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Java application for cytoskeleton filament characterization (JACFC)

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Abstract

JACFC is a Java web application (<http://neuronanobiophysics.utsa.edu/>) that provides both experts and non-experts in the field suitable tools for elucidating the molecular mechanisms modulating the electrical signal propagation, stability, and bundle formation of microtubules and actin filaments under different molecular (wild type, isoforms, mutants) and environmental (physiological and pathological) conditions. This acknowledgment might reveal the potential role of cytoskeleton filaments in neuronal activities, including molecular-level processing of information and neural regeneration. Molecular understanding of the polyelectrolyte properties of bionanowires, is also crucial for development of reliability, highly functioning small devices with biotechnological applications such as bionanosensors and computing bionanoprocessors.

Keywords

Cytoskeleton filaments; Neuron information processing; Electrical activities in single neurons

Code metadata

Current code version	v1.0
Permanent link to code/repository used for this code version	https://github.com/SoftwareImpacts/SIMPAC-2021-22
Permanent link to Reproducible Capsule Legal Code License	GENERAL PUBLIC LICENSE
Code versioning system used	none
Software code languages, tools, and services used	JAVA Swing, Fortran, Webswing, Jmol, pdb2pqr, Propka, Provol, 3v.
Compilation requirements, operating environments & dependencies	
If available Link to developer documentation/manual	http://neuronanobiophysics.utsa.edu/
Support email for questions	csdfts.comphys@gmail.com

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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.

1. Introduction

Actin filaments (F-actin) and microtubules (MTs) are highly charged double stranded rod-like polyelectrolytes formed by polymerization of G-actin and tubulin subunits, respectively. These cytoskeleton filaments are essential for various biological activities in eukaryotic cellular processes as diverse as directional growth, shape, division, plasticity, and migration [1,2]. They are able to overcome repulsive electrostatic interactions to form higher-order structures (bundles and networks). According to available experimental data, cytoskeleton filaments may also transport ions preferentially along the surface of F-actin and microtubules [3]. This new direct path for transporting ions inside neurons might be of fundamental importance for many electrical processes in ion channels, dendrites, axon, terminals and soma [4]. The basis for these filaments to form higher-order structures and enhance their electrical conductivity appears primarily or exclusively dominated by their biochemical and biophysical (polyelectrolyte) properties. However, the underlying principles that support the polyelectrolyte nature of MTs and F-actins on their biological functions are still poorly understood due to the lack of appropriate methodologies. Conventional computational tools and approaches break down for cytoskeleton filaments because they are limited by their approximations and computational cost. The current understanding of the complex interplay between the polyelectrolyte properties of cytoskeleton filaments and biological environment is based mainly on mean-field theories like the non linear Poisson–Boltzmann (NLPB) formalism and its modifications [5], which consider electrostatic potential interactions only. They do not account for water crowding, ion size asymmetry, or electrostatic ion correlation effects. Only when accounting for all of these features can one formulate a quantitative description of the conducting and bundling formation properties of these filaments. More accurate methodologies, e.g., full atomistic molecular dynamics and Monte Carlo simulations, involve extremely high computational cost and parallel computing resources. Thus, they cannot be used to explore a large number of molecular structures (wild type, mutants, isoforms) and intracellular environments. Additionally, scientific software developed to characterize biomolecules in aqueous solutions usually require specialized training and expertise in computational biology, expensive commercial licenses, and access to clusters or supercomputers, which are often an obstacle for many researchers, experimentalists, even students lacking these requirements [6]. Thus, it is essential to develop not only more accurate and efficient approaches but also readily accessible, friendly implementation of a software package that provides experts and non-experts a visualized guide (graphical user interface) to perform these calculations without limitations.

