Stochastic Kinetics of Nanocatalytic Systems

Jingyu Kang,[1,2] Seong Jun Park,[1,2] Ji-Hyun Kim,[1,2] Peng Chen,[3,*] and Jaeyoung Sung[1,2,†]
[1]*Creative Research Initiative Center for Chemical Dynamics in Living Cells, Chung-Ang University, Seoul 06974, Korea*
[2]*Department of Chemistry, Chung-Ang University, Seoul 06974, Korea*
[3]*Department of Chemistry and Chemical Biology, Cornell University, Ithaca, New York 14853, USA*

(Received 2 April 2019; revised 18 August 2020; accepted 3 February 2021; published 24 March 2021)

Catalytic reaction events occurring on the surface of a nanoparticle constitute a complex stochastic process. Although advances in modern single-molecule experiments enable direct measurements of individual catalytic turnover events occurring on a segment of a single nanoparticle, we do not yet know how to measure the number of catalytic sites in each segment or how the catalytic turnover counting statistics and the catalytic turnover time distribution are related to the microscopic dynamics of catalytic reactions. Here, we address these issues by presenting a stochastic kinetics for nanoparticle catalytic systems. We propose a new experimental measure of the number of catalytic sites in terms of the mean and variance of the catalytic event count. By considering three types of nanocatalytic systems, we investigate how the mean, the variance, and the distribution of the catalytic turnover time depend on the catalytic reaction dynamics, the heterogeneity of catalytic activity, and communication among catalytic sites. This work enables accurate quantitative analyses of single-molecule experiments for nanocatalytic systems and enzymes with multiple catalytic sites.

DOI: 10.1103/PhysRevLett.126.126001

Nanoparticle catalysis has attracted increasing interest over the last 60 years and is now one of the most important topics in nanoscience. Nanocatalysts are widely used in chemistry [1–7], energy [8–14], and environmental science [15–18]. However, despite the nanoparticle structure being visualizable down to an atomic resolution [19–22], catalytic reactions of nanoparticles have been investigated mostly at macroscopic scales.

Notable exceptions are single-molecule studies of nanocatalytic reactions [23–39], which make it possible to monitor individual catalytic events at subparticle segments of a nanocatalyst. One such study shows that the rate of catalytic reaction at one site is influenced by the product molecules created at other sites, similar to allosteric enzymes [40], which is reflected in the correlation between turnover times at different catalytic sites, an observable of single-molecule nanocatalysis [28].

Other important experimental observables of single-molecule nanocatalysis are the counting statistics of catalytic reaction events [41] and the catalytic turnover time distribution (CTD) [42]. These observables carry far more information about reaction systems than the mean reaction rate measured in macroscopic experiments [43–48]. For single enzyme systems, it is already understood how the enzymatic turnover time distribution and counting statistics of enzymatic turnovers are related to reaction dynamics of the single enzyme [49–53]. Despite its similarity with enzyme, however, we have yet to understand the corresponding relationships for nanocatalytic systems. This is mainly because there exist multiple catalytic sites on a nanocatalytic system [54] so that we only observe a superposition of catalytic events occurring at multiple sites [Figs. 1(a) and 1(b)], which forms a more complicated stochastic process than the catalytic reaction at an individual site. To make matters worse, there is no currently available method for estimating the number of catalytic sites in a nanocatalytic system, which is required for accurate analysis of single-molecule kinetics of nanocatalytic systems. For this reason, quantitative understanding of single nanocatalytic systems has remained a challenging problem [23,55].

Addressing these issues, we here present stochastic kinetics for nanocatalytic systems. On the basis of counting statistics of single-molecule reactions [41,56], we propose a new method to estimate the number of catalytic sites in a nanocatalytic system. We then show how the CTD of a nanocatalytic system with multiple catalytic sites depends on the number of catalytic sites and the mechanism and dynamics of individual catalytic site. We also investigate how the segment-to-segment variation in the catalytic activity and communications between catalytic sites [28] affect experimental observables of single nanocatalytic systems.

The number N of catalytic sites in a nanocatalytic system can be estimated from the counting statistics of catalytic reactions, more specifically, the mean and variance of the total number $z_N(t)$ of the catalytic events occurring in N catalytic sites on time interval $(0, t)$. Under the typical nonstationary initial condition, shown in Fig. 1(a), the mean catalytic turnover number $\langle z_N(t)\rangle$ of N sites in time

