Available online at www.sciencedirect.com
SCIENCE DIRECT®
Chemical Physics 284 (2002) 469–479
Chemical Physics
www.elsevier.com/locate/chemphys

Number fluctuations and the threshold model of kinetic switches

Ralf Metzler[a,b,*], Peter G. Wolynes[c]

[a] Department of Physics, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Room 12-109, Cambridge, MA 02139, USA
[b] NORDITA, Blegdamsvej 17, DK-2100 København Ø, Denmark
[c] Department of Chemistry, University of California at San Diego, La Jolla, CA 92093, USA

Received 2 January 2002

Abstract

The dynamics within nanoscale systems, in biological cells, or in macroscopic ecosystems often involves low populations of molecules or members, provoking the need for a discrete description instead of a continuum theory. We consider a classical birth–immigration–death process in such a few number system and show in how far fluctuations become prominent in the system's dynamics. The exact analytical results are investigated and new functions for the characterisation of the population dynamics established. We investigate the corresponding continuum approximation of the process and derive a Fokker–Planck equation for the fluctuations.

PACS: 02.50.−r; 05.40.−a; 87.10.+e; 87.16.−b

1. Introduction

Recently, interest in the modifications of macroscopic chemical kinetic laws required by the discreteness of molecular entities has been revivified by two technological developments. One of these is the dramatic improvement of analytical techniques leading to methods which now routinely can experimentally access the dynamics of even single molecules. This development opens up new vistas in unravelling the dynamics of complex molecular systems where new phenomena such as intermittency can be observed. Concomitantly, the drive forward building miniaturised systems makes more urgent understanding how various machines function in the face of inevitable molecular fluctuations. This problem arises both in designing the artificial systems envisioned by nanotechnologists and in describing the existing nanotechnology embodied in the biological cell.

Single molecule kinetics enters into the description of ion channels regulating electrical information transfer between cells and the description of biomolecular motors which power

* Corresponding author. Tel.: +45-353-25507; fax: +45-353-89157.
E-mail addresses: metz@nordita.dk (R. Metzler), pwolynes@chem.ucsd.edu (P.G. Wolynes).

0301-0104/02/$ - see front matter
PII: S0301-0104(02)00674-2

not only material transport within cells but also much of the machinery for transcribing and translating genetic information. Molecular number fluctuations also will affect the regulation of genes. Not only is an individual gene a single molecule itself but furthermore its activity is usually regulated by a nanoscale chemical kinetic switch which involves the binding of other molecules. These repressor or promoter molecules are often present in only low concentrations and therefore are sometimes few in total number. The macroscopic description of several individual genetic switches has been elegantly worked out. The effects of number fluctuations on such switches has also begun to be discussed. For some well studied cases the detailed macroscopic mechanism of genetic switches turns out to be quite complex so it is hard to analyse fluctuation effects without simulation. However, crudely speaking the kinetic switches can be described by a threshold model: when a crucial molecular component reaches a certain level the system flips, from one collective state to an other. With this in mind we analyse here, in some detail, a simple model of a kinetic switch involving a finite number of molecular entities. Although we have in mind the application of the threshold model to cell biological and nanotechnological systems, the model may also be of interest in areas ranging from ecology and macroscopic population demographics to quantum optics.

Population processes are traditionally described through a rate equation of the form [1]

$$\frac{\mathrm{d}\phi(t)}{\mathrm{d}t} = k_{\mathrm{i}} + (k_{\mathrm{b}} - k_{\mathrm{d}})\phi(t) \tag{1}$$

which describes the temporal evolution of the "concentration" $\phi(t)$, a macroscopic quantity. In Eq. (1), the parameters k_{i} represent the rate constants of dimension $[k_{\mathrm{i}}] = \sec^{-1}$ for immigration, birth and death where the latter two are assumed to be proportional to $\phi(t)$. For a chemical process $\emptyset \rightleftharpoons \mathrm{X}$, where $\emptyset$ acts as a bath for molecules of the species X, $\phi(t)$ is the concentration of the substance X in the corresponding reaction volume (e.g., the beaker), k_{i} is the synthesis rate of X and k_{d} the decay rate, and k_{b} corresponds to an autocatalytic reaction. For a nanophysical system, Eq. (1) could describe the number of electrons or other charge carriers in a certain volume; and for a biological population, it would just literally describe the biological processes of immigration, birth, and death.

It is obvious that Eq. (1) contains only very limited information on the system under consideration. Especially, it does not permit the study of concentration *fluctuations*. To do so, one needs a more fundamental equation, usually this is the master equation [2]

$$\frac{\partial P(n,t)}{\partial t} = (\mathbb{E}^{-1} - 1)G(n)P(n,t) + (\mathbb{E} - 1)R(n)P(n,t), \tag{2a}$$

where $\mathbb{E}^{\pm}P(n,t) \equiv P(n \pm 1, t)$. G and R refer to the *G*eneration and *R*emoval of particles the number of which is measured by n [3]. Thus, one can rewrite Eq. (2a) in the alternative form

$$\frac{\partial P(n,t)}{\partial t} = G(n-1)P(n-1,t) + R(n+1)P(n+1,t) - (G(n) + R(n))P(n,t). \tag{2b}$$

The master equation, mathematically, involves a differential in the continuous time variable, and it is discrete in the number n. It is therefore sometimes called a difference-differential equation. For the specific model described through Eq. (1), we have

$$G(n) = k_{\mathrm{i}} + k_{\mathrm{b}}n \tag{2c}$$

and

$$R(n) = k_{\mathrm{d}}n. \tag{2d}$$

Physically, the master equation (2a)–(2d) could be referred to as a *mesoscopic* description of the system in so far as it contains the probability density function $P(n,t)$ to find n particles at a given time t, i.e., a quantity which is obtained through some average over the number field $n(\mathbf{x},t)$, but it still gives the image of the microscopic process of creation and annihilation. In an abstract sense, the set of equations (2a)–(2d) define a random walk in the n-space.

