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Dynamic modeling of mapk/erk signaling pathways

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Abstract. MAPK/ERK pathways have been shown to play a key role in transduction extracellular signals to cellular responses. Its Transduces signals by phosphorylation and has an essential role in cell proliferation, differentiation, and apoptosis. Through several assumptions, we simplify the pathways to develop a model for ERK1/2 activation in a system of differential equations based on enzyme catalyzed reaction processes. Then we study dynamic behaviour of the interactions among these two important molecules in this signaling patways. We used nondimensionalizations and Homotopy Perturbation Method (HPM) to find approximation solutions to the system. In addition to the approximation analytical expressions, we also computed numerical solutions for our system equations. We compared both types of solutions graphically and obtained that the results are in good agreement.

1. Introduction

Signal transduction pathway is a biochemical reaction network that primarily concerned with programming information. Signal transduction is an overall molecular event that takes place in the delivery of information from the cytoplasm to the cell nucleus. One of the mechanisms of signal transduction is the phosphorylation of the protein kinase [1]. Mitogen activated protein kinase (MAPK) pathways is one of the most important signal in the regulation of many biological processes. Activation of the MAPK/ERK pathways is initiated by ligand binding to receptor tyrosine kinases (RTK) at the cell surface and via Ras, then Raf, then MEK (mitogen-activated protein kinase), culminates in the regulation of gene transcription in the nucleus by the last pathway component, extracellular signal regulated kinase (ERK1/2) [2]. Deregulated of these signaling pathways has been observed in human cancers with potential involvement in most if not all cellular processes leading to tumorigenesis [3].

The biological systems approach can be used to develop predictive models based on an understanding of the structure and dynamics of molecular interactions in tissues [4]. In a study of mathematical modeling of signaling pathways, the the dynamic of MAPK pathways has ben constructed in [3] and [5]. Ordinary diferential equations (ODEs) are the most commonly used to represent the dynamics of signaling pathways. The typical reaction kinetics in signaling pathways include the law of mass action, Michaelis Menten kinetics, and Hill equation. In a study of biochemical reaction processes, protein-protein interactions can be described by Michaelis Menten kinetics. The Michaelis Menten kinetic rate law was derived under the assumption that reaction substrates are more significantly more abundant tthan the catalysing enzyme [1]. Here, we use this model to study the MAPK/ERK signaling pathways.

Munoz-Alicea [6] has use a multiple timescales analysis to study a basic model for enzim kinetics. Recently, Varadharajan and Rajendran [7] have derived the analytical solution of coupled nonlinear second order reaction differential equations in enzym kinetics by using homotopy perturbation method

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(HPM). In this paper, we develop a mathematical model of MEK activation in MAPK/ERK signaling pathways. We also present the analytic expression for MAPK/ERK signaling pathways where RAS concentration (s), RAS.Raf complex (c) and concentration of MEK (p) in terms of nondimensional parameters k, λ, and ε using He's homotopy perturbation method (HPM). We also compare the result with numerical sumulation.

2. Mathematical Formulation of Problem

The model of MEK activation in MAP/ERK signaling pathways is assumed as a basic enzym reaction model that can be represented with the following schematic diagram:

$$RAS + Raf \rightleftharpoons RAS.Raf \rightarrow MEK + Raf \tag{1}$$

This schematic diagram states that RAS as a substrate bind Raf as an enzyme to form a molecule of $RAS.Raf$ substate-enzyme complex. The $RAS.Raf$ could decompose back into Raf and RAS or may give rise to one olecule of MEK as a product and one molecule Raf as an enzyme. The law of mass action states that "the rate of the reaction is proportional to the product of the reactant concentration". Let, $s = [RAS], e = [Raf], c = [RAS.Raf]$, and $p = [MEK]$, "[.]" denotes the concentration of the substance. We use the law of mass action to get the following equation:

$$\begin{aligned} \frac{ds}{dt} &= -k_1 e_0 s + (k_1 s + k_{-1})c \\ \frac{dc}{dt} &= k_1 e_0 s - (k_1 s + k_{-1} + k_2)k \\ \frac{dp}{dt} &= k_2 c \end{aligned} \tag{2}$$

with initial conditions $s(0) = s_0, c(0) = 0, p(0) = 0$ and k_{-1}, k_1, k_2, e_0 are positive rate constant.

