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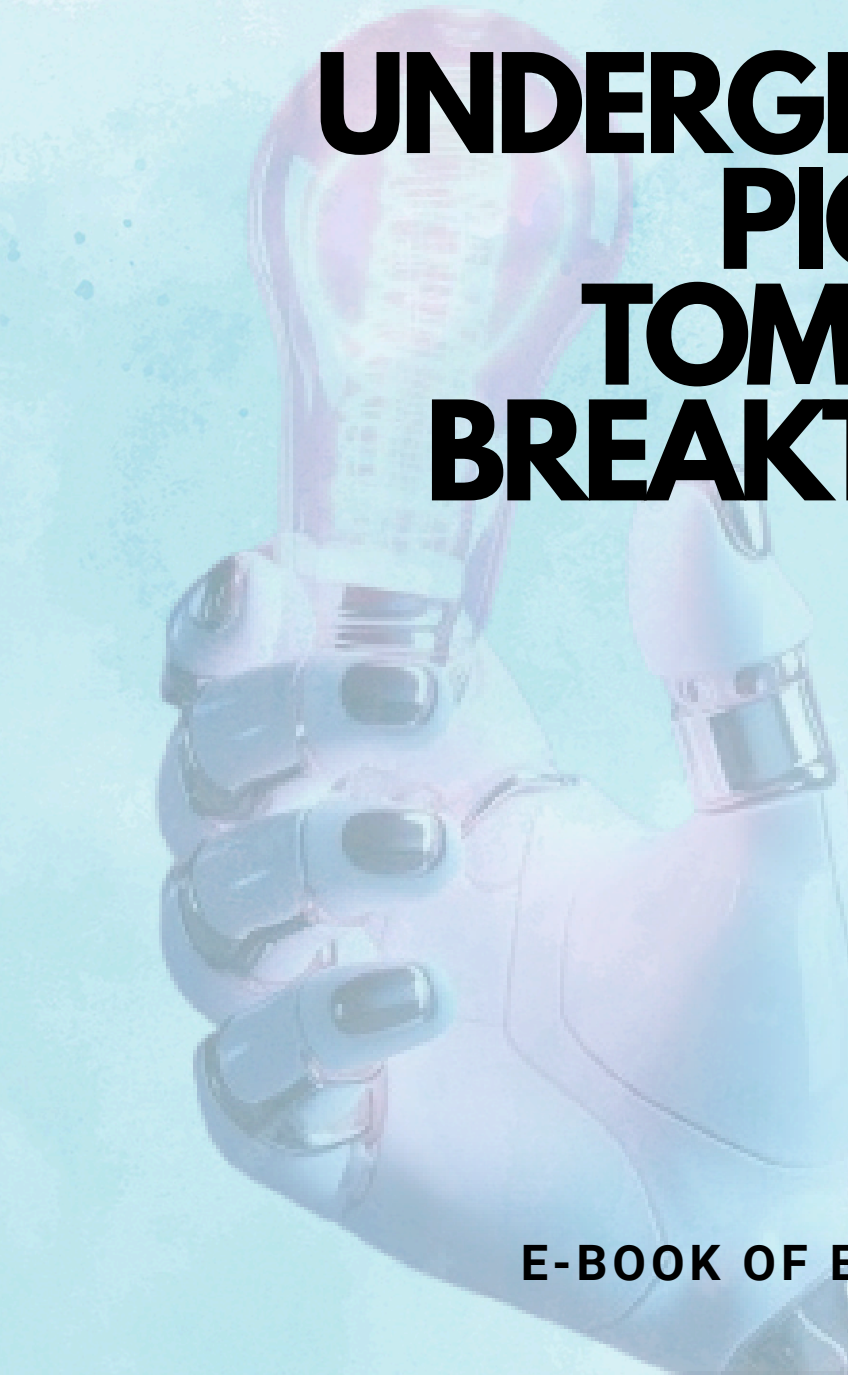

E-BOOK OF EXTENDED ABSTRACTS

ACTIN-RICH PROTRUSIONS: LEADING TO CANCER CELL INVASION THROUGH MATHEMATICAL FORMULATION

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ABSTRACT

Metastasis accounts for most cancer-related deaths, with invadopodia formation playing a central role in tumor cell invasion. Invadopodia are actin-rich protrusions that degrade the extracellular matrix (ECM), enabling cancer cells to penetrate and spread. This research presents a simplified mathematical model to investigate the effect of signal decay on invadopodia dynamics using the level set method. The model incorporates ligand diffusion and intracellular signaling with a decay term to capture essential biological behavior while remaining computationally efficient. The plasma membrane is represented as a moving interface driven by jump velocity, defined by the gradients of ligand and signal variables. Numerical discretisation techniques are applied to simulate signal distribution, ligand interaction, and interface deformation. The findings suggest that signal decay significantly influences membrane protrusion behavior, where reduced signaling activity leads to shrinking of the interface while stronger gradients sustain invadopodia growth. This approach provides both visual and quantitative insights into cancer cell invasion mechanisms, demonstrating the potential of mathematical modeling as a tool to support future therapeutic strategies targeting metastasis.

