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

Lecture Learning Objectives

Each student should be able to:

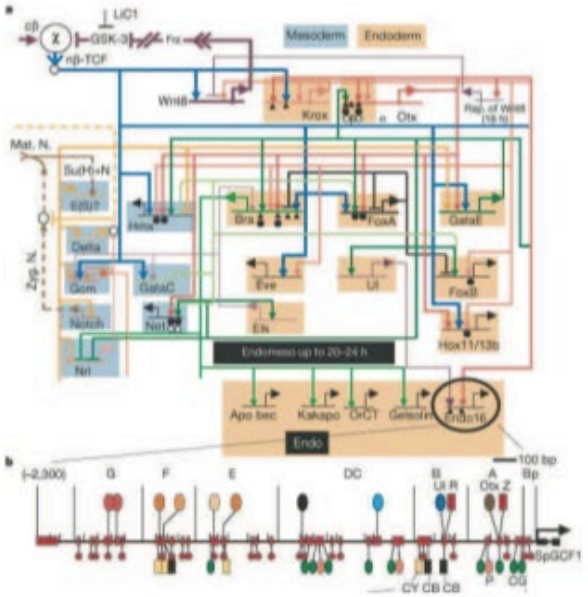
- Explain the limitations of constraint-based modeling
- Explain the basic topics to be covered in the course
- Understand and use the course website
- Explain the course expectations
- Explain the grading process
- Explain the expectations for the course project

Course Introduction

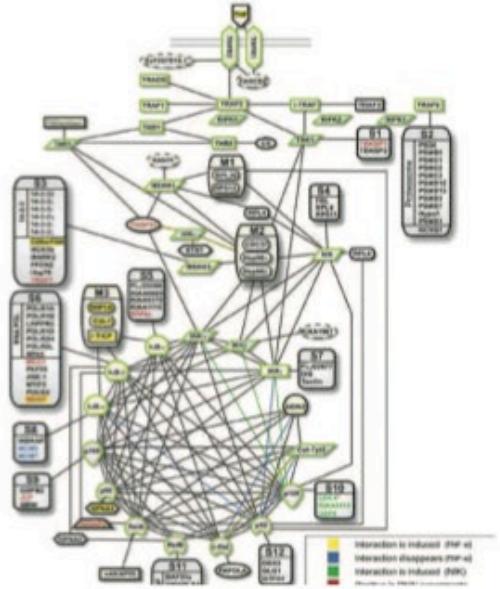
- Content Overview
- Course Website
- Course Learning Process
- Course Grading & Expectations

Types of Biological Networks

Metabolism



Regulation

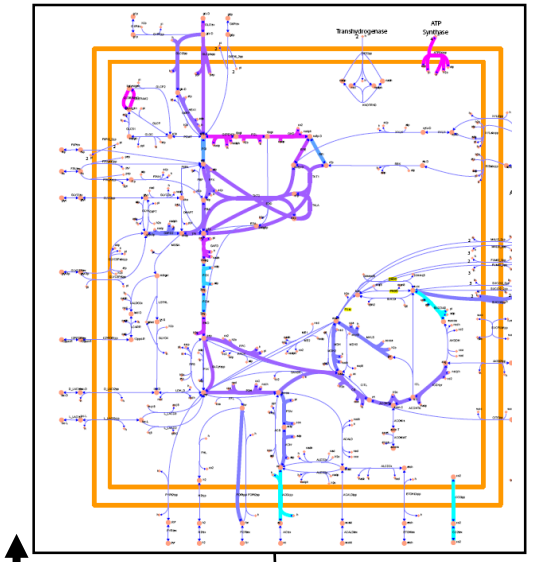


Signaling

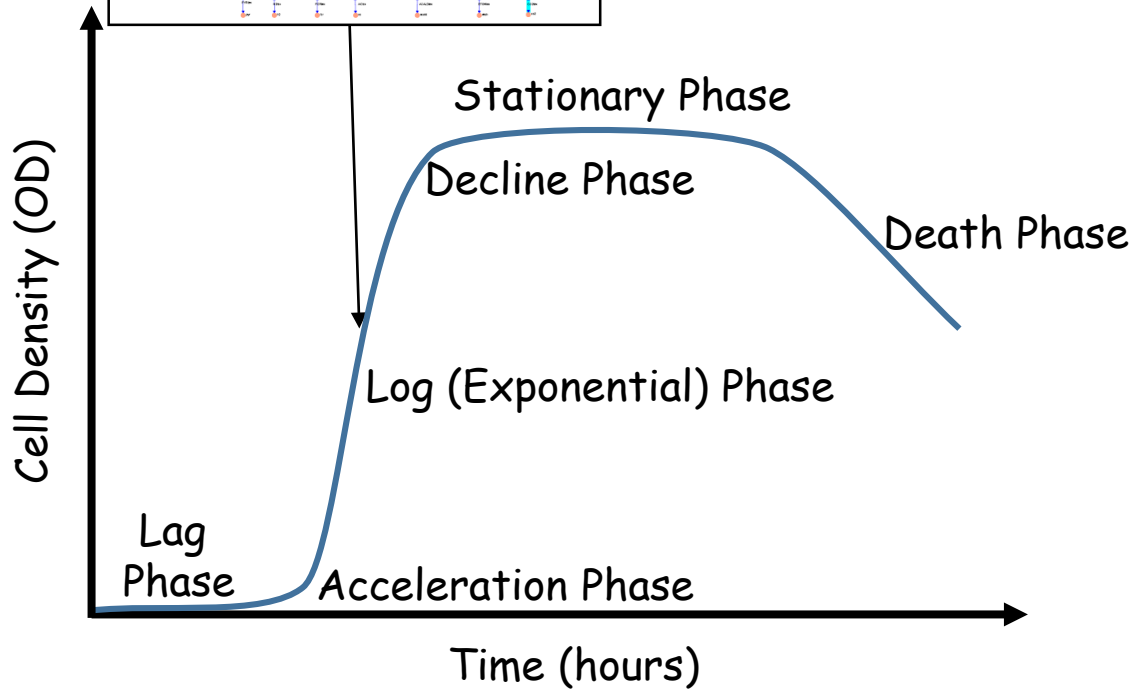
B. Palsson, Lectures from Systems Biology: Simulation of Dynamic Network States, Chapter 1

Constraint-based Modeling

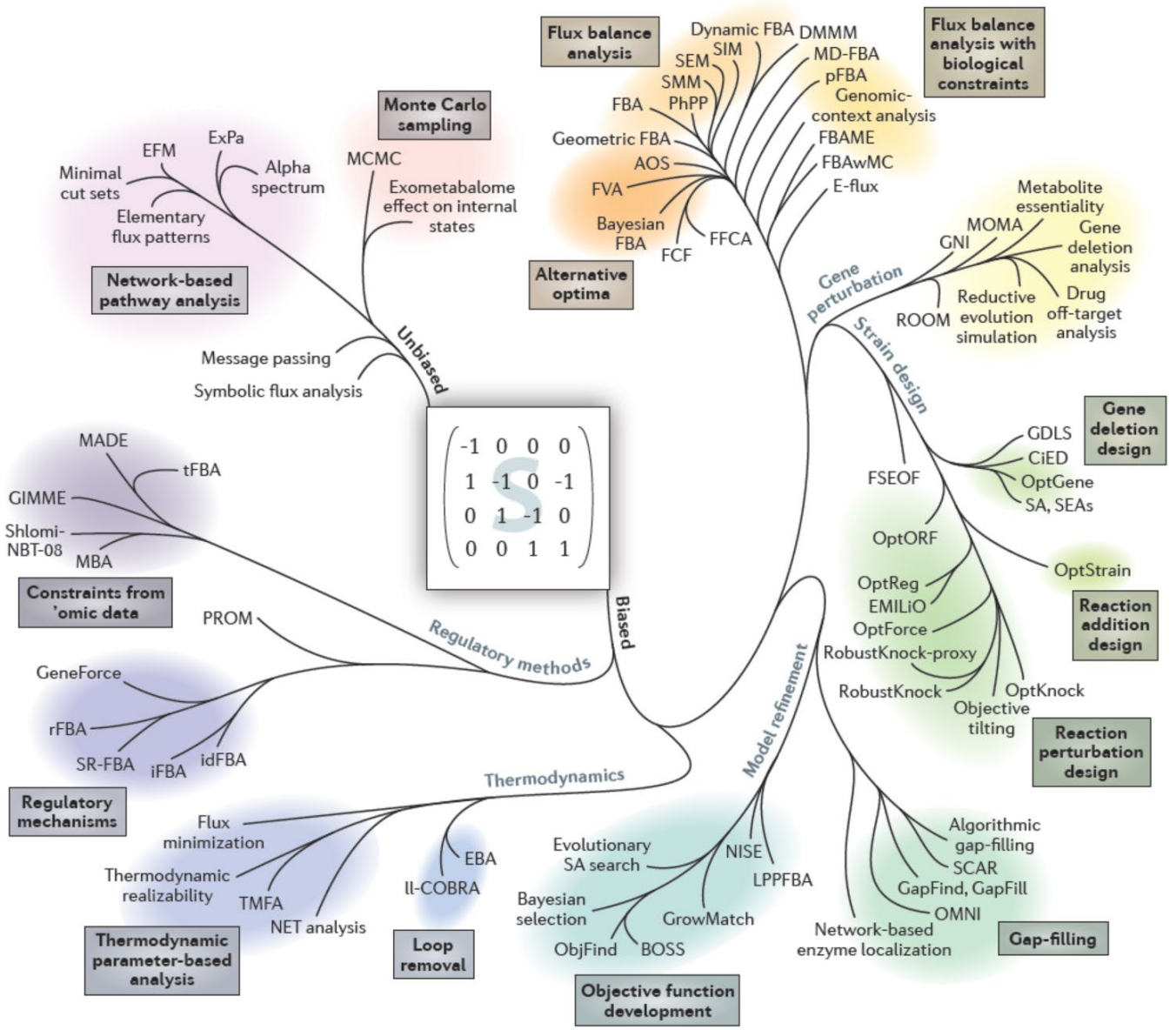
- Model cell steady-state phenotypes during exponential growth phase.
  - ✓ Can model the different phenotypes that can exist during the exponential growth phase.
  - ✓ Can understand the capabilities of each phenotype
  - ✓ Can identify and modify cellular pathways to favor specific bioproduct producing 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.



