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Biophysical Chemistry 106 (2003) 75–80

Biophysical Chemistry

www.elsevier.com/locate/bpc

A local friction model to develop microscopic transport parameters for membrane-soluble ions in bilayer membranes

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Received 18 March 2003; received in revised form 30 May 2003; accepted 30 May 2003

Abstract

Charged membrane-soluble ions in bilayer membranes move between opposing interfacial states on application of an electric field. The kinetics of this transition is modeled as discrete state electrophoresis using a Langevin formulation that focuses on local velocities at points along the spatial trajectory of the ion. These local velocities are used to establish both the decay time for the transition and the activation energy profile along the trajectory. The local velocities depend on local frictional coefficients. These coefficients are developed from the molecular structure along the trajectory by introducing a microscopic frictional force. This frictional force is produced by the lateral displacement of segments of the surrounding membrane molecules as the ion passes. The displaced molecular chains produce a non-linear resistive force that translates into a frictional force directly proportional to both ion radius and velocity.

Keywords: Membrane displacement friction; Non-linear displacement; Membrane soluble ions; Ion velocity distributions; Activation energy profile

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1. Introduction

Ionophores such as lasalocid or A23187 dissolve in lipid bilayer membranes, and can bind polyvalent ions from a bathing solution to produce a membrane soluble complex. This ion/ionophore complex (IIC) moves across the membrane under a concentration gradient or an applied electric field.

Carrier systems like the IIC are often described using four state models [1,2]. (1) The ionophore at interface 1 binds an ion from solution to form the IIC; (2) the IIC crosses the membrane; (3) the IIC releases the ion into the bathing solution; (4) the bare ionophore returns to interface 1 to initiate a new cycle. This reversible stationary state transport system requires a total of eight empirical rate constants. The net ion flux for this cycle is determined as products of these rate constants making it difficult to establish individual rate constants from experimental flux data. Experiments to monitor the evolution to the stationary state also involve all the rate constants so that determination of individual rate constants by this technique is also difficult.

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doi:10.1016/S0301-4622(03)00184-4

Sections of the liquid crystalline array of lipids that constitute the membrane restrict the dominant ion motion normal to the membrane surface and the large electric field produced across the thin bilayer membrane by an applied potential provides the force to displace segments of the surrounding polymers and drive the ion to the opposite interfacial site.

A single kinetic step, the motion of the IIC across the membrane has been monitored using environment sensitive Eu(III) emission spectroscopy [3,4]. Eu(III) ion as Eu(III)/lasalocid complex in the membrane can be selectively excited using a tunable dye laser and monitored. The IIC motion across the membrane might also be observed using laser Doppler spectroscopy that has been used successfully to observe a stream of ions in a gramicidin channel [5]. The observed velocities correlate directly with the rate constants for transport across the membrane [6].

IIC transport differs from transport through ion channels. The channel is an embedded protein with a pore whose geometry controls the flow of ions across the membrane. Structural changes produced by an ion in the pore are localized. By contrast, an IIC must displace sections of the long lipid chains of the membrane and must continue to displace new (and different) sections of the lipids as it traverses the membrane. Since the IIC is large relative to the membrane, the membrane distortion is significant. However, because the membrane is thin, an applied electric field is very large and provides the force to displace the lipid chains and propel the complex through the membrane. Since the field is large, the dominant motion of the complex is directly normal to the membrane surface. The lipid chains themselves also limit lateral motions, so that, a 1D formulation for IIC transport is justified.

Although a single decay constant is observed experimentally, the 1D transport of the IIC is modeled using a series of microscopic steps along the IIC trajectory across the membrane [2]. The empirical rate constants for these microscopic steps are then combined to give a net rate of transport and a decay constant. Such systems are intrinsically ill-conditioned—different sets of empirical rate constants can give the same rate and decay constant. Such models cannot be used to prove a mechanism unless these microscopic rate constants or the local velocities [6] can be determined using other experimental techniques.

