Enhancement of charged macromolecule capture by nanopores in a salt gradient

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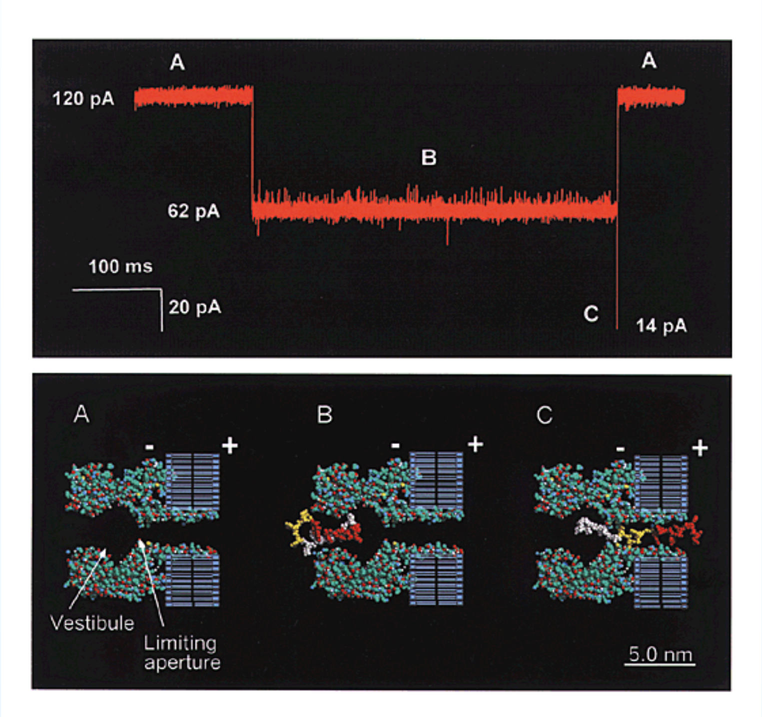
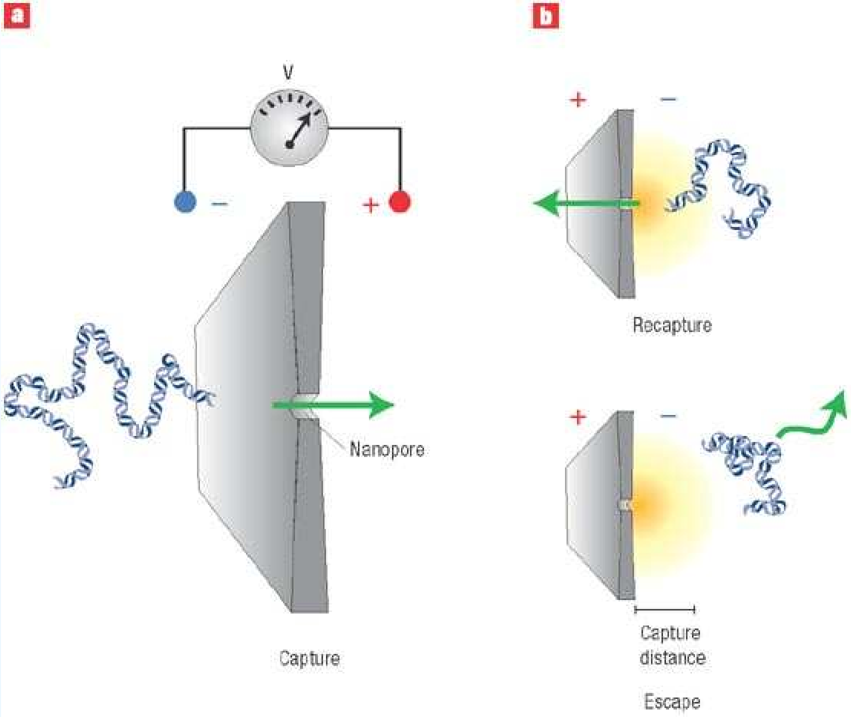
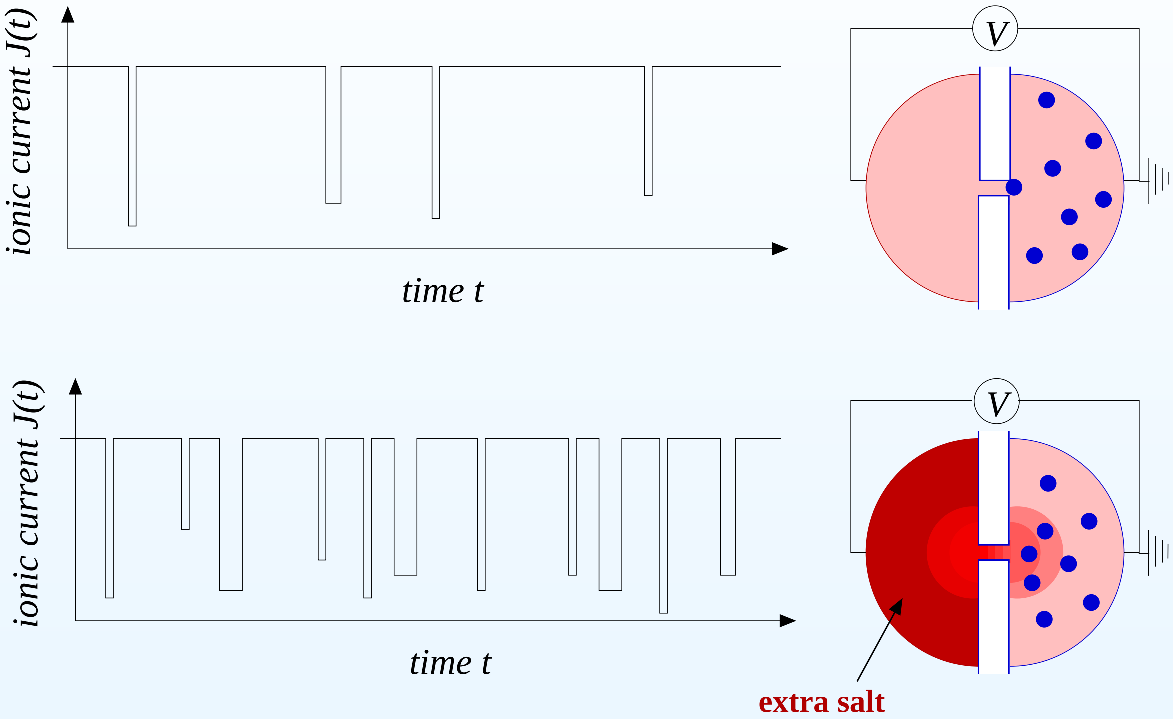
Background - DNA Capture and Sequencing