2. JACFC

JACFC is a Java web application based on an innovative multi-scale approach for cytoskeleton filaments. The software allows the user to use various models and approaches for elucidating the molecular mechanisms modulating the electrical signal propagation, stability and bundle formation of microtubules and actin filaments under different molecular (wild type, isoforms, mutants) and environmental (physiological and pathological) conditions. It is able to account for the atomistic details of the filament molecular structure, its biological environment, and its impact on these phenomena. The electrical signal propagation formulation includes non-trivial contributions to the ionic electrical conductivity

and capacitance coming from the diffuse part of the electrical double layer of G-actins. JACFC utilizes this monomer characterization in a non-linear inhomogeneous transmission line prototype model to account for the monomer–monomer interactions, dissipation, and damping perturbations along the filament length [7]. While the approach to calculate stability and bundle formation is based on a solvation classical density functional theory which accounts for not only the electrostatic but also the entropic and many-body interactions [8]. This feature has been particularly useful for identifying and characterizing dominant interactions and molecular mechanisms governing the stability and aggregation of biomolecules under a variety of electrolyte conditions. As a unique feature, users can perform these calculations on the JACFC webserver without computational restrictions. 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 can find in each screen helpful information about how to fill out the input data. The user can also use default values for key input parameters and preselected algorithms to speed up the input data setup. 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. JACFC website includes tutorial videos, user guides, a discussion forum, and examples to illustrate its use and applicability.

2.1. Design and implementation

JACFC web application offers two modules : 1- *Electrical signal propagation*, 2- *Stability and aggregation* (see Fig. 1).

On the first screen, 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. To select the *Stability and Aggregation* module, the user has two options: *Dilute conc.* (single filament characterization) and *High conc.* (Bundle and Network formation). Only the former option is 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. *CSDFT* uses an explicit solvent model and considers the electric and the entropic and ion–ion correlation interactions.

On the second screen (Figs. 2 and 3), the electrolyte section is used to define the ionic species and concentrations, as well as the solvent properties, temperature and pH level of the electrolyte solution. The default numerical solver configuration can be changed if needed. For electrical signal propagation applications, the Cytoskeleton filament model is used to define the external input voltage applied along the filament, as well as the monomer

characterization (G-actins). Whereas, for stability and aggregation applications, this section is used to define either the molecular structure or the surface charge and radius of filament. Finally, the button Run JACFC is used to run the numerical simulation. The results can be downloaded to the user's computer in a zip file using the Download Results button. After the simulations are over, a third screen automatically opens to visualize the results in 2D plots. The logistic flow diagram is provided in Fig. 4.

2.2. Publications and impact

JACFC has enabled the investigation of the electrical signal propagation of wild-type actin filaments for the range of voltage stimulus and electrolyte solutions typically present for intracellular and in vitro conditions [7]. The approach predicts a lower electrical conductivity with higher linear capacitance and non-linear accumulation of charge for intracellular conditions. The 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.

As a unique feature, JACFC is able to account for molecular structure conformation (mutation) [9,10] and biological environment (protonations/deprotonations) changes often present in pathological conditions. Ultimately, these studies may elucidate whether molecular and cellular alterations substantially alter the equilibrium of interactions and trigger abnormalities in the bundling and signal propagation during various disease states. This acknowledgment might reveal the potential role of cytoskeleton filaments in neuronal activities, including molecular-level processing of information [11] and neural regeneration [12,13]. Molecular understanding of the polyelectrolyte properties of bionanowires, is also crucial for development of reliability, highly functioning small devices with biotechnological applications such as bionanosensors and computing bionanoprocessors [14–16].

