ABSTRACT. In this paper we model the spatial and temporal dynamics of the STAT signaling protein by means of nonlinear partial differential equations. We show that the diffusion together with the corresponding biochemical reactions plays an important role in governing the dynamical behavior of the STAT protein concentration. The general model of the STAT protein dynamics is reduced to an analytically tractable partial differential equation (PDE). By applying the modified method of simplest equation to the described model we obtain its analytical solution. This solution describes nonlinear kink and solitary waves in the STAT signaling dynamics.

KEY WORDS: STAT signaling protein, diffusion, PDEs, Modified method of simplest equation, analytic solution, kinks.

1. Introduction
The specificity of biological responses is often achieved in a combinatorial fashion through the concerted interaction of signaling pathways. Here we will discuss the eventual interaction between the units of MEK/ERK (Mitogen-Activated Protein Kinase/Extracellular signal-Regulated Kinase) and JAK/STAT (Janus Kinase/Signal Transducers and Activators of Transcription) signaling pathways. In cell signaling the pathways are understood as networks of recurrent biochemical reactions, by which the information transmission (in a signal form) is accomplished. The disturbance of the intracellular signal transmission from the membrane receptors to the nucleus genes is assumed as a general reason for a cancer progress. In [1] the cross talk between ERK- and STAT- signaling pathways is modeled in a form of a system of four nonlinear ODEs for the protein concentrations. The model is based on the experimental results given in papers [2], where the interaction between STAT 5a and the MAPKs (Extracellular signal-Regulated Kinases ERK1 and 2) is analyzed. Next, the spatial modeling of the same interaction is accomplished, by introducing an appropriate reaction-diffusion model in [3]. The model is investigated qualitatively and the authors demonstrate that the effects of compartmentalization and molecular crowding can be interpreted as inhomogeneous distributions of protein concentrations (densities). This is a qualitative indication that modeling signaling pathways by reaction-diffusion systems affords a realistic approach for the analysis of spatially restricted biochemical reactions in the cell signaling.
2. A Modified Method of Simplest Equation

Let us briefly describe the modified method of simplest equation [4, 5], which is powerful tool for obtaining exact and approximate solutions of nonlinear PDEs. We have to solve a partial differential equation and let by means of an appropriate ansatz this equation be reduced to a nonlinear ordinary differential equation

\[
P(F(\xi), \frac{dF}{d\xi}, \frac{d^2 F}{d\xi^2}, \ldots) = 0
\]

For large class of equations from the kind (2.1) exact solution can be constructed as finite series

\[
F(\xi) = \sum_{\mu=0}^{v_i} P_\mu [\Phi(\xi)]^\mu
\]

where \( \Phi(\xi) \) is a solution of some ordinary differential equation referred to as the simplest equation. The simplest equation is of lesser order than (2.1) and we know the general solution of the simplest equation or we know at least exact analytical particular solution(s) of the simplest equation. The modified method of simplest equation can be applied to equations of the kind

\[
E(\frac{\partial^{\omega_x} F}{\partial x^{\omega_x}}, \frac{\partial^{\omega_t} F}{\partial t^{\omega_t}}, \frac{\partial^{\omega_x} \partial^{\omega_t} F}{\partial x^{\omega_x} \partial t^{\omega_t}}) = G(F)
\]

where \( \omega_x = \omega + \omega_3 \). In the paper [4] the application of the modified method of simplest equation is based on the following steps: 1) By means of an appropriate ansatz (for an example the traveling-wave ansatz) the solved class of nonlinear PDE of kind (2.3) is reduced to a class of nonlinear ODEs of the kind (2.1); 2) The finite-series solution (2.2) is substituted in (2.1) and as a result a polynomial of \( \Phi(\xi) \) is obtained. (2.2) will be a solution of (2.3) if all coefficients of the obtained polynomial of \( \Phi(\xi) \) are equal to 0; 3) By means of a balance equation one ensures that there are at least two terms in the coefficient of the highest power of \( \Phi(\xi) \). The balance equation gives a relationship between the parameters of the solved class of equations and the parameters of the solution; 4) The application of the balance equation and the equalizing the coefficients of the polynomial of \( \Phi(\xi) \) to 0 leads to a system of nonlinear relationships among the parameters of the solution and the parameters of the solved class of the equation; 5) Each solution of the obtained system of nonlinear algebraic equations leads to a solution a nonlinear PDE from the investigated class of nonlinear PDEs.
3. A Reaction (ODE) Model of the STAT Signaling Protein

