Part 2: Dynamical cell models

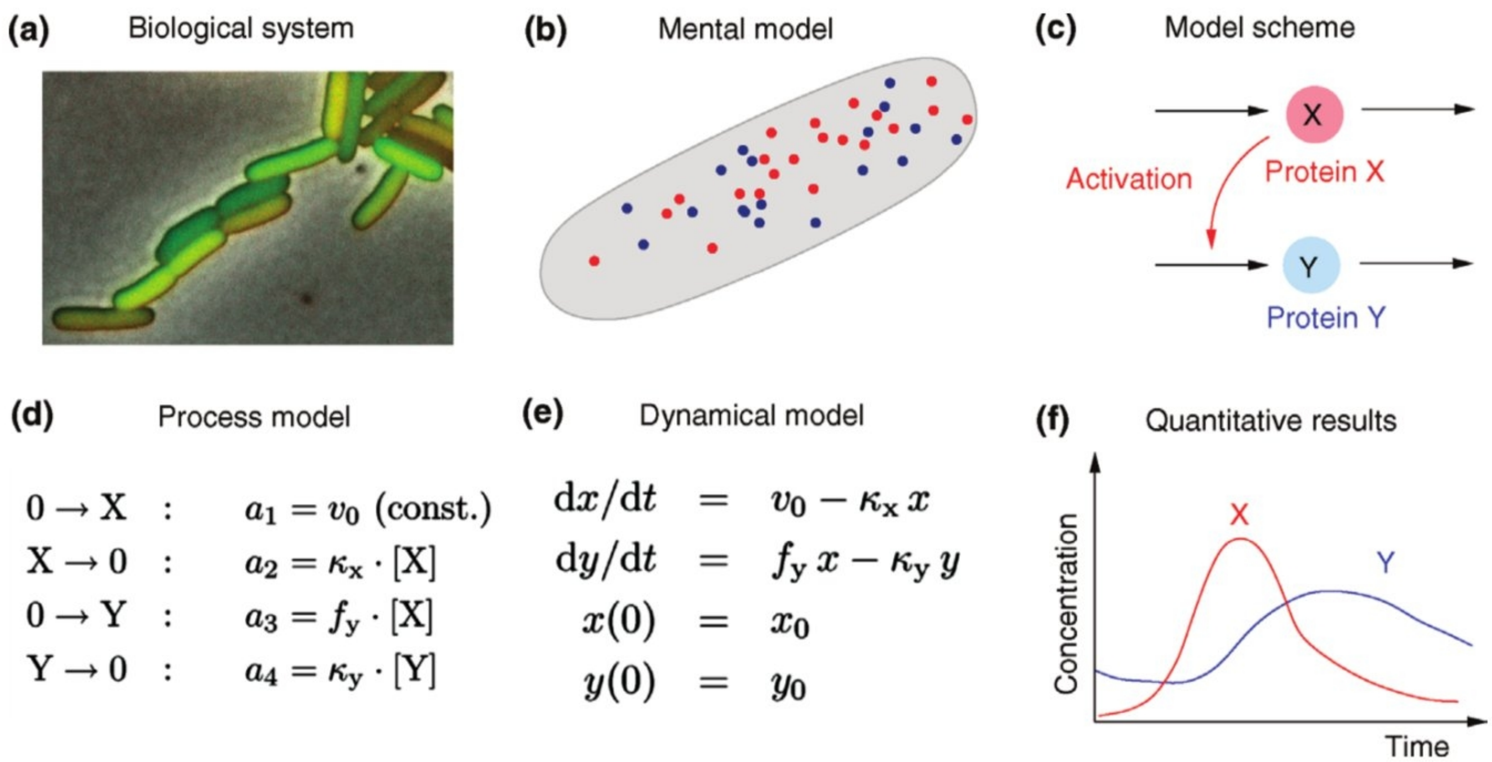
What is a cell model?

How would you design a mathematical model of a cell?

