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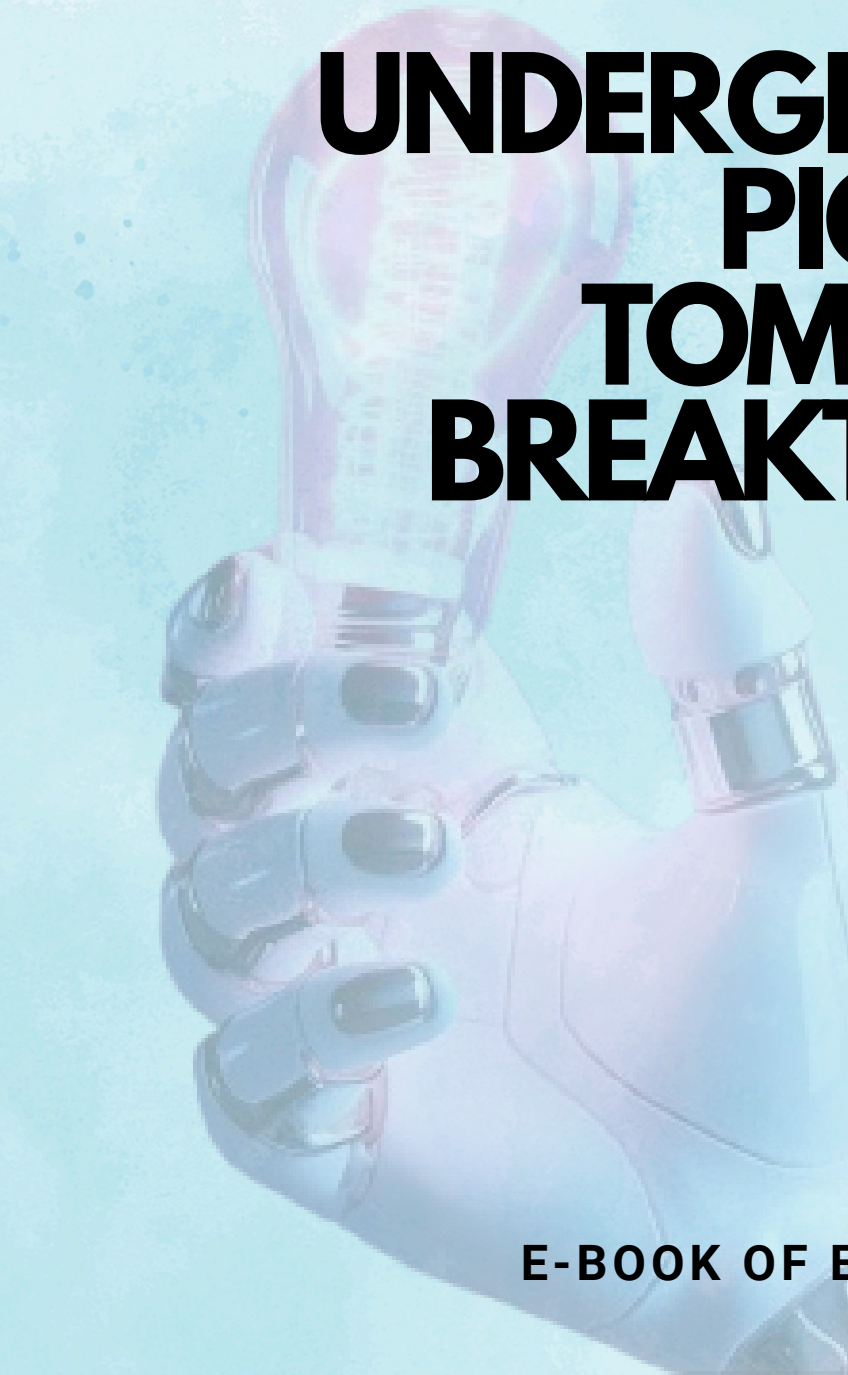

