

Stability and Bifurcation Analysis of a Model for the Signal Transduction Process with a Signal Amplification Delay

Wanwarat Anlamlert, Yongwimon Lenbury, and Warunee Sarika

Abstract—All living cells need to sense and respond to their environment. Cells communicate with each other through extracellular signaling molecules [1]. Signal transduction is the process by which information from an extracellular signal is transmitted from the plasma membrane into the cell and along an intracellular chain of signaling molecules to stimulate a cellular response. Many situations have been reported where altered signaling pathways produce dramatic changes in cell survival, cell proliferation, morphology, angiogenesis, longevity, or other properties that characterize cancer cells. Signal transduction abnormalities have been linked to the development of many serious disorders, such as chronic myelogenous leukemia and Alzheimer's disease [2, 3]. In this study, a model with delay of the signal transduction process is analyzed. After showing that the model admits positive solutions, we derive conditions on the system parameters which give rise to different dynamical behaviors which could be expected in the signaling pathway under the impact of delays. Numerical simulations are carried out and discussed in support of the theoretical analysis. We found that the system changes its dynamic behavior from stable to unstable around the system's steady state when the delay increases in value so that it crosses a critical value via a Hopf bifurcation and bifurcation of a family of periodic solutions can be expected if the delay is in the vicinity of the critical value. Numerical simulations are carried out to support the theoretical predictions concerning various dynamical behaviours permitted by different values of the amplification effect delay.

Keywords—signal transduction, delayed response, system stability, bifurcation, oscillations.

I. INTRODUCTION

ACCORDING to the American Cancer Society [4], "Cancer is a group of diseases characterized by

Manuscript received May 17, 2012; Revised version received May 17, 2012. This work was supported in part by the Centre of Excellence in Mathematics, CHE, Thailand.

W. Anlamlert is with the Department of Mathematics, Faculty of Science, Mahidol University, Rama 6 Road, Bangkok 10400 and the Centre of Excellence in Mathematics, CHE, 328 Si Ayutthaya Road, Bangkok, THAILAND (e-mail: orange_an@hotmail.com).

Y. Lenbury is with the Department of Mathematics, Faculty of Science, Mahidol University, Rama 6 Road, Bangkok 10400 and the Centre of Excellence in Mathematics, CHE, 328 Si Ayutthaya Road, Bangkok, THAILAND (corresponding author, phone: 662-201-5448; fax: 662-201-5343; e-mail: yongwimon.len@mahidol.ac.th).

W. Sarika is with the Department of Mathematics, Faculty of Science, Mahidol University, Rama 6 Road, Bangkok 10400 and the Centre of Excellence in Mathematics, CHE, 328 Si Ayutthaya Road, Bangkok, THAILAND (e-mail: warunee.kha@mahidol.ac.th).

uncontrolled growth and spread of abnormal cells. If the spread is not controlled, it can result in death. Cancer is caused by both external factors (tobacco, infectious organisms, chemicals, and radiation) and internal factors (inherited mutations, hormones, immune conditions, and mutations that occur from metabolism). These causal factors may act together or in sequence to initiate or promote carcinogenesis. Ten or more years often pass between exposure to external factors and detectable cancer. Cancer is treated with surgery, radiation, chemotherapy, hormone therapy, biological therapy, and targeted therapy."

A common characteristics of all cancers is the unrestrained proliferation of cancer cells which eventually spread to other parts of the body through the blood and lymph systems, invading normal tissues and organs and leading to death of the patient. In cancer cells, the signaling pathway is often altered and results in a phenotype characterized by uncontrolled growth and increased capability to invade surrounding tissue [5].

All living cells need to sense and respond to their environment. Cells communicate with each other through extracellular signaling molecules [1]. Extracellular signaling can travel a short distance and stimulate cells that are near to the origin of the signal, or they can travel throughout the body, capable of stimulating cells that are far away from the source of the signal [6].

A common feature in all signal transduction pathways is that a component in the environment is recognized, typically by a protein in the plasma membrane. The environmental trigger is called the ligand, and the plasma membrane protein is called the receptor. The receptor usually spans the membrane, and binding to the ligand on the extracellular side triggers a change that activates its function on the intracellular side. The part of this process is called signal transduction [7].

Signal transduction is the process by which an extracellular signal molecule activates a membrane receptor that in turn alters intracellular molecules to stimulate a response. Extracellular signaling molecules are synthesized and secreted by signaling cell and produces a specific response only in target cells that have receptors for the signalling molecule. Binding of the extracellular signalling molecules causes a conformational change in the receptor that initiates a sequence of reactions in the target cell leading to a

change in cellular response [1]. After a signal transduction pathway has been initiated and the information has been “transduced” to give rise to other cellular processes, the signalling processes must be terminated. As observed by Bianco et al. [10], without such termination, cells lose their responsiveness to new signals. Signal processes that fail to properly terminate can lead to uncontrolled cell growth and the possibility of cancer [10].

Signal transduction pathways commonly are named based on the general class of receptor involved, (e.g., GPCRs, receptor tyrosine kinases), the type of ligand (e.g. TGF β , Wnt, Hedgehog), or as key intracellular signal transduction component (e.g., NF- κ B) [1]. Several recent research reports have studied models of signal transduction pathways.

In 2001, Huse et.al. [11] studied the TGF β receptor signaling pathway. They studied the molecular mechanism of receptor activation using a homogenously tetraphosphorylated form of the type I TGF β receptor (TGF β -I), prepared using protein semisynthesis. In their work, phosphorylation activates TGF β -I by switching the Gs region from a binding site for an inhibitor into a binding site for substrate.

In 2003, Williams et.al. [12] studied the Hedgehog (Hh) signaling pathway. In their work, the basal cell carcinoma (BCC) was used to screen for Hh inhibitors and test their validity as potential treatments for BCC. They identified a novel small molecule Hh inhibitor (CUR61414) that can block elevated Hh signaling activity resulting from oncogenic mutations in Patched-1. Furthermore, CUR61414 can suppress proliferation and induce apoptosis of basaloid nests in the BCC model systems, and having no effect on normal skin cells. These results demonstrate that the use of Hh inhibitors could be a valid therapeutic approach for treating BCC.

