Electrical impulse characterization along actin filaments in pathological conditions

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A B S T R A C T

We present an interactive Mathematica notebook that characterizes the electrical impulses along actin filaments in both muscle and non-muscle cells for a wide range of physiological and pathological conditions. The simplicity of the theoretical formulation, and high performance of the Mathematica software, enable the analysis of multiple conditions without computational restrictions. The program is based on a multi-scale (atomic → monomer → filament) approach capable of accounting for the atomistic details of a protein molecular structure, its biological environment, and their impact on the travel distance, velocity, and attenuation of monovalent ionic wave packets propagating along microfilaments. The interactive component allows investigators to choose the experimental conditions (intracellular Vs in vitro), nucleotide state (ATP Vs ADP), actin isoform (alpha, gamma, beta, and muscle or non-muscle cell), as well as a conformation model that covers a variety of mutants and wild-type (the control) actin filaments. We used the computational tool to analyze environmental changes such as temperature effects and pH changes of the surrounding solutions, as well as structural changes to an actin monomer due to radius changes. Additionally, we investigated for the first time the electrostatic consequences of actin mutations from different disease conditions. These studies may provide an unprecedented molecular understanding of why and how age, inheritance, and disease conditions induce dysfunctions in the biophysical mechanisms underlying the propagation of electrical signals along actin filaments.

Program summary

Title: EIAF (Electrical Impulse along Actin Filaments)
CPC Library link to program files: https://doi.org/10.17632/k8vw4j6y75.1
Developer's repository link: https://github.com/ MarceloMarucho/SignalPropagationPathologicalCondition
Licensing provisions: GPLv2
Programming language: Mathematica

Nature of program: Electrophysiological properties of actin filaments in pathological conditions have yet to be studied, despite previous work showing important consequences for physiological conditions on wild type actins.

Solution method: Interactive Mathematica notebook is based on the Multi-scale Approach for electrical impulses along cytoskeletal filaments and uses non-linear considerations for the Boltzmann statistics of ionic distributions in the electrical double layer (EDL). Using the numerical methods incorporated in Mathematica’s default libraries, and an interactive GUI, the program allows users to conduct their own research by choosing the experimental conditions (intracellular Vs in vitro), nucleotide state (ATP Vs ADP), actin isoform (including muscle and non-muscles cells), as well as a conformation model that covers a variety of mutants and wild-type (the control) actin filament configurations.

Additional comments including restrictions and unusual features: The program allows users to adjust pH values, input voltages, as well as study two default electrolyte conditions without rerunning the program.

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** This paper and its associated computer program are available via the Computer Physics Communications homepage on ScienceDirect (http://www.sciencedirect.com/science/journal/00104655).

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1. Introduction

Actin filaments are a major component of the cytoskeleton, and essential for various biological activities in eukaryotic cellular processes such as directional growth, shape, division, plasticity, and migration [1–5]. Recent research on the electrical properties of actin under in vitro conditions revealed an unprecedented role for the microfilaments as bionanowires capable of propagating ionic information [6]. This finding may provide new insights on many electrical processes taking place within smooth muscle, skeletal, and cardiac cells near the membrane or in the nucleus. Furthermore, an additional information delivery system in neuronal cells might be beneficial for intracellular communication in dendrites, the soma, axon, and axonal terminal [7]. Indeed, further clarification on the electrical conductivity and ionic transmission properties of actin filaments is vital for a complete understanding of their contributions to cellular functions and information transfer inside cells.

The use of conventional computational tools and approaches to study the interplay between the polyelectrolyte properties of polymer chains and their biological environment break down for cytoskeleton filaments, because they are limited by their approximations and computational cost [8]. We recently introduced an accurate and efficient multi-scale theory (atomic → monomer → filament) that overcomes some of these limitations when investigating electrical signal propagation along single wild-type actin filaments in physiological conditions [9]. The electrical signal that characterizes ion wave packets was shown to propagate as a monotonically decreasing soliton [10]. For the range of voltage stimuli and electrolyte solutions typically present in intracellular and in vitro conditions, the approach was able to predict a lower electrical conductivity with higher linear capacitance and non-linear accumulation of charge under the intracellular conditions. Additionally, the results showed a significant influence of the voltage input on the electrical impulse shape, attenuation, and packet propagation velocity. The filament sustained the soliton propagation at almost constant velocity for in vitro conditions, whereas intracellular conditions displayed a remarkable deceleration. Furthermore, the solitons were narrower and traveled faster at higher voltage input. As a unique feature, the multi-scale theory is able to account for the molecular structure conformation and biological environment changes often present in pathological conditions.

In this work we present a Mathematica notebook, [11] which utilizes an extension of the multi-scale approach that includes a non-linear Boltzmann description of the ionic distribution in the electrical double layer, and provides an in depth study of monovalent ion wave packets traveling along single actin filaments in a variety molecular conformations and biological environments (https://github.com/MarceloMarucho/SignalPropagation(PathologicalCondition). The program performs on single computers at very low computational cost, and does not require specialized training in computational methods, which can often be an obstacle for many students, researchers, and even experts in the field. Specific analyses can be achieved by selecting the desired nucleotide state (ATP or ADP), isoform (alpha-smooth, alpha-skeletal, alpha-cardiac, gamma-smooth, gamma-cyttoplasmic, beta-cyttoplasmic), and conformation model (wild-type or mutant) of the actin monomer. As a distinctive characteristic, a series of interactive plots are generated to elucidate the impact of pH, voltage input, and temperature on the filament conductivity, electric potential, velocity, peak attenuation and ionic wave packet profile. Overall, the program is fully editable. This feature allows users to change the default electrolyte aqueous solution and filament model parameters provided in the notebook.

In the following section, we describe the changes introduced to the multi-scale approach that make it adaptable for study of pathological conditions. In section 3, we describe the electric charge model of an actin monomer for different molecular conformations. The results of a study on increasing the intracellular temperature, changes to the actin radius, pH changes, and missense mutations using the interactive Mathematica notebook are presented in Section 4. A discussion on the results is given in section 5 and a conclusion follows in section 6. In the appendix we provide a more detailed explanation of the interactive Mathematica notebook where appendix section A includes the organization, design and implementation of the interactive program. In appendix section B, we present an illustrative example. A general overview of the multi-scale approach applied to a single (alpha-smooth muscle) wild-type actin filament is presented in the appendix section C. The explicit details of the theory can be found in a preceding article [9].

