J Math Chem (2013) 51:2074–2103
DOI 10.1007/s10910-013-0200-5

ORIGINAL PAPER

Bistable stochastic biochemical networks: large chemical networks and systems with many molecules

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Received: 8 February 2013 / Accepted: 27 May 2013 / Published online: 9 June 2013

Abstract In this paper we continue the program started in Hwang and Velázquez (J Math Chem, to appear). We describe some chemical systems exhibiting bistable behavior with reaction constants of order one, but where bistability is due to the presence of a large number of chemical species or a large number of molecules of some of the species. We derive generalizations of the classical Kramers' formula that gives the switching times for some particular systems exhibiting a large number of species.

Keywords Biochemical reactions · Stochastic effects · Kramers' formula

1 Introduction

This paper, together with its companion paper [33], investigates the mathematical properties of biochemical systems yielding deterministic behaviour in suitable rescaling limits. More precisely, our goal is to study the underlying mechanisms which can yield deterministic behaviour in spite of the fact that the system itself could behave stochastically, due to the smallness of the number of molecules or the large size of the molecular fluctuations.

As discussed in [33] there exist several biological processes where the stochastic character of some systems seems to play a relevant role (cf. [5,7,19,24,36,42,46]).

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Biochemical networks with stochastic behaviour have been extensively studied since the seminal work of Gillespie (cf. [29]). Analytical and computational works can be found in [21,22,27,28,34,41,49,51,52]. In [33] we have studied the way in which biochemical networks consisting of a small number of molecules can yield bistable behaviours with long switching times between the possible stable equilibria due to the highly specific behaviour of the molecules of the system.

The main difference between the type of biochemical networks considered in this paper and the ones in [33] is that the source of bistability for the models considered in this paper will be the presence in the system either of many molecules, or many chemical species. In particular we will derive a generalization of the well known Kramers' formula (cf. [37]) for a class of biochemical networks containing many chemical species.

The key ingredient for the existence of bistability in the models under consideration will be the presence in the system of large and small parameters. The large parameters considered in [33] were the relative sizes between the chemical rate constants associated to some specific reactions. The parameters in this paper will be, either the number of molecules or the number of chemical species.

As discussed in [33] it is natural to ask why to compute the switching times between different multiple states. There are several reasons for studying switching times. First, they are intrinsically interesting for themselves. On the other hand, their size provides a measure of how deterministic is the behaviour of a biochemical system, since the switching times provide an estimate of the time required to switch to another steady state among the many possible ones of a system. A detailed computation of switching times in some asymptotic limits can provide insights on the factors (like chemical coefficients, network structure or others) that can yield more deterministic or more "random-like" type of behaviours.

The study of the computation on the rates of chemical reactions which take place to overcome an activation energy has deserved a lot of attention. Usually in these cases the switching times rescale exponentially with the activation energy. The first results in this direction were obtained in one-dimensional models by Eyring (cf. [18]) and Kramers (cf. [37]). Kramers' formula has been extensively used to compute switching times in biochemical systems (cf. [20]). A rigorous formulation as well as a generalization of this approach to finite dimensional systems were obtained in the Freidlin–Wentzell theory (cf [25]). Actually these ideas can be extended to rather general Markov processes. Several definitions of metastability have been given for such systems as well as extensions of Kramers' formula to some infinite dimensional systems (cf. [8–11,14–16]).

The applicability of the ideas of metastability and switching times that underly the theories mentioned above is very wide, since it can be used generally in problems exhibiting metastable states separated by energy barriers. For instance, these methods have been applied in [48–51] to describe conformational dynamics as transitions between metastable states.

It should be pointed out, however, that the usual Kramers' formula, can be only applied strictly to the case where the dynamics of the system can be approximated by means of a Fokker–Planck equation. The master equations describing the number of molecules in a system can be found in [29] and they are reduced to such type of PDEs that the number of molecules in the system approaches infinity, as it was shown in [38].

If the number of molecules remains of order one, the usual Kramers' formula cannot be applied and different methods must be used to compute switching times. Although the mathematical theories required to compute switching times are well established in the general theory of Markov processes, its specific applications to biochemical systems seem to pose some interesting questions. For instance, the combinatorics of the reactions could play a crucial role for large networks.

A large part of the approaches in this paper is based on asymptotic methods. We will use repeatedly the asymptotic symbols $\sim$, $\ll$ to denote the following:

$$f \sim g \text{ as } x \to x_0 \text{ iff } \lim_{x \to x_0} \frac{f(x)}{g(x)} = 1$$

$$f \ll g \text{ as } x \to x_0 \text{ iff } \lim_{x \to x_0} \frac{f(x)}{g(x)} = 0$$

The plan of this paper is the following. In Sect. 2 we briefly describe the class of stochastic biochemical networks that we are considering in this paper. Section 3 revises some particular problems whose dynamics can be approximated using Fokker–Planck equations with small parameters where Kramers formula can be used to compute switching times. In Sect. 4 we introduce a type of systems containing many different chemical substances and that can yield long switching times under suitable circumstances. We remark that the systems considered in Sect. 4 do not produce bistability due to the presence of nonlinear interactions. On the contrary the bistability is due to the presence of strong drifting terms that tend to bring the state of the system to the presence of one type of molecule. The mathematical structure of the systems considered in Sect. 4 is simple enough to allow a detailed computation of formulas for the switching times in suitable asymptotic limits. Section 5 considers a system containing also many different chemicals, but also some nonlinear interactions that allow to obtain a stronger bistable behaviour than the one obtained for the systems considered in Sect. 4. A closed formula for the invariant measures or the switching times is more difficult to obtain than in the case of the systems considered in Sect. 4. Therefore, some numerical simulations showing their behaviour are described in Sect. 6. Section 7 summarizes the main results obtained in the paper.

2 General framework: discrete stochastic processes

The type of stochastic molecular dynamics considered in this paper is similar to the one previously considered in the literature (cf. [4,6,13,26,29,38,40,41,45]). We summarize here the main assumptions.

We will assume that the systems under consideration consist of N different types of chemical substances. It will be also assumed that the number of molecules of each chemical species is typically a finite number. Such a number is a random variable that might change in time as a consequence of the chemical reactions. We are interested in understanding the dynamics of these stochastic systems in suitable limit regimes: (1) for the number of molecules of some of the chemical species, in the limit of large numbers of molecules, or (2) for the number of chemical species, in the limit of large

numbers of species or (3) for suitable choices of large or small coefficients for some of the reaction rates.

The chemical reactions will be assumed to be due to at most binary collisions between molecules and with a maximum number of two products in each reaction. We will not assume that the number of molecules is conserved in the reactions, as it is common in many of these studies (see for instance [23]). In particular this means that we will accept the possibility of having reactions not preserving the molecules like $A \to \varnothing$ or $\varnothing \to A$. We will suppose that in the reactions including the empty set $\varnothing$ only one molecule is involved. This does not lose much of the generality because similar reactions involving more than one molecule could be described by means of sequences of very fast reactions involving intermediate molecular complexes.

It will be assumed that the environment where the molecules react is well stirred. Therefore, the spatial dependence of the molecules will be ignored. We will suppose that the chemical reactions take place according to independent Poisson processes. Correlation effects between the different reactions will not be taken into account.

The variables needed to describe this type of systems are the number of molecules of each of the chemical species $\{n_\ell\}_{\ell=1}^N$. Let us denote as $A_\ell,\ \ell = 1, \ldots, N$ the different chemicals in the system. The restrictions imposed on the reactions mean that they fall into one of the following types:

$$\varnothing \to A_\ell,\ \ K_\ell;\ \ A_\ell \to \varnothing,\ \ \lambda_\ell \tag{1}$$

$$A_\ell + A_j \to A_k,\ \ \alpha_{\ell,j;k}\,; \qquad A_k \to A_\ell + A_j,\ \ \beta_{k;\ell,j} \tag{2}$$

$$A_j \to A_k,\ \ \mu_{j;k} \tag{3}$$

More general forms for the reactions that include also arbitrary collisions have been considered for instance in [4]. We consider one specific example in the paper [33] where one of the reactions contains three molecules on the right hand side. We have written to the right end of each equation the parameters characterizing the rates of the chemical reactions for each group of molecules written to the left. More precisely, if the state of the systems is characterized by the set of numbers $\{n_\ell\}_{\ell=1}^N$ the probability for unit of time of having each of the five types of reactions in the equations (1)–(3) is given respectively by the numbers

$$K_\ell,\ \ \lambda_\ell n_\ell,\ \ \alpha_{\ell,j;k} n_\ell \left(n_j - \delta_{\ell,j}\right),\ \ \beta_{k;\ell,j} n_k,\ \ \mu_{j;k} n_j \tag{4}$$

where the term $\delta_{\ell,j}$ is just a combinatorial factor that plays a role only if $\ell = j$. The basic function which will be described throughout the paper is the probability of each of the states of the system and it will be denoted as $p\left(\{n_\ell\}_{\ell=1}^N, t\right)$. Notice that from the mathematical point of view $p \in C\left(\mathbb{R}^+; \mathcal{M}_1\left(\mathbb{N}_*^N\right)\right)$, where from now on $\mathbb{N}_* = \mathbb{N} \cup \{0\}$ and $\mathcal{M}_1\left(\mathbb{N}_*^N\right)$ is the set of probability measures in $\mathbb{N}_*^N$. Notice in particular that this implies $p(\xi, t) \geq 0$ for $\xi \in \mathbb{N}_*^N$ and $\sum_{\xi \in \mathbb{N}_*^N} p(\xi, t) = 1$.

As we indicated in the Introduction we will study in this paper very particular criteria for deterministic behaviour, namely the existence of long switching times in molecular systems. In particular, systems that tend to just one equilibrium distribution will be left completely outside of the consideration in this paper.

3 Systems with many molecules for some of the species: Kramers' dynamics

The case in which there are many molecules in the system has been extensively studied (cf. [6,37,38]). In this case the master equation becomes a Fokker–Planck equation.

We consider a system of reactions in which the number of molecules is very large. More precisely, let us restrict our attention to the case in which we have a system of chemical reactions of the form:

$$\begin{aligned} &A_i + A_j \rightleftarrows A_k \quad : \quad K_{i,j}, \quad \Gamma_k \ , \ \ k = k\,(i,j) \\ &i, j, k \in \{1, \ldots, L\} \end{aligned}$$

There is an easy way of writing a large system of these equations, that is the following:

$$\sum_{j=1}^{L} \nu_{j,\ell} A_j \rightleftarrows 0, \quad \ell = 1, \ldots, M$$

where M is the number of reactions, and the coefficients $\nu_{j,\ell}$ take the values $0, +1, -1$. Let us denote the coefficients for the direct and inverse reaction as K_ℓ, Γ_ℓ respectively. Notice that in principle they depend on the whole distribution of molecules $\{n_j\}$. We will make this dependence explicit by writing $K_\ell\left[\{n_j\}\right]$, $\Gamma_\ell\left[\{n_j\}\right]$.

