MODELS OF CELLULAR REGULATION: *Growth, Proliferation & Survival*

Baltazar Aguda & Avner Friedman

PREFACE (draft)

This textbook originates from many years of combined research and teaching by the authors at the interfaces of mathematics, chemistry and biology. Several chapters grew out of two of Professor Aguda's university courses, one on 'self-organization in far-from-equilibrium chemical reaction systems' and the other on 'mechanisms and models of cellular regulation' (taught at Canadian and US universities); the latter was intended for graduate students of bioinformatics, biomedical engineering, mathematics and physics. Professor Friedman, the current director of the Mathematical Biosciences Institute at Ohio State University (USA), brings into the textbook an extraordinary perspective of an accomplished mathematician and teacher who is now committed to applying the quantitative and physical sciences to the analysis of complex biological systems. This textbook also benefits from numerous interdisciplinary workshops on cellular processes held in the last few years at Professor Friedman's institute.

The general outline and presentation of the chapters in the textbook is governed by the biological story of a cell - how it grows, proliferates, differentiates, and dies. The known molecular mechanisms of these cellular processes are thoroughly discussed in order to demonstrate to the student how to build mathematical models. The current frenzy in high throughput data acquisition technologies in molecular biology is providing the modeler a lot of data to work on, and this textbook will illustrate how various types of models can be extracted from bioinformatic or pathways databases. The common thread linking the chapters in the textbook is the view that the cell is one huge connected regulatory network of physico-chemical interactions. To cope with the complexity of this network, various levels of abstractions or granularities of models are considered. Detailed mathematical analyses are then applied to these abstract models to unravel their properties and their predictive power. In addition, the textbook illustrates the use of various computational methods and software, including dynamic simulation and whole-cell modeling platforms.

The book begins with a general introductory chapter dissecting the paradigm that the cell is the modular unit of life and explaining why we concentrate on models at the cellular level. Part I of the book consists of chapters that lay the foundation of cell modeling – the meaning and granularities of models, essential cell biology and biochemistry, and a survey of the mathematical and computational toolbox for modeling. Part II examines cell growth including chapters on phenomenological models as well as detailed molecular mechanisms in growth-factor signaling, gene expression and metabolism. Part III deals with cell proliferation and the detailed molecular machinery of the cell division cycle in prokaryotes and eukaryotes. Part IV tackles topics related to cell survival including cell death, aging, and repairing damaged genes. The penultimate chapter of the textbook, in Part V, introduces cell systems biology that employs high throughput data (genomic, transcriptomic, proteomic, etc.) from which network models can be inferred. The final chapter deals with models of human diseases related to the cellular processes studied in the book, including cancer.

This textbook will be of interest to graduate students in applied mathematics and physics, and to biologists, undergraduate students and researchers who have some familiarity with differential equations and computer programming. Extensive appendices giving primers on the required mathematics, chemical kinetics, computer software, and bioinformatics are provided to render the textbook self-contained as much as possible. Each chapter will end with a list of further readings from the relevant literature and a set of problems or exercises reinforcing the concepts discussed in the chapter.

MODELS OF CELLULAR REGULATION: *Growth, Proliferation & Survival*

Baltazar Aguda & Avner Friedman

TABLE OF CONTENTS

Part I : Essentials of Cell Modeling

Part II : Cell Growth

Chapter 5. *Phenomenological Models of Cell Growth*
[Approx. # pages: 10]

Unicellular organisms
Growth and development of multicellular organisms

Chapter 6. *Molecular Pathways to Cell Growth* [Approx. # pages: 20]

Gene expression networks
Growth-factor signaling
Metabolic pathways

Part III : Cell Proliferation

Chapter 7. *The Prokaryotic Cell Cycle* [Approx. # pages: 15]

The cell division cycle of bacteria
Mathematical models & their analysis

Chapter 8. *The Eukaryotic Cell Cycle* [Approx. # pages: 20]