Purpose: Identify phenotypes that can exist in exponential growth phase



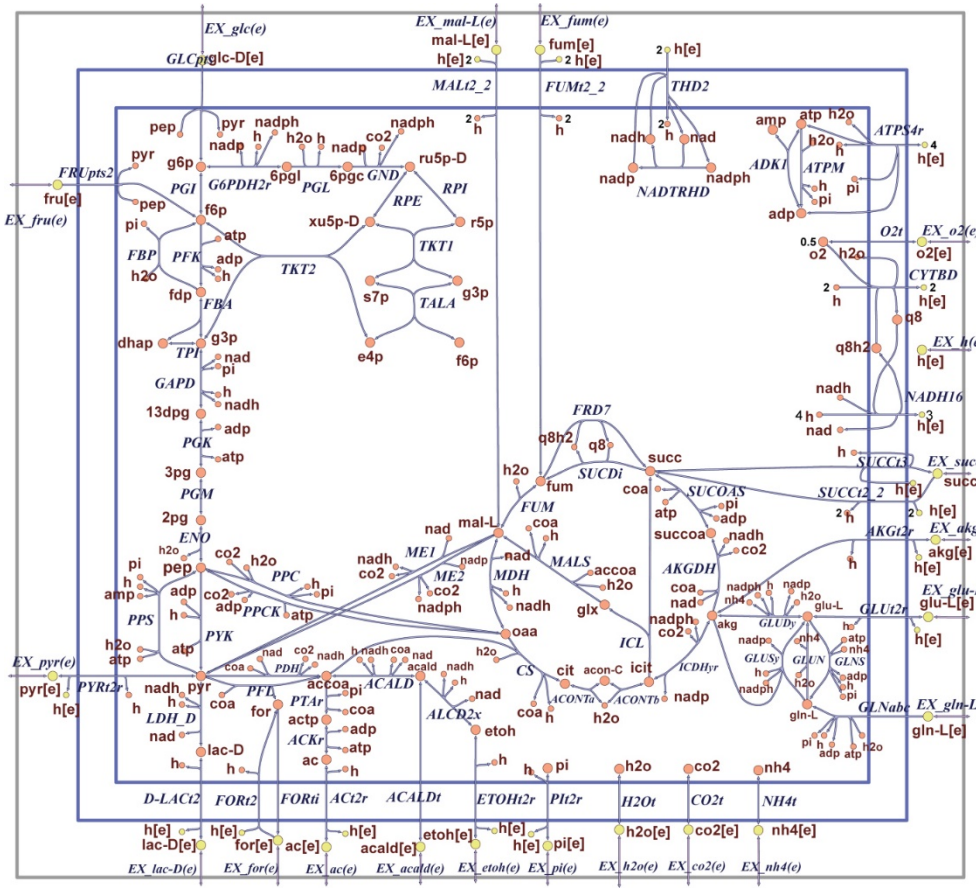
The 'Phylogeny' of Constraint-based Modeling Methods



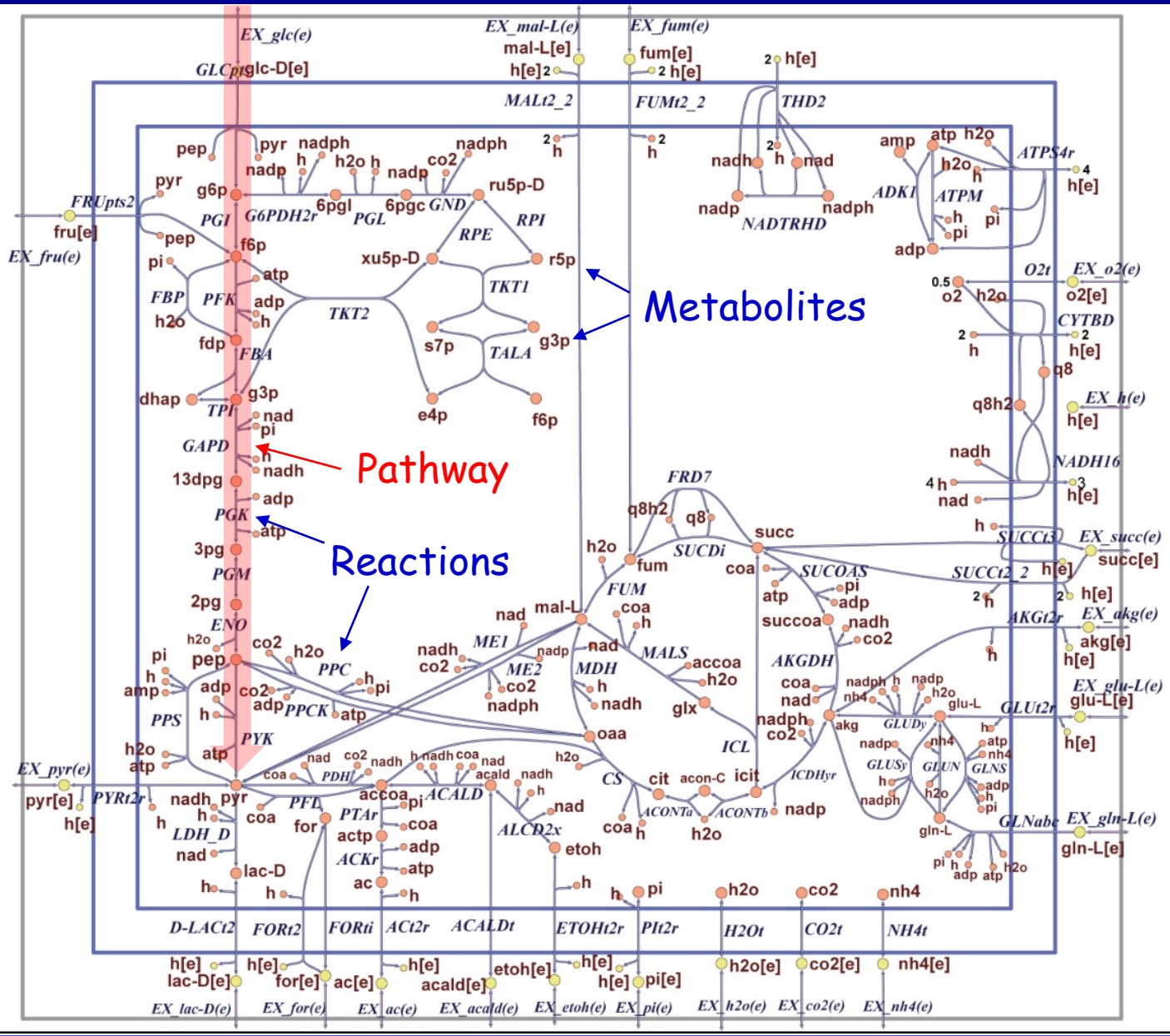
Lewis, N. E., H. Nagarajan, et al. (2012). "Constraining the metabolic genotype-phenotype relationship using a phylogeny of in silico methods." Nature reviews. Microbiology 10(4): 291-305.

Course Content

- Course Introduction
- Flux Balance Analysis
- Cobra Toolbox v.3.0
- Robustness Analysis & Phenotype Phase Plane Analysis
- Flux Variability Analysis & Parsimonious Flux Balance Analysis
- Gene/Reaction Knockouts
- Randomized Sampling
- Dynamic Flux Balance Analysis
- Transcriptional Regulatory Networks
- Bioproduct Production