Then the set of master equations would have the following form:

$$\begin{aligned} \frac{\partial f}{\partial t}\,(n_1, \ldots, n_L) = &-\sum_\ell \left(K_\ell\left[\{n_j\}\right] + \Gamma_\ell\left[\{n_j\}\right]\right) f\,(n_1, \ldots, n_L) \\ &+\sum_\ell K_\ell\left[\{n_j + \nu_{j,\ell}\}\right] f\left(n_1 + \nu_{1,\ell}, \ldots, \ n_j + \nu_{j,\ell}, \ldots, n_L + \nu_{L,\ell}\right) \\ &+\sum_\ell \Gamma_\ell\left[\{n_j - \nu_{j,\ell}\}\right] f\left(n_1 - \nu_{1,\ell}, \ldots, \ n_j - \nu_{j,\ell}, \ldots, n_L - \nu_{L,\ell}\right) \end{aligned} \tag{5}$$

where for simplicity the dependence on time of f is not indicated explicitly. This equation can be reformulated as a discrete equation resembling a second order differential equation. To this end, we define a family of fluxes by means of:

$$\begin{aligned} J_\ell\left(\{n_j\}\right) = &-K_\ell\left[\{n_j + \nu_{j,\ell}\}\right] f\left(n_1 + \nu_{1,\ell}, \ldots, \ n_j + \nu_{j,\ell}, \ldots, n_L + \nu_{L,\ell}\right) \\ &+\Gamma_\ell\left[\{n_j\}\right] f\,(n_1, \ldots, n_L) \end{aligned} \tag{6}$$

and we define a discrete divergence operator as:

$$\begin{aligned} &Div\,(J_\ell)\,(n_1, \ldots, n_L) \\ &\quad = \sum_\ell \left[J_\ell\,(n_1, \ldots, n_L) - J_\ell\left(n_1 - \nu_{1,\ell}, \ldots, \ n_j - \nu_{j,\ell}, \ldots, n_L - \nu_{L,\ell}\right)\right] \end{aligned} \tag{7}$$

Roughly speaking, J_ℓ yields the probability flux from the state $\{n_j\}$ to the state $\{n_j + \nu_{j,\ell}\}$. The divergence operator measures the probability change at the state

$\{n_j\}$ to adjacent states due to all the possible fluxes. Using this notation we can write (5) as;

$$\frac{\partial f}{\partial t}(n_1,\ldots,n_L) + Div(J_\ell) = 0 \tag{8}$$

If the numbers $\{n_j\}$ are large it is possible to approximate the operator Div in (7) as well as the formulas for the fluxes $J_\ell(\{n_j\})$ in (6) using differential operators. More precisely we will write:

$$Div(J_\ell)(n_1,\ldots,n_L) = \sum_\ell \sum_j \nu_{j,\ell} \frac{\partial J_\ell}{\partial n_j}(n_1,\ldots,n_L) \tag{9}$$

On the other hand, in order to approximate the fluxes $J_\ell(\{n_j\})$ we write:

$$\begin{aligned} J_\ell(\{n_j\}) = &-K_\ell[\{n_j+\nu_{j,\ell}\}] f(n_1+\nu_{1,\ell},\ldots,\ n_j+\nu_{j,\ell},\ldots,n_L+\nu_{L,\ell}) \\ &+K_\ell[\{n_j\}] f(n_1,\ldots,n_L) \\ &+\Gamma_\ell[\{n_j\}] f(n_1,\ldots,n_L) - K_\ell[\{n_j\}] f(n_1,\ldots,n_L) \end{aligned}$$

and approximate the discrete operators by means of derivatives:

$$\begin{aligned} J_\ell(\{n_j\}) = &-\sum_j \nu_{j,\ell} \frac{\partial\left(K_\ell[\{n_j\}] f\right)}{\partial n_j}(n_1,\ldots,n_L) \\ &+\left(\Gamma_\ell[\{n_j\}] - K_\ell[\{n_j\}]\right) f(n_1,\ldots,n_L) \end{aligned} \tag{10}$$

Combining the approximations (9), (10) we then obtain the following PDE approximation for (5):

$$\begin{aligned} \frac{\partial f}{\partial t}(n_1,\ldots,n_L) = &\sum_\ell \sum_j \nu_{j,\ell} \frac{\partial}{\partial n_j} \\ &\times \left(\sum_k \nu_{k,\ell} \frac{\partial\left(K_\ell[\{n_j\}] f\right)}{\partial n_k} - \left(\Gamma_\ell[\{n_j\}] - K_\ell[\{n_j\}]\right) f \right)(n_1,\ldots,n_L) \end{aligned} \tag{11}$$

It is important to take into account that (11) is in general a degenerate parabolic equation, due to the fact that the changes of the numbers of $\{n_j\}$ can take place only in the stoichiometric hyperplanes. It is also important to mention that the terms containing second derivatives are smaller if this approximation, that relies on the fact that Taylor's series can be used to approximate the different functions, is valid. The derivation of (11) requires some precise rescaling properties for the chemical coefficients $K_\ell[\{n_j\}]$, $\Gamma_\ell[\{n_j\}]$ in order to apply Taylor's Theorem neglecting higher order corrections. We will precise this type of choice in a particular example later.

Switching times in some equations with the form of (11) can be computed using Kramers' formula (cf. [20,30]). We illustrate this by means of a well known simple example of chemical reactions yielding bistability (cf. [47]):

$$\begin{aligned} 2A &\rightleftharpoons 3A, \quad k_1, \quad k_2 \\ \varnothing &\rightleftharpoons A, \quad k_3, \quad k_4 \end{aligned}$$

where the constants $k_1,\ k_3$ are the chemical constants associated to the direct reactions and $k_2,\ k_4$ the ones associated to the reverse reactions respectively. The stochastic version of this system can be described using the probability of having n molecules in the system. This probability will be denoted as $p\,(n,t)$. The corresponding master equation is:

$$\begin{aligned} \frac{\partial p\,(n)}{\partial t} = &-\left(k_1 n\,(n-1) + k_2 n\,(n-1)\,(n-2) + k_3 + k_4 n\right) p\,(n) \\ &+k_1\,(n-1)\,(n-2)\,p\,(n-1) + k_2\,(n+1)\,n\,(n-1)\,p\,(n+1) \\ &+k_3 p\,(n-1) + k_4\,(n+1)\,p\,(n+1) \end{aligned}$$

where the dependence of p on t is assumed but not explicitly written. This equation can be rewritten as:

$$\frac{\partial p\,(n)}{\partial t} + J\,(n) - J\,(n-1) = 0$$

with:

$$\begin{aligned} -J\,(n) = &\,k_2\,(n+1)\,n\,(n-1)\,p\,(n+1) + k_4\,(n+1)\,p\,(n+1) \\ &-k_1 n\,(n-1)\,p\,(n) - k_3 p\,(n) \end{aligned}$$

We can rewrite $J\,(n)$ as:

$$\begin{aligned} -J\,(n) = &\,k_2\left[(n+1)\,n\,(n-1)\,p\,(n+1) - n\,(n-1)\,(n-2)\,p\,(n)\right] \\ &+k_4\left[(n+1)\,p\,(n+1) - np\,(n)\right] \\ &+\left[k_2 n\,(n-1)\,(n-2) + k_4 n - k_1 n\,(n-1) - k_3\right] p\,(n) \end{aligned}$$

In order to derive a continuous limit we need to choose the coefficients $k_1, \ldots, k_4$ and the number of particles rescaling in a suitable way. More precisely, we will obtain solutions where p can be approximated as:

$$p\,(n,t) = f\,(\xi,t)\,, \quad \xi = \frac{n}{N}$$

and where it is assumed that $f\,(\xi,t)$ converges to a smooth limit function as $N \to \infty$ for ξ of order one. Therefore:

$$p\,(n+1,t) = f\left(\xi + \frac{1}{N}, t\right) \tag{12}$$

Moreover:

$$k_1 = \frac{\alpha_1}{N}, \quad k_2 = \frac{\alpha_2}{N^2}, \quad k_3 = \alpha_3 N, \quad k_4 = \alpha_4$$

We then obtain the following approximations, linearizing in (12) and neglecting terms that formally converge to zero as $N \to \infty$:

$$\begin{aligned} -J(n) &= \alpha_2 \frac{\partial}{\partial \xi}\left[\xi^3 f(\xi,t)\right] + \alpha_4 \frac{\partial}{\partial \xi}\left(\xi f(\xi,t)\right) \\ &\quad + N\left[\alpha_2 \xi^3 + \alpha_4 \xi - \alpha_1 \xi^2 - \alpha_3 - \frac{3\alpha_2 \xi^2}{N} + \frac{\alpha_1 \xi}{N}\right] f(\xi,t) \end{aligned}$$

$$\begin{aligned} &J(n) - J(n-1) \\ &= -\frac{1}{N}\frac{\partial^2}{\partial \xi^2}\left(\left(\alpha_2 \xi^3 + \alpha_4 \xi\right) f(\xi,t)\right) \\ &\quad - \frac{\partial}{\partial \xi}\left(\left[\alpha_2 \xi^3 + \alpha_4 \xi - \alpha_1 \xi^2 - \alpha_3 - \frac{3\alpha_2 \xi^2}{N} + \frac{\alpha_1 \xi}{N}\right] f(\xi,t)\right) \end{aligned}$$

We then obtain the following Fokker–Planck approximation for the master equation:

$$\begin{aligned} \frac{\partial f(\xi,t)}{\partial t} &= \frac{1}{N}\frac{\partial^2}{\partial \xi^2}\left(\left(\alpha_2 \xi^3 + \alpha_4 \xi\right) f(\xi,t)\right) \\ &\quad + \frac{\partial}{\partial \xi}\left(\left[\alpha_2 \xi^3 + \alpha_4 \xi - \alpha_1 \xi^2 - \alpha_3 - \frac{3\alpha_2 \xi^2}{N} + \frac{\alpha_1 \xi}{N}\right] f(\xi,t)\right) \end{aligned}$$

This is a typical problem where Kramers' formula can be applied. Since the terms $-\frac{3\alpha_2 \xi^2}{N} + \frac{\alpha_1 \xi}{N}$ give lower order corrections both to the equilibrium associated to this problem and to the switching times, we will ignore them in the following:

$$\begin{aligned} \frac{\partial f(\xi,t)}{\partial t} &= \frac{1}{N}\frac{\partial^2}{\partial \xi^2}\left(\left(\alpha_2 \xi^3 + \alpha_4 \xi\right) f(\xi,t)\right) \\ &\quad + \frac{\partial}{\partial \xi}\left(\left[\alpha_2 \xi^3 + \alpha_4 \xi - \alpha_1 \xi^2 - \alpha_3\right] f(\xi,t)\right) \end{aligned} \tag{13}$$

Suppose that we choose the coefficients $\alpha_1,\ \alpha_2,\ \alpha_3,\ \alpha_4$ in order to have:

$$P'(\xi_1) > 0, \quad P'(\xi_0) < 0, \quad P'(\xi_2) > 0,$$

where $P(\xi) = \alpha_2 \xi^3 + \alpha_4 \xi - \alpha_1 \xi^2 - \alpha_3$.

