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Numerical Modeling for Nonlinear Biochemical Reaction Networks

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ABSTRACT

Nowadays, numerical models have great importance in every field of science, especially for solving the nonlinear differential equations, partial differential equations, biochemical reactions, etc. The total time evolution of the reactant concentrations in the basic enzyme-substrate reaction is simulated by the Runge-Kutta of order four (RK4) and by Non-standard finite difference (NSFD) method. ANSFD model has been constructed for the biochemical reaction problem and numerical experiments are performed for different values of discretization parameter 'h'. The results are compared with the well–known numerical scheme, i.e. RK4. Unlike RK4 which fails for large time steps, the developed scheme NSFD gives results that converge to true steady states for any time step used.

1. INTRODUCTION AND PRELIMINARIES

In this paper, we consider the well-known Michaelis-Menten biochemical reaction model [1], i.e., the single enzyme substrate reaction scheme

$$E + A \rightleftharpoons Y \longrightarrow E + X, \tag{1}$$

where E is the enzyme, A the substrate, Y the intermediate complex and X the product. The time evolution of scheme (1) can be determined from the solution of the system of coupled nonlinear ODE [2].

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$$\frac{dA}{dE} = -k_1 EA + k_{-1} Y\,, \tag{2}$$

$$\frac{dE}{dt} = -k_1 EA + (k_{-1} + k_2)Y, \tag{3}$$

$$\frac{dY}{dt} = k_1 EA - (k_{-1} + k_2)Y, \tag{4}$$

$$\frac{dX}{dt} = k_2 Y, \tag{5}$$

subject to the initial conditions

$$A(0) = A_0, E(0) = E_0, Y(0) = 0, X(0) = 0 \tag{6}$$

where the parameters k_1, k_{-1} and k_2 are positive rate constants for each reaction. Systems (2) – (5) can be reduced to only two equations for A and Y and in dimensionless form of concentrations of substrate x, and intermediate complex between enzyme and substrate$y$, are given by [2].

$$\frac{dx}{dt} = -x + (\beta - \alpha)y + xy \tag{7}$$

$$\frac{dy}{dt} = \frac{1}{\sigma}(x - \beta y - xy) \tag{8}$$

subject to the initial conditions

$$x(0) = 1, y(0) = 0 \tag{9}$$

where α,β and σ are dimensionless parameters.

The time evolution of the reaction can be determined from the traditional purely numerical methods like the classical fourth order Runge-Kutta method (RK4), but we are interested in this work to solve the system of coupled nonlinear ODEs (7) and (8) by using NSFD. To do so, we proceed as follows:

1.1 EQUILIBRIUM POINT

To calculate equilibrium point, equate (7) and (8) equal to zero i.e,

$$-x + (\beta - \alpha)y + xy = 0 \tag{10}$$

$$\frac{1}{\sigma}(x - \beta y - xy) = 0 \tag{11}$$

we obtain $(x^*, y^*) = (0,0)$,that is the equilibrium point.

2. RK4 METHOD

In this section, we solve the systems (7) and (8) by RK4 Scheme as follows:

$$
\begin{aligned}
k_1 &= h(-x_n + (\beta-\alpha)y_n + x_n y_n) \\
m_1 &= \frac{h}{\sigma}(x_n - \beta y_n - x_n y_n) \\
k_2 &= h[-(x_n + \frac{k_1}{2}) + (\beta-\alpha)(y_n + \frac{m_1}{2}) + (x_n + \frac{k_1}{2})(y_n + \frac{m_1}{2})] \\
m_2 &= \frac{h}{\sigma}[(x_n + \frac{k_1}{2}) - \beta(y_n + \frac{m_1}{2}) - (x_n + \frac{k_1}{2})(y_n + \frac{m_1}{2})] \\
k_3 &= h[-(x_n + \frac{k_2}{2}) + (\beta-\alpha)(y_n + \frac{m_2}{2}) + (x_n + \frac{k_2}{2})(y_n + \frac{m_2}{2})] \\
m_3 &= \frac{h}{\sigma}[(x_n + \frac{k_2}{2}) - \beta(y_n + \frac{m_2}{2}) - (x_n + \frac{k_2}{2})(y_n + \frac{m_2}{2})] \\
k_4 &= h[-(x_n + k_3) + (\beta-\alpha)(y_n + m_3) + (x_n + k_3)(y_n + m_3)] \\
m_4 &= \frac{h}{\sigma}[(x_n + k_3) - \beta(y_n + m_3) - (x_n + k_3)(y_n + m_3)]
\end{aligned}
$$

$$x_{n+1} = x_n + \frac{1}{6}[k_1 + 2k_2 + 2k_3 + k_4] \tag{12}$$

$$y_{n+1} = y_n + \frac{1}{6}[m_1 + 2m_2 + 2m_3 + m_4] \tag{13}$$

2.1 NUMERICAL EXPERIMENTS

Numerical experiments are performed using values of parameters given in Table 2.1.