2. A multi-scale model for pathological conditions and the interactive program

The formulation of the multi-scale approach includes: (1) the atomistic scale; accounts for the pH of the aqueous solution, de-protonation of active residues on the protein, and the ionic composition of the biological environment, (2) the monomeric scale; models the ionic layering next to the charged protein (i.e. the capacitance), as well as resistance to flow of ions in both the radial and axial directions along the filament, and (3) the filament scale; determines the velocity, acceleration, and soliton profile, along with the maximum travel time and distance of an ionic wave using a transmission line prototype model.

2.1. Atomistic scale changes to the biological environment

We use two default ionic conditions, which with some effort can be modified in the interactive note book. One is the invitro condition modeled by sodium chloride (KCl) at 0.1M concentrations. The other environment is the intracellular condition, which also uses KCl and includes sodium (Na), as well as hydrogen-phosphate (HPO_4^{2-}) to represent larger charged anions in the biological environment (see Table 1).

2.1.1. Aqueous solution

The pathological and physiological intracellular temperature gradient has been shown to range from 308 K to 315 K in the cytoplasm [12], around 1°C higher in the nucleus (when compared to the cytoplasm) [13], and around 321 K at the mitochondria [14]. The interactive notebook allows users to choose a temperature between 298 K and 320 K for both invitro and intracellular conditions. In this work, we account for the temperature dependence of the viscosity \( \mu \) by using the temperature dependent equation \( \log(\mu) = -4.5318 - 247/(140 - T) \), where \( T \) represents the temperature in Kelvin and \( \mu \) the viscosity in Kg/ms [15]. Lastly, the relative permittivities for the intracellular and in vitro conditions
Table 1
Ionic species used in both the intracellular and in vitro conditions. The last two columns represent the default concentrations used in the multi-scale approach for intracellular and in vitro conditions. The mobility is in units of mol m² J⁻¹ s⁻¹, and $K_b$ and $T$ represent the Boltzmann constant and temperature in Kelvin. The unit for the bulk concentration is mol m⁻³.

<table>
<thead>
<tr>
<th>Ion species</th>
<th>Valence</th>
<th>Mobility (μ)</th>
<th>Bulk conc. intracellular</th>
<th>Conc. in vitro</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K^+$</td>
<td>+1</td>
<td>$5.0148 \times 10^{-10} \exp[-2.65449 \times 10^{-20}/K_b T]$</td>
<td>140</td>
<td>100</td>
</tr>
<tr>
<td>$Na^+$</td>
<td>+1</td>
<td>$3.25164 \times 10^{-10} \exp[-2.64981 \times 10^{-20}/K_b T]$</td>
<td>12</td>
<td>-</td>
</tr>
<tr>
<td>$Cl^-$</td>
<td>-1</td>
<td>$3.57995 \times 10^{-10} \exp[-2.51681 \times 10^{-20}/K_b T]$</td>
<td>4</td>
<td>100</td>
</tr>
<tr>
<td>$HPO_4^{2-}$</td>
<td>-2</td>
<td>$1.83587 \times 10^{-10} \exp[-2.64981 \times 10^{-20}/K_b T]$</td>
<td>74</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 2
The filament surface charge density (SCD) and electric charge obtained from the Cong (https://www.rcsb.org/structure/385U) molecular structure model for pH values 5-9, using the ATP state for a single (alpha-smooth muscle) wild-type actin filament. The electric charge was calculated using pdb2pqr webserver with an Amber force field (https://server.poissonboltzmann.org/pdb2pqr/).

<table>
<thead>
<tr>
<th>pH</th>
<th>14 monomers filament charge [e⁻]</th>
<th>Surface charge density σ [C/m²]</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>23</td>
<td>0.006</td>
</tr>
<tr>
<td>6</td>
<td>-82</td>
<td>-0.021</td>
</tr>
<tr>
<td>7</td>
<td>-154</td>
<td>-0.039</td>
</tr>
<tr>
<td>8</td>
<td>-184</td>
<td>-0.047</td>
</tr>
<tr>
<td>9</td>
<td>-222</td>
<td>-0.056</td>
</tr>
</tbody>
</table>

are set to 80ε₀ and 78.358ε₀, respectively, were ε₀ is the permittivity of free space.

2.1.2. Electrolyte
In this work, the dynamic mobility $u$ for each ion species is estimated using the temperature dependent function $u(T) = u_0 \exp[-U_0/K_b T]$ [16,17]. We obtained the parameters $u_0$ and $U_0$ using the FindFit Mathematica function [18] and the experimental mobility values for several temperatures [19,20]. This and other ionic species properties are shown in Table 1. For instance, in Fig. 1a we show the fitting function for the sodium mobility for intermediate temperatures values between 275 K and 320 K (solid blue curve) and the corresponding experimental values (red dots).

2.2. Filament model
In Table 2 (details are provided in the appendix) we tabulated the electric charge and surface charge density of the Cong molecular structure model [21] for the alpha wild type actin filament using the ATP state in physiological conditions. Information on other molecular structure models for actin filaments, including PDB ID’s 3B63(Holmes), 3MFP (Namba), 22WH (Oda), and 3BJ(Egelman), can be retrieved from the protein data base website (https://www.rcsb.org/). The intracellular pH for healthy cells lies between 6.8 and 7.3. On the other hand unhealthy cells, such as those infected with cancer, have been seen with a pH value between 7.2 and 7.8. Additionally, Alzheimer’s disease (AD) cells have shown a decrease in pH value when compared to healthy cells [22], being 6.5 the lowest pH found in brain ischemia [23]. As a unique feature, the surface charge density for intermediate pH values in the range between 6.0 and 8.0 were accurately estimated using the Mathematica Interpolation function [18], which uses third order fitting polynomial curves between successive data points. For illustration purposes, we display the discrete surface charge density values coming from the molecular structure and those coming from the interpolating function in Fig. 1b.

2.3. Monomer model
The actin monomer length (l) is set to 5.4 nm. The Mathematica interpolation function was used with surface charge density values to account for the pH dependence of the electric potential, electrical conductivity, resistances and impedance.

A Java Application for Cytoskeleton Filament Characterization (JACF) web application [24-26] was used to obtain the capacitance parameters for different temperatures and filament radii.

A Mathematica interpolation was used to generate interpolating functions for the nonlinear parameter b and capacitance $C_0$ for temperatures ranging from 292.15 K to 321.15 K, and filament radii ranging from 23.83 Å to 50 Å. Surface interpolating functions with JACF data points are displayed in the Figs. 2 and 3 for intracellular and in vitro conditions, respectively.

3. Electric charge models for the nucleotide states, isoforms, and missense mutations
In the following subsections, we outline the method for determining the electric charge model for the nucleotide states, isoforms, and missense mutations. We also state the options available in the interactive program when choosing a mutation. It is worth highlighting that the electric charge model introduced in this version of the interactive notebook does not account for molecular structure differences between each actin filament conformations.

