ANALYSIS OF AN INTEGRO-DIFFERENTIAL EQUATION FOR 1D CELL MIGRATION

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Abbreviation

ν Volterra kernels of various type

C^{n*n} Space of n*n matrices

K kernel

$\|\cdot\|$ The Euclidean Norm

$|\cdot|$ The Absolute value

$\mathbb{R}$ The set of real number

B^{∞} Borel measurable,bounded functions;sup norm

Contents

Abstract

In this thesis we concerned 1-dimension cell migration by filopodial force.We consider the reduction of the force equilibrium to an integro-differential equation.We discuses linear force function and linear volter equation formalism.We discuss existence and uniqueness,sign and boundedness property of the cell.

Chapter 1

INTRODUCTION

1.1 Background of the Study

Cell is the smallest unit of organisms that carries on all life process.All organisms are made up of cells[12].A cell is the basic structural and functional unit of living things.The cell is a fantastic representation of biology.It literally encapsulates life in elemental form.By understanding the components of a cell, we are able to discern and decipher many of the complexities of living organisms.Each component of a cell has larger-scale counterparts which can be examined in multicellular organisms such as a human.For instance, the end some in a cell filters, excretes, or saves different components of a cell just as the digestive system filters, excretes, and save components of humans.Another example is cellular respiration.While it is a complex process at the biochemical level,it is, in the end,taking in oxygen and releasing carbon dioxide similar to the actions of the lungs in a human.

The circulatory system in the human consists of a series of interconnected tubes powered by a muscular pump,the heart.While not emulated with interconnected tubular structures,in the cell, a comparable variety of molecular pumps and channels are used to regulate fluids and electrolytes in the cell.The cell also migrate from one place to other.[5] Cell migration is a fundamental biological phenomenon involved for example in development,wound healing,cancer and immune response.Understanding its key features is therefore a burning issue.Wound healing requires a variety of cell to increasing their metabolic activity,in a high oxygen demand.Oxygen at the wound site has been show to promote wound healing by stimulating several processes including the following. Anti-bacterial activities, Neo-vasculrisation and Degradation of nectotic wound tissue.

Cell migration, the active translocation of cells is involved in various biological processes,example.development of tissues and organs, tumor invasion and also wound healing.While biophysical cell migration mechanisms vary for different cell phenotypes [8] the resulting cell migration behavior can be classified based on shared features. Cell migration behavior can be divided into two distinct classes: single cell migration and collective cell migration [27] single cell migration describes the migration of cells without interaction with other cells in their environment.During single cell migration cells can be guided by external cues, however collective cell migration is the joint, active movement of multiple cells, example.in the form of

strands, cohorts or sheets which emerge as the result of individual cell-cell interactions [26].Collective cell migration can be observed during branching morphogenesis, vascular sprouting and embryogenesis.Then we study about an integro-differential equation. In recent years,the studies of mixed integro differential equations are developed very rapidly and intensively.Integro-differential equation is an equation that the unknown function appears under the sign of integration and it also contains the derivatives and functional arguments of the unknown function[2].

Filopodia:[21]The dynamic,hair-like cell protrusions called filopodia have attracted considerable attention.They have been found in a multitude of different cell type and are often called " Sensory organelles" since they seem to sense the mechanical and chemical environment of a cell.Once formed,filopodia can exhibit complex behavior,they can grow and retract,push or pull,and transform into distinct structures.They are often found to make first adhesive contact with the extra-cellular matrix,pathogens or with adjacent cells and to subsequently exert pulling forces.

Filopodia (also micros pikes) are slender cytoplasmic projections that extend beyond the leading edge of lamellipodia in migrating cells. They contain actin filaments cross-linked into bundles by actin-binding proteins, e.g. fascin and fimbrin.Filopodia form focal adhesions with the substratum, linking it to the cell surface.Many types of migrating cells display filopodia, which are thought to be involved in both sensation of chemotropic cues, and resulting changes in directed locomotion. Filopodia have roles in sensing, migration and cell-cell interaction.To close a wound in vertebrates, growth factors stimulate the formation of filopodia in fibroblasts to direct fibroblast migration and wound closure.In developing neurons,filopodia extend from the growth cone at the leading edge.In neurons deprived of filopodia by partial inhibition of actin fiilaments polymerization,growth cone extension continues as normal but direction of growth is disrupted and highly irregular. Filopodia-like projections have also been linked to dendrite creation when new synapses are formed in the brain.In macrophages,filopodia act as phagocytic tentacles and pull bound objects towards the cell for phagocytosis.Filopodia are also used for movement of bacteria between cells, so as to evade the host immune system. The intracellular bacteria Ehrlichia are transported between cells through the host cell filopodia induced by the pathogen during initial stages of infection.[30] Viruses were shown to be transported along filopodia toward the cell body, leading to cell infection[4]. Directed transport of receptor-bound epidermal growth factor (EGF) along filopodia has also been described, supporting the proposed sensing function of filopodia.

Crawling is the ability to crawl is one of the most striking cellular behaviors.Crawling migration is displayed by the vast majority of animal cells,both in culture conditions and in vivo, and by a number of unicellular organisms such as amoeba.
Friction[14] is the force resisting the relative motion of solid surfaces,fluid layers, and material elements sliding against each other.There are several types of friction
Frictional Forced[22] Frictional force is the opposing force that is created between two surfaces that try to move in the same direction or that try to move in opposite directions.The main purpose of a frictional force is to create resistance to the motion of one surface over the other surface.The frictional force depends on the body surface textures.

1.2 Statement of the problem

Some cells can move on an adherent substrate by a crawling process,where motion comes from the formation of finger-like extensions named filopodia that adhere to the substrate for some time.Filopodia are key structures within many cells that serve as sensors constantly probing the local environment.Although filopodia are involved in a number of different cellular processes,their function in migration is often analyzed with special focus on early processes of filopodia formation and the elucidation of filopodia molecular architecture.When the cell contracts, non-adherent filopodia retract, whereas adherent ones exert force that induce motion [18].When a cell is set on a flat homogenous substrate,it performs a random-like motion.However,it can also become polarized and move in a preferential direction.A non homogenous substrate imposes geometrical constraints that are sufficient to direct 1D cell motion [11].We consider the model of 1D Cell migration relying on the filopodial activity.Assume the center of mass of the cell,whose position at time t is denoted $x(t) \in \mathbb{R}$.Force equilibrium leads to

$$C\frac{dx}{dt}(t) = -F_\ell + F_r \tag{1.1}$$

where $F_r \geq 0$ is the force exerted by filopodia located on the right of the cell,$F_\ell \geq 0$ is the force exerted by filopodia located on the left of the cell and C is the friction parameter, that can be set equal to $1nN.h.\mu m^{-1}$

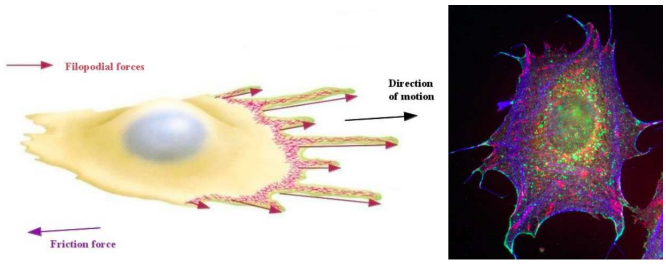

Figure 1.1: Illustration of a moving cell, and picture of a fibroblast

We can now focus on the forces F_r and F_ℓ. Following biological knowledge, we Assume that the forces exerted by filopodia on the cell at time t depend on:

- Densities of filopodia sent to the right and left, denoted by $\psi_r \geq 0$ and $\psi_\ell \geq 0$, respectively
- Their existence time, fixed by the lifetime function $\rho : \mathbb{R}^+ \longrightarrow \mathbb{R}^+$
- The force exerted by one filopodium on the cell, related to its orientation.