As it involves the probability density function $P(n,t)$, the master equation (2a), or (2b), contains

considerably more information than the rate equation (1). In what follows, we discuss the relevance of this additional information to systems in which the mean number of particles is small. We discuss the analytical properties of the closed form solution and then embark for the definition of certain characterising system quantities by help of which also such systems can be investigated whose closed form solution, or even whose governing processes, are not known. We will argue that these newly defined quantities may also serve to determine probabilities that possibly fatal turnovers within the system occur. Special emphasis will be given to genetic switches and the detailed dynamical patterns involved, showing that as simple a process as the birth-immigration-death (BID) dynamics is able to grasp some effects involved in the in vivo system.

Before we do so and consider the BID process, it should, however, be noted that, in general, it has to be guaranteed that n is a non-negative integer as it counts the number of individuals of the species under consideration. This can either be guaranteed through appropriate boundary conditions, or through the proportionality of the removal rate $R(n)$ to powers of n, i.e., $R(n) = \sum_{i=1}^{\infty} r_i n^i$: if the population is zero, the removal ceases. Usually, removal is considered to be proportional to n. In both versions of the master equation, (2a) and (2b), the change of the probability density $P(n,t)$ in time involves the removal of the "state" n and its replacement by states $n+1$ and $n-1$, with certain, assigned weights. As initial condition, we choose the sharp initial value $\lim_{t\to 0+} P(n,t) = \delta_{n,m}$. Note that conservation of the normalisation implies that the sum over all n of the right-hand side of Eq. (2a) and (2b) vanishes. It should further be mentioned that a master equation of the type (2a), or (2b), does not necessarily fulfil the condition of detailed balance.

2. Solution of the BID process

Consider the BID process, specified through the rates k_i, k_b and k_d. In this process, the coefficients are at most linear in n, so that the moments of the process can be extracted from the corresponding master equation, (2a)–(2d). The obtaining differential equation for the mean number and the second moment, e.g., are given by

$$\frac{\mathrm{d}\langle n(t)\rangle}{\mathrm{d}t} = \Delta\langle n(t)\rangle + k_i \tag{3a}$$

$$\frac{\mathrm{d}\langle n^2(t)\rangle}{\mathrm{d}t} = 2\Delta\langle n^2(t)\rangle + \sigma\langle n(t)\rangle + k_i \tag{3b}$$

where $\Delta \equiv k_b - k_d$ and $\sigma \equiv k_b + k_d + 2k_i$. Note that Eq. (3a) for the mean number is equivalent to the macroscopic rate Eq. (1). The solutions for $\langle n(t)\rangle$ and the variance $\mathrm{var}(t) \equiv \langle n^2(t)\rangle - \langle n(t)\rangle^2$ for the initial number m of molecules read

$$\langle n(t)\rangle = m\mathrm{e}^{\Delta t} + \frac{k_i(\mathrm{e}^{\Delta t}-1)}{\Delta} \tag{4a}$$

and

$$\begin{aligned}\mathrm{var}\{n(t)\} = {} & \frac{m(k_b+k_d)}{\Delta}(\mathrm{e}^{\Delta t}-1)\mathrm{e}^{\Delta t} \\ & + \frac{k_i}{2\Delta^2}(\Delta(\mathrm{e}^{2\Delta t}-1) \\ & + (k_b+k_d)(\mathrm{e}^{2\Delta t}-2\mathrm{e}^{\Delta t}+1)).\end{aligned} \tag{4b}$$

Obviously, the mean number is unbounded if $\Delta > 0$, $\langle n(t)\rangle \to k_i/|\Delta|$ for $t\to\infty$ if $\Delta < 0$, and $\langle n(t)\rangle \sim k_i t$ if $\Delta = 0$. Similarly, the variance is unbounded for $\Delta > 0$ (i.e., the fluctuations become extremely large), $\mathrm{var}\{n(t)\} \to k_i k_d/\Delta^2$ for $t\to\infty$ if $\Delta < 0$, and $\mathrm{var}\{n(t)\} \sim m(k_b+k_d)t + k_i t + k_i\,(k_b + k_d)t^2/2$ if $\Delta = 0$. Note that due to their mathematical structure, both expressions (4a) and (4b) are always positive.

It should also be noted that for long times, $\Delta t \gg 1$, the quotient of standard deviation $\mathrm{std}(t) \equiv \sqrt{\mathrm{var}(t)}$ and mean number becomes time independent: (i) for $\Delta > 0$, $\mathrm{std}(t)/\langle n(t)\rangle \sim \sqrt{\frac{m}{\Delta}(k_b+k_d) + k_i k_b/2}/(m + k_i/\Delta)$. Especially, for $m = 0$, one obtains the relation $\mathrm{std}(t)/\langle n(t)\rangle \sim \sqrt{k_b/(\Delta k_i)}$, and for $k_i = 0$, $\mathrm{std}(t)/\langle n(t)\rangle \sim \sqrt{(k_b+k_d)/(m\Delta)}$ is found. As expected, for growing m, the fluctuations die out. (ii) Conversely, for $\Delta < 0$, fluctuations can only pertain if immigration takes place, $k_i > 0$. Then, $\mathrm{var}(t)/\langle n(t)\rangle \sim k_d/(k_d - k_b)$, and $\mathrm{std}(t)/\langle n(t)\rangle \sim \sqrt{k_d/k_i}$.

The probability density $P(n,t|m,0)$ defined through Eq. (2b) for the initial condition $\lim_{t\to 0+} P(n,t) = \delta_{m,n}$ is given in terms of the hypergeometric function ${}_2F_1$ [3–5]

$$P(n,t|m,0) = \left(\frac{k_b}{k_d}\right)^n \left(\frac{\Delta}{k_b e^{\Delta t} - k_d}\right)^{k_i/k_b} \times \left(\frac{1-e^{\Delta t}}{1-k_b e^{\Delta t}/k_d}\right)^{m+n} \frac{\Gamma(k_i/k_b + n + m)}{n!\Gamma(k_i/k_b + m)} \times {}_2F_1\left(-m,-n;1-\frac{k_i}{k_b}-m-n; \frac{(1-k_d e^{\Delta t}/k_b)(1-k_b e^{\Delta t}/k_d)}{(1-e^{\Delta t})^2}\right) \quad (5)$$

for $k_b \gtrless k_d$. The corresponding propagator ($m = 0$) takes on the simpler form

$$P(n,t|0,0) = \left(\frac{k_b}{k_d}\right)^n \left(\frac{\Delta}{k_b e^{\Delta t} - k_d}\right)^{k_i/k_b} \times \frac{\Gamma(n + k_i/k_b)}{n!\Gamma(k_i/k_b)} \left(\frac{1-e^{\Delta t}}{1-k_b e^{\Delta t}/k_d}\right)^n. \quad (6)$$

