
Biomolecular Feedback Systems

Domitilla Del Vecchio
MIT

Richard M. Murray
Caltech

Classroom Copy v0.6c, July 11, 2012
© 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.

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, fifth edition edition, 2008.
- [3] U. Alon. *An introduction to systems biology. Design principles of biological circuits*. Chapman-Hall, 2007.
- [4] W. Arber and S. Linn. DNA modification and restriction. *Annual Review of Biochemistry*, 38:467–500, 1969.
- [5] 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.
- [6] 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.
- [7] 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.
- [8] N Barkai and S Leibler. Robustness in simple biochemical networks. *Nature*, 387(6636):913–7, 1997.
- [9] S Basu, R Mehreja, S. Thiberge, M-T Chen, and R. Weiss. Spatiotemporal control of gene expression with pulse-generating networks. *PNAS*, 101(17):6355–6360, 2004.
- [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] BioNumbers: The database of useful biological numbers. <http://bionumbers.org>, 2012.
- [13] 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.

- [14] 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 Neidhart F. C. et al.), ASM Press, Washington DC, 183:1553–1569, 1996.
- [15] H Bremer, P Dennis, and M Ehrenberg. Free rna polymerase and modeling global transcription in *escherichia coli*. *Biochimie*, 85:597–609, 2003.
- [16] B. Canton, A. Labno, and D. Endy. Refinement and standardization of synthetic biological parts and devices. *Nature Biotechnology*, 26(7):787–93, 2008.
- [17] 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.
- [18] A. J. Courey. *Mechanisms in Transcriptional Regulation*. Wiley-Blackwell, 2008.
- [19] R. S. III Cox, M. G. Surette, and M. B. Elowitz. Programming gene expression with combinatorial promoters. *Mol Syst Biol*, page 3:145, 2007.
- [20] D. Del Vecchio. Design and analysis of an activator-repressor clock in *e. coli*. In *Proc. American Control Conference*, 2007.
- [21] D. Del Vecchio and H. El-Samad. Repressilators and promotilators: Loop dynamics in gene regulatory networks. In *Proc. American Control Conference*, 2005.
- [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. Desborough and R. Miller. Increasing customer value of industrial control performance monitoring—Honeywell’s experience. In *Sixth International Conference on Chemical Process Control*. AIChE Symposium Series Number 326 (Vol. 98), 2002.
- [24] 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.
- [25] 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.
- [26] S. P. Ellner and J. Guckenheimer. *Dynamic Models in Biology*. Princeton University Press, Princeton, NJ, 2005.
- [27] M. B. Elowitz and S. Leibler. A synthetic oscillatory network of transcriptional regulators. *Nature*, 403(6767):335–338, 2000.
- [28] Michael B Elowitz, Arnold J Levine, Eric D Siggia, and Peter S Swain. Stochastic gene expression in a single cell. *Science (New York, NY)*, 297(5584):1183–1186, 2002.
- [29] D. Endy. Foundations for engineering biology. *Nature*, 438:449–452, 2005.
- [30] B. Friedland. *Control System Design: An Introduction to State Space Methods*. Dover, New York, 2004.
- [31] T.S. Gardner, C.R. Cantor, and J.J. Collins. Construction of the genetic toggle switch in *Escherichia Coli*. *Nature*, page 339342, 2000.

