Model of Polarization and Bistability of Cell Fragments

Summary of the Model in the Article by Michael M. Kozlov and Alex Mogilner

Don Ciglenečki, Tereza Šestáková, Ana Maria Žinić and Maryam Rahimi

The presented model is based on observations of fragments of epithelial fish keratocyte cells (for simplification called cells in the following). This is probably the simplest system exhibiting polarization and directional crawling.

The model describes the two possible states of these cells, the nonpolarized/circular shape and the polarized/crescent shape. It brings a possible explanation, why are these two states stable.

It deals exclusively with the stability of the two states and transition between them; the authors state that they can even assume that the cell center is not moving relative to the substrate, as they are interested only in the time of transition.

The cell structure is very simplified. The forces and energy loads caused by actin-network growth, myosin contraction and the membrane tension are evaluated, but it is assumed that they are very gradually distributed, to extent that the graded radial extension model, mentioned in the other article, couldn't work here.

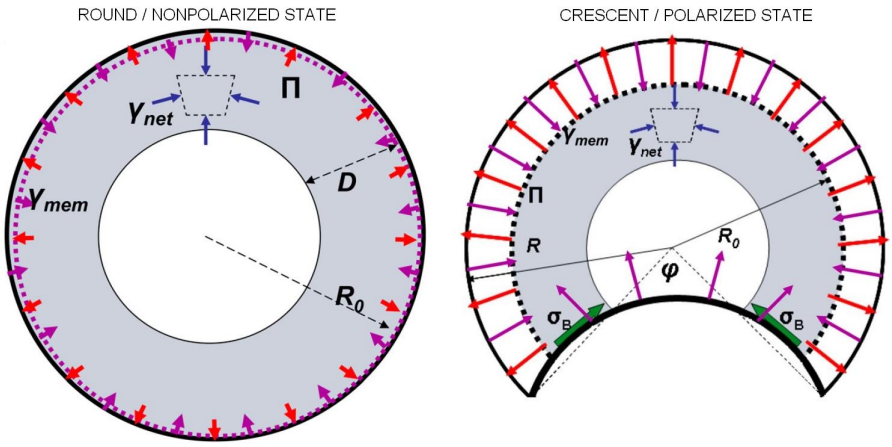
The quantities are being compared by the methods of thermodynamics. Thermodynamic analysis does not deal with exact physical mechanisms; it rather deals with amounts of energy. Moreover, it doesn't predict actual movements or the rate at which energy is transferred to work; it just predicts tendencies. As long a transition is associated with a decrease in free energy, this transition will proceed spontaneously. This makes possible a simple and clear model, but excludes many processes, that could influence the result. However, for the very simple structure of fish keratocyte fragments, this influences are of manageable size.

1 Physical model of the cell (or cellfragment)

The cell fragments are flat enough to consider them as two-dimensional objects (they are about $10\mu m$ long and 0.1 to $0.2\mu m$ thick).

The area of this 2D-object remains constant in the course of the cell polarization (only the shape changes). This is based on biological observations.

In our model of the cell (or cell fragment!), almost all cell components are missing, especially those, which would allow signaling between different parts of the cell. The cell consists only of membrane and different structures of myosin and actin gradients (including lamelipodium) as presented in the following on example of a cell in nonpolarized state:



1.1 Nonpolarized Round State

- The fragment is a disc of radius R_0 with area $A = \pi R_0^2$
- It is surrounded by the cell membrane (bold black line), which is unstretchable and uncompressible and is pulled tight around it.
- Tightly on the inner side of the membrane is the lamellipodium (dashed line)
- On the inner side of the membrane, there is the ring of actin-myosin network of width D (gray), where actin and myosin are distributed uniformly. For simplicity it is assumed that $D = \frac{R_0}{2}$

The three major cell structures - actin, myosin and membrane - are the sources of the three principal forces:

1. The pushing force of the growing actin filaments; designated by red arrows. This force can be quantified by the 2D pressure Π applied to the membrane and equal to the normal force per unit length of the circumference or by the total normal force f given by the integral of the pressure over the fragment perimeter, $f = \oint \Pi dL$.
2. The membrane tension γ_{mem}, designated by purple arrows.
3. The myosin contractile stress. In the actin-myosin network it is designated by γ_{net} and assumed constant.

1.2 Polarized Crescent-like State

If some mechanical load strong enough deforms one side of the circular cell (referred to as the rear side), then the folowing events take place within a few seconds:

1. The actin network at the rear collapses and forms a bundle. The exact mechanism of the bundle formation is beyond the scope of the model; the authors are interested only in contribution to the cell energy. The actin and myosin on the bundle rearrange and consolidate the bundle, which is contractile, as " the actin filaments are not cross - linked ".
2. All myosin molecules, that were distributed evenly throughout the lamellipodial network around the bundle, collapse to the bundle which makes it more contractile

3. As membrane tension is relieved, the actin can grow away of the actin-myosin bundle (gray), till the membrane is streched again. As the myosin redistribution is much slower than the actin growth, it is assumed, that the newly formed area (white) stays myosin-free and contains only actin.

With these events the forces/tensions in the cell fragment are redistributed such that:

1. As the majority of actin is now in the front of the cell, the total normal actin force acting on the front is now equal to the total normal actin force f from before.