The development of theoretical rate constants directly from the microscopic properties of the system is difficult because a model must account not only for the motion of the complex but the concomitant motions of the long lipid molecules that surround this moving complex. An ion moving in a bulk homogeneous medium experiences friction, since the solvent molecules of the medium must be displaced by the moving ion. In bulk media, the frictional force is described by Stokes law where, the constant frictional force is proportional to both the ion velocity and radius. For the IIC in the membrane, the microscopic frictional force can be different at each point along the trajectory. IIC near the interface, displaces only the terminal segments of the chains but can be affected by interfacial phenomena such as lipid charge. An IIC in the middle of the membrane displaces not only the segments of lipid chain that it touches but also the adjoining segments because, these segments are bound together in the chain.

The Langevin equation can be used to describe the constant velocity of an ion in homogeneous solvent where a single constant frictional coefficient is required. In this work, a multi-state Langevin equation that gives local velocities in terms of local frictional coefficients is developed. Techniques for calculating these frictional coefficients from the structures of IIC and lipid chains are introduced. The local velocities are related to the local rate constants along the ion's spatial trajectory [6].

The local velocities provide a bridge to the calculation of macroscopic parameters like the decay constant and microscopic parameters like the activation energies for each step along the reaction trajectory. The multi-state Langevin equation is developed in a matrix formulation, so that the coupled displacement between linked segments of the lipid chains can be included.

The local frictional coefficients are calculated using a lipid displacement model where the displacements of chain segments closest to the moving complex also displace concentric rings of lipid segments. The cumulative displacement produces a non-linear force equation. This model produces an expression for the frictional force that is proportional to both the IIC radius and its velocity for consistency with the macroscopic Stokes law for homogeneous systems.

2. Theory

2.1. Local flux and velocity

A velocity based model would define the flux for membrane-soluble ions in a unit area of membrane for some segment i of the trajectory between interfaces as the product of the local velocity, v_i, and local concentration, c_i,

$$J_i = v_i c_i$$

For current continuity, fluxes in all N segments, $J_{i,}$ must be equal. The local velocities in each segment might differ but the constant flux is maintained by different concentrations in those unit area segments.

The length, a, of the trajectory in this section defines both a rate constant,

$$a k_i = v_i$$

and a rate of change for the local concentration,

$$\frac{a \mathrm{d}c_i}{\mathrm{d}t} = J_i$$

$$\frac{\mathrm{d}c}{\mathrm{d}t} = J/a = vc/a = kc$$

the more traditional kinetic format.

3. The decay time

If the local velocities along the spatial reaction coordinate are known, either from observation or theory, the average decay time (the transition lifetime) for the full interface–interface transition is determined as a mean first passage time [7], the sum of times for each microscopic transition. This mean first passage time and its inverse, the macroscopic decay constant, are

$$\tau = \frac{1}{k} = \sum_i \frac{a_i}{v_i}$$

These observable parameters arise naturally as a summation of individual transition times.

3.1. Activation energy on the spatial trajectory

The local velocities determine the activation energy profile along the spatial trajectory. The acceleration between segment i and segment $i+1$ is defined parametrically through the distance a_i between segments

$$\frac{\mathrm{d}v}{\mathrm{d}t} = \frac{v_{i+1} - v_i}{a_i} \frac{a_i}{\Delta t} = \frac{\Delta v}{a_i} v_i$$

The energy change between states is the force (mass times this acceleration) multiplied by the distance traveled (a_i)

$$\Delta E = Fxa_i = m \left[\frac{v_i \Delta v}{a_i} \right] a_i = m v_i \Delta v$$

This equation defines the energy change for each segment along the spatial trajectory to give an activation energy profile for the transition.

Equal local velocities $(\Delta v = 0)$ generate a constant energy profile along the trajectory. If the segment nearest to the membrane/aqueous solution interface has excessive retarding interactions to make a large initial velocity differential, the activation energy profile assumes a trapezoidal shape where the initial activation barrier dominates. The profile can be more complicated but is always determined directly from the same central set of local velocities.

4. The matrix Langevin equation

The continuum Langevin equation assumes a homogeneous medium where the moving ion experiences the same environment and has the same frictional coefficient at each point along its trajectory. The ion rapidly attains its limiting hydrodynamic velocity and electrophoretic mobility. The frictional coefficient often obeys Stokes law where the frictional coefficient is proportional to both ion radius and the coefficient of viscosity for the bulk medium.

