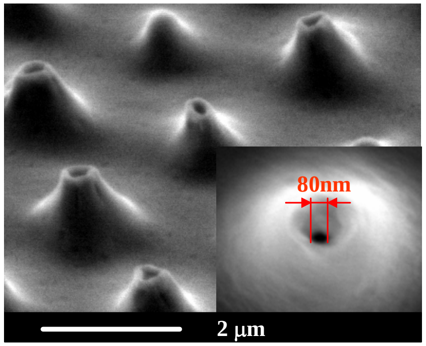
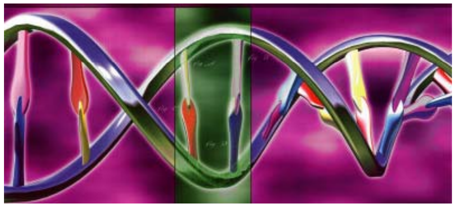
Nanopore Membranes: Mathematical Models for Ionic and Biomolecular Transport





by

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Workshop on Continuum Modeling of Biomolecules
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Cleveland Clinic

Outline

- Background and motivation (applications)
- When molecular dynamics: molecular simulation of electroosmotic flow
- Membrane sieving in a renal assist device (RAD)
- DNA transport for analysis
- Summary

Applications

- Engineering Microfluidics devices:
  - Microelectro mechanical systems (MEMS)
  - Micro-aerial vehicles
  - Micro propulsion: pumps and compressors
  - Microjets: inkjet printing
  - Control systems: sensors and actuators
  - Fuel cells
  - Desalination, water purification
- Biomedical/chemical Devices:
  - Drug delivery and control
  - DNA manipulation and transport
  - Separations/filtration
  - Lab-on-a-chip applications: rapid molecular analysis (molecular dimensions)
  - Biochemical sensing

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Liquid nanoflows: what happens at nanoscale?

- **Adsorption of species on wall: induced roughness**
- **Hydrophobic vs. hydrophilic surface**
- **Electrokinetic effects**
- **Intrinsic surface roughness**
- **Viscosity change? Is viscosity at the wall different at bulk.**
- **Equivalent *Kn* small- flow is continuum to nanoscale!**

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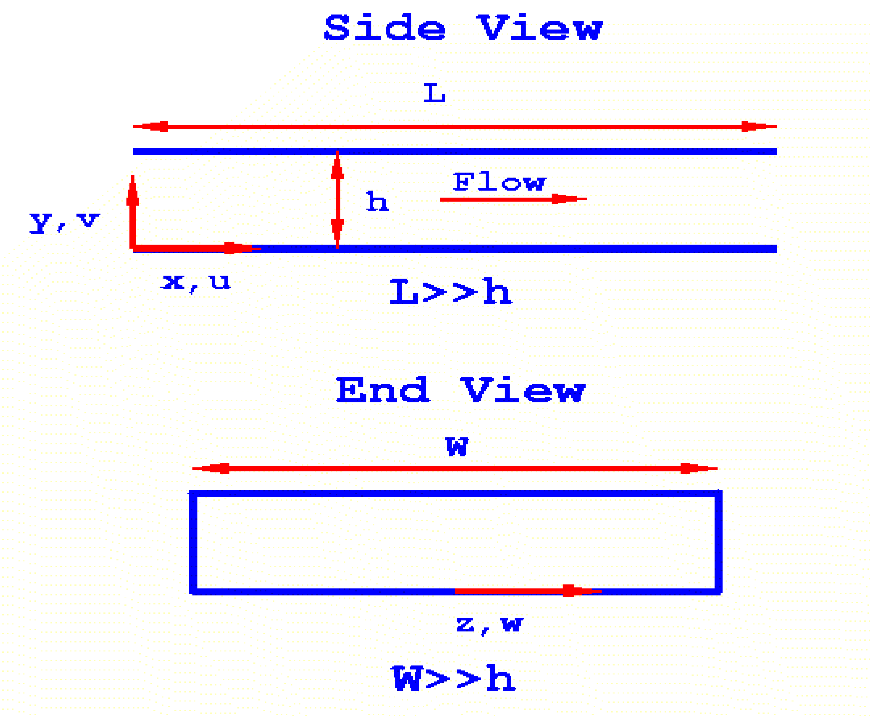
$$Kn_L = \frac{a}{h}$$

a=Molecular Scale

Role of surface properties at nanoscale vs. microscale



Volume=*hWL*

Surface area=*2WL*

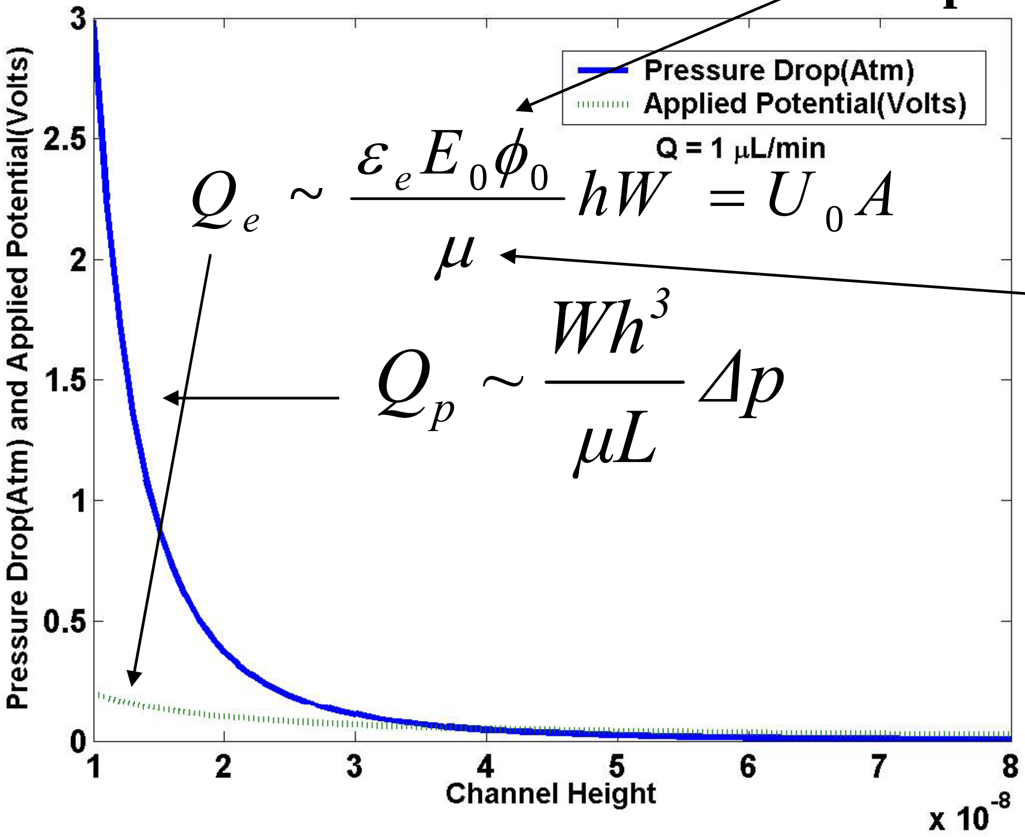
$$\frac{S}{V} = \frac{2}{h} = 2\times10^{8}\, m^{-1}$$

for h=10 nm

Why electrokinetics? Can’t transport liquids by pressure at nanoscale

Q=1μL/min

Permittivity, E-field, potential



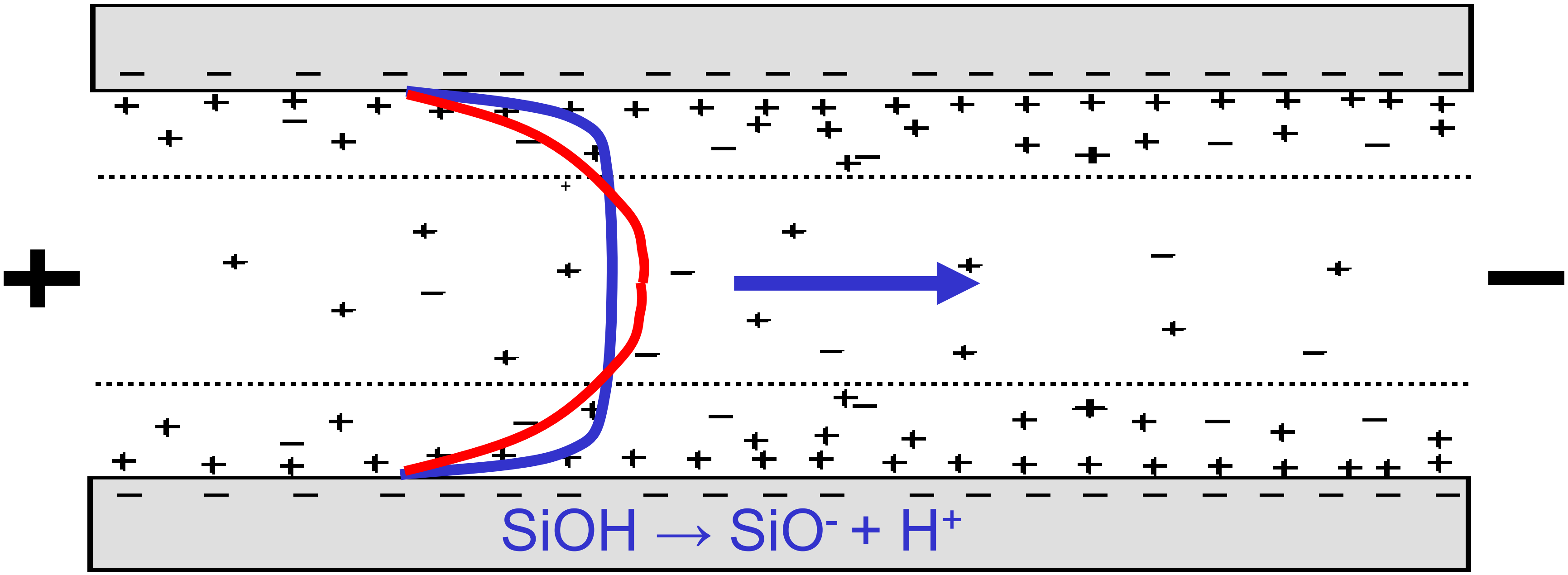
$$Q_e \sim \frac{\varepsilon_e E_0 \phi_0}{\mu} hW = U_0 A$$

viscosity

$$Q_p \sim \frac{Wh^3}{\mu L} \Delta p$$

$$\lambda = \frac{1}{F}\sqrt{\frac{\varepsilon_r \varepsilon_0 RT}{I}}$$

Electroosmosis



SiOH → $SiO^- + H^+$

Insertion of electrodes upstream and downstream will induce bulk fluid motion.

Conlisk, *Introduction to Micro and Nanofluidics, with Application to The Biological and Chemical Sciences*, Cambridge, 2010; Conlisk *et al* *Analytical Chemistry*, Vol . 74, issue 9, 2002; Conlisk, *Electrophoresis, 26, 2005;* Sadr, *et al, J. Fluid Mech,* Vol . 506, 2004 and *App. Phy. Let*. Vol. 89, 2006; Ramirez and Conlisk, BMMD, Vol. 8, no. 4, 2006, Chen, *BMMD*, Vol. 10, no. 2, 2007

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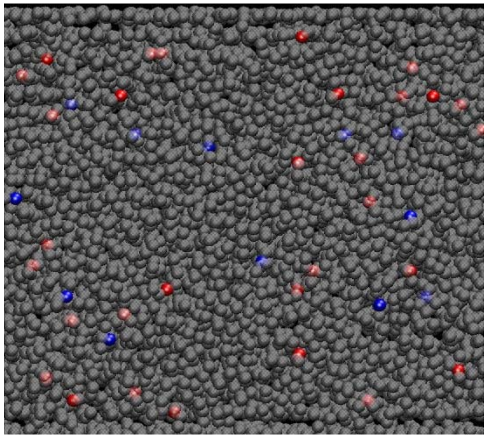
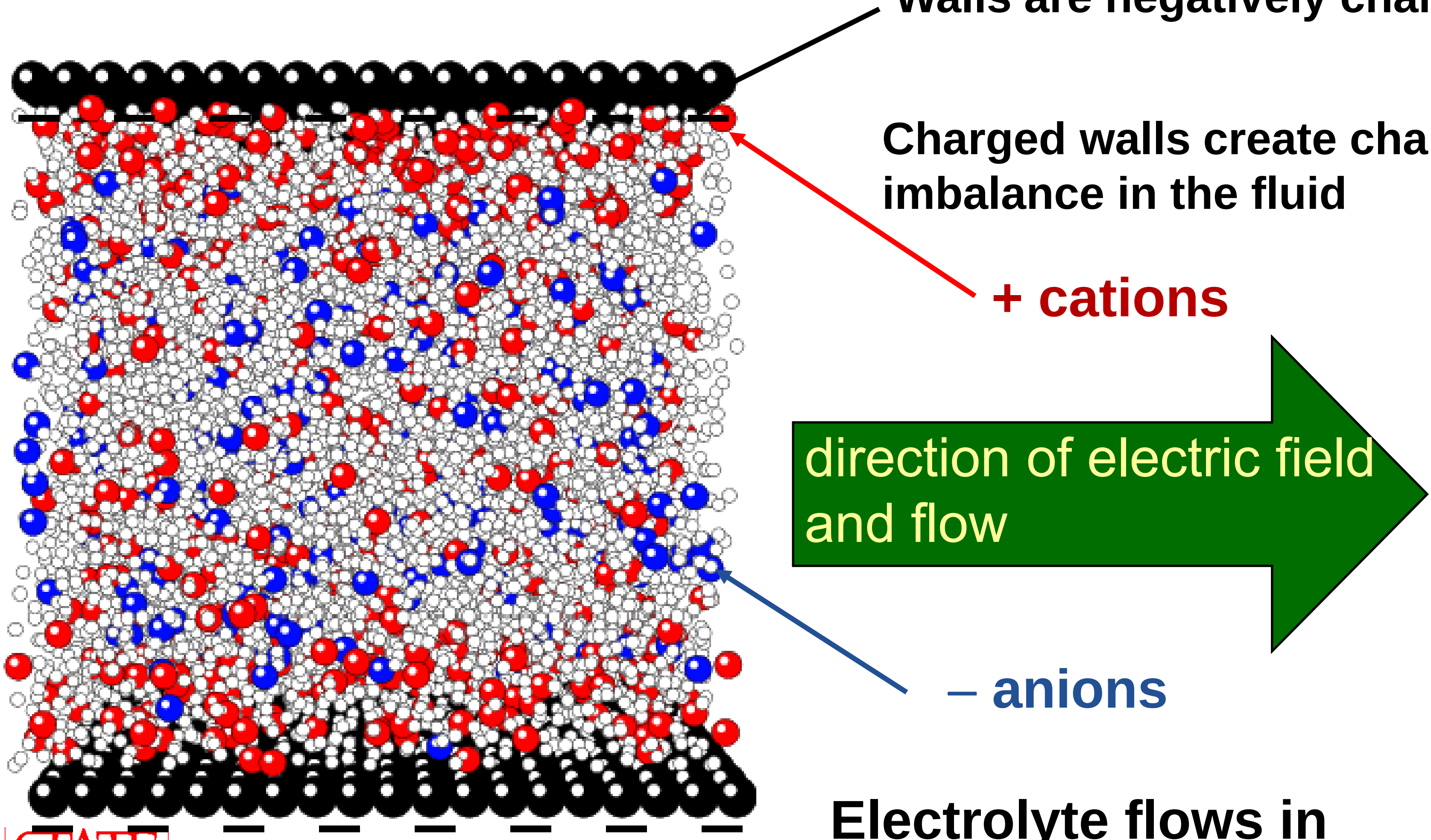
Molecular dynamics simulation