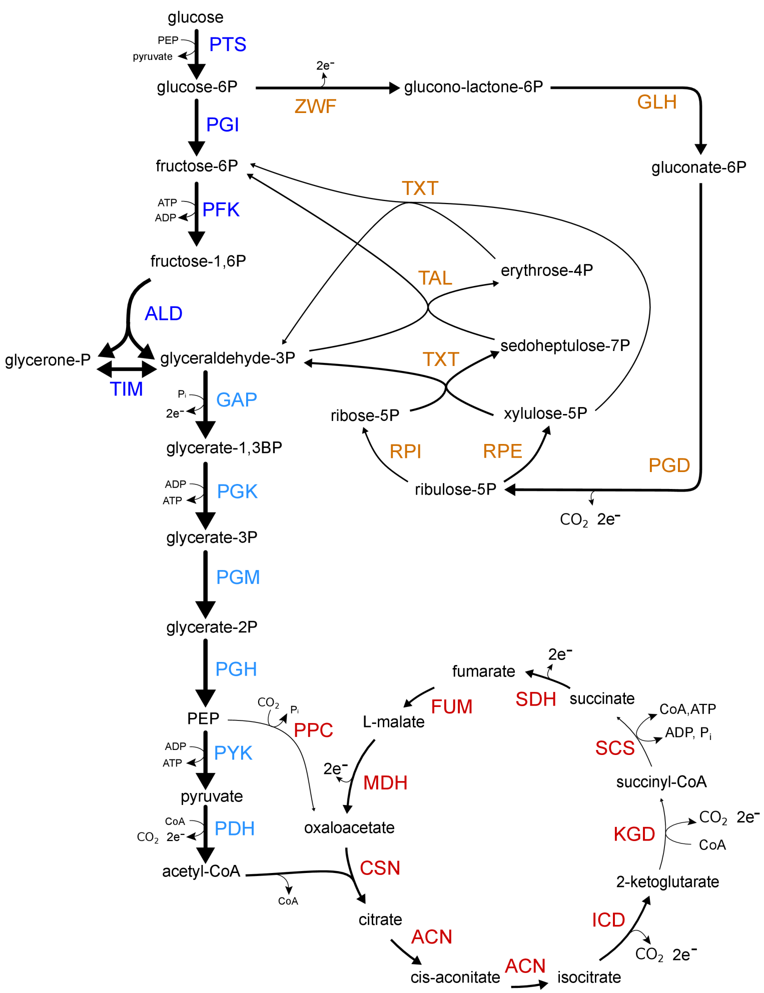
What do you recall about differential equations and linear algebra?

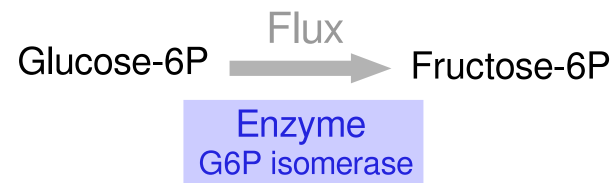
From pictures of cells to mathematical models

Simulation models are simple pictures of cells, in a mathematical form



Metabolic pathway models





Rate law

$$v = [\mathrm{enzyme}]\,\frac{k_{\mathrm{cat}}\,[\mathrm{G6P}]}{[\mathrm{G6P}] + K_{\mathrm{M}}}$$

Main model types

Kinetic models

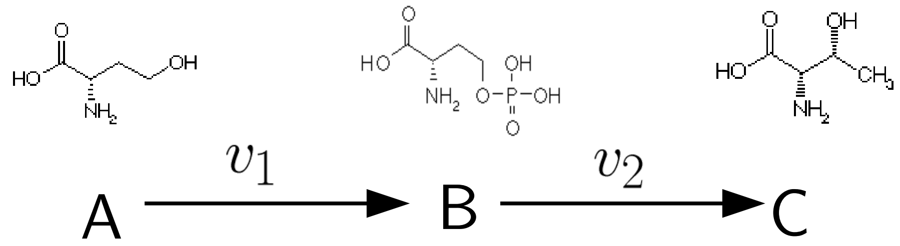
- predict dynamics
- high data demand
- fully mechanistic

Constraint-based models

- predict stationary fluxes
- use network structure only
- use heuristic principles

Kinetic models of metabolic pathways

Kinetic models describe the dynamics of biochemical reactions

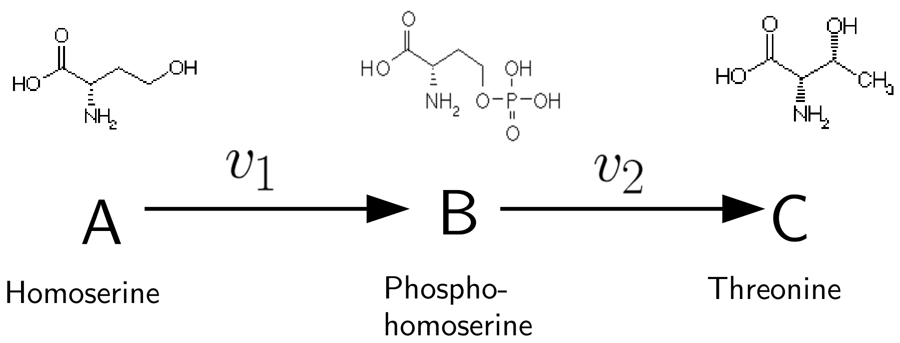


Homoserine

Phospho-homoserine

Threonine

Kinetic models describe the dynamics of biochemical reactions



Kinetic rate law: "mass-action kinetics"

How often does the reaction occur per time ?