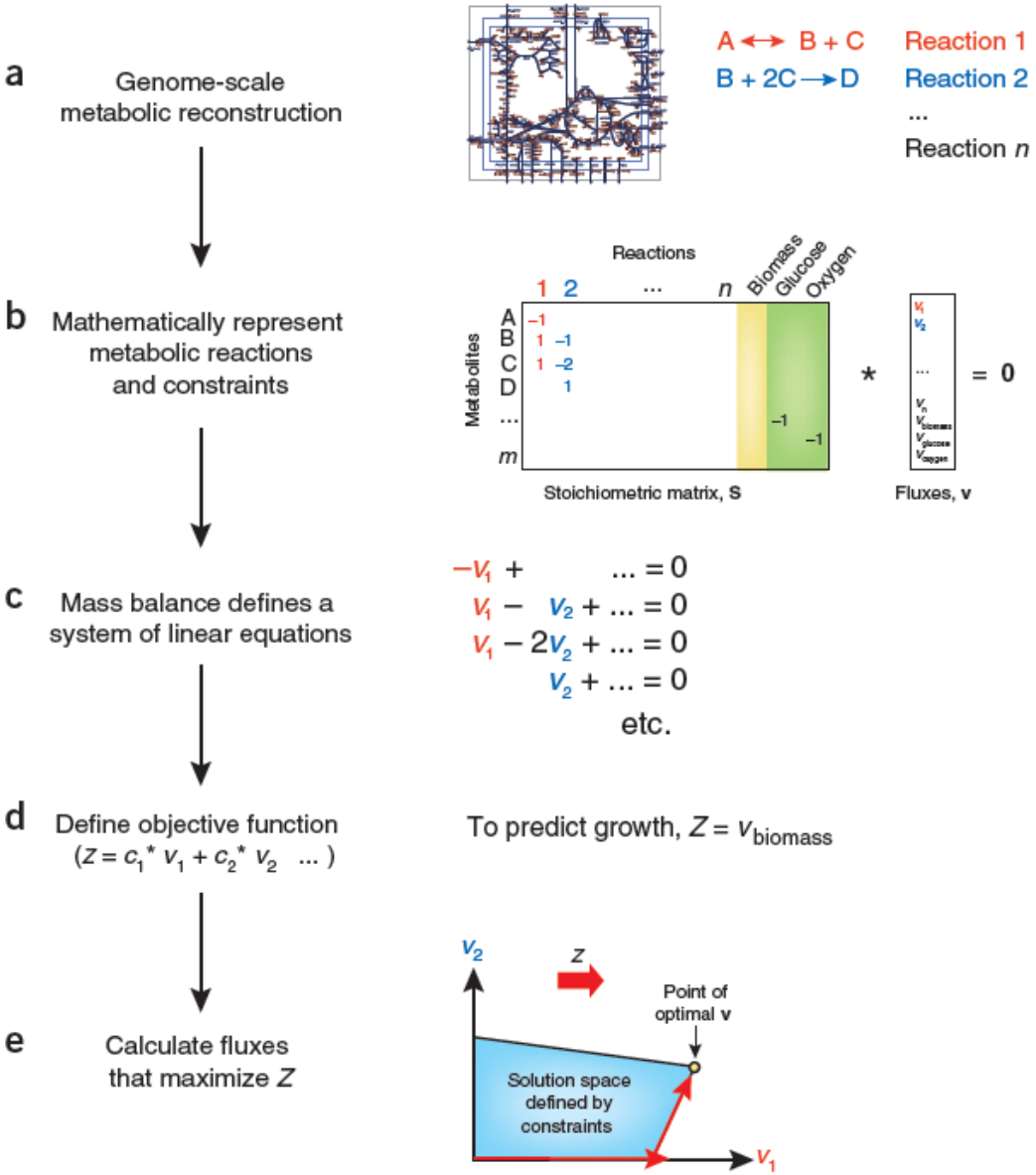


Metabolic Models



Orth, J. D., I. Thiele, et al. (2010). "What is flux balance analysis?" Nature biotechnology **28(3): 245-248.**

Flux Balance Analysis



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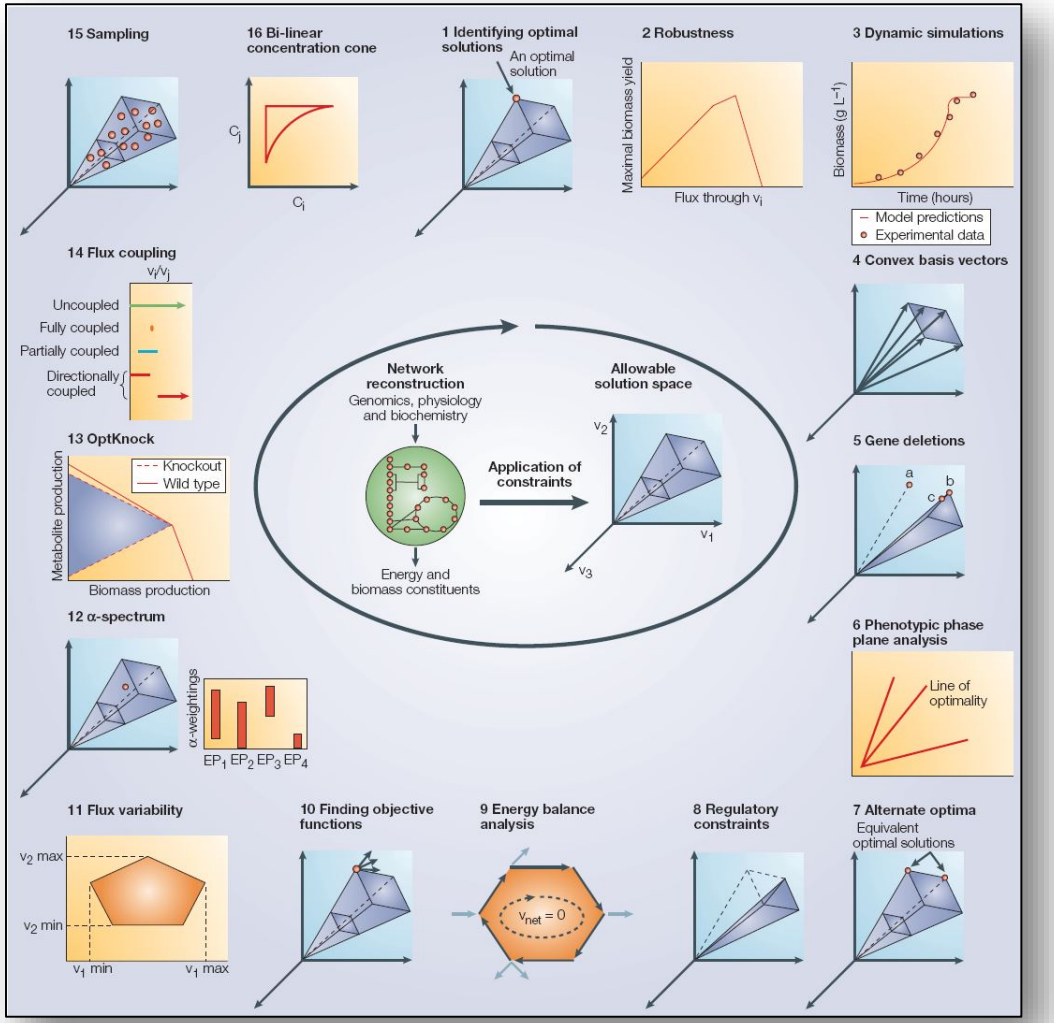
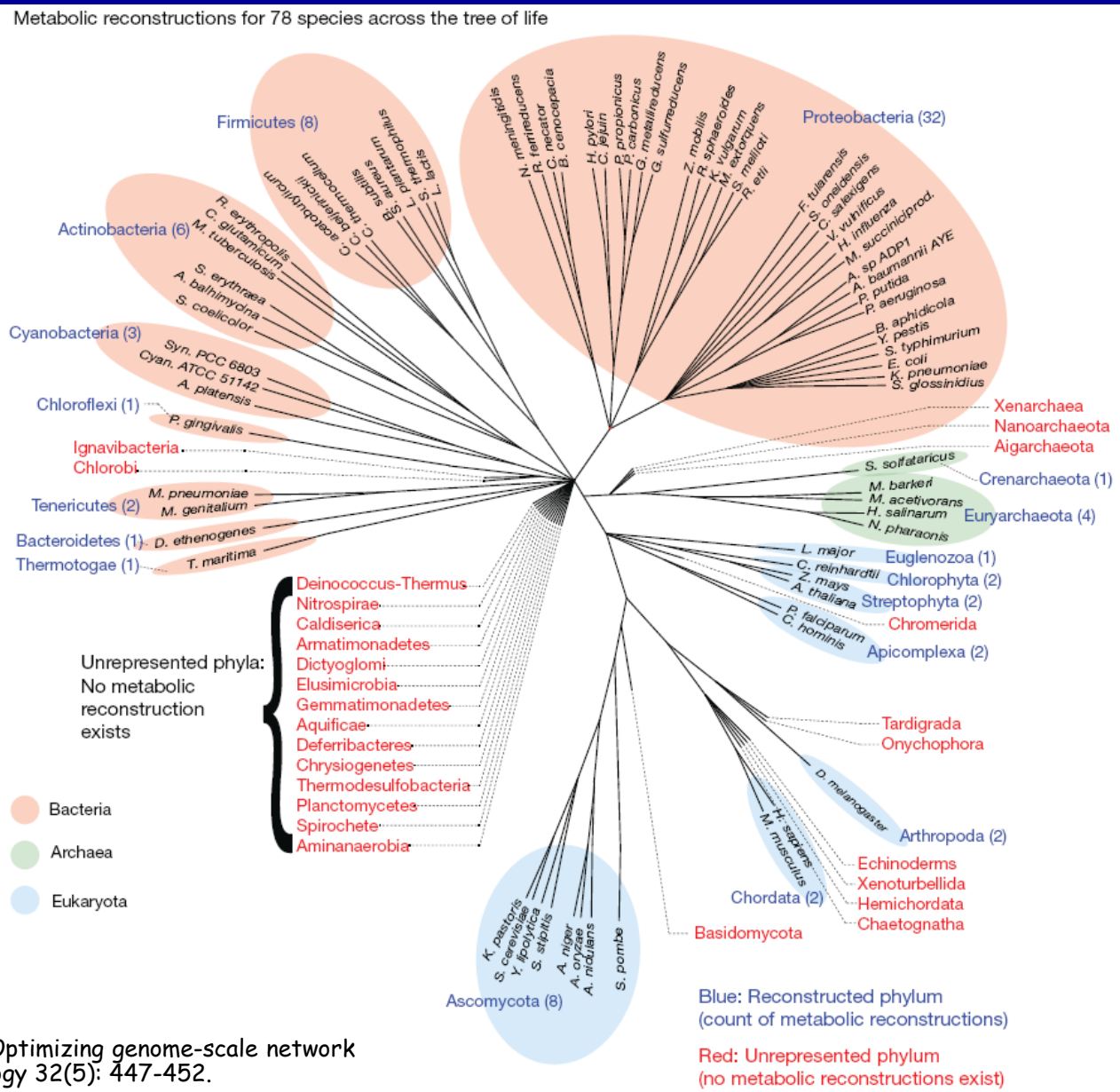


Price, N. D., J. L. Reed, et al. (2004). "Genome-scale models of microbial cells: evaluating the consequences of constraints." Nature reviews. Microbiology 2(11): 886-897.