Phases of the eukaryotic cell cycle
The cell cycle engine: cylin-dependent kinases
Mathematical models & their analysis

Chapter 9. *Cell Cycle Control* [Approx. # pages: 15]

Cell cycle checkpoint mechanisms
Cell cycle arrest and terminal differentiation
Mathematical models & their analysis

Part IV : Cell Survival

Chapter 10. *Cell Death* [Approx. # pages: 20]

Necrosis
Apoptosis
Survival signaling pathways
Mathematical models & their analysis

Chapter 11. *Cell Maintenance* [Approx. # pages: 15]

DNA damage and repair mechanisms
Cellular senescence and aging
Mathematical models & their analysis

Part V : Systems Biology of the Cell & Applications

Chapter 12. *Integrated Cell Biology* [Approx. # pages: 15]

Genomic, Transcriptomic, and Proteomic Data Sources
From Pathways Databases to Kinetic Models
Whole-cell software modeling platforms

Chapter 13. *Towards Controlling Cell Fates* [Approx. # pages: 20]

Cancer as a network stability problem
Models of other human diseases
Genetic Engineering and Synthetic Biology

Appendices: [Approx. # pages: 30]

A – Summary of essential mathematics
B – Primer on chemical kinetics, including enzyme kinetics
C – Summary of software platforms
D - Summary of bioinformatic databases for cell modeling

References
Index

List of Books Similar or Related to the Proposed Aguda-Friedman Textbook

---

[1] Michael Kraus & Bernhard Wolf, **Structured Biological Modelling: A New Approach to Biophysical Cell Biology,** CRC Press; (July 31, 1995), 219 pages, ISBN: 0849347726

Although there are major similarities in the systems viewpoint pursued in the Aguda-Friedman textbook and the book above, the latter is *old* (published in 1995) and caters to a *very wide audience* of experimentalists and biologists. This book is described as follows: "Presents a synthesis of experimental biological techniques and concepts of systems analysis and modeling, examining the regulation of biological systems, especially cellular signalling networks, from a systems-oriented viewpoint, and showing how data can be converted into a consistent computer model that comprises functional properties of the system." (Book News, Inc). Also, "This book will be useful to cell and molecular biologists, oncologists, physiologists, theoretical biologists, computer scientists, and all other researchers and students studying functional aspects of cellular signaling." (Amazon.com)

[2] C. Fall, E. Marland, J. Wagner, and J. J. Tyson, **Computational Cell Biology**, Springer-Verlag Telos; 1st edition (July 9, 2002), 488 pages, ISBN: 0387953698.

The mathematical and computational methods illustrated in this book are similar to those used in the proposed Aguda-Friedman textbook. However, the book above emphasizes the computational techniques illustrated in a *wide range* of cellular processes instead of developing a coherent biological theme as the Aguda-Friedman book does. The book above "was conceived of and begun by Professor Joel Keizer based on his many years of teaching and research together with his colleagues. The project was expanded and finished by his students and friends after his untimely death in 1999." (Amazon.com)

[3] Lee A. Segel, **Modeling Dynamic Phenomena in Molecular and Cellular Biology,** Cambridge University Press; (March 30, 1984), 304 pages, ISBN: 052127477X

Although this is a well-written textbook, it is old and uses a very wide range of examples under the heading of dynamic biological phenomena.

[4] James M. Bower & Hamid Bolouri (Eds.), **Computational Modeling of Genetic and Biochemical Networks (Computational Molecular Biology)**, Bradford Books; 1st edition (January 22, 2001), 390 pages, **ISBN:** 0262024810

This is really not a textbook but a compendium of topics from active researchers in the field covered by the title of the book. "This book provides specific examples, across a wide range of molecular and cellular systems, of how modeling techniques can be used to explore functionally relevant molecular and cellular relationships. The modeling techniques covered are applicable to cell, developmental, structural, and mathematical biology; genetics; and computational neuroscience." (Amazon.com)