In 2005, Wistrand et.al. [13] studied the G-protein coupled receptors (GPCRs) signaling pathways. They analyzed a divergent set of GPCRs and found distinct loop length patterns and differences in amino acid composition between cytosolic loops, extracellular loops, and membrane regions. A hidden Markov model, GPCRHMM, was configured to fit the features and trained it on a large dataset representing the entire superfamily. They applied GPCRHMM to five proteomes and detected a large number of sequences that have no other annotation. The results from *Caenorhabditis elegans* are particularly interesting, and include a large number of sequences with no annotation, which are prime candidates for being previously undetected GPCRs. GPCRHMM gave strong negative predictions to a family of arthropod-specific odorant receptors believed to be GPCRs.

In 2008, Shin et.al. [14] studied the signal transduction through the extracellular signal-regulated kinases (ERKs) pathway. They considered feedback loops in ERK signaling pathway, such as negative and positive feedback loops. They showed that the negative feedback loop of the ERK pathway had a crucial role in generating an oscillatory behavior of ERK activity. The positive feedback loop in which ERK functionally inactivates Raf kinase inhibitor protein also raised the oscillatory pattern of ERK dynamic. Therefore, the combination of positive and negative feedback loops were

crucial to produce the dynamic characteristics of ERK activity.

It is well recognized that many serious diseases, can be caused by molecular changes that affect signal transduction systems. According to Bronchud et al. [15], in cancer cells, the signalling pathway is often altered and results in a phenotype characterized by uncontrolled growth and increased capability to invade surrounding tissue [15]. In addition, many situations have been known where altered signalling pathways produce dramatic changes in cell survival, cell proliferation, morphology, angiogenesis, longevity, or other properties that characterize cancer cells [15].

Since G protein coupled receptors (GPCRs) constitute the largest family of cell surface receptors and they mediate most responses to signals from other cells, we shall use G protein pathways as a model of the signal transduction process.

The work of Levchenko and Iglesias [8] studied the signal transduction pathway in the social amoebae *Dictyostelium Discoideum*. The original idea of mathematical model of signal transduction can be found in their work. We can see how the model was logically formulated according to biological principle and biochemical mechanism.

In 2003, Iglesias [9] studied the role of feedback control mechanism in the cell signaling pathway associated with the chemotaxis in *D. Discoideum*. His study proposed the model of the signaling pathway of *D. Discoideum* involving cAMP was as follows:

$$\frac{dI}{dt} = -a_1 I + a_2 S \quad (1)$$

$$\frac{dS}{dt} = -a_3 S + \frac{a_4 S^2}{(a_5 S + I)^2} + a_6 \quad (2)$$

where I and S represent the concentration of the inhibiting agent and the external signal, respectively. In the work of Iglesias [9], the sufficient condition was given for which the equilibrium is stable and it was also shown that the system may exhibit a stable limit cycle.

In the work of Rattanukul et al. [16] a model was proposed for the signal transduction pathway, involving the G protein coupled receptors (GPCRs), that consists of a system of two differential equations governing the interaction between the inhibitor protein and the ligand-receptor complexes as follows:

$$\frac{dI}{dt} = \alpha S(t) - \beta I(t) \quad (3)$$

$$\frac{dS}{dt} = \gamma + \frac{\eta S^2(t)}{(\kappa S(t) + I)^2} - \frac{\mu S(t)}{S(t) + w} - \rho S(t) \quad (4)$$

In 2011, Sarika et al. [17] modified the above model of the signal transduction pathway by incorporating two time delays τ_I and τ_S . Their model for the signal transduction process consists of the following equations:

$$\frac{dI}{dt} = \alpha S(t - \tau_s) - \beta I(t) \tag{5}$$

$$\frac{dS}{dt} = \gamma + \frac{\eta S^2(t)}{(\kappa S(t) + I(t - \tau_i))^2} - \frac{\mu S(t)}{S(t) + w} - \rho S(t) \tag{6}$$

We add to the results of the above works by investigating the system's stability and, through a bifurcation analysis, the existence of sustained oscillations, utilizing the techniques in earlier investigations and modeling efforts of Kaddar [18, 19].

In this work, the following events are considered. The signal amplification of the ligand-receptor complex is due to the secondary hormone with a time delay. In [7], the concentration of the secondary hormone was found to depend on S and I as in the second term on the right of equation (2). We therefore incorporate a delay into this term.

We also consider that the ligand-receptor complex is removed from the system in response to how high its level is with a delay in time. Thus, assuming that the delays are the same in both these responses, we incorporate the time delay τ into the model system (3)–(4) to arrive at the following equations:

$$\frac{dI}{dt} = \alpha S(t) - \beta I(t) \tag{7}$$

$$\frac{dS}{dt} = \gamma + \frac{\eta S^2(t - \tau)}{(\kappa S(t - \tau) + I(t - \tau))^2} - \frac{\mu S(t)}{S(t) + w} - \rho S(t - \tau) \tag{8}$$

where the first term on the right of (7) is the production rate of the inhibiting protein in response of the increase in the ligand-receptor complexes and the second term is the removal rate of the inhibiting protein. The first term on the right of (8) is the zero order production rate of the ligand-receptor complexes, the second term accounts for the amplification effect on the production of the ligand-receptor complexes due to the secondary hormone with a delay τ , the third term on the right of (8) is the rate at which the ligand-receptor complexes is internalized through the cell membrane and the last term is the removal rate of the ligand-receptor complex depending on the level of the complex at τ units of time earlier.

II. PHYSICALLY MEANINGFUL SOLUTION

Clearly, the smoothness of the functions f_1 and f_2 guarantees the global existence and uniqueness of solutions to the system (7)–(8). We now show that the model system admits positive solutions for each positive initial condition and small enough removal rate constant ρ .

Theorem 1 For each given initial condition such that $I(t) > 0$, and $S(t) > 0$ on the initial interval $[-\tau, 0]$, the model system (7)–(8) admits positive solution, provided that ρ is sufficiently small.

