Exact results for a noise-induced bistable system

Bahram Houchmandzadeh and Marcel Vallade
Université Grenoble Alpes, LIPHY, F-38000 Grenoble, France
and CNRS, LIPHY, F-38000 Grenoble, France
(Received 17 December 2014; published 11 February 2015)

A stochastic system where bistability is caused by noise has been recently investigated by Biancalani *et al.* [Phys. Rev. Lett. **112**, 038101 (2014)]. They have computed the mean switching time for such a system using a continuous Fokker-Planck equation derived from the Taylor expansion of the master equation to estimate the parameter of such a system from experiment. In this article, we provide the exact solution for the full discrete system without resorting to continuous approximation and obtain the expression for the mean switching time. We further extend this investigation by solving exactly the master equation and obtaining the expression of other quantities of interests such as the dynamics of the moments and the equilibrium time.

DOI: 10.1103/PhysRevE.91.022115 PACS number(s): 05.40.−a, 87.23.Cc, 02.50.Ey

I. INTRODUCTION

In some stochastic systems, noise can have counterintuitive effects and the behavior of the system can be markedly different from its deterministic, mean-field approximations. In some oscillatory gene networks, the regular oscillations are caused by noise and cease in their absence [1]. In population genetics, the noise term can explain the emergence of less fit "altruistic" individuals [2]. In ecology, the spatial aggregation of individuals can be caused by noise [3,4]; a similar explanation lies behind neutron clustering in nuclear reactors [5].

The general theory of noise-induced transition in nonequilibrium systems has been extensively investigated by Horsthemke and Lefeve [6]. In the context of chemical equations and specifically genetic regulatory networks, there has been an intense investigation of systems where bistability is caused by noise and is absent from the deterministic formulation of kinetic rate equations. Samoilov *et al.* [7] have considered the enzymatic futile cycle reaction and have shown that addition of noise can cause bistability and dynamic switching in the concentration of the substrate. Artyomov *et al.* [8] have considered a simple model of T cells response and have shown again that in the presence of noise, the steady-state distribution can become bimodal. Qian *et al.* [9] and Thomas *et al.* [10], using different approaches, have derived a general framework to elicit the role of fluctuation time scales separation in the appearance of noise-induced bistability. In an elegant experiment, To and Maheshri [11] have investigated a synthetic transcriptional feedback loop and have demonstrated the bimodality of the response without cooperative binding of the transcription factor, a usual hypothesis to explain bistability of genetic switches.

Recently, Biancalani *et al.* [12] investigated another stochastic system where bistability is caused by noise: in this system, individuals (or molecules) can be in one of the two configurations A and B and can switch from one to the other according to the following transition rates:

$$W^-(n) = W(n \to n-1) = (r(N-n)+\epsilon)n \qquad (1)$$

$$W^+(n) = W(n \to n+1) = (rn+\epsilon)(N-n), \qquad (2)$$

where n is the number of individuals in configuration A and N is the total number of individuals. In the following, n is used to characterize the state of the stochastic system at a given time. The rate r characterizes the two-body interactions

$$X_i + X_j \xrightarrow{r} 2X_i \quad i = A,B; \quad j = B,A$$

while the rate ϵ characterizes spontaneous switching of an individual from one configuration to the other:

$$X_i \xrightarrow{\epsilon} X_j.$$

Without loss of generality, we will set $r = 1$ in the following. This is achieved by scaling both time and ϵ by the factor r.

Such a system can model for example a colony of foraging ants collecting food from two sources. In population genetics, this is the Moran model for two competing alleles A and B with bidirectional mutations [13]. Such systems were also proposed in the context of autocatalytic chemical reactions with small number of molecules [14–16], or the dynamic Ising model [17] for a set of fully connected spins. The general properties of this stochastic system, and its application to population genetics in fluctuating environment were discussed by Horsthemke and Lefeve [6].

The behavior of this system is markedly different from its mean-field, deterministic approximation. Indeed, the equation for $\langle n \rangle$, the mean number of individuals in one state, is

$$\frac{d\langle n \rangle}{dt} = \langle W^+(n) - W^-(n) \rangle = \epsilon(N - 2\langle n \rangle) \qquad (3)$$

and has a stable stationary solution $\langle n \rangle = N/2$. However, for small values of ϵ, i.e., $\epsilon \ll 1/N$, the system is observed most of the time in one of the two boundary states $n = 0$ or $n = N$, and seldom in states close to $n = N/2$. The bistability of the system is caused solely by the noise and cannot be captured by the mean-field equation (3).

The reason behind the bistability is the following: in the absence of spontaneous switching ($\epsilon = 0$), the states $n = 0$ (all individuals in configuration B) and $n = N$ (all individuals in configuration A) are absorbing: $W^+(0) = W^-(N) = 0$. Eventually, the system will end up in one of these two states and remain there. When $\epsilon > 0$, these states cease to be absorbing. However, the mean residence time τ in these states is $[W^+(\alpha) + W^-(\alpha)]^{-1} = 1/\epsilon N$ (where $\alpha = 0, N$) while the residence time in other states is $O(1)$. Therefore, in the regime $\epsilon N \ll 1$, the system is observed mostly in the boundary states.

