Microtubule Feedback Loop Induced Self-polarization
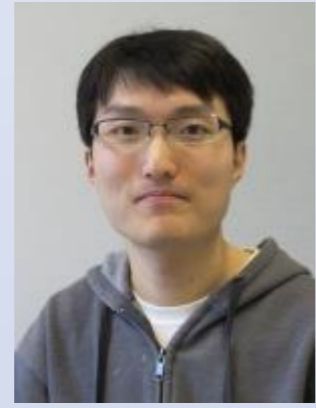
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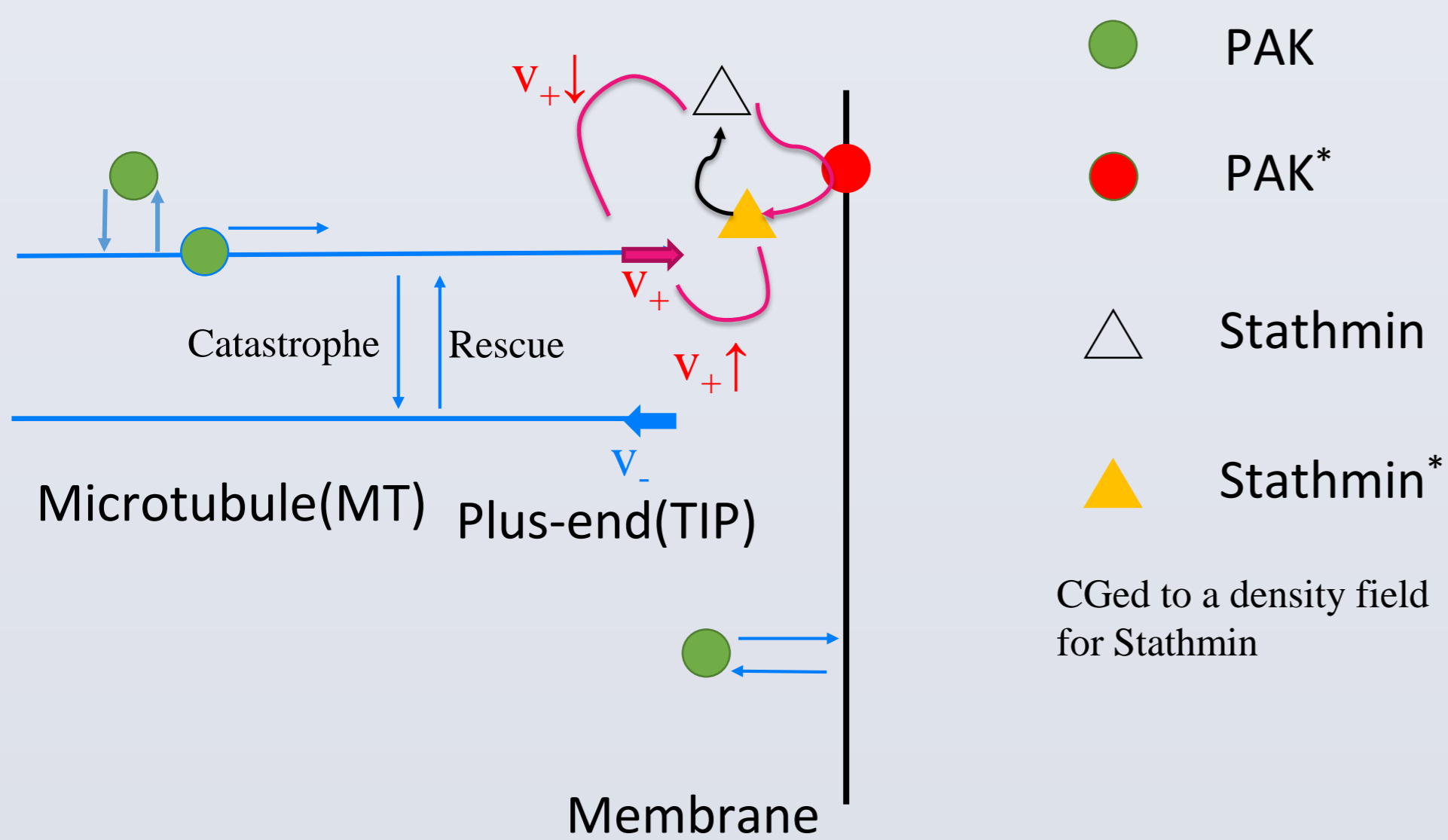
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Introduction

We develop a 3D particle-based simulation method bridging filament dynamics and reaction networks together. Nedelec's method is employed for filament dynamics, and we use Brownian Dynamics and/or GFRD to treat biomelocular reaction dynamics.