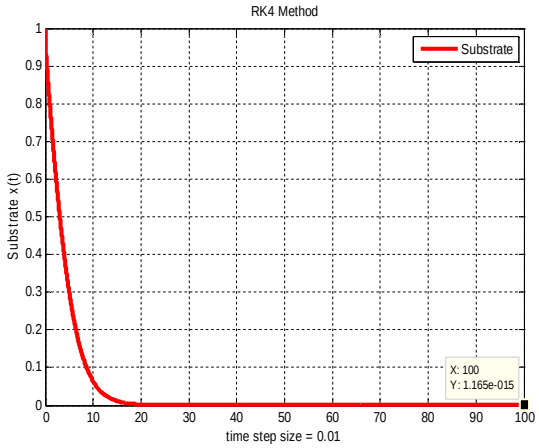

Figure 2.1. Concentration of Substrate.

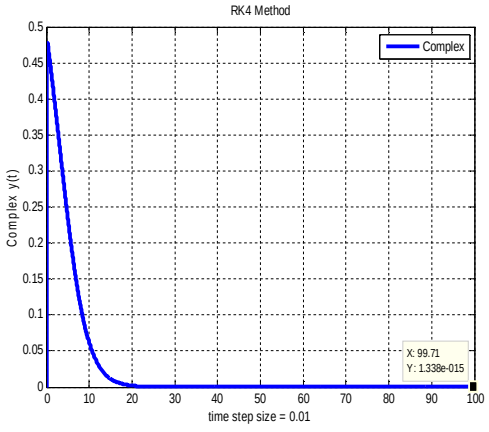

Figure 2.2. Concentration of Intermediate Complex between Enzyme and Substrate.

Table 2.1. The Parameters α, β and σ.

Parameters	Value
α	0.375
β	1
σ	0.1

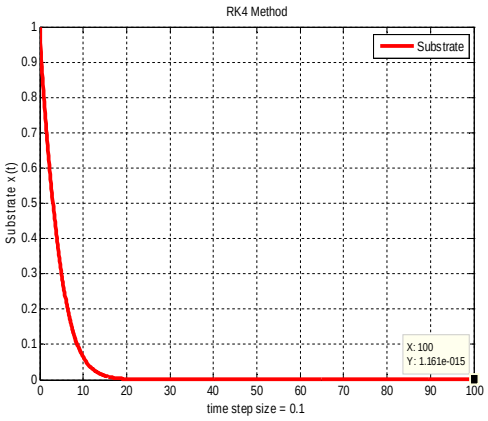

Figure 2.3. Concentration of Substrate.

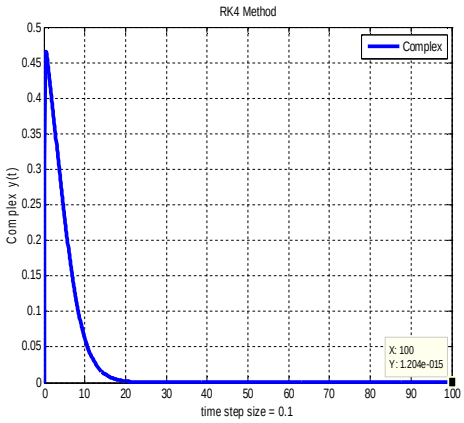

Figure 2.4. Concentration of Intermediate Complex between Enzyme and Substrate.

