A computational study of actin network formation and intracellular transport

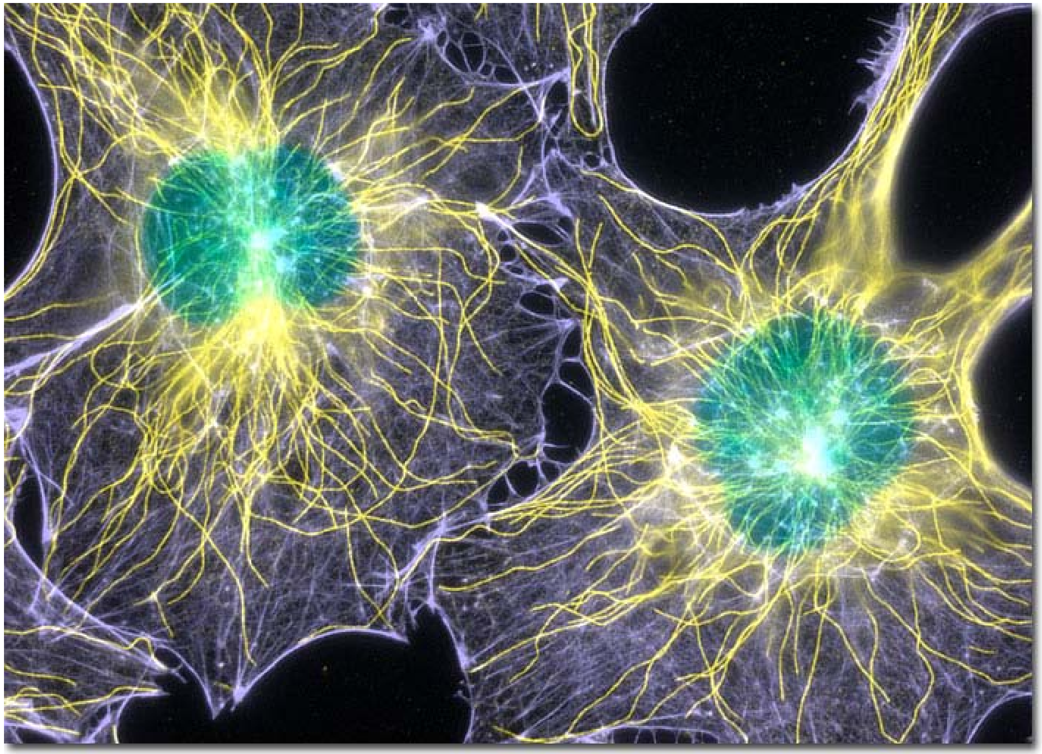
Youngseok Kim, Giray Enkavi, Anthony Ho

PHYS 466 class project
University of Illinois at Urbana-Champaign

May 12, 2011

A cell is like a city

- Cellular environment is highly complex
- 10^6 proteins being produced per second
- Proteins have to be transported from the production sites (ribosomes) to various destinations



http://publications.nigms.nih.gov/insidethecell/chapter1.html

How do things move inside a cell?

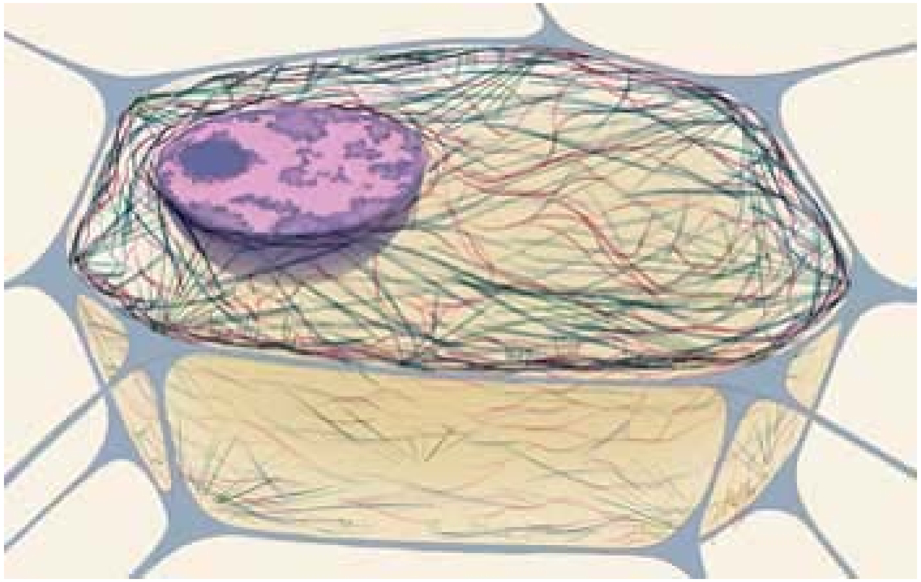
http://www.physorg.com/news4101.html

- Diffusion
  - Only sufficient for small molecules (such as ATP or caetyl CoA)
- Active transport
  - “Cargos” carried by molecular motors along a system of polymerized filaments (cytosolic fibers)
  - Like trucks on roadways
  - Allows larger “cargos” to be transported

Cytoskeleton is the cell's skeleton

- Responsible for:
  - Cell shape and structure
  - Cellular division
  - Cellular motility
  - Intracellular transport

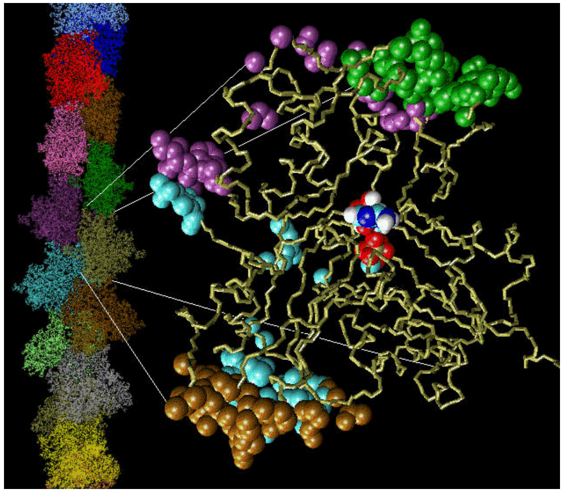
- Made of 3 types of fibers:
  - Microtubules (like highway)
  - Intermediate filaments
  - Actin filaments (like local roads)



