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Model Reduction and Analysis for ERK Cell Signalling Pathway Using Implicit-Explicit Rung-Kutta Methods

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ABSTRACT

Many complex cell signalling pathways and chemical reaction networks include many variables and parameters; this is sometimes a big issue for identifying critical model elements and describing the model dynamics. Therefore, model reduction approaches can be employed as a mathematical tool to reduce the number of elements. In this study, we use a new technique for model reduction: the Lumping of parameters for the simple linear chemical reaction network and the complex cell signalling pathway that is extracellular-signal-regulated kinase (ERK) pathways. Moreover, we propose a high-order and accurate method for solving stiff nonlinear ordinary differential equations. The curtail idea of this scheme is based on splitting the problem into stiff and non-stiff terms. More specifically, stiff discretization uses the implicit method, and nonlinear discretization uses the explicit method. This is consequently leading to a reduction in the computational cost of the scheme.

The main aim of this study is to reduce the complex cell signalling pathway models by proposing an accurate numerical approximation Runge-Kutta method. This improves one's understanding of such behaviour of these systems and gives an accurate approximate solution. Based on the suggested technique, the simple model's parameters are minimized from 6 to 3, and the complex models from 11 to 8. Results show that there is a good agreement between the original models and the simplified models.

KEYWORDS: ERK Cell signalling pathways, Mathematical model, Runge-Kutta method, Model dynamics, Numerical simulation, Comparison simulations.

1 INTRODUCTION

Mathematical modelling is a helpful tool for describing the model dynamics of different cell signalling pathways. They may be expressed as equations with constant rates of change. While most of these systems are nonlinear and have many dimensional components, they require certain model simplifications and reductions to determine approximate analytical solutions and describe model dynamics. There are many methods and technique for model reduction, readers can see more applied techniques in [1-4]. Lumping of parameter technique is suggested to simplified the number of parameters in this study, and to evaluate the difference between the original and reduced models at each stage we use function of deviation, for more detail of this formulas readers can see [5]. In this study we work on the complex cell signalling pathways ERK pathway, the signalling system under investigation regulates ERK (extracellular signal-regulated kinase) signalling [6]. Furthermore, cell signalling pathway models can be modelled as system of stiff ordinary differential equations. The key idea of stiff problems is to give a great role in understanding and identifying these effects on the model dynamics. Because of their difficulties, most of these problems do not have exact analytic. Furthermore, these problems have very different time scales occurring simultaneously. Consequently, a lot of study has garnered interest, and over the years, a lot of numerical systems have been developed, such as Runge kutta method, Euler method, multistep methods [7-9], Finite difference method [10], Finite element methods [11]. Runge Kutta method is one of the most applicable methods for solving stiff problems. Disadvantages of the of these methods are not work well for stiff differential equations in spite of it is provide a good understanding for the model dynamical behaviour. In addition, we propose a method to avoid the difficulties that appear when the models of ERK cell signalling pathway transfer to stiff nonlinear equations with an implicit method. This method is called Implicit - Explicit (IMEX) schemes for more details [12-15]. Consider the numerical method of the following system of stiff ordinary differential equation:

$$\frac{\mathrm{d}\boldsymbol{u}}{\partial \mathrm{t}} = F\big(t, \boldsymbol{u}(t)\big) + G\big(t, \boldsymbol{u}(t)\big), \tag{1.1}$$

A main factor of the suggested technique is the separation of the right-hand side of (1) into stiff $\mathrm{F}(\mathrm{t}, \mathbf{u}(\mathrm{t}))$ and no stiff $\mathrm{G}(\mathrm{t}, \mathbf{u}(\mathrm{t}))$. Note that an explicit Runge-Kutta (*ERK*) method is used to solve the non-stiff part F and a diagonally implicit Runge-Kutta (*DIRK*) method is employed to solve the stiff part G. Popular family of IMEX schemes for DIRK and ERK terms take the follow form:

c_1	a_{11}	0	0	$\cdots$	0
c_2	a_{21}	a_{22}	0	$\cdots$	0
c_3	a_{31}	a_{32}	a_{33}	$\cdots$	0
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\ddots$	$\vdots$
c_s	a_{s1}	a_{s2}	a_{s3}	$\cdots$	a_{ss}
	b_1	b_2	b_3	$\cdots$	b_s

$\hat{c}_1$	0	0	0	$\cdots$	0
$\hat{c}_2$	$\hat{a}_{21}$	0	0	$\cdots$	0
$\hat{c}_3$	$\hat{a}_{31}$	$\hat{a}_{32}$	0	$\cdots$	0
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\ddots$	$\vdots$
$\hat{c}_s$	$\hat{a}_{s1}$	$\hat{a}_{s2}$	$\hat{a}_{s3}$	$\cdots$	0
	$\hat{b}_1$	$\hat{b}_2$	$\hat{b}_3$	$\cdots$	$\hat{b}_s$

