Stochastic simulations

Application to molecular networks

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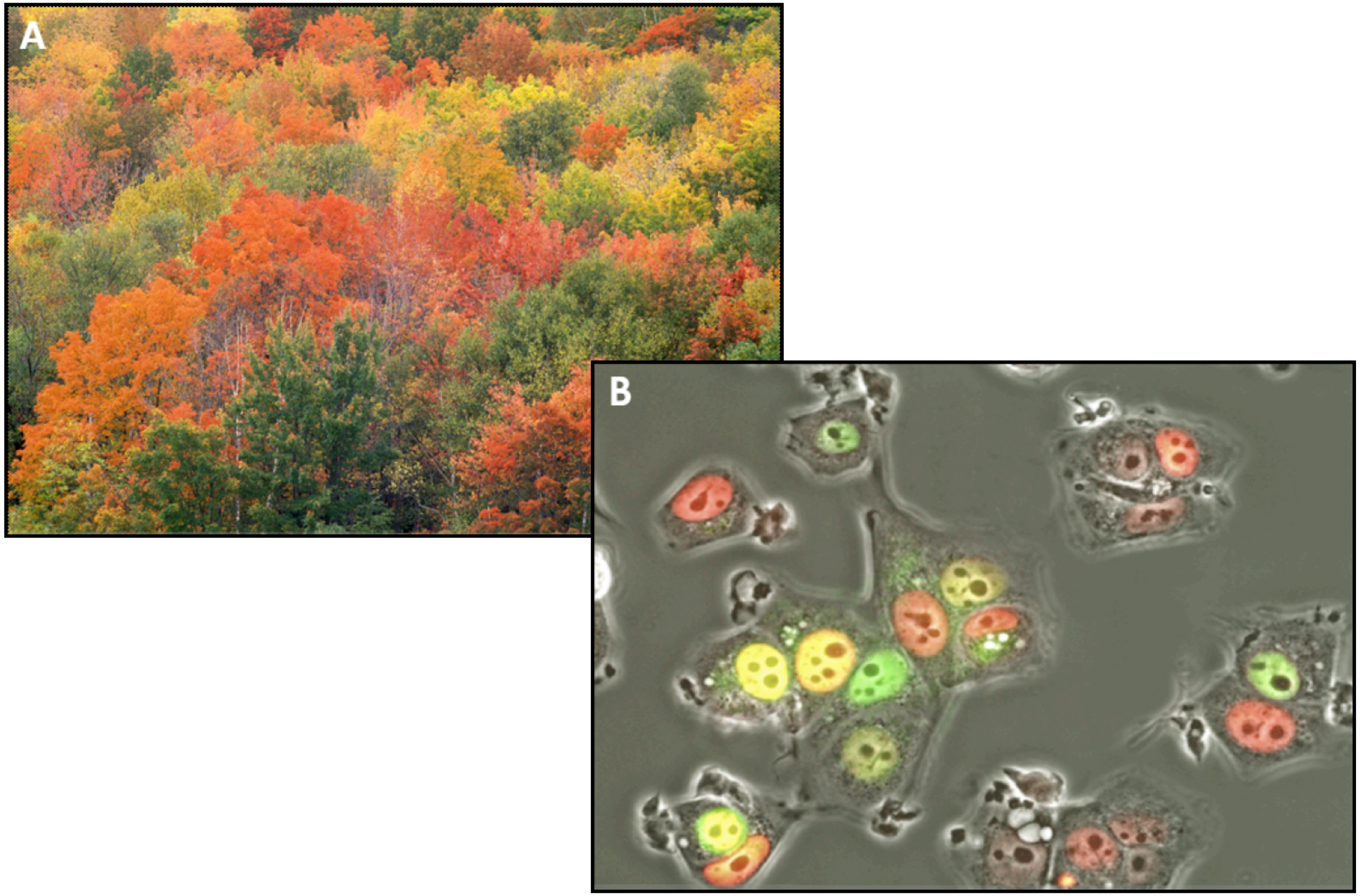
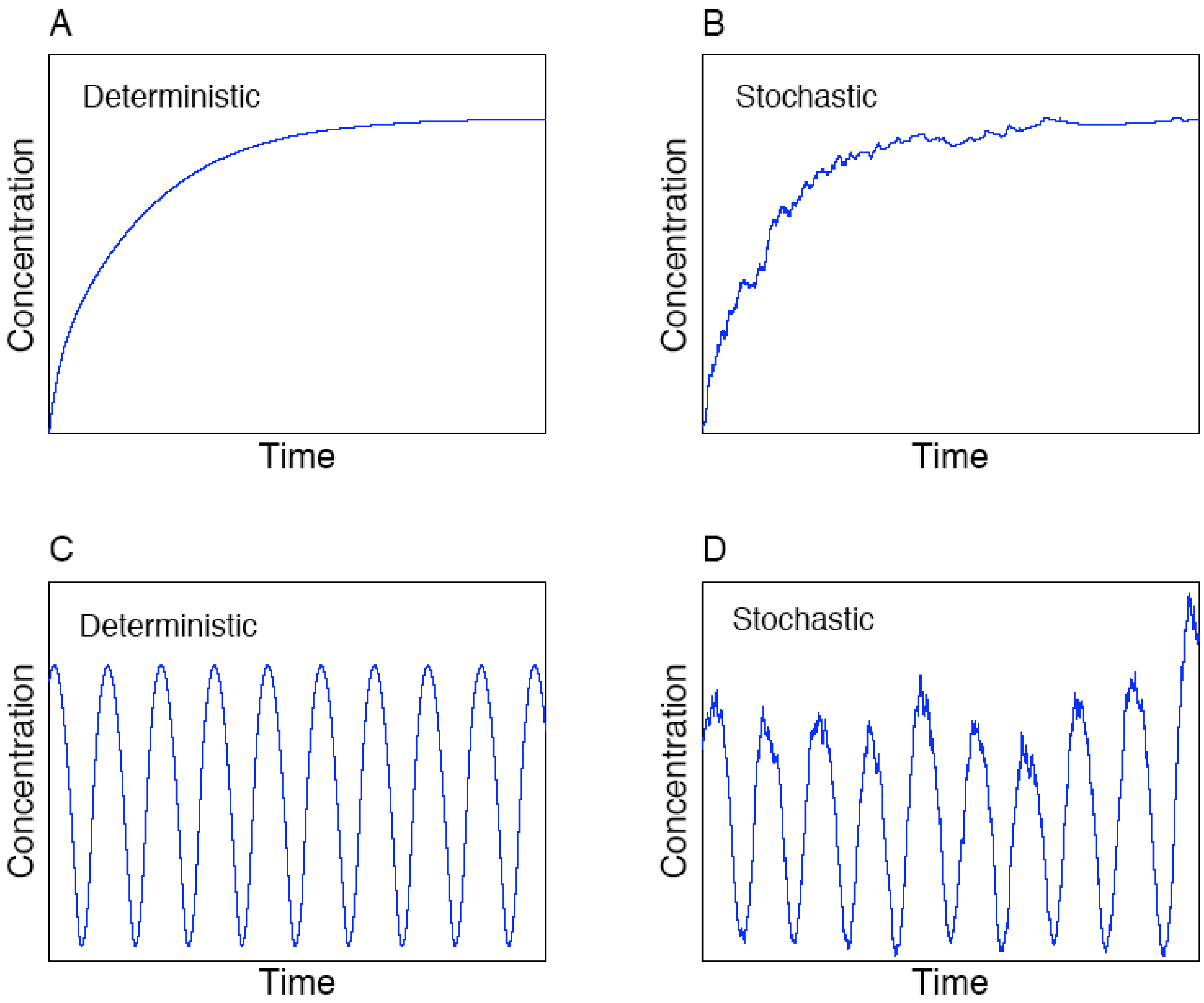


Lahav (2004) *Science STKE*

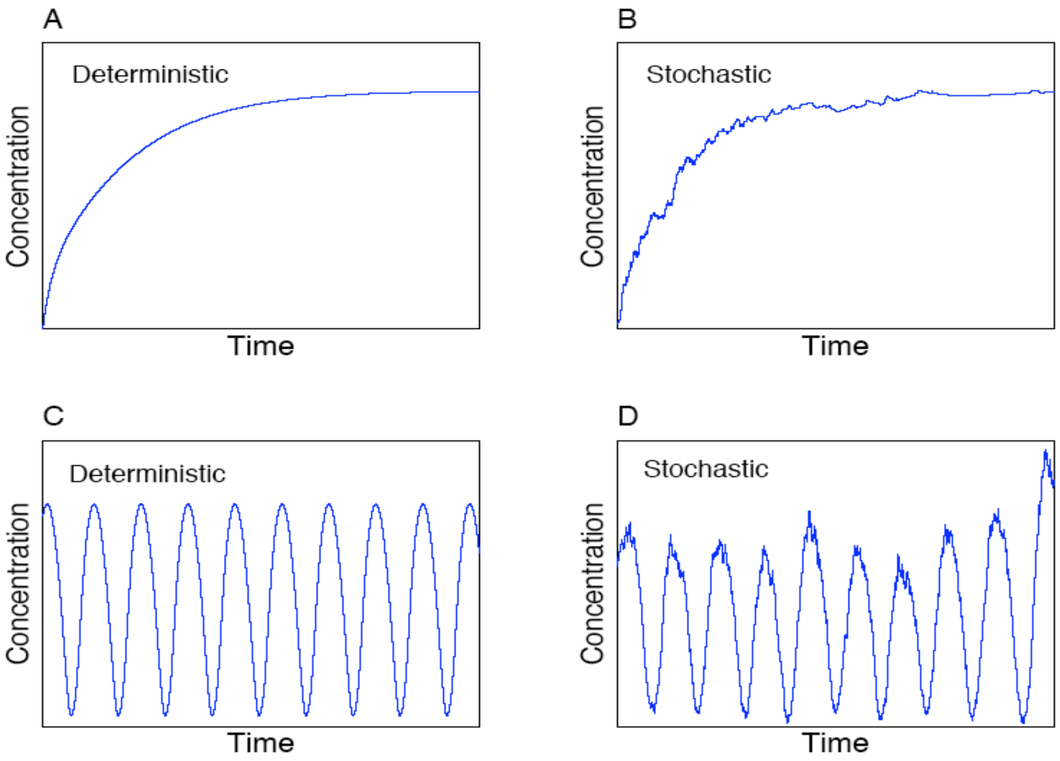
Overview

- **Introduction: theory and simulation methods**
  - Definitions (intrinsic vs extrinsic noise, robustness,...)
  - Deterministic vs stochastic approaches
  - Master equation, birth-and-death processes
  - Gillespie and Langevin approaches
  - Application to simple systems
- **Literature overview**
  - Measuring the noise, intrinsic vs extrinsic noise
  - Determining the souces of noise
  - Assessing the robustness of biological systems
- **Application to circadian clocks**
  - Molecular bases of circadian clocks
  - Robustness of circadian rhythms to noise

Deterministic vs stochastic appraoches



Deterministic vs stochastic appraoches



Ordinary differential equations

$$\frac{dX}{dt} = f_{productoin}(X) - f_{consumption}(X)$$

Stochastic differential equations

$$\frac{dX}{dt} = f_{productoin}(X) - f_{consumption}(X) + f_{noise}$$

Discrete stochastic simulations

$$\xrightarrow{P(production)} X \xrightarrow{P(consumption)}$$

Sources of noise

Intrinsic noise

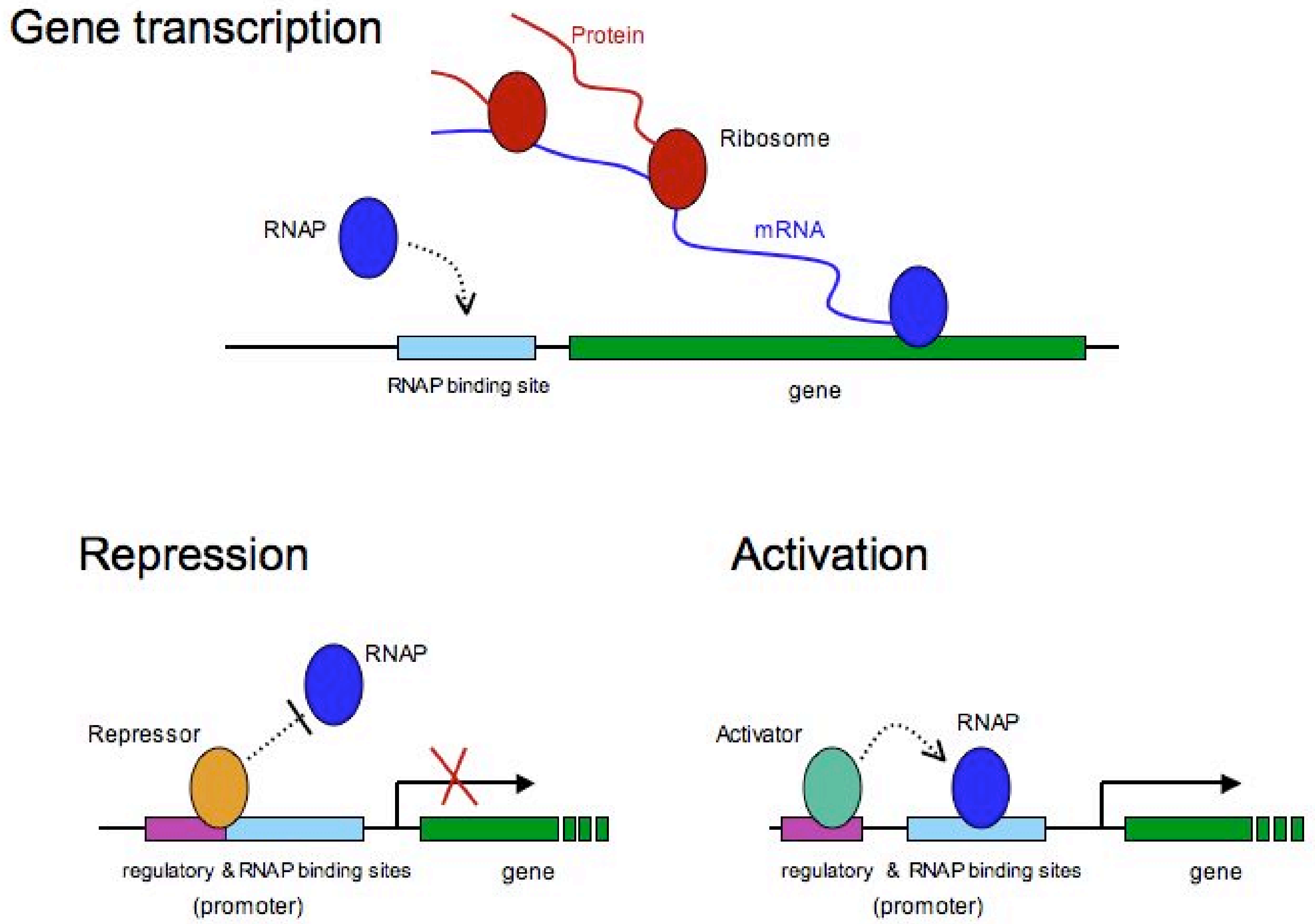
Noise resulting form the **probabilistic character of the (bio)chemical reactions**. It is particularly important when the number of reacting molecules is low. It is inherent to the dynamics of any genetic or biochemical systems.