Proof. Due to the continuity of the solution of the model differential equations, $S(t)$ would become non-positive if there existed $t_0 > 0$ such that

$$S(t_0) = 0 \text{ and } S(t) > 0$$

for any $t, 0 \leq t < t_0$. Then, we would have

$$S'(t_0) \leq 0$$

However, if

$$\rho < \frac{\gamma}{S(t_0 - \tau)}$$

then, (8) gives

$$S'(t_0) = \gamma + \frac{\eta S^2(t_0 - \tau)}{(\kappa S(t_0 - \tau) + I(t_0 - \tau))^2} - \frac{\mu S(t_0)}{S(t_0) + w} - \rho S(t_0 - \tau) > 0$$

which contradicts the fact that $S'(t_0) \leq 0$.

Similarly, by solution's continuity, $I(t)$ would become non-positive if there existed a $t_1 > 0$ such that $I(t_1) = 0$ and $I(t) > 0$ for any $t, 0 \leq t < t_1$.

Then, necessarily, $I'(t_1) \leq 0$, which means, from (7), that

$$\left. \frac{dI}{dt} \right|_{t=t_1} = \alpha S(t_1) - \beta I(t_1) = \alpha S(t_1) \leq 0$$

which contradicts the above proven fact that S never becomes non-positive. \square

III. STEADY STATE AND LOCAL STABILITY

We next discuss the local stability of the delay model (7)–(8) for the signal transduction process which governs the interaction between the ligand-receptor complexes $S(t)$ and the inhibiting protein $I(t)$ discussed in the previous section. The system (7)–(8) always admits a positive equilibrium $E^* = (I^*, S^*)$, where $I' = S' = 0$, according to the following equations.

$$I^* = \frac{\alpha}{2\beta} \left[\left(\gamma + \frac{\eta\beta^2}{(\kappa\beta + \alpha S^*)^2} - \mu - \rho w \right) + \left(\left(\mu + \rho w - \gamma - \frac{\eta\beta^2}{(\kappa\beta + \alpha S^*)^2} \right)^2 + 4\rho w \left(\gamma + \frac{\eta\beta^2}{(\kappa\beta + \alpha S^*)^2} \right) \right)^{1/2} \right],$$

and

$$S^* = \frac{1}{2} \left[\left(\gamma + \frac{\eta\beta^2}{(\kappa\beta + \alpha S^*)^2} - \mu - \rho w \right) + \left(\left(\mu + \rho w - \gamma - \frac{\eta\beta^2}{(\kappa\beta + \alpha S^*)^2} \right)^2 + 4\rho w \left(\gamma + \frac{\eta\beta^2}{(\kappa\beta + \alpha S^*)^2} \right) \right)^{1/2} \right].$$

In what follows, we let

$$R_0 = \frac{\rho(S^* + w)^2}{\mu w} \tag{9}$$

$$R_1 = \frac{4\eta S^* I^*}{\rho(\kappa S^* + I^*)^3}. \tag{10}$$

Letting $x = I - I^*$ and $y = S - S^*$, linearization of the system (7)–(8) around the equilibrium $E^* = (I^*, S^*)$ yields

$$\frac{dx}{dt} = -\beta x(t) + \alpha y(t) \tag{11}$$

$$\frac{dy}{dt} = -\frac{2\eta S^*}{(\kappa S^* + I^*)^3} x(t - \tau) + \left[\frac{2\eta S^* I^*}{(\kappa S^* + I^*)^3} - \rho \right] y(t - \tau) - \frac{\mu w}{(S^* + w)^2} y(t) \tag{12}$$

The characteristic equation associated to system (7)–(8) is $\lambda^2 + p\lambda + s\lambda \exp(-\tau\lambda) + r + q \exp(-\tau\lambda) = 0$, (13)

where

$$p = \beta + \frac{\mu w}{(S^* + w)^2}, \quad s = \rho - \frac{2\eta S^* I^*}{(\kappa S^* + I^*)^3},$$

$$q = \beta\rho, \quad r = \frac{\beta\mu w}{(S^* + w)^2}.$$

The determination of local stability of the steady state E^* is a result of the localization of the roots of the characteristic equation (13).

In order to investigate the local stability of the steady state, we begin by considering the case without delay $\tau = 0$. In this case, the characteristic equation (13) reduces to

$$\lambda^2 + (p + s)\lambda + r + q = 0, \tag{14}$$

where

$$p + s = \beta + \rho + \frac{\mu w}{(S^* + w)^2} - \frac{2\eta S^* I^*}{(\kappa S^* + I^*)^3},$$

$$r + q = \beta\rho + \frac{\beta\mu w}{(S^* + w)^2}.$$

If $R_1 < 1$, we obtain

$$p + s = \beta + \rho + \frac{\mu w}{(S^* + w)^2} - \frac{2\eta S^* I^*}{(\kappa S^* + I^*)^3} > 0,$$

and since

$$r + q = \beta\rho + \frac{\beta\mu w}{(S^* + w)^2} > 0,$$

according to the Routh Hurwitz criterion, we have the following proposition.

Proposition 2 For $\tau = 0$, the steady state E^* is locally asymptotically stable if and only if $R_1 < 1$.

We now return to the study of equation (13) with $\tau > 0$. We first prove the following theorem.

Theorem 3 If $R_0 < 1$ and $R_1 < 1$, then the equilibrium E^* is locally asymptotically stable for all $\tau \geq 0$.

Proof. From the hypotheses $R_0 < 1$ and $R_1 < 1$, the roots of characteristic equation (13) have negative real parts for $\tau = 0$ by Proposition 2.

