



Course Overview

The goal of the **Systems Biology & Disease** Journal Club Course ISTP 30440 is to introduce students to well designed systems biology experiments published in high quality journals. Systems biology investigators characterize biological networks at multiple levels of molecular and cellular complexity. Research focuses on how complex systems induce and sustain homeostasis, preserve health, develop/evolve life, and initiate/modulate disease states.

Core Students

Medical Scientist Training Program (MSTP) Students
 Graduate Students
 Undergraduate Students (special permission required)

Course Planning, Syllabus & Lead

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Institute for Genomics & Systems Biology, BSCD, GGSB & Chicago Center for Systems Biology

Instructors

- Nancy Cox
- Eric Bertolino
- Christopher Brown
- Rebecca Spokony
- Yves Lussier
- Ken Onel
- Funmi Olopade
- Kevin White
- TBD

Instructors are assigned students for a particular week of the course and attend one practice session to offer mentoring feedback. Instructors may present papers, too. Students presenting will bring food and drinks for the class.

Teaching Assistant

David Blair, GGSB and The Institute for Genomics & Systems Biology daveblair@uchicago.edu

Schedule

Tuesday/Thursday	4:00 - 5:50pm	KCBD, 10th Floor, South Conf. Rm 10160C
10 weeks	20 meetings	
<i>Wks 1-9</i>	<i>Introduction & Core Papers</i>	

Wk 10

Last Paper, Wrap-up discussion, reports due, future courses

Background and Framework

Multiple hierarchies of molecular and cellular mechanisms interplay within complex biological systems. Their components are characterized experimentally, mathematically, and computationally in order to organize and relate diverse molecular roles, genetic interactions, and emergent properties and behaviors. Analysis of physiological, genetic, environmental signals and biological activities help decipher complex states of living matter. These systems, at multiple levels of organization, induce and maintain homeostasis. Some systems are capable of generating strong buffering effects linked to robust gene expression networks and self-maintaining metabolic pathways. Their fragility and breakdown correlate with induction and modulation of disease states in humans. Understanding these kinds of biomedical changes offers opportunities to develop new systems-level tools to diagnose disease and invent therapies to transform the practice of medicine.

The **Systems Biology & Disease** course will review outstanding papers that report on investigations that studied complex systems at different hierarchical levels and multiple overlapping temporal frameworks. Students will present research papers to their peers and course instructors. They will give clear overviews and background information about the published experimental results. Key data and important findings will be summarized and related to physiological, genetic, cellular, molecular, and environmental networks. Examples may include physical interactions between proteins and DNA, such as hormone receptor transcription factors and genetic enhancers that regulate transcription. Some reports may be about large-scale data collections linked through statistical and quantitative analyses with human disease conditions.

By studying systems biology research papers and clarifying their reported use of computational biological modeling, students will learn how predictive computer-based simulations are relevant to advances in molecular medicine. Useful experimental techniques, protocols, and cross-disciplinary applications will be explained. Tools especially relevant to diagnostic and therapeutic advancements will be discussed. The journal club course will highlight diverse molecular and cellular components in model organisms that link to homologous ones in humans. Large-scale data integration and analyses will be explored to promote better understandings about how physiological and clinically relevant molecular behaviors and properties emerge from complex biological systems.

Papers selected are sufficiently well written and important to spark engaging discussions. Students must read all the assigned papers and be prepared to talk about them. Those presenting at each session will introduce the papers and will briefly explain the relevant historical scientific background, investigators' key question(s), experimental frameworks, approaches, techniques, results, and conclusions. Active student discussion will be encouraged. Strengths and weaknesses of the experiments and related published interpretations will be reviewed. A key "take home" message, or set of conclusions, will be discussed.

The journal club course will serve as a conceptual vehicle to develop a useful framework for new undergraduate and graduate systems biology courses at the University of Chicago. This generative process will produce learning goals and experiments to profile in future lectures. Investigations, both historic and contemporary, related to these “big ideas,” will be discussed.

Examples of core ideas include:

- The number of interaction partners or their level of transcriptional network connectivity predicts essentiality.
- Networks are made of repeating patterns called motifs, each of which perform a defined information processing function.
- Genes tightly linked in different probabilistic networks are very likely involved in the same biological process. Therefore, these genes share similar loss-of-function phenotypes.
- Biological networks insensitive to fluctuations in their components are robust and resist phenotypic variation.