- Ions are charged Lennard-Jones particles,
- Uniform negative wall charge,
- Lennard-Jones solvent, with large ion-solvent attractions mimics solvation in a polar solvent.
- 31 cations (.22*M*), 12 anions (.085*M*), 7757 solvent (ρ^*=0.8)
- **Objective: to construct system that is appropriate for comparison with existing continuum theory - Does continuum theory apply at the nanometer scale?**
- **Verified for Poiseuille Flow (pressure driven)**

Zhu, Singer, Zheng and Conlisk, Phys. Rev. E(2005)

Electroosmotic flow



Walls are negatively charged.

Charged walls create charge imbalance in the fluid

+ cations

direction of electric field and flow

– anions

Electrolyte flows in response to electric field

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Relative ionic interaction strength

A key parameter is the ratio of the Coulomb interaction strength between the ions to the Lennard-Jones well depth.

$$\zeta = \frac{e^2}{\varepsilon_e \varepsilon \sigma}$$

e = electron charge

ε_r = dielectric constant

σ = LJ particle diameter

ε = LJ well depth

- ζ =5 and ζ = 1, which brackets expected range for water.
- When ζ is large, strong ion-solvent interactions are required to stabilize ions in solution.

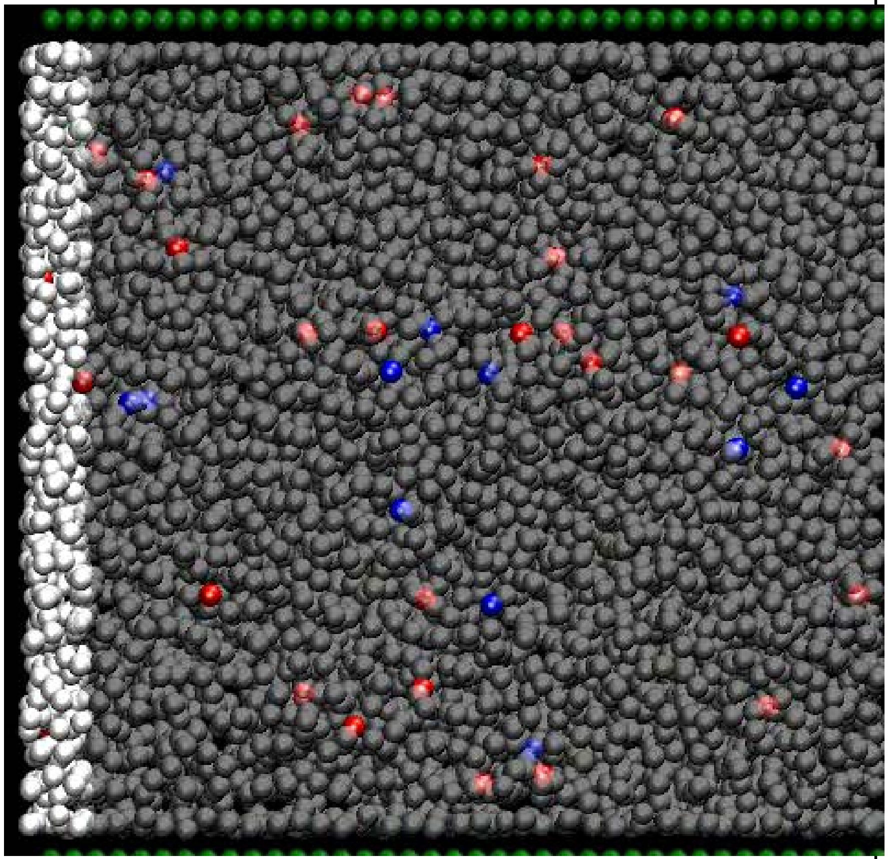
🔴 cation

🔵 anion

⚪ solvent

MD simulation of electroosmotic flow

- The fluid is layered near the walls.
- Anions are in the center.
- Cations move most rapidly to the right, faster than the solvent.
- Anions net motion is to the right, but slower than cations or solvent.
- Occasionally a cation and ion will form a temporary bound pair.



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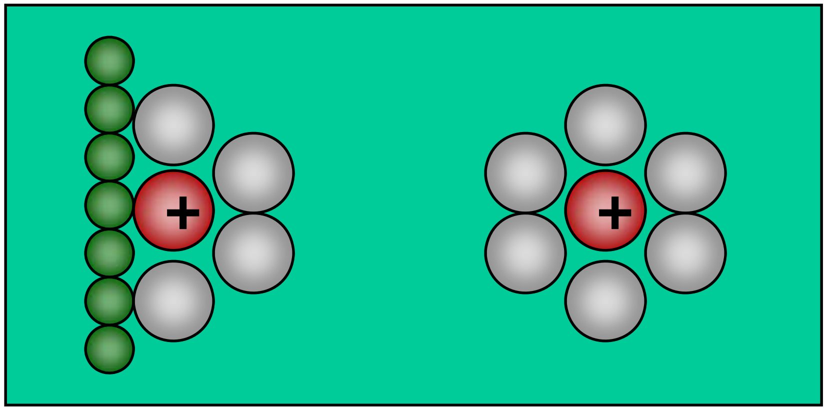
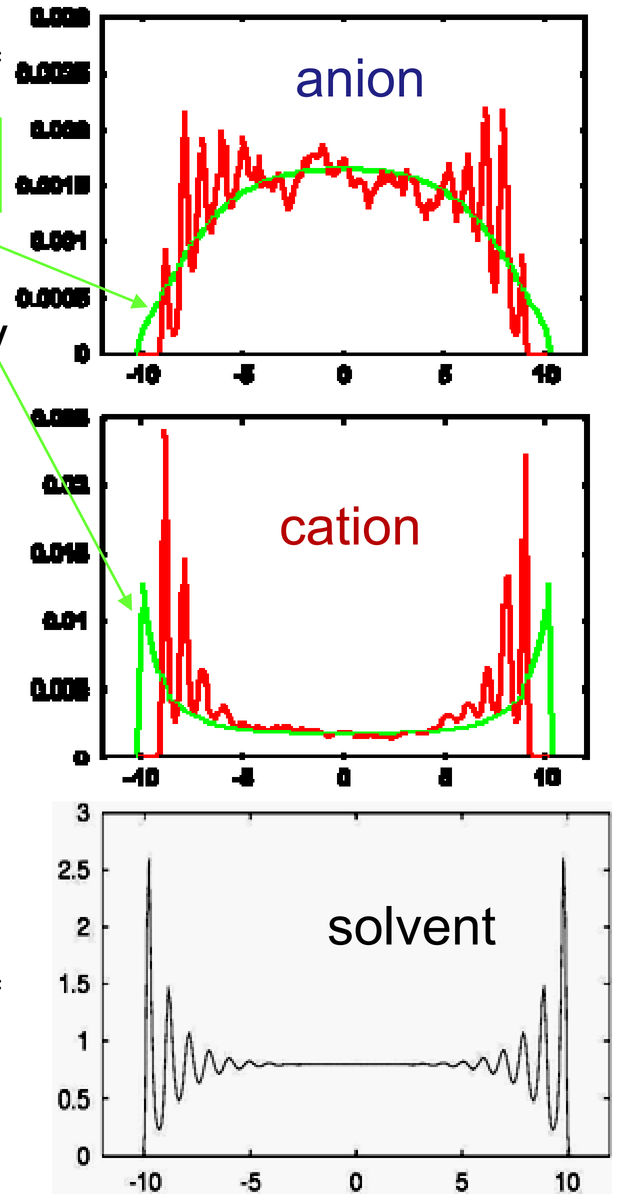
Ion density profiles: $\zeta = 5$

Poisson-Boltzmann theory

- For strong ion-solvent interactions, ions do not enter the layer closest to the walls because they would lose some solvent stabilization.



- Failure to describe layering and exclusion of ions from the wall layer are the main shortcomings of Poisson-Boltzmann theory.



20 molecular diameters

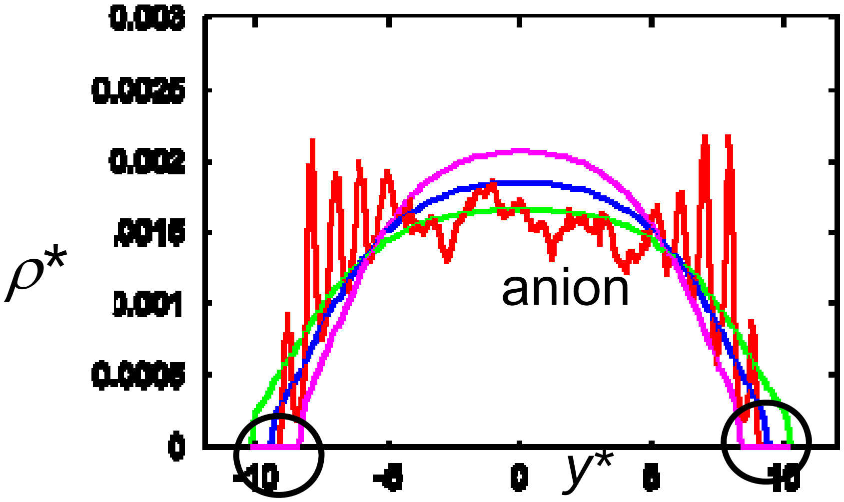
Modified Poisson-Boltzmann theory

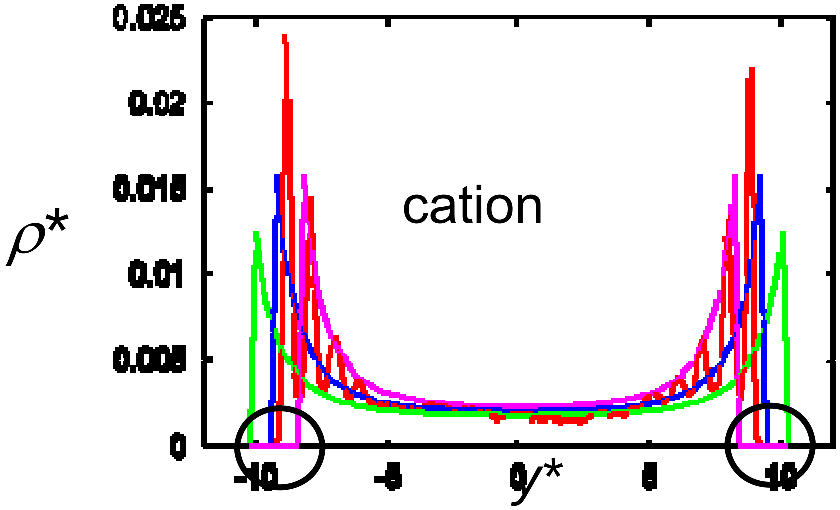
To qualitatively treat the effect of the ion density on the velocity profile, we consider a modified PB theory in which ions are excluded from the walls by a distance Δ*y. Analytically solve NS.**

Δ*y** = 0
(unmodified PB)

