COME TO BIOPHYSICS FOR

Paul Cézanne

Mt. St. Victoire

Philadelphia Art Museum*

**also*
> 69 Cézanne
>200 Renoir (!)
at
The Barnes

Discrete Selective Conductance in a **Continuous Model** of a Calcium Channel

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based on

http:\arxiv.org/abs/1209.2381

Preview

Brownian dynamics were simulated using Igor Kaufman's code for the simple model of Ca channels introduced in 1998 by Nonner & Eisenberg, computing electric forces from all charges.

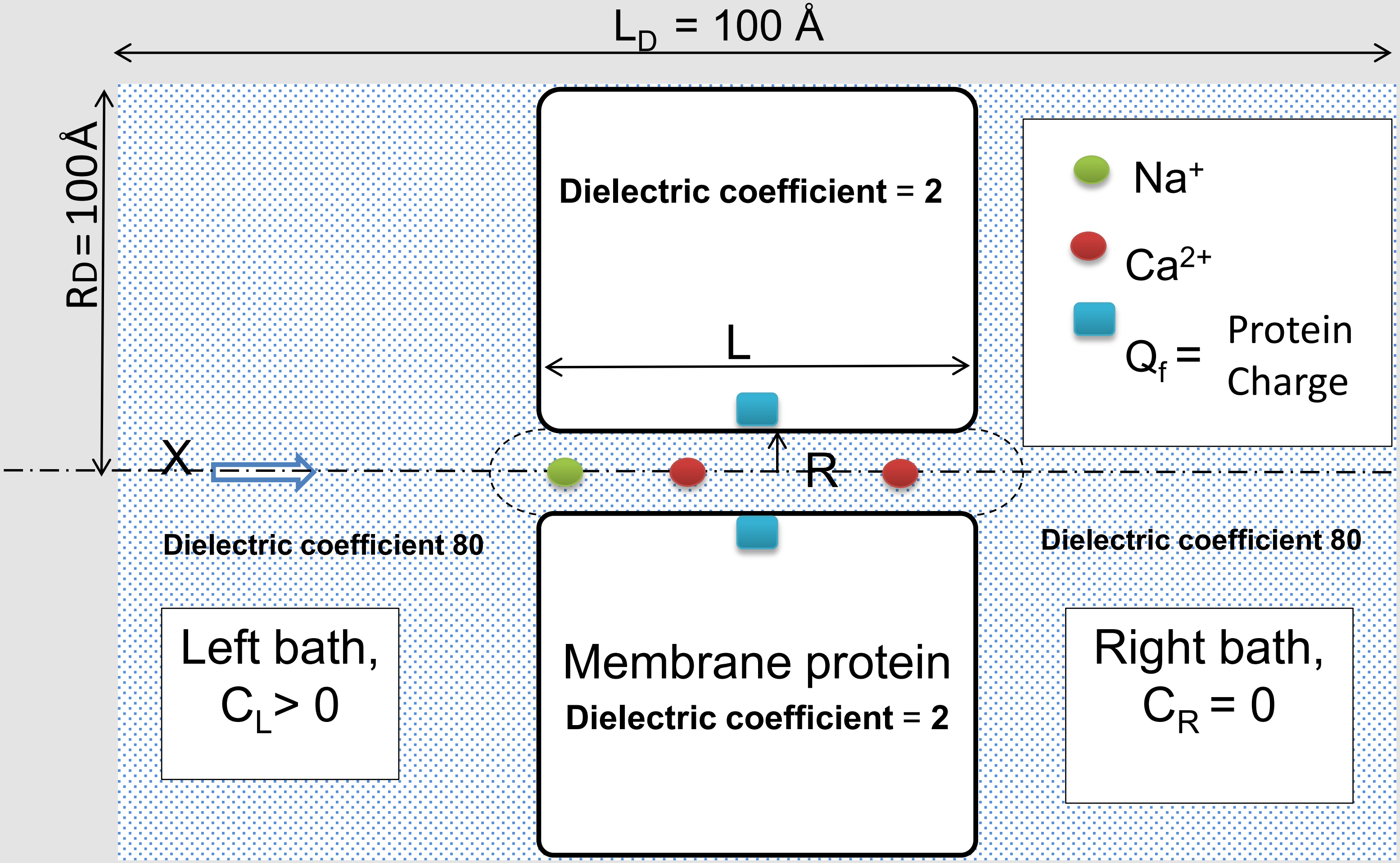
Permanent charge Q_f (of acidic side chains) **was varied**.

Substantial conduction was found only at <u>discrete integral values</u> of permanent charge Q_f

Different conduction states had different selectivity,
one resembling L-type CaV_1
the other resembling RyR channels

