**Research Article**
Volume 9:1, 2020
DOI: 10.37421/jacm.2020.9.457

Journal of
Applied & Computational Mathematics

ISSN: 2168-9679 Open Access

# Numerical Approach for Determining Impact of Steric Effects in Biological Ion Channel

**Abidha Monica Gwecho[1]*, Wang Shu[1] and Onyango Thomas Mboya[2]**

[1]*School of Mathematics Beijing University of Technology, Ping Le Yuan 100, Chaoyang District, Beijing 100124, China*

[2]*Technical University of Kenya*

## Abstract

Flow through biological ion channel is understandably complex to support numerous and vital processes that promote life. To account for the biological evolution, mathematical modelling that incorporates electrostatic interaction of ions and effects due to size exclusion has been studied, conceivably with element of difficulty and inaccuracy. In this paper the Nernst-Planck(NP) equation for ion fluxes that uses Lennard Jonnes(LJ) potential to incorporate finite size effects in terms of hard sphere repulsion is examined. To minimize emerging numerical intricacy, the LJ potential is modified by a band limit function with a cut-off length to eliminate troublesome high frequencies in the integral function. This process is achieved through Fourier transform to simplify and hence render the mPNP equation solvable with precision. The resultant modified NP and Poisson equation representing electrostatic potential are then coupled to form system of equation which describes a realistic transport phenomena in ion channel. Consequently, to discretize the 2D steady system of equations, mixed finite element approach based on Taylor hood eight node square referenced elements is adopted. In the method, Galerkin weighted residual approach help obtain sparse matrix and finally Picard Method applied to the nonlinear terms in the algebraic equations to linearize them and improve rate of convergence. Iterative solution for the system of equations then obtained and concentration profiles of ion species under varied steric effects for mPNP are computed and analysed.

**Keywords:** Modified PNP • Lennard Jonnes • Taylor-Hood • Galerkin weighted residual • Picard method

## Introduction

Biological ion channels are proteins with pores down their middle, found in nearly all membranes of biological cells [1]. These channels control the access to the interior of cells to perform biological functions such as; signal transfers in the nervous system, regulation of secretion of hormones among others. The mechanisms of ionic flow within a channel as a function of ionic concentration, membrane potential and the structure of the channel is a central problem in molecular biophysics such as in [2]. One of the most popular continuum theories describing ion transport in complex biological system is the Poisson Nernst Planck (PNP) model [3]. The PNP equations describe the electro diffusion of ions under the effect of electric field induced by ion charges themselves. The model uses a combinatation of Poissons equation to describe how ions and the channel protein creates electrical potential and the Nernst–Planck equations to describe migration and diffusion of ions in gradients of concentration and electrical potential. The two are coupled to form the PNP model, also known as the drift diffusion equations which are widely used to describe the behaviour of semiconductors, solid state devices like transistors, nano-devices in biophysics and physical chemistry as illustrated in [1-5]. Given that classical PNP model have known limitations; it neglects the finite size effects of ion particles and does not account for non-electrostatic interaction between ions see [4,6-8]. As a result the PNP model cannot adequately describe the flow behaviour of biological ion channel. In recent years, mathematical studies in this area have modified the PNP equation to include finite volume effects and electrostatic interactions. Among the numerical techniques used to model these equations include Finite difference(FD) [5,9,10], spectral methods [4,11] and Finite Element methods(FEM) [7,12-14]. Amongst the most appropriate numerical method for biological channels is FEM as it can adequately handle irregular geometries and no uniform boundaries. The adaptive finite element solver for simulating ion transport through three dimensional ion channel system that consists of protein and membrane was employed by [15]. This was implemented using a parallel finite element package capable of large scale parallel computations, efficiency and accuracy. The simulator was applied to the gramicidin A channel protein, to calculate the electrostatic potential, ion concentration and I-V curve and their numerical performance studied [8] used stabilized schemes in simulation of ion transport through 3D models. Streamline upwind Petrov-Galerkin (SUPG) method and the Pseudo Residual free bubble function was introduced to enhance the numerical robustness and convergence performance of the finite element algorithm in the ion channel. The two schemes gave reasonable results for the proteins in agreement with experimental data and Brownian motion. Validity of the PNP model was extended by adding an excess chemical potential (ECP) correction to account for finite ion size and water occupation in [4]. The modification of the standard drift diffusion solution methodology was accomplished by adding an outer iteration for the correction achieving feasible convergence rates with simple test structures considered. Under equilibrium conditions in the absence of fixed charge on the membrane, PNP theory predicted uniform ion densities while PNP/ECP predicted non-uniform charge distribution. A mathematical model for finite size effects using a regularized Lennard Jones (LJ) repulsive potential under energy variational framework and its numerical verification to recover layering behaviour was presented by [12]. Edge finite element method was used to solve system of modified PNP and convex iteration scheme to ensure self consistency between ionic concentrations and electrostatic potentials. Both PNP with LJ repulsive potential and Density function theory hard sphere potential have same overall behaviour of ion concentration in that, ion concentration near the boundary was found to be larger than in bulk. The integral term in the LJ potential has been established to reduces the numerical convergence of solution this computations. Thus in this study we modify the kernel in this potential to reduce computation time and obtain more accurate solution. Consequently, we employ picard linearisation to nonlinear terms to determine the iterative solution in the numerical scheme making them less costly on time. Numerous mathematical studies in simulation of PNP with steric effects using FEM are mostly limited to 1D cases [12] since simulation of realistic ion channel is computationally expensive or 3D cases [9] with difficulty in numerical convergence. In this work we adopt new approximation of the LJ potential in the energy functional with hard-sphere repulsion using band limit function which cut-off higher frequencies and preserve spatial frequencies in fourier modes. This approximation is done

