COMP 150 CSB –
Computational Systems Biology

Systems Biology – A Detailed Overview

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Reading

Palsson, B. Ø. (2015). Systems biology: constraint-based reconstruction and analysis. Cambridge University Press.

- Chapter 15 (1,2,3)
  - https://doi-org.ezproxy.library.tufts.edu/10.1017/CBO9781139854610.019
- Chapter 16 (1,3,4)
  - https://doi-org.ezproxy.library.tufts.edu/10.1017/CBO9781139854610.020

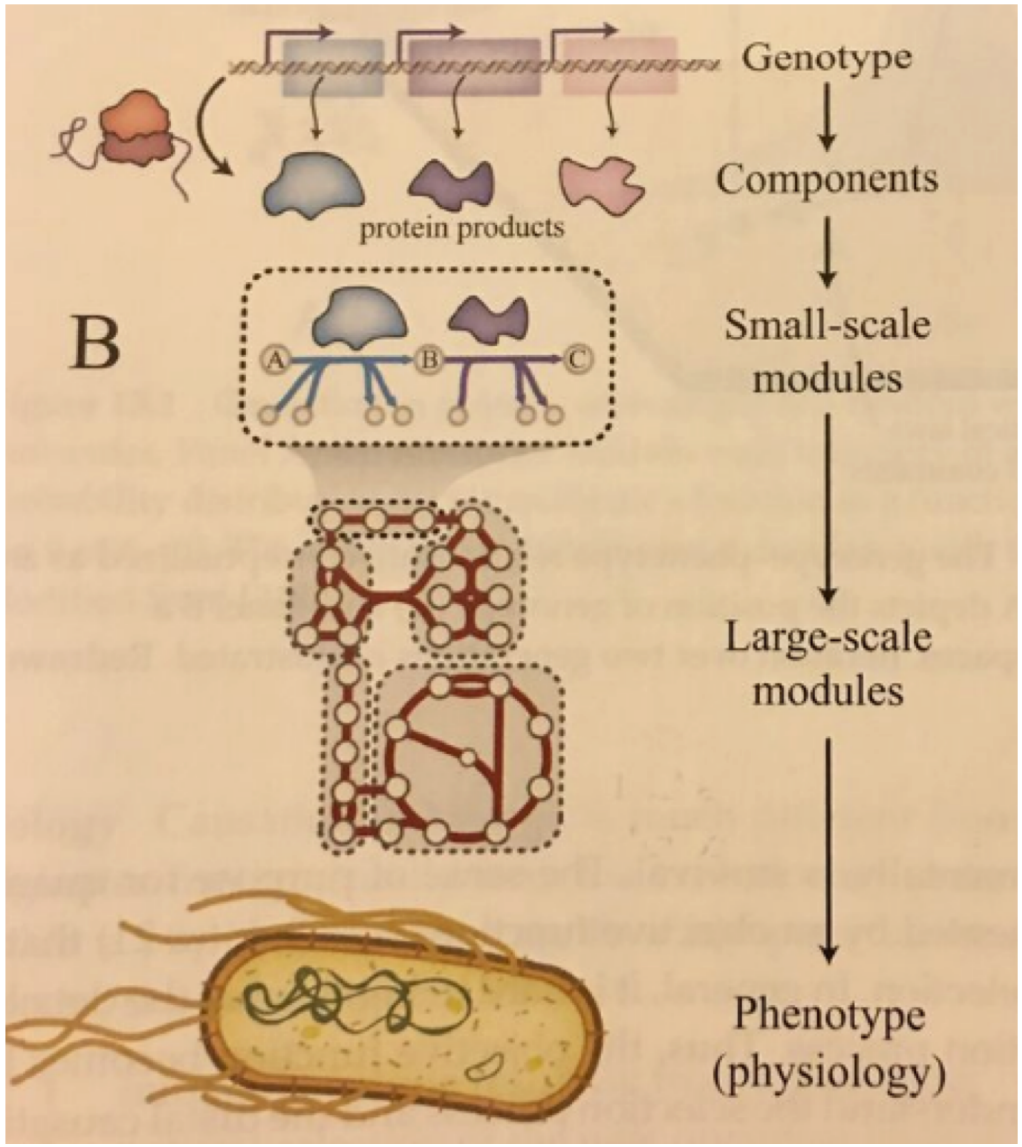
- Book available on line through Jumbo Search

