G_{PID}(s) = K_r (K_p + \frac{1}{sT_n} + \frac{T_{e1}}{sT_f1 + 1})$$ \hspace{2cm} (6.24)

Letting $K_r = 1$ results in the standard Ziegler-Nichols form and letting $K_r = 1$ in the parallel structure. The resulting discrete controller scheme can be seen in figure 6.15. The implemented anti reset windup (ARW) strategy will freeze the integral value during saturation of the controlled variable. This strategy has shown to be appropriate for a control strategy with a dominant $P$ action and a slow $I$ action used for steady state compensation. During a step change or a fast change of the error due to disturbances, $K_p$ will lead to a saturated control variable. A classical ARW strategy will continuously update the integral value in order to reach the saturation limit. This can lead to long rise times if a slow integral action will be applied. In our case the integral part has a physical meaning: it is a value affine to the actual $O_2$ consumption in the body. Therefore one can assume that no fast changes on the integral actions will apply during saturation of the control action.

![Figure 6.14](image-url)

Figure 6.14: Structure of the fuzzy controller of the endtidal concentration. The controller is characterized by a PID controller with feed forward path and a fuzzy engine setting the PID parameter.

The feed forward path is motivated by the fact that the DC gain of the plant is known and equal to one. The integral part of the PID controller will be therefore only used for error compensation. After the tuning phase, best results were obtained with the fuzzy engine described by the input and output membership functions of figure 6.16 respectively figure 6.17, and the rules given in table 6.3. The control strategy can be resumed in the following way:

- if the error is big: then use mainly a $P$-Controller
- if the error is small: then use mainly a $I$-Controller to compensate unmodeled disturbances (the $P$-gain will be decreased).
Figure 6.15: Structure of the discretized PID controller of the endtidal concentration. The parameters of the controller are set by a fuzzy engine.

- if the fresh gas flow is big: then reduce the P gain and decrease the I-time constant

In fact it is a PI controller: the factors $K_{r1}$ and $T_{v1}$ were not used and are only presented to reflect the implemented software structure.
Figure 6.16: Input membership functions for the control of the endtidal anaesthesia concentration.

Figure 6.17: Output membership functions for the control of the endtidal anaesthesia concentration.
<table>
<thead>
<tr>
<th>Nr</th>
<th>INPUTS</th>
<th>OUTPUTS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>erEndt</td>
<td>Flow</td>
</tr>
<tr>
<td>1</td>
<td>nb</td>
<td>ps</td>
</tr>
<tr>
<td>2</td>
<td>pb</td>
<td>ps</td>
</tr>
<tr>
<td>3</td>
<td>nb</td>
<td>pm</td>
</tr>
<tr>
<td>4</td>
<td>pb</td>
<td>pm</td>
</tr>
<tr>
<td>5</td>
<td>nb</td>
<td>pb</td>
</tr>
<tr>
<td>6</td>
<td>pb</td>
<td>pb</td>
</tr>
<tr>
<td>7</td>
<td>ze</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>pb</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>nb</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>ze</td>
<td>ps</td>
</tr>
<tr>
<td>11</td>
<td>ze</td>
<td>pm</td>
</tr>
<tr>
<td>12</td>
<td>ze</td>
<td>pb</td>
</tr>
<tr>
<td>13</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 6.3: Rule base for the determination of the parameter of the PID controller for the control of endtidal anaesthesia gas concentration. nb: negative big, nm: negative medium, ns: negative small, ze: zero, ps: positive small, pm: positive medium, pb: positive big.
6.5 Fuzzy logic control of the endtidal anaesthesia gas concentration

6.5.2 Results

Figure 6.5.2 shows some step responses measured during a pilot study with a constant fresh gas flow of 1 litre/min. Although the rise time (to ±15% of the set value) is fast, the settling time is not satisfactory. The anaesthetists evaluated the controller as “good enough” but wished a “faster and better” step response. Especially the settling phase around $t = 15\ [min]$ and $t = 55\ [min]$ of figure 6.5.2 was felt to be insufficient. This effect is the consequence of the internal regulator windup and should be addressed in a future phase.
Figure 6.18: Clinical study with PID control of endtidal concentration switched by a fuzzy rule engine. The endtidal anaesthesia gas controller is set in cascade with the inspiratory anaesthesia gas controller of section 6.3.
6.6 Fuzzy logic control of mechanical ventilation during anaesthesia

6.6.1 Problem description

During anaesthesia, the mechanical ventilation must continuously be controlled and adjusted in order to maintain a suitable arterial CO₂ partial pressure $P_{acO_2}$ (also called tension). In anaesthesia for intracranial surgery, for example, hypocapnia (reduced $P_{acO_2}$ from the normal value) is used to reduce brain volume and intracranial pressure. Even though there exist recommendations for initial settings of the respirator parameters to achieve a certain $P_{acO_2}$ ([92], [93], [94], [95]), it will usually be necessary to individually adjust these parameters during anaesthesia for the following reasons:

- there is a broad variability among different patients and it is not likely that initial parameter settings will result in exact desired $P_{acO_2}$
- physiological parameters such as CO₂ production and the ratio of alveolar ventilation to pulmonary perfusion may change during anaesthesia and surgery.

Non invasive estimates for $P_{acO_2}$ can be obtained through monitoring the endtidal CO₂ fraction ($F_{ecO_2}$). This is measured with capnometry ([96], [97]) online in the surgery room (after each breath cycle a new measurement is available). Direct measurement of $P_{acO_2}$ analyzing arterial blood gases is very time consuming and expensive. Therefore, this type of analysis is normally used only once or twice during surgery to check the difference between $P_{acO_2}$ and $F_{ecO_2}$. Because $P_{acO_2}$ is influenced by the effectiveness of the gas exchange mechanism on the lung, it can be influenced by the ventilator settings. A possible control variable is the ventilation of the lung represented by the respiratory minute volume ($MV$, breathing volume per minute). This value represents the mean value of gas flow circulating from the breathing machine through the mouth of the patient in the trachea and lung. Increasing the ventilation of the lung will increase the "wash out" of CO₂ from the body and therefore decrease $F_{ecO_2}$ and vice versa (see measured step responses on figure 6.19). The respiratory minute volume is given by

$$MV = f_R \cdot V_T$$

(6.25)

where $f_R$ denotes the respiratory frequency (breath per minute) and $V_T$ denotes the tidal volume (inspired breath volume). The ratio of duration of the inspired phase $T_i$ to $V_T$ and the ratio of duration $T_i$ of the inspiratory phase to the duration $T_e$ of the expired phase (see figure 6.20) influences pulmonary pressures (e.g. $p_{plateau}$, $p_{peak}$). For this application the second ratio was set by the anaesthetist and was kept constant during operation. As explained before, fuzzy logic has proved to be especially useful for application where heuristic control schemes, given as linguistic rules, were to be translated into a control algorithm. Since every anaesthetist does a fairly good job in controlling $F_{ecO_2}$, the goal was not to develop a completely new control strategy but to use these heuristic rules to design a reliable controller that takes over the task of maintaining a certain $F_{ecO_2}$. Fuzzy logic was therefore a logical choice.
Figure 6.19: Measured step responses of endtidal CO$_2$ concentration changing the ventilation of the lung MV.

Figure 6.20: The different phases of a respiratory cycle.

6.6.2 The control scheme

For the structure of the controller we again have been inspired by the anaesthetists strategy. In a first step the increment $\Delta MV$ per kg of body weight is determined based on the error
6.6 Fuzzy logic control of mechanical ventilation during anaesthesia

and the derivative of the error of the endtidal CO$_2$ fraction by a first fuzzy rule block (see figure 6.21). So the first block of the controller is basically a nonlinear PI-controller. This block accounts for the dynamic part of the controller.

![Figure 6.21: Controller structure of fuzzy control of endtidal CO$_2$ concentration: first step.](image)

In a second step the ventilator parameters $f_R$ and $V_T$ are determined (see figure 6.22). The respiratory frequency $f_R$ is computed based on the desired $MV$, allowed $p_{plateau}$ and the actual $f_R$ by a second fuzzy rule block. In this stage fuzzy logic is applied for decision making: with exception of the dynamics of $p_{plateau}$ this block does not really contribute to the main dynamics of the controller. It is mainly a mapping of three input variables to one output. This strategy is essentially the same as performed by an anaesthetist. He first decides about increasing, decreasing or maintaining the minute volume based on the actual value of $F_{eCO_2}$ and its trend. He will also take the patient’s weight into account to determine the size of the corrective steps. In a second stage he will decide how to split $MV$ into $f_R$ and $V_T$.

![Figure 6.22: Controller structure of fuzzy control of endtidal CO$_2$ concentration: second step.](image)

6.6.3 First step: setting the $MV$

The capnograph (Capnomac Ultima-SV, Datex Instrumentarium Corp., Helsinki, Finland) gives new $F_{eCO_2}$ measurements 6 time a minute. Therefore a sampling rate $f_s$ of 6 [1/min] was chosen. The error of the endtidal $CO_2$ ($e_{CO_2}$) is calculated with the difference between
the actual set and measured value while the derivative is calculated as the difference between
the actual and the one minute past error value:

\[ e_{CO_2}(k) = SetF_{eco_2}(k) - F_{eco_2}(k) \tag{6.26} \]
\[ \Delta e_{CO_2} = e_{CO_2}(k) - e_{CO_2}(k-6) \tag{6.27} \]

This simple differentiator is near to anaesthetists' thinking and is approximatively equivalent
to a differentiation with low pass filtering. After the tuning phase, the resulting input and
output membership functions of the first block (see figure 6.23 respectively figure 6.23)
had triangular and trapezoidal form, mainly symmetric with some asymmetric exceptions
(coming from tuning process). For each input and output values five fuzzy sets were defined:

1. **nb**: negative big
2. **ns**: negative small
3. **ze**: zero
4. **ps**: positive small
5. **pb**: positive big

*From our experience five sets are the maximum number of divisions that can be done to
describe heuristic experience based rules. The same division could be expressed by: “very
low, medium low, it is ok, medium high, very high”*

![Valuename: erCO2 Type: Input](image1)
![Valuename: derCO2 Type: Input](image2)

**Figure 6.23: Input membership functions for the control of \( F_{eco_2} \).**

A rule base of 19 rules were used to define the inference machine of the first block (see
figure(6.25). All rules are intuitive and follow the intuitive linguistic rules, e.g.:
Figure 6.24: Output membership functions for the control of $F_{\text{eCO}_2}$.

- If the error is big, then act rapidly to reduce the error (rules 14 and 19),
- If the error is medium but a small progressive error reduction was observed, then no action is required (rules 7 and 10),
- If the error is medium but a big progressive error reduction was observed, then a "breaking" action is required to stop the tendency (rules 8 and 9),

Rule 15 or 16 can be fully active with rule 14. This was done to reduce the effect of the more general rule 14, since there is no contradiction between these rules, no instability problems are expected from this implementation. The same structure was symmetrically applied in rules 17 to 19.

6.6.4 Second step: splitting of $MV$ in to $V_T$ and $f_R$

The aim of the second fuzzy block is to split the calculated new value of ventilation $MV$ into tidal volume and breathing frequency holding the plateau pressure within bounds. The main rule was to maintain $V_T$ and $f_R$ in the "middle" region (described in both cases with fuzzy set pm, see figures 6.26 and 6.27 for the input respectively the output membership functions). Because breathing frequency can only be set to cardinal values (from 6 to 20), the small changes were realized by modifying the tidal volume.

The main principle of the second block is therefore based on the decision if the frequency $f_R$ should be modified or not from the actual value. The fuzzy engine is based on 10 rules (see figure 6.28). Rules 20 to 28 describe the intention to shift both $f_R$ and $V_T$, to the medium set pm. Rule 29 activates a strong reaction on the output in case of a high value of $p_{\text{plateau}}$ (see membership function of pb of the output value $\Delta F_R$ on figure 6.27).
<table>
<thead>
<tr>
<th>Nr</th>
<th>INPUTS</th>
<th>OUTPUTS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>erCO2</td>
<td>derCO2</td>
</tr>
<tr>
<td>1</td>
<td>ze</td>
<td>ze</td>
</tr>
<tr>
<td>2</td>
<td>ze</td>
<td>ns</td>
</tr>
<tr>
<td>3</td>
<td>ze</td>
<td>ps</td>
</tr>
<tr>
<td>4</td>
<td>ns</td>
<td>nb</td>
</tr>
<tr>
<td>5</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>6</td>
<td>ns</td>
<td>ze</td>
</tr>
<tr>
<td>7</td>
<td>ns</td>
<td>ps</td>
</tr>
<tr>
<td>8</td>
<td>ns</td>
<td>pb</td>
</tr>
<tr>
<td>9</td>
<td>ps</td>
<td>nb</td>
</tr>
<tr>
<td>10</td>
<td>ps</td>
<td>ns</td>
</tr>
<tr>
<td>11</td>
<td>ps</td>
<td>ze</td>
</tr>
<tr>
<td>12</td>
<td>ps</td>
<td>ps</td>
</tr>
<tr>
<td>13</td>
<td>ps</td>
<td>pb</td>
</tr>
<tr>
<td>14</td>
<td>nb</td>
<td>–</td>
</tr>
<tr>
<td>15</td>
<td>nb</td>
<td>ps</td>
</tr>
<tr>
<td>16</td>
<td>nb</td>
<td>pb</td>
</tr>
<tr>
<td>17</td>
<td>pb</td>
<td>nb</td>
</tr>
<tr>
<td>18</td>
<td>pb</td>
<td>ns</td>
</tr>
<tr>
<td>19</td>
<td>pb</td>
<td>–</td>
</tr>
</tbody>
</table>

Figure 6.25: Fuzzy rule base of block I to set the rate change for MV per kg ($\Delta MV$).
6.6 Fuzzy logic control of mechanical ventilation during anaesthesia

The output of this block is a real value between $-2.5$ and $2.5$. The value is first converted to an integer value with following nonlinear function $F$:

$$F(\Delta F_R) = \begin{cases} 
2 & \Delta F_R > 1.5 \\
1 & 0.5 > \Delta F_R \geq 1.5 \\
0 & -0.5 \geq \Delta F_R \geq 0.5 \\
-1 & -1.5 \leq \Delta F_R < -0.5 \\
-2 & \Delta F_R < -1.5 
\end{cases}$$

(6.28)

This function corresponds to a discretization of $\Delta F_R$. The following additional crisp meta rules at the output of the second block were defined ($F$):

- New changes to $f_R$ are only possible after 30 seconds (3 time periods) with exception of the case that the needed tidal volume is out of the bounds. This meta rule was introduced to avoid frequent frequency changes and to take into account the response time of $p_{plateau}$ after big changes in $V_T$ and $f_R$. 

