An introduction to Computational Systems Biology.

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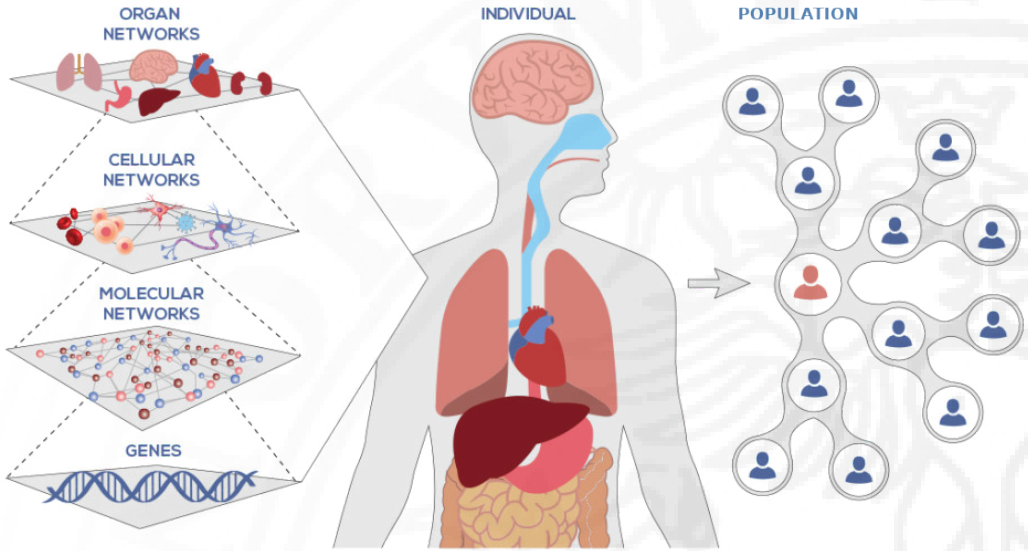
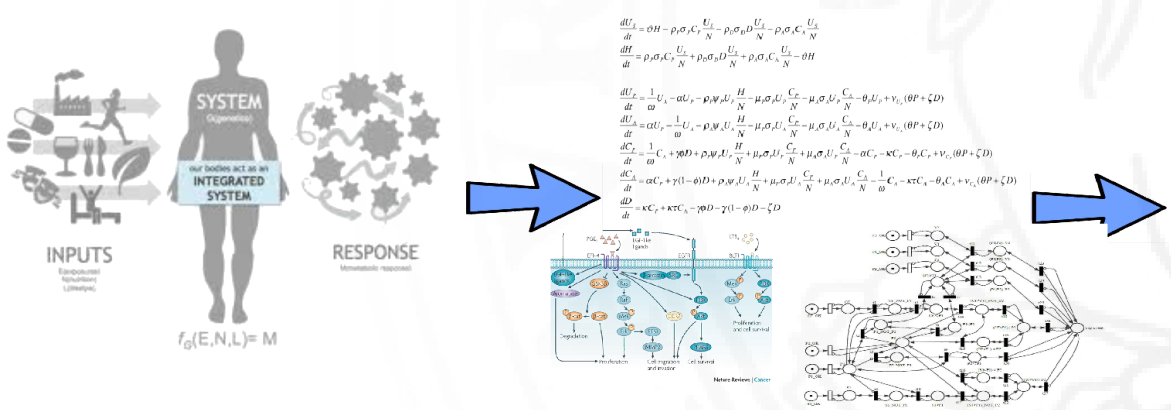
Systems biology in a nutshell.

- A biological system is a *complex system* characterized by several interacting components (i.e. *holistic approach*);



- In Systems Biology *mathematical and computational modeling* is exploited to help scientists in the study of biological systems;

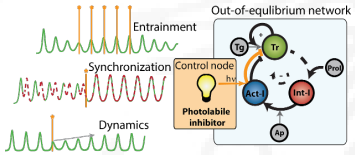


Computational modeling

What is a model?

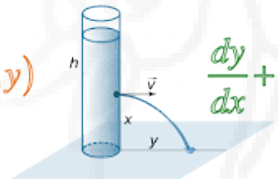
- It depends on who you are talking:
  - Genetist: the mouse family Ts65DN serves as a model for human trisomy 21;

  - Chemist: a reaction network, described by dots (for metabolites) and arrows (for reactions)



  - Mathematician/Engineer: the same reaction network can be modeled by a system of nonlinear ODEs;

$$\frac{dy}{dx} = f(x,y) \qquad \frac{dy}{dx} + a(x)y = f(x)$$



Abstract representation of objects or processes that explains features of these objects or processes.

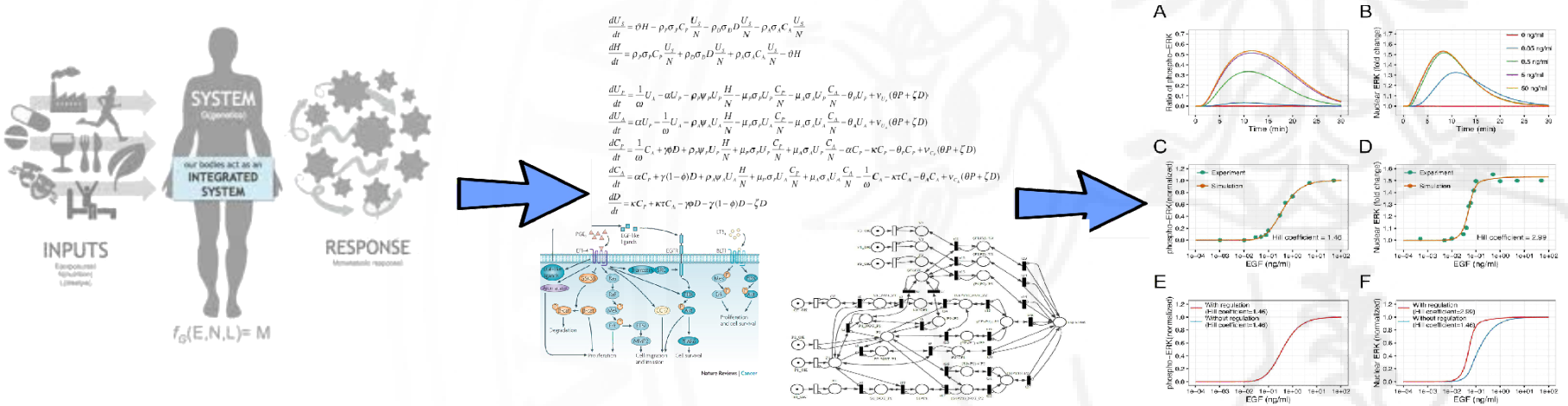
What is a model?

- Models are only an **abstract representations** of their biological counterparts;
- Nevertheless, models must enable to:
  - Elucidate network properties;
  - Check the reliability of basic assumptions;
  - Uncover lack of knowledge and requirements for clarification;
  - Create large repository of current knowledge, formalized in a non ambiguous way.

Select the right level of abstraction is a complex task!!

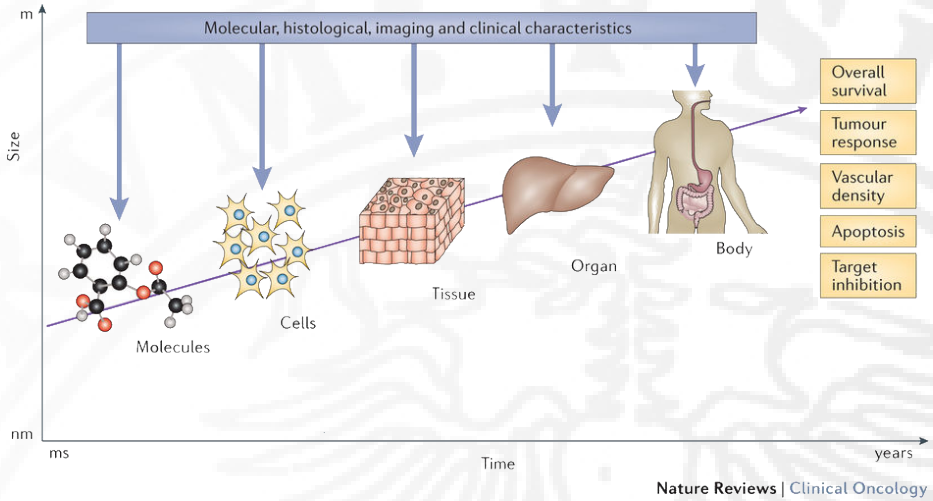
Mathematical Models for biological systems.

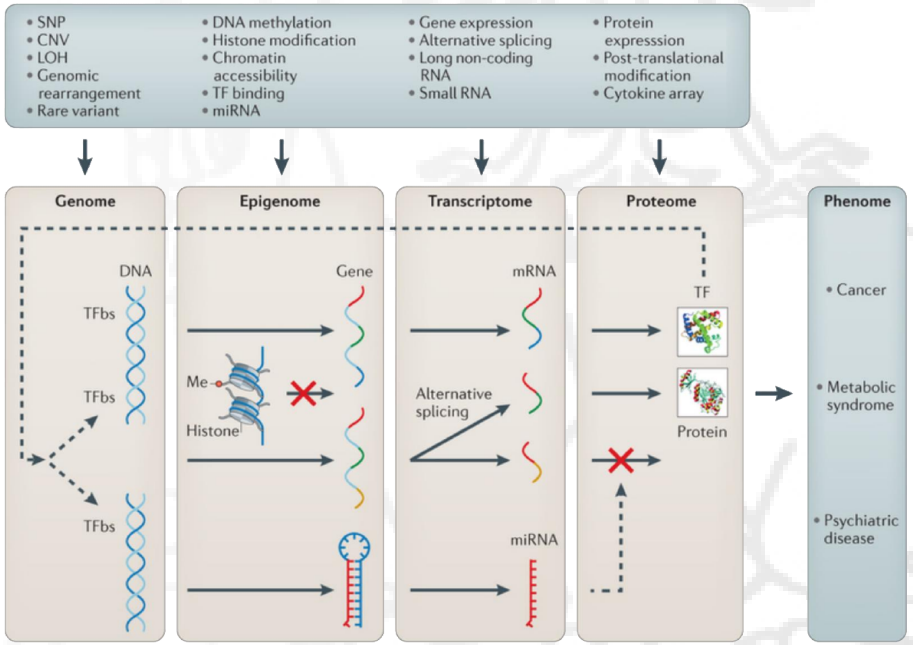
- Biological systems can be described in mathematical terms, however:
  - it can be described through different (mathematical) models;
  - the choice of a mathematical model depends on the problem, the purpose, and the intention of the investigator;
  - different models may highlight different aspects of the same instance.



Mathematical Models for biological systems.

- A biological system can be viewed as a composition of sub-models with different *time and space scales*;
- These sub-models can be parameterized using *different input data*.





Challenge:

How to efficiently model and study biological systems

How to create a model for biological systems

Model Development.

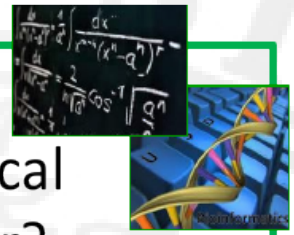
- Making the right assumptions:

> *...The modelling process itself is more important than the model. Discussion between the experimentalist and the theoretician. Systems Biology is the art of making the right assumptions in the modelling...*
>
> *Wolkenhauer, U. Klingmuller, Systems Biology: From a Buzzword to a Life Sciences Approach, BIOforum Europe 4:22-23, 2004.*

- Modeling process must be driven by the biological question;
- Continuous discussion between biologists and computer scientists is indispensable.

Model Development.

