Ionic Transport Along Actin Filaments

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Abstract

Changes in the intracellular electric potential and membrane current can induce electrical signal transmission, in the form of ionic wave packets, along conducting surface of cytoskeletal filaments. This feature provides the cytoskeletal matrix with a novel esoteric mechanism for neuron information processing. Age, cell type, and local conditions also affect cytoskeleton filament properties. This presentation will introduce a Mathematica application that implements a multiscale theory to study ionic currents along actin filaments. This computational and visualization tool characterizes actin from both muscle and non-muscle cells in physiological and pathological conditions. Users can select the environmental conditions, nucleotide state, actin isoform, and various mutants or wild-type actin filaments to study ionic signal properties. In our study, temperature changes, mutations, and pH differences resulted in different ion accumulations at the surface of the actin filament and variations in ionic conductivities. Consequently, wave packet velocity is affected moderately. As these effects are detectable, we conclude that the Mathematica application is crucial in understanding cytoskeleton filament dysfunctions and abnormalities, thus, advancing the prevention and treatment of cytoskeleton-associated diseases.

Multiscale theory

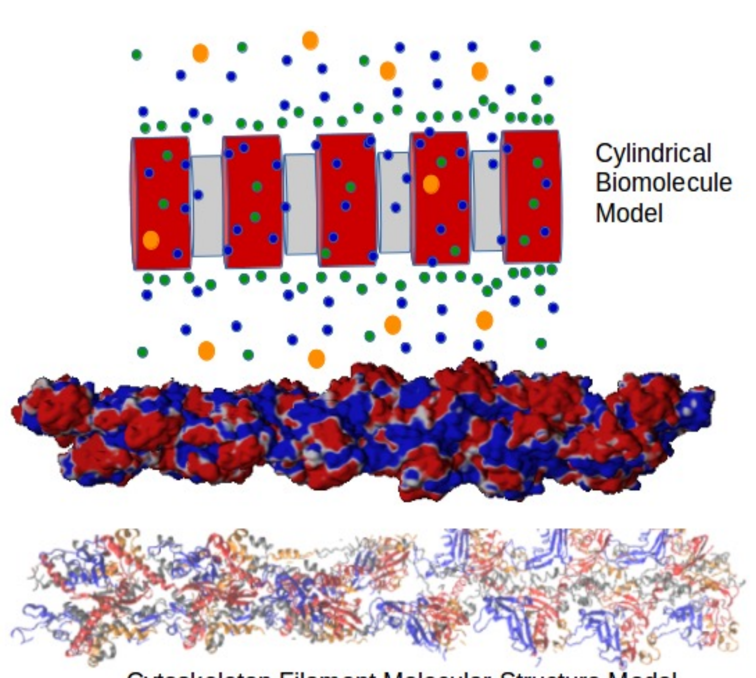


Figure: Actin; molecular structure model to cylindrical model.

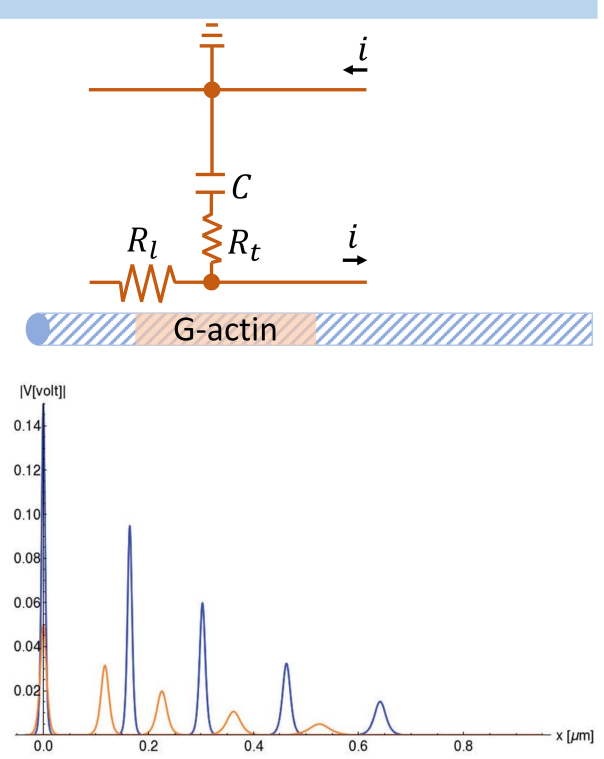


Figure: (top) Transmission line model—one cell of the transmission line represents an actin monomer; (bottom) soliton solution.

