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The Quasicontinuum Fokker-Planck Equation

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Abstract

We present a regularized Fokker-Planck equation with more accurate short-time and high-frequency behavior for continuous-time, *discrete-state* systems. The regularization preserves crucial aspects of state-space discreteness lost in the standard Kramers-Moyal expansion. We apply the method to a simple example of biochemical reaction kinetics and to a two-dimensional symmetric random walk, and suggest its application to more complex systems.

1 Introduction

Only within the last few years has it become generally accepted that many cellular biophysical and biochemical processes require stochastic descriptions [1][2]. Since these processes often involve only small numbers of relevant molecules and or occur at spatially distinct locations, they furthermore require *discrete* descriptions – discrete in physical and/or state space. Examples include random walks and bubble dynamics on DNA [3], gene expression with small numbers of participating molecules [4], molecular motors [5], and ratchets [6] with distinct potential wells, and diffusion of cancer cells [7].

When modeling such systems over long time intervals and/or over large spatial/state-space scales, one can often safely ignore the effects of discreteness. The coarse-grained density field of a continuous-time, symmetric random walk on a lattice, for example converges to the solution of a linear diffusion equation in these limits. (See Doering et al [8] for some notable exceptions to this). However, for short times, and/or at short space/number scales, such a macroscopic/hydrodynamic approximation often breaks down. In this regime, discrete fluctuations are important, and the standard differential equation / mean field approaches (which treat the state space of the system as a continuous variable) are inadequate.

Therefore, in reacting systems with few molecules, a discrete state, master equation approach is often adopted. Instead of modeling the dynamics of the low-order statistics such as mean chemical concentrations, the master equation tracks the probability that the system is in a specific, discrete, microscopic state s

$$P(\mathrm{s}, t+dt) = P(\mathrm{s}, t) + \sum_{\mathrm{s}' \neq \mathrm{s}} T(\mathrm{s}' \to \mathrm{s}) P(\mathrm{s}', t) dt - \sum_{\mathrm{s} \neq \mathrm{s}'} T(\mathrm{s} \to \mathrm{s}') P(\mathrm{s}, t) dt. \tag{1}$$

Here $T(\mathrm{s}' \to \mathrm{s})$ is the rate at which the system transitions from the state s to the state s′. The quantity $P(\mathrm{s}, t)$ may be the probability of having a specified number s of particles of a given type at time t, or the probability that a particle is at a specified site s on a discrete

lattice, or may describe more generally the probability that the system is in a given discrete state s.

The solution of the coupled set of equations Eqn (1) contains information about all single-time statistics of the process under investigation. Unfortunately, these solutions are rarely available in closed form and can be quite costly to obtain numerically [9],[10],[11],[12],[13], [14],[15]. A promising alternative to straightforward discretization of the CME has been developed by Munsky and Khammash [16],[17], [18],[19].

A number of stochastic, particle-based methods have been developed over the years, beginning with, and building upon the method of Gillespie [20][21][22][23]. In these methods $P(\mathbf{s}, t)$ is typically determined by averaging over an ensemble of stochastic simulations. For high quality statistics, this ensemble may require a large number of copies of the system and thus might be quite expensive computationally.

As a result of these computational demands, constructing a quasi-continuum approximation[24] to the discrete master equation would capture many of the relevant features of the original discrete system and yet be more amenable to analysis and numerical solution. This includes the arsenal of computational methods for time-dependent PDE's including Galerkin, adaptive mesh, and variational approaches.

This approximation should also accurately model the physics across the full set of temporal and spatial scales. To accomplish this, we would therefore like to restore some semblance of this state-discreteness to the FP description. In particular we would like a description which enables the recovery, at least in part, of time-dependent, higher-order (beyond 2nd order) fluctuations.

In Section 2 we describe the master equation and its Kramers-Moyal expansion and the regularization procedure used. In Section 3 we apply the method to a simple model of reaction kinetics. We then test the regularization method on a random walk in two spatial dimensions in Section 4. Section ?? includes a summary of results and future directions.