Professor Baltazar D. Aguda
Dept. of Genetics & Genomics
Boston University School of Medicine
715 Albany Street, E632
Boston, Massachusetts
USA 02118
Tel: (617) 414 1654 (office), (617) 864 3122 (home)
Email: bdaguda@bu.edu

Baltazar Aguda is currently associate professor of Genetics & Genomics at the Boston University School of Medicine. He holds joint appointments in Biomedical Engineering, in the Bioinformatics & Systems Biology program at Boston University, and a membership in the Center for Biodynamics in the same university. Recently, he was appointed member of the National Science Foundation's (NSF, USA) research proposal review panel in molecular & cellular biosciences (2004-7). He was a visiting faculty at the Mathematical Biosciences Institute at Ohio State University (2003), at the Weizmann Institute of Science in Israel (2000), and a visiting associate at the California Institute of Technology (2000-2001). Dr. Aguda obtained his PhD in Chemistry (Chemical Physics Program) from the University of Alberta in Canada (1986), and was a tenured faculty member of the Department of Chemistry & Biochemistry at Laurentian University in Canada (1994-2002) before moving to Boston.

Prof. Aguda's PhD and postdoctoral work focused on stoichiometric network analysis, nonlinear dynamics and bifurcation theory of complex enzyme reaction networks. About six years ago, he began applying these mathematical methods to the complex regulatory networks of the mammalian cell cycle and associated signaling pathways. He has taught interdisciplinary courses at both undergraduate and graduate levels, including subjects on 'self-organization in far-from-equilibrium reaction systems' and 'mechanisms and models of cellular regulation.' He was invited in this year's Annual American Physical Society Meeting (2004) in Montreal to provide a tutorial lecture on the mathematical modeling of the cell division cycle. He also gave a series of lectures in a summer school on biological modeling at Humboldt University in Berlin last year (2003).

PUBLICATIONS

BOOK CHAPTERS

B. D. Aguda and H. M. Sauro, "Computer Simulation of MAPK Signal Transduction," pp. 167-175 in Methods in Molecular Biology, vol 250: Protocols in MAPK Signaling (R. Seger, Ed.), Humana Press (2004).

B.D. Aguda, G. Craciun, R. Cetin-Atalay, "Data Sources and Computational Approaches for Generating Models of Gene RegulatoryNetworks," in Reviews in Computational Chemistry, to appear.

B.D. Aguda, "Modeling the Cell Division Cycle," in Lectures in Mathematical Biology (A. Friedman, Ed.), to appear.

REFEREED PAPERS

G. Craciun, B.D. Aguda & A. Friedman, “A detailed mathematical analysis of a model that couples the cell cycle and apoptosis,” submitted (2004).

B.D. Aguda & C.K. Algar, “Structural analysis of the qualitative networks regulating the cell cycle and apoptosis”, Cell Cycle 2: 538-544 (2003).

B.D. Aguda, "Kick-starting the cell cycle: From growth-factor stimulation to initiation of DNA replication", Chaos 11: 269-276 (2001).
B.D. Aguda, "A quantitative analysis of the kinetics of the G2 DNA damage checkpoint system", Proc. Natl. Acad. Sci. USA 96 : 11352-11357 (1999).

B.D. Aguda & Y. Tang, "The kinetic origins of the restriction point in the mammalian cell cycle", Cell Proliferation 32: 321-335 (1999).

B.D. Aguda, "Instabilities in Phosphorylation-Dephosphorylation Cascades and Cell cycle Checkpoints", Oncogene 18 : 2846-2851 (1999).

B.D. Aguda, "Emergent Properties of Coupled Enzyme Reaction Systems. 1. Switching and Clustering Behaviour", Biophysical Chemistry 61 : 1-7 (1996).

M.T.M. Koper and B.D. Aguda, "Experimental Demonstration of Delay and Memory Effects in the Bifurcations of Nickel Electrodissolution", Physical Review E 54 : 960-963 (1996).