For instance, a conformational change to actin coming from a mutation that maintains the same charge will produce the same result. Therefore, the electric charge model is aimed to elucidate how even small changes in charge can have a consequential impact on the electrical conductivity and ionic packet waves propagation along actin filaments. Whereas, structural changes to the monomer are considered in sections 4.2 and 5.2. A summary of the models is provided in Table 3. More information on disease associated with actin, as well as a large list of phenotypes, genes and amino acid mutations can be found in the article by Parker et al. [27].
3.1. Nucleotide states and isoforms

From our work on physiological conditions, we found using the Cong molecular model, that an alpha-skeletal actin monomer has a net negative charge of $-11e$, where $e$ is the fundamental charge unit [9]. Based on previous studies, we assume that the surface charge density of the alpha wild type filament falls approximately 9% ($1/11$) when a $P_i$ (phosphorus ion) is released from the wild type actin filament following hydrolysis of the actin-bound ATP to ADP-$P_i$. This results in a minus one charge difference between the ATP and ADP actin monomers. An in depth understanding of ATP and ADP actin states can be found in the work by Kudryashov et al. [28]. Similarly, we model gamma-smooth muscle, as well as gamma ($\gamma$) and beta ($\beta$) non-muscle (cytoplasmic) actin isoforms to have one less net negative charge than alpha ($\alpha$) actin isoforms according to their amino acid sequence [29].

3.2. Missense mutations

The most common mutation in G-actin comes from missense mutations, which result in a substitution of a single amino acid on the wild-type actin monomer. The substitution on the mutated monomer may come in one of the following amino acid exchanges, where the symbol (q) is used to represent a charged amino acid residue that is affected by the pH of the solution (i.e. may lose (gain) a charge with an increase (decrease) in the pH level): (1) amino acid (q) residue $\rightarrow$ different amino acid (q) residue, (2) amino acid (q) residue $\rightarrow$ amino acid residue, (3) amino acid residue $\rightarrow$ amino acid (q) residue, or (4) amino acid residue $\rightarrow$
4. Results

4.1. Environmental changes due to temperature

The use of a more detailed description for solvent viscosity, which becomes necessary when considering different temperatures in the environment surrounding actin, allows for an investigation on how the ionic redistribution in the electrical double layer (EDL), conductivity, and soliton profiles are affected by changes to the temperature. For the invivo condition we compared room temperature (298.15 K) with body temperature (310 K). On the other hand, for the intracellular condition we compared body temperature (310 K) with a high fever temperature (313 K). Our analysis (not presented here) showed negligible effects on the electric potential and ion concentration profiles due to the temperature changes. This was expected before hand, because there is only an indirect influence of the temperature arising through Debye length on the potential (see eqn (2)). Additionally, the differences in temperature values used are rather narrow for biological conditions, that is a 3% increase for invivo and an even smaller 0.009% increase for the intracellular case. However, the effective electric conductivity in the region between the actin surface and the bulk layer, as well as the ion current density distribution had noticeable changes. These results are shown in Fig. 4 and Fig. 5, respectively.

From the change in the conductivity there is a change in resistance due to their inverse relationship. In a previous work, we...
showed the resistance plays a role in deceleration of the time averaged soliton velocity [9]. To better understand the transport of ionic information along actin filaments in different temperatures we looked at the velocity and peak attenuation of the traveling ionic soliton. The velocity is shown in Fig. 6 and the peak decay in Fig. 7.

4.2. Structural changes to the monomer

With a more accurate description of the diffuse layer coming from the non-linear behavior of the Poisson-Boltzmann distribution function, we looked at the impact of the actin radius on the radial ion distribution. Using two different values for the radius, \( r = 23.83 \, \text{Å} \) and \( r = 40 \, \text{Å} \), we compared the electric potential in Fig. 8.

Different behaviors for the ion concentration in the radial direction starting at the actin surface are shown in Fig. 9 for different actin radius values, as well as changes to the effective electric conductivity (Fig. 4(a) against Fig. 10) and ion velocity (Fig. 11).

The results of these changes on the soliton are represented in Fig. 12 by showing the velocity of the soliton wave packet for an actin radius of \( R = 23.83 \, \text{Å} \) and \( R = 40 \, \text{Å} \). The temperature is \( T = 298.15 \) for the blue curves showing invitro type conditions, and \( T = 310 \, \text{K} \) for the orange curves which represent intracellular conditions.

4.3. Environmental changes due to pH of the solution

Changes to the environment that result in different pH values of the surrounding solution have consequences on the ion concentration profiles and show a more drastic impact for the intracellular condition. In Fig. 13, we show the results of the ion concentration profiles for the counterion \( K^+ \) and coion \( \text{HPO}_4^{2-} \) using a wild type actin monomer with a radius of \( R = 23.83 \, \text{Å} \) for pH 6 and pH 8.
Fig. 7. Temperature effects on the soliton peak attenuation. The radius is set to $R = 23.83$ Å with the blue curves used for invitro conditions and the orange curves for intracellular conditions. The temperature is $T = 298.15$ (invitro) and $T = 310$ K (intracellular) for subfigure (a) and $T = 310$ K (invitro) and $T = 313$ K (intracellular) for subfigure (b).

Fig. 8. Impact of the actin radius on the electric potential profile. The subfigure (a) shows the electric potential with an actin radius of $R = 23.83$ Å, whereas subfigure (b) uses a radius of $R = 40$ Å. The blue curves are for invitro conditions with $T = 298.15$ K and the orange curves are for intracellular conditions with $T = 310$ K.

Fig. 9. Impact of the actin radius on the ion distribution in the radial direction is shown for $K^+$ in subfigures (a) and (b) for radius comparisons of $R = 23.83$ Å and $R = 40$ Å, respectively. In subfigures (c) and (d) we show the coin $HPO_4^{2-}$ for $R = 23.83$ Å and $R = 40$ Å, respectively. The temperature is $T = 298.15$ for the blue curves showing invitro type conditions and $T = 310$ K for the orange curves which represent an intracellular electrolyte mixture condition.
The current density for pH 6 and pH 8 were also compared in Fig. 14, where the longitudinal (axial) profiles are shown in subfigures (a) and (b), and the transversal (radial) profiles are presented in subfigures (c) and (d).

4.4. Mutations

The high impact on the results coming from two different considerations for the radius in section 4.2 is due to changes in the surface charge density. In other words, an inversely proportional relationship results in a decrease in the surface charge density due to an increase in the actin radius. However, there is an alternative way to affect the surface charge density, which is by changing the charge of the actin monomer.