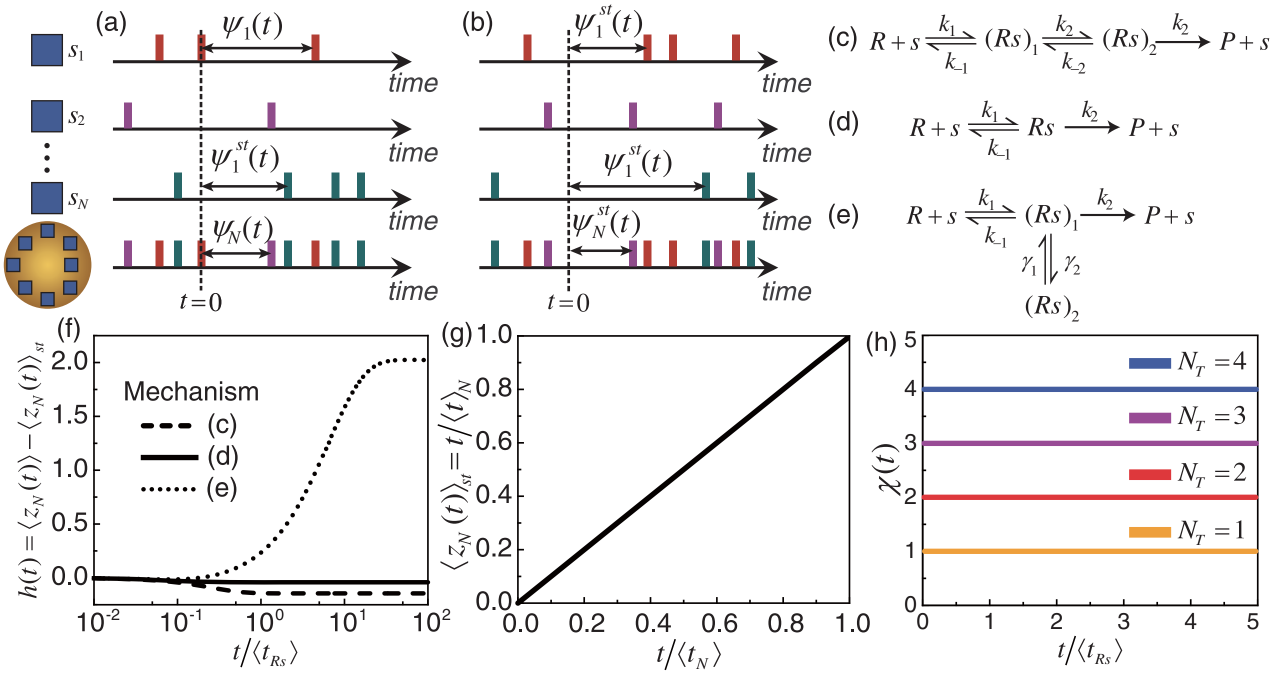

FIG. 1. (a),(b) Schematic representation of the time series of reaction events occurring at multiple catalytic sites (a) the typical nonstationary and (b) the stationary initial conditions. The bars and dashed line represent time points at which reaction events take place and the time at which our observation begins, respectively. $\psi_1(t)$ represents the probability density that a catalytic reaction is completed at time t at a single site, given that the catalytic reaction begins at time 0; $\psi_1^{\mathrm{st}}(t)$ represents the probability density that a catalytic reaction is completed at another catalytic site at time t. (c),(d),(e) Three mechanisms of a catalytic reaction: k_i and γ_i represent the rate coefficients of the elementary reaction processes. (f) Time dependence of $h(t)[\equiv\langle z_N(t)\rangle-\langle z_N(t)\rangle_{\mathrm{st}}]$ for mechanism (c),(d),(e). The value of the mean catalytic turnover time $\langle t_1\rangle$ at a single site is set to be $(5/11)\langle t_{Rs}\rangle$ where the mean lifetime $\langle t_{Rs}\rangle$ of Rs complex is chosen as the time unit. The value of the randomness parameter of the Rs lifetime depends on the mechanism: -0.5, 0, and 10 for mechanism (c), (d), and (e), respectively. (f) $\langle z_N(t)\rangle$ ($\langle z_N(t)\rangle_{\mathrm{st}}$) designates the mean turnover number under the typical nonstationary (stationary) initial condition. (g) Time dependence of $\langle z_N(t)\rangle_{\mathrm{st}}$. (h) Time dependence of $\chi(t)$ defined in Eq. (1). The value of $\chi(t)$ is the same as the number of catalytic sites at all times for any catalytic reaction mechanism.

interval $(0,t)$ is decomposable into two terms, i.e., $\langle z_N(t)\rangle=t/\langle t_N\rangle+h(t)$ where $\langle t_N\rangle$ denotes the mean turnover time of our system with N catalytic sites (see Supplemental Material [57] for the derivation). $t/\langle t_N\rangle(\equiv\langle z_N(t)\rangle_{\mathrm{st}})$ [58] is the same as the mean catalytic turnover number of N catalytic sites under the stationary initial condition [59], shown in Fig. 1(b). On the other hand, $h(t)$ is nonlinear in time, whose value approaches a constant at long times. The time profile of $h(t)$ is determined by the catalytic reaction mechanism and the shape of the CTD of an individual catalytic site (see Supplemental Material [57]), but is independent of the number of catalytic sites [see Fig. 1(f)]. As shown later, $\langle t_N\rangle$ is given by $\langle t_1\rangle/N$ so that $\langle z_N(t)\rangle_{\mathrm{st}}$ is directly proportional to the number N of catalytic sites. Likewise, the variance of $z_N(t)$ under the stationary initial condition is directly proportional to N, i.e., $\langle\delta z_N^2(t)\rangle_{\mathrm{st}}=N\langle\delta z_1^2(t)\rangle_{\mathrm{st}}$. However, it is difficult to estimate N separately from $\langle t_1\rangle$ and $\langle\delta z_1^2(t)\rangle_{\mathrm{st}}$ using currently available methods. Here, we report that the number of catalytic sites can be estimated by the following measure [see Fig. 1(h) and Supplemental Material [57]],

$$\chi(t)=\frac{2\int_0^t d\tau\langle z_N(\tau)\rangle_{\mathrm{st}}[h(t-\tau)-h(\tau)]}{\int_0^t d\tau[\langle\delta z_N^2(\tau)\rangle-\langle z_N(\tau)\rangle]-2\int_0^t d\tau\langle z_N(t-\tau)\rangle h(\tau)+\int_0^t d\tau h(\tau)^2},\tag{1}$$

where $\langle\delta z_N^2(t)\rangle$ denotes the variance in the turnover number under the typical nonstationary initial condition (see Supplemental Material [57]). The value of $\chi(t)$ is the same as the number of catalytic sites at all times for any catalytic mechanism when the catalytic turnover at each site is a renewal process [59] [see Fig. 1(h)]. Even when a catalytic reaction occurring at each site is a nonrenewal process caused by temporal activity fluctuation, turnover-event counting statistics resumes renewal statistics at long times [41,56,60], and the long-time limit of $\chi(t)$ can serve as a measure of N. This is also the case for catalytic sites with weak quenched disorder in catalytic activity.

