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Global Compartmental Pharmacokinetic Models for Spatiotemporal SPECT and PET Imaging*

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Abstract

A new mathematical framework is introduced for combining the linear compartmental models used in pharmacokinetics with the spatiotemporal distributions of activity that are measured in single photon emission computed tomography (SPECT) and PET imaging. This approach is global in the sense that the compartmental differential equations involve only the overall spatially integrated activity in each compartment. The kinetics for the local compartmental activities are not specified by the model and would be determined from data. It is shown that an increase in information about the spatial distribution of the local compartmental activities leads to an increase in the number of identifiable quantities associated with the compartmental matrix. These identifiable quantities, which are important kinetic parameters in applications, are determined by computing the invariants of a symmetry group. This group generates the space of compartmental matrices that are compatible with a given activity distribution, input function, and set of support constraints. An example is provided where all of the compartmental spatial supports have been separated, except that of the vascular compartment. The question of estimating the identifiable parameters from SPECT and PET data is also discussed.

Keywords

pharmacokinetics; biomedical imaging; compartmental modeling; single photon emission computed tomography; positron emission tomography

1. Introduction

Linear compartmental models have been used successfully to describe tracer kinetics in biomedical research and to explain the results of pharmacokinetic experiments [1]. For a bolus input, the basic form for the activity or tracer concentration in any given compartment, after the bolus has been administered, is a sum of decaying exponentials as a function of time. For this reason, in single photon emission computed tomography (SPECT) and PET imaging, multiple exponential models are often used to model the time course of activity in individual voxels [2,3,4,5,6], in regions of interest [7,8,9,10], or in voxels within regions of interest [11,12,13]. The justification for this type of kinetic model is usually an appeal to compartmental models. We might call this approach local compartmental modeling.

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However, conventional compartmental modeling in pharmacokinetics is a global model; that is, it deals with the whole organism. As will be shown below, when this type of global compartmental modeling is combined with the spatiotemporal distributions of activity that are the objects of SPECT and PET imaging, the resulting temporal behavior of the local activity is not a sum of decaying exponentials except under special, and probably unrealistic, circumstances. This is one motivation for finding out which aspects of conventional compartmental modeling do carry over to the imaging context.

In section 2, we introduce the basic object model that allows us to combine SPECT or PET imaging with a compartmental description of kinetic behavior. This object model represents the simplest way to combine the concept of a spatiotemporal distribution of activity with compartmental kinetic equations. In sections 3 and 4, we derive some alternate expressions for the activity distribution that can be derived from the original object model. In section 3, we introduce the local input function and relate it to the activity distribution. In section 4, we use the eigenvector decomposition for the compartmental matrix to decompose the activity distribution into a sum of functions, one for each eigenvalue. These three sections provide three equivalent mathematical expressions for a spatiotemporal activity distribution that are all consistent with the compartmental kinetic equations. The relations between the object model presented here and the standard multiexponential models are described in section 5.

Beginning in section 6, we address the identifiability problem for the compartmental matrix. For this discussion, we assume that we have a spatiotemporal activity distribution, an input function, and information about the spatial support of each compartment. In practice, the activity distribution would be the result of a reconstruction algorithm, the input function would be measured as the tracer is being administered, and the support information would be the result of prior knowledge about the anatomy, possibly from another imaging modality such as CT or magnetic resonance imaging (MRI). We then ask whether there is more than one compartmental matrix that is compatible with all of this information. If that is true, we also want to know which quantities associated with the compartmental matrix will be constant across all compatible matrices. These invariants are the identifiable quantities of the compartmental matrix, and they represent the most information about the compartmental matrix that we can hope to extract from our imaging experiment.

In section 6, we find these invariants when there is no support information and, in section 7, we go to the opposite extreme, where we are able to completely separate the compartments spatially. With no support information, the results are very similar to those in standard compartmental modeling, while with complete support information, we find that the entire compartmental matrix is identifiable. The more common situation, where we have partial support information, is described in sections 8–10. We find in this case that there is a symmetry group that describes all of the uncertainty in the compartmental matrix and that the invariants of this symmetry group are the identifiable quantities associated with the compartmental matrix. We then determine what these invariants are in the general case.

In actual imaging situations, we may be able to spatially separate all of the anatomical compartments except the vascular compartment. We examine this important special case in detail in section 11 and relate the identifiable quantities of the compartmental matrix to its eigenvalues and eigenvectors. In section 12, we introduce the SPECT or PET imaging system in general terms and discuss how it may be used to identify the kinetic parameters associated with the compartmental matrix. Finally, in section 13, we discuss the limitations of this model and possible directions for future work.

2. Linear kinetic model for SPECT or PET imaging

In this section, we describe the kinetic model for the activity distribution $f(\mathbf{r}, t)$. This model describes the simplest way to combine a compartmental temporal model, of the type used in conventional pharmacokinetics, with the spatial activity distribution that is the object of interest in SPECT or PET imaging. The basic idea is that the spatial integrals of spatiotemporal compartmental activity functions are the temporal compartmental functions that appear in the first-order linear system of differential equations that make up the temporal model. This is the most obvious way to link the pharmacokinetic model with imaging.

In order to motivate this approach to combining compartmental models with imaging, we present a simple example with two compartments and two voxels. The activity in each compartment is spread across both voxels and is allowed to move between voxels as time goes on. Governing the movement of activity between voxels and compartments in the simulation was a linear model that was consistent with a linear model for the activities in the compartments summed over the two voxels. The input was a constant bolus into the first compartment between $t = 0$ and $t = 1$. In Figure 1, we show the time activity curves for each voxel on the left and, on the right, a double exponential fit for times after the input bolus. If each voxel is governed by a two-compartment model, then the double exponential behavior is what we would expect after $t = 1$. The decay rates for the exponential functions in the fitted curves, which are also the eigenvalues of the compartmental matrices for each voxel, are $\lambda_1 = 1.560$ and $\lambda_2 = 0.295$ for voxel 1, and $\lambda_1 = 0.240$ and $\lambda_2 = 0.239$ for voxel 2. In Figure 2, we show the actual time activity curves for the two compartments on the left and double exponential fits for times after the bolus on the right. These curves would not be available in an imaging experiment, since we cannot determine from imaging the level of activity in a given voxel in each compartment. The rate constants for the compartmental activities are $\lambda_1 = 0.8$ and $\lambda_2 = 0.3$. In this example, these are the correct rate constants, and they are not predicted by the voxel-fitting approach. If we now use the local, voxel-fitting, approach to derive compartmental matrices for each voxel, then there can be no expectation that these local compartmental matrices are related in any way to the actual compartmental matrix governing the compartmental model. The problem is that the local compartmental model does not allow for activity moving between voxels. Since voxels are not anatomical features and can be very small, it seems to be unwise to assume that activity cannot move from one voxel to another. This is one of the main motivations for the present work. More details for this example are given in the appendix.

Although the compartments in standard compartmental models for pharmacokinetics are regarded as somewhat abstract entities, when we wish to combine these models with imaging we must accept the fact that the activity in each compartment has a spatial distribution within the body. For this reason, we assume that the activity distribution $f(\mathbf{r}, t)$ can be decomposed into a sum of separate contributions from different tissue types and/or different biological environments, i.e., different compartments:

$$f(\mathbf{r}, t) = a_1(\mathbf{r}, t) + a_2(\mathbf{r}, t) + \cdots + a_L(\mathbf{r}, t). \tag{2.1}$$

Examples of tissue types could be normal tissue from various organs, cancerous tissue, blood, muscle, and so forth. Examples of different environments could be intercellular and intracellular environments within a given tissue type. The number L of terms in the sum will depend, among other things, on the tracer and the amount of detail we wish to include in the model. There is no easy answer to the question of how many terms should be included in this sum; typically we try to explain the data with as few terms as possible, but there may be

biological justifications for having more terms. The terms in this sum will be called the local compartmental activities and are assumed to be nonnegative functions. It must be emphasized that the imaging system can, at best, provide the overall activity distribution $f(\mathbf{r}, t)$ for the entire organism. We will assume that we are in this best case scenario, so that $f(\mathbf{r}, t)$ for the entire organism is known for all points in the subject being imaged and at all times. It is important to note that, even in this situation, the individual local compartmental activities are not distinguished by either the SPECT or PET imaging system. With actual imaging systems, there are, of course, other problems as well, such as limited sampling in space and time, choice of reconstruction algorithm, imaging-system noise, and a limited field of view. We will discuss some of these issues in section 12.

We need to introduce the space-integrated compartmental activities in order to describe the kinetic model for the activity distribution. In the following equation, and others to appear below, space-integrated quantities will always be denoted by overbars. The space-integrated compartmental activities are functions of time given by

$$\bar{a}_l(t) = \int_{S_l} a_l(\mathbf{r}, t)\, d^3 r, \tag{2.2}$$

where the region S_l is a spatial support region for the function $a_l(\mathbf{r}, t)$ for all t. What we mean by this condition on S_l is that we have prior knowledge that the function $a_l(\mathbf{r}, t)$ vanishes outside S_l for all t. The function $a_l(\mathbf{r}, t)$ may in fact vanish outside a smaller region; therefore, S_l is not necessarily the mathematical spatial support of $a_l(\mathbf{r}, t)$, which is usually defined as the smallest closed region outside of which the function vanishes. The region S_l represents the state of our prior knowledge about the mathematical support of $a_l(\mathbf{r}, t)$; i.e., we know that this support is inside S_l. The source of this prior knowledge would typically be anatomical information based on our knowledge of the normal anatomy of the subject species or derived from another imaging modality, such as CT or MRI. In the latter situation, we will see that dual-modality imaging could be very useful for estimating pharmacokinetic parameters.

