

Overdispersed molecular clocks: applications in disordered kinetics and genetics

Marcel Ovidiu Vlad^{#,*}, Gianfranco Cerofolini⁺ and Peter Oefner[§]

[#]*Institute of Applied Mathematics and Mathematical Statistics, Casa Academiei Romane, Calea*

Septembrie 13 Bucharest, Romania

^{*}*Department of Chemistry, Stanford University, Stanford CA 94305-5080*

⁺*ST Microelectronics, 20041 Agrate MI, Italy*

[§]*Institute of Functional Genomics, University of Regensburg, Josef-Engert Strasse 9, 93053 Regensburg,*

Germany

1. Introduction

Random rates are commonly used for describing various phenomena in physics, chemistry and biology¹⁻³³. In physical chemistry, random rate coefficients have been used for describing rate¹⁻⁶ or transport⁷⁻⁹ processes in disordered systems. Related approaches are connected to the theory of Taylor transport¹⁰⁻¹³ and single molecule kinetics¹⁴⁻²⁴. In molecular biology random substitution rates have been used for describing the fluctuations of the evolution rates measured by the time frequency of the nucleotide or amino-acid substitution events (overdispersed molecular clocks²⁵⁻³³). The purpose of this chapter is to develop a unified statistical approach for the description of overdispersed molecular clocks in evolutionary biology and the theory of rate processes in disordered kinetics, with special focus on developing methods for extracting statistical information from experimental data. In disordered kinetics, special attention has been paid to this problem and various methods have been developed for determining rate distributions for systems with static and even with dynamic disorder. In contrast, in molecular biology little attention has been paid to extracting statistical properties of substitution rates from observed statistics of the substitution events; our intention is to introduce methods for doing it. Data of molecular biology³⁰⁻³³ suggest that the evolutionary rates vary and extracting statistical information about their random variations from molecular clock data would be very important for understanding the evolution process. The analogies between the random rates in disordered kinetics and molecular biology have been overlooked mostly because the experimental observables are different for the two classes of phenomena: in disordered kinetics the observables are either average survival functions (chemical kinetics) or moments or probability densities of the displacement vector of a moving particle (disordered transport), whereas in biology the observables are

the statistical properties of the number of substitution events. Recent advances in theoretical and experimental disordered and single molecule kinetics¹⁴⁻²⁴ makes it possible to measure the number of reaction events, by using spectroscopic experiments, which is essentially the same type of random variable as the number of substitution events in molecular biology; they are both numbers of 'transition' or 'jump' events corresponding to a random point process. This opens the way for developing a unified approach for both types of phenomena, which is one purpose of this chapter. In addition to the problem of molecular clocks in biology, other various problems of physics, chemistry and biology may benefit from our approach. For transport phenomena in disordered systems, the kinetics of the process can be expressed in terms of the statistics of hopping events⁷⁻¹³. In traditional kinetics the observables are concentrations rather than numbers of reaction events. However, in single molecule and disordered kinetics^{1-6,14-24}, individual reaction events are directly observed, which makes it necessary to reformulate the laws of chemical kinetics. Typical experiments which make it possible to evaluate the numbers of reaction events involve the transitions forth and back of a molecule or of a set of molecules from a fluorescent state to a non-fluorescent state¹⁴⁻²⁴.

In this chapter we study the relations between the statistical properties of the kinetic parameters of the process (statistical distributions and the cumulants of the rate coefficients, the densities of states) and the statistical properties of the numbers of transition (reaction, substitution, transport) events, expressed in terms of probability distributions and cumulants. We examine the possibilities of extracting statistical kinetic information about the rate coefficients and densities of states from the statistical information of the transition events gathered through observation or experiments. If only one time statistical data are available, then the evaluation of the statistical properties of the kinetic parameters is possible only for systems with static disorder. For systems with dynamic disorder multi-time joint probability densities of the numbers of the transition events are necessary

The structure of the chapter is the following. In Section 2 we give a general formulation for the statistical description of the fluctuations of the number of transition events for random point processes with a single random rate with collective fluctuations. In Section 3 we develop methods for evaluating the statistical properties of the transition events for systems with dynamic disorder. In Section 4 we study systems with static disorder and show that in this case it is possible to solve both the direct and the inverse

problem, that is, starting from a theoretical statistical model for the kinetics, we can compute the statistical properties of the numbers of the transition events; vice versa, starting from the observed statistical properties of the numbers of the transition events we can compute the statistical properties of the kinetic process. In Section 5 we discuss the implications of our approach in genetics and chemical kinetics and its applicability for processing experimental data.

2. Formulation of the problem

2A. Statistics of transition events, random rate coefficients and transport channels

We consider a chemical reaction, a hopping transport process, or a genetic evolutionary system which starts at time zero; these processes are described in terms of different types of transition events n_1, \dots, n_m which occur from time zero up to time t . For chemical reactions the transition events are reaction events, for transport phenomena that are jump events, whereas for evolutionary processes they are nucleotide or amino-acid substitution events. The process is characterized by a set of rate coefficients $k_1(t'), \dots, k_w(t')$ which are random functions of time (in general $w \geq k$). The statistical properties of the rate coefficients $\mathbf{k}(t') = (k_1(t'), \dots, k_w(t'))$ can be described in terms of a probability density functional:

$$\mathcal{R}[\mathbf{k}(t')] \mathcal{D}[\mathbf{k}(t')], \text{ with } \overline{\int \int \mathcal{R}[\mathbf{k}(t')] \mathcal{D}[\mathbf{k}(t')] = 1}, \quad (1)$$

and the corresponding characteristic functional:

$$\mathcal{G}[\mathbf{q}(t')] = \left\langle \exp \left[i \int \mathbf{q}(t') \bullet \mathbf{k}(t') dt' \right] \right\rangle = \overline{\int \int \exp \left[i \int \mathbf{q}(t') \bullet \mathbf{k}(t') dt' \right] \mathcal{R}[\mathbf{k}(t')] \mathcal{D}[\mathbf{k}(t')]}, \quad (2)$$

where $\mathbf{q}(t')$ is a state vector conjugated to the vector of the rate coefficients $\mathbf{k}(t')$, $\overline{\int \int}$ stands for the operation of path integration and $\mathcal{D}[\mathbf{k}(t')]$ is a suitable integration measure over the space of functions $\mathbf{k}(t')$. In disordered and single-molecule kinetics, the representation of the stochastic properties of the rate coefficients $\mathbf{k}(t')$ in terms of the functions $\mathcal{R}[\mathbf{k}(t')] \mathcal{D}[\mathbf{k}(t')]$ or $\mathcal{G}[\mathbf{q}(t')]$ is called 'random rate representation'³⁴.