DNA capture and threading experiments with α-hemolysin pores (1nm pores) and synthetic nanopores (5-10nm radius)

Background - DNA Capture and Sequencing



- Adding extra salt (KCl) in non-DNA side increased capture rates superlinearly
- Adding extra salt in DNA side decreased capture rates superlinearly
- Adding neutral solute in non-DNA side increased capture rates slightly

Possible explanations

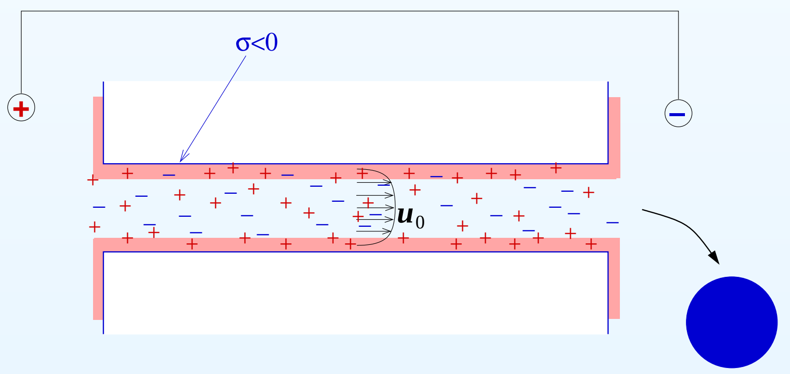
- Osmosis:

  $\Pi \propto k_B T \Delta\Sigma$

  velocity $\mathbf{u}_{\text{osmotic}} \propto \Pi \propto \Delta\Sigma$ salt difference

