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# Biomolecular Feedback Systems

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## Bibliography

- [1] K. J. Åström and R. M. Murray. *Feedback Systems: An Introduction for Scientists and Engineers*. Princeton University Press, 2008. Available at <http://www.cds.caltech.edu/~murray/amwiki>.
- [2] B. Alberts, D. Bray, J. Lewis, M. Raff, K. Roberts, and J. D. Watson. *The Molecular Biology of the Cell*. Garland Science, 5th edition, 2008.
- [3] R. Algar, T. Ellis, and G.-B. Stan. Modelling the burden caused by gene expression: an in silico investigation into the interactions between synthetic gene circuits and their chassis cell. *arXiv:1309.7798*, 2013.
- [4] U. Alon. *An Introduction to Systems Biology. Design Principles of Biological Circuits*. Chapman-Hall, 2007.
- [5] W. Arber and S. Linn. DNA modification and restriction. *Annual Review of Biochemistry*, 38:467–500, 1969.
- [6] M. R. Atkinson, M. A. Savageau, J. T. Meyers, and A. J. Ninfa. Development of genetic circuitry exhibiting toggle switch or oscillatory behavior in *Escherichia coli*. *Cell*, pages 597–607, 2003.
- [7] D. W. Austin, M. S. Allen, J. M. McCollum, R. D. Dar, J. R. Wilgus, G. S. Sayler, N. F. Samatova, C. D. Cox, and M. L. Simpson. Gene network shaping of inherent noise spectra. *Nature*, 2076:608–611, 2006.
- [8] D. Baker, G. Church, J. Collins, D. Endy, J. Jacobson, J. Keasling, P. Modrich, C. Smolke, and R. Weiss. ENGINEERING LIFE: Building a FAB for biology. *Scientific American*, June 2006.
- [9] N. Barkai and S. Leibler. Robustness in simple biochemical networks. *Nature*, 387(6636):913–917, 1997.
- [10] A. Becskei and L. Serrano. Engineering stability in gene networks by autoregulation. *Nature*, 405:590–593, 2000.
- [11] D. Bell-Pedersen, V. M. Cassone, D. J. Earnest, S. S. Golden, P. E. Hardin, T. L. Thomas, and M. J. Zoran. Circadian rhythms from multiple oscillators: lessons from diverse organisms. *Nature Reviews Genetics*, 6(7):544, 2005.
- [12] W. E. Bentley, N. Mirjalili, D. C. Andersen, R. H. Davis, and D. S. Kompala. Plasmid-encoded protein: the principal factor in the “metabolic burden” associated with recombinant bacteria. *Biotechnol. Bioeng.*, 35(7):668–681, 1990.
- [13] BioNumbers: The database of useful biological numbers. <http://bionumbers.org>, 2012.

- [14] L. Bleris, Z. Xie, D. Glass, A. Adadey, E. Sontag, and Y. Benenson. Synthetic incoherent feedforward circuits show adaptation to the amount of their genetic template. *Molecular Systems Biology*, 7:519, 2011.
- [15] H. Bremer and P. Dennis. Modulation of chemical composition and other parameters of the cell by growth rate. In *Escherichia coli and Salmonella: Cellular and Molecular Biology* (edited by F. C. Neidhart et al.), ASM Press, Washington, DC, 183:1553–1569, 1996.
- [16] H. Bremer, P. P. Dennis, and M. Ehrenberg. Free RNA polymerase and modeling global transcription in *Escherichia coli*. *Biochimie*, 85(6):597–609, 2003.
- [17] C. I. Byrnes, F. D. Prisco, and A. Isidori. *Output Regulation of Uncertain Nonlinear Systems*. Birkhauser, 1997.
- [18] B. Canton, A. Labno, and D. Endy. Refinement and standardization of synthetic biological parts and devices. *Nature Biotechnology*, 26(7):787–793, 2008.
- [19] M. Chalfie, Y. Tu, G. Euskirchen, W. Ward, and D. Prasher. Green fluorescent protein as a marker for gene expression. *Science*, 263(5148):802–805, 1994.
- [20] A. J. Courey. *Mechanisms in Transcriptional Regulation*. Wiley-Blackwell, 2008.
- [21] D. Del Vecchio. Design and analysis of an activator-repressor clock in *e. coli*. In *Proc. American Control Conference*, 2007.
- [22] D. Del Vecchio, A. J. Ninfa, and E. D. Sontag. Modular cell biology: Retroactivity and insulation. *Nature/EMBO Molecular Systems Biology*, 4:161, 2008.
- [23] L. N. M. Duysens and J. Ames. Fluorescence spectrophotometry of reduced phosphopyridine nucleotide in intact cells in the near-ultraviolet and visible region. *Biochim. Biophys. Acta*, 24:19–26, 1957.
- [24] H. El-Samad, J. P. Goff, and M. Khammash. Calcium homeostasis and parturient hypocalcemia: An integral feedback perspective. *J. Theoret. Biol.*, 214:17–29, 2002.
- [25] S. P. Ellner and J. Guckenheimer. *Dynamic Models in Biology*. Princeton University Press, Princeton, NJ, 2005.
- [26] M. B. Elowitz and S. Leibler. A synthetic oscillatory network of transcriptional regulators. *Nature*, 403(6767):335–338, 2000.
- [27] M. B. Elowitz, A. J. Levine, E. D. Siggia, and P. Swain. Stochastic gene expression in a single cell. *Science*, 297(5584):1183–1186, 2002.
- [28] D. Endy. Foundations for engineering biology. *Nature*, 438:449–452, 2005.
- [29] K. M. Eveker, D. L. Gysling, C. N. Nett, and O. P. Sharma. Integrated control of rotating stall and surge in high-speed multistage compression systems. *Journal of Turbomachinery*, 120(3):440–445, 1998.
- [30] T. S. Gardner, C. R. Cantor, and J. J. Collins. Construction of the genetic toggle switch in *Escherichia coli*. *Nature*, 403:339–342, 2000.

