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ORIGINAL PAPER

Bistable stochastic biochemical networks: highly specific systems with few chemicals

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Abstract In this paper we describe a class of stochastic biochemical systems exhibiting bistable behavior, in the sense that the invariant measure associated to the system is concentrated near two different classes of states of the system. We develop methods that allow us to describe the behavior of the invariant measure in some suitable asymptotic limits, as well as the switching times for the transitions between the states close to each of the states with high probability. Due to the discrete character of the problem, switching times cannot be computed using the classical Kramers' formula, and alternative methods are required.

Keywords Stochastic chemical system · Bistable behavior · Switching times · Markov processes

1 Introduction

A remarkable property of the biochemical systems already noticed in [43] is the fact that they behave in a deterministic manner even if some of the mechanisms driving the whole biochemical machinery are made of few molecules. A natural question that arises is that how the biological systems manage to behave in a deterministic manner under a very noisy environment, where the molecules involved are affected by Brownian motions as well as the stochasticity induced by the probabilistic character of chemical reactions.

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On the other hand, there exist many biological processes where stochastic events seem to play a crucial role. There is strong experimental evidence indicating that cellular variability is due in some cases to the stochastic character of gene expression (cf. [9,17,49]). In particular, stochasticity plays a role in cell fate decision of stem cells (cf. [37,44]). It has also been suggested, being motivated by the analysis for stochastic models of biochemical reactions, that the random variation observed in some pathogenic organisms could be due to the fluctuations of the chemical reactions (cf. [2]) in their regulatory circuits. The variability of pathogenic bacteria has several important functional consequences, for instance helping them to evade host defenses (cf. [25,50]). The role of stochastic cell behaviour in the generation of collective oscillatory behaviours has deserved a lot of attention both from the experimental and theoretical points of view (cf. [16,27,32]).

There are some biological examples where multistable biochemical networks seem to play a role in the functionality of the system. The best documented system seems to be the MAPK cascade in Xenopus oocytes (cf. [24]). It is also widely accepted that there are cases in which cell fate can be determined by stochastic choices among the different equilibria of a chemical system, and that cells can change their state due to fluctuations of molecular concentrations. The best known example is probably the choice of lisis–lisogeny decision in λ-phage where computer simulations support the stochastic origin of the choice (cf. [2]). Other candidates for bistable behaviour in biological systems can be found in the review paper [24]. Bistable behaviour is more clearly established in engineered genetic systems. The first example constructed was the so-called genetic-toggle switch in *Escherichia coli* and its construction was described in [28]. The first bistable engineered system in eukariotes was an artificial genetic circuit built in *Saccharomyces cerevisiae* (cf. [7]).

Due to the importance of stochasticity in biochemical processes it is relevant to develop mathematical techniques for the analysis of stochastic biochemical networks. Stochastic chemical systems have been studied long time ago (cf. [10]) and numerical algorithms to simulate these processes were introduced in the seventies (cf. [3,31]). In particular Gillespie's algorithm has become increasingly popular in order to simulate the dynamics of stochastic chemical processes. Some examples of the study of stochastic chemical networks that use both analytical and numerical methods can be found in [19,20,36,42,52–54].

Most of these papers describe the dynamics of molecular chemical reactions assuming that these take place by means of independent Poisson processes (cf. [31]). The evolution of such a system is modeled using a master equation. The resulting mathematical model is a linear system of infinitely many differential equations for the probabilities of having a given number of molecules for the different chemicals involved in the process. A stochastic simulation algorithm is suggested in [30,31] in order to approximate such probabilities. Some numerical studies of molecular dynamics based on the methods of Gillespie can be found in [20,29,54].

There are relatively few analytical studies of the master equations describing the evolution of the number of molecules in a chemical system. Such analysis can provide meaningful results only in some specific asymptotic regimes, due to the increasing complexity of the equation with the growth of the number of chemicals involved.

Several such studies have been made in the limit of many molecules, beginning with the seminal work in [40]. (cf. for instance [4]).

On the other hand, several papers have considered the study of master equations with different time scales. Roughly speaking, in such analysis, it is assumed that the chemical reactions can be split into a group of fast reactions and a group of slow reactions. Fast reactions reach equilibria very quickly and this allows us to define a reduced system for the set of variables that do not reach equilibria rapidly. This reduction of the system allows us to introduce more efficient simulation methods for molecular systems since it reduces the complexity of the system under consideration. Some works in this direction are for instance, [11,12,33,42,41,45,46,48]. Meanwhile, many works use the fact that stochastic chemical networks with first order kinetics can be solved explicitly by iteration or using the formalism of generating functions (cf. [5,6,10,15,26,51]).

There have been several studies on the connection between the topological properties of the biochemical network and the dynamical behaviour of the network. A paradigmatic example of this approach is the so-called "Zero Deficiency Theorem" (cf. [22,35]). This Theorem states that a large class of chemical networks satisfying some topological constraints can have only one nontrivial steady state in each stoichiometric class. The constraints are easy to check in each specific example. The original result was proved for deterministic systems (cf. [22]), but it has been also proved that mass action reaction networks with zero deficiency have invariant measures which can be written as convex combinations of products of Poisson distributions for each of the chemical concentrations (cf. [1]). On the other hand, the articles [13,14] contain necessary and sufficient conditions in order for a network to have multiple quasi-steady-states. We remark that the aim of these studies is not to derive conditions for a given chemical reaction to ensure a particular type of behaviour, but to obtain conditions for the topology of the network which allow possible behaviours of the chemical system with a choice of reaction coefficients, or its impossibility with any choice of coefficients.

Our goal is to study conditions on the network structure and on the distribution of chemical coefficients for ensuring that a molecular system behaves in a deterministic manner. More precisely, we intend to obtain molecular systems which evolve according to stochastic dynamics and exhibit multistability with large switching times between the different steady states of the system.

In this paper as well as in the companion paper [34] we will describe some simple examples of biochemical networks yielding bistability, where we compute long switching times in some suitable sense that will be precised later. We will not intend to study existing molecular systems, but we will concentrate on the study of abstract systems of stochastic chemical reactions that could help to clarify the underlying principles yielding deterministic behaviour. The systems under consideration will be studied using classical asymptotic methods and it will provide some insight on how the network structure and the choice of the coefficients can influence multistability and switching times.

We will focus on the study of stochastic biochemical networks containing large (or small) parameters. The large parameters considered in this paper will be the relative size of some of the chemical coefficients. In [34] a different type of limit will

be considered, namely, the number of chemical species involved in the reactions. Among all the possible quantities that can be computed, we will focus on the switching times between different multiple states. There are several reasons for studying switching times. First, they are intrinsically interesting by 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 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. In particular we will focus in this paper on finding examples of biochemical networks that could give deterministic behaviour.

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. [21]) and Kramers (cf. [39]). Kramers' formula has been often used to compute switching times in biochemical systems (cf. for instance [18]). Kramer's formula will not be considered in this paper, but it will be shortly discussed in [34].

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

$$f \sim g \text{ as } x \to x_0 \text{ if and only if } \lim_{x \to x_0} \frac{f(x)}{g(x)} = 1,$$

$$f \ll g \text{ as } x \to x_0 \text{ if and only if } \lim_{x \to x_0} \frac{f(x)}{g(x)} = 0.$$

The plan of the paper is the following. In Sect. 2 we describe the general framework of problems considered in this paper. Section 3 studies a particular chemical system made of few molecules, yielding bistable behaviour due to the different orders of magnitude of their coefficients. This section contains also the study of this system if one particular parameter ε is set to be zero. Section 4 derives the reduced system that describes the evolution of the system in Sect. 3 if $\varepsilon \to 0^+$. This section includes also the description of the (bistable) steady states in that particular regime. Section 5 computes the switching times between the two stable states of the system under consideration for small ε by means of an asymptotic analysis of the corresponding master equations. Section 6 contains a technical computation of some transition probabilities which has been used in Sect. 4. Last section summarizes the main results of 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. [1,4,11,26,31,40–42,45]). We summarize here the main assumptions.

We will assume that the systems under consideration consist of N different types of chemical substances. The number of molecules of each chemical species 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 [22]). 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_ℓ, $\ell = 1, \ldots, N$ the different chemicals in the system. The restrictions imposed in the reactions means that they are of one of the following types:

$$\varnothing \to A_\ell, \quad K_\ell; \quad A_\ell \to \varnothing, \quad \lambda_\ell \tag{2.1}$$

$$A_\ell + A_j \to A_k, \quad \alpha_{\ell,j;k}; \quad A_k \to A_\ell + A_j, \quad \beta_{k;\ell,j} \tag{2.2}$$

$$A_j \to A_k, \quad \mu_{j;k} \tag{2.3}$$

More general forms for the reactions that include also arbitrary collisions have been considered for instance in [1]. We will consider one specific example in the paper [34] 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 Eqs. (2.1)–(2.3) is given respectively by the numbers

$$K_\ell, \quad \lambda_\ell n_\ell, \quad \alpha_{\ell,j;k} n_\ell \left(n_j - \delta_{\ell,j}\right), \quad \beta_{k;\ell,j} n_k, \quad \mu_{j;k} n_j \tag{2.4}$$

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

$$\mathbb{N}_* = \mathbb{N} \cup \{0\} \cup \{\infty\} \tag{2.5}$$

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

$$p(\xi, t) \geq 0 \text{ for } \xi \in \mathbb{N}_*^N \text{ and } \sum_{\xi \in \mathbb{N}_*^N} p(\xi, t) = 1$$

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 A system with few molecules but with highly specific kinetic coefficients: general properties

In one of the systems mentioned above, namely the genetic toggle described in [28] the detailed biochemistry of the system is well known. It turns out that such a system is not composed of many different chemical species. There are not many molecules of each of the species either. Nevertheless, this chemical system is able to produce a clearly distinguishable bistable system.

In this section we will describe a simple abstract example of biochemical network which illustrate how to obtain bistable systems with long-lived states and with a relatively small number of both chemical species and molecules. This will be achieved with a choice of chemical reactions acting in very different time scales. This means that the long lives of the molecular states are built in the chemical coefficients and characteristic lifetimes of the chemicals involved. In spite of the fact that this mechanism may not require the analysis of many molecules it could often be the way in which biological systems with several molecular states manage to work in a deterministic way. Roughly speaking deterministic behaviour would be a consequence of the high specificity of the molecules involved in the process. More precisely, very large chemical rates could produce bistability and very long switching times.

