Finite-volume Poisson solver with applications to conduction in biological ion channels

I. Kaufman[1], R. Tindjong[1], D. G. Luchinsky[1,2] , P. V. E. McClintock[1]
[1]Department of Physics, Lancaster University, Lancaster, LA1 4YB, UK
[2]NASA Ames Research Center, MS 269-3, Moffett Field, CA, 94035, USA

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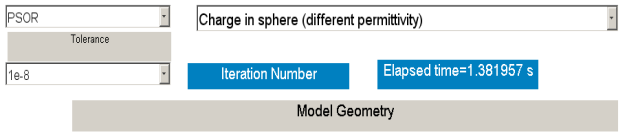

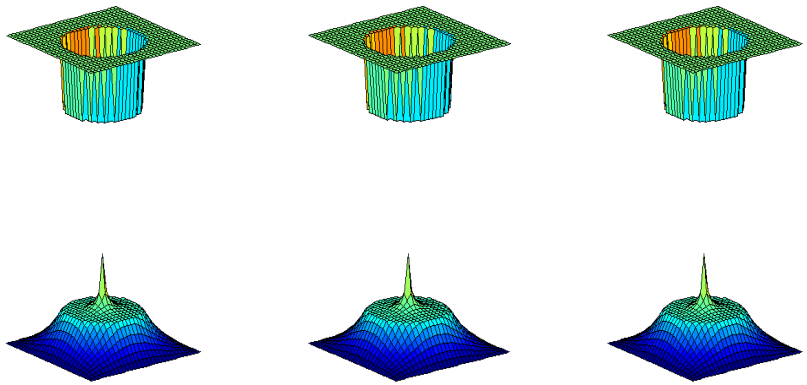

Cross-sections of potential for a point charge in a dielectric sphere

- ✓ A finite-volume 2D/3D Poisson/Poisson-Boltzmann solver has been designed and used for calculations of electrostatic potentials and forces in biological ion channels.
- ✓ The Solver has been implemented as embedded C-library and Matlab Toolbox.
- ✓ The Solver has been using for Brownian Dynamics and Reaction Rate simulations in modelling ion channels

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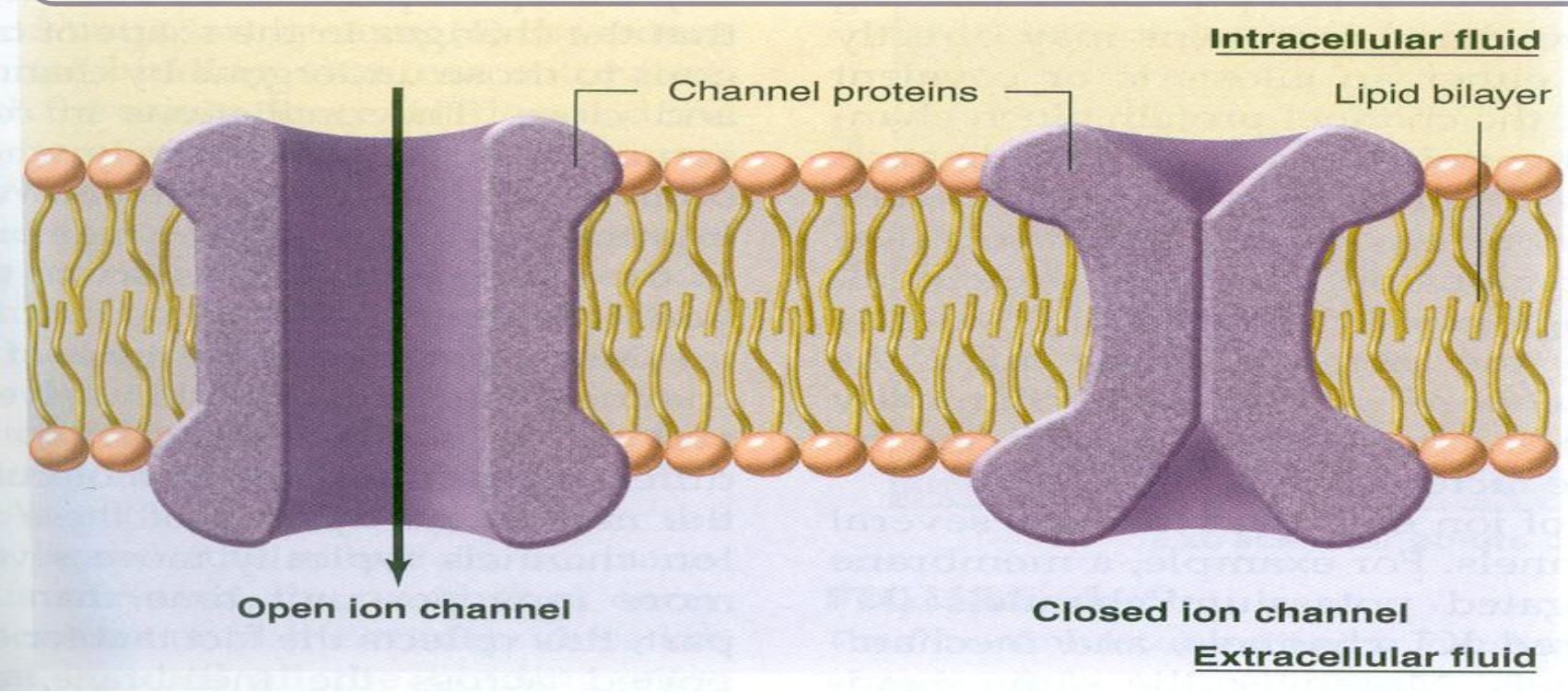
1. Ion channels Physical Model

Biological ion channels are natural nano-tubes regulating the flow of ions across the membranes of all living cells. They can be also described as biological transistors.



- The physical model of an ion channel consists of a narrow water-filled hole through a protein connecting the intracellular and extracellular spaces, with vestibules and fixed charges [1,2].

2. Ion channels basic physical features

Ion Channels represent three main biophysical phenomena: conductivity, selectivity and gating

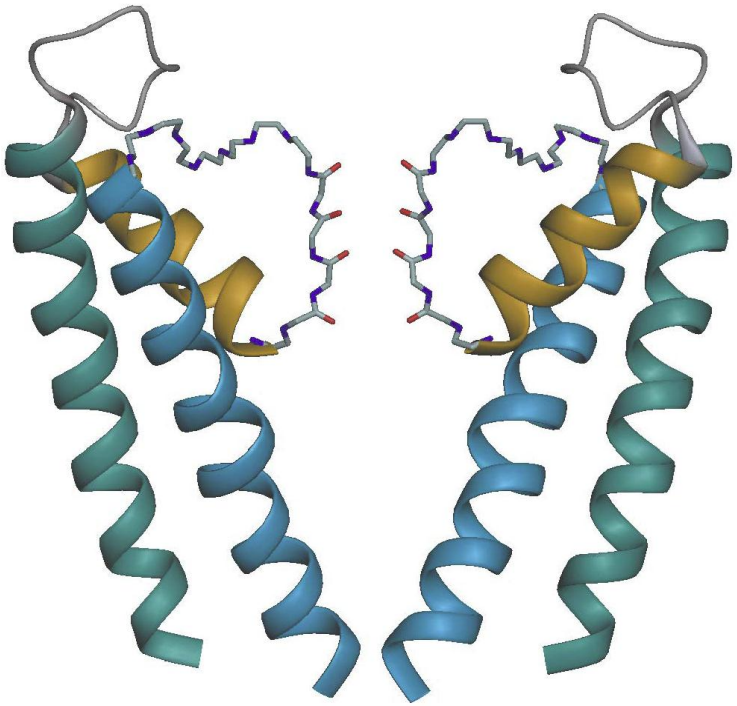
- Conductivity: The ability of open channels to conduct ion current when external voltage and/or concentration gradient are applied. A channel of conductance 100pS in a membrane across which there is a potential difference of 100mV would allow by Ohm's law an electric current corresponding to about **6.2×10^7 ions/s.**

- Selectivity: The ability of ion channels to discriminate between the ions that they let in or out of the cell. Potassium channels are more than 1000-fold selective for K^+ over Na^+ although the difference between their radius is very small (**R_{K^+} = 1.33 Angstrom** and **R_{Na^+} = 0.95 Angstrom**). Selectivity can also be related to ions valence and charge.