Or

c	A
	$\mathfrak{b}^T$

$\hat{c}$	$\hat{A}$
	$\hat{\mathfrak{b}}^T$

(Ex) and (Im) are denoted to the explicit and implicit components. Implicit-Explicit scheme, defined by its Butcher coefficients $(A^{[Ex]}, A^{[Im]}, b^{[Ex]}, b^{[Im]}, c^{[Ex]}, c^{[Im]})$ is given by:

$$\boldsymbol{u}^{n+1} = \boldsymbol{u}^n + \Delta t \sum_{i=1}^{s} \left(b_i^{[Im]} \boldsymbol{k}_i^{[Im]} + b_i^{[Ex]} \boldsymbol{k}_i^{[Ex]} \right), \tag{1.2}$$

where $\boldsymbol{k}_i^{[Im]}$ and $\boldsymbol{k}_i^{[Ex]}$ are now the discrete equivalents of both the stiff as well as nonstiff operators, correspondingly in (1.2), F_s and F_{ns},

$$\boldsymbol{k}_i^{[Im]} = F\left(t_i + c_i \Delta t, \boldsymbol{u}_i(t)\right), \quad \boldsymbol{k}_i^{[Ex]} = G\left(t_i + c_i \Delta t, \boldsymbol{u}_i(t)\right),$$

and the stage values are defined as

$$\boldsymbol{u}_i = \boldsymbol{u}^n + \Delta t \sum_{j=1}^{s} \left(a_{ij} \boldsymbol{k}_i^{[Im]} + \hat{a}_{ij} \boldsymbol{k}_i^{[Ex]} \right). \tag{1.3}$$

Applying DIRK schemes for the implicit part, the above expression, gives

$$\boldsymbol{u}_i = \boldsymbol{u}^n + \Delta t \sum_{j=1}^{i-1} \left(a_{ij} \boldsymbol{k}_i^{[Im]} + \hat{a}_{ij} \boldsymbol{k}_i^{[Ex]} \right) + \Delta t a_{ii} \boldsymbol{k}_i^{[Im]}. \tag{1.4}$$

To deal with linear implicit part, we use

$$(\boldsymbol{I} - \Delta t a_{ii} \boldsymbol{K}) \boldsymbol{u}_i = \boldsymbol{u}^n + \Delta t \sum_{j=1}^{i-1} \left(a_{ij} \boldsymbol{k}_i^{[Im]} + \hat{a}_{ij} \boldsymbol{k}_i^{[Ex]} \right), \tag{1.5}$$

where $\boldsymbol{k}_i^{[Im]} = F\left(t_i + c_i \Delta t, \boldsymbol{u}_i(t)\right)$, $\boldsymbol{k}_i^{[Ex]} = G\left(t_i + c_i \Delta t, \boldsymbol{u}_i(t)\right)$.

This study focuses on two points; in the first one, we will use a good technique called lumping parameters for model reduction for the simple linear chemical reaction network and the complex cell signalling pathways ERK pathway. The model includes 11 variables and 11 parameters. The proposed technique has minimized the parameters from 11 to 8. Moreover, the second point is applying the robust and accurate numerical technique, the Runge-Kutta method, to simulate and compare the original and simplified ERK model. By computing, the numerical simulation results show that there is still a close agreement here between the numerical solutions of each variable in full and the reduced models.

2 LUMPING OF PARAMETERS

In this study we use a power full approach for model reduction which is based on the lumping of species technique[16]. This is used to minimize the number of constants (parameters). In the equation (2.1), we assume that this interval includes all parameters.

$$k_j \in [\beta_1, \beta_n] \in \mathbb{R}^+, \text{ for } \text{j=1,2, ..., m.} \tag{2.1}$$

We divide the current interval (2.1) in to the subintervals like follows to identify the most effective technique of parameter lumping:

$$[\beta_1, \beta_n] = \cup_{i=1}^{n-1}[\beta_i, \beta_{i+1}]. \tag{2.2}$$

Despite the fact that the suggested intervals might not be evenly spaced, they can be chosen under the condition that they are equally spaced.

$$|\beta_{i+1} - \beta_i| < \alpha; \alpha \in \mathbb{R}^+ \cup \{0\}.$$

Then a new parameter vector will be introduced such as follows.

$$k^* = ({k_1}^*, {k_2}^*, \dots, {k_{m1}}^*), m_1 \leq m\,,$$

While each component of k^* is described as follows:

$$k^* = \sum_{j \in \mathcal{J}} k_j \tag{2.3}$$

Where $\mathcal{J}$={1,2, . . . ,m}, and $i = 1,2,\dots,m_1$. This is referred to as a parameter lumping (constants). A lumping matrix M is defined as follows:

$$M = \begin{matrix} \\ {k^*}_1 \\ {k^*}_2 \\ \vdots \\ {k^*}_{m_1} \end{matrix} \begin{matrix} \begin{matrix} k_1 & k_2 & \cdots & k_m \end{matrix} \\ \begin{pmatrix} a_{11} & a_{12} & \cdots & a_{1m} \\ a_{21} & a_{22} & \cdots & a_{2m} \\ \vdots & \vdots & \ddots & \vdots \\ a_{m_1 1} & a_{m_1 2} & \cdots & a_{m_1 m} \end{pmatrix} \end{matrix}, \tag{2.4}$$

Where $a_{i\mathcal{J}} \in \{0,1\}$ for $i = 1,2,\dots,m_1$ and $\mathcal{J} = 1,2,\dots,m.$

This is an essential equation called parameter lumping transformation.

$$k^* = Mk \tag{2.5}$$

The initial parameter set k could be calculated using Eq. (2.1.5) as follows:

$$k = M^{+}k^{*} \tag{2.6}$$

where M^{+} is called pseudo-inverse matrix of M that is $MM^{+} = I$. Therefore, the Eq

$$\frac{dc}{dt} = \mathcal{H}(c, k^{*}) \tag{2.7}$$

The simplified model of the system with fewer parameters is equation (2.7). This method is a significant step forward in dimensionless for complex biological process networks [17].

