JACFC (Electrical Signal Propagation Simulations)

User's Guide

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I. OVERVIEW

The Java Application for Cytoskeleton Filament Characterization (JACFC) provides both experts and non-experts in the field suitable tools to determine the polyelectrolyte nature of cytoskeleton filaments. By using comprehensive computer models and high performance algorithms, the software aims to produce valuable data for elucidating the molecular mechanisms modulating the electrical signal propagation, stability and bundle formation of microtubules and F-actin filaments under different molecular (wild type, isoforms, mutants) and environmental (physiological and non-physiological) conditions. As a unique feature, JACFC web application allows users to perform these calculations online without computational restrictions. Ultimately, these studies may figure out whether molecular and cellular alterations substantially alter the equilibrium of interactions and trigger abnormalities in the bundling and signal propagation during various disease states.

JACFC functionality and design build up from our previous JAVA Swing platform CSDFTS [1] and Matlab platform MPBEC [2] graphical user interface software. The first application aims to characterize nanomaterials and molecules of approximately spherical and cylindrical shapes immersed in aqueous electrolyte mixture solutions. Whereas, the second applications is able to perform biomolecular electrostatic calculation on biomolecules with irregular shapes. JACFC performs calculations based on our theories and models published in references [3, 4]. The web application version of JACFC was deployed using webswing application [5].

The version 1.0 of the JACFC offers two modules : 1- Electrical signal propagation, 2- Stability and aggregation. In this guide, we will discuss the first application. Eukaryotic cells may transport metal ions such as calcium preferentially along the surface of F-actin and microtubules. This is related to the condensation of counterions in the diffusive layer of the electrical double layer, which move freely along these filaments. These (bionanowire) ionic currents have been investigated theoretically using conventional nonlinear dispersive electric circuit transmission line models, revealing slow localized traveling waves (solitons) along F- actin and microtubules. JACFC aims to account for extremely sensitive and compelling polyelectrolyte properties of cytoskeleton filaments and environmental conditions playing a fundamental role in the electrical conductivity of these filaments. For instance, the charge accumulated in the polymerization state has been shown to alter its ability to interact electrostatically. Similarly, tubulin and G-actin isoforms have different charges according to their amino acid sequence. In a similar vein, mutations reduce the charge of actin and have reportedly caused the mutant filaments to spontaneously bundle. Thus, filaments formed by these isoforms and mutants might have different conducting properties. Another charging / discharging mechanism is related with alterations in the pH solution and electrolyte conditions affecting the titration of surface groups. All of these observations provide evidence on the polyelectrolyte nature of F-actin and microtubules associated with the formation of an electrical double layer, which provides unique, even still poorly understood, conducting and bundling formation properties.

To elucidate the molecular mechanisms modulating the electrical signal propagation, this JACFC module implements the theory recently published in our article for F-actins[]. The innovative multi-scale approach is able to account for the atomistic details of a protein molecular structure, its biological environment, and their impact on electrical impulses propagating along wild type actin filaments. The formulation includes non-trivial contribu-

tions to the ionic electrical conductivity and capacitance coming from the diffuse part of the electrical double layer of G-actins. This monomer characterization is utilized in a non-linear inhomogeneous transmission line prototype model to account for the monomer–monomer interactions, dissipation and damping perturbations along the filament length. The approach provides novel, simple, accurate, approximate analytic expressions for the soliton (ionic wave) for the transmission line model and electric circuit elements. Additionally, JACFC uses a the numerical solver that takes advantage of high performance Fortran90 routines and optimized libraries that enable the user to obtain solutions at low-to-moderate computational cost depending on the the time and distance grid resolutions, and the characterization of the actin filament and the electrolyte solution, among other factors. As a unique feature, this multi-scale theory is able to account for molecular structure conformation (mutation) and biological environment (protonations/deprotonations.

Overall, JACFC does not require specialized training and expertise in computational and theoretical biology, which is often an obstacle for many researchers, experimentalists, even students lacking these requirements. By simply holding the mouse pointer over the corresponding text or blank box, the user will find in each screen helpful information about how to fill out the input data. The user will also find default values for key input parameters and preselected algorithms to speed up the setup of the input data. However, they may be easily changed at any time. Moreover, JACFC tests all the input data before running the application to avoid the incorrect use of the software and prevent meaningless results. At the end of the calculations, JACFC generates two-dimension plots of selected output files to provide graphical visualization of the electrical impulse shape, attenuation and kern propagation velocity of the ionic waves (solitons) traveling along F- actins. Finally, all the output data files are properly saved and organized in a user-designated folder for post-analysis purposes. This user's guide also includes examples to illustrate the solver performance and applicability. Further information including a tutorial video and the web application can be found in our website

http://marucholab.myqnapcloud.com/WordPress/electricalsignalpropagation/

II. ELECTRICAL SIGNAL PROPAGATION MODULE

A. Description

In this section we describe the screen sequence generated by the web application. The first, second and third screens correspond to "*project window*", "*model window*", and "*results visualization window*", respectively. Each screen provides information to help the user fill out the input data by moving the mouse pointer over the corresponding text or blank box (see Figure 1).

1. Main Window: Module Selection

The Project window shown in Figure 2 is the main screen which provides user access to the *Menu*, *Information* and *Model Sections*.