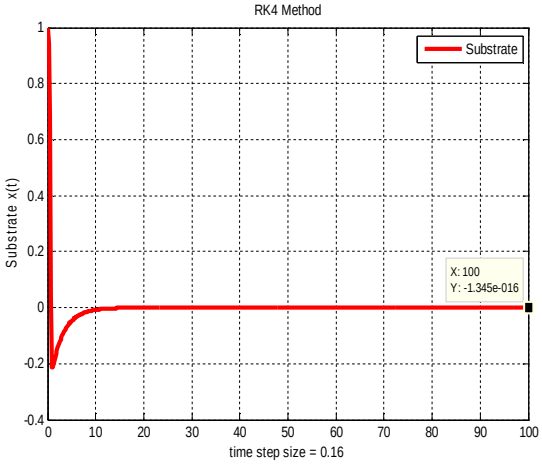

Figure 2.5. Concentration of Substrate.

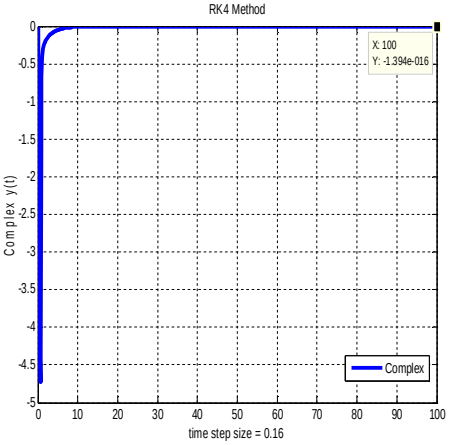

Figure 2.6. Concentation of Intermediate Complex between Enzyme and Substrate.

3. NONSTANDARD FINITE DIFFERENCE METHOD

In this section we shall construct Non-Standard Finite Difference Scheme for the equations (7) and (8). First order time derivatives are described by using forward difference approximation [4, 5]. $\dot{f}(t)$ can be approximated as

$$\frac{df(t)}{dt} = \lim_{l \to 0} \frac{f(t+l) - f(t)}{l} + O(l)$$

x^n and y^n are the approximations of $x(nl)$ and $y(nl)$, for $n = 0,1,2, \ldots,$ and where 'l' is step size of time. For satisfying biological nature of the continuous time model, it should be non–negative. The numerical method which has been developed to solve the system must hold Conservation law proposed by Mickens [6, 7]. To construct the NSFD scheme for system (7)−(8) we note the following statements

(i) The linear and nonlinear terms on the right hand side of Equation (7) are in the form $-x \approx -x^{n+1}$, $(\beta - \alpha)y \approx (\beta - \alpha)y^n$, $xy \approx x^n y^n$

(ii) The linear and nonlinear terms on the right hand side of Equation (8) are in the form $x \approx x^n$, $-\beta y \approx -\beta y^{n+1}$, $-xy \approx -x^n y^{n+1}$

So,

$$\frac{x^{n+1} - x^n}{h} = -x^{n+1} + (\beta - \alpha)y^n + x^n y^n \tag{14}$$

$$\frac{y^{n+1} - y^n}{h} = \frac{1}{\sigma}\{x^n - \beta y^{n+1} - x^n y^{n+1}\} \tag{15}$$

Eq. (14) implies that

$$x^{n+1} = \frac{x^n + h\{(\beta - \alpha)y^n + x^n y^n\}}{1 + h} \tag{16}$$

and Eq. (15) implies that

$$y^{n+1} = \frac{y^n + \frac{h}{\sigma}x^n}{1 + \frac{h\beta}{\sigma} + \frac{h}{\sigma}x^n}.$$

3.1 CONVERGENCE ANALYSIS

The stability and convergence of the proposed NSFD scheme about equilibrium point (0,0) are discussed here. Let

$$F = \frac{x + h\{(\beta - \alpha)y + xy\}}{1 + h},$$

$$G = \frac{y + \frac{h}{\sigma}x}{1 + \frac{h\beta}{\sigma} + \frac{h}{\sigma}x},$$

and the Jacobian matrix is

$$J(F^*)=\begin{bmatrix}\frac{\partial F}{\partial x} & \frac{\partial F}{\partial y}\\ \frac{\partial G}{\partial x} & \frac{\partial G}{\partial y}\end{bmatrix}$$

where as

$$\frac{\partial F}{\partial x}=\frac{1+hy}{1+h},\quad \frac{\partial F}{\partial y}=\frac{h\{(\beta-\alpha)+x\}}{1+h},$$

$$\frac{\partial G}{\partial x}=\frac{(1+\frac{h\beta}{\sigma}+\frac{h}{\sigma}x)\frac{h}{\sigma}}{(1+\frac{h\beta}{\sigma}+\frac{h}{\sigma}x)^2},\quad \frac{\partial G}{\partial y}=\frac{1}{1+\frac{h\beta}{\sigma}+\frac{h}{\sigma}x}$$

