DISCRETE AND CONTINUOUS
DYNAMICAL SYSTEMS–SERIES B
Volume **7**, Number **3**, May **2007**

Website: http://AIMsciences.org

pp. **515–525**

NUMERICAL METHODS FOR STIFF REACTION-DIFFUSION SYSTEMS

Ching-Shan Chou

Center for Mathematical and Computational Biology
Department of Mathematics, University of California, Irvine
Irvine, CA 92697-3875, USA

Yong-Tao Zhang

Department of Mathematics
University of Notre Dame, Notre Dame, IN 46556-4618, USA

Rui Zhao

Center for Mathematical and Computational Biology
Department of Mathematics, University of California, Irvine
Irvine, CA 92697-3875, USA

Qing Nie[1]

Center for Mathematical and Computational Biology
Department of Mathematics, University of California, Irvine
Irvine, CA 92697-3875, USA

Contributed in honor of Fred Wan on the occasion of his 70^{th} *birthday*

Abstract. In a previous study [21], a class of efficient semi-implicit schemes was developed for stiff reaction-diffusion systems. This method which treats linear diffusion terms exactly and nonlinear reaction terms implicitly has excellent stability properties, and its second-order version, with a name IIF2, is linearly unconditionally stable. In this paper, we present another linearly unconditionally stable method that approximates both diffusions and reactions implicitly using a second order Crank-Nicholson scheme. The nonlinear system resulted from the implicit approximation at each time step is solved using a multi-grid method. We compare this method (CN-MG) with IIF2 for their accuracy and efficiency. Numerical simulations demonstrate that both methods are accurate and robust with convergence using even very large size of time steps. IIF2 is found to be more accurate for systems with large diffusion while CN-MG is more efficient when the number of spatial grid points is large.

1. **Introduction.** Mathematical equations for many physical and biological applications are of the form:

$$\frac{\partial \mathbf{u}}{\partial t} = D\Delta \mathbf{u} + \mathbf{F}(\mathbf{u}), \tag{1.1}$$

2000 *Mathematics Subject Classification.* 65MXX.

Key words and phrases. Integration factor methods, Crank-Nicholson, multi-grids, reaction-diffusion equations, morphogen gradients.

[1]Corresponding author: qnie@math.uci.edu.

where $\mathbf{u} \in \mathbf{R}^m$ represents a group of physical or biological species, $D \in \mathbf{R}^{m\times m}$ is the diffusion constant matrix, $\Delta\mathbf{u}$ is the Laplacian associated with the diffusion of the species $\mathbf{u}$, and $\mathbf{F}(\mathbf{u})$ describes the chemical or biological reactions.

When the diffusion term is discretized using finite difference methods, the reaction-diffusion system (1.1) is first reduced to a system of ODEs:

$$u_t = \mathcal{C}u + \mathcal{F}(u), \tag{1.2}$$

where $\mathcal{C}u$ is a finite difference approximation of $D\Delta\mathbf{u}$. Let N denote the number of spatial grid points for the approximation of the Laplacian $\Delta\mathbf{u}$, then $u(t) \in R^{N\cdot m}$ and $\mathcal{C}$ is a $(N \cdot m) \times (N \cdot m)$ matrix. For instance, $\mathcal{C}$ is a tri-diagonal matrix in a one dimensional system when a second order central difference is carried out on the diffusion.

For a time integrator applied to Eq. (1.2), the time step is constrained by the size of the eigenvalues of the diffusion matrix $\mathcal{C}$, which are proportional to diffusion coefficients and spatial resolutions as well as the stiffness of the nonlinear reaction term $\mathcal{F}(u)$. The constraint due to diffusion can be totally removed by treating the term $\mathcal{C}u$ exactly [9, 1, 2]. Different approximations on the temporal integral involving $\mathcal{F}(u)$ in this approach result in either Integration Factor (IF) method [18, 21] or Exponential Time Differencing (ETD) method [13, 6, 7, 8].

Although the stability constraint due to diffusion is totally removed in the IF and ETD methods, the time step is still constrained by stiffness of the reaction term $\mathcal{F}(u)$ due to their explicit treatment of $\mathcal{F}(u)$ through either linear multi-step methods [9, 2] or Runge-Kutta approximations [5]. These methods are efficient for diffusion-dominated systems but not for systems with highly stiff reactions as well as strong diffusive effects, as often is the case in many biological applications. In diffusive morphogen gradient systems [16, 11, 19, 20], for instance, the reaction rate constants usually differ by four to six magnitudes and the system is very stiff as a result.