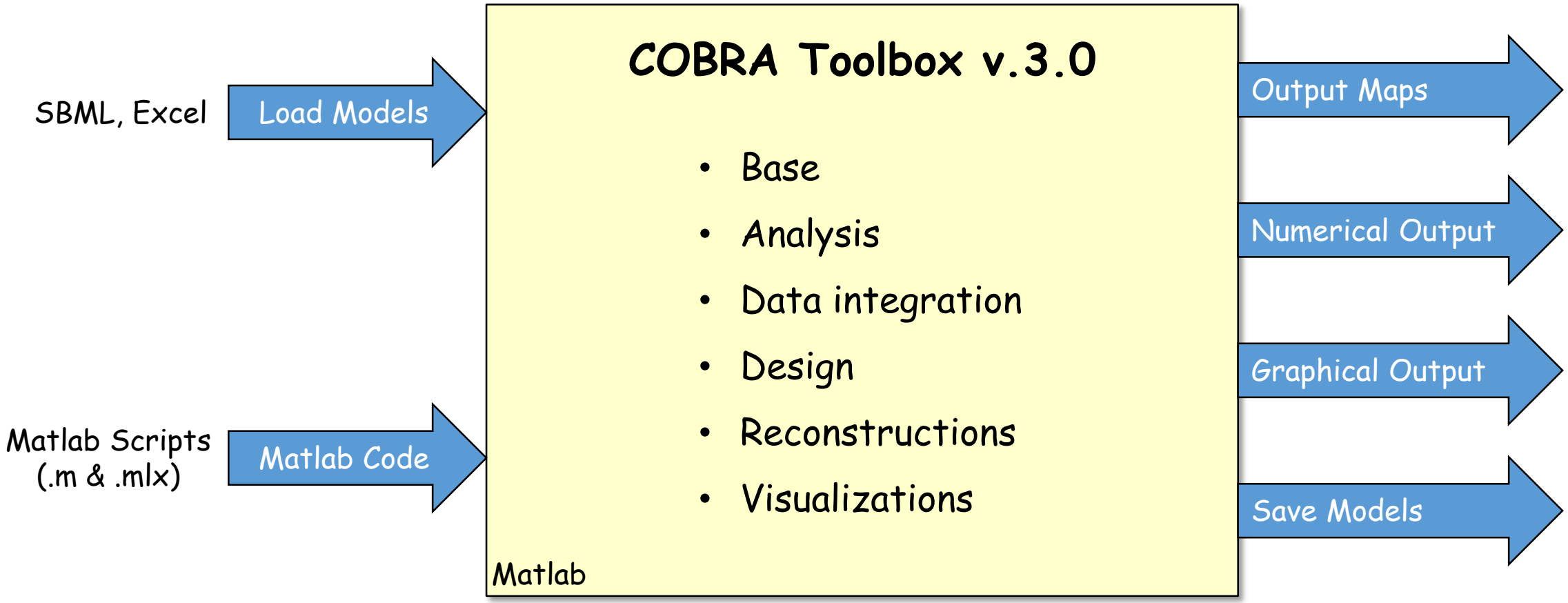
Metabolic Reconstructions

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.



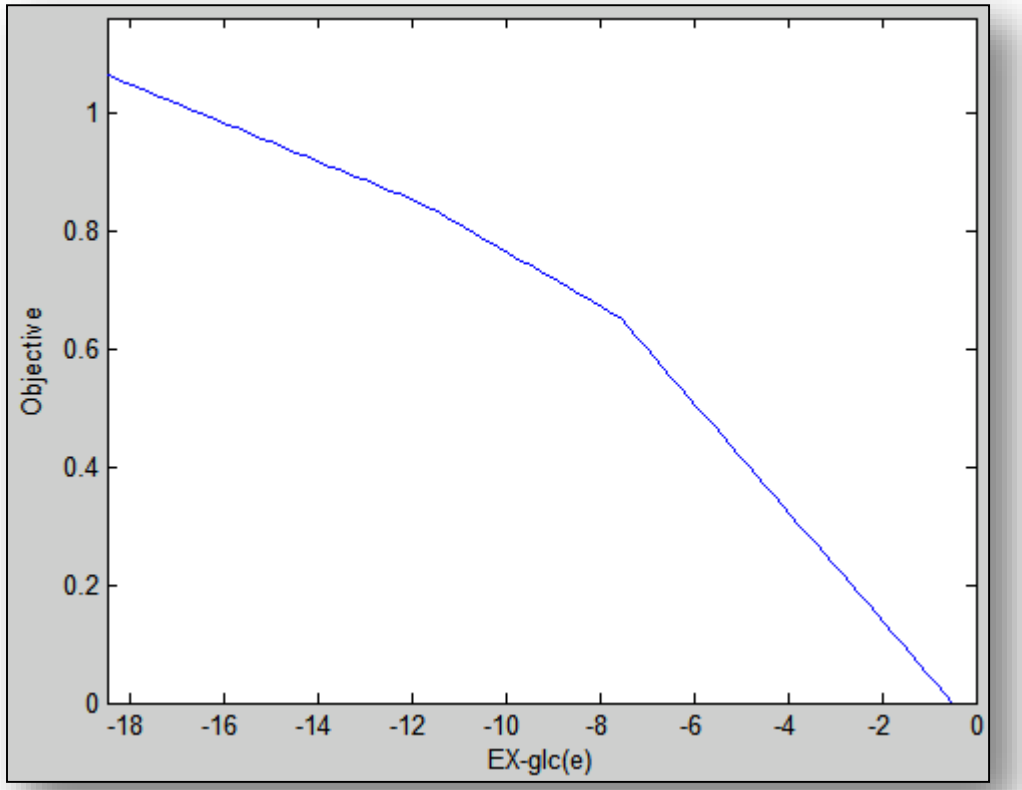
Monk, J., J. Nogales, et al. (2014). "Optimizing genome-scale network reconstructions." Nature biotechnology 32(5): 447-452.

COBRA Toolbox v.3.0 Overview

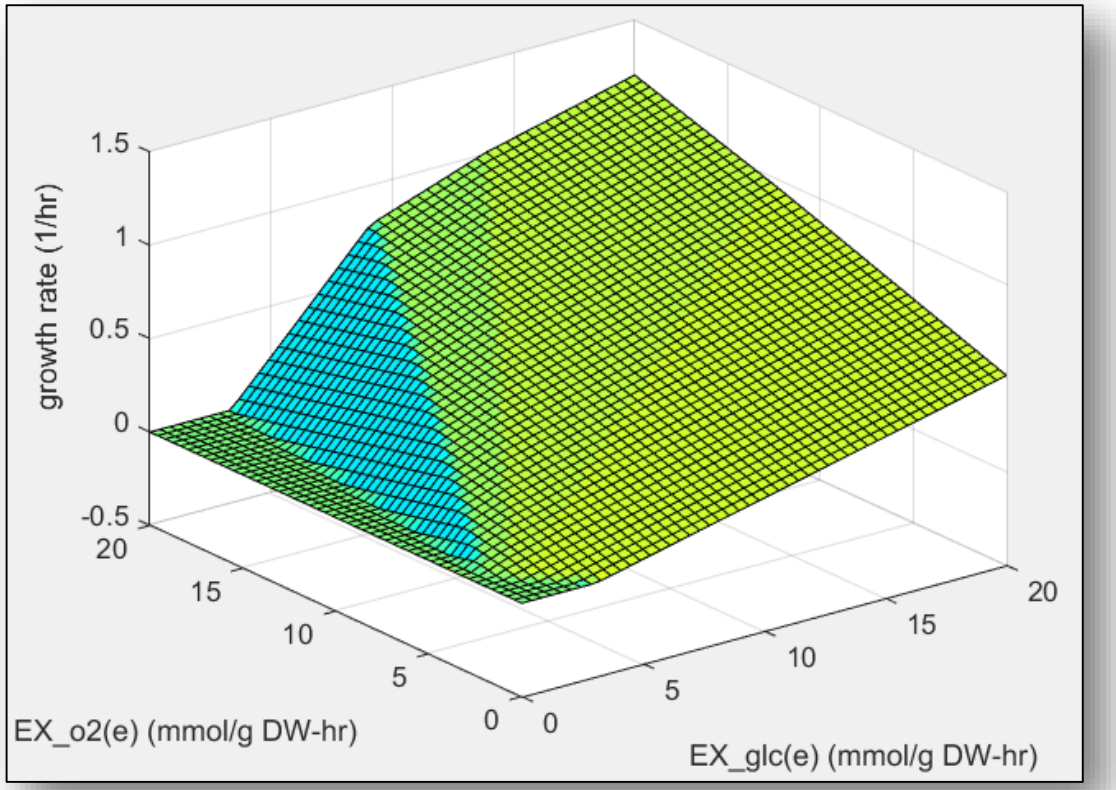


Laurent Heirendt et al, Creation and analysis of biochemical constraint-based models: the COBRA Toolbox v3.0, Nature Protocols, volume 14, pages 639–702, 2019

