
Stochastic simulations

Application to biomolecular networks

Didier Gonze and Adama Ouattara

February 24, 2014

Lisbon - Systems Biology - March 3-8, 2014

Contents

1	Introduction	3
1.1	Noise in biology	3
1.2	Sources of noise	4
1.3	Measuring the noise	7
1.4	Effects of noise	8
1.5	Noise, robustness and evolution	9
2	Theory of stochastic processes	11
2.1	Deterministic vs stochastic approaches	12
2.2	Examples and definitions	13
2.3	Master equation	18
3	Numerical methods for stochastic simulations	25
3.1	Gillespie algorithm	25
3.2	Langevin equation	28
3.3	Spatial stochastic modeling	33
3.4	Programs and softwares	36
4	Applications	37
4.1	Gene expression	37
4.2	Isomerization	42
4.3	Michaelis-Menten	44
4.4	Brusselator	49
4.5	Schlögl model	53
4.6	Lotka-Volterra	55
4.7	Fitzhugh-Nagumo	57
5	Appendixes	60
5.1	Solving the master equation	60
5.2	Fokker-Planck Equation	62
5.3	Gillespie algorithm: Time to the next reaction	64
5.4	Generating random numbers according to a given distribution	65
5.5	Chemical Langevin Equation	67
5.6	Brusselator: MATLAB code (Gillespie simulation)	69

1 Introduction

1.1 Noise in biology

Physiological processes are dynamically controlled by genetic and metabolic networks [117]. Gene regulation ensures that specific genes are expressed when required, in response to the environmental change for example. Gene regulatory networks are also responsible for cell differentiation, as well as for circadian rhythms. Likewise, metabolic regulations ensure that specific compounds are synthesized when needed and remain at some homeostatic level. These networks are formed by complex assemblies of proteins, DNA, and metabolites and various levels of regulations (transcription, mRNA processing, allosteric modifications of proteins, protein phosphorylation, complexations, catalysis, etc).

Biological systems are successful despite existing in a **stochastic environment** and despite the **probabilistic nature of the biochemical reactions**. Experimentalists and modelers, however, are just beginning to unravel the intricate interplay of noise with determinism in these systems. They are guided by an increasing number of theoretical, computational, and experimental tools. These techniques have been proven successful in each area of biology, including neural, genetic, and metabolic networks.

The **importance of noise in molecular biology** has long been recognized [23, 24] but it is only within the last 15 years that stochastic effects have been unambiguously measured during gene expression in both bacteria [29, 83, 95] and eukaryotes [19, 91, 122], including human cells [102] (for reviews, see [92, 112]). At the same time, the rediscovery of the Gillespie algorithm [38] and the availability of large amounts of *in vivo* data, has led to a new recognition of the importance of modeling and quantitative data analysis in both the experimental and theoretical communities, spawning the new field of **systems biology** [25, 30, 69]. Seminal modeling papers demonstrating that stochastic effects could alter cellular phenotypes were those of Arkin, McAdams and co-workers [8, 74]. Since then, **synthetic biology** has allowed theoretical conjectures to be tested in living cells [75, 105] and there has been an explosion in both modeling and experimental work (see refs. [50, 89, 61, 92, 58, 15, 103, 72, 20] for reviews and [12, 28, 31, 34, 45, 46, 53, 56, 65] for specific applications of synthetic biology). Interesting parallels can be drawn between electric circuits and genetic modules [7, 123]

New experimental techniques are driving understanding, and models can now be directly compared with experiments. **Molecular biology** has been revolutionized by the development of **fluorescent reporters** and, indeed, they have allowed stochastic gene expression to be quantified *in vivo*. Today's challenge is to understand the consequences of such stochasticity for cellular "design" [112]: is noise a hindrance, potentially degrading the function of biochemical networks, or is it a source of variability that cells exploit? Another relevant question is to understand how the noise is propagated in genetics and biomolecular networks [53, 85].

1.2 Sources of noise

Intrinsic vs extrinsic noise

Noise has multiple sources. It can be intrinsic or extrinsic [29, 110]. **Intrinsic noise**, also called molecular noise, is the noise resulting from the probabilist character of the biochemical reactions, particularly important when the number of reacting molecules is low. This kind of noise is inherent to the dynamics of any genetic or biochemical systems. **Extrinsic noise** is due to the random fluctuations in environmental parameters (such as temperature, pH, kinetic rates...). Both intrinsic and extrinsic noises lead to fluctuations in a single cell and result in cell-to-cell variability. In many experimental or modeling efforts, the challenge is to unambiguously identify these sources. Indeed, noise in one system may be considered as dynamics in another. The challenge of appropriately bridging spatiotemporal scales is a central theme in these issues [112].

Noise in genetic networks

Gene expression is a complex, two-stage process. First, the DNA of the gene is transcribed into messenger RNA (mRNA) by the enzyme RNA polymerase: the information stored in the nucleotide order on the DNA is copied into information stored by the nucleotide order on the mRNA. An expressed gene can give rise to several mRNA transcripts. Second, the mRNA is translated into protein by enzymes called ribosomes: the information stored in nucleotides on the mRNA is translated into the amino acids sequence of the protein. Several ribosomes can bind to and translate a single mRNA simultaneously. In eukaryotic cells, an entire mRNA is synthesized, processed in the nucleus (splicing), and then exported to the cytosol for translation. In bacteria, which have no nucleus, translation occurs as soon as part of the mRNA is synthesized.

A region of DNA, called the promoter, controls transcription, and thereby gene expression. An unregulated gene (said to be constitutively expressed) is shown in Fig. 1 for a bacteria. The promoter contains only a binding site for RNA polymerase. Nearly all genes *in vivo*, however, are regulated. **Regulation** is mediated by proteins, called transcription factors. These proteins are able to bind to operator sites in the DNA of the promoter region. Once bound, they either hinder the binding of RNA polymerase to the promoter (Fig. 1) and thus repress gene expression (the transcription factors are then called repressors) or they encourage the binding of RNA polymerase to the promoter Fig. 1 and activate gene expression (the transcription factors are then called activators). Any particular promoter can often be bound by both activators and repressors, leading to gene expression that can be a highly nonlinear function of the transcription factor concentration. A further level of control is that the transcription factor's ability to bind DNA can be a nonlinear function of the concentration of another molecule, called an inducer.

Most **transcription factors** in bacteria consist of two identical proteins bound to each other (they are then called dimers) or sometimes of four identical proteins bound to each other (they are then called tetramers). Such multimers aid the recognition of DNA binding sites and contribute to the **nonlinearity** in expression of a gene as the inducer changes. Each protein in the multimer can potentially bind to the inducer and, through what is known as an allosteric interaction, the binding of an inducer to one protein in

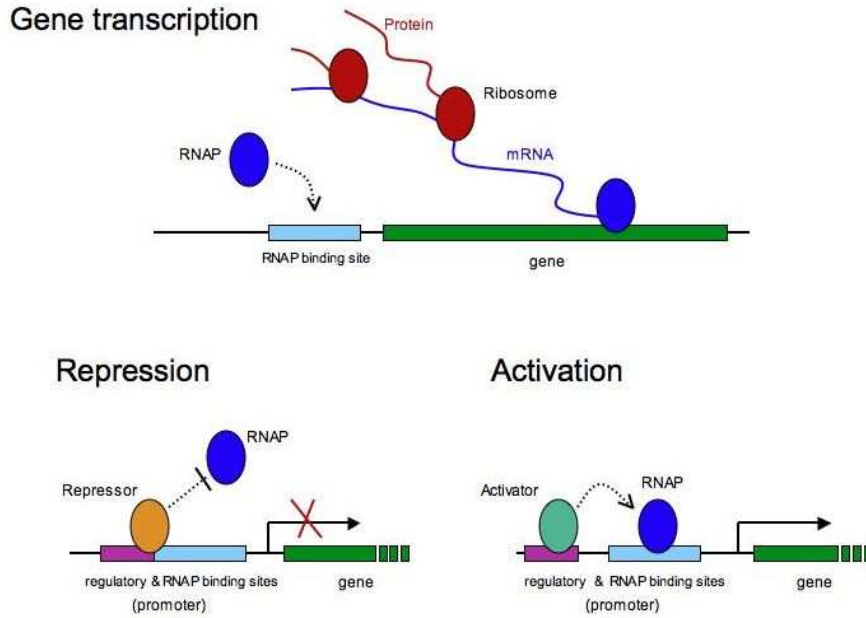


Figure 1: Gene expression in bacteria (adapted from Swain and Longtin, 2006 [112]).

the multimer increases the probability that an inducer will bind to another protein in the multimer. Thus the transition of a transcription factor from being unable to bind DNA to being able to bind DNA can be a very steep sigmoidal function of the inducer concentration. Such non-linearities are often referred to as cooperativities, because one protein cooperates with the other to help it to bind to the inducer.

All these processes are chemical reactions and are therefore potentially significantly **stochastic**. Reacting molecules come together by diffusion, their motion being driven by random collisions with other molecules. Once together, such collisions randomly alter the internal energies of the reactants and thereby their propensity to react. Such stochastic effects, however, are only important when mean numbers of molecules are low. Then, individual reactions, which at most change the numbers of molecules by one or two, matter. This stochasticity is referred to as **intrinsic noise** as it is inherent in the dynamics of any biochemical system [29, 110]. When the number of molecules is high however, as occur in many other processes, the fluctuations are averaged out and this molecular noise can be neglected.

It is not just the stochasticity intrinsic to a cellular process that generates variation; other cellular processes are also fluctuating and interact with the process of interest. The variation generated in this way is termed **extrinsic noise** [29, 110]. There are numerous extrinsic variables. For example, as a cell grows, the number of ribosomes and the variance in the number of ribosomes can change altering the noise in gene expression. Similarly, fluctuations in the numbers of nutrients in the extracellular environment, in the temperature, in the number of amino acids available intracellularly, etc., could all influence gene expression. Experimentally, in fact, it is the extrinsic noise that dominates intrinsic noise and sets cell-to-cell variation [29, 91].

Noise-producing steps and noise propagation

Several steps in gene expression are stochastic and contribute to the overall noise. Noise can be generated at the level of the protein (because translation is a stochastic process), at the level of mRNA (because transcription is a stochastic process), or at the level of the gene (because gene regulation is a stochastic process) (fig 2). The relative contribution of these different sources of noise is the object of several theoretical and experimental studies [83].

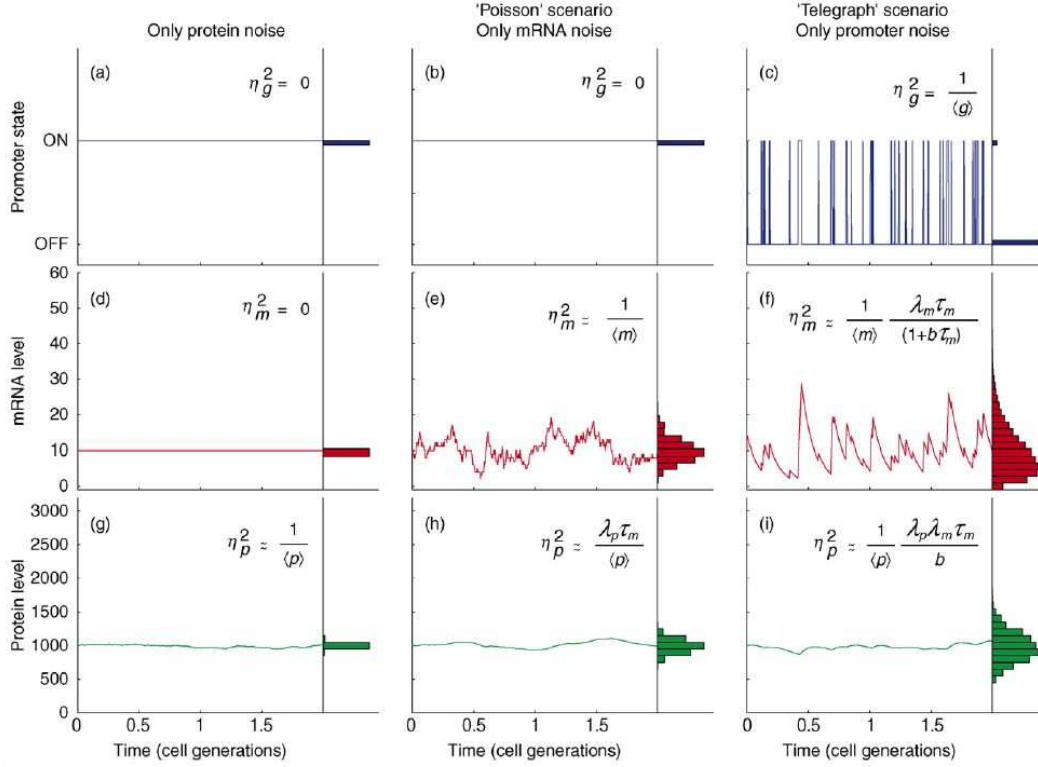


Figure 2: Noise-producing steps in gene expression (figure from [57]).

Noise propagates in gene and metabolic network (fig. 3). A key question is whether network connectivity, and in particular the presence of positive or negative regulatory feedbacks, can modulate the effect of molecular noise, either by reducing (buffering) or amplifying it [53, 54, 55].

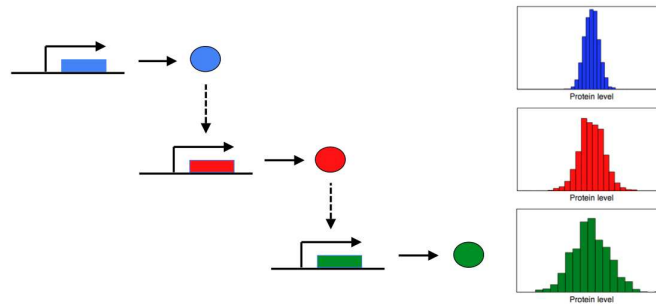


Figure 3: Noise propagation.

1.3 Measuring the noise

Noise experiments begin with the insertion of a reporter gene (e.g. green fluorescent protein driven by a promoter of interest) into the genome (fig. 4A). Cells are then cultured, usually in a swirling flask to provide a uniform environment. Finally, the fluorescence of many individual cells in that population is ascertained by microscopy or flow cytometry [29, 19, 85, 91, 95, 83] (fig. 4B). Alternatively, individual cells can also be followed over time, yielding important information on the dynamics of stochastic gene expression [95, 77, 102] (see reviews by [69] and [57]).

To quantify the heterogeneity of the population, the variance across the population divided by the mean squared is typically used, a parameter called the “noise” (fig. 4C). The measured variable used to compute this differs from experiment to experiment, with options including total fluorescence, mean fluorescence, or fluorescence among cells that share similar morphological traits. In order to reduce to “growth” heterogeneity due to the fact that all cell do not divide at the same time, the cells usually either synchronized or selected at specific stage of the cell cycle [85, 29, 91, 102, 122].

Recently, experiments have begun to address the relationship between such extrinsic variability and intrinsic noise in gene regulation. An elegant approach recently developed is based on detecting the expression of two different reporter genes that are controlled by identical promoters in a single cell. The variation between the levels of reporter proteins indicates the size of the intrinsic noise component, whereas the variance of the correlated component of both realizations yields the size of the extrinsic fluctuations (fig. 4D). This method was applied to both prokaryots (*E. coli*) [29] and eukaryots (*S. cerevisiae*) [19, 91].

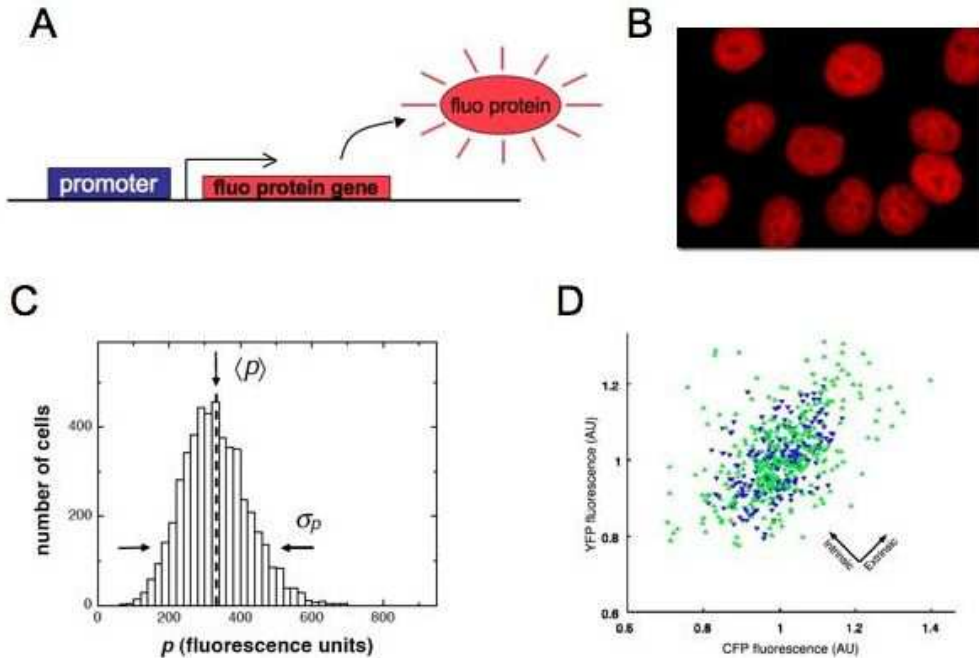


Figure 4: Measuring noise in gene expression (C, figure from [83]; D, fig. from [29]).

1.4 Effects of noise

Precise internal regulation of biochemical reactions is essential for cell growth and survival. Initiation of replication, gene expression, and metabolic activity must be controlled to coordinate the cell cycle, supervise cellular development, respond to changes in the environment, or correct random internal fluctuations. The precision of these controls are expect to be affected by the noise.

Noise can have various effects on the dynamics of the system. Since it induces fluctuations (i.e. imprecision) in the behavior, it is often seen as **destructive**. Because cell viability depends on precise regulation of key events, such signal noise has been thought to impose a threat that cells must eliminate, or, at least, minimise. This noise-induced variability in the cells is responsible for population heterogeneity [74], phenotypic variations [8, 106] or imprecision in biological clocks [10]. Fortunately, cells have developed robustness mechanisms to attenuate those bad effects of noise (see next section).

On the other hand, since cells have to deal with noise, **constructive** effect of noise whereby cells can take advantage of the noise have been postulated. These effects encompass noise-induced behaviors, tuning of the response (sensitivity of the signal) and stochastic resonance (amplification of the response).

Noise-induced behaviors include noise-induced oscillations [98, 107, 121], noise-induced synchronization [21, 73, 124], noise-induced excitability [119], or noise-induced bistability [59, 98]. All these properties are revealed by the noise and are in principle not observed in the deterministic formulation. However, to display these noise-induced phenomenon, the system should present some characteristics. For example, noise-induced oscillations can easily be obtained when the deterministic counterpart presents excitability. Many of theoretical works aim at determining the conditions required for a system to exhibit noise-induced behaviors.

Stochastic resonance, initially described in chemical systems [33] and later in biological systems (see ref. [51] for a review), refers to the fact that an optimal level of noise can boost the response of the system by modulating the signal-to-noise ratio. Such an effect has been observed and measured in fish predation behavior [97].

Stochastic focusing refers to the phenomenon whereby cells utilize the noise to enhance the sensitivity of intrinsic regulation through a gradual tuning of the response [84]. Although the precision of regulatory controls is usually greatly affected by the noise, under some conditions an opposite effect can be observed: noise converts a gradual response into a threshold driven mechanism. Stochastic focusing resembles stochastic resonance in that noise facilitates signal detection in nonlinear systems, but stochastic resonance is related to how noise in threshold systems allows for detection of subthreshold signals and stochastic focusing describes how fluctuations can make a gradual response mechanism work more like a threshold mechanism. Thus in addition to the regulatory control through feedback loops, stochastic focusing plays an important role in affecting precision control and imposing checkpoints in critical cellular processes.

1.5 Noise, robustness and evolution

Robustness is a property that allows a system to maintain its functions despite external and internal noise. Despite constructive effects observed in specific systems, noise is often perceived as a nuisance for the organism. Therefore it is commonly believed that robust traits have been selected by **evolution**. This was made possible by specific architectural features observed in robust systems. Recently the discovery of fundamental, systems-level principles that underly complex biological systems became an issue of primary importance in systems biology. It is one of the fundamental and ubiquitously observed systems-level phenomena that cannot be understood by looking at the individual components. A system must be robust to function in unpredictable environments using unreliable components [62].

The role of the topology of gene networks, and in particular the regulations, has been investigated by several authors [1, 13, 14, 82, 83, 104]. These works underly the role of positive and negative feedback in the stability of the behavior of the networks and give insight on how the networks have evolved (see also the comment by Gardner and Collins [34])

A nice experimental demonstration of the role played by auto-regulation in the robustness of gene expression was published by Becskei & Serrano [14]. Using a simple genetic construction consisting of a regulator and transcriptional repressor modules in *E. coli*, they have shown the gain of robustness produced by negative feedback loops.

Another typical example used to assess the robustness of biological systems pertains to the transduction networks responsible for chemotaxis in the bacteria *E. coli* [3, 9]. Barkai & Leibler [9] propose a mechanism for robust adaptation in this simple signal transduction networks. They show that adaptation property is a consequence of the network's connectivity and does not require fine-tuning of parameters. Kollman *et al.* [63] combine theoretical and experimental analyses to investigate an optimal design for this same signalling network. They demonstrate that among these topologies the experimentally established chemotaxis network of *E. coli* has the smallest sufficiently robust network structure, allowing accurate chemotactic response for almost all individuals within a population. These results suggest that this pathway has evolved to show an optimal chemotactic performance while minimizing the cost of resources associated with high levels of protein expression.

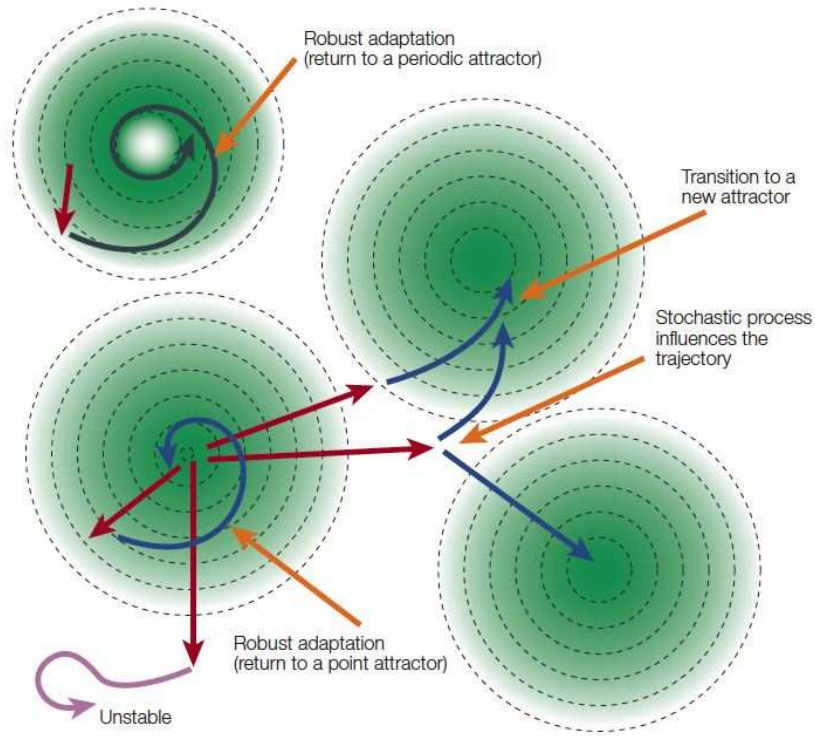


Figure 5: The state of a system can be shown as a point in the state space. In this figure, the state space is simplified into two dimensions. Perturbations forcefully move the point representing the systems state. The state of the system might return to its original attractor by adapting to perturbations, often using a negative feedback loop. There are basins of attractions in the state space within which the state of the system moves back to that attractor. If the boundary is exceeded, the system might move into an unstable region or move to other attractors. Positive feedback can either move the systems state away from the current attractor, or push the system towards a new state. Often, stochastic processes affect transition between attractors, but maintenance of a new state has to be robust against minor perturbations (Figure from [62]).

2 Theory of stochastic processes

Long before being used in biology, stochastic formalisms and methods have been developed, namely in the study of stochastic effects in systems of chemical reactions [32, 81, 93, 120]. In biology, similar mathematical models and simulation methods are used and have been extended to account for the constraints imposed by the biological systems.

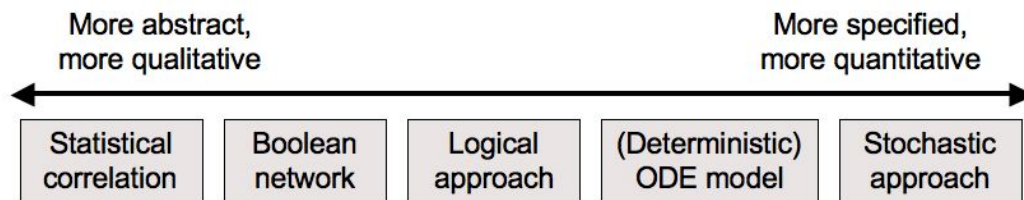
If the noise is intrinsic, a master equation governing the time evolution of the probability of the states of the system is adopted. If the noise is extrinsic, noise terms are added to the deterministic equations. In some case, noise in specific parameters can be considered.