Δ*y** = 1

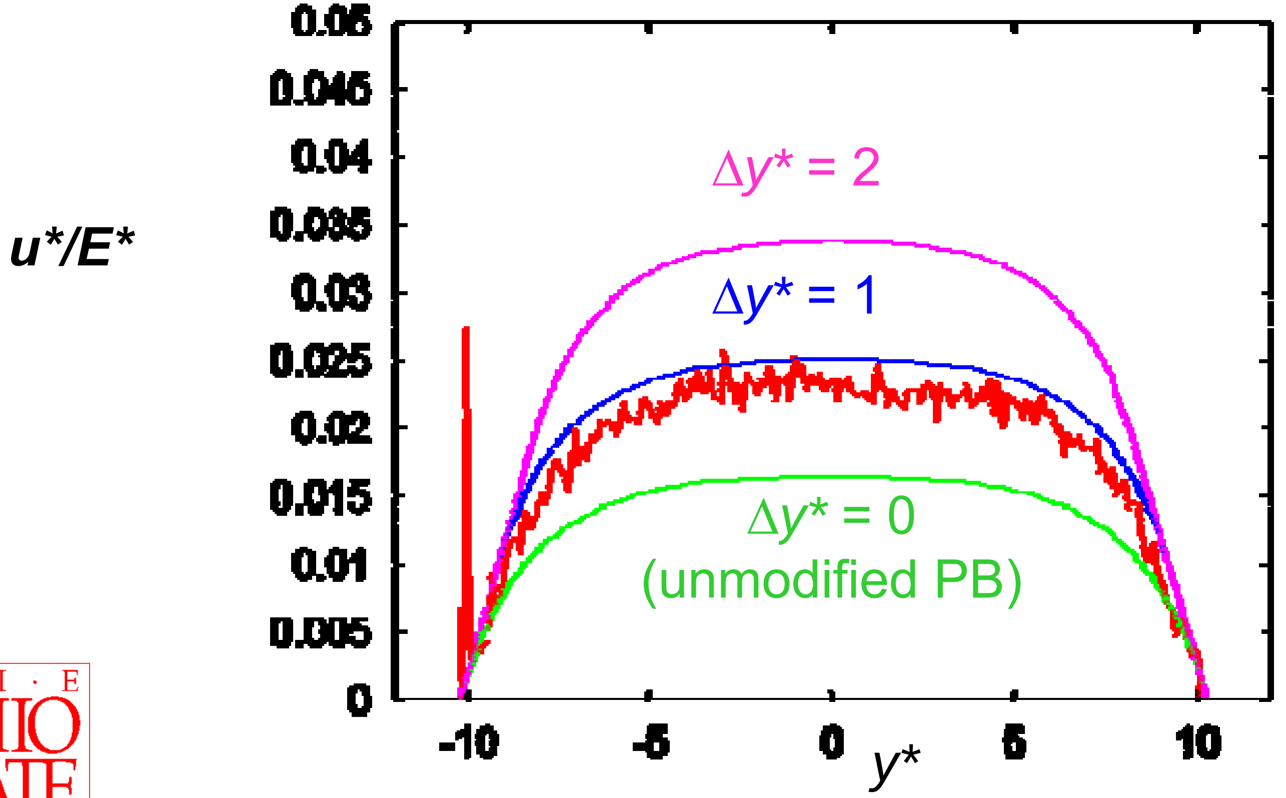
Δ*y** = 2





Velocity (mobility) profile $\zeta=5$

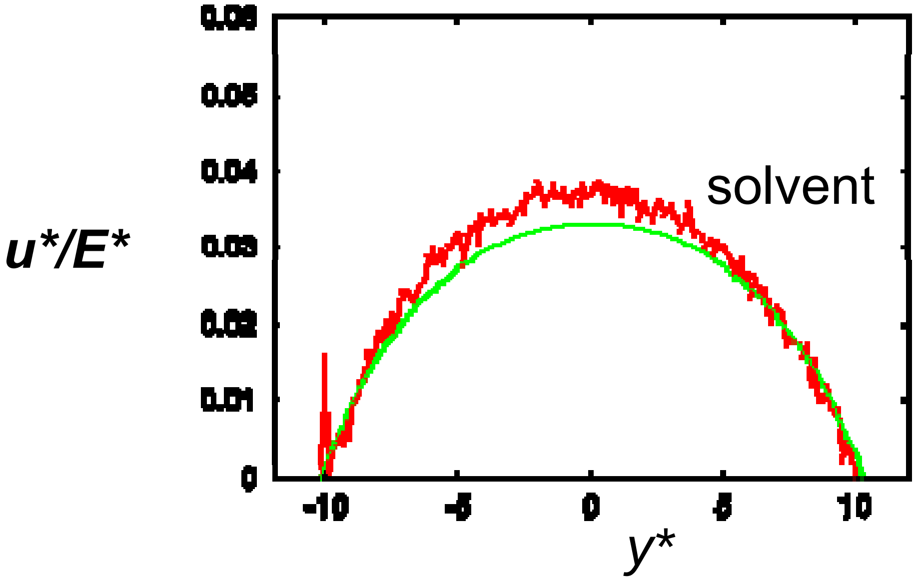
When $\Delta y^*=1$, velocity profile calculated from modified PB theory best agrees with simulation



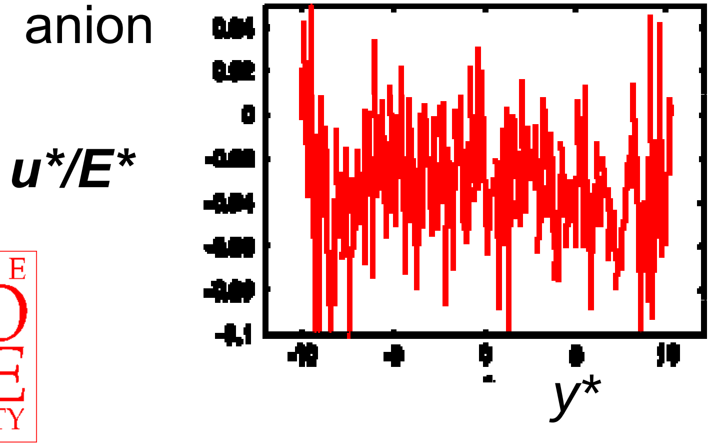
Move lots of excess charge from the wall!

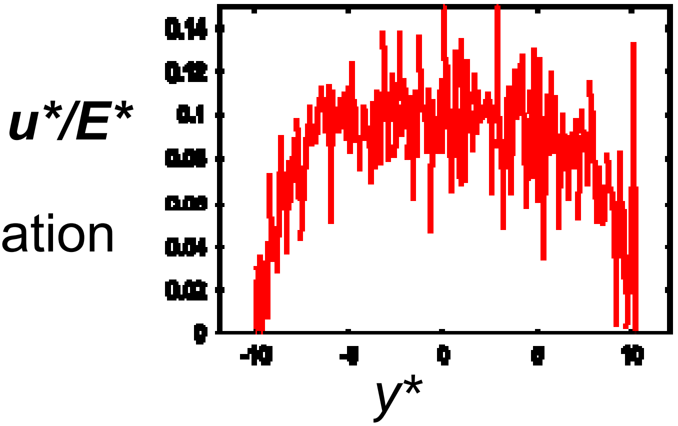
Travis and Giddens (2000): breakdown for ~5 mol diameters

Velocity (mobility) profile at ζ=1



Because ion exclusion is very small when z = 1, solvent velocity is only slightly faster than continuum theory prediction.





cation

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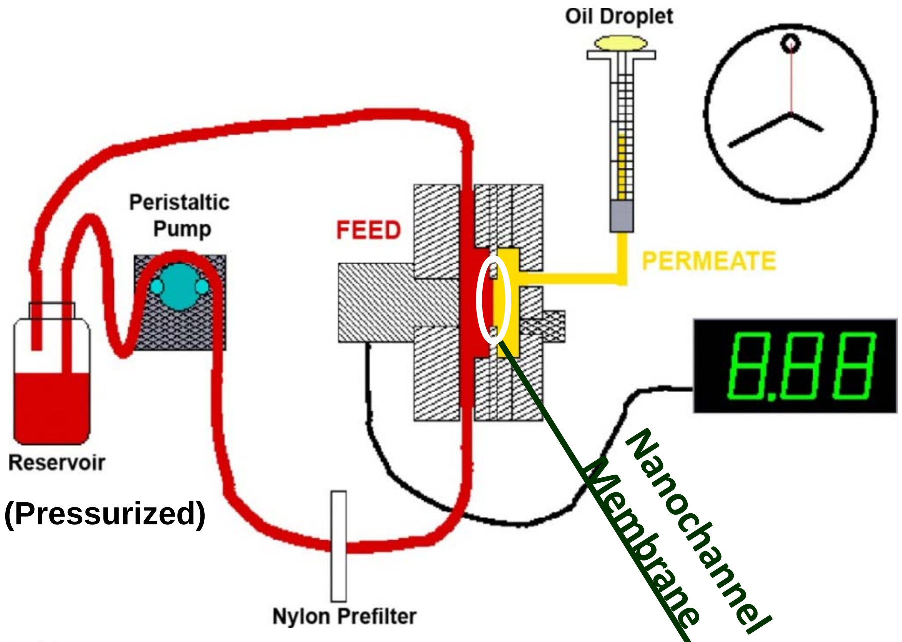
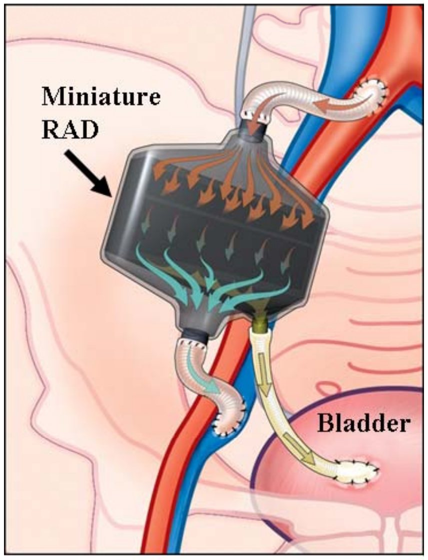
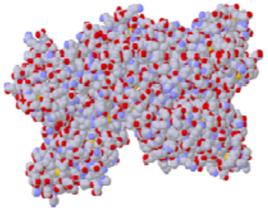
Hemofiltration using synthetic nanochannel membrane for a renal assist device (RAD)



Implantable artificial kidney



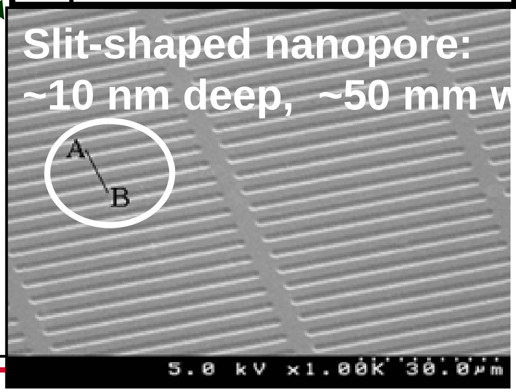
Hindered transport of large (>10,000 Da) solutes such as serum albumin in synthetic nanochannel membrane for hemofiltration by a Renal Assist Device



SEM of membrane

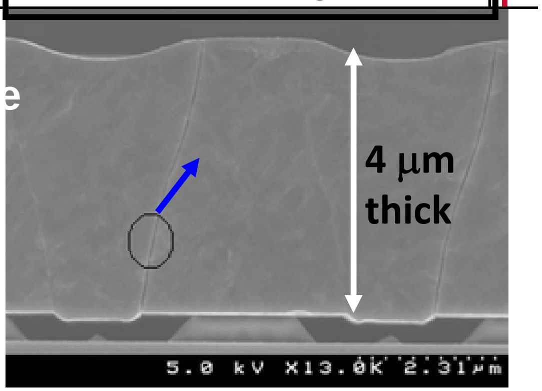
Fissell *et al., Am. J. of Physiol.-Renal Physiol.*, 293,4,F1209,2007

Upstream surface



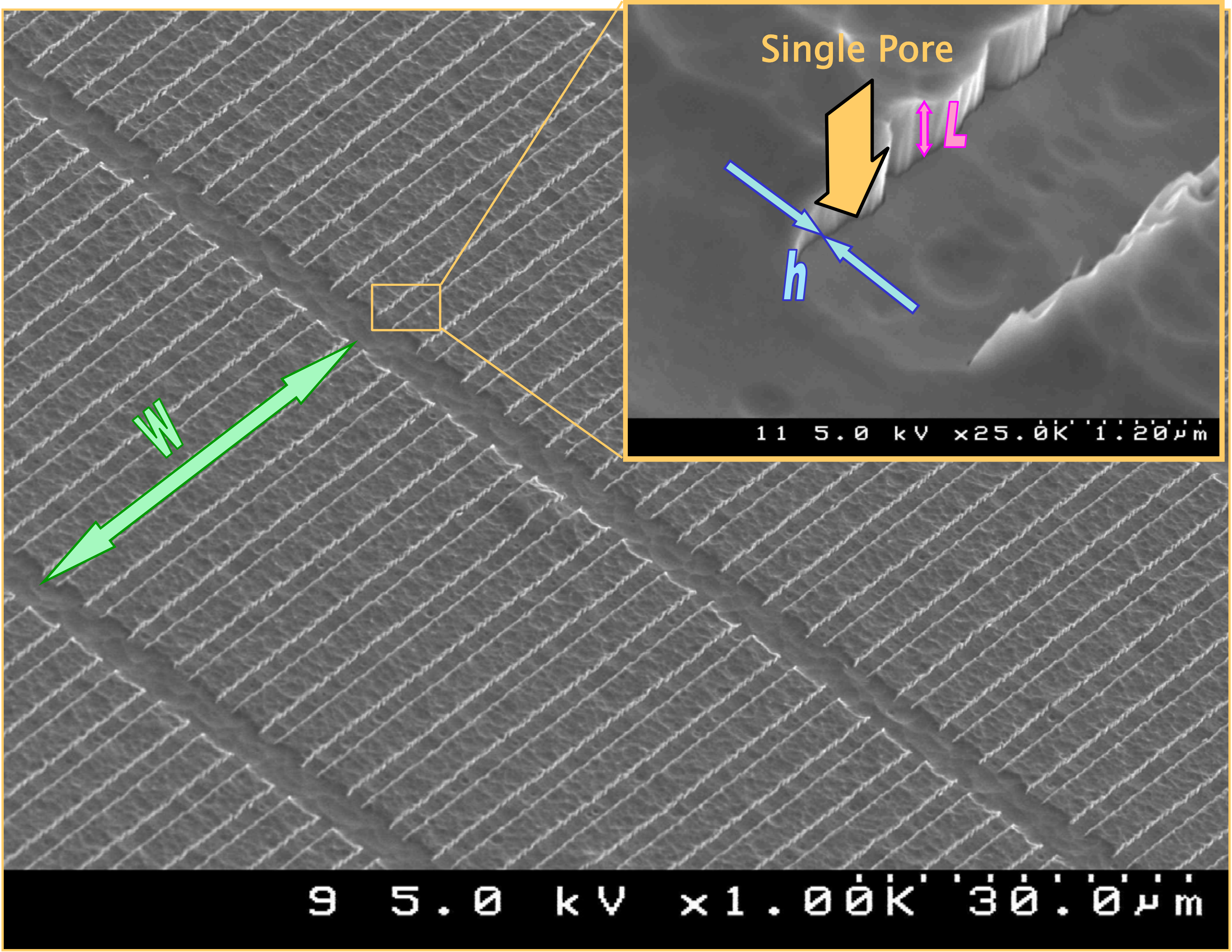
Slit-shaped nanopore: ~10 nm deep, ~50 mm w e