Acknowledgments

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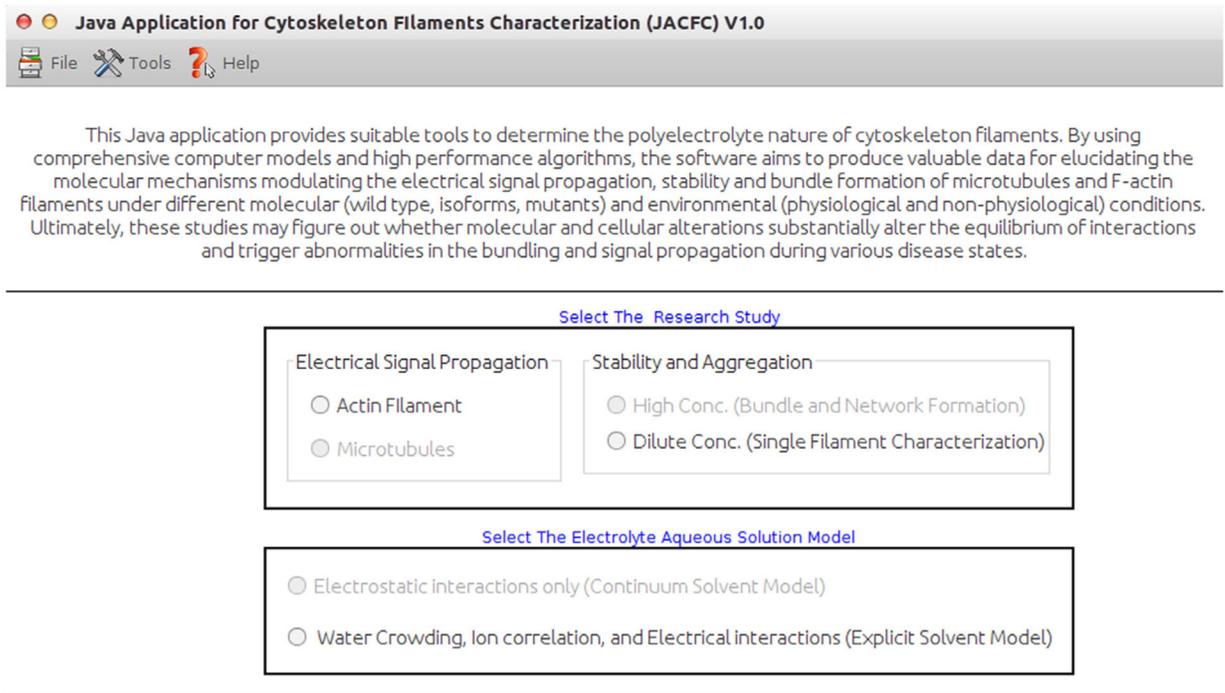


Fig. 1.
JACFC modules option (first screen).