- [31] D. C. Gibson, J. I. Glass, C. Lartigue, V. N. Noskov, R. Y. Chuang, M. A. Algire, G. A. Benders, M. G. Montague, L. Ma, M. M. Moodie, C. Merryman, S. Vashee, R. Krishnakumar, N. Assad-Garcia, C. Andrews-Pfannkoch, E. A. Denisova, L. Young, Z.-Q. Qi, T. H. Segall-Shapiro, C. H. Calvey, P. P. Parmar, C. A. Hutchison, H. O. Smith, and J. C. Venter. Creation of a bacterial cell controlled by a chemically synthesized genome. *Science*, 329(5987):52–56, 2010.
- [32] D. T. Gillespie. *Markov Processes: An Introduction For Physical Scientists*. Academic Press, 1976.
- [33] D. T. Gillespie. Exact stochastic simulation of coupled chemical reactions. *Journal of Physical Chemistry*, 81(25):2340–2361, 1977.
- [34] D. T. Gillespie. The chemical Langevin equation. *Journal of Chemical Physics*, 113(1):297–306, 2000.
- [35] L. Goentoro, O. Shoval, M. W. Kirschner, and U. Alon. The incoherent feedforward loop can provide fold-change detection in gene regulation. *Molecular Cell*, 36:894–899, 2009.
- [36] A. Goldbeter and D. E. Koshland. An amplified sensitivity arising from covalent modification in biological systems. *Proc. of the National Academy of Sciences*, pages 6840–6844, 1981.
- [37] J. Greenblatt, J. R. Nodwell, and S. W. Mason. Transcriptional antitermination. *Nature*, 364(6436):401–406, 1993.
- [38] I. L. Grigiriva, N. J. Phleger, V. K. Mutalik, and C. A. Gross. Insights into transcriptional regulation and  $\sigma$  competition from an equilibrium model of RNA polymerase binding to DNA. *Proc. of the National Academy of Sciences*, 103(14):5332–5337, 2006.
- [39] J. Guckenheimer and P. Holmes. *Nonlinear Oscillations, Dynamical Systems, and Bifurcations of Vector Fields*. Springer, 1983.
- [40] S. Hastings, J. Tyson, and D. Webster. Existence of periodic solutions for negative feedback cellular systems. *J. of Differential Equations*, 25:39–64, 1977.
- [41] R. Heinrich, B. G. Neel, and T. A. Rapoport. Mathematical models of protein kinase signal transduction. *Molecular Cell*, 9:957–970, 2002.
- [42] B. Hess, A. Boiteux, and J. Kruger. Cooperation of glycolytic enzymes. *Adv. Enzyme Regul*, 7:149–167, 1969.
- [43] A. Hilfinger and J. Paulsson. Separating intrinsic from extrinsic fluctuations in dynamic biological systems. *Proc. of the National Academy of Sciences*, 108(29):12167–12172, 2011.
- [44] C. F. Huang and J. E. Ferrell. Ultrasensitivity in the mitogen-activated proteinkinase cascade. *Proc. of the National Academy of Sciences*, 93(19):10078–10083, 1996.
- [45] T. P. Hughes. *Elmer Sperry: Inventor and Engineer*. Johns Hopkins University Press, Baltimore, MD, 1993.
- [46] R. S. Cox III, M. G. Surette, and M. B. Elowitz. Programming gene expression with combinatorial promoters. *Mol. Syst. Biol.*, 3:145, 2007.

- [47] A. Ishihama. Functional modulation of *E. coli* RNA polymerase. *Ann. Rev. Microbiol.*, 54:499–518, 2000.
- [48] F. Jacob and J. Monod. Genetic regulatory mechanisms in the synthesis of proteins. *J. Mol. Biol.*, 3:318–356, 1961.
- [49] S. Jayanthi and D. Del Vecchio. On the compromise between retroactivity attenuation and noise amplification in gene regulatory networks. In *Proc. Conference on Decision and Control*, pages 4565–4571, 2009.
- [50] S. Jayanthi and D. Del Vecchio. Retroactivity attenuation in bio-molecular systems based on timescale separation. *IEEE Transactions on Automatic Control*, 56:748–761, 2011.
- [51] S. Jayanthi, K. Nilgiriwala, and D. Del Vecchio. Retroactivity controls the temporal dynamics of gene transcription. *ACS Synthetic Biology*, DOI: 10.1021/sb300098w, 2013.
- [52] P. Jiang, A. C. Ventura, S. D. Merajver, E. D. Sontag, A. J. Ninfa, and D. Del Vecchio. Load-induced modulation of signal transduction networks. *Science Signaling*, 4(194):ra67, 2011.
- [53] N. G. Van Kampen. *Stochastic Processes in Physics and Chemistry*. Elsevier, 1992.
- [54] A. S. Khalil and J. J. Collins. Synthetic biology: Applications come of age. *Nature Reviews Genetics*, 11(5):367, 2010.
- [55] H. K. Khalil. *Nonlinear Systems*. Macmillan, 1992.
- [56] E. Klipp, W. Liebermeister, C. Wierling, A. Kowald, H. Lehrach, and R. Herwig. *Systems Biology: A Textbook*. Wiley-VCH, 2009.
- [57] S. Klumpp and T. Hwa. Growth-rate-dependent partitioning of RNA polymerases in bacteria. *Proc. of the National Academy of Sciences*, 105(51):20245–20250, 2008.
- [58] P. Kundur. *Power System Stability and Control*. McGraw-Hill, New York, 1993.
- [59] M. T. Laub, L. Shapiro, and H. H. McAdams. Systems biology of *Caulobacter*. *Annual Review of Genetics*, 51:429–441, 2007.
- [60] J.-C. Leloup and A. Goldbeter. A molecular explanation for the long-term suppression of circadian rhythms by a single light pulse. *American Journal of Physiology*, 280:1206–1212, 2001.
- [61] J. J. Lemke, P. Sanchez-Vazquez, H. L. Burgos, G. Hedberg, W. Ross, and R. L. Gourse. Direct regulation of *Escherichia coli* ribosomal protein promoters by the transcription factors ppGpp and DksA. *Proc. of the National Academy of Sciences*, pages 1–6, 2012.
- [62] W. Lohmiller and J. J. E. Slotine. On contraction analysis for non-linear systems. *Automatica*, 34:683–696, 1998.
- [63] H. Madhani. *From  $\alpha$  to  $\alpha$ : Yeast as a Model for Cellular Differentiation*. CSHL Press, 2007.
- [64] J. Mallet-Paret and H. L. Smith. The Poincaré-Bendixson theorem for monotone cyclic feedback systems. *J. of Differential Equations*, 2:367–421, 1990.