Recently, a new class of semi-implicit integration factor (IIF) methods [21] has been introduced to address this issue. The new IIF method treats diffusion terms exactly and nonlinear reaction terms $\mathcal{F}(u)$ implicitly in such a way that the implicit approximation of the nonlinear terms is *decoupled* from the global calculation of the diffusion term. Consequently, it avoids solving a large nonlinear system with $N \cdot m$ unknowns; instead, a system of size m, the number of the original differential equations, has to be solved at each spatial grid point. The structure of the the small nonlinear system is particularly suitable for simple iterative nonlinear solvers such as the fixed point iteration. The overall computational cost is of the same order as the explicit IF or ETD methods, and it mainly comes from the matrix-vector multiplications due to the exact representation of diffusion operators. The IIF methods have much better stability properties than the explicit IF or ETD methods, and the second-order IIF (IIF2) is unconditionally stable.

In this paper, we will compare this semi-implicit method (IIF2) with a fully implicit and unconditionally stable method. In the fully implicit method, a second-order Crank-Nicholson approximation [4] is applied to Eq. (1.1). As a result, a large system of nonlinear equations with $(N \cdot m)$ equations and $(N \cdot m)$ unknowns has to be solved at every time step. Because the size of the nonlinear system linearly depends on the spatial resolution N, using a standard nonlinear solver for such system is usually very expensive. To speed up the calculation, we incorporate an efficient multi-grid method [3] to solve the system at every time step. Finally, we

study accuracy and efficiency for the two methods, IIF2 and the Crank-Nicholson method with multi-grid (CN-MG) based on simulations of a test problem with an analytical solution and a set of fully nonlinear equations which models a morphogen system in developmental biology.

The rest of the paper is organized as following. In section 2, we review briefly the IIF schemes, and introduce the Crank-Nicholson scheme with a nonlinear multi-grid solver for the reaction-diffusion equations. In section 3, we compare the accuracy and efficiency between the second-order IIF scheme and CN-MG scheme, using two examples. We conclude the paper in section 4.

2. **Two numerical methods.**

In this section, we will briefly describe two unconditionally stable methods with second-order of accuracy for reaction-diffusion systems.

2.1. **Implicit integration factor (IIF).**

First, we present the Implicit Integration Factor (IIF) method [21] based on a scalar case of the semi-discrete system (1.2) of the form

$$u_t = cu + f(u), \qquad t > 0, \qquad u(0) = u_0, \tag{2.3}$$

where c is a constant representing the diffusion and f is a nonlinear function representing the reaction.

After multiplying (2.3) by an integration factor e^{-ct}, we integrate the equation over one time step from t_n to $t_{n+1} \equiv t_n + \Delta t$ to obtain

$$u(t_{n+1}) = u(t_n)e^{c\Delta t} + e^{c\Delta t}\int_0^{\Delta t} e^{-c\tau} f(u(t_n+\tau))d\tau. \tag{2.4}$$

For a scheme of r-th order truncation error, we first approximate the integrand, $e^{-c\tau}f(u(t_n+\tau))$, using an $(r-1)$-th order Lagrange polynomial, $p(\tau)$, with interpolation points at $t_{n+1}, t_n, ..., t_{n+2-r}$:

$$p(\tau) = \sum_{i=-1}^{r-2} e^{ic\Delta t} f(u_{n-i}) \prod_{\substack{j=-1 \\ j\neq i}}^{r-2} \frac{\tau + j\Delta t}{(j-i)\Delta t}. \tag{2.5}$$

where u_n is the approximated solution for $u(t_n)$. Next, we integrate the polynomial $p(\tau)$ with respect to τ, and derive

$$u_{n+1} = e^{c\Delta t}u_n + \Delta t\left(\alpha_{n+1}f(u_{n+1}) + \sum_{i=0}^{r-2}\alpha_{n-i}f(u_{n-i})\right), \tag{2.6}$$

where $\alpha_{n+1}, \alpha_n, \alpha_{n-1}, \cdots, \alpha_{n-r+2}$ calculated from the integrals of the polynomial $p(\tau)$ are listed in [21]. The second-order scheme (IIF2) is of the following form

$$u_{n+1} = e^{c\Delta t}\left(u_n + \frac{\Delta t}{2}f(u_n)\right) + \frac{\Delta t}{2}f(u_{n+1}), \tag{2.7}$$

with a local truncation error

$$-\frac{1}{12}\left(c^2 f_n - 2c\dot{f}_n + \ddot{f}_n\right)\Delta t^3. \tag{2.8}$$

The IIF method has excellent stability properties compared to explicit integration factor methods and other exponential time difference schemes. In real practice, Eq. (2.3) is usually a system where u and f are vectors, and $e^{c\Delta t}$ is a matrix. Unlike most other implicit methods, the dominant computational cost for IIF is usually from the exact treatment of diffusion terms instead of solving the nonlinear systems

due to implicit treatment of the nonlinear equations. In particular, in IIF2 the matrix-vector multiplication in the first term of the right-hand side of Eq. (2.7) dominates the cost of calculation for a system of reaction-diffusion equations. From the stability point of view, IIF2 is the best among IIF methods, and it is linearly unconditionally stable.

