Dynamic States of Biological Networks

Chapter 1:
Introduction

Outline

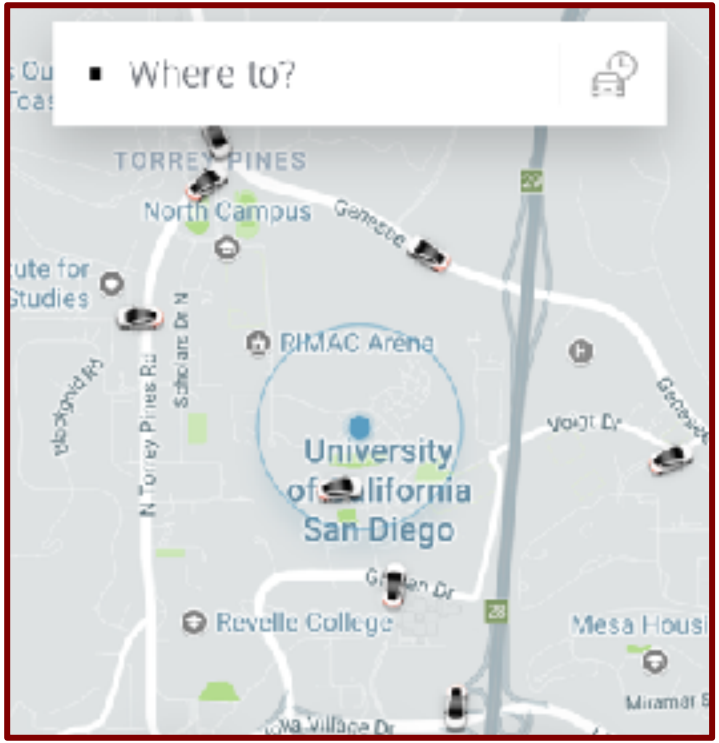
- What is a network?
- How can we mathematically model networks?
- Key concepts in dynamic analysis
- How do we build models?
- Why do we build models?

Our daily lives are managed through networks

What is a network?

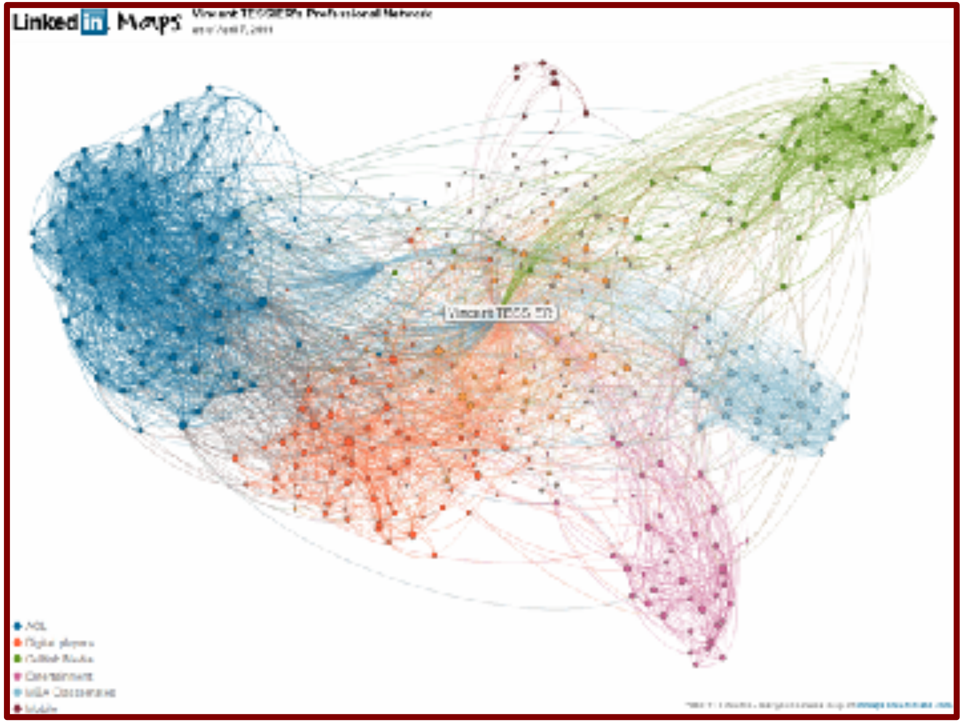
Uber

- ➢ Data analytics have helped Uber develop algorithms to determine frequent destinations (“hotspots”)
- ➢ This knowledge allows the driver network to be structured around particular locations to offer the quickest service

