NUMERICAL COMPUTATION OF FREE BOUNDARY SIGNAL TRANSDUCTION DURING THE FORMATION OF INVADOPODIA

NUR AZURA BINTI NOOR AZHUAN

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DEDICATION

This thesis is dedicated to:

My beloved father and mother.

My warmly siblings
(abang, akak, imah, ira, adik).

My lovely niece and nephew
(ammar, amany, alif, fateh, amzar),

My devotedly supervisors
(Dr Ariff, Dr Sharidan, Prof Clair, Suzuki Sensei).

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ABSTRACT

Mathematical simulation is one of the methods that has been beneficial to the knowledge of cancer cell invasion, especially in listing the important components that are the main causes of the invasion. In fact, at subcellular view, invadopodia which are actin based protrusions formed on the cancer cell membrane degrade the extracellular proteins and lead the invasion. In this study, a mathematical model of invadopodia formation associated with signal transduction is investigated. The main objective of this study is to obtain the numerical solution of invadopodia formation of signal transduction in one and two dimensions. The signal equation is represented by heat-like equation with initial and boundary conditions. The free boundary of plasma membrane is considered and is moved by the velocity of the cancer cell which is equal to the gradient of the intracellular signal. The governing partial differential equation for a one-dimensional case with initial and boundary conditions is transformed into an approximation model by using a signal transformation variable. Then, the integrated penalty technique is applied to solve the model numerically. The results are validated with the exact solution obtained using separable variable approach with suitable similarity variable. From this study, it is discovered that both results have shown the same outcome with the constant boundary condition restriction. Simulation results demonstrated that the interface position increases from its initial location as time increases. This implies that the plasma membrane has moved in tandem with the increase in time. Meanwhile, in a two-dimensional case, free boundary of plasma membrane is represented by a zero level set function. The partial differential equations are discretized by using the level set method which combines the features of ghost points and extrapolation methods in order to solve the model numerically. The stability condition of the solution is enforced by using Gershgorin circle theorem. It is observed that some protrusions are developed on the membrane surface due to the presence of the signal density inside the cell with types of cosine and exponential boundary conditions. The highest concentration of signal is identified on the interface due to the stimulation of signal through contact between the ligand and the membrane associated receptor on the membrane. All numerical schemes obtained in this thesis by numerical methods (integrated penalty method in one dimension and level set method in two dimensions) and an analytical method (separable variable method in one dimension) are useful to solve the free boundary problem of an invadopodia formation model particularly on the signal transduction factor.