- [65] J. E. Marsden and M. J. Hoffman. *Elementary Classical Analysis*. Freeman, 2000.
- [66] J. E. Marsden and M. McCracken. *The Hopf Bifurcation and Its Applications*. Springer-Verlag, New York, 1976.
- [67] S. Marsigliante, M. G. Elia, B. Di Jeso, S. Greco, A. Muscella, and C. Storelli. Increase of  $[Ca^{2+}]_i$  via activation of ATP receptors in PC-C13 rat thyroid cell line. *Cell. Signal*, 14:61–67, 2002.
- [68] H. H. McAdams and A. Arkin. Stochastic mechanisms in gene expression. *Proc. of the National Academy of Sciences*, 94:814–819, 1997.
- [69] C. R. McClung. Plant circadian rhythms. *Plant Cell*, 18:792–803, 2006.
- [70] M. W. McFarland, editor. *The Papers of Wilbur and Orville Wright*. McGraw-Hill, New York, 1953.
- [71] P. Miller and X. J. Wang. Inhibitory control by an integral feedback signal in pre-frontal cortex: A model of discrimination between sequential stimuli. *Proc. of the National Academy of Sciences*, 103:201–206, 2006.
- [72] C. J. Morton-Firth, T. S. Shimizu, and D. Bray. A free-energy-based stochastic simulation of the tar receptor complex. *Journal of Molecular Biology*, 286(4):1059–1074, 1999.
- [73] J. D. Murray. *Mathematical Biology*, Vols. I and II. Springer-Verlag, New York, 3rd edition, 2004.
- [74] C. J. Myers. *Engineering Genetic Circuits*. Chapman and Hall/CRC Press, 2009.
- [75] T. Nagashima, H. Shimodaira, K. Ide, T. Nakakuki, Y. Tani, K. Takahashi, N. Yumoto, and M. Hatakeyama. Quantitative transcriptional control of ErbB receptor signaling undergoes graded to biphasic response for cell differentiation. *J. Biol. Chem.*, 282:4045–4056, 2007.
- [76] R. Neshler and E. Cerasi. Modeling phasic insulin release: Immediate and time-dependent effects of glucose. *Diabetes*, 51:53–59, 2002.
- [77] H. R. Ossareh, A. C. Ventura, S. D. Merajver, and D. Del Vecchio. Long signaling cascades tend to attenuate retroactivity. *Biophysical Journal*, 10:1617–1626, 2011.
- [78] R. Phillips, J. Kondev, and J. Theriot. *Physical Biology of the Cell*. Garland Science, 2009.
- [79] M. Ptashne. *A Genetic Switch*. Blackwell Science, Inc., 1992.
- [80] P. E. M. Purnick and R. Weiss. The second wave of synthetic biology: From modules to systems. *Nature Reviews Molecular Cell Biology*, 10(6):410–422, 2009.
- [81] E. K. Pye. Periodicities in intermediary metabolism. *Biochronometry*, pages 623–636, 1971.
- [82] L. Qiao, R. B. Nachbar, I. G. Kevrekidis, and S. Y. Shvartsman. Bistability and oscillations in the Huang-Ferrell model of MAPK signaling. *PLoS Computational Biology*, 3:e184, 2007.

