Absolutely Stable Explicit Schemes for Reaction Systems*

Eun-Hee Park†, Chang-Ock Lee†‡, Jae Boum Youm§, Chae Hun Leem¶‖

Abstract

We introduce two numerical schemes for solving a system of ordinary differential equations which characterizes several kinds of linear reactions and diffusion from biochemistry, physiology, etc. The methods consist of sequential applications of the simple exact solver for a reversible reaction. We prove absolute stability and convergence of the proposed explicit methods. One is of first order and the other is of second order. Numerical results are included. In addition, we apply the second-order method to a computational model for the transport of the fatty acids from the blood plasma into the myocyte.

Keywords: reaction systems, chemical diffusion, absolutely stable scheme, explicit scheme.

1 Introduction

Many phenomena of interest in physiology and biochemistry are characterized by reactions among several chemical species and diffusion in various mediums (see [7, 9, 10, 13]). In a closed system, both reactions and diffusion are governed by a system of ordinary differential equations (ODEs)

$$\dot{\mathbf{y}}(t) = M\mathbf{y}(t), \tag{1.1}$$

which guarantees conservation of the total amount of $\mathbf{y}(t)$ for any $t \geq 0$. Since we are concerned with the steady-state solution as well as the transient in simulations of very large systems of chemical reactions or molecular dynamics, we need to take the overall computational cost into consideration. Many physiologists and biochemists prefer explicit methods to implicit methods since implementation of the explicit methods is easier than the others. The popular methods for reaction systems are simple explicit schemes such as Euler's method, Runge-Kutta method, etc. However, it is well-known that conditional stability, the typical weak point of explicit methods, is very fatal for stiff problems. In the past few decades, many studies on numerical methods for stiff ODEs have been done in various aspects (see [3, 4, 6]).

The aim of this paper is to present two absolutely stable explicit schemes which are applicable to a general reaction system (1.1). In 1978, Rush and Larsen [12] introduced an iterative procedure for the Hodgkin-Huxley model for cell membrane behavior, which is composed of a circuit equation

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†Division of Applied Mathematics, KAIST, Daejeon, 305-701, Korea.

‡Corresponding author, e-mail: colee@amath.kaist.ac.kr

§Department of Physiology, College of Medicine, Inje University, Pusan, 614-735, Korea.

¶Department of Physiology, College of Medicine, University of Ulsan, Seoul, 138-736, Korea.

‖Co-corresponding author, e-mail: leemch@amc.seoul.kr

for currents and a coupled system of nonlinear ODEs for the ionic gates. An integration algorithm was suggested for a numerical solution to the ODEs for the ionic gates, which was based on the exact solution of a linearized ionic gate equation. Similarly, the methods in this paper are motivated by the simple exact solver for a reversible reaction. In spite of their explicitness, we have unconditional stability, that is, stability without any condition on the step size. Furthermore, we proved the convergence of the proposed methods; one is of first order and the other is of second order.

This paper is organized as follows. In Section 2, we introduce the reaction systems of our interest and propose two numerical methods for a general reaction system. Section 3 provides theoretical results for convergence and stability of the proposed methods. In Section 4, we provide numerical experiments for typical reaction systems and apply one of our methods to a physiological model which illustrates the transport mechanism of the fatty acids.

2 Reaction systems and numerical methods

We consider two typical types of reactions: reversible reactions and circular reactions. A reaction of the type

$$A \underset{k_b}{\overset{k_f}{\rightleftharpoons}} B$$

is called the reversible reaction, where k_f and k_b are the rate constants for the forward and backward reactions. One interesting biochemical system to which the reversible first order equations apply is the carbonic acid system:

$$CO_2 + H_2O \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} H_2CO_3 \underset{very\ fast}{\overset{K_a}{\rightarrow}} H^+ + HCO_3^- \tag{2.1}$$

Equation (2.1) reduces to

$$CO_2 \underset{k_b}{\overset{k_f}{\rightleftharpoons}} HCO_3^-$$

(see [10]). Then, the rate equations are written down as

$$\begin{aligned} \frac{dA}{dt} &= -k_b A + k_f B \\ \frac{dB}{dt} &= k_b A - k_f B \end{aligned} \tag{2.2}$$

where $A(t)$ and $B(t)$ are the concentrations of CO_2 and HCO_3^- as functions of time t. Another interesting example of such a type occurs frequently in metabolic studies. The other type is a circular reaction shown in Figure 1. We may write the differential equations describing this process as

$$\frac{d}{dt}\begin{bmatrix} A_0(t) \\ A_1(t) \\ A_2(t) \end{bmatrix} = \begin{bmatrix} -b_{10} - b_{20} & f_{10} & f_{20} \\ b_{10} & -f_{10} - b_{21} & f_{21} \\ b_{20} & b_{21} & -f_{21} - f_{20} \end{bmatrix} \begin{bmatrix} A_0(t) \\ A_1(t) \\ A_2(t) \end{bmatrix}. \tag{2.3}$$

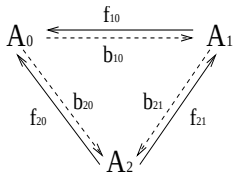


Figure 1: A circular reaction system with 3 substances A_0, A_1 and A_2.

From the fact that the total concentration $A(t)+B(t)$ remains constant for all $t \geq 0$ in a closed system, the exact solution of (2.2) is written in a form

$$\begin{bmatrix} A(t) \\ B(t) \end{bmatrix} = \begin{bmatrix} \frac{1}{k_f+k_b}(k_f + k_b e^{-(k_f+k_b)t}) & \frac{k_f}{k_f+k_b}(1 - e^{-(k_f+k_b)t}) \\ \frac{k_b}{k_f+k_b}(1 - e^{-(k_f+k_b)t}) & \frac{1}{k_f+k_b}(k_b + k_f e^{-(k_f+k_b)t}) \end{bmatrix} \begin{bmatrix} A(0) \\ B(0) \end{bmatrix}.$$

Similarly, we can find the exact solution for the circular reaction in Figure 1. In general, a reaction system is characterized by a coupled system of ODEs. To solve a relevant eigenvalue problem is the first step in solving such a coupled system exactly (see [17]). But as the number of substances increases, the exact solver suffers from typical difficulties in large scale eigenvalue problems. There are some numerical techniques in common use: the *Euler method*, which is the simplest one, but requires a small size of time step Δt; the *Runge-Kutta method*, which is more complicated, but allows much bigger time steps to be taken. Now for the circular reaction case, we propose new numerical methods motivated by the above process that is used to find the exact solution to a reversible reaction. For the sake of simplicity, we illustrate these algorithms for a simple circular reaction (2.3) although they are applicable to general reaction systems.

Algorithm 1: CR^2

1. For each $k \in \mathbb{N}$, let $A_{i,k}$ be the approximate solution to $A_i(t)$ at time $t_k = k\Delta t$.
2. For $k = 0, 1, 2, \cdots$ do:
   (a) Set $A_0^{ic} = A_{0,k}, A_1^{ic} = A_{1,k}$ and $A_2^{ic} = A_{2,k}$.
   (b) Find the exact solution $A_0^{temp}(t)$ and $A_1^{temp}(t)$ of the reversible reaction with the initial values A_0^{ic} and A_1^{ic}:
   $$A_0 \underset{b_{10}}{\overset{f_{10}}{\rightleftharpoons}} A_1$$
   Set $A_0^{ic} = A_0^{temp}(t_{k+1})$ and $A_1^{ic} = A_1^{temp}(t_{k+1})$.
   (c) Find the exact solution $A_0^{temp}(t)$ and $A_2^{temp}(t)$ of the reversible reaction with the initial values A_0^{ic} and A_2^{ic}:
   $$A_0 \underset{b_{20}}{\overset{f_{20}}{\rightleftharpoons}} A_2$$
   Set $A_{0,k+1} = A_0^{temp}(t_{k+1})$ and $A_2^{ic} = A_2^{temp}(t_{k+1})$.

(d) Find the exact solution $A_1^{temp}(t)$ and $A_2^{temp}(t)$ of the reversible reaction with the initial values A_1^{ic} and A_2^{ic}:

$$A_1 \underset{b_{21}}{\overset{f_{21}}{\leftrightharpoons}} A_2$$

Set $A_{1,k+1} = A_1^{temp}(t_{k+1})$ and $A_{2,k+1} = A_2^{temp}(t_{k+1})$.

Remark 2.1 *CR^2 stands for Consecutive Reversible Reactions.*

The key idea of Algorithm 1 is that we approximately regard a circular reaction as a consecutive reaction which consists of three separated reversible reactions. Although we solve three reversible reactions in the following order

$$A_0 \leftrightharpoons A_1, A_0 \leftrightharpoons A_2, A_1 \leftrightharpoons A_2,$$

the algorithm does not depend upon the ordering we adopt to split a circular reaction into a chain of reversible reactions. By the simple calculation, Algorithm 1 is characterized by the following linear system:

$$\begin{aligned}\begin{bmatrix} A_{0,k+1} \\ A_{1,k+1} \\ A_{2,k+1} \end{bmatrix} &= \begin{bmatrix} X_{20}X_{10} & X_{20}Y_{10} & Y_{20} \\ X_{21}Z_{10} + Y_{21}Z_{20}X_{10} & X_{21}W_{10} + Y_{21}Z_{20}Y_{10} & Y_{21}W_{20} \\ Z_{21}Z_{10} + W_{21}Z_{20}X_{10} & Z_{21}W_{10} + W_{21}Z_{20}Y_{10} & W_{21}W_{20} \end{bmatrix} \begin{bmatrix} A_{0,k} \\ A_{1,k} \\ A_{1,k} \end{bmatrix} \\ &\overset{\text{def}}{=} L_2 \begin{bmatrix} A_{0,k} \\ A_{1,k} \\ A_{2,k} \end{bmatrix},\end{aligned}$$

where

$$\begin{bmatrix} X_{ij} & Y_{ij} \\ Z_{ij} & W_{ij} \end{bmatrix} = \begin{bmatrix} \frac{1}{f_{ij}+b_{ij}}(f_{ij} + b_{ij}e^{-(f_{ij}+b_{ij})\Delta t}) & \frac{f_{ij}}{f_{ij}+b_{ij}}(1 - e^{-(f_{ij}+b_{ij})\Delta t}) \\ \frac{b_{ij}}{f_{ij}+b_{ij}}(1 - e^{-(f_{ij}+b_{ij})\Delta t}) & \frac{1}{f_{ij}+b_{ij}}(b_{ij} + f_{ij}e^{-(f_{ij}+b_{ij})\Delta t}) \end{bmatrix}.$$

