Steady State Flux-Flux Correlation Functions for Elementary Processes

Joel Keizer

SFI WORKING PAPER: 1992-06-026

SANTA FE INSTITUTE

Steady State Flux-Flux Correlation Functions for Elementary Processes

Joel Keizer*

Institute of Theoretical Dynamics

and Department of Chemistry

University of California

Davis, CA 95616

May 28, 1992

Abstract

We provide a simple derivation of the flux-flux correlation functions for a system of elementary processes governed by a master equation. A particularly simple expression for the spectral density of the flux-flux correlation function is given, which is shown to be useful computationally. The general formulae are illustrated with several examples related to membrane current noise. The relationship between these formulae and those obtained by Frehland are discussed.

1 Introduction

It is possible to describe a wide number of physical, chemical, and biological processes using the idea of an "elementary process." In addition to the classical notion

---

*Supported by NSF Grant DIR 90-06104 and the Agricultural Experiment Station of the University of California. This work was carried out during a sabbatical leave at the Santa Fe Institute.

2 Flux Correlations for Elementary Processes

The rate of an elementary process is given by the difference between a forward rate, V_κ^+, and a reverse rate, V_κ^-, where κ lables the elementary process [2,3]. The extensive variables, given by the column vector $\mathbf{n}$, change in time according to

$$dn_i/t = \sum_\kappa \omega_{\kappa i}(V_\kappa^+ - V_\kappa^-), \tag{1}$$

where $\omega_{\kappa i}$ is the net change of n_i (stoichiometric coefficient) for the process κ. The rate of an elementary process is the same as the flux due to that process, *i.e.*, the net number of times per second that the process has occurred. It can be used to define the progress variable [11,12] for the process, ξ_κ, using

$$d\xi_\kappa/t = V_\kappa^+ - V_\kappa^-. \tag{2}$$

Thought of as a matrix, $\omega_{\kappa i}$ is the linear transformation between the intensive variables and the progress variables. The back transformation is given by the matrix $B_{\kappa i}$, which satisfies [13]

$$\delta_{ij} = \sum_\kappa \omega_{\kappa i} B_{\kappa j}, \tag{3}$$

where δ_{ij} is the Kroeneker delta. The matrix B exists only for linearly independent elementary processes, *i.e.*, those for which the equation

$$\sum_\kappa \omega_{\kappa i} b_\kappa = 0 \tag{4}$$

has the unique solution $b_\kappa = 0$ for all κ. In this case, however, one can freely transform between the extensive variables, $\mathbf{n}$, and the progress variables, $\boldsymbol{\xi}$.

In the master equation formalism, which is utilized here to describe the stochastic process associated with elementary processes, the rates, V_κ^+ and V_κ^-, are interpreted as providing the transition probability per unit time for the process κ [4]. This yields a linear differential difference equation for the time-dependent probability for observing the extensive variables, $\mathbf{n}$. Here we are interested in fluctuations in the extensive variables (and the fluxes) around stable steady state values. At an equilbrium steady state, the rates of all elementary processes vanish on the average. This is the condition of detailed balance [2,3,14]. At nonequilibrium steady states this is no longer true and (2) shows that the ξ_κ will increase linearly with time on the average since the extensive variables are constant at steady state. Deviations around the average values at steady state will be denoted by $\delta n_i = n_i - n_i^s$ and $d\delta\xi_\kappa/dt = d\xi_\kappa/dt - d\xi_\kappa^s/dt$, where the superscript s implies the steady state value.

For elementary process that are linear, *i.e.*, for which all the V_κ^+ and V_κ^- are proportional to a single extensive variable, it is well-known that the two-time correlation function of the extensive variables is exponential at asymptotically stable steady states [15]. Explicitly, for $t \leq t'$

$$C(t'-t) \equiv \langle \delta \boldsymbol{n}(t) \delta \boldsymbol{n}^T(t') \rangle = \sigma^s \exp(H^T(t'-t), \tag{5}$$

where the superscript T indicates the transpose of the linearized relaxation matrix of the extensive variables, H, and $\sigma^s = C(0)$ is the steady state covariance matrix that satisfies [2,15]

$$H\sigma^s + \sigma^s H^T = -\gamma \tag{6}$$

where $\gamma_{ij} = \sum_\kappa \omega_{\kappa i}(V_\kappa^+ + V_\kappa^-)\omega_{\kappa j}$. Because of stationarity, the correlation function depends only on the time difference, $t' - t$. *Equations (5) and (6) are also valid for the progress variables if the appropriately transformed matrices H, σ, and γ are used.* The form of H and γ for the progress variables is particularly simple. Using (1) and (2) it is easy to show that

$$H_{\alpha\kappa} = \sum_l \frac{\partial(V_\alpha^+ - V_\alpha^-)}{\partial n_l} \omega_{\kappa l} \tag{7}$$

while it is well-known that for progress variables γ has the form [12,13]

$$\gamma_{\alpha\kappa} = \delta_{\alpha\kappa}(V_\kappa^+ + V_\kappa^-). \tag{8}$$