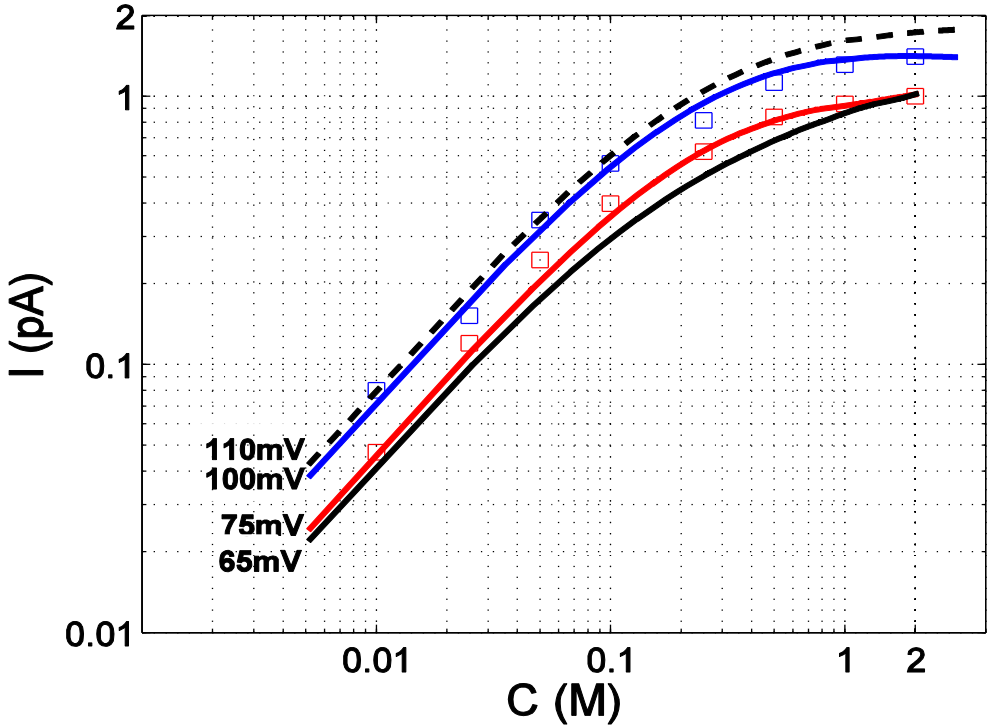
- Gating: Is related to the stochastic opening and closing of the channel due to the voltage across the cell, ions concentration and ligand-binding.

3. Ion channels experimental studies

Experimental studies of conductance, identification of protein structure through crystallography were greatly successful and have given us detailed atomic structure of biological ion channels as well as numerous conductance data .



The KcsA K+ channel X-ray structure



Current-concentration for the Gramicidin A channel

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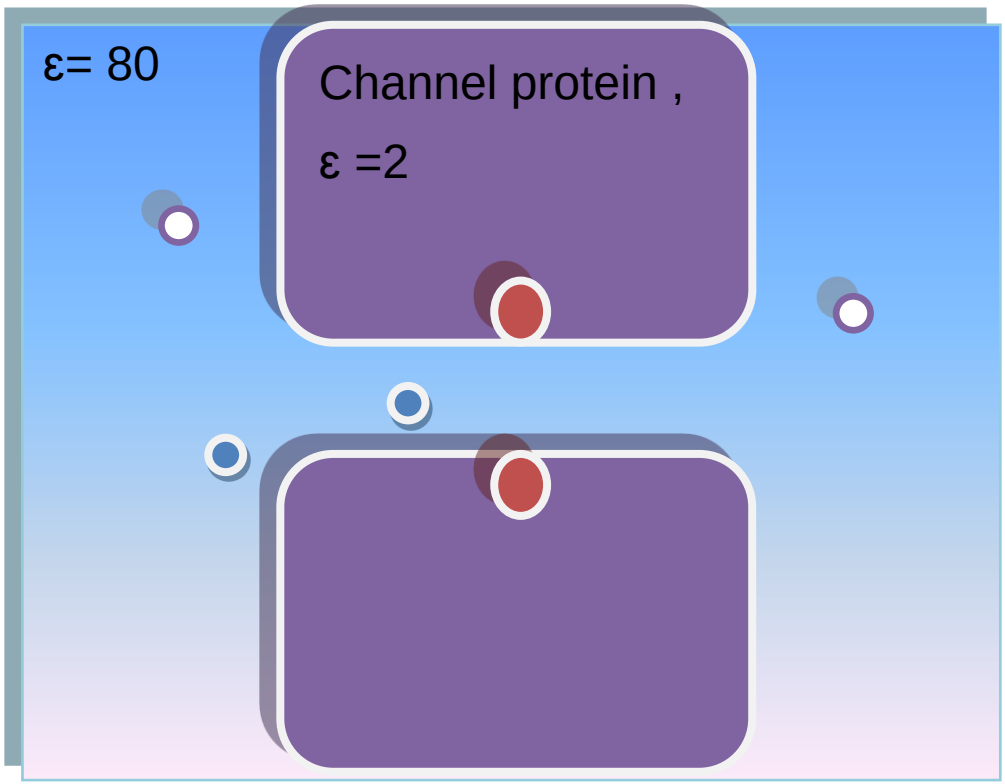
4. Ion channel modelling

Substantial progress has been achieved in modelling channel properties by use of molecular dynamics (MD), Brownian dynamics (BD), and MonteCarlo (MC) simulations and by the Poisson-Nernst-Planck45 and reaction-rate(RR)theories.

- **Molecular dynamics simulations**: Track position of all the water molecules in addition to the ions. Typically there are at least 100 water molecules per ion.
- **Brownian dynamics simulations:** Track positions and velocities of ions only. Interaction with water is accounted through diffusion coefficient (related to viscosity) and electric permittivity constant.
- Electro-diffusion **approach**: Numerical solution for Poisson-Nernst-Planck (PNP) equation.
- **Reaction rate approach:** Represents the movements of ions as a sequence of sudden stochastic "hopping events" across free energy barriers separating energetically favourable discrete wells (Eyring, 1934).

5. Ion channel reduced model for numerical analysis

To successfully simulate ion transport in open channel one needs to know electrical field inside the channel including image forces, creating a potential barrier for ions. This data can be derived from numerical solution of Poisson equation with respect to geometry of channel and to dielectric constants of water and channels protein.



Ion Channel reduced model

- We use the reduced model of a cylindrical channel with slightly rounded edges, with values of electrical permittivity ε= 80 for water and ε =2 for protein.
- External Voltage should be applied across the membrane
- The length L and radius R of the channel have been taken as follows: L = 20-30A, R=3-5A. Fixed charges were positioned near the centre of channel.

6. Poisson Electrostatic Equation

Poisson electrostatic equation (PE) describes electrostatic potential for arbitrary space distributed system of charges and/or dielectric domains, such as biological ion channels, Quantum Dot Molecules (QDM) and more.

The Poisson equation for in matter reads :

$$-\nabla(\varepsilon\nabla U) = f = \frac{\sum e z_i n_i}{\varepsilon_0} \qquad (1)$$

where: ε_0 - dielectric permittivity of vacuum, ε – dielectric permittivity of media, U - electric potential, f- source density, e – elementary charge, z_i - charge number , n_i – number density of ions.

Appropriate boundary conditions (BC) should be applied to the PE to get the unique solution in a given space domain.

➢ Numerical solution of (1) is the common subject for Computational Fluid Dynamics

The numerical solution of Poisson's equation involves the following main stages [3,4]

- ✓ Creation of a numerical grid for space discretization of PDE into domain of interest.
- ✓ Derivation of a discrete version of the PDE.
- ✓ Solution of the algebraic linear system arising from the discrete version of the PDE.