Stationary solutions exist if $k_d > k_b$, irrespectively of the magnitude of the rate of immigration k_i, as the removal is proportional to the absolute number of molecules present. In this case, the stationary form of the probability density $P(n,t)$ from Eq. (5) is given by

$$P_{st}(n|m) = \left(\frac{k_b}{k_d}\right)^n (1-k_b/k_d)^{k_i/k_b} \times \frac{\Gamma(k_i/k_b + n + m)}{n!\Gamma(k_i/k_b + m)} \times \frac{\Gamma(1-k_i/k_b - m - n)\Gamma(1-k_i/k_b)}{\Gamma(1-k_i/k_b - m)\Gamma(1-k_i/k_b - n)}, \quad (7)$$

k_b being incommensurable with k_i. Note that the stationary solution still depends on the initial condition m. For $m = 0$, this expression reduces to

$$P_{st}(n|0) = \left(\frac{k_b}{k_d}\right)^n (1-k_b/k_d)^{k_i/k_b} \frac{\Gamma(k_i/k_b + n)}{n!\Gamma(k_i/k_b)}. \quad (8)$$

In Fig. 1, the probability density $P(n,t|m,0)$ is plotted in dependence of n for successive times. This illustration makes it clear that fluctuations in the particle number cannot be neglected a priori. In contrast, for the parameters assumed for the plots, the probability density function is relatively broad, indicating the relevance of the number fluctuations. From the expressions above (and below) which involve the hypergeometric and Γ-functions, it is not always directly obvious how the associated functions behave. However, their closed form expression allows for a straightforward numerical analysis with symbolic mathematical programs. Moreover, limiting formulae exist, allowing for simplifications in certain asymptotic limits.

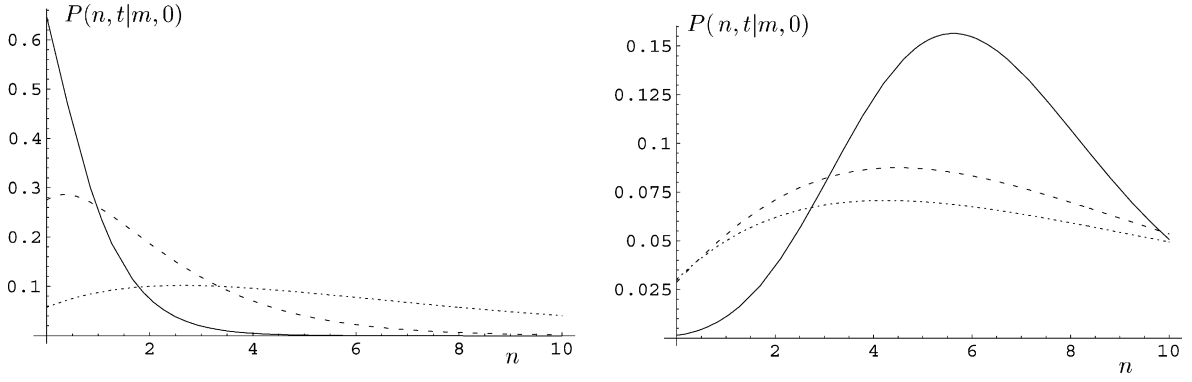

Fig. 1. Probability density $P(n,t|m,0)$ for the BID process as a function of the number n. The chosen parameters are: Left: $\{m, k_i, k_b, k_d\} = \{0, 1, 0.5, 0.6\}$, at the times $t = 0.5$ (full line), 2 (dashed) and 10 (dashed-dotted). Right: $\{m, k_i, k_b, k_d\} = \{6, 1, 0.5, 0.6\}$, at the times $t = 1$ (full line), 5 (dashed) and 20 (dashed-dotted). Note the broadness of the distribution for higher times, indicating the relevance of fluctuations.

Before dealing with the quantification of this phenomenon, however, we first examine the border case of vanishing birth rate, $k_b \equiv 0$. In this case, the probability density is given through

$$P(n,t|m,0) = \left(\frac{k_i}{k_d}\right)^n \exp\left(-\frac{k_i(1-e^{-k_d t})}{k_d}\right) \times \left(1-e^{-k_d t}\right)\left(\frac{k_i}{k_d}e^{k_d t}\left(1-e^{-k_d t}\right)^2\right)^{-m} \times {}_1F_1\left(-m;1+n-m;-\frac{k_i}{k_d}e^{k_d t} \times \left(1-e^{-k_d t}\right)^2\right) \quad (9a)$$

if $k_d > 0$, and where ${}_1F_1$ denotes the confluent hypergeometric function. The further special case $k_b = k_d = 0$ is called a Poisson process [2,6] and is solved by $P(n,t|m,0) = e^{-k_i t}(k_i t)^{n-m}/(n-m)!$, and $P(n,t|m,0) = 0$ for $n < m$.

Another particular case which has to be considered separately, is the balanced system $k_b = k_d$ in which the probability density takes on the form

$$P(n,t|m,0) = \frac{(k_b t)^{n+m}}{(1+k_b t)^{n+m+k_i/k_b}} \frac{\Gamma(m+n+k_i/k_b)}{\Gamma(m+k_i/k_b)n!} \times {}_2F_1\left(-m,-n;1-n-m-\frac{k_i}{k_b};-\frac{1-k_b^2t^2}{k_b^2t^2}\right). \quad (9b)$$

Closer inspection shows that in this case detailed balance is fulfilled. For $k_b = k_d = 0$, we again obtain the Poisson process, and for a vanishing immigration, $k_i = 0$, the probability density reduces to

$$P(n,t|m,0) = \left(1+(k_b t)^{-1}\right)^{-(m+n)}\binom{m+n-1}{n} \times {}_2F_1\left(-m,-n;1-n-m;-\frac{1-k_b^2t^2}{k_b^2t^2}\right). \quad (9c)$$

3. Characterisation of the BID process

The probability density $P(n,t|m,0)$, the solution of the master equation (2a)–(2d) for a given initial condition $\delta_{n,m}$, contains the complete information on the system under consideration, on the mesoscopic level of the master equation (2a)–(2d). To characterise certain properties of interest of some system, quantities derived from $P(n,t|m,0)$ turn out to be more transparent. In this section, we introduce some functions which characterise correlations of the system, or the probability that the system is on either side of a specified threshold. These quantities are then a measure for the importance of fluctuations in this system, and they may also serve as a basis for investigations of systems for which the complete solution is not known.