S.N. Krylov, B.D. Aguda & M.L. Ljubimova, "Bistability and Reaction Thresholds in the Phenol-inhibited Peroxidase-catalyzed oxidation of Indole-3-acetic Acid", Biophysical Chemistry 53 : 213-218 (1995).

C. Steinmetz, R. Larter & B.D. Aguda, "Modeling a Biochemical Oscillator", Proc. Indiana Acad. Sci., 98 : 157-168 (1994).

B.D. Aguda, "Differential Flow-Induced Chemical Instability in a Model Enzyme Mechanism", Journal of Chemical Physics 99 : 5091-5096 (1993).

J. Logan, J. Treurniet, A.D.O. Bawagan, S. Rizzetto, J.M. Braun & B.D. Aguda, "A Simple Apparatus for the Study of Experimental Fractal Structures in Gaseous Dielectric Breakdown", Canadian Journal of Chemistry 71 : 2079-2083 (1993).

P.Q.E. Clothier, B.D. Aguda, A. Moise & H.O. Pritchard, "How do Diesel-Ignition Improvers Work?", Chemical Society Reviews 22 : 101-108 (1993).

B.D. Aguda & H.O. Pritchard, "Reversible and Irreversible Formulations of Unimolecular Reactions", Journal of Chemical Physics 96 : 5908-5914 (1992).

B.D. Aguda & R. Larter, "Periodic-chaotic Sequences in a Detailed Mechanism of the Peroxidase-Oxidase Reaction", Journal of the American Chemical Society 113 : 7913-7916 (1991).

B.D. Aguda, L-L. Hofmann-Frisch & L.F. Olsen, "Experimental Evidence for the Coexistence of Oscillatory and Steady States in the Peroxidase-Oxidase Reaction", Journal of the American Chemical Society 112 : 6652-6656 (1990).

B.D. Aguda & R. Larter, "Sustained Oscillations and Bistability in a Detailed Mechanism of the Peroxidase-Oxidase Reaction", Journal of the American Chemical Society 112 : 2167-2174 (1990).

B.D. Aguda & R. Larter, "A Bistable and Oscillatory Mechanism for the Peroxidase-Oxidase Reaction", React. Kinet. Catal. Lett. 42 : 339-342 (1990).

B.D. Aguda, R. Larter & B.L. Clarke, "Dynamic Elements of Mixed-Mode Oscillations and Chaos in a Peroxidase-Oxidase Model Network", Journal of Chemical Physics 90 : 4168-4175 (1989).

B.D. Aguda & B.L. Clarke, "Dynamic Elements of Chaos in the Willamowski-Rossler Network", Journal of Chemical Physics 89 : 7428-7434 (1988).

R. Larter, C. Steinmetz & B.D. Aguda, "Fast-Slow Variable Analysis of the Transition to Mixed-Mode Oscillations and Chaos in the Peroxidase Reaction", Journal of Chemical Physics 89 : 6506-6514 (1988).

R. Gordon & B.D. Aguda, “Diatom morphogenesis: natural fractal fabrication of a complex microstructure”. In: Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, Part 1/4: Cardiology and Imaging, New York: Institute of Electrical and Electronics Engineers 10: 273-274 (1988).

R. Larter, C. Bush, T. Lonis & B.D. Aguda, "Multiple Steady States, Complex Oscillations and the Devil's Staircase in the Peroxidase-Oxidase Reaction", Journal of Chemical Physics 87 : 5765-5771 (1987).

B.D. Aguda & B.L. Clarke, "Bistability in Chemical Reaction Networks : Theory and Application to the Peroxidase-Oxidase Reaction", Journal of Chemical Physics 87 : 3461-3470 (1987).