A different representation is defined by expressing each set of rates as the sum of random contributions corresponding to different pathways (reaction or transport channels³⁴⁻⁴⁰)

$$\mathbf{k}(t') = \sum_{u'=1}^u \boldsymbol{\lambda}_{u'}(t'), \quad (3)$$

where the number of channels u and the corresponding contributions are random variables described by a set of grand canonical functional probability densities:

$$\mathcal{Q}_0, \mathcal{Q}_1[\boldsymbol{\lambda}_1(t')] \mathcal{D}[\boldsymbol{\lambda}_1(t')], \dots, \mathcal{Q}_u[\boldsymbol{\lambda}_1(t'), \dots, \boldsymbol{\lambda}_u(t')] \mathcal{D}[\boldsymbol{\lambda}_1(t')] \dots \mathcal{D}[\boldsymbol{\lambda}_u(t')], \quad (4)$$

which obey the normalization condition

$$Q_0 + \sum_{u=1}^{\infty} \frac{1}{u!} \overline{\int \int} \dots \overline{\int \int} Q_u[\lambda_1(t'), \dots, \lambda_u(t')] \mathcal{D}[\lambda_1(t')] \dots \mathcal{D}[\lambda_u(t')] = 1. \quad (5)$$

The random channel representation, based on Eqs.(3)-(4), can be easily related to the random rate representation (Eqs.(1)-(2)). According to Eq.(3) the probability functional $\mathcal{R}[\mathbf{k}(t')] \mathcal{D}[\mathbf{k}(t')]$ can be expressed as the average of a delta functional:

$$\begin{aligned} \mathcal{R}[\mathbf{k}(t')] \mathcal{D}[\mathbf{k}(t')] &= \left\langle \delta \left[\mathbf{k}(t') - \sum_{u=1}^u \lambda_u(t') \right] \mathcal{D}[\mathbf{k}(t')] \right\rangle = Q_0 \delta[\mathbf{k}(t')] \mathcal{D}[\mathbf{k}(t')] + \\ &+ \sum_{u=1}^{\infty} \frac{1}{u!} \overline{\int \int} \dots \overline{\int \int} \delta \left[\mathbf{k}(t') - \sum_{u'=1}^u \lambda_{u'}(t') \right] \mathcal{D}[\mathbf{k}(t')] Q_u[\lambda_1(t'), \dots, \lambda_u(t')] \mathcal{D}[\lambda_1(t')] \dots \mathcal{D}[\lambda_u(t')]. \end{aligned} \quad (6)$$

By inserting Eq.(6) into Eq.(2) we come to:

$$\mathcal{G}[\mathbf{q}(t')] = \Theta \left[\mathcal{W}[\lambda(t')] = \exp \left[i \int \mathbf{q}(t') \bullet \lambda(t') dt' \right] \right], \quad (7)$$

where

$$\Theta \left[\mathcal{W}[\lambda(t')] \right] = Q_0 + \sum_{u=1}^{\infty} \frac{1}{u!} \overline{\int \int} \dots \overline{\int \int} \prod_{u'=1}^u \{ \mathcal{W}[\lambda_{u'}(t')] \} Q_u[\lambda_1(t'), \dots, \lambda_u(t')] \mathcal{D}[\lambda_1(t')] \dots \mathcal{D}[\lambda_u(t')], \quad (8)$$

is the characteristic functional of the grand canonical probability density functionals (4) and $\mathcal{W}[\lambda(t')]$ is a suitable test functional. Eqs. (6) and (7) establish a relationship between random rate and random channel representations. If the stochastic properties of the contributions of different rates $\lambda_u(t')$ are known, then the stochastic properties of the rates $k_u(t')$ can be evaluated from Eqs. (6.) and (7); in particular, relationships between the moments or cumulants of these two types of random variables can be derived by repeated functional differentiation of Eq.(7).

2B. Relations among transition events, random rate coefficients and transport channels

Next, we need to establish relationship between the stochastic properties of the different types of transition events n_1, \dots, n_m and the stochastic properties of the rates $k_u(t')$ or of the contributions $\lambda_u(t')$. The general procedure is the following. We evaluate the stochastic properties of n_1, \dots, n_m for a given

realization of the functions $k_u(t')$ or $\lambda_u(t')$; afterwards we average over all possible functions $k_u(t')$ or $\lambda(t')$. In particular, if we are interested in the probability

$$P(n_1, \dots, n_m; t), \text{ with } \sum_{n_1} \dots \sum_{n_m} P(n_1, \dots, n_m; t) = 1, \quad (9)$$

of the number of reaction events we evaluate the conditional probabilities

$$P(n_1, \dots, n_m; t | \mathbf{k}(t')), \text{ with } \sum_{n_1} \dots \sum_{n_m} P(n_1, \dots, n_m; t | \mathbf{k}(t')) = 1, \quad (10)$$

or

$$P(n_1, \dots, n_m; t | \boldsymbol{\lambda}(t')), \text{ with } \sum_{n_1} \dots \sum_{n_m} P(n_1, \dots, n_m; t | \boldsymbol{\lambda}(t')) = 1, \quad (11)$$

and then evaluate the dynamic averages

$$P(n_1, \dots, n_m; t) = \langle P(n_1, \dots, n_m; t | \mathbf{k}(t')) \rangle = \langle P(n_1, \dots, n_m; t | \boldsymbol{\lambda}(t')) \rangle. \quad (12)$$

In the literature there are different methods for evaluating the probabilities $P(n_1, \dots, n_m; t | \mathbf{k}(t'))$ and $P(n_1, \dots, n_m; t | \boldsymbol{\lambda}(t'))$. In particular, we have developed a method of evaluating $P(n_1, \dots, n_m; t | \mathbf{k}(t'))$ for complex reaction system based on an exact, infinite order perturbation expansion of the characteristic function of the solution of a Markovian master equation⁴¹. These probabilities can be also evaluated numerically by using lattice-gas automata techniques⁴²⁻⁴⁵. Different methods exist for the evaluation $P(n_1, \dots, n_m; t | \boldsymbol{\lambda}(t'))$ for the biological problem of molecular clocks²⁵⁻³³. In many cases, the dynamic averages in Eq.(12) can be evaluated in terms of the characteristic functionals $\mathcal{G}[\mathbf{q}(t')]$ or $\Theta[\mathcal{W}[\boldsymbol{\lambda}(t')]]$.

