Signal transduction in the invadopodia formation using fixed domain method

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\textbf{Abstract.} The degradation of the extracellular matrix is driven by actin-based protrusions known as invadopodia, lead to the cancer cell invasion across the surrounding tissue barriers. Signal transduction through the binding between ligand and membrane associated receptor is important in order to establish the actin polymerization, and consequently push the membrane of migrating cells. In this study, we considered one-dimensional Stefan-like problem of the signal transduction and cell membrane is treated as a free boundary surface to separate any activity that happened on intra- and extra-cellular regions. The velocity concerning the movement of the free boundary is calculated by the decrease of signal gradient on the front. The problem is solved numerically using finite-difference scheme of fixed-domain method. Our results showed that both free boundary positions and signal distributions are increasing as time progresses.

1. Introduction

Cell movement is important for its own reason. On a good side, white blood cells swim to heal cuts. On the other side, tumor cells travel and invade the surrounding tissue or extracellular matrix (ECM) to form the secondary tumor known as metastasis, which is the main cause of mortality among cancer patients, [1]. Tumorigenesis is a complex multi-step process that results from genetic changes and cause malignant transformation of normal cells, [2]. The common characteristics for cancers are:

(i) abnormal signal transduction resulting in uncontrolled cell proliferation,
(ii) loss of apoptosis or programmed cell death,
(iii) angiogenesis leading to the enhanced blood supply of tumors, and
(iv) tissue invasion and metastasis permitting the spread of the cancer.

Concentrating on the fourth feature, proteolytic deterioration of the ECM is a vital phenomenon in tumor invasion and metastasis [3][4]. This issue is driven by actin-rich protrusions of the plasma membrane or known as invadopodia. Over the pass decade, many works had been carried out in order to understand how invadopodia contributes in degrading the surrounding tissue barriers that lead to the cancer cell migration [5][6].

Invadopodia are subcellular structure found in invasive cancer cells uniquely formed by metastatic carcinoma cells. Formation of invadopodia and ECM degradation activity involves
the coordination of many cell biological processes including ligand (or known as ECM fragment) and epidermal growth factor receptor (EGFR) signaling, actin cytoskeletal polymerization and reorganization. These lead to physical force towards membrane surface and matrix metalloproteinase (MMP) localization, activation and secretion [7][8][9]. Later, the degradation of the ECM by MMP will produce more ligand and this process is repeated. Generally, binding of ligand and EGFR such as transforming growth factor alpha (TGF-α) plays an important role in the formation of the invadopodia, which activates a signaling pathway for actin branching and MMPs regulation [10].

Mathematical approaches using continuous and discrete models, particularly by considering partial and ordinary differential equations in tumor growth take the role in the relationship between mathematics and medical oncology [2][11][12][13][14][15][16]. Furthermore, investigation on the cancer cell invasion through invadopodia formation have been considered by [10] and [17] from the mathematical point of view.

Saitou et al. [10] investigated the formation of invadopodia by introducing the mathematical models for several fundamental processes involving actin organization, $n(x,t)$, ECM degradation, $c(x,t)$, ligand formation, $c_*(x,t)$ and MMP regulation, $f(x,t)$. They marked the effect of MMP rate constant, $\kappa_f$ in the invadopodia appearances. Small value of $\kappa_f$ generated similar protrusions in term of space and time scales as seen in the biological experiments. However a problem in numerical simulation arises where the region of actins, $n > 0$ become disconnected as the time passes. In fact, $n$ must lie inside the cancer cell which is located near to the invasion front, and its polymerization activities exert some pushing forces for the movement of a cancer cell.

In this study, we focused on the signal transduction (only happen inside a cell) which is stimulated by the binding activity between ligand and EGFR. This signal is a new parameter that was not accounted previously in [10]. Since the events inside and outside of the cell are different, we considered a new domain with free boundary of plasma membrane to overcome the problem of actin disconnection. We solved the partial differential equations using fixed domain method (FDM) and investigated the spatio-temporal dynamics of the system using one (spatial) dimensional numerical simulations.

