Computational Models of Self Organization of Neuronal Cytoskeleton

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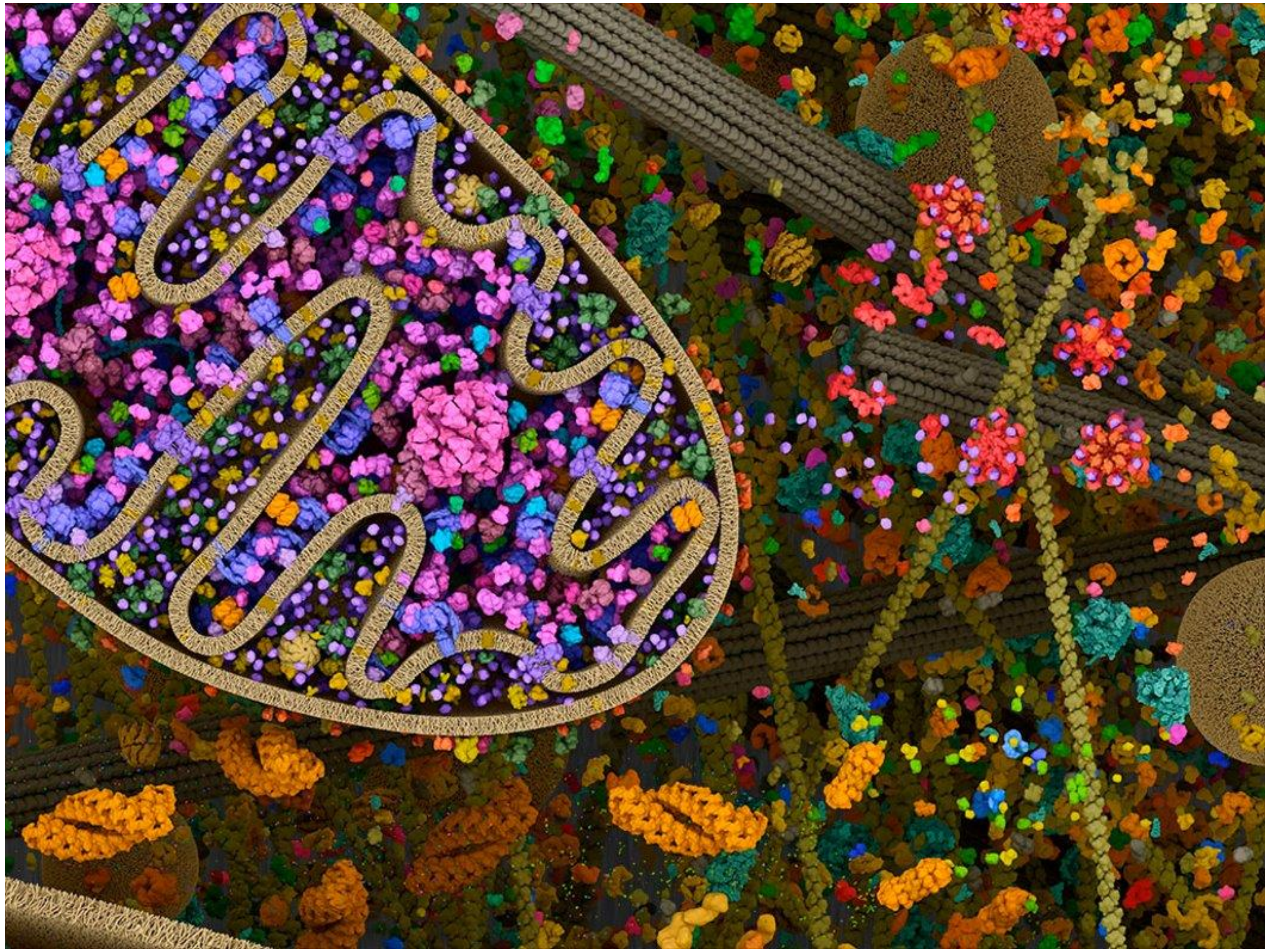
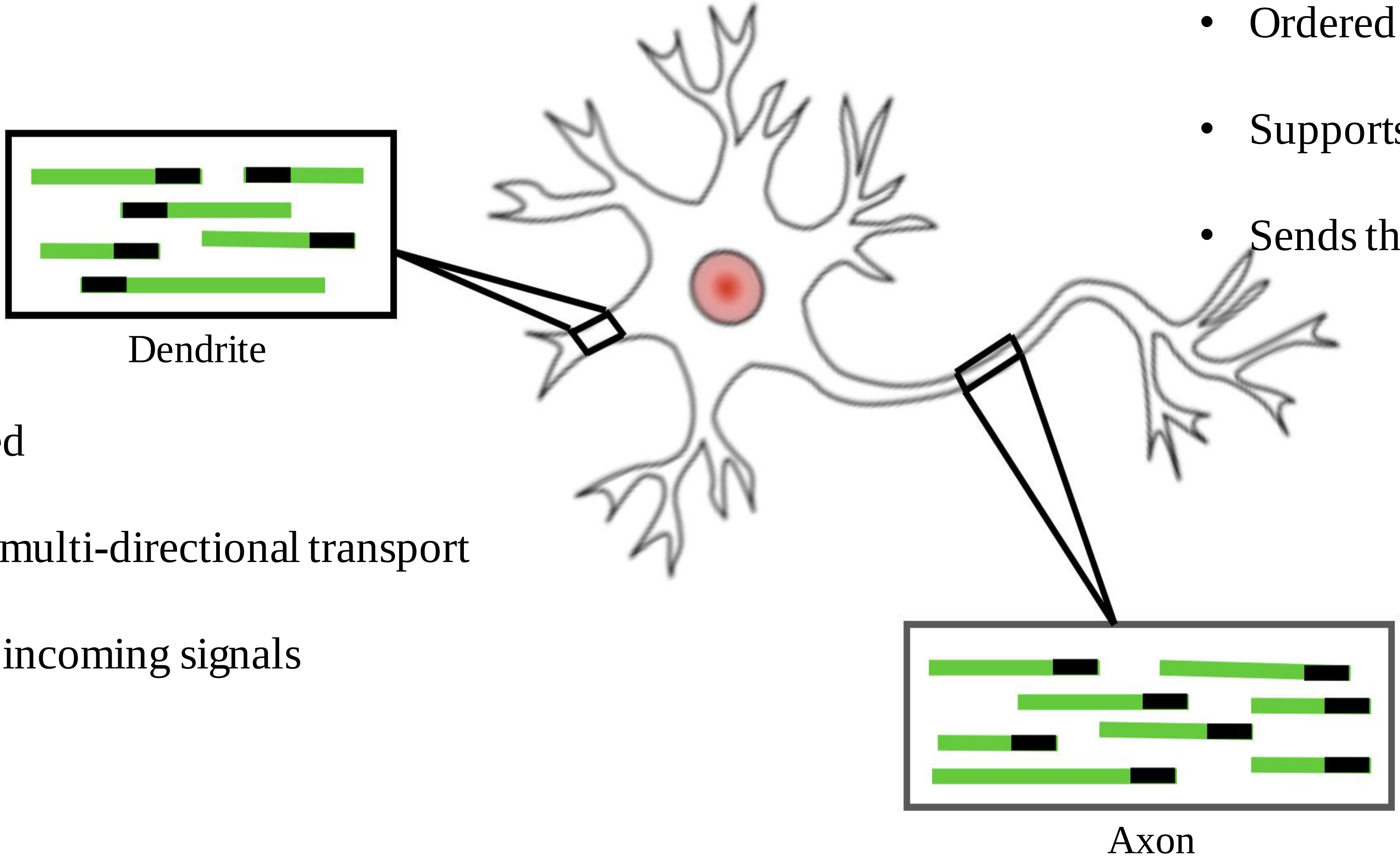
Physics of Cell Biology