Extrinsic noise

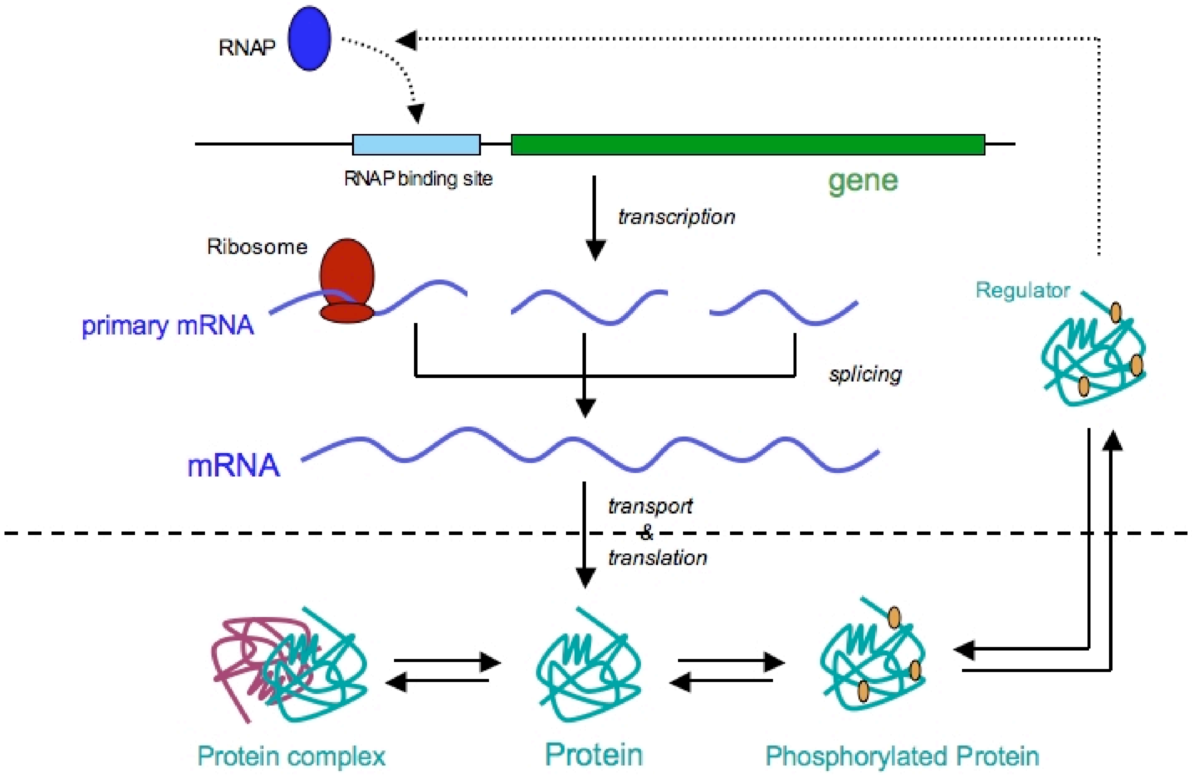
Noise due to the random fluctuations in **environmental parameters** (such as cell-to-cell variation in temperature, pH, kinetics parameters, number of ribosomes,...).

Both Intrinsic and extrinsic noise lead to fluctuations in a single cell and results in cell-to-cell variability

Noise in biology



Noise in biology



- Regulation and binding to DNA
- Transcription to mRNA
- Splicing of mRNA
- Transportation of mRNA to cytoplasm
- Translation to protein

- Conformation of the protein
- Post-translational changes of protein
- Protein complexes formation
- Proteins and mRNA degradation
- Transportation of proteins to nucleus
- ...

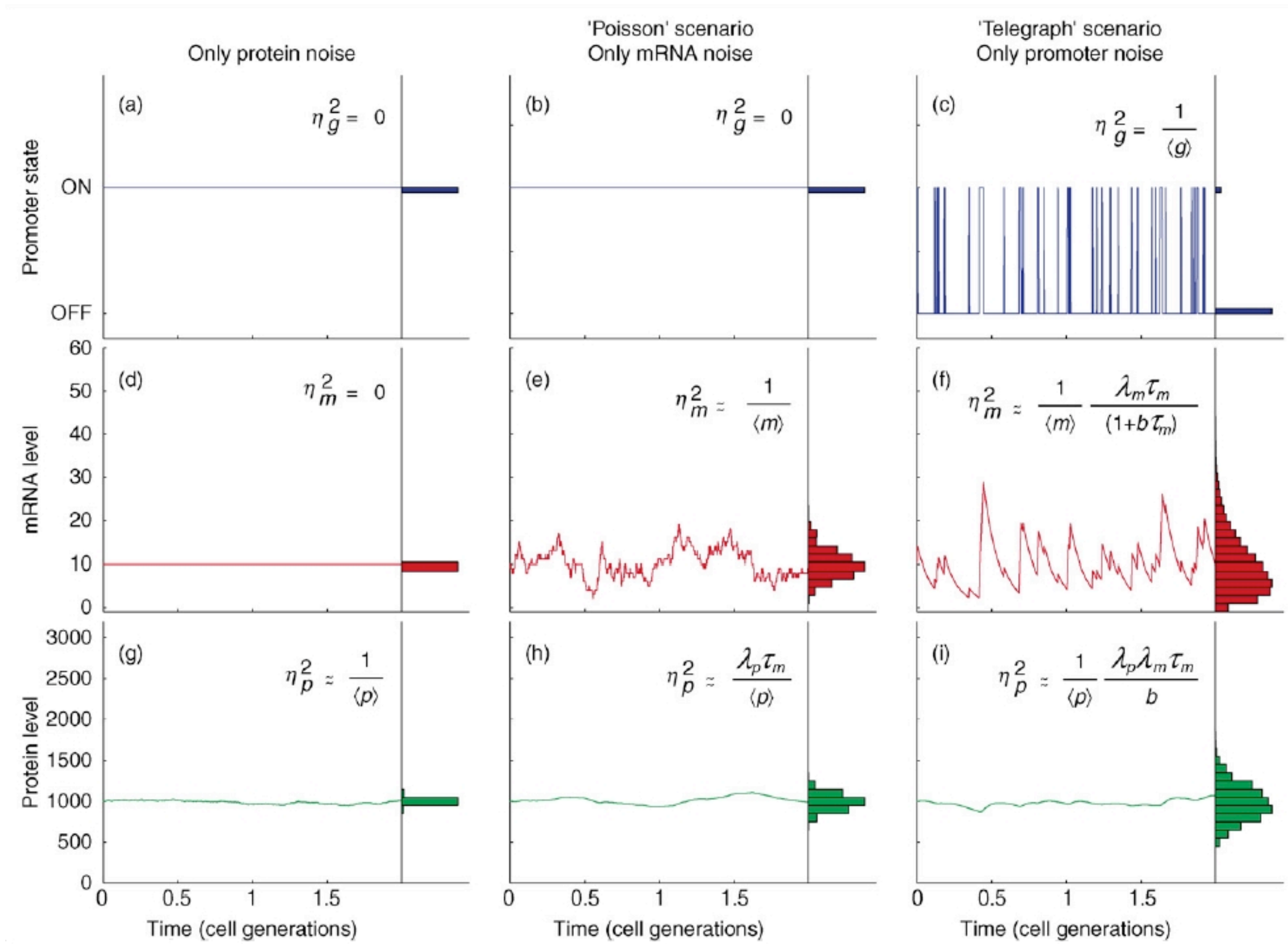
Noise in biology

Noise-producing steps in biology

Promoter state

mRNA

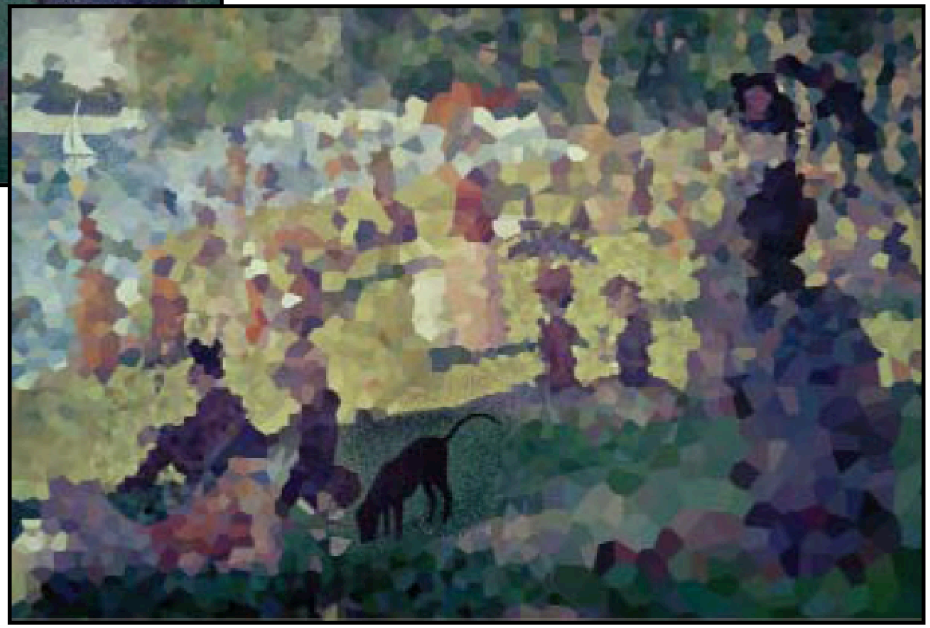
Protein



Kaufmann & van Oudenaarden (2007) *Curr. Opin. Gen. Dev.* , in press

Effects of noise

Georges Seurat
Un dimanche après-midi
à la Grande Jatte



Fedoroff & Fontana (2002) *Science*

Effects of noise

Destructive effect of noise

- Imprecision in the timing of genetic events
- Imprecision in biological clocks
- Phenotypic variations

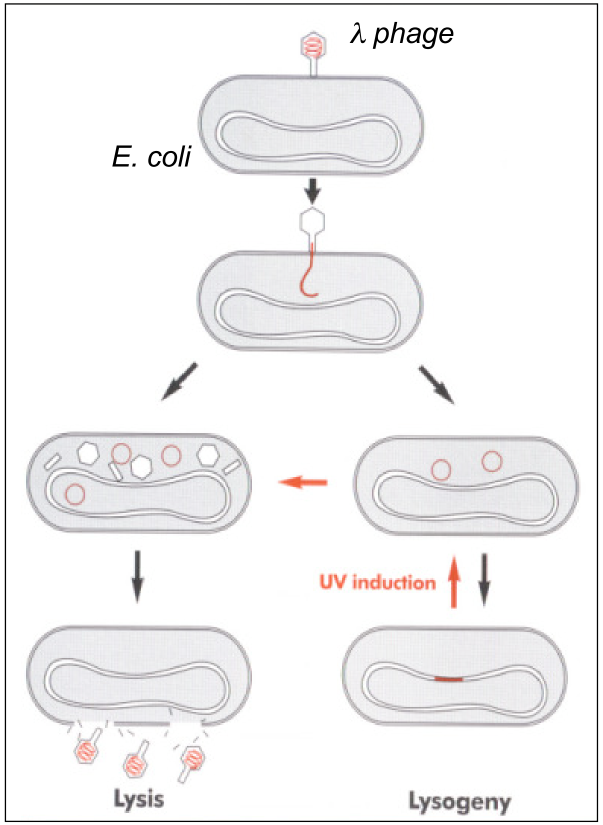
Constructive effect noise

- Noise-induced behaviors
- Stochastic resonance
- Stochastic focusing

Noise-induced phenotypic variations

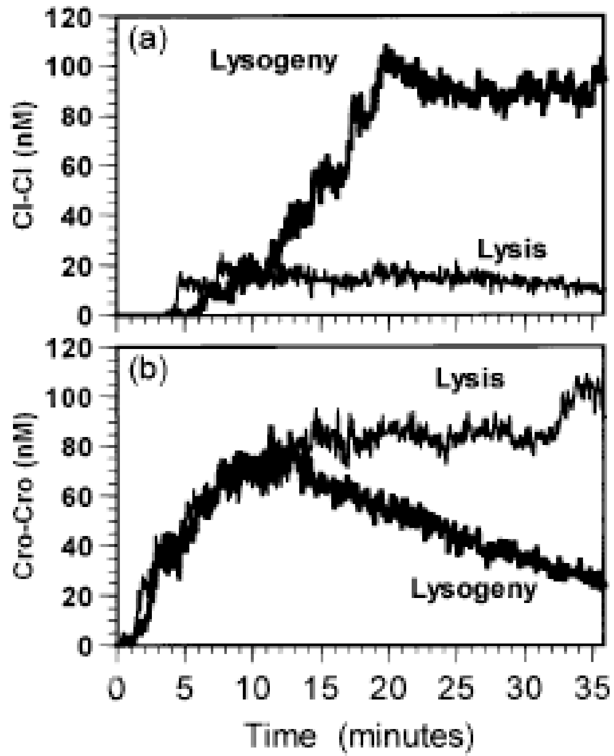
Stochastic kinetic analysis of a developmental pathway bifurcation in phage-λ *Escherichia coli* cell

Arkin, Ross, McAdams (1998) *Genetics* 149: 1633-48



Fluctuations in rates of gene expression can produce highly **erratic time patterns** of protein production in individual cells and wide diversity in instantaneous protein concentrations across cell populations.

