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by Yudi Adi Cek-analytical Approximation For The Nonlinear Dyn

Submission date: 20-Apr-2021 09:03AM (UTC+0700)
Submission ID: 1564212797
File name: 2020-msmk.pdf (1.81M)
Word count: 2637
Character count: 14106

ZIBELINE INTERNATIONAL PUBLISHING

ISSN: 2521-0831 (Print)
ISSN: 2521-084X (Online)
CODEN: MSMADH

Matrix Science Mathematic (MSMK)

DOI: http://doi.org/10.26480/msmk.01.2020.10.13

RESEARCH ARTICLE

ANALYTICAL APPROXIMATION FOR THE NONLINEAR DYNAMICS OF ERK ACTIVATION IN THE PRESENCE OF COMPETITIVE INHIBITOR

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ARTICLE DETAILS

Article History:

Received 10 May 2020
Accepted 14 June 2020
Available online 13 July 2020

ABSTRACT

The extracellular signal-regulated protein kinase (ERK), a subfamily of Mitogen-Activated Protein Kinase (MAPK) pathways, is one of the most important signals in the regulation of many biological processes. Deregulated of MAPK signaling pathways has been observed in human cancers with potential involvement in most of all cellular processes leading to tumorigenesis so that became a potential target for therapy in cancer patients. In this paper, we discuss a Mathematical model of ERK activation in the presence of a small molecule inhibitor that competes with RAS. We present analytical expressions for the concentration of RAS, complex RAS-ERK, complex RAS-Inhibitor, and activated ERK in terms of dimensionless parameters using He's Homotopy Perturbation Method (HPM). The analytical results are compared with numerical simulation and satisfactory agreement is obtained.

KEYWORDS

ERK activation, Competitif Inhibitor, Homotopy Perturbation Methods, Analytical Solution.

1. INTRODUCTION

MAPK pathways activated by growth and stress signals as well as cytokines by way of cell receptors such as tyrosine kinase receptors (RTKs) and G-protein coupled receptors (GCPR) (Dhillon et al., 2007). The MAPK signaling pathway is vital in regulating many cellular processes, including inflammation, cell stress response, differentiation, division, proliferation, metabolism and apoptosis. The known major MAPK cascades distinguished by four distinct cascades, including the extracellular signal-related kinases (ERK1/2), Jun amino-terminal kinases (JNK1/2/3), p38-MAPK and ERK5. Activation of these pathways is started by ligand binding to receptor tyrosine kinases (RTK) at the cell surface and via Ras, Raf, MEK (mitogen-activated protein kinase), culminates in the regulation of gene transcription in the nucleus by the last pathway component, extracellular signal-regulated kinase (ERK) (Knight and Irving, 2014).

The RAS/ERK pathway is activated by the adaptor protein Grb2 that recruited to the tyrosine phosphorylated ErbB1 through its Src homology 2 (SH2) domain. Grb2 then brings in the guanyl nucleotide-release protein SOS to the plasma membrane by Grb2 binding to SOS through its Src homology 3 (SH3) domain. The mitogen-activated protein kinase kinase kinase (MKKK) RAF then binds to the activated RAS. This activates RAF, which leads to the phosphorylation of the mitogen-activated protein kinase kinase (MKK) MEK1/2 following activates the mitogen-activated protein kinase (MAPK) ERK1/2 through phosphorylation. This leads to the activation of a variety of ERK1/2 downstream signaling pathways, including transcription factors, and ultimately to increased proliferation and cell survival (Henson and Gibson, 2010).

The RAS/ERK pathways are frequently deregulated in human cancers as a result of abnormal activation of receptor tyrosine kinases or gain-of-function mutations, mainly in the RAS or RAF genes. The deregulated activation of the RAS/ERK pathway has been reported in many types of carcinomas that affect the skin breasts, pancreas, liver, and the thyroid, respectively (Santarpia et al., 2012; Cseh et al., 2014; Wellbrock and Arozarena, 2016). In this paper, we focus on the RAS/ERK pathway as an application example for the proposed modeling approach. The deregulated activation of the Ras-ERK pathway includes overexpression of cell membrane receptors and ligands, mutations of receptors and signaling proteins, and the sustained ligand-receptor stimuli mediated by autocrine or paracrine means. This understanding of the RAS-ERK signaling pathway inspired various therapeutic approaches focused on drug-mediated inhibition of the mutant RAS-RAF axis, respected to be the key driver of the deregulated activation of ERK. Unfortunately, this target inhibition is deflected by cancerous cells through the activation of the PI3K-mTOR pathway, whose deregulated control of cell growth and survival coexist with that of the Ras-ERK signaling pathway for many of cancers (Derbal, 2014).

