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ARTICLES

Transient Effects and the Identifiability of Excited-State Processes

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The identifiability of excited-state processes in the presence of transient effects is studied. The Smoluchowski and Collins-Kimball models of diffusion-mediated association are considered. The kinetic parameters of single-species quenching and related kinetic schemes (double-species quenching without excited-state interchange, and irreversible association with separated excited-species spectra) can be uniquely recovered from the same or a smaller number of decay traces than are necessary within classical kinetics where time-invariant rate constants are used. For single-species quenching in low dimensions, 1D and 2D, the system parameters can be uniquely recovered from a single decay trace at one nonzero quencher concentration. In three dimensions, decays traces measured at two concentrations are necessary and sufficient to recover the parameters. For double-species quenching without interchange of the excited states, decay traces at two wavelengths collected in the absence and presence of quencher guarantee local identifiability of the model in each dimension with or without transient effects. Irreversible association with separate excited-species spectra is identifiable in each dimension, given decay traces at two quencher concentrations and two wavelengths.

1. Introduction

The identifiability problem is concerned with determining values of model parameters when observations are available. Identifiability with perfect observations is known under the name of structural or *deterministic identifiability*. There are three possible outcomes to the deterministic identifiability analysis: (i) The parameters of an assumed model can be estimated uniquely, and the model is *uniquely (globally) identifiable* from the experiment. (ii) There are a finite number of alternative estimates for the model parameters that fit the data, and the model is *locally identifiable*. (iii) There are an infinite number of model parameter estimates that fit the data, and the model is *unidentifiable* from the experiment.

Although identifiability analyses have been extensively used in biomedicine, pharmacology, ecology, and engineering,[1,2] their use in photophysics is of recent vintage.[3−14] We have reported on the deterministic identifiability of inter- and intramolecular two-state and three-state excited-state processes in the presence and absence of added quencher.[3,5−13] For the linear, time-invariant models that we considered, the parameters to be identified are rate constants and spectral parameters related to absorption (the excited-state species concentrations at time zero) and emission (the emission weighting factors). It was found that some excited-state processes are uniquely identifiable, others are only locally identifiable, and still others are unidentifiable without prior knowledge of some of the system parameters; for example, for intramolecular two-state excited-state processes in the presence of added quencher it is possible to determine only bounds on the rate constants.[7,10] The methods available for testing deterministic identifiability of linear, time-invariant models are well-established[1,2] and include among others the Laplace transform approach, the normal-mode method, the Markov parameters, and the similarity transformation method.[15] For time-varying models no general methods are available for assessing the deterministic identifiability problem. Time-varying systems have been studied very rarely, and only one report has been published describing the identifiability of an excited-state process with a time-varying rate coefficient.[14] The conditions necessary for the simultaneous recovery of the rate constants of deactivation, k_{01} and k_{02}, of a two-state excited-state process were investigated, without making any specific assumptions as to the mechanism of interchange of the excited species. Only a subset of kinetic parameters of a complex reaction scheme involving transients was studied.

In this paper we study deterministic identifiability of the full set of kinetic parameters of single-species quenching and related kinetic schemes (double-species quenching without excited-state interchange and irreversible association with separated excited-species spectra), assuming the Smoluchowski and Collins-Kimball models of diffusion-mediated association.[16] We will show that these kinetic models are identifiable (i.e., their parameters can be estimated) from the same or a smaller number of decay traces than are necessary within classical kinetics where time-invariant rate constants are used. It should be noted that the kinetic description of transient effects involves more parameters than their classical kinetics counterparts.

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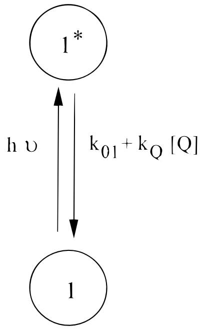
SCHEME 1



The deterministic identifiability conditions we develop here establish the minimal experimental design, that is, the number of decays that have to be collected at different wavelengths and concentrations, such that the system response to an external excitation (or the output of an ideal measuring device that convolutes the system response with a noiseless instrument response function) carries information sufficient for estimating the kinetic parameters. However, in practice measurements introduce errors and the system response is convoluted with a noisy instrument function, which reduces the information content of the data compared to that in an "ideal" system. The value of a deterministic identifiability analysis to the practitioner is thus in providing the upper limit on the kinetic information contained in real experimental data. For identifiable kinetic schemes, the goal of the deterministic analysis is to find the conditions that are necessary for parameter recovery. If the experimental design does not meet the identifiability criteria, the parameters cannot be recovered no matter how many decays are collected. Similarly, when a kinetic scheme is shown to be deterministically unidentifiable, no experimental design will lead to parameter recovery.

