Physics of Ligand Migration in Biomolecules

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The study of migration of ligands in heme proteins is one of the methods used to obtain information about the dynamics and function of biomolecules. An appropriate description of the kinetics involves the modeling of transport over a series of sequential barriers. Utilizing random walk theory, the physics of ligand migration enters the modeling of the kinetics on several levels of description: By use of generalized Brownian motion theory, we develop models for biomolecular rates in presence of a frequency-dependent damping of the ligand motion. The results have the form of a modified Kramers relation. If more than one ligand moves inside a biomolecule, nonlinear blocking effects become important. The migration kinetics can then be adequately modeled by a multivariable stochastic process with nonlinear transition probabilities. Further, we discuss the limit of validity of a description of ligand migration in terms of a set of linearly coupled deterministic rate equations.

1. INTRODUCTION

The fact that proteins are interesting dynamical systems is fully recognized by now.[1-3] While the three-dimensional structures, which have been determined for an increasing number of proteins, provide insight into the architecture of those systems, taken alone they cannot explain the observed properties. Proteins can assume a very large number of structurally different conformational substates.[1-4] At physiological temperatures, the protein fluctuates rapidly from one substate to another. Ligand migration, motility, allostery, etc. are clearly processes that depend on internal mobility. Mobility is related to the intrinsic excitation field (random forces)

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which provides the driving force in protein reactions. One of the methods to disentangle dynamic features in biomolecules is the study of migration of ligands in heme proteins such as O_2 or CO-migration in Myoglobin (Mb).[1,5,6]

The paper is organized as follows: In Section 2 we elaborate on the experimental approach. Section 3 deals with a description of ligand migration valid in the limit of a small ligand concentration in the protein–solvent environment. The method of random processes has found various applications in describing biophysical phenomena.[7,8] In the context of ligand migration, fluctuation effects play a role on several levels of description: Familiar transport laws often become modified in an unexpected way by the presence of protein fluctuations. Two such examples are the modeling of biomolecular reaction rates under the influence of a nonuniform damping and frequency-dependent transport treated in Section 4 by use of generalized Brownian motion theory, and the nonlinear migration at a high ligand concentration in solvent sketched in Section 5 in terms of a multivariable stochastic model which accounts for the blocking effect at the heme site.

2. EXPERIMENTAL APPROACH

In a typical experiment, ligand migration is monitored optically. The optical absorption spectra of a free heme protein and one with the ligand (re)bound differ. From the absorbance measured at a suitable wavelength, the fraction $N(t)$ of biomolecules with the ligand not rebound after an initial laser flash can therefore be determined. A measurement of $N(t)$ constitutes an ensemble realization with small fluctuations (central limit theorem). In contrast, the fluctuations within a single biomolecule are more dominant and impact crucially the details of the dynamics. Typical examples of relaxation for Mb–CO migration are plotted in Fig. 1. Below $\sim$200 K, each protein is frozen into a particular substate with a given activation energy. Migration after photodissociation reflects a distribution of barrier heights.[1,5] Processes occurring over an enormous time range from 10^{-6} to 10^{3} sec are important. The migration follows approximately a power law. At very low temperatures, $T < 40$ K, molecular tunneling becomes important.[9] At high temperatures, the protein breathes and moves from one conformational substate to another; the ligand probes an "average barrier" and the time dependence becomes exponential. On varying the solvent viscosity, one observes systematic effects of the protein dynamics[10] which ask for a challenging generalization of reaction theory. On varying the pH in the solvent one finds that O_2 migration is practically independent of pH;

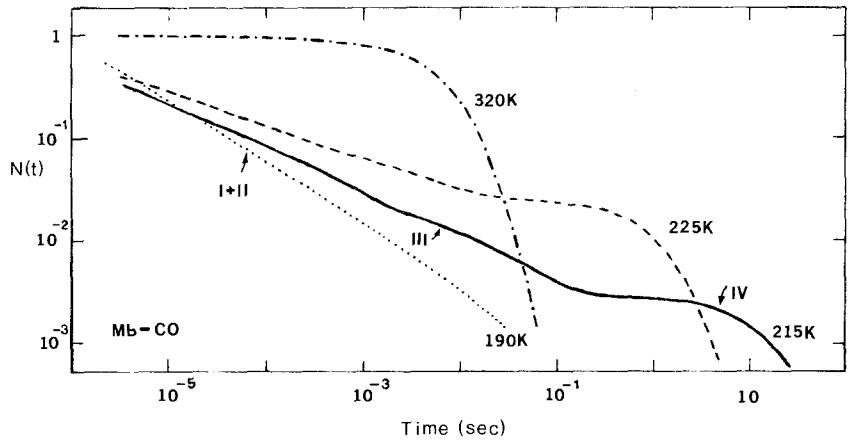

Fig. 1. Recombination of CO after photodissociation of MbCO in glycerol–water solvent (3:1 v/v; after Ref. 5). Four different processes are observed.

