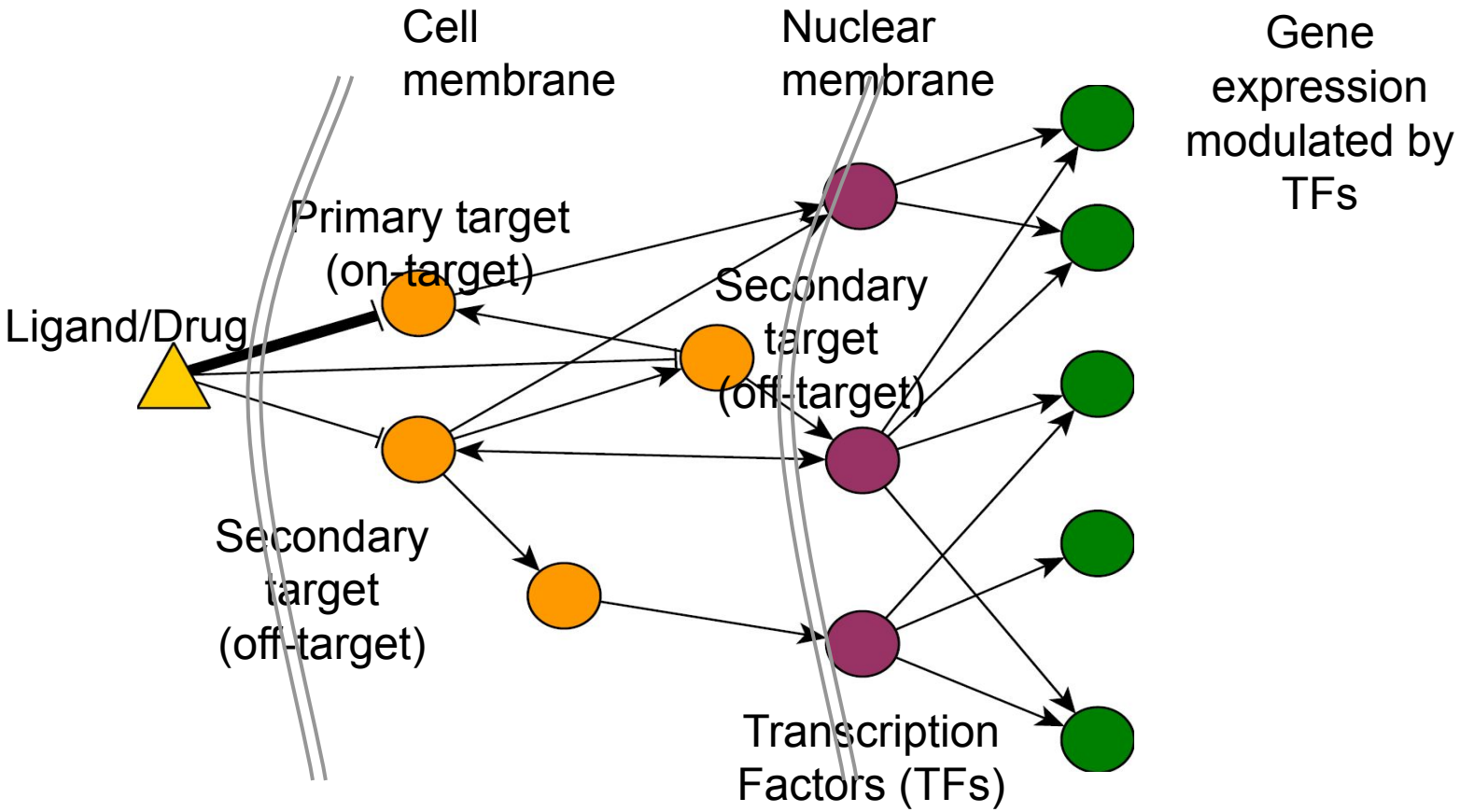
AMIDD Lecture 8: Methods to study biological networks



Dr. Jitao David Zhang, Computational Biologist

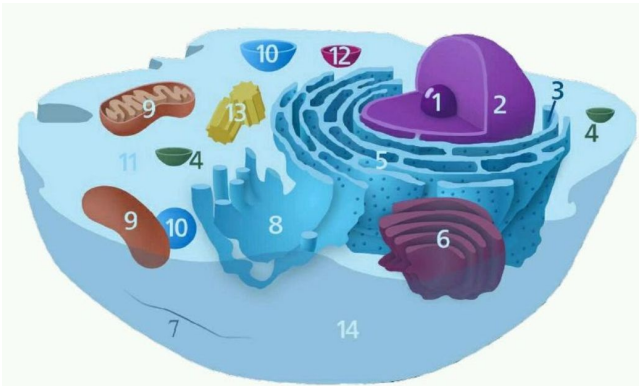
[1] Pharmaceutical Sciences, Pharma Research and Early Development, Roche Innovation Center Basel, F. Hoffmann-La Roche

[2] Department of Mathematics and Informatics, University of Basel

Outline

- Compartment models and Hill function to model drug-target interactions
- Buttom-up study of biological networks with deterministic and stochastic models
- Introduction to top-down study of biological networks with omics and cellular models

Biological networks interact with drugs and manifest its efficacy and safety



Cell membrane

Nuclear membrane

Gene expression modulated by TFs

Primary target (on-target)

Secondary target (off-target)

Ligand/Drug

Protein translation

Phenotype

Secondary target (off-target)

Transcription Factors (TFs)

Ordinary differential equations (ODEs) model ligand-receptor interactions, a common type of edges in biological network

$$\mathrm{L} + \mathrm{R} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \mathrm{LR}$$