In their article, Biancalani *et al.* computed $T(0)$, the mean switching time (the mean first passage time) from state $n = 0$ to state $n = N$, and show that the observation of this quantity can lead to the measure of the parameter ϵ of this stochastic system. For this computation, they expanded the master equation of the stochastic system in powers of $1/N$ and neglected terms of $O(1/N^3)$ to obtain the forward and backward Fokker-Plank equation, from which the mean switching time can be obtained [Ref. [12], Eq. (4) and Supplemental Material, Eqs. (4) and (11)]. This approximation is fragile, especially for small N where the noise is strong. In particular, to compute $T(0)$, they have used two different approximations, one of which is valid for $0.2 \lesssim N\epsilon$ and the other for $N\epsilon \to 0$, and there is no clear criterion for their overlap. In this article, we compute the exact expression for $T(0)$ without any approximation, which is valid for all values of ϵ. We further extend this investigation by giving the exact solution of the discrete master equation through the use of the probability generating function associated to the probabilities. Other quantities that we compute, such as the dynamics of the moments or the dynamics of the boundary states probabilities, provide other useful tools to measure and investigate this system.

This article is organized as follows: in the next section, we give the exact expression for the mean first passage time $T(n)$. The following section is devoted to the solution of the master equation. The final section is devoted to discussion and conclusion.

II. SWITCHING TIME

Preparing the system at time $t = 0$ in the initial state $n = m$, the system evolves and will reach the state $n = N$ for the first time at some time $T(m)$. The mean first passage times $\bar{T}(m)$ are obtained from the backward Kolmogorov equation and form the linear system [18]

$$W^+(0)[\bar{T}(1) - \bar{T}(0)] = -1 \tag{4}$$

$$W^+(m)[\bar{T}(m+1) - \bar{T}(m)] + W^-(m)[\bar{T}(m-1) - \bar{T}(m)] = -1, \tag{5}$$

where $0 < m < N$. Note that as $W^-(0) = 0$, we don't need to write a separate equation (4) for the boundary term $\bar{T}(0)$; the above notation however is clearer and highlights the boundary condition. Note also that by definition, $\bar{T}(N) = 0$, so the above square system of linear equations is well posed.

Using the continuous approximation $n \to x = n/N$, $\bar{T}(m) \to \bar{t}(x)$, and developing Eq. (5) to the second order in $(1/N)$, one obtains the second-order differential equation for $\bar{t}(x)$, which can be solved in terms of the hypergeometric function, as was done by Biancalani *et al.* [12] (see Appendix A 2). The continuous limit is however fragile when $\epsilon \to 0$, and the first solution obtained by Biancalani *et al.* does not converge to the right value in this limit. This is due to the absorbing boundary condition $t'(0) = 0$ used in the continuous approximation, which fails in the limit $\epsilon \to 0$ as it can be observed directly from Eq. (4) (see also Supplemental Material in Ref. [12]). In order to resolve this problem, they have resorted to a limit process for the case $\epsilon \to 0$ by approximating [Ref. [12], Eq. (28)]

$${}_2F_1\left(\tfrac{1}{2},u;\tfrac{3}{2};\tfrac{1}{1+2\epsilon}\right) \approx {}_2F_1\left(\tfrac{1}{2},u;\tfrac{3}{2};1\right),$$

where $u = N\epsilon$ or $1 - N\epsilon$, i.e., setting $\epsilon = 0$ in the fourth argument of the hypergeometric function, but not in the second. This *ad hoc* approximation gives the correct solution for $\epsilon \to 0$; no criterion however can be obtained for the overlap between the two solutions (Fig. 2).

These complications are due to the continuous approximation and can be avoided if the solution is computed directly for the discrete Eqs. (4), (5). The discrete solution is computationally much simpler, is valid for the whole range of ϵ and N, and does not involve any approximation; specifically, the boundary conditions are set naturally and don't need to be adjusted as a function of ϵ. The solution is obtained by setting $y_k = \bar{T}(k) - \bar{T}(k-1)$, which transforms Eqs. (4), (5) into a simple one-term recurrence equation. The exact solution is then

$$y_{k+1} = -\sum_{i=0}^{k} \frac{(N-k+\epsilon)_{(k-i)}}{(N-k)_{(k-i+1)}} \frac{(i+1)_{(k-i)}}{(i+\epsilon)_{(k-i+1)}} \quad 0 \leqslant k < N,$$

where $(\alpha)_{(m)} = \alpha(\alpha+1)\ldots(\alpha+m-1) = \Gamma(\alpha+m)/\Gamma(\alpha)$ is the Pochhammer symbol.

