M, W, F, 12:30-1:20, DEN 111

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

## **1** Course Description

### **1.1 In the official catalog**

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 setting 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.

### **1.2 Updated course description**

While you are going to learn plenty of applications of mathematics in biology, the real theme of this class is not about mathematical biology per se. In this course, the term cellular dynamics is defined as follows: A complex systems with many, many bodies, or individuals. We assume each and everyone is different from each and everyone else according to classical-mechanics point of view. In other words, two hemoglobin molecules are two different mechanical systems, so are two lung cells in your body. However, we introduce a classification that groups certain individuals into one species in the case of chemistry, different individual molecules are grouped according to their molecular formulae, in cell biology often this is done by different morphologies and functions. After this classification, the number of individuals within each species will have statistical behavior as integer-valued Markov process. It is this mathematical representation and its ramification, e.g., results derivable via mathematical derivations, new concepts, and entire discussions of complex behaviors, that are the focus of this course. As you can see, biological cell is just used as one very concrete example for this non-mechanical (shall we call this a biochemical?) representation of the world; but the theory is applicable to many other situations. I would like to use this non-Newtonian mathematical representation as an physical science in contrast the current data-driven paradigm: The mathematics is based on a " 'non-mechanical' stochastic, mechanistic" understanding of a problem, not based on data, per se.

## **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.<sup>1</sup> 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.

For lack of a better terminology, the new mathematical foundation will be called "chemical representation" of the world in contrast of the "mechanical representation" of the world. The latter has been the main thread of applied mathematics for the past three hundred years.

## **3** Reference Texts

There is no textbook for this new emerging subject. A set of notes from two years ago is posted online. But I am re-writing and modifying it as time goes, so please try to always check the newest version: There is a time stamp on the front page. We shall also read research and review papers. Here is one paper, which is already posted online, you **must** download and use as required readings:

H. Qian (2018) Stochastic population kinetics and its underlying mathematicothermodynamics. To appear In *Biological Dynamics*, A. Bianchi, T. Hillen, M.A. Lewis, and Y. Yi. editors, Springer, New York.

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 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.

<sup>&</sup>lt;sup>1</sup>The term "analytical" here is used to indicate systematic, logical, scientific, not the "analytical versus numerical".

(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 papes). The paper is due on **Friday, December 7**; *Submit your paper via email in PDF format*. There will be no formal exam.

## 7 Important Dates

Sept. 26, Wednesday, Instruction begins.Oct. 5, Friday, No class.Dec. 7, Friday, Last day of instruction; term paper due.

# 8 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
- (h) Cancer, epigenetics, and evolution

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

- (k) Kinetic isomorphism and general population dynamics
- (i) The middle way: Classical dynamics, statistical inference, and their synthesis [4, 5]

#### (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 [7]

- (e) Biochemical signaling and signaling network [7]
- (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 [8]
- (b) Michaelis-Menten kinetics revisited [9]
- (c) Basics of jump Markov processes with continuous time (HMTSK,CWG,LJSA)
- (d) The chemical master equation (CME) and master equation graph (CWG) [7]
- (e) Gillespie algorithm and stochastic trajectories [3, 7]

### (4) Simple Mathematical Models for Stochastic, Nonlinear Homogeneous Biochemical Reaction Systems [7]

- (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 [10]
- (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] 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.
- [5] Qian, H., Ao, P., Tu, Y. and Wang, J. (2016) A framework towards understanding mesoscopic phenomena: Emergent unpredictability, symmetry breaking and dynamics across scales. *Chemical Physics Letters*, 665, 153–161.
- [6] 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.

Prof. Hong Qian

- [7] 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.
- [8] Delbrück, M. (1940) Statistical fluctuations in autocatalytic reactions. J. Chem. Phys. 8, 120–124.
- [9] Qian, H. (2008) Cooperativity and specificity in enzyme kinetics: A single-molecule timebased perspective (Mini Review). *Biophys. J.* **95**, 10–17.
- [10] Ge, H. and Qian, H. (2016) Mesoscopic kinetic basis of macroscopic chemical thermodynamics: A mathematical theory. *Physical Review E*, **94**, 052150.