Modeling Mesenchymal to Epithelial Transition in Endodermal Cells

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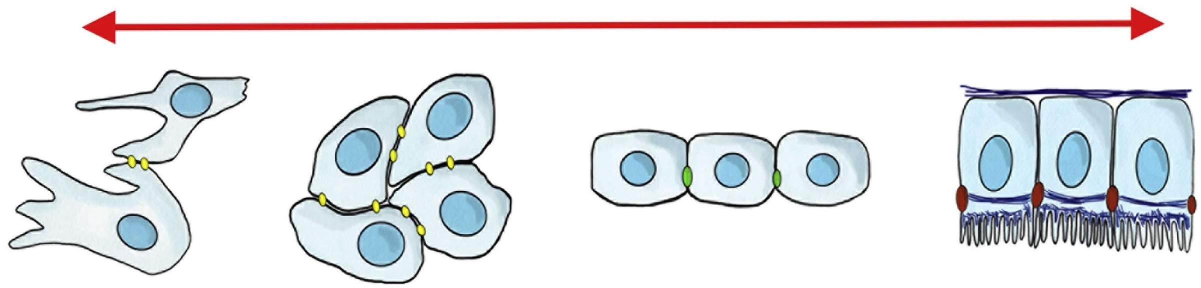
Motivation

Mesenchymal to Epithelial Transition



Cancer invasion

Reprogramming and cell fate

Wound healing

Diagram courtesy of Campbell, 2018

Previous Models

EMT/MET in cancer cells

- Partial Differential Equations

Our Model

MET in development

- Langevin Dynamics

Objectives

- Simulate the mesenchymal phase of MET: cells have random motion
- Simulate the epithelial phase of MET: cells have directed motion and begin to adhere to one another
- Model the interaction between the cell and extracellular matrix to visualize how it affects the cell migration transition