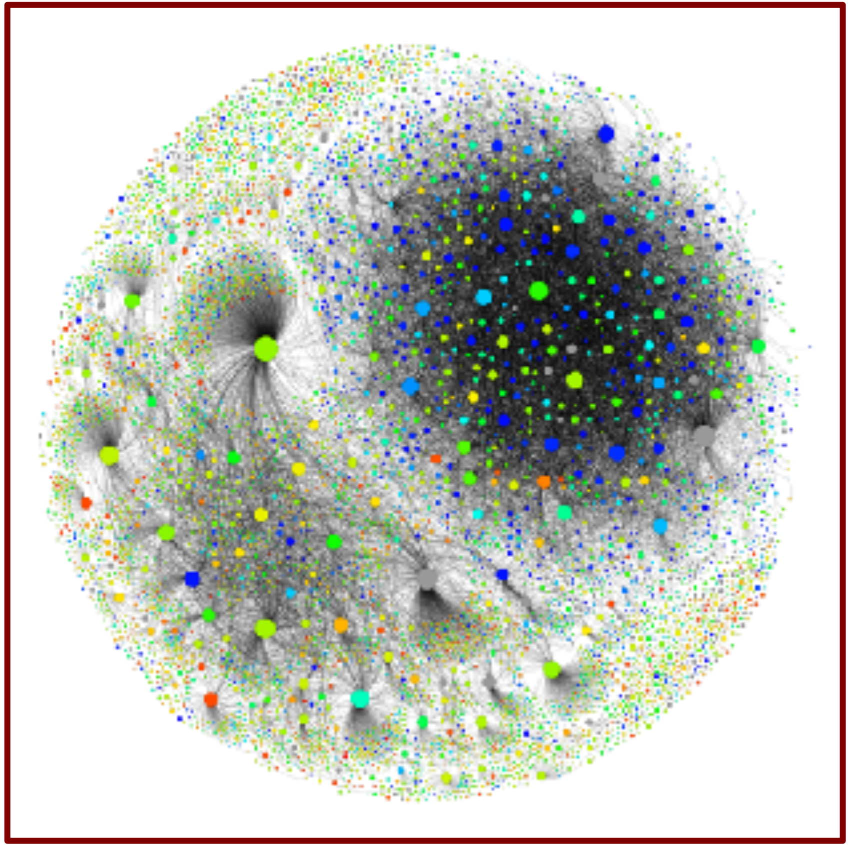


Social networks

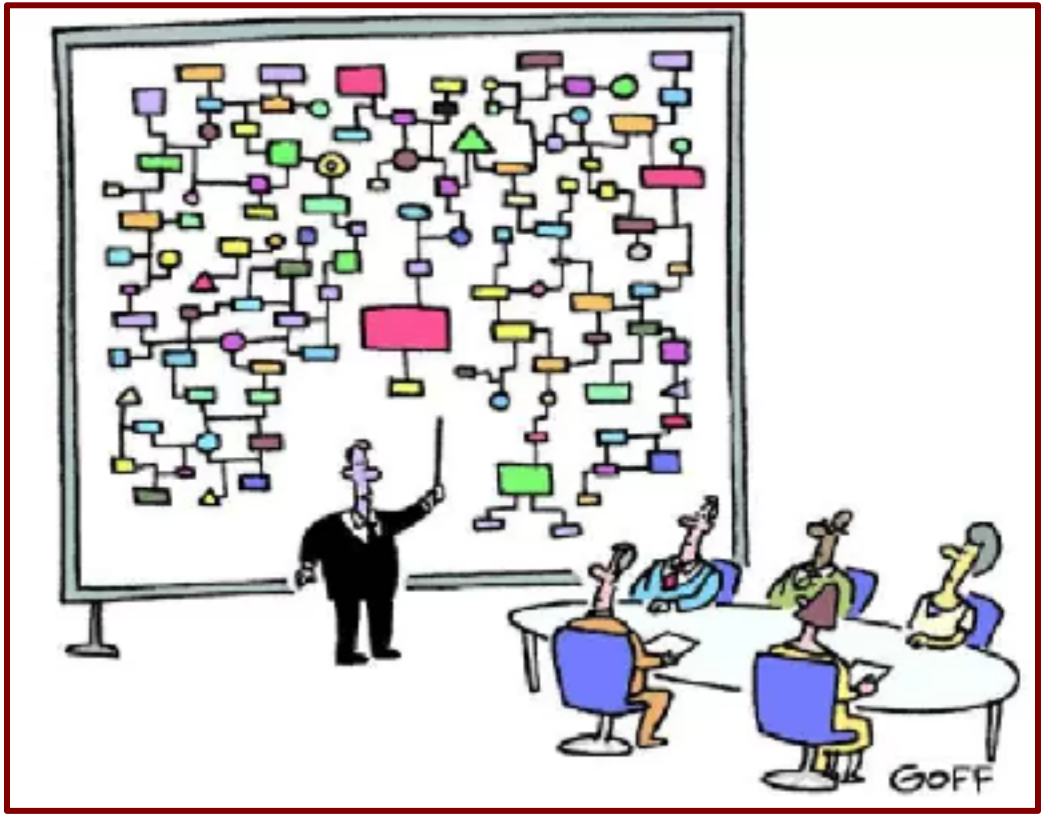
- ➢ Networks like Facebook and LinkedIn can be easily mapped
- ➢ By viewing a particular topological feature in a network, we can draw meaningful conclusions
  - ○ If many nodes are interconnected, perhaps those people work together?
  - ○ If nodes are unique, perhaps these represent individual clients



Networks



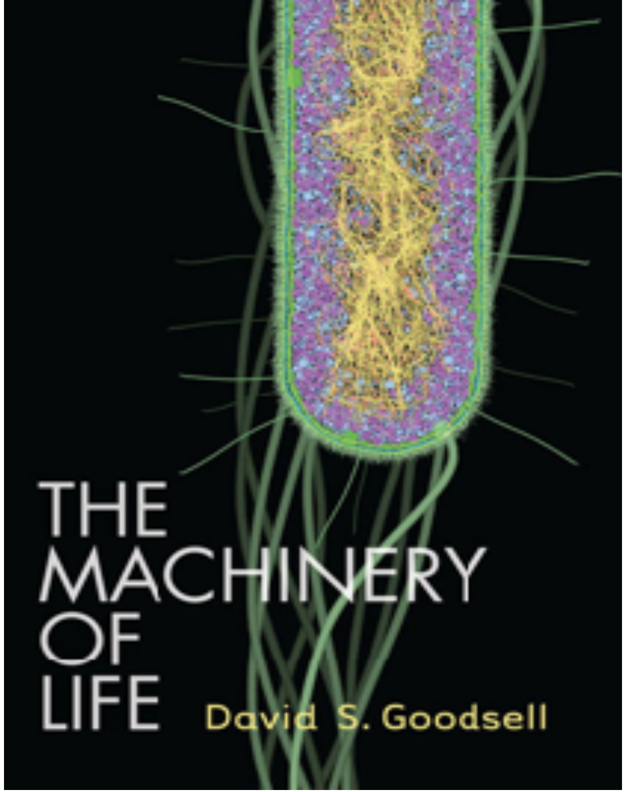
- ➢ As networks get larger and more complicated, we lose the ability to visually inspect a network and draw meaningful conclusions
- ➢ How do we extract information from complex networks?



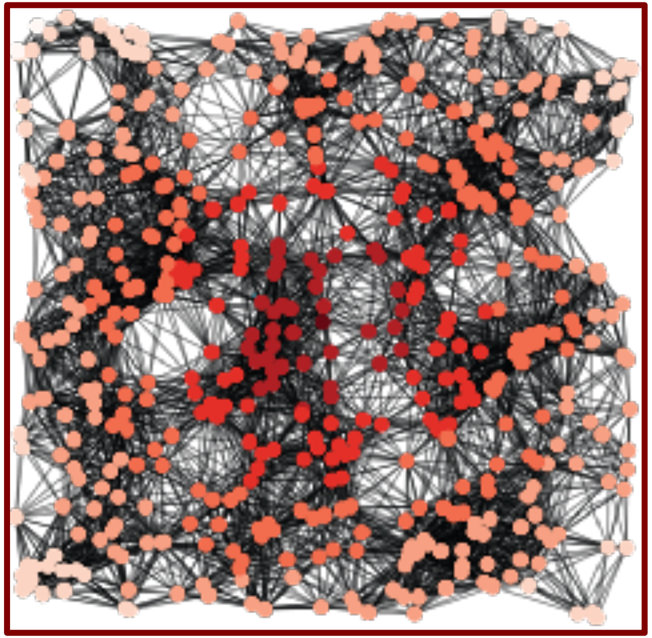
"...and that's why we need a computer."