- Crowded
- Highly viscous
- Intricately-timed dynamic processes
- Physical principles determine biological function

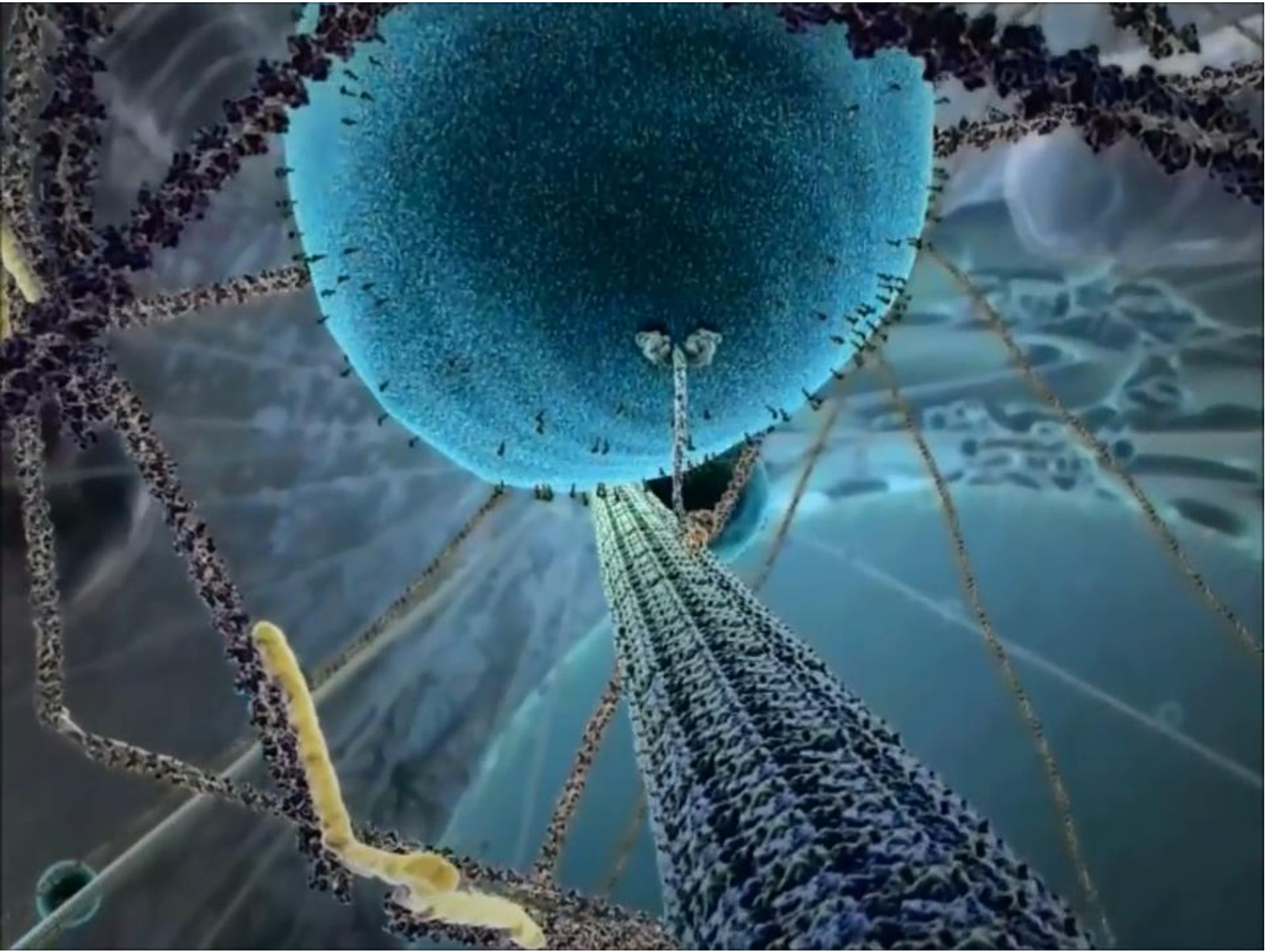
Microtubule Organization in the Neuron



- Unordered
- Supports multi-directional transport
- Receives incoming signals

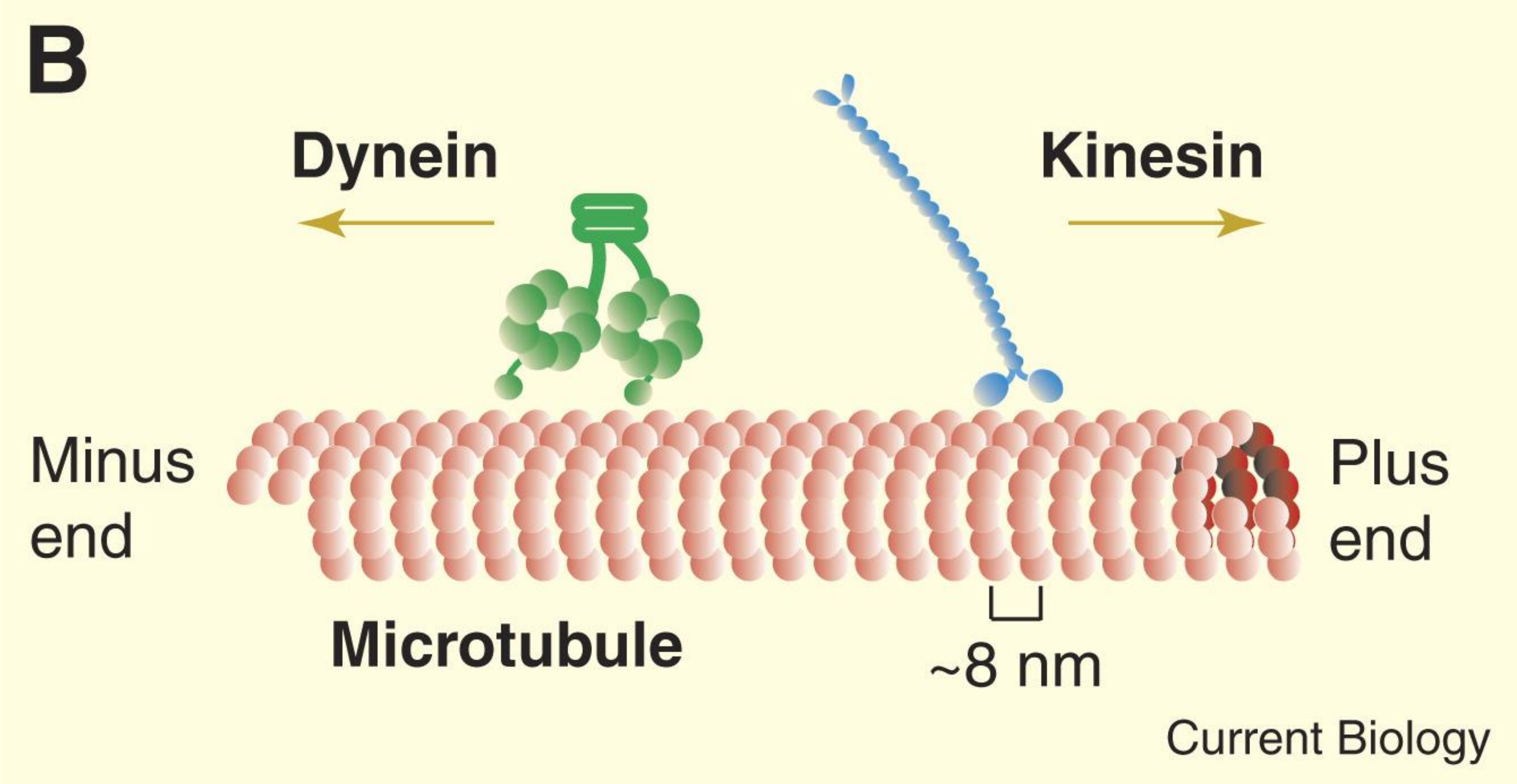
- Ordered in healthy neurons
- Supports one-way transport
- Sends the outgoing signals

