

Efficient variants of the minimal diffusion formulation of Markov chain ensembles

Marifi Güler*

Department of Computer Engineering, Eastern Mediterranean University, Famagusta, via Mersin-10, Turkey

(Received 7 September 2015; published 16 February 2016)

This study is concerned with ensembles of continuous-time Markov chains evolving independently under a common transition rate matrix in some finite state space. In this context, our prior work [[Phys. Rev. E **91**, 062116 \(2015\)](#)] has formulated an approximation scheme, called the minimal diffusion formulation, to deduce how the number of chains in a prescribed relevant state evolves in time. The formulation consists of two specifically coupled Ornstein-Uhlenbeck processes in a stochastic differential equation representation; it is minimal in the sense that its structure does not change with the state space size or the transition matrix density, and it requires no matrix square-root operations. In the present study, we first calculate the autocorrelation function of the relevant state density in the minimal diffusion formulation, which is fundamental to the identification of the ensemble dynamics. The obtained autocorrelation function is then employed to develop two diffusion formulations that reduce the structural complexity of the minimal diffusion formulation without significant loss of accuracy in the dynamics. One of these variant formulations includes one less noise term than the minimal diffusion formulation and still satisfies the above-mentioned autocorrelation function in its dynamics. The second variant is in the form of a one-dimensional Langevin equation, therefore it is the simplest possible diffusion formulation one can obtain for the problem, yet its autocorrelation function is first-order accurate in time gap. Numerical simulations supporting the theoretical analysis are delivered.

DOI: [10.1103/PhysRevE.93.022123](https://doi.org/10.1103/PhysRevE.93.022123)**I. INTRODUCTION**

Markov processes are the most commonly used mathematical models for random phenomena evolving in time [1,2]. Analysis of the temporal evolution of one Markov chain is comparatively easy [3,4], but the mathematics becomes quite complicated for the collective behavior of an ensemble of chains, dating back to Doob [5] and Spitzer [6]. The complication applies even in the absence of interaction among the chains. In this context, Kurtz [7] has approximated density-dependent Markov processes, for large system size, with a diffusion model represented by a system of stochastic differential equations (for a detailed account, see Ref. [8]). The approach assumes the chains in the ensemble to be evolving independently in the same finite state space with some continuous-time Markov transition rules common to all the chains. The Kurtz approach was later rediscovered by Fox and Lu [9] in the study of ion channel clusters. Density-dependent Markov models appeared not only in computational neuroscience to model the gating by ion channel clusters [9–14], but also in a variety of biological and physical contexts, including chemical kinetics, ecological modeling, epidemics, metapopulations, and telecommunications (see, e.g., Ref. [15]). In some problems, the autocorrelation time of the fluctuations plays a role as critical as the amplitude of the state density fluctuations [16].

The use of the diffusion approximation is, however, deterred by the inherent requirement of a calculation of a matrix square root at each time step in it [7,9]. In addition, the number of noise terms required there increases with the state space size. Approaches that circumvent the matrix square-root calculations were introduced [13,17], but at the expense that the number of noise terms employed increases not only with the state space size, but also with the transition rate matrix

density. The approaches of Refs. [13] and [17] yield the same resulting formulation (see the Appendix in Ref. [18]).

To overcome the above difficulties, we have recently put forward a model [14], which we named “the minimal diffusion formulation,” that provides a simple analytic formulation and a fast computation algorithm for the problem. The model exploits the fact that in many applications, only a subset of states (often just one) is relevant, the others being hidden or not of direct concern. That fact was previously exploited to shorten the computing time of the exact microscopic Markov simulations [19]. The minimal diffusion formulation was developed to determine the temporal evolution of the relevant state density of chains in such a way that its structural complexity does not change with the underlying state transition diagram. It accommodates two stochastic variables and two noise terms (in the form of coupled Ornstein-Uhlenbeck processes in a stochastic differential equation representation) irrespective of the state space size or the transition matrix density, and it is not hindered by the matrix square-root operations. This was made possible by treating the effects of the state density fluctuations, other than of the relevant state, collectively instead of using the density fluctuations of the individual states explicitly. Note at this point that the diffusion models, other than the minimal formulation, suffer from the aforementioned increase in the numbers of stochastic variables and noise terms even when one is interested in the dynamics specific to the relevant state only.

The first step of our work in the present paper is analytic calculation of the autocorrelation function of the relevant state density in the minimal diffusion formulation. The autocorrelation function is found to consist of two exponentially decaying additive terms. The calculation is not only important on its own, but it is also crucial for our subsequent analysis. After that, we develop two formulations as variants of the minimal diffusion formulation. We will refer to the variants as $2v1n$ and $1v1n$. The former contains two stochastic variables, whereas

*marifi.guler@gmail.com

the latter contains one stochastic variable; both variants include one noise term. Recall that the minimal diffusion formulation accommodates two stochastic variables and one stochastic variable; therefore, the term “2v2n formulation” or “2v2n model” will be used interchangeably with minimal diffusion formulation. The variants 2v1n and 1v1n were developed with the objective of reducing the structural complexity of the 2v2n formulation without a significant loss of accuracy in the dynamical activity. For that, we make use of the autocorrelation function of the 2v2n formulation. The variant 2v1n yields the same autocorrelation function as the 2v2n model. The simpler variant 1v1n is capable of capturing the 2v2n autocorrelation function up to first order in the time gap.

This paper is organized as follows. Section II gives the essentials of the original minimal diffusion formulation. Calculation of the 2v2n model’s relevant state density autocorrelation function is the subject of Sec. III. Elaborations of the variants 2v1n and 1v1n are presented in Secs. IV and V, respectively. Section VI includes comparative numerical simulation results that complement the theory. Finally, Sec. VII includes some concluding remarks.