Networks are prevalent in biology

Example biological networks



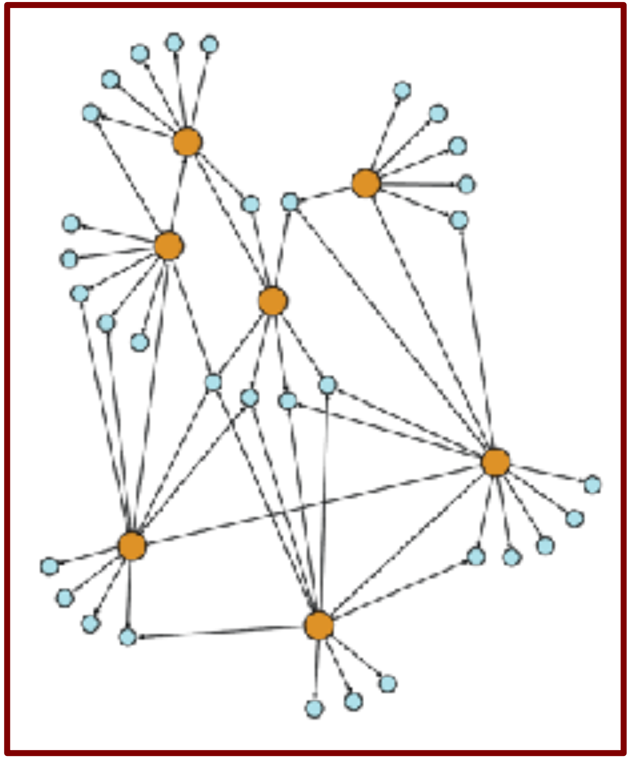
Protein-protein networks



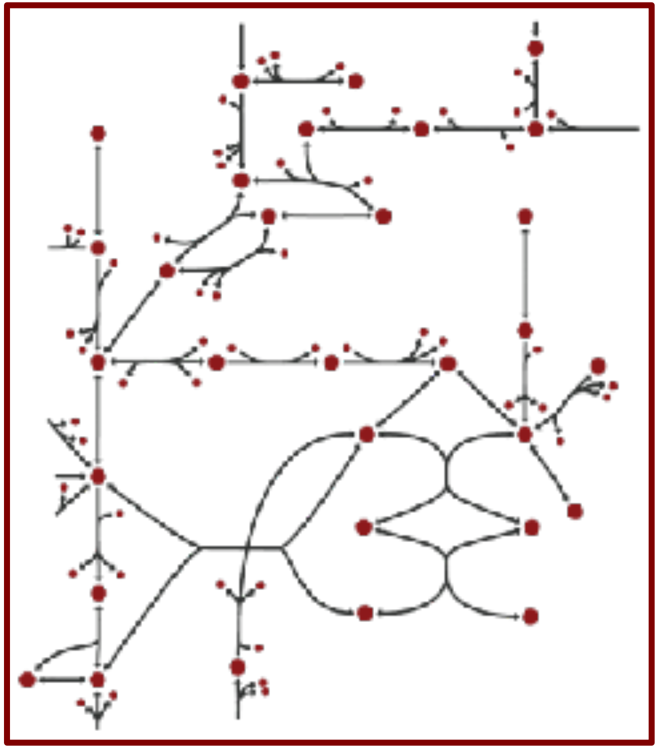
- ➢ We can look at the interaction between different proteins in the network
- ➢ These interaction networks allow us to identify so-called “hubs”: highly-connected nodes in the network

Regulatory networks

- We can use a Boolean network to model the state of various genes, denoting them as “on” or “off”
- Models are built from network topology



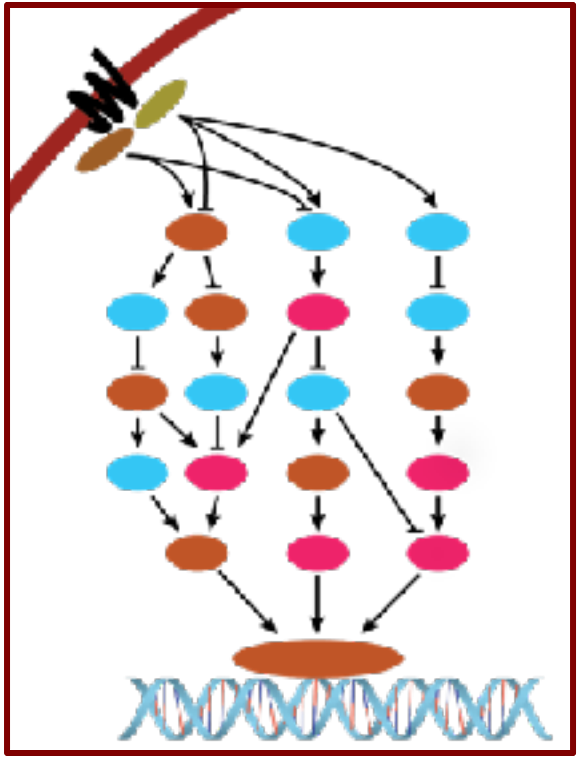
Metabolic networks



- ➢ Modeling the “mass flow” through each reaction in the network allows for the prediction of the state of the network
- ➢ Models can be built from network topology alone
- ➢ Taught in BENG 212

Signaling networks

- ➢ Modeling these networks with ODEs and PDEs plays important roles in understanding cellular functions and in synthetic biology
- ➢ Relies on kinetic rates and parameters

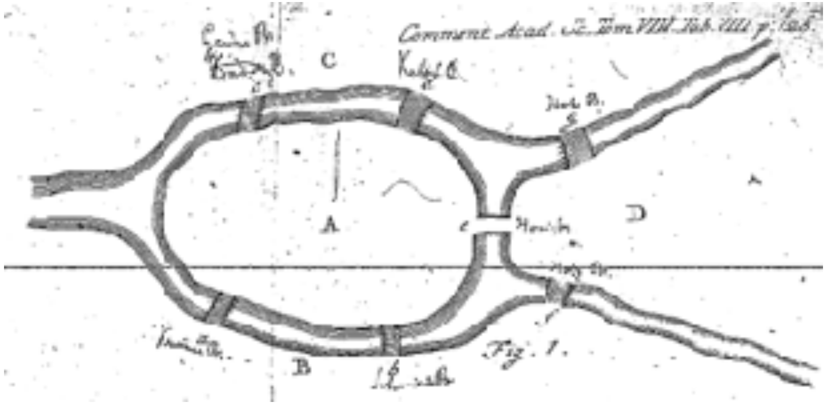


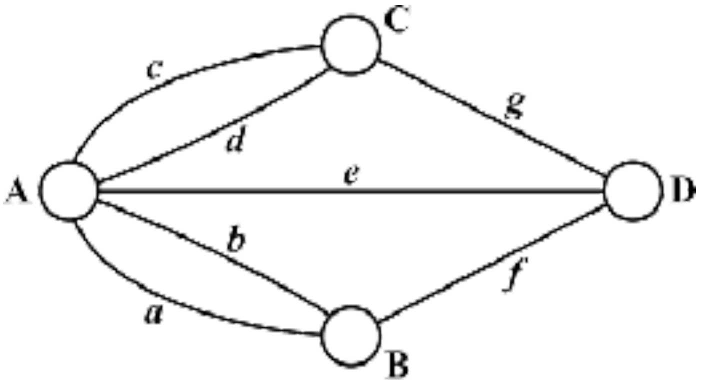
Modeling networks

Mathematics describe the world around us

The beginnings of graph theory

- ➢ The city of Känisberg was built on the banks of the Pregel River, which divided the city into four quadrants connected by seven bridges
- ➢ Citizens used to play a game in which the objective was to walk around the city crossing each bridge exactly once
- ➢ In order to prove that this problem had no solution, the mathematician Euler visualized the bridges as a network
  - ○ Each node represents a quadrant of the city
  - ○ Each edge represents a bridge





Euler (1741), *Commentarii academiae scientiarum Petropolitanae*

Applying graph theory to traffic patterns

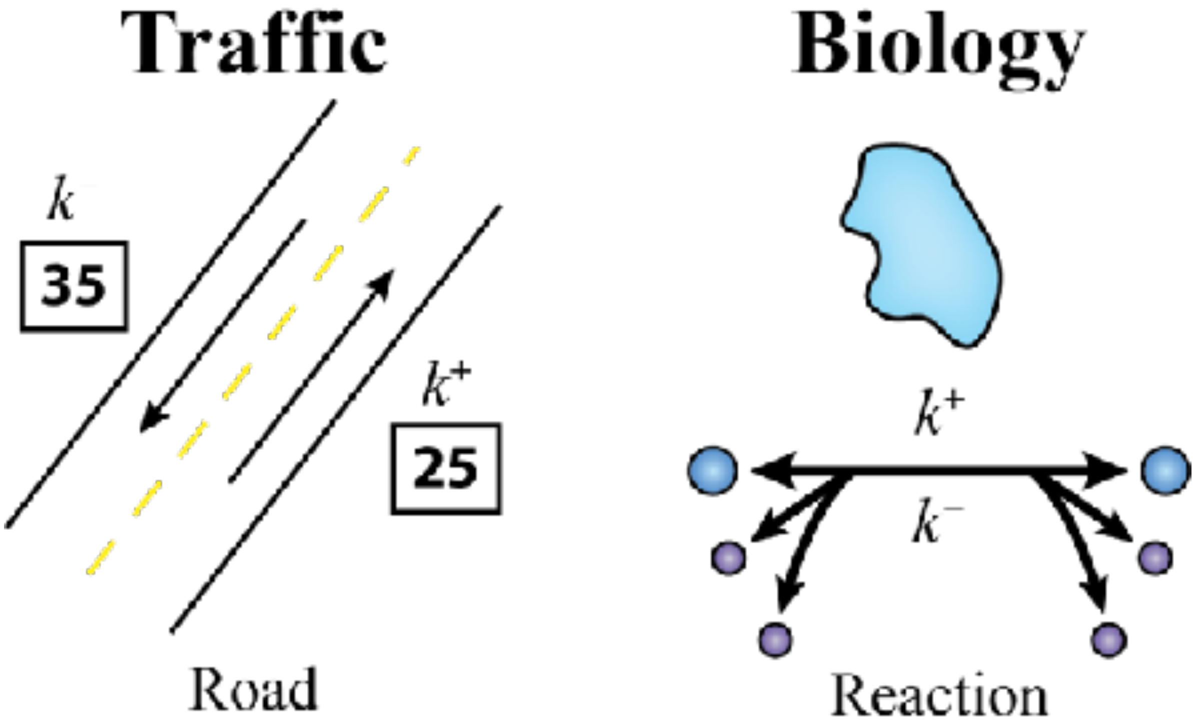
- ➢ Intersections become nodes and the connecting roads are edges
- ➢ We can start to form “pathways” by connecting roads and intersections together
- ➢ There can be multiple routes to a given destination
- ➢ We can now begin to predict how changes in traffic patterns may affect traffic in the surrounding area