As $\bar{T}(N) = 0$, the first passage times $\bar{T}(m)$ are easily recovered from the y_k:

$$\bar{T}(m) = -\sum_{k=m}^{N-1} y_{k+1}.$$

In particular, the mean time to move from one boundary state to the other is

$$\bar{T}(0) = \sum_{k=0}^{N-1}\sum_{i=0}^{k} \frac{(N-k+\epsilon)_{(k-i)}}{(N-k)_{(k-i+1)}} \frac{(i+1)_{(k-i)}}{(i+\epsilon)_{k-i+1}}. \tag{6}$$

The above expression is computationally simpler than the product of two hypergeometric functions and involves only simple, finite arithmetics. Its expansion in the first two powers of ϵ gives (see Appendix):

$$\bar{T}(0) = \frac{1}{\epsilon} + 2\frac{N-1}{N} + O(\epsilon). \tag{7}$$

Figure 1 shows the remarkable accuracy of this formula for $N\epsilon \in [0,1]$ and $N \lesssim 100$, i.e., the relevant range where bistability can be observed. The analysis can be extended to compute the linear term in ϵ in Eq. (7) (see Appendix A 1)

Equations (6), (7) have been obtained by setting $r = 1$, i.e., by scaling time and ϵ by the factor r. Restoring the nonscaled time ($t \to t/r$, $\epsilon \to \epsilon/r$), we have

$$\bar{T}^{(\mathrm{ns})}_{\epsilon,r}(0) = \frac{1}{r}\bar{T}_{\epsilon/r}(0)$$

and in particular, the leading terms of the development are

$$\bar{T}^{(\mathrm{ns})}_{\epsilon,r}(0) = \frac{1}{\epsilon} + \frac{2}{r}\frac{N-1}{N} + \frac{1}{r}O\left(\frac{\epsilon}{r}\right).$$

Therefore, it is possible in principle, by measuring the switching time for different system size N, to measure independently the parameters ϵ and r.

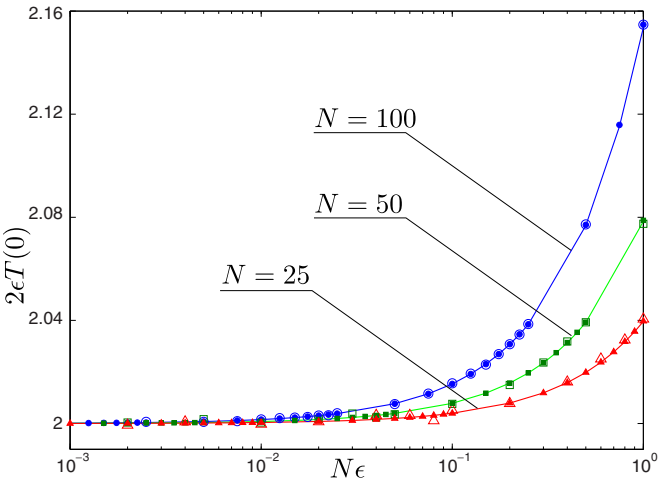

FIG. 1. (Color online) Switching time as a function of ϵ for three different values of N. Empty symbols: Numerical simulation by a Gillespie algorithm over 10^7 paths; filled symbols: numerical solution of the linear system (5)–(4); Solid lines: theoretical expression (7).

Note that the rate coefficients used by Biancalani *et al.* are given in terms of proportions, i.e., $r^{\mathrm{B}} = N^2 r$ and $\epsilon^{\mathrm{B}} = N\epsilon$. Figure 2 shows the comparison between our exact result and the Biancalani *et al.* approximate solutions when this scaling is taken into account, for the full range of $N\epsilon$. It can be observed that the two solutions obtained by Biancalani *et al.* and their overlap can be recovered from the exact solution we provide here.

Saito and Kaneko [19] have also computed the switching time for this stochastic system. Their method consists in obtaining an approximation for the residence time $t_{0,j}$ in each state j beginning from state 0 and then summing up these

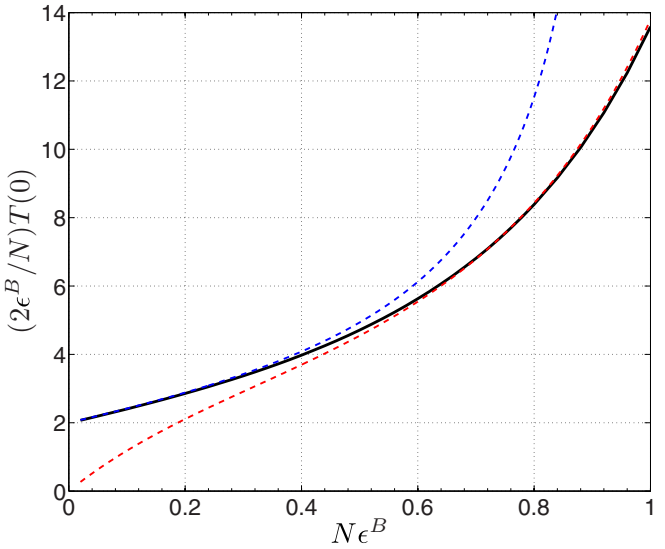

FIG. 2. (Color online) Exact result for the first passage time (solid line, black) as a function of N for $\epsilon^{\mathrm{B}} = 1/500$, $r = 1$ and its comparison to the two solutions provided by Biancalani *et al.* (Ref. [12], Fig. 5) : dotted curve, blue for $\epsilon \to 0$; dotted curve, red for $N\epsilon^{\mathrm{B}} \gtrsim 0.5$.

residence times to obtain the switching time. Their analytical result for the switching time has a very different form that the relation (6) and doesn't seem amenable to easy computation of the interesting limiting case $N\epsilon \ll 1$. However, their formula produces the same numerical results as the relation (6) of this article.