II. THE ORIGINAL MINIMAL DIFFUSION (OR 2v2n) FORMULATION

The formulation [14] is for the temporal evolution of state density fluctuations in Markov chain ensembles at equilibrium. For easier physical visualization, each chain in the ensemble can be imagined as a particle. The formulation is valid after the relaxation of the system, and it provides a diffusion approximation to deduce the dynamics of the number (or the density) of chains that are in a given relevant state. The ensemble was assumed to consist of ergodic (irreducible) continuous-time Markov chains evolving independently under a common transition rate matrix in some finite space of states. The advantage of the formulation lies in its minimal complexity: It always accommodates only two stochastic variables and two noise terms irrespective of the state space size or the transition matrix density, and it is not hindered by the matrix square-root operations. This was facilitated by treating the effect of the state density fluctuations, other than of the relevant state, collectively rather than using the density fluctuations of the individual states explicitly.

Let N be the number of Markov chains in the ensemble, and $\{0, 1, \dots, L\}$ be the space of states. Also let θ_l ($l = 0, 1, \dots, L$) be the number of chains in state l at a particular time, and refer to the synonym $\psi_l := \theta_l/N$ as the density of state l . Symbolize the fluctuation in the state density ψ_l by ϕ_l , that is,

$$\psi_l := \langle \psi_l \rangle + \phi_l \quad (l = 0, 1, \dots, L),$$

where $\langle \dots \rangle$ denotes the expectation value. Note that the average state density $\langle \psi_l \rangle$ corresponds to the probability of finding a chain in state l . By definition, it reads

$$\sum_{l=0}^L \langle \psi_l \rangle = \sum_{l=0}^L \psi_l = 1, \quad (1)$$

$$\sum_{l=0}^L \phi_l = 0, \quad (2)$$

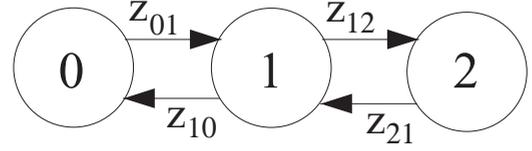


FIG. 1. Example of a state transition diagram used in demonstrating the implementation of the master equation. z ’s denote the transition rates.

and

$$\langle \phi_l \rangle = 0 \quad (l = 0, 1, \dots, L). \quad (3)$$

The evolution of the expectation values $\langle \psi_l \rangle$ ($l = 0, 1, \dots, L$) can be computed from the L coupled linear deterministic differential equations governed by the master equation. A fundamental property of the master equation in Markov processes is that, as $t \rightarrow \infty$, all solutions tend to a stationary solution if the state set contains strictly a finite number of discrete states and the transition rates are constant in time. There exists only one stationary solution if the transition rate matrix is not decomposable. Therefore, with constant transition rates, $\langle \psi_l \rangle$ ($l = 0, 1, \dots, L$) reaches the unique steady state in the long-time limit. The minimal diffusion formulation assumes the transition rates to be constant or slowly varying. For demonstration, consider the example state transition diagram given in Fig. 1. In this particular case, the master equation reads

$$\begin{aligned} \frac{d\langle \psi_0 \rangle}{dt} &= -z_{01}\langle \psi_0 \rangle + z_{10}\langle \psi_1 \rangle, \\ \frac{d\langle \psi_1 \rangle}{dt} &= z_{01}\langle \psi_0 \rangle - (z_{10} + z_{12})\langle \psi_1 \rangle + z_{21}\langle \psi_2 \rangle, \\ \frac{d\langle \psi_2 \rangle}{dt} &= z_{12}\langle \psi_1 \rangle - z_{21}\langle \psi_2 \rangle, \end{aligned} \quad (4)$$

and Eq. (1) becomes

$$\langle \psi_0 \rangle + \langle \psi_1 \rangle + \langle \psi_2 \rangle = 1. \quad (5)$$

For time-dependent transition rates, the average state densities can be solved iteratively from Eq. (4), subject to the constraint (5). For constant transition rates, the steady state

$$\frac{d\langle \psi_0 \rangle}{dt} = \frac{d\langle \psi_1 \rangle}{dt} = \frac{d\langle \psi_2 \rangle}{dt} = 0 \quad (6)$$

prevails in the long-time limit. Then, after noting that only two of the equations in the set given by Eq. (4) are linearly independent, Eqs. (4)–(6) uniquely solve $\langle \psi_0 \rangle$, $\langle \psi_1 \rangle$, and $\langle \psi_2 \rangle$.

In presenting the formulation for the dynamics of the density fluctuation ϕ_r , where the subscript r stands for the relevant state, let us start with the special case in which the relevant state is directly connected only to one state—say to state s —in the transition diagram (see Fig. 2). The governing model equations are given by the following coupled stochastic

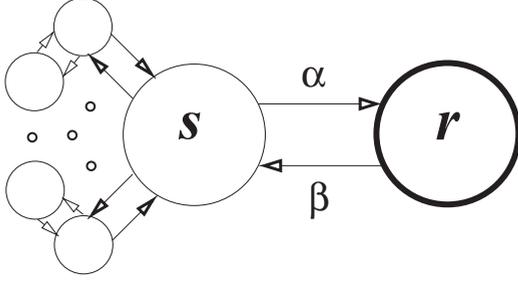


FIG. 2. Sketch of the relevant state when it makes a direct connection with one state only. α and β denote transition rates.

differential equations:

$$\dot{\phi}_r = -\beta\phi_r + \alpha\phi_s + \xi, \quad (7a)$$

$$\dot{\phi}_s = -\gamma\phi_s - \xi + \eta, \quad (7b)$$

where the parameter γ is given as

$$\gamma = \frac{\alpha\langle\psi_s\rangle^2 + \beta\langle\psi_r\rangle(1 - \langle\psi_s\rangle)}{\langle\psi_s\rangle\langle\psi_r\rangle}. \quad (8)$$

The terms ξ and η in Eq. (7) are independent zero mean Gaussian white noises with the mean squares given by

$$\langle\xi(t)\xi(t')\rangle = \frac{\alpha\langle\psi_s\rangle + \beta\langle\psi_r\rangle}{N}\delta(t - t') \quad (9)$$

and

$$\langle\eta(t)\eta(t')\rangle = \frac{\alpha\langle\psi_s\rangle C_\alpha + \beta\langle\psi_r\rangle C_\beta}{N\langle\psi_r\rangle}\delta(t - t'), \quad (10)$$

respectively. The synonyms C_α and C_β in Eq. (10) stand for

$$C_\alpha := 2\langle\psi_s\rangle(1 - \langle\psi_s\rangle) - \langle\psi_r\rangle,$$

$$C_\beta := 2(1 - \langle\psi_s\rangle)^2 - \langle\psi_r\rangle.$$

Then, solving the relevant state density fluctuation ϕ_r from the formulation here and using $\langle\psi_r\rangle$ as obtained from the master equation, the evolution of ψ_r is concluded by means of $\psi_r = \langle\psi_r\rangle + \phi_r$.

