# Identifiability and Identification of Switched Linear Biological Systems

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## Difficulties in Biological System Identification

(1) Biological systems often involve complex biochemical reactions that result in high-order kinetics with many unknown parameters.

(2) Experimental observations are often limited. It is common that not all the state variables are continuously measurable, which can incur non-unique solution problems and limit the use of parameter identification algorithms.

(3) Rich perturbations are very important to parameter identification, but there are usually restrictions on executing complex excitation signals.

# Research Objective

To analyze the identifiability and identification of a class of switched linear models whose system matrix depends on the input.

$$\dot{\boldsymbol{x}} = \mathrm{A}(u)\boldsymbol{x} + \mathrm{B}u\,,\ \ \boldsymbol{x} \in R^{n}\,,$$

$$\mathrm{A}(u) \in R^{n\times n},\ \ \mathrm{B} \in R^{n\times 1},\ \ u \in R^{1}$$

$$u = \begin{cases} u_0 & 0 \le t \le t_d \\ 0 & t > t_d \end{cases}$$

# Determination System Eigenvector Matrix

$$A(u_0) = PD_1Q = \begin{bmatrix} p_{11} & p_{12} \cdots p_{1n} \\ p_{21} & p_{22} \cdots p_{2n} \\ \vdots & \vdots \ddots \vdots \\ p_{n1} & p_{n2} \cdots p_{nn} \end{bmatrix} \begin{bmatrix} \lambda_1^1 & 0 \cdots 0 \\ 0 & \lambda_1^2 \cdots 0 \\ \vdots & \vdots \ddots \vdots \\ 0 & 0 \cdots \lambda_1^n \end{bmatrix} \begin{bmatrix} q_{11} & q_{12} \cdots q_{1n} \\ q_{21} & q_{22} \cdots q_{2n} \\ \vdots & \vdots \ddots \vdots \\ q_{n1} & q_{n2} \cdots q_{nn} \end{bmatrix}$$

$$A(0) = UD_2V = \begin{bmatrix} u_{11} & u_{12} \cdots u_{1n} \\ u_{21} & u_{22} \cdots u_{2n} \\ \vdots & \vdots \ddots \vdots \\ u_{n1} & u_{n2} \cdots u_{nn} \end{bmatrix} \begin{bmatrix} \lambda_2^1 & 0 \cdots 0 \\ 0 & \lambda_2^2 \cdots 0 \\ \vdots & \vdots \ddots \vdots \\ 0 & 0 \cdots \lambda_2^n \end{bmatrix} \begin{bmatrix} v_{11} & v_{12} \cdots v_{1n} \\ v_{21} & v_{22} \cdots v_{2n} \\ \vdots & \vdots \ddots \vdots \\ v_{n1} & v_{n2} \cdots v_{nn} \end{bmatrix}$$

# System Response during Excitation

$$x = \int_0^t e^{A\tau} Bu(t-\tau)\,d\tau = \Phi \begin{bmatrix} \frac{1}{\lambda_1^1} e^{\lambda_1^1 \tau} \\ \frac{1}{\lambda_1^2} e^{\lambda_1^2 \tau} \\ \vdots \\ \frac{1}{\lambda_1^n} e^{\lambda_1^n \tau} \end{bmatrix}_0^t$$

$$\Phi = \begin{bmatrix} p_{11}\sum_{i=1}^{n} q_{1i}(Bu_0)_i & p_{12}\sum_{i=1}^{n} q_{2i}(Bu_0)_i \cdots p_{1n}\sum_{i=1}^{n} q_{ni}(Bu_0)_i \\ p_{21}\sum_{i=1}^{n} q_{1i}(Bu_0)_i & p_{22}\sum_{i=1}^{n} q_{2i}(Bu_0)_i \cdots p_{2n}\sum_{i=1}^{n} q_{ni}(Bu)_i \\ \vdots & \vdots \quad \ddots \quad \vdots \\ p_{n1}\sum_{i=1}^{n} q_{1i}(Bu_0)_i & p_{n2}\sum_{i=1}^{n} q_{2i}(Bu_0)_i \cdots p_{nn}\sum_{i=1}^{n} q_{ni}(Bu_0)_i \end{bmatrix}$$

