Generalized conservation equation for multicompartmental systems

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A projection operator technique is used to derive an equation for local tissue tracer content $Q(t)$, assuming linear multicompartmental kinetics for tracer utilization. The resulting equation has the form $(d/dt)\,Q(t) = FC_a(t) - \Lambda Q(t) - \int_0^t d\tau[\xi(\tau)C_a(t-\tau) - \psi(\tau)Q(t-\tau)]$, where F and $C_a(t)$ denote local blood flow and concentration of tracer, respectively. Tissue complexity is contained within the new parameters Λ, $\xi(t)$, and $\psi(t)$, where the time-dependent coefficients are expressed as sums of exponentials. Two simple applications are considered: tissue heterogeneity and internal trapping of tracer. The relationship to effective single compartmental analysis, as is used for local cerebral blow flow determination, is evaluated.

I. INTRODUCTION

Physiological imaging schemes rely heavily on a basic understanding of the mechanisms whereby a radiolabeled substrate is utilized. Analysis of data obtained in this way provides a mean for estimating important system parameters. In many situations, mathematical description by linear compartmental models is sufficient. A simple example is the evaluation of local cerebral flow F from tomographic data obtained from[15] 0-labeled water. Solution of the first-order differential equation[1-7,11]

$$\frac{d}{dt}Q(t) = F[C_a(t) - Q(t)/V_d], \tag{1.1}$$

where $Q(t)$ and $C_a(t)$ represent tissue tracer content and arterial concentration of tracer at times t, respectively, results in an estimate for F. V_d is the local distribution volume estimated from the data or taken as a specific value. More complex models are applied to determination of local tissue oxygen and glucose utilization.[8-10] Since one cannot sample individual compartments, parameters are extracted from two measured quantities: local tissue tracer content $Q(t)$ and the measured arterial input $C_a(t)$.

Generalization of Eq. (1.1) to include more complex situations is readily accomplished. Inasmuch as one only measures $Q(t)$ and $C_a(t)$, an equation in terms of these quantities alone is sufficient to describe a given measurement. To this end, a projection operator technique is employed to transform a class of multicompartmental models (Sec. II) to a single equation in $Q(t)$ and $C_a(t)$.[12,13] The resulting expression bears a formal resemblance to Eq. (1.1). Tissue complexity is contained in two new time-dependent functions $\psi(t)$ and $\xi(t)$, and an effective partition coefficient Λ^{-1}. General expressions for $\psi(t)$, $\xi(t)$, and Λ are derived.

The general formalism derived in Sec. II is then applied to two specific examples: internal trapping of tracer[14] represented by a two-compartment model and tissue heterogeneity.[6] In the former, only a fraction of tissue tracer activity is available for washout at a given time. One supposes that within the cellular-interstitial space other processes occur which bind tracer. Such analysis indicates that short-time and steady-state determination of compartment parameters from an effective "one compartmental" model can be in disagreement.

Tissue heterogeneity is of particular importance when sampling at an interface (i.e., grey–white matter). An equation for local tissue activity is derived for the model considered by Herscovitch *et al.* The nature of time dependence introduced by tissue elements with different blood flows is evaluated, as well as conditions for which such time dependence may be neglected.

The relationship between the technique presented herein and deconvolution schemes for the tissue transfer function is evaluated.

II. GENERALIZED CONSERVATION EQUATION

Consider the situation in which radiolabeled pharmaceutical is delivered to a tissue element. Suppose that the tissue element is divided into N compartments, a subset A of which may exchange directly with the plasma. Let F_i denote the blood flow to the ith compartment, then the corresponding input function if $F_i\ C_a(t)$. $C_a(t)$ is the instantaneous arterial concentration of tracer at time t. Furthermore, let $Q_j(t)$ represent the tracer activity in compartment j at time t. We shall consider the following class of kinetic equations for $Q_j(t)$:

$$\frac{d}{dt}Q_j = -\sum_{k=1}^{N} M_{jk}Q_k(t) + f_j(t), \tag{2.1}$$

where the matrix element M_{jk} describes the rate of substrate exchange between compartments j and k, and

$$f_j(t) = \begin{cases} F_jC_a(t), & j \in A, \\ 0, & \text{otherwise.} \end{cases} \tag{2.2}$$

