# Averaging methods for stochastic dynamics of complex reaction networks: description of multi-scale couplings

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This paper is concerned with classes of models of stochastic reaction dynamics with time-scales separation. We demonstrate that the existence of the time-scale separation naturally leads to the application of the averaging principle and elimination of degrees of freedom via the renormalization of transition rates of slow reactions. The method suggested in this work is more general than other approaches presented previously: it is not limited to a particular type of stochastic processes and can be applied to different types of processes describing fast dynamics, and also provides crossover to the case when separation of time scales is not well pronounced. We derive a family of exact fluctuation-dissipation relations which establish the connection between effective rates and the statistics of the reaction events in fast reaction channels. An illustration of the technique is provided. Examples show that renormalized transition rates exhibit in general non-exponential relaxation behavior with a broad range of possible scenarios.

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#### I. INTRODUCTION

Chemical reaction networks are systems of molecular species of different types interacting with each other by means of multiple reactions [1]. In classical chemical systems, the volume of the reactor and population numbers of species of each types are usually large giving the accurate description of the system in terms of the concentrations. Reactors with complex chemistry give rise to complicated systems of nonlinear equations for the concentrations of chemical species that do not lend themselves to analytic solution. Dynamics of these quantities can be modeled via sets of ordinary differential equations (ODEs) which are powerful tools for predicting the dynamical behavior of macroscopic chemical mixtures. There is a recent renewal of interest in stochastic modeling of chemical systems which came with the recent realization of importance of noise in cellular information processing. At the level of a single cell, number of molecules involved in some processes can be very small and concentrations are described as nano-molar [2, 3]. In addition to that, different processes are also characterized by significantly different times scales [4].

Presence of this time-scale separation and highly different copy numbers of molecular species usually complicates the study of biological processes with computer simulations. There is an obvious need for computationally tractable stochastic models on a macro-scale that can provide insights into joint, qualitative, effects arising from interaction of several sub-networks. In deterministic systems of ordinary differential equations, time-scale separation is usually related to the concept of stiffness. It is obviously hard to define the same concept in case of the stochastic systems [5].

In spite of these obvious complications some progress has been made in modeling of biochemical networks which express the separation of time-scales. One difficulty is heterogeneity of simulation techniques used for simulation of ODEs/SDEs and stochastic simulation algorithm. One strategy exploited in the literature [5, 6] is based on grouping together of reaction events taking place in a single reaction channel in a fast succession and applying diffusion approximation [7]. In [8] Rao et.al. discuss a computational approach for performing elimination of the fast species based on rapid equilibrium in the limit of the infinite time-scale separation. This method was termed quasi-steady state approximation (QSSA). A somewhat similar approach is taken in [9]. Formally, this method stems from the classical deterministic QSSA applied to the chemical master equation itself rather then to the (stochastic) differential equation underlying the dynamics of the state vector (numbers of molecular species). The method developed by Cao et al. in [10] can be viewed as generalization of approach of Rao et.al. [8] but still have the limitations of being derived through the application of deterministic techniques and assumptions to the chemical master equation. It also assumes that averaging procedure can be done by solving the system of algebraic equations for the expectations of the fast variables given slow, termed in [10] as a virtual fast process. We note here that studies of stochastic dynamics of diffusion-type processes evolving on different time scales were pioneered by Bogolubov, Khasminski and Freidlin and we refer the reader to monographs [11, 12, 13].

This paper has two purposes. First, we present the formulation of stochastic reaction dynamics of

reaction network consisting of two subnetworks. Compared to many previous results, where usual description of stochastic reaction dynamics follows the approach based on chemical master equation (CME), current publication follows the path-sampling approach and represents the dynamics as a jump-type stochastic differential equations (SDEs).

Second purpose is to provide rigorous procedure for the renormalization of the transition rates of slow reactions in the presence of fast ones. Following the picture of the stochastic dynamics developed in the first part of this paper, we outline the main guidelines for use of stochastic averaging principle including error control analysis. Despite of the recent rebirth of interest to the method of stochastic averaging in applications to stochastic chemical kinetics, very few examples deal with situations when this procedure might break down. We demonstrate here, in a constructive way, how to perform the averaging over fast reaction events and how to obtain the effective slow-scale transition rate.

Organization of this paper is as follows. In the next section we discuss the general probabilistic framework for stochastic dynamics of reaction networks and introduce a scheme for the partition of species and reactions. In Section III we investigate the consequences of possible time-scales separation and present a procedure based on renormalization of transition rates. We also put emphasis on error analysis, outlining main sources of the numerical error on different steps of the procedure. Our paper will end with discussion of examples.

### **II. NETWORK PARTITIONING**

We begin our discussion with a general set-up, introducing basic concepts and notation.

Assume that a well mixed, isothermal system has S different molecular species indexed by  $i = 1 \dots S$  and there are R reaction channels, index by  $r = 1 \dots R$ , transforming the molecular composition of these species. For the basic notation and examples we direct reader to [14, 15]. State vector of the system can be represented as following:

$$(\mathbf{X}, \boldsymbol{Z}) \tag{1}$$

where fist part of the state vector  $X_i \in \mathbb{Z}_+, i = 1 \dots S_X$  represents *main* species while the second part  $Z_i \in \mathbb{Z}_+, i = 1 \dots S_z$  represents *intermidiate* species  $Z_i, i = 1 \dots S_Z$ . Total number of all types of species:  $S_X + S_Z = S$ . Vectors  $\boldsymbol{\nu}_r^X$ ,  $\boldsymbol{\nu}_r^Z$  and  $\boldsymbol{\nu}_r^{XZ}$  are stoichiometric changes of components **X** and **Z** if reaction event *r* takes place. We will not make any assumptions about actual number of molecular species of each type, i.e. we will not assume low or large copy numbers.