This is precisely the consequence of diseases that result in missense mutations. To analyze the impact of mutated actin monomers we choose an actin alpha-skeletal mutation (ACTA1), actin alpha-smooth muscle mutation (ACTA2), and an actin beta-cytoskeleton non-muscle mutation (ACTB1). Respectively, these correspond with nemaline myopathy (Glu4Lys); an actin monomer with −9e charges, falilal thoracic aortic aneurysm (Glu362Lys); an actin monomer with −8e charges, and Neutrophil dysfunction (Gly36Arg); an actin monomer with −12e charges. A comparison between ACTA2 and ACTB1 is seen using the electric potential in Fig. 15 and the ionic conductivity in Fig. 16.

The diseased conditions resulted in different ion concentration profiles. This is demonstrated in Fig. 17 for the intracellular condition, where we show the ACTA1 and ACTB1 results for K⁺ in Figs. 17(a) and 17(b), respectively. In Figs. 17(c) and 17(d) we show the results for the divalent cation HPO₄²⁻.

The ion concentration profiles describe the way the ions are distributed in the diffuse layer. Results show counterionic species accumulate near the actin surface. Therefore, the counterions contribute to the larger conductivity along the filament, as confirmed by the ionic conductivity profiles in Fig. 16. This means there is a competitive relationship between the counter- and co-ions when it comes to conductivity contributions which, therefore, impact the resistance and result in different soliton velocities (Fig. 18).

5. Discussion

5.1. Temperature

The temperature changes for the values chosen in this work show a difference of ΔT_invitro = 11.85 K for invitro conditions and ΔT_intracellular = 3 K for intracellular conditions. These values were used because an invitro experiment may measure at room temperature (298.15 K = 25 °C) and also at body temperature (310 K = 36.85 °C). The intracellular condition is a much smaller difference since we started at body temperature, and therefore, only increased to a high fever temperature of (313 K = 39.85 °C). Certainly, the larger change for invitro conditions has a more impressive impact in all results analyzed.

For the effective electric conductivity we see an increase due to increasing the temperature (Fig. 4). Mathematically, this comes from the Boltzmann distribution, where the temperature is in the denominator of the decreasing exponential term. Physically, the result is due to increased thermal motion causing a smaller restraining force on the counterions near the surface, and an intensified presence of the external field on the ions. This is also visualized in Fig. 5 by the invitro results shown by the blue curves. The axial current density equation is analyzed by showing how the ion current density distribution contributes in different parts of the diffuse layer. Near the surface of the actin there is a very evident increase in the current density between Figs. 5(a) and 5(b) for the invitro results. For the intracellular results the smaller increase in temperature leads to a much smaller increase in the current density. The rise in the horizontal asymptote in both conditions reveals that the conductivity in the bulk layer is also affected by the temperature change.

We also analyzed the Bjerrum length, a measurement of the separation between counterions and coions due to the competition between the electrostatic and the thermal energies. Since the Bjerrum length is inversely proportional to the temperature, a temperature increase results in a more narrow electrical double layer. These changes in the Bjerrum length indeed affect the radial ion current distribution. Figs. 5(c) and 5(d) display an increase in the radial current density throughout the diffuse layer that may be associated to ions moving in toward the actin surface.

Temperature changes also affected the traveling soliton, since the increase in conductivity corresponds to a decreased resistance and, therefore, an ionic wave packet with a faster velocity. In Fig. 6 we show how the soliton velocity changes with increasing temperature. A comparison between the invitro and intracellular curves in Figs. 6(a) and 6(b) show a temperature increase does indeed result in a wave packet with a faster velocity. However, Fig. 7 revealed a faster decay for a soliton with a larger velocity. We concluded that increasing the temperature produces faster moving solitons that may travel approximately the same distance as the solitons with a slower velocity.

5.2. Increase in actin radius

An increase of the actin radius will decrease the surface charge density since they have an inverse relationship. Additionally, the magnitude of the electrostatic potential will decrease because it is proportional to the surface charge density. This change in the electric potential is shown in Figs. 8(a) and 8(b) for actin with radius values of R = 23.83 Å and R = 40 Å, respectively. Furthermore, the electric potential changes affect the ionic Boltzmann distribution by generating a smaller accumulation of counterionic species at the surface and a larger number of coionic species due to the reduced electrostatic forces. Fig. 9 shows the larger radius had a 28% decrease in K⁺ ions at the surface, whereas the HPO₄²⁻ ions had a 86% increase.

Interestingly, Fig. 4(a) compared against 10 reveals that the ionic concentration changes resulted in a drastic change to the electrical conductivity with a 21% decrease for the intracellular results (orange) curve and 35% decrease for the invitro results. The smaller decrease in the intracellular conditions could be a result of the divalent coions HPO₄²⁻ constraining some counterions in the region near the surface.

A decrease in the electric potential also affected the ion velocity, because it is proportional to the potential difference of the
Fig. 11. Ion velocity plots for invivo (blue) and intracellular (orange) electrolyte mixtures at temperatures $T = 298.15$ K and $T = 310$ K. Subfigure (a) is for 23.83 Å and (b) is for 40 Å.

Fig. 12. Impact of the actin radius on the velocity using a radius of $R = 40$ Å. The temperature is $T = 298.15$ K for the blue curve which represents invivo electrolyte concentration conditions, whereas the orange curve demonstrates intracellular electrolyte concentration conditions with $T = 310$ K.

location measured in the EDL and the slipping plane. This can be visualized in Figs. 11(a) and 11(b) by the decrease in the horizontal asymptote of the larger radius 11(b). On the other hand, the soliton velocity plots show an increase due to the larger radius (compare Figs. 11(a) and 12). Certainly, this result was counter intuitive because the ionic axial velocity was found to decrease. However, resistance is inversely proportional to cross-sectional area which means an increase in actin radius also decreases the resistance. We concluded that there is a competitive relationship between the decrease in the axial velocity profile and the decrease in the resistance when it comes to the soliton velocity.

5.3. Changes to the pH of the solution

To investigate the impact of pH we considered the ion concentration profiles and current density profiles for the axial and radial directions. The consequence of pH changes on actin can be seen in Table 2, where we see that a larger pH results in a more negative charge on the actin monomer in physiological conditions (pH 6-8). In turn, this generates a stronger attraction by counterions, along with a stronger repulsion for coions when increasing the pH values. In fact, Fig. 13 displays a $K^+$ increase of 82%, and a 68% decrease for $HPO_4^{2-}$ at the actin surface. This can be correlated with a large increase in the longitudinal (axial) current density profile near the surface (14(a) and 14(b)). Unlike the results on current density for temperature changes, there was no increase in conductivity for the bulk layer. Additionally, a larger electrostatic attraction implies a increase in counterion current density as the distance from the actin surface gets smaller. This is seen in Figs. 14(c) and 14(d) for the radial current density profile comparison at pH 6 and pH 8.