III. SOLVING THE MASTER EQUATION

The mean first passage is one tool to study the stochastic system described by the transition rates (1), (2). A complete description can be obtained by solving directly the master equation governing the probabilities $P(n,t)$ to observe n individuals in state A at time t:

$$\frac{\partial P(n,t)}{\partial t} = W^+(n-1)P(n-1,t) - W^+(n)P(n,t) + W^-(n+1)P(n+1,t) - W^-(n)P(n,t). \quad (8)$$

We note that the above stochastic system does not need a moment closure approximation, i.e., the equation for the kth moment involves only moments of order lower than k. Therefore, a hierarchical system of equations can be established to derive all the moments of this system. The probability generating function is a powerful tool to investigate such master equations [18,20]. The PGF is defined as

$$\phi(z,t) = \langle z^n \rangle = \sum_{n=0}^{N} P(n,t) z^n$$

and contains the most complete information we can have on the given stochastic process: all the moments and probabilities can be obtained from its derivatives at either $z = 1$ or $z = 0$. The equation governing the PGF can be extracted from the master equation (8) (see Appendix A 3) and reads:

$$\frac{\partial \phi}{\partial t} = -z(z-1)^2 \frac{\partial^2 \phi}{\partial z^2} + (z-1)\left[(N-1-\epsilon)z - (N-1+\epsilon)\right] \frac{\partial \phi}{\partial z} + \epsilon N (z-1)\phi. \quad (9)$$

The solution of Eq. (9) can be exactly computed (see Appendix A 3) as the superposition of polynomial eigenfunctions

$$\phi(z,t) = \sum_{n=0}^{N} C_n \phi_n(z) e^{\lambda_n t}, \quad (10)$$

where the eigenvalues are

$$\lambda_n = -n(n-1+2\epsilon),$$

the eigenfunctions are polynomials in z

$$\phi_n(z) = \sum_{k=n}^{N} a_k^n (1-z)^k$$

and the coefficients C_n depend on the initial condition. The initial condition we use here is the same as in the previous section, i.e., $P(n,0) = \delta_{n,0}$, which implies that $\phi(z,0) = 1$. The exact expression for the coefficients a_k^n, C_n and their product are given in Appendix A 3. The agreement between the

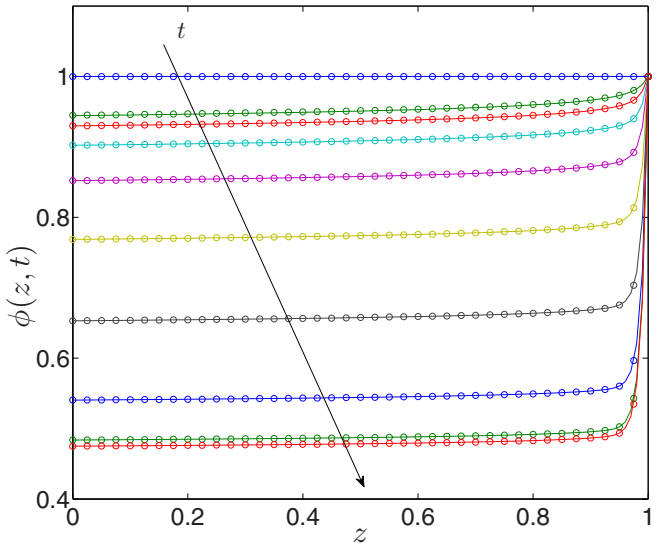

FIG. 3. (Color online) The PGF function $\phi(z,t)$ as a function of z at times $t \in \{0,1,2,4,8,16,32,64,128,256\}/(128\epsilon)$ for $N = 100$ and $\epsilon = 0.01$. Solid lines: theoretical expression (10). Circles: solution obtained by the numerical resolution of the master equation (8) and computation of its PGF.

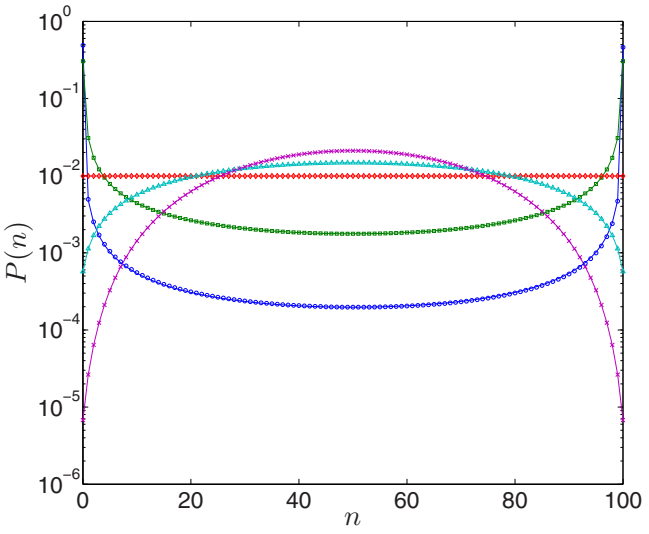

FIG. 4. (Color online) The stationary probabilities $P(n,\infty)$ as a function of n for $N = 100$ and various ϵ. Solid lines: exact expression (11), symbols: numerical resolution of the master equation. $\epsilon = 0.01$ (blue circles), 0.1 (green squares), 1 (red diamonds), 2 (diamonds, cyan), and 4 ($\times$, purple).

solution (10) and the direct numerical solution of the master equation is displayed in Fig. 3.