The menu section, located at the top left corner of the window, contains the *File*, *Tools* and *Help menu*s. The *File Menu* contains the *Results Visualization* and *Exit* options (see

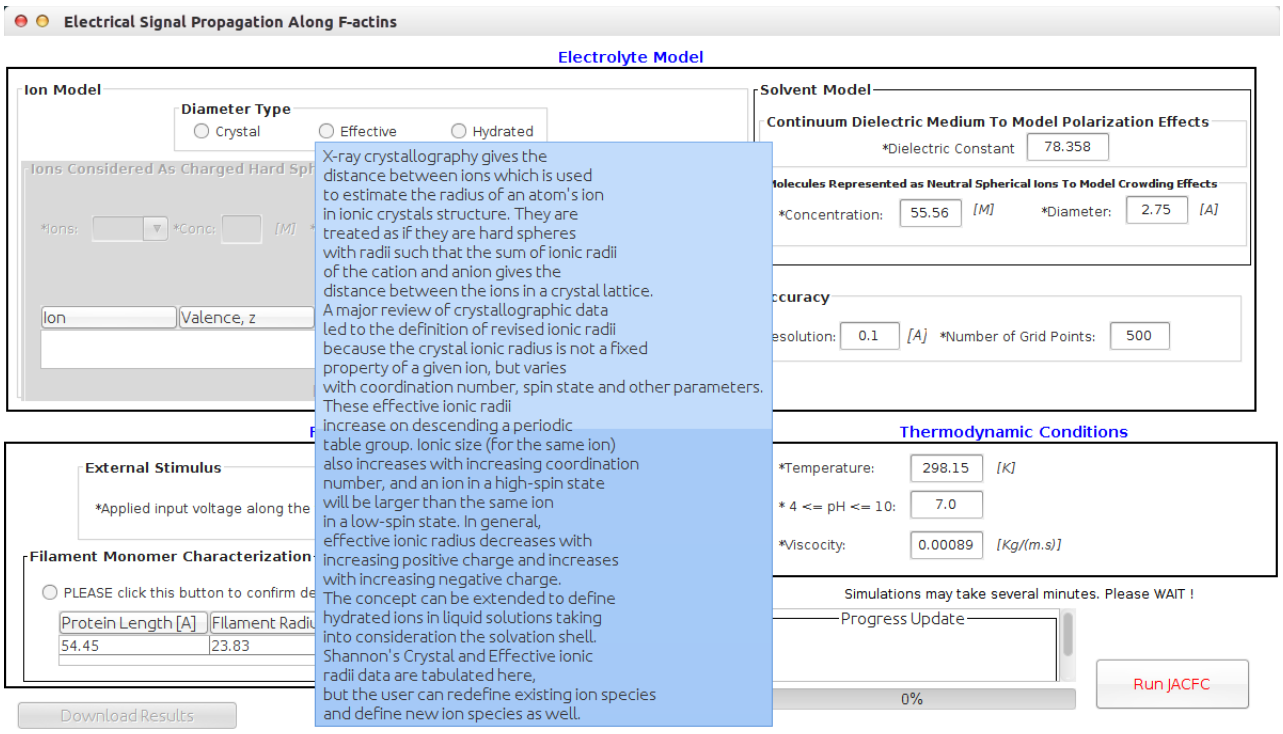


Figure 1: Help Messages.

Figure 3(a)). The *Results Visualization* option may be used after running the simulation. This option allows users to select output file(s) and visualize the solution(s) in two dimensional plot(s).

The *Tools Menu* contains the *Browse PDB files, Crystal Ion Library, Effective Ion Library* and Hydrated Ion Library options (see Figure 3(b)). The tool *Browse PDB files* is used for biophysical applications only. It allows users to open a web browser and download protein molecular structure(s) from the protein data base web page (http://www.rcsb.org/). The user may use this tool at anytime. The *Ion Library* tools provide the user access to the tables pretabulated with specific information on ion species, valences and diameters that are required to characterize the electrolyte aqueous solution. These tools can be used to redefine existing ion species and define new ion species as well. The last menu in Figure 3(c) is the *Help Menu* which provides access to the user's guide, software license and contact information.

The *Select the research study* section is located at the central-bottom part of the window. To select the Electrical signal propagation module, the user has two options: *Actin filaments* and *Microtubules.* The former option is only available in this JACFC version.

The *Electrolyte Aqueous Solution Model* is located right below the *Select the research study* section. JACFC offers two electrolyte aqueous solution theories. NLPB uses an implicit solvent model and considers electric interactions only, whereas, CSDFT uses an explicit solvent model (SPM) and considers not only the electric, but also the entropic and ion-ion correlation interactions (see comparative Figure 4). The latter option is only available for this module, which is required to perform the capacitance calculations.