2 Kramers-Moyal Expansion and Regularization

Our starting point is the master equation, Eqn (1). Consider, for simplicity the case with only one species of particle of type A. The master equation is given by

$$P(n, t+dt) = P(n,t) + \sum_{n' \neq n} T(n' \to n) P(n', t) dt - \sum_{n' \neq n} T(n \to n') P(n,t) dt \tag{2}$$

where n is the number of particles of type A. The standard approach to deriving a partial differential equation for the distribution function, P, (continuous in state space) is via the Kramers-Moyal expansion [25][26]. In order to work with densities, we replace the the discrete index n by the density variable $x = n/\Omega$, where Ω is the system volume. We then expand

$$\partial_t P(x,t) = \sum_{m=1}^{\infty} (-\partial_x)^m D^{(m)}(x) P(x,t), \tag{3}$$

where

$$D^{(m)}(x) = \lim_{\tau \to 0} \frac{1}{\tau} \frac{1}{m!} \int dx' (x' - x)^m P(x', t+\tau | x, t) \tag{4}$$

The resulting equation is then supplemented with the initial conditions

$$P(x,0) = \mathcal{P}(\S). \tag{5}$$

As we shall explain shortly, in order to maintain non-negativity, $P \geq 0$, at later times only the first and second terms are retained[27]. It is well established that the Fokker-Planck equation approximates well the behavior of the system in the limits of long times and large distances (large numbers in state space). One of the weaknesses of the Fokker-Planck equation however, is that it fails to capture accurately the short-time, short-distance (small "copy" number) behavior. At the level of the Fokker-Planck equation all traces of discreteness have been washed away. We shall go beyond that level in order to retain some of the effects of a discrete state space[24]. However, to this end, one cannot simply use the truncated (at second order) Kramers-Moyal expansion, but rather must use a regularized version of the Kramers-Moyal expansion.

Though the approach to regularization developed by Rosenau and collaborators and is described in a number of works (e.g., [28][29][30]), for the sake of completeness we outline it again. Imagine a continuous time, spatially discrete process describing the dynamics of a symmetric random walker on a one-dimensional lattice. Let h be the constant distance between the lattice sites and σ be the jump rate. For this situation, the master equation (1) takes the simple form

$$\frac{d}{dt}P(nh,t) = \frac{\sigma}{h^2}(P((n+1)h,t) - 2P(nh,t) + P((n-1)h,t)) \tag{6}$$

and the Kramer-Moyal Expansion amounts to a Taylor expansion, with the usual identification of $P(x,t) = P(nh,t)$,

$$P_t(x,t) = \sigma(P_{xx}(x,t) + \frac{h^2}{12}P_{4x}(x,t) + \frac{2h^4}{6!}P_{6x}(x,t) + ...). \tag{7}$$

The conundrum of this expansion is the following: to include the effects due to discreteness, one has to go beyond second order, where second order leads to the usual Fokker-Planck equation. However, rather than improve the situation, the 4th order correction yields an ill-posed problem. At 6th order the ill-posedness is removed, but then so is the positivity of P. This is best seen in Fourier space. Using the usual identification of $\partial_x \rightarrow iK$ we have

$$\hat{P}_t(x,t) = -\sigma(K^2 - \frac{h^2}{12}K^4 + \frac{2h^6}{6!}K^6)\hat{P} \tag{8}$$

where $\hat{P} = \mathcal{F}[P]$. To resolve the difficulty we note that expression (8) can be written in Fourier space as

$$\hat{P}_t(x,t) = -\sigma\frac{4\sin^2(Kh/2)}{h^2}\hat{P}. \tag{9}$$

We recognize Equation (8) as a truncated expansion of Equation (9). However, this expansion is precisely the source of the difficulty. While the exact discrete operator as given in Equation (9) is bounded from below (and above), its expansion results in an unbounded polynomial after truncation. This leads to the apparent difficulties. The problem is resolved if instead we use a Pade' representation which preserves the boundedness. We thus approximate

$$\frac{4\sin^2(Kh/2)}{h^2} \sim \frac{K^2}{1+\frac{h^2K^2}{12}} \tag{10}$$

which is bounded both from below and above. With this approximation, the right hand side of Equation(10) becomes a convolution after taking a Fourier transformation. In the particular case of Equation(10), its simplicity enables one to obtain a completely local description. To this end, we multiply it by the denominator and then transform. The resulting equation reads

$$P_t = \sigma P_{xx} + \frac{h^2}{12} P_{xxt} \tag{11}$$

which not only is well-posed but also restores a number of features washed away by not using higher order derivatives in the Kramers-Moyal expansion.

The corrections due to discreteness in number/lattice spacing for reaction systems will be $O(1)$ where 1 is the smallest unit of change. For a continuous-time random walk of fixed jump size, h, there will be corrections to the Fokker-Planck equation for moments beyond 2nd order. These corrections will be order h (see Doering et al. [24]) In this paper we extend work of Doering et al [24] to higher dimensional systems and to systems with nonuniform drift terms.