Let us now turn our attention to the CTD, $\psi_N(t)$, of a system of N catalytic sites under the typical nonstationary initial condition. $\psi_N(t)$ is related to reaction-free probability $S_N(t)$, by $\psi_N(t) = -\partial S_N(t)/\partial t$ or $S_N(t) = 1 - \int_0^t d\tau\psi_N(\tau)$; $S_N(t)$ designates the probability that none of N catalytic sites undergoes a catalytic turnover as of time t, given that a catalytic reaction event begins at time 0 at a catalytic site (see Fig. 1). The first two moments, $\langle t_N\rangle$ and $\langle t_N^2\rangle$, of $\psi_N(t)$ are related to $S_N(t)$ by

$$\langle t_N\rangle = \int_0^\infty dt S_N(t)\,, \tag{2a}$$

$$\langle t_N^2\rangle = 2\int_0^\infty dt t S_N(t). \tag{2b}$$

From the first two moments, we can compute the randomness parameter R_N, defined by $R_N = (\langle t_N^2\rangle - \langle t_N\rangle^2)/\langle t_N\rangle^2 - 1$. R_N vanishes for a Poisson process; R_N is negative for a sub-Poisson process, such as multistep reaction processes [Fig. 1(c)], and positive for a super-Poisson process, such as multichannel reaction processes [Fig. 1(e)]. We note that the term "randomness parameter" is used to designate $R_N + 1$ in Refs. [42,54] or used with a different meaning [61].

When the catalytic reactions occurring at all sites are statistically equivalent, independent processes, the CTD of N sites can be obtained from $S_N^{\mathrm{hom}}(t)$ [62],

$$S_N^{\mathrm{hom}}(t) = S_1(t) S_1^{\mathrm{st}}(t)^{N-1}, \tag{3}$$

where $S_1(t)$ and $S_1^{\mathrm{st}}(t)$ denote, respectively, the reaction-free probability of the single catalytic site that begins a catalytic reaction event at time 0 and the reaction-free probability of each of the remaining $N-1$ sites in the steady state (see Fig. 1). It is known that $S_1^{\mathrm{st}}(t)$ is related to $S_1(t)$ by $S_1^{\mathrm{st}}(t) = \int_t^\infty d\tau S_1(\tau)/\int_0^\infty d\tau S_1(\tau)$ [59,63]. It is also known how $S_1(t)$ is dependent on the catalytic reaction mechanism and dynamics of the elementary processes constituting the catalytic reaction [49,50,52,53]. For three different catalytic reaction schemes shown in Figs. 1(c)–1(e), analytic expressions of $S_1(t)$ can be obtained (see Supplemental Material [57]). Then, from Eq. (3), the CTD of the homogenous nanocatalytic system, defined by $\psi_N^{\mathrm{hom}}(t) = -\partial_t S_N^{\mathrm{hom}}(t)$, can be obtained as $\psi_N^{\mathrm{hom}}(t) = [\psi_1(t)S_1^{\mathrm{st}}(t) + (N-1)\psi_1^{\mathrm{st}}(t)S_1(t)][S_1^{\mathrm{st}}(t)]^{N-2}$, with $\psi_1(t) = -\partial_t S_1(t)$ and $\psi_1^{\mathrm{st}}(t) = -\partial_t S_1^{\mathrm{st}}(t) = S_1(t)/\langle t_1\rangle$. We note here that the CTD differs from the first turnover time distribution (FTD), $\psi_N^{\mathrm{sync}}(t|1)[= N\psi_1(t)S_1(t)^{N-1}]$, of N catalytic sites under the synchronized initial condition [48], although the FTD is sometimes mistakenly assumed to be the same as the CTD in the literature [64].

For the homogeneous catalyst, the mean catalytic turnover time $\langle t_N\rangle$ of N site is given by [62]

$$\langle t_N\rangle = \langle t_1\rangle/N, \tag{3a}$$

where $\langle t_1\rangle$ denotes the mean turnover time of a single catalytic site [Fig. 2(b)]. This result can be obtained by noting Eq. (3) can be written as $S_N(t) = -(\langle t_1\rangle/N)\partial_t S_1^{st}(t)^N$ and by substituting this result into Eq. (2a). Note that $N\langle t_N\rangle$ is given by $\langle t_1\rangle$, independent of N [see Fig 2(b)]. For our models considered in Fig 2(a), $\langle t_1\rangle$ is linear in the inverse reactant concentration C_R^{-1}.

In comparison, the randomness parameter R_N of N catalytic sites is not so simply related to R_1 of a single catalytic site; instead, R_N is related to the entire time profile of $S_1^{\mathrm{st}}(t)$:

$$R_N = 2\left[\langle t_N\rangle^{-1}\int_0^\infty dt S_1^{st}(t)^N - 1\right] \tag{3b}$$

(see Supplemental Material [57]). For a homogeneous catalytic system, R_N is a single-peaked nonmonotonic function of reactant concentration [55], and its value approaches zero as the number of catalytic sites grows large or in the low-reactant concentration limit [54] [see Fig 2(c) and Supplemental Material for details [57]].

