M, W, F, 10:30–11:20, MEB 235

Course Website: **http://faculty.washington.edu/hqian/amath531/**

1 Course Description

Biological cells are biochemical systems that obey the laws of physics. This course develops a coherent mathematical theory for processes inside living cells. It focuses on settng up a general theory for all cellular modeling, and then develop specific models and analyzing their dynamics leading to functions of cellular components (gene regulation, signaling biochemisty, metabolic networks, cytoskeletal biomechanics, epigenetic differentiation) using deterministic and nonlinear stochastic dynamic models. ***Prerequisites:*** *402 and 403 and working knowledge of probability.*

2 Brief Introduction

Cell theory is one of the fundamental organization principles in essentially all life sciences. One of its main statements is "life comes from life" which, in the post-genomic era, is exclusively interpreted as DNA is replicated from DNA - one key step in the central dogma of molecular biology. Cells, as the basic unit of structures and functions, divide the inanimate materials in biochemistry and living organisms.

The theory of cellular dynamics establishes a mathematical foundation for analytical studies of cells.[1] Its intellectual significance resides in its ability to "mathematically explain" how inanimate molecules collectively give rise to a living cell; bridging physics and biology through chemistry and applied mathematics.

3 Referenece Texts

There is essentially no textbook for this new emerging subject. We shall mainly read research and review papers. Here are first two papers you **must** download and use as required readings, over the entire course period though. They are already posted on the course webpage:

D. A. McQuarrie, Stochastic approach to chemical kinetics. *J. Appl. Prob.* **4**, 413–478 (1967).
D. T. Gillespie, Stochastic simulation of chemical kinetics. *Ann. Rev. Phys. Chem.* **58**, 35–55 (2007).

There are general reference books from which you can learn various terminologies. These are not required readings. You might also find terminologies and definitions from online resources, but be

[1]The term "analytical" here is used to indicate systematic, logical, scientific, not the "analytical versus numerical".

aware of the accuracy of what you read.

(PEGL) P. Érdi and G. Lente (2014) *Stochastic Chemical Kinetics: Theory and (Mostly) Systems Biological Applications.* Springer
(JDM) J.D. Murray (2004) *Mathematical Biology I: An Introduction*. Springer.
(JKJS) J. Keener and J. Sneyd (1998) *Mathematical Physiology*. Springer.
(HMTSK) H.M. Taylor and S. Karlin (1998) *An Introduction to Stochastic Modeling*. 3rd Ed., Academic Press.
(CWG) C.W. Gardiner (2004) *Handbook of Stochastic Methods: For Physics, Chemistry, and the Natural Sciences*. 3rd Ed., Springer.
(LJSA) L.J.S. Allen (2003) *An Introduction to Stochastic Processes with Biology Applications*. Prentice Hall.
(MBTC) B. Alberts, A. Johnson, J. Lewis, M. Raff, K. Roberts and P. Walter (2002) *Molecular Biology of the Cell*. 4th Ed., Garland Science.
(PBTC) R. Phillips, J. Kondev and J. Theriot (2008) *Physical Biology of the Cell*. Garland Science.

4 Homework Problems and Reading Materials

Please regularly check online for updated information and materials.

5 Learning Goals/Objectives

Independent and critical thinking and mathematical language useful to cellular biology, and quantitative modeling of complex systems in general.

6 Evaluation and Grading

Homework problems ($\sim$ 5 total) constitute 50% of the final grade, another 20% from class participation, with the balance (30%) from a term project with a term paper (15-20 papges). The paper is due on **December 9**, the friday. **Submit your paper via email in PDF format**. There will be no formal exam.

7 Syllabus

(1) Introduction to Cellular Dynamics:

(a) Cell biology in terms of genetics and biochemistry

(b) Cellular biochemistry in terms of chemistry, which in terms of classic physics

(c) What is fundamental physics — reading assignment [1, 2]

P. W. Anderson (1972), "More is different"

J. J. Hopfield (1994) "Physics, computation, and why biology looks so different?"

(d) Dynamics of a single biological macromolecule — review Newtonian mechanics: few body problem, many-body problem, molecular dynamics, and stochastic processes — transition from physics to chemistry

(e) Celluarl biochemical dynamics in terms of nonlinear, stochastic processes [3]

(f) Deterministic dynamical systems and ordinary differntial equations

(g) Birth-and-death processes and stochastic biochemical dynamics — ***start reading McQuarrie's and Gillespie's papers***

(h) Cancer, epigenetics, and evolution

(j) Nonlinear, stochastic cellular biochemical dynamics as a new paradigm for complex systems [3, 4].