The PGF contains the most complete information on the stochastic process under investigation. Some quantities of interest extracted from it are given below.

A. Stationary probabilities

The stationary probabilities attained at large times are

$$P(n,\infty) = \binom{N}{n} \frac{(\epsilon)_{(n)}(\epsilon)_{(N-n)}}{(2\epsilon)_{(N)}}, \tag{11}$$

(see Appendix A 3) and their comparison to numerical solution of the master equation is displayed in Fig. 4. Note the qualitative change of behavior at $\epsilon = 1$. Expression (11) is equivalent to the expression found by Biancalani *et al.* [12] in the continuous approximation, with the advantage of being well defined for all n, including $n = 0, N$. In particular, for $\epsilon N \ll 1$,

$$P(n,\infty) \begin{cases} (1 - H_{N-1}\epsilon)/2 + O(\epsilon^2) & n = 0, N \\ \frac{N\epsilon}{2n(N-n)} + O(\epsilon^2) & n \neq 0, N, \end{cases}$$

where H_m is the harmonic number $\sum_{i=1}^{m} i^{-1}$.

B. Factorial moments

For the purposes of experimental measurements of the parameters, other dynamical quantities can be of interest. The most robust of these quantities are the factorial moments

$$\langle (n,q) \rangle = \langle n(n-1)\dots(n-q+1) \rangle$$

where (n,q) is used to denote the decreasing Pochhammer symbol. The factorial moments are obtained by successive derivation of the PGF

$$\langle (n,q) \rangle = q! \left. \frac{\partial^q \phi}{\partial z^q} \right|_{z=1} = (-1)^q q! \sum_{i=0}^{q} C_i a_q^i e^{\lambda_i t}. \tag{12}$$

Note that the qth factorial moment involves only $q+1$ eigenfunctions. The two first factorial moments are

$$\langle n \rangle = \frac{N}{2}(1 - e^{-2\epsilon t})$$

$$\langle n(n-1) \rangle = \frac{N(N-1)}{2} \times \left(\frac{1+\epsilon}{1+2\epsilon} - e^{-2\epsilon t} + \frac{\epsilon}{1+2\epsilon} e^{-2(1+2\epsilon)t} \right).$$

For $N\epsilon \ll 1$, only the two first terms in the sum (12) contribute significantly to the factorial moments for $t \gtrsim 1$. In particular, for large times,

$$\langle (n,q) \rangle \to (N,q) \frac{1 - H_{q-1}\epsilon}{2}.$$

C. Equilibrium time

Finally, we can define an equilibrium time T_{eq} by studying the dynamics of the decrease in $P(0,t)$ or increase in $P(N,t)$. The measure we choose to use here is

$$T_{eq} = \int_0^\infty \{P(N,\infty) - P(N,t)\}\, dt, \tag{13}$$

which is a generalization of the mean first passage time (see Appendix A 3). The expressions for the two boundary

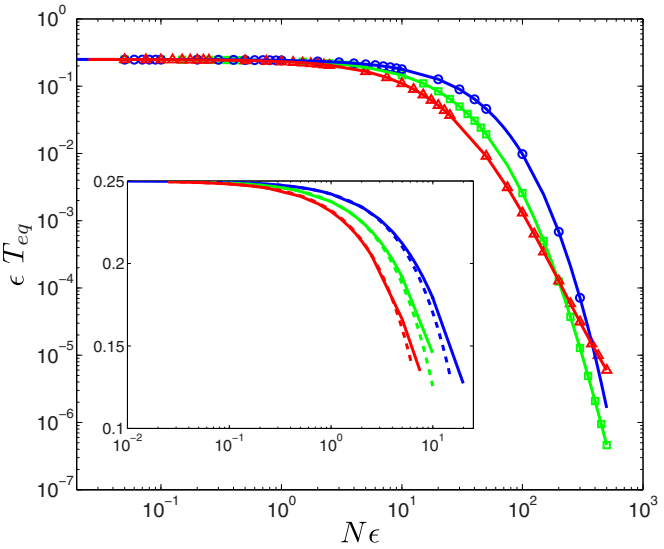

FIG. 5. (Color online) T_{eq} as a function of ϵ for different values of N. Solid lines: theoretical expression (14); symbols: numerical resolution of the master equation (blue circles $N = 100$; green squares $N = 50$; red triangles $N = 25$). Inset: comparison between the exact expression (14) (solid lines) and its approximation (15) (dashed lines) for $N\epsilon \lesssim 1$ and $N = 100$, 50, and 25.

probabilities are found to be

$$P(0,t) = \sum_{n=0}^{N} (-)^{N-n} C_n a_N^n e^{\lambda_n t}$$

$$P(N,t) = (-)^N \sum_{n=0}^{N} C_n a_N^n e^{\lambda_n t}$$

and therefore

$$T_{eq} = (-)^N \sum_{n=1}^{N} C_n a_N^n / \lambda_n. \tag{14}$$

For $N\epsilon \lesssim 1$, Eq. (14) is approximated by

$$T_{eq} = \frac{1}{4\epsilon} - \frac{1}{4}\left(H_{N-1} - 2 + \frac{2}{N}\right). \tag{15}$$

Figure 5 displays T_{eq} as a function of ϵ and its comparison to numerical solution of the master equation.