The CTD of multiple catalytic sites has a finite value in the short-time limit, $\langle t_N\rangle\lim_{t\to 0}\psi_N^{\mathrm{hom}}(t) = 1 - N^{-1}$, whereas the short-time limit value of the CTD of a single catalytic site vanishes [see inset of Fig. 2(c)]. The finite value of $\psi_N^{\mathrm{hom}}(0)$ emerges from the N-1 catalytic sites undergoing the stationary reaction processes, excluding the catalytic site that begins a catalytic reaction at time 0 [see Fig. 1(a)]. For a system with heterogeneous catalytic sites as well, the short-time limit value of the CTD is closely related to the total number of catalytic sites (see Supplemental Material [57]).

Let us now consider a nanocatalytic system composed of two different types, say A and B, of catalytic sites with differing catalytic activities [Fig. 2(d)]. This is the simplest model of a nanocatalyst composed of catalytic sites with heterogeneous catalytic activity [26,65,66]. For this model, the reaction-free probability under the typical nonstationary initial condition is given by

$$\begin{aligned} S_{N_A,N_B}^{(2)}(t) = {}& S_{1,A}(t)S_{1,A}^{\mathrm{st}}(t)^{N_A-1}S_{1,B}^{\mathrm{st}}(t)^{N_B}p_A \\ & + S_{1,B}(t)S_{1,B}^{\mathrm{st}}(t)^{N_B-1}S_{1,A}^{\mathrm{st}}(t)^{N_A}p_B, \end{aligned} \tag{4}$$

where the subscripts designate the type of catalytic site (see Supplemental Material [57]); $S_{1,A(B)}(t)$ is the reaction-free probability of a single catalytic site of the $A(B)$ variety. $S_{1,A(B)}^{\mathrm{st}}(t)$ is defined as $S_{1,A(B)}^{\mathrm{st}}(t) = \int_t^\infty d\tau S_{1,A(B)}(\tau)/\int_0^\infty d\tau S_{1,A(B)}(\tau)$. In Eq. (4), $p_{A(B)}$ denotes the probability that we observe a catalytic reaction occurring at type-$A(B)$