Suppose that the characteristic equation (13) has a purely imaginary root $i\omega$, with ω real and positive. Then, by separating real and imaginary parts of both sides of equation (13), we have

$$r - \omega^2 + s\omega \sin(\omega\tau) + q \cos(\omega\tau) = 0 \tag{15}$$

$$p\omega + s\omega \cos(\omega\tau) - q \sin(\omega\tau) = 0. \tag{16}$$

Hence,

$$\omega^4 + (p^2 - s^2 - 2r)\omega^2 + r^2 - q^2 = 0. \tag{17}$$

From the expression of r and q , we have $r + q > 0$ and from the hypothesis $R_0 < 1$, we can deduce that

$$r^2 - q^2 > 0.$$

Evaluating $p^2 - s^2 - 2r$, we find that

$$p^2 - s^2 - 2r = \beta^2 + \left(\frac{\mu w}{(S^* + w)^2} \right)^2 - \rho^2 + \frac{4\eta S^* I^*}{(\kappa S^* + I^*)^3} \left(\rho - \frac{\eta S^* I^*}{(\kappa S^* + I^*)^3} \right).$$

Since for $R_0 < 1$ and $R_1 < 1$, we have

$$p^2 - s^2 - 2r > \beta^2 + 12 \left(\frac{\eta S^* I^*}{(\kappa S^* + I^*)^3} \right)^2 > 0.$$

Then, equation (17) has no positive solution for $R_0 > 1$ and $R_1 > 1$. This concludes the proof. □

Theorem 4 If

$$R_0 > 1 \tag{18}$$

$$R_1 < 1 \tag{19}$$

hold, then there exists a $\tau_0 > 0$ such that, when $\tau \in [0, \tau_0)$ the equilibrium E^* is locally asymptotically stable, when $\tau > \tau_0$, E^* is unstable when $\tau = \tau_0$, equation (13) has a pair of purely imaginary roots $\pm i\omega_0$, with

$$\omega_0^2 = \frac{1}{2} \left[(s^2 + 2r - p^2) + \left((s^2 + 2r - p^2)^2 - 4(r^2 - q^2) \right)^{1/2} \right] \quad (20)$$

and

$$\tau_0 = \frac{1}{\omega_0} \arccos \left(-\frac{ps\omega_0^2 + (r - \omega_0^2)q}{s^2\omega_0^2 + q^2} \right), \quad (21)$$

where p, s, q , and r are as defined in (13).

Proof. According to the proof of Theorem 3, when $\tau = \tau_0$, $i\omega_0$ is a purely imaginary root of the characteristic equation (13) if

$$r - \omega_0^2 + s\omega_0 \sin(\omega_0\tau_0) + q \cos(\omega_0\tau_0) = 0 \quad (22)$$

$$p\omega_0 + s\omega_0 \cos(\omega_0\tau_0) - q \sin(\omega_0\tau_0) = 0 \quad (23)$$

which leads to

$$\omega_0^4 + (p^2 - s^2 - 2r)\omega_0^2 + r^2 - q^2 = 0. \quad (24)$$

Solving (24) for ω_0^2 , we have

$$\omega_0^2 = \frac{1}{2} \left[(s^2 + 2r - p^2) + \left((s^2 + 2r - p^2)^2 - 4(r^2 - q^2) \right)^{1/2} \right]$$

From the expression of r and q , we have $r + q > 0$ and under the hypothesis $R_0 > 1$, we have

$$r - q = \frac{\beta\mu w}{(S^* + w)^2} - \beta\rho = \beta \left(\frac{\mu w}{(S^* + w)^2} - \rho \right) < 0$$

Hence, we obtain

$$r^2 - q^2 < 0$$

when $R_0 > 1$. Therefore, there are two purely imaginary roots $\pm i\omega_0$ with $\omega_0 > 0$.

The critical value of the delay τ_0 is determined in the usual way by the equations (22) and (23). We obtain

$$(r - \omega_0^2)q + ps\omega_0^2 = -(s^2\omega_0^2 + q^2) \cos(\omega_0\tau_0).$$

Therefore, the delay τ_0 is defined by

$$\tau_0 = \frac{1}{\omega_0} \arccos \left(-\frac{(r - \omega_0^2)q + ps\omega_0^2}{s^2\omega_0^2 + q^2} \right). \quad \square$$

IV. HOPF BIFURCATION

From Theorem 4, we have the following result.

Theorem 5 Suppose (18), (19) and

$$\left(\frac{4\eta S^* I^*}{(\kappa S^* + I^*)^3} \right)^2 < \beta^2 + \left(\frac{\mu w}{(S^* + w)^2} \right)^2 \quad (25)$$

hold. Then there exists $\varepsilon_0 > 0$ such that for each $0 \leq \varepsilon < \varepsilon_0$, system (5)–(6) has a family of periodic solutions $P = P(\varepsilon)$

with period $T = T(\varepsilon)$, for the parameter values $\tau = \tau(\varepsilon)$ such that $P(0) = 0, T(0) = \frac{2\pi}{\omega_0}$ and $\tau(0) = \tau_0$.

Proof. We show that $i\omega_0$ is simple, by considering the branch of the characteristic root $\lambda(\tau) = \mu(\tau) + i\nu(\tau)$, of the characteristic equation (13), bifurcating from $i\omega_0$ at $\tau = \tau_0$. By differentiating equation (13) with respect to the delay τ , we obtain

$$(2\lambda + p + s \exp(-\tau\lambda) - (s\lambda + q)\tau \exp(-\tau\lambda)) \frac{d\lambda}{d\tau} - (s\lambda + q)\lambda \exp(-\tau\lambda) = 0. \quad (26)$$

Suppose, by contradiction, that $i\omega_0$ is not simple, then

$$(s\lambda + q)\lambda \exp(-\tau\lambda) = 0 \quad (27)$$

Substituting $\lambda = i\omega_0$ with $\omega_0 > 0$, equation (27) yields

$$si\omega_0 + q = 0 \quad (28)$$

This leads to a contradiction to the fact that

$$s = \rho - \frac{2\eta S^* I^*}{(\kappa S^* + I^*)^3} > \frac{\rho}{2} > 0 \quad \text{and} \quad q = \beta\rho > 0.$$