# System Response following Pulse Excitation

$$x_i = \left[\varphi_i \, \boldsymbol{x}(t_d)\right]^T \begin{bmatrix} e^{\lambda_2^1 t} \\ e^{\lambda_2^2 t} \\ \vdots \\ e^{\lambda_2^n t} \end{bmatrix} = \left[ \Psi_i \begin{bmatrix} \frac{1}{\lambda_1^1} e^{\lambda_1^1 t_d} - \frac{1}{\lambda_1^1} \\ \frac{1}{\lambda_1^2} e^{\lambda_1^2 t_d} - \frac{1}{\lambda_1^2} \\ \vdots \\ \frac{1}{\lambda_1^n} e^{\lambda_1^n t_d} - \frac{1}{\lambda_1^n} \end{bmatrix} \right]^T \begin{bmatrix} e^{\lambda_2^1 t} \\ e^{\lambda_2^2 t} \\ \vdots \\ e^{\lambda_2^n t} \end{bmatrix}$$

$$\varphi_i = \begin{pmatrix} u_{i1} v_{11} & u_{i1} v_{12} \cdots u_{i1} v_{1n} \\ u_{i2} v_{21} & u_{i2} v_{22} \cdots u_{i2} v_{2n} \\ \vdots & \vdots \quad \ddots \quad \vdots \\ u_{in} v_{n1} & u_{in} v_{n2} \cdots u_{in} v_{nn} \end{pmatrix}$$

$$\Psi_i = \begin{pmatrix} u_{i1} \sum_{r=1}^{n} q_{1r} (\mathrm{B}u_0)_r \sum_{j=1}^{n} p_{1j} v_{j1} & u_{i1} \sum_{r=1}^{n} q_{2r} (\mathrm{B}u_0)_r \sum_{j=1}^{n} p_{1j} v_{j2} \cdots u_{i1} \sum_{r=1}^{n} q_{nr} (\mathrm{B}u_0)_r \sum_{j=1}^{n} p_{1j} v_{jn} \\ u_{i2} \sum_{r=1}^{n} q_{1r} (\mathrm{B}u_0)_r \sum_{j=1}^{n} p_{2j} v_{j1} & u_{i2} \sum_{r=1}^{n} q_{2r} (\mathrm{B}u_0)_r \sum_{j=1}^{n} p_{2j} v_{j2} \cdots u_{i2} \sum_{r=1}^{n} q_{nr} (\mathrm{B}u_0)_r \sum_{j=1}^{n} p_{2j} v_{jn} \\ \vdots & \vdots \qquad \ddots \qquad \vdots \\ u_{in} \sum_{r=1}^{n} q_{1r} (\mathrm{B}u_0)_r \sum_{j=1}^{n} p_{nj} v_{j1} & u_{in} \sum_{r=1}^{n} q_{2r} (\mathrm{B}u_0)_r \sum_{j=1}^{n} p_{nj} v_{j2} \cdots u_{in} \sum_{ri=1}^{n} q_{nr} (\mathrm{B}u_0)_r \sum_{j=1}^{n} p_{nj} v_{jn} \end{pmatrix}$$

# Identifiability Analysis

(I) All States Measurable

- Φ can be determined from experimental data from a single pulse excitation. Since each column vector of Φ is just a multiple of the column vector of the P matrix, Φ itself is another eigenvector matrix for $A(u_0)$. $A(u_0)$ can thus be uniquely reconstructed.

- A(0) can be determined from a single pulse excitation if at least *n* data points of all the states are measured after the pulse is turned off.

## (II) Partial States Measurable and Recurrent-pulse Excitation

- A common and most limiting case is that only one state variable is measurable.

- By using the Vandermonde determinant, it is easy to verify that $\boldsymbol{x}(t_1)$, $\boldsymbol{x}(t_2)$ … $\boldsymbol{x}(t_n)$ are linearly independent, where $\boldsymbol{x}(t_1)$, $\boldsymbol{x}(t_2)$ … $\boldsymbol{x}(t_n)$ are the state variable values at the end of pulses with durations $t_1$, $t_2$ … $t_n$, respectively. The measured state variable responses will allow unique determination of the $\Psi_i$ matrix, which provides constraints for the eigenvectors for both $A(u_0)$ and $A(0)$.