The law of mass action

$$\frac{d[LR]}{dt} = k_1[L][R] - k_2[LR]$$

At equilibrium, no net change of [LR]

$$k_1[L][R] = k_2[LR]$$

$$R_{total} = [R] + [LR]$$

$$k_1[L]([R_{total}] - [LR]) = k_2[LR],$$

$$[LR] = \frac{k_1[L][R_{total}]}{k_1[L] + k_2}$$

$K_D \equiv k_2/k_1$

$$[LR] = \frac{[R_{total}][L]}{[L] + K_D}$$

The Michaelis-Menten model of enzyme kinetics, an type of interaction important for drug discovery

$$\mathrm{E} + \mathrm{S} \underset{k_r}{\overset{k_f}{\rightleftharpoons}} \mathrm{ES} \xrightarrow{k_{cat}} \mathrm{E} + \mathrm{P}$$

The law of mass action

$$\frac{d[E]}{dt} = -k_f[E][S] + k_r[ES] + k_{cat}[ES],$$
$$\frac{d[S]}{dt} = -k_f[E][S] + k_r[ES],$$
$$\frac{d[ES]}{dt} = k_f[E][S] - k_r[ES] - k_{cat}[ES],$$
$$\frac{d[P]}{dt} = k_{cat}[ES],$$

Assuming that $k_f[E][S] = k_r[ES]$

$$k_f([E]_0 - [ES])[S] = k_r[ES]$$
$$k_f[E]_0[S] - k_f[ES][S] = k_r[ES]$$
$$k_f[E]_0[S] = k_r[ES] + k_f[ES][S]$$
$$k_f[E]_0[S] = [ES](k_r + k_f[S])$$
$$[ES] = \frac{k_f[E]_0[S]}{k_r + k_f[S]}$$
$$[ES] = \frac{k_f[E]_0[S]}{k_f(\frac{k_r}{k_f} + [S])}$$

$$K_D \equiv \frac{k_r}{k_f}$$

$$[ES] = \frac{[E]_0[S]}{K_D + [S]}$$

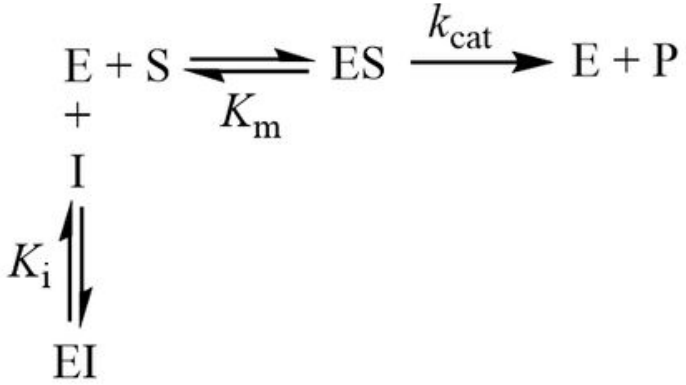
$$v = \frac{d[P]}{dt} = k_{cat}[ES] = \frac{k_{cat}[E]_0[S]}{K_D + [S]}$$

$$V_{max} \equiv k_{cat}[E]_0$$

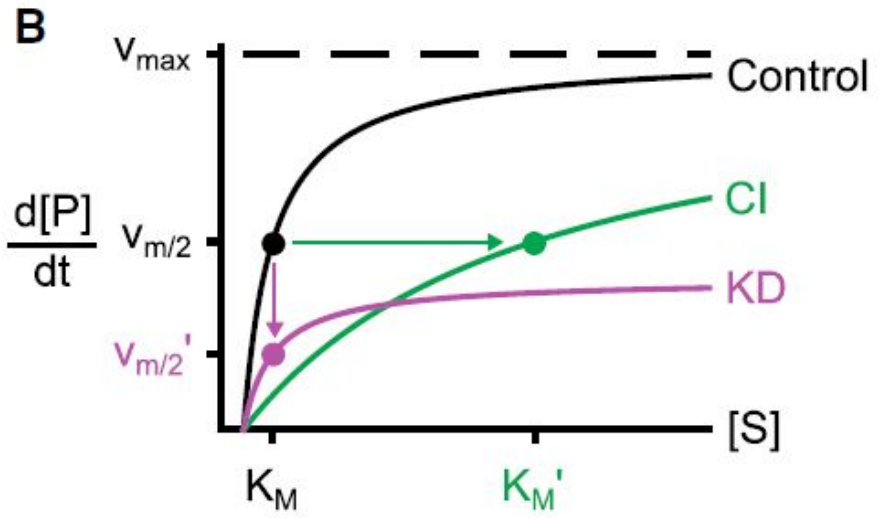
$$v = \frac{V_{max}[S]}{K_D + [S]}$$

Many drugs act as competitive inhibitor to reduce the rate of biochemical reactions

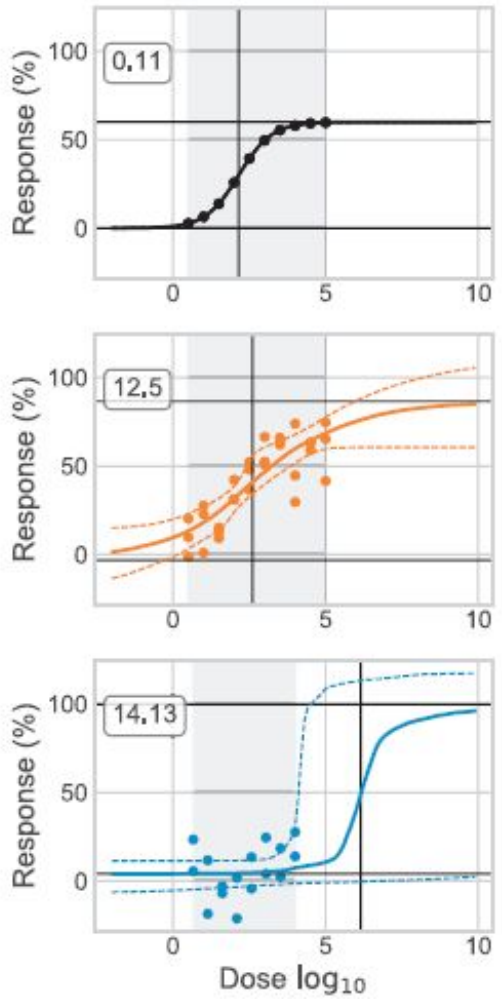
Competitive inhibition (CI)



