Alma Mater Studiorum · Università di Bologna

FACOLTÀ DI SCIENZE MATEMATICHE, FISICHE E NATURALI
Dottorato in Fisica
SETTORE CONCORSUALE: 02/B3-FISICA APPLICATA
SETTORE SCIENTIFICO-DISCIPLINARE:FIS/07-FISICA APPLICATA

Master Equation: Biological Applications and Thermodynamic Description

Thesis Advisor:
Chiar.mo Prof.
GASTONE CASTELLANI

Presented by:
LUCIANA RENATA DE OLIVEIRA

PhD coordinator:
Chiar.mo Prof.
FABIO ORTOLANI

aa 2013/2014
January 10, 2014

I dedicate this thesis
to my parents.

Introduction

It is well known that many realistic mathematical models of biological systems, such as cell growth, cellular development and differentiation, gene expression, gene regulatory networks, enzyme cascades, synaptic plasticity, aging and population growth need to include stochasticity. These systems are not isolated, but rather subject to intrinsic and extrinsic fluctuations, which leads to a quasi equilibrium state (homeostasis). Any bio-system is the result of a combined action of genetics and environment where the presence of fluctuations and noise cannot be neglected. Dealing with population dynamics of individuals (or cells) of one single species (or of different species) the deterministic description is usually not adequate unless the populations are very large. Indeed the number of individuals varies randomly around a mean value, which obeys deterministic laws, but the relative size of fluctuations increases as the size of the population becomes smaller and smaller. As consequence, very large populations can be described by logistic type or chemical kinetics equations but as long as the size is below $N = 10^3 \sim 10^4$ units a new framework needs to be introduced. The natural framework is provided by Markov processes and the Master equation (ME) describes the temporal evolution of the probability of each state, specified by the number of units of each species. The system evolves and asymptotically reaches a stationary equilibrium after a specific relaxation time. The deterministic model does not determine uniquely the ME since the nature of the noise needs to be specified. For a single population of size N the ME gives the probability p_n of having $n \leq N$ individuals and the relative size of the fluctuations with

respect to and average value $< n >$ is of order $N^{-1/2}$. For large populations the continuous interpolation $p(n)$ of the probability distribution satisfies the Fokker-Planck equation and in the limit for $N \to \infty$, where the fluctuations disappear, it satisfies the continuity equation for to the deterministic evolution (mean field equation).

The ME is a relevant tool for modeling realistic biological systems and allow also to explore the behavior of open systems. These systems may exhibit not only the classical thermodynamic equilibrium states but also the non-equilibrium steady states (NESS). When the system is in an equilibrium state there is no flux of energy and molecules; this is known as the principle of detailed balance (DB) and the system is time-reversible, that is, the system will have equal probability to forward and backward transitions. When the system is in a NESS it does not change with time in a statistical sense, namely the probability distribution are stationary. However, the system is not at equilibrium and its fluctuations do not obey Boltzmann's law. The principal property of a NESS is that it only exists when it is driven by an external energy source. Using the concepts of DB and NESS a non-equilibrium thermodynamic description can be developed in terms of the ME, which provides a natural framework integrating a consistent theory of biological systems.

This thesis is organized into six chapters which are grouped in two parts: the **biological applications of the Master equation** and the **nonequilibrium thermodynamics in terms of the Master equation**, with three chapters each one. There are four new scientific works and a correspondence of the level of complexity between then.

First part: *Biological applications of the Master equation*

In Chapter 1- ***Master Equation-*** we introduce the general concepts of stochastic systems, given a mathematical derivation of the master equation from the Chapman-Kolmogorov equation, with the characterization of the one-step process, which are the basilar concepts used throughout the thesis. The Chapters 2- ***Stochastic analysis of a miRNA-protein toggle***

switch- deals with the stochastic properties of a toggle switch, involving a protein compound and a miRNA cluster, known to control the eukaryotic cell cycle and possibly involved in oncogenesis. We address the problem by proposing a simplified version of the model that allows analytical treatment, and by performing numerical simulations for the full model. In general, we observed optimal agreement between the stochastic and the deterministic description of the circuit in a large range of parameters, but some substantial differences arise when the deterministic system is in the proximity of a transition from a monostable to a bistable configuration and when bistability (in the deterministic system) is "masked" in the stochastic system by the distribution tails. The approach provides interesting estimates of the optimal number of molecules involved in the toggle. In the Chapter 3- ***One parameter family of master equations for logistic growth***- we propose a one parameter family of master equations for the evolution of a population having the logistic equation as mean field limit, studying the dependence of the stationary state distributions, the relaxation time with our parameter for systems with and without absorbing state. We also propose an analytical solution for the stationary distribution and the results agree with those calculate with the CME.

Second Part: *Nonequilibrium thermodynamics in terms of the Master equation.*

The Chapter 4- ***Nonequilibrium thermodynamics in terms of the ME***- introduce the differences between equilibrium (DB) and nonequilibrium steady states (NESS), review the principal concepts of equilibrium thermodynamics and the principal mathematical features of nonequilibrium thermodynamics. We also describe mathematically the nonequilibrium approach based on the CME and Gibbs entropy. In the Chapter 5-The role of nonequilibrium fluxes in the relaxation processes of the Linear Chemical Master Equation- we have studied the dynamical role of chemical fluxes that characterize the NESS of a chemical network. Using the correspondence between the CME and a discrete Fokker-Planck equation we are able to show that the chemical

fluxes are linearly proportional to a non-conservative "external vector field" whose work on the system is directly related to the entropy production rate in the NESS. We study the effect of the fluxes on the relaxation time of the CME in the case of NESS. Our main result is to show that the presence of stationary fluxes reduces the characteristic relaxation time with respect the DB condition and it allows bifurcation phenomena for the eigenvalues of the linearize dynamics around a local maximum of the probability distribution. We conjecture that this is a generic results that can be generalized to non-linear CME. In the Chapter 6- ***Energy consumption and entropy production in a stochastic formulation of BCM learning***- we propose a one parameter parametrization of BCM learning[1], that was originally proposed to describe plasticity processes, to study the differences between systems in DB and NESS. We calculate the work done by the system as a function of our parameter, our results show that when the system is not in the detailed balance condition, the work necessary to reach the stable state is less than that requested when the detailed balance holds. This means that the system requires less energy to memorize a pattern when the detailed balance is not satisfied. Hence the system is more plastic: a part of the energy that is requested to maintain the NESS is recovered when the system learns and develops selectivity to input pattern. We believe that this can be an hallmark of biological systems and that this can explain why these systems spend a large part of their metabolic energy to maintain NESS states; this energy is recovered during crucial developmental steps such as differentiation and learning.

[1]Named after Elie Bienenstock, Leon Cooper and Paul Munro, the BCM rule is a physical theory of learning in the visual cortex developed in 1982.

Contents

List of Figures

FIRST PART-Biological applications of the Master equation

Chapter 1

Master Equation

1.1 Stochastic Process

A stochastic process with state space S is a collection of random variables $\{X_t, t \in T\}$ defined on the same probability space [2, 3]. The set T is called its *parameter set*. The index t represents the time, and then one thinks of X_t as the "state" or the "position" of the process at time t. A stochastic variable is defined by specifying the set of possible values of the set of states and the probability distribution over this. It can be discrete as the number of molecules of a component in a reacting mixture, continuous as the velocity of a Brownian particle or multidimensional as the velocity at a point in a turbulent wind field.

1.1.1 Markov Process

A system has the Markov property if its evolution from a determinate state depends only on that state, it is a system without memory, the events depend just of time t_n and not the time t_{n-1}.

1.1.2 The Markov Property

Consider a discrete-parameter stochastic process X_n. Think of $X_0, X_1, ..., X_{n-1}$ as "the past", X_n as "the present" and $X_{n+1}, X_{n+2}, ...$ as "the future" of the process relative to time t_n. In this way, a Markov process can be defined in terms of conditional probability density at t_n as follows [3]:

$$P_{1|n-1}(X_n, t_n; X_1, t_1; ...; X_{n-1}, t_{n-1}) = P_{1|1}(X_n, t_n|X_{n-1}, t_{n-1}). \tag{1.1}$$

That is, the conditional probability density at t_n, given the value X_{n-1} at t_{n-1}, is uniquely determined and is not affected by any knowledge of the values at earlier times. $P_{1|1}$ is called the *transition probability*. Indeed, one has for instance, taking $t_1 < t_2 < t_3$,

$$\begin{aligned} P_3(X_1, t_1; X_2, t_2; X_3, t_3) &= P_2(X_1, t_1; X_2, t_2) P_{1|2}(X_3, t_3|X_1, t_1; X_2, t_2) \\ &= P_1(X_1, t_1) P_{1|1}(X_2, t_2|X_1, t_1) P_{1|1}(X_3, t_3|X_2, t_2). \end{aligned} \tag{1.2}$$

The value X_{n-1} at t_{n-1}, is uniquely determined and is not affected by any knowledge of the values at earlier times. A Markov process is fully determined by the two functions $P_1(X_1, t_1)$ and $P_{1|1}(X_2, t_2|X_1, t_1)$; the whole hierarchy can be constructed from them. That is, the conditional probability of some future event, indeed to t_{n+1} be the present at t_n, is independent of past event and it depends only of the present state of the process. Continuing this algorithm one finds successively all P_n. This property makes Markov processes manageable, with is the reason why they are so useful in applications [3].

1.1.3 The Chapman-Kolmogorov (C-K) equation

In mathematics, specifically in probability theory and in particular the theory of Markovian stochastic processes, the Chapman-Kolmogorov equation is an identity relating the joint probability distributions of different sets of coordinates on a stochastic process. Taking the relation (1.2) for $t_1 < t_2 < t_3$, integrating it over X_2 and dividing both sides by P_1 gives us the Chapman-Kolmogorov equation [3]

$$P_{1|1}(X_3, t_3|X_1, t_1) = \int P_{1|1}(X_3, t_3|X_2, t_2) P_{1|1}(X_2, t_2|X_1, t_1) dX_2. \tag{1.3}$$

This equation states that a process starting at t_1 with value X_1 reaches X_3 at t_3 via any one of the possible values X_2 at the intermediate time t_2 [4]. This equation holds also when X is a vector with r components; or when X only takes discrete values then, the integral is replaced by a sum [3, 4]. As we have said in section 1.1.2, P_1 and $P_{1|1}$ entirely determine a Markov processes, because the whole hierarchy of P_n can be constructed from them. These two functions cannot be chosen arbitrarily, however, but obey two identities [3]:

1. the Chapman-Kolmogorov equation (1.3);

2. The necessary relation

$$P_1(X_2, t_2) = \int P_{1|1}(X_2, t_2|X_1, t_1)P_1(X_1, t_1)dX_1.$$

Therefore, any two nonnegative functions P_1 and $P_{1|1}$ that obey these consistency conditions define uniquely a Markov process.

Stationary and homogeneous Markov process

A process X_n is stationary if it is not affected by a shift in time, i.e. X_n and X_{n+1} have the same probability distribution. In that case, a special notation [3] is used for the transition probability

$$P_{1|1}(X_2, t_2; X_1, t_1) = T_\tau(X_2|X_1) \tag{1.4}$$

with $\tau = t_2 - t_1$ and the C-K equation, for $\tau, \tau' > 0$

$$T_{\tau+\tau'}(X_3|X_1) = \int T_{\tau'}(X_3|X_2)T_\tau(X_2|X_1)dX_2. \tag{1.5}$$

These processes are non-stationary because the condition singled out a certain time t_0. Yet their transition probability depends on the time interval alone as it is the same as the transition probability of the underlying stationary process. Non-stationary Markov process whose transition probability depends on the time difference alone are called homogeneous processes [3, 4].

1.2 The Master Equation

In general, the term "master equation" is associated with a set of equations that describe the temporal evolution of the probability of a particular system. In mathematical terms, the master equation is an equivalent form of the Chapman-Kolmogorov equation for Markov process, but it is easier to handle and more directly related to physical concepts [3]. This equation is universal and has been applied in many problems in physics, chemistry, biology, population dynamics, and economy [3, 4, 5, 6, 7, 8, 9, 10, 11, 12].

1.2.1 Derivation of the Master Equation from the C-K equation

The Chapman-Kolmogorov equation (1.5) for T_τ is a functional relation, the master equation is a more convenient version of the same equation [3]: it is a differential equation obtained by going to the limit of vanishing time difference τ'. Therefore, considering the equation (1.5) and T_τ as the transition probability

$$T_{\tau+\tau'}(X_3|X_1) = \int T_{\tau'}(X_3|X_2)T_\tau(X_2|X_1)dX_2, \tag{1.6}$$

which have the following normalization condition

$$\int T_\tau(X_2|X_1)dX_1 = 1. \tag{1.7}$$

Taking T_τ for $\tau' \to 0$

$$T_{\tau'}(X_3|X_2) = (1 - \alpha_0\tau')\delta(X_2 - X_3) + \tau' W(X_3|X_2), \tag{1.8}$$

the delta function expresses the probability to stay at the same state for $\tau = 0$, whereas the probability to change state for $\tau > 0$ is equals zero. $W(X_3|X_2)$ is transition probability per unity time from X_2 to X_3 and hence

$$W(X_3|X_2) \geq 0. \tag{1.9}$$

The expression (1.8) must satisfy the normalization property. Therefore, taking its integral over X_3

$$\int T_{\tau'}(X_3|X_2)dX_3 = \int [(1-\alpha_0\tau')\delta(X_2-X_3) + \tau' W(X_3|X_2)]dX_3, \quad (1.10)$$

but from (1.7) we have $\int T_{\tau'}(X_3|X_2)dX_3 = 1$, therefore

$$1 = 1 - \alpha_0\tau' + \tau' \int W(X_3|X_2)dX_3$$

$$\alpha_0 = \int W(X_3|X_2)dX_3 \quad (1.11)$$

where the delta function has been corrected by the coefficient $1-\alpha_0\tau'$ with corresponds to the probability for transition to have taken place at all. Using the definition (1.11) we can rewrite (1.8) as

$$T_{\tau'}(X_3|X_2) = \delta(X_2-X_3) - \tau'\delta(X_2-X_3)\int W(X_3|X_2)dX_3 + \tau' W(X_3|X_2), \quad (1.12)$$

Putting (1.12) into (1.6),

$$\begin{aligned} T_{\tau+\tau'}(X_3|X_1) &= T_\tau(X_3|X_1) + \tau' \int W(X_3|X_2)T_\tau(X_2|X_1)dX_2 \quad (1.13) \\ &+ \tau' \int \delta(X_2-X_3)W(X_3|X_2)T_\tau(X_2|X_1)dX_2 \\ &- \tau' \int \delta(X_2-X_3)W(X_3|X_2)T_\tau(X_2|X_1)dX_2dX_3. \end{aligned}$$

simplifying

$$\begin{aligned} T_{\tau+\tau'}(X_3|X_1) &= T_\tau(X_3|X_1) + \tau' \int W(X_3|X_2)T_\tau(X_2|X_1)dX_2 \quad (1.14) \\ &- \tau' \int W(X_2|X_3)T_\tau(X_3|X_1)dX_2. \end{aligned}$$

Dividing by τ' and going to the limit $\tau' \to 0$ gives us the differential form of the Chapman - Kolmogorov equation which is called the Master Equation [3, 4]:

$$\frac{\partial}{\partial\tau}T_\tau(X_3|X_1) = \int [W(X_3|X_2)T_\tau(X_2|X_1) - W(X_2|X_3)T_\tau(X_3|X_1)]dX_2 \quad (1.15)$$

It is useful to cast the equation in a more intuitive form. Noting that all transition probabilities are for a given value X_1 at t_1, we may write, suppressing redundant indices:

$$\frac{\partial}{\partial t}P(X,t) = \int [W(X|X')P(X'|t) - W(X'|X)P(X|t)]dX' \tag{1.16}$$

This equation must be interpreted as follows: taking a time t_1 and a value X_1 and considering the solution of (1.16) that determined for $t \geq t_1$ by the initial condition $P(X,t_1) = \delta(t-t_1)$. This solution is the transition probability $T_{\tau-\tau_1}(X|X_1)$ of the Markov process for any choice of t_1 and X_1. The master equation is not meant as an equation for the single-time distribution $P_1(X,t)$, but it determines the entire probability distribution $P(X,t)$ [3]. If the range of X is a discrete set of states with labels n, the equation reduces to:

$$\frac{dp_n(t)}{dt} = \sum_{n'}[W_{n,n'}p_{n'}(t) - W_{n',n}p_n(t)]. \tag{1.17}$$

This form of the master equation makes the physical meaning more clear: the master equation is a gain-loss equation for the probability of each state n. The first term is the gain due to transitions from n' to n states, and the second term is the loss due to transitions from n to n' states. When we will study the one-step process (section 1.3), the interpretation of the master equation as a gain-loss equation will be more clear. Remember that $W_{n,n'} \geq 0$ when $n \neq n'$, and that the term with $n = n'$ does not contribute to the sum [3].

Note: A fundamental property of the master equation is: As $t \to \infty$ all solutions tend to the stationary solution.

1.2.2 Detailed Balance

As we presented in section 1.1.3 a steady state is a condition for which the probability distribution does not change in time. If the master equation (1.17) is in a stationary state, we have $\frac{dp_n(t)}{dt} = 0$ and consequently

$$\sum_{n'}[W_{n,n'}p^s_{n'}(t) - W_{n',n}p^s_n(t)] = 0 \tag{1.18}$$

where p_n^s is the steady state probability. Therefore the steady state condition property has the form:

$$\sum_{n'} W_{n,n'} p_{n'}^s = \big(\sum_{n'} W_{n',n}\big) p_n^s. \tag{1.19}$$

This relation express the fact that in the steady state, the *sum* of all transitions per unit time into any state n must be balanced by the *sum* of all transitions from n into other states n'.

However, there is a special case for closed, isolated, finite physical system, which is known as *detailed balance* condition. It is associated with thermodynamic equilibrium and we can replace p_n^s by the equilibrium probability p_n^e. In that case, we have [3]

$$W_{n,n'} p_{n'}^e = W_{n',n} p_n^e. \tag{1.20}$$

Which means that the transitions for *each pair* n, n' separately must be balanced. In the Chapter 4 we will treat the detailed balance condition in more details.

1.2.3 Transition Matrix

In order to describe the stationary solutions methods of the master equation we consider the convenient notation for discrete states. Defining the transition matrix $\mathbb{W}$ as [3]

$$\mathbb{W} = \begin{cases} \mathbb{W}_{n,n'} = W_{n,n'} & \text{for} \qquad n \neq n' \\ \mathbb{W}_{n,n} = -\sum_{n \neq n'} W_{n',n} \end{cases} \tag{1.21}$$

Using the definition (1.21) we can simplify the master equation (1.17) as a linear dynamic system:

$$\dot{\mathbf{p}}(t) = \mathbb{W}\mathbf{p}(t) \tag{1.22}$$

where $\mathbf{p}$ is a column vector with components p_n. The next results are valid when the matrix $\mathbb{W}$ is symmetric and its solution is known

$$\mathbf{p}(t) = e^{\mathbb{W}t} p(0). \tag{1.23}$$

This expression for $\mathbf{p}(t)$ is sometimes convenient, but does not help to find $\mathbf{p}(t)$ explicitly. The familiar method for solving equations of type (1.22) by means eigenvectors and eigenvalues of $\mathbb{W}$ cannot be used as a general method, because $\mathbb{W}$ need not be symmetric, so that it is not certain that all solutions can be obtained as superpositions of these eigensolutions [3]. In the general case, the matrix $\mathbb{W}_{n,n'}$ should obey the following properties

$$\mathbb{W}_{n,n'} \geq 0 \quad \text{for} \quad n \neq n'; \tag{1.24}$$

$$\sum_{n} \mathbb{W}_{n,n'} = 0 \quad \text{for each} \quad n'. \tag{1.25}$$

The equation (1.25) states that the matrix $\mathbb{W}$ has zero determinant, as we can confirm in the example for example for $N = 3$,

$$\mathbb{W}_{=} \begin{pmatrix} -(W_{2,1} + W_{3,1}) & W_{1,2} & W_{1,3} \\ W_{2,1} & -(W_{1,2} + W_{3,2}) & W_{2,3} \\ W_{3,1} & W_{3,2} & -(W_{1,3} + W_{2,3}) \end{pmatrix}. \tag{1.26}$$

Introducing the eigenvector ψ and the eigenvalue λ of the matrix $\mathbb{W}$, defined by the equation

$$\mathbb{W}\psi = \lambda\psi. \tag{1.27}$$

A zero determinant states that $\mathbb{W}$ has a left eigenvector $\psi = (1, 1, 1, ...)$ with zero eigenvalue. There is at least one zero eigenvalue, whose corresponding eigenvector is the so-called stationary distribution, the distribution to which the stochastic process always converges, i.e. $\mathbf{p}(t) = 0$, as long as the transition propensities $W_{n,n'}$ are not a function of time. The stationary distribution will be obviously positive, i.e. all its terms are with positive sign and the sum of all its components is 1 (being a probability distribution). All the other eigenvalues will be with negative module, and the corresponding eigenvectors will have total sum of the components equal to zero, as they can be interpreted as the difference between the present distribution and the stationary one, both having total sums of the components equal to 1. A special role is played by the eigenvalue with the smallest absolute value, which it means that its eigenvector is the longest-standing one. This eigenvector is

referred as the metastable state and its eigenvalue gives a time-scale of the time of convergence to the stationary distribution.

1.3 One-Step processes

In this thesis we will treat only problems that can be described by the formalism of one-step processes. They represent a very important family of Markov processes and they are also known as generation-recombination or birth-death processes. These processes are continuous in time, their range consists of integers n, and only jumps between adjacent states are permitted [3], that is, just the transitions $n-1 \rightleftharpoons n$ and $n \rightleftharpoons n+1$ are permitted. In that case, the Master equation (1.17) is written as

$$\frac{dp_n(t)}{dt} = W_{n,n+1}p_{n+1}(t) + W_{n,n-1}p_{n-1}(t) - W_{n-1,n}p_n(t) - W_{n+1,n}p_n(t) \quad (1.28)$$

The transition rates, $W_{n',n}$, are written in a special notation for these processes (see Figure 1.1)

$$W_{n+1,n} = g_n \quad \text{and} \quad W_{n-1,n} = r_n. \quad (1.29)$$

Therefore, g_n is the gain term, that is the probability per unit time for a jump from n to $n+1$ and r_n is the recombination term, that is the probability per unit time for a jump from state n to state $n-1$.

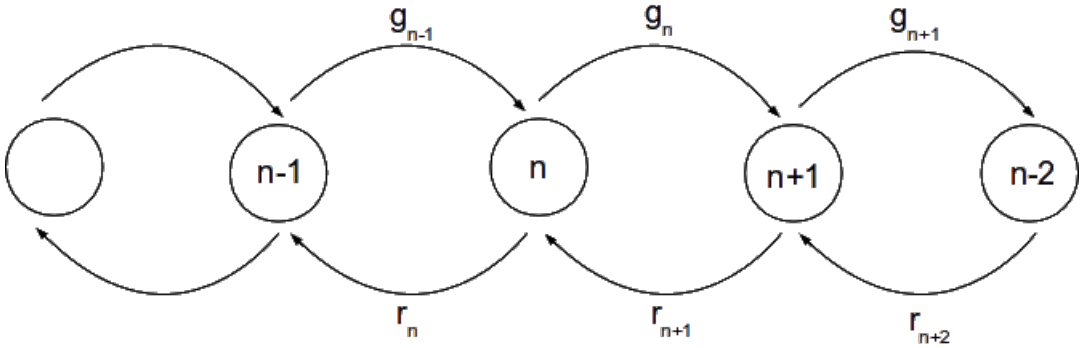


Figure 1.1: The one-step process and its transition probabilities

Ergo, the Master equation for such process can be rewritten as

$$\dot{p_n} = r_{n+1}p_{n+1} + g_{n-1}p_{n-1} - (r_n + g_n)p_n. \tag{1.30}$$

One-step processes occur for example at generation and recombination processes of charge carriers, single-electron tunneling, surface growth at atoms, birth and death of individuals. And one-step processes can be subdivided based on the coefficients r_n and g_n into the following categories: linear, if the coefficients are linear functions of n, nonlinear, if the coefficients are nonlinear functions of n and random walks, if the coefficients are constant [3, 4].

A important point to consider is the boundaries conditions, if the possible states n variate as $0 \leq n \leq N$, we consider both boundaries: $n = 0$ and $n = N$. For $n = 0$, the Master equation (1.30) is $\dot{p_0} = r_1p_1 + g_{-1}p_{-1} - (r_0 + g_0)p_0$, but the terms $g_{-1}p_{-1}$ and r_0p_0 are physically inconsistent, p_{-1} obviously cannot exist, and the term r_0 represents a transition from the state n_0 to $n_0 - 1$, which is not permitted. In the other extreme we have $n = N$ and the Master equation is $\dot{p_N} = r_{N+1}p_{N+1} + g_{N-1}p_{N-1} - (r_N + g_N)p_N$. Here the inconsistencies are $r_{N+1}p_{N+1}$ and g_Np_N, because the state $N + 1$ does not exist and g_N represents a transition from the state N to $N+1$. Then $\dot{p_0}$ and $\dot{p_N}$ are

$$\dot{p_0} = r_1p_1 + g_0p_0 \quad \text{and} \quad \dot{p_N} = g_{N-1}p_{N-1} - r_Np_N \tag{1.31}$$

Introducing the "step operator" or "van Kampen operator" $\mathbb{E}_n$ and $\mathbb{E}_n^{-1}$, and defining its effect on arbitrary function $f(n)$

$$\mathbb{E}_n f_n = f_{n+1} \quad \text{and} \quad \mathbb{E}_n^{-1} f_n = f_{n-1}. \tag{1.32}$$

Then, the equation (1.30) for a generic one-step process can be written in the equivalent and compact form:

$$\dot{p_n} \;=\; (\mathbb{E}_n - 1)r_np_n + (\mathbb{E}_n^{-1} - 1)g_np_n. \tag{1.33}$$

1.3.1 Nonlinear one-step processes

When r_n and g_n are both nonlinear in n we normally can give an explicit solution of the master equation only for the stationary state. The distinction between linear and nonlinear one-step processes has more physical significance than appears from the mathematical distinction between linear and nonlinear functions r_n and g_n [3]. Frequently, n is associated with the number of individuals of a population, such as electrons, neurotransmitters, quanta, chemical species or bacteria.

In terms of the master equation, p_n is linear in n when these individuals do not interact, but follow their own individual random history regardless of the others. While, a nonlinear term in the equation means that the fate of each individual is affected by the total number of others present. Therefore, linear master equations play a role similar to the ideal gas, in gas theory.

1.3.2 Mean field approximation

The master equation determines the probability distribution of a Markov system at all $t > 0$. But in a macroscopic physical description, one ignores fluctuations and treat the system as deterministic. The evolution of $n(t)$ is described by a deterministic differential equation for n, called the macroscopic or phenomenological equation. Examples are Ohm's law, the rate equations of chemical kinetics and the growth equations for populations. As the Master equation determines the entire probability distribution it must be possible to derive from it the macroscopic equation as an approximation for the case that the fluctuations are negligible [3]. Assuming that for $t = 0$ the quantity n has the precisely value n_0, then the probability density is initially $p_n(0) = \delta_{n,n_0}$. At any later time n has the value $n(t)$ and consequently one should have $p_n(t) = \delta_{n,n(t)}$. The fluctuation vanish in the limit $N \to \infty$ where N is the largest value that n can reach. In general we define the mean value $< n(t) >$

$$n(t) =< n >_t = \sum_{n=0}^{\infty} n p_n(t). \tag{1.34}$$

In the case of the one-step process governed by the master equation (1.33), we can calculate the time derivative of $< n >$ as

$$\begin{aligned} \frac{d}{dt} < n >= & \sum n(\mathbb{E}_n - 1) r_n p_n + \sum n(\mathbb{E}_n^{-1} - 1) g_n p_n \\ = & \sum r_n p_n (\mathbb{E}_n^{-1} - 1) n + \sum g_n p_n (\mathbb{E}_n - 1) n \\ = & - < r_n > + < g_n > . \end{aligned} \tag{1.35}$$

This is an equation for $< n >$ only when $< r_n >= r_{<n>}$ and $< g_n >= g_{<n>}$. This condition is satisfied by linear systems for any N whereas for a generic system it holds only when $N \to \infty$. In this limit the fluctuations vanish and $n(t) =< n >_t$ satisfies the deterministic equation for the evolution of the macroscopic system.

1.3.3 Fokker-Planck equation

The Fokker-Planck equation gives the time evolution of the probability density function for the system [4]. This equation is a special type of master equation [3], that is, for $N \to \infty$ the master can be written in terms of the Fokker-Planck equation. Through a Taylor expansion of the master equation (1.33) we have

$$\begin{aligned} (\mathbb{E}_n - 1) f(n) = f(n+1) - f(n) = \frac{\partial f}{\partial n} + \frac{\partial^2 f}{\partial n^2} + ... \\ (\mathbb{E}_n^{-1} - 1) f(n) = f(n-1) - f(n) = -\frac{\partial f}{\partial n} + \frac{\partial^2 f}{\partial n^2} + ... \end{aligned} \tag{1.36}$$

Putting (1.36) into (1.33) we obtain the functions $P(n,t)$,$g(n)$ and $r(n)$ that interpolates $p_n(t)$, g_n and r_n in n

$$\frac{\partial P(n,t)}{\partial t} = \frac{\partial [(r_n - g_n) P_n]}{\partial n} + \frac{1}{2} \frac{\partial^2}{\partial n^2} [(r_n + g_n) P_n]. \tag{1.37}$$

The range of n is necessarily continuous, the coefficients $r(n) - g(n)$ and $r(n) + g(n)$ may be any real differentiable functions with the only restriction $r(n) + g(n) > 0$ [3]. The equation can be broken up into a continuity equation for the probability density

$$\frac{\partial P(n,t)}{\partial t} = \frac{\partial J(n,t)}{\partial n}, \tag{1.38}$$

where $J(n,t)$ is the probability flux, and a "constitutive equation"

$$J(n,t) = (r(n) - g(n))P(n) + \frac{1}{2}\frac{\partial}{\partial n}[(r(n) + g(n))P(n)]. \tag{1.39}$$

If we define $q \equiv (r(n) + g(n))P(n)$ the stationary solution is found with

$$\frac{\partial q}{\partial n} = 2q\frac{(g(n) - r(n))}{(r(n) + g(n))} \tag{1.40}$$

we obtain by separation of variables

$$q(n) = q(0)exp\left(2\int_0^N \frac{g(n') - r(n')}{r(n') + g(n')}dn'\right) \tag{1.41}$$

where $q(0)$ should be determined imposing the normalization.

It is appropriate to rewrite the Fokker-Planck equation considering the normalized variable $\phi = n/N$, $P(\phi,t) = NP_n(t)$ and the functions $a_\pm(\phi)$ defined by

$$a_-(\phi) = \frac{g(n) - r(n)}{N} \qquad a_+(\phi) = \frac{g(n) + r(n)}{N}. \tag{1.42}$$

where $P(\phi,t)$ and $a_\pm$ are defined as $\phi \in \mathbb{R}$. And (1.37) is rewritten as

$$\frac{\partial P(\phi,t)}{\partial t} = -\frac{\partial[a_-P(\phi)]}{\partial \phi} + \frac{1}{2N}\frac{\partial^2}{\partial \phi^2}[a_+P(\phi)]. \tag{1.43}$$

The Fokker-Planck equation is obtained through an expansion in $1/N$ and the therm $\frac{1}{2N}\frac{\partial^2}{\partial\phi^2}[a_+P(\phi)]$ represents the fluctuations. the magnitude of the noise is $1/N$ and obviously disappears when $N \to \infty$. In that limit the equation becomes

$$\frac{\partial P(\phi,t)}{\partial t} + \frac{\partial[a_-P(\phi)]}{\partial \phi} = 0, \tag{1.44}$$

which is the continuity equation associated with the deterministic equation $\frac{d\phi}{dt} = a_-(\phi)$.

1.3.4 General expression for the stationary solution of linear one-step process (with detailed balance)

From (1.33) we have that the stationary solution is written as

$$\begin{aligned} 0 &= (\mathbb{E}_n - 1)r_n p_n^s + (\mathbb{E}_n^{-1} - 1)g_n p_n^s \\ &= (\mathbb{E}_n - 1)[r_n p_n^s - \mathbb{E}_n^{-1} g_n p_n^s]. \end{aligned} \tag{1.45}$$

This equation states that the terms in the square brackets are independent of n, then we define the net flow of probability J from n to $n-1$ as

$$-J = r_n p_n^s - \mathbb{E}_n^{-1} g_n p_n^s \tag{1.46}$$

If the detailed balance holds we have that $J = 0$, then

$$r_n p_n^s = g_{n-1} p_{n-1}^s. \tag{1.47}$$

Applying this relation repeatedly, we obtain

$$p_n^s = \frac{g_{n-1} g_{n-2} \cdots g_1 g_0}{r_n r_{n-1} \ldots r_2 r_1} p_0^s$$

which can be written in the more compact form,

$$p_n^s = \prod_{n=1}^{N} \frac{g_{n-1}}{r_n} p_0^s. \tag{1.48}$$

This equation determines all p_n^s in terms of p_0^s, which is subsequently fixed by the normalization condition

$$\frac{1}{p_0^s} = 1 + \sum_{n=1}^{N} \frac{g_0 g_1 \ldots g_{n-1}}{r_1 r_2 \ldots r_n}. \tag{1.49}$$

For an isolated system the stationary solution of the master equation p^s is identical with the thermodynamic equilibrium p^e [3].