2. Single-Species Quenching

We first focus on single-species quenching as depicted in Scheme 1. In this scheme species 1 is excited to its corresponding excited state 1*, which decays with the composite rate constant k_{01} and is quenched by an added quencher whose concentration is [Q]. After δ-pulse excitation, the decay trace $f(t)$ of species 1* monitored by fluorescence or transient absorption is proportional to the survival probability $S(t)$:[16]

$$f(t) = [1^*]_0 c(\lambda)\, S(t) \tag{1}$$

where $[1^*]_0$ is the initial concentration of 1* dependent on the wavelength of the pump pulse, and with the proportionality factor $c(\lambda)$ dependent on the wavelength λ, which is either the emission wavelength (fluorescence) or the wavelength of the probe pulse (transient absorption).

In classical kinetics the rate of quenching is determined by the time-invariant quenching rate constant k_Q, and the survival probability $S(t)$ is given by

$$S(t) = \exp(-k_{01}t - [\mathrm{Q}]k_Q t) \tag{2}$$

When transient effects are present, the quenching rate constant, k_Q, is replaced by the time-varying rate coefficient $k(t)$, and the survival probability becomes

$$S(t) = \exp(-k_{01}t - [\mathrm{Q}]\int_0^t k(t')\,\mathrm{d}t') \tag{3}$$

where the rate coefficient $k(t)$ depends on the mutual diffusion constant D, the reaction radius R, the intrinsic reaction rate constant k_a, and possibly on other parameters. In this paper we consider only the Smoluchowski and Collins-Kimball models of diffusion-mediated association.[16] When the two-dimensional (2D) and three-dimensional (3D) Smoluchowski models of $k(t)$ are used in Scheme 1, the model parameters of interest are $\{k_{01}, D, R\}$. In one dimension (1D) this set reduces to k_{01} and D. When the Collins-Kimball model is employed, one more parameter, k_a, is always involved.

The product of the pre-exponential factors in eq 1 is equal to the initial value of a decay trace $f(0) = [1^*]_0 c(\lambda)$. Hence the identifiability problem for single-species quenching translates to the following question: given a model of diffusion-mediated association, can one find different sets of parameters, $\{k_{01}, D, R, k_a\}$ and $\{\tilde{k}_{01}, \tilde{D}, \tilde{R}, \tilde{k}_a\}$, such that

$$S(t[\mathrm{Q}], k_{01}, D, R, k_a) = S(t|[\mathrm{Q}], \tilde{k}_{01}, \tilde{D}, \tilde{R}, \tilde{k}_a) \tag{4}$$

The notation of eq 4 serves as a reminder that the survival probability $S(t)$ is parametrized by the quencher concentration [Q], which is considered to be known, and the kinetic parameters of an association model. If two or more different sets of parameters reproduce $S(t)$, the system is not uniquely identifiable. However, if eq 4 entails that

$$k_{01} = \tilde{k}_{01}, \quad D = \tilde{D}, \quad R = \tilde{R}, \quad k_a = \tilde{k}_a \tag{5}$$

the system is uniquely identifiable; that is, its parameters can be uniquely recovered from decay traces.

Let us consider the survival probability determining a decay trace at a nonzero quencher concentration. Taking the logarithm and then the time derivative of each side of eq 4 with $S(t)$ given by eq 3 one gets

$$k(t|D, R, k_a) - k(t|\tilde{D}, \tilde{R}, \tilde{k}_a) = [\mathrm{Q}]^{-1}(\tilde{k}_{01} - k_{01}) \tag{6}$$

where the notation on the lhs indicates that the rate coefficient $k(t)$ depends on D, R, and k_a. Since k_{01} can be determined from a measurement with no added quencher, [Q] = 0, we first focus on the case when k_{01} is known, so that $k_{01} = \tilde{k}_{01}$ and the right-hand side of eq 6 is equal to zero. Now a condition necessary and sufficient for global identifiability is that

$$k(t|D, R, k_a) = k(t|\tilde{D}, \tilde{R}, \tilde{k}_a) \Rightarrow D = \tilde{D}, R = \tilde{R}, k_a = \tilde{k}_a \tag{7}$$

or, equivalently, in terms of Laplace transforms

$$\hat{k}(z|D, R, k_a) = \hat{k}(z|\tilde{D}, \tilde{R}, \tilde{k}_a) \Rightarrow D = \tilde{D}, R = \tilde{R}, k_a = \tilde{k}_a \tag{8}$$

