ROLLINS SCHOOL OF PUBLIC HEALTH
EMORY

DEPARTMENT: Environmental Health

COURSE NUMBER: EHS 730 **SECTION:** 1 **SEMESTER:** Fall 2018

CREDIT HOURS: 2

COURSE TITLE: Computational Systems Biology: Modeling Biological Responses

COURSE LOCATION: TBD

PREREQUISITE: General knowledge of cell, molecular biology or biochemistry

INSTRUCTOR: Qiang Zhang, MD, PhD
EMAIL: qiang.zhang@emory.edu
PHONE: 404-727-0154
OFFICE: Claudia Nance Rollins Building, Room 2017
OFFICE HOURS: By appointment

BRIEF COURSE DESCRIPTION

Understanding biological responses to external perturbations, their health outcomes and risks increasingly requires a systems biology approach. This course teaches the dynamical modeling aspect of systems biology. Such an approach is necessary to make sense of biological pathways/circuitries comprising genes, RNAs, proteins, and metabolites, and to understand how they are quantitatively organized as complex networks to carry out integrated, systems-level functions and respond to biological, pharmaceutical and environmental perturbations. This interdisciplinary course introduces the basic concepts and principles in systems biology, and numerical simulation techniques for mechanically understanding and predicting biological responses.

The course covers:

- Linear and nonlinear biological responses including sigmoidal, switch-like, threshold, non-monotonic, and other nonlinear responses.
- Common biological network motif structures underlying nonlinear responses: ultrasensitive motifs, positive and negative feedback loops, and feedforward loops.
- How these network motifs are organized into larger, complex biological networks that underpin systems-level functions, including stress response, adaptation, homeostasis, proliferation, differentiation, and biological rhythms.
- Use of numerical simulation techniques to develop computational systems biology models of biological pathway perturbations to mechanistically interpret and to predict nonlinear response behaviors of environmental toxicants and drugs.

Target students:

- Students interested in nonlinear dose-response relationships and risk assessment and their underlying biological mechanisms.
- Pharmacology and toxicology students interested in the quantitative aspects of biological responses to drug and environmental perturbations for a mechanistic, systems-level understanding of pharmacodynamics and toxicodynamics.
- Biological, biomedical and bioengineering students interested in how cells and organisms work as dynamic systems to carry out integrated functions including binary decision-making, differentiation, proliferation, homeostasis, adaptation, stress response, apoptosis, and rhythmic behaviors.
- Students interested in using computational systems biology modeling to understand cellular and organismal phenomena, interpret experimental data, and design synthetic biology circuits.

Course format: The course comprises lectures and hands-on computer simulation exercises. Each student will be required to bring a laptop computer (PC preferred) to simulation sessions.

TEXTBOOKS AND LIST OF REFERENCES

- Optional textbooks:
  (1) An Introduction to Systems Biology: Design Principles of Biological Circuits (2nd Edition), by Uri Alon, Chapman and Hall/CRC, ISBN-10: 1439837171.
  (2) A First Course in Systems Biology (2nd Edition), by Eberhard Voit, Garland Science, ISBN: 9780815345688.

- Additional list of papers for reading assignment will be provided in class.

LIST SCHOOL LEVEL, DEPARTMENT, AND/ OR PROGRAM COMPETENCIES

- To learn nonlinear dose-response relationships and how they arise mechanistically in biological systems.

- To learn how to use numerical simulation tools to model biological responses to environmental and pharmaceutical perturbations as dynamic, complex systems.

LIST LEARNING OBJECTIVES ASSOCIATED WITH THE COMPETENCIES

- Quantitative concepts associated with biological responses.
- How molecular networks and circuits comprising genes, proteins and metabolites give rise to different dynamics and dose response behaviors.
- Nonlinear responses: sigmoidal, switch-like, threshold and non-monotonic.
- How to use numerical simulation programs such as Berkeley Madonna to model biological response to perturbations.

EVALUATION

Your grade in this class will be based upon attendance and three homework assignments.

Attendance	10%
Homework #1	25%
Homework #2	30%
Homework #3	35%

Homework assignments will involve using numerical simulation methods learned in class to build computational biological pathway and response models.

