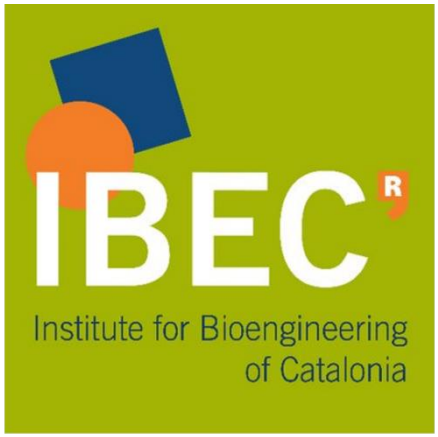
Modeling actin flow mediated cell polarity dynamics



Pradeep Kumar Bal

Supervised by Prof. Marino Arroyo

Industrial Training Report

Master of Science in Computational Mechanics

CIMNE, Universitat Politècnica de Catalunya, UPC, Barcelona

ACKNOWLEDGEMENTS

I would like to sincerely thank my supervisor, Prof. Marino Arroyo, for guiding and supporting me as well as for devoting his time and resources for my work. His cheerful and friendly nature and his encouragements provide me with a lot of motivation and enthusiasm to work on my project.

I would also like to express my gratitude to Dr. Sohan Kale for his guidance throughout the project, whose useful insights on the topic have been very valuable and kept me motivated. My group-mates Dr. Nikhil Walani and Jordi Font had suggested me many useful things related the concepts of mechanobiology. I sincerely thank Dr. Esther Sala-Lardies for her valuable suggestions.

I also express my appreciation for the support given to me by the lab technologist during the course of the project.

The motivation and support from my family have been immensely invaluable during the course of my ongoing work.

Modeling actin flow mediated cell polarity dynamics

PRADEEP KUMAR BAL

September 1, 2018

Contents

1 Abstract:

Cell movement has essential functions in development, immunity, and cancer. Various cell migration patterns have been reported, and a general rule has recently emerged, the so-called universal coupling between cell speed and cell persistence. This rule says that cell persistence, which quantifies the straightness of trajectories, is robustly coupled to migration speed. In [2], the advection of polarity cues by a dynamic actin cytoskeleton undergoing flows at the cellular scale was proposed as a first explanation of this universal coupling. Here, following ideas proposed in that work, we present and study a simple numerical model to describe motility initiation in crawling cells. This universal coupling constitutes a generic law of cell migration, which originates in the advection of polarity cues by an actin cytoskeleton undergoing flows at the cellular scale. We formulate the governing equations for the advection-diffusion of polarity markers coupled with the flow of active viscous actomyosin cortex. The continuity equation for the actin flow which is a hyperbolic convection-reaction equation, which considers the actin polymerization and depolymerisation,and thus obtaining a coupled system of equations for advection-diffusion of the polarity markers, convection-reaction of the cortex, and the force balance on the cell. In this work, we present an implicit numerical scheme to solve these coupled non-linear system of equations representing in-plane cell migration on a substrate. First, we study the feedback between actin flows generated by gradients in polarity concentration, which can be in turn maintained due to advection of polarity cues with the actin flow depending on the value of the diffusion coefficient of the polarity cue. Then, we investigate how the actin flows are affected by perturbing a crawling cell with an external force.

2 Introduction:

Cell migration is a fundamental biological process involved in morphogenesis, tumor spreading, and wound healing. One of its most spectacular instances is cell crawling, which is crucial to immune cells in order to reach an inflammation spot, but it is also observed, e.g., in tumor cells during metastasis formation. Identifying key mechanisms involved in cell migration is then a major issue both for our fundamental understanding and for clinical research. It is unclear whether a general rule can account for the diversity of cell migration patterns observed in vivo and in vitro. By analysing trajectories of cells migrating in live tissues and under various in vitro conditions, Maiuri et al.[2] revealed a universal coupling between cell migration speed and cell persistence (the capacity to maintain the direction of motion). The authors developed a physical model to explain how faster cells move straighter. In this model, coupling between cell speed and persistence relies on cellular actin retrograde flows that transport polarity cues from the front to the rear of migrating cells. In the paper [1] , the authors have theoretically proposed that due to the presence of the initial gradient in the concentration of the polarity cues, the actin flow in the cell is induced towards the direction having the higher concentration of the polarity cues. Due to this actin flow(only advection), the gradient of the polarity cues further increases in the initial direction, which induces faster actin flow. This loop further continues making the faster moving cells persistent. Figure 1 represents these concepts lucidly. We propose a numerical model and present a suitable solution method to replicate their theoretical findings numerically. We focus here on cells crawling on a flat substrate.

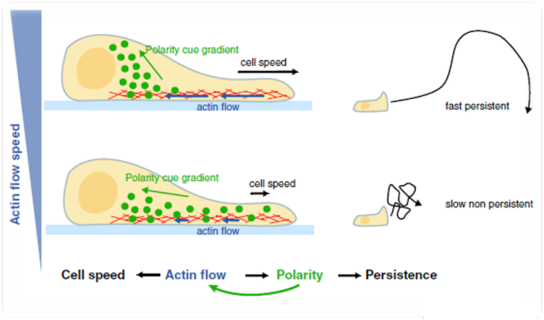


Figure 1: Actin flows couple cell speed and cell persistence

3 Modeling formulation:

The main ingredients of the model are as follows. The cell shape is assumed to be unchanged for this preliminary study. The model is formulated in the frame of reference of the cell moving at a velocity denoted as $\mathbf{u}_{cell}$. The relative velocity of the actin flow with respect to the cell is considered as $\mathbf{u}$; So the actin flow velocity, $\mathbf{u}_{actin} = \mathbf{u} + \mathbf{u}_{cell}$. From the balance of forces on the whole cell,assuming that the drag force on the cell balances the force due to the friction of the substrate, we obtain: $\int \mu_d \, \mathbf{u}_{cell} \, ds = \int \mu_s \, \mathbf{u}_{actin} \, ds = \int \mu_s \, (\mathbf{u}_{cell} + \mathbf{u}) \, ds$. Thus,the cell velocity can be interpreted as $\mathbf{u}_{cell} = \mathbf{u}_{cell,avg} = \frac{\mu_s}{\mu_d - \mu_s} \, \frac{\int \mathbf{u} \, ds}{A}$; where,$\mu_s$ is the coefficient due to the substrate friction and μ_d is the coefficient due to the drag. The continuity equation for the actin flow which can be modelled as a hyperbolic convection-reaction equation, which considers the actin polymerization and depolymerisation. The equation is represented as:

$$\frac{\partial \rho}{\partial t} + \boldsymbol{\nabla}.(\rho \, \mathbf{u}) = K_p C_0 - K_d \, \rho \qquad in \ (0,T) \times \Omega \tag{1}$$

Where, K_d is the actin depolymerization rate constant, K_p is the actin polymerization rate constant and C_0 is the bulk actin concentration. Actin is considered as a viscous fluid.