We next consider the case in which the relevant state connects directly to two states—say to states j and k . Assume that the transition rates from state r to states j and k are denoted by β_j and β_k , and the rates from j to r and from k to r are denoted by α_j and α_k , all correspondingly. The above governing equations are valid also in this case provided that the transition rates β and α , and the probability $\langle\psi_s\rangle$, are now set, in terms of the parameters related to the states j and k , as follows:

$$\beta = \beta_j + \beta_k, \quad (11)$$

$$\alpha = A + \frac{B}{A}, \quad (12)$$

and

$$\langle\psi_s\rangle = \frac{A^2}{A^2 + B}, \quad (13)$$

with

$$A := \alpha_j\langle\psi_j\rangle + \alpha_k\langle\psi_k\rangle,$$

$$B := \alpha_j^2\langle\psi_j\rangle(1 - \langle\psi_j\rangle) - 2\alpha_j\alpha_k\langle\psi_j\rangle\langle\psi_k\rangle + \alpha_k^2\langle\psi_k\rangle(1 - \langle\psi_k\rangle).$$

Similarly, the formulation can be extended to a case in which the relevant state makes a direct connection with an arbitrary number of states (see Ref. [14] for further details).

III. AUTOCORRELATION OF THE RELEVANT STATE DENSITY IN THE 2v2n MODEL

In this section, we calculate the autocorrelation function of the relevant state density in the 2v2n formulation. The calculation is important not only for its own sake, but also because the development of both the 2v1n and 1v1n models relies on that autocorrelation function. The evaluation is compelling in the long-time limit and assumes the transition rates are constant.

The differential equations (7a) and (7b) yield the solutions

$$\phi_r(t) = e^{-\beta t} \left\{ \phi_r(0) + \int_0^t e^{\beta t^*} [\alpha\phi_s(t^*) + \xi(t^*)] dt^* \right\} \quad (14)$$

and

$$\phi_s(t) = e^{-\gamma t} \left\{ \phi_s(0) - \int_0^t e^{\gamma t^*} [\xi(t^*) - \eta(t^*)] dt^* \right\}, \quad (15)$$

respectively. Although not necessary, it is useful to assume here that the system at time 0 has already reached equilibrium. Equation (15), with the utilization of $\langle\eta\xi\rangle = 0$, reads in the limit $t \rightarrow \infty$ that

$$\langle\phi_s(t)\xi(t')\rangle = \begin{cases} -\langle\xi^2\rangle e^{-\gamma(t-t')} & \text{if } t \geq t', \\ 0 & \text{otherwise} \end{cases} \quad (16)$$

and

$$\langle\phi_s(t)\phi_s(t')\rangle = \langle\phi_s^2\rangle e^{-\gamma|t-t'|}, \quad (17)$$

where $\langle\phi_s^2\rangle$ reads [14]

$$\langle\phi_s^2\rangle = \frac{\langle\psi_s\rangle(1 - \langle\psi_s\rangle)}{N}. \quad (18)$$

The reader is also referred to Ref. [20]. Note that the expectation values $\langle\xi^2\rangle$ and $\langle\phi_s^2\rangle$ are constants at equilibrium for time-independent transition rates.

For the relevant state density autocorrelation, we obtain from Eq. (14) that

$$\begin{aligned} & \langle\phi_r(t)\phi_r(t+\tau)\rangle \\ &= e^{-\beta(2t+\tau)} \int_0^t \int_0^{t+\tau} e^{\beta(t_1+t_2)} \\ & \quad \times \{ \alpha^2 \langle\phi_s(t_1)\phi_s(t_2)\rangle + \alpha \langle\phi_s(t_1)\xi(t_2)\rangle \\ & \quad + \alpha \langle\phi_s(t_2)\xi(t_1)\rangle + \langle\xi(t_1)\xi(t_2)\rangle \} dt_1 dt_2, \end{aligned} \quad (19)$$

which can be decomposed into

$$\begin{aligned} \langle \phi_r(t)\phi_r(t+\tau) \rangle &= e^{-\beta(2t+\tau)} \int_0^t e^{\beta t_2} \left\{ \alpha^2 \int_0^{t_2} e^{\beta t_1} \langle \phi_s(t_1)\phi_s(t_2) \rangle dt_1 + \alpha^2 \int_{t_2}^{t+\tau} e^{\beta t_1} \langle \phi_s(t_1)\phi_s(t_2) \rangle dt_1 \right. \\ &\quad + \alpha \int_0^{t_2} e^{\beta t_1} \langle \phi_s(t_1)\xi(t_2) \rangle dt_1 + \alpha \int_{t_2}^{t+\tau} e^{\beta t_1} \langle \phi_s(t_1)\xi(t_2) \rangle dt_1 + \alpha \int_0^{t_2} e^{\beta t_1} \langle \phi_s(t_2)\xi(t_1) \rangle dt_1 \\ &\quad \left. + \alpha \int_{t_2}^{t+\tau} e^{\beta t_1} \langle \phi_s(t_2)\xi(t_1) \rangle dt_1 + \int_0^{t+\tau} e^{\beta t_1} \langle \xi(t_1)\xi(t_2) \rangle dt_1 \right\} dt_2. \end{aligned} \quad (20)$$