- We refer to the repeated application of pulses as recurrent-pulse excitation.

## (a) Known A($u_0$)--the whole system is identifiable even if only one state variable is measurable.

(1) For the $j^{th}$ recurrent pulse excitation, let $\xi_j$ denote $\varphi_i\, \boldsymbol{x}(t_j)$ and $\xi_j$ .

$\xi_j$ can be calculated from the $i^{th}$ measurable state.

(2) Let $X_0$=[ $\boldsymbol{x}(t_1)$, $\boldsymbol{x}(t_2)$ ,…, $\boldsymbol{x}(t_n)$] and $\xi$ =[ $\xi_1$ , $\xi_2$ ,…, $\xi_n$ ], then

$$\varphi_i = \xi X_0^{-1}$$

(3) Since $\varphi_i$ is a right eigenvector matrix for A(0), A(0) can be reconstructed as:

$$A(0) = X_0 \xi^{-1} D_2 \xi\, X_0^{-1} = X_0 M_2 X_0^{-1}$$

where $M_2 = \xi^{-1} D_2 \xi$

# (b) Known A(0)--the whole system is identifiable even if only one state variable is measurable.

Let $X_0=[\boldsymbol{x}(t_1), \boldsymbol{x}(t_2), \ldots, \boldsymbol{x}(t_n)]$.

$\Phi = X_0 \xi^{-1}$

$$\text{where } \xi = \begin{bmatrix} \frac{1}{\lambda_1^1}(e^{\lambda_1^1 t_1}-1) & \frac{1}{\lambda_2^1}(e^{\lambda_2^1 t_1}-1) & \cdots & \frac{1}{\lambda_n^1}(e^{\lambda_n^1 t_1}-1) \\ \frac{1}{\lambda_1^1}(e^{\lambda_1^1 t_2}-1) & \frac{1}{\lambda_2^1}(e^{\lambda_2^1 t_2}-1) & \cdots & \frac{1}{\lambda_n^1}(e^{\lambda_n^1 t_2}-1) \\ \vdots & \vdots & \ddots & \vdots \\ \frac{1}{\lambda_1^1}(e^{\lambda_1^1 t_n}-1) & \frac{1}{\lambda_2^1}(e^{\lambda_2^1 t_n}-1) & \cdots & \frac{1}{\lambda_n^1}(e^{\lambda_n^1 t_n}-1) \end{bmatrix}^T$$

$\Phi$ is a left eigenvector matrix for $A(u_0)$

$A(u_0) = X_0 \xi^{-1} D_1 \xi X_0^{-1} = X_0 M_1 X_0^{-1}$

where $M_1 = \xi^{-1} D_1 \xi$ .

**(c) When none of the matrices are known, a system may still be identifiable if there are sufficient known relationships among the cells of A($u_0$) and A(0).**

- When there is a linear relationship between A($u_0$) and A(0), system identifiability boils down to the unique solution of equation $X_0(aM_1-bM_2)=CX_0$.

- When the relationships are too complex, another iterative least-squares algorithm can be developed.

# Least-squares Algorithm Design for Recurrent-Pulse Excitation

$$\dot{\vec{x}}^{j} = A(u^{j})\vec{x}^{j} + Bu^{j} \qquad y^{j} = C\vec{x}^{j}$$

$$\begin{bmatrix} \dot{\vec{x}}^{1} \\ \dot{\vec{x}}^{2} \\ \vdots \\ \dot{\vec{x}}^{n} \end{bmatrix} = \begin{bmatrix} A(u^{1}) & O & \cdots & O \\ O & A(u^{2}) & \cdots & O \\ \vdots & \vdots & \ddots & \vdots \\ O & O & \cdots & A(u^{n}) \end{bmatrix} \begin{bmatrix} \vec{x}^{1} \\ \vec{x}^{2} \\ \vdots \\ \vec{x}^{n} \end{bmatrix} + \begin{bmatrix} Bu^{1} \\ Bu^{2} \\ \vdots \\ Bu^{n} \end{bmatrix}$$