  Problem: salt flows through 5nm pores

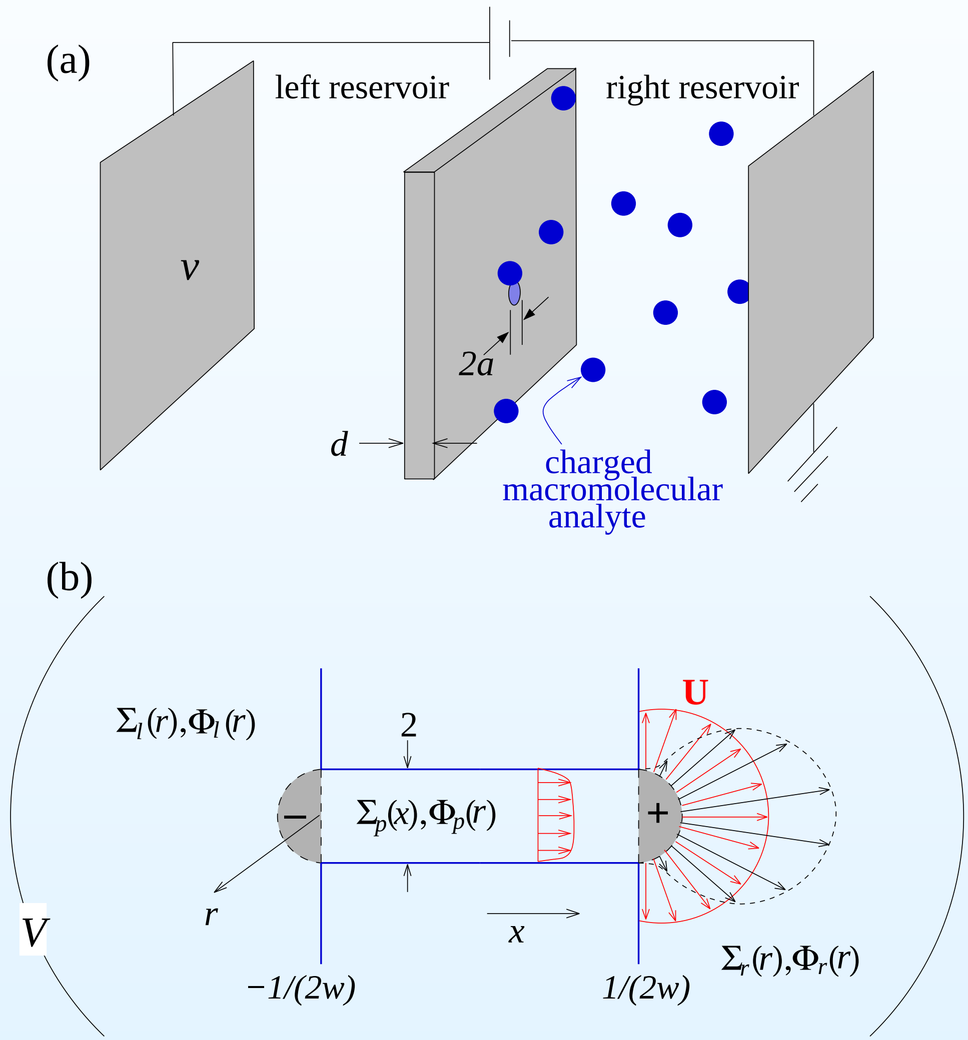
- Electroosmotic flow



$$u_0 \propto -\frac{\sigma}{\kappa\gamma}\Delta\phi$$

Problem: if surface charge $\sigma < 0$, $u_0 > 0$

Simpler Electrostatic Explanation?



Problem set-up: Equations

Electrokinetic equations for potential Φ, ion concentration C_i, and local fluid velocity $\mathbf{U}$:

$$\nabla \cdot (\epsilon \nabla \Phi(\mathbf{r}, t)) = -4\pi e \sum_i z_i C_i(\mathbf{r}, t)$$

$$\frac{\partial C_i(\mathbf{r},t)}{\partial t} + \nabla \cdot (\mathbf{U} C_i) = \nabla \cdot (D_i \nabla C_i) + e z_i \mu_i \nabla \cdot (C_i \nabla \Phi)$$

$$\rho_0 \dot{\mathbf{U}} = -\nabla P + \mu \nabla^2 \mathbf{U} + e \nabla \Phi \sum_i z_i C_i$$

Nondimensionalization of steady-state equations

$$c_{\pm} = C_{\pm}/C_L, \;\; \phi = e\Phi/k_B T, \;\; \mathbf{u} = \frac{L}{D_{\text{ion}}}\mathbf{U}, \;\; p = \frac{P}{C_L k_B T}$$

Steady-state equations become:

$$\nabla \cdot (\epsilon \nabla \Phi(\mathbf{r})) + \Lambda_R Q(\mathbf{r}) = 0$$

$$\nabla \cdot [\nabla \Sigma(\mathbf{r}) + Q(\mathbf{r}) \nabla \Phi(\mathbf{r}) - \mathbf{U}(\mathbf{r}) \Sigma(\mathbf{r})] = 0$$

$$\nabla \cdot [\nabla Q(\mathbf{r}) + \Sigma(\mathbf{r}) \nabla \Phi(\mathbf{r}) - \mathbf{U}(\mathbf{r}) Q(\mathbf{r})] = 0$$

$$\mu \nabla^2 \mathbf{U}(\mathbf{r}) - \nabla P(\mathbf{r}) + Q(\mathbf{r}) \nabla \Phi(\mathbf{r}) = 0$$

where $Q(\mathbf{r}) = \frac{1}{2}(C_+(\mathbf{r}) - C_-(\mathbf{r}))$, $\Sigma(\mathbf{r}) = \frac{1}{2}(C_+(\mathbf{r}) + C_-(\mathbf{r}))$, and

$$\Lambda_R \equiv \frac{8\pi e^2 c_R a^2}{k_B T} \equiv (\kappa_R a)^2.$$

Model Equations

In the $\Lambda_R^{-1} \equiv \varepsilon \to 0$ limit, The “outer” solutions can be expressed in the form

$$\begin{aligned}
\Phi(\mathbf{r}) &= \Phi_0(\mathbf{r}) + \varepsilon\Phi_1(\mathbf{r}) + \varepsilon^2\Phi_2(\mathbf{r}) + \ldots \\
\Sigma(\mathbf{r}) &= \Sigma_0(\mathbf{r}) + \varepsilon\Sigma_1(\mathbf{r}) + \varepsilon^2\Sigma_2(\mathbf{r}) + \ldots \\
Q(\mathbf{r}) &= Q_0(\mathbf{r}) + \varepsilon Q_1(\mathbf{r}) + \varepsilon^2 Q_2(\mathbf{r}) + \ldots \\
\mathbf{U}(\mathbf{r}) &= \mathbf{U}_0(\mathbf{r}) + \varepsilon\mathbf{U}_1(\mathbf{r}) + \varepsilon^2\mathbf{U}_2(\mathbf{r}) + \ldots \\
P(\mathbf{r}) &= P_0(\mathbf{r}) + \varepsilon P_1(\mathbf{r}) + \varepsilon^2 P_2(\mathbf{r}) + \ldots .
\end{aligned}$$