The easiest way to describe the linear kinetic model is to first form the vector of space-integrated compartmental activities

$$\bar{\mathbf{a}}(t) = \begin{bmatrix} \bar{a}_1(t) \\ \bar{a}_2(t) \\ \vdots \\ \bar{a}_L(t) \end{bmatrix}. \tag{2.3}$$

In the linear kinetic model, this vector-valued function is assumed to satisfy the vector differential equation

$$\frac{d}{dt}\bar{\mathbf{a}}(t) = \mathbf{K}\bar{\mathbf{a}}(t) + \bar{\mathbf{I}}(t), \tag{2.4}$$

where the $L \times L$ matrix $\mathbf{K}$ is called the compartmental matrix, and the L-dimensional vector function $\bar{\mathbf{I}}(t)$ is the input function. Typically, we would identify the first compartment with the vascular system and

$$\bar{\mathbf{I}}(t) = \begin{bmatrix} \bar{I}(t) \\ 0 \\ \vdots \\ 0 \end{bmatrix} = \bar{I}(t)\ \mathbf{e}_1, \tag{2.5}$$

where $\bar{I}(t)$ is the input function to the bloodstream and $\mathbf{e}_1$ is the vector with 1 in the first entry and the rest 0. For simplicity, we will assume in all of our discussions below that the input function has this form. Other forms for the input vector function result in some simple modifications of some of the equations to follow. The authors are aware that obtaining the input function, from samples or otherwise, is one of the major problems in applications of compartmental modeling to experiments. We will not address that problem in this work in any detail and will assume a best case scenario—that the input function is known.

There are standard assumptions about the compartmental matrix in pharmacokinetic theory. The first constraint on this matrix is that the off-diagonal elements are nonnegative: $K_{ij} \geq 0$ for $i \neq j$. These numbers represent a relative rate of flow of activity from compartment j into compartment i. The second constraint is that the diagonal elements are nonpositive: $K_{ii} \leq 0$. These numbers represent a relative rate of flow of activity out of compartment i. The third constraint is that the magnitude of a diagonal element is at least as large as the sum of the other elements in the same column:

$$|K_{jj}| \geq \sum_{i \neq j} K_{ij}. \tag{2.6}$$

This relation guarantees that activity is conserved.

To see this last point, we first define an L-dimensional vector $\mathbf{u}$ by $u_l = 1$ for all l. If S is a support set for the observed activity distribution, then the integrated activity is given by

$$\bar{f}(t) = \int_S f(\mathbf{r}, t)\ d^3r = \mathbf{u}^\dagger \bar{\mathbf{a}}(t). \tag{2.7}$$

The dagger symbol refers to the transpose operation and converts a column vector to a row vector. Differentiating this equation gives us

$$\frac{d\bar{f}(t)}{dt} = \left(\mathbf{K}^\dagger \mathbf{u}\right)^\dagger \bar{\mathbf{a}}(t) + \mathbf{u}^\dagger \bar{\mathbf{I}}(t). \tag{2.8}$$

The three constraints on the compartmental matrix imply that the components of the vector $\mathbf{K}^\dagger\mathbf{u}$ are nonpositive. If we have equality in the third constraint, then these components all vanish, and the rate of change in the overall activity in the organism is equal to the overall input. If the left side in the third constraint is greater than the right side, then some activity is being diverted outside of the organism. For SPECT or PET imaging, there is also an overall decrease of activity in all compartments because the images are produced by the radioactive decay of an unstable isotope. Note that, by Gershgorin's circle theorem [14], the constraints on $\mathbf{K}$ also imply that the real parts of the eigenvalues of $\mathbf{K}$ are nonpositive.

The kinetic equation can also be formulated in terms of concentrations of the activity in each compartment. First, let V_l be the volume of compartment l, i.e., the volume of the

mathematical spatial support of the function $a_l(\mathbf{r}, t)$. We will assume that V_l is independent of time. Then, the concentration vector $\bar{\mathbf{C}}(t)$ is defined componentwise by

$$\bar{c}_m(t) = \frac{\bar{a}_m(t)}{V_m}. \tag{2.9}$$

If we define the diagonal matrix $\mathbf{T}$ by $T_{mn} = \delta_{mn} V_m^{-1}$, then we may write the kinetic equation as

$$\frac{d}{dt}\bar{\mathbf{c}}(t) = \mathbf{T}\mathbf{K}\mathbf{T}^{-1}\bar{\mathbf{c}}(t) + \mathbf{T}\bar{\mathbf{I}}(t) = \mathbf{K}_c\bar{\mathbf{c}}(t) + \bar{\mathbf{I}}_c(t), \tag{2.10}$$

where the middle expression defines the matrix $\mathbf{K}_c$ and the vector $\bar{\mathbf{I}}_c(t)$. In the imaging context, the volumes V_m are often unknown. For this reason, we will focus on activities rather than concentrations. Note that, since the matrices $\mathbf{K}$ and $\mathbf{K}_c$ are related by a similarity transformation, they have the same eigenvalues.

3. The local input function

In this section, we will derive an alternative expression for the activity function $f(\mathbf{r}, t)$ that explicitly contains the compartmental matrix. To do this, we must introduce the idea of a local input function $\mathbf{I}(\mathbf{r}, t)$. It is tempting to think of the local input function in physical terms, but this can lead to problems, as will be discussed below. It is probably better to think of the introduction of the local input function more as a change of variable that is made for mathematical convenience.

Theorem 3.1

If there is initially no activity in the organism, then the activity distribution can be written in the following form:

$$f(\mathbf{r}, t) = \int_0^t \mathbf{u}^\dagger \exp\left[\mathbf{K}(t - t')\right] \mathbf{I}(\mathbf{r}, t')\, dt', \tag{3.1}$$

where the vector function $\mathbf{I}(\mathbf{r}, t')$ *satisfies the constraint*

$$\int_s \mathbf{I}(\mathbf{r}, t)\, d^3r = \bar{\mathbf{I}}(t). \tag{3.2}$$

Proof—We start with the local compartmental activity vector

$$\mathbf{a}(\mathbf{r}, t) = \begin{bmatrix} a_1(\mathbf{r}, t) \\ a_2(\mathbf{r}, t) \\ \vdots \\ a_L(\mathbf{r}, t) \end{bmatrix} \tag{3.3}$$

and note that $f(\mathbf{r}, t) = \mathbf{u}^\dagger \mathbf{a}(\mathbf{r}, t)$. In terms of this vector function, the kinetic equation may be written as

$$\int_S \left[\frac{d}{dt}\mathbf{a}\ (\mathbf{r},t) - \mathbf{K}\mathbf{a}\ (\mathbf{r},t) \right] d^3r = \bar{\mathbf{I}}\ (t)\,. \tag{3.4}$$

We are supposing that the interchange of differentiation and integration used to obtain this equation can be justified by assuming, for example, that **a** (**r**, *t*) and its time derivative are continuous in *S*, but we will not pursue this question in detail. This last equation suggests that we define the vector-valued local input function by a local kinetic equation

$$\frac{d}{dt}\mathbf{a}\ (\mathbf{r},t) - \mathbf{K}\mathbf{a}\ (\mathbf{r},t) \equiv \mathbf{I}\ (\mathbf{r},t)\,. \tag{3.5}$$

Again, at this point, the local input function is a purely mathematical construction defined by (3.5). The possible physical meaning, or lack thereof, of this function will be addressed below. By definition, the local input function is constrained by (3.2). The original kinetic model given in (2.4) is equivalent to the combination of (3.2) and (3.5).

We assume that there is initially no activity in the field of view. This assumption is not essential, and background radiation can be taken into account, but it does simplify the mathematics somewhat. Since the compartmental activities are all nonnegative, this gives the initial condition **a** (**r**, 0) = **0**. With this initial condition, the solution to the local kinetic equation (3.5) can be written in the form [15]

$$\mathbf{a}\ (\mathbf{r},t) = \int_0^t \exp\ [\mathbf{K}\ (t-t')]\ \mathbf{I}\ (\mathbf{r},t')\ dt'. \tag{3.6}$$

This equation shows us that if we know the vector function **I** (**r**, *t*) and the matrix **K**, then the vector function **a** (**r**, *t*) is determined. Similarly, (3.5) shows us that if we know **a** (**r**, *t*) and **K**, then **I** (**r**, *t*) is determined. In any case, the model for the activity distribution now has the form given in (3.1).

The expression for the activity distribution given in this theorem incorporates the kinetic model into an expression for *f* (**r**, *t*), with the assumption that the function **I** (**r**, *t*) satisfies the constraint in (3.2). The kinetic model for the activity distribution is now summarized in (2.1) and (2.4) or, equivalently, in (3.1) and (3.2). The two ways of representing the activity distribution are linked by (3.5).