3 APPLICATIONS:

This study aims to reduce the number of components in biochemical systems and cell signaling pathways by applying a new model reduction method. We use this strategy to reduce the number of parameters in simple chemical reactions and complex non-linear biological reaction models. We used the method on a typical non-linear model of a network of chemical reactions. The first case is a simple example that is a model with chemical reactions. The system has been minimized from 5 to 3 parameters based on the suggested technique. A complicated cell signaling system is the second model used in this study. This pathway is the ERK cell signal pathway [6, 18].

3.1 A simple chemical reaction network

In a simple chemical network model, the concept of lumping parameters can be easily implemented. Given a linear network containing 3 species with 6 parameters to further understand how this approach might be used [19].

$$x_1 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} 2x_2$$

$$x_1 + x_2 \underset{k_4}{\overset{k_3}{\rightleftharpoons}} x_3 \underset{k_6}{\overset{k_5}{\rightleftharpoons}} x_2$$

The stoichiometric vectors can be calculated as follows

$$\gamma_1 = \begin{pmatrix}1\\0\\0\end{pmatrix},\ \gamma_2 = \begin{pmatrix}-1\\0\\0\end{pmatrix},\ \gamma_3 = \begin{pmatrix}-1\\-1\\1\end{pmatrix},\ \gamma_4 = \begin{pmatrix}1\\1\\-1\end{pmatrix},\ \gamma_5 = \begin{pmatrix}0\\1\\-1\end{pmatrix},\ \gamma_6 = \begin{pmatrix}0\\-1\\1\end{pmatrix}$$

And the reaction rates are calculated

$$v_1 = k_1x_1\ ,\quad v_2 = k_2{x_1}^2,\ \ v_3 = k_3x_1x_2\ ,\ v_4 = k_4x_3\ ,\ v_5 = k_5x_3\ ,\ v_6 = k_6x_2\ .$$

$$\frac{d}{dt}\begin{pmatrix}x_1\\x_2\\x_3\end{pmatrix} = \sum_{i=1}^{6} v_i\gamma_i$$

Then the system of ordinary differential equation could be obtained:

$$\frac{dx_1}{dt} = k_1x_1 - k_2{x_1}^2 - k_3x_1x_2 + k_4x_3 \,,$$
$$\frac{dx_2}{dt} = -k_3x_1x_2 \; + k_4x_3 + k_5x_3 - k_6x_2 \,, \qquad (3.1.1)$$
$$\frac{dx_3}{dt} = k_3x_1x_2 - k_4x_3 - k_5x_3 + k_6x_2 \;\; .$$

Where $k_1 = 8.5$, $k_2 = \; k_3 = k_4 = k_5 = 1$, $k_6 = 0.2$.

Now by applying lumping technique as mentioned before, we make the following suppositions

$${k_1}^* = k_1 = 8.5$$
$${k_2}^* = k_2 + k_3 + k_4 + k_5 = 4$$
$${k_3}^* = k_6 = 0.2$$

Then we define the lumping matrix as follows:

$$M = \begin{matrix} k_1 & k_2 & k_3 & k_4 & k_5 & k_6 \end{matrix} \begin{matrix} {k_1}^* \\ {k_2}^* \\ {k_3}^* \end{matrix}$$
$$\begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 1 & 1 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix}$$

Then the pseudo inverse can be calculated as follows:

$$M^T = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 1 & 0 \\ 0 & 1 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}, \quad M * M^T = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 4 & 0 \\ 0 & 0 & 1 \end{bmatrix}$$

And since $A^{-1} = \frac{1}{detA}(AdjA)$

$$(M * M^T)^{-1} = \begin{bmatrix} 0 & 0 & 0 \\ 0 & \frac{1}{4} & 0 \\ 0 & 0 & 1 \end{bmatrix}$$

i.e $M^+ = M^T * (M * M^T)^{-1} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1/4 & 0 \\ 0 & 1/4 & 0 \\ 0 & 1/4 & 0 \\ 0 & 1/4 & 0 \\ 0 & 0 & 1 \end{bmatrix}$

then $k_{old} = M^T \, k_{new} = M^T$

$$\begin{pmatrix} k_1 \\ k_2 \\ k_3 \\ k_4 \\ k_5 \\ k_6 \end{pmatrix} = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1/4 & 0 \\ 0 & 1/4 & 0 \\ 0 & 1/4 & 0 \\ 0 & 1/4 & 0 \\ 0 & 0 & 1 \end{pmatrix} * \begin{pmatrix} {k_1}^* \\ {k_2}^* \\ {k_3}^* \end{pmatrix}$$

$$\begin{pmatrix} k_1 \\ k_2 \\ k_3 \\ k_4 \\ k_5 \\ k_6 \end{pmatrix} = \begin{pmatrix} {k_1}^* \\ \frac{1}{4}{k_2}^* \\ \frac{1}{4}{k_2}^* \\ \frac{1}{4}{k_2}^* \\ \frac{1}{4}{k_2}^* \\ {k_3}^* \end{pmatrix}$$