Figure 6.26: Input membership functions for the splitting of MV in to $V_T$ and $f_R$. 

![Respiratory frequency and Tidal volume membership functions](image1)

![Plateau Pressure membership function](image2)
6.6.5 Tuning and test phase

Before being able to test the controller during surgery, it had to be tested and tuned in simulations. For that purpose input-output-data recordings \((MV(k), F_{eco_2}(k))\) of four patients were acquired. \(MV\) was frequently changed to ensure persistent excitation. Then linear models

\[
\delta F_{eco_2}(k) = \frac{B_i(q)}{A_i(q)} \delta MV(k) \quad i = 1, \ldots 4
\]

with e.g.

\[
B_1 = \begin{bmatrix} 0.00e + 0 & -4.81e - 4 & 2.84e - 4 & 1.61e - 4 & 0.00e + 0 & 0.00e + 0 & 0.0e + 00 \end{bmatrix}
\]

\[
A_1 = \begin{bmatrix} 1.00e + 0 & -1.08e + 0 & -7.13e - 1 & 7.91e - 1 & 1.49e - 1 & -1.64e - 1 & 2.31e - 2 \end{bmatrix}
\]

were identified using ARX model structures. The parameter estimation was done using Least-Squares method (see [98]). In a second step, fine tuning was done during 20 clinical tests.
6.6 Fuzzy logic control of mechanical ventilation during anaesthesia

<table>
<thead>
<tr>
<th>Nr</th>
<th>INPUTS</th>
<th>OUTPUTS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>freq</td>
<td>vol</td>
</tr>
<tr>
<td>20</td>
<td>ps</td>
<td>ps</td>
</tr>
<tr>
<td>21</td>
<td>pm</td>
<td>pm</td>
</tr>
<tr>
<td>22</td>
<td>pb</td>
<td>pb</td>
</tr>
<tr>
<td>23</td>
<td>ps</td>
<td>pb</td>
</tr>
<tr>
<td>24</td>
<td>pb</td>
<td>ps</td>
</tr>
<tr>
<td>25</td>
<td>ps</td>
<td>pm</td>
</tr>
<tr>
<td>26</td>
<td>pm</td>
<td>ps</td>
</tr>
<tr>
<td>27</td>
<td>pm</td>
<td>pb</td>
</tr>
<tr>
<td>28</td>
<td>pb</td>
<td>pm</td>
</tr>
<tr>
<td>29</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Figure 6.28: Fuzzy rule base of block II to set the change of breathing rate given $f_R$, MV and $P_{plateau}$.

Basically only 5 were used to tune the first block while additional 15 where used for the decision block. This can be explained by the difficulty of clearly stating linguistic rules for intuitive decisions where individual anaesthetist may be of different opinion. The meta rules added to the controller were also tuned during this additional test phase.

6.6.6 Results

After obtaining the approval of the ethics committee, the performance of the controller was evaluated in the operating theater in an extensive clinical study ([99, 100]). Here we will only recapitulate the main results. The criterion for comparison was the ability to track a step change in the reference signal $SetF_{eCO_2}$. With every patient two such step experiments were conducted, one to evaluate the performance of the fuzzy logic controller and one to evaluate manual control. A wide variety of patients differing in age, sex, weight and type of surgery had been selected to get an idea of the robustness of the controller.

In all experiments both fuzzy control and manual control yielded satisfactory results. The sequence of figures 6.29 and 6.30 show a selection of variables for fuzzy and manual control for a typical procedure. The left part of figure 6.29 shows the response of the endtidal CO$_2$ fraction. As it was mostly the case, no significant difference between fuzzy and manual control can be observed. The right part of figure 6.29 shows the time history for the respiratory frequency set during the experiment. In figure 6.30 on the right, the corresponding selected tidal volume is shown. And finally, the resulting plateau airway pressure is shown in the left side of the same figure.

A slightly different result is obtained if a whole set of responses (for different patients) for either control are plotted all on top of each other. In this case fuzzy control on the average follows the desired $F_{eCO_2}$ with greater precision than manual control does. The reason for a spread in manual control is that as long as the anaesthetist was able to pay close attention
to the task of tracking, the reference input he performed well but as soon as his attention was absorbed elsewhere, the performance significantly decreased.
6.7 Concluding observation about fuzzy logic in control

Fuzzy logic was successful applied during this work. With this heuristic control method, the expert knowledge could be translated into automatic control algorithms. Performances similar to human manual control, could be easily reached as soon that human knowledge was formulated correctly or that a a simple mathematical model was available for the tuning phase. However, the necessary extraction of expert knowledge about the process to be controlled required much time. Additional performance enhancement through adequate tuning was certainly the main problem while applying fuzzy logic control. In our work any attempt to further improve the implemented controllers, led to long tuning phases with relatively poor results. This effect is certainly also due to the parameter variability in a group of patients: since no specific parameters (such as weight or ventilation) was considered in the fuzzy algorithm, only conservative settings could guarantee sufficiently robust performances. Introducing some specific information about the actual plant characteristic (such as weight or ventilation) would certainly help to improve the control performance. However the tuning effort will drastically increase and need many more clinical tests. Very good experiences were made using fuzzy logic for decision based functions. In this case human decision strategy could be implemented in a direct way and a short time delay.

Figure 6.31: A set (6) of $F_{\text{eCO}_2}$ responses plotted on top of each other. The results for manual control are shown in the right graphic and those for fuzzy control in the left graphic.
Chapter 7

State feedback control

7.1 General Structure of an observer based state feedback controller with reference tracking

To find a mathematical model of the system is a large effort, but leads to better understanding of its behaviour and a more precise description of the internal processes. This increased amount of information about the plant can be used to increase control performance. Model based control techniques were developed to use the information of mathematical models. If the internal states of a plant are not measurable then an observer is necessary to get estimates of these values. The most important model based control strategy is certainly state feedback control. The general scheme of a observer based state feedback controller is shown in figure 7.1.

Figure 7.1: General structure of an observer based state feedback controller with reference tracking. $K$ is the controller gain Matrix, $r$ is the reference value vector, $r^*$ is the filtered reference vector, $u$ is the control value vector, $y$ is the vector of measured outputs and $\hat{x}$ is the vector of estimated states.
The system is assumed to be linear (through linearization, if necessary):
\[ \dot{x} = Ax + Bu \]
\[ y = Cx + Du \]

where
- \( x \) : vector of system states
- \( A, B, C, D \): system matrices
- \( u \) : vector of control variables
- \( y \) : vector of measured outputs of the system

In the following sections, \( A, B, C, D \) represents the plant description resulting from the modeling. The effective real plant can differ from this linear model.

### 7.1.1 The observer

When not all internal states are measurable, an observer is needed. The general observer structure can be seen on figure 7.2.

![Observer Diagram](image)

Figure 7.2: Detailed structure of an observer based state feedback controller with reference tracking. \( K \) is the controller gain matrix, \( r \) is the reference value vector, \( r^* \) is the filtered reference vector, \( u \) is the control value vector, \( y \) is the vector of measured outputs, \( \hat{x} \) is the vector of estimated states and \( \hat{y} \) is the vector of estimated measurements.

The differential equation of the observer can be written as:
\[ \dot{\hat{x}} = [A - LC]\hat{x} + [B - LD]u + Ly \]  \hspace{1cm} (7.3)
\[ \hat{y} = C\hat{x} + Du \]  \hspace{1cm} (7.4)
where \( \dot{x} \) is the vector of estimated states and \( \dot{y} \) the vector of estimated outputs.

### 7.1.2 The state feedback controller

The controller output of a state feedback controller is the weighted sum of the actual state of the plant:

\[
u = r^* - K \dot{x}
\]

where \( K \) is the design matrix of weights ("gains") to apply to the states. The values of \( K \) establish the position of poles of the closed loop system. Usually the determination of \( K \) depends on the minimization of a cost function. We will apply the so called Linear Quadratic Regulator (LQR for short, see [101]): the algorithm minimizes the weighted quadratic norm over the time of \( x \) and \( u \):

\[
J = \int_0^\infty \left\{ x^T(t)Q x(t) + u^T(t)R u(t) \right\} dt
\]

### 7.1.3 Trajectory tracking

The state feedback controller has to follow a reference state that can be different from the zero steady state. To do this, an external compensation \( \Phi \) (see figure 7.2) of the reference value is necessary to adjust the input-output gain which should be equal to one. This means:

\[
\Phi = \left( \lim_{s \to 0} G_{tot}(s) \right)^{-1}
\]

\[
\lim_{s \to 0} G_{tot}(s) = -C_{tot}A_{tot}^{-1}B_{tot} + D_{tot}
\]

\( G_{tot} \) is the closed loop transfer function of the system with observer and state feedback loop:

\[
\begin{bmatrix}
\dot{x} \\
\dot{\hat{x}}
\end{bmatrix} = \begin{bmatrix}
A & -BK \\
LC & A - LC - BK
\end{bmatrix} \begin{bmatrix}
x \\
\dot{x}
\end{bmatrix} + \begin{bmatrix}
B \\
B_{tot}
\end{bmatrix} r^*
\]

\[
y = \begin{bmatrix}
C \\
D_{tot}
\end{bmatrix} \begin{bmatrix}
x \\
\dot{x}
\end{bmatrix} + D_{tot} r^*
\]

\[
G_{tot} = C_{tot}(sI - A_{tot})^{-1}B_{tot} + D_{tot}
\]

**LQR trajectory tracking**

In our case we want to solve the problem of achieving a desired trajectory. In other terms, we want to control the system such that its output \( y(.) \) tracks a desired trajectory \( \dot{y}(.) \). The
solution of this problem is given in [101]. First it is necessary to define a cost term in the performance index involving the error \((y - \hat{y})\):

\[
J = \int_0^\infty \{\hat{y}^T Q_1 \hat{y} + (y - \hat{y})^T Q_2 (y - \hat{y}) + u^T R u\} \, dt
\] (7.12)

\(Q_1\) and \(Q_2\) are nonnegative definite symmetric matrices. The performance index is derived from the following form:

\[
J = \int_0^\infty \{(x - \hat{x})^T Q (x - \hat{x}) + u^T R u\} \, dt
\] (7.13)

with:

\[
L = C^T (C C^T)^{-1}
\] (7.14)

\[
\hat{C} = I - L C
\] (7.15)

\[
\hat{y} = \hat{C} x
\] (7.16)

\[
Q = \hat{C}^T Q_1 \hat{C} + \hat{C}^T Q_2 \hat{C}
\] (7.17)

Notice that \(C \hat{y} = 0\). It is possible to interpret \(\hat{x}\) as the desired state trajectory. The authors warn about choosing the terminal time of the integration to infinity (mainly for reasons of the convergence time of the error which is approaching infinity). In this case however, the problem does not appear due to the following reasons: a high parameter uncertainty forces us to add an additional integral part to the controller that will shorten the convergence time. In addition, we are mainly tracking constant set points (step changes). This kind of tracking signal is less critical in term of convergence.

**Reference trajectory tracking**

The MPC controller (see next chapter) allows to find an optimal solution through knowledge of the given reference trajectory or a known disturbance trajectory. The LQR control strategy can also be expanded to include such a priori knowledge. Defining a reference model for the desired output \(\hat{y}\):

\[
\dot{z} = M z + u_r
\] (7.18)

\[
\hat{y} = O z
\] (7.19)

with \([M, O]\) being completely observable. Expanding the original model with this reference model

\[
\dot{x} = \begin{bmatrix} x \\ z \end{bmatrix}
\] (7.20)

\[
\dot{\hat{x}} = \hat{F} \hat{x} + \hat{G} u
\] (7.21)

\[
\hat{F} = \begin{bmatrix} A & \emptyset \\ \emptyset & M \end{bmatrix}
\] (7.22)

\[
\hat{G} = \begin{bmatrix} B \\ \emptyset \end{bmatrix}
\] (7.23)

\[
\hat{Q} = \begin{bmatrix} Q & -Q H O \\ -O H^T Q & O^T H^T Q H O \end{bmatrix}
\] (7.24)
We obtain the standard linear quadratic regulator problem with performance index:

\[ J = \int_0^T \{ \dot{x}^T Q \dot{x} + u^T R u \} dt \]  

(7.25)

Solving the known Riccati equation, we find the gain matrices \( K, K_1 \) and thus the optimal control \( u^* \):

\[ u^* = \tilde{K} \dot{x} \]

(7.26)

\[ = \begin{bmatrix} K \\ K_1 \end{bmatrix} \begin{bmatrix} x \\ z \end{bmatrix} \]  

(7.27)

**Tracking step changes**

There exists a solution for the special case of tracking step changes (see [101]). To conserve a general structure and avoid changing the implemented algorithm in the future, one can use a numerical approximation of a more general problem setting. Tracking step changes can be seen as tracking a system with a very fast reference model, e.g. \( M \) 100 time faster than the fastest mode in \( A \). The resulting gain \( K_1 \) are very low compared to the values of \( K \) and does can be neglected.