5.4. Mutations

In Fig. 15, we analyzed the electrostatic potential changes due to the missense mutations Gly36Arg and Glu362Lys. These missense mutations can result in a change to the charge of an actin monomer due to removal and replacement of an amino acid residue. In some instances, the mutations exchange amino acids that respond to the pH of a solution. For example, replacing glutamic acid (Glu) with a lysine (Lys) has a consequence to the monomer at physiological pH values. The Gly36Arg amino acid exchange is a ACTA2 isoform mutation that results in an actin monomer with a $-12e$ charge (see Fig. 15(a) for the electrostatic potential results). On the other hand, the Glu362Lys amino acid exchange is a ACTB1 isoform mutation that results in an actin monomer with a $-9e$ charge (see Fig. 15(b) for the electrostatic potential results). Hence, the ACTA2 isoform mutation in this case results in a stronger electrostatic response. Consequently, Fig. 16 shows a larger ionic conductivity coming from the ACTA2 mutation (Fig. 16 (a)) when compared to the ACTB1 mutation (Fig. 16 (b)).

We also compared the actin-skeletal muscle isoform mutation (ACTA1) with the actin non-muscle cytoskeletal isoform mutation (ACTB1). In this case, the amino acid exchange for the ACTA1 isoform was Glu36Lys, which results in a $-9e$ charge of the actin monomer. A comparison of the ionic concentration distributions for $K^+$ and $HPO_4^{2-}$ is represented in Fig. 17. These figures show more counterions and fewer coions approaching the actin surface for the ACTA1 isoform mutation (i.e. for the Glu36Lys amino acid exchange).

The analysis on velocity profiles for the traveling ionic wave packet is seen in Fig. 18. A mutation resulting in a larger negative charge shows a faster traveling wave (Fig. 18(a)) when compared to an actin monomer with a smaller charge (Fig. 18(b)). This is a result of the increased conductivity (Fig. 16) causing a lower resistance. Other studies can be performed on temperature, radius, and pH changes, as well as mutations for numerous different diseases resulting in missense mutations by using the interactive Mathematica notebook outlined in the appendix.

6. Conclusion

Due to their conducting bionanowire properties, actin filaments have been experimentally demonstrated and theoretically modeled to be capable of transmitting ions across their filament length when an external voltage stimulus is applied to the filament. The solitons produced by the transmission line model represent ionic waves, which travel distances in the neighborhood of a micron, and could be a biological consequence in the local vicinity of cells [31].

In this article, we introduced a novel interactive Mathematica notebook that allows for the characterization of the soliton propa-
Fig. 13. Ion concentration profiles for $K^+$ and $HPO_4^{2-}$ at two different pH values. In subfigures (a) and (b) we show the counterion distribution of $K^+$ for pH 6 and pH 8, respectively. In subfigures (c) and (d) we show the coion distribution of $HPO_4^{2-}$ for pH 6 and pH 8, respectively. The independent variable on the horizontal axis starts at the radius of the actin monomer and extends in the radial direction toward the bulk layer.

Fig. 14. Current density profiles for the axial and radial directions at two different pH values using an actin radius of 23.83 Å. The blue curves are for invitro conditions with temperature $T = 298.15$ K, whereas the orange curves are for intracellular conditions with $T = 310$ K. The subfigures (a) and (b) are for the axial direction with pH 6 and pH 7, respectively. The subfigures (c) and (d) are for the radial direction with pH 6 and pH 7, respectively.
Fig. 15. Impact of mutations on the electric potential profile. A comparison of the results on the electric potential response due to missense mutations from the isoforms α-smooth muscle (ACTA2) and non-muscle cytoplasmic (ACTB1) are shown. The mutation on ACTA2 is the amino acid residue replacement Gly36Arg in subfigure (a), whereas the ACTB1 is from the replacement of Glu362Lys in subfigure (b). The temperatures used in this analysis are $T = 298.15$ K and $T = 310$ K for in vitro and intracellular electrolyte mixture conditions, respectively.

Fig. 16. The affect of missense mutations on the ionic conductivity. The mutations from the isoforms α-smooth muscle (ACTA2) and non-muscle cytoplasmic (ACTB1) are shown. The mutation on ACTA2 is the amino acid residue replacement Gly36Arg in subfigure (a), whereas the ACTB1 is from the replacement of Glu362Lys in subfigure (b). The temperatures used in this analysis are $T = 298.15$ K and $T = 310$ K for in vitro (blue) and intracellular (orange) electrolyte mixture conditions, respectively.

Fig. 17. Mutation results for ion concentration distribution in the radial direction starting at the actin surface. The temperatures used in this analysis are $T = 298.15$ K and $T = 310$ K for in vitro (blue) and intracellular (orange) electrolyte mixture conditions, respectively. The ions represented here are the counterion $K^+$ in subfigures (a) and (b) for a mutation to the isoforms ACTA1 and ACTB1, respectively, and the coion $HPO_4^{2-}$ in plots (c) and (d) for a mutation to the isoforms ACTA1 and ACTB1, respectively.
gation along actin filaments for a wide range of physiological and pathological conditions. In particular, the user has the option of selecting a nucleotide state, isoform of interest and its associated disease. As a unique feature, the investigator may perform their own detailed study on the conductivity, mean electric potential, velocity, and peak decay by using an interactive slider for adjustments of the pH (6.0–8.0), and voltage input (0.05 V–0.40 V). This simple and easy to use program requires no specialized training or expertise in the field, and is designed to conduct a detailed analysis on both wild-type and mutated conformations. The simplicity of the theoretical formulation, and the high performance of the Mathematica software, enable the analysis of multiple conditions without computational restrictions.

In this work, we used the computational tool to perform a detailed and accurate analysis on the potential profile, ion velocity, effective electric conductivity, ion concentration profile, ion current density, soliton velocity, and amplitude attenuation of a ionic soliton wave. We studied environmental changes such as temperature effects and pH changes of the surrounding solutions, as well as structural changes to an actin monomer due to radius changes. Additionally, we investigated for the first time the electrostatic consequences of actin mutations from different disease conditions.

Temperature changes and pH differences, which are known to occur in unhealthy muscle and non-muscle cells, were shown to result in different ion accumulations at the surface of the actin monomer (and filament), ionic conductivities, and ionic soliton wave packet velocities. The changes in radius showed a competition between the ion velocity profiles and the resistance when influencing the soliton propagation velocity.