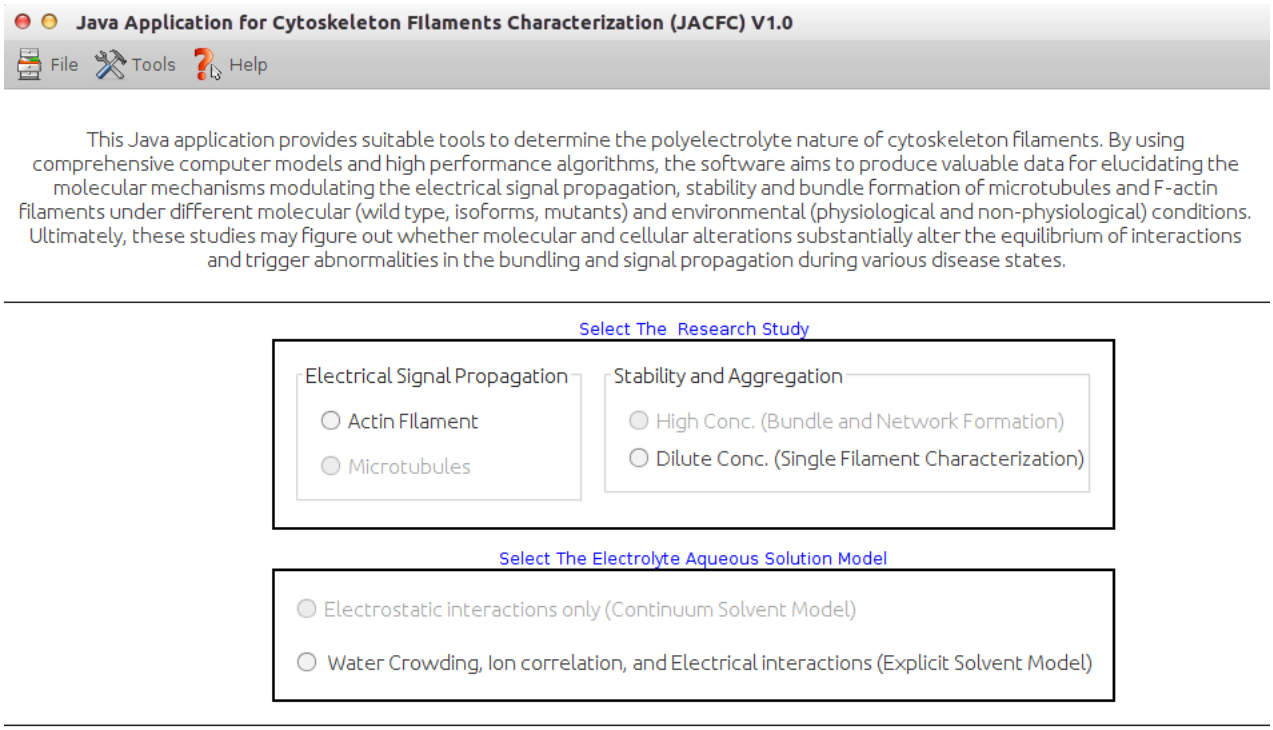


Figure 2: Project Window - main screen.

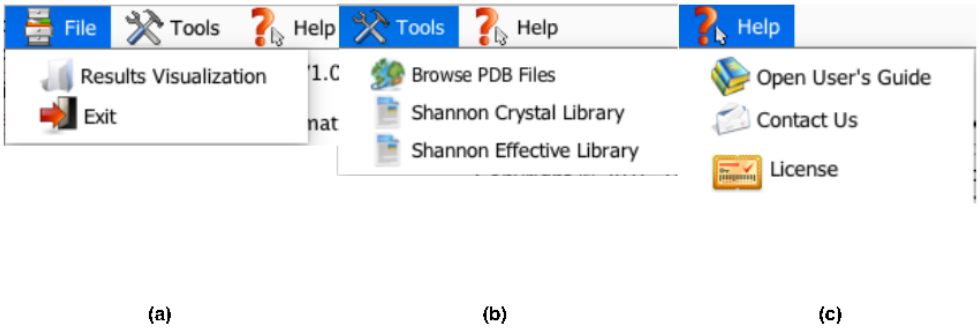


Figure 3: (a) File Menu. (b) Tools Menu. (c) Help Menu.

2. Model Window: system and solver configuration

In this screen, most of the text based user interaction occurs (see Figure 5). It contains the following modules: *Electrolyte* Model, *Filament Model*, and *Thermodynamic conditions* Options.

The *Ion Model* section shown in Figure 6 allows users to characterize the electrolyte solution by providing the bulk concentration $[\rho_i^0]$ and the valence z_i for each ion species i. Each ionic species i is represented by charged hard spheres of diameter d_i and relative mobility Mb_i (e.g., ionic mobility per Potassium mobility). JACFC offers a pretabulated crystal, effective and hydrated ionic diameter types and relative mobilities which are estimated using different experimental techniques [**?**]. To characterize the electrolyte solution, the user has to select the first ion species and its properties, then click the button “Add”, and subsequently repeat the procedure to add more ion species. The “Delete” and “Update”