Then, there exist an invariant measure having two peaks at the positive roots of the polynomial $P(\xi)$ where $P'(\xi) > 0$. Such positive roots exist for many choices of the coefficients $\alpha_1,\ \alpha_2,\ \alpha_3,\ \alpha_4$, for instance if α_1 is small enough to ensure that

$\left[\alpha_4\xi - \alpha_1\xi^2 - \alpha_3\right]$ has two positive roots and α_2 is then chosen sufficiently small. The equilibrium associated to (13) is given by:

$$f_s(\xi) = C_N \exp\left(-N\int_0^{\xi} \frac{\alpha_2\eta^3 + \alpha_4\eta - \alpha_1\eta^2 - \alpha_3}{\alpha_2\eta^3 + \alpha_4\eta} d\eta\right) \times \frac{1}{\alpha_2\xi^3 + \alpha_4\xi},$$

where C_N is a normalization constant that is chosen to ensure that $\int_0^{\infty} f_s(\xi)\, d\xi = 1$. The computation of switching times cannot be made using the the usual Kramers' formula due to the dependence of the term containing second derivatives in (13) on ξ. However, similar ideas to the ones in [37] yield easily the following approximation of the switching times up to exponential orders:

$$\log(\tau_{1\to 2}) \sim N\int_{\xi_1}^{\xi_0} \frac{\alpha_2\eta^3 + \alpha_4\eta - \alpha_1\eta^2 - \alpha_3}{\alpha_2\eta^3 + \alpha_4\eta} d\eta$$

$$\log(\tau_{2\to 1}) \sim N\int_{\xi_0}^{\xi_2} \frac{\alpha_2\eta^3 + \alpha_4\eta - \alpha_1\eta^2 - \alpha_3}{\alpha_2\eta^3 + \alpha_4\eta} d\eta$$

where $\xi_1 < \xi_0 < \xi_2$ are the three roots of $P(\xi)$ in $\xi > 0$. Notice that we compute two different switching times $\tau_{1\to 2},\ \tau_{2\to 1}$, because in general the switching times depend on the direction in which the transition takes place.

Since the analysis of Kramers' transitions is well understood both at the formal and rigorous level (cf. [17,31,32,39,43,44]), and since this case has been studied repeatedly in the context of chemical systems we will not continue with this study in this paper.

4 Systems with very long switching times with for macromolecules containing many similar pieces

In the next two Sections we study some specific bionetworks containing many different chemical species. In real biochemical networks containing many different elements there could be complex topological links between the different elements of the system. We will restrict our study to some simple examples where the chemical reactions are arranged in some linear chains. Such type of chains have been used often in order to study how the size of the network can influence the response of the system. A deterministic linear chain was studied in [35] in order to study how the sensitivity of the system changes to the chain length. Linear stochastic chains have been considered in [1–3].

We now describe a simple example of an ideal macromolecule that can produce very long switching times due to the fact the formation of such a molecule requires the addition of many similar molecules. The example will be very simple, but we just wish to emphasize the fact that random fluctuations are able to create some kind of

directionality in complex molecules and then long time switches between two different states of a biochemical network, even in the absence of strong interactions between the different portions of the network. As a matter of fact, the evolution of the states of the system will take place by means of a random walk with drifting. We will assume that the reaction rates are of order one, therefore the long switching times will not be due to the smallness of some of the coefficients, but to the fact that there are a very long number of intermediate species that must be formed for the switching to take place.

The system of reactions would be:

$$X \rightleftarrows XA_1 \rightleftarrows XA_2 \rightleftarrows \cdots \rightleftarrows XA_N \tag{14}$$

$$X \rightleftarrows A_1X \rightleftarrows A_2X \rightleftarrows \cdots \rightleftarrows A_NX \tag{15}$$

where we indicate by XA_k the combination of a macromolecule X with k molecules of type A and by A_kX a similar combination of molecules but in a different configurational shape. We assume that the transition between the different molecular structures can take place only through the sequence of steps (14), (15). Let us write:

$$B_k = XA_k, \quad B_{-k} = A_kX, \quad k = 0, 1, \ldots, N \tag{16}$$

Notice that by definition $B_0 = A_0X = XA_0 = X$. We can then write the system of chemical reactions (14), (15) as:

It is easier perhaps to write it as:

$$B_{-N} \underset{\beta^-_{-(N-1)}}{\overset{\alpha^-_{-(N-1)}}{\rightleftarrows}} \cdots \underset{\beta^-_{-k}}{\overset{\alpha^-_{-k}}{\rightleftarrows}} B_{-k} \rightleftarrows \cdots \underset{\beta^-_0}{\overset{\alpha^-_0}{\rightleftarrows}} B_0 \underset{\alpha^+_0}{\overset{\beta^+_0}{\rightleftarrows}} \cdots \rightleftarrows$$
$$B_k \underset{\alpha^+_k}{\overset{\beta^+_k}{\rightleftarrows}} B_{k+1} \rightleftarrows \cdots \underset{\alpha^+_{N-1}}{\overset{\beta^+_{N-1}}{\rightleftarrows}} B_N. \tag{17}$$

where we also include the values of the reaction constants. Notice that we write for convenience $B_k \underset{\alpha^+_k}{\overset{\beta^+_k}{\rightleftarrows}} B_{k+1}$ instead of:

$$B_k + A \underset{\alpha^+_k}{\overset{\beta^+_k}{\rightleftarrows}} B_{k+1}, \quad k = 0, 1, 2, \ldots, N-1$$

$$B_k + A \underset{\alpha^-_k}{\overset{\beta^-_k}{\rightleftarrows}} B_{k-1}, \quad k = 0, -1, -2, \ldots, -(N-1)$$

Let the number of molecules of B_k be $n_{B_k} = n_k$. Let

$$\xi = (n_k)_{k=-N}^{k=N} \in (\mathbb{N}^*)^{2N+1}, \quad n_l(\xi) = n_l.$$

We define the following operators acting on $(\mathbb{N}^*)^{2N+1}$ as follows.

$$\mathcal{T}_l^+, \mathcal{T}_l^-, \mathcal{S}_l^+, \mathcal{T}_l^- : (\mathbb{N}^*)^{2N+1} \to (\mathbb{N}^*)^{2N+1},$$

$$\mathcal{T}_l^+(\xi) = \mathcal{T}_l^+(n_k) = (n_k + \delta_{k,l} - \delta_{k,l+1}),\ l = 0, \ldots, N-1,$$
$$\mathcal{T}_l^-(\xi) = \mathcal{T}_l^-(n_k) = (n_k + \delta_{k,-l} - \delta_{k,-(l+1)}),\ l = 0, \ldots, N-1,$$
$$\mathcal{S}_l^+(\xi) = \mathcal{S}_l^+(n_k) = (n_k - \delta_{k,l} + \delta_{k,l+1}),\ l = 0, \ldots, N-1,$$
$$\mathcal{S}_l^-(\xi) = \mathcal{S}_l^-(n_k) = (n_k - \delta_{k,-l} + \delta_{k,-(l+1)}),\ l = 0, \ldots, N-1.$$

Then we note that

$$\mathcal{T}_l^+ = \left(\mathcal{S}_l^+\right)^{-1},\ \mathcal{T}_l^- = \left(\mathcal{S}_l^-\right)^{-1}.$$

Let the probability of the phase state ξ at time t be $p(\xi, t)$. Then p satisfies the following master equation:

$$\begin{aligned}\partial_t p(\xi,t) = &-\sum_{l=0}^{N-1}\left[\beta_l^+ n_l(\xi) + \alpha_l^+ n_{l+1}(\xi) + \beta_l^- n_{-l}(\xi) + \alpha_l^- n_{-(l+1)}(\xi)\right] p(\xi,t)\\ &+\sum_{l=0}^{N-1}\beta_l^+ n_l\left(\mathcal{T}_l^+(\xi)\right) p\left(\mathcal{T}_l^+(\xi),t\right) + \sum_{l=0}^{N-1}\alpha_l^+ n_{l+1}\left(\mathcal{S}_l^+(\xi)\right) p\left(\mathcal{S}_l^+(\xi),t\right)\\ &+\sum_{l=0}^{N-1}\beta_l^- n_{-l}\left(\mathcal{T}_l^-(\xi)\right) p\left(\mathcal{T}_l^-(\xi),t\right)\\ &+\sum_{l=0}^{N-1}\alpha_l^- n_{-(l+1)}\left(\mathcal{S}_l^-(\xi)\right) p\left(\mathcal{S}_l^-(\xi),t\right). \end{aligned} \tag{18}$$

We can assume that there is a "drifting term" pointing towards the states XA_N, A_NX in the sense that at least in some average sense the probability of the state closer to these extremes is larger than the probability of the other states.

It is easier to understand the dynamics described by (18) noticing that we can describe the state of the system B_k as the position of a particle moving in a biased random walk. The probability of finding the system in the state B_k is given by the following system of equations:

$$\begin{aligned}\frac{dp(B_k,t)}{dt} &= -\left(\beta_k^+ + \alpha_{k-1}^+\right) p(B_k,t) + \beta_{k-1}^+ p(B_{k-1},t) + \alpha_k^+ p(B_{k+1},t),\\ &\quad k = 1, 2, \ldots, N\\ \frac{dp(B_0,t)}{dt} &= -\left(\beta_0^+ + \beta_0^-\right) p(B_0,t) + \alpha_0^+ p(B_1,t) + \alpha_0^- p(B_{-1},t)\\ \frac{dp(B_k,t)}{dt} &= -\left(\beta_k^- + \alpha_{k+1}^-\right) p(B_k,t) + \beta_{k+1}^- p(B_{k+1},t) + \alpha_k^- p(B_{k-1},t),\\ &\quad k = -1, -2, \ldots, -N\end{aligned} \tag{19}$$

where we assume $\alpha_N^+ = \alpha_N^- = 0$, for simplicity.

The system (19) that describes the dynamics of (18) is just a biased random walk in a one-dimensional lattice. The chemical coefficients tend to push the system towards both extreme points at $k = N, -N$.