3 Biochemical Reaction

To illustrate the ideas above, we consider one of the simplest examples of reaction kinetics. Reactant A is created (from the vacuum) at a rate k and decays at a rate qA i.e., proportional to the number of A molecules present. This could be model of mRNA production and decay, or it could represent particle number fluctuations in a well-mixed vessel which is coupled to a particle bath through a membrane.

$$\emptyset \rightarrow^{k} A \quad A \rightarrow^{qa} \emptyset \tag{12}$$

From the Kramers-Moyal expansion, we obtain the following terms:

$$D^{(1)} = k - qx; \quad D^{(2)} = \frac{k+qx}{2}; \quad D^{(3)} = \frac{k-qx}{6}; \quad D^{(4)} = \frac{k+qx}{24}. \tag{13}$$

More generally, if n is even, then

$$D^{(n)} = \frac{k+qx}{n!} \tag{14}$$

and, if n is odd, then

$$D^{(n)} = \frac{k-qx}{n!}. \tag{15}$$

This gives rise to the following

$$\partial_t P = -\partial_x((k-qx)P(x,t)) + \partial_{xx}(\frac{k+qx}{2}P(x,t)) - \partial_{xxx}(\frac{k-qx}{6}P(x,t)) + \partial_{xxxx}(\frac{k+qx}{24}P(x,t)) + ... \tag{16}$$

The (usual) Fokker-Planck equation that results from keeping only the first two terms is

$$\partial_t P = -\partial_x((k-qx)P(x,t)) + \partial_{xx}(\frac{k+qx}{2}P(x,t)) \tag{17}$$

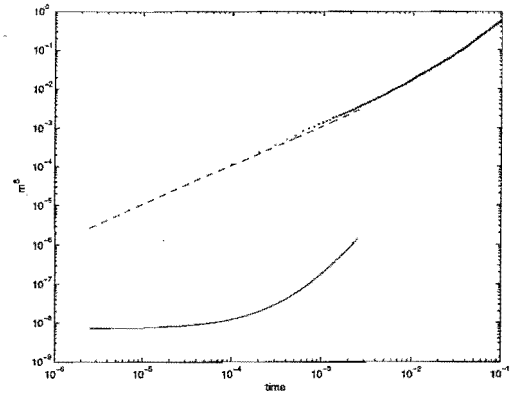

Figure 1: Evolution of the 6th moment as a function of time for the exact process (red), the regularized FPE (dashed line) and the FPE (solid line).

Using the regularization procedure described above, we can associate the all odd expansion terms with $\sinh(\partial_x P)$ which in Fourier space is just $\sin(K)$ and thus regularized as $K/(1+K^2/6)$. For the even part the regularization is $K/(1+K^2/12)$. This leads to

$$\partial_t P^{RFP} = \frac{\partial}{\partial x}\Big[\frac{1}{1-6\partial_x^2}\Big(A_-(x)P^{RFP}\Big)\Big] + \frac{1}{2}\frac{\partial^2}{\partial^2 x}\Big[\frac{1}{1-12\partial_x^2}\Big(A_+(x)P^{RFP}\Big)\Big], \qquad (18)$$

where $A_\pm = qx \pm k$.

The formal operators should be understood in the Fourier sense with $\partial_x \to iK$. Unlike the simple case of Equation10), we cannot effectively invert both nonlocal operators. Thus, their action in real space becomes a convolution and we have

$$\partial_t P^{RFP}(x,t) = \partial_x \int_{-\infty}^{\infty} \exp(-|\frac{x-\xi}{6}|)A_-(\xi)P^{RFP}(\xi,t)d\xi + \partial_{xx}\int_{-\infty}^{\infty}\exp(-|\frac{x-\xi}{12}|)A_+(\xi)P^{RFP}(\xi,t)d\xi \qquad (19)$$

with a no-flux boundary condition at the origin.

To demonstrate the improvement, we compare the short-time solutions of the Fokker-Planck Equation (17) and the Regularized Fokker-Planck Equation (19) with the behavior of the fully discrete process. For the initial condition of the discrete process, we consider a system with $n = 5$. We then look at the time evolution of various low-order moments of this distrubution, $m_1 = \langle x \rangle$ and $m^j = \langle (x - m_1)^j \rangle$. We compare the evolution of the discrete process to solutions of the FP and RFP with initial conditions $P(x,0) = P^{RFP}(x,0) = \delta(x-5)$.

