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## CACPPAF, a COMSOL application to characterize polyelectrolyte properties of actin filaments

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### Abstract

We present an interactive COMSOL web application that allows both expert and non-expert users to numerically evaluate the electric potential, ionic concentration distribution, velocity profile, and ionic current along a molecular structure surface characterizing actin filaments. This online computational and visualization tool runs on a high performance server (<http://marucholab.physics.utsa.edu:2036>), that enables users to perform multiple analyses and comparisons without compromising computational resources. As a unique feature, the multiphysics formulation accounts for the filament surface roughness, the finite filament size, and the ionic condensation, providing a deeper understanding of the electrochemical phenomena taking place at the interface between the irregular charged shape of the filament and its biological environment. Overall, the interactive component allows investigators to characterize polyelectrolyte properties of healthy and abnormal actin filaments in physiological and pathological conditions.

### Keywords

Comsol application; Actin filament; Polyelectrolyte properties; Electrochemical interactions; Scientific software; Electrochemical phenomena

## 1. Motivation and significance

Actin filaments are highly charged double-stranded semiflexible polyelectrolytes formed by polymerization of G-actin. They are one of the major components of the cytoskeleton playing a key role in several biological activities in eukaryotic cells, including directional growth, shape, division, plasticity, and migration [1–5]. Recent research also revealed their ability to transmit electrical currents in the form of ionic package waves around the filament surface [6–11]. This novel property has potential applications range from neuronal information processing [12] to 3D chips [13,14], semiconductor nanowires [15], bio-nanotrans porters [16,17], and iontronic devices [18]. Thus, an accurate and efficient characterization of these polyelectrolytes' electrical conductivity and capacitance properties

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under different conditions and configurations is vital to the molecular understanding of electrical signal propagation in actin filaments.

Theoretical models and computational tools have been developed to bring new light upon phenomena occurring around the filament's surface, such as the formation of an electrical double layer (EDL) due to inhomogeneous arrangements of counter- and co-ions [19,20], and the conductive and capacitance properties intrinsic to this layer [20,21]. These tools usually use an infinitely long cylindrical filament model and a linearized Poisson–Boltzmann (PB) solution for the electric potential [22,23] to facilitate calculations and obtain analytic expressions. For the range of voltage stimuli and electrolyte solutions typically present in intracellular and *in vitro* conditions, these approaches were able to predict a lower electrical conductivity with higher linear capacitance and non-linear accumulation of charge under the intracellular conditions [20]. Additionally, 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 wave packet velocities [23].

This article presents CACPPAF (COMSOL Application to Characterize Polyelectrolyte Properties of Actin Filaments), an online COMSOL Multiphysics® tool for educators and researchers. This tool allows expert and non-expert users to numerically evaluate the electric potential, ionic concentration distribution, velocity profile, and ionic current along a molecular structure surface characterizing actin filaments. As a unique feature, our software accounts for surface roughness on the filament surface, the finite filament size, and the ion condensation effects on these polyelectrolyte properties. To increase accuracy, CACPPAF uses a molecular structure model for wild-type actin filaments and implements the solution for non-linear PB without increasing substantially the computational cost. Additionally, the user can change predefined input parameters such as the temperature, voltage input, ion concentrations, and filament surface charge density to study actin filaments in various conditions. The software does not require knowledge of specific programming languages or expertise in computational modeling and comes with a detailed user guide.

## 2. Software description

### 2.1. Software architecture

CACPPAF uses a modified (smoother) molecular structure surface model for actin filaments obtained from the Protein Data Bank having a volume  $V_f = 5365700 \text{ \AA}^3$ , a surface area  $A_f = 245700 \text{ \AA}^2$ , and length  $L_f = 767.24 \text{ \AA}$ . This version of the application considers filaments with a uniform surface charge density. Additionally, CACPPAF implements the finite element method (FEM) to discretize into 3,330,646 elements the governing non-linear electrostatics and fluid flow equations. Further details on the computational modeling can be found in Ref. [24]. It is worth mentioning that the solver configuration, boundary conditions, mesh definitions and filament model are predefined and cannot be changed. Leaving these features in a behind-the-scenes manner prevents users from running simulations in unphysical and impractical situations, mainly for those without computational modeling expertise. We deployed CACPPAF in our COMSOL Server website (<http://marucholab.physics.utsa.edu:2036>) and can be accessed through any web browser.