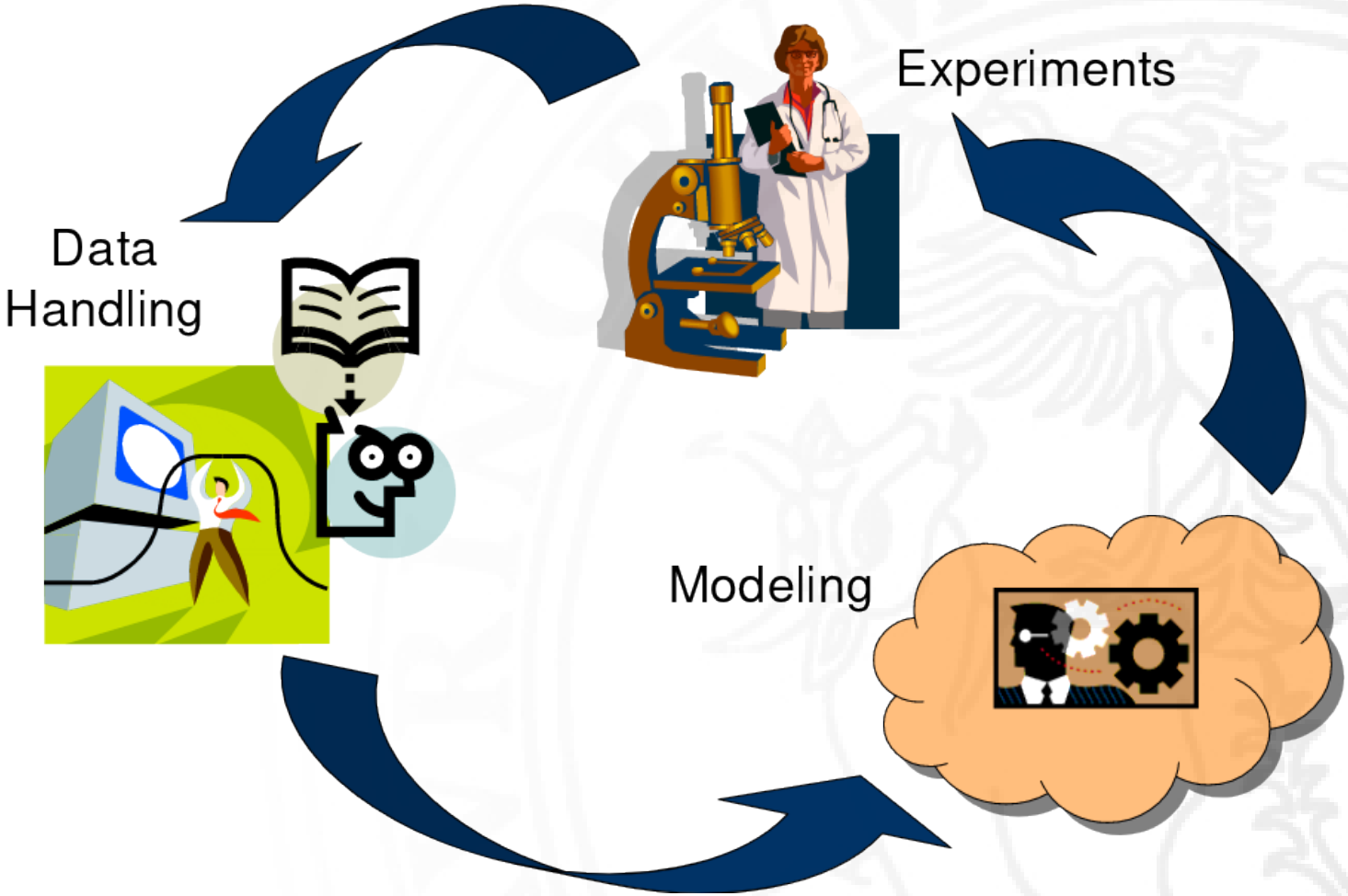
- What is (NOT) known already?
- What kind of wet data are available?
- What kind of wet data could be measured?
- ....



- Which mathematical formalism is better?
- Which computational tools are needed?
- What kind of predictions are we expected to give?
- ....

Model Development.

- Modeling process is thus an iterative approach:



Model Development in details

- Formulation of the problem;
- Research of the available knowledge and data;
- Selection of model structure;
- Model creation;
- Sensitivity analysis/parameter estimation and model calibration;
- Model validation.

Model Development in details

- Formulation of the problem:
  - Identify the specific questions that shall be answered, along with background, problem and hypotheses;

Model Development in details

- Research of the available knowledge and data:
  - To check and collect quantitative and structural knowledge and data;
  - To identify the system components and their interactions;
  - To define how the available date can be used to parameterize the model;
  - To discover the missing parameters/information.
  - ...

Model Development in details

- Selection of model structure:
  - Level of description (atomistic, molecular, cellular, population . . .)
  - Deterministic or stochastic model;
  - Discrete or continuous variables;
  - Static, dynamical, spatio-temporal dynamical;
  - . . .

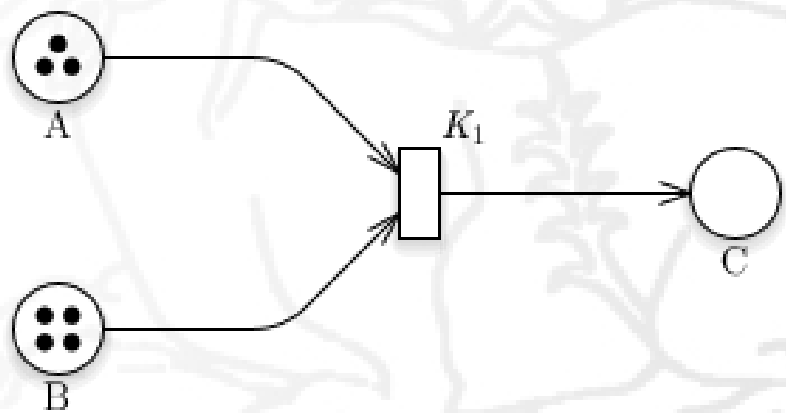
Model Development in details

- Model creation:
  - Computational models can take many forms: dynamical systems, statistical models, differential equations, or game theoretic models;
  - Graphical formalisms (e.g. Petri net, Bayes network, dynamic network, . . .) can be used to make easier the modeling phase.

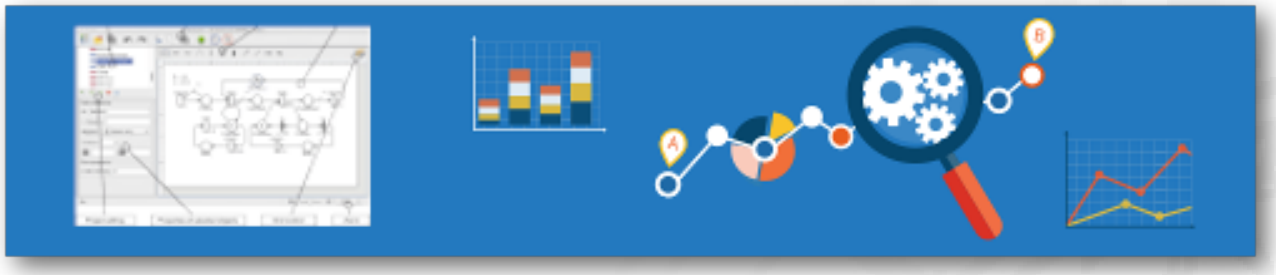
$$A + B \xrightarrow{k_1} C$$

Ordinary differential equation (ODE) system:

$$\begin{cases} dA(t) = -k_1 A(t)B(t)\ dt \\ dB(t) = -k_1 A(t)B(t)\ dt \\ dC(t) = +k_1 A(t)B(t)\ dt \\ A(0) = 3 \\ B(0) = 4 \\ C(0) = 0 \end{cases}$$



Model Development in details



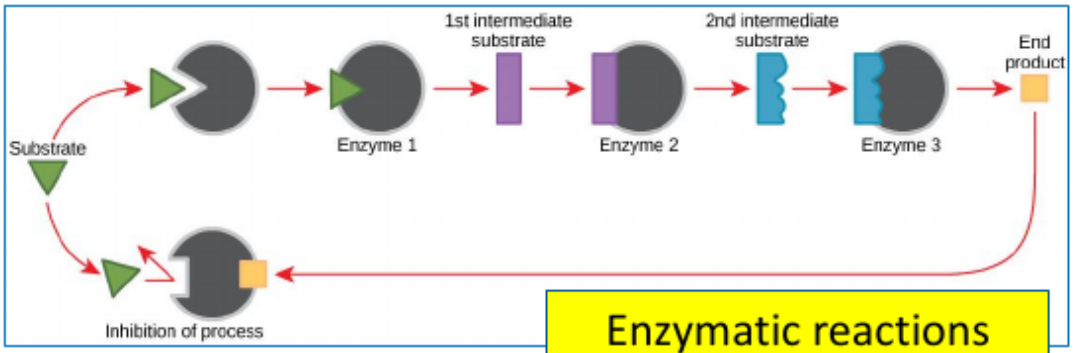
- Sensitivity Analysis/Parameter estimation:
  - To test the dependence of the system behavior on changes of the parameters
  - To choice of parameters to be carefully measured and estimated;
  - ...
- Model calibration:
  - To estimate the missing parameters.

Model Development in details

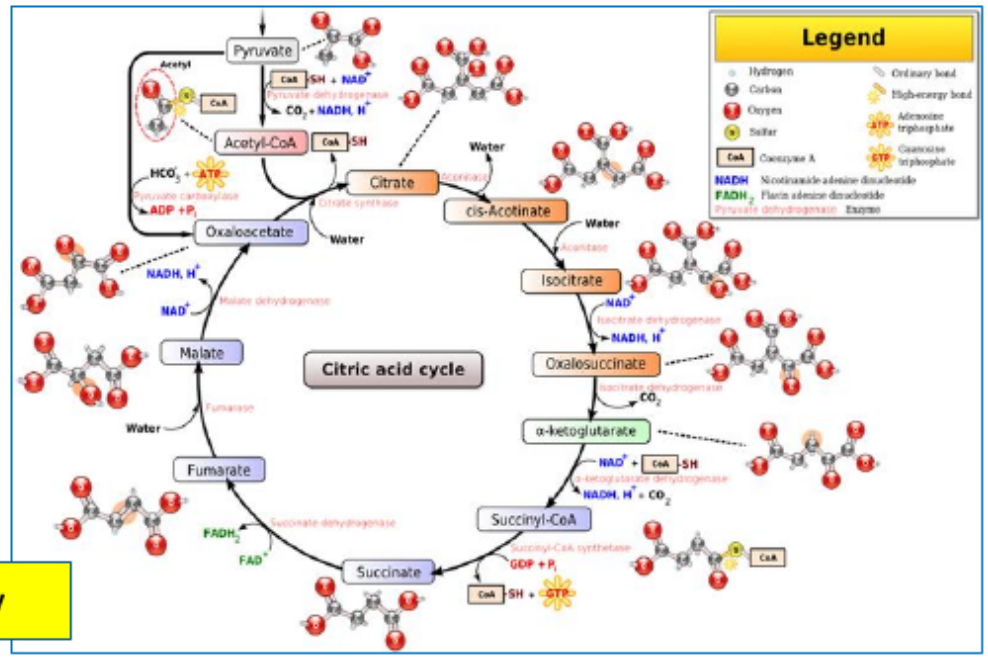
- Model validation:
  - Assessment of the agreement and divergences between experimental results and model behavior.

Modeling approaches

Different biological systems...