For any system of biochemical reactions, the ultimate level of description is the **chemical master equation** (Fig. 7). This equation describes how the probability changes with time for any state of the system, where each state is defined by the number of molecules present of each chemical species. The master equation contains the deterministic, differential equation approximation that is often used to describe system dynamics: the mean of each chemical species obeys these deterministic equations as the numbers of molecules of all species increase.

The master equation itself is analytically solvable only for systems with first-order reactions. Nevertheless, several approximations exist, all of which exploit the tendency of fluctuations to decrease as the numbers of molecules increase. The most systematic and complex is the linear noise approach of van Kampen [120]. If the concentration of each chemical species is fixed, then changing the system size (volume) Ω , alters the number of molecules of every chemical species. The linear noise approximation is based on a systematic expansion of the master equation in Ω^{-1} . It leads to **Fokker-Planck equations** that accurately describe small fluctuations around the stable attractor of the system.

For systems that just tend to steady state, a **Langevin approach** is also often used (see examples in [49, 111]). Here white noise terms are added to the deterministic equations, with their magnitude being determined by the steady-state chemical reactions. At steady state, the Langevin and linear noise approaches are equivalent.

Unfortunately, all these methods usually become intractable once the number of chemical species in the system reaches more than three. One then needs analytical inversions of 4x4 matrices or a calculation of their eigenvalues. Rather than numerically solving the master equation, the **Gillespie algorithm** [38], a Monte Carlo method, is often used to simulate one sample time course from the master equation. By doing many simulations and averaging, the mean and variance for each chemical species can be calculated as a function of time. The equivalence between the discrete description and the continuous master equation has been demonstrated by Gillespie [39].



2.1 Deterministic vs stochastic approaches

Stochastic models should be opposed to deterministic models. **Deterministic models** includes several classes of models, whose the most usual is represented by systems of ordinary differential equations (ODE). In these approaches the behavior of the model is perfectly predictable. In **stochastic models**, the probabilistic aspects are taken into account. Therefore the entirely predictable character is lost (fig. 6). When large numbers of molecules are present (bio)chemical reactions usually proceed in a predictable manner because the fluctuations are averaged out. However when only a few molecules take part to a reaction, as typically occurred in a cell, stochastic effects become prominent. They are manifested by occurrence of fluctuations in the time course of the reactants. Deterministic behavior can be seen as a limit of the stochastic behavior when the number of molecules is high.

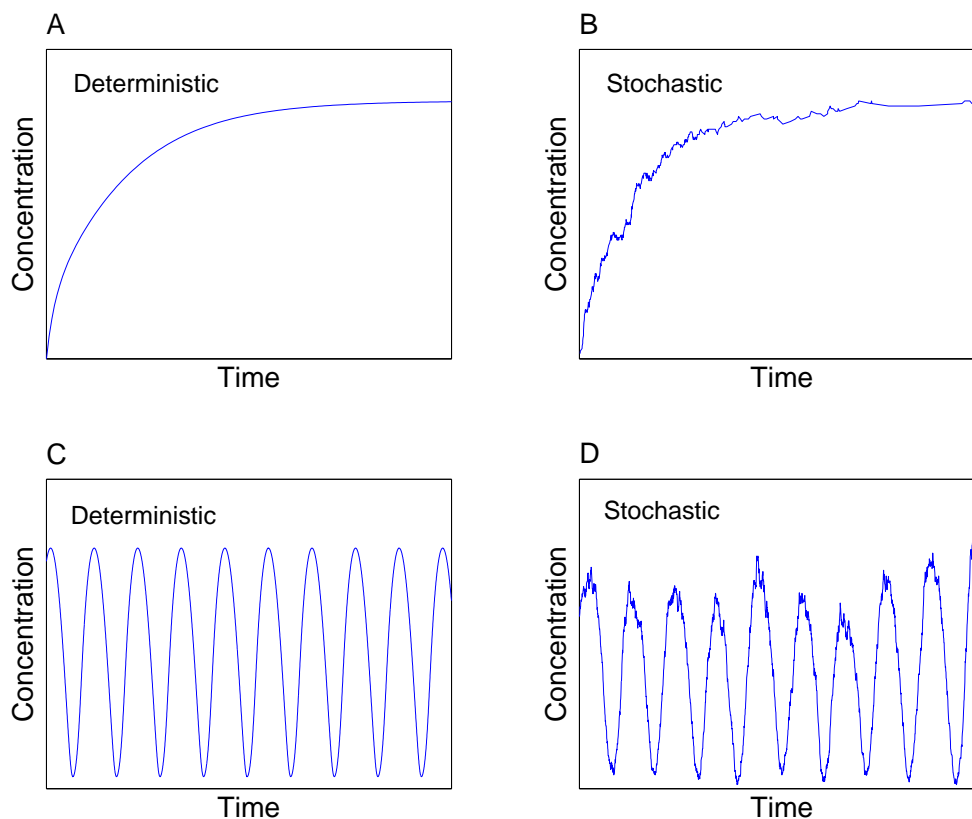


Figure 6: Deterministic versus stochastic time series. (A,B) Evolution to a steady state. (C,D) Self-sustained oscillations.

2.2 Examples and definitions

Deterministic description

Consider the following reaction



The deterministic time evolution of the reactants A , B and the product C in the reaction R_1 is classically described by the following differential equations:

$$\frac{d[A]}{dt} = \frac{d[B]}{dt} = -k_1[A][B] \quad (2)$$

$$\frac{d[C]}{dt} = k_1[A][B] \quad (3)$$

This deterministic approach assumes that the time evolution of concentrations $[A]$, $[B]$, and $[C]$ is *continuous* and obeys to the *mass action law*. The *law of mass action* stipulates that the rate of a chemical reaction is proportional to probability that the reacting molecules will be found together in a small volume. The probability of finding one reactant in a small volume is independent of finding another reactant in the same volume; therefore, the probability of finding them both in the same volume is the product of their concentration and the reaction rate is given by

$$v = k_1[A][B] \quad (4)$$

The kinetic constant k_1 characterizes the *reactive*¹ collisions of molecules; it will depend on factors like the *physical properties of the molecules* or the *temperature*.

Similarly, for the reaction



the deterministic evolution equation for the concentration $[A]$ writes

$$\frac{d[A]}{dt} = -2k_2[A]^2 \quad (6)$$

This deterministic description is valid for high concentrations of reactants. For the case where the number of reactants is low compared to the total volume (low concentration) this deterministic behavior may not be valid anymore. For low concentrations, one can see that each reactant will have a low chance to collide with the other. The reaction process will not occur *continuously* but *discretely*. We talk about *jump (discrete) Markov*² process instead of *continuous Markov* process.

We must also keep in mind that, with low numbers of molecules, the effect molecular fluctuations (or molecular noise) on the probabilities of reaction will not be negligible. To account for these fluctuations a stochastic description is required.

¹Some collisions may be non-reactive *i.e.* collisions that do not give reaction

²Markov process because the future state of the system at time $t + dt$ depends *only* on its passed state at time t , where dt is the time unit of the process.

Stochastic description

In order to track the time evolution of a quantity X_A of molecules A in reaction R_1 , we will consider the problem in term of probability of reaction: *what is the probability that reaction R_1 occurs ?*

Definition 1 (State Probability) We will define by $P(X_A, X_B, t)$, the probability that the system is in the state (X_A, X_B) at time t , i.e the probability to have X_A molecules of A and X_B molecules of B at time t .

More generally, we will denote by $P(X_1, \dots, X_n, t)$ the probability that a given system is in the state (X_1, \dots, X_n) at time t .

Definition 2 (Reaction Probability) We will define by $P(R_i, [t; t + dt])$, where $i \in \mathbb{N}$, the probability that a given reaction R_i occurs in the time interval $[t; t + dt]$.

The stochastic reaction constant c

We assume that the *average* probability that a reaction R_i occurs in the time interval $[t; t + dt]$ is given by $c_i \times dt$, where c_i is called the *stochastic reaction constant* of the process. That means that

$$\langle P(R_i, [t, t + dt]) \rangle = c_i \times dt. \quad (7)$$

The stochastic reaction constant c_i will depend on *reactive* collisions of molecules. It enables characterizing *chemical reactions* in terms of "reaction probability per unit of time" instead of "reaction rate" as it is in the RRE case.

We say reaction probability per unit of time but we must keep in mind that this time unit is fixed by dt (the time variation). For simplicity $P(R_i, [t, t + dt])$ will be simply denoted $P(R_i, t)$.

Propensity function For the case of reaction R_1 , with X_A molecules of A and X_B molecules of B there exists $X_A X_B$ possible distinct pairs of molecules (A, B) . So,

$$P(R_1, [t; t + dt]) \triangleq P(R_1, t) = X_A(t)X_B(t) \cdot c_1 \cdot dt \quad (8)$$

$$\triangleq w_1(X_A, X_B) \cdot dt. \quad (9)$$

Function $w_1(X_A, X_B) = c_1 X_A(t)X_B(t)$ is called the *propensity function* of reaction R_1 . More generally, for R reactions involving N different types of reactants, we can define R propensity functions $w_r(X_1, \dots, X_N)$, with $r = 1, \dots, R$, that depend on all the N reactants of the process.

Example 1 Consider the reaction process



With X_A molecules of A , the reaction probability is

$$P(R_2, t) = \frac{X_A(X_A - 1)}{2!} \cdot c_2 \cdot dt. \quad (11)$$

We have $\binom{X_A}{2}$ possible combinations of 2 molecules A in a total number of X_A molecules of A (we have $\binom{X_A}{2} = \frac{X_A!}{2!(X_A-2)!} = \frac{X_A(X_A-1)}{2!}$). The deterministic time evolution of A is characterized by

$$\frac{d[A]}{dt} = -2k_2[A][A]. \quad (12)$$

Relationships between c and k

We will show here relations between the reaction rate constant k_i and the stochastic reaction constant c_i . Since the deterministic and the stochastic approaches are equivalents when we work with a large number of molecules, *we do the assumption that, there exists a very large number of reactants.*

To illustrate these relations between k_i and c_i let present these two simple cases of reactions.

Notation: We will denote by V the total volume where the reaction occurs. So $[A]$ is a concentration equal to $\frac{X_A}{V}$. For simplicity we will write X_A instead of $X_A(t)$.

Case 1: Consider reaction R_1 defined by $A + B \xrightarrow{k_1} C$.

Reaction R_1 : $A + B \xrightarrow{k_1} C$	
DETERMINISTIC	STOCHASTIC
$d[C] = k_1[A][B]dt$	$dX_C \triangleq P(R_1, t) = c_1 X_A X_B dt$
$\frac{dX_C}{V} = k_1 \frac{X_A X_B}{V^2} dt \Leftrightarrow dX_C = \frac{k_1}{V} X_A X_B dt$	$dX_C = c_1 X_A X_B dt$

Since the evolutions of number of molecules $X_C(t)$ are the same in the deterministic and the stochastic cases (because of the assumption X_A, X_B large), one deduces that

$$c_1 = \frac{k_1}{V}. \quad (13)$$

Remark 1 Moles instead of Number of molecules are usually used for molecular concentrations in chemical reactions. So the Avogadro's number (denoted \mathcal{N}_A) has to be taken into account in this case. We will have $c_1 = \frac{k_1}{V\mathcal{N}_A}$.

This relation between k_i and c_i is not unique and depends on the type of reaction.

Case 2: For reaction R_2 : $2A \xrightarrow{k_2} B$ of example (1), we have

Reaction R_2 : $2A \xrightarrow{k_2} B$	
DETERMINISTIC	STOCHASTIC
$d[B] = k_2[A]^2 dt$	$dX_B \triangleq P(R_2, t) = \frac{X_A(X_A-1)}{2!} \cdot c_2 \cdot dt$
$\frac{dX_B}{V} = k_2 \frac{X_A^2}{V^2} dt \Leftrightarrow dX_B = \frac{k_2}{V} X_A^2 dt$	$dX_B = c_2 \frac{X_A(X_A-1)}{2!} dt \simeq \frac{c_2}{2!} X_A^2 dt$

When X_A is large, then $X_A - 1 \simeq X_A$. Then

$$c_2 \simeq \frac{2k_2}{V}. \quad (14)$$

Remark 2 Notice that for reaction R_2 one can also write that

DETERMINISTIC	STOCHASTIC
$d[A] = -2k_2[A]^2 dt$	$dX_A \triangleq -2P(R_2, t) = -2 \frac{X_A(X_A-1)}{2!} \cdot c_2 \cdot dt$
$dX_A = -\frac{2k_2}{V} X_A^2 dt$	$dX_A = -2c_2 \frac{X_A(X_A-1)}{2!} dt \simeq -\frac{2c_2}{2!} X_A^2 dt$

That means that

$$c_2 \simeq \frac{2k_2}{V}, \quad (15)$$

which is consistent with equation (14).

The stoichiometry of the reaction is taken into account when populations of chemical species are updated. For instance, for reaction $2A \xrightarrow{k_2} B$, quantities of reactants and products will be updated by $A = A - 2$, $B = B + 1$ at each reaction step in the Gillespie's algorithm (see Chap. 3).

Table (1) presents relations between the stochastic reaction constant c and the reaction rate constant k for various types of reactions. In the 2nd column of Table (1), we also give the total number, h , of distinct reactive n -tuples ($n \in \mathbb{N}$) of reactant for each type of reaction.

Reaction	Number h	Relation between c and k
$A \xrightarrow{k}$	X_A	$c = k$
$A_1 + A_2 \xrightarrow{k}$	$X_{A_1} X_{A_2}$	$c = \frac{k}{V}$
$A_1 + A_2 + \dots + A_n \xrightarrow{k}$	$\prod X_{A_i}$	$c = \frac{k}{V^{n-1}}$
$2A \xrightarrow{k}$	$\frac{X_A(X_A - 1)}{2!}$	$c = \frac{2k}{V} \frac{X_A}{X_A - 1} \simeq \frac{2k}{V}$
$3A \xrightarrow{k}$	$\frac{X_A(X_A - 1)(X_A - 2)}{3!}$	$c = \frac{3!k}{V^2} \frac{X_A^2}{(X_A - 1)(X_A - 2)} \simeq \frac{3!k}{V^2}$
$nA \xrightarrow{k}$	$\frac{\prod_{i=1}^n (X_A - i - 1)}{n!}$	$c = \frac{n!k}{V^{n-1}} \frac{X_A^{n-1}}{\prod_{i=1}^{n-1} (X_A - i)} \simeq \frac{n!k}{V^{n-1}}$
$2A_1 + A_2 \xrightarrow{k}$	$\frac{X_{A_1}(X_{A_1} - 1)}{2!} X_{A_2}$	$c = \dots \simeq \frac{2k}{V^2}$
$n_1 A_1 + \dots + n_N A_N \xrightarrow{k}$	$\prod_{j=1}^N \left[\frac{\prod_{i=1}^{n_j} (X_{A_j} - i - 1)}{n_j!} \right]$	$c = \dots \simeq \frac{\prod_{i=1}^N n_i! k}{V^{(\sum_{i=1}^N (n_i - 1))}}$
$\star \xrightarrow{k}$	1	$c = kV$

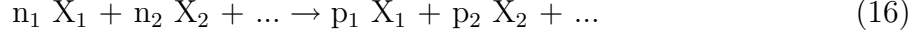
Table 1: Relations between c and k . The propensity function is $w = h \times c$. h is the total number of distinct combinations of reactive reactants. Reaction $\star \xrightarrow{k}$ denotes a constant production source of products.

2.3 Master equation

The master equation governs the stochastic dynamics of Markov process [81, 93]. This equation is universal and has been applied in problems in physics, chemistry, biology, population dynamics, and economy. For a review of the theory of stochastic systems applied to genetics and molecular networks, see [76, 116, 115].

From the deterministic to the stochastic formulation

We will show here how to derive the master equation for a system of chemical reactions. We start from the **deterministic formulation**. Let's consider the reaction:



The evolution equation for the concentration of X_i is governed by the mass action law:

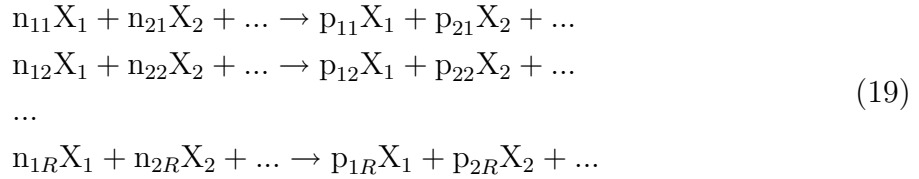
$$\frac{d[X_i]}{dt} = \eta_i v \text{ with } \eta_i = p_i - n_i \quad (17)$$

In equation (17), v is the reaction rate and is proportional to the product of the reacting species:

$$v = k[X_1]^{n_1}[X_2]^{n_2}\dots = k \prod_i [X_i]^{n_i} \quad (18)$$

Parameter k is the rate constant. Parameter η is called the stoichiometric coefficient. This coefficient is positive if, globally, the species i is produced ($p_i > n_i$) and negative if the species is consumed (or transformed) ($n_i > p_i$).

We are usually interested by systems of coupled chemical reactions involving several chemical species:



The variation of a given compound X_i involved in R reactions is defined by:

$$\frac{d[X_i]}{dt} = \sum_{r=1}^R \eta_{ir} v_r = \eta_{i1} v_1 + \eta_{i2} v_2 + \dots + \eta_{iR} v_R \quad (20)$$

where

v_r = kinetic rate of reaction r ($r = 1, 2, \dots, R$).

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

For a given initial condition ($[X_i](0)$), the system of ordinary differential equations (20) has a unique solution which describes the evolution of X_i with time.

Usually these equations can not be solved manually, but standard numerical methods can be used to compute the solution (Euler, Runge-Kutta, Stiff).

The **stochastic formulation** proceeds by considering the probability function $P(\mathbf{X}, t)$ defined as the probability that there will be at time t , X_i molecules of species X_i . Let's define $\mathbf{X} = (X_1, X_2, \dots, X_N)$ the vector of molecular species populations. Knowledge of this function provides a complete understanding of the probability distribution of all possible states at all times. By considering a discrete infinitesimal time interval $[t, t + dt]$ in which either 0 or 1 reaction occurs (the probability of more than one reaction occurring in time interval $[t, t + dt]$ is $O(dt)$ and hence vanishes in the limit $dt \rightarrow 0$), we see that there exist only $R+1$ distinct configurations at time t that can lead to the state \mathbf{X} at time $t + dt$ (R possible reactions or no reaction). We can then write our probability function at time $t + dt$ as a function of all possible precursor states at time t :

$$P(\mathbf{X}, t + dt) = P(\mathbf{X}, t)P(\text{no change over } dt) + \sum_{r=1}^R P(\mathbf{X} - \boldsymbol{\eta}_r, t)P\left(\begin{array}{c} \text{state change over } dt \\ \text{due to reaction } r \end{array}\right) \quad (21)$$

where $\boldsymbol{\eta}_r$ is a stoichiometric vector defining the result of reaction r on state vector \mathbf{X} , i.e. $\mathbf{X} \rightarrow \mathbf{X} + \boldsymbol{\eta}_r$ after an occurrence of reaction r . It is straightforward to show that

$$P\left(\begin{array}{c} \text{state change over } dt \\ \text{due to reaction } r \end{array}\right) = P(\text{reaction } r \text{ occurs}) \quad (22)$$

$$= w_r(\mathbf{X} - \boldsymbol{\eta}_r)dt \quad (23)$$

$$P(\text{no change over } dt) = P(\text{no reaction occurs}) \quad (24)$$

$$= 1 - \sum_{r=1}^R w_r(\mathbf{X})dt \quad (25)$$

where w_r is the probability that reaction r occurs in the time interval $[t, t + dt]$. w_r is also called the propensity of reaction r . Note that the propensity function also depends on the system size Ω . The more molecules are present, the higher is their probability to react.

If we then note that

$$\lim_{dt \rightarrow 0} \frac{P(\mathbf{X}, t + dt) - P(\mathbf{X}, t)}{dt} = \frac{\partial P(\mathbf{X}, t)}{\partial t} \quad (26)$$

we arrive at the **chemical master equation** that describes the stochastic dynamics of the system

$$\frac{\partial P(\mathbf{X}, t)}{\partial t} = \sum_{r=1}^R (w_r(\mathbf{X} - \boldsymbol{\eta}_r)P(\mathbf{X} - \boldsymbol{\eta}_r, t) - w_r(\mathbf{X})P(\mathbf{X}, t)) \quad (27)$$

Note that the evolution of the system only depends on its previous state and not on its history. Such a property is referred to as a **Markov process**. One of the simplest type of Markov process is the Markov chain. Markov chains are processes in which transitions occur between realization of discrete stochastic variables at discrete times, as in the case of chemical reactions.

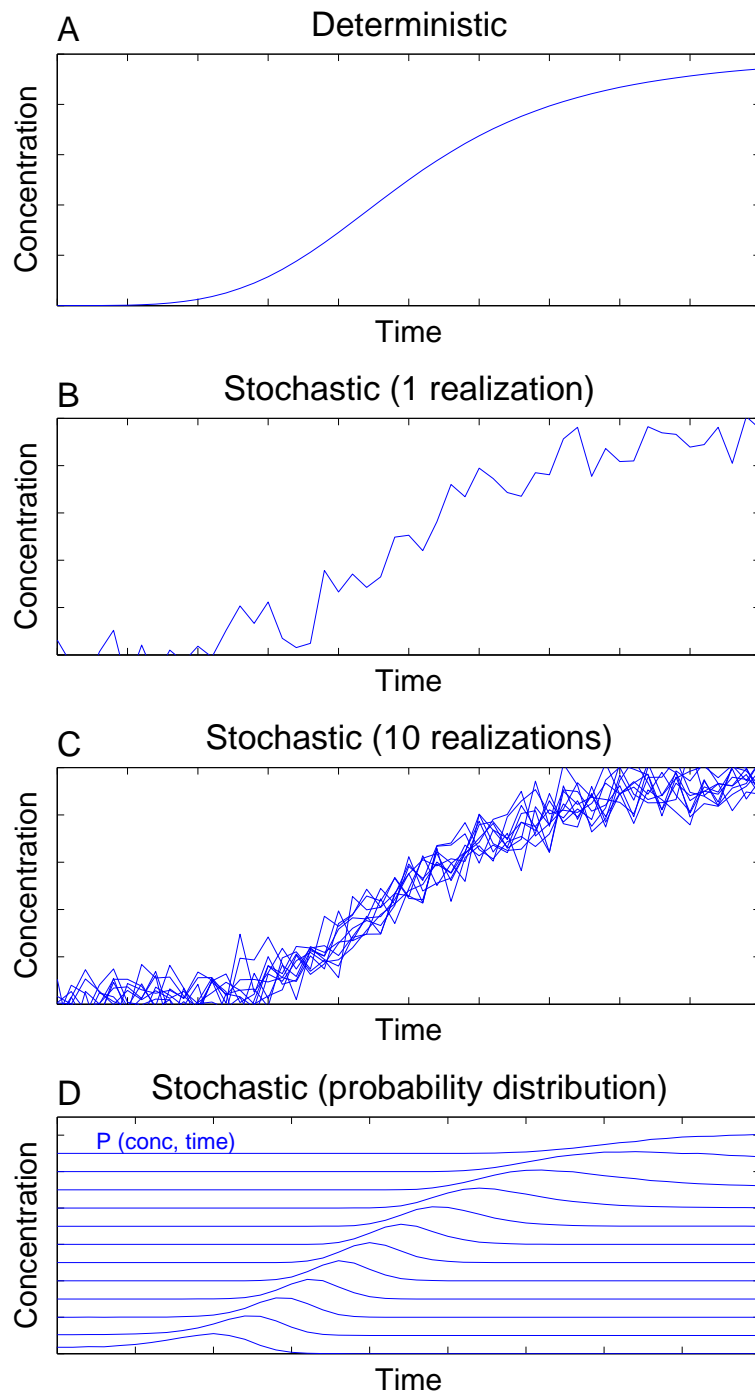


Figure 7: Illustration of the different formalisms: (A) Deterministic evolution. (B) Stochastic evolution (one realization of the process). (C) Stochastic evolution (10 realizations). (D) Master equation.

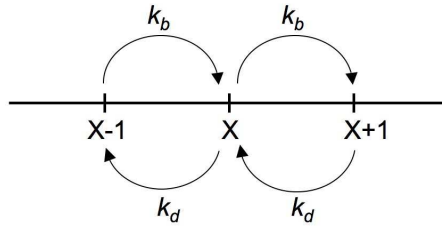
Birth-and-Death process

One of the most common application of the master equation is the description of **birth-and-death processes** such as those one finds in chemistry and population dynamics. Birth-and-death processes are processes in which transitions can only take place between nearest neighbor states. For example, if one considers a population in which only one individual (molecule) is produced at each birth and one individual (molecule) dies (is degraded) at each death, then we have a typical birth-and-death process [81, 93].