An ion moving through the array of aligned chain molecules that constitute the membrane must displace segments of the chain molecules that surround it along its trajectory. The molecular structure of each segment can be different to produce a different frictional resistant to the ion. The ion is generally large enough so that the ion displaces the segments for a number of concentric polymer segments in the *i*th region of the trajectory. In addition, the displacement of polymer segments in section i can cause a concurrent displacement in segments $i+1$ and $i-1$ because, these segments are bonded to segment i. These features can all be incorporated into a matrix Langevin model with a frictional coefficient matrix that includes all these features. The behavior for any region i along the trajectory is then described by a local frictional coefficient f_i, a local electric field E_i and the local velocity v_i in that region. The local velocities and concentrations c_i in the *i*th region give the constant flux,

$$J = v_i c_i$$

for every region along the trajectory to maintain current continuity along the trajectory.

The set of local velocities and local electric fields along the trajectory are ordered as N component vectors. The matrix of local frictional coefficients can include off-diagonal elements reflecting displacements of adjacent chain segments by the moving ion. Although some fluctuations and lateral movement are possible for the ion in each region, the dominant force is the large electric field normal to the surface. Lateral deviations as the complex moves through the ordered lipid array are ignored.

The time to the hydrodynamic limiting velocity is short even for motion in the small regions of membrane and the time-dependent equation

$$\frac{\mathrm{d}|v\rangle}{\mathrm{d}t} = -\mathbf{F}|v\rangle + \mathrm{ze}|E\rangle$$

evolves rapidly to its stationary state limit

$$|v\rangle^{\mathrm{ss}} = \mathbf{F}^{-1}\mathrm{ze}|E\rangle$$

In the limit of zero coupling, each region has a local velocity based only on the corresponding local electric fields and frictional coefficient

$$v_i = \mathrm{ze}E/f_i$$

with mean transit time

$$\tau = \left\langle a_i \middle| \frac{1}{v_i} \right\rangle = \sum \frac{a_i}{v_i}$$

For systems with displacement coupling, the local velocities are determined from the inverse matrix $\mathbf{F}^{-1}$ operating on the vector of local applied forces.

The local frictional coefficients for regions near the membrane/solution interfaces can incorporate the special properties expected for the ion near the interface.

5. Friction

Polymer segments must be displaced perpendicular to the motion of an ion to produce a local friction. The frictional force for a homogeneous solvent is proportional to the ion's lateral surface area, the solvent coefficient of viscosity η and the velocity gradient in the y direction perpendicular to the motion of the ion

$$F_x = \eta A \frac{\mathrm{d}v_y}{\mathrm{d}y}$$

An ion membrane does not encounter a homogeneous surface contact area. Instead, it must displace membrane segments that surround it. This special environment requires a new, dimensionally consistent definition for friction. The new frictional force is now the product of this momentum and the lateral (y) velocity gradient produced by ion displacement of the polymer segments

$$F_x = mv_x \mathrm{d}v_y/\mathrm{d}y$$

The lateral displacement parameter y might also be the displacement of a ring of polymer segments surrounding the moving ion.

The y velocity gradient reflects the membrane resistance to displacement by the passing ion. The local friction is now related to momentum imparted to the polymer segment rings that surround the moving ion. The ion can force the nearest segments against segments in the adjoining concentric ring of polymer so that the ion displaces an increasingly larger mass as the lateral displacement by the ion increases.