From equation (26), we have

$$\left(\frac{d\lambda}{d\tau} \right)^{-1} = \frac{(2\lambda + p) \exp(\tau\lambda) + s}{\lambda(s\lambda + q)} - \frac{\tau}{\lambda} \quad (29)$$

and from equation (13), we have

$$\exp(\tau\lambda) = -\frac{s\lambda + q}{\lambda^2 + p\lambda + r}. \quad (30)$$

Hence, by substituting (30) into (29), we obtain

$$\left(\frac{d\lambda}{d\tau} \right)^{-1} = \frac{-s\lambda^2 - 2\lambda q - pq + sr}{\lambda(s\lambda + q)(\lambda^2 + p\lambda + r)} - \frac{\tau}{\lambda} \quad (31)$$

Since

$$\text{sign} \frac{d \text{Re}(\lambda)}{d\tau} \Big|_{\tau=\tau_0} = \text{sign} \text{Re} \left(\frac{d\lambda}{d\tau} \right)^{-1} \Big|_{\tau=\tau_0},$$

by substituting $\lambda = i\omega_0$ into (31), we obtain

$$\text{sign} \frac{d \text{Re}(\lambda)}{d\tau} \Big|_{\tau=\tau_0} = \text{sign} \left(\frac{s^2\omega_0^6 + 2q^2\omega_0^4 + (p^2q^2 - s^2r^2 - 2q^2r)\omega_0^2}{(s\omega_0^4 - (pq + sr)\omega_0^2)^2 + ((ps + q)\omega_0^3 - qr\omega_0)^2} \right)$$

Under the hypotheses (18), (19) and (25) we have

$$s^2 + 2r - p^2 < 0$$

and

$$r^2 - q^2 < 0.$$

Therefore,

$$\frac{d \text{Re}(\lambda)}{d\tau} \Big|_{\tau=\tau_0} > 0.$$

The proof is complete. \square

V. NUMERICAL SIMULATION

In this section, we present a numerical simulation of the model system with the following parametric values:

$$\alpha = 0.3, \beta = 0.7, \gamma = 0.1, \eta = 0.3,$$

$$\kappa = 0.5, \mu = 0.5, w = 0.1, \rho = 0.9.$$

System (7)–(8) has a unique positive equilibrium $E^* = (0.0661, 0.3085)$. It follows from Theorem 3 that the critical positive time delay $\tau_0 = 1.6933$.

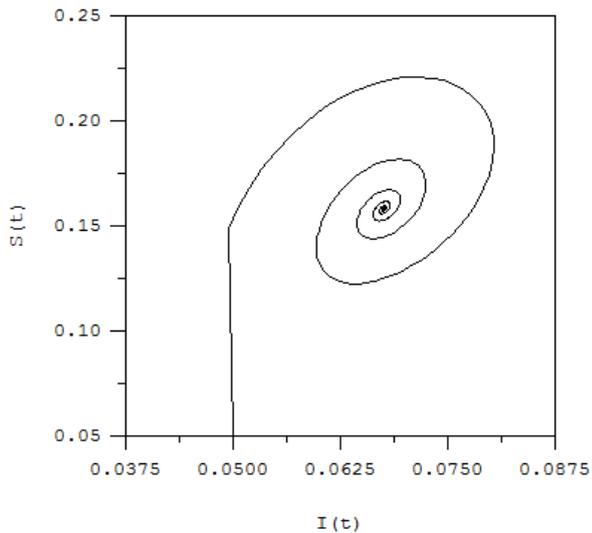


Fig. 1 For $\tau = 0$, the solution $(I(t), S(t))$ of the system (7)–(8) is asymptotically stable and converges to the equilibrium E^* .

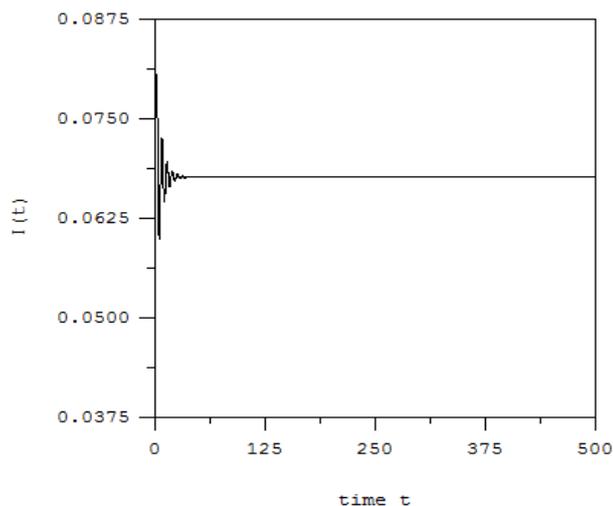


Fig. 2 Computer simulation of the model system in the case seen in Fig. 1, showing the inhibiting protein eventually tending to the steady state value.

Thus, we know that when $0 \leq \tau < \tau_0$, E^* is asymptotically stable. Fig. 1 shows a numerical simulation of the model system when $\tau = 0$, and the solution $(I(t), S(t))$ of the system (7)–(8) are asymptotically stable and converge to the equilibrium E^* . Fig 3 and 4 show the corresponding time series of the solution seen in Fig. 1, converging to the steady state values as time passes.

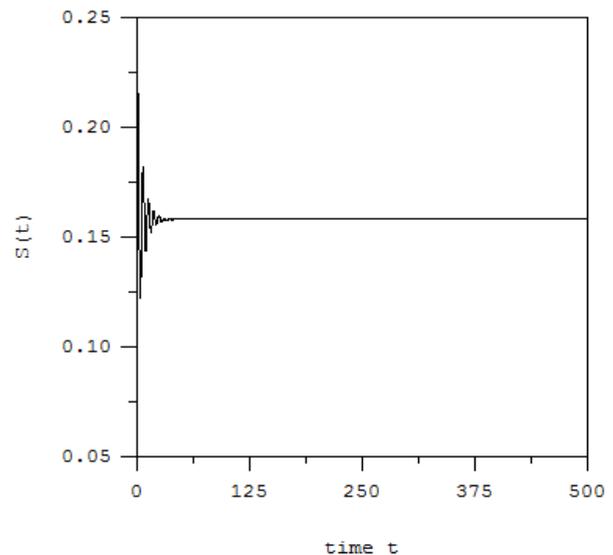


Fig. 3 Computer simulation of the model system in the case seen in Fig. 1, showing the level of the ligand-receptor complex eventually tending toward its steady state value.