Model Equations

To find solutions accurate to $O(\varepsilon^0)$, we must solve the remaining equations

$$\nabla \cdot [\nabla \Sigma_0(\mathbf{r}) - \mathbf{U}_0(\mathbf{r})\Sigma_0(\mathbf{r})] = 0$$

$$\nabla \cdot [\Sigma_0(\mathbf{r})\nabla\Phi_0(\mathbf{r})] = 0$$

$$\mu\nabla^2\mathbf{U}_0(\mathbf{r}) - \nabla P_0(\mathbf{r}) = 0$$

Henceforth, we consider only the zeroth order solutions and drop the subscript (0) notation.

Solution for concentration Σ

define: $G \equiv \exp\left[\frac{U}{2}\right]$ and $H \equiv \exp\left[\frac{Ud}{a}\right] \equiv \exp\left[\frac{U}{w}\right]$, Imposing conservation of ion flux across pore mouths, we find

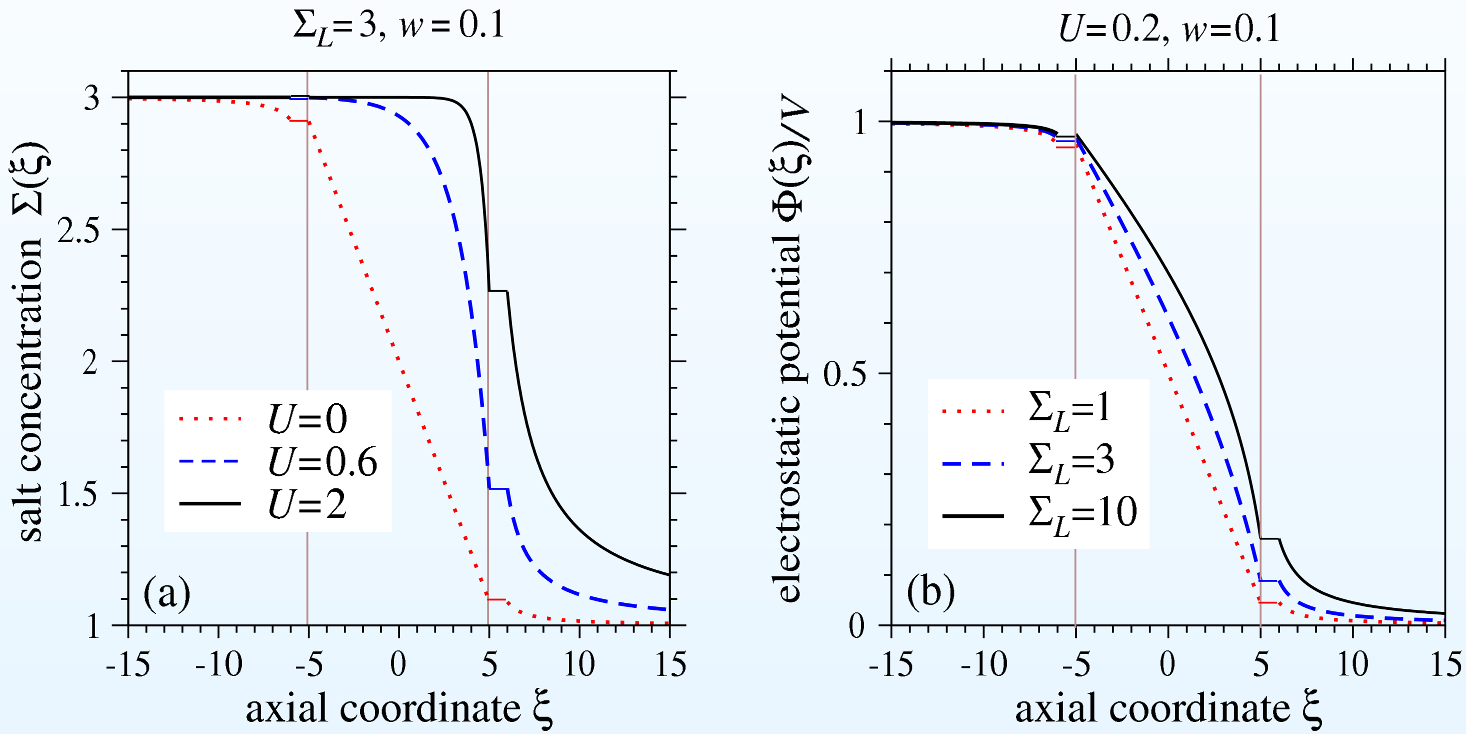
$$\Sigma_\ell(r) = \frac{\Sigma_L GH - 1}{GH - 1} - \frac{(\Sigma_L - 1)}{GH - 1} \exp\left[\frac{U}{2r}\right],$$