1.3.5 Gaussian approximation and stable equilibrium

For systems without the absorbing state we can establish an analytical approximation for the equilibrium state, as long as p_n^s have a sharp maximum for $n = n_* \gg 1$. Introducing the functions $g(n) = g_n$ and $r(n) = r_n$ defined for real n which interpolates g_n and r_n and considering the deterministic mean field equation for the variable $\phi = n/N$. This equation follows in the limit $N \to \infty$ as a consequence of (1.44) and reads

$$\frac{d\phi}{dt} = a_-(\phi) \qquad a_-(\phi) = \frac{g(n) - r(n)}{N} = \frac{g(N\phi) - r(N\phi)}{N} \tag{1.50}$$

The $a_-(\phi)$ should be defined in the limit $N \to \infty$. For every N large we could write the equation for the n variable as

$$\frac{dn}{dt} = r(n) - g(n). \tag{1.51}$$

Supposing $a_-(\phi)$ has a critical point in $\phi = \phi_*$, where $n_* = N\phi_*$ this condition stands

$$a_-(\phi_*) = 0 \qquad a'_-(\phi_*) = g'(n_*) - r'(n_) < 0. \tag{1.52}$$

Where we consider $a'_-(\phi) = da_-(\phi)/d\phi = N^{-1}d/d\phi[g(n\phi) - r(N\phi)] = g'(n) - r'(n)$. Linearizing $a_-(\phi) = a'_-(\phi_*)(\phi - \phi_*)$ one find

$$\phi(t) = \phi_* + (\phi(0) - \phi_*)\, e^{a'(\phi_*)\, t} \tag{1.53}$$

In this way we can determine the relaxation time (τ) of the system

$$\tau = -\frac{1}{a'_-(\phi_*)} = -\frac{1}{g'(n_*) - r'(n_*)} \tag{1.54}$$

Assuming $n_* \simeq N$, namely ϕ_* not goes to zero for $N \to \infty$ we can obtain the equilibrium distribution by the detailed balance. Introducing the function $p(n) = p^s_n$ for integer n and considering equation (1.48) we define

$$f(n) = \log p(n) = \sum_{n=1}^{N} [\log g(n-1) - \log r(n)] \simeq \int_1^N [\log g(n-1) - \log r(n)]\, dn + \log p_1 \tag{1.55}$$

As $N \to \infty$ we replace the sum by an integral. If $f(n)$ has a maximum for $n = n_*$ the it is determinate by

$$f'(n_*) = 0 \qquad f'(n) = \log g(n-1) - \log r(n) = 0 \tag{1.56}$$

and by

$$f''(n_*) < 0 \qquad f''(n) = \frac{g'(n-1)}{g(n-1)} - \frac{r'(n)}{r(n)} \tag{1.57}$$

which reads

$$g(n_* - 1) = r(n_*) \tag{1.58}$$

If $n_* \simeq N$ we have [1]

$$g(n_*) = r(n_*) \qquad f''(n_*) = \frac{g'(n_*) - r'(n_*)}{g(n_*)} < 0 \tag{1.59}$$

Making for $f(n)$ a Taylor expansion on the second order around its maximum n_* we find

$$f(n) = f(n_*) - \frac{f''(n_*)}{2\ (n - n_*)^2}, \tag{1.60}$$

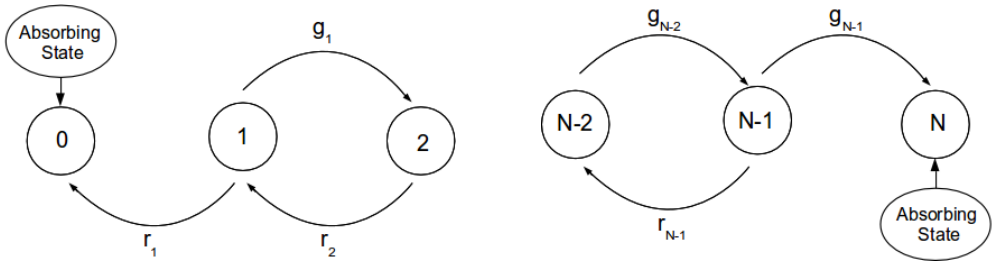
obtaining for $p(n)$ a Gaussian approximation

$$p(n) = C \exp\left(- \frac{(n - n_*)^2}{2\sigma^2} \right) \qquad \sigma^2 = -\frac{1}{f''(n_*)} \tag{1.61}$$

where the constant C is determined imposing that the $p(n)$ are normalized. We note that σ is in order of N.

1.3.6 Absorbing states

A state n_i is defined as absorbing when $t \to \infty$, $p^s_{n_i} \to 0$, that is, all probability distribution tends asymptotically to n_i and the equilibrium distribution can be write as $p^s_n \simeq \delta_{nn'}$. For the one-step process we can consider the Figure 1.2 to visualize how the transition rates behave. For an absorbing



(a) (b)

Figure 1.2: Illustration of an absorbing state: (a) at $n = 0$ and (b) at $n = N$.

state at $n = 0$ (see Figure 1.2a) we have: $g_0 = 0$, $r_1 \neq 0$ and $\frac{dp_0}{dt} = r_1 p_0$, what means when $t \to \infty$ the probability at the state $n = 0$,p_0 tends to

[1] Unless a correction of order $1/N$ respect to 1.

one. When we use the ideas of Master equation to model living organisms, a common interpretation for the absorbing state at $n = 0$ is death. Once the organism enters that state, it is not possible to leave. In this situation, the organism has entered an absorbing state. We also can analyze the behavior for an absorbing state at $n = N$ (see Figure 1.2b), in this case $g_{N-1} \neq 0$, $r_N = 0$ and $\frac{dp_N}{dt} = g_{N-1}p_{N-1}$ and for $t \to \infty$ all probability is concentrated in the state $n = N$.

The problem of a Master equation with an absorbing state for populations has been investigated by Dykman [13] and Assaf [14] with eikonal approximation, by Newman [15] with the moment closure approximation and by Nasell [16] with the quasi-stationary distribution, while Thomas [17] investigated the open biochemical reaction networks thought the linear noise approximation. In the Chapters 3 and 6 dedicate to the logistic growth and the BCM theory we will propose an alternative method to eliminate the absorbing state.

1.3.7 Chemical Master Equation

As we saw in the introduction the stochastic description of natural phenomena has been applied to a variety of problems and during the last decade has gained increasing popularity in other fields of science, such as Biology and Medicine. A reason for this expansion is that many biological processes are molecularly-based and hence the role of fluctuations can not be ignored. A natural way to cope with this problem is the chemical master equation (CME), that realizes in an exact way the probabilistic dynamics of a finite number of molecules, and recovers the chemical kinetics of the Law of Mass Action, in the thermodynamic limit ($N \to \infty$), using the mean field approximation [18, 8]. It is not a competing theory to the Law of Mass Action, rather, it extends the latter to the mesoscopic chemistry and biochemistry. The CME for a given system invokes the same rate constants as the associated deterministic kinetic model. Just as Schrödinger's equation is the fundamental equation for modeling motions of atomic and subatomic particle systems,

the CME is the fundamental equation for reaction systems. The CME can be understood as a huge system of coupled ordinary differential equations, there is one differential equation per state of the system, in contrast to the traditional reaction-rate approach where only one differential equation per species is required [19].

According to the theory of the CME, the stability of a state of a biochemical reaction system, i.e., the peak in the stationary distribution, is due to the biochemical reaction network. In other words, the epigenetic code could be distributive, namely, properties such as state stabilities are the outcome of the collective behavior of many components of a biochemical network. [5] The CME is a set of linear ordinary differential equations, there will be a unique steady state to which the system tends, the probability steady state, $p^s_{n,n'}$.

One naturally would like to approximate the CME in terms of a Fokker-Planck equation, van Kampen [3] has repeatedly emphasized that the Fokker-Planck approximation can be obtained for master equations only with small individual jumps.

Chapter 2

Stochastic analysis of a miRNA-protein toggle switch

Abstract

Within systems biology there is an increasing interest in the stochastic behavior of genetic and biochemical reaction networks. An appropriate stochastic description is provided by the chemical master equation, which represents a continuous time Markov chain (CTMC). In this work we consider the stochastic properties of a toggle switch, involving a protein compound and a miRNA cluster, known to control the eukaryotic cell cycle and possibly involved in oncogenesis, recently proposed in the literature within a deterministic framework. Due to the inherent stochasticity of biochemical processes and the small number of molecules involved, the stochastic approach should be more correct in describing the real system: we study the agreement between the two approaches by exploring the system parameter space. We address the problem by proposing a simplified version of the model that allows analytical treatment, and by performing numerical simulations for the full model. We observed optimal agreement between the stochastic and the deterministic description of the circuit in a large range of parameters, but some substantial differences arise in at least two cases:

1) when the deterministic system is in the proximity of a transition from a monostable to a bistable configuration, and 2) when bistability (in the deterministic system) is "masked" in the stochastic system by the distribution tails. The approach provides interesting estimates of the optimal number of molecules involved in the toggle. Our discussion of the points of strengths, potentiality and weakness of the chemical master equation in systems biology and the differences with respect to deterministic modeling are leveraged in order to provide useful advice for both the bioinformatician practitioner and the theoretical scientist.

Title: Stochastic analysis of a miRNA-protein toggle switch

Authors: E. Giampieri, D. Remondini, L. de Oliveira, G. Castellani, P. Lió

Journal: Molecular BioSystems - 2011 (published)

doi:10.1039/c1mb05086a.

Motivation of the work

Complex cellular responses are often modeled as switching between phenotype states, and despite the large body of deterministic studies and the increasing work aimed to elucidate the effect of intrinsic and extrinsic noise in such systems, some aspects still remain unclear. Molecular noise, which arises from the randomness of the discrete events in the cell (for example DNA mutations and repair) and experimental studies have reported the presence of stochastic mechanisms in cellular processes such as gene expression [20], [21], [22], decisions of the cell fate [23], and circadian oscillations [24]. Particularly, low copy numbers of important cellular components and molecules give rise to stochasticity in gene expression and protein synthesis, and it is a fundamental aspect to be taken into account for studying such biochemical models [25, 26]. In this work, we consider a simplified circuit that is known to govern a fundamental step during the eukaryotic cell cycle that defines cell fate, previously studied by means of a deterministic modeling approach [1]. Let set

the scene by reminding that "all models are wrong, but some are useful" (said by George Edward Pelham Box, who was the son-in-law of Ronald Fisher). Biologists make use of qualitative models through graphs; quantitative modeling in biochemistry has been mainly based on the Law of Mass Action which has been used to frame the entire kinetic modeling of biochemical reactions for individual enzymes and for enzymatic reaction network systems [27]. The state of the system at any particular instant is therefore regarded as a vector (or list) of amounts or concentrations and the changes in amount or concentration are assumed to occur by a continuous and deterministic process that is computed using the ordinary differential equation (ODE) approach. However, the theory based on the Law of Mass Action does not consider the effect of fluctuations. If the concentration of the molecules is not large enough, we cannot ignore fluctuations. Moreover, biological systems also show heterogeneity which occurs as a phenotypic consequence for a cell population given stochastic single-cell dynamics (when the population is not isogenic and in the same conditions). From a practical point of view, for concentrations greater than about 10 nM, we are safe using ODEs; considering a cell with a volume of 10^{-13} liters this corresponds to thousands of molecules that, under poissonian hypothesis, has an uncertainty in the order of 1%. If the total number of molecules of any particular substance, say, a transcription factor, is less than 1,000, then a stochastic differential equation or a Monte Carlo model would be more appropriate. Similarly to the deterministic case, only simple systems are analytically tractable in the stochastic approach, i.e. the full probability distribution for the state of the biological system over time can be calculated explicitly, becoming computationally infeasible for systems with distinct processes operating on different timescales. An active area of research is represented by development of approximate stochastic simulation algorithms. As commented recently by Wilkinson the difference between an âapproximateâ and âexactâ model is usually remarkably less than the difference between the "exact" model and the real biological process [28]. Given we can see this either as an unsatisfactorily state of art or as a promising

advancement, we can summarise the methodological approaches as following. Biochemical networks have been modeled using differential equations when considering continuous variables changing deterministically with time. Single stochastic trajectories have been modeled using stochastic differential equations (SDE) for continuous random variables, and using the Gillespie algorithm for discrete random variables changing with time. Another choice consists in characterizing the time evolution of the whole probability distribution. The corresponding equation for the SDE is the Fokker-Planck equation, and the corresponding equation for the Gillespie algorithm is called the Chemical Master Equation (CME) [5]. Therefore, as we said in the section 1.3 the CME could be thought as the mesoscopic version of the Law of Mass Action, i.e. it extends the Law of Mass Action to the mesoscopic chemistry and biochemistry, see for example [12, 29].

Here we compare the results of a stochastic versus deterministic analysis of a microRNA-protein toggle switch involved in tumorigenesis with the aim of identifying the most meaningful amount of information to discriminate cancer and healthy states. We show that the stochastic counterpart of such deterministic model has many commonalities with the deterministic one, but some differences arise, in particular regarding the number of stable states that can be explored by the system. In this work we consider a simplified, biologically meaningful, version of the model that allows to calculate an exact solution.

2.1 Properties of a microRNA toggle switch

The two pivotal factors in tumorigenesis are: oncogenes[1] and tumor-suppressor genes[2] [30]. Recent evidences indicate that MicroRNAs (miR-

[1]Oncogene is a gene that normally directs cell growth. If altered, an oncogene can promote or allow the uncontrolled growth of cancer. Alterations can be inherited or caused by an environmental exposure to carcinogens.

[2]Tumor-suppressor genes are genes that protects a cell from one step on the path to cancer. When these genes are mutated to cause a loss or reduction in they function, the

NAs) can function as tumor suppressors and oncogenes, and these miRNAs associated with cancer are referred to as oncomirs. MiRNAs are small, non-coding RNAs that modulate the expression of target mRNAs. The biogenesis pathway of miRNAs in animals was elucidated by Bartel [31]. In normal tissue, proper regulation of miRNAs maintains a normal rate of development, cell growth, proliferation, differentiation and apoptosis. Tumorigenesis can be observed when the target gene is an oncogene, and the loss of the miRNA, which functions as a tumor suppressor, might lead to a high expression level of the oncoprotein. When a miRNA functions as an oncogene, its constitutive amplification or overexpression could cause repression of its target gene, which has a role of tumor suppressor gene, thus, in this situation, cell is likely to enter tumorigenesis. MiRNAs are often part of toggle switches [32, 33]: important examples involve gene pairs built with oncogenes and tumour suppressor genes [34, 35]. Here we focus on the amplification of 13q31-q32, which is the locus of the the miR-17-92. The miR-17-92 cluster forms a bistable switch with Myc and the E2F proteins [36, 37, 1]. The oncogene Myc regulates an estimated 10% to 15% of genes in the human genome, while the disregulated function of Myc is one of the most common abnormalities in human malignancy [38, 39]. The other component of the toggle is the E2F family of transcription factors, including E2F1, E2F2 and E2F3, all driving the mammalian cell cycle progression from G1 into S phase. High levels of E2Fs, E2F1 in particular, can induce apoptosis in response to DNA damage. The toggle also interacts with dozens of genes (see figure 2.1 depicts a portion), particularly with Rb and other key cell-cycle players. A summary of the experiments perturbing miRNA/Myc/E2F and E2F/RB behaviours have suggested the following:

- The Rb/E2F toggle switch is OFF when RB inhibits E2F, i.e. stopping cell proliferation; it is ON when E2F prevails and induces proliferation.

cell can progress to cancer, usually in combination with other genetic changes. The loss of these genes may be even more important than oncogene activation for the formation of many kinds of human cancer cells

Once turned ON by sufficient stimulation, E2F can memorize and maintain this ON state independently of continuous serum stimulation.

- The proteins E2F and Myc facilitate the expression of each other and the E2F protein induces the expression of its own gene (positive feedback loop). They also induce the transcription of microRNA-17-92 which in turn inhibits both E2F and Myc (negative feedback loop).

Moreover, the increasing levels of E2F or Myc drive the sequence of cellular states, namely, quiescence, cell proliferation (cancer) or cell death (apoptosis).

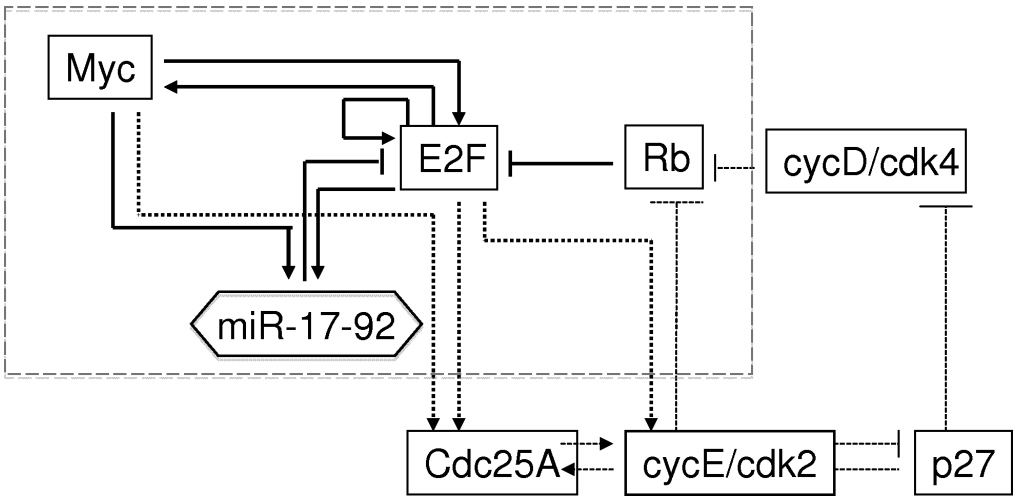


Figure 2.1: The E2F-MYC-miR-17-92 toggle switch with its biochemical environment (derived form [1]). Arrows represent activation, and bar-headed lines inhibition, respectively. The elements inside the dashed box represent the protein compound p (Myc-E2F) and the miRNA cluster m (miR-17-92), modelized in eq. 2.1 and 2.2.

Although there is increasing amount of research on cell cycle regulation, the mathematical description of even a minimal portion of the E2F, Myc and miR-17-92 toggle switch is far from trivial. Aguda and collaborators [1] have developed a deterministic model, which reduces the full biochemical network

of the toggle switch to a protein (representing the E2F-Myc compound) and the microRNA-17-92 cluster (seen as a single element).

It is a 2-dimensional open system, in which p represents the E2f-myc complex and m the miRNA cluster: thus no Mass Action Law holds, *and the total p and m concentration is not conserved.* The dynamics of p and m concentrations are described by

$$\dot{p} = \alpha + \frac{k_1 \cdot p^2}{\Gamma_1 + p^2 + \Gamma_2 \cdot m} - \delta \cdot p \tag{2.1}$$

$$\dot{m} = \beta + k_2 \cdot p - \gamma \cdot m \tag{2.2}$$

The model is conceptually quite simple: we have two creation-destruction processes for p and m driven by α, δp, β and γm, with a term $k_2 p$ which represents an additional source of miRNA due to the protein complex p. The interesting part is the nonlinear term of the p derivative, which is a modified Hill equation of order 2 driven by the k_1 parameter. This term is a representation of a self-promotion effect driven by a sigmoidal activation curve, a very common fenomena in gene regulation systems. The Γ_1 term is the "critical value" where the sigmoid switch to it's higher status and the Γ_2 term represent the inibition due to the miRNA regulation machinery.

All the effects described in this work are very robust to the choice of the specific order of the Hill reaction (here chosen as 2 for continuity with the original work [1]), as long as it's greater than one. It's actually robust even if a different functional form is hypotized, as long as it retains it's sigmoidal structure.

The system can be rewritten in an adimensional form as follows:

$$\epsilon\dot{\phi} = \alpha' + \frac{k \cdot \phi^2}{\Gamma'_1 + \phi^2 + \Gamma'_2 \cdot \mu} - \phi \tag{2.3}$$

$$\dot{\mu} = 1 + \phi - \mu \tag{2.4}$$

Where the parameters are: $\alpha' = \frac{k_2}{\delta \cdot \beta}\alpha$, $k = \frac{k_1 k_2}{\delta\beta}$, $\Gamma'_1 = \frac{k_2^2}{\beta^2}\Gamma_1$, $\Gamma'_2 = \frac{k_2^2}{\beta\gamma}\Gamma_2$, $\epsilon = \frac{\gamma}{\delta}$ and the change of variables is: $\phi = \frac{k_2}{\beta}p$, $\mu = \frac{\gamma}{\beta}m$ and $\tau = \gamma t$. In this way, the fixed points for the system are determined by

$$\alpha' + \frac{k \cdot \phi^2}{\Gamma'_1 + \phi^2 + \Gamma'_2 \cdot \mu} - \phi = 0 \tag{2.5}$$

and

$$1 + \phi - \mu = 0. \tag{2.6}$$

From equation (2.6) we have $1 + \phi = \mu$, replacing this result in (2.5) we obtain following cubic equation:

$$\alpha' + \frac{k\phi^2}{\Gamma'_1 + \phi^2 + \Gamma'_2 \cdot (1 + \phi)} - \phi = 0, \tag{2.7}$$

whose can be reduced as

$$\phi^3 + a\phi^2 + b\phi + c = 0 \tag{2.8}$$

where

$$\begin{aligned} a &= \Gamma'_2 - (\alpha' + k) \\ b &= \Gamma'_1 + \Gamma'_2(1 - \alpha') \\ c &= -\alpha'(\Gamma'_1 + \Gamma'_2). \end{aligned} \tag{2.9}$$

The solutions of (2.8) should be real and positive, because ϕ represents the concentration of molecules of p. From the Descartes' rule of signs [40] a polynomial with degree n has a number of positive zeros corresponding to the number of signal changes between two consecutive coefficients. Therefore, from (2.8) we have

$$\begin{aligned} a &< 0 \Rightarrow \Gamma'_2 - (\alpha' + k) < 0 \\ b &> 0 \Rightarrow \Gamma'_1 + \Gamma'_2(1 - \alpha') > 0 \\ c &< 0 \Rightarrow -\alpha'(\Gamma'_1 + \Gamma'_2) < 0. \end{aligned} \tag{2.10}$$

Which lead us to determine the necessary (but not sufficient) condition for the existence of 3 steady states (and thus a bistable system)

$$(\Gamma'_2 - k) < \alpha' < \left(1 + \frac{\Gamma'_1}{\Gamma'_2}\right). \tag{2.11}$$

The system represented by equations (2.1) and (2.2) is a one-step process (see section 1.3), therefore we can study it as a stochastic system through

the CME approach. The resulting CME has two variables, the number of p and m molecules, labeled as n and m. The mean field equations can be written replacing $\Phi_1 = p/N$ and $\Phi_2 = m/N$, where N is the total number of molecules

$$\dot{\Phi}_1 = \frac{\alpha}{N} + \frac{k_1 \cdot \Phi_1^2}{N\Gamma_1 + \Phi_1^2/N + \Gamma_2 \cdot \Phi_2} - \delta \cdot \Phi_1 \qquad (2.12)$$
$$\dot{\Phi}_2 = \beta/N + k_2 \cdot \Phi_1 - \gamma \cdot \Phi_2.$$

The temporal evolution in the probability, $p_{n,m}(t)$, to have n and m molecules at time t is described by the following bidimensional master equation:

$$\dot{p}_{n,m} = (\mathbb{E}_n - 1) r_n p_{nm} + (\mathbb{E}_n^{-1} - 1) g_n p_{nm} + (\mathbb{E}_m - 1) r_m p_{nm} + (\mathbb{E}_m^{-1} - 1) g_m p_{nm} \qquad (2.13)$$

The two generation and recombination terms associated with the n and m variables are respectively:

$$g_n = \alpha/N + \frac{k_1 \cdot n^2}{N\Gamma_1 + n^2/N + \Gamma_2 \cdot m}; \qquad r_n = \delta \cdot n \qquad (2.14)$$

$$g_m = \beta/N + k_2 \cdot n; \qquad r_m = \gamma \cdot m. \qquad (2.15)$$

2.1.1 The one-dimensional model

We can reduce the problem from two to one dimension, by considering a different time scale for the two reactions (in particular considering $\dot{m} \gg \dot{p}$) and thus considering the steady state solution for the m:

$$m = \frac{\beta + k_2 \cdot p}{\gamma} = \beta' + k' \cdot p, \qquad (2.16)$$

therefore we have

$$\dot{p} = \alpha + \frac{k_1 \cdot p^2}{\Gamma' + \Gamma'' \cdot p + p^2} - \delta \cdot p \qquad (2.17)$$

where $\Gamma' = \frac{\Gamma_2 \cdot k_2}{\gamma}$ and $\Gamma'' = \Gamma_1 + \frac{\Gamma_2 \beta}{\gamma}$. Following what we have done in (2.13) we can replace $\Phi = p/N$ and obtain the one-dimensional deterministic equation

$$\dot{\Phi} = N\alpha + \frac{k_1 \cdot \Phi^2}{N\Gamma' + \Gamma'' \cdot \Phi + \Phi^2/N} - \delta \cdot \Phi \qquad (2.18)$$

The stochastic equation for p_n is thus as follows:

$$\dot{p_n} = (\mathbb{E} - 1)r_n \cdot p_n + (\mathbb{E}^{-1} - 1)g_n \cdot p_n \tag{2.19}$$

$$g_n = \alpha N + \frac{k_1 \cdot n^2}{N\Gamma' + \Gamma'' \cdot n + n^2/N}; \qquad r_n = \delta \cdot n \tag{2.20}$$

The one-dimensional system presents detailed balance condition, therefore we can obtain the general solution, as introduced in (see 1.3.4),

$$p_n^s = \prod_{i=1}^{N} \frac{g(i-1)}{r(i)} \cdot p_0 = \prod_{i=1}^{N} \frac{\alpha N + \frac{k_1 \cdot i^2}{N\Gamma' + \Gamma'' \cdot i + i^2/N}}{\delta \cdot i} \cdot p_0 \tag{2.21}$$

with an adequate normalization factor imposed on p_0:

$$p_0 = \frac{1}{1 + \sum_{i=1}^{N} \prod_{i=1}^{N} p_n^s}. \tag{2.22}$$

We remark that the system is open, thus in theory N is not fixed, but we can truncate the product to a sufficiently high value of N obtaining a good approximation of the whole distribution. This one-dimensional system (for which an analytical solution can be obtained) will be compared to numerical simulations of the exact one-dimensional and two-dimensional systems.

2.2 Model Analysis

2.2.1 The stationary distribution

The one-dimensional model can show monomodal as well as bimodal stationary distributions, depending on the parameters considered. As an example, we obtain bistability with a set of parameters as shown in Fig. 2.2.

Thus the qualitative features of the two-dimensional deterministic model (i.e. the possibility of being bistable depending on the parameter range) are recovered for the one-dimensional approximation of the stochastic system. Also the two-dimensional stochastic system shows bistability for the same parameters, and they are in optimal agreement for a range of parameters in

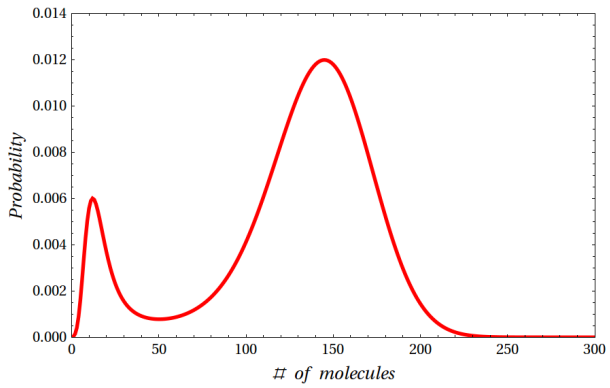


Figure 2.2: The stationary distribution for the one-dimensional space, obtained using the following parameters: $\alpha = 0.0056(molecule/h)$, $\beta = 6.7 \cdot 10^{-4}(molecule/h)$, $\delta = 0.2(h^{-1})$, $\gamma = 0.2(h^{-1})$, $\Gamma_1 = 34.3333(molecule^2)$, $\Gamma_2 = 1006(molecule)$, $k_1 = 0.3(molecule/h)$ and $k_2 = 5.5 \cdot 10^{-}7(h^{-}1)$.

which the $\dot{m} \gg \dot{p}$ condition holds

We also observe some remarkable differences between the deterministic and the stochastic models: there are regions in parameter space in which the deterministic approach shows only one stable state, but in the stochastic system two maxima in the stationary distribution are observed (see Fig. 2.3). This difference can be explained qualitatively as follows: for the deterministic system, there are parameter values for which the system is monostable but very close to the "transition point" in which the system becomes bistable. It is known that in these situations a "ghost" remains in the region where the stable point has disappeared [41], for which the systems dynamics has a sensible slowing down (i.e. when the system is close to the disappeared fixed point, it remains "trapped" for a longer time close to it, in comparison with other regions). This behaviour results in the presence of a peak in the stationary distribution of the corresponding stochastic systems, that thus remains bistable also when the deterministic system is not anymore.

Another difference is observed: for some parameter values the deterministic system is bistable, but the stochastic distribution shows a clear peak

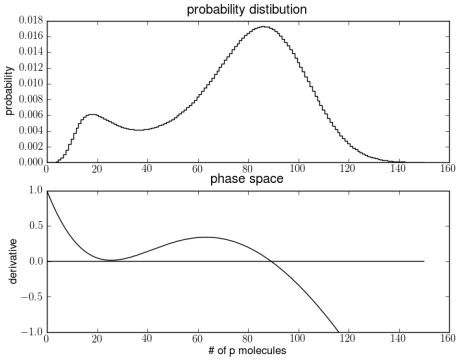


Figure 2.3: Comparison between the deterministic vetorial field (bottom) and the stationary distribution (top) for the parameter set as in Table 2.1, case 3.

for the maximum with the largest basin of attraction and the smaller peak results "masked" by the tail of the distribution around the first peak (see Fig. 2.4), thus resulting in a monomodal distribution with a long tail. In practice, the highest state behaves like a sort of metastable state, since the states of the system with a high protein level are visited only occasionally.

2.2.2 Numerical analysis

Here we implemented numerical methods to find the stationary distribution of a CME. The most accurate is the Kernel resolution method (see 1.2.3): given the complete transition matrix of the system, it is possible to solve numerically the eigenvalue problem, obtaining the correct stationary distribution. This method, in this case, has a serious drawback: the system is of non-finite size, preventing a complete enumeration of the possible states. Even with a truncation, the system size rises in a dramatic way: the state space for a bidimensional system is of order N^2 if N is the truncation limit, and thus the respective transition matrix is of order N^4. This means that even for a relatively small system (with a few hundred of molecules) the matrix size explodes well beyond the computational limits. The only

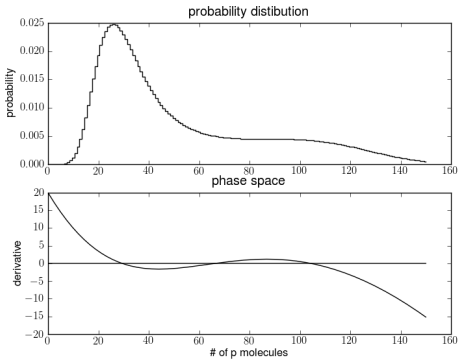


Figure 2.4: Comparison between the deterministic vetorial field solution (bottom) and the stationary distribution (top) for the parameter set as in Table 2.1, case 4.

feasible resolution strategy is a massive exploration of state space by Montecarlo methods, in which single trajectories of the system are simulated: performing this simulations long enough for several times allows to estimate the stationary distribution.

The Montecarlo method we chose is a modified version of the SSA algorithm (also known as the Gillespie algorithm) named logarithmic direct method [42, 43], which is a statistically correct simulation of an ergodic Markov system. It is not the fastest algorithm available, as compared to other methods like the next-reaction or the τ-leap method, but it produces a correct estimation of the statistical dispersion of the final state.

For each parameter set we performed 10 simulations for about $10^6 - 10^7$ iteration steps each. The multiple simulations were averaged together for a better estimation of the stationary distribution, and they allowed also an estimation of the variance over this average distribution.

In the following we discuss four cases that describe the system behaviour for different parameter settings, shown in Table 2.1.

In case 1, we have a system in which the hypothesis of a time-scale separation between m and p is strongly satisfied. The simulation was performed up to a time limit of 10^3: we can see how the two resulting distributions are

Table 2.1: Table of the parameter sets for the cases considered.

Par	Case 1	Case 2	Case 3	Case 4
α (molecule/h)	0.0033	0.0056	0.0033	0.0666
δ (h^{-1})	1.0	0.20	0.09	1.19
β (molecule/h)	0.0033	$6.7 \cdot 10^{-4}$	0.0	0.0033
γ (h^{-1})	100.0	0.20	10.0	1.0
k_1 (molecule/h)	0.1	0.3	0.0416	0.7666
k_2 ($h^{-}1$)	0.0011	$5.5 \cdot 10^{-}7$	$1.1 \cdot 10^{-4}$	$1.1 \cdot 10^{-4}$
Γ_1 (molecule^2)	0.2	34.33	17.66	40.33
Γ_2 (molecule)	10.0	1006.0	10.0	10.0

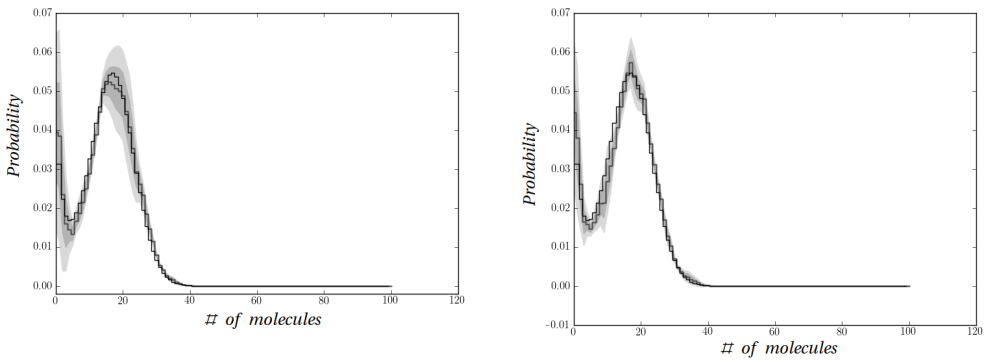


Figure 2.5: Case of good agreement between the theoretical and obtained distribution (see Tab. 2.1, case 1). Left: one-dimensional system, right: two-dimensional system. The thin black line is the theoretical distribution obtained from Eq. 2.21. The thick dark grey line is the average of the various simulations, while the grey and light grey areas represent the range of one and two standard deviations from the average distribution.

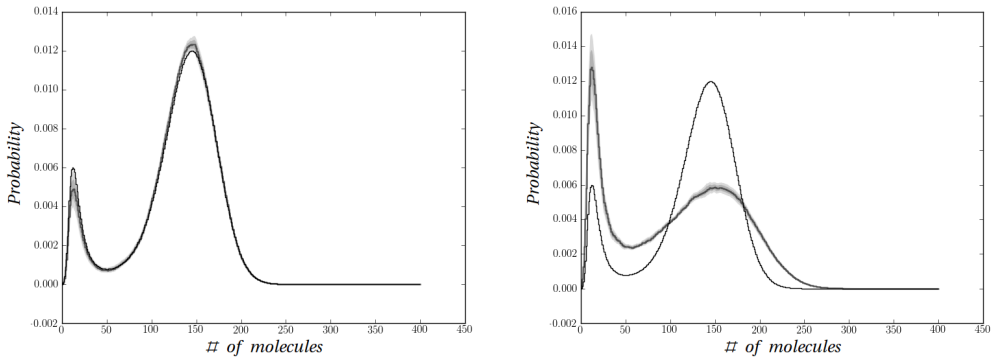


Figure 2.6: Case of poor agreement between the theoretical and obtained distribution (see Tab. 2.1, case 2). Left: one-dimensional system, right: two-dimensional system. The thin black line is the theoretical distribution obtained from Eq. 2.21. The thick dark grey line is the average of the various simulation, while the grey and light grey areas represent the range of one and two standard deviations from the average distribution.

in good agreement with the theoretical one (see Fig. 2.5), with the regions of higher variance of the histogram around the maxima and minima of the distribution.

In case 2, the time-scale separation assumption does not hold, due to the very low value of γ and k_2: even if this condition doesn't guarantee that the stationary state will be different from the approximate one-dimensional solution, with this set of parameters we can see a huge difference between the two distributions (Fig. 2.6).

In case 3, as defined before, we observe a "ghost" in which, even if a deterministic stable state does not exist, we can clearly see a second peak in the distribution (Fig. 2.7). In this system the time-scale separation assumption holds, and we can see how both distributions show similar features.

In this final case (Tab. 2.1, case 4, Fig. 2.8) we can see another effect, in which the peak related to a deterministic stable state is masked by the tail of the stronger peak, becoming just a fat tail. Even without a strong time-scale separation for the m and p variables, we can see how both systems give a very

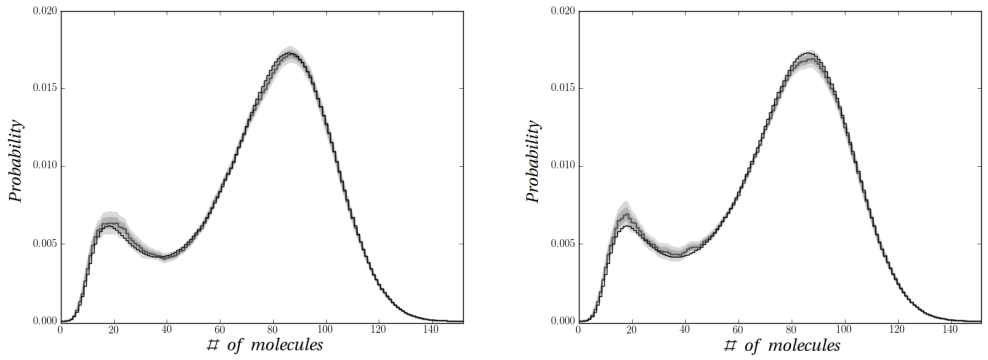


Figure 2.7: Case 3, "ghost effect": only the biggest peak comes from a deterministic stable point. Left: one-dimensional system, right: two-dimensional system. The thick dark gray line is the average of the various simulation, while the gray and light gray areas represent the range of one and two standard deviations from the average distribution.