We assume, however, that there are three subsets of reactions in the system:

- (i) reactions which transform only species  $\mathbf{X}$  (we denote this subset  $\mathcal{R}_1$ ),
- (ii) reactions which transform only species Z (subset  $\mathcal{R}_2$ )
- (iii) "linker" reactions which mix species  $\mathbf{X}$  and  $\mathbf{Z}$  (subset  $\mathcal{R}_3$ ).

Each reaction channel can be specified by the transition rates  $a_r$  (a positive function) which describes the probability  $a_r dt$  of reaction event to take place in the interval of time dt. Transition rate  $a_r$  can be further specified as positive functions of **X**, **Z**, or, in general, on both components **X** and **Z**. Based on the definition of subsets  $\mathcal{R}_{1,2,3}$  we have:

$$a_r(\mathbf{X}), \quad r \in \mathcal{R}_1$$
 (2a)

$$a_r(\mathbf{Z}), \quad r \in \mathcal{R}_2$$
 (2b)

$$a_r(\mathbf{X}, \mathbf{Z}), \quad r \in \mathcal{R}_3$$
 (2c)

We do not assume specific dependence of  $a_r(\cdot)$  on the state variables **X** and **Z** but usually, in the framework of mass action kinetics, it is a product of kinetic rate  $k_r$  and function  $h_r(\cdot)$  which represents the number of reactive configurations available at a given state **X**, **Z** [14].

There exist different methods to characterize the stochastic chemical dynamics. One of the most popular approach is to provide an equation for the joint probability density  $p_t(\mathbf{X}, \mathbf{Z})$ , which gives all information about instantaneous state of the system at generic moment of time t. Such equation is known as chemical master equation (CME) [14, 16] and it has been intensively described and utilized in recent literature [8, 9, 10]. But even if we can obtain [17] the solution of CME, which is usually a very hard problem even for simple chemical networks, this approach still have certain limitations, coming from instantaneous description provided by the density  $p_t(\cdot)$ .

To describe the stochastic dynamics of the chemical network one can introduce the set of independent point processes  $N_r(t), N_r(0) = 0$  representing the numbers of reaction events which took place in channels  $r \in \mathcal{R}$  up to time t and use the mass balance relations:

$$\mathbf{X}_{t} = \mathbf{X}(0) + \sum_{r \in \mathcal{R}_{1}} \boldsymbol{\nu}_{r}^{X} N_{r}(t) + \sum_{r \in \mathcal{R}_{3}} \boldsymbol{\nu}_{r}^{XZ} N_{r}(t),$$
(3a)

$$\boldsymbol{Z}_{t} = \boldsymbol{Z}(0) + \sum_{r \in \mathcal{R}_{2}} \boldsymbol{\nu}_{r}^{Z} N_{r}(t) + \sum_{r \in \mathcal{R}_{3}} \boldsymbol{\nu}_{r}^{XZ} N_{r}(t),$$
(3b)

where vectors  $\boldsymbol{\nu}_r^Z, \boldsymbol{\nu}_r^X$  and  $\boldsymbol{\nu}_r^{XZ}$  describe the composition change of the system due to the reaction event in the channel r. Average number of reaction events in each reaction channel  $r \in \mathcal{R}_{1,2,3}$ during the small time interval  $[t, t + \delta t)$  are proportional to the transition rates (2):

$$\mathbb{E}(N_r(t+\delta t) - N_r(t)|\mathbf{X}_t, \mathbf{Z}_t) = a_r(\mathbf{X}_t, \mathbf{Z}_t)\delta t + O(\delta t^2)$$
(4)

Processes  $N_r(t)$  can be considered as time-changed, unit-rate independent Poisson processes  $\Pi_r(t)$  [7]:

$$N_r(t) = \Pi_r(\int_0^t a_r(\mathbf{X}_{t'}, \mathbf{Z}_{t'}) dt')$$
(5a)

Thus, the large class of discrete event systems with totally inaccessible event times can be viewed as a standard *Poisson process* with appropriate change of the time scale:

$$t \mapsto \int_0^t a_r(\mathbf{X}_{t'}, \mathbf{Z}_{t'}) dt'$$
(5b)

The time change generates path-dependent or self-affecting point processes whose dynamics depend on the information generated by the arrivals of the process  $(\mathbf{X}_t, \mathbf{Z}_t)$ . It is important to take into account that the stochastic differential equation does not only introduce the probability distribution for the pair  $(\mathbf{X}, \mathbf{Z})$  but also generates a measure on the paths, which contains much more information. For almost any realization of the set of  $1 \dots R$  standard Poisson processes,  $\Pi_r(t, \omega)$ , parametrized by the element  $\omega$  of event space [7, 18] and any deterministic initial condition the solution  $(\mathbf{X}(t, \omega), \mathbf{Z}(t, \omega))$  is a step-wise stochastic process.