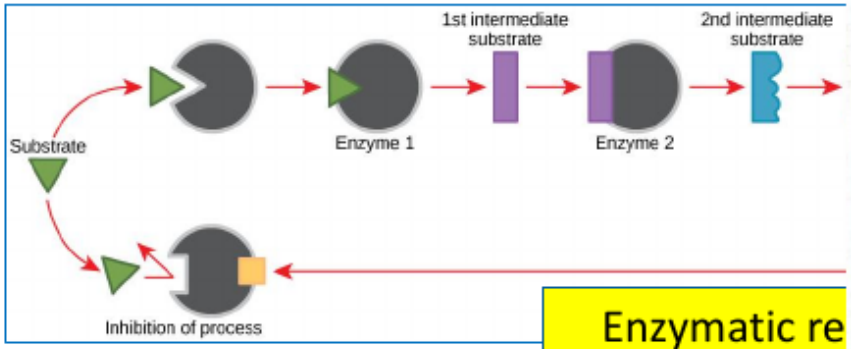


Enzymatic reactions with negative feedback

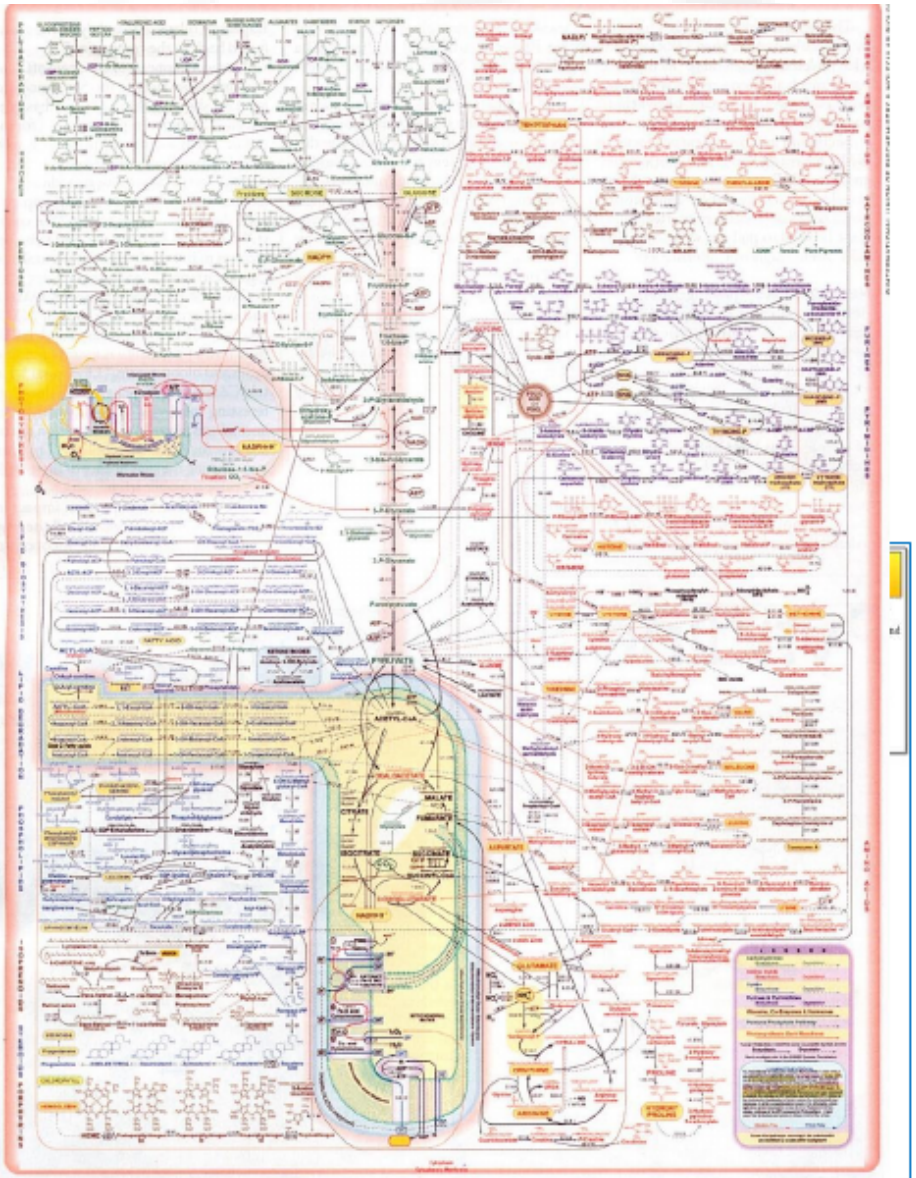


Metabolic pathway

Different biological systems...

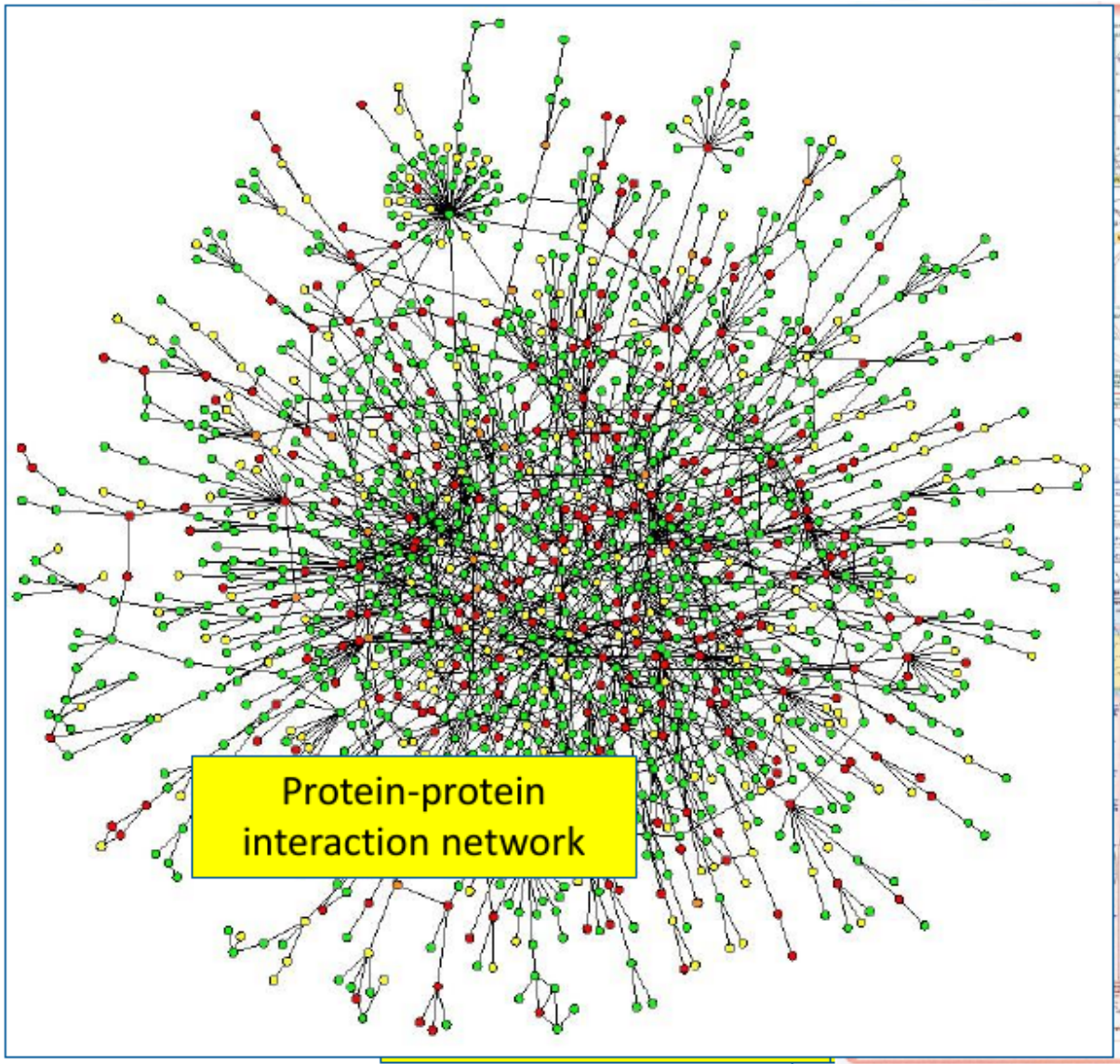


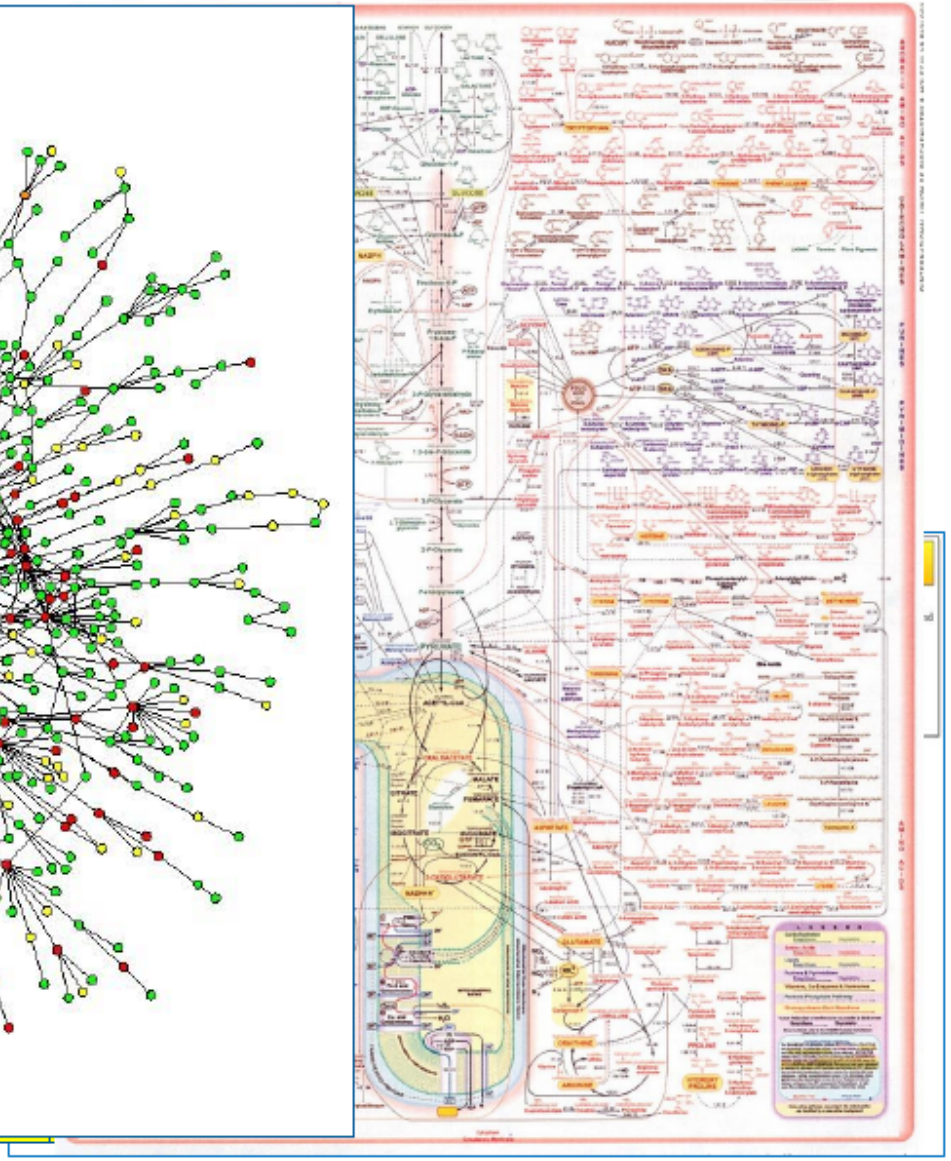
Enzymatic re
with negative f



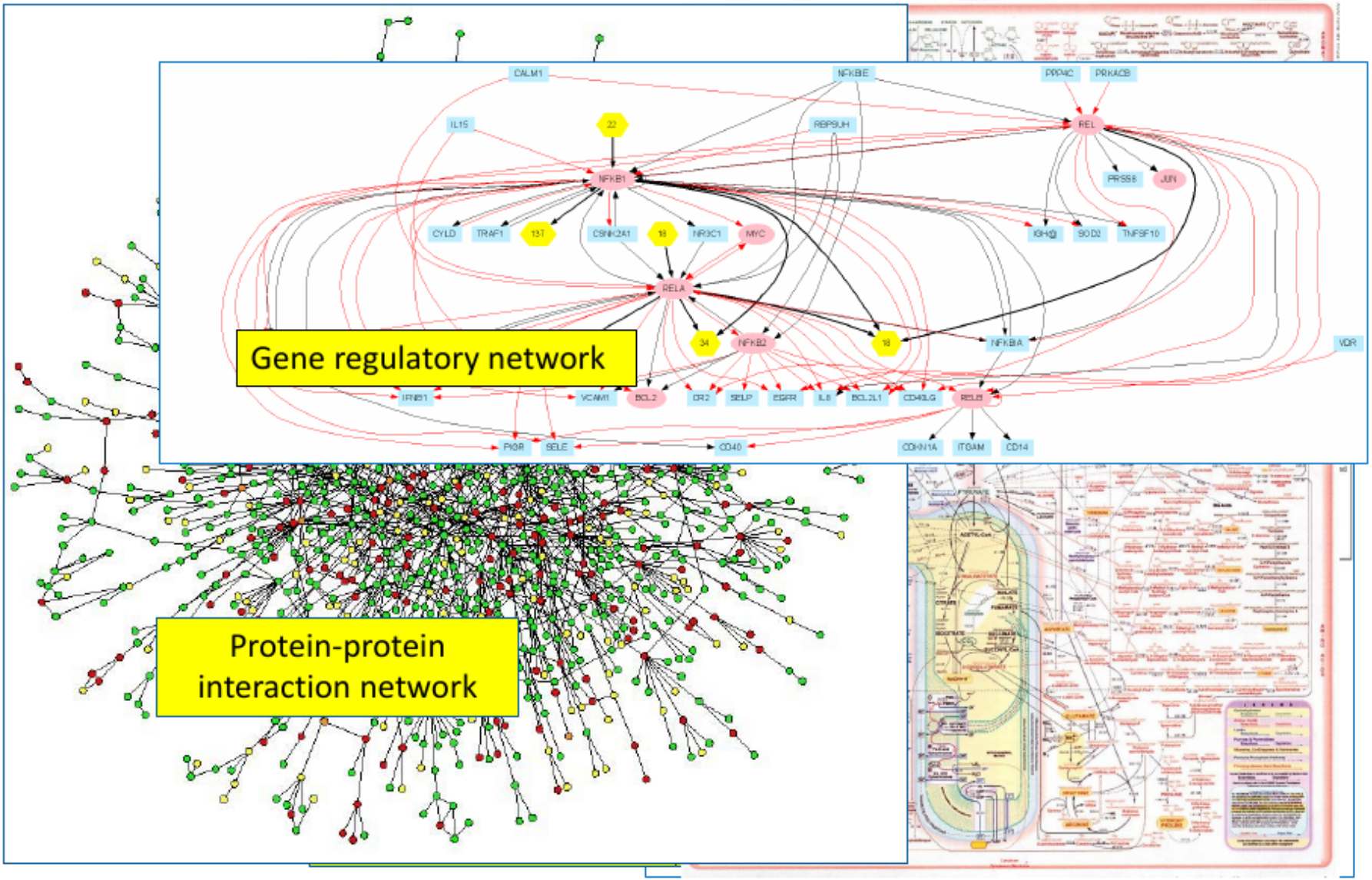
Whole-cell metabolism

Different biological systems...