Class Schedule (subject to change)

Week 1

Introduction
- Background on systems biology
- Biochemical pathways, circuits, and networks
- Applicable theoretical frameworks
- Numerical simulation methods

Week 2

Simple Responses
- Mass action of biochemical reactions
- Synthesis/degradation: linear response
- Reversible binding: rectangular hyperbolic response
- Michaelis-Menten: rectangular hyperbolic response

Numerical Simulation Methods (simulation exercise)
- Deterministic modeling using ordinary differential equations
- Introduction to Berkeley-Madonna numerical solver software
- Simulation exercise: Synthesis/degradation
- Simulation exercise: Reversible binding

Week 3

Sigmoidal Responses
- Weber's law: What matters is percentage change
- Hill function, sigmoidal dose response,
- Ultrasensitivity: signal amplification in biochemical networks

Ultrasensitive Motifs I
- Positive cooperative binding
- Homodimerization
- Multistep signaling

Simulation Exercises
- Homo-multimerization
- Hill function

Week 4

Ultrasensitive Motifs II
- Molecular titration and saturable pathway branching
- Zero-order ultrasensitivity via covalent modification cycle
- Positive feedback
- Motif combinations: MAPK cascade

Simulation Exercises
- Zero-order covalent modification cycle
- MAPK cascade and ultrasensitivity

*<u>**Homework #1 assignment</u>*

Week 5

Binary and Irreversible Responses in Biological Systems

- Discrete cell fate and irreversible, binary decision-making, biological switches
- Waddington epigenetic landscape, cell differentiation and lineage specification
- Network motif conditions required to achieve bistability:
(1) Positive (or double-negative) feedback loops
(2) and Ultrasensitivity
- Bistable switch, threshold, and hysteresis
- Nullcline, stability, attractor, separatrix, and basin of attraction

Week 6

Simulation Exercise: A Bistable Gene Auto-Regulation Model

- Exploring bistable behavior
- Modeling response to continuous vs. pulse input
- Phase Plane, Phase Portrait, Saddle Node, and Basins of Attraction
- Nullclines, saddle-node bifurcation diagram

Homework #1 due

Week 7

Homeostasis, Stress Response and Adaptation

- Concepts of homeostasis, adaptation and stress response
- Negative feedback: the primary network motif underpinning homeostasis
- Ultrasensitivity revisited
- Signal transfer analysis
- Proportional feedback: partial adaptation and low-dose nonlinear response
- Integral feedback: perfect adaptation and low-dose threshold response

***Homework #2 assignment*

Week 8

Simulation Exercises: Negative Feedback Control and Nonlinear Dose Response

- Proportional feedback control
- Integral feedback control

Week 9

Feedforward Control, Cellular Stress Response, and Hormesis

- Definition and types of feedforward loop (FFL) motifs
- Type I coherent FFL
- Type I incoherent FFL
- Feedforward control of cellular stress responses
- Hormesis
- Oxidative stress response, antioxidants, and insulin secretion
- Cascade of FFLs and dynamic responses

Homework #2 due

Week 10

Simulation Exercises: Feedforward Loops and Nonlinear Responses
- Type I coherent feedforward
- Type I incoherent feedforward
- Nonlinear and hormetic responses in feedforward and feedback loops

Week 11

Biological Rhythms: Modeling Oscillatory Behaviors
- Biological rhythmic behaviors and functions
- Negative feedback loop as the network motif structure for oscillation
- Kinetic conditions required for autonomous, sustained oscillation
(1) Sufficient time delay
(2) Signal amplification (through ultrasensitivity)
- Two major types of oscillators
(1) Resonant oscillators: negative feedback loops only
(2) Relaxation oscillators: negative feedback loops coupled with positive ones
- How oscillation arises: stable limit cycle as the attractor, Hopf bifurcation

***Homework #3 assignment*

Week 12

Simulation Exercises: Modeling Oscillatory Behaviors
- Resonant oscillator
- Relaxation oscillator

Week 13

Eukaryotic Cell Cycle and Checkpoint Control – Conserved Circuits with Multiple Network Motifs

Week 14

Stochasticity in Gene Expression and their Implication for Dose Response
- Intrinsic and extrinsic gene expression noise
- Effect of gene expression noise on dose response
- Stochastic simulation method: Gillespie algorithm

Homework #3 due

ACADEMIC HONOR CODE
The RSPH requires that all material submitted by a student in fulfilling his or her academic course of study must be the original work of the student.