Note also, that dynamics of each component  $\mathbf{X}$  or  $\mathbf{Z}$  is non-Markovian if considered separately but the dynamics of the pair  $(\mathbf{X}, \mathbf{Z})$  is Markovian.

So far we have introduced only the basic notation: quite generic system of SDEs given by (3) outlined in this section have not invoked any assumptions on particular relations between different transition rates  $a_r$  and was totally based on prior information about existence of two groups of

species, i.e.  $X_i$  and  $Z_i$  which uniquely identified the partition of the reactions into the subsets  $\mathcal{R}_1, \mathcal{R}_2$  and  $\mathcal{R}_3$ .

In the next section we consider the particular implication of time-scale separation including the extensions of the stochastic averaging principle and diffusion approximation.

## III. SEPARATION OF TIME-SCALES AND ELIMINATION OF FAST STOCHASTIC VARIABLES.

In many situations, dynamics of main species X is propagated via large number of fast transitions which transform mainly intermediate species Z. One usually desires to construct an approximate, time coarse-grained model, which involve only main species. It is important that approximate problem describes the dynamics of the system on a large time scale and thus is more advantageous for performing simulations without significant sacrifice in accuracy. This section deals with substitution of the original problem with approximate one and demonstrates the form convergence of the approximation under certain assumptions.

We assume that at certain region of state space the following assumption can be made about transition rates  $a_r(\cdot)$ :

$$\sum_{r \in \mathcal{R}_1 \cup \mathcal{R}_3} a_r \propto O(1) \text{ while } \sum_{r \in \mathcal{R}_2} a_r \propto O(\epsilon^{-1})$$
(6)

where separation of the time-scales is introduced via the small parameter  $\epsilon \ll 1$ . Problems of this type are challenge for direct application of Stochastic Simulation Algorithm (SSA) [15, 19] because they will require the time steps of the order  $O(\epsilon)$  with a total computational cost of order  $\epsilon^{-1}$ . If we want to advance through the time interval [0, t],  $t \sim O(1)$  most of the simulation time will be spent on simulation of reaction events with the high intensity ( $\sum_{r \in \mathcal{R}_2} a_r \propto O(\epsilon^{-1})$ ). We would like to find an effective transition rates  $\bar{a}_r(\cdot)$  for the "linker" reactions (subset  $\mathcal{R}_3$ ), which describe the transition events of the slow reactions "coarse-grained" over the possible events corresponding to the reaction events in subset  $\mathcal{R}_2$ .

It is instructive to consider a simple reaction scheme involving three species  $X_1, Z_{1,2}$  similar to

one considered in [10]:

$$\mathsf{Z}_{1} \underset{k_{3}\epsilon^{-1}}{\overset{k_{2}\epsilon^{-1}}{\rightleftharpoons}} \mathsf{Z}_{2} \underset{k_{1}}{\overset{k_{1}}{\rightarrow}} \mathsf{X}_{1} \tag{7}$$

where rates  $k_{1,2} \propto \epsilon^{-1}$  are parametrized by small  $\epsilon$  and  $k_3 \propto O(1)$ . In this case reactions  $Z_1 \rightleftharpoons Z_2$ forms the subset  $\mathcal{R}_2$  while reaction  $Z_2 \rightarrow X_1$  corresponds to the subset  $\mathcal{R}_3$  and subset  $\mathcal{R}_1$  is empty, i.e  $\mathcal{R}_1 = \{\emptyset\}$ . Then systems of equations for components  $(X_1, Z_1, Z_2)$  is the following one:

$$Z_{1t} = Z_{10} - N_2(t) + N_3(t), (8a)$$

$$Z_{2t} = Z_{20} + N_2(t) - N_3(t) - N_1(t),$$
(8b)

$$X_{1t} = X_1(0) + N_1(t)$$
(8c)

Presence of the scaling factor  $\epsilon^{-1}$  in reaction constants  $k_{1,2}\epsilon^{-1}$  allows us to consider family of solutions parameterized by  $\epsilon$ . We expect  $Z_{1,2}$  to follow adiabatically the  $X_{1t}$ . To make that apparent, one can apply the functional law of large numbers to the processes  $N_{2,3}(t)$  in time interval [0, t] (see Eqn. (5a)):

$$N_{2}(t) - N_{3}(t) \rightarrow \frac{1}{\epsilon} \left( \int_{0}^{t} k_{2} Z_{1t'} dt' - \int_{0}^{t} k_{3} Z_{2t'} dt' \right) +$$
(9)

$$+\frac{1}{\sqrt{\epsilon}}\left(W_2(\int_0^t k_2 Z_{1t'} dt') - W_3(\int_0^t k_3 Z_{2t'} dt')\right), \ \epsilon \to 0$$
(10)

where  $W_{2,3}(\cdot)$  are two independent Wiener processes [7]. Since parameter  $\epsilon^{-1}$  is large, we can conclude that difference

$$\left|\int_0^t k_2 Z_{1s} ds - \int_0^t k_3 Z_{2s} ds\right|$$

also converges to zero for times  $t \leq \epsilon/(k_2 + k_3)$  in the limit of small  $\epsilon$ , and we can conclude that:

$$\sup_{0 \le t' \le t} |k_2 Z_{1t'} - k_3 Z_{2t'}| \to 0$$
(11)

