

IBS/BMB 7141: Computational Modeling of Cellular Metabolism

Course Information:

Credits: 3

Class type: synchronous zoom sessions every Monday and Wednesday from 2:30 to 4:30.

Class recordings: available on Canvas

Course Description:

Modern medicine increasingly relies on computational tools to analyze and model complex biological systems, from understanding disease mechanisms to optimizing drug interventions. This course introduces medical and graduate students to computational systems biology, focusing on metabolic network analysis using Python-based tools.

Students will learn to apply kinetic modeling (KM) and constraint-based modeling (CBM) to simulate biochemical reactions, study metabolic diseases, and predict therapeutic outcomes. The course will emphasize real-world biomedical applications, including cancer metabolism, metabolic syndromes (e.g., diabetes, obesity), infectious diseases, drug discovery, and systems pharmacology.

Through hands-on coding exercises, students will explore the mathematical techniques that are essential for modeling metabolic networks in health and disease. By the end of the course, students will be equipped to develop computational models for personalized medicine, precision nutrition, and host-pathogen interactions — key areas in modern biomedical research.

Learning Outcomes:

By completing this course, students will be able to:

1. Develop proficiency in Python programming for biological and medical data analysis.
2. Apply linear algebra and optimization techniques to analyze metabolic networks.
3. Implement kinetic modeling to simulate enzymatic reactions and pharmacokinetic / pharmacodynamic (PKPD) models.
4. Utilize constraint-based modeling (CBM) to study metabolic diseases and predict therapeutic interventions.
5. Perform metabolic network reconstruction and flux balance analysis (FBA) using COBRA (COntstraint Based Reconstruction and Analysis) methods to explore disease metabolism and microbial interactions.

- Investigate metabolic perturbations in human physiology, including host-pathogen and host-drug interactions.

Course Prerequisites:

- Basic knowledge of algebra and univariate calculus.
- No prior programming experience required; introductory Python programming will be covered

Course Syllabus:

Module 1: Introduction to Python Programming

- Basic Python objects (lists, arrays, dictionaries)
- Libraries
- Loops
- Functions
- Classes

Module 2: Linear Algebra and Optimization in Biomedical Modeling

- Matrix operations, eigenvalues and eigenvectors, Singular Value Decomposition (SVD)
- Linear programming and optimization

Module 3: Simulation of Biochemical and Enzymatic Reactions

- Modeling metabolic pathways involved in diseases (e.g., glycolysis in cancer)

Module 4: Metabolic Control Analysis (MCA)

- Reductionist vs. Systems theory
 - Regulation and control
 - Time scales
 - Metabolic Steady states
- Metabolic Control Analysis
 - Flux Control Coefficients
 - The Summation theorem
 - Metabolites effects and Elasticities
 - The Connectivity theorem
 - Response Coefficients
- Conclusion: MCA vs. traditional approaches

Module 5: Kinetic Modeling of Drug Metabolism and Disease Progression

- Pharmacokinetics/pharmacodynamics (PKPD) modeling for drug dosing strategies. This module will include hands-on experience with two Python-based tools for PKPD:

PySB (Python Systems Biology):

- Best for Modeling signaling pathways and drug-target interactions in PKPD:
 - Enables rule-based modeling of biochemical systems.

- Can simulate drug-receptor binding dynamics.
- Integrates with ODE solvers and parameter estimation tools.

PKSim and MoBi (via Python API)

Best for Comprehensive PKPD modeling:

- Can simulate drug absorption, distribution, metabolism, and excretion (ADME).
- Models species-specific and tissue-specific pharmacokinetics.
- Python Integration: Uses Open Systems Pharmacology Suite with Python.

Module 6: Constraint-Based Modeling (CBM) of Cellular Metabolism

- Principles of Flux Balance Analysis (FBA).

Module 7: Metabolic Network Reconstruction and Precision Medicine

- Computational reconstruction of human metabolic pathways. The RECON metabolic model of human metabolism.
- COBRA (Constraints Based Reconstruction and Analysis) methods for cancer and metabolic disorders.
- Applications in personalized medicine and nutrition (Example Study: Tumor-specific Genome-Scale Metabolic Models (GSMs) are used to predict vulnerabilities in cancer metabolism. CBM can be applied to patient-derived genomic data to simulate individualized cancer metabolism, leading to personalized treatment strategies)
- Computational Drug Repurposing for Cancer Therapy (Computational approaches use metabolic modeling to screen for existing drugs that could inhibit cancer growth. Example Study: Identifying FDA-approved drugs that target metabolic enzymes upregulated in cancer cells.)

This module will include hands-on experience with popular Python-based tools (COBRApy, COBRAme, ESCHER) for FBA and the representation of metabolic pathways.