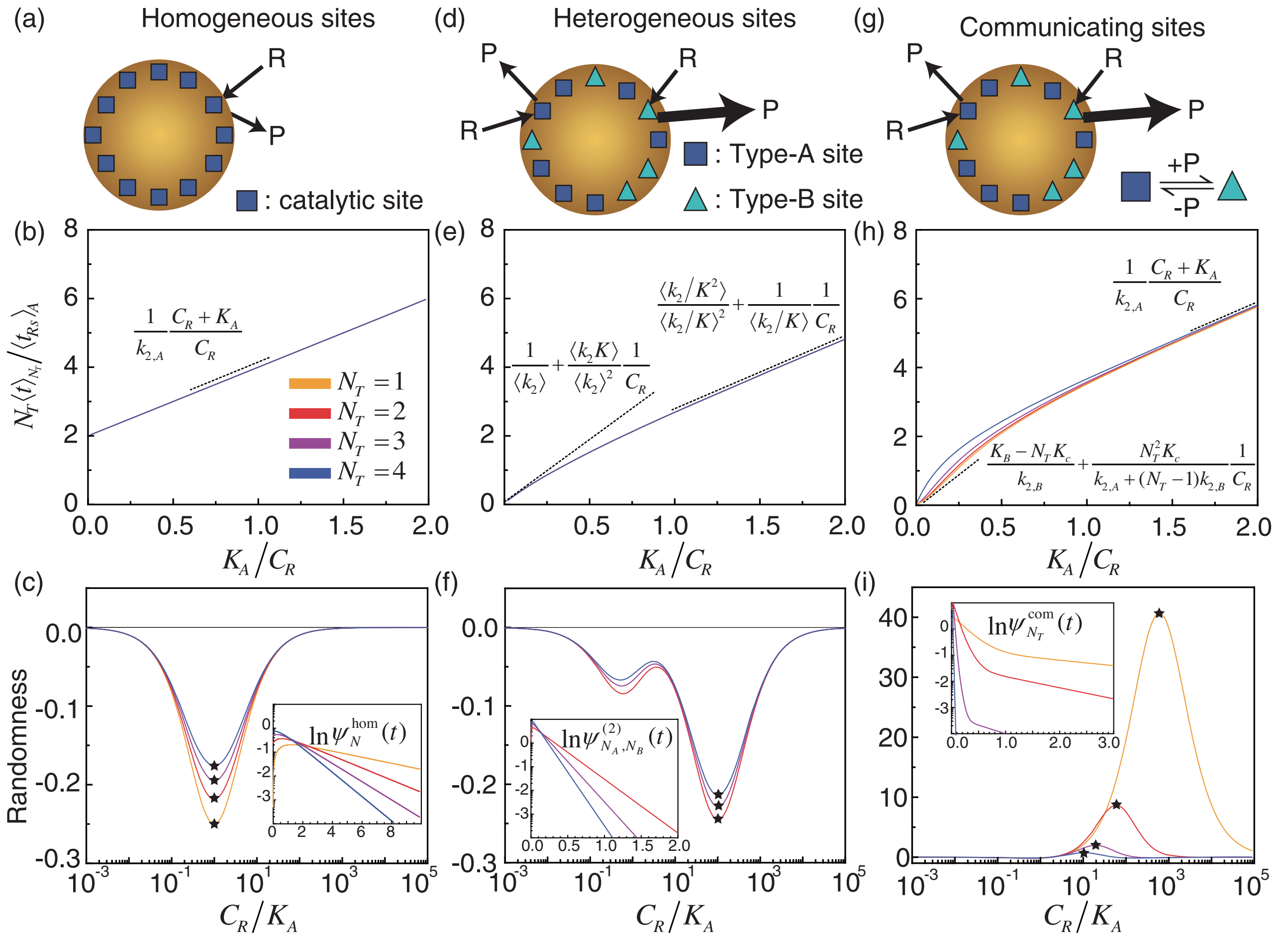

FIG. 2. (a),(d),(g) Schematic representation of nanocatalytic systems of (a) homogeneous, (d) heterogeneous, and (g) communicating sites. (b),(e),(h) Mean turnover time $\langle t\rangle_{N_T}$ multiplied by the total number of catalytic sites N_T scaled by Rs complex lifetime $\langle t_{Rs}\rangle_A$ of type-A catalytic site plotted against the inverse reactant concentration C_R^{-1} scaled by K_A. $K_{A(B)}$ denotes the reactant concentration at which the mean turnover time of a type $A(B)$ site is twice the turnover time in the high reactant concentration limit. (c),(f), (i) Dependence of randomness parameter on the reactant concentration. (Inset) the natural log of the CTD, $\ln\psi_N(t)$, plotted against $t/\langle t_{Rs}\rangle_A$ at concentrations denoted by the stars. The values of parameters used are $K_B/K_A = 10^2$, $N_B/N_A = 1$, $\langle t_{Rs}\rangle_B/\langle t_{Rs}\rangle_A = 10^{-2}$, $p_{2,A} = p_{2,B} = 0.5$ $\mathrm{K}_c/K_A = 5$, $\langle\delta t_{Rs}^2\rangle/\langle t_{Rs}\rangle^2 = 1$, where $N_{A(B)}$, $\langle t_{Rs}\rangle_{A(B)}$, and $p_{2,A(B)}$ denote the number of catalytic sites, the mean lifetime of the Rs complex, and the probability of catalytic reaction per formation of the Rs complex at type $A(B)$ site.

catalytic sites, defined by $p_{A(B)} = N_{A(B)}\langle t_1\rangle_{A(B)}^{-1}/(N_A\langle t_1\rangle_A^{-1} + N_B\langle t_1\rangle_B^{-1})$. Substituting Eq. (4) into Eq. (2a), we obtain the analytic expression of the mean turnover time as

$$\langle t_{N_A,N_B}\rangle = (N_A\langle t_1\rangle_A^{-1} + N_B\langle t_1\rangle_B^{-1})^{-1}. \tag{4a}$$

Equation (4a) indicates that the mean turnover rate, $\langle t_{N_A,N_B}\rangle^{-1}$ is given by the sum of the mean turnover rate at every site in the nanocatalytic system. Note that, for the heterogeneous model [Fig. 2(d)] as well, $(N_A + N_B)\langle t_{N_A,N_B}\rangle$ is independent of the total number of catalytic sites if N_A/N_B has a constant value. In contrast to the homogeneous model, however, the mean catalytic turnover time is no longer linear in C_R^{-1} [Fig. 2(e)].

We find the randomness parameter of the nanocatalyst with two types of catalytic sites to be

$$R_{N_A,N_B} = 2[\langle t_{N_A,N_B}\rangle^{-1}\int_0^\infty dt S_{1,A}^{\text{st}}(t)^{N_A} S_{1,B}^{\text{st}}(t)^{N_B} - 1]. \tag{4b}$$

This result is easily obtainable by noting that Eq. (4) can be rewritten as $S_{N_A,N_B}^{(2)}(t) = -\langle t_{N_A,N_B}\rangle\partial_t[S_{1,A}^{\text{st}}(t)^{N_A} S_{1,B}^{\text{st}}(t)^{N_B}]$ and substituting this into Eq. (2). For the heterogeneous model [Fig. 2(d)], the randomness parameter can have a more complex dependence on the reactant concentration than the randomness parameter of the homogeneous model [Fig. 2(f)]. Our results can be easily extended to a nanocatalytic system composed of more than two types of catalytic sites (see Supplemental Material for more details [57]).

So far, we have considered nanocatalytic systems in which catalytic sites do not communicate with each other. However, product molecules produced at one site can diffuse and interact with other sites to alter catalytic activity, exemplified by the spillover effect [67–69]. This catalytic communication increases with reactant concentration, because the product creation rate increases with the reactant concentration, which was observed in nanocatalytic systems [14,28,30,55,66,70].

Let us designate catalytic sites whose activity is affected by catalytic communication as type B and the unaffected sites as type A. Since the probability P_A of being a type-A site must decrease with the product concentration that increases with reactant concentration C_R, we model $P_A(=1-P_B)$ by $P_A = K_c/(K_c + C_R)$ with K_c being the reactant concentration at which $P_A = P_B = 1/2$. Then, the number N_A of type-A catalytic sites has a binominal distribution, ${}_{N_T}C_{N_A} P_A^{N_A}(1-P_A)^{N_T-N_A}$, where N_T and ${}_{N_T}C_{N_A}$, respectively, denote the total number of sites and $N_T!/N_A!(N_T-N_A)!$. For this system, the reaction-free probability is given by

$$S^{\mathrm{com}}_{N_T}(t) = \sum_{N_A=0}^{N_T} {}_{N_T}C_{N_A} P_A^{N_A}(1-P_A)^{N_T-N_A} S^{(2)}_{N_A,N_T-N_A}(t), \qquad (5)$$

where $S^{(2)}_{N_A,N_T-N_A}(t)$ is given in Eq. (4). Substituting Eq. (5) into Eq. (2a), we obtain the mean turnover time of the nanocatalyst with communicating sites:

$$\langle t_{N_T}\rangle^{\mathrm{com}} = \int_0^\infty (P_A e^{-t/\langle t_1\rangle_A} + P_B e^{-t/\langle t_1\rangle_B})^{N_T} dt. \qquad (5a)$$