Approach

Experiments

- Timelapse microscopy of developing embryos

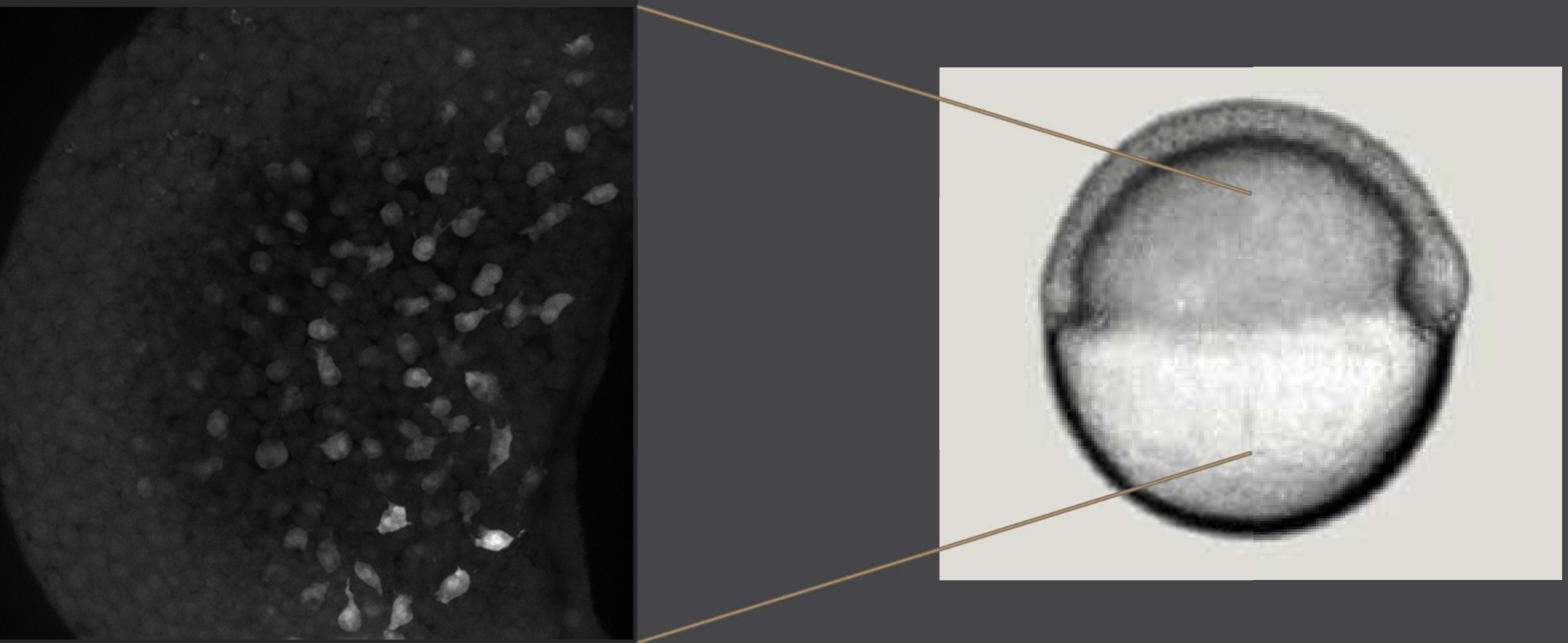
Data

- Tracking cell trajectories in ImageJ

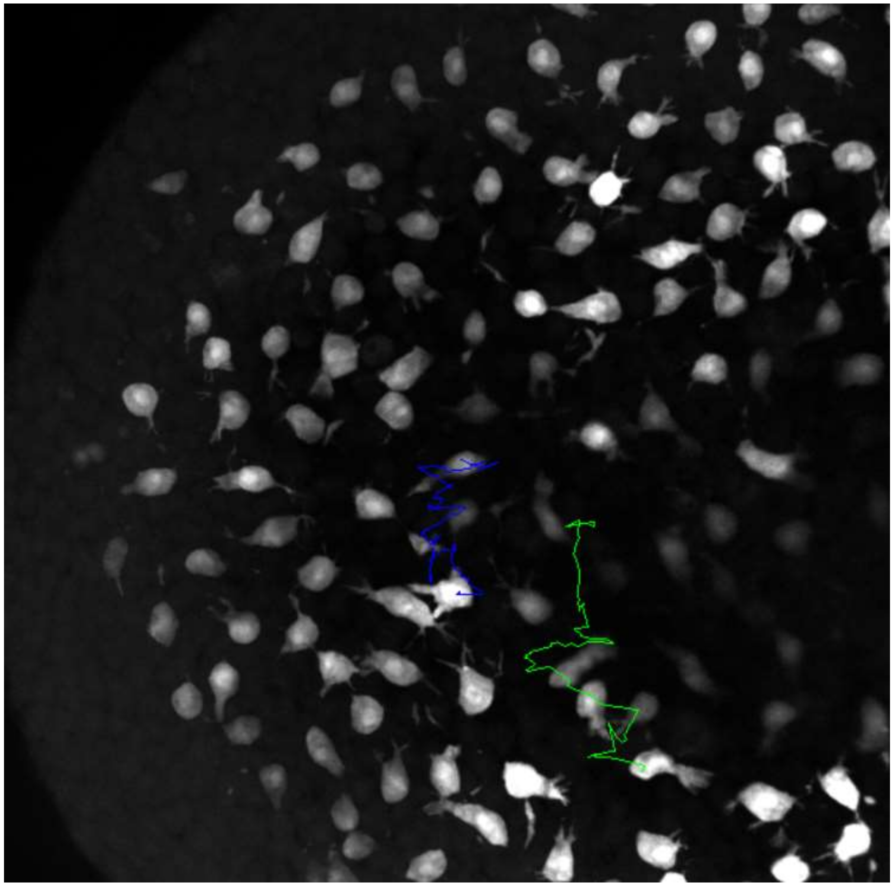
Model

- Active Brownian dynamics

Endodermal cells undergo MET during gastrulation



Experimental Data



Measured Parameters

Average Velocity

Confinement Ratio

Results
Mean-Squared Displacement (MSD)