Module 8: Systems Biology Approaches to Infectious Diseases

- Host-pathogen metabolic interactions: (i.e., malaria, tuberculosis)
- Drug resistance modeling in bacterial and viral infections

Module 9: Final Project - Metabolic Modeling of Cancer or Infectious Disease to Identify Therapeutic Targets

Students, individually or in groups, will carry out a Final Project that will combine systems biology, computational modeling, and biomedical applications. The project will use real-world datasets and Python tools applicable to drug discovery and precision medicine. Students will choose between cancer or infectious disease based on their interests.

Project Overview:

Students will develop and analyze a constraint-based metabolic model using Python-based tools (COBRApy or CBMPy) to simulate metabolism in cancer cells or a pathogen (e.g., *Mycobacterium tuberculosis*, *Plasmodium falciparum*). The goal is to predict metabolic vulnerabilities and propose potential drug targets.

Project Steps:

1. Choose a Disease System:
 - Cancer: Model the metabolism of a specific cancer type (e.g., lung cancer, glioblastoma).
 - Infection: Model host-pathogen interactions (e.g., tuberculosis, malaria).
2. Reconstruct a Metabolic Network:
 - Obtain genome-scale metabolic models (GEMs) from repositories like BIGG Models or BioModels Database.
 - Use COBRApy to load and analyze the network.
3. Perform Flux Balance Analysis (FBA):
 - Simulate metabolic fluxes under normal and diseased conditions.
 - Identify bottleneck reactions essential for cell survival.
4. Simulate Drug Inhibition or Gene Knockouts:
 - Implement single or multiple gene knockouts to assess their effect on metabolic function.
 - Identify potential drug targets that selectively inhibit disease metabolism without harming normal cells.
5. Compare Host and Pathogen Metabolism (Optional for Infectious Diseases):
 - Identify nutrient dependencies that the pathogen exploits from the host.
 - Predict strategies to starve the pathogen while preserving host metabolism.
6. Visualize and Interpret the Results:
 - Generate flux maps to show how metabolism changes under different conditions (i.e., use ESCHER to visualize metabolic maps)
 - Use Python visualization libraries (Matplotlib, Seaborn) to create plots comparing metabolic flux distributions.
7. Report Findings and Clinical Relevance:
 - Discuss how your findings could guide drug discovery or metabolic therapy.
 - Suggest future directions for experimental validation.

Expected Deliverables:

- Python scripts for model simulation and analysis.
- Graphs/figures illustrating metabolic fluxes and knockout effects.
- A written report (~3-5 pages) summarizing methodology, results, and clinical significance.
- Optional: A short presentation summarizing findings.

Module 10: Final Exam

The final exam will test students' comprehension of key concepts, mathematical foundations, and hands-on computational skills. Three types of questions will be included:

Conceptual Questions (30%)

Will assess students' understanding of fundamental principles.

Example Questions:

1. (Multiple Choice) What is the main advantage of Flux Balance Analysis (FBA) compared to kinetic modeling?
 - A. It requires fewer parameters and experimental data
 - B. It provides exact reaction rates at all time points
 - C. It does not require optimization techniques
 - D. It can model dynamic systems in real-time

2. (Short Answer) Explain why gene essentiality analysis is useful in drug discovery using metabolic models.
3. (True/False) Linear programming is used in Constraint-Based Modeling (CBM) to solve underdetermined metabolic systems. Explain your reasoning.

Mathematical & Theoretical Problems (30%)

Will evaluate students' ability to apply mathematical principles to metabolic modeling.

Example Problems:

1. (Linear Algebra) Given the following stoichiometric matrix S, determine whether the system has a unique solution, infinite solutions, or no solution.

$$S = \begin{bmatrix} 1 & -1 & 0 \\ 0 & 1 & -1 \\ 1 & 0 & -1 \end{bmatrix}$$

Find the null space of S and interpret its biological meaning.

2. (Optimization in FBA)
 - Define the objective function for biomass production in an FBA problem.
 - If a reaction in the metabolic network has flux constraints $0 \leq v_1 \leq 10$ and the optimal solution suggests $v_1 = 0$, what biological interpretation can you infer?

Hands-On Computational Challenge (Python-Based) (40%)

Will test students' ability to implement and analyze metabolic models using Python.

Example Task: Simulate a Small Metabolic Network Using COBRApy

- Students will be given a simple metabolic model (Stoichiometric Matrix S and Reaction Bounds) in Python.
- Students will have to:
 1. Load the metabolic model using COBRApy
 2. Perform Flux Balance Analysis (FBA)
 3. Identify the limiting metabolic reactions
 4. Perform a single-gene knockout simulation and analyze its effect on biomass production

Course Grading

Final Project (50%) + Final Exam (50%)

Who Should Take This Course?

- Medical students interested in systems medicine and computational approaches
- Graduate students in biomedical sciences, pharmacology, and bioinformatics
- Clinicians and researchers interested in modeling disease metabolism and drug action