7. Finite Volume method

The Finite Volume method (FVM) derives the discretized equations from integral form of Maxwell equation when Gauss theorem is applied to each grid cell or Control Volume (CV).

- To convert the governing PDE to the system of algebraic equations the number of choices is available. The most common are finite difference, finite volume, finite elements and spectral methods.

- The Finite Volume method (FVM) derives the discretized equations from integral form of Maxwell equation when Gauss theorem is applied to each grid cell or Control Volume (CV).

Integral form of Poisson equation (Gauss law)

$$\int_S \vec{D} d\vec{S} = \int_{CV} f dV = \sum_{CV}^{i} f_i \qquad (2)$$

Where

$$D = \varepsilon E, \; E = -\nabla U$$

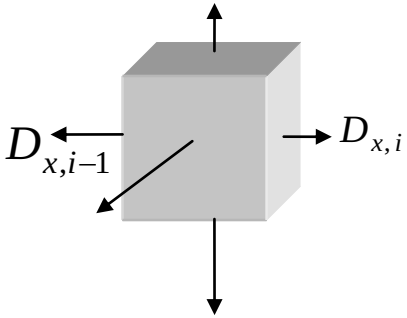
- Finite Volume Method provides automatic fulfilment of flux conservation law.

8. Numerical grid & Control Volumes

The solver uses a uniform rectangular CV-centered grid.

- The discrete locations of the variables are defined by the numerical grid. The solution domain is subdivided into a finite number of contiguous control volumes (CV). The solver uses a uniform rectangular CV-centered grid. All variables of interest – potential, electric field, charge density, dielectric permittivity – are mapped against the grid and uniformly describe all properties as 3-D tables in Cartesian coordinates.

Scalar variables (ρ, ε) are located at the centres of CV, appropriate components of vectors (D, E) – at the centres of cell faces. This arrangement allows direct way for computation of surface integral in Gauss law (2)



- The coupling between neighbour's intrinsic cells is derived from first principle Maxwell boundary conditions. FVM provides simple and natural way to adopt water-protein boundary in ionic channel model geometry.

9. Discretisation of Poisson equation

➢ Finite difference formula

We use common 5-points 2D and 7-points 3D *computational molecules* (central difference scheme) and common operator notation for finite difference formula:

$$\delta_x^2 U_{i,j} \Leftrightarrow aU_{i-1,j} + bU_{i,j} + cU_{i+1,j}$$

, and shorthand for coefficients as

$\delta_x^2 = \{a, b, c\}$, note that $b = -a - c$

Discrete version of Poisson equation for 2D case in operator notation reads:

$$\delta_x^2 U_{i,j} + \chi^2 \delta_y^2 U_{i,j} = v_{i,j}, \qquad (3)$$

where $\chi = h_x / h_y$, $v_{i,j} = -f_{i,j} h_x^2$

➢ Boundary conditions. The Poisson solver accepts mixed boundary conditions in the following form [3]:

$$\alpha U + \beta \frac{\partial U}{\partial n} = \gamma$$

10. Solving of sparse linear system

The Solver uses Gauss-Seidel Over-relaxation method to solve algebraic linear system

- Algebraic system (3) is linear system with very regular sparse structure. The number of equations is equal the number of grid points, so it can be very large for 2D and 3D cases.

- We used standard iterative methods [3,4] to solve algebraic linear system grows from discrete Poisson equation. Generic relaxation formula can be written in our case as follows:

$$U^{k+1} - U^{k} = \frac{\omega}{b_x + \chi^2 b_y} \cdot \left\{ \delta_x^2 U^{(k,k+1)} + \chi^2 \delta_y^2 U^{(k,k+1)} - v \right\}, \qquad (4)$$

where $0 < \omega < 2$- so called relaxation parameter, introduced to control convergence rate of (4). Over-relaxed values ($1 < \omega < 2$) are selected to increase convergence rate.

- Three variants have been implemented in Solver:

1. PSOR: Point Successive Gauss-Seidel Over-relaxation.
2. LSOR: Line Successive Over-relaxation.
3. ADI: Alternative Direction Implicit (LSOR+ alternative of scan direction after each iteration).

11. Software Implementation

FVPS has been implemented as embedded library and Matlab 2D&3D Toolbox to run from within Matlab programs.

- The C/C++ library implements a numerical solution of Poisson's equation for Cartesian 2D, axis-symmetrical cylindrical and full 3D Cartesian coordinates.

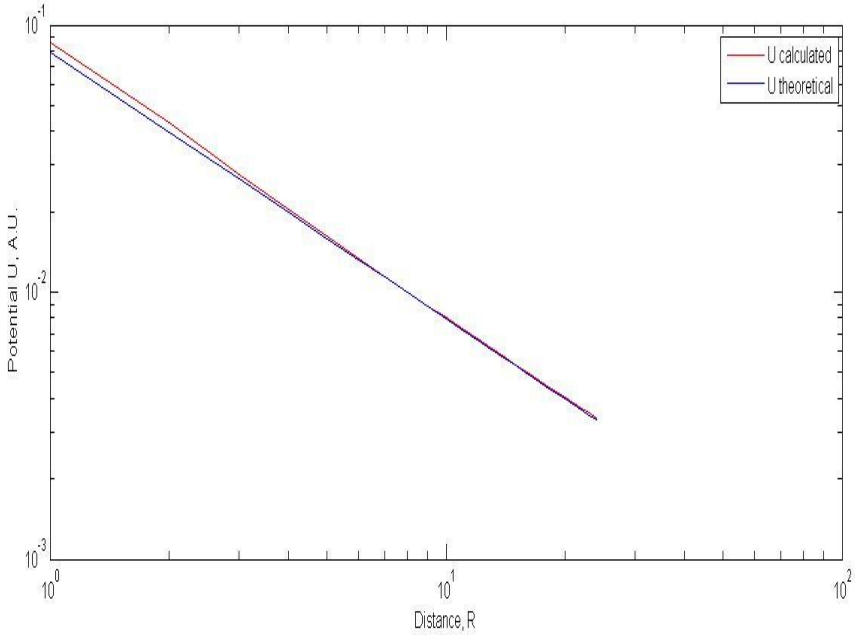
- The solver has been used to calculate image forces and self-generated potential barriers for single/multiple charges in an axis-symmetrical ion channel model with different channel parameters. It has also been using for the calculation of lookup tables [1] for the electrostatic forces in 1D and 3D BD simulations.

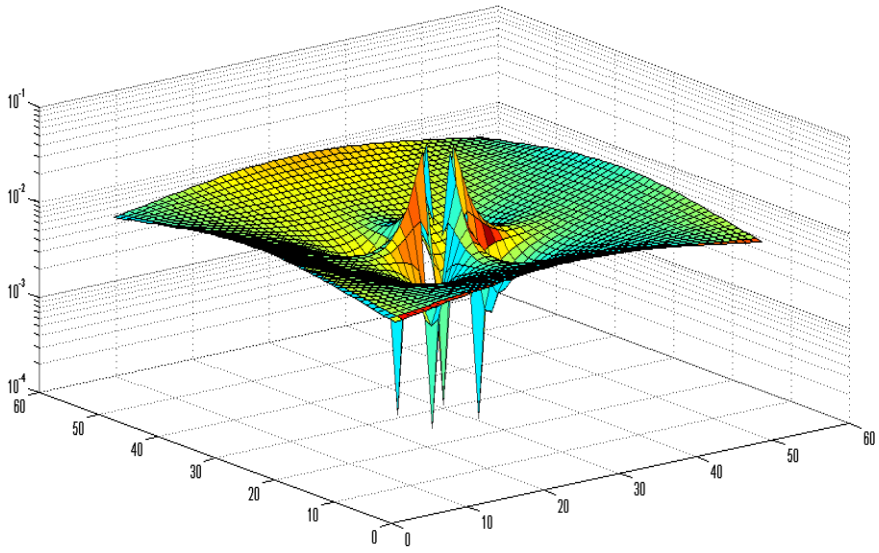
- The FVPS has been contributed to the public domain via the Matlab Central File Exchange under the terms of the BSD license at http://www.mathworks.com/matlabcentral/fileexchange/28651-3d-finite-volume-poisson-solver-for-ion-channels

12. Tests of accuracy. Coulomb law

FVPS shows reasonable accuracy and agreement with Comsol.