Let's consider first a single compound X which is produced at a rate k_b and consumed (transformed or degraded) at a rate k_d :



The master equation gives the evolution of the probability $P(X, t)$ to have X molecules of the compound X at time t . A change in the number X of molecules X can result from four events: (1) Starting from X molecules and having one "birth" reaction ($X \rightarrow X + 1$), (2) Starting from X molecules and having one "death" reaction ($X \rightarrow X - 1$), (3) Starting from $X - 1$ molecules and having one "birth" reaction ($X - 1 \rightarrow X$), (4) Starting from $X + 1$ molecules and having "death" reaction ($X + 1 \rightarrow X$). These four possible events are illustrated on the following scheme:



The master eq. (117) can be rewritten

$$\frac{\partial P(X, t)}{\partial t} = k_b P(X - 1, t) + k_d (X + 1) P(X + 1, t) - k_b P(X, t) - k_d X P(X, t) \quad (29)$$

Note that k_d is multiplied by the number of molecules present in the system (X or $X + 1$) because the reaction rate for the degradation depends on the number of molecules: $w_d(X) = k_d X$.

If the birth and death rate k_b and k_d are constant, equation (29) is linear and can easily be solved analytically (see tutorial), while if k_b and k_d are function of time, i.e. $k_b = k_b(t)$, and $k_d = k_d(t)$, then the equation is non-linear, and usually unsolvable analytically.

The **general master equation for a birth-and-death process** can be written [81]:

$$\begin{aligned} \frac{\partial P(\{X_i\}, t)}{\partial t} = & \sum_{r=1}^R [k_{br}(\{X_i - \eta_{ir}\}) P(\{X_{j \neq i}, X_i - \eta_{ir}\}, t) \\ & + k_{dr}(\{X_i + \eta_{ir}\}) P(\{X_{j \neq i}, X_i + \eta_{ir}\}, t) - k_{br}(\{X_i\}) P(\{X_i\}, t) - k_{dr}(\{X_i\}) P(\{X_i\}, t)] \end{aligned} \quad (30)$$

Examples

- We consider first a simple example involving three species X, Y, and Z reacting as:



The transition probability is $w(X, Y) = kXY$ and the master equation is written

$$\begin{aligned} \frac{\partial P(X, Y, Z, t)}{\partial t} &= w(X+1, Y+1)P(X+1, Y+1, Z-1) - w(X, Y)P(X, Y, Z) \\ &= k(X+1)(Y+1)P(X+1, Y+1, Z-1) - kXYP(X, Y, Z) \end{aligned} \quad (32)$$

- As a second example we consider the autocatalytic reaction:



The transition probability is $w(A, X) = kAX$ and the master equation is written

$$\begin{aligned} \frac{\partial P(A, X, t)}{\partial t} &= w(A+1, X-1)P(A+1, X-1) - w(A, X)P(A, X) \\ &= k(A+1)(X-1)P(A+1, X-1) - kAXP(A, X) \end{aligned} \quad (34)$$

- The third example describes the reaction of X with itself (this could be for example an homodimerisation)



The transition probability is $w(X) = \frac{k}{2}X(X-1)$ and the master equation is written

$$\begin{aligned} \frac{\partial P(X, E, t)}{\partial t} &= w(X+2)P(X+2, E-1) - w(X)P(X, E) \\ &= \frac{k}{2}(X+1)(X+2)P(X+2, E-1) - \frac{k}{2}(X-1)(X)P(X, E) \end{aligned} \quad (36)$$

Fokker-Planck equation

In a number of problems involving Markov chains the “spacing” between states (the number of molecules produced or consumed in a given step) is small compared to the total number of molecules. This is the case of a system of chemical reactions, because the step appearing in the birth-and-death master equation (30) (i.e. the number η_{ir} of molecules produced or destroyed in a given reaction is typically equal to one or two), is small compared to the instantaneous values of the number of molecules (typically about 100 or 1000). In this condition the master equation can be approximated by the **Fokker-Planck equation** [81], which can be derived from an expansion in Ω^{-1} (Ω being the system size, or, in other terms, the number of molecules):

$$\frac{\partial P(\mathbf{X}, t)}{\partial t} = - \sum_i \left(\frac{\partial}{\partial X_i} F_i(\mathbf{X}) P(\mathbf{X}, t) \right) + \sum_{i,j} \left(\frac{\partial^2}{\partial X_i \partial X_j} G_{i,j}(\mathbf{X}) P(\mathbf{X}, t) \right) \quad (37)$$

The first term in the right-hand side is called the *drift term* and the second term is called the *diffusion term*. The drift term is related to the birth-and-death probabilities (i.e. the kinetics), while the diffusion term describes the effect of noise (fig. 8). Both $F_i(\mathbf{X})$ and $G_{i,j}(\mathbf{X})$ functions are related to the kinetics of the system:

$$F_i(\mathbf{X}) = \sum_{r=1}^R \eta_{r,i} w_r(\mathbf{X}) \quad (38)$$

$$G_{i,j}(\mathbf{X}) = \sum_{r=1}^R \eta_{r,i} \eta_{r,j} w_r(\mathbf{X}) \quad (39)$$

where R is the number of reactions, η_r is the stoichiometry vector and w_r is the propensity of reaction r .

The Fokker-Planck equation is exact for the case when noise is a Gaussian white noise (i.e. at the limit $\Omega \rightarrow \infty$).

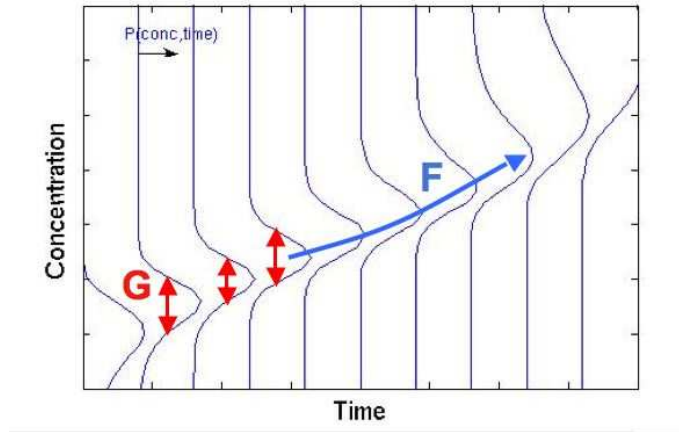


Figure 8: Interpretation of the Fokker-Planck equation.

Remark: Limitation of the theory

The chemical master equation provides a complete description for the chemical kinetics. Even though the chemical master equation is linear, we are usually unable to solve it either analytically or numerically as the dimension explodes with the number of molecules and reactions. For example, if we consider a reaction



then the order of the chemical master equation is equal the number of possible molecular combinations. For 200 molecules, there are one million different molecular combinations [90].

Gillespie (1976) gives another example of a chemical systems that involves 4 species (see Gillespie 1976, p. 422):



The corresponding master equation can readily be written (this is left as an exercise):

$$\frac{\partial P(X, Y, Z, W, t)}{\partial t} = \dots \quad (42)$$

In theory the time evolution of the probability distribution can be solved once the initial condition is given Starting from

$$P(X, Y, Z, W, t) = \delta_{x,x0} \delta_{y,y0} \delta_{z,z0} \delta_{w,w0} \quad (43)$$

we can in principle compute $P(X, Y, Z, W, t)$ for all t . In practice, however, this equation is virtually intractable, due to the astronomic amount of computer memory that would be required to store the values of P on a 4-dimensional lattice for each t . Indeed, if we assume that every variable can vary from 1 to 10000, then at a given time the probability distribution is $(10000)^4 = 10^{12}$. If we then simulate the system over 10^6 time steps, we need to store 10^{18} values!

Thus an alternative approach is to generate multiple realizations of the stochastic process described by the chemical master equation, using for example Monte Carlo strategies, as described in the next section. These realizations are usually sufficient to address our questions, i.e. what is the mean and the standard deviation of the variable at steady state, as well as along the trajectory from a given initial condition to the attractor.

3 Numerical methods for stochastic simulations

3.1 Gillespie algorithm

In 1976-1977, Gillespie proposed an **exact stochastic simulation algorithm** to solve the chemical master equation based on the assumptions that the system is homogeneous and well mixed [37, 38]. The idea is to directly simulate the time evolution of the system. At each time step, the chemical system is exactly in one state (i.e. the number of molecules of each species is determined). The algorithm determines the nature of the next reaction as well as the time interval Δt till this reaction takes place, given that the system is in a given state at time t . These two events are determined stochastically, according to well-defined probabilities. The probability of a reaction depends on its kinetics rate which is a function of its corresponding kinetics constant and the number of molecules. Thus using these rate constants and calculating the transition probabilities (kinetic rate), and using two random numbers z_1 and z_2 (between 0 and 1), the algorithm determines which reaction occurs and at which time interval.

If w_i is the transition rate (propensity) of reaction i , then the probability that reaction r occurs is

$$P_r = \frac{w_r}{\sum_{i=1}^R w_i} = \frac{w_r}{C_R} \quad (44)$$

and the reaction that will take place is reaction r if

$$\frac{C_{r-1}}{C_R} < z_1 \leq \frac{C_r}{C_R} \quad (45)$$

which is equivalent to

$$C_{r-1} < z_1 C_R \leq C_r \quad (46)$$

where

$$C_r = \sum_{k=1}^r w_k \quad (47)$$

is the cumulative function (Fig. 9)

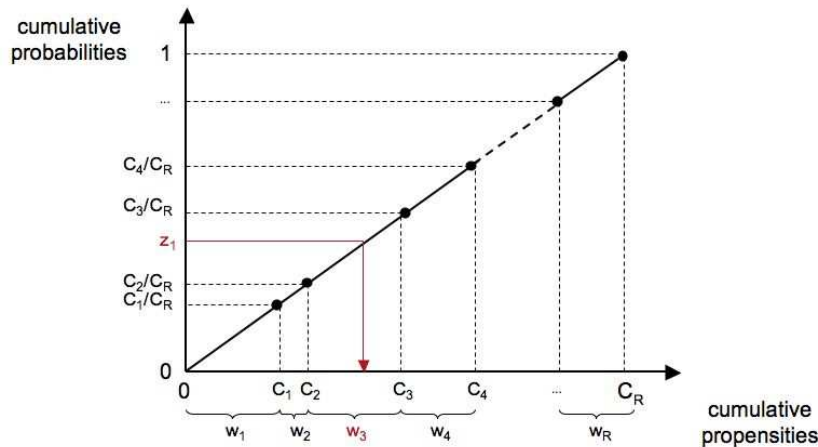


Figure 9: Cumulative function used in the Gillespie algorithm.

The time till this reaction occurs can be shown to follow the following probability distribution (see Appendix 5.3):

$$P(\tau, \mu) = C_R \exp(-C_R \tau) \quad (48)$$

and can be computed using the second random number, z_2 as (see Appendix 5.4):

$$\Delta t = \frac{1}{\sum_{i=1}^R w_i} \ln \frac{1}{z_2} = \frac{1}{C_R} \ln \frac{1}{z_2} \quad (49)$$

In practice, after setting the initial species populations X_i and reaction constants k_r the algorithm runs in loop the following steps (until the final time is reached):

1. Calculate the transition probabilities w_i which are functions of k_r and X_i .
2. Generate z_1 and z_2 and calculate the reaction that occurs as well as the time till this reaction occurs according eqs. (44)-(48).
3. Increase t by Δt and adjust X to take account the occurrence of reaction r .

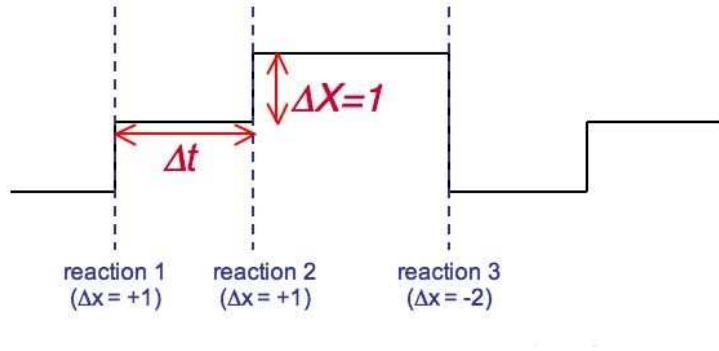


Figure 10: Gillespie's algorithm output.

A key parameter in this approach is the **system size**, often denoted by Ω . This parameter has the unit of a volume and is used to convert a deterministic model (where the variables and kinetics parameters are expressed in term of concentration) into a stochastic model (where the variables and kinetics parameters are expressed in terms of number of molecules). 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 directly control 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.

Next Reaction Method (Gibson & Bruck)

Gibson and Bruck, 2000 [44], proposed the **Next Reaction Method** as an enhancement of Gillespie’s method. The Next Reaction method manages to improve time performance of Gillespie algorithms substantially while maintaining exactness of the algorithm. As mentioned above, Gillespie algorithms require enormous computational time for a system with a large number of reactions. Gibson and Bruck’s algorithm avoids calculation that is repeated in every iteration of the computation causing additional computational cost in the Gillespie’s algorithm (table 2).

Tau-Leap Method

In 2001, Gillespie [40] presented the **Tau-Leap Method** to produce significant gains in the computational speed with an acceptable loss in accuracy. Gillespie algorithms solve the master equation exactly and obtain the exact temporal behavior of the system by generating exact timing of each reaction. However, it is sometimes unnecessary to obtain so much details from the simulation. Instead of finding out which reaction happens at which time step, one may like to know how many of each reaction occur in a certain time interval. If the time interval is large enough for many reactions to happen, one can expect substantial gain in the computational speed. However, in order to maintain accuracy of the method, one has to select an appropriate time interval, which needs to be small enough so that the change in propensity function, is acceptable (table 2).

Delay Stochastic Simulation algorithm

Recently, Bratsun *et al.* [16] extended the Gillespie’s algorithm to account for the delay in the kinetics (**delay stochastic simulation algorithm**) and show how such time delay in gene expression can cause a system to be oscillatory even when its deterministic counterpart exhibits no oscillations. Barrio *et al* [11] also used a delay stochastic simulation algorithm to simulated delay differential model. They applied their algorithm to the oscillatory regulation of Hes1. An analog procedure was used by Ribeiro *et al* [94] to simulate a delay variant of the toggle switch. Roussel and Zhou [96] presented a generalized algorithm that accounts for single of multiple delays which can be fixed or distributed.

Alternative methods

In 1998, Morton-Firth *et al.*, developed the **Stochsim** algorithm [66, 79]. The algorithm treats the biological components, for example, enzymes and proteins, as individual objects interacting according to probability distribution derived from experimental data. In every iteration, a pair of molecules is tested for reaction. Due to the probabilistic treatment of the interactions between the molecules, Stochsim is capable of reproducing realistic stochastic phenomena in the biological system. Both the Gillespie algorithm and the Stochsim algorithm are based on identical assumptions [79] (table 2).

Stochsim has been employed successfully in several biological systems, e.g. for examination of the fluctuations of molecules in a chemotactic signaling pathway of bacteria [79, 101].

Algorithm	Accuracy	Computational cost	Speed
Gillespie	very high	very high	slow
Tau-leap	medium	low	medium
Gibson & Bruck	very high	high	very high
Stochsim	high	high	high

Table 2: Comparison of the performance of various stochastic algorithms (according to Meng *et al.* [76]).

3.2 Langevin equation

An alternative way to simulate stochastic systems is to introduce a stochastic term $\xi(t)$ in the deterministic evolution equation. In this approach, the description is not in term of molecules as in the Gillespie algorithm, but in terms of the concentration as in the deterministic case. Such a system is referred to as **stochastic differential equations**.

The general stochastic equation is:

$$\frac{d\mathbf{X}}{dt} = f(\mathbf{X}) + \xi(t) \quad (50)$$

The definition of the additional term $\xi(t)$ differs according to the formalism adopted. If this term is assumed to account for a white (uncorrelated) noise, $\xi(t)$ is chosen such as its means is zero:

$$\langle \xi(t) \rangle = 0 \quad (51)$$

and its variance is given by

$$\langle \xi(t)\xi(t') \rangle = D\delta(t - t') \quad (52)$$

In this equation, D is proportional to the strength of the fluctuations and $\delta(t - t')$ is the Dirac function. D is therefore the key parameter to control the amplitude of noise in the Langevin approach.

However, the noise depends on the number of molecules (concentration). A rigorous equivalent between the master equation and the Langevin equation can be obtained by considering a multiplicative noise (Gillespie, 2000):

$$\frac{d\mathbf{X}}{dt} = f(\mathbf{X}) + g(\mathbf{X})\xi(t) \quad (53)$$

Here the function $g(\mathbf{X})$ describes the stochasticity resulting from the internal dynamics of the system (cf. the *diffusion term* in the Fokker-Planck equation) and should be appropriately chosen.

Gillespie demonstrated that in the limit of low noise the chemical master equation is equivalent to the following equation - that he named the **Chemical Langevin Equation** (see derivation in Appendix 5.5):

$$\frac{d\mathbf{X}}{dt} = \sum_{r=1}^R \boldsymbol{\eta}_r w_r(\mathbf{X}(t)) + \sum_{r=1}^R \boldsymbol{\eta}_r \sqrt{w_r(\mathbf{X}(t))} \xi_r(t) \quad (54)$$

where ξ_r is a Gaussian white noise:

$$\xi_r(t) = \delta_{rr'} \delta(t - t') \quad (55)$$

where the first δ function is the Kronecker's and the second is Dirac's.

The time evolution of \mathbf{X} is thus governed by the sum of two terms: a deterministic *drift term*, and a *fluctuating term*, as obtained in the Fokker-Planck equation.

Example

To illustrate the Langevin approach, let's consider again the simple reaction scheme (28).

From the deterministic point of view, the evolution of X is given by:

$$\frac{dX}{dt} = k_b - k_d X \quad (56)$$

From the stochastic point of view, each reaction is a noisy process, and the mean is equal to the variance of the noise. Separating the birth and the death process, we can write:

$$\left(\frac{dX}{dt} \right)_{birth} = k_b + \sqrt{k_b} \xi(t) \quad (57)$$

$$\left(\frac{dX}{dt} \right)_{death} = -k_d X + \sqrt{k_d X} \xi(t) \quad (58)$$

Since the reactions are uncorrelated, the variances add as follows:

$$\frac{dX}{dt} = k_b - k_d X + \sqrt{k_b + k_d X} \xi(t) \quad (59)$$

The corresponding Fokker-Planck equation can then be written as (see [120]):

$$\frac{\partial P(X, t)}{\partial t} = -\frac{\partial}{\partial X} [(k_b - k_d X) P(X, t)] + \frac{1}{2} \frac{\partial^2}{\partial X^2} [(k_b + k_d X) P(X, t)] \quad (60)$$

In practice...

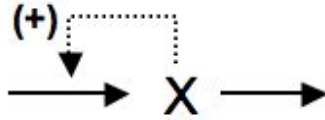
Integrating equation (53) or (54) is not straightforward because the integration time step should be chosen appropriately to avoid to introduce artefactual correlations in the noise. The easiest way to proceed is via Euler's method, which is one of the simplest possible numerical method for solving ordinary differential equations.

The principle is as follows: To solve $dx/dt = f(x)$, with initial condition $x(0) = x_0$, Euler's method requires to specify a small increment of time h , and then update, at each time step, the value of x as $x(t+h) = x(t) + hf(x)$, thus using straight-line interpolation between the points at time $t=0, h, 2h, 3h, \dots$. Smaller h , more accurate the solution. To accomodate a stochastic term on the right-hand side, say $dx/dt = f(x) + \xi(t)$, where $\xi(t)$ is random noise, we approximate $x(t+h) - x(t)$ by $hf(x) + \xi(t+h) - \xi(t)$. Then, once again, we let the integration time step be as small as possible.

A slightly more accurate method is the Runge-Kutta algorithm (with a constant time step). Note that due to the stochastic nature of the noise, an absolute precision is usually not required, but be aware that in most biological applications, X must remain positive.

Gillespie vs Langevin simulation

To compare both the Gillespie and the Langevin approaches, we run some simulations of a simple 1-variable system. A compound (e.g. a protein) is synthetized in an autocatalytic way and degraded linearly.



The evolution of the concentration X writes:

$$\frac{dX}{dt} = v_s \frac{X}{K_M + X} - k_d X \quad (61)$$

The propensity used in the Gillespie algorithm are defined by:

process	reaction	propensity
synthesis	$\rightarrow X$	$w_1 = v_s \Omega \frac{X}{K_M \Omega + X}$
degradation	$X \rightarrow$	$w_2 = k_d X$

Parameter Ω is the system size. It controls the number of molecules and thereby the level of noise. Note that we use here the nonlinear Michaelis-Menten kinetics as a propensity. This point is discussed in Section 4.3.

Gillespie simulations have been performed for various levels of noise (Fig. 11, left panels).

The Langevin equation writes:

$$\frac{dX}{dt} = v_s \frac{X}{K_M + X} - k_d X + \xi(t) \quad (62)$$

In a first test, we adjusted the level of noise, D , arbitrarily, so as to reproduce similar results as with the Gillespie algorithm (Fig. 11, right panels).

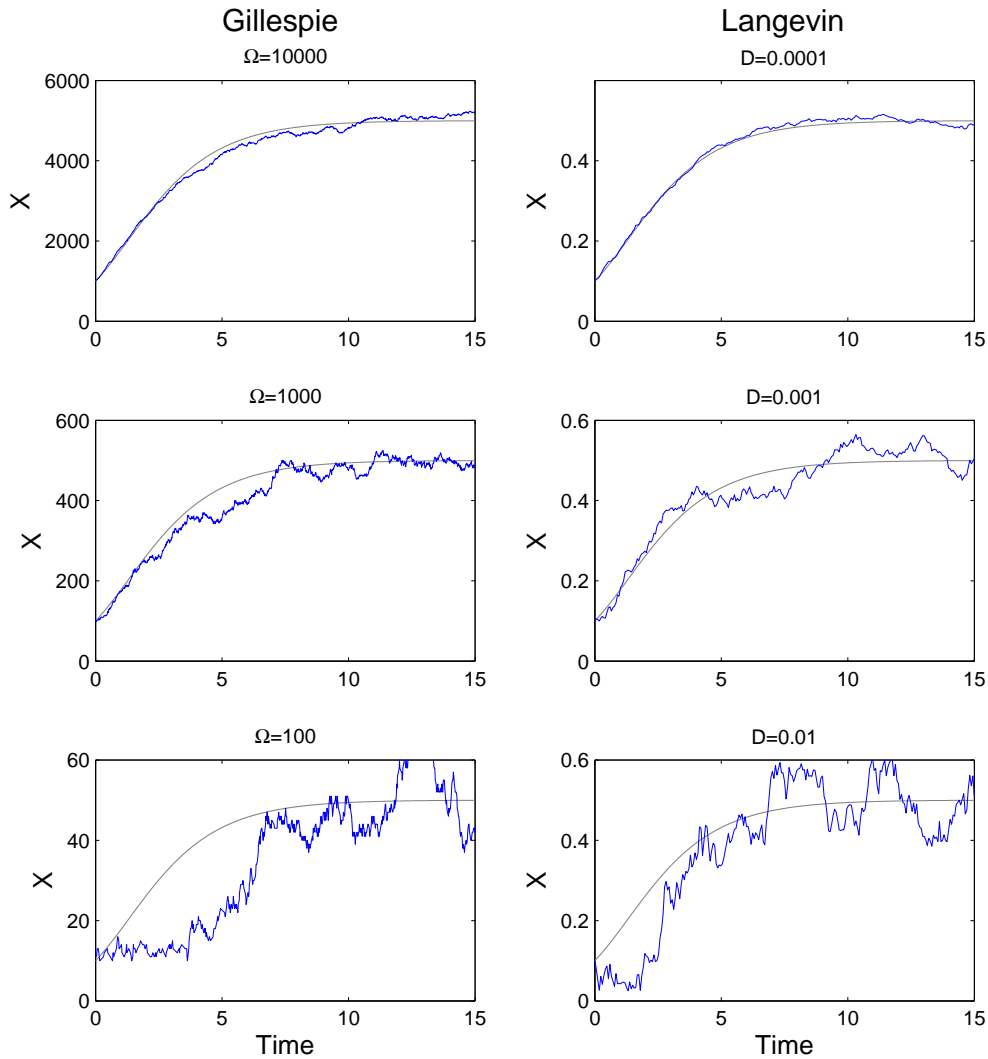


Figure 11: Comparison of the Gillespie and the Langevin approaches. The system (61) is simulated on the left by the Gillespie algorithm and on the right with the Langevin equation (62), with the noise amplitude D as indicated on each panel. Parameter values: $K_M = 0.5$, $k_d = 1$, $v_m = 1$. Initial condition: $X(0) = 0.1$. In each panel the grey curve is the deterministic solution.

We then run simulations according to Eq. (54) which defines the noise amplitude D as a function of Ω (through the propensities w_r) (Fig. 12, right panels). A rigorous quantitative comparison would require some statistics but a visual comparison shows that the two approaches yield similar results.