The momentum equation, also termed the equation of motion, is a relation equating the rate of change of momentum of a selected portion of the fluid(actin) and the sum of all forces acting on that portion of actin considering the force due to the friction of the substrate. The external body force which is applied throughout the volume of the actin flow to perturb a crawling cell is denoted by $\mathbf{b}^{3D}(t)$. Thus, the momentum equation can be represented as:

$$\boldsymbol{\nabla}.\boldsymbol{\sigma}^{3D} = \mu_s \, \mathbf{u}_{cell} - \mathbf{b}^{3D}(t) \qquad in \ (0,T) \times \Omega \tag{2}$$

Where, the constitutive expression of the Cauchy stress in 3D is considered as: $\boldsymbol{\sigma}^{3D} = \xi_0 \, c^* \mathbf{I} + 2\eta \mathbf{d} - p\mathbf{I}$. The viscosity of actin in 3D is denoted as, η , which is a constant. The active stress, $\sigma_a = \xi_0 \, c^* \mathbf{I}$. Where, c^* denotes the fraction of activated cues, i.e., cues that induce active tension [2]. The expression for the $c^*(\mathbf{x},t)$ is considered as: $c^*(\mathbf{x},t) = \frac{c^n(\mathbf{x},t)}{C_s^n + c^{*n}(\mathbf{x},t)}$, where, n is the index of the assumed classical Hill response function. $C_s^n$is the concentration of cues above which activation is saturated and is therefore determined by the maximal concentration of activated cues.

The polarity cue can diffuse in the cytosol, with diffusion coefficient D, and, depending on its affinity for actin, be advected by the cytoskeletal flow. We are interested in the dynamics of the concentration of a generic polarity cue, $c(\mathbf{x},t)$, and we basically focus on the resulting motion which is a biased diffusion equation with advection field in the cell frame,$\mathbf{u}(\mathbf{x},t)$ together with a zero-flux boundary condition on $\partial\Omega$ in order to conserve the molecular content. The dynamics of $c(\mathbf{x},t)$ depends on advective transport and on diffusion as follows:

$$\frac{\partial c}{\partial t} + \boldsymbol{\nabla}. \, (c \, \mathbf{u}) = D\boldsymbol{\nabla}^2 c \qquad\qquad in \ (0,T) \times \Omega \tag{3}$$

3.1 Governing equations for the 2D domain:

In 2D,we basically assume the $'zz'$ component of the active stress, $\sigma_{a,33} = 0$. The Cortical thickness in 3D is denoted as h. The expression of the stress in 2D is considered as, $\sigma^{2D} = h\sigma^{3D}$. The cortical thickness,$h = h_0 \frac{\rho}{\rho_0} = \lambda_0 \, \rho$.The expression of the pressure can be written as: $p = 2\eta \, d_{33} = -2\eta \, \boldsymbol{\nabla}.\mathbf{u}^{2D}$; It can be obtained by imposing, $\sigma_{33}^{3D} = 0 \ in \ 2D \, with \ \rho_{3D} = Const.$ So, the equation (1) $\Rightarrow \boldsymbol{\nabla}.\mathbf{d}^{3D} = 0 \, at \ the \ equilibrium \ (where, K_p C_0 = K_d \rho_{eq})$. So, $d_{33} = -(d_{11} + d_{22}) = -\boldsymbol{\nabla}.\mathbf{u}^{2D}$.

$$\boldsymbol{\sigma} = \boldsymbol{\sigma}^{2D} = h\boldsymbol{\sigma}^{3D} = \xi_0 \ \lambda_0 \rho \ c^* \ \mathbf{I} + 2\eta \ h(\mathbf{d}^{2D} + \boldsymbol{\nabla}.\mathbf{u}^{2D}\mathbf{I})$$

In 2D, Equation 2 becomes,

$$\boldsymbol{\nabla}.\boldsymbol{\sigma} = \frac{\mu_s \mathbf{u}_{cell} - \mathbf{b}^{2D}(t)}{h} = \frac{\mu_s \mathbf{u}_{cell} - \mathbf{b}^{2D}(t)}{\lambda_0\ \rho}$$

As $\mathbf{d} = \frac{(\boldsymbol{\nabla}\mathbf{u}+\boldsymbol{\nabla}\mathbf{u}^T)}{2}$, in 2D,

$$\boldsymbol{\nabla}.\boldsymbol{\sigma} = \xi_0\ \boldsymbol{\nabla}(c^*) + \eta\ \boldsymbol{\nabla}^2\ \mathbf{u} + 3\eta\ \boldsymbol{\nabla}(\boldsymbol{\nabla}.\mathbf{u}) = \frac{\mu_s\ \mathbf{u}_{cell} - \mathbf{b}^{2D}(t)}{\lambda_0\ \rho}$$

The simplified governing equations can be written in 2D as:

$$\frac{\partial \rho}{\partial t} = -\boldsymbol{\nabla}.(\rho\ \mathbf{u}) + K_p C_0 - K_d\ \rho \qquad in\ (0,T) \times \Omega \tag{4}$$

$$\xi_0\ \boldsymbol{\nabla}(c^*) + \eta\ \boldsymbol{\nabla}^2\ \mathbf{u} + 3\eta\ \boldsymbol{\nabla}(\boldsymbol{\nabla}.\mathbf{u}) = \frac{\mu_s\ \mathbf{u}_{cell} - \mathbf{b}^{2D}(t)}{\lambda_0\ \rho} \qquad in\ (0,T) \times \Omega \tag{5}$$

$$\frac{\partial c}{\partial t} = -\boldsymbol{\nabla}.(c\ \mathbf{u}) + D\boldsymbol{\nabla}^2 c \qquad in\ (0,T) \times \Omega \tag{6}$$

3.2 Parameters:

We consider a viscous active fuid(actin) filling a two-dimensional bounded domain of fixed rectangular shape figuring the cell to describe the cytoskeleton. For simplicity,we have considered a fixed rectangular domain having unit length and width. The values of the parameters which are considered for the numerical simulation have been delineated in this section. These are as follows: $K_d = 0.1\ s^{-1}$, $K_p = 1$, D= 0.01 $\mu m^2/s$, η=$10^3 pN.s/\mu m$, $\mu_d = 50$,$\mu_s = 100$,a=1;b=1;Total time=30s.
C_0=The bulk actin concentration,which,at the equilibrium satisfies, $K_p C_o = K_d \rho_{eq}$
ρ_{eq}=Equilibrium actin density=$K_p * C_0/K_d$
ξ_0=Constant in the active stress=1000
n=index in the hill response function=0.5;
$C_s = 5$=Concentration of cues above which activation is saturated, $\lambda_0 = 1$
Boundary conditions:

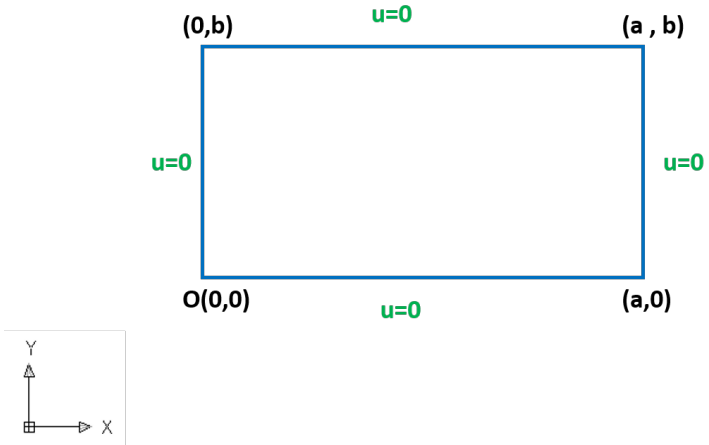


Figure 2: Computational Domain

- The Actin density satisfies the zero flux boundary condition at the each edge of the boundary;as the first equation is a hyperbolic equation ,only boundary conditions at the inflow boundary is required
- No flux boundary conditions are considered for the concentration of the polarity marker, c on all the boundaries(total mass is conserved)
- $\mathbf{u} = 0$ for velocity at each boundary

Implemented initial Conditions:

$\mathbf{u}(\mathbf{x}, t=0) = 0$; $\rho(\mathbf{x}, t=0) = 3\rho_{eq} - 2\frac{\rho_{eq} y}{L_y}$, and $c(\mathbf{x}, t=0) = 40 - \frac{20y}{L_y}$, where $\mathbf{x} \in \Omega$.
The applied continuous time dependent force (in pN) is considered as:

$$\mathbf{b}(t) = \begin{cases} (0,0) & t \leq 15s \\ (0, -400t + 6000) & 15s \leq t \leq 20s \\ (0, -2000) & t \geq 20s \end{cases}$$

4 Method:

The most popular methods for transient problems are the θ family of methods. Among the θ family methods, it is known that the Crank-Nicolson, $\theta = 1/2$, is the only second-order accurate method.It is an implicit method. As to solve the given true transient problems where the time accuracy is important, the Crank-Nicolson scheme is preferred due to its accuracy and unconditional stability.

Crank-Nicolson scheme:($\theta = \frac{1}{2}$)**:**

The CN scheme is obtained by considering ($\theta = \frac{1}{2}$) in the scheme for the θ method.Using CN scheme , the above equations(eq. 4-6) can be written as:

$$\frac{\rho(t^{n+1}) - \rho(t^n)}{\triangle\, t} = \frac{1}{2}\rho_t(t^{n+1}) + \frac{1}{2}\rho_t(t^n) + \mathcal{O}(\triangle\, t^2)$$
$$\frac{c(t^{n+1}) - c(t^n)}{\triangle\, t} = \frac{1}{2}c_t(t^{n+1}) + \frac{1}{2}c_t(t^n) + \mathcal{O}(\triangle\, t^2)$$

The equation 5 is written at the n+1 *th* time step. By substituting the given ρ_t *and* c_t values mentioned in the equations (4) and (6) in to the above two equations respectively, and neglecting the temporal truncation error,we can write the discretized form of all the equations in the 2D domain as :

$$\frac{\rho(t^{n+1}))}{\triangle\, t} + \frac{\boldsymbol{\nabla}.(\rho^{n+1}\ \mathbf{u}^{n+1}) + K_d\ \rho^{n+1}}{2} = \frac{\rho(t^n)}{\triangle\, t} + \frac{-\boldsymbol{\nabla}.(\rho^n\ \mathbf{u}^n) - K_d\ \rho^n}{2} + K_p C_0 \qquad in\ (0,T) \times \Omega \quad (7)$$

$$\xi_0\ \boldsymbol{\nabla}(c^*)^{n+1} + \eta\ \boldsymbol{\nabla}^2\ \mathbf{u}^{n+1} + 3\eta\ \boldsymbol{\nabla}(\boldsymbol{\nabla}.\mathbf{u}^{n+1}) = \frac{\mu_s\ \mathbf{u}^n_{cell} - \mathbf{b}^{2D}(t)}{\lambda_0\ \rho^n} \qquad in\ (0,T) \times \Omega \quad (8)$$

$$\frac{c(t^{n+1})}{\triangle\, t} + \left[\frac{\boldsymbol{\nabla}.(c^{n+1}\ \mathbf{u}^{n+1}) - D\boldsymbol{\nabla}^2 c^{n+1}}{2}\right] = \frac{c(t^n)}{\triangle\, t} + \frac{-\boldsymbol{\nabla}.(c^n\ \mathbf{u}^n) + D\boldsymbol{\nabla}^2 c^n}{2} \qquad in\ (0,T) \times \Omega \quad (9)$$

4.1 Weak Form:

Here, we present the Galerkin formulation associated with the strong form of the equations 7,8, and 9. The space of weighting functions denoted by $\mathcal{V}$ and $\boldsymbol{V}$satisfies the dirichlet boundary conditions on Γ_D. The functions, w and $\mathbf{w}$, in $\mathcal{V}$ and $\boldsymbol{V}$, respectively, do not depend on time.$\mathcal{V} = \{w \in H^1(\Omega) | w = 0\ on\ \Gamma_D\}$ and $\boldsymbol{V} = \{\mathbf{w} \in H^1(\Omega) | \mathbf{w} = \mathbf{0}\ on\ \Gamma_D\}$. The weak forms are obtained multiplying the equations (7 and 9) by the test function w,and the equation 8 by the test function $\mathbf{w}$,respectively,and the result integrated over the computational domain Ω, and following this, integrating by parts the term involving $\boldsymbol{\nabla}^2$ in the equations 7 and 9,and to all the terms of the equation 8; thereby generating the natural boundary condition on $\rho, c, and\ \mathbf{u}$ on Γ_N.
The weak form corresponding to equation 7 is:

$$\begin{aligned} &(w, \frac{\rho^{n+1}}{\triangle\, t}) - (\boldsymbol{\nabla} w, \frac{\rho^{n+1}\ \mathbf{u}^{n+1}}{2}) + \frac{1}{2}(w, \rho^{n+1}\mathbf{u}^{n+1}.\mathbf{n})_{\Gamma_N} + \frac{K_d}{2}(w, \rho^{n+1}) \\ &= (w, \frac{\rho^n}{\triangle\, t}) + (\boldsymbol{\nabla} w, \frac{\rho^n\ \mathbf{u}^n}{2}) - \frac{1}{2}(w, \rho^n \mathbf{u}^n.\mathbf{n})_{\Gamma_N} - \frac{K_d}{2}(w, \rho^n) + (w, K_p C_0) \end{aligned} \quad (10)$$

The weak form corresponding to equation 8 is obtained by integrating by parts to all the terms and we obtain:

$$\xi_0(\boldsymbol{\nabla}.\mathbf{w}, c^{*n+1}) + \eta(\boldsymbol{\nabla}\mathbf{w} : \boldsymbol{\nabla}\mathbf{u}^{n+1}) + 3\eta(\boldsymbol{\nabla}.\mathbf{w}, \boldsymbol{\nabla}.\mathbf{u}^{n+1}) - (\mathbf{w}, \mathbf{t})_{\Gamma_N} = (\mathbf{w}, \frac{\mu_s\ \mathbf{u}^n_{cell} - \mathbf{b}^{2D}(t)}{\lambda_0\ \rho^n}) \quad (11)$$