(k) Kinetic isomorphism and general population dynamics [4]

(i) The middle way: Classical dynamics, statistical inference, and their synthesis [5, 6]

(2) Nonlinear Homogeneous Chemical Reaction Dynamics:

(a) Arrhenius law, Eyring's transition state, and Kramers' theory of a chemical reaction and its rate

(b) The Law of Mass Action (JDM,JKJS)

(c) Enzyme reactions and Michaelis-Menten Theory (JDM,JKJS)

(d) Nonlinear biochemical reaction systems: Logistic, Lotka-Volterra, Schlögl, Schnakenberg [8]

(e) Biochemical signaling and signaling network [8]

(f) Saddle-node bifurcation and transcritical bifurcation (JDM)

(3) Stochastic, Nonlinear Homogeneous Biochemical Reaction Systems in a Cell

(a) Delbrück's theory of biochemical reactions in a small volume [9]

(b) Michaelis-Menten kinetics revisited [10]

(c) Basics of jump Markov processes with continuous time (HMTSK,CWG,LJSA)

(d) The chemical master equation (CME) and master equation graph (CWG) [8]

(e) Gillespie algorithm and stochastic trajectories [3, 8]

(4) Simple Mathematical Models for Stochastic, Nonlinear Homogeneous Biochemical Reaction Systems [8, 4]

(a) Logistic equation revisited and Keizer's paradox

(b) Biostability and Schlögl model revisited

(c) Rotational random walk, oscillation and Schnakengerg model revisited

(d) Signaling networks and gene regulatory networks

(5) Ornstein-Uhlenbeck Processes and Linear, Gaussian Theory (CWG)

(a) Linear stochastic differential equations

(b) Diffusion equations

(c) Law of large numbers and central limit theorem

(d) Van Kampen's system size expansion

(e) Conditional Fokker-Planck equations

(f) Complete solution to the linear Gaussian theory

(6) Nonlinear Bifurcation, Maxwell Construction and Phase Transition [3]

(a) Kurtz's theory

(b) Saddle-node bifurcation and transcritical bifurcation (JDM)

(c) Maxwell construction

(d) Evolutionary dynamics of cellular systems

(7) Helmholtz theorem and a law of conservation in stochastic dynamics

(a) Energy and thermodynamics

(b) WKB theory and emergent landscape [11]

(c) General stochastic thermodynamics

(d) Emergence of a law of conservation

(8) From Cellular Dynamics to Evolutionary Stable Strategy and Back

(a) Discrete versus continuous time dynamics

(b) Life-histroy strategies in fluctuating environments

(c) Population dynamics and frequency dynamics

References

[1] Anderson, P.W. (1972) More is different. *Science*, **177**, 393–396.

[2] Hopfield, J.J. (1994) Physics, computation, and why biology looks so different? *J. Theoret. Biol.* **171**, 53–60.

[3] Qian, H. (2010) Cellular biology in terms of stochastic nonlinear biochemical dynamics: Emergent properties, isogenetic variations and chemical system inheritability (Review), *J. Stat. Phys.* **141**, 990–1013.

[4] Qian, H. (2011) Nonlinear stochastic dynamics of mesoscopic homogeneous biochemical reactions systems - An analytical theory. *Nonlinearity* **24**, R19–R49.

[5] Laughlin, R.B., Pines, D., Schmalian, J., Stojkovi B.P. and Wolynes, P.G. (2000) The middle way. *Proc. Natl. Acad. Sci. USA* **97**, 32–37.

[6] Ao, P., Qian, H., Tu, Y. and Wang, J. (2013) A theory of mesoscopic phenomena: Time scales, emergent unpredictability, symmetry breaking and dynamics across different levels. *arXiv.org/abs/1310.5585*.

[7] Qian, H. (2012) Cooperativity in cellular biochemical processes: Noise-enhanced sensitivity, fluctuating enzyme, bistability with nonlinear feedback, and other mechanisms for sigmoidal responses. *Annual Review of Biophysics*, **41**, 179–204.

[8] Qian, H. and Bishop, L.M. (2010) The chemical master equation approach to nonequilibrium steady-state of open biochemical systems: Linear single-molecule enzyme kinetics and nonlinear biochemical reaction networks. *Int. J. Mol. Sci.* **11**, 3472–3500.

[9] Delbrück, M. (1940) Statistical fluctuations in autocatalytic reactions. *J. Chem. Phys.* **8**, 120–124.

[10] Qian, H. (2008) Cooperativity and specificity in enzyme kinetics: A single-molecule time-based perspective (Mini Review). *Biophys. J.* **95**, 10–17.

[11] Ge, H. and Qian, H. (2012) Landscapes of non-gradient dynamics without detailed balance: Stable limit cycles and multiple attractors. *Chaos*, **22**, 023140.