$$v = \frac{V_{max}[S]}{K_D + [S]}$$



Fixed drug concentration, varying substrate concentration



Fixed substrate concentration, varying drug concentration

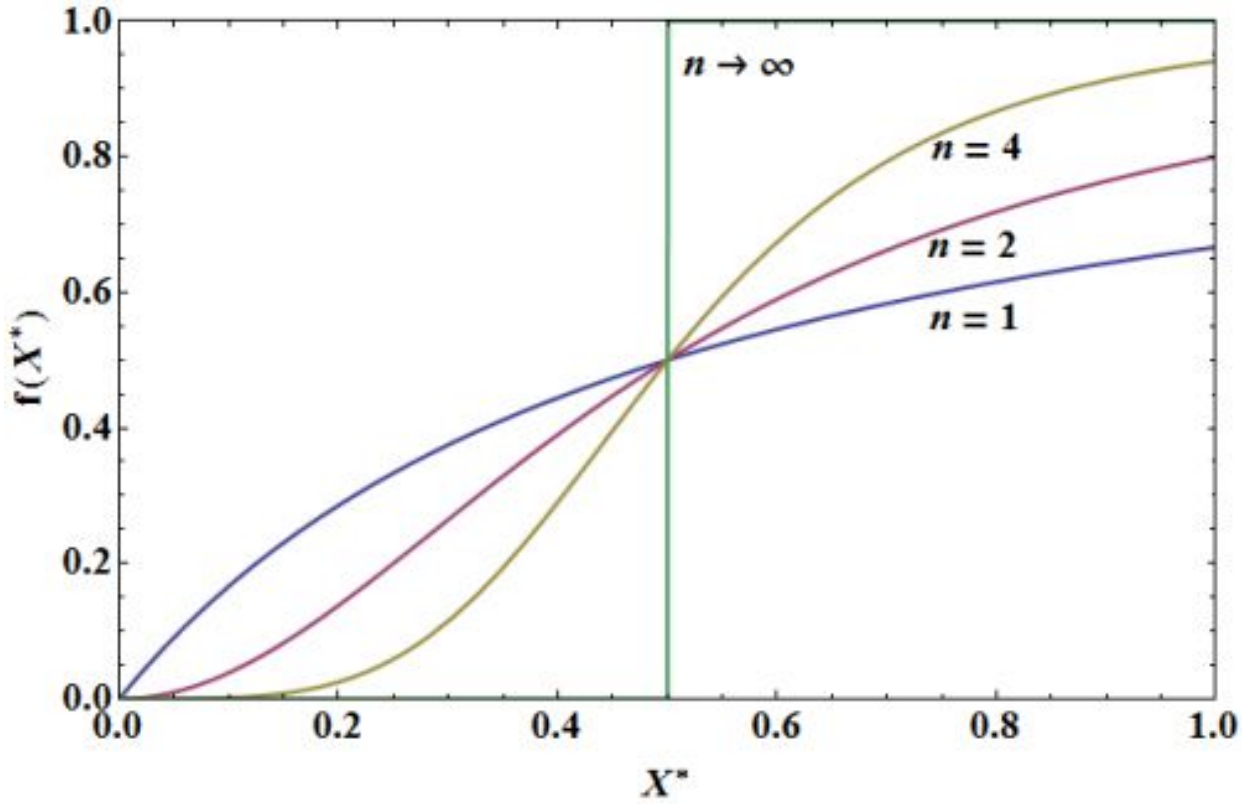
The *Hill Function* is a commonly used mathematical model in pharmacology

$$H = H_{max} \frac{x^n}{k^n + x^n}$$

The general form of the Hill function

$$E = E_{max} \frac{[L]^n}{EC_{50}^n + [L]^n}$$
$$= E_{max} \frac{1}{1 + (\frac{EC_{50}}{[L]})^n}$$

Modelling the dose-dependent effect



Simulation of biological networks with ordinary differential expression: the simplest case

Given the reaction $\mathrm{S} + \mathrm{E} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \mathrm{C} \xrightarrow{k_3} \mathrm{P} + \mathrm{E}$

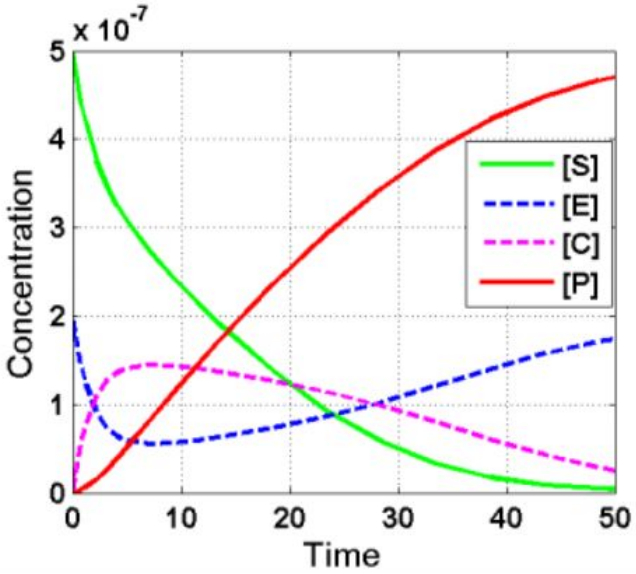
Given the initial values and rate constants

- $S(0) = 5e^{-7}$
- $E(0) = 2e^{-7}$
- $C(0) = P(0) = 0$
- $k_1 = 1e^{6}$
- $k_2 = 1e^{-4}$
- $k_3 = 0.1$

According to the law of mass action

$$\frac{d[S]}{dt} = -k_1[E][S] + k_2[C],$$
$$\frac{d[E]}{dt} = -k_1[E][S] + (k_2 + k_3)[C],$$
$$\frac{d[C]}{dt} = k_1[E][S] - (k_2 + k_3)[C],$$
$$\frac{d[P]}{dt} = k_3[C],$$

It is possible to simulate the concentration changes by time *deterministically*.