- We considered actin filaments as cylinders; a condensed ionic layer on the surface forms a nanoconductor, which is modeled by transmission line circuits.
- Multiscale theory by Hunley *et al.* [1] accurately calculated nonlinear capacitance. They considered the biological environment and found that propagating solitons decelerate and attenuate.

Pathological conditions

We extended the multiscale approach for developing a Mathematica application to study soliton properties in physiological and pathological conditions [2].

- **Ionic conditions**: invitro—modeled by 0.1M KCl, and intracellular—includes Na^+ and HPO_4^{2-} in addition to KCl.
- **Temperature**: our considered range is 298K–320K.
- **pH:** in the range 6–8.
- **filament radius:** in the range 23.83Å–50.00Å.
- **Nonlinear capacitance:** Classical density functional theory(CSDFT) calculations by JACFC web application—a Java web application developed by our group [3]—to get nonlinear capacitance parameters of actin filament for different temperatures and radii.

Pathological conditions (continued…)

- **Surface Charge**: Our calculated surface charge for the alpha-skeletal actin monomer is -11e. We estimated the surface charge densities of other actin isoforms by comparing the amino acid sequences.
- **Mutations**: We considered all the charge-changing mutations reported in Parker *et al.* (2020) [4].
- **Study**: In the software, users can input the radius and temperature. Also, they can select a nucleotide model (ATP/ADP), an actin isoform, and a conformation model (wild-type/mutant). Also, application users can choose a mutation from a dropdown list based on isoform selection. Once the program finishes the calculations, a researcher can analyze and visualize results (plots) for different pH, 6.0–8.0, and input voltages, 0.05V–0.40V.

Actin isoform (gene)	Charge per monomer	Mutation	Change in charge
skeletal α-actin (ACTA1)	-11e	Glu4Lys	+2e
		Arg254His	-1e
smooth α-actin (ACTA2)	-11e	Gly36Arg	+1e
		Arg36His	-1e
cardiac α-actin (ACTC1)	-11e	Glu99Lys	+2e
		Arg312His	-1e
β-actin (ACTB)	-10e	Glu362Lys	+2e
		Arg194His	-1e
γ-actin (ACTG1)	-10e	Glu314Lys	+2e
		Arg252Trp	-1e
smooth γ-actin (ACTG2)	-10e	Arg164Ser	-1e

