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ORIGINAL ARTICLE

Noise effect and parameter estimation in excitable dynamic media

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Abstract

Stochasticity in gene expression arises from fluctuations in transcription and translation. This phenomenon has implications for cellular regulation. The novel techniques for single-cell analysis have provided new experimental and theoretical investigations. As a result, a coherent picture of stochasticity in prokaryotic and eukaryotic gene expression has been obtained. In this paper, we analyze the behavior of a stochastic process applied to Brusselator, investigating the noise affecting this system. Once the noise has been retrieved, the maximum likelihood estimation may be used to retrieve the parameters of the system itself. Although these techniques have been applied to simple reaction processes as those hypothesized with Brusselator, the methodology is general and can be used to any reaction and related linear and nonlinear ODEs.

Keywords: noise, stochasticity, cell behavior, kinetics reaction

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1. Introduction

Genetically identical cells can show phenotypic variability caused by stochastic events due to randomness process in gene expression. Then the control of biological random noise, that from now on we call only noise {see Bravi and Longo 2015 for a discussion on the term of noise in biology), is crucial to understand the behavior of the cell. Since 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 is expected to be affected by the noise. Noise can have various effects on the dynamics of the system: it can induce fluctuations (i.e., imprecision) in its behavior and often can be destructive. Because cell viability depends on precise regulation of key events, signal noise has been thought to impose a threat that cells must eliminate, or, at least, minimize. This noise-induced variability in the cells is responsible for population heterogeneity (Belousov 1959,1985) phenotypic variations (Spudich et al. 1976) or imprecision in biological clocks (Barkai et al. 2000). On the other hand, cells can take advantage of the constructive effect of noise itself. 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 (Samoilov et al. 2005) noise-induced synchronization (Steurer et al. 2004), noise-induced excitability (Ellner et al. 2003) or noise-induced bistability (Samoilov et al. 2005). All these properties are revealed by the noise and are in principle, not observed in a deterministic formulation. However, to display this 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.

Alan Turing, in 1952, was the first that hypothesized, under certain conditions, the influence of a perturbation on a system realizing spatially inhomogeneous structure may be formed in a self-organized way. His paradox was supported by showing the equilibrium solution of a stable reaction system could begin unstable when diffusion terms, which have a smoothing effect on spatial heterogeneity, are added. As a consequence, the system exhibited spatially inhomogeneous structures. His mathematical theory was published in his seminal paper the "The Chemical Basis of Morphogenesis". He based his work on the morphogenesis, which means the formation of the body's shape, seeking for an understanding of how cells in embryos, before dividing, "feels" in which direction the differentiation will follow and what procedures determine the shaping of different organs in an organism. It was straightforward: when a cell undergoes a change in shape its symmetry is broken, and this process must be governed by some substances, creating a new branch.

2. Turing morphogenesis and subsequent works

Turing proposed this substance be represented by a chemical, which he called a morphogen regulating cell differentiation. The source of the morphogens and the position of cells trigger genes in a slightly different manner. Since every chemical reaction is a local process and cannot alone describe spatial patterning, Turing suggested chemical substances, traveling randomly by impact of thermal effects (Brownian motion), influenced the non-local reaction process. Furthermore, to gain a complete understanding of the procedure, he also pointed out that morphogenesis consisted of both a chemical and a mechanical part. This last would describe the physical properties of the motions and forces acting in and between cells even though he noted that introducing the mechanical part produced complexities which were hard to treat and for that reason he omitted in his equations. Turing was revolutionary in putting morphogens as a central concept in developmental biology.

At the same time, Belousov 1985 and Zhabotinsky 1985 (from now named as B-Z) discovered that a series of complicated reactions in systems driven by chemical substances, due to non-equilibrium thermodynamics, resulting in the establishment of a nonlinear chemical oscillator, gave rise patterns. The basic chemistry of the B-Z oscillations involves jumps between high and low states, which is in the relaxation oscillator nature of the Oregonator (Field et al. 1985) that is the simplest realistic model of the chemical dynamics of the oscillatory Belousov-Zhabotinsky reaction. Another model that exhibits patterns is the Brusselator model that was proposed by I. Prigogine and his collaborators at the Free University of Brussels as a theoretical model for a type of autocatalytic reaction. The system of the ordinary differential equation is in (Hairer et al. 1987, p. 112; Zwillinger 1997, p. 136).