$$\Sigma_p(x) = \frac{\Sigma_L GH - 1}{GH - 1} - \frac{(\Sigma_L - 1)\sqrt{GH}}{GH - 1} e^{Ux},$$

and

$$\Sigma_r(r) = \frac{\Sigma_L GH - 1}{GH - 1} - \frac{(\Sigma_L - 1)GH}{GH - 1} \exp\left[-\frac{U}{2r}\right].$$

Solution for concentration Σ



Solution for electroosmotically-driven $\mathbf{U}$

U must be self-consistently solved by finding the root to

$$U = \Gamma(U, \Sigma_L)(\Phi_+[U, \Sigma_L] - \Phi_-[U, \Sigma_L]),$$

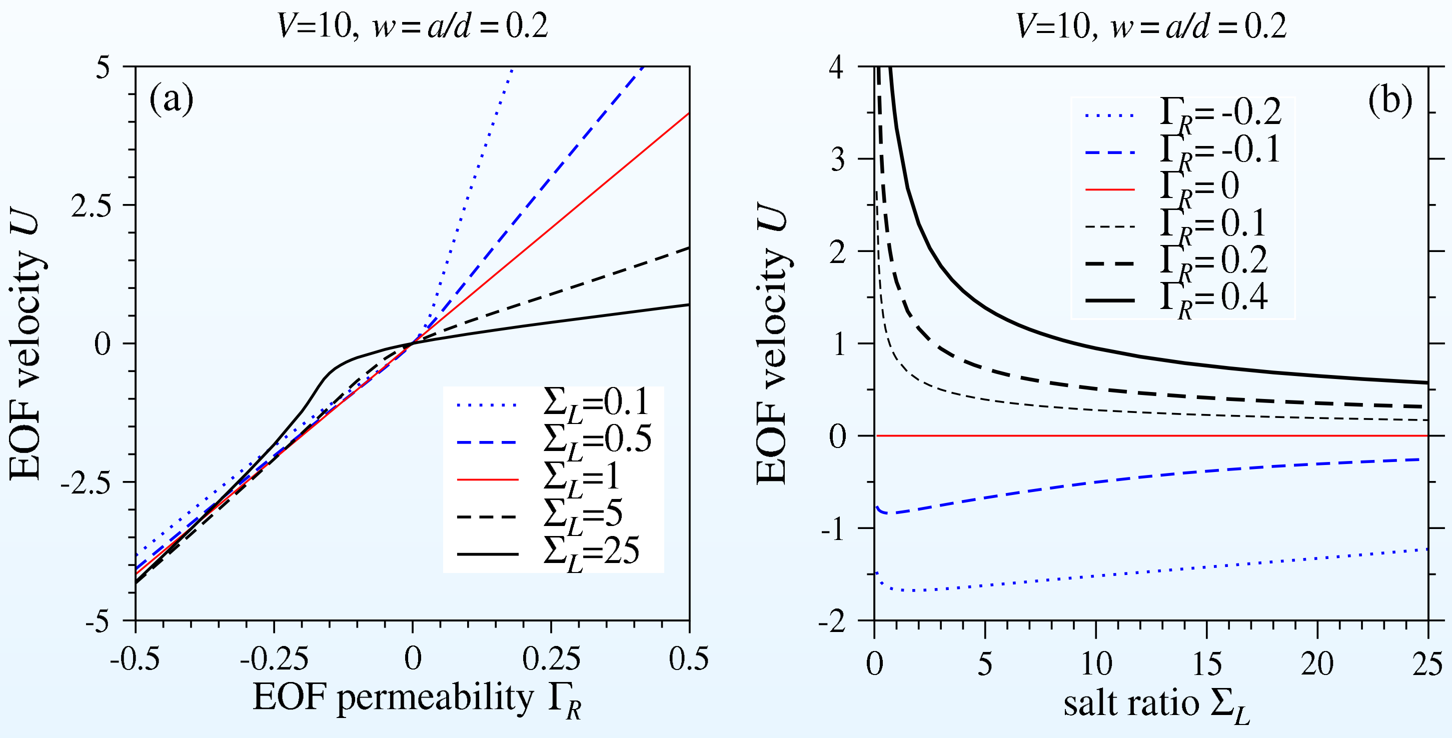
where

$$\Gamma(U, \Sigma_L) \equiv \left(\frac{\sigma k_B T}{\eta d e}\right) \frac{1}{d} \int_{-d/2}^{d/2} \frac{\mathrm{d}x}{\kappa(x)} \equiv \Gamma_R\, w \int_{-1/(2w)}^{1/(2w)} \frac{\mathrm{d}x}{\sqrt{\Sigma_p(x)}},$$