This study found that when comparing the results of pH changes and actin mutations that common trends resulted in both the analyses. Specifically, there were impacts to the ion concentration profiles, current density, and traveling ionic solitons. This is because pH fluctuations in the solvent change the charge of the protein. This is shown in Table 2 where the charge of the Cong unit is -83e, -154e, and -184e, for pH values 6, 7, and 8, respectively. That represents approximately -6e, -11e, and -13e charges per monomer for increasing pH. In the analysis on mutations, we used -8e, -9e, and -12e for the mutated actin monomeric isoforms ACTB1, ACTA1, and ACTA2. This leaves an open question regarding the connection between the pH value in the intracellular space of cells and diseases involving missense mutations with at least one of the seven pH dependent amino acid. Despite a missense mutation only replacing one amino acid on an actin monomer, the results on the ionic wave packet velocity show a consequential outcome.

Unfortunately, there is a lack of experimental data on electrical signals propagation along actin filaments, mainly in pathological conditions. Additionally, experimental and theoretical conditions may be different. However, our predictions and experimental data on wild-type actin filaments in physiological conditions revealed similar trends, namely, higher voltages caused larger peaks and a faster traveling wave, which arise from a condensed ionic cloud that allows the soliton to travel along the filament [9].

These studies may provide an unprecedented molecular understanding on how actin filaments are related to aging and disease, due to a more complete understanding of their electrical properties in both muscle and non-muscle cells [32]. A future version of this program will account for the propagation of divergent ionic waves along actin filaments.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Design and implementation

The organization of the Mathematica notebook is presented in Fig. 19. In section 1 on the notebook, we included and processed numerous reported missense mutations on actin monomers [27]. In section 2 and 3 on the notebook we defined the electrolyte aqueous solution and filament model parameters described in sections 2 and 3 of this article. While section 4 of the program contains the soliton equations corresponding to the transmission line theory for actin filaments outlined in the appendix section C. Finally, the interactive plots are provided in section 5 on the notebook.

The initiation of the program is started by clicking the “run notebook” box located at the top of the interactive Mathematica notebook (Fig. 20). The program allows for simple to use input parameters (radius and surrounding temperature), along with the choice of actin ATP or ADP assembled monomers, six choices of actin isoforms, and either a wild-type or mutated actin conformation (see Fig. 21). If the mutant option is selected, two additional windows will open, one will show all the mutations along with the related disease name, and the other will provide a drop down list of all the mutations to select from (see Fig. 22). After the program has completed all computations and rendering of all plots, the last screen will open to notify the user that the calculations are finished (see Fig. 23). A text file named actin_input.txt will be downloadable to the current directory containing key input parameters for the run. For additional runs the text files will be numbered.
chloride $KCl$ as the electrolyte, and the intracellular model includes potassium chloride $KCl$, sodium (Na), as well as hydrogen-phosphate ($HPO_4^{2-}$) to represent larger charged anions in the biological environment (see Table 1). For the velocity and amplitude attenuation plots, the in vitro and intracellular conditions can be selected independently, or chosen simultaneously. However, there are two sections for the soliton results that represent the in-vitro and intracellular conditions separately.

A.1.2. Voltage input

In some plots, the input voltage is being used to compare in vitro and intracellular conditions, while a pre-defined domain or range is used in others. In the first situation the input voltage cannot be adjusted by the user (see Figs. 28a and 31). Otherwise, the input voltage can be chosen using the slider for values between $0.05\text{V} - 0.4\text{V}$ volts. This voltage input range includes the values used in invivo experiments [33,6]. For the soliton profiles, both in vitro and intracellular sections have an animation that compares two voltage inputs of $0.05\text{V}$ and $0.15\text{V}$ while the slider represents the change in time.

A.1.3. pH

The interactive notebook allows users to analyze pH solutions in the range between 6.0 and 8.0. A lower pH value comes from a greater number of hydroxide ions in the solution. This means more positively charged hydrogen ions protonate the residues on the actin monomer and decrease the charge of the filament when the G-actin is negative (see Table 2). Otherwise, a higher pH increases the number of hydroxide ions in solution, which results in an increase in the negative charge of actin at physiological conditions. Thereby, the pH of the solution effects the formation of the EDL by changing the concentration of counterions and coions that accumulate at the filament surface (see section 5.3).

A.1.4. Using the slider

The results in the Radial Electric Potential, Velocity, and Amplitude Attenuation sections include interactive plots with an adjustable slider that allows extensive analyses of the pH and input voltage. The sliders can be adjusted manually by sliding left or right, and also by clicking the “+” sign at the end of the bar for finer adjustments (Fig. 25). Additionally, a pH value can be fine tuned to a tenth of the value desired (Figs. 25a, 25c), where as the voltage can be adjusted to two hundredths of the nearest whole number (Figs. 25b, 25d).

Appendix B. Illustrative example

For physiological conditions, the Mathematica program produces the results and plots provided in reference [9]. Below, we provide the results and a brief analysis for an actin filament of radius equal to 35Å in the ADP nucleotide state and immersed in a electrolyte solution at 310 K.

B.1. Effective filament conductivity

Fig. 26 shows the effective filament conductivity results as a function of the pH. It can be seen that the relative filament conductivity in a in vitro electrolyte aqueous solution (blue curves) is...
lower than in the intracellular condition (orange curves). This behavior was observed in invitro experiments with actin filaments [33].

B.2. Radial electric potential

The absolute value of the linearized Poisson-Boltzmann radial electric potential as a function of the distance is displayed in Fig. 27 for both electrolyte conditions. The Fig. 27a reveals a higher electric potential magnitude in the intracellular condition (orange curve) when compared to in vitro condition (blue curve). The slider was used to increase the pH value showing an increasing relationship with the magnitude of the electric potential (Fig. 27b). This is an expected result, because the increase of the pH removes hydrogen ions from amino acid residues and exposes more negative charges on the protein.

B.3. Velocity profiles

The time average soliton velocities are shown as functions of the voltage input and pH for both electrolyte conditions in Figs. 28a and 28b, respectively. With increasing input voltage, the average velocity remains almost constant for the in vitro condition. Whereas, the average velocity is enhanced with increasing input voltage for the intracellular condition. Additionally, the average velocity increases with pH for the in vitro condition at a higher rate relative to the intracellular condition. A decay in the velocity over time is demonstrated in Fig. 29, and concludes that initially solitons travel faster under intracellular conditions when compared to intracellular conditions, however they decelerate faster and eventually become slower than those under in vitro conditions.

B.4. Amplitude attenuation profiles

The first amplitude plot (Fig. 30) demonstrates the soliton attenuation while allowing for the input voltage and pH to be adjusted using the slider. The peak of a decreasing soliton profile over time can be analyzed in Fig. 30. Here the pH of the solution has been adjusted between 6 and 8. For intracellular conditions, a lower pH value results in a faster decay of the soliton due to a weaker electrostatic screening of the EDL (Fig. 30a). The result of an increased pH is shown in Fig. 30b, where a soliton peak travels further for intracellular conditions.