Mathematical modeling of biopathways with molecule inhibition have

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Cite the Article: Yudi Ari Adi, M. Irawan Jayadi, Agung Budiantoro (2020). Analytical Approximation For The Nonlinear Dynamics Of Erk Activation In The Presence Of Competitive Inhibitor. *Matrix Science Mathematic, 4(1): 10-13*

studied (Adi et al., 2016). The other model of the MAPK pathway also has been conducted in (Derbal, 2014; Papalardo et al., 2016). In this paper, we develop a Mathematical model of ERK activation in the presence of a small molecule inhibitor that competes with RAS. Several papers have studied the modeling of some nonlinear problems in enzyme kinetics and provide an analytical solution by using the Homotopy Perturbation Method (HPM) (Varadharajan and Rajendran, 2011; Sivasamy et al., 2016). Recently presented the use of HPM to give an analytical approximate solution of the nonlinear problem (Haq, 2019). Now, HPM has been widely used to solving numerous problems of the nonlinear system because of its rapid convergence (Sinan, 2020). In this paper, we use the HPM methods in ERK activation under the condition that the initial ERK concentration is much smaller than the initial concentration of the RAS, $s_0 << e_0$. The purpose of this works is to present analytical expressions for the concentration of ERK, complex RAS-ERK, complex RAS-Inhibitor, and activated ERK in terms of dimensionless parameters. We also offer a comparative study of the same with numerical simulation by using Runge Kutta fourth order (RK).

2. Model Development

In this model, we assume that a small molecule inhibitor act as a competitive inhibitor that mimics ERK but doesn't undergo a reaction. We then follow Ingalls in modeling reaction enzyme subtract in presence competitive inhibitor (Ingalls, 2013). The formulation of biochemical reaction considers a reaction where *ERK* as a substrate bind *RAS* as an enzyme to form a complex *RAS*: *ERK*. The Inhibitor is structurally similar to the substrate so that it competes for the active site by developing a dead-end complex. The schematic representation of this reaction follows:

$$RAS + RAF \underset{d_1}{\overset{a_1}{\leftrightarrow}} RAS:ERK \xrightarrow{k_1} RAS + ERKa$$

$$RAS + I \underset{d_2}{\overset{a_2}{\leftrightarrow}} RAS:I$$

where a_i, d_i and k_i is the rate of association, dissociation, and activation of protein assumed to be constant.

In order to describe the mathematical model of the biochemical reaction above, we use the law of mass action in an ordinary differential equations (ODE) system. Let us define states of the system; $s=[ERK]=$ concentration of ERK, $e=[RAS]=the$ concentration of RAS, $c=[RAS:ERK]=$ the concentration of RAS:ERK complex, $p=[ERKa]=$ the concentration of activated ERK, $i=[I]=$ the concentration of inhibitor, $c_I=[RAS:I]=$ concentration of RAS-Inhibitor complex.

With the law of mass action and quasi-steady-state assumption, the mathematical model is given by the ODE system

$$\frac{ds}{dt} = d_1 c - a_1 s(e_0 - c - c_I) \tag{1}$$

$$\frac{dc}{dt} = a_1 s(e_0 - c - c_I) - d_1 c - k_1 c \tag{2}$$

$$\frac{dp}{dt} = k_1 c \tag{3}$$

$$\frac{dc_I}{dt} = a_2(e_0 - c - c_I)i - d_2 c_I \tag{4}$$

With initial condition

$$s = s_0, c = 0, p = 0, c_I = 0 \tag{5}$$

By introducing the following parameters

$$\tau = \frac{a_1 e_0 t}{\varepsilon}, u(\tau) = \frac{s}{s_0}, v(\tau) = \frac{c}{e_0}, w(\tau) = \frac{c_I}{e_0}, z(\tau) = \frac{p}{e_0},$$

$$\lambda_5 = \frac{d_1}{a_1 s_0}, \varepsilon = \frac{e_0}{s_0}, \lambda_2 = \frac{(d_1 + k_1)}{a_1 s_0}, \lambda_3 = \frac{\varepsilon a_2 i}{a_1},$$

$$\lambda_4 = \frac{\varepsilon(a_2 i + d_2)}{a_1}, \lambda_5 = \frac{\varepsilon k_1}{a_1 e_0}.$$