For linear elementary processes, for which V_κ^+ and V_κ^- are proportional to a single one of the n_i, the expression for H can be written explcitly as

$$H_{\alpha\kappa} = k_\alpha^+ \omega_{\kappa i} - k_\alpha^- \omega_{\kappa j} \tag{9}$$

where in this case $V_\kappa^+ = k_\alpha^+ n_i$ and $V_\kappa^- = k_\alpha^+ n_j$ with $k_\alpha^\pm$ first order rate constants.

According to (2) the time derviatives of the progress variables equal the net flux in an elementary process. Thus the two-time flux correlation function can be obtained by differentiating the two-time progress variable correlation function with respect to t and t'. This is done most easily by taking advantage of the symmetry property [3,16] $C(t'-t) = C(t-t')^T$ to rewrite (5) for $-\infty < t'-t < \infty$

$$C(t'-t) = \Delta(t'-t)\sigma^s \exp(H^T(t'-t)) + \Delta(t-t')\exp(H(t-t'))\sigma^s, \tag{10}$$

where $\Delta(t)$ is the Heaviside function. Equation (10) is equally applicable to correlations in $\boldsymbol{\xi}$ or $\mathbf{n}$, depending on the representation of the matrices. Differentiating this with respect to t' yields

$$\begin{aligned} dC(t'-t)/dt' &= \delta(t'-t)[\sigma^s \exp(H^T(t'-t)) - \\ &\quad \exp(H(t-t'))\sigma^s] + \Delta(t'-t)\sigma^s H^T \exp(H^T(t'-t)) \\ &\quad + \Delta(t-t')\exp(H(t-t'))H\sigma^s. \end{aligned} \tag{11}$$

Since the coefficient of the Dirac delta function vanishes when $t = t'$, that term vanishes identically. Thus differentiating (11) with respect to t gives the result:

$$\begin{aligned} D(t'-t) &= \gamma\delta(t'-t) - [\Delta(t'-t)\sigma^s H^{T2} \exp(H^T(t'-t)) + \\ &\quad \Delta(t-t')\exp(H(t-t'))H^2\sigma^s], \end{aligned} \tag{12}$$

where $D(t'-t) \equiv \langle (d\delta\boldsymbol{\xi}/dt)(d\delta\boldsymbol{\xi}/dt')\rangle$ and the coefficient of the Dirac delta function was rewritten using (6). Notice that since the derivatives of $\mathbf{n}$ are odd functions of time, the flux-flux correlation function must satisfy the symmetry property [3,16] $D(t'-t) = D(t-t')^T$, which is easily checked using (12) and that fact that σ^s is symmetric. Using (6), eq.(12) can be expressed equivalently (for $0 \leq t$) as:

$$D(t) = \gamma\delta(t) + [\gamma + H\sigma^s]H^T \exp(H^T t) \tag{13}$$

At equilibrium, where one has [2,15] $H\sigma^s = -\gamma/2$, (13) further simplifies to

$$D(t) = \gamma\delta(t) + (\gamma/2)H^T \exp(H^T t). \tag{14}$$

Equations (12-14) can be compared to equations obtained from Frehland's formalism [5] by taking appropriate linear combinations of the one-way fluxes. Although formally different, we show in the next section – after a little algebra – that they are equivalent.