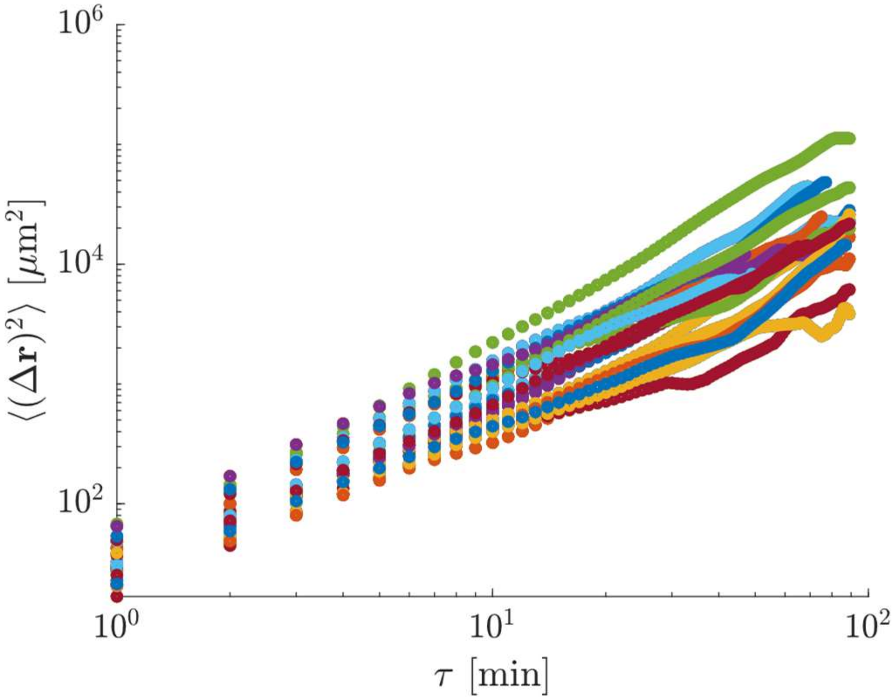
number of dimensions

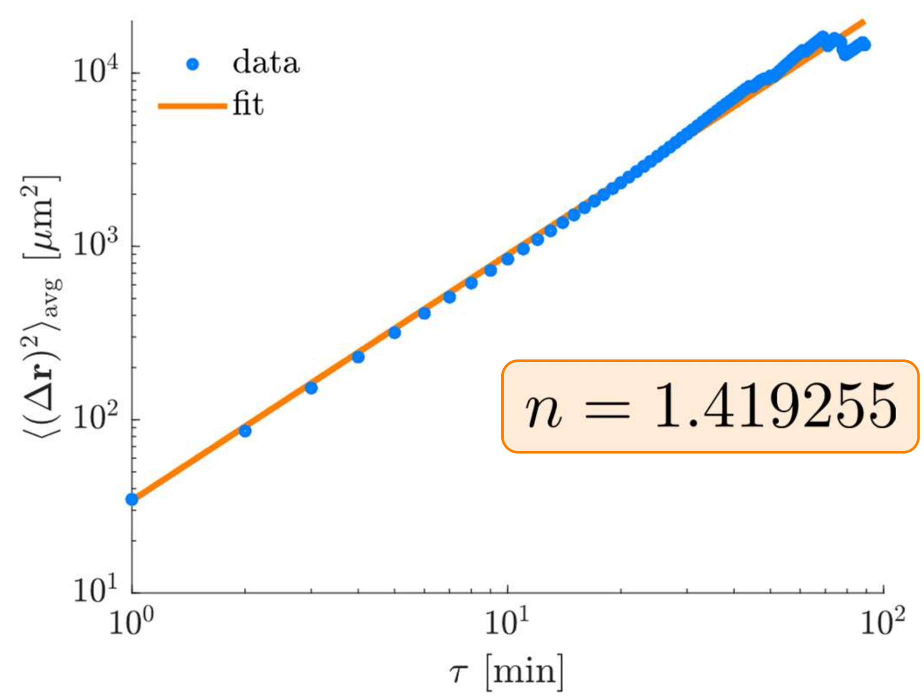
$$\langle(\Delta\mathbf{r})^2\rangle = 2\boxed{d}\boxed{\mathcal{D}}t^{\boxed{n}}$$