Due to Eq. (16), the third and sixth additive integral terms in Eq. (20) vanish, that is,

$$\begin{aligned} \int_0^{t_2} e^{\beta t_1} \langle \phi_s(t_1)\xi(t_2) \rangle dt_1 \\ = \int_{t_2}^{t+\tau} e^{\beta t_1} \langle \phi_s(t_2)\xi(t_1) \rangle dt_1 = 0. \end{aligned} \quad (21)$$

The first and second integral terms yield, by means of Eq. (17), that

$$\int_0^{t_2} e^{\beta t_1} \langle \phi_s(t_1)\phi_s(t_2) \rangle dt_1 = \frac{\langle \phi_s^2 \rangle}{\beta + \gamma} (e^{\beta t_2} - e^{-\gamma t_2}) \quad (22)$$

and

$$\begin{aligned} \int_{t_2}^{t+\tau} e^{\beta t_1} \langle \phi_s(t_1)\phi_s(t_2) \rangle dt_1 \\ = \frac{\langle \phi_s^2 \rangle}{\beta - \gamma} e^{\gamma t_2} [e^{(\beta-\gamma)(t+\tau)} - e^{(\beta-\gamma)t_2}]. \end{aligned} \quad (23)$$

The fourth and fifth terms are evaluated, by means of Eq. (16), as

$$\begin{aligned} \int_{t_2}^{t+\tau} e^{\beta t_1} \langle \phi_s(t_1)\xi(t_2) \rangle dt_1 \\ = -\frac{\langle \xi^2 \rangle}{\beta - \gamma} [e^{\gamma t_2} e^{(\beta-\gamma)(t+\tau)} - e^{\beta t_2}] \end{aligned} \quad (24)$$

and

$$\int_0^{t_2} e^{\beta t_1} \langle \phi_s(t_2)\xi(t_1) \rangle dt_1 = -\frac{\langle \xi^2 \rangle}{\beta + \gamma} [e^{\beta t_2} - e^{-\gamma t_2}]. \quad (25)$$

The last term reads

$$\begin{aligned} \int_0^{t+\tau} e^{\beta t_1} \langle \xi(t_1)\xi(t_2) \rangle dt_1 \\ = \langle \xi^2 \rangle e^{\beta t_2} \quad \text{for } 0 < t_2 < t + \tau. \end{aligned} \quad (26)$$

Then, substituting Eqs. (21)–(26) into Eq. (20) and evaluating the overall integral in the limit $t \rightarrow \infty$ results in the autocorrelation function

$$\begin{aligned} \langle \phi_r(t)\phi_r(t+\tau) \rangle \\ = \left[\frac{\langle \xi^2 \rangle}{2\beta} - \frac{\alpha\gamma}{\beta(\gamma^2 - \beta^2)} (\langle \xi^2 \rangle - \alpha\langle \phi_s^2 \rangle) \right] e^{-\beta\tau} \\ + \frac{\alpha}{\gamma^2 - \beta^2} (\langle \xi^2 \rangle - \alpha\langle \phi_s^2 \rangle) e^{-\gamma\tau}. \end{aligned} \quad (27)$$

Since our analysis assumes the transition rates to be time-independent, the average state densities at the steady state can

be used to write Eq. (27) in a simpler way. The master equation for $\langle \psi_r \rangle$ reads

$$\frac{d\langle \psi_r \rangle}{dt} = -\beta\langle \psi_r \rangle + \alpha\langle \psi_s \rangle, \quad (28)$$

which gives

$$\alpha\langle \psi_s \rangle = \beta\langle \psi_r \rangle \quad (29)$$

at the steady state. Then, utilizing Eq. (29) in Eqs. (8), (9), and (18) yields

$$\begin{aligned} N\langle \phi_r(t)\phi_r(t+\tau) \rangle \\ = \langle \psi_r \rangle \left(1 - \frac{\langle \psi_r \rangle}{1 - \frac{\beta}{\alpha}\langle \psi_r \rangle} \right) e^{-\beta\tau} + \frac{\beta\langle \psi_r \rangle^3}{\alpha - \beta\langle \psi_r \rangle} e^{-\gamma\tau}. \end{aligned} \quad (30)$$

This autocorrelation function can be seen, using Eq. (29) and the inequality $\langle \psi_r \rangle + \langle \psi_s \rangle < 1$, to be always positive and finite. Note that this equation gives at $\tau = 0$ the variance

$$\langle \phi_r^2 \rangle = \frac{\langle \psi_r \rangle (1 - \langle \psi_r \rangle)}{N}, \quad (31)$$

in agreement with the binomial distribution dispersion relation given in Ref. [14].

IV. THE VARIANT 2v1n

The 2v1n formulation is a system of two stochastic variables and one noise term, that is, it contains one less noise term than the 2v2n formulation. It gives the same autocorrelation function (and the standard deviation) for the relevant state density fluctuations as in the 2v2n formulation.

The variant formulates the density fluctuation ϕ_r by

$$\dot{\phi}_r = k_a\phi_{r,a} + k_b\phi_{r,b}, \quad (32)$$

where k_a and k_b are some parameters, and $\phi_{r,a}$ and $\phi_{r,b}$ are two diffusively coupled Ornstein-Uhlenbeck processes characterized by the Langevin-type equations

$$\dot{\phi}_{r,a} = -\beta\phi_{r,a} + \xi, \quad (33a)$$

$$\dot{\phi}_{r,b} = -\gamma\phi_{r,b} + \xi. \quad (33b)$$

Here the zero mean Gaussian white noise ξ has the mean square given by Eq. (9). The parameters k_a and k_b are set, with the objective of achieving an autocorrelation function identical to that of the 2v2n model, as follows:

$$k_a = \sqrt{\frac{2\beta(\beta + \gamma)C_2}{2\beta C_3 + \beta + \gamma}} \quad (34)$$

and

$$k_b = C_3 k_a, \quad (35)$$

where the coefficients C_2 and C_3 are given recurrently by

$$C_1 := \frac{\alpha}{\gamma^2 - \beta^2} \left(1 - \alpha \frac{\langle \phi_s^2 \rangle}{\langle \xi^2 \rangle} \right),$$