http://publications.nigms.nih.gov/insidethecell/chapter1.html

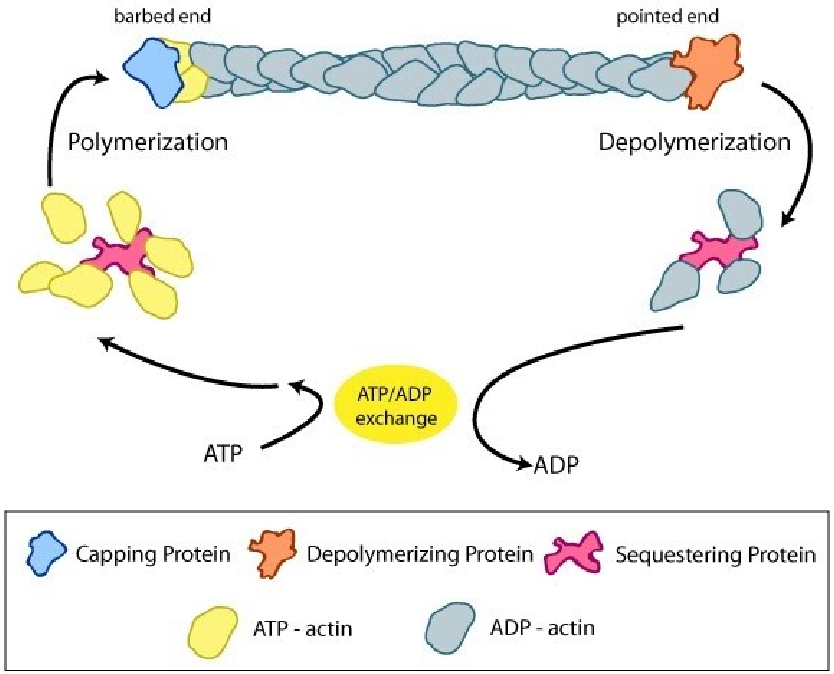
Actin filaments are consisted of actin monomers

- Polarity: barbed end (+) and pointed end (–)



http://biomachina.org/research/projects/actin/

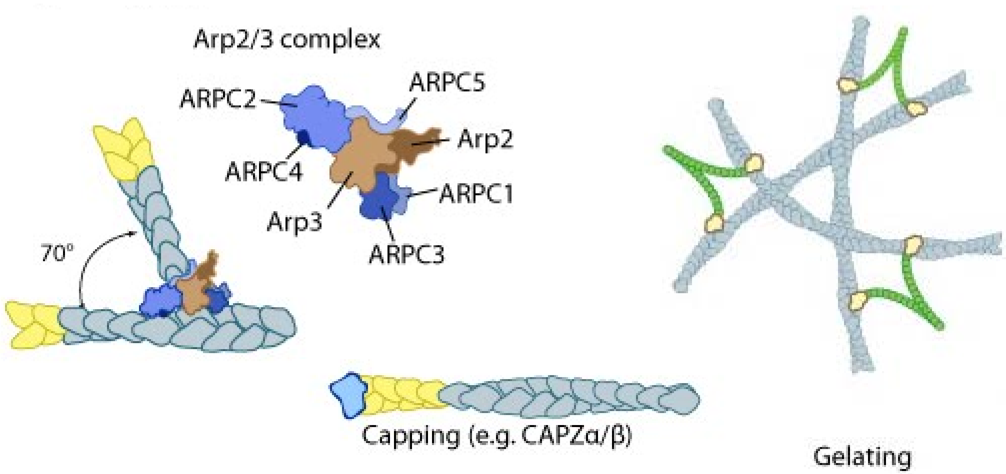
- Actin monomers can polymerize and depolymerize at both ends; but barbed ends favor polymerizations while pointed ends favor depolymerizations



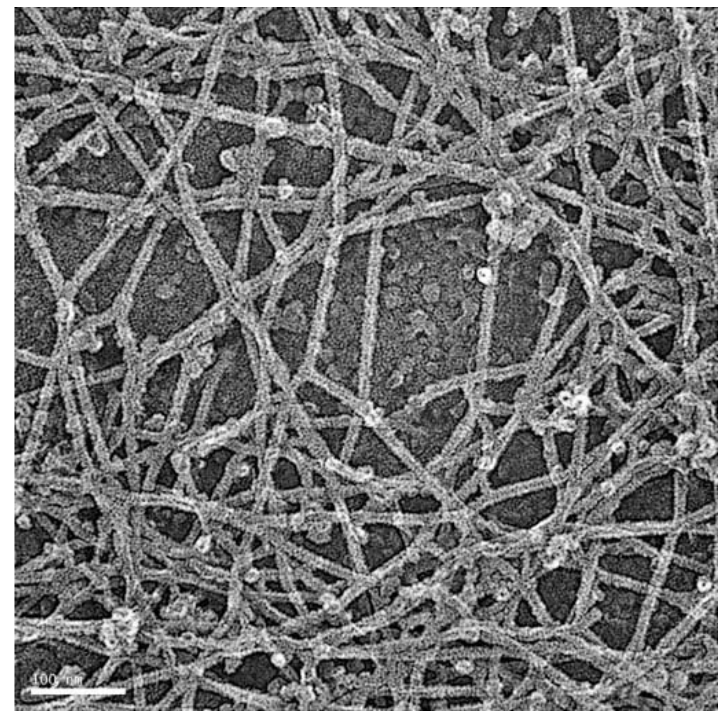
http://manual.blueprint.org/Home/glossary-of-terms/mechano-glossary--a/mechano-glossary-treadmilling/glossary-factors-influencing-actin-filaments

Actin filaments, with actin binding proteins, can form a network

- Different actin-binding proteins affecting actin dynamics:
  - Arp2/3 (branching protein)
  - CAPZα/β (capping protein)
  - Fliamin (cross linking protein)



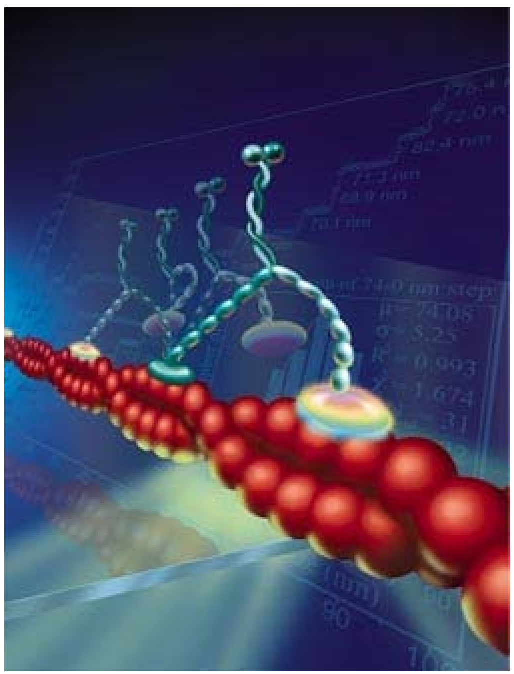
http://manual.blueprint.org/Home/glossary-of-terms/mechano-glossary--a/mechano-glossary-treadmilling/glossary-factors-influencing-actin-filaments