$$\begin{bmatrix} y^{1} \\ y^{2} \\ \vdots \\ y^{n} \end{bmatrix} = \begin{bmatrix} C & O & \cdots & O \\ O & C & \cdots & O \\ \vdots & \vdots & \ddots & \vdots \\ O & O & \cdots & C \end{bmatrix} \begin{bmatrix} \vec{x}^{1} \\ \vec{x}^{2} \\ \vdots \\ \vec{x}^{n} \end{bmatrix}$$

$$z = [y^{1} \quad y^{2} \quad \cdots \quad y^{n}]^{T}$$

$$E = \sum_{r=1}^{sn} (\bar{z}^{r} - z^{r})^{T} (\bar{z}^{r} - z^{r})$$

$$\Delta k = (\lambda I + \sum_{r=1}^{sn} J_{r}^{T} J_{r})^{-1} \sum_{r=1}^{sn} J_{r}^{T} (\bar{z}^{r} - z^{r})$$

$$k = k + \Delta k$$

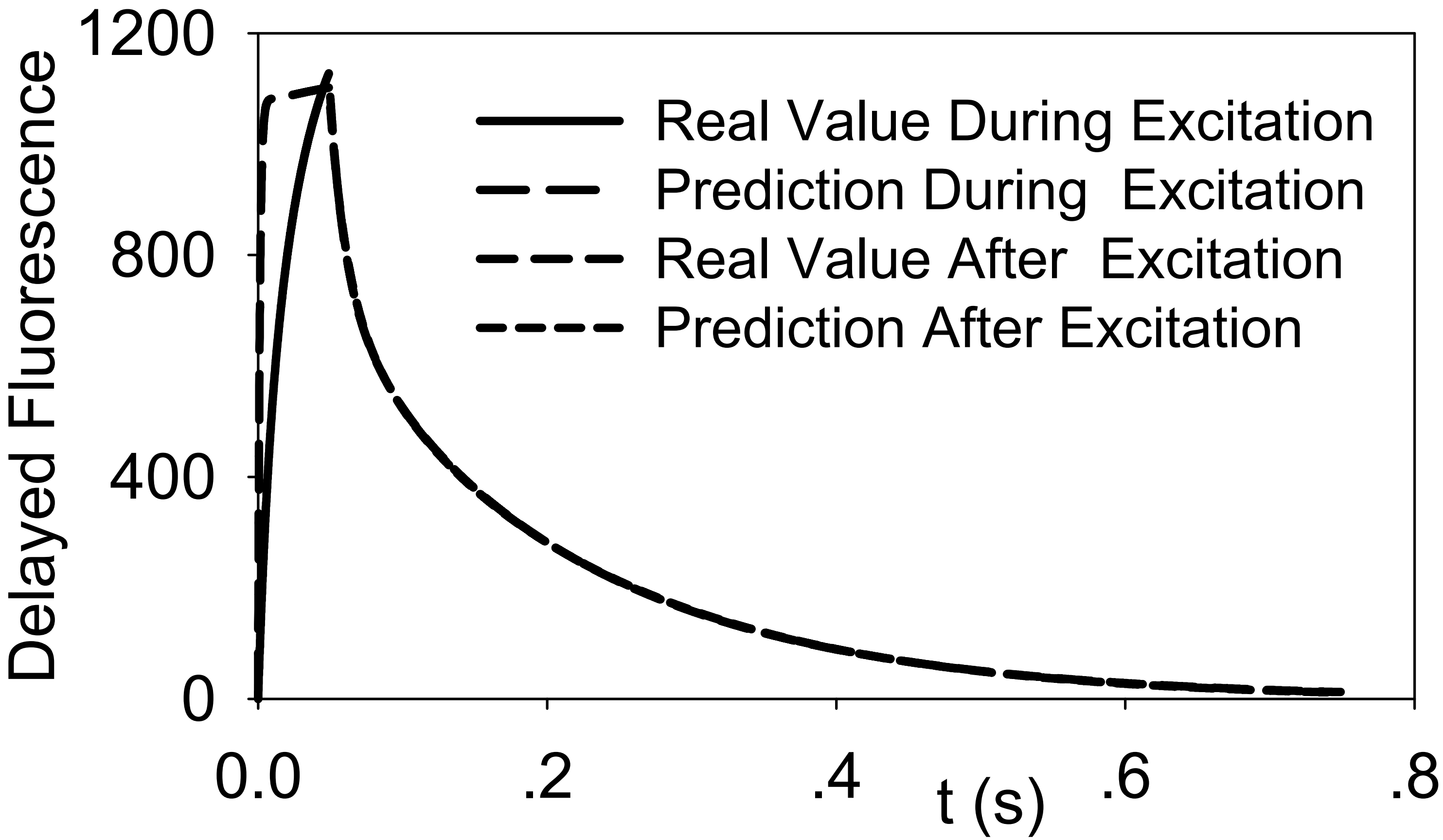
# An Application of Recurrent-pulse Excitation