Fig. 1 shows the server homepage and additional information regarding the user account request. The COMSOL server license is limited to 300 user accounts. Users must be students, faculty, and staff of any academic or research institution worldwide. Therefore, users must request Dr. M. Marucho an account to access the server. In this version of the application, the COMSOL's solver configuration, boundary conditions, mesh definitions, and filament model are predefined and cannot be changed.

The computation is carried out in a Linux server equipped with 1.5 TiB (~ 1.6 TB) memory space, and 192 processors Intel® Xeon(R) Platinum 8360H CPU @ 3 GHz. Thus, none of the computational burdens rely on the user's machine capabilities. Additionally, users do not need Comsol licenses to use our application through our web server. On average, the application takes 7.5 min to perform the calculations on 24 CPU cores using the default configuration for a wild-type filament in physiological conditions. Users can change this configuration to elucidate the impact of surface irregularities, finite size of the filament, and electrolyte alterations on the polyelectrolyte properties of actin filaments. Once the simulation is over, the application offers the option to create a report compiling the simulation results (e.g. inputs, outputs, and graphs) in a Word document for post-processing analysis.

Additionally, users can download the application to their local machines from the Computer Physics Communications database. Running the application locally requires users to have their own COMSOL Multiphysics® and Chemical Reaction Engineering Module licenses. Additionally, the performance will highly depend upon their machine's capabilities. For instance, a PC with 64-bit Windows 10, 24 GB RAM, and 12 Intel(R) Xeon(R) CPU W3680 @ 3.33 GHz processor will take approximately 30 min to run the simulation, and use up to 85% of RAM Memory.

## 2.2. Software functionalities

Once users login into our COMSOL Server webpage (<http://marucholab.physics.utsa.edu:2036>), they will find our application under the title "CACPPAF (COMSOL Application to Characterize Polyelectrolyte Properties of Actin Filaments). Hitting the "Run in browser" button will prompt a new browser tab and launch the application. As shown in Fig. 2, the layout is divided into four main sections: *Home* ribbon at the top, *Simulation Info* panel on the middle left, *Geometry* graphics window on the bottom left, and *Results* graphics window on the middle right

On the top of the GUI and above the *Home* ribbon, the users can find the *File* tab. This tab contains the *Exit* button, allowing users to close and quit the application at anytime. Note that closing the browser tab with the application will not close the application, and additional action must be taken on the server home page.

The *Home* ribbon is separated into three sections: *Documentation*, *Simulation*, and *Results*. Hovering over the buttons on the ribbon gives users details about the button's functions. The *Documentation* section contains the *ReadMe* and *Report* buttons. The first one provides access to a document containing detailed instructions on how to use the application. Whereas, the other button generates a Microsoft Word document including the input

parameter values and the simulation results. The *Simulation* section has three buttons: *Geometry*, *Mesh*, and *Compute*. The *Geometry* and *Mesh* buttons display the filament and its surrounding medium in the *Geometry* graphics window (see Fig. 3). By default, when the application is launched for the first time, the *Geometry* window displays the 3-dimensional computational model for the actin filament molecular structure. The *Mesh* button allows users to visualize the discretization of the geometry utilized in the calculations. Whereas the *Geometry* button hides the mesh and displays the default 3D model.

Additional features are located at the top of the graphics windows (*Geometry* and *Results*). As shown in Fig. 4, these features allow users to further interact with the model.

Similar to the *Home* ribbon buttons, hovering over each icon inside the graphics window provides a hint of the button's functionality. Additionally, users can use the mouse buttons to enable further interactivity with the model. For instance, pressing and holding the left click enables rotation of the model; likewise, the right click enables translation, and the scroll button acts as a *Zoom in/Zoom out* tool when pressed and dragged.

The *Compute* button runs the simulation using the parameters set up in the *Inputs* section (see Section 2.3 for more details) and displays the results on the *Results* graphics window (see Fig. 2).