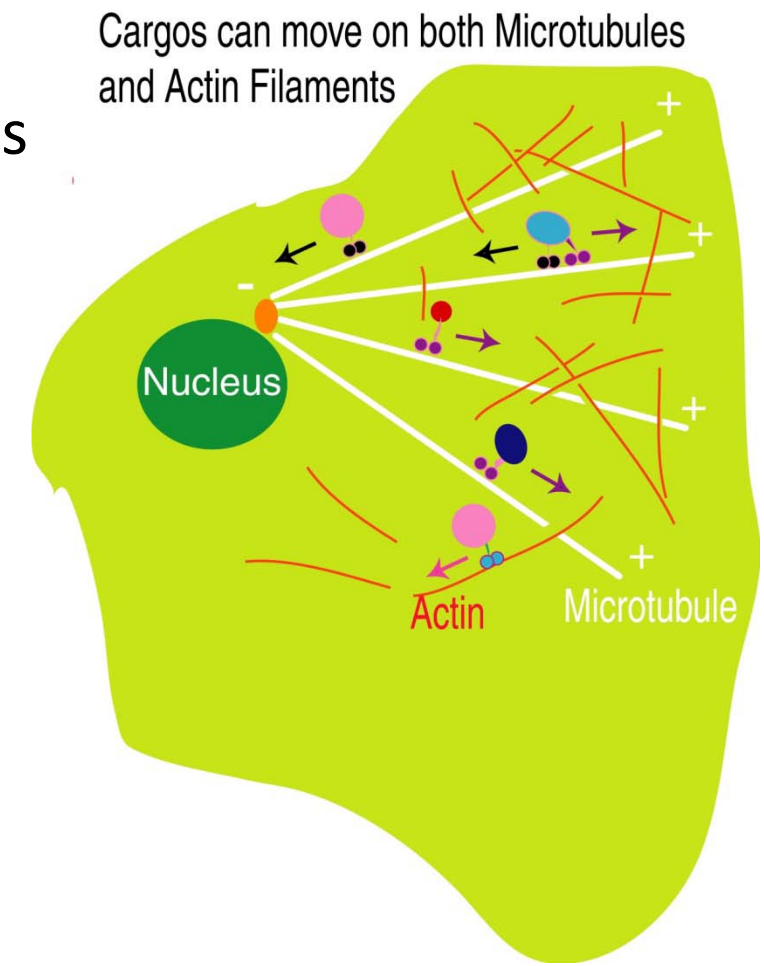
https://science.nichd.nih.gov/confluence/display/sob/Actin+Filament+Networks

Molecular motors carries cargos on microtubules and actin filaments

- Myosin V, an ATP-dependent motor, "walks" on actin filaments with a step size of 37nm



Yildiz *et al*, Science 2003



Modeling the actin network

- Actin monomers:
  - Modeled as a 5-nm-long rigid rods
- Polymerization
  - Adding a free actin monomer to an existing actin filament
  - Assuming only at the barbed end
- Depolymerization
  - Removing a bounded actin monomer from an existing actin filament
  - Assuming only at the pointed end
- Branching
  - Attaching a free actin monomer to anywhere along an actin filament with a branching angle of 70°
- Capping
  - Adding a capping protein to the barbed end of an actin filament
  - Prevents the filament from further polymerization

Generating an actin network

- Place a randomly oriented actin monomer at the origin
- At each iteration:
  - Actin polymerization occurs at a randomly chosen filament with a probability P_+
  - Actin depolymerization occurs at a randomly chosen filament with a probability P_-
  - Branching occurs at a randomly chosen filament with a probability P_{br}
  - Capping occurs at a randomly chosen filament with a probability of P_{cap}

Probabilities and reaction rates

- Experimental actin polymerization/depolymerization rates are known (at both ends): $k_B^+, k_P^+, k_B^-, k_P^-$

- Assuming only net polymerization occurs at barbed ends, and net depolymerization occurs at pointed ends:

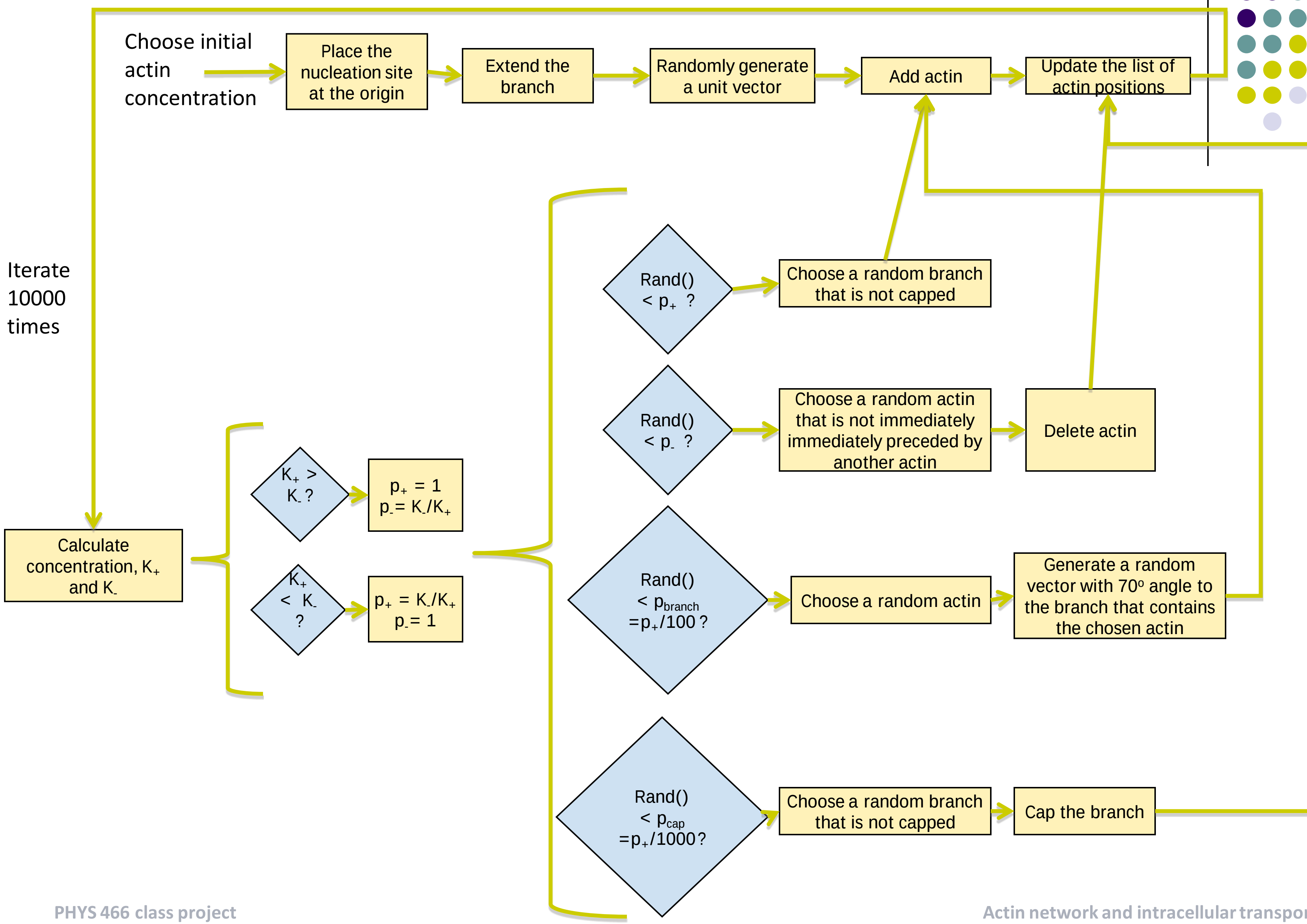
$$\text{Net polymerization rate at b-end} = K_+ = k_B^+ C - k_B^-$$
$$\text{Net depolymerization rate at p-end} = K_- = k_P^- - k_P^+ C$$