Equation (5a) reduces to $\langle t_{N_T}\rangle^{\mathrm{com}} \cong N_T^{-1}\langle t_1\rangle_A$ $(\cong N_T^{-1}\langle t_1\rangle_B)$ when $C_R \ll K_c (C_R \gg K_c)$. Unlike the two communication-free types, the nanocatalyst with catalytic communication has $N_T\langle t_{N_T}\rangle^{\mathrm{com}}$ that is dependent on N_T [Fig. 2(h)]. $N_T\langle t_{N_T}\rangle^{\mathrm{com}}$ is a more complex function of the reactant concentration than $\langle t_1\rangle_{A(B)}$, but it is still a monotonically decreasing function of reactant concentration so long as catalytic communication increases the catalytic activity [28]. If catalytic communication decreases the activity, the $N_T\langle t_{N_T}\rangle^{\mathrm{com}}$ may increase with reactant concentration (see Supplemental Material, Fig. S1 [57]).

Catalytic communication has dramatic effects on the randomness parameter. For our model of the nanocatalytic system with communicating sites, we obtain the following expression of the randomness parameter,

$$R^{\mathrm{com}}_{N_T} = \sum_{N_A=0}^{N_T} {}_{N_T}C_{N_A} P_A^{N_A}(1-P_A)^{N_T-N_A} \frac{\langle t^2_{N_A,N_T-N_A}\rangle}{(\langle t_{N_T}\rangle^{\mathrm{com}})^2} - 2, \qquad (5b)$$

where $\langle t^2_{N_A,N_B}\rangle$ is given by $\langle t^2_{N_A,N_B}\rangle = (R_{N_A,N_B}+2)\langle t_{N_A,N_B}\rangle^2$ with $\langle t_{N_A,N_B}\rangle$ and R_{N_A,N_B} being given in Eqs. (4a) and (4b), respectively. The randomness parameter of communicating sites can have a qualitatively different reactant concentration dependence than the randomness parameter of a homogeneous or heterogeneous nanocatalytic system. The randomness parameter of the communicating catalytic sites can become a positive, nonmonotonic function of the reactant concentration even if the randomness parameter of the noninteracting catalytic sites is a negative [Fig. 2(i)]. This striking surge in the randomness parameter value in the intermediate reactant concentration regime occurs because the randomness originating from the binomial distribution of the two types of catalytic sites reaches its maximum in the intermediate reactant concentration regime. This positive, nonmonotonic behavior in the randomness parameter is experimentally observed in the nanocatalytic system [55], in which the catalytic sites communicate through the adsorbate-induced dynamic surface restructuring mechanism [71]. The dependence of the randomness parameter on the reactant concentration can provide us with information about the heterogeneity in catalytic activity and the presence of catalytic communication (see Supplemental Material, Fig. S2).

We note that the CTD of communicating sites has a qualitatively different shape from the CTD of the heterogeneous sites. For example, when the CTD of each individual site has an exponential tail [Fig. 2(c)], the CTD of the heterogeneous sites also has an exponential tail [Fig. 2(f)], but the CTD of communicating sites has a nonexponential tail [Fig. 2(i)], which originates from fluctuation in the number of the communication-influenced sites. When we neglect this population fluctuation of communicating sites and account for only the maximum term in Eq. (8), the approximate CTD of communicating catalytic sites has an exponential tail.

Finally, let us consider a nanocatalytic system consisting of subsystems with a distributed number of catalytic sites. For this system, the value of the randomness parameter in the low-reactant concentration limit is given by $\lim_{C_R\to 0} R = 2(\langle N^{-2}\rangle/\langle N^{-1}\rangle^2 - 1)$ (see Supplemental Material [57]), which does not vanish whenever N is a random variable. In general, a finite value of $\lim_{C_R\to 0} R$ signifies heterogeneity in some parameters of nanocatalytic systems [49,50].

We presented stochastic kinetics for nanocatalytic systems. A new experimental measure of the number of catalytic sites is proposed in Eq. (1). Its long-time limit value corresponds to the number of catalytic sites in a nanocatalytic system regardless of the mechanism and dynamics of catalytic reactions. We also showed how the CTD of a nanocatalyst is related to the mechanism and dynamics of a catalytic reaction through the single-site CTD. By considering three different types of nanocatalytic systems, we investigated the dependence of the mean, the randomness parameter, and the CTD on the reactant concentration, the heterogeneity of catalytic activity, and communication among catalytic sites. This work enables quantitative explanation of stochastic kinetics of nanocatalytic systems and can be extended to investigate the stochastic dynamics of other physicochemical processes occurring in small systems.

This work was supported by the Creative Research Initiative Project program (2015R1A3A2066497) funded by the national research foundation (NRF) of Korea and the NRF grant (MSIT) (No. 2020R1A5A1018052) funded by the Korean government. P. C. acknowledges support from the U.S. Army Research Office (W911NF-17-1-0590) and the Department of Energy, the Office of Science, Basic Energy Sciences, the Catalysis Science Program (DE-SC0004911).