Robustness Analysis & Phenotype Phase Plane Analysis

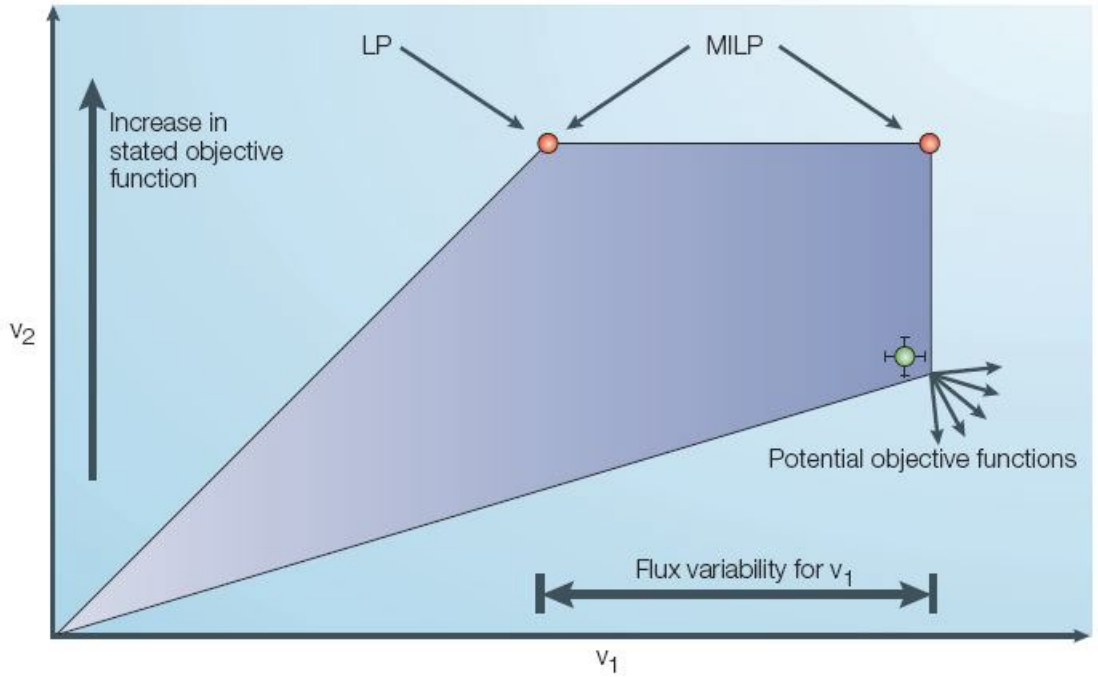


Robustness Analysis

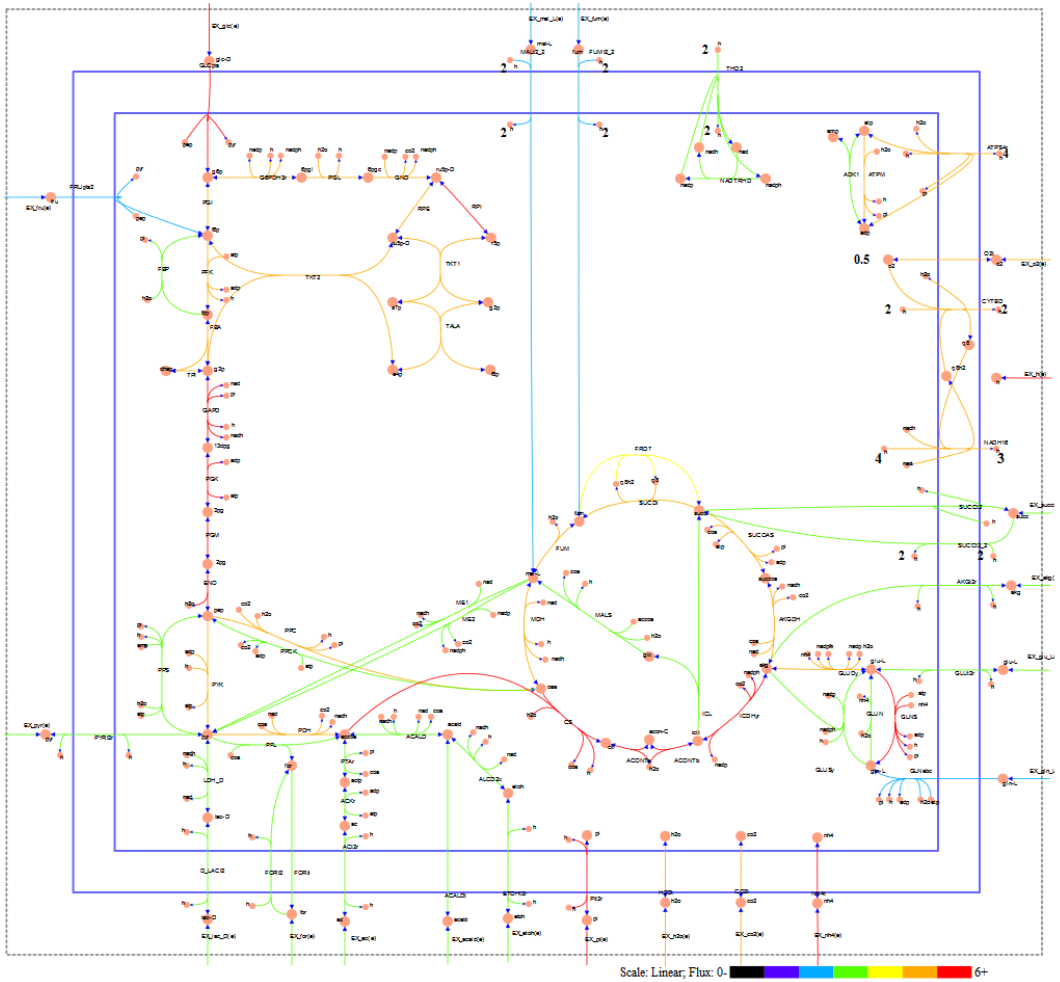


Phenotype Phase Plane Analysis

Flux Variability Analysis & Parsimonious Flux Balance Analysis