$$v_1(a,b) = k_{1+}\, a - k_{1-}\, b$$

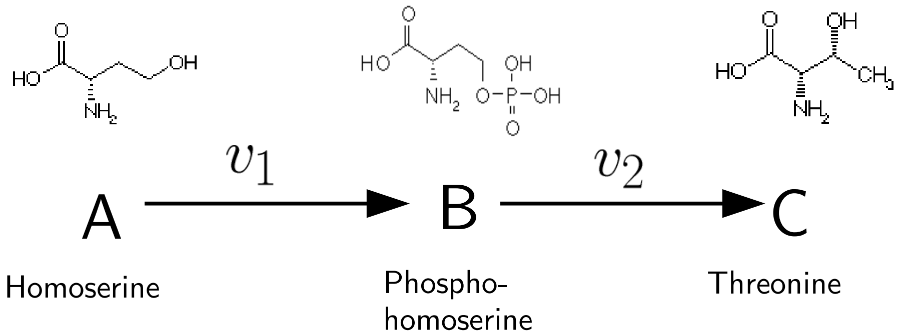
$$v_2(b,c) = k_{2+}\, b - k_{2-}\, c$$

reaction rate

kinetic constant

metabolite concentration

Kinetic models describe the dynamics of biochemical reactions



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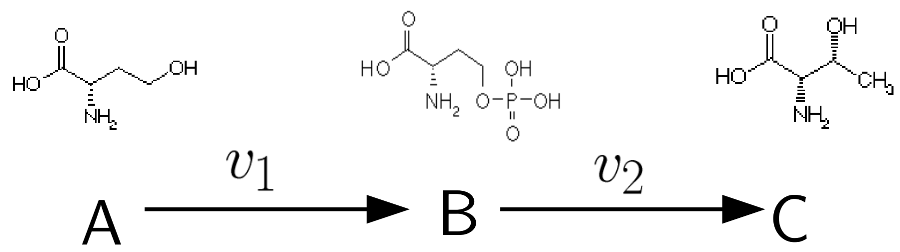
System equations

How do the concentrations change over time?

$$\mathrm{d}a/\mathrm{d}t = -v_1$$
$$\mathrm{d}b/\mathrm{d}t = v_1 - v_2$$
$$\mathrm{d}c/\mathrm{d}t = v_2$$

Kinetic models describe the dynamics of biochemical reactions



Homoserine | Phospho-homoserine | Threonine

Kinetic rate law: "mass-action kinetics"
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$$v_2(b,c) = k_{2+}\,b - k_{2-}\,c$$

reaction rate — kinetic constant — metabolite concentration

concentration change; stoichiometric coefficient; kinetic rate law (reaction rate)

$$\frac{\mathrm{d}s_i}{\mathrm{d}t} = \sum_l n_{il}\, v_l(s,k)$$

metabolite concentrations; kinetic parameters, enzyme concentrations

System equations
How do the concentrations change over time?

$$\mathrm{d}a/\mathrm{d}t = -v_1$$
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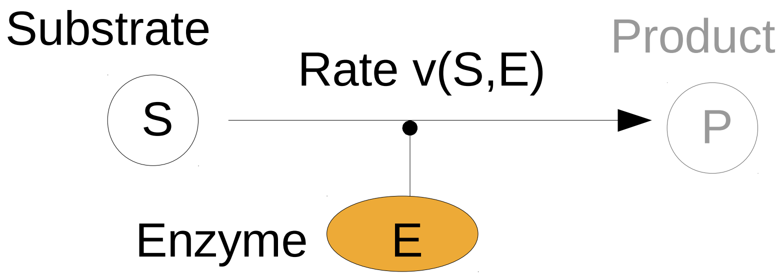
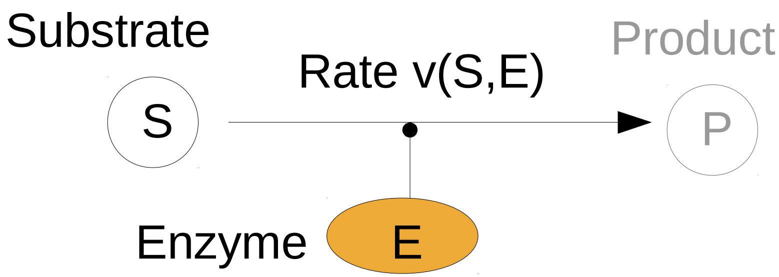
The irreversible Michaelis-Menten rate law