See Systems Engineering Wiki (tue.nl) for MATLAB/COPASI codes and *Stochastic Modelling for Systems Biology* by Darren J. Wilkinson

Chemical Master Equations (CME): a particle model of chemical reaction

Given the reaction $\mathrm{A} + \mathrm{B} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \mathrm{C} + \mathrm{D}$ and the initial condition $X(0) = \begin{bmatrix} K \\ K \\ 0 \\ 0 \end{bmatrix}$ (*K* molecules of species A and of species B respectively)

The state vector $X(t)$ can take at any time point *one* of the values $\begin{bmatrix} K \\ K \\ 0 \\ 0 \end{bmatrix}, \begin{bmatrix} K-1 \\ K-1 \\ 1 \\ 1 \end{bmatrix}, \begin{bmatrix} K-2 \\ K-2 \\ 2 \\ 2 \end{bmatrix}, \ldots, \begin{bmatrix} 0 \\ 0 \\ K \\ K \end{bmatrix},$

Theoretically we can build an ODE system with *K+1* equations to model *every state of the reaction*, down to every particle. In reality, the dimension is so high so that a simulation is not feasible.

CME is a set of ODEs, with each ODE representing one possible state of the system. Solution of the *k*th equation at time *t* is a real number giving the probability of system being in that particular state at that time.

Reaction Rate Equations (RRE): the compartment model that we have seen before

$$\mathrm{E} + \mathrm{S} \underset{k_r}{\overset{k_f}{\rightleftharpoons}} \mathrm{ES} \xrightarrow{k_{cat}} \mathrm{E} + \mathrm{P}$$

$$v = \frac{V_{max}[S]}{K_D + [S]}$$

$V_{max} \equiv k_{cat}[E]_0$

$$v = \frac{d[P]}{dt} = k_{cat}[ES] = \frac{k_{cat}[E]_0[S]}{K_D + [S]}$$

$$[ES] = \frac{[E]_0[S]}{K_D + [S]}$$

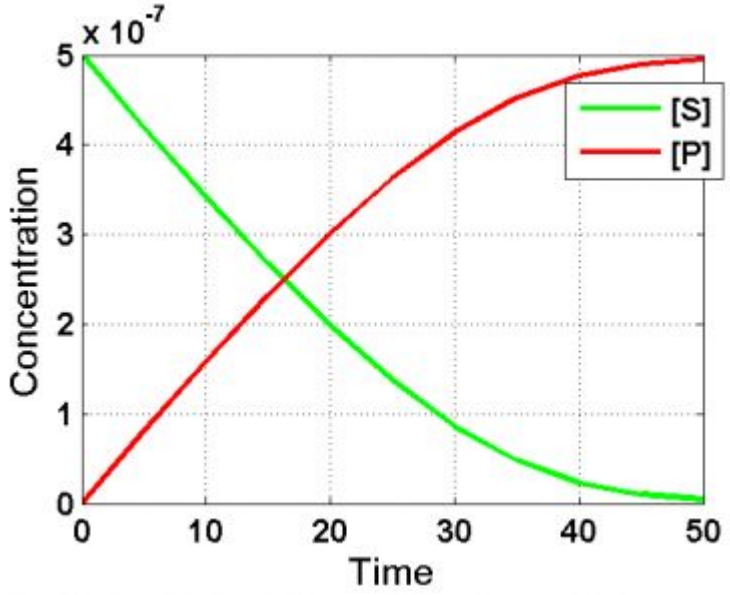
$K_D \equiv \frac{k_r}{k_f}$

$$\begin{aligned}
\frac{d[E]}{dt} &= -k_f[E][S] + k_r[ES] + k_{cat}[ES], \\
\frac{d[S]}{dt} &= -k_f[E][S] + k_r[ES], \\
\frac{d[ES]}{dt} &= k_f[E][S] - k_r[ES] - k_{cat}[ES], \\
\frac{d[P]}{dt} &= k_{cat}[ES],
\end{aligned}$$

$k_f[E][S] = k_r[ES]$

$$\begin{aligned}
k_f([E]_0 - [ES])[S] &= k_r[ES] \\
k_f[E]_0[S] - k_f[ES][S] &= k_r[ES] \\
k_f[E]_0[S] &= k_r[ES] + k_f[ES][S] \\
k_f[E]_0[S] &= [ES](k_r + k_f[S]) \\
[ES] &= \frac{k_f[E]_0[S]}{k_r + k_f[S]} \\
[ES] &= \frac{k_f[E]_0[S]}{k_f(\frac{k_r}{k_f} + [S])}
\end{aligned}$$