power

“diffusion” coefficient

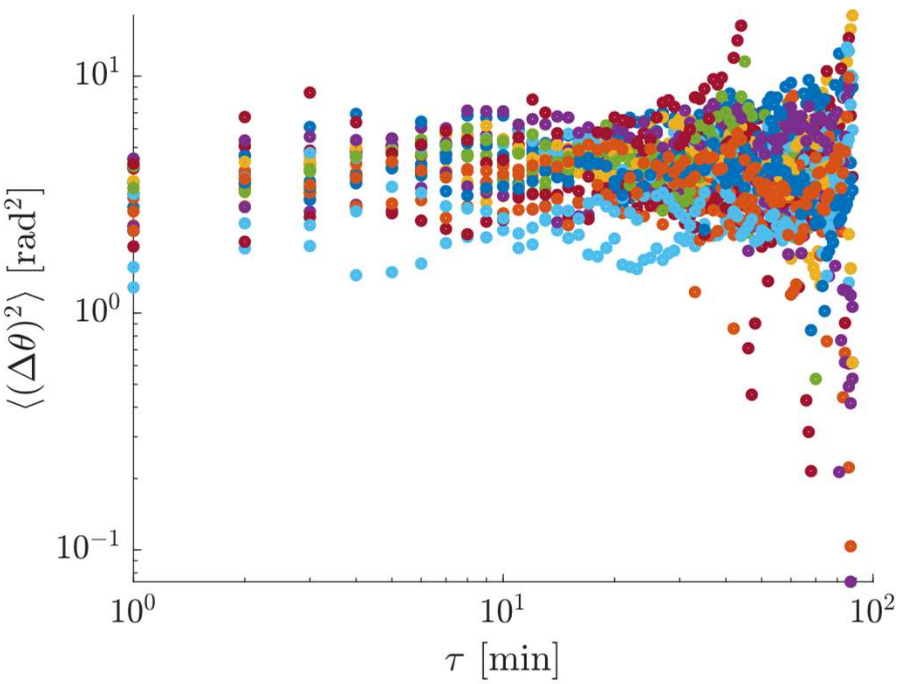
Results
Translational MSD

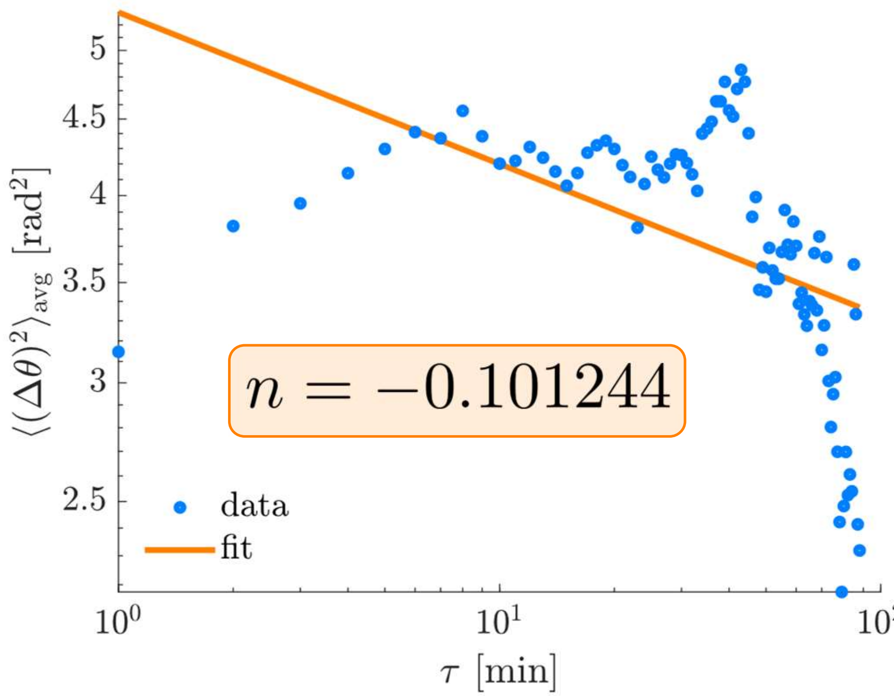