4. Eigenvalue decomposition of the compartmental matrix

In keeping with the usual convention in compartmental modeling, we will write the eigenvalue equation for the compartmental matrix with a negative sign: $\mathbf{K}\mathbf{v}_l = -\lambda_l \mathbf{v}_l$. As noted above, the constraints on **K** imply that the real parts of the λ_l are positive. In fact, it is usually assumed that these numbers are real and that there are *L* distinct eigenvectors; i.e., **K** is diagonalizable. Because diagonalizability is a generic property of matrices, this assumption is not too difficult to justify. On the other hand, the property that all of the eigenvalues of a matrix are real is not a generic property and is therefore an implicit nontrivial constraint on the compartmental matrix. It is difficult to formulate this constraint in terms of properties of the elements of **K**, but we will assume that the eigenvalues are all real.

We will say that a quantity associated with the compartmental matrix is identifiable if it is uniquely determined by the activity distribution and the support information. If a quantity

associated with **K** is not identifiable, then it will be impossible to determine uniquely, even under the best conditions. On the other hand, for identifiable quantities, there is at least the possibility of obtaining an accurate estimate.

Theorem 4.1

Under generic assumptions about the compartmental matrix, the eigenvalues of the compartmental matrix are identifiable when the input is time-limited.

Proof—The local input function can be expanded in the eigenvector basis as $\mathbf{I}(\mathbf{r},t)=\sum_l I_l'(\mathbf{r},t)\,\mathbf{v}_l$. This expansion leads to the corresponding expansion for the global input function by integrating over the field of view: $\bar{\mathbf{I}}(t)=\sum_l \bar{I}_l'(t)\,\mathbf{v}_l$. The object model now consists of functions that have expansions of the form

$$f(\mathbf{r},t)=\sum_l \mathbf{u}^\dagger\mathbf{v}_l\int_0^t \exp\left[-\lambda_l(t-t')\right] I_l'(\mathbf{r},t')\,dt'. \tag{4.1}$$

From this equation, we find that the integrated activity can be written as

$$\bar{f}(t)=\sum_l \mathbf{u}^\dagger\mathbf{v}_l\int_0^t \exp\left[-\lambda_l(t-t')\right] \bar{I}_l'(t')\,dt'. \tag{4.2}$$

Now suppose that $\mathbf{u}^\dagger\mathbf{v}_l \neq 0$ for all l, and $\bar{I}_l'(t')$ is not identically zero for any l. These conditions on the eigenvectors and input function components are generic properties of the compartmental matrix and input function. We may now normalize the eigenvectors so that $\mathbf{u}^\dagger\mathbf{v}_l = 1$ for all l. By taking the Laplace transform of both sides of (4.2), we find that

$$\bar{F}(s)=\sum_l \frac{\mathcal{L}\bar{I}_l'(s)}{s-\lambda_l}, \tag{4.3}$$

where $\mathcal{L}\bar{I}_l'(s)$ is the Laplace transform of the function $\bar{I}_l'(t)$. If the input function is time-limited, then the functions $\mathcal{L}\bar{I}_l'(s)$ are analytic, and therefore the only singularities of $\bar{F}(s)$ are at the eigenvalues. Thus, the eigenvalues λ_l can be determined from $f(\mathbf{r}, t)$ when we have time-limited input.

We will always assume that the input is time-limited and therefore that the eigenvalues of the compartmental matrix are identifiable. If the input function is not time-limited, then (4.3) may still lead to an identification of the eigenvalues, for example, when the numerators are analytic functions. This is also a standard result in conventional compartmental modeling of pharmacokinetics [1]. We will also always assume that the normalization $\mathbf{u}^\dagger\mathbf{v}_l = 1$ has been enforced for the eigenvectors of the compartmental matrix.

5. Multiexponential models

If the input function is time-limited to the time interval between 0 and T, then, for all times later than T, we have

$$\bar{f}(t) = \sum_l \left[\int_0^T \exp(\lambda_l t') \, \bar{I}_l'(t') \, dt' \right] \exp(-\lambda_l t). \tag{5.1}$$

This is a multiexponential function, i.e., a linear combination of decaying exponentials. Multiexponential functions are therefore expected for the integrated activity when the input function is time-limited.

The assumption that $\bar{\mathbf{I}}(t) = 0$ for $t > T$ is consistent with, but does not necessarily imply that, $\mathbf{I}(\mathbf{r}, t) = 0$ for $t > T$. If we make this latter, more questionable, assumption, then, for $t > T$, we have

$$f(\mathbf{r}, t) = \sum_l \left[\int_0^T \exp(\lambda_l t') \, I_l'(\mathbf{r}, t') \, dt' \right] \exp(-\lambda_l t). \tag{5.2}$$

This equation is consistent with a local multiexponential model for $t > T$:

$$f(\mathbf{r}, t) = \sum_l b_l(\mathbf{r}) \exp(-\lambda_l t). \tag{5.3}$$

Local multiexponential models have been used extensively to fit time activity curves from SPECT and PET imaging systems [2,3,4,5,[6],[7],[8],[9],10,11,12,13]. If an activity distribution of this form is integrated over a voxel or a region of interest, then the result is a temporal function that is a sum of decaying exponentials. Often, such time activity curves are fit to a finite sum of exponentials, and the time constants λ_l are extracted. This procedure is justified by an appeal to compartmental models, where such sums of decaying exponentials are indeed the form that components of solutions to the differential equation take for $t > T$. However, this method ignores the fact that the constants λ_l are eigenvalues of the compartmental matrix for the biological system as a whole, and not properties of an individual voxel or region of interest. This is one motivation for considering the global compartmental model proposed here.

For comparison purposes, we can write the object model derived in the last section as

$$f(\mathbf{r}, t) = \sum_l \left[\int_0^t \exp(\lambda_l t') \, I_l'(\mathbf{r}, t') \, dt' \right] \exp(-\lambda_l t), \tag{5.4}$$

with an input constraint that now takes the following form: There are vectors $\mathbf{v}_l$ such that

$$\sum_l \left[\int_s I_l'(\mathbf{r}, t) \, d^3 r \right] \mathbf{v}_l = \bar{\mathbf{I}}(t). \tag{5.5}$$

The eigenvalues λ_l and eigenvectors $\mathbf{v}_l$ then determine $\mathbf{K}$. This object model imposes no further constraints on the activity distribution beyond those given in section 2. Of course, this object model is more difficult to deal with than the multiexponential model, but it does take into account the fact that we cannot isolate a voxel or region of interest from the rest of the organism being imaged.

The assumption that $\mathbf{I}(\mathbf{r}, t) = 0$ for $t > T$ is also incompatible with localized compartments, which are important for imaging applications. If $a_m(\mathbf{r}, t) = 0$ in some region in the field of view where the overall activity is nonvanishing, then

$$I_m(\mathbf{r}, t) = -\sum_{n \neq m} K_{mn} a_n(\mathbf{r}, t) < 0 \tag{5.6}$$

in that region. This means that if we have support information available, we cannot make the blanket assumption that $\mathbf{I}(\mathbf{r}, t) = 0$ for $t > T$. Support information from imaging is therefore incompatible with a multiexponential object model in the context of the assumptions of the global compartmental model. If we make this assumption, we are, in effect, abandoning the global compartmental model and going back to models that do not account for activity moving between voxels. Equation (5.6) also shows that the local input function does not have an obvious physical interpretation since a component of this vector function must be nonzero in regions where the corresponding local compartmental activity component vanishes.

6. Identifiability with no support information

For a given activity distribution $f(\mathbf{r}, t)$, suppose that we have no compartmental support information; i.e., $S_l = S$ for $l = 1, \ldots, L$. Let us assume that, by some means, we have determined a compartmental matrix $\mathbf{K}$ and a vector function $\mathbf{I}(\mathbf{r}, t)$ that satisfy (3.1) and (3.2). The identifiability question for the matrix $\mathbf{K}$ as a whole is whether there is a different compartmental matrix $\tilde{\mathbf{K}}$ together with a vector function $\tilde{\mathbf{I}}(\mathbf{r}, t)$ that also satisfies (3.1) and (3.2). If the answer to this question is yes, then, in the absence of further information, there is no way to distinguish the pair $\mathbf{K}$ and $\mathbf{I}(\mathbf{r}, t)$ from the pair $\tilde{\mathbf{K}}$ and $\tilde{\mathbf{I}}(\mathbf{r}, t)$. This implies that $\tilde{\mathbf{K}}$ and $\tilde{\mathbf{a}}(\mathbf{r}, t)$ are equally valid as a model for the observed activity distribution and input function as $\mathbf{K}$ and $\mathbf{a}(\mathbf{r}, t)$. There is an additional constraint here which should also be taken into account, namely, that we must have $a_l(\mathbf{r}, t) \geq 0$ and $\tilde{a}_l(\mathbf{r}, t) \geq 0$ for all l and $\mathbf{r}$ and t. For now, we will ignore this constraint, but we will discuss positivity in greater detail below.

Theorem 6.1

In the absence of support constraints, the compartmental matrix is not identifiable.