Moreover, we assume that $f_r = f_r\left(x\left(t'\right), x\left(t\right)\right)$ and $f_\ell = f_\ell\left(x\left(t'\right), x\left(t\right)\right)$ depend on the positions of both the tip of the filopodium,related to the cell position at creation time t' and the actual cell position. Consequently, equation (1.1) rewrites as an integro-differential equation[18]

$$\begin{aligned} \frac{dx}{dt}(t) &= \int_0^t \rho(a)\left(\psi_r f_r(x(t-a), x(t)) - \psi_\ell f_\ell(x(t-a), x(t))\right) da \\ x\left(0\right) &= x_0 \end{aligned} \tag{1.2}$$

Where ψ_r and ψ_ℓ are positive constants
Therefore,the researcher conducted the study to answer the following research questions.

1. Use an Intgro-Differential Equation and Investigate one case of non linear elastic force
2. We focus on the 1D cell migration motion bring forth by the filopodial activity

1.3 Objectives of the Study

1.3.1 General Objective

The general objective of the study is to analyze the Integro-Differential Equation for 1D cell migration based on the filopodial activity of the cell.

1.3.2 Specific Objective

The specific objectives of the study are: -

1. prove of a linear Volterra equation using an Integro-Differential equation
2. Prove the existence and uniqueness of a solution for a cell
3. Investigate boundedness and asymptotic behavior of the solution

1.3.3 Significance of the study

The main significance of this study

- This study serves as a basic for individual who has an interest to conduct further research.
- To provide advice and how can a cell migrate using filopodial activity.
- Improve our understanding of an integro-differential equation of for 1D cell migration

Chapter 2

Review Of Literature

Cell migration relies on traction forces in order to propel a cell.Several computational models have been developed that help explain the trajectory that cells take during migration, but little attention has been placed on traction forces during this process cell migration plays an essential role in wound healing,vascular remodelling,immune response and cancer metastasis [4].To better understand how each of these biological events occurs, a wide range of mathematical and computational models were developed.

Cell migration in these models was commonly simulated using a partial differential equation based on diffusion physics, because importance was placed on the number of cells that were guided to a spatial point chemotactically.On the cellular level, however, migration involves the integration of dynamic changes in focal adhesions, cytoskeletal structures, and chemical and mechanical signals from the extracellular matrix. These changes are incorporated into a cyclic progress where a cell extends its leading edge,forms new adhesions at the front, contracts its cytoskeleton and releases adhesions at the rear.Although mechanical and/or chemical gradients in the environment can affect the direction that a cell migrates , it is the traction forces that actually drive the migration.Myosin-based traction forces are transmitted to a substrate via focal adhesions to pull a cell in the direction of its polarised leading edge[12].

The adhesions at the rear need to detach in order to allow a cell to move forward.Although adhesion release depends on interactions among actin,actin-binding proteins,signalling molecules and enzymes, traction forces may also contribute to the release by breaking adhesive bonds at the rear Whole cell models were developed which incorporate the signalling and mechanics in actin polymerisation, myosin contraction and adhesion dynamics [22].These models have provided significant insights into trajectory of cells during directed cell migration,example. chemotaxis, haptotaxis and durotaxis.However, modelling of cell migration would be more accurate if it could describe the traction forces that cells generate in addition to locomotion. Several kinds of assays have recently been developed to measure and characterise traction forces of cells [16].In particular,arrays of microfabricated posts were used to study single cell contractility, cell-cell adhesion strength platelet contractile force and traction forces during the migration of cell monolayers.Even though the topology of the post arrays is not continuous, cells are not restricted from spreading and

migrating[28].

Cell transmigration is a crucial process during many physiological and pathological events, such as inflammation, cancer metastasis or atherosclerosis.Cell transmigration is a highly integrated multistep mechanism comprising three well-defined steps, namely initial contact between the cell and the wall, cell wall adhesion and finally firm adhesion leading to cell transmigration.The molecular events orchestrating cell transmigration are still largely unknown.Nonetheless,some key regulatory molecules involved in cell adhesion have now been identified and [29] Adhesion requires the creation of bonds between the circulating cell and endothelial cells which counterbalance the drag force of the blood flow.Such knowledge has allowed for cell adhesion events to be both experimentally and mathematically reconstructed and further elucidated.

Chapter 3

Mathematical Preliminaries

Definition 3.0.1 *A compact set in a metric space X is closed and bounded,but the converse is false unless X is finite dimensional*

Definition 3.0.2 *A subset A of topological space X is compact if every open cover of A is reducible to a finite cover.*

Definition 3.0.3 *Banach space is a complete,normed,vector space.*

Banach's Fixed Point Theorem

Definition 3.0.4 *Contraction mapping:let f:X⟶X be mapping from a set X to it self*

Theorem 3.0.5 *Suppose that (X,d) is a complete metric space.Then every contraction F on X has a uniquely determined fixed point.[25]*

proof 3.0.6 *Let α denote the contraction constant of F. Then,according to the triangle inequality,*

$$d(x_1, x_2) \leq d(F(x_1, F(x_1)) + d(F(x_1), F(x_2)) + d(x_2, F(x_2))$$

$$\leq d(x_1, F(x_1)) + \alpha\ d(x_1, x_2) + d(x_2 + F(x_2)),$$

which means

$$d(x_1, x_2) \leq \frac{d(x), F(x_1) + d(x_2), F(x_2)}{1 - \alpha} \tag{3.1}$$

for all point $x_1, x_2 \in X$.This inequality immediately implies that F cannot have more than one fixed point.
Let F^n denote the composition of F with itself n times.It is easy to show that F^n is a contraction constant α^n.If we now apply (3.1) to the points $x_1 = F^m(x_0)$ and $x_2 = F^n(x_0)$,where $x \in X$ is arbitrary,we obtain that

$$d(F^m(x_0), F^n(x_0) \leq \frac{d(F^m(x_0), F^m(F(x_0))) + d(F^n(x_0), F^n(F(x_0)))}{1 - \alpha} \tag{3.2}$$

$$\leq \frac{\alpha^m + \alpha^n}{1 - \alpha}\ d(x_0, F(x_0)).$$

since $0 \leq \alpha < 1$,this implies that the sequence $(F^n(x_0))_n^\infty = 1$ is a cauchy sequence

and theefore that $F^n(x_0) \longmapsto$x for some x ∈ X.Finally,because F is continuous,

$$F(x) = F(\lim_{n\to\infty} F^n(x_0)) = \lim_{n\longrightarrow\infty} F^{n+1}(x_0) = x$$

so x is a fixed point of F

Theorem 3.0.7 *If X is a complete metric space and f: X⟶X is mapping such that some iterate f^n:X⟶X is contraction,then f has a unique fixed point.Moreover,the fixed point of f can be obtained by iteration of f starting from any $x_0 \in X$[25]*

proof:by the contraction mapping theorem.f^N has a unique fixed point.Call it is a so $f^N = a$.To show that a is the only possible fixed point of f, observe that a fixed point of f is a fixed of f^N,and thus must be a.To show a really is a fixed point of f,we note that $f(a) = f(f^N(a)) = f^N(f(a))$,so f(a) is a fixed point of f^N. Therefore $f(a)$ and a are both fixed point of f^N.Since f^N has a unique fixed point ,$f(a) = a$
We show that for any $x_0 \in X$,the points $f^n(x_0)$ converge to a as $n \longmapsto \infty$.
Consider the iterates $f^n(x_0)$ as n runs through a convergence calls modulo N.That is pick a $0 \leq r \leq N-1$ and look $f^{NK} + r(x_0)$ as $n \longmapsto \infty$.since
$f^{NK} + r(x_0) = f^{NK}(F^r(x_0)) = (f^N)^K(f^r(x_0))$.Thus points can be viewed (for each r) as iterates of f^N starting at the point $y_0 = f^r(x_0)$
since f^N is a contraction,these iterates of f^N(from any initial point,such that as y_0) must tends to a by contraction mapping theorem.
This limit is independent of the value of r in the range 1,....N-1 so all N sequences
$\{f^{NK+r}(x_0)k \geq 1\}$ tend to a as $k \longmapsto \infty$