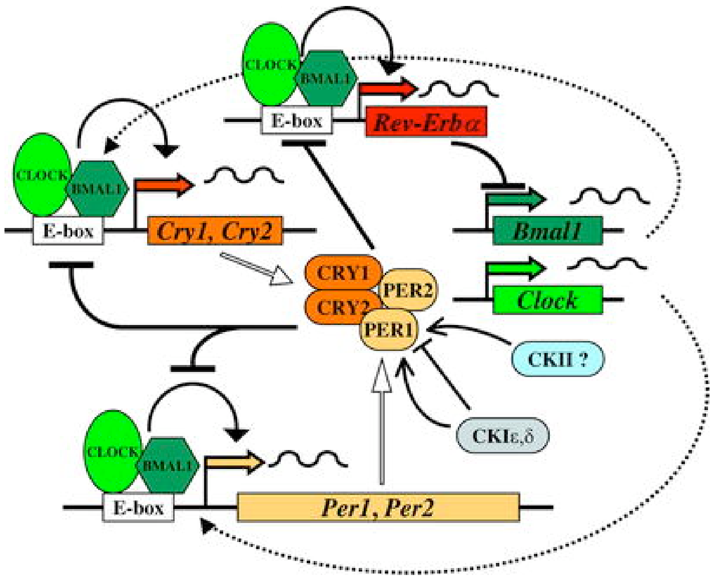
When two independently produced regulatory proteins acting at low cellular concentrations competitively control a **switch point in a pathway**, stochastic variations in their concentrations can produce **probabilistic pathway selection**, so that an initially homogeneous cell population partitions into **distinct phenotypic subpopulations**

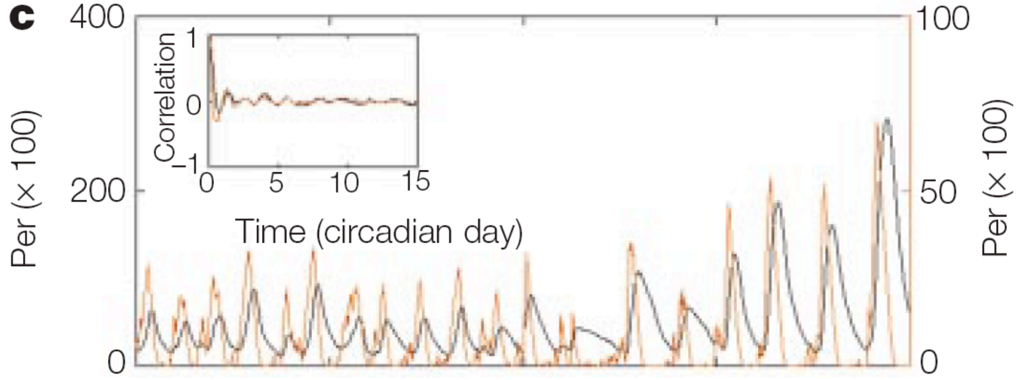


Imprecision in biological clocks

Circadian clocks limited by noise

Barkai, Leibler (2000) ***Nature*** **403: 267-268**





For example, in a previously studied model that depends on a **time-delayed negative feedback**, reliable oscillations were found when reaction kinetics were approximated by continuous differential equations. However, when the **discrete nature of reaction events** is taken into account, the oscillations persist but with **periods and amplitudes** that **fluctuate widely in time**. Noise resistance should therefore be considered in any postulated molecular mechanism of circadian rhythms.

Noise-induced behaviors

Noise-induced oscillations

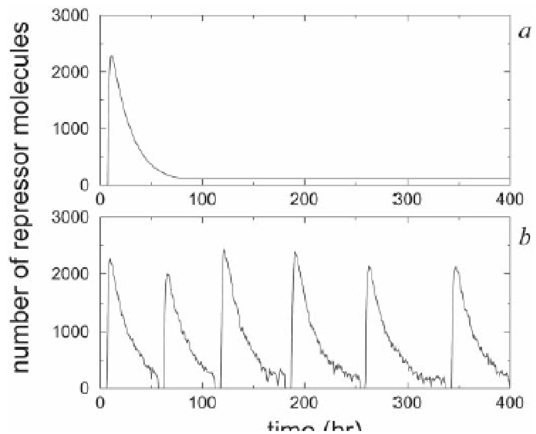
Noise-induced synchronization

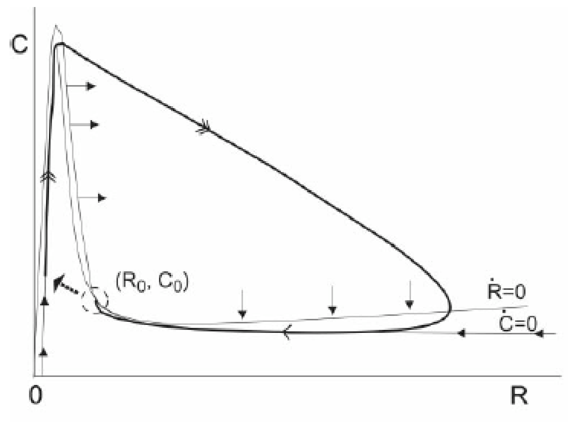
Noise-induced excitability

Noise-induced bistability

Noise-induced pattern formation

Noise-induced oscillations in an excitable system

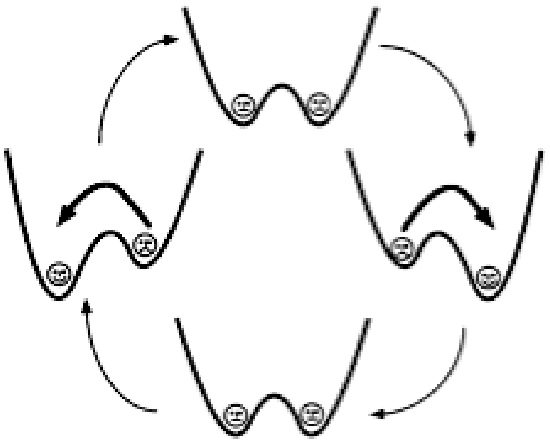


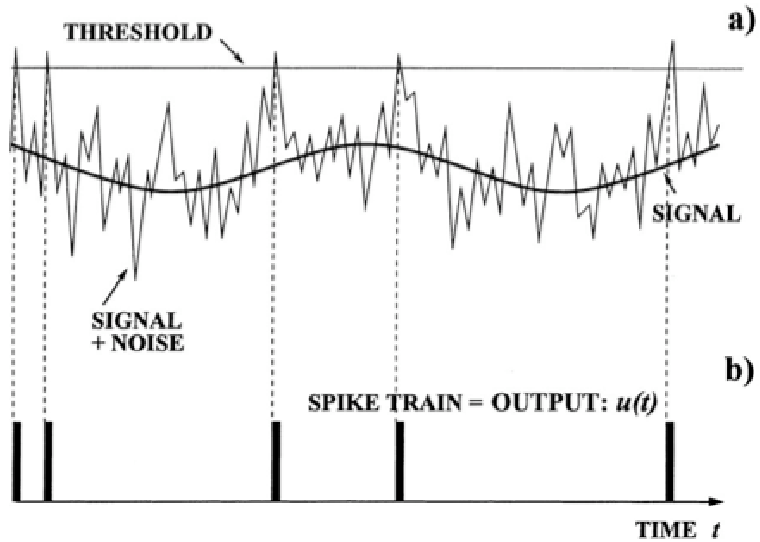


Vilar et al, PNAS, 2002

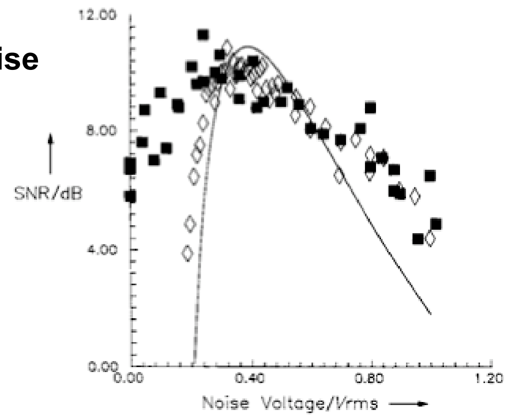
Stochastic resonance

Stochastic resonance is the phenomenon whereby the addition of an **optimal level of noise** to a weak information-carrying input to certain nonlinear systems can **enhance the information** content at their outputs.





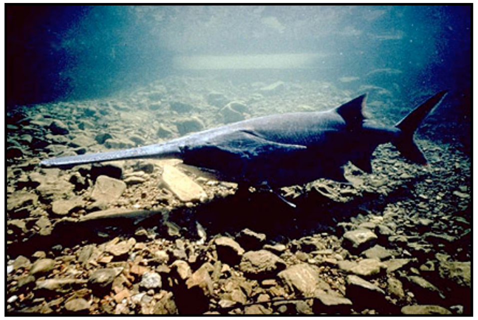
Signal-to-noise Ratio (SNR)



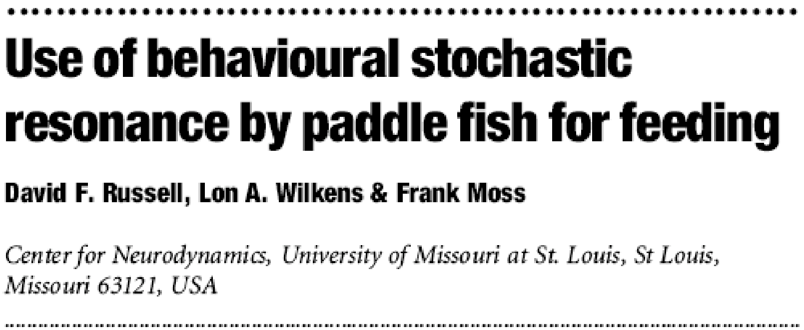
noise

Hanggi (2002) Stochastic resonance in biology. *Chem Phys Chem* 3: 285

Stochastic resonance



paddle fish

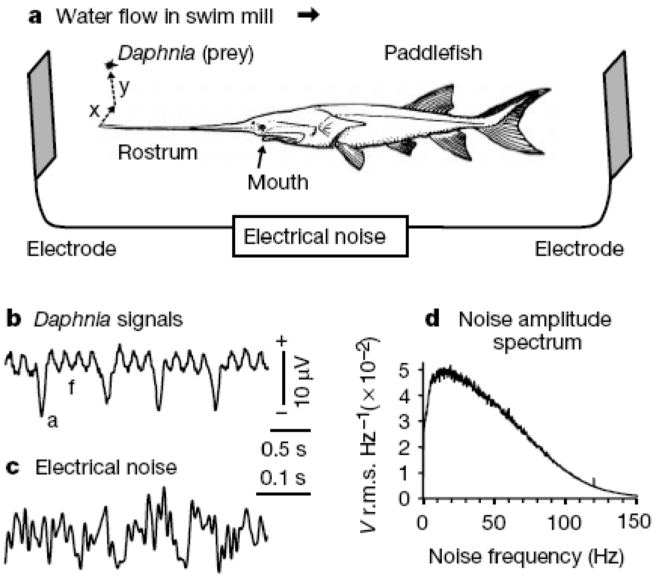


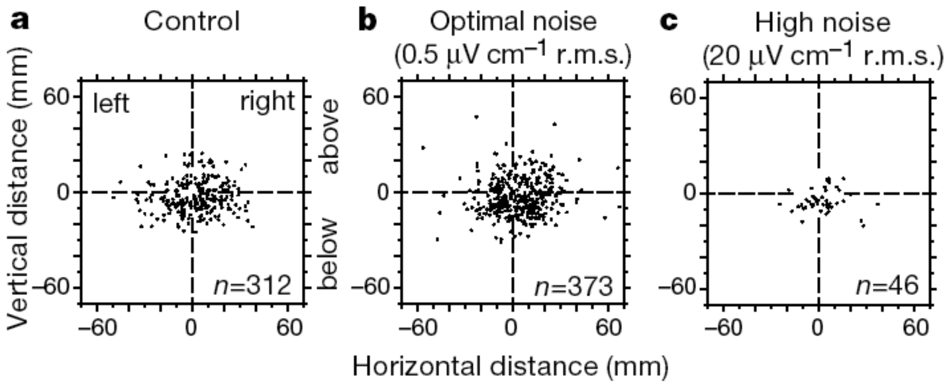
Use of behavioural stochastic resonance by paddle fish for feeding

David F. Russell, Lon A. Wilkens & Frank Moss

Center for Neurodynamics, University of Missouri at St. Louis, St Louis, Missouri 63121, USA

Here, we show that stochastic resonance enhances the normal feeding behaviour of paddle fish (*Polyodon spathula*) which use passive electroreceptors to detect electrical signals from planktonic prey (*Daphnia*).





Noise, robustness and evolution

Robustness is a property that allows a system to maintain its functions despite external and internal noise.

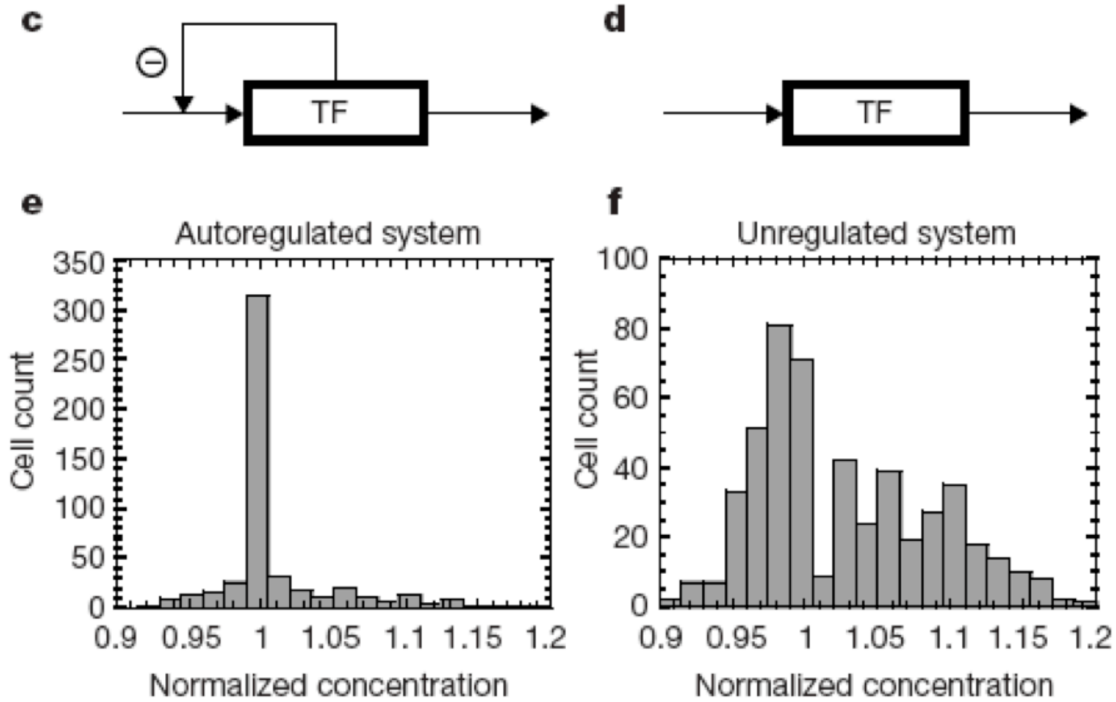
It is commonly believed that robust traits have been selected by **evolution**.

