MODELING TALK:
CELLULAR TRANSPORT

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For cells to function properly, protein molecules and structures have to move around and organize into complex patterns.

How do they move on the **precise time and spatial scales** observed inside cells?

How do we understand their **large-time dynamics**?

Video source: Vale Lab at [https://valelab.ucsf.edu/motility/](https://valelab.ucsf.edu/motility/)
INTRACELLULAR TRANSPORT

- Cargo (proteins, RNA, vesicles), vehicles (motor proteins), cellular road interactions.

- Switching between different biophysical states.

- E.g.: diffusion, active (bidirectional) transport, pausing.

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1. MICROTUBULE-BASED TRANSPORT
SPECIFIC MOTIVATION

- In early development, many organisms have distinct spatial features and patterns.

- Egg cells are often **asymmetrical**, ensuring a healthy embryo body plan.

This asymmetry is achieved through asymmetric accumulation of messenger RNAs.

**Messenger RNA** (mRNA): RNA molecule with function in gene expression.
mRNA localization: accumulation of mRNA in some spatial domain

Achieving localization in 1-2 days is key in healthy development, but the mechanisms are not well understood.

A key mechanism is active transport on microtubules (MT).

Gagnon et al., 2013 (Mowry Lab)
MATHEMATICAL MODELS

Account for dynamics such as:

- Diffusion of free mRNA particles
- Active transport of motor-mRNA complexes
- Unbinding from / binding to microtubules
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- Diffusion of free mRNA particles
- Active transport of motor-mRNA complexes
- Unbinding from / binding to microtubules

\[
\begin{align*}
    u_t & = cu_y - \beta_1 u + \beta_2 v \\
    v_t & = D\Delta v + \beta_1 u - \beta_2 v
\end{align*}
\]
Account for dynamics such as:

- Diffusion of free mRNA particles
- Bidirectional transport of motor-mRNA complexes
- Unbinding from / binding to microtubules
- Pausing on the MT tracks
DETERMINISTIC: PDE

- Represented by the forward Kolmogorov equation:

\[
\frac{\partial u(y, t)}{\partial t} = A u + V \partial_y u + D \Delta u , \quad A, V, D \in \mathbb{R}^{n \times n}.
\]

- \( u \) column vector of particle population in each state
- \( A^T \) matrix of transition rates
- \( V = \text{diag}\{v_i\} \) diagonal matrix of transport speeds
- \( D = \text{diag}\{d_i\} \) diagonal matrix of diffusion coefficients
Ciocanel and Sandstede; *Analysis of Active Transport by FRAP, Biophysical Journal (2017)*
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ASYMPTOTIC TECHNIQUES

\[
\frac{\partial c(y, t)}{\partial t} = v_{\text{eff}} \partial_y c(y, t) + D_{\text{eff}} \Delta c(y, t),
\]
\[
c(y, t) = \sum_{i=1}^{n} u_i(y, t).
\]

Previous approaches:

- Quasi-steady-state analysis (Bressloff and Newby)
- Homogenization theory (Pavliotis, Stuart, Kramer)
LARGE-TIME DYNAMICS

- Lyapunov-Schmidt reduction on low wavenumber asymptotics of the Fourier transform (Ciocanel, Sandstede)

\[ \nu_{\text{eff}} = \frac{\langle \psi_0, Vu_0 \rangle}{\langle \psi_0, u_0 \rangle}, \]

\[ D_{\text{eff}} = 2 \frac{\langle \psi_0, (D - V\tilde{A}^{-1}\tilde{V})u_0 \rangle}{\langle \psi_0, u_0 \rangle}. \]

\( u_0, \psi_0 \): eigenvectors of the 0 eigenvalue of \( A, A^* \)

pure diffusion

correlations with advection and reaction

Ciocanel and Sandstede; Biophysical Journal (2017)
STOCHASTIC: CTMC

- Emphasize cyclic structure of the dynamics and use renewal rewards theory.
- Extend to semi-Markov settings.

Ciocanel, Fricks, Kramer, McKinley, *in preparation*
STOCHASTIC: CTMC

Base state (0)

Position $Y(t)$:

- $t_1$
- $t_1 + t_2$
- $T_1$
- $T_1 + T_2$

Scott McKinley, John Fricks, Peter Kramer
SPATIAL DEPENDENCE: MICROTUBULES

Movement along one MT: appropriate for short experiments

Movement along any MT: appropriate for long processes
Prior work

Hawkins, 2009; Bressloff and Xu, 2015
Determined the large-time dynamics of the particles given knowledge of the microtubule density and no parameter assumptions.

\[ \frac{\partial u}{\partial t} = A(x)u + C\partial_y u + D\partial^2_y u. \]
MODEL OF COMPLEX SPATIAL DEPENDENCE

- In frog oocytes, microtubules are random with a radial bias.
NUMERICAL SIMULATIONS

Model microtubule structures

Initial condition

Ciocanel et al.; SIADS (2018)
TIME COURSE OF LOCALIZATION

Experiment

4 hours  10 hours  24 hours

Model

Ciocanel et al.; SIADS (2018)
Spatial distribution of RNA particles resembles experiments.