This shows $f^n(x_0) \longmapsto$ a

as $n \longmapsto \infty$

Banach's Theorem

Definition 3.0.8 *Let (X,d) be metric space mapping T:X⟶X is Lipschitz continuas if there exists a constant α>0 such that $(T_x, T_y) \leq \alpha d(X,Y)$ for all x,y∈ X .If 0≤ a<1,Then T is called a contraction mapping.α is called the contactivity factor of T (not necessarily Lipschitz) mapping T:X⟶X is said to have to fixed point if there exists x ∈X such that T_x=X*

Definition 3.0.9 *Let V be a linear space over the field of scalars K A real-valed function ‖ . ‖ on V is called a norm on V if it satisfies the following condition [29]*

1. non-negativity:‖ . ‖∈ $[0, \infty]$ for U∈ V.

2. ‖ U ‖=0 if and only if U=0 ∈ V

3. positive homogeneity: ‖ αV ‖ =| α |‖ V ‖ for U∈ V and α ∈K

4. triangle inequality:‖U+V‖≤‖ U ‖ +‖ V ‖ for u ,v ∈ V .

A linear space V with a norm ‖ . ‖ defined it is called a normed linear space and we write $(v, \|.\|)$ for it
Observation 3.1 Let ‖ . ‖ be a norm on a linear space V. Then | ‖ U ‖ -‖ V ‖ | ≤ ‖ U-V ‖

Definition 3.0.10 *The convolution a ⋆b of two functions a and b defined on an interval [0,T] is the function*

(a ⋆b)(t)=$\int_0^t a(t-s)$b(s)d(s).Which is defined for all those t∈[0,T] for which the integral exists.

Definition 3.0.11 *The convolution a ⋆ b of two functions a and b defined on R is the functions[10]*

(a⋆b)(t)=$\int_{-\infty}^{\infty} a(t-s)$b(s)d(s).defined for all t ∈ $\mathbb{R}$ for which the integral exists.

Definition 3.0.12 *The convolution of f and g is written f ⋆ g using asterik or star.If is defined as the integral of product the two function after one is reversed and shifted.As such,it is particular kind of integral transform:[10]*

$$(f \star g)(t) = \int_{\infty}^{\infty} f(\tau)g(t-\tau)d\tau$$

$$=\int_{\infty}^{\infty} f(t-\tau)g(\tau)d\tau$$

While the symbol t is used above,it need not represent the time domain.But in that context,the convolution formula can be amount t.As t change weighted average of the function $f(\tau)$ at the moment t where the weighting is given by $g(-\tau)$ simply shifted by amount t.As t changes,the weighting function emphasizes different parts of the input function.For function f,g supported on only $[0,\infty]$ (i.e zero for negative arguments),the integration limits can be truncated,resulting in.[11]

$$(f \star g)(t) = \int_0^t f(\tau)g(t-\tau)d\tau for, g, f : [0,\infty] \longmapsto R$$

Notation A primarily engineering convolution that one often sees is

$$f(t) \star g(t) = \int_{\infty}^{\infty} f(t)g(t-\tau)d\tau=(f \star g)(t)$$

Relation ship with differentiation

$$(f \star g)' = f' \star g = f \star g'$$

proof:$(f \star g)' = \frac{d}{dt}\int_{-\infty}^{\infty} f(\tau)g(t-\tau)d\tau$

$$=\int_{-\infty}^{\infty} f(\tau)\frac{\partial}{\partial t}g(t-\tau)d\tau$$

$$= \int_{\infty}^{\infty} f(\tau)g'(t-\tau)d\tau$$

$$= f \star g'$$

Relation ship with Integration

$$\text{If} f(t) = \int_{-\infty}^{t} f(\tau)d\tau, and \quad G(t) = \int_{-\infty}^{t} g(\tau)d\tau.$$

$(f \star g)(t) = (F \star G)(t) = \int_{-\infty}^{t}(f \star g)(\tau)d\tau$

If f and g are integration functions,then the integral of their convolution on the whole space is simply obtained as the product of their integral

$$\int_{R^d}(f \star g)(x)dx = (\int_{R^d} f(x)dx(\int_{R^d} g(x)dx)$$

3.1 Convolution and Fundamental Solution

The classical definition of convolution of two functions defined on R^m is[32]

$$f \star g(x) = \int_{R^m} f(x-y)g(y)dy \tag{3.3}$$

3.1.1 The Direct Product of Distributions

Definition 3.1.1 *Let $f \in D^{'}(R^p), g \in D^{'}(R^q)$. Then the direct product f(x)g(y) is the distribution on R^{p+q} given by*

$$\langle f(x)g(y), \phi(x,y)\rangle = \langle f(x)\langle g(y), \phi(x,y)\rangle\rangle. \tag{3.4}$$

3.1.2 Convolution of Distribution

Definition 3.1.2 *Let f,g $\in D^{'}(R^m)$. Then the convolution of f and g is defined by*

$$\langle f \star g, \phi\rangle = \langle f(x)g(y), \phi(x+y)\rangle \tag{3.5}$$

under either of the following condition

1. Either f or g has compact support

2. In one dimension,the supports of f and g are bounded from the same side.

From the corresponding properties of the direct product ,it follows that convolution is commutative and associative where it is defined. Let us consider some special cases: 1.We have

$$\begin{aligned}\langle \delta \star f, \phi\rangle &= \langle \delta(x)f(y), \phi(x+y)\rangle \\ &= \langle f(y), \langle \delta(x), \phi(x+y)\rangle\rangle \\ &= \langle f(y), \langle \delta(x), \phi(x+y)\rangle\rangle \\ &= \langle f(y), \phi(y)\rangle = \langle f, \phi\rangle\end{aligned}$$

i,e.,$\delta \star f = f$

2.Let us consider f $*\psi$,where $\psi \in D(R^m)$. We have

$$\begin{aligned}\langle f * \psi, \phi\rangle &= \langle f(x)\psi(y), \phi(x+y)\rangle \\ &= \langle f(x), \textstyle\int_{R^m} \psi(y)\phi(x+y)dy\rangle \\ &= \langle f(x), \textstyle\int_{R^m} \psi(y-x)\phi(y)dy\rangle\end{aligned}$$

$$= \int_{R^m} \langle f(x), \psi(y-x)\phi(y)\rangle ds.$$

Here $f * \psi(y)$ is equal to the function $\langle f(x), \psi(y-x)\rangle$.This function is of class C^∞,and if f has compact support,it is a test function. We next consider differentiation of a convolution.By definition,we have

$$\begin{aligned} D^\alpha(f*g),\phi\rangle &= (-1)^{|\alpha|}\langle f*g, D^\alpha\phi\rangle \\ &= (-1)^{|\alpha|}\langle g(y), \langle f(x), D^\alpha\phi(x+y)\rangle\rangle \\ &= \langle g(y), \langle D^\alpha f(x), \phi(x+y)\rangle\rangle \\ &= \langle D^\alpha * g, \phi\rangle. \text{ Thus } D^\alpha(f*g) = D^\alpha f * g, \end{aligned}$$

and using commutativity,we also find$D^\alpha(f*g) = f * D^\alpha g$.A convolution is differentiated by differentiating either one of the factors.