***Address for Correspondence:** Abidha Monica Gwech, School of Mathematics Beijing University of Technology, Ping Le Yuan 100, Chaoyang District, Beijing 100124, China, Email: abidha.monica@yahoo.com*



**Received** 23 Aug 2020; **Accepted** 02 Sep 2020; **Published** 09 Sep 2020

with the help of a cutoff length $\sigma$ approaching zero, see [11] to simplify the kernel in the functional. As a result the new energy functional is used to derive equations of PNP with steric effects (mPNP), which is simple and numerically viable than the later. The mixed FEM based on Taylor-hood elements is described for the mPNP equations to simulate two dimension flow in ion channel.

## Poisson Nernst-Planck equation with Steric effects

In this section we consider a continuum flow in a two dimensional steady state domain to represent a channel in cell membrane. The energy variational approach is used to derive a system of differential equations including finite size effects of ions using the Lennard Jones repulsive potential. This potential introduces the ion interaction which are modeled as hard spheres. The contribution of the repulsive potential to the total free energy functional is given by

$$E = \Big[\int K_BT\sum_{i=1}^{N} c_i \ln c_i + \frac{1}{2}\big((\rho_0 + \sum_{i=1}^{N} z_i e c_i)\phi\big) + \sum_{i,j=1}^{N}\int\int \frac{\varepsilon_{ij}}{2}\frac{(a_i+a_j)^{12}}{|x-y|^{12}} c_i(x)c_j(y)dy\Big]dx \quad (1)$$

where $c_i$ and $z_i$ are concentration and valence for the $i$th ion. $\varphi$ is the electrostatic potential, $K_B$ is the Boltzmann constant, $T$ is the absolute temperature, $N$ is the number of ions, $e$ is the unit charge, $\rho_0$ is the permanent charge density. Given that $a_i$ and $a_j$ are the radii of the $i^th$ and $j^th$ in equation (1) and $\varepsilon_{ij}$ becomes their coupling energy constant.