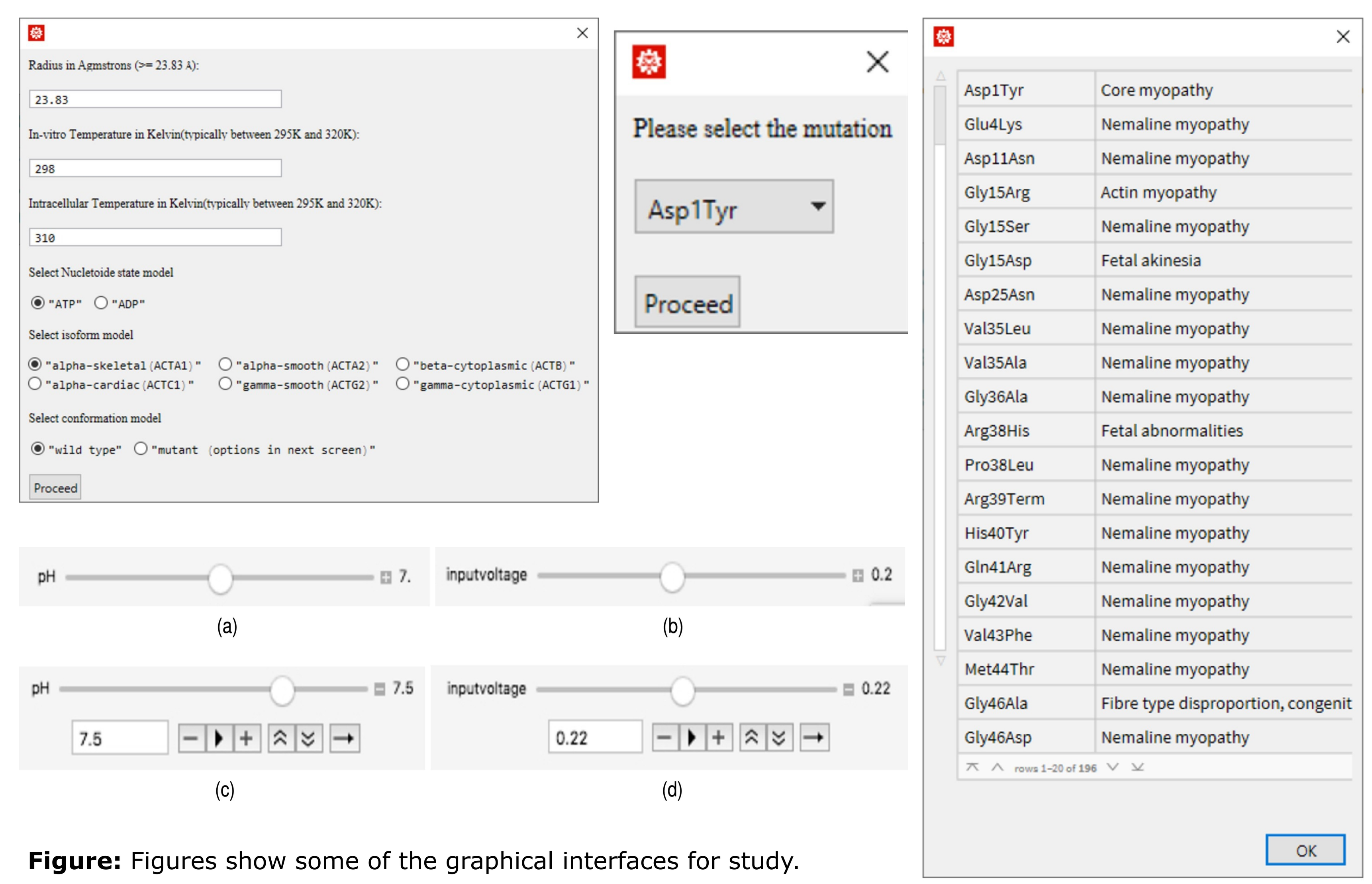


Figure: Figures show some of the graphical interfaces for study.

Effects of mutation on soliton propagation

- A mutation that results in a higher negative charge shows a faster traveling wave.