ABSTRAK

Simulasi matematik merupakan salah satu daripada kaedah yang telah memberi manfaat kepada pengetahuan tentang pencerobohan sel kanser, terutamanya dalam menyenaraikan komponen-komponen penting yang menjadi penyebab pencerobohan. Secara faktanya, dalam pandangan sub sel, invadopodia yang merupakan tonjolan berasaskan aktin yang terbentuk pada membran sel kanser telah mendegradasi protein ekstrasel dan menjadi punca pencerobohan. Dalam kajian ini, model matematik bagi penghasilan invadopodia yang berkaitan dengan transduksi signal dikaji. Objektif utama kajian ini adalah untuk mendapatkan penyelesaian berangka bagi penghasilan invadopodia transduksi signal dalam satu dan dua dimensi. Persamaan signal diwakili oleh persamaan berbentuk haba berserta dengan syarat awal dan syarat sempadan. Sempadan bebas membran plasma dipertimbangkan dan digerakkan oleh halaju sel kanser di mana ia adalah bersamaan dengan kecerunan signal intrasel. Penghasilan persamaan pembezaan separa untuk kes satu dimensi berserta dengan syarat awal dan syarat sempadan diterbitkan pada model anggaran menggunakan pembolehubah transformasi signal. Kemudian, teknik penalti paduan digunakan untuk menghasilkan penyelesaian secara berangka. Hasil penyelesaian disahkan dengan penyelesaian tepat yang diperoleh menggunakan pendekatan pembolehubah boleh pisah dengan pembolehubah keserupaan yang bersesuaian. Daripada kajian ini, didapati bahawa kedua-dua penyelesaian menunjukkan hasil yang sama dengan batasan syarat sempadan pemalar. Hasil simulasi menunjukkan bahawa posisi antara muka meningkat dari kedudukan awal apabila masa meningkat. Ini menunjukkan membran plasma telah bergerak seiring dengan peningkatan masa. Sementara itu, dalam kes dua dimensi, sempadan bebas membran plasma diwakili oleh fungsi sifar set aras. Persamaan pembezaan separa diturunkan menggunakan kaedah set aras yang menggabungkan kaedah titik bayang dan penentuluaran untuk menyelesaikan model secara berangka. Keadaan kestabilan penyelesaian dilaksanakan dengan menggunakan teorem bulatan Gershgorin. Diperhatikan bahawa beberapa tonjolan terhasil pada permukaan membran disebabkan oleh kehadiran ketumpatan signal di dalam sel bersama dengan syarat sempadan untuk jenis-jenis kosinus dan eksponen. Kepekatan signal tertinggi dikenal pasti pada antara muka disebabkan oleh rangsangan signal melalui sentuhan diantara ligan dan reseptor sekutu membran pada membran. Keseluruhan skim berangka yang diperolehi di dalam tesis ini dengan penggunaan kaedah-kaedah berangka (teknik penalti paduan dalam satu dimensi dan kaedah set aras dalam dua dimensi) dan kaedah analisis (pembolehubah boleh pisah dalam satu dimensi) adalah bermanfaat untuk menyelesaikan masalah sempadan bebas bagi model penghasilan invadopodia terutama pada faktor signal transduksi.

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LIST OF ABBREVIATIONS

ADAMTS	-	Adamalysin-like metalloprotinases with thrombospin
	-	motifs
APN	-	Aminopeptides N
Cdc	-	Cell division cycle
CFL	-	Courant-Friedreichs-Lewy
CSF	-	Colony-stimulating factor
D	-	Dimensional
Dyn	-	Dynamin
EC-TC	-	Endothelial cell-tumor cell
ECM	-	Extracellular matrix
EGFR	-	Endothelial growth factor receptor
EMT	-	Epithelial-mesenchymal transition
F	-	Filamen
FGF	-	Fibroblast growth factor
G	-	Monomer
GEF	-	Guanine-nucleotide exchange factor
HGF	-	Hepatocyte growth factor
HIF	-	Hypoxia inducible factor
IPM	-	Integrated penalty method
LRP	-	Receptor-related protein
MAL	-	Mass action law
MCL	-	Mass conservation law
MMP	-	Matrix metalloprotease
MT	-	Membrane tethered
N-WASP	-	Neural Wiskott- Aldrich syndrome protein
ODE	-	Ordinary differential equation

PDE	-	Partial differential equation
PDGF	-	Platelet derived growth factor
PWN	-	Pathway network
TAF	-	Tumor angiogenesis factor
TEM	-	Transcendothelial migration
TIMP	-	Tissue inhibitors of metalloproteinase
uPA	-	Urokinase plasminogen activation
VEGF	-	Vascular endothelial growth factor

LIST OF SYMBOLS

C	–	Continuous function
c	–	Extracellular matrix
c_*	–	Ligand
cs	–	Compact support
D'	–	Anti distribution
d_{c_*}	–	Diffusion coefficient for ligand
d_f	–	Diffusion coefficient for MMP
d_n	–	Diffusion coefficient for actin
d_σ	–	Diffusion coefficient for signal
dx, h	–	Space grid
dt, k	–	Time step sizes
f	–	Matrix metalloproteinaise
$f(\mathbf{x})$	–	Flux of MT1-MMP enzymes
$f(\mathbf{x}, t)$	–	Boundary condition of signal variable for unsteady case
$g(t)$	–	Arbitrary function
g^n	–	Exact function
I_t^σ	–	Interior points
L	–	Length of domain Ω
l	–	Left boundary
r	–	Right boundary
M	–	Number of space grids
N	–	Number of time grids
$N_{\Gamma_t}^\sigma$	–	Neighbouring points

n	–	Actin
r	–	Radius of a circle
s	–	Free boundary
T	–	Maximum time taken
t	–	Time taken
V_x	–	Velocity components in $x-$ direction
V_y	–	Velocity components in $y-$ direction
v	–	Driving force
$v(x,t)$	–	Signal transformation variable
v_λ	–	Eigenvector
$\mathbf{W}$	–	Velocity extension
$\mathbf{x}$	–	Spatio-vector in x and y axis
$x_-(t)$	–	Left interface with time dependent
$x_+(t)$	–	Right interface with time dependent