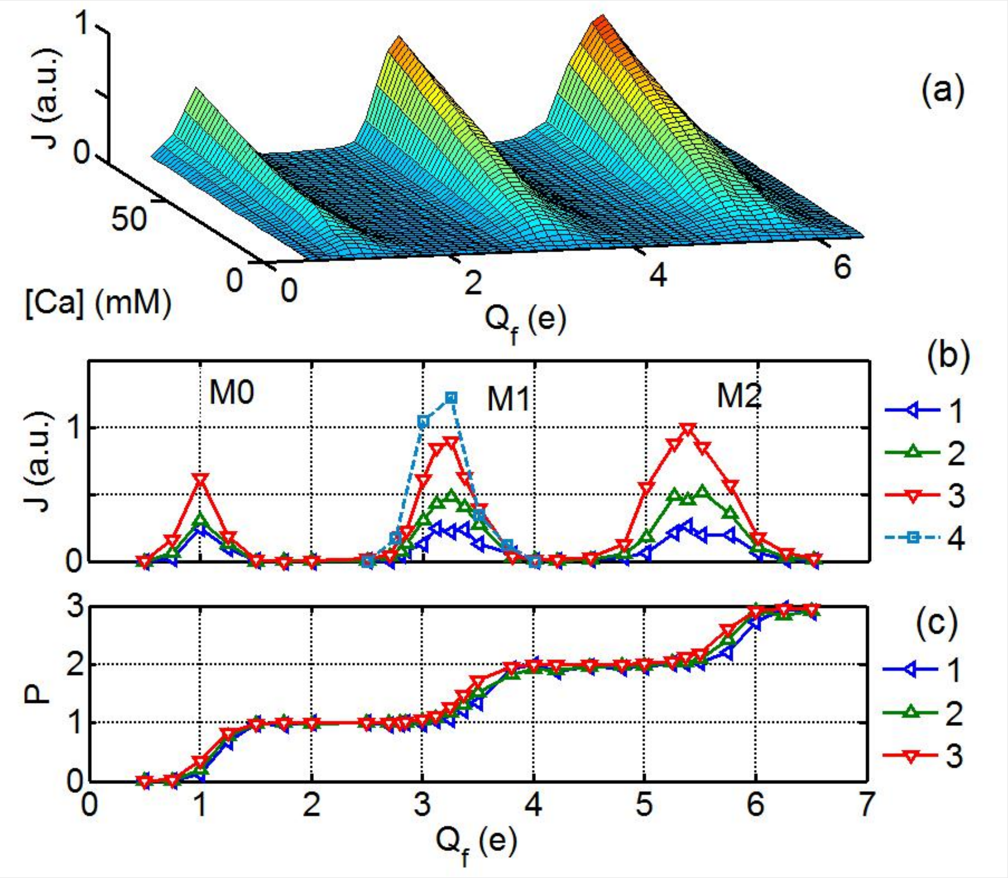
We speculate:
some types of spontaneous gating could arise from thermal fluctuations in Q_f that switch between conductance states.

Setup and Model of Calcium Channel



Simple electrostatic model of the calcium channel: water-filled cylindrical hole of radius *R* = 3 Å and length *L* = 12-16 Å through the charged protein hub in the cellular membrane.

Conduction and Selectivity Bands



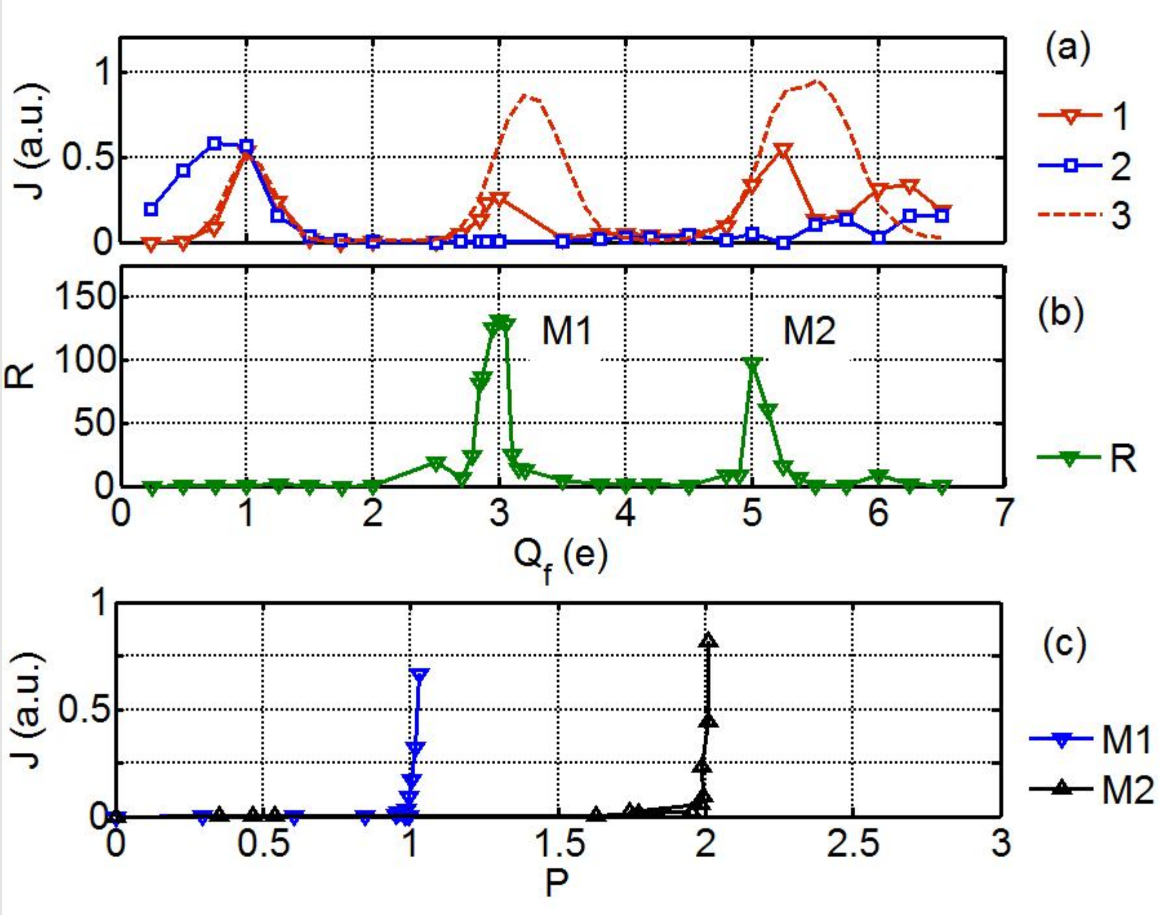
(a) **Band Structure** in *3D* plot of Ca current J *vs* fixed charge Q_f and concentration [Ca].