Other models, cell-based mechanisms, generate periodic patterns by cell-cell interactions, for example, in zebrafish pigment cell patterning (Nakamasu et al. 2009). Mechanical behavior also produces regular patterns due to mechanical instabilities depending on the material properties (Milinkovitch et al. 2013). The logic of those models is similar, but the biology is different. For example, a reaction-diffusion model uses a short-ranged activator and a long-range inhibitor to generate a periodic pattern, while a mechanical model consists of short-ranged mechanical interactions, as resistance to bending, and a long-ranged mechanical interaction, as compression of the tissue. At the same time, it can be challenging to distinguish them experimentally. Furthermore, to understand the general properties of periodic patterns, it is necessary to consider the combinations between a variety of mode as spanning molecular, cellular and or mechanical processes and the pattern orientation due to boundary conditions. However, the most straightforward logic is based on local activation and long-range inhibition (LALI) (Meinhardt 1972) that requires a simple assumption about the patterning mechanism and different coefficients between spot patterns or stripes. Hiscock and Megason 2015, propose that a deterministic mathematical approach can help to guide the design of experiments that can distinguish between different mechanisms, and illustrate the potential value of this approach with specific biological examples.

Another important chapter of modelling cellular network is the occurrence of intrinsic and extrinsic stochastic or random events and noise and their impact on biological system because gene transcription, gene regulation, and signal transduction often occur in low copy numbers. As examples of intrinsic stochastic events and noise example, among the others we may cite the work by Ozbudak et al. 2002, that observed gene expression

as transcription and translation in individual cells had a stochastic nature. Elowitz et al. (2000) constructed strains of Esterichia cole for detecting noise and discriminating between the intrinsic and extrinsic noise. Other studies showed that the messenger RNA production is an entity quantized (Hume, 2000) and is produced in random pulses (Ross et al., 1994). Protein production occurs in short "bursts" at random time intervals rather than in a continuous manner (Yarchuk et al., 1992). Same initial conditions, such as concentrations of chemical species, temperature, pressure, etc., may produce qualitatively different outcomes in the temporal evolution of a regulatory network. A classic example is the lysis/lysogenic switch of bacteriophage λ infecting *Escherichia coli*. Due to noise, the network may randomly evolve into one of the two bi-stable states (Hasty and Issacs 2001). The role of the noise has also been seen in bacterial chemotaxis (Morton-Firth and Bray 1998), and cellular selection (Till et al., 1964). Besides the intrinsic noise, there also exists an extrinsic component of noise arising from random fluctuations in other factors, e. g. for instance the number of ribosomes, the stage of the cell cycle, mRNA degradation, and the cellular environment. These are due to external environmental conditions. For example, a transcription factor for a particular gene is mostly the protein product of another gene, and thus its production is also probabilistic. In these situations, a protein product arising out of a stochastic activation of a gene leads to a cascade of downstream stochastic events. The timings of such triggers can result in vastly different outcomes (McAdams and Arkin, 1997, 1998). Of course, the biological system may have both intrinsic stochasticity and noise either extrinsic or both. Since, in general, cellular pathways exhibit nonlinear behaviour due to the complex underlying mechanisms of interactions, the networks often exhibit multiple stable states and bifurcations. As a result, the stochastic effects may drive the system randomly into distinct pathways. Noise may also be constructive in helping a cell to respond in totally different ways depending upon external signals, for example, reproducing phenotypic diversity. Pathogenic organisms utilize random fluctuations on the surface to evade host responses (van de Putte and Goosen, 1992). The cell sensitivity to noise can be explored by the Stochastic Resonance (SR) and Stochastic Focusing (SF). Both are due to the interaction of noise with a nonlinear cell system. Stochastic resonance has been an area of intense research recently, particularly in the field of Climate physics (Benzi et al. 1981). SR is a cooperative effect in which a small periodic influence entrains extrinsic random noise. Using SR, a low amplitude periodic signal (difficult to measure) can be detected by utilizing the relatively high amplitude noise. In the case of bi-stability, only a stochastic system can explore the two stable states in a dynamic environment. In a deterministic setting, an initial condition would always guide a cell through a particular trajectory with no scope for flexibility of response. There has been conclusive evidence of SR in biological systems, particularly in sensory systems at the tissue and sub-cellular levels (Douglass et al., 1993; Levin and Miller, 1996). Stochastic focusing refers to the phenomenon where cells utilize the noise to tune a gradual response, resembling somewhat to a threshold driven mechanism (Paulsson et al., 2000). In addition to the regulatory control through feedback loops, stochastic focusing plays an essential role in effecting precision control and imposing checkpointing in critical cellular processes. Stochastic resonance and focusing can together produce determinism through higher regulatory control, even though experimental evidence to validate these concepts is yet unavailable.