Let us first show that eqs 7 and 8 are satisfied by the Smoluchowski model of $k(t)$. In 1D and 3D it follows directly from the explicit forms of the Laplace-transformed Smoluchowski rate coefficient $\hat{k}_S(z)$:[16]

$$\text{1D:}\quad \hat{k}_S(z) = (4D/z)^{1/2} \tag{9}$$

$$\text{3D:}\quad \hat{k}_S(z) = \frac{k_D}{x}(1 + (z\tau_D)^{1/2}), \quad k_D = 4\pi DR, \quad \tau_D = R^2/D \tag{10}$$

For instance, the lhs of the identifiability condition eq 8 becomes in 3D:

$$\frac{k_D}{z}(1 + (z\tau_D)^{1/2}) = \frac{\tilde{k}_D}{z}(1 + (z\tilde{\tau}_D)^{1/2}) \tag{11}$$

Since eq 11 must hold for all z, it follows that $k_D = \tilde{k}_D$ and τ_D

$= \tilde{\tau}_D$ and, therefore, that R and D are uniquely determined. Similar argument applies to $\hat{k}_S(z)$ in 1D. The Laplace transform of k_S in 2D is more involved:

$$\text{2D:}\ \hat{k}_S(z) = \frac{2\pi x K_1(x)}{zK_0(x)},\quad x = (z\tau_D)^{1/2},\quad \tau_D = R^2/D \tag{12}$$

where K_0 and K_1 are modified Bessel functions. However, to see that the parameters $\{D, R\}$ also identifiable in 2D, it is sufficient to consider the short-time expansion of $k_S(t)$:[16]

$$\text{2D:}\ k_S(t) = 2\pi D((\pi\tau)^{-1/2} + 1/2 - (\tau/\pi)^{1/2}/4 + ...),\quad \tau = t/\tau_D \tag{13}$$

in the identifiability condition 7. We conclude that the parameters of the Smoluchowski model can be determined from a decay trace at a nonzero [Q], given k_{01} measured in the absence of quencher. Next we show that a similar conclusion holds for the Collins-Kimball model.

The Collins-Kimball rate coefficient k_{CK} is related to the Smoluchowski rate coefficient k_S via a Laplace transform relation:[16]

$$\hat{k}_{CK} = \frac{k_a\hat{k}_S(z)}{k_a + z\hat{k}_S(z)} \tag{14}$$

The lhs of the identifiability condition 8 for the Collins-Kimball model reads

$$\frac{k_a\hat{k}_S(z)}{k_a + z\hat{k}_S(z)} = \frac{\tilde{k}_a + \tilde{\hat{k}}_S(z)}{\tilde{k}_a + z\tilde{\hat{k}}_S(z)} \tag{15}$$

Multiplying eq 15 by the Laplace variable z and taking the short-time limit, $z \to \infty$, one finds that $k_a = \tilde{k}_a$. If one applies to eq 15 formula 16,

$$L[f'(t)] = z\hat{f}(z) - f(0+) \tag{16}$$

where $L[...]$ denotes a Laplace transform, and uses the fact that $k_{CK}(0+) = k_a$ one obtains

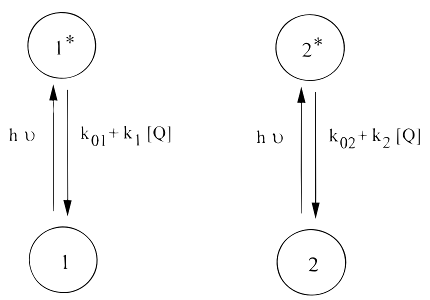
$$\frac{k_a^{\,2}}{k_a + z\hat{k}_S(z)} = \frac{\tilde{k}_a^{\,2}}{\tilde{k}_a + z\tilde{\hat{k}}_S(z)} \tag{17}$$

which implies that $k_S = \tilde{k}_S$. It follows that the parameters of the Collins-Kimball model are uniquely determined from a measurement at $[Q] > 0$, given k_{01} measured at $[Q] = 0$.