- We tested the accuracy for a point charge in the centre of a cube. Comparison shows close agreement between numerical and analytical results. The relative error does not exceed 0.02, excluding points nearest to the singularity.





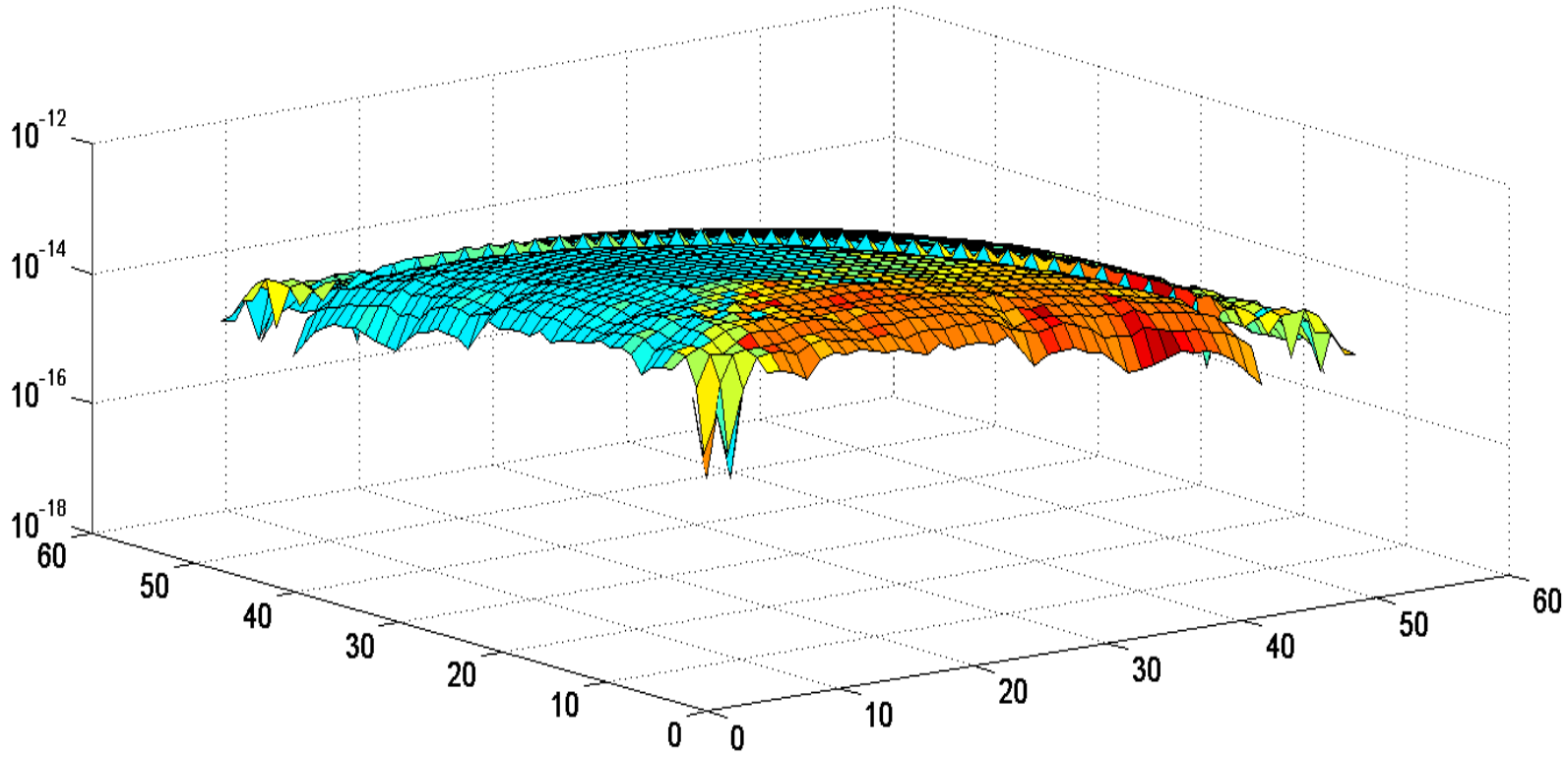
Accuracy test results: comparison with Coulomb's law; and error map

- FVPS have been also compared with COMSOL Multiphysics industrial standard FEM-based PDE Solver with reasonable agreement in the results.

13. Tests of accuracy. Gauss Law

The Solver FVM scheme provides automatic fulfilment of Gauss's law.

The finite-volume scheme automatically fulfils Gauss's law for each grid cell within the limits of the method's tolerance (10^{-12}) as shown below.

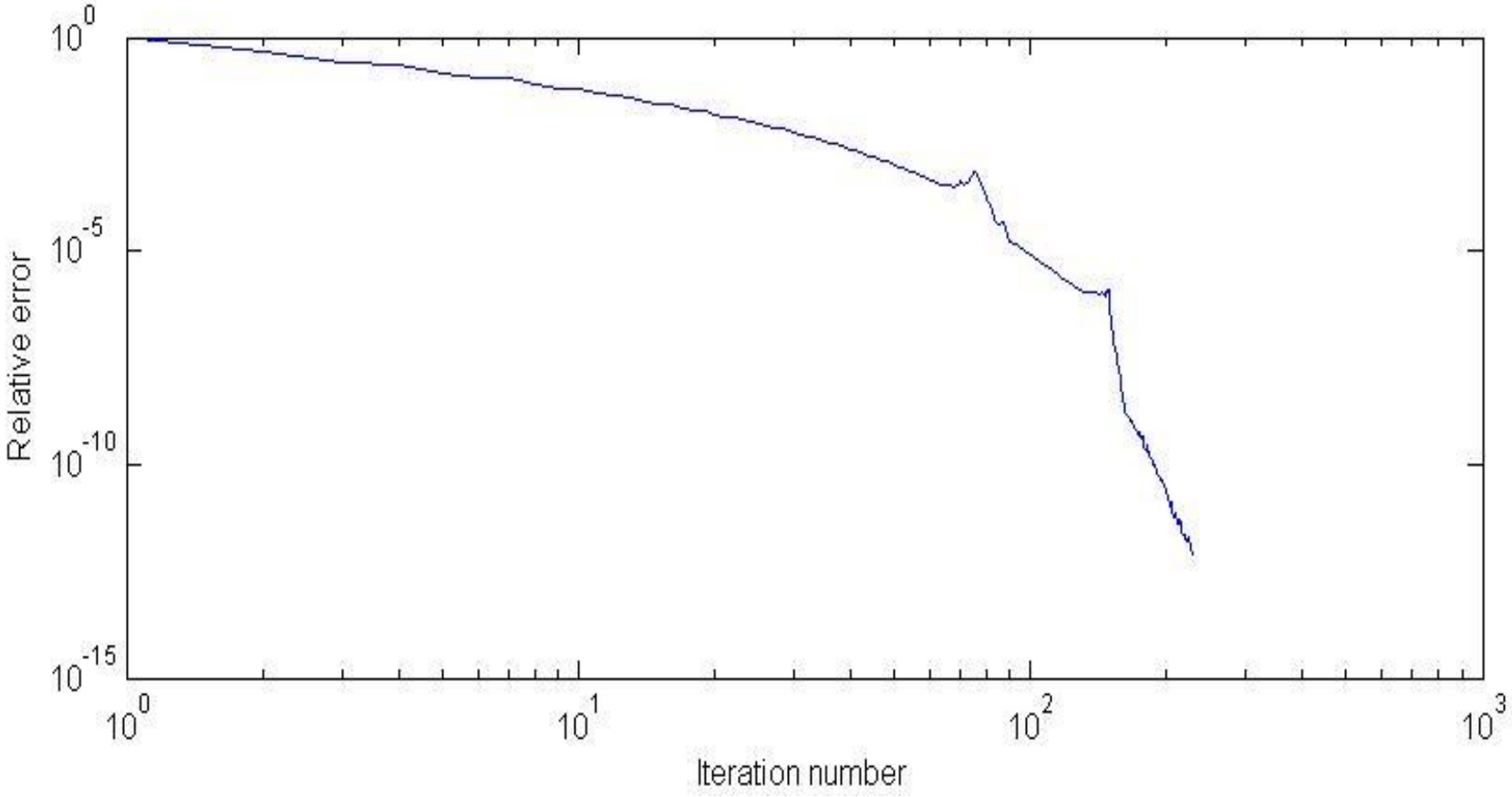


Gauss's law residuals map for the point charge's field (cross-section).