The steady states of (19) satisfy:

$$\begin{aligned} 0 &= -\left(\beta_k^+ + \alpha_{k-1}^+\right) p\left(B_k\right) + \beta_{k-1}^+ p\left(B_{k-1}\right) + \alpha_k^+ p\left(B_{k+1}\right), \quad k = 1, 2, \ldots, N \\ 0 &= -\left(\beta_0^+ + \beta_0^-\right) p\left(B_0\right) + \alpha_0^+ p\left(B_1\right) + \alpha_0^- p\left(B_{-1}\right) \\ 0 &= -\left(\beta_k^- + \alpha_{k+1}^-\right) p\left(B_k\right) + \beta_{k+1}^- p\left(B_{k+1}\right) + \alpha_k^- p\left(B_{k-1}\right), \quad k = -1, -2, \ldots, -N \end{aligned} \tag{20}$$

We will assume the following symmetry property for the coefficients in order to simplify the analysis:

$$\begin{aligned} \alpha_k^+ &= \alpha_{-k}^-, \quad k = 0, 1, 2, \ldots, (N-1) \\ \beta_k^+ &= \beta_{-k}^-, \quad k = 0, 1, 2, \ldots, (N-1) \end{aligned}$$

Therefore, the steady state distribution satisfies the following symmetry property:

$$p\left(B_k\right) = p\left(B_{-k}\right), \quad k = 0, 1, 2, \ldots, N \tag{21}$$

The first equation in (20) can be written in a more convenient form:

$$J_k = J_{k-1}, \quad k = 1, 2, \ldots (N-1)$$

where:

$$J_k = \alpha_k^+ p\left(B_{k+1}\right) - \beta_k^+ p\left(B_k\right), \quad k = 1, 2, \ldots (N-1)$$

We are interested in computing solutions without probability fluxes. Therefore $J_k = 0$. Then:

$$p\left(B_{k+1}\right) = \frac{\beta_k^+}{\alpha_k^+} p\left(B_k\right), \quad k = 1, 2, \ldots (N-1) \tag{22}$$

that must be solved using the values of $p\left(B_1\right)$. We can compute $p\left(B_1\right)$ using the second equation in (20) as well as the symmetry condition (21). Therefore we have

$$p\left(B_1\right) = \frac{\beta_0^+ + \beta_0^-}{\alpha_0^+ + \alpha_0^-} p\left(B_0\right) = \frac{\beta_0^+}{\alpha_0^+} p\left(B_0\right) \tag{23}$$

We can solve (22) iteratively

$$p\left(B_{-k}\right) = p\left(B_k\right) = \left[\prod_{\ell=0}^{k-1} \left(\frac{\beta_\ell^+}{\alpha_\ell^+}\right)\right] p\left(B_0\right), \quad k = 2, 3, \ldots, N. \tag{24}$$

Finally imposing the normalization condition $\sum_{k=-N}^{N} p\left(B_k\right)=1$ we obtain

$$p\left(B_0\right)=\frac{1}{1+2\left(\frac{\beta_0^+ +\beta_0^-}{\alpha_0^+ +\alpha_0^-}\right)+2\left(\frac{\beta_0^+ +\beta_0^-}{\alpha_0^+ +\alpha_0^-}\right)\sum_{k=2}^{N}\prod_{\ell=1}^{k-1}\left(\frac{\beta_\ell^+}{\alpha_\ell^+}\right)} \tag{25}$$

Suppose now that we assume:

$$\frac{\beta_k^+}{\alpha_k^+}\geq\theta>1,\quad \frac{\beta_k^-}{\alpha_k^-}\geq\theta>1 \tag{26}$$

or some weaker assumption like:

$$\prod_{\ell=1}^{N-1}\left(\frac{\beta_\ell^+}{\alpha_\ell^+}\right)\geq\theta^N,\quad \prod_{\ell=1}^{N-1}\left(\frac{\beta_\ell^-}{\alpha_\ell^-}\right)\geq\theta^N,\quad \theta>1 \tag{27}$$

Any of the assumptions imply the formation of two peaks near the states $k=-N$ and $k=N$ due to (25). The probability of finding the system near the states B_N and B_{-N} would be much larger than in the regions close to B_0. The switching times between both states would be exponentially large. On the other hand, the state of the system is "stochastic", because during most of the time the system is not either at B_N or B_{-N}, but in some of the states nearby. The fluctuations would be of order one, but due to the large size of the chain connecting the states, it would take a very long time to make a switching between them.

We now estimate the switching times associated to this system. To this end, a generalization of Kramers' formula for systems like (19) must be found. Suppose that the initial probability distribution is given by

$$p\left(B_k,0\right)=\delta_{k,N}$$

Our goal is to solve (19) with this initial probability distribution and estimate the times that it takes to have probabilities of order one in the range of values where $k\leq-\frac{N}{2}$. In order to solve this problem we introduce the following change of variables [cf. (24)]:

$$p\left(B_k,t\right)=\varphi\left(B_k,t\right)\theta_k \tag{28}$$

where:

$$\theta_{-k}=\theta_k=\prod_{\ell=0}^{k-1}\left(\frac{\beta_\ell^+}{\alpha_\ell^+}\right),\quad k=1,2,3,\ldots,N$$
$$\theta_0=1$$

These formulas imply:

$$\frac{\theta_{k+1}}{\theta_k} = \frac{\beta_k^+}{\alpha_k^+}, \quad k = 1, 2, 3, 4, \ldots, \quad \frac{\theta_{k-1}}{\theta_k} = \frac{\alpha_{k-1}^+}{\beta_{k-1}^+}, \quad k = 2, 3, 4, \ldots \tag{29}$$

Then, plugging (28) into (19) and using (29) as well as the symmetry property

$$\theta_{-k} = \theta_k, \quad k = 1, 2, 3, \ldots$$

we obtain after some computations, and assuming the symmetry property

$$\frac{d\varphi(B_k,t)}{dt} = \alpha_{k-1}^+ \left[\varphi(B_{k-1},t) - \varphi(B_k,t)\right] + \beta_k^+ \left[\varphi(B_{k+1},t) - \varphi(B_k,t)\right], \quad k = 1, 2, 3, \ldots, N \tag{30}$$

$$\frac{d\varphi(B_k,t)}{dt} = \alpha_{k+1}^- \left[\varphi(B_{k+1},t) - \varphi(B_k,t)\right] + \beta_k^- \left[\varphi(B_{k-1},t) - \varphi(B_k,t)\right], \quad k = -1, -2, \ldots, -N \tag{31}$$

$$\frac{d\varphi(B_0,t)}{dt} = \beta_0^+ \left[\varphi(B_1,t) - \varphi(B_0,t)\right] + \beta_0^+ \left[\varphi(B_{-1},t) - \varphi(B_0,t)\right]. \tag{32}$$

In the derivation of the equation for $\varphi(B_0,t)$ we have used the identities $\frac{\theta_0}{\theta_1} = \frac{\alpha_0^+}{\beta_0^+}$, $\frac{\theta_0}{\theta_{-1}} = \frac{\alpha_0^+}{\beta_0^+}$.

We now derive the analogous of Kramers' formula for the system (30)–(32). Suppose that (26) or (27) holds. Then, assuming that the differences $\left[\varphi(B_{k+1},t) - \varphi(B_k,t)\right]$ can be approximated by derivatives, we can see that the "convective" effects in (30)–(32) tend to propagate the values of φ from the points $k = \pm N$ towards smaller values of k. Therefore, assuming that the chemical coefficients are of order one, we expect that in times t of order N, the function φ should behave like a constant in each of the regions $\{k > 0\}$, and $\{k < 0\}$. More precisely, these approximations can be expected to be valid for $1 \ll |k| \ll N$. We will then write the approximations

$$\varphi(B_k,t) = \Phi_+(t), \quad k > 0, \quad 1 \ll |k| \ll N \tag{33}$$

$$\varphi(B_k,t) = \Phi_-(t), \quad k < 0, \quad 1 \ll |k| \ll N \tag{34}$$

On the other hand, we can expect to have approximations to steady solutions of (30)–(32) for some time scales t of order N (or smaller), in the region where $|k| = O(1)$. These steady states satisfy

$$\alpha_{k-1}^+ \left[\psi(B_{k-1}) - \psi(B_k)\right] + \beta_k^+ \left[\psi(B_{k+1}) - \psi(B_k)\right] = 0, \quad k \geq 1$$

$$\alpha_{k+1}^- \left[\psi(B_{k+1}) - \psi(B_k)\right] + \beta_k^- \left[\psi(B_{k-1}) - \psi(B_k)\right] = 0, \quad k \leq -1$$

$$\alpha_0^+ \left[\psi(B_1) - \psi(B_0)\right] + \alpha_0^- \left[\psi(B_{-1}) - \psi(B_0)\right] = 0$$

Two linearly independent solutions of this system are

$$\psi_1(B_k) = 1 \quad , \quad k = 0, \pm 1, \pm 2, \ldots$$

$$\psi_2(B_k) = \frac{1 + \sum_{\ell=1}^{k-1} \prod_{m=1}^{\ell} \left(\frac{\alpha_{m-1}^+}{\beta_m^+} \right)}{1 + \sum_{\ell=1}^{\infty} \prod_{m=1}^{\ell} \left(\frac{\alpha_{m-1}^+}{\beta_m^+} \right)}, \quad k \geq 1,$$

$$\psi_2(B_k) = -\psi_2(B_{-k}), \quad k \leq -1, \quad \psi_2(B_0) = 0 \tag{35}$$

where we assume that the sequences of chemical coefficients $\{\alpha_k^{\pm}\}$, $\{\beta_k^{\pm}\}$ are defined for arbitrarily large values of $|k|$. Notice that we have normalized ψ_2 in such a way that

$$\lim_{|k| \to \infty} \psi_2(B_k) = \pm 1$$

Using (33), (34) as matching conditions we obtain the following approximation for $\varphi(B_k, t)$ for $|k|$ of order one

$$\varphi(B_k, t) = \frac{1}{2} \left[(\Phi_+(t) + \Phi_-(t)) \psi_1(B_k) + (\Phi_+(t) - \Phi_-(t)) \psi_2(B_k) \right], \quad k = 0, \pm 1, \pm 2, \ldots \tag{36}$$

The generalization of Kramers' formula in which we are interested must provide an equation for the rate of change of the quantities $\Phi_+(t)$, $\Phi_-(t)$ for time scales much longer than N. Such a formula will be derived with the following argument, that essentially generalizes the analogous argument yielding Kramers' formula for Fokker–Planck equations. Let us write:

$$\bar{\Delta}_k^+ = \prod_{m=1}^{k} \left(\frac{\alpha_{m-1}^+}{\beta_m^+} \right), \quad k \geq 1, \quad \bar{\Delta}_0^+ = 1, \quad \bar{\Delta}_{-k}^- = -\bar{\Delta}_k^+, \quad k \leq -1, \quad \bar{\Delta}_0^- = -1 \,,$$

$$\Delta_k^+ = \varphi(B_{k+1}, t) - \varphi(B_k, t), \quad k \geq 0 \,,$$
$$\Delta_k^- = \varphi(B_{k-1}, t) - \varphi(B_k, t), \quad k \leq 0.$$