At $(x^*,y^*)=(0,0)$ we have

$$\frac{\partial F}{\partial x}=\frac{1}{1+h},\quad \frac{\partial F}{\partial y}=\frac{h(\beta-\alpha)}{1+h},\quad \frac{\partial G}{\partial x}=\frac{\frac{h}{\sigma}}{(1+\frac{h\beta}{\sigma})},\quad \frac{\partial G}{\partial y}=\frac{1}{1+\frac{h\beta}{\sigma}}.$$

Define,

$$J=\begin{bmatrix}\frac{1}{1+h} & \frac{h(\beta-\alpha)}{1+h}\\ \frac{\frac{h}{\sigma}}{(1+\frac{h\beta}{\sigma})} & \frac{1}{1+\frac{h\beta}{\sigma}}\end{bmatrix}.$$

Lemma [11]: For the quadratic equation $\mu^2-\mu A+B=0$, both roots satisfy $|\mu_i|<1; i=1,2$ if and only if the following conditions are satisfied:

(i) $1+B>A$

(ii) $1+A+B>0$

(iii) $B<1$

Let us define$A=trace(J)$ and $B=\det(J)$, where

$$trace(J)=\frac{1}{1+h}+\frac{1}{1+\frac{h\beta}{\sigma}}=\frac{2+h+\frac{h\beta}{\sigma}}{(1+h)(1+\frac{h\beta}{\sigma})}$$

and

$$\det(J)=\left(\frac{1}{1+h}\times\frac{1}{1+\frac{h\beta}{\sigma}}\right)-\left(\frac{h(\beta-\alpha)}{1+h}\times\frac{\frac{h}{\sigma}}{1+\frac{h\beta}{\sigma}}\right)=\frac{1-(\beta-\alpha)\frac{h^2}{\sigma}}{(1+h)(1+\frac{h\beta}{\sigma})}$$

The first condition of the Lemma is $1+B>A$, so by using the values of A and B we have

$$1+\frac{1-(\beta-\alpha)\frac{h^2}{\sigma}}{(1+h)(1+\frac{h\beta}{\sigma})}>\frac{2+h+\frac{h\beta}{\sigma}}{(1+h)(1+\frac{h\beta}{\sigma})}\Rightarrow(1+h)(1+\frac{h\beta}{\sigma})+1-(\beta-\alpha)\frac{h^2}{\sigma}>2+h+\frac{h\beta}{\sigma}$$

which proves that $h^2>0$.

The second condition of the Lemma is $1+A+B>0$, so by using the values of A and B we get

$$2+2h+2\frac{h\beta}{\sigma}+\frac{h^2\alpha}{\sigma}>0.$$

The third condition of the Lemma is $1>B$, so by using the values of A and B we obtain

$$h\alpha<\sigma+\beta+2h\beta\Rightarrow 0<\sigma+\beta+(2\beta-\alpha)h.$$

Since $h>0$ and all conditions of the theorem are true, the *System is Stable* for all values of h and converges to steady state.

3.2 NUMERICAL EXPERIMENTS

Numerical experiments are performed using values of parameters given in Table 2.1.

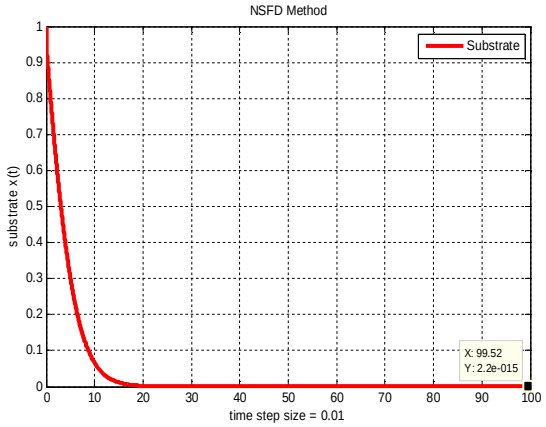

Figure 3.1. Concentration of Substrate.