2.2. **A Crank-Nicholson method with a Multi-Grid solver (CN-MG).** An alternative approach to construct an unconditionally stable method for reaction-diffusion systems is to treat both reaction and diffusion terms implicitly. A Crank-Nicholson approximation for the diffusion and reaction terms leads to a fully implicit scheme:

$$\begin{aligned}\frac{\mathbf{u}_j^{n+1}-\mathbf{u}_j^n}{\Delta t} &= D\cdot\frac{1}{2}\left(\frac{\mathbf{u}_{j+1}^{n+1}-2\mathbf{u}_j^{n+1}+\mathbf{u}_{j-1}^{n+1}}{(\Delta x)^2}+\frac{\mathbf{u}_{j+1}^{n}-2\mathbf{u}_j^{n}+\mathbf{u}_{j-1}^{n}}{(\Delta x)^2}\right))\\ &\quad+\frac{1}{2}\left(\mathbf{F}(\mathbf{u}_j^{n+1})+\mathbf{F}(\mathbf{u}_j^n)\right),\end{aligned}\tag{2.9}$$

for a one-spatial dimensional form of Eq. (1.1). Define $\lambda \triangleq D\frac{\Delta t}{(\Delta x)^2}$, then Eq. (2.9) can be re-written as

$$\mathbf{u}_j^{n+1}-\frac{\lambda}{2}\left(\mathbf{u}_{j+1}^{n+1}-2\mathbf{u}_j^{n+1}+\mathbf{u}_{j-1}^{n+1}\right)-\frac{\Delta t}{2}\mathbf{F}(\mathbf{u}_j^{n+1})=\mathbf{G}_j^n\tag{2.10}$$

where

$$\mathbf{G}_j^n \triangleq \mathbf{u}_j^n+\frac{\lambda}{2}\left(\mathbf{u}_{j+1}^{n}-2\mathbf{u}_j^{n}+\mathbf{u}_{j-1}^{n}\right)+\frac{\Delta t}{2}\mathbf{F}(\mathbf{u}_j^n).$$

This method is linearly unconditionally stable [4], similar to IIF2, and its local truncation error is

$$-\frac{1}{12}\left((c+\dot{f}_n)^2(cu_n+f_n)+\ddot{f}_n(cu_n+f_n)^2\right)\Delta t^3\tag{2.11}$$

when the Crank-Nicholson scheme (2.10) is applied to Eq. (2.3).

In particular, cu represents the finite difference approximation of the diffusion $D\Delta u$ as in the ODE system (1.2), and the eigenvalues of $\mathcal{C}$ are proportional to DN^2. If the number of spatial grid points N or the diffusion constant D is large enough, terms involving c will dominate in the truncation errors (2.8) and (2.11). In these cases, the truncation error (2.8) of IIF2 has the leading term $O(c^2\Delta t^3)$, while that (2.11) of the Crank-Nicholson scheme has the leading term $O(c^3\Delta t^3)$. So we expect that IIF2 is more accurate than the Crank-Nicholson scheme for diffusion dominated problems. Direct numerical simulations on a test problem in Section 3 indicate that the errors of the solutions computed from IIF2 are no larger than those from the Crank-Nicholson scheme.

To advance the Crank-Nicholson scheme from the n-th time step to the $(n+1)$-th, one has to solve a nonlinear system (2.10) of $(m\cdot N)$ unknowns at every time step. A direct nonlinear solver usually has at least computational complexity with an order of N^2 and is very expensive. In this paper, we will use one of the nonlinear multi-grid methods, the full approximation scheme (FAS) [3], to speed up solving (2.10). The FAS method is based on a nonlinear Gauss-Seidel relaxation scheme [22] and it has a computational complexity with an order of N. More details and the implementations of FAS method are given in the next subsection. We denote the Crank-Nicholson scheme with a multi-grid solver as CN-MG in short.

In the multi-level FAS method [3], solutions of a local nonlinear system of m equations are needed at each grid point. The system (2.10) can be written in a

form of fixed point iteration:

$$\mathbf{w}_j = \frac{\Delta t}{2(1+\lambda)}\mathbf{F}(\mathbf{w}_j) + \frac{\lambda}{2(1+\lambda)}(\mathbf{w}_{j+1} + \mathbf{w}_{j-1}) + \frac{\mathbf{G}_j^n}{1+\lambda}, \tag{2.12}$$

where $\mathbf{w}_j \in R^m, 1 \le j \le N$. When $\frac{\Delta t}{2(1+\lambda)} \ll 1$, $\frac{\Delta t}{2(1+\lambda)}\mathbf{F}$ is likely to be a contractive mapping [15] which ensures convergence of a fixed point iteration. We also implement a Newton's method [14, 15] to solve the system (2.12) in addition to the fixed point iteration.