- [32] Daniel G. Gibson, John I. Glass, Carole Lartigue, Vladimir N. Noskov, Ray-Yuan Chuang, Mikkel A. Algire, Gwynedd A. Benders, Michael G. Montague, Li Ma, Monzia M. Moodie, Chuck Merryman, Sanjay Vashee, Radha Krishnakumar, Nacyra Assad-Garcia, Cynthia Andrews-Pfannkoch, Evgeniya A. Denisova, Lei Young, Zhi-Qing Qi, Thomas H. Segall-Shapiro, Christopher H. Calvey, Prashanth P. Parmar, Clyde A. Hutchison, Hamilton O. Smith, and J. Craig Venter. Creation of a Bacterial Cell Controlled by a Chemically Synthesized Genome. *Science*, 329(5987):52–56, 2010.
- [33] D. T. Gillespie. *Markov Processes: An Introduction For Physical Scientists*. Academic Press, 1976.
- [34] D. T. Gillespie. Exact stochastic simulation of coupled chemical reactions. *Journal of Physical Chemistry*, 81(25):2340–2361, 1977.
- [35] D. T. Gillespie. A rigorous derivation of the chemical master equation. *Physica A*, 188:404–425, 1992.
- [36] 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.
- [37] A. Goldbeter and D. E. Koshland. An amplified sensitivity arising from covalent modification in biological systems. *PNAS*, pages 6840–6844, 1981.
- [38] J. Greenblatt, J. R. Nodwell, and S. W. Mason. Transcriptional antitermination. *Nature*, 364(6436):401–406, 1993.
- [39] J. Greenblatt, J. R. Nodwell, and S. W. Mason. Transcriptional antitermination. *Nature*, 364(6436):401–406, 1993.
- [40] I.L. Grigiriva, N.J. Phleger, V.K. Mutalik, and C.A. Gross. Insights into transcriptional regulation and σ competition from an equilibrium model of RNA polymerase binding to DNA. *PNAS*, 103(14):5332–5337, 2006.
- [41] J. Guckenheimer and P. Holmes. *Nonlinear Oscillations, Dynamical Systems, and Bifurcations of Vector Fields*. Springer, 1983.
- [42] R. Heinrich, B. G. Neel, and T. A. Rapoport. Mathematical models of protein kinase signal transduction. *Molecular Cell*, 9:957–970, 2002.
- [43] B. Hess, A. Boiteux, and J. Kruger. Cooperation of glycolytic enzymes. *Adv. Enzyme Regul*, 7:149–167, 1969.
- [44] Andreas Hilfinger and Johan Paulsson. Separating intrinsic from extrinsic fluctuations in dynamic biological systems. *Proceedings of the National Academy of Sciences*, 108(29):12167–12172, 2011.
- [45] C. F. Huang and J. E. Ferrell. Ultrasensitivity in the mitogen-activated protein kinase cascade. *Proc. Natl. Acad. Sci.*, 93(19):10078–10083, 1996.
- [46] T. P. Hughes. *Elmer Sperry: Inventor and Engineer*. John Hopkins University Press, Baltimore, MD, 1993.

- [47] B. Ingalls. A frequency domain approach to sensitivity analysis of biochemical networks. *Journal of Physical Chemistry B-Condensed Phase*, 108(3):143–152, 2004.
- [48] A Ishihama. Functional modulation of *e. coli* rna polymerase. *Ann. Rev. Microbiol.*, 54:499–518, 2000.
- [49] F. Jacob and J. Monod. Genetic regulatory mechanisms in the synthesis of proteins. *J. Mol. Biol.*, 3:318–56, 1961.
- [50] K. F. Jensen and S. Pedersen. Metabolic growth rate control in *Escherichia coli* may be a consequence of subsaturation of the macromolecular biosynthetic apparatus with substrates and catalytic components. *MICROBIOLOGICAL REVIEWS*, 54(2):89–100, 1990.
- [51] 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.
- [52] N. G. Van Kampen. *Stochastic Processes in Physics and Chemistry*. Elsevier, 1992.
- [53] A. S. Khalil and J. J. Collins. Synthetic biology: applications come of age. *Nature Reviews Genetics*, 11(5):367, 2010.
- [54] H. K. Khalil. *Nonlinear Systems*. Macmillan, 1992.
- [55] E. Klipp, W. Liebermeister, C. Wierling, A. Kowald, H. Lehrach, and R. Herwig. *Systems Biology: A Textbook*. Wiley-VCH, 2009.
- [56] P. Kundur. *Power System Stability and Control*. McGraw-Hill, New York, 1993.
- [57] M. T. Laub, L. Shapiro, and H. H. McAdams. Systems biology of *caulobacter*. *Annual Review of Genetics*, 51:429–441, 2007.
- [58] 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.
- [59] 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. *PNAS*, pages 1–6, 2012.
- [60] W. Lohmiller and J. J. E. Slotine. On contraction analysis for non-linear systems. *Automatica*, 34:683–696, 1998.
- [61] H. Madhani. *From α to α : Yeast as a Model for Cellular Differentiation*. CSHL Press, 2007.
- [62] J. Mallet-Paret and H.L. Smith. The Poincaré-Bendixson theorem for monotone cyclic feedback systems. *J. of Dynamics and Differential Equations.*, 2:367–421, 1990.
- [63] J. E. Marsden and M. J. Hoffman. *Elementary Classical Analysis*. Freeman, 2000.
- [64] 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-cl3 rat thyroid cell line. *Cell. Signal*, 14:61–67, 2002.