We have shown that two decay traces, with and without quencher, guarantee recovery of the kinetic parameters $\{k_{01}, D, R, k_a\}$. It is not difficult to see, however, that two decay traces at nonzero quencher concentrations also lead to a unique parameter recovery. Since in this case eq 6 is satisfied for two $[Q] > 0$, it follows that the rhs must be equal to zero so that $k_{01} = \tilde{k}_{01}$ and the deactivation constant k_{01} is uniquely determined. Consequently, the identifiability conditions 7 and 8 for the parameters $\{D, R, k_a\}$ apply again, and these parameters are also uniquely determined.

Now the question remains, what is the minimum number of decays measured at different concentrations [Q] necessary to determine the kinetic parameters, including the deactivation rate constant k_{01}? Interestingly, in low dimensions (1D and 2D) the kinetic parameters can be identified from one decay at a nonzero quencher concentration. This follows from the fact that in low dimensions $k(t)$ tends to zero at long times, $k(\infty) = 0$. Taking the long-time limit of eq 6, one finds that $k_{01} = \tilde{k}_{01}$ and, therefore, that the deactivation constant k_{01} and the remaining parameters $\{D, R, k_a\}$ are uniquely determined from a decay trace at one nonzero quencher concentration.

SCHEME 2



It is well-known that in classical kinetics where the quenching rate coefficient is constant (i.e., $k(t) = k_Q =$ constant), the two relevant parameters, k_{01} and k_Q, can be recovered from decays at two different quencher concentrations, irrespective of the dimensionality of the system. Since we find that in low dimensions (1D and 2D) a *single* decay trace at one nonzero quencher concentration uniquely determines the full set of kinetic parameters, we conclude that transient effects can change identifiability criteria compared to the case when the time-invariant quenching rate constant k_Q is used.

3. Double-Species Quenching without Excited-State Interchange

In Scheme 2 species 1 and 2 are excited and their corresponding excited-state species 1* and 2* deactivate with different rate constants k_{01} and k_{02} and are quenched by the same quencher with the rate coefficients k_1 and k_2, respectively. This scheme corresponds, for example, to a situation where a probe is attached to a protein or is part of its polypeptide backbone (e.g., a tryptophyl residue), which assumes two conformations with different spectral properties and the conformational changes are slow compared to the fluorescence time scale of the probe.

Let us denote by $f(t|\lambda_1)$ and $f(t|\lambda_2)$ the decay traces originating from the system shown in Scheme 2 and collected at two different wavelengths indicated as λ_1 and λ_2. In fluorescence these wavelengths are emission wavelengths, whereas in transient absorption they are the wavelengths of the probe pulse. We assume that the spectra of species 1* and 2* may overlap, but are sufficiently different so that the concentrations of the excited species can be reconstructed as[14]

$$\begin{gathered} p_1(t) = x_1(\lambda_1)\, f(t|\lambda_1) + x_1(\lambda_2)\, f(t|\lambda_2),\\ p_2(t) = x_2(\lambda_1)\, f(t|\lambda_1) + x_2(\lambda_2)\, f(t|\lambda_2) \end{gathered} \tag{18}$$

where p_1 and p_2 denote the scaled concentrations,

$$p_1(t) = \frac{[1^*(t)]}{[1^*(0)] + [2^*(0)]},\quad p_2(t) = \frac{[2^*(t)]}{[1^*(0)] + [2^*(0)]} \tag{19}$$

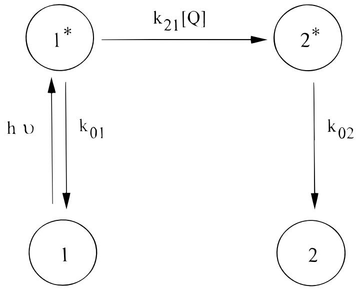
and the species- and wavelength-dependent coefficients $x(\lambda)$ are in general unknown. Let us denote by S_{qi} the survival probability of species i* with respect to quenching:

$$S_{qi}(t) = \exp(-[Q]\int_0^t k_i(t')\, dt'),\quad i = 1, 2 \tag{20}$$

Since at time $t = 0$ we have

$$p_i(0) = x_i(\lambda_1)\, f(0|\lambda_1) + x_i(\lambda_2)\, f(0|\lambda_2),\quad i = 1, 2 \tag{21}$$