Our purpose is to suggest methods for evaluating the stochastic properties of the random rates $k_u(t')$ or of the contributions $\lambda_u(t')$ from an observed probability $P(n_1, \dots, n_m; t)$.

3. Molecular clocks with random rates. Dynamic disorder

3A. Random rate statistics

We start out by considering the random rate approach. For a multiple clock with independent rates the probability $P(n_1, \dots, n_m; t | \mathbf{k}(t'))$ is given by a multidimensional Poissonian law:

$$P(n_1, \dots, n_m; t | \mathbf{k}(t')) = \prod_u \{P(n_u; t | k_u(t'))\}. \quad (13)$$

where

$$P(n_u; t | k_u(t')) = \frac{1}{n_u!} \left[\int_0^t k_u(t') dt' \right]^{n_u} \exp \left[- \int_0^t k_u(t') dt' \right], \quad (14)$$

are conditional probabilities attached to different transition events and $w = k$. We notice that the different numbers of transition events are independent random variables, and thus, without loss of generality, we can study the behavior of a single number $n = n_u$. For simplicity we drop the label u in Eq.(14), resulting in

$$P(n; t | k(t')) = \frac{1}{n!} \left[\int_0^t k(t') dt' \right]^n \exp \left[- \int_0^t k(t') dt' \right]. \quad (15)$$

The non-conditional probability $P(n; t)$ is given by

$$P(n; t) = \langle P(n; t | k(t')) \rangle = \langle P(n; t | \lambda(t')) \rangle. \quad (16)$$

We start out by considering random rate statistics, for which the characteristic function:

$$\mathcal{X}(b; t) = \sum_{n=0}^{\infty} \exp(ibn) P(n; t), \quad (17)$$

of the probability $P(n; t)$ of the number of transition events can be easily evaluated. In Eq.(17) b is the Fourier variable conjugated to the number n of transition events. We assume that the sum over the number of transition events and the dynamic averaging commute; we come to:

$$\mathcal{X}(b; t) = \sum_{n=0}^{\infty} \exp(ibn) \langle P(n; t | k(t')) \rangle = \left\langle \exp \left\{ \left[\exp(ib) - 1 \right] \int_0^t k(t') dt' \right\} \right\rangle, \quad (18)$$

from which, by taking into account the definition (2) of the characteristic function $\mathcal{G}[q(t')]$ we come to:

$$\mathcal{X}(b; t) = \sum_{n=0}^{\infty} \exp(ibn) \langle P(n; t | k(t')) \rangle = \left\langle \exp \left\{ \left[\exp(ib) - 1 \right] \int_0^t k(t') dt' \right\} \right\rangle, \quad (19)$$

and thus

$$\mathcal{X}(b; t) = \mathcal{G} \left[q(t') = \left[\exp(ib) - 1 \right] \vartheta(t - t') - \vartheta(t) \right], \quad (20)$$

where $b, |b| \leq 1$ is a complex variable conjugated to the number of transition events n , $\vartheta(t)$ is the Heaviside step function. The cumulants $\langle \langle n^m(t) \rangle \rangle$, $m = 1, 2, \dots$ of the number of transition events as well as

the cumulants $\langle\langle k_1(t_1)\dots k_\nu(t_m)\rangle\rangle$, $\nu=1,2,\dots$ of the rate coefficient can be evaluated by expressing the logarithms $\ln \mathcal{L}(b;t)$ and $\ln \mathcal{G}[q(t')]$ in Taylor expansions. We have:

$$\ln \mathcal{L}(b;t) = \sum_{m=1}^{\infty} \frac{(ib)^m}{m!} \langle\langle n^m(t)\rangle\rangle, \quad (21)$$

and

$$\ln \mathcal{G}[q(t')] = \sum_{\nu=1}^{\infty} \frac{i^\nu}{\nu!} \int_0^t \dots \int_0^t \langle\langle k_1(t'_1)\dots k_\nu(t'_\nu)\rangle\rangle q(t'_1)\dots q(t'_\nu) dt'_1 \dots dt'_\nu. \quad (22)$$

In order to establish a connection between the stochastic properties of the number of transition events, expressed by the cumulants $\langle\langle n^m(t)\rangle\rangle$, $m=1,2,\dots$ and the stochastic properties of the rate coefficients, expressed by $\langle\langle k_1(t_1)\dots k_\nu(t_m)\rangle\rangle$, $\nu=1,2,\dots$, we take the logarithm of Eq.(20), insert Eqs (21)-(22), expand the factors $[\exp(ib) - 1]^\nu$ in terms of power series in b and equate the coefficients of the different powers in b in the resulting equation. After some calculations we come to:

$$\langle\langle n^m(t)\rangle\rangle = \sum_{\nu=1}^m \mathcal{S}_m^{(\nu)} \int_0^t \dots \int_0^t \langle\langle k_1(t'_1)\dots k_\nu(t'_\nu)\rangle\rangle dt'_1 \dots dt'_\nu. \quad (23)$$

where

$$\mathcal{S}_m^{(\nu)} = \sum_{k=0}^{\nu} \frac{(-1)^{\nu-k} k^m}{k!(\nu-k)!}, \quad (24)$$

are the Stirling numbers of the second kind.

From Eqs.(23) we notice that if the cumulants of the numbers of the transition events are known from experiment or observation, then in general it is not possible to evaluate the cumulants of the rate coefficient.