IV. CONCLUSION

As discussed in the introduction, noise induced bistability has been intensely investigated, specially in genetic networks. In general, the chemical master equations are too complex to be solved exactly and various approximation techniques have been developed to tackle this problem. In some cases, exact analytical solutions have been obtained using the probability generating function. Shahrezaei and Swain [21] have studied a three-stage model of simple gene expression (DNA state, RNA, protein) and obtained the protein number distribution. Grima *et al.* [22] have investigated the steady-state distribution of a two-component (DNA state, protein) genetic feedback loop and have been able to obtain exact analytical results using the PGF technique. In the first case, the PGF equation is a first-order partial differential equation and can be solved by the method of characteristics. In the second case, the model can be reduced to two coupled one-component systems and the PGF equation reduced to two ordinary coupled first-order differential equations. Chemical master equations analogous to these cases could in principle be investigated with the same technique.

In this work, we have extended the investigation by Biancalani *et al.* [12] of another noise induced bistable system, which belongs to the second class of models discussed above. First, we have obtained the exact solution for the mean first passage time, which is the main result of the above cited article. Second, we have solved the full master equation associated with this system and obtained other useful quantities for parameter estimations of such systems. We have obtained these results for the original, discrete system without resorting to the Taylor expansion of the master equation in powers of $1/N$. Discrete solutions have the advantage of being clearly defined and avoid spurious effect happening at the boundaries, specially for the interesting case of small ϵ. Moreover, these solutions involve only simple arithmetic and are easily computed.

APPENDIX: MATHEMATICAL DETAILS

1. Series expansion of the exact solution of the switching time

The exact solution (6) contains a double sum, where only the terms $i = 0$ contain ϵ^{-1} factors. Separating these two contributions, the solution becomes:

$$\bar{T}(0) = \frac{1}{N\epsilon} \sum_{k=0}^{N-1} \frac{(1)_k}{(1+\epsilon)_k} \frac{(N-k+\epsilon)_k}{(N-k)_k} + \sum_{k=1}^{N-1} \sum_{i=1}^{k} \frac{(N-k+\epsilon)_{(k-i)}}{(N-k)_{(k-i+1)}} \frac{(i+1)_{(k-i)}}{(i+\epsilon)_{k-i+1}}.$$

Expanding the first sum to the first order in ϵ necessitates only simple expansion in factors of the form $m/(m+\epsilon) = 1 - \epsilon/m + O(\epsilon^2)$ and leads to

$$\frac{1}{\epsilon} - H_{N-1} + 2\frac{N-1}{N},$$

where the harmonic number $H_m = \sum_{i=1}^{m}(1/i)$. Evaluating the second sum for $\epsilon = 0$ results in

$$\sum_{k=1}^{N-1} \sum_{i=1}^{k} \frac{1}{i(N-i)} = H_{N-1}.$$

Adding the two contributions results in Eq. (7):

$$\bar{T}(0) = \frac{1}{\epsilon} + 2\frac{N-1}{N}.$$

The next term in the series expansion of $\bar{T}(0)$ is found to be

$$-\frac{2\epsilon}{N}\left[H_{N-1} + N H_{N-1}^{(2)} - 2(N-1)\right].$$

Note that algorithmically, the computation of $\bar{T}(0)$ [expression (6)] necessitates only the calculation of N ratios of the form $(m+1)/(m+\epsilon)$ and $(m+\epsilon)/m$, which can be stored in an

array. The $\bar{T}(0)$ involves then only multiplications and sums of these elements. The hypergeometric function on the other hand is defined as

$$ {}_2F_1(a,b;c;z) = \sum_{n=0}^{\infty} \frac{(a)_{(n)}(b)_{(n)}}{(c)_{(n)}} \frac{z^n}{n!} $$

and its efficient implementation requires specific algorithms.

2. Solution of Biancalani *et al.* for the switching time

In nonscaled time, the Biancalani *et al.* solution is

$$ \bar{T}^{\rm ns}(0) = \frac{1}{r'} \frac{2N^2}{1+2\epsilon'/r'} {}_2F_1\left(\frac{1}{2},1-N\frac{\epsilon'}{r'};\frac{3}{2};\frac{1}{1+2\epsilon'/r'}\right) \times {}_2F_1\left(\frac{1}{2},N\frac{\epsilon'}{r'};\frac{3}{2};\frac{1}{1+2\epsilon'/r'}\right), $$

where the rates ϵ' and r' are related to the rates ϵ, r used in this article through:

$$ \epsilon' = N\epsilon \ ; \ r' = N^2 r. $$

3. Deriving and solving the PGF equation

PGF. The equation for the evolution of the PGF is obtained by multiplying the master Eq. (8) by z^n and summing over n [23]. This operation leads to

$$ \frac{\partial \phi}{\partial t} = \langle (z^{n+1}-z^n) W^+(n) \rangle + \langle (z^{n-1}-z^n) W^-(n) \rangle. \quad \text{(A1)} $$

The rates $W^{\pm}(n)$ are polynomials of second degree in n and by the definition of the PGF,

$$ \langle n^r z^n \rangle = \left(z \frac{\partial}{\partial z} \right)^r \phi. $$

Application of the above rule to Eq. (A1) leads to Eq. (9).