2.3. **Implementations of the multi-grid FAS method in CN-MG.** In this subsection, we explain in detail the implementations of solving Eq. (2.10) using the FAS method [3]. As mentioned in the Section 2.2, a nonlinear system Eq. (2.10) with $(m \times N)$ unknowns has to be solved at each time step. The system can be rewritten in the general form

$$A\mathbf{u} = \mathbf{f} \tag{2.13}$$

where A is a linear or nonlinear operator, $\mathbf{u} = (u_1; u_2; \cdots; u_N)$, and $u_j \in R^m, 1 \le j \le N$. Let Ω^h denote the grid with grid size h, which is the total length of the domain divided by N. If $N = 2k$ for some integer k, Ω^{2h} then represents a coarse grid imbeded in Ω^h with grid size $2h$. The two-grid FAS method for solving system (2.13) is outlined here:

1. Relax ν_1 times on $A^h\mathbf{u}^h = \mathbf{f}^h$ on Ω^h with initial guess $\mathbf{v}^h$.
2. Restrict the current approximation and its fine-grid residual to the coarse grid Ω^{2h}: $\mathbf{r}^{2h} = I_h^{2h}(\mathbf{f}^h - A^h(\mathbf{v}^h))$ and $\mathbf{v}^{2h} = I_h^{2h}\mathbf{v}^h$.
3. Solve the coarse-grid problem $A^{2h}(\mathbf{u}^{2h}) = A^{2h}(\mathbf{v}^{2h}) + \mathbf{r}^{2h}$.
4. Compute the coarse-grid approximation to the error: $\mathbf{e}^{2h} = \mathbf{u}^{2h} - \mathbf{v}^{2h}$.
5. Interpolate the error approximation up to the fine grid and correct the current fine-grid approximation: $\mathbf{v}^h \leftarrow \mathbf{v}^h + I_{2h}^h\mathbf{e}^{2h}$.
6. Relax ν_2 times on $A^h\mathbf{v}^h = \mathbf{f}^h$ on Ω^h with initial guess $\mathbf{v}^h$.

where I_h^{2h} and I_{2h}^h are restriction and interpolation operators, and the superscript h or $2h$ indicates the operators or variables on the corresponding grid. The number of relaxations ν_1, ν_2 are chosen depending on the problem for the best efficiency. Furthermore, if $N = 2^L$, there is a series of grids $\{\Omega^{2^l h}, l = 0, \cdots, L\}$, and the two-grid FAS can be applied to multi-grid by imbedding the two-grid scheme within itself. More details about the various implementations of the multi-grid scheme can be found in [3].

In step 1, 3 and 6, one needs to use Gauss-Seidel relaxation scheme for the nonlinear system $\mathcal{G}(\mathbf{u}) = \mathbf{0}$ where $\mathcal{G} = (g_1; g_2; \cdots; g_N), g_j \in R^m, 1 \le j \le N$. Let $u^k = (u_1^k; u_2^k; \cdots; u_N^k)$ denote the k-th step during the iteration, the Gauss-Seidel relaxation can be outlined as

$k = 0$;
Given a initial guess for $\mathbf{u}^0$;
While $||\mathbf{u}^k - \mathbf{u}^{k-1}|| > \varepsilon$ or $k = 0$
    $k = k + 1$;
    for $l = 1$ to N
        solve $g_l(u_1^k, \cdots, u_{l-1}^k, u_l^k, u_{l+1}^{k-1} \cdots; u_N^{k-1}) = 0$ for u_l^k;
    end
end

In the inner part of the above loop, one needs to solve a nonlinear system at each grid point with m unknowns and m equations. We use either Newton's method or

a fixed point iteration [14, 15] to solve this system. For example, Eq. (2.12) is of a form convenient for a fixed point iteration.

3. Numerical results.

In this section, we will compare the accuracy and efficiency of IIF2 and CN-MG when they are applied to a test reaction-diffusion system and a morphogen system in developmental biology.