Kitano (2004) biological robustness. *Nat. Rev. Genet.* 5: 826-837

Noise, robustness and evolution

Engineering stability in gene networks by autoregulation

Becskei, Serrano (2000) *Nature* 405: 590-3

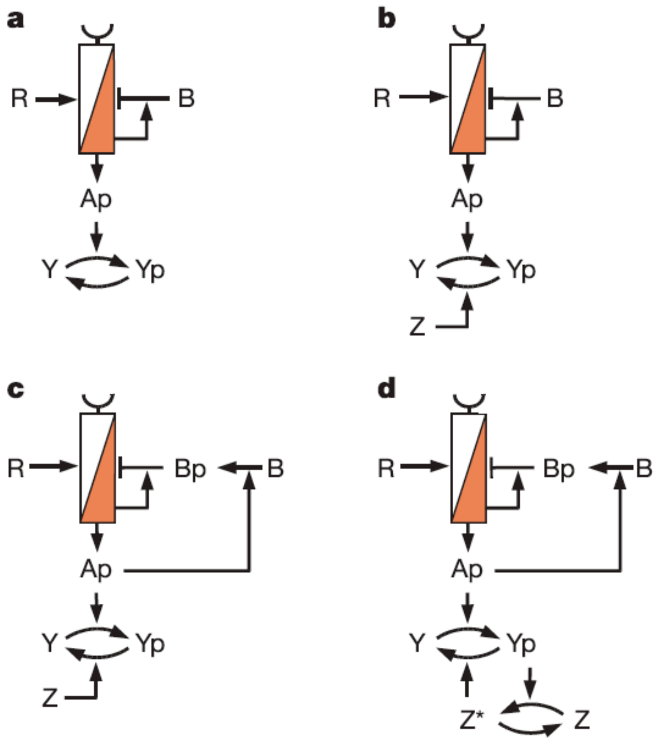


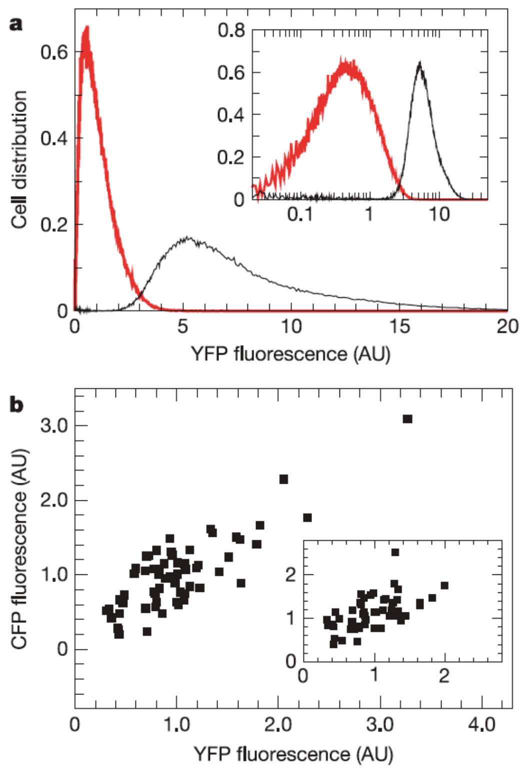
Autoregulation (negative feedback loops) in gene circuits provide **stability**, thereby limiting the range over which the concentrations of network components fluctuate.

Noise, robustness and evolution

Design principles of a bacterial signalling network

Kollmann, Lodvok, Bartholomé, Timmer, Sourjik (2005) ***Nature*** **438: 504-507**





Among these **topologies** the experimentally established chemotaxis network of *Escherichia coli* has the smallest sufficiently **robust network structure**, allowing **accurate chemotactic response** for almost all individuals within a population.

Theory of stochastic systems

Deterministic formulation

Let's consider a single species (X) involved in a single reaction:

$$\mathrm{n\ X} + \ldots \rightarrow \mathrm{p\ X} + \ldots$$

Deterministic description of its time evolution (ODE):

$$\frac{dX}{dt} = \eta v \text{ with } \eta = p - n$$

η = stoechiometric coefficient
v = reaction rate:

$$v = kX^n$$

Deterministic formulation

Let's now consider a several species (X_i) involved in a couple of reactions:

$$\mathrm{n}_{11}\mathrm{X}_1 + \mathrm{n}_{21}\mathrm{X}_2 + \ldots \longrightarrow \mathrm{p}_{11}\mathrm{X}_1 + \mathrm{p}_{21}\mathrm{X}_2 + \ldots$$

$$\mathrm{n}_{12}\mathrm{X}_1 + \mathrm{n}_{22}\mathrm{X}_2 + \ldots \longrightarrow \mathrm{p}_{12}\mathrm{X}_1 + \mathrm{p}_{22}\mathrm{X}_2 + \ldots$$

$$\ldots$$

$$\mathrm{n}_{1R}\mathrm{X}_1 + \mathrm{n}_{2R}\mathrm{X}_2 + \ldots \longrightarrow \mathrm{p}_{1R}\mathrm{X}_1 + \mathrm{p}_{2R}\mathrm{X}_2 + \ldots$$

Deterministic description of their time evolution (ODE):

$$\boxed{\frac{dX_i}{dt} = \sum_{r=1}^{R} \eta_{ir} v_r = \eta_{i1} v_1 + \eta_{i2} v_2 + \ldots + \eta_{iR} v_R}$$

v_r = rate of the different reactions ($r = 1, 2, \ldots R$).

$\eta_{ir} = p_{ir} - n_{ir}$ = stoechiometric coefficient of compound X_i in reaction r.

Stochastic formulation

Stochastic description (in terms of the probabilities):

$$P(\boldsymbol{X}, t+dt) = P(\boldsymbol{X}, t)P(\text{no change over dt}) + \sum_{r=1}^{R} P(\boldsymbol{X} - \boldsymbol{\eta_r}, t)P(\text{state change over dt})$$

$$P(\text{no change over dt}) = 1 - \sum_{r=1}^{R} w_r(\boldsymbol{X})dt$$

$$P(\text{state change over dt}) = w_r(\boldsymbol{X} - \boldsymbol{\eta_r})dt$$

$$\lim_{dt \to 0} \frac{P(\boldsymbol{X}, t+dt) - P(\boldsymbol{X}, t)}{dt} = \frac{\partial P(\boldsymbol{X}, t)}{\partial t}$$

$$\boxed{\frac{\partial P(\boldsymbol{X}, t)}{\partial t} = \sum_{r=1}^{R} \left(w_r(\boldsymbol{X} - \boldsymbol{\eta_r})P(\boldsymbol{X} - \boldsymbol{\eta_r}, t) - w_r(\boldsymbol{X})P(\boldsymbol{X}, t)\right)}$$

Chemical master equation

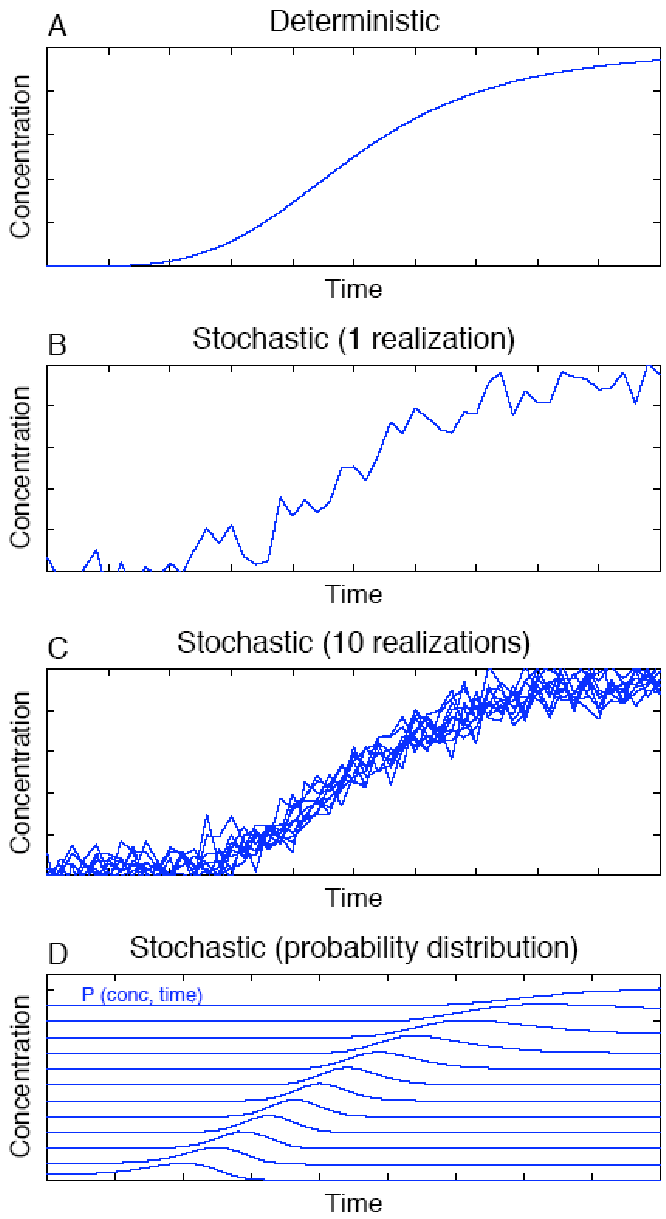
Comparison of the different formalisms

Deterministic description

Stochastic description (1 possible realization)

Stochastic description (10 possible realizations)

Stochastic description (probability distribution)

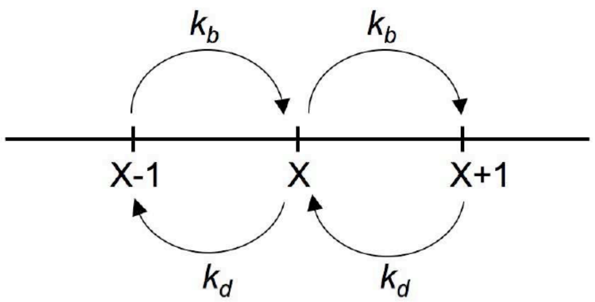


Stochastic formulation: birth-and-death

Birth-and-death process (single species):

$$\xrightarrow{k_b} \mathrm{X} \xrightarrow{k_d}$$

State transitions



Master equation for a birth-and-death process

$$\frac{\partial P(X,t)}{\partial t} = k_b P(X-1,t) + k_d (X+1) P(X+1,t) - k_b P(X,t) - k_d X P(X,t)$$

Stochastic formulation: birth-and-death

Birth-and-death process (multiple species):

$$\xrightarrow{k_{b1}} X_1 \xrightarrow{k_{d1}}$$

$$\xrightarrow{k_{b2}} X_2 \xrightarrow{k_{d2}}$$

$$\xrightarrow{k_{b3}} X_3 \xrightarrow{k_{d3}}$$

…

Master equation for a birth-and-death process

$$\frac{\partial P(\{X_i\},t)}{\partial t} = \sum_{r=1}^{R} [k_{br}(\{X_i - \eta_{ir}\})P(\{X_{j\neq i}, X_i - \eta_{ir}\},t)$$

$$+k_{dr}(\{X_i + \eta_{ir}\})P(\{X_{j\neq i}, X_i + \eta_{ir}\},t) - k_{br}(\{X_i\})P(X_i,t) - k_{dr}(\{X_i\})P(\{X_i\},t)]$$

Stochastic formulation: examples

$$\mathrm{X}+\mathrm{Y} \xrightarrow{k} \mathrm{Z}$$

$$w(X,Y) = kXY$$

$$\begin{aligned}
\frac{\partial P(X,Y,Z,t)}{\partial t} &= w(X+1,Y+1)P(X+1,Y+1,Z-1) \\
&- w(X,Y)P(X,Y,Z) \\
&= k(X+1)(Y+1)P(X+1,Y+1,Z-1) \\
&- kXYP(X,Y,Z)
\end{aligned}$$

Stochastic formulation: examples

$$\mathrm{A+X} \xrightarrow{k} \mathrm{2X}$$

$$w(A,X) = kAX$$

$$\begin{aligned}\frac{\partial P(A,X,t)}{\partial t} &= w(A+1,X-1)P(A+1,X-1) \\ &- w(A,X)P(A,X) \\ &= k(A+1)(X-1)P(A+1,X-1) \\ &- kAXP(A,X)\end{aligned}$$

Stochastic formulation: examples

$$2\mathrm{X} \xrightarrow{k} \mathrm{E}$$

$$w(X) = \frac{k}{2} X(X-1)$$

$$\begin{aligned}
\frac{\partial P(X,E,t)}{\partial t} &= w(X+2)P(X+2,E-1) \\
&- w(X)P(X,E) \\
&= \frac{k}{2}(X+1)(X+2)P(X+2,E-1) \\
&- \frac{k}{2}(X-1)(X)P(X,E)
\end{aligned}$$

Stochastic formulation: Fokker-Planck

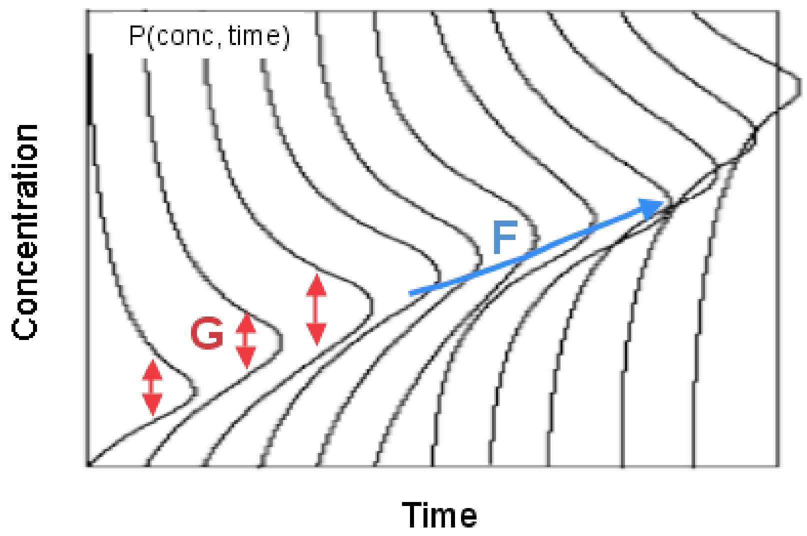
Fokker-Planck equation

$$\frac{\partial P(\boldsymbol{X},t)}{\partial t} = -\sum_i \left(\frac{\partial}{\partial X_i} F_i(\boldsymbol{X}) P(\boldsymbol{X},t) \right) + \sum_{i,j} \left(\frac{\partial^2}{\partial X_i X_j} G_{i,j}(\boldsymbol{X}) P(\boldsymbol{X},t) \right)$$

Drift term   Diffusion term

$$F_i(\boldsymbol{X}) = \sum_{r=1}^{R} \boldsymbol{\eta_r} w_r(\boldsymbol{X})$$

$$G_{i,j}(\boldsymbol{X}) = \sum_{r=1}^{R} \boldsymbol{\eta_r} \boldsymbol{\eta_r}^T w_r(\boldsymbol{X})$$



Stochastic formulation: remark

This is a nice theory, but...

$$\mathrm{A} \rightleftharpoons \mathrm{B} \rightleftharpoons \mathrm{C}$$

For *N* = 200 there are more than 1000000 possible molecular combinaisons!