By introduction the following parameters

$$\tau = k_1 e_0 t\,,\ u(\tau) = \frac{s(t)}{s_0},\ v(\tau) = \frac{c(t)}{e_0}, w(\tau) = \frac{p(t)}{e_0}$$

$$\lambda = \frac{k_2}{k_1 s_0}, K = \frac{k_{-1} + k_2}{k_1 s_0} = \frac{Km}{s_0}, \varepsilon = \frac{e_0}{s_0}$$

the systems can be represented in dimensionless form as follow;

$$\frac{du}{d\tau} = -u + (u + K - \lambda)v,$$

$$\varepsilon \frac{dv}{d\tau} = u - (u + K)v, \tag{3}$$

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$$\varepsilon \frac{dw}{d\tau} = \lambda v$$

with

$$u(0) = 1, v(0) = 0, w(0) = 0.$$

3. Analytical Solution Using Homotopy Pertubration Method

To find the analytical solution expressions for concentration of RAS, RAS.Raf complex, and MEK we first construct a homotopy to determine the solution of equation (3) as folllows:

$$(1-p)\left[\frac{du}{d\tau} + u\right] + p\left[\frac{du}{d\tau} + u - uv - Kv + \lambda v\right] = 0 \quad (4)$$

$$(1-p)\left[\varepsilon \frac{dv}{d\tau} + Kv\right] + p\left[\frac{dv}{d\tau} + Kv - u + uv\right] = 0 \quad (5)$$

With the initial condition:

$$u(0) = 1, v(0) = 0 \quad (6)$$

Approximation solution of (4) and (5) are:

$$u = u_0 + pu_1 + p^2 u_2 + \ldots \quad (7)$$

$$v = v_0 + pv_1 + p^2 v_2 + \ldots \quad (8)$$

Substituting equation (6) (7) into equation (4) (5) respectively, comparing the coefisien of like power of p we obtain for the RAS concentration:

$$p^0 : \frac{du_0}{d\tau} + u_0 = 0 \quad (9)$$

$$p^1 : \frac{du_1}{d\tau} + u_1 - u_0 v_0 + Kv_0 + \lambda v_0 = 0 \quad (10)$$

$$p^2 : \frac{du_2}{d\tau} + u_2 - u_0 v_1 - u_1 v_0 + Kv_1 + \lambda v_1 = 0 \quad (11)$$

For RAS.Raf complex concentration we have:

$$p^0 : \varepsilon \frac{dv_0}{d\tau} + Kv_0 = 0 \quad (12)$$

$$p^1 : \varepsilon \frac{dv_1}{d\tau} + Kv_1 - u_0 + v_0 u_0 = 0 \quad (13)$$

$$p^2 : \varepsilon \frac{dv_2}{d\tau} + Kv_2 - u_1 + u_0 v_1 + u_1 v_0 = 0 \quad (14)$$

Solving the equation (9)-(14), and using the boundary condition (6), we can find the following result

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$$u(\tau)=e^{-\tau}+\frac{(K\varepsilon-\lambda\varepsilon)e^{-\left(\frac{K}{\varepsilon}\right)\tau}}{(K-\varepsilon)^2}-\frac{e^{-2\tau}+e^{-\tau}}{K-\varepsilon}+\frac{(\varepsilon e^{-\tau}+\lambda)e^{-\left(\frac{K}{\varepsilon}\right)\tau}}{K(K-\varepsilon)}+\frac{(K-\lambda)\tau e^{-\tau}}{K-\varepsilon}$$
$$-\frac{(K-\lambda)\varepsilon e^{-\tau}}{(K-\varepsilon)} \quad (15)$$