By default, the 3D total current figure appears when the application is first launched. Details about the plots generated in the *Results* window are discussed in Section 3.

### 2.3. Inputs and outputs

The inputs and outputs that govern the model are located in the *Inputs* section located under the *Simulation Info* panel, on the left side of the GUI, and above the *Geometry* graphics window. The default input parameter values for the filament model and electrolyte characterize a wild-type filament in physiological conditions (see [24] for more details). Users can change these predefined input parameter values for the temperature, voltage input, ion concentrations, and filament surface charge density. For instance, CACPPAF allows users to consider temperature gradients in pathological and physiological intracellular conditions ranging from 308 K to 315 K in the cytoplasm [7], around 1°C higher in the nucleus (when compared to the cytoplasm) [24], and around 321 K at the mitochondria [22]. Moreover, the user can consider a variety of filament surface charge densities depending on the nucleotide states, isoforms, missense mutations, and pH solution [23]. Also, they can model different ionic bulk concentrations and species, and the longitudinal voltage gradient depending on the cellular compartment.

Finally, pressing the *Compute* button initiates the computation process and subsequently updates the Zeta potential and the plots in the *Results* graphics window.

## 3. Results

It has been shown that the irregular shape of the filament induces a notorious angular dependence on the mean electric potential (MEP) profile distribution [24]. Furthermore, the accumulation of counter-ions and depletion of co-ions follow the Boltzmann statistics,

which depend exponentially on the MEP (see Eq. (2)). Thus, the angular dependence on the MEP also affects the ionic concentration distributions around the filament surface. Additionally, the longitudinal voltage gradient, and the electrochemical interaction between the filament surface charge and surrounding ions drive the electrolyte velocity profile. These three quantities (MEP, concentration, and velocity) contribute to the current surface density profiles as follows

$$J_x = kE_x + v_x\rho_e, \quad J_y = -k\frac{\partial V}{\partial y}, \quad J_z = -k\frac{\partial V}{\partial z} \quad (1)$$

where  $E_x = V_p/L$  stands for the external electric field applied on the system,  $V_p$  represents the longitudinal voltage gradient (input),  $v_x$  is the axial velocity profile,  $V$  is the mean electric potential,  $k = F^2 \sum z_i^2 u_i c_i$  represents the electrolyte conductivity, and  $\rho_e = F \sum z_i c_i$  describes the total charge density distribution. Here,  $F$  is the Faraday constant, and the parameters  $z_i$  and  $u_i$  stand for the valence and mobility of ionic species  $i$ , respectively. Additionally, the ionic concentrations are characterized by the Boltzmann distribution

$$c_i = c_{i0} e^{\left(\frac{-z_i F V}{RT}\right)} \quad (2)$$

where  $c_{i0}$  is the bulk concentration of species  $i$ ,  $z_i$  is the charge of species  $i$ ,  $R$  is the gas constant, and  $T$  is the electrolyte temperature (More details on the mathematical formulation can be found in Ref. [24].)

As a distinctive feature, CACPPAF provides the average Zeta potential of the filament, which is calculated as the average electric potential around the filament surface. This value is displayed in the *Simulation Output* section. Additionally, the *Results* graphics window includes three types of plots: a 3-dimensional volume and arrow field, a surface map, and a line profile, as illustrated in Fig. 5.

The *Total Current* button displays the 3D plot. The color scale on the filament surface indicates the MEP around the filament, while the arrows surrounding the filament represent the total ionic current density vector direction and their color the total ionic current magnitude. Additionally, the semi-transparent plane along the filament's longitudinal axis shows the electric potential around the filament and illustrates the EDL formation.

The *Surface Profiles* menu enables users to visualize the surface distribution of all the quantities measured around the filament surface on a plane perpendicular to the filament's longitudinal axis. The plane is located at the center of the model. It is defined as a function of the angle around the filament (in radians) and the distance away from the filament as follow

$$x = X_0, \quad y = r \sin(\theta), \quad z = r \cos(\theta) \quad (3)$$

Here,  $X_0$  refers to the center of the filament along the  $X$ -axis,  $r$  ranges between the surface of the filament and  $100 \text{ \AA}$  away from the surface, and  $\theta$  is an angle between  $0$  and  $2\pi$  measured perpendicularly to the filament axis.