The weak form corresponding to equation 9 is:

$$\begin{aligned}(w, \frac{c^{n+1}}{\triangle\ t}) - (\boldsymbol{\nabla}w, \frac{c^{n+1}\ \mathbf{u}^{n+1}}{2}) + \frac{D}{2}(\boldsymbol{\nabla}w, \boldsymbol{\nabla}c^{n+1}) + \frac{1}{2}(w, (c^{n+1}\ \mathbf{u}^{n+1} - \boldsymbol{\nabla}c^{n+1}).\mathbf{n})_{\Gamma_N} \\ = (w, \frac{c^n}{\triangle\ t}) + (\boldsymbol{\nabla}w, \frac{c^n\ \mathbf{u}^n}{2}) - \frac{D}{2}(\boldsymbol{\nabla}w, \boldsymbol{\nabla}c^n) - \frac{1}{2}(w, (c^n\ \mathbf{u}^n - \boldsymbol{\nabla}c^n).\mathbf{n})_{\Gamma_N}\end{aligned} \quad (12)$$

In order to apply the zero total flux boundary conditions on the Neumann Boundary,we implement $\rho\mathbf{u}.\mathbf{n} = 0$ in equation 10 and $(c\ \mathbf{u} - \boldsymbol{\nabla}c).\mathbf{n} = 0$ in equation 12 on Γ_N.

Equation (10) can be written as :

$$\frac{\mathbf{M}}{\triangle\ t}\rho^{n+1} - \mathbf{G}(\rho^{n+1})\mathbf{u}^{n+1} + \frac{K_d}{2}\mathbf{M}\rho^{n+1} = \frac{\mathbf{M}}{\triangle\ t}\rho^n + \mathbf{G}(\rho^n)\mathbf{u}^n - \frac{K_d}{2}\mathbf{M}\rho^n + \mathbf{F} \quad (13)$$

The operators used in the equation 10 are:
$(w, \frac{\rho^{n+1}}{\triangle t}) = \frac{\mathbf{M}}{\triangle t}\rho^{n+1}$
$(\boldsymbol{\nabla}w, \frac{\rho^{n+1}\ \mathbf{u}^{n+1}}{2}) = \frac{\mathbf{G}(\rho^{n+1})}{2}\mathbf{u}^{n+1}$
$\frac{K_d}{2}(w, \rho^{n+1}) = \frac{K_d}{2}\mathbf{M}\rho^{n+1}$
$(w, K_pC_0) = \mathbf{F}$

Equation (11) can be written as :

$$\mathbf{S}(c^{n+1})\boldsymbol{c}^{n+1} + \mathbf{K}\mathbf{u}^{n+1} + \mathbf{T}\mathbf{u}^{n+1} = \mathbf{F_2}(\rho^n) \quad (14)$$

The operators used in the equation 11 are:
$\xi_0(\boldsymbol{\nabla}.\mathbf{w}, \frac{c^{*n+1}}{c^{n+1}}c^{n+1}) = \mathbf{S}c^{n+1}$
$\eta(\boldsymbol{\nabla}\mathbf{w} : \boldsymbol{\nabla}\mathbf{u}^{n+1}) = \mathbf{K}\mathbf{u}^{n+1}$
$3\eta(\boldsymbol{\nabla}.\mathbf{w}, \boldsymbol{\nabla}.\mathbf{u}^{n+1}) = \mathbf{T}\mathbf{u}^{n+1}$
$(\mathbf{w}, \frac{\mu_s\ \mathbf{u}^n_{cell} - \mathbf{b}^{2D}(t)}{\lambda_0\ \rho^n}) = \mathbf{F_2}(\rho^n)$
Equation (12) can be written as :

$$\frac{\mathbf{M}}{\triangle\ t}c^{n+1} - \mathbf{Q}(\mathbf{u}^{n+1})\ c^{n+1} + \frac{D}{2}\mathbf{P}c^{n+1} = \frac{\mathbf{M}}{\triangle\ t}c^n + \mathbf{Q}(\mathbf{u}^n).c^n - \frac{D}{2}\mathbf{P}c^n \quad (15)$$

The operators used in the equation 12 are:
$(w, \frac{c^{n+1}}{\triangle t}) = \frac{\mathbf{M}}{\triangle t}c^{n+1}$
$(\boldsymbol{\nabla}w, \boldsymbol{\nabla}c^{n+1}) = \mathbf{P}c^{n+1}$
$(\boldsymbol{\nabla}w, \frac{c^{n+1}\ \mathbf{u}^{n+1}}{2}) = Q(\mathbf{u}^{n+1}).c^{n+1}$

Global System of Equations: The system of equations to be solved at each time step using the Picard's method can be written as:

$$\begin{pmatrix} \frac{\mathbf{M}}{\triangle t} + \frac{K_d}{2}\mathbf{M} & -\frac{1}{2}\mathbf{G}({}^k\rho^{n+1}) & 0 \\ 0 & \mathbf{K} + 3\mathbf{T} & \mathbf{S}({}^kc^{n+1}) \\ 0 & 0 & \frac{\mathbf{M}}{\triangle t} - \mathbf{Q}({}^k\mathbf{u}^{n+1}) + \frac{D}{2}\mathbf{P} \end{pmatrix} \begin{pmatrix} {}^{k+1}\boldsymbol{\rho}^{n+1} \\ {}^{k+1}\boldsymbol{u}^{n+1} \\ {}^{k+1}\boldsymbol{c}^{n+1} \end{pmatrix} = \begin{pmatrix} \boldsymbol{F_1^n} \\ \boldsymbol{F_2^n} \\ \boldsymbol{F_3^n} \end{pmatrix}$$

Where, $\boldsymbol{F_1^n} = \frac{\mathbf{M}}{\triangle t}\rho^n + \mathbf{G}(\rho^n)\mathbf{u}^n - \frac{K_d}{2}\mathbf{M}\rho^n + \mathbf{F}$, $\mathbf{F_2}(\rho^n) = (\mathbf{w}, \frac{\mu_s\ \mathbf{u}^n_{cell} - \mathbf{b}^{2D}(t)}{\lambda_0\ \rho^n})$

$\boldsymbol{F_3^n} = \frac{\mathbf{M}}{\triangle t}c^n + \frac{1}{2}\mathbf{Q}(\mathbf{u}^n)c^n - \frac{D}{2}\mathbf{P}c^n$

The boundary conditions are implemented using the Lagrange multiplier method to the above system of equations. The given essential boundary conditions must be imposed, i.e.,$\mathbf{u} = \mathbf{u}_d$ *on* Γ_D. We need to solve $\mathbf{Au} = \mathbf{f}$ restricted to $\mathbf{A}_d\mathbf{u}_d = \mathbf{b}_d$,which arises due to the given essential boundary conditions. After solving this constrained optimisation problem implementing the Lagrange multiplier method, the actual system of equations needed to be solved becomes: $\begin{bmatrix} \mathbf{A} & \mathbf{A}_d^T \\ \mathbf{A}_d & \mathbf{0} \end{bmatrix} \begin{bmatrix} \mathbf{u} \\ \lambda \end{bmatrix} = \begin{bmatrix} \mathbf{f} \\ \mathbf{b}_d \end{bmatrix} \Rightarrow$ $\mathbb{AU} = \mathbb{F}$. Where λ is the Lagrange multiplier which is also to be determined along with other unknown variables.

