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Electrophoresis and Electroosmosis in the Intracellular Transport of Macromolecules

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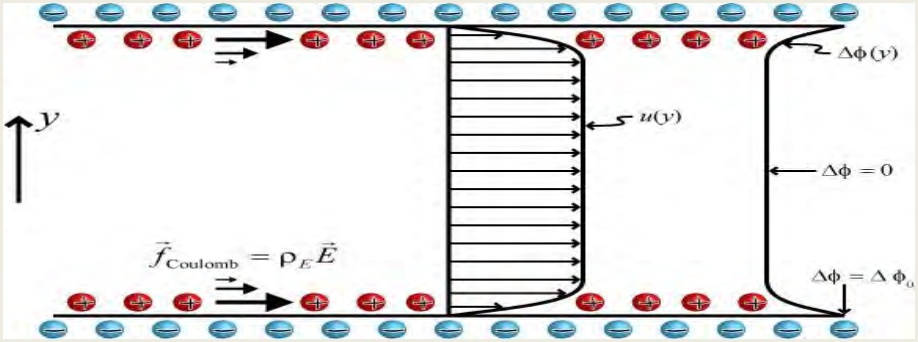
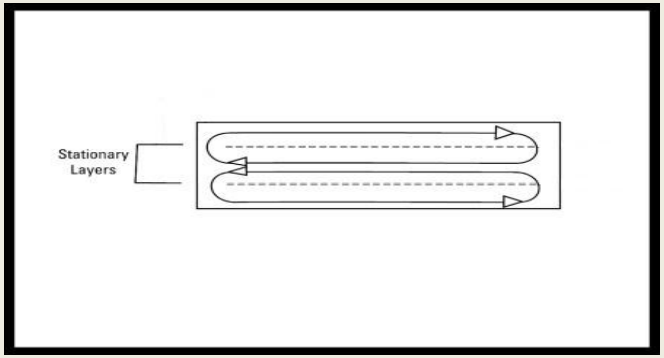
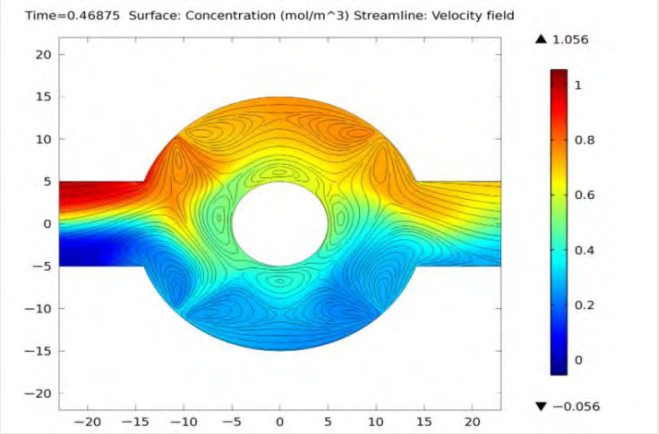
Electroosmotic flow results from the action of electric field on the electrical double layer, formed at the fluid/solid or fluid/membrane interface







H. Chen, Y.T. Zhang, I. Mezic, C.D. Meinhart, and L. Petzold, Numerical Simulation of an Electroosmotic Micromixer. *Proc Microfluidics 2003 (ASME IMECE), (2003).*

Electroosmosis is known to be important in capillary electrophoresis and microfluidics. Why is it ignored in the models of the intracellular transport of biopolymers?

$$v_{ep} = \frac{Z*e*E}{6\pi*\eta*r_s} = \frac{Z*e*D*E}{k_B*T};\ v_{osm} = \frac{\varepsilon*\varepsilon_0*\xi*E}{\eta};\ \text{so}\ \frac{v_{osm}}{v_{ep}} = \frac{\varepsilon*\varepsilon_0*\xi*k_B*T}{\eta*D*Z*e}$$

For zeta-potential of -50mV, and Z=1, $D=10^{-11}m^2/s$
electroosmosis is 10-fold faster than electrophoresis

Necessary conditions for electroosmosis:

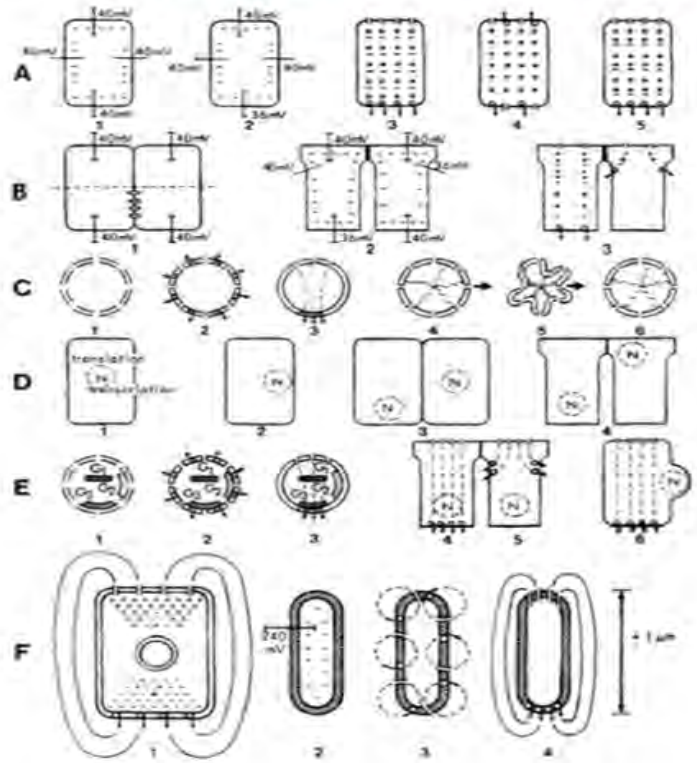
- **Charged surface**
- **Electric field component parallel to the surface**

Both conditions are present in the cytoplasm of the polarized cell

"in the case of the ion pump/channel activity being asymmetrically distributed, the cell behaves as a miniature electrophoresis chamber".

