Modeling mRNA transport in *Xenopus*

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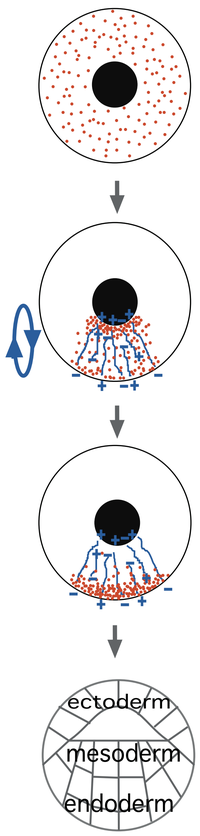
mRNA Localization



mRNA (messenger RNA, red dots) are collections of RNA particles. Maternal mRNA influences gene expression in the growing organism. At the start of egg formation, mRNA is distributed in the cell cytoplasm.

Molecular motor proteins then move mRNA from the nucleus (black circle) along tubular polymers called microtubules (MTs, in blue).
→ Bidirectional transport

After more than 24h, the mRNA becomes fully localized at the bottom of the egg cell.
→ Anchoring mechanism
Failure to fully localize mRNA leads to compromised cell development.

- mRNA localization is **key** in forming a top - bottom cell axis.
- This **axis polarity** ensures that layers in the early formation of the embryo are properly specified.

Experiments and Key parameters

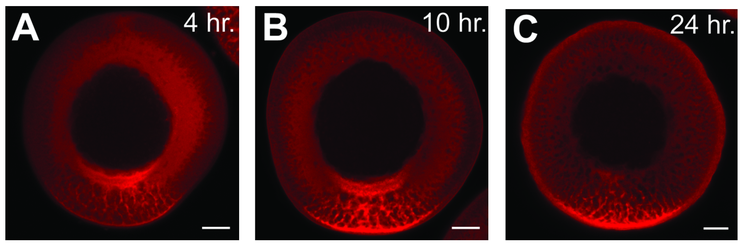


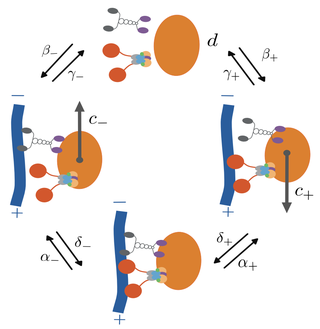
Figure: Localization of mRNA 4, 10 and 24 hours after injection in an egg cell [3].

Key parameters

- Free mRNA particles diffuse with **diffusion constant** $\boldsymbol{D}$.
- Motor-mRNA move along the MTs with **speeds** $\boldsymbol{c}_{+/-}$(down/up).
- Unbinding, binding and pausing **rates** from/to MTs provide the connection between moving and diffusing or paused particles.
- mRNA may remain **anchored** at the cortex.

PDE Model

- Red particles denote mRNA that can bind to two types of motors.
- We assume diffusion of motor-mRNA particles that are not bound to MTs.
- Bound motor-mRNA particles move up or down MTs.
- We assume there is a population of paused mRNA particles.



PDE Model Analysis

We consider linear model systems in [2]. Here we incorporate the effect of the MT structure on transport. Therefore we consider a density of MTs $\rho(\boldsymbol{r}, \theta)$ at location $\boldsymbol{r}$ with orientation θ and focus on a 2-state model with diffusion and transport down only.

To simplify the analysis, we consider the parallel microtubule setup on the right (as in [1]).We also assume the spatial domain $x \in [0, 1]$ and an infinite domain in the z direction, with homogeneous Neumann boundary conditions.

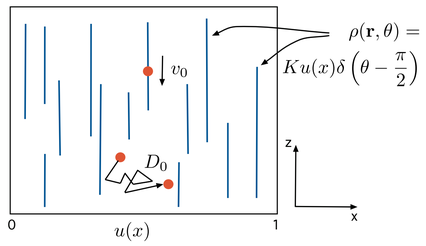


Figure: Illustration of 2-state model with transport restricted to MT structures.

