Towards closed-loop muscle relaxation control for daily clinical practice
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Chapter 7: SUMMARY AND CONCLUSION

Chapter 1 briefly describes muscle relaxation monitoring and control and presents the motivation for muscle relaxation control research.

Chapter 2 presents the basics of closed loop control systems, the neuromuscular junction and muscle relaxation. Neuror muscular monitoring is described along with stimulation patterns and measurement techniques used in clinical conditions. Current pharmacokinetic-pharmacodynamic (PK-PD) models to predict a patient’s response to muscle relaxation are also introduced. A short history of muscle relaxation controller research is given and some of the practical applications of muscle relaxation controllers are described. An application of a closed loop muscle relaxation controller for long-term muscle relaxation maintenance is shown in detail in Appendix 1. We found that rocuronium requirements diminished over time and recovery from muscle relaxation was within 2 hours even after almost 48 hours muscle relaxation maintenance with the closed loop controller.

Chapter 3 presents the design goals for a muscle relaxation controller within the context of existing closed loop muscle relaxation controller research. The design goals are intended to direct the development process towards a clinically useful muscle relaxation controller. We address the shortcomings of current relevant research and propose design solutions to avoid these problems.

Chapter 4 addresses diverse supporting elements for the muscle relaxation controller design process. It contains development of:

A model for twitch potentiation

Appropriate control twitch values measured in the absence of neuromuscular block are often difficult to determine because repeated motor nerve stimulation enhances the evoked mechanical response of the corresponding muscle resulting in an increased twitch response. This enhancement of twitch response is known as twitch potentiation or the staircase phenomenon. We found that a two-exponential model can predict the degree of twitch potentiation more accurately than a one-exponential model for various stimulation frequencies (Appendix 2). However, if only one stimulation frequency is used, a one-exponential model can provide good accuracy.

For neuromuscular modelling research, twitch stabilisation techniques are often used to reduce the visible effect of potentiation but such techniques are not always effective. Neither have these techniques been validated. We combined a PK-PD model and twitch potentiation model and to estimate NMB in the presence of twitch potentiation. We found that a PK-PD-Potentiation model can estimate the degree of twitch potentiation and the degree of NMB during neuromuscular monitoring and leads to different PD parameter estimations than the standard PK-PD model (Appendix 3). The model also accurately predicts data from twitch stabilisation, which is ignored with the standard PK-PD model.

Because twitch potentiation is initiated by postjunctional processes, it has limited relevance to closed loop muscle relaxation control. For this reason we did not further consider twitch potentiation during the muscle relaxation controller design process.
A PK-PD model to predict train-of-four (TOF) ratio and TOF count
The TOF stimulation pattern is used in daily anaesthesiological practice to determine the degree of relaxation caused by muscle relaxants. We extended the Bartkowski and Epstein PK-PD model to simulate all four TOF twitches (Appendix 4). We fit this model to data from the pig and compared the results to fitted models using separate PD models for each TOF twitch (extended Sheiner model). We found that the extended Bartkowski and Epstein model predicted TOF twitch height better than the extended Sheiner model.

A method to simulate special patient groups
Various clinically occurring conditions influence a patients muscle relaxation characteristics. We present a summary of patient muscle relaxation PK-PD characteristics that may occur under clinical conditions and their estimated frequency of occurrence based on existing literature and expert opinion (Appendix 5).

A direct muscle stimulation (DMS) compensation algorithm
DMS is the result of stimulation of muscle fibres close to stimulating electrodes and may disturb accelerometry measurements. We show that a linear function can estimate the effect of DMS and the estimated DMS effect can be subtracted from the TOF twitches to give corrected TOF ratio and TOF count values (Appendix 6). The function is useful over a limited range of muscle relaxation and this range corresponds well to most applications of closed loop muscle relaxation controllers.

Testing procedures for syringe pumps
We tested four syringe pumps for suitability in a closed loop muscle relaxation control system (Appendix 7), two with internal stepper motors and two with internal DC motors. Under the test conditions, the syringe pumps with internal DC motors do not move the syringe plunger sufficiently to deliver the requested drug infusion rate. Of the syringe pumps tested, pumps with internal stepper motors had better accuracy.

A safe maximum infusion limit for rocuronium
We did literature studies to determine the amount of rocuronium that would be sufficient to achieve clinical levels of muscle relaxation. We also did Monte-Carlo analysis to determine the effects of infusing maximum dosing levels for two hours in low-dose-requirement patients. Based on published data of rocuronium dose requirements, maintenance dosing of 1.2 mg.kg⁻¹.hr⁻¹ of rocuronium appears to be sufficient to achieve clinical levels of muscle relaxation (Appendix 8). With this maximum infusion limit the risk of delayed recovery from a closed-loop controller hardware failure seems to be within the range of clinical acceptability.

Chapter 5 addresses the design choices, optimisation and testing of a muscle relaxation controller designed for routine clinical application. The control algorithm avoids the usability restrictions of existing controllers and is optimised using an objective method to avoid the uncertainties of ‘hand-crafted’ controller algorithms. We show that the controller maintained the target TOF count values under the clinical conditions tested and remains useful even in the presence of disturbances that can arise in routine clinical conditions (Appendix 9). The clinical results of the controller are shown in detail (Appendix 10).

In Chapter 6 suggestions for future work related to this thesis are discussed as well as some of the limitations of the scope of the research.

Conclusion
The aim of this thesis algorithm suitable for goals and the controller closed loop muscle relaxnt feasible.
Conclusion

The aim of this thesis is the design and testing of a closed-loop muscle relaxation control algorithm suitable for routine clinical use. This aim was defined in terms of controller design goals and the controller achieved all of the stated design goals. This thesis shows that a closed-loop muscle relaxation control algorithm suitable for routine clinical use is technically feasible.