- [83] C. V. Rao, J. R. Kirby, and A. P. Arkin. Design and diversity in bacterial chemotaxis: A comparative study in *Escherichia coli* and *Bacillus subtilis*. *PLoS Biology*, 2(2):239–252, 2004.
- [84] H. M. Sauro and B. N. Kholodenko. Quantitative analysis of signaling networks. *Progress in Biophysics & Molecular Biology*, 86:5–43, 2004.
- [85] M. Scott, C. W. Gunderson, E. M. Mateescu, Z. Zhang, and T. Hwa. Interdependence of cell growth and gene expression: Origins and consequences. *Science*, 330:1099–1202, 2010.
- [86] D. E. Seborg, T. F. Edgar, and D. A. Mellichamp. *Process Dynamics and Control*. Wiley, Hoboken, NJ, 2nd edition, 2004.
- [87] Thomas S Shimizu, Yuhai Tu, and Howard C Berg. A modular gradient-sensing network for chemotaxis in *Escherichia coli* revealed by responses to time-varying stimuli. *Molecular Systems Biology*, 6:382, 2010.
- [88] O. Shimomura, F. Johnson, and Y. Saiga. Extraction, purification and properties of Aequorin, a bioluminescent protein from the luminous hydromedusan, *Aequorea*. *J. Cell. Comp. Physiol.*, 59(3):223–239, 1962.
- [89] O. Shoval, U. Alon, and E. Sontag. Symmetry invariance for adapting biological systems. *SIAM J. Applied Dynamical Systems*, 10:857886, 2011.
- [90] E. D. Sontag. *Mathematical Control Theory: Deterministic Finite Dimensional Systems*. Springer, New York, 2nd edition, 1998.
- [91] E. D. Sontag. Remarks on feedforward circuits, adaptation, and pulse memory. *IET Systems Biology*, 4:39–51, 2010.
- [92] P. S. Swain, M. B. Elowitz, and E. D. Siggia. Intrinsic and extrinsic contributions to stochasticity in gene expression. *Proc. of the National Academy of Sciences*, 99(20):12795–12800, 2002.
- [93] J. Tsang, J. Zhu, and A. van Oudenaarden. MicroRNA-mediated feedback and feed-forward loops are recurrent network motifs in mammals. *Mol. Cell.*, 26:753–767, 2007.
- [94] K. V. Venkatesh, S. Bhartiya, and A. Ruhela. Multiple feedback loops are key to a robust dynamic performance of tryptophan regulation in *Escherichia coli*. *FEBS Letters*, 563:234–240, 2004.
- [95] A. C. Ventura, P. Jiang, L. van Wassenhove, D. Del Vecchio, S. D. Merajver, and A. J. Ninfa. The signaling properties of a covalent modification cycle are altered by a downstream target. *Proc. of the National Academy of Sciences*, 107(22):10032–10037, 2010.
- [96] O. S. Venturelli, H. El-Samad, and R. M. Murray. Synergistic dual positive feedback loops established by molecular sequestration generate robust bimodal response. *Proc. of the National Academy of Sciences*, 109(48):E3324–3333, 2012.
- [97] L. Villa-Komaroff, A. Efstratiadis, S. Broome, P. Lomedico, R. Tizard, S. P. Naber, W. L. Chick, and W. Gilbert. A bacterial clone synthesizing proinsulin. *Proc. of the National Academy of Sciences*, 75(8):3727–3731, 1978.

- [98] J. Vind, M. A. Sørensen, M. D. Rasmussen, and S. Pedersen. Synthesis of proteins in *Escherichia coli* is limited by the concentration of free ribosomes. *J. Mol. Biol.*, 231:678–688, 1993.
- [99] C. A. Voigt. Genetic parts to program bacteria. *Current Opinions in Biotechnology*, 17(5):548–557, 2006.
- [100] S. Wiggins. *Introduction to Applied Nonlinear Dynamical Systems and Chaos*. Springer, 2003.
- [101] L. Yang and P. A. Iglesias. Positive feedback may cause the biphasic response observed in the chemoattractant-induced response of Dictyostelium cells. *Systems Control Lett.*, 55:329–337, 2006.
- [102] T.-M. Yi, Y. Huang, M. I. Simon, and J. C. Doyle. Robust perfect adaptation in bacterial chemotaxis through integral feedback control. *Proc. of the National Academy of Sciences*, 97(9):4649–4653, 2000.
- [103] N. Yildirim and M. C. Mackey. Feedback regulation in the lactose operon: A mathematical modeling study and comparison with experimental data. *Biophysical Journal*, 84(5):2841–2851, 2003.





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## Index

- $\omega$ -limit point, 121
- $\omega$ -limit set, 121–123, 186
- absolute activator, 71–73
- acceptor, 79, 234
- acetylation, 74
- activation, 45, 55, 57, 60, 71, 73, 87, 88, 110, 114, 135, 169, 171, 182, 222, 243, 245, 252
  - allosteric activation, 70–73
  - in activator-repressor clock, 136, 184–189, 203, 207, 237, 241
  - in combinatorial promoters, 143
  - reaction model, 62, 64–66
- actuators, 20
- adaptation, 10, 107–110, 135, 189, 190, 199, 204
- adenine, 45, 48
- adenosine triphosphate, *see also* ATP
- adenosine triphosphate (ATP), 38
- aequorea victoria, 24
- aerospace systems, 15
- affinity, 40, 73, 170, 190, 212, 232
- AHL, 171
- allosteric regulation, 56, 62, 70–74
- amino acid, 48, 51–52, 74, 171
- amplification, 205, 221–227, 243, 253, 257
- amplifier, 14, 18, 169
- amplitude of response, 98–100, 212, 213, 255
- antibiotic, 23–25
- antitermination, 60–61
- arabinose, 171
- association rate constant, 39, 62, 207
- asymptotic stability, 91, 92, 96, 97
- asynchronous, 50
- aTc, 58, 171
- ATP, 9, 15, 38, 74, 75, 79, 110
- attenuation, 103, 213
- attractant, 191–193
- attractor (equilibrium point), 92
- autocatalysis, 119
- autophosphorylation, 193
- autopilot, 15, 16
- autoregulation, 66–68, 94, 98, 165, 171–177, 203, 240
- back-effect
  - retroactivity, 208
- bacteria, 22, 57, 191
- bandwidth, 98–100, 255
  - effect of retroactivity, 213, 218–219
  - in a covalent modification cycle, 133
- basal expression rate, 64–69, 87, 183
- base, 26, 45
- base-pair, 48, 50, 54, 170, 190
- Bell Labs, 14
- Bendixson’s criterion, 121, 135, 136
- bifurcation, 124–127
  - Hopf, *see* Hopf bifurcation
  - Hopf bifurcation, 187–189
- bifurcation diagram, 125
- bimodality, 7
- binding
  - competitive, 42, 68, 86
  - cooperative, 40, 68, 86, 241
  - of RNA polymerase, 61–66, 142
  - reaction, 39, 215, 248
  - reactions, 72, 129, 208
  - receptor-ligand, 193–202
  - site, 189, 248
- biobrick, 26
- biofuels, 22
- biological circuits, 4, 22–28, 169–191, 206, 243
  - repressilator, 24
- birth process, 154
- bistability, 6, 25
  - bistable system, 25, 93, 125, 178, 203
- bistable, 125
- Black, H. S., 14, 16
- block diagonal systems, 96