3.1 Description of the model

We assume that there are two substances (they could be for instance genes, although the specific biology of their characters will not be made precise), X_1, X_2 that can be activated by a molecule Z in the background. The activation of a molecule X_i triggers the production of a repressor R that can be attached to a free molecule X_j, $j \neq i$ and

inhibits it. Therefore the molecules X_i can be in the three states, namely free (X_i), activated ($X_i Z$) and repressed ($X_i R$). We will denote the activated and repressed states as Z_i and R_i respectively for brevity. The system of reactions that we will use to describe the system is the following:

$$\begin{aligned} \emptyset &\rightleftarrows Z, \quad (K;\lambda) \\ X_i + Z &\rightleftarrows Z_i, \quad (\alpha;\beta) \\ Z_i &\to Z_i + R, \quad \frac{g}{\varepsilon} \\ R &\to \emptyset, \quad \frac{\mu}{\varepsilon} \\ X_i + R &\rightleftarrows R_i, \quad \left(\frac{\gamma}{\varepsilon};\sigma\right) \end{aligned} \tag{3.1}$$

The coefficients are the stochastic reaction rates for the direct and inverse reactions respectively. In reactions where only the direct reaction takes place only one constant rate has been written. A small rescaling parameter $\varepsilon > 0$ has been introduced. The meaning of this parameter is that some of the reactions associated to the repressor R are much faster than the others. All the numbers $K, \lambda, \alpha, \beta, g, \mu, \gamma, \sigma$ will be assumed to be positive and of order one. Nevertheless, in order to have a probability density concentrated in two types of states, we will need some smallness assumption on β. The reactions in (3.1) are reactions between individual molecules that take place according to independent Poisson processes with the rates indicated there. Let us denote as $n_Z, n_R, n_{X_i}, n_{Z_i}, n_{R_i}$ the number of molecules Z, R, X_i, $X_i Z$, $X_i R$ respectively. Notice that $n_{X_i} = 0$ if the molecule X_i is activated or repressed. We then have the following relations

$$n_{X_i} + n_{Z_i} + n_{R_i} = 1, \ i = 1, 2 \tag{3.2}$$

On the other hand we have

$$n_{X_i}, n_{Z_i}, n_{R_i} \in \{0, 1\} \tag{3.3}$$

The main consequence of (3.2), (3.3) is that the three numbers $n_{X_i}, n_{Z_i}, n_{R_i}$ can be replaced by just one variable of the set

$$\mathcal{E} = \{R_i, X_i, Z_i\}$$

The remaining variables characterizing the system are the numbers n_Z, n_R that can take any nonnegative integer. Therefore, the space of states that characterizes the system is

$$\mathcal{X} = \mathbb{N}_*^2 \times \mathcal{E}^2$$

where $\mathbb{N}_*$ is as in (2.5).

In order to write the master equation defining the evolution of the probabilities associated to the reactions in (3.1) we define some auxiliary operators as follows. Let us denote $\xi \in \mathcal{X}$ as

$$\xi = (n_Z, n_R, \eta_1, \eta_2)$$

with $n_Z, n_R \in \mathbb{N}_*$, $\eta_i \in \mathcal{E}$ for $i = 1, 2$. We define the following operators by

$$\begin{aligned} &T_Z^+ : \mathcal{X} \to \mathcal{X}\,, \quad T_Z^- : \mathcal{X} \to \mathcal{X}\,, \quad T_R^+ : \mathcal{X} \to \mathcal{X}, \quad T_R^- : \mathcal{X} \to \mathcal{X} \\ &A_{Z,i} : \mathcal{X} \to \mathcal{X}\,, \quad D_{Z,i} : \mathcal{X} \to \mathcal{X}\,, \quad A_{R,i} : \mathcal{X} \to \mathcal{X}, \quad D_{R,i} : \mathcal{X} \to \mathcal{X} \end{aligned}$$

$$\begin{aligned} &T_Z^+ (n_Z, n_R, \eta_1, \eta_2) = (n_Z + 1, n_R, \eta_1, \eta_2)\,, \quad T_Z^- (n_Z, n_R, \eta_1, \eta_2) = \left((n_Z - 1)_+, n_R, \eta_1, \eta_2\right) \\ &T_R^+ (n_Z, n_R, \eta_1, \eta_2) = (n_Z, n_R + 1, \eta_1, \eta_2)\,, \quad T_R^- (n_Z, n_R, \eta_1, \eta_2) = \left(n_Z, (n_R - 1)_+, \eta_1, \eta_2\right) \\ &A_{\omega,1} (n_Z, n_R, \eta_1, \eta_2) = \left(n_Z, n_R, A_{\omega,1} (\eta_1), \eta_2\right), \quad A_{\omega,2} (n_Z, n_R, \eta_1, \eta_2) = \left(n_Z, n_R, \eta_1, A_{\omega,2} (\eta_2)\right) \\ &D_{\omega,1} (n_Z, n_R, \eta_1, \eta_2) = \left(n_Z, n_R, D_{\omega,1} (\eta_1), \eta_2\right), \quad D_{\omega,2} (n_Z, n_R, \eta_1, \eta_2) = \left(n_Z, n_R, \eta_1, D_{\omega,2} (\eta_2)\right) \end{aligned} \tag{3.4}$$

where the operators $A_{\omega,i}$, $D_{\omega,i}$ are defined in $\mathcal{E}$ for $\omega \in \{Z, R\}$ by

$$\begin{aligned} &A_{Z,i} (X_i) = Z_i, \; A_{Z,i} (Z_i) = Z_i, \; A_{Z,i} (R_i) = R_i, \quad i = 1, 2 \\ &A_{R,i} (X_i) = R_i, \; A_{R,i} (Z_i) = Z_i, \; A_{R,i} (R_i) = R_i, \quad i = 1, 2 \\ &D_{Z,i} (X_i) = X_i, \; D_{Z,i} (Z_i) = X_i, \; D_{Z,i} (R_i) = R_i, \quad i = 1, 2 \\ &D_{R,i} (X_i) = X_i, \; D_{R,i} (Z_i) = Z_i, \; D_{R,i} (R_i) = X_i, \quad i = 1, 2 \end{aligned} \tag{3.5}$$

Given $\xi = (n_Z, n_R, \eta_1, \eta_2) \in \mathcal{X}$ we define the following functions

$$n_Z : \mathcal{X} \to \mathbb{N}_*; \quad n_R : \mathcal{X} \to \mathbb{N}_*; \quad \eta_1 : \mathcal{X} \to \mathcal{E}; \quad \eta_2 : \mathcal{X} \to \mathcal{E} \tag{3.6}$$

They are defined by means of the corresponding components of ξ. We will also use the notation n_{Z_j}, n_{X_j}, n_{R_j} to denote functions that have the value 1 if η_j is Z_j, X_j, R_j respectively, or 0 otherwise.

Let us denote as $p(\xi, t)$ the probability of the state ξ at the time t, assuming that the initial probability distribution is $p(\xi, 0) = p_0(\xi)$.

Using the operators defined in (3.4), (3.5) we can write, using standard probability methods (cf. [23]), the master equation that characterizes the evolution of the probability $p(\xi, t)$ in the following way

$$\frac{\partial p}{\partial t} (\xi, t) = frac1\varepsilon L_1 p (\xi, t) + L_2 p (\xi, t) \equiv L_\varepsilon p (\xi, t) \tag{3.7}$$

$$\begin{aligned} L_1 p (\xi, t) = &- \left(g \left(n_{Z_1} + n_{Z_2}\right) + \mu n_R\right) p (\xi, t) + \left(g \left(n_{Z_1} + n_{Z_2}\right) p \left(T_R^- \xi, t\right)\right. \\ &\left. + \mu (n_R + 1)\, p \left(T_R^+ \xi, t\right)\right) - \sum_{j=1}^{2} \gamma n_R n_{X_j} p (\xi, t) \\ &+ \sum_{j=1}^{2} \gamma (n_R + 1)\, n_{R_j} p \left(T_R^+ D_{R,j} \xi, t\right) \end{aligned} \tag{3.8}$$

$$L_2 p(\xi,t) = -(K+\lambda n_Z)\, p(\xi,t) + K\mathbf{1}_{\{n_Z\geq 1\}} p\left(T_Z^- \xi,t\right) + \lambda (n_Z+1)\, p\left(T_Z^+\xi,t\right)$$
$$-\sum_{j=1}^{2}\left[\alpha n_Z n_{X_j} + \beta n_{Z_i}\right] p(\xi,t) + \sum_{j=1}^{2}\left[\alpha (n_Z+1)\, n_{Z_j}\, p\left(T_Z^+ D_{Z,j}\xi,t\right)\right.$$
$$\left.+\beta n_{X_j}\, p\left(T_Z^- A_{Z,j}\xi,t\right)\right] - \sum_{j=1}^{2}\sigma n_{R_j}\, p(\xi,t) + \sum_{j=1}^{2}\sigma n_{X_j}\, p\left(T_R^- A_{R,j}\xi,t\right) \tag{3.9}$$

Notice that we have included in L_1 all the fast chemical reactions and in L_2 the reactions that take place in times of order one.

In (3.8), (3.9) we denote as n_{Z_j}, n_Z, n_R, n_{X_j}, n_{R_j} the corresponding values of these functions evaluated at the state ξ.

Notice that the system (3.7)–(3.9), although it is linear, can not be solved explicitly and we will derive information about it using a perturbative method. This analysis will provide as well information about the structure of the steady states.

3.2 Steady states: the limit case $\varepsilon = 0$

Multiple scale methods for the analysis of stochastic systems with two different scales have been developed in [11,41,42,45,46]. We will use the type of methods in these references adapted to the particular problem (3.7)–(3.9).

Our first goal is to study the steady states of (3.7) as $\varepsilon \to 0^+$. Since reactions associated to the part L_1 of the operator L_ε are much faster, it is natural to begin by considering the steady states associated to the operator L_1, more precisely, we will describe the solutions of the equation

$$L_1 p(\xi) = 0 \tag{3.10}$$

Notice that, since all the reactions involving change in the value of n_Z are contained in the operator L_2 it follows that the variable n_Z just plays the role of a parameter in (3.10). The problem then reduces to a finite system of discrete equations in the variable n_R for the different choices of η_1, η_2. Most of the resulting discrete equations in n_R are decoupled due to the fact that the operators $D_{R,j}$ only change the values of η_j if they take the value R_j.

We then consider the different choices of $(\eta_1, \eta_2) \in \mathcal{E}^2$.

(1) The case $(\eta_1, \eta_2) = (Z_1, Z_2)$. The element (Z_1, Z_2) is not connected to any other element of $\mathcal{E}^2$ by means of the fast reactions. Therefore for $\xi = (n_Z, n_R, Z_1, Z_2)$, (3.10) becomes

$$-(2g+\mu n_R)\, p(n_R) + (2gp(n_R-1) + \mu(n_R+1)\, p(n_R+1)) = 0, \tag{3.11}$$

where we do not write the dependence of p on the variables n_Z, Z_1, Z_2 just for brevity. As a rule we will not write in the following the dependence on the variables that just

play the role of parameters if they are not relevant to the equation under consideration. Notice that (3.11) can be rewritten as

$$-J(n+1)+J(n)=0 \tag{3.12}$$

with

$$\begin{aligned} J(n) &= -\mu n p(n)+2gp(n-1), \quad n\geq 1\\ J(0) &= 0 \end{aligned}$$

and where $n_R = n$. Then $J(n) = 0$, whence

$$p(n_Z, n_R, Z_1, Z_2) = \frac{1}{n_R!}\left(\frac{2g}{\mu}\right)^{n_R} p(n_Z, 0, Z_1, Z_2) \tag{3.13}$$

This yields the solution of (3.10) if $(\eta_1, \eta_2) = (Z_1, Z_2)$

(2) The case $(\eta_1, \eta_2) = (Z_1, R_2)$. These states are also disconnected from the other equations by means of the reactions in L_1. Therefore for $\xi = (n_Z, n_R, Z_1, X_2)$, (3.10) becomes

$$-(g+\mu n_R)\,p(n_R)+(gp(n_R-1)+\mu(n_R+1)\,p(n_R+1))-\gamma n_R p(n_R)=0 \tag{3.14}$$

The solutions of (3.14) cannot be computed in a closed form due to the fact that this equation cannot be written as a conservation law. However (3.14) is a second order difference equation whose solutions can be studied easily. The main properties of its solutions are in the following lemma.