The second amplitude attenuation plot (Fig. 31) shows the decay of two different soliton peaks with voltage inputs $V_0 = 0.05 V$ (dashed curves) and $V_0 = 0.15 V$ (solid curves) for in-vitro (blue color) and intracellular (orange color) conditions and pH 7. It can be seen that larger input voltages generate faster amplitude decay rates.

B.5. Soliton animation profiles

By clicking the button (▶), the animations in Figs. 32, 33, and 34 show how a soliton propagates down the filament length. Fig. 32 includes two snapshots of in vitro soliton animations at pH 7. On the other hand, Fig. 33 includes snapshots of the soliton propagation in intracellular conditions which initially show a faster soliton at higher voltage input but decelerate faster to eventually become slower than lower voltage input. In Fig. 34, we show the impact of pH on the soliton profiles in in vitro (a) and intracellular (b) conditions. We noticed that pH does not affect the soliton propagation in in vitro conditions. Whereas, a slightly faster soliton is produced at low pH in intracellular conditions. It can be seen that larger voltage inputs generate higher amplitudes, which is in agreement with experimental studies in invitro conditions [6].

Appendix C. Theory

In the following sections, we give a general explanation of the multi-scale approach used to produce the results for the interactive computational program. A detailed explanation on the theory can be found in a proceeding article [9].
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C.1. The atomistic scale (Å)

The residues on the protein and pH of the solution play a large role in the formation of the EDL, which is particularly important for consideration of mutated proteins. To allow for a model that reflects changes at the atomistic scale, we performed titration curves on the most recent actin models in the protein data bank, and used a zeta potential comparison to determine the most accurate description based on the polyelectrolyte nature of actin. The Cong model (385U) [21] was then uploaded into the pdb2pqr webserver to determine the pH dependent amino acids exposed on the protein. The volume of the filament was determined by using the “3v: voss volume voxelator” webserver, which was then used to calculate the radius (R = 23.83 Å), linear charge density (λ), and the surface charge density (σ).

C.1.1. Mutations, isoforms, and nucleotide states

Mutations can be found in all of the six human actin genes, and most often result in a substitution of an amino acid due to the change in a single base pair (missense mutation) [34]. The removal of a pH dependent residue has an effect even at the monomer scale, which is compounded in filament form by the number of added monomers. The replacement of a residue with another pH dependent amino acid will change the capacitance and both resistances for a given pH value.

C.2. The monomeric scale (nm)

The intrinsic properties of the actin monomer relate to the charge build up near the surface, and the ionic current next to the polymer. This can be described by an RLC circuit model, where R represents the resistor, C is the capacitor, and L is the inductor. The inductance has been shown to be negligible, and therefore, is not considered in the multi-scale approach [9].

C.2.1. Ion profiles in the electrical double layer

A detailed description of the ionic behavior in the electrical double layer is described using non-linear Boltzmann distribution of ionic concentrations.

\[ c_i(r) = c_i^{\text{bulk}} \exp \left[ - \frac{z_i e}{RT} \phi(r) \right] \]  

(1)

This equation describes the concentration of an ion between the surface of the actin and the bulk layer by using the ion concentration in the bulk \( c_i^{\text{bulk}} \), ion valence \( z_i \), Faraday’s constant \( F \), and a
scaling by the energy $RT$, where $R$ is the gas constant and $T$ the temperature.

Using the surface charge density ($\sigma$), Debye length ($\lambda_D = \epsilon RT / (F^2 \sum_i z_i^2 e_i^2)$), and dielectric permittivity ($\epsilon = \epsilon_r \epsilon_o$), along with the Bessel function of the second kind gives the potential energy

$$\phi(r) = \frac{\sigma \lambda_D}{\epsilon} \frac{K_0(r/\lambda_D)}{K_1(\lambda_D/\lambda_D)}$$ (2)

The parameter $r_1$ is the position of the zeta potential or slipping plane, and $r$ is a distance from the surface larger than the actin radius.

The ionic current is derived from the ionic flow equation

$$I_z = k(r)E_z + v_z(r)\rho_e(r)$$ (3)

where the electric field in the longitudinal (axial) direction $E_z$ is a result of the voltage input divided by the monomer length $V_o/\ell$, and $k(r)$ is the effective electric conductivity given by

$$k(r) = F^2 \sum_i z_i^2 u_i c_i(r)$$ (4)

The axial ion velocity profile is given by

$$v_z(r) = \frac{\mu E_z}{\rho \epsilon} \left( \phi(r) - \phi(r_1) \right)$$ (5)

where $\mu$ is the viscosity described in section 2.1.1.

The ionic charge density distribution is represented by

$$\rho_e(r) = F \sum_i z_i c_i(r)$$ (6)

Integration over the ionic flow equation gives ionic current density profile in the longitudinal direction when using $r_1$ and $l_b + r_1$ as the limits of integration with $r$ as the integration variable

$$I_z(r) = \int_{r_1}^{l_b + r_1} dr$$

where $l_b = e^2/(4\pi \epsilon_o k_B T)$ is the Bjerrum length. Therefore, we have

$$I_z = E_z \int_{r_1}^{l_b + r_1} dr + \int_{r_1}^{l_b + r_1} r v_z(r) \rho_e(r) dr$$

On the other hand, integration over the ionic flow equation in the transversal (radial) direction gives the radial current density from the solution of

$$\int_{r_1}^{l_b + r_1} \frac{l_b + r_1}{2\pi \ell^3} dr = \int_{r_1}^{l_b + r_1} \frac{\partial}{\partial r} \phi(r) dr + \frac{F^3}{RT} \sum_i z_i^2 u_i^{\text{bulk}} \int_{r_1}^{l_b + r_1} \phi(r) \frac{\partial}{\partial r} \phi(r) dr$$ (8)

The parameter $\ell$ is the diameter of an actin monomer and $u_i$ is the ion mobility of species $i$.

The numerical solution to these integrals, which contains the non-linear predictions from the Boltzmann statistics, were performed using mathematica software [11].

C.2.2. Resistance

From the solution of the ion current density profiles $I_1$ and $I_r$, Ohm’s law can be used along with the voltage drop $\Delta V = E_z/\ell$ to get the longitudinal and transversal resistances

$$R_l = \frac{\ell}{\pi ((l_b + r_1)^2 - r_1^2)|k_{\infty} + \Delta k_1|}$$ (9)

and

$$R_r = \frac{\ln((l_b + r_1)/r_1)}{2\pi \ell |k_{\infty} + \Delta k_1|}$$ (10)

respectively.