CO migration, however, probes the charge-dipole interaction near the heme site.[11]

3. KINETIC DESCRIPTION OF MIGRATION OF LIGANDS

In the limit of small ligand concentration in the solvent S, the observed relaxation of O_2 or CO migration in Mb can be adequately parametrized by a model of sequential barriers, that the ligand encounters as it moves along some reaction coordinate[5] (Fig. 2). In this case, a

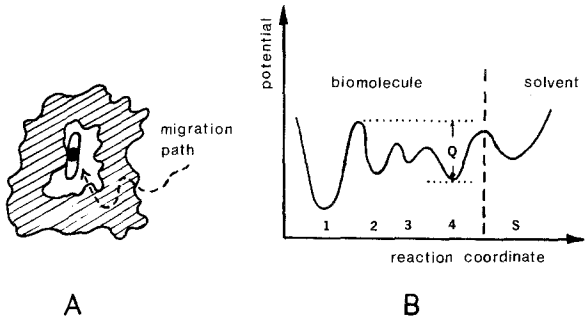

Fig. 2. Migration of the ligand to the heme site is governed by multiple barriers. (A) migration path. (B) potential along reaction coordinate x.

multivariable stochastic model of the migration and a deterministic model based on linearly coupled rate equations yield identical results.[12] For instance, the rate of change of $N_i(t)$, where $N_i(t)$ denotes the fraction of biomolecules with a CO or O_2 ligand in well $i \neq 1$ ($i = 1$: binding site at heme), obeys the deterministic equation

$$\dot{N}_i = r_{i,i-1}N_{i-1} + r_{i,i+1}N_{i+1} - [r_{i+1,i} + r_{i-1,i}]N_i \tag{3.1}$$

For CO migration in Mb one can resolve four barriers, and for O_2 migration one can resolve three barriers.[5] The set $\{r_{i\pm1,i}\}$ are rate coefficients $i \to i \pm 1$, which have the general form

$$r \equiv r(\boldsymbol{\lambda}) = \nu(\boldsymbol{\lambda})\exp - \phi(\boldsymbol{\lambda}) \tag{3.2}$$

$\boldsymbol{\lambda}$ denotes the set of control parameters such as temperature, solvent viscosity, etc. The experimentally observed relaxation, $N(t)$, is then given by

$$N(t) = 1 - N_1(t) = P_t(x_1 = 0; \boldsymbol{\lambda}) \tag{3.3}$$

where $P_t(x_1 = 0; \boldsymbol{\lambda})$ is the probability that the binding site with the occupation $x_1 = 0$ or 1 is not occupied. Because in the limit of low concentration the total number of ligands within a given biomolecule is one or zero for all times t, nonlinear blocking effects (see Section 5) do not enter. Clearly, the real eigenvalues $\mu_i \leqslant 0$ of the corresponding relaxation matrix in (3.1), which govern the time dependence of $N(t)$, depend generally on the whole set of rates $\{r_{i\pm1,i}\}$. The fastest time scale obeys

$$\max\{|\mu_i|\} \leqslant 2\max\{r_{i+1,i} + r_{i-1,i}\} \tag{3.4}$$

The smallest nonzero eigenvalue $\tilde{\mu}$, which is a measure for the longest time scale in the problem, satisfies

$$\min\{r_{i\pm1,i}\} \leqslant |\tilde{\mu}| \simeq \frac{1}{\tau} \propto \exp\left(-\frac{Q}{kT}\right) \tag{3.5}$$

where τ is the average (first passage) time it takes a ligand to surmount the highest potential barrier on its way to the deepest well (binding site). Q denotes the highest relative barrier the ligand has to overcome to reach absorption at well $i = 1$ (see Fig. 2). The observed power laws at low temperatures result from a distribution of activation energies $\{\phi\}$.[1,5,6]