Grading

General Participation:	20% (40 points)
Papers presented:	30% (60 points) each
Daily Assignments	10% (20 points)
Final Report:	10% (20 points)

General participation: Each student will be expected to make a meaningful contribution to the daily discussion. Students will receive 2 points for every class period indicative of their participation. Everyone should receive a perfect score as long as they do the required reading and participate!

Papers presented: Each student will give two presentations during the quarter. Students will be expected to have a reasonable understanding of the background, methods, models/assumptions, and experimental logic underlying each research article. Some of these articles may be difficult to follow since they will utilize novel and complex mathematical and statistical models. Students will therefore need to consult with primary literature, the TA, and your faculty advisor (preferably in that order) in order to gain the required understanding. It is imperative that presentations include group discussion.

Students will be expected to stimulate discussion by thoroughly analyzing the assumptions, experiments, and conclusions of the research. Presentations will be graded according to the following scheme:

I. Background: 10 points

- A. Importance of the research question/approach (What is new?).
- B. Necessary background required for a thorough understanding.
- C. Is there background/information not (or apparently not) considered by the authors?

II. Model/Methods: 15 points

- A. General description of the experimental approach utilized by the authors (not too specific).
- B. Description of the modeling/data analysis techniques utilized by the authors.
 1. Focus on assumptions, advantages, and pitfalls of the approach.
 2. Only include aspects of the model that are necessary for a general understanding (i.e. do not include complicated mathematical derivations).
- C. Pose questions for discussion about techniques/methods.
 1. Why were some assumptions made vs. others?
 2. Are there alternative approaches with advantages/disadvantages?

III. Experimental analysis: 20 points

- A. Give a thorough description of experimental results. Consider the following:
 1. Why did the authors perform these experiments?
 2. What alternative experiments were possible?
 3. How were the results interpreted?
 4. What were the conclusions made by the authors?
 - a) Are they justified?
 - b) What alternative conclusions can be offered?

IV. Overall conclusions and future directions: 15 points

- A. How did the research expand the previous knowledge base?
- B. Are the authors' final conclusions consistent and reasonable?
- C. What experiments would strengthen the conclusions?
- D. What are the future directions?

***Note: The presentation should NOT be a restatement of the above outline. It should be organic and preferably follow the logic laid out in the paper. Furthermore, the statements and questions listed beneath each main point are there as examples and ideas. They are neither necessary or sufficient for a good presentation.

Daily assignments: It is expected that students will have come to each class period having read the paper and obtained a basic understanding of methods, results, conclusions, etc. In addition, each student should turn in two "pearls of wisdom" (per Doug Bishop) about each article. A "pearl" is simply an observation or statement (no more than one or two sentences each) that goes beyond what was written in the article. Examples include:

1. Alternative conclusions of experimental results not stated by the author.
2. Proposal of an alternative experiment.
3. Critical assessment of methods/assumptions.

4. Alternative modeling approaches (do not need to be very specific).
5. Future experiments.
6. Experiments that would have supported/disproved conclusions.
7. Implication of results not addressed by the author.
8. Application of methods/results to new problems.

***Note: Students do NOT need to turn in “pearls” for the articles that they present. Furthermore, there will be NO daily assignment due on the first or last class period. Therefore, students will complete a total of 16 daily assignments each worth 1.25 points.

Final report: Discuss what you found to be most challenging about reading and analyzing these articles, and describe future measures that the class could take that would make the required reading more worthwhile and enjoyable. The eventual goal of the IGSB is to create a curriculum that will give students the necessary background and training required to perform research in the fields of computational biology, genomics, and systems biology. Having now been exposed to a variety of research in these fields, what subjects/classes do you think would be important to include in such a curricula? The report should be one to two pages (double spaced) in length. Due March 11, 2010.

Course Organization

- I. Introduction: Systems Biology and Disease
- II. Synthetic Biology and Application to Human Disease
- III. Deterministic Models of Cell Physiology
- IV. Stochastic Processes in Cell Physiology
- V. Robustness in Eukaryotic Systems
- VI. Reverse Engineering Cellular Networks in Health and Disease
- VII. Genetic Variation and Human Disease
- VIII. Genome Wide Genetic Screens in Human Disease
- IX. Characterization of Human Disease through Bioinformatics
- X. Summary and Final Paper

Papers for Presentations

Introduction: Systems Biology and Disease (Jan. 5)

Jan. 5, 2010: Systems Biology & Medicine

- o Auffray, Charles et al. (2009). Systems Medicine: The Future of Medical Genomics and Healthcare. (Review), Genome Medicine, 1:2.
- o Komili, Suzanne and Silver, Pamela A. (2008). Coupling and Coordination in Gene Expression Processes: A Systems Biology View. Nature Reviews, 9, 38-48.