### 7.2 State feedback control with additional integral action

A state feedback controller in the form described in section 7.1 guarantees the compensation of unknown disturbance impulses but not of unknown constant disturbances (or very slow ones in comparison to the dominant time constant). To compensate such disturbances, it is necessary for the controller to have integral action. This can be done by adding an integral part on the input (see figure 7.3). Because of the saturation element on the output (the limitation on the gas concentration in the fresh gas flow), an anti reset windup feedback was applied to this additional integral action. The additional tuning parameter \( K_i \) (the gain of integral part) was integrated in the LQ calculation of the state feedback gain vector. One can augment the original system \( A, B, C, D \) to the system \( \tilde{A}, \tilde{B}, \tilde{C}, \tilde{D} \) by adding an integral part on the input

\[ \tilde{A} = \begin{bmatrix} 0 & -C \\ 0 & A \end{bmatrix} \]  

(7.28)

\[ \tilde{B} = \begin{bmatrix} 0 \\ B \end{bmatrix} \]  

(7.29)

\[ \tilde{C} = \begin{bmatrix} \gamma & C \end{bmatrix} \]  

(7.30)

\[ \tilde{D} = [D] \]  

(7.31)
In our SISO case $\gamma$ is a real number (different from zero) and for stability reasons must be different from every eigenvalue of $A$ (see [102]). $\gamma$ is now the new tuning factor for the added integral part (it represents a weighting factor for the LQ optimisation).

### 7.3 Linear quadratic Gaussian (LQG) controllers and loop transfer recovery (LTR)

Using an estimator we must deal with additional input ($\nu$) and output noise ($w$). The system is then described by:

\[
\begin{align*}
\dot{x} &= Ax + Bu + \nu \\
y &=Cx + Du + w
\end{align*}
\]  \hspace{1cm} (7.32)

\hspace{1cm} (7.33)

assuming

\[
E[w] = E[\nu] = 0, \quad E[ww^T] = \bar{Q}, \quad E[\nu \nu^T] = \bar{R}, \quad E[\nu^T] = 0
\]  \hspace{1cm} (7.34)

The optimal control problem can then be defined by:

\[
J = \lim_{T \to \infty} \frac{1}{T} \left\{ \int_0^T \left[ x^T \bar{Q} x + u^T \bar{R} u \right] dt \right\}
\]  \hspace{1cm} (7.35)
To solve this optimisation problem, the *Separation Theorem* or *Certainty Equivalence Principle* can be applied. The Theorem says that the optimal solution can be found by applying the minimum variance estimate \( \hat{x} \) of the states \( x \) to the optimal control law found with the LQR algorithm for the deterministic problem. The problem is therefore split into an optimal estimation of a stochastic problem and a optimal control algorithm for deterministic systems. Like the state feedback gain vector \( K \), the observer gain vector \( L \) is calculated through optimisation of a quadratic cost function. To find the optimal estimation gain vector, the duality property of the LQR algorithm can be exploited (see table 7.1). This strategy is often called

<table>
<thead>
<tr>
<th>LQR</th>
<th>Estimator</th>
</tr>
</thead>
<tbody>
<tr>
<td>( A )</td>
<td>( A^T )</td>
</tr>
<tr>
<td>( B )</td>
<td>( C^T )</td>
</tr>
<tr>
<td>( Q )</td>
<td>( B \hat{Q} B^T )</td>
</tr>
<tr>
<td>( R )</td>
<td>( \hat{R} )</td>
</tr>
</tbody>
</table>

Table 7.1: *Duality between the LQR problem for deterministic systems (see equation 7.6) and the minimum variance estimation problem of a stochastic system (see equation 7.35). Both problems can be solved with the solution of the LQR algorithm using the respective parameter set.*

Linear Quadratic Gaussian (LQG). It is a well established fact that the introduction of a state estimator will deteriorate the passband robustness properties ([101]). To partially overcome this drawback, the *dual state estimator recovery design method* from [101] was implemented. It defines the weight matrices \( Q \) and \( R \) as follows:

\[
Q = \rho B B^T \\
R = I
\]  

(7.36) \hspace{1cm} (7.37)

The scalar parameter \( \rho \) can be varied between zero and infinity to achieve a trade-off between performance for a nominal plant and noise environment (\( \rho \) low) and input (or output) robustness in LQG. Applying this LTR strategy, \( \rho \) remains the only tuning parameter. For all state feedback controllers good behaviour was obtained with:

\[
\rho := 100
\]  

(7.38)

### 7.4 Control algorithm and tuning parameters

The control algorithm can be resumed as follows:

\[
\dot{x} = \dot{A}x + \dot{B} \begin{bmatrix} r \\ y \end{bmatrix} \\
u = -K \dot{x} - K{_1}r + r\Phi
\]  

(7.39) \hspace{1cm} (7.40)
Where the pair \( \{\tilde{A}, \tilde{B}\} \) are the matrices of the system composed by the observer, state feedback loop and compensation \( \Phi \).

\[
\tilde{A} = [A - LC] \quad (7.41)
\]

\[
\tilde{B} = \begin{bmatrix} (B - LD) \\ L \end{bmatrix} \quad (7.42)
\]

The controller algorithm is defined through following tuning parameters:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Tuning (yes/no)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( Q_1 )</td>
<td>0</td>
<td>no</td>
</tr>
<tr>
<td>( Q_2 )</td>
<td>1</td>
<td>no</td>
</tr>
<tr>
<td>( R )</td>
<td>-</td>
<td>yes</td>
</tr>
<tr>
<td>( \gamma )</td>
<td>-</td>
<td>yes</td>
</tr>
<tr>
<td>( \rho )</td>
<td>100</td>
<td>no</td>
</tr>
</tbody>
</table>

The final tuning will be done only through two parameters: the weight of the integral action in the cost function and \( R \). This will limit the degree of freedom on the structure but simplify the tuning for different fresh gas flows and ventilations. This tuning strategy does not pretend to be optimal but leads to a robust and transparent controller implementation. More sophisticated optimisation strategies can be applied as soon as more information about the model parameters, the disturbances and the measurement noise are available.

### 7.5 Structure realization

The system is assumed to be quasi continuous and was therefore designed with a continuous model, for the practical implementation it will be converted to discrete time assuming a zero order hold on the inputs (see MATLAB \texttt{c2dm} function).

![Discrete Controller Diagram](image)

Figure 7.4: Discretization, signal filtering and artifact handling are important aspects of the realization phase of a feedback controller.

This section will also discuss other implementation aspects as signal filtering and artifact handling (see figure 7.4). These algorithms was mainly used for model based control. In
the last section a short description of the implemented system and the parameter setting procedure will be given.

### 7.5.1 Synchronization

The inspired and the endtidal concentrations are measured once a respiratory cycle. To avoid irregular measurement time delays and loss of measurement points (see figure 7.5), the sampling time was synchronized with the breathing movement (see figure 7.6). The synchronization between breathing frequency and sampling time will therefore allow regular measurement time delays.

![Figure 7.5: Example of the effect of asynchronous measurement.](image)

Figure 7.5: Example of the effect of asynchronous measurement. The first line show the time scheduling of concentration measurements (B data points) during artificial breathing with \( f_R = 9 \, [1/min] \). The second line shows the measurement scheduling (M data points) done for control using a sampling time \( T_s = 10 \, [sec] \). This configuration is characterized by irregular measurement time delays and loss of measurement points (e.g. \( B_k \) and \( B_{k+3} \)).

![Figure 7.6: Example of the effect of synchronous measurement.](image)

Figure 7.6: Example of the effect of synchronous measurement. The first line show the time scheduling of concentration measurements (A data points) during artificial breathing with \( f_R = 6 \, [1/min] \). The second line shows the measurement scheduling (M data points) done for control using a sampling time \( T_s = 10 \, [sec] \). This configuration is characterized by regular measurement time delays.
7.5.2 Signal filtering

Signal filtering normally is used to suppress undesired dynamic behavior: in measurement signals mainly to suppress high frequency measurement noise and on reference signals to smooth step changes. In both cases, the suppression of high frequency signals avoids undesired high frequency variations in the controlled variables. These variations are often amplified by the derivative properties of the observer (see [103]).

Reference filtering

The reference filter we used for state space controllers is composed by a discrete first order low pass filter with two saturation blocks. The first sets the maximal amount of reference value changes in both direction ($e_{up}$ and $e_{down}$), the seconds take into account the general reference value limits (see figure 7.7). Figure 7.8 shows a comparison between a ideal step change, a step change filtered with a linear filter and a step change filtered with the implemented nonlinear reference filter. The nonlinearity allows the setting of a limited slope without affecting small signal response.

![Figure 7.7: Structure of the nonlinear reference filter.](image)

![Figure 7.8: Comparison between filter with (-) and without (—) nonlinear saturation](image)

Comparison between filter with (-) and without (—) nonlinear saturation

Figure 7.8: Comparison between the non filtered reference step (...), the filtered response of a linear first order filter ($K_R = 1$, $T_r = 6.T_s$, $T_s = 1/6$), and a first order filter with saturation of the reference change ($K_R = 1$, $T_r = 6.T_s$, $T_s = 1/6$, $e_{up} = 0.2$, $e_{down} = -0.2$).
7.5 Structure realization

7.5.3 Artifacts Handling

Artifacts are measurement errors due to invalid working conditions of the measurement device (e.g.: calibration processes, wash outs, deconnections, ...). The detection of this kind of disturbances can be very complex and is often solved with nonlinear algorithms. In this work a simple solution will be used. Further investigations should be done when implementing the supervisor system.

The complexity of the problem will be illustrated by the example of artifact handling for the MAP signal. There are basically three main artifacts that have to be identified and suppressed during surgery: the extraction of a blood probe sample, the wash out process of the sensor, and a switch to measurements of the central venous catheter pressure. All three artifacts are generated by the anaesthetist but are not registered by electrical devices. These artifacts must therefore be identified from the measured signal. The block-diagram of figure 7.9 shows the resulting implemented simple artifacts handler. The artifact handler has to decide whether or not the actual blood pressure value \( MAP \) is valid. We set following rules for the decision:

- \( MAP \) cannot be bigger than \( MAP_{\text{max}} \)
- \( MAP \) cannot be smaller than \( MAP_{\text{min}} \)
- \( \Delta MAP \) defined as the absolute value of the difference between the actual value and the last valid value \( MAP_{\text{o}} \) should not be bigger than \( \Delta MAP_{\text{max}} \)
- \( MAP_{\text{o}} \) is only updated if:
  - a new value has been accepted
  - \( \Delta MAP \) is outside the permitted range, but the last value was outside the range \([MAP_{\text{min}}, MAP_{\text{max}}]\) and the actual value is in this range.
  - if more than \( Counter_{\text{max}} \) consecutive values were rejected. This additional rule is inserted in order to avoid blocking. Although this may lead to incorrect control behaviour and must be detected by the human supervisor.

The results applied to our benchmark signal with the settings:

\[
\begin{align*}
\Delta MAP_{\text{max}} &= 5 \text{ [mmHg]} & Counter_{\text{max}} &= 8 \text{ [samplingsteps]} \\
MAP_{\text{min}} &= 50 \text{ [mmHg]} & MAP_{\text{max}} &= 150 \text{ [mmHg]}
\end{align*}
\]

are acceptable (see figure 7.10), but are only valid in routine situations and unfortunately filters also some effects of surgical disturbances (see the bottom left graphic at time equal 381 min). This suggest that a more systematic approach is needed for this important supervising functionality.
Figure 7.9: Block-diagram of the decision based artifact handling for the MAP signal. MAP is the measured blood pressure value, MAP; the filtered MAP value, MAP₀ is the last MAP valid value, ΔMAP_max is the maximal allowed change on MAP, MAP_min and MAP_max are the allowed limits of valid MAP values, Counter is the number of sample times where the new MAP value was refused, Counter_max is the maximal number of sample times where a new MAP value can be refused.
7.5 Structure realization

Figure 7.10: Filtering of the 2. benchmark MAP signal: detailed view of artifacts handling without linear filtering. All four artifacts are detected correctly

7.5.4 Implementation

The structure implemented for clinical tests is composed of:

1. a MATLAB simulation environment
2. a monitoring system (host, with OBERON as operating system)
3. a real time system (target, with XOBERON as operating system).

The MATLAB environment is used for simulations and definition of the controller’s parameter. The host provides the MMI (man machine interface), the communication with the real time system and serves as backup utility. The feedback loop is implemented on the real time system (target) with all its components (input/output devices, filters, supervisor and controllers).