Eigenfunctions. Equation (9) can be transformed into a hypergeometric equation by a change of variable $x = (z-1)^{-1}$. It is however much simpler to use the fact that by definition, the function $\phi(z,t)$ is a polynomial of degree N in z and search for the eigenfunctions of Eq. (9) in term of polynomials of the following form:

$$ \phi_n(z) = \sum_{k=0}^{N} a_k^n (1-z)^k, $$

i.e.,

$$ \phi(z,t) = \sum_{n=0}^{N} C_n \phi_n(z) e^{\lambda_n t}. $$

Insertion of these polynomials into Eq. (9) shows that nontrivial solutions (i.e., $\neq 0$) are possible only for the eigenvalues

$$ \lambda_n = -n(n-1+2\epsilon) \quad n = 0,1,\ldots,N, $$

which leads to a one term recurrence relation on the coefficients a_k^n:

$$ a_k^n = 0 \quad (k<n) $$
$$ a_n^n = 1 $$
$$ a_{k+1}^n = -\frac{(N-k)(k+\epsilon)}{(k+1)(k+2\epsilon)-n(n-1+2\epsilon)} a_k^n \quad (n \leqslant k < N). $$

As it can be noticed, ϕ_n is written as polynomial in powers of $(1-z)$ and not z. This choice is not arbitrary: it is this change of variable that allows us to obtain a one-term recurrence relation between the coefficients a_k^n. Writing ϕ_n as a polynomial in z leads to a two-term recurrence relation, which is much more intricate to solve exactly.

The coefficients a_k^n can be computed in explicit forms:

$$ a_k^n = (-)^{k-n} \binom{N-n}{k-n} \frac{(\epsilon+n)_{(k-n)}}{(2\epsilon+2n)_{(k-n)}} \quad (n \leqslant k < N). \quad \text{(A2)} $$

Alternatively, the eigenfunctions can also be given in terms of the hypergeometric function:

$$ \phi_n(z) = (1-z)^n \ {}_2F_1(n-N,n+\epsilon;2n+2\epsilon;1-z). \quad \text{(A3)} $$

The amplitudes C_n depend on the initial condition. For $P(n,0) = \delta_{n,0}$ and therefore $\phi(z,0) = 1$, the amplitudes obey the triangular linear system

$$ C_0 = 1 $$
$$ \sum_{n=0}^{k} C_n a_k^n = 0 \quad (k>0), $$

which can be explicitly solved

$$ C_n = \binom{N}{n} \frac{(\epsilon)_{(n)}}{(2\epsilon+n-1)_{(n)}} \quad \text{(A4)} $$

and therefore,

$$ C_n a_k^n = (-)^{k-n} \binom{N}{k} \binom{k}{n} \frac{(\epsilon)_{(k)}}{(\epsilon+n)_{(k)}} \frac{2\epsilon+2n-1}{2\epsilon+n-1}. $$

Stationary probabilities. As all eigenvalues except λ_0 are negative, for large times the PGF is simply

$$ \phi(z) = {}_2F_1(-N,\epsilon;2\epsilon;1-z), $$

where we have used the hypergeometric representation [Eq. (A3)] of the eigenfunctions. Using the relations

$$ {}_2F_1(-m,b;c;1) = \frac{(c-b)_{(m)}}{(c)_{(m)}} $$
$$ \frac{d^n}{dz^n} {}_2F_1(a,b;c;z) = \frac{(a)_{(n)}(b)_{(n)}}{(c)_{(n)}} {}_2F_1(a+n,b+n;c+n;z) $$

we obtain

$$ P(n) = \frac{1}{n!} \left. \frac{d^n \phi}{dz^n} \right|_{z=0} = (-1)^n \frac{(-N)_{(n)}}{n!} \frac{(\epsilon)_{(n)}}{(2\epsilon)_{(n)}} \frac{(\epsilon)_{(N-n)}}{(2\epsilon+n)_{(N-n)}}. \quad \text{(A5)} $$

As

$$(2\epsilon)_{(n)}(2\epsilon+n)_{(N-n)} = (2\epsilon)_N$$

we recover the relation (11) on the stationary probabilities.

Factorial moments. Using the above expression, the factorial moments are

$$\langle (n,q)\rangle = (N,q)\sum_{i=0}^{q}(-)^i\binom{q}{i}\frac{(\epsilon)_{(q)}}{(2\epsilon+i)_{(q)}}\frac{2\epsilon+2i-1}{2\epsilon+i-1}e^{\lambda_i t}.$$

Equilibrium times. Many different measures can be used for the equilibrium time of the system. The expression we use

$$T_{eq} = \int_0^\infty [P(N,\infty) - P(N,t)]\,dt \tag{A6}$$

is the extension of the mean time to absorption to the case when the boundary state is not absorbing. The reason is the following: If the state N were the only absorbing state, whatever the initial condition m, $P(N,t) \to 1$ as $t \to \infty$. The probability of survival until time T, beginning in the state m is

$$Q(m,T) = 1 - P(N,T)$$

and the probability density of not being absorbed during $[T, T+dt]$ is therefore $-\partial_T Q(m,T)$. Therefore, the mean time to absorption is

$$\begin{aligned}\bar{T}(m) &= -\int_0^\infty T\,\partial_T Q(m,T)dT \\ &= \int_0^\infty [1 - P(N,T)]\,dT \\ &= \int_0^\infty [P(N,\infty) - P(N,T)]\,dT.\end{aligned}$$

We see that in the case of an absorbing state N, our definition of T_{eq} and the mean time to absorption are the same. We continue to use T_{eq} as a measure of the equilibrium time when N is not absorbing.