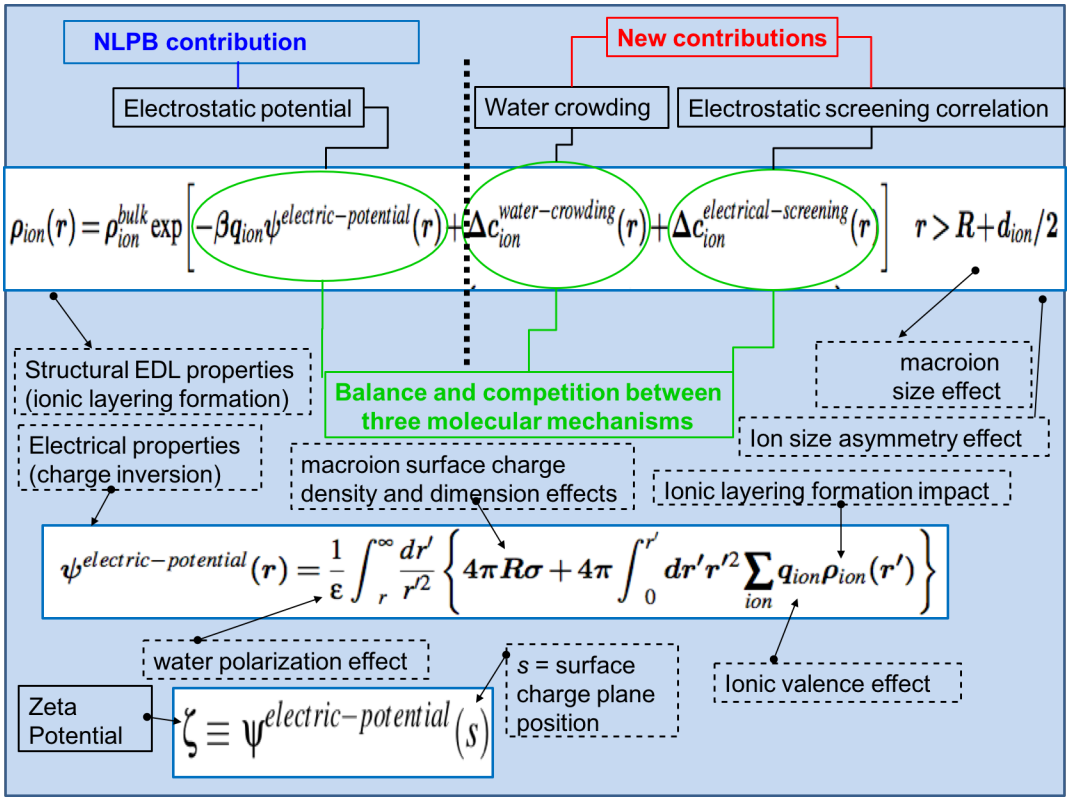
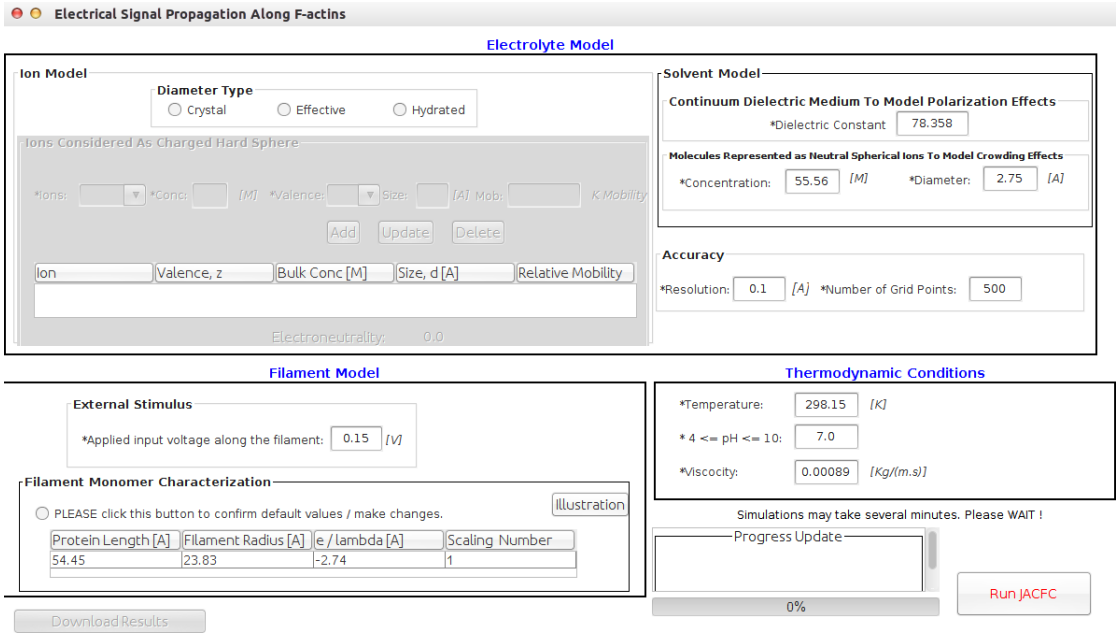


Figure 4: CSDFT theory

buttons allow users to remove and change the properties of a previously selected ion. Once the user selects all the ion species (e.g. valence and bulk concentration), the electroneutrality condition (e.g. $\sum_i z_i[\rho_i^0] = 0$) must be satisfied. Otherwise, the user will receive an error message to correct the input data. The status of this condition is displayed at the bottom of this section. Note that only ion species comprising the electrolyte solution must be defined in this section. Hydrogen and Hydroxide ions controlling the pH level of the electrolyte solution are assigned by JACFC automatically.