Plethora of Cytoplasmic Electric Field and Electric Current Configurations

A.De Loof. The Cell as a Miniature Electrophoresis Chamber.
Comparative Biochem . Physiol. 80A, 453-459, 1985



Different types of ion pumps and Ion channels (symmetrical and asymmetrical)

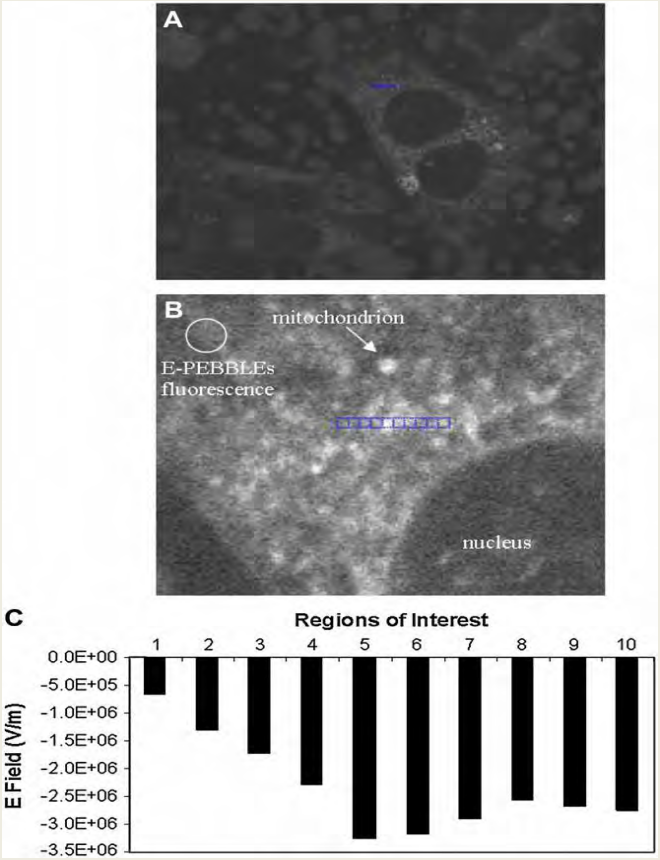
Cytoplasmic bridges, tight junctions and gap junctions

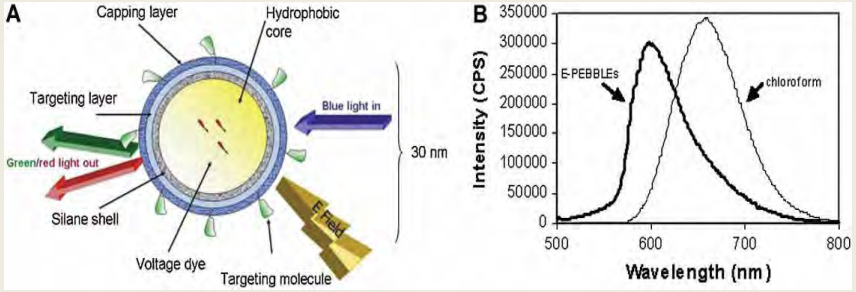
Nuclear envelope: open, close, symmetrical, asymmetrical

Position of nucleus: in or out of main transcytoplasmic ionic flux

Possible charge distributions in case of asymmetrical distribution of ion pump/channel activity

Cytoplasmic Electric Field





Nanosized Voltmeter'' Enables Cellular-Wide Electric Field Mapping.
K.M. Tyner, R. Kopelman, M. A. Philbert.
Biophysical J, **93:** 1163-1174 (2007)