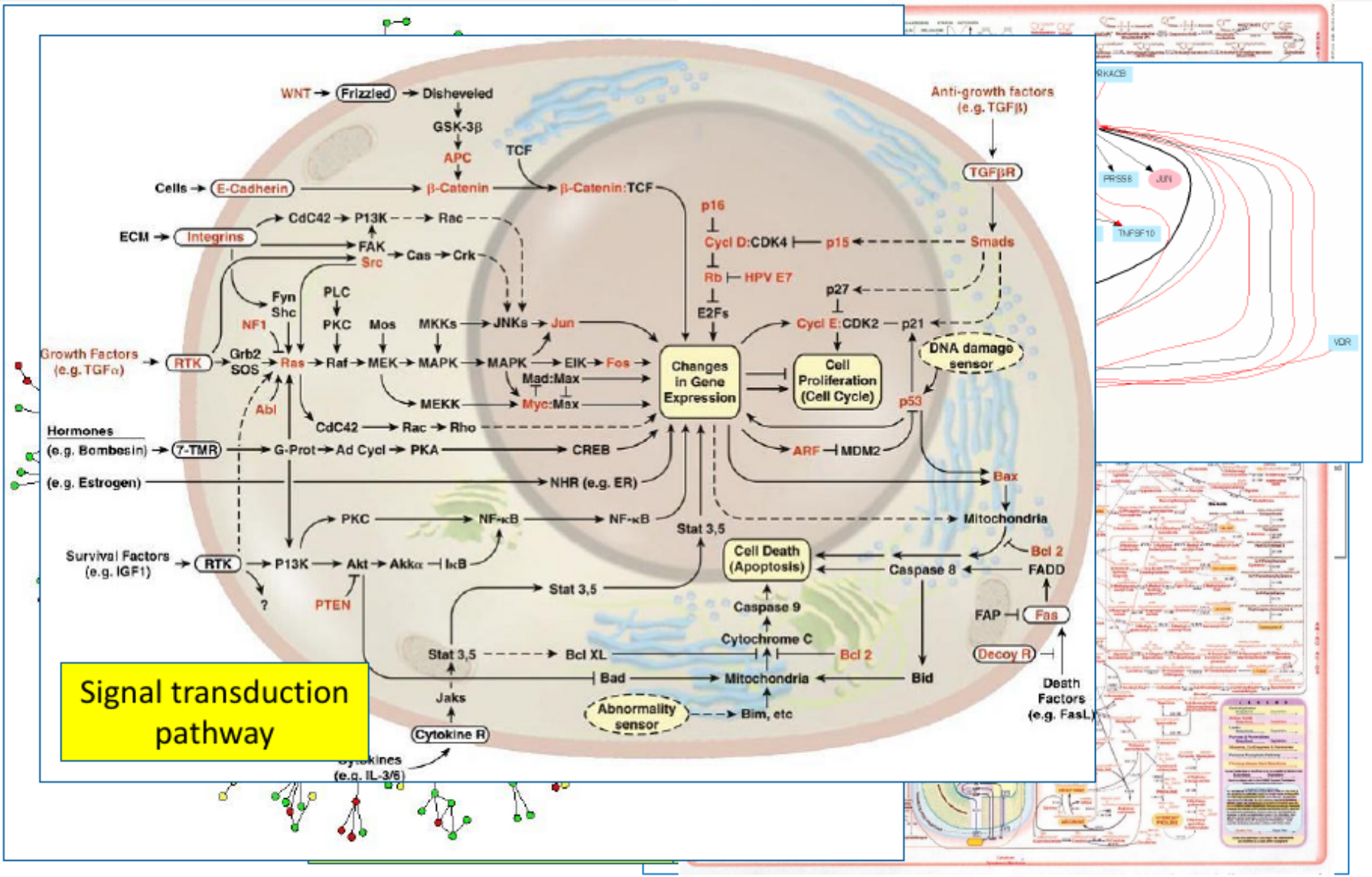




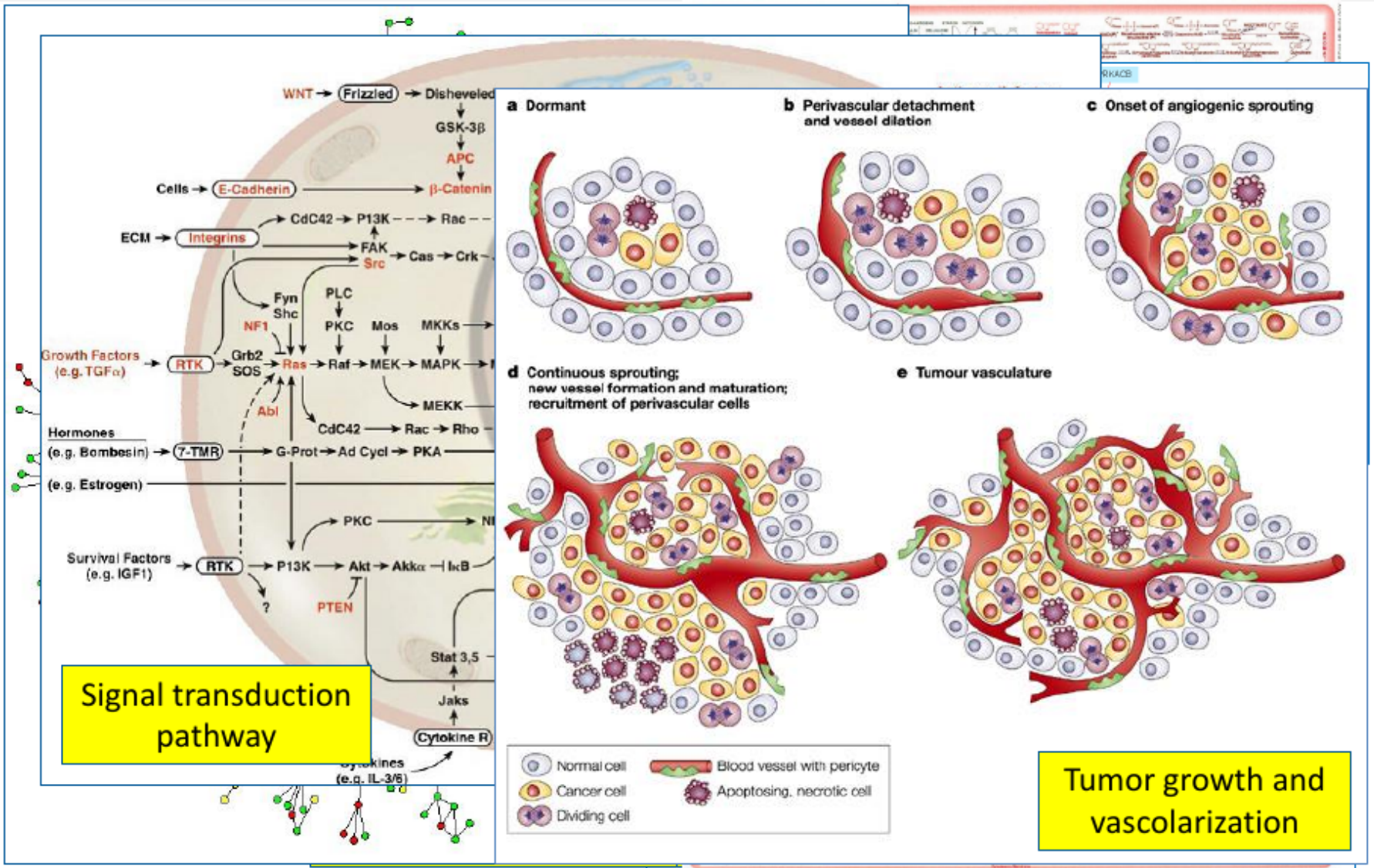
Different biological systems...



Different biological systems...



Different biological systems...



... require different modeling approaches

- **interaction-based approaches**
  - protein-protein interaction network;
  - gene regulatory network.

  based on graph theory $\rightarrow$ *topological analysis*.

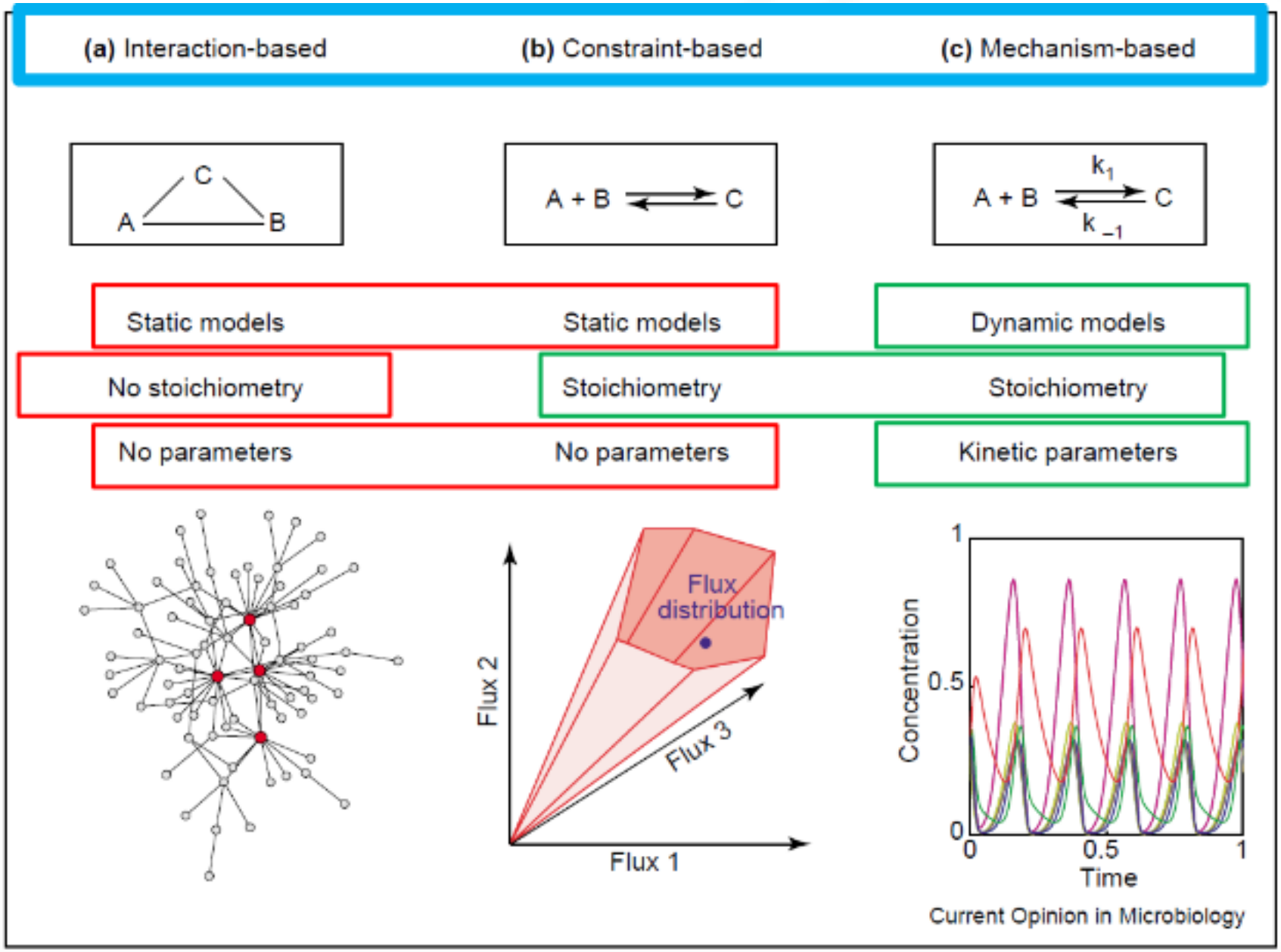
- **constraint-based approaches**
  - metabolic network.

  based on linear algebra and optimization with linear programming $\rightarrow$ *Flux balance analysis*.