The Role of Motor Proteins



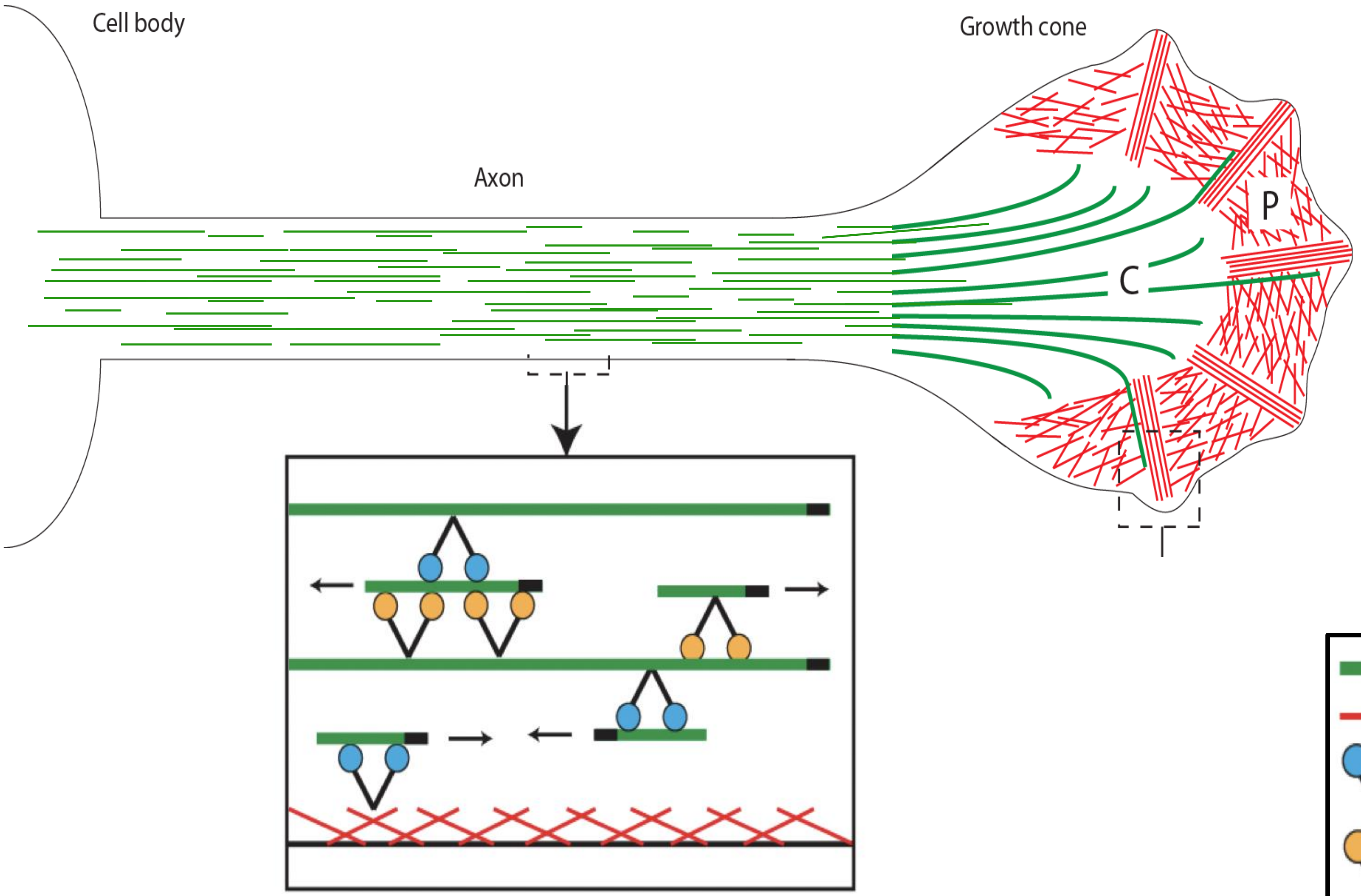
- A motor protein carries cargo along a microtube
- The motion of the “feet” has been smoothed; on the cellular level it is random with a tendency towards forward motion

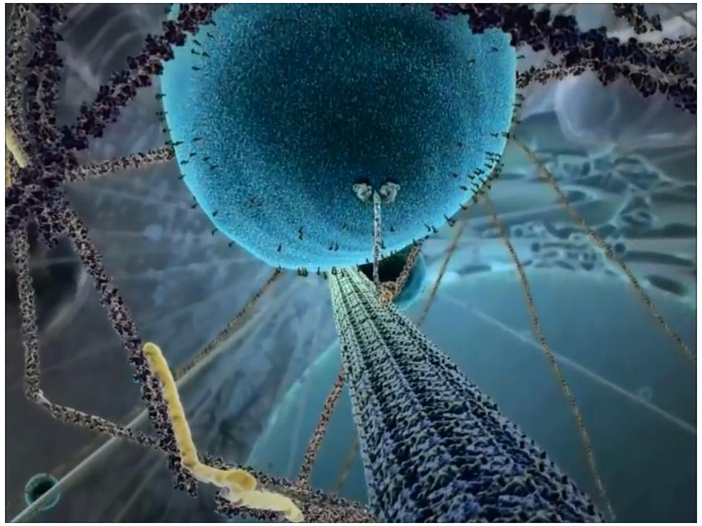
The Type of Motor Proteins

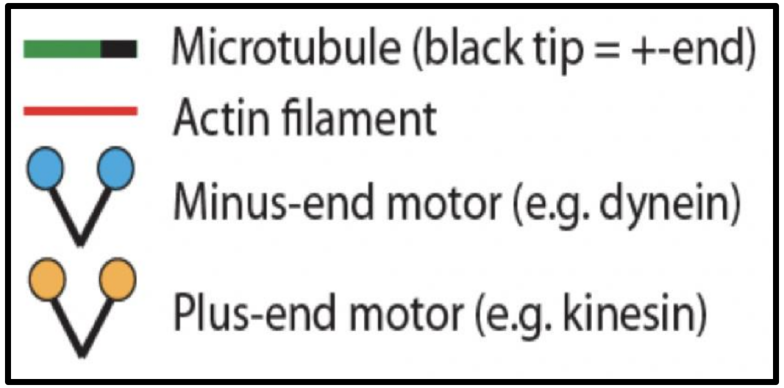


Each motor has a preferred direction to walk on the microtube. Kinesin walks in the same direction the microtube points while Dynein walks in the opposite direction.