- See lectures online:
  - http://systemsbiology.ucsd.edu/Publications/Books

Outline

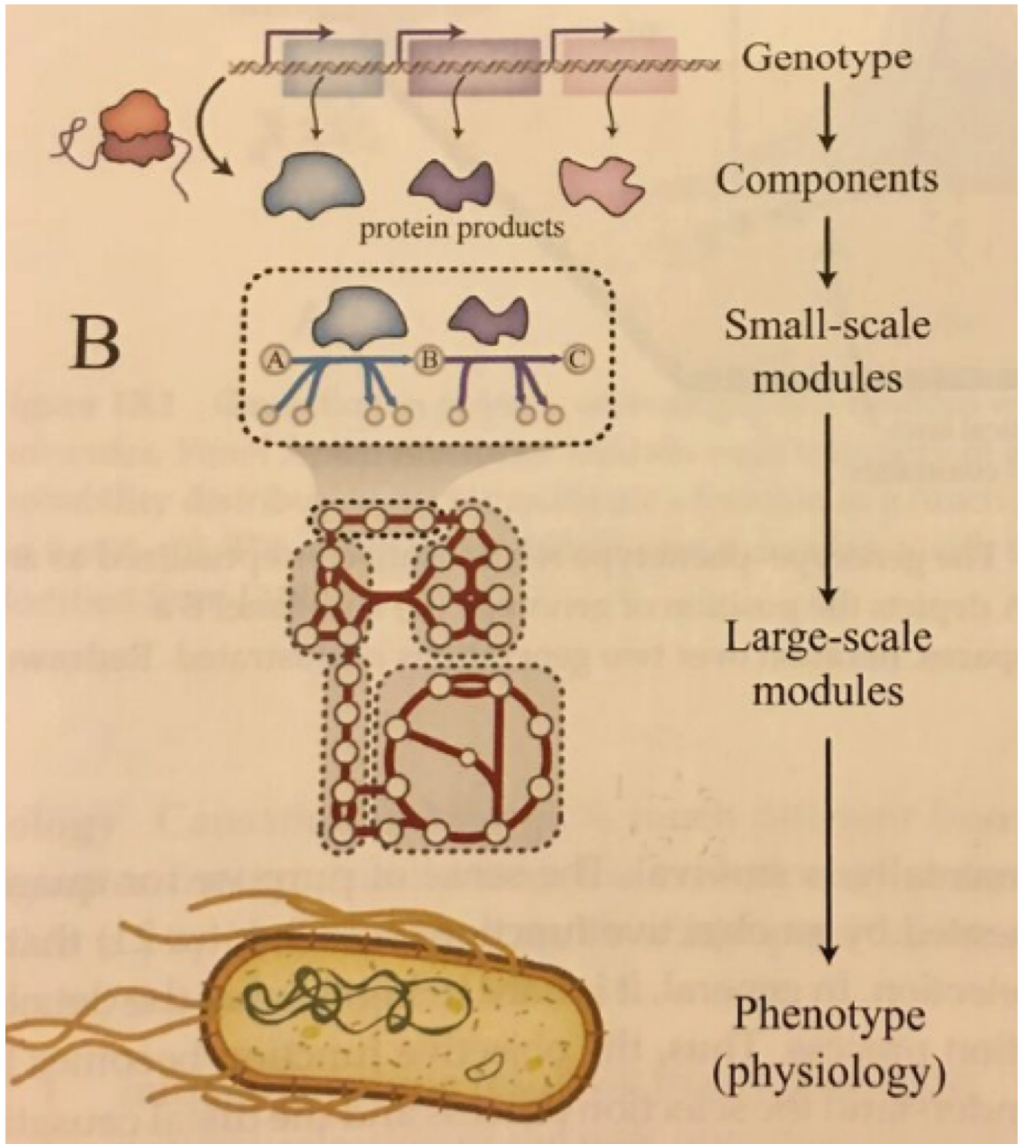
- How did we get to systems biology?
  - Genotype-phenotype relationship (fig 15.3)
  - Dual Causation (chemical law and biological law, Chapter 15.1)
- What is systems biology?
  - Quantitative models for systems
  - What should the models model/predict/analyze?
  - Why physics-like models don't work?
- Alternative paradigm: constraint based
  - Constraints in Biology (15.3)
  - Constraint-based solutions
  - Systems Biology Paradigm (1.3)
- Building Foundations - Axioms (1.4)