***RRE simulation of the Michaelis-Menten* model**

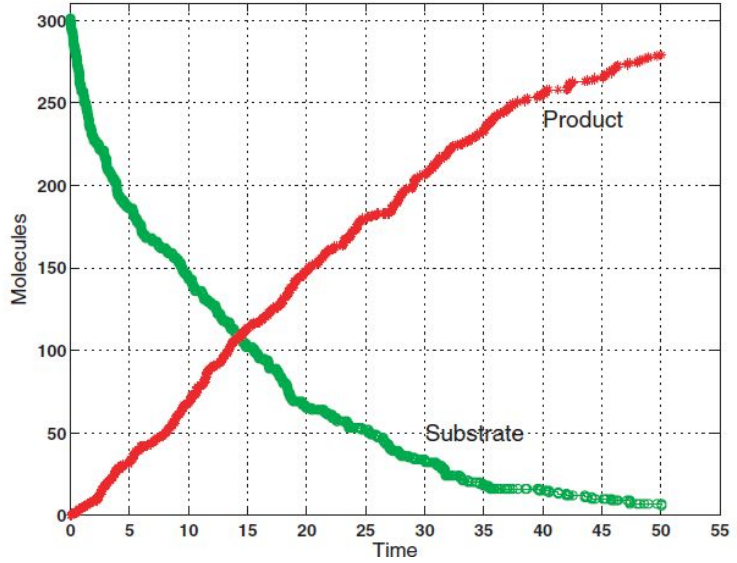


Source: Systems Engineering Wiki (tue.nl)

RRE is a set of ODEs, with each ODE representing one chemical species. Solution of the *j*th equation at time *t* is a real number representing the concentration of species *j* at time *t*.

The Gillespie's algorithm and the chemical Langevin equation allow stochastic simulation of biological networks

- The *stochastic simulation algorithm* (exact SSA), also called *Gillespie's algorithm*, allows stochastic simulation of a reaction. It is done in four steps:
  1. **initialize** the system with initial conditions
  2. Given a state at time *t*, we can define a probability *p* that reaction *j* takes place in the time interval $[t+\tau, t+\tau+d\tau)$. It is the product of two density functions of two random variables: the probability of reaction *j* happens (proportional to the number of substrate molecules), multiplied by the time until next reaction, which is exponentially distributed. This is known as the ***Monte Carlo*** step.
  3. Let the randomly selected reaction happen and **update** the time.
  4. **Iterate** until substrates are exhausted or simulation time is over.
- Further computation tricks, .e. 'tau-leaping', are used to lump together reactions. The chemical Langevin equation (CLE) further accelerates stochastic simulation by approximating *Poisson* with normal distribution.



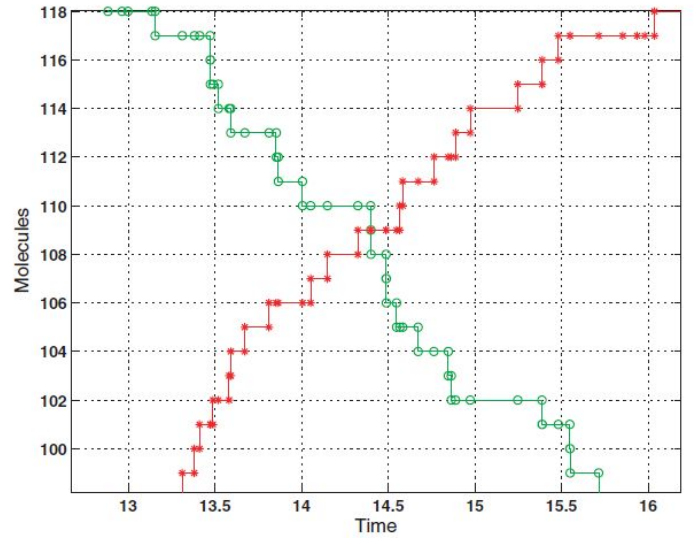
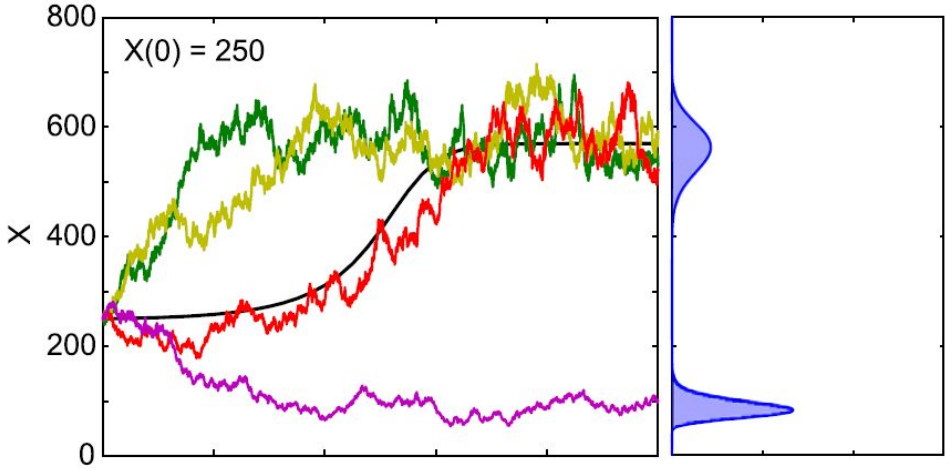
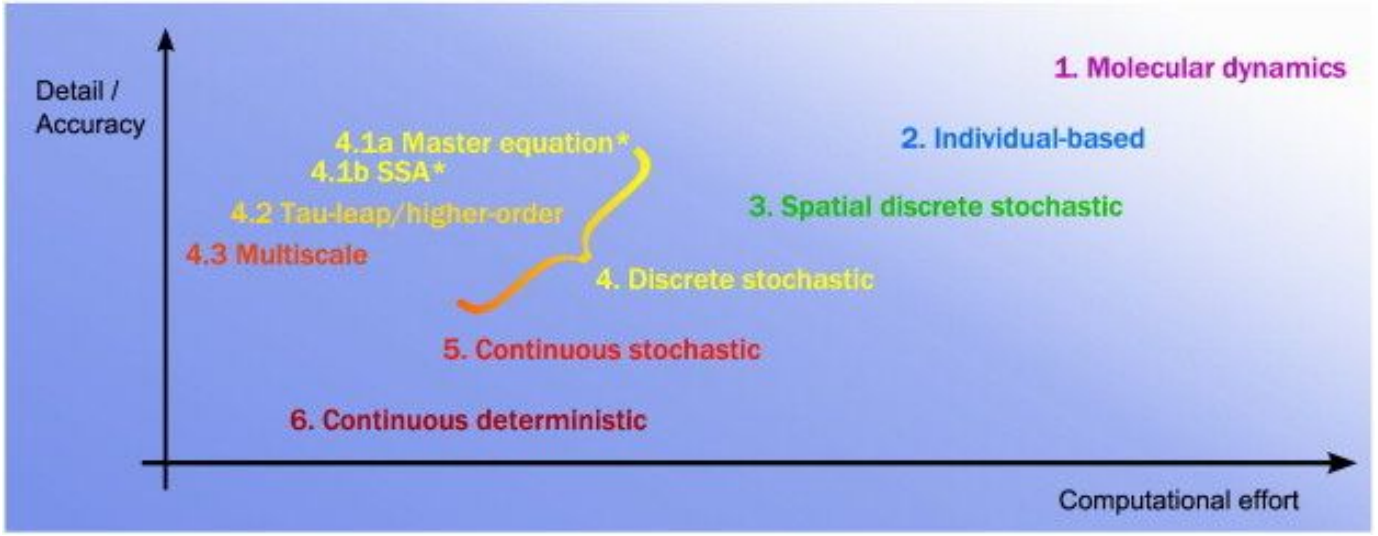