Keywords: Cancer Cell Invasion, Invadopodia, Level Set Method, Metastasis, Signal Decay

INTRODUCTION

It is reported that 90% of cancer-related fatalities are caused by cancer metastasis, which continues to be one of the most significant challenges in medical science (Neophytou *et al*., 2021). A crucial component of this process is the formation of invadopodia that enable cancer cells to degrade the ECM and infiltrate surrounding tissues (Augoff *et al*., 2020). While it is important to comprehend the dynamics of invadopodia to develop methods for preventing or forecasting metastasis, the complexity of biological interactions make the experimental methods alone are costly and time-consuming. For instance, invadopodia formation is tightly regulated by various signaling pathways, including kinases and actin remodeling proteins, which connect extracellular cues with the dynamics of intracellular protrusion (Masi *et al*., 2020).

Building on this, recent studies emphasize that molecular regulators like NADPH oxidase and reactive oxygen species further amplify these processes, significantly enhancing invadopodia-mediated invasion (Quilaqueo-Millaqueo *et al*., 2024). Taken together, these findings highlight the complex regulation of invadopodia and raise questions about the specific ways in which signal strength and decay influence their formation and progression (Admon & Suzuki, 2017; Saitou *et al*., 2012).

The issue addressed by this research is the absence of a simplified but biologically relevant framework for simulating the formation and progression of invadopodia in response to decaying signals. Driven by this issue, this study aims to build a mathematical model and numerical simulation of invadopodia formation including ligand variables and signal degradation. Utilising advanced numerical techniques, the model presents a systematic approach in a two-dimensional system to replicate membrane deformation, ligand diffusion, and signal transduction by employing sophisticated numerical methods, notably the level set

method, in conjunction with finite difference methods (Yaacob *et al*., 2021; Yaacob *et al*., 2022, Yaacob *et al*., 2024).

The novelty of this research lies in highlighting signal decay within invadopodia modeling, providing new perspectives compared to existing approaches. In addition, the use of the level set method to capture the progression of the plasma membrane provides a more accurate representation of dynamic protrusion behavior compared to conventional models. Together, these innovations make the framework both computationally efficient and biologically meaningful. The outcomes of this research are expected to provide deeper insight into cancer invasion mechanisms and contribute to future strategies in preventing metastasis.

In line with SDG 3 Good Health and Well-being, this research emphasises the importance of mathematical modelling of invadopodia formation. Since invadopodia are key structures in cancer invasion during metastasis, developing a comprehensive model can help medical researchers gain deeper insights into strategies for preventing metastasis. Ultimately, such insights contribute to advancing human health and well-being.

MATHEMATICAL FORMULATION

Chemoattractants such as epidermal growth factor (EGF) bind to epidermal growth factor receptor (EGFR), initiating intracellular signaling that regulates the reorganization of the actin cytoskeleton and promotes the development of a polarized cell morphology through localised actin polymerization. At the invasive front of cancer cells, matrix metalloproteinases are secreted to degrade the ECM, producing fragments that act as ligands and further stimulate signaling. The movement of the plasma membrane is directed by velocity acting perpendicular to its surface, a process commonly illustrated in schematic diagrams of invadopodia formation, such as in Figure 1.

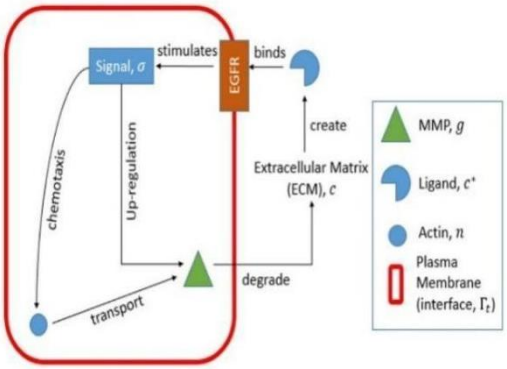


Figure 1: A schematic representation of invadopodia formation within an invasive cancer cell.