Genotype and phenotype relationship



Goodsell, *Machinery of Life*, 1993

Genotype and phenotype relationship & dual causation



Chemical Causation:
Can apply natural laws and get causality on a small scale

SYSTEMS BIOLOGY

Biological Causation:
Genome-scale changes and description of thousands of variables.

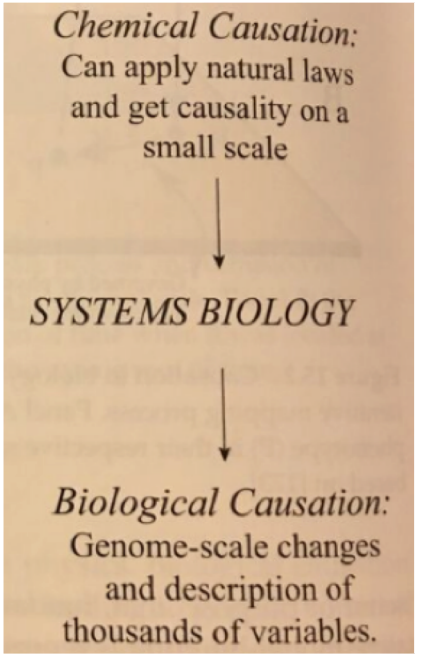
Goodsell, *Machinery of Life*, 1993

Dual Causality

- Biology is subject to dual causation. It is governed by:
- Physics:
  - Cause and effect is mathematically formulated modeling physical phenomena
  - Often well understood and established
    - e.g. diffusion
- Genetic programming:
  - Evolutionary process:
    - Initial phenotype results from genotype
    - Natural selection leads to produce offspring
    - Processes such as mutation and recombination or mating leads to formation of new genotype
  - Outcome is stochastic influenced by environmental variables
  - There is a "Sense of Purpose" - survival

Systems Biology

- New field (mid 1990s)
- Driven by availability of whole-genome sequences, giving us info about each component within an organism
- Develops quantitative and mechanistic genotype-phenotype relations



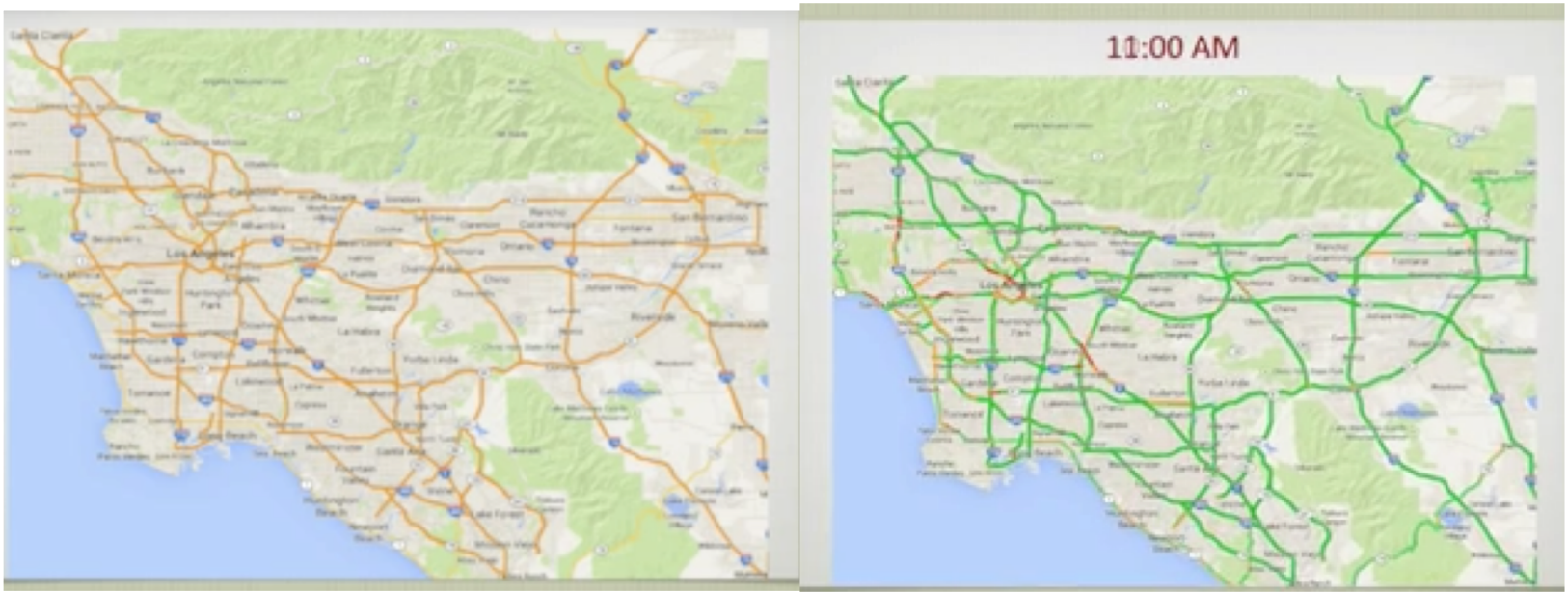
Building genome-scale quantitative models