The importance of the intricate interplay between membrane pattern formation, transport along cytoskeletal filaments is now increasingly being recognized. Yet, our understanding of these processes is still highly limited, largely because of the complexity of living of a living cell.

As a first application of our method, we investigate a feedback-loop through signaling protein transports, activation and microtubule dynamics.

Model

**Feedback-loop through signaling protein transports, activation and microtubule dynamics**

- $v_+ \downarrow$
- v_+
- $v_+ \uparrow$
- v_-

Microtubule(MT)   Plus-end(TIP)

Catastrophe   Rescue

- ● PAK
- ● PAK*
- △ Stathmin
- ▲ Stathmin*

CGed to a density field for Stathmin

Membrane

Reaction Network:

- PAK + Membrane ←→ PAK* absorbed on Membrane
- Stathmin + PAK* ←→ Stathmin* + PAK*
- Stathmin* → Stathmin
- Stathmin + 2Tublin → Stathmin2Tublin [$v_+ \downarrow$]
- TIP(+) ←→ TIP(-)

Methods: Reaction Dynamics

Brute force Brownian Dynamics

And/or

Green's Function Reaction Dynamics (GFRD)
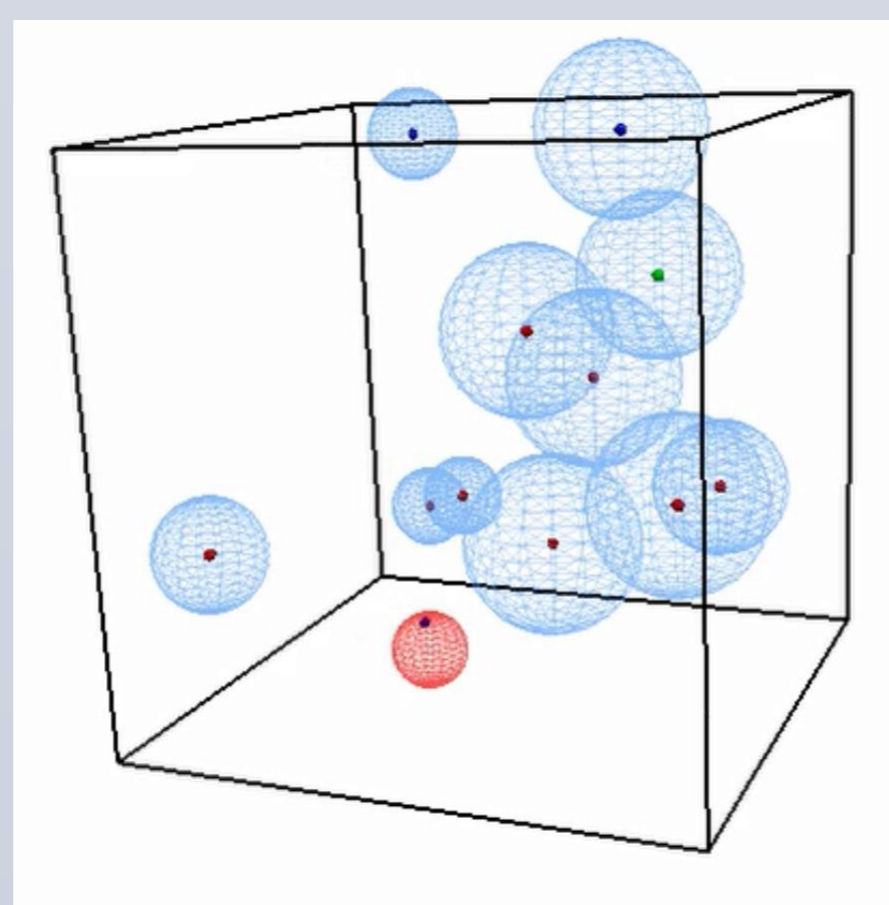
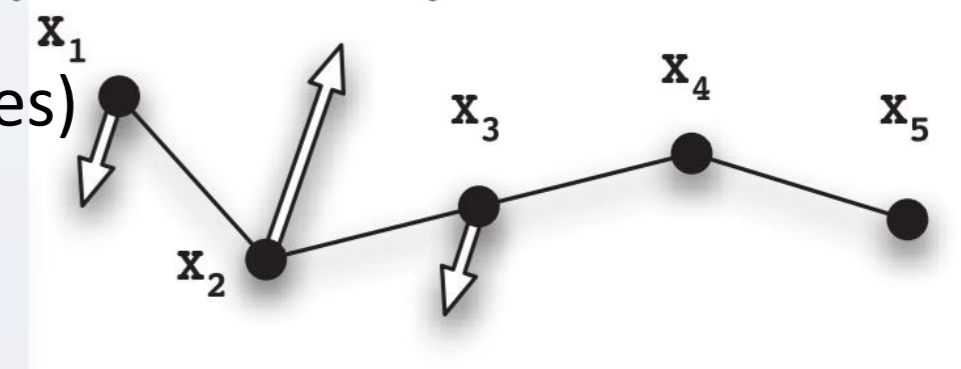## Methods: Filaments Dynamics