Modeling traffic patterns

- We start by defining the fundamental unit in our system: a road
- Each road is parameterized with forward and reverse rates (speed limits)
- This allows us to model the traffic flow of a given road with an ODE

$$\overbrace{\frac{dx}{dt}}^{\text{traffic flow}} = \underbrace{\alpha}_{\text{forward speed limit}}\overbrace{x}^{\text{forward traffic "concentration"}} - \overbrace{\beta}^{\text{reverse speed limit}}\underbrace{x}_{\text{reverse traffic "concentration"}}$$

From traffic to biology

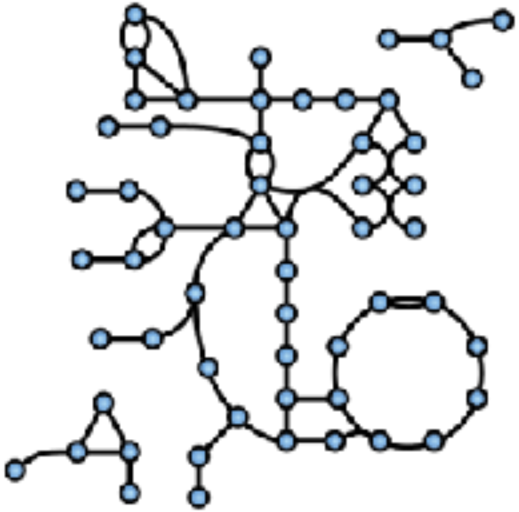


From traffic to biology

Traffic

Network

Biology



Network

Life is an optimization problem - simulating and solving

Objective: get food (on campus)

Lots of different choices…

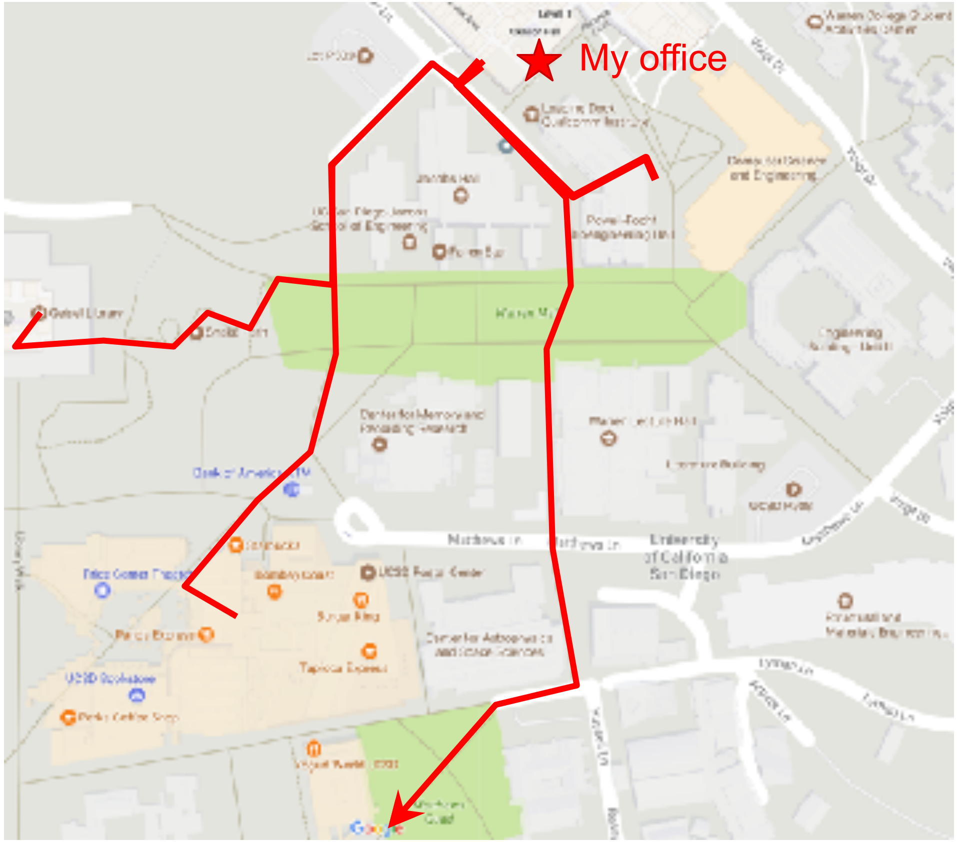
Constraint #1: time (Cups)

Constraint #2: healthiness (Croutons)

Constraint #3: cost (Price Center)

Constraint #4: caffeine (Audrey’s)

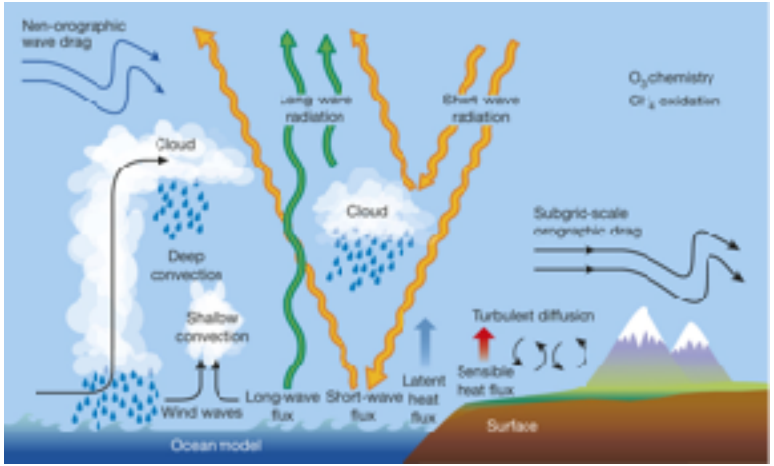
Constraints change under different conditions (e.g., environmental stresses)!