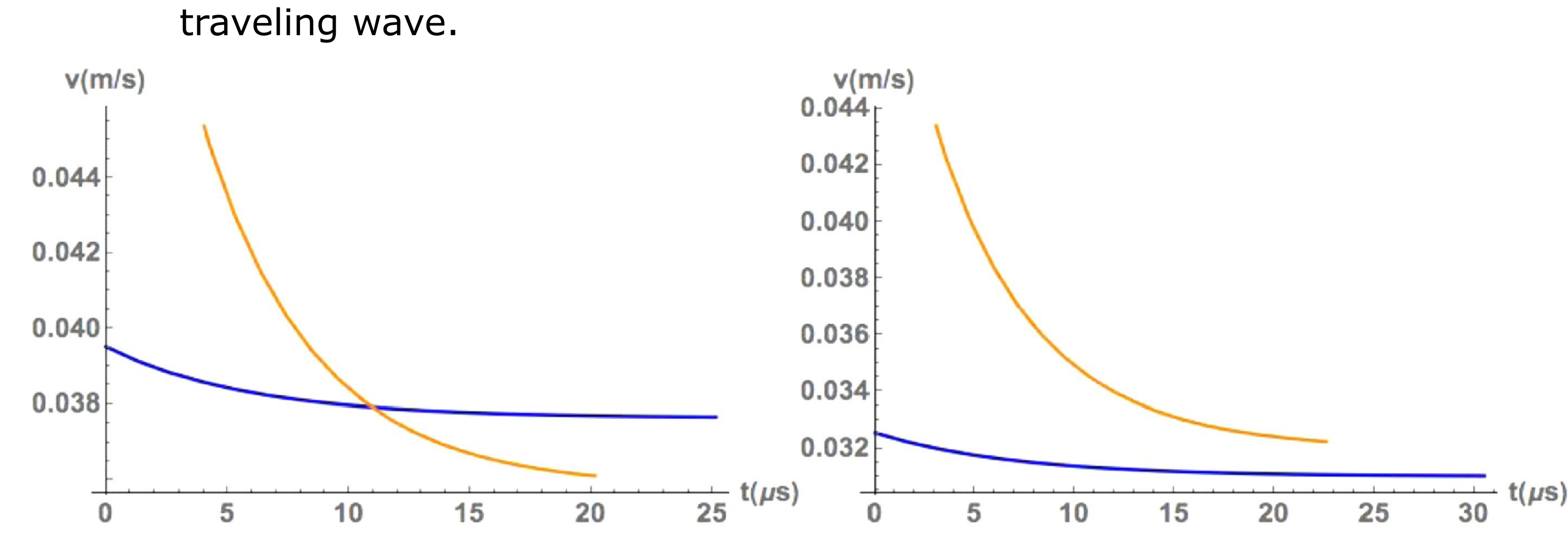


Figure. Impact of mutations on soliton velocity using the Gly36Arg and Glu362Lys missense mutations in subfigures (a) and (b), respectively. (T = 298.15K and T = 310K for invitro (blue) and intracellular (orange) electrolyte conditions.)

Pathological conditions (continued…)

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.

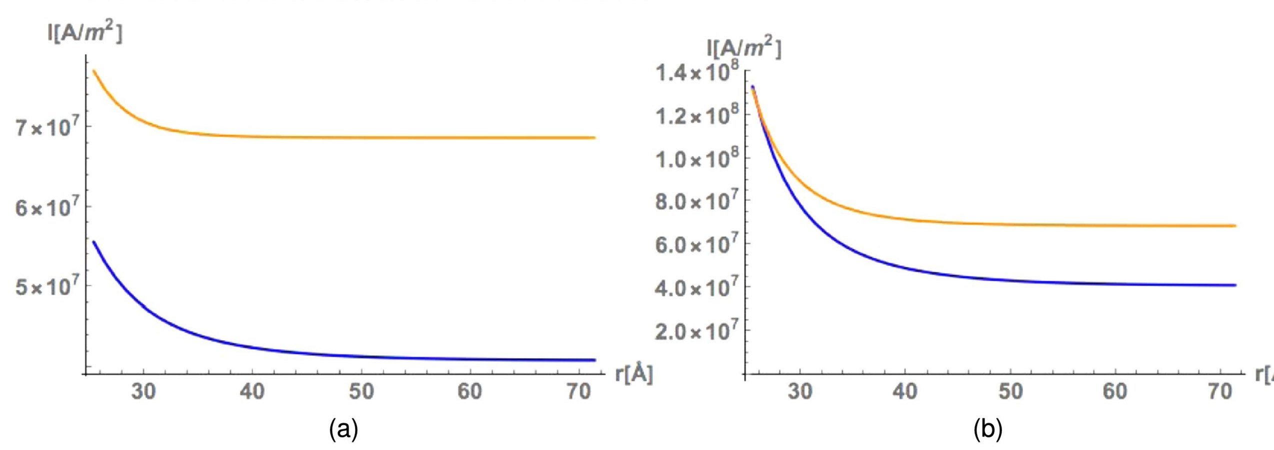
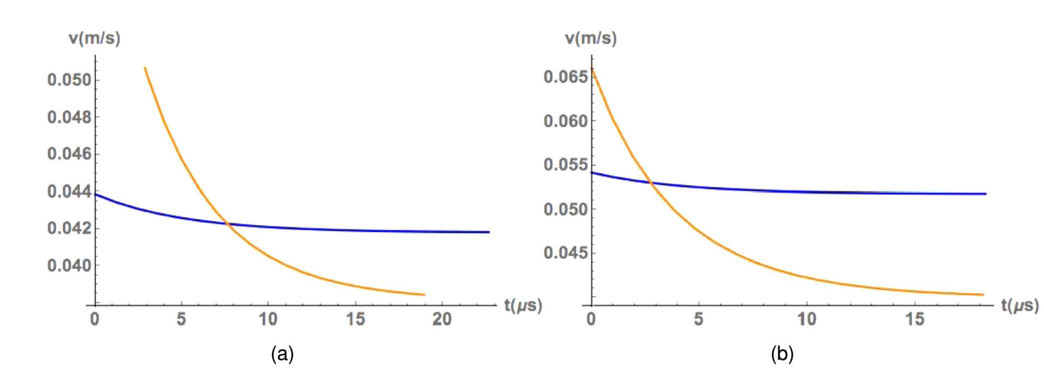