3.1. Critical measure: the threshold function

A significant measure for many sparsely populated systems is the probability to have at least n_{crit} members of the species present. This probability is a critical threshold measure in many systems, for instance in biological regulatory cycles. In this section, we develop an abstract measure for this critical probability, and we will comment on its significance in a specific system in more detail below. For a system with probability density function $P(n,m|m,0)$, the probability to find at least n_{crit} elements of the species is given by

$$\Pr\{n \geqslant n_{crit}\} \equiv \sum_{n=n_{crit}}^{\infty} P(n,t|m,0) \equiv 1 - \sum_{n=0}^{n_{crit}-1} P(n,t|m,0). \quad (10)$$

For the process defined by Eqs. (2a)–(2d), a general closed form expression for this critical probability does not exist. In the particular case of the propagator, i.e., $m = 0$, one finds the expression

$$\Pr\{n \geqslant n_{crit}\} = \left(\frac{\Delta}{k_b e^{\Delta t} - k_d}\right)^{k_i/k_b}\left(\frac{1-e^{-\Delta t}}{k_d/k_b - e^{\Delta t}}\right)^{n_{crit}} \times \frac{\Gamma(n_{crit}+k_i/k_b)}{n_{crit}!\Gamma(k_i/k_b)} \times {}_2F_1\left(1,n_{crit}+\frac{k_i}{k_b};1+n_{crit};\frac{1-e^{\Delta t}}{k_d/k_b - e^{\Delta t}}\right). \quad (11)$$

The critical probability for the propagator, Eq. (11), is plotted for different parameters in Fig. 2

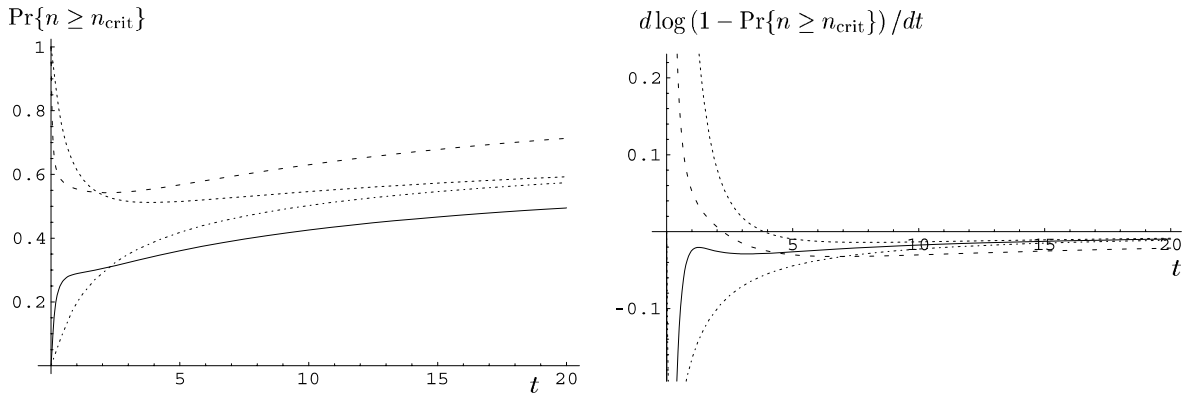

Fig. 2. Critical probability for the parameter sets: $\{m, n_{\rm crit}, k_{\rm i}, k_{\rm b}, k_{\rm d}\} = \{2, 4, 1, 4, 4.01\}$ (full line), $\{4, 4, 1, 2, 1.99\}$ (long-dashed), $\{4, 2, 1, 4, 4.01\}$ (short-dashed), and $\{0, 2, 1, 4, 4.01\}$ (dash-dotted). Left: linear axes. Right: logarithmic derivative of the probability of not going critical up to time t.

versus time. It is obvious that for certain parameter combinations the value of this critical measure is low, indicating that the system is sub-critical with a relatively high probability, and thus liable to crossover (in the sense defined below). It is also remarkable that there exist minima for certain sets of parameters such that the system, although asymptotically completely stable, might exhibit *intermittent* domains in which the probability for crossovers is fairly high. We also plot the logarithmic derivative of the probability of not going critical up to time t in Fig. 2. While on a linear abscissa, the functional behaviour of the critical probability is smooth, a parameter-specific fine structure, i.e., the occurrence of plateaus, minima (and maxima), can be discerned on a logarithmic scale, as demonstrated in Fig. 3. Note that some of this fine structure pertains to relatively long times for the chosen parameters, and the stationary behaviour is approached rather slowly.

From Eq. (3a) it follows that the mean population for $k_{\rm b} > k_{\rm d}$ grows beyond limit, and therefore $\Pr\{n \geqslant n_{\rm crit}\} \to 1$. In the opposite case $k_{\rm d} > k_{\rm b}$, a stationary state is reached whose population number is determined by the ratio $k_{\rm i}/|\Delta|$. Consequently, even in the absorption dominated case $k_{\rm d} > k_{\rm b}$, a minimum value $0 < \mathrm{P}\{n \geqslant n_{\rm crit}\} < 1$ is reached. For $n_{\rm crit} = 1$, the stationary value approached by the system is $\mathrm{P}\{n \geqslant n_{\rm crit}\} = 1 - (1 + k_{\rm i}/k_{\rm d})(1 - k_{\rm b}/k_{\rm d})^{k_{\rm i}/k_{\rm b}}$. The existence of a minimum state is connected to the time dependence of

