Engineering Genetic Circuits

Chris J. Myers

Lecture 0: Preface
Engineering is the art or science of making practical.
One man’s “magic” is another man’s engineering.
Biology is now both a lab-based science and an information science.

Biologists have had to draw assistance from those in mathematics, computer science, and engineering.

Result was development of bioinformatics and computational biology.

Major goal is to extract new biological insights from large and noisy sets of data generated by high throughput technologies.

Must create and maintain databases with massive amounts of data.

Must be able to efficiently access, submit, and revise this data.

Latest software must even analyze and interpret this data.

In this course, we use the term bioinformatics to refer to the analysis of static data such as sequence analysis of DNA and protein sequences, techniques for finding genes or evolutionary patterns, and cluster analysis of microarray data.

Bioinformatics algorithms are not covered in this course.
The focus of this course is the modeling, analysis, and design methods for *systems biology*.

Systems biology is the study of the mechanisms underlying complex molecular processes as integrated into systems or pathways made up of many interacting genes and proteins.

Concerned with the analysis of *dynamic* models.

Made possible by new experimental methods such as:
- cDNA microarrays and oligonucleotide chips.
- Mass spectrometric identification of gel-separated proteins.
- 2-hybrid systems.
- Genome-wide location analysis (ChIP-to-chip)
Systems Biology (cont)

- Systems biology involves:
  - Collection of large experimental data sets,
  - Constructing mathematical models from this data,
  - Designing software to accurately and efficiently analyze these models *in silico* (i.e., on a computer),
  - Comparing numerical simulations with the experimental data, and
  - Designing new synthetic biological systems.

- Ultimate goal is to develop methods which can give reasonable predictions of experimental results.

- While it will never replace experimental methods, may help experimentalists make better use of their time.

- Also may gain insight into mechanisms used by these biological processes which may not be obtained by experiments.

- Eventually, may be possible that they could have substantial impact on our society such as aiding in drug discovery.
Biological Networks

- **Metabolic networks** are enzymatic processes that transform food into energy, and perform both biosynthesis and biodegradation.

- **Protein networks** are communication and signaling networks which are composed of basic reactions between two or more proteins.

- **Genetic regulatory networks**, or **genetic circuits**, regulate gene expression at many molecular levels.

- The focus of this course are methods for modeling, analysis, and design of genetic circuits.
Standards for sequence data were absolutely essential.

For systems biology, standard data formats are being developed.

One is the *systems biology markup language* (SBML).

XML-based language to represent chemical reaction networks.

All networks described in this lecture can be reduced to a set of bio-chemical reactions.

SBML model consists of a list of the species and their reactions.

A reaction includes a list of reactants, products, and modifiers.

Also includes a mathematical description of the kinetic rate law governing the dynamics of this reaction.

SBML is ugly, but GUIs have been developed.
Another essential item in the genomic-age was the development of biological databases.

These provide repositories for storing large bodies of data that can be easily updated, queried, and retrieved.

Databases store many things ranging from nucleotide sequences within GenBank to biomedical literature at PubMed.

Recently, a database for SBML models has been started.
Last essential piece is tools.

Excellent list of bioinformatics tools at the NCBI website.

List of systems biology tools that support SBML can be found at the SBML website.

The remainder of this course concentrates on describing the methods used by tools being developed for systems and synthetic biology.
Engineers have experience in modeling and analyzing systems. Can take a circuit view of a genetic circuit (Science1995). Collaborations needed between engineers and biologists. **Goal of this course is to facilitate these collaborations.**
The Engineering Approach

Set of Experiments → Perform Experiments → Experimental Data → Learn Model → Models → Construct Experiments

Genetic Circuit ← Insert into Host ← Plasmid

Construct Plasmid ← DNA Sequence

Learn Model ← Biological Knowledge → SBML Model

TechMap ← Logic Equations

Library ← HDL

Abstraction/Simulation → Simulation Data → Synthesis

Construct Experiments ← Simulation Data

Modeling → Analysis → Design
Chapter 2: Learning Models

Set of Experiments → Perform Experiments → Experimental Data

Learn Model → Models → Construct Experiments

Genetic Circuit

Insert into Host → Plasmid → Construct Plasmid → DNA Sequence

Biological Knowledge

Learn Model → SBML Model → Simulation Data

Abstraction/Simulation → Simulation Data

Models

Construct Experiments

HDL

Logic Equations

Synthesis

TechMap

Library

Analysis

Design

Modeling
Chapter 3: Differential Equation Analysis

Set of Experiments → Perform Experiments → Experimental Data → Learn Model → Models → Construct Experiments

Genetic Circuit ← Insert into Host ← Plasmid ← Construct Plasmid

DNA Sequence ← DNA Sequence → TechMap

Abstraction/Simulation → Simulation Data

SBML Model ← SBML Model

Models ← Models

Construct Experiments ← Construct Experiments

Biochemical Knowledge

Logic Equations ← Logic Equations

Library

Synthesis ← Synthesis

HDL

Design

Analysis

Modeling
Chapter 4: Stochastic Analysis

Set of Experiments → Perform Experiments → Experimental Data → Learn Model → Models → Construct Experiments

Genetic Circuit ← Insert into Host ← Plasmid

Biological Knowledge ← DNA Sequence

SBML Model ← TechMap

Abstraction/Simulation ← Logic Equations

Simulation Data ← Synthesis

Construct Plasmid ← Library

Simulation Data → Synthesis → HDL

Models → Construct Experiments

Analysis

Design

Modeling
Chapter 5: Reaction-Based Abstraction

Set of Experiments → Perform Experiments → Experimental Data → Learn Model → Models → Construct Experiments

Genetic Circuit ← Insert into Host → Plasmid

Biological Knowledge → DNA Sequence → TechMap → Library

SBML Model ← Abstraction/Simulation → Simulation Data

Construct Plasmid → Models

Synthesis → HDL

Modeling → Analysis → Design
Chapter 6: Logical Abstraction

Set of Experiments → Perform Experiments → Experimental Data → Learn Model → Models → Construct Experiments

Genetic Circuit ← Insert into Host → Plasmid → Construct Plasmid → DNA Sequence → TechMap → Library

Biological Knowledge → SBML Model → Abstraction/Simulation → Simulation Data → Synthesis → HDL

Models → Constructs Experiments

Modeling → Analysis → Design