4. THEORY OF BIOMOLECULAR REACTION RATES

In a kinetic description of ligand migration, most of the physics is transferred to the modeling of the rate coefficients. Namely, what equation

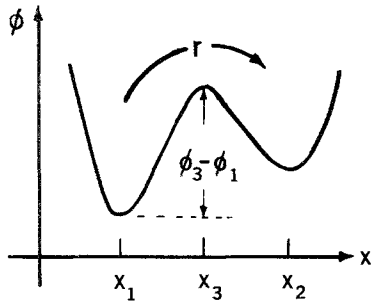

Fig. 3. Potential field used in text.

should be used to evaluate the dependence on the parameters λ of biomolecular rates in condensed phases. The evaluation of the rate is related to the control of dissipation which again is related to the fluctuation dynamics (fluctuation–dissipation relations). At temperatures above ~40 K, where quantum effects can be neglected, a common approach widely used in chemistry and condensed matter theory is based on the standard transition state theory (or absolute rate theory).[13–15] In what follows, we restrict the discussion to a quasi-one-dimensional reaction path and model the rate as the passage over a mean barrier in a double-well potential ϕ (Fig. 3). The transition state theory (TST) result for the rate, r^{TST}, has the form

$$r^{\mathrm{TST}} = \nu_1 \exp\left[-(\phi_3 - \phi_1)/kT\right] \tag{4.1}$$

ν_1 denotes the frequency of the locally stable well at x_1. Processes in a dynamically moving system should, however, be influenced by the strength of damping (viscosity). There is no such dependence on transport coefficients in the prefactor ν_1 of the transition state rate. Taking nonequilibrium effects into account, Kramers derived in a classic investigation the result[16]

$$r^K = \frac{\omega_1}{2\pi\omega_3}\left[\left(\frac{\gamma^2}{4} + \omega_3^2\right)^{1/2} - \frac{\gamma}{2}\right]\exp\left[-\frac{(\phi_3 - \phi_1)}{kT}\right] \tag{4.2}$$

being valid for a moderate and large damping γ. In the large damping limit, $\gamma \gg \omega_3$, (4.2) simplifies to

$$r^K = \frac{\omega_1\omega_3}{2\pi\gamma}\exp\left[-\frac{(\phi_3 - \phi_1)}{kT}\right] \tag{4.3}$$

ω_1 and ω_3 (> 0) denote the angular frequencies at the locally stable well at x_1 and barrier at x_3, respectively. Water at 293 K has a viscosity of about

10^{-2} poise (g cm^{-1} sec^{-1}); for O_2, the critical viscosity, η_c, for overdamped motion is of the order 10^{-3} poise. Thus essentially all biochemical studies are in the high damping regime.

None of the rate relations is general enough to cope with the experimentally measured viscosity dependence of biomolecular rates in the range of 10^{-3}–10^{2} poise.[10] The experimental data can be fitted by the heuristic expression[10]

$$r^{\text{expt}} = \left(\frac{A}{\gamma_s^{\kappa}} + A^0 \right) \exp\left[- \frac{(\phi_3 - \phi_1)}{kT} \right] \tag{4.4}$$

where γ_s is the solvent damping ($\propto$ solvent viscosity) and $0 \leqslant \kappa \leqslant 1$ an attenuation coefficient (which may differ for different wells but is not dependent on type of solvent). For CO and O_2 migration in Mb, κ is typically of the order $\kappa \approx \frac{1}{2}$.[10] The term involving A^0 describes a small but finite rate at viscosities $\eta > 10$ poise. In the following subsections, we investigate possible physical generalizations of the above rate laws.

4.1. Influence of Nonuniform Damping

Kramers' result can readily be generalized to the case of nonuniform damping.[17] We inject particles at x_1 and remove them the moment they arrive at x_2. The resulting nonequilibrium current, j_0, builds up a total integrated density, n_0, proportional to the escape time $\tau_0 = 1/r$; i.e.,

$$r = j_0 / n_0 \tag{4.5}$$

Taking fully into account the nonlinearities of the potential field $\phi(x)$, we obtain in the overdamped limit (Smoluchowski limit) the result (see, e.g., Ref. 18)

$$r = kT \left[\int_{x_1}^{x_2} \bar{p}(x)\, dx \int_{x}^{x_2} \frac{\gamma(y)}{\bar{p}(y)}\, dy \right]^{-1} \tag{4.6}$$

where $\bar{p} \propto \exp - \phi(x)/kT$ denotes the equilibrium probability. By use of approximately harmonic potential extrema, we can simplify (4.6) to give[17–19]

$$r = \frac{\omega_1 \omega_3}{2\pi\gamma(x_3)} \exp\left[- \frac{(\phi_3 - \phi_1)}{kT} \right] \tag{4.7}$$

with no explicit temperature dependence in the prefactor. Note that a

sharply domed barrier region would imply via (4.6) a temperature-dependent prefactor $\propto T^{-1/2}$.