Synthetic Biology and Application to Human Disease (Jan. 7, 12)

Jan. 7, 2010: Introduction to Synthetic Biology: Engineering, Novel Biological Networks & Systems Biology

- o Gardner, Timothy et al. (2000). Construction of a Genetic Toggle Switch in E. Coli. Nature, 403, 339-342.
- o You, Lingchong et al. (2004). Programmed Population Control by Cell-Cell Communication and Regulated Killing. Nature, 428, 868-871.
- o Haynes, Karmella A. and Silver, Pamela A. (2009). Eukaryotic Systems Broaden the Scope of Synthetic Biology. Journal of Cell Biology, 187, 589-596. (Review)

Jan 12, 2010: Application of Synthetic Biology to Treatment

- o Anderson, JC et al., (2007). Environmental signal integration by a molecular AND gate. Molecular Systems Biology. 3: 133.

Deterministic Models of Cell Physiology

Jan. 14, 2010: Revisiting the Lac Operon

- o Ozbudak et al. (2004). Multistability in the Lactose Utilization Network of Escherichia Coli. Nature, 427, 737-740.

Jan. 19, 2010: Deterministic Modeling of a Eukaryotic Kinase Network

- o Justman, Qiomceu A. et al., Tuning the Activation Threshold of a Kinase Network by Nested Feedback Loops (2009). Science, 324, 509-512.

Jan. 21, 2010: Utility of Negative Feedback Loops in Cell Signaling

- o Yu, Richard C. et al. (2008). Negative Feedback that Improves Information Transmission in Yeast Signaling. Nature, 456, 755-761.

Stochastic Processes in Mammalian Cell Physiology

Jan. 26, 2010: Network Variability Through Protein and Apoptosis

- o Spencer, Sabrina L., (2009). Non-Genetic Origins of Cell-To-Cell Variability in TRAIL-Induced Apoptosis. Nature, 459, 428-432.

Jan. 28, 2010: Transcriptome Variability and Cell Fate

- o Chang, HH et al. (2008). Transcriptome-wide noise controls lineage choice in mammalian progenitor cells. Nature, 453, 544-547.

Robustness in Eukaryotic Systems

Feb. 2, 2010: Developmental Tuning Through a miRNA

- o Li, Xin et al. (2009). A MicroRNA Imparts Robustness Against Environmental Fluctuation During Development, Cell, 137, 273-282.

Feb. 4, 2010: HSF-1 & Robustness of Stress Response Networks Linked to Disease

- o Dai, Chengkai, Whitesell, Luke, Rogers, Arlin B. and Linquist, Susan (2007). Heat Shock Factor 1 is a Powerful Multifaceted Modifier of Carcinogenesis, Cell, 130, 1005-1018.

Reverse Engineering Cellular Networks in Health and Disease

Feb. 9, 2010: B-cell Transcriptional Network Inference

- o Basso, K., et al. (2005). Reverse engineering of regulatory networks in human B cells. Nature Genetics, 37, 382-390.

Feb. 11, 2010: Phenotypic Predictions from a Reverse Engineered Network

- o Lee, I, et al. (2008). A single gene network accurately predicts phenotypic effects of gene perturbation in *Caenorhabditis elegans*. Nature Genetics 40, 181-188.

Feb. 16, 2010: A Network Approach to Antibiotics

- o Kohanski, MA, et al. (2008). Mistranslation of membrane proteins and two-component system activation trigger antibiotic-mediated cell death. Cell, 135, 679-690.

Feb. 18, 2010: Transcriptional Network Reconstruction in Activated Dendritic Cells

- o Amit, Ido, et al. (2009) Unbiased Reconstruction of a Mammalian Transcriptional Network Mediating Pathogen Responses. Science, 326, 257-263.

Genetic Variation and Human Disease

Feb. 23, 2010: Integrating Genetic Data to Create a Disease Network

- o Chen., Yanqing et al. (2008). Variations in DNA Elucidate Molecular Networks that Cause Disease, Nature, 429-435.

Feb. 25, 2010: Transcriptome Sequencing to Detect Novel Gene Fusions

- o Maher, Christopher A., et al. Transcriptome Sequencing to Detect Gene Fusions in Cancer. Nature. 458, 97-101.