C.2.3. Capacitance

Capacitance arises from the build up of counterion charge near its negatively charged surface. Therefore, the short range forces of water crowding, ion size asymmetry, and ion-ion repulsion cannot be ignored. To include these, CSDFT calculations were used for an accurate consideration of the surface electric potential $\psi_0 = \phi(R)$. This process was explained in the supplement of a previous work [9], and can easily be done by using JACFC web application [24–26].

The differential capacitance representing a monomer is found to be

$$C_d = \frac{d\psi}{d\psi_0} = \tilde{C}_0 (1 - 2\theta \psi_0 + 3\tilde{C} \psi_0^2 + O(\psi_0^3))$$ (11)
Fig. 27. Absolute value of electrical potential as function of distance from the filament axes. Here plots for pH 6.5 (a) and pH 7.5 (b) are shown by using the slider. The orange and blue curves correspond to the intracellular and in vitro conditions, respectively.

Fig. 28. Average velocities as functions of input voltage for pH 7 (a) and as function of pH for input voltage 0.05 V (b). The orange and blue lines correspond to the intracellular and in-vitro conditions, respectively.

Fig. 29. Velocity as a function of time. The orange solid and blue dashed lines correspond to the intracellular and in vitro conditions, respectively.

For the total charge we integrate over the voltage drop and get

$$Q = 2\pi r \xi \hat{C}_o(V - bV^2) = VC_o(1 - bV^2) = VC(V)$$

where $b$ characterizes the non-linear behavior of the capacitance.

C.3. The filament scale (µm)

The flow of ions $I_l(x, t) = V(x, t)/Z$ along a polymerized actin filament comes from the transfer of ions from one unit cell (actin monomer) to the next. This is accomplished by using Kirchhoff’s laws on the discrete transmission line composed of $N$ unit cells, where $N$ represents the number of monomers in the filament. We then use a continuum approximation and a Taylor series expansion to get the perturbed Korteweg-de Vries (pKdV) differential equation

$$\frac{\partial W}{\partial \tau} - 6W \frac{\partial W}{\partial \xi} + \frac{\partial^3 W}{\partial \xi^3} = \mu_2 \frac{\partial^2 W}{\partial \xi^2} - \mu_3 W$$

where $W(\xi, \tau) = \frac{24}{\beta} Z^{-1/2} V(\xi, \tau) = \frac{24}{\beta} V^{1/2} I_l(\xi, \tau)$, $\xi = \frac{x}{\beta} - \frac{t}{\alpha}$, $\tau = \frac{t}{24\alpha}, \alpha = C_o Z > 0, \beta = 2\ell, \mu_2 = \frac{6\ell}{\beta}$ and $\mu_3 = \frac{24\ell}{\beta}$.

The approximate analytic solution for the soliton is

$$W(x, t) = -2 \left[ \Omega \left( \frac{t}{24\alpha} \right) \right]^2 \text{sech}^2 \left( \Omega \left( \frac{t}{24\alpha} \right) \left[ \frac{x}{\beta} - \frac{t}{\alpha} \right] \right)$$

where

$$Q = 2\pi r \xi \hat{C}_o(V - bV^2) = VC_o(1 - bV^2) = VC(V)$$

$$W(x, t) = -2 \left[ \Omega \left( \frac{t}{24\alpha} \right) \right]^2 \text{sech}^2 \left( \Omega \left( \frac{t}{24\alpha} \right) \left[ \frac{x}{\beta} - \frac{t}{\alpha} \right] \right) - \eta \left( \frac{t}{24\alpha} \right)$$
Fig. 30. Soliton peak attenuation as a function of time at a voltage input of 0.05 V and for pH 7 (a) and pH 8 (b) for in-vitro (blue) and intracellular (orange) conditions.

Fig. 31. Attenuation of input voltages 0.15 V (solid lines) and 0.05 V (dashed lines) for in-vitro (blue color) and intracellular (orange color) conditions and pH 7.

Fig. 32. Snapshots of soliton propagation animation in in-vitro condition at the beginning (a) and at an intermediate (b) distance along the filament. Both input pulses move at same speed.
\[ \eta(\tau) = -\frac{5}{4\mu_2} \left[ 4\mu_3 \tau + 3 \ln(5\mu_3) - 3 \ln\left(-4\Omega_0^2 \mu_2 \right) \right. 
\] 
\[ + \exp\left(\frac{4\tau \mu_3}{3}\right) \left[ 4\Omega_0^2 \mu_2 + 5\mu_3 \right] \]\] (15)

and

\[ \Omega(\tau) = \Omega_0 \left[ \frac{\exp\left(-\frac{4\tau \mu_3}{3}\right)}{1 + \frac{4\mu_3\Omega_0^2}{3\mu_2} \left(1 - \exp\left(-\frac{4\tau \mu_3}{3}\right)\right)} \right] \] (16)

\[ \Omega_0^2 = 24V_o/(2^{1/2} \gamma) \] with \( \gamma = 3\frac{C_0^2}{\rho Z^2} \)

The soliton propagation velocity is given by

\[ v(\tau) = -\frac{5}{4\mu_2} \left[ 4\mu_3 \right. \]
\[ \left. - \frac{4 \exp\left(\frac{4\tau \mu_3}{3}\right) \times \mu_3 \left[ 4\Omega_0^2 \mu_2 + 5\mu_3 \right]}{-4\Omega_0^2 \mu_2 + \exp\left(\frac{4\tau \mu_3}{3}\right) \times \left[ 4\Omega_0^2 \mu_2 + 5\mu_3 \right]} \right] \]

The expression for the impedance is \( Z \approx R^2_{\text{equiv}} + X^2_{\text{equiv}} \), where \( R_{\text{equiv}} = R_1 + R_2 \), \( X_{\text{equiv}} = T_0 \) actin/\( (2\pi C_0) \), and \( T_0 \) actin characterizes the time scale of the circuit unit.

Other important considerations are the maximum travel distance, average velocity and vanishing time represented by \( x_{\text{max}} \), \( v_{\text{avg}} \), and \( t_{\text{max}} \), respectively. The maximum travel distance is given by

\[ x_{\text{max}} = |(1 - t_{\text{max}}/\alpha)\beta| \]

and the average velocity is

\[ v_{\text{avg}} = \frac{1}{t_{\text{max}}} \int_0^{t_{\text{max}}} v(t) dt \]

The vanishing time is the solution of the implicit equation

\[ \Omega^2 \left[ (\text{max} \times 24\alpha) \right] = 0.01 \times \Omega_0^2 \]

which represents the time when the soliton amplitude attenuates to 1% of its initial amplitude.

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