New Course to be offered Spring 2004
Instructor: Baltazar D. Aguda

***Title*:** Mechanisms and Models of Cellular Regulation

***Course Number**: BE700*

Course catalog description:

Regulatory and control processes in cells are presented from a genetic and biochemical network perspective. Systems analysis of networks include logical (Boolean), deterministic (differential equations), and stochastic approaches. Case studies of gene regulatory networks as well as metabolic, signaling, cell survival, proliferation and death pathways are discussed. Existing modeling platforms of systems biology and bioinformatic pathways databases are introduced.

Specific teaching goals:

A primary goal of this course is to provide students with an integrated view of the regulatory and control mechanisms in a biological cell at the genetic and biochemical levels. This integration is essential for students in engineering and bioinformatics to appreciate the meaning and implications of the exploding fields of genomics, proteomics and other high-throughput data-generating technologies. The *systems viewpoint* emphasized in this course requires a *sufficient overview of the molecular biology* of the cell – a requirement that will be carefully provided by the instructor.

The coverage of this course is admittedly quite broad and the instructor should be aware of the danger that students could be swamped with biological details and end up not learning concrete or tangible research tools. The instructor will emphasize basic and well-developed *modeling tools (mathematical and computational) for analyzing complex regulatory networks* in general, as well as identify research areas that are still open for development. *After sufficient introduction* of the various cellular processes covered in this course, a *case-study teaching approach* (using examples from the recent literature) will be adopted so that students are exposed to the details and rigor of modeling complex systems.

An important goal of this course is to make students aware of the existing and rapidly accumulating bioinformatics and systems biology resources, as well as biotechnological trends. Thus, an important component of this course is a set of invited lectures given by active researchers in the field (see syllabus).

Syllabus:

Week 1: Basic cell biology & levels of cellular regulation

- The cell as a unit of life: components and cell architecture
- Unicellular versus multicellular organisms
- What are the essential cellular processes? The big picture of what is covered in this course: gene expression, metabolism, signaling, cell division, cell death
- Levels in the complexity of gene expression: an overview of the basics
  - The central dogma: DNA, RNA, proteins
  - Transcription, RNA processing, translation, post-translational processes

Week 2: Gene structure & transcription control elements

- Genetics, genomics
- Gene structure and regulatory elements
- Examples of prokaryotic and eukaryotic genomes
- Bioinformatics resources

Weeks 3: Gene regulatory networks (GRNs)

- The *fim* genetic switch in *E. coli* illustrating the dynamic nature of the genome
- The bacteriophage λ lysis/lysogeny switch
- Operons, regulons, stimulons
- Transcriptional network in *S. cerevisiae*

Weeks 4-6: Mathematical modeling and computer simulation of GRNs

- Boolean networks, generalized logical networks
- Nonlinear ordinary differential equations
- Qualitative differential equations
- Stochastic master equations
- Network analysis: stability, bifurcations

Week 7-8: Engineering & control of GRNs

- Perturbation of GRNs: gene knock-outs/knock-ins, chemical genetics, RNAi
- Guest lecturer: try to invite Prof. S. Schreiber of Harvard (chemical genetics)
- Designer gene networks
- Guest lecturer: try to invite Prof. J. Collins of BU

Week 9: Metabolic networks

- Overview of metabolism in cells, metabolic map of E. coli
- Metabolic control analysis
- Metabolic engineering
- Guest lecturer: try to invite Prof. Stephanopoulos of MIT

Week 10: Signal transduction pathways

- Receptor tyrosine kinases, G-protein coupled receptors
- Ultrasensitivity in the MAP kinase cascade
- Proliferative, survival and death pathways
- Guest lecturer: try to invite Prof. Lauffenburger of MIT

Week 11: Cell division and death (apoptosis)

- Models of the yeast cell cycle
- Checkpoints in the mammalian cell cycle
- Modeling apoptosis

Week 12: Platforms of Systems Biology

Whole-cell modeling computer software: E-Cell, Virtual Cell, SBW/SBML(Caltech)
Pathways database systems
Institutes of Systems Biology

Week 13: Pathway inference & pathways databases

Reverse engineering from microarray gene expression data analysis
Bayesian networks
Pathways databases: KEGG, PathDB, EcoCyc, BIND, etc.
Guest lecturers: TBA

Week 14: Biotechnology trends

Proteomics, mass spectrometry, the omics industry
Guest lecturer: try to invite Dr. Stephen Naylor of Beyond Genomics

Week 15: Course summary (1 lecture)

Grading System:

One term paper/project	30%
Homework assignments	20%
One midterm exam	20%
Final exam	30%

***Target audience & Pre-requisites*:**

Graduate students in BME, Bioinformatics; ordinary differential equations and at least one course in computer programming.