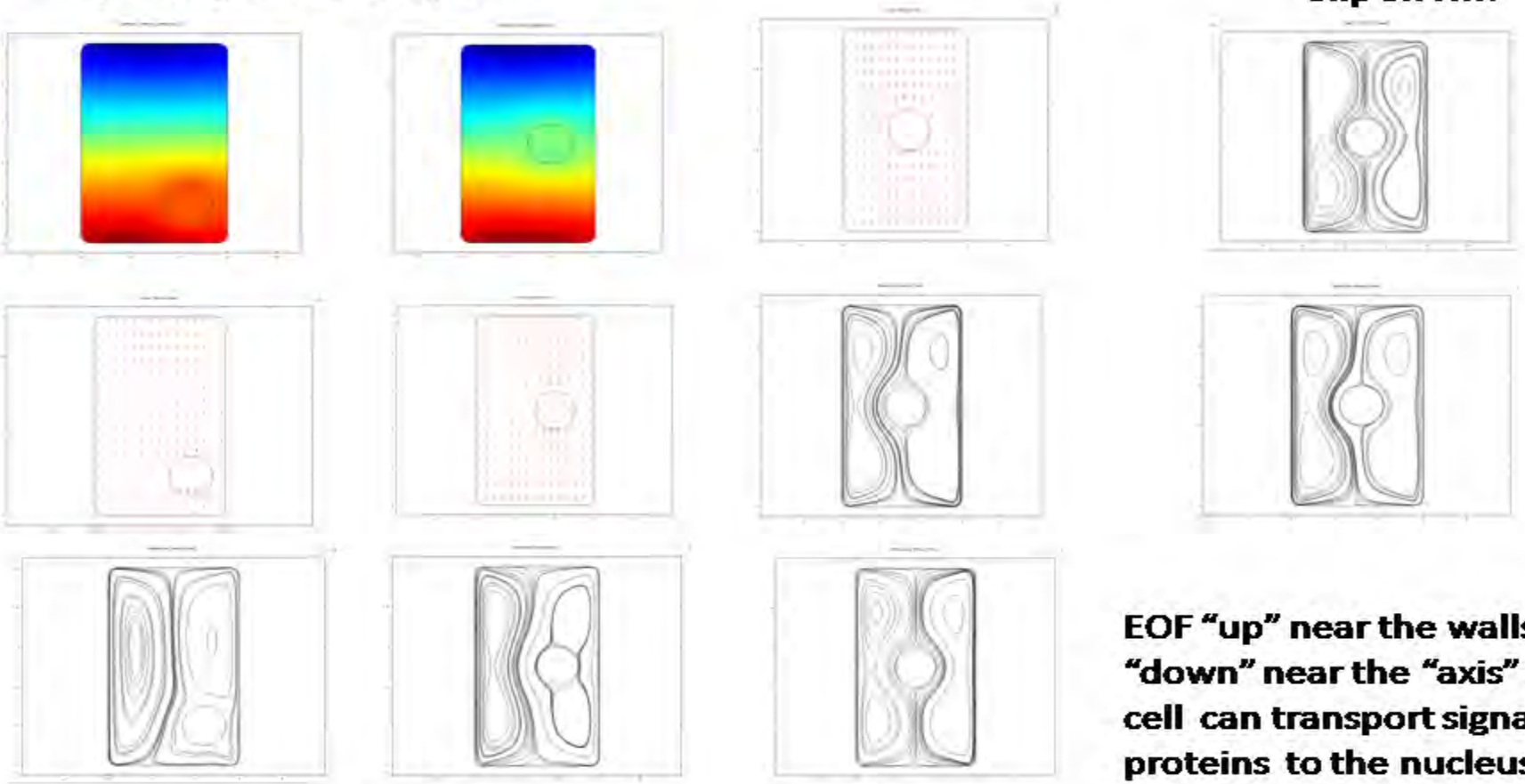
Coulomb Interactions between Cytoplasmic Electric Fields and Phosphorylated Messenger Proteins Optimize Information Flow in Cells.
Robert A. Gatenby, B. Roy Frieden.
PLoS ONE | www.plosone.org August 2010 | Volume 5 | Issue 8 | e12084

Examples of possible electroosmotic flow configurations in the cell

Simplistic model of EOF in the Cell

- Asymmetric ion pumps, negatively charged cellular membrane,
- Conductivity and permittivity of nucleoplasm 2-fold higher than of cytoplasm σ_c=0.25 S/m, ε_c=60; σ_n=0.5 S/m, ε_n=120

Slip on NM



EOF "up" near the walls and "down" near the "axis" of the cell can transport signalling proteins to the nucleus

No slip on nuclear membrane (NM)

Model and Computational Methods:

- 2D
- Ion pump/channel activity asymmetrically distributed, electric current entering and leaving cell through the opposite horizontal sides of the square, σ_c=0.25 S/m, ε_c=60; σ_n=0.5 S/m, ε_n=120
- Navier-Stokes equations in the approximation of the creeping flow, η_c=0.008 Pa·s
- No slip boundary condition at the nucleus membrane
- Electroosmotic velocity condition at the cellular membrane, zeta-potential=-50mV
- Diffusion-convection-migration equations for transport of macromolecules, $D_m = 10^{-12} m^2/s$
- Messenger proteins introduced as a 0.01 s pulse at the left lower corner of the cell
- Interaction with cytoskeleton binding sites:

  $R_2 = -k_m C_m C_2 + k_{rm} C_5 - k_e C_e C_2 + k_{re} C_3$

COMSOL 4.2: Electric Currents, Creeping Flow, and Transport of Diluted Species

Results. Free messenger proteins

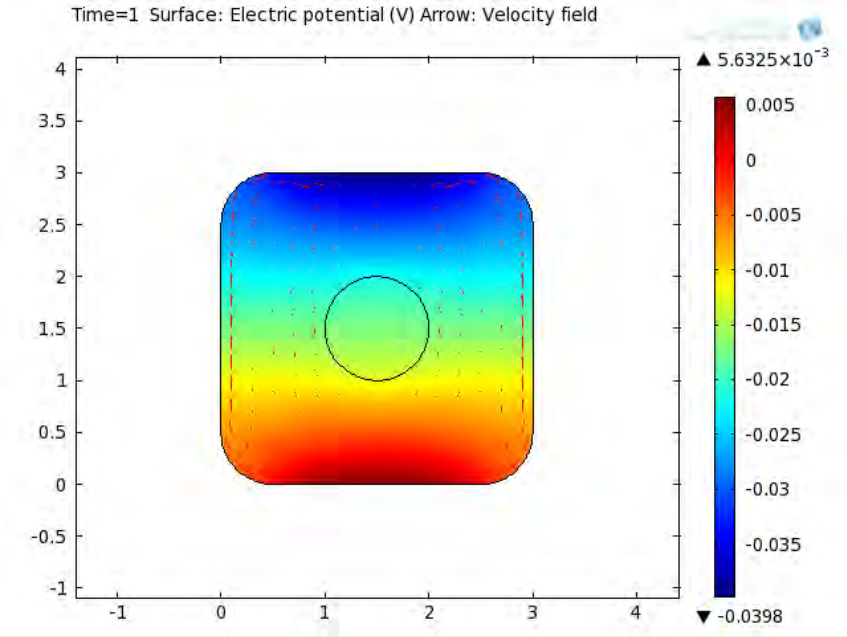


Figure 1. Electrical potential and flow velocity in a simple model of polarized cell