3B. Random channel statistics

The above analysis can be easily extended to random channel kinetics. Fom Eq.(7) we can evaluate the cumulants of the rate coefficient in terms of the stochastic properties of the contributions $\lambda_u(t')$. Most models used in the literature involve independent channels , for which the grand canonical

probability densities (4) are Poissonian. For this reason, in this chapter we limit ourselves to Poissonian statistics for which

$$Q_0 = \exp\left\{-\int \overline{\int} \rho[\lambda(t')] \mathcal{D}[\lambda(t')]\right\}, \quad (25)$$

$$Q_1[\lambda_1(t')] \mathcal{D}[\lambda_1(t')] = \exp\left\{-\int \overline{\int} \rho[\lambda(t')] \mathcal{D}[\lambda(t')]\right\} \rho[\lambda_1(t')] \mathcal{D}[\lambda_1(t')], \quad (26)$$

$$\begin{aligned} Q_u[\lambda_1(t'), \dots, \lambda_u(t')] \mathcal{D}[\lambda_1(t')] \dots \mathcal{D}[\lambda_u(t')] &= \\ &= \exp\left\{-\int \overline{\int} \rho[\lambda(t')] \mathcal{D}[\lambda(t')]\right\} \rho[\lambda_1(t')] \mathcal{D}[\lambda_1(t')] \dots \rho[\lambda_u(t')] \mathcal{D}[\lambda_u(t')], \end{aligned} \quad (27)$$

where $\rho[\lambda(t')] \mathcal{D}[\lambda(t')]$ is the average functional density of channels. For Poissonian statistics the characteristic functional $\Theta[W[\lambda(t')]]$ can be easily evaluated. From Eqs.(8) and (25)-(27) we have

$$\Theta[W[\lambda(t')]] = \exp\left\{-\int \overline{\int} [1 - W[\lambda(t')]] \rho[\lambda(t')] \mathcal{D}[\lambda(t')]\right\}, \quad (28)$$

and thus, from Eq.(7) we come to:

$$\mathcal{G}[q(t')] = \exp\left\{-\int \overline{\int} [1 - \exp[i \int q(t') \lambda(t') dt']]\rho[\lambda(t')] \mathcal{D}[\lambda(t')]\right\}. \quad (29)$$

Eqs.(28)-(29) are general results which establish a connection between independent random channel statistics and random rate statistics, which is valid not only for overdispersed clocks but also for other types of independent rate processes with dynamic disorder.

We expand the exponent in Eq.(29) in a functional Taylor series in $q(t')$ and compare the result with Eq.(22). It follows that the cumulants $\langle\langle k_1(t'_1) \dots k_\nu(t'_\nu) \rangle\rangle$ of the rate coefficient can be expressed as:

$$\langle\langle k_1(t'_1) \dots k_\nu(t'_\nu) \rangle\rangle = \int \overline{\int} \lambda_1(t'_1) \dots \lambda_\nu(t'_\nu) \rho[\lambda(t')] \mathcal{D}[\lambda(t')], \quad (30)$$

and thus

$$\langle\langle n^m(t) \rangle\rangle = \sum_{\nu=1}^m S_m^{(\nu)} \int_0^t \dots \int_0^t dt'_1 \dots dt'_\nu \int \overline{\int} \lambda_1(t'_1) \dots \lambda_\nu(t'_\nu) \rho[\lambda(t')] \mathcal{D}[\lambda(t')], \quad (31)$$

We notice that the stochastic properties of the random channels, determined by the average functional density of states $\rho[\lambda(t')]\mathcal{D}[\lambda(t')]$, cannot be determined from the cumulants $\langle\langle n^m(t) \rangle\rangle$ of the numbers of transition events.

In conclusion, in this section we have developed general methods for expressing the stochastic properties of the numbers of transition events in terms of the stochastic properties of the random rate coefficients. We have derived two general relationships, Eq.(28)-(29), which relate independent random channel statistics to random rate statistics, and a particular relation, Eq.(20) which relates the stochastic properties of the kinetic process to the stochastic properties of the numbers of transition events of the overdispersed clocks. If the cumulants of the numbers of transition events and of the rate coefficients exist and are finite then the stochastic properties of the numbers of transition events can be evaluated from random rate or channel statistics; however the reverse operation is not possible. Fortunately the evaluation of random rate or random channel statistics from the statistics of the transition events is possible for processes with static disorder. The case of static disorder is investigated in detail in the next section.

4. Molecular clocks with random rates. Static disorder

4A. Random rate statistics

For systems with static disorder a fluctuation of the rate coefficients, once it occurs, lasts forever. This is an extreme case, which offers a satisfactory description of various systems both in disordered kinetics as well as in genetics. For systems with static disorder the general theory developed in the previous section turns into a simpler form. We start out with the analysis of random-rate approach. For static disorder the rate coefficients are random numbers, not random functions, and their statistical properties can be described in terms of a probability density

$$R(\mathbf{k})d\mathbf{k} \text{ with } \int R(\mathbf{k})d\mathbf{k} = 1, \quad (32)$$

or in terms of the characteristic function:

$$G(\mathbf{q}) = \langle \exp(i\mathbf{q} \bullet \mathbf{k}) \rangle = \int \exp(i\mathbf{q} \bullet \mathbf{k})R(\mathbf{k})d\mathbf{k}. \quad (33)$$

For a multiple clock with static disorder and independent rates the conditional probability $P(n_1, \dots, n_m; t | \mathbf{k})$ is also given by Eq.(13) with:

$$P(n_u; t | k_u) = \frac{1}{n_u!} [k_u t]^{n_u} \exp[-k_u t]. \quad (34)$$

Once again, we study, without loss of generality, the statistical behavior of a single number of transition events, $n = n_u$. The non-conditional probability $P(n; t)$ and its characteristic function $\mathcal{Z}(b; t)$ are given by:

$$P(n; t) = \langle P(n; t | k) \rangle = \int_0^\infty R(k) \frac{(kt)^n}{n!} \exp(-kt) dk, \quad (35)$$

$$\mathcal{Z}(b; t) = \langle \exp\{[\exp(ib) - 1]kt\} \rangle = G[q = -i[\exp(ib) - 1]t]. \quad (36)$$

By following the same steps as in Section 2, we can show that the cumulants of the number of transition events, and the cumulants of the rate coefficient, in case they exist and are finite, are related to each other through the relation:

$$\langle \langle n^m(t) \rangle \rangle = \sum_{\nu=1}^m S_m^{(\nu)} t^\nu \langle \langle k^\nu \rangle \rangle. \quad (37)$$