(b) J as a function of Q_f and [Ca] shows the **nonselective M0, L type M1, and RyR M2 bands**: plots **1,2,3** are for [Ca] = 20 mM, 40 mM, 80 mM, respectively;
and **4** is from Corry *et al*, Biophys. J., (2001) 80 195-214, compare to M1.

(c) **Occupancy P shows stepwise growth** as Q_f increases. The flat steps are saturated occupancy values P = 1, 2, 3, ..

Conduction and **Selectivity Bands**

for a **[Na] = 30 mM**, **[Ca] = 40 mM** mixed salt bath



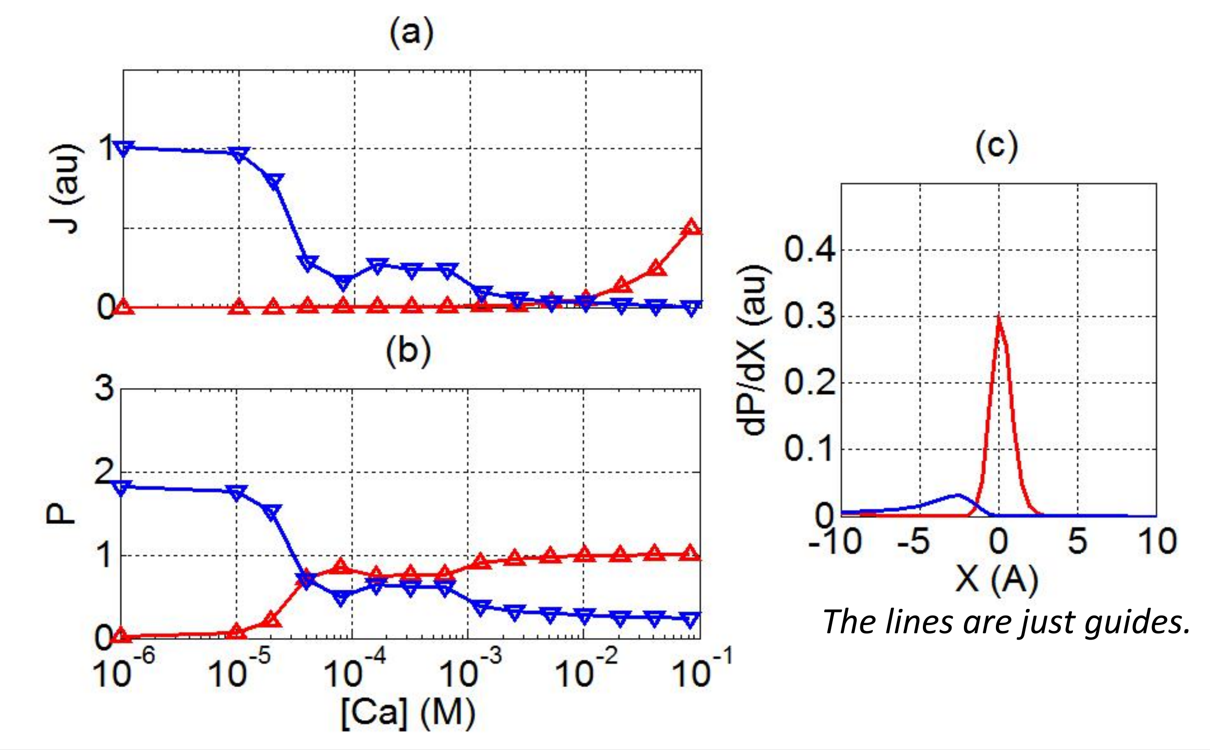
(a) Currents *J vs* fixed charge Q_f. Curves: **1 Ca**; **2 Na;**

only for reference **3 Ca** is a pure bath *(from Fig 1).*

(b) The selectivity ratio $R_S = J_{Ca}/J_{Na}$ shows sharp peaks **for L type M1** and **RyR M2 bands.**

(c) J_{Ca} *vs* Ca^{2+} occupancy *P*. conductance saturates at nearly constant P for L-type and RyR

AMFE for the **L-type M1 channel Blockade** in a mixed salt bath



The lines are just guides.

