Theory of macromolecular transport through protein channels and nanopores

M. Muthukumar
University of Massachusetts

Ljubljana
September 20, 2012

Joey Kong, Chris Forrey, Andrew Wong, Xiangdong Gu, Rajeev Kumar, Jyoti Mahalik, Yanbo Wang, Byoung-jin Jeon, Steve Mirigian, Harsh Katkar

NIH, NSF
Applicability of **General Concepts** from Polymer Physics?

Living & Diseases = Macromolecular

“Coulomb Soup”

\[ F = E - TS \]

Biology = “Specificity” ? ?
VIRAL INFECTION:


GENE SWAPPING:

m-RNP (ribonucleoprotein) ~complex of RNA
The Road to the $1,000 Genome
Polymer Translocation

$\lambda \ll R$

$\lambda < R$

$\lambda \sim R$

$\lambda >> R$

$\alpha$-hemolysin pore

Solid-state nanopores and channels

5 nm

Bewildering experimental FACTS!
How to organize key concepts?

Capillary electrophoresis

“Polymer speed is independent of length”
Single-file single molecule translocation


Typically,

Why so fast and so stochastic?

Topologically correlated charged string in a neutralizing plasma

Coupling of topological and electrostatic correlations

\[ F = E - T S \]

Significant entropy
Pores are complex too

\(\alpha\)-Hemolysin protein nanopore

- Green: Hydrophobic
- Red: Negative
- Blue: Positive
- Gray: Hydrophilic

Local charge distribution + sticky hydrophobic groups perturb translocation dynamics
Entropic Barrier Model

\[ F = E - T S \]

\[ -\varepsilon + T |\Delta S| \]
“NUCLEATION and GROWTH”

Entropic Barrier Model

\[-\epsilon + T|\Delta S|\]

Nucleation and Growth
Free Energy of a Tethered Polymer

Number of configurations: \[ Z \sim N^{\gamma_1 - 1} e^{-\mu N} \]

\( \gamma_1 = \begin{cases} 
\frac{1}{2} & \text{Random Walk} \\
\approx 0.69 & \text{High Salt} \\
\approx 1 & \text{Low Salt} 
\end{cases} \)

E. Eisenriegler
\[
\begin{align*}
\frac{\partial W_m(t)}{\partial t} &= k_{m-1} W_{m-1} - k \ W_m - k \ W_m + k_{m+1} W_{m+1} \\
&= \frac{\partial}{\partial m} \left[ k_m \frac{\partial}{\partial m} \left( \frac{F_m}{k_B T} \right) W_m(t) + k_m \frac{\partial}{\partial m} W_m(t) \right]
\end{align*}
\]
Translocation is Drift-Diffusion, after Nucleation

\[ Z_m = m^\gamma'^{-1} q^m \]

\( \gamma' = 0.69 \), high salt
\( q = \) electrochemical potential

\[ \tau \sim N/\Delta V \]

α-hemolysin channel

End View  Side View

β-barrel  vestibule

Polymer

side-chain incorporated model

MM, CY Kong, PNAS, 103, 5273 (2006)
Langevin Dynamics

(bond stretch, bond angle, tortional angle)

\[
\begin{align*}
    m_i \ddot{a}_i(t) + \zeta \dot{v}_i(t) - F_i[\{R\}(t)] &= f(t) \\
    \langle f(t) \cdot f(t') \rangle &= 6k_B T \zeta \delta(t-t')
\end{align*}
\]

MM, CY Kong, PNAS, 103, 5273 (2006)
Modified Poisson-Nernst-Planck

\[ \frac{\partial c_v}{\partial t} = -\nabla \cdot \vec{J}_v \]

\[ \vec{J}_v = -D_v (\nabla c_v + \frac{z_v e c_v}{kT} \nabla V) \]

\[ \varepsilon_o \nabla \cdot [\varepsilon(\vec{r}) \nabla V(\vec{r})] = -\sum v z_v e c_v - \rho_{ex} - \rho_p \]

\[ I = \vec{A} \cdot [\vec{J}_p + \sum_v \vec{J}_v ] \]