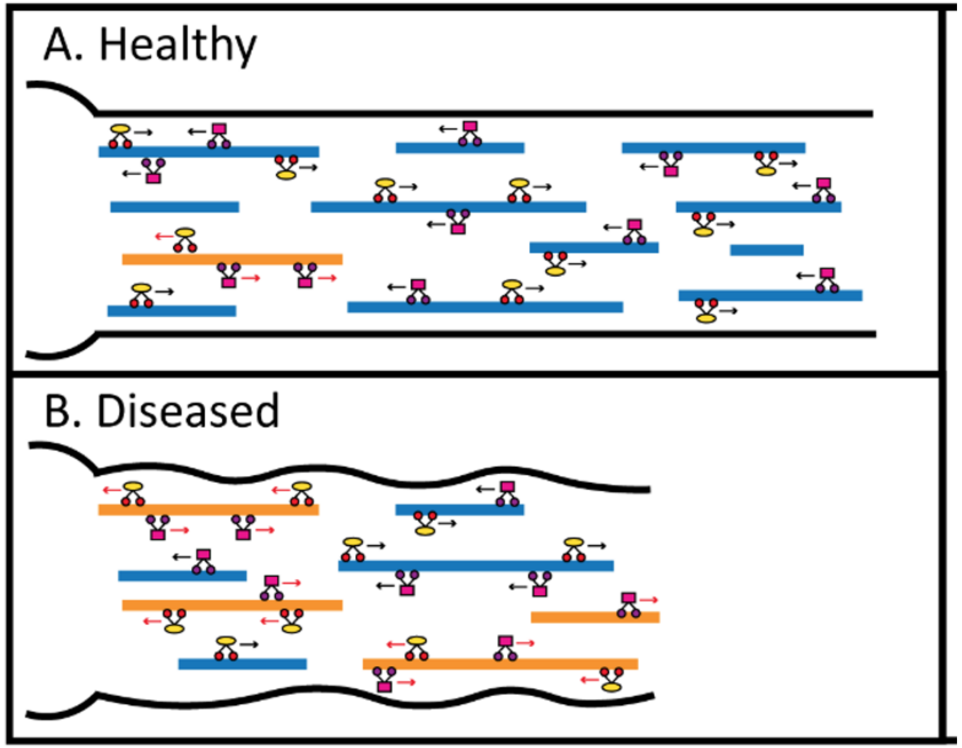
Microtubule Organization in the Axon

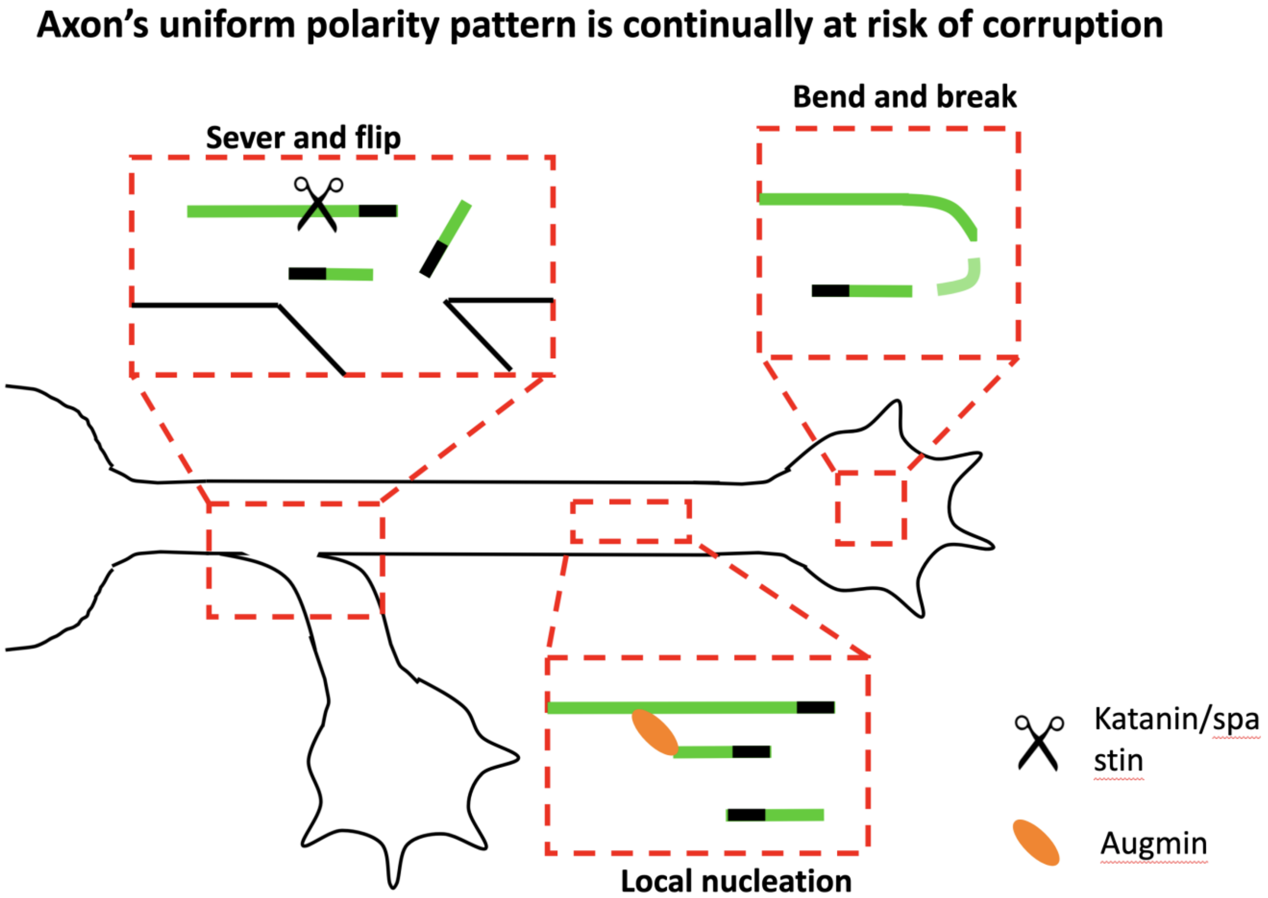






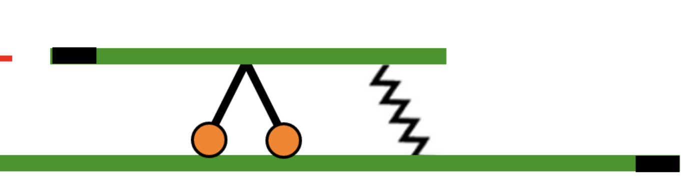
Corruption of the Polarity Pattern

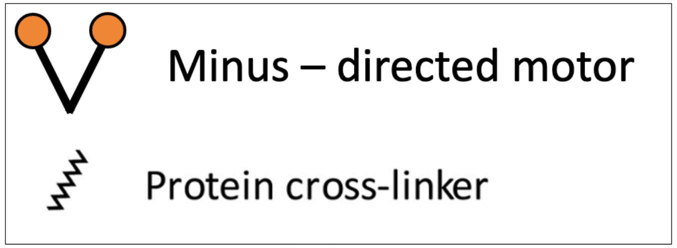




Damage to the polarity pattern may arise from a variety of sources. Significant local damage to the polarity pattern impacts cargo transport and creates traffic jams of molecular motor proteins.