For static disorder it is possible to express the cumulants of the rate coefficient k , in terms of the cumulants of the number of transition events, which are available from observation or experiment. We rewrite Eq.(36) in the equivalent form:

$$G(q; t) = \mathcal{Z}\left(b = -i \ln\left(1 + \frac{iq}{t}\right); t\right), \quad (38)$$

from which, by performing cumulant expansions in both sides we come to:

$$\begin{aligned} \sum_{m=1}^{\infty} \frac{(iq)^m}{m!} \langle \langle k^m \rangle \rangle &= \sum_{m=1}^{\infty} \left[\ln\left(1 + \frac{iq}{t}\right) \right]^m \frac{1}{m!} \langle \langle n^m(t) \rangle \rangle = \\ &= \sum_{m=1}^{\infty} \sum_{\nu_1=1}^{\infty} \dots \sum_{\nu_m=1}^{\infty} (-1)^{m+\sum_u \nu_u} \left(\frac{iq}{t}\right)^{\sum_u \nu_u} \prod_u (\nu_u)^{-1} \frac{1}{m!} \langle \langle n^m(t) \rangle \rangle = \\ &= \sum_{w=1}^{\infty} \frac{(iq)^w}{w!} \sum_{\substack{\nu_1, \dots, \nu_m \\ \sum_u \nu_u = w}}^w (-1)^{m+w} \prod_u (\nu_u)^{-1} \frac{w! t^{-w}}{m!} \langle \langle n^m(t) \rangle \rangle = \sum_{w=1}^{\infty} \frac{(iq)^w}{w!} \sum_{m=1}^w \Phi_{mw} t^{-w} \langle \langle n^m(t) \rangle \rangle = \\ &= \sum_{w=1}^{\infty} \frac{(iq)^w}{w!} \sum_{m=1}^w \Phi_{mw} t^{-w} \langle \langle n^m(t) \rangle \rangle, \end{aligned} \quad (39)$$

where

$$\Phi_{mw} = \sum_{\substack{V_1, \dots, V_m \\ \sum_u V_u = w}} (-1)^{m+w} \frac{w!}{m!} \prod_u (V_u)^{-1}, \quad (40)$$

are special numbers, similar to the Stirling numbers of the second kind from Eq.(37). From Eq.(39) it follows that:

$$\langle\langle k^m \rangle\rangle = \sum_{m=1}^w \Phi_{mw} t^{-w} \langle\langle n^m(t) \rangle\rangle. \quad (41)$$

Eqs.(41) makes it possible to compute the cumulants of the rate coefficient in terms of the cumulants of the number of transition events.

4B. Statistical properties of rate coefficients

The statistical properties of the rate coefficients can be easily evaluated from the probability that there are no transition events, $P(0;t)$, which can be obtained from experimental data. From Eq.(35) it follows that $P(0;t)$ is the Laplace transform of the probability density $R(k)$ of the rate coefficient:

$$P(0;t) = \int_0^{\infty} R(k) \exp(-kt) dk, \quad (42)$$

and thus can be evaluated from $P(0;t)$ by inverse numerical Laplace transformation

$$R(k) = \mathcal{L}_k^{-1} P(0;t), \quad (43)$$

where \mathcal{L}_k^{-1} denotes the inverse Laplace transformation. If numerical data are not accurate, then the evaluation of the inverse Laplace transform is not possible. However, the moments and cumulants of the rate coefficient can be evaluated from $P(0;t)$. From Eq.(42) we notice that $P(0;t) = G(q=t)$ is the generating function of the probability density $R(k)$ of the rate coefficient. If the moments $\langle k^m \rangle$ and $\langle\langle k^m \rangle\rangle$ and cumulants of the rate coefficient exist and are finite, then we can carry out the moment and cumulant expansions:

$$P(0;t) = G(q=t) = 1 + \sum_{m=1}^{\infty} \frac{(-1)^m t^m}{m!} \langle k^m \rangle = \exp \left[\sum_{m=1}^{\infty} \frac{(-1)^m t^m}{m!} \langle\langle k^m \rangle\rangle \right], \quad (44)$$

from which we come to:

$$\langle k^m \rangle = (-1)^m \frac{d^m}{dt^m} P(0;t), \quad \langle \langle k^m \rangle \rangle = (-1)^m \ln \frac{d^m}{dt^m} P(0;t), \quad (45-6)$$

4C. Statistical properties of random channels

The random channel approach can be carried out in a similar way. For systems with static disorder the rate coefficients are random variables which can be expressed as the contributions of different channels corresponding to different pathways (reaction or transport channels)

$$\mathbf{k} = \sum_{u'=1}^u \lambda_{u'}, \quad (47)$$

where the number of channels u and the corresponding contributions are random numbers described by a set of grand canonical probability densities:

$$Q_0, Q_1(\lambda_1)d\lambda_1, \dots, Q_u(\lambda_1, \dots, \lambda_u)d\lambda_1 \dots d\lambda_u, \quad (48)$$

with the normalization conditions:

$$Q_0 + \sum_{u=1}^{\infty} \frac{1}{u!} \int_0^{\infty} \dots \int_0^{\infty} Q_u(\lambda_1, \dots, \lambda_u) d\lambda_1 \dots d\lambda_u = 1, \quad (49)$$

Eqs.(47)-(49) are similar to Eqs.(3)-(5) with the difference that the random functions are replaced by random numbers. The probability density $R(\mathbf{k})$ of the total rate vector is given by:

$$\begin{aligned} R(\mathbf{k}) &= \left\langle \delta \left(\mathbf{k} - \sum_{u'=1}^u \lambda_{u'} \right) \right\rangle = Q_0 \delta(\mathbf{k}) + \\ &+ \sum_{u=1}^{\infty} \frac{1}{u!} \int_0^{\infty} \dots \int_0^{\infty} \delta \left(\mathbf{k} - \sum_{u'=1}^u \lambda_{u'} \right) Q_u(\lambda_1, \dots, \lambda_u) d\lambda_1 \dots d\lambda_u. \end{aligned} \quad (50)$$

The characteristic function $G(\mathbf{q})$ can be easily evaluated from Eqs.(33) and (50). We have:

$$G(\mathbf{q}) = \Theta_{\text{static}} [w(\boldsymbol{\lambda}) = \exp(i\mathbf{q} \cdot \boldsymbol{\lambda})], \quad (51)$$

where

$$\Theta_{\text{static}} [w(\boldsymbol{\lambda})] = Q_0 \delta(\mathbf{k}) + \sum_{u=1}^{\infty} \frac{1}{u!} \int_0^{\infty} \dots \int_0^{\infty} Q_u(\lambda_1, \dots, \lambda_u) w(\lambda_1) \dots w(\lambda_u) d\lambda_1 \dots d\lambda_u, \quad (52)$$

is the characteristic functional attached to the canonical probability densities (48) and $w(\lambda)$ is a suitable test function. The unconditional and conditional probabilities for the numbers of transition events can be

expressed by Eqs.(9)-(12), with the difference that now the rate coefficients and the contributions λ_u are random numbers, not random functions.