Section through AB



4 µm thick

Miniaturized Hemofilter



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Nanochannel membranes for hemofiltration: must retain albumin

Feed composition in a typical hemofiltration experiment:

NaCl (mM)	154
BSA (mM)	0.6

(~physiological)

M=moles/liter

$S<10^{-4}$ desired for albumin

but fast passage of water, small ions (Na+, Cl^-), urea etc. should be insured

Properties of bovine serum albumin (BSA)

Molecular Weight (Da)	67,000
Hydrodynamic diameter (nm)	7.12
Charge Number (“valence”)	-20
Diffusivity of Albumin D (m^2/s)	6.1×10^{-11}

Da=gm/mole

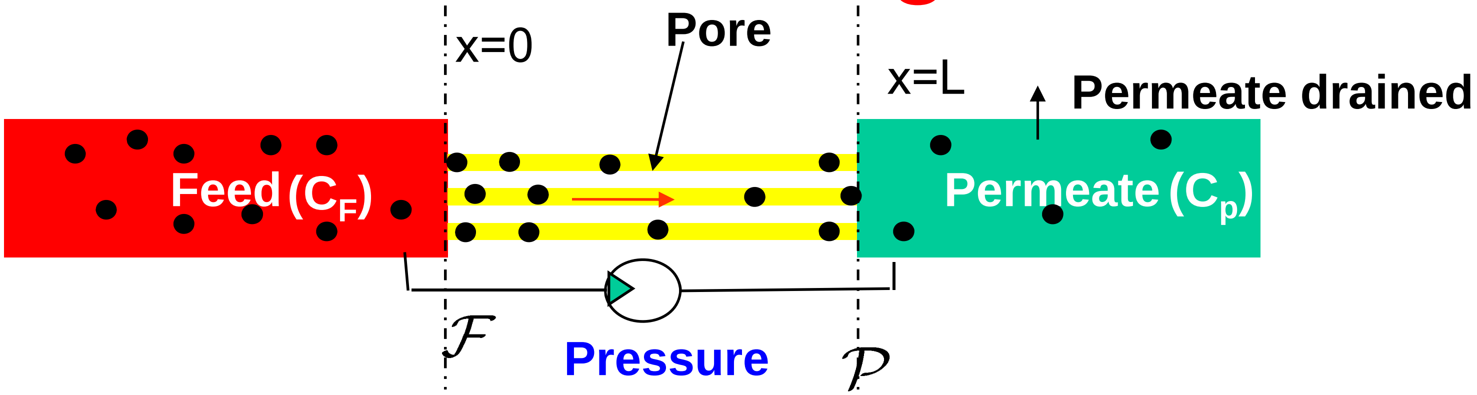
Transmembrane pressure : »1 -2 psi (close to physiological; Poiseuille flow)

Pore size»10 nm Pores per mm^2»10,000

Concentration of BSA and other large solutes in permeate needs to be predicted

$$\text{Sieving Coefficient (S)} = \frac{\text{Solute concentration in permeate}}{\text{Solute concentration in feed}}$$

Interactions between solute, pore, solutions and driving forces

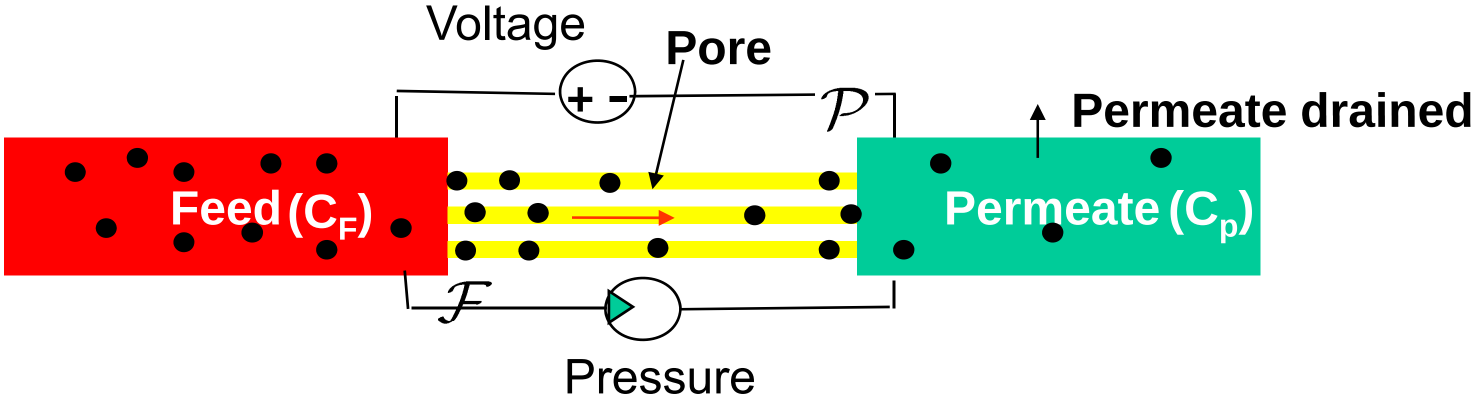


Partition coefficient=Ratio of equilibrium concentration inside pore to that in adjacent free solutions.

Feed side partitioning→ $\mathcal{F}$

Permeate-side partitioning→ $\mathcal{P}$

Pressure + applied/Induced electric fields



Datta, *et al, ABME,* Vol. 37, no. 4, 2009

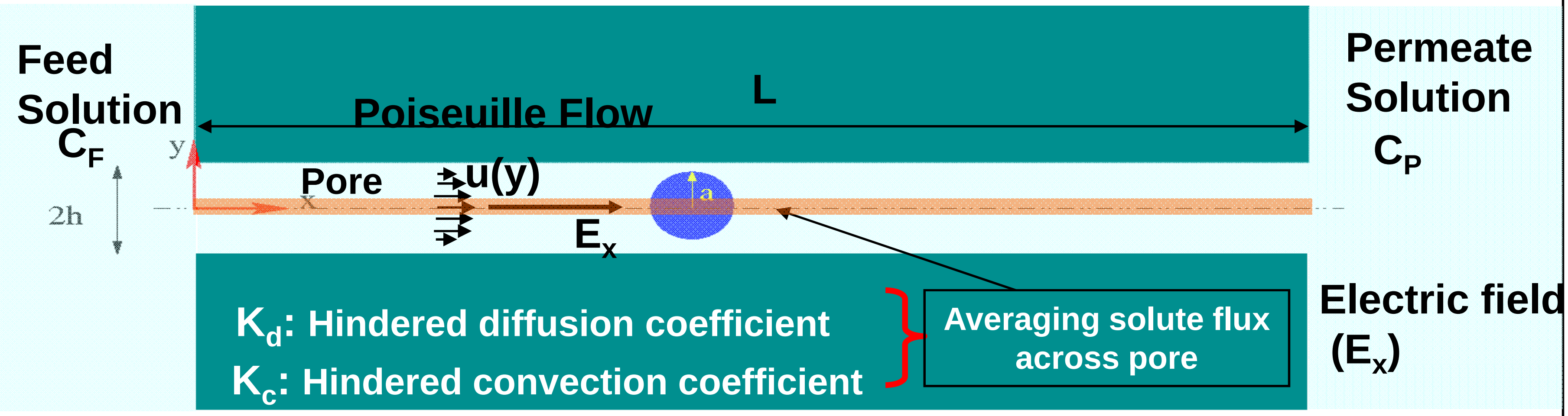
Physical processes in transport through small pores

Objective: calculate S

Large particles in small pores are characterized by :

- **Unfavorable entrance and favorable exit due to large molecules fitting tightly into small pores (steric partitioning)**
- **If charged, favorable/unfavorable entry due to attraction/repulsion between wall and solute charges mediated by electrical double layers (electrostatic partitioning)**
- **Slower diffusion across concentration gradients in the pore than in the bulk (hindered diffusion)**
- **Velocity lagging fluid velocity at its centroid (hindered convection)**
- **If charged, slower migration under electric field than in the bulk (hindered electrophoretic motion)**

Definition of hindered transport coefficients



K_d: Hindered diffusion coefficient

K_c: Hindered convection coefficient

Averaging solute flux across pore

N→ solute flux

bar→ average over *y*

$$\bar{N} = -K_d D \left(\frac{d\bar{C}}{dx} + \frac{zFE_x}{RT}\bar{C} \right) + K_c \bar{u} \bar{C}$$

K_d → area average of drag coefficient →hindered diffusion

K_c→ area average of lag coefficient → hindered convection

$$K_c = \frac{1 - 3.02\chi^2 + 5.776\chi^3 - 12.3675\chi^4 + 18.9775\chi^5 - 15.2185\chi^6 + 4.8525\chi^7}{1-\chi}$$

$$K_d = \frac{1 + \frac{9}{16}\chi log(\chi) - 1.19358\chi + 0.4285\chi^3 - 0.3192\chi^4 + 0.08428\chi^5}{1-\chi}$$

Dechadilok & Deen, 2006→From curve fit to analysis/computations of translational/rotational equilibrium of a moving/stationary sphere inside slit pore by Bungay et al. (1973), Weinbaum (1981), Dagan et al.(1982).

Solute distribution and sieving coefficient

→ Pore inlet: Feed concentration is known $\mathcal{F}C_F = \overline{C(0)}$

→ Pore Outlet: Solute is drained out convectively $\bar{N} = \bar{u}C_P$

→ Within pore $\frac{d\bar{N}}{dx} = 0$

$$Pe_H = \frac{K_c \bar{u} L}{K_d D}$$

Dimensionless solute distribution in the pore

$$\bar{C}(x) = C_F \mathcal{F} \frac{1 + [(1+s)\mathcal{P}K_c - 1]\exp[-\enclose{circle}{Pe_H}\bar{u}(1+s)(1-x)]}{1 + [(1+s)\mathcal{P}K_c - 1]\exp[-\enclose{circle}{Pe_H}\bar{u}(1+s)]}$$

$$S = \frac{C_P}{C_F} = \frac{\bar{C}(1)}{\mathcal{P}C_F} << 1 \qquad S = \frac{(1+s)\mathcal{F}K_c}{1 + [(1+s)\mathcal{P}K_c - 1]\exp[-\enclose{circle}{Pe_H}\bar{u}(1+s)]}$$

Datta, *et al, ABME,* Vol. 37, no. 4, 2009

$$s = \frac{zE_x FL}{Pe_H RT}$$

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Effect of filtration rate: Pe_H ↑ S↓
→ asymptotic value

Effect of feed-pore and pore-permeate partitioning (effect of Pe)

$$Pe_H = \frac{K_c \bar{u} L}{K_d D}$$

Partition coefficient=Ratio of equilibrium concentration inside pore to that in adjacent free solutions.

Feed side partitioning→ $\mathcal{F}$

Permeate-side partitioning→ $\mathcal{P}$

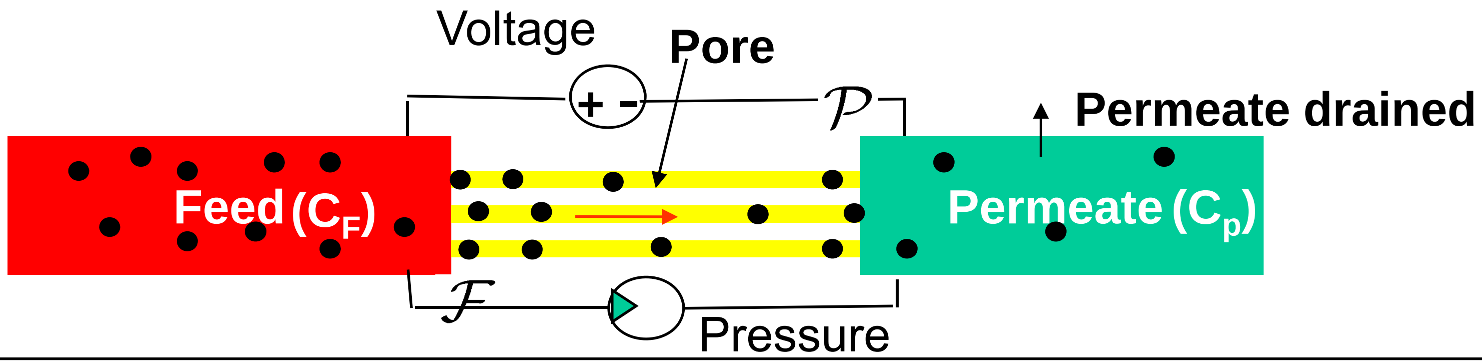
$$S = \frac{C_P}{C_F} = \frac{\bar{C}(1)}{\mathcal{P} C_F}$$

If filtration is fast (large *Pe*$_H$): $S_\infty = \mathcal{F} K_c (1 + s) \text{ for } Pe_H \gg 1$

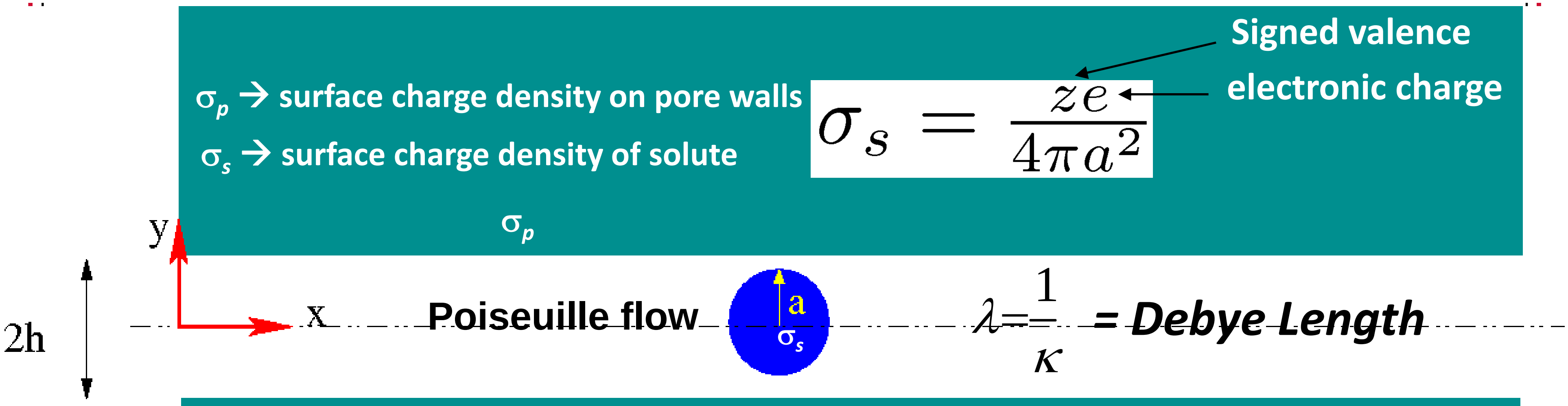
Sieving not affected by exit conditions; co-flow electric field can reduce sieving of negatively charged solutes.

