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How Reaction Kinetics with Time-Dependent Rate Coefficients Differs from Generalized Mass Action

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Reactions occurring in low-dimensional media have been the subject of intense study for over two decades. These media can be either homogeneous or heterogeneous. Reactions in intracellular environments are a typical example of biochemical reactions occurring in low-dimensional and heterogeneous media.[1] Other examples are excitation trapping in molecular aggregates, charge recombination in colloids, reactions taking place at interfaces of different phases and surface catalysis.[2]

Reactions occurring in such conditions have been investigated by Monte Carlo simulations of point particles diffusing and reacting in a discrete space.[1,3,4] This space is characterized by a dimension d. Fractal spaces (those in which d is fractional), such as percolation clusters, provide a useful representation of a heterogeneous low-dimensional medium.

Using Monte Carlo simulations, Kopelmann[4] showed that the diffusion-limited reaction rate for the elementary reaction $A+A\rightarrow\emptyset$ in a fractal medium is proportional to $t^{-h}[A]^2$ for batch conditions. Here the square brackets denote concentrations. The parameter h is a function of the dimensionality of the reaction media, such that $0<h<1$. For example, in three dimensions $h=0$ (concordant with the law of mass action), on a percolation cluster $h=1/3$ and in a one-dimensional channel $h=1/2$. The increase in h with decreasing dimensionality reflects deviations from the classical law of mass action. These deviations are the result of dimensional or topological constraints in which convective or diffusive stirring is inefficient.[2] The above results are also correct for a reaction $A+B\rightarrow\emptyset$ with initial conditions $[A_0]=[B_0]$,[5] with the exception that h is different. Reaction kinetics characterized by a time-dependent rate coefficient $k(t)$ is also known as fractal-like reaction kinetics.[2] Such effective rate equations have been shown to describe the kinetics of more complex reactions[3,6] such as batch reactions of the type $A+B\rightarrow\emptyset$ with general initial conditions $[A_0]\neq[B_0]$.

Savageau[7,8] introduced the power-law formalism in the context of biochemical systems theory. It is also known as generalized mass action kinetics. In this general framework the rate of reaction, v is of the form represented in Equation (1):

$$v=\alpha\prod_{j=1}^{n}\left[A_j\right]^{g_j}, \qquad (1)$$

where α and g_j correspond to the rate constant and kinetic order of classical kinetics, respectively. The special case of the kinetic orders being equal to the molecularity of the reaction with respect to each of the reactants corresponds to the classical law of mass action.

Savageau[9–11] assumes that the power-law formalism and fractal-like reaction kinetics are equivalent, based on work by Kopelmann and co-workers.[4,12] The rational for this assumed equivalence is that for the reaction $A+A\rightarrow\emptyset$ or $A+B\rightarrow\emptyset$ with equal initial concentrations of A and B, the temporal variation of the concentration is equally well described by equations with time-dependent reaction coefficients and those based on the power-law formalism. For example for the reaction $A+A\rightarrow\emptyset$, the effective time-dependent rate equation found by Kopelmann: $\mathrm{d}[A(t)]/\mathrm{d}t\propto -t^{-h}[A(t)]^2$ has the same solution as an effective equation based on the power-law formalism of the form: $\mathrm{d}[A(t)]/\mathrm{d}t\propto[A(t)]^{(2-h/(1-h)}$. An advantage of the power-law formalism over the fractal-like kinetics approach is that it is more convenient for mathematical analysis. This combined with its assumed general equivalence to fractal-like kinetics has led to its extensive use in investigating the reaction kinetics of complex biochemical pathways occurring in the intracellular environment.[13–22] A notable example is the single-enzyme, single-substrate Michaelis–Menten mechanism,[23] which has been described using the power law approximation in dimensionally-restricted conditions.[10] Given the assumed general connection between fractal-like kinetics and the power-law approximation, models based on the latter are now commonly assumed in the biochemical kinetics community to describe fractal-like kinetics behavior.

Please note, that to date, there exists no theoretical or experimental evidence that reactions more complex than the simple elementary ones considered above can be described by the power-law formalism. On the contrary, fractal-like kinetics has been shown to describe bimolecular reactions of the type $A+B\rightarrow\emptyset$ for general initial concentrations of A and B,[3,6] and also simple enzymatic reactions.[1,24,25] The application of the power-law formalism rests simply on the assumption that its equivalence to fractal-like kinetics for simple reactions holds true in general for more complex reactions.

The central goal of this communication is to prove whether or not fractal-like kinetics and the power-law approximation are generally equivalent. A full reaction mechanism is the set of elementary steps that specifies how a chemical reaction takes places. Elementary steps are those that cannot be decomposed to reveal reaction intermediates on a relevant timescale.[26] These are usually monomolecular or bimolecular. Of these steps, only the bimolecular are diffusion-limited since two molecules have to diffuse before colliding and reacting with a certain probability. In this case the rate law will strongly depend on the dimensionality and topology of the medium in which the reaction occurs.