$$\begin{Bmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \\ \dot{x}_4 \\ \dot{x}_5 \end{Bmatrix} = \mathrm{A} \begin{Bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \\ x_5 \end{Bmatrix} + \begin{Bmatrix} k_1 \\ 0 \\ 0 \\ 0 \\ 0 \end{Bmatrix} u$$

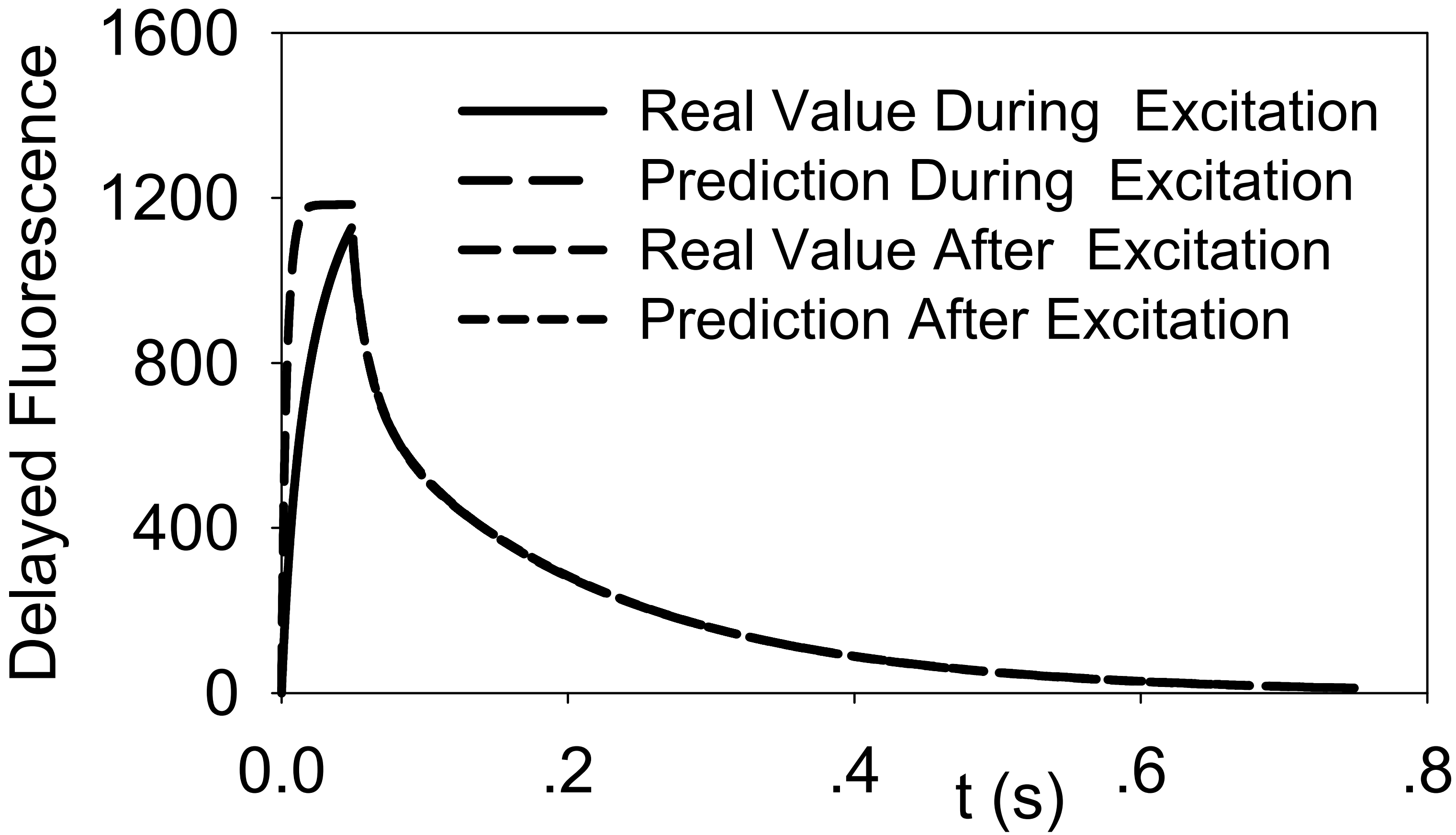
$$y = k_6 k_2 (x_1 + x_3 + x_5)$$

$$\mathrm{A} = -\begin{bmatrix} (k_1 u + k_2 + k_3) & (k_1 u - k_4) & k_1 u & k_1 u & (k_1 u - k_5) \\ -k_3 & (k_1 u + k_4) & -k_2 & 