Note that

$$X_{ij} + Z_{ij} = Y_{ij} + W_{ij} = 1.$$

We interpret the Algorithm 1 for n substances inductively, i.e., at $t = t_k$, we assume that the general reaction system with j substances $A_0, A_1, \cdots, A_{j-1} (1 \le j \le n-1)$ is solved, then we solve the parallel reaction that consists of j reversible reactions:

$$\begin{aligned} A_j &\underset{b_{j0}}{\overset{f_{j0}}{\rightleftharpoons}} A_0 \\ A_j &\underset{b_{j1}}{\overset{f_{j1}}{\rightleftharpoons}} A_1 \\ &\vdots \\ A_j &\underset{b_{j(j-1)}}{\overset{f_{j(j-1)}}{\rightleftharpoons}} A_{j-1} \end{aligned}$$

Algorithm 2: SCR^2

1. For each $k \in \mathbb{N}$, let $A^s_{i,k}$ be the approximate solution to $A_i(t)$ at time $t_k = k\Delta t$.
2. For $k = 0, 1, 2, \cdots$ do:
   (a) Set $A^{ic}_0 = A_{0,k}, A^{ic}_1 = A_{1,k}$ and $A^{ic}_2 = A_{2,k}$.
   (b) As in Algorithm 1, solve three reversible reactions according to chosen ordering: $A_0 \leftrightharpoons A_1, A_0 \leftrightharpoons A_2, A_1 \leftrightharpoons A_2$. Define $A^{s_1}_{i,k+1}$ by the obtained approximation $A_{i,k+1}$ for $i = 1, 2, 3$.
   (c) Solve three reversible reactions in reverse order: $A_2 \leftrightharpoons A_1, A_2 \leftrightharpoons A_0, A_1 \leftrightharpoons A_0$. Define $A^{s_2}_{i,k+1}$ by the obtained approximation $A_{i,k+1}$ for $i = 1, 2, 3$.
   (d) Set
$$A^s_{i,k+1} = \frac{A^{s_1}_{i,k+1} + A^{s_2}_{i,k+1}}{2} \text{ for } i = 1, 2, 3.$$

Remark 2.2 *Algorithm 2 is a symmetrized version of Algorithm 1 and can be applied to n substances inductively as in the Algorithm 1.*

3 Stability and convergence results

Now, we consider a general reaction system with $(n + 1)$ substances:

$$\frac{d}{dt}\begin{bmatrix} A_0(t) \\ A_1(t) \\ \vdots \\ A_n(t) \end{bmatrix} = M_n \begin{bmatrix} A_0(t) \\ A_1(t) \\ \vdots \\ A_n(t) \end{bmatrix}, \tag{3.1}$$

where

$$M_n = \begin{bmatrix} -\sum_{i=1}^n b_{i0} & f_{10} & \cdots & f_{(n-1)0} & f_{n0} \\ b_{10} & -f_{10} - \sum_{i=2}^n b_{i1} & \cdots & f_{(n-1)1} & f_{n1} \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ b_{(n-1)0} & b_{(n-1)1} & \cdots & -\sum_{j=0}^{n-2} f_{(n-1)j} - b_{n(n-1)} & f_{n(n-1)} \\ b_{n0} & b_{n1} & \cdots & b_{n(n-1)} & -\sum_{j=0}^{n-1} f_{nj} \end{bmatrix}.$$

Note that the general reaction system (3.1) includes a chain of reversible reactions and circular reactions. We can easily confirm that M_n always has 0 as an eigenvalue and the real parts of all eigenvalues except 0 are negative, i.e., (3.1) is *neutrally stable*. Hence the exact solution to the problem (3.1) does not have a vanishing property:

$$\text{as } t \to \infty, A_i(t) \to 0 \text{ for all } i.$$

Instead of *A-stability*, we shall adopt a more appropriate concept of stability for the numerical methods applied to (3.1). A numerical method for the neutrally stable problem like (3.1) is said to be *stable* if it does not blow up as $t \to \infty$ (see [14, 17]).

3.1 Stability and convergence of CR^2 for general reaction systems

When applying the CR^2 algorithm to (3.1), we get the approximation $(A_{i,k+1})_{i=0}^n$ such that

$$\begin{bmatrix} A_{0,k+1} \\ A_{1,k+1} \\ \vdots \\ A_{n,k+1} \end{bmatrix} = L_n \begin{bmatrix} A_{0,k} \\ A_{1,k} \\ \vdots \\ A_{n,k} \end{bmatrix}, \tag{3.2}$$

where L_n is an $(n+1)\times(n+1)$ matrix with entries $\{l_{ij}^{(n)}\}_{i,j=1}^{n+1}$.

Lemma 3.1 *Consider a parallel reaction with $(n+1)$ substances, that is composed of n reversible reactions:*

$$\begin{array}{lcl} A_n & \underset{b_{n0}}{\overset{f_{n0}}{\rightleftharpoons}} & A_0 \\ A_n & \underset{b_{n1}}{\overset{f_{n1}}{\rightleftharpoons}} & A_1 \\ & \vdots & \\ A_n & \underset{b_{n(n-1)}}{\overset{f_{n(n-1)}}{\rightleftharpoons}} & A_{n-1} \end{array}$$

Applying the CR^2 algorithm to this problem in the following ordering:

$$A_0 \leftrightharpoons A_n, A_1 \leftrightharpoons A_n, \cdots, A_{n-1} \leftrightharpoons A_n$$

gives

$$\begin{bmatrix} A_{0,k+1} \\ A_{1,k+1} \\ \vdots \\ A_{n,k+1} \end{bmatrix} = \Lambda_n \begin{bmatrix} A_{0,k} \\ A_{1,k} \\ \vdots \\ A_{n,k} \end{bmatrix},$$

where $(A_{i,k+1})_{i=0}^n$ is an approximation to $(A_i(t))_{i=0}^n$ at $t = t_{k+1}$, and Λ_n is an $(n+1)\times(n+1)$ matrix with entries $\{\lambda_{ij}^{(n)}\}_{i,j=1}^{n+1}$.
Then, we have

$$\sum_{i=1}^{n+1} \lambda_{ij}^{(n)} = 1 \quad \forall j = 1, \cdots, n+1. \tag{3.3}$$

Proof. The proof is done by induction on n. For $n = 2$, we have

$$\begin{aligned} \begin{bmatrix} A_{0,k+1} \\ A_{1,k+1} \\ A_{2,k+1} \end{bmatrix} &= \begin{bmatrix} 1 & 0 & 0 \\ 0 & X_{21} & Y_{21} \\ 0 & Z_{21} & W_{21} \end{bmatrix} \begin{bmatrix} X_{20} & 0 & Y_{20} \\ 0 & 1 & 0 \\ Z_{20} & 0 & W_{20} \end{bmatrix} \begin{bmatrix} A_{0,k} \\ A_{1,k} \\ A_{2,k} \end{bmatrix} \\ &= \Lambda_2 \begin{bmatrix} A_{0,k} \\ A_{1,k} \\ A_{2,k} \end{bmatrix}. \end{aligned}$$

Using the relations $X_{ij} + Z_{ij} = 1$ and $Y_{ij} + W_{ij} = 1$ gives

$$\sum_{i=1}^{3} \lambda_{ij}^{(2)} = 1, \text{ for } j = 1, 2, 3.$$

Hence for three substances, the statement holds. Suppose that the statement is true for n substances. Consider a parallel reaction with $(n+1)$ substances $A_0, A_1, \cdots, A_{n-1}$ and A_n:

$$\begin{aligned} A_n &\rightleftharpoons A_0 \\ A_n &\rightleftharpoons A_1 \\ &\vdots \\ A_n &\rightleftharpoons A_{n-1} \end{aligned}$$

The approximate solution $(A_{i,k+1})_{i=0}^{n}$ given by the CR^2 algorithm is characterized as follows:

$$\begin{bmatrix} A_{0,k+1} \\ A_n^{temp} \end{bmatrix} = \begin{bmatrix} X_{n0} & Y_{n0} \\ Z_{n0} & W_{n0} \end{bmatrix} \begin{bmatrix} A_{0,k} \\ A_{n,k} \end{bmatrix}, \tag{3.4a}$$

$$\begin{bmatrix} A_{1,k+1} \\ \vdots \\ A_{n-1,k+1} \\ A_{n,k+1} \end{bmatrix} = \Lambda_{n-1} \begin{bmatrix} A_{1,k} \\ \vdots \\ A_{n-1,k} \\ A_n^{temp} \end{bmatrix}. \tag{3.4b}$$

By the inductive hypothesis, we have

$$\sum_{i=1}^{n} \lambda_{ij}^{(n-1)} = 1, \quad \forall j = 1, \cdots, n. \tag{3.5}$$

Combining (3.4a) and (3.4b) yields

$$\begin{aligned} \begin{bmatrix} A_{0,k+1} \\ A_{1,k+1} \\ \vdots \\ A_{n-1,k+1} \\ A_{n,k+1} \end{bmatrix} &= \begin{bmatrix} \begin{bmatrix} X_{n0} & Y_{n0} \end{bmatrix} \begin{bmatrix} A_{0,k} \\ A_{n,k} \end{bmatrix} \\ \Lambda_{n-1} \begin{bmatrix} A_{1,k} \\ \vdots \\ A_{n-1,k} \\ \begin{bmatrix} Z_{n0} & W_{n0} \end{bmatrix} \begin{bmatrix} A_{0,k} \\ A_{n,k} \end{bmatrix} \end{bmatrix} \end{bmatrix} \\ &= \Lambda_n \begin{bmatrix} A_{0,k} \\ A_{1,k} \\ \vdots \\ A_{n-1,k} \\ A_{n,k} \end{bmatrix}. \end{aligned}$$