However, despite the work done by the authors cited above, it is clear that the behavior of cellular networks, due its complexity of interactions and a large number of components involved, it is almost impossible to understand. However, we have gained an understanding of biology at a higher level, with the analysis of the complex collection of networks and pathways by the Systems Biology where the convergence of different *omics* fields integrate. Since the role of generating global data sets is essential, Systems Biology has been built on a three-pillars, consisting of experimentation, computation, and theory. These combinations give us a robust set of tools for better understanding of the complexity of the systems. Even though the mathematical models will get too complicated, they and computer simulation techniques have proved useful for understanding the topology and dynamics of such networks. Silicon biology has the edge over conventional experimental biology in terms of cost, ease, and speed. Furthermore, experiments that are infeasible in vivo can be conducted in Silicon, exploring, for instance, how to knock out many essential genes from the cells and monitor their individual and collective impact on cellular metabolism. Of course, such experiments cannot be done in vivo because the cell may not survive. Then Silicon models offer opportunities for unprecedented control over the system. In contrast to physicists, biologists still do not yet understand the fundamental laws of biology. Modeling can provide valuable information into the

working and general principles of organization of biological systems, also suggesting new experiments for testing hypotheses, based on the modeling experiences.

In this paper, we analyze the effects of a perturbation on Turing morphogenesis using the Brusselator, an abstract model, which does not describe any particular chemical reaction, but that was used to show how the chemical reaction could oscillate. In the second part of this article, we introduce a stochastic process, for example, by an intrinsic noise (fluctuation) again applied to the Brusselator. In the third part of the paper, we show how to retrieve the parameter information of the system itself once obtained results of the mean, standard deviation, and noise of the reaction system.

2.1 The Turing's morphogenesis by Brusselator

Before to introduce the stochasticity, we show how the Turing's model implicitly assumes that some physical, chemical or biochemical or mechanical constraints are satisfied, because outside of their range of application their accuracy is not guaranteed. Let's see, in general, how to proceed when we consider a chemical reaction occurring in a small cube box with sides of length l. The state of the mixture at any point in time is fully described by the total number of particles of each molecular species inside the cube in which the concentration gradients are zero. That state defines the homogeneous assumption. If we define n_i, be the total number of particles of species i in the box, then the concentration, denoted by [i], of the species is equal to n_i/l^{33}. We have homogeneity if the effective diffusion coefficient D are sufficiently large. In the case of our box, $D\tau \gg l^2$ where τ is the average lifetime of a reactant molecule, the mean free path $l_k = \sqrt{D\tau}$ defining the diffusion regime.

If $l_k \ll l$, the fluctuation remains localized in the region where it occurs, and the homogeneity assumption is no more valid. Vice versa if $l_k \gg l$ the homogeneity is maintained all the time. l_k sometimes, is also called Kuramoto length (1974) and defines cases characterized by the distance over which molecule diffuses before reaction. Once we have defined the level of homogeneity, inside the box where we have the reaction and diffusion, we need to analyze the average number of particle n. If the fluctuation about the average value is small, we can apply the deterministic model otherwise when it is of the order of $\sqrt{n}$, then it is comparable to the average number of particles and a stochastic model is unavoidable.

In case of heterogeneous conditions, the conceptual approach is the same, but the reaction volume is divided into m small volumes with side length δL such that the reaction is well mixed in each volume. Then the diffusion is computed between the adjacent sizes.