Given the above considerations we study a batch reaction of the type $A+B\rightarrow\emptyset$ with initial conditions $[A_0]<[B_0]$ and an environment characterized by dimensionality $d<4$. All species are assumed to be mobile. This reaction has been the subject of intense theoretical and computational work.[6,27,28] The time course of the limiting species concentration, $[A]$, is governed

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for intermediate to long times[6] by Equation (2):

$$[A(t)] \propto \exp(-ct^{\gamma}), \tag{2}$$

where c is a constant depending on initial conditions and $\gamma = d/2$ for $d < 2$ and $\gamma = 1$ for $d \geq 3$. Here d is the spectral (or fracton) dimension of the space (for a definition see ref. [2]) in which the reaction occurs. Note that for Euclidean spaces, the spectral dimension is equal to the dimension of the Euclidean space. In two dimensions, $\gamma = d/2$ with logarithmic corrections. For dimensions greater or equal to three, $\gamma = 1$. For the special case $[A_0] = [B_0]$, the time course has a completely different form[29] as shown by Equation (3):

$$[A(t)] \propto t^{-d/4}. \tag{3}$$

In either case $[A(t)]$ is the asymptotic solution to the effective rate equation given by Equation (4):

$$\mathrm{d}[A(t)]/\mathrm{d}t = -c_0 k(t)[A(t)][B(t)], \tag{4}$$

where c_0 is a constant. The rate coefficient has to have a long time dependence of the form $k(t) \propto t^{\gamma-1}$. Note that the short time dependence of $k(t)$ is irrelevant, providing that the function is defined at all times, including at $t = 0$.

We wish to find out whether Equation (4) is equivalent to one written using the power-law expression [Eq. (5)]:

$$d[A(t)]/dt = -c_1[A(t)]^{m_1}[B(t)]^{m_2}, \tag{5}$$

where m_1 and m_2 are kinetic orders strictly greater than one.

Let us assume that Equation (4) and Equation (5) are equivalent. We define $\delta = m_2 - m_1$, where δ can be positive or negative. Raising the time derivative in Equation (4) to the power of m_1 results in Equation (6):

$$\{d[A(t)]/dt\}^{m_1} = -1^{m_1} c_0^{m_1} k(t)^{m_1}[A(t)]^{m_1}[B(t)]^{m_1}. \tag{6}$$

Substituting for $[A(t)]^{m_1}[B(t)]^{m_1}$ from Equation (5) into Equation (6) we find:

$$\{d[A(t)]/dt\}^{m_1-1} \propto k(t)^{m_1}[B(t)]^{-\delta} \tag{7}$$

By noting that $\mathrm{d}[A(t)]/\mathrm{d}t = \mathrm{d}[B(t)]/\mathrm{d}t$, Equation (7) leads to Equation (8):

$$d[B(t)]/dt \propto k(t)^{m_1/(m_1-1)}[B(t)]^{\delta/(m_1-1)} \tag{8}$$

Since the long time dependence of the rate coefficient is $k(t) \propto t^{\gamma-1}$ then the only solution to the above equation is of the form $[B(t)] \propto t^{-\beta}$. As can be verified by direct integration of Equation (4), a solution of this form is only possible if the initial conditions are $[A_0] = [B_0]$: this is not compatible with general initial conditions.

Thus we have shown that ordinary differential equations based on fractal-like kinetics and the power-law approximation are not equivalent in general for the simple bimolecular reaction $A + B \rightarrow C$. This non-equivalence is apparent for intermediate to long times. For short time, simulations and theory[3,30] show that the concentration of the minority species A decays as t^{-h} rather than the stretched exponential decay of longer times. This temporal dependence cannot be obtained from effective rate equations with a time-dependent rate coefficient or from those based on the power-law formalism. This follows by noting that the general solution to Equation (4) is of the form shown in Equation (9):

$$[A(t)] = ([B_0] - [A_0])\left(\frac{[B_0]}{[A_0]}\exp(x) - 1\right)^{-1} \tag{9}$$

where

$$x = ([B_0] - [A_0])\int_0^t k(t')dt'$$

Also it is only possible to obtain t^{-h} behavior from Equation (5) if the initial concentrations of species A and B are equal or approximately equal. Thus for short times neither of the two approaches appear to provide a satisfactory description of the reaction kinetics.

In summary, for long times, the two descriptions are kinetically indistinguishable only for the special case $[A_0] = [B_0]$, a condition which is not generally met in nature. This result holds for complex biochemical reactions, such as enzyme-catalyzed reactions, in which we typically find diffusion-limited elementary steps. Our theoretical result supports recent observations by Schnell & Turner:[1] data obtained from lattice-gas simulations of enzyme catalyzed reaction in heterogeneous environments cannot be reproduced by differential equations based on the power-law formalism. In fact, they are governed by kinetic equations with time-dependent rate coefficients.

One of the major challenges facing biochemistry is the determination of the kinetic parameters for reactions occurring in intracellular environments. The power-law formalism is considered an appropriate theoretical framework to be used in experiments to measure the reaction kinetics in vivo, because it is either assumed to be equivalent or a reasonably accurate approximation[9,10,31] to the fractal-like kinetics. Theory and simulations have clearly indicated that non-ideal reaction kinetics are described by effective differential equations with a time-dependent rate coefficient. The use of generalized mass-action ODEs, though more attractive from a mathematical point of view, is only of limited applicability as a description of reaction kinetics in vivo conditions. Biochemists have to be cautious in using the power law approximation as equivalent to fractal-like kinetics.

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