Cytoskeleton Filaments and Their Potential Role in Electrical Activities of Healthy and Dysfunctional Neurons

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Abstract

Actin and microtubule are two cytoskeleton filaments found in all eukaryotic cells. The binding protein tau secures microtubule bundles in neuronal axons. In Alzheimer's disease, tau proteins detach from microtubules and polymerize into filaments. These tau filaments then amass into neurofibrillary tangles. On the other hand, actin filaments in Alzheimer's disease neurons stabilize to form rods or paracrystals. Though these cytoskeleton pathologies can produce synaptic dysfunction, the relations between them and the pathways developing dementia associated with Alzheimer's disease are unknown.

Learning and memory, impaired in dementia, are formed through synaptic potentiation—strengthening of neuronal connections, the synapses. The biophysical understanding of synaptic potentiation still needs to be completed. Nevertheless, we know that potentiation is a frequency-dependent phenomenon.

Due to their electrical properties, actin filaments and microtubules act as bio nanowires capable of transmitting electric currents. In addition to transmission, microtubules can amplify signals and generate oscillations. The frequency of microtubule oscillation is compatible with brain frequencies. However, biophysical models for microtubule oscillation still need to be developed.

Tauopathies in Alzheimer's disease can potentially disrupt microtubule bundling in axons, which can then affect oscillation and alter potentiation, i.e., memory and learning. Therefore, the electrical properties of the cytoskeleton can presumably determine the onset of Alzheimer's disease and many more.

This presentation comprises software—developed by our group—to study electrical signal propagation along cytoskeleton filaments in physiological and pathological conditions. We found that changes in the filament surface charge, intracellular temperature, pH level, and mutations—usually associated with many disease conditions—produced significant modifications to the electrical current properties. Currently, we are extending our actin model to microtubules to elucidate oscillation. These approaches will create a new direction for studying the connection between cytoskeletal pathologies associated with Alzheimer's disease and related dementia.

Actin and microtubule pathologies

In Alzheimer's disease:
- tau proteins detach from **microtubules** and form neurofibrillary tangles
- **actins** stabilize to rods and paracrystals

We **hypothesize** that the properties of electrical currents along actin and microtubules can provide pathological information for neurodegeneration.

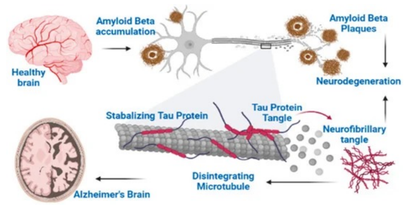


Figure. Neurofibrillary tangle is one of the hallmarks of Alzheimer's disease [1].

Electrical current along actin—Multiscale theory

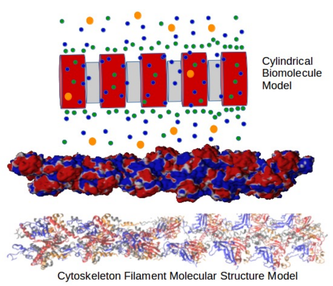


Figure: Actin; molecular structure model to cylindrical model.

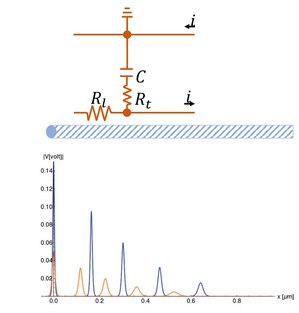


Figure: (top) Transmission line model; (bottom) soliton solution.

Electrical current pulses along cylindrical actin filaments in transmission line models decelerate and attenuate [2].

Modeling physiological and pathological conditions

Using multiscale theory, we used biophysical environmental parameters to model pathological and physiological conditions of actin filaments [3].

- **Ionic conditions**: invitro—modeled by 0.1M KCl, and intracellular—includes Na+ and HPO42- in addition to KCl.
- **Temperature**: Our considered range is 298K–320K.
- **pH:** in the range 6–8.
- **filament radius:** in the range of 23.83Å–50.00Å.
- **Nonlinear capacitance:** Classical density functional theory(CSDFT) calculations by JACFC web application—a Java web application developed by our group [4]—to get nonlinear capacitance parameters of actin filament for different temperatures and radii.
- **Surface Charge**: We estimated the surface charge densities of actin isoforms from our calculated surface charge for the alpha-skeletal actin monomer (-11e) and compared the amino acid sequences.
- **Mutations**: We considered all the charge-changing mutations reported by Parker *et al.* (2020) [5].

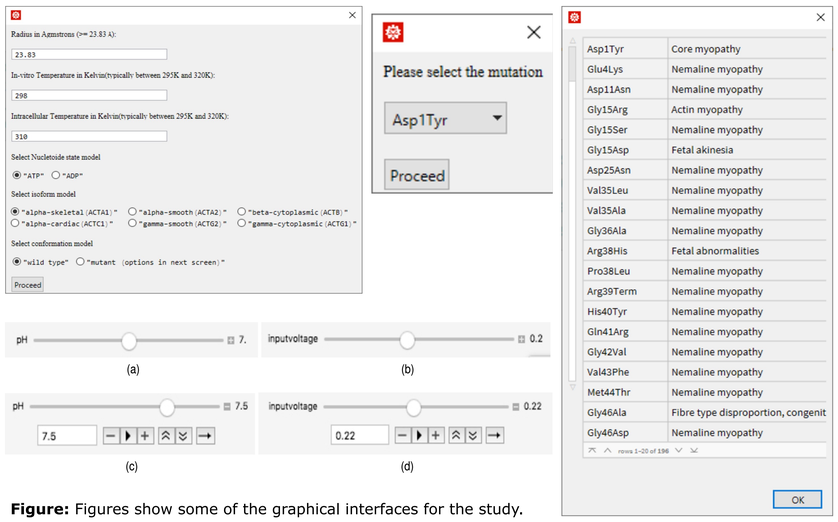


Figure: Figures show some of the graphical interfaces for the study.

