Computational Systems Biology And Dose Response Modeling Workshop, September 22 – 26, 2008

Division of Computational Biology, The Hamner Institutes for Health Sciences

Qiang Zhang[1], Sudin Bhattacharya[1], Courtney Woods[1], Rory B. Conolly[2] and Melvin E. Andersen[1]

[1]Division of Computational Biology, The Hamner Institutes for Health Sciences , RTP, North Carolina 27709

[2]National Center for Computational Toxicology, U.S. Environmental Protection Agency, RTP, North Carolina 27711

Overview

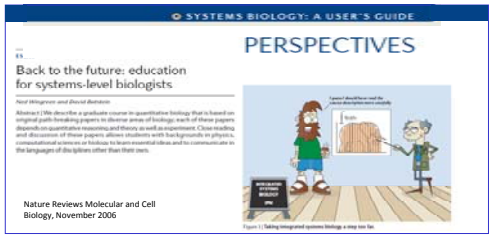
- The recently published National Academy of Sciences report "Toxicity Testing in the 21st Century" (NAS Press, Washington, DC, 2007) recommends a new approach to toxicity testing, based on evaluating cellular responses in a suite of toxicity pathway assays in human cells or cells lines *in vitro*.
- Such a paradigm shift would benefit from mechanism-based computational modeling of the molecular circuitry involved in the targeted cellular pathways, which should produce improved dose response assessment of the toxic actions of compounds.
- In accordance with the goals set forth by the NAS report, an inaugural 5-day workshop on Computational Systems Biology and Dose Response Modeling was offered by the Division of Computational Biology at The Hamner Institutes for Health Sciences September 22 – 26, 2008.
- The course was attended by 36 students of varied backgrounds from regulatory agencies, academia, and industry, as well as internal members of the institute.
- The focus of the course was on common themes in signal transduction and gene regulatory networks that underlie systems-level cellular behaviors, including linear and nonlinear response motifs, homeostasis, adaptation, binary cell fate decisions, and stochasticity in gene expression.
- A number of specific biological examples were discussed in detail, including ultrasensitivity and bistability in MAP kinase signaling cascades, checkpoint control in the eukaryotic cell cycle, and oxidative/electrophilic stress response.
- Lectures on the various topics were accompanied by exercises on computational modeling of cellular responses using the Berkeley Madonna® simulation program. Implications for toxicology and dose-response modeling were emphasized throughout the course.

Overall Workshop Learning Goals

- Current computational modeling techniques for the quantitative investigation of how biological systems respond to perturbations at the cellular level.
- Common themes in signal transduction and gene regulatory networks that underlie systems-level cellular behaviors including homeostasis, adaptation, threshold response, binary cell fate decisions, and irreversible differentiation.
- To use these techniques to develop computational models for understanding and predicting dose response behaviors of drugs and environmental agents.

Origins

- Workshop originated as a journal club at the Division of Computational Biology at The Hamner Institutes for Health Sciences from June 2007 to January 2008, covering various aspects of Systems Biology and Dose Response Modeling.
- Inspiration came from a 2006 review paper by Wingreen and Botstein on designing a Systems Biology curriculum and references listed therein.
- Tentative agenda put together by March 2008 and workshop publicized at SOT Annual Meeting, as well as through BMSS and RASS of SOT, SRA, ACC, ICSB, and EPA/NCCT, etc.



Nature Reviews Molecular and Cell Biology, November 2006

Specific Learning Objectives

- The quantitative concepts underlying cell signaling and gene regulation
- How molecular circuits comprising genes, proteins, and their interactions give rise to different dose response behaviors
- The shapes of dose response curves in feedback/feedforward-mediated cellular homeostatic systems
- The molecular engine driving the cell cycle and checkpoint control, and its implications for modeling dose responses with respect to cell proliferation
- How binary (either/or) decisions are made and how cells remember the results of these decisions
- The noisy (stochastic) nature of gene expression and its implications for the shapes of dose response curves
- Approaches to modeling signal transduction and gene regulatory networks
- To use programs such as Berkeley Madonna® for computational modeling of cellular response to perturbations

Workshop Faculty

Qiang Zhang, M.D., Ph.D., Course Director
Starting as a biomedical scientist, Dr. Zhang is a computational biologist interested in using simulations to understand how biological systems behave in response to perturbations. His research has focused on the nonlinear dose response behavior arising from cellular homeostatic control and the genetic toggle switch underlying irreversible binary cell fate decisions.

