Modeling in Biology
(Introduction)

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Introduction: What can Informatics do for Biology?

Systems Biology. *New approaches are needed to determine the logical and informational processes that underpin cellular behaviorur.*

Paul Nurse. *Understanding Cells.* **Nature** vol. 24 (2003)

[...] An important part of the search for such explanations is the identification, characterization and classification of the logical and informational modules that operate in cells. For example, the types of modules that may be involved in the dynamics of intracellular communication include feedback loops, switches, timers, oscillators and amplifiers. Many of these could be similar in formal structure to those already studied in the development of machine theory, computing and electronic circuitry. When these modules are coupled in space by processes such as reaction diffusion and regulated cytoskeletal transport, they help to provide a basis for the spatial organization of the cell. The identification and characterization of these modules will require extensive experimental investigation, followed by realistic modelling of the processes involved.[...]

Computational Systems Biology

Computational Systems Biology.

H. Kitano. *Computational Systems Biology.* **Nature** vol. 420 (2002)

To understand complex biological systems requires the integration of experimental and computational research - in other words a systems biology approach. Computational biology, through pragmatic modelling and theoretical exploration, provides a powerful foundation from which to address critical scientific questions head-on. The reviews in this Insight cover many different aspects of this energetic field, although all, in one way or another, illuminate the functioning of modular circuits, including their robustness, design and manipulation. Computational systems biology addresses questions fundamental to our understanding of life, yet progress here will lead to practical innovations in medicine, drug discovery and engineering. [...]

Outline

What does it mean modeling?

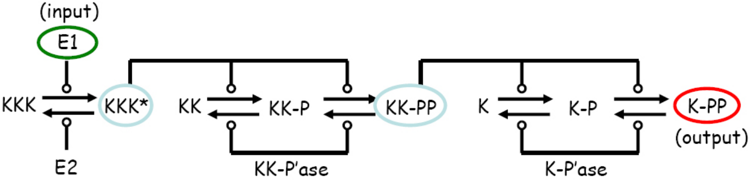
modeling = describing “systems” using the precise and formal language of mathematics. Useful for:

- (re)organization of knowledge;
- simulation;
- prediction of properties and behaviors.

What we can model in biology?

- Protein interaction networks, genetic regulation networks... (already now)
- cells, tissues, organs, organisms... (in the future)

An example: MAPKinase



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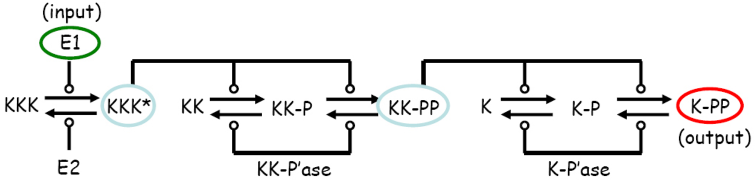

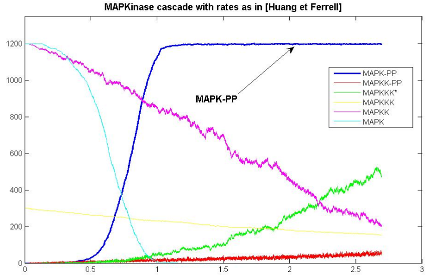

Choosing the detail of models

The choice of the *level of detail* of models is an art, depending on the phenomenon one wishes to describe.