3.1. A test problem.

First, we test both algorithms for a one-dimensional reaction-diffusion system with known analytical solutions. The equations are

$$\begin{aligned} u_t &= d\ u_{xx} - a\ u + v \\ v_t &= d\ v_{xx} - b\ v \end{aligned} \tag{3.14}$$

on $(0, \frac{\pi}{2})$ with boundary conditions

$$u_x(0,t) = 0, \quad v_x(0,t) = 0, \quad u(\frac{\pi}{2}, t) = 0, \quad v(\frac{\pi}{2}, t) = 0.$$

The exact solutions of the system are

$$u(x,t) = \left(e^{-(a+d)t} + e^{-(b+d)t}\right)\cos(x)\ , \qquad v(x,t) = (a-b)\ e^{-(b+d)t}\cos(x).$$

TABLE 3.1. Error, order of accuracy, and CPU time for a diffusion dominated case: $(a, b, d) = (0.1, 0.01, 1)$.

	CN-MG				IIF2		
Δt	L^∞ error	order	CPU time	Δt	L^∞ error	order	CPU time
0.04	1.09E-04	-	0.16	1	2.73E-05	-	0.009
0.02	2.67E-05	2.02	0.31	0.5	6.40E-06	2.09	0.017
0.01	6.27E-06	2.09	0.57	0.25	1.19E-06	2.42	0.033
0.005	1.16E-06	2.43	1.02	0.125	1.07E-07	3.48	0.065

Because the reaction terms in Eq. (3.14) are linear, the nonlinear systems in IIF2 can be solved analytically. Similarly, in CN-MG the analytical solution of the local nonlinear system is constructed at each level of the multi-grid method during every time step. In CN-MG, the tolerance for convergence of the multi-grid solver is taken as 10^{-10}.

For the spatial discretization on the Laplacian operator, we use a second-order central difference with a consistent approximation on the no-flux boundary condition at $x = 0$. In all the numerical experiments, the spatial grid is set to be fine enough such that the errors are dominated by those from the time integration. From the numerical tests, it is found $N = 512$ is sufficient, and all the results presented for the test problem are based on $N = 512$. The errors between the numerical solutions and the exact solutions are evaluated at $t = 1$. The calculations are performed on Opteron CPUs of 1.4GHz and 1GB memory, and the CPU time are presented with a unit of second in this paper.

To study how both algorithms behave under different situations, we examine several sets of parameters (a, b, d) in equation (3.14). First, we take $(a, b, d) = (0.1, 0.01, 1)$, a diffusion dominated case. In IIF2 the time integration of the diffusion term should be exact when the reaction term is zero, i.e. $a = b = 0$. In CN-MG, however, the time integration is only treated approximately. Therefore, for the case with relatively small reactions we expect IIF2 have better accuracy than CN-MG.

This is the case as seen in Table (3.1). In IIF2 very small errors are achieved even for a Δt as large as one. In contrast, it takes $\Delta t = 0.02$ for CN-MG to reach an error of the same size. Overall, the CN-MG needs time steps that are a factor of 50 times smaller than IIF2 to achieve the same accuracy. Consequently, IIF2 is much more efficient than CN-MG for a diffusion-dominated case.

Next, a reaction dominated case $(a, b, d) = (2, 1, 10^{-3})$ is considered. In this case, the two methods produce similar errors using the same Δt, as demonstrated in Table (3.2). Because the errors are dominated by approximation of the reaction terms in this case, the two methods with a similar treatment on reactions are expected to have similar accuracy. However, CN-MG usually takes less CPU time than IIF2 to achieve the same level of accuracy since all IF and ETD type of schemes (see Eq. (2.4)), including IIF2, need a global matrix-vector multiplication of an order of N^2 at each time step. In IIF2, the CPU time is doubled when Δt is halved, as expected, while the CPU time for CN-MG increases slower than linear as seen in Table (3.2). It is observed that the multi-grid method in CN-MG needs a smaller number of iteration to converge for a smaller time-step. In the CN-MG implementation, we always use the solution at the previous time step as the initial guess for the multi-grid iteration. As a result, a smaller Δt results in a better initial guess, consequently a smaller number of iterations. Of course, this initial guess can be improved if one uses extrapolation through the solutions at previous time steps.

TABLE 3.2. Error, order of accuracy, and CPU time for a reaction dominated case: $(a, b, d) = (2, 1, 0.001)$.

	CN-MG			IIF2		
Δt	L^∞ error	order	CPU time	L^∞ error	order	CPU time
0.04	1.94E-04	-	0.06	1.93E-04	-	0.20
0.02	4.84E-05	2.00	0.09	4.83E-05	2.00	0.40
0.01	1.21E-05	2.00	0.13	1.21E-05	2.00	0.80
0.005	3.02E-06	2.00	0.23	3.02E-06	2.00	1.63

Lastly, we study $(a, b, d) = (100, 1, 10^{-3})$, which is a reaction dominated case with stiff reaction. In Table (3.3), the overall behavior of IIF2 and CN-MG is similar to the reaction dominated case shown in Table (3.2). Because both schemes are unconditionally stable, they exhibit second order of accuracy even for relatively large Δt similar to the non-stiff cases. However, the magnitude of errors for both schemes are larger (around a factor of 25) than the non-stiff case in Table (3.2) because of a much larger coefficient in front of the reaction term: $a = 100$, compared to $a = 2$ in Table (3.2).