In [1] the interaction between the activated ERK protein (ε) and phosphorylated STAT protein (s) is presented by the following system of nonlinear ordinary differential equations:

\[
\begin{align*}
\frac{d\varepsilon}{dt} &= k_1 ES - (k_2 \varepsilon + k_3)\varepsilon - k_4 Es + k_6 \varepsilon s, \\
\frac{ds}{dt} &= -I + k_1 ES - k_4 E\varepsilon - (k_4 E + k_5)s + k_3 \varepsilon s,
\end{align*}
\]

where \(k_1\) is a rate constant of reactions of associations; \(k_2\) and \(k_3\) are constants of exponential growths and disintegrations; \(E\) and \(S\) are initial values of the sums of corresponding concentrations of inactive and active ERKs and non-phosphorylated and phosphorylated STATs; \(I\) is inhibitor source respectively. The source \(I\) inhibits the phosphorylation of non-phosphorylated STAT5a. A more concrete interpretation of the inhibitor \(I\) can be given in connection with the role of the SOCS proteins in linking JAK/STAT pathway. Biological responses elicited by the JAK/STAT pathway are modulated by inhibition of JAK (and respective attenuation of STAT) by a member of the Suppressors Of Cytokine Signalling (SOCS) proteins. In [1] this inhibition is presented by the following manner:

\[I = k\Sigma\]

where \(\Sigma\) is a constant concentration of SOCS proteins and \(k\) is a reaction rate constant of inhibition respectively. It is clear that the considered interaction between ERK and STAT pathways can occur only if \(I\) is sufficiently small, i.e. phosphorylation of the protein STAT5a exists. Therefore we assume the concentration of SOCS proteins to be sufficiently small.

Next we assume for (3.1) that the inequality \(\varepsilon \ll s\) holds, in view of the fact that the amount of ERK molecules is essentially smaller than the amount of STAT ones [6, 7]. Further in accordance with the QSSA (Quasi-Steady-State Approximation) theorem [8] we consider the first equation of (3.1) to be linear with respect to \(\varepsilon\) and we treat it as an attached system [8], i.e. we take into consideration that \(\varepsilon\) is a sufficiently small ‘constant’. According to the requirements of the QSSA theorem we prove that the attached system has a stable steady state (then well-known Lyapunov’s definition of stability is satisfied). After replacing the steady state value of \(\varepsilon\) in the second equation of (3.1) (the degenerate system), the quasi-stationary approximation of (3.1) is obtained in the form:
3.2
\[
\frac{ds}{dt} = \frac{as^2 - bs + c}{ds - e} - fs + g
\]

where the new coefficients are positive and have the following form:

\[
a = k_1^2 E, \quad b = 2k_1\Sigma E S, \quad c = k_1^2 E S^2, \quad d = k_1, \\
e = k_1S + k_2, \quad f = k_1E + k_3, \quad g = k_1ES - k\Sigma
\]

4. A Reaction-Diffusion (PDE) Model of the STAT concentration

4.1. Space-Temporal modeling of the STAT Signaling Protein.

The STAT concentration is homogeneous distributed in the cell cytoplasm in absence of an appropriate nucleus response in the form of ERK or SOCS protein production initiated by cell signaling. However, when a similar response (ERK or SOCS proteins increase) is available, the STAT protein dramatically increases or decreases near the nucleus membrane and some inhomogeneous radial distribution of its concentration takes place in the intracellular space. This means that the diffusion involves in the process and it can be presented by the following partial differential equation:

\[
\frac{\partial s}{\partial t} = \frac{as^2 - bs + c}{ds - e} - fs + g + D_s \frac{\partial^2 s}{\partial r^2}
\]

where \( r \) is the space coordinate from the cell membrane to the nucleus, and \( D_s \) is a diffusion coefficient of the STAT concentration. We fix some boundary conditions for the gradients of concentrations at the cell membrane and the nucleus one in the form:

\[
\frac{\partial s}{\partial r} \bigg|_{r=0} = 0
\]

where \( l \) is the distance between the membrane and the nucleus.