Photosynthesis - simplified model

$6CO_2 + 6H_2O \rightarrow C_6H_{12}O_6 + 6O_2$

Photosynthesis - extended model

Light-dependent phase

$2H_2O + ADP + Pi + 2NADP^+ \rightarrow O_2 + ATP + 2NADPH + 2H^+$

Carbon-fixation phase

$CO_2 + ATP + 2NADPH + 2H^+ \rightarrow$
$(CH_2O) + H_2O + ADP + Pi + 2NADP^+$

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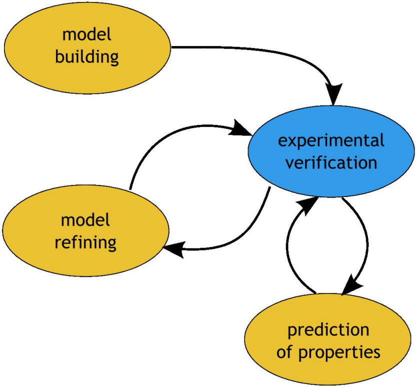
Modeling process



What mathematics?

What we want to capture of biological systems?

The dynamics, i.e. their temporal evolution.

Differential Equations

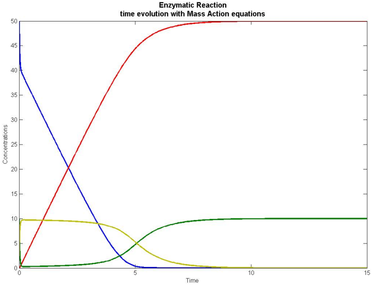
- Concentration of molecules
- The instantaneous variation of the concentration of a molecule is given by the balance of ingoing and outgoing fluxes.

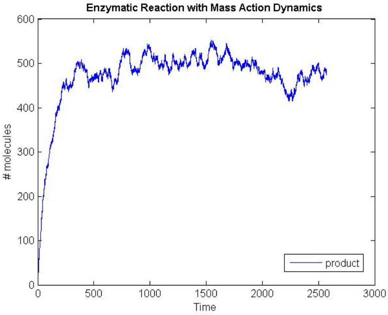
Stochastic Processes

- Number of molecules
- The variation of the number of molecules is governed by probabilistic laws (noise).

An example: reaction catalyzed by an enzyme

$$S \xrightarrow{E} P$$





The dilemma: deterministic or stochastic?

Let's consider a colony of bacteria, in which every bacteria generates new offspring with rate λ (i.e. it generates λ new bacteria per unit of time) and dies with rate μ (i.e. the fraction of bacteria dying per unit of time is μ).

Formalization

$X(t)$ is the number of bacteria at time t.

Birth rate at time t: $\propto X(t)$ $(= \lambda X(t))$

Death rate at time t: $\propto X(t)$ $(= \mu X(t))$

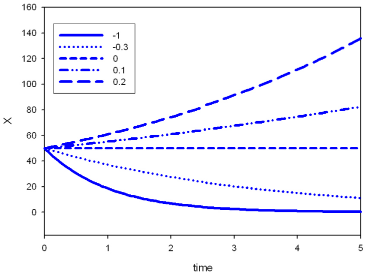
Model with differential equations

$X(t)$ is a continuous variable (taking values in $\mathbb{R}$).
The speed of change of $X(t)$:

$$\frac{dX(t)}{dt} = \lambda X(t) - \mu X(t) = (\lambda - \mu)X(t)$$

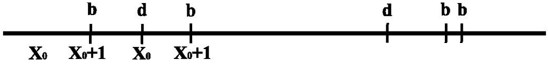
This differential equation has solution

$$X(t) = X_0 e^{(\lambda-\mu)t}.$$



Model with stochastic processes

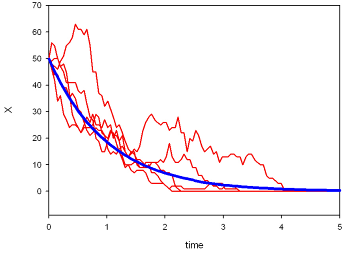
$X(t)$ is a discrete variable (values in $\mathbb{N}$).
We observe a sequence of (discrete) events in (continuous) time, each happening with a certain probability. Mathematically, the model is a Continuous Time Markov Chain.