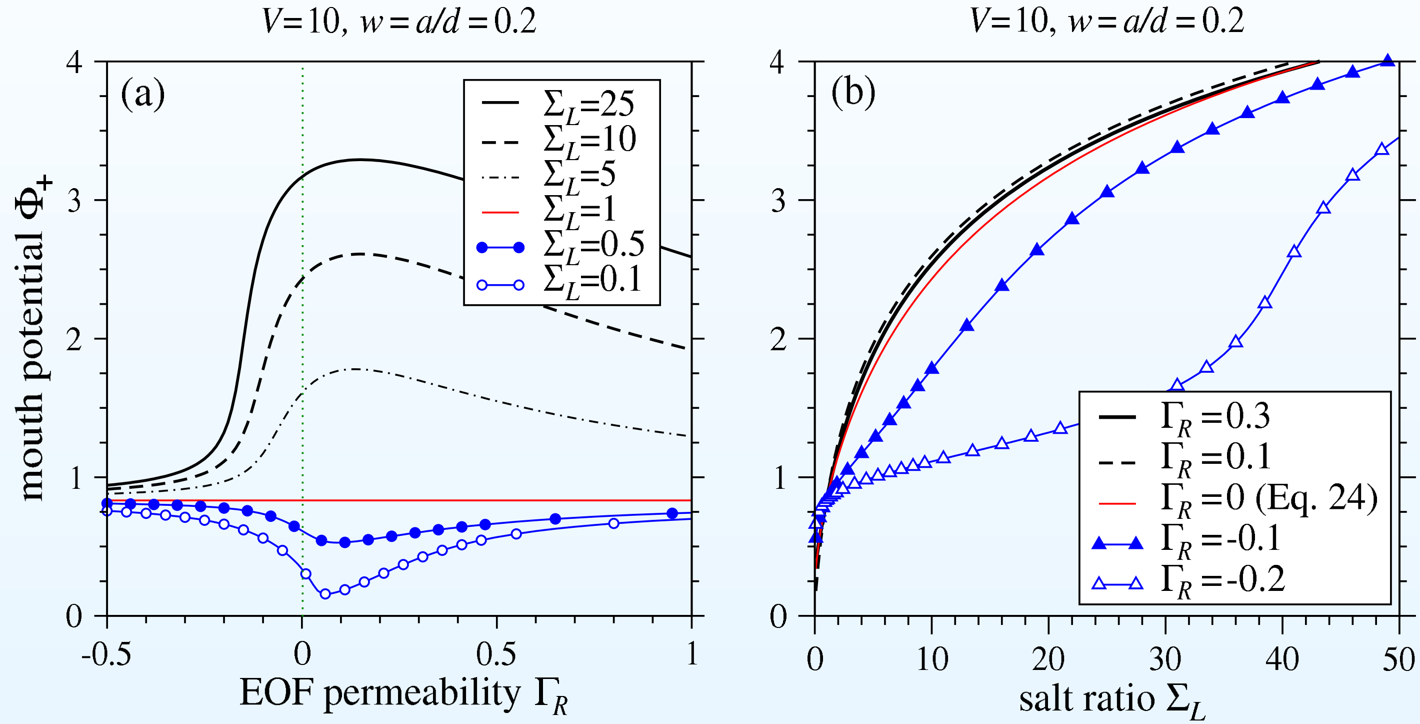
and

$$\Gamma_R \equiv \left(\frac{\sigma}{e a c_R}\right) \frac{w}{\mu \Lambda_R^{1/2}}$$

Solution for $\mathbf{U}$



Solution for potential Φ



Pore blocking probability

Blocking probability = pore mouth occupation θ:

$$k_{\rm on}\rho(1)(1-\theta) = (k_{\rm off} + k_{\rm t})\theta,$$

where $\rho(1) \equiv \lim_{r\to 1^+} \rho(r)$ is analyte density just outside the cap and

$k_{\rm off}$ is desorption rate

$k_{\rm on}$ is adsorption rate from just outside cap

$k_{\rm t}$ is translocation rate

Pore mouth occupation

Stochastically switching convection-diffusion Eq:

$$(1-\theta)\nabla\cdot[\mathbf{A}(r)\rho(r)] = \nabla^2\rho(r), \quad r>1,$$

where $q \equiv$ effective analyte charge and

$$\mathbf{A}(r) = A(r)\hat{r} = \left[\frac{U}{2Dr^2} + q\frac{\partial\Phi_r(r)}{\partial r}\right]\hat{r}$$

Solve using boundary condition:

$$D\partial_r\rho(r)\Big|_{r=1^+} - (1-\theta)\left[\frac{U}{2} + Dq\nabla\Phi_+\right]\rho(1) = k_{\rm on}\rho(1)(1-\theta) - k_{\rm off}\theta,$$