The system of equations (1)- (4) with initial conditions (5) can be represented in dimensionless form as follows:

$$\frac{du}{d\tau} = \lambda_1 \varepsilon v - \varepsilon u + \varepsilon u v + \varepsilon u w \tag{6}$$

$$\frac{dv}{d\tau} = \varepsilon u - uv - uw - \lambda_2 v \tag{7}$$

$$\frac{dw}{d\tau} = \lambda_3 - \lambda_3 v - \lambda_4 w \tag{8}$$

$$\frac{dz}{d\tau} = \lambda_5 v \tag{9}$$

with initial conditions

$$u(0) = 1, v(0) = 0, w(0) = 0, z(0) = 0 \tag{10}$$

3. Analytical Solution of Steady State Concentration Using HPM

To find the analytical expressions for the concentration of *ERK*, *RAS*: *ERK* complex, *RAS*: *Inhibitor* complex, and *ERKa*, we first construct a homotopy to determine the solution of equation (6)-(8) as follows:

$$(1-p)\left[\frac{du}{d\tau} + \varepsilon u\right] + p\left[\frac{du}{d\tau} + \varepsilon u - \lambda_1 \varepsilon v - \varepsilon uv - \varepsilon uw\right] = 0 \tag{11}$$

$$(1-p)\left[\frac{dv}{d\tau} + \lambda_2 v\right] + p\left[\frac{dv}{d\tau} + \lambda_2 v - u + uv + uw\right] = 0 \tag{12}$$

$$(1-p)\left[\frac{dw}{d\tau} + \lambda_4 w\right] + p\left[\frac{dw}{d\tau} + \lambda_4 w - \lambda_3 + \lambda_3 v\right] = 0 \tag{13}$$

with the initial conditions are as follows:

$$u(0)=1, v(0)=0, w(0)=0 \tag{14}$$

Approximate solutions of (11), (12), and (13) are

$$u = u_0 + pu_1 + p^2 u_2 + p^3 u_3 + \ldots \tag{15}$$

$$v = v_0 + pv_1 + p^2 v_2 + p^3 v_3 + \ldots \tag{16}$$

$$w = w_0 + pw_1 + p^2 w_2 + p^3 w_3 + \ldots \tag{17}$$

After substituting equations (15), (16), and (17) into equations (11), (12), and (13) respectively, and comparing the coefficient of like powers of p we obtain for the ERK concentration:

$$p^0 : \frac{du_0}{d\tau} + \varepsilon u_0 = 0 \tag{18}$$

$$p^1 : \frac{du_1}{d\tau} + \varepsilon u_1 - \varepsilon\lambda v_0 - \varepsilon u_0 v_0 - \varepsilon u_0 w_0 = 0 \tag{19}$$

$$p^2 : \frac{dv_2}{d\tau} + \varepsilon u_2 - \varepsilon\lambda_1 v_1 - \varepsilon u_0 v_1 - \varepsilon u_1 v_0 - \varepsilon u_0 w_1 - \varepsilon u_1 w_0 = 0 \tag{20}$$

For *RAS*: *ERK* complex concentration we have

$$p^0 : \frac{dv_0}{d\tau} + \lambda_2 v_0 = 0 \tag{21}$$

$$p^1 : \frac{dv_1}{d\tau} + \lambda_2 v_1 - u_0 + u_0 v_0 - u_0 w_0 = 0 \tag{22}$$

$$p^2 : \frac{dv_2}{d\tau} + \lambda_2 v_2 - u_1 + u_1 v_0 + u_0 v_1 + u_0 w_1 - u_1 w_0 = 0 \quad (23)$$