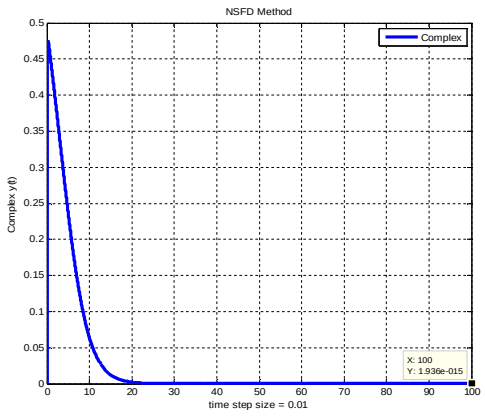

Figure 3.2. Concentration of Intermediate Complex between Enzyme and Substrate.

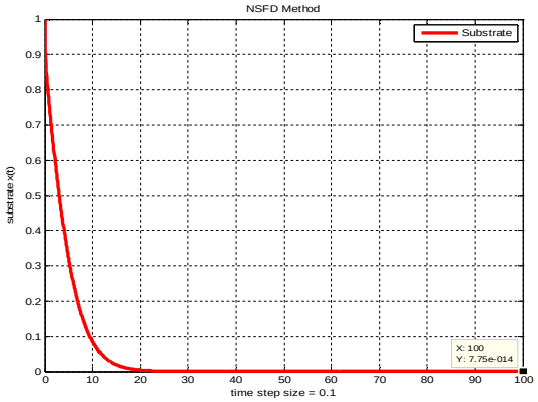

Figure 3.3. Concentration of Substrate.

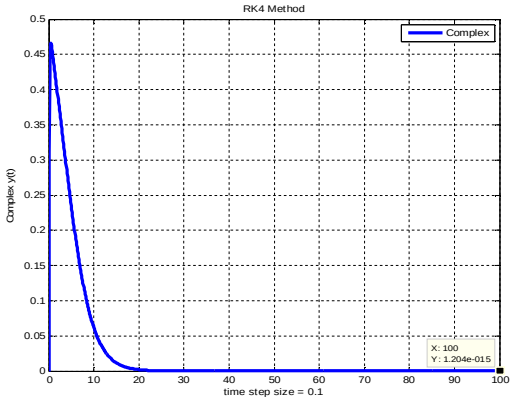

Figure 3.4. Concentration of Intermediate Complex between Enzyme and Substrate.

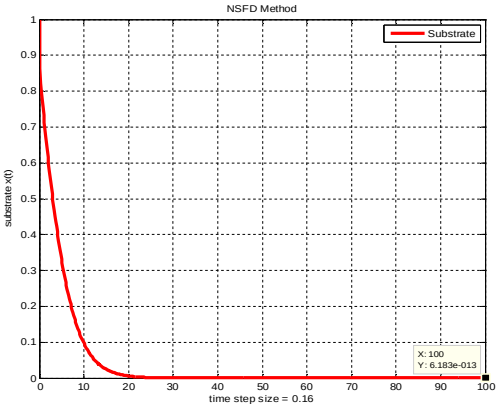

Figure 3.5. Concentration of Substrate.

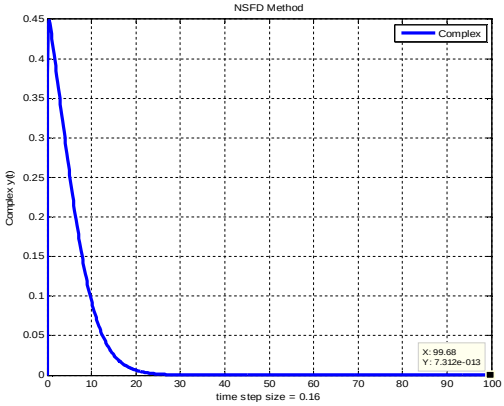

Figure 3.6. Concentration of Intermediate Complex between Enzyme and Substrate.

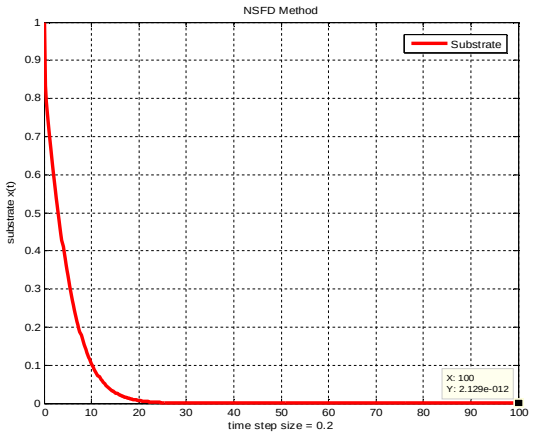

Figure 3.7. Concentration of Substrate.