The *Accuracy* section shown in Figure 5 allows the user to configure key parameters that play a fundamental role in the solver performance. They control the accuracy and computational cost. The radial grid *resolution* represents the regular separation distance *h* between two consecutive points in the domain discretized of the radial distance to solve electrostatic potential en the EDL, and consequently, the capacitance numerically. The value recommended for this parameter is 0.1Å. The domain of the solution ranges from the filament surface (e.g. the radius *R)* to the cutoff *L.* The latter is automatically determined to provide the correct (long range) asymptotic behavior of the mean electrostatic potential, and consequently, satisfy the electroneutrality condition of the system. The *number of grid points* N_s determines the traveling distance and time resolution for the soliton solution as follow: $h_x = X_{max}/(N_s - 1)$ and $h_t = T_{max}/(N_s - 1)$, where X_{max} and T_{max} are the maximum traveled distance and the vanishing time, respectively. The value recommended for this parameter is 500.

We note that the computing time is highly dependent on radial grid *resolution* for the electric potential, rather than the number of grid points for the soliton solution calculations. The non linear capacitance parameter b (saved in the bco.txt output file) is indeed very



(a) Electrical Signal propagation along F-actins

Figure 5: Model window

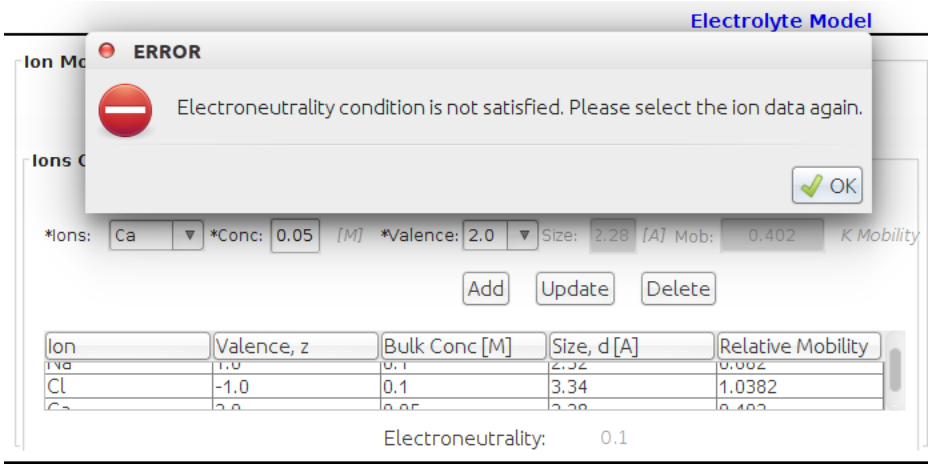


Figure 6: Ion Model.

sensitive to the radial grid resolution. The user may use a lower *resolution* to speed up the calculations and reduce the allocated RAM memory at the risk of loosing accuracy in the capacitance calculations.

The *Solvent Model section* shown in Figure 7 allows users to characterize the structural and electric properties of the solvent. JACFC considers the solvent as neutral polar molecules. It requires the value of the uniform bulk dielectric permittivity constant ϵ to model the solvent electrical properties. Additionally, it requires the solvent molar bulk concentration $[\rho_w^0]$ and molecular diameter d_w to model the solvent entropy properties. The default values displayed in this section correspond to the experimental values for water.

In the *Filament Model section,* the filament is represented as a long cylindrical rigid biomolecule characterized by a voltage (external stimulus) difference between the ends of

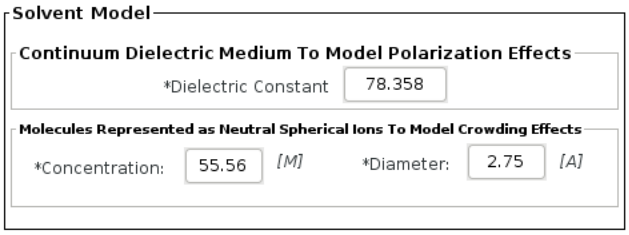
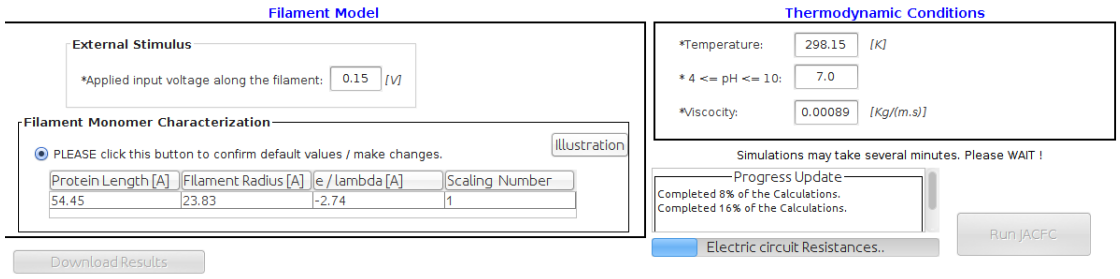


Figure 7: Solvent Model.

the filament V, the effective radius R, as well as, the characteristic longitudinal length $\ell = e/\lambda$ (electron charge e per axial charge density λ at pH 7). Additionally, the G-actin protein (monomer) is characterized by a short rid cylinder of length equal to the size of the protein and radius and characteristic longitudinal length equal to those used for the filament. Other important parameter of the transmission line model is the definition of the number of G-actin proteins (e.g., the scaling number parameter) represented by each electric circuit unit. In the linear biomolecule model used in our article [], only one G-actin is considered per electric circuit. Thus, the corresponding value for this parameter is one (default value). However, the user is able to assign a different parameter value to investigate other transmission line models.