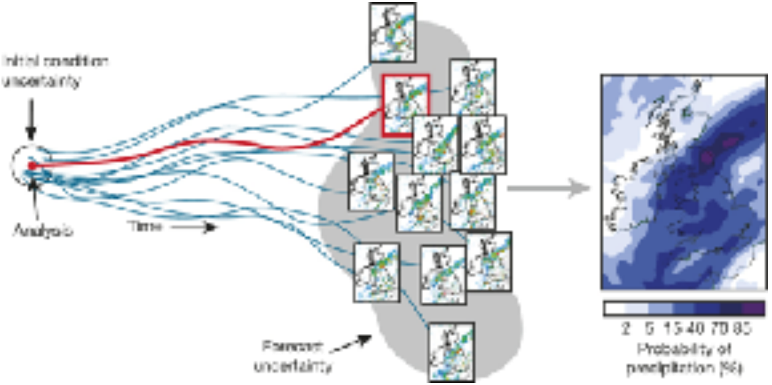


Building models for dynamic simulation

Understanding system responses

Weather forecasting





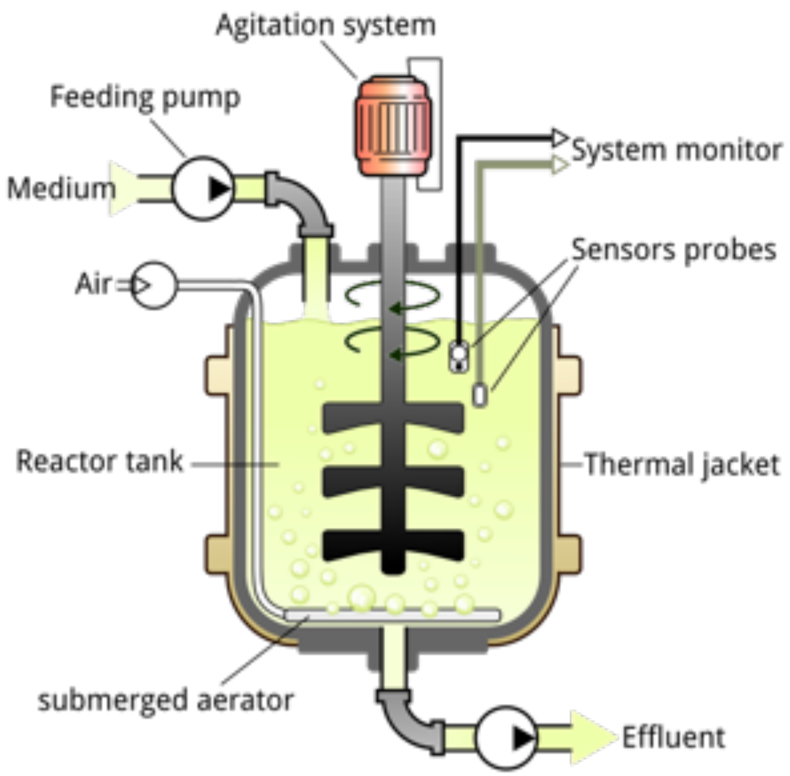
- ➢ The atmosphere is a network, with energy flowing in and out through radiation, evaporation, and condensation
- ➢ Combining world-wide measurement systems and fundamental physical equations, we can predict the temperature across the country or estimate the path of a hurricane

Process control

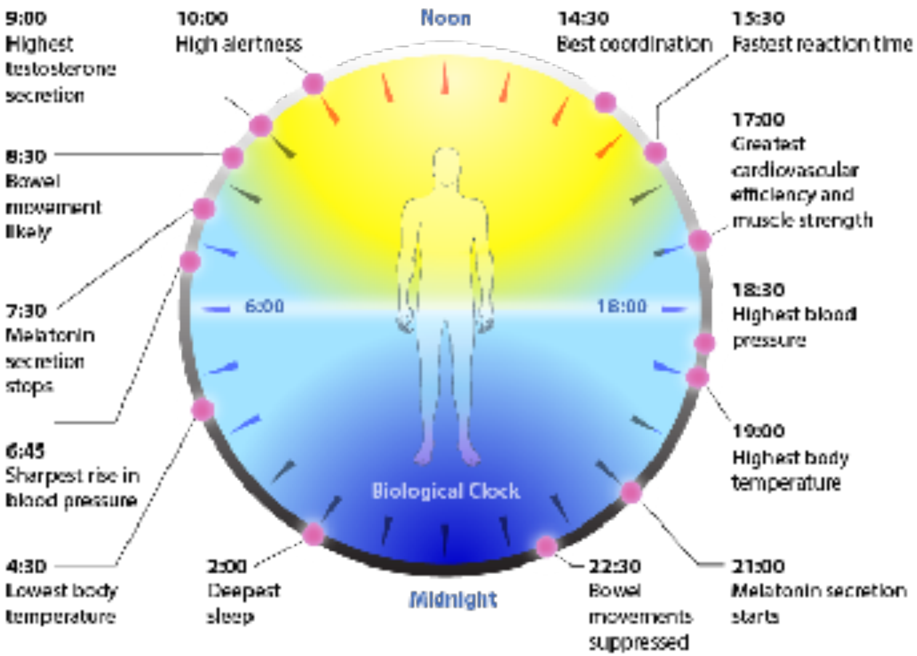
- ➢ The conversion of chemicals from products to reactions can be modeled by a set of ODEs that follow the conservation of mass

$$\underbrace{\frac{dA}{dt}}_{\text{accumulation}} = \underbrace{A_{\text{in}}}_{\text{input}} - \overbrace{A_{\text{out}}}^{\text{output}} + \overbrace{k_{-1}B}^{\text{generation}} - \underbrace{k_1 A}_{\text{consumption}}$$

- ➢ Equations can be built for all species in the reactor to create a system of ODEs



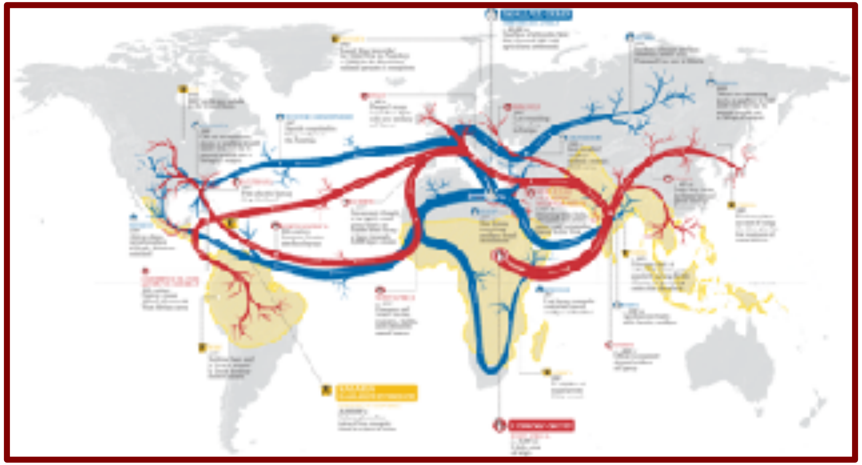
Physiological processes:
Example; Circadian rhythms

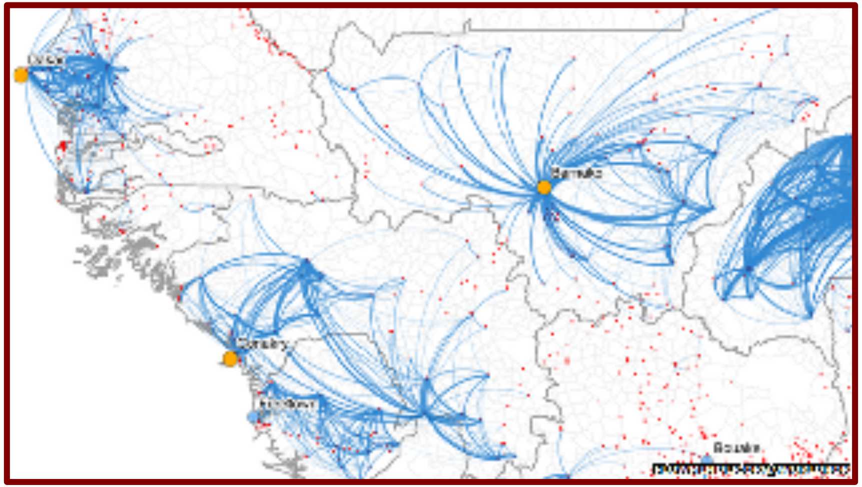


- ➢ We can model Circadian rhythms with a set of ODEs and then dynamically simulate 24 hour cycles
- ➢ These models depend on kinetic rates and other experimentally measured parameters