We can not solve the master equation by hand.

We need to perform **simulations** (using computers).

Numerical simulation

The Gillespie algorithm

Direct simulation of the master equation

$$\xrightarrow{P(production)} X \xrightarrow{P(consumption)}$$

The Langevin approach

Stochastic differential equation

$$\frac{dX}{dt} = f_{productoin}(X) - f_{consumption}(X) + f_{noise}$$

Gillespie algorithm

The Gillespie algorithm

A **reaction rate** $\boldsymbol{w_i}$ is associated to each reaction step. These probabilites are related to the kinetics constants.

Initial number of molecules of each species are specified.

The **time interval** is computed stochastically according the reation rates.

At each time interval, the **reaction** that occurs is chosen randomly according to the probabilities w_i and both the number of molecules and the reaction rates are updated.

$$A \xrightarrow{w_1} B$$

$$B + C \xrightarrow{w_2} D$$

$$D \xrightarrow{w_3} E + F$$

...

Gillespie algorithm

Principle of the Gillespie algorithm

$$A \xrightarrow{w_1} B$$

$$B + C \xrightarrow{w_2} D$$

$$D \xrightarrow{w_3} E + F$$

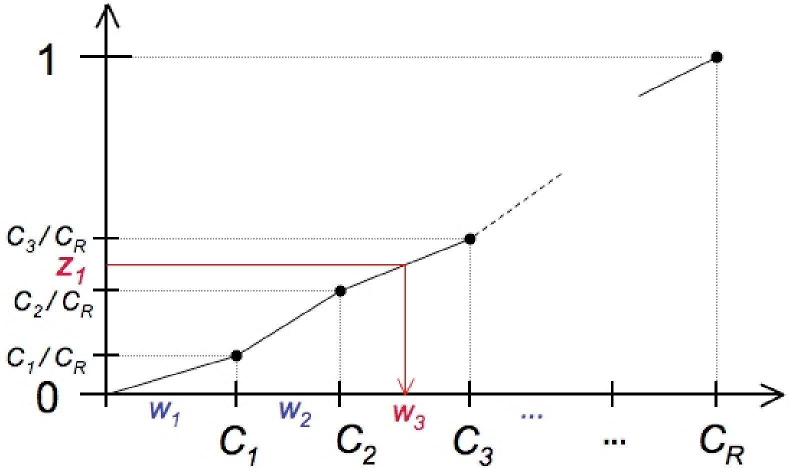
...

Probability that reaction *r* occurs

$$P_r = \frac{w_r}{\sum_{i=1}^{R} w_i}$$

Reaction *r* occurs if

$$P_{r-1} < z_1 \leq P_{r-1} + P_r$$



Time step to the next reaction

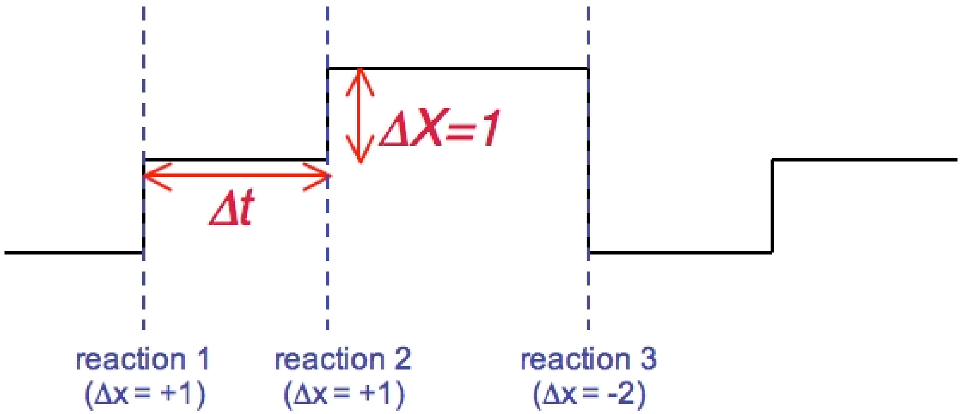
$$\Delta t = \frac{1}{\sum_{i=1}^{R} w_i} ln \frac{1}{z_2}$$

Gillespie D.T. (1977) Exact stochastic simulation of coupled chemical reactions. *J. Phys. Chem.* 81: 2340-2361.
Gillespie D.T., (1976) A General Method for Numerically Simulating the Stochastic Time Evolution of Coupled Chemical Reactions. *J. Comp. Phys.*, 22: 403-434.

Gillespie algorithm

In practice...

1. Calculate the transition probability w_i which are functions of the kinetics parameters k_r and the variables X_i .
2. Generate z_1 and z_2 and calculate the reaction that occurs as well as the time till this reaction occurs.
3. Increase t by Δt and adjust X to take into account the occurrence of the reaction that just occured.



Gillespie algorithm

Remark

A key parameter in this approach is the **system size Ω**. This parameter has the unit of a volume and is used to convert **concentration x** into a **number of molecules X**:

$$X = \Omega x$$

For a given concentration (defined by the deterministic model), bigger is the system size (Ω), larger is the number of molecules. Therefore, Ω allows us to control directly the number of molecules present in the system (hence the noise).

Typically, Ω appears in the reaction steps involving two (or more) molecular species because these reactions require the collision between two (or more) molecules and their rate thus depends on the number of molecules present in the system.

$$A + B \rightarrow C \qquad\qquad 2A \rightarrow D$$

$$v = A\,B / \Omega \qquad\qquad v = A\,(A-1) / 2\,\Omega$$

Gillespie algorithm: improvements & extensions

Next Reaction Method (Gibson & Bruck, 2000)

Gibson & Bruck's algorithm avoids calculation that is repeated in every iteration of the computation. This adaptation improves the time performance while maintaining exactness of the algorithm.

Tau-Leap Method (Gillespie, 2001)

Instead of which reaction occurs at which time step, the Tau-Leap algorithm estimated how many of each reaction occur in a certin time interval. We gain a substantial computation time, but this method is approximative and its accuracy depends on the time interval chosen.

Delay Stochastic Simulation (Bratsun et al., 2005)

Bratsun *et al.* have extended the Gillespie algorithm to account for the delay in the kinetics. This adaptation can therefore be used to simulate the stochastic model corresponding to delay differential equations.

Langevin stochastic equation

Langevin stochastic differential equation

$$\frac{dX}{dt} = f(X) + g(X)\xi(t)$$

If the noise is white (uncorrelated), we have:

$$< \xi(t) >= 0$$

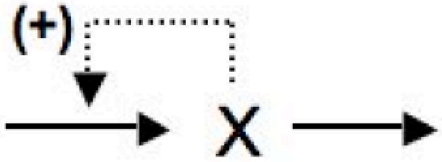
mean of the noise

$$< \xi(t)\xi(t') >= D\delta(t - t')$$

variance of the noise

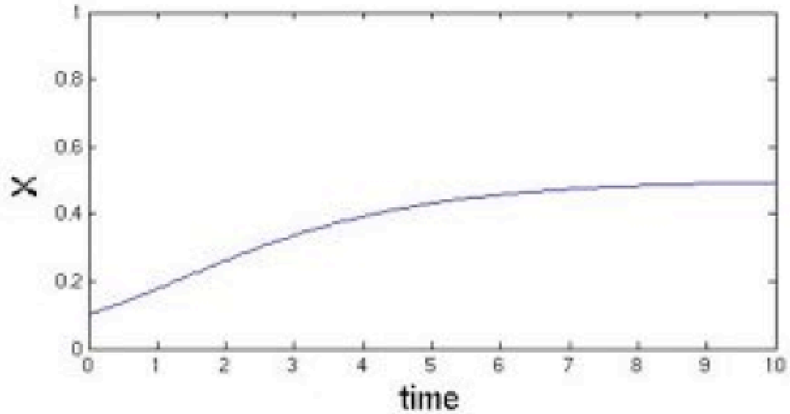
D measures the strength of the fluctuations

Gillespie vs Langevin modeling



$$\frac{dX}{dt} = v_m \frac{X}{K_M + X} - v_d X$$

Deterministic approach



Gillespie approach

$$\xrightarrow{w_1 = v_m \frac{X}{K_M + X}} X$$

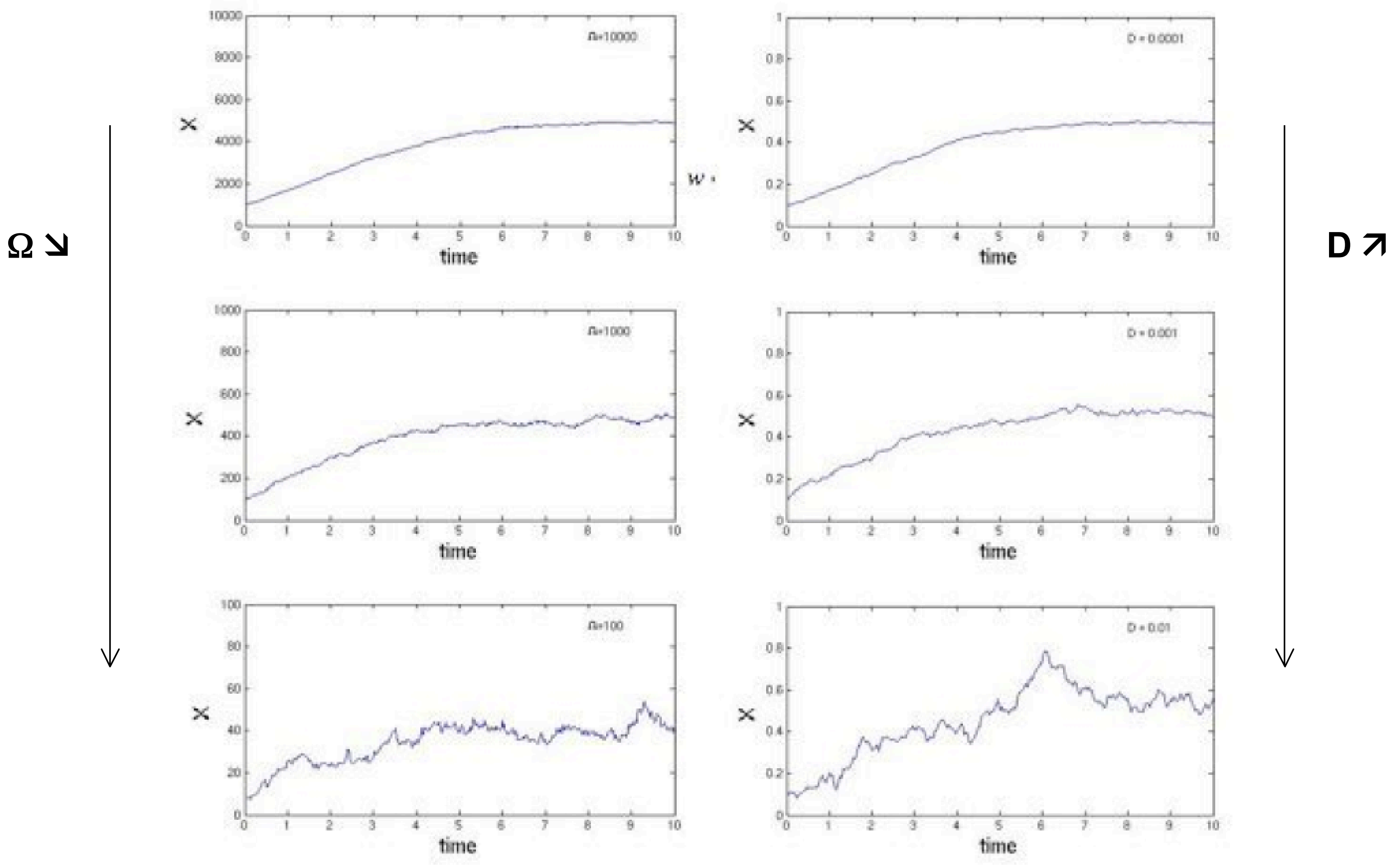
$$X \xrightarrow{w_2 = v_d X}$$

Langevin approach

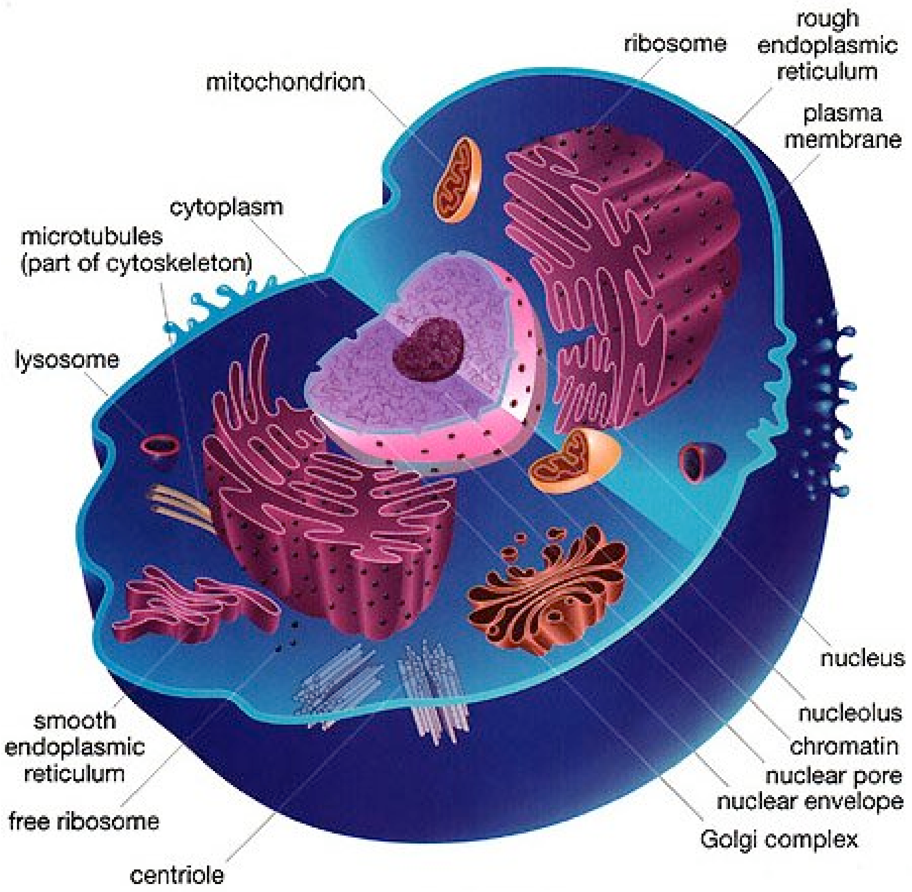
$$\frac{dX}{dt} = v_m \frac{X}{K_M + X} - v_d X + \xi(t)$$