The *Line Profiles* menu provides users with a new perspective on the distribution profiles of the different quantities measured around the filament profile. Instead of one parametric surface, the Line Profiles are measured along various straight lines arranged at different angles ( $0^\circ$ ,  $60^\circ$ ,  $90^\circ$ ,  $135^\circ$ ,  $240^\circ$ , and  $315^\circ$ ) to further reveal the high angular dependence arising from the filament's irregular shape. These lines are located at the center of the filament and run perpendicular to its longitudinal axis.

Finally, the *save numerical data* button is located at the rightmost end of the Results ribbon section. This button contains a drop-down menu listing the available 2D data sets that the user can save onto their machines (see Fig. 6). Each available data set will provide the user with a single four-column table containing the distance away from the filament surface ( $r$ ) in Angstrom, the angle ( $s$ ) in Radians, the quantity of interest (electric potential, longitudinal current, radial current, velocity, or concentration) and the radius of the point in the graph. The final column can be ignored, as the radius of the point is set to 1 for all plots.

#### 4. Impact

CACPPAF was recently used to characterize ionic currents along wild-type actin filaments in physiological conditions [24]. It was found that the irregular shape of the filament structure model generated pockets, or hot spots, where the current density reached higher or lower magnitudes than those in neighboring areas throughout the filament surface. It also revealed the formation of a well-defined asymmetric electrical double layer with a thickness larger than that commonly used for symmetric models. New versions of the application will consider an inhomogeneous (double helical) filament surface charge density model, explicit ions in the electrolyte, and the time-dependent calculations accounting for external dissipation and damping forces.

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#### Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Marcelo Marucho reports financial support was provided by National Institutes of Health.

#### Data availability

We have included the link to the code in the section of the manuscript "Code metadata".

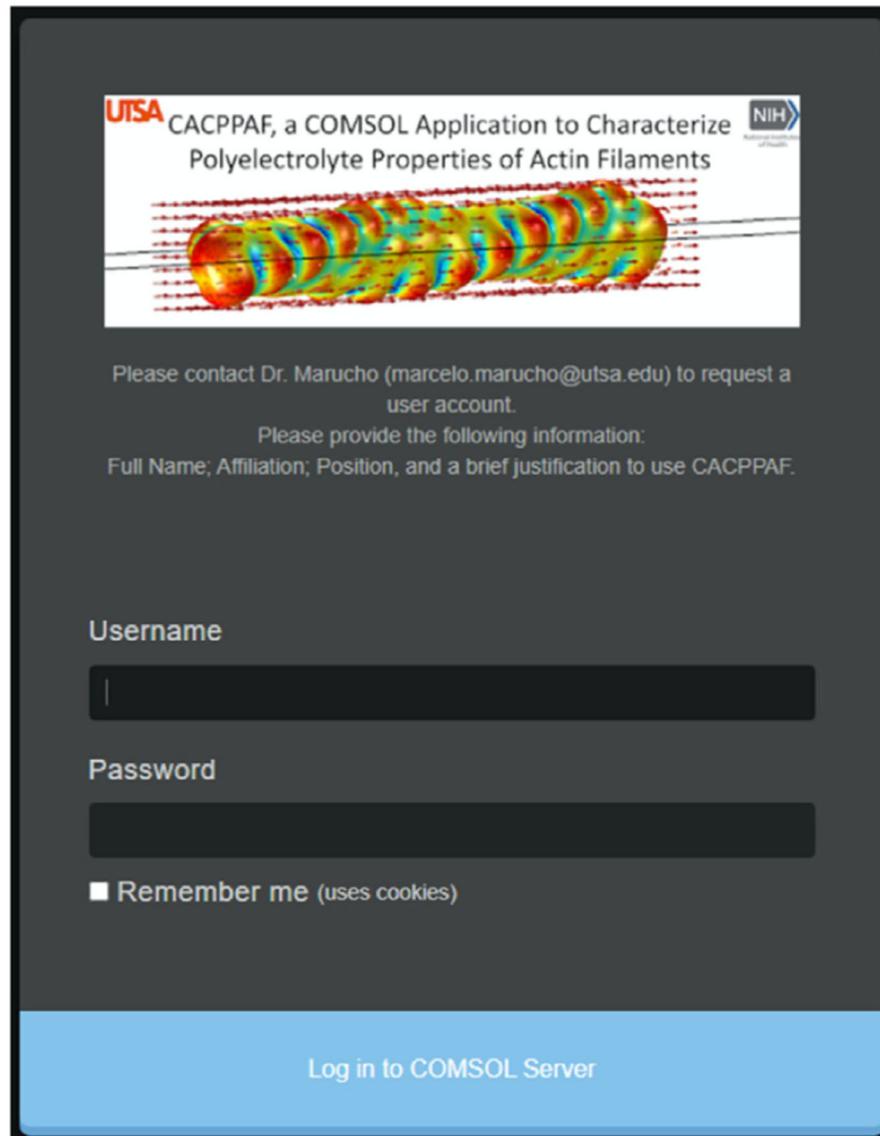
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Please contact Dr. Marucho (marcelo.marucho@utsa.edu) to request a user account.

