

Dynamic averaging for reaction networks with random rate coefficients. Application to reaction kinetics in intracellular systems with crowding: transition from regular to fractal kinetics

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Abstract

We develop a general dynamic average technique for the kinetics of chemical or biochemical networks with random rate coefficients. We derive an analytic expression for the average concentrations of the various chemical species in terms of the characteristic functionals of the rate coefficients. If the fluctuations of the different rate coefficients are independent of each other we can express the average concentrations of the different species in term of a set of effective rate coefficients. The averaging technique developed in this paper can be used for solving various problems of reaction kinetics, genetics and molecular biology such as gene expression studies from noisy microarray data or in vivo, intracellular reaction kinetics with macromolecular crowding. We use a stochastic renormalization group approach for investigating the changes of reaction kinetics in vivo conditions due to macromolecular crowding. We get a set of time-dependent effective rate coefficients, which display a transition from classical kinetics for short times and to fractal kinetics for large times. These time-dependent effective rate coefficients can be expressed in terms of the incomplete gamma function. We give a physical interpretation of our results in terms of normal mode theory and show that our time-dependent rate coefficients correspond to a power law, Debye like fracton spectrum with an upper cutoff. By using the maximum information theory approach we get a modified Debye like spectrum which can be described by an gamma distribution which corresponds to adjusted fractal kinetics for which the rate coefficients display the time dependence $k_u(t) = k_u^0(h+t)^{-\alpha}$. Our theoretical results are in good agreement with simulation studies of intracellular kinetics presented in the literature.

1. Introduction

Various problems of chemical kinetics, genetics and molecular biology require the development of kinetic models for which the rate coefficients are random functions of time. Random rate coefficients describe environmental fluctuations in environmental chemistry [1], disordered chemical and biochemical kinetics [2] and molecular evolution [3]. Studies of gene expressions from noisy microarray data [4] can be also described in terms of kinetic models with fluctuating rate coefficients. In a related field, experimental and simulation studies of reaction kinetics in ‘in vivo’, [5] intracellular conditions have shown that macromolecular crowding leads to changes in the kinetics of the process which can be described by time dependent rate coefficients obeying fractal scaling laws.

In this article we present a general method for computing average concentrations for reaction systems with fluctuating rate coefficients, based on the use of characteristic functionals and illustrate our approach by studying in vivo, intracellular kinetics with macromolecular crowding. There are three different sources of inspiration for our approach. The first two problems which motivated our research is the gene expression studies from noisy microarray data [4] and intracellular kinetics with macromolecular crowding. [5] The last problem is the study of wave function collapse in non-ordinary quantum statistical mechanics, which inspired us in developing the general averaging technique presented in this article [6].

The structure of the article is the following. In Section 2 we present our general method for computing average concentrations for kinetic systems with fluctuating rate coefficients. In Section 3 we apply our method for studying reaction kinetics in intracellular systems with macromolecular crowding. In Section 4 we study simple reaction systems with generalized fractal kinetics for which the evolution equations can be solved analytically.

2. Dynamic averaging for reaction systems with fluctuating rate coefficients

We consider a reaction system described by the following kinetic equations

$$d\mathbf{x}(t)/dt = \mathbf{R}(\mathbf{k}(t), \mathbf{x}(t)), \quad (1)$$

with the initial condition

$$\mathbf{x}(t_0) = \mathbf{x}_0, \quad (2)$$

where $\mathbf{x}(t)$ is the vector of the concentrations of the chemical species of interest, $\mathbf{k}(t)$ is the vector of the rate coefficients which are assumed to be random functions of time and $\mathbf{R}(\mathbf{k}(t), \mathbf{x}(t))$ is the vector of the reaction rates. In this paper we neglect the concentration fluctuations due to the molecular nature of chemical reactions; however our method can be extended to systems for which the molecular fluctuations are important. The averaging method presented in the following is rather general and applied to various types of kinetic system obeying evolution equations of type (1)-(2). For illustration, we mention a few examples. A first example corresponds to the situation where the process can be described in terms of a set of elementary reactions and there are no constraints which prevent the system from reaching thermodynamic equilibrium. In this case, according to the principle of detailed balance, even though the rate coefficients of various pairs of forward and backward reactions are fluctuating in time their ratios must be constant and equal to the equilibrium constants of the net reactions, respectively. Sometimes the kinetics of the process is modeled by reactions including irreversible steps, or some constraints exist which prevent the system from reaching thermodynamic equilibrium; in these cases the constraints required by detailed balance, need not be considered. In other cases the elementary reactions are not known and the kinetics of the process can be described in terms of one or more overall reaction steps and the kinetic equations attached to these overall steps do not obey the mass action law. Nevertheless in these complex cases it may be necessary to assume that some or all rate coefficients entering the overall rate equations are random functions of time. For other systems the concentrations of some of the species are in large excess and can be assumed constant or can be varied according to given functions of time by the experimenters. Even these types of systems can be described by the kinetic equations (1)-(2). It may be necessary to use modified definitions for the rate coefficients, for example some of the rate coefficients are effective rate coefficients including the concentrations for which the concentrations are constant or can be controlled.

The solution of the vector evolution equation (1) with the initial condition (2) can be represented as a functional of the vector $\mathbf{k}(t)$ of rate coefficients

$$\mathbf{x}(t) = \Xi[\mathbf{k}(t'); \mathbf{x}_0] \text{ with } t \geq t' \geq t_0, \quad (3)$$

By using a standard approach in statistical physics we introduce a discrete representation of the functional

(3). We divide the time interval between t_0 and t into m pieces of length $\Delta t = (t - t_0)/m$. The functional

(3) can be approximated by a finite-dimensional function

$$\mathbf{x}(t) = \Xi[\mathbf{k}(t_0), \dots, \mathbf{k}(t_m); \mathbf{x}_0], \text{ with } t_w = t_0 + w\Delta t, t_m = t, \quad (4)$$

We denote by

$$\begin{aligned} \tilde{\Xi}[\boldsymbol{\sigma}(t_0), \dots, \boldsymbol{\sigma}(t_m); \mathbf{x}_0] &= \\ &= \int_0^\infty \dots \int_0^\infty \exp\left[-i \sum_{w=0}^m \mathbf{k}(t_w) \cdot \boldsymbol{\sigma}(t_w) \Delta t\right] \Xi[\mathbf{k}(t_0), \dots, \mathbf{k}(t_m); \mathbf{x}_0] d\mathbf{k}(t_0) \dots d\mathbf{k}(t_m), \end{aligned} \quad (5)$$

the Fourier transform of the discrete representation (4) of the functional (3). We have:

$$\begin{aligned} \Xi[\mathbf{k}(t_0), \dots, \mathbf{k}(t_m); \mathbf{x}_0] &= \\ &= \int_0^\infty \dots \int_{-\infty}^\infty \exp\left[i \sum_{w=0}^m \mathbf{k}(t_w) \cdot \boldsymbol{\sigma}(t_w) \Delta t\right] \tilde{\Xi}[\boldsymbol{\sigma}(t_0), \dots, \boldsymbol{\sigma}(t_m); \mathbf{x}_0] \frac{\Delta t d\boldsymbol{\sigma}(t_0)}{(2\pi)^n} \dots \frac{\Delta t d\boldsymbol{\sigma}(t_m)}{(2\pi)^n}, \end{aligned} \quad (6)$$