MM, JCP 107, 2619 (1997)
Sodium polystyrene sulfonate through $\alpha$-hemolysin pore

Translocation of synthetic polyelectrolyte

More than 90% don’t go through!
Pores are charged heterogeneously

$\alpha$-Hemolysin protein nanopore

Green: Hydrophobic
Red: Negative
Blue: Positive
Gray: Hydrophilic

Charged Ring

1.5 nm constriction

Net charge responds to pH

G. Maglia et al. PNAS, 105, 19720 (2008) (site-directed mutagenesis)
Frequency of polymer-pore encounters

Prediction/control for:

1. Capture rate of the target DNA, $R_c$
2. Success rate of threading, $S_t$

$$R_c \equiv \frac{1}{\langle t_0 \rangle}$$

$$S_t \equiv \frac{t_2}{t_1 + t_2}$$
$R_c$ increases with $N$

Three Stages of Translocation

(1) Drift-diffusion
(2) Capture
(3) Threading

M. Muthukumar, “Polymer Translocation”, 2011
1. Drift-diffusion

Polymer concentration, $c$:

$$\frac{\partial c}{\partial t} = -\nabla \cdot \vec{J}$$

Polymer flux, $J$:

$$\vec{J} = -D\nabla c + c\mu\vec{E}$$

Electrophoretic mobility ($\mu$) is given by the Einstein relation:

$$\frac{\mu}{QD} = 39.6 \text{V}^{-1} \text{at}20^\circ \text{C}$$

~ NOT valid for polymers
Einstein’s equation fails!

\[ \mu Q D \]

39.6 V^{-1}

1. Drift-diffusion

Polymer concentration, c:

\[ \frac{\partial c}{\partial t} = - \nabla \cdot \vec{J} \]

Polymer flux, J:

\[ \vec{J} = -D \nabla c + c \mu \vec{E} \]

- Diffusion
- Drift

Electrophoretic mobility (\( \mu \)) is given by the Einstein relation:

\( \frac{\mu}{QD} = 39.6 \text{ V}^{-1} \text{ at } 20^\circ C \)

(Q=polymer charge)

~ NOT valid for polymers

Electrophoretic mobility is independent of polymer length N
\[ \mu = \frac{QD}{k_B T} \Theta(R_g \sqrt{c_s}) \]

\[ \vec{J} = -D \nabla c + c \mu \vec{E} \]

If DRIFT dominates,

- \( R_c \) vs. \( c \)
- \( R_c \) vs. \( \Delta v \)
- \( R_c \) vs. \( \log N \)

\( R_g = \) coil size
\( C_s = \) salt concentration
2. Capture
Large capture radius in solid-state nanopores

Nanopore diameter ~ 15 nm Si₃N₄(Coated with Al₂O₃)
dsDNA pulled, 1 M KCl solution, pH 8
Absorbing region ~ 2.2 µm (at 500mV)

Coil stretching by electro-osmotic flow?

Critical radius $R_c$

DNA

Surface potential $\Phi_0$

Velocity $v(r)$

Ez
Poisson-Boltzmann equation:

\[ \nabla^2 \Phi(r) = -\frac{ne}{\varepsilon} \left( e^{-e\Phi/kT} - e^{e\Phi/kT} \right) = \frac{2ne}{\varepsilon} \sinh\left( \frac{e\Phi}{kT} \right) \approx \kappa^2 \Phi(r) \]

Potential: \[ \Phi(r) = \Phi_0 \frac{I_0(\kappa r)}{I_0(\kappa a)} \]

Inverse Debye length \[ \kappa = \sqrt{\frac{2ne^2}{\varepsilon kT}} \]

Charge density: \[ \rho(r) = -\varepsilon \nabla^2 \Phi(r) = -\varepsilon \kappa^2 \Phi_0 \frac{I_0(\kappa r)}{I_0(\kappa a)} \]
Navier-Stokes equation:

\[-\eta \nabla^2 v(r) = \rho(r)E\]

velocity

\[v_z(r) = -\frac{\Phi_0 E \varepsilon}{\eta} \left[ 1 - \frac{I_0(\kappa r)}{I_0(\kappa a)} \right]\]