If filtration is slow (low *Pe*$_H$): $S_0 = \frac{\mathcal{F}}{\mathcal{P}} \text{ for } Pe_H \ll 1$

$$s = \frac{z E_x F L}{Pe_H R T}$$



Charged pores: sieving coefficient of charged biomolecules



σ_p → surface charge density on pore walls

σ_s → surface charge density of solute

$$\sigma_s = \frac{ze}{4\pi a^2}$$

Poiseuille flow

$\lambda = \frac{1}{\kappa}$ ***= Debye Length***

$$\frac{E_{int}}{RT} = \frac{\pi a I}{\kappa^2}\left[(\zeta_p F/RT)^2 + (\zeta_s F/RT)^2\right] \times \left(\frac{2\zeta_p\zeta_s}{\zeta_p^2+\zeta_s^2}\log\left(\frac{1+\exp(-\kappa(h-a))}{1-\exp(-\kappa(h-a))}\right) - \log\left[1-\exp(-2\kappa(h-a))\right]\right)$$

$$\zeta_p = \epsilon_e \kappa \sigma_p$$

$$\zeta_s = \frac{\epsilon_e \sigma_s a}{1+\kappa a}$$

$$S = \mathcal{F} K_c \exp\left(-\frac{E_{Int}}{RT}\right)$$

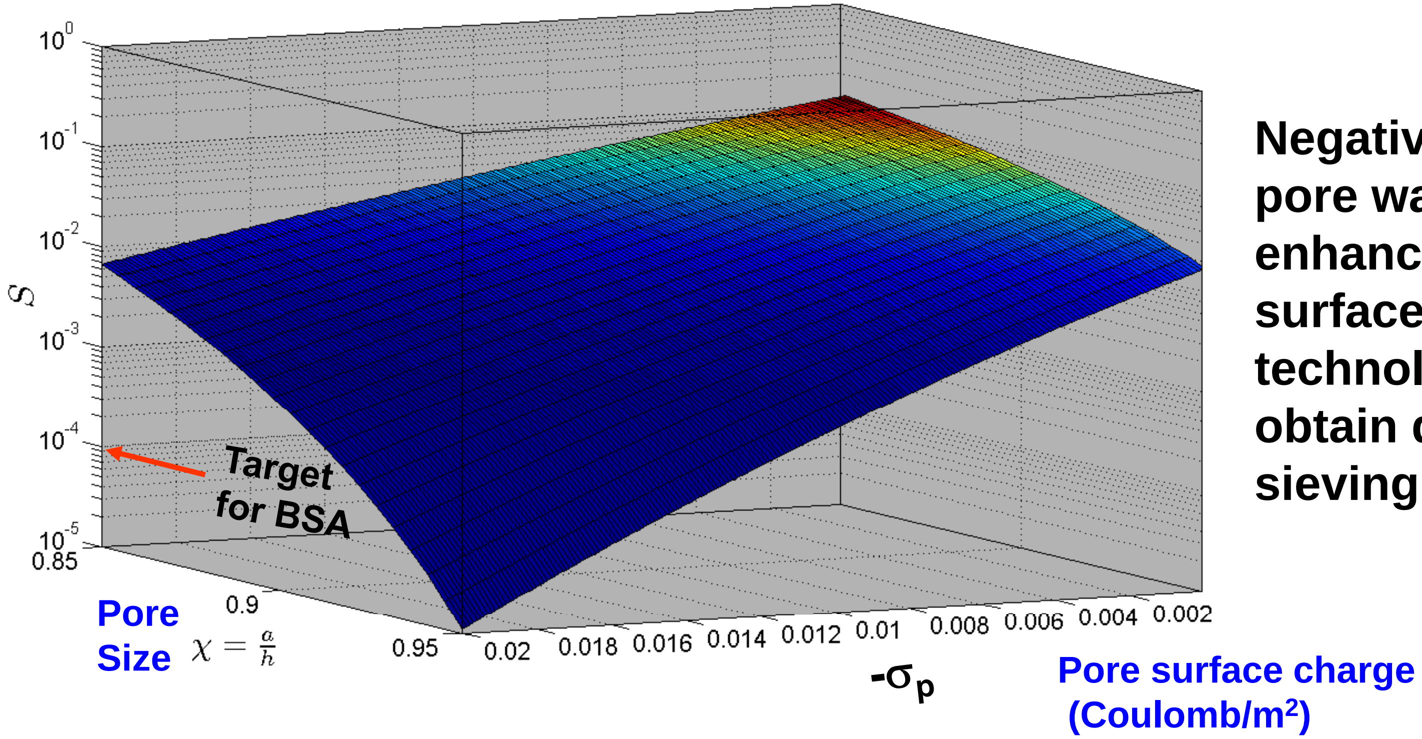
Derjaguin approximation

Conlisk *et al.*, ABME 37(4),722, 2009

E = change in electrostatic potential energy to bring particle into pore (DH). Integrate potential across gap.

Hogg *et al* (1966), Elimelech (1998)

Electrostatic interaction: effect of surface charge density and pore size

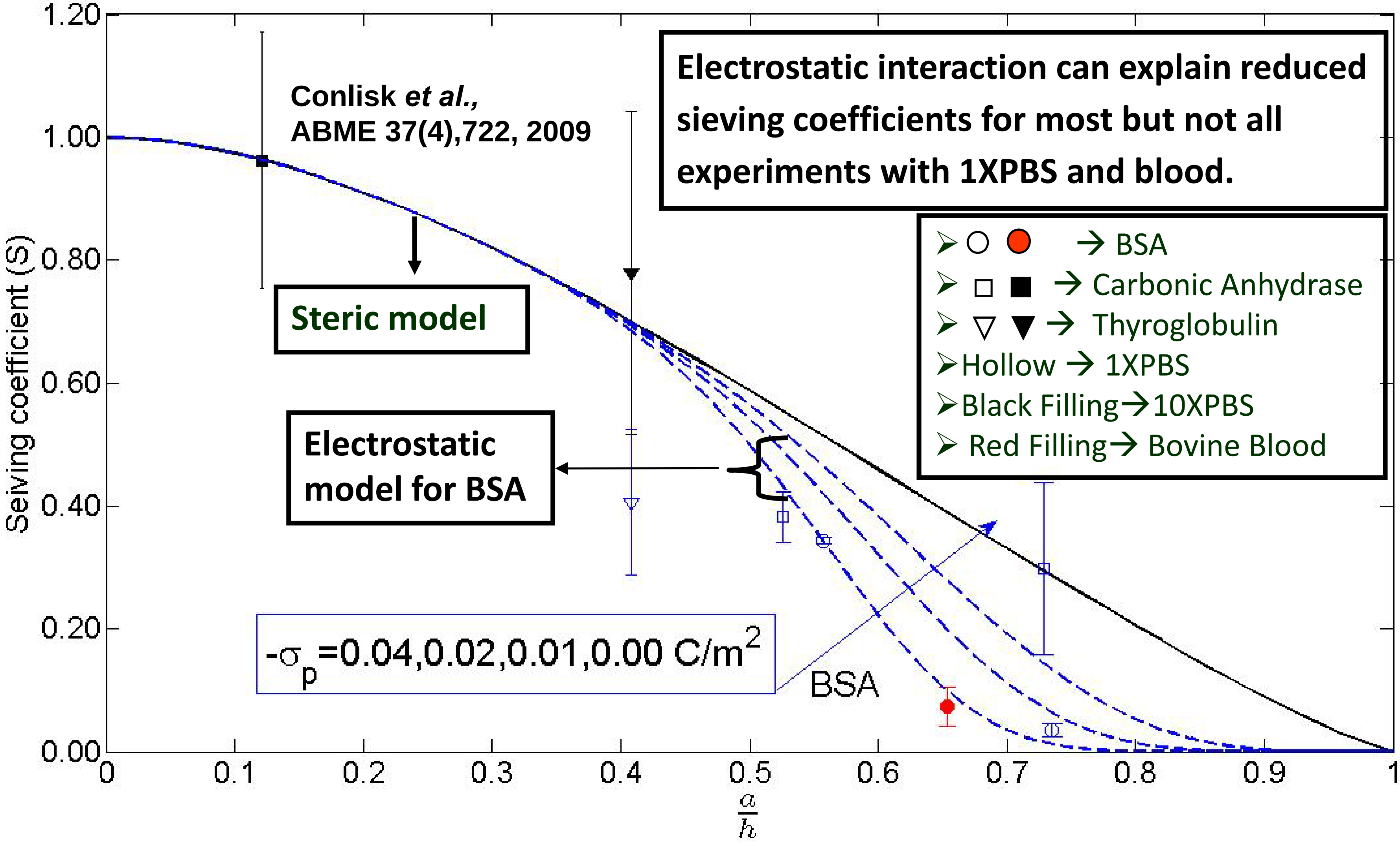


Negative charge on pore walls can be enhanced through surface modification technologies to obtain desired low sieving coefficients

Charge Number of BSA: -20

$$\chi = \frac{\text{Solute radius (a)}}{\text{Pore half-height (h)}}$$

Ultrafiltration of proteins: comparison with experiments



Conlisk *et al.*, ABME 37(4),722, 2009

Electrostatic interaction can explain reduced sieving coefficients for most but not all experiments with 1XPBS and blood.

- ○ ● → BSA
- □ ■ → Carbonic Anhydrase
- ▽ ▼ → Thyroglobulin
- Hollow → 1XPBS
- Black Filling→10XPBS
- Red Filling→ Bovine Blood

Steric model

Electrostatic model for BSA

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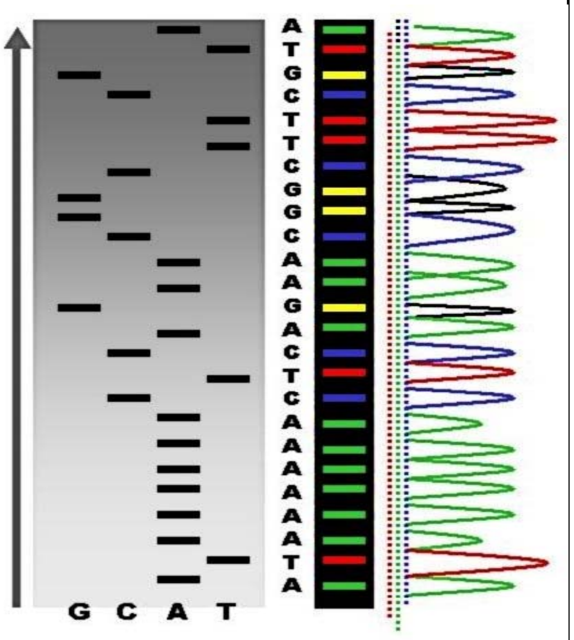
Why nanopore sequencing?

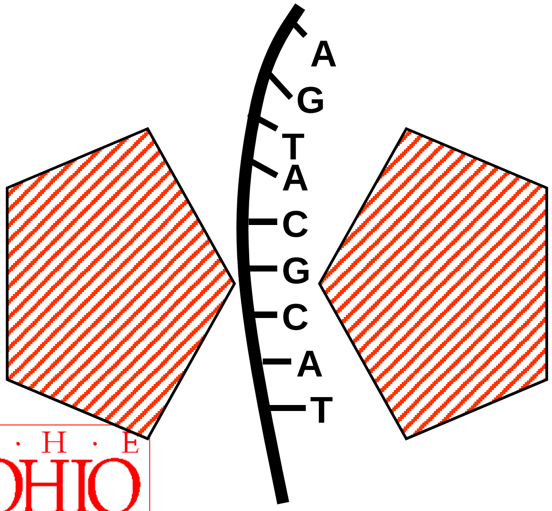
Current technique for sequencing a single human genome cost *$10 million* and several months!

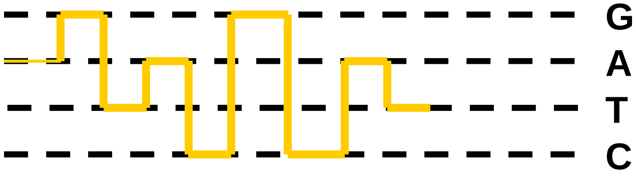
Goal of nanopore sequencing: $1000 and days to sequence a single human genome!