where $\boldsymbol{\sigma}(t_0), \dots, \boldsymbol{\sigma}(t_m)$ are values of a vectorial test function of time $\boldsymbol{\sigma}(t')$ conjugated to the vector of rate coefficients $\mathbf{k}(t')$, and n is the number of rate coefficients. In Eq.(5) we have taken into account that the rate coefficients are non-negative. In the continuous limit Eqs.(5)-(6) lead to:

$$\tilde{\Xi}[\boldsymbol{\sigma}(t'); \mathbf{x}_0] = \overline{\int \int_{\mathbf{k}(t')} \exp\left[-i \int_{t_0}^t \mathbf{k}(t') \cdot \boldsymbol{\sigma}(t') dt'\right] \Xi[\mathbf{k}(t'); \mathbf{x}_0] \mathcal{D}_{\text{dir}}[\mathbf{k}(t')]}, \quad (7)$$

and

$$\Xi[\mathbf{k}(t'); \mathbf{x}_0] = \overline{\int \int_{\boldsymbol{\sigma}(t')} \exp\left[i \int_{t_0}^t \mathbf{k}(t') \cdot \boldsymbol{\sigma}(t') dt'\right] \tilde{\Xi}[\boldsymbol{\sigma}(t'); \mathbf{x}_0] \mathcal{D}_{\text{inv}}[\boldsymbol{\sigma}(t')]}, \quad (8)$$

where

$$\mathcal{D}_{\text{dir}}[\mathbf{k}(t')] = \lim_{m \rightarrow \infty} \prod_{w=0}^m [d\mathbf{k}(t_w)], \quad \mathcal{D}_{\text{inv}}[\boldsymbol{\sigma}(t')] = \lim_{m \rightarrow \infty} \prod_{w=0}^m \left[\frac{\Delta t d\boldsymbol{\sigma}(t_w)}{(2\pi)^n} \right], \quad (9)$$

are integration measures and $\overline{\int \int}$ denotes the operation of path integration. Eqs.(7)-(8) are functional

generalizations of the direct and inverse Fourier transforms.

Our purpose is to evaluate the dynamic average of the concentration vector

$$\langle \mathbf{x}(t) \rangle = \langle \Xi[\mathbf{k}(t'); \mathbf{x}_0] \rangle = \overline{\int \int_{\mathbf{k}(t')} \Xi[\mathbf{k}(t'); \mathbf{x}_0] \mathcal{P}[\mathbf{k}(t')] \mathcal{D}_{\text{dir}}[\mathbf{k}(t')]} \quad (10)$$

where

$$\mathcal{P}[\mathbf{k}(t')] \mathcal{D}_{\text{dir}}[\mathbf{k}(t')], \text{ with } \overline{\int \int_{\mathbf{k}(t')} \mathcal{P}[\mathbf{k}(t')] \mathcal{D}_{\text{dir}}[\mathbf{k}(t')]} = 1, \quad (11)$$

is the probability functional of the vector of the rate coefficients. The characteristic functional of $\mathcal{P}[\mathbf{k}(t')] \mathcal{D}_{\text{dir}}[\mathbf{k}(t')]$ is defined as

$$\mathcal{G}[\boldsymbol{\sigma}(t')] = \overline{\int \int_{\mathbf{k}(t')} \exp\left[i \int_{t_0}^{t'} \mathbf{k}(t') \cdot \boldsymbol{\sigma}(t') dt'\right] \mathcal{P}[\mathbf{k}(t')] \mathcal{D}_{\text{dir}}[\mathbf{k}(t')]} \quad (12)$$

By combining Eqs.(8) and(10) we have:

$$\langle \mathbf{x}(t) \rangle = \overline{\int \int_{\boldsymbol{\sigma}(t')} \Xi[\boldsymbol{\sigma}(t'); \mathbf{x}_0] \mathcal{D}_{\text{inv}}[\boldsymbol{\sigma}(t')] \int \int_{\mathbf{k}(t')} \exp\left[i \int_{t_0}^{t'} \mathbf{k}(t') \cdot \boldsymbol{\sigma}(t') dt'\right] \mathcal{P}[\mathbf{k}(t')] \mathcal{D}_{\text{dir}}[\mathbf{k}(t')]} \quad (13)$$

from which, by using Eq.(12) we come to:

$$\begin{aligned} \langle \mathbf{x}(t) \rangle &= \overline{\int \int_{\boldsymbol{\sigma}(t')} \mathcal{G}[\boldsymbol{\sigma}(t')] \Xi[\boldsymbol{\sigma}(t'); \mathbf{x}_0] \mathcal{D}_{\text{inv}}[\boldsymbol{\sigma}(t')]} \\ &= \overline{\int \int_{\boldsymbol{\sigma}(t')} \mathcal{G}[\boldsymbol{\sigma}(t')] \mathcal{D}_{\text{inv}}[\boldsymbol{\sigma}(t')] \int \int_{\mathbf{k}(t')} \exp\left[-i \int_{t_0}^{t'} \mathbf{k}(t') \cdot \boldsymbol{\sigma}(t') dt'\right] \Xi[\mathbf{k}(t'); \mathbf{x}_0] \mathcal{D}_{\text{dir}}[\mathbf{k}(t')]} \quad (14) \end{aligned}$$

Eq.(14) is the main formal result of this paper. It makes it possible to compute the average concentration vector in terms of the stochastic properties of the rate coefficients, expressed in terms of the characteristic functional $\mathcal{G}[\boldsymbol{\sigma}(t')]$. If the cumulants of the rate

coefficients $\langle\langle k_{w_1}(t_1), \dots, k_{w_q}(t_q) \rangle\rangle, q = 1, 2, \dots$ exist and are finite then the characteristic functional $\mathcal{G}[\boldsymbol{\sigma}(t')]$

can be expressed by a cluster (cumulant) expansion:

$$\mathcal{E}[\boldsymbol{\sigma}(t')] = \exp \left\{ \sum_{q=1}^{\infty} \frac{i^q}{q!} \sum_{w_1} \dots \sum_{w_q} \int_{t_0}^t \dots \int_{t_0}^t \sigma_{w_1}(t'_1) \dots \sigma_{w_q}(t'_q) \langle \langle k_{w_1}(t'_1) \dots k_{w_q}(t'_q) \rangle \rangle dt'_1 \dots dt'_q \right\}, \quad (15)$$

The relative fluctuations of the rate coefficients of different orders are defined as:

$$\rho_{w_1 \dots w_q}(t'_1, \dots, t'_q) = \frac{\langle \langle k_{w_1}(t'_1) \dots k_{w_q}(t'_q) \rangle \rangle}{\langle \langle k_{w_1}(t'_1) \rangle \rangle \dots \langle \langle k_{w_q}(t'_q) \rangle \rangle}. \quad (16)$$