- Bode plot, 100, 102  
 Boltzmann constant, 31  
 buffer, 213, 250  
 burst, 119  
 CAP, 59  
 cascade, 136
  - MAPK, 81–86, 227
  - of covalent modification cycles, 169
  - of phosphorylation cycles, 74
  - of transcriptional activators, 86
  - signaling cascade, 9, 10
 catalytic rate constant, 43, 77, 230  
 catalytic site, 71  
 CDKs, *see* cyclin dependent kinases  
 center (equilibrium point), 93  
 center manifold, 127  
 central dogma, 45–50  
 characteristic curve, 77, 214–217, 240  
 characteristic polynomial, 95, 181  
 CheA kinase, 26, 193, 200  
 CheB protein, 193  
 chemical kinetics, 30, 32–34, 144  
 chemical Langevin equation, 36, 150–152, 167, 173, 253  
 chemical master equation, 144–150  
 chemotaxis, 9, 191  
 CheW protein, 193  
 circadian rhythm, 114–117  
 circuit motifs, 109, 170  
 circuits
  - activator-repressor clock, 184–189
  - chemotaxis, 191–202
  - incoherent feedforward loop, 189
  - insulation device, 222–227, 229–235
  - interconnection of, 236–238
  - repressilator, 180–184
  - toggle switch, 177–180
 clock
  - activator-repressor, 184–189, 203, 207, 236, 241
  - repressilator, 180–184
 cloning, 23  
 closed complex, 45, 147  
 closed loop, 12, 14, 101, 102, 105, 172
  - versus open loop, 12
 coding region, 45–47, 170  
 coefficient
  - Hill, 41, 183, 203
  - of variation, 150
  - response, 77, 216
 coherent feedforward loop, 69  
 combinatorial promoter, 58, 68, 87, 142, 184, 191  
 competitive binding, *see* binding  
 competitive inhibition, 70, 88  
 complexity, of control systems, 17  
 concentration, 34  
 conservation, 229, 241
  - of DNA, 63, 251
  - of enzyme, 72, 81
  - of protein, 83, 98, 197, 215
  - of RNA polymerase, 246
  - of species, 37, 43
 context-dependence, 256  
 contracting, 112  
 contracting system, 112  
 control, 11, 20, 108
  - early examples, 14
  - in chemotaxis, 191
  - in post-transcriptional regulation, 74
 control matrix, 22  
 control signal, 20  
 cooperative, 41  
 cooperative binding, *see* binding  
 cooperativity, 41, 68, 183, 204  
 coordinate transformations, 96  
 COPASI, 107  
 copy number
  - of plasmid, 170, 189, 249
 covalent modification, 38, 74, 133
  - in insulation devices, 227
  - model, 74–79
  - retroactivity effects, 214
 crosstalk, 17, 133, 243  
 cruise control, 13–14
  - robustness, 14
 Curtiss seaplane, 16  
 cut-off frequency, 98  
 cycle
  - cell cycle, 114
  - limit, *see* limit cycle
  - modification, *see* covalent modification
  - phosphorylation, *see* phosphorylation
 cyclic AMP, 58  
 cyclic feedback system, 123, 180–184

- cyclin dependent kinases, 114
- cyclins, 114
- cytoplasm, 45
- decay
  - of a protein, 53, 130, 133
  - rate, 171, 172
- degradation, 75, 222, 253
  - effect on repressilator, 184
  - model, 37, 53–55
  - of mRNA, 52, 102
  - tag, 37, 171, 173, 189, 190
- delay
  - in protein production, 53–54, 87
  - in transcriptional regulation, 87
  - load-induced, 228
- demand for resources, 243
- density
  - probability, 152, 155
- dephosphorylation, *see* phosphorylation
- design
  - of circuits, *see* biological circuits
  - of dynamics, 15–16, 97
  - of insulation devices, *see* insulation device
- device, *see* insulation device
- diagonal systems, 95
  - transforming to, 96
- differential equation, *see* ordinary differential equation (ODE)
- diffusion
  - of protein along DNA, 49
  - of RNA polymerase along DNA, 50
  - term, 152
- dilution, 53–55, 240
  - model, 53–55
  - rate, 184
- dimer, 40, 56, 86
- dimerization, 40, 129
- direct term, 22
- dissociation constant, 40, 71, 73, 179, 190, 195, 203
  - of inducer, 65
  - of RNA polymerase, 48, 49, 63
  - of transcription factor, 49, 68, 212, 248, 249, 252
- dissociation rate constant, 39, 43, 210, 252
- distribution
  - Poisson, 155
  - probability, 148, 150, 152, 154
- disturbance, 5, 17, 21, 134, 166
  - adaptation to, 199
  - limitations, 134
  - response to, 101
- disturbance attenuation, 111
  - in biological systems, 102
  - in retroactivity, 220
- disturbance rejection, 108, 111
- DNA, 45–46
  - ligase, 23
  - looping, 56
- donor
  - of phosphate, *see* phosphate donor
- doubling time, 248
- drift term, 152
- duplication, 114
- dynamical systems, 12, 89
  - linear, 95
- dynamics matrix, 22, 96
- E. coli*
  - as a cell chassis, 169
  - cell division time, 114
  - characteristic concentrations, 248
  - characteristic rates, 49
  - chemotaxis, 191
  - sigma factors, 57
- economic systems, 17
- effective load, 212, 216, 240
- eigenvalues, 95, 96
- eigenvector, 95, 96
- electrical circuits, 4
- electrical engineering, 18–20
- elongation
  - in transcription, 50
  - in translation, 51
  - TEC, 47
- energy level
  - in receptor complex, 193
  - of microstates, 31, 140–144
- engineered circuits, 26
- entropy, 140
- enzymatic reaction, 43–44, 71, 130
- enzyme, 43, 130, 137
  - kinase, *see* kinase
  - phosphatase, *see* phosphatase