Proof—Since the eigenvalues of the compartmental matrix $\mathbf{K}$ are identifiable, they must also be the eigenvalues of $\tilde{\mathbf{K}}$, so we must have $\tilde{\mathbf{K}} = \mathbf{M}\mathbf{K}\mathbf{M}^{-1}$ for some invertible matrix $\mathbf{M}$. By expanding the exponential in (3.1) in a power series, we see that $\tilde{\mathbf{K}}$ and $\tilde{\mathbf{I}}(\mathbf{r}, t)$ will satisfy this equation if and only if

$$\mathbf{u}^\dagger \mathbf{M}\mathbf{K}^k\mathbf{M}^{-1}\,\tilde{\mathbf{I}}(\mathbf{r}, t) = \mathbf{u}^\dagger \mathbf{K}^k \mathbf{I}(\mathbf{r}, t) \tag{6.1}$$

for all nonnegative integers k. If (6.1) is true for $k = 0, \ldots, L - 1$, then we can use the characteristic polynomial for $\mathbf{K}$ to show that it is true for larger k. We also must have

$$\int_S \tilde{\mathbf{I}}(\mathbf{r}, t)\, d^3r = \int_S \mathbf{I}(\mathbf{r}, t)\, d^3r = \bar{\mathbf{I}}(t). \tag{6.2}$$

Taken together, these last two equations imply that

$$\mathbf{u}^\dagger \mathbf{M}\mathbf{K}^k\mathbf{M}^{-1}\bar{\mathbf{I}}(t) = \mathbf{u}^\dagger \mathbf{K}^k \bar{\mathbf{I}}(t). \tag{6.3}$$

Since we are assuming that the input function is known, this last equation gives $L - 1$ independent conditions that **M** needs to satisfy. We do not have L conditions since (6.3) is trivially satisfied for $l = 0$.

One way to satisfy the conditions in (6.1), (6.2), and (6.3) on **M** and $\tilde{\mathbf{I}}(\mathbf{r}, t)$ is to do the following:

a. Set **M** = **AB**, where **B** commutes with **K**.

b. Define

$$\tilde{\mathbf{I}}(\mathbf{r}, t) = \mathbf{A}\mathbf{I}(\mathbf{r}, t). \tag{6.4}$$

c. Enforce the constraints $\mathbf{A}\bar{\mathbf{I}}(t) = \bar{\mathbf{I}}(t)$ and $\mathbf{A}^{\dagger}\mathbf{u} = \mathbf{u}$.

For the standard input function, the first constraint implies that the first column of **A** is a 1 followed by zeros. The second constraint implies that the columns of **A** all sum to 1. These two equations therefore give $2L - 1$ constraints on **A**. Since we are assuming that **K** is diagonalizable, the dimension of the space of matrices that commute with it is L. The dimension of the space of matrices **M** that we obtain from this construction is therefore $L^2 - (L - 1)$, which is also the dimension of the space of matrices satisfying (6.3). Since $L^2 - (L - 1) > 0$, we know that **K** is not identifiable.

In addition, since the construction in the proof of this theorem gives $\tilde{\mathbf{K}} = \mathbf{A}\mathbf{K}\mathbf{A}^{-1}$, we expect that the dimension of the space of alternate compartmental matrices **K** that are produced via this construction will be $L^2 - (2L - 1)$. This in turn implies that there are $2L - 1$ invariants that describe this space, and therefore no more than $2L - 1$ invariants for the whole space of alternate compartmental matrices. We know that there are at least $2L-1$ independent invariants for the space of alternate compartmental matrices. These invariants are the eigenvalues $\lambda_1, \ldots, \lambda_L$ and the numbers $\mathbf{u}^{\dagger}\mathbf{K}^{k}\bar{\mathbf{I}}(t)$ for $l = 1, \ldots, L - 1$. These dimensional arguments raise the following question: Is the construction in (a)–(c) above the only way to satisfy the constraints on **M** and $\tilde{\mathbf{I}}(\mathbf{r}, t)$ contained in (6.1), (6.2), and (6.3)? We show below that there is an affirmative answer to this question. This affirmative answer implies that the identifiable quantities associated with the compartmental matrix are the $2L - 1$ invariants noted above.

With the function $\tilde{\mathbf{I}}(\mathbf{r}, t)$ given in (6.4), the corresponding vector activity function is given by

$$\tilde{\mathbf{a}}(\mathbf{r}, t) = \mathbf{A}\mathbf{a}(\mathbf{r}, t). \tag{6.5}$$

This fact will be exploited below to show how support information places more constraints on the matrix **A**. The existence of these additional constraints implies that there are more invariants and hence more identifiable quantities associated with **K** when support information is available.

Theorem 6.2

If the input function is time-limited, then the functions $\mathbf{u}^{\dagger}\mathbf{K}^{k}\bar{\mathbf{I}}(t)$ *are identifiable.*

Proof—If we return to the eigenvalue analysis, we can see a way to determine the functions $\mathbf{u}^{\dagger}\mathbf{K}^{k}\bar{\mathbf{I}}(t)$. Using (4.3), we can show that the functions $\mathscr{L}\bar{I}_l'(s)$ are determined by $\bar{f}(t)$ when the input function is time-limited. This follows from the fact that the expansion of $\bar{F}(s)$

given in (4.3) is unique when the numerators are entire functions, which they are when the input is time-limited. The constraint

$$\sum_{j=1}^{L} \bar{I}_j'(t) = \mathbf{u}^\dagger \bar{\mathbf{I}}(t) \tag{6.6}$$

implies that only $L - 1$ of the identifiable functions $\bar{I}_l'(t)$ are independent. Now we can write

$$\mathbf{u}^\dagger \mathbf{K}^k \bar{\mathbf{I}}(t) = \sum_{j=1}^{L} \lambda_j^k \bar{I}_j'(t'), \tag{6.7}$$

which shows that the functions $\mathbf{u}^\dagger \mathbf{K}^k \bar{\mathbf{I}}(t)$ can, in principle, be recovered.

Using the assumption that the input function is into the first compartment only, and that the scalar function $I(t)$ is known, the independent identifiable quantities associated with the compartmental matrix are the eigenvalues of $\mathbf{K}$ and the numbers

$$\sum_{i=1}^{L} \left[\mathbf{K}^k\right]_{i1} \tag{6.8}$$

for $k = 1,\ldots, L - 1$. These results are very similar to results in standard compartmental analysis for pharmacokinetics when there is one accessible compartment [1].

7. Identifiability with complete support information

Now we will examine the opposite extreme from the previous section in terms of support information. We will say that we have complete support information when $S_l \cap S_k = \emptyset$ for $l \neq k$. Of course, this condition may be difficult or impossible to satisfy since it may require subcellular resolution in our imaging system in order to separate all of the compartment supports. In particular, separating the support of the vascular compartment from other support regions would require very high resolution in our imaging system. The reason for considering this case is that it represents the ultimate in what an imaging system could deliver.

Theorem 7.1

Under generic assumptions about the compartmental matrix, if we have complete support information, then the compartmental matrix is identifiable.

Proof—If we have complete support information, then $f(\mathbf{r}, t) = a_l(\mathbf{r}, t)$ for $\mathbf{r} \in S_l$. This means that $\mathbf{a}(\mathbf{r}, t)$ is known and hence that $\bar{\mathbf{a}}(t)$ is known. Taking a derivative, we find that $\mathbf{K}\bar{\mathbf{a}}(t)$ is known for all t. If the span of the vectors $\bar{\mathbf{a}}(t)$ as t varies is all of $\mathbb{R}^L$, then $\mathbf{K}$ can be identified in its entirety. This spanning condition will fail if the vectors $\mathbf{K}^k \bar{\mathbf{I}}(t)$ all lie in a proper subspace for $k = 0, 1,\ldots, L - 1$ and all t. However, this subspace condition is not a generic property of matrices and so is unlikely to occur in practice.

We can say then, that with complete support information, all of the quantities in the model are identifiable, the compartmental functions $a_l(\mathbf{r}, t)$ and the compartmental matrix $\mathbf{K}$.

8. A symmetry group

Now we consider the more likely situation where we have some support information for the compartments, but not complete support information. In this case, the variability in the possible compartmental matrices that are compatible with the given activity distribution, input function, and support constraints can be described in terms of a symmetry group. For brevity, we will sometimes call such a compartmental matrix "compatible." The invariants of the symmetry group then provide us with the identifiable quantities associated with the compatible compartmental matrices.

The symmetry group in question consists of the invertible matrices **A** that satisfy three properties:

Symmetry group property 1: $\mathbf{A}\bar{\mathbf{I}}(t) = \bar{\mathbf{I}}(t)$.

Symmetry group property 2: $\mathbf{A}^{\dagger}\mathbf{u} = \mathbf{u}$.

Symmetry group property 3: $A_{ij} \neq 0$ implies $S_j \subset S_i$.

The first two properties have already been mentioned in section 6 and guarantee that the constraint in (6.3) is satisfied. By definition, a matrix in the symmetry group acts on any compatible compartmental matrix **K** and the corresponding local compartmental activity vector $\mathbf{a}(\mathbf{r}, t)$ to produce a new compartmental matrix $\tilde{\mathbf{K}} = \mathbf{AKA}^{-1}$ and a new local compartmental activity vector $\tilde{\mathbf{a}}(\mathbf{r}, t) = \mathbf{Aa}(\mathbf{r}, t)$. Since

$$\tilde{a}_l(\mathbf{r}, t) = \sum_{j=1}^{L} A_{lj} a_j(\mathbf{r}, t), \tag{8.1}$$

the third property of **A** is needed to preserve compatibility with the support information. The new compartmental matrix, with the new local compartmental activity, is compatible with the given activity distribution, input function, and support constraints.

When there is support information, this symmetry group has lower dimension than the corresponding group when there is no support information, i.e., when the third symmetry group property is deleted. Therefore, we would expect more invariants, i.e., more identifiable quantities, when there is support information from imaging. What are these invariants and how do we identify them from the activity distribution, the input function, and the support sets? We answer the first of these questions below. First, though, we will show that we really do have a symmetry group.