In applications it is frequently easier to measure the power spectrum of correlations rather than their time dependence [8]. Defining the Fourier transform of any function of time, $f(t)$, as

$$\hat{f}(\omega) = \frac{1}{2\pi} \int_{-\infty}^{\infty} f(t) \exp(i\omega t) dt, \tag{15}$$

gives the well-known relationship [16] between the power spectrum of $\boldsymbol{\xi}$ and the power spectrum of the flux, $d\delta\boldsymbol{\xi}/dt$:

$$\hat{D}(\omega) = \omega^2 \hat{C}(\omega). \tag{16}$$

Using the general form [3] of $\hat{C}(\omega)$ based on (10), thus, gives

$$\hat{D}(\omega) = (i\omega + H)^{-1}(\omega^2\gamma/2\pi)(-i\omega + H^T)^{-1}. \tag{17}$$

Because γ is diagonal (c.f. eq. (8)), the diagonal elements of $\hat{D}$ can be written as

$$\hat{D}_{\alpha\alpha}(\omega) = (\omega^2/2\pi) \sum_{\kappa} \mid (i\omega + H)^{-1}_{\alpha\kappa} \mid^2 (V_\kappa^+ + V_\kappa^-). \tag{18}$$

Thus the power spectrum of an individual flux is given by a sum of terms weighted by the sum of the fluxes through each elementary process. Note that equations (16 – 18) depend only on the linearized rate martix H and γ. As neither of these matrices are dependent on the existence of the matrix B that transforms the extensive variables into the progress variables, these equations are valid even for *linearly dependent* elementary processes. Equation (18) is particularly simple to apply, as we show in the next section.

Although the master equation formalism provides the most fundamental interpretation of elementary processes [4], at asymptotically stable steady states it can be shown in the thermodynamic limit to reduce to a linear Langevin type theory [3,17]. In fact, if one is interested only in first and second moments, then calculations with the two theories are identical if exclusively first-order elementary processes are involved – even for small systems [14,15]. In either case the Langevin equation governing fluctuations in the progress variables around a steady state takes the form

$$d\delta\boldsymbol{\xi}/dt = H\delta\boldsymbol{\xi} + \tilde{\boldsymbol{f}}, \tag{19}$$

where H comes from eq.(7) and $\tilde{\mathbf{f}}$ is the random term with the two-time correlation matrix [3,13]

$$\langle f_\alpha(t) f_\beta(t')\rangle = \gamma_{\alpha\beta}\delta(t'-t), \tag{20}$$

with γ given by eq.(8). Using (20) one can calculate the two-time flux correlation directly, thereby verifying the result in eq. (12). This shows that the equations for the power spectra (16-18) are valid for all elementary processes in the thermodynamic limit, in addition to exclusively first order elementary processes in systems of any size.

3 Illustrative Examples

The simplest case of an elementary process to which the results in Section II can be applied is a single linear process,

$$1 \leftrightarrow 2 \tag{21}$$

with the forward and reverse rates $V^+ = k^+ n_1$ and $V^- = k^- n_2$. For this process $\omega_1 = -1$ and $\omega_2 = 1$. Thus according to (8-9) $\gamma = k^+ n_1^s + k^- n_2^s$ and $H = -(k^+ + k^-) \equiv -\lambda$. Since the steady state for this process is an equilibrium, *i.e.*, at steady state $V^+ = V^-$, we can use the formula in (14) to obtain,

$$D(t) = 2n(k^+k^-/\lambda)\delta(t) + nk^+k^- \exp(-\lambda t), \tag{22}$$

where $n = n_1 + n_2$ and the fact that $n_1^s = nk^-/\lambda$ has been used. Equation (22) is identical to that obtained using different techniques [9,18,19]. Using the formula in (18), it is even easier to obtain the spectral density, which is

$$\hat{D}(\omega) = 2nk^+k^-(\omega^2/2\pi\lambda)/(\omega^2 + \lambda^2), \tag{23}$$

also in agreement with previous work.

The scheme in eq.(21) is the simplest in the schemes of linear elementary processes that can be used to describe elecrical noise generated by hydrophobic ions in closed pores [7,9,19]. In this case the n_i are interpreted as the number of ions in the membrane in a well on the left-hand-side (1) or right-hand-side (2) of the barrier. This scheme is easily generalized to a N-barrier model in which now the n_i are the number of ions in the *ith* well, *i.e.*

$$1 \leftrightarrow 2 \leftrightarrow \ldots \leftrightarrow N-1 \leftrightarrow N \tag{24}$$

This scheme could be further generalized with side branches, as long as no cycles are included, without changing the fact that the steady state is an equilibrium state.