Expressed in matrix form, Eq. (2.1) becomes

$$\frac{d}{dt}\mathbf{Q}(t) = -\mathbf{M}\mathbf{Q}(t) + \mathbf{f}(t), \tag{2.3}$$

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with $\mathbf{Q}(t) \equiv \text{col}\ \{Q_j(t)\}$, $\mathbf{f}(t) = \text{col}\ \{f_j(t)\}$, $\mathsf{M} = \{M_{ij}\}$ and col≡column. Equation (2.3) is in a form particularly amenable to the application of projection operator techniques. Such methods have proven to be useful in reducing equations with multiple degrees of freedom to a few relevant variables.[12,13] Inasmuch as total tissue element activity is sampled, the relevant variable is

$$Q(t) = \sum_{j=1}^{N} Q_j(t) = \boldsymbol{\alpha}^T \mathbf{Q}(t). \tag{2.4}$$

$\boldsymbol{\alpha}$ is a column vector whose elements are unity and T denotes transpose operation. Given these relations, it is demonstrated in Appendix A that $Q(t)$ satisfies the equation

$$\frac{d}{dt} Q(t) = F C_a(t) - \Lambda Q(t) - \int_0^t d\tau [\xi(\tau) C_a(t-\tau) - \psi(\tau) Q(t-\tau)], \tag{2.5}$$

where F is the total blood flow to the tissue element and the coefficients Λ, $\xi(t)$ and $\psi(t)$ are defined by

$$\Lambda = \frac{1}{N} \sum_{ij} M_{ij}, \tag{2.6a}$$

$$\psi(t) = -\frac{1}{N} \frac{d}{dt} \hat{\boldsymbol{\alpha}}(t)^T \mathsf{M}_2 \boldsymbol{\alpha}, \tag{2.6b}$$

$$\xi(t) = -\frac{d}{dt} \sum_{j \in A} \hat{\alpha}_j(t) F_j, \tag{2.6c}$$

and the time-dependent vector $\hat{\boldsymbol{\alpha}}(t)$ is given by Eq. (A9). The entire system of Eqs. (2.1) are reduced to a single expression for the measured substrate and arterial input. Tissue complexity is contained within the coefficients Λ, $\psi(t)$, and $\xi(t)$ given by Eqs. (2.6).

We next demonstrate that $\psi(t)$ and $\xi(t)$ are expressable as sums of exponentials:

$$\psi(t) = \sum_{j=1}^{N-1} \psi_j e^{-t/\tau_j}, \tag{2.7a}$$

$$\xi(t) = \sum_{j=1}^{N-1} \xi_j e^{-t/\tau_j}, \tag{2.7b}$$

where the set $\{\psi_i, \xi_i\}$ are constant coefficients and the set $\{1/\tau_i\}$ are the characteristic values for $\hat{\mathsf{M}}_2$, Eqs. (B2)–(B4). This decomposition contains $N-1$ terms corresponding to the remaining $N-1$ degrees of freedom projected out of Eq. (2.1). The details are presented in Appendix B. The set $\{\xi_j, \psi_j, \tau_j\}$ are therefore easily calculated for a specific model or alternatively may serve as parameters to be determined empirically.

Equations (2.5) and (2.7) form a basis for experimentally characterizing a tissue element in a manner analogous to deconvolution techniques. Let $I(t)$ denote the tissue response function to the unit impulse input, then for arbitrary input, $C_a(t)$,

$$Q(t) = \int_0^t d\tau C_a(t-\tau) I(\tau). \tag{2.8}$$

Defining the Laplace transform of a function $g(t)$ by

$$\tilde{g}(s) \equiv \int_0^\infty dt e^{-st} g(t), \tag{2.9}$$

results in

$$\tilde{Q}(s) = \tilde{C}_a(s) \tilde{I}(s). \tag{2.10}$$

Taking the Laplace transform of Eqs. (2.5)–(2.7) and solving for $\tilde{Q}(s)$ allows identification of $\tilde{I}(s)$:

$$\tilde{I}(s) = [F - \tilde{\xi}(s)]/[s + \Lambda - \tilde{\psi}(s)], \tag{2.11}$$

with

$$\tilde{\xi}(s) = \sum_{j=1}^{N-1} \xi_j \Big/ \left(s + \frac{1}{\tau_j}\right), \tag{2.12a}$$

$$\tilde{\psi}(s) = \sum_{j=1}^{N-1} \psi_j \Big/ \left(s + \frac{1}{\tau_j}\right). \tag{2.12b}$$

In the subsequent sections, two simple applications of this general formalism are considered.