- RNA polymerase, *see* RNA polymerase
- RNase, *see* RNase
- equilibrium point, 90–93, 95
  - bifurcations of, 124
  - for planar systems, 92
  - region of attraction, 92
- eukaryotes, 45, 51, 74
- exons, 47
- expected value, 158
- expression, *see* gene expression
- extrinsic noise, 8
- factor, *see* transcription factor
- feedback, 12–18, 22, 67, 94, 97, 102, 106, 115, 171, 177
  - as technology enabler, 16
  - drawbacks of, 13, 16
  - high gain, 111–112, 220
  - in biomolecular systems, 5, 7
  - in cruise control, 14
  - in oscillator, *see* cyclic feedback system
  - integral, *see* integral feedback
  - limitations of, 134
  - robustness through, 13
  - versus feedforward, 17
  - versus retroactivity, 209
- feedforward, 17
- feedforward loop, 69, 108–111
  - circuit, 189, 204
- filter
  - low-pass, 98
  - noise filtering, 173, 255
- first-order kinetics, 44
- flagella, 10, 191–192
- flagellar motor, 191
- flight control, 15
- fluorescent reporters, 24, 171
- Fokker-Planck equation, 152–153
- fold-change detection, 112–113
- folding of a protein, 48, 51
- forward Kolmogorov equation, 145
- Fourier transform, 163, 164
- fragmentation of DNA, 23
- frequency response, 19–21, 98–101, 133, 134, 173–177, 203
  - effects of retroactivity, 213–214
- fusion of proteins, 171
- gain, 100
  - in high gain feedback, *see* feedback
  - in integral feedback, 108
  - loop, 123
  - of a frequency response, 100
  - zero frequency, 100
- Gaussian distribution, 165
- Gaussian random variable, 151
- Gaussian white noise, 152, 167, 254
- gene, 45–46
- gene expression, 44–55
- genetic circuits, *see* biological circuits
- genetic switch, 25
- genome, 22
- GFP, 24, 171
- Gillespie algorithm, 157
- global behavior, 92
- globally stable system, 92
- glucose, 60
- glycolytic oscillations, 119, 127
- glycolysis, *see* glycolytic oscillations
- green fluorescent protein, *see* GFP
- growth rate, 53, 246, 248
- half-life, 49, 172
- harmonic oscillator, 117–119
- heat shock, 57, 58
- heteroclinic orbit, 119, 123
- high-copy plasmid, *see* plasmid
- Hill coefficient
  - in MAPKKK cascade, 85
- Hill function, 41, 86, 129
  - for a repressor, 63
  - for an activator, 65
  - response coefficient, 77
- homeostasis, 109
- homoclinic orbit, 118
- Hopf bifurcation, 125–127, 188
- hysteresis, 18
- impedance in biomolecular systems, 208
- implicit function theorem, 128
- impulse response, 160
- independent random variables, 151
- inducers, 58, 65–66
- inducible promoter, 227
- inhibition
  - allosteric inhibition, 71–72

- input/output models, 18, 20, 21
- inputs, 21
- insulation device, 219–235
- insulin production, 22
- integral feedback, 108–109, 135, 193
- interconnection of systems, 205
- intrinsic noise, 8, 177
- invariant region, 122
- IPTG, 58, 171
- irreversible reaction, 77
- isolated system, 209
- isomerization, 45, 50, 62, 65
  
- Jacobian matrix, 97, 181, 186, 202
- jellyfish, 24, 171
  
- Kelvin degrees, 31
- kinase, 38, 74, 75, 81, 88, 133, 225, 236
- Kolmogorov equation, 145
- Kozak sequence, 48
  
- LacI (Lac repressor), 60
- lactose, 58
- Langevin equation, *see* chemical Langevin equation
- Laplace transforms, 19
- leakiness of transcription, 62, 64, 87
- leucine, 59
- ligand, 10, 27, 74, 193
- ligation, 23
- limit cycle, 116–123, 125, 135, 180, 183, 188, 241
- limitations in design, 135
- linear time-invariant systems, 19, 22, 94
- linearization, 94–98, 106–112, 123, 126, 134, 172, 181, 186, 203, 213, 218, 254
- load, 206, 216, 249
  - robustness to, 235
- load-induced delay, *see* delay
- loading in biological circuits, 205
- local behavior, 92, 97
- low-pass filter, *see* filter
- lysine, 74
- lysis/lysogeny, 25
  