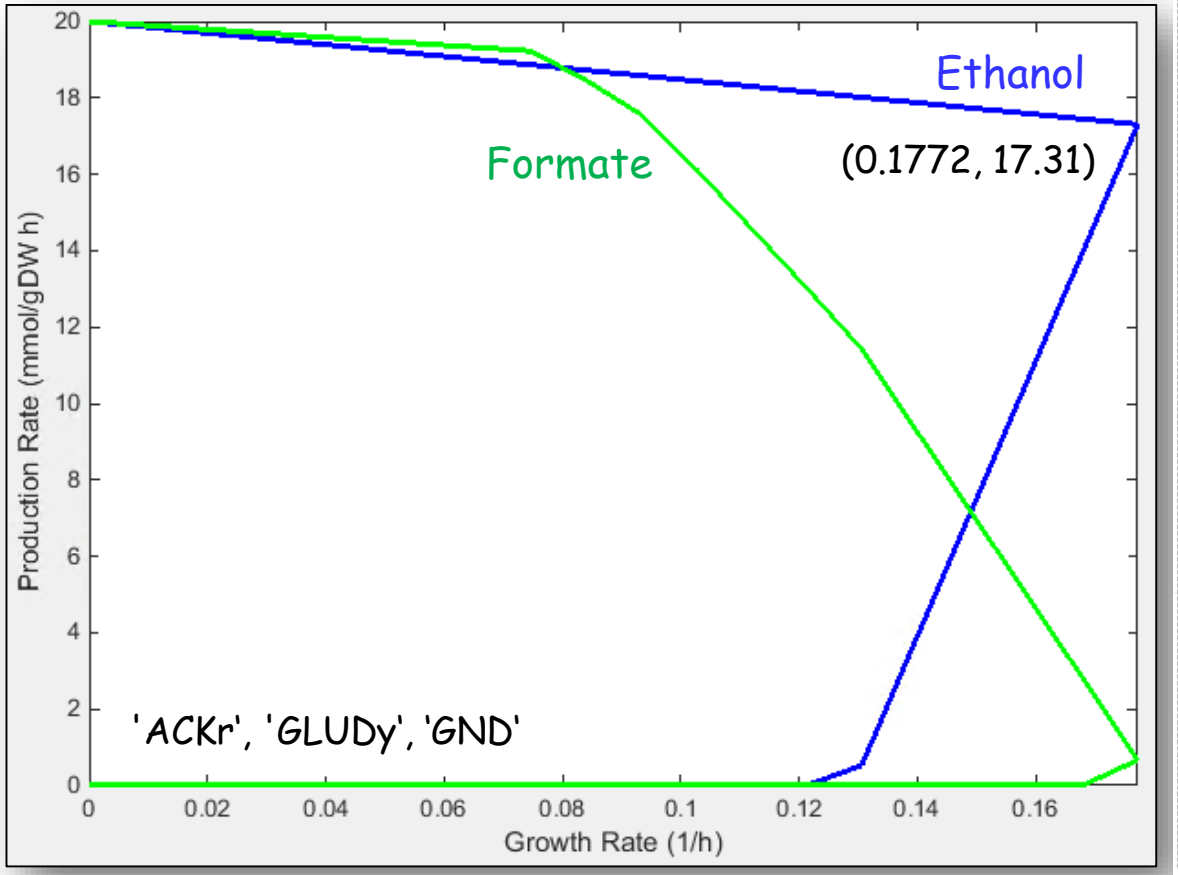


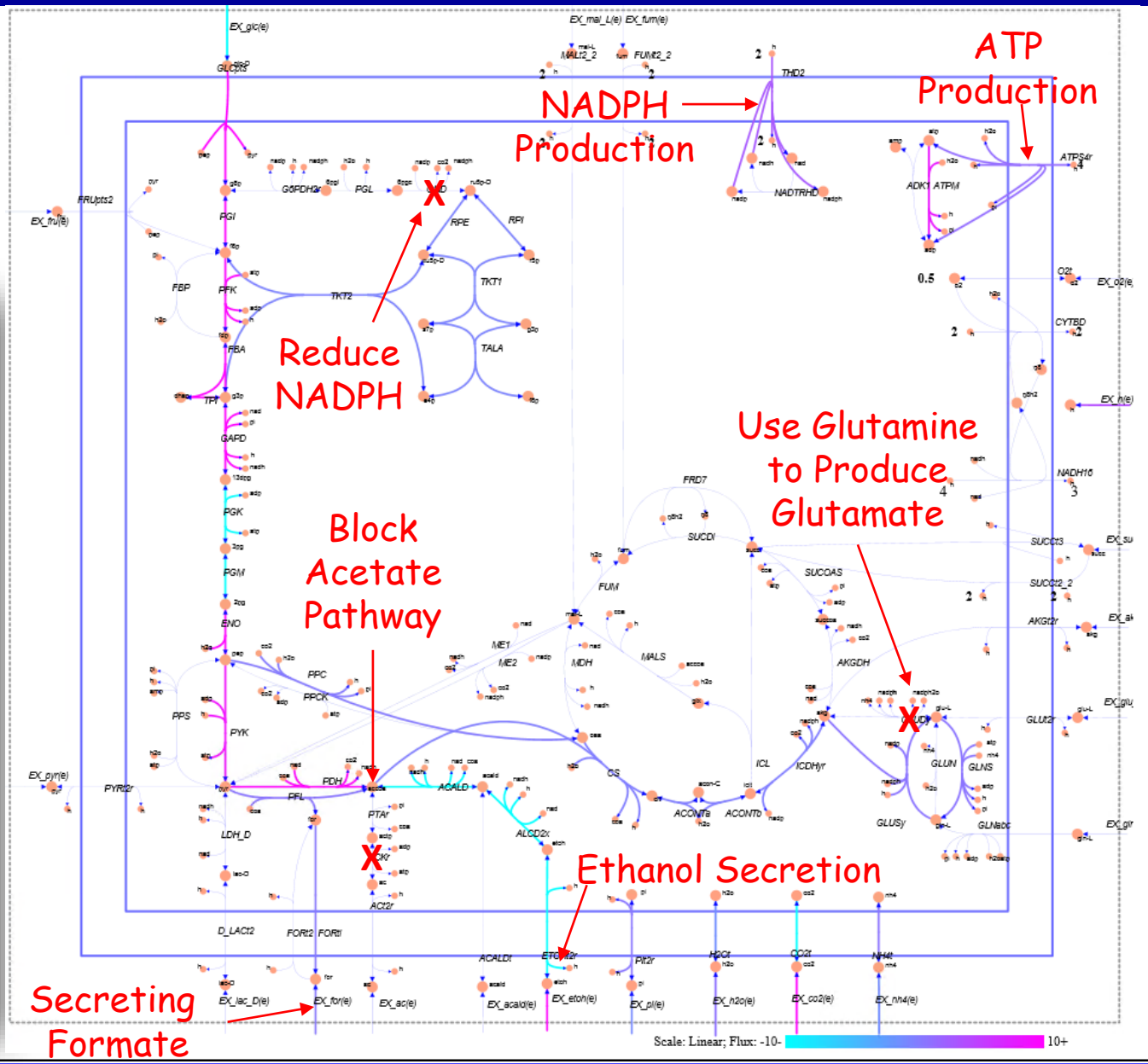
Flux Variability Analysis



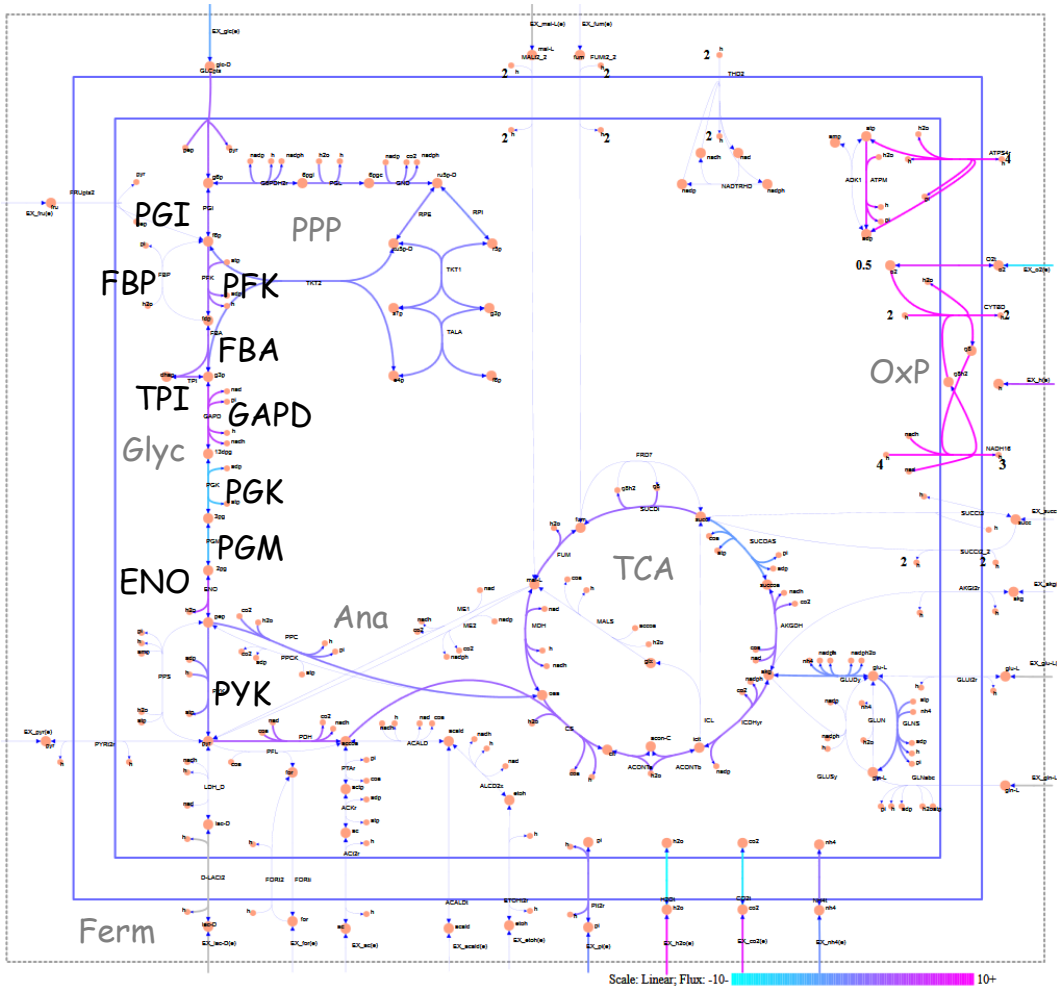
Parsimonious Flux Balance Analysis

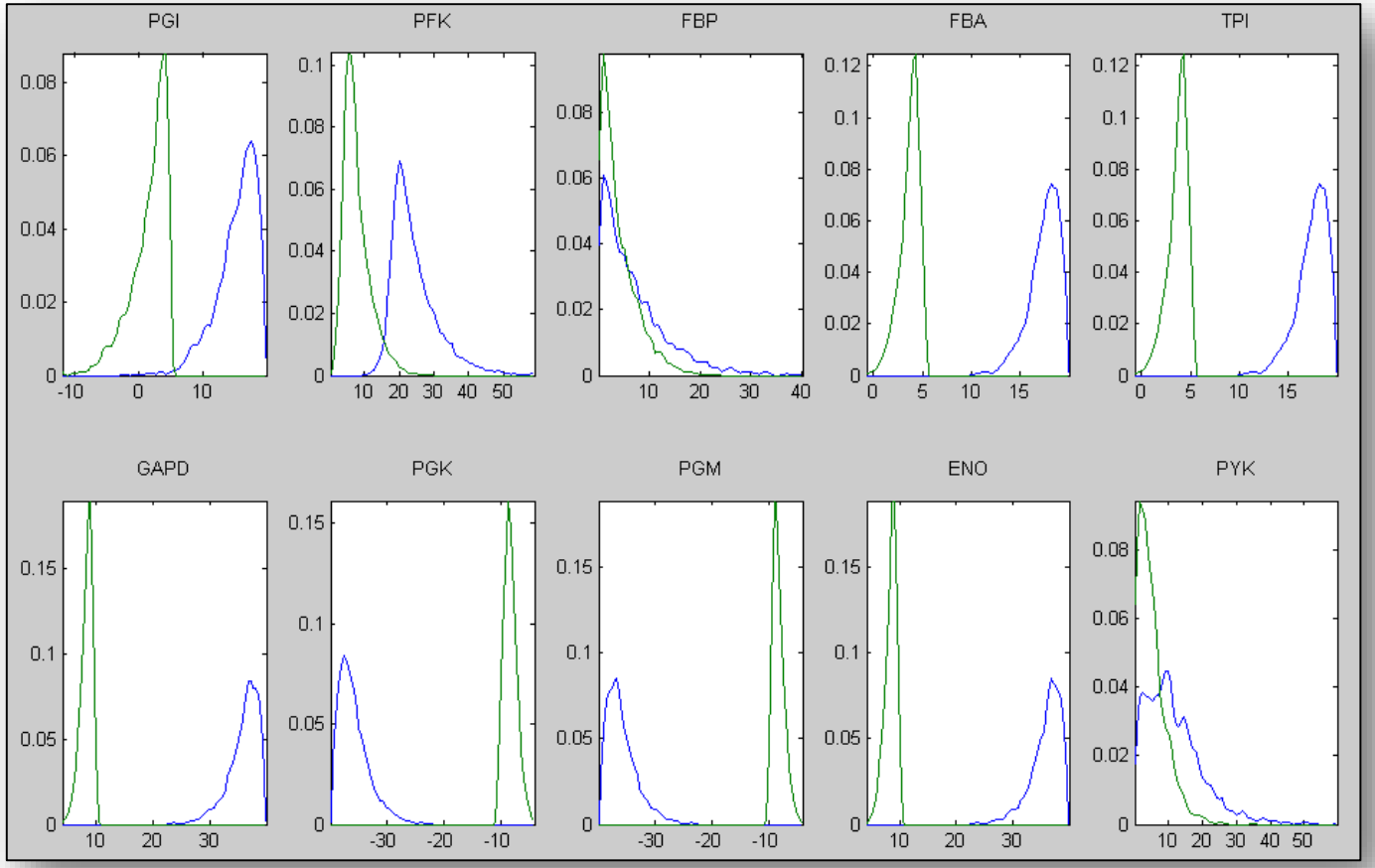
Gene/Reaction Knockouts