14. Convergence

The Solver demonstrates reasonably fast and monotonic solution's convergence.

The solver uses an iterative method to solve the linear system and convergence is reliable. It demonstrates fast and monotonic convergence in most cases.



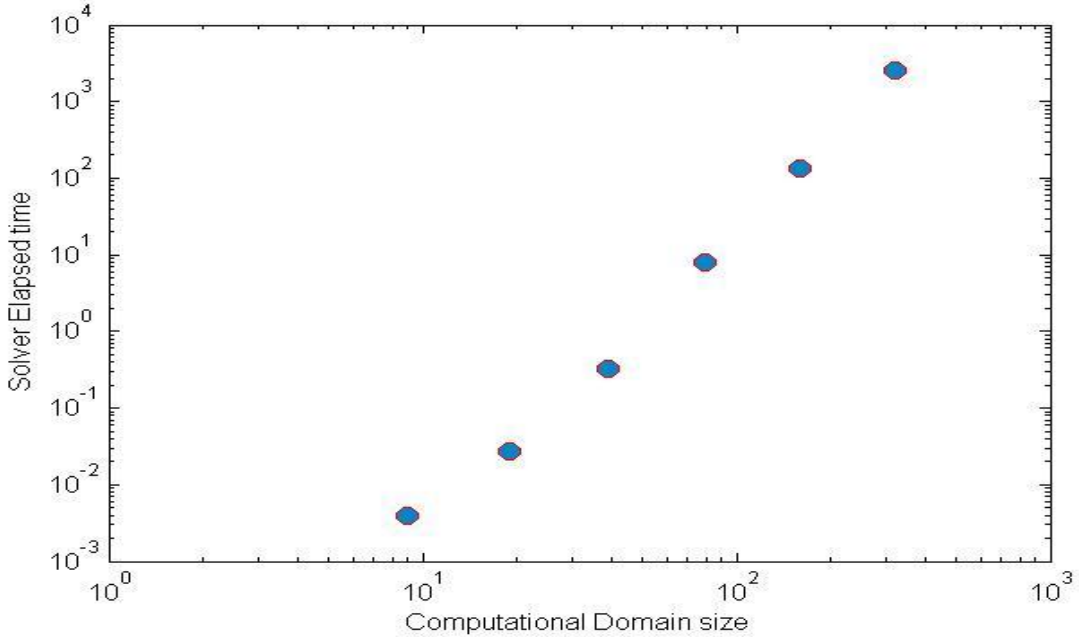
Solution's convergence for a point charge

15. Computational efficiency

The FVPS is easily parallelized with the Matlab Parallel Computing toolbox.

The solver uses simplest iteration technique so solution time sharply depends on domain size. The Figure represents the typical dependence of elapsed time on domain size for 3D single point charge configuration at 3.26GHz Intel CPU (DELL WorkStation). Benchmark of 1s is obtained for 100x100x100 box.

The FVPS algorithm is easily parallelized. The Matlab Parallel Computing toolbox has been used to accelerate solution on modern multi-core/multiprocessor PC's, CUDA GPU's or clusters.



Using of Parallel toolbox increases computational speed quite heavy allowing to compute large tables for reasonable time.

Computational time vs grid size

16. FVPS Applications Structure & Domain

Ion channel Applications: BD Simulation, PNP Simulation, RR theory approach

Ion Channel Model: geometry & Parameters

Other nanoscale models & Applications: QDM,

Finite-Volume Poisson Solver:

Software Library & Matlab Toolbox

Maps for physical variables:

Electrostatic Potential & Field,

Self-Potential,

Polarisation, Induced Charges Density,

Interaction Matrixes,

Lookup Tables

17. Solution: Point charge in sphere with different permittivity (QDM)

PSOR

Charge in sphere (different permittivity)

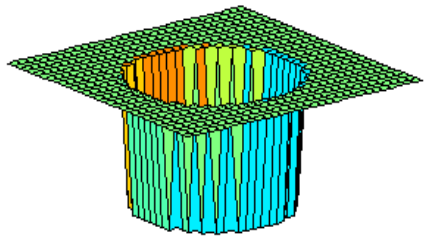
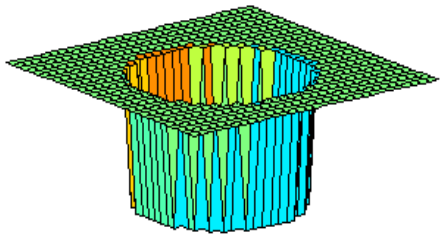
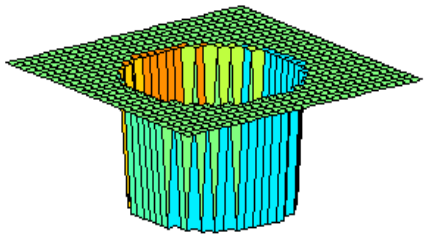
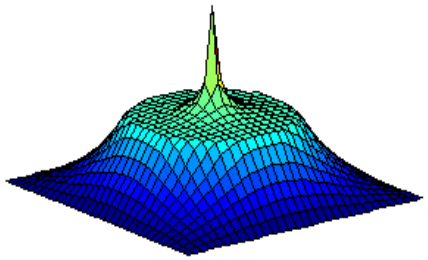
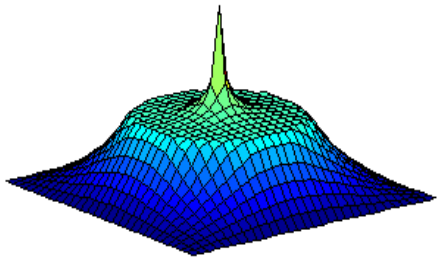
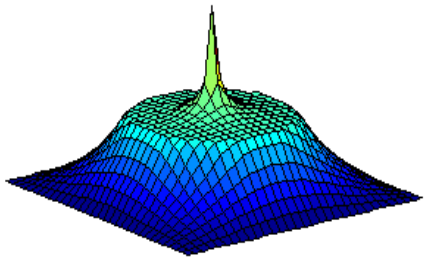
Tolerance