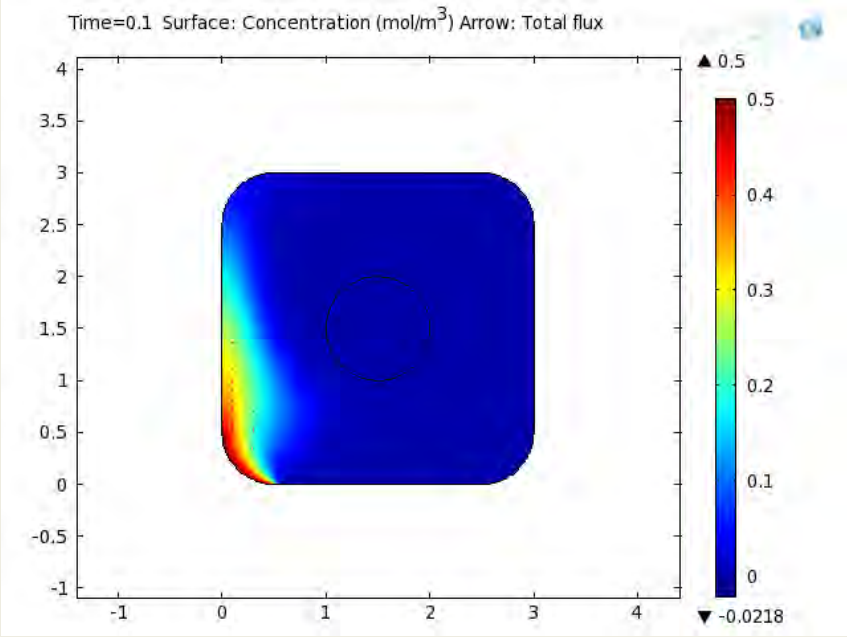


Figure 2. Concentration and flux of free messenger protein at t=0.1 s. Electroosmosis is present.

Transport with and without EOF compared

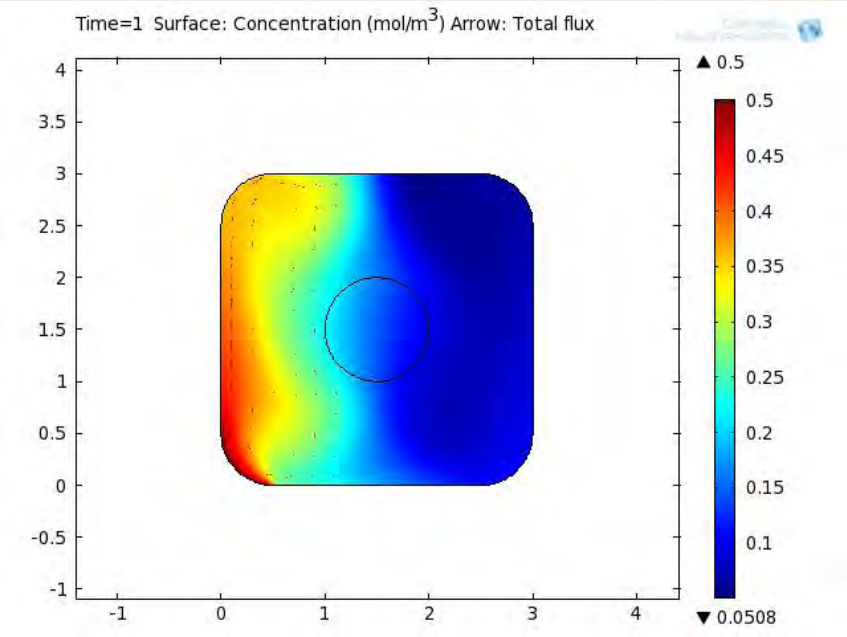


Figure 3. Concentration and flux of free messenger protein at t=1 s. Electroosmosis is present.

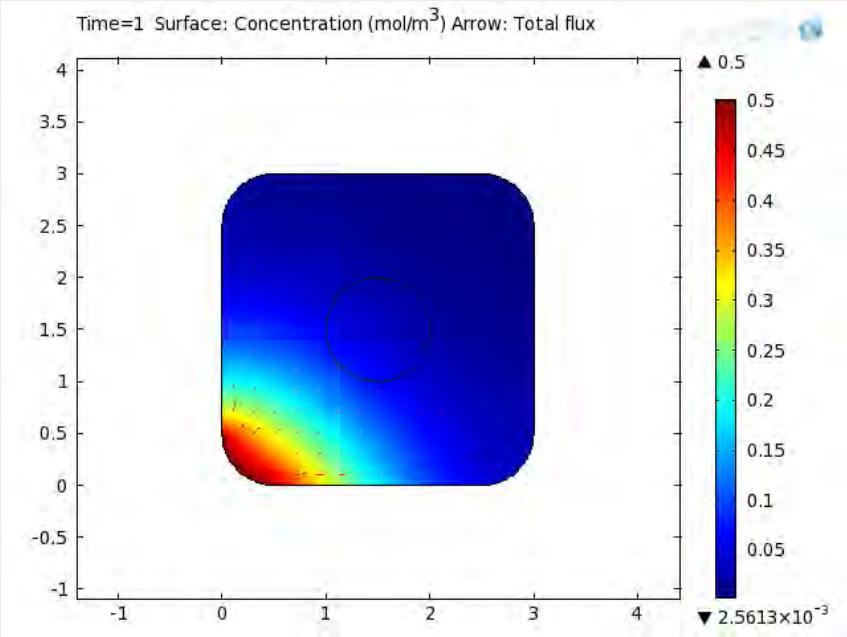
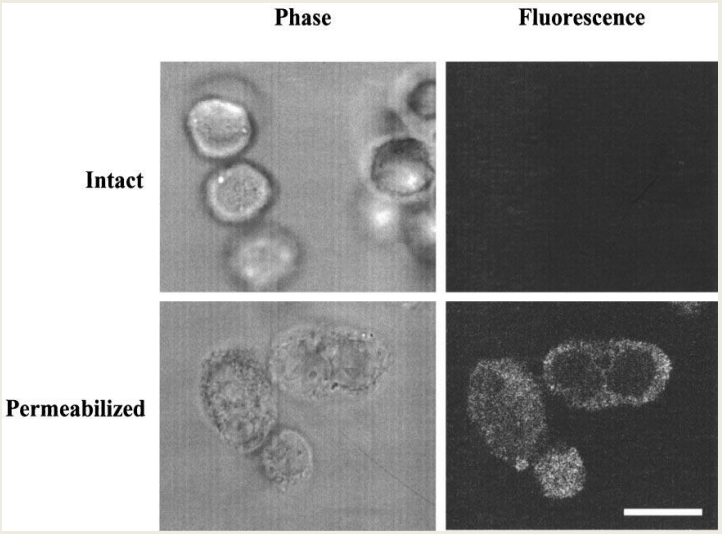