Nédélec's mothods are employed

Bending Energy
$$E_b = \frac{\kappa}{2}\int_0^L ds(\partial_s \mathbf{t})^2 = \frac{\kappa}{2}\int_0^L ds(\partial_s \phi(s))^2$$
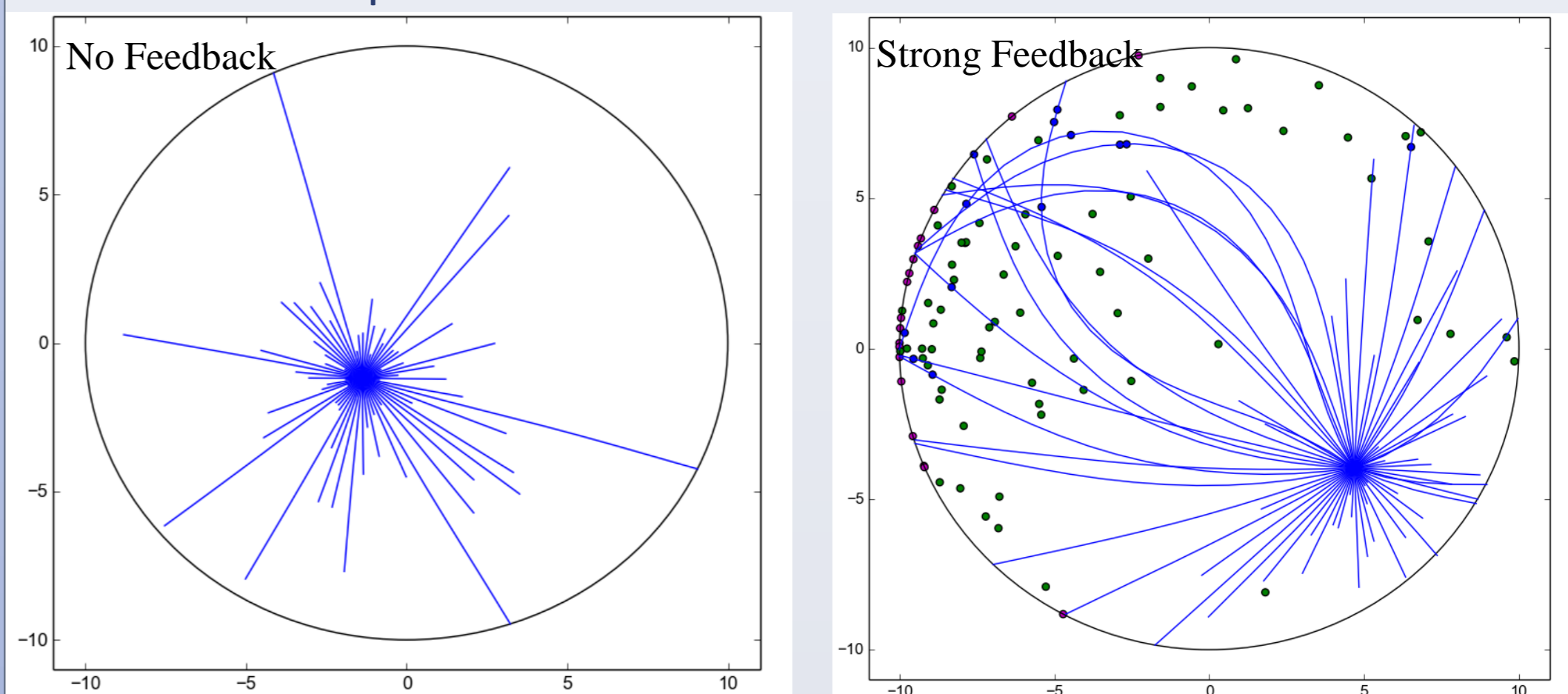
Length: L , p segments (p+1 nodes)