$$C_2 := \frac{1}{2\beta} (1 - 2\gamma C_1),$$

$$C_0 := \frac{\gamma}{\beta + \gamma} \left(\frac{C_1}{C_2} - 1 \right),$$

$$C_3 := C_0 + \sqrt{C_0^2 + \frac{\gamma C_1}{\beta C_2}}.$$

The differential equations (33a) and (33b) give the solutions

$$\phi_{r,a}(t) = e^{-\beta t} \left\{ \phi_{r,a}(0) + \int_0^t e^{\beta t^*} \xi(t^*) dt^* \right\} \quad (36)$$

and

$$\phi_{r,b}(t) = e^{-\gamma t} \left\{ \phi_{r,b}(0) + \int_0^t e^{\gamma t^*} \xi(t^*) dt^* \right\}, \quad (37)$$

respectively. It then follows that

$$\langle \phi_{r,a}(t) \phi_{r,a}(t + \tau) \rangle = \frac{\langle \xi^2 \rangle}{2\beta} e^{-\beta \tau}, \quad (38)$$

$$\langle \phi_{r,b}(t) \phi_{r,b}(t + \tau) \rangle = \frac{\langle \xi^2 \rangle}{2\gamma} e^{-\gamma \tau}, \quad (39)$$

$$\langle \phi_{r,a}(t) \phi_{r,b}(t + \tau) \rangle = \frac{\langle \xi^2 \rangle}{\beta + \gamma} e^{-\gamma \tau}, \quad (40)$$

and

$$\langle \phi_{r,a}(t + \tau) \phi_{r,b}(t) \rangle = \frac{\langle \xi^2 \rangle}{\beta + \gamma} e^{-\beta \tau}. \quad (41)$$

Equations (38)–(41) together with Eq. (32) give the autocorrelation function

$$\begin{aligned} \langle \phi_r(t) \phi_r(t + \tau) \rangle &= \langle \xi^2 \rangle \left[\left(\frac{k_a^2}{2\beta} + \frac{k_a k_b}{\beta + \gamma} \right) e^{-\beta \tau} + \left(\frac{k_b^2}{2\gamma} + \frac{k_a k_b}{\beta + \gamma} \right) e^{-\gamma \tau} \right] \\ & \quad (42) \end{aligned}$$

in the long-time limit $t \rightarrow \infty$. Then, substituting the parameters k_a and k_b from Eqs. (34) and (35) results consistently in the autocorrelation function of the 2v2n formulation given by Eq. (27).

This, however, does not prove the equivalence between the 2v1n and 2v2n formulations; their transition probability functions still might not be the same. However, even if the two formulations are not equivalent, the complete agreement between their autocorrelation functions ensures that the 2v1n formulation is highly compatible with the 2v2n formulation in describing the statistics of the state density fluctuations.

V. THE VARIANT 1v1n

The 1v1n formulation is simpler than both the 2v2n formulation and the variant 2v1n: It contains just one stochastic

variable and one noise term. However, the relevant state density autocorrelation function in it does not exactly match the autocorrelation function of the 2v2n formulation; instead, it agrees with it up to first order in the time gap.

The diffusive dynamics in this case is governed by the Langevin equation

$$\dot{\phi}_r = -\tilde{\gamma} \phi_r + \xi, \quad (43)$$

in which ξ is zero mean Gaussian white noise with the mean square as given by Eq. (9), and the friction coefficient $\tilde{\gamma}$ is given by

$$\tilde{\gamma} = \frac{\alpha \langle \psi_s \rangle + \beta \langle \psi_r \rangle}{2 \langle \psi_r \rangle (1 - \langle \psi_r \rangle)}. \quad (44)$$

It is not difficult to derive the autocorrelation function in this variant as

$$\langle \phi_r(t) \phi_r(t + \tau) \rangle = \frac{\langle \xi^2 \rangle}{2\tilde{\gamma}} e^{-\tilde{\gamma} \tau}, \quad (45)$$

which reads

$$\langle \phi_r(t) \phi_r(t + \tau) \rangle = \frac{\langle \psi_r \rangle (1 - \langle \psi_r \rangle)}{N} e^{-\frac{\beta}{1 - \langle \psi_r \rangle} \tau} \quad (46)$$

at the steady state of the average state densities. Equation (46) approximates the autocorrelation function of the 2v2n formulation, given by Eq. (30), up to first order in τ .

The idea of approximating the sum of exponentials by the Taylor series down to a single exponential in diffusion formulations was previously used [11]. The resultant Ornstein-Uhlenbeck process in Ref. [11] is not the same as our 1v1n formulation since the minimal diffusion formulation is different from the unreduced multiexponential formulation (developed specifically for ion channel clusters) of that reference.

At this point, we address a study [19] that argues that the computing time of the exact microscopic Markov simulations can be shortened considerably, without significant loss in accuracy, by regarding fluctuations only in those states directly connected to the relevant state in every chain. The method was named ‘‘stochastic shielding.’’ Consider the case in which the relevant state makes a direct connection with one state only, as in Fig. 2. The sum of fluctuations over the states vanishes:

$$\sum_{l=0}^L \phi_l = 0.$$

Since the stochastic shielding approach sets the state density fluctuations other than ϕ_r and ϕ_s to zero, one gets $\phi_s = -\phi_r$ in it. Then, the diffusion approximation to the stochastic shielding simulation method gives

$$\dot{\phi}_r = -(\alpha + \beta) \phi_r + \xi, \quad (47)$$

where the noise ξ is the same as that given by Eq. (9). This stochastic differential equation can be easily obtained from Ref. [9] or Ref. [13], or from the minimal diffusion formula (7a). Comparison with Eq. (43) shows that the stochastic shielding diffusion approximation and 1v1n formulation are characterized by the same differential equation with the same noise variance, but they differ in the parameter $\tilde{\gamma}$. Equation (47)