- The probability P_+ and P_- can be related to the experimental rates by:

$$\frac{P^+}{P^-} = \frac{K^+}{K^-}$$

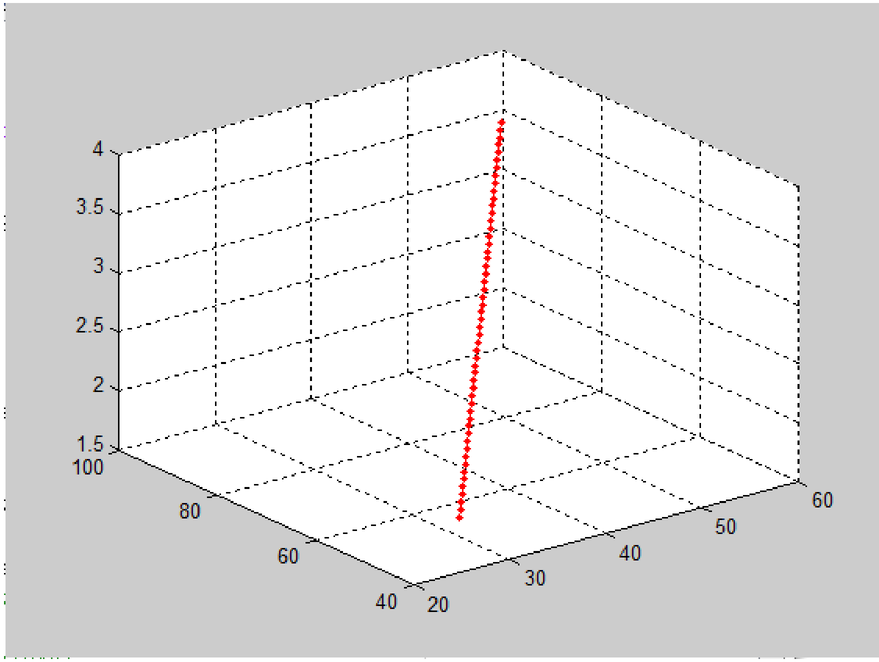
- The probability P_{br} and P_{cap} can be adjusted to optimize the network