Fluid Flux

\[J = -\frac{\Phi_0 E \varepsilon}{\eta} (\pi a^2) \left[ 1 - \frac{1}{\kappa a} \frac{2I_1(\kappa a)}{I_0(\kappa a)} \right] \beta\]
Fluid flow is continuous

\[ 2\pi R^2 u(R) = J \quad \text{(Far field)} \]

Velocity of fluid at \( R \)

\[ u(R) = \frac{J}{2\pi R^2} \]

Velocity gradient:

\[ \dot{\gamma}(R) = \frac{dv(R)}{dR} = \frac{J}{\pi R^3} \]

Coil stretching:

\[ \dot{\gamma}_C \tau_Z = 0.5 \]

Zimm relaxation time:

\[ \tau_Z = 0.3\eta R_g^3 / kT \]
\[ R_C = \left( \frac{0.6 \beta \Phi_0 E \varepsilon a^2}{kT} \right)^{1/3} R_g \]

a = 7.5 nm  
E = 500 mV / 10^{-6} cm  
\varepsilon = 80 \varepsilon_0  
T = 300 K  
\Phi_0 = 0.1 V (\sigma = 1.4 e/nm^2)  
\kappa^{-1} = 0.304 nm (1 M KCl)

\( R_C = 3.0 R_g \)  

Lesson 1: Very large capture well, tunable

Lesson 2: Control of translocation speed by electro-osmotic flow

3. Barrier

(a)

(b)

(c)
Entry of a polyelectrolyte with its counterions to a pore

Must account for:

- Electrostatics
- Chain entropy
- Counterion cloud
- Electrolyte ion correlations
- Solvent entropy

Self-Consistent Field Theory = Polymer conformations + Poisson-Boltzmann

$$\left[ \frac{\partial}{\partial N} - \frac{\ell^2}{6} \nabla^2 \right] + \omega n_p(\vec{R}) + \frac{z_p e}{k_B T} \psi(\vec{R})]G(\vec{R}, \vec{R}'; N) = \delta(\vec{R} - \vec{R}') \delta(N)$$

$$\psi(\vec{r}) = \frac{1}{4 \pi \epsilon_0 \epsilon} \int d\vec{r}' \frac{1}{|\vec{r} - \vec{r}'|} \left[ z_p e n_p(\vec{r}') + \sum_i z_i e n_i(\vec{r}') \right]$$

$$n_p(\vec{r}) = \frac{\int_0^N ds G(\vec{R}, \vec{r}; N - s) G(\vec{r}, \vec{R}'; s)}{G(\vec{R}, \vec{R}'; N)}$$

$$n_i(\vec{r}) = n_{i0} \exp \left[ -\frac{z_i e}{k_B T} \psi(\vec{r}) \right]$$

Entropic barrier decreases with chain length

Putting all three components together

Capture rate

\[ \mathbf{J} = -D \frac{\partial c}{\partial x} - c \mu \frac{\partial V(x)}{\partial x} - c \frac{D}{k_B T} \frac{\partial U(x)}{\partial x} \]

Diffusion  Drift  Barrier

(Fokker-Planck Analysis)

{Drift-diffusion + Entropic barrier for a charged polymer}

Closed form equations are derived for $R_c$

CONCLUSIONS

POLYMER (entropy)

FLOW (electrohydrodynamics)

PROTEIN CHANNELS NANOPORES (hydrophobicity + electrostatics)

(ONE theoretical frame to explain translocation phenomenology)

All of these contribute
Implications in Biology

(1) Chemical Amplification: Recognition, nucleation, threading

(2) Kinetics of virus genome ejection
Theory of macromolecular transport through protein channels and nanopores

M. Muthukumar
University of Massachusetts

Ljubljana
September 20, 2012

Joey Kong, Chris Forrey, Andrew Wong, Xiangdong Gu, Rajeev Kumar, Jyoti Mahalik, Yanbo Wang, Byoung-jin Jeon, Steve Mirigian, Harsh Katkar

NIH, NSF