E-BOOK OF EXTENDED ABSTRACTS

INVADOPODIA: THE FORMATION THROUGH THE LENS OF LIGAND DECAY

Azyyati Syamimi Mohd Saifuddin, Nge Xiao Wei, Nurdiana Natasya Wan Saharudin, Insyirah Md Ghazali, and Noorehan Yaacob*

Department of Mathematical Sciences, Faculty of Science, Universiti Teknologi Malaysia, 81310 UTM Johor Bahru, Johor, Malaysia

* noorehan@utm.my

ABSTRACT

Cancer is a major global health challenge, with metastasis identified as the leading cause of cancer-related deaths. A critical step in this process is the formation of invadopodia, actin-based membrane protrusions that enable cancer cells to degrade the extracellular matrix (ECM) and invade surrounding tissues. This research designs a two-dimensional mathematical model to examine the role of ligand decay in invadopodia formation. The model incorporated ligand-signal interactions with decay terms, while actin polymerisation is represented as plasma membrane velocity. Numerical algorithms were implemented using the level set method, second-order finite difference schemes, and the ghost fluid method to capture the movement of the free boundary membrane. Simulation results show that ligand concentration highest at the membrane interface due to receptor-ligand binding, with decay rates strongly influencing the extent and behavior of protrusion formation. These findings demonstrate that mathematical modeling provides an effective framework to capture the dynamics of invadopodia formation and offer new insights into the role of ligand decay in cancer cell invasion.

Keywords: Decay rate, Invadopodia formation, Level set method, Ligand, Mathematical modeling

INTRODUCTION

Cancer remains one of the most formidable and devastating causes of mortality worldwide. According to data from the World Health Organization (WHO), there were 19,976,499 total cancer cases and 9,743,832 cancer-related deaths (WHO, 2022). The deadly aspect of cancer lies in metastasis, which represents the key phenomenon observed in patients approaching death. Evidence from Norway supports this, showing that for solid tumors, 66.7% of cancer deaths were registered with metastasis as a contributing cause (Dillekås *et al.*, 2019). Metastasis is facilitated by the formation of invadopodia, actin-rich protrusions that degrade the ECM and enable cancer cells to invade surrounding tissues and disseminate to distant organs (Yaacob *et al.*, 2022).

The study of invadopodia formation was initially introduced by (Saito *et al.*, 2012), who described the process in terms of detailed actin reorganisation, ECM degradation, receptor signaling, and matrix metalloproteinase (MMP) transmission, though the model was limited by insufficient consideration of actin connectivity. Subsequent research sought to address this limitation. For example, there is a study that proposed a one-dimensional signal transduction model that treated the plasma membrane as a free boundary to represent continuous actin connections (Admon & Suzuki, 2017), while another explored actin polymerisation and boundary conditions through the application of Laplace's equation (Gallinato *et al.*, 2017). In addition, an extended model incorporated ligand dynamic, signaling pathways, actin, MMPs, and ECM interactions into a more comprehensive framework (Yaacob *et al.*, 2021, Yaacob *et al.*, 2022, Yaacob *et al.*, 2024). The present research builds on these efforts by introducing a decay constant, while focusing specifically on the role of ligands and signal transduction in invadopodia formation.

This research aims to investigate two-dimensional mathematical model describing the formation of invadopodia during cancer cell invasion. It focuses on formulating simplified representations of ligand interactions and signaling processes with the inclusion of decay terms, while also developing numerical algorithms that employ the level set method and finite difference techniques to solve the proposed

equations. Furthermore, this research analyses the resulting ligand and signal distributions at the membrane interface, with particular attention to their relationship to the protrusive behavior of the plasma membrane. The significance of this research lies in its potential to advance understanding of the mechanistic role of invadopodia in cancer cell invasion, thereby contributing to the development of therapeutic strategies aimed at curtailing metastatic dissemination.