Hence we have

$$\Lambda_n = \begin{bmatrix} X_{n0} & 0 & \cdots & 0 & Y_{n0} \\ \lambda_{1n}^{(n-1)} Z_{n0} & \lambda_{11}^{(n-1)} & \cdots & \lambda_{1(n-1)}^{(n-1)} & \lambda_{1n}^{(n-1)} W_{n0} \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ \lambda_{(n-1)n}^{(n-1)} Z_{n0} & \lambda_{(n-1)1}^{(n-1)} & \cdots & \lambda_{(n-1)(n-1)}^{(n-1)} & \lambda_{(n-1)n}^{(n-1)} W_{n0} \\ \lambda_{nn}^{(n-1)} Z_{n0} & \lambda_{n1}^{(n-1)} & \cdots & \lambda_{n(n-1)}^{(n-1)} & \lambda_{nn}^{(n-1)} W_{n0} \end{bmatrix}. \tag{3.6}$$

It follows from (3.5) and $X_{n0} + Z_{n0} = 1, Y_{n0} + W_{n0} = 1$ that

$$\sum_{i=1}^{n+1} \lambda_{ij}^{(n)} = 1, \quad \forall j = 1, \cdots, n+1. \qquad \square$$

Lemma 3.2 *The matrix* $L_n = [l_{ij}^{(n)}]_{i,j=1}^{n+1}$ *in* (3.2) *satisfies*

$$\sum_{i=1}^{n+1} l_{ij}^{(n)} = 1 \quad \forall j = 1, \cdots, n+1.$$

Proof. The proof is done by induction on n. From relationships

$$X_{ij} + Z_{ij} = 1, Y_{ij} + W_{ij} = 1 \quad \text{for all } i, j \text{ with } 0 \le i, j \le 2,$$

it is obvious that the statement is true for three substances. Suppose that the statement is true for n substances, that is, applying the CR^2 algorithm to a general reaction system with n substances $A_0, \cdots, A_{n-1}$ gives the approximate solution $(A_{i,k+1})_{i=0}^{n-1}$ to $(A_i(t))_{i=0}^{n-1}$ at $t = t_{k+1}$:

$$\begin{bmatrix} A_{0,k+1} \\ A_{1,k+1} \\ \vdots \\ A_{n-1,k+1} \end{bmatrix} = L_{n-1} \begin{bmatrix} A_{0,k} \\ A_{1,k} \\ \vdots \\ A_{n-1,k} \end{bmatrix}, \tag{3.7}$$

where $\sum_{i=1}^{n} l_{ij}^{(n-1)} = 1 \quad \forall j = 1, \cdots, n$. As mentioned in Section 2, adding a substance A_n into the general reaction system with n substances $A_0, \cdots, A_{n-1}$ results in n additional reversible reactions:

$$\begin{array}{ccc} A_n & \underset{b_{n0}}{\overset{f_{n0}}{\rightleftharpoons}} & A_0 \\ A_n & \underset{b_{n1}}{\overset{f_{n1}}{\rightleftharpoons}} & A_1 \\ & \vdots & \\ A_n & \underset{b_{n(n-1)}}{\overset{f_{n(n-1)}}{\rightleftharpoons}} & A_{n-1} \end{array}$$

By (3.7), we have

$$\begin{aligned}\begin{bmatrix} A_{0,k+1} \\ A_{1,k+1} \\ \vdots \\ A_{n-1,k+1} \\ A_{n,k+1} \end{bmatrix} &= \Lambda_n \begin{bmatrix} L_{n-1} \begin{bmatrix} A_{0,k} \\ A_{1,k} \\ \vdots \\ A_{n-1,k} \end{bmatrix} \\ A_{n,k} \end{bmatrix} \\ &= L_n \begin{bmatrix} A_{0,k} \\ A_{1,k} \\ \vdots \\ A_{n-1,k} \\ A_{n,k} \end{bmatrix}.\end{aligned}$$

Hence we have

$$L_n = \Lambda_n \begin{bmatrix} & & & 0 \\ & L_{n-1} & & \vdots \\ & & & 0 \\ 0 & \cdots & 0 & 1 \end{bmatrix} \tag{3.8}$$

and by Lemma 3.1 and the induction hypothesis, it follows that

$$\sum_{i=1}^{n+1} l_{ij}^{(n)} = 1 \quad \forall j = 1, \cdots, n+1. \qquad \square$$

Let $\|\mathbf{x}\|_1 = \sum_{i=1}^{n} |x_i|$ be a norm on $\mathbb{R}^n$.

Theorem 3.1 *The algorithm CR^2 applied to general reaction systems is absolutely stable.*

Proof. The CR^2 algorithm gives an approximate solution to (3.1) such that $\mathbf{y}^{k+1} = L_n \mathbf{y}^k$ with $\mathbf{y}^k = (A_{0,k} \cdots \ A_{n,k})^T$. Since all entries of L_n are nonnegative, it follows from Lemma 3.2 that

$$\|\mathbf{y}^{k+1}\|_1 = \|\mathbf{y}^k\|_1,$$

that is, the approximation does not blow up independently of Δt. $\square$

Lemma 3.3 *Under the same assumptions as in* Lemma 3.1*, we have*

$$\Lambda_n = \begin{bmatrix} & & & f_{n0}\Delta t \\ & \mathrm{diag}(1 - b_{nj}\Delta t)_{j=0}^{n-1} & & \vdots \\ & & & f_{n(n-1)}\Delta t \\ b_{n0}\Delta t & \cdots & b_{n(n-1)}\Delta t & 1 - (\sum_{j=0}^{n-1} f_{nj})\Delta t \end{bmatrix} + O((\Delta t)^2).$$

Proof. It is easy to show that the statement holds for $n = 2$ by using Taylor's theorem. Suppose that the statement is true for a parallel reaction which consists of n substances. Consider a parallel

reaction with $(n+1)$ substances:

$$A_n \underset{b_{n0}}{\overset{f_{n0}}{\rightleftharpoons}} A_0 \tag{3.9a}$$

$$A_n \underset{b_{n1}}{\overset{f_{n1}}{\rightleftharpoons}} A_1 \tag{3.9b}$$

$$\vdots$$

$$A_n \underset{b_{n(n-1)}}{\overset{f_{n(n-1)}}{\rightleftharpoons}} A_{n-1} \tag{3.9c}$$

By the inductive hypothesis, the approximate solution $(A_{i,k+1})_{i=0}^n$ to the solution $(A_i(t))_{i=0}^n$ at $t = t_{k+1}$ obtained by applying CR^2 to (3.9) is written as follows:

$$\begin{aligned}
\begin{bmatrix} A_{0,k+1} \\ A_n^{temp} \end{bmatrix} &= \begin{bmatrix} X_{n0} & Y_{n0} \\ Z_{n0} & W_{n0} \end{bmatrix} \begin{bmatrix} A_{0,k} \\ A_{n,k} \end{bmatrix} \\
&= \begin{bmatrix} 1 - b_{n0}\Delta t + O((\Delta t)^2) & f_{n0}\Delta t + O((\Delta t)^2) \\ b_{n0}\Delta t + O((\Delta t)^2) & 1 - f_{n0}\Delta t + O((\Delta t)^2) \end{bmatrix} \begin{bmatrix} A_{0,k} \\ A_{n,k} \end{bmatrix} \\
\begin{bmatrix} A_{1,k+1} \\ \vdots \\ A_{n-1,k+1} \\ A_{n,k+1} \end{bmatrix} &= \Lambda_{n-1} \begin{bmatrix} A_{1,k} \\ \vdots \\ A_{n-1,k} \\ A_n^{temp} \end{bmatrix}
\end{aligned} \tag{3.10}$$

where

$$\Lambda_{n-1} = \begin{bmatrix} & & f_{n1}\Delta t \\ & \mathrm{diag}(1 - b_{nj}\Delta t)_{j=1}^{n-1} & \vdots \\ & & f_{n(n-1)}\Delta t \\ b_{n1}\Delta t & \cdots & b_{n(n-1)}\Delta t \quad 1 - (\sum_{j=1}^{n-1} f_{nj})\Delta t \end{bmatrix} + O((\Delta t)^2).$$

Hence by (3.6) and (3.10), we have the expansion form of Λ_n, that is, the statement is true for a parallel reaction with $(n+1)$ substances. □

Lemma 3.4 *We have*

$$\begin{aligned}
L_n &= L_{n,0} + L_{n,1}\Delta t + L_{n,2}(\Delta t)^2 + O((\Delta t)^3) \\
&= I + M_n \Delta t + O((\Delta t)^2)
\end{aligned}$$

where L_n and M_n are matrices in (3.2) *and* (3.1)*, respectively.*

Proof. By Taylor's theorem, we can rewrite L_n as

$$L_n = L_{n,0} + L_{n,1}\Delta t + L_{n,2}(\Delta t)^2 + \cdots .$$

Moreover, by induction on n, we can confirm that $L_{n,0} = I \quad \forall n \in \mathbb{N}$ with $n \geq 2$. For $n = 2$, it is easy to show that the statement holds by applying Taylor's theorem to each entry of L_2. Suppose that the statement is true for $(n-1)$. When a substance A_n is added to the general reaction

system with n substances $A_0, \cdots, A_{n-1}$, we need to find out the difference between M_{n-1} and M_n. Because the supplementary substance A_n makes n reversible reactions occur additionally:

$$\begin{array}{lcl} A_n & \underset{b_{n0}}{\overset{f_{n0}}{\rightleftharpoons}} & A_0 \\ A_n & \underset{b_{n1}}{\overset{f_{n1}}{\rightleftharpoons}} & A_1 \\ & \vdots & \\ A_n & \underset{b_{n(n-1)}}{\overset{f_{n(n-1)}}{\rightleftharpoons}} & A_{n-1}, \end{array}$$

it follows that

$$M_n = \begin{bmatrix} & & f_{n0} \\ M_{n-1} - \mathrm{diag}(b_{nj})_{j=0}^{n-1} & & \vdots \\ & & f_{n(n-1)} \\ b_{n0} \quad \cdots & b_{n(n-1)} & -\sum_{j=0}^{n-1} f_{nj} \end{bmatrix}. \tag{3.11}$$

Equation (3.8) and Lemma 3.3 yield

$$L_n = \begin{bmatrix} & & f_{n0}\Delta t \\ \mathrm{diag}(1 - b_{nj}\Delta t)_{j=0}^{n-1} * L_{n-1} & & \vdots \\ & & f_{n(n-1)}\Delta t \\ b_{n0}\Delta t \quad \cdots & b_{n(n-1)}\Delta t & 1 - (\sum_{j=0}^{n-1} f_{nj})\Delta t \end{bmatrix} + O((\Delta t)^2).$$

By the induction hypothesis, we can easily confirm that $L_n = I + M_n\Delta t + O((\Delta t)^2)$. □

Let $\|A\|_1 = \max_{1\le j\le n}\sum_{i=1}^{n}|a_{ij}|$ be a matrix norm on $\mathbb{R}^{n\times n}$. We are now ready to prove convergence of the CR^2 algorithm.