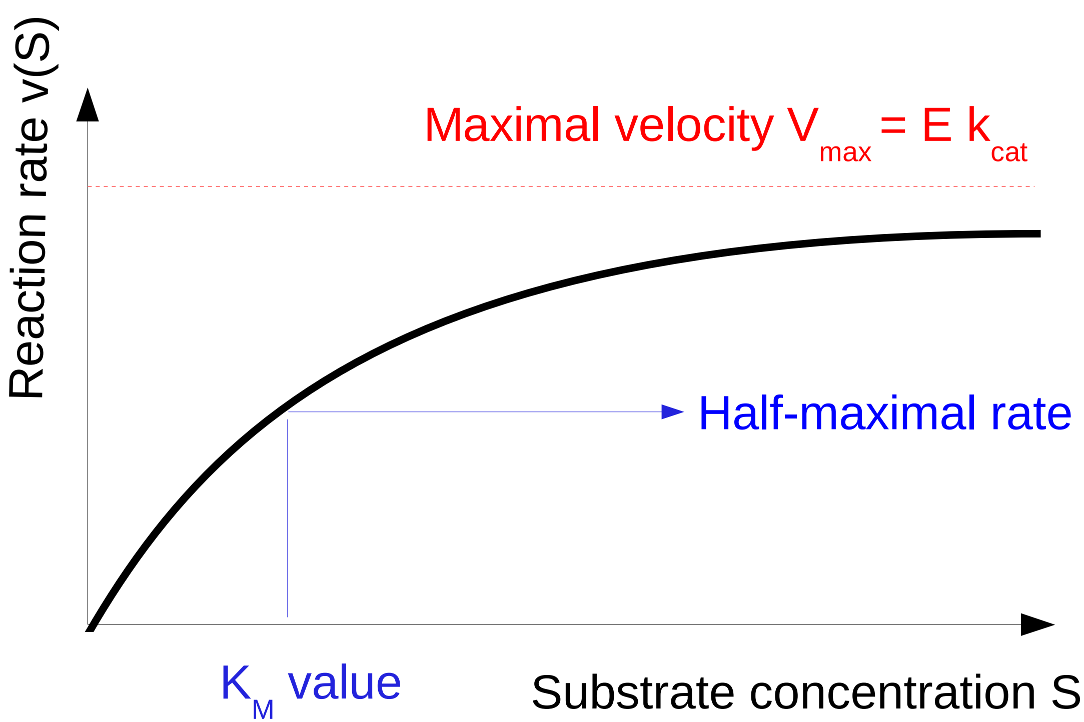


$$v(S,E) = \underbrace{E\,k_{\mathrm{cat}}}_{V_{\mathrm{max}}}\,\frac{S}{S+K_M}$$

The irreversible Michaelis-Menten rate law



$$v(S,E) = \underbrace{E\,k_{\mathrm{cat}}}_{V_{\mathrm{max}}} \frac{S}{S + K_M}$$



Variables:

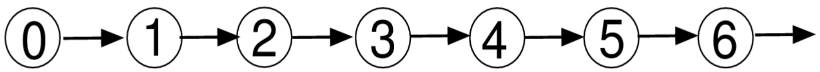
- Substrate concentration s
- Enzyme concentration E

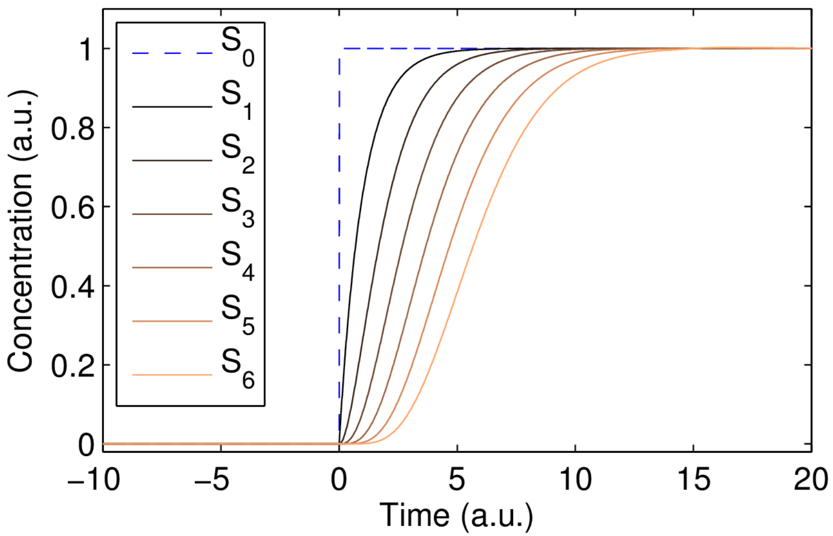
Parameters:

- K_M value (in mM): inverse binding affinity
- Catalytic constant k_{cat} (in 1/s)
  Maximal number of conversions
  per time and enzyme molecule

Dynamic behaviour and steady state

Differential equations describe the change in a moment - numerical integration yields the overall behaviour in time