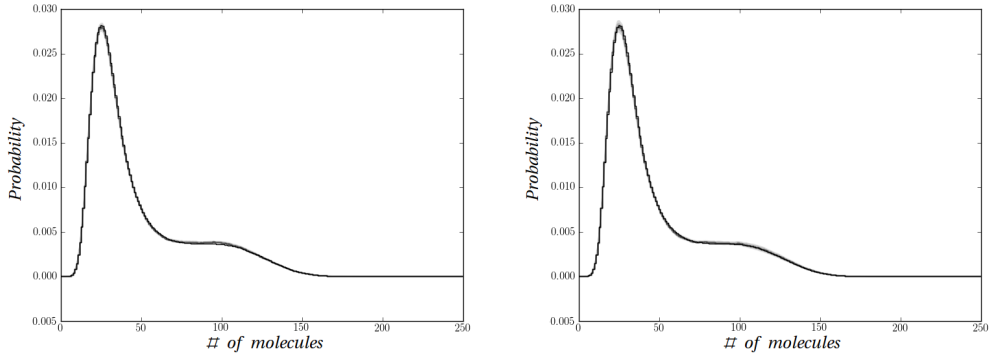


Figure 2.8: Case 4, peak masking effect (parameters as in Tab. 2.1, case 4). The deterministic system has two stable points, but only the peak related to the smallest stable point (with the largest basin of attraction) is visible. Left: one-dimensional system, right: two-dimensional system.

similar response, evidencing that this effect is very robust. Increasing the γ and k_2 values does not affect the distribution as long as their ratio is kept constant. Note that while there are several computational tools for discrete-state Markov processes such as PRISM [44], APNNtoolbox [45], SHARPE [46], or Mobius [47], there is very little for CMTC (see for instance [48]). Different modeling approaches for toggle switches do exists in the area of formal methods (see for example [49, 50]).

2.3 Discussion of the results

We have studied a stochastic version of a biochemical circuit that is supposed to be involved in cell cycle control, with implications for the onset of severe diseases such as cancer, consisting of a gene cluster (Myc-E2F) and a miRNA cluster (mir-17-92). This cluster has been reported in very large number of cancer types: particularly in different types of lymphomas, glioma, non-small cell lung cancer, bladder cancer, squamous-cell carcinoma of the head and neck, peripheral nerve sheath tumor, malignant fibrous histiocytoma, alveolar rhabdomyosarcoma, liposarcoma and colon carcinomas. This huge variety of cancer stresses the centrality of this toggle switch and suggests that advancement in modeling this toggle could lead to insights into differences between these cancers. This aim is still far but we are delighted to report that our modeling approach shows important results inching to that direction. First of all, many features are recovered as observed for the deterministic version of the same system, also by means of a further approximation that reduces the system to an unique variable: in this case the system can be treated analytically, and compared to the one- and two-dimensional numerical simulations.

The stochastic approach, that is the exact approach when the number of molecules involved is low, shows a different behaviour than the deterministic one in two situations we have observed. It is noteworthy that the number of molecules involved shows some agreement with the estimates by [51] and

by [52] for other miRNA-systems (see also [53]). The cell volume is assumed 10^{-13} liters, then 1 nM =100 molecules.

First, bistability in the stochastic system (namely, the possibility of having two stable states, one associated to a resting and the other to a proliferative cell state) is observed also in situations in which the corresponding deterministic system is monostable, and this can be explained by the presence of a "ghost" state in the deterministic system that is strong enough to produce a second peak in the stationary distribution of the stochastic model.

Secondly, there are situations in which the peak for the stochastic distribution related to the highest level of expression (with parameter values for which the deterministic system is bistable) is masked by the tail of the distribution of the lowest-expression maximum (that is related to the largest basin of attraction in the deterministic model), making the "proliferative state" appear almost as a scarcely visited metastable state. This is an interesting behaviour, that should be further investigated in real experimental data of protein concentration and gene expression related to the biochemical circuit considered. The "metastable" and the "fully" bimodal distributions could be associated to healthy and tumoral cell states respectively, because the highest "proliferative" state has different properties in the two cases. From a biological point of view such state, being associated to a dysregulated, disease-related conditions, could actually represent a compendium of several dysregulated states.

We argue that the deterministic approach to this biochemical circuit is not capable to characterize it completely, and the stochastic approach appears more informative: further features unique to the stochastic model could be obtained by considering different time patterns for the molecular influxes to the system, and this point in our opinion should deserve more investigation in a future work. MicroRNAs (miRNAs) express differently in normal and cancerous tissues and thus are regarded as potent cancer biomarkers for early diagnosis. We believe that the potential use of oncomirs in cancer diagnosis, therapies and prognosis will benefit accurate cancer mathematical models.

Given that MiR-17-5p seems to act as both oncogene and tumor suppressor through decreasing the expression levels of anti-proliferative genes and proliferative genes, this behavior is suggestive of a cell type dependent toggle switch. Therefore fitting of experimental data could provide insights into differences among cancer types and on which cell type is behaving differently.

Chapter 3

One parameter family of master equations for logistic growth

Abstract

We propose a one parameter family of master equations for the evolution of a population having the logistic equation as mean field limit. The parameter α determines the relative weight of linear versus non linear terms in the population number $n \leq N$ entering the loss term. By varying α from 0 to 1 the equilibrium distribution changes from a Gaussian centered near the stable critical point of the mean field equation to a power law peaked at the unstable critical point. A bimodal distribution is observed in the transition region. In the mean field limit $N \to \infty$, for any fixed value of α, only the Gaussian solution, whose limit is a δ function, survives and allows a consistent interpretation of the model. The choice of the master equation in this family depends on the equilibrium distribution for finite values of N. The presence of an absorbing state for $n = 0$ does not change this picture since the extinction mean time grows exponentially fast with N with a coefficient which vanishes for $\alpha = 1$. As a consequence for α close to zero extinction is not observed, wheres as α approaches 1 the relaxation to a power law occurs before the extinction occurs with relaxation time exponential in $(1 - \alpha)N$.

Motivation of the work

Many biological phenomena are intrinsically stochastic and this seems to be a distinctive feature of fundamental processes such as cell growth [54], cellular development and differentiation [55, 56, 28], gene expression [57, 58, 59, 60, 61, 62], synaptic plasticity [63, 64] and aging [65, 66, 67]. The natural way to deal with such a stochasticity is the master equation approach, that allows a precise treatment of noise and fluctuations and to derive analytically, in some cases, the resulting probability distribution. A possible example is provided by the dynamics of genetic networks which involve a large number of biochemical reactions. This dynamics is non linear and has a stochastic character, since the number of a given species of molecules is small and fluctuations are relevant [68, 17]. As a consequence a master equation, rather than a deterministic differential equation, is frequently used for modeling [69, 70, 71]. A difficulty related to this approach [17] is that the macroscopic dynamics, specified by a deterministic differential equation for the population(s), does not uniquely determine the master equation which depends on the noise field, corresponding to the diffusive term in the related Fokker-Planck equation [3, 4]. Its specification requires additional information on the microscopic dynamics which is usually not available. The arbitrariness can be partially removed by some additional information concerning the equilibrium distribution and the relaxation time required to reach it [68, 72]. The fact that different master equations can have the same mean field limit leads to different statistical properties (different variances) and to the possible presence of absorbing states. The boundary conditions play a relevant role and various options are allowed [13, 16, 73, 74]. A possible choice leads to an absorbing null state, namely its probability monotonically increases with time until it reaches the value 1 asymptotically [13, 16]. The presence of an absorbing state is allowed even when the mean field equation has a stable equilibrium with a finite population . This apparent contradiction is resolved taking into account that the relaxation time grows exponentially fast with the maximum number N of individuals. As a consequence

for N large enough the null state is never reached in the time scales relevant for the problem. The presence on an absorbing state leads, in the large N limit [3], to a Fokker-Planck equation whose equilibrium solution is not normalizable. In some cases however the presence of an absorbing is physically significant since it describes the extinction of a population, but it is relevant to control the time required to reach such a state. The stochastic logistic process has been studied using a variety of techniques in more recent years. In particular, numerous authors have derived exact summation formulas for the mean extinction time of the population [16, 15, 14, 75]. We propose here a one parameter family of master equation models, having the same mean field population equation and corresponding each one to a specific noise. Starting from macroscopic data, the choice of the parameter specifying the model can be achieved by considering the equilibrium state for a fixed value of N. The family we propose depends on a parameter $\alpha \in [0, 1]$ such that for $\alpha \to 0$ the probability distribution p_n is a Gaussian peaked near the stable equilibrium of the deterministic equation $n = N$, whereas for $\alpha \to 1$ a Pareto like power law distribution is obtained, so that all the states are populated the low ones being preferred. For intermediate values of α a smooth transition between these states is observed and a bimodal distributions appears. The approach based on a one parameter family of master equations is applied to the logistic growth of one population. In this case the family of master equations for two populations depends on the parameter $\alpha \in [0, 1]$. For $\alpha \to 0$ the equilibrium distribution corresponds to the stable equilibrium of the mean field equation, whereas for $\alpha \to 1$ a power law is obtained so that the populated states are close to the unstable equilibrium of the mean field equation corresponding to total extinction. We show that letting $N \to \infty$ the system for any value of $\alpha < 1$ evolves towards the stable equilibrium of the mean field equation.

3.1 The logistic model

The logistic model describes the limited growth of a population due to a finite availability of resources and it is formulated as a one dimensional differential equation with a linear Malthusian term and a quadratic one controlling the growth. The mean field equation for the logistic growth reads

$$\frac{dx}{dt} = x(1 - \frac{x}{N}), \tag{3.1}$$

which has an unstable equilibrium at $x = 0$ and a stable one at $x = N$. We can rewrite (3.1) considering the relative population and defining $\phi = x/N$

$$\dot{\phi} = \phi(1 - \phi). \tag{3.2}$$

Letting n and N be the the number of individuals at time t, when N is a small integer number the fluctuations are relevant and the process must be described by a master equation, then for equation (3.1) the generation and recombination terms can be chosen as

$$g_n = n \quad \text{and} \quad r_n = \frac{n(n-1)}{N}, \tag{3.3}$$

and the master equation is (1.33)

$$\dot{p}_n = (\mathbb{E}_n - 1)\frac{n(n-1)}{N}p_n + (\mathbb{E}_n^{-1} - 1)np_n. \tag{3.4}$$

We have that $g_0 = r_1 = 0$, as a consequence $\frac{dp_0}{dt} = 0 \rightarrow p_0 = constant$, we choose $p_0 = 0$ because in this manner we decouple the state $n = 0$ of rest of the system. Therefore the equilibrium solution, obtained from the detailed balance condition (1.48), is written in function of the state p_1,

$$p_n^s = \prod_{i=2}^{N} \frac{g_{i-1}}{r_i}\, p_1. \tag{3.5}$$

And from the normalization we have, $\sum_{n=1}^{N} p_n^s = 1$.

We are also interesting to study the behavior for $N \rightarrow \infty$, then we use (as we presented in section 1.3.3) the definition of the Fokker-Planck equation

(1.37), where

$$a_-(\phi) = \phi\left(1 - \phi + \frac{1}{N}\right) \qquad a_+(\phi) = \phi\left(1 + \phi - \frac{1}{N}\right). \tag{3.6}$$

In this way, the probabilities $P(\phi, t)$ are

$$\frac{\partial P(\phi,t)}{\partial t} = \frac{\partial}{\partial P(\phi)}[(\phi(\phi - 1 - \frac{1}{N})P(\phi)] + \frac{1}{2N}\frac{\partial^2}{\partial P(\phi)^2}[(\phi(\phi + 1 - \frac{1}{N})P(\phi)]. \tag{3.7}$$

To determine the stationary solution P^s_ϕ we note that

$$\frac{a_-}{a_+} = -1 + \frac{2}{1 + \phi - 1/N}, \tag{3.8}$$

by a simple integration we find

$$P^s(\phi) = P(0)\frac{\exp(2NF(\phi))}{\phi(\phi + 1 - \frac{1}{N})} \qquad F(\phi) = -\phi + 2\log(1 + \phi - \frac{1}{N}). \tag{3.9}$$

where $P(0)$ is a normalization constant and $P(\phi)$ is defined in the interval $[1/N, 1]$.

The choice of the generation and recombination terms is arbitrary, for example, if we choose the generation and recombination terms as

$$g_n = n \quad \text{and} \quad r_n = \frac{n^2}{N}, \tag{3.10}$$

We have that $g_0 = 0$ and $r_1 = 1/N$, in this way $\frac{dp_0}{dt} = \frac{p_1}{N}$, and the stationary solution is given by

$$p^s_n = \prod_{i=1}^{N} \frac{g_{i-1}}{r_i}\, p_0. \tag{3.11}$$

Analyzing the first 3 stationary states we have

$$\begin{aligned} \text{For} \quad n = 1 \qquad & p^s_0 = \frac{g_0}{r_1} p_1 = 0, \\ \text{for} \quad n = 2 \qquad & p^s_2 = \frac{g_1}{r_2}\, p_1 = 0, \\ \text{for} \quad n = 3 \qquad & p^s_3 = \frac{g_2}{r_3}\, p_2 = 0. \end{aligned} \tag{3.12}$$

It is clear from (3.13) that $n = 0$ is an absorbing state [3], because we have $\sum_{n=1}^{N} p_n^s = 0$, because $p_1^s = p_2^s = \ldots = p_N^s = 0$, therefore the stationary solution can be only,

$$p_n^s = \delta_{n,0}. \tag{3.13}$$

All other solutions of the master equation tend towards it, i.e., with that probability the population will ultimately die out, which was not observed in the last case.

We can also analyze the behavior of the Fokker-Planck equation, in this case

$$a_-(\phi) = \phi - \phi^2 \qquad a_+(\phi) = \phi + \phi^2. \tag{3.14}$$

where $P(\phi, t)$ are

$$\frac{\partial P(\phi,t)}{\partial t} = \frac{\partial}{\partial \phi}[(\phi - \phi^2)P(\phi)] + \frac{1}{2N}\frac{\partial^2}{\partial \phi^2}[(\phi + \phi^2)P(\phi)]. \tag{3.15}$$

To determine the stationary solution P_ϕ^s we note that

$$\frac{a_-}{a_+} = \frac{(1-\phi)}{(1+\phi)} \tag{3.16}$$

by a simple integration we find

$$P^s(\phi) = P(0)\frac{\exp(2NF(\phi))}{\phi + \phi^2} \qquad F(\phi) = -\phi + 2\log(1+\phi). \tag{3.17}$$

where $P(0)$ is a normalization constant.

Note: $P(\phi)$ is defined in $[0, 1]$, but for $n = 0$ the equation (3.17) has a singularity and $P(\phi)$ is not normalizable. Furthermore in the same point[1] the master equation presents an absorbing state. Consequently, an absorbing state in the master equation is associated with a singularity in the Fokker-Planck equation.

3.1.1 One parameter family and elimination of the absorbing state

Considering the logistic equation as written in (3.2), we can rescale the time (t) according to the following parametrization $t' = t(1 - \alpha)$, hence we

[1] Remember: $n = 0 \to \phi = n/N = 0$

obtain,

$$\frac{d\phi}{dt} = \phi - \alpha\phi - (1-\alpha)\phi^2. \tag{3.18}$$

If we choose $g_n = (1-\alpha)n$ and $r_n = (1-\alpha)\frac{n(n-1)}{N}$, it coincides with the equation (3.3) except for the term $(1-\alpha)$ that serve as the rescaling the time. Nevertheless, we choose $g_n = n$ and $r_n = \alpha n + (1-\alpha)\frac{n(n-1)}{N}$, because we obtain a Master equation for which the difference $a_- = (g_n - r_n)/N$ change just for a multiplicative factor $(1-\alpha)$ whereas $a_+ = (g_n + r_n)/N$ has a dependence in α different from $(1-\alpha)$, consequently changing α we change the noise. The parameter α determines the relative weight of linear versus non linear terms in the population number. By varying α we can study the variation of the stationary solution. The choice of the model in the one parameter family and the eventual presence of an absorbing state can be determined by some additional information on the system. Since the information on the noise term is hardly accessible the knowledge of the equilibrium distribution for different values values of N and eventually the relaxation time might allow the specification of the model master equation.

Reminding the results presented in Section 3.1, the master equation (3.4) has an absorbing state in $n = 0$. If we set the transitions from the state $n = 1$ to $n = 0$ can not happen, that is, imposing $r_1 = 0$, the two first states are

$$\frac{dp_1}{dt} = r_2 p_2 - g_1 p_1 = (1-\alpha)p_2 - p_1$$

and

$$\frac{dp_2}{dt} = -r_2 p_2 + g_1 p_1 = -(1-\alpha)p_2 + p_1. \tag{3.19}$$

The normalization is conserved and the state $n = 0$ has $p_0 = 0$. In that way, we have a new equilibrium distribution, obtained from the DB condition (1.48)

$$\begin{aligned} p_n^s &= \frac{g_{n-1}}{r_n} p_{n-1} \\ &= \frac{n-1}{\alpha n + (n-\alpha)(n-1)\frac{n}{N}} p_{n-1} \qquad n \geq 2. \end{aligned} \tag{3.20}$$

The the stationary solution (3.21) is then rewritten as

$$p_n^s = \prod_{i=2}^{N} \frac{g_{i-1}}{r_i}\, p_1. \tag{3.21}$$

Regarding our parametrization and elimination of the absorbing state we have the following gain and loss terms

$$g_n = n \quad \text{and} \quad r_n = \alpha n(1-\delta_{n,1}) + (1-\alpha)\frac{n(n-1)}{N}, \tag{3.22}$$

where the term $\delta_{n,1}$ ensure the elimination of the absorbing state.

The choice of the model in the one parameter family is arbitrary, because different master equations can be associated with the same mean field equation. For example we could choose the the parameterized time as $t' = \frac{t}{(1-\alpha)}$ which leads to following generation and recombination terms:

$$g_n = \frac{n}{(1-\alpha)} \quad \text{and} \quad r_n = \frac{n}{(1-\alpha)} + (1-\delta_{n,1})\frac{n(n-1)}{(1-\alpha)N}, \tag{3.23}$$

also for this parametrization we recover the original system (3.2) for $\alpha = 0$. Following the same scheme that we presents before, we retrieve the most general equation with a linear and quadratic term can be reduced after a scaling of the variables t, ϕ. We preferred to choose the definition (3.18) for the transition probabilities in order to avoid their diverge when $\alpha \to 1$.

The justifications of our elimination of the absorbing state are: for a system with sufficiently large N the transitions of the state $n = 0$ to $n = 1$ are low importance in the total probability p_n. From equation (3.22) we can do a "check" considering the extreme values of α: for $\alpha = 0$, $g_n = n$ and $r_n = \frac{n(n-1)}{N}$, where the linear loss term vanishes. While, for $\alpha = 1$, $g_n = n$ and $r_n = n$, where the linear gain and loss terms are equal, whereas the quadratic term vanishes, as we expect. In the nest section we will prove that the system has the expected behavior after the elimination of the absorbing state.

Equilibrium of the Fokker-Planck equation

Considering the elimination of the absorbing state and the parametrization we can rewrite the Fokker-Planck equation as

$$a_+ = (1+\alpha)\phi + (1-\alpha)\phi\left(\phi - \frac{1}{N}\right)$$

$$a_- = (1-\alpha)\phi - (1-\alpha)\phi\left(\phi - \frac{1}{N}\right) \tag{3.24}$$

The stationary solution $P^s(\phi)$ is therefore

$$P^s(\phi) = P_0 \frac{\exp(-2NF_\phi)}{\alpha\phi + (1-\alpha)\phi(\phi - 1/N) + \phi}, \tag{3.25}$$

where

$$F(\phi) = -\phi + \frac{2}{1-\alpha}\ \log\left(\phi - \frac{1}{N} + \frac{1+\alpha}{1-\alpha}\right).$$

In this case, $1/N \leq \phi \leq 1$ and the normalization constant is determined imposing

$$\int_{1/N}^{1} F(\phi)d\phi = 1. \tag{3.26}$$

Here we do not have any singularity for n or ϕ. We can recover the stationary distribution $p^s(n)$, because we defined $P^s(\phi)d\phi = p^s(n)dn$, then

$$p^s(n) = \frac{1}{N} P_0\left(\frac{n}{N}\right) \tag{3.27}$$

where $p^s(n)$ interpolates p^s_n. As the constant P_0 can not be determinate analytically, to evaluate $p^s(n)$ we calculate it numerically, imposing

$$\sum_{n=1}^{N} \frac{1}{N}\, P_0\left(\frac{n}{N}\right) = 1. \tag{3.28}$$

The comparison between the result of p_n gives by (3.21) and the Fokker-Planck equation (3.25) are very similar also for relative low values of N and for every value of α between 0 and 1. In the results we will confront $P^s(\phi)$ with the result obtained with the master equation p^s_n.

From equation (3.25) a *Gaussian approximation* for $\alpha \sim 0$ can be obtained. Considering the maximum value of $F(\phi)$ is given by

$$F'(\phi) = \frac{a_-}{a_+} = 0 \tag{3.29}$$

and its solution is $\phi = 1 + \frac{1}{N}$, then we have

$$F''(1+1/N) = -\frac{2}{1-\alpha}\frac{1}{\left(\ 1+(1+\alpha)/(1-\alpha)\ \right)^2} = -\frac{1-\alpha}{2}. \tag{3.30}$$

Near the maximum value we can approximate $F(\phi)$ with its second order Taylor expansion, approximating its denominator with a constant, because it varies rather slowly with its value at the point of maximum ϕ. Hence, $P^s(\phi)$ results be approximate by a Gaussian

$$P^s(\phi) = P_0\ \frac{\exp\left(-\dfrac{N(1-\alpha)}{2}(\phi-1)^2\right)}{a_+(\phi)}. \tag{3.31}$$

When $\alpha \sim 0$ the halfwidth of the Gaussian tends to $N^{-1/2}$ and then is justified approximate $a_+(\phi)$ that is a quadratic function in ϕ with its value in $\phi = 1$. Therefore, for $\alpha \sim 0$ we approximate the function $P^s(\phi)$ by

$$P(\phi) = \left(\frac{2N\,(1-\alpha)}{\pi}\right)^{1/2}\ \exp\left(-\frac{N(1-\alpha)}{2}(1-\phi)^2\right) \tag{3.32}$$

or in terms of $p(n)$

$$p(n) = \left(\frac{2\,(1-\alpha)}{\pi\,N}\right)^{1/2}\ \exp\left(-\frac{(1-\alpha)}{2N}(N-n)^2\right). \tag{3.33}$$

For $\alpha \sim 1$ the situation changes drastically. The derivative $F'(\phi)$ tends to zero as $1-\alpha$, that is, $F(\phi)$ is almost constant. The function in $\phi = 1$ and in $\phi = 1/N$ assumes the following values

$$F(1) = -1 + \frac{2}{1-\alpha}\log\left(\frac{2}{1-\alpha}\right) \qquad F(1/N) = -\frac{1}{N} + \frac{2}{1-\alpha}\log\left(\frac{1+\alpha}{1-\alpha}\right). \tag{3.34}$$

The difference is positive $F(1) - F(1/N) \to 1/N$ for $\alpha \to 1$. In this way we can approximate $e^{2N\,F(\phi)}$ with a constant and write

$$P(\phi) = \frac{C}{\phi}\big(\ 1 + O(1-\alpha)\ \big) \tag{3.35}$$

calculating the normalization constant $C^{-1} = \int_{1/N}^{1} \phi^{-1}\, d\phi$ we have

$$P(\phi) = \frac{1}{\log N}\,\frac{1}{\phi}. \tag{3.36}$$

Calculation of equilibrium by detailed balance

Following the results presented in section 1.3.5, the equilibrium solution can be obtained for any value of α and N, defining $f(n) = \log p^s(n)$, indeed for $N \gg 1$, obtained from eq. (3.21)

$$f(n) = \log p^s(n) - \log p(1) = \sum_{i=2}^{N} \log g(i-1) - \log r(i) \simeq \int_{i=2}^{N} \log g(i-1) - \log r(i) d_i \tag{3.37}$$

where we consider the approximation with an integral of the sum and $g(n)$, $r(n)$ interpolates g_n, r_n on the $\mathbb{R}$. To analyze the behavior of the function $f(n)$ we take $f(n)' = \log g(n-1) - \log r(n)$

$$f'(n) = \log(n-1) - \log\left(\alpha n + \frac{1-\alpha}{N} n(n-1)\right) \tag{3.38}$$

and in the stationary point n_*, $f'(n_*) = 0$ which leads to the condition $r_n = g_{n-1}$, that is

$$n^2 - n(N+1) + \frac{N}{1-\alpha} = 0 \tag{3.39}$$

which have solutions

$$n = \frac{N+1}{2}\left(1 \pm \left(1 - \frac{4}{1-\alpha)\frac{N}{(N+1)^2}}\right)^{1/2}. \tag{3.40}$$

Provided that $N(1-\alpha) \gg 1$, and expand the solutions only the terms in the first order of $1/[N(1-\alpha)]$ the largest solution can be approximated by

$$n_+ = (N+1)\left(1 - \frac{1}{1-\alpha}\ \frac{N}{(N+1)^2}\right) \simeq N + 1 - \frac{1}{1-\alpha} = N - \frac{\alpha}{1-\alpha} \tag{3.41}$$

and the smallest solution is

$$n_- = \frac{1}{1-\alpha}\,\frac{N}{N+1} \simeq \frac{1}{1-\alpha} \tag{3.42}$$

In this way we have $n_+ \simeq N$ and $n_- \ll N$. To determine what solution is a maximum we should calculate $f''(n)$, then we have

$$f''(n) = \frac{1}{n-1} - \frac{\alpha + \frac{1-\alpha}{N}\,(2n-1)}{\alpha n + \frac{1-\alpha}{N}\,n(n-1)} \tag{3.43}$$

For $N \gg 1$ we establish

$$f''(N) = \frac{1}{N} - \frac{2-\alpha}{N} = -\frac{1-\alpha}{N} \qquad f''\left(\frac{1}{1-\alpha}\right) = \frac{(1-\alpha)^2}{\alpha} \tag{3.44}$$

Then the maximum value is [2]

$$n_* = N\left(1 - \frac{\alpha}{N(1-\alpha)}\right) \simeq N \tag{3.45}$$

to approximate with quite accurately p_n^s with a Gaussian centered at $n = n_*$ having a width σ namely

$$p_n^s = C\exp\left(-\frac{(n-n_*)^2}{2\sigma^2}\right) \qquad n_* = N - \frac{\alpha}{1-\alpha} \qquad \sigma^2 = \frac{N}{1-\alpha} \tag{3.46}$$

If we normalize on $[0,\infty]$ the constant is $C = \left(\frac{2}{\pi\sigma^2}\right)^{1/2}$, therefore we have a general equation for the Gaussian approximation for different values of α. In the section 3.4 we will analyze the robustness of this approximation, studying also the behavior in the extremes points $\alpha = 0$ and $\alpha = 1$.

Note: Since $n_* \simeq N$ the result (3.46) correspond with the result obtained with the Fokker-Planck. Actually, for $n = N\phi$ we have $P(\phi) = p_n dn/d\phi = np_n$, which reads,

$$P^s(\phi) = Np_n^s = \left(\frac{2N^2}{\pi\sigma^2}\right)\exp\left(-\frac{N^2}{2\sigma^2}(\phi-1)^2\right) \qquad \frac{N^2}{\sigma^2} = N(1-\alpha) \tag{3.47}$$

Therefore, we obtain the same result with 2 different pathways.

[2]Remark: This result is valid for $N(1-\alpha) \gg 1$, in this way, $N\left(1 - \frac{\alpha}{N(1-\alpha)}\right) \simeq N$.

For $\alpha \sim 1$ we have from (3.21)

$$p_n = \frac{p_1}{n\alpha^{n-1}} \prod_{m=2}^{N} \frac{1}{1 + ((1-\alpha)/\alpha)((m-1)/N)} = \frac{p_1}{n\alpha^{n-1}} \exp(f(n)) \quad (3.48)$$

Then we have that $f(n)$ is

$$f(n) = -\int_2^N \log\left(1 + \frac{1-\alpha}{\alpha}\frac{m-1}{N}\right) dm \simeq -\frac{1-\alpha}{\alpha\, N}\int_2^N m\, dm = -\frac{1-\alpha}{\alpha\, N}\,\frac{n^2}{2} \quad (3.49)$$

with solution

$$p(n) \simeq \frac{c}{n} \exp\left((1-\alpha)n - (1-\alpha)\,\frac{n^2}{2N}\right). \quad (3.50)$$

For $N \to \infty$ we have simply,

$$p(n) \simeq \frac{c}{n}. \quad (3.51)$$

In the results we will compare the error on the Fokker-Plank and by the Gaussian approximation for different values of n and α.

3.1.2 Relaxation to equilibrium

In the mean field limit, we can write the equation (3.18) as

$$\frac{d\phi}{dt} = (1-\alpha)(\phi - \phi^2) \quad (3.52)$$

the linearized equation around the equilibrium position is given by

$$\frac{d\phi}{dt} = (1-\alpha)(1-\phi) \quad (3.53)$$

which solution is

$$x(t) = 1 + (x(0) - 1)e^{-(1-\alpha)t}. \quad (3.54)$$

The relaxation time is defined as the exponential decay $\tau = 1/(1-\alpha)$. In general, if we consider the function $f(t)$ that gives the logarithmic of the error at time t we have

$$f(t) = \log|x(t) - 1| = \log|x(0) - 1| - \frac{t}{\tau} \quad (3.55)$$

which leads to

$$\tau = -1/f'(t). \tag{3.56}$$

As the master equation is linear, the convergence to the equilibrium is determined by the norm of its bigger eigenvalue $\lambda = -1/\tau$, where $\tau > 0$ represents the relaxation time. Considering $p_n(t)$ the solution in the time t and p_n^e the equilibrium solution, then we can write

$$p_n(t) = p_n^e + (p_n(0) - p_n^e)e^{-t/\tau}. \tag{3.57}$$

For any initial condition, the error is $||p_n(t) - p_n^s||$ tends to zero exponentially, therefore we have

$$\frac{1}{\tau} = -\lim_{t\to\infty} \frac{1}{t} \log ||p_n(t) - p_n^s||. \tag{3.58}$$

In that way we have a general formulation for the error of the solution of the ME in respect of the equilibrium solution.

3.2 The BCM model

We will introduce another population model that can be studied as a one dimensional family of master equations, the BCM theory for the synaptic plasticity. Here we just study this model as a population, because in the Chapter 6 we will study it in more details. We consider the equation for the limited growth write as

$$\frac{dx}{dt} = x^2 - \alpha x^2 - (1-\alpha)x^3 \tag{3.59}$$

then the mean field equation reads

$$\dot{\phi} = (1-\alpha)(\phi^2 - \phi^3). \tag{3.60}$$

The generation and recombination terms are

$$g_n = \frac{n^2}{N} \qquad r_n = \alpha\frac{n^2}{N}(1-\delta_{n,1}) + (1-\alpha)\frac{n^2}{N^2}(n-1) \tag{3.61}$$

then $g_0 = r_0 = 0$ and $dp_0/dt = 0$ where we choose $p(0) = 0$. Therefore the states varies from $n = 1$ to $n = N$ and the master equation is

$$\frac{dp_n}{dt} = (\mathbb{E} - 1)(r_n - \mathbb{E}^{-1} g_n) \qquad 2 \leq n \leq N - 1 \tag{3.62}$$

We have also calculate the Fokker-Planck equation (1.37) and in this case the stationary distribution is

$$P(\phi) = \frac{P_0}{\phi^2} \frac{\exp(2N(F(\phi) - F(0))}{1 + \alpha + (1 - \alpha)\left(\phi + \frac{1}{N}\right)} \tag{3.63}$$

where

$$F(\phi) = -\phi + \frac{2}{1 - \alpha} \log\left(\phi - \frac{1}{N} + \frac{1 + \alpha}{1 - \alpha}\right) \tag{3.64}$$

To calculate $p(n)$ we use

$$p(n) = \frac{1}{N} P\left(\frac{n}{N}\right) \tag{3.65}$$

For $\alpha \to 0$ we find a maximum for $F(\phi)$ in $\phi = 1 + 1/N$ and then we can use the same Gaussian approximation used before

$$p(n) = c \frac{\exp\left[(1 - \alpha) n \left(1 - \frac{n}{2N}\right)\right]}{n^2} \tag{3.66}$$

For $\alpha \to 1$ we find that

$$p_n = \frac{p_1}{n^2} \tag{3.67}$$

where p_1 is calculated with the normalization.