Greek Letters

α	–	Signal diffusivity coefficient
$\chi(c)$	–	Gauss symbol
$\chi(c)$	–	Monotonic increasing function
Δ	–	Laplace operator
ϵ	–	Positive constant with chosen length
η	–	Stability value
$\Gamma(t)$	–	Boundary between two phases
γ_{c_*}	–	Positive constant
γ_f	–	Positive constant

γ_n	–	Signal transmission rate constant for actin
κ_c	–	Chemical reaction rate constant for ECM
κ_f	–	MMP production rate constant
λ_{c_*}	–	Ligand degradation rate constant
λ_f	–	MMP degradation rate constant
λ_σ	–	Signal degradation rate constant
$>$	–	Greater than
$\in$	–	An element of
∞	–	Arbitrary often
$<$	–	Less than
∇	–	Gradient operator
Ω	–	Domain occupied individual cancer cell
Ω_n^c	–	Exterior region
Ω_n^σ	–	Interior region
ω_t^c	–	Exterior region
Ω_t^σ	–	Interior region
ω_c^t	–	Intracellular
ω_n^t	–	Extracellular
$\psi(\mathbf{x}, t)$	–	Level set function
∂	–	Partial derivative
σ	–	Signal inside the cell
$\sigma(x, 0)$	–	Initial condition of signal variable with respect to space
$\sigma(0, t)$	–	Initial condition of signal variable with respect to time
σ^x	–	Derivative of signal with respect to x
σ^y	–	Derivative of signal with respect to y
$(\sigma_{\Gamma_n})_{i,j}^l$	–	left signal on-grid interface

$(\sigma_{\Gamma_n})^r_{i,j}$	–	right signal on-grid interface
$(\sigma_{\Gamma_n})^b_{i,j}$	–	below signal on-grid interface
$(\sigma_{\Gamma_n})^a_{i,j}$	–	above signal on-grid interface
$(\sigma_{\Gamma_n})^L_{i,j}$	–	left signal off-grid interface
$(\sigma_{\Gamma_n})^R_{i,j}$	–	right signal off-grid interface
$(\sigma_{\Gamma_n})^B_{i,j}$	–	below signal off-grid interface
$(\sigma_{\Gamma_n})^A_{i,j}$	–	above signal off-grid interface
$\subset$	–	Subset of
$\tilde{v}$	–	Penalty term
φ	–	Test function
ζ	–	Similarity variable

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CHAPTER 1

INTRODUCTION

1.1 Introduction

This chapter discusses the main area of study, where the first section covers the research background on cancer invasion. The background of this research is divided into two subsections; (i) biological approach, and (ii) mathematical approach on cancer invasion, specifically at subcellular view. The problem statements corresponding to the aim of this research are outlined thoroughly in Section 1.3. The research objectives, scope of research, significance of study, research methodology and the thesis organization are also included in this chapter.

1.2 Research Background

The World Health Organization [1] reported cancer as the third leading cause of death. Lung (1.69 Million), liver (788, 000) and colorectal (774, 000) are top three body parts where cancer cells (tumor) are frequently detected (three most vulnerable body parts to cancer) [2]. Throughout the past decade, intensive studies had been done through biological and mathematical approaches to understand the mechanism of cancer cell invasion since there is potential of the development of anti-invasion therapy for treating cancer patients [3].