- [65] C. R. McClung. Plant circadian rhythms. *Plant Cell*, 18:792–803, 2006.
- [66] M. W. McFarland, editor. *The Papers of Wilbur and Orville Wright*. McGraw-Hill, New York, 1953.
- [67] P. Miller and X. J. Wang. Inhibitory control by an integral feedback signal in prefrontal cortex: A model of discrimination between sequential stimuli. *PNAS*, 103:201–206, 2006.
- [68] 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):1059–74, 1999.
- [69] J. D. Murray. *Mathematical Biology*, Vols. I and II. Springer-Verlag, New York, 3rd edition, 2004.
- [70] R. M. Murray. *Optimization-Based Control*. <http://www.cds.caltech.edu/~murray/amwiki/OBC>, Retrieved 20 December 2009.
- [71] C. J. Myers. *Engineering Genetic Circuits*. Chapman and Hall/CRC Press, 2009.
- [72] 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.*, 282:40454056, 2007.
- [73] National Center for Biotechnology Information. A science primer. Retrieved 20 December 2009, 2004. <http://www.ncbi.nlm.nih.gov/About/primer/genetics.html>.
- [74] National Human Genome Research Institute. Talking glossary of genetic terms. Retrieved 20 December 2009. <http://www.genome.gov/glossary>.
- [75] R. Neshler and E. Cerasi. Modeling phasic insulin release: Immediate and time-dependent effects of glucose. *Diabetes*, 51:53–59, 2002.
- [76] R. Phillips, J. Kondev, and J. Theriot. *Physical Biology of the Cell*. Garland Science, 2008.
- [77] M. Ptashne. *A genetic switch*. Blackwell Science, Inc., 1992.
- [78] 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.
- [79] E. K. Pye. Periodicities in intermediary metabolism. *Biochronometry, National Acad. Sci.*, 1971.
- [80] 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.
- [81] 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.

- [82] J. M. Rohwer, N. D. Meadow, S. Roseman, H. V. Westerhoff, and P. W. Postma. Understanding glucose transport by the bacterial phosphoenolpyruvate: glucose phosphotransferase system on the basis of kinetic measurements in vitro. *The Journal of biological chemistry*, 275(45):34909–34921, November 2000.
- [83] H. M. Sauro and B. Ingalls. MAPK cascades as feedback amplifiers. Technical report, <http://arxiv.org/abs/0710.5195>, Oct 2007.
- [84] H. M. Sauro and B. N. Kholodenko. Quantitative analysis of signaling networks. *Progress in Biophysics & Molecular Biology*, 86:5–43, 2004.
- [85] D. E. Seborg, T. F. Edgar, and D. A. Mellichamp. *Process Dynamics and Control*. Wiley, Hoboken, NJ, 2nd edition, 2004.
- [86] N. Shepherd, P. Dennis, and H. Bremer. Cytoplasmic RNA polymerase in *escherichia coli*. *J. Bacteriol*, 183:2527–2534, 2001.
- [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] J. Stricker, S. Cookson, M. R. Bennett, W. H. Mather, L. S. Tsimring, and J. Hasty. A fast, robust and tunable synthetic gene oscillator. *Nature*, 456(7221):516–519, 2008.
- [91] J. Stülke and W. Hillen. Coupling physiology and gene regulation in bacteria: the phosphotransferase sugar uptake system delivers the signals. *Die Naturwissenschaften*, 85(12):583–592, December 1998.
- [92] Peter S Swain, Michael B Elowitz, and Eric D Siggia. Intrinsic and extrinsic contributions to stochasticity in gene expression. *Proceedings of the National Academy of Sciences of the United States of America*, 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. Natl. Acad. Sci. USA*, 107(22):10032–10037, 2010.
- [96] O. Venturelli, H. El-Samad, and R. M. Murray. Dual positive feedback loops compensate for generating robust bistability in the gal regulatory network. In preparation, 2012.