3.2.1 The 2D extension

We have considered the two population version of the BCM model which reads

$$\begin{aligned} \dot{\phi}_x &= \phi_x^2 - \alpha \phi_x^2 - (1 - \alpha)\phi_x(\phi_x + \phi_y)^2 \quad \text{and} \\ \dot{\phi}_y &= \phi_y^2 - \alpha \phi_y^2 - (1 - \alpha)\phi_y(\phi_x + \phi_y)^2. \end{aligned} \tag{3.68}$$

Following what is introduced in section 3.1.1 we write the gain and the recombination terms as

$$g^{(x)}_{n_x,n_y} = \frac{n_x^2}{N} \qquad g^{(y)}_{n_x,n_y} = \frac{n_y^2}{N} \tag{3.69}$$

$$\begin{aligned} r^{(x)}_{n_x,n_y} &= \alpha \frac{n_x^2}{N}\left(1-\delta_{n_x,1}\right) + (1-\alpha)\frac{(n_x-1)(n_x+n_y)^2}{N^2} \\ r^{(y)}_{n_x,n_y} &= \alpha \frac{n_y^2}{N}\left(1-\delta_{n_y,1}\right) + (1-\alpha)\frac{(n_y-1)(n_x+n_y)^2}{N^2}. \end{aligned} \tag{3.70}$$

The bidimensional master equation associated with the system (3.71) is

$$\frac{dp_{\mathbf{n}}}{dt} = (\mathbb{E}_x^{-1}-1)g^{(x)}_{\mathbf{n}}\, p_{\mathbf{n}} + (\mathbb{E}_x - 1)r^{(x)}_{\mathbf{n}}\, p_{\mathbf{n}} + (\mathbb{E}_y^{-1}-1)g^{(y)}_{\mathbf{n}}\, p_{\mathbf{n}} + (\mathbb{E}_y - 1)r^{(y)}_{\mathbf{n}}\, p_{\mathbf{n}} \tag{3.71}$$

where $\mathbf{n} \equiv (n_x, n_y)$ and $\mathbb{E}_x$, $\mathbb{E}_y$ denote the raising operators for the indexes n_x, n_y respectively. The boundary conditions are specified by imposing the transitions to non existing states to vanish $g^{(x)}_{-1,n_y} = 0$, $g^{(y)}_{n_x,-1} = 0$, $r^{(x)}_{0,n_y} = 0$, $r^{(y)}_{n_x,0} = 0$ and $g^{(x)}_{N,n_y} = 0$, $g^{(y)}_{n_x,N} = 0$, $r^{(x)}_{N+1,n_y} = 0$, $r^{(y)}_{n_x,N+1} = 0$. In addition supposing that $g^{(x)}_{0,n_y} = 0$, $g^{(y)}_{n_x,0} = 0$ by imposing that $r^{(x)}_{1,n_y} = 0$, $r^{(y)}_{n_x,1} = 0$ we insure the absence of absorbing states. In order to have a well behaved solution we impose the initial probabilities for one null population vanish $p_{0,n_y}(0) = p_{n_x,0}(0) = 0$. This insures that the condition $p_{0,n_y}(t) = p_{n_x,0}(t) = 0$ is satisfied at any time time t and that any other probability $p_{\mathbf{n}}(t)$ is always positive. The r.h.s. of equation (3.71) can be written as a discrete divergence $-D_x J^x - D_y J^y$ where the currents are given by $J^x_{n_x,n_y} = \mathbb{E}_x^{-1} g^{(x)}_{n_x,n_y} p_{n_x,n_y} - r^{(x)}_{n_x,n_y} p_{n_x,n_y}$ and $J^y_{n_x,n_y} = \mathbb{E}_y^{-1} g^{(y)}_{n_x,n_y} p_{n_x,n_y} - r^{(y)}_{n_x,n_y} p_{n_x,n_y}$. By imposing the currents to vanish separately we obtain an equilibrium distribution which is uniquely defined provided that the relation between p_{n_x+1,n_y+1} and p_{n_x,n_y} is the same computed along two distinct paths on the elementary cell having p_{n_x,n_y+1} and p_{n_x+1,n_y} as intermediate steps respectively. The necessary condition for equality, known as detailed balance, is consequently

$$\frac{g^{(y)}_{n_x+1,n_y}}{r^{(y)}_{n_x+1,n_y+1}}\,\frac{g^{(x)}_{n_x,n_y}}{r^{(x)}_{n_x+1,n_y}} = \frac{g^{(x)}_{n_x,n_y+1}}{r^{(x)}_{n_x+1,n_y+1}}\,\frac{g^{(y)}_{n_x,n_y}}{r^{(y)}_{n_x,n_y+1}}. \tag{3.72}$$

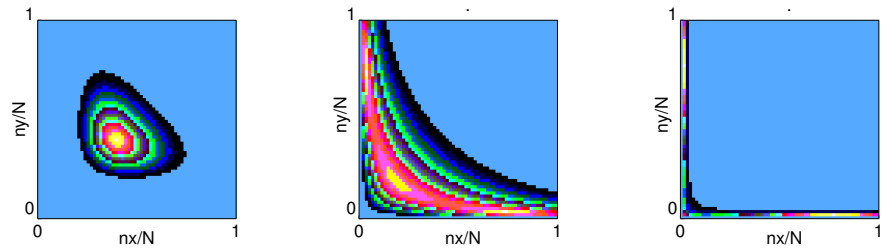


Figure 3.1: Plot of p_{n_x,n_y} for $N = 63$ and $\alpha = 0.85$ for the master equation defined by equation (3.71). The color scale is linear and illustrates the evolution of the probabilities with time $t = 2$ (left frame), $t = 20$ (center frame) $t = 100$ (right frame) for an initial condition $p_{n_x,n_y}(0) = \delta_{n_x,N/2}\,\delta_{n_xy,N/2}$. Even though the equilibrium is fully reached at $t = 1000$ at $t = 100$ we are already close to it.

The stable equilibrium are $(0, 1)$ and $(1, 0)$ whereas the unstable equilibrium are $(0, 0)$ and $(1/4, 1/4)$. The model satisfies the detailed balance equation for $\alpha = 0$ and $\alpha = 1$. The equilibrium distribution for $\alpha = 0$ is approximated by a Gaussian $p_{n_x,1} = \frac{1}{2}\,G(n_x)$ and $p_{1,n_y} = \frac{1}{2}\,G(n_y)$ where $G(n)$ is defined by equation (3.46) and $p_{n_x,n_y} = 0$ if $n_x > 1, n_y > 1$. For $\alpha \to 1$ the solution is a power law $p_{n_x,n_y} = c/(n_x^2 n_y^2)$ for $n_x, n_y \geq 1$. The solutions obtained by numerical integration of equations (3.71) confirm these results and allow us to compute the equilibrium distribution for any value of α in the interval $[0, 1]$. These equilibrium solutions are rather close to the results obtained by computing p_{n_x,n_y} from $p_{1,1}$ along two distinct paths parallel to the x, y axis in the n_x, n_y lattice. The transients can also be computed and show the way the equilibrium solutions are reached. In figure 3.1 we show the the results for $\alpha = 0.85$ where the equilibrium distribution is a superposition of the Gaussian and power law distributions.

3.3 Entropy for 1D master equation

For large N the solution of master equation for population dynamics is approximated by the solution of the corresponding Fokker-Planck equation. The stationary solution corresponding to a stable equilibrium of the mean field equation is approximated by a Gaussian and consequently the entropy can computed analytically. The entropy diverges as $-\log N$ in agreement with the fact that in the limit $N \to \infty$ the probability distribution tends to a δ function namely it is perfectly localized at the equilibrium point of the mean field equation. If the mean field equation depends on a parameter η then the Master equation will also depend on it and the dependence of the entropy on η can be evaluated. Since the relaxation time τ also depends on this parameter it is interesting to analyze how $S(\eta)$ and $\tau(\eta)$ are related. We start with the following mean field equations

$$\frac{dx}{dt} = x - x^{1+\eta} \qquad\qquad \frac{dx}{dt} = x^2 - x^{2+\eta} \tag{3.73}$$

which for $\eta = 1, 2$ become the logistic and the BCM equations, respectively. The fields given by the right hand side of these equations vanish at $x = 1$ and have a first derivative at this point equal to $-\eta$. As a consequence $\phi = 1$ is a stable equilibrium and the relaxation time is $\tau = 1/\eta$. Consider now the corresponding Master equation defined by the gain and loss terms

$$\begin{aligned} g(n) &= n \qquad r(n) = (n-1)\frac{n^\eta}{N^\eta} \\ g(n) &= \frac{n^2}{N} \qquad r(n) = (n-1)\frac{n^{1+\eta}}{N^{1+\eta}} \end{aligned} \tag{3.74}$$

The equilibrium conditions are given by $f'(n) = \log g(n-1) - \log r(n) = 0$ which is satisfied for $n = N$ with $f''(n) = -\eta/N$. As a consequence the equilibrium distribution in both cases is a semi Gaussian with maximum at $n = N$ and width $\sigma = N/\eta$. Letting $\phi = n/N$ the probability $P(\phi) = Np(n)$ is a Gaussian with maximum at $\phi = 1$ and width $\sigma = (N\eta)^{-1/2}$ defined in the interval $[1/N, 1]$ where it is normalized

$$P(\phi) = \left(\frac{2\eta N}{\pi}\right)^{1/2} \exp\left(-\frac{N\eta}{2}(\phi - 1)^2\right) \tag{3.75}$$

We can now compute the entropy

$$\begin{aligned} S(\eta, N) &= \int_{1/N}^{1} P(\phi) \log P(\phi) d\phi \qquad (3.76) \\ &= -\left(\frac{2\eta N}{\pi}\right)^{1/2} \int_{1/N}^{1} \frac{1}{2} \log\left(\frac{2N\eta}{\pi}\right) - \frac{N\eta}{2}(\phi-1)^2 \exp\left(-\frac{N\eta}{2}\right)(\phi-1)^2 \\ &= \frac{2}{\pi^{1/2}} \int_{0}^{(\eta N/2)^{1/2}} -\frac{1}{2} \log\left(\frac{2N\eta}{\pi}\right) + w^2 e^{-w^2} dw \\ S(\eta, N) &= -\frac{1}{2} \log \frac{2\eta\, N}{\pi} + \frac{1}{2} \end{aligned}$$

where we have set $w = (N\eta/2)^{1/2}(1-\phi)$. We can write the result as

$$S(\eta, N) = -\frac{1}{2} \log \eta - \frac{1}{2} \log N + c \qquad (3.77)$$

where $c = \frac{1}{2}[1 - \log(2/\pi)]$ is a fixed numerical constant. For any fixed value of N the variation of the entropy is simply given by the term $\hat{S}(\eta) = -\frac{1}{2}\log(\eta)$ which is a decreasing function of η just as the relaxation time $\tau = 1/\eta$. This means that when η increases the system becomes more stable and less disordered.

Remarks: Let us remark that the relaxation time can be varied simply by scaling the field. In this case, however, the entropy does not change. Indeed if you consider the equations

$$\frac{dx}{dt} = \eta(x - x^2) \qquad\qquad \frac{dx}{dt} = \eta(x^2 - x^3) \qquad (3.78)$$

the relaxation time is $\tau = 1/\eta$ but the entropy for the related master equation is $S(1, N)$ as for the unscaled equation. This is evident since the equilibrium distribution is invariant under a scaling of g_n and r_n with the same scaling factor η.

If we compute the entropy $\bar{S}$ from the Master equation we notice that there is an additive factor with respect to the entropy S we computed from the solution of the Fokker-Planck equation. Indeed recall that if $p(n)$ interpolate the equilibrium distribution p_n then $P(\phi) = N\, p(n)$ where $\phi = n/N$.

As a consequence

$$\begin{aligned} \bar{S} &= -\sum_{n=1}^{N} p_n \log p_n \int_1^N p(n) \log p(n) dn \qquad (3.79) \\ &= -\int_{1/N}^{1} P(\phi) \log(\, P(\phi)/N)\, d\phi = S + \log N \end{aligned}$$

3.3.1 The 2D models

The same considerations apply to a two dimensional model such as

$$\frac{dx}{dt} = x^2 - x(x+y)^{1+\eta} \qquad \frac{dy}{dt} = y^2 - y(x+y)^{1+\eta} \qquad (3.80)$$

Such a model has $x = 1$, $y = 0$ and $x = 0, y = 1$ as stable critical points and the eigenvalues of the matrix for the linearized equation are $-1, -\eta$. For the master equation the Gaussian approximation to the equilibrium leads to the same expression for the entropy we found for the one dimensional system. In view of a further analysis on the BCM model we consider the parameter η to be a function of another parameter α according to

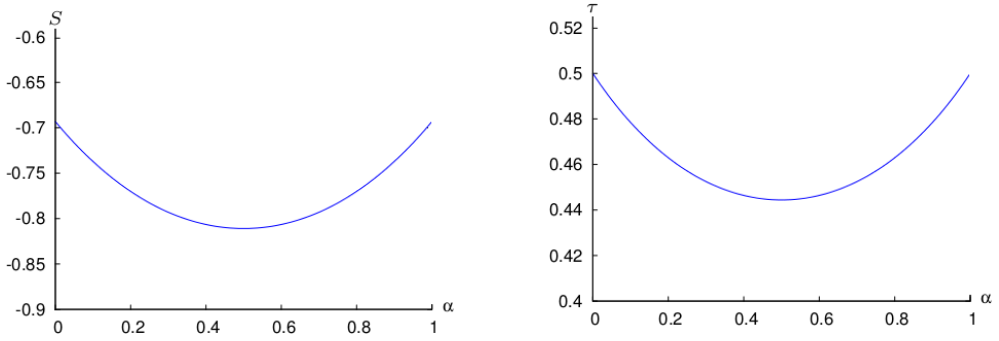
$$\eta = (1+\alpha)(2-\alpha)$$

where $\alpha \in [0, 1]$. The function is symmetric with respect to $\alpha = 1/2$ where it reaches a maximum. As a consequence taken as a function of α both the relaxation time and the entropy for the corresponding master equation have a minimum as shown by figure 3.2.

The previous 2D equation with η chosen as a function of α corresponds for $\alpha = 0, 1$ to the BCM equation and the corresponding Master equation has for any value of α an equilibrium which fulfills the detailed balance condition. Instead the equations

$$\frac{dx}{dt} = x^2 - x(x^{1+\alpha} + y^{1+\alpha})^{2-\alpha} \qquad \frac{dy}{dt} = y^2 - (x^{1+\alpha} + y^{1+\alpha})^{2-\alpha} \qquad (3.81)$$

correspond for $\alpha = 0$ to the BCM82 model and for $\alpha = 1$ to the BCM92 model. The equilibrium for the associate master equation satisfies the detailed balance condition only for $\alpha = 0$. The entropy can be computed



(a) (b)

Figure 3.2: Change of (a) entropy S and (b) the relaxation time τ, for the one dimensional population model where $\eta = (1+\alpha)(2-\alpha)$

numerically and also exhibits a minimum close to $\alpha = 1/2$. The problem now is to disentangle whether this is due to the loss of the detailed balance or mainly to the asymptotic behavior of the loss terms which depends on α.

We consider then the one parameter family of master equations associated to the scaled logistic equation

$$\frac{dx}{dt} = x - \alpha x - (1-\alpha)x^2$$
$$g_n = n \quad r_n = \alpha n\,(1-\delta_{1,n}) + (1-\alpha)\,(n-1)\frac{n}{N}. \tag{3.82}$$

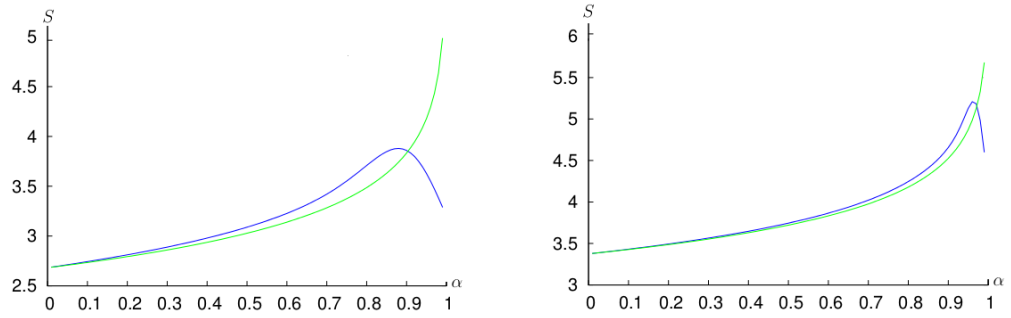
The mean field equation is simply the logistic equation with the time scaled by $1-\alpha$. As a consequence the entropy $\bar{S}$ which depends on α is the same as for the unscaled master equation

$$\frac{dx}{dt} = x - x^2 \qquad g_n = \frac{n}{1-\alpha} \qquad r_n = \frac{n}{1-\alpha}(1-\delta_{1,n}) + (n-1)\frac{n}{N}. \tag{3.83}$$

The equilibrium solution is a Gaussian with $\eta = 1-\alpha$. As a consequence for α close to zero we have

$$\bar{S} = S + \log N = -\frac{1}{2}\log(1-\alpha) + \frac{1}{2}\log N + \frac{1}{2}(1 - \log\frac{2}{\pi}) \tag{3.84}$$

In Figure 3.3 we compare the exact solution with the previous approximation. As it can be seen it is less and accurate as we approach $\alpha = 1$. Here



(a) (b)

Figure 3.3: Change of entropy S for the one parameter master equation associated to the logistic equation $\dot{x} = (1-\alpha)x - x^2$ with gain and loss terms defined by $g_n = n,\ r_n = \alpha n(1-\delta_{n,1} + (1-\alpha)n(n-1)/N$. Blue line exact and green line the approximated solution. (a) $N = 50$ and (b)$N = 200$

.

we can make a further approximation starting from the approximate solution for $\alpha = 1$ which is given by

$$p(n) = \frac{1}{n\ \log N} \tag{3.85}$$

So the entropy is given by

$$\bar{S} = \log N + \log\log N + \frac{1}{\log N}\int_{1/N}^{1} \frac{\log\phi}{\phi}\, d\phi = \log\log N + \frac{1}{2}\log N. \tag{3.86}$$

The dependence on α for α close to 1 is obtained from

$$P(\phi) = \frac{C}{\phi}\ \exp{(1-\alpha)N\phi 1 - \frac{\phi}{2}} \simeq C\frac{1}{\phi} + \epsilon 1 - \frac{\phi}{2} \qquad \epsilon = (1-\alpha)N \tag{3.87}$$

where the normalization constant is given by

$$C^{-1} = \log N + \frac{3}{4}\epsilon \tag{3.88}$$

and we have assumed that $\epsilon = (1-\alpha)N \ll 1$ and that $N \gg 1$ for the continuous interpolation in n to hold. Computing the entropy at the first order in ϵ and neglecting $1/N$ with respect to 1 we finally find

$$\bar{S} = \log\log N + \frac{1}{2}\log N + \frac{3}{8}\epsilon - \frac{3}{2}\frac{\epsilon}{\log N}. \tag{3.89}$$

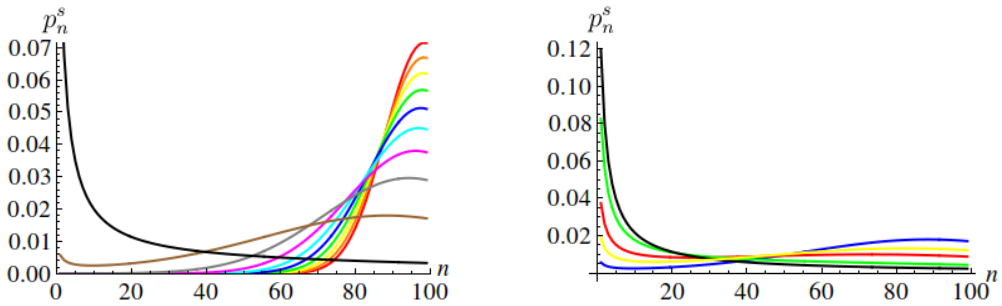
3.4 Results

The asymptotic behavior of the probabilities $p_n(t)$ for the master equation with an absorbing state has been investigated [76], but here we propose also an approximation for the elimination of the absorbing state. Therefore we will study both cases: with and without absorbing states, to focus our attention in the extinction time of a population (with absorbing state) and on a family of equations depending on a parameter α. We will study the dependence of p_n^s with α calculating it analytically, we also will make a numerical study, calculating the time of extinction for systems that presents an absorbing state and the relaxation time for systems without absorbing states.

3.4.1 Dependence the stationary distribution with α

For the following results we consider the one parameter family of master equations represented by (3.22) (for which the absorbing state has been eliminated), to investigate the behavior of the stationary distribution in function of the parameter α. The stationary distribution is calculated analytically directly from (3.21) and in this case n varies as $1 \leq n \leq N$. In figure 3.4 we show p_n^s in function of n and α, where the maximum number of individuals is $N = 100$. Specifically for figure 3.4a, we varies α in intervals of 0.1 and we see a continuous transition from $\alpha = 0$ to $\alpha = 1$. While in figure 3.4b, we plot the distributions for $\alpha = 0.9, 0.93, 0.95, 0.98$ and 1.

For low values of α we observe that the equilibrium solution initially is a semi-Gaussian centered in $n_* \simeq N$, when α increases, the maximum moves to lower values with respect to N. Particularly for $\alpha \simeq 0.9$ a bimodal distribution appears and for $\alpha \to 1$ the distribution is a power law peak at $n = 1$ (see Fig. 3.4). Further increasing α so that $N < 1/(1-\alpha)$ only the peak at $n = 1$ remains and the distribution becomes a genuine power law. However unlikely when the absorbing state is present if we keep the value of α fixed close to 1 and let N grow, only the states with $n \simeq N$ become populated



(a) (b)

Figure 3.4: Plot of the p_n^s in function of n for different values of α. (a) The colors correspond to: $\alpha = 0.1 \rightarrow$ red, $\alpha = 0.2 \rightarrow$ orange, $\alpha = 0.3 \rightarrow$ yellow, $\alpha = 0.4 \rightarrow$ green, $\alpha = 0.5 \rightarrow$ blue, $\alpha = 0.6 \rightarrow$ light blue, $\alpha = 0.7 \rightarrow$ violet, $\alpha = 0.8$ gray, $\alpha = 0.9 \rightarrow$ brown, $\alpha = 0.99 \rightarrow$ black. (b) The colors correspond to: $\alpha = 0.1 \rightarrow$ red, $\alpha = 0.2 \rightarrow$ orange, $\alpha = 0.3 \rightarrow$ yellow, $\alpha = 0.4 \rightarrow$ green, $\alpha = 0.5 \rightarrow$ blue, $\alpha = 0.6 \rightarrow$ light blue, $\alpha = 0.7 \rightarrow$ violet, $\alpha = 0.8$ gray, $\alpha = 0.9 \rightarrow$ brown, $\alpha = 0.99 \rightarrow$ black . In the right figure the colors correspond to: $\alpha = 0.9 \rightarrow$ blue, $\alpha = 0.93 \rightarrow$ yellow, $\alpha = 0.95 \rightarrow$ red, $\alpha = 0.98 \rightarrow$ green, $\alpha = 1 \rightarrow$ black.

with a spread of order $N^{-1/2}$, so that in the limit $N \rightarrow \infty$ the equilibrium $\phi = 1$ is recovered. In [77] a power law equilibrium was obtained for a linear equation by preventing the presence of the absorbing state with a constant term in the gain factor g_n so that $g_0 > 0$. For $\alpha \rightarrow 0$ the maximum value is for $n = N$, that is $\phi = 1$, while for $\alpha \rightarrow 1$ we observe that the maximum value is for $n = 1$. Ergo, our results show that the equilibrium solution for $\alpha \rightarrow 0$ is a Gaussian distribution, while for $\alpha \rightarrow 1$ is a Pareto distribution. To summarize the situation we first consider the equilibrium distribution for a fixed value of N: the transition from a Gaussian distribution peaked close to $n = N$ to a power law distribution peaked near $n = 1$ occurs at $N \simeq 1/(1-\alpha)$ and close to the transition a bimodal distribution is observed. Conversely if we keep α fixed and increase N only the first equilibrium is observed as long as $N \gg 1/(1-\alpha)$. The limit the distribution in the variable $\phi = n/N$ becomes $\delta(\phi)$ corresponding to the stable equilibrium of the mean

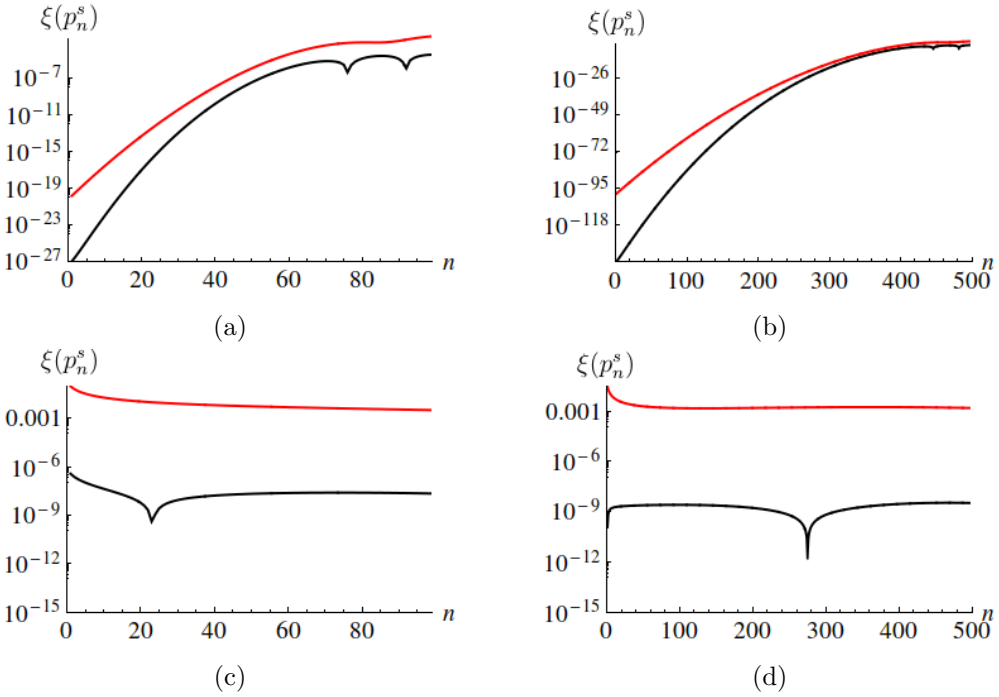


Figure 3.5: Plot of the error $\xi(p_n^s)$ of estimate p_n^s , in function of n for different values of α. (a) Black line corresponds to the plot of the error of Fokker-Planck $\xi(p_n^s) = |p_n^s - p_{FP}^s(n)|$ and the red line corresponds to the error of Gaussian approximation $\xi(p_n^s) = |p_n - p_G^s(n)|$ for $N = 100$ for $\alpha = 0.1$. (b) Black line corresponds to the plot of the error of Fokker-Planck $\xi(p_n^s) = |p_n^s - p_{FP}^s(n)|$ and the red line corresponds to the error of Gaussian approximation $\xi(p_n^s) = |p_n - p_G^s(n)|$ for $N = 500$ for $\alpha = 0.1$. (c) Black line corresponds to the plot of the error of Fokker-Planck $\xi(p_n^s) = |p_n^s - p_{FP}^s(n)|$ and the red line corresponds to the error of approximation with $(1 - \alpha)$ $\xi(p_n^s) = |p_n - p_{app}^s)|$ for $N = 100$ for $\alpha = 0.99$. (d) Black line corresponds to the plot of the error of Fokker-Planck $\xi(p_n^s) = |p_n^s - p_{FP}^s(n)|$ and the red line corresponds to the error of approximation with $(1-\alpha)$ $\xi(p_n^s) = |p_n - p_{app}^s|$ for $N = 500$ for $\alpha = 0.99$. The stationary distributions were calculated as: p_n^s with the equation (3.21), $p_{FP}^s(n)$ with the equation (3.25), $G^S(n)$ with the equation (3.46) and p_{app}^s with the equation (3.51).

field equation. In this case we recall that when α is close to 1 the relaxation time of the mean field equation grows as $(1-\alpha)^{-1}$.

To test the efficiency of our approximations introduced in sections (3.1.1 and 3.1.1), now we are going to study the error on the evaluation of the stationary distribution p_n^s by the Fokker-Planck equation, the Gaussian approximation and the approximation with $(1-\alpha)$. We calculate the distributions with the equations: eq. (3.21) for the exact solution (p_n^s), eq. (3.25) for the Fokker-Planck equation ($p_{FP}^s(n)$), eq. (3.46) for the Gaussian approximation ($p_G^s(n)$) and eq. (3.51) for the approximation with $(1-\alpha)$ (p_{app}^s). We define the error ξ as

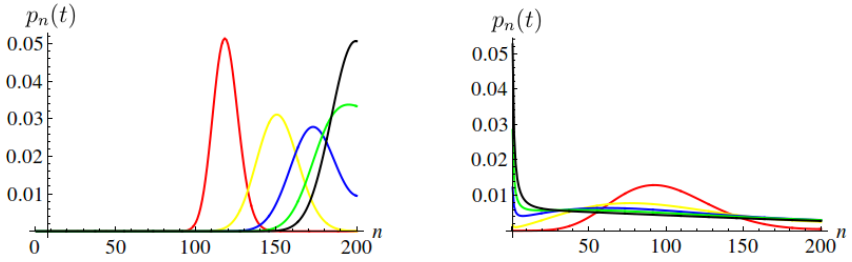
$$\xi(p_n^s) = |p_n^s - p_i^s(n)| \qquad p_i^s(n) = p_{FP}^s(n), p_G^s(n), p_{app}^s \tag{3.90}$$

In Figure 3.5 we plot the error $\xi(p_n^s)$ for the Fokker-Planck equation, Gaussian approximation and approximation with $(1-\alpha)$ in function of n for different values of α. We show the results for $\alpha = 0.1$ and $\alpha = 0.99$ for $N = 100$ and 500. The results show that the error for $\alpha \to 1$ of the Fokker-Planck is very small, in order of 10^{-10} for $N = 100$ and 10^{-25} for $N = 500$, while for the Gaussian approximation is in order of 10^{-6} for $N = 100$ and 10^{-25} for $N = 500$. For $\alpha \to 1$ the error Fokker-Planck is in order of 10^{-6} for $N = 100$ and 10^{-9} for $N = 500$, while for the approximation with $(1-\alpha)$ 10^{-3} for $N = 100$ and $N = 500$.

3.4.2 Relaxation time

For the system without absorbing state (eq. (3.22)) we can study the behavior of the relaxation time τ, that is, the time needed for the system from an initial condition reach the steady state. We are interesting to study the dependence of τ with the parameter α.

In the Figure 3.6 we plot the evolution of $p_n(t)$ for $\alpha = 0$ and $\alpha = 1$, the total number of molecules is $N = 400$ and we choose the initial condition $p_n(0) = \delta_{n,N/2}$. From figure 3.6 we observe that the relaxation time is different for the distinct values of α, which lead us to do the Figures 3.7 and 3.8. Here



(a) (b)

Figure 3.6: Plot of the $p_n(t)$ in function of n and t for systems with $N = 200$ molecules. (a) $\alpha = 0$ The colors correspond to: $t = 0 \rightarrow$ red, $t = 3 \rightarrow$ yellow, $t = 5 \rightarrow$ blue, $t = 7 \rightarrow$ green and $t = \infty \rightarrow$ black. Where $= 150$ steps of integration. (b) $\alpha = 1$ The colors correspond to: $t = 0 \rightarrow$ red, $t = 3 \rightarrow$ yellow, $t = 5 \rightarrow$ blue, $t = 7 \rightarrow$ green and $t = \infty \rightarrow$ black.

we plot τ in function of α. To establish if the system is in the stationary state we use the distributions calculated analytically in section 3.4.1. The behavior of the relaxation time in function of N shows a trend as plot in Figure 3.7. There is a change around $\alpha = 0.5$. For $\alpha = 1$ the relaxation time grows linearly with N, which agrees with the fact that in the mean field the equilibrium does not exist anymore. The Figure 3.8 shows that in the interval $0 \leq \alpha \leq 1$, τ varies quite linearly with α, while there is a discontinuity between $\alpha = 0.9$ and $\alpha = 1$. As we demonstrate in the Figure 3.4 this interval represents a phase transition, and as it is known one characteristic of a phase transition is the relaxation time largest. The other interesting result is that τ grows with α.

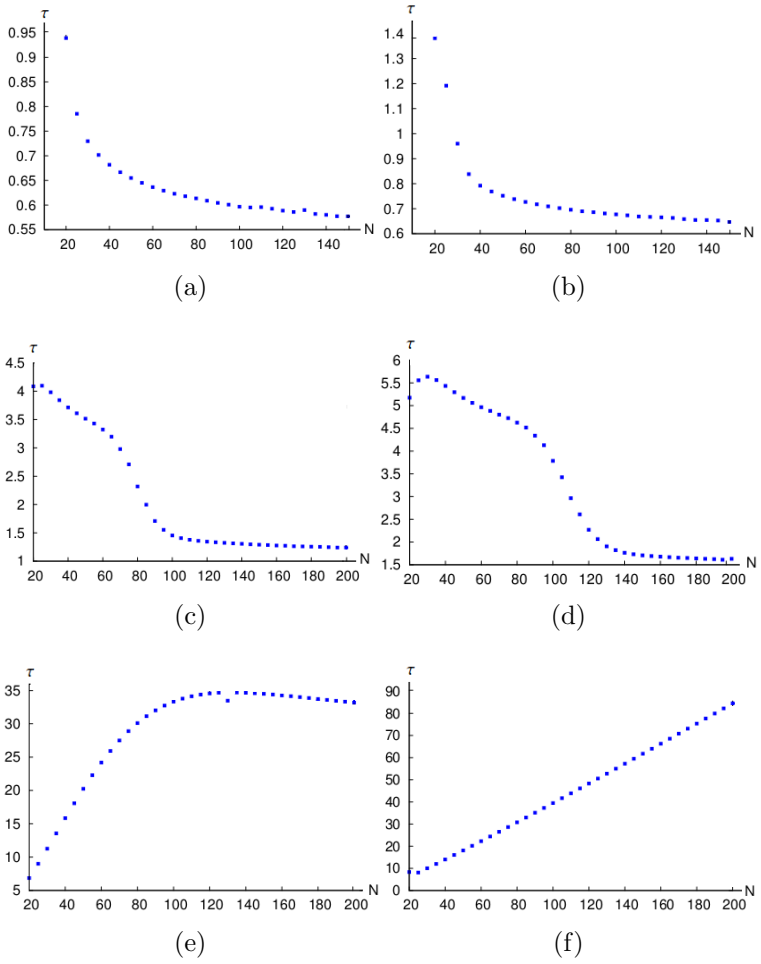


Figure 3.7: Plot of τ in function of N: (a) $\alpha = 0$; (b) $\alpha = 0.1$; (c) $\alpha = 0.4$; (d) $\alpha = 0.6$; (e) $\alpha = 0.9$ and (f) $\alpha = 1$.

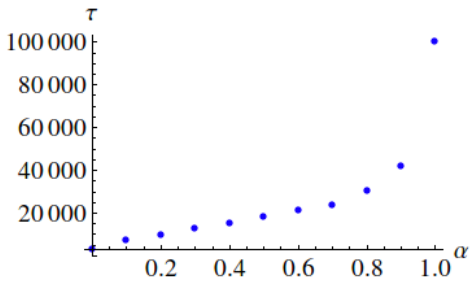


Figure 3.8: Plot of the time τ in function of α for $N = 300$ and the system without absorbing state.

3.4.3 Extinction time

To analyze the behavior of the parametrized system with an absorbing state, we consider $g_n = n$ and $r_n = \alpha n + (1-\alpha)\frac{n(n-1)}{N}$. The stationary solution p_n^s is calculated with the equation (3.21), but n varies from 1 to N and the equation is normalized in function of p_0. In this way we have $r_1 = \alpha$ and $g_0 = 0$, then $n = 0$ is absorbing. Letting $\tau_0(N)$ be the time needed for a population of N units to have a probability $p_0 = 0.98$ of being in the null state, we plot in Figure 3.9 $\tau_0(N)$ in function of N for a system with $N = 16$ as maximum number of individuals, here we plot just for $\alpha = 0.1$, $\alpha = 0.5$ and $\alpha = 0.9$. A simple numerical analyses shows that the growth with N is exponential,

$$\tau_0(N) \simeq \tau_0(N_0)\, e^{\lambda(N-N_0)}. \tag{3.91}$$

We are also interesting in the behavior of $\tau_0(N)$ in function of α. For this study we fixed N and analyzed how $\tau_0(N)$ changes in function of α that varies α from zero to one, as show in figure 3.10a. We plot λ in function of α, estimating λ with (3.91) and $0 \leq \alpha \leq 1$, as in figure 3.10b. We observe that λ depends on α and tends to zero when $\alpha \to 1$. For instance $\lambda \simeq 0.7$ for $\alpha = 0.1$ and $\lambda \simeq 0.044$ for $\alpha = 0.9$. This means that when $\alpha \to 1$ the state $n = 0$ is no longer absorbing and we expect that the relaxation time diverges. Indeed for $N_0 = 2, 3, 4, ...$ we find $\tau_0(N_0, \alpha) = \frac{cN_0}{\alpha}$. Conversely when the nonlinear term has a small weight $\alpha \sim 1$ the extinction is rather rapid.