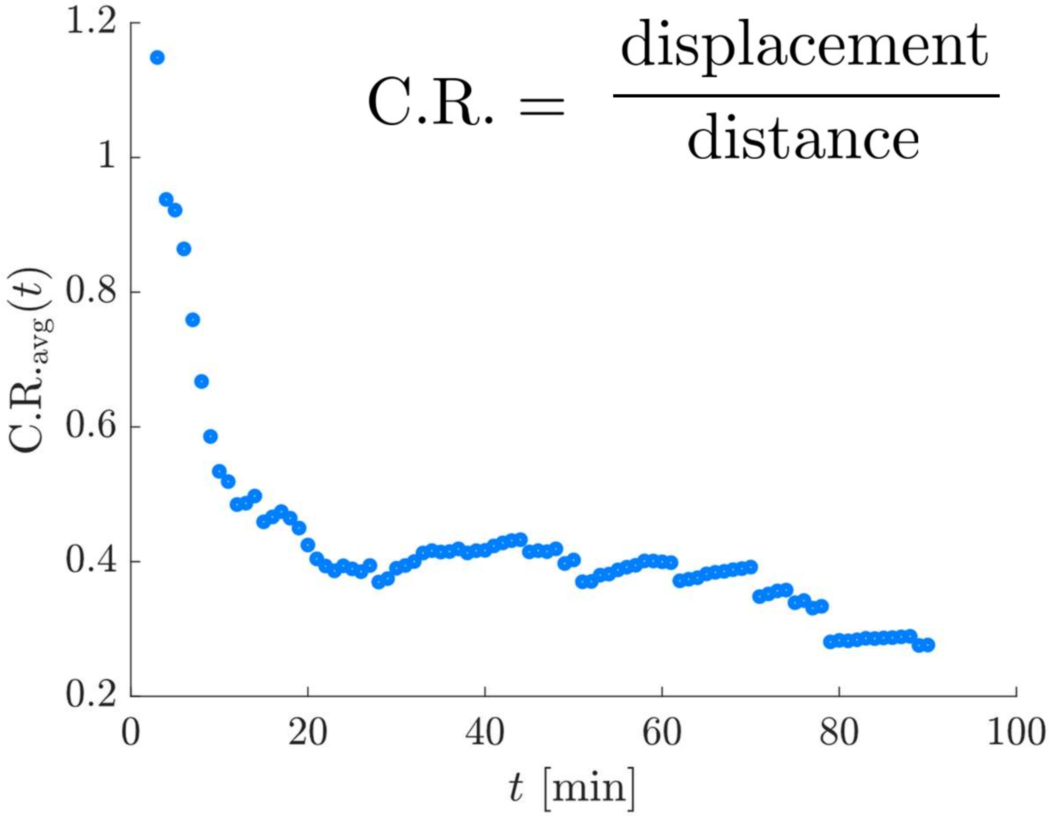
Results

Rotational MSD

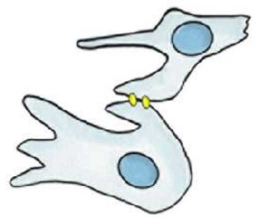
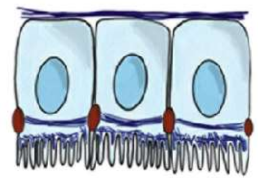