- [97] O. Venturelli, H El-Samad, and R. M. Murray. Synergistic dual positive feedback loops generate robust bimodal response. Submitted, 2012.
- [98] 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. Natl. Acad. Sci. U.S.A.*, 75(8):372731, 1978.
- [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.
- [104] N. Yildirim, M. Santillan, D. Horike, and M. C. Mackey. Dynamics and bistability in a reduced model of the lac operon. *Chaos*, 14(2):279–292, 2004.

Index

- Ω expansion, 164
- A site, 296
- absorption, 291
- acceptor site, 296
- acetyl CoA, 283
- acetylation, 21
- activated genes, 292
- activation, 14
- activator, 14
- activators, 316
- actuators, 32
- adaptive/inducible repair, 300
- adenine, 303
- adenosine triphosphate (ATP), 282, 305
- aerobically, 306
- aerospace systems, 25
- agarose, 324
- alleles, 288
- alternative splicing, 316
- aminoacyl tRNA synthetase, 296
- amplification, *see also* polymerase chain reaction
 - action
- amplification, of DNA, 322, 323
- amplified, 321
- anaerobic metabolism, 282
- anaerobically, 306
- anaphase, 287
- Anaphase I, 288
- Anaphase II, 288
- annealed, 326
- anti-codon, 296
- anti-codon site, 296
- antibodies, 308
- anticipation, in controllers, 29
- antisense strand, 295
- antitermination, 18
- archaea, 276
- asexual reproduction, 285
- assembly, of a virus, 291
- asymptotic stability, 93, 94, 98, 99
- ATP, 282
- attachment, 291
- attractor (equilibrium point), 94
- automotive control systems, 26
- autopilot, 25, 26
- bacteria, 289
- bacterial artificial chromosomes (BACs), 323
- bacterial plasmids, 323
- bacteriophages, 290
- bacteriophages, 289, 323
- base excision repair, 300
- base pairs, 304
- Bell Labs, 24
- bifurcation, 133
- bifurcation diagram, 133
- bifurcations, 132–134
- bimodality, 7
- binary fission, 285, 289
- binomial distribution, 330
- biological circuits, 4
 - repressilator, 37–38, 64–65
- birth-death, 343
- bistability, 6, 38, 39
- bistable, 133
- Black, H. S., 24, 26
- blastocyst, 292
- block diagonal systems, 98
- blotting, 325
- blunt ends, 322
- Bode plot, 102
- capsid, *see* viral capsid 290, 291
- carbon dioxide, 282
- CDKs, *see* cyclin dependent kinases 122
- cell
 - organization, 276–277
- cell duplication, 285
- cell envelope, 277
- cell genome, 277
- cell mass, 292
- cell membrane, 278

- cell types, 285, 292
- cell wall, 277
- center (equilibrium point), 94
- Central Dogma, 308
- centromeres, 288, 314
- chain termination method, 326
- chaperones, 291
- characteristic polynomial, 97
- charger protein, 296
- chemical degradation method, 326
- chemical kinetics, 46–47
- chemical Langevin equation, 162
- chemotaxis, 187
- chloroplast, 304
- chloroplasts, 283
- cholesterol receptor protein, 320
- chromatid arms, 288
- chromosome, 279, 286, 287
- chromosomes, 287, 288
- cis-acting, 317, 318
- citric acid cycle, 282
- cleaved, 296
- cloning, 321, 322
- cloning vector, 322
- closed complex, 9
- closed loop, 22
 - versus open loop, 22
- secoenzyme A, 283
- coding strand, 295
- codon, 296
- codons, 309
- coenzyme A, 283
- cohesive ends, 322
- combinatorial promoters, 17
- complementary, 304
- complexity, of control systems, 26
- conjunction, 289
- contracting, 115
- control
 - early examples, 23, 26
 - control matrix, 34
 - control signal, 32
 - cooperative, 53
 - coordinate transformations, 98
 - core gene sequence, 310
 - cosmids, 323
 - cristae, 281
 - crossovers, 288
 - cruise control, 23
 - robustness, 23
 - Curtiss seaplane, 26
 - cycle sequencing, 328
 - cyclin dependent kinases, 122
 - cyclins, 122
 - cytokinesis, 288
 - cytoplasm, 279
 - cytoplasmic region, 277
 - cytoplasmic streaming, 279
 - cytosine, 303
 - cytoskeleton, 278, 279
 - cytosol, 279
 - daughter nuclei, 285
 - dead zone, 28
 - deamination, 300
 - deleterious mutation, 298
 - denatured, 325
 - deoxynucleotides, 327
 - deoxyribonucleic acid, 320
 - deoxyribonucleic acid (DNA), 279, 303
 - derivative action, 29, 30
 - derived cells, 292
 - design of dynamics, 24–26, 99
 - diagonal systems, 97
 - transforming to, 98
 - dideoxynucleotide, 327
 - differentiation, 292, 318
 - diffusion term, 163
 - diploid, 287, 288, 292
 - direct term, 34
 - dissociation constant, 52
 - disturbance attenuation
 - in biological systems, 104
 - disturbances, 33
 - DNA, 303
 - DNA ligase, 294, 299
 - DNA looping, 15
 - DNA nucleotides, 323
 - DNA polymerase, 294, 299, 327
 - DNA repair systems, 299
 - DNA replication, 292, 293
 - DNA template, 327
 - drift term, 163
 - dyes, 324
 - dynamical systems, 21
 - linear, 97