For multidimensional clocks with independent channels, the grand canonical probability densities (48) are Poissonian, and for systems characterized by a single rate coefficient we have:

$$Q_0 = \exp\left\{-\int \rho(\lambda)d\lambda\right\}, \quad (53)$$

$$Q_1(\lambda_1)d\lambda_1 = \exp\left\{-\int \rho(\lambda)d\lambda\right\}\rho(\lambda_1)d\lambda_1, \quad (54)$$

$$Q_u(\lambda_1, \dots, \lambda_u)d\lambda_1 \dots d\lambda_u = \exp\left\{-\int \rho(\lambda)d\lambda\right\}\rho(\lambda_1)d\lambda_1 \dots \rho(\lambda_u)d\lambda_u. \quad (55)$$

The term $\rho(\lambda)d\lambda$ is the average functional density of channels. For Poissonian statistics the characteristic functional for one rate, $\Theta_{\text{static}}[w(\lambda)]$, can be evaluated from Eqs.(52)-(55).

$$\Theta_{\text{static}}[w(\lambda)] = \exp\left\{-\int [1-w(\lambda)]\rho(\lambda)d\lambda\right\}, \quad (56)$$

and thus, according to Eq.(51) the characteristic function $G(q)$ of the rate coefficient k is given by

$$G(q) = \exp\left\{-\int [1-\exp(iq\lambda)]\rho(\lambda)d\lambda\right\}. \quad (57)$$

We perform a cumulant expansion on both sides of Eq.(57). By comparing the various coefficients of q we can compute the cumulants of the rate coefficient. We obtain:

$$\langle\langle k^m \rangle\rangle = \int_0^\infty \lambda^m \rho(\lambda)d\lambda. \quad (58)$$

Eq.(58) makes a connection between random rate statistics, expressed by the cumulants $\langle\langle k^m \rangle\rangle$ of the rate coefficient, and random channel statistics, expressed by the average density of states $\rho(\lambda)$.

The probability density of the rate coefficients can be obtained from Eqs.(56)-(57) through inverse Laplace transformation:

$$\begin{aligned} R(k) &= \frac{1}{2\pi} \int_{-\infty}^{+\infty} \exp(-ikq)G(q)dq = \frac{1}{2\pi} \int_{-\infty}^{+\infty} \exp\left\{-ikq - \int [1-\exp(iq\lambda)]\rho(\lambda)d\lambda\right\}dq = \\ &= \frac{1}{\pi} \int_0^\infty \exp\left\{-\int_0^\infty \rho(\lambda)[1-\cos(q\lambda)]d\lambda\right\} \cos\left[qk + \int_0^\infty \rho(\lambda)\sin(q\lambda)d\lambda\right]dq. \end{aligned} \quad (59)$$

It is also possible to express the average number of channels $\rho(\lambda)$ in terms of the probability density $R(k)$ of the rate coefficients. In Eq.(57) we switch from the Fourier to the Laplace transformation and take into account that the rate coefficient k is non-negative, $R(k < 0) = 0$, resulting in:

$$\int_0^{\infty} R(k) \exp(-\vartheta k) dk = \exp\left\{-\int_0^{\infty} [1 - \exp(-\vartheta \lambda)] \rho(\lambda) d\lambda\right\}. \quad (60)$$

We differentiate Eq.(60) with respect to the Laplace variable ϑ

$$\int_0^{\infty} kR(k) \exp(-\vartheta k) dk = \exp\left\{-\int_0^{\infty} [1 - \exp(-\vartheta \lambda)] \rho(\lambda) d\lambda\right\} \int_0^{\infty} \exp(-\vartheta \lambda) \lambda \rho(\lambda) d\lambda. \quad (61)$$

By combining Eq.(60)-(61) we obtain:

$$\int_0^{\infty} kR(k) \exp(-\vartheta k) dk = \left\{ \int_0^{\infty} R(k) \exp(-\vartheta k) dk \right\} \int_0^{\infty} \exp(-\vartheta \lambda) \lambda \rho(\lambda) d\lambda. \quad (62)$$

In Eq.(62) we pass from the Laplace variable ϑ to the original variable k . Equation (62) becomes a linear convolution equation in the average density of states $\rho(\lambda)$:

$$kR(k) = \int_0^k \lambda \rho(\lambda) R(k - \lambda) d\lambda. \quad (63)$$

The integral equation (63) can be solved analytically or numerically. The analytic solution for the average density of states $\rho(\lambda)$ is:

$$\rho(\lambda) = \frac{1}{\lambda} \mathcal{L}_\lambda^{-1} \left[\frac{\mathcal{L}_q(kR(k))}{\mathcal{L}_q(R(k))} \right], \quad (64)$$

where \mathcal{L}_q and \mathcal{L}_λ^{-1} denote the direct and inverse Laplace transformations, respectively.

4D. Connections between random rate and random channel statistics

Now we can discuss the relations between the statistical properties of the number of transition events and the average density of states $\rho(\lambda)$. We insert Eq. (57) into Eq.(36), resulting in:

$$\mathcal{Z}(b; t) = \exp\left\{-\int [1 - \exp(\lambda t [\exp(ib) - 1])] \rho(\lambda) d\lambda\right\}. \quad (65)$$

From Eqs.(65) we can express the cumulants of the number of transition events $\langle\langle n^m(t) \rangle\rangle$ in terms of the average density of states $\rho(\lambda)$. We get:

$$\langle\langle n^m(t) \rangle\rangle = \sum_{\nu=1}^m S_m^{(\nu)} t^\nu \int_0^\infty \lambda^\nu \rho(\lambda) d\lambda. \quad (66)$$

The reverse problem, the evaluation of the average density of states $\rho(\lambda)$ from the cumulants of the number of transition events, is more complicated. We combine Eqs. (41) and (58), resulting in

$$\int_0^\infty \lambda^m \rho(\lambda) d\lambda = \sum_{w=1}^m \Phi_{mw} t^{-w} \langle\langle n^m(t) \rangle\rangle. \quad (67)$$

Eqs.(67) is a system of integral equations for the average density of states which can be solved numerically. This method of evaluation is inconvenient, because it requires knowledge of cumulants of different orders. A more convenient approach is based on the evaluation of the probability density of the rate coefficient from Eq.(43), followed by solving the integral equation (63). By combining Eqs.(43) and (63) we get:

$$\rho(\lambda) = \frac{1}{\lambda} \mathcal{L}_\lambda^{-1} \left[\frac{\mathcal{L}_t(k \mathcal{L}_k^{-1} P(0;t))}{P(0;t)} \right]. \quad (68)$$

In conclusion, in this section we have investigated the general relationships among the stochastic properties of random rate coefficients and random channels and the statistical properties of the numbers of reaction events for systems with static disorder. For static disorder it is possible to evaluate the statistical properties of the kinetic parameters from one-time distributions of the number of transition events. The implications of these results for the analysis of experimental or observational data for the number of transition events are investigated in section 5.