2. The model
Consider a domain $\Omega = (0, t) \subset \mathbb{R}^1$ occupied by an individual cancer cell. Let $\omega^i_n \subset \subset \Omega$ defined by $\omega^i_n = (0, x(t))$ and $\omega^e = \Omega \setminus (0, x(t))$ represent intra-cellular and extra-cellular, respectively. We assume that the signal may diffuse upon contact between ligand and receptor and lose their ability to enhance the assembly of actin by their random diffusive behaviour. Hence, the signal transduction process is modelled by the following simple equation:

$$\sigma_t = \underbrace{d_\sigma \sigma_{xx}}_{\text{diffusion}} - \underbrace{\lambda_\sigma \sigma}_{\text{decay}}, \quad \text{in} \quad \bigcup_{0<t<T} \omega^i_n \times \{t\}, \quad (1)$$

where $\sigma(x, t)$, $d_\sigma$ and $\lambda_\sigma$ are the signal density, signal diffusivity coefficient and decay rate constant, respectively.

Meanwhile, the interface separates one region from another and the velocity, $v$ indicates how the interface moves either shrinks (pulling the plasma membrane towards the inner region of a cell) or expands (pushing the plasma membrane towards the outer region of a cell). We assume $v$ is equal to the gradient of the signal inside a cell:

$$v = \gamma_n \sigma_x, \quad \text{on} \quad \bigcup_{0<t<T} x(t) \times \{t\}, \quad (2)$$

where $\gamma_n$ is a positive constant and the velocity is defined by $v = \frac{dx(t)}{dt}$. 

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Figure 1. Fixed space domain in $y$ is transformed from free space domain in $x$.

For the simplicity in all our experiments, we omit the decay term in equation (1), and set the diffusion coefficient $\sigma$ and constant $\gamma_n$ to be equal to one. Thus, our simplified cancer cell problem for one-dimensional signaling pathways system becomes that of finding $\sigma(x, t)$ and $x(t)$ such that,

\[
\begin{aligned}
\sigma_t &= \sigma_{xx}, & 0 < x < x(t), & 0 < t \leq T, \\
\sigma(0, t) &= 0, & 0 \leq t \leq T, \\
\sigma(x(t), t) &= g(t), & 0 \leq t \leq T, \\
\sigma(x, 0) &= \varphi(x), & 0 < x \leq x(0), \\
\frac{dx(t)}{dt} &= \sigma_x(x(t), t), & 0 < t \leq T.
\end{aligned}
\]

where the second and third equations are boundary conditions and the fourth one is an initial condition. Otherwise, $x(0)$ is an initial free boundary (plasma membrane) position.

Next, we introduce a new signal transformation variable, $v(x, t)$ as follows,

\[
v(x, t) = g(t) - \sigma(x, t).
\]

Therefore, we obtain the signal transformed model for CM-A as

\[
\begin{aligned}
v_t &= v_{xx} + g(t), & 0 < x < x(t), & 0 < t \leq T, \\
v(0, t) &= g(t), & 0 \leq t \leq T, \\
v(x(t), t) &= 0, & 0 \leq t \leq T, \\
v(x, 0) &= \varphi(x), & 0 < x \leq x(0), \\
\frac{dx(t)}{dt} &= -v_x(x(t), t), & 0 < t \leq T.
\end{aligned}
\]

Generally, all numerical works for free boundary problem face a crucial difficulty in dealing with the moving boundary. In order to overcome this complication, numerous works have been proposed and we can divide them into two classes. One of them is to transform the original free boundary problem into an approximation fixed boundary problem, [18]. The other is to trail directly the free boundary and FDM is dropped in this category. FDM, [19] introduces a variable transform in order to fix the computational free space domain, $0 \leq x \leq x(t)$ to the fixed space domain, $0 \leq y \leq 1$ (see Figure 1). This transformation locates a moving front, $x(t)$ on a given mesh point at the boundary-end, $y = 1$, where $y$ is the transformation space variable for space $x$.