1e-8

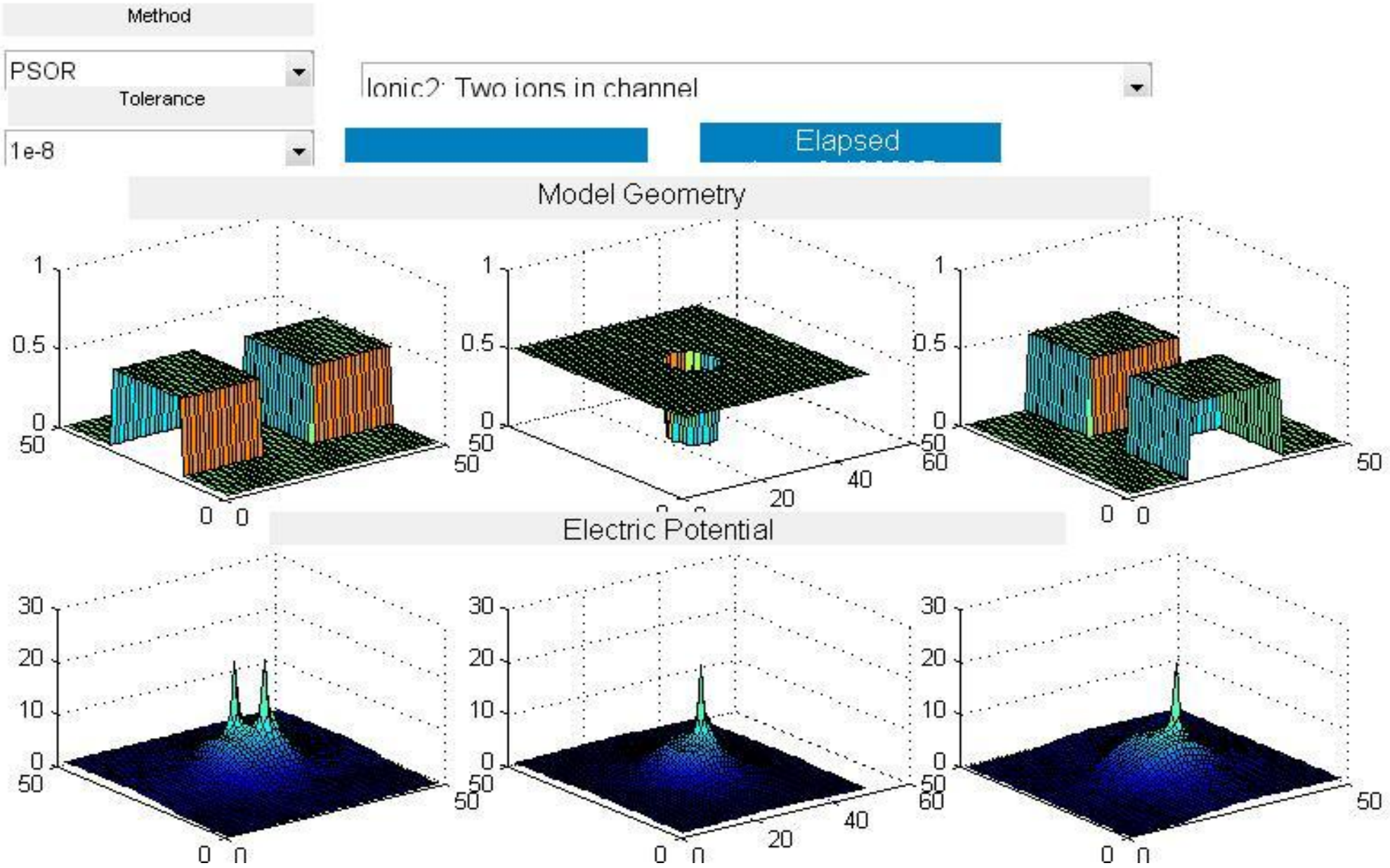
Iteration Number

Elapsed time=1.381957 s

Model Geometry

18. Solution: Ions inside ion channel



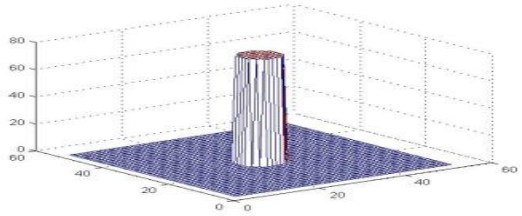
19. Ion Channel. Polarisation force

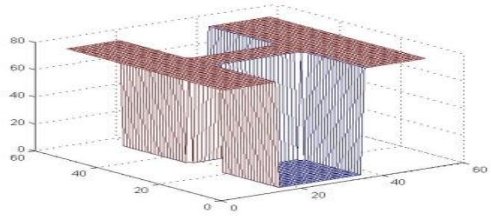
An additional polarisation field appears from the induced polarisation of the channel walls by an ion located inside the channel. This polarisation leads to an increase of the repulsive force between two ions with charges of the same sign.

XY Cross-section

YZ Cross-Section

a)





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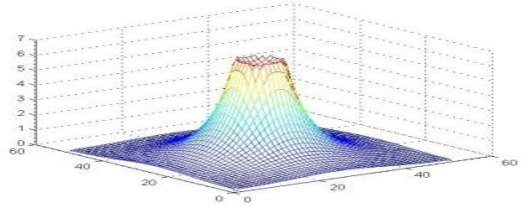
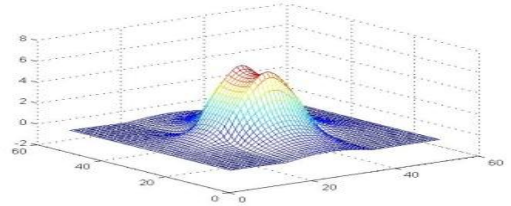
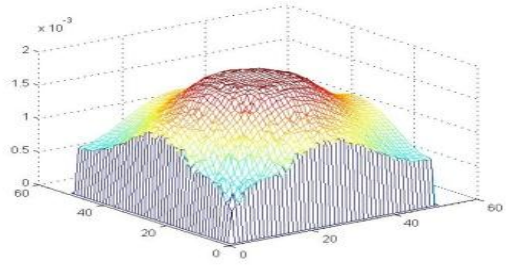
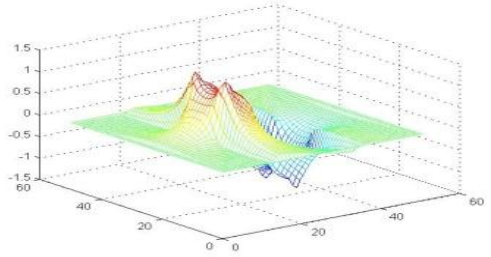




c)





Additional field created by a moving ion inside the channel.

20. BD simulation of ion permeation in biological ion channels

BD simulations introduce powerful method for modelling of current and provide I-V and I-C dependencies to compare with experiment.

- BD simulation techniques require calculation of electrostatic forces driving to all moving ions for each time step which is heavy computational task for 3D simulations.

Solution of Poisson/PB equation could be separated into a number of additive superposed components:

- The Coulomb interaction with all other moving charges (ions).
- The force arising from external field applied to channel, fixed charges etc with respect to channel geometry.
- The self-action, i.e. interaction between ion and charges induced by this ion itself in protein walls (image forces).
- Interaction between the ion and charges induced by other ions, i.e. a repulsive force.

- Linearity of PE and superposition principle allow to pre-calculated lookup tables for above components and dramatically decrease computation time for BD simulations steps [1]. At run-time electrostatic potential is recomposed from tables using lookup and interpolation without actual solving of Poisson equation.

21. Ion Channel. Axial Electric Field

Component and total forces and potential have been calculated by the 2-D axes-symmetrical solver and the 3-D solver. The following figures shows examples of 2-D field calculations for Na+ ion inside channel with L=20A, R=3A [5,6].