- macrostate, 31, 141, 143
- magnitude (of frequency response), 99, 100
- MAPK cascade, 81–86
  - maturation time, 48, 49
  - mature mRNA, 48
  - mean, 150, 153, 160, 166
  - measured signals, 20–22
  - mechanics, 20
  - membrane-bound protein, 193
  - memory, 6
  - messenger RNA (mRNA), 47, 49
  - metabolic burden, 256
  - metabolic network, 119
  - metabolism, 8
  - methylation, 74
    - in bacterial chemotaxis, 194
  - methylation reaction rates, 198, 201
  - methylation reactions, 195, 201
  - Michaelis-Menten constant, 43, 72
    - and ultrasensitivity, 79
  - Michaelis-Menten kinetics, 44, 72
    - and quasi-steady state approximation, 132
    - in double phosphorylation, 82
    - in methylation, 201
  - micro-RNA, 110
  - microstate, 30, 140–144, 154
  - mitogen activated protein kinase (MAPK), 81
  - mitosis, 114
  - model reduction, *see* reduction of models
    - in retroactivity analysis, 240
  - model uncertainty, 6
  - modeling
    - chemotaxis, 194
    - chemical reactions, 29
    - input/output modeling, 205
    - stochastic systems, 139
  - modeling simplified models, use of, 21
  - modification
    - allosteric, *see* allosteric regulation
    - covalent, *see* covalent modification
  - modular interconnection, 205
  - modularity, 16, 26, 206
  - modularity assumption
    - in circuit design, 206
    - validity, 212
  - molecular dynamics, 30
  - motor, *see* flagellar motor
  - mRNA
    - degradation, *see* degradation

- production, 50
- translation, 51
- multistable, 125
- mutations, 7
- negative autoregulation, *see* autoregulation
- negative chemotaxis, 10, 191
- negative inducer, 58, 65, 171, 179
- networking, 4
- neutral stability, 91, 93
- neutrophil, 110
- noise
  - extrinsic, *see* extrinsic noise
  - intrinsic, *see* intrinsic noise
- noise filtering, *see* filter
- noise intensity, 160
- non-absolute activator, 71, 88
- nonlinear systems, 21, 97, 124
  - linear approximation, 97
- nucleotides, 45
- nullcline analysis, 93–94
  - of the activator-repressor clock, 185
  - of the toggle switch, 177
- nut region, 61
- Nyquist plot, 101
- observability, 21
- one-step reaction model
  - in enzymatic reactions, 231
  - in gene expression, 257
  - in phosphorylation, 77, 88, 196, 241
- open complex, 45, 50, 62, 146
- open loop, 12
- operator, 61, 236
- operator region, 55
- operator sites, 191, 241
- operon, 56
  - lac, 25, 56
- orbit, 117
  - heteroclinic, *see* heteroclinic orbit
  - homoclinic, *see* homoclinic orbit
  - periodic, 117, 125, 181, 186, 189
- order, of a system, 21
- ordinary differential equation (ODE), 35
- Ornstein-Uhlenbeck process, 159, 162
- oscillations, *see* limit cycle
- oscillator
  - activator-repressor clock, 189
  - harmonic, *see* harmonic oscillator
  - in glycolysis, 127
  - loaded, 210
  - loop, 183
  - natural, 114
  - repressilator, 170
  - with two genes, 136
- p53, 59
- parametric stability, *see* bifurcation
- parametric uncertainty, 103–107
- partition function, 31, 141, 144
- pathway
  - chemotaxis, 199
  - metabolic, 9
  - signal transduction, 81
  - signaling, 9
  - weakly activated, 226
- PCR amplification, 23
- periodic orbit, *see* orbit
- perturbation
  - attenuation, *see* attenuation
  - sensitivity to, *see* sensitivity
  - singular, *see* singular perturbation
- phage  $\lambda$ , 61
- phase lag, 99, 100, 213
- phase portrait, 91, 118, 124
- phenotype, 4
- phosphatase, 74, 75, 99, 226, 241, 257
- phosphate donor, 79, 233
- phosphate group, 9, 38, 74, 75, 79
- phosphorylation, 74, 88, 98, 133, 134, 241, 257
  - double, 81
  - in chemotaxis, 194
  - in insulation devices, 225, 229
  - in MAPKKK cascade, 81
  - reactions, 38
  - system model, 76
- phosphotransfer
  - in chemotaxis, 198
  - in insulation devices, 233
  - model, 79–81, 88
- PI control, 13
- pitchfork bifurcation, 125, *see* bifurcation
- planar dynamical systems, 92
- plasmid, 23, 170, 189, 212, 247
- Poincaré-Bendixson theorem, 122, 185