By construction, the first and second moments are identical for the discrete process, the FP equation and the RFP equation. However, beyond the second moment, the FP and discrete process begin to disagree. The RFP, which uses information about the 4th moment, is identical to the discrete process. Moreover, there is good agreement for the 6th moment as well shown in Figure (1).

4 Two-Dimensional Random Walk

Next we consider the symmetric random walk on a two-dimensional square lattice. We assume the jump rate to nearest-neighbor sites in both x and y directions is μ. The Kramers-Moyal expansion for this process gives

$$D^{(1)} = D^{(3)} = 0 \quad D^{(2)} = \frac{\mu}{2} \quad D^{(4)} = \frac{\mu}{24}. \tag{20}$$

Keeping terms up to second order leads to the following Fokker-Planck/Diffusion equation

$$\partial_t P^{FP} = \mu(\partial_{xx} + \partial_{yy})P^{FP} \tag{21}$$

Applying the same set of techniques as in the previous section, we obtain the associated regularized FP equation

$$\partial_t P^{RFP} = \frac{1}{2}\frac{\partial^2}{\partial^2 x}\Big[\frac{1}{1-12\partial_x^2}P^{RFP}\Big] + \frac{1}{2}\frac{\partial^2}{\partial^2 y}\Big[\frac{1}{1-12\partial_y^2}P^{RFP}\Big], \tag{22}$$

Consider the lattice random walk with the single walker initially ($t = 0$) located the origin $x = 0$,$y = 0$. The analogous initial condition for both FP and RFP have the Dirac function $P^{FP} = P^{RFP} = (x, y, 0) = \delta(x)\delta(y)$. We compare the moments for short times for all three processes.

A short-time expansion for the moments $\langle x^\alpha y^\beta\rangle(t)$ can be worked out exactly combinatorially for the discrete process, and the moments $\langle x^\alpha y^\beta\rangle(t)$ for the FP and RFP can be worked out analytically. The results are given in Table (4). As can be seen, the moments of the RFP and the original, discrete process are identical up to 4th order. A comparison of the 6th order moment is given in Figure (2).

Process	$\langle x^2\rangle$	$\langle x^4\rangle$	$\langle x^6\rangle$
Discrete	$\frac{t}{2}$	$\frac{3}{4}t^2 + \frac{t}{2}$	see figure
FP	$\frac{t}{2}$	$\frac{3}{4}t^2$	$\frac{15}{8}t^3$
Regularized FP	$\frac{t}{2}$	$\frac{3}{4}t^2 + \frac{t}{2}$	$\frac{15}{8}t^3 + \frac{15}{4}t^2 + \frac{5}{4}t$

5 Conclusion

We derived and solved numerically a regularized Fokker-Planck equation for the short time / high frequency behavior of reaction kinetics, and for a two-dimensional, lattice random walk. We demonstrated that the solutions of these regularized equations better track the statistics of high order moments than the solutions to the standard Fokker-Planck equation. The regularized Fokker-Planck, an integrodifferential PDE formulation better informs the short-time asymptotics than original discrete process.

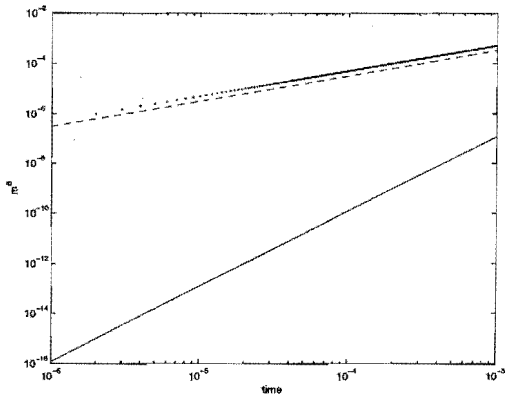

Figure 2: Time dependence of the 6th moment for the two dimensional process. Discrete process (red), regularized FPE (dashed line) and FPE (solid line).

Several questions arise: What continous state Langevin processes also give rise to these regularized FP equations? Can one apply the regularization procedure effectively to more general types of reaction rates (beyond polynomial). Can one develop regularized FPEs for systems in which transitions change several variables at once (e.g., reactions where $A \to A+1$ and $B \to B-1$ simultaneously)?

Areas of future application include queueing systems moving beyond the diffusion /heavy traffic limit [31], filtering / optimal estimation where the regularized FP would replace the Kushner-Stratnovich equation[32],[33] and Kushner-Stratonovich-Pardoux [34] equations. This approach can be used for state/parameter estimation where short time data is available.

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