Figure source and further reading: Higham, Desmond J. 2008. "Modeling and Simulating Chemical Reactions." *SIAM Review* 50 (2): 347–68. https://doi.org/10.1137/060666457.

Why stochastic modelling?





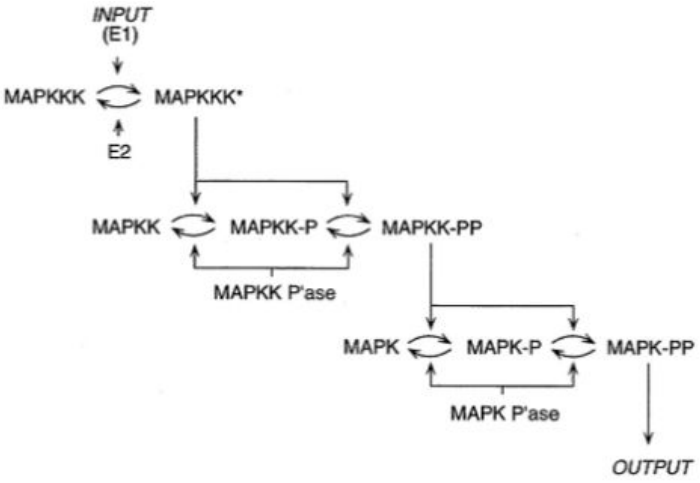
- Stochastic modelling can reveal individual trajectories that are otherwise ‘averaged’ by ODE models.
- Small systems and single-molecule studies show stochastic behaviour.
- It is possible to consider both extrinsic and intrinsic factors and take them into the model.

Székely and Burrage. 2014. “Stochastic Simulation in Systems Biology.” *Computational and Structural Biotechnology Journal* 12 (20–21): 14–25.

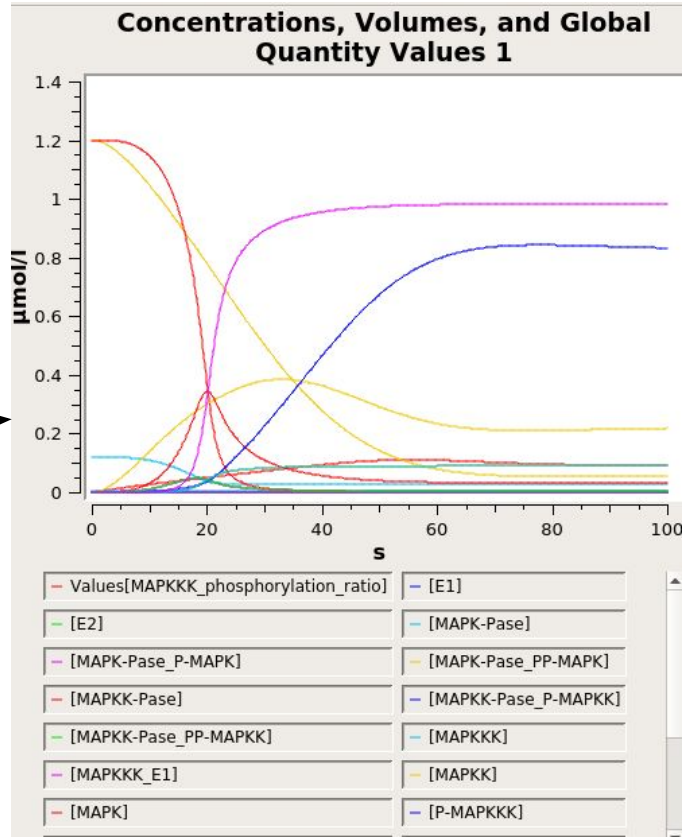
Also see *Stochastic Modelling for Systems Biology* by Darren J. Wilkinson.