Taking the variational derivative with respect to each ion $\frac{\delta E}{\delta c_i}$ to obtain the repulsive energy term into the system of equations which leads to the Nernst-Planck equation for charge densities

$$\frac{\partial c_i}{\partial t} + \nabla \cdot \vec{J_i} = 0 \quad (2)$$

where $\vec{J_i}$ is the flux given by

$$\vec{J_i} = -D_i\nabla c_i - \frac{D_i c_i}{K_BT} z_i e\nabla\phi - \frac{D_i c_i}{K_BT}\sum_{i=1}^{N}\nabla\int \varepsilon_{ij}\frac{(a_i+a_j)^{12}}{|x-y|^{12}} c_j(y)dy \quad (3)$$

where $D_i$ is the diffusion coefficient. The first, second and third terms in equation (3) are respectively, diffusion, drift driven by electrostatic potential in the field and the hard sphere potential that characterizes finite size of ions depending on the ion species.

$$-\nabla\cdot(\varepsilon\nabla\varphi) = \rho_0 + \sum_{i=1}^{N} z_i e c_i \quad (4)$$

The main computational challenge in equations (2)-(4) is the inaccuracy and inefficiency in simulation due to the effects of high frequencies, in order to address the problem, this paper employs a band-limit function which depends on a cut-off length $\sigma$ to eliminate the high spatial frequencies and preserve the bounded spatial frequencies, see [11,16]. The cutoff length is taken to be small parameter tending to zero for better approximation. Using this band-limit function and fourier analysis an approximate energy functional is derived which reduces the numerical complexity of the repulsive term in the LJ potential describing ion interaction.

Energy functional in equation (1) is replaced by an equivalent approximate energy functional derived in [16] represented as

$$E_\delta = \Big[\int K_BT\sum_{i=1}^{N} c_i \ln c_i + \frac{1}{2}\big((\rho_0 + \sum_{i=1}^{N} z_i e c_i)\phi\big) + \sum_{i,j=1}^{N}\frac{\varepsilon_{ij}}{2}(a_i+a_j)^{12} S_\sigma \int c_i(x)c_j(y)dy\Big]dx \quad (5)$$

where $S_\sigma \approx \sigma^{d-12}$, the dimensional space $d \le 3$. Applying the energy variational method, we obtain a new mathematical model for NP equation given by

$$\frac{\partial c_i}{\partial t} = \frac{D_i}{K_BT}\nabla\cdot\Big(c_i\nabla\frac{\delta E_\sigma}{\delta c_i}\Big) = -\nabla\cdot J_i \; i = 1,.....N \quad (6)$$

where the flux $J_i$ is given by

$$J_i = -D_i\nabla c_i - \frac{D_i c_i}{K_BT} z_i e\nabla\phi - \frac{D_i c_i}{K_BT}\sum_{i=1}^{N}\nabla S_\sigma\varepsilon_{ij}(a_i+a_j)^{12}c_j(y)dy$$

Coupling equation (4) and (6) forms a system of PNP equations with steric effects, which satisfies the dissipation law given below

$$\frac{dE_\sigma}{dt} = -\int\sum_{i=1}^{N}\frac{D_i c_i}{K_BT}|\nabla(K_BTlogc_i + z_i e\phi + \mu_i) \quad (7)$$

where $\mu_i = \frac{\delta E_\sigma}{\delta c_i}$ is the chemical potential.

Simplifying equation(6) above we obtain rates of concentration for the two ions $c_n$(negative) and $c_p$(positive) given by

$$\frac{\partial c_n}{\partial t} = D_n\Big[\nabla\cdot(\nabla c_n + \frac{z_n e}{K_BT}c_n\nabla\phi) + S_\sigma\nabla\cdot(g_{nn}c_n\nabla c_n + g_{np}c_n\nabla c_p)\Big] \quad (8)$$

$$\frac{\partial c_p}{\partial t} = D_p\Big[\nabla\cdot(\nabla c_p + \frac{z_p e}{K_BT}c_p\nabla\phi) + S_\sigma\nabla\cdot(g_{pp}c_p\nabla c_p + g_{np}c_p\nabla c_n)\Big] \quad (9)$$

where $gnn = \varepsilon 11(2a11)12$, $gnp = \varepsilon 12(a1 + a2)12$, $gpp = \varepsilon 22(2a22)12$. Coupling these equations with equation (4) for $\rho_0$=0, to obtain the system of equations which we aim to solve in this paper.