- Quantitative model: understand or predict behavior using mathematical and/or statistical models

- What should we be modeling for a cellular system?

Multiple functional states

- Roads are the same, but activities differ



- Biological networks have multiple functional states that are a function of the environment
- We would like to compute/analyze these functional states

Alternative states of the same network

Two alternative cycles for oxidation of PEP

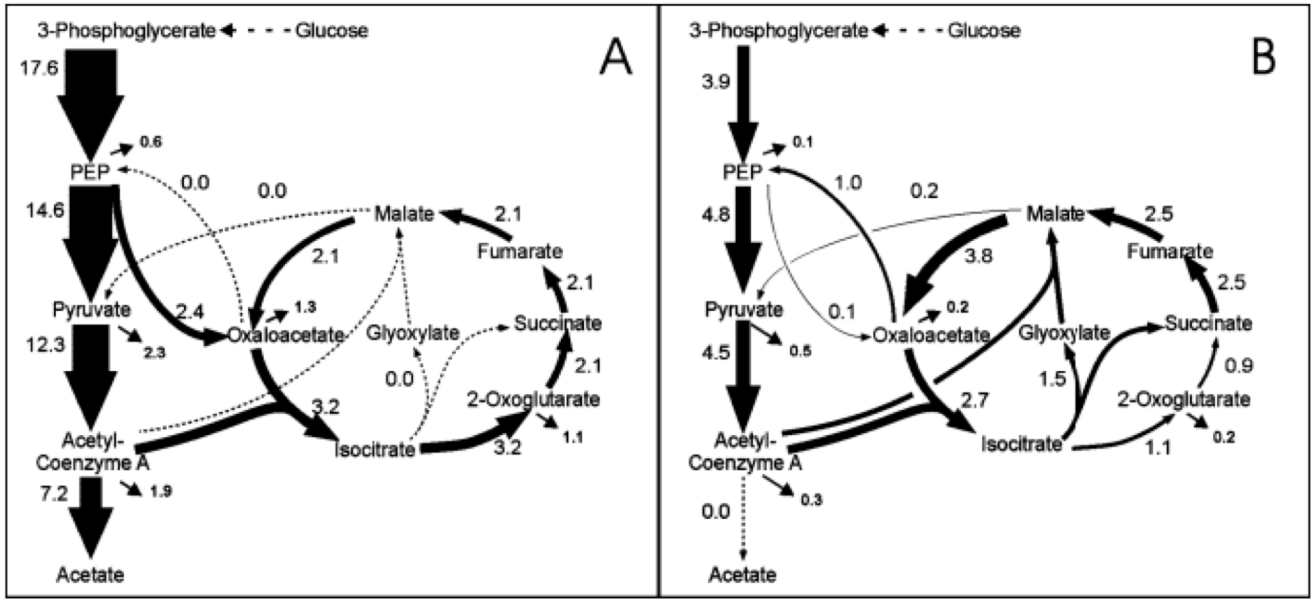
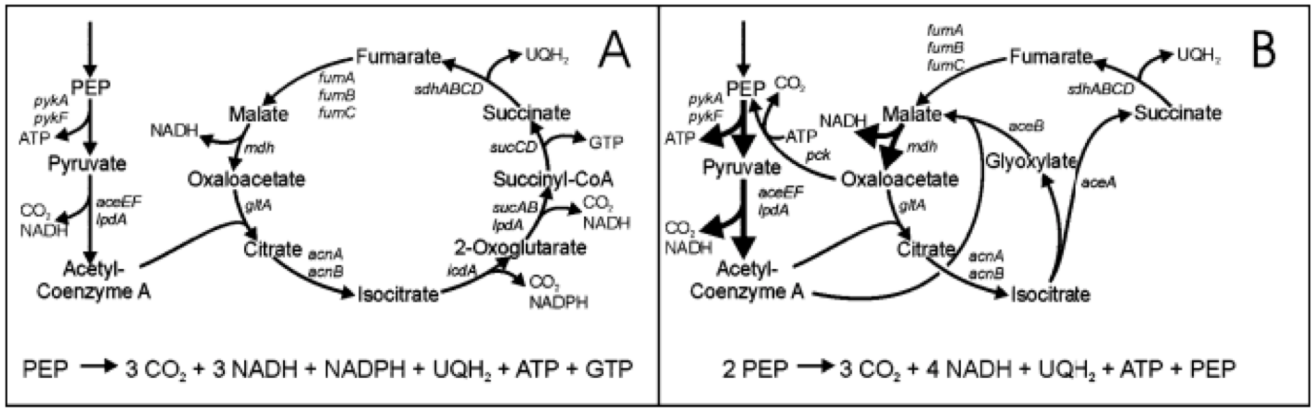