Then, the equations (30)–(32) can be rewritten as:

$$\frac{d\varphi(B_k, t)}{dt} = \beta_k^+ \Delta_k^+ - \alpha_{k-1}^+ \Delta_{k-1}^+, \quad k = 1, 2, 3, \ldots, N \tag{37}$$

$$\frac{d\varphi(B_k, t)}{dt} = \beta_k^- \Delta_k^- - \alpha_{k+1}^- \Delta_{k+1}^-, \quad k = -1, -2, -3, \ldots, -N \tag{38}$$

$$\frac{d\varphi(B_0, t)}{dt} = \beta_0^+ \left(\Delta_0^+ + \Delta_0^- \right) \tag{39}$$

$$\frac{d\varphi\left(B_k,t\right)}{dt}=\beta_k^+\bar{\Delta}_k^+\left(\frac{\Delta_k^+}{\bar{\Delta}_k^+}-\frac{\Delta_{k-1}^+}{\bar{\Delta}_{k-1}^+}\right),\quad k=1,2,3,\ldots,N \tag{40}$$

$$\frac{d\varphi\left(B_k,t\right)}{dt}=\beta_k^-\bar{\Delta}_k^-\left(\frac{\Delta_k^-}{\bar{\Delta}_k^-}-\frac{\Delta_{k+1}^-}{\bar{\Delta}_{k+1}^-}\right),\quad k=-1,-2,-3,\ldots,-N \tag{41}$$

$$\frac{d\varphi\left(B_0,t\right)}{dt}=\beta_0^+\left(\Delta_0^++\Delta_0^-\right) \tag{42}$$

Dividing (40) by $\beta_k^+\bar{\Delta}_k^+$ and adding for all the values of k we obtain

$$\frac{d}{dt}\left(\sum_{k=1}^{N}\frac{\varphi\left(B_k,t\right)}{\beta_k^+\bar{\Delta}_k^+}\right)=\sum_{k=1}^{N}\left(\frac{\Delta_k^+}{\bar{\Delta}_k^+}-\frac{\Delta_{k-1}^+}{\bar{\Delta}_{k-1}^+}\right)=\frac{\Delta_N^+}{\bar{\Delta}_N^+}-\frac{\Delta_0^+}{\bar{\Delta}_0^+}=-\frac{\Delta_0^+}{\bar{\Delta}_0^+} \tag{43}$$

where we use the fact that $\Delta_N^+=0$ due to the absence of particle fluxes beyond the maximal particle.

Due to the fact that $\bar{\Delta}_k^+$ decreases exponentially as $k\to\infty$ and since $\varphi\left(B_k,t\right)$ approaches a constant for large k, it follows that the main contribution to the sum in the first term of (43) is due to the terms with $k\gg 1$. We can then use the approximation (33) to obtain

$$\left(\sum_{k=1}^{N}\frac{1}{\beta_k^+\bar{\Delta}_k^+}\right)\frac{d\Phi_+(t)}{dt}=-\frac{\Delta_0^+}{\bar{\Delta}_0^+}$$

and using the approximation (36) we obtain

$$\frac{d\Phi_+(t)}{dt}=-\left(\sum_{k=1}^{N}\frac{1}{\beta_k^+\bar{\Delta}_k^+}\right)^{-1}\left[\frac{\psi_2\left(B_1\right)-\psi_2\left(B_0\right)}{2\bar{\Delta}_0^+}\right]\left(\Phi_+\left(t\right)-\Phi_-(t)\right). \tag{44}$$

A similar computation yields:

$$\frac{d\Phi_-(t)}{dt}=-\left(\sum_{k=-N}^{-1}\frac{1}{\beta_k^-\bar{\Delta}_k^-}\right)^{-1}\left[\frac{\psi_2\left(B_{-1}\right)-\psi_2\left(B_0\right)}{2\bar{\Delta}_0^-}\right]\left(\Phi_+\left(t\right)-\Phi_-(t)\right)$$

and using the asymmetric and symmetric properties of $\bar{\Delta}_0^-$, $\bar{\Delta}_0^+$, β_k^+ and ψ_2 we obtain

$$\frac{d\Phi_-(t)}{dt}=\left(\sum_{k=1}^{N}\frac{1}{\beta_k^+\bar{\Delta}_k^+}\right)^{-1}\left[\frac{\psi_2\left(B_1\right)-\psi_2\left(B_0\right)}{2\bar{\Delta}_0^+}\right]\left(\Phi_+\left(t\right)-\Phi_-(t)\right). \tag{45}$$

Subtracting (44), (45) we obtain

$$\frac{d\left(\Phi_+(t)-\Phi_-(t)\right)}{dt}=-\left(\sum_{k=1}^{N}\frac{1}{\beta_k^+\bar{\Delta}_k^+}\right)^{-1}\left[\frac{\psi_2\left(B_1\right)-\psi_2\left(B_0\right)}{\bar{\Delta}_0^+}\right]\left(\Phi_+\left(t\right)-\Phi_-(t)\right).$$

Since $\left(\psi_2\left(B_1\right)-\psi_2\left(B_0\right)\right)>0$ we obtain that $\left(\Phi_+(t)-\Phi_-(t)\right)$ approaches zero for long times. The characteristic time scale is given by

$$\frac{\bar{\Delta}_0^+}{\left(\psi_2\left(B_1\right)-\psi_2\left(B_0\right)\right)}\sum_{k=1}^{N}\frac{1}{\beta_k^+\bar{\Delta}_k^+}=\frac{1}{\left(\psi_2\left(B_1\right)-\psi_2\left(B_0\right)\right)}\sum_{k=1}^{N}\prod_{l=1}^{k-1}\left(\frac{\beta_l^+}{\alpha_l^+}\right).$$

This number is exponentially large on N due to the growth assumptions in the quotients $\frac{\beta_l^+}{\alpha_l^+}$.

The detailed analysis of the conditions on the chemical coefficients yielding exponential switching times would require a more careful study.

5 Large chemical networks that can produce bistability and long switching times

The goal is to show that it is possible to obtain large switching times for a system with a large number of species, having a finite number of molecules of each type of species, and having coefficients of order one for all the chemical reactions. The goal is to study the following system of equations. We assume that by means of the attachment of a given monomer we can have a sequence of nonidentical molecules

$$B_0 \rightleftarrows B_1 \rightleftarrows B_2 \rightleftarrows \cdots \rightleftarrows B_N \tag{46}$$

$$B_0 \rightleftarrows B_1 \rightleftarrows B_2 \rightleftarrows \cdots \rightleftarrows \ B_N \tag{47}$$

Then we have

$$B_k + A \underset{\alpha_k^+}{\overset{\beta_k^+}{\rightleftarrows}} B_{k+1}\,, \quad k=1,2,3,\ldots$$

$$B_{-k} + A \underset{\alpha_k^-}{\overset{\beta_k^-}{\rightleftarrows}} B_{-(k+1)}\,, \quad k=1,2,3,\ldots$$

We assume that the molecules $B_{-k},\ B_k$ produce receptors $R^-,\ R^+$ respectively

$$B_k \to^{\lambda_k} B_k + R^+, \quad k=1,2,3,\ldots$$

$$B_{-k} \to^{\lambda_k} B_{-k} + R^-, \quad k=1,2,3,\ldots$$

$$B_{-k} + R^+ \to^{\mu_k} B_0, \quad k=1,2,3,\ldots$$

$$B_k + R^- \to^{\mu_k} B_0, \quad k=1,2,3,\ldots$$

There is also spontaneous degradation

$$R^+ \to^{\theta} \emptyset$$
$$R^- \to^{\theta} \emptyset$$

The transitions (46), (47) could have different meanings. They could be due to the addition of some monomer a at specific molecular sites, or to a change of molecular configuration, or any other fact. We will not be concerned with the details of the process producing the transitions between these different states.

We will assume that there are L elements of this type of system, where L is a number of order one. The state of each of the elements is basically determined by one variable B_k that is active (or more precisely by the index k that is active at each time). The system is dynamic and the variable k is really a stochastic variable changing in time.

The idea of the analysis is the following. Suppose first that there is no long range inhibition (therefore that there are no receptors $R^+,\ R^-$). Then, the system is just the motion of a set of L independent particles in a random walk. We choose the probability transitions of the random walk to produce bias in specific directions. In particular, we can assume, as in the random graph indicated above, that the bias is trying to push the state of the networks close to the points B_N and B_{-N}.

The problem is the following. If the L systems are working without any interaction, and the probabilities of the system moving towards the states $B_N,\ B_{-N}$ are similar, then the L systems would be more or less evenly distributed among both final states. This would be the case in the system studied in Sect. 4 and that would yield just L independent systems.

However, the situation could change in the presence of interactions. The idea is that a sufficiently strong inhibitory effect should be able to eliminate one of the two possible peaks. The conjecture is the following. In the absence of inhibitory effects (or with small interaction) the measure describing the equilibrium equations for the system above, should be the following. Suppose that, under sufficiently strong drifting, the equilibrium values for a system with strong tendency to move towards $\ell = 0$ are given by the set of numbers

$$\beta_\ell \geq 0, \qquad \ell = 0, 1, 2, \ldots$$

We need to approximate the invariant measure associated to the system of equations above using the following formula. In the case of absence of interactions, the invariant measure can be expected to be obtained by distributing the L particles among the two peaks. Suppose that the situation is symmetric for the moment. Then, the L molecules are distributed according to a binomial distribution with equal probabilities. The number of molecules in each side would be $N_-,\ N_+$ respectively, with probabilities

$$\binom{L}{N_+} \left(\frac{1}{2}\right)^{N_+} \left(\frac{1}{2}\right)^{L-N_+}$$

On the other hand, the distribution among the states $k = -N, -(N-1), \ldots$ or $k = N,\ (N-1),\ (N-2), \ldots$ would be obtained by using a multinomial distribution. Therefore, if the number of particles near $k = N$ is N_+ we would obtain a probability distribution

$$\frac{(N_+)!}{n_N! n_{N-1}! \ldots} \beta_0^{n_N} \beta_1^{n_{N-1}} \ldots$$

and a similar distribution near $k = -N$. Therefore, in the purely random case (without inhibitory effects) we can expect the invariant measure to be, as $N \to \infty$

$$\sum_{N_+=0}^{L} \binom{L}{N_+} \left(\frac{1}{2}\right)^{N_+} \left(\frac{1}{2}\right)^{L-N_+} \left[\frac{(N_+)!}{n_N! n_{N-1}! \ldots} \left(\beta_0^{n_N} \beta_1^{n_{N-1}} \ldots\right) + \frac{(L-N_+)!}{n_{-N}! n_{-N+1}! \ldots} \left(\beta_0^{n_{-N}} \beta_1^{n_{-N+1}} \ldots\right)\right] \tag{48}$$

where in each of the sums we have $n_N + n_{N-1} + \cdots = N_+$ and $n_{-N} + n_{-N+1} + \cdots = N_-$ respectively.

On the contrary, in the case of strong inhibitory effects, if the inhibition is able to eliminate completely the other state we would obtain the following invariant measure

$$\frac{1}{2}\left[\frac{(L)!}{n_N! n_{N-1}! \ldots} \left(\beta_0^{n_N} \beta_1^{n_{N-1}} \ldots\right) + \frac{(L)!}{n_{-N}! n_{-N+1}! \ldots} \left(\beta_0^{n_{-N}} \beta_1^{n_{-N+1}} \ldots\right)\right] \tag{49}$$

with the constraints $n_N + n_{N-1} + \cdots = L,\ n_{-N} + n_{-N+1} + \cdots = L$.