Typically, the effective filament radius and characteristic longitudinal length are obtained from experiments. Different experiments generate different values, though. Other way to estimate these parameters is from the filament molecular structures. This calculations can be performed using the other JACFC module: Stability and Aggregation. In fact, the default values for the parameters ℓ and R are those predicted by the Cong molecular structure model for wild-type actin filaments [] (see Figure 9). The web application has pre-loaded the most recent wild-type molecular structure models for actin filaments. However, the user may upload other molecular structures in pdb format including those accounting for mutations and isoforms.



(a) Biomolecules

Figure 8: Filament Model.

The *Thermodynamic Conditions* option is used to define the electrolyte solution temperature, pH and viscosity. The default value displayed in Figure 8 corresponds to an aqueous solution at room temperature. If the user changes the pH value, the application will not consider the value assigned for the parameter ℓ in the soliton calculations. Instead, it will use the value obtained from the following expression for the total charge in e units of the

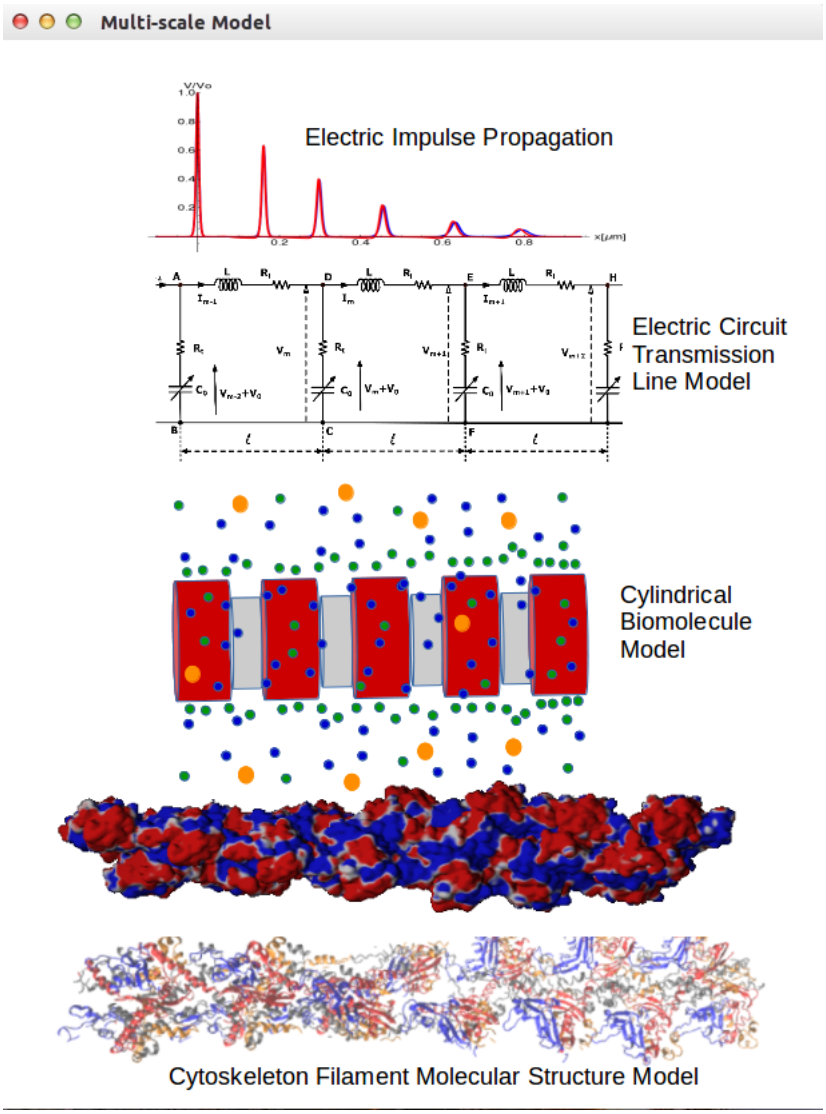


Figure 9: Filament Model illustration.

13 monomers filament

$$Q(pH) = 31530 - 24213.44pH + 7128.25pH^2 - 887.94pH^3 + 7.42pH^4 + 9.60pH^5 - 0.92pH + 0.0277pH^7$$

This expression comes from the interpolation of the values obtained for Q at pH values 4,5,6,7,8, and 10. These values were calculated using the JACFC module: Stability and Aggregation and the Cong molecular structure model for the actin filament. If the pH is not equal to 7.0, the application will also add an small amount of HCL and NaOH solution to model the assigned value of the pH in the electrolyte.

After all changes on preselected parameters and options are completed, all boxes are filled out and precalculations are over, the user is ready to press the button *"Run JACFC*. The web application will test all the input data, and send the user warning messages if unusual/nonphysical values are assigned to the required parameters or missing information is detected. Once the configuration pass all the tests, the application will run the simulation and show the performed calculations in the progress bar.