Biochemical system simulator COPASI

- COPASI , freely available at http://COPASI.org/, supports two types of simulations: (1) **ordinary differential equation (ODE)** based simulation**, (2) stochastic kinetic simulation**, among others using the stochastic Runge–Kutta method (RI5) and Gillespie's algorithm.
- Resources to learn more about stochastic modelling: MIT OpenCourseWare by Jeff Gore, and Stochastic Processes: An Introduction, Third Edition by Jones and Smith. Tutorials also available on the website of European Bioinformatics Institute (EBI)
- Both mathematical concept and software tools are important for detailed analysis of enzymatic reactions, especially in the presence of drugs and/or disease-relevant mutation



Huang and Ferrell, PNAS, 2006



ODE-based simulation of dynamics

Five classes of mathematical models drug discovery

Compartment models

$$\frac{d[LR]}{dt} = k_1[L][R] - k_2[LR]$$

Kinetics of ligand-target interaction

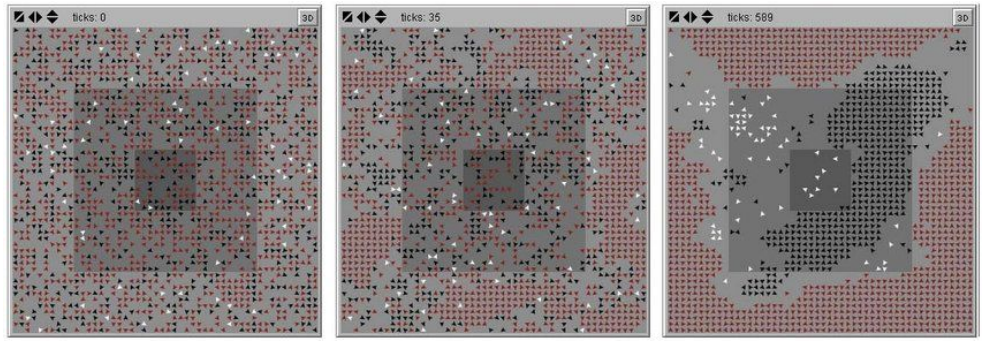
$$\frac{dx}{dt} = \alpha x - \beta xy,$$
$$\frac{dy}{dt} = -\gamma y + \delta xy,$$

The Lotka-Volterra equations modelling predator-prey relationships.

$$\frac{dS}{dt} = -\frac{\beta IS}{N},$$
$$\frac{dI}{dt} = \frac{\beta IS}{N} - \gamma I,$$
$$\frac{dR}{dt} = \gamma I$$

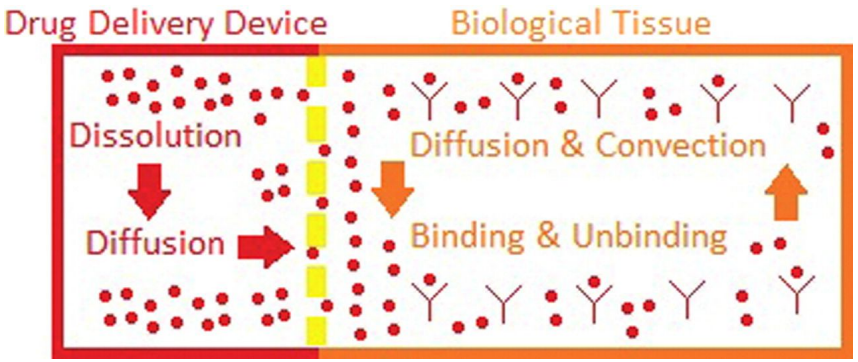
The SIR (S=susceptible, I=infectious, R=removed) model of epidemiology

Particle models

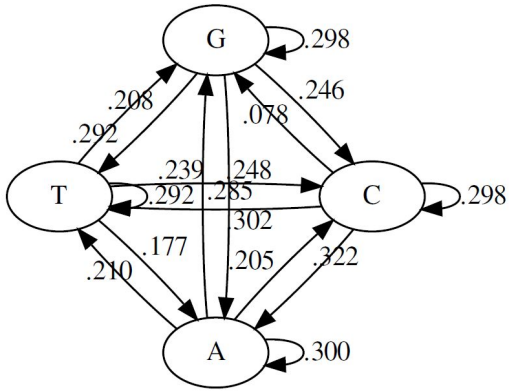


A Study on Socio-spatial Segregation Models Based on Multi-agent Systems by Quadros *et al*. (2012). 10.1109/BWSS.2012.14.

