

Modelling Cortical Force Balance (2D)

August 15, 2018

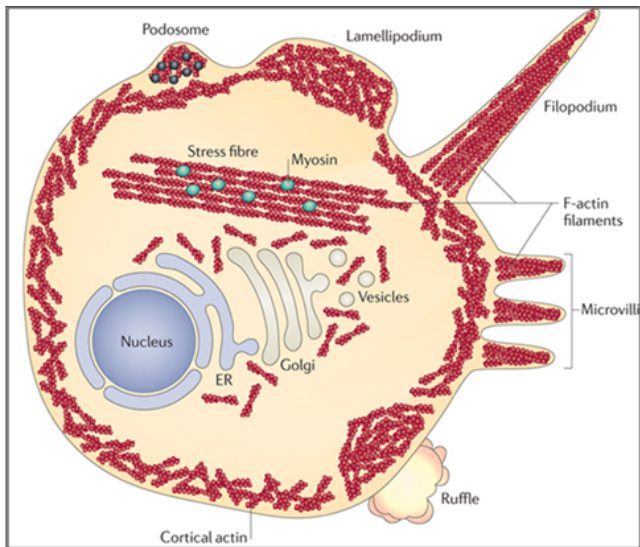
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Introduction

- Animal cell shape is controlled primarily by the cell cortex, a thin network of actin filaments, myosin motors, and actin-binding proteins that lies directly beneath the plasma membrane.
- Local changes in cortex mechanical properties, particularly in cortical tension, drive cellular deformations, such as those occurring during mitotic cell rounding, cytokinesis, migration and tissue morphogenesis.
- Thus, understanding cortical tension regulation is essential for understanding how cells change shape.

Actin Architecture



Modelling the Membrane

The membrane is made up of points $\bar{X}_i = x_i \hat{i} + y_i \hat{j}$, where 'i' goes from 1 to 'n'. Let 'Em' be the total energy of the membrane. Since we are working in 2D, this energy has to be per some characteristic length dz . This energy has three components.

1. Bending Component:

$$\begin{aligned}\frac{E_{m1}}{dz} &= -A \sum_{i=2}^{n-1} (\bar{X}_i - \bar{X}_{i-1}) \cdot (\bar{X}_{i+1} - \bar{X}_i) \\ &= -A \sum_{i=2}^{n-1} ((x_i - x_{i-1})(x_{i+1} - x_i) \\ &\quad + (y_i - y_{i-1})(y_{i+1} - y_i))\end{aligned}$$

2. Pressure Component:

$$\frac{Em_2}{dz} = -p \text{ (area under the membrane)}$$

$$\frac{Em_2}{dz} = -p \sum_{i=1}^{n-1} (y_i + y_{i+1})(x_{i+1} - x_i)$$

{using Trapezoidal Rule}

3. Tension Component:

$$\begin{aligned} \frac{Em_3}{dz} &= \frac{1}{2}k \sum_{i=2}^n ((\bar{X}_i - \bar{X}_{i-1}) - a)^2 \\ &= \frac{1}{2}k \sum_{i=2}^n (\sqrt{(x_i - x_{i-1})^2 + (y_i - y_{i-1})^2} - a)^2 \end{aligned}$$

Here, 'a' is the distance between two membrane points if all the membrane points were equidistant.

Total energy is given by $\frac{Em}{dz} = \frac{Em_1 + Em_2 + Em_3}{dz}$.

The membrane points are the variables. Their solutions are given by the differential equations:

$$\gamma \frac{d\bar{X}_i}{dt} = -\frac{1}{dz} \frac{\partial Em}{\partial \bar{X}_i} \implies \gamma \frac{dx_i}{dt} = -\frac{1}{dz} \frac{\partial Em}{\partial x_i},$$
$$\gamma \frac{dy_i}{dt} = -\frac{1}{dz} \frac{\partial Em}{\partial y_i}$$

γ is a constant. 'dz' can be assumed to be unity for now. These differential equations are solved numerically in MATLAB, using Fourth Order Runge Kutta Method. Thus, $x_i(t)$ and $y_i(t)$ give the membrane behaviour over a period of time.

Radius of Curvature

By Young-Laplace Equation, we must have $p = T/R$. We can calculate the radius of curvature of the membrane from the plot, and from the above formula, and see whether they match.

- 1 Radius of curvature from the plot: MATLAB has a function to find the radius of curvature of a series of points.
- 2 Radius of curvature from Young-Laplace Equation:

$$r = \frac{k}{p} \sum_{i=1}^{n-1} (\sqrt{(x_i - x_{i-1})^2 + (y_i - y_{i-1})^2} - a)$$

