Introduction to Systems Biology: Constraint-based Metabolic Reconstructions & Analysis
Lecture Learning Objectives

Each student should be able to:

- Explain the limitations of constraint-based modeling
- Explain the basic topics to be covered in the course
- Understand and use the course website
- Explain the course expectations
- Explain the grading process
- Explain the expectations for the course project
Course Introduction

- Content Overview
- Course Website
- Course Learning Process
- Course Grading & Expectations
Types of Biological Networks

Metabolism

Regulation

Signaling

B. Palsson, Lectures from Systems Biology: Simulation of Dynamic Network States, Chapter 1
Constraint-based Modeling

- Model cell steady-state phenotypes during exponential growth phase.
  - Can model the different phenotypes that can exist during the exponential growth phase.
  - Can understand the capabilities of each phenotype.
  - Can identify and modify cellular pathways to favor specific bioproduct producing phenotypes.
  - Constraint-based models do not model transitions between phenotypes.
  - Most genome-scale models do not include the genes required for the stationary phase (proteases, etc.).
  - Most genome-scale models do not include the complete transcription and translation pathways.
- The biomass function represents the average metabolic load required during exponential cell growth.
  - The biomass function represents the average percentages of the component parts (amino acids, nucleotides, energy, etc.) that are included in 1 gm of cell biomass.

Goal: Identify phenotypes that can exist in exponential growth phase.
The 'Phylogeny' of Constraint-based Modeling Methods

Course Content

• Course Introduction
• Flux Balance Analysis
• Cobra Toolbox & Visualization Tools
• Robustness Analysis & Phenotype Phase Plane Analysis
• Flux Variability Analysis & Parsimonious Flux Balance Analysis
• Gene/Reaction Knockouts
• Randomized Sampling
• Bioproduct Production
• Dynamic Flux Balance Analysis
• Transcriptional Regulatory Networks
• Large Metabolic Reconstructions
• Genome-scale Metabolic Reconstructions
• Tissues
Metabolic Models

Flux Balance Analysis


Cobra Toolbox & Visualization Tools

Matlab Cobra Toolbox

- Flux Optimization
- Robustness Analysis
- Phenotype Phase Plane Analysis
- Flux Variability Analysis
- Gene Additions & Knockouts
- Production Envelopes
- More Tools

Load Models
SBML, Excel, Matlab

Matlab Code
M-Files

Output Maps
Graphical Output
Numerical Output
Save Models

Robustness Analysis & Phenotype Phase Plane Analysis
Flux Variability Analysis & Parsimonious Flux Balance Analysis

Flux Variability Analysis

Parsimonious Flux Balance Analysis
Randomized Sampling

Gene/Reaction Knockouts

'ACKr', 'GLUDy', 'GND'

Ethanol

Formate

(0.1772, 17.31)

Ethanol Secretion

Use Glutamine to Produce Glutamate

NADPH Production

Reduce NADPH

Block Acetate Pathway

Secreting Formate

ATP Production
Dynamic FBA & Dynamic Regulatory FBA

Dynamic FBA

Dynamic Regulatory FBA
Purpose: Identify phenotypes that can exist in exponential growth phase.
Large Metabolic Reconstructions

A GEnome scale Network Reconstructions (GENREs) serves as a structured knowledge base of established biochemical facts, while a GEnome scale Models (GEMs) is a model which supplements the established biochemical information with additional (potentially hypothetical) information to enable computational simulation and analysis.

Tissues

'Google Map' of Human Metabolism

Opportunities Provided by Genome-scale Metabolic Reconstructions

Course Introduction

• Content Overview

• Course Website

• Course Learning Process

• Course Grading & Expectations
Course Website

http://systemsbiology.usu.edu
Course Introduction

- Content Overview

- Course Website

→ Course Learning Process

- Course Grading & Expectations
Course Learning Objectives

Each student should be able to:

• Explain flux balance analysis
• Explain the basic *E.coli* core metabolic model
• Demonstrate the ability to effectively use the “Cobra Toolbox”
• Explain and demonstrate robustness analysis
• Explain and demonstrate flux variability analysis
• Explain and demonstrate phenotype phase plane analysis
• Explain and demonstrate parsimonious analysis
• Explain and demonstrate dynamic flux balance analysis
• Explain and demonstrate dynamic regulatory flux balance analysis
• Explain and demonstrate the process of determining gene knockouts for optimizing bioproduct production
• Explain and demonstrate the process of optimizing bioproduct production
• Explain and demonstrate constraint-based modeling using randomized sampling
• Explain the process of creating genome-scale metabolic reconstructions
• Explain the creation of tissue models from genome-scale metabolic reconstructions
Course Learning Process

• Weekly class periods
  ✓ Attend class (attendance is expected)
  ✓ Tuesdays will typically be lectures.
  ✓ There will be a five minute quiz at the beginning of every lecture.
    ▪ The quizzes will only cover, 1) the material presented in the previous lecture and/or 2) some of the reflective questions from the webpage associated with the previous lecture.
    ▪ The two lowest quizzes will be dropped at the end of the semester.
  ✓ Thursdays will typically be labs covering the material learned in previous lectures.
    ▪ A first draft of the code you have written for each lab will be due at the beginning of that lab
    ▪ All lab assignments should be turned in at the beginning of class the following Thursday.
    ▪ There will be no late labs accepted!

• Class project
  ✓ Each student must complete a class project.
  ✓ A paper and presentation will be required for each project
Course Introduction

• Content Overview

• Course Website

• Course Learning Process

⇒ • Course Grading & Expectations
Grading

Labs 40%
Quizzes 10%
Project
  Paper 30%
  Presentation 20%
Teacher Expectations

- Estimated homework for a B student
  - Approximately 3 hours out-of-class work for every hour in class
- All assignments and materials will be provided through the course website.
- Computer compatibility is your responsibility.
- Students are expected to attend every class.
- Students will check the course website at least two times per week.
- Students are expected to know (or re-learn on their own) material covered in prerequisite courses.
Course Introduction

- Content Overview
- Course Website
- Course Learning Process
- Course Grading & Expectations