Equation (24) provides a more complicated example that illustrates the identity of the present formalism with Frehland's formalism [5]. It is easy to verify that the elementary processes in this scheme are linearly independent. Thus, as with the scheme in (21), eq. (14) can be applied. Because the algebra is messy, we will illustrate the equivalence of the two approaches only for the diagonal elements of $D(t)$. Consider the flux over the *ith* barrier, *i.e.*,

$$i \leftrightarrow i+1, \tag{25}$$

which we call the αth process with $V_\alpha^+ = k_\alpha^+ n_i$ and $V_\alpha^- = k_\alpha^- n_{i+1}$. Thus according to (14),

$$D_{\alpha\alpha}(t) = 2V_\alpha\delta(t) + V_\alpha[(H\exp(Ht))_{\alpha\alpha}], \tag{26}$$

where we have taken advantage of the fact that γ is diagonal and we have set $V_\alpha = V_\alpha^+ = V_\alpha^-$. We show in the Appendix that the term in square brackets in this equation is equal to

$$(H\exp(Ht))_{\alpha\alpha} = [k_\alpha^+(\exp(Ht))_{ii+1} - k_\alpha^-(\exp(Ht))_{i+1i+1} - k_\alpha^+(\exp(Ht))_{ii} + k_\alpha^-(\exp(Ht))_{i+1i}] \quad (27)$$

by using the fact that

$$\omega_{\alpha m} = \delta_{mi+1} - \delta_{mi} \quad (28)$$

and transforming between the extensive variable and progress variable representation. Subtracting Frehland's expressions for the one-way fluxes [5,9] it is possible to derive the expression

$$D_{\alpha\alpha}(t) = (V_\alpha^+ + V_\alpha^-)\delta(t) + V_\alpha^+(k_\alpha^+\Omega_{ii+1} - k_\alpha^-\Omega_{i+1i+1}) + V_\alpha^-(k_\alpha\Omega_{i+1i} - k_\alpha^+\Omega_{ii}), \quad (29)$$

where in our notation $\Omega_{ij} = (\exp(Ht))_{ij} - n_i^{ss}$. Using the fact that the steady state is an equilibrium, so that $V_\alpha^+ = V_\alpha^-$, (29) reduces to

$$D_{\alpha\alpha}(t) = 2V_\alpha\delta(t) + V_\alpha[k_\alpha^+(\exp(Ht))_{ii+1} - k_\alpha^-(\exp(Ht))_{i+1i+1} - k_\alpha^+(\exp(Ht))_{ii} + k_\alpha^-(\exp(Ht))_{i+1i}]. \quad (30)$$

Comparing our equations (26) and (27) with Frehland's result in eq.(30), we see that the two expressions are identical, as they should be.

As a final example, we consider the two-state model in Fig.1A. This model could be construed either as nonlinear, if the species L and R are assumed to have variable concentrations, or linear, if L and R are assumed constant and their fluctuations negligible. In the first case, the mechanism is identical to the Michaelis-Menten scheme of enzyme catalysis, with L representing substrate, 1 being the free enzyme, 2 the enzyme-substrate complex, and L the product. Alternatively, the model could represent transport through an open ion channel, with L the ion on the left-hand-side, 1 the unoccupied channel, 2 the singly occupied channel, and R the ion on the right-hand-side. This interpretation corresponds to a open channel with a single binding site and barriers to binding at the left and right [20]. As we have seen in the previous section, flux correlations for either of these interpretations can be treated using our formalism – although it is valid for the enzyme flux model only in the thermodynamic limit.

For simplicity, and because it may be of some experimental relevance [8,21], we focus on the open channel interpretation. Notice that by using a single well model that treats the extensive variables as channel states (1 and 2) rather than as the location of the ion (in the well) [9], that the rates of both elementary processes, α and β, are coupled in this example. Since the spectral density of open channel noise is accessible experimentally, we use (18) for this example. That formula is particularly useful since it is easy to show that the two elementary processes are *not* linearly independent. Note also that with this interpretation the concentrations of the ion, L and R, are absorbed into the rate constants, k_α^+ and k_β^-.