Then the reduced system can be obtained

$$\begin{aligned} \frac{dx_1}{dt} &= {k_1}^* x_1 - \frac{1}{4}{k_2}^*({x_1}^2 + x_1 x_2 - x_3)\,, \\ \frac{dx_2}{dt} &= -\frac{1}{4}{k_2}^*(x_1\, x_2 - 2x_3) - {k_3}^* x_2\,, \\ \frac{dx_3}{dt} &= \frac{1}{4}{k_2}^*(x_1\, x_2 - 2x_3) + {k_3}^* x_2\,. \end{aligned} \tag{3.2.1}$$

The reduced system (3.1.2) contains only three parameters.

3.2 Extracellular signal-regulated kinase signalling pathway

ERKs are part of a wider family of mitogen-activated protein kinases that includes ERK5, c-JunNh2-terminal kinases (JNKs), and p38 MAP kinases, among others [6]. The best-studied MAPK pathway, the ERK1/2 cascade, has been found to play key roles in proliferation, differentiation, cancer, and other physiological and pathological processes. It's critical to keep ERR signalling under control in order to keep cells functioning normally. The cell can regulate the ERK signalling pathway by a variety of mechanisms, including feedback loops, upstream and downstream scaffolds, phosphatase, and inhibitors of the ERK signalling pathway. This ERK pathway is involved in a variety of biological functions, including [20] :

- Cell proliferation regulation, such as T cell activation
- Synaptic plasticity in hippocampal neurons, such as long-term potentiation (LTP)
- Endothelial cell proliferation during angiogenesis
- Phosphorylation of the transcription factor p53
- Activation of phospholipase A2 (PLA2) in mast cells may contribute to the development of poly-cystic kidney disease by remodelling the ERK signalling pathway[21].

ERK is a complex signalling pathway and includes 11 variables and parameters. Figure (1) only shows a piece of the ERK pathway. The chemical reaction network of the ERK signalling pathways is given, see Figure (1). There are also a set of data for state variables and parameters, see Tables (1) and (2).

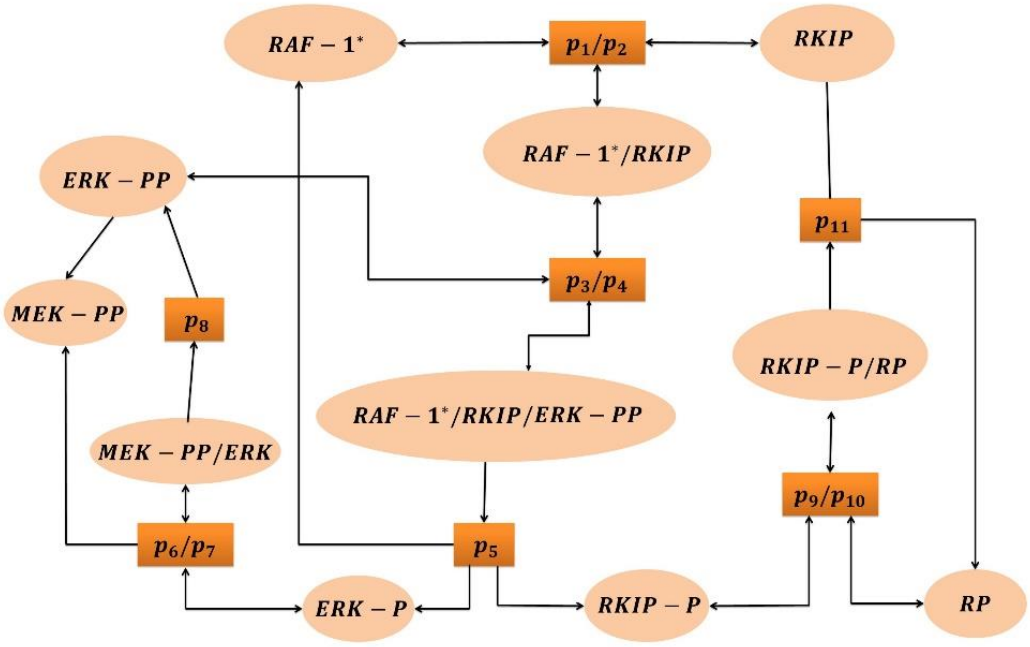

Figure1: Graphical representation of the ERK signalling pathways[18].

Table 1: Stationary values of state variables for ERK signalling pathways[18].