1.2.1 Cancer cell invasion: Biological point of views

There are two main biological approaches to investigate the cancer cell invasion, which are by $in-vivo$, or $in-vitro$ approach. Note that, $in-vivo$ refers to work that is performed in a whole by the living organism meanwhile $in-vitro$ happens outside

of a living organism where it usually happen by experimental observation [4]. By $in - vivo$ approach, the basic mechanism of cancer cell invasion are observed directly by using microarray analysis. At cellular level, at first, a cancer cell is formed through multiple mutations in an individual normal cell's key genes. Proliferation of cancer cells continues until a lump (avascular cancer cells) is formed. This process is known as primary stage of tumor. Until one time, these avascular cancer cells cannot grow any further at the local site. The cancer cells then transform into metastatic ones, which allow them to invade the surrounding tissue, while the surviving cells enter the other site and proliferate themselves; forming a new colony, hence forming secondary stage of tumor. In order to move and invade the other site, the cells have to undergo two main processes named angiogenesis and metastasis.

Angiogenesis is a process where new capillaries are form and link the blood vessel to the cancer cells [5]. At this stage, the avascular cancer cells produce an angiogenic factor, called as vascular endothelial growth factor-A (VEGF-A)[6]. The factor promotes blood vessel proliferation by splitting their vessel of membrane, forming new blood vessels sprout, and hence connecting the blood circulation system to the cancer cells. The cells gain enough nutrient to invade and grow further at the new site by undergo metastasis.

Metastasis is a process where some cancer cells are able to move and invade the surrounding tissue barrier and escape from their local site to colonize a new distant site. Note that metastasis is the main cause of death among cancer patients [7]. Initially, the groups of cells invade the surrounding tissue through cells adhesion. An epithelial-mesenchymal transition (EMT) process then takes place, where the epithelial cells convert into mesenchymal cells, allowing the cancer cells to pass through the tissue. The cells then form protrusions; elongating themselves and degrading the extracellular membrane (ECM) proteins (to converge onto the blood vessels) with helps from matrix metalloproteases (MMPs) [8, 9, 10]. This process is known as intravasation. The cells then move through the blood stream by three different ways of cell's motility; either by collective mode, mesenchymal mode, or amoeboid mode. Collective movement means that the cells move in a group, while mesenchymal and amoeboid movement imply individual movement. The only difference between mesenchymal and amoeboid

movement is that, an amoeboid movement does not need to undergo EMT process. The surviving cells are needed to once again pass through the tissue membrane barrier to completely locate in the other site. This process is called as extravasation, where the cells form protusions again and transmigrate the entire body through the vascular wall [11]. The surviving cells then proliferate themselves, hence a new colony is formed, establishing the second stage of tumor.

Mechanism of cancer cell invasion at subcellular level has remained a focus of research for many years. Invasion of a cancer cell on tissue compartment is initiated by the formation of protrusions known as invadopodia, and degradation of ECM barrier [12, 13]. There are four types of protrusions, which are filopodia, lamellipodia, invadopodia, and podosomes. The study on invadopodia formation is important since this actin based protrusions are form and have the ability to degrade the ECM proteins, causing cells to penetrate the blood stream, as previously proven in $in-vitro$ studies by [14]. The formation of invadopodia and degradation of ECM proteins key processes lead by actin polymerization and assembly (chemotaxis), up-regulation of MMPs, degradation of ECM, ligand formation, and signal transduction.

During chemotaxis, endothelial growth factor receptor (EGFR), which is a chemoattractant, provides signal to activate the actin polymerization during the precursor formation. After filament (F)-actin is formed in bundle, the actin matures and stabilizes, through nucleation, elongation and annealing processes. The EGFR also gives signal to the MMPs to undergo up-regulation process, and consequently pushes the plasma membrane outwards and degrades the ECM proteins outside the cell. The ECM fragment, known as ligand, then binds on the plasma membrane and stimulates the signal once again. These processes are repeated until protrusions exist with size around 8μm diameter, and 5μm height [15, 16]. Recently, Aron and Alissa [17] reviewed the invadopodia formation, and concluded that it is mediated from signalling pathway inside the cell.