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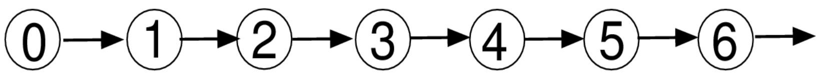
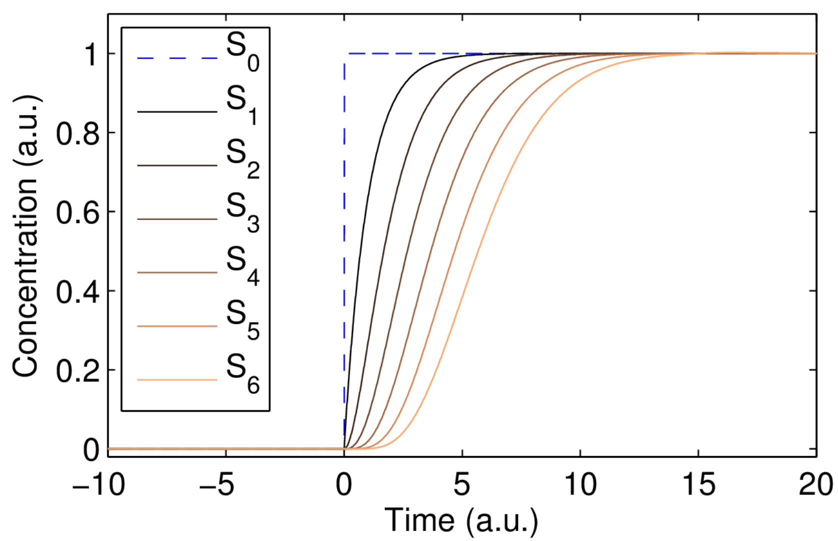




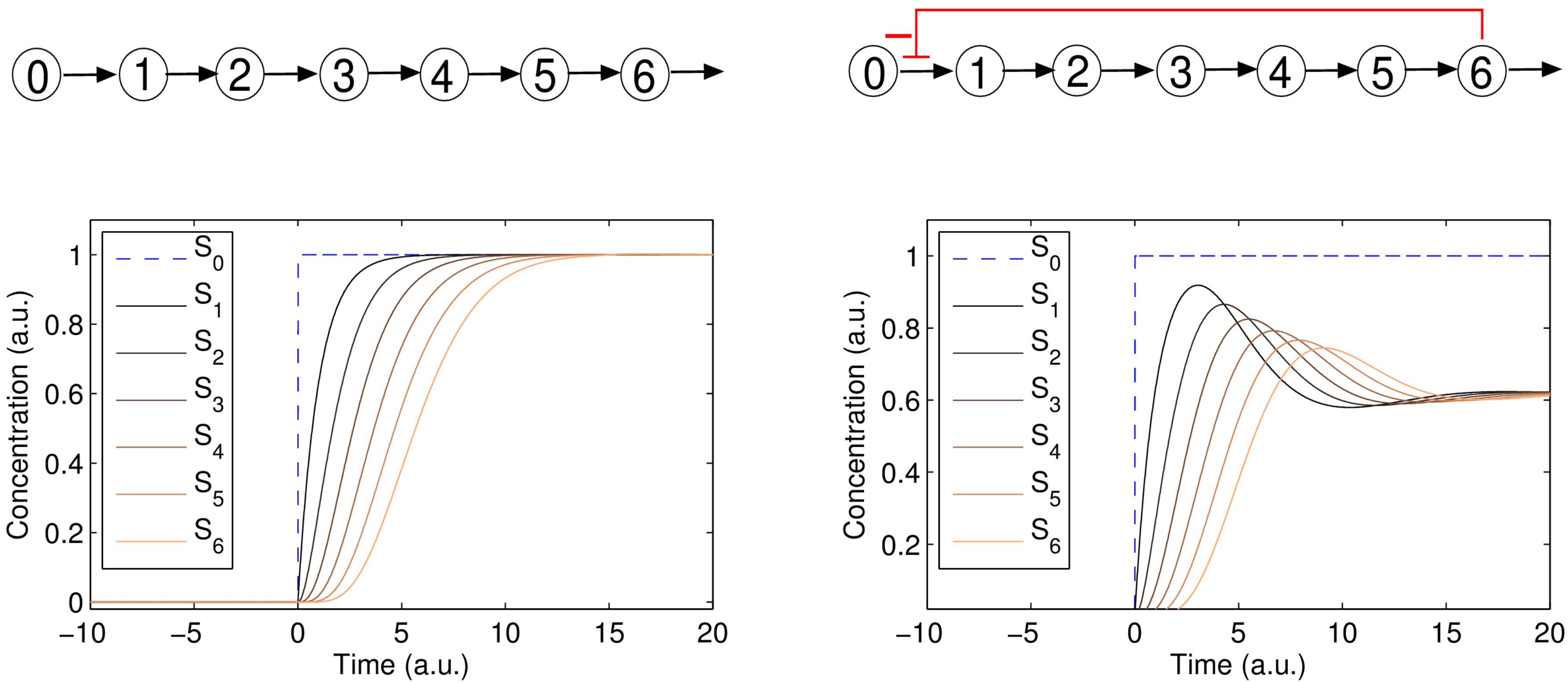
A simple way to solve differential equations numerically (“Euler method”)

- Consider fixed, small time step!
- Start with initial values s(t=0)
- Use the updating rule:

$$\mathrm{s}(\mathrm{t} + \Delta t) = s(t) + \frac{\mathrm{d}s}{\mathrm{d}t}\,\Delta t$$

- Repeat the last step many times

Dynamic behaviour depends on small details of a model



In steady states, all substance levels remain constant in time

Stationarity condition in kinetic models

$$\frac{\mathrm{d}c}{\mathrm{d}t} = N\,v = 0$$

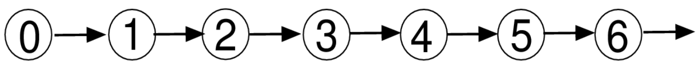
Condition on the flux vector
Kinetic rate laws do not play a role!