Picard's Iteration method:At each time step ,the solution of the above system of equations are determined using the Picard's method. It is simple to implement though it's convergence is slower in-comparison to the Newton-Raphson's method. Only the function values are evaluated in this method. The algorithm of this method has been delineated below. For any $(n+1)$ th time step,the problem to be solved is: $\mathbb{A}(\rho^{n+1}, c^{n+1}, \mathbf{u}^{n+1})\mathbb{U}^{n+1} = \mathbb{F}^n$

- Initialise: For $k = 0$; ${}^k\rho^{n+1}, {}^k c^{n+1}, {}^k \mathbf{u}^{n+1} = \rho^n, c^n, \mathbf{u}^n$ respectively and initialise ${}^k\mathbb{U}^{n+1} = \mathbb{U}^n$, and Choose a suitable tolerance, tol
- Evaluate the residual: $\mathbb{F}^* = \mathbb{F}^n - \mathbb{A}({}^k\rho^{n+1}, {}^k c^{n+1}, {}^k \mathbf{u}^{n+1})\ {}^k\mathbb{U}^{n+1}$
- ${}^{k+1}\Delta\mathbb{U}^{n+1} = \mathbb{A}({}^k\rho^{n+1}, {}^k c^{n+1}, {}^k \mathbf{u}^{n+1})^{-1}\ \mathbb{F}^*$
- ${}^{k+1}\mathbb{U}^{n+1} = {}^{k+1}\Delta\mathbb{U}^{n+1} + {}^k\mathbb{U}^{n+1}$
- **Convergence**:Check if $max|\mathbb{F}^*| \leq tol\ and\ max|{}^{k+1}\Delta\mathbb{U}^{n+1}| \leq tol * max|{}^{k+1}\mathbb{U}^{n+1}|$,else, $k = k+1$ and repeat step 2
- $\mathbb{U}^{n+1} = {}^{k+1}\mathbb{U}^{n+1}$

5 Results and Discussions:

The above system of equations with the implemented appropriate boundary conditions are solved in the desired computational domain. At the beginning, we investigate how the initial gradient of the polarity marker,c$(\mathbf{x}, t = 0)$ affects the cell velocity. We have considered three different initial gradient of the polarity markers in such a manner that the total mass of c is same for all the three cases: (a) $c(\mathbf{x}, t = 0) = 30, (b)\ c(\mathbf{x}, t = 0) = 35 - 10y, and\ (c)\ c(\mathbf{x}, t = 0) = 40 - 20y$. The results for these three cases have been depicted in the Figure 3. For this observation a suitable value for the diffusion coefficient, D=0.0001 $\mu m^2/s$ has been considered. The equations are solved for a time period of 30 seconds. We observe higher cell velocity corresponding to the third case(Case-c), where the initial gradient in c was higher. In the first case (Case-a), where there was no gradient in c, we observe zero cell velocity. It means in this case the actin flow is not induced. So, higher initial gradient of polarity cue induces faster actin flow.

To study the effect of the diffusion coefficient,D on the cell velocity, we consider three cases corresponding to the three different considered D values:(a)D=0.00185,(b)D=0.0001, and (c)0.01 $\mu m^2/s$ respectively. It is observed that in the first case (Case-a), the initial gradient of the polarity marker is maintained with time due to the combined effect of advection of polarity cues with the actin flow and due to the diffusion of the polarity cues. As a result we observe a constant cell velocity over time (Figure 4(a)). In the second case, we consider a very low value for the diffusion coefficient,D. So, in this case the advection dominates over the diffusion. Due to the presence of the initial gradient in the concentration of the polarity cues, the actin flow in the cell is induced towards the direction having the higher concentration of the polarity cues. Due to this actin flow(only advection), the gradient of the polarity cues further increases in the initial direction, which induces faster actin flow. It can be observed from Figure 4(b). In the third case, we consider a very high value for the diffusion coefficient,D, where the effect of the diffusion is also prominent. Due to the high diffusion rate, over time, the gradient of the polarity marker gradually decreases, which reduces the cell velocity(Figure 4(c)).

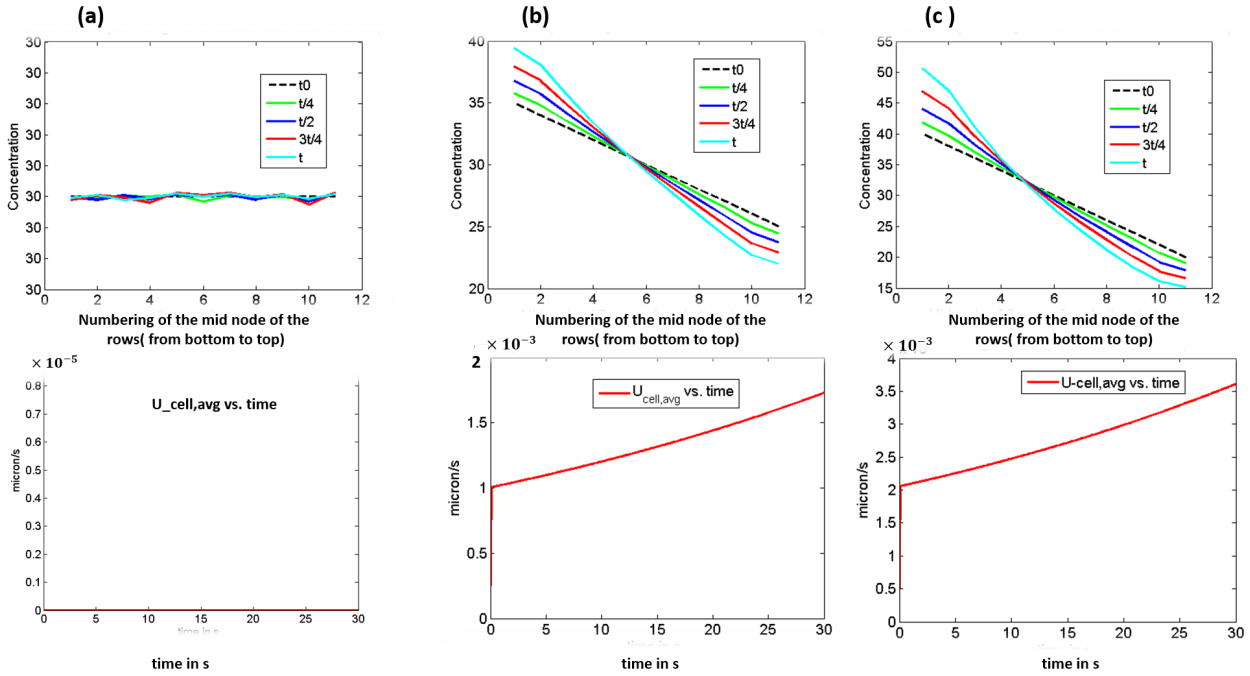


Figure 3: Comparison of the cell velocity at different initial gradient of Polarity marker,c: (a)$c(\mathbf{x}, t = 0) = 30, (b)c(\mathbf{x}, t = 0) = 35 - 10y, and\ (c)c(\mathbf{x}, t = 0) = 40 - 20y$