For RAS: Inhibitor complex concentration we have:

$$p^0 : \frac{dw_0}{d\tau} + \lambda_4 w_0 = 0 \quad (24)$$

$$p^1 : \frac{dw_1}{d\tau} + \lambda_4 w_1 - \lambda_3 + \lambda_3 v_0 = 0 \quad (25)$$

$$p^2 : \frac{dw_2}{d\tau} + \lambda_4 w_2 + \lambda_3 v_1 = 0 \quad (26)$$

Solving (18)-(26) using initial conditions (14) and according to HPM, we set $p \to 1$ in (15)-(17) and obtain the final results for solutions (6)-(10) as follows:

$$u(\tau) = e^{-\varepsilon\tau} + \frac{\varepsilon\lambda_1\tau e^{-\varepsilon\tau}}{\lambda_2 - \varepsilon} + \frac{\lambda_1\varepsilon\left(e^{-\lambda_2\tau} - e^{-\varepsilon\tau}\right)}{\left(\lambda_2 - \varepsilon\right)^2} - \frac{\left(e^{-\varepsilon\tau} - e^{-2\varepsilon\tau}\right)}{\left(\lambda_2 - \varepsilon\right)} - \frac{\varepsilon\left(e^{-(\varepsilon+\lambda_2)\tau} - e^{-\varepsilon\tau}\right)}{\lambda_2(\lambda_2 - \varepsilon)} + \frac{\varepsilon\lambda_3\tau e^{-\varepsilon\tau}}{\lambda_4} + \frac{\varepsilon\lambda_3 e^{-(\varepsilon+\lambda_4)\tau}}{\lambda_4^2\left(\lambda_2 - \varepsilon\right)} - \frac{\varepsilon\lambda_3 e^{-\varepsilon\tau}}{\lambda_4^2}, \quad (27)$$

$$v(\tau) = \frac{\left(e^{-\varepsilon\tau} - e^{-\lambda_2\tau}\right)}{\lambda_2 - \varepsilon} + \frac{\left(e^{-\lambda_2\tau} - e^{-(\varepsilon+\lambda_2)\tau}\right)}{\varepsilon\left(\lambda_2 - \varepsilon\right)} - \frac{\left(e^{-2\varepsilon\tau} - e^{-\lambda_2\tau}\right)}{\left(\lambda_2 - \varepsilon\right)\left(\lambda_2 - 2\varepsilon\right)} + \frac{\lambda_3\left(e^{-(\varepsilon+\lambda_4)\tau} - e^{-\lambda_2\tau}\right)}{\lambda_4\left(\lambda_2 - \varepsilon - \lambda_4\right)} + \frac{\lambda_3\left(e^{-\lambda_2\tau} - e^{-\varepsilon\tau}\right)}{\lambda_4\left(\lambda_2 - \varepsilon\right)} \quad (28)$$

$$w(\tau) = \frac{\lambda_3}{\lambda_4}\left(1 - e^{-\lambda_4\tau}\right) + \frac{\lambda_3\left(e^{-2\lambda_4\tau} - e^{-\lambda_2\tau}\right)}{\left(\lambda_4 - \varepsilon\right)\left(\lambda_2 - \varepsilon\right)} - \frac{\lambda_3\left(e^{(\lambda_4-\varepsilon)\tau} + e^{-\lambda_4\tau}\right)}{\left(\lambda_4 - \varepsilon\right)\left(\lambda_4 - \lambda_2\right)} \quad (29)$$

The dimensionless concentration of active ERK, ERKa is given by

$$z(\tau) = \lambda_5 \int_0^\tau v(\tau) d\tau \quad (30)$$

Equatian (30) is easy to solve, represent the product $z(\tau)$ for all values parameters given in equation (28).

4. Result and Discussion

The concentration of RAS, complex $RAS - RAF$, complex RAF: Inhibitor, and Activated ERK versus time is plotted in Figure 2 using (27) - (30). The nonlinear ODE system (1) - (4) with initial condition (5) is also solved using numerical methods. The numerical method is done by using the Runge-Kutta fourth order with Ode45, one of differential solvers in Matlab. Figure 1 shows the numerical result, and we have a good agreement with analytical expression using HPM in Figure 2. It is observed that the dimensionless RAS concentration, u and complex RAS: RAF, v decreases gradually from its initial value and becomes zero. It is also observed that the concentration ERK, z and complex $RAS{:}I$ w increases. This simulation result alsoggests that ERK is a potential target for improving the success of molecular therapy. We also give comparation these two methods in Figures 3 - 6 for various values of dimensionless parameters ε .