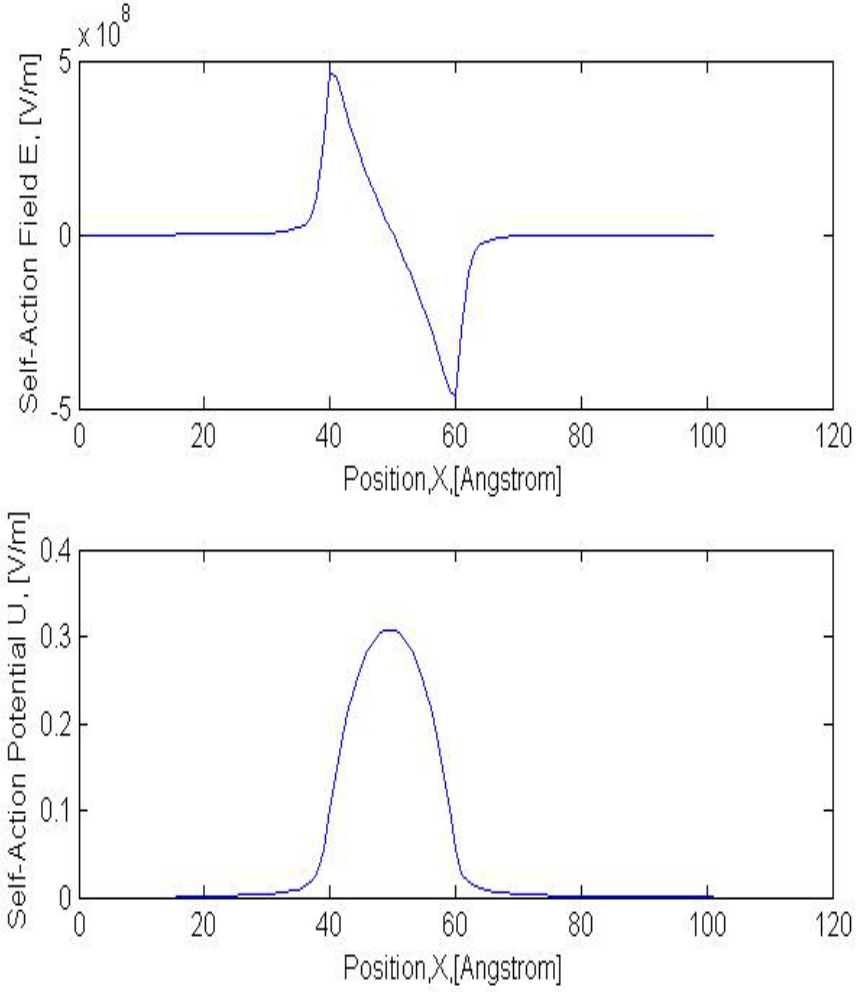
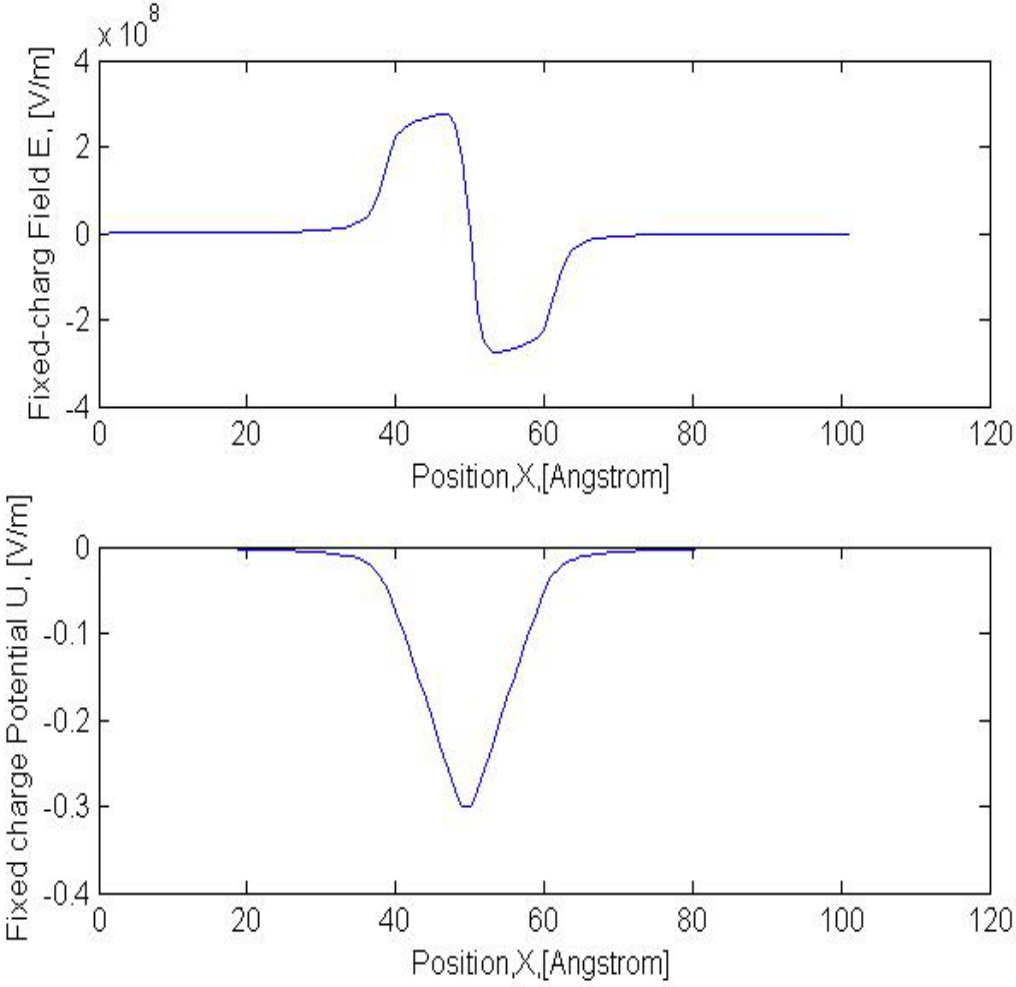
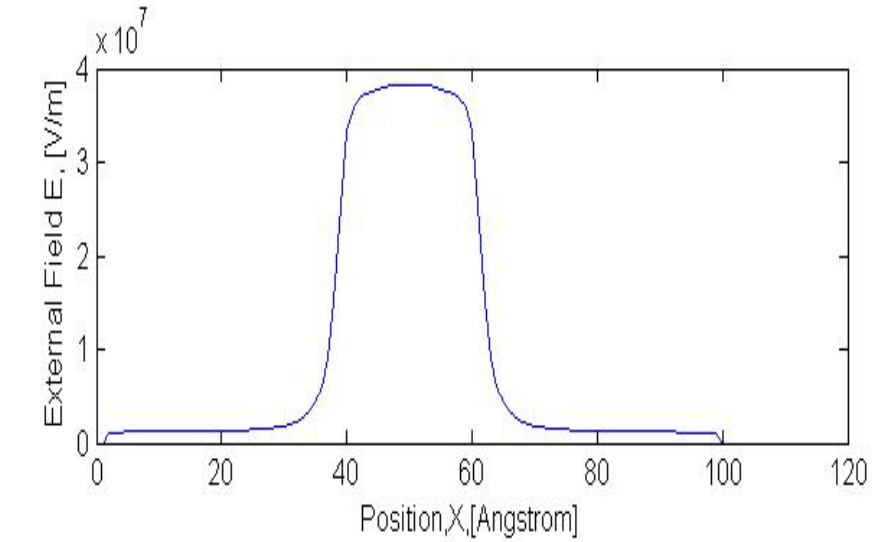