Theorem 3.2 *The algorithm CR^2 applied to* (3.1) *has the order of convergence* 1.

Proof. We denote the exact solution of (3.1) by $\mathbf{y}(t) = (A_0(t)\cdots\ A_n(t))^T$. CR^2 gives an approximation to (3.1) such that $\mathbf{y}^{k+1} = L_n\mathbf{y}^k$ with $\mathbf{y}^k = (A_{0,k}\cdots\ A_{n,k})^T$. We will show that

$$\|\mathbf{y}(t_{k+1}) - \mathbf{y}^{k+1}\|_1 \le C\Delta t,$$

where C is a constant independent of Δt. Using Taylor's theorem and Lemma 3.4 yield

$$\mathbf{y}(t_{k+1}) = (I + \Delta t M_n + \frac{(\Delta t)^2}{2}M_n^2)\mathbf{y}(t_k) + O((\Delta t)^3) \tag{3.12a}$$

$$\mathbf{y}^{k+1} = L_n\mathbf{y}^k = (I + M_n\Delta t + L_{n,2}(\Delta t)^2)\mathbf{y}^k + O((\Delta t)^3) \tag{3.12b}$$

Let $\mathbf{e}_k = \mathbf{y}(t_k) - \mathbf{y}^k$ denote the numerical error. Subtracting (3.12b) from (3.12a) gives

$$\begin{aligned} \mathbf{e}_{k+1} &= (I + \Delta t M_n + (\Delta t)^2 L_{n,2})\mathbf{e}_k + \left(\frac{M_n^2}{2} - L_{n,2}\right)(\Delta t)^2\mathbf{y}(t_k) + O((\Delta t)^3) \\ &= L_n\mathbf{e}_k + O((\Delta t)^2). \end{aligned}$$

Since $\|L_n\|_1 = 1$ by Lemma 3.2, it follows that

$$\|\mathbf{e}_{k+1}\|_1 \leq \|\mathbf{e}_k\|_1 + C(\Delta t)^2$$

with a constant C independent of Δt and k. We can check by induction on k that

$$\|\mathbf{e}_k\|_1 \leq kC(\Delta t)^2 \quad \forall k = 0, 1, \cdots.$$

If we restrict t to the finite interval $[0, t_F]$, then we have that $\forall k = 0, 1, \cdots, \lfloor t_F/\Delta t \rfloor$,

$$\begin{aligned} \|\mathbf{e}_k\|_1 &\leq \lfloor t_F/\Delta t \rfloor C(\Delta t)^2 \\ &\leq Ct_F\Delta t. \end{aligned}$$

Since C is independent of Δt, it follows that

$$\lim_{\substack{\Delta t \to 0 \\ 0 \leq k \leq \lfloor t_F/\Delta t \rfloor}} \|\mathbf{e}_k\|_1 = 0.$$

In other words, the algorithm CR^2 is convergent and has the order of convergence 1. □

3.2 Convergence of SCR^2 for general reaction systems

In order to look into the procedure of the SCR^2 algorithm applied to general reaction systems, we consider the circular reaction with 3 substances shown in Figure 1. Applying SCR^2 to the reaction system gives

$$\begin{bmatrix} A^{s_1}_{0,k+1} \\ A^{s_1}_{1,k+1} \\ A^{s_1}_{2,k+1} \end{bmatrix} = L_2^{s_1} \begin{bmatrix} A^{s}_{0,k} \\ A^{s}_{1,k} \\ A^{s}_{2,k} \end{bmatrix}, \quad \begin{bmatrix} A^{s_2}_{2,k+1} \\ A^{s_2}_{1,k+1} \\ A^{s_2}_{0,k+1} \end{bmatrix} = \overline{L}_2^{s_2} \begin{bmatrix} A^{s}_{2,k} \\ A^{s}_{1,k} \\ A^{s}_{0,k} \end{bmatrix}.$$

Then, we have

$$\begin{bmatrix} A^{s}_{0,k+1} \\ A^{s}_{1,k+1} \\ A^{s}_{2,k+1} \end{bmatrix} = \frac{1}{2}(L_2^{s_1} + L_2^{s_2}) \begin{bmatrix} A^{s}_{0,k} \\ A^{s}_{1,k} \\ A^{s}_{2,k} \end{bmatrix},$$

where

$$L_2^{s_2} = P_2 \overline{L}_2^{s_2} P_2, \quad P_2 = \begin{bmatrix} 0 & 0 & 1 \\ 0 & 1 & 0 \\ 1 & 0 & 0 \end{bmatrix}.$$

Considering Taylor expansions of $L_2^{s_1}$ and $\overline{L}_2^{s_2}$ yields

$$L^{s_1}_{2,2} - \frac{1}{2}M_2^2 = \frac{1}{2}\begin{bmatrix} 0 & -b_{20}f_{10} + b_{21}f_{10} - b_{21}f_{20} & b_{10}f_{20} - f_{10}f_{21} + f_{20}f_{21} \\ b_{10}b_{20} - b_{10}b_{21} + b_{20}f_{21} & 0 & -b_{10}f_{20} + f_{10}f_{21} - f_{20}f_{21} \\ -b_{10}b_{20} + b_{10}b_{21} - b_{20}f_{21} & b_{20}f_{10} - b_{21}f_{10} + b_{21}f_{20} & 0 \end{bmatrix}$$

and

$$\overline{L}^{s_2}_{2,2} - \frac{1}{2}P_2M_2^2P_2 = \frac{1}{2}\begin{bmatrix} 0 & -b_{20}f_{10} + b_{21}f_{10} - b_{21}f_{20} & b_{10}b_{20} - b_{10}b_{21} + b_{20}f_{21} \\ b_{10}f_{20} - f_{10}f_{21} + f_{20}f_{21} & 0 & -b_{10}b_{20} + b_{10}b_{21} - b_{20}f_{21} \\ -b_{10}f_{20} + f_{10}f_{21} - f_{20}f_{21} & b_{20}f_{10} - b_{21}f_{10} + b_{21}f_{20} & 0 \end{bmatrix}.$$

Then, we have

$$L_{2,2}^{s_1} + L_{2,2}^{s_2} - M_2^2 = 0 \tag{3.13}$$

In general, to solve (3.1) with SCR^2, we obtain the approximation $(A_{i,k+1}^s)_{i=0}^n$ such that

$$\begin{bmatrix} A_{0,k+1}^s \\ A_{1,k+1}^s \\ \vdots \\ A_{n,k+1}^s \end{bmatrix} = L_n^s \begin{bmatrix} A_{0,k}^s \\ A_{1,k}^s \\ \vdots \\ A_{n,k}^s \end{bmatrix} = \frac{1}{2}(L_n^{s_1} + L_n^{s_2}) \begin{bmatrix} A_{0,k}^s \\ A_{1,k}^s \\ \vdots \\ A_{n,k}^s \end{bmatrix} \tag{3.14}$$

where

$$L_n^{s_2} = P_n \overline{L}_n^{s_2} P_n$$

and P_n is the $(n+1) \times (n+1)$ permutation matrix such that

$$(P_n)_{ij} = \begin{cases} 1 & \text{if } i+j = n+2, \\ 0 & \text{otherwise.} \end{cases}$$

Lemma 3.5 *Under the same assumptions as in* Lemma 3.1*, we assume that*

$$\Lambda_n = \Lambda_{n,0} + \Lambda_{n,1}\Delta t + \Lambda_{n,2}(\Delta t)^2 + O((\Delta t)^3).$$

Then,

$$\Lambda_{n,2} = \begin{bmatrix} \frac{b_{n0}}{2}(b_{n0}+f_{n0}) & 0 & 0 & \cdots & 0 & -\frac{f_{n0}}{2}(b_{n0}+f_{n0}) \\ b_{n0}f_{n1} & \frac{b_{n1}}{2}(b_{n1}+f_{n1}) & 0 & \ddots & \vdots & -\frac{f_{n1}}{2}(2f_{n0}+b_{n1}+f_{n1}) \\ b_{n0}f_{n2} & b_{n1}f_{n2} & \ddots & \ddots & \vdots & \vdots \\ \vdots & \vdots & & \ddots & 0 & \vdots \\ b_{n0}f_{n(n-1)} & b_{n1}f_{n(n-1)} & \cdots & \cdots & \frac{b_{n(n-1)}}{2}(b_{n(n-1)}+f_{n(n-1)}) & \text{(I)} \\ \text{(II)} & \text{(III)} & \cdots & \cdots & -\frac{b_{n(n-1)}}{2}(b_{n(n-1)}+f_{n(n-1)}) & \text{(IV)} \end{bmatrix},$$

where

$$\text{(I)} = -\frac{f_{n(n-1)}}{2}(2\sum_{i=0}^{n-2} f_{ni} + b_{n(n-1)} + f_{n(n-1)})$$

$$\text{(II)} = -\frac{b_{n0}}{2}(b_{n0} + f_{n0} + 2\sum_{i=1}^{n-1} f_{ni})$$

$$\text{(III)} = -\frac{b_{n1}}{2}(b_{n1} + f_{n1} + 2\sum_{i=2}^{n-2} f_{ni})$$

$$\text{(IV)} = \frac{1}{2}\sum_{i=0}^{n-1} f_{ni}(b_{ni} + f_{ni}) + \sum_{i<j} f_{ni}f_{nj}.$$