5. Implications in genetics and chemical kinetics

In this chapter we have developed general methods for the evaluation of one-time statistical properties of the number of transition events for overdispersed molecular clocks in molecular biology and disordered and single-molecule kinetics. We developed such methods both for static as well as dynamic disorder. We have shown that for static disorder it is possible to solve both the direct as well as the inverse problem, that is to compute the one time statistical properties of the number of transition events in terms of the statistical properties of the rate coefficients of random channel statistics and, vice versa, to evaluate the statistical properties of the kinetic parameters from observed one-time statistical properties of the numbers of transition events. For dynamic disorder, one-time statistical properties of the numbers of transition events are not enough for the evaluation of the statistical properties of the kinetic parameters; additional

statistical information about joint multi-time probability densities of multi-time cumulants is needed. Current observations or experiments in molecular biology and disordered or single molecule experiments do not provide such data. After new types of experiments are designed, our approach on dynamic disorder from Section 3 might serve as a basis for developing new methods of processing experimental data.

For static disorder we have developed two types of methods for extracting kinetic information from observed or experimental data. A first method is based on the use cumulants both for the observed numbers of transition events and for the rate coefficients, see Eq.(41). This method can be applied even if the data regarding the fluctuations of the numbers of transition events is not accurate. The knowledge of the first few cumulants of the number of transition events up to a given order m makes it possible to evaluate the cumulants of the rate coefficient up to the same order m . The evaluation of the probability density of the rate coefficient requires knowledge of the probability $P(0;t)$ that no transition events occur in a given time interval. The knowledge of the probability $P(0;t)$ from observation or experiment is also required for the evaluation of the density of states for random-channel statistics.

Regarding the applicability of our method in chemical kinetics, we expect it to be especially useful in single molecule kinetics, where the probability $P(0;t)$ is simply related to the average probability density $p(t)dt$ of off-times, through the relation $p(t) = -\partial P(0;t)/\partial t$. In molecular biology the evaluation of the distribution of substitution rates is related to an important problem, that is, to the question if the rate of evolution throughout a genome is constant or variable. A nucleotide is part of a gene; if significant fluctuations of the rate of substitution for a nucleotide exists, some fluctuations are also expected to occur at the level of a gene, or even further for the part of a genome or for the whole genome. The fluctuations at the upper levels of the genome can be described as multiple convolutions of the probability densities for the rates of substitution corresponding to the lower levels.

For disordered transport the experimental observables are usually not numbers of transition events, but related variables, such as the stochastic properties (moments, cumulants, probability densities) of the displacement vector of a moving particle. However these experimental observables can be easily related to the statistics of the transition events and thus our approach may be also applied to disordered transport.

There are many open problems related to our approach; here we mention only two. For static disorder, most studies in the literature assume that the fluctuations of the rate coefficients are collective; an open problem is developing methods for testing whether this assumption holds or not for a given set of experimental data. The second problem is suggesting new experiments for systems with dynamic disorder for collecting multitime statistical data for the numbers of transition events and developing techniques for processing such data. Work on these problems is progress.

Appendix. Statistics of transition events for stretched exponential kinetics

Although not encountered in molecular clocks, exponential kinetics is used for the description of a broad class of transport, relaxation and kinetic processes in disordered systems. In this section we study the fluctuation of transition events for collective fluctuations with static disorder described by stretched exponential kinetics.

For stretched exponential kinetics processes described by a single type of transition event the average density of channels is given by a negative power law:

$$\rho(\lambda) \sim \lambda^{-(1+\alpha)} = \frac{\alpha \Omega^\alpha}{\Gamma(1-\alpha) \lambda^{1+\alpha}}, \quad (\text{A.1})$$

where α is a fractal exponent between zero and one, Ω is a characteristic frequency, and $\Gamma(x)$ is the complete gamma function. The probability density $R(k)$ of the rate coefficient can be easily evaluated from Eqs.(59) and (A.1):

$$R(k) = \frac{1}{\pi} \int_0^\infty \exp\left[-(q\Omega)^\alpha \cos\left(\frac{\pi\alpha}{2}\right)\right] \cos\left[qk + (q\Omega)^\alpha \sin\left(\frac{\pi\alpha}{2}\right)\right] dq = \Omega^{-1} \psi_\alpha(k/\Omega), \quad (\text{A.2})$$

where

$$\psi_\alpha(x) = \mathcal{L}_x^{-1} \exp(-\nu^\alpha). \quad (\text{A.3})$$

By using an asymptotic expansion for $\psi_\alpha(x)$ presented in the literature⁴⁶ it follows that the probability density $R(k)$ of the rate coefficient has a long tail of the negative power law type:

$$R(k) \sim \frac{\Gamma(1+\alpha) \sin(\pi\alpha)}{\pi\Omega} \left(\frac{k}{\Omega}\right)^{-(1+\alpha)} \text{ as } k \rightarrow \infty \quad (\text{A.4})$$

The characteristic function $\mathcal{L}(b;t)$ of the provability for the number of transition events can be computed from Eqs.(65) and (A.1)

$$\mathcal{L}(b;t) = \exp\left\{-\int_0^\infty \frac{\alpha\Omega^\alpha}{\Gamma(1-\alpha)\lambda^{1+\alpha}} [1 - \exp(\lambda[\exp(ib) - 1])] d\lambda\right\} = \exp\left\{-[\Omega t [1 - \exp(ib)]]^\alpha\right\}. \quad (\text{A.5})$$

From Eq.(A.5), through differentiation of $\ln\mathcal{L}(b;t)$ it is easy to check that for stretched exponential kinetics all cumulants of the number of transition events are divergent. The same result can be obtained from Eqs.(A.1) and (66). It follows that the distribution of the transition events for stretched exponential is very broad. In general $P(n;t)$ cannot be evaluated analytically, only numerically from Eq.(A.5) through inverse Fourier transformation. The probability that there are no transition events $P(0;t)$, can be easily computed from Eq.(A.5). We introduce a modified generating function for $P(n;t)$ by using a variable conjugated to n defined by $x = \exp(ib)$:

$$Z(x;t) = \sum_{n=0}^{\infty} x^n P(n;t) = \mathcal{L}(-i \ln x; t), \quad (\text{A.6})$$

and from Eqs.(A.5)-(A.6) we come to:

$$Z(x;t) = \exp\left\{-[\Omega t (1-x)]^\alpha\right\}, \quad (\text{A.7})$$

and therefore:

$$P(0,t) = \lim_{x \rightarrow 0} Z(x;t) = \exp\left[-(\Omega t)^\alpha\right]. \quad (\text{A.8})$$

Acknowledgments

This research has been supported in part by, the CEEX grant M1-C2-3004/2006-Response of the Romanian Ministry of Research and Education, by BayGene and the National Science Foundation.