$$v(\tau)=\frac{e^{-\tau}-e^{-\left(\frac{K}{\varepsilon}\right)\tau}}{K-\varepsilon}-\frac{e^{-2\tau}}{(K-\varepsilon)(K-2\varepsilon)}-\frac{e^{-\left(\frac{K}{\varepsilon}-1\right)\tau}}{\varepsilon(K-\varepsilon)}+\frac{\varepsilon e^{-\left(\frac{K}{\varepsilon}\right)\tau}}{(K-2\varepsilon)}+\frac{e^{-\left(\frac{K}{\varepsilon}\right)\tau}}{\varepsilon(K-\varepsilon)} \quad (16)$$

The concentration of MEK is given by

$$w(\tau)=\int_0^\tau \frac{\lambda}{\varepsilon}v(\tau)\,d\tau$$

$$=\frac{\lambda(e^{-2\tau}-1)}{2\varepsilon(K-\varepsilon)(K-2\varepsilon)}+\frac{\lambda\left(e^{-\left(\frac{K\tau}{\varepsilon}+\tau\right)}-1\right)}{\varepsilon(K-\varepsilon)(K+\varepsilon)}-\frac{\lambda\left(e^{-\frac{K\tau}{\varepsilon}}-1\right)}{(K-\varepsilon)(K-2\varepsilon)}-\frac{\lambda\left(e^{-\frac{K\tau}{\varepsilon}}-1\right)}{(K-\varepsilon)} \quad (17)$$
$$-\frac{\lambda(e^{-\tau}-1)}{\varepsilon(K-\varepsilon)}+\frac{\lambda\left(e^{-\frac{K\tau}{\varepsilon}}-1\right)}{K(K-\varepsilon)}.$$

4. Result and Discussion

Figure 1-3 show the analytical expression of concentration of $RAS\,u$, $RAS.Raf$ complex v and MEK, w for various of dimensionless reaction parameters k,λ,ε where in k and λ values are same and ε is different.

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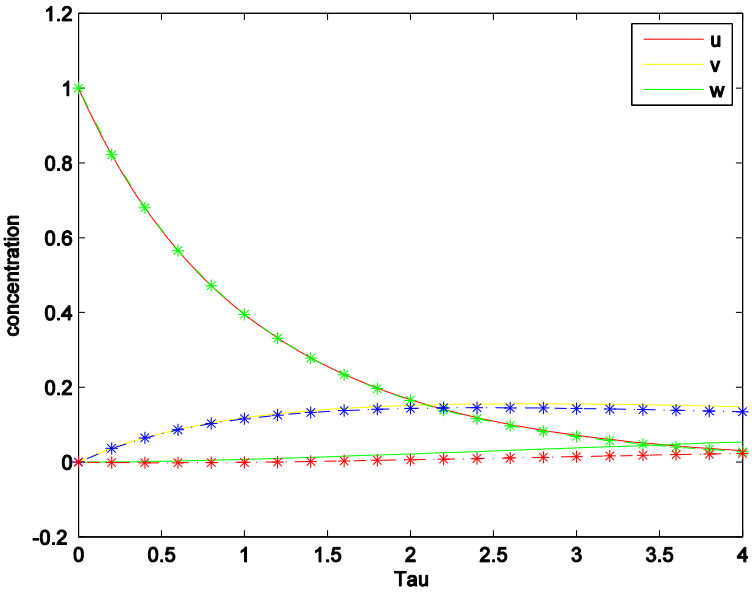