In addition, this research also connects with SDG 3: Good Health and Well-being, as understanding invadopodia dynamics is essential in the broader fight against cancer metastasis. By modeling the ligand decay influences protrusion growth, this work provides insights that can help medical researches explore new ways to interrupt or slow down metastasis. In the long term, such mathematical models can contribute to strategies that improve treatment outcomes and support healthier lives.

THE FORMULATION OF MATHEMATICAL MODEL

This research develops a mathematical model to describe the formation on invadopodia in invasive cancer cells. The model considers the extracellular, intracellular and membrane interface regions where MMPs degrade the ECM and release ligands. These ligands bind to epidermal growth factor receptors (EGFR) on the cell surface, triggering signal transduction that reorganizes the actin cytoskeleton and promotes actin polymerization. The resulting changes push the plasma membrane outward, giving rise to invadopodia.

In this research, the new mathematical model approach has been introduced by considering a ligand decay term into the formulation. This additional term captures the natural degradation of ligands over time, which has not been explicity highlighted in earlier models. In reality, ligands do not stay constant, they gradually fade as they spread out, attach to receptors, or break down in the surrounding environment. By including this decay effect, our model captures the biological process more realistically. This approach highlights the novelty of our research, as it allows us to directly explore how different rates of ligand decay shape the growth and persistence of invadopodia.

Rather than replicating the entire complexity of the biological system, the model focuses on the essential mechanisms that diretly influence invadopodia growth: ligand density, $c^*(x,t)$, signal transduction, $\sigma(x,t)$, ECM degradation, and membrane movement, $v(x,t)$. By highlighting these key factors, the model provides insight into how small-scale molecular interactions translate into large-scale structural changes at the cell surface.

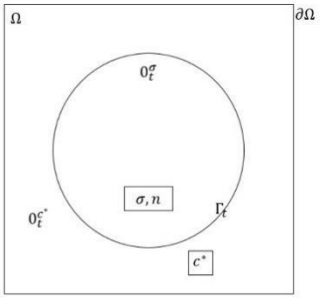

Figure 1: Illustaration of the domain structure applied in the two-dimensional model of invadopodia formation

The formation of invadopodia is explained using the following mathematical model:

a) For Ligand, (c^*):

$$\begin{aligned} c_t^* &= d_{c^*}\Delta c^* - \lambda c^*, && x \in 0_t^{c^*}, && t \in (0,T], \\ c^* &= 0, && x \in 0_t^{\sigma}, && t \in (0,T], \\ c^*(x,0) &= c_0^*(x), && x \in 0_t^{c^*} \end{aligned} \qquad (1)$$

$$\begin{aligned} c^*(x,t) &= 0, && x \in \partial\Omega, && t \in (0,T], \\ c^*(x,t) &= g(x), && x \in \Gamma_t, && t \in (0,T], \end{aligned}$$

where the first line introduces the decay term, λc^*. This term is the novelty of this research, representing the natural loss of ligand concentration due to degradation and receptor binding.

b) Signal Transduction, (σ):

$$\begin{aligned} \sigma_t &= d_\sigma \Delta\sigma, && x \in 0_t^\sigma, && t \in (0,T], \\ \sigma &= 0, && x \in 0_t^{c^*}, && t \in (0,T], \\ \sigma(x,0) &= \sigma_0(x), && x \in 0_t^\sigma, \\ \sigma(x,t) &= c^*(x,t), && x \in \Gamma_t, && t \in (0,T], \end{aligned} \tag{2}$$

c) On the Interface, (Γ_t):

$$\begin{aligned} \Gamma_t &= \{\psi(x,t) = 0\}, && t \in (0,T), \\ \psi_t + v.\nabla\psi &= 0, && x \in \Gamma_t, && t \in (0,T), \\ v &= \nabla\sigma - \nabla c^*, && x \in \Gamma_t, && t \in (0,T), \end{aligned} \tag{3}$$

d) Velocity Extension, (w):

$$(\nabla\psi.\nabla)w = 0, \quad x \in \Omega, \quad t \in (0,T), \tag{4}$$

RESULTS AND DISCUSSION

The simulations reveal that ligand decay is a critical factor in invadopodia formation. Slow decay preserves ligand availability at the plasma membrane, sustaining receptor binding and signal transduction, which drives the growth of larger and more stable protrusions. In contrast, fast decay reduces ligand concentration, limits signaling, and produces smaller, short-lived protrusions. Over time, protrusions expand only in regions where ligands persist, confirming that ligand decay directly governs both the scale and persistence of invadopodia.