The control parameters depend on the patient’s weight $W_{kg}$ and the respiratory parameters $f_R$ and $V_T$. The code generation of a parameter set is done through the following semiautomatic procedure:

- In MATLAB the controller parameter obtained from the design process are automatically transformed in OBERON source file.
• Transfer of this source file to host.
• Compilation of the generated source code on the host
• Transfer of the compiled code from host to target
• The controller program can be started

This generation procedure requires 20 to 30 minutes. To increase flexibility during runtime, 3 different parameter sets (with different $f_R$) are loaded simultaneously. In the future a larger number of parameter set will cover the usual ranges used in the clinic.

7.6 Control of the inspired anaesthesia concentration

The inspired anaesthesia gas concentration has a relatively fast response and a high correlation with the internal time delays. Therefore this controller will be most sensitive to errors in the estimated time delays and in the simplified model of the breathing system. In high fresh gas flow anaesthesia, almost no gas will be reused in the breathing circuit (see chapter 3). Closed loop control is in this case only necessary to compensate low frequency errors due to artifacts (such as leakages). In spite of the high fresh gas flows the internal delay values remain constant. High gain closed loop control can therefore result in instability (or at least will cause undesired overshooting). This is why the tuning parameter $R$ is set to a high value during high flow as compared to the value for low fresh gas flows. To avoid overshooting, a reference filter was used. The reference filter parameter $T_r$ is decreasing with increasing fresh gas flow. This is due to the faster time response of the system:

$$R = 0.015 \quad \gamma = 3 \quad T_r = 6.7s \quad \text{for } FF = 1 \text{ [liter/min]} \quad \quad (7.45)$$

$$R = 3.0 \quad \gamma = 3 \quad T_r = 4.7s \quad \text{for } FF = 10 \text{ [liter/min]} \quad \quad (7.46)$$
Figure 7.11: Simulated step responses of the observer based state feedback controller of the inspired anaesthesia gas concentration with 1 liter/min (on the left) and 10 liter/min (on the right).
7.7 Control of the endtidal anaesthesia concentration

The endtidal anaesthesia gas concentration has slower time response than the inspired concentration. This is mainly due to the very fast gas exchange into the lung which makes the endtidal value strongly dependent on the venous anaesthesia partial pressure. The gas shunt $K_s$ defined in section 3.6 is set to 30% and has therefore a limited power to modify the transient response. This low frequency characteristic is accentuated with low and minimal fresh gas flows. In these conditions the refreshing rate of the systems gas volume is very low. The controllers parameters were set to:

$$R = 0.05 \quad \gamma = 0.3 \quad T_r = 9. T_s \quad \text{for } FF = 1 \ [\text{liter/min}] \ (7.47)$$

$$R = 1.5 \quad \gamma = 0.3 \quad T_r = 6. T_s \quad \text{for } FF = 10 \ [\text{liter/min}] \ (7.48)$$

If we compare these settings with those used with the inspired anaesthesia gas controller, we notice that $R$ is larger for low flows and smaller for high flows. Considering the low frequency behaviour a small $R$ value would result in a high gain controller which will bring the controlled value very fast into saturation. Such an aggressive controller has a smaller gain margin and going outside the linear working point environment does not guarantee the LQG robustness properties. On the other hands, during high fresh gas flow conditions, the lower frequency response of the system allows a stronger closed loop control ($R$ is therefore set lower than in the controller of inspired concentration). The time constants of the reference filtering was set 50% higher than for the inspiratory controller due to the slower time response. Simulation results of step responses for different fresh gas flows, lung ventilation values (figure 7.13) and step heights (figure 7.12) show the behaviour of the implemented controllers. Remark that for low flow step changes, the controlled variable goes in saturation. The overshoot is eliminated by the implemented anti windup solution.

7.7.1 Clinical test validation

The controller has been applied during two clinical tests. Different steps were done on two different patients with different weights (65 and 88 kg) and breathing parameters ($V_T = 0.65$ liter and $f_R = 8$ 1/min for the first patient, $V_T = 0.85$ liter and $f_R = 10$ 1/min for the second). The simulation result with the light overshothing is clearly confirmed by the obtained results. (see figure 7.14 for the first patient and figure 7.15 for the second patient). In both episodes, the simulation parameter set was applied and adapted to the patient (following the procedure described in section 7.5.4).
7.7 Control of the endtidal anaesthesia concentration

Figure 7.12: Step responses of the observer based state feedback controller for the endtidal anaesthesia gas concentration with 1 liter/min (on the left) and 10 liter/min (on the right).
Figure 7.13: Simulated step responses of the observer based state feedback controller for the endtidal anaesthesia gas concentration. On each column three different steps with different ventilation values were simulated ($V_T = 0.8$ [liter], $f_R = [8, 10, 12]$ [1/min]). A higher ventilation corresponds to a faster step response. The fresh gas flow was constant and set to 1 liter/min. The step height between the steps simulated on the left ($\Delta r = 0.4$ vol%) and on the right ($\Delta r = 1.0$ vol%) is different.
Figure 7.14: Result of the first clinical trial with an observer based state feedback controller of the endtidal anaesthesia gas concentration
Figure 7.15: Result of the second clinical trial with a observer based state feedback controller of the endtidal anaesthesia gas concentration
These results not only confirmed the controller structure but also the models used. This approach allowed to reduce the tuning effort to one single experiment. During this experiment an incorrect breathing parameter was set and the simulation analysis could clearly locate the setup error (see figure 7.16). All three results of figure 7.16 were obtained by the same controller parameter set calculated for $K_{kg} = 70 \text{ [Kg]}$, $V_T = 0.6 \text{ [liter]}$ and $f_R = 6 \text{ [1/min]}$. The correct parameter set would have been: $K_{kg} = 80 \text{ [Kg]}$, $V_T = 0.6 \text{ [liter]}$ and $f_R = 9 \text{ [1/min]}$. This set was used to generate the first simulation (top left column). The second simulation was done with the same parameter set excepted for $f_R = 12 \text{ [1/min]}$. As we can notice, simulation and measurements show the same response behaviour. Especially when increasing $f_R$, the measured effect is confirmed by simulation. This maybe seen as an additional validation of the model and the regulator design and therefore was included here as a result.

### 7.8 Control of Mean Arterial Pressure

As explained on the introduction of section 4, the behaviour of MAP can be influenced by many different factors (e.g.: by i.v. drug delivery, blood loss, surgical stimulations, etc.). Beside the physiological and surgical reasons to hold a constant low blood pressure, strong reactions of MAP to surgical stimulations allow using this value as an indicator of anaesthesia depth. Using anaesthetic gases to compensate such MAP changes will certainly contribute to stabilize the patient's anaesthesia. Therefore the MAP controller is mainly used for disturbance rejection. Reference point tracking will be less considered because MAP reference point changes are rare and must normally not be achieved with first priority. The main performance goal for MAP control is to maintain the pressure value in a band of $\pm 5 \text{ [mmHg]}$ around the reference point. This specification can not be met at all times, as the signal frequency band of the disturbance is wider than the passband of the closed loop. This means that not all MAP changes can be compensated through the inhaled anaesthesia technique. Combined drug anaesthesia (inhaled and infused) is better suited to solve this problem. The endtidal concentration gives information about the saturation of anaesthesia drug in the body. Therefore, to avoid toxicity or too deep anaesthesia, the endtidal gas concentration must never exceed a given limit $P_{e,max}$. For the opposite reason (the patient must not become awake) the endtidal anaesthesia concentration must never be less than $P_{e,min}$. Resuming, the controller must fulfill the following requirements:

- **Reference band**: the measured MAP should remain in a band of $\pm 5 \text{mmHg}$ around the reference point
- **Input constraints**: the anaesthesia fresh gas concentration can be set between 0 and 5 vol %
- **Output constraints**: the measured endtidal concentration $P_e$ must be between $P_{e,min}$ and $P_{e,max}$.
- **Fresh gas flow**: the controller will be used at low fresh gas flow (1 l/min).
Figure 7.16: Comparison between simulations (the two columns on the top) and measured data during a clinical test of the endtidal controller with incorrect parameter setting. In each of three columns the first graphic shows the inspired (.) and the endtidal (-) isoflurane concentration, while the second shows the set isoflurane concentration in the fresh gas.
7.8 Control of Mean Arterial Pressure

7.8.1 Override control

From the requirements listed above, the new one is the definition of constraints on the output. In this specific case it is possible to solve the problem by defining a controller switch over strategy. We will first consider the case of the upper output constraint $P_{e,max}$. If in spite of a high fresh gas anaesthesia gas concentration, the MAP will not decrease sufficiently (in respect to the desired MAP value), the $P_{e,max}$ will rapidly be achieved. To maintain the defined constraint the controller must momentarily abandon the objective of MAP control and saturate to the maximum allowed endtidal anaesthesia amount. This strategy was applied through addition of an endtidal controller with a fixed set point value equal to $P_{e,max}$. Both controller outputs are constantly evaluated. The final control value is given by selecting the minimum between the proposed values from the MAP and the endtidal controllers (see figure 7.17). This principle can be extended to an additional endtidal controller for the minimal output constraint. In this case the maximal value between the proposed controlled value of the first selector and this additional controller have to be done in a second selector block. This control structure is called override structure (see [104]).

![Figure 7.17: Structure of the override controller to hold the upper limit of an output constraints. The minimum value of the proposed controlled values of both controllers is selected as the actual controlled value](image)

7.8.2 Controller settings and simulations

As for the other controllers, the $R$ parameter was set to a larger value for high flows, but in this case there is a smaller difference between the $R$ for high and low flow. This is mainly due for two reasons. First, also for high flows the dynamic of the system remains slow (due to the pharmacokinetic in the human body) and together with the transport time delays does not allow high gain control. Second, reference tracking will be less weighted than disturbance rejection. The MAP controller was therefore set with following parameters:

$$R = 7.5 \quad \gamma = 3 \quad T_r = T_s \quad \text{for} \quad FF = 1 \text{ [liter/min]} \quad (7.49)$$
$$R = 30 \quad \gamma = 3 \quad T_r = T_s \quad \text{for} \quad FF = 10 \text{ [liter/min]} \quad (7.50)$$

Due to the slow system response, no reference filtering was necessary ($T_r = T_s$). Figure 7.18 shows the simulation of the controller with the first benchmark disturbance signal (see section
Table 7.2: Short analysis of the obtained controller behaviour of the simulation with the second benchmark signals for different fresh gas flows.

<table>
<thead>
<tr>
<th>Calculated value</th>
<th>FF=1 [liter/min]</th>
<th>FF=10 [liter/min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean of $MAP_{error}$: $\int_0^T \frac{e}{T} , dt$ [mmHg]</td>
<td>-2.73</td>
<td>-3.36</td>
</tr>
<tr>
<td>Max of $MAP_{error}$: $\max(e)$ [mmHg]</td>
<td>+8.72</td>
<td>+8.5</td>
</tr>
<tr>
<td>Min of $MAP_{error}$: $\min(e)$ [mmHg]</td>
<td>-46.3</td>
<td>-45.8</td>
</tr>
<tr>
<td>Percentage of time $0 &lt; MAP_{error} \leq 5$</td>
<td>40.3 %</td>
<td>26.7 %</td>
</tr>
<tr>
<td>Percentage of time $5 &lt; MAP_{error} \leq 10$</td>
<td>2.0 %</td>
<td>1.0 %</td>
</tr>
<tr>
<td>Percentage of time $-5 &lt; MAP_{error} \leq 0$</td>
<td>41.2 %</td>
<td>54.5 %</td>
</tr>
<tr>
<td>Percentage of time $-10 &lt; MAP_{error} \leq -5$</td>
<td>5.3 %</td>
<td>7.4 %</td>
</tr>
<tr>
<td>Percentage of time $</td>
<td>MAP_{error}</td>
<td>\leq 5$</td>
</tr>
<tr>
<td>Percentage of time $</td>
<td>MAP_{error}</td>
<td>\leq 7.5$</td>
</tr>
<tr>
<td>Percentage of time $</td>
<td>MAP_{error}</td>
<td>\leq 10$</td>
</tr>
</tbody>
</table>

5.1.1). A satisfactory behaviour can be observed both with 1 and 10 liter/min fresh gas flow. The override control strategy not only allows to avoid exaggerated endtidal concentrations but also avoids dangerous undershooting during fast decreases of surgical stimulations. Later, we will observe this phenomena with a simple MPC controller. At the beginning a reference step was applied. Figure 7.19 presents the simulation results of the same controller with the second benchmark MAP disturbance signal as disturbance (see section 5.1.1). As expected MAP control is activated if MAP is lower or around the set value. With both fresh gas flows (1 and 10 liter/min) approx. 89 % of the measured pressures was within a band of \pm10 [mmHg] (see table 7.2); 81 % was within the specified band of \pm5 [mmHg]. The low pass filtering effect of the low flow does not allow timely reaction to the fast disturbances. Nevertheless its performance is nearly the same as with high flow. On the other side, the high flow controller shows of course a better performance for positive errors: during only 26.7 % of the time the measured value was between zero and 5 [mmHg] below the set value against the 41.2 % simulated for the low flow controller. This is explained by the higher refreshing rate of the gas mass in the breathing circuit which allow a higher concentration gradient between the gas on the lung and the blood and therefore a higher mass flow from the body to the breathing system. For fast anaesthesia wash outs, high fresh gas flows are therefore the best solution.