No.	State variable	Symbols	Stationary values
1	$RAF-1^*$	C_1	0.01
2	$RKIP$	C_2	0.1
3	$RAF-1^*/RKIP$	C_3	0.4
4	$RAF-1^*/RKIP/ERK-pp$	C_4	0.4
5	$ERK-P$	C_5	0.1
6	$RKIP-P$	C_6	0.05
7	$MEK-PP$	C_7	0.55
8	$MEK-pp/ERK$	C_8	0.5
9	$ERK-PP$	C_9	0.4
10	RP	C_{10}	0.19
11	$RKIP-P/RP$	C_{11}	0.1

Table 2: Summary of parameter values for ERK signalling pathways [18]

Parameters	Estimated value
p_1	0.191
p_2	0.09
p_3	0.443
p_4	0.93
p_5	5
p_6	0.031
p_7	0.95
p_8	4
p_9	0.9
p_{10}	10
p_{11}	7

Then the model equations of the biochemical diagram (1) are given bellow [18]:

$$\begin{aligned}
\frac{\mathrm{dC}_1}{\mathrm{dt}} &= -\mathrm{p}_1\mathrm{c}_1\mathrm{c}_2 + \mathrm{p}_2\mathrm{c}_3 + \mathrm{p}_5\mathrm{c}_4\,,\\
\frac{dC_2}{dt} &= -\mathrm{p}_1\mathrm{c}_1\mathrm{c}_2 + \mathrm{p}_2\mathrm{c}_3 + p_{11}c_{11}\,,\\
\frac{dC_3}{dt} &= p_1c_1c_2 - p_2c_3 - p_3c_3c_9 + p_4c_4\,,\\
\frac{dC_4}{dt} &= p_3c_3c_9 - p_4c_4 - p_5c_4\,,\\
\frac{dC_5}{dt} &= p_5c_4 - p_6c_5c_7 + p_7c_8\,,\\
\frac{dC_6}{dt} &= p_5c_4 - p_9c_6c_{10} + p_{10}c_{11}\,,\\
\frac{dC_7}{dt} &= -p_6c_5c_7 + p_7c_8 + p_8c_8\,,\\
\frac{dC_8}{dt} &= p_6c_5c_7 - p_7c_8 - p_8c_8\,,\\
\frac{dC_9}{dt} &= -p_3c_3c_9 + p_4c_4 + p_8c_8\ ,\\
\frac{dC_{10}}{dt} &= -p_9c_6c_{10} + p_{10}c_{11} + p_{11}c_{11}\,,\\
\frac{dC_{11}}{dt} &= p_9c_6c_{10} - p_{10}c_{11} - p_{11}c_{11}\,.
\end{aligned} \tag{3.2.1}$$

In this chemical reaction pathways, we can apply the proposed technique of model reduction. This is done to reduce the number of parameters. So, we use the following lump

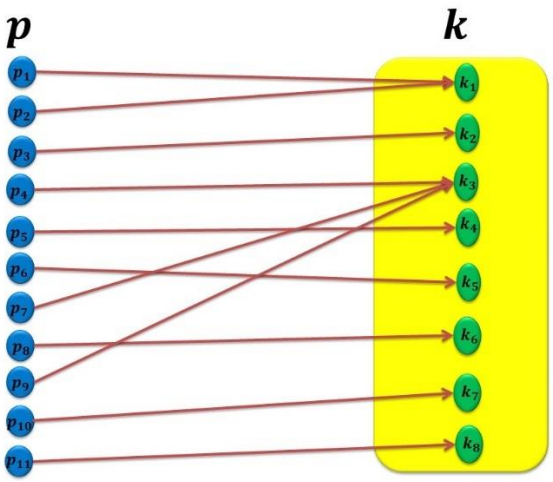

Figure 2: Lumping of parameters for ERK signaling.

After applying the lumping method for the original system (3.2.1), therefore the simplified system could be defined as follows:

$$
\begin{aligned}
&\frac{\mathrm{dC_1}}{\mathrm{dt}} = -\frac{1}{2}k_1\mathrm{c_1c_2} + \frac{1}{2}k_1\mathrm{c_3} + \mathrm{k_4c_4}\,,\\
&\frac{dC_2}{dt} = \frac{1}{2}\mathrm{k_1c_3} + k_8\mathrm{c_{11}} - \frac{1}{2}k_1c_1c_2\,,\\
&\frac{dC_3}{dt} = \frac{1}{2}k_1c_1c_2 - \frac{1}{2}k_1c_3 - k_2c_3c_9 + \frac{1}{3}k_3c_4\,,\\
&\frac{dC_4}{dt} = k_2c_3c_9 - (k_4 + \frac{1}{3}k_3)c_4\,,\\
&\frac{dC_5}{dt} = k_4c_4 - k_5c_5c_7 + \frac{1}{3}k_3c_8\,,\\
&\frac{dC_6}{dt} = k_4c_4 - \frac{1}{3}k_3c_6c_{10} + k_7c_{11}\,,\\
&\frac{dC_7}{dt} = -k_5c_5c_7 + (k_6 + \frac{1}{3}k_3)c_8\,,\\
&\frac{dC_8}{dt} = k_5c_5c_7 - (k_6 + \frac{1}{3}k_3)c_8\,,\\
&\frac{dC_9}{dt} = -k_2c_3c_9 + \frac{1}{3}k_3c_4 + k_6c_8\ ,\\
&\frac{dC_{10}}{dt} = -\frac{1}{3}k_3c_6c_{10} + (k_8 + k_7)c_{11}\,,\\
&\frac{dC_{11}}{dt} = \frac{1}{3}k_3c_6c_{10} - (k_8 + k_7)c_{11}\,.
\end{aligned}
\tag{3.2.2}
$$

We compare both full and simplified systems using IMEX Runge-Kutta and classic Runge-Kutta approaches. This is for state variables$\{c_i, i = 1,2,\dots,11\}$, see Figure (3).