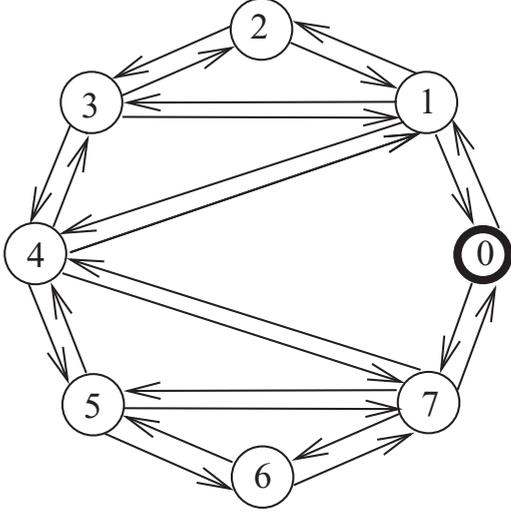


FIG. 3. State transition diagram used in the simulations. The state 0 is the relevant state.

yields the variance

$$\langle \phi_r^2 \rangle = \frac{\beta \langle \psi_r \rangle}{N(\alpha + \beta)} \quad (48)$$

at equilibrium, which is not in agreement with the dispersion relation (31). Hence, it appears that (at least for small time gaps) the 1v1n formulation is more accurate than the stochastic shielding diffusion approximation in approximating the autocorrelation function. See also the discussion in Ref. [14] on the issue of stochastic shielding in relation with the minimal diffusion formulation.

VI. NUMERICAL EXPERIMENTS

In applying the Euler-Maruyama method [21] as the simplest effective method for numerical solutions of ϕ_s by Eq. (7b) and $\phi_{r,2}$ by Eq. (33b), the step size Δt should satisfy, for stability reasons, that $\Delta t \gamma < 1$. However, γ can attain large values, which dictates the usage of a very small Δt , or else ϕ_s in the 2v2n formulation and $\phi_{r,2}$ in the variant 2v1n can be set directly to zero for γ values that violates the inequality $\Delta t \gamma < 1$. Similarly, ϕ_r in the 1v1n formulation can be taken directly as zero if the parameter $\tilde{\gamma}$ given by Eq. (44) does not obey $\Delta t \tilde{\gamma} < 1$.

We perform simulations on an ensemble of 300 Markov chains each characterized by the state transition diagram in Fig. 3, in which the state 0 is used as the relevant state. In this particular case, the master equation gives at the steady state the following set of coupled equations for the average state densities:

$$\begin{aligned} 0 &= -(z_{01} + z_{07})\langle \psi_0 \rangle + z_{10}\langle \psi_1 \rangle + z_{70}\langle \psi_7 \rangle, \\ 0 &= -(z_{10} + z_{12} + z_{13} + z_{14})\langle \psi_1 \rangle + z_{01}\langle \psi_0 \rangle \\ &\quad + z_{21}\langle \psi_2 \rangle + z_{31}\langle \psi_3 \rangle + z_{41}\langle \psi_4 \rangle, \\ 0 &= -(z_{21} + z_{23})\langle \psi_2 \rangle + z_{12}\langle \psi_1 \rangle + z_{32}\langle \psi_3 \rangle, \\ 0 &= -(z_{31} + z_{32} + z_{34})\langle \psi_3 \rangle + z_{13}\langle \psi_1 \rangle + z_{23}\langle \psi_2 \rangle + z_{43}\langle \psi_4 \rangle, \\ 0 &= -(z_{41} + z_{43} + z_{45} + z_{47})\langle \psi_4 \rangle + z_{14}\langle \psi_1 \rangle \\ &\quad + z_{34}\langle \psi_3 \rangle + z_{54}\langle \psi_5 \rangle + z_{74}\langle \psi_7 \rangle, \end{aligned}$$

$$\begin{aligned} 0 &= -(z_{54} + z_{56} + z_{57})\langle \psi_5 \rangle + z_{45}\langle \psi_4 \rangle + z_{65}\langle \psi_6 \rangle + z_{75}\langle \psi_7 \rangle, \\ 0 &= -(z_{65} + z_{67})\langle \psi_6 \rangle + z_{56}\langle \psi_5 \rangle + z_{76}\langle \psi_7 \rangle, \\ 0 &= -(z_{70} + z_{74} + z_{75} + z_{76})\langle \psi_7 \rangle + z_{07}\langle \psi_0 \rangle \\ &\quad + z_{47}\langle \psi_4 \rangle + z_{57}\langle \psi_5 \rangle + z_{67}\langle \psi_6 \rangle, \end{aligned} \quad (49)$$

where z_{ij} ($i, j = 0, 1, \dots, 7$) denotes the transition rate from the state i to the state j . Note that one of the equations in Eq. (49) is dependent on the others, and, therefore, it can be eliminated. Thus, Eq. (49) together with

$$\sum_{l=0}^7 \langle \psi_l \rangle = 1$$

uniquely solves the average state densities. Then, it is straightforward to implement our above diffusion formulations

