
Biomolecular Feedback Systems

Domitilla Del Vecchio
U. Michigan/MIT

Richard M. Murray
Caltech

DRAFT v0.3, December 23, 2009
© California Institute of Technology
All rights reserved.

This manuscript is for review purposes only and may not be reproduced, in whole or in part, without written consent from the authors.

Contents

Preface	iii
PART 1. MODELING AND ANALYSIS	1
Chapter 1. Core Processes	3
1.1 The Cell as a Dynamical System	3
1.2 Modeling Techniques	9
1.3 Transcription and Translation	19
1.4 Transcriptional Regulation	21
1.5 Post-Transcriptional Regulation	24
1.6 Cellular subsystems	26
Chapter 2. Dynamic Behavior	27
2.1 Analysis near equilibria	27
2.2 Analysis of Reaction Rate Equations	32
2.3 Analysis of Limit Cycles using Harmonic Balance	37
2.4 Bifurcations	42
2.5 Model Reduction Techniques	42
Chapter 3. Stochastic Behavior	45
3.1 Stochastic systems	45
3.2 Stochastic Modeling of Biochemical Systems	53
3.3 Analysis of Stochastic Systems	55
3.4 Linearized Modeling and Analysis	55
3.5 Markov chain modeling and analysis	61
3.6 System identification techniques	61
Chapter 4. Feedback Examples	63
4.1 The Lac Operon	63
4.2 Heat Shock Response in Bacteria	63
4.3 Bacteriophage λ	63
4.4 Yeast mating response	63

PART 2. DESIGN AND SYNTHESIS	67
Chapter 5. Biological Circuit Components	69
5.1 Biology Circuit Design	69
Chapter 6. Interconnecting Components	73
6.1 Input/Output Modeling and the Modularity Assumption	73
6.2 Beyond the Modularity Assumption: Retroactivity	74
6.3 Insulation Devices to Enforce Modularity	82
6.4 Design of genetic circuits under the modularity assumption	85
6.5 Biological realizations of an insulation component	91
Chapter 7. Design Tradeoffs	103
Chapter 8. Design Examples	105
Bibliography	107
Index	109

Preface

This text serves as a supplement to *Feedback Systems* by Åström and Murray [1] (referred to throughout the text as AM08) and is intended for researchers interested in the application of feedback and control to biomolecular systems. The text has been designed so that it can be used in parallel with *Feedback Systems* as part of a course on biomolecular feedback and control systems, or as a standalone reference for readers who have had a basic course in feedback and control theory. The full text for AM08, along with additional supplemental material and a copy of these notes, is available on a companion web site:

<http://www.cds.caltech.edu/~murray/AMwiki/BFS>

The text is intended to be useful to three overlapping audiences: graduate students in biology and bioengineering interested in understanding the role of feedback in natural and engineered biomolecular systems; advanced undergraduates and graduate students in engineering disciplines who are interested the use of feedback in biological circuit design; and established researchers in the the biological sciences who want to explore the potential application of principles and tools from control theory to biomolecular systems. We have written the text assuming familiarity with the material in AM08, but have tried to provide insights and motivation so that the material can be learned in parallel. We also assume some familiarity with cell biology, at the level of a freshman course for non-majors. The individual chapters in the text indicate the pre-requisites in more detail, most of which are covered either in AM08 or in the supplemental information available from the companion web site.

Notation

This is an internal chapter that is intended for use by the authors in fixing the notation that is used throughout the text. In the first pass of the book we are anticipating several conflicts in notation and the notes here may be useful to early users of the text.

Protein dynamics

We use P to refer to a protein, mP to refer to the mRNA associated with that protein and p to refer to the gene that encodes P . The concentration of P can be written either as P or $[P]$, with a preference for the former. The concentration of mP can be written either as m_p (preferred) or $[mP]$. Parameters that are specific to gene p are written with a subscripted p : α_p, δ_p , etc.

The dynamics of protein production are given by

$$\frac{dm_p}{dt} = \alpha_{p,0} - \gamma_p m_p, \quad \frac{dP}{dt} = \beta_p m_p - \delta_p P,$$

where $\alpha_{p,0}$ is the (constitutive) rate of production, γ_p parameterizes the rate of dilution and degradation of the mRNA mP , β_p is the kinetic rate of protein production and δ_p parameterizes the rate of dilution and degradation of the protein P .

When we ignore the mRNA concentration, we write the simplified protein dynamics as

$$\frac{dP}{dt} = \beta_{p,0} - \delta_p P.$$

Assuming that the mRNA dynamics are fast compared to protein production, then the constant $\beta_{p,0}$ is given by

$$\beta_{p,0} = \beta_p \frac{\gamma_p}{\alpha_{p,0}}.$$

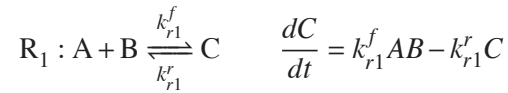
For regulated production of proteins using Hill functions, we modify the constitutive rate of production to be $f_p(Q)$ instead of $\alpha_{p,0}$ or $\beta_{p,0}$ as appropriate. The Hill function is written in the form

$$f_p(Q) = \frac{\alpha_{pq}}{k_{pq} + Q^{n_{pq}}}.$$

The subscripts can be dropped if there is only one Hill function in use.

Chemical reactions

We write the symbol for a chemical species A using roman type. The number of molecules of a species A is written as n_a . The concentration of the species is occasionally written as $[A]$, but we more often use the notation A , as in the case of proteins, or x_a . For a reaction $A + B \longleftrightarrow C$, we use the notation



It will often be the case that two species A and B will form a covalent bond, in which case we write the resulting species as AB . We will distinguish covalent bonds from much weaker hydrogen bonding by writing the latter as $A:B$. Finally, in some situations we will have labeled section of DNA that are connected together, which we write as $A-B$, where here A represents the first portion of the DNA strand and B represents the second portion. When describing (single) strands of DNA, we write A' to represent the Watson-Crick complement of the strand A . Thus $A-B:B'-A'$ would represent a double stranded length of DNA with domains A and B .

The choice of representing covalent molecules using the conventional chemical notation AB can lead to some confusion when writing the reaction dynamics using A and B to represent the concentrations of those species. Namely, the symbol AB could represent either the concentration of A times the concentration of B or the concentration of AB . To remove this ambiguity, when using this notation we will write $[A][B]$ as $A \cdot B$.

When working with a system of chemical reactions, we write S_i , $i = 1, \dots, n$ for the species and R_j , $j = 1, \dots, m$ for the reactions. We write n_i to refer to the molecular count for species i and $x_i = [S_i]$ to refer to the concentration of the species. The individual equations for a given species are written

Missing. Figure out notation here. BST?

The collection of reactions are written as

$$\dot{x} = Nv(x, \mu), \quad \dot{x}_i = N_{ij}v_j(x, \mu)$$

where x_i is the concentration of species S_i , $N \in \mathbb{R}^{n \times m}$ is the stoichiometry matrix, v_j is the reaction flux vector for reaction j , and μ is the collection of parameters that define the reaction rates.