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Reaction–diffusion systems in protein networks: Global existence and identification

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ABSTRACT

Spatio-temporal biochemical signaling in a large class of protein–protein interaction networks is well modeled by a reaction–diffusion system. The global existence of the solution to the reaction–diffusion system is determined by the reaction kinetics model and the protein network topology. We propose a novel reaction kinetics model that guarantees that the reaction–diffusion system with this model has a nonnegative invariant global classical solution for any network topology. We then present a computational method to identify the unknown parameters and initial values for a reaction–diffusion system with this reaction kinetics model. The identification approach solves an optimization problem that minimizes the cost function defined as the L^2-norm of the difference between the data and the solution of the reaction–diffusion system. We utilize an adjoint-based optimal control method to obtain the gradients of the cost function with respect to the parameters and initial values. The regularity of the global classical solutions of the reaction–diffusion system and its corresponding adjoint system avoids situations in which the gradients blow up, and therefore guarantees the success of the identification method for any network structure. Utilizing this gradient information, an efficient algorithm to solve the optimization problem is proposed and applied to estimate the mass diffusivities, rate constants and initial values of a reaction–diffusion system that models protein–protein interactions in a signaling network that regulates the actin cytoskeleton in a malignant breast cell.

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1. Introduction

Reaction–diffusion systems have been widely used as fundamental models for the spatio-temporal dynamics of biochemical concentrations in complex protein networks [1]. Either data from new experiments or data from the literature can be used to directly determine the parameters of these reaction–diffusion systems, such as the mass diffusivities, rate constants, and initial values. However, the number and types of parameters that can be obtained via these sources are limited. Although these parameters have physical meanings, the estimates of the model parameters solely based on physical laws often give ranges at best. The lower and upper bounds of these ranges can vary by many orders of magnitude. Furthermore, the system may not explain the experimental data, even when all of the parameters are within their respective ranges. Thus, a method that finds the set of parameters and initial values within a physically reasonable range that best matches the reaction–diffusion system with the experimental data is of considerable interest. To computationally identify the parameters and initial values, we pose an optimization problem whose objective is to minimize the difference between the solution of the reaction–diffusion system and the data.

Several optimization-based parameter identification methods for reaction–diffusion partial differential equations (PDEs) have been developed in the more general context of parabolic equations. (i) *Semi-discrete* methods pose an approximate optimization problem by approximating a parabolic equation with a system of ordinary differential equations (ODEs) [2,3]. However, the appropriate spatial discretization scheme for which the solution of the adjoint system (the dual of the ODE system) converges to that of the adjoint equation of the parabolic equation is difficult to select [4]. (ii) *Discretize-then-optimize* methods fully discretize a weak form of the problem in time and space and then optimize the discretized problem [5]. (iii) *Optimize-then-discretize* methods first obtain an analytic form of the gradient of the cost function with respect to the parameters by utilizing weak formulations of the state

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and adjoint equations and then discretize the problem to numerically solve the optimization problem [6]. However, when the weak solution of the reaction–diffusion system blows up in finite time and so does that of the adjoint system, neither (ii) nor (iii) is able to compute the gradient of the cost function with respect to the initial values. In this case, neither framework is able to identify the initial values. The existing parameter identification methods may fail for some protein network topology, since the blow up property of reaction–diffusion systems is related to the network connectivity [7]. Because protein network structures of interest are diverse and complicated, an identification approach with guaranteed success for any network topology is highly desired.

In this article, we propose a novel reaction kinetics model such that the reaction–diffusion system with this model has a global classical solution regardless of the protein network topology. The reaction kinetics model has two key advantages. First, a reaction–diffusion system that implements this reaction kinetics model is an adequate modeling framework for general protein–protein interactions because the solution is nonnegative invariant and does not blow up in finite time. Second, regardless of the protein network topology, we have well-defined and bounded gradients of the cost function with respect to the mass diffusivities, rate constants, and initial values if we employ the reaction kinetics model. With an analytic formula for the gradients based on an adjoint system, we are able to efficiently solve the identification problem by simultaneously optimizing all unknown parameters and initial values of the system. The boundedness of the gradients enhances the robustness of the optimization algorithms by preventing potential failure of the adjoint-based optimal control method: if the gradients tend to infinity, the algorithms might be terminated before finding an optimum. Thus, for any network topology, the reaction kinetics model that we propose guarantees the *well-posedness* of the adjoint-based optimal control technique for the identification of reaction–diffusion systems.

2. Reaction–diffusion systems in protein networks

Assume that the domain Ω is an open, bounded and connected subset of $\mathbb{R}^\eta$ with the boundary $\partial\Omega$ and outer normal vector ν. We consider the following reaction–diffusion system to model the spatio-temporal dynamics of the biochemical concentrations (or densities) in a protein network: for $i = 1, \ldots, N$,

$$\frac{\partial u_i}{\partial t} - d_i \Delta u_i = r_i(u, k) \quad \text{in } \Omega \times (0, T) \tag{1a}$$

$$\frac{\partial u_i}{\partial \nu} = 0 \quad \text{on } \partial\Omega \times (0, T) \tag{1b}$$