To apply (18) all that is needed is to calculate the inverse of $(i\omega + H)$ since the form of H can be obtained from eq. (9). From Fig.1 it is easy to see that $\omega_{\alpha l} = -1, \omega_{\alpha 2} = 1, \omega_{\beta 1} = 1, \omega_{\beta 2} = -1$. Thus (9) shows that

$$H = \begin{array}{c c} & \begin{array}{cc} \alpha & \beta \end{array} \\ \begin{array}{c} \alpha \\ \beta \end{array} & \begin{pmatrix} -k_\alpha & k_\alpha \\ k_\beta & -k_\beta \end{pmatrix} \end{array}, \tag{31}$$

where $k_\alpha = (k_\alpha^+ + k_\alpha^-)$ and $k_\beta = (k_\beta^+ + k_\beta^-)$. Because the elementary processes are linearly dependent, H is not invertible. Nonetheless, eq.(18) can still be used to calculate the spectral density. Indeed, using eq. (31) and the well known relationship for the inversion of a 2×2 matrix one finds that the inverse of $(i\omega + H)$ is

$$(i\omega + H)^{-1} = \begin{pmatrix} i\omega - k_\beta & -k_\alpha \\ -k_\beta & i\omega - k_\alpha \end{pmatrix} /(-i\omega\lambda - \omega^2), \tag{32}$$

where $\lambda = (k_\alpha + k_\beta)$. According to eq.(18) the absolute square of the matrix elements in (32), weighted by the diagonal elements of γ, give the spectral density. For example, the $\alpha - \alpha$ element of (32) yields

$$\hat{D}_{\alpha\alpha}(\omega) = [(\omega^2 + k_\beta^2)(V_\alpha^+ + V_\alpha^-) + k_\alpha^2(V_\beta^+ + V_\beta^-)]/2\pi(\lambda^2 + \omega^2). \tag{33}$$

Equation (33) shows that the spectral density is a sum of a Lorentzian term and what has been called an "inverse Lorentzian" [20], reminiscent of that for the closed pore in eq.(23). Since the inverse Lorentzian vanishes as $\omega \to 0$, it follows that the low frequency behavior approaches the constant value

$$\hat{D}_{\alpha\alpha}(0) = k_\beta^2(V_\alpha^+ + V_\alpha^-) + k_\alpha^2(V_\beta^+ + V_\beta^-)]/2\pi\lambda^2, \tag{34}$$

and that for $\omega \gg \lambda$

$$\hat{D}_{\alpha\alpha}(\omega) \to (V_\alpha^+ + V_\alpha^-)/2\pi. \tag{35}$$

Using the steady state condition, which gives $n_1^s = k_\alpha/\lambda$, it is not difficult to show that the value of $\hat{D}_{\alpha\alpha}(0)$ in eq.(34) is less than or equal to its asymptotic value in eq.(35). Thus the spectral density for this model always has the qualitative shape shown for the particular values of rate constants used in obtaining Fig.1B.

4 Concluding Remarks

The purpose of this work has been to use the master equation formalism to derive formulae for flux-flux correlation functions for elementary processes that are valid when the relaxation equations near an asymptotically stable steady state are linear. As we have discussed, this includes intrinsically linear elementary processes [5,15], such as those used to describe noise in ion channels or mass diffusion, or any set of nonlinear processes in the thermodynamic limit [3]. Starting as it does from the same master equation formalism as Frehland [5], it is not surprising that the results for linear elementary processes can be shown to be identical to those obtained from his formalism. In contrast to Frehland's approach, which rests on the fact that one-way fluxes consist of a stream of delta function pulses, the present formalism relies only on very general macroscopic relationships [3,11] and gives rise to expressions that involve only the net fluxes in the elementary processes. As it is these latter fluxes that are measureable experimentally, the resulting formulae have a close connection to experiment.

We have considered both linearly independent and linearly dependent elementary processes. For linearly independent elementary processes we have obtained explicit expression for the time correlation functions of the fluxes, eq.(12-14), as well as a very simple formula, eq.(18), for the spectral density. This latter formula is independent of the existence of an invertible transformation between the extensive variables and the progress variables, and so applies as well to linearly *dependent* elementary processes. As we have illustrated with several examples, this result for the spectral density is particularly simple to apply. We believe that it will be useful in helping to model the effect of various types of molecular noise on fluxes, especially in open ion channels [8,21].

Acknowledgements

This work has profited from correspondence with Dr. Yi-der Chen and Dr. Pedro Colmenares.

Figure Caption

Figure 1. Part A: Diagram of the two state elementary processes for treating either Michaelis–Menten kinetics or single site binding to an open ion channel. Part B: The spectral density for the $\alpha - \alpha$ flux correlation function for the diagram in A, when interpreted as a scheme for a *single* open ion channel. Rate constants were chosen as $k_\alpha^+ = 1, k_\alpha^- = 2, k_\beta^+ = 5, k_\beta^- = 1.0$, with units in μs^{-1} to correspond to typical open channel fluxes under nonequilibrium conditions.