This means that variables  $Z_{1t}$  and  $Z_{2t}$  reach a stationary binomial distribution:

$$\pi^{\epsilon \to 0}(Z_1, Z_2 | X_1) \propto \alpha^{Z_1} (1 - \alpha)^{Z_2},$$
(12)

$$Z_0 = Z_1(0) + Z_2(0) = Z_1 + Z_2, \ \alpha = \frac{k_2 Z_0}{k_2 + k_3}$$
(13)

on the time scale  $t \propto O(\epsilon)$  while sum  $Z_{1t} + Z_{2t}$  changes on the much larger time-scale  $t \geq O(1)$ :

$$Z_{1t} + Z_{2t} \approx Z_1(0) + Z_2(0) - N_1(t), \qquad (14a)$$

$$X_{1t} \approx N_1(t) \tag{14b}$$

By exploiting the separation of time-scales using the stationary distribution  $\pi^{\epsilon}(Z_1, Z_2|X_1)$  one can replace dynamical quantities  $f(Z_{1t}, Z_{2t}, X_{1t})$  averaged on the time interval [0, t],  $\frac{\epsilon}{k_2+k_3} \ll$  $t < \frac{1}{k_1}$  with their conditional averages:

$$f(Z_{1t}, Z_{2t}, X_{1t}) \approx \frac{1}{t} \int_0^t f(Z_{1t'}, Z_{2t'}, X_{1t'}) dt' \approx$$
(15)

$$\approx \bar{f}(X_{1t}) = \sum_{Z_1, Z_2} f(Z_1, Z_2, X_{1t}) \pi^{\epsilon}(Z_1, Z_2 | X_{1t})$$
(16)

and *eliminate* fast variables  $Z_{1,2}$  from the description even though the total number of molecules  $Z_1 + Z_2$  may be not a large quantity. Thus, taking  $f(\cdot)$  to be the "linker" transition rates  $a_r(\mathbf{X}, \mathbf{Z})$ ,  $r \in \mathcal{R}_3$  one obtains averaged transition rates  $\bar{a}_r(\mathbf{X})$  which now depend only on the slow variable  $\mathbf{X}$ . Results of the large deviation theory [11] demonstrate weak convergence bounds of the original problem with small but non-zero  $\epsilon$  to the solution of the averaged system. But as we mentioned it before, one of the goals of this publication is to analyze and extend averaging process to the situation when  $\epsilon$  may be small, but not 'infinitesimally' small. In the next section III A we will try to answer this question.

#### A. Renormalization of fast fluctuating reaction rates and reduced evolution equations

Recall that transition rates  $a_r(\cdot)$  of a jump Markovian process can be used to describe distributions of the waiting times of the reaction events via the survival probability of a given state  $(\mathbf{X}, \mathbf{Z})$ has an exponential form  $S(t) = e^{-\sum_{r=1}^{R} a_r(\mathbf{X}, \mathbf{Z})t}$  and describes probability that no reaction event take place in any of  $1 \dots R$  reaction channels in time interval [0, t] [20].

Consider the first jump time of a particular reaction r in the subset of the "linker" reactions,  $\tau_{r,3}$ and first jump times of any reaction in the subset of the fast reactions which we will denote  $\tau_{r,2}$ . Reaction in the group  $\mathcal{R}_3$  have both types of chemical species (X and Z) as their substrates, that means that reaction rates in this subset are fluctuate with fast variables Z. If system is originally prepared at the state (X<sub>0</sub>, Z<sub>0</sub>) at t = 0 then at any moment of time t > 0 one is interested in finding the probabilities of events { $\tau_{r,3} > t$ } and { $\tau_{r,2} < t$ }. In other words one has to find an averaged survival probabilities:

$$S_r(t|\mathbf{X}) = P(\{\tau_{r,3} > t\}) = \left\langle \exp(-\int_0^t a_r(\mathbf{X}_0, \mathbf{Z}_{t'}^x) dt') \right\rangle_Z, \quad r \in \mathcal{R}_3$$
(17)

Average  $\langle ... \rangle_Z$  stands for the average over the possible trajectories of the stochastic process  $Z^x([0,t]), Z_0^x = Z_0$  at *fixed* X which depends on X as on parameter [11].

Probabilities (17) can be used to introduce time-dependent transition rates  $\bar{a}_r(\mathbf{X}, t)$  which effectively describe the dynamics for reactions in the groups  $\mathcal{R}_3$ . Taking the logarithm of the averaged survival probabilities (17) we obtain:

$$S_r(t|\mathbf{X}) = \exp(-\int_0^t dt' \,\bar{a}_r(\mathbf{X}, t')),\tag{18a}$$

$$\bar{a}_r(t, \mathbf{X}) = -\frac{\partial}{\partial t} \ln \left\langle \exp(-\int_0^t dt' \, a_r(\mathbf{X}_0, \mathbf{Z}_{t'}) \right\rangle_Z \tag{18b}$$