0 & 0 \\ 0 & -k_1 u & (k_2 + k_3) & -k_4 & 0 \\ 0 & 0 & -k_3 & (k_1 u + k_4 + k_5) & -k_2 \\ 0 & 0 & 0 & -k_1 u & (k_2 + k_5) \end{bmatrix}$$

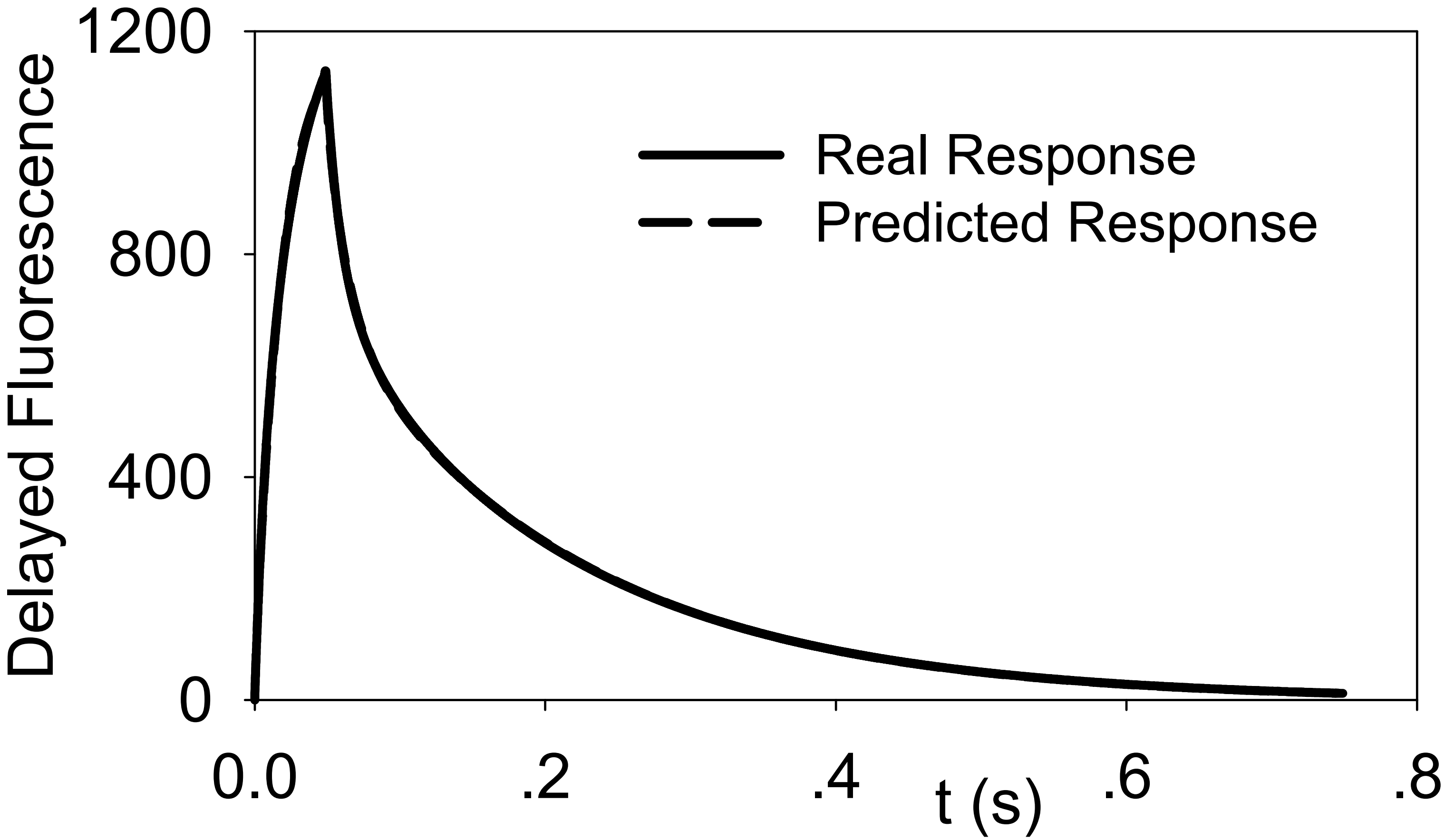
| Real Value $K_0$ | | 26.000 | 14.000 | 55.000 | 44.000 | 56.000 | 220.000 |
|---|---|---|---|---|---|---|---|
| Simulation1 | Start at $K_{01}$ | 805.284 | 40.034 | 85.613 | 85.346 | 30.000 | 483.364 |
| | Converge to $K_1$ | 772.723 | 13.064 | 37.964 | 40.535 | 7.953 | 88.044 |