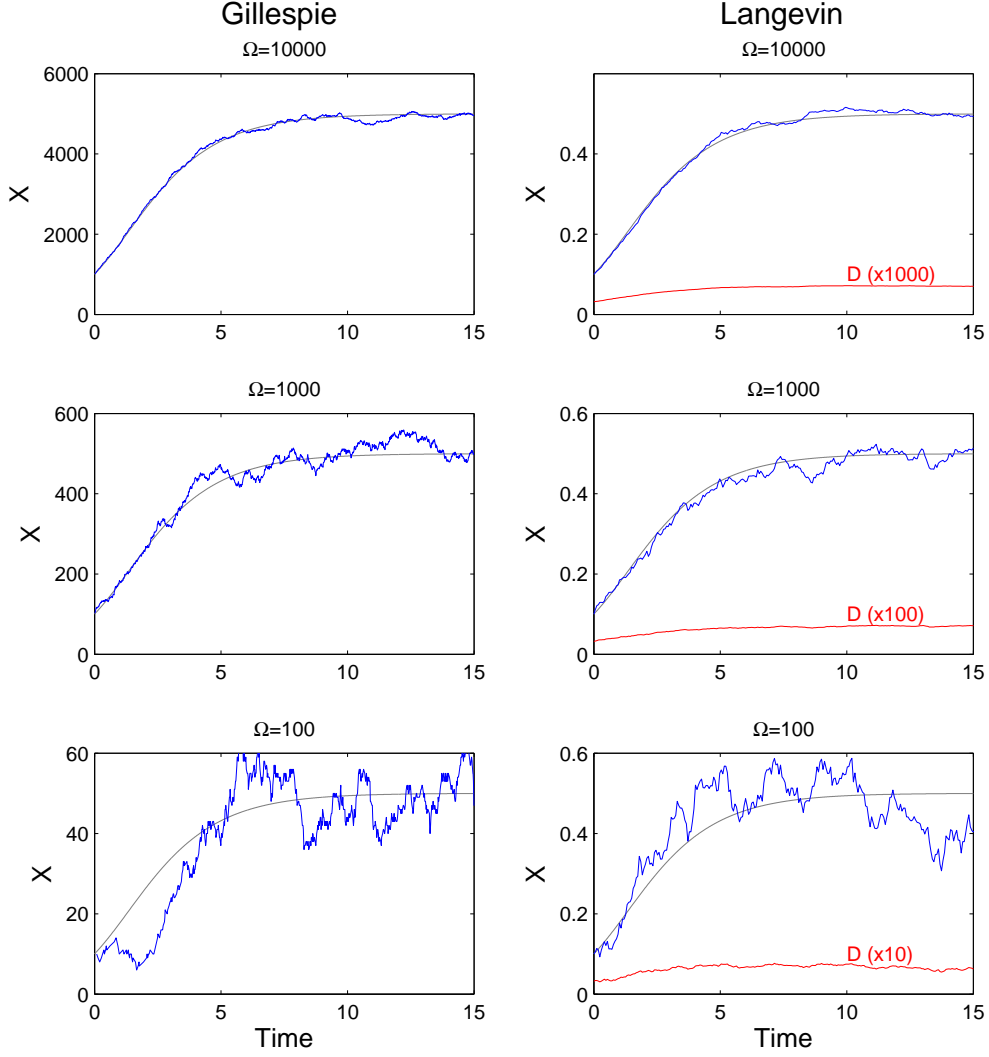


Figure 12: Comparison of the Gillespie and the Langevin approaches. In the Langevin approach, we define the noise amplitude as in Eq. (54). The corresponding value of D is indicated in red. It agrees with the value empirically found in Fig. 11 but undergoes here some fluctuations because it is related to the propensities w_r themselves dependent on X .

3.3 Spatial stochastic modeling

The **spatial organization** of cellular components and the dynamical localization of proteins and other cellular compounds play a key role in cellular processes ranging from cell shape, to cell cycle, and signaling cascades. This organization can be modeled by compartmentalization or by explicitly accounting for space (and diffusion) in addition to the biochemical reactions [4].

There is no general theory to analyse spatial stochastic systems, but several approaches have been attempted to deal with spatial effects. The two general approaches, described above, i.e. the Langevin and Gillespie methods, have been extended to account for space.

Cell compartmentalization

When modeling cellular processes, it is often desirable to distinguish cell compartments. Typically signal transduction involves receptors at the cell membrane, a cascade of proteins activations (e.g. via phosphorylations), and the activation of transcription factors, which, eventually, activate gene expression in the nucleus. Because proteins may have different functions or activity in the various cell compartments and because protein transport may induce delay, it is common to distinguish the molecules with respect to their localization. Moreover since the number of proteins in the nucleus may be strongly reduced compared to the cytosol, stochastic effects may also be important.

The simplest way to account for such compartmentalization is to treat nuclear, cytosolic and membrane proteins as different entities, and transport can be modeled in first approximation, by standard mass action law (to be converted into propensities, as the chemical reaction rates). Such scheme can thus be simulated by the Gillespie algorithm.

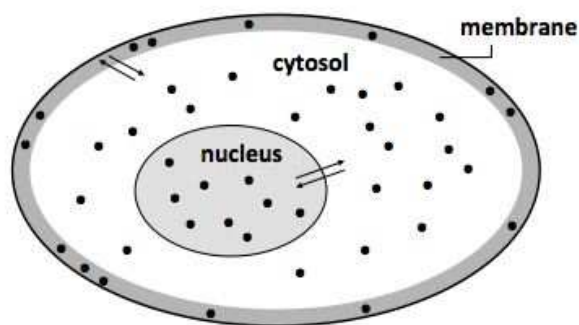


Figure 13: Cell compartmentalization.

Space and diffusion

Discrete spatial stochastic methods can be classified into lattice- and off-lattice-based approaches [18]. In off-lattice methods, all particles in the system have explicit spatial coordinates, at all times. At each time step, molecules with non-zero diffusion coefficients are able to move, in a random walk fashion, to new positions. When 2 reacting species are sufficiently close to each other, they may react, with a certain probability. Such particle methods can provide very detailed simulations of highly complex systems at the cost of exceedingly large amounts of computational time and, possibly, restrictions on the size

of the simulation domain. Hence, such detailed simulations can often only yield short simulation time spans that, in many cases, are of limited interest to simulated cellular processes.

For lattice methods, a computational grid (generally two dimensional or three dimensional) is used to represent a cellular compartment, such as a membrane or the interior of some part of a cell. The lattice is then populated with particles of the different molecular species that comprise the system, either at random or at chosen spatial locations, depending on the problem at hand. All particles with non-zero diffusion coefficient are able to diffuse throughout the simulation domain by jumping to empty neighbouring sites and, depending on user-specified reaction rules, appropriate chemical reactions can take place with a certain probability. It is worth noting that the grid can represent microscopic or mesoscopic domains. In the former, each lattice site is allowed to host at most one molecule. These microscopic lattice-based simulators are sometimes called *Kinetic Monte Carlo Methods* [18].

A less computationally intensive alternative, albeit still costly in many scenarios, is to consider molecular interactions in the mesoscopic scale. Here, the discretization of the Reaction-Diffusion Master Equation (RDME) results in reactive neighbouring subvolumes within which several particles can coexist, while well-mixedness is assumed in each subvolume. Following this line of thought, there are a few algorithms in the literature extending discrete stochastic simulators to approximate solutions of the RDME by introducing diffusion steps as first order reactions, with a reaction rate constant proportional to the diffusion coefficient. To simulate such system, an extension of the *next reaction method*, called the *next subvolume method* has been developed [27].

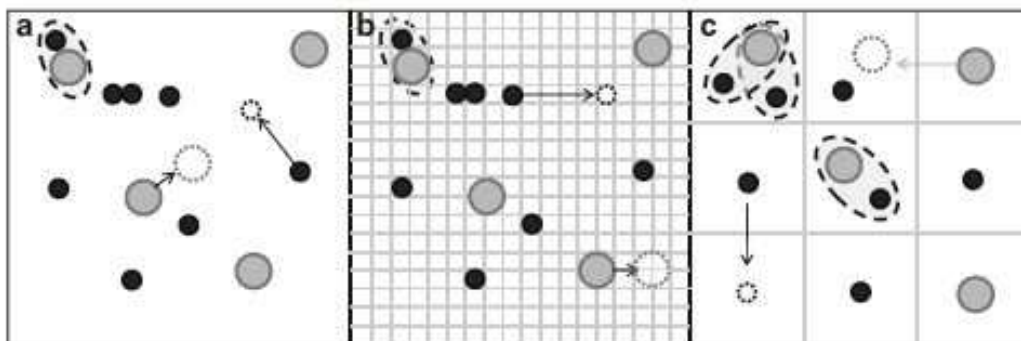
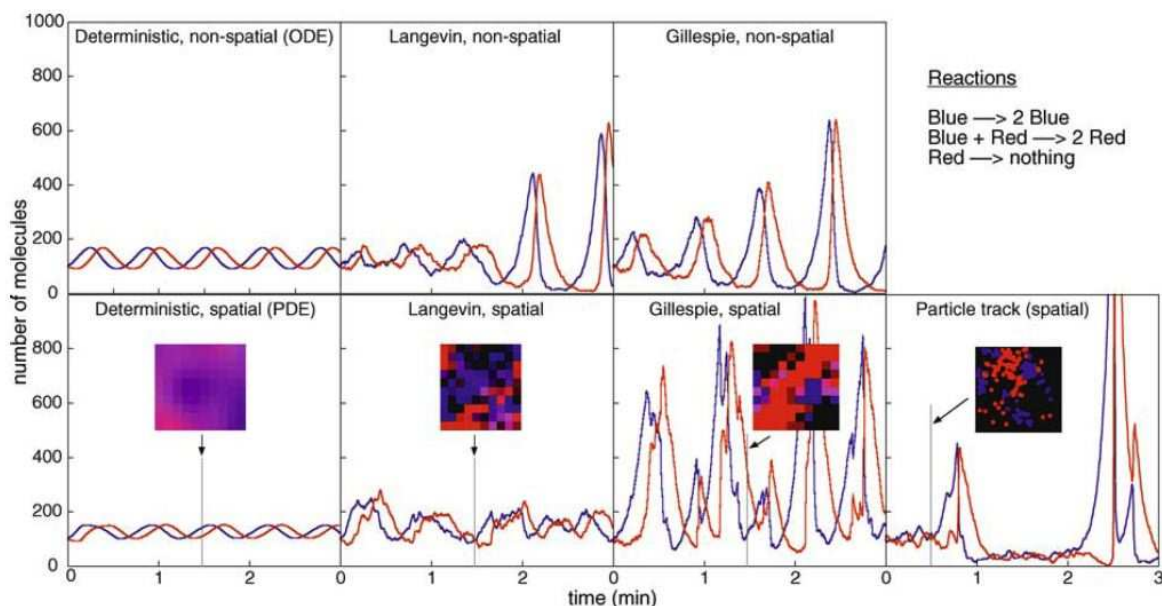


Figure 14: Method for spatial stochastic approaches (figure from [18]).



Stochastic Models of Biological Processes, Figure 1

Simulation results for a simple chemical oscillator using different simulation methods. The Lotka–Volterra system is shown, which shares key features with cellular oscillators such as circadian rhythms. *Insets* show the spatial distributions of molecules at the indicated times. In the *top panels*, note that stochasticity allows the system to drift to large amplitude oscillations and that the Langevin and Gillespie methods yield similar results. In the *bottom panels*, all of which were started with nearly homogeneous initial states, differences arise from the approximations: the PDE simulation has predictable oscillations due to the minimal stochasticity (which is only in the initial state); the Gillespie simulation has larger peaks than the Langevin one because it only allows integer numbers of molecules in each bin; and the particle tracking simulation shows larger and fewer bursts than does the Gillespie simulation because it accurately treats diffusion at all length scales (this difference was reduced with a spatial Gillespie simulation that used smaller subvolumes). Parameters: rate constants are 10 min^{-1} , $8000 \text{ nm}^3 \text{ molec}^{-1} \text{ min}^{-1}$, and 10 min^{-1} , for the respective reactions shown in the *top-right corner*, systems start with 100 of each *blue* and *red* molecules, their diffusion coefficients are $100 \text{ nm}^2 \text{ min}^{-1}$, the volume is 100 nm high and wide by 10 nm deep, and the first three spatial simulations divide this volume into cubic subvolumes that are 10 nm on a side. This figure is reproduced from [8]

Figure 15: Comparison of various modeling approaches (figure from [5]).

Remarks:

A few additional aspects are worth considering:

- First, in mesoscopic lattice methods, as well as inefficiently posed off-lattice methods, problems may arise due to neglecting the “volume exclusion” effect (for example, whenever a (sub)domain is populated by a large number of molecules that would not physically fit). The same would hold for inefficiently posed microscopic lattice methods, where each molecule is set to occupy a single site, irrespective of its physical size.
- Secondly, molecular crowding can prevent reacting molecules from reaching regions of the domain, due to the high concentration of macromolecules impeding their passage. While this effect can be explicitly treated by microscopic lattice methods (as well as some off-lattice methods), mesoscopic lattice methods are in a great disadvantage, their expected accuracy being low when treating these cases.
- Lastly, the artificial nature of the lattice may not only limit the spatial resolution of the simulation, but also introduce lattice anisotropy (boundary effects).

3.4 Programs and softwares

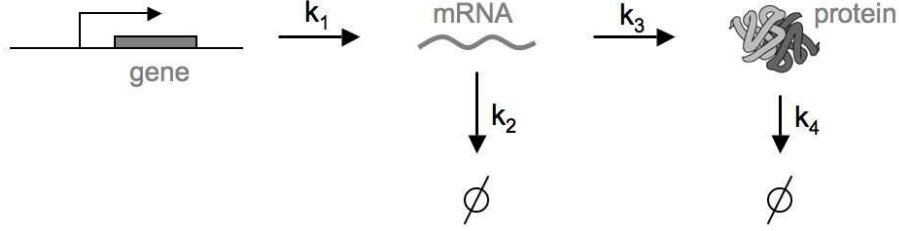
Several softwares and scripts to simulate stochastic models have been recently developed:

- **Copasi:** COPASI [52] is a software application for simulation and analysis of biochemical networks and their dynamics. COPASI is a stand-alone program that supports models in the SBML standard and can simulate their behavior using ODEs or Gillespie's stochastic simulation algorithm; arbitrary discrete events can be included in such simulations.
Availability: <http://www.copasi.org/>
- **BioNetS:** BioNetS [2] is capable of performing full discrete simulations using an efficient implementation of the Gillespie algorithm. It is also able to set up and solve the chemical Langevin equations, which are a good approximation to the discrete dynamics in the limit of large abundances. Finally, BioNetS can handle hybrid models in which chemical species that are present in low abundances are treated discretely, whereas those present at high abundances are handled continuously.
Availability: <http://x.amath.unc.edu:16080/BioNetS/>
- **Stochkit** (Prof. L. Petzold) [60]: Stochkit contains the popular Gillespie algorithm, but also the tau-leaping and variants of this method. Stochkit also provides some basic tools to verify the accuracy of a stochastic solver, given the inherently random nature of stochastic simulation.
Availability: <http://www.engineering.ucsb.edu/~cse/StochKit/>
- **StochSim** (Prof. D. Bray) [66, 79]: StochSim provides a general purpose biochemical simulator in which individual molecules or molecular complexes are represented as individual objects. Reactions between molecules occur stochastically, according to probabilities derived from known rate constants. An important feature of the program is its ability to represent multiple post-translational modifications and conformational states of protein molecules.
Availability: <http://www.pdn.cam.ac.uk/groups/comp-cell/StochSim.html>
- **Dizzy** (Prof. H. Boulouri) [88]: Dizzy is a software tool for stochastically and deterministically modeling the spatially homogeneous kinetics of integrated large-scale genetic, metabolic, and signaling networks. Notable features include a modular simulation framework, reusable modeling elements, complex kinetic rate laws, multi-step reaction processes, steady-state noise estimation, and spatial compartmentalization.
Availability: <http://magnet.systemsbiology.net/software/Dizzy/>
- **MATLAB:** Ullah et al [118] provide a set of MATLAB tools for dynamical modeling of biochemical networks:
Availability: www.sbi.uni-rostock.de/publications_matlab-paper.html

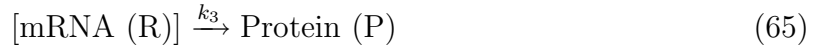
4 Applications

4.1 Gene expression

Thattai and van Oudenaarden [113] proposed the following model for the single gene expression:



The four steps of this simple model are the transcription (reaction 63), mRNA degradation (reaction 64), translation (reaction 65), and protein degradation (reaction 66):



The brackets indicate that these compounds are not consumed in the reaction.

We can directly see that the dynamics of mRNA is independent from the dynamics of protein. In the deterministic case, mRNA reaches a steady state equal to

$$R_{SS} = k_1/k_2$$

At the steady state, the protein level however depends on mRNA and is equal to

$$P_{SS} = k_3 R_{SS} / k_4 = k_3 k_1 / k_2 k_4$$

Stochastic simulation of this model reveals fluctuation at the level of both mRNA and protein (Fig. 16), but with different characteristics. At steady state, the number of mRNA molecules equilibrates independently of the protein molecules and reach a Poisson distribution with a mean k_1/k_2 . The synthesis rate of proteins, however, depends on the number of mRNA molecules present. Protein numbers have a distribution that is much broader than Poisson. The analysis of this model is left as an exercise.

This model and its variants were used to assess the relative role of transcription and translation on the overall noise, the role of auto-regulation, and the propagation of noise in genetic networks [113].

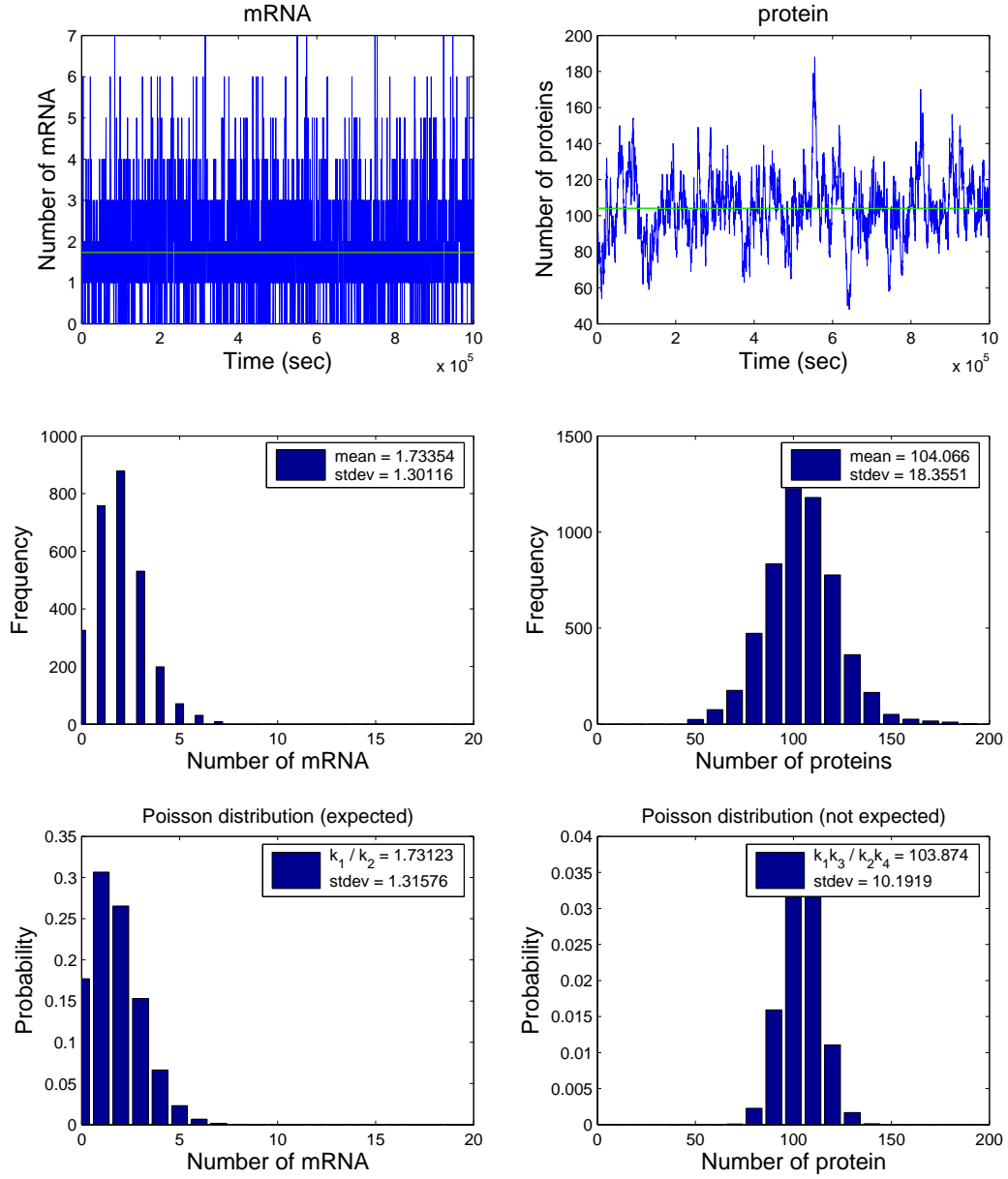
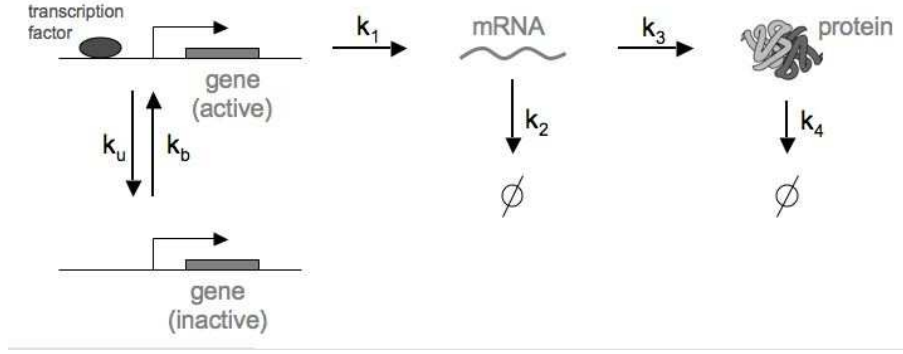


Figure 16: Gene expression (Thattai - van Oudenaarden model): stochastic simulation and steady state distributions of mRNA and protein. Bottom panel: theoretical Poisson distribution. The green lines on the top panels correspond to the deterministic steady state. Parameters: $k_1 = 0.01$, $k_2 = \log(2)/\tau_r$, $k_3 = bk_2$, $k_4 = \log(2)/\tau_p$, $\tau_r = 120$, $\tau_p = 3600$, $b=2$. τ_r and τ_p are the half-life of the mRNA and protein respectively, and b is the burst factor (see [113]).

Transcriptional bursting

We consider here an extended version of the previous model, where we explicitly describe the activation and inactivation forms of the gene [58]. The “activity” of a gene can be controlled by multiple factors: chromatin remodeling, DNA methylation, or the binding of transcription factors (which can act as activators or repressors). The activity of the gene (i.e. its ability to be transcribed) depends on the state of the promoter.

Here we assume that the gene (promoter) stochastically switches between an active state (e.g. bound to a transcriptional activator) and an inactive state (e.g. unbound):



We further assume that the binding/unbinding of the transcription factor occurs randomly and with the same rate ($k_b = k_u$). If these rates are very fast, the system behaves like in the previous scheme, where gene activity is constant and equal to the average of the gene activity here (Fig. 17). If the binding/unbinding rates are slow, then transcription occurs through bursts, a phenomenon called “transcriptional bursting” (Fig. 18). (See [22] and [108] for experimental characterization of the transcriptional bursting).