# Finite Element Discretisation and Linearisation

In this section, we consider a two dimensional steady state mPNP given by equations (8) and (9) for two ion species denoted by $n$ and $p$, with valencies taken to be $z_n = -1$ and $z_p = 1$, and radii $a_1 = 1.5^{\circ}A$ and $a_2 = 2.0^{\circ}A$, respectively. Dirichlet boundary conditions of concentration and potential are specified at the channel inlet and outlet while adiabatic conditions is prescribed at the channel walls.

$$c_n(x,0) = c_p(x,0) = 80, \quad c_n(x,1) = c_p(x,1) = 0,$$
$$\Phi(x,0) = 80, \quad \Phi(x,1) = -20, \quad \frac{\partial c_n}{\partial\eta} = \frac{\partial c_p}{\partial\eta} = \frac{\partial\Phi}{\partial\eta} = 0$$

where $\eta$ is unit normal to the boundaries $x = 0,1$.

To simulate the system of steady state mPNP equations we apply Mixed Finite Element Method(MFEM) based on Taylor-hood elements. This method consists rectangular elements with eight nodes each to model concentration components $c_n$ and $c_p$ and four nodes to model potential, $\varphi$ see, [17,18] and Figure 1 below. The quadratic interpolation functions are used for concentration

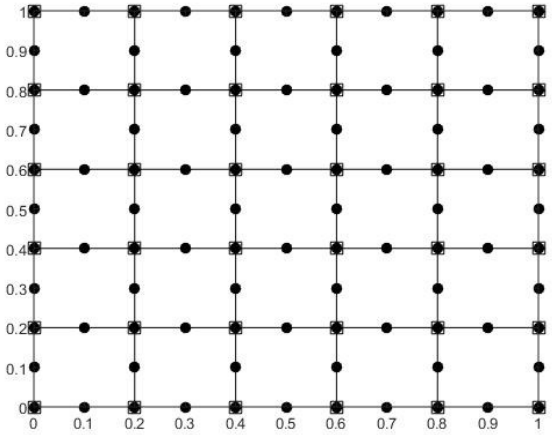



**Figure 1**: 2D Taylor-hood elements consisting of (•) biquadratic concentration elements and () bilinear potential elements.

components while bilinear interpolation functions for potential, resulting into 20 unknown variables for each element.

The variables $c_n$, $c_p$ and $\varphi$ can be expressed in form of the shape functions as

$$\begin{cases} C_\eta = \sum_{j=1}^{8} N_j C_{\eta j} \\ C_p = \sum_{j=1}^{8} N_j C_{pj} \\ \phi = \sum_{j=1}^{4} M_j C_{\phi j} \end{cases}$$

where $c_{nj}$, $c_{pj}$ and $\varphi_j$ are the parameter measurements at the nodes. This system of mPNP equations are coupled then discretized using Galerkin weighted residual approach. The resulting algebraic equations contains nonlinear terms which are linearized using Picards method, in order to obtain an iterative solution. The following are results obtained for flux and potential

$$\begin{aligned} &\Big[-(1+S_\sigma\overline{c_n}g_{nn})\Big(\int\int\Big(\frac{\partial N_i}{\partial x}\frac{\partial N_j}{\partial x}+\frac{\partial N_i}{\partial y}\frac{\partial N_j}{\partial y}\Big)dA\Big)+\oint_\Gamma N_i\frac{\partial N_j}{\partial \eta}\Big]c_{nj} \\ &+\Big[-\int\int\Big(\frac{\partial N_i}{\partial x}\frac{\partial M_j}{\partial x}+\frac{\partial N_i}{\partial y}\frac{\partial M_j}{\partial y}\Big)dA+\oint_\Gamma N_i\frac{\partial M_j}{\partial \eta}\Big]\phi_j \\ &+\Big[-(1+S_\sigma\overline{c_n}g_{np})\Big(\int\int\Big(\frac{\partial N_i}{\partial x}\frac{\partial N_j}{\partial x}+\frac{\partial N_i}{\partial y}\frac{\partial N_j}{\partial y}\Big)dA\Big)+\oint_\Gamma N_i\frac{\partial N_j}{\partial \eta}\Big]c_{pj}=0 \end{aligned} \quad (10)$$