Definition 3.1.3 *Let $S > 0$.Afunction $k{:}R^2 \longrightarrow C^{n*n}$ is called a kernel of type of $[B^\infty;T_s;C^{n*n}]$ (or of bounded periodic type with period S) if k is a kernel of bounded type on R,and if,in addition,for all t∈R, and almost all s,k(t+S,s+S)=k(t,s).If,moreover,k is a kernel of continuous type, then we call k a kernel of type $[C;T_s;C^{n*n}]$ (or of continuous periodic type with period S)Kernels of type $[B_\infty;T_s;C^{n*n}]$ are denoted by $K(B^\infty;T_s;C^{n*n})$,and kernels of type $[B^\infty;T_s;C^{n*n}]$ are denoted by $K(C;T_s;C^{n*n})$. Note that every (Volterra type) convolution kernel in $L^1(R^1;C^{n*n})$,and every(fredholm type)convolution kernel in $L^1(R;C^{n*n})$,is of continuous periodic type with period S,for every S>0*

Theorem 3.1.4 *If k is kernel of bounded type (bounded continuous type) [bounded uniformly continuous] on an interval J⊂R,and K has a resolvent r of type L^∞ on J,then r is of the same type as K(after redefiinition on a set of measure zero).Moreover,for every bounded and Borel measurable (bouned and continuous)[bounded and uniformly continuous] function f and J,there is a unique bounded and Borel measurable (bounded and continuous)[bounded and uniformly continuous]*

Theorem 3.1.5 *Let The classes $K(B^\infty;T_s;C^{n*n})$ and $K(C;T_S;C^{n*n})$ are closed subalgebras of $K(B^\infty;R;C^{n*n})$.Moreover,$B^\infty(T_s;C^n)$ is left banach module over $K(B^\infty T_s;C^{n*n})$,and $C(T_s;C^n)$ is a left Banach module over $K(C;T_s;C^{n*n})$.*

Proof :let B stand for either B^∞or.It is obvious that $K(B;T_s;C^{n*n})$ is a closed subspace of K$(B^\infty;R;C^{n*n})$.That it is a subalgebra follows from the fact that,if both a and b belong to K$(B;T_s;C^n)$,then,

$$\begin{aligned} (a\star b)(t+S,s+S) &= \int_R a(t+S,v)b(v,s+S)ds \\ &= \int_R b(t+S,v+S)b(v+S,s+S)dv \\ &= \int_R a(t,v)b(v,s)ds = (a\star b)(t,s) \end{aligned}$$

A completely analogous computation show that a $\star$ f $\in B(T_s;C^n)$ when-ever a $\in K(B;T_s;C^{n*n})$ and f $\in L^\infty(T_s;C^n)$. Kernels of periodic type have the interesting property that,if they have a resolvent of bounded type,then this resolvent must be periodic.

3.2 Theory of linear volterra integral equation

A linear volterra integral equation (VIE)of the second kind is a functional equation of the form

$$u(t) = g(t) + \int_0^t K(t,s)u(s)ds, \qquad t \in I := [0,T].$$

Here,g(t) and K(t,s) are given functions,and u(t) is an unknown function.The function K(t,s)is called the kernel of VIE.A linear VIE of the first kind is given by

$$\int_0^t K(t,s)u(s)ds = g(t), \qquad t \in I$$

Here,the unknown function occurs only under the integral sign.
A linear VIE of the third kind has the form

$$r(t)u(t) = g(t) + \int_0^t K(t,s)u(s)ds, \qquad t \in I,$$

Where the given function r(t)=0 at some points (or on a subinterval) of [0,T].

3.3 Linear volterra integral operators:

- The classical volterra integral operator $\nu : C(I) \longrightarrow C(I)$ is defined by

$$(\nu_u)(t) := \int_0^t K(t,s)u(s)ds, \qquad t \in I$$

- The weakly singular volterra integral operator $\nu_\alpha : C(I) \longrightarrow C(I)$ has the form

$$(\nu_\alpha u)(t) := \int_0^t (t-s)^{-\alpha} K(t,s)u(s)ds, \qquad 0 < \alpha < 1,$$

with algebraic singularity $(t-s)^{-\alpha}$,and $K \in C(D)$,$K(t,t) \neq 0$ $(t \in I)$. The weakly singular volterra integral operator corresponding to a logarithmic singularity,

ν_1:C(I)$\longrightarrow$C(I) is given by

$$(\nu_1 u)(t) := \int_0^t log(t-s)K(t,s)u(s)ds,$$

$$with \qquad K \in C(D), K(t,t) \neq 0 \qquad (t \in I)$$

3.4 Volterra Equations

Studied so far (integral equations;integro-differential equations, equations with function or with measures as kernels) have all been of convolution type.
the linear volterra equation of the second kind of the form

$$x(t) + \int_0^t K(t,s)x(s)ds = f(t), \qquad t \in R^+ \tag{3.6}$$

There we shall also analyses (3.6) with K replaced by measure k.The kernel k in (3.6) is a known function defined for $0 \leq t < \infty$,with value in the space C^{n*n} of n by n matrices.The forcing function f is defined for $t \geq 0$,and it takes (column vector) values in C^n.rewrite (3.6) as convolution equation

$t \longrightarrow \int_0^t K(t,s)x(s)ds$ *in* (3.6) *by* $k \star x$ *then* (3.6) *become*

$$x(t) + (k \star x)(t) = f(t), t \in R^+$$

3.5 Linear elastic model

$$x^{'}(t) = v(t) \tag{3.7}$$

$$v(t) = u - k\int_0^t (x(t) - x(t-a))p(a), \tag{3.8}$$

Where P stand for p_1 and $k = \dfrac{k\alpha}{v\beta}$ is the unique parameter of the model.Note that $\frac{\alpha}{\beta}$ is the number of bonds in a unit time while $\frac{1}{\beta}$ is the mean life-time of one bond. Supposing that the averaged position and velocity are related by (3.7) equation (3.7)-(3.8) is a volterra integro-differential equation.

$$v(t) = u + k\int_0^t (x(t-a) - x(t))p(a)da,$$

$$u + k\int_0^t x(t-a)p(a)da - x(t)\int_0^t p(a)da$$

Where Q denotes the anti-derivative of P:$Q' = P$ with $Q(0) = 0$.

$$Q(t) = \int_0^t p(a)da$$

mean

let u=x(t-a) dv=p(a)da

$$du = -v(t-a)da, v = \int_0^t p(a)da$$

$$v(t) = u + k\int_0^t v(t-a)d(a)da - x(t)Q(t)$$

assume s=t-a

$$v(t) = u + k\int_0^t (v(s)Q(a)da - v(s)Q(t))ds$$

$$v(t) = u - k\int_0^t v(s)(Q(t) - Q(t-s))ds \tag{3.9}$$

It can be written as a volterra equation. on the velocity:

In the case $P(a) = e^{-a}$,we can actually find out the explicit solution:

$$v(t) = u(1 - kA(t)e^{-t}), \tag{3.10}$$

Where

$$A(t) = \left[\int_0^t (e^s - 1)e^{k(s+e^{-s})}ds\right] e^{-k(t+e^{-t})}, \tag{3.11}$$

3.6 Asymptotic friction force:

One way to understand the qualitative behavior of this model is to study its long-time asymptotics.
It can be proved that the velocity v is bounded,with $v(t) \in (0, u)$for all times t>0 .Moreover,under some assumptions on P,then

$$v(t) \longrightarrow \frac{u}{1+K}, withK = k\int_0^{+\infty} aP(a)da \tag{3.12}$$

Thus,the linear elastic microscopic force is asymptotically similar to a friction force of parameter K.In particular,this friction force only depends on the second moment of g_β,which is actually the mean bond age.Indeed, we can compute

$$K = \frac{k\alpha}{v}\frac{1}{\beta^2}\int_0^{+\infty} aP(a)da = \frac{k\alpha}{2v}\int_0^{+\infty} a^2 g_\beta(a)da.$$

In the case $p(a) = e^{-a}$,we obtain K=k,which means that $\lim v(t) = \dfrac{u}{1+k}$ as $t \longrightarrow +\infty$

3.7 The variation of constant method

we start with the homogeneous equation

$$y^{'} + p(x)y = 0 \quad where \quad y \neq 0 \tag{3.13}$$

integrate both side

$$\int \frac{y^{'}}{y} + P(x) = \int 0d(x)$$

$$\ln \mid y \mid + \int^t p(s)ds = K$$

where K is integration constant then we took both side exponential

$$| y | + e^{\int^t p(s)} d(s) = e^k$$

$$| y | exp(\int^t p(s))ds = e^k$$

$$y = \pm e^k exp(-\int^t p(s))ds$$

we define a new constant $C = \pm e^k$ so we can put the solution in the form

$$y = Cexp(-\int^t p(s))ds$$

we look Inhomogeneous equation

$$y' + p(x)y = q(t)$$

The idea of the variation of constants method is to look for a solution in a similar (3.13) obviously,something has to change since the equation has changed.The change is that the constant C is replaced by a function C(t)

$$Y = C(t)exp(-\int^t p(s)ds)$$

We differentiate using the product and chain rule find

$$Y^{'} = C(t)exp(-\int^t p(s)ds) - (C(t)p(t)exp(-\int^t p(s))ds$$

$$Y^{'} + P(t)y = q(t)exp(-\int^t p(s)ds)$$

this our differential equation becomes

$$C^{'}(t)exp(-\int^t p(s))ds = g(t)$$

$$C^{'}(t) = g(t)exp(\int^t p(s)ds)$$

we can then find C(t) by integrating this equation the result is evidently the same as what we found using the integrating factor method,but the ideas leading to the result were different while for first order linear equations the integrating factor method and the variation of constant method are the same,the difference is in how they can be generalized to some non-linear equations of first order.The variation of constants method,on the other hand,can be generalized to linear equations of higher and to linear equations systems.

3.8 Gaussian Integrals

$$\int_{-\infty}^{\infty} e^{-x^2} dx = \sqrt{\pi} \tag{3.14}$$

$$\int_{0}^{\infty} e^{-ax^2} dx = \frac{1}{2}\sqrt{\frac{\pi}{a}} \tag{3.15}$$

$$\int_{-\infty}^{\infty} e^{-ax^2+bx} dx = e^{\frac{b^2}{4a}}\sqrt{\frac{\pi}{a}} \tag{3.16}$$

$$\int_{0}^{\infty} e^{-iax^2} dx = \frac{1}{2}\sqrt{\frac{i\pi}{a}} \tag{3.17}$$

$$\int_{0}^{\infty} e^{-iax^2} dx = \frac{1}{2}\sqrt{\frac{\pi}{ia}} \tag{3.18}$$

$$\int_{0}^{\infty} x^n e^{-ax^2} dx \approx a^{-(\frac{n+1}{2})} \tag{3.19}$$

and in particular;

$$\int_{0}^{\infty} x^n e^{-ax^2} dx = \begin{cases} \frac{(n-1)(n-3)...3*1}{2^{\frac{n+1}{2}}} a^{\frac{n}{2}} \sqrt{\frac{\pi}{a}} & for\ n\ even \\ \frac{[\frac{1}{2}(n-1)]}{2a^{\frac{n+1}{2}}}, for\ n\ odd \end{cases} \tag{3.20}$$

Notes on proving these integrals:integral (3.14) is done by squaring the the exponents to $x^2 + y^2$ switching to polar coordinates, and taking the R integral (3.14).Integral(3.16) is done by completing the square in the exponent and then changing variables to use equation (3.14).Integral (3.17)(3.18) can be done by integrating over a wedge with angle $\frac{\pi}{4}(\frac{-\pi}{4})$ using Cauchy's theory to relate the integral over the real number to the other side of the wedge,and then using Integral (3.14). For n even integral (3.20) can be done by taking of equation (3.15) with respect to (1.17). For n odd,Integral (1.20) can be done with the substitution $u = ax^2$,and then integrating by parts.

Chapter 4

AN INTGRO-DIFFERENTIAL EQUATION

4.1 Linear Force Functions

Let us start with the force functions of force form the right and force form the left

$$f_{r(y,x)} = k[\ell - (x-y)]_+ \text{ and}$$

$$f_\ell(y,x) = k[\ell - (y-x)]_+$$

where $[.]_+$ denoted the positve part function and $\kappa, \ell \in \mathbb{R}$ are two constants.Taking

$$f_r\left(x\left(t-a\right), x\left(t\right)\right)$$

and

$$f_\ell\left(x\left(t-a\right), x\left(t\right)\right),$$

,it corresponds to hypothesis of filopodia having a constant size ℓ,and exerting elastic forces as long as the cell at position $x\left(t\right)$ has not reached their tip $x\left(t-a\right) \underline{+} \ell$. (1.2) Taking

$$\begin{aligned} &f_r(x(t-a), x(t)) \\ &f_\ell(x(t-a), x(t)) \\ &f_r(y,x) = f_r(x(t-a), x(t) \end{aligned}$$

$$\begin{aligned} \frac{dx}{dt}(t) &= \int_0^t \rho(a)\left(\psi_r f_r(y,x) - \psi_\ell f_\ell(y,x)\right) da \\ &= \int_0^t \rho(a)\left(\psi_r k[\ell - (x-y)]_+ - \psi_\ell k[\ell - (y-x)]_+\right) da \\ &= k\int_0^t \rho(a)\left(\psi_r[\ell - x(t) + x(t-a)]_+ - \psi_\ell[\ell - x(t-a) = x(t)]_+\right) da \\ \frac{dx}{dt}\left(t\right) &= k\int_0^t \rho\left(a\right)\left(\psi_r[\ell + x\left(t-a\right) - x\left(t\right)]_+ - \psi_\ell[\ell + x\left(t\right) - x\left(t-a\right)]_+\right) da \end{aligned} \tag{4.1}$$

linear force function by integro-differential equation in filopodial force.
Where $\psi_{r,\ell}$ are densities of filopodial,a is the presences of filopdial,and $\rho(a)$ is life time of filopodial