3.2. **A morphogen system.** In this section, we apply both IIF2 and CN-MG to a system of nonlinear reaction-diffusion equations arising from modeling morphogen gradients in developmental biology. The system, also studied in [21], describes how Dally-like protein (*Dlp*) regulates Wingless (*Wg*) morphogen distribution in an imaginal disc of *Drosophila* [10, 12].

In the model, $[L], [LR], [N^*]$ and $[LN^*]$ denote the concentration of *Wg*, *Wg-D-fz2* (a ligand-receptor complex), the enzymatic modification of *Dlp*, and the complex produced by interaction between *Wg* and the enzymatic modification of *Dlp* respectively; $\bar{V}_L$ and $\bar{V}_N$ represent the production rate of L and N^* respectively;

TABLE 3.3. Error, order of accuracy, and CPU time for a stiff reaction case: $(a, b, d) = (100, 1, 0.001)$.

	CN-MG			IIF2		
Δt	L^∞ error	order	CPU time	L^∞ error	order	CPU time
0.04	4.87E-03	-	0.06	4.89E-03	-	0.21
0.02	1.22E-03	2.00	0.10	1.21E-03	2.00	0.41
0.01	3.04E-04	2.00	0.16	3.03E-04	2.00	0.81
0.005	7.60E-05	2.00	0.25	7.58E-05	2.00	1.63

$\{K_{on}, J_{on}\}$, $\{K_{off}, J_{off}\}$, and $\{K_{deg}, J_{deg}\}$ denote binding rates, off rates, and degradation rates respectively. The interaction relationship among those components is illustrated in [21].

The three diffusive species $[L], [N^*]$ and $[LN^*]$ are assumed with the same diffusion coefficient D. The total amount of receptor *D-fz2*, denoted by R_0, is assumed fixed [19]. The mid-point of the *Wg* production region, the dorsal-ventral boundary, is denoted as $-\bar{d}$ ([16, 17]) while the edge of the imaginal wing disc in the dorsal-ventral direction is denoted as $X_{\max}$. The governing equations for the four quantities in $(-\bar{d}, X_{\max})$ then have the following form [21]:

$$\begin{aligned}
\frac{\partial [L]}{\partial T} &= D\frac{\partial^2 [L]}{\partial X^2} - K_{on}[L]\cdot(R_0 - [LR]) \\
&+ K_{off}[LR] - J_{on}[L]\cdot[N^*] + (J_{off} + J_{deg})[LN^*] + \bar{V}_L(X), \quad (3.15)\\
\frac{\partial [LR]}{\partial T} &= K_{on}[L]\cdot(R_0 - [LR]) - (K_{off} + K_{deg})[LR], \quad (3.16)\\
\frac{\partial [LN^*]}{\partial T} &= D\frac{\partial^2 [LN^*]}{\partial X^2} + J_{on}[L]\cdot[N^*] - (J_{off} + J_{deg})[LN^*], \quad (3.17)\\
\frac{\partial [N^*]}{\partial T} &= D\frac{\partial^2 [N^*]}{\partial X^2} - J_{on}[L]\cdot[N^*] + J_{off}[LN^*] + \bar{V}_N(X). \quad (3.18)
\end{aligned}$$

The boundary conditions at $X = -\bar{d}$ are

$$\frac{\partial [L]}{\partial X}(T, -\bar{d}) = 0, \qquad \frac{\partial [LN^*]}{\partial X}(T, -\bar{d}) = 0, \qquad \frac{\partial [N^*]}{\partial X}(T, -\bar{d}) = 0.$$

The boundary conditions at $X = X_{\max}$ are

$$L(T, X_{\max}) = 0, \qquad [LN^*](T, X_{\max}) = 0, \qquad [N^*](T, X_{\max}) = 0.$$

In the *Wg* production region $[-\bar{d}, 0]$, $\bar{V}_L(X) = v_L$, where v_L is a constant. For $X \in (0, X_{\max})$, $\bar{V}_L(X) = 0$. Because *Dlp* is produced everywhere, $\bar{V}_N(X) = v_N$ in $(-\bar{d}, X_{\max})$ with v_N as a constant.