4 THE PROPOSED METHOD

This section aims to use the high-order IMEX-RK scheme presented in Section 1 for solving the model equations presented in section 3. To do this, recalling (3.2.1) and (3.2.2), and for brevity, this can be written as

$$\frac{d\boldsymbol{C}}{dt} = F_{Im}\big(t, \boldsymbol{C}(t)\big) + F_{Ex}\big(t, \boldsymbol{C}(t)\big), \tag{4.1}$$

Where $\boldsymbol{C}(t) = [c_1(t), \dots, c_{11}(t)]^T$, and we can write $F_{Im}\big(t, \boldsymbol{C}(t)\big)$ and $F_{Ex}\big(t, \boldsymbol{C}(t)\big)$ the equation (3.2.1) as follow:

$$F_{Im}\big(t, \boldsymbol{C}(t)\big) = \begin{bmatrix} \mathrm{p}_2\mathrm{c}_3 + \mathrm{p}_5\mathrm{c}_4 \\ \mathrm{p}_2\mathrm{c}_3 + p_{11}c_{11} \\ -p_2c_2 + p_4c_4 \\ -p_4c_4 - p_5c_4 \\ p_5c_4 + p_7c_8 \\ p_5c_4 + p_{10}c_{11} \\ p_7c_8 + p_8c_8 \\ -p_7c_8 - p_8c_8 \\ p_4c_4 + p_8c_8 \\ p_{10}c_{11} + p_{11}c_{11} \\ -p_{10}c_{11} - p_{11}c_{11} \end{bmatrix}, \quad F_{Ex}\big(t, \boldsymbol{C}(t)\big) = \begin{bmatrix} -\mathrm{p}_1\mathrm{c}_1\mathrm{c}_2 \\ -\mathrm{p}_1\mathrm{c}_1\mathrm{c}_2 \\ p_1c_1c_2 - p_3c_3c_9 \\ p_3c_3c_9 \\ -p_6c_5c_7 \\ -p_9c_6c_{10} \\ -p_6c_5c_7 \\ p_6c_5c_7 \\ -p_3c_3c_9 \\ -p_9c_6c_{10} \\ p_9c_6c_{10} \end{bmatrix}$$

Similarly, we can write $F_{Im}\big(t, \boldsymbol{C}(t)\big)$ and $F_{Ex}\big(t, \boldsymbol{C}(t)\big)$ the equation (3.2.2) as follow:

$$F_{Im}\big(t, \boldsymbol{C}(t)\big) = \begin{bmatrix} \frac{1}{2}k_1\mathrm{c}_3 + \mathrm{k}_4\mathrm{c}_4 \\ \frac{1}{2}\mathrm{k}_1\mathrm{c}_3 + k_8\mathrm{c}_{11} \\ -\frac{1}{2}k_1c_3 + \frac{1}{3}k_3c_4 \\ -(k_4 + \frac{1}{3}k_3)c_4 \\ k_4c_4 + \frac{1}{3}k_3c_8 \\ k_4c_4 + k_7c_{11} \\ (k_6 + \frac{1}{3}k_3)c_8 \\ -(k_6 + \frac{1}{3}k_3)c_8 \\ \frac{1}{3}k_3c_4 + k_6c_8 \\ (k_8 + k_7)c_{11} \\ -(k_8 + k_7)c_{11} \end{bmatrix}, \quad F_{Ex}\big(t, \boldsymbol{C}(t)\big) = \begin{bmatrix} -\frac{1}{2}k_1\mathrm{c}_1\mathrm{c}_2 \\ -\frac{1}{2}k_1c_1c_2 \\ \frac{1}{2}k_1c_1c_2 - k_2c_3c_9 \\ k_2c_3c_9 \\ -k_5c_5c_7 \\ -\frac{1}{3}k_3c_6c_{10} \\ -k_5c_5c_7 \\ k_5c_5c_7 \\ -k_2c_3c_9 \\ -\frac{1}{3}k_3c_6c_{10} \\ \frac{1}{3}k_3c_6c_{10} \end{bmatrix}.$$

A main factor of the suggested technique is the separation of the right-hand side of (4.1) into stiff $\mathrm{F}_{\mathrm{Im}}\big(\mathrm{t}, \mathbf{C}(\mathrm{t})\big)$ and nonstiff $\Big(\mathrm{F}_{\mathrm{Ex}}\big(\mathrm{t}, \mathbf{C}(\mathrm{t})\big)\Big)$. Note that an explicit Runge-Kutta (*ERK*) method is used to solve

the no stiff part (F_{Ex}) and a diagonally implicit Runge-Kutta (*DIRK*) method is employed to solve the stiff part (F_{Im}).

c_1	1/4	0	0	0
0				
c_2	0.34114705729739	1/4	0	0
0				
c_3	0.80458720789763	−0.07095262154540		1/4
0	0			
c_4	−0.52932607329103	1.15137638494253	−0.80248263237803	
1/4	0			
c_5	0.11933093090075	0.55125531344927	−0.1216872844994	
0.20110104014943	1/4			
	0.11933093090075	0.55125531344927	−0.1216872844994	
0.20110104014943	1/4			

And

$\hat{c}_1$	0	0	0	0
0				
$\hat{c}_2$	0.39098372452428	0	0	0
0				
$\hat{c}_3$	1.09436646160460	0.33181504274704	0	0
0				
$\hat{c}_4$	0.14631668003312	0.69488738277516	0.46893381306619	
0	0			
$\hat{c}_5$	−1.33389883143642	2.90509214801204	−1.06511748457024	
0.27210900509137	0			
	0.11933093090075	0.55125531344927	−0.1216872844994	
0.20110104014943	1/4			

Algorithm 1 IMEX-RK(4, 5, 5)

1: Input $\boldsymbol{u}_0$,no of stages, no of iterations, Time

2: Put h $=$ Time/no of iterations

3: The matrices $A^{[E]}$, $A^{[I]}$, $b^{[E]}$ and $b^{[I]}$ can be obtained in the Butcher Table.