Lemma 1 *For any set of positive numbers* g, μ, γ *there exists a unique solution* $\varphi : \mathbb{N}_* \to \mathbb{R}$ *of the difference equation*

$$\begin{aligned} &-(g+\mu n)\varphi(n)+(g\varphi(n-1)+\mu(n+1)\varphi(n+1))-\gamma n\varphi(n)=0,\\ &\quad n=1,2,\ldots \end{aligned} \tag{3.15}$$

such that

$$\varphi(0)=1 \tag{3.16}$$

$$\lim_{n\to\infty}\varphi(n)=0. \tag{3.17}$$

Moreover, $\varphi(n)$ *is decreasing and there exists* $K = K(g, \mu, \gamma) > 0$ *such that*

$$\varphi(n)\sim\frac{K}{n!}\left(\frac{g}{\mu+\gamma}\right)^{n} \quad as \quad n\to\infty.$$

Proof Equation (3.15) can be written as an iterative equation

$$\varphi(n+1) = \frac{1}{\mu(n+1)}\left[-g\varphi(n-1) + (\gamma n + g + \mu n)\varphi(n)\right], \quad n = 1, 2, \ldots$$

This can be solved uniquely in terms of the values of $\varphi(0)$, $\varphi(1)$. Therefore the space of solutions of (3.15) is two-dimensional. The methods of computing the asymptotics of the solutions of second order linear difference equations are well established (cf. [8]). It turns out that there exist two linearly independent solutions of (3.15) that will be denoted as $\varphi_1(n)$, $\varphi_2(n)$ with the following asymptotic behaviours respectively

$$\varphi_1(n) \sim \frac{1}{n!}\left(\frac{g}{\mu+\gamma}\right)^n n^{-\frac{\gamma g}{(\gamma+\mu)^2}} \text{ as } n \to \infty \tag{3.18}$$

$$\varphi_2(n) \sim \left(\frac{\mu+\gamma}{\mu}\right)^n n^{-1-\frac{g\mu}{(\gamma+\mu)^2}+\frac{g}{(\gamma+\mu)}} \text{ as } n \to \infty \tag{3.19}$$

Since only one of the asymptotics (3.18), (3.19) yields decay of the solutions as $n \to \infty$ it follows that there is at most one solution of (3.15)–(3.17). Notice that, assuming (3.16), the value of $\varphi(1)$ determines uniquely the function $\varphi(n)$. In order to prove the existence of one value of $\varphi(1)$ yielding (3.16) and (3.17) we use a shooting argument. To this end, we rewrite (3.15) as

$$[\mu(n+1)\varphi(n+1) - g\varphi(n)] - [\mu n\varphi(n) - g\varphi(n-1)] = \gamma n\varphi(n) \tag{3.20}$$

Suppose first that $\varphi(1) > \frac{g\varphi(0)}{\mu} = \frac{g}{\mu}$. We then claim that $\lim_{n\to\infty}\varphi(n) = \infty$. Indeed, using (3.20) with $n = 1$, we obtain $[2\mu\varphi(2) - g\varphi(1)] > 0$ whence $\varphi(2) > 0$. An induction argument then yields $\mu(n+1)\varphi(n+1) - g\varphi(n) > 0$ for every $n \geq 0$ and the corresponding solution $\varphi(n)$ satisfies $\mu(n+1)\varphi(n+1) - g\varphi(n) > \gamma n\varphi(n)$. Then $\varphi(n) \gg \varphi_1(n)$ as $n \to \infty$ and therefore $\varphi(n) \sim K_1\varphi_2(n)$ as $n \to \infty$ for some $K_1 > 0$, whence the claim follows.

Let us assume now that $\varphi(1) < 0$. We claim that in such a case $\lim_{n\to\infty}\varphi(n) = -\infty$. Indeed, our assumption on $\varphi(1)$ implies $[\mu\varphi(1) - g\varphi(0)] < 0$ and (3.20) yields $[2\mu\varphi(2) - g\varphi(1)] < 0$ and $\varphi(2) < 0$. Arguing by induction we obtain $[\mu n\varphi(n) - g\varphi(n-1)] < 0$ for any $n \geq 1$, whence $[\mu(n+1)\varphi(n+1) - g\varphi(n)] < \gamma n\varphi(n)$. Then $|\varphi(n)| > \frac{C}{n}\left(\frac{\gamma}{\mu}\right)^n$ for some $C > 0$. Due to (3.18), (3.19) we can have $\limsup_{n\to\infty}|\varphi(n)|$ bounded if $\varphi(n) = C^*\varphi_1(n)$, but since this is not the case, it then follows that $\lim_{n\to\infty}\varphi(n) = -\infty$.

Therefore, by continuity there exists a value of $\varphi(1) \in \left[0, \frac{g}{\mu}\right]$ such that

$$\varphi(n) \sim K\varphi_1(n) \text{ as } n \to \infty \tag{3.21}$$

for some $K \in \mathbb{R}$. We now want to show that $K > 0$. We first notice that $K \neq 0$, since otherwise $\varphi(n) = 0$. Suppose that $K < 0$. Then we would have

$$J(n) = [\mu(n+1)\varphi(n+1) - g\varphi(n)]$$
$$= \frac{Kg}{n!}\left(\frac{g}{\mu+\gamma}\right)^n \left[\frac{\mu}{\mu+\gamma} - 1\right] n^{-\frac{\gamma g}{(\gamma+\mu)^2}} (1 + o(1))$$

as $n \to \infty$. Since $K < 0$ we then have $J(n) > 0$ for large n. On the other hand $J(0) < 0$. Then, there exists at least one value $n_0 \geq 1$ such that $J(n_0 - 1) < 0$ and $J(n_0) \geq 0$. Due to (3.20) we would have $\varphi(n_0) > 0$. Therefore $\varphi(n_0 + 1) > 0$ and it would follow by induction that $J(n) > 0$ for any $n \geq n_0$, whence (3.21) would not take place. This contradiction implies that $K > 0$. □

Remark 2 It is possible to find an explicit formula for the solutions of (3.15)–(3.17), but this involves an integral expression of hypergeometric functions that are not particularly illuminating. Therefore, we prefered to prove Lemma 1 with the argument above which could be used for more general classes of coefficients.

Remark 3 Notice that Lemma 1 and (3.14) yield

$$p(n_Z, n_R, Z_1, X_2) = p(n_Z, 0, Z_1, X_2)\varphi(n_R) \tag{3.22}$$

(3) The case $(\eta_1, \eta_2) = (R_1, Z_2)$. It can be studied exactly as the previous case by symmetry. Moreover, we have also

$$p(n_Z, n_R, X_1, Z_2) = p(n_Z, 0, X_1, Z_2)\varphi(n_R) \tag{3.23}$$

(4) The case $(\eta_1, \eta_2) = (X_1, X_2)$. In this case (3.10) reduces to

$$p(n_R + 1) = \frac{2\gamma + \mu}{\mu}\frac{n_R}{n_R + 1} p(n_R), \quad n_R \geq 0 \tag{3.24}$$

The only solutions of (3.24) with finite mass are

$$p(n_Z, n_R, X_1, X_2) = p(n_Z, 0, X_1, X_2)\delta_{n_R,0} \tag{3.25}$$

(5) The case $(\eta_1, \eta_2) = (X_1, R_2)$. Equation (3.10) takes the form

$$-(\mu+\gamma) n_R p(n_R, X_1, R_2) + \mu(n_R + 1) p(n_R + 1, X_1, R_2)$$
$$+\gamma(n_R + 1) p(n_R + 1, X_1, X_2) = 0 \tag{3.26}$$

Taking into account (3.25) we obtain $p(n_Z, n_R + 1, X_1, X_2) = 0$ and (3.26) becomes

$$-(\mu+\gamma) n_R p(n_R, X_1, R_2) + \mu(n_R + 1) p(n_R + 1, X_1, R_2) = 0$$

The only solutions of this equation with finite mass are

$$p(n_Z, n_R, X_1, R_2) = p(n_Z, 0, X_1, R_2)\delta_{n_R,0} \tag{3.27}$$

(6) The case $(\eta_1, \eta_2) = (R_1, X_2)$. A completely symmetric argument yields

$$p\,(n_Z, n_R, R_1, X_2) = p\,(n_Z, 0, R_1, X_2)\,\delta_{n_R,0} \tag{3.28}$$

(7) The case $(\eta_1, \eta_2) = (R_1, R_2)$. In this case (3.10) becomes

$$\begin{aligned} &-\mu n_R p\,(n_R) + \mu\,(n_R+1)\,p\,(n_R+1) + \gamma\,(n_R+1)\left[p\left(T_R^+ D_{R,1}\xi\right)\right. \\ &\left.+p\left(T_R^+ D_{R,2}\xi\right)\right] = 0 \end{aligned} \tag{3.29}$$

Using the fact that $p\left(T_R^+ D_{R,1}\xi\right) = p\left(T_R^+ D_{R,2}\xi\right) = 0$ [cf. (3.27), (3.28)] we obtain

$$p\,(n_R+1) = \frac{n_R}{n_R+1}\,p\,(n_R)$$

The general solution of this equation has the form

$$p\,(n_R) = K_1\delta_{n_R,0} + \frac{K_2}{n_R}\left(1-\delta_{n_R,0}\right)$$

for suitable constants K_1, K_2. Therefore, the solutions of (3.29) with finite mass have the form

$$p\,(n_Z, n_R, R_1, R_2) = p\,(n_Z, 0, R_1, R_2)\,\delta_{n_R,0} \tag{3.30}$$

(8) The case $(\eta_1, \eta_2) = (Z_1, R_2)$. Equation (3.10) becomes

$$\begin{aligned} &-(g+\mu n_R)\,p\,(\xi) + \left(gp\left(T_R^-\xi\right) + \mu\,(n_R+1)\,p\left(T_R^+\xi\right)\right) + \gamma\,(n_R+1) \\ &\times p\left(T_R^+ D_{R,2}\xi\right) = 0 \end{aligned}$$

Then, using $p\left(T_R^+ D_{R,2}\xi\right) = p\,(n_Z, n_R+1, Z_1, X_2) = p\,(n_Z, 0, Z_1, X_2)\,\varphi\,(n_R+1)$ [cf. (3.22)] we obtain

$$\begin{aligned} &-(g+\mu n_R)\,p\,(n_R, Z_1, R_2) + (gp\,(n_R-1, Z_1, R_2) \\ &+\mu\,(n_R+1)\,p\,(n_R+1, Z_1, R_2)) \\ &+\gamma\,(n_R+1)\,p\,(n_Z, 0, Z_1, X_2)\,\varphi\,(n_R+1) = 0 \end{aligned} \tag{3.31}$$

We can rewrite (3.31) as

$$J\,(n_R) - J\,(n_R+1) + \gamma\,(n_R+1)\,p\,(n_Z, 0, Z_1, X_2)\,\varphi\,(n_R+1) = 0, \quad n_R \geq 0 \tag{3.32}$$

where

$$J\,(n_R) = -\mu n_R p\,(n_R, Z_1, R_2) + gp\,(n_R-1, Z_1, R_2)\,, n_R \geq 1$$

Equation (3.32) must be solved with the boundary condition $J(0) = 0$. Adding (3.32) for $n_R \geq 0$ we obtain

$$0 = \gamma p(n_Z, 0, X_1, Z_2) \sum_{n_R=1}^{\infty} n_R \varphi(n_R)$$

and since $\sum_{n_R=1}^{\infty} n_R \varphi(n_R) > 0$, it then follows that

$$p(n_Z, 0, X_1, Z_2) = 0 \tag{3.33}$$

(9) The case $(\eta_1, \eta_2) = (R_1, Z_2)$. Similarly, we obtain by symmetry

$$p(n_Z, 0, Z_1, X_2) = 0 \tag{3.34}$$

The system of equations (3.13), (3.22), (3.23), (3.25), (3.27), (3.28) provides the most general solution of (3.10) having probability one.

4 On the dynamics of the process given by (3.7) for $\varepsilon \to 0$: reduced system

We recall that our goal is to describe the evolution of the stochastic process described by means of (3.7) for small ε. The key idea of our (formal) analysis is the following. The operator L_ε consists of two pieces. The part $\frac{1}{\varepsilon} L_1$ acts in times of order ε. Therefore, the corresponding distribution probability in the space of states $\mathcal{X}$ is then driven in times of order ε to one of the quasi-steady-states associated to the operator L_1. Such a set of equilibria is a convex set given by (3.13), (3.22), (3.23), (3.25), (3.27), (3.28) and it will be denoted as $\mathcal{M}_{s,1}$.