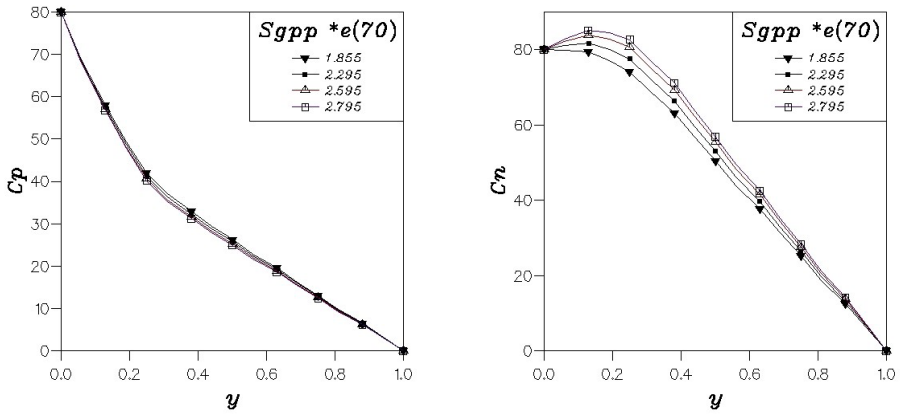
$$\begin{aligned} &\Big[-(1+S_\sigma\overline{c_n}g_{np})\Big(\int\int\Big(\frac{\partial N_i}{\partial x}\frac{\partial N_j}{\partial x}+\frac{\partial N_i}{\partial y}\frac{\partial N_j}{\partial y}\Big)dA\Big)+\oint_\Gamma N_i\frac{\partial N_j}{\partial \eta}\Big]c_{nj} \\ &+\Big[-\int\int\Big(\frac{\partial N_i}{\partial x}\frac{\partial M_j}{\partial x}+\frac{\partial N_i}{\partial y}\frac{\partial M_j}{\partial y}\Big)dA+\oint_\Gamma N_i\frac{\partial M_j}{\partial \eta}\Big]\phi_j \\ &+\Big[-(1+S_\sigma\overline{c_n}g_{pp})\Big(\int\int\Big(\frac{\partial N_i}{\partial x}\frac{\partial N_j}{\partial x}+\frac{\partial N_i}{\partial y}\frac{\partial N_j}{\partial y}\Big)dA\Big)+\oint_\Gamma N_i\frac{\partial N_j}{\partial \eta}\Big]c_{pj}=0 \end{aligned} \quad (11)$$

$$\Big[-\int\int\Big(\frac{\partial M_i}{\partial x}\frac{\partial M_j}{\partial x}+\frac{\partial M_i}{\partial y}\frac{\partial M_j}{\partial y}\Big)dA+\oint_\Gamma M_i\frac{\partial M_j}{\partial \eta}\Big]\phi_j - M_iN_jc_{nj}+M_iN_jc_{pj}=0, \quad (12)$$

where $N_i$ and $M_i$ are the weight functions for concentration and potential respectively, $\eta$ is the unit outward normal for each control volume and $c_n$ is the linearized term for concentration. Equation(10)-(12) forms sparse matrix.