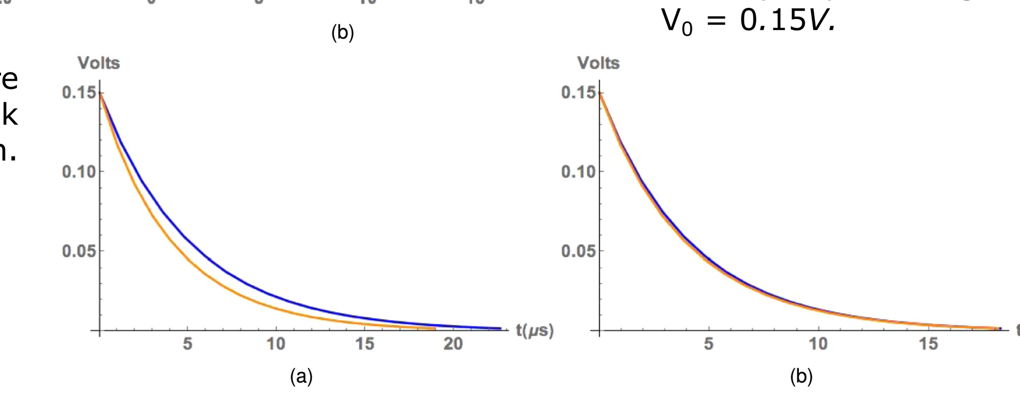
Figure: Current density profiles in the axial direction for pH 6 (subfigure a) and pH 7 (subfigure b). [R = 23.83Å]. The blue curves are for invitro conditions with T = 298.15K; the orange curves are for intracellular conditions with T = 310K.

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 K (invitro) and T = 310K (intracellular) for subfigures (a), and T=310K (invitro) and T = 313K (intracellular) for subfigures (b).

Conclusions

- 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.

References

[1] 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.

[2] Hunley, Christian, **Md Mohsin**, and Marcelo Marucho. "Electrical Impulse Characterization along Actin Filaments in Pathological Conditions." *Computer Physics Communications* 275 (June 2022): 108317.

[3] Marucho, Marcelo. "Java Application for Cytoskeleton Filament Characterization (JACFC)." *Software Impacts* 8 (May 1, 2021): 100072.

[4] Parker, Francine, Thomas G. Baboolal, and Michelle Peckham. "Actin Mutations and Their Role in Disease." *International Journal of Molecular Sciences* 21, no. 9 (January 2020): 3371.

[1] [2]