Proof. By the Taylor expansion of Λ_2, the statement holds for $n = 2$. Suppose that the statement is true for $\Lambda_{n-1,2}$. As we mentioned in the proof of Lemma 3.1,

$$\Lambda_n \begin{bmatrix} A_{0,k} \\ A_{1,k} \\ \vdots \\ A_{n-1,k} \\ A_{n,k} \end{bmatrix} = \begin{bmatrix} 1 & 0 & \cdots & 0 \\ 0 & & & \\ \vdots & & \Lambda_{n-1} & \\ 0 & & & \end{bmatrix} \begin{bmatrix} X_{n0} & 0 & \cdots & 0 & Y_{n0} \\ 0 & 1 & \cdots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & 1 & 0 \\ Z_{n0} & 0 & \cdots & 0 & W_{n0} \end{bmatrix} \begin{bmatrix} A_{0,k} \\ A_{1,k} \\ \vdots \\ A_{n-1,k} \\ A_{n,k} \end{bmatrix}.$$

By Lemma 3.3, we have

$$\Lambda_{n-1} = I + \begin{bmatrix} -b_{n1} & & & f_{n1} \\ & \ddots & & \vdots \\ & & -b_{n(n-1)} & f_{n(n-1)} \\ b_{n1} & \cdots & b_{n(n-1)} & -\sum_{i=1}^{n-1} f_{ni} \end{bmatrix} \Delta t + \Lambda_{n-1,2}(\Delta t)^2 + O((\Delta t)^3).$$

It follows

$$\begin{aligned} \Lambda_{n,2} &= \begin{bmatrix} 0 & 0 \\ 0 & \Lambda_{n-1,2} \end{bmatrix} + \begin{bmatrix} 0 & 0 & \cdots & 0 & 0 \\ 0 & -b_{n1} & & & f_{n1} \\ \vdots & & \ddots & & \vdots \\ 0 & & & -b_{n(n-1)} & f_{n(n-1)} \\ 0 & b_{n1} & \cdots & b_{n(n-1)} & -\sum_{i=1}^{n-1} f_{ni} \end{bmatrix} \begin{bmatrix} -b_{n0} & & & & f_{n0} \\ & 0 & & & \\ & & \ddots & & \\ & & & 0 & \\ b_{n0} & & & & -f_{n0} \end{bmatrix} \\ &\quad + \frac{1}{2} \begin{bmatrix} b_{n0}(b_{n0}+f_{n0}) & & & & -f_{n0}(b_{n0}+f_{n0}) \\ & 0 & & & \\ & & \ddots & & \\ & & & 0 & \\ -b_{n0}(b_{n0}+f_{n0}) & & & & f_{n0}(b_{n0}+f_{n0}) \end{bmatrix} \\ &= \begin{bmatrix} 0 & 0 \\ 0 & \Lambda_{n-1,2} \end{bmatrix} + \begin{bmatrix} \frac{b_{n0}}{2}(b_{n0}+f_{n0}) & 0 & \cdots & 0 & -\frac{f_{n0}}{2}(b_{n0}+f_{n0}) \\ b_{n0}f_{n1} & 0 & \cdots & 0 & -f_{n0}f_{n1} \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ b_{n0}f_{n(n-1)} & 0 & \cdots & 0 & -f_{n0}f_{n(n-1)} \\ \text{(I)} & 0 & \cdots & 0 & \text{(II)} \end{bmatrix}, \end{aligned}$$

where

$$\begin{aligned} \text{(I)} &= -\frac{b_{n0}}{2}(b_{n0} + f_{n0} + 2\sum_{i=1}^{n-1} f_{ni}) \\ \text{(II)} &= \frac{f_{n0}}{2}(b_{n0} + f_{n0} + 2\sum_{i=1}^{n-1} f_{ni})). \end{aligned}$$

Hence, by the inductive hypothesis, we conclude that the statement is true for $\Lambda_{n,2}$. □

Lemma 3.6 *The matrix L_n^s in* (3.14) *has the Taylor expansion*

$$\begin{aligned} L_n^s &= L_{n,0}^s + L_{n,1}^s \Delta t + L_{n,2}^s (\Delta t)^2 + O((\Delta t)^3) \\ &= I + M_n \Delta t + \frac{1}{2} M_n^2 (\Delta t)^2 + O((\Delta t)^3) \end{aligned}$$

where M_n is the matrix in (3.1).

Proof. Since SCR^2 is a symmetrized version of CR^2, each $L_n^{s_i}$ has the same properties as L_n. Thus, according to Lemma 3.4, it is obvious that

$$L_{n,0}^s = I, \quad L_{n,1}^s = M_n.$$

Let $D_n^{s_i} = L_{n,2}^{s_i} - \frac{1}{2} M_n^2$ for $i = 1, 2$. To complete the proof, it suffices to show that

$$D_n^{s_1} + D_n^{s_2} = 0.$$

Because $D_n^{s_2}$ can be associated with $D_n^{s_1}$ by the permutation matrix P_n, we only need to characterize entries of $D_n^{s_1}$.

We first claim that

$$D_n^{s_1} = \sum_{i<j<k} D_{(i,j,k)}, \quad 0 \le i, j, k \le n \tag{3.15}$$

where

$$\begin{aligned} & D_{(i,j,k)} \\ & \qquad \begin{matrix} \qquad\quad (i+1)\text{th} & \qquad\quad (j+1)\text{th} & \qquad\quad (k+1)\text{th} \\ \qquad\quad \downarrow & \qquad\quad \downarrow & \qquad\quad \downarrow \end{matrix} \\ = & \quad \tfrac{1}{2} \begin{bmatrix} 0 & -b_{ki}f_{ji} + b_{kj}f_{ji} - b_{kj}f_{ki} & b_{ji}f_{ki} - f_{ji}f_{kj} + f_{ki}f_{kj} \\ b_{ji}b_{ki} - b_{ji}b_{kj} + b_{ki}f_{kj} & 0 & -b_{ji}f_{ki} + f_{ji}f_{kj} - f_{ki}f_{kj} \\ -b_{ji}b_{ki} + b_{ji}b_{kj} - b_{ki}f_{kj} & b_{ki}f_{ji} - b_{kj}f_{ji} + b_{kj}f_{ki} & 0 \end{bmatrix} \begin{matrix} \leftarrow (i+1)\text{th} \\ \leftarrow (j+1)\text{th} \\ \leftarrow (k+1)\text{th} \end{matrix} \end{aligned}$$

and other entries are zeros. The claim is verified by induction on n. By the previous argument, we already know that

$$D_2^{s_1} = D_{(0,1,2)}.$$

We assume that the claim is true for a general reaction system with n substances $A_0, A_1, \cdots, A_{n-1}$, i.e.,

$$D_{n-1}^{s_1} = \sum_{i<j<k} D_{(i,j,k)}, \quad 0 \le i, j, k \le n-1.$$

Let us see how $L_n^{s_1}$ and M_n change when adding A_n into the general reaction system with n substances. Since

$$\begin{aligned} L_n^{s_1} &= \Lambda_n \begin{bmatrix} L_{n-1}^{s_1} & 0 \\ 0 & 1 \end{bmatrix} \\ &= (I + \Lambda_{n,1}\Delta t + \Lambda_{n,2}(\Delta t)^2 + O((\Delta t)^3) \begin{bmatrix} I + M_{n-1}\Delta t + L_{n-1,2}^{s_1}(\Delta t)^2 + O((\Delta t)^3) & 0 \\ 0 & 1 \end{bmatrix}, \end{aligned}$$

it follows that

$$L_{n,2}^{s_1} = \begin{bmatrix} L_{n-1,2}^{s_1} & 0 \\ 0 & 0 \end{bmatrix} + \Lambda_{n,1} \begin{bmatrix} M_{n-1} & 0 \\ 0 & 0 \end{bmatrix} + \Lambda_{n,2}.$$

Also, Lemma 3.3 and (3.11) give

$$\begin{aligned} M_n^2 &= \left(\begin{bmatrix} M_{n-1} & 0 \\ 0 & 0 \end{bmatrix} + \Lambda_{n,1}\right)^2 \\ &= \begin{bmatrix} M_{n-1}^2 & 0 \\ 0 & 0 \end{bmatrix} + \begin{bmatrix} M_{n-1} & 0 \\ 0 & 0 \end{bmatrix} \Lambda_{n,1} + \Lambda_{n,1} \begin{bmatrix} M_{n-1} & 0 \\ 0 & 0 \end{bmatrix} + \Lambda_{n,1}^2. \end{aligned}$$

Then, we have that

$$\begin{aligned} D_n^{s_1} &= L_{n,2}^{s_1} - \frac{1}{2} M_n^2 \\ &= \begin{bmatrix} L_{n-1,2}^{s_1} - \frac{1}{2} M_{n-1}^2 & 0 \\ 0 & 0 \end{bmatrix} + \frac{1}{2} \Lambda_{n,1} \begin{bmatrix} M_{n-1} & 0 \\ 0 & 0 \end{bmatrix} - \frac{1}{2} \begin{bmatrix} M_{n-1} & 0 \\ 0 & 0 \end{bmatrix} \Lambda_{n,1} + \Lambda_{n,2} - \frac{1}{2} \Lambda_{n,1}^2. \end{aligned}$$