Computational Model for Forces on Microtubes





- Net 0 force assumption due to high fluid viscosity
- Essentially objects do not move except when under active forces

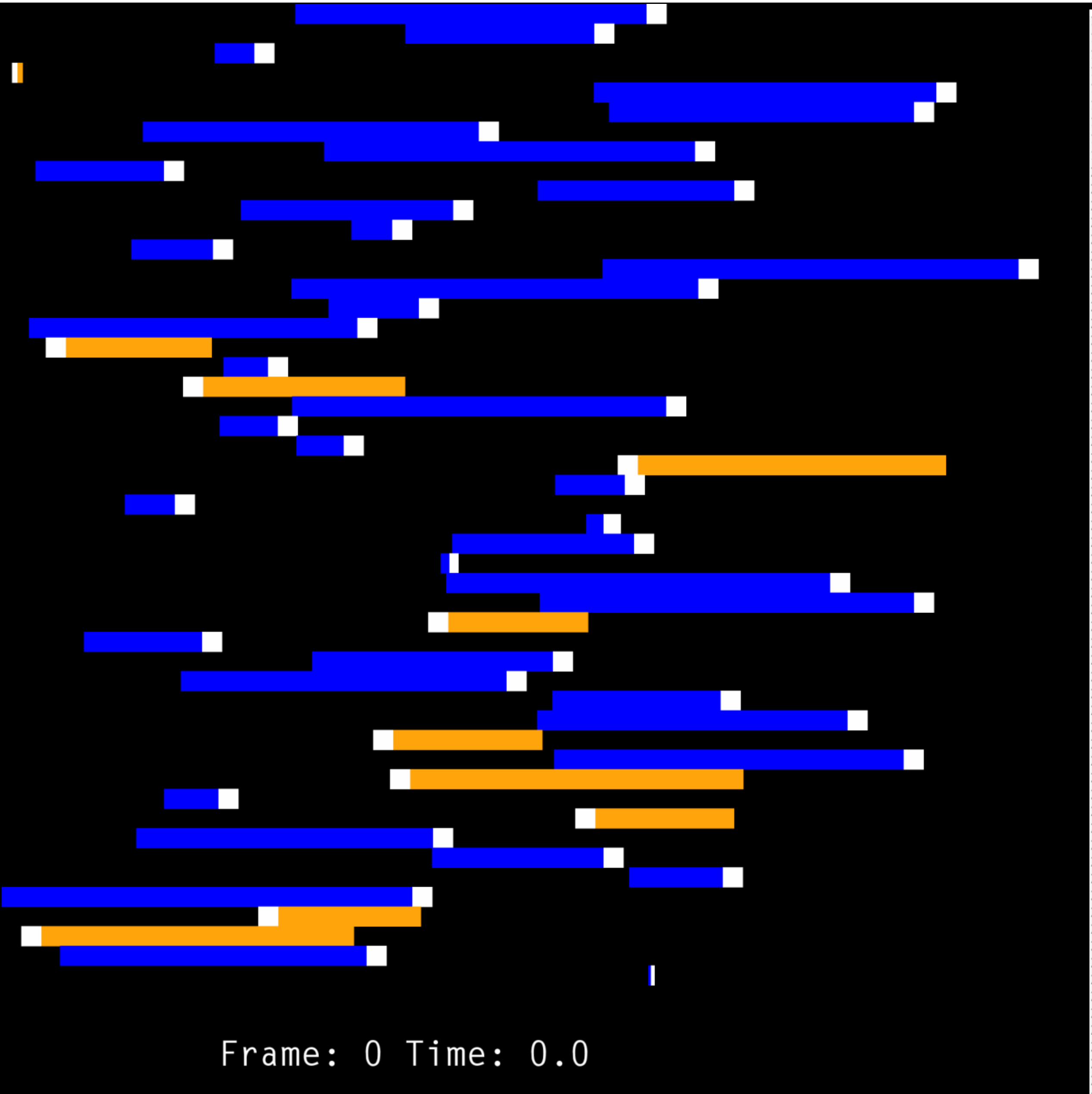
nber of attached cytoplasmic dynein motors, N_d:

$$\frac{dN_d}{dt} = \underbrace{r_{d,on}}_{\substack{\text{achment} \\ \text{nds on \# of} \\ \text{able sites)}}} - \underbrace{r_{d,off} N_d}_{\substack{\text{Detachment} \\ \text{(Force-dependent)}}}$$

Balance of forces:

$$\underbrace{F_{d+}}_{\substack{\text{Motor forces} \\ \text{(+ end leading)}}} = \underbrace{F_{d-}}_{\substack{\text{Motor forces} \\ \text{(- end leading)}}} + \underbrace{N_x \gamma v}_{\substack{\text{Resistance from} \\ \text{cross-linkers}}} + \underbrace{\xi L v}_{\substack{\text{Filament drag} \\ \text{force}}}$$

