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Biomedical Applications of Control Engineering

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For

İlhan Kandan because she taught me to read and write,
Erol İnelmen because he taught me about science,
Vasfi Bingöl because he taught me to think independently,
Mohamed Mansour because he taught me control engineering,
Emel and Salih Hacısalihzade because they were my parents.

Preface

Countless scientists and engineers have contributed untold volumes of work applying control engineering techniques to biomedical problems since the pioneering efforts of Norbert Wiener who coined the term "cybernetics" more than half a century ago. Although that word has gradually lost its glamor in the decades that followed, ingenious researchers have not failed to come up with new fields of application. Therefore, even a superficial review of the field which claims to be exhaustive would have to cover several volumes. Hence, any textbook in this field has either to take one specific application area and explore it in depth or be an eclectic collection of several application areas. I have chosen to take the latter path even tough many examples of both are available in the press.

This book presents different control engineering applications in the medical field. It is intended for senior undergraduate or graduate students in both control engineering and biomedical engineering programs. For control engineering students, it shows the application of various techniques they have already learnt in theoretical lectures, in the biomedical arena. For biomedical engineering students, it shows solutions to various problems in their field using methods commonly used by control engineers. On the other hand, it should also appeal to medical students and practitioners who want to enhance their quantitative understanding of physiological processes and perhaps get a new vantage point from which they can attack their current problems.

There are no *sine qua non* prerequisites for reading, enjoying and learning from this book other than basic engineering mathematics and a rudimentary understanding of control engineering concepts.

The book is organized in seven Chapters and two Appendices. Every chapter includes three types of exercises at its conclusion which help the reader to better understand the topic. Type A exercises are mostly verbal and review the main points of the chapter; they help the reader to gauge her[1] understanding of the topic. Type B

[1] To avoid the clumsy constructs like "his/her", where appropriate, both male and female personal pronouns are used throughout the book alternatingly and they are interchangeable with no preference for or a prejudice against either gender.

exercises require some calculation and they are intended to deepen the understanding of the methods discussed in the chapter. Type C exercises involve open ended questions and their solutions typically require significant time, effort and creativity; they might be solved as term projects or graduation projects and indicate directions for thesis work.

Chapter 1, Introduction to Systems, begins by introducing some basic definitions and concepts of mathematical system theory. Mathematical description and analysis of systems like input-output relationships in time and frequency domains as well as in the state space are discussed. Some important system properties like controllability, observability and stability are introduced. Students familiar with basic control engineering should know everything in this Chapter and can skip it altogether. However, medical and biomedical engineering students not familiar with the contents of this Chapter should study it carefully.

Chapter 2, Modeling and Identification, gives an introduction to a very important topic which is often neglected in most engineering curricula, namely mathematical modeling of physical and physiological systems. It begins by discussing what a model is and gives various classification methods for different types of models. The actual modeling process is illustrated using the popular inverted pendulum and the stock prices. The determination of the parameters in the system once the mathematical structure of the model is fixed, the so called parameter identification, is handled together with the question of experiment design. Finally, the importance of integrating model validation in the modeling process is emphasized. A small philosophical excursion in this Chapter is intended to motivate the reader to increase his awareness of the difference between reality and models.

Chapter 3, The Human Operator, looks into the mathematical modeling of the human operator and manual control with emphasis on control of dynamic systems like aircraft by human beings. Different types of manual control systems and popular human operator models like the second order linear model, the describing function model and the optimal control model are discussed in detail. In this Chapter, the reader is also given a concise description of how and why an airplane flies.

Chapter 4, Drug Administration and Dosage Optimization, studies the question of drug administration with special emphasis on the optimization of the "when" and "how much" of the administered drug. This problem is analyzed using various tools and a number of different solutions are described in detail. Specifically, optimization of drug delivery based on both pharmacokinetic and pharmacodynamic data is handled. It is shown how the choice of the objective function leads to different mathematical problems like linear programming, Gaussian least squares, dynamic programming or Prony algorithms. In short, numerical optimization methods are discussed for the cases where analytical solutions are not possible.

Chapter 5, Parkinsons Disease, starts off by defining the disease, its etiology, pathophysiology, symptoms and treatment. Measuring Parkinsonian symptoms like tremor and bradykinesia objectively and quantitatively is explained in detail. Both a low tech approach and a computer based measurement technique assessing the tracking ability of the patients is introduced and evaluated. Finally, some of the techniques explained in Chapter 4 are applied to optimize drug therapy with respect to both pharmacokinetic and pharmacodynamic criteria.

Chapter 6, Diabetes and Control of Blood Glucose, begins by reviewing a global epidemic, diabetes, and methods to measure blood glucose levels applying invasive techniques, minimally-invasive techniques and non-invasive techniques. Various methods of insulin delivery are discussed and a broad spectrum of mathematical models of varying complexity ranging from linear models to nonlinear and comprehensive methods for patient dynamics are reviewed. Also, a choice of control algorithms for regulating the blood glucose levels in diabetes are explained. Those algorithms are grouped under the headings rule based control (making use of black box models to PID controllers) and model based control (making use of pole placement, adaptive control and optimal control methods). Finally, a number of common commercial insulin pumps and advisory devices are listed and a market leader product's functioning is described in detail.

Chapter 7, Controlling Depth of Anaesthesia, introduces the problem of anaesthesia. Various methods of measuring depth of anaesthesia are discussed before talking about the most common anaesthetic agents. A simple fuzzy controller which controls the blood pressure during surgery as a proxy for depth of anaesthesia is described and results from its use in real life conditions are discussed. A more advanced and complex multivariable controller which is used as a mean arterial pressure (MAP) controller, as an endtidal anaesthetic gas controller, as an inspired anaesthetic gas controller and as a cascade controller where a MAP or an endtidal anaesthetic gas controller defines an inspired anaesthetic gas set value that is controlled by an internal loop is described in detail. A 12th order model of the patient is developed and reduced to a third order model for practical purposes. Similarly comprehensive models of the breathing system and of the patient's reaction to surgical stimulation are developed. Subsequently, all these models are integrated to be used in the control loop. In the end an observer based state feedback controller with reference tracking is designed and implemented using optimal control theory.

The Appendices deal with topics which are often not covered in undergraduate courses. They are intended for the reader to get an idea about some advanced concepts used in the book with which she might not be familiar. The Appendices are neither meant to be mathematically rigorous nor as substitutes for corresponding courses. Appendix A is a refresher for optimal control. Calculus of variations is used to derive the Pontryagin - Bellman solutions and the optimality principle for the deterministic case. The extension of the solutions to the stochastic case is also briefly reviewed. Several simple examples are used for illustrative purposes. Appendix B covers fuzzy control which is explained using the example of speed control of a car.

As always, there is a long list of people to acknowledge and thank for their support in preparing this book. I want to begin by thanking Jürg Tödtli who initiated my interest in the field while we were at the Institute of Automatic Control at the ETH Zurich many years ago and who later became my boss at Landis & Gyr and a life long friend in the mean while. Special thanks are certainly due to late Günter Baumgartner and Carlo Albani at the Zurich University Hospital's Neurological Clinic for introducing me to interdisciplinary research through his coaching and mentoring in

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I want to thank Alex Zbinden at the Institute of Critical Care and Anaesthesiology of the University of Bern's Inselspital for introducing me to the field of anaesthesiology and a very pleasant collaboration over years which bore many fruits. One of these fruits was a Ph.D. thesis by my former student Marco Derighetti on which the Chapter on the Control of Depth of Anaesthesia is modeled. I must thank Marco also for reading the manuscript and suggesting corrections and changes.

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Istanbul, 2013

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