If we express the average concentration vector in terms of relative fluctuations we come to:

$$\begin{aligned} \langle \mathbf{x}(t) \rangle &= \overline{\int \int_{\boldsymbol{\sigma}(t')} \tilde{\Xi}[\boldsymbol{\sigma}(t'); \mathbf{x}_0] \mathcal{D}_{\text{inv}}[\boldsymbol{\sigma}(t')] \times} \\ &\times \exp \left\{ \sum_{q=1}^{\infty} \frac{i^q}{q!} \sum_{w_1} \dots \sum_{w_q} \int_{t_0}^t \dots \int_{t_0}^t \sigma_{w_1}(t'_1) \dots \sigma_{w_q}(t'_q) \rho_{w_1 \dots w_q}(t'_1, \dots, t'_q) \langle \langle k_{w_1}(t'_1) \rangle \rangle \dots \langle \langle k_{w_q}(t'_q) \rangle \rangle dt'_1 \dots dt'_q \right\}. \end{aligned} \quad (17)$$

Now we consider a particular case, important for applications. We assume that the correlation times of the fluctuations of the rate coefficients are small and that the cumulants of the rate coefficients remain finite as the correlation times tend towards zero; this approximation holds for fast fluctuations with finite amplitudes. Under these circumstances the average concentration vector can be expressed as:

$$\langle \mathbf{x}(t) \rangle = \overline{\int \int_{\boldsymbol{\sigma}(t')} \exp \left\{ i \sum_{w=1}^n \int_{t_0}^t \sigma_w(t') \langle \langle k_w(t') \rangle \rangle dt' + \mathcal{E}[\boldsymbol{\sigma}(t')] \right\} \tilde{\Xi}[\boldsymbol{\sigma}(t'); \mathbf{x}_0] \mathcal{D}_{\text{inv}}[\boldsymbol{\sigma}(t')]}, \quad (18)$$

where

$$\begin{aligned} \mathcal{E}[\boldsymbol{\sigma}(t')] &= \\ &= \sum_{q=2}^{\infty} \frac{i^q}{q!} \sum_{w_1} \dots \sum_{w_q} \int_{t_0}^t \dots \int_{t_0}^t \sigma_{w_1}(t'_1) \dots \sigma_{w_q}(t'_q) \rho_{w_1 \dots w_q}(t'_1, \dots, t'_q) \langle \langle k_{w_1}(t'_1) \rangle \rangle \dots \langle \langle k_{w_q}(t'_q) \rangle \rangle dt'_1 \dots dt'_q, \end{aligned} \quad (19)$$

is a correction term depending on the relative fluctuations of the rate coefficients. If the correction term can be neglected, then from Eqs. (8) and (18) we come to:

$$\langle \mathbf{x}(t) \rangle \approx \overline{\int \int_{\boldsymbol{\sigma}(t')} \exp \left\{ i \sum_{w=1}^n \int_{t_0}^t \sigma_w(t') \langle k_w(t') \rangle dt' \right\} \tilde{\Xi}[\boldsymbol{\sigma}(t'); \mathbf{x}_0] \mathcal{D}_{\text{inv}}[\boldsymbol{\sigma}(t')] = \Xi[\langle k_w(t') \rangle; \mathbf{x}_0]}.$$
(20)

By comparing Eqs.(3) and (19) we note that for rapid, finite fluctuations with short correlation times and finite cumulants the average concentration vector $\langle \mathbf{x}(t) \rangle$ is the solution of the vector kinetic equation (1) where $\mathbf{x}(t)$ is replaced by the average value $\langle \mathbf{x}(t) \rangle$ and the fluctuating rate coefficient $\mathbf{k}(t)$ is replaced by its first cumulant $\langle \langle \mathbf{k}(t) \rangle \rangle$, which is identical to the average value $\langle \mathbf{k}(t) \rangle$. We have:

$$d\langle \mathbf{x}(t) \rangle / dt = \mathbf{R}(\langle \mathbf{k}(t) \rangle, \langle \mathbf{x}(t) \rangle),$$
(21)

with the initial condition

$$\langle \mathbf{x}(t_0) \rangle = \mathbf{x}_0,$$
(22)

In conclusion, in this section we have developed a general method for computing the average concentration vector for a complex reaction system with fluctuating rate coefficients. The method is based on a functional generalization of direct and inverse Fourier transformation and makes it possible to express the average concentration vector in terms of the characteristic functional of the fluctuating rate coefficients. We have shown that for fast fluctuations with short correlation times and finite cumulants the average concentration vector can be approximated by the solution of the kinetic equation where the fluctuating concentrations and rate coefficients are replaced by their average values, respectively. In the next section this result is used for the analysis of intracellular reaction kinetics.

3. Reaction kinetics for intracellular reactions with macromolecular crowding

The study of in vivo, intracellular reaction kinetics is a subject of topical interest in molecular biology. There is experimental and simulation evidence that there are fundamental differences between ‘in vivo’ and ‘in vitro’ kinetics [5]. Within a cell there is high macromolecular content, even though the concentrations of different macromolecules are rather small. It is said that the medium is crowded rather than concentrated because no individual macromolecular species has high concentrations but the totals macromolecular content is significant[7]. Macromolecular crowding reduces the efficiency of the transport processes due to the excluded volume effect as well as due to the occurrence of inhomogeneous structures

within the cell. This decrease in reaction efficiency increases as the reaction goes on: the longer the time the higher the decrease of the reaction efficiency. Such a decrease of the reaction efficiency cannot be described in terms of classical chemical kinetics, for example simple models considering activity corrections to the mass action law usually fail. Various new kinetic approaches have been developed for the analysis of reaction kinetics with macromolecular crowding. Some models assume that are certain local areas within the cell for which the mass action laws is valid but that for the cell as a whole there are violations of the mass action law [8]. Another approach was suggested by Savageau and collaborators [9] based on the assumption that macromolecular crowding can be described by non-ideal reaction kinetics with unusually large effective reaction orders. Another approach was initiated by Kopelman [10], based on the use of fractal kinetic laws with time dependent rate coefficients obeying fractal scaling laws of the type:

$$k_w \sim t^{-\alpha_w}, \text{ for } t \gg 0, \quad (23)$$

where α_w are fractal exponents between zero and unity. It has been shown that various models, for example taking the exclude volume effect into account or geometrical constraints lead to the same asymptotic scaling laws (23), which are independent of the detailed mechanism of the process. Fractal kinetic laws of type (23) have a serious limitation, they lead to a singular behavior as $t \rightarrow 0$, which is physically inconsistent. Recent stimulation studies [5] based on the use of lattice gas reactive automata have shown that slightly modified fractal kinetic laws lead to a best fit of the simulation data for reaction kinetics with macromolecular crowding. These modified fractal kinetic laws which remove the singularity for small times:

$$k_w \sim (h_w + t)^{-\alpha_w} \quad (24)$$

and lead to a better fit of the simulation than other kinetic models for macromolecular crowding used in the literature.

In the following we use the general results derived in the previous section in order to develop a consistent fractal kinetic model, which does not display singularities for small times and leads to fractal scaling laws of the type (23) for large times. Since there are different physical models which all lead to the scaling behavior of the type (23) we suspect that the fractal kinetics is a universality class which emerges for large times and is independent of the details of the physical mechanism, in the same way as the central

limit theorem leads to Gaussian or Levy statistics in probability theory. We explore this universality class by using a renormalization group approach and show that the resulting rate coefficients are properly defined, that is for short times we get constant rate coefficients, corresponding to classical kinetics, whereas for long times we recover fractal kinetics. We give a physical interpretation of our expression for the time-dependent rate coefficient in terms of the normal mode theory. We also investigate the possible origin of modified fractal kinetic laws of the type (24).