7.8.3 Clinical test validation

The Override controller was applied in 2 clinical studies during approximately one hour during surgery (see figure 7.20). On both studies the controller was applied during the cutting and opening surgery phase. In the first study, no override switching was necessary to control
the desired level of MAP ($P_{\text{e,max}}$ was set to 1.5 [vol%]). The second part of the first study is characterized by low surgical stimulations. During this part a reference step was done to show the effect of closed loop control. In the second study override control switching can be clearly observed ($P_{\text{e,max}}$ was set to 1.0 [vol%]). The switching behaviour is very similar to the simulated one. During the last 30 minutes the requested set point could only be achieved with a very low anaesthesia concentration. In this case, a high fresh gas flow controller could increase the “wash out” of human body and therefore reach the desired value more quickly. The last two fast MAP increases (around $t = 45$ [min] and $t = 55$ [min]) are clearly too fast in respect to the closed loop response and thus are non controllable.
7.9 Concluding remarks

The first clinical results reflects the behavior observed in simulation. State feedback control can therefore be applied to control in anaesthesia. Comparing to fuzzy control, the tuning effort was reduced considerably, while a big modeling effort was necessary. Nevertheless, this additional knowledge can be systematically used to improve systems performance: e.g. expanding the patients group considered or changing the anaesthetic gas type. The implementation of reference tracking, the handling of saturations on the controlled variables and on the output variables could be implemented by introduction of additional functions.
Figure 7.20: Result of two clinical trials with a state feedback override controller of the MAP during surgery. The big MAP values at the beginning of both data sets is the cutting and opening phase of a surgical operation (unfortunately, the incision phase and consecutive rise is not available in the data set on the left). Different artifacts can be observed in the data set: on the left, a blood sample extraction at minute 26 and 2 calibration processes of the anaesthesia gas sensors; on the right, a blood sample extraction and sensor washing procedure at minutes 19 to 20.
7 State feedback control
Chapter 8

MPC-control

8.1 Introduction

Model Predictive Control (MPC) was conceived in the 1970s primarily in industry. The algorithm is based on the real time solution of an optimisation problem at each sampling time. It is a technique demanding high computational power. The interest in this design method and its application were growing with the increasing computer power of the 1980s and 1990s. In addition to “simple” SISO linear System, MPC can generally handle large MIMO Systems with nonlinearities. It has been reported that MPC shows good behaviour on systems ([105]):

- with time delays
- with a large number of manipulated and controlled variables
- constraints on the manipulated variables (due often to actuator limits) and on the controlled variables.
- some nonlinear systems (convexity of the optimisation problem is not guaranteed for all nonlinear system, this is an open problem).

The particular structure of the controller is also able to handle changing control objectives and/or detectable system structures (due to known switching processes or sensor/actuator failures).

These general characteristics of MPC justify an application test in this field:

- Due to the breathing circuit, depending on the breathing parameter and the fresh gas flow amount, there exists a non negligible time delay.
- There exist constraints on the manipulated and in the controlled variables
In the future systems with multiple manipulated and controlled variables (MIMO-Systems) will be used.

Switches between different model structures (depending on the actual working points) and control objectives are not unusual in the operating room.

In this chapter the basic principle of MPC will be shortly explained by focusing mainly on the features used for our control purpose (for more details consult [106, 107, 108, 105, 109]). After that, the structure, some simulations and results of all three implemented controllers will be presented. At the end, will finish with some concluding remarks.

8.2 Basics of MPC

The strategy of Model Predictive Control (MPC) consist of the optimisation of a performance index with respect to some future control sequence, using predictions of the output signal based on a process model. There exist many techniques to implement such a control strategy. All techniques are based on a same general structure (see figure 8.1). As on the state feedback controller (see chapter 7), an observer is used to compute the state estimates \( \hat{x} \) using the plant input \( u \) and output \( y \). The reference values \( r \) and the estimates \( \hat{x} \) are used to compute the optimal manipulated variables with respect to a given performance index.

![Figure 8.1: General structure for MPC](image)
algorithm is also explicitly taking into account the defined input and output constraints (respectively \( u \) and \( y \)).

The performance index generally depends on the predicted controlled variables \( \hat{y} \) over a defined prediction horizon \( P \) (\( \{\hat{y}(k+1) \ldots \hat{y}(k+P)\} \)) and of the manipulated variables \( u \) changes over a defined control horizon \( M \) (\( M \leq P, u(k | k) \ldots u(k + M - 1 | k) \)). At time \( k \) only the first control move of the computed sequence \( u(k | k) \) is implemented on the real plant. At each future step, the observer uses the predicted input and output values to compute the predicted state estimates \( \hat{x}(k+i) \). At the next sample time, the algorithm will be restarted after shifting one sample of the horizons (\( P \) and \( M \)) and with new information on the measurements (see explaining figure 8.2). This strategy is called moving horizon (or receding horizon). Using infinite horizon values \( P \) and \( M \), a linear system without constraints and a quadratic performance index, the optimisation problem has an analytic solution (solution of the Riccati Equation) and is identical to an equivalent linear quadratic state feedback regulator (same problem formulation). While it was shown that with infinite horizon values \( P \) and \( M \) it is possible to guarantee nominal closed loop stability of the system ([110]), it was however observed that it is not so with finite output horizon \( P \). Positive results were obtained by keeping only the moving control horizon \( M \) finite. In most cases, it has been shown that an appropriate choice of the horizon parameters can give good stability results (but without guarantees) while keeping computational effort at reasonable level. Choosing \( M \) and \( P \) longer that the main time constants of the plant is intuitively a good choice (but of course not a guarantee for a stable behaviour). Because this plant is asymptotically stable without integral character (see section 5), stability has mainly to be checked in case of parameter uncertainty and noise disturbances.

Figure 8.2: Moving horizon principle used on MPC
8.3 Models

A general structure of a model used by the MPC algorithm is described on figure 8.3. The

\[ x(k + 1) = \Phi x(k) + \Gamma_u u(k) + \Gamma_d d(k) + \Gamma_w w(k) \]  
\[ y(k) = c x(k) + D_u u(k) + D_w w(k) + z(k) \]  

(8.1)  
(8.2)

where \( x \) is a vector of \( n \) state variables, \( u \) represents the \( n_u \) manipulated variables, \( d \) represents the \( n_d \) measured input disturbances, \( w \) the \( n_w \) unmeasured input disturbances, \( y \) is a vector of \( n_y \) plant outputs and \( z \) the measurement noise.

8.4 Performance index

The performance index used by the optimisation algorithm is based on the manipulated variables \( u \) and on the reference tracking error:

\[ J(u, k) = \sum_{j=1}^{P} ||W_y(k) [\hat{y}(k + j \mid k) - r(k + j)]||^2 \]

\[ + \sum_{j=1}^{P} ||W_u(k)u(k + j)||^2 \]

\[ + \sum_{j=1}^{P} ||W_{du}(k) \Delta u(k + j)||^2 \]  

(8.3)

where:
8.5 Constraints

For safety and for reasons of technical limitations, there will be constraints on the manipulated variables, states or the output signals. Constraints can be often expressed as bounds:

\[
\begin{align*}
\mathbf{u} & \leq \mathbf{u}(k) \leq \mathbf{u}, \quad \forall k \\
\Delta \mathbf{u} & \leq \Delta \mathbf{u}(k) \leq \Delta \mathbf{u}, \quad \forall k \\
y & \leq y(k) \leq \bar{y}, \quad \forall k \\
\bar{x} & \leq x_i(k) \leq \bar{x}, \quad \forall k
\end{align*}
\]

Using the predicted values \(\hat{y}(k)\) and \(\hat{x}_i(k)\), all constraints 8.4-8.7 can be expressed on \(u(k)\):

\[
C_u \mathbf{u}(k) \leq 1
\]

Equation 8.8 must hold under any circumstances, no violation is allowed. This condition is generally not a problem for input constraints but can become a big problem if output or state constraints are defined. If the linear quadratic programming (LQP) problem is not feasible, depending on the optimisation algorithm, not even a suboptimal solution can be found. For reasons of security and stability, any unfeasible situation should be strictly avoided. There exists different possible strategies in case of unfeasibility:

1. **Modification of constraints limit** Input or output constraints should be modified (if physically and ethically possible) in order to give a larger degree of freedom to the LQP algorithm. The optimisation step can then be repeated to find a feasible solution.

2. **Defining soft constraints** Output constraints can be softened introducing a highly weighted penalty in the performance index.

3. **Using the last valid optimisation result** The last valid manipulated variable vector should be used to control the real plant. This solution can only be applied for a short number of steps, because it is a open loop control.

4. **Using a multiple model approach (MMA) or a multiple control approach (MCA)** Defining multiple models or/and controller types, it is possible to switch from
one to another control/model depending on feasibility or any other switching strategy. For stability purposes, it is important to avoid fast switches between completely different strategies. In this case the same override control structure as described in section 7.8.1 can be used.

### 8.6 Observer, Filter

As in any model based technique, the actual states of the system are used as inputs to the feedback. If these are not measurable, it is necessary to use an observer to estimate the state vector. As state estimator, a Kalman filter is used. We used the filter form implemented in the MPC Matlab Toolbox (see [105]) that we will shortly describe at this point. Considering a state space description of the form 8.1 and 8.2 with $\Gamma_d = 0$, and $D_w = 0$ and assuming $w$ and $z$ as stationary random-normal signal with covariances:

\[
E\{w(k)w^T(k)\} = Q \quad \text{(8.9)}
\]
\[
E\{w(k)z^T(k)\} = R_{12} = 0 \quad \text{(8.10)}
\]
\[
E\{z(k)z^T(k)\} = R \quad \text{(8.11)}
\]

For such a system we obtain the following steady state Kalman filter:

\[
\hat{x}(k | k) = \hat{x}(k | k - 1) + K[y(k) - C\hat{x}(k | k - 1)] - Du(k) \quad \text{(8.12)}
\]
\[
\hat{x}(k + 1 | k) = \Theta \hat{x}(k | k) + \Gamma uu(k) \quad \text{(8.13)}
\]
\[
\hat{y}(k | k) = C\hat{x}(k | k) + DU(k) \quad \text{(8.14)}
\]

where $K$ is the solution of a Riccati-Equation ([101]) applying the *Certainty Equivalence Theorem* (see section 7.3).

### 8.7 Disturbance rejection and steady state error compensation

As mentioned in the last section, structured disturbances can be estimated by a Kalman filter structure. The main problem is to have a enough good model approximation in order to correctly estimate the contribution of the unexpected output errors due to the disturbance from the output errors, parameter variation of the plant and the measurement noise. Of course in order to implement such an estimator, it is necessary that the states of the plant and the disturbance are observable and distinguishable.

If the plant is characterized by an open integrator (this means one pole $p = 0$), steady state errors will be estimated by the Kalman filter by correction of the respective integral state. If instead the plant is not characterized by an open integrator, correction of steady state errors can be done by adding an output disturbance model of the form (see figure 8.4):

\[
G_w(s) = \frac{1}{s} \quad \text{(8.15)}
\]
or in discrete form:

$$\Gamma_w(z) = \frac{T_s}{1-z}$$  \hfill (8.16)

The unmeasured input \( w \) is assumed to be ideal white noise. Consequently to assume constant step changes in the output, an integrator is used as model. This configuration was used

![Diagram](Figure 8.4: Addition of an output disturbance model to the plant for steady state compensation. The unmeasured input is assumed to be ideal white noise.)

for control of the inspiratory and endtidal anaesthesia concentration. For the control of MAP, rectangular pulses were assumed to model surgical stimulations. The model was then expanded with the model of MAP reaction of pain described in chapter 4 (see figure 8.5).

![Diagram](Figure 8.5: Addition of an output disturbance model to the plant as model of the MAP reaction to surgical stimulation. After an integrator, to model step changes on the surgical stimulation, the dynamics of MAP reaction of pain is added to the plant model.)

### 8.8 Tuning and implementation of the MPC

All implemented controllers use a prediction horizon of 24 and a control horizon of 18 samples (higher values were not possible due to implementation constraints). No reference filtering
was used in the algorithms: the reference trajectory was hold constant at the actual set point value. As input constraints the controller output was limited between 0 and 5 [vol%]. No output constraints were defined. With this configuration the optimal solution of the MPC algorithm is found in maximal M iteration steps (in this case \( M = 18 \)). With the actual hardware (VMS based 603 Power PC Card, 66 MHz, 32 MB RAM) 18 iterations are done in approximatively 4.5 seconds. The algorithm requires approximatively 1 MB of RAM. The remaining tuning parameters will be set individually for each controller:

\[
W_y, \quad W_u, \quad W_{du}, \quad Q, \quad R
\]  

(8.17)

The sampling frequency is synchronized with the respiratory frequency \( f_R \) (see section 7.5.1).

### 8.8.1 Implementation problems for the feed forward path

The optimal way to solve a reference tracking problem with MPC is done by adding a feed forward path. In this case the model must be expanded with a new input (the feed forward value) that will add a value to the systems controlled input. Unfortunately, to avoid algebraic loops, the feed forward path must be delayed by a time constant. The effective controlled value (the sum of the feed forward value with the MPC controlled value) is a new output. This new output must be limited by the actuator constraints. In other word, with the feed forward extension, the input constraints become output constraints with no holding guarantee, since the new output is only a rough estimate of the effective value. If the reference value is constant, the feed forward value is correctly estimated and the procedure can be successful applied. Unfortunately the real time software used for the realization did not allow a simple realization of such a structure. We decided therefore to implement a controller without feed forward compensation. This will limit the possibility of using \( W_u \) to reduce movement on \( u \), since any weights of \( W_u \) will allow steady state errors in the optimal solution. Although this first version has been performing up to specifications (as we will describe below), it was not possible to implement the optimal solution for MPC. Therefore there are still many open questions wich have to be solved before this method is fit for general use in anaesthesia.

