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## Computers and Mathematics with Applications

journal homepage: [www.elsevier.com/locate/camwa](http://www.elsevier.com/locate/camwa)

# Modeling of first-order photobleaching kinetics using Krylov subspace spectral methods

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## ARTICLE INFO

## Article history:

Available online xxxx

## Keywords:

Lanczos algorithm

Spectral methods

Gaussian quadrature

FRAP

Photobleaching kinetics equation

## ABSTRACT

We solve the first order 2-D reaction–diffusion equations which describe binding–diffusion kinetics using the photobleaching scanning profile of a confocal laser scanning microscope, approximated by a Gaussian laser profile. We show how to solve the first-order photobleaching kinetics partial differential equations (PDEs) using a time-stepping method known as a Krylov subspace spectral (KSS) method. KSS methods are explicit methods for solving time-dependent variable-coefficient partial differential equations. They approximate Fourier coefficients of the solution using Gaussian quadrature rules in the spectral domain. In this paper, we show how a KSS method can be used to obtain not only an approximate numerical solution, but also an approximate analytical solution when using initial conditions that come from pre-bleach steady states and also general initial conditions, to facilitate asymptotic analysis. Analytical and numerical results are presented. It is observed that although KSS methods are explicit, it is possible to use a time step that is far greater than what the CFL condition would indicate.

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## 1. Introduction

Fluorescence recovery after photobleaching (FRAP) is a method used to obtain information about the dynamic behavior of the molecules in a cell membrane. A high-intensity laser beam is used to bleach molecules in a region of the cell. The redistribution of the molecules is monitored in both bleached and unbleached regions over time to investigate the movements of molecules within membrane domains. The FRAP method was established by Jacobson et al. in 1976 [1]. The chemical equation of the binding–diffusion process that happens in FRAP is



where  $u$  denotes unbound molecules,  $a$  refers to specific binding sites, and  $b$  represents bound complexes ( $ua$ ). The rate of the forward binding reaction is called  $k_{\text{on}}$ , where a molecule binds to a binding site to form a bound complex, and  $k_{\text{off}}$  refers to the rate of the reverse unbinding reaction where a molecule is released from its binding site. The first-order reaction–diffusion equations which describe binding–diffusion kinetics are

$$\frac{\partial u}{\partial t} = -k_b I_{r_n}(x, y)u + D_1 \Delta u - k_{\text{on}}u + k_{\text{off}}b$$

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$$\frac{\partial b}{\partial t} = -k_b I_{rn}(x, y)b + D_2 \Delta b + k_{on}u - k_{off}b \tag{2}$$

$$\Delta = \frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2}, \quad D_1 > D_2$$

where the initial conditions from the pre-bleach steady state are

$$u(x, y, 0) = \frac{k_{off}}{k_{on} + k_{off}} c_i \tag{3}$$

$$b(x, y, 0) = \frac{k_{on}}{k_{on} + k_{off}} c_i. \tag{4}$$

$D_1$  and  $D_2$  are diffusion coefficients of  $u$  and  $b$ , respectively;  $k_{on}$  and  $k_{off}$  are the on and off binding-rate constants,  $k_b$  is a bleach constant which is the intensity of the bleaching laser, determined from the properties of the fluorophore, and  $c_i$  is the initial concentration of the fluorescent molecules inside the bleached zone. Also,  $D_1, D_2, k_{on}$  and  $k_{off}$  are positive constants. The photobleaching scanning profile of the confocal of the Gaussian laser can be approximated by [2–4]

$$I_{rn}(x, y) = \frac{2I_0}{\pi r_n^2} e^{-\frac{2((x-x_c)^2+(y-y_c)^2)}{r_n^2}}$$

where  $r_n$  is the nominal radius of the laser beam and  $(x_c, y_c)$  is the center.

First-order photobleaching kinetics which are mathematically modeled in Eq. (2) were solved numerically by Kang et al. [4,5]. These equations were also solved numerically using an inversion method (methods of lines, with backward Euler in time and central differencing in space) in [6]. In this paper we apply an explicit time-stepping method known as a Krylov subspace spectral (KSS) method to solve the first-order photobleaching kinetics PDEs. KSS methods developed by Lambers [7] use Gaussian quadrature rules in the spectral domain, as described in [8], to approximate each Fourier coefficient of the solution. This component-wise approach yields high-order accuracy in time, stability characteristic of implicit methods even though KSS methods are themselves explicit [7,9], and superior scalability compared to other time-stepping approaches [10]. We will use a KSS method to solve the first-order photobleaching kinetics equations with initial conditions (3), (4). By applying KSS symbolically to compute each Fourier coefficient, we can also obtain an approximate analytical solution valid for a sufficiently small time step, to facilitate qualitative analysis of the solution.

The outline of the paper is as follows. In Section 2, we describe KSS methods. In Section 3 we use a first-order KSS method to derive formulas for the Fourier coefficients of an approximate solution with general initial data. In Section 4 we derive formulas for the Fourier coefficients of an approximate analytical solution, for sufficiently small time, with initial data obtained from pre-bleach steady states. In Section 5 we explain how this KSS method can be implemented efficiently. Section 6 presents numerical results to validate our approximate analytical solution and demonstrate the accuracy and efficiency of the corresponding numerical method, and Section 7 gives concluding remarks and discussion of future work, including generalizations.

## 2. Methodology

### 2.1. Krylov subspace spectral methods

In order to solve Eq. (2), we apply a Krylov subspace spectral (KSS) method [7] in  $[0, 2\pi]^2$  and  $t > 0$  with periodic boundary conditions. To describe KSS methods, we scale down to a simpler problem, a single 1-D PDE on  $[0, 2\pi]$  rather than a system of two 2-D PDEs:

$$\frac{\partial u}{\partial t} + L(x, D)u = 0, \quad u(x, 0) = u_0(x)$$

$$u(0, t) = u(2\pi, t)$$

where  $D = \partial/\partial x$  and  $L(x, D)$  is a differential operator which includes both differentiation operators and coefficients that are functions of  $x$ . The inner product  $\langle \cdot, \cdot \rangle$  is the standard  $L^2$  inner product of functions on  $[0, 2\pi]$ . The Fourier coefficients of the exact solution as inner products are calculated as follows:

$$\langle f, g \rangle = \int_0^{2\pi} \overline{f(x)}g(x) dx$$

$$\hat{u}(\omega, t_{n+1}) = \left\langle \frac{1}{\sqrt{2\pi}} e^{i\omega x}, S(x, D; \Delta t)u(x, t_n) \right\rangle, \quad |\omega| \leq N/2 \tag{5}$$

where  $S(x, D; \Delta t) = e^{-L(x,D)\Delta t}$  is the exact solution operator and  $N$  is the number of equally-spaced grid points. After spatial discretization, (5) becomes

$$[\hat{u}^{n+1}]_\omega = \hat{e}_\omega^H S_N(\Delta t)u(t_n), \quad S_N = e^{-L_N \Delta t} \tag{6}$$

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