Pore mouth occupation

Solution:

$$\rho(r) = e^{(1-\theta)\int_1^r A(y)dy} \left[\frac{k_{\rm t}\theta}{D} \int_1^r y^{-2} e^{-(1-\theta)\int_1^y A(y')dy'} dy + \frac{(k_{\rm off}+k_{\rm t})\theta}{k_{\rm on}(1-\theta)} \right].$$

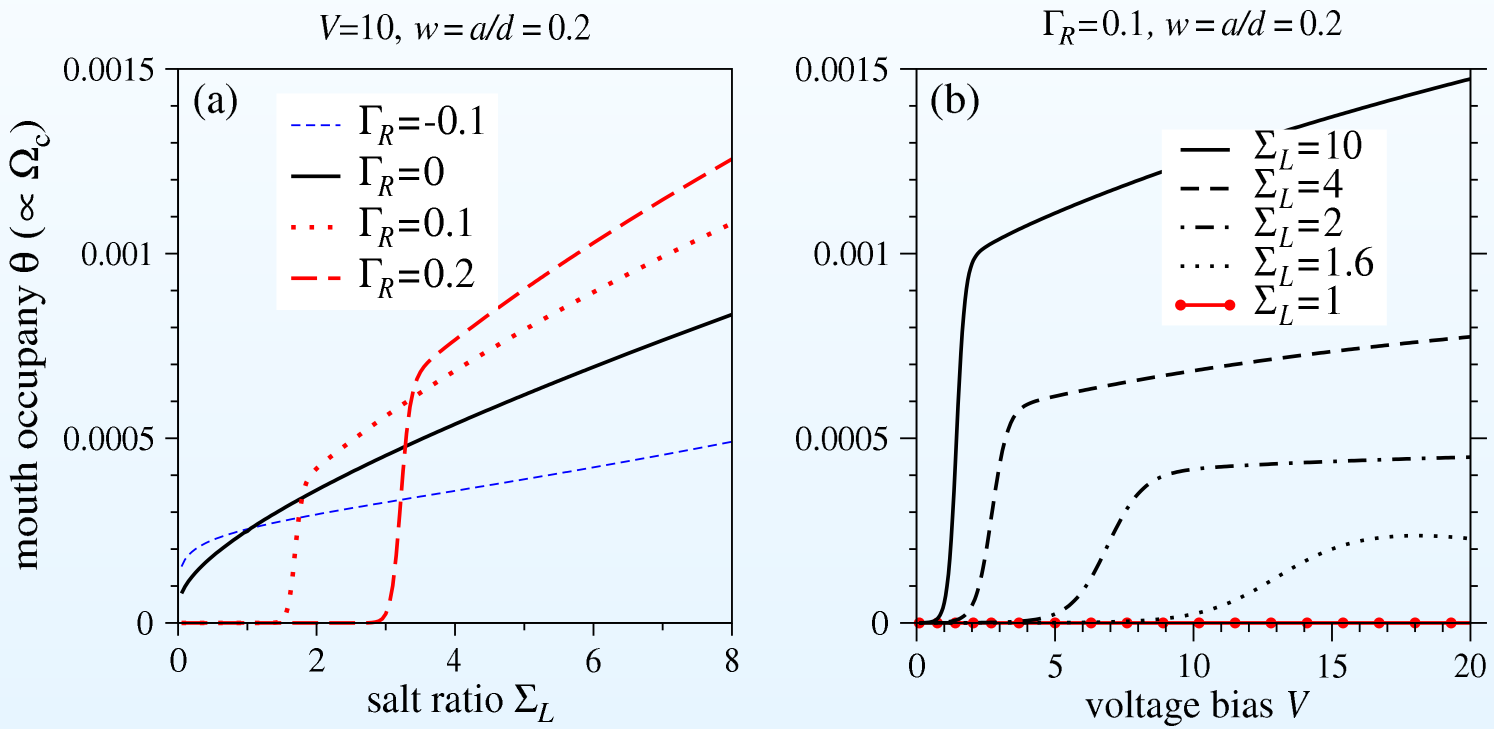
at $r \to \infty: \quad \rho_\infty = \frac{k_{\rm t}\theta}{D} I(\theta) + \frac{(k_{\rm off}+k_{\rm t})\theta}{k_{\rm on}(1-\theta)} e^{(1-\theta)(U/(2D)-q\Phi_+)},$

where

$$I(\theta) \equiv \int_1^\infty e^{(1-\theta)\left(\frac{U}{2Dr}-q\Phi_r(r)\right)} r^{-2}\mathrm{d}r.$$

Pore mouth occupation

Assume: $k_{\text{off}} = \omega_{\text{off}} e^{-fqV}$, $k_{\text{on}} = \omega_{\text{on}}$, $k_{\text{t}} = \omega_{\text{t}} V$,



Capture rates

Average times that a pore stays open and blocked are

$$T_{\rm o} \approx \frac{1}{k_{\rm on}\rho(1)} = \frac{1-\theta}{(k_{\rm off}+k_{\rm t})\theta} \quad \text{and} \quad T_{\rm b} \approx \frac{1}{k_{\rm off}+k_{\rm t}},$$