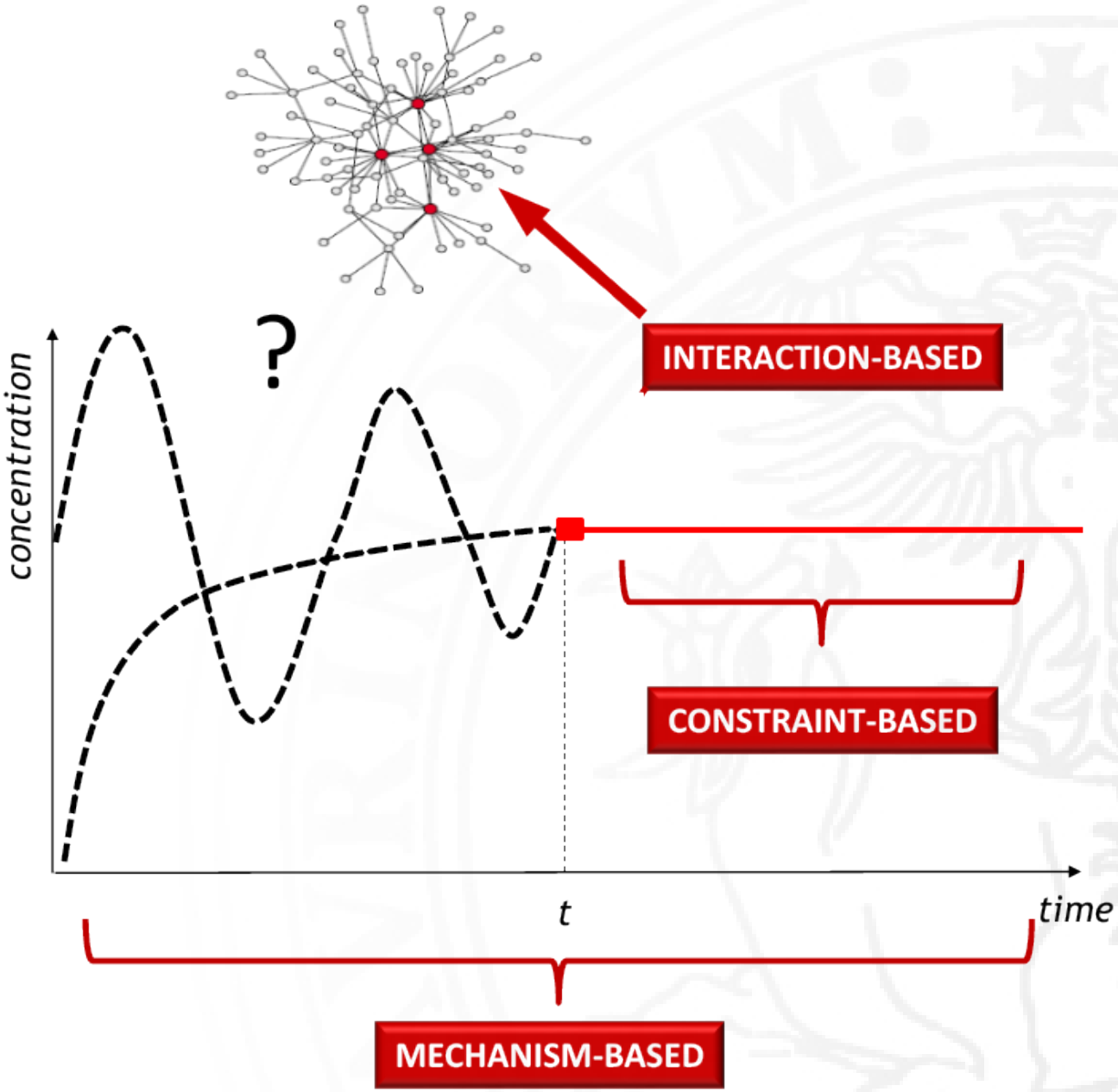
- **mechanism-based approaches**
  - metabolic pathways;
  - signal transduction pathways;
  - cell population.

  based ordinary/stochastic differential equations, stochastic simulation ... $\rightarrow$ *dynamic behavior analysis*.

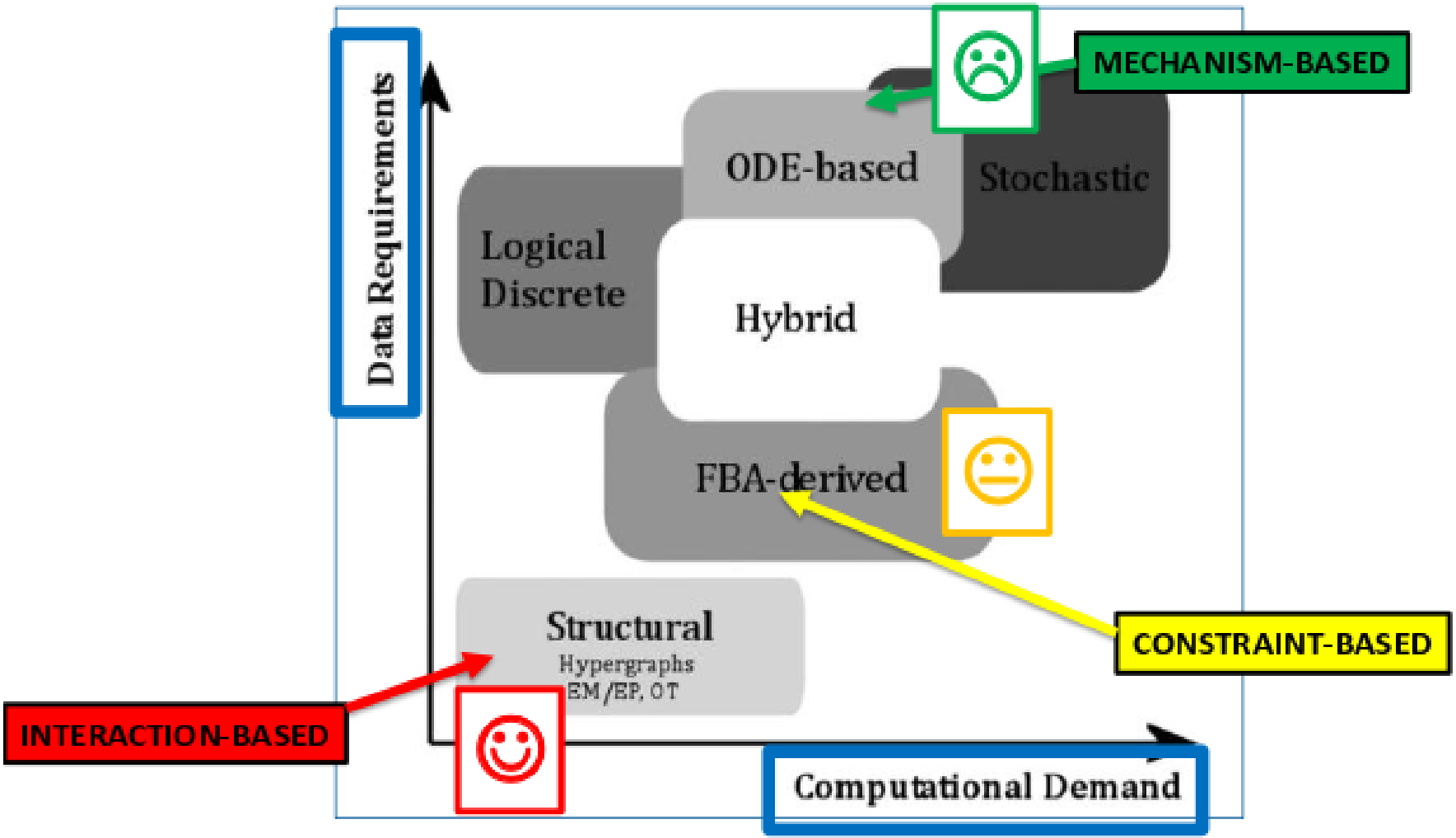
Different modeling approaches.



Static, steady-state or dynamic?



Data requirements VS Computational demand



Tenazinha and Vinga *IEEE Trans Comp Biol Bioinf* 8:4, 2011

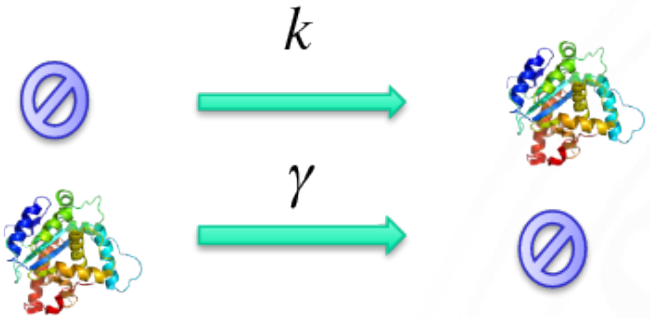
Mechanism-based approaches

Deterministic vs. Stochastic Models

Deterministic	Stochastic
Ordinary differential equations	Continuous time Markov chains
Concentrations of molecules	Numbers of molecules
Future is "predictable" given present knowledge	Includes randomness; every simulation is different
Wide range of techniques available for analysis	Not as many techniques for analysis; often rely on simulations
Good for large number of individuals; qualitative analysis	Better for simulating dynamics with small numbers of molecules
Represents population average	Represents population variability

An example of deterministic model

- A constitutively expressed protein
- Two types of reaction:

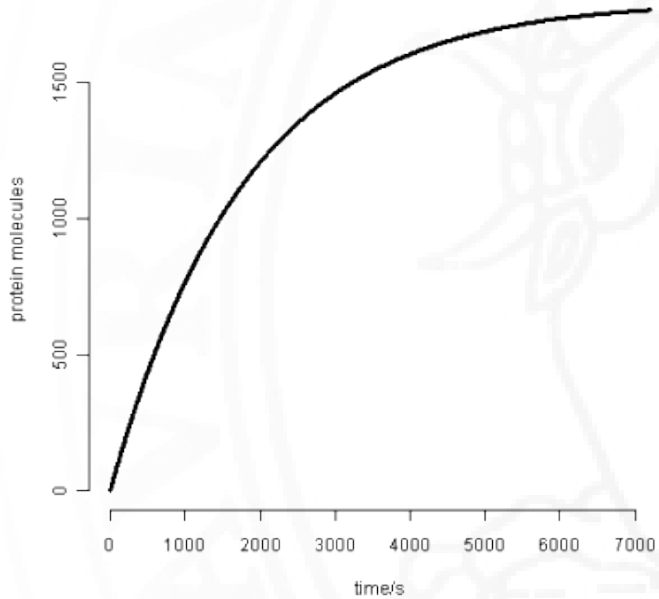


Protein synthesis (constant rate)

Protein degradation

ODE Model:

$$\frac{dP}{dt} = k - \gamma P$$

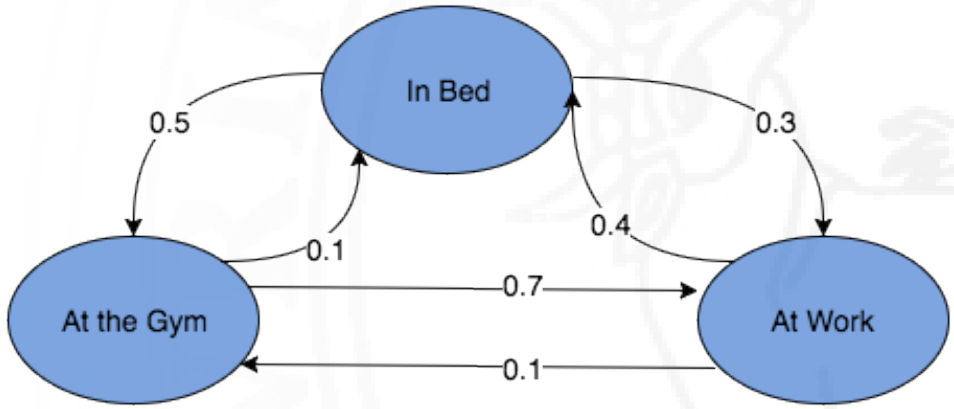


Parameters:

- $k = 1\ \mathrm{Ms}^{-1}$
- $\gamma = 1/1800\ \mathrm{s}^{-1}$
- $P_0 = 0$

An example of stochastic model

- *Markov Chain (MC)*: is a stochastic model describing a sequence of possible events in which the probability of each event depends only on the state attained in the previous event;
- *Continuous Time Markov Chain (CTMC)*: the state transitions may occur at any time, and the time between transitions is exponentially distributed;
- It can be used to compute the probability to be in a system state at time T.