SCHEME 3



we can write the following expression for the time evolution of the decay originating from species $i^* = 1, 2$:

$$[x_i(\lambda_1)\, f(0|\lambda_1) + x_i(\lambda_2)\, f(0|\lambda_2)]\, \exp(-k_{0i}t)\, S_{qi}(t) = x_i(\lambda_1)\, f(t|\lambda_1) + x_i(\lambda_2)\, f(t|\lambda_2) \quad (22)$$

Dividing eq 22 by $x_i(\lambda_1)$, we have

$$\exp(-k_{0i}t)\, S_{qi}(t) = \frac{f(t|\lambda_1) + y_i f(t|\lambda_2)}{f(0|\lambda_1) + y_i f(0|\lambda_2)}, \quad y_i = x_i(\lambda_2)/x_i(\lambda_1) \quad (23)$$

which for the case with no quencher becomes

$$\exp(-k_{0i}t) = \frac{f_0(t|\lambda_1) + y_i f_0(t|\lambda_2)}{f(0|\lambda_1) + y_i f(0|\lambda_2)} \quad (24)$$

where the subscript 0 on f refers to $[Q] = 0$. Equations 23 and 24 involve three unknown quantities $\{y_i, k_{0i}, S_{qi}\}$ so that additional information is needed to determine them. The biexponential shape of $f_0(t|\lambda_1)$ and $f_0(t|\lambda_2)$ with exponents $-k_{01}t$ and $-k_{02}t$ provides this essential information. Let us assume that there exist alternative values $\{\tilde{y}_i, \tilde{k}_{0i}\}$ satisfying eq 24:

$$\exp(-\tilde{k}_{0i}t) = \frac{f_0(t|\lambda_1) + \tilde{y}_i f_0(t|\lambda_2)}{f(0|\lambda_1) + \tilde{y}_i f(0|\lambda_2)}, \quad \tilde{y}_i = \tilde{x}_i(\lambda_2)/\tilde{x}_i(\lambda_1) \quad (25)$$

The numerator of the rhs of eq 25 is a biexponential function with exponential factors $-k_{01}t$ and $-k_{02}t$. It follows that $\tilde{k}_{0i} = k_{01}$ or $\tilde{k}_{0i} = k_{02}$, and correspondingly there are two different solutions for $\tilde{y}_i$. From eq 23 it follows that for each $\{\tilde{y}_i, \tilde{k}_{0i}\}$ there is one solution for S_{qi}. The presence of two sets of solutions of the parameters is due to the symmetry of the system when the labels of the two species are interchanged and is an example of a trivial case of local identifiability. We conclude that decay traces collected in the absence and presence of added quencher at two wavelengths guarantee local identifiability of the entire kinetic scheme. Note that this is valid in each dimension whether transient effects are present or not.

4. Irreversible Association with Separated Excited-Species Spectra

In this section we discuss identifiability for the irreversible excited-state association shown in Scheme 3. The composite deactivation rate constants of species 1* and 2* are denoted as k_{01} and k_{02}, respectively. We assume that the excited-species spectra are such that one can choose the wavelengths λ_1 and λ_2 to follow the individual decays of 1* and 2*, respectively. The kinetic parameters of the system $\{k_{01}, k_{02}, D, R, k_a\}$ include the deactivation rate constants k_{01}, k_{02} and the set $\{D, R, k_a\}$ parametrizing the time-varying association rate coefficient k_{21}.

Our interest in Scheme 3 was motivated by results of Martinho et al.,[17] who studied excimer formation by pyrene in cyclohexanol ($Q \equiv 1$ in this case) and found that at 25 and 45 °C the effect of the back reaction is negligible. For these temperatures monomer fluorescence decays were fitted to eq 3 with the Collins-Kimball model for k_{21}, and a novel method of simultaneous fitting of monomer and excimer fluorescence decays was used to recover the excimer deactivation rate constant k_{02}.

When the wavelength λ_1 is chosen so that only the decay of 1* is seen, the decay traces $f(t|\lambda_1)$ are those of single-species quenching, as discussed in section 2. Hence the parameters $\{k_{01}, D, R, k_a\}$ are uniquely determined from decay traces at two concentrations, and the question whether the entire kinetic system is identifiable reduces to the question whether the deactivation rate constant k_{02} of species 2* can be determined.