On the other hand, the part L_2 of the operator L_ε acts in times of order one. Since the part of the evolution induced by $\frac{1}{\varepsilon} L_1$ is much faster we can assume that the dynamics induced by L_2 produces transitions between the quasi-steady-states in $\mathcal{M}_{s,1}$. Notice that this approach allows us to deduce a reduced dynamics much simpler than the original one. This approximation, however, is valid for times t of order one. A similar idea of computing reduced dynamics for two scale stochastic processes has been used in [45].

We describe in Fig. 1 the transitions that can take place between the different elements of $\mathcal{E}^2$. Notice that in Fig. 1 we have classified all possible transitions in three possible classes. The transitions represented by continuous arrows take place in times of order ε. The transitions represented by dashed arrows take place in times of order one. Finally, the transitions represented by dotted arrows, take place in times of order one, but they are extremely unlikely, because they have as starting point a short lived state, with a lifetime of order ε.

The set of quasi-steady-states $\mathcal{M}_{s,1}$ is a convex set generated by convex combinations of the following eight functions, which are concentrated only on the sets $S_{(\eta_1,\eta_2)} = \{(n_Z, \eta_1, \eta_2)\}$. We just write the terms of the functions P that are different from zero [see (3.13), (3.22), (3.23), (3.25), (3.27), (3.28)]

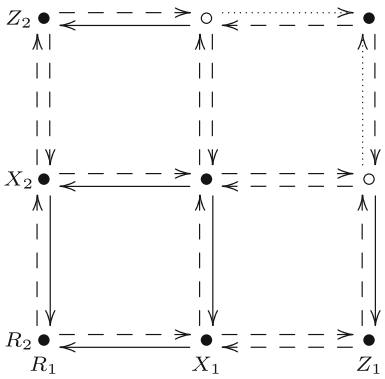

Fig. 1 *Solid arrow* fast, *dashed arrow* slow, *dotted arrow* slow and extremely unlikely

$$
\begin{aligned}
&(n_Z, R_1, Z_2) : P(n_R) = \frac{1}{(n_R)!}\left(\frac{g}{\mu}\right)^{n_R} e^{-\frac{g}{\mu}} \\
&(n_Z, R_1, X_2) : P(n_R) = \delta_{n_R,0} \\
&(n_Z, R_1, R_2) : P(n_R) = \delta_{n_R,0} \\
&(n_Z, X_1, X_2) : P(n_R) = \delta_{n_R,0} \\
&(n_Z, X_1, R_2) : P(n_R) = \delta_{n_R,0} \\
&(n_Z, Z_1, Z_2) : P(n_R) = \frac{1}{(n_R)!}\left(\frac{2g}{\mu}\right)^{n_R} e^{-\frac{2g}{\mu}} \\
&(n_Z, Z_1, R_2) : P(n_R) = \frac{1}{(n_R)!}\left(\frac{g}{\mu}\right)^{n_R} e^{-\frac{g}{\mu}}.
\end{aligned}
\tag{4.1}
$$

Notice that the family of states for the reduced system is

$$(A, n_R) \in \mathcal{F} \times \mathbb{N}_*$$

where

$$A \in \mathcal{F} = \{(R_1, Z_2), (R_1, X_2), (R_1, R_2), (X_1, X_2), (X_1, R_2), (Z_1, Z_2), (Z_1, R_2)\}$$

Notice that $\mathcal{F}$ is smaller than $\mathcal{E}^2$ due to the fact that the states with $(X_1, Z_2), (Z_1, X_2)$ disappear in times of order ε. On the other hand, in the subset of $\mathcal{F}$ given by $\{(R_1, R_2), (R_1, X_2), (X_1, R_2), (X_1, X_2)\}$ it is possible to have only $n_R = 0$, since otherwise the $R's$ would combine with X_i or desintegrate in times of order ε too. In other words, the fast transitions indicated in Fig. 1 having as starting point the states $(R_1, X_2), (X_1, X_2), (X_1, R_2)$ can take place only if $n_R \neq 0$. Therefore, the state of the system can remain during times of order one at the states labeled by those elements of $\mathcal{F}$ if $n_R = 0$.

We now compute the transition probabilities between the states given in (4.1) in time scales of order one, or more precisely in times δt satisfying $\varepsilon \ll \delta t \ll 1$. During these time scales we can have with probability very close to one only one slow transition

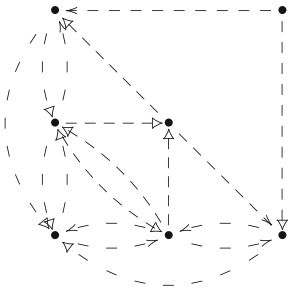

Fig. 2 *Dashed arrow* one slow transition and arbitrarily many fast

combined with arbitrarily many fast transitions. The list of admissible transitions, with the corresponding probabilities, for the reduced Markov process is the following

$$
\begin{aligned}
&X_1X_2 \to \begin{cases} R_1Z_2 : \alpha n_Z \\ Z_1R_2 : \alpha n_Z \end{cases}, \quad Z_1Z_2 \to \begin{cases} Z_1R_2 : \beta \\ R_1Z_2 : \beta \end{cases}, \quad R_1R_2 \to \begin{cases} X_1R_2 : \frac{\sigma\mu}{\mu+\gamma} \\ R_1X_2 : \frac{\sigma\mu}{\mu+\gamma} \end{cases} \\
&R_1X_2 \to \begin{cases} R_1Z_2 : \alpha n_Z \\ X_1X_2 : \frac{\sigma\mu}{\mu+2\gamma} \\ X_1R_2 : \frac{\sigma\gamma}{\mu+2\gamma} \end{cases}, \quad X_1R_2 \to \begin{cases} Z_1R_2 : \alpha n_Z \\ X_1X_2 : \frac{\sigma\mu}{\mu+2\gamma} \\ R_1X_2 : \frac{\sigma\gamma}{\mu+2\gamma} \end{cases} \\
&R_1Z_2 \to \begin{cases} R_1X_2 : \beta\Gamma \\ R_1R_2 : \beta\,(1-\Gamma) \end{cases}, \quad Z_1R_2 \to \begin{cases} X_1R_2 : \beta\Gamma \\ R_1R_2 : \beta\,(1-\Gamma) \end{cases}
\end{aligned}
\tag{4.2}
$$

where

$$
\Gamma = \sum_{n_R=0}^{\infty} \frac{1}{(n_R)!} \frac{\left(\frac{g}{\mu}\right)^{n_R} e^{-\frac{g}{\mu}}}{\prod_{k=1}^{n_R}\left(1+\frac{\gamma}{\mu}\cdot k\right)} \tag{4.3}
$$

We have represented in the Fig. 2 the set of states in $\mathcal{F}$, as well as the possible transitions between them in time scales of order one. The details of these computations are included in Sect. 6. The computation of some of the probabilities in (4.2) requires some care, because all possible ways of combining a slow transition with many fast transitions must be taken into account. The details of these computation are given in Sect. 6. It is relevant to remark (cf. Sect. 6) that $\Gamma < 1$. It is also important to remark that in time scales where t is of order one, the state Z_1Z_2 is transient, because there are no transitions which can bring the state of the system to it.

The equation describing the evolution of the probabilities $f\,(\eta_1, \eta_2, n_Z, t)$, the solution of the reduced model, which evolve according to the transition probabilities (4.2) are the following ones

$$
\begin{aligned}
f_t\,(R_1, R_2, n_Z) = {} & \mathcal{L}\,(f)\,(R_1, R_2, n_Z) - \frac{2\sigma\mu}{\mu+\gamma} f\,(R_1, R_2, n_Z) \\
& + \beta\,(1-\Gamma)\,[f\,(R_1, Z_2, n_Z) + f\,(Z_1, R_2, n_Z)]
\end{aligned}
$$

$$
\begin{aligned}
f_t(X_1,R_2,n_Z) &= \mathcal{L}(f)(X_1,R_2,n_Z) - \left(\alpha n_Z + \frac{\sigma(\mu+\gamma)}{\mu+2\gamma}\right) f(X_1,R_2,n_Z) \\
&\quad + \frac{\sigma\gamma}{\mu+2\gamma} f(R_1,X_2,n_Z) + \frac{\sigma\mu}{\mu+\gamma} f(R_1,R_2,n_Z) \\
&\quad + \beta\Gamma \mathbf{1}_{\{n_Z\geq 1\}} f(Z_1,R_2,n_Z-1) \\
f_t(R_1,X_2,n_Z) &= \mathcal{L}(f)(R_1,X_2,n_Z) - \left(\alpha n_Z + \frac{\sigma(\mu+\gamma)}{\mu+2\gamma}\right) f(R_1,X_2,n_Z) \\
&\quad + \frac{\sigma\gamma}{\mu+2\gamma} f(X_1,R_2,n_Z) + \frac{\sigma\mu}{\mu+\gamma} f(R_1,R_2,n_Z) \\
&\quad + \beta\Gamma \mathbf{1}_{\{n_Z\geq 1\}} f(R_1,Z_2,n_Z-1) \\
f_t(Z_1,R_2,n_Z) &= \mathcal{L}(f)(Z_1,R_2,n_Z) - \beta f(Z_1,R_2,n_Z) + \alpha(n_Z+1) f(X_1,R_2,n_Z+1) \\
&\quad + \beta \mathbf{1}_{\{n_Z\geq 1\}} f(Z_1,Z_2,n_Z-1) + \alpha(n_Z+1) f(X_1,X_2,n_Z+1) \\
f_t(R_1,Z_2,n_Z) &= \mathcal{L}(f)(R_1,Z_2,n_Z) - \beta f(R_1,Z_2,n_Z) + \alpha(n_Z+1) f(R_1,X_2,n_Z+1) \\
&\quad + \beta \mathbf{1}_{\{n_Z\geq 1\}} f(Z_1,Z_2,n_Z-1) + \alpha(n_Z+1) f(X_1,X_2,n_Z+1) \\
f_t(X_1,X_2,n_Z) &= \mathcal{L}(f)(X_1,X_2,n_Z) - 2\alpha n_Z f(X_1,X_2,n_Z) \\
&\quad + \frac{\sigma\mu}{\mu+2\gamma}\left[f(X_1,R_2,n_Z) + f(R_1,X_2,n_Z)\right] \\
f_t(Z_1,Z_2,n_Z) &= \mathcal{L}(f)(Z_1,Z_2,n_Z) - 2\beta f(Z_1,Z_2,n_Z)
\end{aligned} \tag{4.4}
$$

where

$$
\begin{aligned}
\mathcal{L}(f)(\eta_1,\eta_2,n_Z) &= -(K+\lambda n_Z) f(\eta_1,\eta_2,n_Z) + \lambda(n_Z+1) f(\eta_1,\eta_2,n_Z+1) \\
&\quad + K\mathbf{1}_{\{n_Z\geq 1\}} f(\eta_1,\eta_2,n_Z-1)
\end{aligned} \tag{4.5}
$$

4.1 Equilibrium distribution for the reduced system in the limit $\beta \to 0$

There are no well defined peaks for the stationary solutions of the reduced system (4.4) if all the transition probabilities are of order one. Therefore, we will assume that one of the coefficients is small, in order to obtain a clear bistable system. More precisely, we will assume that $\beta > 0$ is sufficiently small. In the original chemical system this just means that the deactivation reaction for the complex ZX_i is slower than the other reactions.