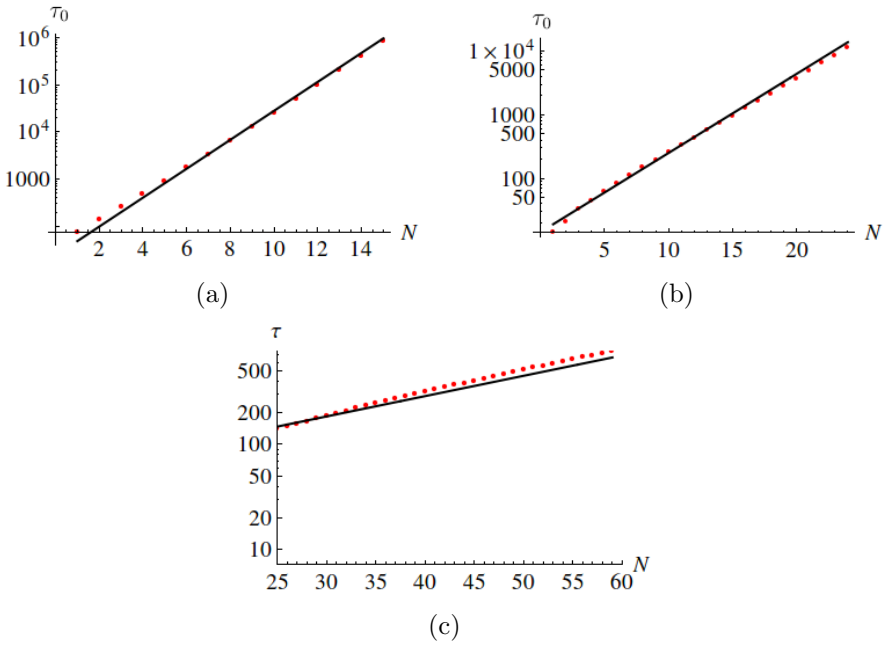


Figure 3.9: Plot of the time $\tau_0(N)$ required for extinction of a population with N individuals, namely for the null state probability to reach the value $p_0 = 0.98$. Red line is the time given by the simulation and the black line is the plot of relation (3.91). Figure (a) refers to the value $\alpha = 0.1$ and $\tau_0(2)$, (b) to $\alpha = 0.5$ and $\tau_0(2)$ and (c) to $\alpha = 0.9$ and $\tau_0(25)$.

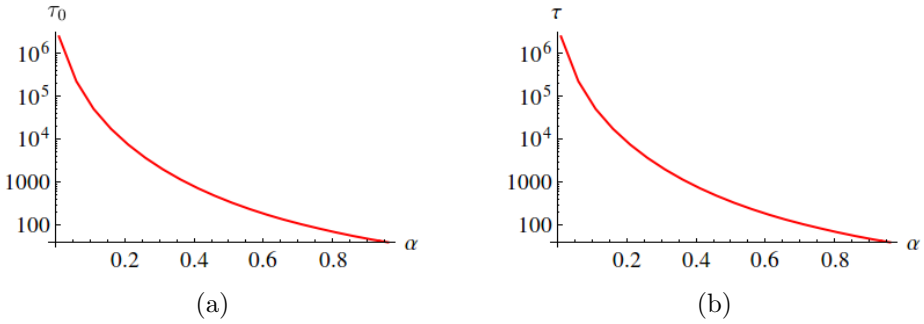


Figure 3.10: (a) Plot of the time τ_0 for $N = 20$ in function of the parameter α. (b)Plot of λ calculated with the equation (3.91) in function of the parameter α.

3.5 Discussion of the results

We have proposed a one parameter family of master equations associated to the logistic population model. For each value of the parameter $\alpha \in [0,1]$ and of the maximum value N of the population number a specific equilibrium is reached. In the transition probability r_n describing the loss, the term linear in n has a weight α whereas the quadratic term has a weight $(1-\alpha)$. As a consequence when the quadratic term dominates ($\alpha \to 0$) the equilibrium distribution is Gaussian with a maximum at $n = N$ and a width $N^{-1/2}$, whereas when the linear term dominates ($\alpha \to 1$) the distribution becomes a power law and the low population states are the most probable. In the limit $N \to \infty$ the same mean field equation is recovered, up to a time scale, and the equilibrium distribution of the master equation converges, for any fixed value of α, to the stable equilibrium of the mean field equation. As a consequence the Pareto like equilibrium which is close, for N large, to total extinction, namely to the unstable equilibrium of the mean field equation, is never observed in the previous limit. If we scale the time so that the mean field limit is the logistic equation with relaxation time equal to 1, any master equation, corresponding to a given value of α, is associated to a specific noise namely to a specific microscopic dynamics, and can be determined by looking at the equilibrium distribution for finite values of N.

The presence of an absorbing state does not change the picture substantially. Indeed when α is close to 1 the relaxation time grows so fast with N that when N is large enough only the metastable equilibrium corresponding to $n = N$ is observed in any reasonable time interval. Conversely when $\alpha \to 1$ the relaxation time increases as $e^{(1-\alpha)N}$ so that one first observes the relaxation to a power law distribution followed by total extinction.

The detailed balance conditions, which allows to determine analytically the equilibrium, holds only for the limit cases $\alpha = 0, 1$. However the numerical analysis shows that the behavior of the equilibrium distribution when $N \to \infty$ for α fixed is the same namely that the stable equilibrium of the mean field equation are recovered.

A one parameter family of master equations has been proposed for the BCM model as well and the conclusions on the equilibrium are very similar. The extension of the model to two populations has been considered and the equilibrium distributions have been analyzed. The detailed balance conditions, which allows to determine analytically the equilibrium, holds only for the limit cases $\alpha = 0, 1$. However the numerical analysis shows that the the equilibrium distributions depend on α and N as in the previous one population models.

SECOND PART-Nonequilibrium thermodynamics in terms of the master equation

Chapter 4

Nonequilibrium thermodynamics in terms of the master equation

In this chapter we will see how to derivate the thermodynamic formalism in terms of the master equation. Starting with the differentiation between equilibrium and nonequilibrium steady states we will understand the nonequilibrium approach. We will review the statistical mechanics of equilibrium, because it is the base for the nonequilibrium approach. And finally we will derivate all thermodynamic variables in terms of the master equation, which we will use in the Chapters 5 and 6.

4.1 Introduction

A much larger variety of phenomena can be described as stationary states of open systems, i.e., systems that can exchange molecules or/and energy with its environment, which exist away from thermodynamic equilibrium. In this way it is important to extend equilibrium thermodynamics to nonequilibrium process [3, 8, 78, 9, 10], in particular we are interested in biological systems (populations, living cells, gene networks, RNA, proteins and en-

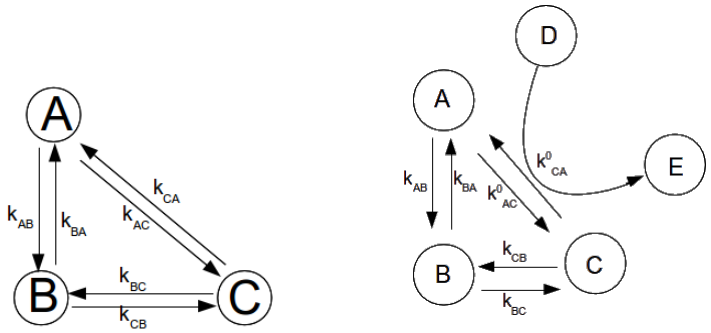
zymes).

To develop a nonequilibrium thermodynamic theory we should know clearly the concepts of detailed balance (closed systems) and nonequilibrium steady states (open systems). The thermodynamic characterization of systems in equilibrium got its microscopic justification from equilibrium statistical mechanics which states for a system in contact with a heat bath the probability to find it in any specific microstate is given by the Boltzmann factor [79, 78]. In contrast to systems in thermal equilibrium, systems far from equilibrium carry non-trivial fluxes of physical quantities such as particles or energy. These fluxes are induced and maintained by coupling the system to multiple reservoirs, acting as sources and sinks (of particles or energy) for the system. The non-zero probability flux implies the breaking down of the detailed balance which is a quantitative signature of the systems being in nonequilibrium states [80, 81].

Nonequilibrium thermodynamics as here understood applies to small systems and it is described by a probability distribution p_n evolving according to a Markovian Master equation [82, 78], which provides a framework for extending the notions of classical thermodynamics like work, heat and entropy production. Hence, the exchange of energy (heat) or particles with the environment and the other thermodynamic quantities associated to the system states n become stochastic variables. The system entropy is defined using the Gibbs expression $S = -k_b \sum_n p_n \ln p_n$ and entropy balance equations of the usual form can be derived via the identification of a non-negative entropy production consistent with macroscopic nonequilibrium thermodynamics [83, 84, 9].

4.1.1 Equilibrium and nonequilibrium steady states

In terms of the master equation, the system can reach, after a sufficiently long time, two types of stationary solution: an equilibrium or nonequilibrium steady state. The equilibrium is a special-case steady state that is obtained by closed and isolated systems, which is associated with detailed



(a) (b)

Figure 4.1: (a)Simple, unimolecular chemical reaction cycle. (b) Cyclic enzyme reactions with substrates D and E.

balance (DB) condition [3, 10, 9, 80, 78, 7]. These systems do not exchange molecules and energy with its environment and the concentrations of all chemical species are constant macroscopically. A closed system can only approach a chemical equilibrium with zero flux in each reaction, it means that each forward reaction is balanced by the reverse one [10, 11]. While a nonequilibrium steady state (NESS) is related to an open system that exchange molecules or/and energy with its environment [3, 10, 9, 80, 78, 7]. It is a chemical system with all the concentrations and fluctuations being stationary, the system is no longer changing with time in a statistical sense, i.e., all the probability distributions are stationary; nevertheless, the system is not at equilibrium. The system fluctuate, but not obey Boltzmann's law. Such a system only exists when it is driven by a sustained chemical energy input, the system has fluxes and dissipates heat [10, 11, 12].

To clarify the differences between DB and NESS we will use the cyclic enzyme reaction represented in Figure 4.1. We can let A, B, and C be three conformations of a single enzyme, D and E be substrates and $k_{i,j}$ the transition rates between the single elements $i, j = A, B, C$. The Figure 4.1a represents a simple, unimolecular, closed chemical reaction. For this system the D.B. condition is $\gamma = k_{AB}k_{BC}k_{CA}/k_{BA}k_{CB}k_{AC} = 1$, that is the forward reaction $A \to B \to C$ is balanced by the backward reaction $C \to$

$B \to A$. The open cycle (Figure 4.1b) brings in two more substrates D and E which can break the DB to generate a nonequilibrium steady state flux, characterizing the NESS. Cyclic enzyme reactions with substrates D and E can be mapped into the unimolecular cycle in terms of pseudo-first-order rate constants: $k_{CA} = k^0_{CA}[D]$ and $k_{AC} = k^0_{AC}[E]$. If the species D and E are in equilibrium, then we have $\gamma = k_{AB}k_{BC}k^0_{CA}[D]/k_{BA}k_{CB}k^0_{AC}[E] = 1$ and the system is in a detailed balance condition. However, if $[D]$ and $[E]$ are sustained under nonequilibrium conditions in an open system, then $\gamma \neq 1$ and the DB condition is broken. Therefore, a closed system tends to be an equilibrium, whereas an open system tends to be an NESS.

4.1.2 Equilibrium thermodynamics

Equilibrium thermodynamics is defined by a set of parameters (measured macroscopically) which specify a thermodynamic state. When the thermodynamic state does not change with time we are in a situation known as thermodynamic equilibrium. We can describe a thermodynamic system through the statistical mechanics, that is concerned with the properties of matter in equilibrium in the empirical sense used in thermodynamics [79]. The aim of statistical mechanics is to derive all the equilibrium properties of a macroscopic molecular system from the laws of molecular dynamics. Thus it aims to derive not only the general laws of thermodynamics but also the specific thermodynamic functions of a given system [85, 79, 86]. For our purposes we need to know the canonical ensemble, as is described bellow.

The Canonical Ensemble

The canonical ensemble is characterized by a closed system that can exchange heat with its surrounds and as a consequence will have a fluctuating total energy. In order to obtain the thermodynamic variables for the system we must extremize the Gibbs entropy

$$S = -k_b \sum_i p_i \ln p_i \tag{4.1}$$

where the constant k_B is typically consider the Boltzmann's constant and the p_i can be interpreted as a representation of our knowledge of the system. We require that the probability be normalized

$$\sum_i p_i = 1 \tag{4.2}$$

and we demand that the average energy be fixed to some constant value $< U >$

$$\sum_i u_i p_i =< U > . \tag{4.3}$$

With these choices we have that the canonical distribution of equilibrium is $p_i^e = \frac{e^{-\frac{u_i}{k_B T}}}{Z}$, where $Z = \sum_i e^{-\frac{u_i}{k_B T}}$ is Gibbs canonical partition function and $u_i = k_b T \ln Z_i$. The Gibbs functional $S = -k_B \sum_i p_i \ln p_i$ have the maximum value for $p_i = p_i^e$, to all distributions that have $< U >= \sum_i u_i p_i =$ constant.

In a conservative system, mechanical work can be stored into the form of potential energy and subsequently retrieved it in form of work. Under certain circumstances the same is true for thermodynamic systems. We can stored energy in a thermodynamic system by doing work on it through a reversible process, and we can eventually retrieve that energy in the form of work. The energy which is stored and retrievable in the form of work is called the free energy [79]. For the canonical ensemble we have that the Helmholtz free energy is defined as:

$$F = U - TS. \tag{4.4}$$

For a process carried out at fixed temperature (T), volume (V) and number of molecules (N) we find

$$\Delta F \leq -\Delta W \tag{4.5}$$

where ΔW is the work make in the system. If no work is done the equation (4.5) becomes

$$\Delta F \leq 0. \tag{4.6}$$

Thus, an equilibrium state is a state of minimum Helmholtz free energy [1].

[1] In this thesis we will assume that $k_B = 1$ and the temperature T is constant.

4.1.3 From Classical to nonequilibrium thermodynamics

At the heart of the classical thermodynamics we have general laws governing the transformations of a system, these transformations involve the exchange of heat, work and matter with the environment. In the classical formulation of the second law (due to Clausius) we have a central result: the total entropy production can *never decrease*, it increases monotonically until it reaches its maximum at the state of thermodynamic equilibrium

$$\frac{dS}{dt} \geq 0. \tag{4.7}$$

This statement applies to the stages of the evolution in which the entropy is well defined. For example, for a system in equilibrium at initial and final times, the final entropy will be larger than the initial one, even though the entropy may not be well defined during the intermediate evolution. However, it is often a very good approximation to assume that the system is in a state of local equilibrium, so that the entropy is well defined at any stage of the process [82]. The relation (4.7) is valid for system in equilibrium, but as we will see in the next sections, we can extend this formulation to systems which exchange energy and matter with the outside world.

As is well known, the statistical mechanics gives a characterization for systems in equilibrium with a microscopic perspective, determining the probability to find the system in any specific microstate by the Boltzmann distribution. On a more phenomenological level, linear irreversible thermodynamics provides a relation between such transport coefficients and entropy production in terms of forces and fluxes [78]. When we change our perspective we can realize that besides the fluctuations of the entropy production in the heat bath one should similarly assign a fluctuating, or stochastic, entropy to the system proper [87].

Therefore, as a natural way to understand the properties of a nonequilibrium thermodynamics we can consider the laws of equilibrium thermodynamics, taking the energy conservation, i.e., the first law, and entropy production

on the mesoscopic level [78].

4.2 Nonequilibrium thermodynamics

Here we understand as nonequilibrium thermodynamics the set of state functions written in terms of the master equation. Following the important works of Schnakenberg [7], Oono and Paniconi [88], Qian [8, 10, 9], Seifert [78, 87] and Zia [80, 89], in the next sections we will derivate this general theory, which describes systems in DB and NESS.

4.2.1 Entropy production

As we saw in the section 4.1.3, the second law of the thermodynamics specifies the existence of the entropy S, ascertains that the total entropy of an isolated macroscopic system cannot decrease in time and that it increases monotonically until it reaches its maximum at the state of thermodynamic equilibrium

$$\frac{dS}{dt} \geq 0. \tag{4.8}$$

The relation (4.8) is valid for systems in equilibrium, to extend to nonequilibrium processes we need an explicit expression for the entropy production [83]. In open systems the corresponding quantity to entropy change dS turns out to have two contributions [84]:

$$dS = d_iS + d_eS. \tag{4.9}$$

Where d_iS is the entropy produced inside the system due to spontaneous process and d_eS is the transfer of entropy across the boundaries of the system (see Figure 4.2). According with second law of thermodynamics d_iS must be zero for reversible (or equilibrium) transformations and positive for irreversible transformations of the system, i.e., $d_iS \geq 0$. The entropy supplied, d_eS, may be positive, zero or negative depending on the interaction of the system with its surroundings.

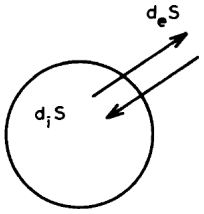


Figure 4.2: The exchange of entropy between the outside and the inside for an open system.

The heat dissipated into the environment can be identified with an increase in entropy of the medium and the basic distinction here is between reversible and irreversible processes [78, 83]. Only irreversible processes contribute to entropy production, because in the steady state the system still exchange energy with the environment to maintain the NESS.

4.2.2 Housekeeping heat Q_{hk} and Excess heat Q_{ex}:

Oono and Paniconi [88] constructed a phenomenological framework corresponding to equilibrium thermodynamics for steady states. They focused on transitions between steady states and decomposed the total heat dissipation (Q_{tot}) into a housekeeping part (Q_{hk}) and an excess part (Q_{ex}). Since we are in a NESS we dissipate energy as heat (Q_{hk}) to maintain the steady state, then we must somehow subtract the contribution of Q_{hk} in the Q_{tot} and the Q_{ex} is defined as [88]:

$$Q_{ex} \equiv Q_{tot} - Q_{hk}. \tag{4.10}$$

To understand the meaning of Q_{hk} and Q_{ex} we can consider the system represented in the Figure 4.3. The subsystem A is in a NESS condition and B is its heat bath. Whereas this system is described by the grand canonical ensemble, A and B can exchange energy and molecules. To sustain the NESS the part A dissipate heat, what is known as housekeeping heat, while the heat exchange by B and A is the excess heat. By convention, we take the sign of heat to be positive when it flows from the system to the heat bath. The housekeeping heat rate Q_{hk} does note account for the total energy difference

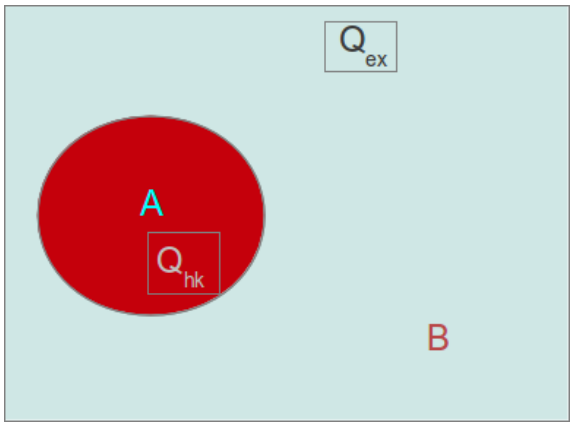


Figure 4.3: Subsystem A in a NESS situation in contact with its heat bath B.

ΔU between different steady states. $\Delta U - Q_{ex}$ is the remaining systematic part called (excess) work, that is, the portion of energy stored in the system in the systematic form [88]. For equilibrium systems Q_{ex} reduces to the total heat Q_{tot}, because in this case the system does not dissipate energy and $Q_{hk} = 0$ [88, 90].

In the Hatano and Sasa's work [90] they employed the phenomenological framework of steady-state thermodynamics constructed by Oono and Paniconi [88], they find the extended form of second law holed for transitions between steady states and the Shannon entropy (also accepted as the common definition of Gibbs entropy) difference is related to the excess heat produced in a infinitely slow operation. Because any proper formulation of steady-state thermodynamics (SST) should reduce to equilibrium thermodynamics in the appropriate limit, Q_{ex} should correspond to the change of a generalized entropy S within the SST. Considering systems in contact with a single heat bath whose temperature is denoted by T, the second law of SST reads

$$T\Delta S \geq -Q_{ex}. \tag{4.11}$$

The generalized entropy difference ΔS between two steady states can be measured as $-Q_{ex}/T$ resulting from a slow process connecting these two states. This allows us to define the generalized entropy of nonequilibrium

steady states experimentally, by measuring the excess heat obtained in a slow process between any nonequilibrium steady state and an equilibrium state, whose entropy is known [88, 90].

4.3 Nonequilibrium Thermodynamics based on Master equation and Gibbs Entropy

Now we have all features to derive the nonequilibrium variables in terms of the master equation. Considering the generic form of the master equation defined in Chapter 1 by eq. (1.17)

$$\frac{dp_i(t)}{dt} = \sum_j [W_{i,j}p_j - W_{j,i}p_i]. \tag{4.12}$$

and the Gibbs entropy defined by (4.1), which derivative is express by

$$\frac{dS(t)}{dt} = -\sum_i \frac{dp_i}{dt}\ln p_i - \frac{d}{dt}\sum_i p_i. \tag{4.13}$$

The term $\frac{d}{dt}\sum_i p_i$ is obviously null, because by the normalization we have $\sum_i p_i = 1$. Replacing the term $\frac{dp_i}{dt}$ in (4.13) by the master equation (4.12) we obtain

$$\frac{dS(t)}{dt} = -\sum_{i,j} [W_{i,j}p_j - W_{j,i}p_i]\ln p_i. \tag{4.14}$$

If we exchange the indexes i and j we rewrite $\frac{dS(t)}{dt}$ as

$$\begin{aligned}\frac{dS(t)}{dt} = &-\frac{1}{2}\sum_{i,j} [W_{i,j}p_j - W_{j,i}p_i]\ln\frac{W_{j,i}p_i}{W_{i,j}p_j} \\ &+\frac{1}{2}\sum_{i,j} [W_{i,j}p_j - W_{j,i}p_i]\ln\frac{W_{j,i}}{W_{i,j}}.\end{aligned} \tag{4.15}$$

On the other rand we have that the derivative of entropy from eq. (4.9) is

$$\frac{dS(t)}{dt} = \frac{d_iS}{dt} + \frac{d_eS}{dt}, \tag{4.16}$$

Ge and Qian [9] defined $\frac{d_i S}{dt} = e_p$ and $\frac{d_e S}{dt} = -h_d$, then the time-dependent variation of entropy reads

$$\frac{dS(t)}{dt} = e_p(t) - h_d(t) \tag{4.17}$$

where e_p is the instantaneous entropy production rate and h_d is the rate dissipation heat. Comparing the equations (4.15) and (4.17) we can identify

$$e_p = -\frac{1}{2}\sum_{i,j}[W_{i,j}p_j - W_{j,i}p_i]\ln\frac{W_{j,i}p_i}{W_{i,j}p_j} \tag{4.18}$$

and

$$h_d = -\frac{1}{2}\sum_{i,j}[W_{i,j}p_j - W_{j,i}p_i]\ln\frac{W_{j,i}}{W_{i,j}}. \tag{4.19}$$

We still can relate h_d and e_p with the thermodynamic variables from equilibrium. If we consider the definition of the Helmholtz free energy (eq. (4.4)), $F = U - S$, writing in function of S and taking its time derivative we obtain

$$\frac{dS(t)}{dt} = -\frac{dF}{dt} + \frac{dU}{dt}. \tag{4.20}$$

Therefore, comparing with equation (4.17) we identify,

$$h_d = -\frac{dU(t)}{dt} \quad \text{and} \quad e_p = -\frac{dF(t)}{dt}. \tag{4.21}$$

In this way we have the mathematical formulation for the thermodynamic variables in terms of the master equation. When the system presents detailed balance condition, for $t \to \infty$ it reaches an equilibrium state with $e_p = h_d = \frac{dS(t)}{dt} = 0$. In contrast to systems in equilibrium, systems in NESS present fluxes of physical quantities, such as particles or energy. Thus DB is violated and there is a continuous useful energy being pumped into the system that sustains the NESS [9, 81, 11] and then e_p and h_d are not null, but will be equal, this is necessary to ensure that S is finite asymptotically and $\frac{dS(t)}{dt} = 0$.

We will use these results in the Chapters 5 to analyze the general thermodynamic properties of a linear system using the chemical fluxes to characterize the NESS of a chemical chain reaction and in Chapter 6 to establish how

the entropy variation can be used to find the optimal value (corresponding to increased robustness and stability) for a parametrization doing in the well known model of synaptic plasticity, the so called BCM theory, calculating also the work as the parameter of the plasticity of these systems.

Chapter 5

The role of nonequilibrium fluxes in the relaxation processes of the Linear Chemical Master Equation

5.1 Motivations of the work

We consider the dynamics of a chemical cycle chain reaction among m different species, the reaction cycles are fundamental to biochemical network kinetics [81, 11], they are the chemical basis of cellular signal transduction [91, 92] and biological morphogenesis [93, 94]. As it is known the determination of the global stability of the dynamical systems and the networks is still an open field, because these systems are not in isolation and their description are not trivial. [81, 95, 9, 10, 11, 12, 78, 78, 80, 89]. A possible method to describe global stability for these systems is the probabilistic (or nonequilibrium) approach, whereas these processes involves less number of molecules and thus the role of fluctuations should be considered [81, 7, 9, 11, 78, 87, 80, 89].

An important consideration for the nonequilibrium approach is whether

the system is isolated or open to interactions with the environment. After a sufficient long time, isolated systems reaches an equilibrium state (detailed balance), which the probability chemical fluxes are null. While an open system (if the exchange with its surroundings is sustained) approaches a nonequilibrium steady state (NESS) [3, 4, 7, 9, 78, 89], probability chemical fluxes are not null leading the breaking down of the DB. When the DB holds the equilibrium distribution can be written as a Maxwell-Boltzmann distribution, which means there is a unique equilibrium constant for every chemical reaction in a system, regardless of how complex the system is. However, in a NESS, the stationary chemical currents are different from zero and this can be associated with the existence of an external non-conservative field interacting with the system.

We propose a general theory for the dynamics of a chemical chain reaction among m different species, based in the in previous works [7, 9, 81, 78, 87, 80, 89] we present a nonequilibrium thermodynamical description in terms of the chemical master equation (CME). The determination of stationary fluxes allows us to completely describe systems in equilibrium (DB) as well as in NESS. We are interested in the role of fluxes in the transient states and, in particular, in the relaxation process towards the stationary distribution. Indeed the relaxation times of biochemical reactions could be related to the plasticity properties of biological systems.

5.2 Nonequilibrium fluxes and stationary states for the CME

Let us consider the dynamics of a chemical chain reaction among m different species as represented in Figure 5.1. Introducing the transition probability $\pi_{k-1,k}$ that a single particle of the chemical specie $k-1$ is transformed in a particle of the specie k in a time unit and assuming that the particles are independent, the transition rate from the specie $k-1$ to the specie k is given by $\pi_{k-1,k}n_{k-1}$ where n_{k-1} denotes the number of particles of the $k-1$

species. In a generic situation, the transition probability $\pi_{k-1,k}$ may depend on the state $n = (n_1, ..., n_m) \in \mathbb{N}^m$ that gives the distribution of particles into the different chemical species. Here we consider the case for which the $\pi_{k-1,k}$ are independent on n_k and the total number of particles is constant

$$|n| = \sum_{k=1}^{m} n_k = N.$$

The deterministic mean field equations for the m states are

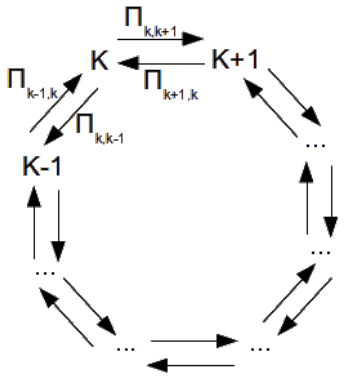


Figure 5.1: Chemical chain reaction among m different species.

$$\begin{aligned}
\dot{n}_k(t) &= \pi_{k-1,k} n_{k-1} + \pi_{k+1,k} n_{k+1} - (\pi_{k,k-1} + \pi_{k,k+1}) n_k \\
&\vdots \\
\dot{n}_m(t) &= \pi_{m-1,m} n_{m-1} + \pi_{m+1,m} n_{m+1} - (\pi_{m,m-1} + \pi_{m,m+1}) n_m
\end{aligned} \tag{5.1}$$

If the reaction chain is a cycle, we impose periodic boundary conditions in the sum $m + 1 \sim 1$. In this way we can write the CME that describes the evolution of the probability distribution $p_n(t)$ of the system (5.1), according to (1.33) introduced in the Chapter 1

$$\begin{aligned}
\dot{p}_n(t) &= \sum_{k=1}^{m} \left(E_{k-1}^{+} E_k^{-} \pi_{k-1,k} n_{k-1} p_n(t) - \pi_{k,k-1} n_k p_n(t) \right) \\
&+ \left(E_k^{-} E_{k+1}^{+} \pi_{k+1,k} n_{k+1} p_n(t) - \pi_{k,k+1} n_k p_n(t) \right)
\end{aligned} \tag{5.2}$$

To write the equation (5.2) in a discrete form of the Fokker-Planck equation, we introduce the difference operator $\mathbf{D_k} = D_k^+$ or D_k^- defined as

$$\begin{aligned} D_k^+ &\equiv E_{k-1}^+ E_k^- - 1 \\ D_k^- &\equiv E_{k-1}^- E_k^+ - 1. \end{aligned} \tag{5.3}$$

The operator $\mathbf{D_k}$ has the following properties:

1. We can write the relation

$$D_k^- = E_{k-1}^- E_k^+ (1 - E_{k-1}^+ E_k^-) = -D_k^+ E_{k-1}^- E_k^+ \tag{5.4}$$

2. We can write a discretized Laplacian

$$\begin{aligned} -D_k^+ D_k^- &= -(E_{k-1}^+ E_k^- - 1)(E_{k-1}^- E_k^+ - 1) \\ &= E_{k-1}^- E_k^+ - 2 + E_{k-1}^+ E_k^- \end{aligned} \tag{5.5}$$

3. The operator $\mathbf{D_k}$ has similar properties to a derivative and in particular the product rule reads

$$\begin{aligned} D_k^+ f(n)g(n) &= E_{k-1}^+ E_k^- f(n) D_k^+ g(n) + g(n) D_k^+ f(n) \\ D_k^- f(n)g(n) &= E_{k-1}^- E_k^+ f(n) D_k^- g(n) + g(n) D_k^- f(n) \end{aligned} \tag{5.6}$$

for any real function $f(n)$ and $g(n)$ with $n \in \mathbb{N}^m$.

4. The commutativity property holds

$$\mathbf{D_k D_h} = \mathbf{D_h D_k}. \tag{5.7}$$

5. We can extend the definition of the operator D_k to any subset $\Gamma \subseteq \{|n| = N\}$ according to

$$\begin{aligned} D_k^+ \Gamma &= \{E_{k-1}^+ E_k^- \Gamma \backslash \Gamma\} \cup \{\Gamma \backslash E_{k-1}^+ E_k^- \Gamma\} \\ D_k^- \Gamma &= \{E_{k-1}^- E_k^+ \Gamma \backslash \Gamma\} \cup \{\Gamma \backslash E_{k-1}^- E_k^+ \Gamma\} \end{aligned} \tag{5.8}$$

and we have the relation

$$\sum_{\Gamma} \mathbf{D_k} f(n) = \sum_{\mathbf{D_k}\Gamma} f(n) \qquad \forall\, k. \tag{5.9}$$

As a consequence if $f(n)$ vanishes at the boundary points we have,

$$\sum_{\Gamma} \mathbf{D_k} f(n) = 0. \tag{5.10}$$

Using the definition (5.3), the CME (5.2) can be written in the form of discrete continuity equation in the hyperplane $\{|n| = N\}$

$$\dot{p}_n(t) = -\sum_{k=1}^{m} D_k^+ J_k(n,t) \tag{5.11}$$

where J_k are the chemical fluxes and are defined according to

$$\begin{aligned} J_k(n,t) &= -\pi_{k-1,k}(n) n_{k-1} p_n(t) + E_{k-1}^- E_k^+ \pi_{k,k-1}(n) n_k p_n(t) \\ &= (-\pi_{k-1,k}(n) n_{k-1} + \pi_{k,k-1}(n) n_k) p_n(t) + D_k^- \pi_{k,k-1}(n) n_k p_n(t) \end{aligned} \tag{5.12}$$

On the other hand we have that the Fokker-Planck (see section 1.3.3) equation is defined as

$$\frac{\partial P_n(t)}{\partial t} = -\frac{\partial J_k(n,t)}{\partial n} = -\sum_{k=1}^{m} \frac{\partial}{\partial n}\left(A_k(n) - \frac{\partial B_k(n)}{\partial n} \right) P_n(t) \tag{5.13}$$

where $A_k(n)$ is the drift field and $B_k(n)$ the diffusion coefficient. Comparing the equations (5.11) and (5.13) we can rewrite $\dot{p}_n(t)$ as

$$\dot{p}_n(t) = -\sum_{k=1}^{m} D_k^+ (A_k(n) p_n(t) + D_k^- B_k(n) p_n(t)) \tag{5.14}$$

and therefore the fluxes $J_k(n,t)$ are

$$J_k(n,t) = A_k(n) p_n(t) + D_k^- B_k(n) p_n(t). \tag{5.15}$$

We have defined the drift field

$$A_k(n) = -\pi_{k-1,k}(n) n_{k-1} + \pi_{k,k-1}(n) n_k \tag{5.16}$$

and the diffusion coefficient

$$B_k(n) = \pi_{k,k-1}(n) n_k. \tag{5.17}$$

The drift field is directly correlated to the average dynamics: suppose that exist a subset $\Gamma \subseteq |n| = N$ obyes the condition 5.9, such that the distribution $p_n(t)$ almost vanishes at the boundary. To compute the average dynamics for the CME (5.11) we use the equation for the mean field $< n_k >_\Gamma = \sum_\Gamma n_k p_n(t)$. Then we have

$$\begin{aligned} < \dot{n}_k >_\Gamma &= \sum_\Gamma n_k \dot{p}_n(t) = -\sum_\Gamma n_k D_k J_k \\ &\simeq -\sum_\Gamma D_k(n_k+1) J_k(n) - \sum_\Gamma J_k(n) \\ &- \sum_\Gamma D_{k+1}(n_k-1) J_{k+1}(n) + \sum_\Gamma J_{k+1}(n). \end{aligned} \tag{5.18}$$

Using the definition (5.15) we have

$$\begin{aligned} < \dot{n}_k >_\Gamma &\simeq \sum_\Gamma (A_{k+1}(n) - A_k(n)) p(n,t) - (D_{k+1}B_{k+1}(n) - D_k B_k(n)) p(n,t) \\ &\simeq \sum_\Gamma A_{k+1}(n) p(n,t) - \sum_\Gamma A_k(n) p(n,t) \end{aligned} \tag{5.19}$$

where we use the relation (5.9), consequently the term $\sum_\Gamma (D_{k+1}B_{k+1}(n) - D_k B_k(n)) p(n,t)$ is null. Therefore we can write the average equations as

$$< \dot{n}_k >_\Gamma \simeq \langle A_{k+1}(n) \rangle_\Gamma - \langle A_k(n) \rangle_\Gamma \qquad k = 1, .., m \tag{5.20}$$

The average field approximation can be applied to eq. (5.20) on Γ, if

$$< \dot{n}_k > \simeq A_{k+1}(< n >) - A_k(< n >) \qquad k = 1, .., m. \tag{5.21}$$

As a consequence, this approximation is correctly applied when the fluctuations with respect to the average values and it becomes exact when the transition probabilities $\pi_{k-1,k}$ are constant. In the last case we get a linear

CME whose solution can be explicitly computed in the form of a multinomial distribution

$$p_l(t) = N! \prod_{k=1}^{m} \frac{\lambda_k^{n_k}(t)}{n_k!} \qquad |n| = N \tag{5.22}$$

where the quantities λ_k are the non trivial solutions of the linear system (5.21) according to

$$\dot{\lambda}_k = -\pi_{k,k+1}\lambda_k + \pi_{k+1,k}\lambda_{k+1} + \pi_{k-1,k}\lambda_{k-1} - \pi_{k,k-1}\lambda_k \qquad k = 1, .., m \tag{5.23}$$

with the constraint

$$|\lambda| = \sum_{k=1}^{m} \lambda_k = 1 \qquad \lambda_k > 0. \tag{5.24}$$

Letting $t \to \infty$ we get the stationary solution with $\lambda_k^* = \lim_{t\to\infty} \lambda_k(t)$ that satisfies the condition

$$A_{k+1}(\lambda^*) = A_k(\lambda^*) \tag{5.25}$$

and corresponds to the maximum value of the stationary distribution $p_l(n)$ at $n_k^* \simeq N\lambda_k^*$. Therefore in the linear case the critical value of the stationary distribution corresponds to the stable fixed point of the average systems (5.21). The previous results can be generalized to a non-linear CME provided one could apply the average field approximation.