Probabilities. The probabilities are extracted from the PGF by collecting the coefficients of powers of z:

$$P(n,t) = \sum_{k=0}^{N} b_k^n \exp(\lambda_k t),$$

where

$$b_k^n = (-)^n C_k \sum_{j=k}^{N}\binom{j}{n} a_j^k.$$

[1] José M. G. Vilar, Hao Yuan Kueh, Naama Barkai, and Stanislas Leibler, Mechanisms of noise-resistance in genetic oscillators, Proc. Natl. Acad. Sci. USA **99**, 5988 (2002).

[2] Bahram Houchmandzadeh and Marcel Vallade, Selection for altruism through random drift in variable size populations, BMC Evol. Biol. **12**, 61 (2012).

[3] K. S. Korolev, Mikkel Avlund, Oskar Hallatschek, and David R. Nelson, Genetic demixing and evolution in linear stepping stone models, Rev. Mod. Phys. **82**, 1691 (2010).

[4] B. Houchmandzadeh, Neutral clustering in a simple experimental ecological community, Phys. Rev. Lett. **101**, 078103 (2008).

[5] Eric Dumonteil, Fausto Malvagi, Andrea Zoia, Alain Mazzolo, Davide Artusio, Cyril Dieudonné, and Clélia De Mulatier, Particle clustering in Monte Carlo criticality simulations, Ann. Nucl. Energy **63**, 612 (2014).

[6] W. Horsthemke and R. Lefeve, *Noise-Induced Transitions: Theory and Applications in Physics, Chemistry, and Biology* (Springer-Verlag, Berlin, 1986).

[7] Michael Samoilov, Sergey Plyasunov, and Adam P. Arkin, Stochastic amplification and signaling in enzymatic futile cycles through noise-induced bistability with oscillations, Proc. Natl. Acad. Sci. USA **102**, 2310 (2005).

[8] Maxim N. Artyomov, Jayajit Das, Mehran Kardar, and Arup K. Chakraborty, Purely stochastic binary decisions in cell signaling models without underlying deterministic bistabilities, Proc. Natl. Acad. Sci. USA **104**, 18958 (2007).

[9] Hong Qian, Pei-Zhe Shi, and Jianhua Xing, Stochastic bifurcation, slow fluctuations and bistability as an origin of biochemical complexity, Phys. Chem. Chem. Phys. **11**, 4861 (2009).

[10] Philipp Thomas, Nikola Popović, and Ramon Grima, Phenotypic switching in gene regulatory networks, Proc. Natl. Acad. Sci. USA **111**, 6994 (2014).

[11] Tsz-Leung To and Narendra Maheshri, Noise can induce bimodality in positive transcriptional feedback loops without bistability, Science **327**, 1142 (2010).

[12] Tommaso Biancalani, Louise Dyson, and Alan J. McKane, Noise-induced bistable states and their mean switching time in foraging colonies, Phys. Rev. Lett. **112**, 038101 (2014).

[13] P. A. P. Moran, *The Statistical Processes of of Evolutionary Theory* (Oxford University Press, Oxford, 1962).

[14] Yuichi Togashi and Kunihiko Kaneko, Transitions induced by the discreteness of molecules in a small autocatalytic system, Phys. Rev. Lett. **86**, 2459 (2001).

[15] Jun Ohkubo, Nadav Shnerb, and David A. Kessler, Transition phenomena induced by internal noise and quasi-absorbing state, J. Phys. Soc. Jpn. **77**, 044002 (2008).

[16] Tommaso Biancalani, Tim Rogers, and Alan J. McKane, Noise-induced metastability in biochemical networks, Phys. Rev. E **86**, 010106 (2012).

[17] Roy J. Glauber, Time-dependent statistics of the ising model, J. Math. Phys. **4**, 294 (1963).

[18] C. Gardiner, *Handbook of Stochastic Methods: for Physics, Chemistry and the Natural Sciences* (Springer, New York, 2004).

[19] Nen Saito and Kunihiko Kaneko, Theoretical analysis of discreteness-induced transition in autocatalytic reaction dynamics. arXiv:1403.6222.

[20] N. G. Van Kampen, *Stochastic Processes in Physics and Chemistry*, Vol. 11 (North-Holland, Amsterdam, 1992).

[21] Vahid Shahrezaei and Peter S. Swain, Analytical distributions for stochastic gene expression, Proc. Natl. Acad. Sci. USA **105**, 17256 (2008).

[22] R. Grima, D. R. Schmidt, and T. J. Newman, Steady-state fluctuations of a genetic feedback loop: an exact solution, J. Chem. Phys. **137**, 035104 (2012).

[23] B. Houchmandzadeh and M. Vallade, Alternative to the diffusion equation in population genetics, Phys. Rev. E **82**, 051913 (2010).