The starting point of our approach is a naïve, mean field, normal mode theory. We assume that the interaction with a crowded environment reduces the efficiency of chemical reaction, resulting in the decay of rate coefficients. The simplest way of describing this decay is in term of a single normal mode, ν_w , for each rate coefficient k_w . The rate coefficients obey the decay law

$$\partial k_w / \partial t = -\nu_w k_w, \quad (25)$$

resulting in an exponential decay law

$$k_w(t) = k_w^0 \exp(-\nu_w t), \quad (26)$$

where for simplicity we have assumed that $t_0 = 0$. Usually this simple, mean field approach overestimates the decay of the rate coefficients due to the interaction with the environment. By analogy with the renormalization group approach in quantum field theory the exponentially decaying rate coefficients (26) can be considered as ‘bare’ rate coefficients. By applying the renormalization group approach we get a set of ‘dressed’ rate coefficients, which express the interaction of the process with the macromolecular environment in a proper way. The renormalization transformation \mathcal{R} , leads to renormalized, averaged rate coefficients and can be viewed as an averaging procedure. For this reason we chose to use the Shlesinger-Hughes renormalization approach [12] because it can be interpreted as an averaging procedure [13]. We have:

$$\langle k_w(t) \rangle = \mathcal{R}[k_w(t)], \quad (27)$$

where $\langle k_w(t) \rangle$ are the average rate coefficients which enter the kinetic evolution equations (21) derived in Section 2. On the other hand, from the point of view of the normal mode theory the interaction with the macromolecular environment leads to a continuous distribution of eigenmodes; the average, dressed rate

coefficients $\langle k_w(t) \rangle$ can be expressed as averages of the bare rate coefficients (26) over a frequency spectrum:

$$\langle k_w(t) \rangle = k_w^0 \int_0^\infty g_w(\omega_w) \exp(-\omega_w t) d\omega_w = k_w^0 \bar{g}_w(t), \quad (28)$$

where

$$g_w(\omega_w) \text{ with } \int_0^\infty g_w(\omega_w) d\omega_w = 1, \quad (29)$$

are probability densities of the eigemodes which describe frequency spectra attached to the different rate coefficients and

$$\bar{g}_w(t) = \int_0^\infty g_w(\omega_w) \exp(-\omega_w t) d\omega_w \quad (30)$$

are their Laplace transforms.

In Appendix A we show that, if we start out from the bare rate coefficients (26) the renormalization group approach leads to the following dressed rate coefficients:

$$\langle k_w(t) \rangle = k_w^0 \frac{\alpha_w \gamma(\nu_w t, \alpha_w)}{(\nu_w t)^{\alpha_w}}, \quad (31)$$

where $\gamma(a, x) = \int_0^x x^{a-1} \exp(-x) dx$, $a, x > 0$ is the incomplete gamma function. By inserting Eq.(31) into Eq.(28) we come to a set of integral equations for the frequency spectra $g_w(\omega_w)$. By solving these integral equations for $g_w(\omega_w)$ we come to:

$$g_w(\omega_w) = \frac{\alpha_w (\omega_w)^{\alpha_w - 1}}{(\nu_w)^{\alpha_w}} \vartheta(\nu_w - \omega_w), \quad (32)$$

where $\vartheta(x)$ is the Heaviside's step function. Eqs.(32) correspond to fracton spectra of Debye type with upper cutoffs $\omega_w = \nu_w$. Such fracton spectra are commonly used for describing the transport properties of disordered materials [14]. We notice that the average frequencies of the fracton spectra (32) are finite and equal to:

$$\langle \omega_w \rangle = \int_0^\infty \omega_w g_w(\omega_w) d\omega_w = \int_0^{\nu_w} \frac{\alpha_w (\omega_w)^{\alpha_w}}{(\nu_w)^{\alpha_w}} d\omega_w = \frac{\alpha_w}{\alpha_w + 1} \nu_w. \quad (33)$$

In fractal transport theory upper cutoffs are usually artifacts introduced in order to ensure the normalization of the frequency spectra (avoiding ultraviolet divergences). In many cases power spectra occur only for low frequency and are replaced by exponential tails. In our cases we do not have a specific theory in order to interpolate from fracton spectra for low frequencies to exponential tails for large frequencies. Such an interpolation formula can be derived by using the principle of minimum information gain (Kullback information). We use the fracton spectra with cutoffs, $g_w^{\text{fracton}}(\omega_w)$, Eqs.(32) as a priori distributions, introduce the information gain functions:

$$K[g_w^{\text{interp}}(\omega_w); g_w^{\text{fracton}}(\omega_w)] = \int_0^\infty g_w^{\text{interp}}(\omega_w) \ln \left[\frac{g_w^{\text{interp}}(\omega_w)}{g_w^{\text{fracton}}(\omega_w)} \right] d\omega_w, \quad (34)$$

and minimize them with the constrains resulting from the preservation of the normalization conditions for the aposteriori distributions $g_w^{\text{interp}}(\omega_w)$ and of the average values (33). If we carry out the computations we obtain aposteriori frequency spectra obeying distributions of the gamma type:

$$g_w(\omega_w) = \frac{1}{\Gamma(\alpha_w)} \left(\frac{\alpha_w + 1}{\nu_w} \right) (\omega_w)^{\alpha_w - 1} \exp\left(-\omega_w \frac{\alpha_w + 1}{\nu_w}\right), \quad (35)$$

where $\Gamma(a) = \int_0^\infty x^{a-1} \exp(-x) dx$, $a > 0$ is the complete gamma function. The dressed (renormalized) rate coefficients corresponding to the gamma frequency spectra (35) can be derived from Eqs.(28) and (35) We obtain:

$$\langle k_w(t) \rangle = k_w^0 \left(1 + \frac{\nu_w t}{\alpha_w + 1} \right)^{-\alpha_w} = \frac{k_w^0 (h_w)^{\alpha_w}}{(h_w + t)^{\alpha_w}}, \quad (36)$$

where

$$h_w = \frac{\alpha_w + 1}{\nu_w}. \quad (37)$$

We notice that Eqs.(36) are identical with the modified fractal kinetic laws (24) which lead to a best fit for the simulation data of ‘in vivo’ kinetics based on lattice gas automata algorithms.

In this section we have combined a naïve, eigenmode analysis with the renormalization group theory in order to derive a consistent formulation for fractal kinetics, which does not lead to singularities for small times. We have derived a set of renormalized rate coefficients, which are constant for small times

and have self-similar fractal tails. Our renormalized coefficients correspond to power law fracton spectra of the Debye type with upper cutoff values. We have used a Kullback information gain approach in order to derive an interpolation formula from power law fracton spectra for low frequencies to exponential tails for large frequencies. We obtained a set of gamma distributions, which lead to the modified fractal kinetic laws which provide a best fit for the simulation data of intracellular kinetics.