Without further ad hoc assumptions, the result in (4.7) cannot explain the experimental findings in (4.4). Only if we impose without further justification a relation of the form[19]

$$d\log\left[1/\gamma(x_3)\right] = \kappa d\log(1/\gamma_s) \tag{4.8}$$

we find

$$d\log r/d\log\gamma_s = -\kappa \tag{4.9}$$

4.2. Influence of Frequency-Dependent Damping

Inherent in Kramers' treatment is the assumption of a clear-out separation between time scales of "particle" (ligand) and "heat bath" motion. However, this is not always the physical situation. The rate of motion of the excitation field inside the protein can be of the same order as that of the ligand motion. In particular, the local motion of a ligand can be as fast as or faster than conformational fluctuations. Thus the preconditions for Kramers' theory in general and TST in particular are not met. In order to account for these frequency effects we must model the Brownian motion within the barrier region by a generalized Langevin equation in phase space (y,u) of coordinate and velocity (we use a unit mass for the particle and a notation $y = x - x_3$)

$$\begin{aligned} \dot{y} &= u \\ \dot{u} &= \omega_3^2 y - \int_0^t \gamma(t-\tau)u(\tau)\,d\tau + \xi(t), \qquad \omega_3^2 > 0 \end{aligned} \tag{4.10}$$

Hereby, we have neglected in the barrier region effects of anharmonic potential contributions and assumed that a possible functionally nonuniform damping has a smooth behavior around x_3. $\xi(t)$ is a stationary Gaussian thermal noise satisfying the fluctuation–dissipation relation

$$\langle \xi(\tau)\xi(0)\rangle = kT\gamma(|\tau|) \tag{4.11}$$

(4.10 and 4.11) define a non-Markovian process whose Gaussian conditional probability $p_t(y,u \mid y_0,u_0)$ satisfies the time-convolutionless (but not memoryless) non-Markovian master equation[20]

$$\begin{aligned} \dot{p}_t = &\left[-u\frac{\partial}{\partial y} - \bar{\omega}^2(t)y\frac{\partial}{\partial u}\right]p_t + \bar{\gamma}(t)\frac{\partial}{\partial u}(up_t) \\ &+ kT\bar{\gamma}(t)\frac{\partial^2}{\partial u^2}p_t + \frac{kT}{\omega_3^2}\left[\bar{\omega}^2(t) - \omega_3^2\right]\frac{\partial^2}{\partial u\partial y}p_t \end{aligned} \tag{4.12}$$

where

$$\bar{\gamma}(t) = -\dot{a}(t)/a(t), \qquad \bar{\omega}^2(t) = -b(t)/a(t) \tag{4.13}$$

and

$$\begin{aligned} a(t) &= \dot{\rho}(t)\left[1 + \omega_3^2 \int_0^t \rho(\tau)\, d\tau\right] - \omega_3^2 \rho^2(t) \\ b(t) &= \omega_3^2\left[\rho(t)\ddot{\rho}(t) - \dot{\rho}^2(t)\right] \end{aligned} \tag{4.14a}$$

The correlation, $\rho(t)$, is defined by the inverse Laplace transform (L^{-1})

$$\rho(t) = L^{-1}\left[\hat{\rho}(z)\right] = L^{-1}\left[\frac{1}{z^2 - \omega_3^2 + z\hat{\gamma}(z)}\right], \qquad \rho(t=0) = 0 \tag{4.14b}$$

The escape rate, (4.5), has been evaluated in Ref. 20

$$r = \frac{\omega_1}{2\pi\omega_3}\left[\left(\frac{\bar{\gamma}^2}{4} + \bar{\omega}^2\right)^{1/2} - \frac{\bar{\gamma}}{2}\right]\exp\left[-\frac{(\phi_3 - \phi_1)}{kT}\right] \tag{4.15}$$

with

$$\bar{\gamma} = \lim_{t\to\infty} \bar{\gamma}(t), \qquad \bar{\omega}^2 = \lim_{t\to\infty} \bar{\omega}^2(t) \tag{4.16}$$