Looking at $M_{n-1}, \Lambda_{n,1}$ and $\Lambda_{n,2}$ carefully, all (i,j) entries contain subindex $n, (i-1)$ or $(j-1)$. It implies that we can write

$$\frac{1}{2} \Lambda_{n,1} \begin{bmatrix} M_{n-1} & 0 \\ 0 & 0 \end{bmatrix} - \frac{1}{2} \begin{bmatrix} M_{n-1} & 0 \\ 0 & 0 \end{bmatrix} \Lambda_{n,1} + \Lambda_{n,2} - \frac{1}{2} \Lambda_{n,1}^2 = \sum_{i<j} B_{ijn} \quad 0 \le i, j < n,$$

where B_{ijn} is a matrix whose entries consist of products of $b_{ni}, f_{ni}, b_{nj}, f_{nj}, b_{ji}$ and f_{ji}. Now let us compute B_{ijn} in details. For a matrix M, we define $(M)_{ijn}$ by a matrix whose entries consist of products of $b_{ni}, f_{ni}, b_{nj}, f_{nj}, b_{ji}$ and f_{ji} among entries of M. We detail B_{ijn} for all i, j with $0 \le i, j < n$ as follows:

$$\begin{aligned} E_1 &= \left(\Lambda_{n,1} \begin{bmatrix} M_{n-1} & 0 \\ 0 & 0 \end{bmatrix}\right)_{ijn} \\ &\qquad \begin{matrix} (i+1)\text{th} & (j+1)\text{th} & (n+1)\text{th} \\ \downarrow & \downarrow & \downarrow \end{matrix} \\ &= \begin{bmatrix} b_{ji} b_{ni} & -b_{ni} f_{ji} & 0 \\ -b_{ji} b_{nj} & b_{nj} f_{ji} & 0 \\ b_{ji}(b_{nj} - b_{ni}) & f_{ji}(b_{ni} - b_{nj}) & 0 \end{bmatrix} \begin{matrix} \leftarrow (i+1)\text{th} \\ \leftarrow (j+1)\text{th} \\ \leftarrow (n+1)\text{th} \end{matrix} \\ E_2 &= \left(\begin{bmatrix} M_{n-1} & 0 \\ 0 & 0 \end{bmatrix} \Lambda_{n,1}\right)_{ijn} \\ &\qquad \begin{matrix} (i+1)\text{th} & (j+1)\text{th} & (n+1)\text{th} \\ \downarrow & \downarrow & \downarrow \end{matrix} \\ &= \begin{bmatrix} b_{ji} b_{ni} & -f_{ji} b_{nj} & -b_{ji} f_{ni} + f_{ji} f_{nj} \\ -b_{ji} b_{ni} & f_{ji} b_{nj} & b_{ji} f_{ni} - f_{ji} f_{nj} \\ 0 & 0 & 0 \end{bmatrix} \begin{matrix} \leftarrow (i+1)\text{th} \\ \leftarrow (j+1)\text{th} \\ \leftarrow (n+1)\text{th} \end{matrix} \\ E_3 &= (\Lambda_{n,2})_{ijn} \\ &= \begin{matrix} \scriptstyle (i+1)\text{th} \\ \scriptstyle \downarrow \end{matrix} \quad \begin{matrix} \scriptstyle (j+1)\text{th} \\ \scriptstyle \downarrow \end{matrix} \quad \begin{matrix} \scriptstyle (n+1)\text{th} \\ \scriptstyle \downarrow \end{matrix} \\ &\quad \begin{bmatrix} \frac{1}{2(n-1)} b_{ni}(b_{ni} + f_{ni}) & 0 & -\frac{1}{2(n-1)} f_{ni}(b_{ni} + f_{ni}) \\ b_{ni} f_{nj} & \frac{1}{2(n-1)} b_{nj}(b_{nj} + f_{nj}) & -\frac{1}{2(n-1)} f_{nj}(b_{nj} + f_{nj}) - f_{ni} f_{nj} \\ -\frac{1}{2(n-1)} b_{ni}(b_{ni} + f_{ni}) - b_{ni} f_{nj} & -\frac{1}{2(n-1)} b_{nj}(b_{nj} + f_{nj}) & \text{(I)} \end{bmatrix} \begin{matrix} \scriptstyle \leftarrow (i+1)\text{th} \\ \scriptstyle \leftarrow (j+1)\text{th} \\ \scriptstyle \leftarrow (n+1)\text{th} \end{matrix} \\ &\quad \text{(I)} = \frac{1}{2(n-1)} f_{ni}(b_{ni} + f_{ni}) + \frac{1}{2(n-1)} f_{nj}(b_{nj} + f_{nj}) + f_{ni} f_{nj} \end{aligned}$$

Note that $(n-1)$ appears in the denominators. In the $(i+1,i+1)$ entry, $\frac{1}{2}b_{ni}(b_{ni}+f_{ni})$ is independent of j. Therefore, we distribute it equally to all $(\Lambda_{n,2})_{ijn}$ of which $(i+1)$th column is nonzero. In other entries, $(n-1)$ appears with the same reason.

$$
\begin{aligned}
E_4 &= \left((\Lambda_{n,1})^2\right)_{ijn} \\
&= \begin{matrix} \\ \\ \\ \end{matrix}
\begin{matrix} (i+1)\text{th} \\ \downarrow \end{matrix}
\begin{matrix} (j+1)\text{th} \\ \downarrow \end{matrix}
\begin{matrix} (n+1)\text{th} \\ \downarrow \end{matrix} \\
&\quad \begin{bmatrix}
\frac{1}{(n-1)}b_{ni}(b_{ni}+f_{ni}) & b_{nj}f_{ni} & -\frac{1}{(n-1)}f_{ni}(b_{ni}+f_{ni}) - f_{ni}f_{nj} \\
b_{ni}f_{nj} & \frac{1}{(n-1)}b_{nj}(b_{nj}+f_{nj}) & -\frac{1}{(n-1)}f_{nj}(b_{nj}+f_{nj}) - f_{ni}f_{nj} \\
-\frac{1}{(n-1)}b_{ni}(b_{ni}+f_{ni}) - b_{ni}f_{nj} & -\frac{1}{(n-1)}b_{nj}(b_{nj}+f_{nj}) - b_{nj}f_{ni} & \text{(II)}
\end{bmatrix}
\begin{matrix} \leftarrow (i+1)\text{th} \\ \leftarrow (j+1)\text{th} \\ \leftarrow (n+1)\text{th} \end{matrix} \\
&\quad \text{(II)} = \tfrac{1}{(n-1)}f_{ni}(b_{ni}+f_{ni}) + \tfrac{1}{(n-1)}f_{nj}(b_{nj}+f_{nj}) + 2f_{ni}f_{nj}
\end{aligned}
$$

where, for each E_l, $E_l(m_1,m_2)=0 \quad \forall m_1,m_2 \notin \{i+1,j+1,n+1\}$. Then, we have

$$
\begin{aligned}
B_{ijn} &= \frac{1}{2}E_1 - \frac{1}{2}E_2 + E_3 - \frac{1}{2}E_4 \\
&= \begin{matrix} \\ \\ \\ \end{matrix}
\begin{matrix} (i+1)\text{th} \\ \downarrow \end{matrix}
\begin{matrix} (j+1)\text{th} \\ \downarrow \end{matrix}
\begin{matrix} (n+1)\text{th} \\ \downarrow \end{matrix} \\
&\quad \tfrac{1}{2}\begin{bmatrix}
0 & -b_{ni}f_{ji} + b_{nj}f_{ji} - b_{nj}f_{ni} & b_{ji}f_{ni} - f_{ji}f_{nj} + f_{ni}f_{nj} \\
b_{ji}b_{ni} - b_{ji}b_{nj} + b_{ni}f_{nj} & 0 & -b_{ji}f_{ni} + f_{ji}f_{nj} - f_{ni}f_{nj} \\
-b_{ji}b_{ni} + b_{ji}b_{nj} - b_{ni}f_{nj} & b_{ni}f_{ji} - b_{nj}f_{ji} + b_{nj}f_{ni} & 0
\end{bmatrix}
\begin{matrix} \leftarrow (i+1)\text{th} \\ \leftarrow (j+1)\text{th} \\ \leftarrow (n+1)\text{th} \end{matrix} \\
&= D_{(i,j,n)}.
\end{aligned}
$$

The inductive hypothesis yields

$$
\begin{aligned}
D_n^{s_1} &= \sum_{i<j<k<n} D_{(i,j,k)} + \sum_{i<j<n} D_{(i,j,n)} \\
&= \sum_{i<j<k} D_{(i,j,k)}.
\end{aligned}
$$

Similarly, we obtain the relationship

$$
\overline{L}_{n,2}^{s_2} - \frac{1}{2}P_n M_n^2 P_n = \sum_{i<j<k} D_{(n-k,n-j,n-i)}.
$$

Note that

$$
D_{(i,j,k)} + P_n D_{(n-k,n-j,n-i)} P_n = 0.
$$

Consequently, we find that

$$
\begin{aligned}
D_n^{s_2} &= L_{n,2}^{s_2} - \frac{1}{2}M_n^2 \\
&= P_n(\overline{L}_{n,2}^{s_2} - \frac{1}{2}P_n M_n^2 P_n)P_n \\
&= P_n(\sum_{i<j<k} D_{(n-k,n-j,n-i)})P_n \\
&= -\sum_{i<j<k} D_{(i,j,k)},
\end{aligned}
$$

that is,

$$
D_n^{s_1} + D_n^{s_2} = 0.
$$

The proof is complete. $\square$

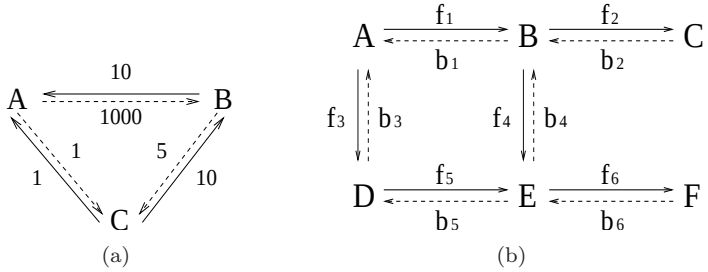


Figure 2: (a) A circular reaction. (b) A general reaction system.

By using the same arguments as in Theorem 3.2 based on Lemma 3.6, we can easily get the following theorem.

Theorem 3.3 *The algorithm SCR*^{2} *applied to* (3.1) *has the order of convergence* 2.

4 Numerical experiments

In this section, we present numerical results which verify the theoretical results in the previous sections. In addition, we introduce a model of interest in the fatty acid physiology and apply our numerical method to the transport model of fatty acids from the blood plasma into the heart muscle cell.