Therefore, we will study asympotic behaviours for the bistability in the regime of $\varepsilon \to 0$ and $\beta \to 0$ in the following subsections.

We will need a general solvability result for a class of problems that will be used repeatedly in the following arguments.

Lemma 4 *Suppose that $A > 0$ and that the operator $\mathcal{L}(f)$ is defined as in (4.5). Assume that*
$\{g(n_Z) \mid n_z = 0,1,2,\ldots\}$ is a sequence satisfying $\sum_{n_Z=0}^{\infty} |g(n_Z)| < \infty$. Then, there exists a unique solution of the equation

$$
\mathcal{L}(f)(n_Z) - Af(n_Z) + g(n_Z) = 0, \quad n_Z = 0,1,2,3,\ldots. \tag{4.6}
$$

satisfying $\sum_{n_Z=0}^{\infty} |f(n_Z)| < \infty$.

Proof Equation (4.6) is a difference equation with a one-parameter family of solutions which can be parametrized using $f(0)$, since $f(1)$ is determined by the equation in (4.6) with $n_Z = 0$ due to the definition of $\mathcal{L}(f)$ in (4.5). The operator $\mathcal{L}(f)$ can be written in the divergence form for $n_Z \geq 1$:

$$\mathcal{L}(f)(n_Z) = \varphi(n_Z + 1) - \varphi(n_Z)$$

where

$$\varphi(n_Z) = \lambda n_Z f(n_Z) - K f(n_Z - 1)$$

We can then argue as in the proof of Lemma 1 to show that $f(n_Z) \to +\infty$ as $n_Z \to \infty$ if $f(0)$ is positive, sufficiently large and $f(n_Z) \to -\infty$ as $n_Z \to \infty$ if $f(0)$ is negative and $|f(0)|$ are sufficiently large. We can then argue as in the proof of Lemma 1 to show that there exist a value $f(0)$ such that the corresponding solution $f(n_Z)$ remains bounded. A detailed analysis of the asymptotics of $f(n_Z)$ using the methods in [8] shows $\sum_{n_Z=0}^{\infty} |f(n_Z)| < \infty$. The uniqueness of this solution follows from Maximum Principle Argument. □

We now proceed to study the steady states of (4.4) with $\beta > 0$. We first notice that, since $\sum_{n_R=0}^{\infty} \mathcal{L}(f)(Z_1, Z_2, n_Z) = 0$, the steady states satisfy

$$f(Z_1, Z_2, n_Z) = 0 \tag{4.7}$$

for any $\beta > 0$.

In order to compute the asymptotics of the steady states of (4.4) we compute first the steady states with $\beta = 0$. It is possible to have such steady states with $f(Z_1, Z_2, n_Z) \neq 0$, but, since any positive β implies (4.7) we will restrict our analysis to the steady states satisfying this identity. The steady states satisfying (4.7) are:

$$f(\eta_1, \eta_2, n_Z) = 0 \text{ for } (\eta_1, \eta_2) \notin \{(R_1, Z_2), (Z_1, R_2)\} \tag{4.8}$$

$$f_0(R_1, Z_2, n_Z) = \frac{A}{n_Z!}\left(\frac{K}{\lambda}\right)^{n_Z} e^{-\frac{K}{\lambda}} \quad f_0(Z_1, R_2, n_Z) = \frac{B}{n_Z!}\left(\frac{K}{\lambda}\right)^{n_Z} e^{-\frac{K}{\lambda}},$$
$$A + B = 1, A \geq 0, B \geq 0, \tag{4.9}$$

where A and B will be determined in the analysis that follows.

We now compute the steady states associated to (4.4) using a perturbative argument for $\beta \to 0$. We obtain that $f(R_1, R_2, n_Z)$ is of order β and it can be computed to this order solving the equation

$$0 = \mathcal{L}(f)(R_1, R_2, n_Z) - \frac{2\sigma\mu}{\mu + \gamma} f(R_1, R_2, n_Z) + \beta(1 - \Gamma)[f_0(R_1, Z_2, n_Z) + f_0(Z_1, R_2, n_Z)] \tag{4.10}$$

where the functions f_0 are as in (4.9). Notice that (4.10) has a unique solution due to Lemma 4. Moreover, since

$$[f_0(R_1, Z_2, n_Z) + f_0(Z_1, R_2, n_Z)] = \frac{1}{n_Z!}\left(\frac{K}{\lambda}\right)^{n_Z} e^{-\frac{K}{\lambda}}$$

it follows that $f(R_1, R_2, n_Z)$ is independent of the specific values of A, B, at least to order β.

On the other hand, we can compute the functions $f(X_1, R_2, n_Z)$, $f(R_1, X_2, n_Z)$ to order β using the equations

$$0 = \mathcal{L}(f)(X_1, R_2, n_Z) - \left(\alpha n_Z + \frac{\sigma(\mu+\gamma)}{\mu+2\gamma}\right) f(X_1, R_2, n_Z) + \frac{\sigma\gamma}{\mu+2\gamma} f(R_1, X_2, n_Z) + \frac{\sigma\mu}{\mu+\gamma} f(R_1, R_2, n_Z) + \beta\Gamma \mathbf{1}_{\{n_Z\geq 1\}} f_0(Z_1, R_2, n_Z - 1) \tag{4.11}$$

$$0 = \mathcal{L}(f)(R_1, X_2, n_Z) - \left(\alpha n_Z + \frac{\sigma(\mu+\gamma)}{\mu+2\gamma}\right) f(R_1, X_2, n_Z) + \frac{\sigma\gamma}{\mu+2\gamma} f(X_1, R_2, n_Z) + \frac{\sigma\mu}{\mu+\gamma} f(R_1, R_2, n_Z) + \beta\Gamma \mathbf{1}_{\{n_Z\geq 1\}} f_0(R_1, Z_2, n_Z - 1) \tag{4.12}$$

Adding (4.11), (4.12) we obtain

$$0 = \mathcal{L}(\Phi)(X_1, R_2, n_Z) - \left(\alpha n_Z + \frac{\sigma\mu}{\mu+2\gamma}\right)\Phi(X_1, R_2, n_Z) + \frac{2\sigma\mu}{\mu+\gamma}\frac{f}{\beta}(R_1, R_2, n_Z) + \Gamma \mathbf{1}_{\{n_Z\geq 1\}}[f_0(Z_1, R_2, n_Z - 1) + f_0(R_1, Z_2, n_Z - 1)], \tag{4.13}$$

where

$$\beta\Phi(n_Z) = f(X_1, R_2, n_Z) + f(R_1, X_2, n_Z) \tag{4.14}$$

Using the fact that $f(R_1, R_2, n_Z)$ can be solved to order β using (4.10) we can obtain also a solution Φ of (4.13) using Lemma 4. Since neither $f(R_1, R_2, n_Z)$ nor $[f_0(Z_1, R_2, n_Z) + f_0(R_1, Z_2, n_Z)]$ depends on the specific choice of A, B the same happens for the function $\Phi(n_Z)$.

We can now compute a closed equation for $f(X_1, R_2, n_Z)$ eliminating $f(R_1, X_2, n_Z)$ from (4.11) using (4.14). Then

$$0 = \mathcal{L}(f)(X_1, R_2, n_Z) - (\alpha n_Z + \sigma) f(X_1, R_2, n_Z) + \frac{\sigma\gamma}{\mu+2\gamma}\Phi(n_Z) + \frac{\sigma\mu}{\mu+\gamma} f(R_1, R_2, n_Z) + \beta\Gamma \mathbf{1}_{\{n_Z\geq 1\}} f_0(Z_1, R_2, n_Z - 1) \tag{4.15}$$

and we have a similar equation for $f(R_1, X_2, n_Z)$. We can then prove existence and uniqueness of $f(R_1, X_2, n_Z)$ using again Lemma 4. Notice that the functions

$f(X_1, R_2, n_Z)$, $f(R_1, X_2, n_Z)$ depend on the choice of the values A, B. More precisely, we can write these functions to order β as

$$f(X_1, R_2, n_Z) = \beta[\varphi_1(n_Z) + B\varphi_2(n_Z)], \quad f(R_1, X_2, n_Z) = \beta[\varphi_1(n_Z) + A\varphi_2(n_Z)] \tag{4.16}$$

where φ_1, φ_2 are the unique solutions of

$$\mathcal{L}(\varphi_1)(n_Z) - (\alpha n_Z + \sigma)\varphi_1(n_Z) + \frac{\sigma\gamma}{\mu + 2\gamma}\Phi(n_Z) + \frac{\sigma\mu}{\mu + \gamma}\frac{f(R_1, R_2, n_Z)}{\beta} = 0 \tag{4.17}$$

$$\mathcal{L}(\varphi_2)(n_Z) - (\alpha n_Z + \sigma)\varphi_2(n_Z) + \Gamma \mathbf{1}_{\{n_Z \geq 1\}}\frac{1}{(n_Z - 1)!}\left(\frac{K}{\lambda}\right)^{n_Z - 1} e^{-\frac{K}{\lambda}} = 0 \tag{4.18}$$

We can now compute $f(X_1, X_2, n_Z)$ to order β solving

$$0 = \mathcal{L}(f)(X_1, X_2, n_Z) - 2\alpha n_Z f(X_1, X_2, n_Z) + \frac{\sigma\mu\beta}{\mu + 2\gamma}\Phi(n_Z) \tag{4.19}$$

where Φ is as in (4.14). Since Φ is independent of the specific choice of A, B the same happens for $f(X_1, X_2, n_Z)$.

Finally we can use the equations for $f(Z_1, R_2, n_Z)$, $f(R_1, Z_2, n_Z)$ to determine the values of A, B. Adding these equations with respect to n_Z we obtain up to order β

$$\begin{aligned} 0 = &-\beta\sum_{n_Z=0}^{\infty} f_0(Z_1, R_2, n_Z) + \alpha\sum_{n_Z=1}^{\infty} n_Z f(X_1, R_2, n_Z) + \beta\sum_{n_Z=0}^{\infty} f(Z_1, Z_2, n_Z) \\ &+\alpha\sum_{n_Z=1}^{\infty} n_Z f(X_1, X_2, n_Z) \\ 0 = &-\beta\sum_{n_Z=0}^{\infty} f_0(R_1, Z_2, n_Z) + \alpha\sum_{n_Z=1}^{\infty} n_Z f(R_1, X_2, n_Z) + \beta\sum_{n_Z=0}^{\infty} f(Z_1, Z_2, n_Z) \\ &+\alpha\sum_{n_Z=1}^{\infty} n_Z f(X_1, X_2, n_Z) \end{aligned}$$

Using now (4.9), (4.16) we obtain

$$\left[\sum_{n_Z=0}^{\infty}\frac{e^{-\frac{K}{\lambda}}}{n_Z!}\left(\frac{K}{\lambda}\right)^{n_Z} - \alpha\sum_{n_Z=1}^{\infty} n_Z\varphi_2(n_Z)\right] B = D \tag{4.20}$$

$$\left[\sum_{n_Z=0}^{\infty}\frac{e^{-\frac{K}{\lambda}}}{n_Z!}\left(\frac{K}{\lambda}\right)^{n_Z} - \alpha\sum_{n_Z=1}^{\infty} n_Z\varphi_2(n_Z)\right] A = D \tag{4.21}$$

where

$$D = \alpha \sum_{n_Z=1}^{\infty} n_Z \varphi_1 (n_Z) + \sum_{n_Z=0}^{\infty} f (Z_1, Z_2, n_Z) + \frac{\alpha}{\beta} \sum_{n_Z=1}^{\infty} n_Z f (X_1, X_2, n_Z)$$

is independent of the specific choice of A, B. Adding in (4.18) with respect to n_Z we obtain

$$\alpha \sum_{n_Z=1}^{\infty} n_Z \varphi_2 (n_Z) + \sigma \sum_{n_Z=0}^{\infty} \varphi_2 (n_Z) = \Gamma \sum_{n_Z=1}^{\infty} \frac{1}{n_Z!} \left(\frac{K}{\lambda}\right)^{n_Z} e^{-\frac{K}{\lambda}}$$

whence, using that $\Gamma < 1$

$$\alpha \sum_{n_Z=1}^{\infty} n_Z \varphi_2 (n_Z) < \Gamma \sum_{n_Z=1}^{\infty} \frac{1}{n_Z!} \left(\frac{K}{\lambda}\right)^{n_Z} e^{-\frac{K}{\lambda}} \leq \sum_{n_Z=1}^{\infty} \frac{1}{n_Z!} \left(\frac{K}{\lambda}\right)^{n_Z} e^{-\frac{K}{\lambda}}$$

Therefore it follows from (4.20), (4.21) that

$$A = B = \frac{1}{2}$$

It is worthwhile to remark that a similar selection of the probability $\frac{1}{2}$ has been obtained in the alignment models studied in [47] for a different type of model, namely a kinetic model, and where the term responsible for the selection is the nondeterministic character of the alignment mechanisms. The results in [47] contrast the ones in [38] where the deterministic character of the dynamics there does not provide any selection mechanism among the two states of the system.