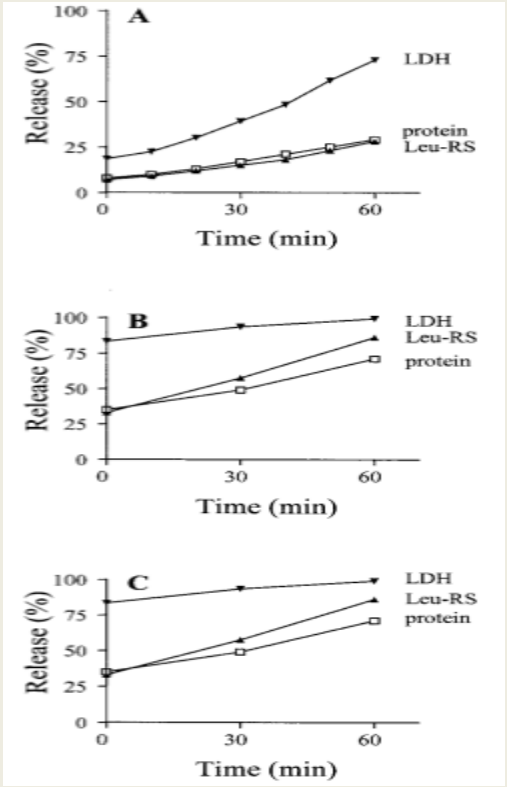
Figure 3. Concentration and flux of free messenger protein at t=1 s. Electroosmosis is absent. Transport by diffusion and electrophoresis.

3-fold higher amount of messenger protein reached nucleus when EOF is present

Transport in the presence of protein sorption to cytoskeleton

A. Hudder, L. Nathanson, M.P. Deutscher. Organization of mammalian cytoplasm. *Mol Cell Biol,* **23,** 9318-9326 (2003).





Around 10% of total protein amount left cytoplasm after 10 minutes and about 25% after an hour after permeabilization of the membrane with saponin.

Endogenous proteins in mammalian cytoplasm are normally not free to diffuse over large distances due to bonding to cytoskeleton

Protein transport with reversible sorption to cytoskeleton. Leakage of endogenous proteins.

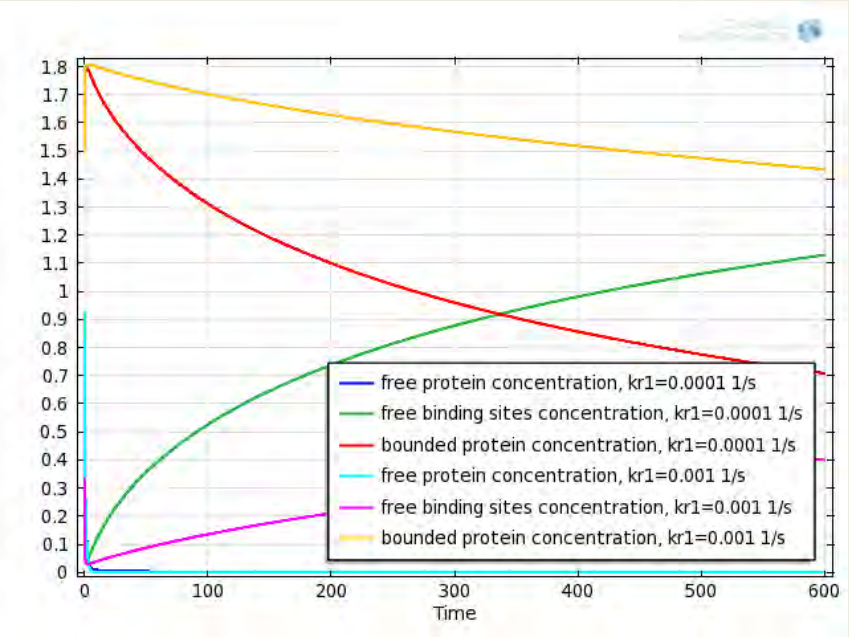


Figure 4. Rate of release of endogenous protein from the cytoplasm. Initial values: C_e=1mM, C_2=1mM, C_3=1mM, k_1=1 $m^3/(mol \cdot s)$