### Implementation

The structure implemented for clinical tests as well the procedure of generation of the controller's parameters are identical as for the state feedback controller (see section 7.5.4). No additional tuning of the parameters were done during the clinical tests.

### 8.9 MPC of the inspired anaesthesia gas concentration

This MPC controller will set the inspired anaesthesia gas concentration on the fresh gas measuring the actual inspired and endtidal concentrations. The endtidal concentration is
8.10 MPC of the endtidal anaesthesia gas concentration

used in the observer part. The weights of the performance index (equation 8.3) were set to:

\[ W_y = \begin{bmatrix} 1 \\ 0 \end{bmatrix} = \begin{bmatrix} W_{y,P_i} \\ W_{y,P_e} \end{bmatrix} \quad W_u = 0.01 \quad W_{du} = \begin{cases} 0.1 & \text{for FF}=1 \text{ liter/min} \\ 0.5 & \text{for FF}=10 \text{ liter/min} \end{cases} \tag{8.18} \]

where \( W_{y,P_i} \) and \( W_{y,P_e} \) are the weights on the error for the inspiratory, respectively endtidal anaesthesia gas concentration. Obviously \( W_{y,P_e} = 0 \) since only the error of the inspired concentration should be minimized. To minimize the steady state error \( W_u \) was set to a very low value: such a low value does not smooth the reactions on the control variable sufficiently. Therefore a higher weight on \( W_{du} \) was chosen. Due to the low sampling frequency and the pure time delays on the circuit a higher value of \( W_{du} \) was necessary for high fresh gas flow. The Kalman estimator was set with:

\[ Q = 5 \quad R = \begin{bmatrix} 0.1 & 0 \\ 0 & 0.1 \end{bmatrix} \tag{8.19} \]

These settings will produce a high gain to the model of the unmeasured disturbances, that will mainly absorb the unexplained error of the signal. Simulation results of this MPC implementation (see figures 8.6 and 8.7) show a rather strong reaction on the control variable. Smoother control is rather possible with the above explained feed forward structure (see section 8.8), which would allow a bigger weighting of \( u \). Some smoother control algorithms can be achieved through stronger weighting of \( W_{du} \).

The short clinical pilot study (see figure 8.8) confirms the results obtained in simulation. To obtain a better performance of the controller without expanding it with the feed forward path one can introduce the same reference filter signal used for state space control on anticipating the reference shape to the MPC controller. This will be in some way equivalent to a time limited limitation of movements on \( u \).

8.10 MPC of the endtidal anaesthesia gas concentration

This controller uses the same measurements as in the inspired anaesthesia gas controller (section 8.9). Two different parameter set were tested in clinical studies. Both used the same values for \( W_y \), which considers errors on the endtidal anaesthesia concentration, and for \( W_{du} \):

\[ W_y = \begin{bmatrix} 0 \\ 1 \end{bmatrix} = \begin{bmatrix} W_{y,P_i} \\ W_{y,P_e} \end{bmatrix} \quad W_{du} = \begin{cases} 0.1 & \text{for FF}=1 \text{ liter/min} \\ 0.5 & \text{for FF}=10 \text{ liter/min} \end{cases} \tag{8.20} \]

The first parameter set was:

\[ W_u = 0.01 \quad Q = 10 \quad R = \begin{bmatrix} 0.1 & 0 \\ 0 & 1 \end{bmatrix} \tag{8.21} \]

Although good results in simulation were achieved (similar to figures 8.9 and 8.10), clinical data gives good damped dynamical behaviour but a large steady state error (see left side of
This weighting leads basically to an integral control action. This is possible thanks to the dominating low pass characteristics of the input/output behaviour, which slow down the reactions on the control variable. Unfortunately, due to \( W_u = 0 \), the resulting control behaviour will not be sufficiently damped in clinical studies (as we will see later). The controller was successfully tested in simulation at the nominal point (see figures 8.9 and 8.10).

This new parameter setting was obtained after detailed analysis of the results of the first trial. The MPC performance index of the used algorithm operates on the estimated measurement vector \( \hat{y} \). If this estimation has a steady state error, then this error will be transferred to the closed loop performance. To overcome this problem, the Kalman filter was forced to suppress with more priority modeling errors into the disturbance model. In addition to increase the integral action, \( W_u \) was set to zero. The second implementation shows a better steady state
8.10 MPC of the endtidal anaesthesia gas concentration

Figure 8.7: MPC of inspired anaesthesia concentration. On each column three different steps with different ventilation values were simulated ($V_T = 0.8$, $f_R = [8, 10, 12]$). The fresh gas flow was constant and set to 1 liter/min. The step height between the steps simulated on the left ($\Delta r = 0.4 \text{ vol\%}$) and on the right ($\Delta r = 1.0 \text{ vol\%}$) is different.

behaviour but (due to $W_u = 0$) is not sufficiently damped around the working region. To sum up: the performance of both clinical studies was just acceptable but obviously needs further improvement. Due to the implementation limits (see section 8.8) the optimal MPC structure (e.g. with feed forward path) could not be implemented. A considerable additional effort is needed to advance the MPC to the same level of performance as the state feedback controllers. Nevertheless, this first implementation has shown, that this model based technique can be successfully applied.
Figure 8.8: Result of one clinical trial with a MPC of the inspired anaesthesia gas concentration

8.11 MPC of the MAP

The MAP controller will use the inspired and the endtidal anaesthesia concentration and of course the MAP as measurements values. The following settings resulted after tuning in simulation:

\[
W_y = \begin{bmatrix}
0 \\
0 \\
1
\end{bmatrix} = \begin{bmatrix}
W_{y,P_i} \\
W_{y,P_e} \\
W_{y,MAP}
\end{bmatrix} \quad W_u = 0.5 \quad W_{du} = \begin{cases}
1 & \text{for FF}=1 \text{ liter/min} \\
1 & \text{for FF}=10 \text{ liter/min}
\end{cases}
\]

(8.23)

where \(W_{y,P_i}\) and \(W_{y,P_e}\) are the weights on the error for the inspiratory, respectively endtidal anaesthesia gas concentration and \(W_{y,MAP}\) the weight on the error for MAP. The Kalman estimator was set with:

\[
Q = 10 \quad R = \begin{bmatrix}
0.1 & 0 & 0 \\
0 & 0.1 & 0 \\
0 & 0 & 0.1
\end{bmatrix}
\]

(8.24)

in addition, \(\Delta u\) was limited to 1.0 [vol%]. As expected, during low fresh gas flows a steady state error can be observed (see simulations on figure 8.12), due to using \(W_u \neq 0\) without the introduction of a feed forward path. For comparison, on the left side of figure 8.13 the same disturbance was controlled with \(W_u = 0\). If we observe the right part of the same figure, this
8.11 MPC of the MAP

Figure 8.9: MPC of endtidal anaesthesia concentration. Simulation steps for different flows (1 liter/min on the left, 10 on the right)

setting leads to a behaviour where the controlled variable goes very fast from one saturation point to the other, although \( \Delta u \) was limited to 1.0 [vol%]. To smooth the control action the weight \( W_u \) was set to 0.5. The validation was done on comparing the control action of the second benchmark disturbance signal (see table 8.1 for some trivial statistics, figure 8.14 for the final version with different fresh gas flows and the right part of figure 8.13 for the simulation result for 1 liter/min fresh gas flow and \( W_u = 0 \)). As expected, due to the steady state error, the mean value of the error is slightly larger in the final implementation with low flows. This can also be observed in the percentage of errors between 0 and -5 [mmHg] (55.3 %) which is clearly higher than the errors between 0 and 5 [mmHg] (16.5 %). The implementation with \( W_u = 0 \) gives more balanced results (34.5 % and 36.7 %). It is therefore surprising that the percentage of errors in the ±5 [mmHg] band does not differ significantly (74.8 % for \( W_u = 0.5 \), 75.9 % for \( W_u = 0 \)). Considering this very small difference on the controller performance and the resulting smoother control action, \( W_u \neq 0 \) was preferred.

A direct comparison between these controller techniques in this work can not be done because of the implementation limits of the MPC-controller. State feedback control was applied...
Figure 8.10: MPC of endtidal anaesthesia concentration. On each column three different steps with different ventilation values were simulated ($V_T = 0.8$, $f_R = [8, 10, 12]$). A bigger ventilation corresponds to a faster control behaviour. The fresh gas flow was constant and set to 1 liter/min. The step height between the steps simulated on the left ($\Delta r = 0.4$ vol%) and on the right ($\Delta r = 1.0$ vol%) is different.

with the OVR structure which allows the limitation of $P_e$. The MPC-controller could not be implemented with output constraints, which would have allowed a feed forward feed and limitations on $P_e$. As a consequence the MPC controller shows a faster dynamic than the implemented state space controller. Nevertheless, comparing the results of the analyses of the simulations with the second benchmark signals (see tables 7.2) a similar behaviour can be observed. Following important points should be observed:

1. Due to the smoother control action and the better integral action, the state feedback controller shows a better mean error value.

2. Due to the stronger control action, the high flow MPC controller shows a better set point tracking performance: see percentages of time where $|MAPerror|$ is in a given value region around zero.
8.12 Clinical test validation

Figure 8.11: Two clinical trials with a MPC of the endtidal anaesthesia gas concentration. On the left the first trial with large steady state error (parameter setting of eq. 8.21); on the right the second trial (parameter setting of eq. 8.22).

8.12 Clinical test validation

Figure 8.15 shows the only clinical test of the MAP controller. Unfortunately it was not possible to test the controller behaviour during skin incision (as for the state feedback controller). Nevertheless the behaviour during two set point changes changes could be observed. During the step changes, there was no over- or undershooting problem, confirming the simulation results. The test was done during a central phase of the surgery with low surgical disturbances, which can be observed around \( t = 20 \) [min] and between \( t = 50 \) and \( t = 60 \) [min].

8.13 Concluding remarks

The first clinical tests have shown that the MPC approach seems feasible. However the control performance is not yet acceptable to anaesthetists. This is mainly due to the limited facilities for real time implementation, which puts severe restrictions on the prediction and control horizon. The available real time software does not yet allow to introduce output constraints in order to implement appropriate feedforward and integral action. Much effort has to be invested in the MPC implementation and design method to tuning it up to the
<table>
<thead>
<tr>
<th>Calculated value</th>
<th>FF=1 [liter/min]</th>
<th>FF=10 [liter/min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean of $MAP_{error}$: $\int_0^T \frac{\delta}{\tau} , dt$ [mmHg]</td>
<td>$W_u = 0.5$</td>
<td>$W_u = 0.0$</td>
</tr>
<tr>
<td>-4.39</td>
<td>-3.1</td>
<td>-7.31</td>
</tr>
<tr>
<td>Max of $MAP_{error}$: $\max(e)$ [mmHg]</td>
<td>+9.1</td>
<td>+10.34</td>
</tr>
<tr>
<td>Min of $MAP_{error}$: $\min(e)$ [mmHg]</td>
<td>-45.2</td>
<td>-44.2</td>
</tr>
<tr>
<td>% of time $0 &lt; MAP_{error} \leq 5$</td>
<td>16.5</td>
<td>39.2</td>
</tr>
<tr>
<td>% of time $5 &lt; MAP_{error} \leq 10$</td>
<td>2.4</td>
<td>4.2</td>
</tr>
<tr>
<td>% of time $-5 &lt; MAP_{error} \leq 0$</td>
<td>58.3</td>
<td>36.7</td>
</tr>
<tr>
<td>% of time $-10 &lt; MAP_{error} \leq -5$</td>
<td>11.7</td>
<td>10.4</td>
</tr>
<tr>
<td>% of time $</td>
<td>MAP_{error}</td>
<td>\leq 5$</td>
</tr>
<tr>
<td>% of time $</td>
<td>MAP_{error}</td>
<td>\leq 7.5$</td>
</tr>
<tr>
<td>% of time $</td>
<td>MAP_{error}</td>
<td>\leq 10$</td>
</tr>
</tbody>
</table>

Table 8.1: Short analysis of the obtained controller behaviour of the simulation with the second benchmark signals for different fresh gas flows and 2 different controller implementations: with $W_u = 0.5$ and with $W_u = 0.0$

same level of performance as observer based state feedback with overrides. It is still to early for an adequate comparison of both design method.