An example of stochastic model

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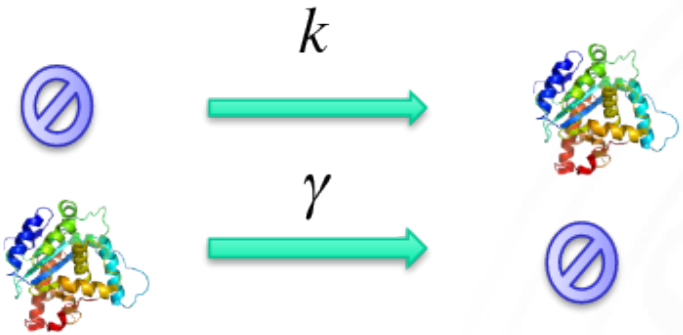

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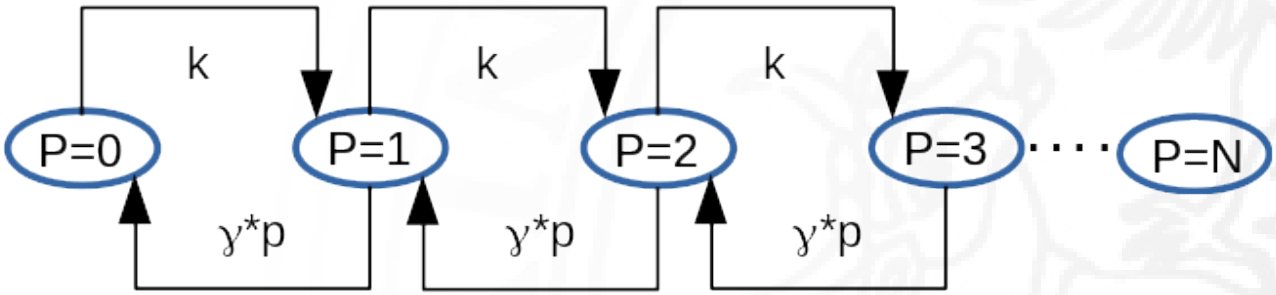
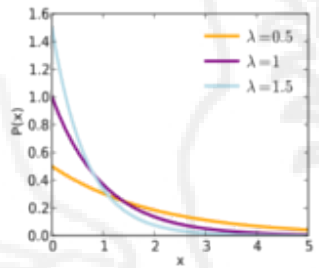
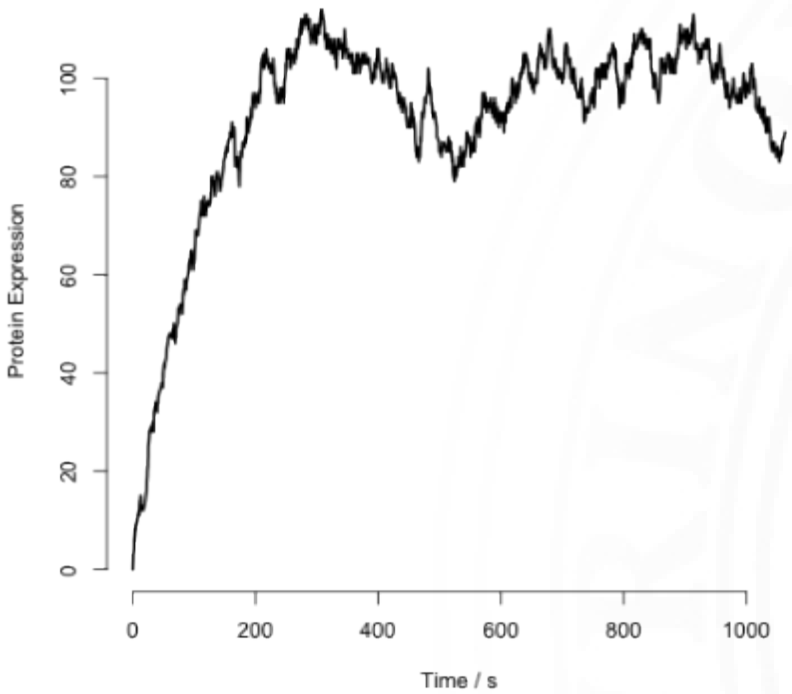


In 1977 **Daniel T. Gillespie showed that system events follow a negative exponential distribution with mean equal to the inverse of event rate (i.e. k and γ*p)**

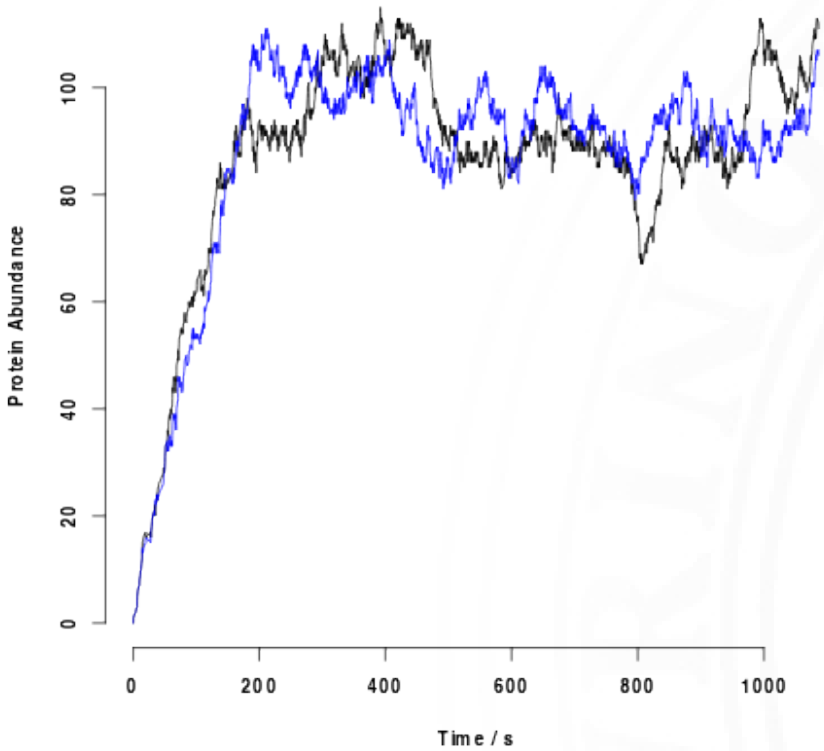


An example of stochastic model



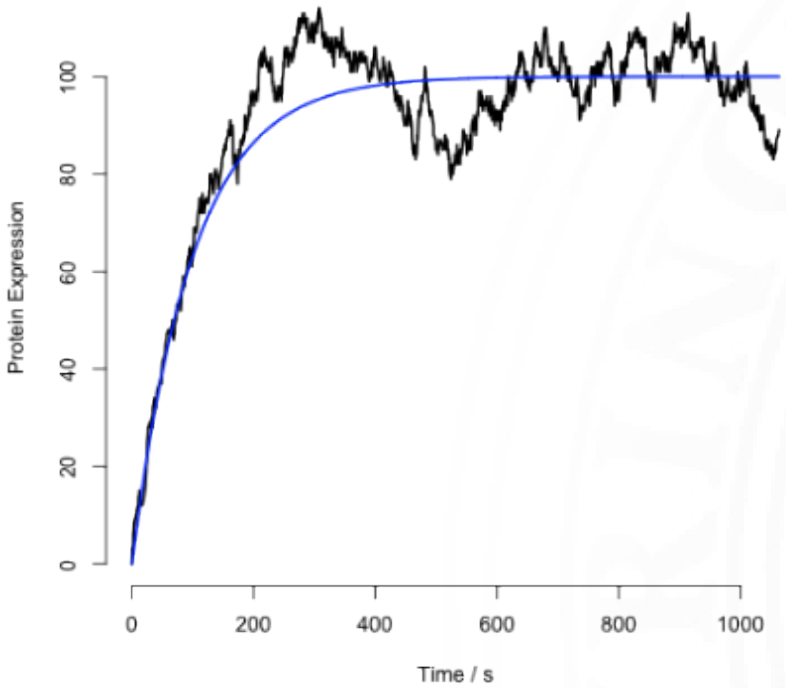
- Parameters:
  - $k = 1\ s^{-1}$
  - $\gamma = 0.01\ s^{-1}$
  - $P_0 = 0$
- Random fluctuations in numbers of molecules

An example of stochastic model



- Two simulations show different time courses because of stochasticity
- Statistical properties are the same
- Average of many stochastic simulations can look like the deterministic model

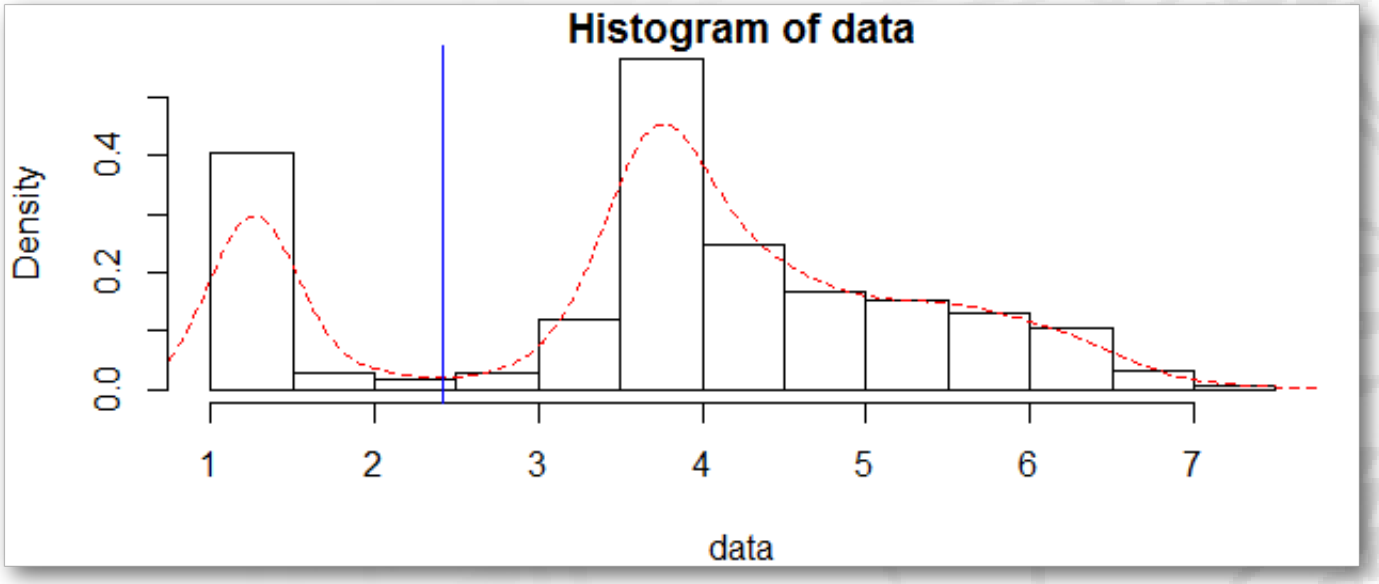
An example of stochastic model



- Both models have same mean and rise to that mean
- Stochastic model includes fluctuations about mean
- In this case, the mean is as given by the deterministic model

Deterministic vs. Stochastic Models

- Deterministic models can be solved easier, but they provide only the average system behavior;
- Stochastic models are more computational demanding, but they can capture the stochastic nature of a biological process.