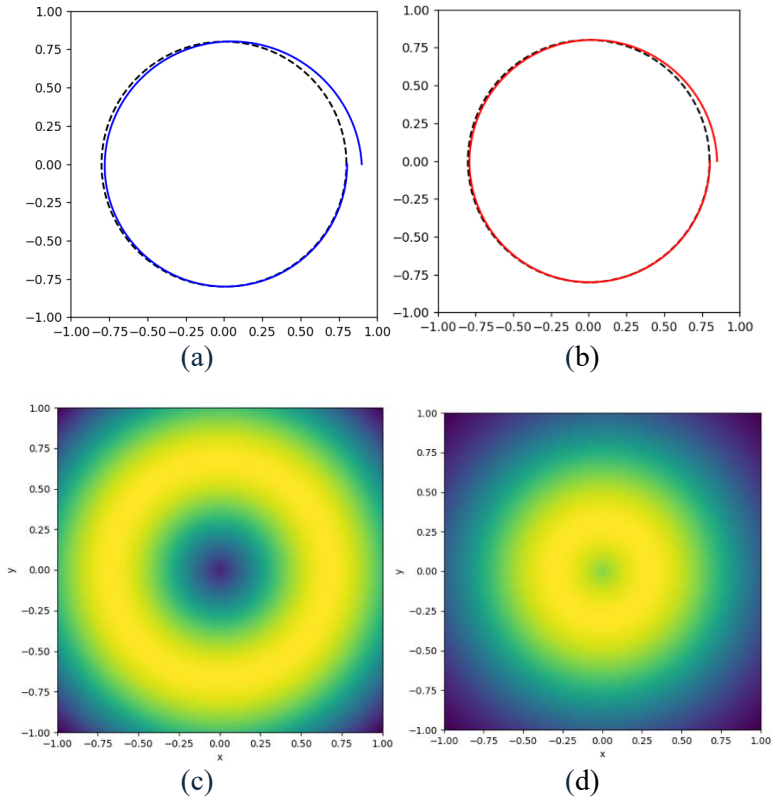

Figure 2: Effect of ligand decay on invadopodia formation. (a) Interface position with slow ligand decay, (b) Interface position with fast ligand decay, (c) Ligand density distribution for slow decay and (d) Ligand density distribution for fast decay.

As indicated in Figures (a) and (b), it can be seen that at the slow decay case, the interface extends further outward, indicating that ligand availability supports sustained protrusion growth. In contrast, at the fast decay case, the interface remains closer to the initial position, reflecting limited protrusion development. Meanwhile, Figures (c) and (d) compare the ligand density distributions, where slow decay maintains higher concentrations near the plasma membrane, while fast decay shows a reduction in ligand levels.

CONCLUSION

This research highlight the role of ligand decay in invadopodia formation through mathematical modeling and simulation. The results show that slow ligand decay sustains higher ligand concentration at the plasma membrane, supporting continuous receptor binding and stronger signal transduction, which promote the development of larger and more stable protrusions. In contrast, fast ligand decay limits ligand availability, weakens signaling, and results in smaller, short-lived protrusions. These findings demonstrate that the rate of ligand decay is a key factor governing both the persistence and scale of invadopodia. By showing how molecular turnover shapes membrane dynamics, these findings provide new insight into the mechanisms of metastasis and underscore the importance of ligand decay in controlling invasive behavior.

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