Theorem 8.1

The three symmetry group properties listed above define a group of matrices with the ordinary matrix product as the group multiplication operation.

Proof—To show that the set of matrices described above is a group, first note that it is easy to show that the first two properties are compatible with matrix products and inverses. To address the third property, we first suppose that $\mathbf{A}'' = \mathbf{A}'\mathrm{A}$ and $A''_{ij} \neq 0$. Then, for some k, we must have $A'_{ik} \neq 0$ and $A_{kj} \neq 0$. This implies that $S_j \subset S_k$ and $S_k \subset S_i$. Therefore, $S_j \subset S_i$ and the collection of matrices satisfying the three properties is closed under matrix multiplication.

To show that this set of matrices is closed under inverses, we first prove a certain subspace property that is equivalent to the third property. Define subspaces of $\mathbb{R}^L$ by $V_l = span\ \{\mathbf{e}_k : S_l \subset S_k\}$ and $W_l = span\{e_j : S_j \subset S_l\}$. If $\mathbf{v} \in V_l$, then

$$[\mathbf{Av}]_i = \sum_{k=1}^{L} A_{ik} v_k. \tag{8.2}$$

If this number is not zero, then, for some k, we have $S_l \subset S_k$ and $S_k \subset S_i$. This implies that $S_l \subset S_i$. Since the index i is arbitrary, this gives $\mathbf{Av} \in V_l$ also. Thus, the subspaces V_l are invariant under $\mathbf{A}$. On the other hand, if these subspaces are invariant under $\mathbf{A}$ and $A_{ij} \neq 0$, then $[\mathbf{Ae}_j]_i \neq 0$. By the invariance property, this implies that $\mathbf{e}_i \in V_j$. This in turn gives $S_j \subset S_i$. The invariance property, $\mathbf{A}V_l = V_l$ for all l, is therefore equivalent to the third property for the symmetry group. Now we can prove closure under the inverse operation. If $\mathbf{A}$ is in the symmetry group, then $\mathbf{A}V_l = V_l$ for all l, and the same will be true of the inverse matrix.

Note that $\mathbf{A}^\dagger W_l = W_l$ for all l. This property specifies the matrices in the adjoint symmetry group. If the W_l are all one-dimensional, so that no support set is contained in any other, then, by the third group property, $\mathbf{A}$ must be diagonal. Using the second group property, we then find that $\mathbf{A}$ must be the identity matrix. This in turn implies that $\mathbf{K}$ is completely identifiable in this case. Therefore, complete support information is not necessary in order for the compartmental matrix to be identifiable. However, the question that remains even in this situation is how to identify the elements of this matrix. In other words, we know there is a unique solution for $\mathbf{K}$ in this circumstance, but we do not at present know how to obtain it. If the W_l are not all one-dimensional, then we will see that $\mathbf{K}$ is not completely identifiable from the given information.

In contrast to the compartmental matrix, in the absence of complete support information, the $a_m(\mathbf{r}, t)$ are not completely identifiable. To see this, note that if $S_m \cap S_n \neq \emptyset$, then the operation

$$a_m(\mathbf{r}, t) \rightarrow a_m(\mathbf{r}, t) + b(\mathbf{r}, t), \tag{8.3}$$

$$a_n(\mathbf{r}, t) \rightarrow a_n(\mathbf{r}, t) - b(\mathbf{r}, t) \tag{8.4}$$

leaves $f(\mathbf{r}, t)$ invariant, and, if the spatial integral of the function $b(\mathbf{r}, t)$ is zero, also leaves $\mathbf{a}(t)$ invariant. This in turn implies that $\mathbf{K}$ and $\mathbf{I}(t)$ are unchanged by this operation. If the support of $b(\mathbf{r}, t)$ is in $S_m \cap S_n$, then the support information is also unchanged. Thus, this operation gives a new compartmental activity function which is compatible with the activity distribution, the input function, and the support constraints.

9. Identifiability and the symmetry group

Before continuing with our discussion of the symmetry group, we need to tie up a loose end from section 6. In that section, we found that the matrix $\mathbf{M}$ which relates the compartmental matrix $\mathbf{K}$ to the alternate compartmental matrix $\tilde{\mathbf{K}} = \mathbf{MKM}^{-1}$ must satisfy (6.1) and (6.2). These two equations then give us (6.3). We provided a construction in Theorem 6.1 that resulted in a matrix $\mathbf{M}$ satisfying these three equations. We want to show that this is the only way to obtain such an $\mathbf{M}$.

Theorem 9.1

Under generic conditions on the compartmental matrix, the conditions in (6.1) *and* (6.2) *imply that* $\mathbf{M} = \mathbf{AB}$ *and* $\tilde{\mathbf{I}}(\mathbf{r}, t) = \mathbf{AI}(\mathbf{r}, t)$, *with the matrices* $\mathbf{A}$ *and* $\mathbf{B}$ *satisfying* $\mathbf{A}\bar{\mathbf{I}}(t) = \bar{\mathbf{I}}(t)$, $\mathbf{A}^{\dagger}\mathbf{u} = \mathbf{u}$, *and* $\mathbf{BK} = \mathbf{KB}$.

Proof—To begin with, we fix t and set $\bar{\mathbf{I}} = \bar{\mathbf{I}}(t)$. We will make three generic assumptions about the compartmental matrix. Assumption 1 is that the eigenvalues of $\mathbf{K}$ are distinct. As noted before, this is generally assumed in standard compartmental modeling. Assumption 2 is that the vectors $\mathbf{K}^k\bar{\mathbf{I}}$ for $k = 0, 1,\ldots, L-1$ are linearly independent. Assumption 3 is that the vectors $\mathbf{K}^k\mathbf{u}$ for $k = 0, 1,\ldots, L-1$ are linearly independent.

Now we write $\mathbf{K} = \mathbf{VDV}^{-1}$, where $\mathbf{D}$ is a diagonal matrix. We can write the constraint equation (6.3) as

$$\left(\mathbf{V}^{\dagger}\mathbf{u}\right)^{\dagger}(\mathbf{V}^{-1}\mathbf{MV})\mathbf{D}^k(\mathbf{V}^{-1}\mathbf{MV})^{-1}(\mathbf{V}^{-1}\bar{\mathbf{I}})=\left(\mathbf{V}^{\dagger}\mathbf{u}\right)^{\dagger}\mathbf{D}^k(\mathbf{V}^{-1}\bar{\mathbf{I}}). \tag{9.1}$$

With the obvious definitions for $\mathbf{M}_1$, $\mathbf{u}_1$, and $\mathbf{I}_1$, we rewrite this equation as

$$\mathbf{u}_1^{\dagger}\mathbf{M}_1\mathbf{D}^k\mathbf{M}_1^{-1}\mathbf{I}_1=\mathbf{u}_1^{\dagger}\mathbf{D}^k\mathbf{I}_1. \tag{9.2}$$

The three generic assumptions now imply that the entries along the diagonal of the matrix $\mathbf{D}$ are all different, and that all entries in the vectors $\mathbf{I}_1$ and $\mathbf{u}_1$ are nonzero. Now we want to show that $\mathbf{M}_1 = \mathbf{A}_1\mathbf{B}_1$, with the conditions $\mathbf{DB}_1 = \mathbf{B}_1\mathbf{D}$, $\mathbf{A}_1\mathbf{I}_1 = \mathbf{I}_1$, and $A_1^{\dagger}\mathbf{u}_1=\mathbf{u}_1$. The first of these conditions implies that $\mathbf{B}_1$ is diagonal. Choose the vector $\mathbf{w}$ to satisfy $\mathbf{M}_1\mathbf{w} = \mathbf{I}_1$ and choose $\mathbf{B}_1$ so that $\mathbf{B}_1\mathbf{w} = \mathbf{I}_1$. A necessary condition for this step is that all entries in $\mathbf{w}$ are nonzero. For now, we will assume that this property of $\mathbf{w}$ is true and show why it is true later. Now the matrix $\mathbf{A}_1$ is chosen to satisfy $\mathbf{M}_1 = \mathbf{A}_1\mathbf{B}_1$. Then we have

$$\mathbf{A}_1\mathbf{I}_1=\mathbf{M}_1\mathbf{B}_1^{-1}\mathbf{I}_1=\mathbf{M}_1\mathbf{w}=\mathbf{I}_1. \tag{9.3}$$

This gives us

$$\begin{aligned}\mathbf{u}_1^{\dagger}\mathbf{D}^k\mathbf{I}_1 &= \mathbf{u}_1^{\dagger}\mathbf{M}_1\mathbf{D}^k\mathbf{M}_1^{-1}\mathbf{I}_1\\ &= \mathbf{u}_1^{\dagger}\mathbf{A}_1\mathbf{B}_1\mathbf{D}^k\mathbf{B}_1^{-1}\mathbf{A}_1^{-1}\mathbf{I}_1\\ &= \mathbf{u}_1^{\dagger}\mathbf{A}_1\mathbf{D}^k\mathbf{I}_1.\end{aligned} \tag{9.4}$$

By assumption 2, this implies that $\mathbf{A}_1^{\dagger}\mathbf{u}_1=\mathbf{u}_1$. Now we set $\mathbf{A} = \mathbf{VA}_1\mathbf{V}^{-1}$ and $\mathbf{B} = \mathbf{VB}_1\mathbf{V}^{-1}$ to obtain the required factorization of $\mathbf{M}$.