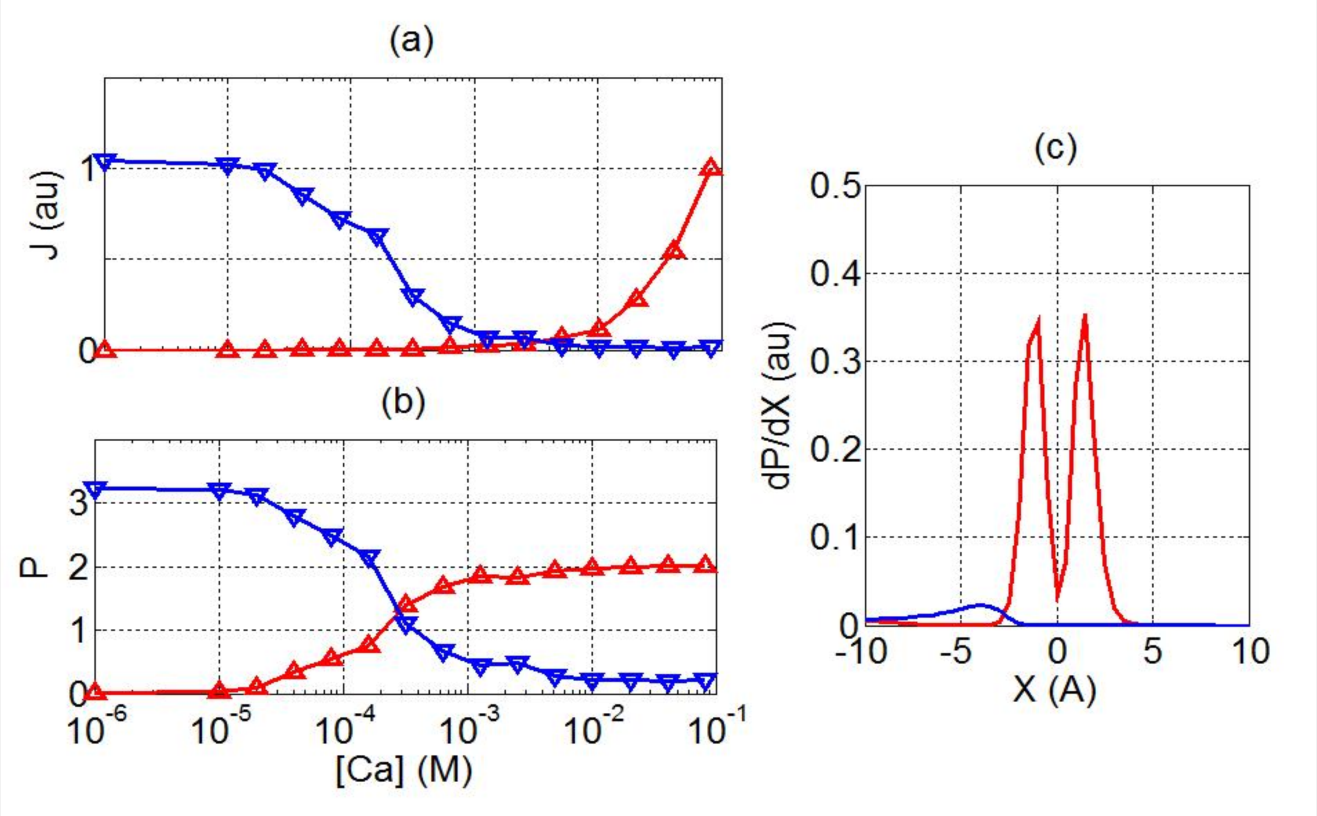
(a),(b) Na blue, point-down, triangles and **Ca red**, point-up, triangles currents *J* and occupancies *P vs* [Ca] concentration in the L type M1 channel for [Na] = 30mM.

L-type shows strong blockade and AMFE at $P_{Ca} = 1$ with threshold $[Ca]_{50} \approx 30\mu M$.

(c) Mutual occupancy profiles for **Na left, blue**, and **Ca right, red**

note Blockade of **Na ions by the first Ca ion**

AMFE for the **RyR M2 channel**
Blockade in a mixed salt bath



(a),(b) **Na blue** triangles and **Ca red**, triangles currents J and occupancies P vs [Ca] concentration in **moderately selective RyR M2** channel for [Na] = 30mM.

RyR M2 shows moderate blockade and AMFE at P_{Ca} = 2 with threshold $[Ca]_{\mathbf{50}}$ ≈ 200μM.

(c) Mutual occupancy profiles for **Na left, blue**, and **Ca right, red**

note **Blockade** of **Na ions by two Ca ions**

Conduction and **Selectivity Bands**

Conduction band	Fixed protein charge	Na conductivity	Ca conductivity	Blockade of Na current by Ca ions	AMFE	Channel(s)	Residues locus
M0 nonselective	≈ 1e	High	High	No blockade	No AMFE	Non-selective cation channel, OmpF channel	
M1 L type	≈ 3e	High	High	Yes, sodium ion is blocked by one Ca^{2+} low blockade offset (30µM)	Yes, blockade is followed by moderate calcium current	L-type Calcium channel	EEEE
M2 Ryanodine Receptor	≈ 5e	High	High	Yes, sodium ion is blocked by two Ca^{2+} higher blockade offset (200µM)	Yes, blockade is followed by strong calcium current	RyR Channel	DDDD

Table shows how **non-selective OmpF porin becomes a Ca selective channel** after mutations Miedema *et al, Biophys. J.* (2004) 87 3137