We will check numerically that the measures (48), (49) describe the stationary measure associated to the system under consideration in the absence of inhibitory effects or in their presence respectively.

Since each of the subsystems is a biased random walk, we describe it using the state $k \in \{-N, \ldots, N\} \equiv \mathcal{S}_N$ instead of the numbers n_l. Let us denote as $\eta_k,\ k = 1, \ldots, L$ the state of each of the subsystems. Therefore, the state of the complete system, including the repressors can be described by means of

$$\xi = \left(\eta_1, \ldots, \eta_L, n^+, n^-\right) \in (\mathcal{S}_N)^L \times (\mathbb{N}^*)^2 \equiv \mathcal{E}$$

We then define the transition operators by means of the following

$$\mathcal{T}_\ell^+, \mathcal{T}_\ell^-, \mathcal{S}_\ell^+, \mathcal{S}_\ell^- : \mathcal{E} \to \mathcal{E},$$

$$\mathcal{T}_\ell^+(\xi) = \mathcal{T}_\ell^+\left(\eta_\ell, n^+, n^-\right) = (\eta_\ell + 1, n^+, n^-),\ \ell = 1, \ldots, L$$
$$\mathcal{T}_\ell^-(\xi) = \mathcal{T}_\ell^-\left(\eta_\ell, n^+, n^-\right) = (\eta_\ell - 1, n^+, n^-),\ l = 1, \ldots, L$$

This operators just describe the displacement of the state of each of the subsystems in a random biased walk.

On the other hand we introduce additional operators to describe the change in the number of repressor molecules

$$\mathcal{U}^+ : \mathcal{E} \to \mathcal{E}, \;\; \mathcal{U}^- : \mathcal{E} \to \mathcal{E}, \;\; \mathcal{V}^+ : \mathcal{E} \to \mathcal{E}, \mathcal{V}^- : \mathcal{E} \to \mathcal{E}$$

$$\mathcal{U}^+ \left(\eta_\ell, n^+, n^-\right) = \left(\eta_\ell, n^+ + 1, n^-\right), \quad \mathcal{U}^- \left(\eta_\ell, n^+, n^-\right) = \left(\eta_\ell, n^+, n^- + 1\right)$$

$$\begin{aligned} \mathcal{V}^+ \left(\eta_\ell, n^+, n^-\right) &= \left(\eta_\ell, n^+ - 1, n^-\right), \; n^+ \geq 1, \quad \mathcal{V}^- \left(\eta_\ell, n^+, n^-\right) \\ &= \left(\eta_\ell, n^+, n^- - 1\right), \quad n^- \geq 1 \end{aligned}$$

Finally we need one operator to describe the inhibitory effect of the repressers over some of the molecules

$$\mathcal{Z}^+_{k,\ell} : \mathcal{E} \to \mathcal{E}, \;\; \mathcal{Z}^-_{k,\ell} : \mathcal{E} \to \mathcal{E}, \;\; k \in \mathcal{S}_N \setminus \{0\}, \;\; \ell = 1, \ldots, L$$

$$\begin{aligned} &\mathcal{Z}^+_{k,\ell} \left(\eta_1, \ldots, \eta_{\ell-1}, 0, \eta_{\ell+1}, \ldots, \eta_L, n^+, n^-\right) \\ &\quad = \left(\eta_1, \ldots, \eta_{\ell-1}, -k, \eta_{\ell+1}, \ldots, \eta_L, n^+ + 1, n^-\right) \\ &\mathcal{Z}^-_{k,\ell} \left(\eta_1, \ldots, \eta_{\ell-1}, 0, \eta_{\ell+1}, \ldots, \eta_L, n^+, n^-\right) \\ &\quad = \left(\eta_1, \ldots, \eta_{\ell-1}, k, \eta_{\ell+1}, \ldots, \eta_L, n^+, n^- + 1\right) \end{aligned}$$

The evolution of the probability distribution associated to the system (46), (47) is then given by

$$\begin{aligned} \partial_t p\left(\xi, t\right) = &- \sum_{\ell=1}^{N} \left[A^+_\ell\left(\xi\right) + B^+_\ell\left(\xi\right) + A^-_\ell\left(\xi\right) + B^-_\ell\left(\xi\right)\right] p\left(\xi, t\right) \\ &- \sum_{\ell=1}^{N} \left(\Lambda^+_\ell\left(\xi\right) + \Lambda^-_\ell\left(\xi\right)\right) p\left(\xi, t\right) \\ &- \theta \sum_{\ell=1}^{N} \left(n^+ + n^-\right) p\left(\xi, t\right) - \sum_{\ell=1}^{N} \left(\Omega^+_k\left(\xi\right) n^+ + \Omega^-_k\left(\xi\right) n^-\right) p\left(\xi, t\right) \\ &+ \sum_{\ell=1}^{N} \left[A^+_\ell\left(\mathcal{T}^+_\ell\left(\xi\right)\right) p\left(\mathcal{T}^+_\ell\left(\xi\right), t\right) + A^-_\ell\left(\mathcal{T}^-_\ell\left(\xi\right)\right) p\left(\mathcal{T}^-_\ell\left(\xi\right), t\right)\right] \\ &+ \sum_{\ell=1}^{N} \left[B^+_\ell\left(\mathcal{T}^-_\ell\left(\xi\right)\right) p\left(\mathcal{T}^-_\ell\left(\xi\right), t\right) + B^-_\ell\left(\mathcal{T}^+_\ell\left(\xi\right)\right) p\left(\mathcal{T}^+_\ell\left(\xi\right), t\right)\right] \\ &+ \sum_{\ell=1}^{N} \left[\Lambda^+_\ell\left(\mathcal{V}^+\left(\xi\right)\right) p\left(\mathcal{V}^+\left(\xi\right), t\right) + \Lambda^-_\ell\left(\mathcal{V}^-\left(\xi\right)\right) p\left(\mathcal{V}^-\left(\xi\right), t\right)\right] \end{aligned}$$

$$+\theta\sum_{\ell=1}^{N}\left(n^{+}+1\right)p\left(\mathcal{U}^{+}(\xi),t\right)+\theta\sum_{\ell=1}^{N}\left(n^{-}+1\right)p\left(\mathcal{U}^{-}(\xi),t\right)$$
$$+\sum_{\ell=1}^{N}\sum_{k=-N}^{N}\left[\Omega_{\ell}^{+}\left(\mathcal{Z}_{k,\ell}^{+}(\xi)\right)\left(n^{+}+1\right)p\left(\mathcal{Z}_{k,\ell}^{+}(\xi),t\right)\right.$$
$$\left.+\Omega_{k}^{-}\left(\mathcal{Z}_{k,\ell}^{-}(\xi)\right)\left(n^{-}+1\right)p\left(\mathcal{Z}_{k,\ell}^{-}(\xi),t\right)\right], \tag{50}$$

where

$$A_{\ell}^{+}(\xi)=A_{\ell}^{+}\left(\eta_{\ell},n^{+},n^{-}\right)=\alpha_{k}^{+}\ \text{ if }\ \eta_{\ell}-1=k=0,1,\ldots,N,\ \ \ell=1,\ldots,L$$
$$A_{\ell}^{-}(\xi)=A_{\ell}^{-}\left(\eta_{\ell},n^{+},n^{-}\right)=\alpha_{k}^{-}\ \text{ if }\ \eta_{\ell}+1=k=0,-1,\ldots,-N,\ \ \ell=1,\ldots,L$$

$$B_{\ell}^{+}(\xi)=B_{\ell}^{+}\left(\eta_{\ell},n^{+},n^{-}\right)=\beta_{k}^{+}\ \text{ if }\ \eta_{\ell}=k=0,1,\ldots,N,\ \ \ell=1,\ldots,L$$
$$B_{\ell}^{-}(\xi)=B_{\ell}^{-}\left(\eta_{\ell},n^{+},n^{-}\right)=\beta_{k}^{-}\ \text{ if }\ \eta_{\ell}=k=0,-1,\ldots,-N,\ \ \ell=1,\ldots,L$$

$$\Lambda_{\ell}^{+}(\xi)=\Lambda_{\ell}\left(\eta_{\ell},n^{+},n^{-}\right)=\lambda_{k}\ \text{ if }\ \eta_{\ell}=k,\ \ k=0,1,\ldots,N,\ \ \ell=1,\ldots,L$$
$$\Lambda_{\ell}^{-}(\xi)=\Lambda_{\ell}\left(\eta_{\ell},n^{+},n^{-}\right)=\lambda_{k}\ \text{ if }\ \eta_{\ell}=k,\ \ k=0\pm1,\ldots,N,\ \ \ell=1,\ldots,L$$

$$\Omega_{k}^{+}(\xi)=\Omega_{k}^{+}\left(\eta_{\ell},n^{+},n^{-}\right)=\mu_{k}\ \text{ if }\ \eta_{\ell}=-k,\ \ k=0,1,\ldots,N,\ \ \ell=1,\ldots,L$$
$$\Omega_{k}^{-}(\xi)=\Omega_{k}^{-}\left(\eta_{\ell},n^{+},n^{-}\right)=\mu_{k}\ \text{ if }\ \eta_{\ell}=k,\ \ k=0,1,\ldots,N,\ \ \ell=1,\ldots,L.$$