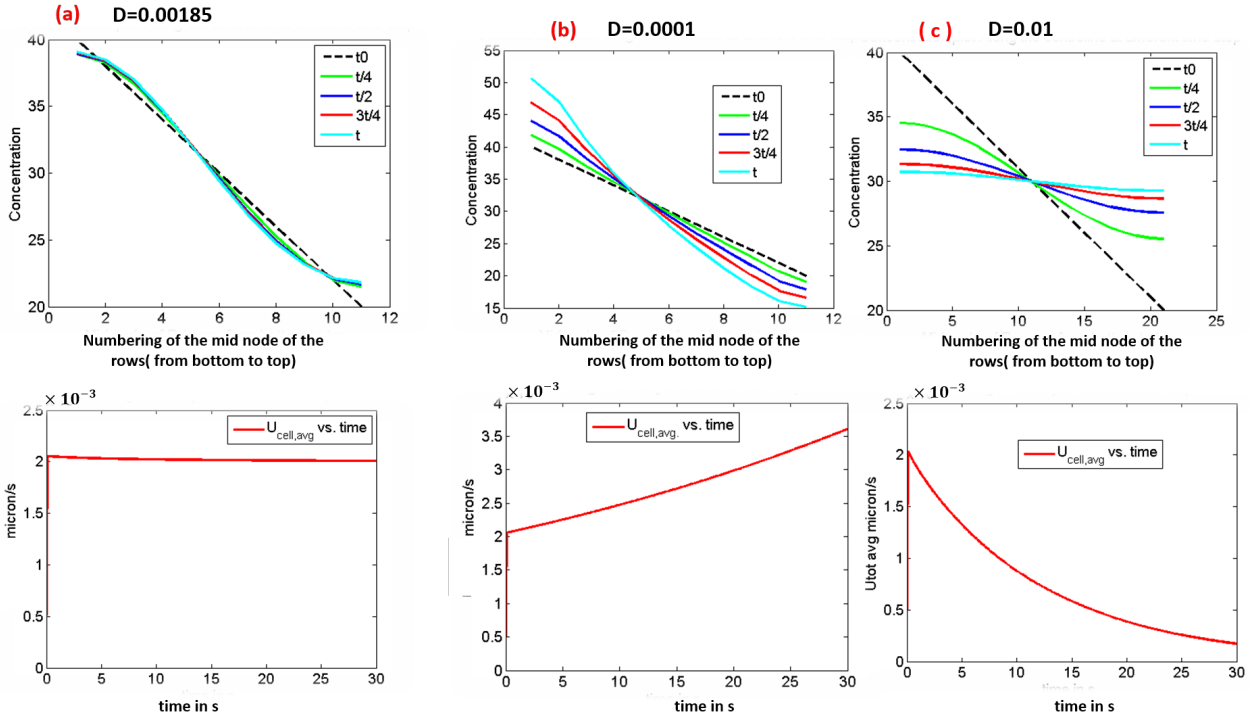


Figure 4: Comparison of the cell velocity at different D values

To understand the distribution of the actin density , the concentration profile of the polarity marker and the actin flow velocity in the whole computational domain further depth, we study one particular case in details. We consider the case, where the initial gradient of the c is considered as $c(\mathbf{x}, t = 0) = 40 - 20y$. A diffusion coefficient value, D=0.0001 $\mu m^2/s$ is considered, such that, the convection is dominant over the diffusion. Here, we consider zero external applied force. The equations are solved for a time period of 30 seconds with the mentioned values of the other parameters in the previous section. For the concentration of the polarity marker,c, the total mass is considered as conserved in the whole domain, which means the total flux due to combined both the convection and diffusion is zero at all the boundaries of the domain. A small time step value is considered in order to keep the Courant's number low. A mesh of 10*10 elements is considered. The value of the other considered parameters have been mentioned under the section of Parameters. For this case, the obtained profile for the density of the actin filaments(ρ), relative velocity of the actin flow from the reference of the cell($\mathbf{u}$), and the concentration of the polarity marker(c) have been presented in the figures below. Initially, due to the presence of the applied initial gradient in the concentration of the polarity markers(c), the actin flow is induced. As the applied initial values for c are higher at the bottom boundary (the concentration gradually increase from top to the bottom with a constant gradient initially), the actin flow takes place towards the bottom which can be observed in the Figure 5. Depending upon the chosen drag and friction coefficients, the direction of the cell velocity is determined. As the considered friction coefficient exceeds than the considered drag coefficient, the velocity of the cell is observed towards the top(Positive Y) direction in this case. With time, ρ gets advected in the whole domain due to the actin flow, which results in the reduction of the initial gradient of the density. Also the polymerisation and de-polymerisation of the actin filament takes place in the whole domain. On the other hand, due to the advection dominant flow, the gradient in the concentration of the polarity marker also increases over time inducing faster actin flow. More c gets accumulated at the bottom. The concentration of the polarity cue gets reduced at the top keeping the total mass of c is conserved. It increases the cell velocity further with time. It can be observed from the Figure 7(c). The profiles of the $\rho, \mathbf{u}$, and c have been plotted at the final time step. ξ_0 affects the magnitude of the actin flow velocity. But at a very high ξ_0 value, the actin flow becomes very fast, which makes the solutions unstable. So, a suitable value of the ξ_0 has been considered for the simulation.