Gillespie vs Langevin modeling

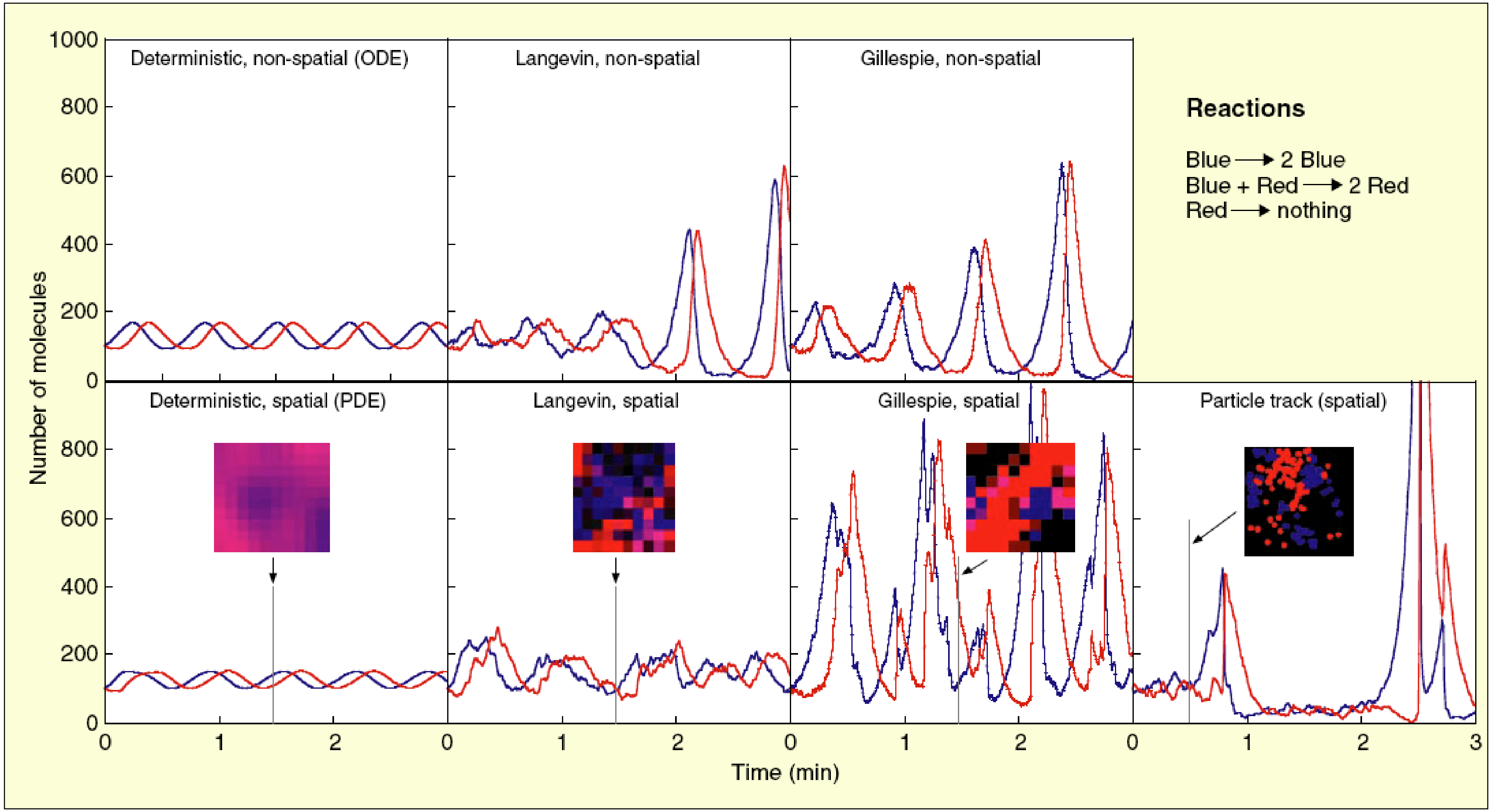
Gillespie **Langevin**



Spatial stochastic modeling

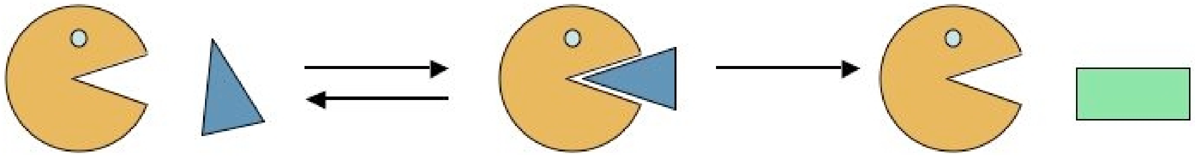


Spatial stochastic modeling



Andrews SS, Arkin AP (2006) Simulating cell biology. 16: R523-527.

Michaelis-Menten



Reactional scheme

$$\mathrm{E} + \mathrm{S} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{C} \overset{k_2}{\rightarrow} \mathrm{E} + \mathrm{P}$$

Deterministic evolution equations

$$\begin{cases} \dfrac{dS}{dt} = -k_1 ES + k_{-1}C \\ \dfrac{dE}{dt} = -k_1 ES + k_{-1}C + k_2 C \\ \dfrac{dC}{dt} = k_1 ES - k_{-1}C - k_2 C \\ \dfrac{dP}{dt} = k_2 C \end{cases}$$

Michaelis-Menten

Reactional scheme

$$\mathrm{E} + \mathrm{S} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{C} \xrightarrow{k_2} \mathrm{E} + \mathrm{P}$$

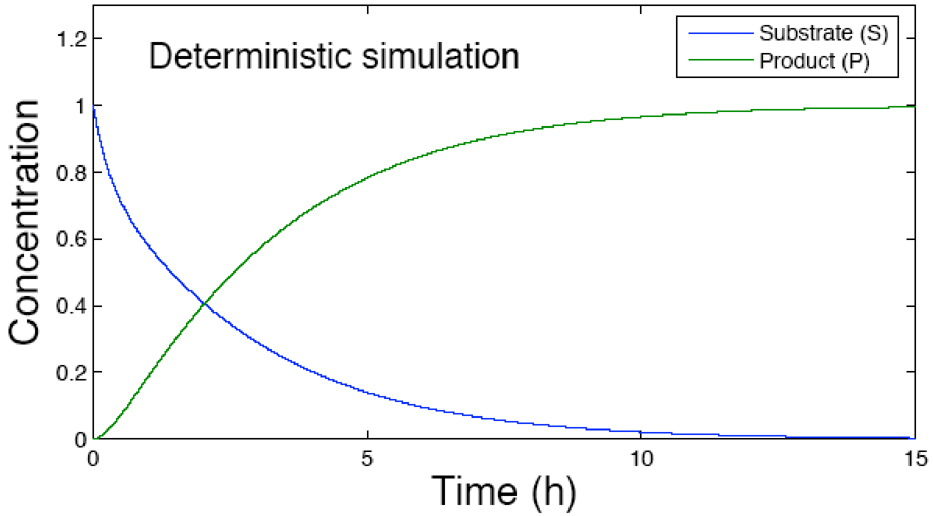
Stochastic transition table

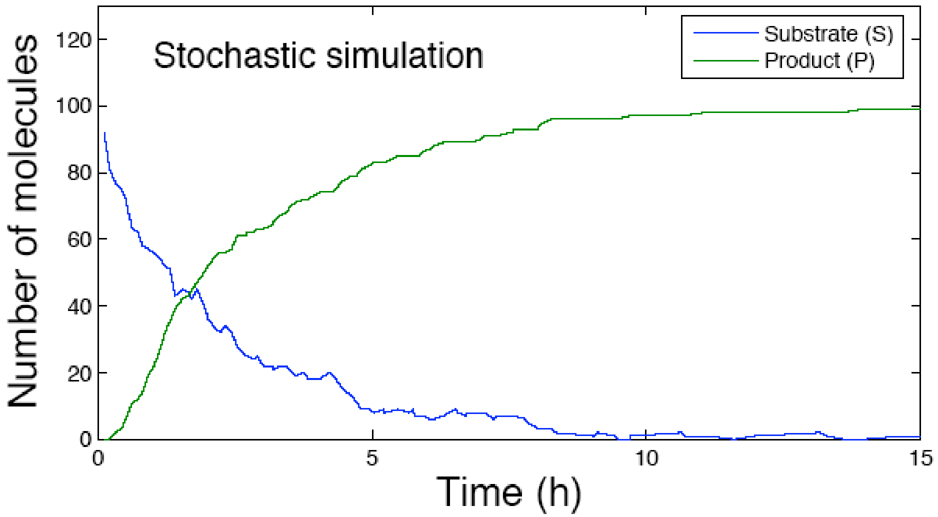
r	reaction	reaction rate
1	$\mathrm{E} + \mathrm{S} \xrightarrow{k_1} \mathrm{C}$	$w_1 = k_1 ES/\Omega$
2	$\mathrm{C} \xrightarrow{k_{-1}} \mathrm{E} + \mathrm{S}$	$w_2 = k_{-1}C$
3	$\mathrm{C} \xrightarrow{k_2} \mathrm{E} + \mathrm{P}$	$w_3 = k_2 C$

Master equation

$$\begin{aligned}\frac{\partial P(S,C,E;t)}{\partial t} = & -(k_1 SE + (k_{-1} + k_2)C)(P(S,C;t)) \\ & + k_1(S+1)(E+1)P(S+1,C-1;t) \\ & + k_{-1}(C+1)P(S-1,C+1;t) \\ & + k_2(C+1)P(S,C+1;t)\end{aligned}$$

Michaelis-Menten





Michaelis-Menten

Quasi-steady state assumption

If $E << S_0$ $\quad dC/dt = 0 \quad$ quasi-steady state

$$C = \frac{E_T S}{\frac{k_{-1} + k_2}{k_1} + S}$$

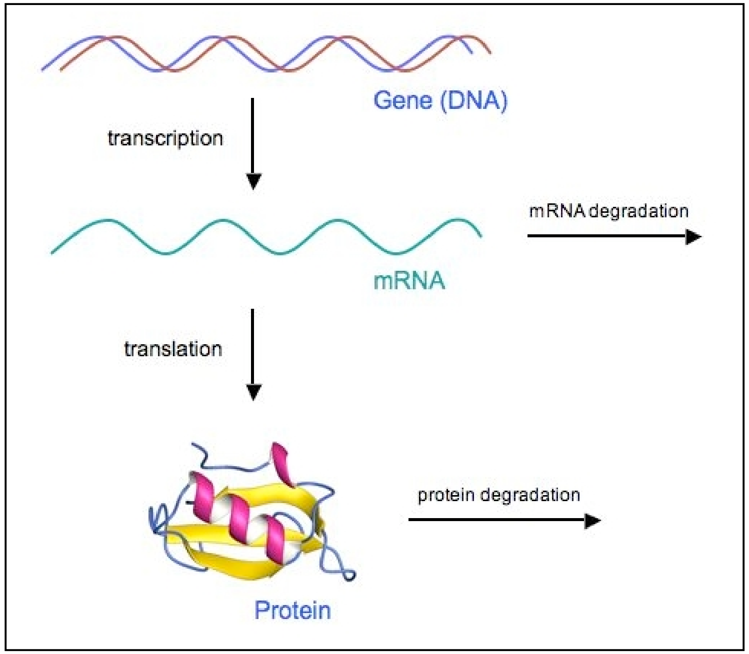
Rate of production of P $\quad v = \frac{dP}{dt} = k_2 C = V_{max} \frac{S}{K_M + S}$

$$V_{max} = k_2 E_T \text{ and } K_M = \frac{k_{-1} + k_2}{k_1}$$

Stochastic transition table

r	reaction	reaction rate
1	$\mathrm{S} \xrightarrow{v} \mathrm{P}$	$w_1 = V_{max} \Omega \frac{S}{K_S \Omega + S}$

Gene expression



Reactional scheme

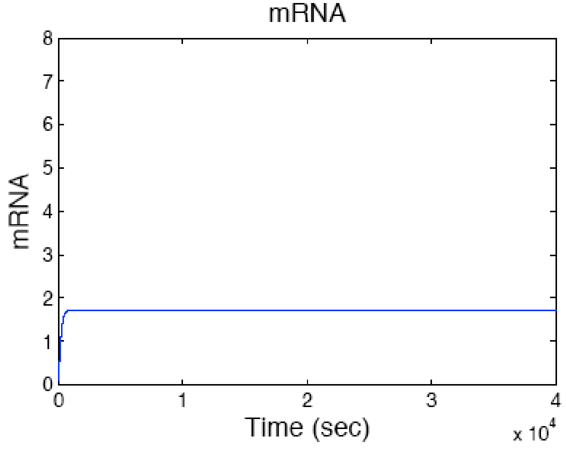
Thattai - van Oudenaarden model

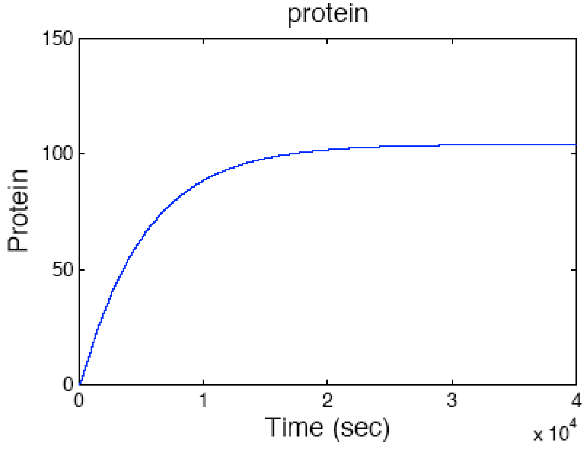
$$[\mathrm{Gene\ (G)}] \xrightarrow{k_1} \mathrm{mRNA\ (R)}$$

$$\mathrm{mRNA\ (R)} \xrightarrow{k_2}$$

$$[\mathrm{mRNA\ (R)}] \xrightarrow{k_3} \mathrm{Protein\ (P)}$$

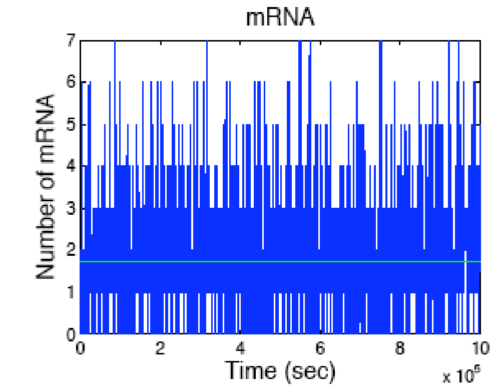
$$\mathrm{Protein\ (P)} \xrightarrow{k_4}$$