5.3 Thermodynamical properties of CME

The CME can model both the evolution of equilibrium and non equilibrium systems and a thermodynamical approach has been proposed to characterize the properties of the stationary solutions $\dot{p}_n^s(t) = 0$. In particular one distinguishes the equilibrium states at which the chemical fluxes $J_k^s(n) = 0$ (Detailed Balance (DB) condition), and the Non Equilibrium Stationary States (NESS) where the weaker condition holds

$$\sum_{k=1}^{m} D_k J_k^s(n) = 0. \tag{5.26}$$

We will explicitly recall some properties of the stationary solution for the equation (5.11). To characterize the properties of the stationary solution of the CME we first analyze the DB case. Using the definition (5.15) the DB equilibrium can be written in the form

$$D_k B_k(n) p_n^s = A_k(n) p_n^s \tag{5.27}$$

the DB equilibrium satisfies to

$$D_k \ln B_k(n) p_n^s = \ln\left(1 + \frac{D_k B_k(n) p_n^s}{B_k(n) p_n^s}\right) = \ln\left(1 + \frac{A_k(n)}{B_k(n)}\right) \tag{5.28}$$

Then we get the relation

$$D_k \ln p_n^s = \ln \frac{B_k(n) + A_k(n)}{E_{k-1}^+ E_k^- B_k(n)} = \ln\left(1 + \frac{A_k(n) - D_k B_k(n)}{E_{k-1}^+ E_k^- B_k(n)}\right) \tag{5.29}$$

that allows to compute the distribution p_n^s in a recursive way using any path connecting a fixed point n_0 with a generic point n in the surface $|n| = N$. Then we define an *internal interaction energy* $V(n)$

$$D_k V(n) = -\ln\left(1 + \frac{A_k(n) - D_k B_k(n)}{E_k^+ E_{k-1}^- B_k(n)}\right) \tag{5.30}$$

and an *internal energy* as

$$E(t) = \sum_{|n|=N} V(n) p_n(t) \tag{5.31}$$

Therefore, when the DB holds the equilibrium distribution can be written as a Maxwell-Boltzmann distribution

$$p_n^s \propto \exp(-V(n)) \tag{5.32}$$

where the $V(n)$ is an interaction microscopic energy, according to (5.30).

In a NESS, the stationary chemical currents $J_k^s(n)$ are different from zero and this can be associated with the existence of an external field $A_k^{ext}(n)$, which lead us to split the drift field into an internal and external vector field [78, 87]

$$A_k(n) = A_k^{in}(n) + A_k^{ext}(n). \tag{5.33}$$

Where $A_k^{ext}(n)$ is an external non-conservative field which generates the stationary fluxes

$$A_k^{ex}(n) = \frac{J_k^s(n)}{p_n^s} \tag{5.34}$$

and $A_k^{in}(n)$ is a conservative vector whose potential satisfies $V^{in}(n) = -\ln p_n^s$. *Remark*: The splitting is possible only if one knows the stationary distribution and the stationary fluxes.

We will present an alternative thermodynamic description from which introduced in Chapter 4. We follow the same procedure, but here we consider the CME written in terms of the difference operators $\mathbf{D_k}$. Considering the Gibbs entropy (see 4.1) we write the internal entropy

$$S_{in} = -\sum_{|n|=N} p_n(t) \ln p_n(t) \tag{5.35}$$

taking its time derivative we obtain

$$\begin{aligned} \dot{S}_{in} &= -\sum_{|n|=N} \dot{p}_n(t)(1 + \ln p_n(t)) \qquad (5.36) \\ \dot{S}_{in} &= -\sum_{|n|=N} \dot{p}_n(t) - \sum_{|n|=N} \dot{p}_n(t) \ln p_n(t) = -\sum_{|n|=N} \dot{p}_n(t) \ln p_n(t) \end{aligned}$$

replacing $\dot{p}_n(t)$ by the CME (5.11) we have

$$\dot{S}_{in} = \sum_{k=1}^{m} \sum_{|n|=N} D_k^+ J_k(n,t) \ln p_n(t), \tag{5.37}$$

where we can use the property (5.6) and get the extend form

$$\dot{S}_{in} = \sum_{k=1}^{m} \sum_{|n|=N} E_{k-1}^+ E_k^- J_k(n,t) D_k^+ \ln p_n(t). \tag{5.38}$$

We can approximate $D_k^+ \ln p_n(t)$ as

$$D_k^+ \ln p_n = \ln \frac{E_{k-1}^+ E_k^- p_n}{p_n} = \ln \left(1 + \frac{D_k^+ p_n}{p_n}\right) \simeq \frac{D_k^+ p_n}{p_n} \tag{5.39}$$

To determine $D_k^+ \ln p_n(t)$ we consider the definition of currents (5.15)

$$J_k(n) - A_k(n) p_n(t) = D_k^- B_k(n) p_n(t), \tag{5.40}$$

using (5.6) we write

$$D_k^- B_k(n) p_n(t) = (E_{k-1}^- E_k^+ p_n(t)) D_k^- B_k(n) + B_k(n) D_k^- p_n(t) \tag{5.41}$$

putting (5.41) in (5.40)

$$J_k(n) - A_k(n) p_n(t) = (E_{k-1}^- E_k^+ p_n(t)) D_k^- B_k(n) + B_k(n) D_k^- p_n(t) \tag{5.42}$$

dividing by: $(E_{k-1}^- E_k^+ p_n(t)) B_k(n)$

$$\frac{E_{k-1}^- E_k^+ D_k^+ p_n(t)}{E_{k-1}^- E_k^+ p_n(t)} = \frac{(J_k(n) - A_k(n) p_n(t))}{(E_{k-1}^- E_k^+ p_n(t)) B_k(n)} - \frac{D_k^- B_k(n)}{B_k(n)} \tag{5.43}$$

To find $\frac{D_k^+ p_n(t)}{p_n(t)}$ we use the relation (5.4)

$$\frac{E_{k-1}^- E_k^+ D_k^+ p_n(t)}{E_{k-1}^- E_k^+ p_n(t)} = \frac{(J_k(n) - A_k(n) p_n(t))}{(E_{k-1}^- E_k^+ p_n(t)) B_k(n)} - \frac{D_k^- B_k(n)}{B_k(n)} \tag{5.44}$$

multiplying by $\frac{E_{k-1}^+ E_k^-}{E_{k-1}^+ E_k^-}$

$$\frac{D_k^+ p_n(t)}{p_n(t)} = \frac{E_{k-1}^+ E_k^- (J_k(n) - A_k(n) p_n(t))}{p_n(t) B_k(n)} - \frac{E_{k-1}^+ E_k^- D_k^- B_k(n)}{E_{k-1}^+ E_k^- B_k(n)} \tag{5.45}$$

Therefore we can write the entropy production (5.38) as

$$\begin{aligned}
\dot{S}_{in} &= \sum_{k=1}^{m} \sum_{|n|=N} E_{k-1}^+ E_k^- J_k(n,t) \frac{D_k^+ p_n}{p_n} \qquad (5.46)\\
&= \sum_{k=1}^{m} \sum_{|n|=N} E_{k-1}^+ E_k^- J_k(n,t) \left(\frac{E_{k-1}^+ E_k^- (J_k(n) - A_k(n) p_n(t))}{p_n(t) B_k(n)} - \frac{E_{k-1}^+ E_k^- D_k^+ B_k(n)}{E_{k-1}^+ E_k^- B_k(n)} \right) \\
&= \sum_{k=1}^{m} \sum_{|n|=N} \frac{(E_{k-1}^+ E_k^- J_k(n))^2}{p_n(t) B_k(n)} \\
&+ \sum_{k=1}^{m} \sum_{|n|=N} E_{k-1}^+ E_k^- J_k(n,t) \left(\frac{-E_{k-1}^+ E_k^- A_k(n) p_n(t) + (E_{k-1}^- E_k^+ p_n(t)) D_k^- B_k(n)}{p_n(t) B_k(n)} \right) \\
&= \sum_{k=1}^{m} \sum_{|n|=N} \frac{(E_{k-1}^+ E_k^- J_k(n))^2}{p_n(t) B_k(n)} + \sum_{k=1}^{m} \sum_{|n|=N} E_{k-1}^+ E_k^- J_k(n,t) \left(\frac{-A_k(n) - D_k^- B_k(n)}{E_{k-1}^+ E_k^- B_k(n)} \right)
\end{aligned}$$

multiplying by $\frac{-D_k^+ E_{k-1}^- E_k^+}{D_k^+ E_{k-1}^- E_k^+}$

$$\dot{S}_{in} = \sum_{k=1}^{m} \sum_{|n|=N} \frac{D_k^+ J_k^2(n)}{p_n(t) D_k^- B_k(n)} - D_k^+ J_k(n,t) \left(\frac{A_k(n) + D_k^- B_k(n)}{D_k^- B_k(n)} \right) \quad (5.47)$$

Since the changes of p_n and J_k are negligible for a single exchange in the particle numbers, i.e. $N \gg 1$, we can approximate

$$\dot{S}_{in} = \sum_{k=1}^{m} \sum_{|n|=N} \frac{J_k^2(n)}{p_n(t) D_k^- B_k(n)} - \sum_{k=1}^{m} \sum_{|n|=N} J_k(n,t) \left(\frac{A_k(n) + D_k^- B_k(n)}{D_k^- B_k(n)} \right) \quad (5.48)$$

In the r.h.s. of eq. (5.48) one recognizes the total Entropy production $\dot{S}$ and the Environment entropy production $\dot{S}_{en}^S$ according to

$$\begin{aligned} \dot{S} &= \sum_{k=1}^{m} \sum_{|n|=N} \frac{J_k^2(n)}{p_n(t) D_k^- B_k(n)} \\ \dot{S}_{en} &= -\sum_{k=1}^{m} \sum_{|n|=N} J_k(n,t) \left(\frac{A_k(n) + D_k^- B_k(n)}{D_k^- B_k(n)} \right) \end{aligned} \quad (5.49)$$

At the stationary condition

$$\dot{S}_{in}^s = \sum_{k=1}^{m} \sum_{|n|=N} E_k^+ E_{k-1}^- J_k^s(n) D_k V^{in}(n) = 0 \quad (5.50)$$

which means that the average "work" of the currents due to internal interactions is zero for a NESS. Therefore in a NESS it is straightforward to observe that the total stationary Entropy production is always positive, so that to maintain the stationary distribution the environment is exchanging energy with the system through the work done on the system, which is dissipated. Conversely in a DB equilibrium the total entropy production is zero and there is no dissipated work. By using the decomposition (5.33) it is possible to modulate the external field by changing the drift term according to

$$\hat{A}_k(n) = A_k(n) - \lambda A_k^{ex}(n) \quad (5.51)$$

where λ is a parameter: $\lambda = 0$ corresponds to the initial case and $\lambda = 1$ to the DB equilibrium when the external field vanishes. Moreover it is possible to

prove that the stationary distribution does not depend on λ, the stationary condition for the modulated drift (defined in eq. (5.51)) reads

$$\sum_{k=1}^{m} D_k \left(\hat{A}_k(n)\hat{p}_n^s - D_k B_k(n)\hat{p}_n^s \right) =$$
$$\sum_{k=1}^{m} D_k \left(A_k(n)\hat{p}_n^s - D_k B_k(n)\hat{p}_n^s \right) - \lambda \sum_{k=1}^{m} D_k A_k^{ex}(n)\hat{p}_n^s = 0 \tag{5.52}$$

and it is satisfied if we set $\hat{p}_n^s = p_n^s$ since the first term vanishes as a consequence of eq. (5.26), whereas the second term becomes

$$\lambda \sum_{k=1}^{m} D_k A_k^{ex}(n) p_n^s = \lambda \sum_{k=1}^{m} D_k J_k^s(n) = 0 \tag{5.53}$$

due to the definition of $A_k^{ex}(n)$. The new stationary current vector reads

$$\begin{aligned} \hat{J}_k^s(n) &= J_k^s(n) - \lambda A_k^{ex}(n) p_n^s \\ &= (1-\lambda) J_k^s(n). \end{aligned} \tag{5.54}$$

Therefore from this point of view it seems to be not convenient for a system to create NESSs due to its energetic and entropic cost. Nevertheless the CME models many biochemical reactions that relax towards NESSs. The question is then to study the effect of fluxes in the transient states and, in particular, in the relaxation process towards the stationary distribution.

5.4 Nonequilibrium fluxes the linear CME

We study the relaxation time of a linear CME in DB equilibrium and NESS to understand the influence of the nonequilibrium fluxes in the behavior of the system. For seek of simplicity we have chosen a chemical reaction with three states, as represented in Figure 5.2, which deterministic mean field equations are

$$\dot{n}_A = -\pi_{AB} n_A - \pi_{AC} n_A + \pi_{BA} n_B + \pi_{CA} n_C$$

$$\dot{n}_B = -\pi_{BA} n_B - \pi_{BC} n_B + \pi_{AB} n_A + \pi_{CB} n_C$$

$$\dot{n}_C = -\pi_{CA} n_C - \pi_{CB} n_C + \pi_{AC} n_A + \pi_{BC} n_B \tag{5.55}$$

where n_A, n_B and n_C are the number of molecules of the species A, B and

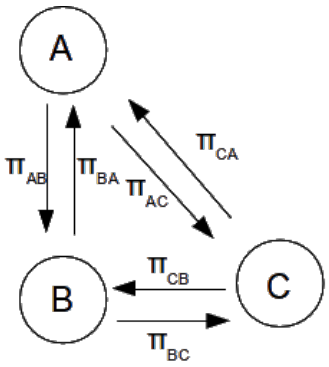


Figure 5.2: Unimolecular chemical reaction cycle

C respectively, with the constraint $n_A + n_B + n_C = N$. The CME (5.2) associated with this process is

$$\begin{aligned}\dot{p}_n(t) = {} & \mathbb{E}_C^+ \mathbb{E}_A^- \pi_{CA} n_C p_n(t) - \pi_{AC} n_A p_n(t) + \mathbb{E}_A^- \mathbb{E}_B^+ \pi_{BA} n_B p_n(t) - \pi_{AB} n_A p_n(t) \\ & \mathbb{E}_A^+ \mathbb{E}_B^- \pi_{AB} n_A p_n(t) - \pi_{BA} n_B p_n(t) + \mathbb{E}_B^- \mathbb{E}_C^+ \pi_{CB} n_C p_n(t) - \pi_{BC} n_B p_n(t) \\ & \mathbb{E}_B^+ \mathbb{E}_C^- \pi_{BC} n_B p_n(t) - \pi_{CB} n_C p_n(t) + \mathbb{E}_C^- \mathbb{E}_A^+ \pi_{AC} n_A p_n(t) - \pi_{CA} n_C p_n(t)\end{aligned} \tag{5.56}$$

The particle distribution is a multinomial distribution (5.22),

$$p_n(t) = N! \frac{\lambda_A(t) \lambda_B(t) \lambda_C(t)}{n_A! n_B! n_C!} \tag{5.57}$$

where $\lambda_A(t)$, $\lambda_B(t)$, $\lambda_C(t)$ are the solutions of the linear system

$$\begin{aligned}\dot{\lambda}_A(t) &= -(\pi_{AB} + \pi_{AC}) \lambda_A(t) + \pi_{BA} \lambda_B(t) + \pi_{CA} \lambda_C(t) \\ \dot{\lambda}_B(t) &= \pi_{AB} \lambda_A(t) - (\pi_{BA} + \pi_{BC}) \lambda_B(t) + \pi_{CB} \lambda_C(t) \\ \dot{\lambda}_C(t) &= \pi_{AC} \lambda_A(t) + \pi_{BC} \lambda_B(t) - (\pi_{CA} + \pi_{CB}) \lambda_C(t)\end{aligned} \tag{5.58}$$

with the constraint $\lambda_A + \lambda_B + \lambda_C = 1$. The steady state solution p_n^s is computed taking the limit $t \to \infty$ in the equation (5.57) and the limit values λ^s can be explicitly computed

$$\begin{aligned} \lambda_A^s &\propto \pi_{BA}\pi_{CA} + \pi_{BC}\pi_{CA} + \pi_{BA}\pi_{CB} \\ \lambda_B^s &\propto \pi_{AB}\pi_{CA} + \pi_{AB}\pi_{CB} + \pi_{AC}\pi_{CB} \\ \lambda_C^s &\propto \pi_{AC}\pi_{BA} + \pi_{AB}\pi_{BC} + \pi_{AC}\pi_{BC} \end{aligned} \tag{5.59}$$

In Figure 5.3 it is represented the stationary distribution of the CME (5.56),

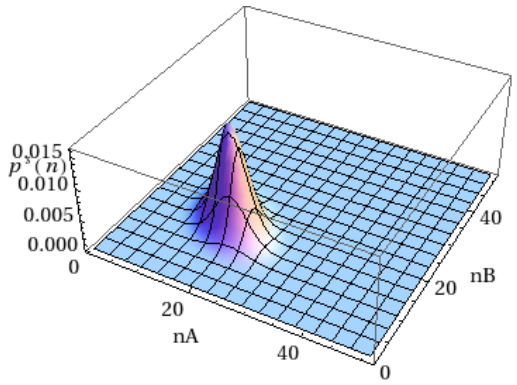


Figure 5.3: Stationary distribution from eq.(5.57)

for $N = 50$ as a function of n_A and n_B: the maximal value corresponds to $n_A = N\lambda_A^s$ and $n_B = N\lambda_B^s$. For an explicit computation of the chemical fluxes we reduce the systems dimensionality using $n_A = n_x$; $n_B = n_y$ and $n_C = N - n_x - n_y$. Then eq. (5.56) reads

$$\begin{aligned} \dot{p}_{n_x,n_y}(t) = \pi_{AB}(\mathbb{E}_x^+\mathbb{E}_y^- - 1)n_x p_{n_x,n_y} + \pi_{BA}(\mathbb{E}_x^-\mathbb{E}_y^+ - 1)n_y p_{n_x,n_y} + \\ +\pi_{CA}(\mathbb{E}_x^- - 1)(N - n_x - n_y)p_{n_x,n_y} + \pi_{CB}(\mathbb{E}_y^- - 1)(N - n_x - n_y)p_{n_x,n_y} \\ +\pi_{AC}(\mathbb{E}_x^+ - 1)n_x p_{n_x,n_y} + \pi_{BC}(\mathbb{E}_y^+ - 1)n_y p_{n_x,n_y} \end{aligned} \tag{5.60}$$

We write the CME (5.60) in the form of a continuity equation (5.11) without any constraint

$$\dot{p}(n_x, n_y) = -D_x^+ J_x(n_x, n_y) - D_y^+ J_y(n_x, n_y) \tag{5.61}$$

where the discrete difference operators are: $D_x^+ = \mathbb{E}_x^+$ and $D_y^+ = \mathbb{E}_y^+$. Then we identify the fluxes $J_x(n_x, n_y) = J_A(n) - J_B(n)$ and $J_y(n_x, n_y) = J_B(n) - J_C(n)$ as (cfr. eq. (5.13)):

$$\begin{aligned} J_x(n_x, n_y) &= -(\pi_{AB}\mathbb{E}_y^- n_x - \pi_{BA}\mathbb{E}_x^- n_y + \pi_{AC} n_x - \pi_{CA}\mathbb{E}_x^-(N - n_x - n_y))p_{n_x,n_y} \\ J_y(n_x, n_y) &= -(\pi_{BA}\mathbb{E}_x^- n_y - \pi_{AB}\mathbb{E}_y^- n_x + \pi_{BC} n_y - \pi_{CB}\mathbb{E}_y^-(N - n_x - n_y))p_{n_x,n_y} \end{aligned} \quad (5.62)$$

Substituting the explicit form of the steady state solution $p^s_{n_x,n_y}$ in (5.62), we determine the stationary nonequilibrium fluxes $J_x^s(n_x, n_y)$ and $J_y^s(n_x, n_y)$:

$$\begin{aligned} J_x^s(n_x, n_y) &= \left(\frac{\pi_{BA} n_x n_y (\lambda_A^s)^{-1}\lambda_C^s}{(N - n_x - n_y + 1)} - \frac{\pi_{AB} n_x n_y (\lambda_B^s)^{-1}\lambda_C^s}{(N - n_x - n_y + 1)}\right. \quad (5.63) \\ &+ \left.\pi_{CA} n_x (\lambda_A^s)^{-1}\lambda_C^s - \pi_{AC} n_x\right) p^s_{n_x,n_y} \\ J_y^s(n_x, n_y) &= \left(\frac{\pi_{AB} n_x n_y (\lambda_B^s)^{-1}\lambda_C^s}{(N - n_x - n_y + 1)} - \frac{\pi_{BA} n_x n_y (\lambda_A^s)^{-1}\lambda_C^s}{(N - n_x - n_y + 1)}\right. \quad (5.64) \\ &+ \left.\pi_{CB} n_y (\lambda_B^s)^{-1}\lambda_C^s - \pi_{BC} n_y\right) p^s_{n_x,n_y} \end{aligned}$$

According to eq. (5.13), we write the nonequilibrium fluxes introducing a drift term and a diffusion coefficient

$$\begin{aligned} J_x(n_x, n_y) &= A_x(n_x, n_y)p_{n_x,n_y} - D_x^- B_{xx} p(n_x - 1, ny) - D_y^- B_{xy} p(n_x, n_y - 1) \\ J_y(n_x, n_y) &= A_y(n_x, n_y)p_{n_x,n_y} - D_x^- B_{yx} p(n_x - 1, ny) - D_y^- B_{yy} p(n_x, n_y - 1) \end{aligned} \quad (5.65)$$

Where$D_x^- = \mathbb{E}_x^-$ and $D_y^- = \mathbb{E}_y^-$ and the drift vector $A(n_x, n_y)$ is

$$\begin{aligned} A_x(n_x, n_y) &= -(\pi_{AB} + \pi_{AC})n_x + \pi_{BA} n_y + \pi_{CA}(N - n_x - n_y) \\ A_y(n_x, n_y) &= \pi_{AB} n_x - (\pi_{BA} + \pi_{BC})n_y + \pi_{CB}(N - n_x - n_y) \end{aligned} \quad (5.66)$$

and the diffusion matrix B is

$$B = \begin{pmatrix} \pi_{BA} n_y + \pi_{CA}(N - n_x - n_y + 1) & -\pi_{AB} n_x \\ -\pi_{BA} n_y & \pi_{AB} n_x + \pi_{CB}(N - n_x - n_y + 1) \end{pmatrix}$$

Then we define an external field A^{ex} (cfr. eq. (5.34)) related to the nonequilibrium fluxes as

$$\begin{aligned} J_x^s(n_x, n_y) &= A_x^{ex}(n_x, n_y) p^s_{n_x,n_y} \\ J_y^s(n_x, n_y) &= A_y^{ex}(n_x, n_y) p^s_{n_x,n_y} \end{aligned} \tag{5.67}$$

The non-equilibrium fluxes are orthogonal to the gradient of probability if the following equality holds

$$J^s(n_x+1, n_y) D_x^+ p^s_{n_x,n_y} + J^s(n_x, n_y+1) D_y^+ p^s_{n_x,n_y} = 0 \tag{5.68}$$

To prove the previous equality, we apply the operators D_x^+ and D_y^+ to the multinomial stationary distribution $p^s_{n_x,n_y}$ according to

$$D_x^+ p^s_{n_x,n_y} = \left(\frac{(N-n_x-n_y)\lambda_A^s (\lambda_C^s)^{-1}}{nx+1} - 1 \right) p^s_{n_x,n_y} \tag{5.69}$$

and

$$D_y^+ p^s_{n_x,n_y} = \left(\frac{(N-n_x-n_y)\lambda_B^s (\lambda_C^s)^{-1}}{ny+1} - 1 \right) p^s_{n_x,n_y} \tag{5.70}$$

Therefor, an explicit calculation of (5.68) provides

$$J^s(n_x+1, n_y) D_x^+ p^s_{n_x,n_y} + J^s(n_x, n_y+1) D_y^+ p^s_{n_x,n_y} =$$

$$= \left(\frac{(N-n_x-n_y)\lambda_A^s (\lambda_C^s)^{-1}}{nx+1} - 1 \right) + \left(\frac{\pi_{BA} n_x n_y (\lambda_A^s)^{-1} \lambda_C^s}{(N-n_x-n_y)} - \frac{\pi_{AB} n_x n_y (\lambda_B^s)^{-1} \lambda_C^s}{(N-n_x-n_y)} \right.$$

$$\left. + \pi_{CA} n_x (\lambda_A^s)^{-1} \lambda_C^s - \pi_{AC} n_x \right) p^s_{n_x,n_y} +$$

$$\left(\frac{(N-n_x-n_y)\lambda_B^s (\lambda_C^s)^{-1}}{ny+1} - 1 \right) + \left(\frac{\pi_{AB} n_x n_y (\lambda_B^s)^{-1} \lambda_C^s}{(N-n_x-n_y)} - \frac{\pi_{BA} n_x n_y (\lambda_A^s)^{-1} \lambda_C^s}{(N-n_x-n_y)} \right.$$

$$\left. + \pi_{CB} n_y (\lambda_B^s)^{-1} \lambda_C^s - \pi_{BC} n_y \right) p^s_{n_x,n_y} = 0$$

where we have used the average equation (5.58). This means that in the NESS the *work* of the internal field A^{in} (cfr. eq, (5.33)) on the chemical fluxes is zero at any point (n_x, n_y) since the level curves of the stationary distribution coincide with the field lines of the chemical fluxes.

5.5 Results

To compute the relaxation time towards the stationary distribution we take advantage from the fact that a multinomial distribution is completely determined by the average values. Then we study the average dynamics, written (5.55) in function of n_x and n_y

$$\begin{aligned}\dot{n}_x &= -(\pi_{AB}+\pi_{AC})n_x + \pi_{BA}n_y + \pi_{CA}(N-n_x-n_y)\\ \dot{n}_y &= \pi_{AB}n_x - (\pi_{BA}+\pi_{BC})n_y + \pi_{CB}(N-n_x-n_y)\end{aligned} \tag{5.71}$$

The relaxation process towards the limit values $N\lambda_A^s, N\lambda_B^s$ is an exponential whose exponents are the eigenvalues of (5.71). To study the effects of the chemical fluxes we modulate the external field which produces the fluxes by changing the drift term according to $\hat{A}_k(n) = A_k(n) - \lambda A_k^{ex}(n)$ (see eq.(5.51)). In this way we change the nonequilibrium fluxes without modifying the stationary distribution (see (5.53)). From (5.55) the new nonequilibrium fluxes reads

$$\begin{aligned}\hat{J}_x(n_x,n_y,t) &= J_x(n_x,n_y,t) - \lambda A_x^{ex}(n_x,n_y)p(n_x,n_y,t)\\ \hat{J}_y(n_x,n_y,t) &= J_y(n_x,n_y,t) - \lambda A_y^{ex}(n_x,n_y)p(n_x,n_y,t)\end{aligned} \tag{5.72}$$

It is convenient to set $\lambda = 1+\epsilon$, in this way $\epsilon = 0$ corresponds to the DB equilibrium and changing ϵ we drive the system to a NESS condition. From (5.61) we write the following modified CME

$$\begin{aligned}\dot{p}(n_x,n_y,t) = &-D_x(J_x(n_x,n_y,t) - (1+\epsilon)A_x^{ex}(n_x,n_y,t)p(n_x,n_y,t))\\ &-D_y(J_y(n_x,n_y,t) - (1+\epsilon)A_y^{ex}(n_x,n_y,t)p(n_x,n_y,t))\end{aligned} \tag{5.73}$$

where

$$A_x^{ex}(n_x,n_y) = \left(\frac{\pi_{BA}n_xn_y(\lambda_A^s)^{-1}\lambda_C^s}{(N-n_x-n_y+1)} - \frac{\pi_{AB}n_xn_y(\lambda_B^s)^{-1}\lambda_C^s}{(N-n_x-n_y+1)} + \pi_{CA}n_x(\lambda_A^s)^{-1}\lambda_C^s - \pi_{AC}n_x\right)$$

$$A_y^{ex}(n_x,n_y) = \left(\frac{\pi_{AB}n_xn_y(\lambda_B^s)^{-1}\lambda_C^s}{(N-n_x-n_y+1)} - \frac{\pi_{BA}n_xn_y(\lambda_A^s)^{-1}\lambda_C^s}{(N-n_x-n_y+1)} + \pi_{CB}n_y(\lambda_B^s)^{-1}\lambda_C^s - \pi_{BC}n_y\right)$$

We remark that the external fields are not linearly dependent on n_x and n_y, therefore we can not compute in an exact way the average equations. The

solution for this problem is to apply the mean field approximation (5.21), because this approximation gives good results when it is near the critical point of the distribution $p_{n_x,n_y}(t)$. Consequently, we obtain

$$\begin{aligned}
< \dot{n}_x > &= -\left(\pi_{AB} + \pi_{AC} + \pi_{CA} + (1+\epsilon)\frac{\partial A_x^{ex}(n_x,n_y)}{\partial n_x}\bigg|_{n_x^*}\right) < n_x > + \\
&+ \left(\pi_{BA} - \pi_{CA} - (1+\epsilon)\frac{\partial A_x^{ex}(n_x,n_y)}{\partial n_y}\bigg|_{n_y^*}\right) < n_y > \\
< \dot{n}_y > &= \left(\pi_{AB} - \pi_{CB} - (1+\epsilon)\frac{\partial A_y^{ex}(n_x,n_y)}{\partial n_x}\bigg|_{n_x^*}\right) < n_x > + \\
&- \left(\pi_{BA} + \pi_{BC} + \pi_{CB} + (1+\epsilon)\frac{\partial A_y^{ex}(n_x,n_y)}{\partial n_y}\bigg|_{n_y^*}\right) < n_y > \quad (5.74)
\end{aligned}$$

In order to evaluate the relaxation time, we compute the eigenvalues α_k of the system (5.74) and we define a characteristic relaxation time $\tau = \frac{1}{Min|\mathbf{Re}(\alpha_1,\alpha_2)|}$. To prove that our choice represents the relaxation time of the system we performed a numerical simulation, through the integration of the system (5.73), for $\epsilon = 0.9$, precisely we set the transition rates as $\pi_{AB} = 1$; $\pi_{CA} = 1.1$; $\pi_{BC} = 1$; $\pi_{BA} = 1$; $\pi_{AC} = 1$; $\pi_{CB} = 1$, the total number of molecules as $N = 50$ and initial condition $p_{n_x,n_y}(0) = 1/N^2$, so we plot $||p_{n_x,n_y}(t) - p^s_{n_x,n_y}||$ in function of the relaxation time τ, fitting as an exponential function. We determine the exponent of the function and compare with the eigenvalues of equation (5.74) for the stationary state. The value of the exponent of the simulation is the same of the eigenvalue, what follow us to believe that our definition of relaxation time is correct. In Figure 5.4 we show the plot of $||p(t) - p^s||$ x τ.

To performed a numerical study we set the transition rate values near a DB condition, and specifically $\pi_{AB} = 1$; $\pi_{CA} = 1.1$; $\pi_{BC} = 1$; $\pi_{BA} = 1$; $\pi_{AC} = 1$; $\pi_{CB} = 1$. Using $N = 50$ for the total number of molecules and $0 \leq \epsilon \leq 1$ we plot in Figure 5.5a the change of the relaxation time τ as a function of ϵ, the numerical results show a linear dependence of the norm of the stationary nonequilibrium fluxes ($||\vec{J}^s||$) on ϵ as expected (see Figure 5.5b). Moreover in Figures 5.5c and 5.5d we show the dependence on ϵ of

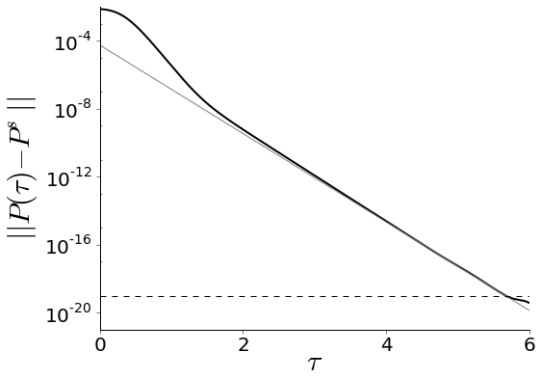


Figure 5.4: Relaxation time of a numerical simulation performed on system (5.73) with initial condition $p_{n_x,n_y}(0) = 1/N^2$,$\pi_{AB} = 1$; $\pi_{CA} = 1.1$; $\pi_{BC} = 1$; $\pi_{BA} = 1$; $\pi_{AC} = 1$; $\pi_{CB} = 1$, $\epsilon = -0.9$ and $N = 50$. Black line: $||p(t) - p^s||$ from the simulation; Gray line: Expect behavior of the relaxation time; Dotted line: limit of precision of the simulation

the eigenvalues α.

We remark that the relaxation time τ decreases as the fluxes increases up a constant value which denoted a bifurcation phenomenon in the eigenvalues (see Figure 5.5c and Figure 5.5d) of the average equation (5.74). After this critical value ($\epsilon \simeq 0.6799$) the relaxation time is not affected by the chemical fluxes.

5.6 Discussion of the results

In this work we have studied the dynamical role of chemical fluxes that characterize the NESS of a chemical chain reaction. Using the correspondence between the CME and a discrete Fokker-Planck equation we are able to show that the chemical fluxes are linearly proportional to a non-conservative to an "external vector field" whose work on the system is directly related to the entropy production rate in the NESS. As a consequence by modulating the external field we can change the chemical fluxes without affecting the stationary probability distribution of the chemical species. In such a way it

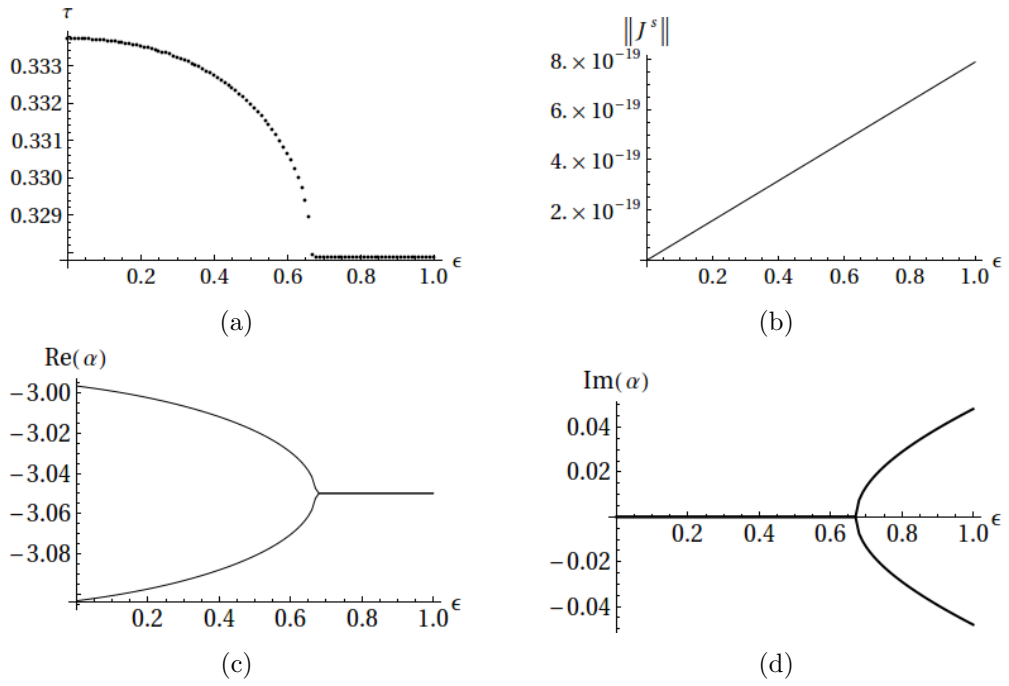


Figure 5.5: (a) τ x ϵ, (b) $||\vec{J}^s||$ x ϵ (c) **Re**(α) x ϵ and (d)**Im**(α) x ϵ. The calculation is performed using $N = 50$ and $\pi_{AB} = 1$; $\pi_{CA} = 1.1$; $\pi_{BC} = 1$; $\pi_{BA} = 1$; $\pi_{AC} = 1$; $\pi_{CB} = 1$.

is possible to study the effect of the fluxes on the relaxation characteristic time of the CME in the case of NESS. We have performed explicit calculations on a linear CME for which it is possible to compute explicitly compute the stationary probability distribution, the chemical fluxes and the external non-linear field. Our main result is to show that the presence of stationary fluxes reduces the characteristic relaxation time with respect the DB condition and it allows bifurcation phenomena for eigenvalues of the linearize dynamics around a local maximum of he probability distribution. We conjecture that this is a generic results that can be generalized to non-linear CME.