4. Reaction kinetics for intracellular reactions with macromolecular crowding. Examples

In the previous section we have introduced two generalized fractal kinetic laws for the dressed rate coefficients: Eqs. (31), which correspond to fracton Debye spectra with upper cutoffs and Eqs.(36), which correspond to fracton spectra described by gamma distributions. Both kinetic laws display a similar behavior. For small times the dressed rate coefficients are practically constant and the time evolution of the process is described by classical kinetics. For large times we recover the fractal chemical kinetics suggested by Kopelman [10]. We have

$$\langle k_w(t) \rangle \sim k_w^0 \text{ constant}, \quad (38)$$

for small times and

$$\langle k_w(t) \rangle \sim \mathcal{A}_w t^{-\alpha_w}, \quad (39)$$

for large times, where

$$\mathcal{A}_w = \alpha_w \Gamma(\alpha_w) (\nu_w)^{-\alpha_w} k_w^0, \quad (40)$$

for Debye fracton spectra and

$$\mathcal{A}_w = (h_w)^{\alpha_w} k_w^0 = (\alpha_w + 1)^{\alpha_w} (\nu_w)^{-\alpha_w} k_w^0, \quad (41)$$

for gamma fracton spectra.

In general the evolution equations (21) for generalized fractal kinetics can only be solved numerically. However, for systems involving a single overall reaction it is possible to derive analytical solutions. We consider a chemical system involving a single overall reaction, that is a single reaction route, in the sense of Horiuti theory [15]

$$\sum_{s=1}^S n_s X_s = 0, \quad (42)$$

where X_1, \dots, X_S are chemical species and n_1, \dots, n_S are overall stoichiometric coefficients. We assume that the reaction is operated in a closed system at constant volume and temperature. Under these circumstances the evolution of the process can be described in terms of a single chemical variable the intensive reaction extent ξ , which is defined by the differential equations:

$$\delta\xi = \delta\langle x_1 \rangle / n_1 = \dots = \delta\langle x_S \rangle / n_S, \quad (43)$$

and thus

$$\langle \mathbf{x}(t) \rangle = \langle \mathbf{x}(0) \rangle + (\xi(t) - \xi(0))\mathbf{n}, \quad (44)$$

where $\mathbf{n} = (n_s)$ is the vector of the overall stoichiometric coefficients. The time evolution of the average concentration vector $\langle \mathbf{x}(t) \rangle$ is determined by Eq.(44) and by the kinetic equation

$$d\xi/dt = R_\xi^+(\langle \mathbf{k} \rangle, \langle \mathbf{x} \rangle) - R_\xi^-(\langle \mathbf{k} \rangle, \langle \mathbf{x} \rangle), \quad (45)$$

where $R_\xi^+(\langle \mathbf{k} \rangle, \langle \mathbf{x} \rangle)$ and $R_\xi^-(\langle \mathbf{k} \rangle, \langle \mathbf{x} \rangle)$ are forward and backward reaction rates attached to the overall reaction (42), respectively. In some cases $R_\xi^\pm(\langle \mathbf{k} \rangle, \langle \mathbf{x} \rangle)$ obey expressions of the mass action law type

$$R_\xi^\pm(\langle \mathbf{k} \rangle, \langle \mathbf{x} \rangle) = \langle k_\pm(t) \rangle \prod_u \langle x_u \rangle^{m_u^\pm}, \quad (46)$$

where m_u^\pm are reaction orders., In other cases the rates $R_\xi^\pm(\langle \mathbf{k} \rangle, \langle \mathbf{x} \rangle)$ are given by more general expressions

$$R_\xi^\pm(\langle \mathbf{k} \rangle, \langle \mathbf{x} \rangle) = \langle k_\pm(t) \rangle f_\pm(\mathbf{K}, \langle \mathbf{x} \rangle), \quad (47)$$

which include Eqs.(47) as a particular case. Here $f_\pm(\mathbf{K}, \langle \mathbf{x} \rangle)$ are nonlinear functions which depend on the composition vector $\langle \mathbf{x} \rangle$ and possibly in some quasi-equilibrium constants, $\mathbf{K} = (K_u)$ such as adsorption coefficients or Mihaelis constants which do not depend on time. In both cases, in order that the kinetic equation (45) be compatible with the conditions of thermodynamic equilibrium it is necessary that

$$\langle k_\pm(t) \rangle = k_\pm^0 \varphi(t), \quad (48)$$

where $\varphi(t)$ is a function of time which is independent of the label, + or - of the rate coefficient. We have

$$\varphi(t) = \alpha(\nu t)^{-\alpha} \gamma(\nu t, \alpha), \quad (49)$$

for Debye fracton spectra and

$$\varphi(t) = \left(1 + \frac{\nu t}{\alpha + 1}\right)^{-\alpha} = \frac{h^\alpha}{(h+t)^\alpha}, \quad (50)$$

for gamma fracton spectra. Under these circumstance it is useful to introduce an intrinsic time scale

$$\theta(t) = \int_0^t \varphi(t') dt'. \quad (51)$$

We have

$$\theta(t) = \frac{1}{\nu(1-\alpha)} \left[(\nu t)^{1-\alpha} \gamma(\alpha+1, \nu t) + (\nu t + \alpha) \exp(-\nu t) - \alpha \right], \quad (52)$$

for Debye fracton spectra and

$$\theta(t) = \frac{h}{1-\alpha} \left[\left(1 + \frac{t}{h}\right)^{1-\alpha} - 1 \right], \quad (53)$$

for gamma fracton spectra. For small time in both cases we have $\varphi(t) \sim 1$ and thus $\theta(t) \sim t$. For long times

we have

$$\theta(t) \sim \mathcal{U} t^{1-\alpha} \text{ for } t \gg 0, \quad (54)$$

where

$$\mathcal{U} = \Gamma(1+\alpha) / \nu^\alpha (1-\alpha), \quad (55)$$

for Debye fracton spectra and

$$\mathcal{U} = h^\alpha / (1-\alpha), \quad (56)$$

for gamma fracton spectra.

We express the kinetic equation (45) in terms of the intrinsic time scale θ , resulting in:

$$d\xi/d\theta = R_\xi^+(\mathbf{k}_0, \langle \mathbf{x} \rangle) - R_\xi^-(\mathbf{k}_0, \langle \mathbf{x} \rangle), \quad (57)$$

where $\mathbf{k}_0 = [k_\pm^0]$ is the vector of time-independent, classical rate coefficients. We notice that Eq.(57) is the

same as the evolution equation for a system obeying classical kinetics

$$d\xi/dt = R_\xi^+(\mathbf{k}_0, \langle \mathbf{x} \rangle) - R_\xi^-(\mathbf{k}_0, \langle \mathbf{x} \rangle), \quad (58)$$

with the difference that the laboratory time t is replaced by the intrinsic time θ . If the solution

$$\xi_{\text{classical}}(t) = \Xi(t; \xi(0)), \quad (59)$$

is known then the solution of the evolution equation (45) with time-dependent rate coefficients can be expressed as:

$$\xi(t) = \Xi(\theta(t); \xi(0)). \quad (60)$$

Finally, by combining Eqs.(44) and (60) we can express the average concentrations of different species as functions of time.

