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
- Know 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.

Purpose: Identify phenotypes that can exist in exponential growth phase
Course Content

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

- **Constraint-based Metabolic Reconstructions & Analysis**
  - **Lesson: Introduction**
  - **BENG 5500/6500 Utah State University**

**Flux Balance Analysis** is a systems biology approach that models the metabolic network of an organism. It is based on the principles of mass balance and thermodynamics, and it uses stoichiometric and thermodynamic constraints to predict the possible metabolic fluxes of a cell.

- **a** Genome-scale metabolic reconstruction
- **b** Mathematically represent metabolic reactions and constraints
- **c** Mass balance defines a system of linear equations
- **d** Define objective function ($Z = c_1v_1 + c_2v_2 + ...$) To predict growth, $Z = v_{\text{biomass}}$
- **e** Calculate fluxes that maximize $Z$


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**Diagram**
- Reaction 1: $A \leftrightarrow B + C$
- Reaction 2: $B + 2C \rightarrow D$
- Reaction $n$
- Stoichiometric matrix $S$
- Fluxes: $v$
- Solution space defined by constraints

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**Notes**
- Constraint-based models are used to understand metabolic networks.
- They are based on the stoichiometry of the reactions and thermodynamic principles.
- The goal is to predict the flux distribution within the network that maximizes an objective function, typically related to growth.

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**References**
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

SBML, Excel
Load Models

M-Files
Matlab Code

Output Maps
Numerical Output
Graphical 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)

NADPH Production

Use Glutamine to Produce Glutamate

ATP Production

Block Acetate Pathway

Reduce NADPH

Extracellular Protons

Secreting Formate
Dynamic FBA & Dynamic Regulatory FBA

Dynamic FBA

Dynamic Regulatory FBA
Purpose: Identify phenotypes that can exist in exponential growth phase

Bioprocess Production

Desired Operating Region

- Cell Density (OD)
- Time (hours)
- Stationary Phase
- Decline Phase
- Death Phase
- Log (Exponential) Phase
- Lag Phase
- Acceleration Phase
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
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.
  • Thursdays will typically be labs covering the material learned in previous lectures.

• 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  50%

Project
  Paper  30%
  Presentation  20%
Expectations

- Estimated homework for a B student
  - ~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 three times per week.
- Students are expected to know (or re-learn on their own) material covered in prerequisite courses.
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