We still need to check that the components of the vector $\mathbf{w}$ are all nonzero. Suppose that the first component of $\mathbf{w}$ is zero. This discussion will apply to any other component also. We have the equation $\mathbf{u}_1^{\dagger}\mathbf{M}_1\mathbf{D}^k\mathbf{w}=\mathbf{u}_1^{\dagger}\mathbf{D}^k\mathbf{I}_1$. If the diagonal entries in $\mathbf{D}$ are λ_m, then we have

$$\sum_{m=2}^{L}\alpha_m\lambda_m^k=\sum_{m=1}^{L}\beta_m\lambda_m^k \tag{9.5}$$

for some numbers α_m and β_m, and $k = 0, 1, \ldots, L-1$. Note that all of the β_m are nonzero by assumptions 2 and 3. By subtracting and dividing, we find that

$$\lambda_1^k = \sum_{m=2}^{L} \gamma_m \lambda_m^k \tag{9.6}$$

for some real numbers γ_m. However, this contradicts the fact that the vectors in $\mathbb{R}^L$ given by $[\lambda_m]_k = \lambda_m^{k-1}$ for $m = 1, \ldots, L$ are linearly independent since the eigenvalues λ_m are distinct. Therefore, all entries in $\mathbf{w}$ must be nonzero.

Now that we know what $\mathbf{M}$ looks like, we return to the original equation

$$\mathbf{u}^\dagger \mathbf{M} \mathbf{K}^k \mathbf{M}^{-1} \tilde{\mathbf{I}}(\mathbf{r}, t) = \mathbf{u}^\dagger \mathbf{K}^k \mathbf{I}(\mathbf{r}, t), \tag{9.7}$$

which reduces to

$$\mathbf{u}^\dagger \mathbf{K}^k \mathbf{A}^{-1} \tilde{\mathbf{I}}(\mathbf{r}, t) = \mathbf{u}^\dagger \mathbf{K}^k \mathbf{I}(\mathbf{r}, t). \tag{9.8}$$

By assumption 3, this implies that $\tilde{\mathbf{I}}(\mathbf{r}, t) = \mathbf{A}\mathbf{I}(\mathbf{r}, t)$.

Note that $\tilde{\mathbf{K}} = \mathbf{M}\mathbf{K}^k\mathbf{M}^{-1} = \mathbf{A}\mathbf{K}^k\mathbf{A}^{-1}$. This means that the symmetry group given above in section 8 describes all of the uncertainty in the compartmental matrix. This statement in turn implies that a quantity associated with the compartmental matrix is identifiable if and only if this quantity is an invariant of the symmetry group as it acts on the compartmental matrices via similarity transformations. In the next section, we will determine what these invariants are.

10. Invariants of the symmetry group

As discussed earlier, we will suppose that, for every eigenvector $\mathbf{v}_l$ of $\mathbf{K}$, we have $\mathbf{u}^\dagger \mathbf{v}_l \neq 0$. If this condition fails for some eigenvector, then the corresponding component of $\mathbf{a}(\mathbf{r}, t)$ will not affect the activity distribution $f(\mathbf{r}, t)$. This means that this component and the corresponding eigenvalue will not be identifiable. Since this nonorthogonality condition is a generic property of matrices, it is unlikely to fail in applications. If the eigenvectors satisfy this condition, then we may assume as before that they are all normalized so that $\mathbf{u}^\dagger \mathbf{v}_l = 1$.

As in the last section, a matrix $\mathbf{A}$ from the symmetry group produces a new compartmental matrix $\tilde{\mathbf{K}} = \mathbf{A}\mathbf{K}\mathbf{A}^{-1}$ that is also compatible with the given activity distribution, input function, and support constraints. This matrix has eigenvectors $\tilde{\mathbf{K}}\tilde{\mathbf{v}}_l = -\lambda_l \tilde{\mathbf{v}}_l$ which can also be normalized such that $\mathbf{u}^\dagger \tilde{\mathbf{v}}_l = 1$. Since $\mathbf{A}^\dagger \mathbf{u} = \mathbf{u}$ and the eigenvalues are distinct, we must have $\tilde{\mathbf{v}}_l = \mathbf{A}\mathbf{v}_l$. The constraints on the matrix $\mathbf{A}$ can now be used to determine invariant quantities associated with these eigenvectors.

Theorem 10.1

The ratios of determinants given in (10.7) *below are invariants of the symmetry group and are therefore identifiable quantities associated with the compartmental matrix.*

Proof—We begin by fixing k with $1 \leq k \leq L$ and choosing j so that $\mathbf{e}_j$ is in the subspace W_k. The jth component of the eigenvector $\tilde{\mathbf{v}}_l$ is then given by

$$\mathbf{e}_j^\dagger \tilde{\mathbf{v}}_l = \mathbf{e}_j^\dagger \mathbf{A} \mathbf{v}_l = \left(\mathbf{A}^\dagger \mathbf{e}_j\right)^\dagger \mathbf{v}_l. \tag{10.1}$$

Since W_k is an invariant subspace of the symmetry group, this vector component is given by

$$\mathbf{e}_j^\dagger \tilde{\mathbf{v}}_l = \sum_{\mathbf{e}_i \in W_k} \mathbf{A}_{ji} [\mathbf{v}_l]_i. \tag{10.2}$$

This means that the W_k component of $\tilde{\mathbf{v}}_l$ is related to the W_k component of $\mathbf{v}_l$ by a square submatrix of the matrix $\mathbf{A}$. This square submatrix consists of the elements A_{ji} such that $\mathbf{e}_i$ and $\mathbf{e}_j$ are in W_k. To produce invariants from this relation, we need to introduce some notation. Let d_k be the dimension of the subspace W_k. To avoid triple subscripts, and since k is fixed thoughout this discussion, we will set $d = d_k$ in the equations below.

We know that $W_k = span\ \{e_{k_1},\ldots, e_{k_d}\}$, where $S_{k_i} \subset S_k$ for $i = 1,\ldots, d$. For any ordered set $(l_1,\ldots, l_d)$ of distinct indices, we define the $d \times d$ matrices $\mathbf{V}_k(l_1,\ldots, l_d)$ and $\tilde{\mathbf{V}}_k(l_1,\ldots, l_d)$ by

$$[\mathbf{V}_k\ (l_1,\ldots, l_d)]_{ij} = \mathbf{e}_{k_i}^\dagger \mathbf{v}_{l_j} \tag{10.3}$$

and

$$\left[\tilde{\mathbf{V}}_k\ (l_1,\ldots, l_d)\right]_{ij} = \mathbf{e}_{k_i}^\dagger \tilde{\mathbf{v}}_{l_j}. \tag{10.4}$$

We also define the $d \times d$ submatrix $\mathbf{A}^{(k)}$ of $\mathbf{A}$ by

$$\left[\mathbf{A}^{(k)}\right]_{ij} = A_{k_i k_j}. \tag{10.5}$$

With these definitions in place, we now have, by the discussion above,

$$\tilde{\mathbf{V}}_k(l_1,\ldots, l_d) = \mathbf{A}^{(k)} \mathbf{V}_k(l_1,\ldots, l_d). \tag{10.6}$$

If $(m_1,\ldots, m_d)$ is another ordered set of distinct indices, then, by taking determinants and ratios, we find that

$$\frac{\mathrm{Det}\left[\tilde{\mathbf{V}}_k\ (l_1,\ldots, l_d)\right]}{\mathrm{Det}\left[\tilde{\mathbf{V}}_k\ (m_1,\ldots, m_d)\right]} = \frac{\mathrm{Det}\ [\mathbf{V}_k\ (l_1,\ldots, l_d)]}{\mathrm{Det}\ [\mathbf{V}_k\ (m_1,\ldots, m_d)]}. \tag{10.7}$$

This equation tells us that the quantity on the right is invariant under the action of the symmetry group on the compartmental matrices and is therefore an identifiable quantity associated with the compartmental matrix $\mathbf{K}$.

In the next section, we consider an example where we can list these invariants fairly easily. In general, however, there is a problem in determining a list of independent invariants from

the collection provided by this theorem. Beyond this mathematical question, there is also the question of the possible biological significance of these identifiable quantities.

11. Identifiability with $L - 1$ nonoverlapping compartments and a vascular compartment

We will assume that the support for the first compartment, the vascular compartment, is all of the field of view. The supports for the other compartments are contained within the vascular support and are nonoverlapping with each other. In other words, for $l \neq k$ and both larger than 1, we have $S_l \cap S_k = \emptyset$. This may be a reasonable model when the nonvascular compartments correspond to different organs.