(NIH 2004)

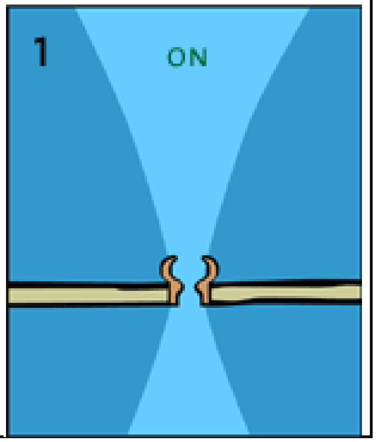


Sequence ladder by radioactive sequencing





Deamer 1996



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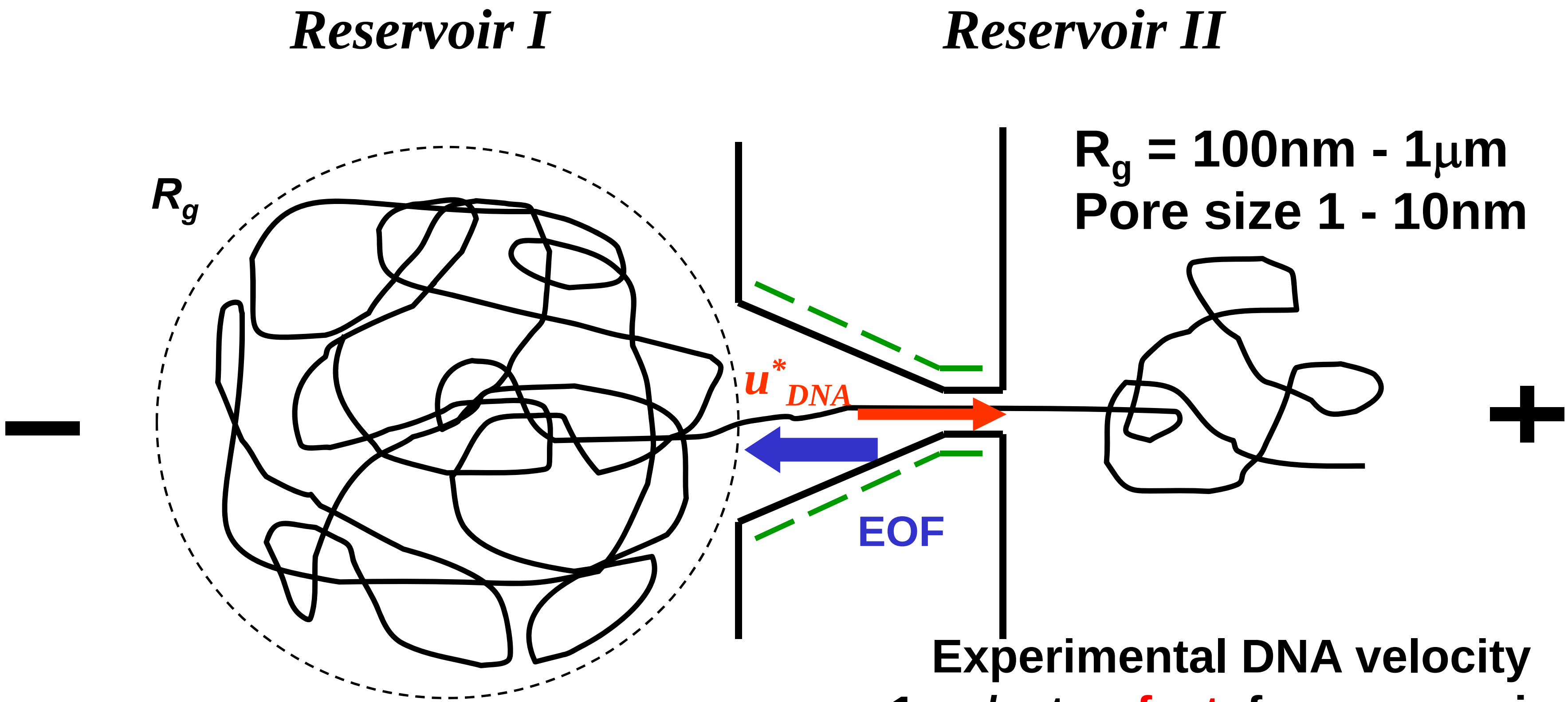
Objective: slow DNA translocation through a nanopore for analysis



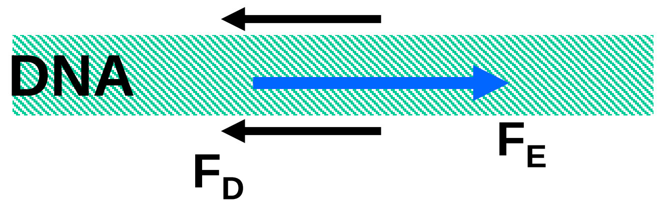
R_g = 100nm - 1μm
Pore size 1 - 10nm

Experimental DNA velocity
~1cm/s, too fast for sequencing!

Modeling DNA translocation

- **Which forces affect DNA transport?**
- **Which parameters slow down DNA?**

Force balance: still equilibrium



$$F_0 = \mu h_0 U_0$$

Force acting on the DNA(dimensionless):

Electric driving force: $$F_E = \int_0^L 2\pi a \sigma_D E_{i,x} dx$$

Viscous drag force: $$F_D = \int_0^L 2\pi a \left.\frac{\partial u}{\partial r}\right|_{r=a} dx$$

Two types of calculations:

- **To predict tethering force** $F_t = F_E - F_D, u_{DNA} = 0$
- **To predict DNA velocity** $\sum F = F_E + F_D = ma = 0$

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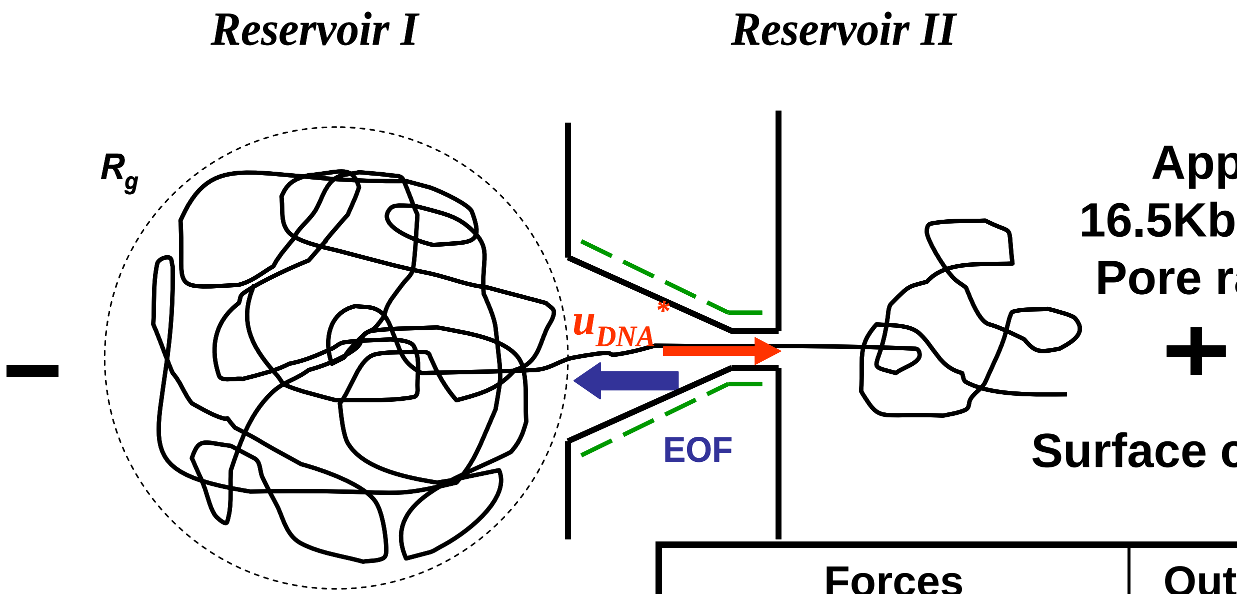
Forces affecting DNA transport



Keyser *et al.* 2006

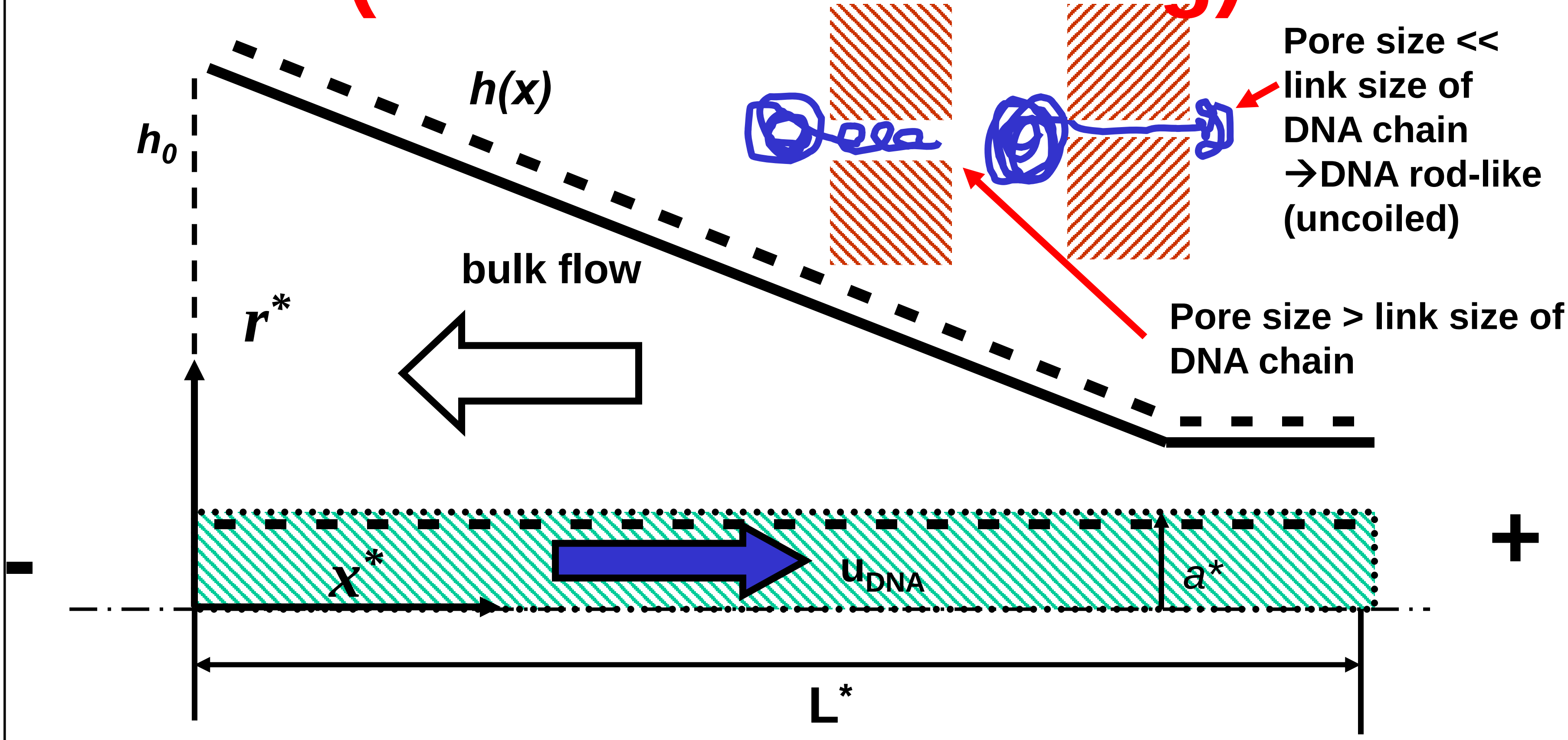
Applied voltage drop:120mV
16.5Kbps double-stranded DNA
Pore radius: 200nm (large end)
5nm (small end)
Pore length 340nm
Surface charge density: 0.06C/m2

Forces	Outside/Inside the nanopore	Magnitude
Electrical driving force	Inside	O(100pN)
Viscous drag on the linear DNA	Inside	O(100pN)
Entropic uncoiling and recoiling forces	Outside	<O(1)pN
Viscous drag on the DNA blob	Outside	O(1~10pN)

Same order

Small!
Considered to be
the main resisting
forces in some
previous work

Geometry: DNA in a nanopore (tethered or moving)



Pore size << link size of DNA chain →DNA rod-like (uncoiled)

Pore size > link size of DNA chain

- DNA modeled as a rigid rod – DNA radius 1nm
- Charged wall and DNA – DNA line charge -2e/bp
- Slowly converging pore – lubrication theory applicable

Dimensionless governing equations

$\boxed{u = \phi - \zeta}$ **Sadr *et al* (2006)**

- **Poisson-Boltzmann equation for electric potential ϕ, ionic species mole fraction X_i;**

$$\boxed{\nabla^2 \phi = -\frac{\beta}{\varepsilon^2}\sum_i z_i X_i}$$

$$X_i = X_i^0 \exp\left(-z_i \phi\right)$$

$$\sum F = 0$$

for a fluid

- **Stokes equation for the flow field**

$$\boxed{\nabla^2 u = -\frac{E_{i,x}\beta}{\varepsilon^2}\sum_i z_i X_i} + \varepsilon_1 \frac{\partial p}{\partial x}$$

$$\nabla^2 v = -\frac{E_{i,y}\beta}{\varepsilon^2}\sum_i z_i X_i + \frac{\partial p}{\partial y}$$

$$\varepsilon_1 \frac{\partial u}{\partial x} + \frac{\partial v}{\partial y} = 0$$

Dimensionless parameters

$\varepsilon = \frac{\lambda}{h_0}; \lambda - \text{Debye length}$

$\varepsilon_1 = \frac{h_0}{L^*}$ (aspect ratio)

$$\beta = \frac{c}{I} = \frac{c_{water} + \sum_i c_i^0}{\sum_i z_i^2 X_i^0}$$

Velocity equation is similar to the potential equation

Scales

$$U_0 = \frac{\varepsilon_e R T E_0}{\mu F}$$

$$\phi_0 = \frac{RT}{F}$$

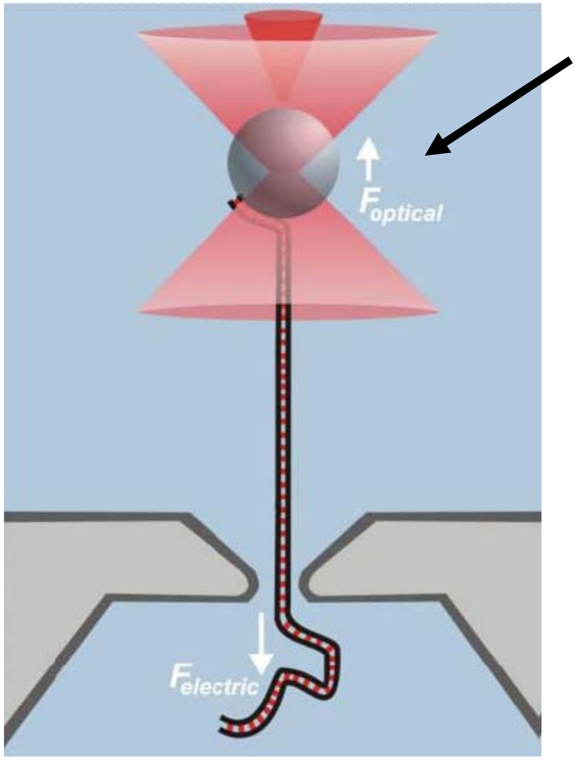
$$P_0 = \frac{\mu U_0}{L^*}$$

Chen and Conlisk
AIAA 2009-1121, 2009

Chen, *BMMD,* Vol. 10, no. 2, 2007

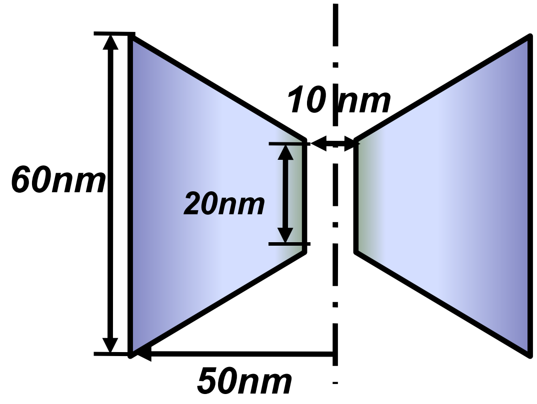
Validation of the model through tethering force evaluation

Keyser *et al.* 2006



DNA immobilized by a tethering force from the optical tweezer.