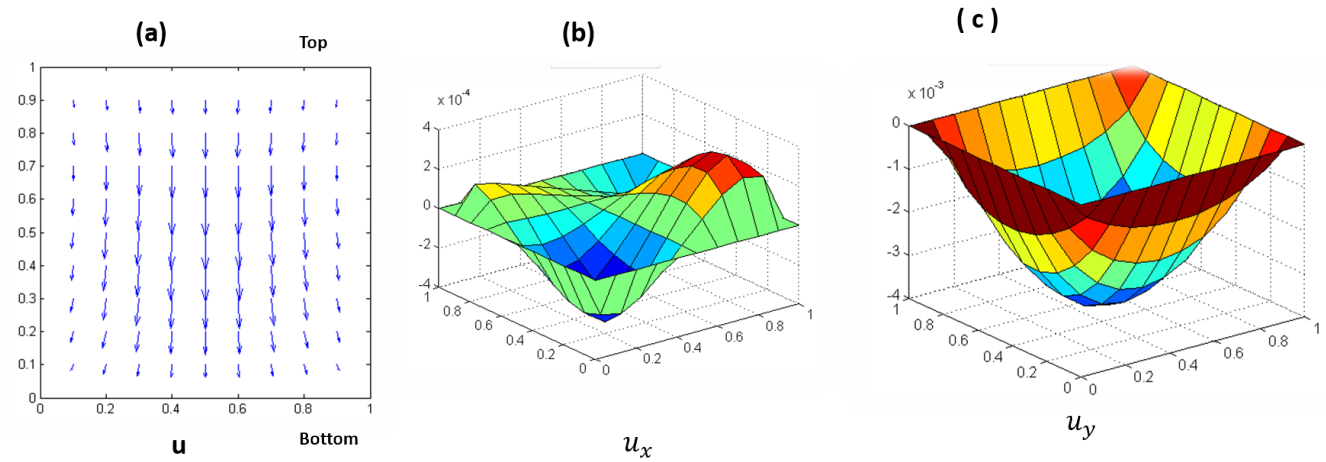


Figure 5: Velocity profile of the Actin flow from the cell reference

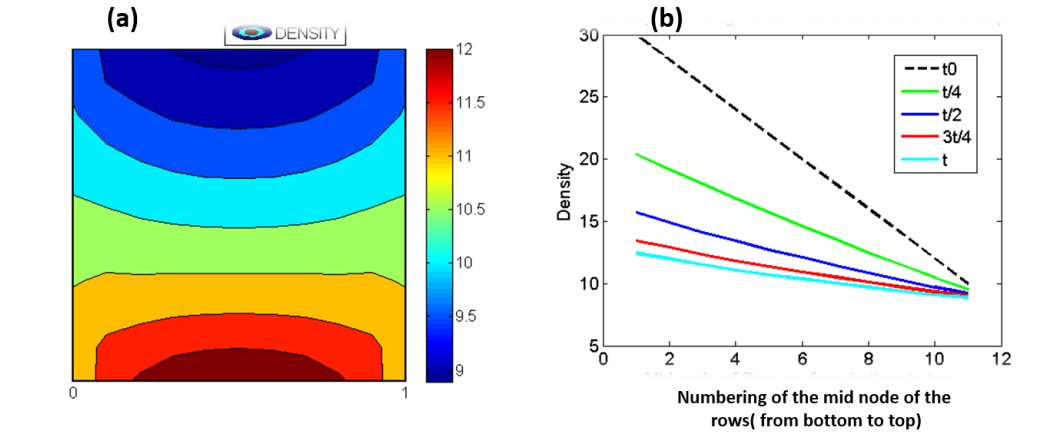


Figure 6: (a)Contour of the actin density (b)Density along the vertical mid row at different time

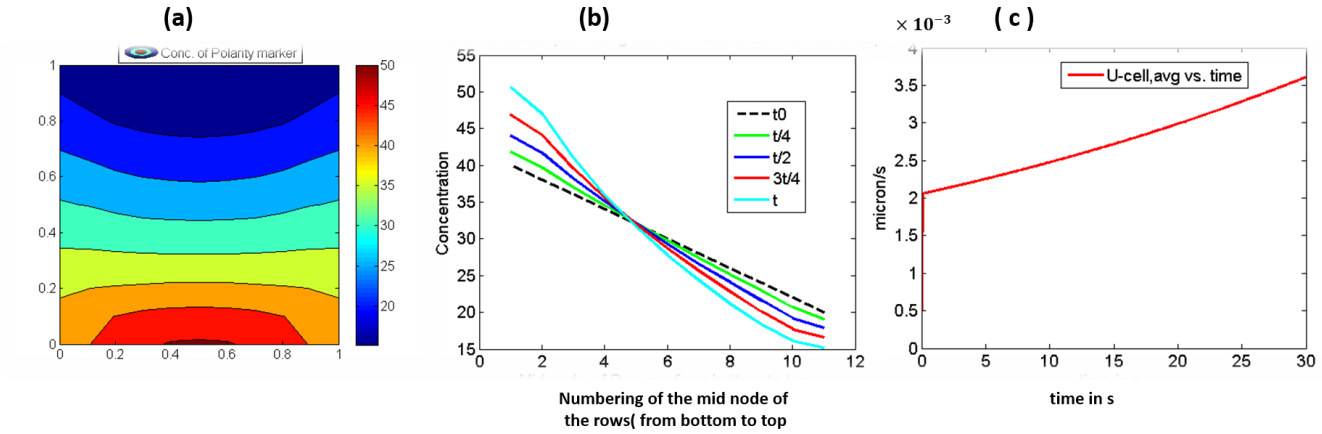


Figure 7: (a)Contour of the Concentration(b) Concentration along the vertical mid row at different time (c) Cell velocity

Effect of an external force($\mathbf{b}(t) \neq 0$):When cells are under the influence of any mechanical environment or any surrounding medium, they experience certain amount of external force. If the cells are part of an tissue, they are surrounded by other different cells, which exert certain amount of force externally on the cell. So, under this case, the influence of an externally applied continuous and time varying force on the motion of the cell has been studied. For the considered case,from 0 to 15 seconds no external forces are applied. In this period of time the flow is induced only due to the presence of the gradient of the concentration of the polarity marker which is similar to the previously discussed cases. The cell velocity magnitude in this regime depends on the value of the diffusion coefficient and on initial gradients in c. We consider the case, where the convection dominates the diffusion. The value value of the diffusion coefficient, D is considered as 0.0001 $\mu m^2/s$. The initial gradient of the c is considered as $c(\mathbf{x}, t = 0) = 40 - 20y$. From 15 to 20 seconds, a constantly decreasing external force is applied only in the negative Y direction. It can be observed that it influences the cell velocity and it starts decreasing due to the application of the external force, following which it becomes zero,and after that it increases in the opposite direction. The relative velocity of the actin flow becomes upward gradually with time as we consider that the friction coefficient exceeds the drag coefficient. After 20 seconds, a constant force is applied in the negative Y direction. Due to the application of this constant force, the cell velocity increases but in the negative Y direction. In these cases flow is induced due to both the presence of the gradient in the gradient in c (in the opposite direction), and due to the effect of the applied external force. But the later dominates the former. Depending upon the chosen drag and friction coefficients the direction of the average cell velocity is determined. These effects can be observed from the figures 8 and 9.