FIG. 3. **Net flux analysis in batch and chemostat culture.** Molar net fluxes (mmol g^{-1} h^{-1}) in batch culture (*A*) and in glucose-limited chemostat culture at a growth rate of 0.12 h^{-1} (*B*) of *E. coli*. The *arrows* are drawn in proportion to the flux. Mass spectral data of proteinogenic amino acids from cultures grown on a mixture of 20% [U-^{13}C]glucose and 80% natural glucose and the physiological data of Table I were used for the flux estimation. Fluxes to biomass building blocks are indicated by the *short arrows*.



Fischer, E., & Sauer, U. (2003). A novel metabolic cycle catalyzes glucose oxidation and anaplerosis in hungry Escherichia coli. Journal of Biological Chemistry, 278(47), 46446-46451. Chicago

Multiple phenotypic functional states

- Functional state
  - Viewed as outcome of execution of genetic program written in DNA
  - Represents a physiologically observed state

Limitations to building quantitative models

- Limitations to building such models
  - Intracellular chemical environment is complex
  - Unknown governing equations
  - Even if known, how do we measure parameters
    - Unlike physical systems with fixed parameters, biological parameters vary with environment and over time

- Systems Biology: modeling using a different paradigm
  - Based on what we know!!
    - We don't know a lot, but we have lots of constraints

Biological constraints (1)

Physico-chemical (physics + chemistry) constraints:

- Hard constraints (must be met)
- Examples:
  - Conservation of mass, elements and energy
  - Viscous environment (100-1000 times that of water)
  - Diffusion rates within cell may be slow
  - Biochemical reactions need to have negative free energy to proceed
  - Reaction rates are a function of local concentrations within cells

Biological constraints (2)

Spatial or Topological Constraints

- 3-D constraints due to crowding of molecules
- DNA is tightly packed (to fit in the cell) but must be accessible
- Location of tRNA relative to ribosomes
- Not much progress has been made in bringing topological constraints into systems biology modeling

Biological constraints (3)