- Poisson distribution, 150  
poles, 101  
PoPS, 206  
portrait, *see* phase portrait  
positive autoregulation, 66, 114  
positive chemotaxis, 10, 191  
positive feedback, 18, *see also* positive autoregulation  
positive inducer, 58, 65, 171  
post-transcriptional regulation, 70–81  
power spectral density function, 163  
pre-mRNA, 48  
probability density function, 152  
probability of a microstate, 31, 140, 154  
probability of a reaction, 35  
process control, 4  
product of enzymatic reaction, 71  
production of proteins, *see* central dogma  
promoter, 46  
propensity function, 32, 145  
protease, 37  
    in insulation devices, 222  
pyruvate, 119
- quasi-steady state, 63, 65, 72, 81, 85, 129, 171, 174, 185, 190, 195, 212, 227, 246  
quasi-steady state approximation, 43, 132  
queuing, 52, 249
- random, *see* Gaussian random variable  
rate, *see* reaction rate  
reachability, 21  
reaction  
    bimolecular, 33, 35, 146, 166  
    unimolecular, 33, 145, 154  
reaction kinetics, 30  
reaction models  
    enzymatic reaction, *see* two-step reaction model  
    gene expression, 50–52  
    transcriptional regulation, 61–70  
reaction rate, 37  
reaction rate equations, 34–39  
receptor, 193  
recombinant DNA, 22  
recruitment model, 62  
reduction of models, 127–133, 174  
    in clocks, 188  
    in phosphorylation, 136  
    in retroactivity analysis, 211, 224, 241  
    in the design of insulation devices, 228  
regulation  
    in post-transcriptional regulation, *see* post-transcriptional regulation  
    in transcriptional regulation, *see* transcriptional regulation  
rejection, *see* disturbance rejection  
repellent, 191  
reporter genes, 170  
repressilator, 24, *see* clock  
repression, 55–57, 86, 87, 114, 136, 141, 143, 146, 170, *see* LacI (Lac repressor)  
    in activator-repressor clock, 184, 237, 241  
    in combinatorial promoters, 143  
    in repressilator, 180  
    leaky, 87  
    model, 62  
resource, 243  
restriction enzymes, 22  
retroactivity, 206–209  
    in gene circuits, 209–214  
    in signaling systems, 214–219  
retroactivity attenuation, 219–235, 243, 257  
rhythm, *see* circadian rhythm  
ribosome, 46  
ribosome binding site, 46–54, 67, 170, 175, 191  
ribosome binding site (RBS), 46  
RNA polymerase, 30, 45, 55, 141, 148  
    and repressor, 146  
    competition for, 243–253  
    in transcription reactions, 50  
    in transcriptional regulation, 61–65  
RNase, 52  
robustness, 13–14, 103–113, 134, 235
- saddle (equilibrium point), 92, 118, 122, 186  
saddle node bifurcation, 125  
scale invariance, 112–113  
screening, 23  
self-repression, 105  
sensing system, 8  
    in chemotaxis, 191, 193  
sensitivity



- in covalent modification, 77–79
  - in covalent modification cycles, 214
  - in the MAPKKK cascade, 84
  - in the repressilator, 183
  - in transcriptional regulation, 102
  - to perturbations, 103–107, 134
- sensor matrix, 22
- separation
  - of time scales, 187, 211, 229
- separatrix, 93
- serine, 74
- Shine-Dalgarno, 46
- sigma factors, 57
- sigmoidal stimulus response, 84
- signaling
  - intracellular, 81
- signaling cascades, 86
- signaling molecule, 5, 74, 171
- signaling system, 8
  - retroactivity in, *see* retroactivity
- simulation of stochastic systems, 154–157
- single-cell microscopy, 2
- singular perturbation, 127–133
- sink (equilibrium point), 92
- slow manifold, 128, 133, 137, 211, 217, 228, 241
- sniffer, 110, 135, 190
- source (equilibrium point), 92
- specific binding, 248
- spectral shift, 177
- stability, 15, 90
  - asymptotic stability, 91, 97
  - in the sense of Lyapunov, 91
  - local versus global, 92
  - neutrally stable, 91, 93
  - of a system, 95
  - of equilibrium points, 90–98
  - of linear systems, 94–97
  - of solutions, 91
  - unstable solutions, 92
  - using linear approximation, 97
- start codon, 46, 48
- state, of a dynamical system, 20, 21
- state space, 18, 21, 35
- state vector, 21
- statistical mechanics, 30–32, 139–144
- steady state characteristic, *see* characteristic curve
- steady state response, 99, 162
- step input, 19
- step response, 19, 20
  - in transcriptional components, 211
  - of a covalent modification cycle, 218
- stochastic linear systems, 157–164
- stochastic simulation algorithm, 157
- stochastic systems models, *see* modeling
- stoichiometry matrix, 37, 145, 229
- stop codon, 46, 48, 51
- subcritical Hopf bifurcation, *see* bifurcation
- substrate, 38, 43, 70, 85, 130
- supercritical Hopf bifurcation, *see* bifurcation
- superposition, 19
- switch-like response, 77
- switching behavior, 18
- synthesis of proteins, *see* central dogma
- synthetic biology, 22–28, 170–171
- system state, 141
- systems biology, 1–8
- termination of transcription, 45, 50
  - termination region, 46
  - terminator, 46
  - tetracycline, 24
  - thermodynamics, 30, 139
  - threonine, 74
  - time-invariant systems, 21
  - toggle switch, *see* circuits
  - tradeoffs in design, 232, 243–257
  - transcription, 44–55
  - transcription factor, 55
  - transcriptional regulation, 55–70, 105, 136
  - transcritical bifurcation, 125, *see* bifurcation
  - transfection, 23, 170
  - transfer function, 100
  - transformation, 23, 170
  - translation, 44–55
  - tRNA, 48
  - tryptophan, 109
  - tumor suppressor, 59
  - two-step reaction model, 75
  - tyrosine, 74
- ubiquitination, 75
- ultrasensitive response, 78
  - effects of retroactivity, 214

- uncertainty, 13–14, 21, *see* parametric uncertainty
  - disturbances and noise, 21
- unidirectional transmission, 85
- unmodeled dynamics, 6, 107
- unstable solution, for a dynamical system, 92, 97
- uracil, 46
- uridylylation, 214
  
- viral DNA, 59
- virus, 7
  
- waterbed effect, 177
- white noise, 160, 163
- Wright, W., 15
  
- yeast, 7, 28
  
- zero frequency gain, 100
- zero-order kinetics, 44
- zero-order ultrasensitivity, 78, 84
- zeros, 101
- zinc finger, 59