Computational Model for Forces on MTs




```
        % Update position at time i+1 based on position and velocity at time i

        A(i+1,2,j)=A(i,2,j)+A(i,3,j)*dt; % Translocate MT based on vel calculated for this time step
        A(i+1,11,j)=A(i,11,j); % Default is for orientation to stay the same. Several possibilities later for this to flip.
        % Apply conditions for if MT reaches a boundary
        if (A(i+1,2,j)<0) % MT has been cleared from axon into cell body
            'MT cleared';
            % Replaced cleared MT with a new short growing MT, random
            % location and orientation
            A(i+1,2,j)=Laxon*rand([1,1,1]); % random location
            A(i+1,3,j)=0.0; % Initial velocity (v)
            A(i+1,4,j)=0.0; % Initial force (Fdp)
            A(i+1,5,j)=0.0; % Initial force (Fdm)
            A(i+1,6,j)= 0.0; % Initial dynein attachment number, forward pulling (Ndp)
            A(i+1,7,j)=0.0; % Initial dynein attachment number, backward pulling (Ndm)
            A(i+1,8,j)=0.0; % Initial cross-linker attachment number, parallel MTs (Nxpar)
            A(i+1,9,j)=0.0; % Initial cross-linker attachment number, anti-parallel MTs (Nxanti)
            A(i+1,10,j)=0.1; % Short initial length, 0.1micron for newly nucleated MT

            % Fraction of plus-out MTs at new MT's location
            loc=round(A(i+1,2,j));
            Fmin=Polarity(loc+1,3);
            if(rand<Fmin) % Newly nucleated MT has random orientation