III. TWO-COMPARTMENT MODEL: INTERNAL TRAPPING OF TRACER

Two basic assumptions of the Kety–Schmidt equation,[11,15] Eq. (1.1), are

(1) Rapid equilibration across the blood-brain barrier.

(2) Structureless tissue element.

We extend the latter assumption by supposing that within the cellular-interstitial space, other processes occur which bind tracer. The amount of tracer available for exchange with the plasma is thereby reduced. The representative equations are then given by[14]

$$\frac{d}{dt} Q_f(t) = F[C_a(t) - Q_f(t)/V] - k_1 Q_f(t) + k_2 Q_b(t), \tag{3.1a}$$

$$\frac{d}{dt} Q_b(t) = k_1 Q_f(t) - k_2 Q_b(t), \tag{3.1b}$$

where the subscripts f and b designate "free" and "bound" components, respectively. In addition the following local quantities have been introduced:

$Q_f(t)$ = local tracer activity that freely exchanges with the plasma,

$Q_b(t)$ = nonfreely exchangeable tracer,

k_1, k_2 = rate constants for accumulation and decline of tracer, respectively,

and V has dimensions of volume. Equations (3.1) are transformed into matrix form by making the identifications:

$$\mathbf{Q} = \begin{pmatrix} Q_f \\ Q_b \end{pmatrix}, \tag{3.2a}$$

$$\mathbf{f} = \begin{pmatrix} F \\ 0 \end{pmatrix} C_a(t), \tag{3.2b}$$

$$\mathsf{M} = \begin{pmatrix} k_1 + F/V & -k_2 \\ -k_1 & k_2 \end{pmatrix}. \tag{3.2c}$$

With this definition, it is demonstrated in Appendix B that the local tissue tracer content satisfies the conservation equation:

$$\frac{d}{dt}Q(t) = F[C_a(t) - Q(t)/2V] - \int_0^t d\tau[\xi(t-\tau)C_a(\tau) - \psi(t-\tau)Q(\tau)], \tag{3.3}$$

with $\xi(\tau)$, $\psi(\tau)$ given by

$$\xi(\tau) = \frac{F^2}{2V}e^{-\mu\tau/2}, \tag{3.4a}$$

$$\psi(\tau) = \frac{F}{2V}\left(\frac{F}{2V} + k_1 - k_2\right)e^{-\mu\tau/2}, \tag{3.4b}$$

$$\mu = \frac{F}{V} + 2(k_1 + k_2). \tag{3.4c}$$

Further analysis of $Q(t)$ is facilitated in the Laplace domain. Applying Eq. (2.9) to Eqs. (3.3) and (3.4) results in the following expression for the tissue transfer function,

$$\tilde{I}(s) = [F - \tilde{\xi}(s)]\Big/\left[s + \left(\frac{F}{2V} - \tilde{\psi}(s)\right)\right], \tag{3.5a}$$

$$\tilde{\xi}(s) = \frac{F^2}{2V}\Big/(s + \mu/2), \tag{3.5b}$$

$$\tilde{\psi}(s) = \frac{F}{2V}\left(\frac{F}{2V} + k_1 - k_2\right)\Big/(s + \mu/2). \tag{3.5c}$$

For short times, the high-frequency ($s \to \infty$) components of $\tilde{I}(s)$ are most important. The leading behavior of $\tilde{I}(s)$ in powers of $1/s$ is

$$\tilde{I}(s) \sim \left(1 - \frac{F}{sV}\right)\frac{F}{s}, \quad s \to \infty,$$

indicating that V is the effective "short-time" distribution volume; incorporation of tracer into a bound compartment has not yet occurred. Alternatively, for times such that $\mu t \gg 1$ (i.e., $\mu \gg s$), we may approximate $\tilde{\xi}(s) \sim \tilde{\xi}(0)$, $\tilde{\psi}(s) \sim \tilde{\psi}(0)$. Making these replacements in Eq. (3.5) and reconverting to an equation for $Q(t)$ results in the asymptotic equation,

$$\frac{d}{dt}Q(t) \simeq \frac{2F}{\mu}[(k_1 + k_2)C_a(t) - 2k_2Q(t)/2V], \tag{3.6}$$

or in situations for which $C_a(t)$ approaches a steady-state value,

$$Q(\infty)/C_a(\infty) \to V\left(\frac{k_1 + k_2}{k_2}\right). \tag{3.7}$$

Equation (3.6) reflects the additional volume occupied by bound tracer at steady-state conditions.