Environmental Constraints

- Nutrient availability, pH, and temperature are time- and condition dependent
- *Examples:*
- *H.* pylori, a human gastric pathogen, lives in a relatively sufficiently constant environment, but constrained by low pH.
  - it produces ammonia to sufficiently neutralize pH in immediate surrounding to stay alive
- *E. coli,* adaptable and flexible, adjusting its internal state to surrounding environment
- Use known environment constraints to better model organism

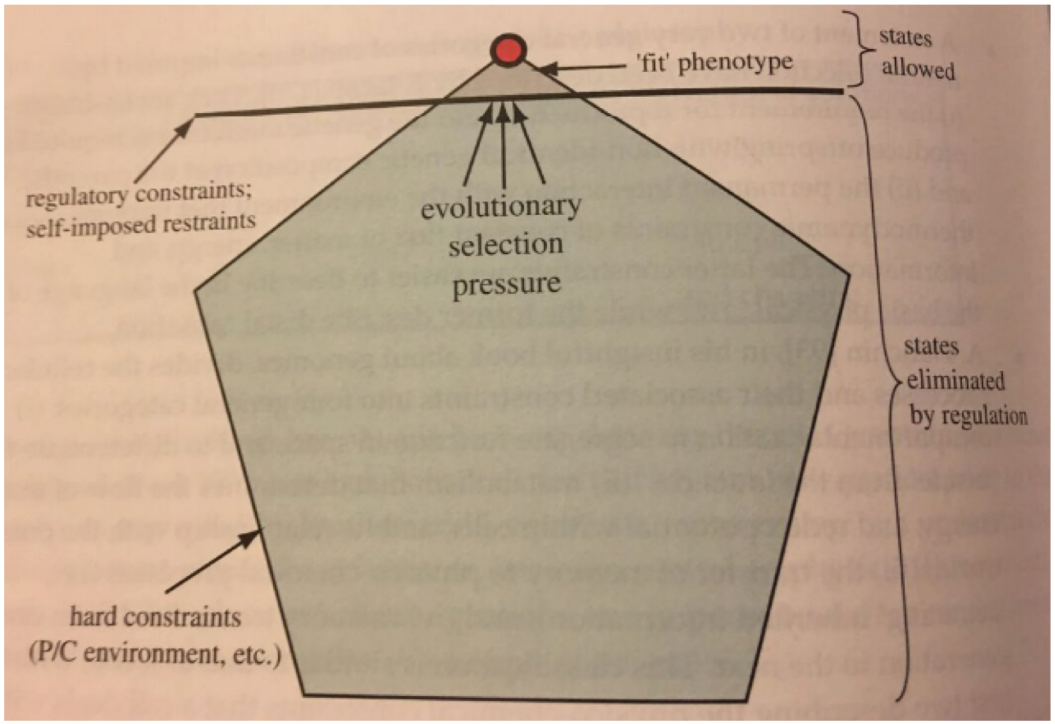
Biological constraints (4)

Regulatory Constraints (restraints)