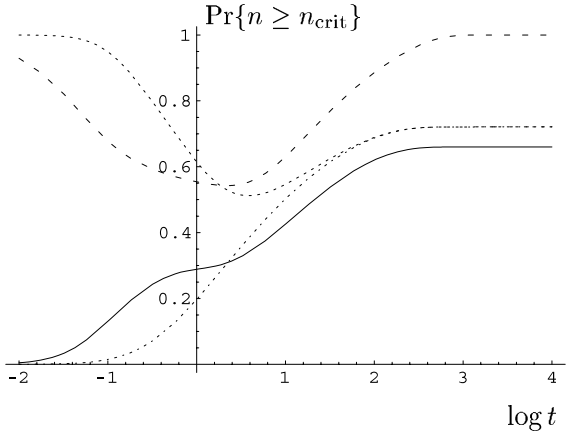

Fig. 3. Fine structure of the critical probability, revealed on a logarithmic time scale. The parameters are the same as in Fig. 2.

the mean number. If $\langle n(t)\rangle$ is strictly monotonic, no plateau, minimum, or maximum in $\Pr\{n \geqslant n_{\rm crit}\}$ exists, and vice versa. The existence of a minimum is guaranteed if $\lim_{t\to 0} \mathrm{d}\langle n(t)\rangle/\mathrm{d}t = m\Delta + k_{\rm i} < 0$, and $\mathrm{d}/\mathrm{d}t\langle n(t)\rangle > 0$ at later times.

In the balanced case $k_{\rm b} = k_{\rm d}$, the associated critical probability can be calculated explicitly, however, the expressions become involved. For $n_{\rm crit} = 1$, one finds

$$\Pr\{n \geqslant 1\} = 1 - (k_{\rm b}t)^m/(1 + k_{\rm b}t)^{k_{\rm i}/k_{\rm b}+m}, \qquad (12a)$$

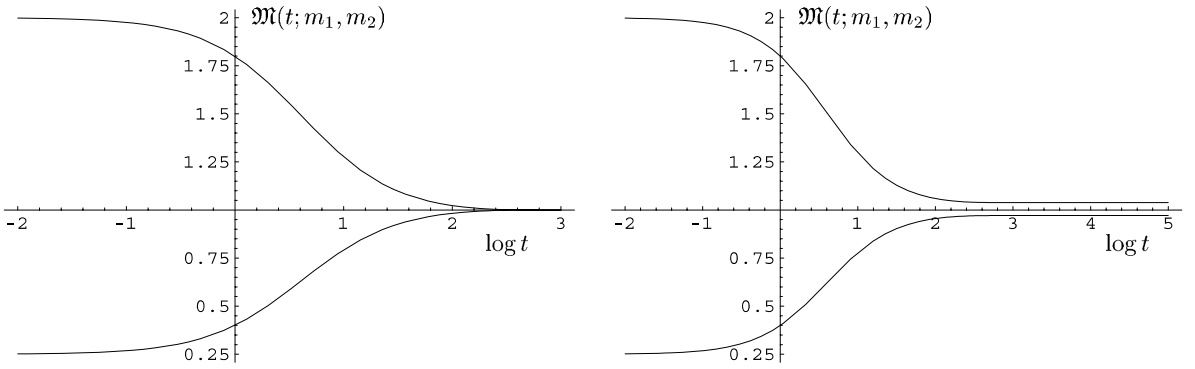

Fig. 4. Left: ratio function of the means of a given system and its replica, for the initial conditions $m_1 = 1$, $m_2 = 4$ (lower line) and $m_1 = 8$, $m_2 = 4$ (upper line), with the parameters $\{k_i, k_b, k_d\} = \{1, 0.1, 0.11\}$. Both cases converge. Right: same as above, but for the parameters $\{k_i, k_b, k_d\} = \{1, 0.11, 0.1\}$. Now, the stationary values of both functions differ.

and for $n_{\text{crit}} = 2$, the expression

$$\Pr\{n \geqslant 2\} = \Big(\Big(k_b t\Big((1+k_b t)^{m+k_i/k_b} - (k_b t)^m\Big) (1+k_b t) - k_i t (k_b t)^m\Big) - m(k_b t)^m\Big) \Big/ k_b t (1+k_b t)^{1+m+k_i/k_b} \tag{12b}$$

yields. In general, one recovers the asymptotic limit $\Pr\{n \geqslant n_{\text{crit}}\} \to 1$ for $k_i > 0$, and $\to 0$ ($k_i = 0$). Thus, for increasing population, the fluctuations become less prominent and finally die out.

3.2. Dependence on initial condition

A different characterisation method of the system dynamics defined by the master equation (2a)–(2d) is the information on the dependence of the initial condition in which the process is prepared. Thus, one can compare a system with initial condition m_1 with a "replica", i.e., a system with the identical set of parameters but different initial condition m_2. Whereas the method of replica correlations is well-established in certain types of dynamical systems [7], one can define a number of replica functions for the set of Eqs. (2a)–(2d). Here, we investigate a very simple replica function, the mean ratio function

$$\mathfrak{M}(t;m_1,m_2) \equiv \frac{\langle n(t)\rangle_{m_1}}{\langle n(t)\rangle_{m_2}}, \tag{13}$$

where the indices on the right-hand side indicate the different initial conditions. We plot two different examples in Fig. 4. It becomes obvious that already this function gives some non-trivial information: i.e., whether the system loses its memory of the initial condition or not.

More information on the system under investigation can be obtained in a similar fashion from higher order moments such as the ratio of the variances for the system and a replica. The system–replica pair can be defined for different parameters, as well. Also, properly normalised differences of such quantities could be investigated, or replica correlation functions proper could be employed. It should always be kept in mind that some fine structure might be discernible on a logarithmic time scale.