Genome Wide Genetic Screens in Human Disease

March 2, 2010: High Throughput Screening for Host-HIV Interactions

- o Brass, Abraham L. et al. (2008). Identification of Host Proteins Required for HIV Infection Through a Functional Genomic Screen. Science 319, 921-926.

March 4, 2010: Synthetic Lethal Screen for the Ras Oncogene

- o Luo, J et al. (2009). A genome-wide RNAi screen identifies multiple synthetic lethal interactions with the Ras oncogene. Cell. 137, 835-848.

Characterization of Human Disease through Bioinformatics

March 9, 2010: Network Analysis and Breast Cancer

- o Taylor, IW et al. (2009). Dynamic modularity in protein interaction networks predicts breast cancer outcome. Nature Biotechnology. 27, 199-20.

March 11, 2010: Summary and Final Project

Systems Biology Reviews

- o Brynildsen, Mark P. and Collins, James J., (2009) Systems Biology Makes it Personal, Molecular Cell, 137-138.
- o Davidson, Eric H. et al. (2002). A Genomic Regulatory Network for Development. Science 295, 1669-1678.
- o Oliveri, Paola and Davidson, Eric H., (2007). Built to Run, Not Fail, Science, 315, 1510-1511.
- o Erwin, Douglas H. and Davidson, Eric H. (2009). The Evolution of Hierarchical Gene Regulatory Networks. Nature Review Genetics, 141-148.
- o Skotheim (2009). To Divide or Not to Divide. Science, 324, 474-475.
- o Kwoh, C. K. and Ng, P. Y. (2007). Network Analysis Approach for Biology, Cellular and Molecular Life Sciences, 64, 1739-1751.
- o Vaquerizas, Juan M. et al (2009) Analysis: A Census of Human Transcription Factors: Function, Expression and Evolution. Nature Review Genetics, 10, 252-263.

- o Powers, Evan T. et al (2009). Biological and Chemical Approaches to Diseases of Proteostasis Deficiency, Annual Review of Biochemistry, 78, 959-991.
- o Benfey, Philip N. and Mitchell-Olds, Thomas (2008). From Genotype to Phenotype: Systems Biology Meets Natural Variation. Science, 320, 495-497.
- o Hood, Leroy (2008), Gene Regulatory Networks and Embryonic Specification, PNAS, 105, 5951-5952.
- o Bork, Peer and Serrano, Luis (2005), Towards Cellular Systems in 4D, Cell, 121, 507-509.
- o Aderem, Alan (2005), Systems Biology: Its Practice and Challenges, Cell, 121, 511-513.
- o Kitano, Hiroaki (2002). Systems Biology: A Brief Overview, Science, 292, 1662-1664.
- o Loomis, William F. and Sternberg, Paul W., (1995). Genetic Networks, Science, 649.
- o Hiesinger, Peter Robin and Hassan, Bassem A. (2005). Genetics in the Age of Systems Biology, Cell, 29, 1173-1174.
- o Liu, Edison T. (2005). Systems Biology, Integrative Biology, Predictive Biology, Cell, 121, 505-506.
- o Megason, Sean G. and Fraser, Scott E. (2007) Imaging in Systems Biology, Cell, 130, 784-795.
- o Wheeler, Thomas J. (2007). Analysis, Modeling, Emergence & Integration in Complex Systems: A Modeling and Integration Framework & Systems Biology in Complexity, Wiley Periodicals.
- o Westerhoff, Hans V. and Palsson, Bernhard O. (2004). The Evolution of Molecular Biology Into Systems Biology, Nature Biotechnology, 22, 1249-1252.
- o Camacho, Diogo M. and Collins, James J. (2009). Systems Biology Strikes Gold, Cell, 137, 24-26.
- o Longabaugh, William J. R. et al. (2005). Computational Representation of Developmental Genetic Regulatory Networks, Developmental Biology, 283, 1-16.
- o Istrail, Sorin et al. (2007). The Regulatory Genome and the Computer, Developmental Biology, 310, 187-195.
- o Auffray, Charles et al. (2009). Systems Medicine: The Future of Medical Genomics and Healthcare. (Review), Genome Medicine, 1:2.
- o Butte, Atul J. (2008). The Ultimate Model Organism. Science, 320, 325-327.
- o Mogilner, Alex, Wollman, Roy, and Marshall, Wallace F. (2006). Quantitative Modeling in Cell Biology: What is it Good For? Developmental Cell, 11, 279-287.