$$u_i(x, 0) = u_i^0(x) \quad \text{in } \Omega \times \{t = 0\}, \tag{1c}$$

where $u := u(x, t) = (u_1(x, t), \ldots, u_N(x, t))$ are the concentration levels of N proteins, $d = (d_1, \ldots, d_N) \in (0, +\infty)^N$ are the mass diffusivities, and $k = (k_1, \ldots, k_M) \in (0, +\infty)^M$ are the rate constants. Note that (1b) and (1c) specify the Neumann boundary conditions and initial conditions, respectively. Assume that the initial value u^0 is in $L^\infty(\Omega)^N$ and $u^0(x) > 0$ for all $x \in \Omega$. We call r_i the *reaction function* of the ith protein. The structure of the reaction function is determined by two factors: the *reaction kinetics model* and the *protein network topology*. The structure of r has drawn great interest because it affects the blow up property of (1) [7]. Therefore, we need to answer the following question: '*is there a general reaction kinetics model that guarantees that the reaction–diffusion system does not blow up for any arbitrary network topology*?' As an initial step to answering this question, we suggest the following assumptions with respect to the reaction kinetics among proteins $1, \ldots, N$:

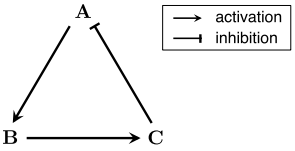

Fig. 1. A simple protein network.

(A) No more than two protein molecules can bind to each other at one time;
(B) Two protein molecules at most are generated by the dissociation of a complex;
(C) Binding and dissociation cannot occur at the same time.

The reaction kinetics model that we propose is a *mass-action kinetics model that satisfies assumptions* (A)–(C). For example, consider the protein network depicted in Fig. 1: Protein **A** phosphorylates protein **B**, **B** phosphorylates protein **C**, and **C** dephosphorylates **A**. The chemical kinetics of the (de) phosphorylations can be modeled as

$$\begin{aligned} &p\mathbf{A} + \mathbf{B} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} p\mathbf{AB}, \qquad p\mathbf{AB} \underset{k_4}{\overset{k_3}{\rightleftharpoons}} p\mathbf{A} + p\mathbf{B}, \\ &p\mathbf{B} + \mathbf{C} \underset{k_6}{\overset{k_5}{\rightleftharpoons}} p\mathbf{BC}, \qquad p\mathbf{BC} \underset{k_8}{\overset{k_7}{\rightleftharpoons}} p\mathbf{B} + p\mathbf{C}, \\ &p\mathbf{C} + p\mathbf{A} \underset{k_{10}}{\overset{k_9}{\rightleftharpoons}} p\mathbf{CA}, \qquad p\mathbf{CA} \underset{k_{12}}{\overset{k_{11}}{\rightleftharpoons}} p\mathbf{C} + \mathbf{A}, \end{aligned} \tag{2}$$

where $p\mathbf{M}$ denotes the phosphorylated $\mathbf{M}$. If we let u_1, u_2, u_3, u_4, u_5, u_6, u_7, u_8, and u_9 denote the concentration levels of $p\mathbf{A}$, $\mathbf{A}$, $p\mathbf{B}$, $\mathbf{B}$, $p\mathbf{C}$, $\mathbf{C}$, $p\mathbf{AB}$, $p\mathbf{BC}$, and $p\mathbf{CA}$, respectively, then the reaction functions that describe (2) with mass-action kinetics are given by

$$\begin{aligned} r_1 &= -k_1u_1u_4 + k_2u_7 + k_3u_7 - k_4u_1u_3 - k_9u_1u_5 + k_{10}u_9 \\ r_2 &= k_{11}u_9 - k_{12}u_2u_5 \\ r_3 &= k_3u_7 - k_4u_1u_3 - k_5u_3u_6 + k_6u_8 + k_7u_8 - k_8u_3u_5 \\ r_4 &= -k_1u_1u_4 + k_2u_7 \\ r_5 &= k_7u_8 - k_8u_3u_5 - k_9u_1u_5 + k_{10}u_9 + k_{11}u_9 - k_{12}u_2u_5 \\ r_6 &= -k_5u_3u_6 + k_6u_8 \\ r_7 &= k_1u_1u_4 - k_2u_7 - k_3u_7 + k_4u_1u_3 \\ r_8 &= k_5x_3x_6 - k_6x_8 - k_7x_8 + k_8x_3x_5 \\ r_9 &= k_9x_1x_5 - k_{10}x_9 - k_{11}x_9 + k_{12}x_2x_5. \end{aligned} \tag{3}$$

Note that the chemical equations (2) satisfy assumptions (A)–(C). These assumptions are not restrictive: they only require that the reaction–diffusion system describe the dynamics of chemical signals in detail to some degree, for example, these assumptions do not allow simplified dynamics such as the composition of more than two protein molecules (due to (A)) or the dissociation into multiple protein molecules (due to (B)). Importantly, these assumptions are independent of the protein network structure; therefore, they do not rule out any network topologies. These assumptions play an important role in proving our key result, the global existence of the classical solution of (1) with the proposed reaction kinetics model. Before we present the key result, we categorize the proteins as follows:

- $\mathbf{Cat}_1 :=$ {a single protein species}.
- $\mathbf{Cat}_\alpha :=$ {a complex of α species}, $\alpha = 2, 3, \ldots$.

By definition, any chemical kinetics can generate protein molecules only within these categories. We assume that $i \le j$ whenever protein i is in $\mathbf{Cat}_\alpha$ and protein j is in $\mathbf{Cat}_\beta$ with $\alpha \le \beta$, by permuting $\{\text{protein } i\}_{i=1}^N$ if necessary.

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