Thus, the rate in (4.15) has the structure of Kramers' equation (4.2), but with the bare damping γ and the bare frequency ω_3^2 substituted by the "renormalized" values $\bar{\gamma}$ [note that $\bar{\gamma} \neq \hat{\gamma}$ $(z = 0)$] and $\bar{\omega}^2$. Introducing the renormalized frequency

$$\alpha = \left(\frac{\bar{\gamma}^2}{4} + \bar{\omega}^2\right)^{1/2} - \frac{\bar{\gamma}}{2} \tag{4.17}$$

we can recast (4.15) as

$$r = \frac{\alpha}{\omega_3} r^{\mathrm{TST}} \tag{4.18}$$

α is a characteristic function of ω_3^2 and of the damping $\gamma(|\tau|)$, but depends on temperature T only implicitly via damping $\gamma(|\tau|)$. The result (4.15) can be simplified further, if $\rho(t)$ is of the specific form

$$\rho(t) = \sum_{i=1}^{n} C_i t^{\beta_i} \exp \lambda_i t, \qquad \beta_i : \text{real} \tag{4.19}$$

with $\mathrm{Re}\lambda_1 \leqslant \cdots \leqslant \mathrm{Re}\lambda_{n-1} < \lambda_n$, real. In this case, the limit α is equal to

$$\alpha = \lim_{t\to\infty} \frac{\dot{\rho}(t)}{\rho(t)} = \lambda_n > 0 \tag{4.20}$$

with λ_n being the largest positive pole of $\hat{\rho}(z)$. This special result, (4.20), presents a generalization of a result given by Grote and Hynes[21]; they derived (4.18), (4.20) utilizing (4.19) with $\beta_i = 0$ for all i, by use of a completely different approach which is based on an equilibrium flux-flux correlation expression of the rate.

Given (4.15), the experimental findings in (4.4) can be understood in terms of a dynamic friction model[22]

$$\gamma(|\tau|) = \frac{\Gamma(\kappa)}{c + |\tau|^{1-\kappa}} \left[\exp\left[-|\tau|\omega^2/\gamma_s\right]\right], \qquad \omega^2 > 0, \quad 0 \leqslant \kappa \leqslant 1 \tag{4.21}$$

where $\Gamma(\kappa)$ denotes the gamma function. The form (4.21) has been proposed by Doster.[22] In his "pac-man" model of dynamic friction, the damping $\gamma(|\tau|)$ is modeled by a correlation of *local* defect fluctuations ($\propto |\tau|^{\kappa-1}$) and an independent coupling to *global* protein-solvent fluctuations [$\propto \exp(-\omega^2|\tau|/\gamma_s)$]. The behavior of $\log\alpha$ versus $\log\gamma_s$ is schematically represented in Fig. 4. Above a transition value, γ_t, one has

$$r = r_t \simeq \frac{\alpha_t}{\omega_3} r^{\mathrm{TST}}, \qquad \gamma_s \geqslant \gamma_t \tag{4.22}$$

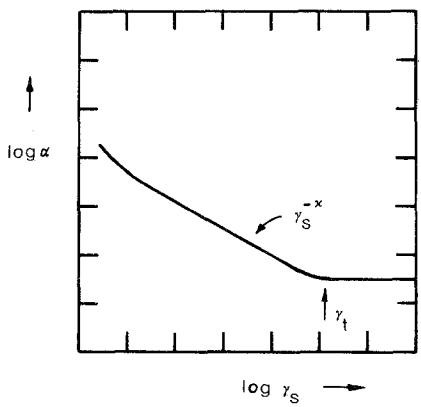

Fig. 4. Schematic diagram of dependence of renormalized frequency α versus solvent damping γ_s.

independent of γ_s. Equation (4.22) gives the rate in the very large viscosity limit, where the first contribution in (4.4) can be neglected. In an intermediate regime, we find $-d\log\alpha/d\log\gamma_s \simeq \kappa$; i.e.,

$$r \simeq (A/\gamma_s^{\kappa})r^{\mathrm{TST}} > r_t, \qquad \gamma_c < \gamma_s < \gamma_t \tag{4.23}$$

