Modelling Biochemical Reaction Networks

Introductory lecture: What to model? Why?

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Recommended reading

- Fall, Marland, Wagner and Tyson, chapter 1

A bit of philosophical background

Popper: Falsification of hypotheses drives science forward.

Modelling as machinery for the falsification of mechanistic hypotheses

- We start with some observations we are trying to explain.
- Someone generates a hypothesis for a mechanism for the phenomenon.
- Mechanistic hypotheses can be converted to mathematical models.
- Does the model replicate the observations that the hypothesis was meant to explain?
- Does the model make any new predictions that could be tested experimentally?

Other reasons to make mathematical models

Discrimination between rival models

Exploration of phenomena not readily studied experimentally

- Exploration of parameter space

Reduction of a phenomenon to its essentials for further study

(Re)engineering of a process

Exploration of possible interventions

Biochemistry as a multiscale discipline

- Biochemical processes depend on and affect phenomena over a wide range of spatial and temporal scales
- Some relevant length scales:

  Chemical bonds: 10^{-10} m
  Macromolecular dimensions: 10^{-9}–10^{-8} m
  Length of a bacterium or of a mitochondrion: 10^{-6} m
  Red blood cell diameter: 10^{-5} m
  Neuron length: 10^{-3}–1 m
- Some relevant time scales:

  Time for Na^+ to transit through a channel: 10^{-8} s
  Macromolecular conformational changes: 10^{-7}–10^{-3} s
  Transcription, translation: 10^{1}–10^{4} s
  Circadian rhythm: 10^{5} s

Number of molecules

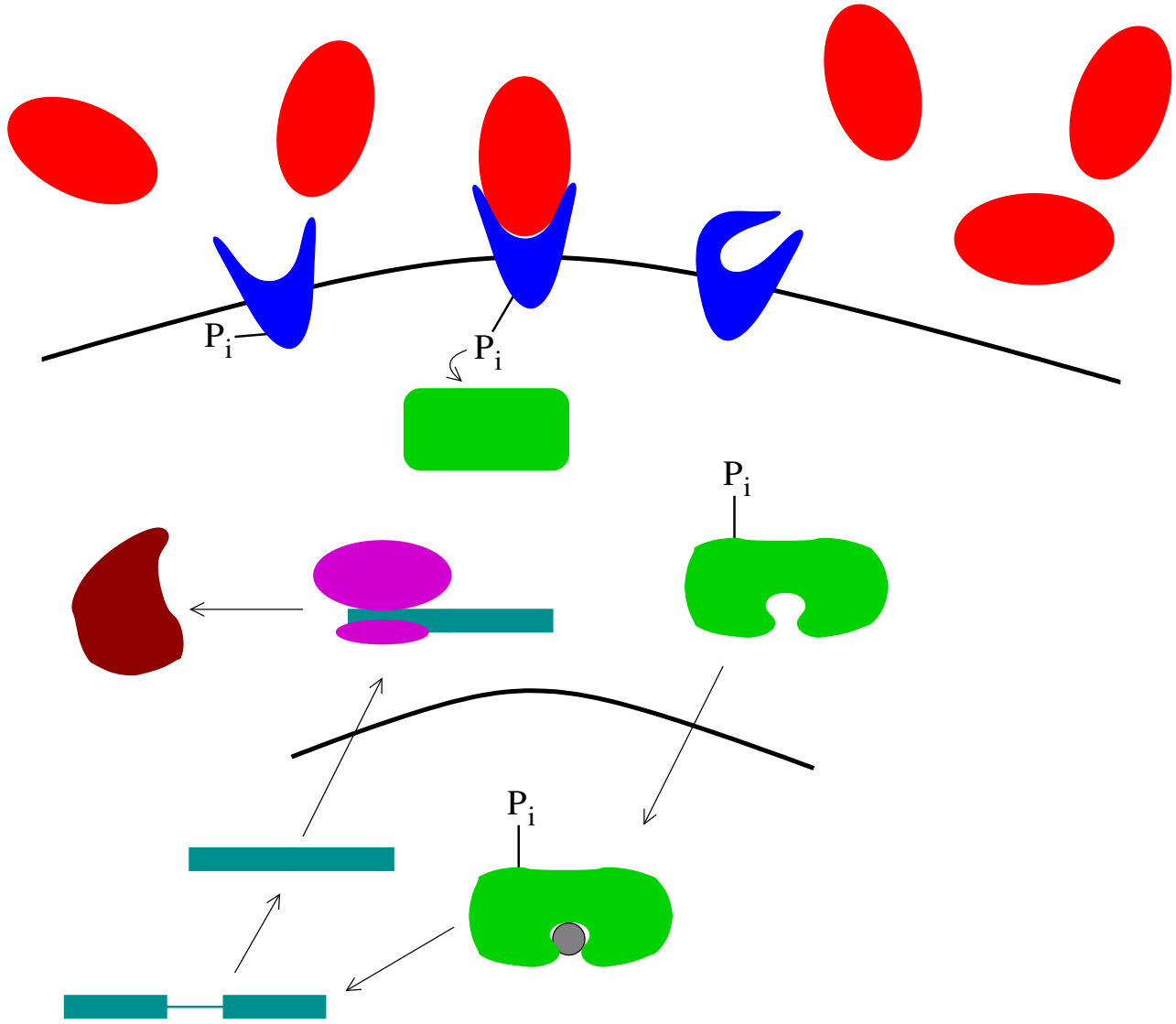
- Suppose that $[\mathrm{X}] = 10\,\mu\mathrm{mol/L}$.
- How many molecules of X do we have?

V/L	Example	N_X
10^{-16}	Axon terminal	600
10^{-15}	Bacterium	6000
10^{-14}	Yeast cell	60 000
10^{-12}	Mammalian cell	6×10^6

Modelling biochemical systems

- You can't model everything completely.
- Many choices to make:
  - Is a qualitative model OK or do you want quantitative agreement?
  - Which physical part of the system (subcellular compartment, cell, group of cells, etc.) do you want to model?
  - Do you need to take the spatial dimension into account explicitly?
    - Do you need to explicitly model diffusive transport?
    - Is it OK to just treat the system as a set of coupled compartments?
  - What range of time scales do you need to cover?
  - What biochemical processes do you need to include? At what level of detail?
  - Number of molecules:
    continuous description (many molecules)
    or stochastic (statistical; few molecules)?

Level of biochemical detail



This course

- Focus on kinetics
- Both differential equation (continuous) and stochastic models covered
- Compartmental descriptions of spatial effects only
- Emphasis on selecting the particular interactions to model, and the level of description required

Some central questions (some of which may not be resolved in this course)

- How do you decide if you have a "good" model?
- Past a certain level of complexity, we tend to rely heavily on computation.
  How do we know if the results of a computation are correct?
- Since kinetic parameters are often difficult to get, is it OK just to get the right structure for a model?