4. Kramers–Moyal expansion and Fokker–Planck approximation

The shift operator $\mathbb{E}^{\pm} f(n) \equiv f(n \pm 1)$ has the representation $\mathbb{E}^{\pm} \equiv e^{\pm \partial/\partial n}$, the latter expression being defined via its series expansion. Accordingly, the master equation (2a) is equivalent to the Kramers–Moyal expansion

$$\frac{\partial P(n,t)}{\partial t} = \sum_{j=1}^{\infty} \left(-\frac{\partial}{\partial n}\right)^j \frac{G(n) + (-1)^j R(n)}{j!} P(n,t), \tag{14}$$

whose "diffusion coefficients" are defined through $1/j!(G(n) + (-1)^j R(n))$. A truncation after the

second order leads to the Fokker–Planck approximation

$$\frac{\partial P(n,t)}{\partial t} = \left(-\frac{\partial}{\partial n}(G(n) - R(n)) + \frac{\partial^2}{\partial n^2}\frac{G(n)+R(n)}{2} \right) \times P(n,t) \tag{15}$$

of the master equation (2a). The first coefficient, $G(n) - R(n)$, represents the difference of generation and removal rates and can thus be viewed as an analogue to the drift coefficient in number space, classifying the response of the first moment to the external field defined through the rates G and R. The second coefficient, $1/2(G(n) + R(n))$, is the algebraic mean of both rates and accounts for the ''diffusive'' entity of changes caused by the rates G and R. In a loose sense, the first two Kramers–Moyal coefficients stand for the energetic (drift) and the entropic contributions to the system dynamics.

An interesting discussion of the convergence of higher order truncations of the Kramers–Moyal expansion for the Poisson process can be found in Risken's book [6].

4.1. Comparison to the master equation

The Fokker–Planck equation which corresponds to the concrete model underlying the master equation (2b) reads

$$\frac{\partial P(n,t)}{\partial t} = \left(-\frac{\partial}{\partial n}(k_\mathrm{i} + \Delta n) + \frac{\partial^2}{\partial n^2}\frac{k_\mathrm{i} + (k_\mathrm{b} + k_\mathrm{d})n}{2} \right) \times P(n,t). \tag{16}$$

As the Kramers–Moyal expansion (14) was truncated after the second term to obtain the Fokker–Planck approximation, the results for the mean and the variance obtained from Eq. (16) exactly match Eqs. (3a) and (4b) derived from Eq. (2b). However, all higher order moments differ. For instance, consider the third moment whose exact differential equation

$$\frac{\mathrm{d}}{\mathrm{d}t}\langle n^3(t)\rangle = 3\Delta\langle n^3(t)\rangle + 3(k_\mathrm{i} + k_\mathrm{b} + k_\mathrm{d})\langle n^2(t)\rangle + (3k_\mathrm{i} + \Delta)\langle n(t)\rangle + k_\mathrm{i} \tag{17}$$

which follows from Eq. (2b), contrasts

$$\frac{\mathrm{d}}{\mathrm{d}t}\langle n^3(t)\rangle = 3\Delta\langle n^3(t)\rangle + 3(k_\mathrm{i} + k_\mathrm{b} + k_\mathrm{d}) \times \langle n^2(t)\rangle + 3\langle n(t)\rangle \tag{18}$$

corresponding to the Fokker–Planck approximation (16). The missing terms in Eq. (18) in respect to Eq. (17) would enter from the third order $-\partial^3/6\partial n^3$ of the Kramers–Moyal expansion. For larger and larger systems, the relative difference of both moments, and of higher order moments, becomes less and less pronounced. A better way to establish the continuum limit of the discrete master Eqs. (2a)–(2d) is the following $1/\Omega$ expansion due to van Kampen.

4.2. The role of fluctuations and van Kampen's $1/\Omega$ expansion

If the system size increases, the relative difference between the discrete steps $n \to n \pm 1$ becomes smaller. Consequently, higher order Kramers–Moyal coefficients become lesser pronounced, and the Fokker–Planck approximation to the master equation (2a) becomes better. At the same time, the fluctuations (deviations from the mean) are expected to be less important.

A straightforward way to investigate the direct impact of the system size is van Kampen's $1/\Omega$ expansion [2]. Let us recall that the differential equation for the mean number, $\mathrm{d}\langle n(t)\rangle/\mathrm{d}t = k_\mathrm{i} + \Delta\langle n(t)\rangle$ which follows from the master equation (2b), is equivalent to the chemical kinetics equation $\dot{\phi}(t) = k_\mathrm{i} + \Delta\phi(t)$ for the concentration $\phi(t)$. On the macroscopic level, the relation between concentration and mean number is given via the system size Ω so that we can rewrite the chemical kinetics equation as

$$\frac{\mathrm{d}\langle n(t)\rangle}{\mathrm{d}t} = \Omega k_\mathrm{i} + \Delta n. \tag{19}$$

On the level of the master equation, this corresponds to

$$\frac{\partial P(n,t)}{\partial t} = \Omega k_\mathrm{i}\left(\mathbb{E}^{-1} - 1\right)P(n,t) + k_\mathrm{b}(\mathbb{E}^{-1} - 1)nP(n,t) + k_\mathrm{d}(\mathbb{E} - 1)nP(n,t). \tag{20}$$

This trick allows therefore for the system size to enter the master equation, its meaning being that

Eq. (20) is the variable system size version of Eq. (2b). On the "mesoscopic level", the number n will be sharply peaked around the macroscopic value, and fluctuations will enter as the square root of the system size,

$$n \equiv \Omega\phi(t) + \Omega^{1/2}\xi, \tag{21}$$

where ξ measures the deviations from the macroscopic value, i.e., it denotes the fluctuations. Note that the relative importance of the fluctuations decreases with increasing system size Ω, in the inverse square root fashion $n/\langle n\rangle = 1 + \xi/\sqrt{\Omega}$. Conversely, for a given system size Ω, the $1/\Omega$ formalism unequivocally demonstrates the intuitively sensible notion that the influence of fluctuations is in direct competition with the concentration of molecules, $\phi = n/\Omega$: the higher the concentration, the less dominant are the fluctuations. Accordingly, we are now seeking the differential equation which defines the evolution of $\Pi(\xi,t)$, the probability density function of the variable ξ. As $n \to n+1$ now corresponds to $\xi \to \xi + \Omega^{-1/2}$, we find expressions for the shift operators $\mathbb{E}^{\pm 1}$,

$$\mathbb{E}^{\pm 1} = 1 \pm \Omega^{-1/2}\frac{\partial}{\partial\xi} + \frac{1}{2}\Omega^{-1}\frac{\partial^2}{\partial\xi^2} + \cdots \tag{22}$$