Equations 18a constitute one of the main results of the paper. In the field of chemical kinetics a similar methodology is known under the label of the "rate dependent processes with dynamical disorder" [21, 22, 23, 24, 25, 26] where it describes the influence of the non-equilibrium environmental degrees of freedom on transport and kinetic properties. Similar approach was used to describe quantum dynamics in fluctuating environment [27]. Using the procedure of the cumulant expansion [16, 28] we can obtain the following interrelationship between  $\bar{a}_r$  and the multi-point cumulants  $C_r^{(m)}(t_1, \ldots, t_m | \mathbf{X})$  of the functions  $a_r(\mathbf{X}, \mathbf{Z}_{\cdot}^x)$ , taken at different temporal points  $t_1, \ldots, t_m$ :

$$S_r(t|\mathbf{X}) = \exp\left[\sum_{m\geq 0} \frac{(-1)^m}{m!} \int_0^t dt_1 \dots \int_0^t dt_m C_r^{(m)}(t_1, \dots, t_m | \mathbf{X})\right],$$
 (19)

$$\bar{a}_r(t, \mathbf{X}) = \langle a_r(\mathbf{X}, \mathbf{Z}_t) \rangle_Z + \sum_{m \ge 2} \frac{(-1)^{m-1}}{m!} \int_0^t dt_1 \dots \int_0^t dt_m \ C_r^{(m)}(t_1, \dots, t_m | \mathbf{X})$$
(20)

Renormalized transition rates  $\bar{a}_r(t, \mathbf{X})$  provide so-called semi-Markov approximation [16, 20]. Term "semi-Markov" generally describes non-Markov processes since the statistical properties of the waiting times can not be provided only by average rate of the process but all the multi-time joint probability distributions for the considered process must be considered. Note that in our case effective rate  $\bar{a}_r$  depend on the statistics of fluctuations of fast variables  $\mathbf{Z}$  through the cumulants  $C_r^{(m)}(t_1, \ldots, t_m | \mathbf{X})$ .

Taking a leading term at  $\epsilon \to 0$ , which sometimes called *Markovian limit*, we formally arrive to the results of the QSS Approximation [8]:

$$\bar{a}_r(\mathbf{X}, t) = C_r^{(1)}(t|\mathbf{X}) = \lim_{\epsilon \to 0} \sum_Z a_r(\mathbf{X}, \mathbf{Z}) \pi_X^{\epsilon}(\mathbf{Z})$$
(21)

where average is taken over the *invariant measure*  $\pi^{\epsilon}(\mathbf{Z}|\mathbf{X})$  of the fast process  $\mathbf{Z}_t^x$  at *fixed*  $\mathbf{X}$ . Note that at this level  $\bar{a}_r$  does not depend on time and correspond to the single exponential form of the survival probability. This level of approximation corresponds to the assumption that at fixed  $\mathbf{X}$  all state space of  $\mathbf{Z}$  is totally accessible, i.e. *ergodic* [11] and for any function  $f(\cdot) : \mathbb{Z}^{n_z} \to \mathbb{R}$ :

$$\bar{f}(\mathbf{X}) = \lim_{t \to \infty} t^{-1} \int_0^t f(\mathbf{X}, \mathbf{Z}_s^x) ds = \lim_{\epsilon \to 0} \sum_Z f(\mathbf{X}, \mathbf{Z}^x) \pi^{\epsilon}(\mathbf{Z}^x | \mathbf{X})$$
(22)

There is a general Jensen inequality, which gives the relationship between the mean value of a convex function of a random variable and the value of this function when its argument equals the mean value of the random variable. According to this inequality:

$$S_r(t|\mathbf{X}) \ge \exp\left(-\int_0^t dt' C_r^{(1)}(t'|\mathbf{X})\right)$$
(23)

Application of this inequality leads to the important conclusion that mean field rate (21) is larger then the rate given by (19). The exponential and non-exponential structure of the averaged survival probability is governed by the hierarchy of the time scales of the dynamics of  $Z_t$  at different values of X. If dynamics of Z is complicated and exhibit metastability at some values of X then Markovian approximation 21 is no longer holds and additional corrections corresponding to the high order cumulants must be taken into consideration. Correction to the Markovian approximation based on the second order cumulants is:

$$\Delta \bar{a}_r(t, \mathbf{X}) \cong -\int_0^t dt' C_r^{(2)}(t, t' | \mathbf{X}), \qquad (24a)$$

$$C_r^{(2)}(t,t'|\mathbf{X}) \equiv \langle a_r(\mathbf{X}, \mathbf{Z}_t^x) a_r(\mathbf{X}, \mathbf{Z}_{t'}^x) \rangle_Z - \langle a_r(\mathbf{X}, \mathbf{Z}_t^x) \rangle_Z \langle a_r(\mathbf{X}, \mathbf{Z}_{t'}^x) \rangle_Z \equiv \langle \langle a_r(\mathbf{X}, \mathbf{Z}_t^x) a_r(\mathbf{X}, \mathbf{Z}_{t'}^x) \rangle_Z \rangle_Z$$
(24b)

The simples assumption for the time dependence of the cumulant  $C_r^{(2)}$  is exponential decay:

$$C_r^{(2)}(t,t'|\mathbf{X}) = K \exp(-\kappa(\mathbf{X})|t-t'|)$$
(25)

where  $\kappa(\mathbf{X})^{-1}$  is a characteristic relaxation time of the regression of fluctuation of species  $\mathbf{Z}$  and  $K = \langle (\Delta a_r^2(\mathbf{X}, Z)) \rangle_Z$ . In this case correction to the Markovian term is given by:

$$\Delta \bar{a}_r(t, \mathbf{X}) \cong -K\kappa^{-1}(\mathbf{X}) \frac{\partial}{\partial t} \left( t - \kappa^{-1}(\mathbf{X}) [1 - \exp(-\kappa(\mathbf{X})t)] \right)$$

Correction to the Markovian approximation given by (24a) is exact for the Gaussian and Markov process since the only possible expression for the correlation function of a stationary Markov and

Gaussian process is the exponential of a form (25). It is also interesting to note that correlation correction (24a) generally decreases the transition rate. This is a result which can not be obtained using only straightforward averaging method presented in publications [8, 10].