Please provide the following information:  
Full Name; Affiliation; Position, and a brief justification to use CACPPAF.

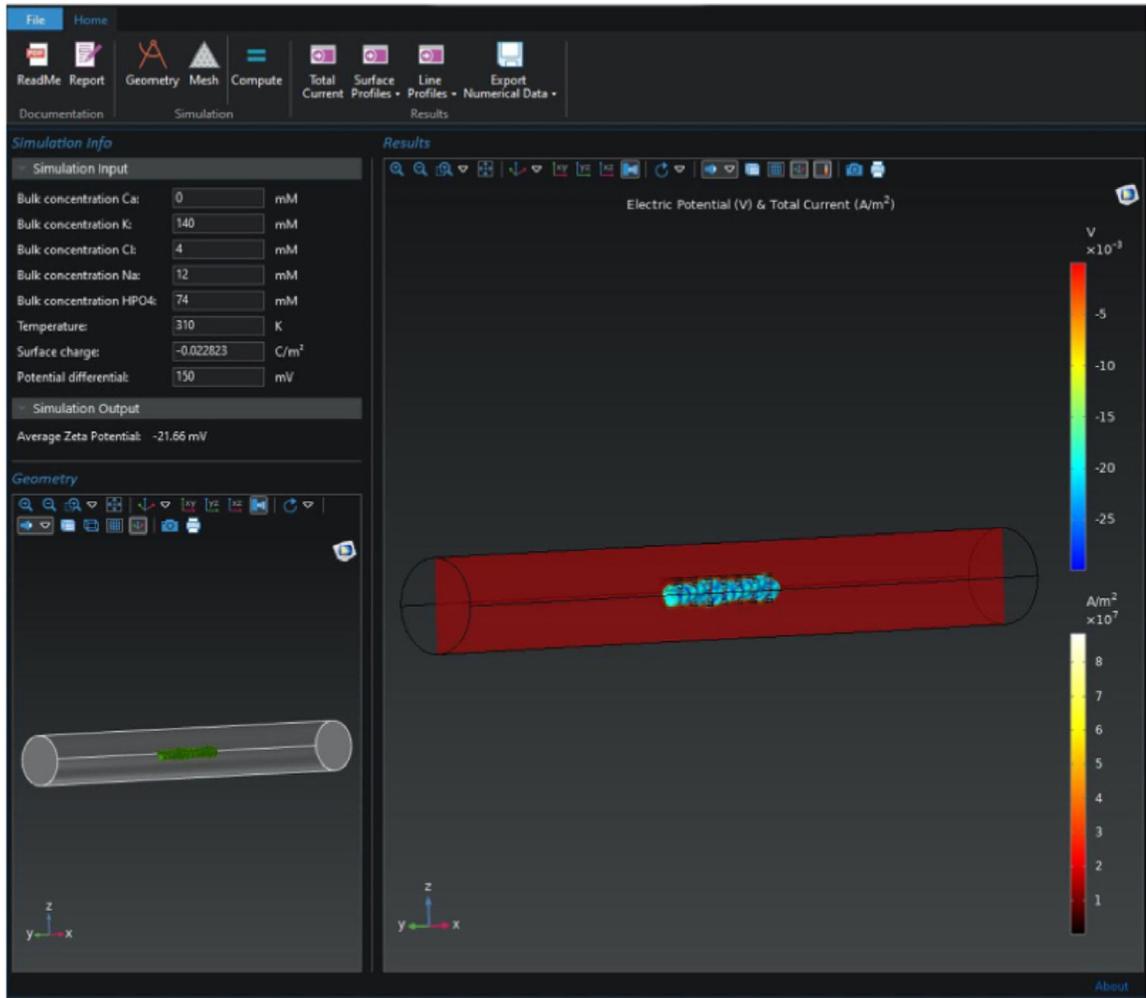
Username

Password

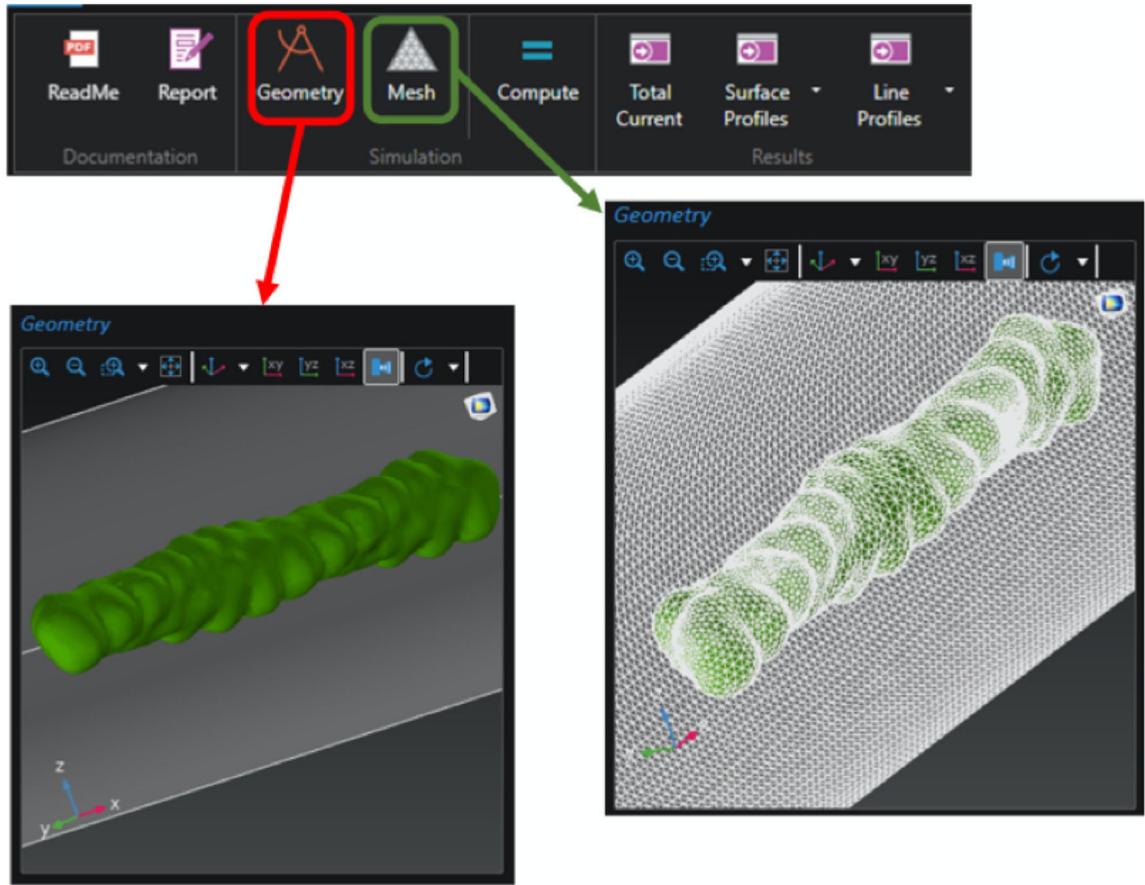
Remember me (uses cookies)