The momentum mv_x of the moving ion displaces a ring of polymer segments to a maximal distance equal to the ionic radius r. For the closely packed polymers and a large ion, the moving ion can produce a cumulative displacement where the innermost ring of polymer segments expands to contact the next ring of polymer segments, etc. The total mass displaced increases with the displacement y to produce a non-linear lateral momentum

$$ky\mathrm{d}y$$

k with units of kg/m/s measures the accrued mass as the unit rings are forced laterally outward. The forward (x) local momentum is transferred to lateral (y) momentum as the ion passes to give Δv_y

$$m\int_0^v \mathrm{d}v_y = \int_0^r ky\mathrm{d}y$$

$$\Delta v_y = kr^2/2m$$

for a maximal lateral displacement equal to the ionic radius r. The y velocity gradient is

$$\mathrm{d}v_y/\mathrm{d}y = kr/2m$$

and the total frictional force is

$$F_{\mathrm{fric}} = v_x kr/2$$

The result is consistent with Stokes law for homogeneous media since it predicts a direct dependence on both r and v_x. For this microscopic model, the empirical coefficient of viscosity η and the area A have been replaced by the parameter k expressing the polymer mass displaced as the moving ion forces the units of the ring in the lateral y direction.

6. Coupling

Because the segments are linked, a displacement at the ith segment can also produce displacements in the $i+1$ and $i-1$ segments. These displacements produce coupled frictional coefficients f'_{i+1} and f'_{i-1} that appear above and below the main diagonal of the friction matrix. These off diagonal elements act to reduce the net friction for each region since the polymer segment is already partially displaced before the ion enters that region. If the distance between the ith unit and its neighbor is a_i, the ith ring unit at maximal displacement produces a displacement $r\cos(\theta)$ in the $(i+1)$th unit where $\tan(\theta) = a/r$. The lateral displacement of the $(i+1)$ or $(i-1)$th ring is

$$r'_{i+1} = \frac{r_i^2}{\sqrt{r_i^2 + a_i^2}}$$

and

$$f' = \frac{k}{2m}\frac{r_i^2}{\sqrt{r_i^2 + a_i^2}}$$

6.1. Discussion

The matrix Langevin formulation for the motion of large ions between interfacial states in bilayer membranes focuses on the local velocities found along the spatial trajectory. For this system, the local velocities serve as the bridge between the macroscopic observable events and the molecular phenomena that dictate these velocities in each region of the trajectory. The full set of local velocities generated in this manner does not imply that the ion is moving in all regions simultaneously.

It generates the velocities for a single ion for each region of its trajectory. The flux J or the current density is determined by the local velocity and concentration in any region along the trajectory. The flux decays exponentially as local concentrations in each region are depleted. The flux equation is easily converted into a rate equation so that, the local rate constants can always be derived from the local velocities. However, the rate constants must be considered as derived parameters. The local velocities are preferable because they can be related to experimental observables, the local velocities for the moving ion.

The local velocities lead directly to parameters for the full ion trajectory. The mean first passage time, the sum of average times in each region of the trajectory, is the time constant for the system and the inverse of the rate constant. A set of local velocities determined using the model must then reproduce the experimentally observed decay time for the transition. The same set of local velocities give the activation energy profile along the spatial trajectory using the differential expression derived here.

Since the local velocities depend on the local frictional coefficients, any theoretical calculation of these coefficients bridges the microscopic and macroscopic views of this system. Knowledge of the molecular structure of the ion and the structure of the polymers that surround the ion in a given region of the trajectory can be used to calculate the mass displaced and the frictional coefficient. The generic derivation presented here is sufficient to illustrate that, the displacement involves concentric rings of polymer segments so that the total mass displaced increases with increasing displacement by the ion. Any modeling for each segment can now focus on evaluation of the non-linear force constant k. The non-linear mass displacement equation that results yields a frictional force directly proportional to both the forward (x) velocity of the moving ion and the ion radius. The expression parallels the Stokes law behavior in a homogeneous medium.

The matrix model can incorporate frictional coupling as the displacement of one segment can produce displacements in neighboring segments because, segments are bonded in the long chain molecule. This coupling produces an overall reduction in the friction encountered by the ion as it moves between interfacial states.

The local friction is developed using a new expression for the frictional force that expresses this friction in terms of the forward momentum of the ion and the lateral momentum of displaced polymer segment mass. The utility of the formulation is reflected in our ability to regenerate Stokes law dependencies for friction using the mass displacement model.

The multi-state Langevin equation provides a framework to derive transport rate constants from the frictional coefficients generated by the elasticity of the aligned lipid medium that surrounds the moving IIC. The decay time, activation energy profile, local velocities and frictional coefficients can all be generated from a determination of this single parameter.

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