4.2 Existence and Uniqueness

Existence and Uniqueness

Theorem 4.2.1 *For $\rho \in L^1(\mathbb{R}^+)$,there exists a unique solution $x \in C^1(\mathbb{R}_+, \mathbb{R})$ of equation*

$$\frac{dx}{dt}(t) = k\int_0^t \rho(a)\left(\psi_r[\ell + x(t-a) - x(t)]_+ - \psi_\ell[\ell + x(t) - x(t-a)]_+\right)da \quad (4.2)$$

proof 4.2.2 *integrating both side equation(4.2)*

$$x(t) = k\int_0^t\int_0^s \rho(a)(\psi_r[x(s-a) + \ell - x(s)]_+ - \psi_\ell[x(s) - x(s-a) + \ell]_+ dads = \phi(x)(t)$$

with $\phi : (C([0,T],\mathbb{R}), \|\|_\infty) \longrightarrow (C([0,T],\mathbb{R}), \|\|_\infty)$

$$x \longrightarrow \phi(x) = (t \longrightarrow \phi(x)(t)),$$

for some $T \geq 0$. We are looking for existence and uniqueness of a fixed point for ϕ. Let us construct a sequence $(x^n)_n \geq 0$ in $C([0,T],\mathbb{R},)$ such that

$$x^0 \equiv x_0,\ x^{n+1} = \phi(x^n)\ \forall_n \geq 0$$

As [0,T] is compact,$(C([0,T],\mathbb{R},), \|\|_\infty)$is a Banach space and we can use the Banach fixed-point theorem.All we need to show now is that, ϕ is a contraction mapping. Consider $(y,z) \in (C([0,T],\mathbb{R}), \|\|_\infty)^2$ and denoting

$$g_{s,a}(y) = y(s-a) + \ell - y(s)$$

$$g_{s,a}(z) = z(s-a) + \ell - z(s)$$

$$h_{s,a}(y) = y(s) - y(s-a) + \ell,$$

$$h_{s,a}(z) = z(s) - z(s-a) + \ell \text{ we have}$$

$$\| \phi(y) - \phi(z) \|_\infty = \sup_{t\in[0,T]} \left| k\int_0^t\int_0^s \rho(a)(\psi_r([g_{s,a}(y)]_+ - [g_{s,a}(z)]_+) - \psi_l([h_{s,a}(y)]_+ - [h_{s,a}(z)]_+)dads \right|$$

$$\leqslant \sup_{t\in[0,T]} \int_0^s |\rho(a)|(\psi_r \mid [g_{s,a}(y)]_+ - [g_{s,a}(z)]_+ \mid + \psi_\ell \mid [h_{s,a}(y)] - [h_{s,a}(z)]_+ \mid)da,$$

since $\psi_r \geq 0$. and also $\psi_\ell \geq 0$.
Denoted by $\psi := \psi_r + \psi_\ell$. Now,for $(A,B) \in \mathbb{R}^2$, the inequality

$$|[A]_+ - [B]_+| \leq |A - B| \text{ holds,leading to}$$

$$\|\phi(y) - \phi(z)\|_\infty \leq kT \sup_{t\in[0,T]} \int_0^s \psi|\rho(a)||(y-z)(s-a) - (y-z)(s)|da,$$

$$\leq 2kT\psi\|\rho\|_{L^1(\mathbb{R}_+)}\|Y - Z\|_\infty,$$

For T small enough such that $2k\psi\|\rho\|_{L'(\mathbb{R}_+)}\ T < 1$,we deduce that ϕ is a contraction mapping.As a consequence of the Banach fixed-point theorem,there exists a unique $x \in C([0,T],\mathbb{R})$.Finally,using (4.1) it is clear that $x \in C^1(\mathbb{R}_+,\mathbb{R})$.

4.3 Linear Forces

The presence of the positive part function in the previous case prevents getting analytical properties of the solution.In this section,we will take the following linearized forces functions:

$$f_r\left(x\left(t-a\right),x\left(t\right)\right)=k\left(x\left(t-a\right)+\ell-x\left(t\right)\right),$$

$$f_\ell\left(x\left(t-a\right),x\left(t\right)\right)=k\left(x(t)-x\left(t-a\right)+\ell\right) \qquad ,$$

with $k,\ell\in\mathbb{R}_+$.This assumption is less connected or appropriate to the current matter from the modeling point of view,since if the cell overtakes the tip of a filopodium,then it will experience a force in the opposite direction.However,for k small enougn,and an appropriate lifetime function,we can assume that the cell is slow enougn so that it does not reach any existing filopodium tip.
Equation (1.2) can be written as a linear volterra equation,which will lead to more analytical results.

4.3.1 Linear Volterra Equation Formalism

Using an integro-differential equation from equation (1.2)

$$\frac{dx}{dt}(t)=\int_0^t p(a)(\psi_r f_r(x(t-a),x(t))-\psi_\ell f_\ell(x(t-a),x(t)))da$$

$x(0)=x_0$

$$v(t)=k\int_0^t\rho(a)\left(\psi_r\left(x\left(t-a\right)+\ell-x(t)\right)-\psi_\ell\left(x(t)-x\left(t-a\right)+\ell\right)\right)da$$

$$=k\ell\left(\psi_r-\psi_\ell\right)\int_0^t\rho(a)da+k\psi\int_0^t\rho(a)\left(x\left(t-a\right)-x(t)\right)da \tag{4.3}$$

$$Denoting\ \ Q(t)\longmapsto\int_0^t\rho(a)da$$

and integrating by parts, we obtain

$$v(t)=k\ell\left(\psi_r-\psi_\ell\right)Q(t)+k\psi\left(\int_0^t Q(a)v\left(t-a\right)da-Q(t)x(t)\right)da,$$

since $Q(0)=0\ \ and\ \ x(0)=0.After\ the\ change\ of\ variable\ \ s=t-a$ we get

$$v(t)=f(t)-k\psi\int_0^t\left(Q(t)-Q\left(t-s\right)\right)v(s)ds, \tag{4.4}$$

with

$$f(t)=k\ell(\psi_r-\psi_\ell)Q(t) \tag{4.5}$$

which is a linear volterra integro-differential equatian for v.

4.3.2 Existence and Uniqueness of a solution

With similar to theorem (4.2.1). we can prove the following property:

Theorem 4.3.1 *For* $\rho \in L^1(\mathbb{R}^+)$ *Equation admits* (4.4) *a unique solution* $v \in C(\mathbb{R}^+, \mathbb{R})$.

Let us define the operator

$$h \star v : t \longmapsto \int_0^\infty h(t,s)v(s)ds$$

Equation (4.4) can then be written as a convolution-like equation:

$$v(t) + (h \star v)(t) = f(t)$$

The function defined for $0 \leq s \leq t < \infty$

$$\int_0^t h(t,s)v(s)ds \leq \int_0^{+\infty} h(t,s)v(s)ds \tag{4.6}$$

form equation (4.4) we have

$$f(t) = v(t) + k\psi \int_0^t (Q(t) - Q(t-s))v(s)ds$$

$$v(t) + (h * v)(t) = v(t) + k\psi \int_0^t (Q(t) - Q(t-s))v(s)ds$$

$$(h * v)(t) = k\psi \int_0^t (Q(t) - Q(t-s))v(s)ds$$

with

$$h(t,s) = k\psi \left(Q(t) - Q\left(t-s\right)\right) 1_{[0,t]}(s).$$

Existence and uniqueness of the a solution can be proved by showing that h is a Volterra kernel of L^∞ type.[10]

4.3.3 Sign and Boundedness property

We now prove a result showing how important the function f is in controlling the migration.Indeed,it captures no less then the range of forces exerted with k,aging,and the potential asymmetry $\psi_r - \psi_\ell \neq 0$ in the formation of filopodia.