Addition of Actin Filaments

A fourth term of energy can be added to the total energy of the membrane. This is due to the interaction between the actin filaments and the membrane at the points where they are attached. Suppose there are 'm' filaments. If 'j'th filament is between the membrane points 'i' and 'i+1', then

$$\frac{Em_4}{dz} = \frac{1}{2}k_{fil} \sum_{j=1}^m \left(\left(\bar{r}_j + \frac{L}{2}\hat{e}(\theta_j) - (\alpha x_i + (1-\alpha)x_{i+1}) \right) \cdot \hat{n} \right)^2$$

where r_j is the centre of mass of the 'j'th filament, θ_j is the angle the 'j'th filament makes with the vertical (so $\theta_j \in [-\frac{\pi}{2}, \frac{\pi}{2}]$), L is the length of the actin filaments, α is the ratio of distance between the point where actin filament is attached to the membrane and the next membrane point, to the distance between the two membrane points between which the actin filament is attached.

$$\alpha = \frac{(\text{Next membrane point}) - (\text{Actin head})}{(\text{Next membrane point}) - (\text{Previous membrane point})}$$

Total energy now is $\frac{E_m}{dz} = \frac{E_{m1} + E_{m2} + E_{m3} + E_{m4}}{dz}$.

Membrane points are again given by:

$$\gamma_1 \frac{d\bar{X}_i}{dt} = -\frac{1}{dz} \frac{\partial E_m}{\partial \bar{X}_i} \implies \gamma_1 \frac{dx_i}{dt} = -\frac{1}{dz} \frac{\partial E_m}{\partial x_i},$$

$$\gamma_1 \frac{dy_i}{dt} = -\frac{1}{dz} \frac{\partial E_m}{\partial y_i}$$

The actin COM points are given by

$$\gamma_2 \frac{d\bar{r}_j}{dt} = -\frac{1}{dz} \frac{\partial E_m}{\partial \bar{r}_j} \implies \gamma_2 \frac{dx_{comj}}{dt} = -\frac{1}{dz} \frac{\partial E_m}{\partial x_{comj}},$$
$$\gamma_2 \frac{dy_{comj}}{dt} = -\frac{1}{dz} \frac{\partial E_m}{\partial y_{comj}}$$

The angles of the actin filaments are given by

$$\gamma_3 \frac{d\theta_j}{dt} = -\frac{1}{dz} \frac{\partial E_m}{\partial \theta_j}$$

$\gamma_1, \gamma_2, \gamma_3$ are constants.

After solving these differential equations, we have $x_i(t)$, $y_i(t)$, $x_{comj}(t)$, $y_{comj}(t)$, $\theta_j(t)$. The actin filament head and the actin filament tail are obtained by:

$$x_{actin_head} = x_{com} - \frac{L}{2} \sin(\theta)$$

$$y_{actin_head} = y_{com} + \frac{L}{2} \cos(\theta)$$

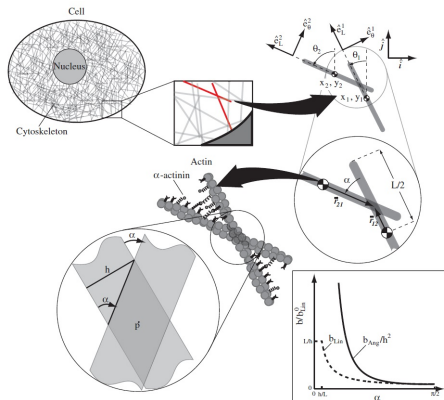
$$x_{actin_tail} = x_{com} + \frac{L}{2} \sin(\theta)$$

$$y_{actin_tail} = y_{com} - \frac{L}{2} \cos(\theta)$$

Using these equations, the membrane as well as the actin filaments can be plotted. The actin filaments are assumed to be attached to the membrane. Thus the actin_head points are considered to be a part of the membrane.

The simulations are run for 1s, 2s, 5s, 10s. Depending on the values of 'A', 'p', 'k', ' k_{fil} ', number of membrane points, number of filaments, length of the filaments, different stages of the membrane can be seen in the steady state.

Friction Between Filaments



Whenever two filaments intersect each other, there is friction between them. We now introduce this friction term into the simulation.

With respect to the shown figure, let $\bar{\mathbf{F}}_{ij}$ be the force on filament i due to the relative sliding of filament j .

Figure: Taken from Ref. 1.

$$\begin{aligned}
\mathbf{F}_{ij} &= b_{\text{Lin}}(\dot{\mathbf{x}}_j + r_{ji}\dot{\mathbf{e}}_L^j - \dot{\mathbf{x}}_i - r_{ij}\dot{\mathbf{e}}_L^i) \\
&= b_{\text{Lin}}(\dot{\mathbf{x}}_j - \dot{\theta}_j r_{ji} \mathbf{e}_\theta^j - \dot{\mathbf{x}}_i + \dot{\theta}_i r_{ij} \mathbf{e}_\theta^i) \\
&= -\mathbf{F}_{ji}
\end{aligned}$$

Here, \mathbf{x}_i is the COM point of the 'i'th filament, r_{ji} is the distance between the COM point of the 'j'th filament to the intersection point.

b_{Lin} is defined as the linear drag coefficient arising from two filaments sliding past one another.

$$b_{\text{Lin}} = \begin{cases} \frac{\rho h^2 b}{\sin(\alpha)} & : \alpha > \frac{h}{L - (r_{12} + r_{21})} \\ \rho h b (L - r_{12} - r_{21}) & : \alpha < \frac{h}{L - (r_{12} + r_{21})} \end{cases}$$

where ρ is density of actin-binding proteins, h is the width of the filaments, b is the viscous drag constant, α is the relative angle between two intersecting filaments, L is the length of the filaments, and r_{12} and r_{21} can be seen in the figure.