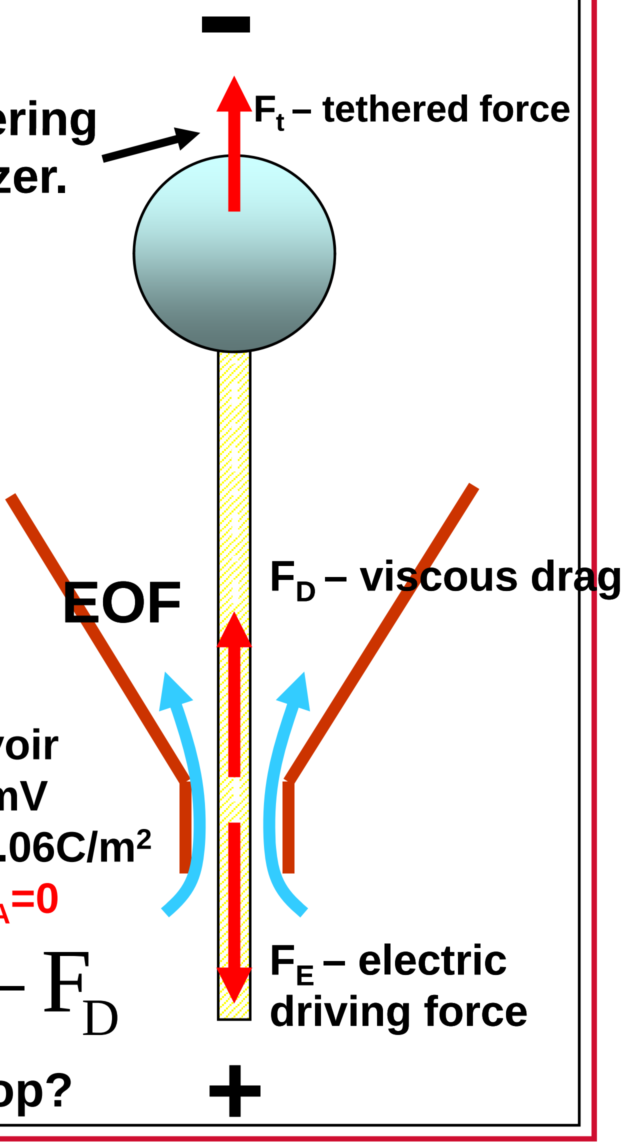
Nanopore geometry



0.1M *KCl* solution in reservoir
applied voltage drop: 120mV
pore surface charge density: -0.06C/m^2
Double stranded DNA, $V_{DNA}=0$

Force balance $F_t = F_E - F_D$

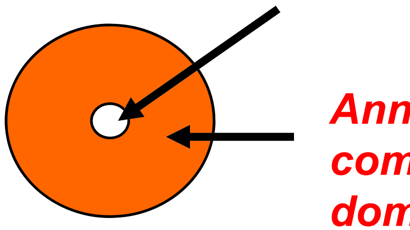
Tethering force vs voltage drop?



Flow field past a tethered DNA

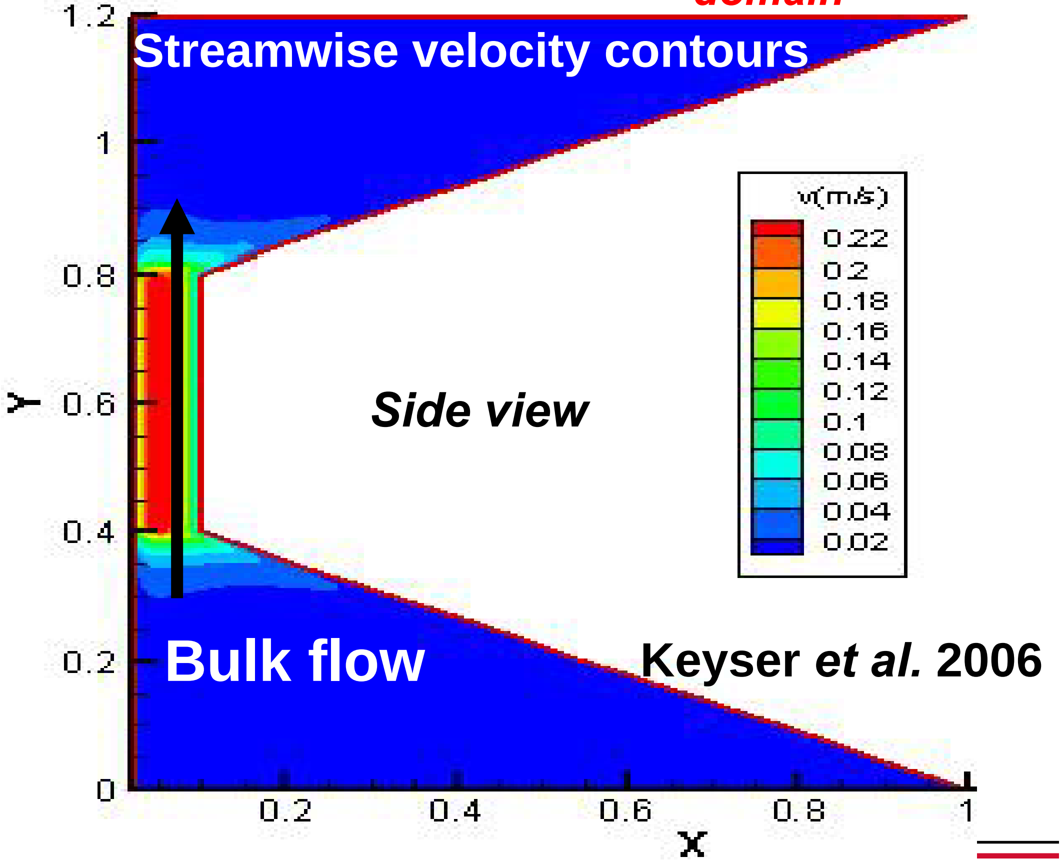
Verification: 161grid=2-3 digits accuracy on velocity

Top view



DNA

Annular computational domain



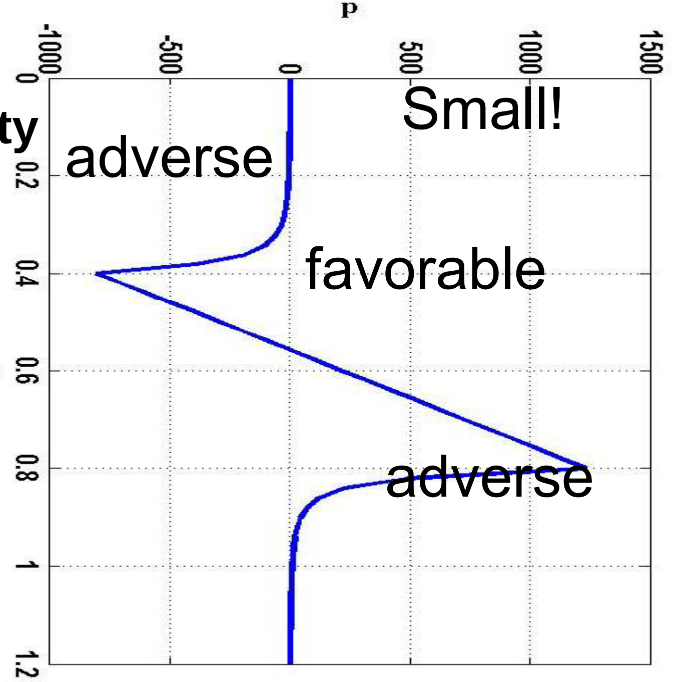
Streamwise velocity contours

Side view

Bulk flow

Keyser *et al.* 2006

Pressure in the nanopore

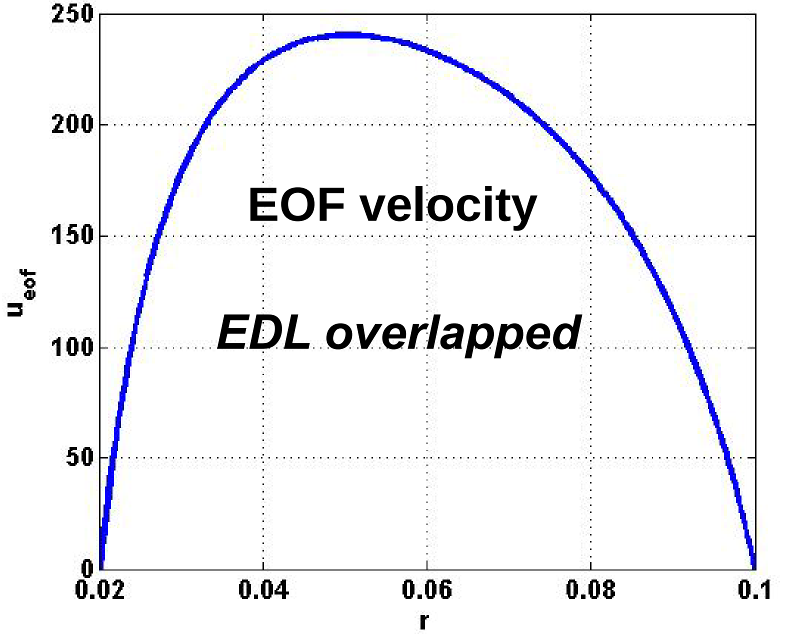


adverse

Small!

favorable

adverse

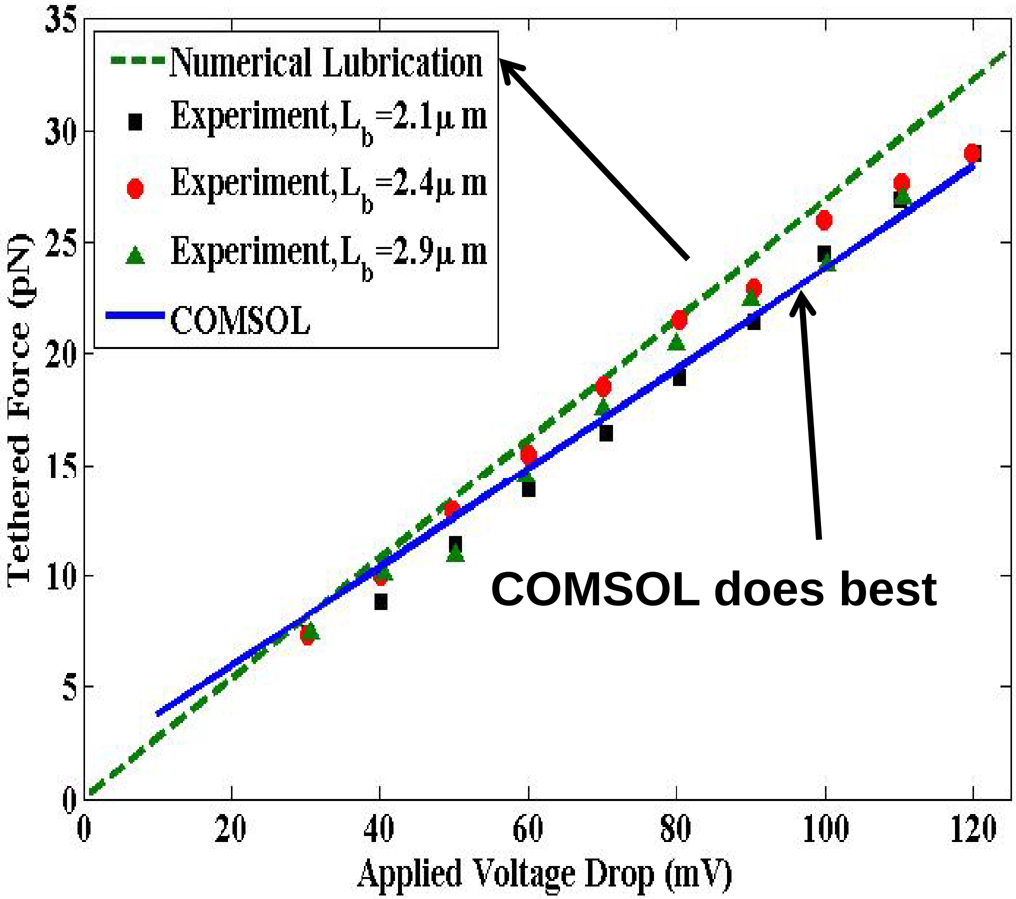


EOF velocity

EDL overlapped

Tethering force results

Keyser *et al.* 2006



COMSOL does best

- **The tethering force F_T is linear with the applied voltage drop**
- **The viscous drag force is ~ 75% of the electric driving force**
- **COMSOL result fits best with the experiment data**
- **Results are good even if lubrication requirement is not satisfied**