The integration method introduced above can be applied to a broad class of simple reaction systems. For illustration we present a few examples. We start out by considering a single species irreversible reaction



We obtain

$$\langle x(t) \rangle = \langle x(0) \rangle \left[1 - (1-n) \langle x(0) \rangle^{-1} k_0 \theta(t) \right]^{\frac{1}{1-n}} \vartheta \left(\frac{\langle x(0) \rangle^{1-n}}{(1-n)k_0} - \theta(t) \right) \text{ for } 0 \leq n < 1, \quad (62)$$

$$\langle x(t) \rangle = \langle x(0) \rangle \exp(-k_0 \theta(t)) \text{ for } n = 1, \quad (63)$$

$$\langle x(t) \rangle = \langle x(0) \rangle \left[1 + (n-1) \langle x(0) \rangle^{-1} k_0 t \right]^{\frac{1}{n-1}} \text{ for } n > 1, \quad (64)$$

where n is the reaction order of the process and k_0 is the classical, time-independent rate coefficient of the reaction (1). As expected, for small times Eqs.(62)-(64) reduce to classical integral kinetic equations attached to Eq.(1). The long time behavior depends on the reaction order n . For $0 \leq n < 1$ the concentration of the species X becomes zero for a finite time t_{limit} which is the solution of the equation

$$\langle x(0) \rangle^{1-n} = (1-n)k_0 \theta(t_{\text{limit}}). \quad (65)$$

For first order reactions, $n = 1$, the asymptotic behavior of the integral kinetic equation is described by a stretched exponential

$$\langle x(t) \rangle \sim \langle x(0) \rangle \exp(-k_0 \theta t^{1-\alpha}) \text{ for } t \gg 0, n = 1, \quad (66)$$

For reaction orders larger than one, $n > 1$, the integral kinetic equation has a self-similar long time tail obeying a negative power law, which is independent of the initial condition $\langle x(0) \rangle$

$$\langle x(t) \rangle \sim [(n-1)k_0^0 \mathcal{U}^{1-\alpha}]^{-\frac{1}{n-1}} t^{-\frac{1-\alpha}{n-1}}, \text{ for } t \gg 0, n > 1 \quad (67)$$

A second example is a reversible first order reaction:



where k_{\pm}^0 are classical, time independent forward and backward rate coefficients, respectively. We obtain:

$$\langle x_1(t) \rangle = \langle x_1(0) \rangle + [\langle x_1^{\text{eq}} \rangle - \langle x_1(0) \rangle] \exp[-\theta(t)(k_+^0 + k_-^0)], \quad (69)$$

where $\langle x_1^{\text{eq}} \rangle = (\langle x_1(0) \rangle + \langle x_2(0) \rangle) k_+^0 / k_-^0$ is the equilibrium concentration of species X_1 ; a similar equation can be derived for the species X_2 . Eq.(69) shows that there is a transition from an exponential decay for small times:

$$\langle x_1(t) \rangle = \langle x_1(0) \rangle + [\langle x_1^{\text{eq}} \rangle - \langle x_1(0) \rangle] \exp[-(k_+^0 + k_-^0)t] \text{ for } t \sim 0, \quad (70)$$

to a stretched exponential decay for large times

$$\langle x_1(t) \rangle = \langle x_1(0) \rangle + [\langle x_1^{\text{eq}} \rangle - \langle x_1(0) \rangle] \exp[-(k_+^0 + k_-^0) \mathcal{U} t^{1-\alpha}] \text{ for } t \gg 0 \quad (71)$$

The last example an autocatalytic second order reaction



where we assume that there is a large supply of species A and thus its concentration a is practically constant. We have:

$$\langle x(t) \rangle = \frac{\langle x(0) \rangle k_+ a}{k_- \langle x(0) \rangle + [k_+ a - k_- \langle x(0) \rangle] \exp(-k_+ a \theta(t))}. \quad (73)$$

For small times Eq.(73) reduces to the well known logistic equation which depends on an exponential function $\exp(-k_+ a t)$ whereas for large times it leads to a modified logistic equation where the negative exponential of time, $\exp(-k_+ a t)$, is replaced by a stretched exponential, $\exp(-k_+ a \mathcal{U} t^\alpha)$.

Many other examples of simple reactions can be discussed in the same way. As expected, for small time the integral kinetic equations reduce to the integral genetic equations of classical kinetics whereas for long time different scaling regimes may emerge, some of them involving negative power laws

or stretched exponentials of time. For more complicated systems the evolution equations cannot be integrated analytically and numerical studies, similar to the ones presented in ref [5], are necessary.

5. Conclusions

In this article we have developed a characteristic functional approach for evaluating dynamic averages of concentrations of various species in chemical and biochemical systems with random rate coefficients. In particular, we have shown that for independent fluctuations it is possible to derive a set of kinetic equations for the average concentrations, which depend on a set of effective rate coefficients. The characteristic functional approach developed in this paper has great potential in solving various problems of reaction kinetics, genetics, genomics and molecular biology. The method introduced in this paper can be easily extended for computing other stochastic properties of the concentrations of different chemical species, which makes it possible to study the propagation of errors for different experimental methods used in molecular biology, or example microarray measurements. Other possible uses are related to gene expression studies; in this field our approach may provide a theoretical justification for the use of Bayesian networks, which may lead to improved methods in data mining. By combining our characteristic functional approach with the method of nonequilibrium statistical ensembles it may be possible to develop methods for identifying privileged pathways in gene networks. Another interesting application is related to the study of error propagation for chemical measurement techniques based on signal amplification by using chain reactions [16].

In this paper we illustrate our approach by studying the modifications of the kinetic laws in ‘in vivo’ systems, due to molecular crowding. By using the renormalization group approach we have derived a set of equations for the dressed rate coefficients, which display a transition from classical kinetics for small time to fractal kinetics for long time. Our equations for the dressed rate coefficients depend on the incomplete gamma function and correspond to Debye fracton spectra with upper frequency cutoffs. We remove the frequency cutoffs from the theory by using an information theory approach, resulting in fracton spectra described by the gamma distribution. The gamma fracton spectra lead to dressed rate coefficients which obey modified fractal laws $k_w \sim (h_w + t)^{-\alpha_w}$ (Eqs.(24)). Recent numerical studies [5] have shown that the modified fractal laws (24) provide a best fit to simulation studies of ‘in vivo’ kinetics based on the use of reactive lattice gas automata [11]. In a recent publication [17] we studied universal scaling laws for

the probability of concentration fluctuations in disordered systems. Although the mathematical techniques in ref [17] and the corresponding asymptotic laws are different from those developed here some analogies still exist. In our future work we try to explore these analogies, and if possible, try to develop a unified approach for both problems.

The renormalization group approach used in this article provides a convenient way for interpolating from classical to fractal kinetics; unfortunately it does not provides any details about the physical mechanisms which are the cause of fractal scaling. For understanding the physics and chemistry of the process studies based on polymer statistics and stochastic chemical kinetics are necessary. It appears that different reaction mechanisms tend to lead to (dressed) effective, time-dependent, rate coefficients which display fractal scaling for long time. Further studies should try to establish a connection between these particular models and the renormalization group approach.

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Appendix A

In this appendix we develop a stochastic renormalization group approach for investigating the self similar scaling properties of the rate coefficients $\langle k_w(t) \rangle$ for large times. The main idea is that the correct application of the renormalization group theory will lead not only to the self similar, negative power scaling laws of the type (23) but also a properly defined, non-singular behavior for small times, allowing to describe the transition from regular to fractal kinetics. We use a version of Shlesinger-Hughes renormalization group approach (SHR, [12]) which has a simple mathematical interpretation; the following computations were inspired by a random theory of dilution used for studying the physical meaning of Dirichlet distribution in environmental chemistry and genomics [13].