External metabolites (e.g. extracellular or buffered)
→ Treated as fixed parameters

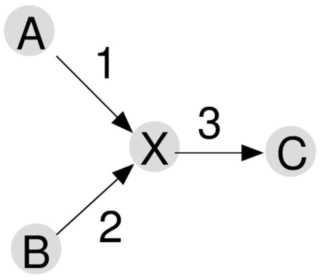
Intracellular metabolites (dynamic)
→ Concentration varies due to chemical reactions

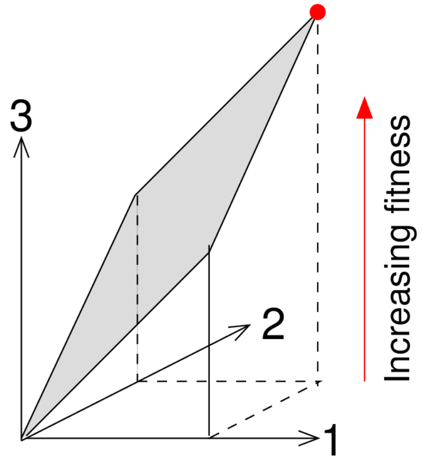
Stationary (=steady) state
A state in which all variables remain constant in time

Linear pathway



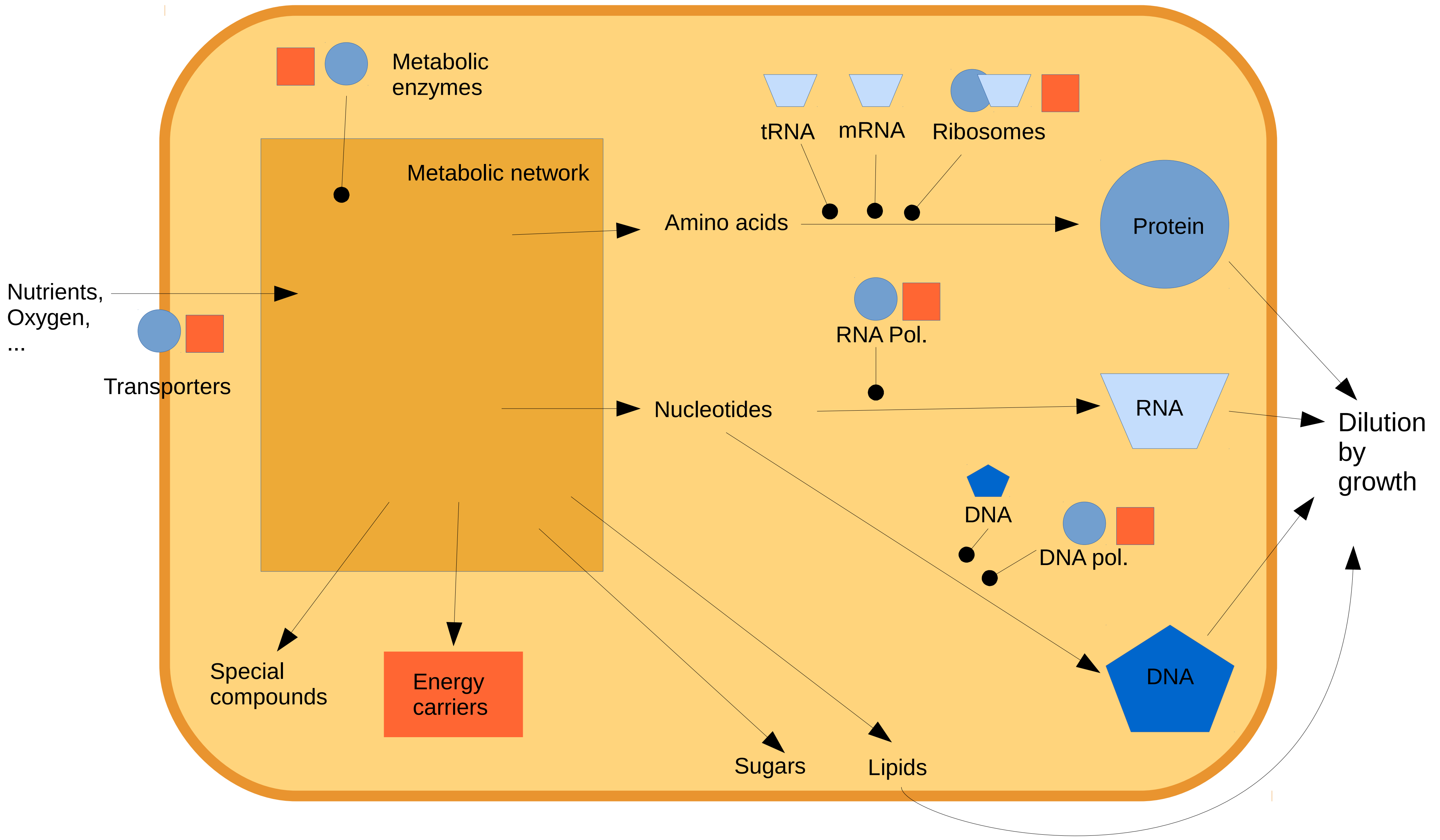
Branch point





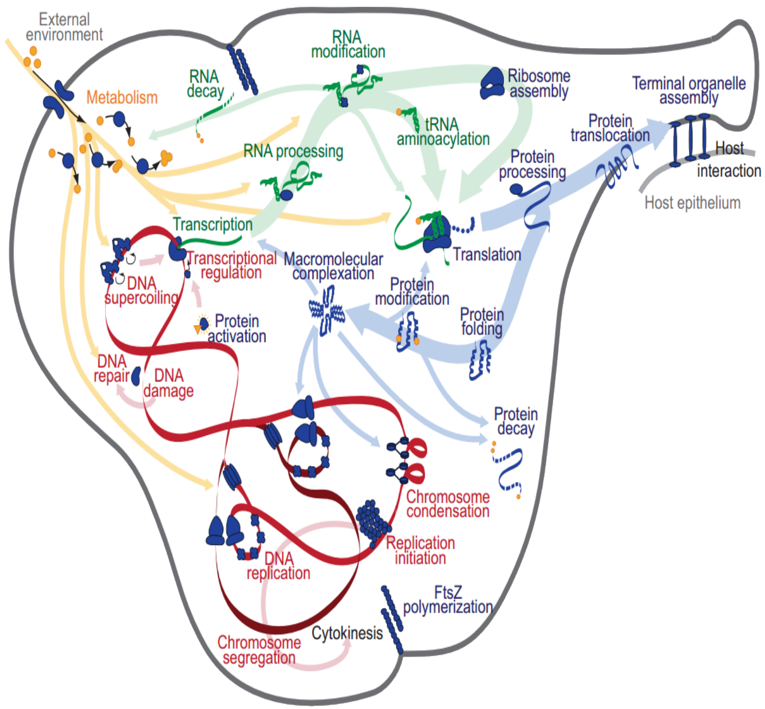
Modular whole-cell models

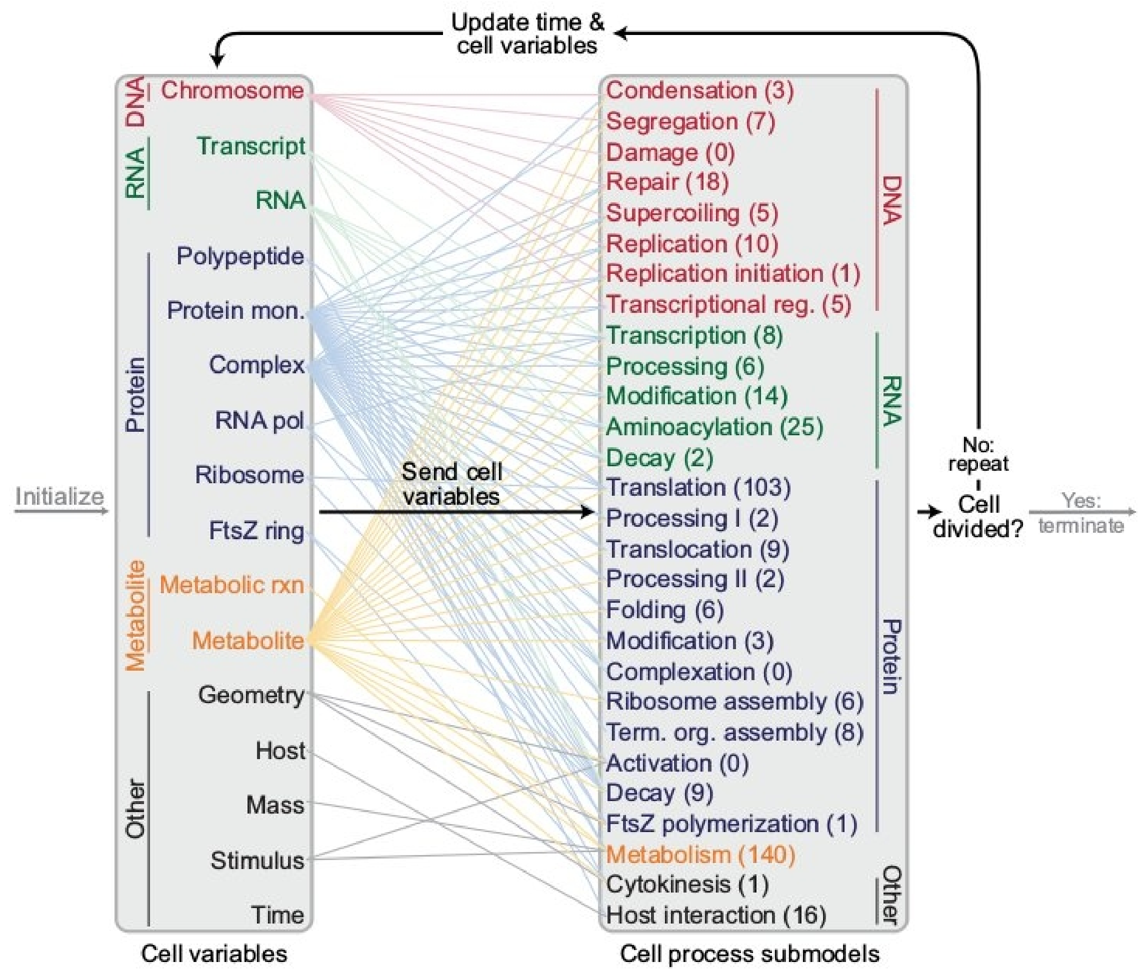
The cell as a self-replicating factory