4.2. Travelling wave solutions of (4.1.1). Application of the Modified method of simplest equation.

In order to apply the methodology described in Section \( II \) to (4.1.1) we firstly transform it in the ordinary differential equation of second order:
**Space-temporal modeling of the STAT signaling protein**

\[(4.2.1) \quad D_s \frac{d^2 s}{d \xi^2} + v \frac{ds}{d \xi} + \frac{as^2 - bs + c}{ds - e} - fs + g = 0\]

by introducing the substitution \(s(r, t) = s(\xi) = s(r - vt)\), where \(v\) is the velocity of some density (concentration) propagation, that we intend to determine. We develop the last three terms of (4.2.1) in a Taylors series centered in \(s = 0\) and retain only the terms up to quadratic power. Then (4.2.1) obtains the form:

\[(4.2.2) \quad D_s \frac{d^2 s}{d \xi^2} + v \frac{ds}{d \xi} + \alpha s^2 + \beta s + \chi = 0\]

where

\[(4.2.3) \quad \alpha = -\frac{a}{e} + \frac{bd}{e^2} - \frac{cd^2}{e^3}, \quad \beta = -\frac{cd}{e^2} + \frac{b}{e} - f, \quad \chi = \frac{-c}{e} + g\]

Next we apply the methodology from Section II to (4.2.2). We construct a solution as finite series

\[(4.2.4) \quad s(\xi) = \sum_{i=0}^{n} a_i \phi^i, \quad \frac{d\phi}{d\xi} = \sqrt{\sum_{j=0}^{r} c_j \phi^j},\]

where \(a_i\) and \(c_j\) are parameters that we will determine below. Following the steps of the modified method of simplest equation we substitute (4.2.4) in (4.2.2) and obtain an equation that contains powers of \(\phi\). Next we balance the highest power arising from the second derivative in (4.2.2) with the highest power arising in the term containing \(s^2\) in the same equation. The resulting balance equation is \(r = n + 2, \quad n = 2, 3, \ldots\). In the simplest case if \(n = 2\), then \(r = 4\). Assuming that \(c_0 = p^2, \quad c_1 = c_3 = 0, \quad c_2 = -2pr, \quad c_4 = r^2 \neq 0\) we search for a solution of the form

\[(4.2.5) \quad s(\xi) = a_0 \phi + a_2 \phi^2, \quad a_2 \neq 0, \quad \frac{d\phi}{d\xi} = r\phi^2 - p\]

Here we use a particular case of the equation of Riccati as simplest equation. Substituting this in (4.2.2) we obtain the following system of 5 algebraic equations
The solution of (4.2.6) is:

\[ a_1 = -\frac{6D_r^2}{\alpha}, \quad a_2 = -\frac{6vr}{5\alpha}, \quad p = \frac{v^2 + 25\beta D_s}{200D_r^2r}, \quad v = \frac{5}{3}\sqrt[3]{\beta D_s} \]

The expression for the solitary wave depends on the solution of the differential equation in (4.2.5) and it is given by

\[ s(\xi) = \frac{-2a_1\sqrt[3]{\beta D_s}p}{\beta}\tanh\left(\frac{\sqrt[3]{\beta D_s}}{6D_s}(\xi + c)\right) - \frac{12a_2D_r^2p^2}{\beta}\tanh\left(\frac{\sqrt[3]{\beta D_s}}{6D_s}(\xi + c)\right)^2 \]

where \( a_1, a_2, p \) are given by (4.2.7), and \( r \) is a free parameter. Value (4.2.8) describes a kink wave (an example is shown in Fig. 1). This kink can be interpreted as a front of the STAT density (concentration) propagation in the intracellular space.

Figure 1. Graph of the solution \( s(\xi) \) at \( \alpha = 1; \beta = 10; \chi = -10; p = 125; ; D_s = 1 \)
5. Discussion

In this paper we have discussed the quasi-stationary dynamics of the cross talk between ERK and STAT signaling pathways. By using biological as well as mathematical assumptions we have proved that near the quasi-stationary state of the considered biomolecular process its behaviour determines by the dynamics of the STAT signaling molecules. Moreover, if some external signals appear in the cell (in a form of additional ERK or SOCS protein production), the inhomogeneous distribution of the STAT concentration will occur in the intracellular space. We have modeled this by introducing an appropriate nonlinear PDE. In addition, by means of traveling-wave ansatz, we have obtained an exact particular analytical solution of the model equation. This solution describes nonlinear kink and solitary wave, expressing the spreading of the STAT density changes in the space.

REFERENCES