For the invariant subspaces of the adjoint symmetry group, we have $W_1 = \mathbb{R}^L$ and, for $k > 1$, $W_k = span\ \{e_k\}$. The symmetry group consists of matrices $\mathbf{A}$ of the form

$$\mathbf{A}=\begin{bmatrix} 1 & 1-A_{22} & 1-A_{33} & \cdots & 1-A_{LL} \\ 0 & A_{22} & 0 & \cdots & 0 \\ 0 & 0 & A_{33} & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \cdots & A_{LL} \end{bmatrix}. \tag{11.1}$$

Because this is an $L - 1$ parameter group, we expect that there will be $L^2 - (L - 1)$ invariants. These invariants are the identifiable quantities associated with the compartmental matrix. If $\tilde{\mathbf{K}} = \mathbf{AKA}^{-1}$, then the first set of invariant quantities are the L eigenvalues, which, for later use, we arrange in the diagonal matrix $\mathbf{D}$:

$$[\mathbf{D}]_{kl}=\delta_{kl}\lambda_l=\delta_{kl}\tilde{\lambda}_l. \tag{11.2}$$

The second set of invariants are the $L - 1$ power matrix elements:

$$\mathbf{u}^\dagger\mathbf{K}^k\mathbf{e}_1=\mathbf{u}^\dagger\tilde{\mathbf{K}}^k\mathbf{e}_1. \tag{11.3}$$

The third set of invariants are the eigenvector component ratios, which we arrange in an $(L - 1) \times (L - 1)$ matrix $\mathbf{C}$:

$$[\mathbf{C}]_{mn}=\frac{[\mathbf{v}_n]_m}{[\mathbf{v}_1]_m}=\frac{\left[\tilde{\mathbf{v}}_n\right]_m}{\left[\tilde{\mathbf{v}}_1\right]_m} \tag{11.4}$$

for n and m running from 2 to L. The reader will notice that we now have L^2 invariants, which is too many. To resolve this problem, we show that the invariants in the second set are all functions of those in the first and third sets.

Define the eigenvector matrix $\mathbf{V}$ by placing the normalized eigenvectors in columns: $\mathbf{V} = [\mathbf{v}_1,\ldots, \mathbf{v}_L]$. Due to normalization, this matrix satisfies $\mathbf{V}^\dagger\mathbf{u} = \mathbf{u}$. The compartmental matrix can be written as before as $\mathbf{K} = \mathbf{VDV}^{-1}$. Now the invariants in the second set can be written as

$$\mathbf{u}^{\dagger}\mathbf{K}^{k}\mathbf{e}_1=\mathbf{u}^{\dagger}\mathbf{D}^{k}\mathbf{V}^{-1}\mathbf{e}_1=\mathbf{u}^{\dagger}\mathbf{D}^{k}\mathbf{x}, \tag{11.5}$$

where the vector **x** satisfies $\mathbf{Vx} = \mathbf{e}_1$. If we write out this system of equations, we have

$$(1-s_1)\,x_1+(1-s_2)\,x_2+\cdots+(1-s_L)\,x_L=1, \tag{11.6}$$

$$[\mathbf{v}_1]_2x_1+[\mathbf{v}_1]_2C_{22}x_2+\cdots+[\mathbf{v}_1]_2C_{L2}x_L=0 \tag{11.7}$$

$$\vdots \tag{11.8}$$

$$[\mathbf{v}_1]_Lx_1+[\mathbf{v}_1]_LC_{L2}x_2+\cdots+[\mathbf{v}_1]_LC_{LL}x_L=0, \tag{11.9}$$

where s_l is the sum of the coefficients in rows 2 through L in the lth column. The solution to this system of equations depends only on the matrix **C**. Therefore, the invariants in the second set are functions of the matrices **C** and **D**. This gives the correct number of invariants and shows that there are $L - 1$ free parameters in the compartmental matrix, which we may take to be the last $L - 1$ components of the first normalized eigenvector. There are $L^2 - L + 1$ identifiable quantities, which we may take to be the eigenvalues of **K** and the entries in the matrix **C**.

The positivity constraint on the local compartmental activity **a** (**r**, t) has the effect of confining the matrix **A** to a neighborhood of the identity in the symmetry group in order for the new local compartmental activity ã (**r**, t) = **Aa** (**r**, t) to also be nonnegative. This neighborhood depends on **a** (**r**, t). The end result is that the positivity constraint will not result in any new invariants, but will produce bounds on the ranges of noninvariant quantities associated with the compartmental matrix.

12. Imaging

For a stationary imaging system with sensitivity functions h_m (**r**) for $m = 1,\ldots, M$, and imaging time intervals $\left[t_1, t_1'\right], \ldots, \left[t_J, t_J'\right]$, the data may be viewed as an $M \times J$ matrix given by

$$g_{mj}=\int_{t_j}^{t_j'}\int_S h_m\,(\mathbf{r})\,f\,(\mathbf{r},t)\,d^3r dt+n_{mj}, \tag{12.1}$$

where the n_{mj} are elements of a zero-mean random matrix describing the imaging-system noise. In SPECT imaging, for example, the g_{mj} are independent Poisson random variables, which determine the statistics of the noise matrix. Other information we may have at our disposal includes the input function $\bar{\mathbf{I}}$ (t), spatial support regions S_m, and compartmental volumes V_m. This information, if available, could come from measurements independent of the functional imaging system that generates the data matrix. For example, the input function may be known from measurements in the input device, and the spatial support regions and their volumes may be estimated from an anatomical modality such as CT.

The mean for the temporal Poisson point process on the *m*th detector is given by the function

$$\bar{g}_m(t) = \int_s h_m(\mathbf{r})\ f(\mathbf{r},t)\ d^3r. \tag{12.2}$$

We can use the object model to derive a form for these functions in terms of the local input function and the compartmental matrix:

$$\bar{g}_m(t) = \int_0^t \mathbf{u}^\dagger \exp\left[\mathbf{K}(t-t')\right] \left[\int_s h_m(\mathbf{r})\ \mathbf{I}\ (\mathbf{r},t')\ d^3r\right] dt'. \tag{12.3}$$

In terms of these functions, the data matrix elements are given by

$$g_{mj} = \int_{t_j}^{t_j'} \bar{g}_m\ (t)\ dt + n_{mj}. \tag{12.4}$$

We may use these last two equations as a model for the data when the object, the activity distribution, follows a linear kinetic SPECT model. The constraint in (3.2) must be included to complete this representation of the data matrix. By fitting this model to the data, we can produce estimates of the identifiable quantities associated with the compartmental matrix.

In terms of the eigenvalues and eigenvectors of the compartmental matrix, the mean data function for the detector point process is given by

$$\bar{g}_m\ (t) = \sum_l \int_0^t \exp\left[-\lambda_l\ (t-t')\right] \left[\int_s h_m\ (\mathbf{r})\ \tilde{I}_l\ (\mathbf{r},t')\ d^3r\right] dt'. \tag{12.5}$$

The sensitivity of our imaging system is the spatial function given by

$$s(\mathbf{r}) = \sum_m h_m(\mathbf{r}). \tag{12.6}$$

In the case where we have constant sensitivity $s = s(\mathbf{r})$, we have

$$\sum_m \bar{g}_m(t) = s \sum_l \left[\int_0^T \exp(-\lambda t)'\, \bar{I}_l(t')\, dt'\right] \exp(-\lambda_l t). \tag{12.7}$$

If we were able to perform our imaging experiment many times with short integration times, we could compute samples of this temporal function to any desired degree of accuracy. If we had $2L$ such samples, then the coefficients and eigenvalues in the sum on the right in this equation would be determined. In this sense, we can say that the eigenvalues are estimable quantities when we have constant sensitivity. Finding a way to estimate the other identifiable quantities seems to be a more difficult problem.

There is an important case where the sensitivity function is not constant—when the field of view does not cover the entire organism. The assumption that we have made throughout this work is that the compartmental model applies to the organism as a whole, and that the activity distribution is known throughout the body. When the field of view is too small to

encompass the entire organism, then this latter assumption cannot be valid, even in the approximate sense of having a reconstruction for the entire activity distribution. Some of the compartmental support sets may be inside the field of view, some may be outside, and others may partially overlap the field of view. One approach to this problem is to define the compartments in such a way that their support sets are inside the field of view and incorporate any flow of activity outside the field of view into the diagonal elements of the compartmental matrix. The input function becomes a problem in this case since the injection site is often outside the field of view. A second approach combines these field-of-view compartments with one more compartment whose spatial support is all of the organism outside the field of view. In this case, flow of activity outside the field of view is incorporated into off-diagonal elements of the compartmental matrix. We still have the input function problem with this method. A third approach is to keep a global compartment model, incorporate the field of view into the sensitivity functions $h_m(\mathbf{r})$, and then determine what identifiable quantities can be estimated from the given data. It is possible that, when we find methods to estimate identifiable quantities when the whole activity distribution is available, it will become clear which of these quantities can be estimated from a limited portion of the activity distribution.

13. Discussion

We have described a method for combining the linear compartmental models used in pharmacokinetics with SPECT and PET imaging of the spatiotemporal distribution of a tracer. The resulting object model for the activity distribution can be written in a form that incorporates the compartmental matrix as a set of parameters. This form then allows us to answer questions about the identifiable quantities that are associated with the compartmental matrix. We have found that, as the spatial information we have about the local compartmental activities improves, the number of degrees of freedom in the compartmental matrix decreases. In other words, as spatial support information increases, the dimension of the space of compartmental matrices compatible with this information, the input function, and the activity distribution decreases. We have shown that the degrees of freedom in the compatible compartmental matrices can be described by a symmetry group. The decrease in the number of degrees of freedom in turn implies that the number of identifiable quantities associated with the compartmental matrix increases. Therefore, there will be more scalar quantities associated with the compartmental matrix that we can have a reasonable expectation of estimating accurately. We have also used the symmetry group to describe a method for finding these identifiable quantities and illustrated this method when all of the compartmental spatial supports are distinct, except that of the vascular compartment.