We then have the advection-reaction-diffusion equation system [1]

$$\frac{\partial \bar{p}(\boldsymbol{r}, t)}{\partial t} = c\boldsymbol{e_z} \cdot \nabla \bar{p}(\boldsymbol{r}, t) - \beta \bar{p}(\boldsymbol{r}, t) + \alpha K u(x) p_0(\boldsymbol{r}, t)\,, \tag{1}$$
$$\frac{\partial p_0(\boldsymbol{r}, t)}{\partial t} = D\nabla^2 p_0(\boldsymbol{r}, t) + \beta \bar{p}(\boldsymbol{r}, t) - \alpha K u(x) p_0(\boldsymbol{r}, t)\,.$$

modeling the dynamics of particles with transport restricted to parallel microtubules.
Using a Fourier-mode ansatz and Lyapunov-Schimdt reduction of the resulting equation, we can determine the effective velocity and effective diffusion of the particles in the direction of transport (z) in the limit $t \to \infty$:

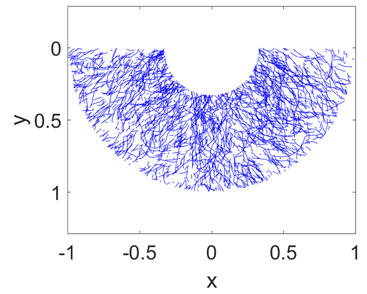
$$v = \frac{\alpha K \bar{u}}{\beta + \alpha K \bar{u}} v_0\,,$$
$$\sigma^2 = \frac{\beta}{\beta + \alpha K \bar{u}} D + \frac{\beta \alpha K \bar{u}}{(\beta + \alpha K \bar{u})^3} v_0^2 + \frac{\beta \alpha K v_0}{(\beta + \alpha K \bar{u})^2} \bar{u}\,,$$

where $\langle f(x), g(x) \rangle = \int_0^1 f(x) g(x) dx$, $\bar{u} = \langle u(x), 1 \rangle$ and w_1 satisfies

$$D(w_1)_{xx} = \frac{\alpha K}{\beta + \alpha K \langle u(x), 1 \rangle} v_0 \left(\langle u(x), 1 \rangle - u(x) \right)\,. \tag{2}$$

Numerical Simulations Results

- To compare timescales of localization, we create model MT structures as in [4].
- Simulations suggest that bidirectional transport (see left) and MT densities play an important role on localization.



The simulations use results of parameter estimates from fitting Fluorescence Recovery after Photobleaching (FRAP) data with the 4-state model on the left [2].

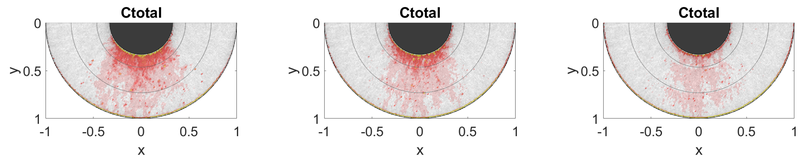
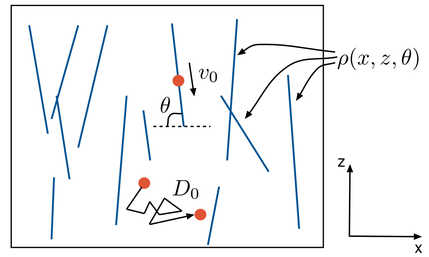


Figure: Simulation of mRNA localization after 4, 10, and respectively 24 hours.

Outlook

- Extend the analysis for large time to more general MT structures.
- Analysis and simulation can test the effect of potential anchoring mechanisms and MT distributions on localization.



References

[1] Paul C Bressloff and Bin Xu. Stochastic active-transport model of cell polarization. *SIAM Journal on Applied Mathematics*, 75(2):652–678, 2015.

[2] Maria-Veronica Ciocanel, Jill A Kreiling, James A Gagnon, Kimberly L Mowry, and Björn Sandstede. Analysis of active transport by fluorescence recovery after photobleaching. *Biophysical Journal*, 112(8):1714–1725, 2017.

[3] James Gagnon, Jill Kreiling, Erin Powrie, Timothy Wood, and Kimberly Mowry. Directional transport is mediated by a dynein-dependent step in an RNA localization pathway. *PLOS Biology*, 11:138–153, 2013.

[4] Philipp Khuc Trong, Helene Doerflinger, Jörn Dunkel, Daniel St Johnston, and Raymond E Goldstein. Cortical microtubule nucleation can organise the cytoskeleton of Drosophila oocytes to define the anteroposterior axis. *eLife*, 4:e06088, 2015.