Nicolis and Prigogine, 1977, developed the Brusselator that can be considered the simplest reaction-diffusion models that exhibit the Turing instability and Hopf bifurcation. The Brusselator is probably the first mathematical model proposed to explain the mechanism of chemical oscillations as also observed in the famous B-Z reaction. Since then, this model serves as a prototype model to study many dynamical properties of oscillatory systems, including the effect of noise.

Let us define the following reactions

r	reaction	reaction rate	dX/dt	dY/dt
1	$A \xrightarrow{k_1} X$	$v_1 = k_1 A$	$+v_1$	0
2	$B + X \xrightarrow{k_2} Y + C$	$v_2 = k_2 BX$	$-v_2$	$+v_2$
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

In this model, A and B are assumed to be held constant in some way (buffering, continuous supply, etc.). C and D are assumed not to participate in any further reactions so that their concentrations are irrelevant. Accordingly, X and Y are the only variables, now as x and y.

We get the equations:

$$\dot{x} = k_1 a - k_2 bx + k_3 x^2 y - k_4 x$$
$$\dot{y} = k_2 bx - k_3 x^2 y$$

If we put $k_1 = k_2 = k_3 = k_4 = 1$ and if we add the diffusion term we obtain:

$$\frac{\partial x}{\partial t} = \frac{\partial^2 x}{\partial z^2} + a - bx + x^2 y - x$$
$$\frac{\partial y}{\partial t} = D\frac{\partial^2 y}{\partial z^2} + bx - x^2 y$$

These Ordinary Differential Equations (ODEs) define the Reaction-Diffusion equations. Here D is the diffusion parameter proportional to the diffusion ratio of the two species D_y/D_x and z is the spatial variable.

The homogeneous steady state of this equation is simply (x, y) = (x*, y*) = (a, b/a). Considering a small perturbation in preceding equation, where there is the diffusion term we can linearize it. Let

x=δx+x*=δx+a
y=δy+y*=δy+b/a
we obtain

$$\frac{\partial}{\partial t}\begin{bmatrix}\delta x\\ \delta y\end{bmatrix}=\mathbf{D}\frac{\partial^2}{\partial z^2}\begin{bmatrix}\delta x\\ \delta y\end{bmatrix}+\mathbf{J}^*\begin{bmatrix}\delta x\\ \delta y\end{bmatrix}$$

where the linearization of the reaction terms is $\mathbf{J}^*[\delta x \quad \delta y]^T$ and $\mathbf{J}^*$ is the Jacobian's Brusselator

$$\mathbf{J}^*=\begin{bmatrix}b-1 & a^2\\ -b & -a^2\end{bmatrix}$$

and $\mathbf{D}$ is the matrix which has the diffusion coefficients on its diagonal, and zeros everywhere else

$$\mathbf{D}=\begin{bmatrix}1 & 0\\ 0 & D\end{bmatrix}$$

In order to determine if the steady state is stable against small perturbations, we introduce a spatial aspect. Suppose therefore that our perturbations are inhomogeneous in space. One convenient form is

$$\begin{bmatrix}\delta x\\ \delta y\end{bmatrix}=\begin{bmatrix}\delta x_0\\ \delta y_0\end{bmatrix}e^{\lambda t}e^{ikz}$$

where λ can be obtain from the eigenvalues of the characteristic equation for the equilibrium point and the term $e^{ikz}=cos(kz)+isin(kz)$ is a convenient way to represent a spatial wave. There are conditions under which the steady state is unstable when a sine waves disturbance is induced? Substituting the perturbation into the linearized equation we get:

$$\lambda\begin{bmatrix}\delta x_0\\ \delta y_0\end{bmatrix}=-k^2\mathbf{D}\begin{bmatrix}\delta x_0\\ \delta y_0\end{bmatrix}+\mathbf{J}^*\begin{bmatrix}\delta x_0\\ \delta y_0\end{bmatrix}$$

where we have cancelled the common factors $e^{\lambda t}e^{ikz}$. Rearranging the previous equation, we obtain:

$$\left\{\lambda\mathbf{I}+k^2\mathbf{D}-\mathbf{J}^*\right\}\begin{bmatrix}\delta x_0\\ \delta y_0\end{bmatrix}=0$$

where $\mathbf{I}$ is the identity matrix. It has a homogeneous equation which has non-trivial solutions if the determinant is