Mathematical Graphical formalism

- Graphical formalism can be exploited to make easier the modeling phase;
- Several graphical formalism were proposed in literature:

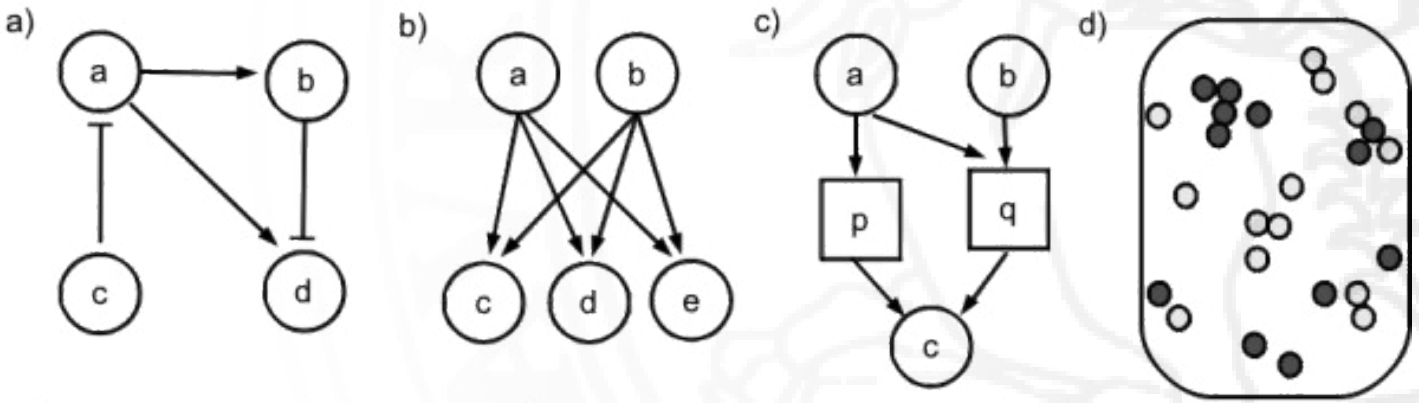
  a) *Boolean network*: genes are represented by nodes and the arrows represent activation and repression;

  b) *Bayesian network*: the value of the output nodes are given by a probability function that depends on the value of the input nodes;

  c) *Petri net*: places represent substances, transitions represent reactions and the arrows represent consumption and production;

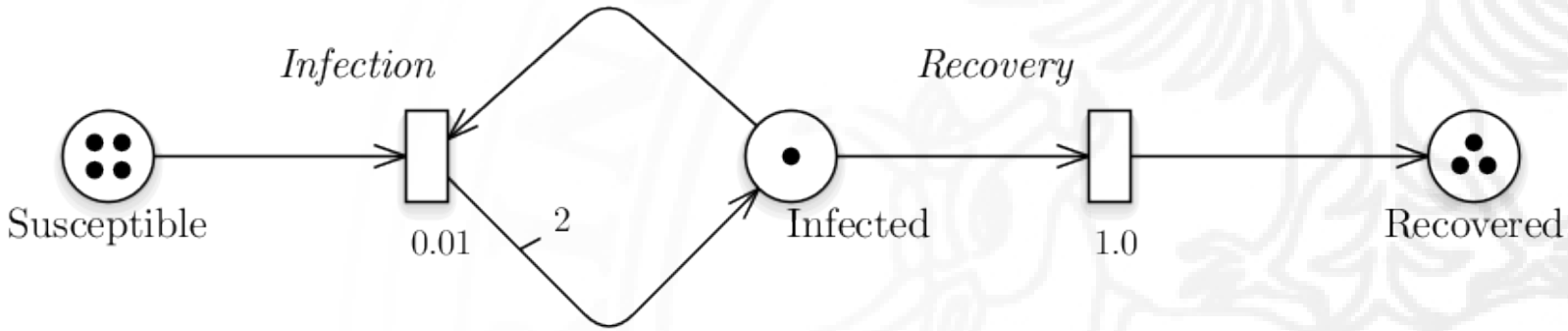
  d) *Agent-based model*: types of agents, representing different kinds of cells can move freely and interact within the containing space

  e) ...



Stochastic Petri Net formalism

- Stochastic Petri Net (SPN) is a mathematical graphical formalism;
- It is conveniently used for the analysis of complex models of Discrete Event Dynamic Systems (DEDS);
- It allow us to derive qualitative and quantitative properties of the system.



System state (marking) : Susceptible(4) + Infected(1) + Recovered(3)

Stochastic Petri Net formalism

Definition (Stochastic Petri Net)

A stochastic Petri net system is a tuple

$$\mathcal{N} = (P, T, I, O, \mathbf{m}_0, \lambda)$$

where:

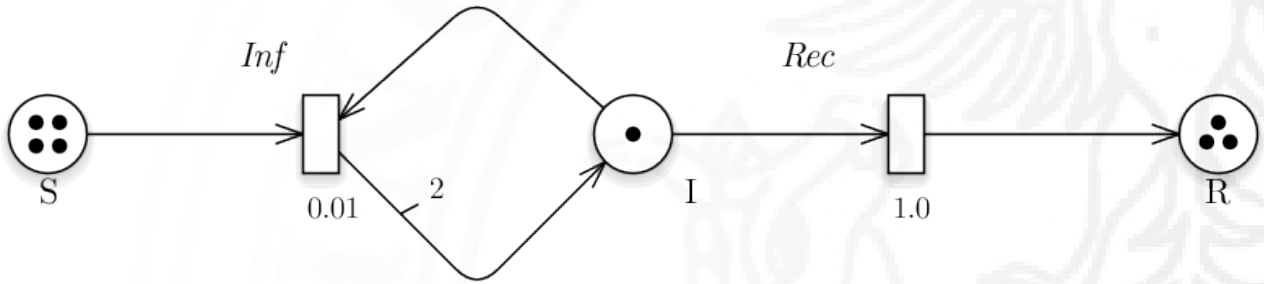
- $P = \{p_i\}_{1 \leq i \leq n}$ is a finite and non empty set of *places*;
- $T = \{t_i\}_{1 \leq i \leq k}$ is a finite, non empty set of *transitions*;
- $I, O : P \times T \to \mathbb{N}$ are the *input*, *output* functions that specify their multiplicities;
- $\mathbf{m_0} : P \to \mathbb{N}$ is a multiset on P representing the *initial marking*;
- $\lambda : T \to \mathbb{R}$ gives the *firing intensities* of the transitions.

Stochastic Petri Net formalism

- It is possible to automatically derive an ODE system from SPN model:

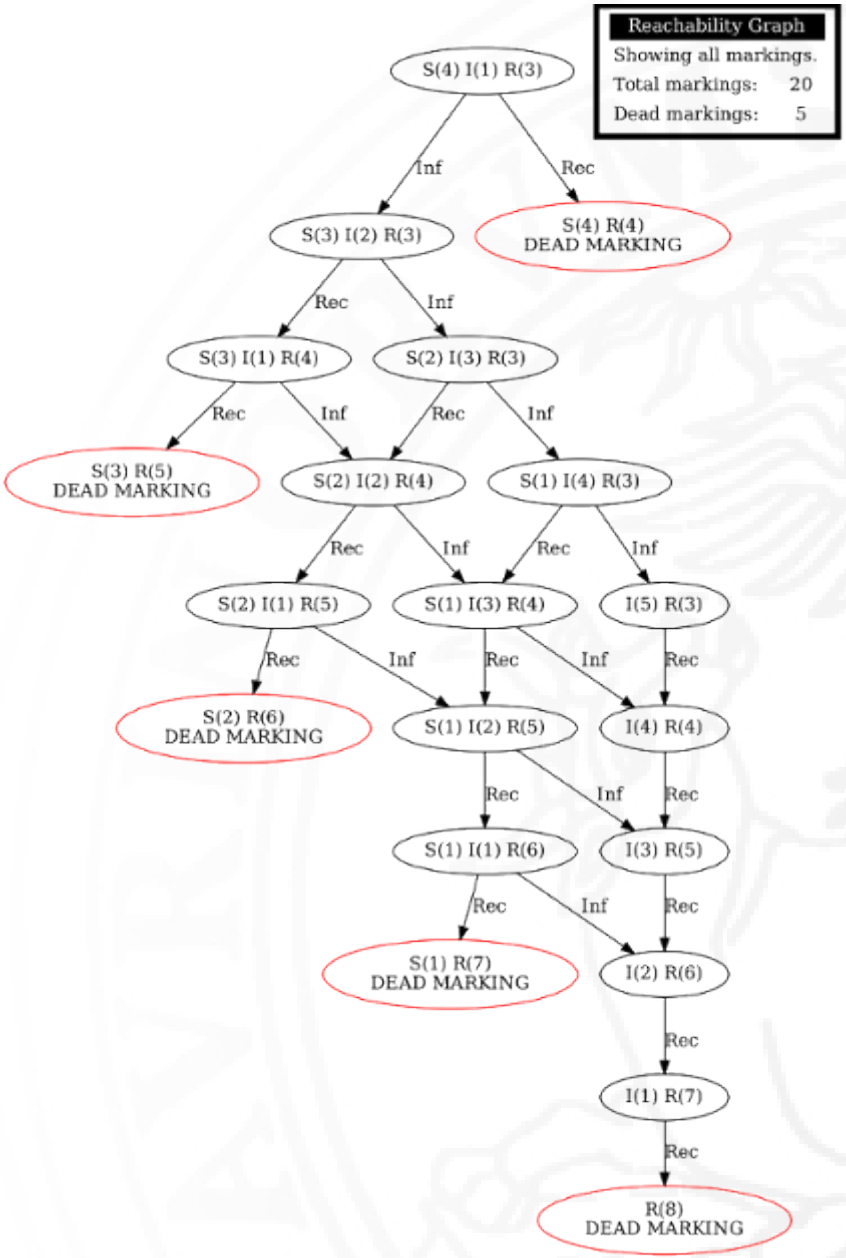
$$\frac{dx_{p_i}(\nu)}{d\nu} = \sum_{t \in T} (O(p_i, t) - I(p_i, t))\lambda(t) \prod_{h: I(p_h,t) \neq 0} x_{p_h}(\nu)^{I(p_h,t)}$$

where $x_{p_i}(\nu)$ represents the amount of the entity in place p_i at time ν with $x_{p_i}(0) = m_0(p_i)$ assuming Mass Action (MA) law as transition intensity law.



$$\begin{aligned}
\frac{dx_S(\nu)}{d\nu} &= -1\lambda(Inf)SI \\
\frac{dx_I(\nu)}{d\nu} &= +1\lambda(Inf)SI - 1\lambda(Rec)I \\
\frac{dx_R(\nu)}{d\nu} &= +1\lambda(Rec)I
\end{aligned} \tag{1}$$

Stochastic Petri Net formalism



Application

A multi-level model for studying ErbB2 breast cancer progression.

- ErbB2 is a transmembrane protein, which belongs to the Epidermal Growth Factor Receptor family;
- 20% of breast cancers overexpresses ErbB2;
- ErbB2 overexpression disrupts normal cell control promoting cell division;
- ErbB2 is an appropriate target for therapies.

- F. Cordero, **M. Beccuti**, C. Fornari, S. Lanzardo, L. Conti, F. Cavallo, G. Balbo and R. Calogero. *Multi-level model for the investigation of oncoantigen-driven vaccination effect.* ***International Journal BMC Bioinformatics***, Volume 14, Suppl. 6, 2013

Applications

2-level model on the ErbB2 breast cancer progression

Molecular level

it describes the regulation aspects of cell proliferation assuming the ErbB2 overexpression;

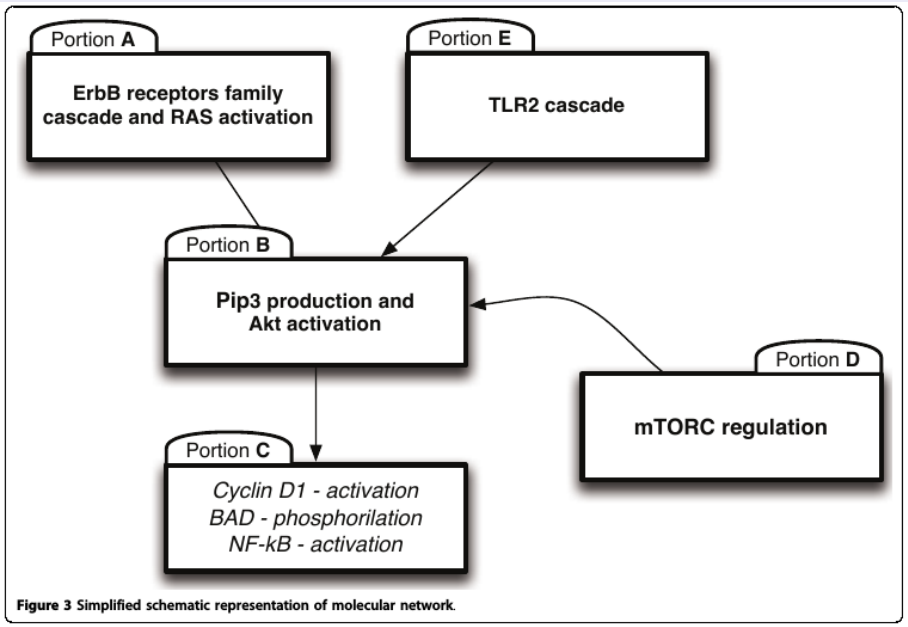
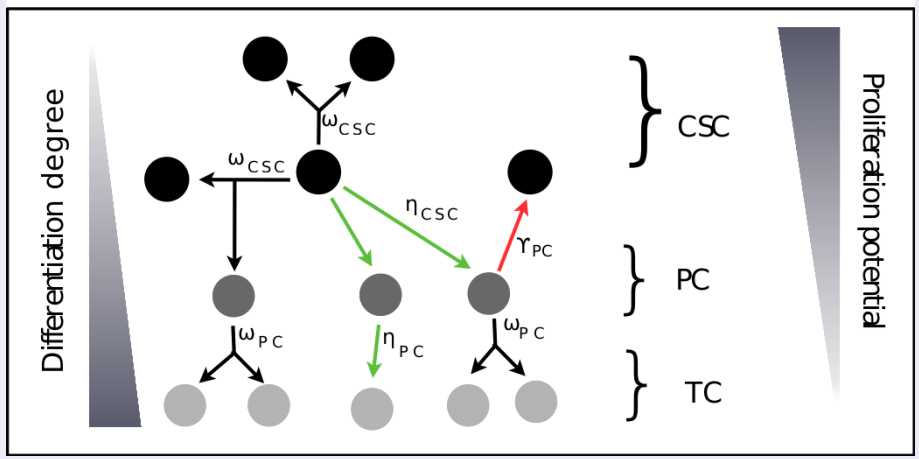


Figure 3 Simplified schematic representation of molecular network.