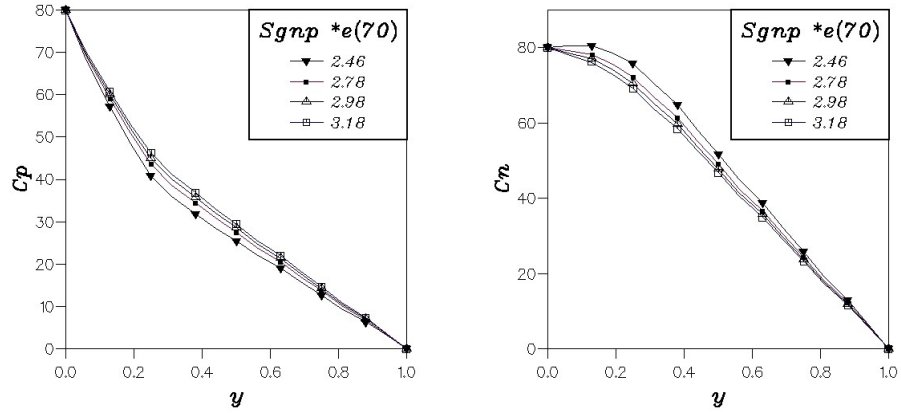
## Numerical Results and Discussion

Given $S_\sigma gpp$,$S_\sigma gnp$ and $S_\sigma gnn$ are the three steric linearized components of the repulsion term in the mPNP system of equations (10)-(12). The principle aim of this section is to demonstrate their effect on the positive and negative ion flow in an electro-neutral biological channel environment under mixed boundary conditions. This is via computation which assumes the diffusion coefficient constant, and the non-linear term $S_\sigma$ responsible for increasing rate of convergence inversely approximated in each of the three components. Results illustrated in Figure 2 demonstrate effect of repulsive forces of cations in the flow whence other steric components are held constant. On the other hand Figures 3 and 4 accounts for the attractive force of the constituent opposite ions and repulsive of anions, respectively, all of which are responsible for ion flow fluctuations. The above three critical forms in variation implies that radius size of an ion plays a role in selectivity as in the subsequent analysis. Upon increasing the positive steric effects *Sgpp* the repulsive forces between ion increases resulting into fewer cations being selected to through the channel see, Figure 2a as compared to anions, permitting anions flow increase in the channel as displayed in Figure 2b. Varying negative steric effects *Sgnn* the repulsive component of anion increases the repulsive forces between them thereby reducing their flow as in Figure 4a and permitting increased cations flow in the channel, see Figure 4b. Lastly we realize insignificant contribution of attractive element of steric effect compared to repulsive effect. But overally, contribution of the increase in the attractive component of the steric effect *Sgnp* in the flow diminishes anion and pronounces cation flows though insignificantly as in Figure 3a and 3b respectively.It can therefore be deduced that the



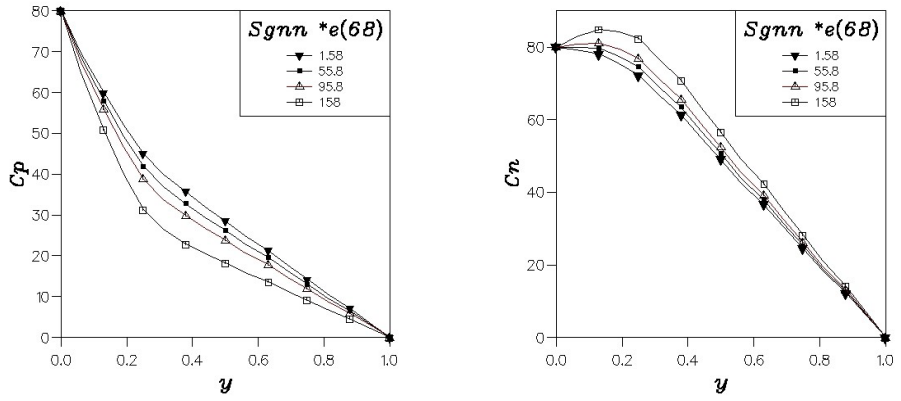

(a) Anions (b) Cations

**Figure 2:** Concentration profiles across the channel when varying positive steric effects measurements $Sgpp(\blacktriangledown) = 1.855, (\blacksquare) = 2.295, (\triangle) = 2.595$ and () = $2.795 \times 10^{70}$.




(a) Anions (b) Cations

**Figure 3:** Concentration profiles across the channel for varying of attraction steric effects measurements $Sgnp(\blacktriangledown) = 2.48, (\blacksquare) = 2.78, (\triangle) = 2.98$ and () = $3.18 \times 10^{70}$.




(a) Anions (b) Cations

**Figure 4:** Ions concentration profiles across the channel for varying negative steric effects measurements $Sgnn(\blacktriangledown) = 1.58, (\blacksquare) = 55.8, (\triangle) = 95.8$ and () = $158.0 \times 10^{68}$

attractive components plays the least role in the selectivity of ion species while the repulsive components have more impact on the flow of ions. However flow of the anions is enhanced in all the situations compared to the cations upon varying the repulsive components *Sgpp* and *Sgnn*. This may be as a result of the size/radius of the ion.