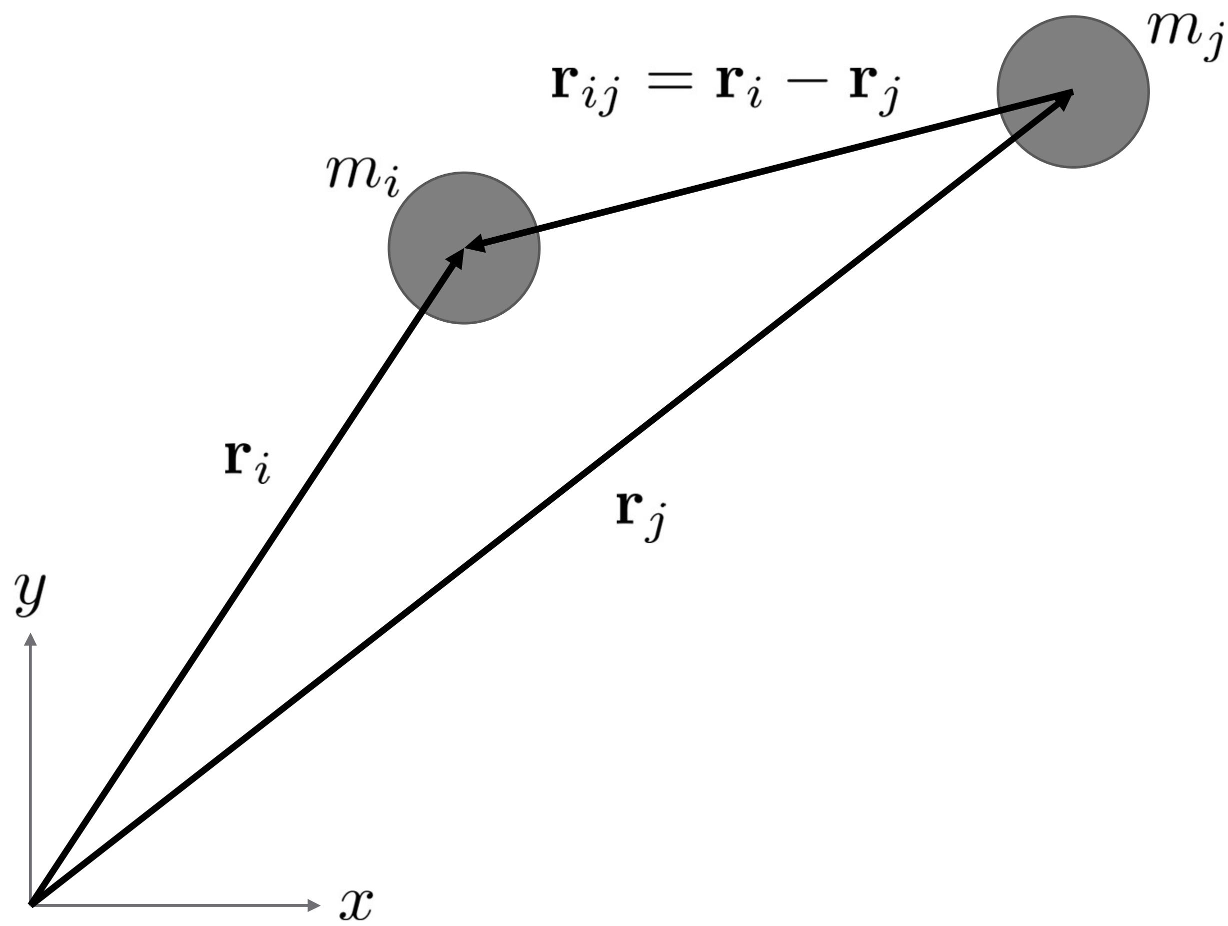
Results
Confinement Ratio



Results

	Mesenchymal	Epithelial
		
Rotational Coefficient	$1.32\ \mathrm{rad}^2/\mathrm{s}^n$	$0.922\ \mathrm{rad}^2/\mathrm{s}^n$
Translational Coefficient	$8.54\ \mu\mathrm{m}^2/\mathrm{s}^n$	$3.32\ \mu\mathrm{m}^2/\mathrm{s}^n$