As with the state feedback controllers, with MPC the model based approach is confirmed during first clinical results. Because of the limited implementation features, it was not possible to introduce output constraints. This fact did not allow the introduction of an integral action on the feedback loop which would require the introduction of output constraints. For this reason a considerable effort is needed to advance to the same level of performance than the state feedback controller. A direct comparison is therefore impossible. MPC has however a big potentiality, since constraints, reference trajectory, and disturbance extrapolations are explicitly considered during online optimization.
Figure 8.12: Simulation results of the MPC MAP controller with $W_u \neq 0$. The first benchmark MAP disturbance was applied to the system (see section 5.1.1). Left column: 1 [liter/min] fresh gas flow. Right column: 10 [liter/min] fresh gas flow.
Figure 8.13: Simulation results of the MPC MAP controller with $1 \text{[l/min]}$ and $W_u = 0$. Left column: first benchmark MAP disturbance signal; right column: second benchmark MAP disturbance signal (see section 5.1.1)
8.13 Concluding remarks

Figure 8.14: Simulation results of the MPC MAP controller. The second benchmark MAP disturbance was applied to the system (see section 5.1.1). The left column 1 liter/min fresh gas flow was applied, on the right 10 liter/min.
Figure 8.15: Result of one clinical trial with a MPC of the MAP during a central phase of the surgery. The controller was switched on around \( t = 8 \) [min].
Chapter 9

Conclusions

The evolution of online monitoring of the patient’s physiological parameters in the last twenty years has contributed to increase the number of complex surgical operations. As a consequence the role of the anaesthetist has become more complex and he must deal with a higher number of control actions. Feedback control may reduce his work load and consequently increase safety of the patient. Feedback control in anaesthesia was subject to many investigations in the past, but none led to practical implementation in the clinic routine. Therefore, all control tasks of the anaesthetist are still performed manually. The main questions to answer during this work were to determine if automatic feedback control can be applied with an acceptable performance in routine cases, if it is possible to apply different kind of control techniques and finally, which controller performs best in this biomedical field. We considered the feedback control of inhaled and exhaled gas concentrations, which are routinely measured online at the University hospital in Berne (Switzerland), and of the mean arterial pressure (MAP). This variable can be influenced by the anaesthetic gas concentration in the human body. The system to be controlled is composed by a breathing circuit and the relevant part of the patient’s body (represented by the pharmacokinetics and pharmacodynamics) and the necessary actuators and sensors. Although some previous investigations were available in the mathematical modeling of some subsystems (especially for the pharmacokinetics), there were many open question about the dynamical behaviour of the system to be controlled. In addition, there is a high individual parameter variability and a lack of measurable variables (especially of body internal values), which must be considered in the modeling and control phase.

The present work describes the results of different feedback control techniques applied to anaesthesia.

The first part shortly introduces the reader to the purposes of anaesthesia and describes the structure and the characteristics of an anaesthesia control system.

In the second part, the mathematical modeling of the system to be controlled is described in detail.

The third part describes the implemented controllers. Three design techniques are used: one
experience based technique (fuzzy logic control) and two model based techniques (state feedback control, and model predictive control). A systematic design procedure (specifications, modeling, design, simulations, pilot tests and standard clinical tests) has been used.

Our experiences from applying different design techniques are summarized in table 9.1.

For all the used control techniques it was fundamental to have a valid mathematical model describing the main dynamical behaviour of the system to be controlled. Such models allow to eliminate animal experiments and reduce the tuning phase in clinical tests. In addition, a good mathematical model allows also to simulate infrequent or particular situations to increase the systems safety, and the understanding of the physiological and physical mechanism involved on the system.

While the model based strategies will systematically use quantitative information in form of mathematical models, the experience based model use qualitative information mainly coming from experts knowledge. These different sources often lead to different implementation time scales: the experience based controller can normally be implemented faster than the model based on (which needs a long modeling phase). In contrast, the quantitative information available in mathematical models allows algebraic or numerical optimisation (which is not possible using experience based controllers) and efficient pretuning in simulation.

Good results were achieved with fuzzy logic control algorithms. This technique has proven to be useful, fast and efficient by translating the manual control strategies and experience into an automatic control algorithm. Especially efficient was the realization of decision based functionalities. However, with fuzzy logic control the tuning phase was very long and inefficient if a substantial improvement of the control performance was required. The computational effort of fuzzy logic controllers depends on the implementation type: low computer power but high memory requirements are needed if the nonlinear function derived from a fuzzy rule engine is memorized as a static input output table; vice versa high computer power and low memory are required if the rule engine is computed in real time.

This work showed that, with a considerable model effort, it is possible to efficiently use linear model based control algorithm even for the variability of patients and the complexity of the system. For technical reasons, the comparison of the two model based techniques could not be done with identical functional specifications (no output constraints were implemented for MPC). Therefore, additional work is necessary to make definitive assertions. Nevertheless, these methods have shown to produce similar results. The main differences can be located in the design, which is rather simpler for MPC and on the computational effort which is clearly lower for state feedback control. MPC implicitly covers all particular functionalities (like input and output constrains, tracking of particular trajectories, time dependent weightings in the performance index, etc.), while state feedback control needs additional design efforts for each of these functionalities.

This work initiated a large research program for the realization of an integrated anaesthesia control system and it constitutes its first major phase. It is a first major step in the right direction. The gathered experience allowed to define when experience based or model based controllers are able to fulfill the specifications. The fact, that model based control can be
## Control Algorithms

<table>
<thead>
<tr>
<th></th>
<th>Model Based</th>
<th>Experience Based</th>
<th>Rule Based</th>
<th>Fuzzy Logics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Model Predictive</strong></td>
<td>Math. model needed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>State Feedback</strong></td>
<td></td>
<td></td>
<td>Rapid first experience based prototype</td>
<td></td>
</tr>
<tr>
<td><strong>Development effort</strong></td>
<td>Rapid first experience based prototype</td>
<td></td>
<td>Large effort (many experiments)</td>
<td></td>
</tr>
<tr>
<td><strong>Optimisation</strong></td>
<td>Numerical, online</td>
<td>Algebraic, off line</td>
<td>No optimisation</td>
<td></td>
</tr>
<tr>
<td><strong>Tuning</strong></td>
<td>Efficient</td>
<td></td>
<td>Large effort (many experiments)</td>
<td></td>
</tr>
<tr>
<td><strong>Constraints</strong></td>
<td>Input and outputs can be explicit limited</td>
<td>Input and outputs not explicit limited, additional functions needed</td>
<td>Difficult</td>
<td></td>
</tr>
<tr>
<td><strong>Tracking behaviour</strong></td>
<td>Good</td>
<td>Good</td>
<td>Acceptable</td>
<td></td>
</tr>
<tr>
<td><strong>Disturbance rejection</strong></td>
<td>Good</td>
<td>Good</td>
<td>Acceptable</td>
<td></td>
</tr>
<tr>
<td><strong>Robustness</strong></td>
<td>Clearly sufficient</td>
<td>Clearly sufficient</td>
<td>Sufficient</td>
<td></td>
</tr>
<tr>
<td><strong>Implementation effort</strong></td>
<td>high</td>
<td>low</td>
<td>high</td>
<td></td>
</tr>
<tr>
<td><strong>PC Power</strong></td>
<td>very high</td>
<td>low</td>
<td>low/high</td>
<td></td>
</tr>
<tr>
<td><strong>PC Memory</strong></td>
<td>very high</td>
<td>low</td>
<td>very high/low</td>
<td></td>
</tr>
</tbody>
</table>

Table 9.1: *Summary of the experienced characteristics of the different control strategies used for control of anaesthesia.*
successfully applied in this field, will help to enhance the control system in a systematic way.

At the moment, only adult patients of the lower healthy risk class where considered (20 to 60 years of age, ASA I & II). For a future integration into standard medical equipment, the patient groups considered must be expanded (higher risk classes, children, etc.) and combined anaesthesia must be introduced. In addition, the supervisor unit is an essential element to be introduced to allow safe automatic control of anaesthesia.

These first results have shown that automatic control in anaesthesia under routine conditions is feasible. Much work has been done...
... and much more work is to be done, until a anaesthesia control system will be used in clinical routine.
Appendix A

Systems of units

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Name</th>
<th>SI Symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td>length</td>
<td>meter</td>
<td>m</td>
</tr>
<tr>
<td>mass</td>
<td>kilogram</td>
<td>kg</td>
</tr>
<tr>
<td>time</td>
<td>second</td>
<td>s</td>
</tr>
<tr>
<td>temperature</td>
<td>Kelvin</td>
<td>K</td>
</tr>
<tr>
<td>amount of substance</td>
<td>mole</td>
<td>mol</td>
</tr>
<tr>
<td>electric current</td>
<td>ampere</td>
<td>A</td>
</tr>
<tr>
<td>luminous intensity</td>
<td>candela</td>
<td>cd</td>
</tr>
</tbody>
</table>

Table A.1: SI units

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Derived Unit</th>
<th>Name</th>
<th>SI Symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td>volume</td>
<td>$m^3$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>velocity</td>
<td>$m/s$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>acceleration</td>
<td>$m/s^2$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>density</td>
<td>$kg/m^3$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>force</td>
<td>$kg \times m/s^2$</td>
<td>newton</td>
<td>N</td>
</tr>
<tr>
<td>pressure</td>
<td>$N/m^2$</td>
<td>pascal</td>
<td>Pa</td>
</tr>
</tbody>
</table>

Table A.2: Derived SI units
<table>
<thead>
<tr>
<th>Quantity</th>
<th>Symbol</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>time</td>
<td>t</td>
<td>minute (min)</td>
</tr>
<tr>
<td>temperature</td>
<td>T</td>
<td>degree Celsius (°C)</td>
</tr>
<tr>
<td>volume</td>
<td>V</td>
<td>Liter (L), milliliter (ml)</td>
</tr>
<tr>
<td>mass</td>
<td>m</td>
<td>gram (g)</td>
</tr>
<tr>
<td>pressure</td>
<td>p</td>
<td>bar (bar), special name for 10^5*Pa</td>
</tr>
<tr>
<td>flow rate</td>
<td>x, f</td>
<td>milliliters per second (ml/sec) or liters per minute (L/min)</td>
</tr>
<tr>
<td>resistance</td>
<td>R</td>
<td>g/(cm^4 * sec) (CGS units)</td>
</tr>
<tr>
<td>flow inertance</td>
<td>L</td>
<td>g/cm^4 (CGS units)</td>
</tr>
<tr>
<td>vessel compliance</td>
<td>C</td>
<td>cm^4 * sec^2/g (CGS units)</td>
</tr>
<tr>
<td>pressure</td>
<td>P</td>
<td>dynes/cm^2 = g/(cm * sec^2) (CGS units)</td>
</tr>
</tbody>
</table>

Table A.3: Alternative units which are not officially a part of SI but are recognized as allowable because of convenience and widespread use.
Appendix B

Parameter set of the model of pharmacokinetics and pharmacodynamics of anaesthesia gases related to $MAP$

B.1 Patient related parameters

<table>
<thead>
<tr>
<th>parameter</th>
<th>values</th>
</tr>
</thead>
<tbody>
<tr>
<td>$I_s$</td>
<td>0.03</td>
</tr>
<tr>
<td>$V_a$</td>
<td>3.00</td>
</tr>
<tr>
<td>$W_{kg}$</td>
<td>70.00</td>
</tr>
<tr>
<td>$K_{wb}$</td>
<td>0.07</td>
</tr>
<tr>
<td>$K_{wt}$</td>
<td>0.75</td>
</tr>
<tr>
<td>$K_{blood,i}$</td>
<td>2.00 6.86 1.85 1.62 2.20 18.00</td>
</tr>
<tr>
<td></td>
<td>7.50 3.00 7.00 17.70 7.00 10.00</td>
</tr>
<tr>
<td>$K_{tissue,i}$</td>
<td>0.50 1.20 1.20 5.00 10.00 7.00</td>
</tr>
<tr>
<td>$MAP_0$</td>
<td>90.00</td>
</tr>
<tr>
<td>$K_{flow,i}$</td>
<td>5.00 10.50 2.50 22.00 3.50 25.00</td>
</tr>
<tr>
<td></td>
<td>20.00 3.50 8.00</td>
</tr>
</tbody>
</table>

B.2 Gas related parameters

B.2.1 Halothane
### B.2.2 Isoflurane

<table>
<thead>
<tr>
<th>parameter</th>
<th>values</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\lambda_i$</td>
<td>1.60 1.60 1.60 1.30 2.40 1.90</td>
</tr>
<tr>
<td>$\lambda_b$</td>
<td>1.46</td>
</tr>
<tr>
<td>$p_{test}$</td>
<td>2.30</td>
</tr>
<tr>
<td>$\Delta MAP_{test}$</td>
<td>-0.50</td>
</tr>
<tr>
<td>$\Delta_{flow,i}$</td>
<td>0.10 0.05 0.05 -0.30 -0.30 -0.25</td>
</tr>
<tr>
<td>$\hat{a}_1$</td>
<td>0.0096</td>
</tr>
<tr>
<td>$\hat{a}_2$</td>
<td>-0.0024</td>
</tr>
<tr>
<td>$\hat{a}_A$</td>
<td>-0.048</td>
</tr>
</tbody>
</table>

### B.2.3 Desflurane

<table>
<thead>
<tr>
<th>parameter</th>
<th>values</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\lambda_i$</td>
<td>1.40 1.30 1.30 1.10 1.90 1.30</td>
</tr>
<tr>
<td>$\lambda_b$</td>
<td>2.00 28.00 0.00 0.42 1.90 0.00</td>
</tr>
<tr>
<td>$p_{test}$</td>
<td>10.00</td>
</tr>
<tr>
<td>$\Delta MAP_{test}$</td>
<td>-0.33</td>
</tr>
<tr>
<td>$\Delta_{flow,i}$</td>
<td>0.05 0.05 0.05 -0.25 -0.25 -0.25</td>
</tr>
<tr>
<td>$\hat{a}_1$</td>
<td>-0.015</td>
</tr>
<tr>
<td>$\hat{a}_2$</td>
<td>-0.00376</td>
</tr>
<tr>
<td>$\hat{a}_A$</td>
<td>-0.075</td>
</tr>
</tbody>
</table>