5 On the computation of the switching times

As we have seen in Sect. 4.1 the equilibrium distribution for the system described by the system of reactions (3.1) is concentrated in two different peaks that correspond to two different states of activation of the molecules involved, if ε and β are small. In systems with many molecules it is common to use Kramers' formula in order to compute the switching times between two different regions of high probability. Kramers' formula, however cannot be used to compute switching times for systems of molecules described by means of (3.7), (3.8), (3.9). Nevertheless, the methods to compute the probability distributions for the escape times of transient states of Markov chains are well established (cf. [23]). We recall them with a simple example and adapt it later to the study of our specific problem.

5.1 Analysis of a simplified model

We consider the following simple model with three molecular states

$$A \underset{\rho}{\overset{\lambda}{\rightleftharpoons}} B \to_{\omega} C \tag{5.1}$$

More precisely, we assume that the system described by means of (5.1) can be just in one of the three states A, B, C, with probabilities p_A, p_B, p_C respectively. Suppose that the system (5.1) is initially at state A and we define a stochastic variable ζ as the time that it takes for the system (5.1) to change its state to C. Notice that C is an absorbing state for this Markov chain. The evolution of such transition probabilities is given by the system of equations

$$\begin{aligned} \frac{dp_A}{dt} &= -\lambda p_A + \rho p_B \\ \frac{dp_B}{dt} &= \lambda p_A - (\rho + \omega)\, p_B \\ \frac{dp_C}{dt} &= \omega p_B \end{aligned} \tag{5.2}$$

with $p_A + p_B + p_C = 1$. We then have

$$\begin{aligned} p\left(\{\zeta > t\}\right) &= 1 - p_C\,(t) \\ p\left(\{\zeta \le t\}\right) &= p_C\,(t) \end{aligned}$$

Therefore, the probability density φ associated to the stochastic variable τ is

$$\varphi\,(\tau) = \frac{dp_C\,(\tau)}{d\tau} = \omega p_B\,(\tau)\,, \quad p\left(\{a \le \tau \le b\}\right) = \int_a^{\tau} \varphi\,(s)\,ds$$

where $(p_A, p_B, p_C)\,(t)$ is obtained by solving (5.2) with initial data $(p_A, p_B, p_C)\,(0) = (1, 0, 0)$. Then we have

$$\begin{aligned} \begin{pmatrix} p_A\,(t) \\ p_B\,(t) \end{pmatrix} = & \frac{\exp\left(-\frac{(\lambda+\omega+\rho)t}{2}\right)}{\Delta} \begin{pmatrix} \frac{1}{2}\,(\lambda - \omega - \rho + \Delta) \\ -\lambda \end{pmatrix} \exp\left(-\frac{\Delta t}{2}\right) \\ & - \frac{\exp\left(-\frac{(\lambda+\omega+\rho)t}{2}\right)}{\Delta} \begin{pmatrix} \frac{1}{2}\,(\lambda - \omega - \rho - \Delta) \\ -\lambda \end{pmatrix} \exp\left(\frac{\Delta t}{2}\right) \end{aligned}$$

with

$$\Delta = \sqrt{\lambda^2 - 2\lambda\omega + 2\lambda\rho + \omega^2 + 2\omega\rho + \rho^2}$$

It then follows that

$$\begin{aligned} p_C\,(t) = 1 - p_A\,(t) - p_B\,(t) = 1 - & \frac{\exp\left(-\frac{(\lambda+\omega+\rho)t}{2}\right)}{\Delta} \\ & \left[(\omega + \rho)\cosh\left(\frac{\Delta t}{2}\right) + (\lambda + \Delta)\sinh\left(\frac{\Delta t}{2}\right) - \lambda \exp\left(-\frac{\Delta t}{2}\right)\right] \end{aligned}$$

Therefore, we obtain that

$$\begin{aligned}\phi(t) &= \frac{dp_C(\tau)}{d\tau} \\ &= \frac{\exp\left(-\frac{(\lambda+\omega+\rho)t}{2}\right)}{2\Delta}\left[(-\lambda(\lambda-3\omega+\rho+\Delta))\cosh\left(\frac{\Delta t}{2}\right)\right. \\ &\quad \left.+(\lambda(\lambda+\omega+\rho+\Delta))\sinh\left(\frac{\Delta t}{2}\right)-\lambda(\lambda+\omega+\rho+\Delta)\exp\left(-\frac{\Delta t}{2}\right)\right]\end{aligned}$$

5.2 Switching times for the reduced system (4.4)

We now use a similar argument in order to compute the switching times for the reduced system (4.4). Since the number of variables involved (and possibilities) is much larger a more precise definition of the switching time is needed. We will develop a procedure to compute such switching times in the limit $\beta \to 0$, something that will allow us to use asymptotic methods.

It has been obtained in Sect. 4.1 that for β close to zero the steady states distributions are concentrated near the two states (Z_1, R_2) and (R_1, Z_2) with the values of n_Z at equilibrium. We define a switching time variable τ by means of the time that it takes for the distribution of molecules to arrive for the first time to the state $(\eta_1, \eta_2) = (R_1, Z_2)$ assuming that the initial distribution of molecules is given by the probability distribution

$$f(Z_1, R_2, n_Z) = \frac{1}{n_Z!}\left(\frac{K}{\lambda}\right)^{n_Z} e^{-\frac{K}{\lambda}}, \quad f(\eta_1, \eta_2, n_Z) = 0 \text{ if } (\eta_1, \eta_2) \neq (Z_1, R_2) \tag{5.3}$$

It would be possible to assume other initial distributions for $f(Z_1, R_2, n_Z)$, for instance $f(Z_1, R_2, n_Z) = \delta_{n_Z,\ell}$ for some fixed ℓ. Since the characteristic time scale for the variation of n_Z is much shorter than the switching time scale all these definitions would give similar results for small $\beta \to 0$. We will then assume that the initial molecule distribution is given by (5.3).

In order to compute the switching time we need to solve the system (4.4) with $f(R_1, Z_2, n_Z) = 0$ that amounts to assuming that the state (R_1, Z_2) is an absorbing one for the system. Moreover, the function $f(Z_1, Z_2, n_Z)$ is decoupled in the resulting system, and its effect can be ignored, since in the initial state $f(Z_1, Z_2, n_Z) = 0$. Then (4.4) becomes

$$\begin{aligned}f_t(R_1, R_2, n_Z) &= \mathcal{L}(f)(R_1, R_2, n_Z) - \frac{2\sigma\mu}{\mu+\gamma} f(R_1, R_2, n_Z) + \beta(1-\Gamma) f(Z_1, R_2, n_Z) \\ f_t(X_1, R_2, n_Z) &= \mathcal{L}(f)(X_1, R_2, n_Z) - \left(\alpha n_Z + \frac{\sigma(\mu+\gamma)}{\mu+2\gamma}\right) f(X_1, R_2, n_Z) \\ &\quad + \frac{\sigma\gamma}{\mu+2\gamma} f(R_1, X_2, n_Z) + \frac{\sigma\mu}{\mu+\gamma} f(R_1, R_2, n_Z) \\ &\quad + \beta\Gamma \mathbf{1}_{\{n_Z \geq 1\}} f(Z_1, R_2, n_Z - 1)\end{aligned}$$

$$
\begin{aligned}
f_t(R_1, X_2, n_Z) &= \mathcal{L}(f)(R_1, X_2, n_Z) - \left(\alpha n_Z + \frac{\sigma(\mu+\gamma)}{\mu+2\gamma}\right) f(R_1, X_2, n_Z) \\
&\quad + \frac{\sigma\gamma}{\mu+2\gamma} f(X_1, R_2, n_Z) + \frac{\sigma\mu}{\mu+\gamma} f(R_1, R_2, n_Z) \\
f_t(Z_1, R_2, n_Z) &= \mathcal{L}(f)(Z_1, R_2, n_Z) - \beta f(Z_1, R_2, n_Z) + \alpha(n_Z+1) f(X_1, R_2, n_Z+1) \\
&\quad + \alpha(n_Z+1) f(X_1, X_2, n_Z+1) \\
f_t(X_1, X_2, n_Z) &= \mathcal{L}(f)(X_1, X_2, n_Z) - 2\alpha n_Z f(X_1, X_2, n_Z) \\
&\quad + \frac{\sigma\mu}{\mu+2\gamma}[f(X_1, R_2, n_Z) + f(R_1, X_2, n_Z)]
\end{aligned} \tag{5.4}
$$

This system must be solved with initial data (5.3). Then, the probability of the state of the system not reaching $(\eta_1, \eta_2) = (R_1, Z_2)$ at time t is

$$
\sum_{\{(\eta_1,\eta_2)\neq(R_1,Z_2)\}} \sum_{n_Z=0}^{\infty} f(\eta_1, \eta_2, n_Z, t)
$$

This probability is the same as $P(\{\zeta > t\})$. Then, the probability density that describes the probability distribution is given by

$$
\varphi(t) = -\sum_{\{(\eta_1,\eta_2)\neq(R_1,Z_2)\}} \sum_{n_Z=0}^{\infty} \frac{\partial f}{\partial t}(\eta_1, \eta_2, n_Z, t) \tag{5.5}
$$

Our goal is to solve the system (5.4) with initial data (5.3) for small β. Kramers' formula is not suitable for this problem. Nevertheless, the structure of the problem suggests to look for solutions depending on two time scales, or more precisely, having the form

$$
f(\eta_1, \eta_2, n_Z, t) = F(\eta_1, \eta_2, n_Z, t, \tau), \quad \tau = \beta t \tag{5.6}
$$

$$
F(\eta_1, \eta_2, n_Z, t, \tau) = F_0(\eta_1, \eta_2, n_Z, t, \tau) + \beta F_1(\eta_1, \eta_2, n_Z, t, \tau) + \cdots \tag{5.7}
$$

where, as usual in problems with multiple scales, the dependence of the functions F_0, F_1 on the variable τ is made in order to avoid the growth of these functions in the variable t.