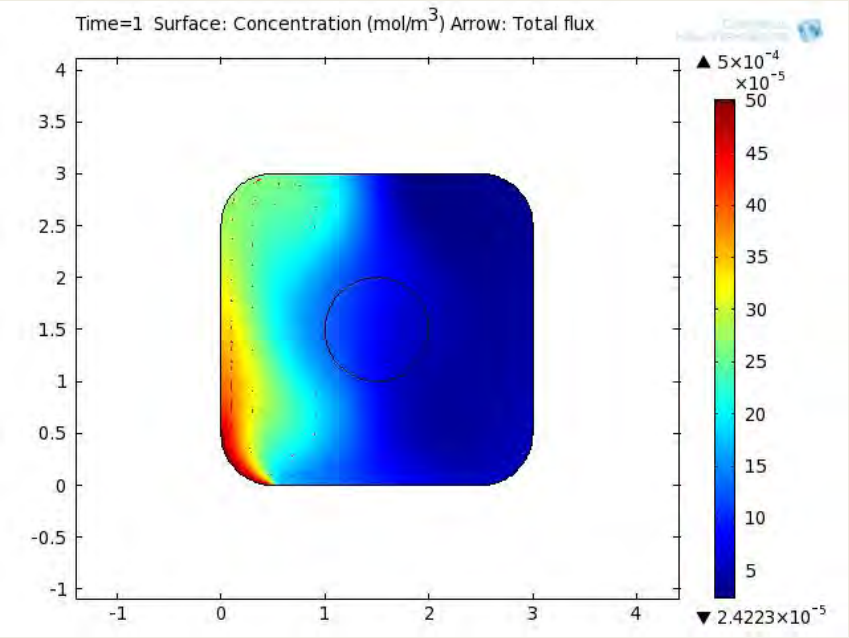
$R_e=-k_1C_eC_2+k_{r1}C_3=R_2=-R_3$

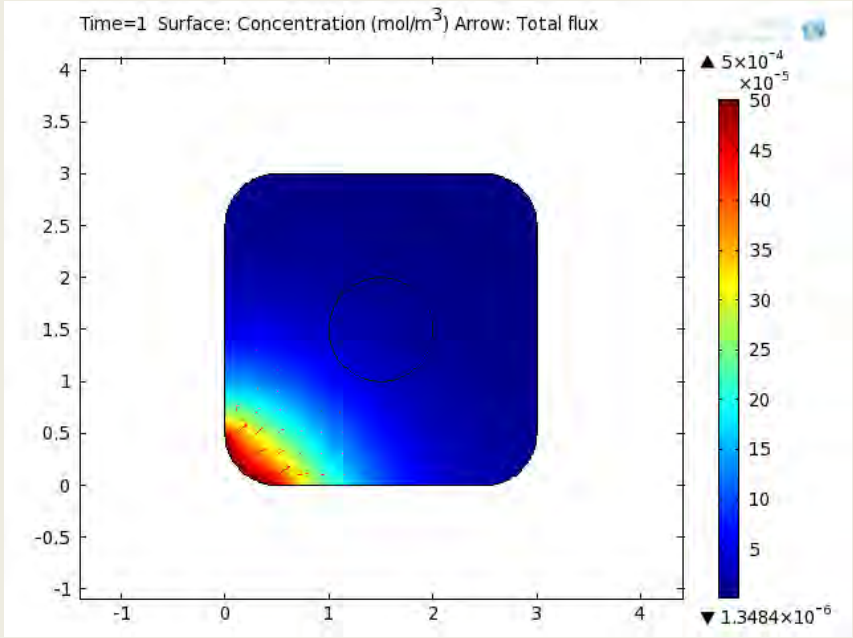
Permeabilization of the cellular membrane makes it permeable to small ions, and therefore eliminates any charged double layer and membrane potential. Therefore, electroosmosis is eliminated in the saponin treated cells. Similarly, cytoplasmic electric field is eliminated. So in this model transport is by diffusion only.

Comparison with experiment resulted in plausible direct and reverse sorption rates: k_1=1 $m^3/(mol \cdot s)$, kr1=0.001 s^{-1}