Actin Network Generation

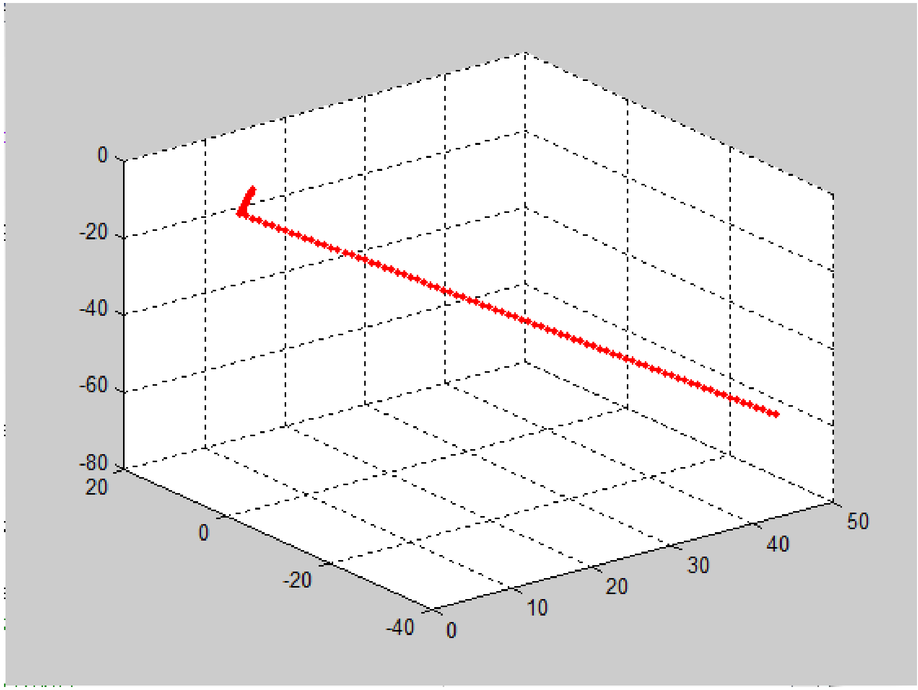


Actin Network Examples

Concentration=0.6 μM



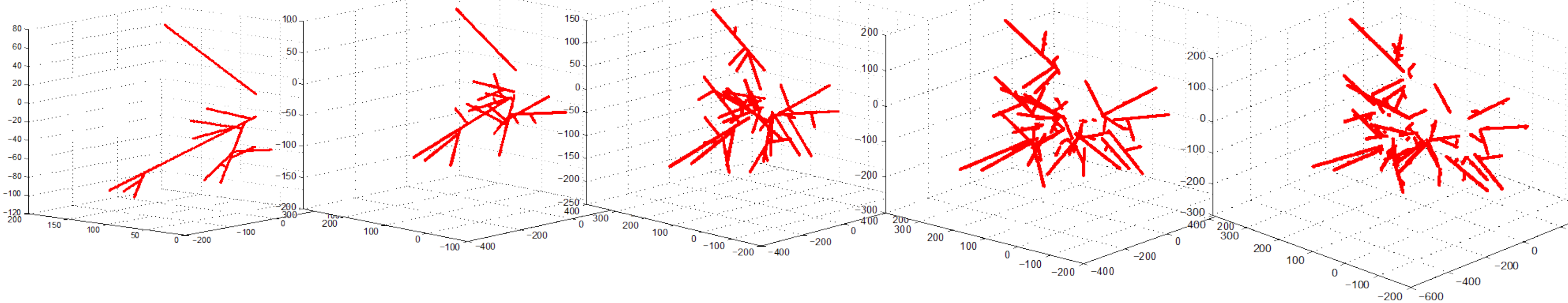
Concentration=1.8 μM



Actin Network Examples

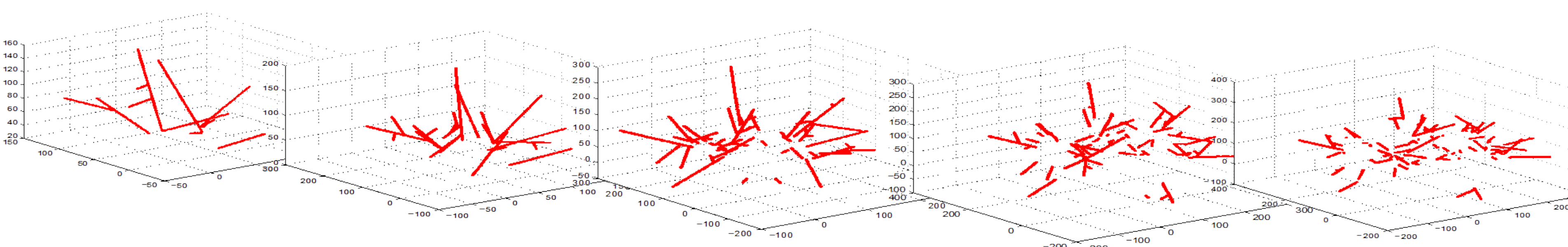
Concentration=1.3 μM

Iteration=1100 2100 5100 8100 9900

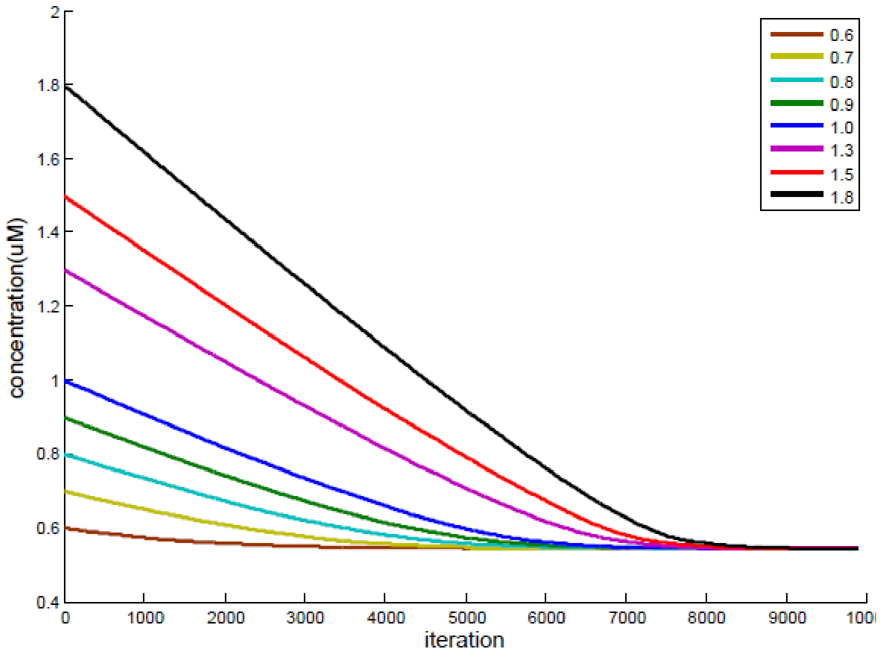


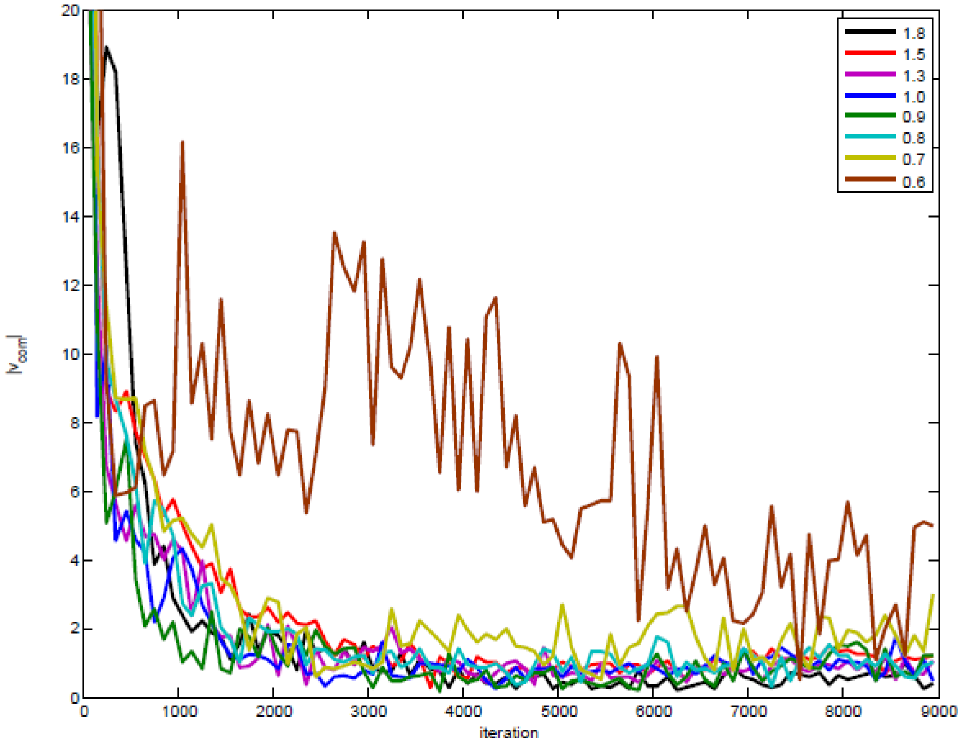
Concentration=0.8 μM

Iteration=1100 2100 5100 8100 9900