Representative References:

Aguda BD. Instabilities in phosphorylation-dephosphorylation cascades and cell cycle checkpoints. Oncogene. 1999 May 6;18(18):2846-51.

Asthagiri A, Lauffenburger D. Bioengineering Models of Cell Signaling. Annual Review of Biomedical Engineering, 2:31-53, 2000.

Bolouri H, Davidson EH. (2002) "Modeling transcriptional regulatory networks", BioEssays 24: 1118-1129.

Bower JM, Bolouri H (Eds.) Computational modeling of genetic and biochemical networks (Computational molecular biology). MIT Press, 2001.

Chen KC, Csikasz-Nagy A, Gyorffy B, Val J, Novak B, Tyson JJ. Kinetic analysis of a molecular model of the budding yeast cell cycle. Mol Biol Cell. 2000 Jan;11(1):369-91.

De Jong H. (2002) "Modeling and simulation of genetic regulatory systems: A literature review", J. Computational Biology 9: 67-103.

Deutsch A (Ed.) Function and regulation of cellular systems: Experiments and models (Mathematics and Biosciences in interaction). Birkhauser (Architectural), August 2003. ISBN 3764369256

Fussenegger M, Bailey JE, Varner J. A mathematical model of caspase function in apoptosis. Nat Biotechnol. 2000 Jul;18(7):768-74. Erratum in: Nat Biotechnol 2001 Feb;19(2):173. Comment in: Nat Biotechnol. 2000 Jul;18(7):717-8.

Gilman A, Arkin AP. (2002) "Genetic 'Code': Representations and dynamical models of genetic components and networks", Annu. Rev. Genomics Hum. Genet. 3:341-369.

Hasty J, McMillen D, Isaacs F, Collins JJ. (2001) "Computational studies of gene regulatory networks: in numero molecular biology", Nature Reviews Genetics 2: 268-279.

Hasty J, McMillen D, Collins JJ. (2002) "Engineered Gene Circuits", Nature 420: 224-230.

Heinrich R, Schuster S. The regulation of cellular systems. Chapman & Hall, 1996.

Ideker T, Galitski T, Hood L. (2001) "A new approach to decoding life: systems biology." Annu. Rev. Genomics Hum. Genet. 2: 343-72.

Koffas M, Roberge C, Lee K, Stephanopoulos G. (1999) "Metabolic engineering", Annu. Rev. Biomed. Eng. 1: 535-57.

Kohane IS, Kho A, Butte AJ. Microarrays for an integrative genomics (Computational molecular biology). MIT Press, 2002. ISBN 026211271X.

McAdams HH, Arkin A. (1998) "Simulation of prokaryotic genetic circuits". Annu. Rev. Biophys. Biomol. Struct. 27: 199-224.

McAdams HH, Arkin A. (2000) "Towards a circuit engineering discipline". Curr. Biol. 10: R318-20.

Ouzounis CA, Karp PD. (2000) Global properties of the metabolic map of Escherichia coli. Genome Res. 2000: 568-678.

Palsson B. (2000) "The challenges of in silico biology." Nat. Biotechnol. 18: 1147-50.

Ptashne M. A Genetic Switch – Phage Lambda and Higher Organisms. 2nd Ed. Cell Press & Blackwell Scientific Publications, c1986.

Ptashne M, Gann A. Genes & Signals. Cold Spring Harbor Lab Press, c2002.

Rao CV, Arkin AP. (2001) "Control motifs for intracellular regulatory networks." Annu. Rev. Biomed. Eng. 3: 391-419.

Schilling C, S. Schuster, B. Palsson and R. Heinrich. Metabolic Pathway Analysis: Basic Concepts and Scientific Applications in the Post-genomic Era. Biotechnology Progress, 15:296-303, 1999.

Smolen P, Baxter DA, Byrne JH. (2000) "Modeling transcriptional control in gene networks – methods, recent results, and future directions." Bull. Math. Biol. 62: 247-92.

Torres NV, Voit EO. Pathway analysis and optimization in metabolic engineering. Cambridge U.P., 2002.

Tomita M, Hashimoto K, Takahashi K, Simizu TS,Matsuzaki Y et al. (1999) "E-CELL: software environment for whole-cell simulation", Bioinformatics 15: 72-84.

Tyson JJ, Csikasz-Nagy A, Novak B. The dynamics of cell cycle regulation. Bioessays. 2002 Dec;24(12):1095-109.