- o Bar-Yam, Yaneer, Harmon, Dion, and Bivort, Benjamin de (2009). Attractors and Democratic Dynamics (Perspective). Science, 323, 1016-1017.
- o Hecker, Michael, Lambeck, Sandro, Toepfer, Susanne, Someren, Eugene van, Guthke, Reinhard (2009). Gene Regulatory Network Inference: Data Integration in Dynamic Models – A Review. BioSystems, 96, 86-103.
- o West, Geoffrey B. and Bergman, Aviv (2009). Toward a Systems Biology Framework for Understanding Aging and Health Span. (Perspective) Journal of Gerontology: Biological Sciences, 64A, 205-208.
- o Komili, Suzanne and Silver, Pamela A. (2008). Coupling and Coordination in Gene Expression Processes: A Systems Biology View. Nature Reviews, 9, 38-48.

Background Books

- o Davidson, Eric, *The Regulatory Genome: Gene Regulatory Networks in Development and Evolution*, Academic Press, 2006.
- Klipp, Edda et al., *Systems Biology: A Textbook*. Wiley-VCH, 2009.
- Bolouri, Hamid, *Computational Modeling of Gene Regulatory Networks. A Primer*: Imperial College Press, 2008.
- o Ptashne, Mark, *A Genetic Switch*, 3rd Edition, Cold Spring Harbor Press, 2004.
- o Palsson, Bernhard O. *Systems Biology: Properties of Reconstructed Networks*, Cambridge University Press, 2006.
- o Alon, Rui. *An Introduction to Systems Biology: Design Principles of Biological Circuits*, Chapman & Hall/CRC, 2007.
- o Campbell, A Malcolm and Heyer, Laurie J. *Discovering Genomics, Proteomics, and Bioinformatics*. 2nd Edition, Cold Spring Harbor Press, 2007.
- o Johnson, Steven, *Emergence: The Connected Lives of Ants, Brains, Cities, and Software*, Scribner, 2001.
- o Strogatz, Steven. *SYNC: The Emerging Science of Spontaneous Order*, Hyperion, 2003.
- o Wilson, Edward O., *Consilience: The Unity of Knowledge*, 1999.
- o Pevsner, Jonathan. *Bioinformatics and Functional Genomics*, 2nd Edition., 2009.

Useful Websites

http://en.wikipedia.org/wiki/Systems_biology

www.systemsbiology.org

<http://csbi.mit.edu>

www.nigms.nih.gov/Initiatives/SysBio/

<http://sysbio.med.harvard.edu>

www.genome.duke.edu/centers/csb/

[/www.cdpcenter.org](http://www.cdpcenter.org)

<http://quantbio.princeton.edu>

Research Project Opportunities

Students interested in expanding their learning experiences are invited to consider research projects in IGSB (www.igsb.org) and CCSB (www.chicago-center-for-systems-biology.org) laboratories. There are opportunities for 2010 summer lab rotations and longer-term research initiatives. See Barry Aprison for details.

Presenter & Faculty Mentor	WK & Date	Activities & Assigned Papers
Barry Aprison	1-1/5/10	<i>Review syllabus, discuss program and goals of the course. General introduction and assignment of papers. (Fill out this table.) Class picture.</i>
David Blair	1-1/7/10	Gardner and You
	2-1/12/10	Richard Young, MIT, IGSB/GGSB Seminar, KCBD, Rm 1103, 4-5pm Anderson: Class 5-5:50pm
	2-1/14/10	Ozbudak: Class in Rm 10260 (North Conf. Rm)
Jeremy Tregler	3-1/19/10	Justman
	3-1/21/10	Yu
Vivian Choi	4-1/26/10	Spencer
Russell Becker	4-1/28/10	Chang
	5-2/2/10	Li
Erin Mowers	5-2/4/10	Dai
Patrick Mann	6-2/9/10	Basso
Jeremy Tregler	6-2/11/10	Lee
Patrick Mann	7-2/16/10	Kohanski
Vivian Choi	7-2/18/10	Amity
	8-2/23/10	Chen
	8-2/25/10	Maher
Russell Becker	9-3/2/10	Brass
Erin Mowers	9-3/4/10	Luo
	10-3/9/10	Taylor
<i>Group Discussion</i>	10-3/11/10	<i>Summary; Future Courses & Final Report Due</i>