The Biophysicist

# Control Theory for Physicists by John Bechhoefer

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**Control Theory for Physicists by John Bechhoefer. 2021. Cambridge University Press, Cambridge, UK. 658 pp. ISBN 978-1107001183**

Control theory, the study of how to alter the behavior of dynamical systems to achieve desired goals, has been one of the mathematical foundations of modern engineering. Recent years have seen a surge of interest in control theory applied to biological systems, from understanding how cellular networks maintain homeostasis (1) or adapt to changing environments (2) to designing cancer therapies (3) and synthetic biological circuits (4). Yet for biophysicists coming from a traditional physics background, their undergraduate and graduate training is likely to have almost entirely ignored formal control ideas. Our closest brush with the subject might have been a short unit on proportional-integral-derivative feedback controllers in an electronics lab course, leaving a vague impression that the topic is undeniably useful but not particularly deep. If we are lucky enough to encounter the broader sweep of control theory later on through research, it comes with a pleasant shock: how can a discipline that yields so many insights into the dynamics of complex systems have escaped our notice for so long? Together with information theory, control theory is the area of engineering that has the most fundamental lessons to teach physicists, and John Bechhoefer's recent textbook, *Control Theory for Physicists*, is an excellent place to start learning them.

The book provides a wide overview of topics that might ordinarily be spread out over several courses—classical control of linear systems, optimal control, adaptive control, and so on—but it also touches on specialized areas of great current interest, including control of complex networks and the limits on control imposed by information theory and thermodynamics. Although it briefly mentions a number of biological systems in passing, it is written for a general physics audience at the upper undergraduate level and above. As a result, the relevance to biophysics may initially seem somewhat tenuous. The canonical problems that are staples of introductory control textbooks like this one (e.g., balancing a pole on a moving cart) seem far removed from the messy realities of living systems. Yet if one is willing to go beyond this apparent disconnect, three aspects make the book essential reading for biophysicists.

The first aspect is pragmatic: if you are an experimental biophysicist using control techniques like feedback and feedforward in your apparatus, the book provides a guide to understanding the nature of those techniques and ways to improve their performance. These ideas are laid out succinctly in chapters 3 and 4, focusing on frequency- and time-domain control, respectively. In his own research, Bechhoefer is an expert in force spectroscopy, and he highlights atomic force microscopy and optical tweezer applications. However, the underlying methods are quite general, and the text nicely balances mathematical formalism with practical rules of thumb for designing control systems. The focus in these chapters is classical control theory: how to make linear systems with time-invariant parameters track a certain input or reach a particular target. This focus becomes the core around which the rest of the book is built, including the experimental complications considered in later chapters: dealing with digital controllers (chapter 5), creating robust protocols for imperfectly parametrized systems that account for worst-case scenarios (chapter 9), control that adapts to time-varying systems (chapter 10), and coping with (and sometimes taking advantage of) nonlinearities (chapter 11). The book returns repeatedly to simple examples introduced early on, contrasting the benefits and tradeoffs of different control approaches. Although the emphasis is on the foundations of the subject, connections to active research areas are made throughout. Two interesting cases are the reservoir computing neural network approach for adaptive control described in chapter 10 and the discussion of graphical algorithms for controlling complex networks in chapter 14, which builds on a resurgence of interest in the topic following the influential 2011 paper by Liu et al. (5). Helpful notes at the end of each chapter point the reader to specialized resources where they can dive deeper into particular topics.

The second aspect of the book that makes it fascinating from a biophysics perspective is the scope of control theory. A diversity of topics that would not seem to be obviously about "control" per se can be interpreted in revealing ways from the vantage point of the theory. The key concept that enables this is laid out in chapter 4: the intimate link between controllability—the ability to drive the internal state of a system toward a future target by an input protocol—and observability—the ability to estimate the internal state of a system from past measurements of its output. The two problems can be seen as time-reversed mirror images of each other, formally related by a mathematical duality in the case of linear systems, an elegant idea which deserves wider appreciation in the physics community. State estimation is ubiquitous in biophysics; for example, in single-molecule experiments we are often faced with the challenge of estimating the conformational state of the biomolecule (i.e., whether a protein is in a native, intermediate, or unfolded state) from noisy, indirect measurements (i.e., the separation of attached beads in an optical tweezer, or the Forster resonance energy transfer efficiency of two fluorophores linked to the molecule). Cellular signaling systems face a similar challenge in estimating the state of the external environment on the basis of the activation of membrane receptors and the propagation of this signal through noisy biochemical reaction networks.