Note that in general relations (18a) can be viewed as a type of fluctuation-dissipation relations; they connect the effective dissipation rate in the slow coarse-grained dynamics and statistics of fluctuations of the fast reaction events given by the cumulants  $C_r^{(m)}(t_1, \ldots, t_m | \mathbf{X})$ .

#### IV. COARSE-GRAINED DYNAMICS AND ERROR CONTROL

Given the renormalized survival probabilities and transition rates at different points of state space of main species X:

$$\bar{a}_r(t, \mathbf{X}) = a_r(\mathbf{X}), \quad r \in \mathcal{R}_1$$

stochastic dynamics of the main species X can be formulated in the straightforward way, similar to the stochastic simulation algorithm (SSA) [14, 15]. At the time point t = 0 state  $X_0$  we consider an overall survival probability:

$$S(t|\mathbf{X}_0) = \prod_{r \in \mathcal{R}_1 \cup \mathcal{R}_3} S_r(t|\mathbf{X}_0)$$
(26)

and define a jump moment of the slow process as a first time  $\tau_1$  when  $S(t|\mathbf{X}_0)$  crosses the value u, where the last one is a random number uniformly distributed on the interval (0, 1) [29]:

$$\tau_1 = \inf\{t > 0 | S(t | \mathbf{X}_0) \le u\}, \quad u \in \mathcal{U}(0, 1)$$
(27)

Post-jump transition kernel is defined by the vector of transition probabilities

$$q_r = \frac{\bar{a}_r(\tau_1, \mathbf{X}_0)}{\sum_{r' \in \mathcal{R}_{1,3}} \bar{a}_{r'}(\tau_1, \mathbf{X}_0)}, \quad r \in \mathcal{R}_{1,3}$$
(28)

i.e. reaction event  $r^* \in \mathcal{R}_{1,3}$  is selected based on the vector  $q_r$  and current state is updated:

$$\mathbf{X}_{ au_1} = \mathbf{X}_0 + oldsymbol{
u}_{r^*}, \quad t_1 = au_1,$$

Then the same procedure is performed starting at the state  $\mathbf{X}_{\tau_1}$  with generation of the interval  $\tau_2$ from the survival probability  $S(t|\mathbf{X}_{\tau_1})$  and new state  $\mathbf{X}_{\tau_1+\tau_2}$  and so on. As a result one obtains a coarse-grained trajectory:

$$(t_n, \mathbf{X}_{t_n}), \quad t_n = \sum_{i=1}^n \tau_i \tag{29}$$

Question about the overall accuracy and the error control is a delicate question. Below we decompose the overall error of the method it into the following main factors:

1. Error in approximating by coarse grained dynamics:

$$e_1 = \sup_{0 \le t \le T} \mathbb{E}(|\mathbf{X}_t - \bar{\mathbf{X}}_t|^2)$$

assuming that transition rates  $\bar{a}_r(\cdot)$  can be obtained without error.

2. Approximation and Monte Carlo error  $e_2$  of  $\bar{a}_r(\cdot)$  via the finite number of samples representing the dynamics of  $Z_t$  at fixed X.

Below we discuss step by step leading terms in  $e_1$ ,  $e_2$ .

Estimation of the error  $e_1$  is related to the answer on the following question: what possible error is introduced while performing averaging of rates of reactions in the subsets  $\mathcal{R}_{1,3}$  at *fixed* **X**?

It is not hard to see that this error is proportional to the probability of the event that minimal jump time over the reactions in group  $\mathcal{R}_1 \cup \mathcal{R}_2$  is smaller then t while the minimal jump-time of reaction in the group  $\mathcal{R}_3$  is larger then t:

$$S_r(t|\mathbf{Z}) = P\left(\left\{\min_{r\in\mathcal{R}_3}\tau_{r,2} < t\right\} \cup \left\{\min_{r\in\mathcal{R}_{1,3}}\tau_r > t\right\}\right) = \left\langle \exp\left(-\int_0^t dt' a_r(\mathbf{X}_{t'}, \mathbf{Z}_0)\right)\right\rangle_X, \quad r\in\mathcal{R}_3$$
(30)

where average  $\langle ... \rangle_X$  is taken over trajectories  $\mathbf{X}_t^z$  at *fixed*  $\mathbf{Z}$  It is not hard to see that this probability is exponentially small, i.e.  $\propto \exp(-\epsilon^{-1}\frac{t}{const})$  in the limit  $\epsilon \to 0$ .

Error  $e_2$  depends on the number of cumulants we have included in Eqn. (19) and cumulant of order *m* usually gives contribution proportional to  $\epsilon^m$ . In Appendix we outline the exact method for calculation of the renormalized survival probability based on eigenvalue decomposition of certain linear operator which is a practical approach in situations when state space of the variable Z is not very large.