SHR can be viewed as a mathematical microscope used for exploring the scaling properties of the rate coefficients for large times. Given a time scale t_q successive scale transformations

$$t_{q+1} = t_q / \varepsilon_{q+1} \tag{A.1}$$

are applied step by step, where $\varepsilon_1, \varepsilon_2, \dots, \varepsilon_q, \varepsilon_{q+1}, \dots$ are random scaling (decimation) factors between one and infinity. For each renormalization (scaling) step there is a variable propagation probability λ_q that a next scaling step will occur after that; $1 - \lambda_q$ is the probability that the scaling ends up after q steps. Although the quantities λ_q, ε_q vary from step to step we assume that they have constant statistical properties described by an infinitesimal probability

$$\Phi(\varepsilon, \lambda) d\varepsilon d\lambda, \text{ with } \int_0^1 \int_1^\infty \Phi(\varepsilon, \lambda) d\varepsilon d\lambda = 1. \tag{A.2}$$

The successive application of the scaling transformations generate a probability density $p(t'|t) dt'$ with the normalization condition $\int p(t'|t) dt' = 1$ which establishes a connection between the bare time scale t' and the ‘dressed’, renormalized time scale t . Under these circumstances the renormalization transformation \mathcal{R} of the rate coefficients introduced in Section 3 (Eq.(26)) can be expressed as an average over the bare time scale t'

$$\langle k(t) \rangle = \int k(t') p(t'|t) dt', \tag{A.3}$$

For simplifying the computations, in this appendix we leave out, without loss of generality, the label w of the rate coefficient.

In order to evaluate the conditional probability density $p(t'|t)$ we introduce the infinitesimal, step, conditional probabilities

$$\Psi_q^\pm(\lambda_q, t_q | t) d\lambda_q dt_q, \quad q = 0, 1, 2, \dots, \quad (\text{A.4})$$

which obey the condition

$$\sum_{q=0}^{\infty} \int_0^1 \int_0^{\infty} \Psi_q^-(\lambda_q, t_q | t) d\lambda_q dt_q = 1. \quad (\text{A.5})$$

$\Psi_q^+(\lambda_q, t_q) d\lambda_q dt_q$ is the probability that q scaling events have occurred and that the propagation probability has a value between λ_q and $\lambda_q + d\lambda_q$ and that the corresponding time scale is between t_q and $t_q + dt_q$: the superscript + means that the scaling (renormalization) process has not been terminated after q steps. The probability $\Psi_q^-(\lambda_q, t_q) d\lambda_q dt_q$ has a similar significance with the difference that the – sign means that the succession of scaling events finishes after q steps. In terms of these probabilities we can write down the following evolution equations:

$$\begin{aligned} \Psi_q^+(\lambda_q, t_q | t) &= \\ &= \lambda_q \int_0^1 \int_0^{\infty} \int_1^{\infty} \Phi_u(\varepsilon_q, \lambda_q) \Psi_{q-1}^+(\lambda_{q-1}, t_{q-1} | t) \delta(t_q - t_{q-1} \varepsilon_q) d\lambda_{q-1} dt_{q-1} d\varepsilon_q, \end{aligned} \quad (\text{A.6})$$

$$\begin{aligned} \Psi_q^-(\lambda_q, t_q | t) &= \\ &= (1 - \lambda_q) \int_0^1 \int_0^{\infty} \int_1^{\infty} \Phi_u(\varepsilon_q, \lambda_q) \Psi_{q-1}^+(\lambda_{q-1}, t_{q-1} | t') \delta(t_q - t_{q-1} / \varepsilon_q) d\lambda_{q-1} dt_{q-1} d\varepsilon_q, \end{aligned} \quad (\text{A.7})$$

with the initial conditions

$$\Psi_0^+(\lambda_0, t_0 | t) = \lambda_0 \delta(t_0 - t') \int_1^{\infty} \Phi_u(\varepsilon_0, \lambda_0) d\varepsilon_0, \quad (\text{A.8})$$

$$\Psi_0^-(\lambda_0, t_0 | t) = (1 - \lambda_0) \delta(t_0 - t) \int_1^{\infty} \Phi_u(\varepsilon_0, \lambda_0) d\varepsilon_0. \quad (\text{A.9})$$

The conditional probability density $p(t'|t)$ can be expressed as

$$p(t'|t) = \sum_{q=1}^{\infty} \int_0^1 \Psi_q^-(\lambda_q, t') d\lambda_q. \quad (\text{A.10})$$

By solving Eqs.(A.6)-(A.9) step by step and inserting the result into Eq.(A.10) we get a Lippmann-Schwinger expansion for $p(t'|t)$:

$$p(t'|t) = \delta(t'-t) \int_1^\infty \int_0^1 (1-\lambda_0) \Phi(\varepsilon_0, \lambda_0) d\varepsilon_0 d\lambda_0 + \\ + \sum_{q=1}^\infty \int_1^\infty \int_0^1 d\varepsilon_q d\lambda_q \dots \int_1^\infty \int_0^1 d\varepsilon_0 d\lambda_0 (1-\lambda_0) \left[\prod_{w=1}^q \varepsilon_w \right] \delta\left(t' \prod_{w=1}^q \varepsilon_w - t\right) \prod_{w=0}^q [\lambda_w \Phi(\varepsilon_w, \lambda_w)]. \quad (\text{A.11})$$

As expected, the Lippmann-Schwinger series (A.11) has a self-similar structure which makes it possible to derive a stochastic renormalization group equation for $p(t'|t)$. By using a new summation label $q' = q-1$ Eq.(A.11) leads to

$$p(t'|t) = \delta(t'-t) \int_1^\infty \int_0^1 (1-\lambda_0) \Phi(\varepsilon_0, \lambda_0) d\varepsilon_0 d\lambda_0 + \\ + \int_1^\infty \int_0^1 d\varepsilon d\lambda \Phi(\varepsilon, \lambda) \varepsilon \lambda \delta(t'\varepsilon - t) \int_1^\infty \int_0^1 (1-\lambda_0) \Phi(\varepsilon_0, \lambda_0) d\varepsilon_0 d\lambda_0 + \\ + \int_1^\infty \int_0^1 d\varepsilon d\lambda \Phi(\varepsilon, \lambda) \varepsilon \lambda \sum_{q'=1}^\infty \int_1^\infty \int_0^1 d\varepsilon_{q'} d\lambda_{q'} \dots \int_1^\infty \int_0^1 d\varepsilon_0 d\lambda_0 (1-\lambda_0) \left[\prod_{w=1}^{q'} \varepsilon_w \right] \times \\ \times \delta\left(t' \prod_{w=1}^{q'} \varepsilon_w - t\right) \prod_{w=0}^{q'} [\lambda_w \Phi(\varepsilon_w, \lambda_w)]. \quad (\text{A.12})$$