3. *Results Visualization*

The *results visualization* window will appear once the simulation is over. This screen allows the user to select the output file(s) and visualize the numerical solution(s) in two dimension plot(s) (see Figures 10). To change the plot properties the user must right click on it. The user can also visualize the data on spreadsheets as shown in Figure 10 d).

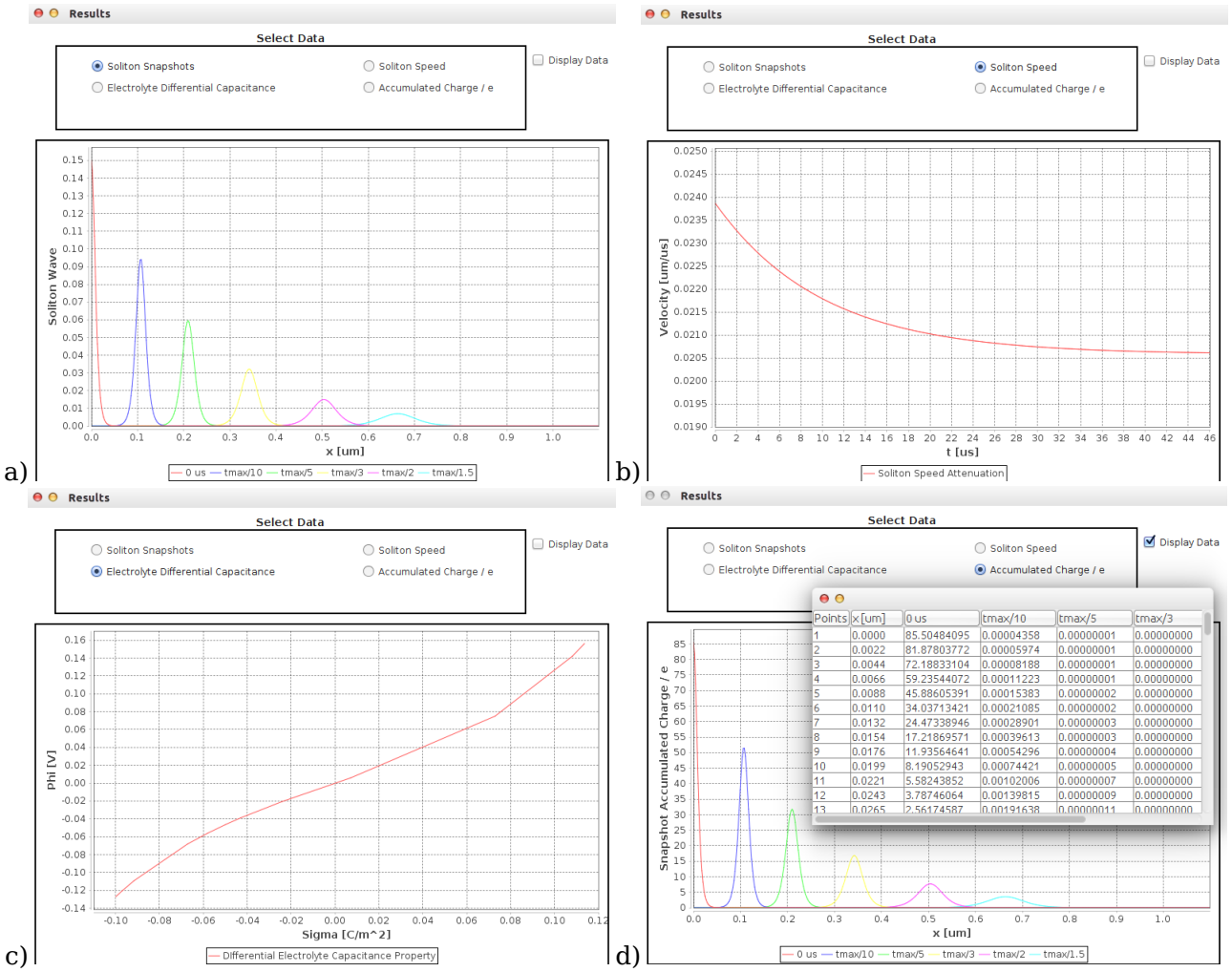


Figure 10: Results Visualization

4. *Output files*

JACFC generates the following output files: “OmegaEta.dat” (eqs. 10 and 11 in reference [3]); “Velocity.dat” (eq. 13 in reference [3]); “Solitonxt.dat” and “Solitonsnap.dat” (eq. 9 in reference [3]), “Qcap.dat” and “Qcapsnap.dat” (eq. 4 in reference [3]). Explicit expressions for these properties are provided in Appendix A. The size of these files may vary depending on the number of ions species, number of grid points, and electrolyte model. These dat format files are formatted in a multi-column arrangement where the row number corresponds to the number of grid points, and the columns provide the discretized distance in unit of

Å, the discretized time in unit of μs, and the numerical solution(s) (see Table I). Relevant information on the capacitance calculations is provided in the txt format files "zipsig.txt" and "bco.txt" whereas the characterization of other electric circuit components and soliton properties are contained in the log file "out.txt" . Additionally, information on the input data and solver configuration are included in the files "inp.in" and "input.file" for signal propagation and capacitance calculations, respectively. If the *molecular structure* option is selected, the GUI generates the following additional files: "input.pdb" (copy of the molecular structure uploaded by the user); "input.pqr" (pdb2pqr output data); "input.propka" (propka output data) ; "out.pdb" (molecular structure information with heterogem atoms removed); "out.xyzr" (atomic positions in xyzr format); "vol.txt" (3v and provol output data including information on the macroion surface and volume as well as the number of residues and atoms); "lengthandcharge.txt" (total macroion charge and dimensions), and "radiusandcharge.txt" (parameters characterizing the macroion radius and charge density).