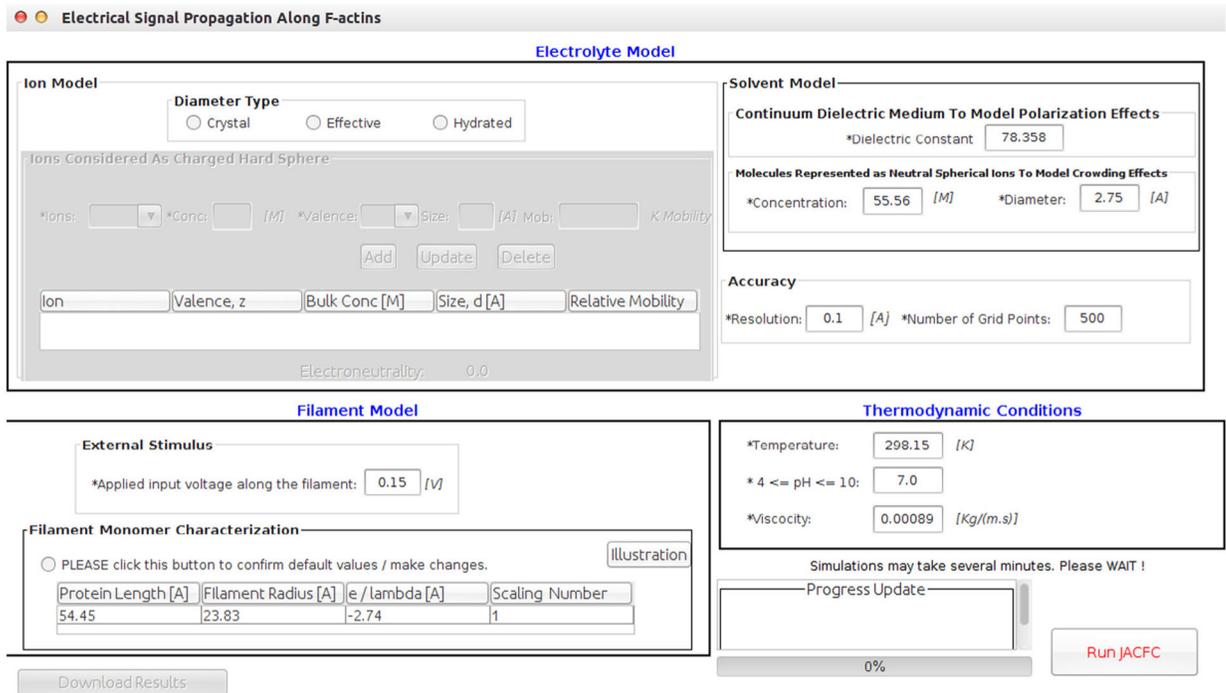


Fig. 2.
Electrical signal propagation module.

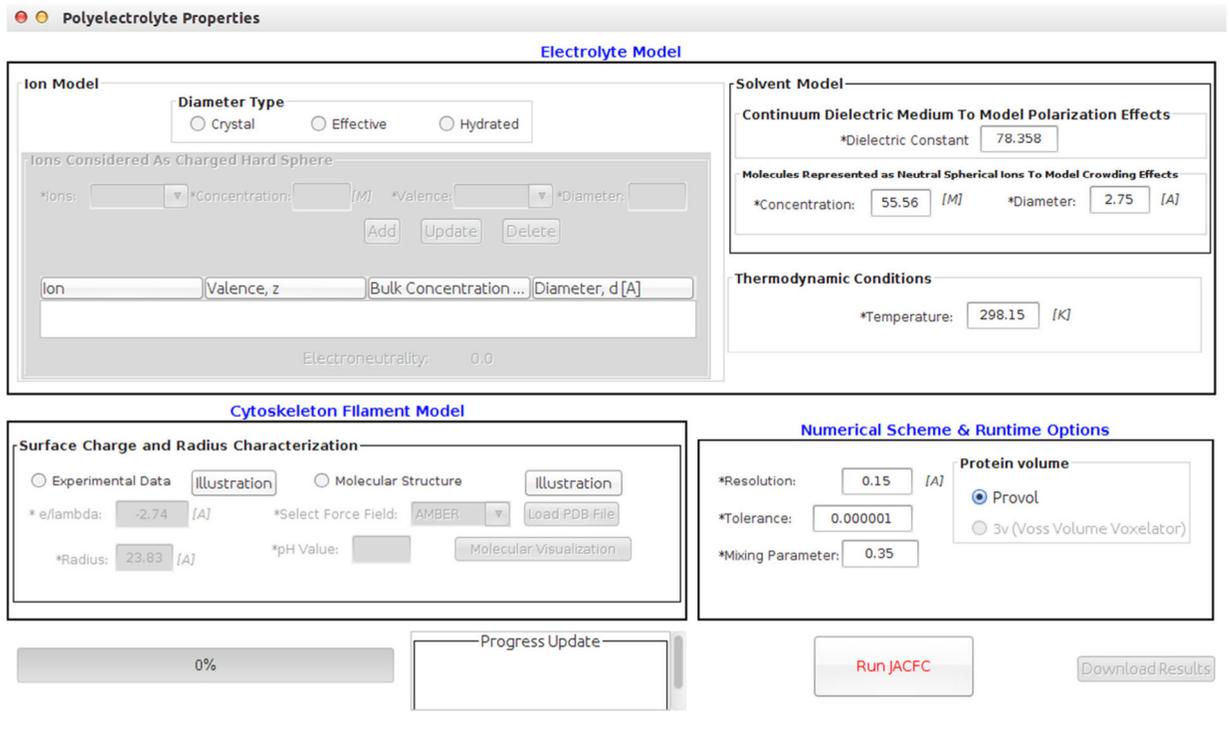


Fig. 3.
Stability and aggregation module.