The solution of this equation shows that depending

$$\left|\lambda\mathbf{I}+k^2\mathbf{D}-\mathbf{J}^*\right|=0$$

from the values of parameters a, b and D the reaction-diffusion system displays a Turing (stationary) patterns and a Hopf bifurcation.
Substituting the corresponding values into the previous determinant we obtain

$$\begin{vmatrix}\lambda+k^2+1-b & -a^2\\ b & \lambda+Dk^2+a^2\end{vmatrix}=0$$

corresponding to

$$\therefore\lambda^2+\lambda\left[k^2(1+D)+1-b+a^2\right]+Dk^4+k^2\left[D(1-b)+a^2\right]+a^2=0$$

This is a quadratic equation of the form

$$\lambda^2+q\lambda+p=0$$

whose solution is

$$\lambda=\frac{1}{2}\left\{-q\pm\sqrt{q^2-4p}\right\}$$

that gives us the stability conditions of the system. In fact, if $q<0$ we will have that

$$b>1+a^2+k^2(1+D)>1+a^2$$

where if $b>1+a^2$ exist values of k such that the steady state is unstable and the system exhibits an Andropov-Hopf instability not depending on diffusion and, in our case, not interesting. While if $q>0$ we obtain the following bifurcation condition (more information is due by deWit, 1999):

$$\left(1+\frac{a}{\sqrt{D}}\right)^2<b<1+a^2$$

that occurs only when the steady state would be stable in the absence of diffusion. In such a case we have a purely diffusive instability that occurs for a finite range of wave numbers k. Then this instability will form a spatial pattern of some sort since adding up a group of sine waves within a finite range of wavelengths should produce a nontrivial wave pattern.

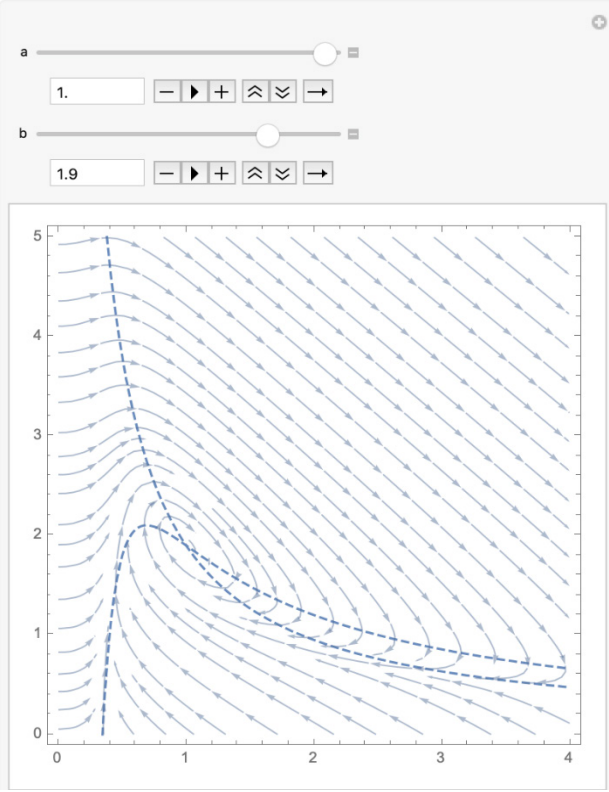

Figure 1: Simulation of Andropov -Hopf bifurcation. The system presents the bifurcation point at a=1 and b=1.9. The behavior of the Brusselator trajectories shows the Andropov-Hopf is supercritical

This is a Turing bifurcation, whichh destabilizes stable steady state by diffusive terms, leading hence to pattern formations. In Figure 1 is drawn a phase portrait and the point of bifurcation for values of a=1 and b=1.9. Using proper parameter's values far from {1; 1.9} we can obtain the classical figure of Turing's morphogenesis (see figure 2).