In $in-vitro$, several experiments had been conducted to observe the mechanism of cancer cell invasion based on the studies by in $in-vivo$ approach. Yu $etal.$ [18] recently studied the factors that trigger the cancer cells invasion in $in-vitro$. They

found that miR-126, which is one of the angiogenesis regulatory microRNAs, up regulates the VEGF expression. Studies on extravasation part were done by [19] and [20]. Michelle *et. al* [19] found that the extravasation begins by the presence of thin tumor cell protrusions across the endothelium. Jessie *et. al* [20] observed that cancer cell has tendency to be in contact with the endothelium in the first 24 hours. $In-vitro$ approach is able to successfully reproduce the mechanism of cancer cell invasion, but this approach is time and cost consuming.

1.2.2 Cancer cell invasion: Mathematical point of views

Mathematical approach to predict/study cancer cell invasion based on the hypothesis and illustration has been considered in order to understand the $in-vivo$ dynamics of invasion, particularly at tissue and cellular levels, in the past decades. In 2005, Chaplain and Lolas [21] thoroughly discussed the urokinase plasminogen activation (uPA) system role in tissue invasion and form the mathematical modelling. They considered the interaction of cancer cell and the chemicals, by an equation called as reaction-diffusion-taxis equation. Vivi *et al.* [22] improved the model, and considered five reaction-diffusion-taxis partial differential equations. The model was used to describe the interactions between cancer cells, uPA, uPA inhibitors, plasmin, and the host tissue. They successfully showed that there are chemotactical and haptotactical reactions to the spatio-temporal effects of the uPA system with the cancer cell.

Recently, mathematical modelling on the study of cancer cell invasion at subcellular level has received much attention, since in *vivo* study claims that cancer cell starts to migrate from the local site by the formation of invadopodia around 1-10 μm, and invade the dense membrane to enter the blood stream [15]. Invadopodia is composed of a variety of proteins such as actin and actin regulatory protein, adhesion molecules, membrane remodeling and signalling proteins. Saitou *et al.* [23] derived a continuous model based on partial differential equations (PDEs) to describe the formation and maturation of invadopodia. The model considered the main processes for invadopodia formation except signal transduction. This model was able to generate

protrusions with small value of the effect of MMP rate constant. However, the region of actin, $n > 0$ became disconnected as time progressed.

Admon [24] proposed a new model by considering signal transduction (inside the cell) during the invadopodia formation, which was not taken into account in [23], and treated the cancer cell membrane as free boundary. Due to the complexity of invadopodia model, and the signal does not depend on the other variables, Admon [25] only considered signal transduction process during invadopodia formation, and solved the model numerically by using fixed domain method in one dimension. The membrane was observed to expand as time advanced, implying that protrusion should exist [24]. Since this formation involves a free boundary problem, two-dimensional (2D) simulation is needed to get a clearer picture of invadopodia formation with presence of signal transduction. Recently, Olivier $et, al.$ [26] successfully modelled the steady state of chemical interaction between the signal transduction and ligand formation during invadopodia formation in 2D with first and second order accuracy [27].

The present research aims to derive analytical solution of signal transduction during invadopodia formation, for comparison with numerical solution obtained by using integrated penalty method. The quasi-static and unsteady states of signal transduction process during the formation of invadopodia in two dimension case based on the model proposed by Admon [24] is considered since it is still not yet available in the literature. The membrane is set to be free-boundary membrane, which would shrink if the membrane is to be pulled inside or expand if the membrane is to be pushed outside the region of cell. The signal equation is represented by heat-like equation with Dirichlet boundary condition, by which the plasma membrane is taken as zero level set function. The membrane is moved by the velocity of the cancer cell, which is equal to the gradient of the signal. The first order Cartesian finite difference scheme of the level set method is used to solve the complete model numerically.