Finally, $\partial P(n,t)/\partial t$ has to be replaced by

$$\frac{\partial}{\partial t}\Pi(\xi,t) - \Omega^{1/2}\dot{\phi}(t)\frac{\partial}{\partial\xi}\Pi(\xi,t),$$

to include the explicit time dependence of the macroscopic concentration, $\phi(t)$ [2]. We therefore obtain the following equation for $\Pi(\xi,t)$,

$$\begin{aligned}\frac{\partial\Pi}{\partial t} - \Omega^{1/2}\dot{\phi}\frac{\partial\Pi}{\partial\xi} &= \Omega k_{\mathrm{i}}\left(-\Omega^{-1/2}\frac{\partial}{\partial\xi} + \frac{1}{2}\Omega^{-1}\frac{\partial^2}{\partial\xi^2} - \cdots\right)\Pi(\xi,t)\\ &\quad + k_{\mathrm{b}}\left(-\Omega^{-1/2}\frac{\partial}{\partial\xi} + \frac{1}{2}\Omega^{-1}\frac{\partial^2}{\partial\xi^2} - \cdots\right)\\ &\quad \times \left(\Omega\phi + \Omega^{1/2}\xi\right)\Pi(\xi,t)\\ &\quad + k_{\mathrm{d}}\left(\Omega^{-1/2}\frac{\partial}{\partial\xi} + \frac{1}{2}\Omega^{-1}\frac{\partial^2}{\partial\xi^2} - \cdots\right)\\ &\quad \times \left(\Omega\phi + \Omega^{1/2}\xi\right)\Pi(\xi,t).\end{aligned} \tag{23}$$

Comparing orders of the parameter Ω, we first encounter the terms proportional to $\Omega^{1/2}$, $\dot{\phi}\Pi_\xi = k_{\mathrm{i}}\Pi_\xi + \Delta\Pi_\xi$, where $\Pi_\xi \equiv \partial\Pi/\partial\xi$. This is but the macroscopic chemical kinetics equation. The next contribution comes from Ω^0. For all other terms, inverse powers of the system size Ω occur, and it therefore becomes a small parameter so that an appropriate method for the system expansion toward the continuum limit has been found. Collecting powers of order Ω^0, we obtain the Fokker–Planck equation

$$\frac{\partial\Pi}{\partial t} = \left(-\Delta\frac{\partial}{\partial\xi}\xi + \frac{k_{\mathrm{i}} + k_{\mathrm{b}} + k_{\mathrm{d}}}{2}\phi(t)\frac{\partial^2}{\partial\xi^2}\right)\Pi(\xi,t). \tag{24}$$

This Ω^0-order derivation is termed "linear noise approximation" by van Kampen [2]. The associated solution $\Pi(\xi,t)$ is normalised, and of a Gaussian nature. The mean of the fluctuations ξ is $\langle\xi(t)\rangle = \mathrm{e}^{\Delta t}$, the standard deviation for our BID process becomes

$$\begin{aligned}\langle\xi^2(t)\rangle = \phi_0^2\mathrm{e}^{2\Delta t} + k_{\mathrm{i}} + k_{\mathrm{b}} + k_{\mathrm{d}}2\Delta^2(k_{\mathrm{i}}(\mathrm{e}^{2\Delta t} - 2\mathrm{e}^{\Delta t} + 1)\\ + 2\phi_0\Delta(\mathrm{e}^{2\Delta t} - \mathrm{e}^{\Delta t})).\end{aligned} \tag{25}$$

5. Threshold model of kinetic switches

Let us examine the threshold model from the point of view of genetic switches. Roughly speaking, a genetic switch is a control unit in the middle of two genes on the DNA strand. Triggered by the presence of certain messenger molecules, repressor or promoter, the switch determines either which of the two genes is to be transcribed and its information processed. The entire biochemistry of such a switching process is generally rather involved. It has been studied in detail for the λ-switch [8] for which an entire genetic circuitry model has been developed [9].

In a recent modelling approach, the volume of the bacterium cell in which the switch is located, it has been argued, can be divided into an interaction volume γ and a "bath" Γ, and some of the essential features of the switching process understood by the consideration of the exchange of repressor and promoter between γ and the bath [10]. During the inert state of the system, repressor is bound to the switch and the cell keeps a constant concentration

of repressor dimers. Whereas in the bath Γ the relative magnitude of fluctuations is relatively small, they play an essential role in the interaction volume γ. If the bound repressor dissociates and is not replaced by another repressor molecule, the λ-switch can be flipped and the cell is brought on the lytic track. This flipping of the switch is therefore subject to the fluctuations of the small number of repressor in γ.

In this picture, k_i corresponds to the rate at which a repressor molecule enters the interaction volume γ from the bath, being independent of the number of repressors in γ as long as the cell is in the lysogenic state. Thus, k_i is roughly proportional to the overall number of repressor dimers in the bath and to the ratio γ/Γ of interaction volume and bath, and inversely proportional to the characteristic exchange time δt which can be viewed as the renewal time of the process [10]. Conversely, the rate k_d at which repressor leaves γ is proportional to $\Gamma/\gamma\delta t$, and in the master equation (2a)–(2d) it is proportional to the number n of molecules in γ. Finally, k_b in this picture is approximately zero so that the lysogenic switch in the stationary state is described to first approximation through Eq. (9a).

Alternatively, in the more traditional picture of genetic switches in which spatial fluctuations are neglected [8], the cell can be viewed as a closed system. As in the inert state the production of repressor is determined by the chemical facilities of the host cell, the associated rate constant is approximately constant (i.e., independent of n) and can be represented by k_i; k_b vanishes (i.e., there is no direct feedback), k_d corresponds to the degradation of repressor molecules.

Whereas this (over)simplified picture of the genetic switch cannot attempt to substitute the existing detailed modelling of the λ-switch and similar biochemical processes [11–13], it can provide some fundamental insights into the origin and relevance of fluctuations, and it can help to find appropriate tools to quantify and interpret data from in vivo and in vitro experiments and computer simulations. By similar considerations, it is apparent that even the simple linear master equation process (2a)–(2d) can reveal interesting information for a diverse range of systems.