There are limitations to this object model for kinetic SPECT and PET imaging. The linear differential equation that governs the temporal evolution of the compartmental activities, while intuitive in many respects, could certainly be generalized to include nonlinear terms. Very little of what we have done here would apply in that situation, and new techniques would be required to determine identifiable quantities. Even for the linear case, while we have determined the identifiable quantities associated with the compartmental matrix, we have not discussed in detail a method for finding values for them in a given experiment. At present, the best advice we can offer is to first numerically search for a solution for the compartmental matrix and local compartmental activities that matches the given reconstruction of the activity distribution, the measured input function, and the support information, and then determine the eigenvalues and eigenvectors of the compartmental matrix. The invariants can then be determined from the eigenvectors and eigenvalues. Because the practicality and numerical stability of such a procedure have yet to be demonstrated, we would obviously prefer to have a better method.

The next step in this research is to simulate a spatiotemporal activity distribution that follows the compartmental kinetic model and determine practical methods for estimating the compartmental matrix. We then need to address the question of performing this estimation from image data, whether through a reconstruction or other means. Finally, we need to test the applicability of this object model to real-world image data and determine which identifiable quantities are useful in medical imaging applications.

Appendix

Two-voxel simulation details

The two-voxel simulation discussed in section 2 was generated by using a four-dimensional linear model for a vector **b** (*t*). In this model components 1 and 2 are in the first voxel, and components 3 and 4 are in the second voxel. The linear model is given by the equation

$$\frac{d}{dt}\mathbf{b}\ (t)=\mathbf{K}_b\mathbf{b}\ (t)+\mathbf{I}\ (t),$$

with the matrix $\mathbf{K}_b$ given by

$$\mathbf{K}_b=\begin{bmatrix} -1 & 0.2 & 0.3 & 0 \\ 0.3 & -1.2 & 0 & 0.4 \\ 0.5 & 0 & -0.8 & 0.2 \\ 0 & 0.6 & 0.3 & -1 \end{bmatrix}.$$

For the input vector I_1 and I_2 were constant between $t = 0$ and $t = 1$, and zero after $t = 1$. The input components I_3 and I_4 were zero for all times.

The compartmental model for the two-voxel organism is described by the vector $\bar{\mathbf{a}}$ (*t*) given by

$$\bar{\mathbf{a}}\ (t)=\begin{bmatrix} 1 & 0 & 1 & 0 \\ 0 & 1 & 0 & 1 \end{bmatrix}\mathbf{b}\ (t).$$

Thus both compartments have activity in both voxels. This activity vector obeys the linear compartmental equation

$$\frac{d}{dt}\bar{\mathbf{a}}\ (t)=\mathbf{K}\bar{\mathbf{a}}\ (t)+\bar{\mathbf{I}}\ (t),$$

with the compartmental matrix

$$\mathbf{K}=\begin{bmatrix} -0.5 & 0.2 \\ 0.3 & -0.6 \end{bmatrix}.$$

Plots of the components of **b** (*t*) are shown in Figure 3. On the left of this figure are components 1 and 2, while on the right we have components 3 and 4.

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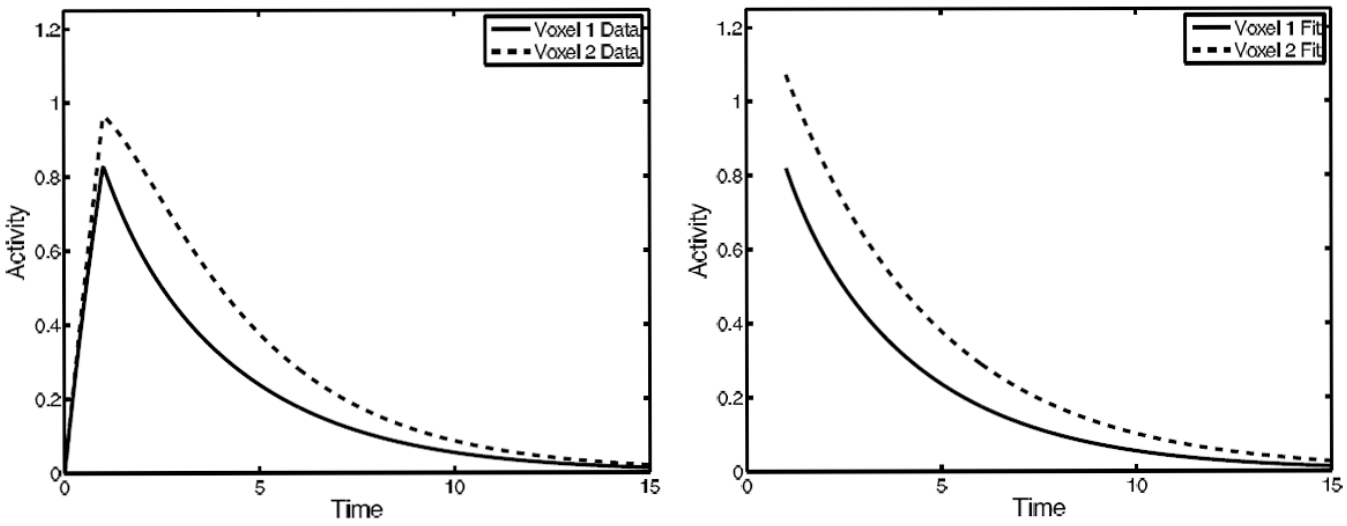

Figure 1.
Actual voxel time activity curves and double exponential fits for the two-voxel, two-compartment example.

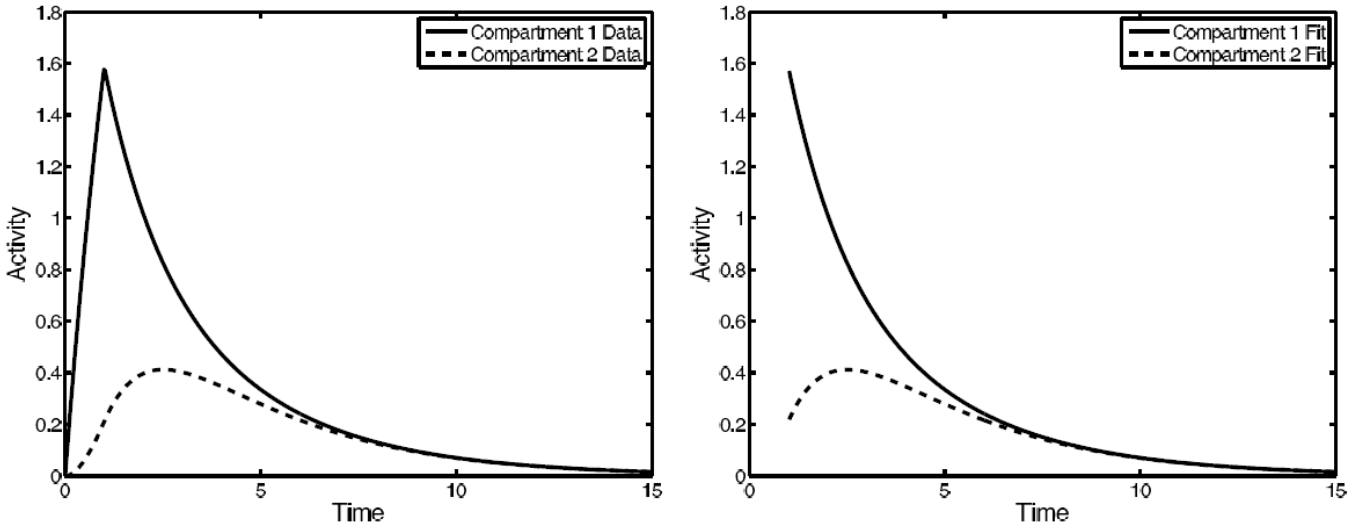

Figure 2.
Actual compartmental time activity curves and double exponential fits for the two-voxel, twocompartment example.

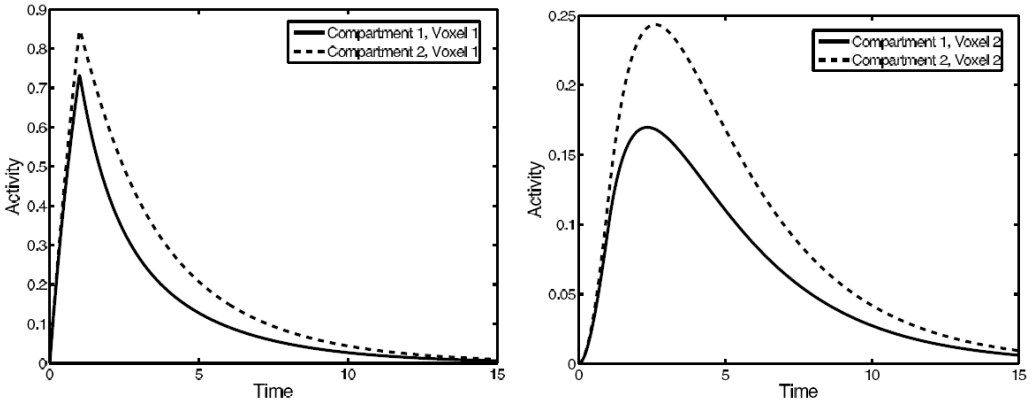

Figure 3.
Time activity curves for the compartmental activities in each voxel for the example in section 2.