Conclusion

Discrete

Selectivity, Occupancy, Blockade

arise as

OUTPUTS

of a

Continuous Model

because of

Correlations

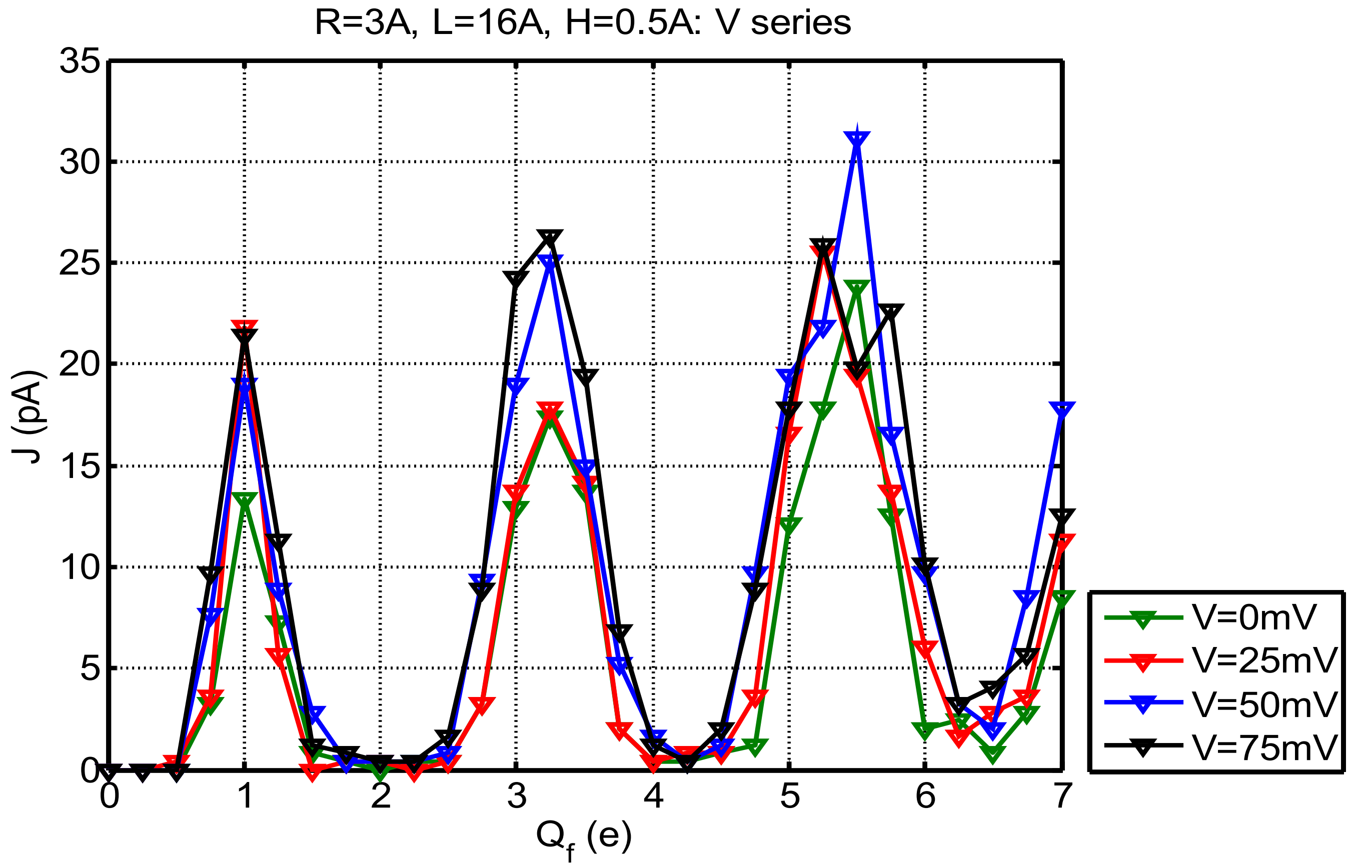
in solutions (outputs) of

PNP ***(with finite size ions)***

Sensitivity Analysis

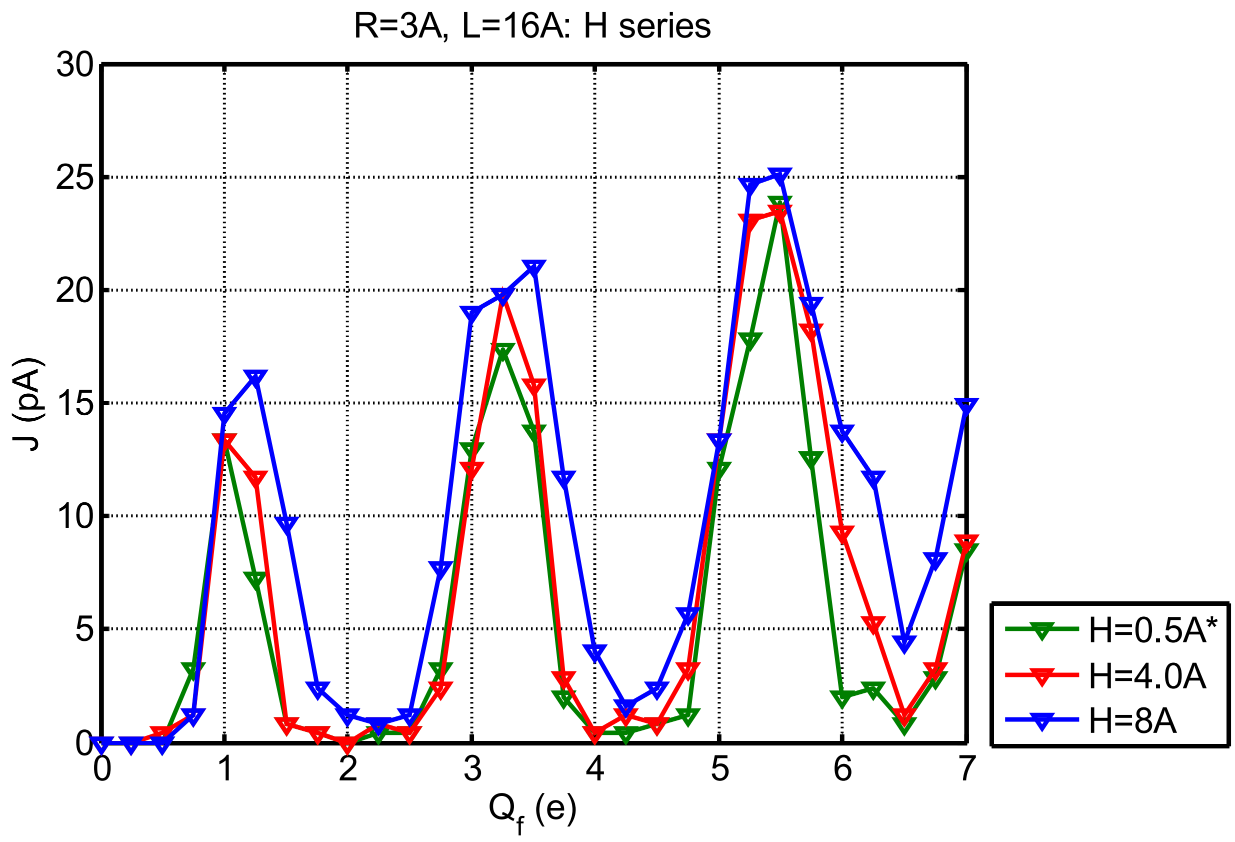
Sensitivity Analysis

Little Dependence on Voltage