1.3 Statement of Problem

By realizing the fact that cancer is a critical societal and scientific problem, the study on cancer cell movement driven by invadopodia is vital, as this movement causes migratory pathways through the ECM. Mathematical studies on the behaviour of the cancer cell invasion has received much attention nowadays since this study able to highlight all the key processes of the invasion by numerical simulation. However, mathematical modelling and numerical simulation of cancer invasion at subcellular view are active yet limited. The main interest of this particular study is due to these few research questions:

i. What is the simplified model of a signal transduction that is reduced from the model of invadopodia formation in [24]?

ii. How to solve the one dimensional unsteady signal transduction model analytically and numerically?

iii. How to solve the two dimensional quasi-static and unsteady signal transduction models numerically?

iv. How to analyse the signal distribution profiles and free boundary positions (plasma membrane locations) of the signal transduction models?

1.4 Objectives of the Study

The aim of this study is to investigate the mathematical modelling of signal transduction associated with invadopodia formation. The objectives of this study are as follows:

i. To construct simplified mathematical formulation of signal transduction of the invadopodia formation based on the model proposed in [24].

ii. To obtain the analytical and numerical solutions for the one dimensional unsteady signal transduction problem using separable technique and integrated penalty method, respectively.

iii. To develop the numerical algorithms for the quasi-static and unsteady signal transduction models in two dimension using finite difference technique of level set method.

iv. To analyse the signal distribution profiles and free boundary positions (plasma membrane locations) for the formation of invadopodia associated with signal transduction.

1.5 Scope of the Study

This study concerns about the modelling of signal transduction for the invadopodia formation in one and two dimensional problems. In one dimension problem, derivation of analytical solution for signal transduction model is conducted. The comparison of the analytical and numerical solutions by using integrated penalty method is obtained.

The modelling of both time independent and time dependent signal transduction in two dimensional problem are simulated by using level set method with first order Cartesian finite difference scheme. The derivative of the interface of cellular membrane is taken as the second order upwind scheme. The combination of first order Cartesian finite difference scheme and upwind scheme are used to get a consistent finite difference approximation to the governing partial differential equation. Forward Euler scheme was then implemented for the time derivative term. Matlab software is utilized in this study to simulate the algorithm, powered by 8^{th} Gen Intel @ Core^{TM} i5 processor. The stability of the solution is obtained by using Gershgorin circle theorem in order to get the Courant-Friedreichs-Lewy condition (CFL condition).

1.6 Significance of the Study

The results obtained from this project should contribute to

i. a better understanding on how the cancer cells invade the other site through angiogenesis (development of blood circulation brancing-path) and metastasis (cancer cells invasion onto tissue compartment) process,

ii. better insight on the mechanism of cancer cell invasion at subcellular level, where the cancer cell start to form protrusions called as invadopodia, which are actin rich protrusions that degrade the extracellular proteins,

iii. The information regarding the behaviour of the invadopodia formation, especially where the signal stimulation plays the key role for the formation process.

iv. enhancement of knowledge on the invadopodia formation from mathematical perspective by treating the cell membrane as a free boundary to researchers and medical practitioner, and

v. wider knowledge on numerical simulation using level set method especially when the case related to the free boundary.

1.7 Thesis Organization

This thesis contains six chapters. Chapter 1 discusses the research background, constituting all definitions of problem, followed by statement of problem, objectives of research, scope of research, significance of research, research methodology, and thesis organization. The following Chapter 2 reviews some published researches related to proposed problems, as acknowledged in the objectives.

Chapter 3 presents the derivation of governing heat-like equations for unsteady signal transduction and free boundary of plasma membrane in one dimension. The velocity on the membrane is derived in one dimension space. The governing equation is transformed into an approximation model by using signal transformation variable. This chapter also provides the solution of the membrane position and signal density profile, which are obtained by using integrated penalty method. These solutions are plotted by using MATLAB software in order to display the solutions graphically, for

detailed discussion. The validation is obtained by comparing the present solution with the exact solution, which is in the form of error function.

Chapter 4 presents the derivation of governing heat-like equations for signal transduction and free boundary of plasma membrane in two dimension, for both quasi-static and unsteady cases. The velocity on the membrane is derived in two dimension space. The free boundary of plasma membrane is represented by level set function. The governing equations are computed numerically by using level set method. The analysis of the stability condition is also highlighted in this chapter. The stability condition is obtained by using Gershgorin circle theorem to ensure the stability of the solution.