#### v. EXAMPLES

We now present a simple intuitive example to show that exponential or non-exponential structure of the averaged survival probability is governed by the relationship between time-scales of "fast" and "slow" species. Assume that for some reaction channel

$$X + Z + \ldots$$
 (31)

rate  $a_r(X, Z) = k_r h_r(X) h'_r(Z)$  jumps reversibly between two values  $a_r(X, 0)$  and  $a_r(X, 1)$  with the stochastic dynamics of  $Z_t$  governed by simple master equation:

$$\begin{pmatrix} \dot{p}_t(0) \\ \dot{p}_t(1) \end{pmatrix} = \begin{pmatrix} -k_{01} & k_{10} \\ k_{01} & -k_{10} \end{pmatrix} \begin{pmatrix} p_t(0) \\ p_t(1) \end{pmatrix}$$
(32)

Equation (32) describes the switching transitions between the two states 0 and 1. Assuming that state of variable Z is prepared according to the equilibrium density  $\pi = (\pi_0, \pi_1) = (\frac{k_{10}}{k_{01}+k_{10}}, \frac{k_{01}}{k_{01}+k_{10}})$ . the average survival probability  $\langle e^{-\int_0^t a_r(X, Z_{t'}^x)dt'} \rangle$  can be obtained as follows (see also Appendix section for the general computational framework):

$$S_r(t|\mathbf{X}) = \begin{pmatrix} 1\\ 1 \end{pmatrix}^T \exp\left(t \begin{pmatrix} -a_r(X,0) - k_{01} & k_{10} \\ k_{01} & -a_r(X,1) - k_{10} \end{pmatrix}\right) \begin{pmatrix} \pi_0\\ \pi_1 \end{pmatrix}$$
(33)

This result is very similar in nature to the result obtained in [23] for the case of identical transition rates. Remarkable and simple result outlined by Eqn. (33) allows us to capture in essence regimes corresponding to the different ratios of the time-scales:  $a_r \ll (k_{10} + k_{01})$  and  $a_r \ge (k_{10} + k_{01})$ . First regime  $(a_r \ll (k_{10} + k_{01}))$  corresponds to the situation when transitions between different states of Z happens much faster then the average rate  $a_r(X,0), a_r(X,1)$  of the "linker" process and represents the mean-field (MF) regime. In this case dependence of  $ln(S_r(t))$  on time t can be very well characterized as linear Fig. 2. Not surprisingly, other regime, i.e.  $a_r \gg (k_{10} + k_{01})$ can be characterized as gated: in this case effective transition rate  $\bar{a}_r$  is characterized by the rate of switching of Z:  $k_{01} + k_{10}$ .

Figure 3 demonstrates influence of the second order correlation correction Eqn. (25):  $\Delta \bar{a}_r(t, \mathbf{X}) = \pi_1 \pi_0 \frac{t}{\kappa} (1 - \frac{\kappa}{t} (1 - e^{-\kappa t})), \quad \kappa = k_{01} + k_{10} \text{ which fluctuation correction to the effective rate } \bar{a}_r(\cdot)$  Dependence of survival probability  $S_r(t|\mathbf{X})$  in the example of a two-state system can be shown to be non-exponential on the longer time scale but  $\ln(S_r(t))$  behaves linearly with time at small times  $t \leq 1/a_r(X, \cdot)$ .

Interesting case of non-exponential relaxation kinetics, and specifically non-exponential kinetics at small times can be presented by the following example. Consider a fast reaction given by the dimerization reaction:

$$\mathsf{S} + \mathsf{S} \underset{k_2 K_{eq}}{\overset{k_2}{\leftrightarrow}} \mathsf{S}_2 \tag{34}$$

where the fast variable  $Z_t$  is the number of reaction event which took place up to time t which relates the numbers of monomers and dimers with the total number of molecules  $N_m = 2S + S_2$ in the following way:

$$S = N_m - 2Z, \quad S_2 = Z \tag{35a}$$

and a "linker" process is described by the relaxation rate depending on the number of dimers X in the following way:

$$a_r(X,Z) = \frac{k_1 X}{Z+X} \tag{36}$$

Current value X serves as an activation threshold: at small values of X ( $X \propto 1$ ) only small values of Z contribute to the effective rate but probability that Z takes values away from its average are exponentially suppressed (Fig. 4). On the contrary, if X is large i.e.  $X \approx \sum_{Z} \pi(Z|X)Z$  then rate given by Eqn. (36) depends on the typical value of Z and  $S_r(t|X)$  manifests time dependence similar to the previous example. One can see that this relaxation process shows non-exponential time dependence at small times due to the fact that process  $Z_t$  rarely visits the states contributing to the maximum of the relaxation rate given by Eqn. (36). We investigate the dependence of the averages survival probability on the level of activation threshold X and value of the equilibrium constant  $K_{eq}$ . Results presented on the Fig. 5 show non-exponential behavior of averaged survival probability for the system at small times t. It is evident that non-exponential behavior of  $S_r(t|X)$ is less pronounced for large values of  $X(X \approx \langle Z \rangle)$ .

Eigenvalue-eigenvector decomposition and calculation of expansion coefficients was performed via standard routines of LAPACK library available at http://www.netlib.org .

