Comment on "Nonrenewal Statistics in the Catalytic Activity of Enzyme Molecules at Mesoscopic Concentrations"

A superposition of independent, renewal processes forms a nonrenewal process with serial correlations among time intervals between successive events [1,2], which is confirmed for the enzyme process in Ref. [3]. The authors of Ref. [3] further claimed that the mean catalytic rate of a system of enzymes at mesoscopic concentration does not obey the Michaelis-Menten (MM) equation, even if the MM equation is correct for a single enzyme and for a macroscopic number of enzymes [4–6]. However, in fact, the MM equation provides the correct steady-state rate for the model in Ref. [3] regardless of enzyme number. Utilizing the relationship between the mean and characteristic function, $d\langle N_P(t)\rangle_{N_E}/dt = d/dt[(\partial/\partial s_2)G(s_1=1,s_2,t)|_{s_2=1}]$ with $G(s_1,s_2,t)$ given in Eq. (4) of Ref. [3], one easily recovers the MM equation in the steady state.

It is known in enzyme kinetics that the MM equation does not hold for a macroscopic enzyme system unless the system is in the steady state. The authors of Ref. [3] obtained the result inconsistent with the MM equation because they investigated the enzyme system in a nonstationary state, not because they investigated a mesoscopic system. For example, Eq. (7) in Ref. [3] represents the probability density of time elapsed during the very first enzymatic turnover in N enzyme system under the synchronized initial condition [Fig. 1(a)], under which all the enzymes in the system synchronously start catalytic reactions at time 0. The authors showed that the first moment of Eq. (7) in Ref. [3] does not satisfy the MM equation, which is expected because the equation is not for enzymes in the steady state.

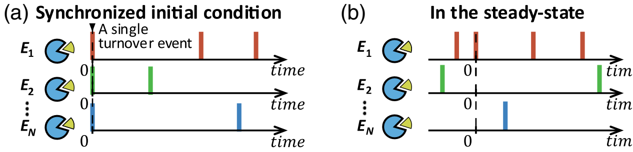

FIG. 1. A system of N enzymes (a) under the synchronized initial condition and (b) in the steady state.

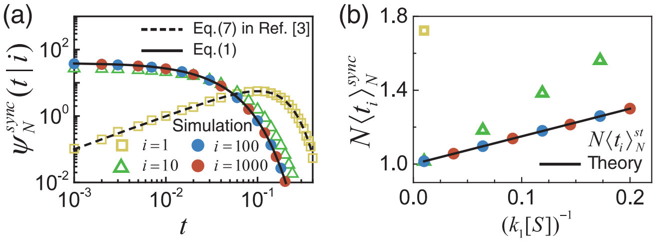

FIG. 2. Comparison between theory and simulation. (a) $\psi_N^{\mathrm{sync}}(t|i)$ (b) $\langle t_i\rangle_N^{\mathrm{sync}}[=\int_0^\infty dt\psi_N^{\mathrm{sync}}(t|i)t]$. $N=100$. The values of other parameters are the same as those used in Ref. [3].

The correct turnover time distribution, $\psi_N^{st}(t)$, for a system of N enzymes in the steady state, shown in Fig. 1(b), is given by $\psi_N^{st}(t) = -\partial S_N(t)/\partial t$ where $S_N(t)$ is the probability that no enzymes in the steady state have completed a catalytic turnover during time t, since an enzyme, say E_i, in the system completed the last catalytic turnover event at time 0. $S_N(t)$ can be factorized into $S_N(t) = S_1(t)[S_1^{st}(t)]^{N-1}$ where $S_1(t)$ and $[S_1^{st}(t)]^{N-1}$ denote, respectively, the probability that enzyme E_i has not completed another catalytic turnover until time t and the probability that none of the remaining $N-1$ enzymes have completed a catalytic turnover event until time t, since E_1 completed the last catalytic turnover at time 0. $S_1(t)$ and $S_1^{st}(t)$ are given by $S_1(t) = \int_t^\infty d\tau\psi_1(\tau)$ and $S_1^{st}(t) = \int_t^\infty d\tau\psi_1^{st}(\tau)$, where $\psi_1(t)$ and $\psi_1^{st}(t)$ denote the turnover time distribution of a single enzyme and $\psi_1^{st}(t) = S_1(t)/\int_0^\infty dtS_1(t)$, respectively [7,8]. For the enzyme model considered in Ref. [3], $\psi_1(t)$ is given by Eq. (3) in Ref. [9]. From these equations, we obtain

$$\psi_N^{st}(t) = \psi_1(t)[S_1^{st}(t)]^{N-1} + (N-1)\psi_1^{st}(t)S_1(t)[S_1^{st}(t)]^{N-2}. \tag{1}$$

The first moment $\langle t\rangle_N^{st}(\equiv\int_0^\infty dtt\psi_N^{st}(t))$ of $\psi_N^{st}(t)$ obeys the MM equation, if the mean enzymatic turnover time $\langle t\rangle_1$ of a single enzyme does [5,6], because $\langle t\rangle_N^{st} = \int_0^\infty dtS_N(t) = -\langle t\rangle_1\int_0^\infty dt[dS_1^{st}(t)/dt][S_1^{st}(t)]^{N-1} = \langle t\rangle_1/N$, which is in direct contradiction with Ref. [3].

In Fig. 2, a comparison between our theory and simulation is provided. It clearly shows that Eq. (1) gives the correct turnover time distribution of the system of N enzymes in the steady state; in contrast, Eq. (7) in Ref. [3] represents the probability density, $\psi_N^{\mathrm{sync}}(t|1)$, of the *first* turnover time in the system of N enzymes under the synchronized initial condition. Under this initial condition, the enzymatic turnover time distribution, $\psi_N^{\mathrm{sync}}(t|i)$, of the ith enzymatic turnover time, t_i, depends on the number, i, of the enzymatic turnover event, but in the large i limit, $\psi_N^{\mathrm{sync}}(t|i)$ approaches $\psi_N^{st}(t)$; therefore, the mean enzymatic turnover time under the synchronized condition approaches $\langle t\rangle_N^{st}$ in the large i limit, which satisfies the MM equation.

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