Model



Model

Translational equation

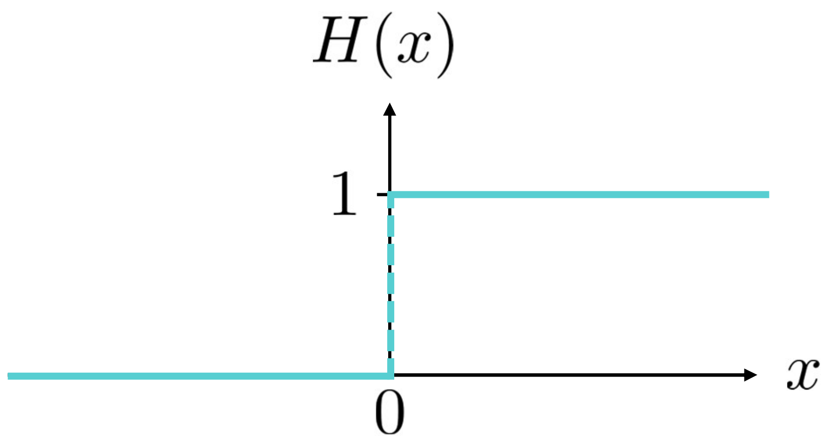
$$m_i \ddot{\mathbf{r}}_i = \overbrace{\boxed{-\gamma \dot{\mathbf{r}}_i}}^{\text{friction}} + \overbrace{\boxed{\sqrt{2D}\gamma \dot{\mathbf{W}}_i}}^{\text{thermal}} \overbrace{\boxed{- \frac{\alpha}{r_{ij}^2} H(r_{ij} - 2\sigma)\hat{\mathbf{r}}_{ij}}}^{\text{attractive}}$$

$$+ \underbrace{\boxed{\beta\, H(2\sigma - r_{ij})\hat{\mathbf{r}}_{ij}}}_{\text{repulsive}} + \underbrace{\boxed{\gamma u\, \hat{\mathbf{n}}}}_{\text{active}}$$

Model

Heaviside function

$$H(x) = \begin{cases} 1 & x > 0 \\ 0 & x \leq 0 \end{cases}$$



Model

Heaviside function

attractive

$$\boxed{H(r_{ij} - 2\sigma)}$$

nonzero outside the disc

$$\boxed{H(2\sigma - r_{ij})}$$

repulsive

nonzero inside the disc

Model

Rotational equation

$$I\ddot{\theta}_i = \underbrace{\boxed{-\gamma_\theta \dot{\theta}_i}}_{\text{friction}} + \underbrace{\boxed{\sqrt{2D_\theta}\gamma_\theta \dot{W}_{\theta,i}}}_{\text{thermal}} \underbrace{\boxed{- \kappa \cdot (\theta_i - \theta_{\text{avg}})}}_{\text{flocking}}$$