INVITED TALKS

2004	Cambridge University, UK Virginia Bioinformatics Institute, Blacksburg, Virginia Institute for Systems Biology, Seattle, Washington Dept of Mathematics, University of the Philippines at Diliman Bioinformatics Institute, Biopolis, Singapore Molec & Quantitative Genetics Seminar Series, Boston U School of Medicine American Physical Society Annual Meeting, Montreal (invited tutorial lecture)
2003	Mathematical Biosciences Institute, Ohio State University Dept Biology, Theoretical Biophysics, Humboldt University, Berlin, Germany
2002	Chem Dept, York University, Canada IBM T.J. Watson Research Center, Yorktown, New York

GlaxoSmithKline, Pennsylvania, USA
Genetics & Genomics Dept, Boston Univ School of Medicine
Dept of Biology, Univ of Waterloo, Canada
Department of Biomedical Informatics, Ohio State University

2001 Whitaker Biomedical Engineering Institute, Johns Hopkins University
Center for Nonlinear Dynamics in Physiol and Med, McGill University
Univ of Southern California (Program in Molec and Computational Biol)
Chemical Biology Seminar Series, Univ of Illinois at Urbana-Champaign

2000 Keck Graduate Institute, Claremont, California
Cornell University (Computational Cancer Group), Ithaca, New York
Dept. of Biological Regulation, Weizmann Institute of Science, Israel
3rd World Congress of Nonlinear Analysts", Catania, Sicily, Italy
Mario Negri Research Institute, Milan, Italy
Workshop on 'Computation in Cells', University of Hertfordshire, UK
California Institute of Technology (Control & Dynamical Systems Group)
Centre for Nonlinear Dynamics in Physiol & Medicine, McGill University

SERVICE TO ACADEMIC COMMUNITY

Co-chair (with Jessie Au) of the workshop on 'Cell Growth, Proliferation and Death' at the Mathematical Biosciences Institute (MBI), Ohio State University, 29 Sept- 3 Oct 2003, Columbus, OH, USA.

Co-chair (with C.D. Thron) of the session on 'Nonlinear dynamics and the cell cycle' at the 3rd World Congress of Nonlinear Analysts in Catania, Italy, 19-26 July 2000.

Chairman of the session on 'Computational Dynamics in Natural and Artificial Systems' at the Second World Congress of Nonlinear Analysts in Athens, Greece, 10-17 July 1996.

Ad hoc reviewer/referee for numerous scientific journals

COURSES TAUGHT

"Mechanisms & Models of Cellular Regulation". A course developed in spring 2004 for graduate students in Biomedical Engineering and Bioinformatics at Boston University.

"Self-organization in nonequilibrium chemical reaction systems". A course developed for senior undergraduate and graduate students in Chemistry. First taught at the Univ of Waterloo (1993) and then at Laurentian University (1997).

"Modeling the Cell Cycle and Apoptosis", a series of 3 invited lectures presented at the Summer Course on Modeling Biological Systems, Dept Biology, Theoretical Biophysics, Humboldt University, Berlin, Germany, July 10-11, 2003.

Undergraduate courses: Quantum Chemistry, Statistical Thermodynamics, Spectroscopy, Physical Chemistry, General Chemistry, General Physics

Professor Avner Friedman
Director, Mathematical Biosciences Institute
The Ohio State University
231 W. 18th Avenue
Columbus, Ohio 43210
614-292-3648
FAX: 614-247-6643

Avner Friedman is a Distinguished Professor of Mathematics and Physical Sciences at the Ohio State University, where he also serves as the Director of the Mathematical Biosciences Institute. He received his Ph.D. degree in 1956 from the Hebrew University. He was Professor of Mathematics at Northwestern University (1962-1985), and a Duncan Distinguished Professor of Mathematics at Purdue University (1985-1987).