Transport of messenger proteins. Binding sites in abundance

A





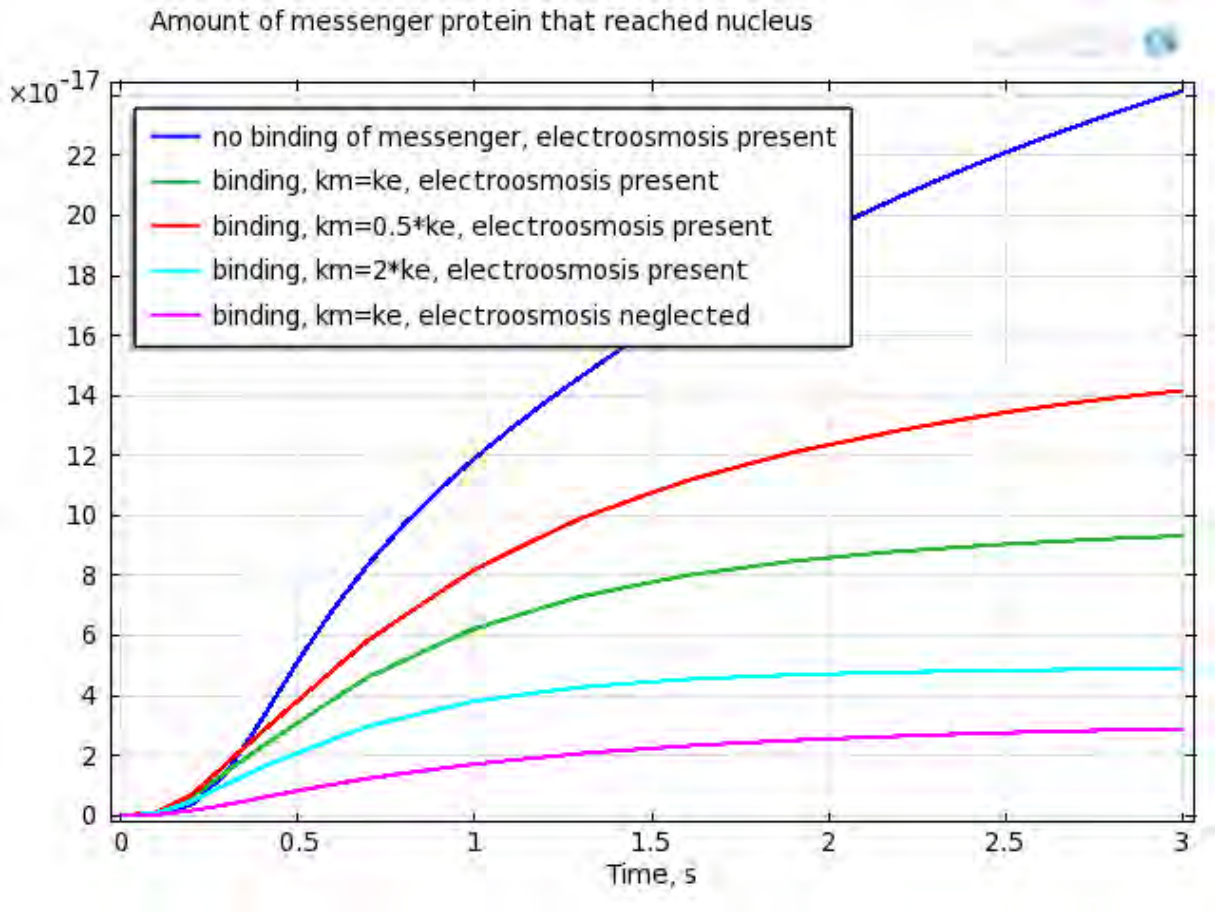
B

Figure 6. Concentration and flux of messenger protein at time t=1s. Binding sites are in abundance. Equal binding reaction rates for endogenous and messenger proteins: $k_m=k_e=1$ $m^3/(mol\cdot s)$. Diffusion coefficient: $10^{-12}m^2/s$, charge: single negative. Initial conditions: $C_e=0.001$, $C_m=0$, $C_2=1$, $C_3=1$, $C_5=0$.

A - electroosmosis present: ζ=-0.05 V;

B – electroosmosis absent

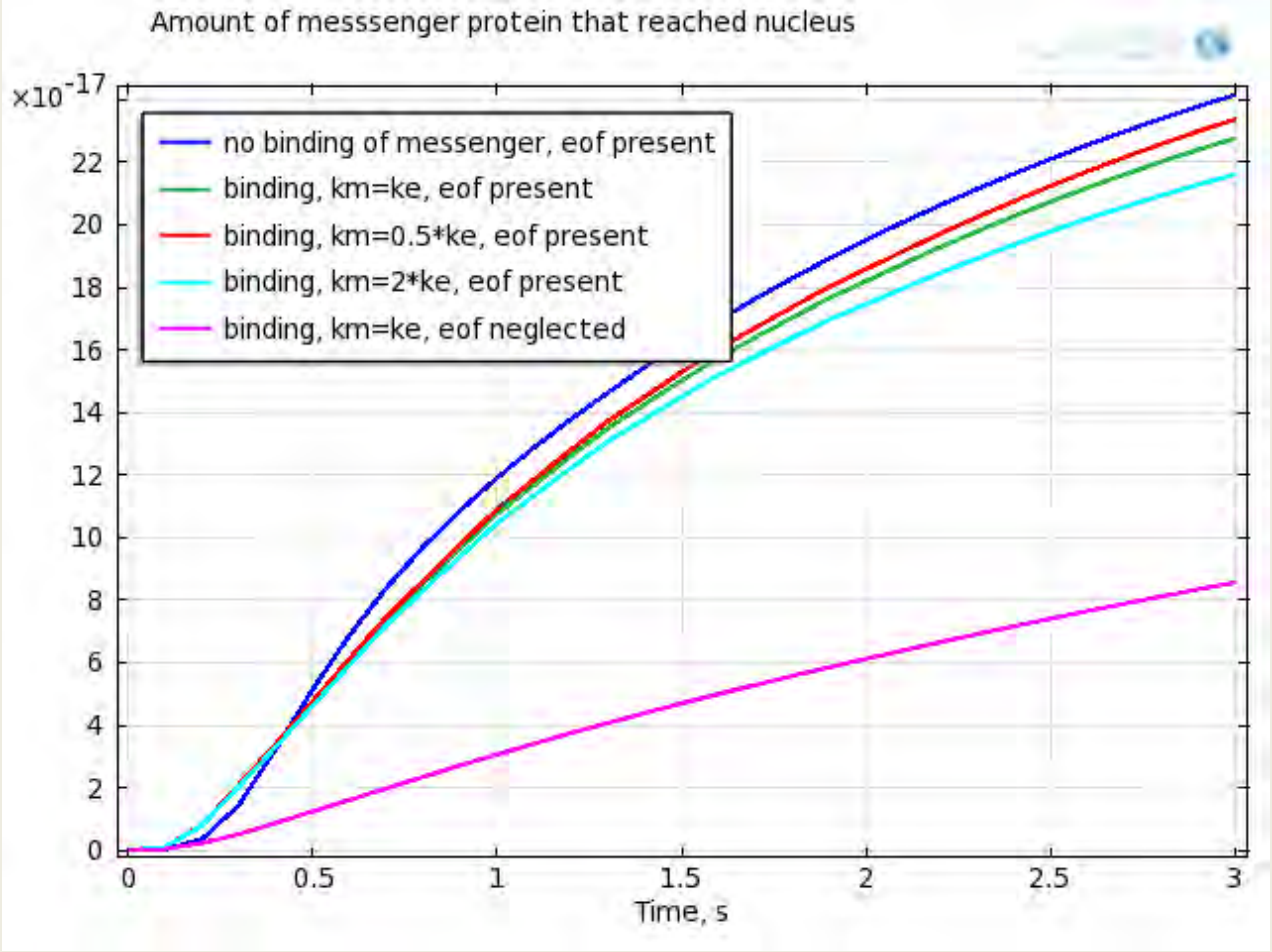
Amount of messenger that reached nucleus versus time. Binding sites in abundance.