Several authors have commented on a nonphysiologic decline of cerebral blood flow as a function of time when determined from single compartmental analysis.[7,16] Suppose that $\hat{F}(t)$ denotes the estimated blood flow obtained by assuming the validity of Eq. (1.1); then for a given data set $\{Q(t), C_a(t)\}$,

$$\hat{F}(t) = Q(t)\Big/\int_0^t d\tau[C_a(\tau) - Q(\tau)/V] \tag{3.8}$$

provides an estimate of local blood flow. In the presence of internal trapping of tracer, we expect $\hat{F}$ should approximate F for sufficiently short times. Solution of Eq. (3.3) for F results in a relatively complicated nonlinear expression for local flow which greatly simplifies for $\mu t \gg 1$,

$$F = Q(t)\Big/\left\{\left(\frac{k_1 + k_2}{F/2V + k_1 + k_2}\right)\int_0^t d\tau \times\left[C_a(\tau) - \frac{Q(\tau)}{V}\left(\frac{k_2}{k_1 + k_2}\right)\right]\right\}, \tag{3.9}$$

where Eq. (3.6) has been used. This expression becomes similar to Eq. (3.8) provided we replace V by the steady-state distribution volume $V(1 + k_1/k_2)$, and the coefficient $(k_1 + k_2)/(F/2V + k_1 + k_2)$ can be set approximately to unity. The latter condition holds when there is rapid equilibration within the internal compartment. Actual variation of $\hat{F}(t)$ may then be detected in nonflow limited situations. Alternatively, comparison of short-time and asymptotic determinations of flow and distribution volume may be used to validate single compartmental analysis.

IV. TWO-COMPARTMENT MODEL: TISSUE HETEROGENEITY

Consider a tissue element as consisting of two compartments, each receiving a separate blood flow. The analogous experimental situation is a measurement of local tracer content at a tissue interface. This model was numerically evaluated by Herscovitch *et al.*, in order to validate the single compartment analysis for cerebral blood flow determination.[6] Let $Q_1(t)$ and $Q_2(t)$ denote local tracer content in each component, and also suppose that Eq. (1.1) is valid in each regime, then

$$\frac{d}{dt}Q_1(t) = F_1[C_a(t) - Q_1(t)/V_1], \tag{4.1a}$$

$$\frac{d}{dt}Q_2(t) = F_2[C_a(t) - Q_2(t)/V_2], \tag{4.1b}$$

where $\{F_i, V_i\}$ refer to local blood flow and distribution volume. Application of the general formalism, Eq. (2.5), to this situation results in an exact equation for $Q(t)$. Equation (4.1) is placed into matrix form by defining

$$\mathbf{Q}(t) = \begin{pmatrix} Q_1(t) \\ Q_2(t) \end{pmatrix}, \tag{4.2a}$$

$$\mathbf{f}(t) = C_a(t)\begin{pmatrix} F_1 \\ F_2 \end{pmatrix}, \tag{4.2b}$$

$$\mathbf{M} = \begin{pmatrix} F_1/V_1 & 0 \\ 0 & F_2/V_2 \end{pmatrix}. \tag{4.2c}$$