Spread of disease

- ➢ Certain diseases like leprosy and smallpox can be tracked throughout history
- ➢ Mapping analytics have helped track, understand, and control the spread of the Ebola virus

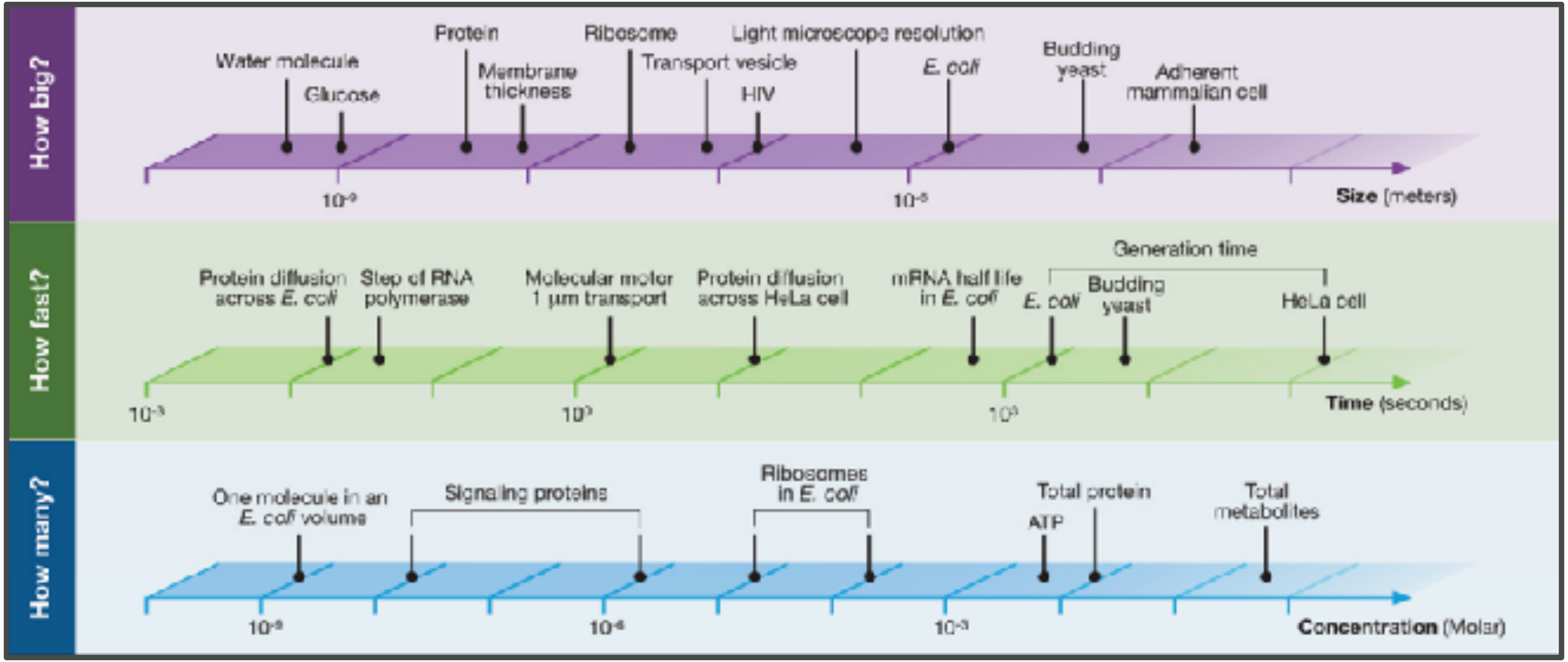




Fundamental concepts

Analyzing dynamics

The multi-scale nature of biology



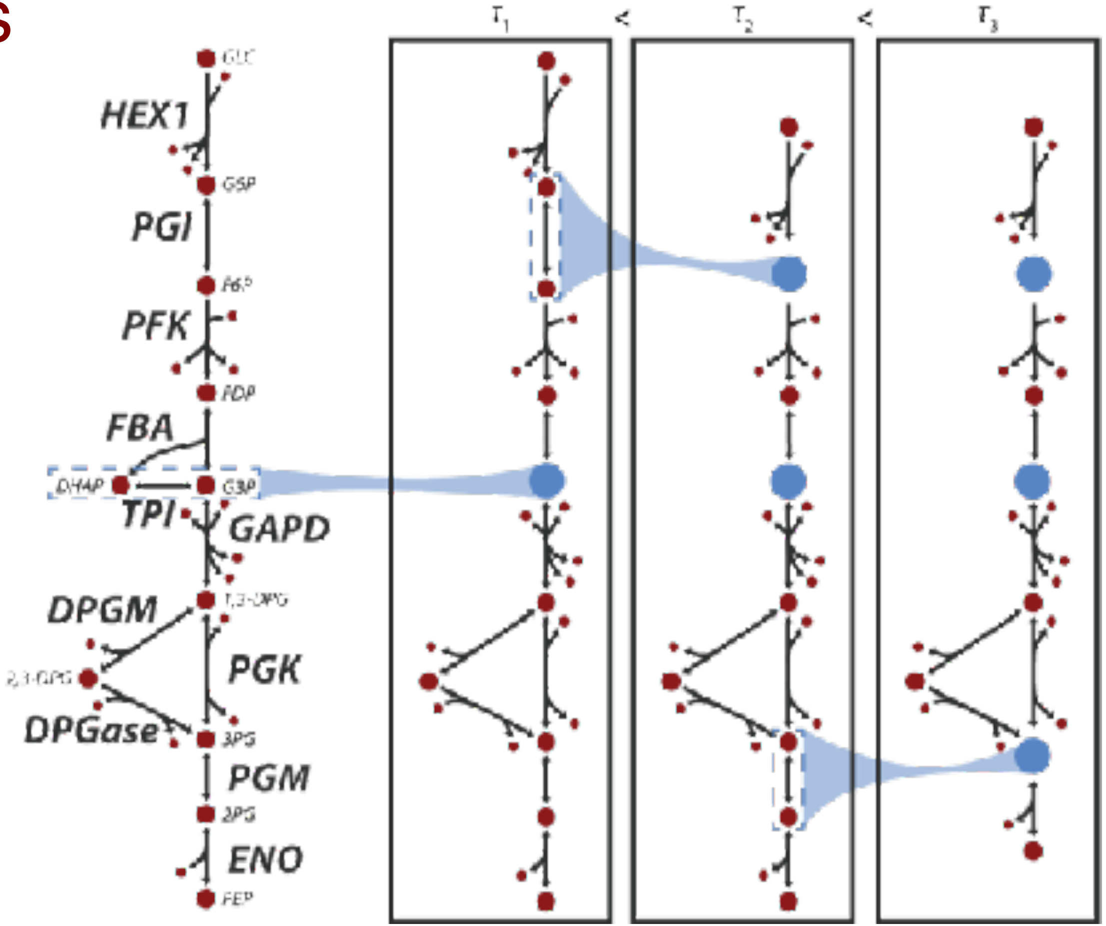
Moran et al. (2010), Cell **141:** 1262

Networks have states

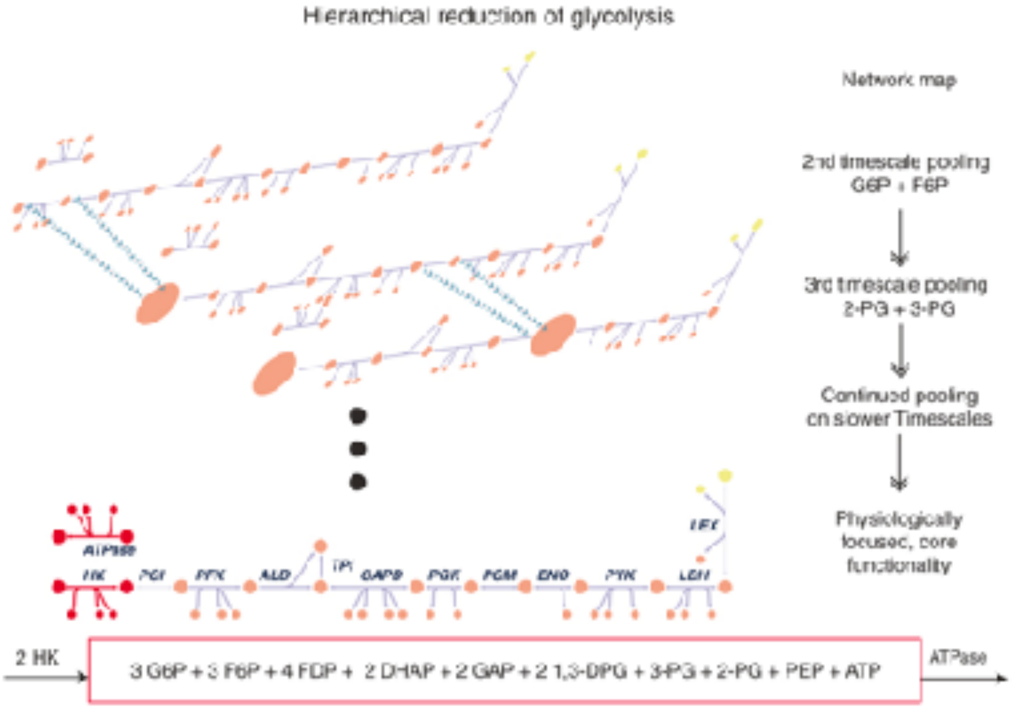
steady, transient, homeostatic, physiological states

Basic concepts in dynamic analysis:

1. Time constant; $t_{1/2}$, τ, …
2. Aggregate variables, multi-scale analysis
3. Transition from one steady-state to another
4. Graphical representation of solution



Multi-scale (hierarchical) analysis



A question of (time) scale

How do we build dynamic models?

Starting point

Two types of approaches

1. Simulation: (1) formulate equations using well-defined assumptions; (2) specify numerical values for parameters; (3) specify the conditions (a case study); (4) numerically solve the system of equations that define your model; (5) graph and analyze the results