From 1987-1997, Dr. Friedman directed the Institute for Mathematics and its Applications (IMA) at the University of Minnesota, which is devoted to bridging the gap between mathematical theory and its applications and between academia and industry. From 1994-2001 he was the Director of the Minnesota Center for Industrial Mathematics and in1996 he became a Regents Professor at the University of Minnesota. Dr. Friedman's research interests include partial differential equations, stochastic processes, mathematical modeling, free boundary problems, and control theory. He published twenty books and over 350 research papers. He serves on numerous editorial boards. He was the Chair of the Board of Mathematical Sciences (1994-1997) and the President of the Society of Industrial and Applied Mathematics (1993-1994). Dr. Friedman has been awarded the Sloan Fellowship (1962-65), the Guggenheim Fellowship (1966-7), the Stampacchia Prize (1982), and the National Science Foundation Special Creativity Award (1983-85; 1991-93). He is a Fellow of the National Academy of Arts and Sciences (since 1987) and a member of the National Academy of Sciences (since 1993).

SELECTED BOOKS (from **a total of 21)**

Friedman A. (1975-76). *Stochastic Differential Equations and Applications*, two volumes. Academic Press.

Friedman A. (1983). *Variational Principles and Free Boundary Problems*. Wiley & Sons.

Friedman A. (1988-1999). *Mathematics in Industrial Problems,* ten volumes. IMA Publications, Springer-Verlag New York.

Friedman A, Ross D. (2002). *Mathematical Models in Photographic Science. Springer-Verlag.*

SELECTED PUBLICATIONS (selected **recent** publications **from a total of 385 publications**)

Friedman A, Reitich F. Analysis of a mathematical model for the growth of tumors. *Journal of Mathematics and Biology,* 38:262-284, 1999.

Friedman A, Cui S. Analysis of mathematical model of protocell. *Journal of Mathematical Analysis and Applications,* 236:171-206, 1999.

Friedman A, Cui S. Analysis of mathematical model of the effect of inhibitors on the growth of tumors. *Mathematical Biosciences,* 164:103-137, 2000.

Friedman A, Reitich F. Symmetry-breaking bifurcation of analytic solutions to free boundary problems: An application to a model of tumor growth. *Trans AMS,* 353:1587-1634, 2000.

Friedman A, Chen X. A free boundary problem arising in a model of wound healing. *SIAM Journal of Mathematical Analysis,* 32:778-800, 2000.

Friedman A, Cui S. Analysis of mathematical model of the growth of necrotic tumors. *Journal of Mathematical Analysis and its Applications,* submitted for publication, 2001.

Friedman A, Reitich F. On the existence of spatially patterned dormant malignancies in a model for the growth of non-necrotic tumors. *Mathematical Models & Methods in Applied Sciences,* 11:1-25, 2001.

Friedman A, Fontelos MA, Hu B. Mathematical analysis of a model for the initiation of angiogenesis. *SIAM Journal of Mathematical Analysis,* 33:1330-1355, 2002.

Friedman A, Bazaliy. A free boundary problem for an elliptic-parabolic system: Application to a model of tumor growth. *Comm. In PDE,* 28:627-675, 2003.

Friedman A, Cui S. Free boundary problems for a singular system of differential equations: An application to a model of tumor growth. *Trans. AMS,* 355:3537-3590, 2003.

Friedman A, Bazaliy B. Global existence and stability for an elliptic-parabolic free boundary problem: Application to a model with tumor growth. *Indiana University Mathematics Journal,* 52:1265-1304, 2003.

Friedman A, Cui S. A hyperbolic free boundary problem modeling tumor growth. *Interfaces and Free Boundaries,* 5:159-182, 2003.

Friedman A, Tao Y. Analysis of a model of virus that replicates selectively in tumor cells. *J. Math. Biology*, 47:391-423, 2003.

Friedman A, Chen X, Cui S. A hyperbolic free boundary problem modeling tumor growth: Asymptotic behavior. Submitted for publication.

Friedman A, Chen X. A free boundary problem for an elliptic-hyperbolic system: An application to tumor growth. *SIAM J. Math. Analysis*, accepted.

Friedman A. A hierarchy of cancer models and their mathematical challenges. *Discrete and Continuous Dynamical Systems,* 4:147-160, 2004.

Friedman A, Craciun G, Aguda B. A detailed mathematical analysis of a model that couples the cell cycle and apoptosis (submitted, 2004).