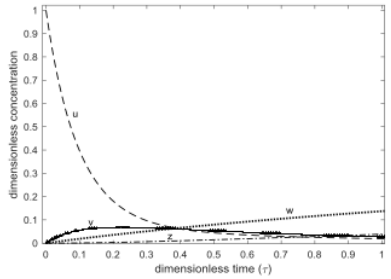

Figure 1: Plot of dimensionless concentration of ERK, complex RAS-ERK, complex RAS-Inhibitor, and ERKa numerically using Runge Kutta fourth-order (RK) parameter value $\varepsilon = 10, \lambda_1 = 0.5, \lambda_2 = 2, \lambda_3 = 0.2, \lambda_4 = 0.7, \lambda_5 = 0.2$.

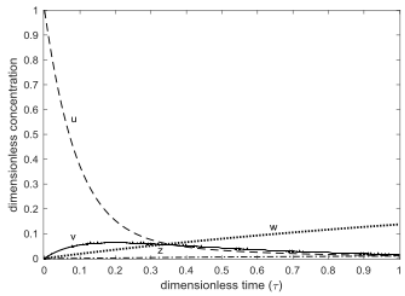

Figure 2: Plot of dimensionless concentration of ERK, complex RAS-ERK, complex RAS-Inhibitor, and ERKa using HPM with parameter value $\varepsilon = 10, \lambda_1 = 0.5, \lambda_2 = 2, \lambda_3 = 0.2, \lambda_4 = 0.7, \lambda_5 = 0.2$.

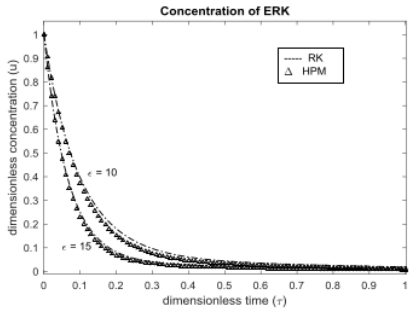

Figure 3: The concentration of dimensionless ERK (u) using HPM $(-\Delta-)$ and RK (--) for various values of dimensionless parameters ε .

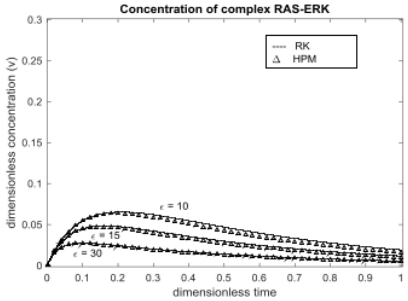

Figure 4: The concentration of dimensionless complex $RAS{:}ERK$ (v) using HPM $(-\Delta-)$ and RK (--) for various values of dimensionless parameters ε .

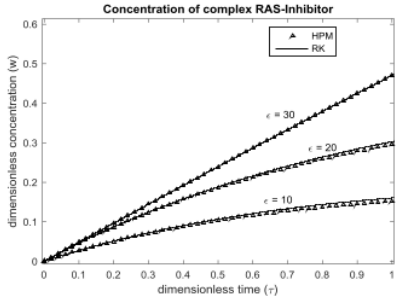

Figure 5: The concentration of dimensionless complex RAS-Inhibitor (w) using HPM $(-\Delta-)$ and RK (--) for various values of dimensionless parameters ε .

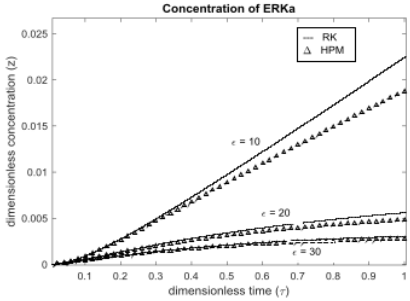

Figure 6: The concentration of dimensionless ERKa (z) using HPM $(-\Delta-)$ and RK (--) for various values of dimensionless parameters ε .

From Figures 3 – 6, it is infered that if the initial concentration of ERK is getting smaller than the contentration of RAS, indicated with the increase value of the dimensionless parameter ε , HPM provide rapid and fast convergence.

5. Conclusion

In this paper, an analytical expression of ERK, complex *RAS*: *ERK*, complex *RAS*:Inhibitor and *ERKa* in terms of dimensionless parameters are derived using He's Homotopy Perturbation Method (HPM). The HPM compared with numerical solutions method, i.e. Runge Kutta fourth-order. We compared both types of solutions graphically and observed that the solution gets closer to each other. This result suggests that the HPM gives a very accurate approximation to the solution of our model under the assumption that the initial concentration of RAS is higher than the initial concentration of ERK.

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