The relative sliding also causes a torque to act on the filament. Let \mathbf{T}_{ij} be the torque about the COM of filament 'i' generated by the relative sliding of the filament 'j'. Then

$$\mathbf{T}_{ij} = (r_{ij} \mathbf{e}_L^i \times \mathbf{F}_{ij}) \cdot \hat{k} + b_{\text{Ang}}(\dot{\theta}_j - \dot{\theta}_i)$$

Here, b_{Ang} is defined as the angular drag coefficient.

$$b_{\text{Ang}} = \begin{cases} b_{\text{Lin}} \frac{2}{3} h^2 \frac{1 + \sin^2(\alpha/2)}{\sin^2(\alpha)} & : \alpha > \frac{h}{L - (r_{12} + r_{21})} \\ b_{\text{Lin}} \frac{2}{3} (L - r_{12} - r_{21})^2 & : \alpha < \frac{h}{L - (r_{12} + r_{21})} \end{cases}$$

During the initial configuration of the membrane and the actin filaments, some MATLAB functions can be used to generate an 'm × m' matrix, where a non-zero entry in the 'ij'th cell implies that the 'i'th and the 'j'th filaments intersect. Three such matrices are obtained - one with the x-coordinates of such intersection points, one with the y-coordinates, and one with the angle between the two intersecting filaments. Other cells in such matrices are zero or NaN.

For the filaments which do intersect initially, the differential equation for the solution of the COM points of the filaments can be written as

$$\gamma_2 \frac{d\bar{r}_j}{dt} = -\frac{1}{dz} \left(\frac{\partial E_m}{\partial \bar{r}_j} + \sum_i \mathbf{F}_{ji} \right)$$

$$\gamma_3 \frac{d\theta_j}{dt} = -\frac{1}{dz} \left(\frac{\partial E_m}{\partial \theta_j} + \sum_i \mathbf{T}_{ji} \right)$$

Stochastic Modelling

- Probabilistic behaviour can be introduced in this model, by implementing Gillespie stochastic simulations.
- Suppose the current state of the membrane and actin filaments has 'n' actin filaments.
- Suppose the current state of the membrane and actin filaments has 'n' actin filaments. Each filament disappearing corresponds to a new distinct state.
- A filament appearing anywhere on the membrane is also a new distinct state. Thus, the current state can go to any one of 'n+1' new states.
- Say the transition rate from current state to state 'i' is k_i . The net escape rate is $K = \sum_{i=1}^{n+1} k_i$.
- The escape time distribution can be considered to be exponential. So, $\Delta t = -(1/K)\ln(u)$ where u is a random number distributed uniformly between 0 and 1.

- The interval 0 to K is divided into subintervals of length k_j . Another random number v is selected from 0 to K , and the subinterval j where v lies is considered to be the destination state of the transition event.
- The jump time is calculated accordingly by updating the current state to the destination state. This process can be repeated for new states. A stochastic trajectory can be obtained by this procedure.

Notation	Variable	Unit	Values simulated
n	Number of Membrane Points	-	21, 51
m	Number of Actin Filaments	-	15, 100
L	Length of an Actin Filament	μm	2, 3
h	Width of an Actin Filament	μm	0.007
ρ	Density of actin-binding proteins	μm^{-2}	100
b	Viscous drag constant	$\text{mN}/(\text{m/s})$	100

p	Pressure	nN/ μm^2	1
k	Membrane Tension	nN/ μm^2	25, 50, 100
k_{fil}	Membrane-Filament Tension	nN/ μm^2	25, 50, 100
$\gamma, \gamma_1, \gamma_2$	Dimensional Constants	nNs/ μm^2	1
γ_3	Dimensional Constant	nNs/rad ²	1
t	Time	s	1, 5, 10, 50, 100
dz	Characteristic length in z-direction	μm	0.1
k_i	Transition Rates	s^{-1}	0 – 1

Force Analysis

The forces can be classified according to the energy components - Bending Force, Pressure Force, Tension Force, Interaction Force (on the membrane and on the actin filaments). These can be defined as

$$F_{\text{Bending Force}_i} = -\frac{\partial E_{m1}}{\partial X_i}$$

$$F_{\text{Pressure Force}_i} = -\frac{\partial E_{m2}}{\partial X_i}$$

$$F_{\text{Tension Force}_i} = -\frac{\partial E_{m3}}{\partial X_i}$$

$$F_{\text{Interaction Force (membrane)}_i} = -\frac{\partial E_{m4}}{\partial X_i}$$

$$F_{\text{Interaction Force (actin)}_i} = -\frac{\partial E_{m4}}{\partial r_i}$$

Substituting the values of membrane points obtained by solving the ODEs above, we can get numerical values of the forces (magnitudes), which can then be plotted for a comparative analysis.