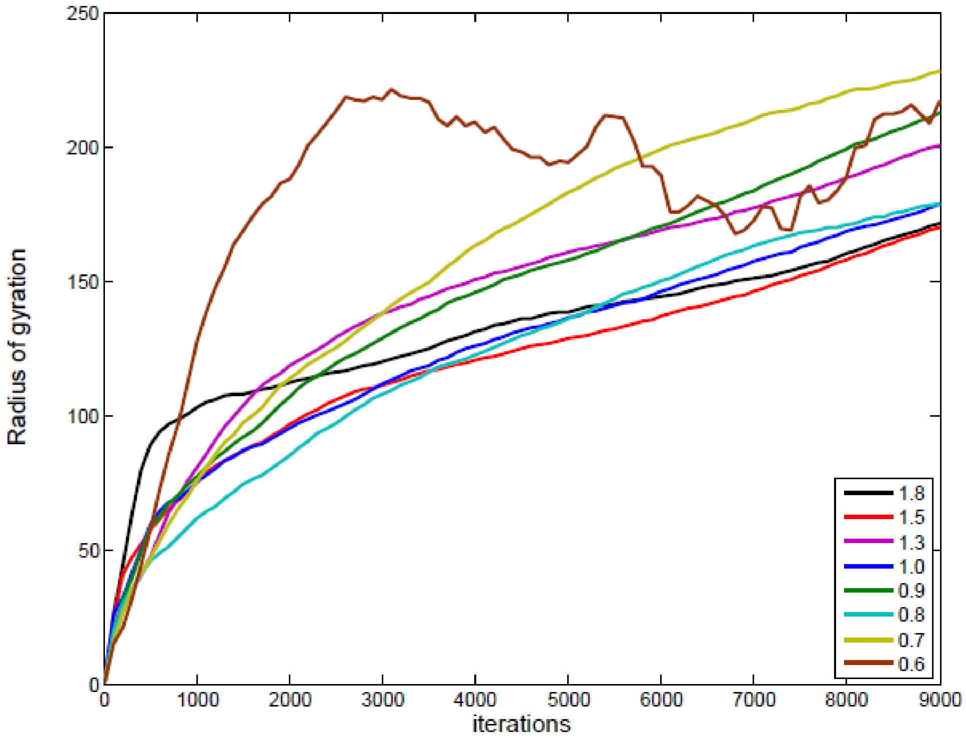


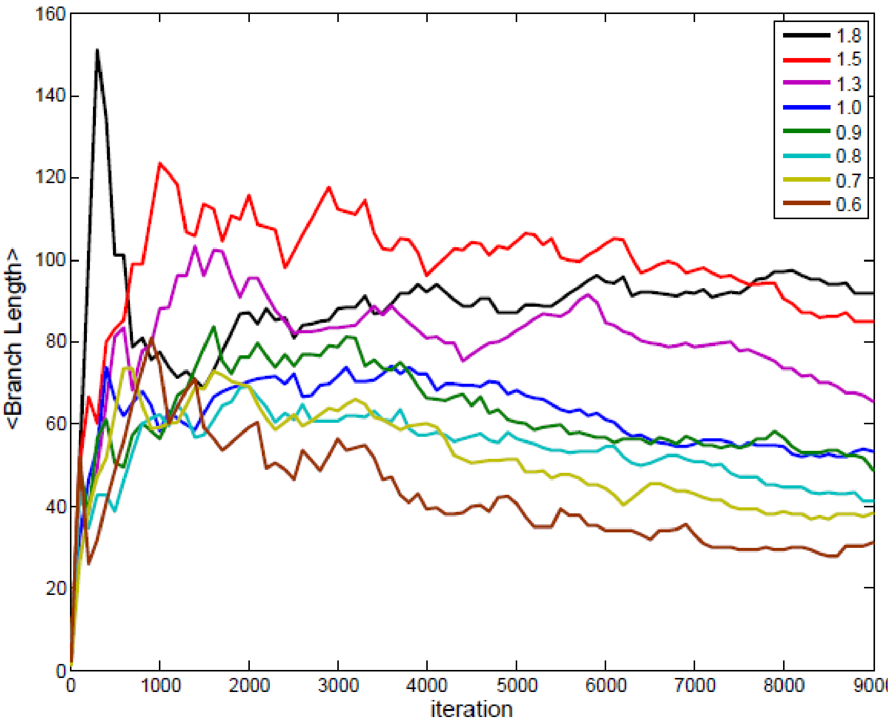
Properties of the networks





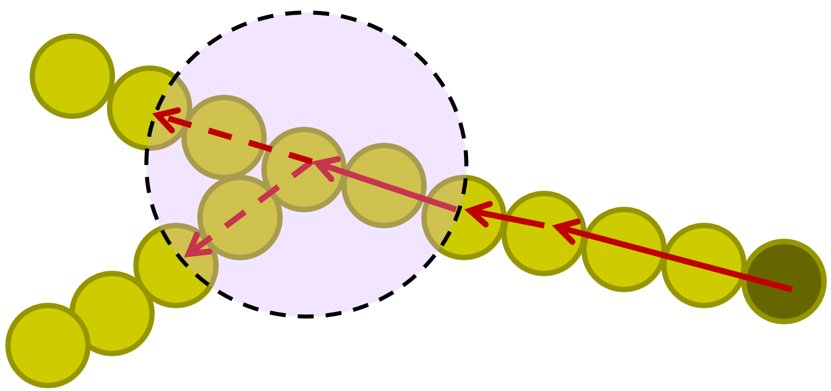
Properties of the networks



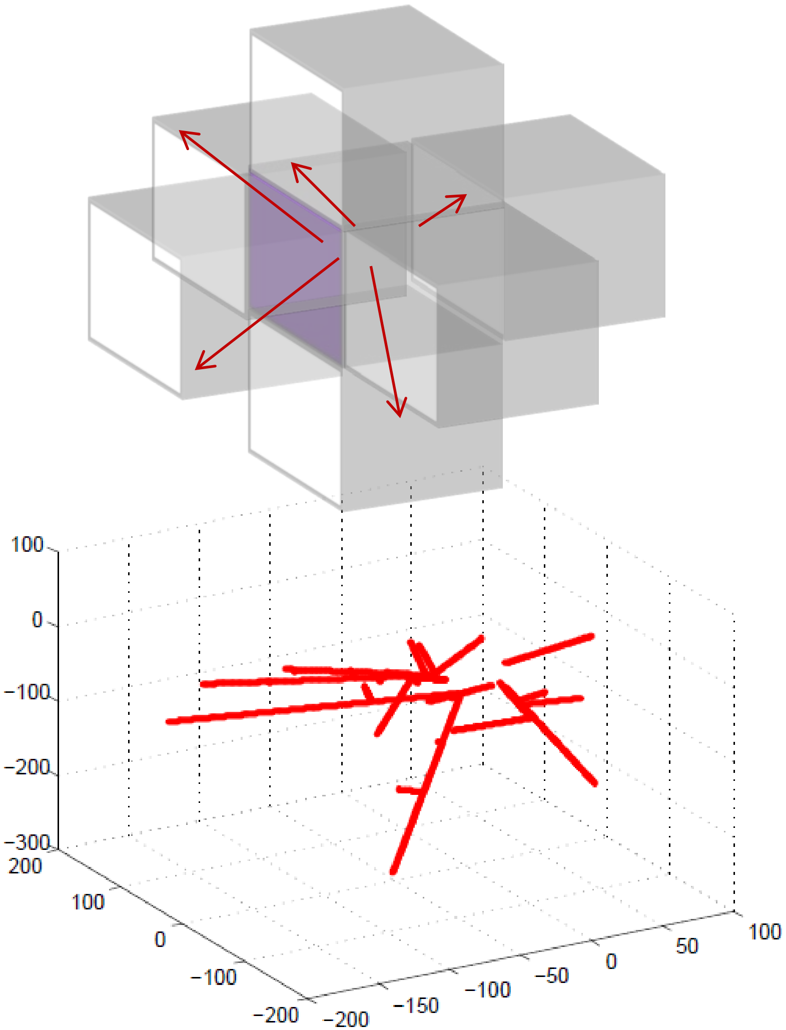


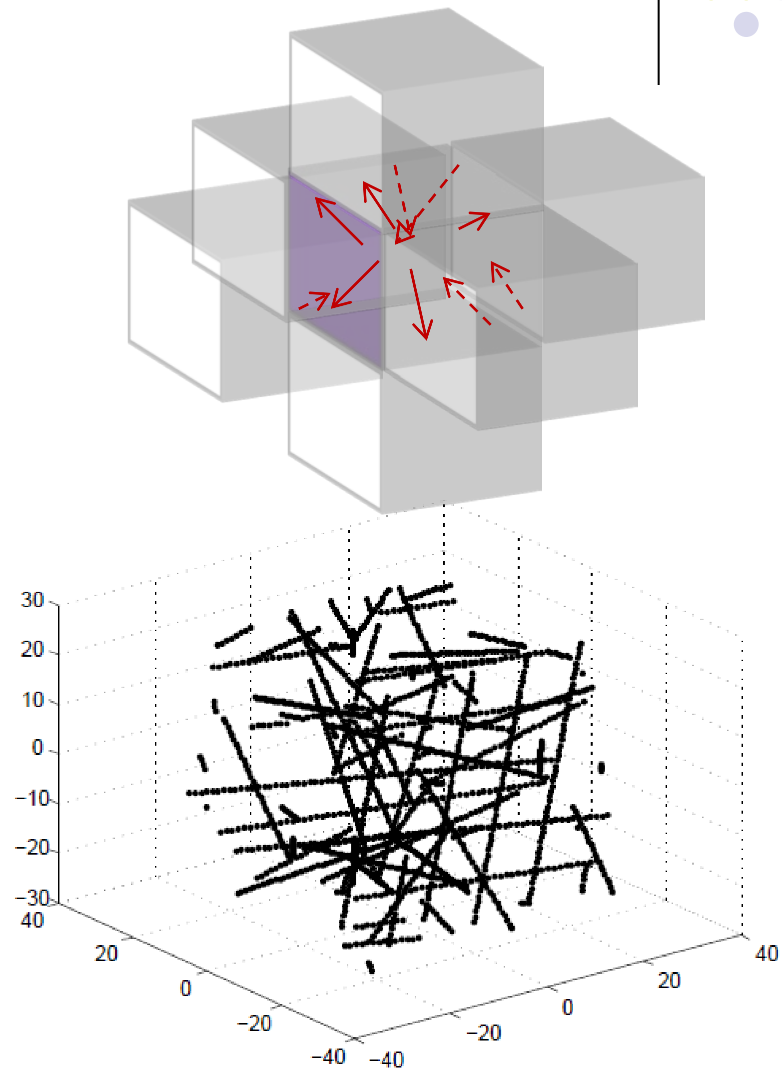
Modeling motor movement

- Put cargo on one of random branch points
- Forward movement 1 ~ 7 actin monomer (5~35nm)
- Equal transition probability when meet branching point