4.1 Simple reaction systems

Figure 2-(a) describes a circular reaction with 3 substances A, B and C with initial values $A(0) = 1, B(0) = 2$ and $C(0) = 3$. The system of ODEs is as follows:

$$\frac{d}{dt}\begin{bmatrix} A(t) \\ B(t) \\ C(t) \end{bmatrix} = \begin{bmatrix} -1001 & 10 & 1 \\ 1000 & -15 & 10 \\ 1 & 5 & -11 \end{bmatrix} \begin{bmatrix} A(t) \\ B(t) \\ C(t) \end{bmatrix} = M \begin{bmatrix} A(t) \\ B(t) \\ C(t) \end{bmatrix}. \tag{4.1}$$

Many explicit numerical methods such as Euler's method and a fourth order Runge-Kutta method (RK4 method) in common use have their pros and cons. The structure of explicit methods is so simple that they are popular and may diminish computing cost at each time step. But, due to its conditional stability, the restriction on the choice of the size of time step is troublesome. For a stiff problem such as (4.1), the drawback of explicit methods is more severe. Note that Euler's method for (4.1) is stable only if

$$\Delta t \leq \frac{S_1}{\lambda_{min}} \approx 1.9782 \times 10^{-3} \text{ with } S_1 = -2$$

and RK4 method for (4.1) is stable only if

$$\Delta t \leq \frac{S_2}{\lambda_{min}} \approx 2.7531 \times 10^{-3} \text{ with } S_2 \approx -2.7853,$$

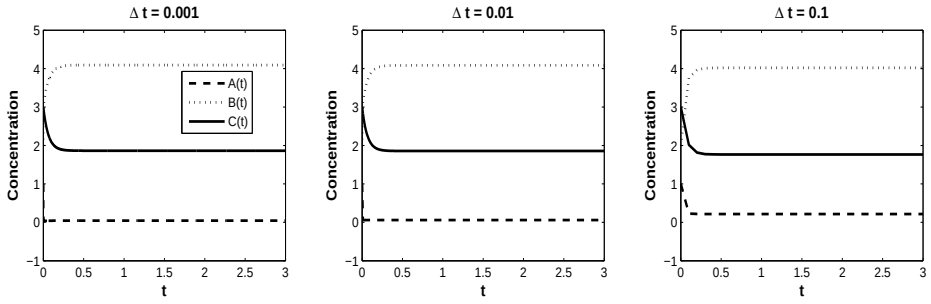


Figure 3: Stability of the CR^2 algorithm.

Δt	$\|\mathbf{y}(t_F) - \mathbf{y}^N\|_1$			$\sum_{i=1}^N \|\mathbf{y}(t_i) - \mathbf{y}^i\|_1 \Delta t$		
	CR^2	SCR^2	$BDF2$	CR^2	SCR^2	$BDF2$
10^{-1}	3.4182e-01	1.6979e-01	3.0723e-12	1.0295	5.2196e-01	6.4610e-02
10^{-2}	3.2857e-02	1.4643e-02	1.5698e-13	9.9615e-02	4.4658e-02	3.5786e-03
10^{-3}	2.1366e-03	3.0403e-04	2.3378e-12	6.5804e-03	9.3141e-04	4.9409e-04
10^{-4}	1.8653e-04	3.0979e-06	2.4701e-11	5.7888e-04	9.5901e-06	8.9323e-06
10^{-5}	1.8376e-05	3.1126e-08	4.2676e-11	5.7083e-05	9.6640e-08	9.6306e-08
10^{-6}	1.8348e-06	3.7633e-10	7.4494e-10	5.7002e-06	1.0620e-09	2.5923e-09

Table 1: Convergence behaviors of CR^2, SCR^2 and BDF2 by means of $\|\mathbf{y}(t_F) - \mathbf{y}^N\|_1$ and $\sum_{i=1}^N \|\mathbf{y}(t_i) - \mathbf{y}^i\|_1 \Delta t$ with Δt varying from 10^{-1} to 10^{-6} where $N = t_F/\Delta t$ with $t_F = 3$.

where λ_{min} is the minimum eigenvalue of M and

$$S_i = \min_{z \in \partial D_i \subset \mathbb{C}} Re(z) \quad i = 1, 2$$

with the linear stability domain D_i of Euler's method and RK4 method, respectively. Figure 3 shows that the CR^2 algorithm gives a stable approximation even if a large Δt is used. For a stiff problem, Gear's method is widely used in order to avoid the problems of instability due to the stiffness. We investigate the difference between two proposed methods and one of Gear's method, a two-step backward differentiation formula (BDF2) which is an *A-stable* method of order 2. BDF2 takes a long time to solve a linear system. Moreover, we should pay special attention during the process of solving the relevant linear system because it may be ill-conditioned for a large Δt. Hence, two explicit algorithms CR^2 and SCR^2 are superior to BDF2 in terms of efficiency and simplicity of implementation. To observe the convergence speed of three methods, two different errors $\|\mathbf{y}(t_F) - \mathbf{y}^N\|_1$ and $\sum_{i=1}^N \|\mathbf{y}(t_i) - \mathbf{y}^i\|_1 \Delta t$ are shown in Table 1, where $\|\mathbf{y}(t_F) - \mathbf{y}^N\|_1$ is computed at the terminal point $t_F = 3$ and $\sum_{i=1}^N \|\mathbf{y}(t_i) - \mathbf{y}^i\|_1 \Delta t$ is calculated over all discrete time steps $t = t_i$ with $N = t_F/\Delta t$. Note that the performance of SCR^2 is comparable to that of BDF2.

Next, we consider a somewhat complicated general reaction system in Figure 2-(b) with initial values

$$A(0) = 1, \quad B(0) = 0, \quad C(0) = 0, \quad D(0) = 0, \quad E(0) = 0 \quad \text{and} \quad F(0) = 0,$$

Δt	CR^2		SCR^2	
	$\|\mathbf{y}(t_F)-\mathbf{y}^N\|_1$	order	$\|\mathbf{y}(t_F)-\mathbf{y}^N\|_1$	order
1/2	5.7923e-02		1.0089e-02	
1/4	2.7704e-02	1.0640	3.4552e-03	1.5460
1/8	1.3454e-02	1.0421	1.2101e-03	1.5137
1/16	6.6209e-03	1.0229	3.6181e-04	1.7418
1/32	3.2836e-03	1.0118	9.9202e-05	1.8668
1/64	1.6350e-03	1.0059	2.5992e-05	1.9323
1/128	8.1584e-04	1.0030	6.6537e-06	1.9659
1/256	4.0750e-04	1.0015	1.6833e-06	1.9829

Table 2: Convergence behaviors of the algorithms CR^2 and SCR^2 by means of $\|\mathbf{y}(t_F)-\mathbf{y}^N\|_1$ with Δt varying from 1/2 to 1/256 where $N = t_F/\Delta t$ with $t_F = 10$.

Δt	CR^2		SCR^2	
	$\sum_{i=1}^N \|\mathbf{y}(t_i)-\mathbf{y}^i\|_1\Delta t$	order	$\sum_{i=1}^N \|\mathbf{y}(t_i)-\mathbf{y}^i\|_1\Delta t$	order
1/2	1.4005		2.6305e-01	
1/4	6.6803e-01	1.0680	7.0304e-02	1.9036
1/8	3.2096e-01	1.0575	1.8225e-02	1.9477
1/16	1.5670e-01	1.0344	4.7130e-03	1.9512
1/32	7.7354e-02	1.0185	1.2067e-03	1.9656
1/64	3.8422e-02	1.0095	3.0594e-04	1.9797
1/128	1.9147e-02	1.0048	7.7070e-05	1.9890
1/256	9.5573e-03	1.0024	1.9344e-05	1.9943

Table 3: Convergence behaviors of the algorithms CR^2 and SCR^2 by means of $\sum_{i=1}^N \|\mathbf{y}(t_i)-\mathbf{y}^i\|_1\Delta t$ with Δt varying from 1/2 to 1/256 where $N = t_F/\Delta t$ with $t_F = 10$.

where

$$f_1 = 0.5, \quad f_2 = 0.01, \quad f_3 = 5.0, \quad f_4 = 0.1, \quad f_5 = 0.1, \quad f_6 = 1.0,$$
$$b_1 = 0.05, \quad b_2 = 0.001, \quad b_3 = 0.5, \quad b_4 = 0.01, \quad b_5 = 0.01, \quad b_6 = 1.0.$$

In order to illustrate convergence properties of two algorithms CR^2 and SCR^2, two kinds of errors measured in the l_1-norm and estimates of the order of convergence are summarized in Table 2 and 3. Table 2 gives errors $\|\mathbf{y}(t_F)-\mathbf{y}^N\|_1$ for varing Δt and estimates of the convergence order corresponding to $\|\mathbf{y}(t_F)-\mathbf{y}^N\|_1$ where $N = t_F/\Delta t$ with the terminal point $t_F = 10$. The numbers presented in Table 2 imply that when the time step Δt is halved, the errors $\|\mathbf{y}(t_F)-\mathbf{y}^N\|_1$ of CR^2 and SCR^2 decay linearly and quadratically, respectively. On the other hand, Table 3 displays the errors $\sum_{i=1}^N \|\mathbf{y}(t_i)-\mathbf{y}^{(i)}\|_1\Delta t$ and estimates of the convergence order. According to Table 3, we confirm that the algorithms CR^2 and SCR^2 converge of order 1 and 2, respectively over the whole interval $(0, 10]$.

4.2 Computational model for transport of fatty acids

The heart plays important roles in the human body; it pumps the blood through the body and supplies sufficient nutrients and oxygen to all organs. About 60-70% of the energy is derived from mitochondrial oxidation of fatty acids (FAs): a long chained carbohydrate with an acid group at the end. Moreover, irregular changes in the FA uptake may severely damage to the heart. A number of relevant studies for FA transport have been done (see [1, 5, 8, 9]). FAs are transported from the blood plasma to the myocardial cell through the endothelial cell and the interstitial tissue (see Figure 4). Although there exist many controversial aspects of FA transport mechanism, we adopt the following simple transport model solely focusing on transport of FAs in order to deal with the whole procedure from the plasma to the myocyte simultaneously (see Figure 5):

- First, FAs are transported through the luminal endothelial membrane to the cytoplasm of endothelial cells.
- Next, FAs move in the endothelium to the abluminal endothelial membrane.
- Finally, FAs diffuse freely in the interstitium and cross the sarcolemma which is the barrier before the myocyte.

