Actin Filaments Acting as Signal Propagation Pathways in Muscle and Non-Muscle Cells

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Abstract

F-actin and microtubules are polymerized from G-actin and tubulin monomers, respectively. These cytoskeletal filaments are essential for various biological activities in eukaryotic cells. Increasing evidence also shows that these bio nanowires can act as electrical conductors of ionic currents. Moreover, microtubules can amplify and generate oscillating signals, acting like a bio transistor. Characterization of signal propagation along these cytoskeletal fibers can be a new diagnostic tool. Also, it has the prospect of understanding sub-neuronal calculation and information processing. Our lab developed a novel multiscale theory to study signal propagation along actin filaments in physiological conditions. Based on the theory, we developed a Mathematica application capable of studying signal propagation along actin filament under different pathological conditions, such as temperature, pH, and radius changes. We also considered charge-changing mutations. Currently, we are trying to develop a new model for signal propagation along microtubules considering its various structural features: pores, lumen, and C-terminal tails. We expect to explain known experimental findings with our model, for example, oscillation, which present models cannot explain.

Multiscale theory

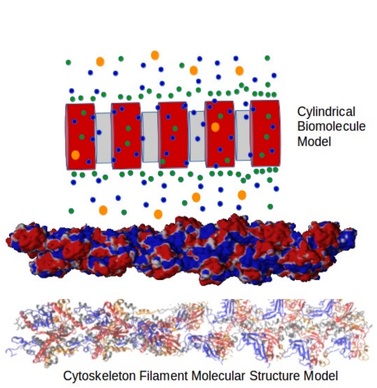


Figure: Actin; molecular structure model to cylindrical model.

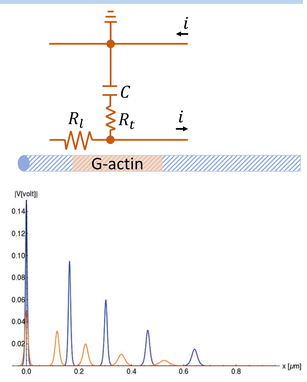


Figure: (top) Transmission line model—one cell of the transmission line represents an actin monomer; (bottom) soliton solution.

- We considered actin filaments as cylinders; a condensed ionic layer on the surface forms a nanoconductor 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:** range 6–8.
- **filament radius:** 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**: We can input the radius and temperature. Also, we can select a nucleotide model (ATP/ADP), an actin isoform, and a conformation model (wild-type/mutant). We can choose a mutation from a dropdown list based on isoform selection. Once the application finishes the calculations, we 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

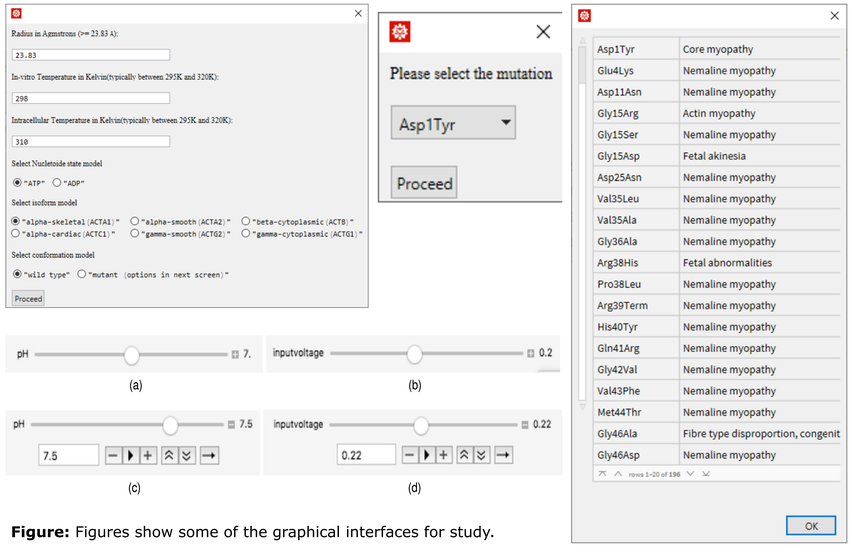


Figure: Figures show some of the graphical interfaces for study.

Effects of mutation on soliton propagation

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

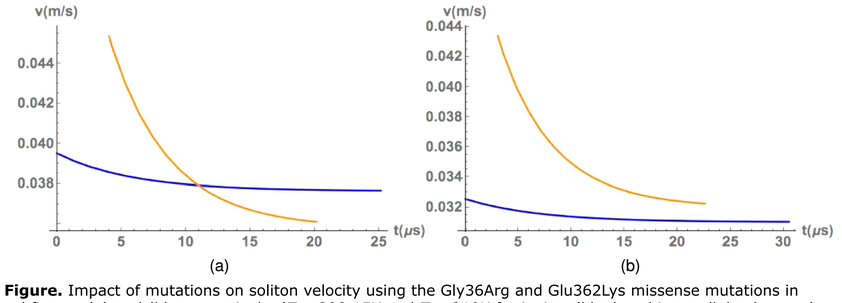


Figure. Impact of mutations on soliton velocity using the Gly36Arg and Glu362Lys missense mutations in subfigures (a) and (b), respectively. (T = 298.15K and T = 310K for invitro (blue) and intracellular (orange) electrolyte conditions.)

Pathological conditions (continued…)

Effects of pH change

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

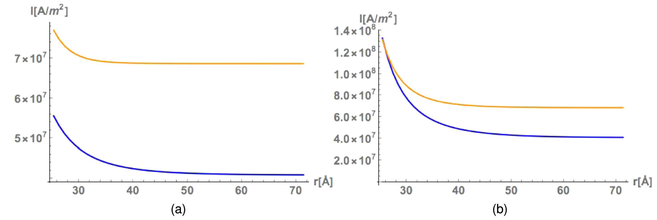
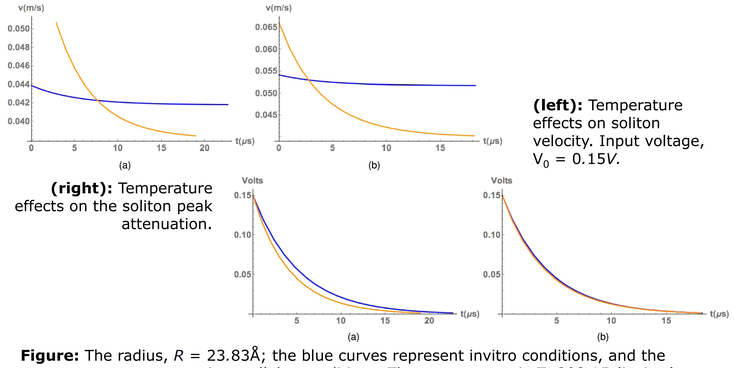


Figure: Current density profiles in the axial direction for pH 6 (subfigure a) and pH 7 (subfigure b). [R = 23.83Å]. The blue curves are for invitro conditions with T = 298.15K; the orange curves are for intracellular conditions with T = 310K.

Effects of temperature change

- A temperature increase results in a wave packet with faster velocity and more rapid decay. 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).

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.
- The changes in radius resulted in a competition between the ion velocity profiles and the resistance to influence the soliton propagation velocity.
- 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]