Chapter 6

Energy consumption and entropy production in a stochastic formulation of BCM learning

Abstract

Biochemical processes in living cells are open systems, therefore they exchange materials with their environment and they consume chemical energy. These processes are molecular-based and for that reason the role of fluctuations can not be ignored and the stochastic description is the most appropriate. The chemical master equation describes in exact way the probabilistic dynamics of a given discrete set of states and helps us to understand and clarify the differences between closed and open systems. A closed system is related to a condition of detailed balance (DB), i.e. an equilibrium state. After a sufficiently long period, an open system will reach a non-equilibrium steady state (NESS) that is sustained by a flux of external energy. We demonstrate that two implementations of the BCM learning rule (BCM82) and (BCM92) are, respectively, always in DB, and never in DB. We define

a one parameter parametrization of the BCM learning rule that interpolates between these two extremes. We compute thermodynamical quantities such as internal energy, free energy (both Helmholtz and Gibbs) and entropy. The entropy variation in the case of open systems (i.e. when DB does not hold) can be divided into internal entropy production and entropy exchanged with surroundings. We show how the entropy variation can be used to find the optimal value (corresponding to increased robustness and stability) for the parameter used in the BCM parametrization. Finally, we use the calculation of the work to drive the system from an initial state to the steady state as the parameter of the plasticity of the system.

6.1 Motivations of the work

The BCM theory [63, 64] was originally proposed to describe plasticity processes in visual cortex as observed by Hubel and Wiesel [96]. One of the main postulates of this theory is the existence of a critical threshold (the sliding threshold θ_M) that depends from the past neuronal history in a non-linear way. This nonlinearity is necessary to ensure stability of synaptic weights in the LTP behavior. The main predictions of the BCM theory have been confirmed in hippocampal slices and visual cortex and recently in in vivo inhibitory avoidance learning experiments[97]. The extension of this results to other brain areas, and ultimately to the whole brain, is not confirmed but is under active study. The motivation for this research is that a proposed biophysical mechanism for the BCM rule is based on calcium influx through NMDA receptors and phosphorylation state of AMPA receptors and that both receptors are widely distributed within the brain[98, 99]. This biophysical mechanism is, at least partly shared, by the plasticity rule STDP (Spike-timing-dependent plasticity) that describes the synaptic functional change on the basis of the timing of action potentials in connected neurons. The main difference between STDP and BCM is that BCM is an average time rule and thus not take out time (i.e. it does not work with spikes but

with rates).

The BCM rule has been classically implemented in two ways that substantially differ for the definition of the moving threshold θ, that is respectively $< c >^2$ and $< c^2 >$, where $<>$ means expectation over all input distribution. This difference in the definition of θ leads to the possibility of deriving the rule from an energy function and in their statistical interpretation [64, 100]. Among various approaches used, the BCM theory still lacks a stochastic implementation of the synaptic weights growth, whereas the stochasticity of the inputs has been extensively studied [64]. The needs for a stochastic version of synaptic growth is motivated by the observation that synaptic activity depends on molecules inserted in the postsynaptic membrane [98, 101, 100] such as AMPA receptors that for a single spine can be on the order of hundreds, and hence the fluctuations in the molecules number and synaptic strength can be not negligible. A "natural" way to cope with this problem is the so-called Chemical Master Equation (CME) approach [3] that realizes in an exact way the probabilistic dynamics of a finite number of states, and recovers, in the thermodynamic limit ($N \to \infty$), the mean field approximation. The CME can be viewed as a Markov process describing the temporal evolution of the probability of a given discrete set of states [3]. Other relevant motivations for the CME implementation of synaptic plasticity processes arise from biological and thermodynamic considerations: 1) this process requires energy that, at a cellular level, is supplied from cells such as astrocytes, 2) the CME approach offers the possibility of computing the thermodynamic state functions of the system both when it is closed and open (i.e. whether satisfies or not the detailed balance condition). An interesting observation is that the two implementations of the BCM rule can satisfy or not the DB condition.

Let $\mathbf{m}$ be the synaptic weights and $\mathbf{d}$ the input signals received by the synapses, the BCM synaptic modification rule for a single neuron [63] has the form

$$\dot{\mathbf{m}}_\mathbf{j} = \phi(c, \theta_M)\mathbf{d}_\mathbf{j} \tag{6.1}$$

where the modification function $\phi(c, \theta_M)$ depends on the neuron activity level

$c \propto \mathbf{d} \cdot \mathbf{m}$ (it is assumed a linear proportionality between the input $\mathbf{d}$ and the output c) and on a moving threshold θ_M, which is a super-linear function of the cell activity history in a stationary situation θ_M can be related to the time averaged value $< c^k >$ where $k > 1$ of a non-linear, momentum of the neuron activity distribution [102]. The modification function ϕ is a non-linear function of the postsynaptic activity c which has two zero crossings, one at $c = 0$ and the other at $c = \theta_M$ (see fig. 6.1). When the neuron activity is over the threshold θ_M than we have the long-term potentiation [103] (LTP) phenomenon [1], whereas the long-term depression [104] (LTD)[2] appears when the activity is below the threshold. In the simplest form the function ϕ is a quadratic function $c^2 - c\theta_M$ and the dynamic threshold θ_M is the time-averaged $< c^2 >$ of the second moment of the neuron activity, which can be replaced by the expectation value over the input probability space $E(c^2)$ under the slow-learning assumption.

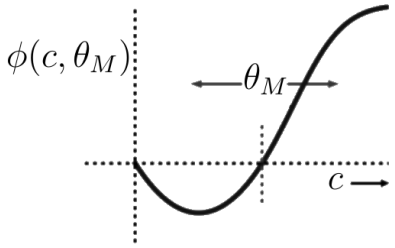


Figure 6.1: The BCM Synaptic Modification Rule. c denotes the output activity of the neuron, θ_M is the modification threshold.

[1] Long-term potentiation (LTP) is a form of synaptic plasticity that fulfils many of the criteria for a neural correlate of memory.

[2] Long-term depression (LTD) is an activity-dependent reduction in the efficacy of neuronal synapses lasting hours or longer following a long patterned stimulus

6.1.1 The averaged BCM rule

The BCM theory has been formulated to describe synaptic weight changes and memory formation in cell response in visual cortex due to changes in visual environment. It has been extensively studied theoretically and in simulation [102] and compared to physiological results [63, 64]. The BCM learning rule can be formulated as "averaged" equations:

$$\dot{\mathbf{m}}(t) = (PD)^T \phi(c, \theta), \tag{6.2}$$

where D is the matrix of inputs, P is a diagonal matrix containing the probabilities of the different input vectors, $c = \mathbf{m} \cdot \mathbf{d}$ is the neuronal activity, output; $\mathbf{m}$ and $\mathbf{d}$ are the synaptic strength and the incoming signal vectors respectively. The function $\phi(c, \theta) = c(c - \theta)$ is a quadratic function that changes sign at a dynamic threshold that is a nonlinear function of some time-averaged measure of cellular activity, which is replaced (under a slow learning assumption) by the expectation over the environment $\theta = E[c^2] = \sum_{i=0}^{n} p_i (m_i \cdot d_i)^2$ [64, 101]. The components of $\phi(c, \theta)$ are given by the values on each input vector: $\phi_i = \phi(m_i \cdot d_i, \theta)$.

It has been shown that a variant of this theory performs exploratory projection pursuit using a projection index that measures multi-modality [64]. This learning model allows modeling and theoretical analysis of various visual deprivation experiments such as monocular deprivation (MD), binocular deprivation (BD) and reversed suture (RS) [64] and is in agreement with many experimental results on visual cortical plasticity [105, 106, 107]. Recently, it has been shown that the consequences of this theory are consistent with experimental results on long term potentation (LTP) and long term depression (LTD) [108, 109, 110] and phosphorylation/dephosphorylation cycle of AMPA receptors [100, 98].

6.1.2 The bidimensional case of the BCM rule

It turns out that the bidimensional version of BCM rule, with two orthogonal inputs is indicative of the general case of stochastic high dimen-

sional non orthogonal inputs. Analysis that connects both has been given in [63, 64, 102, 99, 107]. The averaged version of the BCM learning rule, in the bidimensional case is:

$$\frac{d}{dt}\begin{pmatrix} n_x \\ n_y \end{pmatrix} = (PD)^T \begin{pmatrix} \phi_1 \\ \phi_2 \end{pmatrix} \tag{6.3}$$

where n_x and n_y are the synaptic weights, P is the diagonal matrix with the probability of the inputs p_1 and p_2, D is the inputs matrix (a matrix whose rows are the input vectors $\mathbf{d_1}$ and $\mathbf{d_2}$), and the neuronal output in the linearity region is $c = \mathbf{m} \cdot \mathbf{d}$. The vectors $\mathbf{m}$ and $\phi = (\phi_1, \phi_2)$ are defined as: $\mathbf{m} = (m_1, m_2) = (n_x, n_y)$ and $\phi = (\phi(n_x \cdot \mathbf{d_1}, \theta), \phi(n_y \cdot \mathbf{d_2}, \theta))$. For the sake of simplicity we start by considering two special input vectors as $\mathbf{d_1} = (1, 0)$, and $\mathbf{d_2} = (0, 1)$ with equal probability of appearing: $p_1 = p_2 = 1/2$. With these hypotheses, the equation (6.2) becomes:

$$\begin{cases} \dot{n_x} = \dfrac{1}{2}\phi(n_x, \theta) = \dfrac{n_x}{2}(n_x - \theta) \\ \dot{n_y} = \dfrac{1}{2}\phi(n_y, \theta) = \dfrac{n_y}{2}(n_y - \theta). \end{cases} \tag{6.4}$$

Now we can write the system (6.4) with two definitions of the threshold θ: $\theta =< c >^2$ and $\theta =< c^2 >$, where $<>$ is the average over the inputs environment. For the BCM82 ($\theta =< c >^2$):

$$\begin{cases} \dot{n_x} = \dfrac{n_x}{2}\left(n_x - \left(\dfrac{n_x}{2} + \dfrac{n_y}{2}\right)^2\right) \\ \dot{n_y} = \dfrac{n_y}{2}\left(n_y - \left(\dfrac{n_x}{2} + \dfrac{n_y}{2}\right)^2\right) \end{cases} \tag{6.5}$$

Whereas, for the BCM92 ($\theta =< c^2 >$):

$$\begin{cases} \dot{n_x} = \dfrac{n_x}{2}\left(n_x - \left(\dfrac{n_x^2}{2} + \dfrac{n_y^2}{2}\right)\right) \\ \dot{n_y} = \dfrac{n_y}{2}\left(n_y - \left(\dfrac{n_x^2}{2} + \dfrac{n_y^2}{2}\right)\right) \end{cases} \tag{6.6}$$

6.2 BCM rule and CME

Both systems (6.5 and 6.6) can be studied by the CME because the number of synapses, as with the number of receptors (i.e. the AMPA receptors),

can be small, and the role of fluctuations can be not negligible. On the other hand, if these numbers increase, the CME approaches the deterministic equations (mean field limit). Another motivation for the CME approach, is that we can state conditions for the validity of the detailed balance, and if we can compute the stationary distribution, we can also compute all the relevant thermodynamic quantity as free energy and entropy. The CME for the system (6.4) is:

$$\begin{aligned} \dot{p}_{n_x,n_y} &= (\mathbb{E}_{n_x} - 1) r^{(n_x)}_{n_x,n_y} p_{n_x,n_y} + (\mathbb{E}^{-1}_{n_x} - 1) g^{(n_x)}_{n_x,n_y} p_{n_x,n_y} \\ &+ (\mathbb{E}_{n_y} - 1) r^{(n_y)}_{n_x,n_y} p_{n_x,n_y} + (\mathbb{E}^{-1}_{n_y} - 1) g^{(n_y)}_{n_x,n_y} p_{n_x,n_y}. \end{aligned} \tag{6.7}$$

This CME is derived under the condition of a one-step Poisson process [3], $\mathbb{E}$ and $\mathbb{E}^{-1}$ are the forward and backward step operators: $\mathbb{E}_{n_x} f(n_x, n_y) = f(n_x + 1, n_y), \mathbb{E}^{-1}_{n_x} f(n_x, n_y) = f(n_x - 1, n_y)$ and $g^{(m_i)}_{n_x,n_y} = \frac{m_i^2}{2N}$, $r^{(m_i)}_{n_x,n_y} = \frac{m_i \theta}{2N^2}, i = 1, 2$, are the generation and recombination terms and N is the maximum value of the synaptic weight (proportional to the maximum number of molecules).

As we are interested in the equilibrium properties of the probability distribution, we can derive the stationary distribution. The methods for deriving the stationary distribution are dependent on the fulfillment of the detailed balance (DB) condition. If the DB condition holds, it is possible to find the stationary distribution by iterating the method used for the one dimensional CME, whereas if the DB is broken we have to take into account the correction arising from the presence of a "nonconservative" term [100]. In any case, if the DB does not holds, the stationary distribution can be found numerically by computing the kernel of the transition matrix or by integrating the system (6.8) for a sufficiently long time[3]. To verify if the DB condition holds, we define a quantity that we call "commutator" $\mathcal{C}(n_x, n_y)$, because it is the difference between the two possible paths (i.e. by joining the bottom left vertex with the upper right vertex) in an unitary square. The validity of this definition relies on the structure of the CME that does not contain diagonal terms (i.e. there are no terms with simultaneous variations of n_x and n_y).

$$\mathcal{C}(n_x, n_y) = \frac{g^{(n_y)}_{n_x-1,n_y-1} \cdot g^{(n_x)}_{n_x-1,n_y}}{r^{(n_y)}_{n_x-1,n_y} \cdot r^{(n_x)}_{n_x,n_y}} - \frac{g^{(n_x)}_{n_x-1,n_y-1} \cdot g^{(n_y)}_{n_x,n_y-1}}{r^{(n_x)}_{n_x,n_y-1} \cdot r^{(n_y)}_{n_x,n_y}}. \tag{6.8}$$

If $\mathcal{C}(n_x, n_y) = 0$, the DB condition always holds, whereas if $\mathcal{C}(n_x, n_y) \neq 0$ the DB does not hold. If we consider the two possible implementations of the BCM rule: $\theta =< c >^2$ and $\theta =< c^2 >$, we can observe that in the first case the DB condition holds, while in the latter case we have DB violation being $C(n_x, n_y) \neq 0$.

$$\mathcal{C}(n_x, n_y) = -\frac{8(n_x-1)^2(n_y-1)^2(n_x-n_y)}{n_x n_y \left(n_x^2 + (n_y-1)^2\right)\left(n_x^2+n_y^2\right)\left(n_x^2 - 2n_x + n_y^2 + 1\right)} \tag{6.9}$$

It is interesting to observe that when the Commutator is not zero, this means that the system is no longer a "closed system", but that it will exchange energy with its surroundings and that it will reach a Non Equilibrium Stationary State (NESS) by consuming energy [111, 112, 7, 100].

6.3 Parametrization of the BCM rule and the stationary distribution

As shown in section II, the BCM learning rule can be formulated in two way (6.5) and (6.6), based on two definitions of the moving threshold θ; as $< c^2 >$ and $< c >^2$ respectively. It is possible to find a parametrization that interpolates with continuity between these two extremes by a suitable definition of θ.

$$\theta_\alpha =< c^{1+\alpha} >^{2-\alpha} . \tag{6.10}$$

With this definition of θ, the system (6.4) becomes:

$$\begin{cases} \dot{n_x} = \frac{1}{2}\phi(n_x, \theta_\alpha) = \frac{n_x}{2}\left(n_x - \left(\frac{n_x^{1+\alpha}}{2} + \frac{n_y^{1+\alpha}}{2}\right)^{2-\alpha}\right) \\ \dot{n_y} = \frac{1}{2}\phi(n_y, \theta_\alpha) = \frac{n_y}{2}\left(n_y - \left(\frac{n_x^{1+\alpha}}{2} + \frac{n_y^{1+\alpha}}{2}\right)^{2-\alpha}\right) \end{cases} \tag{6.11}$$

With this parametrization we obtain the BCM82 model for $\alpha = 0$, whereas, for $\alpha = 1$ we obtain the BCM92 model. This behavior is confirmed by the analysis of the commutator

$$\mathcal{C}_\alpha(n_x, n_y) = \frac{1}{n_x n_y}\Bigg(2^{2-\alpha}(n_x-1)^2(n_y-1)^2 N^{(\alpha+1)(2-\alpha)}(n_x^{\alpha+1}+n_y^{\alpha+1})^{\alpha-2} \cdot\frac{1}{2}(n_x-1)^{\alpha+1}+\frac{n_y^{\alpha+1}}{2})^{\alpha-2} - 2^{2-\alpha}(n_x^{\alpha+1}+(n_y-1)^{\alpha+1})^{\alpha-2})\Bigg). \tag{6.12}$$

With the parametrization (6.10) we write the recombination and generation terms of the CME (6.8) as

$$\begin{cases} g^{(n_x)}_{n_x,n_y} = \dfrac{n_x^2}{2} & r^{(n_x)}_{n_x,n_y} = \dfrac{n_x}{2}\left(\dfrac{n_x^{1+\alpha}}{2}+\dfrac{n_y^{1+\alpha}}{2}\right)^{2-\alpha}, \\ g^{(n_y)}_{n_x,n_y} = \dfrac{n_y^2}{2} & r^{(n_y)}_{n_x,n_y} = \dfrac{n_y}{2}\left(\dfrac{n_x^{1+\alpha}}{2}+\dfrac{n_y^{1+\alpha}}{2}\right)^{2-\alpha}. \end{cases} \tag{6.13}$$

The stationary distribution, if the DB holds, is a product of two "one dimensional" distributions computed along the n_x and n_y axes:

$$P^s_{n_x,n_y} = \prod_{i=1}^{n_x}\frac{g^{(n_x)}_{i-1,n_y}}{r^{(n_x)}_{i,n_y}}\cdot\prod_{l=1}^{n_y}\frac{g^{(n_y)}_{0,l-1}}{r^{(n_y)}_{0,l}}P_{00} \qquad n_x, n_y \geq 1. \tag{6.14}$$

Where the term P_{00} is determined by the normalization condition: $\sum_{i,l=1}^{n_x,n_y} P_{i,l} = 1$. We explicitly observe that $(0,0)$ is an absorbing state, so all the solutions of the CME will tend toward it. This means that the deterministic fixed points are not stable in the stochastic sense, but merely metastable, and that when the synaptic weights are close to their values, there is always a small chance for a fluctuation to occur and drive the solutions to $(0,0)$. A way to overcome the problem of the absorbing state is simply by removing it, that is, by defining the transition probability to reach the state $(0,0)$ as 0. In this way we obtain a new stationary distribution written in terms of $P_{1,1}$

$$P_{n_x,n_y} = \prod_{n_x=2}^{N}\prod_{n_y=2}^{N}\frac{g^{(n_x)}_{n_x-1,n_y}g^{(n_y)}_{1,n_y-1}}{r^{(n_x)}_{n_x,n_y}\, r^{(n_y)}_{1,n_y}}P_{1,1} \qquad n_x, n_y \geq 2. \tag{6.15}$$

Evidently $P_{1,1}$ follows the normalization condition $\sum_{i,l=2}^{n_x,n_y} P_{i,l} = 1$. In Figure 6.2 we plot the stationary distribution (6.15) for $N = 100$.

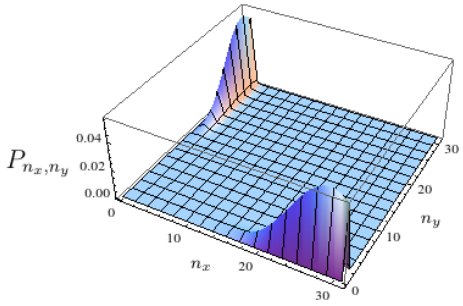


Figure 6.2: Plot of the stationary distribution obtained by (6.15) for $\alpha = 0.5$ and $N = 31$.

6.4 Thermodynamic quantities from CME:

Once has been fixed the CME and we have obtained its stationary distribution, we can compute the thermodynamic quantities such as total energy, Gibbs and Helmholtz energy and entropy, following the results introduced in Chapter 4. The central result is the split of entropy in (4.17) as the sum of two terms:

$$\frac{dS(t)}{dt} = h_d - e_p \tag{6.16}$$

reminding that e_p is the entropy produced inside the system due to spontaneous process and h_d the entropy supplied to the system by its surroundings. So we can explicitly write e_p and h_d for the BCM rule (6.8) following the definitions (4.18) and (4.19) (see section 4.3)

$$e_p = -\sum_{n_x=1}^{N-1}\sum_{n_y=1}^{N} r^{(n_x)}_{n_x+1,n_y} p_{n_x+1,n_y} - g^{(n_x)}_{n_x,n_y} p_{n_x,n_y} \log \frac{p_{n_x,n_y} g^{(n_x)}_{n_x,n_y}}{p_{n_x+1,n_y} r^{(n_x)}_{n_x+1,n_y}}$$

$$-\sum_{n_x=1}^{N}\sum_{n_y=1}^{N-1}(r^{(n_y)}_{n_x,n_y+1}p_{n_x,n_y+1}-g^{(n_y)}_{n_x,n_y}p_{n_x,n_y}\log\frac{p_{n_x,n_y}g^{(n_y)}_{n_x,n_y}}{p_{n_x,n_y+1}r^{(n_y)}_{n_x,n_y+1}} \tag{6.17}$$

and

$$h_d=-\sum_{n_x=1}^{N-1}\sum_{n_y=1}^{N}r^{(n_x)}_{n_x+1,n_y}p_{n_x+1,n_y}-g^{(n_x)}_{n_x,n_y}p_{n_x,n_y}\log\frac{g^{(n_x)}_{n_x,n_y}}{r^{(n_x)}_{n_x+1,n_y}}$$

$$-\sum_{n_x=1}^{N}\sum_{n_y=1}^{N-1}(r^{(n_y)}_{n_x,n_y+1}p_{n_x,n_y+1}-g^{(n_y)}_{n_x,n_y}p_{n_x,n_y}\log\frac{g^{(n_y)}_{n_x,n_y}}{r^{(n_y)}_{n_x,n_y+1}}. \tag{6.18}$$

The entropy variation $\frac{dS(t)}{dt}$ can be expressed in terms of the variation of Internal Energy (U) and Free Energy (F)

$$\frac{dS(t)}{dt}=\frac{dU(t)}{dt}-\frac{dF(t)}{dt} \tag{6.19}$$

Using the result (4.21) we can calculate the work to drive the system from a initial state to the stationary (or equilibrium) state, where each value of e_p and h_d represents a probability configuration for the system. We define the work done by e_p as

$$\begin{aligned}\frac{d(W_{e_p})}{dt} &= \frac{dF(t')}{dt'}-\frac{dF(\infty)}{dt'} \\ W_{e_p} &= \lim_{t\to\infty}\int_0^t(e_p(t')-e_p(\infty))dt'=\lim_{t\to\infty}\left[\int_0^t e_p(t')dt'-te_p(\infty)\right],\end{aligned} \tag{6.20}$$

the work done by h_d as

$$\begin{aligned}\frac{d(W_{h_d})}{dt} &= \frac{dU(t')}{dt'}-\frac{dU(\infty)}{dt'} \\ W_{h_d} &= \lim_{t\to\infty}\int_0^t(h_d(t')-h_d(\infty))dt'=\lim_{t\to\infty}\left[\int_0^t h_d(t')dt'-th_d(\infty)\right],\end{aligned} \tag{6.21}$$

And the total work (work of entropy) is written as the difference between W_{e_p} and W_{h_d}

$$W_S=W_{e_p}-W_{hd}. \tag{6.22}$$

6.4.1 Analytic calculus of Entropy

As we demonstrate in Chapter 3 we can calculate analytically the entropy for the one dimensional BCM model, which reads

$$\frac{dn}{dt} = n^2 - n^{2+\eta} \qquad \eta = (1+\alpha)(2-\alpha) - 1 \tag{6.23}$$

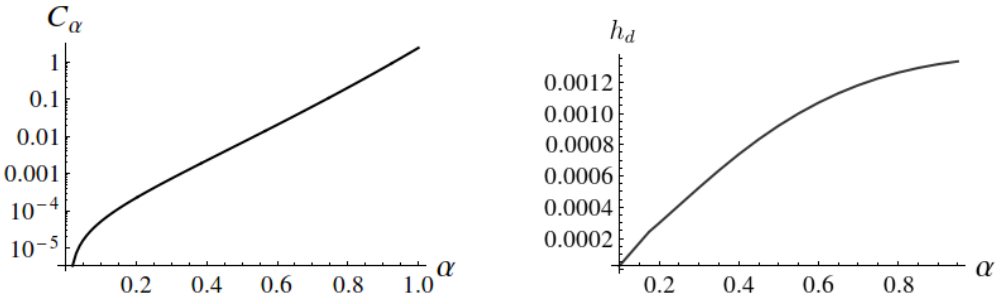
The corresponding CME can be written immediately and for N large has a Gaussian distribution for which the entropy is computed analytically see eq. (3.77)

$$S = -\frac{\log \eta}{2} - \frac{\log N}{2} + c. \tag{6.24}$$

The function $\eta(\alpha)$ is symmetric around $\alpha = 1/2$ where it has a maximum. As a consequence the entropy as a function of α has a minimum for $\alpha = 1/2$. We can also compute the relaxation time which is $\tau = 1/\eta$ and consequently has also a minimum for $\alpha = 1/2$ just as the entropy. As a consequence the behavior for the entropy found for the bi-dimensional model might be correlated to the loss of the detailed balance and the behavior of the NESS when α is varied. However it cannot be excluded that the asymptotic behavior of the fields also determines the behavior of the entropy as in the one-dimensional case.

6.5 Results

In this section we compare the thermodynamical behavior of the parametrized BCM rule (eq. (6.11)) for different values of α. We are interested to study the differences between systems in DB and NESS, specifically we desire determine which model is more plastic. The first step is ascertain the NESS condition for systems with $\alpha \neq 0$, as we introduced in section 6.2 the commutator $\mathcal{C}_\alpha$ measures the breaking or not of DB, but the violation of DB does not completely characterize NESS. To ensure the NESS (as we enunciated in Chapter 4), in the stationary state the system should be sustained by an external energy input, in thermodynamics terms it reads $h_d = e_p \neq 0$.



(a) (b)

Figure 6.3: (a) Commutator (6.13) in function of α. (b) Plot of the stationary state of h_d when α is varied from 0 to 1. The simulations are performed for $N = 31$ and the initial condition $p_{n_x,n_y} = \delta_{n_x,15}\delta_{n_y,15}$.

We calculate the commutator $\mathcal{C}_\alpha$ (eq. 6.13) for $0 \leq \alpha \leq 1$. As we expect only for $\alpha = 0$ the system is in DB and for others values of α the DB condition is broken. We plot the norm of the commutator in Figure (6.3a). To confirm the NESS, we simulate the time evolution of the system (6.13) through the numerical integration of the CME (6.8) over a time span sufficiently long to reach the stationary distribution. Therefore, we can calculate h_d (eq. (6.18)) and e_p (eq. (6.17)) for $0 \leq \alpha \leq 1$. We verify for all values of $\alpha \neq 0$ in the stationary state $h_d = e_p \neq 0$. We plot the stationary state values of h_d in function of α in Figure 6.3b). For example, for $\alpha = 1$ (BCM92) the system presents $h_d = e_p = 0.0013465$ and for $\alpha = 0$ (BCM82) we obtain $h_d = e_p = 0$. Therefore, we can infer that the BCM82 ($\alpha = 0$) reaches an equilibrium state and all systems with $\alpha \neq 0$ reaches a NESS.

With the last results we are pretty sure to study systems in DB and NESS. Using the results for $h_d(t)$ and $e_p(t)$ we can calculate the works,W_{h_d}, W_{e_p} and W_S, done by the system to reach the stationary state configuration (eqs. (6.22), (6.21) and (6.22)). In Figure 6.4 we plot the work done by BCM82 (black line) and BCM92 (red line), for which the simulations are performed for $N = 31$ and the initial condition $p_{n_x,n_y} = \delta_{nx,31}\delta_{ny,31}$. A first comparison between the two BCM models reveals that the work done reach the stationary distribution is lower for BCM92, that is, for $\alpha = 1$ where

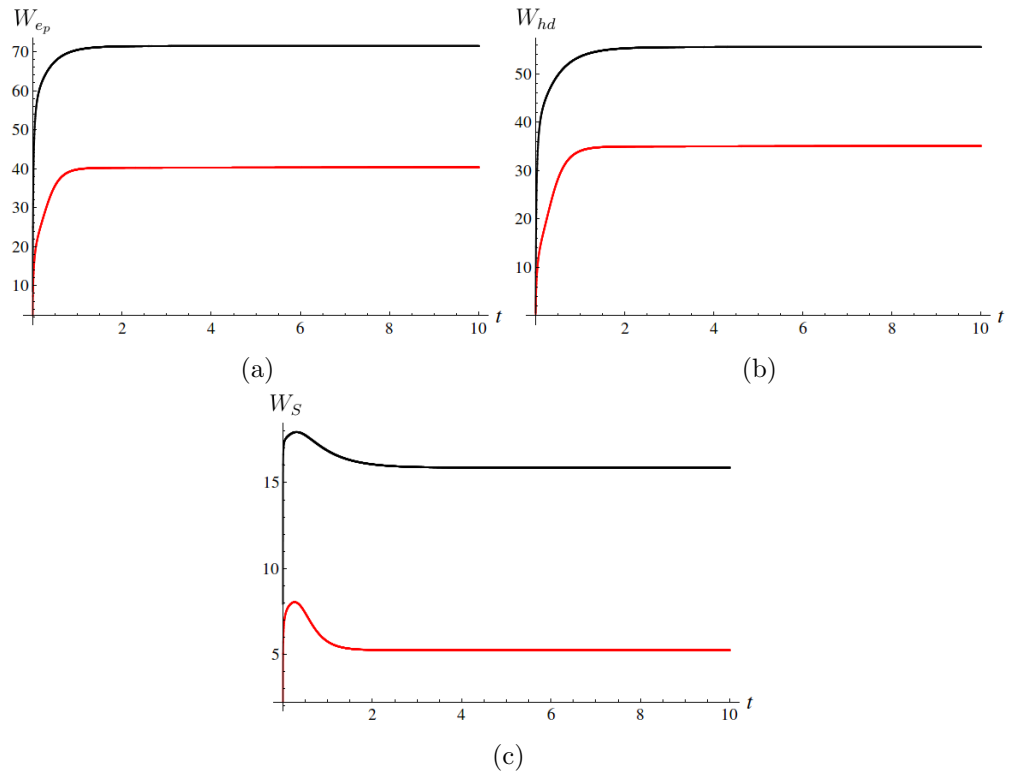


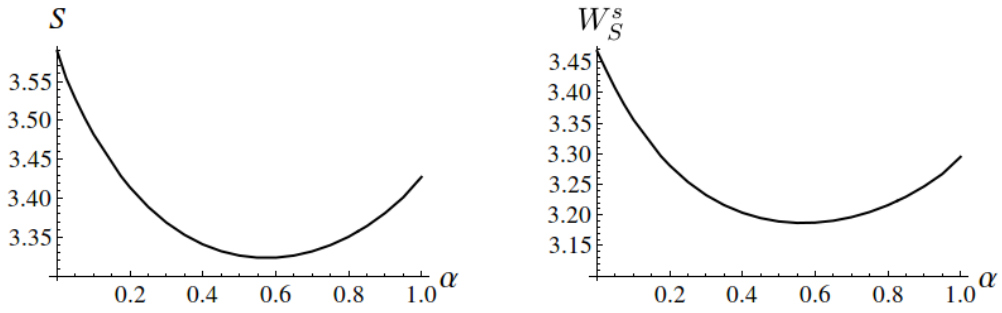
Figure 6.4: Change of (a)W_{hd}, (b)W_{ep} and (c) W_S for BCM82 (black line) and BCM92 (red line). The simulations are performed for $N = 31$ and the initial condition $p_{n_x,n_y} = \delta_{nx,31}\delta_{ny,31}$.

the DB is violated. We confirm this trend by plotting the value of entropy work in the stationary state W_S^s and the entropy S as a function of α (see Figure 6.5b and 6.5a). It is possible to see that the entropy variation shows a minimum for $\alpha \approx 0.55$.

We note that the value of these quantities is dependent on the choice of the initial conditions. This dependence on the initial conditions is easily explainable for the W_S, because from the definition:

$$W_S = \int_0^\infty \frac{dS}{dt'}dt' = \int_0^\infty (e_p(t') - h_d(t'))dt' = W_{ep} - W_{hd} = S(\infty) - S(0)$$

in such a way, the entropy variation depends on the initial value. If for example we choose the initial conditions as: $p_{n_x,n_y} = \delta_{n_x,n_x}\delta_{n_y,n_y}$, the initial entropy is zero, hence $W_{ep} - W_{hd}$ is simply $S(\infty)$.



(a) (b)

Figure 6.5: (a) Plot of the entropy S in function of α. (b)Change of W_S^s when α is varied from 0 to 1. In both cases the simulations are performed for $N = 31$ and the initial condition $p_{n_x,n_y} = \delta_{n_x,15}\delta_{n_y,15}$.

It is possible to relate the minimum of the entropy variation with the stability of the deterministic system (6.11). If we perform a linear stability analysis of the system (6.11) we find that the eigenvalues of the Jacobian matrix computed on the selective fixed points are both of the type $(-1, -\lambda_\alpha)$. If we plot $-\lambda_\alpha$ as a function of α, we see a minimum for $\alpha \approx 0.5$, whereas for $\alpha = 0$ and $\alpha = 1$ we have $-\lambda_\alpha = -1$.