Note that we exclude the introduction of proteins like albumin bound to FA, that is, we use a simple diffusion by concentration differences of chemical species, not facilitated diffusion in order to define transport of FA in the endothelium and the interstitial tissue. Many physiologists and bioengineers commonly use the diffusion equation in the form of ODEs to keep the mathematical model simple. The two-compartment diffusion is modelled as follows:

$$\begin{aligned} J_{2\to 1} &= V_1 \frac{d}{dt} C_1 = \frac{DA}{L}(C_2 - C_1) \\ J_{1\to 2} &= V_2 \frac{d}{dt} C_2 = \frac{DA}{L}(C_1 - C_2) \end{aligned} \tag{4.2}$$

where V_i is the volume of the ith compartment, C_i is the chemical concentration in ith compartment, D is the diffusion constant, and A and L are the cross sectional area and the distance between compartments. We also need to take the transmembrane diffusion into account. Chemical

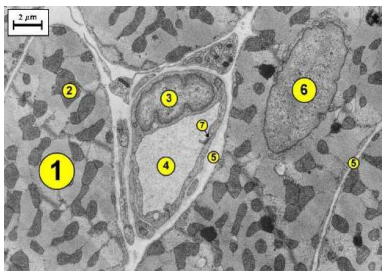


Figure 4: Electron micrograph of the orientation of a capillary which is surrounded by the myocyte. The photograph shows 1)a myocyte, 2)a mitochondria inside the myocyte, 3)the nucleus of an endothelial cell, 4)the intravascular compartment, 5)the interstitial compartment. The picture and description are taken from [2] and [9], respectively.

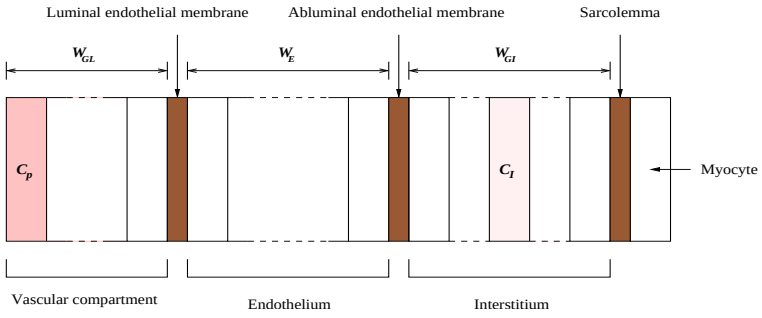


Figure 5: Schematic diagram of the FA diffusion region.

Parameter	Description	Reference
$D = 5.0 \times 10^{-6}$ cm^2/sec	Diffusivity for FA	[1]
$P = 8.3 \times 10^{-3}$ cm/sec	Permeability for a cell membrane to FA	[1]
$W_{GL} = 0.4$ μm	Glycocalyx width on the endothelial luminal side	[15, 16]
$W_E = 0.5$ μm	Endothelium width	[1]
$W_{GI} = 0.6$ μm	Glycocalyx width in the interstitium	[15, 16]
$C_p = 5.1$ nM	FA concentration in the blood plasma	[11]
$C_I = 1.9$ nM	FA concentration in the interstitium	[11]

Table 4: Parameters used in the computational model of FA transport.

diffusion through the biological membranes such as the endothelial membrane and the sarcolemma is governed by an analog of (4.2) when D/L is replaced by the membrane permeability P. We assume that the whole system of FA transport is closed, that is, there is no exterior influence on the FA concentration change. Considering the four diffusion regions: the blood plasma, endothelium, the interstitium, and the threshold of the myocyte, as a serial of small N compartments gives a system of ODEs for the mean concentration C_i, which describes the transport mechanism of FA:

$$V_1 \frac{d}{dt} C_1(t) = K_1^{right}(C_2(t) - C_1(t)), \tag{4.3a}$$

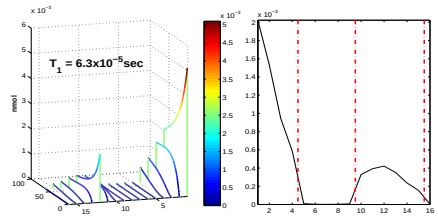
$$V_i \frac{d}{dt} C_i(t) = K_i^{left}(C_{i-1}(t) - C_i(t)) + K_i^{right}(C_{i+1}(t) - C_i(t)) \quad 1 < i < N, \tag{4.3b}$$

$$V_N \frac{d}{dt} C_N(t) = K_N^{left}(C_{N-1}(t) - C_N(t)), \tag{4.3c}$$

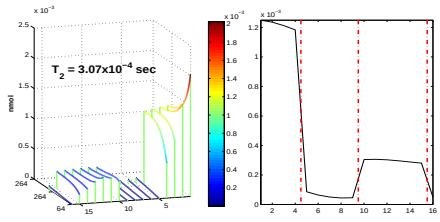
where K_i is a constant dependent on $A, D, L,$ and P chosen properly in the ith compartment (cf. [9]). Since

$$\sum_{i=1}^{N} V_i \frac{d}{dt} C_i(t) = 0 \quad \forall t > 0,$$

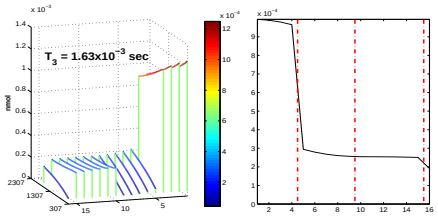
we can apply our methods to (4.3). We adopt the second-order SCR^2 algorithm to solve (4.3) numerically. In the computation of (4.3), we use the parameters derived from the physiological experiments and list them in Table 4 in details. Figure 6 shows how the approximate solution reaches an equilibrium state of FA concentration at the 16 compartments when the three diffusion



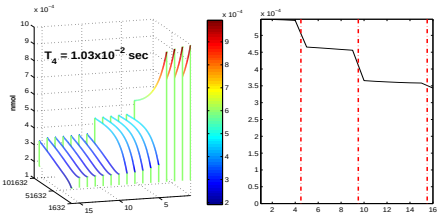
(a) $T_1 = 6.3 \times 10^{-5}$ sec



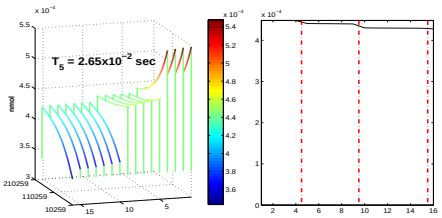
(b) $T_2 = 3.07 \times 10^{-4}$ sec



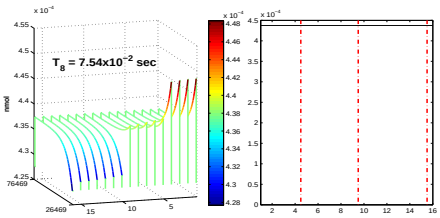
(c) $T_3 = 1.63 \times 10^{-3}$ sec



(d) $T_4 = 1.03 \times 10^{-2}$ sec



(e) $T_5 = 2.65 \times 10^{-2}$ sec



(f) $T_8 = 7.54 \times 10^{-2}$ sec

Figure 6: FA concentration at the 16 compartments: each left one in (a)-(f) shows the sequential change of solution for $T_{i-1} < t < T_i$ with $i = 1, 2, 3, 4, 5, 8$ and the right one is a single shot of solution at $t = T_i$.

	Comp1	Comp2	Comp3	Comp4
T_1	1.2719e-03	4.4648e-06	3.1444e-04	3.5328e-06
T_2	1.2203e-03	5.8132e-05	2.9641e-04	4.9536e-05
T_3	9.8231e-04	2.7189e-04	2.5338e-04	1.9102e-04
T_4	5.4648e-04	4.6056e-04	3.6132e-04	3.4335e-04
T_5	4.4822e-04	4.4028e-04	4.2967e-04	4.2767e-04
T_8	4.3750e-04	4.3750e-04	4.3750e-04	4.3750e-04

Table 5: Average concentration in nmol/cm^3 in 4 compartments at $t = T_i$: the vascular compartment (Comp1), the endothelium (Comp2), the interstitium (Comp3), the myocyte (Comp4).

domains are divided into 4, 5, and 6 compartments, respectively in proportion to $W_{GL} : W_E : W_{GI}$ in Table 4. We measure the relative error

$$E_{rel} = \left(\sum_{i=1}^{N} \left| \frac{C_i(t_{n+1}) - C_i(t_n)}{C_i(t_{n+1})} \right|^2 \right)^{\frac{1}{2}}$$

and T_i which indicates when $E_{rel} < 10^{-i}$ with $i = 1, 2, 3, 4, 5, 8$. Each left figure in Figure 6 (a)-(f) informs the sequential change of solution for $T_{i-1} < t < T_i$ with $T_0 = 0$ while the right one is a single shot of solution at $t = T_i$. Three dotted lines in each right figure display the positions of the luminal membrane, the abluminal membrane, and the sarcolemma in order. The drastic concentration difference across the dotted lines is due to the permeability of the membranes. In Table 5, we present the average concentration in each compartment computed at $t = T_i$ in order to describe the solution property quantitatively.

5 Conclusions

We proposed two numerical schemes CR^2 and SCR^2 applicable to general reaction systems. Since the CR^2 algorithm is motivated by the exact solver for a reversible reaction with 2 substances, it is very easy to implement. On the other hand, the SCR^2 algorithm, a symmetrized version of the CR^2 algorithm, is enhanced in view of the convergence speed. Unlike most of explicit methods, CR^2 and SCR^2 are absolutely stable in spite of their explicitness. We analyzed stability and convergence properties of CR^2 and SCR^2 and confirmed the theoretical results by the numerical experiments. Even if the algorithms CR^2 and SCR^2 were aimed for the numerical solver to reaction systems, the application of our methods could be extended further. As an applicable example, we introduced the myocardial fatty acid uptake phenomenon and adopted our method for solving the computational model obtained by focusing on a serial of diffusion which is a main route of FA transport in a closed system.

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