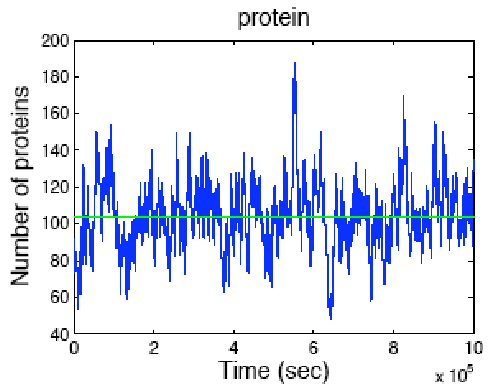




Gene expression

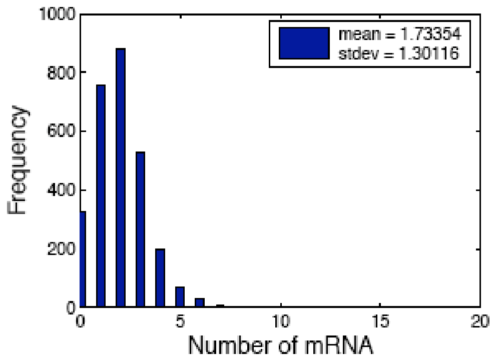
mRNA

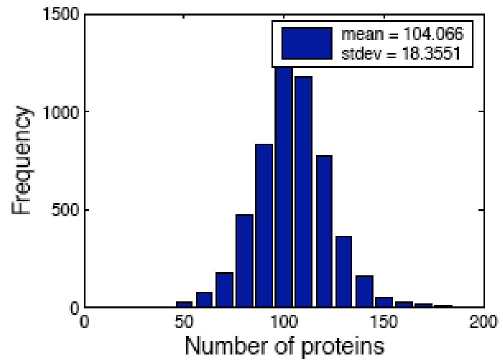




Protein

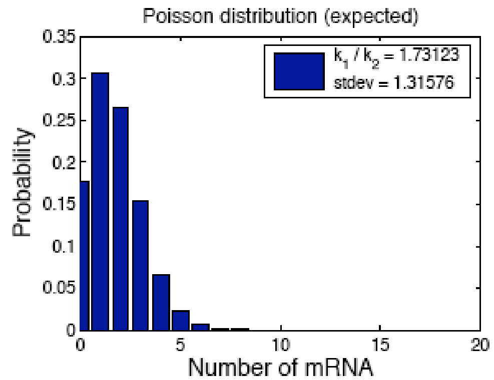
Poisson distribution
(computed from the simulation results)

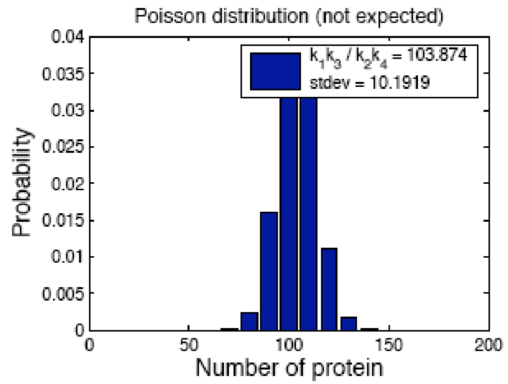




non Poisson distribution
(computed from the simulation results)

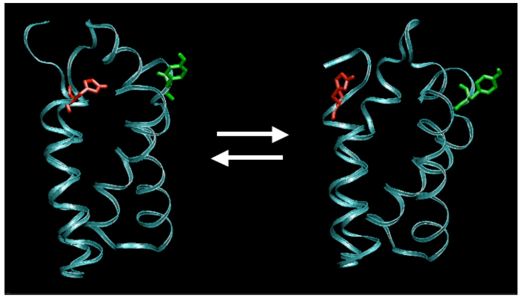
Theoretical Poisson distribution





Theoretical Poisson distribution

Conformational change



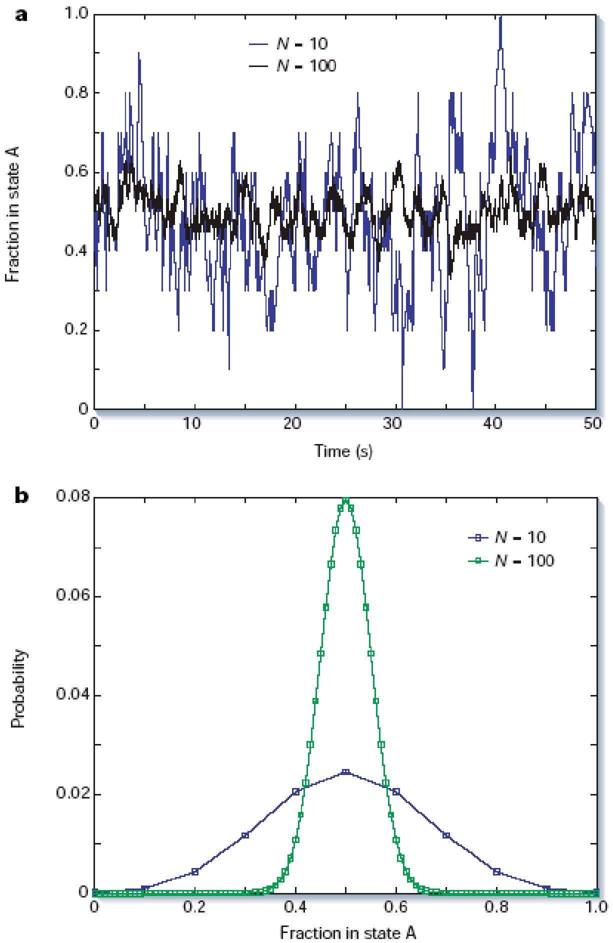
Reactional scheme

$$A \rightleftharpoons B$$

As the number of molecules increases, the steady-state probability density function becomes sharper.

The distribution is given by

$$p(j) = \binom{n}{j} \frac{k_1^j k_2^{n-j}}{(k_1 + k_2)^n}$$



Rao, Wolf, Arkin, (2002) *Nature*

Bruxellator

Reactional scheme

r	reaction	rate
1	$\mathrm{A} \xrightarrow{k_1} \mathrm{X}$	$v_1 = k_1 A$
2	$\mathrm{B} + \mathrm{X} \xrightarrow{k_2} \mathrm{Y} + \mathrm{C}$	$v_2 = k_2 B X$
3	$2\mathrm{X} + \mathrm{Y} \xrightarrow{k_3} 3\mathrm{X}$	$v_3 = k_3 X^2 Y$
4	$\mathrm{X} \xrightarrow{k_4} \mathrm{D}$	$v_4 = k_4 X$

Deterministic evolution equations

$$\begin{cases} \dfrac{dX}{dt} = k_1 a - k_2 b X + k_3 X^2 Y - k_4 X \\ \dfrac{dY}{dt} = k_2 b X - k_3 X^2 Y \end{cases}$$

Bruxellator

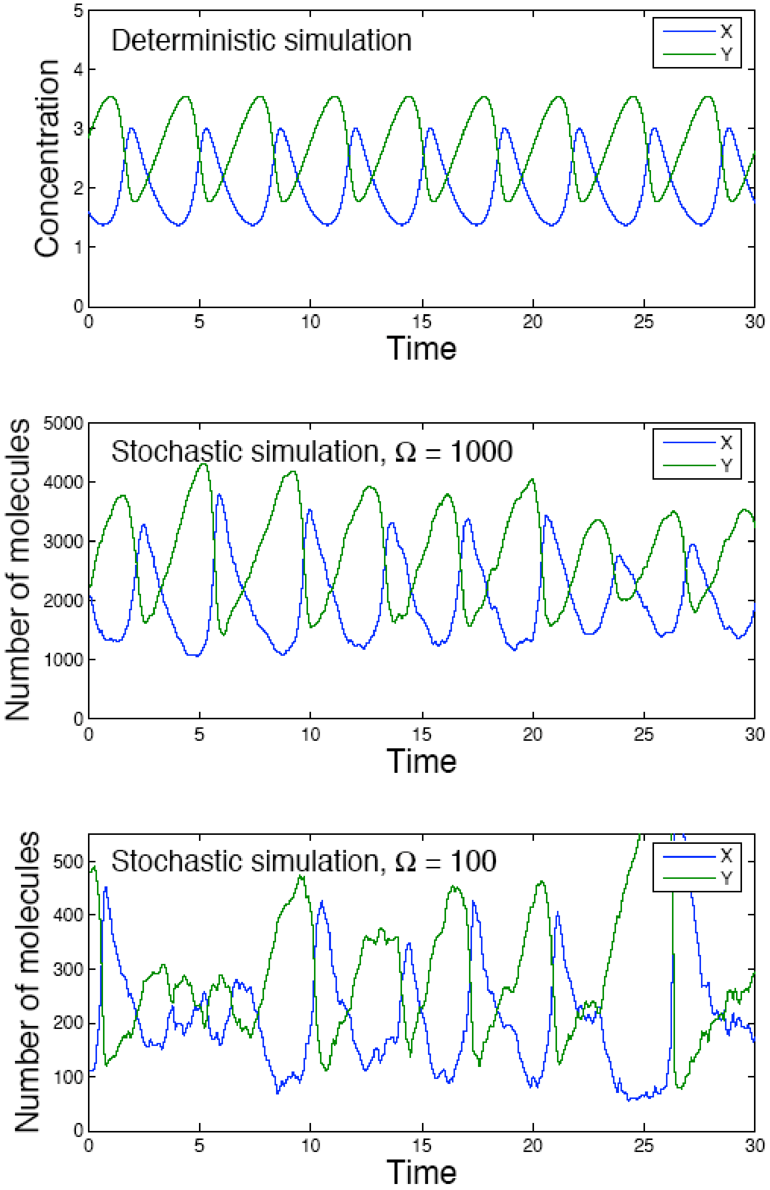
Stochastic transition table

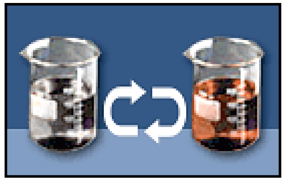
r	reaction	reaction rate
1	$\mathrm{A} \xrightarrow{k_1} \mathrm{X}$	$w_1 = k_1 A$
2	$\mathrm{B} + \mathrm{X} \xrightarrow{k_2} \mathrm{Y} + \mathrm{C}$	$w_2 = k_2 B X / \Omega$
3	$2\mathrm{X} + \mathrm{Y} \xrightarrow{k_3} 3\mathrm{X}$	$w_3 = k_3 X(X-1)Y/2\Omega^2$
4	$\mathrm{X} \xrightarrow{k_4} \mathrm{D}$	$w_4 = k_4 X$

Master equation

$$
\begin{aligned}
\frac{\partial P(X,Y;t)}{\partial t} = & -(k_1 A + k_2 B X + k_3 X^2 Y + k_4 X) P(X,Y;t) \\
& + k_1 A P(X-1,Y;t) \\
& + k_2 B (X+1) P(X+1,Y-1;t) \\
& + k_3 (X-1)^2 (Y+1) P(X-1,Y+1;t) \\
& + k_4 (X+1) P(X+1,Y;t)
\end{aligned}
$$