Model

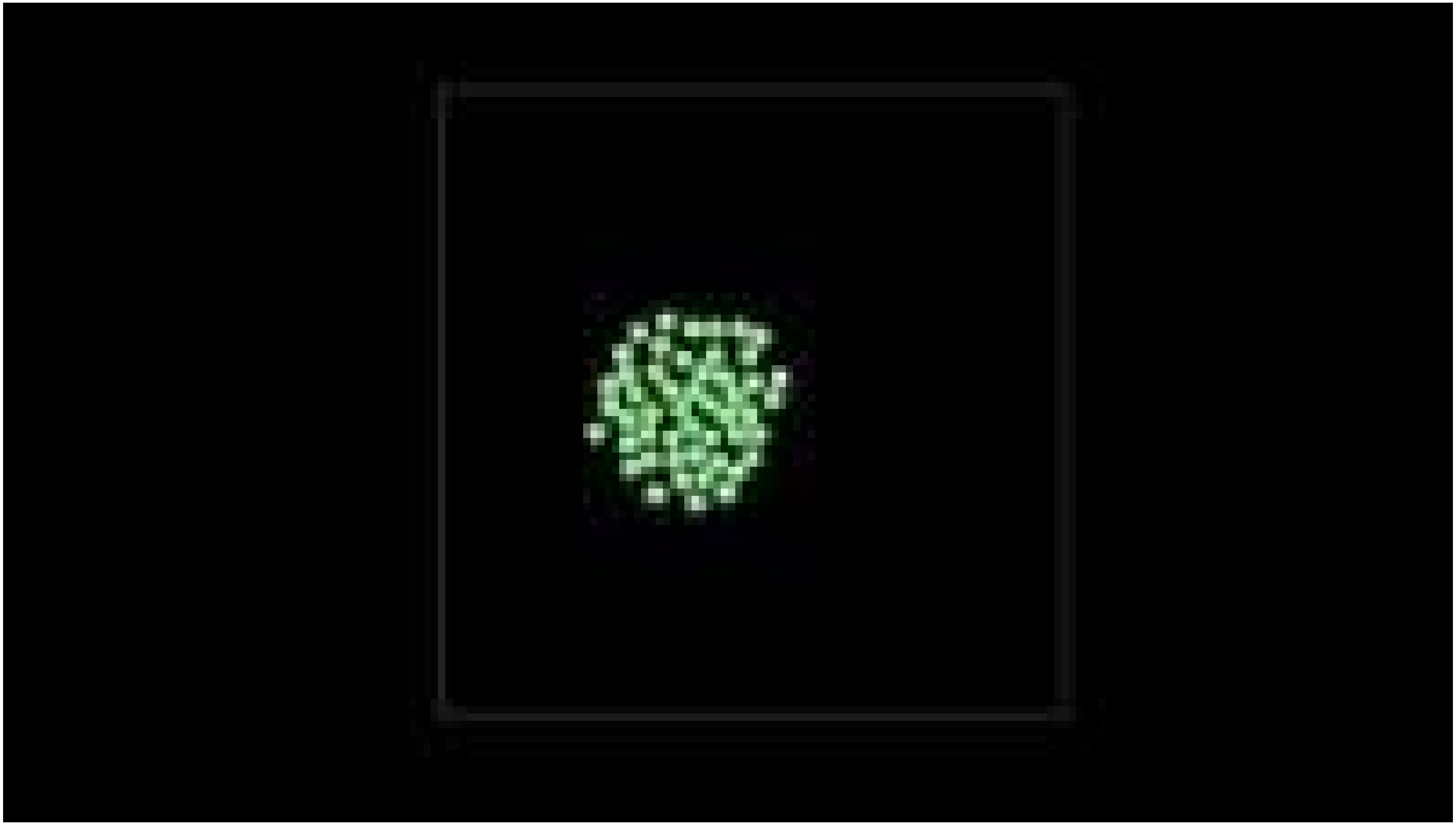
Coupled

$$m_i\ddot{\mathbf{r}}_i = -\gamma\dot{\mathbf{r}}_i + \sqrt{2D}\gamma\dot{\mathbf{W}}_i - \frac{\alpha}{r_{ij}^2} H(r_{ij} - 2\sigma)\hat{\mathbf{r}}_{ij}$$

$$+ \beta\, H(2\sigma - r_{ij})\hat{\mathbf{r}}_{ij} + \gamma u\, \hat{\mathbf{n}}$$

$$I\ddot{\theta}_i = -\gamma_\theta\dot{\theta}_i + \sqrt{2D_\theta}\gamma_\theta\dot{W}_{\theta,i} - \kappa\cdot(\theta_i - \theta_{\mathrm{avg}})$$

Results



Future

Introduce environmental factors

- ECM viscosity
- Cell density

Simulate cell-cell signaling

- Example: reduce cell-repulsion caused by lack of Ephrin signals
- GTPases involved in cytoskeleton

Post-Presentation

Following the class presentation, various attempts were made to produce simulation results that exhibited behavior similar to that shown in videos of zebrafish cells—behavior such as collective motion. However, the suggested changes to the code were not enough to produce desired results. As such, rather than invest further time into rewriting the code, the decision was made to submit what was already complete, though we understand the results are less than desirable.