References

- (1) Blumen, A.; Klafter, J.; Zumofen, G., in *Optical Spectroscopy of Glasses*, edited by I. Zchokke, Reidel: Dordrecht, **1986**;
- (2) Shlesinger, M.F., *Ann.Rev.Phys. Chem.*, **1988**, 39,269;
- (3) Blumen, A.; Schnörer, H. *Angew.Chem.Int.Ed.*, **1990**,29,113;

- (4) Plonka, A.; *Annual Reports, Section C, Royal Society of Chemistry, Cambridge*, **1992**, 89,37;
1994,91,107;
- (5) Ross, J., Vlad, M.O., *Ann. Rev. Phys. Chem.* **1999**, 50, 51 and references therein
- (6) Gaveau, B., Gudowska-Nowak, E., Kapral, R., Moreau, M., *Phys. Rev. A.*, **1992**, 46, 825.
- (7) Haus, J.W., Kehr, K.W., *Phys. Rep.* **1987**, 150, 263.
- (8) Metzler, R., Klafter, J, *Phys Rep*, **2000**, 339, 1.
- (9) Zaslavsky, G.M., *Phys. Rep.* **2002**, 37,1 461.
- (10) Van Kampen, N.G., *Physica A*, **1979**, A96, 435; *Stochastic Processes in Physics and Chemistry*, 2nd Ed., North-Holland Amsterdam **1992**, ch. V;
- (11) Van den Broeck, C. and Mazo, R.M. *Phys. Rev. Lett.* **1983**, 51, 1309;
- (12) Van den Broeck, C. and Mazo, R.M. *J.Chem. Phys.* **1984**;
- (13) Vlad, M.O., Ross, J., Mackey, M.C., *Physica A.*,**1997**, A243, 340
- (14) Dickson, R.M., Cubitt, A.B., Tsien, R.Y., Moerner, E.W., *Nature*, 1997, **388**,355.
- (15) Schenter, G.K., Lu, H.P., Xie, X. S. *J. Phys. Chem. A* 1999, **103**, 10477.
- (16) Peterman, E.J., Brasselet, S., and Moerner, E.W., *J. Phys. Chem. A* 1999, **103**,10553.
- (17) Vlad, M. O., Moran, F., Schneider, F.W. and Ross, J., , *PNAS*, **2002**, 99, 12548.
- (18) Vlad, M. O., Moran, F., Ross J., *Chem. Phys. (Elsevier)*, **2003**, 287, 83
- (19) H. P. Lu, L. Xun, and X. S. Xie, *Science*, **1998**, 282, 1877
- (20) Sunney Xie,X, *J. Chem. Phys* **2002**, 117 11024.
- (21) Renger, T., May, V., Kuhn, O., *Phys. Rep.* **2001**, 343, 137.
- (22) Jang, S., Silbey, R. , *J. Chem.Phys.*, **2003**, 118, 9312
- (23) Barkai, E., Jung Y., Silbey, R., *Phys. Rev. Lett.*, **2001**, 87, 207403.
- (24) Brown, F.L.H., *Phys. Rev. Lett.*, **2003**, 90, 028302
- (25) Gillespie, G.H., *PNAS*, **1984**, 81, 8009
- (26) Gillespie, G.H., *The Causes of Molecular Evolution*, Oxford University Press, Oxford, **1991**.
- (27) Takahata, N., *Genetics*, **1987**, 116, 169;
- (28) Takahata, N., *Theor. Pop. Biol.*, **1991**, 39, 329.
- (29) Takahata, N., *Proc. R. Soc. London*, **1991**, B243, 13.

- (30) Cavalli-Sforza, L. L., Piazza A, Menozzi P., Mountain ., *PNAS*, **1988**, 85, 6002
- (31) Goldstein, D. B.; Linares, A.R., Cavalli-Sforza, L. L., Feldman, M. W., *Genetics*, **1995**, 139, 463.
- (32) Goldstein, D. B.; Linares, A.R., Cavalli-Sforza, L. L., Feldman, M. W., *PNAS*, **1995**, 92, 6723.
- (33) Douzery, E.J.P., Snell, E.A., Bapteste, E., Delsuc, F., Philippe, H., *PNAS* **2004** 101, 15386.
- (34) Vlad, M.O., Huber, D.L., Ross, J., *J. Chem. Phys.*, **1997**, 106, 4157.
- (35) Allinger, K., Blumen, A., *J. Chem. Phys.* **1981** ,75, 2762.
- (36) Huber, D.L., *Phys. Rev. B.*,**1985**, 31, 6070.
- (37) Huber, D.L., *Phys. Rev. E.*,**1996**, 53, 6544.
- (38) Vlad, M.O., Mackey, M.C., *J. Math. Phys.* **1995**, 36, 1834.
- (39) Vlad, M.O., Ross, J., Mackey, M.C., *J. Math. Phys.* **1996**, 37, 803.
- (40) Vlad, M.O., Metzler, R., Nonnenmacher, T., Mackey, M.C., *J. Math. Phys.* **1996**, 37, 2279.
- (41) Vlad, M.O., Ross,J., *J.Phys.Chem.A* **2000**, 104, 3159.
- (42) Chavez, F., Kapral, R., *Phys. Rev.E.*, **2000**, 63, 016211.
- (43) Dab, D., Lawniczak, A., Boon, J.P., Kapral, R., *Phys.Rev.Lett.*, **1990**, 64, 2462.
- (44) Kapral, R., Lawniczak, A., Maisar, P., *Phys.Rev.Lett.*, **1991**, 66, 2539.
- (45) Boon, J.P., Dab, D., Kapral, R., Lawniczak, A., *Phys. Rep.* **1996**, 273, 55
- (46) Montroll, E.W., Bendler, J.T., *J. Stat. Phys.*, **1984**, 34, 129.