Theorem 4.3.2 *If* ρ *is positive and decreasing,then the solution to equation*

$$v(t) = f(t) - k\psi \int_0^t (Q(t) - Q(t-s)v(s)da$$

with

$$f(t) = k\ell(\psi_r - \psi_\ell)Q(t)$$

satisfies

$$\psi_r \geq \psi_\ell \Rightarrow \quad \forall_t \geq 0, \quad v(t) \in [0, f(t)]$$

$$\psi_r \leq \psi_\ell \Rightarrow \quad \forall_t \geq 0, \quad v(t) \ \in \ [f(t), 0],$$

Proof first suppose that $\psi_r \geq \psi_\ell$.*Consequently*, $\forall(t) \geq 0, f(t) \geq 0$ and $f^{'}(t) \geq 0$.then the equation

$$v(t) = f(t) - k\psi \int_0^t (Q(t) - Q(t-s)v(s)da$$

with

$$f(t) = k\ell(\psi_r - \psi_\ell)Q(t)$$

By derivation of ,we obtain

$$v'(t) = f^{'}(t) - k\psi \left(Q(t) - Q(0)\right) v(t) - k\psi \int_0^t \left(\rho(t) - \rho\left(t-s\right)\right) v(s)ds,$$

with

$$f^{'}(t) = k\ell \left(\psi_r - \psi_\ell\right) \rho(t).$$

suppose there exists $t^\star$ such that

$$\forall(t) \leq t^\star, v(t) > 0 \text{ and } v(t^\star) = 0, \text{then}$$

$$v^{'}(t^\star) = f^{'}(t^\star) - k\psi Q(t^\star)v(t^\star) - k\psi \int_0^{t^\star} \left(\rho(t) - \rho\left(t^\star - s\right)\right) v(s)ds$$

is positive (since all the terms are positive).Consequently,

$$\forall t \geq 0, \ v(t) \geq 0.$$

This implies that

$$x(t-a) - x(t) \leq 0, \forall t \geq a \geq 0.$$

Going back to the equivalent equation (4.3) this show that

$$\forall(t) \geq 0, v(t) \leq f(t).$$

Proof.Second,let us assume that $\psi_\ell \geq \psi_r$,which $\forall t \geq 0, f(t) \leq 0$ and $f^{'}(t) \leq 0$. In similar way of the first proof by equation (4.4)

$$v^{'}(t) = f^{'}(t) - k\psi(Q(t) - Q(0))v(t) - k\psi \int_0^t \left(\rho(t) - \rho(t-s)\right) v(s)ds$$

with $\quad f^{'}(t) = k\ell(\psi_r - \psi_\ell)\rho(t)$

also suppose there exists $t^\star$ such that $v(t) \leq t^\star, v(t) \leq 0$ and $v(t^\star) = 0$ then

$$v'(t^\star) = f^{'}(t) - k\psi Q(t^\star)v(t^\star) - k\psi \int_0^t (\rho(t^\star) - \rho(t^\star - s))v(s)ds$$

is negative (because all the terms are negative) that mean

$$v(t) > 0 \ f(t) \leq 0 \text{ and } f^{'}(t) \leq 0.$$

In similar way of the first proof,if there exist $t^\star$ such that $v(t) < t^\star, v(t) < 0$ and $v(t^\star) = 0$, then $v(t^\star)$ is negative. And considering again (4.3) we show that

$$v(t) \geq 0, \ v(t) \geq f(t)$$

4.3.4 Asymptotic Velocity

We now given an expression for the asymptotic velocity of the cell.Here again,f has a crucial importance.Having two different cases can be interpreted as follows:if the mean lifetime of filopodia is finite,then the cell is permanently escaping from the action of older force.As a consequence,if $\psi_r - \psi_\ell \neq 0$,it can get off its position all the time.However,if the mean lifetime of filopodia is infinite,all of them exert elastic forces on the cell,which will be stabilized in finite time.

4.3.5 Particuler Cases

Some choices of function ρ can give more explicit information on the solution.

Infinite Existence Time of Forces ($\rho \equiv 1$)

Taking $\rho \equiv 1$,we are considering elastic forces that never disappear.Here,ρ does not fulfill the hypothesis of (4.3.1) Equation (4.4) writes

$$v(t) = kl(\psi_r - \psi_\ell)t - k\psi \int_0^t sv(s)ds, \tag{4.7}$$

derivate equation (4.7) both side

$$v(t)' = k\ell(\psi_r - \psi_\ell) - k\psi t v(t)$$

$$v(t)' + k\psi t v(t) = k\ell(\psi_r - \psi_\ell)$$

by integrating factor$= e^{\int k\psi t dt}$

$$= e^{k\psi \frac{t^2}{2}}$$

multiplying both side by integrate factor

$$\left(v'(t) + k\psi t v(t) = k\ell(\psi_r - \psi_\ell)\right) e^{\frac{k\psi t^2}{2}}$$

$$(v(t)e^{\frac{k\psi t^2}{2}})' = k\ell(\psi_r - \psi_\ell)e^{k\psi \frac{t^2}{2}}$$

and can be solved after integration with the variation of constants method, to give

$$v(t) = v(0)e^{\frac{-k\psi t^2}{2}} + \ell\sqrt{\frac{k\pi}{2}}(\psi_r - \psi_\ell)\sqrt{e^{\frac{-k\psi t^2}{2}}(1 - e^{\frac{-k\psi t^2}{2}})} \tag{4.8}$$

Know we can observe the sign and boundedness property(4.3.2),where in this case the f(t) bounded is optimal.It is easy to check analytically the convergence of v to $v_\infty = 0$ since we have the equivalence

$$v(t)\ t \overset{\sim}{\to} \infty\ \ell\sqrt{\frac{k\pi}{2}}\,(\psi_r - \psi_\ell)\,e^{\frac{-k\psi t^2}{4}}$$

Exponetial Decay

We now assume that $\rho(a) = e^{-a}$,which was the function chosen.All the results demonstrated before apply.However,we can actually directly solve the equation.Noting that $Q(t) = 1 - e^{-t}$,equation (4.4) becomes

$$v(t) = f(t) - k\psi \int_0^t (Q(t) - Q(t-s))\, v(s)ds,$$

$$v(t) = f(t) - k\psi \int_0^t (Q(t) - Q(t-s))\, v(s)ds,$$

where

$$f(t) = k\ell(\psi_r - \psi_\ell)Q(t)$$

$$v(t) = k\ell(\psi_r - \psi_\ell)Q(t) - k\psi \int_0^t (Q(t) - Q(t-s))\, v(s)ds,$$

$$v(t) = k\ell(\psi_r - \psi_\ell)(1 - e^{-t}) - k\psi \int_0^t (1 - e^{-t} - (1 - e^{-(t-s)}))v(s)ds$$

$$v(t) = k\ell(\psi_r - \psi_\ell)(1 - e^{-t}) - k\psi \int_0^t (1 - e^{t} - 1 + e^{-t+s})v(s)ds$$

$$v(t) = k\ell(\psi_r - \psi_\ell)(1 - e^{-t}) - k\psi \int_0^t (e^{s} - 1)e^{-t}v(s)ds$$

$$v(t) = k\ell(\psi_r - \psi_\ell)(1 - e^{-t}) - k(\psi_r + \psi_\ell)e^{-t}A(t) \tag{4.9}$$

with

$$A(t) = \int_0^t (e^s - 1)v(s)ds;. \tag{4.10}$$

Proposition 1. The solution to (4.4) is given by

$$v(t) = k\ell(\psi_r - \psi_\ell)(1 - e^{-t}) - k^2 l(\psi_r - \psi_\ell)\psi e^{-(k\psi+1)t+k\psi-k\psi e^{-t}} J(t), \tag{4.11}$$

with

$$J(t) = \int_0^t (e^s + e^{-s} - 2)e^{k\psi(s-1+e^{-s})}ds$$

proof.Deriving A with respect to time leads to

$$A^{'}(t) = k\ell(\psi_r - \psi_\ell)(e^t + e^{-t} - 2) - k\psi(1 - e^{-t})A(t).$$

now,by the variation of parameters method we find that

$$A(t) = k\ell(\psi_r - \psi_\ell)e^{-k\psi(t-1+e^{-t})} \int_0^t (e^s + e^{-s} - 2)e^{k\psi(s-1+e^{-s})}ds,$$

leading to expression (4.5) As a consequence,an asympttotic equivalent of the solution can be given.