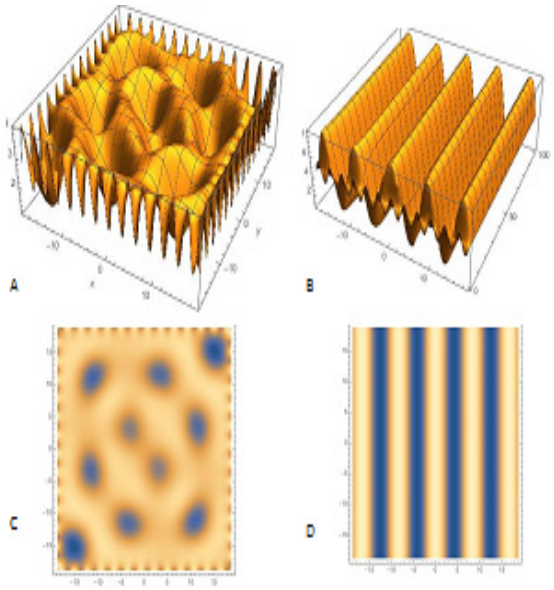

Figure 2: 3D plot A, B, of Turing morphogenesis and related density plot showing the classical dots and rows, C, D respectively.

2.2 Modelling stochastic chemical kinetics

Biological systems exhibit dynamics changes from one state to another whose exact nature is defined by the form of the perturbation in the network. As we have seen above a description of the stochastic system can be done in terms of well-mixed and dilute conditions. Stochasticity in the dynamics arises in one of the two ways: intrinsic stochasticity, inherent to the system, arising due to the relatively small number of reactant molecules or low copy number, extrinsic stochasticity originates from random variation of one or more environmental factors, due to exogenous terms, e. g. temperature and concentrations of the reactant species. The well-mixed conditions mean the expected distance travelled by each particle between successive reactive collisions is much larger than the length scale of the compartment. This implies that the spatial positions of molecules can be ignored and the dynamics of the system only depends on the total molecule numbers. In such a case the molecules can be defined as point particles and the state of the system at any time is fully determined by the state vector

$\mathbf{n} = (n_1 \ldots, n_N)$, where n_i is the molecule number of species X_i in the compartment. Since, in this case, the spatial locations of molecules do not have to be modelled, the system corresponds to a time-continuous and differentiable Markov processes on a finite, discrete state space, called also continuous-time Markov jump process. Following the Anderson and Kurtz formulation (2015) the corresponding Chemical Master Equation (CME) is:

$$\frac{\partial P(x,t)}{\partial t} = \sum_{k=1}^{N_r} \alpha_k \left(x - \mathbf{S}_k\right) P\left(x - \mathbf{S}_k, t\right) - \sum_{k=1}^{N_r} \alpha_k(x) P(x,t)$$

In order to solve this equation, we define the vector to be

$$(P(x,t))_{x\in\Omega}$$

and dp_t/dt as the vector.

$$\left(\partial p(\bar{x},t)/\partial t\right)_{x\in\Omega}$$

Then the solution of the CME is got solving the following initial value problem, differential equation,

$$\begin{cases} \frac{dp_t}{dt} = Ap_t, & t > 0 \\ p_0 = (\delta_{x,x_0})_{x\in\Omega}, & t = 0 \end{cases}$$

Constructing this solution for the above parameters is

referred to as the CME *problem.* Efficient simulation of Reaction-Diffusion Master Equation (RDME) can be achieved by the Gillespie algorithms or Ito's lemma. We have obtained the solution with tools properly developed in Mathematica http://www.wolfram.com/mathematica/.

The introduction to CME can be found in Toth et al. 2018 and in van Kampen, 2007.