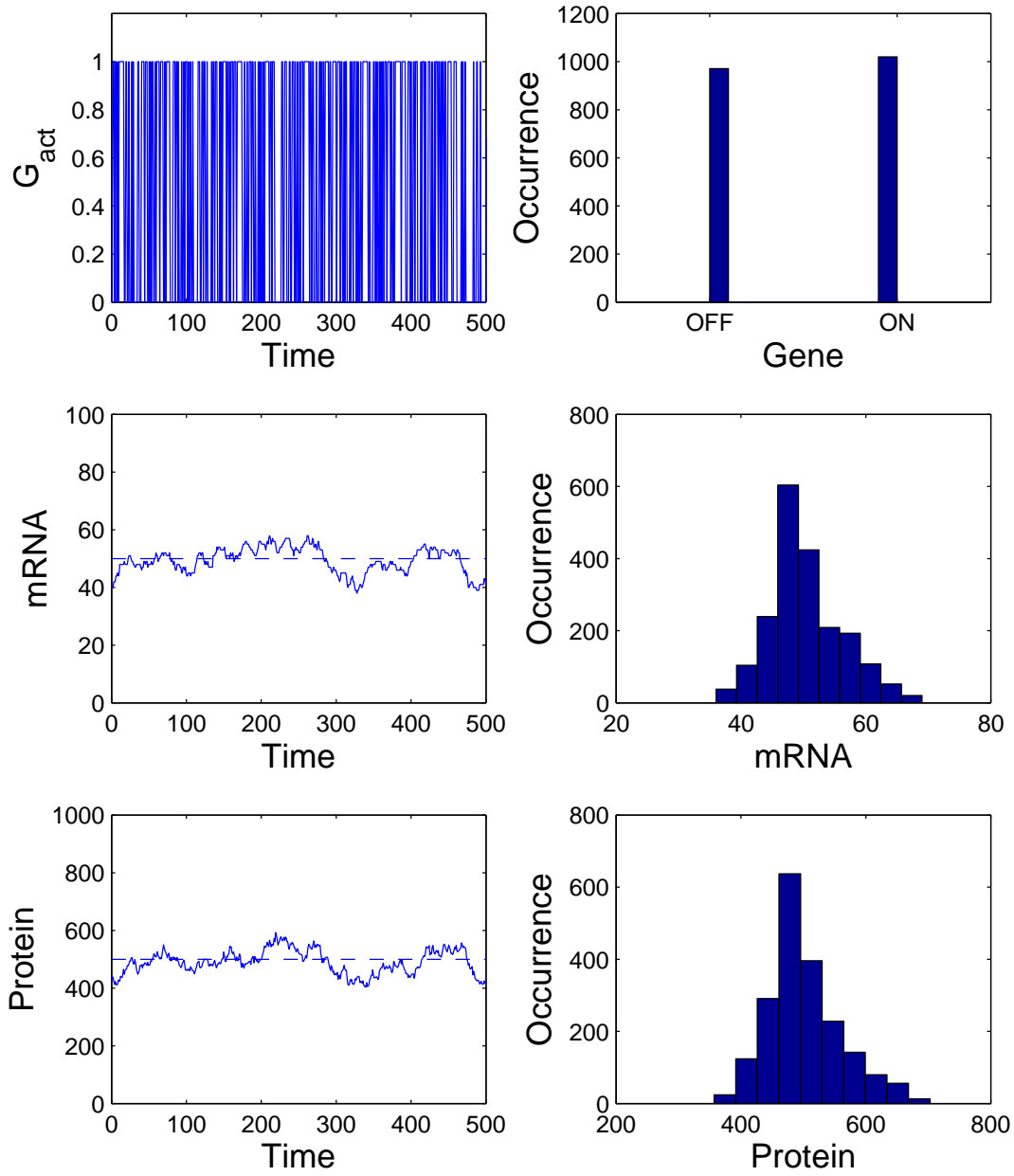


Figure 17: Gene expression with fast gene activation/deactivation. Parameters: $k_b = k_u = 100$, $k_1 = 1$, $k_2 = 0.01$, $k_3 = 1$, $k_4 = 0.1$.

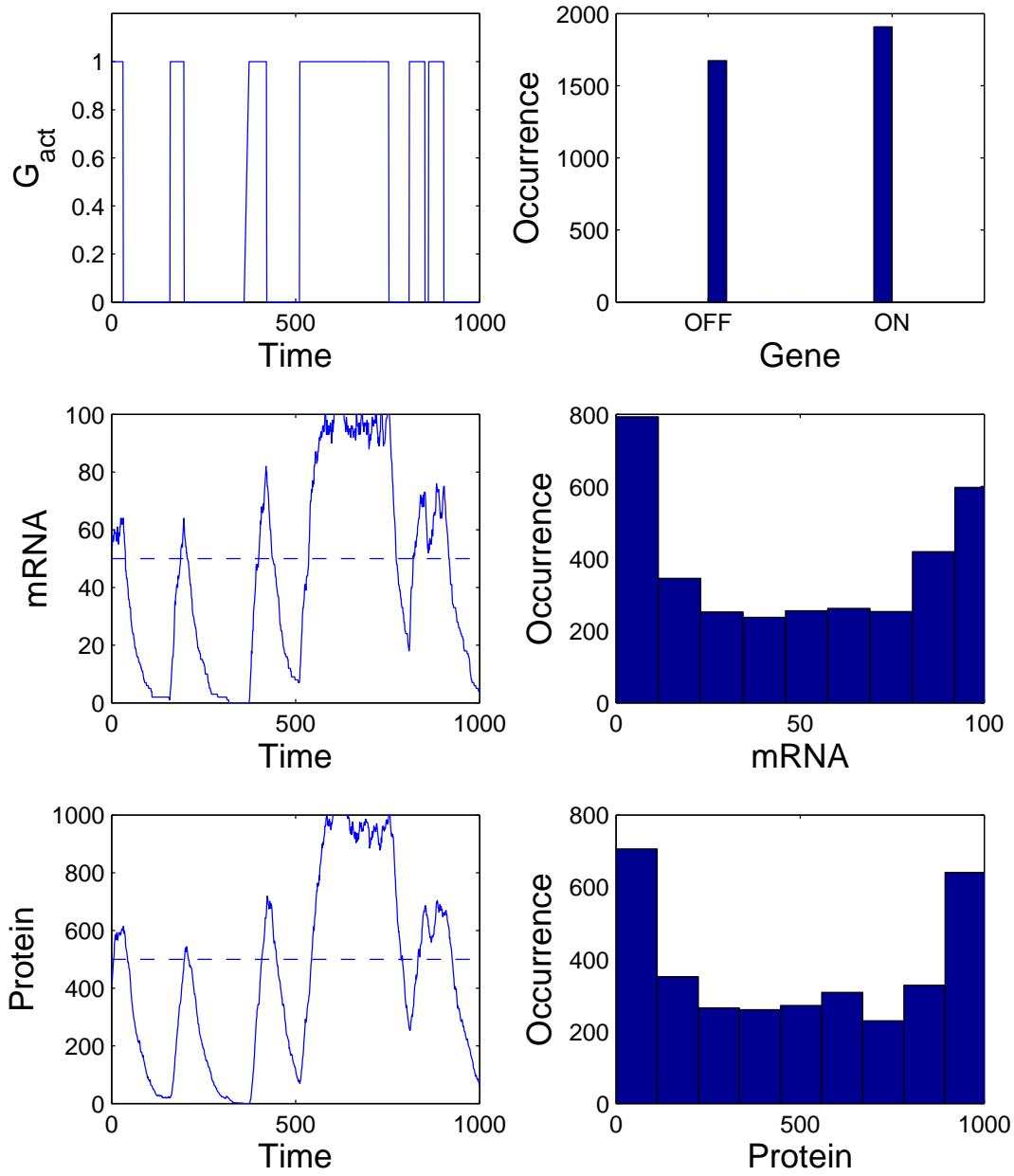


Figure 18: Gene expression and transcriptional bursting. Parameters: $k_b = k_u = 0.01$, $k_1 = 3$, $k_2 = 0.03$, $k_3 = 1$, $k_4 = 0.1$.

4.2 Isomerization

Proteins undergo reversible modifications such as conformational changes (isomerization) or post-translational modifications (e.g. phosphorylations). We discuss here the stochastic dynamics of such system in the most simple case where the protein is not involved in other reactions and where no regulator is involved.



$$\frac{dA}{dt} = -k_1 A + k_2 B \quad (68)$$

$$\frac{dB}{dt} = k_1 A - k_2 B \quad (69)$$

with $N = A + B$ is constant

Steady state:

$$A_s = \frac{k_2 N}{k_1 + k_2} \quad (70)$$

$$B_s = \frac{k_1 N}{k_1 + k_2} = N - A_s \quad (71)$$

Master Equation [89, 41]:

$$\frac{\partial P(a, b)}{\partial t} = k_1(a+1)P(a+1, b-1) + k_2(b+1)P(a-1, b+1) - k_1 a P(a, b) - k_2 b P(a, b) \quad (72)$$

It can be shown that the solution of the this at steady state is (the demonstration is left as an exercise):

$$P(a) = \binom{n}{a} \frac{k_1^a k_2^b}{(k_1 + k_2)^n} \quad (73)$$

with $n = a + b$ molecules.

Fokker-Planck Equation [89, 41]:

$$\frac{\partial P(a, b)}{\partial t} = \frac{\partial}{\partial a} (P(a, t)(k_1 a - k_2 n + k_2 a)) + \frac{1}{2} \frac{\partial^2 P(a, b)}{\partial a^2} (P(a, t)(k_1 a + k_2 n - k_2 a)) \quad (74)$$

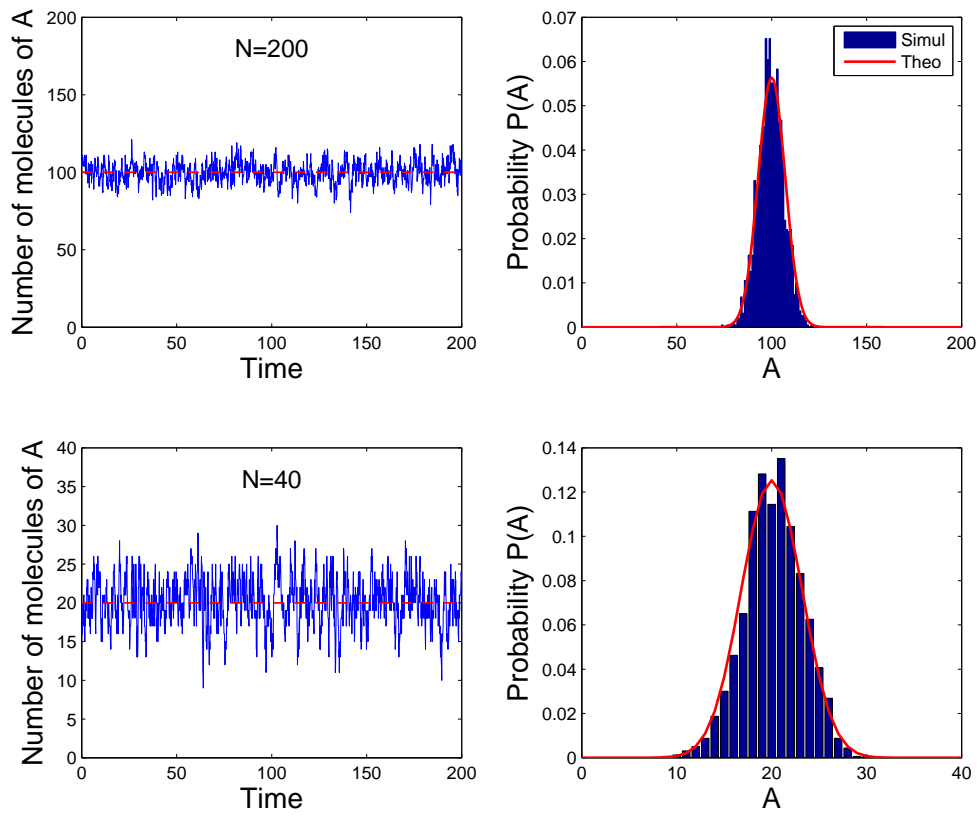


Figure 19: Isomerization. Parameters: $k_1 = k_2 = 1$, $N = 200$ (top) or $N = 40$ (bottom). The red curve corresponds to the theoretical prediction (72) (redone from [89]).

4.3 Michaelis-Menten

Based on experimental observations, Michaelis and Menten (1913) have proposed the following mechanism for the enzyme-catalysed biochemical reactions (C=complex between E and S):



The evolution equation for the different species follow the mass action law:

$$\left\{ \begin{array}{l} \frac{dS}{dt} = -k_1 ES + k_{-1} C \\ \frac{dE}{dt} = -k_1 ES + k_{-1} C + k_2 C \\ \frac{dC}{dt} = k_1 ES - k_{-1} C - k_2 C \\ \frac{dP}{dt} = k_2 C \end{array} \right. \quad (76)$$

The temporal evolution of the substrate S and the product P governed by these deterministic equations is illustrated in fig. 20.

In the stochastic version, we have to consider each reaction step and to associate to each of them a certain probability (reaction rate). The probability table for the model 75 is:

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

As defined above, Ω is the system size. It appears here in the bimolecular reaction 1. Note that Ω can also appear in the initial conditions to convert the initial concentrations into the initial number of molecules.

The master equation corresponding to this system is given by:

$$\begin{aligned} \frac{\partial P(S, C, E; t)}{\partial t} = & - (k_1 SE + (k_{-1} + k_2)C)(P(S, C; t)) \\ & + k_1(S+1)(E+1)P(S+1, C-1; t) \\ & + k_{-1}(C+1)P(S-1, C+1; t) \\ & + k_2(C+1)P(S, C+1; t) \end{aligned} \quad (77)$$

The result of the simulation of this stochastic system (Gillespie method, with $\Omega = 100$) is illustrated in fig. 20. Note that in this formulation, the variables are expressed in terms of the number of molecules.

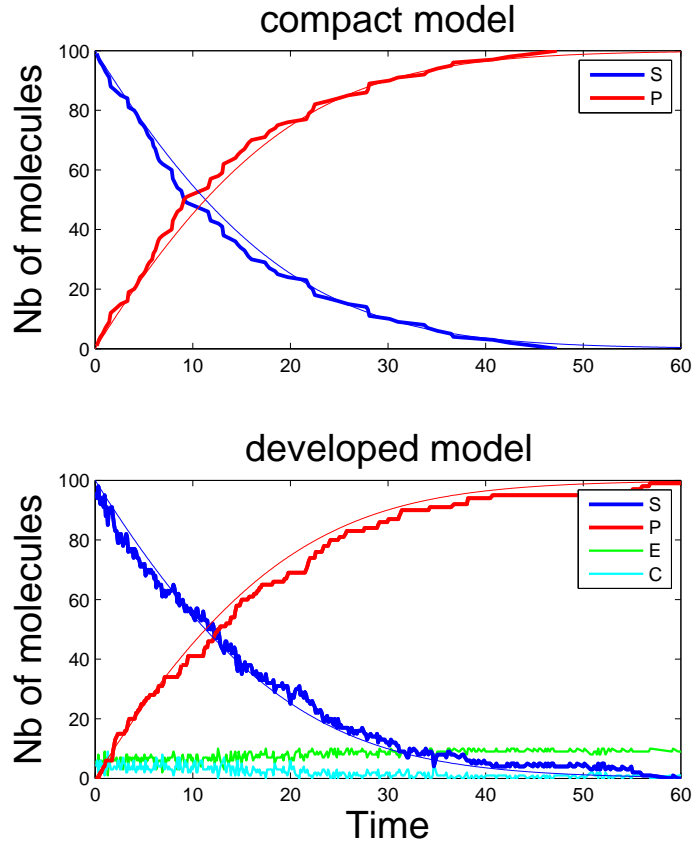


Figure 20: Michaelis-Menten kinetics: deterministic versus stochastic simulation. Parameters: $k_1 = k_{-1} = 10$, $k_2 = 1$, $\Omega = 100$, $E_T = 0.1 * \Omega$, $S_0 = 1 * \Omega$.

Quasi-steady state approximation

When the concentration of substrate is much larger than the enzyme concentration, one may use the quasi-steady-state approximation for the enzyme-substrate complex C to derive the rate law for the enzymatic reaction (75). If we assume $E \ll S_0$, where S_0 denotes the initial or average concentration of S, then $dC/dt = 0$ and one obtains the approximation

$$C = \frac{E_T S}{\frac{k_{-1} + k_2}{k_1} + S} \quad (78)$$

where $E_T = E + C$ is the total (constant) concentration of the enzyme.

The product P of the reaction is thus produced at a rate

$$v = \frac{dP}{dt} = k_2 C = V_{max} \frac{S}{K_M + S} \quad (79)$$

where

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

Rao and Arkin [90] showed that we can equivalently apply the quasi-steady-state approximation to the chemical master equation. In this case, we can use the Michaelis-Menten function as the probability for the reaction $S \rightarrow P$, and the probability table can thus be reduced to:

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

Because the fast reactions $E + S \rightleftharpoons C$ are extremely time-consuming (many occurrences in a given time interval), using this approximation is often a important gain of computational time. More generally, Bundschuh *et al.* [17] show that similar approximations can be reasonably used to eliminate fast reactions. Haseltine and Rawlings [48] propose to approximate fast reactions by deterministic or Langevin equations and to treat slow reaction as stochastic.

Single enzyme kinetics

The stochastic version of the Michaelis-Menten reactional scheme allows to take into account the fluctuations present when the number of enzyme molecules is relatively small. The stochastic theory can even be applied to explore the dynamics of single-enzyme systems. In these cases, stochastic fluctuations can have important consequences on the activity of enzymes, which may be propagated to the phenotypic properties of cells [99, 100].

In Figure 21 we simulated the same system (76) but with a number of enzyme fixed to 1 and a constant level of substrate. E and C thus switch stochastically between 0 and 1 and the number of product molecules increases step-wise.

This model allows us to simulate properties like the distribution of turnover times (Fig. 22). Interestingly, whereas the master equation (77) is of limited use, it can here be applied in a simplified form enabling a theoretical derivation of the distribution of turnover times [64, 100].

Defining the state vector $\mathbf{X} = (E, C)$ with $E + C = 1$, the master equation governing the time evolution of the probability $P(\mathbf{X}, t)$ writes:

$$\begin{aligned}\frac{dP(1, 0, t)}{dt} &= k_2P(0, 1, t) + k_3P(0, 1, t) - k_1SP(1, 0, t) \\ \frac{dP(0, 1, t)}{dt} &= k_1SP(1, 0, t) - (k_2 + k_3)P(0, 1, t)\end{aligned}\quad (80)$$

Note that these equations are actually independent of the number of product molecules.

Starting with initial condition $(0, 1)$, the probability that a product molecule is formed after a time τ can be shown to be given by the following distribution:

$$f(\tau) = \frac{a(e^{(-c+b)\tau/2} - e^{(-c-b)\tau/2})}{b} \quad (81)$$

with

$$\begin{aligned}a &= k_1k_3S \\ b &= \sqrt{-4k_1k_3S + (k_2 + k_3 + k_1S)^2} \\ c &= k_2 + k_3 + k_1S\end{aligned}\quad (82)$$

The mean turnover time is given by

$$\langle \tau \rangle = \int_0^\infty \tau f(\tau) d\tau = \frac{k_2 + k_3 + k_1S}{k_3k_1S} = \frac{K_M + S}{v_{max}S} \quad (83)$$

We thus identify the Michaelis-Menten constant $K_M = \frac{k_2 + k_3}{k_1}$ and the maximal enzyme rate $v_{max} = k_3E_T = k_3(E + C) = k_3$. Hence the mean turnover time is equal to the inverse of the catalysis rate of the enzyme as described by the standard Michaelis-Menten equation.

This theoretical distribution is plotted and compared to the simulated data in Fig. 22.

Similar derivations can be applied to more complex enzymatic reactional schemes (for a review, see [100]).

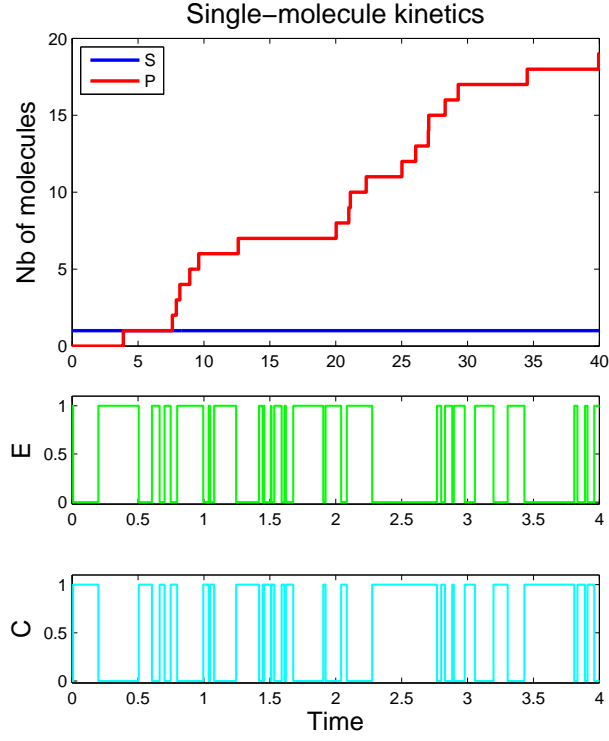


Figure 21: Simulation of the Michaelis-Menten model with the Gillespie algorithm for a single enzyme ($E_T = E + C = 1$) and with S maintained constant ($S = 1$). Parameters: $k_1 = k_2 = 10$, $k_3 = 1$.

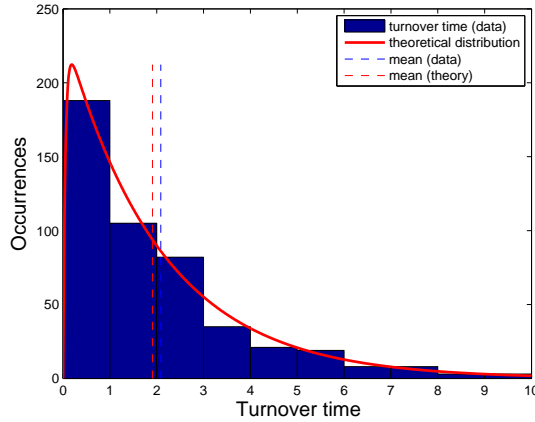


Figure 22: Distribution of turnover times for the Michaelis-Menten model simulated with a single enzyme. The turnover time is defined by the time duration between two successive increments of the number of product molecules, P . The red curve is the theoretical distribution defined by Eq. (81). The red dashed line indicates the theoretical mean turnover time, as defined by Eq. (83).

4.4 Brusselator

The *Brusselator* (proposed in 1967 in Brussels by R. Lefever I. Prigogine et G. Nicolis) is probably the first mathematical model proposed to explain the mechanism of chemical oscillations as observed in the famous Belousov-Zhabotinsky reaction. Since then, this model serves as a prototype model to study many dynamical properties of oscillatory systems, including the effect of noise. The proposed chemical reaction scheme is the following (note the three-molecular reaction in step 3):

r	reaction	reaction rate	dX/dt	dY/dt
1	$A \xrightarrow{k_1} X$	$v_1 = k_1 A$	$+v_1$	0
2	$B + X \xrightarrow{k_2} Y + C$	$v_2 = k_2 B X$	$-v_2$	$+v_2$
3	$2X + Y \xrightarrow{k_3} 3X$	$v_3 = k_3 X^2 Y$	$+v_3$	$-v_3$
4	$X \xrightarrow{k_4} D$	$v_4 = k_4 X$	$-v_4$	0

Assuming that A , B , C and D are constant (because present in excess for example), the evolution equations for X and Y are given by

$$\begin{cases} \frac{dX}{dt} = k_1 a - k_2 b X + k_3 X^2 Y - k_4 X \\ \frac{dY}{dt} = k_2 b X - k_3 X^2 Y \end{cases} \quad (84)$$

The temporal evolution of the reactants X and Y governed by these deterministic equations is illustrated in Fig. 23 (top panel).

In the stochastic version, we have to consider each reaction step and to associate to each of them a certain probability (reaction propensities). The probability table for this model is:

r	reaction	reaction propensity	$c \leftrightarrow k$
1	$A \xrightarrow{k_1} X$	$w_1 = c_1 A$	$c_1 = k_1$
2	$B + X \xrightarrow{k_2} Y + C$	$w_2 = c_2 B X$	$c_2 = k_2 / \Omega$
3	$2X + Y \xrightarrow{k_3} 3X$	$w_3 = c_3 X(X-1)Y/2$	$c_3 = 2k_3 / \Omega^2$
4	$X \xrightarrow{k_4} D$	$w_4 = c_4 X$	$c_4 = k_4$

Again, Ω is the system size and appears in the two-molecular reaction step 2 and in the three-molecular reaction step 3.

The master equation corresponding to this system is given by:

$$\begin{aligned} \frac{\partial P(X, Y; t)}{\partial t} = & - (c_1 A + c_2 B X + c_3 X^2 Y + c_4 X) P(X, Y; t) \\ & + c_1 A P(X-1, Y; t) \\ & + c_2 B (X+1) P(X+1, Y-1; t) \\ & + c_3 (X-1)(X-2)(Y+1) P(X-1, Y+1; t) \\ & + c_4 (X+1) P(X+1, Y; t) \end{aligned} \quad (85)$$

The result of the simulation of this stochastic system (Gillespie method, with $\Omega = 1000$ and $\Omega = 100$) is illustrated in Fig. 23 (middle and bottom panels).

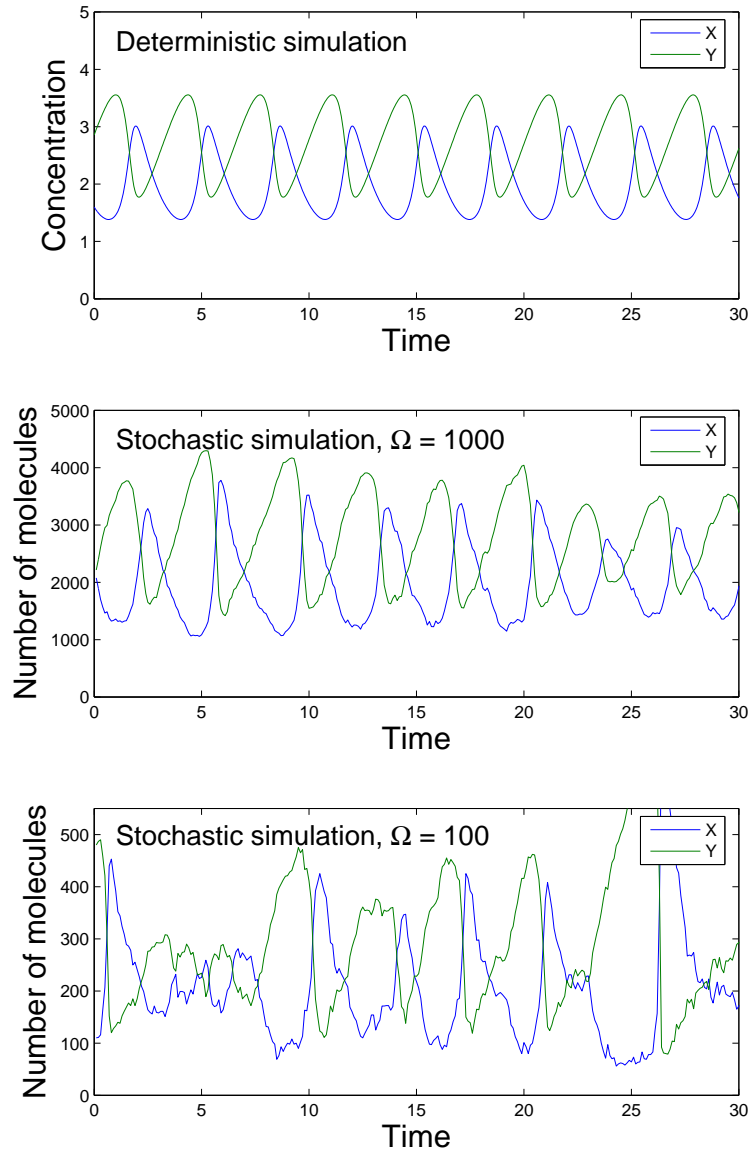


Figure 23: Brusselator: deterministic versus stochastic simulation. Parameters: $k_1 = k_2 = k_3 = k_4 = 1$, $a = 2$, $b = 5.2$.