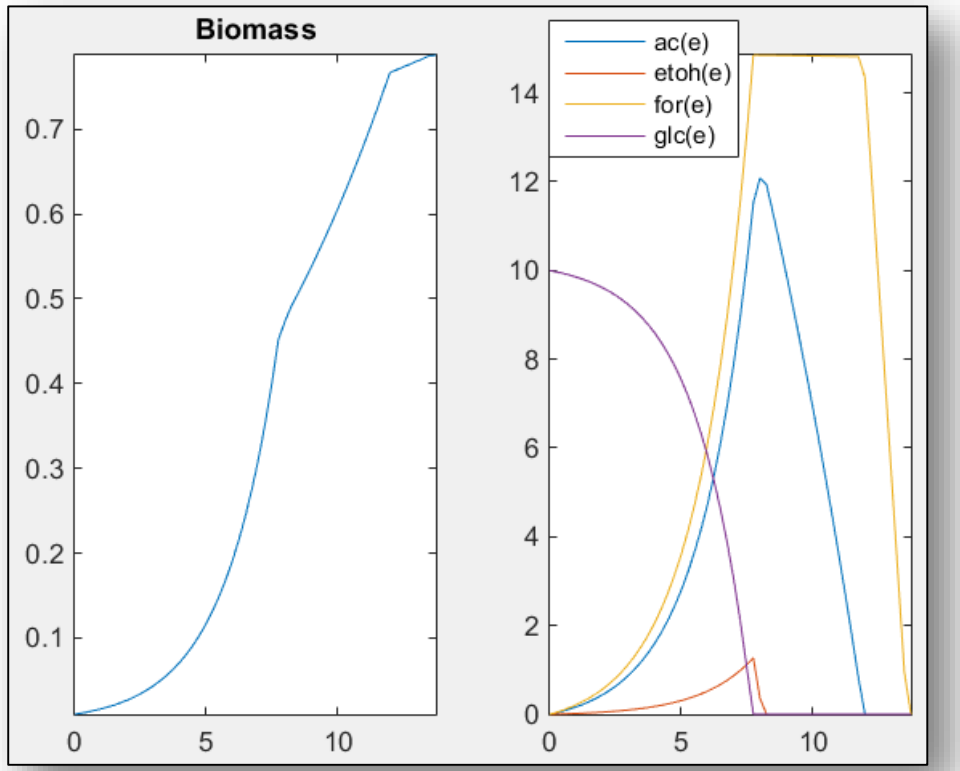
Randomized Sampling



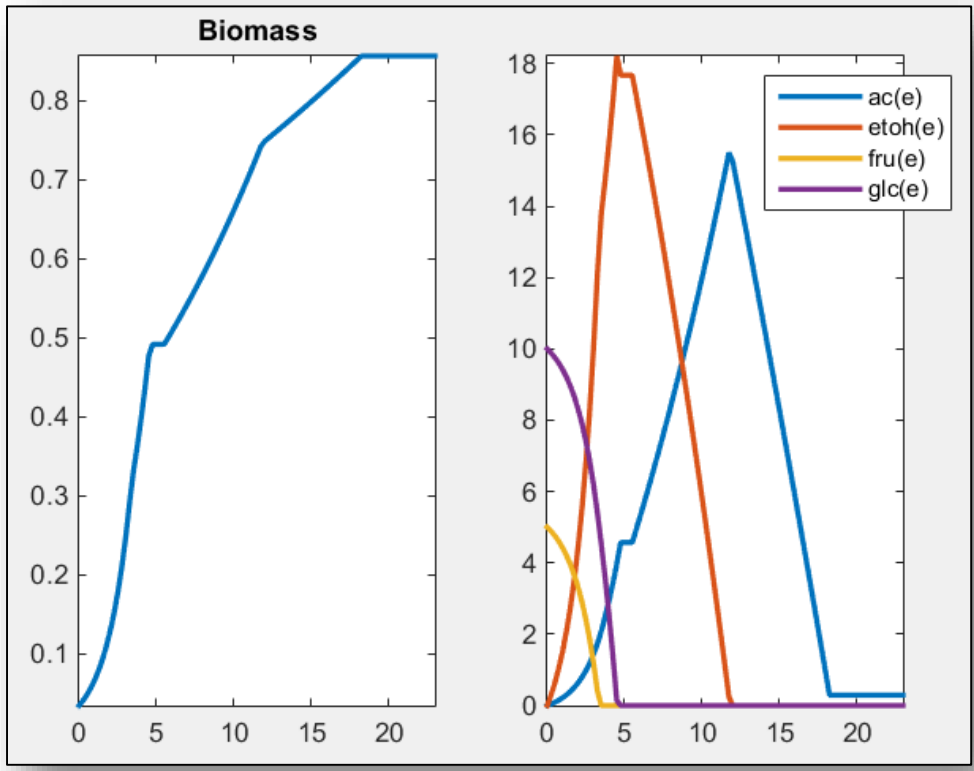


Schellenberger, J., R. Que, et al. (2011). "Quantitative prediction of cellular metabolism with constraint-based models: the COBRA Toolbox v2.0." Nature protocols 6(9): 1290-1307.