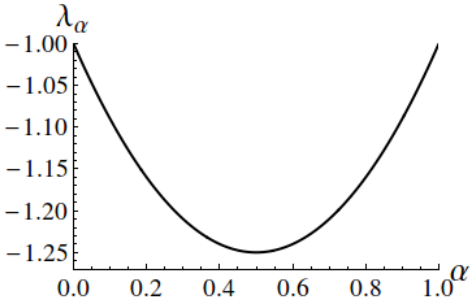


Figure 6.6: Plot of $-\lambda_\alpha$ for a 50 dimensional deterministic system

6.6 Discussion of the results

We propose a one parameter parametrization of the CME to study the differences between systems in DB and NESS. Calculating the values of $\mathcal{C}_\alpha$,

e_p and h_d we ascertain for $\alpha = 0$ the DB holds and for $\alpha \neq 0$ the system is in a NESS. We calculate the work done by the system as α varies, our results show that when the system is not in the detailed balance condition, the work necessary to reach the stable state is less than that requested when the detailed balance holds. We show also the values of stationary state of the total entropy S and the work of entropy W_S^s, which exhibit a minimum value for $\alpha \approx 0.55$. This interesting result, lead us to perform a linear stability analysis of the deterministic system, we calculate the eigenvalues of the Jacobian matrix, computed on the selective fixed points. And also in this case the system present a minimum value, $\alpha \approx 0.5$. Therefore, we believe that the minimum value of the entropy variation associated with $\alpha \approx 0.55$ can be related with the stability of the deterministic system.

The central result is that for our parametrized system, when $\alpha \neq 0$ (NESS) the work is allways less than the work for $\alpha = 0$ (DB). This means that the system requires less energy to memorize a pattern when the detailed balance is not satisfied. Hence the system is more plastic: a part of the energy that is requested to maintain the NESS is recovered when the system learns and develops selectivity to input pattern. We believe that this can be an hallmark of biological systems and that this can explain why these systems spend a large part of their metabolic energy to maintain NESS states; this energy is recovered during crucial developmental steps such as differentiation and learning.

Conclusions

The purpose of the present thesis was to show the biological applications and the nonequilibrium thermodynamic consequences of the Master equation description. Presenting four new studies in the biophysics context, divided into two well defined parts, but connected to each other. In the first part we investigate two nonlinear systems: the stochastic biochemical circuit and the logistic population model. In the second part we analyze a linear chemical chain reaction and the nonlinear BCM model.

The biochemical circuit has two stable equilibrium and the ME we associated to exhibits a bistable stationary distribution. To the logistic equation which has just one stable equilibrium we associated a family of ME which show the transition between two different stationary distributions peaked at the highest and lowest population states via a bimodal distribution which maximizes the entropy. The linearity of the model for the chemical chain reactions allows the exact determination of the stationary distribution and the relaxation time due to currents which do not affect the stationary state. For the synaptic plasticity we propose a family of deterministic equations interpolating the BCM82 and BCM92 models. The entropy and the work for the related ME exhibits a minimum for an intermediate member of the family which might be choose due to a high biological effect.

In the first work we have studied a simplified stochastic version of a biochemical circuit that is supposed to be involved in cell cycle control, with a lot of implications for the onset of several diseases such as cancer. This circuit is bidimensional, but we reduce it to one dimensional obtaining a CME

that can be studied analytically. This approximation shows the same qualitative features of the two-dimensional deterministic model. We also compare the one- and two-dimensional numerical simulations, the stochastic approach shows a different behavior than the deterministic one in two situations we have observed. First, bistability in the stochastic system is observed also in situations in which the corresponding deterministic system is monostable and secondly, there are situations in which the peak for the stochastic distribution related to the highest level of expression is masked by the tail of the distribution of the lowest-expression maximum making the "proliferative state" appear almost as a scarcely visited metastable state. We argue that the deterministic approach to this biochemical circuit is not capable to characterize it completely, and the stochastic approach appears more informative: further features unique to the stochastic model could be obtained by considering different time patterns for the molecular influxes to the system.

In the second one we have proposed a parametrization of the nonlinear master equation associated to the logistic population model. In this way we could study a family of master equations depending on a parameter α with the same mean field equation, but have a different noise depending on α. The standard version of the logistic growth corresponds to $\alpha = 0$ and has no absorbing state since $r_1 = 0$. If we impose the same condition $r_1 = 0$ for any value of α then the equilibrium distribution depends on α and exhibits interesting features. We have shown that the distribution changes from a Gaussian peaked at the maximum population $n = N$ for $\alpha = 0$ to a power law peaked at $n = 1$ to $\alpha = 1$. When we increase α starting from 0 the width of the power law occurs via a bimodal distribution. For $N \gg 1$ the Fokker-Planck equilibrium solution provides a very accurate approximation to the analytic equilibrium solution of the ME and for instance when $N = 100$ the relative error is of the order of 10^{-4}. Near $\alpha = 0$ and $\alpha = 1$ the same simple analytical expressions were obtained from the Fokker-Planck solution and from the detailed balance condition. Even though the ME equilibrium strongly depends on the parameter value we have shown that, keeping α

fixed, for N large enough a Gaussian peaked at $n = N$ with mean square deviation $\sigma = N^{1/2}$ is always recovered. As a consequence for $N \to \infty$ the distribution corresponding to the stable equilibrium of the mean field equation is always recovered. The relaxation time τ for any $\alpha < 1$ reaches a finite value proportional to $\frac{1}{(1-\alpha)}$ when N increases, just as the mean field equation[3]. The dependence of the noise on the parameter α and the population size N is non trivial nor uniform and shows that the choice of a ME given the macroscopic mean field equation requires additional information such as the dependence on the population size N of the equilibrium distribution. if in our model we make the choice $r_1 = \alpha$ rather than $r_1 = 0$ then the same state $n = 0$ becomes absorbing except for $\alpha = 0$ and the equilibrium distribution corresponds to the total extinction since the probability of the null state $n = 0$ is 1. Surprisingly the difference with the previous model is not so sharp. Indeed for $\alpha \sim 0$ the relaxation time to equilibrium grows as $\tau \sim \alpha^{-1} e^N$ which becomes so large, even for moderate values of N, that in practice extinction is not observed, since the system remains for very long time on a state described by a Gaussian distribution peaked at $n = N$. When α approaches 1 the relaxation time grows as $\tau \sim e^{N(1-\alpha)}$ and consequently the system first relaxes to the power law peaked an $n = 1$ and quite rapidly extinction occurs. This results so far obtained are general and can serve as guide to choose the ME suitable to describe the time evolution of a finite size population. The logistic growth gives a framework to treat biological systems such as cell growth, cellular development and differentiation, gene expression, synaptic plasticity and aging.

In the third work we have suggest a general framework to deal with system with a linear CME, concentrating our attention in the modeling of the nonequilibrium thermodynamics of a chemical chain reaction. Where we did not use the classical implementation of the CME, choosing written it in terms of a discretized Fokker-Planck equation, it because our aim was interpreted

[3]For $\alpha = 1$ it increases linearly with N since the equilibrium in the mean field equation is lost.

the influence of the chemical fluxes, that are known to be related with the entropy production, on the relaxation characteristic time of the CME. We derived all thermodynamic variables written in terms of the nonequilibrium fluxes, which are general results because are valid to system in DB and NESS. To systems in NESS we have introduced an external vector field whose work on the system and is directly related to the entropy production rate. This field is responsible to the change of the nonequilibrium fluxes in the stationary state, but in our formulation it does not change the stationary distribution, which ensures us to study the same system in DB and NESS. Here we also use the parametrization of the external field, in this way we have a range of systems with the same stationary distribution. We have used a three states linear CME to illustrate our results, for which the analytically form of the stationary distribution is well known, in this way it is possible to compute explicitly compute the chemical fluxes and the external nonlinear field. Our main result is to show that the presence of stationary fluxes reduces the characteristic relaxation time with respect the DB condition and it allows bifurcation phenomena for eigenvalues of the linearize dynamics around a local maximum of the probability distribution. We conjecture that this is a generic results that can be generalized to non-linear CME.

And in the fourth work we deal with the well known theory of synaptic plasticity BCM, for which there two main formulations: BCM82 and BCM92. The two formulations differ principally because in the stationary state the BCM82 is in an equilibrium state and the BCM92 is in a NESS state. Taking as reference this two models, we propose a one parameter parametrization that interpolates for $\alpha = 0$ the BCM82 and for $\alpha = 1$ the BCM92, and we study the nonequilibrium thermodynamic behavior of the system for different values of alpha between zero and one. We stabilized that for $\alpha \neq 0$ the system is in NESS, through the calculation of the entropy production and rate dissipation heat that are different from zero in the stationary state. We showed the results for the calculation of the work, done by the system from a initial condition to the stationary state, as α varies. For all values of $\alpha \neq 0$

the work is less when the system is in NESS. A interesting result, because to maintain the NESS the system dissipates energy. Analyzing the behavior of the total entropy and the its work is the stationary state in function of α we find a minimal value for $\alpha \approx 0.5$. Therefore, we believe that the minimum value of the entropy variation associated can be related with the stability of the deterministic system. Based on our results we believe that the system requires less energy to memorize a pattern when the detailed balance is not satisfied. Hence the system is more plastic: a part of the energy that is requested to maintain the NESS is recovered when the system learns and develops selectivity to input pattern. We believe that this can be an hallmark of biological systems and that this can explain why these systems spend a large part of their metabolic energy to maintain NESS states; this energy is recovered during crucial developmental steps such as differentiation and learning.

Bibliography

[1] B. D. Aguda, Y. Kim, M. G. Piper-Hunter, A. Friedman, and C. B. Marsh, "MicroRNA regulation of a cancer network: consequences of the feedback loops involving miR-17-92, E2F, and Myc," *Proceedings of the National Academy of Sciences*, vol. 105, p. 19678, 2008.

[2] R. R. N. Bhattacharya and E. C. Waymire, *Stochastic processes with applications*, vol. 61. Siam, 1990.

[3] N. van Kampen, *Stochastic processes in physics and chemistry*. North Holland, 2007.

[4] C. Gardiner, *Handbook of stochastic methods: for physics, chemistry & the natural sciences,(Series in synergetics, Vol. 13)*. Berlin: Springer, 2004.

[5] J. Liang and H. Qian, "Computational cellular dynamics based on the chemical master equation: A challenge for understanding complexity," *Journal of computer science and technology*, vol. 25, no. 1, pp. 154–168, 2010.

[6] V. Sunkara, "The chemical master equation with respect to reaction counts," in *Proc. 18th World IMACS/MODSIM Congress*, 2009.

[7] J. Schnakenberg, "Network theory of behavior of master equation systems," *Reviews of Modern Physics*, vol. 48, pp. 571–585, 1976.

[8] D. A. Beard and H. Qian, *Chemical biophysics: quantitative analysis of cellular systems*. Cambridge University Press, 2008.

[9] H. Ge and H. Qian, "Physical origins of entropy production, free energy dissipation, and their mathematical representations," *Physical Review E*, vol. 81, no. 5, p. 051133, 2010.

[10] H. Qian, "Phosphorylation energy hypothesis: open chemical systems and their biological functions," *Annu. Rev. Phys. Chem.*, vol. 58, pp. 113–142, 2007.

[11] H. Qian, "Open-system nonequilibrium steady state: Statistical thermodynamics, fluctuations, and chemical oscillations," *The Journal of Physical Chemistry B*, vol. 110, no. 31, pp. 15063–15074, 2006.

[12] H. Qian and L. M. Bishop, "The chemical master equation approach to nonequilibrium steady-state of open biochemical systems: Linear single-molecule enzyme kinetics and nonlinear biochemical reaction networks," *International journal of molecular sciences*, vol. 11, no. 9, pp. 3472–3500, 2010.

[13] M. Dykman, E. Mori, J. Ross, and P. Hunt, "Large fluctuations and optimal paths in chemical kinetics," *The Journal of chemical physics*, vol. 100, p. 5735, 1994.

[14] M. Assaf and B. Meerson, "Spectral theory of metastability and extinction in birth-death systems," *Physical review letters*, vol. 97, no. 20, p. 200602, 2006.

[15] T. Newman, J.-B. Ferdy, and C. Quince, "Extinction times and moment closure in the stochastic logistic process," *Theoretical population biology*, vol. 65, no. 2, pp. 115–126, 2004.

[16] I. Nåsell, "Extinction and quasi-stationarity in the Verhulst logistic model," *Journal of Theoretical Biology*, vol. 211, no. 1, pp. 11–27, 2001.

[17] P. Thomas, A. V. Straube, and R. Grima, "Stochastic theory of large-scale enzyme-reaction networks: Finite copy number corrections to rate equation models," *The Journal of chemical physics*, vol. 133, p. 195101, 2010.

[18] A. Bazzani, G. C. Castellani, E. Giampieri, D. Remondini, and L. N. Cooper, "Bistability in the chemical master equation for dual phosphorylation cycles," *The Journal of Chemical Physics*, vol. 136, p. 235102, 2012.

[19] T. Jahnke and W. Huisinga, "Solving the chemical master equation for monomolecular reaction systems analytically," *Journal of Mathematical Biology*, vol. 54, no. 1, pp. 1–26, 2007.

[20] H. H. McAdams and A. Arkin, "Stochastic mechanisms in gene expression," *Proceedings of the National Academy of Sciences*, vol. 94, no. 3, pp. 814–819, 1997.

[21] M. B. Elowitz, A. J. Levine, E. D. Siggia, and P. S. Swain, "Stochastic gene expression in a single cell," *Science*, vol. 297, no. 5584, pp. 1183–1186, 2002.

[22] T. B. Kepler and T. C. Elston, "Stochasticity in transcriptional regulation: origins, consequences, and mathematical representations," *Biophysical Journal*, vol. 81, no. 6, pp. 3116–3136, 2001.

[23] A. Arkin, J. Ross, and H. H. McAdams, "Stochastic kinetic analysis of developmental pathway bifurcation in phage λ-infected Escherichia coli cells," *Genetics*, vol. 149, no. 4, pp. 1633–1648, 1998.

[24] N. Barkai and S. Leibler, "Biological rhythms: Circadian clocks limited by noise," *Nature*, vol. 403, no. 6767, pp. 267–268, 2000.

[25] M. Samoilov, S. Plyasunov, and A. P. Arkin, "Stochastic amplification and signaling in enzymatic futile cycles through noise-induced bistabil-

ity with oscillations," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, no. 7, pp. 2310–2315, 2005.

[26] G. C. Castellani, A. Bazzani, and L. N. Cooper, "Toward a microscopic model of bidirectional synaptic plasticity," *Proceedings of the National Academy of Sciences*, vol. 106, no. 33, pp. 14091–14095, 2009.

[27] E. W. Lund, "Guldberg and waage and the law of mass action," *Journal of Chemical Education*, vol. 42, no. 10, p. 548, 1965.

[28] D. J. Wilkinson, "Stochastic modelling for quantitative description of heterogeneous biological systems," *Nature Reviews Genetics*, vol. 10, no. 2, pp. 122–133, 2009.

[29] V. Wolf, R. Goel, M. Mateescu, and T. A. Henzinger, "Solving the chemical master equation using sliding windows," *BMC systems biology*, vol. 4, no. 1, p. 42, 2010.

[30] R. A. Weinberg, "Tumor suppressor genes," *Science*, vol. 254, no. 5035, pp. 1138–1146, 1991.

[31] D. P. Bartel, "MicroRNAs: genomics, biogenesis, mechanism, and function," *cell*, vol. 116, no. 2, pp. 281–297, 2004.

[32] T. S. Gardner, C. R. Cantor, and J. J. Collins, "Construction of a genetic toggle switch in Escherichia coli," *Nature*, vol. 403, no. 6767, pp. 339–342, 2000.

[33] H. Kobayashi, M. Kærn, M. Araki, K. Chung, T. S. Gardner, C. R. Cantor, and J. J. Collins, "Programmable cells: interfacing natural and engineered gene networks," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 101, no. 22, pp. 8414–8419, 2004.

[34] L. P. Lim, N. C. Lau, P. Garrett-Engele, A. Grimson, J. M. Schelter, J. Castle, D. P. Bartel, P. S. Linsley, and J. M. Johnson, "Microarray

analysis shows that some microRNAs downregulate large numbers of target mRNAs," *Nature*, vol. 433, no. 7027, pp. 769–773, 2005.

[35] J. Lu, G. Getz, E. A. Miska, E. Alvarez-Saavedra, J. Lamb, D. Peck, A. Sweet-Cordero, B. L. Ebert, R. H. Mak, A. A. Ferrando, *et al.*, "MicroRNA expression profiles classify human cancers," *nature*, vol. 435, no. 7043, pp. 834–838, 2005.

[36] K. A. O'Donnell, E. A. Wentzel, K. I. Zeller, C. V. Dang, and J. T. Mendell, "c-Myc-regulated microRNAs modulate E2F1 expression," *Nature*, vol. 435, no. 7043, pp. 839–843, 2005.

[37] M. J. Bueno, I. P. de Castro, and M. Malumbres, "Control of cell proliferation pathways by microRNAs," *Cell Cycle*, vol. 7, no. 20, pp. 3143–3148, 2008.

[38] H. A. Coller, J. J. Forman, and A. Legesse-Miller, ""Myc'ed messages": myc induces transcription of E2F1 while inhibiting its translation via a microRNA polycistron," *PLoS genetics*, vol. 3, no. 8, p. e146, 2007.

[39] D. Remondini, B. O'connell, N. Intrator, J. Sedivy, N. Neretti, G. Castellani, and L. Cooper, "Targeting c-Myc-activated genes with a correlation method: detection of global changes in large gene expression network dynamics," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, no. 19, pp. 6902–6906, 2005.

[40] B. E. Meserve, *Fundamental concepts of algebra*. DoverPublications.com, 1953.

[41] S. Strogatz, "Nonlinear dynamics and chaos: with applications to physics, biology, chemistry and engineering," 2001.

[42] D. T. Gillespie, "Exact stochastic simulation of coupled chemical reactions," *The journal of physical chemistry*, vol. 81, no. 25, pp. 2340–2361, 1977.

[43] H. Li and L. Petzold, "Logarithmic direct method for discrete stochastic simulation of chemically reacting systems," *Journal of Chemical Physics*, 2006.

[44] M. Kwiatkowska, G. Norman, J. Sproston, and F. Wang, "Symbolic model checking for probabilistic timed automata," in *Formal Techniques, Modelling and Analysis of Timed and Fault-Tolerant Systems*, pp. 293–308, Springer, 2004.

[45] P. Buchholz, J.-P. Katoen, P. Kemper, and C. Tepper, "Model-checking large structured Markov chains," *The Journal of Logic and Algebraic Programming*, vol. 56, no. 1, pp. 69–97, 2003.

[46] C. Hirel, R. Sahner, X. Zang, and K. Trivedi, "Reliability and performability modeling using SHARPE 2000," in *Computer Performance Evaluation. Modelling Techniques and Tools*, pp. 345–349, Springer, 2000.

[47] D. Daly, D. D. Deavours, J. M. Doyle, P. G. Webster, and W. H. Sanders, "Möbius: An extensible tool for performance and dependability modeling," in *Computer Performance Evaluation. Modelling Techniques and Tools*, pp. 332–336, Springer, 2000.

[48] F. Didier, T. A. Henzinger, M. Mateescu, and V. Wolf, "Approximation of event probabilities in noisy cellular processes," in *Computational Methods in Systems Biology*, pp. 173–188, Springer, 2009.

[49] G. Bella and P. Liò, "Formal analysis of the genetic toggle," in *Computational Methods in Systems Biology*, pp. 96–110, Springer, 2009.

[50] G. Bella and P. Liò, "Analysing the microRNA-17-92/Myc/E2F/RB Compound Toggle Switch by Theorem Proving," in *Proc. of the 9th Workshop on Network Tools and Applications in Biology (Nettab'09). Liberodiscrivere*, pp. 59–62, 2009.

[51] H.-M. Chan, L.-S. Chan, R. N.-S. Wong, and H.-W. Li, "Direct quantification of single-molecules of microRNA by total internal reflection fluorescence microscopy," *Analytical chemistry*, vol. 82, no. 16, pp. 6911–6918, 2010.

[52] L. P. Lim, N. C. Lau, E. G. Weinstein, A. Abdelhakim, S. Yekta, M. W. Rhoades, C. B. Burge, and D. P. Bartel, "The microRNAs of Caenorhabditis elegans," *Genes & development*, vol. 17, no. 8, pp. 991–1008, 2003.

[53] A. Arvey, E. Larsson, C. Sander, C. S. Leslie, and D. S. Marks, "Target mRNA abundance dilutes microRNA and siRNA activity," *Molecular systems biology*, vol. 6, no. 1, 2010.

[54] B. V. Bronk, G. Dienes, and A. Paskin, "The stochastic theory of cell proliferation," *Biophysical journal*, vol. 8, no. 11, pp. 1353–1398, 1968.

[55] J. E. Till, E. A. McCulloch, and L. Siminovitch, "A stochastic model of stem cell proliferation, based on the growth of spleen colony-forming cells," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 51, no. 1, p. 29, 1964.

[56] L. A. Herndon, P. J. Schmeissner, J. M. Dudaronek, P. A. Brown, K. M. Listner, Y. Sakano, M. C. Paupard, D. H. Hall, and M. Driscoll, "Stochastic and genetic factors influence tissue-specific decline in ageing C. elegans," *Nature*, vol. 419, no. 6909, pp. 808–814, 2002.

[57] D. Volfson, J. Marciniak, W. J. Blake, N. Ostroff, L. S. Tsimring, and J. Hasty, "Origins of extrinsic variability in eukaryotic gene expression," *Nature*, vol. 439, no. 7078, pp. 861–864, 2005.

[58] H. H. McAdams and A. Arkin, "Stochastic mechanisms in gene expression," *Proceedings of the National Academy of Sciences*, vol. 94, no. 3, pp. 814–819, 1997.

[59] J. Paulsson, "Models of stochastic gene expression," *Physics of life reviews*, vol. 2, no. 2, pp. 157–175, 2005.

[60] J. M. Pedraza and J. Paulsson, "Effects of molecular memory and bursting on fluctuations in gene expression," *Science*, vol. 319, no. 5861, pp. 339–343, 2008.

[61] M. Avlund, S. Krishna, S. Semsey, I. B. Dodd, and K. Sneppen, "Minimal gene regulatory circuits for a lysis-lysogeny choice in the presence of noise," *PloS one*, vol. 5, no. 12, p. e15037, 2010.

[62] K. Sneppen, S. Krishna, and S. Semsey, "Simplified models of biological networks," *Annual review of biophysics*, vol. 39, pp. 43–59, 2010.

[63] E. L. Bienenstock, L. N. Cooper, and P. W. Munro, "Theory for the development of neuron selectivity: orientation specificity and binocular interaction in visual cortex," *The Journal of Neuroscience*, vol. 2, no. 1, pp. 32–48, 1982.

[64] N. Intrator and L. Cooper, "Objective function formulation of the BCM theory of visual cortical plasticity: Statistical connections, stability conditions*," *Neural Networks*, vol. 5, no. 1, pp. 3–17, 1992.

[65] F. Luciani, G. Turchetti, C. Franceschi, and S. Valensin, "A mathematical model for the immunosenescence.," *Rivista di biologia*, vol. 94, no. 2, p. 305, 2001.

[66] F. Luciani, S. Valensin, R. Vescovini, P. Sansoni, F. Fagnoni, C. Franceschi, M. Bonafe, and G. Turchetti, "A Stochastic Model for CD8¡ sup¿+¡/sup¿ T Cell Dynamics in Human Immunosenescence: Implications for Survival and Longevity," *Journal of Theoretical Biology*, vol. 213, no. 4, pp. 587–597, 2001.

[67] L. Mariani, G. Turchetti, and C. Franceschi, "Chronic antigenic stress, immunosenescence and human survivorship over the 3 last centuries:

heuristic value of a mathematical model," *Mechanisms of ageing and development*, vol. 124, no. 4, pp. 453–458, 2003.

[68] J. Elf and M. Ehrenberg, "Fast evaluation of fluctuations in biochemical networks with the linear noise approximation," *Genome research*, vol. 13, no. 11, pp. 2475–2484, 2003.

[69] J. Hornos, D. Schultz, G. Innocentini, J. Wang, A. Walczak, J. Onuchic, and P. Wolynes, "Self-regulating gene: An exact solution," *Physical Review E*, vol. 72, no. 5, p. 051907, 2005.

[70] N. Friedman, L. Cai, and X. S. Xie, "Linking stochastic dynamics to population distribution: an analytical framework of gene expression," *Physical review letters*, vol. 97, no. 16, p. 168302, 2006.

[71] V. Shahrezaei and P. S. Swain, "Analytical distributions for stochastic gene expression," *Proceedings of the National Academy of Sciences*, vol. 105, no. 45, pp. 17256–17261, 2008.

[72] A. Eldar and M. B. Elowitz, "Functional roles for noise in genetic circuits," *Nature*, vol. 467, no. 7312, pp. 167–173, 2010.

[73] V. Elgart and A. Kamenev, "Classification of phase transitions in reaction-diffusion models," *Physical Review E*, vol. 74, no. 4, p. 041101, 2006.

[74] A. Kamenev and B. Meerson, "Extinction of an infectious disease: A large fluctuation in a nonequilibrium system," *Physical Review E*, vol. 77, no. 6, p. 061107, 2008.

[75] M. Assaf and B. Meerson, "Extinction of metastable stochastic populations," *Physical Review E*, vol. 81, no. 2, p. 021116, 2010.

[76] F. Di Patti, S. Azaele, J. R. Banavar, and A. Maritan, "System size expansion for systems with an absorbing state," *Physical Review E*, vol. 83, no. 1, p. 010102, 2011.

[77] I. Volkov, J. R. Banavar, S. P. Hubbell, and A. Maritan, "Patterns of relative species abundance in rainforests and coral reefs," *Nature*, vol. 450, no. 7166, pp. 45–49, 2007.

[78] U. Seifert, "Stochastic thermodynamics, fluctuation theorems and molecular machines," *Reports on Progress in Physics*, vol. 75, no. 12, p. 126001, 2012.

[79] L. Reichl, *A modern course in Statistical Physics*. John Wiley & Sons, 1998.

[80] R. Zia and B. Schmittmann, "Probability currents as principal characteristics in the statistical mechanics of non-equilibrium steady states," *Journal of Statistical Mechanics: Theory and Experiment*, vol. 2007, no. 07, p. P07012, 2007.

[81] L. Xu, H. Shi, H. Feng, and J. Wang, "The energy pump and the origin of the non-equilibrium flux of the dynamical systems and the networks," *The Journal of Chemical Physics*, vol. 136, p. 165102, 2012.

[82] M. Esposito and C. V. den Broeck, "The three faces of the Second Law: I. Master equation formulation," *arXiv preprint arXiv:1005.1683*, 2010.

[83] I. Prigogine, "Time, structure, and fluctuations," *Science*, vol. 201, no. 4358, pp. 777–785, 1978.

[84] S. R. M. P. de Groot, *Non-Equilibrium Thermodynamics*. North-Holland, 1962.

[85] K. Huang, *Statistical Mechanics, 2nd*. John Wiley & Sons, 1987.

[86] E. T. Jaynes, "Information theory and statistical mechanics," *Physical review*, vol. 106, no. 4, p. 620, 1957.

[87] U. Seifert, "Entropy production along a stochastic trajectory and an integral fluctuation theorem," *Physical review letters*, vol. 95, no. 4, p. 040602, 2005.

[88] Y. Oono and M. Paniconi, "Steady state thermodynamics," *Progress of Theoretical Physics Supplement*, vol. 130, pp. 29–44, 1998.

[89] R. K. Zia and B. Schmittmann, "A possible classification of nonequilibrium steady states," *Journal of physics A: Mathematical and general*, vol. 39, no. 24, p. L407, 2006.

[90] T. Hatano and S. ichi Sasa, "Steady-state thermodynamics of Langevin systems," *Physical review letters*, vol. 86, no. 16, p. 3463, 2001.

[91] H. V. Westerhoff and B. O. Palsson, "The evolution of molecular biology into systems biology," *Nature biotechnology*, vol. 22, pp. 1249–1252, 2004.

[92] H. Qian and T. C. Reluga, "Nonequilibrium thermodynamics and nonlinear kinetics in a cellular signaling switch," *Physical review letters*, vol. 94, no. 2, p. 028101, 2005.

[93] I. R. Epstein and K. Showalter, "Nonlinear chemical dynamics: oscillations, patterns, and chaos," *The Journal of Physical Chemistry*, vol. 100, no. 31, pp. 13132–13147, 1996.

[94] J. D. Murray, *Mathematical biology*, vol. 2. springer, 2002.

[95] X. Wang and X. Wang, "Systematic identification of microRNA functions by combining target prediction and expression profiling," *Nucleic acids research*, vol. 34, no. 5, pp. 1646–1652, 2006.

[96] T. Wiesel and D. Hubel *Journal of Physiology*, vol. 180, p. 106, 1962.

[97] H. A. S. M. B. M. Whitlock JR, "Learning induces long-term potentiation in the hippocampus," *Science*, vol. 313, pp. 1093–1097, 2006.

[98] G. C. Castellani, E. M. Quinlan, L. N. Cooper, and H. Z. Shouval, "A biophysical model of bidirectional synaptic plasticity: dependence on AMPA and NMDA receptors.," *Proc. Natl. Acad. Sci. U.S.A.*, vol. 98, pp. 12772–7, Oct. 2001.

[99] G. C. Castellani, E. M. Quinlan, F. Bersani, L. N. Cooper, and H. Z. Shouval, "A model of bidirectional synaptic plasticity: from signaling network to channel conductance.," *Learn. Mem.*, vol. 12, no. 4, pp. 423–32.

[100] A. Bazzani, D. Remondini, N. Intrator, and G. C. Castellani *Neural Computation*, vol. 15(7), p. 1621, 2003.

[101] G. Castellani, N. Intrator, H. Shouval, and L. Cooper, "Solutions of the BCM learning rule in a network of lateral interacting nonlinear neurons," *Network: Computation in Neural Systems*, vol. 10, no. 2, pp. 111–121, 1999.

[102] L. N. Cooper, N. Intrator, B. S. Blais, and H. Z. Shouval, *Theory of cortical plasticity*. World Scientific New Jersey, 2004.

[103] S. Cooke and T. Bliss, "Plasticity in the human central nervous system," *Brain*, vol. 129, no. 7, pp. 1659–1673, 2006.

[104] P. V. Massey and Z. I. Bashir, "Long-term depression: multiple forms and implications for brain function," *Trends in neurosciences*, vol. 30, no. 4, pp. 176–184, 2007.

[105] E. Clothiaux and N. Cooper, "L., and bear, mf (1991). synaptic plasticity in visual cortex: Comparison of theory with experiment," *Journal of Neurophysiology*, vol. 66, pp. 1785–1804.

[106] C. C. Law, M. F. Bear, and L. N. Cooper, "receptive fields according to the bcm theory," *The Self-organizing Brain: From Growth Cones to Functional Networks; Proceedings of the 18th International Summer School of Brain Research, Held at the University of Amsterdam and the Academic Medical Center (The Netherlands) from 23 to 27 August 1993*, vol. 102, p. 287, 1994.

[107] H. Shouval, N. Intrator, C. C. Law, and L. N. Cooper, "Effect of binocular cortical misalignment on ocular dominance and orientation selectivity," *Neural Computation*, vol. 8, no. 5, pp. 1021–1040, 1996.

[108] A. P. Bohner, S. M. Dudek, and M. F. Bear, "Effects of n-methyl-d-aspartate on quisqualate-stimulated phosphoinositide hydrolysis in slices of kitten striate cortex," *Brain research*, vol. 594, no. 1, pp. 146–149, 1992.

[109] A. Kirkwood and M. F. Bear, "Hebbian synapses in visual cortex," *The Journal of neuroscience*, vol. 14, no. 3, pp. 1634–1645, 1994.

[110] A. Kirkwood, M. G. Rioult, and M. F. Bear, "Experience-dependent modification of synaptic plasticity in visual cortex," *Nature*, vol. 381, no. 6582, pp. 526–528, 1996.

[111] H. Q. H. Ge, "Physical origins of entropy production, free energy dissipation, and their mathematical representations," *Phy.Rev.E*, vol. 81, p. 051133, 2010.

[112] H. Qian, "Thermodynamic and kinetic analysis of sensitivity amplification in biological signal transduction," *Biophysical chemistry*, vol. 105, no. 2-3, pp. 585–593, 2003.

Agradecimentos

Foram muitas as pessoas que participaram direta ou indiretamente do meu doutorado, mas se o professor Turchetti não tivesse respondido meu e-mail pedindo informações sobre o grupo dele, eu não teria nem feito o doutorado na Itália. Então começo agradecendo ao professor Turchetti por ter acreditado no meu potêncial mesmo antes de me conhecer pessoalmente. Um muítissimo obrigada ao Gastone, que foi um grandíssimo orientador, abrindo a minha mente para ver de maneira mais clara todo fascínio do sistema mais complexo, a vida. Agradeço também as minhas garotas: Angela, Entela, Claudia e Stefania pelas pausas que fizemos juntas, pois elas foram muito importantes para a minha produtividade. Ainda no âmbito profissional, agradeço ao professor Bazzani que foi um criador de dúvidas na minha pesquisa o que me fez buscar por respostas e aprender mais. E claro agradeço aos colegas do grupo de Biofisica: Daniel, Isabella, Enrico e prof. Bersani.

O meu maior agradecimento vai aos meus pais, Cleusa e Florisvino, que sempre acreditaram em mim e me fizeram acreditar que eu era capaz! Se não fossem eles eu não seria nada. Ao Mignon, que foi minha família, meu amigo, meu amor e me aguentou nas horas de felicidade (quando os resultados eram positivos) e de dificuldade (quando eu não nada funcionava). Ao meu amigo Marcelo que não me abandonou e me suportaram mesmo com a distância de um oceano. E as pessoas maravilhosas que eu tive o prazer de conhecer na Itália, que fizeram o meu doutorado ser muito mais do que só o aprendizado acadêmico: Fabio (amininho), Juliana (odio, odio, odio), Matteo, Eleonora, Viola, Filomena, Lili, Fabio, Mauro, Daniela, Alessandro...

E um muito obrigada ao programa Erasmus mundus que financiou o meu doutorado.

Ringraziamenti

Sono state molte le persone che hanno partecipato in forma diretta o indiretta al mio dottorato, ma se il professore Turchetti non avesse risposto alla mia mail quando avevo chiesto informazione sul suo gruppo, io non avrei nemmeno fatto il dottorato in Italia. Allora comincio ringraziando proprio il professore Turchetti per aver creduto nel mio potenziale anche prima di conoscermi personalmente. Un grazie mille a Gastone, che é stato un grandissimo tutore, aprendo la mia mente facendomi vedere nella maniera piú chiara tutto il fascino del sistema piú complesso, la vita. Ringrazio anche le mie garotas: Angela, Entela, Claudia e Stefania per le pause che abbiamo fatto insieme, perché sono state molto importanti per la mia produttività. Ancora nell'ambito professionale, ringrazio il professore Bazzani che é stato un creatore di dubbi sulla mia ricerca, i quali mi hanno fatto cercare le risposte e imparare di piú. E ovviamente ringrazio i compagni del gruppo di Biofisica: Daniel, Isabella, Enrico e prof. Bersani.

Il mio piú sincero grazie va ai miei genitori, Cleusa e Florisvino, che sempre hanno creduto in me e mi hanno fatto credere di essere capace! Senza di loro io non sarei niente. A Mignon, che é stato la mia famiglia, il mio amico, il mio amore e mi ha supportato nelle difficoltà (quando non funzionava niente) e nelle ore di felicità (quando ottenevo risultati positivi). Al mio amico Marcelo che non mi ha mai lasciato e mi ha sostenuto anche con la distanza di un oceano tra di noi. E a tutte le persone meravigliose che ho avuto il piacere di conoscere in Italia, che hanno fatto diventare il mio dottorato molto piú di una formazione accademica: Fabio (amininho), Juliana (odio, odio, odio), Matteo, Eleonora, Viola, Filomena, Lili, Fabio, Mauro, Daniela, Alessandro...

E un grazie mille al programma Erasmus mundus, che ha finanziato il mio dottorato.