Quantification of the effect of noise

Clearly, the noise for $\Omega = 100$ has more effect on the oscillations than for $\Omega = 1000$. How to quantify this effect? We present here two measures:

- **Histogram of period.** Since the stochasticity induces fluctuations in the period, a straightforward measure of the impact of noise consists of plotting the histogram of the peak-to-peak (“period”) intervals, and to calculate the standard deviation of this distribution. Bigger is the influence of the noise on the system, larger is the standard deviation. Although this measure is relatively intuitive, the estimation of the peak-to-peak intervals from the stochastic time series is not trivial. It is for example not easy to determine the maxima of the stochastic time series since they occur extremely often due to the fluctuations. An alternative could be to take the time at which a variable crosses upwards (of downwards) its mean value (nevertheless even in this case some corrections to discard small fluctuations around the crossing point might be necessary). Note also that to have a good statistics, relatively long time series (for ex. 1000 periods) should be used.
- **Auto-correlation function.** Another commonly used measure is the auto-correlation function. This function $C(\tau)$ measures the correlation of a time series with itself shifted by an time lag τ as a function of τ . By definition, auto-correlation function of a signal $x(t)$ is:

$$C(\tau) = \frac{1}{T - \tau} \int_0^{T-\tau} x(t)x(t + \tau)dt \quad (86)$$

For discrete time series of limited size (N points), as generated by the stochastic simulations, this formula becomes:

$$C(m) = \frac{1}{N - m} \sum_{n=0}^{N-m-1} x(n)x(n + m) \quad (87)$$

For a perfectly periodic time serie (such as the one generated by a deterministic model), the auto-correlation $C(\tau)$ is periodic (with the same period as the time series) and reaches 1 at each period because after a shift of one period, the time series is again fully correlated with itself. For stochastic time series, however, the auto-correlation $C(\tau)$ oscillates but its envelop $\tilde{C}(\tau)$ decreases exponentially with the time, reflecting the loss of phase memory. This phenomenon is called **phase diffusion**. The damping rate of the auto-correlation function, measured by the half-life time (i.e. the time required to reach $\tilde{C}(\tau) = 0.5$) is a measure of the impact of noise. Bigger is the influence of the noise on the system, shorter is the half-life time. Again, to have a good statistics, relatively long time series (for ex. 1000 periods) should be used and time interval between the data points should be constant.

These two measures have been applied to the Brusselator model, both for the deterministic and stochastic time series (fig. 24).

Interestingly, when we plot the half-life time as a function of the system size, Ω or the standard deviation of the period distribution as a function of $1/\sqrt{\Omega}$, we observe for large value of Ω a linear relationship (fig. 25). This property is characteristic of non-linear systems perturbed by a white noise [36].

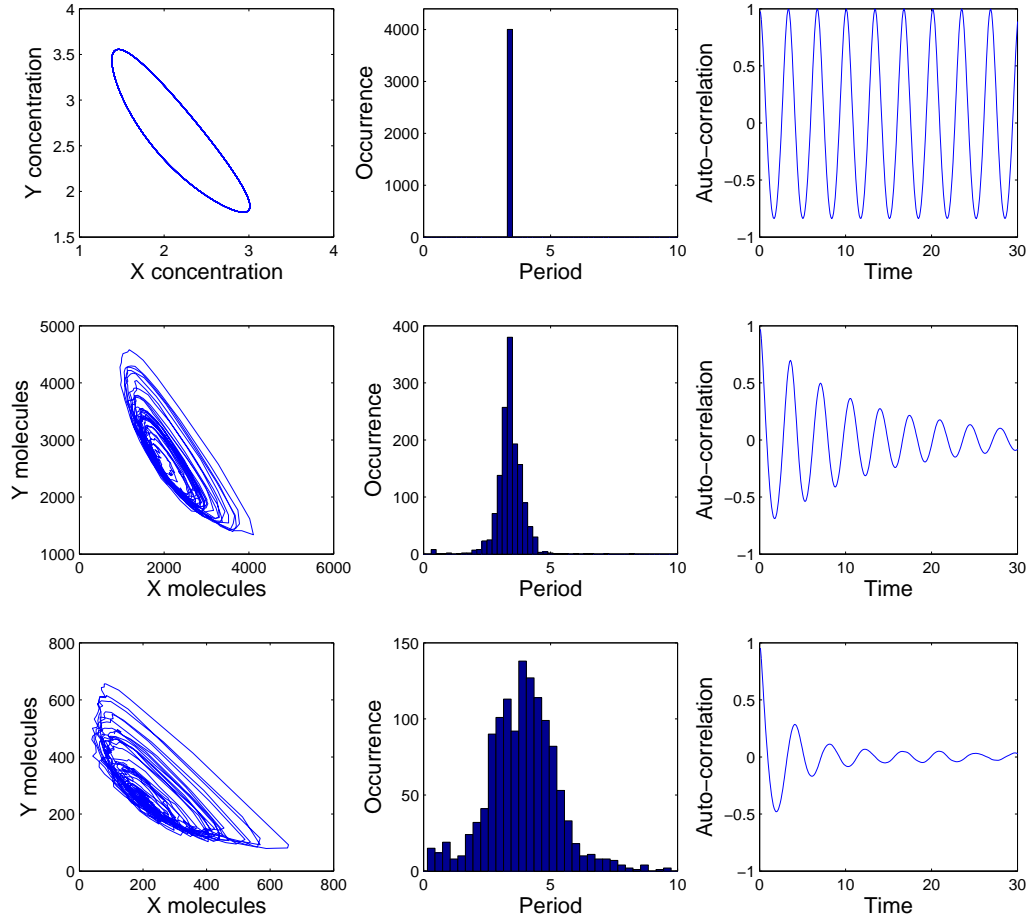


Figure 24: Brusselator: Quantification of the effect of noise. Upper row: deterministic, middle row: $\Omega = 1000$, bottom row: $\Omega = 100$.

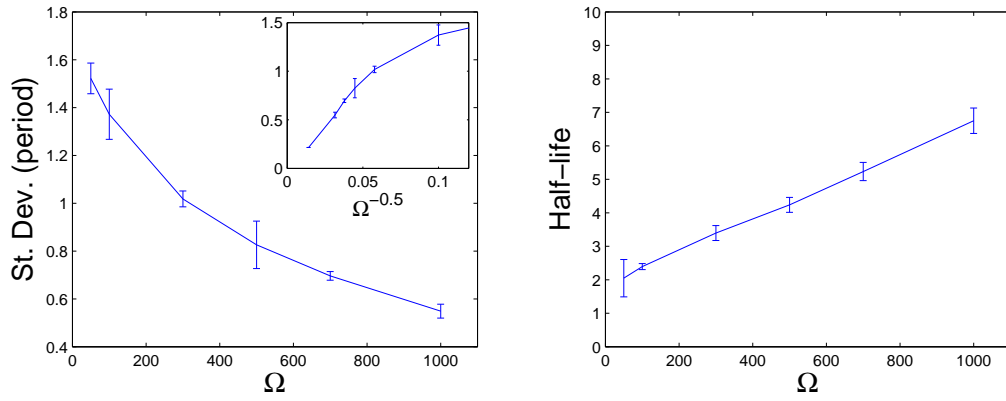


Figure 25: Brusselator: Quantification of the effect of noise.

4.5 Schlögl model

The Schlögl model (originally proposed in 1972 by F. Schlögl) is a simple, 1-variable chemical system displaying bistability:

r	reaction	reaction rate
1	$A+2X \xrightarrow{k_1} 3X$	$v_1 = k_1AX^2$
2	$3X \xrightarrow{k_2} A+2X$	$v_2 = k_2X^3$
3	$X \xrightarrow{k_3} B$	$v_3 = k_3X$
4	$B \xrightarrow{k_4} X$	$v_4 = k_4B$

Assuming that A and B are constant (because present in excess for example), the evolution equations for X is given by

$$\frac{dX}{dt} = k_1AX^2 + k_2X^3 + k_3X + k_4B \quad (88)$$

For appropriate parameter values, this system can present 3 steady states, 2 of them being stable (bistability). Deterministic simulations shows that depending on the initial condition, the system converges towards one or the other second stable state, the unstable state playing the role of the separatrix.

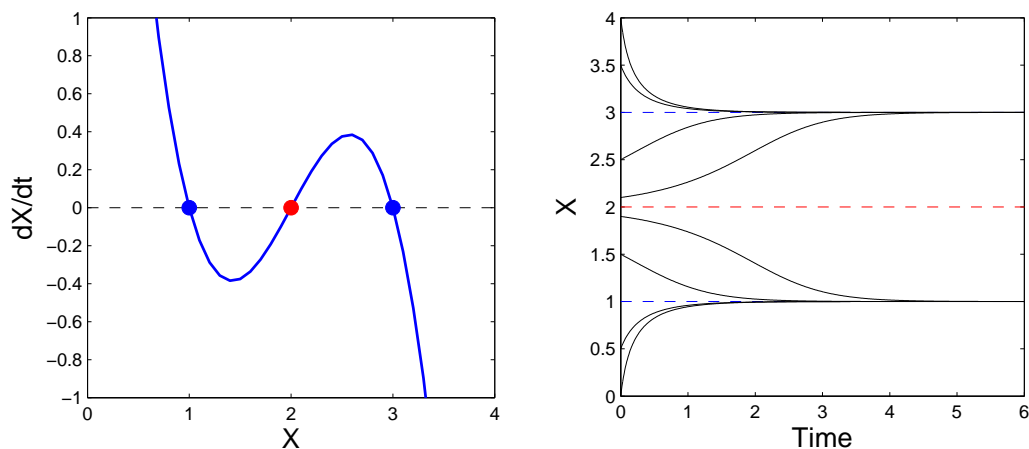


Figure 26: Deterministic simulation of the Schlögl model.

Stochastic simulation (by means of the Gillespie algorithm) of that system (cf. Table here below) shows that if the level noise is sufficient high (i.e. the number of molecules sufficiently small), the system can spontaneously switch from one steady state to the other. The distribution of X is bimodal, but X has a strong preference to remain in the lower steady state. This example shows that the robustness to molecular noise is not the same for the 2 stable steady state.

r	reaction	reaction propensity	$c \leftrightarrow k$
1	$A+2X \xrightarrow{k_1} 3X$	$w_1 = c_1 A X (X - 1)/2$	$c_1 = 2k_1/\Omega^2$
2	$3X \xrightarrow{k_2} A+2X$	$w_2 = c_2 X (X - 1)(X - 2)/3!$	$c_2 = 3!k_2\Omega^2$
3	$X \xrightarrow{k_3} B$	$w_3 = c_3 X$	$c_3 = k_3$
4	$B \xrightarrow{k_4} X$	$w_4 = c_4 B$	$c_4 = k_4$

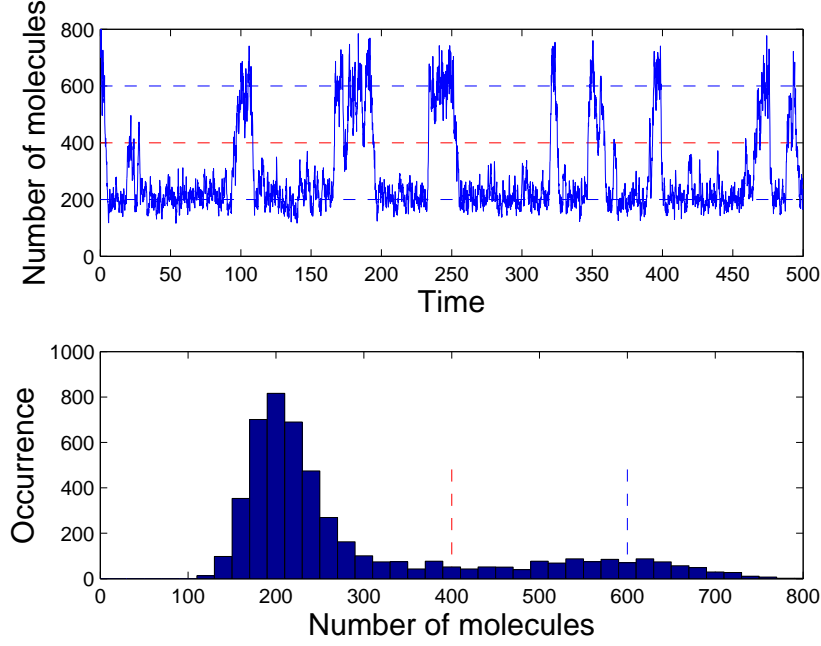


Figure 27: Stochastic simulation of the Schlögl model.

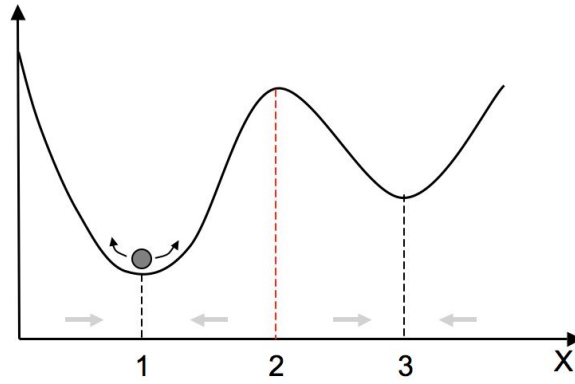


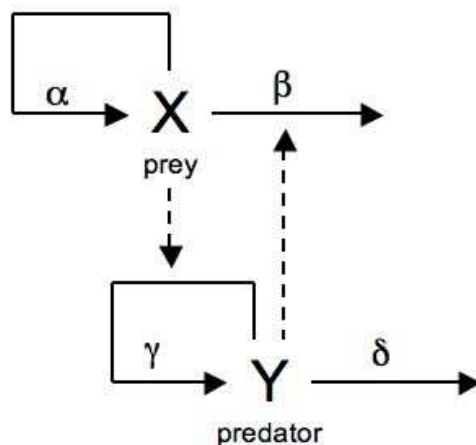
Figure 28: Schlögl model: schematic interpretation of the robustness.

4.6 Lotka-Volterra

In 1925, Lotka and Volterra proposed one of the first models to describe the dynamics resulting from the interactions between predators and preys. This model constitutes the basis of numerous models used today in the analysis of population dynamics.

Here we will deal with original, two species model, but it should be kept in mind that Lotka-Volterra models may be extended to much more species in interaction. Moreover these equations can be used for multi-species competition (including molecular) models.

We denote X the prey, and Y the predator. We assume that the death of the prey is only due to the predation, i.e. the more abundant the predator, the faster the death of the prey and the birth of the predator. We also assume that the birth rate of the prey is linear and that the (natural) mortality rate of the predators is also linear.



The time evolution of X and Y are then given by the following equations:

$$\begin{cases} \frac{dX}{dt} = \alpha X - \beta XY \\ \frac{dY}{dt} = \gamma XY - \delta Y \end{cases} \quad (89)$$

Under appropriate conditions, sustained oscillations of the prey and predator population are observed. Note that these oscillations are not of limit-cycle type. Their amplitude depends on initial numbers of preys and predators.

When this system is simulated stochastically, high variation in the level of the two species is observed. This is because there is no attractive limit-cycle that contracts the trajectories. An other effect of noise, not observed in the deterministic model is that it could happen that through random fluctuations all the predators die. In this case the species is extincted and the happy preys can exponentially multiply.

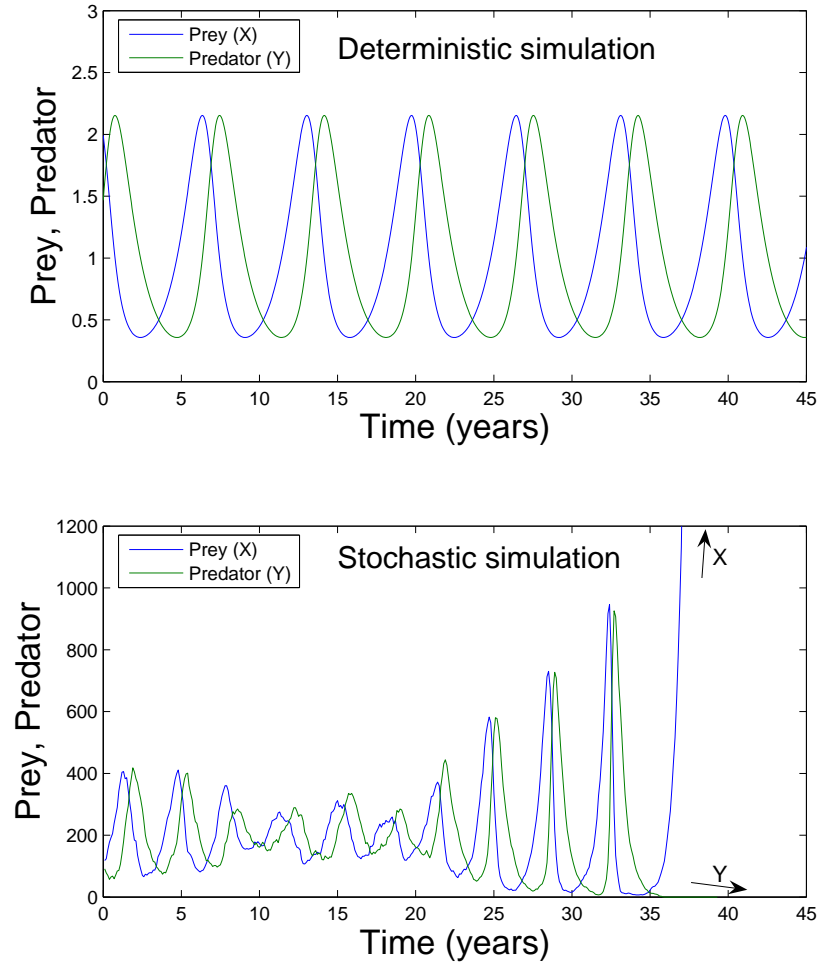


Figure 29: Lotka-Volterra: Deterministic versus stochastic simulation. Parameters: $\alpha = \beta = \gamma = \delta = 1$, $\Omega = 100$.

4.7 Fitzhugh-Nagumo

The Fitzhugh-Nagumo model is a simple example of a two-dimensional excitable system. It was proposed as a simplification of the famous model by Hodgkin and Huxley to describe (phenomenologically) the response of an excitable nerve membrane to external current stimuli. Important features, also found in experiments on real neurons, are the inclusion of a recovery mechanism and the existence of different refractory states after excitation, as well as states of enhanced and depressed excitability depending on the time course of external stimulation (see review by Lindner *et al.* [68]).

A stochastic version of the Fitzhugh-Nagumo model was studied for the first time by Treutlein and Schulten [68]. There the notion of noise-induced limit cycles was introduced in this model. Driving the Fitzhugh-Nagumo model by white noise or by an external signal became popular during the 1990s in the context of stochastic resonance.

One common representation of the stochastic Fitzhugh-Nagumo model is given by:

$$\begin{cases} \frac{\epsilon dx}{dt} = f(x) - y \\ \frac{dy}{dt} = \gamma x - \beta y + b - s(t) + \sqrt{2D}\xi(t) \end{cases} \quad (90)$$

The two non-dimensional variables x and y are a voltage-like and a recovery-like variable, or in the terminology of physical chemists and biologists an activator and an inhibitor variable, respectively. Function $s(t)$ is a periodic signal and $\sqrt{2D}\xi(t)$ is a white Gaussian noise with intensity D . In neuronal models, the time scale ratio ϵ is much smaller than one ($\epsilon \approx 10^{-2}$), implying that $x(t)$ is the fast and $y(t)$ is the slow 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

$$f(x) = x - ax^3 \quad (91)$$

In the excitable regime of the Fitzhugh-Nagumo model, this nullcline intersects only once with the linear nullcline of the y dynamics. The intersection point is a stable fixed point on the left branch of the cubic nullcline the resting state of the system. Sufficiently strong perturbations (either in x or in y) result in a large excursion in phase space along the right branch of $f(x)$ (“firing” of the neuron), and back along the upper left branch (“neuronal refractory state”) into the rest state. In fig. 31 (left, up) this trajectory is shown for the deterministic system started at an appropriate initial condition, caused, for instance by an external stimulation. The time course of $x(t)$ (fig. 31, left, bottom) the excursion in the phase plane appears as a spike.

The excitation process that was in the deterministic case due to the initial condition, occurs repeatedly if noise is present ($D > 0$). This is shown in fig. 31 (right, up), which illustrates a stochastic trajectory in phase space and the corresponding time series $x(t)$ (31, right, bottom). The random force occasionally kicks the phase point out of the vicinity of the stable fixed point towards the region labeled “self-excitatory”. The sequence of action potentials resembles the spontaneous activity of a neuron.

Such noise-induced oscillations are commonly observed in excitable systems (see also [80])

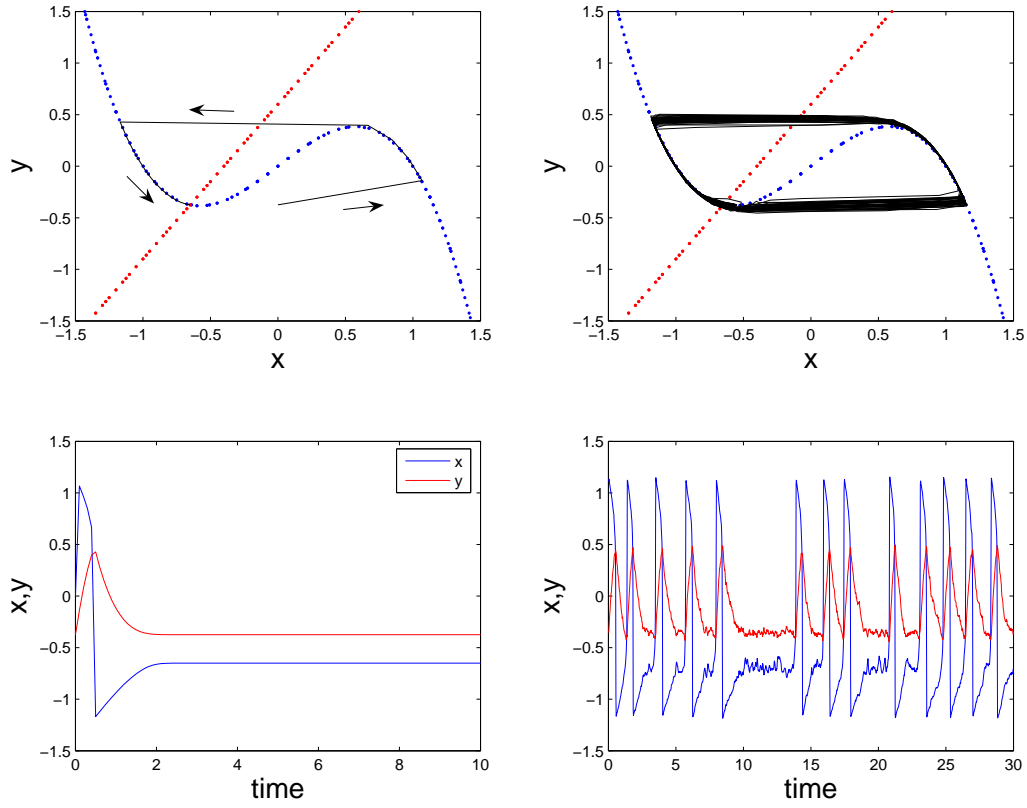


Figure 30: Fitzhugh-Nagumo model: deterministic versus stochastic simulation. Parameters: $\epsilon = 0.01$, $b = 0.6$, $\beta = 1$, $a = 1$, $\gamma = 1.5$, and $D = 0.01$.