- dynamics matrix, 34
- early proteins, 291
- economic systems, 27
- egg, 292
- egg cell, 288
- eigenvalues, 97, 134
 - invariance under coordinate transformation, 98
- eigenvectors, 98
- electrical circuits, 4
- electrodes, 324
- elongation, 297
- Elowitz, M. B., 64
- endocytosis, 278, 290
- endoplasmic reticulum, 281
- endoplasmic reticulum (ER), 283
- energy production, in a cell, 281–283
- enhancers, 317
- enthalpy, 153
- enzymes, 308
- equilibrium points, 92, 97
 - bifurcations of, 132
 - for planar systems, 94
 - region of attraction, 94
- ethidium bromide, 325
- eukaryotes, 276–277, 311
- events, 329
- exocytosis, 291
- exons, 309
- expectation, 335
- exported proteins, 283
- familial hypercholesterolemia, 320
- feedback
 - as technology enabler, 25
 - drawbacks of, 22, 26
 - properties, 27
 - robustness through, 23
 - versus feedforward, 27
- feedback mechanisms, 316
- feedforward, 27
- female life cycles, 288
- filters
 - for measurement signals, 26
- flagella, 277
- flavin-adenine dinucleotide (FAD), 283
- flight control, 25
- fluorescent reporters, 37
- flush ends, 322
- Fokker-Planck equations, 163
- forward Kolmogorov equation, 157
- fragmentation, 37
- free energy, 153
- frequency response, 31, 102
- gametes, 285, 286, 292
- Gaussian distribution, 332
- gel, 324
- gels, 324
- gene, 9
- gene prediction, 310
- gene regulation, 316–318
- gene regulatory sequences, 315
- genes, 279, 303, 320
- genetic marker, 314
- genetic material, 279
- genetic recombination, 288
- genetic switch, 39
- genomes, 303
- genomic imprinting, 318
- germ cells, 292
- germ line cells, 292
- Gibbs free energy, 153
- global behavior, 94
- glucose, 282, 283
- glucose transporters, 282
- glycolysis, 282
- glycoproteins, 291
- Golgi apparatus, 283
- gradient, 325
- granular chromatin, 288
- guanine, 303
- haploid, 287, 288
- heat shock, 16
- helicase, 294
- hemoglobin, 317
- hereditary traits, 320
- Hill functions, 53
- homologous recombination, 300
- Hopf bifurcation theorem, 135
- human development, 292
- human genome, 315
- hysteresis, 28
- implicit function theorem, 137

- inactivated genes, 292
- independent assortment, 289
- inducer, 16
- inducible error-prone repair, 300
- initiator sequence, 311
- inner membrane, of mitochondria, 281
- input/output models, 30, 32
- input/output models relationship to state space models, 32
- inputs, 32
- integral action, 29, 30
- intercalating agent, 325
- interphase, 286, 287
- introns, 309
- isomerization, 9