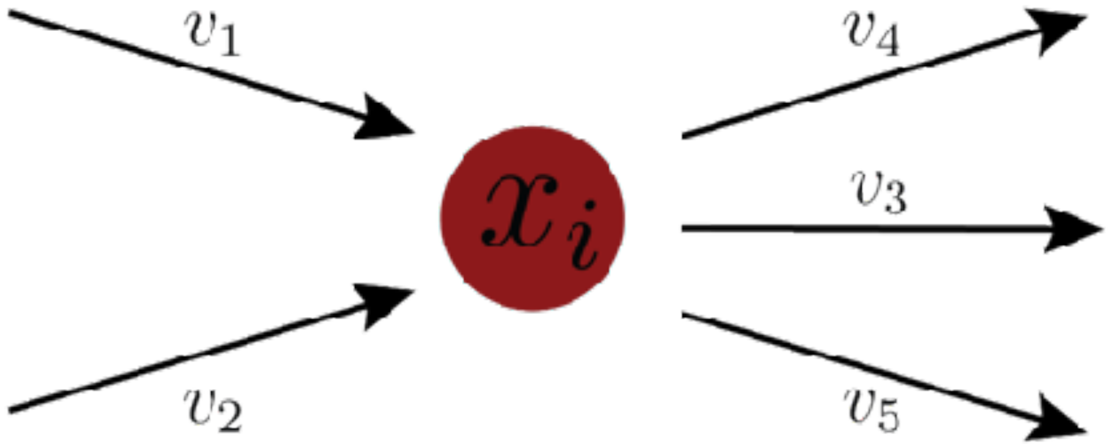
2. Analysis: a model is a formal (mathematical) representation of the data/knowledge that you have about the process/phenomena that you are studying; can analyze model properties to examine how its different components interrelate or contribute to its properties

Assumptions used in model formulation

- Continuum assumption (do not model individual molecules, instead treat medium as continuous)
- Constant volume assumption
- Ignore some physico-chemical factors (e.g., electroneutrality, osmotic pressure)
- Finer spatial structure of cells and organelles is ignored (medium is homogenous at ~100nm)
- Constant temperature; isothermal (also isobaric)

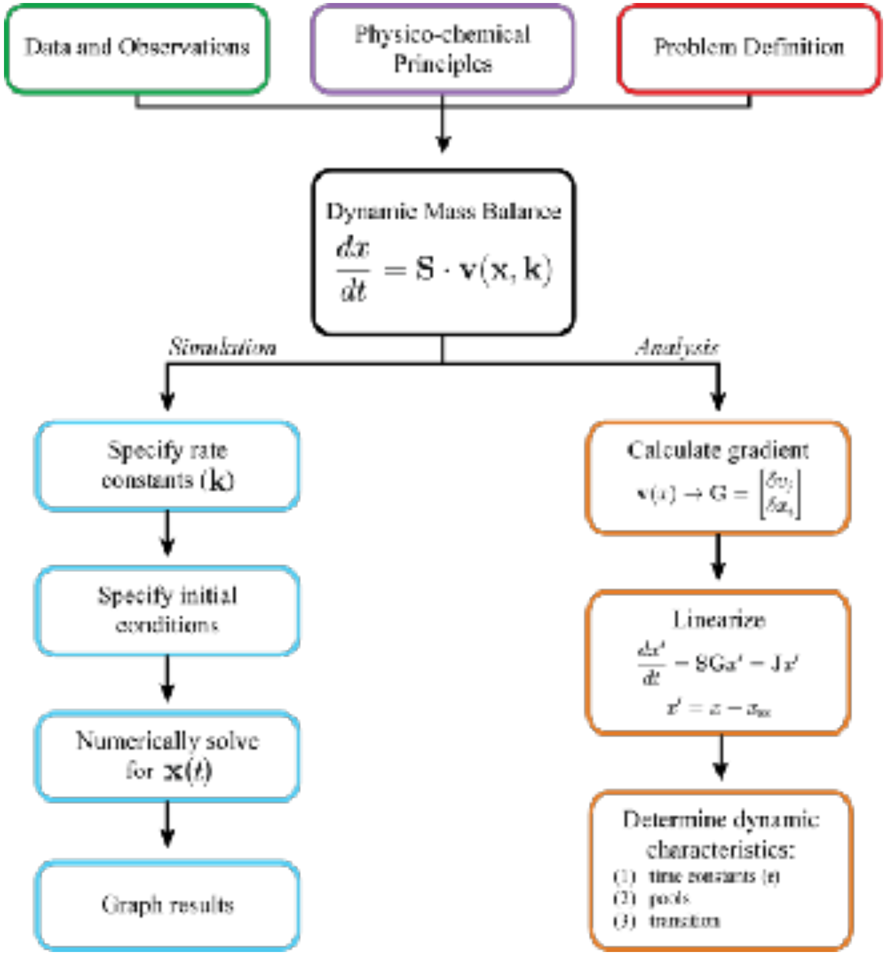
Mass balance equations

A



B

$$
\begin{aligned}
\frac{dx_i}{dt} &= \overbrace{v_1 + v_2}^{\text{formation}} - \overbrace{v_3 - v_4 - v_5}^{\text{degradation}} \\
&= \langle (1, 1, -1, -1, -1), (v_1, v_2, v_3, v_4, v_5)^{\mathrm{T}} \rangle
\end{aligned}
$$