prob. birth $= \frac{\lambda X(t)}{\lambda X(t)+\mu X(t)}$

prob. death $=$

$\frac{\mu X(t)}{\lambda X(t)+\mu X(t)}$



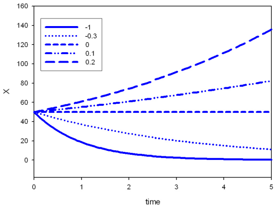
Comparing the two models

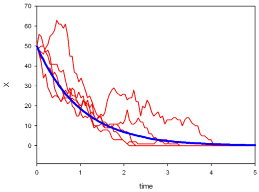
ODE

- Population of bacteria does not fluctuate.
- Bacteria can asymptotically go extinct.
- Dynamics determined by $\lambda - \mu$.

Stochastic Processes

- Noisy evolution.
- Bacteria can extinguish in finite time.
- Dynamics determined by $\lambda - \mu$ (trend) and $\lambda + \mu$ (variance).

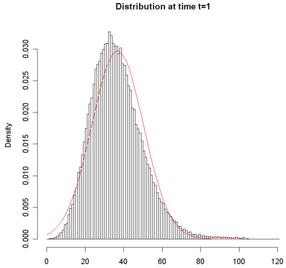




Analysis of the stochastic model

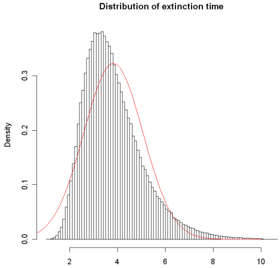
- Analysis are usually performed simulating the model several times.
- We can study the average behavior, or distributions at specific times or of specific events.

Distribution of bacteria at time $t = 1$



100000 runs mean = 37.07; sd = 13.50

Distribution of extinction time

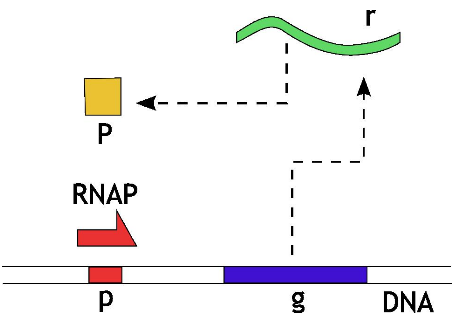


100000 runs mean = 3.82; sd = 1.23

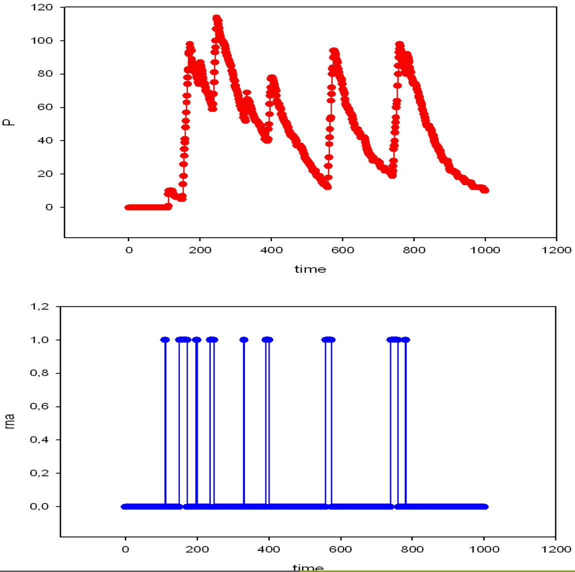
Stochasticity in biological systems?

Stochastic mechanisms act when number of molecules is low. They are central in genetic regulatory networks. For instance, they may be responsible for phenotypic variation in isogenic population of bacteria.

H. H. McAdams and A. Arkin. *Stochastic mechanisms in gene expression.* PNAS, 1997.



Stochasticity in biological systems



Effect of stochasticity

Lotka-Volterra system

$$C \rightarrow_{k_d}$$
$$E \rightarrow_{k_b} 2E$$
$$C + E \rightarrow_{k_e} 2C$$