#### **VI. DISCUSSION AND CONCLUSIONS**

Let us summarize the main aspects of this paper. We have studied reduction approach to eliminate a fast intermediate in the chemical reaction network. To develop this method it is important to consider the time coarse-grained transition rates. We have discussed the limitations of the principle of stochastic averaging and its possible extensions through the rigorous technique for construction of the effective transition rates. We outline the procedure for re-normalization of the transition rates and construction of the effective Markov chain for the slow reactions. The merit of the present approach is that it is based on a conceptually transparent probabilistic approach involving the waitingtime distribution. Technique itself resembles a non-Markovian generalization of the Kubo-Anderson theory of stochastic modulation. Our study clearly indicates importance of details of the statistical structure of averaging process.

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### VIII. FIGURES



FIG. 1: Schematic representation of the two-state model. Relaxation rates  $a_r(\cdot)$  depend on both state Z and X and can be quite general.



FIG. 2: Time dependence of survival probability  $S_r(t)$  for different ratios of transition rates  $\epsilon = a_r(X, 1)/(k_{01} + k_{10})$ for the system with  $a_r(X, 1) \neq 0$  and  $a_r(X, 0) = 0$ .

#### APPENDIX A: CALCULATION OF AVERAGED SURVIVAL PROBABILITY

Calculations of averaged survival probabilities  $S_r(t|\mathbf{X})$  requires, in general, the calculation of the cumulants  $C_r^{(m)}$  of different order m but for some simple cases it can be obtained exactly. This is possible for the class of systems which have only finite number of accessible states of the fast variables.



FIG. 3: Time dependence of the survival probability  $S_r(t)$  calculated with mean-filed (dotted line) approximation and second cumulant correction (dashed line) compared to exact dependence (solid line).

One can study the distribution of values S of the functional

$$\exp(-\int_0^t a_r(\boldsymbol{Z}_{t'})dt'),\tag{A1}$$

where we have omitted the current state  $\mathbf{X}$  to simplify the notation. We introducing the joint



FIG. 4: Trajectory and probability density of the process Z(t). Dotted and dash lines on the probability plot correspond to the profile of the relaxation rate  $a_r(X, Z)$  for different X.

probability density  $q(S, \mathbf{Z}, t)$  of the random variables S and  $\mathbf{Z}$  [30]:

$$\frac{\partial q(S, \boldsymbol{Z}, t)}{\partial t} = a_r(\boldsymbol{Z}) \frac{\partial}{\partial S} (Sq(S, \boldsymbol{Z}, t)) +$$
(A2a)

+ 
$$\sum_{r' \in \mathcal{R}_2} (a_{r'}(\mathbf{Z} - \boldsymbol{\nu}_{r'}))q(S, \mathbf{Z} - \boldsymbol{\nu}_{r'}, t) - a_{r'}(\mathbf{Z}))q(S, \mathbf{Z}, t)) =$$
 (A2b)

$$= a_r(\boldsymbol{Z}) \frac{\partial}{\partial S} (Sq(S, \boldsymbol{Z}, t)) + \sum_{\boldsymbol{Z}'} \mathbb{W}_{\boldsymbol{Z}\boldsymbol{Z}'} q(S, \boldsymbol{Z}, t)$$
(A2c)

Average survival probability can be expressed following:

$$S_r(t) = \sum_{\boldsymbol{Z}} \int_0^1 Sq(S, \boldsymbol{Z}, t) dS = \sum_{\boldsymbol{Z}} \bar{q}_r(\boldsymbol{Z}, t)$$
(A2d)

and  $\bar{q}_r(Z,t)$  is governed by the following master equation:

$$\frac{\partial \bar{q}_r(\boldsymbol{Z}, t)}{\partial t} = -a_r(\boldsymbol{Z})\bar{q}_r(\boldsymbol{Z}, t) + \sum_{\boldsymbol{Z'}} \mathbb{W}_{\boldsymbol{Z}\boldsymbol{Z'}}\bar{q}_r(\boldsymbol{Z'}, t)$$
(A2e)

One can find an averaged survival probability via eigenvalue-eigenvector  $\{\lambda, V_{\lambda}(Z)\}$  decomposi-



FIG. 5: Time dependence of the survival probability  $S_r(t|X)$  for the system where dimerization dynamics of the fast variable Z is described by parameters  $N_m = 200$ ,  $k_1 = 1.0$ ,  $k_2 = 10.0$ ,  $K_{eq} = 10^2$ . Plots are shown for values of X = 1 and 50 clearly manifest non-exponential character of the relaxation process at small time for low values of X. Note that kinetics is non-exponential on time larger then characteristic scale  $t_{non-exp} \approx 0.02$  of fluctuation of Z (  $k_1^{-1}(N/2)^2 \approx 10^{-3}$ ) i.e. on the relevant for time-coarsening interval.

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tion of the linear operator  $\mathbb{W}_{ZZ'} - a_r(Z)\delta_{ZZ'}$ :

$$S_r(t) = \sum_{Z} \sum_{\lambda} c_{\lambda} V_{\lambda}(Z) \exp(\lambda t)$$
(A3)

where coefficients  $c_{\lambda}$  correspond to the decomposition of the invariant probability  $\pi(\mathbf{Z}|\cdot)$ :

$$\pi(\boldsymbol{Z}) = \sum_{\lambda} c_{\lambda} V_{\lambda}(\boldsymbol{Z}) \tag{A4}$$