Allows us to model and test hypotheses about mRNA anchoring.

Ciocanel et al.; SIADS (2018)
2. INTERMEDIATE FILAMENT TRANSPORT
AXONAL TRANSPORT

Tony Brown, OSU

Peter Jung, Ohio University
- **Neurofilaments (NFs)** influence the speed of neuronal communication.
- Ultimately, understanding excessive accumulations of NFs leads to better understanding of neurodegenerative diseases.
AXONAL TRANSPORT

- How do NFs navigate these nodes?
- Preliminary data shows that NFs may move faster in these constrictions.
State-switching model

- Off-track neurofilament
- On-track neurofilament
- Microtubule

Internode | Node | Internode
--- | --- | ---

State-switching model
Neurofilament length distribution

- Off-track neurofilament
- On-track neurofilament
- Microtubule

Neurofilament length distribution

Linear Plot

Frequency

Lengths (μm)
3. ACTIN FILAMENT ORGANIZATION
Intermediate filaments

Microtubules

Actin filaments

Huber et al; *Curr Opin Cell Biol* (2015)
Cells use many channels to communicate, each with different functions.

**Ring channels** play critical roles in oogenesis, wound healing, and cell division.

http://flymove.uni-muenster.de

Celldynamics.org, George von Dassow and Bill Bement

Ring channels can maintain precise diameters over a large time scale.

Certain motor proteins are often “in charge” of creating appropriate constriction of the ring.
In the worm *C. elegans*: ring channels (made of actin) allow for nutrient exchange in development.

Two types of motors, believed to function similarly, are involved in ring channel dynamics.
Experiments show that they antagonize each other with respect to cellularization.

Coffman et al, Biophysical Journal (2016)
Two types of motors, believed to function similarly, are involved in ring channel dynamics. Experiments show that they antagonize each other with respect to cellularization.

Coffman et al, Biophysical Journal (2016)
AGENT-BASED MODELING AND SIMULATION

- Accounts for dynamics and molecular transport of chemical species.
- Diffusion and active transport are modeled as stochastic jumps between compartments.
- Is based on energy minimization.
DATA ANALYSIS MEASURES

- actin filament
- myosin motor
- cross-linker

- Contractility, alignment, filament length distributions

Riley Juenemann, Tulane University

Scott McKinley, Tulane University
DETECTING RING STRUCTURE

Inspiration: Topaz, Zieglemeier, Halverson

Chad Topaz, Williams College

Innovation: Topaz, Zieglemeier, Halverson; PLOS One (2015)
TOPOLOGICAL RINGS THROUGH TIME

Birth/Death radius pairs

Time

0s

500s

1000s

0 500 1000 1500 2000

0 500 1000 1500 2000

0 500 1000 1500 2000

Death

Birth

Death

Birth

Death
Propose a method for connecting pairs through time.
Extract the most significant Betti 1 path.
VISUALIZATION OF SIGNIFICANT PATH (RING STRUCTURE) EMERGENCE

With Riley Juenemann, Adriana Dawes, and Scott McKinley; in preparation
EXPLORE PARAMETER DIFFERENCES: ON-RATE

Small on-rate

Large on-rate
TOPOLOGICAL FEATURES THROUGH TIME

- Birth radius
- Death radius

With Riley Juenemann, Adriana Dawes, and Scott McKinley; in preparation
DETECTING RING STRUCTURE

Small on-rate

Betti1 Significant Path

Death radius

Birth radius

Large on-rate

Betti1 Significant Path

Death radius

Birth radius

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CONNECTION TO IN-VITRO EXPERIMENTAL DATA

- Trace the actin filaments
- Apply data analysis measures and connect to simulations

David Altman, Willamette University
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FUTURE WORK

- Ring formation/maintenance with realistic biological mechanisms
- Quantify significant ring channel formation? Fasy et al (2014)
FUTURE WORK

- Ring formation/maintenance with realistic biological mechanisms
- Quantify significant ring channel formation? Fasy et al (2014)
- Different simplices around filaments?
- Stability? Rigorous measure of significant paths?
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Thank you for your attention!

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