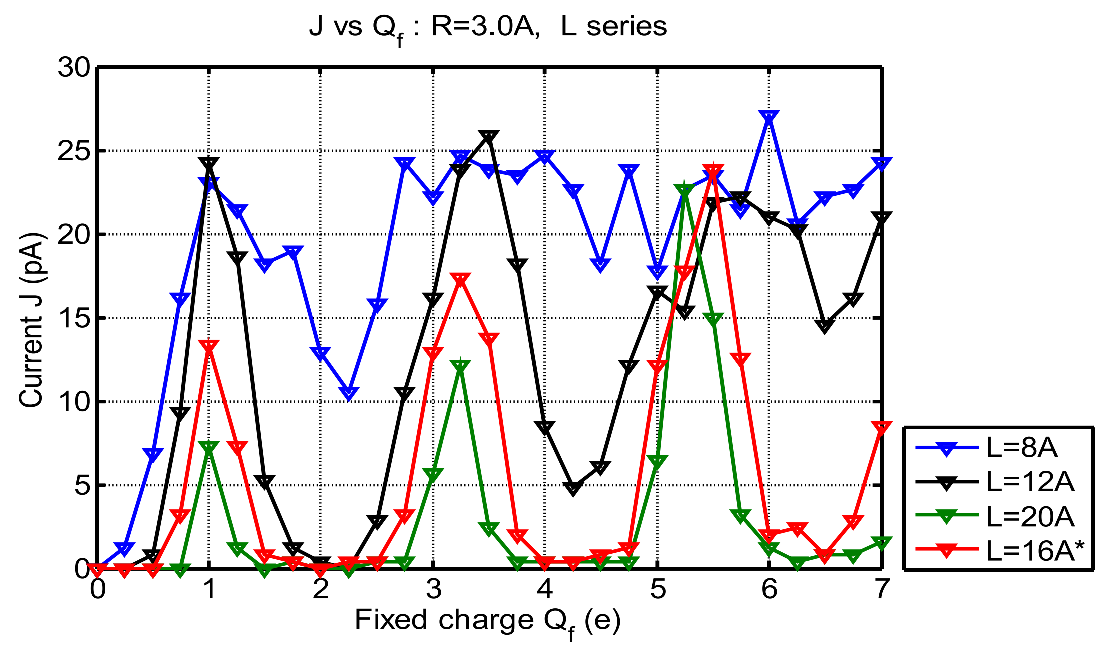


Sensitivity Analysis

Little Dependence on Length *H* of Charged Ring

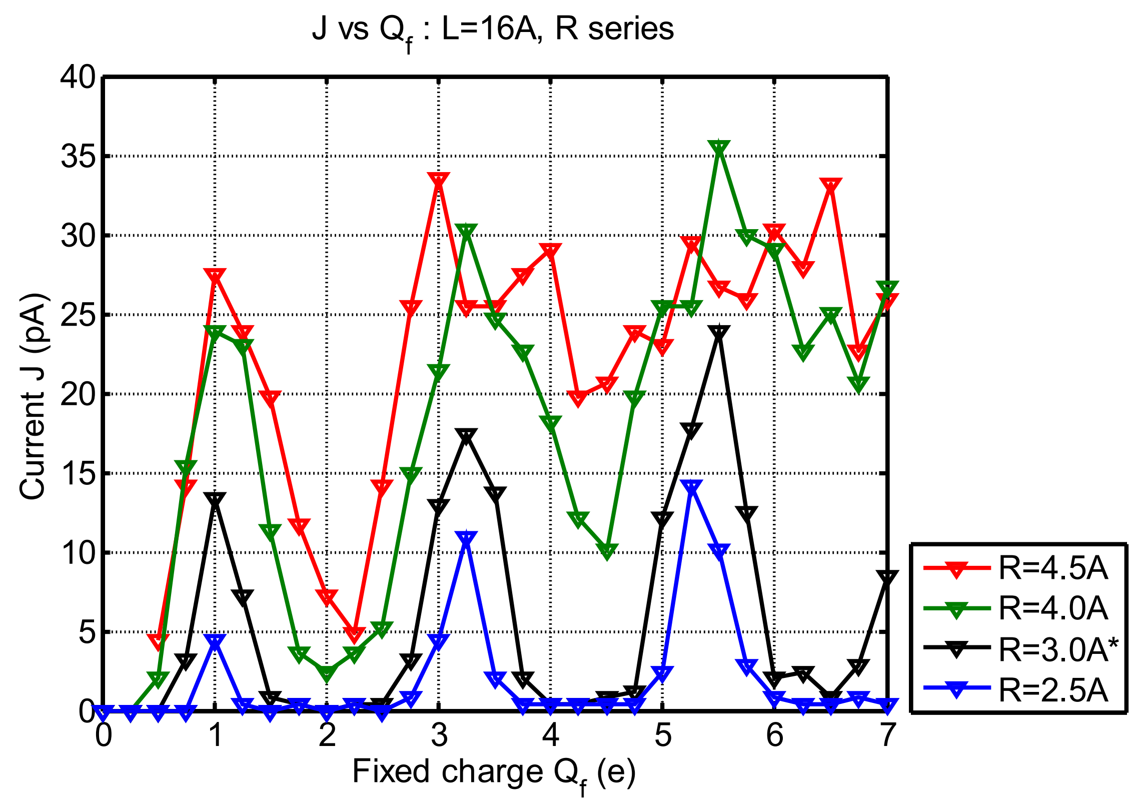


Sensitivity to Channel Length L



Increase of *L* separates the conduction/non-conduction bands and decreases *J.*

Sensitivity to Channel Radius R



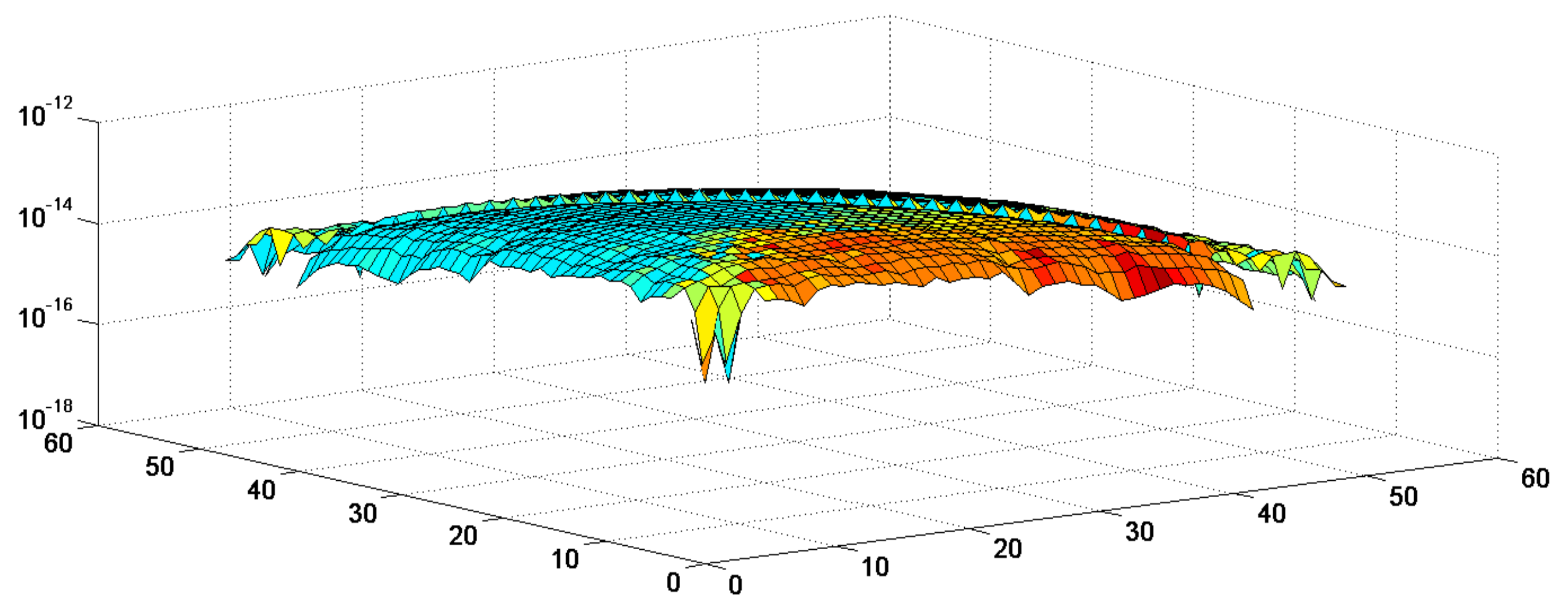