---

[*] pc252@cornell.edu
[†] jaeyoung@cau.ac.kr

[1] L. N. Lewis and N. Lewis, J. Am. Chem. Soc. **108**, 7228 (1986).
[2] M. Beller, H. Fischer, K. Kühlein, C.-P. Reisinger, and W. A. Herrmann, J. Organomet. Chem. **520**, 257 (1996).
[3] W. Yu, M. Liu, H. Liu, X. Ma, and Z. Liu, J. Colloid Interface Sci. **208**, 439 (1998).
[4] A. Roucoux, J. Schulz, and H. Patin, Chem. Rev. **102**, 3757 (2002).
[5] M. Tamura and H. Fujihara, J. Am. Chem. Soc. **125**, 15742 (2003).
[6] M. Buil, M. A. Esteruelas, S. Niembro, M. Oliván, L. Orzechowski, C. Pelayo, and A. Vallribera, Organometallics 2010) 4375 ,29).
[7] V. Polshettiwar, R. Luque, A. Fihri, H. Zhu, M. Bouhrara, and J.-M. Basset, Chem. Rev. **111**, 3036 (2011).
[8] C. L. Hui, X. G. Li, and I.-M. Hsing, Electrochim. Acta **51**, 711 (2005).
[9] V. P. Ananikov, N. V. Orlov, and I. P. Beletskaya, Organometallics **26**, 740 (2007).
[10] A. Y. Khodakov, W. Chu, and P. Fongarland, Chem. Rev. **107**, 1692 (2007).
[11] H.-S. Oh, J.-G. Oh, Y.-G. Hong, and H. Kim, Electrochim. Acta **52**, 7278 (2007).
[12] A. Z. Moshfegh, J. Phys. D **42**, 233001 (2009).
[13] P. S. Vengsarkar, R. Xu, and C. B. Roberts, Ind. Eng. Chem. Res. **54**, 11814 (2015).
[14] M. Hesari, X. Mao, and P. Chen, J. Am. Chem. Soc. **140**, 6729 (2018).
[15] Y. Liu, X. Chen, J. Li, and C. Burda, Chemosphere **61**, 11 (2005).
[16] E. Garrido-Ramírez, B. K. G. Theng, and M. L. Mora, Appl. Clay Sci. **47**, 182 (2010).
[17] S. Chaturvedi, P. N. Dave, and N. K. Shah, J. Saudi Chem. Soc. **16**, 307 (2012).
[18] R. M. Mohamed, D. L. McKinney, and W. M. Sigmund, Mater. Sci. Eng. R **73**, 1 (2012).
[19] T. F. Jaramillo, K. P. Jørgensen, J. Bonde, J. H. Nielsen, S. Horch, and I. Chorkendorff, Science **317**, 100 (2007).
[20] L. P. Hansen, Q. M. Ramasse, C. Kisielowski, M. Brorson, E. Johnson, H. Topsøe, and S. Helveg, Angew. Chem. Int. Ed. **50**, 10153 (2011).
[21] H. L. Xin, J. A. Mundy, Z. Liu, R. Cabezas, R. Hovden, L. F. Kourkoutis, J. Zhang, N. P. Subramanian, R. Makharia, F. T. Wagner, and D. A. Muller, Nano Lett. **12**, 490 (2012).
[22] B. H. Kim, J. Heo, S. Kim, C. F. Reboul, H. Chun, D. Kang, H. Bae, H. Hyun, J. Lim, H. Lee, B. Han, T. Hyeon, A. P. Alivisatos, P. Ercius, H. Elmlund, and J. Park, Science **368**, 60 (2020).
[23] W. Xu, J. S. Kong, Y.-T. E. Yeh, and P. Chen, Nat. Mater. **7**, 992 (2008).
[24] W. Xu, J. S. Kong, and P. Chen, J. Phys. Chem. C **113**, 2393 (2009).
[25] W. Xu, H. Shen, Y. J. Kim, X. Zhou, G. Liu, J. Park, and P. Chen, Nano Lett. **9**, 3968 (2009).
[26] P. Chen, X. Zhou, N. M. Andoy, K.-S. Han, E. Choudhary, N. Zou, G. Chen, and H. Shen, Chem. Soc. Rev. **43**, 1107 (2014).
[27] T. Chen, Y. Zhang, and W. Xu, J. Am. Chem. Soc. **138**, 12414 (2016).
[28] N. Zou, X. Zhou, G. Chen, N. M. Andoy, W. Jung, G. Liu, and P. Chen, Nat. Chem. **10**, 607 (2018).
[29] K. Naito, T. Tachikawa, M. Fujitsuka, and T. Majima, J. Am. Chem. Soc. **131**, 934 (2009).
[30] B. Dong, Y. Pei, F. Zhao, T. W. Goh, Z. Qi, C. Xiao, K. Chen, W. Huang, and N. Fang, Nat. Catal. **1**, 135 (2018).
[31] M. B. J. Roeffaers, B. F. Sels, H. Uji-i, F. C. De Schryver, P. A. Jacobs, D. E. De Vos, and J. Hofkens, Nature (London) **439**, 572 (2006).
[32] M. B. J. Roeffaers, G. De Cremer, H. Uji-i, B. Muls, B. F. Sels, P. A. Jacobs, F. C. De Schryver, D. E. De Vos, and J. Hofkens, Proc. Natl. Acad. Sci. U.S.A. **104**, 12603 (2007).
[33] M. B. J. Roeffaers, B. F. Sels, H. Uji-i, B. Blanpain, P. L'hoëst, P. A. Jacobs, F. C. De Schryver, J. Hofkens, and D. E. De Vos, Angew. Chem. **119**, 1736 (2007).
[34] M. H. F. Kox, E. Stavitski, J. C. Groen, J. Pérez-Ramírez, F. Kapteijn, and B. M. Weckhuysen, Chem. Eur. J. **14**, 1718 (2008).
[35] V. M. Martínez, G. D. Cremer, M. B. J. Roeffaers, M. Sliwa, M. Baruah, D. E. De Vos, J. Hofkens, and B. F. Sels, J. Am. Chem. Soc. **130**, 13192 (2008).
[36] G. De Cremer, M. B. J. Roeffaers, E. Bartholomeeusen, K. Lin, P. Dedecker, P. P. Pescarmona, P. A. Jacobs, D. E. De Vos, J. Hofkens, and B. F. Sels, Angew. Chem. **122**, 920 (2010).
[37] E. Stavitski, M. H. F. Kox, and B. M. Weckhuysen, Chem. Eur. J. **13**, 7057 (2007).
[38] L. Karwacki, M. H. F. Kox, D. A. Matthijs de Winter, M. R. Drury, J. D. Meeldijk, E. Stavitski, W. Schmidt, M. Mertens, P. Cubillas, N. John, A. Chan, N. Kahn, S. R. Bare, M. Anderson, J. Kornatowski, and B. M. Weckhuysen, Nat. Mater. **8**, 959 (2009).
[39] B. M. Weckhuysen, Angew. Chem. Int. Ed. **48**, 4910 (2009).
[40] R. Ye, X. Mao, X. Sun, and P. Chen, ACS Catal. **9**, 1985 (2019).
[41] J. Sung and R. J. Silbey, Chem. Phys. Lett. **415**, 10 (2005).
[42] B. P. English, W. Min, A. M. Van Oijen, K. T. Lee, G. Luo, H. Sun, B. J. Cherayil, S. C. Kou, and X. S. Xie, Nat. Chem. Biol. **2**, 87 (2006).