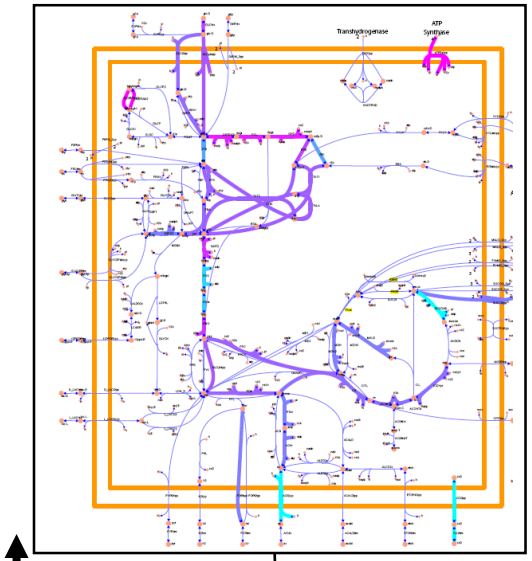
Dynamic FBA & Dynamic Regulatory FBA



Dynamic FBA

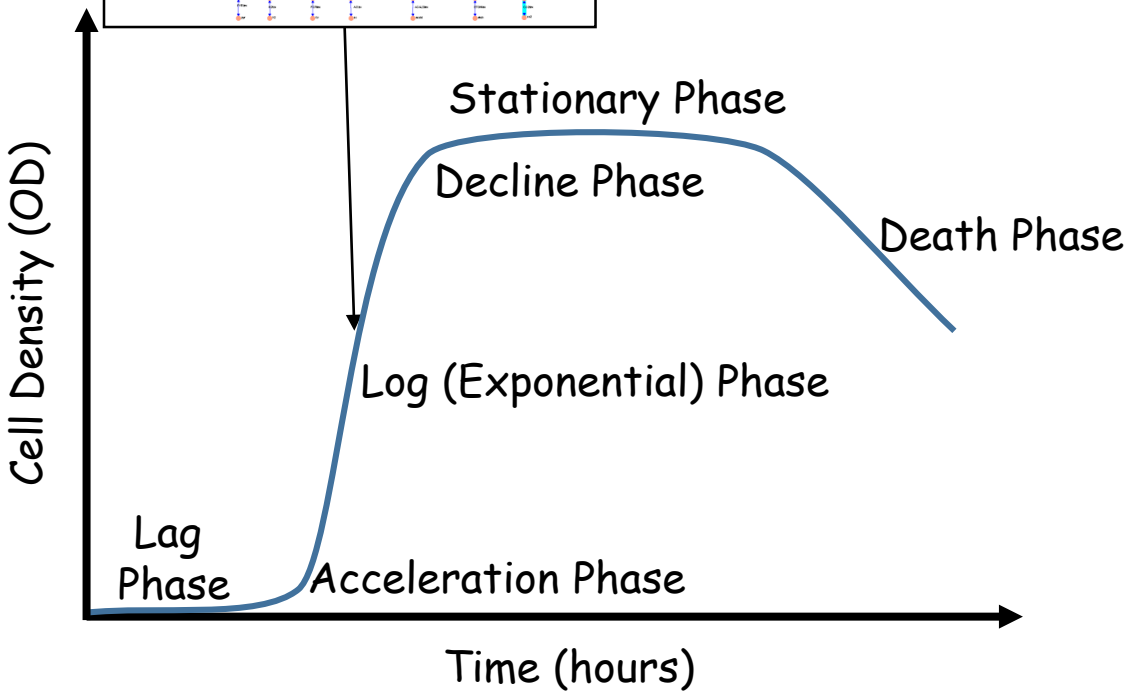


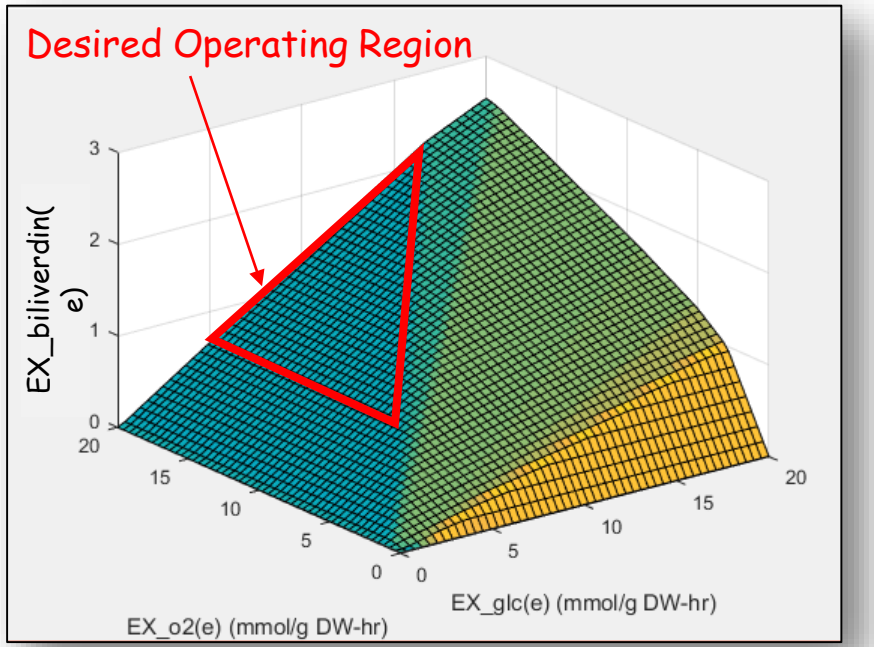
Dynamic Regulatory FBA



Purpose: Identify phenotypes that can exist in exponential growth phase

Bioproduct Production





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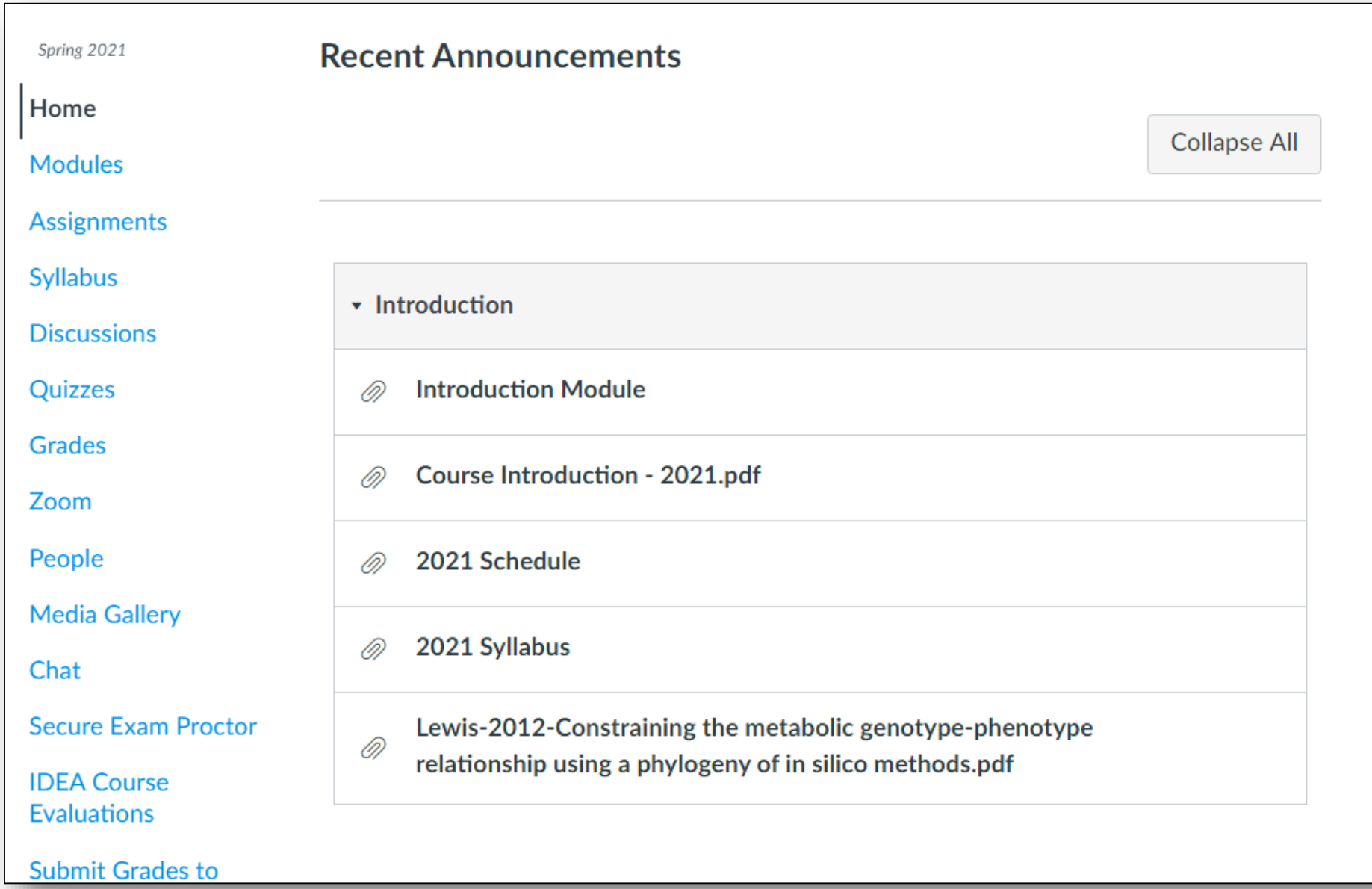
Canvas Website



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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 the process of determining gene knockouts for optimizing bioproduct production
- Explain and demonstrate constraint-based modeling using randomized sampling
- Explain and demonstrate dynamic flux balance analysis
- Explain and demonstrate dynamic regulatory flux balance analysis
- Explain and demonstrate the process of optimizing bioproduct production

Course Learning Process

Required Textbook

Systems Biology: Constraint-based Reconstruction and Analysis, Bernhard O. Palsson, Cambridge University Press, 2015

Weekly Class Period

- The classroom experience is designed to simulate a corporate project team that includes multiple engineers and scientists. In this case, project team will have a weekly group meeting to discuss the project they are working on with their supervisor (Professor). In that meeting everyone reviews their progress on their part of the project and discusses issues they are facing and the concerns they have about the next week's work.
- In principle, this is a collaborative learning environment, where all parties learn from each other through discussion and other forms of interaction. There will be discussion during each class period about the material learned the previous week and material to be learned in the coming week. A student will be chosen to lead the discussion during each class period.

Course Learning Process (2)

Labs

- Labs will be done collaboratively as a team and should typically be held on Thursdays. The students should find a meeting time that works for all of them.
- The students should work independently on the labs but should feel free to talk to other team members when working on the lab and finally to compare final results.
- Professor Hinton can answer lab questions via e-mail.
- The labs will not be graded.

Student Projects

- The class will include a required research project. The research project will require a written paper.
- No late projects will be accepted

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Grading

- Student participation - 40%
  - ✓ Class Attendance
  - ✓ Participation in Class
  - ✓ Lecture Presentations
- Student Project – 60%

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.

Your Choice

- You will only get out of this course what you put into it!
- If you just try to get by, at the end of the course you will be totally confused and walk away with nothing.
- If you work hard and try to understand everything that is covered, at the end of the course you will walk away with a new understanding of the future of the life sciences.
- Since this is a self-learning course, the battle is not between you and the professor, it will be an internal battle between your priorities.

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References

1. Lewis, N. E., H. Nagarajan, et al. (2012). "Constraining the metabolic genotype-phenotype relationship using a phylogeny of *in silico* methods." Nature reviews. Microbiology 10(4): 291-305.
2. Terzer, M., N. D. Maynard, et al. (2009). "Genome-scale metabolic networks." Wiley Interdiscip Rev Syst Biol Med 1(3): 285-297.
3. Feist, A. M. and B. O. Palsson (2008). "The growing scope of applications of genome-scale metabolic reconstructions using Escherichia coli." Nature biotechnology 26(6): 659-667.
4. David S. Goodsell (2009), "Escherichia coli," Biochemistry and Molecular Biology Education, Volume 37, Issue 6, pages 325–332.
5. Jan Koolman and Klaus-Heinrich Roehm, "Color Atlas of Biochemistry", 2nd Edition, 2005.