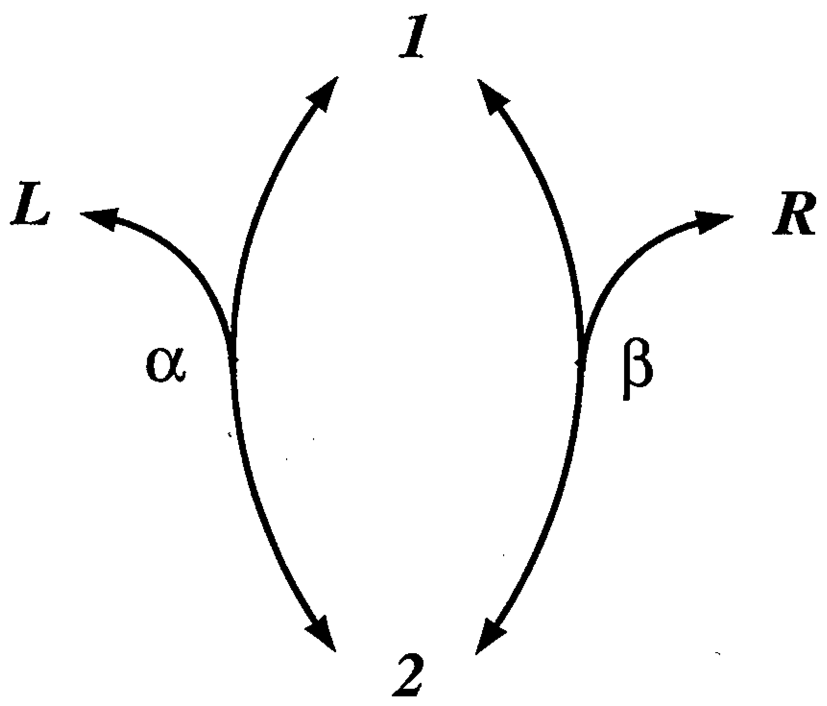

Fig. 1A

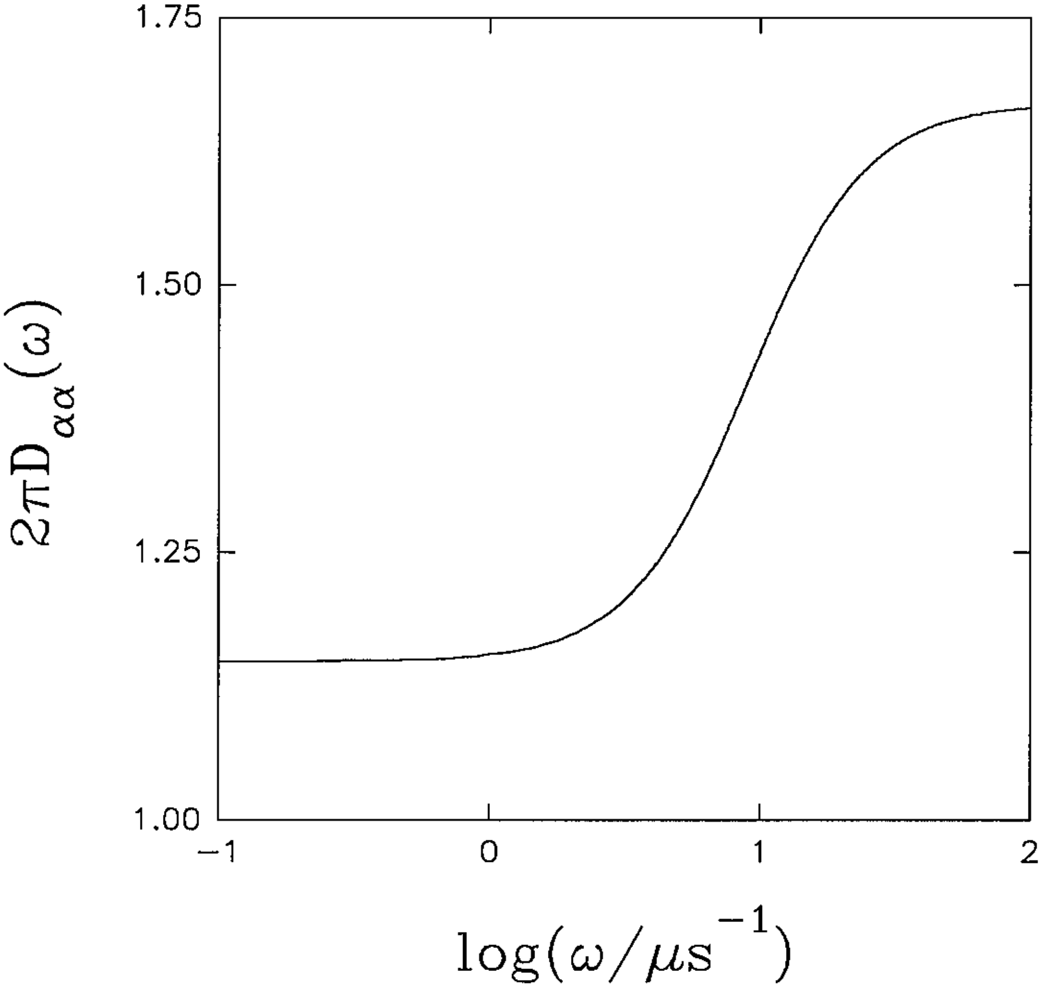

Figure 1B

5 Appendix

Here we show that the square bracketed term in (26) is given by the expression in (27). Transforming the exponential into the extensive variable representation we have

$$
\begin{aligned}
(H\exp(Ht))_{\alpha\alpha} &= \sum_{\beta,j,m} H_{\alpha\beta}B_{\beta j}(\exp(Ht))_{jm}\omega_{\alpha m} && (36)\\
&= \sum_{\beta,j,m} (k_\alpha^+\omega_{\beta i} - k_\alpha^-\omega_{\beta i+1})B_{\beta j}(\exp(Ht))_{jm}\omega_{\alpha m}, && (37)
\end{aligned}
$$

where (9) was used. Further simplication comes from (3), which leads to

$$
\begin{aligned}
(H\exp(Ht))_{\alpha\alpha} &= \sum_m [k_\alpha^+(\exp(Ht))_{im} \\
&\quad -k_\alpha^-(\exp(Ht))_{i+1m}]\omega_{\alpha m} && (38)\\
&= [k_\alpha^+(\exp(Ht))_{ii+1} - k-_\alpha(\exp(Ht))_{i+1i+1} \\
&\quad -k_\alpha^+(\exp(Ht))_{ii} + k-_\alpha(\exp(Ht))_{i+1i}] && (39)
\end{aligned}
$$

where in the last equality, which is identical to (27), (28) was used.

6 References

1. A. A. Frost and R. G. Pearson, *Kinetics and Mechanism*, 2nd ed. (Wiley, New York, 1965).

2. J. Keizer, J. Chem. Phys. **64** (1976) 1679.