Let's now repeat the exercise with the stochastic Brusselator where 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	$B + X \xrightarrow{k_2} Y + C$	$w_2 = c_2 BX$	$c_2 = k_2/\Omega$
3	$2X + Y \xrightarrow{k_3} 3X$	$w_3 = c_3 X(X-1)Y/2$	$c_3 = 2k_3/\Omega^2$
4	$X \xrightarrow{k_4} D$	$w_4 = c_4 X$	$c_4 = k_4$

where Ω is the system size. Then the master equation corresponding to this system is:

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

The figure 3 shows the behavior of the deterministic Brusselator vs. stochastic

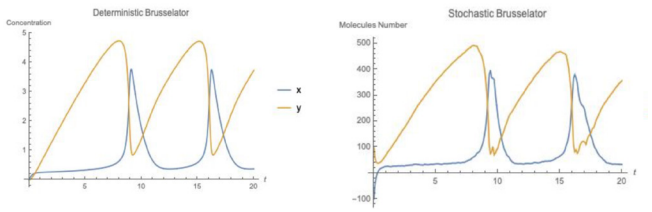

Figure 3: Deterministic Brusselator vs. Stochastic Brusselator (one realization)

3. Retrieving the noise and parameters of the system

Now we apply to the Brusselator CME the procedure to retrieve the level of noise. First of all, we know that one of the important parameters is Ω because of its size depends on its stochasticity fluctuations. One of the main techniques is to estimate the peak-to-peak intervals from stochastic time series. That is nontrivial because they occur extremely often due to fluctuations. Then let's now compute the trajectories for 100 realizations that will produce a cloud of realizations. Slice distributions of the state variables can be calculated at any time point. At the time, for instance, τ=12, we can calculate the mean and standard deviation for both state variables $x(\tau)$and $y(\tau)$, as well as their histograms. Then, we can select certain times, for instance, τ and compute the mean and standard deviation for both state variables $a(\tau)$ and $b(\tau)$, as well as their histograms as is shown in figure 4.

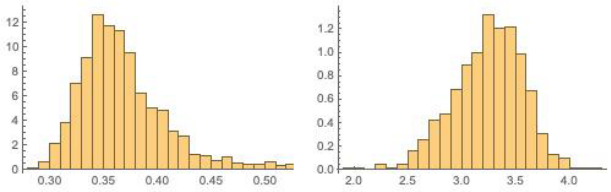

Figure 4: The distribution of $x(\boldsymbol{\tau})$ ans $y(\boldsymbol{\tau})$ in the case of 100 realizations of the Ito's process, at time **τ**=12.

An alternative method is the auto-correlation function that measures the correlation of a time series with itself shifted by a time lag as a function of itself. The autocorrelation of a signal $x(t)$ is :

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

and for a discrete signal generated by the stochastic simulation we have:

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

While in the deterministic model the autocorrelation is periodic, in stochastic time series, however, it oscillates and $C(\tau)$ decreases exponentially with the time, reflecting the loss of phase memory (see figure 5).

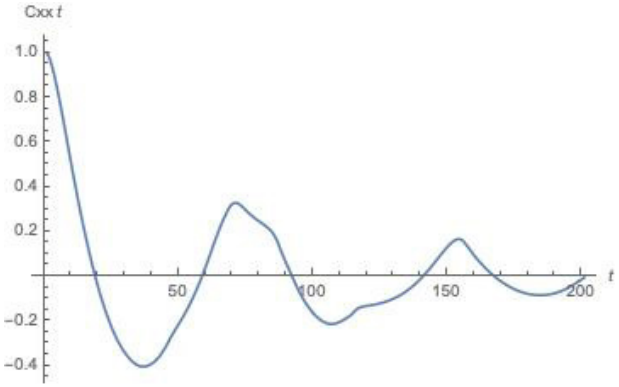

Figura 5: Autocorrelation for **Ω**=100. Cxx(t)= $C(\boldsymbol{\tau})$.

$$C(\tilde{\tau}) = 0.5$$

This phenomenon is called phase diffusion. The damping rate of the auto-correlation function, measured by the half- lifetime (i.e., the time required to reach

that is a measure of the impact of noise. Bigger is the influence of the noise on the system, and shorter is the half-life time. Interestingly plotting 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/Ω, for a large value of Ω a linear relationship is observed. This property is characteristic of nonlinear systems perturbed by a white noise (Gaspard 2002). We compute noise levels from the ratio between the variance σ_{xy} and the temporal average concentration $<x>,< y >$ level of the species at the steady state

$$\sigma_{xy}/(<x> < y >)$$

Once the 100 trajectories have been simulated between time $0 \le t \le 20$, mean, standard deviation and noise can be shown as appears in figure 6