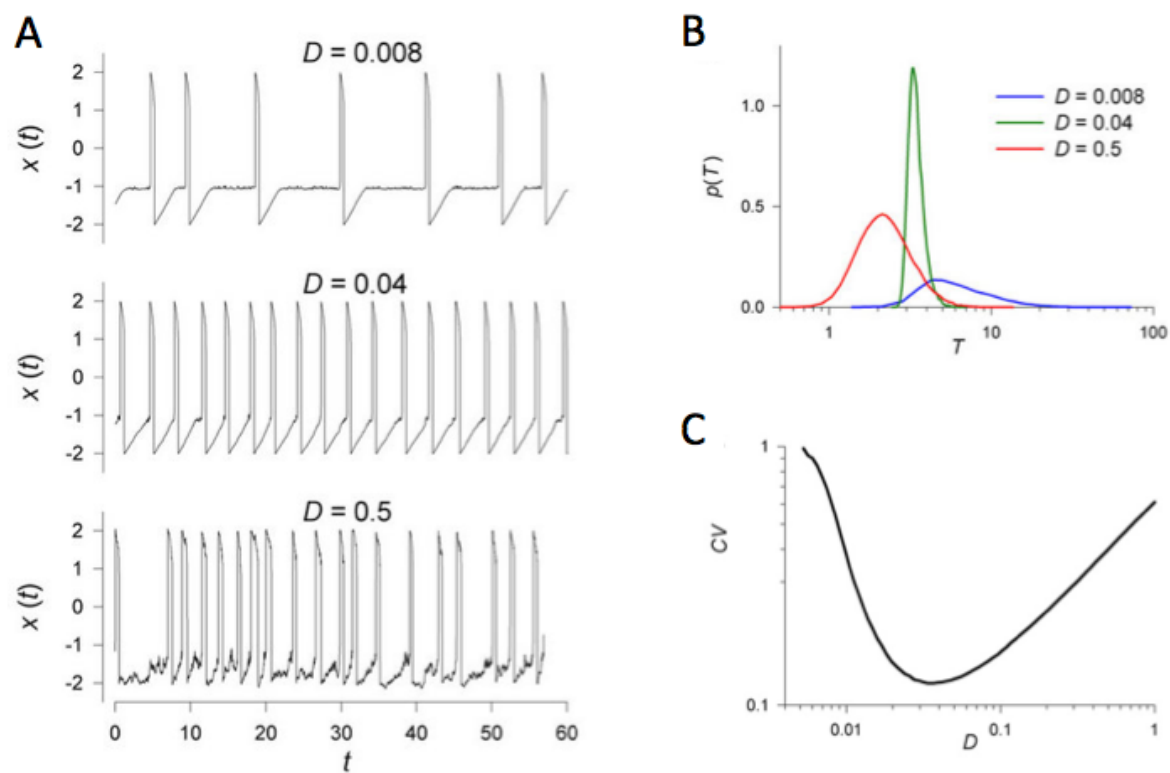


Figure 31: Stochastic coherence in the Fitzhugh-Nagumo model (source: scholarpedia).

5 Appendixes

5.1 Solving the master equation

Solving analytically the master equation is not an easy affair. Of course, this problem can be solved by finding numerical solution. Solving numerically the master equation can begin tiresome when the reaction process involve many species.

A small example

Consider the following system



Then,

$$\begin{aligned} \frac{\partial P(X_A, X_B, t)}{\partial t} = & w_1(X_A + 1, X_B + 1)P(X_A + 1, X_B + 1, t) \\ & - w_1(X_A, X_B)P(X_A, X_B, t) \end{aligned} \quad (93)$$

To solve this equation, we will need to compute recursively for $t = t_0, \dots, t_f$,

$$P(X_A, X_B, t_0), \quad P(X_A, X_B, t_1), \quad \dots, \quad P(X_A, X_B, t_f) \quad (94)$$

for $X_A = 0, 1, \dots, N_A$ and $X_B = 0, 1, \dots, N_B$.

That means $(N_A + 1) \cdot (N_B + 1) \cdot (f + 1)$ different probabilities. The Euler approximation of the master equation is

$$P(X_A, X_B, t + \tau) \approx P(X_A, X_B, t) + \tau \frac{\partial P(X_A, X_B, t)}{\partial t} \quad (95)$$

for τ small enough.

A time t_0 , the number of molecule of A and B is known and equal to X_A^0, X_B^0 . So

$$P(X_A, X_B, t_0) = \delta_{X_A, X_A^0} \delta_{X_B, X_B^0}, \quad (96)$$

where $\delta_{a,b} = 1$ if $a = b$ and $\delta_{a,b} = 0$ if $a \neq b$. Therefore, the time evolution of $P(X_A^0, X_B^0, t)$ can be computed recursively by

$$P(X_A^0, X_B^0, t + \tau) \approx P(X_A^0, X_B^0, t) + \tau \frac{\partial P(X_A^0, X_B^0, t)}{\partial t}. \quad (97)$$

★ For X_A^0, X_B^0 :

we have $a_1(X_A, X_B) = c_1 X_A X_B$, so

$$\begin{aligned} P(X_A^0, X_B^0, t_0) &= 1 \\ P(X_A^0, X_B^0, t_0 + \tau) &= 1 - \tau c_1 X_A^0 X_B^0 \\ P(X_A^0, X_B^0, t_0 + 2\tau) &= P(X_A^0, X_B^0, t_0 + \tau) + \tau \frac{\partial P(X_A^0, X_B^0, t + \tau)}{\partial t} \Big|_{t_0} \\ &\vdots \\ P(X_A^0, X_B^0, t_0 + n\tau) &= \dots \end{aligned} \quad (98)$$

★ For $X_A^0 - 1, X_B^0$:

$$\begin{aligned}
P(X_A^0 - 1, X_B^0, t_0) &= 0 \\
P(X_A^0 - 1, X_B^0, t_0 + \tau) &= 0 \\
&\vdots \\
P(X_A^0, X_B^0, t_0 + n\tau) &= 0
\end{aligned} \tag{99}$$

★ For $X_A^0 - 1, X_B^0 - 1$:

$$\begin{aligned}
P(X_A^0 - 1, X_B^0 - 1, t_0) &= 0 \\
P(X_A^0 - 1, X_B^0 - 1, t_0 + \tau) &= \tau c_1 X_A X_B \\
&\vdots \\
P(X_A^0, X_B^0, t_0 + n\tau) &= \dots
\end{aligned} \tag{100}$$

We can use marginal probabilities to solve this problem. In fact

$$\begin{aligned}
P(X_A, t + \tau) &= \sum_{X_B=0}^{N_B} P(X_A, X_B, t + \tau), \\
&= \sum_{X_B=0}^{N_B} \left[P(X_A, X_B, t) + \tau \frac{\partial P(X_A, X_B, t)}{\partial t} \right], \\
&= \sum_{X_B=0}^{N_B} \left[P(X_A, X_B, t) + \right. \\
&\quad \tau w_1(X_A + 1, X_B + 1) P(X_A + 1, X_B + 1, t) - \\
&\quad \left. \tau w_1(X_A, X_B) P(X_A, X_B, t) \right],
\end{aligned} \tag{101}$$

where $P(X_A, X_B \geq N_B, t) = 0$. The marginal probability takes into account the combinatory between X_A, X_B . That enables computing directly the probability of $P(X_A, t + \tau)$, for any X_A regardless X_B .

Implementing this formula will need a good numerical management of all the $P(X_A, X_B, t)$ to optimized the computation time. Equation

$$\begin{aligned}
P(X_A, X_B, t) &= P(X_A + 1, X_B + 1, t - \tau) \cdot w_1(X_A + 1, X_B + 1) \tau \\
&\quad + P(X_A, X_B, t - \tau) \cdot [1 - w_1(X_A, X_B) \tau]
\end{aligned} \tag{102}$$

which is an equivalent form of the master equation enables computing $P(X_A, X_B, t)$ and so $\frac{\partial P(X_A, X_B, t)}{\partial t}$. This equation use previous values of $P(X_A, X_B, t - \tau)$ computed at time $t - \tau$.

5.2 Fokker-Planck Equation

1-variable

$$\frac{\partial P(x, t)}{\partial t} = P(x - \mu, t)w(x - \mu) - P(x, t)w(x) \quad (103)$$

$\mu \ll x \Rightarrow$ Taylor:

$$\begin{aligned} P(x - \mu, t) &= P(x, t) + \mu \frac{\partial}{\partial x} P(x, t) + \frac{1}{2} \mu^2 \frac{\partial^2}{\partial x^2} P(x, t) \\ w(x - \mu) &= w(x) + \mu \frac{\partial}{\partial x} w(x) + \frac{1}{2} \mu^2 \frac{\partial^2}{\partial x^2} w(x) \end{aligned} \quad (104)$$

$$\begin{aligned} \frac{\partial P(x, t)}{\partial t} &= \left[P(x, t) + \mu \frac{\partial}{\partial x} P(x, t) + \frac{1}{2} \mu^2 \frac{\partial^2}{\partial x^2} P(x, t) \right] \left[\mu \frac{\partial}{\partial x} w(x) + \frac{1}{2} \mu^2 \frac{\partial^2}{\partial x^2} w(x) \right] - P(x, t)w(x) \\ &= P(x, t) \mu \frac{\partial}{\partial x} w(x) + \mu \frac{\partial}{\partial x} P(x, t) w(x) + P(x, t) \frac{1}{2} \mu^2 \frac{\partial^2}{\partial x^2} w(x) \\ &\quad + w(x) \frac{1}{2} \mu^2 \frac{\partial^2}{\partial x^2} P(x, t) + \mu^2 \frac{\partial}{\partial x} P(x, t) \frac{\partial}{\partial x} w(x) + O(\mu^3) \\ &= \mu \frac{\partial}{\partial x} (w(x) P(x, t)) + \frac{1}{2} \mu^2 \frac{\partial^2}{\partial x^2} (w(x) P(x, t)) \end{aligned} \quad (105)$$

N-variable

$$\frac{\partial P(\mathbf{X}, t)}{\partial t} = \sum_{r=1}^R [w_r(\mathbf{X} - \boldsymbol{\eta}_r) P(\mathbf{X} - \boldsymbol{\eta}_r, t) - w_r(\mathbf{X}) P(\mathbf{X}, t)] \quad (106)$$

Taylor

$$f(x) = f(x_0) + (x - x_0) f'(x_0) + \frac{(x - x_0)^2}{2!} f''(x_0) + \dots + \frac{(x - x_0)^n}{n!} f^{(n)}(x_0) + O((x - x_0)^{n+1}) \quad (107)$$

If $x = x_0 + \epsilon$

$$f(x_0 + \epsilon) = f(x_0) + \epsilon f'(x_0) + \frac{\epsilon^2}{2!} f''(x_0) + \dots + \frac{\epsilon^n}{n!} f^{(n)}(x_0) + O((x - x_0)^{n+1}) \quad (108)$$

Here, if we assume $\boldsymbol{\eta}_r \ll \mathbf{X}$,

$$\begin{aligned} w_r(\mathbf{X} - \boldsymbol{\eta}_r) &= w_r(\mathbf{X}) - \boldsymbol{\eta}_r \frac{\partial}{\partial \mathbf{X}} w_r(\mathbf{X}) + \frac{\boldsymbol{\eta}_r^2}{2} \frac{\partial^2}{\partial^2 \mathbf{X}} w_r(\mathbf{X}) + \dots \\ &\approx w_r(\mathbf{X}) - \boldsymbol{\eta}_r \frac{\partial}{\partial \mathbf{X}} w_r(\mathbf{X}) \end{aligned} \quad (109)$$

$$P(\mathbf{X} - \boldsymbol{\eta}_r, t) = P(\mathbf{X}, t) - \boldsymbol{\eta}_r \frac{\partial}{\partial \mathbf{X}} P(\mathbf{X}, t) + \frac{\boldsymbol{\eta}_r^2}{2} \frac{\partial^2}{\partial^2 \mathbf{X}} w_r(\mathbf{X}) + \dots \quad (110)$$

$$\approx P(\mathbf{X}, t) - \boldsymbol{\eta}_r \frac{\partial}{\partial \mathbf{X}} P(\mathbf{X}, t) \quad (111)$$

Thus

$$\frac{\partial P(\mathbf{X}, t)}{\partial t} = \sum_{r=1}^R \left[\left(w_r(\mathbf{X}) - \boldsymbol{\eta}_r \frac{\partial}{\partial \mathbf{X}} w_r(\mathbf{X}) \right) \left(P(\mathbf{X}, t) - \boldsymbol{\eta}_r \frac{\partial}{\partial \mathbf{X}} P(\mathbf{X}, t) \right) - w_r(\mathbf{X}) P(\mathbf{X}, t) \right] \quad (112)$$

$$\begin{aligned} \frac{\partial P(\mathbf{X}, t)}{\partial t} = \sum_{r=1}^R \left[-\boldsymbol{\eta}_r w_r(\mathbf{X}) \frac{\partial}{\partial \mathbf{X}} P(\mathbf{X}, t) - \boldsymbol{\eta}_r P(\mathbf{X}, t) \frac{\partial}{\partial \mathbf{X}} w_r(\mathbf{X}) \right. \\ \left. + \boldsymbol{\eta}_r \boldsymbol{\eta}_r^T \left(\frac{\partial}{\partial \mathbf{X}} w_r(\mathbf{X}) \right)^T \left(\frac{\partial}{\partial \mathbf{X}} P(\mathbf{X}, t) \right) \right] \end{aligned} \quad (113)$$

$$\frac{\partial P(\mathbf{X}, t)}{\partial t} = \sum_{r=1}^R \left[-\frac{\partial}{\partial \mathbf{X}} (\boldsymbol{\eta}_r w_r(\mathbf{X}) P(\mathbf{X}, t)) + \boldsymbol{\eta}_r \boldsymbol{\eta}_r^T \left(\frac{\partial}{\partial \mathbf{X}} w_r(\mathbf{X}) \right)^T \left(\frac{\partial}{\partial \mathbf{X}} P(\mathbf{X}, t) \right) \right] \quad (114)$$

$$\frac{\partial P(\mathbf{X}, t)}{\partial t} = \sum_{r=1}^R \left[-\frac{\partial}{\partial \mathbf{X}} (\boldsymbol{\eta}_r w_r(\mathbf{X}) P(\mathbf{X}, t)) + \boldsymbol{\eta}_r \boldsymbol{\eta}_r^T \sum_{i,j} \frac{\partial^2}{\partial \mathbf{X}_i \partial \mathbf{X}_j} (w_r(\mathbf{X}) P(\mathbf{X}, t)) \right] \quad (115)$$

$$\frac{\partial P(\mathbf{X}, t)}{\partial t} = \sum_{r=1}^R \left[-\sum_i \frac{\partial}{\partial \mathbf{X}_i} (\boldsymbol{\eta}_r w_r(\mathbf{X}) P(\mathbf{X}, t)) + \boldsymbol{\eta}_r \boldsymbol{\eta}_r^T \sum_{i,j} \frac{\partial^2}{\partial \mathbf{X}_i \partial \mathbf{X}_j} (w_r(\mathbf{X}) P(\mathbf{X}, t)) \right] \quad (116)$$

$$\frac{\partial P(\mathbf{X}, t)}{\partial t} = -\sum_i \frac{\partial}{\partial \mathbf{X}_i} \left[\left(\sum_{r=1}^R \boldsymbol{\eta}_r w_r(\mathbf{X}) \right) P(\mathbf{X}, t) \right] + \sum_{i,j} \frac{\partial^2}{\partial \mathbf{X}_i \partial \mathbf{X}_j} \left[\left(\sum_{r=1}^R \boldsymbol{\eta}_r \boldsymbol{\eta}_r^T w_r(\mathbf{X}) \right) P(\mathbf{X}, t) \right] \quad (117)$$

Fokker-Planck:

$$\frac{\partial P(\mathbf{X}, t)}{\partial t} = -\sum_i \frac{\partial}{\partial \mathbf{X}_i} \left[F(\mathbf{X}) P(\mathbf{X}, t) \right] + \sum_{i,j} \frac{\partial^2}{\partial \mathbf{X}_i \partial \mathbf{X}_j} \left[G(\mathbf{X}) P(\mathbf{X}, t) \right] \quad (118)$$

with

$$\begin{aligned} F &= \left(\sum_{r=1}^R \boldsymbol{\eta}_r w_r(\mathbf{X}) \right) \\ G &= \left(\sum_{r=1}^R \boldsymbol{\eta}_r \boldsymbol{\eta}_r^T w_r(\mathbf{X}) \right) \end{aligned} \quad (119)$$

5.3 Gillespie algorithm: Time to the next reaction

Given the state (X_1, \dots, X_N) at time t , let denote by $P(\tau, \mu)d\tau$ the probability to that the next reaction will occur in the time interval $[t + \tau, t + \tau + d\tau]$ and will be a R_μ reaction. $P(\tau, \mu)d\tau$ is thus the probability that

- no reaction will occur during $[t, t + \tau]$ and
- R_μ will occur in the interval $[t + \tau, t + \tau + d\tau]$.

The probability that R_μ will occur in the interval $[t + \tau, t + \tau + d\tau]$ is equal to

$$P(R_\mu, [t + \tau, t + \tau + d\tau]) = w_\mu d\tau \quad (120)$$

Denote by $P_0(\tau)$ the probability that no reaction will occur during $[t, t + \tau]$. Then

$$P_0(\tau' + d\tau') = P_0(\tau')(1 - C_R d\tau') \quad (121)$$

with $C_R = \sum_r w_r$. Indeed the probability to have no reaction in $[t, t + \tau' + d\tau']$ is equal to the probability to have no reaction in $[t, t + \tau']$ ($= P_0(\tau')$) multiplied by the probability to have no reaction in $[t + \tau', t + \tau' + d\tau']$. ($= 1 - C_R d\tau'$). Notice that $C_R d\tau'$ is the probability to have one reaction in a time interval $[t + \tau', t + \tau' + d\tau']$. Therefore,

$$\begin{aligned} \frac{P_0(\tau' + d\tau') - P_0(\tau')}{d\tau'} &= -C_R P_0(\tau'), \\ \Rightarrow P_0(\tau') &= \exp(-C_R \tau'), \quad \text{when } d\tau' \rightarrow 0. \end{aligned}$$

We deduce that

$$P(\tau, \mu)d\tau = P_0(\tau) \cdot P(R_\mu, [t + \tau, t + \tau + d\tau])d\tau, \quad (122)$$

$$= w_\mu \exp(-C_R \tau)d\tau. \quad (123)$$

Finally

$$P(\tau, \mu) = w_\mu \exp(-C_R \tau). \quad (124)$$

Thus the time till the next reaction takes place is distributed according to:

$$P(\tau) = C_R \exp(-C_R \tau). \quad (125)$$

5.4 Generating random numbers according to a given distribution

The probability to have the next reaction after time τ is given by Eq. (48):

$$P(\tau) = C_R \exp(-C_R \tau) \quad (126)$$

When implementing the Gillespie algorithm we need to generate τ in such a way that the τ distribution follows Eq. (126). However most programs - like matlab - have built-in functions to generate random number from a uniform distribution between 0 and 1. We present here the *inversion method* which allows to construct random numbers according to “any” prescribed probability density function (see also Appendix of Gillespie, 1976 [37]).

Let's define

$$\begin{aligned} P(x) &= \text{probability density function} \\ P(s)ds &= \text{probability that } s \text{ lies between } s \text{ and } s + ds \end{aligned} \quad (127)$$

Consider the following function (called the probability distribution function):

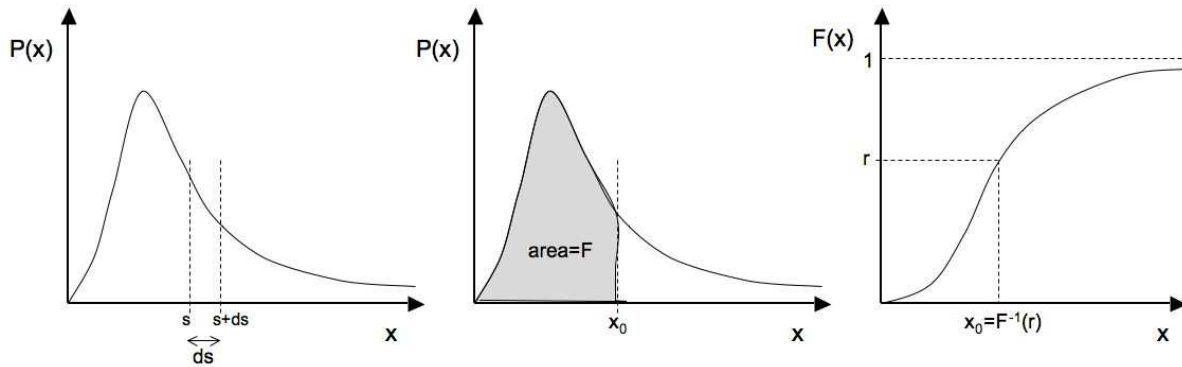
$$F(x) = \int_{-\infty}^x P(s)ds \quad (128)$$

Thus $F(x_0)$ is the probability that $x < x_0$

Notice that

$$\begin{aligned} F(-\infty) &= 0 \\ F(+\infty) &= 1 \end{aligned} \quad (129)$$

The inversion method for generating a random value x according to a given density function $P(x)$ consists of drawing a random number r from the uniform distribution in the unit interval and take for x the value that satisfy $F(x) = r$, i.e. $x = F^{-1}(r)$ where F^{-1} is the inverse of the distribution function corresponding to a given density function.



Let's apply this to our probability density function (126):

$$\begin{aligned} P(x) &= A \exp(-Ax) \text{ for } 0 \leq x \leq \infty \\ &= 0 \quad \text{otherwise} \end{aligned} \quad (130)$$

where A is positive constant ($=C_R$ in the Gillespie algorithm).

The corresponding probability distribution function is:

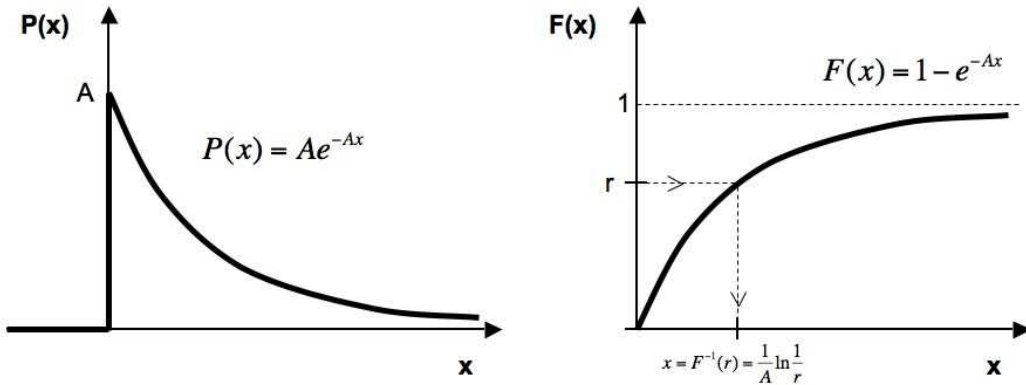
$$\begin{aligned} F(x) &= \int_{-\infty}^x P(s) ds \\ &= \int_{-\infty}^0 P(s) ds + \int_0^x P(s) ds \\ &= \int_0^x A \exp(-As) ds \\ &= A \left[-\frac{1}{A} \exp(-As) \right]_0^x \\ &= A \left[-\frac{1}{A} \exp(-Ax) + \frac{1}{A} \right] \\ &= 1 - \exp(-Ax) \end{aligned} \quad (131)$$

Let's now assume that we generate a random value r , statistically equivalent to $1 - r$

$$F(x) = r \equiv 1 - r \quad (132)$$

Then

$$\begin{aligned} 1 - r &= 1 - \exp(-Ax) \\ r &= \exp(-Ax) \\ -Ax &= \ln(r) \\ x &= -\frac{1}{A} \ln r \\ x &= \frac{1}{A} \ln \frac{1}{r} \end{aligned} \quad (133)$$



5.5 Chemical Langevin Equation

Tau-leap approximation

The Chemical Langevin Equation was derived by Gillespie (2001) from the *tau-leap* approximation. In this method, the system is “advanced” by a pre-selected time step τ during which several reactions take place. In practice, τ should be sufficiently small to ensure that the propensity functions do not change significantly (“ τ -leap” condition).

Let’s define the Poisson random variable $\mathcal{P}(w, \tau)$ as the number of reactions that will occur in time τ given that $w dt$ is the probability that a reaction will occur in any infinitesimal time dt . Then, under the τ -leap condition, the system can be “advanced” by:

$$\mathbf{X}(t + \tau) = \mathbf{X}(t) + \sum_{r=1}^R \boldsymbol{\eta}_r \mathcal{P}_r(w_r(\mathbf{X}(t)), \tau) \quad (134)$$

where \mathbf{X} is the vector of the number of molecule of each type, R the number of chemical reactions, $\boldsymbol{\eta}_r$ is the vector of stoichiometric coefficient of each compound in reaction r , w_r is the propensity of reaction r .

To simulate this system we thus need to generate, at each time step, R Poisson random numbers. The simulation will be much faster than the exact stochastic algorithm (SSA) if several reactions take place during τ . The choice of τ is thus critical. It needs to be sufficiently small to satisfy the τ -leaping condition but large enough to benefit with respect to SSA. This approximation is thus valid when the noise is not too large (i.e. when the number of molecules is relatively large).