For a δ-pulse excitation the rate equation for the sum of the scaled concentrations 19 is given by[14,17]

$$\frac{d}{dt}[p_1(t) + p_2(t)] = -k_{01}p_1(t) - k_{02}p_2(t) \quad (26)$$

Equation 26 states that the overall decay of excited species is determined by the decay rates of 1* and 2* and does not depend on the interchange mechanism. When the spectra of 1* and 2* allow one to follow their respective decays separately, one can chose the wavelengths λ_1 and λ_2 so that

$$p_1(t) = x_1(\lambda_1)\, f(t|\lambda_1), \quad p_2(t) = x_2(\lambda_2)\, f(t|\lambda_2) \quad (27)$$

where $f(t|\lambda_1)$ and $f(t|\lambda_2)$ denote the decays originating from 1* and 2*, respectively.

Laplace transforming rate equation 26, we find

$$z[x_1(\lambda_1)\, \hat{f}(z|\lambda_1) + x_2(\lambda_2)\, \hat{f}(z|\lambda_2)] - 1 = -k_{01}x_1(\lambda_1)\, \hat{f}(z|\lambda_1) - k_{02}x_2(\lambda_2)\, \hat{f}(z|\lambda_1) \quad (28)$$

The species- and wavelength-dependent coefficients $x(\lambda)$ are in general unknown. However, since only species 1* is directly excited, one gets $x_1(\lambda_1) = 1/f(0|\lambda_1)$, so that $x_1(\lambda_1)$ is fixed. The deactivation rate constant k_{01} is known from measurements at λ_1. Hence the question is whether a different set of parameters, $\tilde{x}_2(\lambda_2)$ and $\tilde{k}_{02}$, can satisfy eq 28:

$$z[x_1(\lambda_1)\, \hat{f}(z|\lambda_1) + \tilde{x}_2(\lambda_2)\, \hat{f}(z|\lambda_2)] - 1 = -k_{01}x_1(\lambda_1)\, \hat{f}(z|\lambda_1) - \tilde{k}_{02}\tilde{x}_2(\lambda_2)\, \hat{f}(z|\lambda_1) \quad (29)$$

Upon subtracting eqs 28 and 29, one finds that

$$x_2(\lambda_2)(z + k_{02}) = \tilde{x}_2(\lambda_2)(z + \tilde{k}_{02}) \quad (30)$$

which shows that the deactivation rate constant k_{02} is uniquely determined from two decays at one concentration, provided k_{01} is known. We conclude that the parameters $\{k_{01}, k_{02}, D, R, k_a\}$ of irreversible association with separated excited-species spectra are uniquely determined when decay traces are collected at two wavelengths and two concentrations. Again we note that this identifiability criterion is valid in each dimension irrespective of the presence or absence of transient effects.

To recover k_{02}, Martinho et al.[17] fitted simultaneously monomer and excimer fluorescence decay traces to an equation equivalent to eq 26. Here we showed that indeed eq 26 uniquely determines k_{02}, which supports their method. In ref 14 we showed that the simultaneous recovery of k_{01} and k_{02} from decay traces at one nonzero concentration is only possible when transient effects are present. As we found here, however, transient effects allow, but are not required, for the unique determination of k_{02} and other kinetic parameters, when k_{01} is known.

5. Summary

In this paper we have studied the identifiability problem in the presence of transient effects for the kinetic schemes of single-species quenching, double-species quenching without excited-state interchange, and irreversible association with separated excited-species spectra. The Smoluchowski and Collins-Kimball models of diffusion-mediated association were considered. We showed for single-species quenching in low dimensions, 1D and 2D, that the system parameters can be uniquely determined from a single decay trace at one nonzero quencher concentration. In three dimensions, decays traces measured at two concentrations are necessary and sufficient to recover the parameters. For double-species quenching without interchange of the excited states, decay traces at two wavelengths collected in the absence and presence of quencher guarantee local identifiability of the model in each dimension with or without transient effects. Irreversible association with separate excited-species spectra is a straightforward generalization of the basic single-species quenching model and is also identifiable in each dimension, given decay traces at two quencher concentrations and two wavelengths.

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