From Theorem 4, when τ passes through the critical value τ_0 , E^* loses its stability and a family of periodic solutions with period $T = 10.0867$ bifurcating from E^* exists. Fig. 4 shows the numerical simulation of the model system in this case where the solution trajectory tends toward the limit cycle as theoretically predicted.

In Fig. 5 and 6, the corresponding time series of the densities of the inhibiting protein and the ligand-receptor complex, respectively, are shown to become periodic as time progresses. This numerical result confirms the theoretical prediction in Theorem 4. In such a situation, both state variables eventually exhibit sustained oscillation. This closely resembles qualitatively the experimental data on these factors reported in the literatures [20-22].

Most experimental or clinical data show the concentrations of these variables to eventually tend, often in an oscillatory fashion, toward the steady state values. Our analysis shows that the signal transduction process can admit sustained oscillation as a result of the amplification effect from the system's secondary hormone, provided that the responsive delay is large enough, but still remains in the vicinity of the critical value τ^* , provided certain conditions are satisfied, specifically, conditions (16), (17), and (23).

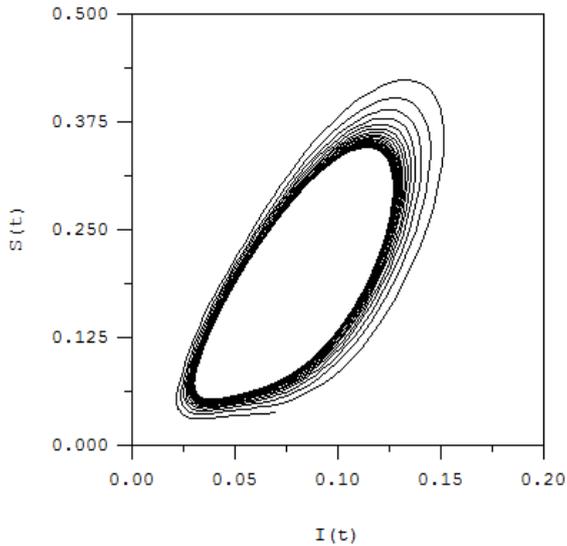


Fig. 4 When $\tau_0 = 1.6933$, a Hopf bifurcation occurs and a periodic solution appear as a limit cycle in the phase plane. Here the period is $T(0) = 10.0867$.

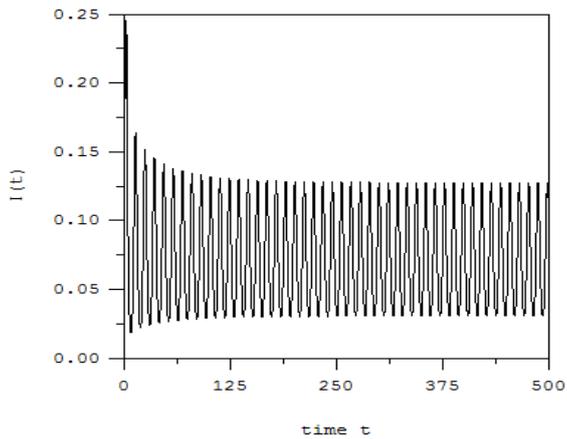


Fig. 5 Computer simulation of the model system in the case seen in Fig. 1, showing the inhibiting protein eventually becomes periodic with period $T(0) = 10.0867$.

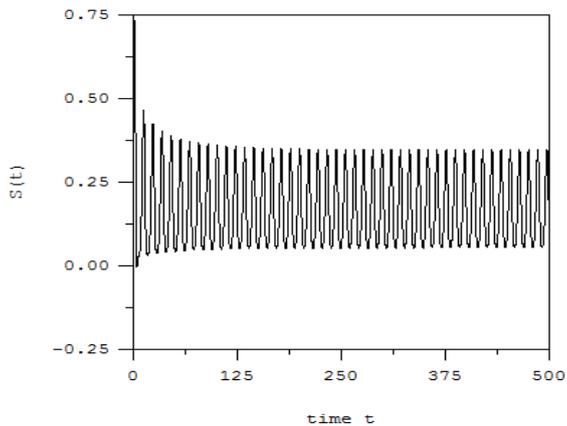


Fig. 6 Computer simulation of the model system in the case seen in Fig. 1, showing the level of the ligand-receptor complex eventually becomes periodic with period $T(0) = 10.0867$.

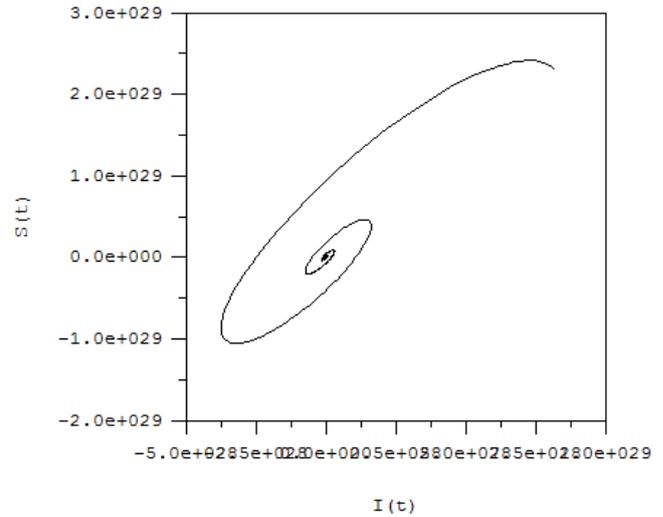


Fig. 7 For $\tau = 3.5$, the equilibrium E^* of the system (7)–(9) is unstable. The solution trajectory tends towards the equilibrium point as time passes.