2. We assume that all myosin molecules from the section of the actin-myosin ring (gray) above the emerging rear edge condense into the actin-myosin bundle, the number of myosin molecules per unit length of the bundle equals the density of myosin in the actin-myosin ring integrated from the outer to the inner radii of the ring. This leads us to the assumption that the line tension (force) in the rear bundle σ_B equals the contractile stress in the actin-myosin ring γ_{net} multiplied by the width of the ring $\frac{R_0}{2}$, i.e.:

$$\sigma_B = \frac{\gamma_{net} R_0}{2} \quad or \quad \gamma_{net} = \frac{2\sigma_B}{R_0}$$

2 Calculation of the free energy

The thermodynamic free energy is defined as the amount of work that a thermodynamic system can perform. All calculations in the article are dealing with the influences of the actin polymerization, the contraction of the actin-myosin network and the contractile line tension to the amount of the free energy. Both actin polymerization and myosin contraction spend energy of the system and therefore cause the decrease of values.

Energy change of the polymerizing actin system	$dF_{Polym} = -\Pi \cdot L_{front} dR = -f \cdot dR$	actin normal force (f) · the change of the diameter (dR)
Energy change of the actin-myosin system	$dG_{net} = \gamma_{net} \cdot dA_{net}$	contractile stress · change of the area containing myosin dA_{net}
Work of the contractile line tension σ_B generated by the actin-myosin bundle	$dF_B = \sigma_B \cdot dL_B$	line tension multiplied by the length of the contraction

Altogether:

$$\begin{aligned} F_{tot} &= -f \cdot R + \gamma_{net} \cdot A_{net} + \sigma_B \cdot L_B + F_0 \\ &= -f \cdot R + \sigma_b \cdot (L_b + 2A_{net}/R_0) + F_0, \end{aligned} \tag{1}$$

where F_0 is part of free energy independent of R, A_{net} and L_B.

2.1 Energy equation, dependent of the angle

On the front edge

It is assumed, that in the state of the mechanical equilibrium, the membrane tension γ_{mem} equals the 2D-pressure Π, generated by the pushing actin filaments. (In the article some other contributing details are mentioned, but are assessed to be small enough to be neglected), i.e. $\gamma_{mem} = \Pi$.

Now, we designate the length of the front part of the cell by L_{front}. It follows $\Pi \cdot L_{front} = f$ and $L_{front} = (2\pi - \varphi) \cdot R$. We obtain:

$$\gamma_{mem} = \frac{f}{(2\pi - \varphi) \cdot R}$$

On the rear edge

For the actin-myosin bundle on the rear part, we can derive analogously:

$$\gamma_{mem} = \frac{\sigma_B}{\rho},$$

while ρ is the radius of the actin-myosin bundle (see sketch). Using these two equations together with the assumption of area conservation and geometric properties, one can eliminate L_B and A_{net} from the equation (1) and get the following formula:

$$F_{tot} = f \cdot R \cdot \left[-\left(1 - \frac{R_0}{R}\right) - \frac{\sigma_B}{f} \cdot \frac{3R_0}{4R} \cdot \varphi + \left(\frac{\sigma_B}{f}\right)^2 \cdot (2\pi - \varphi) \cdot \psi \right], \tag{2}$$

where

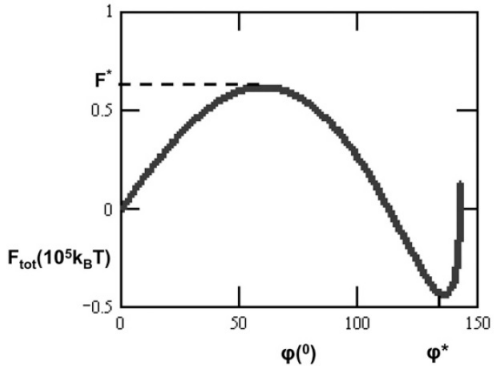
$$\psi = 2 \cdot \arcsin\left(\frac{f}{\sigma_B} \frac{\sin\left(\frac{\varphi}{2}\right)}{2\pi - \varphi} \right)$$

and

$$R = R_0 \frac{1}{\sqrt{1 - \frac{1}{2\pi}(\varphi - \sin\varphi) - \frac{1}{2\pi}\left(\frac{\sigma_B}{f}\right)^2 (2\pi - \varphi)^2 (\psi - \sin\psi)}}$$

The equation 2 determines the system free energy as a function of the degree of the cell polarization described by the polarization angle φ.

The first and the second term on the right hand side describe, respectively, the negative contributions of the actin pushing and network contractile forces to the fragment's free energy. The authors showed by asymptotic analysis, that the contribution of actin polymerization to F_{tot} is proportional to φ^3 and for $\varphi \ll 1$ negligible in comparison to both myosin contributions, which are proportional to φ. On the same time, the effect of the expanding rear contractile bundle turns out to be stronger than that of the shrinking actin-myosin network and as a result, the total free energy increases with the angle. On some state after $\varphi > 1$ the energy start decreasing till it reaches minimum, at the angle denoted by $\varphi*$. We get the following graph:



The curve has two minima; one at $\varphi = 0$ (the nonpolarized state), the other at $\varphi = \varphi*$. According to thermodynamics, the systems tend to the lower energy; therefore both states are stable and resume after small changes. To reach one state from the other, a push of force is necessary, which exceeds the energy barrier $F*$. On can show, that $F*$ depends solely to $\frac{\sigma_B}{f}$, i.e. to the proportion between the contractile line tension of actin-myosin bundle and the total actin normal force.