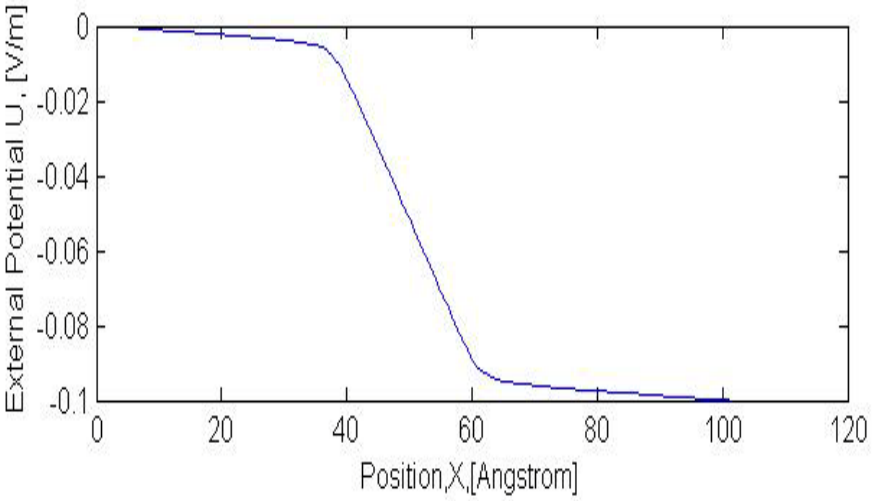
Image force and self-potential

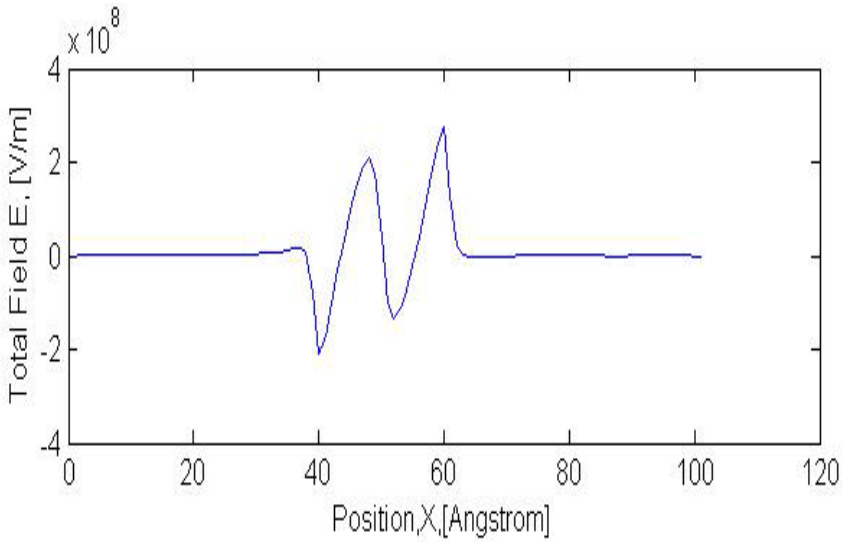


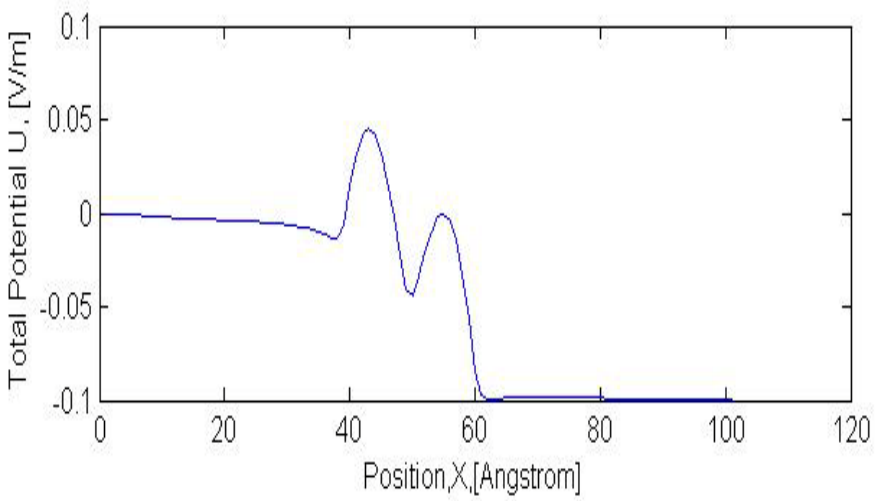
Fixed charge induced force and potential

22. Ion channel. Axial Electric Field









External Field (for V=100 mV)

Total Field

23. Ion-Ion Interaction matrix. Polarisation potential

Amplification of Ion-Ion interaction inside channel plays a significant role in ion permeation

The following figure represents polarisation part of interaction potential – related to interaction of between one ion with charges induced by another ion. This is so-called repulsive force: ions inside channel (or near the channel mouth) effectively repulses and/or pushes each other.

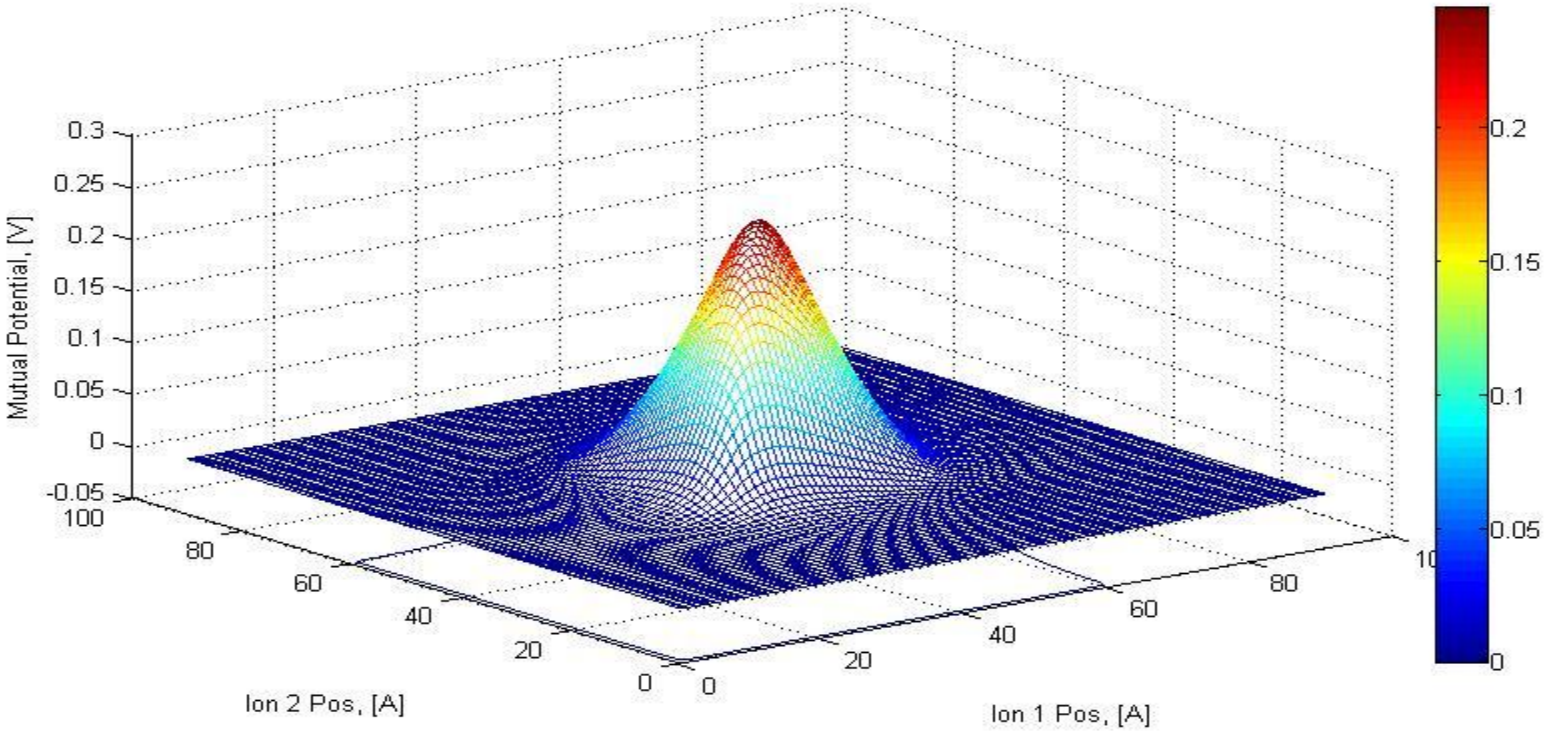


Figure 1 Ion-Ion interaction polarisation potential

24. Summary

FVPS provides simple and effective numerical calculation of electrical field for Ion Channel modeling. Solver has been using in BD simulations and RR modelling

- FVPS has been designed particularly for using in Ion Channel Simulations and has some advantages when used in simulations programs:

  - ✓ Simplicity, Transparency and Openness of Solver code. Simplicity of use, uniform mapping of physical variables to grid
  - ✓ Precision and correctness of FVM-based iteration solution, automatic fulfilment of Gauss law. Adopting of severe jumps in dielectric permittivity due to FVM approach.
  - ✓ Robustness and flexibility of embedded code. Compatibility and portability of open source C/C++ libraries.
  - ✓ Computational efficiency, possibility of parallel computing.
  - ✓ Matlab interface advantage, source code free distribution via MatLab FileExchange under BSD license.

- Solver has been using in BD simulations and RR modelling [5,6]

25. References

[1]. S-H Chung, M Hoyles, T Allen, S Kuyucak, Biophys. Journal, 75, 793, 1998;
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