Results

Effects of mutation on soliton propagation: A mutation that results in a higher negative charge shows a faster traveling wave.

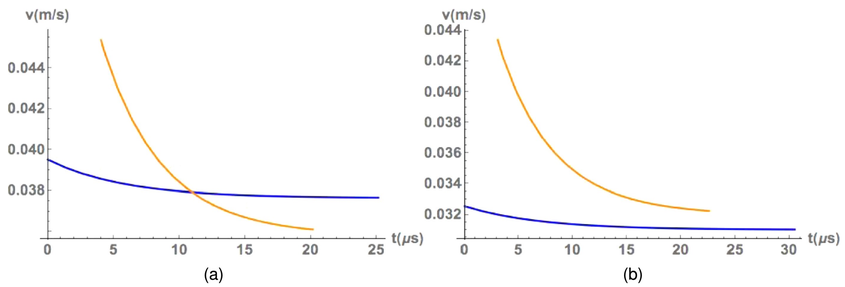


Figure. Impact of mutations on soliton velocity using the Gly36Arg and Glu362Lys missense mutations in subfigures (a) and (b), respectively. (T = 298.15K and T = 310K for invitro (blue) and intracellular (orange) electrolyte conditions.)

Results

Effects of pH change: Changes in the pH of the surrounding solution affect the current density profiles of actin filament and show a more drastic impact on the intracellular condition.

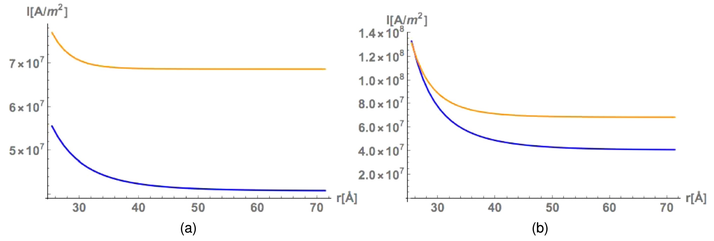
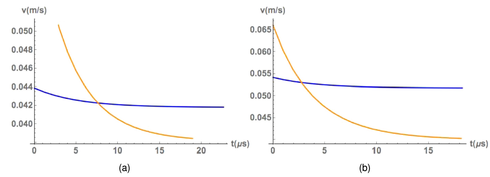


Figure: Current density profiles in the axial direction for pH 6 (subfigure a) and pH 7 (subfigure b). [R = 23.83Å]. The blue curves are for invitro conditions with T = 298.15K; the orange curves are for intracellular conditions with T = 310K.

Effects of temperature change: A temperature increase results in a wave packet with faster velocity, also the packet decay more rapidly. Thus, solitons travel approximately the same distance. (The effects are more pronounced in invitro conditions as we considered a more significant amount of temperature change in this condition.)



(left): Temperature effects on soliton velocity. Input voltage, V_0 = 0.15V.

(right): Temperature effects on the soliton peak attenuation.

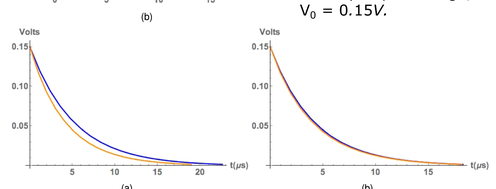


Figure: The radius, R = 23.83Å; the blue curves represent invitro conditions, and the orange curves represent intracellular conditions. The temperature is T=298.15 (invitro) and T = 310K (intracellular) for subfigures (a), and T=310K (invitro) and T = 313K (intracellular) for subfigures (b).

Discussions

- Temperature changes and pH differences, known to occur in disease conditions, resulted in different ion accumulations at the surface of the actin filament. Therefore, ionic conductivities and wave packet velocities are affected.
- A missense mutation only replaces one amino acid in an actin monomer; However, when it changes charge, the wave packet velocity shows a significant effect.
- We are working on a model for propagating and generating electrical oscillation in microtubules.

References

[1] Abduljawad, Asaad A., et al. "Alzheimer's disease as a major public health concern: Role of dietary saponins in mitigating neurodegenerative disorders and their underlying mechanisms." *Molecules* 27.20 (2022): 6804.
[2] Hunley, Christian, Diego Uribe, and Marcelo Marucho. "A Multi-Scale Approach to Describe Electrical Impulses Propagating along Actin Filaments in Both Intracellular and in Vitro Conditions." *RSC Advances* 8, no. 22 (March 26, 2018): 12017–28.
[3] Hunley, Christian, **Md Mohsin**, and Marcelo Marucho. "Electrical Impulse Characterization along Actin Filaments in Pathological Conditions." *Computer Physics Communications* 275 (June 2022): 108317.
[4] Marucho, Marcelo. "Java Application for Cytoskeleton Filament Characterization (JACFC)." *Software Impacts* 8 (May 1, 2021): 100072.
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