When the delay τ becomes too large, the system can become unstable under certain conditions. This can give rise to situation which is medically difficult to control. It is important for the physicians to be able to predict such events, so that preventive steps may be taken to avoid undesirable symptoms.

Fig. 7 shows a computer simulation of the model system when $\tau = 3.5 > \tau^*$ in which case the solution trajectory diverges away from the equilibrium point and becoming unbounded.

The corresponding time series of the inhibiting protein and the ligand-receptor complex are shown in Fig. 8 and 9.

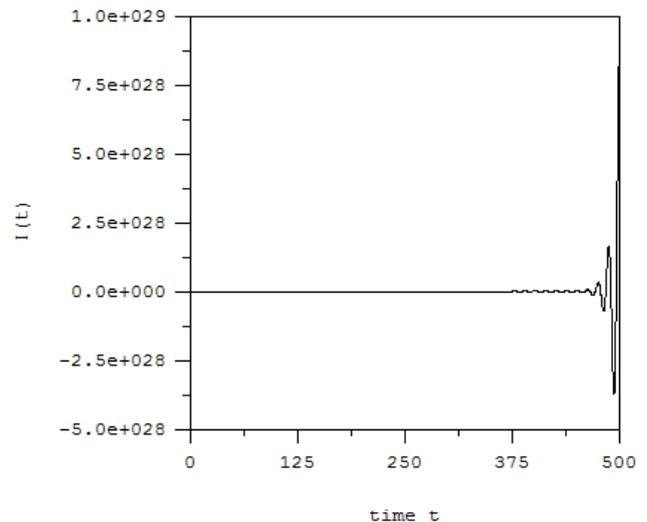


Fig. 8 Computer simulation of the model system in the case seen in Fig. 7, showing the inhibiting protein eventually becoming unbounded.

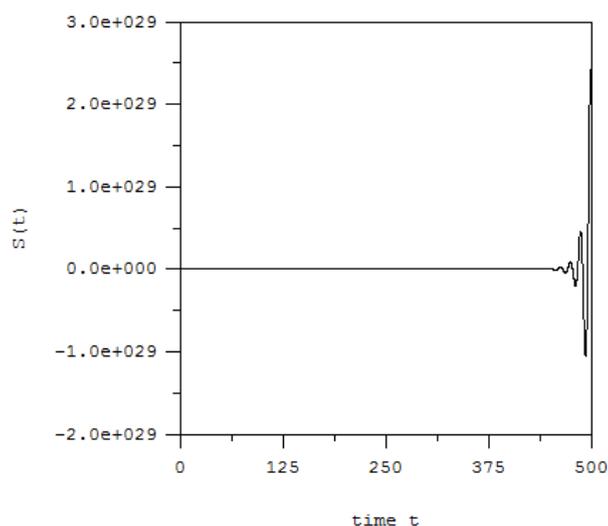


Fig. 9 Computer simulation of the model system in the case seen in Fig. 1, showing the level of the ligand-receptor complex eventually becoming unbounded.

VI. CONCLUSION

According to the World Health Organization, cancer is the world's second biggest killer after cardiovascular diseases [23, 24]. Cancer killed 7.6 million people in 2005. By 2015, that number is expected to rise to 9 million and increase further to 11.5 million in 2030. Every year, at least 7 million people die from cancer, more than HIV/AIDS, malaria and tuberculosis combined. The main types of cancer leading to overall cancer deaths each year are lung, stomach, liver, colorectal and breast cancer [23, 24, 25].

The abnormalities of the signal transduction pathway can also lead to the other human disorders. For example, in the RAS/mitogen-activated kinase pathway, the proteins implicated in signal transduction from cell surface receptors via the RAS pathway, such as Grb2 and SOS-1, were altered in cases of Alzheimer's disease [26]. Furthermore, the abnormality of G-protein coupled receptor signaling pathways causes many diseases. According to Spiegel et al. [27], in this signaling pathway, both decrease and increase in signal transduction activity can lead to human diseases such as retinitis pigmentosa, sporadic pituitary and thyroid tumors, adrenal and ovarian tumors. In the case of decreased signal transduction capability, diseases are caused by reduced expression of G-protein due to defective synthesis and/or membrane targeting, impaired activation of G-protein, and decrease in the time that G-protein remains in an active state due to increased desensitization or GTPase activity, respectively. In other case, increased signal transduction capability, diseases also arise from over expression of G-protein, inappropriate activation of G-protein and increase in the time that G-protein or effector remains in an active state due to decreased desensitization or GTPase activity [27]. For this reason, better understanding of the processes of the signal transduction pathway has been a subject of intense

investigation. Several recent studies have been proposed and studied mathematical models of the signal transduction.

In this study, we have derived conditions on the system parameters which give rise to different dynamical behaviours which could be expected in the signalling pathway under the impact of delays. We proved that if $R_0 < 1$, the equilibrium point E^* is locally asymptotically stable for all $\tau \geq 0$. We have shown that the local stability of the equilibrium point, E^* , depends on the time delay τ . The system changes its behaviour from being stable to unstable near E^* when τ crosses the critical value τ_0 via a Hopf bifurcation and periodic solutions bifurcate from E^* . Finally, some numerical simulations are given to verify our theoretical predictions.

Our work on this delay differential equations model presented in this study and insights gained by our model analysis is expected to be of great benefit in interpreting experimental data which should motivate the design of experiments to confirm our theoretical results which could potentially lead to valuable discoveries.

ACKNOWLEDGMENT

This research is supported by the Centre of Excellence in Mathematics, CHE, Thailand. The first author is supported by a student scholarship from the Development and Promotion of Science and Technology Talents Project (DPST), Thailand.