- Hard constraints on segment length equality
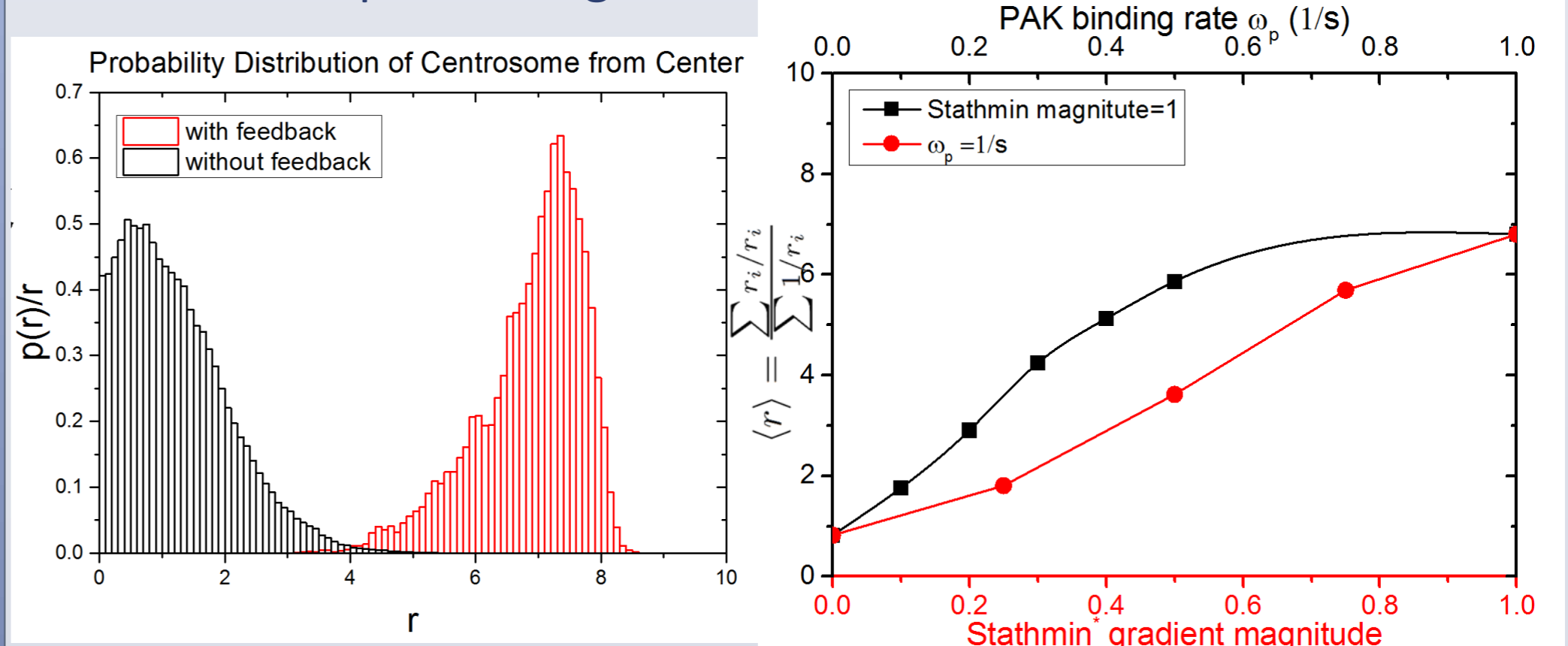- Implicit integrations solving Langevin equations