2-4 fold more messenger protein molecules reach nucleus at t=1 s when electroosmosis is present

C_e=0.001mM, C_2=1mM, C_3=1mM, C_5=0, C_m=0.001·rect1(0.01) mM. ζ=-0.05 V.
D_e= D_m= 10^{-12} m^2/s, z_e= z_m=-1. k_e=1 $m^3/(mol \cdot s)$ and k_{re}=0.001 s^{-1}, k_{rm}=0.01 s^{-1}.

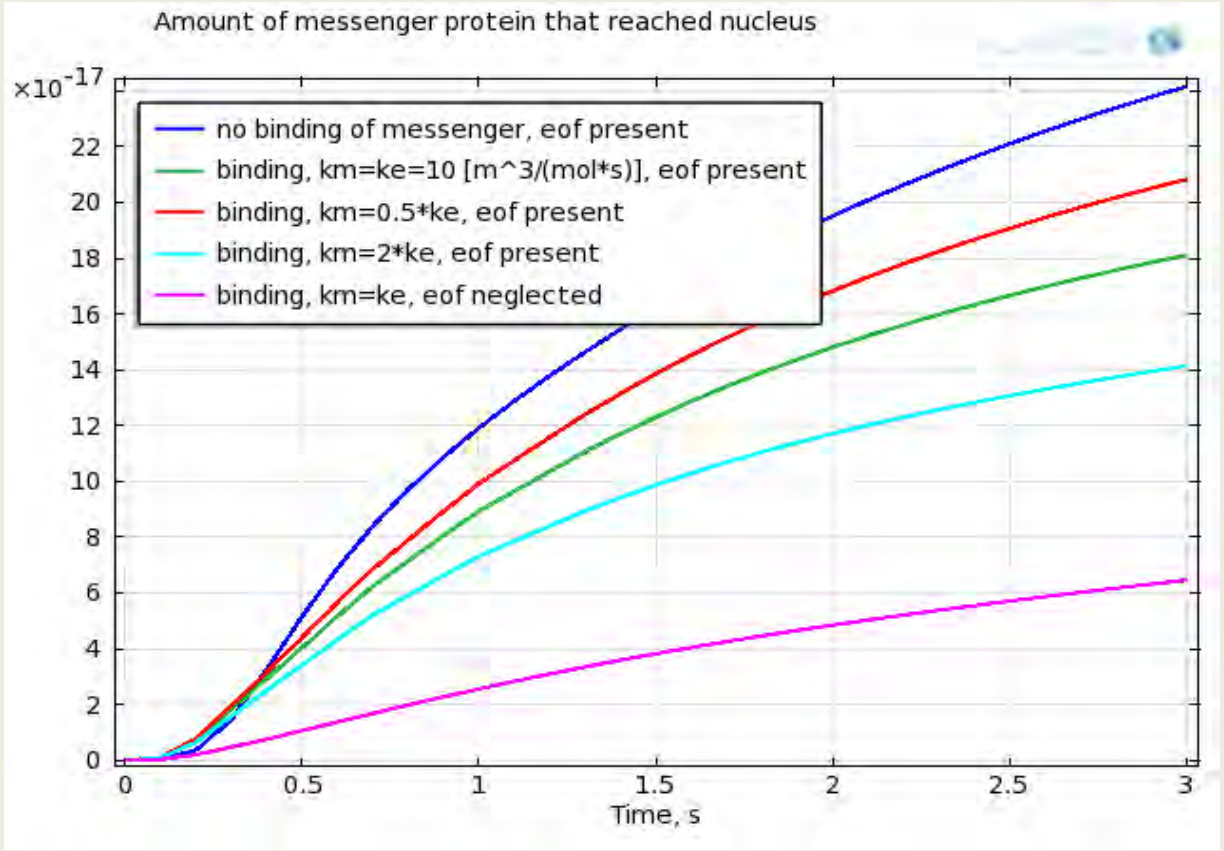
Amount of messenger that reached nucleus versus time. Competition for binding sites. Slow binding



4- fold more messenger protein molecules reach nucleus at t=1 s when electroosmosis is present

Endogenous protein cytoskeleton binding sites are intially in equilibrium:C_e=0.045 mM, C_2=0.044 mM, C_3=1.956 mM. ζ=-0.05 V. D_e= D_m= $10^{-12}m^2/s$, z_e= z_m=-1. k_e=1 $m^3/(mol \cdot s)$ and k_{re}=0.001 s^{-1}, k_{rm}=0.01 s^{-1}.

Amount of messenger that reached nucleus versus time. Competition for binding sites. Fast binding



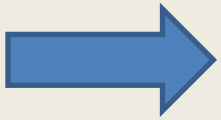
2-3- fold more messenger protein molecules reach nucleus at t=1 s when electroosmosis is present

C_e=0.045 mM, C_2=0.044 mM, C_3=1.956 mM. ζ=-0.05 V. D_e= D_m= $10^{-12}m^2/s$, z_e= z_m=-1. k_e=10 $m^3/(mol \cdot s)$ and k_{re}=0.001 s^{-1}, k_{rm}=0.01 s^{-1}

Conclusion

Electroosmosis can play an important role in the transport of proteins in the cytoplasm of the polarized cells. 3-fold rate increase relative to electrophoresis and diffusion

Next Steps:

- 2D  3D
- More realistic cell geometries
- Active transport

Thanks for Attention!

Questions?