Melvin E. Andersen, Ph.D., CIH, D.A.B.T
Dr. Andersen pioneered the use of PBPK modeling in toxicology and in safety and risk assessments. In recent years, his research emphasis has been on developing mathematical descriptions of the control of genetic circuitry and the dose response and risk assessment implications of these control processes.

Sudin Bhattacharya, Ph.D.
With a background in particle-based modeling in materials science and engineering, Dr. Bhattacharya is currently developing computational models of signal transduction and gene regulatory networks underlying terminal differentiation of B lymphocytes into plasma cells and inflammatory response in the liver, and investigating how dioxin-like toxicants perturb these cellular pathways.

Courtney G. Woods, Ph.D.
With educational training in Chemical Engineering and Toxicology, Dr. Woods has used genomics techniques to study the mechanism of hepatotoxicity of environmental and pharmaceutical compounds in mouse models. Her current research focuses on identifying molecular mediators involved in transcriptional regulation of antioxidant response to chlorine and developing computational models of the anti-oxidant response pathway in mammalian cells.

Course Advisors:

- **Dr. Rory B. Conolly**, National Center for Computational Toxicology, US Environmental Protection Agency
- **Dr. Harvey J. Clewell, III**, Director, Center for Human Health Assessment, The Hamner Institutes for Health Sciences

Topics

Agenda

Monday, September 22

Morning	Welcome, introductions and course overview
	Computational dose response modeling – background
	Response motifs in quantitative cell signaling and dose response
Afternoon	Introduction to Berkeley Madonna®
	Exercise 1: Synthesis/degradation motif
	Exercise 2: Reversible binding motif
	Exercise 3: Homo-multimerization
	Exercise 4: Zero-order ultrasensitivity
	Exercise 5: Hill function

Tuesday, September 23

Morning	Binary decision-making in biological systems
	MAPK-mediated ultrasensitivity and bistability
Afternoon	Exercise 1: A bistable gene auto-regulation model
	Exercise 2: MAPK ultrasensitivity and bistability – modeling *Xenopus* oocyte maturation

Wednesday, September 24

Morning	Response motifs – repeating components controlling biological function
	Exercise 1: Type I coherent feedforward
	Exercise 2: Type I incoherent feedforward
	Exercise 3: Sequential gene activation
Afternoon	The eukaryotic cell cycle and checkpoint control
	Exercise: Modeling a simple cell cycle circuit and checkpoint control

Thursday, September 25

Morning	Cellular homeostasis, adaptation and steady-state dose response
	Oxidative/electrophilic stress response
Afternoon	Exercise 1: Negative feedback and homeostasis (Part I)
	Exercise 2: Negative feedback and homeostasis (Part II)

Friday, September 26

Morning	Stochasticity in gene expression and its implication for dose response
	Computational biology, dose response modeling and risk assessment: where to from here?
Afternoon	Optional Exercise: Switching through activation of cellular circuits and biological consequences (with demonstration of stochastic modeling tool)

Scenes from the Workshop

Workshop Participation

Expected attendees:

- Researchers interested in applying computational systems biology to modeling dose response behaviors of drugs environmental agents, and understanding the underlying cellular mechanisms.
- Risk and safety assessment professionals who would like to link dosimetry models to biologically-based cellular response models.
- Toxicologists and pharmacologists interested in applying quantitative simulation tools to interpreting *in vitro* cellular response data.

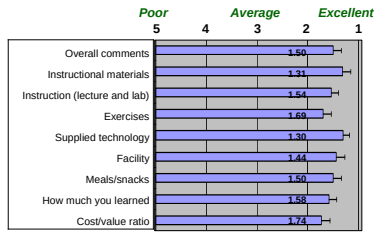
Tuition charged:

- General: **$1600**; Government Employee: **$1200**; Graduate Student and Postdoctoral Fellow: **$1000**.

Total attendance: **35**					
Outside The Hamner Institutes (**21**)					Inside The Hamner Institutes (**14**)
EPA (**9**)	FDA (**5**)	CDC (**1**)	Industry (**4**)	Academia (**2**)	

Student Evaluation and Response

Statistics of anonymous evaluation:



Selected Comments from Attendees:

- *"Synthesis of current literature into a clearly-organized format comprehensible to a very mixed audience and presented with exceptional skill."*
- *"The course was well planned, and accessible to people with various backgrounds."*
- *"For someone without a strong math background, I was able to follow and understand. Exercises really forced that."*
- *"Gave me an idea about where to start with respect to studying the literature and applying the techniques of systems biology to my research."*

This work was supported in part by the NIEHS Superfund program at Michigan State University. This work is not a statement of official policy of the U.S. EPA.