Results

Simulation Snapshots

No Feedback

Strong Feedback

Feedback Loop shifts centrosome away from center

Centrosome repositioning

Probability Distribution of Centrosome from Center
- with feedback
- without feedback

PAK binding rate ω_p (1/s)
- Stathmin magnitute=1
- ω_p =1/s

$\langle r \rangle = \sum \frac{r_i/r_i}{\sum 1/r_i}$

Stathmin gradient magnitude
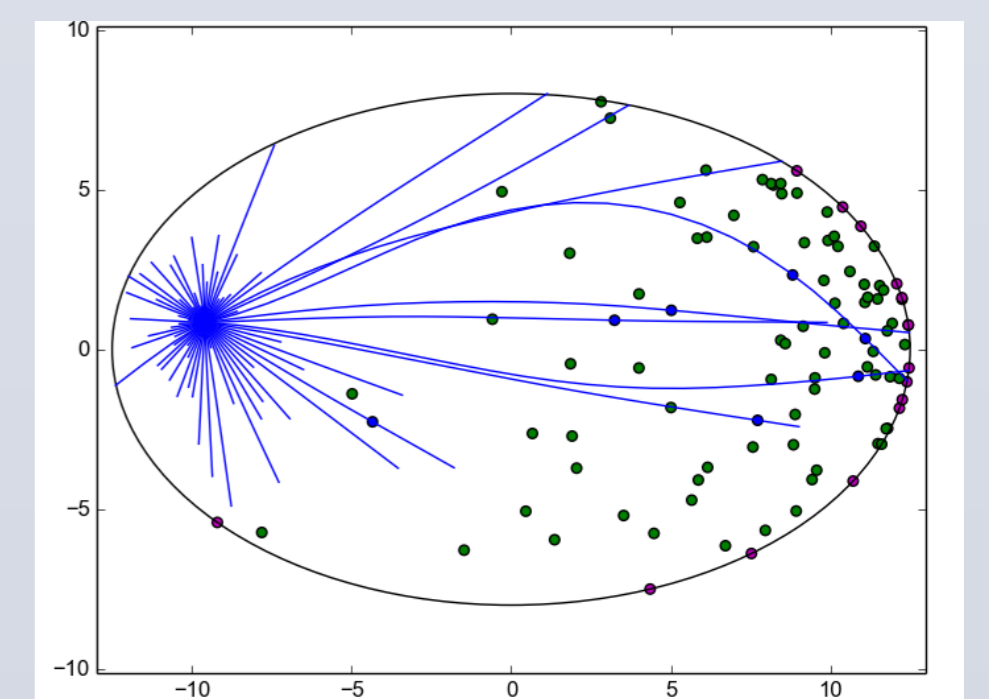
Confinement Geometry

Much higher chance of polarization along long axis

Additional feedback of interplay between MT and (deformable) membrane is on going

Conclusions:

Microtutuble-PAK-Stathmin feedback loop can generate cell self-polarization, showing PAK clustering and centrosome repositioning, breaking geometry symmetry. And it can be tuned by varying PAK binding rate or Stathmin gradient magnitude.

References

[1] F. Nédélec, T. Surrey, A. Maggs et.al. Nature, 1997, 389(6648): 305–8.

[2] J.S. van Zon, P.R. ten Wolde Physical review letters, 2005, 94(12): 128103.

Acknowledgements

Welcome all experimental collaboration of system on cytoskeleton coupled with reaction-diffusion and/or vesicle dynamics
We have the powerful (general) simulation tool in hand

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