In biological systems, invadopodia form through several processes such as the interaction of actin, the ECM, ligands, signaling pathways, and matrix metalloproteinases (MMPs). Since it is difficult to represent all these mechanisms at once, this research focuses on the key elements only. A two-dimensional model of cancer cell invasion related to invadopodia formation is developed, which includes ligand concentration, signal transduction with decay, plasma membrane movement, and velocity extension in the extracellular region.

a) Ligand density, $c^*(x,t)$

$$\begin{aligned} c_t^* &= d_{c^*}\Delta c^*, && x \in 0_t^{c^*}, && t \in (0,T], \\ c^*(x,0) &= c_0^*(x), && x \in 0_0^{c^*}, && \\ c^*(x,t) &= 0, && x \in \partial\Omega\,, && t \in [0,T], \\ c^*(x,t) &= g(x), && x \in \Gamma_t\,, && t \in [0,T], \end{aligned} \tag{1}$$

b) Signal transduction, $\sigma(x,t)$

The novelty of our model lies in Equation. (2), where the decay term into the signal transduction dynamics has been employed. This extension distinguishes our work from existing models and allows us to analyse how variations in signal decay can influence cancer cell invasion.

$$\begin{aligned} \sigma_t &= d_\sigma \Delta\sigma - \lambda\sigma, && x \in 0_t^\sigma, && t \in (0,T], \\ \sigma(x,0) &= \sigma_0(x), && x \in 0_0^\sigma, \\ \sigma(x,t) &= c^*(x,t), && x \in \Gamma_t, && t \in [0,T]. \end{aligned} \tag{2}$$

c) On the interface, Γ_t

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

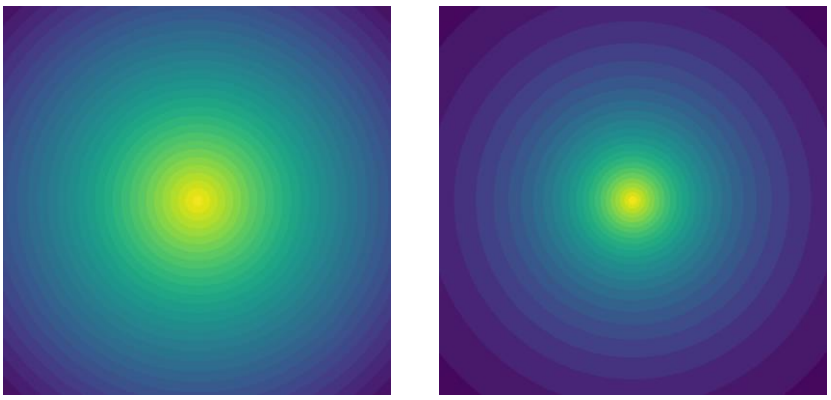
d) Velocity extension, $w(x,t)$

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

RESULTS AND DISCUSSION

Simulation outcomes indicate that ligand concentration diffuses into the extracellular region, while signal activity is localised within the intracellular space. These interactions drive deformation of the plasma membrane, where the interface may either expand or contract depending on the boundary velocity. The rate of signal decay plays a key role in this process, as it directly influences the persistence of protrusive structures.

As shown in Figure 2, two scenarios were compared to illustrate the effect of signal decay on invadopodia formation. In Figure 2(a**)**, representing low signal decay, the protrusion extends outward and remains stable over time, reflecting stronger and more sustained signalling activity that promotes invadopodia persistence. In contrast, Figure 2(b), representing high signal decay, shows the protrusion shrinking and becoming less stable, indicating weaker signals that limit membrane extension.



(a) (b)

Figure 2: Membrane deformation patterns for different signal decay rates: (a) low signal decay and (b) high signal decay.

These results highlight how signal decay serves as a regulatory mechanism in invadopodia dynamics. Lower decay supports cancer cell invasive behaviour by maintaining protrusions, while higher decay restricts protrusion growth, reducing the invasive potential. This demonstrates how mathematical modelling

can provide valuable insights into the relationship between intracellular signalling and cancer cell invasion, offering a framework that aligns with biological observations.

CONCLUSION

This research explores how signal decay influences the formation of invadopodia, which are important for cancer cell invasion. A simplified two-dimensional mathematical model was developed, combining ligand diffusion, signal transduction with decay, and membrane deformation using the level set method. The outcomes suggest that high signal decay reduces invadopodia persistence, while lower decay allows protrusions to grow and remain stable. Overall, the research shows that mathematical modelling can provide valuable insight into cancer cell behaviour and support future work in developing strategies against metastasis.

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