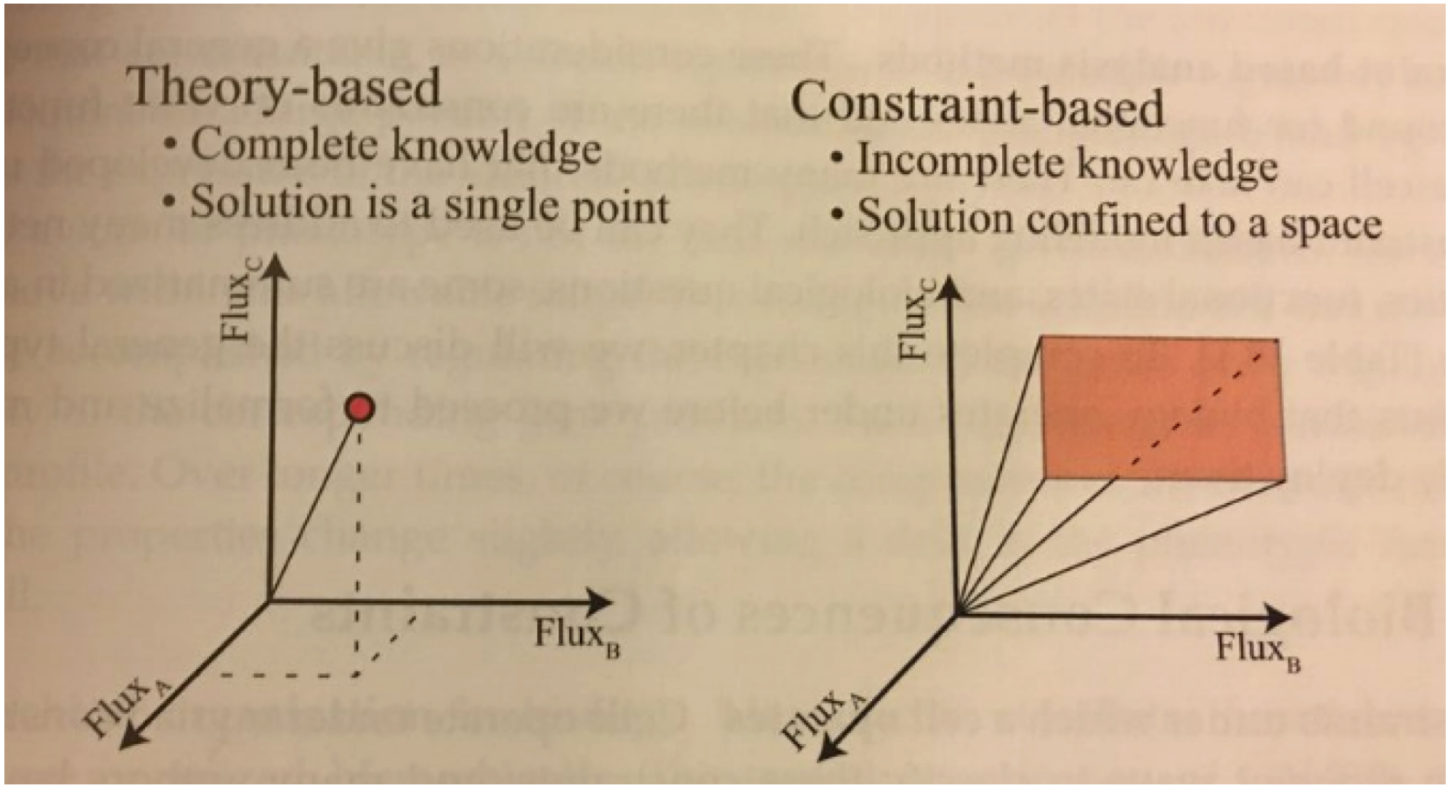
- Operate within physico-chemical constraints
- Self-imposed, subject to evolutionary change and can be time-variant
- Provide mechanism to eliminate suboptimal phenotypic states and confine cellular functions to behaviors of high fitness
- Guides modeling

The Paradigm

- Models utilize constraints (and boundaries) to define feasible solutions spaces of possible functional state
- There are multiple allowed functional states



Constraint-based solutions



Systems Biology paradigm

1. Define and enumerate list of biological components
2. Biochemical reactions reconstruction:
   - Interactions between components (wiring diagram) are reconstructed
   - Genome maps are formed, via iteration and refinement (e.g. KEGG maps)
3. Constructed networks are converted to mathematical models. Models are analyzed, queried, and interpreted
4. Models are used in many applications and for many purposes
   - Prediction, hypothesis testing, ..
   - Re-engineering cellular behavior

Building Foundations - Axioms

- Axiom #1. All cellular functions are based on chemistry.
  - Combined chemical and physiochemical information
  - Chemical equations can be used to describe cellular events
- Axiom #2. Genomic + experimental data allow genome-scale reconstruction of metabolic networks
- Axiom #3. Cells operate under many constraints
  - physiochemical, topological, environmental, and regulatory
- Axiom #4. Cells function in a context-specific manner
  - Cellular components can be profiled using "omics"
    - Transcriptomics, proteomics, fluxomics, metabolomics..
- Axiom #5. Mass (and energy) are conserved
  - Steady-state assumptions leads to mathematic description of network
- Axiom #6. Cells evolve under selective pressure in a given environment
  - Implicit optimality assumption, leading to an objective function