3. J. Keizer, *Statistical Thermodynamics of Nonequilibrium Processes* (Springer-Verlag, New York, 1987).

4. Ref. 3, Chapter 4.

5. E. Frehland, *Stochastic Processes in Discrete Biological Systems* (Springer-Verlag, Berlin, 1982).

6. H. A. Kolb and P. Laüger, J. Membr. Bio. **28** (1977) 321.

7. L. J. Bruner and J. E. Hall, Biophys. J. **28** (1979) 511.

8. F. J. Sigworth, Biophys. J. **47** (1985) 709.

9. E. Frehland, Biophys. Chem. **8** (1978) 255.

10. E. Frehland, Biophys. Chem. **12** (1980) 63.

11. S. R. de Groot and P. Mazur, *Non-equilibrium Thermodynamics* (North Holland, Amsterdam, 1962).

12. J. Keizer, J. Chem. Phys. *63* (1975) 5037.

13. Ref. 3, Chapter 3.

14. T. L. Hill, *Free Energy Transduction in Biology* (Academic Press, New York, 1977).

15. Y. Chen, Proc. Nat. Acad. Sci., USA **72** (1975) 3807.

16. Ref. 11, Chapter VIII.

17. T. G. Kurtz, J. Appl. Prob. **8** (1971) 344.

18. P. Laüger, Biochim. Biophys. Acta **507** (1978) 337.

19. Y. Chen, Biophys. Chem. **17** (1983) 87.

20. P. Solleder and E. Frehland, Biophys. Chem. **25** (1986) 147.

21. S. H. Heinemann and F. J. Sigworth, Biophys. J. **57** (1990) 499.