4: **for** n $=$ 0 : (no of iterations) $-$ 1 **do**

5: **accum1** $\leftarrow$ $\mathbf{u}_n$

6: **for** i $=$ 0 : (no of stages) $-$ 1 **do**

7: **accum2** $\leftarrow$ $\boldsymbol{u}_n + h \cdot (A_{ij}^{[I]} \cdot \mathbf{F_{Im}}(:, \mathbf{u}_n))$.

8: **for** j $=$ 0 : $(i-1)$ **do**

9: **accum2** $\leftarrow$ **accum2**$+h \cdot (A_{ij}^{[Im]} \cdot \mathbf{k_j^{[Im]}} + A_{ij}^{[Ex]} \cdot \mathbf{k_j^{[Ex]}})$.

10: **end do**

11: $\mathbf{k_i^{[Im]}} \leftarrow \mathbf{F_{Im}}(:, \mathbf{accum2})$.

12: $\mathbf{k_i^{[Ex]}} \leftarrow \mathbf{F_{Ex}}(:, \mathbf{accum2})$.

13: **accum1**$\leftarrow$ **accum1**$+h \cdot (b_i^{[Im]} \cdot \mathbf{k_i^{[Im]}} + b_i^{[Ex]} \cdot \mathbf{k_i^{[Ex]}})$.

14: **end do**

15: $\boldsymbol{u}_{n+1} \leftarrow$ **accum1**.

16: **end do**

---

5 NUMERICAL EXPERIMENTS

This section's purpose is to show the feasibility of the method by using an implementation based on Matlab programming. IMEX - RK (4, 5, 5) is used for solving (4.1) and the reduced model by using IMEX – RK as we did in the equation (4.1), where the number of 4 is the order of the scheme, 5 is the number of stages implicit and explicit schemes.