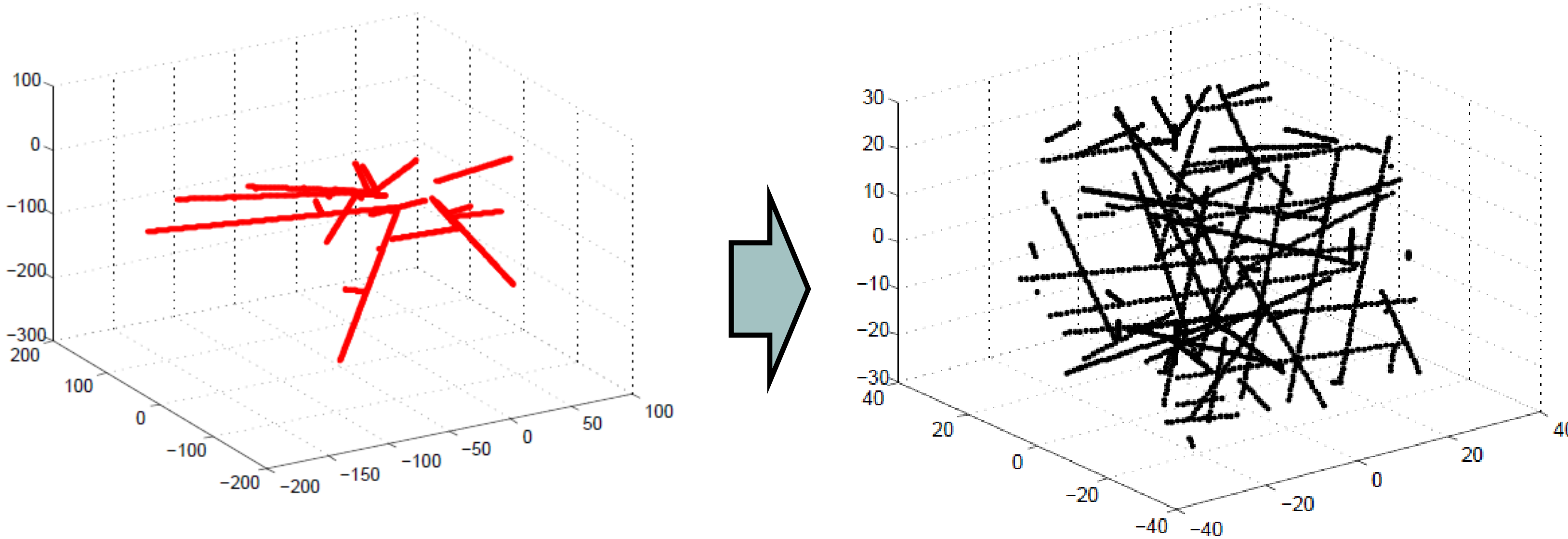


Modeling motor movement



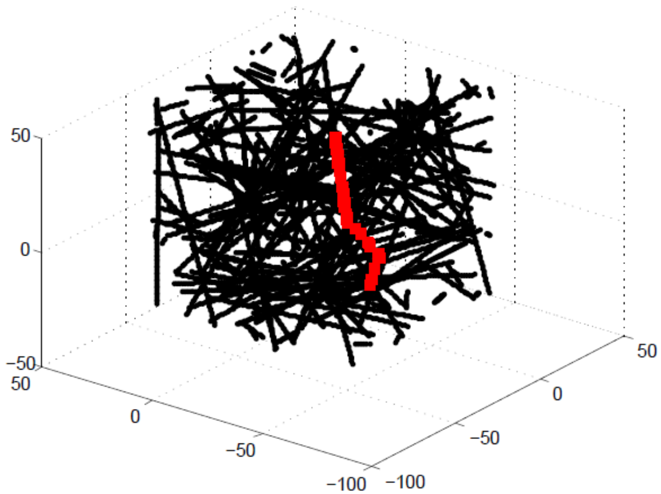


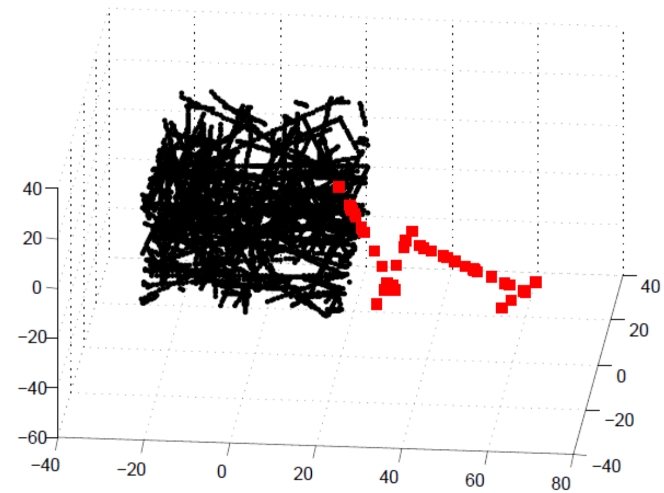
Modeling motor movement



- Impose periodic boundary condition
- Since each branch remembers their own directional vector
- Cargo take directional vector and Cargo can move ‘through’ periodic boundary condition.