The book allows us to understand the methods of state estimation through the lens of the observability–controllability duality. The Kalman filter of chapter 8, which optimally (in the Bayesian sense) estimates the system state from past output measurements, mirrors the mathematical structure of an optimal control solution in chapter 7, which calculates the future input protocol that minimizes a chosen cost function. The Kalman filter approach is not limited to estimating states but also can be adapted to estimate unknown system parameters, taking the form of a recursive least squares technique (chapter 10). These ideas are first introduced for continuous state systems but hold equally well for discrete states, as described in chapter 12. Here, optimal state estimation and optimal control get translated into the language of hidden Markov models and Markov decision processes. The discussion of hidden Markov models, a widely used data analysis tool in biophysics, is notably clear and concise. It allows us to see hidden Markov model techniques in the broader context of control theory; for example, the Viterbi algorithm for estimating the most likely sequence of hidden states is an application of dynamic programming, first introduced for optimal control in chapter 8. The interconnected nature of all these methods is one of the main take-aways of the book, and it is not merely a mathematical curiosity: the more accurately one can estimate system states and parameters, the more accurately one can control the system via feedback, so the two sides of the duality can be harnessed together in practical applications. Intriguingly, optimal state estimation methods may also be part of the natural repertoire of biological function: Kalman (6) and Wiener–Kolmogorov (7) filters can be directly implemented via molecular interactions in biochemical networks and can serve to reduce noise in signaling pathways.

The last aspect of the book of special interest to biophysicists is the discussion on the fundamental limits of control in chapter 15. It starts with Kramers–Kronig relations, showing how causality links the real and imaginary parts of response functions. Most physicists would have initially encountered these relations in an electromagnetism course, where they connect the real and imaginary parts of the refractive index in materials. Here the relations undergo a series of interesting metamorphoses that are less familiar to physicists. They are first translated into constraints between the amplitude and phase of the response function, and then into the Bode waterbed effect. The latter shows that designing feedback to suppress disturbances at low frequencies has the unintended consequence of amplifying those disturbances at high frequencies. By switching from the frequency to the time domain, the waterbed effect is in turn given an information theory interpretation, fixing the amount of information that flows between the time series of disturbances and system output measurements (in other words quantifying how much the former causally affect the later). Finally, information itself is shown to be a physical resource in the thermodynamic sense: measurements on a system can be exploited by feedback to induce dynamics in apparent (but not actual) violation of the second law, as in the classic Maxwell demon thought experiment. The chapter ties together all these varied strands in a tour de force of exposition. It is particularly timely for the biophysics community, where understanding the full implications of the information–thermodynamic paradigm is still a work in progress (8).

On a final note, the pedagogical presentation of the material in the book perfectly complements its engaging subject matter. Numerical results are illustrated through frequent useful sidebar figures, and readers can play around with the models themselves with the use of Mathematica notebooks included in the online supplementary materials. The problems at the end of each chapter are mentioned throughout the text and are often used to work out detailed derivations or drive home key concepts. The associated solutions guide is available online for those using the book in a course or for self-study. Lastly, a comprehensive online appendix covering mathematical details in the text runs to almost 120 pages and is almost like an entire math methods course in miniature. Given the diversity of topics it surveys (among them linear algebra, Fourier and Laplace transforms, optimization, probability, stochastic processes, and information theory), one can even imagine students using it as a handy reference for other classes.

## REFERENCES

1. Lestas, I., G. Vinnicombe, and J. Paulsson. 2010. Fundamental limits on the suppression of molecular fluctuations. *Nature* 467:174–178.
2. Yi, T.-M., Y. Huang, M. I. Simon, and J. Doyle. 2000. Robust perfect adaptation in bacterial chemotaxis through integral feedback control. *Proc Natl Acad Sci U S A* 97:4649–4653.
3. Ledzewicz, U., and H. Schattler. 2015. Optimal Control for Mathematical Models of Cancer Therapies: An Application of Geometric Methods. 1st edition. Springer, New York.
4. Del Vecchio, D., A. J. Dy, and Y. Qian. 2016. Control theory meets synthetic biology. *J R Soc Interface* 13:20160380.
5. Liu, Y.-Y., J.-J. Slotine, and A.-L. Barabási. 2011. Controllability of complex networks. *Nature* 473:167–173.
6. Zechner, C., G. Seelig, M. Rullan, and M. Khammash. 2016. Molecular circuits for dynamic noise filtering. *Proc Natl Acad Sci U S A* 113:4729–4734.
7. Hinczewski, M., and D. Thirumalai. 2014. Cellular signaling networks function as generalized Wiener–Kolmogorov filters to suppress noise. *Phys Rev X* 4:041017.
8. Ito, S., and T. Sagawa. 2015. Maxwell's demon in biochemical signal transduction with feedback loop. *Nat Commun* 6:7498.