                A(i+1,11,j)=1; % minus-end-out
                'minus out new MT';
            else
                A(i+1,11,j)=0; % plus-end-out
                'plus out new MT';
            end


            A(i+1,12,j)=1; % dynamic and growing
        elseif(A(i+1,2,j)>Laxon) % MT hits distal end
            A(i+1,2,j)=Laxon; % Can't grow further
            A(i+1,12,j)=0; % Switches to stable
        end

        % Update length of dynamic MTs
        if(A(i,12,j)==0)
            A(i+1,10,j)=A(i,10,j);
        elseif(A(i,12,j)==1)
            A(i+1,10,j)=A(i,10,j)+V_MTPoly*dt;
            if(A(i+1,10,j)>Laxon)
                A(i+1,10,j)=Laxon;
            end
        elseif(A(i,12,j)==2)
            A(i+1,10,j)=A(i,10,j)-V_MTdePoly*dt;
        end

        % Apply conditions for if MT length shrinks to zero, nucleate new MT
        if(A(i+1,10,j)<0)

            A(i+1,3,j)=0.0; % Initial velocity (v)
            A(i+1,4,j)=0.0; % Initial force (Fdp)
            A(i+1,5,j)=0.0; % Initial force (Fdm)
            A(i+1,6,j)= 0.0; % Initial dynein attachment number, forward pulling (Ndp)
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            A(i+1,9,j)=0.0; % Initial cross-linker attachment number, anti-parallel MTs (Nxanti)
            A(i+1,10,j)=0.1; % Short initial length, 0.1micron for newly nucleated MT

            %
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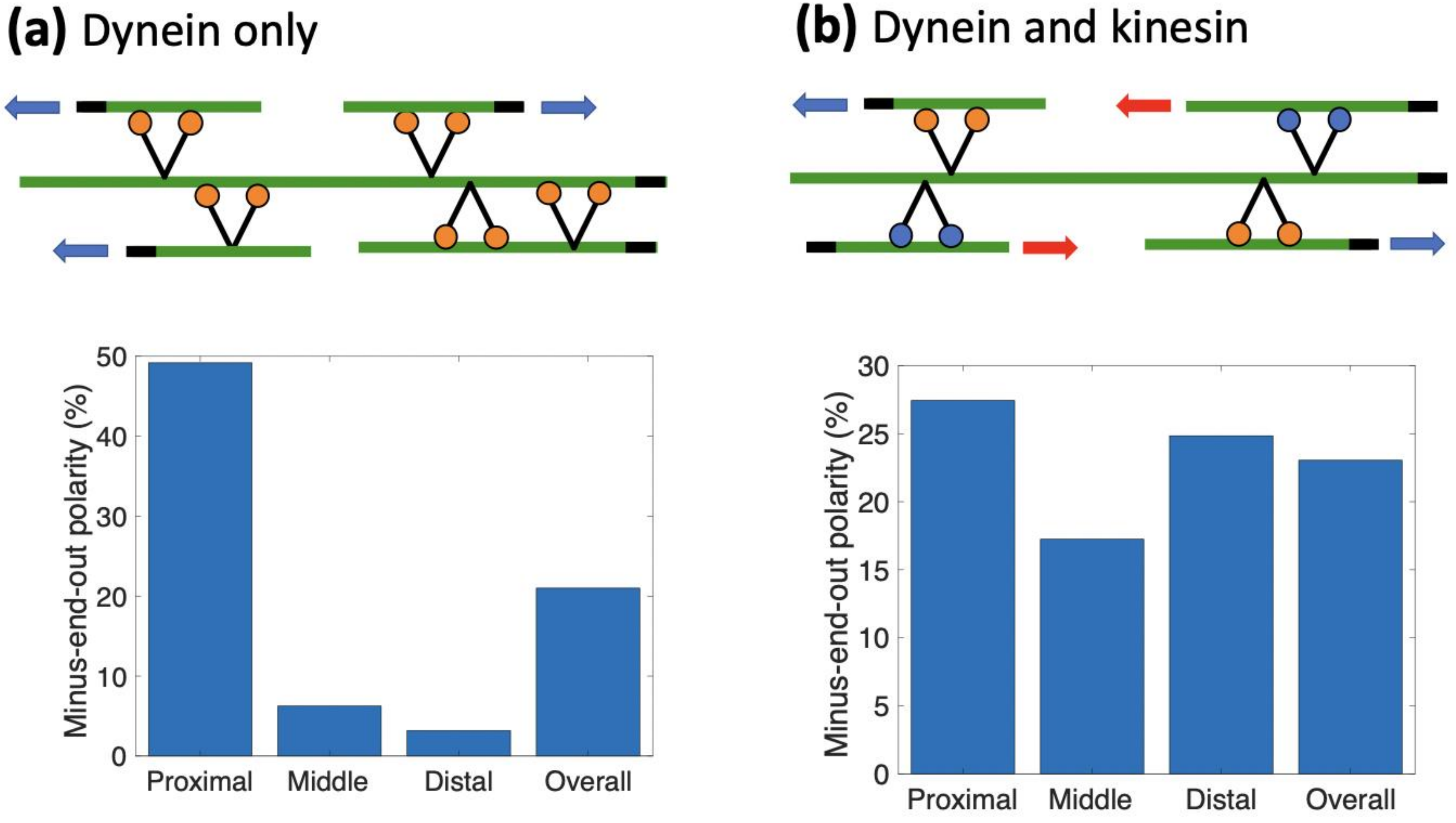
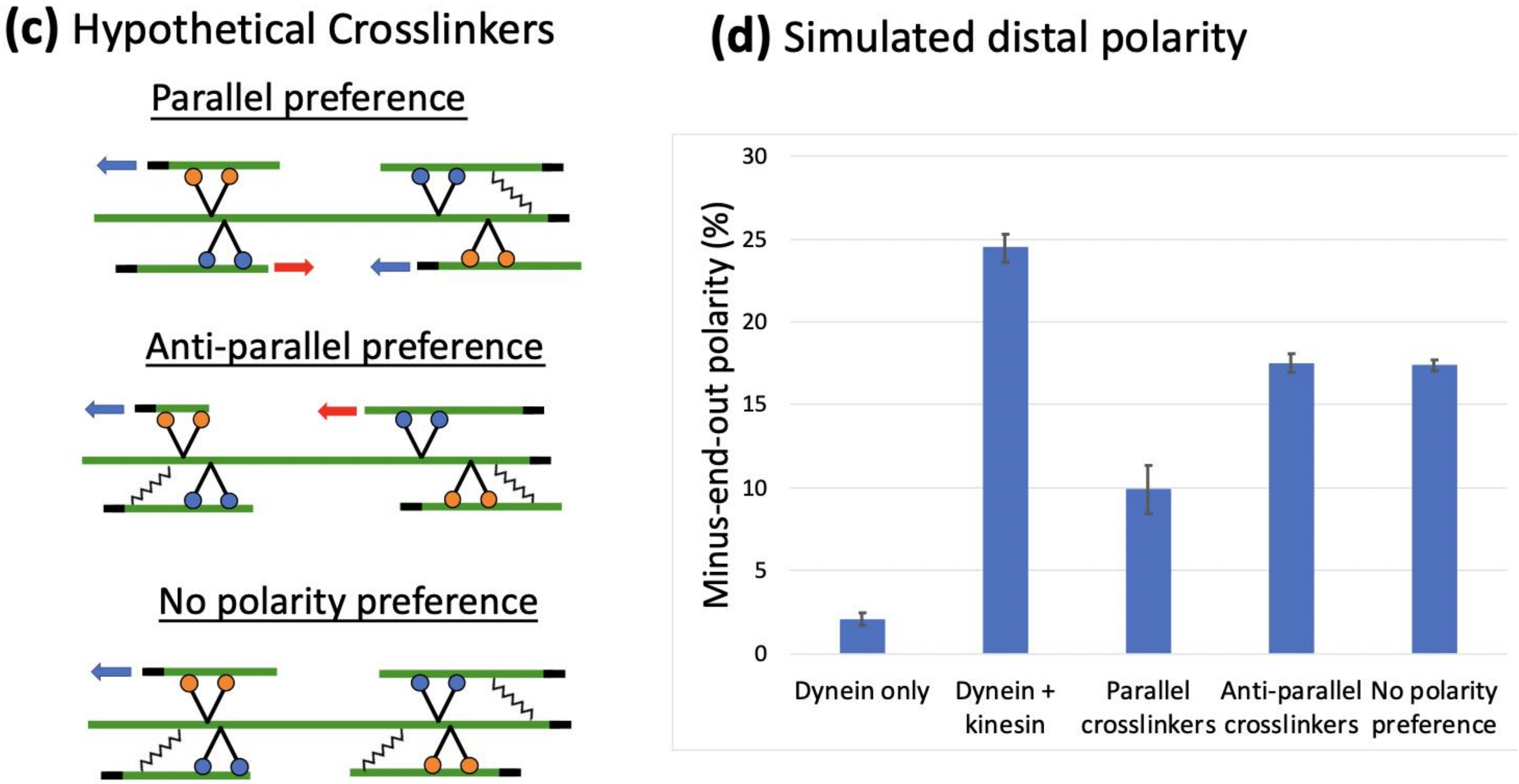
Result:

Kinesin prevents Dynein-based polarity sorting



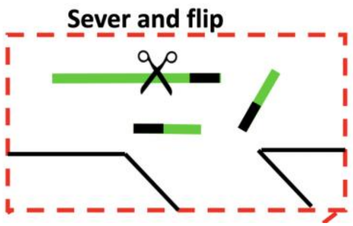
Result:

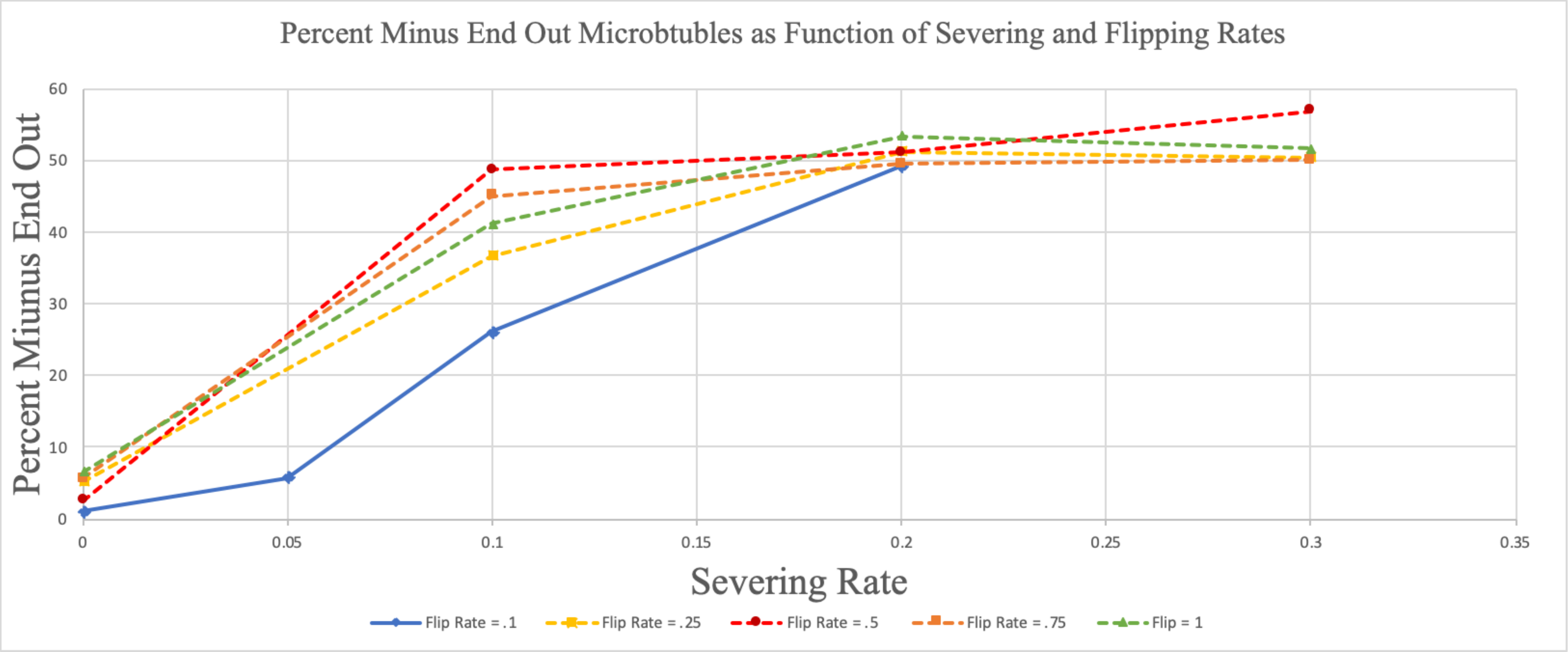
Certain types of crosslinkers impact polarity sorting more than others



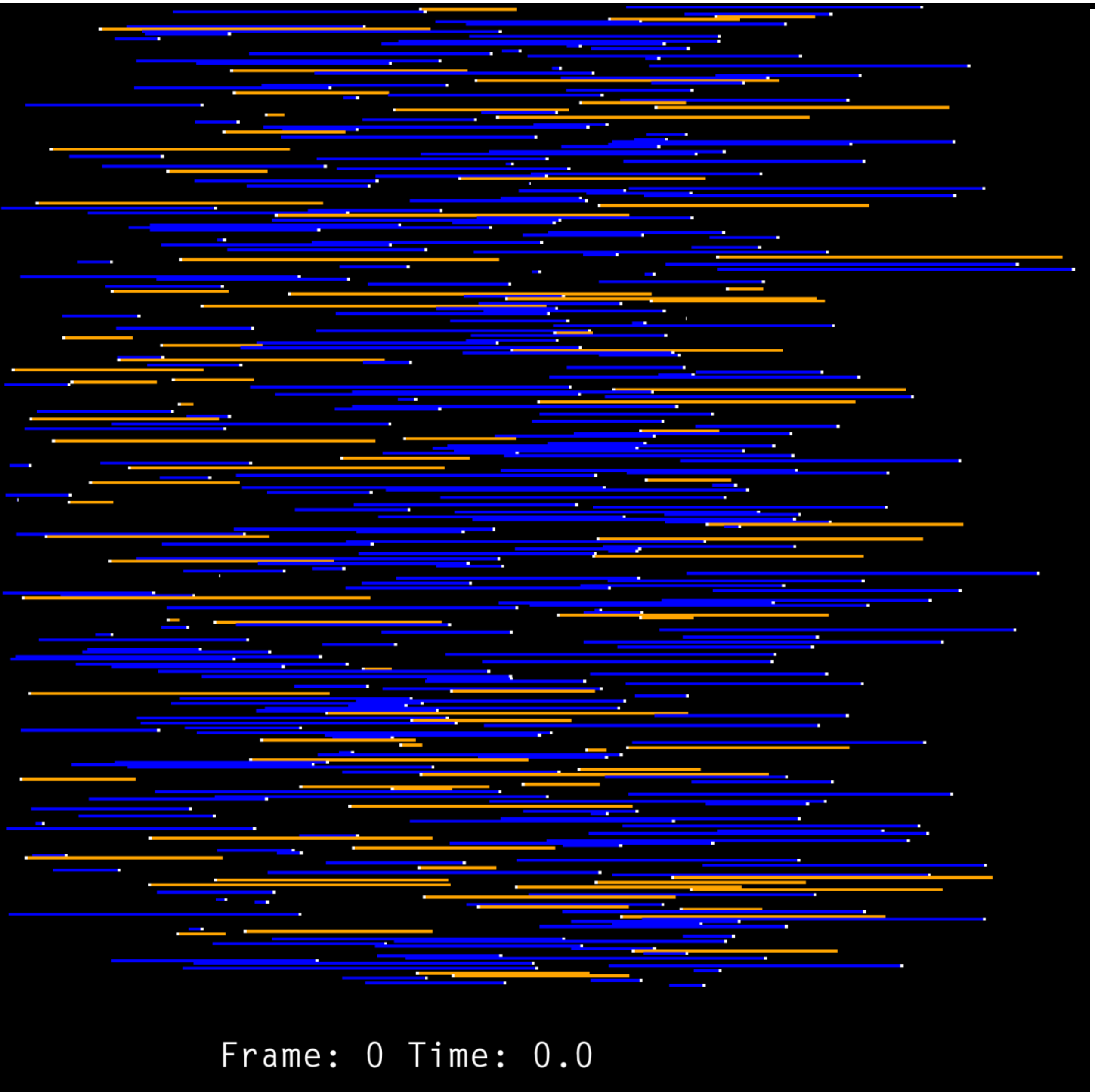
Result:

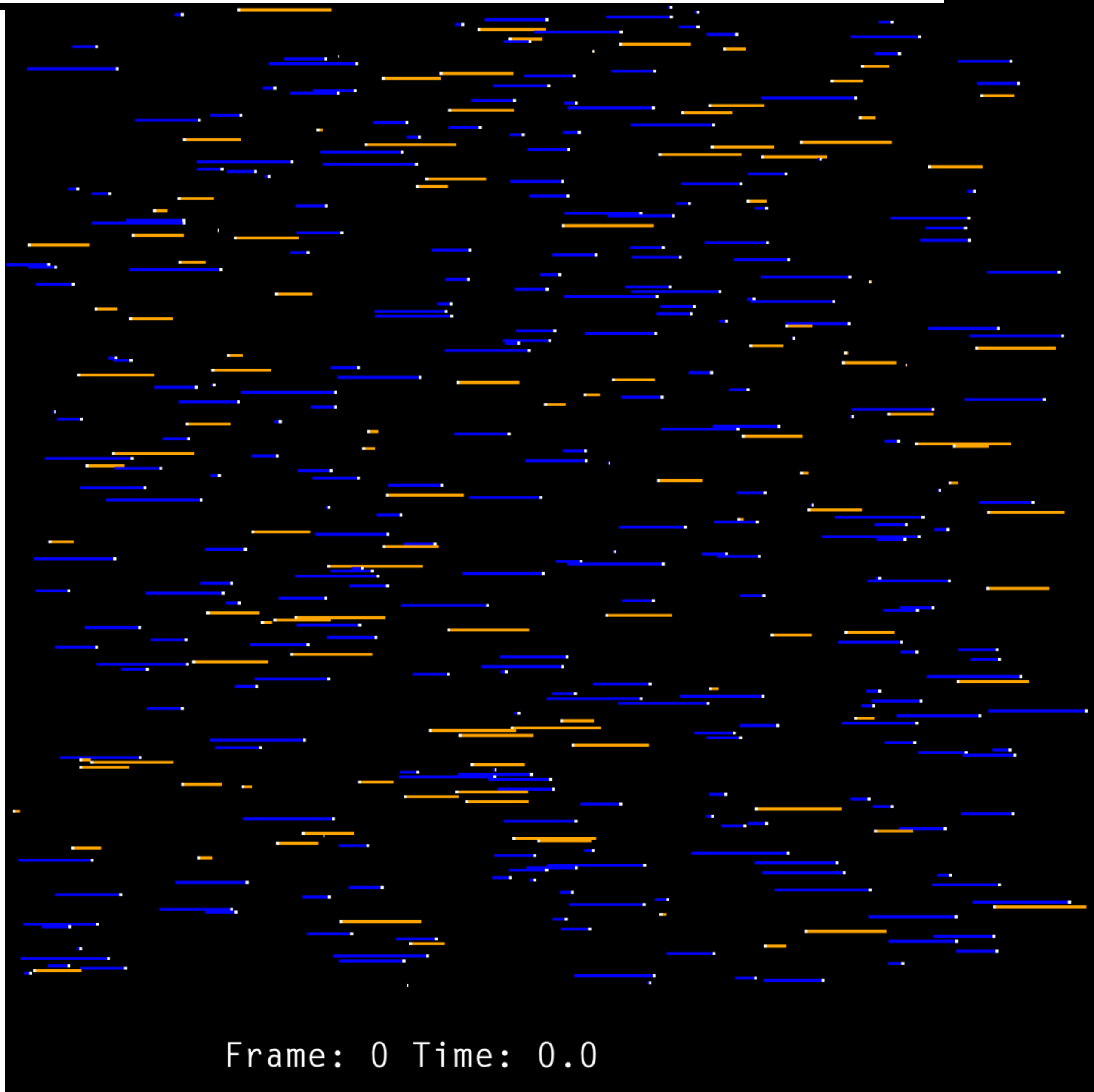
Severing and flipping are important in moderation for polarity sorting





Result:





Conclusion

- Our models show how severing and flipping impact polarity sorting, being necessary but only to an extent
- We can visualize this model to gain further intuition and demonstrate experimentally testable predictions

Next Steps

- Experimental test of model predictions.

  Related study: Rao et al., 2017.

- Investigate the impact of polarity flaws on neuronal function.

  Related study:
  Eckel et al., 2022.

Acknowledgements

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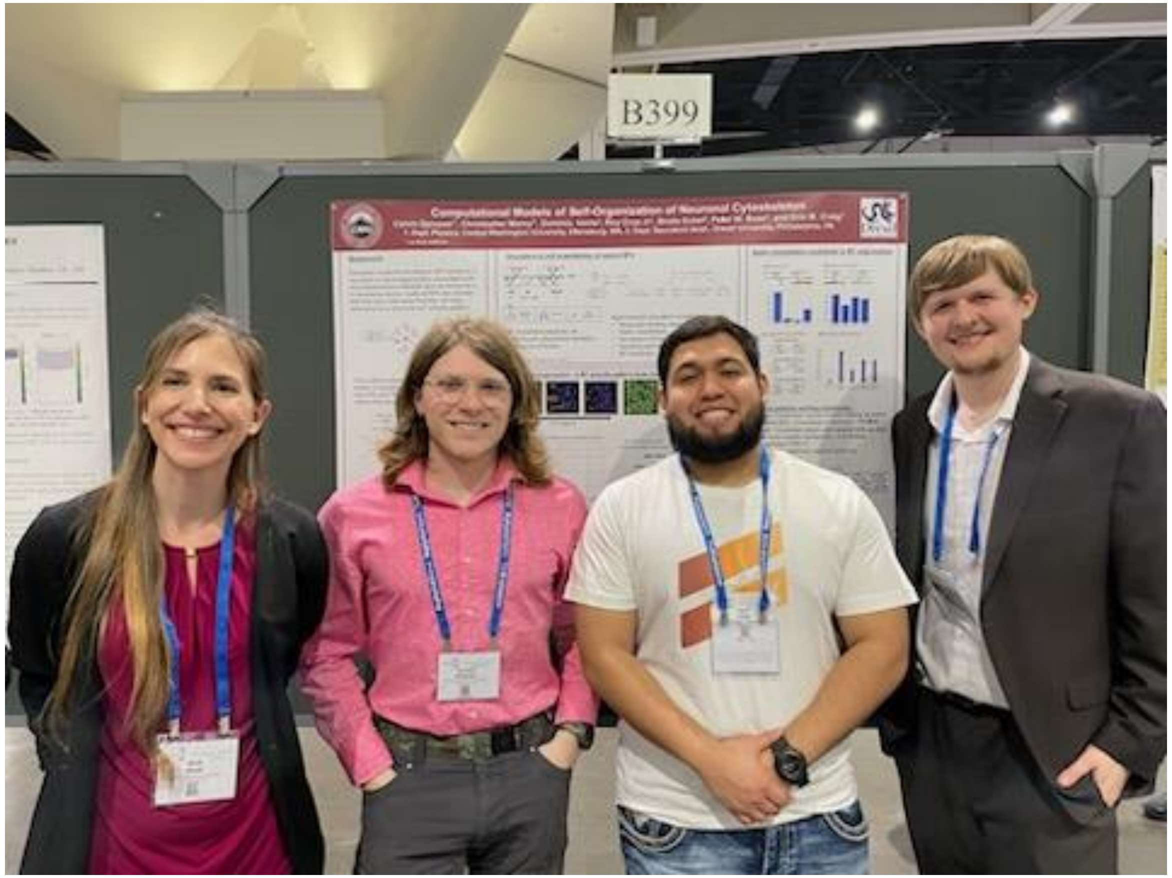

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1. Rao, A.N. and Baas, P.W. (2017), Polarity Sorting of Microtubules in the Axon, Trends in Neuroscience, 41(2):77-88.
2. Craig et al. (2017), Polarity sorting of axonal microtubules: a computational study, Mol. Biol. Cell, 28(23):3271–3285.
3. Rao et al. (2017), Cytoplasmic dynein transports axonal microtubules in a polarity-sorting manner, Cell Reports, 19:2210-2219.
4. Eckel et al. (2022). Microtubule polarity flaws as a treatable driver of neurodegeneration., Brain Research Bulletin, 192:208-215.

See more animations here!