6. Conclusions

We have presented a variation on the old theme of the BID process. We chose the master equation approach for this simple, linear population model, as a paradigm for systems in which small populations prevail and therefore fluctuations become relevant. On this basis, we could establish some relevant and useful functions to quantify the process under consideration. Moreover, some hitherto unknown special cases were derived in closed form.

The analytical and numerical treatment of this master equation with its three parameters k_i, k_b and k_d revealed an a priori unexpected richness in the dynamical behaviour, such as plateaus, minima and maxima in the related critical measures. Some of the fine structure of this temporal behaviour is only discernible on a logarithmic scale; but it could nevertheless contain relevant information on the system. In particular, it has been found that for certain sets of parameters the system can exhibit relatively long-ranging domains of intermittency. It has become apparent that the system actually delicately depends on the parameters, and the initial conditions. We believe that these results for our toy model demonstrate the necessity for analytical modelling of sparsely populated systems or a detailed study of the robustness of the numerical results in respect to variations in the system parameters and initial conditions, in order to make sure about the dependence of the system on the variation of the parameter set. For more complicated models, such an investigation might just be numerically, but it will nevertheless help to understand the underlying system, particularly manifestations of intermittency effects.

For the applications we have in mind, we established a threshold model according to which there exists a critical probability to find at least a population n_{crit} of the species of interest. If this threshold is crossed, a crossover in the system occurs. This threshold could be the number of repressor molecules in the interaction volume in the case of the λ-switch, or a veritable animal population etc. Another class of system-characterising functions compares the difference or ratio between a system with a certain initial con-

dition, and the same (''replica'') system with different initial condition, revealing whether the long time behaviour of the system is uniquely determined or not, and so on. In an analogous way, definitions for system for which a maximum population should not be exceeded or to compare two systems with different parameters could be established.

Throughout, the provided analytical forms can be used to derive related quantities such as the first passage time for a single, or a coupled threshold process.

The role of fluctuations was further assessed in terms of van Kampen's $1/\Omega$ expansion which allows to decide whether a system can be formulated in terms of a differential equation, i.e., in terms of a continuum approach rather than via the difference-differential master equation. An important outcome of this analysis is the Fokker–Planck equation for the fluctuations ξ and the information on the decreasing relevance of fluctuations with increasing system size. From this approach, the expected influence of naturally occurring fluctuations can be determined or, if only an approximate dynamical description is available, estimated.

The investigated master equation brings a variety of systems together, applications ranging from biological physics with population dynamics, genetic switching, or bioinformatics as fields of application, to quantum computing counting the number of set ''pins'' for storing a certain information, or quantum optics where master equations of the investigated type describe the population of certain modes. The main concern for such a modelling therefore comes from typical nanoscale systems, but also from numerous biological systems like cells or habitats of macroscopic organisms like mammals.

The master equation which we employed for this study contains a first order derivative in time which is local. Some systems might rather exhibit long-range correlations in time manifested as memory. A typical form for such slowly decaying memory effects are power-laws. In that case, the master equation can be rephrased as a fractional equation, and its result can be obtained by a transformation of the corresponding Markoffian probability distribution [14].

Acknowledgements

RM acknowledges financial support from the Deutsche Forschungsgemeinschaft within the Emmy Noether programme.

References

[1] L.D. Landau, E.M. Lifshitz, Statistical Physics, Pergamon Press, London, 1958;
J.E. Leffler, E. Grunwald, Rates and Equilibria of Organic Reactions, Wiley, New York, 1963;
J.P. Keener, J. Sneyd, Mathematical Physiology, Springer, New York, 1998.
[2] N.G. van Kampen, Stochastic Processes in Physics and Chemistry, North-Holland, Amsterdam, 1981.
[3] M. Lax, Rev. Mod. Phys. 38 (1966) 359;
Rev. Mod. Phys. 38 (1966) 541.
[4] D.R. Cox, H.D. Miller, The Theory of Stochastic Processes, Methuen, London, 1965;
N.S. Goel, N. Richter-Dyn, Stochastic Models in Biology, Academic Press, New York, 1974;
N.T.J. Bailey, The Elements of Stochastic Processes With Applications to the Natural Sciences, Wiley, New York, 1964;
S. Karlin, J.L. McGregor, Trans. Amer. Math. Soc. 86 (1957) 366;
J.W. Haus, K.W. Kehr, Phys. Rep. 150 (1987) 263.
[5] For $n > m$, the binomial coefficient vanishes: $\binom{m}{m+1} = 0$ whereas for $m > n$, the factorial in the denominator diverges: $(-m)! \to \infty$.
[6] H. Risken, The Fokker–Planck Equation, Springer, Berlin, 1989.
[7] J.N. Onuchic, J. Wang, P.G. Wolynes, Chem. Phys. 247 (1999) 175.
[8] M. Ptashne, A Genetic Switch: Phage λ and Higher Organisms, Cell Press/Blackwell, Cambridge MA, 1992.
[9] H.H. McAdams, A. Arkin, Trends Genet. 15 (1999) 65;
Proc. Natl. Acad. Sci. USA 94 (1997) 814;
D.L. Cook, L.N. Gerber, S.J. Tapscott, Proc. Natl. Acad. Sci. USA. 95 (1998) 6750;
A. Arkin, J. Ross, H.H. McAdams, Genetics 149 (1998) 1633;
H.H. McAdams, A. Arkin, Ann. Rev. Biophys. Biomol. 27 (1998) 199.
[10] R. Metzler, Phys. Rev. Lett. 87 (2001) 068103.
[11] M.S.H. Ko, H. Nakauchi, N. Takahashi, EMBO J. 9 (1990) 2835;
M.S.H. Ko, J. Theor. Biol. 153 (1991) 181;
BioEssays 14 (1992) 341.
[12] J. Peccoud, B. Ycart, Theor. Popul. Biol. 48 (1995) 222.
[13] W. Bialek, cond-mat/0005235; E. Aurell, S. Brown, J. Johanson, K. Sneppen, cond-mat/0010286.
[14] R. Metzler, J. Klafter, Phys. Rep. 339 (2000) 1.