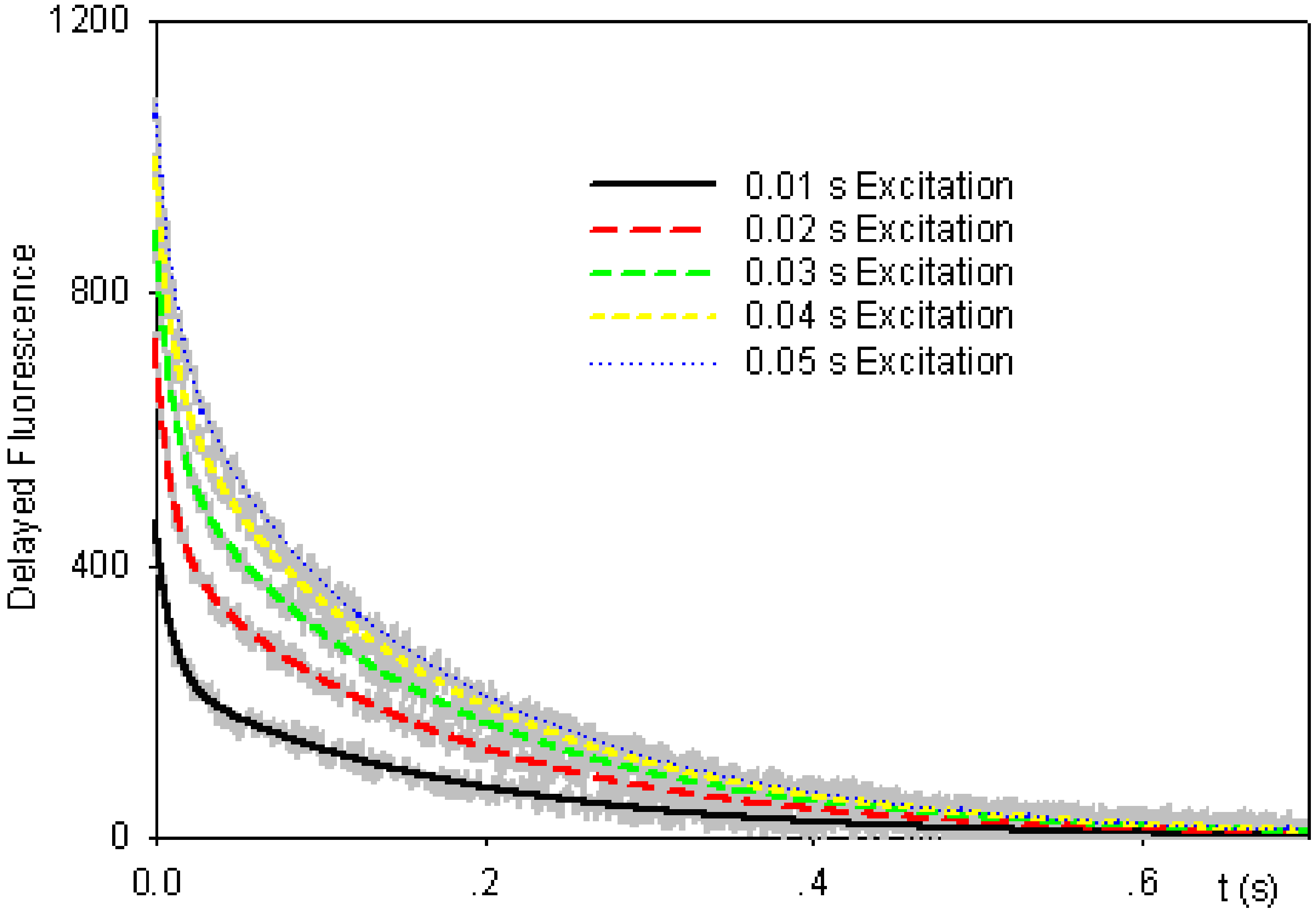
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Real Value $K_0$ | | 26.000 | 14.000 | 55.000 | 44.000 | 56.000 | 220.000 |
| Simulation2 | Start at $K_{02}$ | 405.284 | 20.034 | 45.613 | 85.346 | 30.000 | 883.364 |
| | Converge to $K_2$ | 240.361 | 8.688 | 210.129 | 433.444 | 224.866 | 185.482 |