- Jacobian matrix, 99
- junk DNA, 312

- kinase, 20, 75
- Kozak sequence, 12
- Kreb's cycle, 282, 283

- lagging strand, 294
- large subunit, 296
- late proteins, 291
- leading strand, 294
- licensing factors, 295
- ligation, 37, 322
- limit cycle, 126
- linear noise approximation, 164
- linear systems, 31, 34, 96
- linear time-invariant systems, 31, 34
- linearization, 99
- linkage, 289
- linkage disequilibrium, 289
- local behavior, 93, 99
- locally asymptotically stable, 93
- locus, 288
- Locus Control Region (LCR), 317
- lysis, 291
- lysosomes, 283
- lysozyme, 291
- lytic proteins, 291

- male structures, 288
- Markov chain, 343
- Markov property, 343

- maturation time, 12
- mature mRNA, 12, 310
- mean, 332, 335
- measured signals, 32, 33
- mechanics, 32
- meiosis, 286–288
- Meiosis I, 287, 288
- Meiosis II, 288
- memory, 6
- messenger RNA (mRNA), 307
- Metaphase, 288
- metaphase, 286
- Metaphase II, 288
- metaphase plate, 288
- methionine, 296
- methyl group (-CH₃), 318
- methylation, 21, 318
- Michaelis-Menten constant, 56
- Michaelis-Menten kinetics, 56
- mismatch repair, 300
- mitochondria, 281–283
- mitochondrial DNA (mtDNA), 306
- mitochondrial genome, 279
- Mitochondrial Theory of Aging, 307
- mitochondrion, 304
- mitosis, 285–287
- modeling simplified models, use of, 33
- modularity, 222
- molecular and cellular biology, 291
- molecular dynamics, 44
- molecular genetics, 320
- molecular weights, 324
- multipotent, 293
- multistable, 133
- mutagenesis, 301
- mutations, 288, 298, 320

- NAD⁺, 282
- NADH, 283
- nascent RNA, 296, 311
- negative chemotaxis, 187
- negative inducer, 16
- networking, 4
- neutral stability, 93, 94
- nitrocellulose, 325
- noise intensity, 343
- nonlinear systems, 32, 99
 - linear approximation, 99

- normal distribution, 332
- northern blotting, 325
- nuclear DNA, 305
- nuclear envelope, 280, 286, 287
- nuclear genome, 279
- nuclear membrane, 288
- nucleic acid, 303
- nucleotide, 303
- Nucleotide excision repair, 299
- nucleus, 280, 303
- Nyquist plot, 103

- obligate intracellular parasites, 290
- observability, 32
- Okazaki fragments, 294
- omega limit set, 128
- omega-limit point, 128
- on-off control, 28
- open complex, 9
- open loop, 22
- open reading frames, 315
- operator, 318
- operator region, 15
- operon, 15
- order, of a system, 33
- organelles, 277, 280
- Origin Recognition Complex, 295
- Ornstein-Uhlenbeck process, 173, 342
- outer membrane, of mitochondria, 281
- oxaloacetate, 283

- P site, 296
- parametric stability diagram, 133, 134
- parent of origin differences, 318
- parental, 289
- partition function, 45, 153
- penetration, of a virus, 291
- peroxisomal targeting signal (PTS), 284
- peroxisomes, 283, 284
- phosphatase, 75
- phosphotransferase, 20
- photoreactivation, 299
- photosynthesis, 283
- PI control, 23, 29
- PID control, 28–29
- pili, 277
- planar dynamical systems, 94
- plasma membrane, 277, 278
- plasmids, 289, 322
- platelets, 293
- pluripotent, 293
- Poisson distribution, 331
- poles, 102
- poly(A) tail, 296
- polymerase chain reaction, 321
- polymerase chain reaction (PCR), 323
- polymerization, 324
- polypeptide chain, 297
- positive chemotaxis, 187
- positive feedback, 27
- positive inducer, 16
- positively charged, 325
- post-replication repair, 299
- post-transcriptional modification, 296, 316
- post-translational modification, 297
- pre-mRNA, 12
- prediction, in controllers, 29
- primer, 327
- primers, 323
- probability mass function, 330
- probability measure, 329
- probability space, 329
- probe, 325
- process control, 4
- prokaryotes, 276–277, 311
- promoter sequence, 295, 316
- promoter site, 311
- propensity function, 156
- prophase, 286
- Prophase I, 287
- Prophase II, 288
- protease, 297
- protein transport, 292
- proteins, 308–309
- pseudogene, 314
- purines, 303
- pyrimidines, 303
- pyruvate, 282, 283
- pyruvic acid, 282