Alternatively, memory effects can partially be simulated by random modulations of the frequency parameters ω_1 or ω_3.[23] The results are similar in nature to those above, but the activation energy, $(\phi_3 - \phi_1)$, will also be affected by the strength of random modulation.[23,24]

4.3. Influence of Dimensional Effects

Kramers' arguments have been readily extended to many dimensions in the overdamped (Smoluchowski) limit.[25,26] A similar extension is possible in presence of memory damping: Transport occurs over sequential saddle points with the amount of damping along the z direction, connecting two minima, being in the moderate damping regime. Further, motions "perpendicular" to z are strongly overdamped, such that all the velocities "perpendicular" to $\dot{z}$ can be eliminated adiabatically. The influence of many dimensions is then essentially reduced to a phase-space factor. Using the reasoning in Ref. 20 for $(z,\dot{z})$ motion gives

$$r = (\alpha/\omega_3)r_N^{\mathrm{TST}} \tag{4.24}$$

α is defined in (4.17) and r_N^{TST} is the multidimensional generalization of (4.1).

$$r_N^{\mathrm{TST}} = \left(\prod_{i=1}^{N} \nu_i \Big/ \prod_{i=1}^{N-1} \bar{\nu}_i\right) \exp - \frac{(\phi_3 - \phi_1)}{kT} \tag{4.25}$$

where the ν_i's are the frequencies at the minimum of ϕ and $\bar{\nu}_i$'s are the stable frequencies at the saddle point. Dimensional effects are thus not easy observable in the rate law. More important in biomolecular transport are probably effects caused by "curvature of dimension," as, e.g., migration on surfaces of spherelike protein parts.

5. NONLINEAR MIGRATION: EFFECT OF BLOCKING

If many ligands occupy simultaneously a well i, $i = 1, \ldots, i_{\max}$, the simple deterministic rate description in (3.1) breaks down. The transition probabilities $\Gamma(x_j \mid x_i; \boldsymbol{\lambda})$ between different wells, coupled to a bath of ligand concentration c,

$$(\ldots, x_i, \ldots, x_j - 1, \ldots) \xrightarrow{\Gamma(x_j \mid x_i, \boldsymbol{\lambda})} (\ldots, x_i - 1, \ldots, x_j, \ldots) \tag{5.1}$$

are generally nonlinear functions of the occupancy $x_j = 0, 1, \ldots$

$$\Gamma(x_j \mid x_i, \boldsymbol{\lambda}) = x_i r_{ji}(x_j, \boldsymbol{\lambda}) \tag{5.2}$$

In particular, in Mb the first ligand that rebinds at the heme site blocks further transitions; i.e.,

$$\Gamma(x_1 \mid x_i, \boldsymbol{\lambda}) = x_i r_{1i}(\boldsymbol{\lambda}) \delta_{x_1,1} \tag{5.3}$$

The solution of the probability

$$P_t(x_1 = 0, \boldsymbol{\lambda}) = \sum_{x_2 \ldots x_{\max}} p_t(x_1 = 0, x_2, x_3, \ldots, x_{\max}; \boldsymbol{\lambda}) = 1 - \langle x_1(t, \boldsymbol{\lambda}) \rangle \tag{5.4}$$

must be calculated from a multivariable Markovian master equation with nonlinear rates.[12,27] A rather simple solution is possible if we assume linear rates for all wells $i > 1$ and a complete trap for site $i = 1$ ($r_{i1} = 0$, e.g., Mb–CO migration). Then, $N(t)$ has the form[12]

$$N(t) = P_t(x_1 = 0; \boldsymbol{\lambda}) = \exp - \langle \bar{x}_1(t, \boldsymbol{\lambda}) \rangle, \qquad \langle \bar{x}_1(t = 0, \boldsymbol{\lambda}) \rangle = 0 \tag{5.5}$$

where $\langle \bar{x}_1(t, \boldsymbol{\lambda}) \rangle$ has a simple interpretation: If the recombination were to start with an initial occupation of zero at heme site and equilibrium Poisson probabilities in wells $i = 2, \ldots, i_{\max}$, $\langle \bar{x}_1(t, \boldsymbol{\lambda}) \rangle$ would be the mean occupation of well $i = 1$ if no blocking were to occur [$\langle \bar{x}_1(t) \rangle \to \infty$, $t \to \infty$]. Compared with (3.1), (5.4) gives a faster relaxation[27]; the relaxation exhibits information about the volume capacity in different wells.

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