**Identification with Light On Data:started at $K_{01}$ =[805.284, 40.034, 85.613, 85.346, 30.000, 483.364] and converged to $K_3$ =[48.890, 19.132, 1692.604, 740.814, 71.553, 211.858]**



# Recurrent Pulse Excitation



# Recurrent Pulses Do Not Add New Constraints for a Pure Linear System

Pulses of different durations only provide redundant constraints.

$$\Psi_i = \begin{pmatrix} u_{i1}\sum_{r=1}^{n} q_{1r}(\mathrm{B}u_0)_r \sum_{j=1}^{n} p_{1j}v_{j1} & 0 & \cdots & 0 \\ 0 & u_{i2}\sum_{r=1}^{n} q_{2r}(\mathrm{B}u_0)_r \sum_{j=1}^{n} p_{2j}v_{j2} & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & u_{in}\sum_{i=1}^{n} q_{nr}(\mathrm{B}u_0)_r \sum_{j=1}^{n} p_{nj}v_{jn} \end{pmatrix}$$

$$= \begin{bmatrix} p_{i1}\sum_{r=1}^{n} q_{1r}(\mathrm{B}u_0)_r & 0 & \cdots & 0 \\ 0 & p_{i1}\sum_{r=1}^{n} q_{2r}(\mathrm{B}u_0)_r & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & p_{i1}\sum_{r=1}^{n} q_{nr}(\mathrm{B}u_0)_r \end{bmatrix}$$

# Summary

Different scenarios of switched linear biological system identifiability were investigated and identification algorithms were developed.

It was found that recurrent-pulse excitation can:

- Avoid long-term effect of excitation and make experiments possible.
- Improve parameter identifiability by providing more constraints.
- Provide data for unmeasurable forced responses.