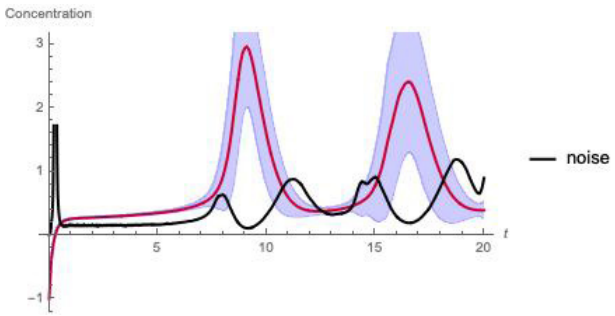

Figura 6: Mean Red), Standard Deviation (blue) and Noise (black) obtained after 100 realizations

Now we want to evaluate the parameter estimation from the measurements. That is critical since it determines how well the model compares to the measurement data. The measurement process itself may also have serially uncorrelated errors due to the imperfect accuracy and precision of the measurement equipment.

Let's write the measurement equation as $y_k = x(t_k) + e_k$ where $e_k \sim N\left(0, \sigma_{m}.\right)$.

The inhibitor $y(t)$ is assumed to be sampled between $t=0$ and $t=20$ at discrete time points t_k , where $k=0,1,2....,N$; $N=40$, with an additive measurement noise σ_m. To get $y(t_k)$, we consider a single realization (as measurements should be) and sample it at time points t_k. Then we add the noise, because as we have seen, the solutions to SDEs are stochastic processes that are described by probability distributions. This property allows for maximum likelihood estimation. Let the deviation of the measurements from the model be

$$\epsilon_k(\theta) = y_k - \mu_R(t_k, \theta)$$

where $\theta(a, b)$ and $\mu_R(t_k, \theta)$ is the mean of the random function. Assuming that the density function of can be approximated reasonably well by Gaussian density, the likelihood function will be:

$$\mathcal{L} = \frac{1}{(2\pi)} \exp\left(-\sum_{k=1}^{N} \epsilon_k(\theta)^2\right)$$

For computation, we use its logarithm. Then we estimate a and b from the SDE model, employing the maximum likelihood method. The optimization of the likelihood function is not an easy task, since the objective function is often flat, with nondifferentiable terms and many local extrema. Also, the model takes a long time to evaluate. Instead of using direct global optimization, first, we compute the values of an objective function on a 25*25 grid to use parallel computation to speed up the evaluation. Employing different global optimization methods, we can compute the parameters that are: a=1.2; b=2.9 for -Log $\mathcal{L}(a, b) = 54.06$. The best results were obtained with the Nelder and Mead method (1965) that is used to find the minimum or maximum of an objective function in a multidimensional space. It uses the direct search method (based on function comparison) and it is often applied to nonlinear optimization problems for which derivatives may not be known. The Nelder-Mead technique is a heuristic search method that can converge to non-stationary points on problems that can be solved by alternative methods. A similar approach can be used in case of forced Brusselator or case of Stochastic Resonance or Focussing Resonance.

4. Conclusions

Several papers introduce the idea that phenotypes are regulated by noise control. Noise control is a task almost mathematically intractable due to the propagation of noise through the reaction network. However, for the simplest reactions, it is possible to obtain the level of noise and eventually to retrieve parameters of the system under examination from measurements. Although the approach we have shown has been applied to the most straightforward system as the Brusselator, it can be used for several SDE. Knowing the reactions and rate constants, it is possible to obtain the linear or nonline-

ar stochastic differential equation by which we can explore the behaviour of the system. We are confident the approach we have used for Brusselator can be applied to other reactions because it is general and straightforward and starts from the CME of kinetics reaction. On a certain number of realizations, it is possible to obtain the probability distribution from which we can recover the mean values and standard deviations of the system. By the use of minimization techniques, the parameters of the system can be retrieved, and the reactions can be statistically controlled. Paszek (2014) suggests to make temporal measurements and to integrate the live-cell imaging with genomic and proteomic end-point assays, for example using microfluidic systems or micro dissection techniques. This requires a more precise measurements of noise. However, he concludes, "[…] it is the integration of different temporal approaches that perhaps can provide a step-change in the field".

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