Data and Observations
Physico-chemical Principles
Problem Definition
Dynamic Mass Balance
$\frac{dx}{dt} = \mathbf{S} \cdot \mathbf{v}(\mathbf{x}, \mathbf{k})$
Simulation
Analysis
Specify rate constants ($\mathbf{k}$)
Specify initial conditions
Numerically solve for $\mathbf{x}(t)$
Graph results
Calculate gradient
Linearize
Determine dynamic characteristics:

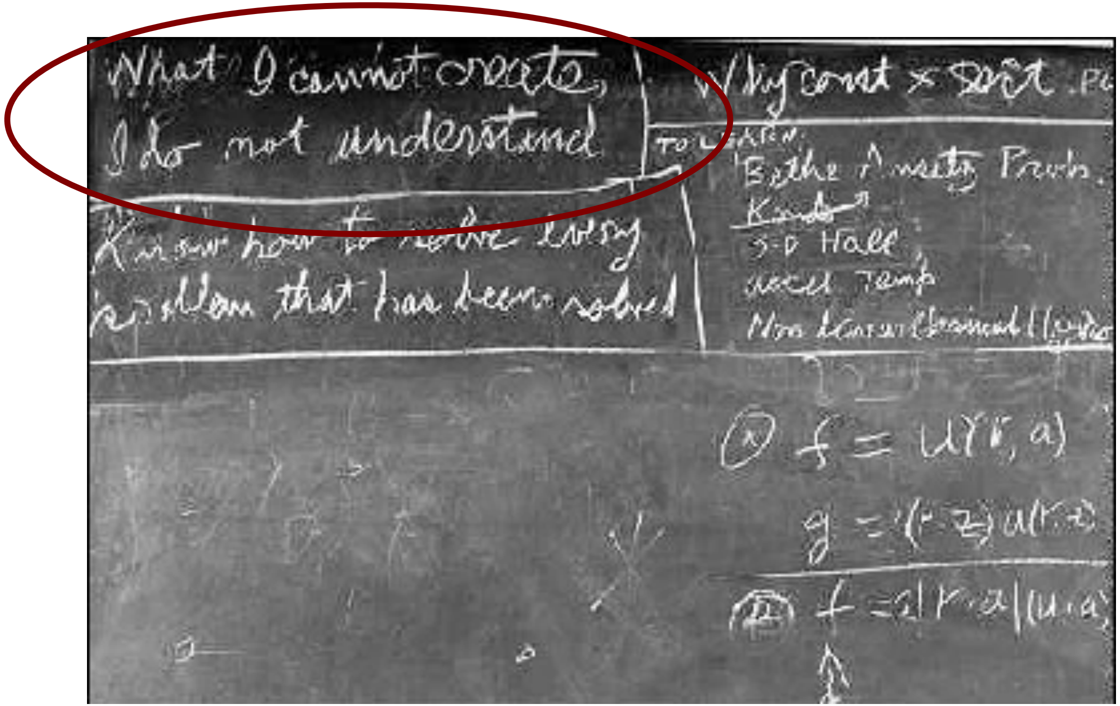
Why do we build dynamic models?

Motivating our learning objectives

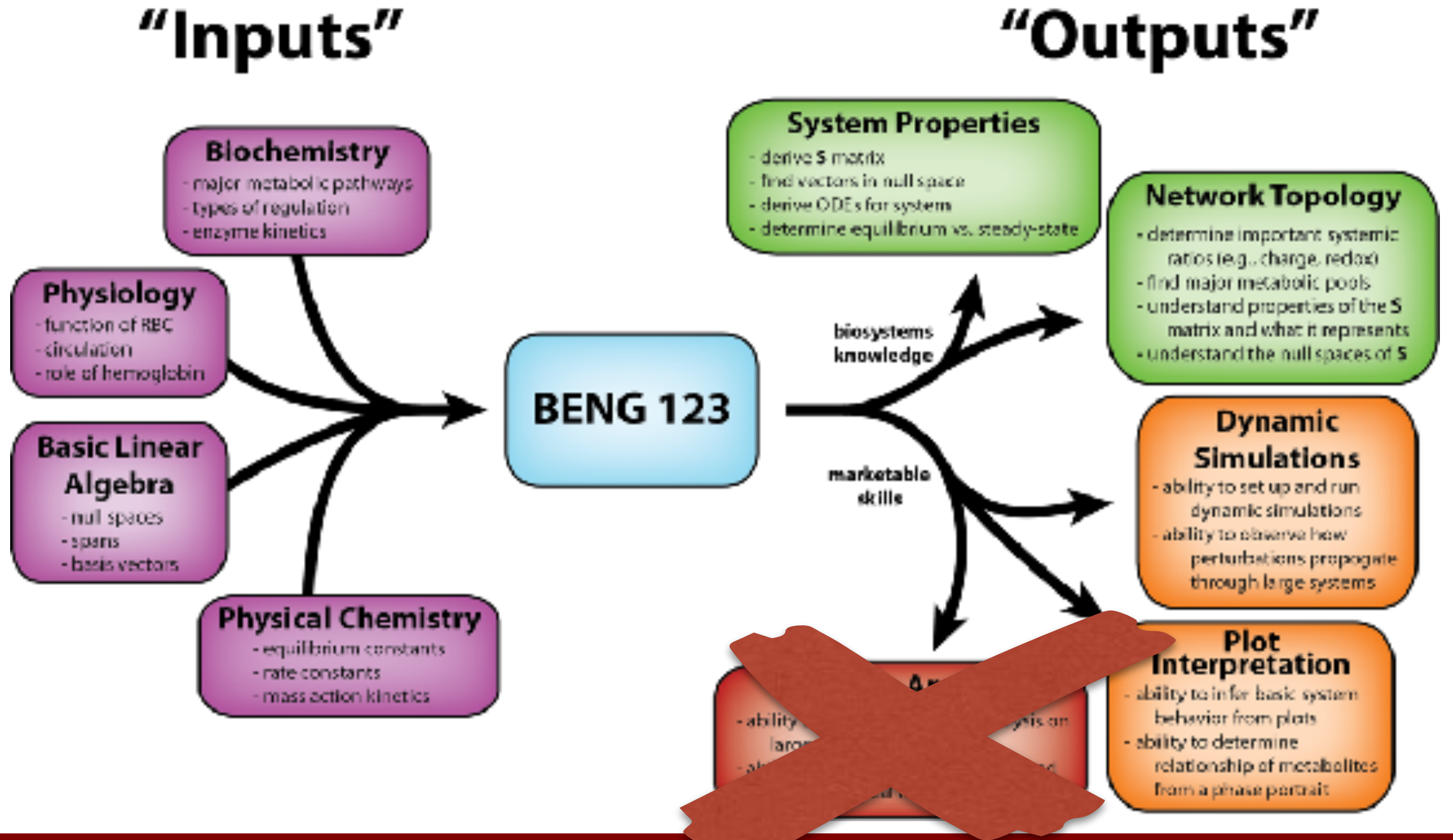
Bailey’s five reasons

1. To organize disparate information into a coherent whole
2. To think (and calculate) logically about what components and interactions are important in a complex system
3. To discover new strategies
4. To make important corrections to conventional wisdom
5. To understand the essential qualitative features

“What I cannot create, I do not understand”



Structure of the course



Summary

“The purpose of a system is the system itself”

- Networks are all around us
  - We are all parts of many networks
- Biological networks can be reconstructed
  - Reconstruction is a laborious effort that integrates disparate sources of information
- Dynamic states of networks are characterized by:
  - Time constants
  - Formation of aggregate variables
  - Characteristic transitions
- Dynamic analysis is a mathematical subject
  - Multi-scale analysis, the spectrum of time scales is a key issue
  - Dynamic models can be simulated and/or analyzed
- There are notable assumptions made while building dynamic models

Extra Material