Once the simulation is over, the output files can be downloaded in a zip file by pressing the *Download Results* button (See Figure 2).

B. Examples

JACFC reproduces the results published in reference [3]. We considered two electrolyte solutions relevant in biophysics, one representing an intracellular biological environment in physiological solution conditions (140mM K^+, 4mM Cl^-, 75mM HPO_4^{2-}, and 012mM Na^+ at 310K), whereas the other represents in vitro conditions 5 (0.1M K^+ and 0.1M Cl^- at 298K). Additionally, we considered both 0.05V and 0.15V peak voltage inputs in order to simulate the typical electric potential used in cells and single microfilament experiments. Our results reveal the propagation of electrical signal impulses in the form of solitons for the range of voltage stimulus and electrolyte solutions typically present for intracellular and in vitro conditions. The approach predicts a lower electrical conductivity with higher linear capacitance and non-linear accumulation of charge for intracellular conditions. Our results show a significant influence of the voltage input on the electrical impulse shape, attenuation and kern propagation velocity. The filament is able to sustain the soliton propagation at almost constant kern velocity for the in vitro condition, whereas the intracellular condition displays a remarkable deceleration. Additionally, the solitons are narrower and travel faster at higher voltage input.

ACKNOWLEDGMENTS

This work is supported by NIH Grant SC1GM127187-03.

File name	Description
OmegaEta.dat	The first column is for the time t [μs]. The second and thrid columns correspond to the dimensionaless expressions $\eta(t)$ and $\omega(t)$ given by equations 11 and 10 in ref. [], respectively.
Velocity.dat	The first column is for the time t [μs]. the second column contains the values of the velocity propagation $v(t)$ [$\mu m/\mu s$]
Solitonxt.dat	The first column is for the distance x [μm]. The second column is for the time t [μs]. the third column corresponds to the expression $V(x,t)$ [mV]
"Solitonsnap.dat	The first column is for the distance x [μm]. The remaining 6 columns correspond to the expressions V$(x,0)$, V$(x, \frac{t_{max}}{10})$, V$(x, \frac{t_{max}}{5})$ V$(x, \frac{t_{max}}{3})$, V$(x, \frac{t_{max}}{2})$, and V$(x, \frac{t_{max}}{1.5})$ in [mV] units. t_{max} [μs] is the vanishing time provided in the out.txt file.
"Qcap.dat	The first column is for the distance x [μm]. The second column is for the time t [μs]. the third column corresponds to the expression $Q(x,t)$ in [e]
"Qcapsnap.dat	The first column is for the distance x [μm]. The remaining 6 columns correspond to the expressions Q$(x,0)$, Q$(x, \frac{t_{max}}{10})$, Q$(x, \frac{t_{max}}{5})$ Q$(x, \frac{t_{max}}{3})$, Q$(x, \frac{t_{max}}{2})$, and Q$(x, \frac{t_{max}}{1.5})$ in [e] units. t_{max} is the vanishing time provided in the out.txt file.
zipsig.txt	Twelve rows, two columns table. The first and second columns are for the surface electric potential ϕ [V] predicted by CSDFT for a given surface charge density σ [$\frac{C}{m^2}$], respectively.
bco.txt	One row, two columns table. The first and second columns are for the non linear parameter b [V^{-1}] and the capacitance per unit of surface C_o [$\frac{F}{\mu m^2}$] .
out.txt	log file contains the values predicted for Maximum traveled distance [A], Vanishing time [μs], Average velocity [$\mu m/\mu s$], Debay Length [A], Distance resolution [μm], time resolution [μs], longuitudinal resistance [Ω], tranversal resistance [Ω], and impedance [Ω], among others.

Table I: Output Files created by JACFC.

[1] M. Marucho, A Java Application to Characterize Biomolecules and Nanomaterials in Electrolyte Aqueous Solutions, Comput Phys Commun. 2019 Sep;242:104-119.

[2] Vergara-Perez, S. and Marucho, M. (2016). MPBEC, a Matlab Program for Biomolecular Electrostatic Calculations, Comput. Phys. Commun. 198 : 179-194

[3] Christian Hunley, Diego Uribe, and Marcelo Marucho, A Multi-scale approach to describe electrical impulses propagating along Actin filaments in both intracellular and in-vitro conditions, RCS Adv. 2018, 1207.

[4] Ovanesyan, Z.; Medasani, B.; Fenley, M. O.; Guerrero-García, G. I.; Olvera de la Cruz, M. and Marucho, M. (2014). Excluded volume and ion-ion correlation effects on the ionic atmosphere around B-DNA: Theory, simulations, and experiments, J Chem Phys 141 : 225103 (PMCID: PMC4265039).

[5] https://www.webswing.org

[6] R. D. Shannon (1976). "Revised effective ionic radii and systematic studies of interatomic distances in halides and chalcogenides". Acta Crystallogr A. 32: 751–767.