Modeling Stochastic Kinetics of Molecular Machines at Multiple Levels: From Molecules to Modules

Debashish Chowdhury*

Department of Physics, Indian Institute of Technology, Kanpur, India

Submitted August 23, 2012, and accepted for publication April 17, 2013.

*Correspondence: debch@iitk.ac.in

Supplementary information

A. Motor kinetics as wandering in a landscape

•*Motor kinetics as wandering in a mechano-chemical landscape*

Suppose the continuous variables $X_1 \equiv X$ and $X_2 \equiv \xi$ denote the mechanical and chemical states of the motor, respectively. The equation governing the time evolution of the probability density $\mathcal{P}(X_1, X_2, t)$ is

$$\frac{\partial \mathcal{P}(X_1, X_2, t)}{\partial t} = \sum_{i=1}^{2} \left[\frac{k_T}{\gamma_i} \frac{\partial^2 \mathcal{P}}{\partial X_i^2} - \frac{1}{\gamma_i} \frac{\partial}{\partial X_i} \left\{ \left(-\frac{\partial U}{\partial X_i} + F_i \right) \mathcal{P} \right\} \right] \tag{1}$$

where $U(X_1, X_2)$ is the potential of mean force and γ_i $(i = 1, 2)$ are the measures of dissipation. The two terms on the right hand side of eq.(1) account for the diffusion and drift of the motor in this landscape.

•*Motor kinetics as wandering in the time-dependent mechanical landscape*

Let X and σ denote the mechanical and chemical states of the motor, respectively, where the latter, unlike ξ, is a discrete variable. An arbitrary value of X is denoted by x while an arbitrary value of σ is denoted by μ. $W_{\mu \to \nu}(x)$ is the transition probability per unit time for the transition from μ to ν while the mechanical variable x remains frozen at the current instantaneous value x. The time evolution of the state of the motor is described by

$$\begin{aligned} \frac{\partial \mathcal{P}(x, \mu, t)}{\partial t} &= \left[\frac{k_B T}{\gamma} \frac{\partial^2 \mathcal{P}}{\partial x^2} - \frac{1}{\gamma} \frac{\partial}{\partial x} \left\{ \left(-\frac{\partial U}{\partial x} + F \right) \mathcal{P} \right\} \right] \\ &+ \sum_{\nu} \mathcal{P}(x, \nu) W_{\nu \to \mu}(x) - \sum_{\lambda} \mathcal{P}(x, \mu) W_{\mu \to \lambda}(x) \end{aligned} \tag{2}$$

which is a hybrid of Fokker-Planck and master equations. Note that there is no term in this equation which would correspond to a mixed mechano-chemical transition.

B. Motor kinetics as a jump process in a fully discrete mechano-chemical network

Let $P_\mu(i, t)$ be the probability of finding the motor at the discrete position labelled by i and in the discrete chemical state μ at time t. The symbol $k_\mu(i \to j)$ denotes a purely mechanical transition $i \to j$ while the chemical state μ remains unaltered. Similarly, $W_{\mu \to \nu}(i)$ denotes a purely chemical transition $\mu \to \nu$ while the mechanical state i remains frozen. Mixed mechano-chemical transitions that involve both the transitions $i \to j$ and $\mu \to \nu$ are denoted by the symbol $\omega_{\mu \to \nu}(i \to j)$.

Then, the master equation for $P_\mu(i, t)$ is given by

$$\begin{aligned} \frac{\partial P(i, \mu, t)}{\partial t} &= [\sum_{j \neq i} P(j, \mu, t) k_\mu(j \to i) - \sum_{j \neq i} P(i, \mu, t) k_\mu(i \to j)] \\ &+ [\sum_{\nu} P(i, \nu, t) W_{\nu \to \mu}(i) - \sum_{\lambda} P(i, \mu, t) W_{\mu \to \lambda}(i)] \end{aligned}$$

$$+ \quad [\sum_{j\neq i}\sum_{\nu} P(j,\nu,t)\omega_{\nu\to\mu}(j\to i) - \sum_{j\neq i}\sum_{\lambda} P(i,\mu,t)\omega_{\mu\to\lambda}(i\to j)] \tag{3}$$

where the terms enclosed by the three different brackets [.] correspond to the purely mechanical, purely chemical and mechano-chemical transitions, respectively.

C. Statistical inference from data: frequentist and Bayesian approaches

For simplicity, let us consider a motor that has only two possible distinct interconvertible states denoted by $\mathcal{E}_1$ and $\mathcal{E}_2$.

$$\mathcal{E}_1 \underset{k_r}{\overset{k_f}{\rightleftharpoons}} \mathcal{E}_2 \tag{4}$$

We begin our discussion assuming that the actual sequence of the states, generated by the Markovian kinetics of the motor, is available over the time interval $0 \leq t \leq T$. Our aim is to extract the magnitudes of the rate constants k_f and k_r.

Suppose $t_j^{(1)}$ and $t_j^{(2)}$ denote the time interval of the j-th residence of the device in states $\mathcal{E}_1$ and $\mathcal{E}_2$, respectively. Moreover, suppose that the device makes N_1 and N_2 visits to the states $\mathcal{E}_1$ and $\mathcal{E}_2$, respectively, and $N = N_1 + N_2$ is the total number of states in the sequence. Therefore, total time of dwell in the two states are $T_1 = \sum_{j=1}^{N_1} t_j^{(1)}$ and $T_2 = \sum_{j=1}^{N_2} t_j^{(2)}$ where $T_1 + T_2 = T$.

Since the times of dwell in each state are exponentially distributed, the likelihood of any state trajectory S is the conditional probability density

$$P(S|\underline{k_f, k_r}) = \left(\Pi_{j=1}^{N_1} k_f e^{-k_f t_j^{(1)}}\right)\left(\Pi_{j=1}^{N_2} k_r e^{-k_r t_j^{(2)}}\right) = \left(k_f^{N_1} e^{-k_f T_1}\right)\left(k_r^{N_2} e^{-k_r T_2}\right) \tag{5}$$

for given k_f and k_r. Using (5) in $d[lnP(S|\underline{k_f, k_r})]/dk_f = 0 = d[lnP(S|\underline{k_f, k_r})]/dk_r$ we get the maximum-likelihood (ML) estimates $k_f = N_1/T_1$ and $k_r = N_2/T_2$ for the two rate constants.

The Bayesian approach is based on the Bayes theorem which, in this case, states that

$$P(k_f, k_r|\underline{S}) = \frac{P(S|\underline{k_f, k_r})P(k_f, k_r)}{P(S)} = \frac{P(S|\underline{k_f, k_r})P(k_f, k_r)}{\sum_{k'_f, k'_r} P(S|\underline{k'_f, k'_r})P(k'_f, k'_r)} \tag{6}$$

where $P(k_f, k_r)$ is the prior. Assuming a uniform prior, i.e., a constant for positive k_f and k_r, but zero otherwise, we get the poster distribution

$$P(k_f, k_r|\underline{S}) = \left[\frac{T_1^{N_1+1}}{\Gamma(N_1+1)} k_f^{N_1} e^{-k_f T_1}\right]\left[\frac{T_2^{N_2+1}}{\Gamma(N_2+1)} k_r^{N_2} e^{-k_r T_2}\right] \tag{7}$$

of the rate constants. Note that the mean of k_f and k_r, obtained from the posterior distribution (7) are $(N_1+1)/T_1$ and $(N_2+1)/T_2$, respectively. The corresponding most probable values, obtained from ML analysis, are N_1/T_1 and N_2/T_2, respectively; the minor differences between the two alternative estimates is insignificant if N_1 and N_2 are sufficiently large.