Modeling motor movement

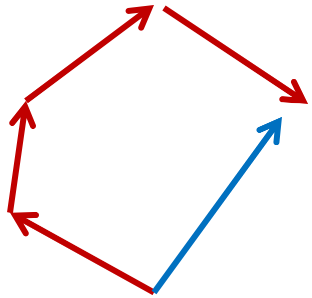




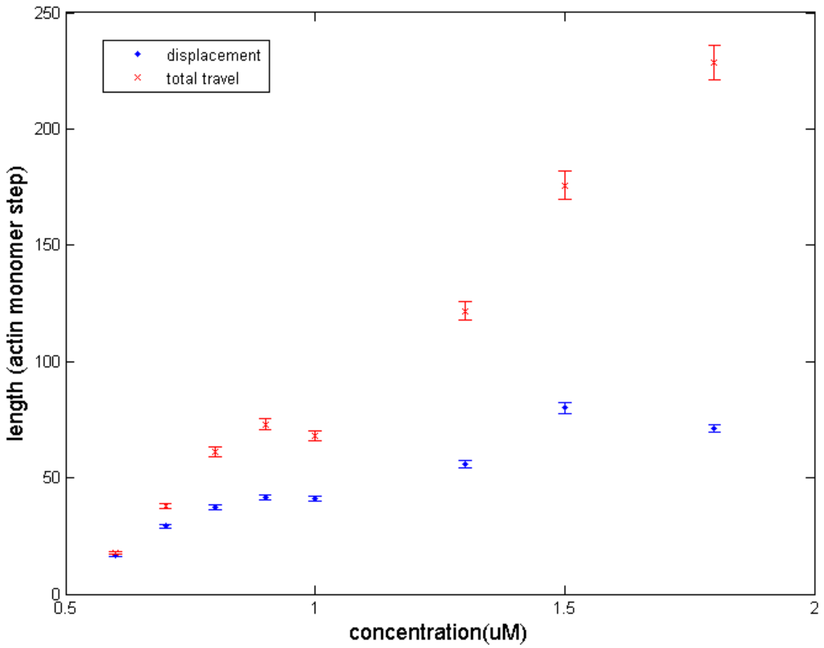
- Depends on initial concentration, branches show dense or sparse picture in periodic boundary condition.
- Cargo movement shows short or long path depends on actin filament patterns.

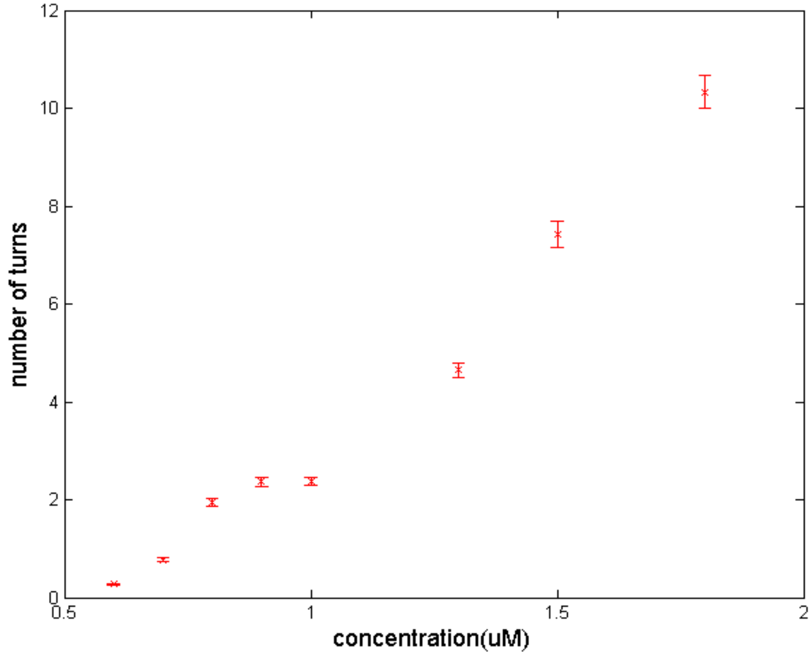
Modeling motor movement

- Extract a configuration of actin filament at given initial concentration from Actin Filament Network simulation.
- Run 1000 run for each initial condition and average out .
- Look at the “travel distance” (Red), and “displacement” (Blue).



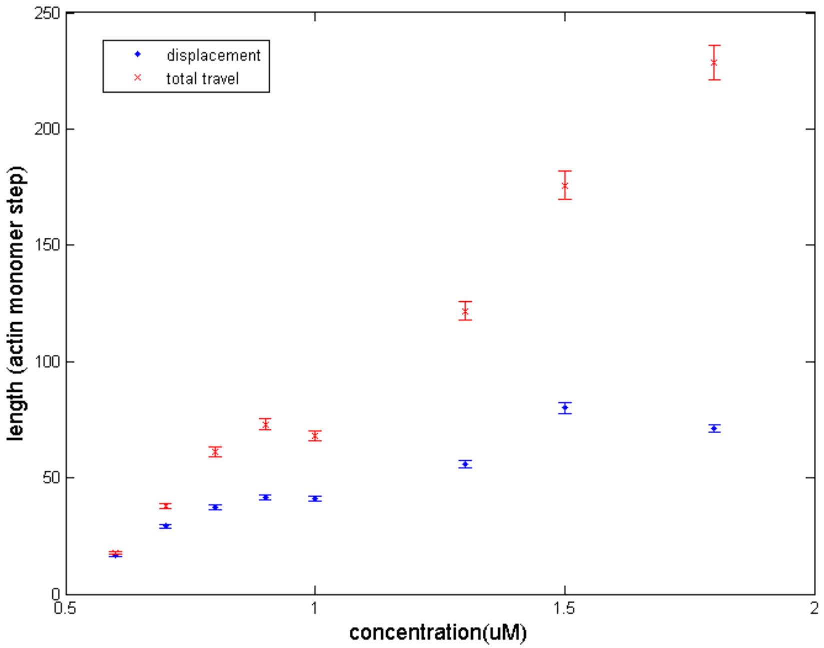
Properties of cargo movement

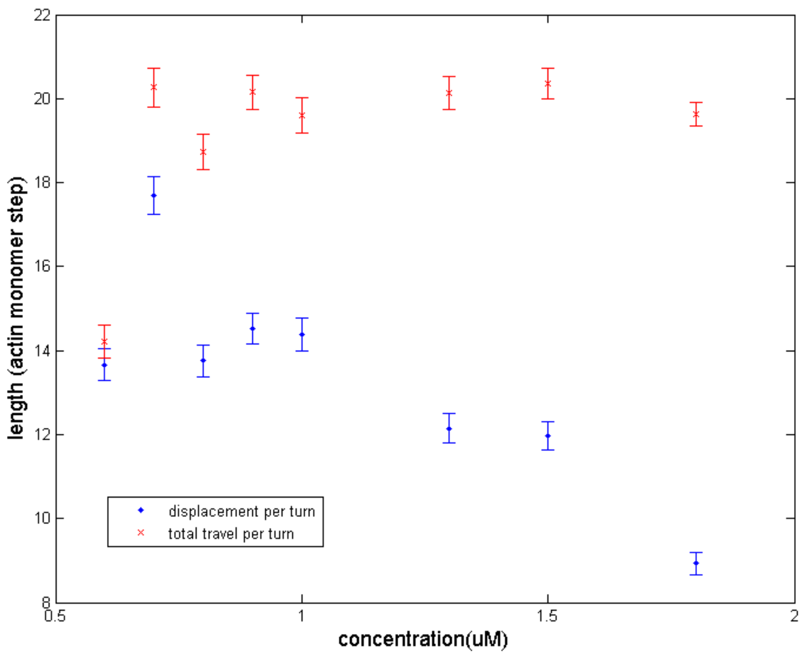




- For higher concentration, cargo makes more turn, and travel more distance.
- While travel distance increases, displacement is saturated.

Properties of cargo movement





- Cargo moves similar distance before it hops to another branch.
- However, displacement goes to saturate which means cargo movement is 'local'.

Conclusion

- Generate Actin filament patterns at different actin concentrations.
- Higher concentration leads to longer branches and low concentration leads sparse patterns and shorter branches.

- The denser the pattern, the more distance cargo travels.
- However, displacement of cargo does not change as much.