Utilizing these definitions, it is demonstrated in Appendix B that $Q(t)$ is a solution of Eq. (2.5), where the coefficients Λ, $\psi(t)$, and $\xi(t)$ are given by

$$\Lambda = \tfrac{1}{2}(F_1/V_1 + F_2/V_2) \tag{4.3a}$$

$$\xi(t) = (F_1/V_1 - F_2/V_2)(F_1 - F_2)e^{-2\Lambda t}, \tag{4.3b}$$

$$\psi(t) = \tfrac{1}{2}(F_1/V_1 - F_2/V_2)^2 e^{-2\Lambda t}. \tag{4.3c}$$

The quantity Λ is the mean rate of transit through the tissue element. Intrinsic time dependence introduced by the functions $\xi(t)$ and $\psi(t)$ is negligible when transit rates through each component are comparable, $F_1/V_1 \sim F_2/V_2$. If we suppose the latter to be true, Eq. (1.1) is satisfied provided we define an effective distribution volume V_{eff} by

$$\frac{1}{V_{\text{eff}}} = \frac{\alpha_1}{V_1} + \frac{\alpha_2}{V_2}, \tag{4.4}$$

with

$$\alpha_i = \tfrac{1}{2}(F_i/F), \quad i = 1,2, \tag{4.5}$$

F being the total flow. In the situation for which $V_1 \sim V_2$, the correction introduced by the time-dependent coefficients $\xi(t)$ and $\psi(t)$ is second order in $(F_1 - F_2)/F$ (i.e., 0 $[(F_1 - F_2)/F]^2$.

V. DISCUSSION

Projection operator techniques have proven to be a useful means of reducing dynamical descriptions of complex systems to several relevant variables. Application to linear multicompartmental analysis results in a simple appearing equation for local tissue tracer content (Sec. II). Tissue complexity is buried in the functions $\psi(t)$ and $\xi(t)$, which may be reduced to expansions involving the characteristic values of the modified evolution matrix $\hat{\mathbf{M}}_2$, Eq. (A9).

We have considered two particular examples herein, that of tissue heterogeneity and internal trapping of tracer. In the latter, tracer washout is primarily determined by the mean rate of transit through the conglomerate tissue element, $\Lambda \simeq 1/2\ (F_1/V_1 + F_2/V_2)$. The time-dependent corrections to the resulting single compartmental equation are roughly second order in the relative fractional flow [i.e., $\sim (F_1 - F_2)^2/F^2$]. When internal trapping of tracer is of importance, the asymptotic distribution volume reflects the additional bound tracer, $V_d \sim V(1 + k_1/k_2)$. Furthermore, flow determination by dynamic single-compartment analysis is approximately valid at sufficiently short times or asymptotically, provided the appropriate distribution volume is used. Time dependence in flow determined from a single compartment analysis should be observed in nonflow-limited situations, as would be expected.

A potential application of this technique relates to situations in which a specific mathematical model for tracer utilization is unavailable. The generalized conservation equation, Eq. (2.5), may then serve as a starting point for data analysis. Empirical determination of the parameters $\{\psi_i, \xi_i, \tau_i\}$ characterize the functions $\psi(t)$ and $\xi(t)$. Such an approach is similar to deconvolution schemes for the tissue transfer function.

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APPENDIX A

Recall the vector $\boldsymbol{\alpha}$ defined by

$$\boldsymbol{\alpha} = \text{col}\{1,1,\ldots\}. \tag{A1}$$

Consider operators p and q defined by

$$p \equiv \frac{1}{N}\boldsymbol{\alpha}\boldsymbol{\alpha}^T, \tag{A2}$$

$$q \equiv \mathsf{I} - p, \tag{A3}$$

I being the identity operator. The operators p and q satisfy the idempotence property, $p^2 = p$ and $q^2 = q$, and therefore, qualify as projection operators.[17] Furthermore, p and q are readily demonstrated to be complementary in the sense that $pq = qp = 0$.

We next show that the operators p and q taken with Eq. (2.3) can be used to derive Eq. (2.5). The methods employed are well known within the context of derivations of transport theory in statistical physics.[12,13] Define the following quantities:

$$\mathbf{Q}_1 = p\mathbf{Q}, \tag{A4a}$$

$$\mathbf{Q}_2 = q\mathbf{Q}, \tag{A4b}$$

$$\mathsf{M}_1 = p\mathsf{M}, \tag{A4c}$$

$$\mathsf{M}_2 = q\mathsf{M}, \tag{A4d}$$

$$\mathbf{f}_1 = p\mathbf{f}, \tag{A4e}$$

$$\mathbf{f}_2 = q\mathbf{f}. \tag{A4f}$$

Applying p and q individually to Eq. (2.3) and using Eqs. (A4) yields equations for $\mathbf{Q}_1$ and $\mathbf{Q}_2$:

$$\left(\frac{d}{dt} + \mathsf{M}_1\right)\mathbf{Q}_1(t) = \mathbf{f}_1(t) - \mathsf{M}_1\mathbf{Q}_2(t), \tag{A5a}$$

$$\left(\frac{d}{dt} + \mathsf{M}_2\right)\mathbf{Q}_2(t) = \mathbf{f}_2(t) - \mathsf{M}_2\mathbf{Q}1(t). \tag{A5b}$$