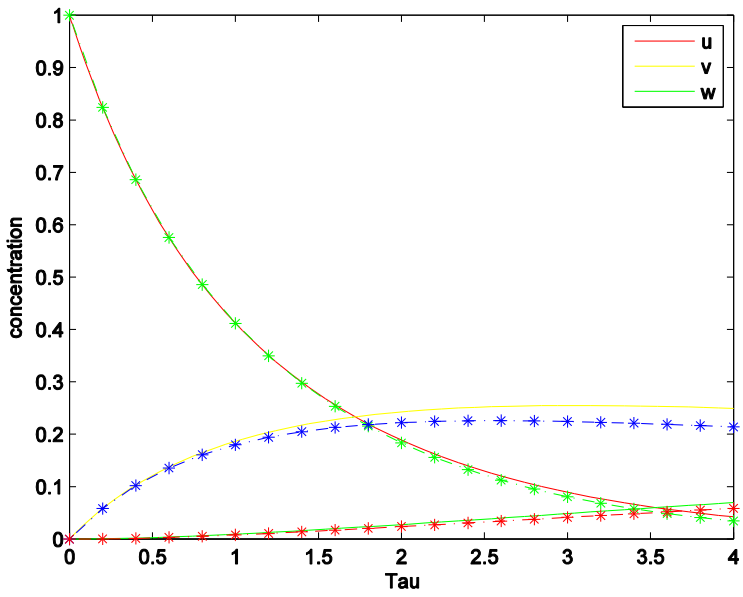

Figure 2. Concentration of RAS, complex RAS.Raf, and MEK using parameters values $k = 0.25, \lambda = 0.25, \varepsilon = 3$. These concentration profiles were computed using eqs. (15) - (17). The line denoted numerical solution and line '-.g*', '-.b*', '-.r*' donoted eqs. (15) – (17).

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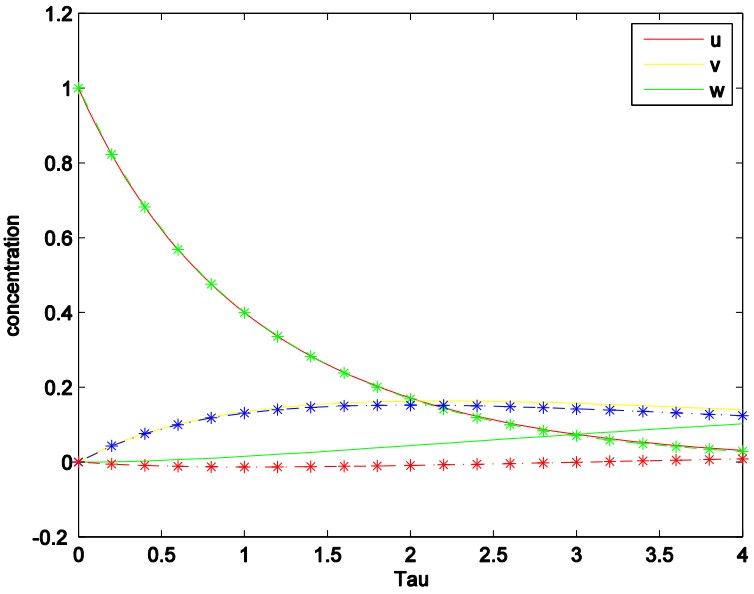

Figure 3. Concentration of RAS, complex RAS.Raf, and MEK using parameters values $k = 0.75, \lambda = 0.75, \varepsilon = 4$. These concentration profiles were computed using eqs. (15) - (17). The line denoted numerical solution and line '-.g*', '-.b*', '-.r*' donoted eqs. (15) – (17).

From these figures, it is inferred that the values of the concentration of RAS (u) decrease gradually from its initial value $(u(0) = 1)$. The complex RAS.Raf concentration increases gradually from its initial value$(v(0) = 0)$. The concentration of MEK increases slowly from the initial value$(w(0) = 0)$.
Our approximation analytical expression of RAS concentration, RAS.Raf complex concentration and Mek-1 concentratin are compared with simulation result in **figure 1 - 3**. A satisfactory agreement is noted.

5. Conclusions

Analytical expression of RAS, complex RAS.Raf, and MEK in term of dimentionless parameters are derived using Homotopy Perturbation Method (HPM). This method extremely simple and easy to solve other non-linear equation. The analytical result are compared with numerical simulation and satisfactory agreement is obtained.

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