An increase of *R* to 3-4 Å leads to a decrease in the band structure, but the general pattern of the bands is still visible.

A (further) increase of *R* to 4.5 Å **destroys the band structure.**

Accuracy Checks are Important

e.g.

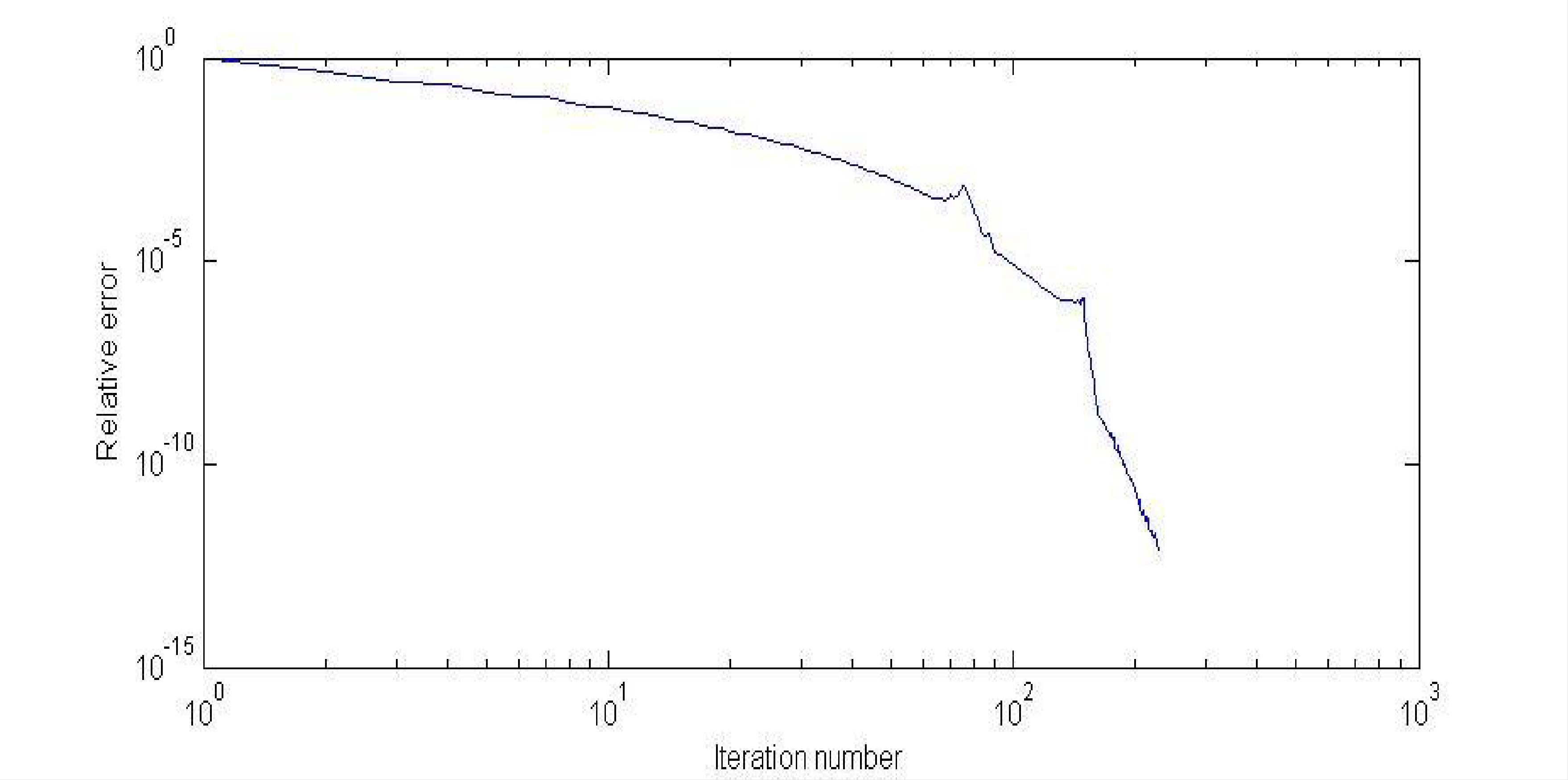
Map of Gauss law residuals for the field of a point