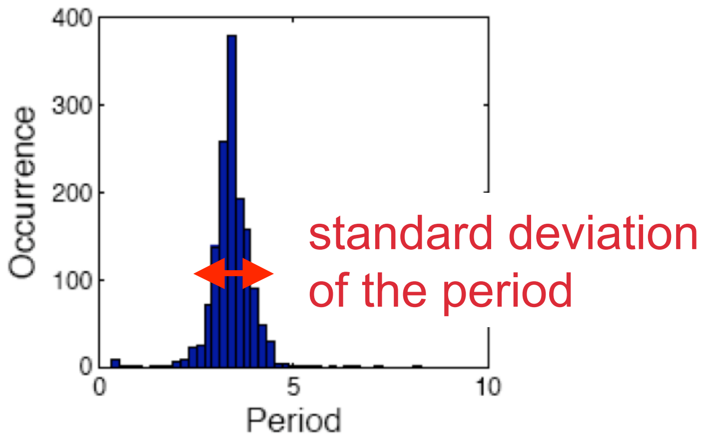
Bruxellator





Quantification of the noise

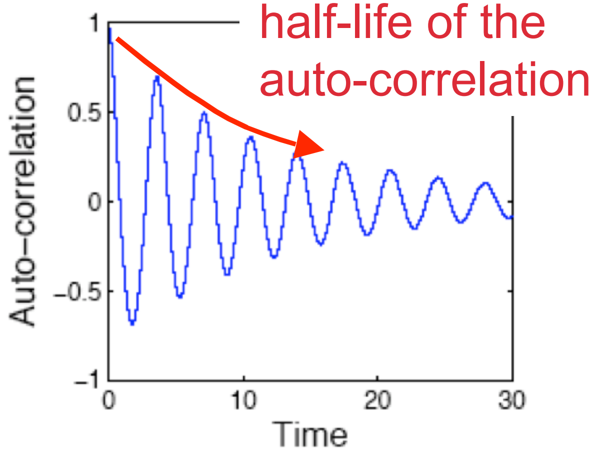
- **Histogram of periods**



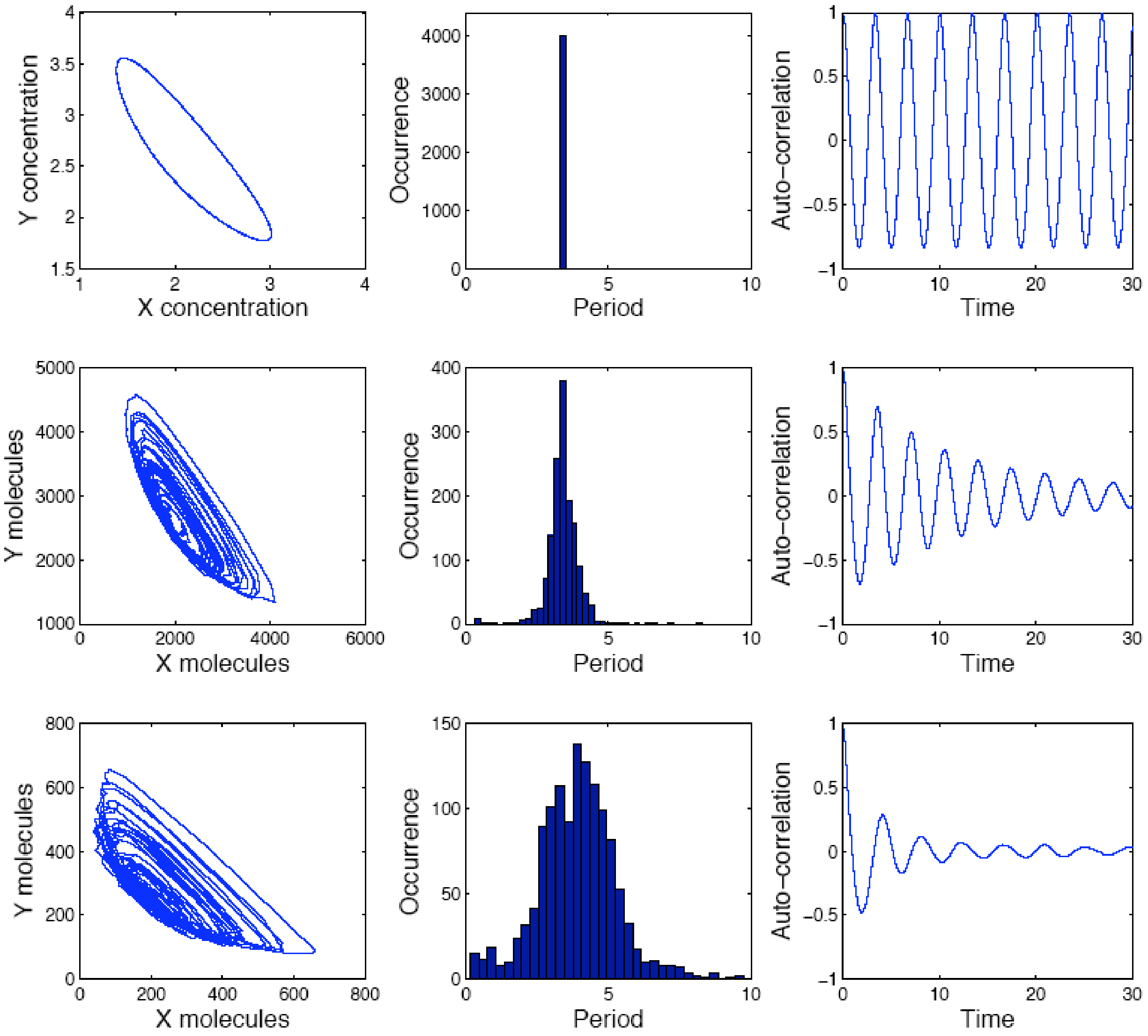
- **Auto-correlation function**

$$C(\tau) = \frac{1}{T-\tau}\int_0^{T-\tau} x(t)x(t+\tau)dt$$

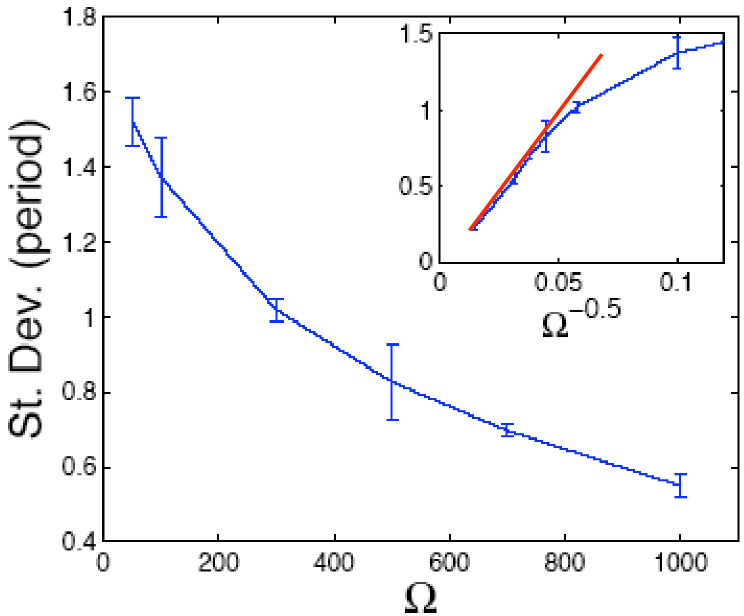
$$C(m) = \frac{1}{N-m}\sum_{n=0}^{N-m-1} x(n)x(n+m)$$

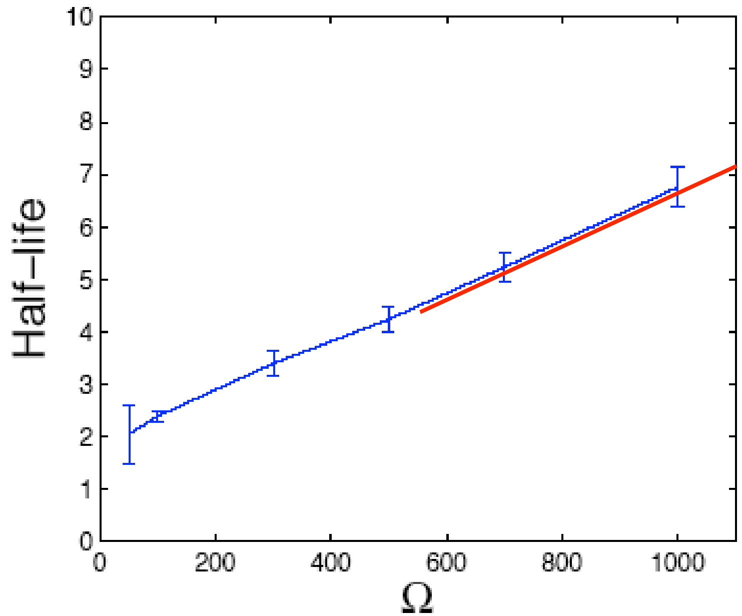


Bruxellator



Bruxellator





linear relationship

Gaspard P (2002) The correlation time of mesoscopic chemical clocks. J. *Chem. Phys.*117: 8905-8916.

Lotka-Volterra

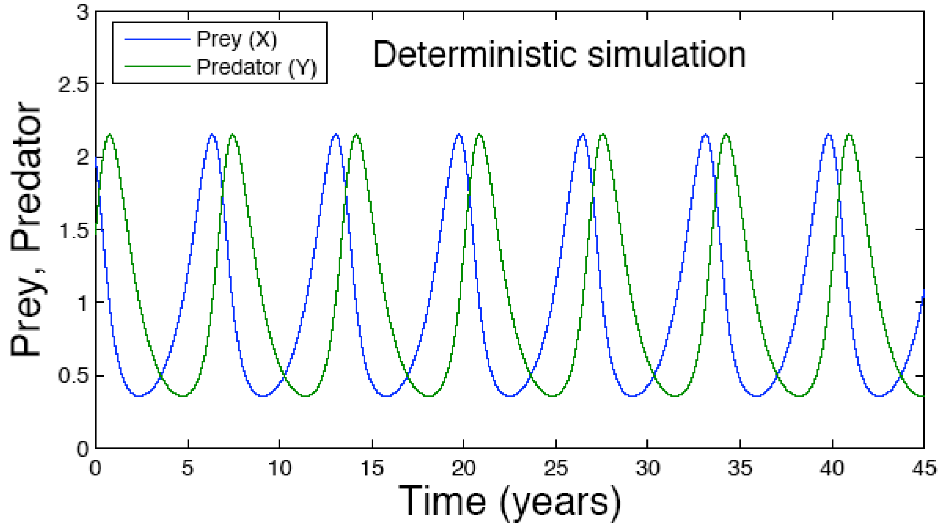
Predator-prey model

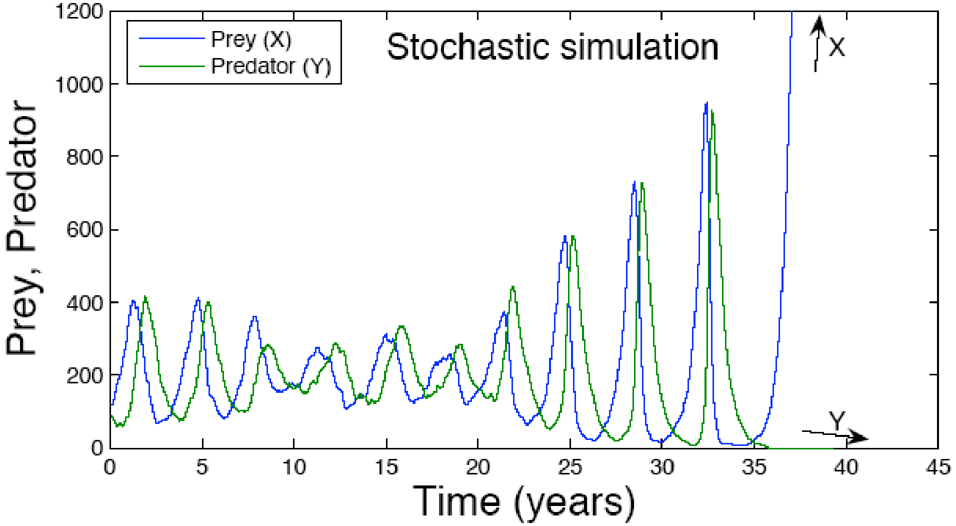
$$\xrightarrow{\alpha} X \longrightarrow Y \xrightarrow{\beta}$$

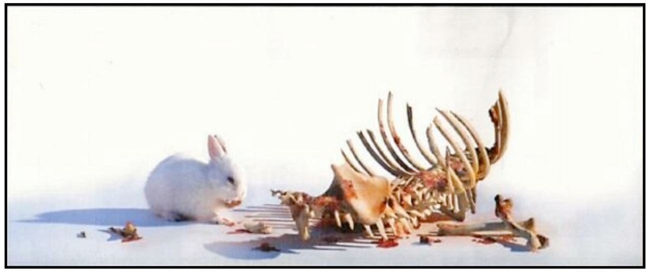
Deterministic equations

$$\begin{cases} \dfrac{dX}{dt} = \alpha X - XY & \text{prey} \\[2ex] \dfrac{dY}{dt} = XY - \beta Y & \text{predator} \end{cases}$$

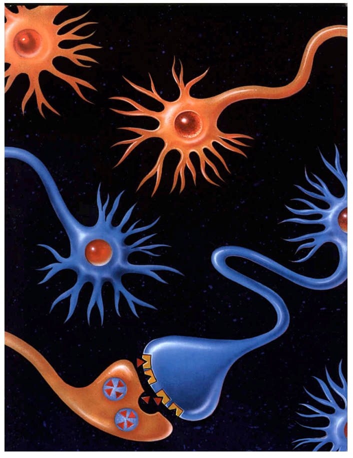
Lotka-Volterra







Fitzhugh-Nagumo



The Fitzhugh-Nagumo model is a example of a two-dimensional excitable system.It was proposed as a simplication of the famous model by Hodgkin and Huxley to describe the response of an excitable nerve membrane to external current stimuli.

$$\begin{cases} \frac{\epsilon dx}{dt} = f(x) - y \\ \frac{dy}{dt} = \gamma x - \beta y + b - s(t) + \sqrt{2D}\xi(t) \end{cases}$$

The two non-dimensional variables *x* and *y* are

x = voltage-like variable (activator) - slow variable
y = recovery-like variable (inhibitor) - fast variable

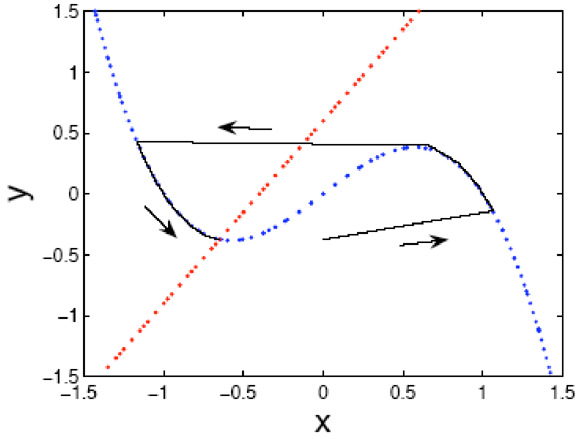
The nonlinear function f(x) (shaped like an inverted N, as shown in figure 2) is one of the nullclines of the deterministic system; a common choice for this function is

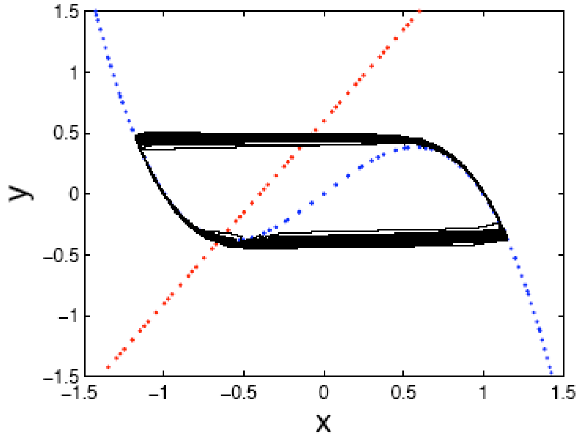
$$f(x) = x - ax^3$$

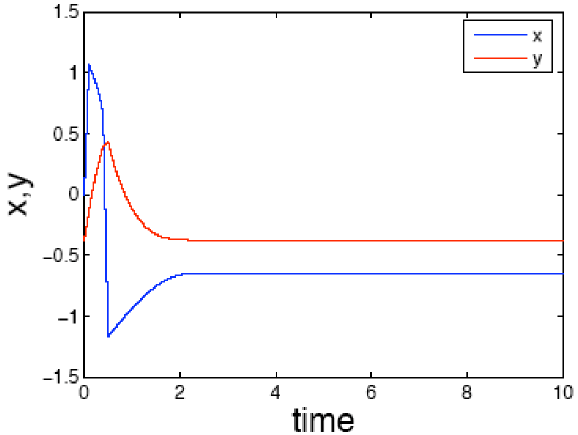
D (t) is a white Gaussian noise with intensity *D*.

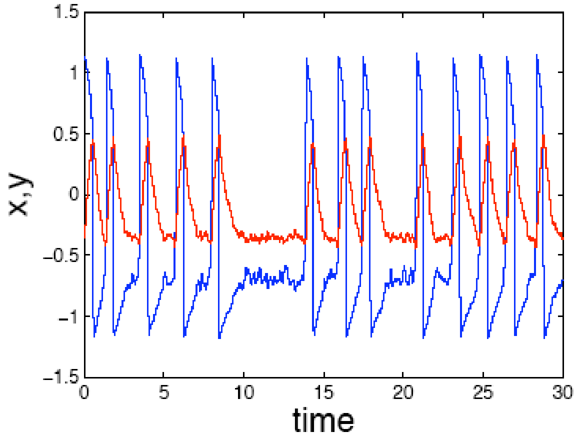
Fitzhugh-Nagumo

Deterministic **Stochastic**









excitability oscillations