We insert Eq.(A.11) into Eq.(A.12), resulting in

$$p(t'|t) = \delta(t'-t) \int_1^\infty \int_0^1 (1-\lambda) \Phi(\varepsilon, \lambda) d\varepsilon d\lambda + \int_1^\infty \int_0^1 d\varepsilon d\lambda \Phi(\varepsilon, \lambda) \varepsilon \lambda p(\varepsilon t'|t). \quad (\text{A.13})$$

Eq.(A.13) is a renormalization group equation which can be solved by using the Mellin transform. Which can be solved by using the Mellin transform. The solution of the equation is made up of the sum of analytic and non-analytic components. The non-analytic part of the solution, which describes the scaling properties of the rate coefficients has the following structure:

$$p(t'|t) \sim (t')^{\alpha-1} A_0 + \sum_{\rho=1}^\infty (t')^{\zeta_\rho-1} A_\rho (\ln t'), \quad (\text{A.14})$$

where $\alpha = \alpha_0$ is the unique real root of a secular transcendental equation

$$I(\alpha) = \int_1^\infty \int_0^1 \lambda \varepsilon^\alpha \Phi(\varepsilon, \lambda) d\varepsilon d\lambda = 1, \quad (\text{A.15})$$

$\alpha_\rho = \zeta_\rho \pm i\sigma_\rho$ are the complex roots of the same equation, A_0 is a constant and $A_\rho[\ln t']$ are periodic functions of $\ln t'$ with periods $2\pi/\sigma_\rho$. From Eq.(A.15) it follows that $I(0) = \langle \lambda \rangle \leq 1$ and $dI(\alpha)/d\alpha > 0$ and thus there is a single real root $\alpha = \alpha_0$, which is non-negative $\alpha_0 \geq 0$. Since Eq.(29) has real coefficients, the complex roots, if they exist, must occur in conjugated pairs $\alpha_\rho = \zeta_\rho \pm i\sigma_\rho$.

The occurrence of logarithmic oscillations due to complex eigenvalues is a known issue in renormalization group theory [12]. Although in some cases they do actually exist [12] in most cases they are mathematical artifacts due to the discrete nature of the renormalization transformations and must be eliminated by a suitable choice of the parameters of the models. In the case of fractal kinetics there is no experimental or theoretical evidence concerning the existence of logarithmic oscillations. For this reason we introduce a special limit for which the scaling features of fractal kinetics are preserved but however the logarithmic oscillation vanish. For our renormalization scheme the logarithmic oscillations are generated by the scaling factor ε , which changes randomly from renormalization step to renormalization step. The logarithmic oscillations vanish for processes involving very large numbers of renormalization steps and for which the variation of the scaling factor from event to event is very small. In order to identify this type of processes we compute the probability χ_q that q renormalization steps take place. We have

$$\begin{aligned}
\chi_q &= \int_0^1 \int_0^\infty \Psi_q^-(\lambda_q, t_q | t) d\lambda_q dt_q = \\
&= \int_0^\infty dt_q \int_1^\infty \int_0^1 d\varepsilon_q d\lambda_q \dots \int_1^\infty \int_0^1 d\varepsilon_0 d\lambda_0 (1 - \lambda_q) \times \\
&\times \prod_{w=1}^q (\varepsilon_w) \delta\left(t_q \prod_{w=1}^q (\varepsilon_w) - t\right) \prod_{w=0}^q [\lambda_w \Phi_u(\varepsilon_w, \lambda_w)] = (1 - \langle \lambda \rangle) \langle \lambda \rangle^q.
\end{aligned} \tag{A.16}$$

where

$$\langle \lambda \rangle = \int_1^\infty \int_0^1 \lambda \Phi(\varepsilon, \lambda_u) d\varepsilon d\lambda, \tag{A.17}$$

is the average probability of occurrence of a renormalization step. According to Eq.(A.16) the average number of renormalization steps

$$\langle q \rangle = \sum_{q=0}^\infty q \chi_q = 1/(1 - \langle \lambda \rangle), \tag{A.18}$$

tends to infinity, $\langle q \rangle \rightarrow \infty$, as the average probability of occurrence of a renormalization step tends to unity $\langle \lambda \rangle \rightarrow 1$. In this limit λ is not random anymore. For $\lambda \rightarrow 1$ we should also consider that $\varepsilon \rightarrow 1$ because otherwise the ε -dependent factors in Eq.(A.11) may lead to the violation of the normalization condition for $p(t'|t)$. It is easy to check that in general that the limit

$$\lambda \rightarrow 1, \varepsilon \rightarrow 1 \quad (\text{A.19})$$

leads to an indetermination. In order to eliminate this indetermination we introduce a constraint with a constraint, which preserves the scaling features of the renormalization group equation (A.13). We consider values of λ , and ε close to unity

$$\lambda = 1 - \zeta_\lambda, \varepsilon = 1 + \zeta_\varepsilon, \text{ with } \zeta_\lambda, \zeta_\varepsilon \text{ close to } 0. \quad (\text{A.20})$$

In this case the probability density $\Phi(\varepsilon, \lambda)$ can be approximated by

$$\Phi(\varepsilon, \lambda) = \delta(\lambda - 1 + \zeta_\lambda) \delta(\varepsilon - 1 - \zeta_\varepsilon). \quad (\text{A.21})$$

By inserting Eq (A.21) into Eq.(A.15) we obtain a secular equation which can be solved exactly. The correspondin eigenvalues are:

$$\alpha_0 = -[\ln(1 - \zeta_\lambda)] / [\ln(1 + \zeta_\varepsilon)], \quad (\text{A.22})$$

$$\alpha_\rho = \zeta_\rho \pm i\sigma_\rho = -[\ln(1 - \zeta_\lambda)] / [\ln(1 + \zeta_\varepsilon)] \pm i2\pi\rho / [\ln(1 + \zeta_\varepsilon)], \rho = 1, 2, \dots \quad (\text{A.23})$$

We introduce a constraint which ensures that the real fractal exponent $\alpha_0 = \alpha$ given by Eq.(A.22), which expresses the scaling properties of the renormalization group equation, remains constant in the limit (A.20).

It follows that

$$\alpha_0 = \alpha = -\ln \lambda / \ln \varepsilon \text{ constant as } \lambda \rightarrow 1, \varepsilon \rightarrow 1, \quad (\text{A.24})$$

In the limit (20) with the constraint (A.24) the renormalization group equation (A.13) reduces to an ordinary differential equation

$$\alpha \delta(t' - t) + t' \frac{\partial}{\partial t'} p(t'|t) = (\alpha - 1) p(t'|t). \quad (\text{A.25})$$

The normalized solution of Eq.(A.25) is

$$p(t'|t) = \alpha'^{\alpha-1} t^{-\alpha} \vartheta(t - t'). \quad (\text{A.26})$$

We insert Eq.(A.26) into Eq. (A.3), resulting in:

$$\langle k_w(t) \rangle = \frac{\alpha_w}{t^{\alpha_w}} \int_0^t t'^{\alpha_w-1} k_w(t') dt', \quad (\text{A.27})$$

where we have reintroduced the labels w attached to the different rate coefficients. Eqs(A.27) establishes a connection between the bare rate coefficients and the renormalized rate coefficients. In particular, the bare rate coefficients are exponential functions of time (single normal mode theory, Eqs.(26)), then Eqs.(A.27) reduce to Eqs.(31).