In order to modify free boundary domain $0 \leq x \leq x(t)$ into fixed boundary domain $0 \leq y \leq 1$, we put a variable transformation,

\[
y = \frac{x}{x(t)}, \quad U(y, t) = v(x, t),
\]

(4)
which implies
\[ \sigma(x, t) = g(t) - U(y, t). \] 

Therefore, CM-B can be transformed into

\[
\begin{cases}
  x(t)^2 U_t = U_{yy} + x(t) y \frac{dx(t)}{dt} U_y + x(t)^2 \frac{dg(t)}{dt}, & 0 < y < 1, \quad 0 < t \leq T, \\
  U(0, t) = g(t), & 0 \leq t \leq T, \\
  U(1, t) = 0, & 0 \leq t \leq T, \\
  U(y, 0) = g(0) - \varphi(y), & 0 \leq y \leq 1, \\
  \frac{dx(t)}{dt} = -\frac{1}{x(t)} U_y(1, t), & 0 < t \leq T.
\end{cases}
\]

3. Results of numerical simulations

The following results were obtained using implicit finite difference scheme which implements the method of Thomas decomposition on CM-C. In the following simulations, we used step length \( h = 1/2^4 \), time step \( k = 1/2^{10} \), maximum time \( T = 10 \) and initial plasma membrane \( x(0) = 1 \). The constants of \( h \) and \( k \) are selected based on the CFL condition where \( \lambda = k/h^2 \) is between 0 and 1/2 (see [18]). Admon, [20] mentioned in his work that the density of signal is equal to the density of ligand on the plasma membrane. He obtained the signal density using characteristic method and hence is taken by an exponential function of \( g(t) = 1 - e^{-t} \). We assume that there is no signal density at the start of the computation and we thus \( \varphi(x) = 0 \).

Figure 2 shows the plasma membrane or interface positions for the whole time computation. It is examined that the plasma membrane position is increasing as time increases. We can see that the passage from the initial free boundary position \( x(0) = 1 \) to the position at the maximum time, \( t = 10 \) takes place smoothly and continuously. The maximum position of the plasma membrane is recorded at the end of the numerical computation, \( t = 10 \) which is located at \( x = 4.0625 \). Here, an invadopodium (since one-dimensional) should be formed or existed since the plasma membrane expanding with respect to time proceeds.

In the next two simulations, Figure 3 and Figure 4, we only consider the effect of random diffusive behaviour of the signal. We make a simple hypothesis that there is a high signal concentration on the plasma membrane as time progressed. Both figures show two different
pattern of signal distributions for the early stage \(0 \leq t \leq 2\) and later time \(2 \leq t \leq 10\). Owing to the increase in time, \(t\), the concentration of the signal on each plasma membrane position is also increasing and recorded the maximum comparing to the other location. These phenomena implies that the transduction of signal from ligand-receptor binding activities stimulate higher signal concentration on the boundary instead of in the inner cell region. At a specific location, i.e. \(x = 1\), it is determined that the signal concentration increasing at the earliest time until it reached the maximum at \(t = 2\) (Figure 3). On the spur of the moment, these profiles contradict the earlier pattern and begin to decrease for the time, \(t = 2.5\) to \(t = 10\) (Figure 4).

4. Conclusion

Previous mathematical model, [10] has considered the positive feedback loops effects on the molecules concentrations involving actin, MMP, ECM and ligand variables. In this study, we have considered a new variable that also plays a significant role in the formation of invadopodia in an individual cancer cell which is signal transduction. This signal is stimulated by the interaction between ligand and EGFR on the plasma membrane. The plasma membrane is treated as a free (moving) boundary in order to avoid parameters located inside a cell diffused into the extra-cellular region.

The model of signal transduction is solved using fixed domain method by transforming the free boundary into fixed boundary domain. Numerical results showed that the plasma membrane expanded as time increases. Meanwhile the signal densities showed two different patterns for two different periods of time. For the time 0 to 2, the signal densities are increasing. On the other hand, the signal densities are decreasing for the later time 2.5 to 10. But it is observed that the concentration of signal remains maximum on the plasma membrane and this justified the hypothesis that we made earlier.

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