From the tau-leap approximation to the Chemical Langevin Equation

Further approximations stem from the following mathematical property: The Poisson random variable $\mathcal{P}(w, \tau)$, which has a mean and variance $w\tau$ can be well approximated when $w\tau \gg 1$, by the Normal random variable with the same mean and variance. Denoting the Normal random variable with the mean μ and variance σ^2 as $\mathcal{N}_r(\mu, \sigma^2)$, we obtain:

$$\begin{aligned} \mathcal{P}_r(w_r(\mathbf{X}(t)), \tau) &= w_r(\mathbf{X}(t))\tau + \sqrt{w_r(\mathbf{X}(t))\tau} \mathcal{N}_r(0, 1) \\ &= \mathcal{N}_r(w_r(\mathbf{X}(t))\tau, w_r(\mathbf{X}(t))\tau) \end{aligned} \quad (135)$$

NB: The second line follows from the fact that:

$$\mathcal{N}(\mu, \sigma^2) = \mu + \sigma \mathcal{N}(0, 1) \quad (136)$$

Inserting Eq. (135) in Eq. (134) gives:

$$\begin{aligned} \mathbf{X}(t + \tau) &= \mathbf{X}(t) + \sum_{r=1}^R \boldsymbol{\eta}_r w_r(\mathbf{X}(t))\tau + \sum_{r=1}^R \boldsymbol{\eta}_r \sqrt{w_r(\mathbf{X}(t))\tau} \mathcal{N}_r(0, 1) \\ &= \mathbf{X}(t) + \tau \sum_{r=1}^R \boldsymbol{\eta}_r w_r(\mathbf{X}(t)) + \sqrt{\tau} \sum_{r=1}^R \boldsymbol{\eta}_r \sqrt{w_r(\mathbf{X}(t))} \mathcal{N}_r(0, 1) \end{aligned} \quad (137)$$

This equation is called the Langevin leaping formula (Gillespie, 2001). It expresses the state increment $\mathbf{X}(t + \tau) - \mathbf{X}(t)$ as the sum of two terms a deterministic *drift term*, proportional to τ , and a *fluctuating term*, proportional to $\sqrt{\tau}$.

Note that by replacing the integer-values Poisson random variable by a real-valued Normal random variable, we have converted the discrete system into a continuous one.

If we now subtract $\mathbf{X}(t)$ in both sides and take the limit $\tau \rightarrow 0$, we obtain the following stochastic equation:

$$\frac{d\mathbf{X}}{dt} = \sum_{r=1}^R \boldsymbol{\eta}_r w_r(\mathbf{X}(t)) + \sum_{r=1}^R \boldsymbol{\eta}_r \sqrt{w_r(\mathbf{X}(t))} \Gamma_r(t) \quad (138)$$

where Γ_r is a Gaussian white noise:

$$\Gamma_r(t) = \delta_{rr'} \delta(t - t') \quad (139)$$

where the first δ function is the Kronecker's and the second is Dirac's.

This is the **Chemical Langevin Equation** (sometimes referred to as CLE).

The standard way to solve Eq. (138) is to use the recurrence (137) for sufficiently small τ .

5.6 Brusselator: MATLAB code (Gillespie simulation)

```
omega=100;      % system size
a=2;b=6;       % model parameters
x=1; y=1;      % initial conditions:
trans=0; tend=100; tech=0.01; % time

t=0; told=0;    % initilisation
results=[];

while (t<tend+trans)    % run simulation

    w(1)=a*omega;
    w(2)=b*x;
    w(3)=x;
    w(4)=x*(x-1)*y/omega^2;

    c(1)=w(1);
    for j=2:4;
        c(j)=c(j-1)+w(j);
    end
    ct=c(4);

    z1=rand();
    z2=rand();

    tau=(-log(z1))/ct;
    uct=z2*ct;
    t=t+tau;

    if (uct < c(1))
        x=x+1;
    elseif (uct < c(2))
        x=x-1;
        y=y+1;
    elseif (uct < c(3))
        x=x-1;
    elseif (uct < c(4))
        x=x+1;
        y=y-1;
    end

    if (t>trans) && (t>told+tech)
        results=[results ; t x y];
        told=t;
    end

end

figure(1) % plot time serie
plot(results(:,1),results(:,2),'b',results(:,1),results(:,3),'r');
xlabel('Time')
ylabel('X (blue), Y (red)')
```

References

- [1] Acar M, Becskei A, van Oudenaarden A. (2005) Enhancement of cellular memory by reducing stochastic transitions. *Nature*. 435:228-232.
- [2] Adalsteinsson D, McMillen D, Elston TC. (2004) Biochemical Network Stochastic Simulator (BioNetS): software for stochastic modeling of biochemical networks. *BMC Bioinformatics*. 8:5-24.
- [3] Alon U, Surette MG, Barkai N, Leibler S. (1999) Robustness in bacterial chemotaxis. *Nature*. 397:168-171.
- [4] Andrews SS, Arkin AP. (2006) Simulating cell biology. *Curr Biol*. 16:R523-7.
- [5] Andrews SS, Bray D. (2004) Stochastic simulation of chemical reactions with spatial resolution and single molecule detail. *Phys Biol*. 1:137-51.
- [6] Andrews SS, Dinh T, Arkin AP (2009) Stochastic Models of Biological Processes, *Encyclopedia of Complexity and Systems Science* 2009:8730-8749.
- [7] Andrianantoandro E, Basu S, Karig DK, Weiss R. (2006) Synthetic biology: new engineering rules for an emerging discipline. *Mol Syst Biol* 2:0028.
- [8] Arkin A, Ross J, McAdams HH (1998) Stochastic kinetic analysis of developmental pathway bifurcation in phage lambda-infected Escherichia coli cells, *Genetics* 149:1633-1648.
- [9] Barkai N, Leibler S. (1997) Robustness in simple biochemical networks. *Nature* 387:913-917.
- [10] Barkai N, Leibler S. (2000) Circadian clocks limited by noise. *Nature* 403:267-8.
- [11] Barrio M, Burrage K, Leier A, Tian T. (2006) Oscillatory regulation of Hes1: Discrete stochastic delay modelling and simulation. *PLoS Comput Biol*. 2:e117.
- [12] Basu S, Gerchman Y, Collins CH, Arnold FH, Weiss R. (2005) A synthetic multicellular system for programmed pattern formation. *Nature*. 434:1130-1134.
- [13] Becskei A, Seraphin B, Serrano L. (2001) Positive feedback in eukaryotic gene networks: cell differentiation by graded to binary response conversion. *EMBO J*. 20:2528-2535.
- [14] Becskei A, Serrano L. (2000) Engineering stability in gene networks by autoregulation. *Nature*. 405:590-593.
- [15] Benner SA, Sismour AM. (2005) Synthetic biology. *Nat Rev Genet*. 6:533-543.
- [16] Bratsun D, Volfson D, Tsimring LS, Hasty J. (2005) Delay-induced stochastic oscillations in gene regulation. *Proc Natl Acad Sci USA* 102:14593-8.
- [17] Bundschuh R, Hayot F, Jayaprakash C. (2003) Fluctuations and slow variables in genetic networks. *Biophys J*. 84:1606-15.
- [18] Burrage K, Burrage PM, Leier A, Marquez-Lago T, Nicolau DV (2011) Chapter 2: Stochastic Simulation for Spatial Modelling of Dynamic Processes in a Living Cell, H. Koepl et al. (eds.), Design and Analysis of Biomolecular Circuits: Engineering Approaches to Systems and Synthetic Biology, DOI 10.1007/978-1-4419-6766-4, Springer.

- [19] Blake WJ, Kaern M, Cantor CR, Collins JJ. (2003) Noise in eukaryotic gene expression. *Nature*. 422:633-637.
- [20] Chalancon G, Ravarani CN, Balaji S, Martinez-Arias A, Aravind L, Jothi R, Babu MM (2012) Interplay between gene expression noise and regulatory network architecture. *Trends Genet* 28:221-32.
- [21] Chen L, Wang R, Zhou T, Aihara K. (2005) Noise-induced cooperative behavior in a multicell system. *Bioinformatics*. 21:2722-2729.
- [22] Dar RD, Razooky BS, Singh A, Trimeloni TV, McCollum JM, Cox CD, Simpson ML, Weinberger LS (2012) Transcriptional burst frequency and burst size are equally modulated across the human genome. *Proc Natl Acad Sci USA* 109:17454-9.
- [23] Delbruck M (1940) Statistical Fluctuations in Autocatalytic Reactions, *J. Chem. Phys.* 8:120.
- [24] Delbruck M (1945) The burst size distribution in the growth of bacterial viruses, *J. Bacteriol.* 50:131-135.
- [25] Di Ventura B, Lemerle C, Michalodimitrakis K, Serrano L. (2006) From in vivo to in silico biology and back. *Nature*. 443:527-533.
- [26] Eldar A, Elowitz MB (2010) Functional roles for noise in genetic circuits. *Nature*. 467:167-73.
- [27] Elf J, Ehrenberg M. (2004) Spontaneous separation of bi-stable biochemical systems into spatial domains of opposite phases. *Syst Biol* 1:230-6.
- [28] Elowitz MB, Leibler S. (2000) A synthetic oscillatory network of transcriptional regulators. *Nature*. 403:335-338.
- [29] Elowitz MB, Levine AJ, Siggia ED, Swain PS. (2002) Stochastic gene expression in a single cell. *Science*. 297:1183-1186.
- [30] Endy D. (2005) Foundations for engineering biology. *Nature*. 438:449-453.
- [31] Fung E, Wong WW, Suen JK, Bulter T, Lee SG, Liao JC. (2005) A synthetic gene-metabolic oscillator. *Nature*. 435:118-122.
- [32] Gardiner C (1996) Handbook of stochastic methods: For physics, chemistry and the natural sciences, Springer Verlag, Berlin.
- [33] Gammaitoni L, Hanggi P, Jung P, Marchesoni F (1998) Stochastic resonance, *Rev. Mod. Phys.* 70:223-287.
- [34] Gardner TS, Cantor CR, Collins JJ. (2000) Construction of a genetic toggle switch in *Escherichia coli*. *Nature*. 403:339-342.
- [35] Gardner TS, Collins JJ. (2000) Neutralizing noise in gene networks. *Nature*. 405:520-521.
- [36] Gaspard P. (2002) The correlation time of mesoscopic chemical clocks. *J. Chem. Phys.* 117:8905-8916.

- [37] Gillespie, Daniel T. (1976) A General Method for Numerically Simulating the Stochastic Time Evolution of Coupled Chemical Reactions. *J Comput Phys* 22:403-434.
- [38] Gillespie DT (1977) Exact stochastic simulation of coupled chemical reactions, *J. Phys. Chem.* 81:2340-2361.
- [39] Gillespie DT (1992) A rigorous derivation of the chemical master equation, *Physica A.* 188:404-425.
- [40] Gillespie DT (2001) Approximate accelerated stochastic simulation of chemically reacting systems. *J. Chem. Phys.* 115:1716-1733.
- [41] Gillespie DT (2002) The Chemical Langevin and Fokker-Planck Equations for the Reversible Isomerization Reaction *J. Phys. Chem A* 106 :5063-5071.
- [42] Gillespie DT (2007) Stochastic simulation of chemical kinetics. *Annu Rev Phys Chem.* 58:35-55.
- [43] Gillespie DT, Hellander A, Petzold LR (2013) Perspective: Stochastic algorithms for chemical kinetics. *J Chem Phys.* 138:170901.
- [44] Gibson MA, Bruck J (2000) Efficient exact stochastic simulation of chemical systems with many species and many channels. *J Chem Phys.* 104: 1876-1889.
- [45] Guet CC, Elowitz MB, Hsing W, Leibler S. (2002) Combinatorial synthesis of genetic networks. *Science.* 296:1466-70.
- [46] Guido NJ, Wang X, Adalsteinsson D, McMillen D, Hasty J, Cantor CR, Elston TC, Collins JJ. (2006) A bottom-up approach to gene regulation. *Nature.* 439:856-860.
- [47] Gunawan R, Cao Y, Petzold L, Doyle FJ (2005) Sensitivity analysis of discrete stochastic systems. *Biophys J.* 88:2530-40
- [48] Haseltine EL, Rawlings JB (2002) Approximate simulation of coupled fast and slow reactions for stochastic chemical kinetics. *J Chem Phys* 117:6959-6969.
- [49] Hasty J, Pradines J, Dolnik M, Collins JJ (2000) Noise-based switches and amplifiers for gene expression, *Proc. Natl. Acad. Sci. USA.* 97:2075-2080.
- [50] Hasty J, Isaacs F, Dolnik M, McMillen D, Collins JJ. (2001) Designer gene networks: Towards fundamental cellular control. *Chaos.* 11:207-220.
- [51] Hanggi P. (2002) Stochastic resonance in biology. How noise can enhance detection of weak signals and help improve biological information processing. *Chemphyschem.* 3:285-290.
- [52] Hoops S, Sahle S, Gauges R, Lee C, Pahle J, Simus N, Singhal M, Xu L, Mendes P, Kummer U (2006). COPASI: a COMplex Pathway SIMulator. *Bioinformatics* 22:3067-74.
- [53] Hooshangi S, Thiberge S, Weiss R. (2005) Ultrasensitivity and noise propagation in a synthetic transcriptional cascade. *Proc Natl Acad Sci USA.* 102:3581-3586.
- [54] Hooshangi S, Weiss R (2006) The effect of negative feedback on noise propagation in transcriptional gene networks. *Chaos* 16:026108.

- [55] Hornung G, Barkai N (2008) Noise propagation and signaling sensitivity in biological networks: a role for positive feedback. *PLoS Comput Biol* 4:e8.
- [56] Isaacs FJ, Hasty J, Cantor CR, Collins JJ. (2003) Prediction and measurement of an autoregulatory genetic module. *Proc Natl Acad Sci USA*. 100:7714-7719
- [57] Kaufmann BB, van Oudenaarden A. (2007) Stochastic gene expression: from single molecules to the proteome. *Curr Opin Genet Dev*, in press.
- [58] Kaern M, Elston TC, Blake WJ, Collins JJ (2005) Stochasticity in gene expression: from theories to phenotypes, *Nat. Rev. Genet.* 6:451-464.
- [59] Kepler TB, Elston TC. (2001) Stochasticity in transcriptional regulation: origins, consequences, and mathematical representations. *Biophys J*. 81:3116-3136.
- [60] Kevin R. Sanft, Sheng Wu, Min Roh, Jin Fu, Rone Kwei Lim and Linda R. Petzold (2011). StochKit2: software for discrete stochastic simulation of biochemical systems with events. *Bioinformatics* 27:2457-2458.
- [61] Kitano H (2002) Systems biology: a brief overview. *Science*. 295: 1662-1664.
- [62] Kitano H (2004) Biological robustness. *Nat Rev Genet* 5: 826-837.
- [63] Kollmann M, Lovdok L, Bartholome K, Timmer J, Sourjik V. (2005) Design principles of a bacterial signalling network. *Nature* 438:504-507.
- [64] Kou SC, Cherayil BJ, Min W, English BP, Xie XS (2005) Single-molecule Michaelis-Menten equations. *J Phys Chem B*. 109:19068-81.
- [65] Kramer BP, Fussenegger M. (2005) Hysteresis in a synthetic mammalian gene network. *Proc Natl Acad Sci USA*. 102:9517-9522.
- [66] Le Novère N, Shimizu TS (2001) STOCHSIM: modelling of stochastic biomolecular processes. *Bioinformatics*. 17:575-576.
- [67] Lestas I, Vinnicombe G, Paulsson J (2010) Fundamental limits on the suppression of molecular fluctuations. *Nature* 467:174-8.
- [68] Lindner B, Garcia-Ojalvo J, Neiman A, Schimansky-Geier L (2004) Effects of noise in excitable systems, *Phys. Rep.* 392:321.
- [69] Longo D, Hasty J. (2006) Dynamics of single-cell gene expression. *Mol Syst Biol*. 2:64.
- [70] Lu HP, Xun L, Xie XS (1998) Single-molecule enzymatic dynamics. *Science* 282:1877-82.
- [71] Maarleveld TR, Olivier BG, Bruggeman FJ (2013) StochPy: A Comprehensive, User-Friendly Tool for Simulating Stochastic Biological Processes. *PLoS One* 8:e79345.
- [72] Maheshri N, O'shea EK (2007) Living with Noisy Genes: How Cells Function Reliably with Inherent Variability in Gene Expression. *Annu Rev Biophys Biomol Struct*. 36:413-434.
- [73] McMillen D, Kopell N. (2003) Noise-stabilized long-distance synchronization in populations of model neurons. *J Comput Neurosci*. 15:143-57.
- [74] McAdams HH, Arkin A (1997) Stochastic mechanisms in gene expression, *Proc. Natl. Acad. Sci. USA*. 94:814-819.

- [75] McDaniel R, Weiss R (2005) Advances in synthetic biology: on the path from prototypes to applications, *Curr. Opin. Biotechnol.* 16:476-483.
- [76] Meng TC, Somani S, Dhar P. (2004) Modeling and simulation of biological systems with stochasticity. *In Silico Biol.* 4:293-309.
- [77] Mettetal JT, Muzzey D, Pedraza JM, Ozbudak EM, van Oudenaarden A (2006) Predicting stochastic gene expression dynamics in single cells. *Proc Natl Acad Sci USA* 103:7304-7309.
- [78] Molina N, Suter DM, Cannavo R, Zoller B, Gotic I, Naef F (2013) Stimulus-induced modulation of transcriptional bursting in a single mammalian gene. *Proc Natl Acad Sci USA* 110:20563-8.
- [79] Morton-Firth CJ, Bray D. (1998) Predicting temporal fluctuations in an intracellular signaling pathway. *J. Theor. Biol.* 192:117-128.
- [80] Muratov CB, Vanden-Eijnden E, Weinan E (2005) Self-induced stochastic resonance in excitable systems. *Physica D* 210:227-240.
- [81] Nicolis G, Prigogine I (1977) *Self-Organization in Non-Equilibrium Systems*, Wiley.
- [82] Ozbudak EM, Thattai M, Lim HN, Shraiman BI, Van Oudenaarden A. (2004) Multistability in the lactose utilization network of *Escherichia coli*. *Nature.* 427:737-740.
- [83] Ozbudak EM, Thattai M, Kurtser I, Grossman AD, van Oudenaarden A. (2002) Regulation of noise in the expression of a single gene. *Nat Genet.* 31:69-73
- [84] Paulsson J, Berg OG, Ehrenberg M. (2000) Stochastic focusing: fluctuation-enhanced sensitivity of intracellular regulation. *Proc Natl Acad Sci USA.* 97: 7148-53.
- [85] Pedraza JM, van Oudenaarden A. (2005) Noise propagation in gene networks. *Science.* 307:1965-1969.
- [86] Qian H, Bishop LM (2010) The chemical master equation approach to nonequilibrium steady-state of open biochemical systems: linear single-molecule enzyme kinetics and non-linear biochemical reaction networks. *Int J Mol Sci.* 11:3472-500.
- [87] Qian H, Elson EL (2002) Single-molecule enzymology: stochastic Michaelis-Menten kinetics. *Biophys Chem.* 101-102:565-76
- [88] Ramsey S, Orrell D, Bolouri H. (2005) Dizzy: stochastic simulation of large-scale genetic regulatory networks. *J Bioinform Comput Biol.* 3:415-36.
- [89] Rao CV, Wolf DM, Arkin AP (2002) Control, exploitation and tolerance of intracellular noise, *Nature* 420:231-237.
- [90] Rao CV, Arkin AP (2003) Stochastic chemical kinetics and the quasi-steady-state assumption: Application to the Gillespie algorithm. *J. Chem. Phys.* 118:4999-5010.
- [91] Raser JM, O'Shea EK (2004) Control of stochasticity in eukaryotic gene expression, *Science* 304:1811-1814.
- [92] Raser JM, O'Shea EK (2005) Noise in gene expression: origins, consequences, and control, *Science* 309:2010-2013.

- [93] Reichl LE (1998) A modern course in statistical physics, Wiley
- [94] Ribeiro A, Zhu R, Kauffman SA. (2006) A general modeling strategy for gene regulatory networks with stochastic dynamics. *J Comput Biol.* 13:1630-9.
- [95] Rosenfeld N, Young JW, Alon U, Swain PS, Elowitz MB.(2005) Gene regulation at the single-cell level. *Science.* 307:1962-1965.
- [96] Roussel MR, Zhu R. (2006) Validation of an algorithm for delay stochastic simulation of transcription and translation in prokaryotic gene expression. *Phys Biol.* 3:274-84.
- [97] Russell DF, Wilkens LA, Moss F (1999) Use of behavioural stochastic resonance by paddle fish for feeding. *Nature* 402:291-294.
- [98] Samoilov M, Plyasunov S, Arkin AP. (2005) Stochastic amplification and signaling in enzymatic futile cycles through noise-induced bistability with oscillations. *Proc Natl Acad Sci USA.* 102:2310-2315.
- [99] Schwabe A, Dobrzynski M, Rybakova K, Verschure P, Bruggeman FJ (2011) Origins of stochastic intracellular processes and consequences for cell-to-cell variability and cellular survival strategies. *Methods Enzymol.* 500:597-625
- [100] Schwabe A, Maarleveld TR, Bruggeman FJ (2013) Exploration of the spontaneous fluctuating activity of single enzyme molecules. *FEBS Lett.* 587:2744-52.
- [101] Shimizu TS, Aksenov SV, Bray D. (2003) A spatially extended stochastic model of the bacterial chemotaxis signalling pathway. *J Mol Biol.* 329:291-309.
- [102] Sigal A, Milo R, Cohen A, Geva-Zatorsky N, Klein Y, Liron Y, Rosenfeld N, Danon T, Perzov N, Alon U. (2006) Variability and memory of protein levels in human cells. *Nature.* 444:643-646.
- [103] Simpson ML, Cox CD, Saylor GS. (2004) Frequency domain chemical Langevin analysis of stochasticity in gene transcriptional regulation. *J Theor Biol.* 229:383-394.
- [104] Simpson ML, Cox CD, Saylor GS. (2003) Frequency domain analysis of noise in autoregulated gene circuits. *Proc Natl Acad Sci USA* 100:4551-4556.
- [105] Sprinzak D, Elowitz MB. (2005) Reconstruction of genetic circuits. *Nature.* 438:443-448.
- [106] Spudich JS, and Koshland DE (1976) Non-genetic individuality: chance in the single cell. *Nature.* 262:467-471.
- [107] Steuer R. (2004) Effects of stochasticity in models of the cell cycle: from quantized cycle times to noise-induced oscillations. *J Theor Biol.* 228:293-301.
- [108] Suter DM, Molina N, Gatfield D, Schneider K, Schibler U, Naef F (2011) Mammalian genes are transcribed with widely different bursting kinetics. *Science* 332:472-4.
- [109] Suter DM, Molina N, Naef F, Schibler U (2011) Origins and consequences of transcriptional discontinuity. *Curr Opin Cell Biol* 23:657-62.
- [110] Swain PS, Elowitz MB, Siggia ED (2002) Intrinsic and extrinsic contributions to stochasticity in gene expression, *Proc. Natl. Acad. Sci. USA.* 99:12795-12800.

- [111] Swain PS (2004) Efficient attenuation of stochasticity in gene expression through post-transcriptional control, *J. Mol. Biol.* 344:965-976.
- [112] Swain PS, Longtin A. (2006) Noise in genetic and neural networks. *Chaos*. 16: 026101.
- [113] Thattai M, van Oudenaarden A. (2001) Intrinsic noise in gene regulatory networks. *Proc Natl Acad Sci USA*. 98: 8614-9.
- [114] Thomas P, Matuschek H, Grima R (2013) How reliable is the linear noise approximation of gene regulatory networks? *BMC Genomics* 14 Suppl 4:S5.
- [115] Tsimring LS, Volfson D, Hasty J. (2006) Stochastically driven genetic circuits. *Chaos* 16:026103.
- [116] Turner TE, Schnell S, Burrage K. (2004) Stochastic approaches for modelling *in vivo* reactions. *Comput Biol Chem*. 28:165-178.
- [117] Tyson JJ, Chen K, Novak B (2001) Network dynamics and cell physiology. *Nat Rev Mol Cell Biol*. 2:908-16.
- [118] Ullah M, Schmidt H, Cho KH, Wolkenhauer O. (2006) Deterministic modelling and stochastic simulation of biochemical pathways using MATLAB. *Syst. Biol.* 153:53-60.
- [119] Ullner E, Zaikin A, Garcia-Ojalvo J, Kurths J. (2003) Noise-induced excitability in oscillatory media. *Phys Rev Lett*. 91:180601.
- [120] van Kampen NG (1990) *Stochastic Processes in Physics and Chemistry* Elsevier, New York.
- [121] Vilar JM, Kueh HY, Barkai N, Leibler S. (2002) Mechanisms of noise-resistance in genetic oscillators. *Proc Natl Acad Sci USA*. 99:5988-5992.
- [122] Volfson D, Marciniak J, Blake WJ, Ostroff N, Tsimring LS, Hasty J. (2006) Origins of extrinsic variability in eukaryotic gene expression. *Nature* 439:861-4.
- [123] Weiss R, Basu S, Hooshangi, Kalmbach A, Karig D, Mehreja R, Netravali I (2003) Genetic circuit building blocks for cellular computation, communications, and signal processing *Natural Computing* 2:47-84.
- [124] Zhou T, Chen L, Aihara K. (2005) Molecular communication through stochastic synchronization induced by extracellular fluctuations. *Phys Rev Lett*. 95: 178103.