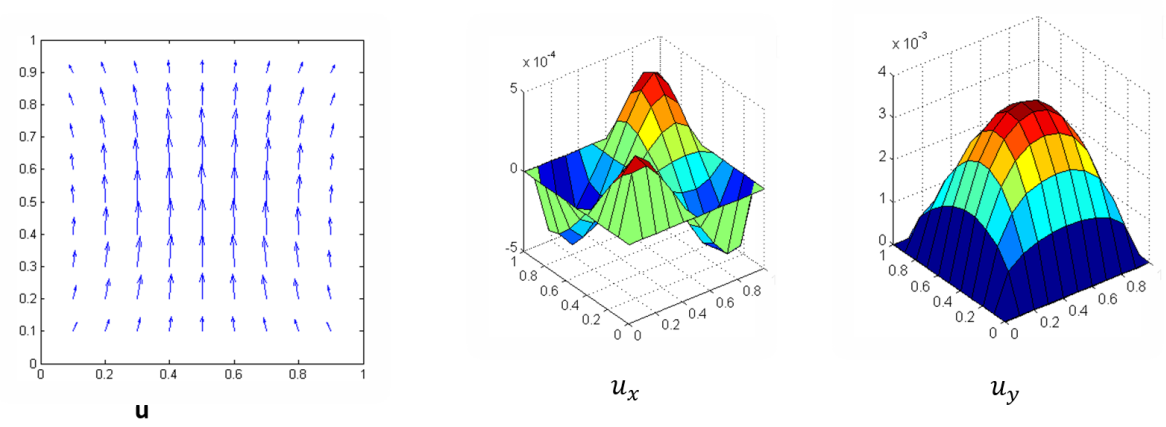


Figure 8: Velocity profile of the Actin flow from cell reference

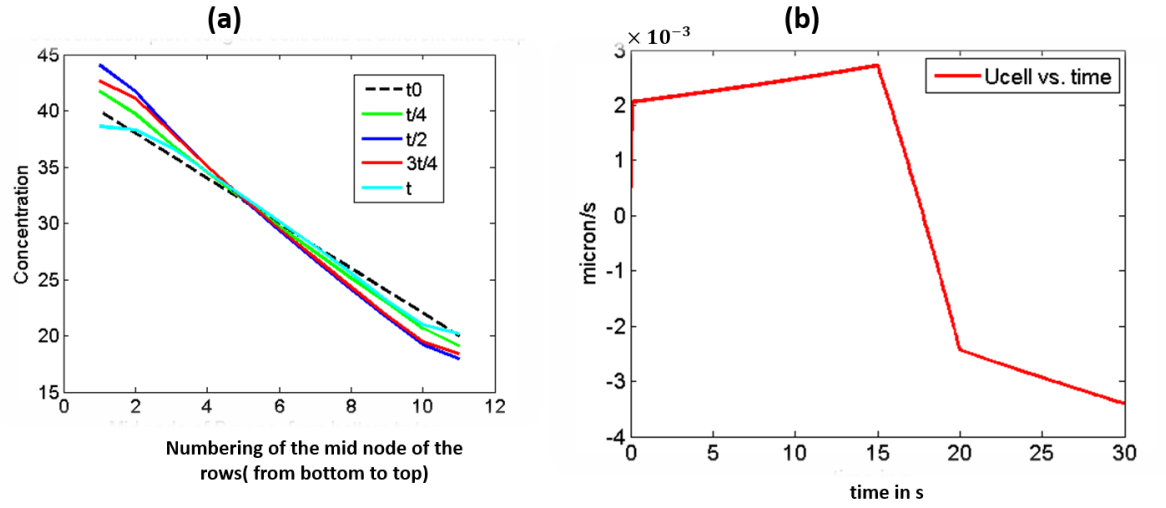


Figure 9: (a)Concentration along the vertical mid row at different time (b) Cell velocity ,$\mathbf{u}_{cell,y}$

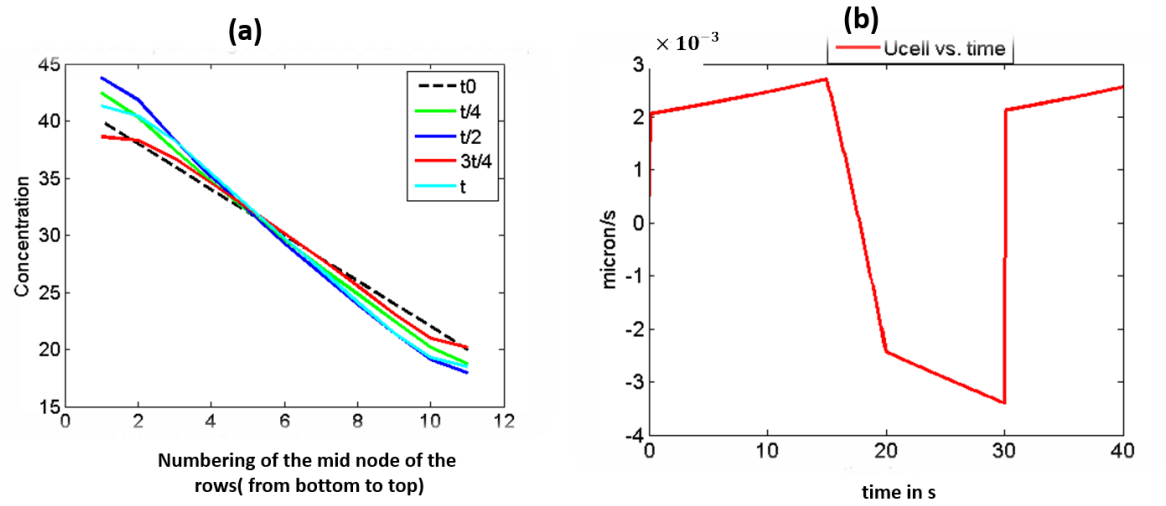


Figure 10: The case in which the applied force is removed after 30s:(a)Concentration along the vertical mid row at different time (b) Cell velocity ,$\mathbf{u}_{cell,y}$

When the applied external force is removed after 30s, then the magnitude of the cell velocity decreases suddenly. The flow is then only induced due to the present gradient in the concentration of the polarity cue. The cell velocity gradually changes its direction from the negative Y direction to the positive Y direction. The direction of the actin flow profile also changes towards the bottom of the cell like it was previously. Now the case becomes like the initial case, where the advection dominates the diffusion. The gradient in the concentration of the polarity marker again increases over time inducing faster actin flow like we discussed in the earlier section. More c gets accumulated at the bottom. The concentration of the polarity cue gets reduced at the top. It can be observed in the Figure 10.

6 Conclusion:

A simple numerical model to describe motility initiation in crawling cells was formulated and an implicit numerical scheme was presented to solve the modelled coupled non-linear system of equations representing in-plane cell migration on a substrate. Due to the presence of the initial gradient in the concentration of the polarity cues, the actin flow in the cell is induced towards the direction having the higher concentration of the polarity cues. It was investigated that the higher initial gradient of polarity cues induces faster actin flow. The advection of the polarity cues by a dynamic actin cytoskeleton undergoing flows at the cellular scale was studied. The effect of the diffusion coefficient of the polarity marker on the cell velocity was observed. Due to this actin flow(advection dominated), the gradient of the polarity cues further increases in the initial direction, which further induces faster actin flow with time, which in turn increases the cell velocity. Actin flow always takes place towards the region having the higher concentration of the polarity markers in the absence of any externally applied forces. The actin flows are affected by perturbing a crawling cell with an external force. The externally applied forces on the cell influence both the direction and magnitude of the cell velocity.

References

[1] A. C. Callan-Jones and R. Voituriez. Actin flows in cell migration: from locomotion and polarity to trajectories. *Current opinion in cell biology*, 38:12–17, 2016.

[2] P. Maiuri, J.-F. Rupprecht, S. Wieser, V. Ruprecht, O. Bénichou, N. Carpi, M. Coppey, S. De Beco, N. Gov, C.-P. Heisenberg, et al. Actin flows mediate a universal coupling between cell speed and cell persistence. *Cell*, 161(2):374–386, 2015.