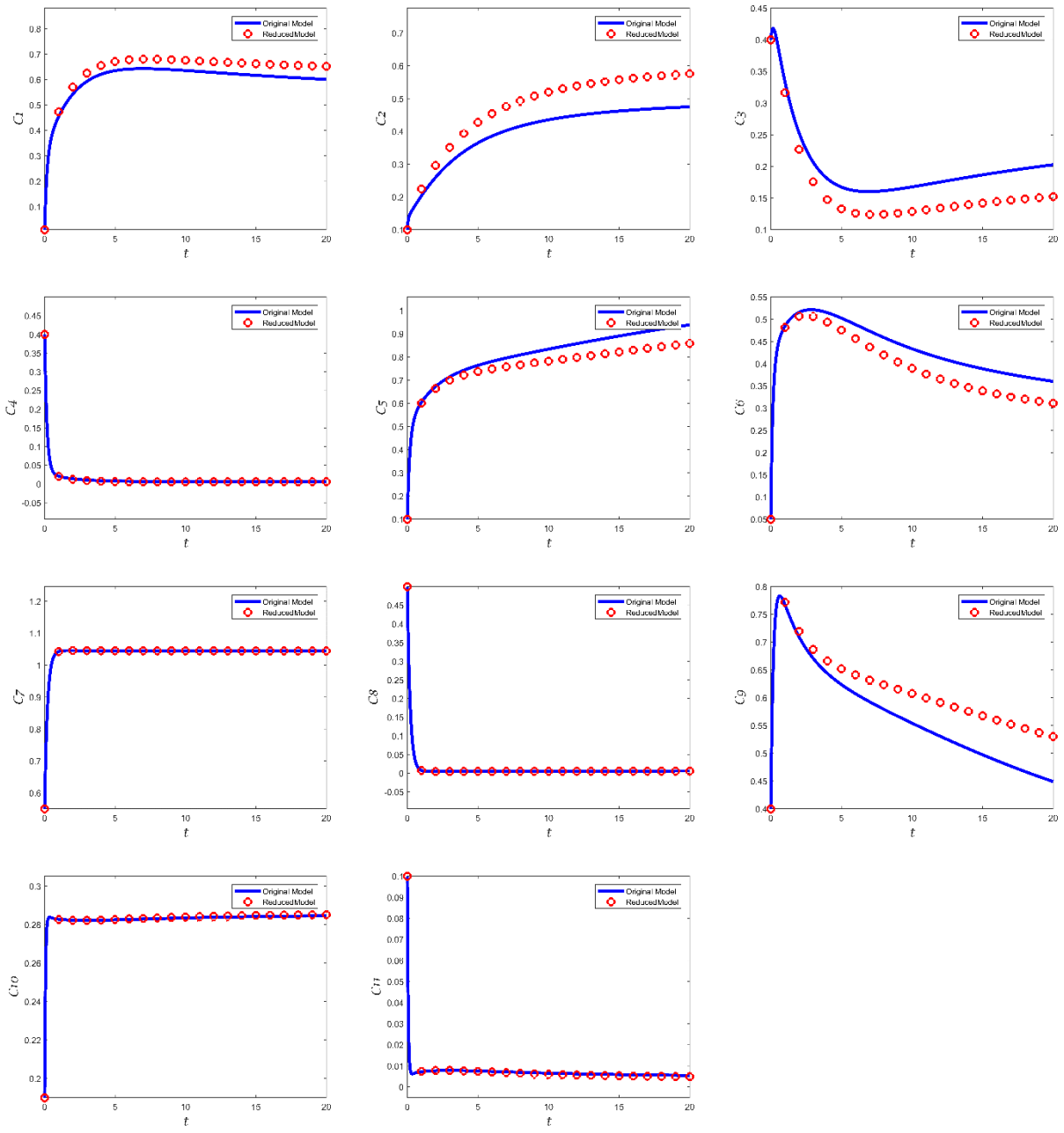

Figure 3: Numerical solutions$\{c_i, i = 1,2, \dots, 11.\}$ by using Implicit-Explicit (IMEX) Runge Kutta for original model (3.2.1) and reduced model (3.2.2).

Table 3: Comparing the numerical results by using IMEX-RK (4,5,5) between the original model (3.2.1) and reduced model (3.2.2) for c_1, c_2 and c_3.

	Original Model			**Reduced Model**		
Time	c_1	c_2	c_3	c_1	c_2	c_3
0	0.01000	0.10000	0.40000	0.01000	0.10000	0.40000
4	0.62048	0.33801	0.18079	0.65497	0.39400	0.14762
8	0.64164	0.41579	0.16151	0.67985	0.49349	0.12447
12	0.62781	0.44880	0.17540	0.66994	0.53885	0.13427
16	0.61305	0.46534	0.19018	0.65967	0.56248	0.14442
20	0.60063	0.47498	0.20272	0.65172	0.57595	0.15237

Table 4: Comparing the numerical results by using IMEX-RK (4,5,5) between the original model (3.2.1) and reduced model (3.2.2) for c_4, c_5 and c_6.

	Original Model			**Reduced Model**		
Time	c_4	c_5	c_6	c_4	c_5	c_6
0	0.4000000	0.10000	0.05000	0.4000000	0.10000	0.05000
4	0.0087251	0.74231	0.51477	0.0074064	0.72161	0.49337
8	0.0068453	0.80851	0.45896	0.0056756	0.76573	0.41986
12	0.0067958	0.85692	0.41280	0.0057948	0.79750	0.36542
16	0.0067659	0.90036	0.38196	0.0059045	0.82886	0.33203
20	0.0066537	0.93808	0.36022	0.0059059	0.85806	0.31094

Table 5: Comparing the numerical results by using IMEX-RK (4,5,5) between the original model (3.2.1) and reduced model (3.2.2) for c_7, c_8 and c_9.

	Original Model			**Reduced Model**		
Time	c_7	c_8	c_9	c_7	c_8	c_9
0	0.5500	0.5000000	0.40000	0.5500	0.5000000	0.40000
4	1.0452	0.0048404	0.64413	1.0453	0.0047353	0.66625

8	1.0447	0.0052895	0.57936	1.0450	0.0050401	0.62355
12	1.0444	0.0056077	0.53068	1.0448	0.005249	0.59145
16	1.0441	0.0058928	0.48698	1.0445	0.0054551	0.55978
20	1.0439	0.0061408	0.44912	1.0444	0.0056476	0.53039

Table 6: Comparing the numerical results by using IMEX-RK (4,5,5) between the original model (3.2.1) and reduced model (3.2.2) for c_{10} and c_{11}.

	Original Model		**Reduced Model**	
Time	c_{10}	c_{11}	c_{10}	c_{11}
0	0.19000	0.1000000	0.19000	0.1000000
4	0.28230	0.0077018	0.28239	0.0076083
8	0.28311	0.0068909	0.28350	0.0065033
12	0.28379	0.0062101	0.28433	0.0056730
16	0.28425	0.0057534	0.28484	0.0051611
20	0.28457	0.0054310	0.28516	0.0048371

6 CONCLUSION

The lumping of parameters is an effective tool for model reduction, especially for complex cell signaling pathways. We have applied the suggested technique to some chemical reaction mechanisms. Firstly, the suggested approach has been applied to simple chemical chains. Their parameters are minimized from 6 to 3, and the deviation value is only. Furthermore, we have also applied the proposed method to the ERK signaling pathways, which include 11 variables and 11 parameters. This model's reduction process is illustrated in Figure (2). This model has reduced from 11 to 8 parameters, and the deviation value is only 1.76%. Finally, we used the implicit-explicit Runge Kutta to find the approximate numerical solutions for ERK signalling pathways problems. Figure (3) contains stiff and no stiff terms. The stiff part is treated by an implicit scheme, while an explicit scheme treats the second part. The main important point in our preferred method is to reduce the number of iterations and, as a result, cause a decrease in the scheme's computational time; for more detail about numerical

methods, see [22-28]. It can be seen that the approximate solutions of the whole and minimized models are incredibly close.

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