We use a same set of parameters given in [21]: $X_{\max} = 0.02$ cm; $\bar{d} = 0.00125$ cm; $D = 8.5\times10^{-7}$ cm^2/s; $K_{on} = 0.12\,\text{s}^{-1}\mu\text{M}^{-1}$; $K_{off} = 1.0\times10^{-5}\,\text{s}^{-1}$; $K_{deg} = 5\times10^{-4}$ s^{-1}; $J_{on} = 285$ s$^{-1}\mu$M^{-1}; $J_{off} = 4\times10^{-6}$ s^{-1}; $J_{deg} = 0.54$ s^{-1}; $v_L = 8\times10^{-4}$ s$^{-1}\mu$M; $v_N = 2\times10^{-3}$ s$^{-1}\mu$M; $R_0 = 1$ μM. e solutions of the system was presented in [21]. re we mainly compare the efficiency of IIF2 and CN-MG.

The implementation of CN-MG is similar to that for the linear system described above, except that a nonlinear system of four unknowns in a form of (2.12) needs to be solved at each grid point during each time step. Here, we use two different approaches to solve the local small nonlinear system at each grid point: a fixed point

iteration or a Newton's method. In both nonlinear solvers, the iteration tolerance is taken as 10^{-10}. In the Newton solver, LAPACK is used to solve the linear system involving the Jacobian.

Table (3.4) displays the CPU time of CN-MG (with either a fixed point or a Newton's method) and IIF2, in which a fixed point iteration method [21] is used to solve the local nonlinear system. As seen in the table, when the time step size is too large, both IIF2 and CN-MG with a fixed point iteration do not converge, but CN-MG with a Newton solver converges. Various numerical tests suggest that this is not due to the stability condition since both methods are unconditionally stable. It is found that the fixed point iteration, which usually is efficient and easy to implement, is sensitive to its initial guess for convergence. When the size of time step is large, the solution at its previous time step, which is used as the initial guess for the fixed point iteration of (2.12) at its current step, is not as good as the case for a smaller time step. This is also the case for IIF2. As a result, the fixed point iteration procedure does not converge at some time during the course of temporal update in either IIF2 or CN-MG. In contrast, the CN-MG with a Newton solver seems to be more robust, and it converges for all time steps tested in Table (3.4).

Although the CN-MG with a Newton solver is robust in terms of convergence, it takes the most CPU time among all three implementations as seen in Table (3.4). For the cases with convergent solutions, the CN-MG with a fixed point iteration usually takes less CPU time than IIF2. When N is doubled, the CPU time for IIF2 increases by a factor of four because in any IF and ETD method the exact treatment of diffusion leads to matrix-vector multiplications with an order of N^2 computational complexity [21]. This is not the case for CN-MG, in which the dominated cost comes from solving the nonlinear systems. When N is doubled in both CN-MG methods, the CPU time increases only by a factor of two to three depending on the size of time steps. Clearly, all three implementations can be improved if better nonlinear solvers and better initial guesses are incorporated for the iterative methods.

TABLE 3.4. CPU time (seconds) for IIF2 and CN-MG for a morphogen system up to $T = 1800$; "NC" stands for no convergence of the method.

	CN-MG (fixed point)		CN-MG (Newton)		IIF2	
Δt	$N = 64$	$N = 128$	$N = 64$	$N = 128$	$N = 64$	$N = 128$
2×10^{-1}	NC	NC	32.61	94.61	NC	NC
1×10^{-1}	2.95	9.82	39.66	135.37	NC	NC
5×10^{-2}	5.36	18.17	71.74	245.77	7.78	27.03
2×10^{-2}	11.94	25.93	153.83	363.35	19.61	65.90
1×10^{-2}	23.31	48.92	294.52	670.12	39.54	131.49
5×10^{-3}	45.55	91.24	557.08	1171.54	78.02	268.67

4. **Conclusion.** In this paper, we have presented an unconditionally stable scheme of second order for the stiff reaction diffusion equations. In this method, the diffusion and reaction terms are treated implicitly using the Crank-Nicholson scheme, and the nonlinear system arising from such implicit approximation is solved by a nonlinear multi-grid method. Through numerical simulations of a test problem and

a nonlinear system arising from modelling morphogen gradients in developmental biology, we have compared this fully implicit method (CN-MG) with a semi-implicit integration factor method (IIF2). It was found that both methods are accurate and robust. For diffusion-dominated systems, the IIF2 method clearly has better performance because of its exact treatment of diffusion; For reaction-dominated systems, the CN-MG and the IIF2 have similar accuracy for time steps of the same size; however CN-MG is more efficient when the spatial mesh size is small. This is due to a relatively more expensive calculation on the diffusion terms in IIF2 compared to a simple implicit approximation on diffusions in CN-MG. Because both methods handle reactions in a similar fashion, the advantage of IIF2 is significant only when the diffusion term is large enough.