Cell population level

it describes how cell subpopulations interact during tumor progression assuming the CSC theory.



Therapies: we study a vaccine on Erb2 and TLR2.

Applications

- **Cell population level.**
  it describes how cell subpopulations interact during tumor progression assuming the CSC theory.

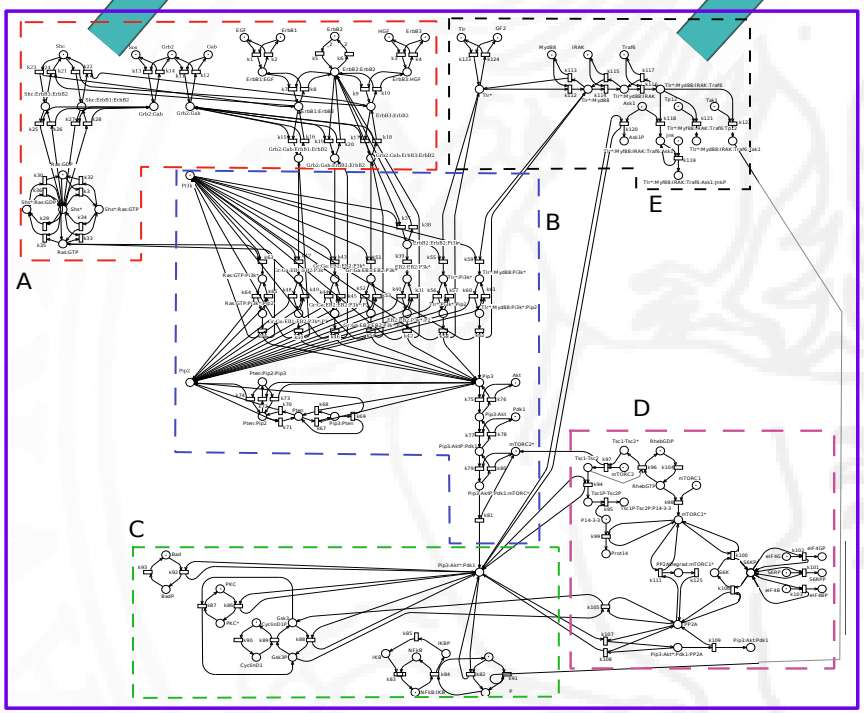
- **Molecular level**
  it describes how cell subpopulations interact during tumor progression assuming the CSC theory.

ODE system

9 cell pop
10 parameters

Cell Population level

$$
\begin{aligned}
\frac{dN_{CSC}}{dt} &= P_{sy}\omega_{CSC}N_{CSC} - \eta_1 N_{CSC} - \delta_1 N_{CSC} + \gamma_{PC}\sum_{j=1}^{3} N_{PC_j} \\
\frac{dN_{PC_1}}{dt} &= P_{asy}\omega_{CSC}N_{CSC} - \gamma_{PC}N_{PC_1} - \eta_1 N_{CSC} - \eta_2 N_{PC_1} - \delta_2 N_{PC_1} - \omega_{PC}N_{PC_1} \\
\frac{dN_{PC_j}}{dt} &= 2\omega_{PC}N_{PC_{j-1}} - \omega_{PC}N_{PC_j} + \eta_2 N_{PC_{j-1}} - \eta_2 N_{PC_j} - \delta_2 N_{PC_j} - \gamma_{PC}N_{PC_j} \qquad j = 2...3 \\
\frac{dN_{PC_i}}{dt} &= 2\omega_{PC}N_{PC_{i-1}} - \omega_{PC}N_{PC_i} + \eta_2 N_{PC_{i-1}} - \eta_2 N_{PC_i} - \delta_2 N_{PC_i} \qquad i = 4...6 \\
\frac{dN_{PC_7}}{dt} &= 2\omega_{PC}N_{PC_6} + \eta_2 N_{PC_6} - \eta_3 N_{PC_7} - \delta_2 N_{PC_7} \\
\frac{dN_{TC}}{dt} &= \eta_3 N_{PC_7} - \delta_3 N_{TC},
\end{aligned}
$$



Molecular Regulatory Network level

Petri Net

111 compounds
124 reactions
235 parameters

Applications: treatment effects

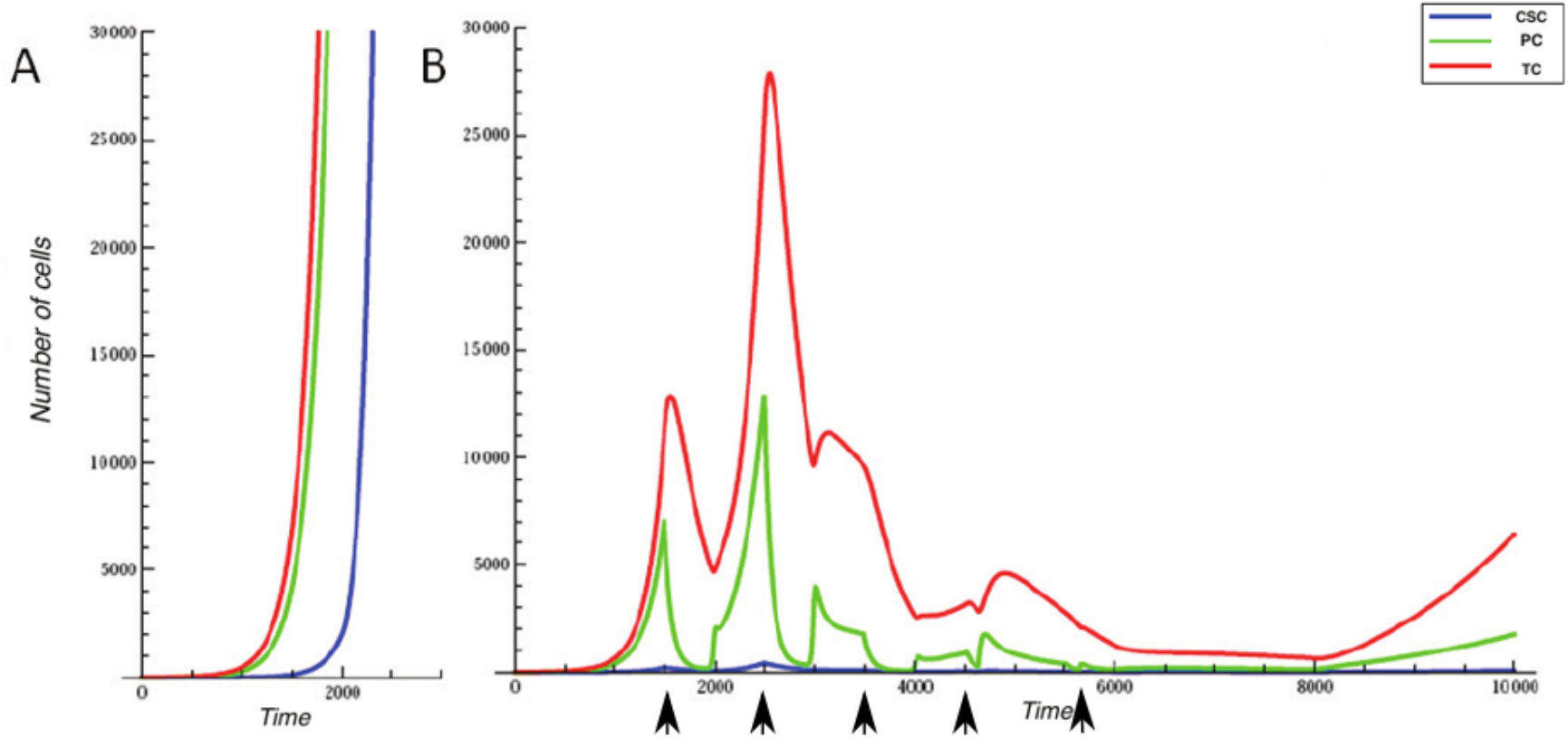


Figure 5 ErbB2 vaccination on breast cancer. Panel A reports the exponential increment of TCs and PCs after time 1000. Otherwise in panel B it is applied a vaccination effect on ErbB 2 receptor in five injection spaced every 1000 time units.

The tumor exponential growth is strongly delayed.

Applications: treatment effects

Experiments show that TLR2 is linked to CSC invasinevess, but how do perturbations on TLR2 affect CSC proliferation?

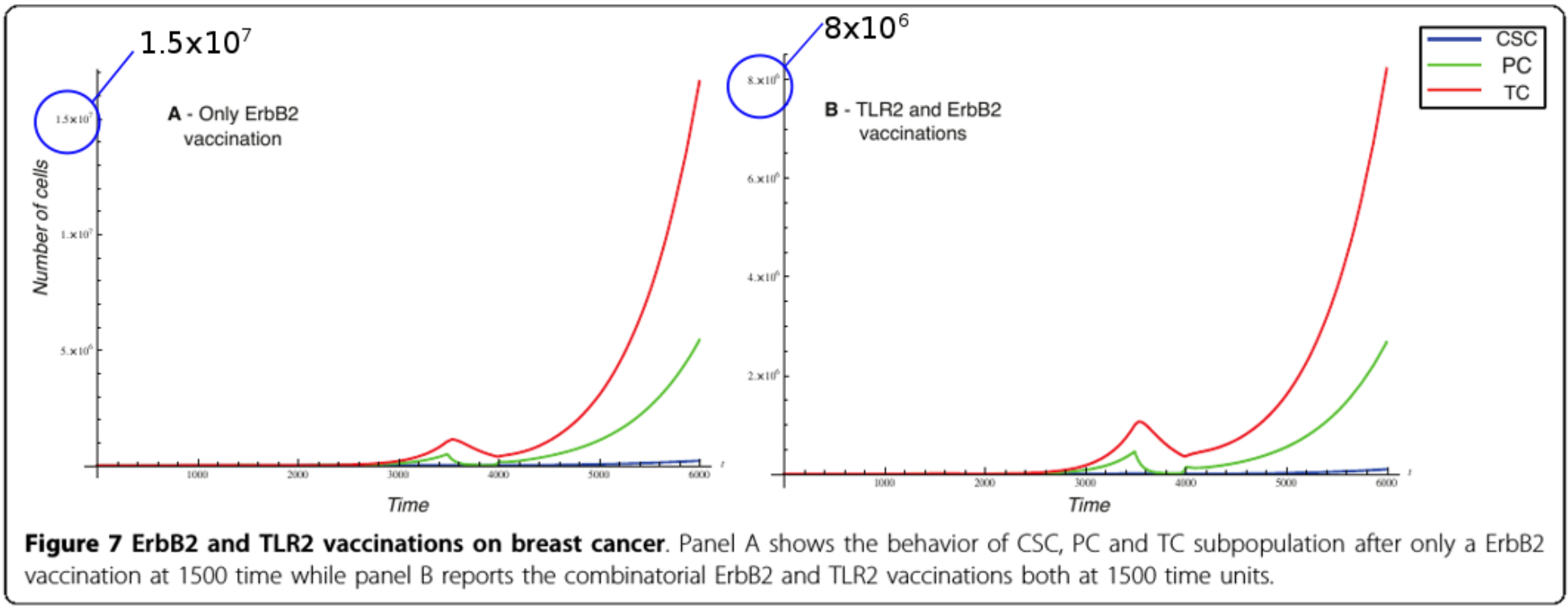


Figure 7 ErbB2 and TLR2 vaccinations on breast cancer. Panel A shows the behavior of CSC, PC and TC subpopulation after only a ErbB2 vaccination at 1500 time while panel B reports the combinatorial ErbB2 and TLR2 vaccinations both at 1500 time units.

The TC number decreases, but the growth shape does not change.

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Thanks!


Any
Questions