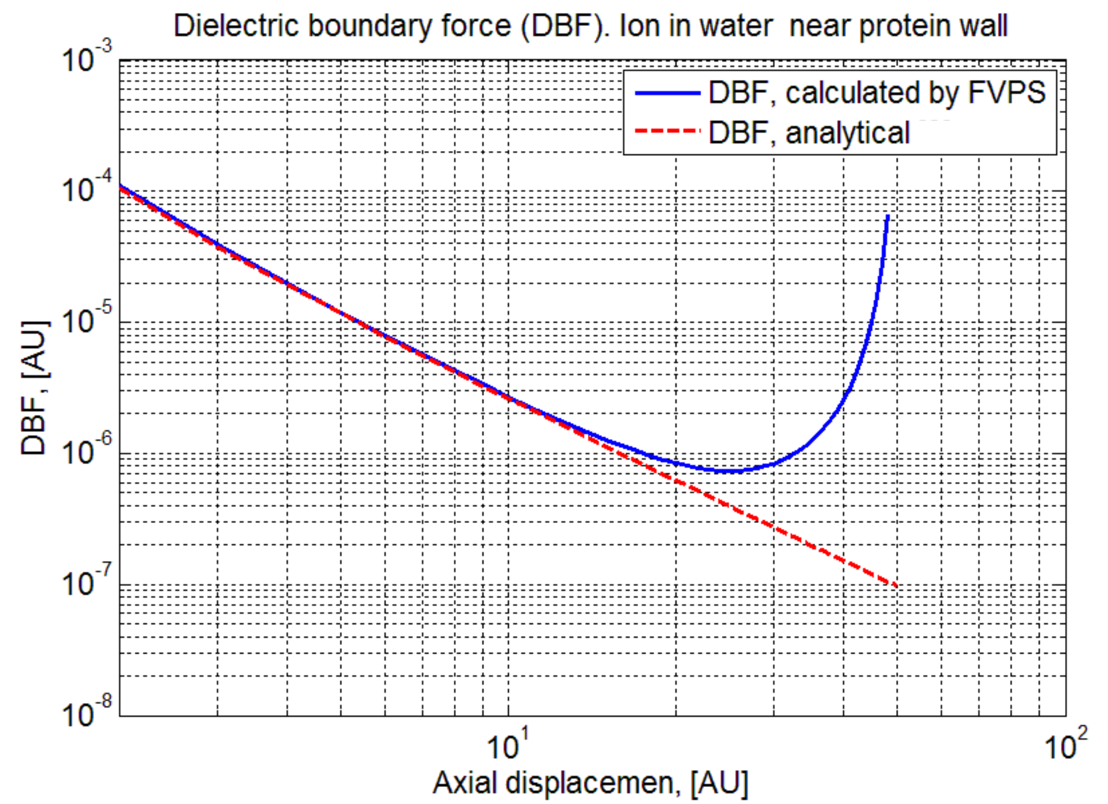
The finite-volume scheme automatically fulfils Gauss's law for each grid cell within the limits of the method's tolerance 10^{-16}

Convergence

for a point charge



Dielectric Boundary Force



Numerical (blue) and analytical values coincide well for two orders of magnitude for DBF

The unavoidable divergence region shows where external boundary condition in numerical analysis restricts validity region of analytical expression of Nadler, *et al, (*2003) Phys Rev E **68**:021905.

Stability Analysis of Related System

Mathematical Stability Analysis

led by **Weishi Liu** (Kansas State University)

to determine

Relation of Instability and Gating

Ji, S. and W. Liu (2012)
Poisson–Nernst–Planck Systems for Ion Flow with Density Functional Theory for Hard-Sphere Potential: **I–V Relations and Critical Potentials**. Part I: Analysis. Journal of Dynamics and Differential Equations:1-29.

Liu, W., X. Tu, and M. Zhang (2012)
Poisson–Nernst–Planck Systems for Ion Flow with Density Functional Theory for Hard-Sphere Potential: **I–V Relations and Critical Potentials**. Part II: Numerics. Journal of Dynamics and Differential Equations:1-20.