Log in to COMSOL Server

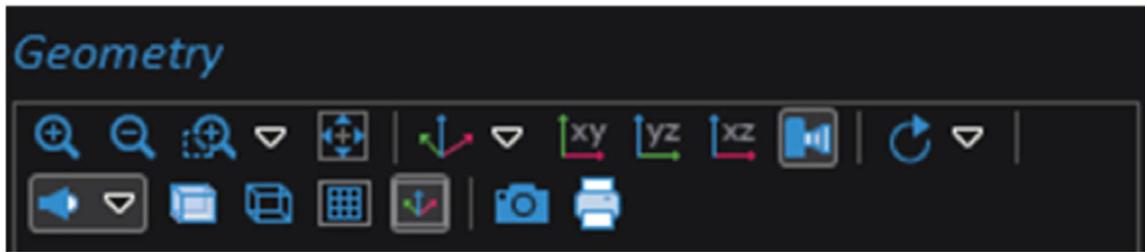
**Fig. 1.**  
Server homepage and user account requirements.



**Fig. 2.** Comsol Application Graphical User Interface.



**Fig. 3.**  
Geometry and Mesh Buttons.



**Fig. 4.**  
Graphics Window Features.

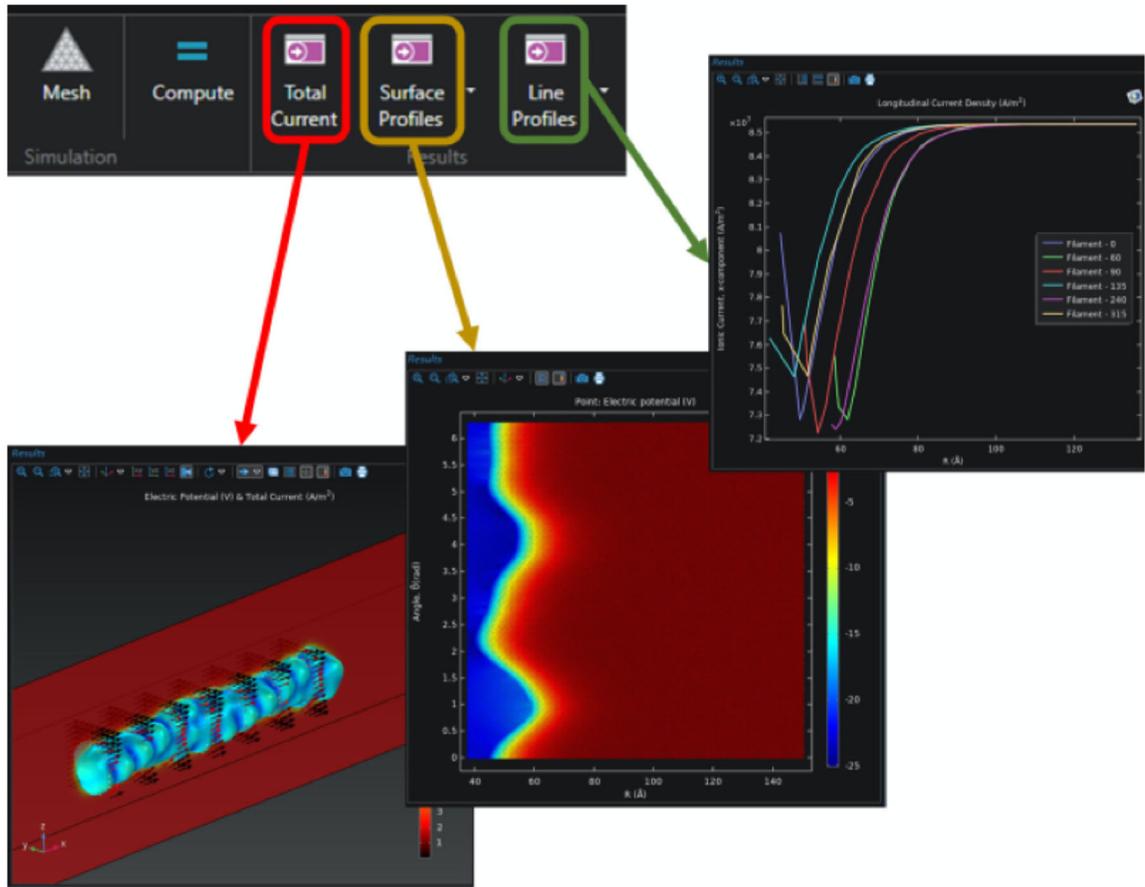
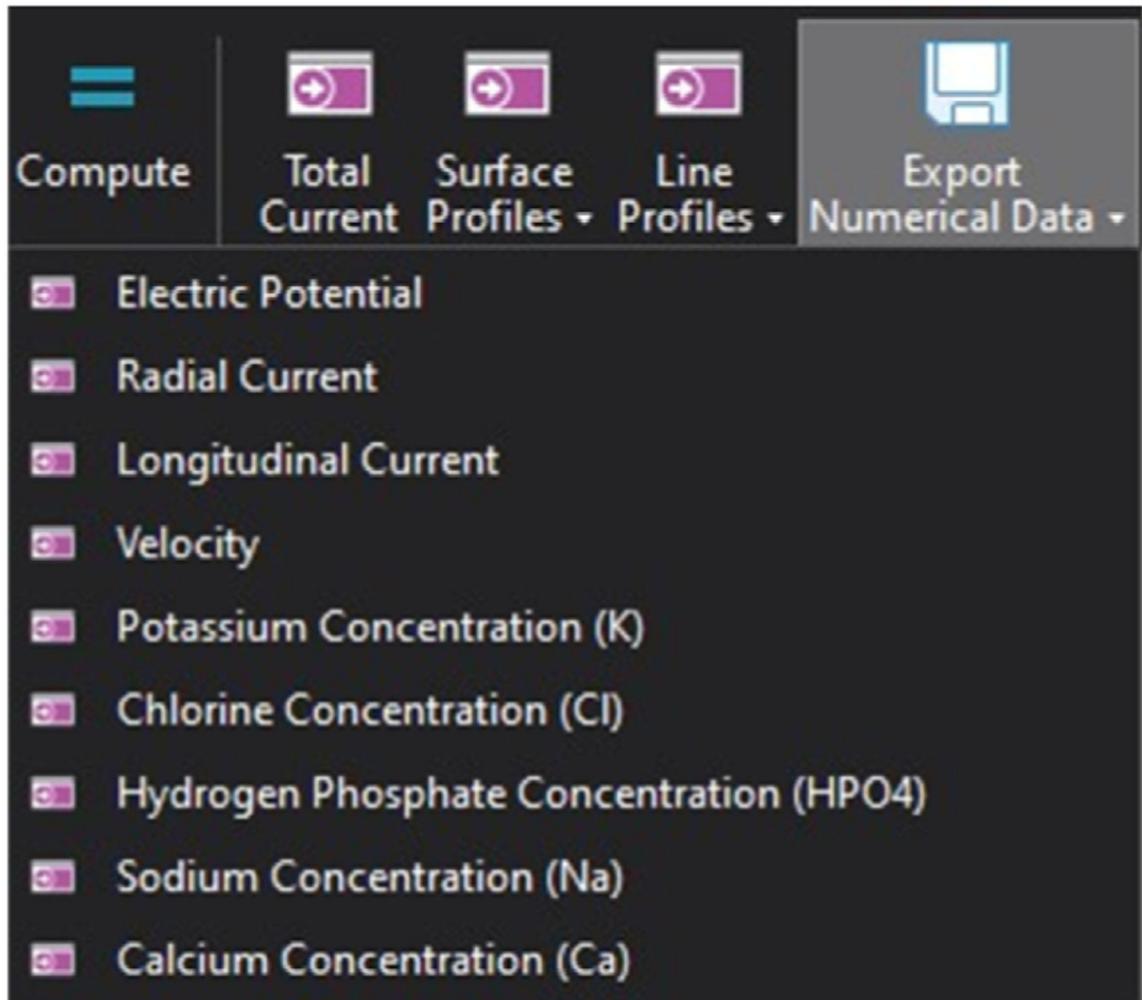


Fig. 5.  
Results Buttons.



**Fig. 6.**  
Numerical data download menu.