### B.2.4 Enflurane
### B.2 Gas related parameters

<table>
<thead>
<tr>
<th>parameter</th>
<th>values</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\lambda_i$</td>
<td>1.60 1.50 1.50 1.90 3.00 2.10</td>
</tr>
<tr>
<td></td>
<td>1.70 36.00 0.0 1.90 3.00 0.00</td>
</tr>
<tr>
<td>$\lambda_b$</td>
<td>1.90</td>
</tr>
<tr>
<td>$P_{test}$</td>
<td>2.50</td>
</tr>
<tr>
<td>$\Delta MAP_{test}$</td>
<td>-0.39</td>
</tr>
<tr>
<td>$\Delta_{flow,i}$</td>
<td>-0.30 0.25 0.25 -0.65 -0.45 -0.45</td>
</tr>
<tr>
<td></td>
<td>-0.30 -0.45 0.30</td>
</tr>
<tr>
<td>$\hat{a}_1$</td>
<td>0.0483</td>
</tr>
<tr>
<td>$\hat{a}_2$</td>
<td>-0.012</td>
</tr>
<tr>
<td>$\hat{a}_A$</td>
<td>-0.024</td>
</tr>
</tbody>
</table>

#### B.2.5 Sevoflurane

<table>
<thead>
<tr>
<th>parameter</th>
<th>values</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\lambda_i$</td>
<td>1.80 1.70 1.70 1.20 2.20 1.80</td>
</tr>
<tr>
<td></td>
<td>3.10 48.00 0.00 0.69 2.20 0.00</td>
</tr>
<tr>
<td>$\lambda_b$</td>
<td>0.69</td>
</tr>
<tr>
<td>$P_{test}$</td>
<td>2.50</td>
</tr>
<tr>
<td>$\Delta MAP_{test}$</td>
<td>-0.33</td>
</tr>
<tr>
<td>$\Delta_{flow,i}$</td>
<td>0.05 0.00 0.00 -0.35 -0.35 -0.275</td>
</tr>
<tr>
<td></td>
<td>0.10 -0.50 0.25</td>
</tr>
<tr>
<td>$\hat{a}_1$</td>
<td>0.0272</td>
</tr>
<tr>
<td>$\hat{a}_2$</td>
<td>-0.0068</td>
</tr>
<tr>
<td>$\hat{a}_A$</td>
<td>-0.1360</td>
</tr>
</tbody>
</table>

#### B.2.6 $N_2O$

<table>
<thead>
<tr>
<th>parameter</th>
<th>values</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\lambda_i$</td>
<td>0.60 1.10 1.10 0.40 0.80 0.80</td>
</tr>
<tr>
<td></td>
<td>1.20 2.30 0.0 0.46 1.00 0.00</td>
</tr>
<tr>
<td>$\lambda_b$</td>
<td>0.46</td>
</tr>
<tr>
<td>$P_{test}$</td>
<td>70.00</td>
</tr>
<tr>
<td>$\Delta MAP_{test}$</td>
<td>+0.06</td>
</tr>
<tr>
<td>$\Delta_{flow,i}$</td>
<td>0.00 0.25 0.25 0.00 0.00 0.00</td>
</tr>
<tr>
<td></td>
<td>0.00 0.00 -0.05</td>
</tr>
<tr>
<td>$\hat{a}_1$</td>
<td>0.0043</td>
</tr>
<tr>
<td>$\hat{a}_2$</td>
<td>-0.0011</td>
</tr>
<tr>
<td>$\hat{a}_A$</td>
<td>-0.0216</td>
</tr>
</tbody>
</table>
Appendix C

Linearization of the model of the patient: nonlinearity measures

C.1 Simulation results

<table>
<thead>
<tr>
<th>$G_{pk}$</th>
<th>$A_0$</th>
<th>$A = 0.10 \omega = 0.001$</th>
<th>$A = 0.10 \omega = 0.010$</th>
<th>$A = 0.10 \omega = 0.100$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0e-01</td>
<td>2.98e-01</td>
<td>3.08e+01</td>
<td>1.38e+02</td>
<td>4.17e+00</td>
</tr>
<tr>
<td>5.0e-01</td>
<td>3.01e+01</td>
<td>1.97e+00</td>
<td>1.99e+01</td>
<td>9.35e+02</td>
</tr>
<tr>
<td>1</td>
<td>1.00e+02</td>
<td>3.76e+01</td>
<td>4.51e+00</td>
<td>3.11e+03</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>$G_{pk}$</th>
<th>$A_0$</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0e-01</td>
<td>1.07e+00</td>
<td>5.78e+02</td>
<td>2.65e+03</td>
<td>4.67e+02</td>
</tr>
<tr>
<td>5.0e-01</td>
<td>4.67e+02</td>
<td>1.92e+00</td>
<td>5.10e+02</td>
<td>1.52e+03</td>
</tr>
</tbody>
</table>
C Linearization of the model of the patient: nonlinearity measures

\[ A = 0.10 \quad \omega = 1.000 \]

<table>
<thead>
<tr>
<th>( G_{P_k} )</th>
<th>( A_0 )</th>
<th>( 1.0e-01 )</th>
<th>( 5.0e-01 )</th>
<th>( 1.0e-01 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0e-01</td>
<td>4.16e+01</td>
<td>5.34e+02</td>
<td>5.21e+03</td>
<td></td>
</tr>
<tr>
<td>5.0e-01</td>
<td>3.52e+02</td>
<td>7.11e+01</td>
<td>1.15e+03</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.04e+03</td>
<td>5.29e+02</td>
<td>1.79e+02</td>
<td></td>
</tr>
</tbody>
</table>

\[ A = 0.20 \quad \omega = 0.001 \]

<table>
<thead>
<tr>
<th>( G_{P_k} )</th>
<th>( A_0 )</th>
<th>( 1.0e-01 )</th>
<th>( 5.0e-01 )</th>
<th>( 1.0e-01 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0e-01</td>
<td>-</td>
<td>8.68e+01</td>
<td>3.32e+02</td>
<td></td>
</tr>
<tr>
<td>5.0e-01</td>
<td>-</td>
<td>1.46e+00</td>
<td>6.21e+01</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>-</td>
<td>5.21e+01</td>
<td>2.24e+00</td>
<td></td>
</tr>
</tbody>
</table>

\[ A = 0.20 \quad \omega = 0.010 \]

<table>
<thead>
<tr>
<th>( G_{P_k} )</th>
<th>( A_0 )</th>
<th>( 1.0e-01 )</th>
<th>( 5.0e-01 )</th>
<th>( 1.0e-01 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0e-01</td>
<td>-</td>
<td>2.20e+03</td>
<td>9.83e+03</td>
<td></td>
</tr>
<tr>
<td>5.0e-01</td>
<td>-</td>
<td>2.39e+01</td>
<td>1.93e+03</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>-</td>
<td>1.80e+03</td>
<td>1.87e+01</td>
<td></td>
</tr>
</tbody>
</table>

\[ A = 0.20 \quad \omega = 0.100 \]

<table>
<thead>
<tr>
<th>( G_{P_k} )</th>
<th>( A_0 )</th>
<th>( 1.0e-01 )</th>
<th>( 5.0e-01 )</th>
<th>( 1.0e-01 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0e-01</td>
<td>-</td>
<td>1.14e+03</td>
<td>5.15e+03</td>
<td></td>
</tr>
<tr>
<td>5.0e-01</td>
<td>-</td>
<td>4.34e+00</td>
<td>9.89e+02</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>-</td>
<td>8.56e+02</td>
<td>4.49e+00</td>
<td></td>
</tr>
</tbody>
</table>

\[ A = 0.20 \quad \omega = 1.000 \]

<table>
<thead>
<tr>
<th>( G_{P_k} )</th>
<th>( A_0 )</th>
<th>( 1.0e-01 )</th>
<th>( 5.0e-01 )</th>
<th>( 1.0e-01 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0e-01</td>
<td>-</td>
<td>7.39e+02</td>
<td>3.96e+03</td>
<td></td>
</tr>
<tr>
<td>5.0e-01</td>
<td>-</td>
<td>7.96e+01</td>
<td>8.43e+02</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>-</td>
<td>7.17e+02</td>
<td>8.58e+01</td>
<td></td>
</tr>
</tbody>
</table>

\[ A = 0.50 \quad \omega = 0.001 \]

<table>
<thead>
<tr>
<th>( G_{P_k} )</th>
<th>( A_0 )</th>
<th>( 1.0e-01 )</th>
<th>( 5.0e-01 )</th>
<th>( 1.0e-01 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0e-01</td>
<td>-</td>
<td>3.80e+02</td>
<td>1.12e+03</td>
<td></td>
</tr>
<tr>
<td>5.0e-01</td>
<td>-</td>
<td>2.81e+01</td>
<td>2.80e+02</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>-</td>
<td>6.10e+01</td>
<td>1.31e+01</td>
<td></td>
</tr>
</tbody>
</table>
### C.1 Simulation results

#### $A = 0.50 \quad \omega = 0.010$

<table>
<thead>
<tr>
<th>$G_{pk}$</th>
<th>1.0e-01</th>
<th>5.0e-01</th>
<th>$A_0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0e-01</td>
<td>-</td>
<td>5.65e+03</td>
<td>2.52e+04</td>
</tr>
<tr>
<td>5.0e-01</td>
<td>-</td>
<td>3.55e+02</td>
<td>4.99e+03</td>
</tr>
<tr>
<td>1</td>
<td>-</td>
<td>5.20e+03</td>
<td>2.19e+02</td>
</tr>
</tbody>
</table>

#### $A = 0.50 \quad \omega = 0.100$

<table>
<thead>
<tr>
<th>$G_{pk}$</th>
<th>1.0e-01</th>
<th>5.0e-01</th>
<th>$A_0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0e-01</td>
<td>-</td>
<td>2.75e+03</td>
<td>1.26e+04</td>
</tr>
<tr>
<td>5.0e-01</td>
<td>-</td>
<td>3.84e+01</td>
<td>2.39e+03</td>
</tr>
<tr>
<td>1</td>
<td>-</td>
<td>2.23e+03</td>
<td>2.58e+01</td>
</tr>
</tbody>
</table>

#### $A = 0.50 \quad \omega = 1.000$

<table>
<thead>
<tr>
<th>$G_{pk}$</th>
<th>1.0e-01</th>
<th>5.0e-01</th>
<th>$A_0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0e-01</td>
<td>-</td>
<td>1.56e+03</td>
<td>7.21e+03</td>
</tr>
<tr>
<td>5.0e-01</td>
<td>-</td>
<td>1.58e+02</td>
<td>1.52e+03</td>
</tr>
<tr>
<td>1</td>
<td>-</td>
<td>1.51e+03</td>
<td>1.31e+02</td>
</tr>
</tbody>
</table>

#### $A = 1.00 \quad \omega = 0.001$

<table>
<thead>
<tr>
<th>$G_{pk}$</th>
<th>1.0e-01</th>
<th>5.0e-01</th>
<th>$A_0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0e-01</td>
<td>-</td>
<td>-</td>
<td>3.19e+03</td>
</tr>
<tr>
<td>5.0e-01</td>
<td>-</td>
<td>-</td>
<td>1.00e+03</td>
</tr>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1.37e+02</td>
</tr>
</tbody>
</table>

#### $A = 1.00 \quad \omega = 0.010$

<table>
<thead>
<tr>
<th>$G_{pk}$</th>
<th>1.0e-01</th>
<th>5.0e-01</th>
<th>$A_0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0e-01</td>
<td>-</td>
<td>-</td>
<td>4.98e+04</td>
</tr>
<tr>
<td>5.0e-01</td>
<td>-</td>
<td>-</td>
<td>1.00e+04</td>
</tr>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>2.00e+03</td>
</tr>
</tbody>
</table>

#### $A = 1.00 \quad \omega = 0.100$

<table>
<thead>
<tr>
<th>$G_{pk}$</th>
<th>1.0e-01</th>
<th>5.0e-01</th>
<th>$A_0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0e-01</td>
<td>-</td>
<td>-</td>
<td>2.41e+04</td>
</tr>
<tr>
<td>5.0e-01</td>
<td>-</td>
<td>-</td>
<td>4.45e+03</td>
</tr>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1.82e+02</td>
</tr>
</tbody>
</table>
\[ A = 1.00 \quad \omega = 1.000 \]

<table>
<thead>
<tr>
<th>( G_{pk} )</th>
<th>1.0e-01</th>
<th>5.0e-01</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0e-01</td>
<td>-</td>
<td>-</td>
<td>1.32e+04</td>
</tr>
<tr>
<td>5.0e-01</td>
<td>-</td>
<td>-</td>
<td>2.78e+03</td>
</tr>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>2.38e+02</td>
</tr>
</tbody>
</table>
Bibliography


[51] P. Niederer, "Vorlesungen in Biomechanik II."


Curriculum vitae

I was born on December 25, 1967 in Locarno, Switzerland, as son of Caterina and René Derighetti. I attended primary school for five years in Muralto and Losone and secondary school in Locarno. I obtained the Matura Certificate Type B (literary sciences) in June 1986. In autumn 1986 I started my studies with the faculty of Electrical Engineering at the Swiss Federal Institute of Technology (ETH) in Zurich where I graduated on March 8, 1991 as an electrical engineer.

In July 1991 I joined the Automatic Control Laboratory at the ETH as a teaching and research assistant.

In October 1991 I began with my post-graduate studies in information technologies at the ETH which I finished with the certificates and with a post-graduate thesis in June 1994.

Since about 1994 I worked on my Ph.D. thesis.

Since 1994 I'm married with my wife Michela (born Grassi, biologist).