REFERENCES

- [1] H. Lodish, A. Berk, S.L. Zipursky, P. Maatsudaira, D. Baltimore, J. Darnell, *Molecular Cell Biology*, 4th Ed. W.H. Freeman, 2000.
- [2] T. Hunter, Signaling—2000 and beyond, *Cell*, Vol. 100, 2000, pp. 113–127.
- [3] H. Zhong, R.R. Neubig, Regulator of G protein signaling proteins: novel multifunctional drug targets, *JPET*, Vol. 297, No. 3, 2001, pp. 837–845.
- [4] The American Cancer Society, *Cancer Facts & Figures 2010*, 2010.
- [5] G.M. Cooper, R.E. Hausman, *The cell: a molecular approach*, 4th ed., Sinauer, 2007.
- [6] L. Cassimeris, V.R. Lingappa, G. Plopper, G., Lewin, *Cells*, 2nd ed., Jones and Bartlett Publishers, 2011.
- [7] B. Alberts, A. Johnson, J. Lewis, M. Raff, K. Roberts, P. Walter, *Molecular Biology of the Cell*, 5th ed., Garland Science, 2008.
- [8] A. Levchenko, P.A. Iglesias, Models of eukaryotic gradient sensing: application to chemotaxis of amoebae and neutrophils, *Biophys. J.*, Vol. 82, No. 1, 2002, pp. 50–63.
- [9] P.A. Iglesias, Feedback control in intracellular signaling pathways: regulating chemotaxis in *Dictyostelium discoideum*, *Europ. J. Contr.*, Vol. 9, 2003, pp. 216–225.
- [10] R. Bianco, D. Melisi, F. Ciardiello, G. Tortora, Key cancer cell signal transduction pathways as therapeutic targets, *Eu. J. Cancer*, Vol.42, No.3, 2006, pp. 290–294.
- [11] M. Huse, T. W. Muir, L. Xu, Y.-G. Chen, J. Kuriyan, J. Massague', The TGF β Receptor activation process: an inhibitor- to substrate-binding switch, *Molecular Cell*, Vol. 8, 2001, 671 – 682.
- [12] J.A. Williams, O.M. Guicherit, B. I. Zaharian, Y. Xu, L. Chai, H. Wichterle, C. Kon, C. Gatchalian, J.A. Porter, L.L. Rubin, F.Y. Wang, Identification of a small molecule inhibitor of the hedgehog signaling pathway: effects on basal cell carcinoma-like lesions *PNAS*, Vol. 100, No. 8, 2003, pp. 4616–462.
- [13] M. Wistrand, L. Kaäll, E.L.L. Sonhammer, A general model of G protein-coupled receptor sequences and its application to detect remote homologs, *Protein Sci*, Vol. 15, 2006, pp. 509–521.

- [14] S.-Y. Shin, O. Rath, S.-M. Choo, F. Fee, B. McFerren, W. Kolch, K.-H. Cho. , Positive-and negative-feedback regulations coordinate the dynamic behavior of the Ras-Raf-MEK-ERK signal transduction pathway, *J. Cell Sci.*, Vol. 122, 2008, pp. 425-435.
- [15] M.H. Bronchud, M. Foote, G. Giaccone, O. Olopade, P. Workman, *Principles of Molecular of Oncology*, Humana Press, 2008.
- [16] C. Rattanakul, Y. Lenbury, J. Bell, V. Chatsudthipong, W. Triampo and P.S. Crooke, Spatial Turing-type Pattern Formation in a Model of Signal Transduction Involving Membrane-based Receptors Coupled by G Proteins, *Cancer Informatics*, Vol.2, 2006, pp. 1-15.
- [17] W. Sarika, Y. Lenbury, W. Anlamlert, Modeling and Analysis of the Signal Transduction Process with Delays Involving G Protein Coupled Receptors as a Drug Target, *International Journal of Mathematical Models and Methods in Applied Science.*, Vol. 4, No. 5, 2011, pp. 839-847.
- [18] A. Kaddar, On the dynamics of a delayed SIR epidemic model with a modified saturated incidence rate, *EJDE*, Vol. 2009, No. 133, 2009, pp. 1-7.
- [19] A. Kaddar, Stability analysis in a delayed SIR epidemic model with a saturated incidence rate, *NLAMC*, Vol. 15, No. 3, 2010, pp.299-306.
- [20] M. Sajadi, K.E. Furse, X-X. Zhang, L. Dehmel, S. A. Kovalenko, S. A. Corcelli, N. P. Ernsting, Detection of DNA-Ligand Binding Oscillations by Stokes-Shift Measurements, *Angewandte Chemie International Edition*, Vol. 50, Issue 40, 2011, pp. 9501-9505.
- [21] C. Rattanakul, T. Sungkaworn, Y. Lenbury, M. Chudoung, V. Chatsudthipong, W. Triampo, B. Novaprateep, Modeling Signal Transduction Involving G Protein Coupled Receptors by Genetic Algorithm and Nonlinear Spatiotemporal Analysis, *Recent Advances in Applied Mathematics and Computational and Information Sciences*, Vol. 1, 2009, pp. 39-44.
- [22] D. Prathumwan, Y. Lenbury, P. Satiracoo, C. Rattanakul, Euler-Maruyama Approximation and Maximum Likelihood Estimator for a Stochastic Differential Equation Model of the Signal Transduction Process, *International Journal of Mathematical Models and Methods in Applied Sciences*, Vol. 6, Issue 2, 2012, pp. 323-331.
- [23] World Health Organization, *The World Health Organization's Fight Against Cancer: Strategies That Prevent, Cure and Care*, 2007.
- [24] World Health Organization, *Action Plan for the Global Strategy for the Prevention and Control of Noncommunicable Diseases*, 2008.
- [25] T.Y. Wah, O.S. Sim, Development of data warehouse for lymphoma cancer diagnosis and treatment decision support, *WSEAS Transactions on Information Science and Applications*, Vol. 6, Issue 3, 2009, pp. 530-543.
- [26] A. McShea, D.A. Zelasko., J.L. Gerst, M.A. Smith, Signal transduction abnormalities in Alzheimer's disease: evidence of a pathogenic stimuli, *Brain Research*, Vol. 815, No. 2, 1999, pp. 237-242.
- [27] A.M. Spiegel, L.S. Weinstein, and A. Shenker, Abnormalities in G protein-coupled signal transduction pathways in human disease, *J. Clin. Invest.*, Vol. 92, 1993, pp. 1119-1125.