Theorem 4.3.3 *The following equivalence holds:*

$$A(t)_{t\longmapsto\tilde{+\infty}} k\ell(\psi_r-\psi_\ell)(1-\frac{k\psi}{k\psi+1}-\frac{k\psi}{k\psi-1}e^{-2t}+2e^{-t}), \tag{4.12}$$

and v converges to the asymptotic velocity

$v_\infty := k\ell(\psi_r-\psi_\ell)(1-\frac{k\psi}{k\psi+1})$.

proof.Using the following equivalence

$\int_0^t e^{as}ds\simeq \frac{e^{at}}{a}$, we easily obtain

$$J(t)_{t\longmapsto\tilde{\infty}} e^{-k\psi}\left(\frac{e^{(k\psi+1)t}}{k\psi+1}+\frac{e^{(k\psi-1)t}}{k\psi-1}-2\frac{e^{k\psi t}}{k\psi}\right)$$

considering expression (4.4),we have

$$v(t)_{t\longmapsto\tilde{+\infty}} k\ell\,(\psi_r-\psi_\ell)\left[1-k\psi e^{-(k\psi+1)t}\left(\frac{e^{(k\psi+1)t}}{k\psi+1}+\frac{e(k\psi-1)t}{k\psi-1}-2\frac{e^{(k\psi t)}}{k\psi}\right)\right],$$

which leads to the resulr.
When can then deduce that the asymptotic behavior of the cell depends on the range of filopodial forces k ,on the global filopodial activity ψ,and on the asymmetry $\psi_r-\psi_\ell$.Moreover,the bigger k,and ψ are faster the the cell velocity reaches equilibrium.the non-trivial equilibrium is a consequence of the lifetime function that lets newer forces lead motion,where as the older ones are 'silenced'.The initial asymmetry is then maintained over time.

constant existence time ($\rho(a)=1_{[0,\tau]}(a)$)

Now,let us look at $\rho(a)=1_{[0,\tau]}(a)$ with $\tau>0$,meaning that all filopodia exert forces during the same finite amount of time.For $t\geq 0$,we have

$$Q(t)=\begin{cases} t & if \quad t<\tau, \\ \tau & if \quad t\geq\tau \end{cases}$$

Existence and uniqueness of a continuous solution. Moreover,we can find an explicit solution for $t\leq\tau$,and bounds for the solution for $t\geq\tau$.

$$v(t)=k\ell(\psi_r-\psi_\ell)t-k\psi\int_0^s sv(s)ds. \qquad for \quad t\leq\tau \tag{4.13}$$

$$v(t)=k\ell(\psi_r-\psi_\ell-k\psi\int_{t-\tau}^t v(s)(\tau-(t-s))ds \qquad for \quad t\geq\tau \tag{4.14}$$

Theorem 4.3.4 *The unique solution to equation (4.13)-(4.14) satisfies*

$$v(t)=\ell(\psi_r-\psi_\ell)\sqrt{\frac{k\pi}{2\psi}}\sqrt{1-e^{\frac{-k\psi}{2}}}) \qquad for \quad t\leq\tau \tag{4.15}$$

$$v(\tau)exp(-k\psi\frac{(t^2-\tau^2)}{2})\leq v(t)\leq k\ell(\psi_r-\psi_\ell) \qquad for \quad t\geq\tau \tag{4.16}$$

Proof.Let us first study the case where t $\leq \tau$.By derivation of (4.13) we have

$$v^{'}(t) = k\ell(\psi_r - \psi_\ell) - k\psi t v(t),$$

and the variation of parameters method leads to expression (4.13) Let us now consider the case where t $\geq \tau$.After a change of variable,equation (4.14) becomes

$$v(t) = k\ell\tau(\psi_r - \psi_\ell) - k\psi \int_0^\tau (\tau - s)v(t-s)ds, \tag{4.17}$$

$$= k\ell\tau(\psi_r - \psi_\ell) - k\psi \int_0^t (t - s)v(t-s)ds + h(t), \tag{4.18}$$

with

$$h(t) = k\psi \int_\tau^t (t - s)v(t-s)ds + k\psi \int_0^\tau (t - \tau)ds.$$

since ρ is positive and decreasing,we deduce from Theorem (4.1.4) that $\forall$ t $\geq$0, v(t) $\geq$0.hence,we know that h $\geq$0 on $[\tau, +\infty]$.Moreover,differentiating h with respect to t,we obtain

$$h^{'}(t) = k\psi(\int_\tau^t \frac{d}{dt}((t-s)v(t-s))ds + \int_0^\tau \frac{d}{dt}((t-\tau)v(t-s)ds),$$

$$= k\psi((t-\tau)v(t) + (x(t) - x(t-\tau))) \geq 0,$$

as v $\geq$0.

Then,differentiating (4.14)leads to

$$v^{'}(t) \geq k\psi t v(t)$$

from which we deduce that

$$v(t) \geq v(\tau)exp(-k\psi\frac{(t^2-\tau^2)}{2})$$

leading to the first inequality.Moreover,as v $\geq$0,the second one is obtained from equation (4.13) and this concludes the proof.

Chapter 5

Conclusion and Perspectives

We have introduced a simple deterministic model of 1D cell migration.based on the filopodial activity of the cell.It describes the formation of antagonistic forces by filopodia on each side of the cell.This model is not able to describe realistic trajectories,as the filopodial activity is taken constant,but it relates explicitly filopodial statistics to the cell velocity and asmptotic behavior,and hence represents a first step in the global description of cell trajectories from filopodial activity. In this work,we have studied a realistic case where filopodia stop exerting a force as soon as the cell overtook their tips.In this case,the highly nonlinear forces prevent us from getting more than an existence and uniqeness result.The case of linear elastic forces is richer.as it gave more information about the sign,boundedness,and asymptotic behavior of the solution.

It is important to keep in mind that the linear model is realistic only in a particular setting:if the cell is slow enough,then they won't be reached by the cell.Typical velocity and filopodium lifetime are closely related to the cell type and experimental setting.Inded, considering the force kℓ exerted by a filopdium of length ℓ on the substrate,it is known that ℓ is variable among cell types.Moreover,k highly depends on the rigidity of the substrate:the more it is rigid,the larger the forces are.Another key player in the filopodial forces is the adhesiveness of the substrate,that scales how strong it is coupled to filopodia,hence how large forces will be.How ever,a very adherent substrate is also less likely to let go of filopodia during the contraction of the cell,leading to a longer lifetime for them.

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