Acknowledgement. This research work was supported by the NSF DMS-0511169 Grant, NIH/NSF initiatives on Mathematical Biology through Grants R01GM57309 and R01GM67247 from the National Institute of General Medical Science, and NSFC Grants 10601029 and 60573168.

REFERENCES

[1] G. Beylkin and J. M. Keiser, *On the adaptive numerical solution of nonlinear partial differential equations in wavelet bases*, J. Comput. Phys., **132** (1997), 233–259.
[2] G. Beylkin, J. M. Keiser and L. Vozovoi, *A new class of time discretization schemes for the solution of nonlinear PDEs*, J. Comput. Phys., **147** (1998), 362–387.
[3] W.L. Briggs, V.E. Henson and S.F. McCormick, "A Multigrid Tutorial," SIAM, 2000.
[4] B. Gustafsson, H.-O. Kreiss and J. Oliger, "Time Dependent Problems and Difference Methods," John Wiley & Sons, Inc, 1995.
[5] S. M. Cox and P. C. Matthews, *Exponential time differencing for stiff systems*, J. Comput. Phys., **176** (2002), 430–455.
[6] Q. Du and W. Zhu, *Stability analysis and applications of the Exponential Time Differencing Schemes*, J. Comput. Math., **22** (2004), 200.
[7] Q. Du and W. Zhu, *Modified exponential time differencing schemes: analysis and applications*, BIT, Numer. Math., **45** (2005), 307–328.
[8] Q. Du and W. Zhu, *Exponential time differencing Schemes for parabolic equations: stability analysis and applications*, SIAM J. Numer. Anal., submitted.
[9] T.Y. Hou, J.S. Lowengrub and M.J. Shelley, *Removing the stiffness from interfacial flows with surface tension*, J. Comput. Phys., **114** (1994), 312.
[10] H.J. Jou, P.H. Leo and J.S. Lowengrub, *Microstructural evolution in inhomogeneous elastic media*, J. Comput. Phys., **131** (1997), 109.
[11] J.Kao, Q.Nie, A.Teng, F.Y.M.Wan, A.D. Lander, J.L.Marsh, *Can Morphogen Activity be Enhanced by Its Inhibitors?*, Proceedings of 2nd MIT Conference on Computational Mechanics, (2003), 1729–1733.
[12] G.E. Karniadakis, M. Israeli and S.A. Orszag, *High order splitting methods for the incompressible Navier-Stodes equations* J. Comput. Phys., **97** (1991), 414.
[13] A.-K. Kassam and L. N. Trefethen, *Fourth-order time stepping for stiff PDEs*, SIAM J. Sci. Comp., **26** (2005), 1214–1233.
[14] C.T. Kelly, "Iterative Methods for Linear and Nonlinear Equations," SIAM, Philadelphia, 1995.
[15] C.T. Kelly, "Solving Nonlinear Equations with Newton's Method," SIAM, Philadelphia, 2003.
[16] A. Lander and Q. Nie and F. Wan, *Do Morphogen gradients arise by diffusion?*, Developmental Cell, **2** (2002), 785–796.
[17] A. Lander and Q. Nie and F. Wan, *Spatially Distributed Morphogen Production and Morphogen gradient Formation*, Mathematical Biosciences and Engineering, **2** (2005), 239–262.
[18] P.H. Leo, J.S. Lowengrub and Qing Nie, *Microstructural Evolution in Orthotropic Elastic Media* , Journal of Computational Physics, **157** (2000), 44–88.
[19] Y. Lou, Q. Nie and F. Wan, *Effects of Sog on Dpp-Receptor Binding*, SIAM J. on Applied Math.", **66** (2005), 1748–1771.

[20] C.M. Mizutani, Q. Nie, F. Wan, Y.-T. Zhang, P. Vilmos, R. Sousa-Neves, E. Bier, L. Marsh and A. Lander, *Formation of the BMP activity gradient in the Drosophila embryo*, Developmental Cell, **8** (2005), 915-924.

[21] Q. Nie, Y.-T. Zhang and R. Zhao, *Efficient semi-implicit schemes for stiff systems*, Journal of Computational Physics, **214** (2006), 521-537.

[22] J.M. Ortega and W.C. Rheinboldt, "Iterative Solution of Nonlinear Equations in Several Variables," Academic Press, San Diego, 1970. Reprinted as vol. 30, Classics in Applied Mathematics, SIAM, Philadelphia, 2000.

Received October 2006; revised January 2007.

E-mail address: cschou@math.uci.edu
E-mail address: yzhang10@nd.edu
E-mail address: rzhao@math.uci.edu
E-mail address: qnie@math.uci.edu