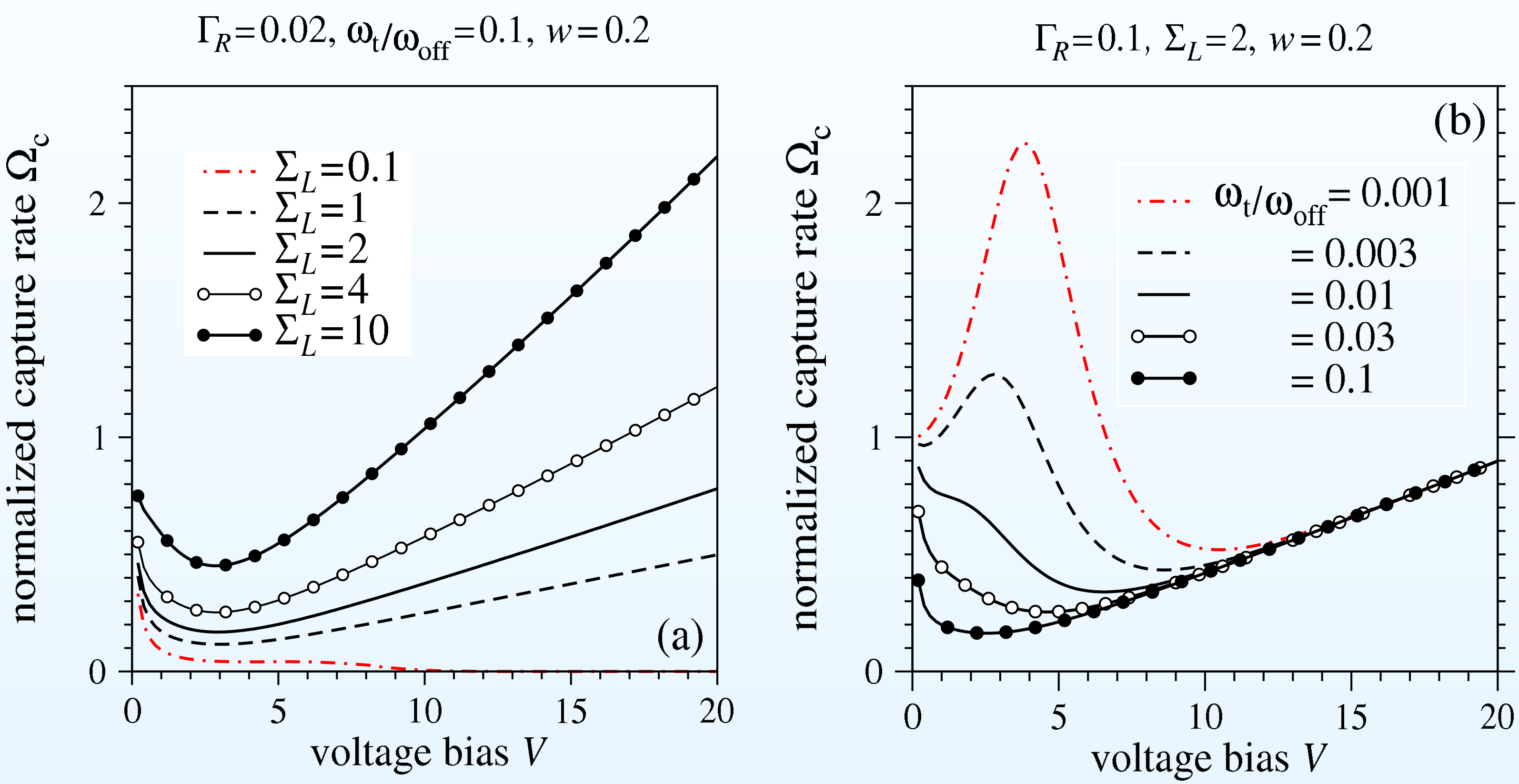
Inverse of mean time between successive capture events defines capture rate $\omega_{\rm c}$:

$$\omega_{\rm c} \approx \frac{1}{T_{\rm b}+T_{\rm o}} = (k_{\rm off}+k_{\rm t})\theta.$$

Formally,

$$\Omega_{\rm c} \equiv \left(\frac{\omega_{\rm c}}{\omega_{\rm off}}\right) \approx \left(e^{-fqV} + \frac{\omega_{\rm t}}{\omega_{\rm off}}V\right)\theta(\Gamma_R, f, q, V, w, \Sigma_L, \rho_\infty, \omega_{\rm off}, \omega_{\rm on}, \omega_{\rm t}),$$

Capture rates



Summary and Conclusions

- Higher [salt] increases conductivity, increasing potential at opposite pore mouth
- Solved outer electrokinetics solution valid for $\Lambda_R^{-1} \ll a \ll d$
- Outward EOM can increase capture rate in presence of salt gradient by spatially changing conductivity