[43] I. Chung, J. B. Witkoskie, J. Cao, and M. G. Bawendi, Phys. Rev. E **73**, 011106 (2006).

[44] G. Margolin, V. Protasenko, M. Kuno, and E. Barkai, J. Phys. Chem. B **110**, 19053 (2006).

[45] I. Chung, J. B. Witkoskie, J. P. Zimmer, J. Cao, and M. G. Bawendi, Phys. Rev. B **75**, 045311 (2007).

[46] E. Barkai, Y. Jung, and R. Silbey, Annu. Rev. Phys. Chem. **55**, 457 (2004).

[47] J. Sung and R. J. Silbey, Phys. Rev. Lett. **91**, 160601 (2003).

[48] Y. R. Lim, S. J. Park, B. J. Park, J. Cao, R. J. Silbey, and J. Sung, J. Chem. Theory Comput. **8**, 1415 (2012).

[49] W. Jung, S. Yang, and J. Sung, J. Phys. Chem. B **114**, 9840 (2010).

[50] S. Yang, J. Cao, R. J. Silbey, and J. Sung, Biophys. J. **101**, 519 (2011).

[51] J. Cao and R. J. Silbey, J. Phys. Chem. B **112**, 12867 (2008).

[52] J. R. Moffitt and C. Bustamante, FEBS J. **281**, 498 (2014).

[53] A. C. Barato and U. Seifert, Phys. Rev. Lett. **115**, 188103 (2015).

[54] S. Chaudhury, D. Singh, and A. B. Kolomeisky, J. Phys. Chem. Lett. **11**, 2330 (2020).

[55] W. Xu, J. S. Kong, and P. Chen, Phys. Chem. Chem. Phys. **11**, 2767 (2009).

[56] J. Cao, J. Phys. Chem. B **110**, 19040 (2006).

[57] See Supplemental Material at http://link.aps.org/supplemental/10.1103/PhysRevLett.126.126001 for derivation and supplemental figures.

[58] Throughout this Letter, subscript or superscript “st” is used to represent a quantity under the stationary initial condition.

[59] D. R. Cox, *Renewal Theory* (Methuen and Co, London, 1962).

[60] S. J. Park, S. Song, I.-C. Jeong, H. R. Koh, J.-H. Kim, and J. Sung, J. Phys. Chem. Lett. **8**, 3152 (2017).

[61] A. B. Kolomeisky and M. E. Fisher, Annu. Rev. Phys. Chem. **58**, 675 (2007).

[62] I.-C. Jeong, S. Song, D. Kim, S. J. Park, J.-H. Kim, and J. Sung, Phys. Rev. Lett. **119**, 099801 (2017).

[63] J. Tunaley, J. Stat. Phys. **15**, 167 (1976).

[64] D. Singh and S. Chaudhury, Phys. Chem. Chem. Phys. **19**, 8889 (2017).

[65] T. Tachikawa, S. Yamashita, and T. Majima, J. Am. Chem. Soc. **133**, 7197 (2011).

[66] T. Chen, S. Chen, Y. Zhang, Y. Qi, Y. Zhao, W. Xu, and J. Zeng, Angew. Chem. **128**, 1871 (2016).

[67] S. S. Collins, M. Cittadini, C. Pecharromán, A. Martucci, and P. Mulvaney, ACS Nano **9**, 7846 (2015).

[68] W. Karim, C. Spreafico, A. Kleibert, J. Gobrecht, J. VandeVondele, Y. Ekinci, and J. A. van Bokhoven, Nature (London) **541**, 68 (2017).

[69] W. C. Conner, Jr. and J. L. Falconer, Chem. Rev. **95**, 759 (1995).

[70] X. Zhou, W. Xu, G. Liu, D. Panda, and P. Chen, J. Am. Chem. Soc. **132**, 138 (2010).

[71] F. Tao, M. E. Grass, Y. Zhang, D. R. Butcher, J. R. Renzas, Z. Liu, J. Y. Chung, B. S. Mun, M. Salmeron, and G. A. Somorjai, Science **322**, 932 (2008).