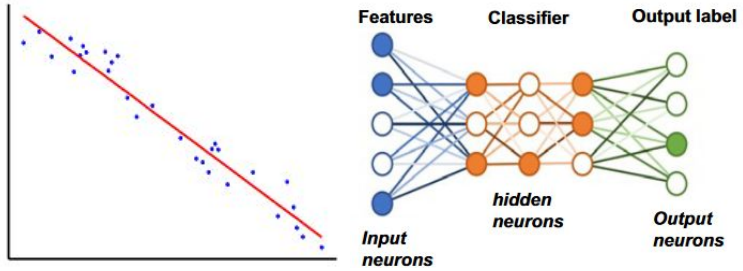
Transport models



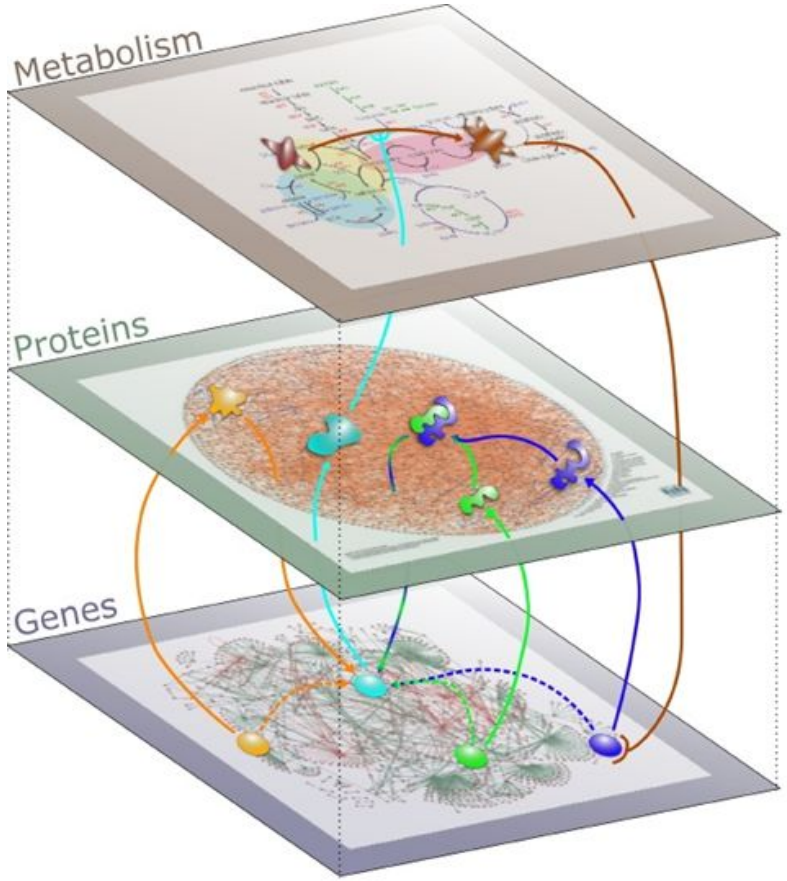
Finite state models



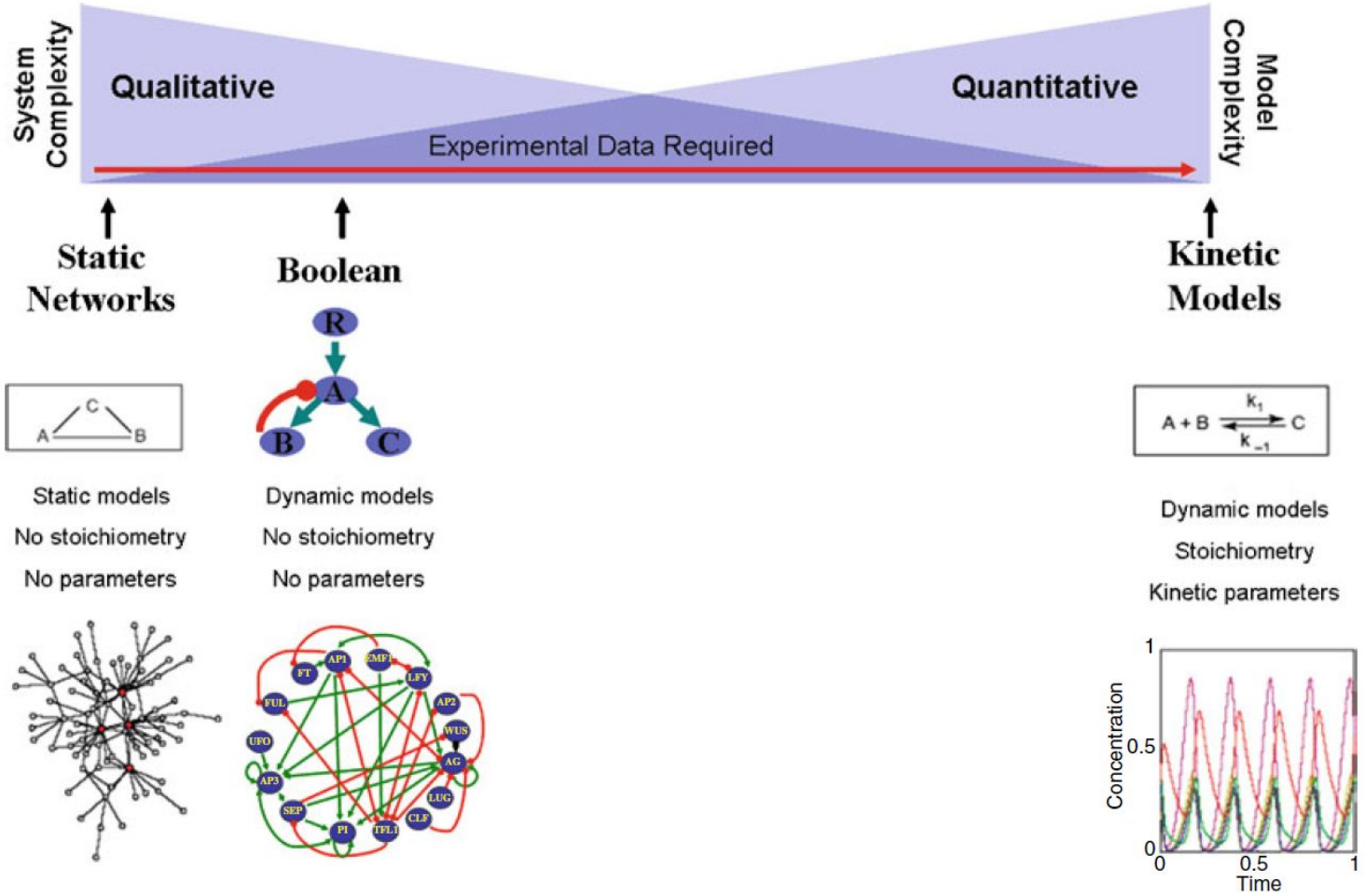
Statistical/machine learning/causal models



Modelling biological networks



Stéphane CHÉDIN & Jean LABARRE, www-dsv.cea.fr



Garg, Abhishek, Kartik Mohanram, Giovanni De Micheli, and Ioannis Xenarios. 2012. "Implicit Methods for Qualitative Modeling of Gene Regulatory Networks." In *Gene Regulatory Networks: Methods and Protocols*, edited by Bart Deplancke and Nele Gheldof, 397–443. Methods in Molecular Biology. Totowa, NJ: Humana Press.

Summary

- Compartment models and Hill function to model drug-target interactions
- Buttom-up study of biological networks with deterministic and stochastic models
- Introduction to top-down study of biological networks with omics and cellular models