Chapter 5 presents details of the discretization of the model by using level set method approach. Five main steps were emphasized, which includes initialization of the level set function and the signal equation, computation of the signal distribution, computation of the velocity in the interior region and on the boundary, extension of the velocity in the exterior region and updating the level set function.

Chapter 6 discusses all the numerical solutions obtained in two dimensional for both cases. The discussion focuses on the position of the membrane as time progresses and the signal density profile throughout the computation. The physical meaning of the solutions is also discussed in this chapter. Finally, Chapter 7 summarizes this research; inclusive of suggestions for future researches. References and appendixes are listed at the end of this thesis.

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LIST OF PUBLICATIONS

Publication

1. **Nur Azura Noor Azhuan**, Clair Poignard, Takashi Suzuki, Sharidan Shafie and Mohd Ariff Admon. Two-Dimensional Signal Transduction during the Formation of Invadopodia. Malaysian Journal of Mathematical Sciences (2019): 13, pp. 155–164. (**Indexed Scopus**)

2. **Nur Azura Noor Azhuan**, Sharidan Shafie and Mohd Ariff Admon. Review on Mathematical Approaches of Cancer Cell Invasion at Subcellular Level. ASM Science Journal (2020): 13. (**Indexed Scopus**)

3. Noorehan Yaacob, **Nur Azura Noor Azhuan**, Sharidan Shafie and Mohd Ariff Admon. Numerical Computation of Signal Stimulation from Ligand-EGFR Binding during Invadopodia Formation. MATEMATIKA (2020): Special Issue. pp. 139-148. (**Indexed Scopus**)

National and International Conferences

1. **Nur Azura Noor Azhuan**, Clair Poignard, Takashi Suzuki, Sharidan Shafie and Mohd Ariff Admon. Two-Dimensional Signal Transduction during the Formation of Invadopodia. International Seminar on Mathematics in Industry International Conference on Theoretical and Applied Statistics 2018 (**ISMI-ICTAS 2018**), organized by UTM Centre for Industrial and Applied Mathematics (UTM-CIAM) and UTM Department of Mathematical Sciences, ITS Department of Statistics , ITS Department of Mathematics, Oxford Centre for Industrial and Applied Mathematics (OCIAM) and Asia Pacific Consortium of Mathematics for Industry (APCMfI) held on 4-6 September 2018 at Universiti Teknologi Malaysia, Kuala Lumpur.

2. **Nur Azura Noor Azhuan**, Sharidan Shafie and Mohd Ariff Admon. Review on Mathematical Approaches of Cancer Cell Invasion at Subcellular Level. Simposium Kebangsaan Sains Matematik ke-26 (**SKSM 26**), organized by

Universiti Malaysia Sabah held on 28-29 November 2018 at Kota Kinabalu, Sabah.

3. **Nur Azura Noor Azhuan**, Noorehan Yaacob, Takashi Suzuki, Sharidan Shafie and Mohd Ariff Admon. Analytical solution of one dimensional signal transduction during the formation of invadopodia. 7th International Conference and Workshop on Basic and Applied Sciences (**ICOWOBAS 2019**), organized by Universiti Teknologi Malaysia held on 15-17 July 2019 at KSL Hotel and Resort, Johor Bahru.

4. **Nur Azura Noor Azhuan**, Clair Poignard, Takashi Suzuki, Sharidan Shafie and Mohd Ariff Admon. Numerical Simulation of Unsteady signal Transduction during the Formation of Invadopodia using Level Set. International Conference on Advanced Research in Mathematical Sciences (**ICARMS - 2021**), organized by Sri Manakula Vinayagar Engineering College, India held on 24-25 February 2021 (online).

Research Attachment

1. International Invitation Program - Workshop Scientific Research Collaboration with Prof Clair Poignard, University of Bordeaux, France, 16-23 December 2017.

2. International Invitation Program - Joint Research Work at Osaka University with Prof Takashi Suzuki, Osaka University, Japan, 29 January 2018 - 2 February 2018.

3. International Research Visit in Japan, Osaka University with Prof Clair Poignard and Prof Takashi Suzuki, 20-24 January 2020.