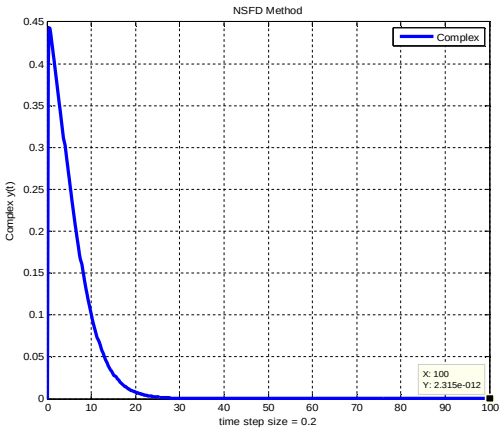

Figure 3.8. Concentration of Intermediate Complex between Enzyme and Substrate.

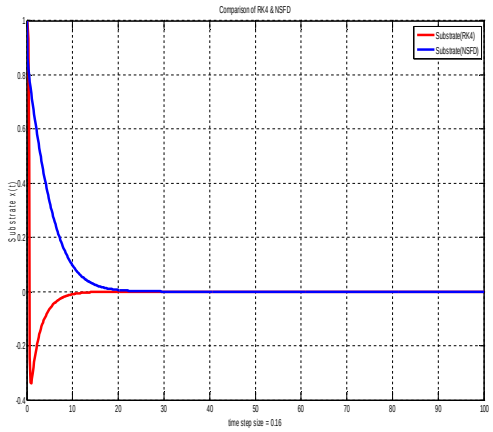

Figure 3.9. Comparison between NSFD and RK4.

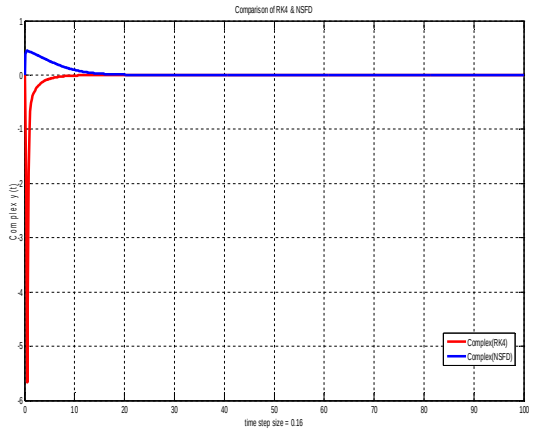

Figure 3.10. Comparison between NSFD and RK4.

4. RESULTS AND DISCUSSION

The Numerical modelling of well–known Michaelis–Menten non–linear reaction system has been analysed in this paper. The model has one equilibrium points. An unconditionally convergent non–standard finite difference numerical model has been constructed and numerical experiments are performed for different values of discretization parameter 'h'. Results are compared with well-known numerical method i.e. Runge–Kutta method of order four (RK4). Table 4.1 shows the effect of different time step, h for both numerical schemes.

Table 4.1. The Effect of Different Time Step.

h	RK4	Numerical Model
.01	Convergence	Convergence
0.1	Convergence	Convergence
0.16	Divergence(method failed)	Convergence
0.2	Divergence	Convergence
2	Divergence	Convergence
10	Divergence	Convergence
100	Divergence	Convergence

Table 4.1 shows that the RK-4 method converge for small values of parameter h and it diverges for the large values but our NSFD model will remain convergent even for a very

large value of discretization parameter i.e. $h = 1000$. It isto be noted that the authors of [11] solved this problem by multistage homotopy perturbation method and homotopy perturbation method. In both cases they statedthat the step size h should be very small otherwise the methods will diverge, but in our case, the step size is irrelevant.

5. CONCLUSION

Figures 3.9 and 3.10 show the comparison of NSFD scheme with Runge-Kutta method of order 4. It can be observed that when step size has been increased up to 0.16, the RK–4 scheme gives negative values of both concentrations, while the proposed NSFD scheme preserves positivity and convergence of the solution for these values of step size. Unlike RK-4 which fails for large time steps, the developed NSFD scheme gives results that converged to true steady states for any time step used. The proposed scheme is easy to implement and numerically stable.

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