It is convenient to eliminate $\mathbf{Q}_2$ in the above equations thereby resulting in a single expression for $\mathbf{Q}_1$:

$$\left(\frac{d}{dt} + \mathsf{M}_1\right)\mathbf{Q}_1(t) = \mathbf{f}_1(t) - \int_0^t d\tau \mathsf{M}_1 e^{-\tau\mathsf{M}_2}[\mathbf{f}_2(t-\tau) - \mathsf{M}_2\mathbf{Q}_1(t-\tau)], \tag{A6}$$

where the initial condition $\mathbf{Q}(0) = 0$ has been used. We make use of the relations,

$$\boldsymbol{\alpha}^T\mathbf{Q}_1(t) = Q(t), \tag{A7a}$$

$$\Lambda \equiv \frac{1}{N}\boldsymbol{\alpha}^T\mathsf{M}\boldsymbol{\alpha} = \frac{1}{N}\sum_{ij} M_{ij}, \tag{A7b}$$

$$\boldsymbol{\alpha}^T\mathbf{f}_1(t) \equiv FC_a(t) = C_a(t)\sum_{j\in A} F_j, \tag{A7c}$$

where Eq. (A7b) defines Λ, and F is the total flow to the tissue element. Now consider evaluation of the term

$$\boldsymbol{\alpha}^T\mathsf{M}_1 e^{-\tau\mathsf{M}_2}\mathsf{M}_2\mathbf{Q}_1(t-\tau) \equiv \psi(\tau)Q(t-\tau),$$

with the new function $\psi(\tau)$ being defined by

$$\psi(\tau) \equiv \frac{1}{N}\boldsymbol{\alpha}^T\mathsf{M}e^{-\tau\mathsf{M}_2}\mathsf{M}_2\boldsymbol{\alpha}. \tag{A8}$$

This expression is further simplified by introducing two new definitions:

$$\hat{\mathsf{M}}_2 \equiv q\mathsf{M}_2^T, \tag{A9a}$$

$$\hat{\boldsymbol{\alpha}}(\tau) \equiv e^{-\tau\hat{\mathsf{M}}_2}\boldsymbol{\alpha}. \tag{A9b}$$

Utilizing the idempotence of q, as well as the property $\mathbf{a}^Tq\mathbf{b} = (q\mathbf{a})^T\mathbf{b}$, the vectors $\mathbf{a}$ and $\mathbf{b}$ being arbitrary, allows us to write

$$\alpha^T M e^{-\tau M_2} M_2 \alpha = (q M^T \alpha)^T e^{-\tau M_2} M_2 \alpha.$$

Expanding the exponential as a power series and again employing idempotence property results in

$$(q M^T \alpha)^T e^{-\tau M_2} M_2 \alpha = (q M^T e^{-\tau q M^T} \alpha)^T M_2 \alpha,$$

which by Eq. (A9) becomes

$$\psi(\tau) = -\frac{1}{N}\frac{d}{dt}\hat{\alpha}(\tau)^T M_2 \alpha. \tag{A10}$$

Similarly, we define a function $\xi(\tau)$ by

$$\xi(\tau) = -\frac{d}{dt}\sum_{j\epsilon A}\hat{\alpha}_j(\tau)F_j, \tag{A11}$$

Then Eq. (A6) simplifies to

$$\frac{d}{dt}Q(t) = FC_a(t) - \Lambda Q(t) - \int_0^t d\tau[\xi(\tau)C_a(t-\tau) - \psi(\tau)Q(t-\tau)]. \tag{A12}$$