The system (50) or its steady states cannot be studied analytically in a simple form, except in the absence of inhibitory effects (i..e. $\mu_k=0$). In such a case the system (50) admits steady state solutions of the form

$$p(\xi)=\left[\prod_{\ell=1}^{L}\varphi(\eta_{\ell})\right]\Psi_{+}\left(\eta,n^{+}\right)\Psi_{-}\left(\eta,n^{-}\right),$$

$$0=-\left[A_{\ell}^{+}(\eta_{\ell})+B_{\ell}^{+}(\eta_{\ell})+A_{\ell}^{-}(\eta_{\ell})+B_{\ell}^{-}(\eta_{\ell})\right]\varphi(\eta_{\ell})$$
$$+\left[A_{\ell}^{+}\left(\mathcal{T}_{\ell}^{+}(\eta_{\ell})\right)\varphi\left(\mathcal{T}_{\ell}^{+}(\eta_{\ell})\right)+A_{\ell}^{-}\left(\mathcal{T}_{\ell}^{-}(\eta_{\ell})\right)\varphi\left(\mathcal{T}_{\ell}^{-}(\eta_{\ell})\right)\right]$$
$$+\left[B_{\ell}^{+}\left(\mathcal{T}_{\ell}^{-}(\eta_{\ell})\right)\varphi\left(\mathcal{T}_{\ell}^{-}(\eta_{\ell})\right)+B_{\ell}^{-}\left(\mathcal{T}_{\ell}^{+}(\eta_{\ell})\right)\varphi\left(\mathcal{T}_{\ell}^{+}(\eta_{\ell})\right)\right], \tag{51}$$

$$0=-\left[\sum_{\ell=1}^{L}\Lambda_{\ell}^{+}(\eta)\right]\Psi_{+}\left(\eta,n^{+}\right)-\theta Ln^{+}\Psi_{+}\left(\eta,n^{+}\right)$$

$$+\left[\sum_{\ell=1}^{L}\Lambda_{\ell}^{+}(\eta)\right]\Psi_{+}\left(\eta,\mathcal{V}^{+}\left(n^{+}\right)\right)+\theta L\left(n^{+}+1\right)\Psi_{+}\left(\eta,\mathcal{U}^{+}\left(n^{+}\right)\right), \quad (52)$$

$$0=-\left[\sum_{\ell=1}^{L}\Lambda_{\ell}^{-}(\eta)\right]\Psi_{-}\left(\eta,n^{-}\right)-\theta L n^{-}\Psi\left(\eta,n^{-}\right) \quad (53)$$
$$+\left[\sum_{\ell=1}^{L}\Lambda_{\ell}^{-}(\eta)\right]\Psi_{-}\left(\eta,\mathcal{V}^{-}\left(n^{-}\right)\right)+\theta L\left(n^{-}+1\right)\Psi_{-}\left(\eta,\mathcal{U}^{-}\left(n^{-}\right)\right),$$

where in the different functions $\mathcal{T}_{\ell}^{+}$, $\mathcal{T}_{\ell}^{-}$, $\mathcal{V}_{k}^{+}$, $\mathcal{V}_{k}^{-}$, $\mathcal{U}^{+}$, $\mathcal{U}^{-}$ only the variables in which they depend are written. The solution of (51) can be obtained as in Sect. 4, and the result is similar to (24), (25), since the state of these molecules is not affected by the repressers in the noninhibitory case. On the other hand (52), (53) describe the statistical concentration of repressers n_{+}, n_{-} assuming that each value of η is given. Their respective solutions are:

$$\Psi_{+}\left(\eta,n^{+}\right)=\frac{1}{(n_{+})!}\left(\frac{\sum_{\ell=1}^{L}\Lambda_{\ell}^{+}(\eta)}{\theta L}\right)^{n_{+}}\exp\left(-\frac{\sum_{\ell=1}^{L}\Lambda_{\ell}^{+}(\eta)}{\theta L}\right)$$
$$\Psi_{-}\left(\eta,n^{-}\right)=\frac{1}{(n_{-})!}\left(\frac{\sum_{\ell=1}^{L}\Lambda_{\ell}^{-}(\eta)}{\theta L}\right)^{n_{-}}\exp\left(-\frac{\sum_{\ell=1}^{L}\Lambda_{\ell}^{-}(\eta)}{\theta L}\right)$$

In the case with inhibition ($\mu_k \neq 0$) the steady states cannot be computed analytically. We have made some numerical simulations of the stochastic process associated to the system (50). This is made in the next Subsection in the case $L = 2$. The numerically computed steady states show bistability as it could be expected. The relevant feature of this bistable behaviour is the fact that the state characterizing the system is a stochastic variable ranging a wide number of possible states. We do not know if this type of "diffuse" bistability is possible in real biochemical systems with small number of molecules, but several possible steady states. However, this mathematical example shows its feasibility.

6 Numerical simulations

In this section we describe numerical simulations performed for the stochastic process associated to (50) for $L = 2$. Since we simulate a continuous process by means of a sequence of discretized times, some care is required.

The system with $L = 2$ is described by two numbers $k_1, k_2 \in \{-N, -(N-1), \ldots, -1, 0, 1, 2, \ldots, N-1, N\}$ as well as two numbers $n^{+}, n^{-} \in \{0, 1, 2, \ldots\}$ that measure the number of inhibitory molecules.

The list of all the reactions is the following

$$B_k + A \underset{\alpha_k^+}{\overset{\beta_k^+}{\rightleftarrows}} B_{k+1}\,, \quad k = 1, 2, 3, \ldots$$
$$B_{-k} + A \underset{\alpha_k^-}{\overset{\beta_k^-}{\rightleftarrows}} B_{-(k+1)}\,, \quad k = 1, 2, 3, \ldots$$

$$B_k \to^{\lambda_k} B_k + R^+, \quad k = 1, 2, 3, \ldots$$
$$B_{-k} \to^{\lambda_k} B_{-k} + R^-, \quad k = 1, 2, 3, \ldots$$
$$B_{-k} + R^+ \to^{\mu_k} B_0, \quad k = 1, 2, 3,$$
$$B_k + R^- \to^{\mu_k} B_0, \quad k = 1, 2, 3, \ldots$$

$$R^+ \to^{\theta} \emptyset$$
$$R^- \to^{\theta} \emptyset$$

All these reactions are described by means of independent Poisson processes. First, we will assume for simplicity that $\beta_k^+ = \beta_k^- = \beta,\ \alpha_k^+ = \alpha_k^- = \alpha$ (i.e., both of them independent of k). We will also assume that $\mu_k = \mu,\ \lambda_k = \lambda$ are also independent of k. Moreover, in order to obtain an average drifting effect towards the values $k = \pm N$, we will assume, that either $\beta = 2\alpha$ or $\beta = 3\alpha$.

Let us assume that the state of the system is given by

$$\left(k_1, k_2, n^+, n^-\right)$$

The list of all the possible transition probabilities is as follows

$$\left(k_1, k_2, n^+, n^-\right) \to \left(k_1 + 1, k_2, n^+, n^-\right), \quad \beta \quad \text{if } k_1 \geq 0, \quad k_1 < N$$
$$\left(k_1, k_2, n^+, n^-\right) \to \left(k_1 - 1, k_2, n^+, n^-\right), \quad \beta \quad \text{if } k_1 \leq 0, \quad k_1 > -N$$

$$\left(k_1, k_2, n^+, n^-\right) \to \left(k_1, k_2 + 1, n^+, n^-\right), \quad \beta \quad \text{if } k_2 \geq 0, \quad k_2 < N$$
$$\left(k_1, k_2, n^+, n^-\right) \to \left(k_1, k_2 - 1, n^+, n^-\right), \quad \beta \quad \text{if } k_2 \leq 0, \quad k_2 > -N$$

$$\left(k_1, k_2, n^+, n^-\right) \to \left(k_1 - 1, k_2, n^+, n^-\right), \quad \alpha \quad \text{if } k_1 > 0, \quad k_1 \leq N$$
$$\left(k_1, k_2, n^+, n^-\right) \to \left(k_1 + 1, k_2, n^+, n^-\right), \quad \alpha \quad \text{if } k_1 < 0, \quad k_1 \geq -N$$

$$\left(k_1, k_2, n^+, n^-\right) \to \left(k_1, k_2 - 1, n^+, n^-\right), \quad \alpha \quad \text{if } k_2 > 0, \quad k_2 \leq N$$
$$\left(k_1, k_2, n^+, n^-\right) \to \left(k_1, k_2 + 1, n^+, n^-\right), \quad \alpha \quad \text{if } k_2 < 0, \quad k_2 \geq -N$$

$$\left(k_1, k_2, n^+, n^-\right) \to \left(k_1, k_2, n^+ + 1, n^-\right), \quad \lambda \text{ if } k_1 > 0$$
$$\left(k_1, k_2, n^+, n^-\right) \to \left(k_1, k_2, n^+, n^- + 1\right), \quad \lambda \text{ if } k_1 < 0$$

$$\left(k_1, k_2, n^+, n^-\right) \to \left(k_1, k_2, n^+ + 1, n^-\right), \quad \lambda \text{ if } k_2 > 0$$
$$\left(k_1, k_2, n^+, n^-\right) \to \left(k_1, k_2, n^+, n^- + 1\right), \quad \lambda \text{ if } k_2 < 0$$

$$\begin{aligned}
\left(k_1, k_2, n^+, n^-\right) &\to \left(k_1, k_2, n^+ - 1, n^-\right), \quad \theta n^+ \\
\left(k_1, k_2, n^+, n^-\right) &\to \left(k_1, k_2, n^+, n^- - 1\right), \quad \theta n^- \\
\left(k_1, k_2, n^+, n^-\right) &\to \left(0, k_2, n^+, n^- - 1\right), \quad \mu n^- \text{ if } k_1 > 0 \\
\left(k_1, k_2, n^+, n^-\right) &\to \left(0, k_2, n^+ - 1, n^-\right), \quad \mu n^+ \text{ if } k_1 < 0 \\
\left(k_1, k_2, n^+, n^-\right) &\to \left(k_1, 0, n^+, n^- - 1\right), \quad \mu n^- \text{ if } k_2 > 0 \\
\left(k_1, k_2, n^+, n^-\right) &\to \left(k_1, 0, n^+ - 1, n^-\right), \quad \mu n^+ \text{ if } k_2 < 0
\end{aligned}$$

This is the sequence of transition probabilities. In order to simulate them we need to transform a continuous process in a sequence of discrete steps. The key point is to decide which process must be activated in each step of the discrete process. To this end we use the following idea. Suppose that we have several times $t_1,\ t_2,\ t_3, \ldots, t_N$ selected by means of Poisson processes with rates $\nu_1,\ \nu_2, \ldots, \nu_N$. The probability of t_1 being the first time selected, i.e. $t_1 = \min\{t_1,\ t_2,\ t_3, \ldots, t_N\}$ can be computed as follows. Since the probability density for these times is

$$\nu_1 \nu_2 \cdots \nu_N \exp\left(-\left(\nu_1 t_1 + \nu_2 t_2 + \cdots + \nu_N t_N\right)\right) \tag{54}$$

Notice that by integrating the distribution (54) in the set $\{t_1 < t_2,\ t_1 < t_3, \ldots\}$, it is easy to see that the probability of the event $t_1 = \min\{t_1,\ t_2,\ t_3, \ldots, t_N\}$ is given by

$$\frac{\nu_1}{\nu_1 + \nu_2 + \cdots + \nu_N}$$

This means that the probabilities must be chosen as follows. Suppose that $k_1 > 0$, $k_2 > 0$, then just by counting the possible transition probabilities we obtain that the probability of making the transition $\left(k_1, k_2, n^+, n^-\right) \to \left(k_1 + 1, k_2, n^+, n^-\right)$ in the next step is given by

$$\frac{\beta}{\beta + \beta + \alpha + \alpha + \lambda + \lambda + \theta n^+ + \theta n^- + \mu n + \mu n^-}$$

All the other transition probabilities can be computed in a similar manner.

This algorithm is essentially the same as the one introduced by Bunker et al. [12]. It is rather close in spirit to Gillespie's algorithm, as it was pointed out in [29]. The only difference is in the fact that this algorithm does not keep track in detail of the times in which the reactions take place. However, since we are just interested in the stationary distribution, this is not particularly relevant. Moreover, this algorithm requires less computational work than Gillespie's, and for this reason it is more convenient for this specific problem.