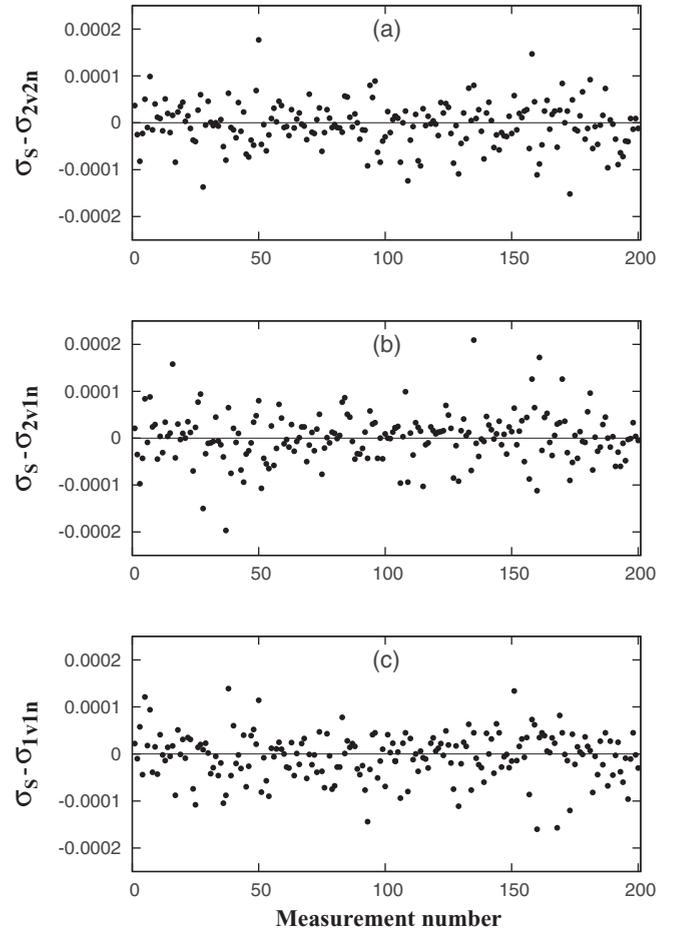


FIG. 4. Relevant state standard deviations measured using the (a) 2v2n, (b) 2v1n, and (c) 1v1n formulations (denoted by σ_{2v2n} , σ_{2v1n} , and σ_{1v1n} , correspondingly), relative to the standard deviation obtained from the exact microscopic Markov simulation (denoted by σ_S). An ensemble of 300 Markov chains, each evolving independently under the state transition diagram given in Fig. 3, was used. A total of 200 sets of standard deviation measurements were performed using a different transition rate matrix, with every matrix element being randomly generated within the range 0–0.5 in each set. The horizontal axis in each plot gives the measurement set number. The straight line, placed in each plot to guide the eye, indicates the situation of a perfect match between the model and the microscopic simulation.

for the relevant state density fluctuations, following the identifications $\psi_r \equiv \psi_0$, $\phi_r \equiv \phi_0$, $\langle \psi_r \rangle \equiv \langle \psi_0 \rangle$, $\langle \psi_j \rangle \equiv \langle \psi_1 \rangle$, $\langle \psi_k \rangle \equiv \langle \psi_7 \rangle$, $\alpha_j \equiv z_{10}$, $\alpha_k \equiv z_{70}$, $\beta_j \equiv z_{01}$, and $\beta_k \equiv z_{07}$.

Our case study examines the 2v2n, 2v1n, and 1v1n formulations with reference to the exact microscopic Markov simulation, in terms of standard deviation and autocorrelation time of the relevant state density ψ_0 . We identify τ as the autocorrelation time if it satisfies the equality

$$\frac{\langle \phi_0(t)\phi_0(t+\tau) \rangle}{\langle \phi_0^2(t) \rangle} = e^{-1}, \quad (50)$$

where the time t is large enough for equilibrium to be reached. Accordingly, we have performed 200 sets of measurements using a different randomly generated transition rate matrix for each set. The obtained standard deviation results are presented

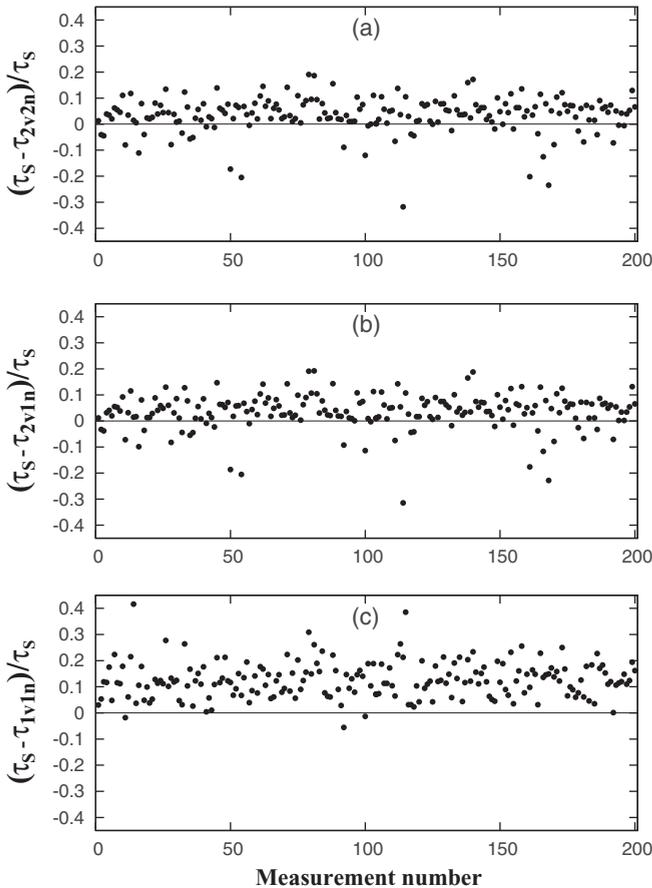


FIG. 5. Relevant state autocorrelation time measured using the (a) 2v2n, (b) 2v1n, and (c) 1v1n formulations (denoted by τ_{2v2n} , τ_{2v1n} , and τ_{1v1n} , correspondingly), relative to the autocorrelation time obtained from the exact microscopic Markov simulation (denoted by τ_S). An ensemble of 300 Markov chains, each evolving independently under the state transition diagram given in Fig. 3, was used. A total of 200 sets of autocorrelation time measurements were performed using a different transition rate matrix, with every matrix element being randomly generated within the range 0–0.5 in each set. The horizontal axis in each plot gives the measurement set number. The straight line, placed in each plot to guide the eye, indicates the situation of a perfect match between the model and the microscopic simulation.

in Fig. 4, and the autocorrelation time results are presented in Fig. 5.

It is seen from Fig. 4 that all three models (2v2n, 2v1n, and 1v1n) predict the microscopic standard deviation with excellent accuracy: The measurements obtained using the models do not differ from the corresponding exact microscopic simulation measurements more than 0.000 22. Concerning the autocorrelation times, it is seen from Fig. 5 that formulations 2v2n and 2v1n give virtually identical results, whereas the 1v1n formulation displays some discrepancy. This is exactly the result expected: Recall that we formulated the 2v1n model in such a way that it produces the same autocorrelation function as the original model 2v2n, but the 1v1n model was formulated just to guarantee first-order accuracy with respect to the 2v2n autocorrelation time. It is observed, with reference to the microscopic simulations, that the 2v2n and 2v1n models give apparently more accurate autocorrelation times than the 1v1n model; this is thought to be because most 1v1n model measurements are biased toward slightly smaller values (about 10% on average) than the corresponding microscopic autocorrelation time measurements.