APPENDIX B

Further decomposition of the functions $\psi(t)$ and $\xi(t)$ is accomplished in terms of the characteristic values of the matrix $\hat{M}_2$, Eq. (A9). Since $\hat{M}_2$ is in general not symmetric, we must separately define left and right eigenvectors by

$$\hat{M}_2 \mathbf{V}_r = \lambda \mathbf{V}_r, \tag{B1a}$$

$$\mathbf{V}_l \hat{M}_2 = \lambda \mathbf{V}_l. \tag{B1b}$$

By virtue of Eq. (A9), $\hat{M}_2$ has at least one zero eigenvalue since $\alpha^T \hat{M}_2 = 0$. Let us assume that the remaining $N-1$ eigenvalues are distinct, then an orthonormal set is easily constructed:

$$\mathbf{V}_l^j \mathbf{V}_r^k = \delta_{jk}, \tag{B2}$$

where

$$\delta_{ij} = \begin{cases} 1, & i = j, \\ 0, & i \neq j, \end{cases} \tag{B3}$$

is the Kronecker delta. By convention choose $\mathbf{V}_l^N = \alpha^T$, then the vector $d/dt\,\hat{\alpha}(t)$ is equivalent to

$$\frac{d}{dt}\hat{\alpha}(t) = -\sum_{j=1}^{N-1}\frac{1}{\tau_j}e^{-t/\tau_j}(\mathbf{V}_l^j \alpha)\mathbf{V}_r^j, \tag{B4}$$

where the set $\{1/\tau_j\}$ are the nonzero eigenvalues of $\hat{M}_2$. Substitution of Eq. (B4) into Eqs. (A10) and (A11) and comparison to Eqs. (2.7) yields general expressions for the coefficients $\{\psi_i, \xi_i\}$:

$$\psi_j = \frac{1}{\tau_j}(\mathbf{V}_l^j \alpha)(\mathbf{V}_r^{jT} M \alpha), \tag{B5a}$$

$$\xi_j = \frac{1}{\tau_j}(\mathbf{V}_l^j \alpha)\sum_{p\epsilon A} V_{r_p}^j F_p. \tag{B5b}$$

We next apply these decompositions to the particular models considered in Secs. III and IV. For M given by Eqs. (3.2), evaluation of $\hat{M}_2$ results in

$$\hat{M}_2 = \tfrac{1}{2}\begin{pmatrix} F/V + k_1 + k_2 & -(k_1+k_2) \\ -(F/V + k_1 + k_2) & (k_1+k_2) \end{pmatrix}, \tag{B6}$$

which has a nonzero eigenvalue

$$\frac{\mu}{2} = \frac{F}{2V} + k_1 + k_2. \tag{B7}$$

The corresponding left and right eigenvectors are

$$\mathbf{V}_r = \frac{1}{\sqrt{\mu}}\begin{pmatrix} 1 \\ -1 \end{pmatrix}, \tag{B8a}$$

$$\mathbf{V}_l = \frac{1}{\sqrt{\mu}}\begin{pmatrix} \frac{F}{V} + k_1 + k_2 & -(k_1+k_2) \end{pmatrix}. \tag{B8b}$$

Applying this to Eq. (B4) then results in

$$-\frac{d}{dt}\hat{\alpha}(t) = \frac{F}{2V}e^{-\mu t/2}\begin{pmatrix} 1 \\ -1 \end{pmatrix},$$

which when substituted into Eqs. (B5) yields Eqs. (3.4).

Similarly, for M given by Eq. (4.2), we find

$$\hat{M}_2 = \begin{pmatrix} F_1/V_1 & -F_2/V_2 \\ -F_1/V_1 & F_2/V_2 \end{pmatrix}, \tag{B9}$$

with eigenvalue

$$2\Lambda = (F_1/V_1 + F_2/V_2) \tag{B10}$$

and eigenvectors

$$\mathbf{V}_r = \frac{1}{\sqrt{2\Lambda}}\begin{pmatrix} 1 \\ -1 \end{pmatrix}, \tag{B11a}$$

$$\mathbf{V}_l = \frac{1}{\sqrt{2\Lambda}}\begin{pmatrix} \frac{F_1}{V_1} & -\frac{F_2}{V_2} \end{pmatrix}, \tag{B11b}$$

which results in

$$\frac{d}{dt}\hat{\alpha}(t) = \left(\frac{F_1}{V_1} - \frac{F_2}{V_2}\right)e^{-2\Lambda t}\begin{pmatrix} 1 \\ -1 \end{pmatrix},$$

and Eq. (4.3) when applied to Eqs. (B4–B5).

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