## Conclusion

The main objective of the study was to developed PNP with steric effects consisting of LJ hard sphere potential which was modified using a band limit function to reduce the complexity of computation. A two dimensional steady state numerical solution of the mPNP system of equations showing the effects of variation of steric effects on ion flow and concentration is discussed. In effect we have observed the effects of repulsive and attractive steric forces on ion flow and deducted the role played by radial size in selectivity. The Mixed Finite element approach enabled the establishment of distinction between the flow in relation to steric components qualitatively. Lastly, it is fundamental to note that an anion has a smaller size compared to cation therefore easing selectivity and flow in the channel as established in the study. Effects of potential variation is also worth examining for such a flow in addition to computational efficiency in triangular elements in Taylor-hood method.

## References

1. Eisenberg B. "Ionic channels in biological membranes-electrostatic analysis of natural nanotube." *Contem Phys* 39(1998): 447–466.
2. Zhongming Z, Shenggao D, Jie and Sun H. "Computational study on hysteresis of ion channels:multiple solutions to steady state poisson-nernst planck equations." *Math* (2017)25.
3. Qiong Z and Guo W. "Poisson-boltzmann-nernst planck model," *J Chem Phys* 134(2011):101.
4. Zchichang Y, Trudy AV and Umberto R. "A coupled 3-d pnp/ecp model for ion transport in biological ion channels." *J Comput Electro* (2005):167-170.
5. Flavell A, Machen M, Eisenberg B, Chun L and Xiaofan L. "A conservative finite difference scheme for poisson nernst-planck equations." *J Comput Electro* 13(213):235-249.
6. Eisenberg B. "Mass action in ionic solutions." *Chem Phys Lett* 511 (2011):1-6.
7. Benzhuo L and Zhou YC. "Poisson nernst equations for simulating biomolecular diffusion-reaction processes ii;size effects on ionic distributions and diffusion reaction rates." *Biophysica J* 100(2011):2475-2485.
8. Bin T, Xie Y, Zhang L and Benzhou L. "Stabilized finite element methods to simulate thge conductance of ion channels." *Comp Physics Commnctns* 188(2015):131-139.
9. Meng D, Bin Z, Guang L and Maria LS. "Numerical solution of 3d poisson nernst-planck equations coupled with classical density function theory for modelling ion and electron transport in a confined environment." *Commun Comput Phys* 16(2014):1298-1322.
10. Farjana S, Zhongming W and Shenggao Z. "A modified poisson nernst-planck model with excluded volume effects; theory and numerical implementation 1 (2017):26.
11. Tzyy-Leng H, Tai-chin L, Chun L and Eisenberg B. "Pnp equations with steric effects; a model of ion flow through channels." *J Physica Chem* 116(2012):11422–11441.
12. Yunkyong H, Eisenberg B and Liu C. "A mathematical model for hard sphere repulsion in ionic solutions." *Commun Math Sci* 9(2011):459-475.
13. Qian Y, Liu X, Chen M and Benzhou L. "A local approximation of fundamental measure theory incorporated into three dimensional poisson-nernst planck equations to account for hard-sphere repulsions among ions." *J Stat Physics* 163(2016):156–174.
14. Vladmir Y, Kiselev M, Lobanov I, Marenduzzo D and Goryachev B. "Lateral dynamics of charged lipids and peripheral proteins in spatially heterogeous membranes:comparison of continous and monte carlo approaches." *J Chem Physics* 135(2011):10.
15. Bin T, Chen M, Xie Y, Zhang L and Eisenberg B, et al. "A parallel finite element simulator for ion transport through three dimensional ion channel systems." *J Comput Chem* (2013): 34.
16. Tai-chia L and Einsenberg B. "A new approach to the lennard-jones potential and a new model:pnp-steric equations." *Commctn Mathematical Sci* (2013):22.
17. Tsega G and Katiyar V. "Finite element solution of the two dimensional incompressible navier stokes equations using matlab." *Applictns Applied Maths* 13(2018):535–565.
18. Rubnau P and Schnorr C. "Optical stokes flow estimation :an image based control approach." *Ex Fluids Springer* 42(2007):61-78.

**How to cite this article:** Abidha Monica Gwecho, Wang Shu and Onyango Thomas Mboya. Banda and Precious Sibanda. Numerical Approach for Determining Impact of Steric Effects in Biological Ion Channel. *J Appl Computat Math* 9 (2020) doi: 10.37421/jacm.2020.9.457