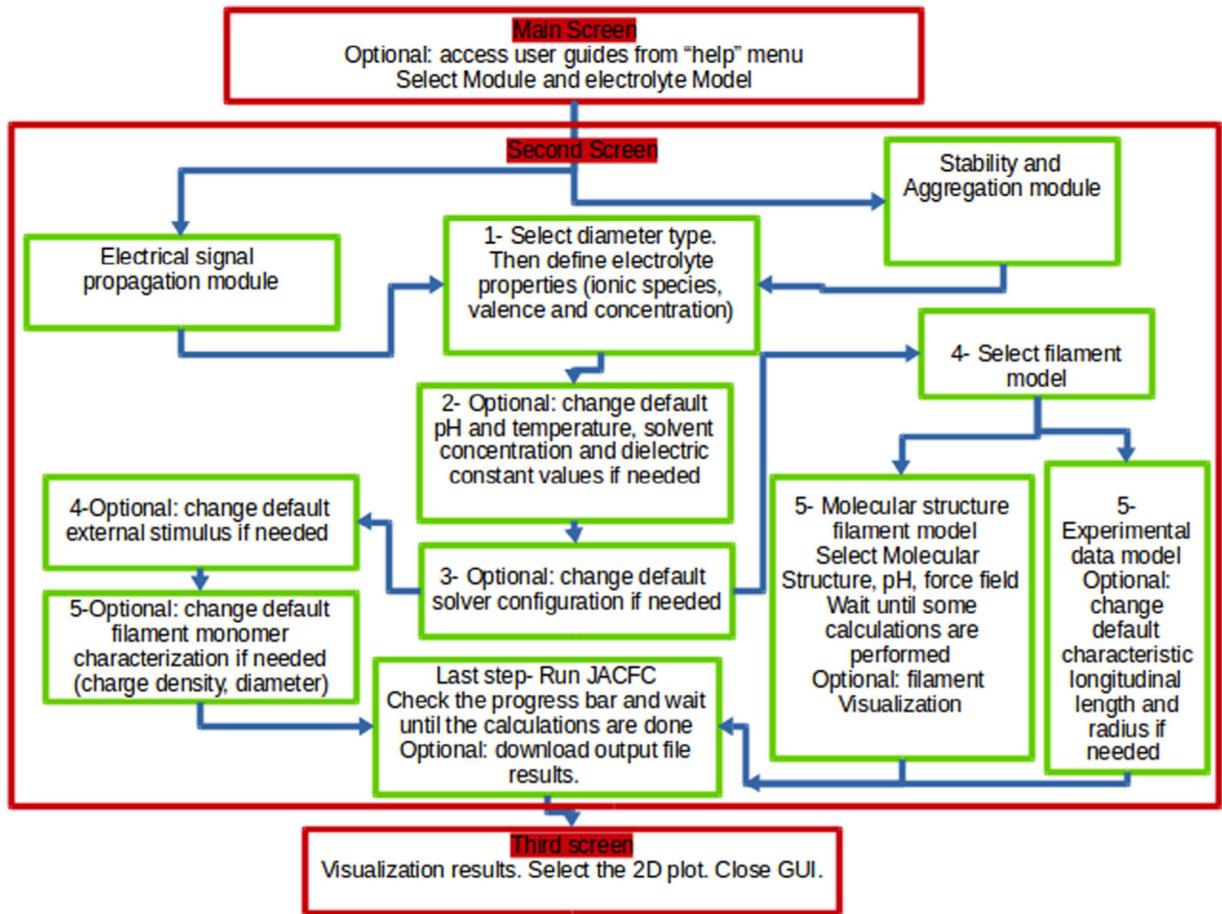


Fig. 4.
Logistic flow diagram.