- quasi-steady state assumption, 56

- random process, 336
- random variable, 329
- reachability, 32
- recombinant DNA molecule, 322

- recombinant plasmid, 322
- recombination, 288–289, 310
- recombination repair, 299
- red blood cells, 292, 293
- reduced stoichiometry matrix, 117
- reduction division, 287
- reference signal, 28
- regulatory sequences, 313
- release, of a virus, 291
- repetitive DNA, 313
- replication, 285, 293, 322
- replication control mechanisms, 294
- replication origin sites, 294
- replication, of a virus, 291
- reporter genes, 201
- repressilator, 37–38, 64–65
- repression, 14
- repressor, 38, 107
- repressor proteins, 318
- repressors, 316
- restriction enzyme, 322
- restriction enzymes, 36
- retroviruses, 290
- reverse transcriptase, 290
- ribonucleic acid (RNA), 279, 307
- ribosomal complex, 309
- ribosome, 296, 307, 309
 - large and small subunits, 281
- ribosome binding site (RBS), 12
- ribosomes, 280
- RNA polymerase, 295, 296, 311, 316
- RNA polymerase II, 311
- RNA processing, 292
- RNA replicase, 290
- robustness, 23–24
- root locus diagram, 134, 135
- rough ER, 283
- running buffer, 324

- saddle (equilibrium point), 94
- sample space, 329
- satellite DNA, 314
- scale invariance, 113
- screening, 37
- self-repression, 106
- sense strand, 295
- sensor matrix, 34
- sequencing, 326

- sexual reproduction, 286
- Shine-Delgarno, 12
- Shine-Delgarno sequence, 312
- sigma factors, 16
- sink (equilibrium point), 94
- sister chromatids, 286
- slow manifold, 137
- small subunit, 296
- smooth ER, 283
- somatic cells, 292
- SOS repair, 300
- source (equilibrium point), 94
- Southern blotting, 325
- sperm, 292
- sperm cells, 288
- spindle, 286, 288
- splice junctions, 315
- spontaneous mutations, 288
- stability, 24, 92
 - asymptotic stability, 93, 99
 - in the sense of Lyapunov, 93
 - local versus global, 93
 - neutrally stable, 93, 94
 - of a system, 97
 - of equilibrium points, 94
 - of linear systems, 96–99
 - of solutions, 93
 - unstable solutions, 93
 - using linear approximation, 99
- standard deviation, 332
- start codon, 12, 296, 315
- state, of a dynamical system, 32, 33
- state space, 33
- state vector, 33
- stationary, 343
- statistical mechanics, 44–46
- steam engines, 23
- stem cells, 292
- step input, 31
- step response, 31, 32
- sticky ends, 322
- stop codon, 12, 297
- structural components, 308
- structural genes, 313
- superposition, 31
- switching (transcriptional regulation), 317
- switching behavior, 27
- symbiotic, 306

- Taq polymerase, 323
- TATA box, 311
- telomeres, 314
- telophase, 287
- Telophase I, 288
- Telophase II, 288
- template DNA, 323, 326
- template strand, 295, 304
- termination region, 11, 296
- terminator, 11
- thalassemias, 317
- thymine, 303
- time-invariant systems, 33
- trans-acting, 317
- transcription, 9, 280, 292, 295, 308, 310, 311, 316–318
- transcription factors, 316
- transcriptional regulation, 14
- transduction, 289
- transfection, 37
- transfer function, 102
- transfer RNA (tRNA), 296
- transformation, 289, 322
- translation, 12, 281, 296, 311, 318
- translational regulation, 318
- transport molecules, 308

- ubiquitination, 21
- uncertainty, 23–24, 33
 - disturbances and noise, 33
- uniform distribution, 332
- unstable solution, for a dynamical system, 93, 94, 99

- vector, 322
- viral capsid, 290
- virion, 290
- virions, 290
- viruses, 284, 289, 291
 - reproduction, 290–291

- Watt steam engine, 23
- wells, 324
- white blood cells, 293
- wild-type, 299
- Wright, W., 25

- X-inactivation, 314

- yeast artificial chromosomes (YACs), 323

- zero frequency gain, 102
- zero-order kinetics, 57
- zeros, 102