Although the admissible transitions depend on the state it is not difficult to program it. We used Matlab as the software package. We choose the random reaction activated in each step using the random number generator of this package.

We have run the algorithm several times with different values of the reaction parameters. We run the program during different time steps. An equilibrium distribution

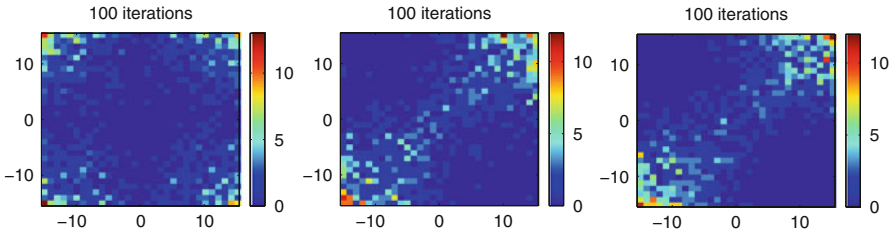

Fig. 1 *Left*: $\mu = 0$, *middle*: $\mu = 0.75$, *right*: $\mu = 1$, and μ is the intensity of inhibition. We commonly used 1,000 runs, $L = 2$, $\alpha = 1$, $\beta = 2$, $\lambda = 1$, $\theta = 1$,

is reached typically after 50 time steps (i.e. 50 iterations). For the range of parameters used in our simulations this is typically sufficient to arrive at a distribution of points where the relative numbers of points in each given region do not change in a significant manner with additional time steps. We interpret this as a signal of the arrival of the system at the invariant measure. We start all the runs assuming that the state of the system is initially at $\left(k_1, k_2, n^+, n^-\right) = (0, 0, 0, 0)$.

The numerical simulations show that the invariant measure exhibit bistable behaviour. Due to the exponential dependence on the probabilities induced by the assumption (26), a clear bistable behaviour arises with not too large values of N, say $N = 10$.

Due to the exponential growths induced by the transition probabilities α_k, β_k, the bistability can be detected with a number N of order 10 or even smaller.

There is a different behaviour for the systems under consideration if $\mu \neq 0$ or $\mu = 0$. We recall that this parameter measures the strength of the inhibitory effects in the system. The left Fig. 1 shows the structure of the invariant measure if $\mu = 0$. On the other hand, Fig. 1, middle and right shows the structure of the invariant measure for $\mu = 0.75$, and $\mu = 1$, respectively. All the other reaction parameters identical for the middle and right. We have obtained similar pictures for other values of the chemical parameters. They show the existence of some kind of bistability for each of the systems under consideration, but independently of each other. On the contrary these bistabilities are strongly correlated in the two subsystems if the inhibitory effect produced by μ is active.

Figures 2 and 3 show how the original distribution of points evolves to a bistable equilibrium. Some care must be taken with these figures because they do not represent the actual evolution of an ensemble of systems starting their evolution at the state $\left(k_1, k_2, n^+, n^-\right) = (0, 0, 0, 0)$. This is due to the fact that the algorithm used does not keep track of the actual time evolution of the states, differently from Gillespie's algorithm.

We have found bistable behaviour in Fig. 4, left, middle, and right, for very small values of $\mu = 0.001$, $\mu = 0.01$, $\mu = 0.1$, respectively. The only relevant difference is that the time required for the distribution to approach a bistable distribution becomes larger for smaller values of μ. Therefore, we have not found any evidence of phase transitions (i.e. changes in the structure of steady distributions) with changing values of μ. Seemingly very small amounts of inhibitory effects are enough to produce the bistable behaviour due to the production of inhibitory molecules that destroy the states of the other subsystem having opposite values of k.

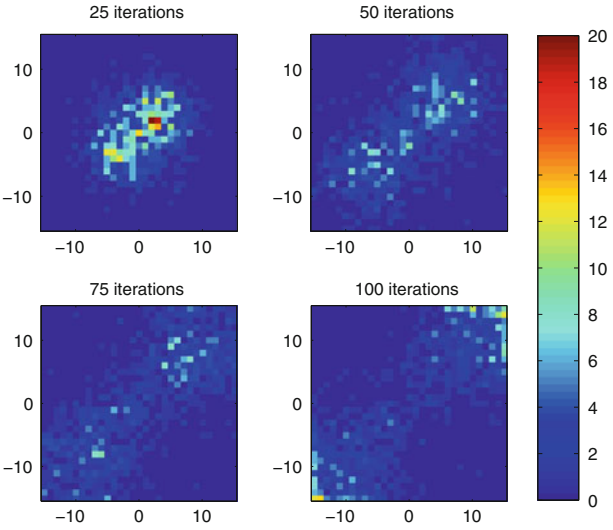

Fig. 2 1,000 runs, $L = 2, \alpha = 1, \beta = 2, \lambda = 1, \mu = 1, \theta = 1$

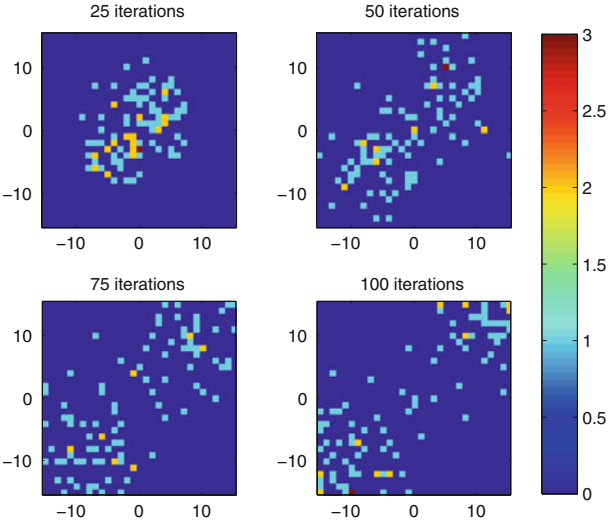

Fig. 3 100 runs, $L = 2, \alpha = 1, \beta = 2, \lambda = 1, \mu = 1, \theta = 1$

We also explored some simulations for various β and with α fixed. Since the ratio of α to β is important for the drifting effect toward the ends, we made only β vary in the simulations. As it can be seen in Fig. 5, left, middle, and right corresponding with $\beta = 1.2$, $\beta = 1.5$, $\beta = 2$, the difference in the values of β affects only on the convergence rate to the invariant measure as expected. Indeed, the bigger the ratio of β to α, the faster the convergence rate.

We have also done simulations in which the ratio β/α (or α/β) is not chosen as constant, but as a random distribution equi-distributed in the interval [1.5,2.5] (or

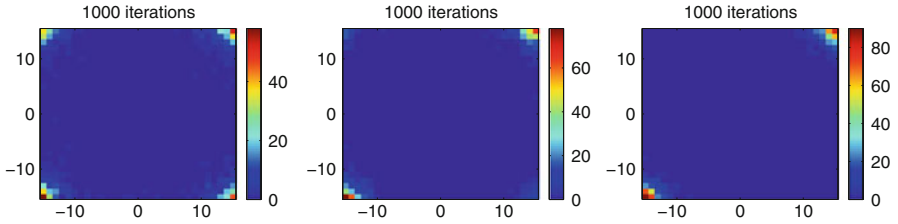

Fig. 4 *Left*: $\mu = 0.001$, *middle*: $\mu = 0.01$, *right*: $\mu = 0.1$ We used commonly 1,000 runs, $L = 2$, $\alpha = 1$, $\beta = 2$, $\lambda = 1$, $\theta = 1$ for all the figures

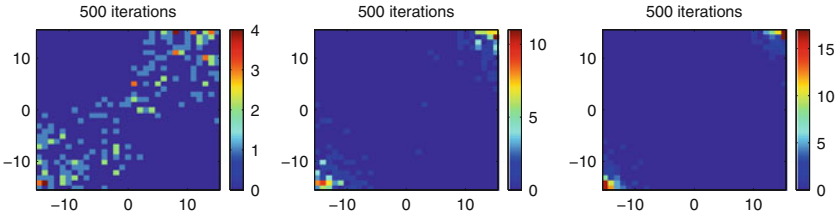

Fig. 5 *Left*: $\beta = 1.2$, *middle*: $\beta = 1.5$, *right*: $\beta = 2$. We used commonly 200 runs, $L = 2$, $\alpha = 1$, $\lambda = 1$, $\mu = 1$, $\theta = 1$ for all the figures

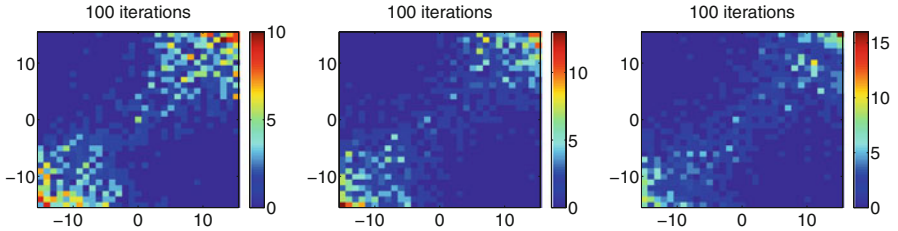

Fig. 6 *Left*: $\alpha = 1$, $\mu = 1$ and β equi-distributed in [1.5, 2.5], *middle*: $\beta = 2$, $\mu = 1$, and α equi-distributed in [0.5, 1.5] *right*: $\alpha = 1$, $\beta = 2$, and μ equi-distributed in [0.5, 1.5]. We commonly used 1,000 runs, $L = 2$, $\lambda = 1$, $\theta = 1$

[0.5/2,1.5/2] respectively). The system has still a tendency to drift to states where k is close to $+N$, $-N$, but in a less rigid way as in the examples considered above. Assuming that μ is equi-distributed in [0.5,1.5] we obtain also bistable behaviour. The aspect of the resulting invariant measure can be seen in Fig. 6.

7 Concluding remarks

In this paper we have continued the analysis of chemical stochastic systems yielding bistable behaviour started in [33]. In that paper we analyzed some examples of biochemical networks where the bistable behaviour was due to the existence of chemical coefficients with very different orders of magnitude. On the contrary, in this paper we have focused on bistabilities induced by the presence either of many molecules in the system or many different chemical species. The bistability in the first case can be studied using classical Kramers' formula. In the second case new techniques must

be developed. We have discussed two specific cases of such systems. The first one can be solved by means of explicit computations. In the second type of model under consideration, bistability is induced by the presence of inhibitory effects between different parts of the chemical networks. We have checked that such bistability takes place, even for rather small inhibitory effects. We have considered systems with some random variation in the chemical coefficients that also tend to move the state of each subsystem towards two extreme states of each subnetwork.

Acknowledgments We would like to thank Seongwon Lee for his help with the numerical simulations done in the last section. HJH acknowledges the support by Basic Science Research Program (2010-0008127) and (2012047640) through the National Research Foundation of Korea (NRF). JJLV was partially supported by DGES Grant MTM2010-16467.

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