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.

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

\[
v_{ep} = \frac{Z\cdot e\cdot E}{6\pi\cdot \eta\cdot r_s} = \frac{Z\cdot e\cdot D\cdot E}{k_B\cdot T}; \quad v_{osm} = \frac{\varepsilon\cdot \varepsilon_0\cdot \xi\cdot E}{\eta}; \quad \text{SO} \quad \frac{v_{osm}}{v_{ep}} = \frac{\varepsilon\cdot \varepsilon_0\cdot \xi\cdot k_B\cdot T}{\eta\cdot D\cdot Z\cdot e}
\]

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


- 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)*

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 $\sigma_c=0.25$ S/m, $\varepsilon_c=60$; $\sigma_n=0.5$ S/m, $\varepsilon_n=120$

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, \( \sigma_c = 0.25 \text{ S/m}, \varepsilon_c = 60; \sigma_n = 0.5 \text{ S/m}, \varepsilon_n = 120 \)
- Navier-Stokes equations in the approximation of the creeping flow, \( \eta_c = 0.008 \text{ Pa\cdot s} \)
- 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, \( D_m = 10^{-12} \text{ m}^2/\text{s} \)
- Messenger proteins introduced as a 0.01 s pulse at the left lower corner of the cell
- Interaction with cytoskeleton binding sites:
  \[ R_2 = -k_mC_mC_2 + k_{rm}C_5 - k_eC_eC_2 + k_{re}C_3 \]

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


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.

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: \( k_1 = 1 \text{ m}^3/(\text{mol} \cdot \text{s}) \), \( kr_1 = 0.001 \text{ s}^{-1} \)

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

\[
R_e = -k_1 C_e C_2 + kr_1 C_3 = R_2 = -R_3
\]
Transport of messenger proteins. Binding sites in abundance

**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: $k_m = k_e = 1 \text{ m}^3/\text{mol} \cdot \text{s}$. Diffusion coefficient: $10^{-12} \text{m}^2/\text{s}$, charge: single negative. Initial conditions: $C_e = 0.001$, $C_m = 0$, $C_2 = 1$, $C_3 = 1$, $C_5 = 0$.

A - electroosmosis present: $\zeta = -0.05 \text{ V}$; 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.

$C_e=0.001 \text{mM}, C_2=1 \text{mM}, C_3=1 \text{mM}, C_5=0, C_m=0.001 \cdot \text{rect}(0.01) \text{ mM. } \zeta=-0.05 \text{ V.}$

$D_e=D_m=10^{-12} \text{m}^2/\text{s}, z_e=z_m=-1. \ k_e=1 \text{ m}^3/(\text{mol}\cdot\text{s})$ and $k_{re}=0.001 \text{ s}^{-1}, k_{rm}=0.01 \text{ s}^{-1}.$
Amount of messenger that reached nucleus versus time. Competition for binding sites. Slow binding

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

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

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