Keeping the leading order terms (of order 1) we obtain

$$
\begin{aligned}
F_{0,t}(R_1, R_2, n_Z) &= \mathcal{L}(F_0)(R_1, R_2, n_Z) - \frac{2\sigma\mu}{\mu+\gamma} F_0(R_1, R_2, n_Z) \\
F_{0,t}(X_1, R_2, n_Z) &= \mathcal{L}(F_0)(X_1, R_2, n_Z) - \left(\alpha n_Z + \frac{\sigma(\mu+\gamma)}{\mu+2\gamma}\right) F_0(X_1, R_2, n_Z) \\
&\quad + \frac{\sigma\gamma}{\mu+2\gamma} F_0(R_1, X_2, n_Z) + \frac{\sigma\mu}{\mu+\gamma} F_0(R_1, R_2, n_Z) \\
F_{0,t}(R_1, X_2, n_Z) &= \mathcal{L}(F_0)(R_1, X_2, n_Z) - \left(\alpha n_Z + \frac{\sigma(\mu+\gamma)}{\mu+2\gamma}\right) F_0(R_1, X_2, n_Z) \\
&\quad + \frac{\sigma\gamma}{\mu+2\gamma} F_0(X_1, R_2, n_Z) + \frac{\sigma\mu}{\mu+\gamma} F_0(R_1, R_2, n_Z)
\end{aligned}
$$

$$
\begin{aligned}
F_{0,t}\left(Z_1, R_2, n_Z\right) &= \mathcal{L}\left(F_0\right)\left(Z_1, R_2, n_Z\right) + \alpha\left(n_Z+1\right) F_0\left(X_1, R_2, n_Z+1\right) \\
&\quad + \alpha\left(n_Z+1\right) F_0\left(X_1, X_2, n_Z+1\right) \\
F_{0,t}\left(X_1, X_2, n_Z\right) &= \mathcal{L}\left(F_0\right)\left(X_1, X_2, n_Z\right) - 2\alpha n_Z F_0\left(X_1, X_2, n_Z\right) \\
&\quad + \frac{\sigma\mu}{\mu+2\gamma}\left[F_0\left(X_1, R_2, n_Z\right) + F_0\left(R_1, X_2, n_Z\right)\right]
\end{aligned}
$$

It is readily seen that the functions $F_0\left(R_1, R_2, n_Z\right)$, $\left[F_0\left(R_1, X_2, n_Z\right) + F_0\left(X_1, R_2, n_Z\right)\right]$, $F_0\left(X_1, X_2, n_Z\right)$ decrease exponentially in time scales of order one. In particular this implies also that $F_0\left(R_1, X_2, n_Z\right)$ and $F_0\left(X_1, R_2, n_Z\right)$ decrease exponentially. On the other hand $F_0\left(Z_1, R_2, n_Z\right)$ approaches to a solution of $\mathcal{L}\left(F_0\right)\left(Z_1, R_2, n_Z\right) = 0$ for these time scales. Therefore, in the long time scale τ we can assume that $F_0\left(\eta_1, \eta_2, n_Z\right) = 0$ for $\left(\eta_1, \eta_2\right) \neq \left(Z_1, R_2\right)$. In order to compute the rate of change of $F_0\left(Z_1, R_2, n_Z\right)$ in the time scale τ we need to compute the equations for $F_1\left(\eta_1, \eta_2, n_Z\right)$, $\left(\eta_1, \eta_2\right) \neq \left(Z_1, R_2\right)$. To this end, we just keep the terms of order β that result from plugging (5.7) into (5.4). We then obtain

$$
\begin{aligned}
F_{1,t}\left(R_1, R_2, n_Z\right) &= \mathcal{L}\left(F_1\right)\left(R_1, R_2, n_Z\right) - \frac{2\sigma\mu}{\mu+\gamma} F_1\left(R_1, R_2, n_Z\right) \\
&\quad + \left(1-\Gamma\right) F_0\left(Z_1, R_2, n_Z\right) \\
F_{1,t}\left(X_1, R_2, n_Z\right) &= \mathcal{L}\left(F_1\right)\left(X_1, R_2, n_Z\right) - \left(\alpha n_Z + \frac{\sigma\left(\mu+\gamma\right)}{\mu+2\gamma}\right) F_1\left(X_1, R_2, n_Z\right) \\
&\quad + \frac{\sigma\gamma\beta}{\mu+2\gamma} F_1\left(R_1, X_2, n_Z\right) + \frac{\sigma\mu}{\mu+\gamma} F_1\left(R_1, R_2, n_Z\right) \\
&\quad + \Gamma \mathbf{1}_{\{n_Z \geq 1\}} F_0\left(Z_1, R_2, n_Z - 1\right) \\
F_{1,t}\left(R_1, X_2, n_Z\right) &= \mathcal{L}\left(F_1\right)\left(R_1, X_2, n_Z\right) - \left(\alpha n_Z + \frac{\sigma\left(\mu+\gamma\right)}{\mu+2\gamma}\right) F_1\left(R_1, X_2, n_Z\right) \\
&\quad + \frac{\sigma\gamma}{\mu+2\gamma} F_1\left(X_1, R_2, n_Z\right) + \frac{\sigma\mu}{\mu+\gamma} F_1\left(R_1, R_2, n_Z\right) \\
F_{0,\tau}\left(Z_1, R_2, n_Z\right) &+ F_{1,t}\left(Z_1, R_2, n_Z\right) \\
&= -F_0\left(Z_1, R_2, n_Z\right) + \mathcal{L}\left(F_1\right)\left(Z_1, R_2, n_Z\right) \\
&\quad + \alpha\left(n_Z+1\right) F_1\left(X_1, R_2, n_Z+1\right) \\
&\quad + \alpha\left(n_Z+1\right) F_1\left(X_1, X_2, n_Z+1\right) \\
F_{1,t}\left(X_1, X_2, n_Z\right) &= \mathcal{L}\left(F_1\right)\left(X_1, X_2, n_Z\right) - 2\alpha n_Z F_1\left(X_1, X_2, n_Z\right) \\
&\quad + \frac{\sigma\mu}{\mu+2\gamma}\left[F_1\left(X_1, R_2, n_Z\right) + F_1\left(R_1, X_2, n_Z\right)\right]
\end{aligned}
\tag{5.8}
$$

Since the time scale for stabilization of the functions $F_1\left(\eta_1, \eta_2, n_Z\right)$, $\left(\eta_1, \eta_2\right) \neq \left(Z_1, R_2\right)$ is of order one, we can assume that all these functions are in the steady regime for relevant changes of the time scale τ. On the other hand, since $F_0\left(Z_1, R_2, n_Z\right)$ reaches the equilibrium in times t of order one we have

$$
F_0\left(Z_1, R_2, n_Z\right) = A\left(\tau\right) \psi_0\left(Z_1, R_2, n_Z\right) \tag{5.9}
$$

where $A(\tau) \geq 0,\ A(0) = 1$ and $\psi_0(Z_1, R_2, n_Z) = \frac{1}{n_Z!}\left(\frac{K}{\lambda}\right)^{n_Z} e^{-\frac{K}{\lambda}}$. Notice that $\sum_{n_Z=0}^{\infty} \psi_0(Z_1, R_2, n_Z) = 1$. Due to the linearity of (5.8) there is a linear mapping

$$F_0(Z_1, R_2, n_Z) \to \{F_1(\eta_1, \eta_2, n_Z),\ (\eta_1, \eta_2) \neq (Z_1, R_2)\}$$

which can be written as follows. We define functions $\psi_1(\eta_1, \eta_2, n_Z),\ (\eta_1, \eta_2) \neq (Z_1, R_2)$ as the solutions of

$$\begin{aligned}
0 &= \mathcal{L}(\psi_1)(R_1, R_2, n_Z) - \frac{2\sigma\mu}{\mu+\gamma}\psi_1(R_1, R_2, n_Z) + (1-\Gamma)\psi_0(Z_1, R_2, n_Z) \\
0 &= \mathcal{L}(\psi_1)(X_1, R_2, n_Z) - \left(\alpha n_Z + \frac{\sigma(\mu+\gamma)}{\mu+2\gamma}\right)\psi_1(X_1, R_2, n_Z) \\
&\quad + \frac{\sigma\gamma\beta}{\mu+2\gamma}\psi_1(R_1, X_2, n_Z) + \frac{\sigma\mu}{\mu+\gamma}\psi_1(R_1, R_2, n_Z) \\
&\quad + \Gamma \mathbf{1}_{\{n_Z \geq 1\}}\psi_0(Z_1, R_2, n_Z - 1) \\
0 &= \mathcal{L}(\psi_1)(R_1, X_2, n_Z) - \left(\alpha n_Z + \frac{\sigma(\mu+\gamma)}{\mu+2\gamma}\right)\psi_1(R_1, X_2, n_Z) \\
&\quad + \frac{\sigma\gamma}{\mu+2\gamma}\psi_1(X_1, R_2, n_Z) + \frac{\sigma\mu}{\mu+\gamma}\psi_1(R_1, R_2, n_Z) \\
0 &= \mathcal{L}(\psi_1)(X_1, X_2, n_Z) - 2\alpha n_Z \psi_1(X_1, X_2, n_Z) \\
&\quad + \frac{\sigma\mu}{\mu+2\gamma}\left[\psi_1(X_1, R_2, n_Z) + \psi_1(R_1, X_2, n_Z)\right]
\end{aligned} \tag{5.10}$$

Existence and uniqueness of these functions follow from Lemma 4. In the case of $\psi_1(X_1, R_2, n_Z),\ \psi_1(R_1, X_2, n_Z)$ we must consider first the equation satisfied by $[\psi_1(X_1, R_2, n_Z) + \psi_1(R_1, X_2, n_Z)]$ as in the analysis of (4.11), (4.12).

Taking into account (5.9) we obtain

$$F_1(\eta_1, \eta_2, n_Z) = A(\tau)\psi_1(\eta_1, \eta_2, n_Z), \quad (\eta_1, \eta_2) \neq (Z_1, R_2) \tag{5.11}$$

On the other hand we must determine $F_{0,\tau}(Z_1, R_2, n_Z)$ that imposes a compatibility condition in order to avoid linear growth of the solutions of the fourth equation of (5.8). This condition reads as

$$\begin{aligned}
\sum_{n_Z=0}^{\infty} F_{0,\tau}(Z_1, R_2, n_Z) &= -\sum_{n_Z=0}^{\infty} F_0(Z_1, R_2, n_Z) + \alpha \sum_{n_Z=0}^{\infty} (n_Z+1) F_1(X_1, R_2, n_Z+1) \\
&\quad + \alpha \sum_{n_Z=0}^{\infty} (n_Z+1) F_1(X_1, X_2, n_Z+1)
\end{aligned} \tag{5.12}$$

Using (5.9), (5.11), as well as the initial distribution (5.3) we obtain

$$\begin{aligned}
\frac{dA(\tau)}{d\tau} &= -\chi A(\tau) \\
A(0) &= 1
\end{aligned} \tag{5.13}$$

where

$$\chi = 1 - \alpha \sum_{n_Z=1}^{\infty} n_Z \psi_1 (X_1, R_2, n_Z) - \alpha \sum_{n_Z=1}^{\infty} n_Z \psi_1 (X_1, X_2, n_Z) \tag{5.14}$$