For ΔV=120mV
Electrical driving force: 113pN
Viscous drag force: 80.7pN
Tethering force: 32.3pN

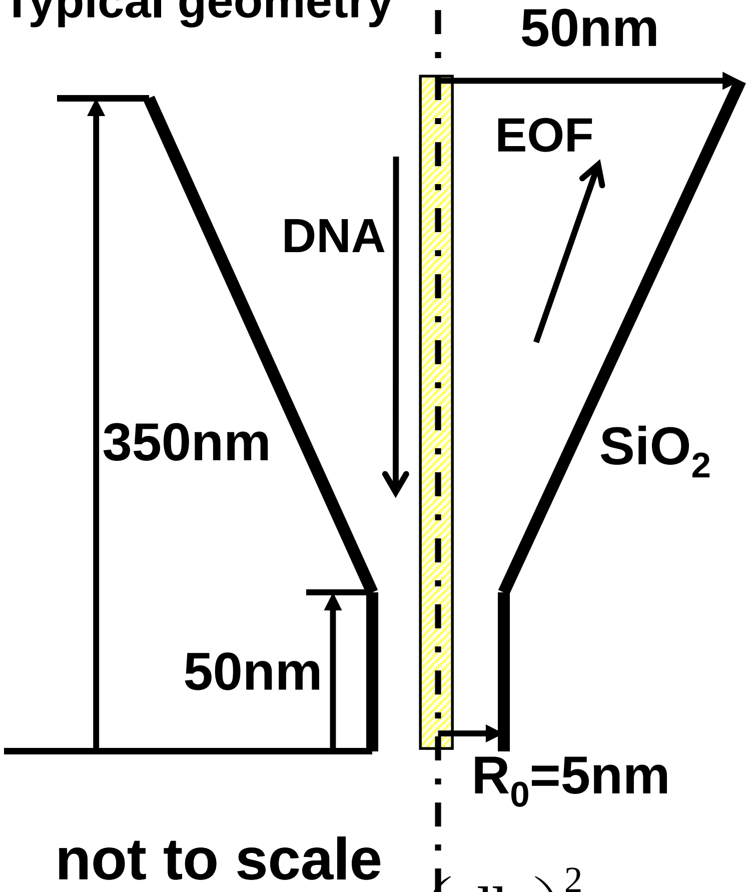
0.1M KCl, σ_{DNA}=-0.15C/m^2 σ_W=-0.06C/m^2

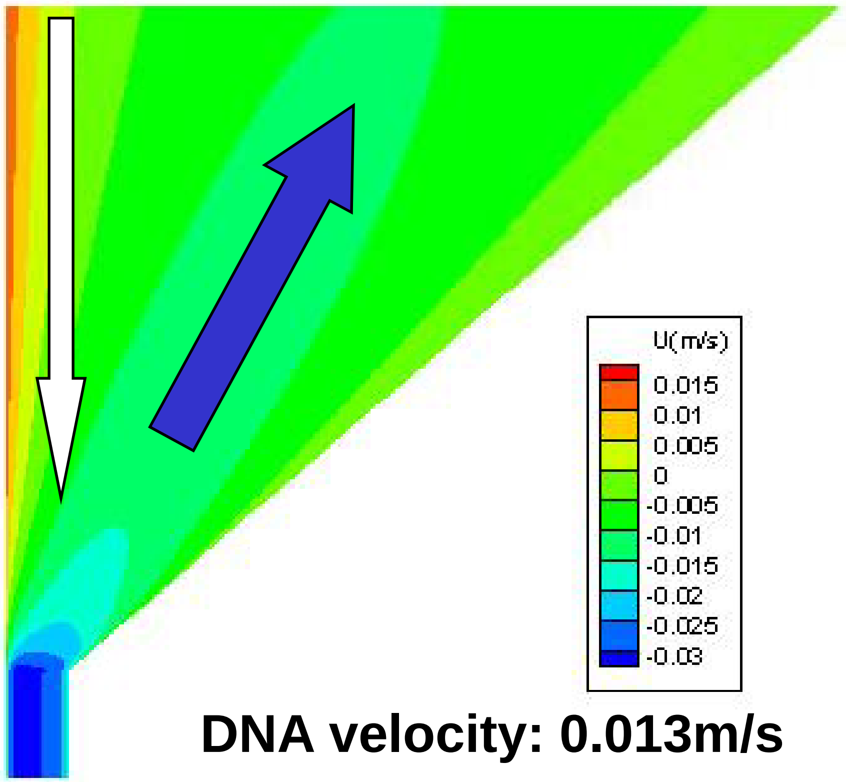
Moving DNA- velocity and potential

Verification: 161grid=2-3 digits accuracy on velocity

Applied voltage drop 120mV, 0.1M KCl solution, σ_{DNA}=-0.15C/m^2, σ_W=-0.06C/m^2

Typical geometry



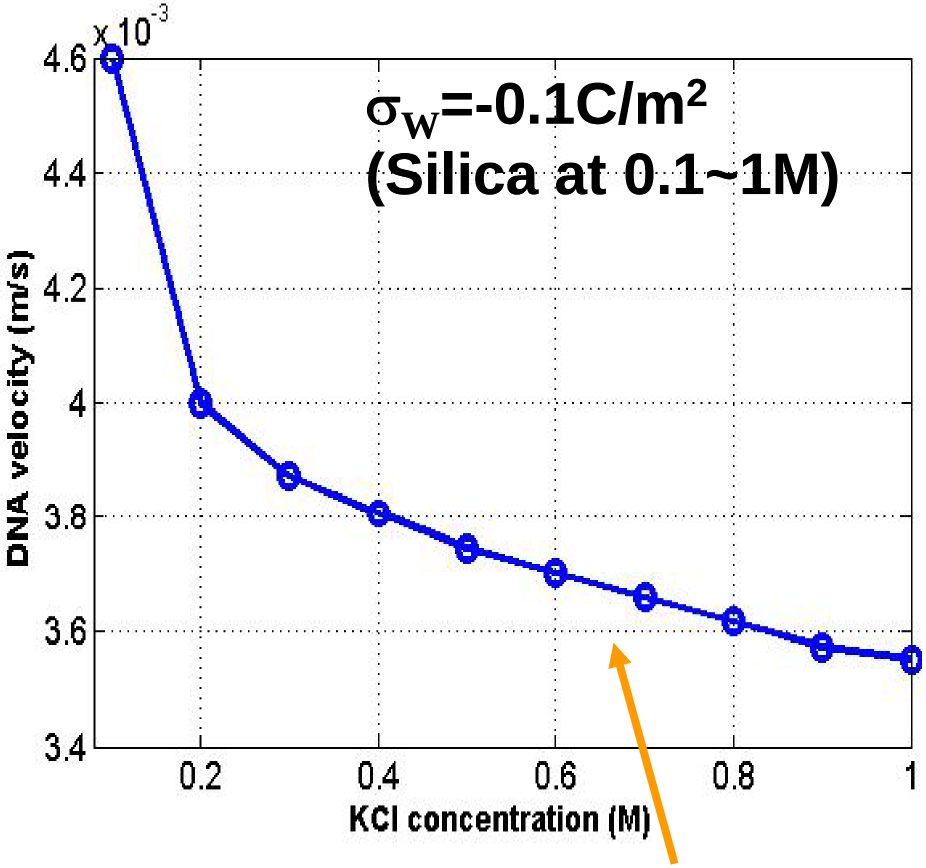


DNA velocity: 0.013m/s

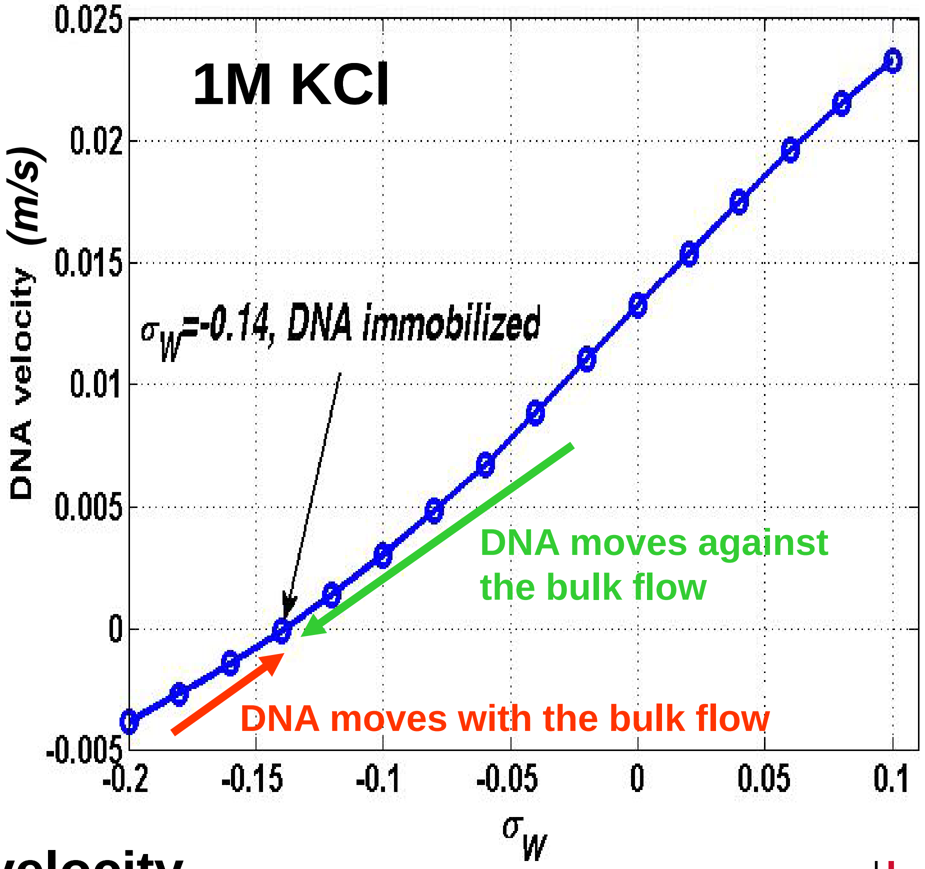
$$\left(\frac{dh}{dx}\right)^2 = 0.02 \ll 1$$

Small slope, lubrication approximation applicable

DNA velocity vs concentration and surface charge density



σ_W=-0.1C/m^2
(Silica at 0.1~1M)



1M KCl

σ_W=-0.14, DNA immobilized

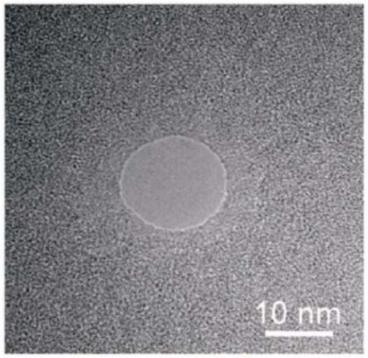
DNA moves against the bulk flow

DNA moves with the bulk flow

Higher concentration, smaller velocity

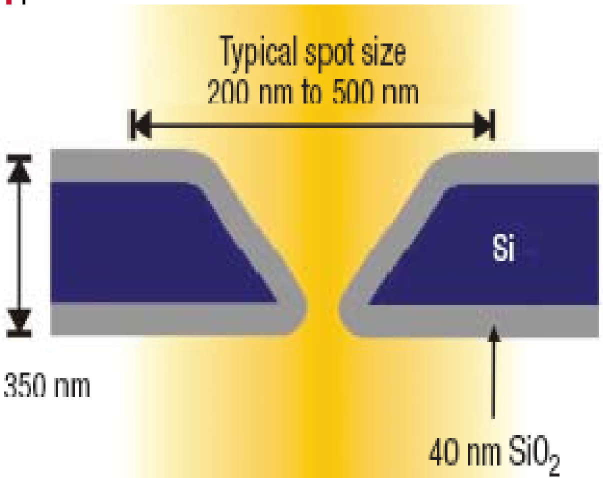
Can slow down DNA by manipulating concentration and surface charge

Comparison with experimental data-DNA velocity



Smeets *et al.* 2006

Source	σ_w(C/m^2)	L_{DNA}(μm)	c_{KCl}(M)	V_{exp}(m/s)	V_{num}(m/s)
Storm 2005	-0.2	3.91	1	0.013	0.0149
Smeets 2006	-0.14	16.5	0.5	0.012	0.0123
Li 2003	-0.14	3.4	1	0.01	0.012



Storm *et al.* (2003),(2005)

- **Results compare well with experimental data**
- **Some pores do not satisfy lubrication approximation**
- **Surface charge density is assumed for some cases**
    - **Difficult to predict DNA velocity in COMSOL**

Outline

- Background and motivation (applications)
- When molecular dynamics: molecular simulation of electroosmotic flow
- Membrane sieving in a renal Assist device (RAD)
- DNA transport for analysis
- Summary

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Summary

- **LJ simulations show that ions are excluded from the wall regions in nanochannels, due to stronger solvation by solvent than by wall molecules, an interaction not accounted for by continuum PB.**
- **However, a small adjustment to the position of walls in PB shows substantial agreement.**
- **Electrostatic repulsion can improve membrane selectivity and explain protein sieving data**
- **DNA velocity can be significant slowed down by adjusting pore surface and solute charge; this aspect of the problem is studied for the first time.**

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Summary

- **When a ds-DNA translocates through a nanopore, force balance is mainly between the viscous drag on the DNA inside the nanopore and the electric driving force.**
- **Based on this force balance, numerical results for tethering force and calculated DNA velocities compare well with experimental data.**

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