A whole-cell model for Mycoplasma pneumoniae

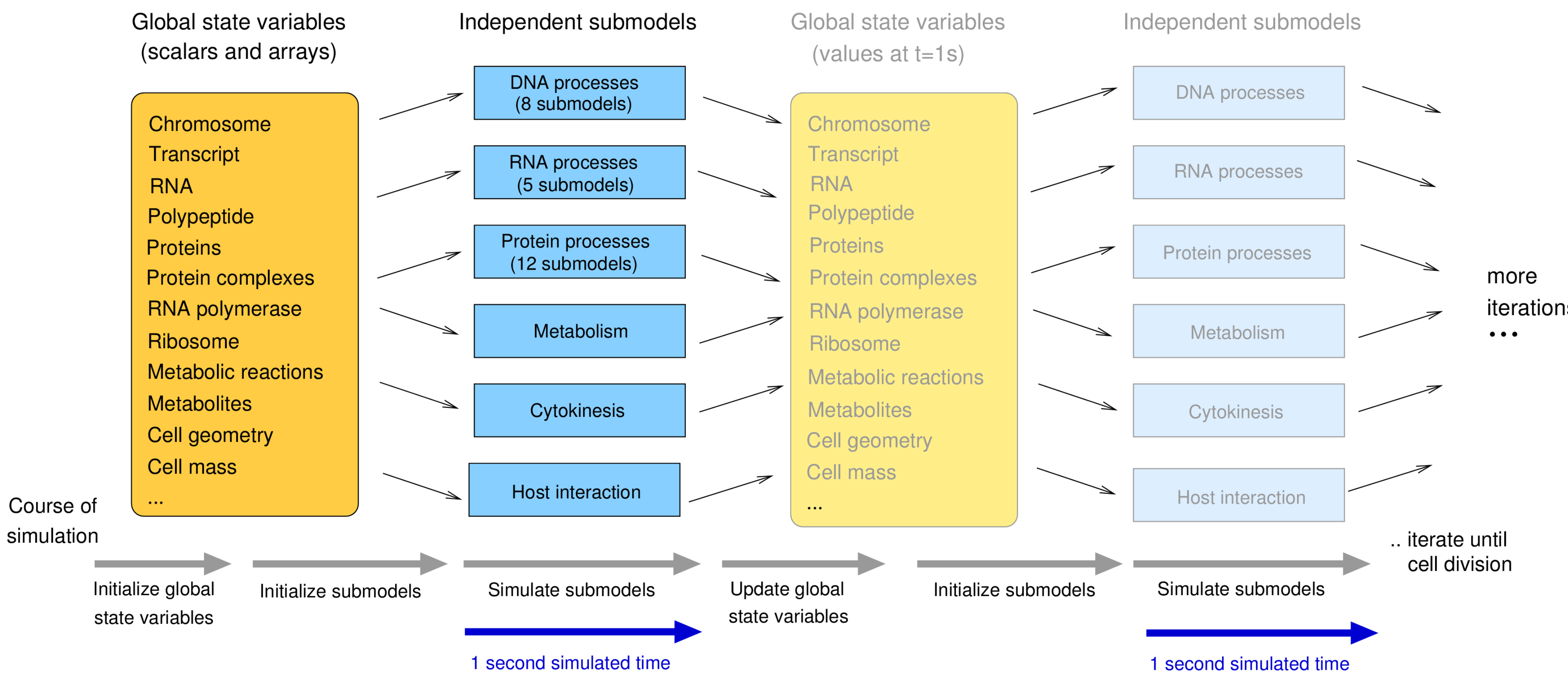
Whole-cell model overview





Karr, J. R. et al (2012): Cell, 150(2), 389–401

How the modular whole-cell model is simulated



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