It follows from Eqs. (30), (31), and (50) that the autocorrelation time is independent of the number of Markov chains N . To substantiate this, we have measured the autocorrelation time for several different N from the models as well as the exact microscopic simulations, and we have indeed observed the independence from the ensemble size.

VII. CONCLUSION

In this paper, we have pursued a study on the so-called minimal diffusion formulation (or 2v2n model, as we named it in this study). First, we calculated the relevant state density autocorrelation function using that formulation, and we found the autocorrelation to be in the form of two additive terms each decaying exponentially. Following that, we introduced two diffusion models (namely 2v1n and 1v1n) that reduce the structural complexity of the 2v2n model and yet efficiently approximate its dynamics. Both the 2v1n and 1v1n models contain just one noise term, one less than the 2v2n model. The variant 1v1n also reduces the number of stochastic variables by 1. The variant 2v1n has higher accuracy than the variant 1v1n: it yields the same autocorrelation function as the 2v2n model, whereas the variant 1v1n is first-order accurate in the time gap. We have provided numerical simulations supporting our theoretical analysis.

Although the original minimal diffusion formulation already provides a simple analytic formulation and a fast computation algorithm for the problem of collective fluctuations in Markov chain ensembles, the variants 2v1n and 1v1n improve these properties even further. Due to their simplicity, these formulations have the potential of being useful in analytic analysis and advancement of the collective evolution of Markov chain ensembles. Between the two, formulation 1v1n is more appropriate to be used in qualitative analyses, while formulation 2v1n should be preferred in the case of quantitative examinations.

Like any other diffusion formulation, the minimal diffusion formulation and its variants 2v1n and 1v1n are models for near-equilibrium dynamics; they fail at far-from-equilibrium

conditions. That was the reason for assuming the transition rates to be constant in our conducted analysis: with rapidly changing rates, the system may not have enough time to reach equilibrium. We have, however, retained both $\langle\psi_s\rangle$ and $\langle\psi_r\rangle$ in the governing equations of our formulations without imposing the steady-state condition (29). That was done in order to facilitate the validity of our models for slowly varying transition rates as well. When a Markov diffusion model is

formulated subject to the steady-state conditions (such as the one in Ref. [11]), it becomes inaccurate at nonequilibrium [13] or under noisy transition rates [12].

ACKNOWLEDGMENTS

I would like to thank the anonymous reviewers for their constructive comments.

-
- [1] N. G. Van Kampen, *Stochastic Processes in Physics and Chemistry*, 3rd ed. (North-Holland, Amsterdam, 2007).
- [2] C. Gardiner, *Stochastic Methods: A Handbook for the Natural and Social Sciences*, 4th ed. (Springer-Verlag, Berlin, 2009).
- [3] W. J. Anderson, *Continuous-Time Markov Chains: An Applications-Oriented Approach* (Springer-Verlag, New York, 1991).
- [4] J. R. Norris, *Markov Chains* (Cambridge University Press, Cambridge, 1998).
- [5] J. L. Doob, *Stochastic Processes* (Wiley, New York, 1953).
- [6] F. Spitzer, *Adv. Math.* **5**, 246 (1970).
- [7] T. G. Kurtz, *Stoch. Process. Appl.* **6**, 223 (1978).
- [8] P. H. Baxendale and P. E. Greenwood, *J. Math. Biol.* **63**, 433 (2011).
- [9] R. F. Fox and Y. N. Lu, *Phys. Rev. E* **49**, 3421 (1994).
- [10] M. Güler, *Phys. Rev. E* **76**, 041918 (2007); *Neural Comput.* **25**, 46 (2013).
- [11] D. Linaro, M. Storace, and M. Giugliano, *PLoS Comput. Biol.* **7**, e1001102 (2011).
- [12] M. Güler, *Neural Comput.* **25**, 2355 (2013).
- [13] P. Orio and D. Soudry, *PLoS One* **7**, e36670 (2012).
- [14] M. Güler, *Phys. Rev. E* **91**, 062116 (2015).
- [15] P. K. Pollett and A. Vassallo, *Adv. Appl. Probab.* **24**, 875 (1992); R. Serfozo, *Introduction to Stochastic Networks* (Springer-Verlag, New York, 1999); D. T. Gillespie, *J. Chem. Phys.* **113**, 297 (2000); I. Nåsell, *Math. Biosci.* **179**, 1 (2002); D. Clancy, *J. Appl. Probab.* **42**, 726 (2005); A. D. Barbour and A. Pugliese, *Ann. Appl. Probab.* **15**, 1306 (2005); J. V. Ross, *J. Math. Biol.* **52**, 788 (2006); R. J. Gibbens, P. J. Hunt, and F. P. Kelly, in *Disorder in Physical Systems*, edited by G. R. Grimmett and D. J. A. Welsh (Oxford University Press, Oxford, 1998), pp. 113–127; A. J. McKane and T. J. Newman, *Phys. Rev. Lett.* **94**, 218102 (2005).
- [16] M. Güler, *J. Comput. Neurosci.* **31**, 713 (2011).
- [17] B. Mélykúti, K. Burrage, and K. C. Zygalakis, *J. Chem. Phys.* **132**, 164109 (2010).
- [18] C. E. Dangerfield, D. Kay, and K. Burrage, *Phys. Rev. E* **85**, 051907 (2012).
- [19] N. T. Schmandt and R. F. Galán, *Phys. Rev. Lett.* **109**, 118101 (2012).
- [20] M. C. Wang and G. E. Uhlenbeck, *Rev. Mod. Phys.* **17**, 323 (1945).
- [21] D. J. Higham, *SIAM Rev.* **43**, 525 (2001).