We now claim that χ is strictly positive. This would imply that $A(\tau)$ approaches asymptotically to its equilibrium value $A = 0$ as $\tau \to \infty$. In order to prove this we must study the properties of the solutions of (5.10). Notice that these equations have many analogies with the steady state equations analyzed in Sect. 4.1. Actually they can be analyzed along similar lines. Notice first that

$$\psi_1 (R_1, R_2, n_Z) = f (R_1, R_2, n_Z)$$

with $f(R_1, R_2, n_Z)$ as in (4.10). On the other hand the equations for $\psi_1 (X_1, R_2, n_Z)$, $\psi_1 (R_1, X_2, n_Z)$ in (5.10) are the same as the ones for $f_1 (X_1, R_2, n_Z)$, $f_1 (R_1, X_2, n_Z)$ in (4.11), (4.12) with $A = 0$, $B = 1$ in (4.9). Then

$$\psi_1 (X_1, R_2, n_Z) = \varphi_1 (n_Z) + \varphi_2 (n_Z), \quad \psi_1 (R_1, X_2, n_Z) = \varphi_1 (n_Z) \tag{5.15}$$

with φ_1, φ_2 as in (4.17), (4.18) with $\frac{f(R_1,R_2,n_Z)}{\beta}$ replaced by $\psi_1 (R_1, R_2, n_Z)$. A similar argument yields

$$\psi_1 (X_1, X_2, n_Z) = \frac{f_1 (X_1, X_2, n_Z)}{\beta}$$

with $f_1 (X_1, X_2, n_Z)$ as in (4.19) and $\Phi (n_Z) = \psi_1 (R_1, X_2, n_Z) + \psi_1 (X_1, R_2, n_Z)$. Using all these identities it follows that

$$\chi = 1 - \alpha \sum_{n_Z=1}^{\infty} n_Z [\varphi_1 (n_Z) + \varphi_2 (n_Z)] - \alpha \sum_{n_Z=1}^{\infty} n_Z \psi_1 (X_1, X_2, n_Z) \tag{5.16}$$

We notice that $\chi > 0$. To check this we argue as follows. Using (5.15) and (4.14) we obtain

$$\Phi (n_Z) = 2\varphi_1 (n_Z) + \varphi_2 (n_Z) \tag{5.17}$$

On the other hand, adding (4.19) with $\frac{f(X_1,X_2,n_Z)}{\beta}$ replaced by $\psi_1 (X_1, X_2, n_Z)$ and using also (5.17) we obtain, after dividing by 2

$$\alpha \sum_{n_Z=1}^{\infty} n_Z \psi_1 (X_1, X_2, n_Z) = \frac{\sigma\mu}{2(\mu + 2\gamma)} \sum_{n_Z=0}^{\infty} \Phi (n_Z) = \frac{\sigma\mu}{\mu + 2\gamma} \sum_{n_Z=0}^{\infty} \varphi_1 (n_Z) + \frac{\sigma\mu}{2(\mu + 2\gamma)} \sum_{n_Z=0}^{\infty} \varphi_2 (n_Z) \tag{5.18}$$

On the other hand, adding (4.17) with $\frac{f(R_1,R_2,n_Z)}{\beta}$ replaced by $\psi_1(R_1, R_2, n_Z)$ we obtain

$$\alpha \sum_{n_Z=1}^{\infty} n_Z \varphi_1(n_Z) + \sigma \sum_{n_Z=0}^{\infty} \varphi_1(n_Z) = \frac{\sigma\gamma}{\mu+2\gamma} \sum_{n_Z=0}^{\infty} \Phi(n_Z) + \frac{\sigma\mu}{\mu+\gamma} \sum_{n_Z=0}^{\infty} \psi_1(R_1, R_2, n_Z)$$

and using (5.17) we obtain

$$\alpha \sum_{n_Z=1}^{\infty} n_Z \varphi_1(n_Z) = -\frac{\sigma\mu}{\mu+2\gamma} \sum_{n_Z=0}^{\infty} \varphi_1(n_Z) + \frac{\sigma\gamma}{\mu+2\gamma} \sum_{n_Z=0}^{\infty} \varphi_2(n_Z) + \frac{\sigma\mu}{\mu+\gamma} \sum_{n_Z=0}^{\infty} \psi_1(R_1, R_2, n_Z) \tag{5.19}$$

On the other hand, adding (4.18) over n_Z we obtain

$$\alpha \sum_{n_Z=1}^{\infty} n_Z \varphi_2(n_Z) + \sigma \sum_{n_Z=0}^{\infty} \varphi_2(n_Z) = \Gamma \tag{5.20}$$

Adding the first equation in (5.10) and dividing by 2

$$\frac{\sigma\mu}{\mu+\gamma} \sum_{n_Z=0}^{\infty} \psi_1(R_1, R_2, n_Z) = \frac{(1-\Gamma)}{2} \tag{5.21}$$

Using (5.21) to eliminate the last term in (5.19) and adding the resulting equation to (5.18) and (5.20) we obtain, after some simplifications

$$\alpha \sum_{n_Z=1}^{\infty} [n_Z \varphi_1(n_Z) + n_Z \varphi_2(n_Z) + n_Z \psi_1(X_1, X_2, n_Z)] = -\frac{\sigma}{2} \sum_{n_Z=0}^{\infty} \varphi_2(n_Z) + \frac{(1+\Gamma)}{2} \tag{5.22}$$

Using the definition of χ in (5.14) we finally obtain

$$\chi = \frac{(1-\Gamma)}{2} + \frac{\sigma}{2} \sum_{n_Z=0}^{\infty} \varphi_2(n_Z)$$

and since $\Gamma \leq 1$ we obtain $\chi > 0$. This gives the desired exponential decay of $A(\tau)$ in (5.13).

6 Computation of the transition probabilities in Sect. 4

In this section, we include the computations of the transition probabilities in Sect. 4. Since the computations on other transition probabilities are either easy to deduce or similar to one of the computations below, we will focus on the transitions from R_1R_2 to R_1X_2 and from R_1Z_2 to R_1X_2 just to illustrate the method used.

(1) To compute the transition probability from R_1R_2 to R_1X_2, we let $\tau = t/\varepsilon$, where $\varepsilon \ll t \ll 1$. Let us denote as $\theta_k,\ k = 1, 2, 3$ the following states

$$\theta_1 = (n_R = 0, R_1, R_2)\,, \quad \theta_2 = (n_R = 1, R_1, X_2)\,, \quad \theta_3 = (n_R = 0, R_1, X_2)\,,$$

and let $f\,(\theta_k, \tau)$ be their probability at θ_k at time τ. Since the lifetime of the state θ_1 is of order ε, and the molecule R has a lifetime of order ε in absence of Z_1 or Z_2 (cf. (3.1) and also (4.1)), the transition from R_1R_2 to R_1X_2 can take place in times of order one, only by means of the transition from θ_1 to θ_3. Using (3.1) we obtain that $f\,(\theta_k, \tau)\,,\ k = 1, 2, 3$ satisfy, to the leading order, the following ODE system

$$\begin{aligned}
\frac{\partial f}{\partial \tau}\,(\theta_1, \tau) &= \gamma f\,(\theta_1, \tau)\\
\frac{\partial f}{\partial \tau}\,(\theta_2, \tau) &= -\,(\mu + \gamma)\, f\,(\theta_2, \tau)\\
\frac{\partial f}{\partial \tau}\,(\theta_3, \tau) &= \mu f\,(\theta_3, \tau)
\end{aligned} \tag{6.1}$$

with the initial condition $f\,(\theta_1, 0) = 0$, $f\,(\theta_2, 0) = 1$, $f\,(\theta_3, 0) = 0$. We have neglected in (6.1) transition probabilities of order ε, associated to fast transitions. Solving (6.1), we find

$$\begin{aligned}
f\,(\theta_2, \tau) = e^{-(\mu+\gamma)\tau},\ f\,(\theta_3, \tau) &= \frac{\mu}{\mu+\gamma}\left[1 - e^{-(\mu+\gamma)\tau}\right],\ f\,(\theta_1, \tau)\\
&= \frac{\gamma}{\mu+\gamma}\left[1 - e^{-(\mu+\gamma)\tau}\right]
\end{aligned} \tag{6.2}$$

Thus, in time scales of order $\varepsilon \ll t \ll 1$, the transition probability for unit of time from R_1R_2 to R_1X_2 is the product of the transition probability from θ_1 to θ_2 by the transition probability during such intermediate scale from θ_2 to θ_3. The former probability is σ, and the second one is, due to our choice of time scales, $f\,(\theta_2, \infty) = \frac{\mu}{\mu+\gamma}$. Therefore, the transition rate from R_1R_2 to R_1X_2 is $\frac{\sigma\mu}{\mu+\gamma}$. The computation of the transition rate from R_1R_2 to X_1R_2 is similar. On the other hand all the transition probabilities starting at the states $R_1X_2,\ X_1R_2, Z_1Z_2,\ X_1X_2,\ R_1R_2$ can be computed in a similar form.

(2) To compute the transition probabilities starting at the point R_1Z_2 we must take into account that the number n_R must eventually jump to zero after a finite number of fast transitions. The states accessible from R_1Z_2 by means of one slow transition and an arbitrary number of fast transitions are $R_1X_2,\ R_1R_2$. The first step

in either of these transitions is a slow transition from the state (n_R, R_1Z_2) to the state (n_R, R_1, X_2). We now notice that there are two different fast ways for the state (n_R, R_1, X_2) to lose one molecule R, that are respectively a transition corresponding to $(n_R - 1, R_1, X_2)$ or a transition to $(n_R - 1, R_1, R_2)$. In the second case, the state of the molecules R_1, R_2 cannot be modified any longer by means of fast transitions, and therefore the final state, for times t satisfying $\varepsilon \ll t \ll 1$ would be (R_1, R_2) with $n_R = 0$. Let us denote as $\theta(n_R)$ the transition probability from (n_R, R_1, X_2) to $(0, R_1, X_2)$. Notice, that in order to have a transition between these two states we must have the following chain of events that takes place by means of fast transitions

$$(n_R, R_1, X_2) \to^{\mu} (n_R - 1, R_1, X_2) \to^{\mu} \cdots \to^{\mu} (0, R_1, X_2)$$

Arguing as in the derivation of (6.2) we obtain that the following transition probability for the transitions $(k, R_1, X_2) \to (k-1, R_1, X_2)$, $k \geq 1$ is given by $\frac{\mu}{\mu+\gamma k}$. Therefore

$$\theta(n_R) = \frac{1}{\prod_{k=1}^{n_R}\left(1 + \frac{\gamma}{\mu}\cdot k\right)}$$

Since the distribution of the variable n_R in the state R_1Z_2, in time scales $\varepsilon \ll t \ll 1$ is the one given in the last formula of (4.1), it then follows that the transition probability of R_1Z_2 to R_1X_2 is $\beta\Gamma$ with

$$\begin{aligned}\Gamma &= \sum_{n_R=0}^{\infty} P(n_R)\,\theta(n_R) = \sum_{n_R=0}^{\infty} \frac{1}{(n_R)!}\frac{\left(\frac{g}{\mu}\right)^{n_R} e^{-\frac{g}{\mu}}}{\prod_{k=1}^{n_R}\left(1+\frac{\gamma}{\mu}\cdot k\right)} \\ &= e^{-\frac{g}{\mu}}\Gamma\left(1+\frac{\mu}{\gamma}\right)\sum_{n_R=0}^{\infty}\frac{\left(\frac{g}{\gamma}\right)^{n_R}}{(n_R)!\Gamma\left(n_R+1+\frac{\mu}{\gamma}\right)} \qquad (6.3)\end{aligned}$$

The computation of the transition probability from R_1Z_2 to R_1R_2 is similar. Notice that since $\theta(n_R) < 1$ it readily follows from (6.3) that $\Gamma < 1$, using the identity $e^{\frac{g}{\mu}} = \sum_{n_R=0}^{\infty}\frac{1}{(n_R)!}\left(\frac{g}{\mu}\right)^{n_R}$.

7 Concluding remarks

In this paper we study a stochastic system of chemical reactions characterized by different times of chemical reaction. We have shown that in some suitable limit, the system under consideration exhibits bistability. We have computed also in the same asymptotic limit formulas for the probability distributions of switching times between the two stable states of the system. Due to the fact that the number of molecules of the system remains of order one, such computation cannot be made using the classical Kramers' formula. Other chemical systems containing a large number of chemical

species, but exhibiting also bistability and where Kramers' formula cannot be used either, are considered in the companion paper [34].

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