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Selectivity and Efficiency in Molecular Channel Transport

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Medizinische Klinik und Poliklinik I

Selectivity and Efficiency in Molecular Channel Transport

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Medizinische Klinik

- Importance of channel transport in biology
  - *Example: nuclear pores*
- The model
- How to increase transport efficiency
- Selectivity

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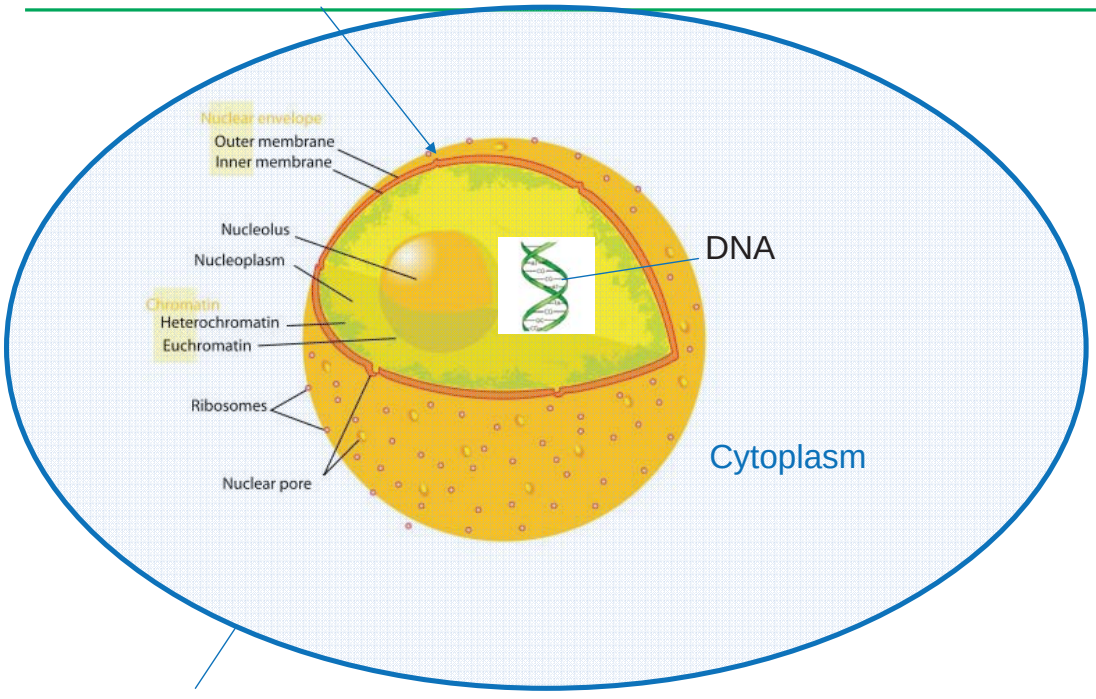
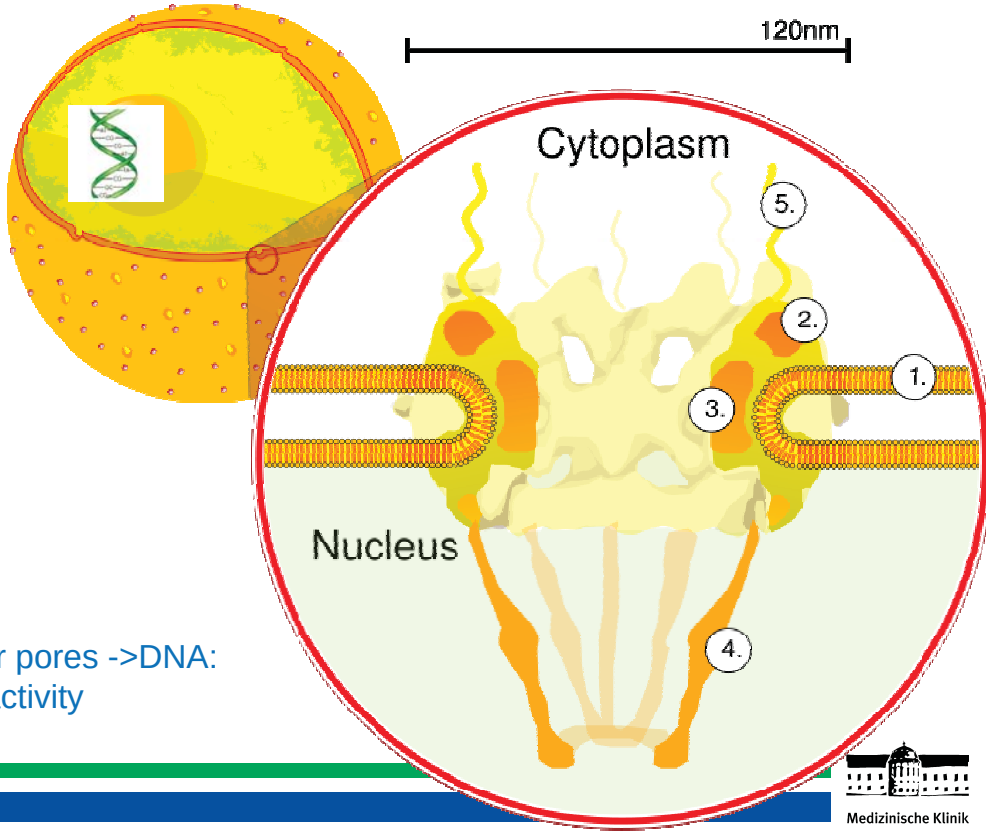
Cell with nucleus



Nuclear pores: Transport between nucleus and cytoplasm



Transport via nuclear pores ->DNA:
Regulation of gene activity

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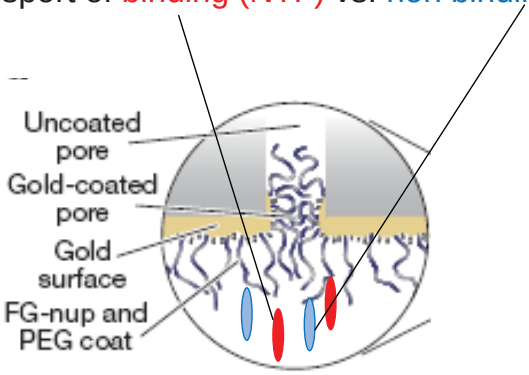
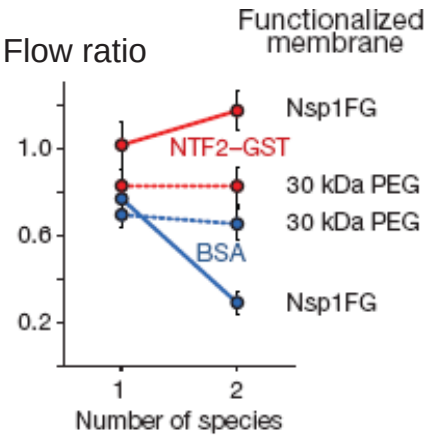
Results from experiments in artificial nuclear pores

Transport of binding (NTF) vs. non binding (BSA) cargo through pores





Modified from Jovanovic-Talisman et al., Nature 2009

- Binding may enhance transport
- Competition: the binding species is favored on cost of the non-binding

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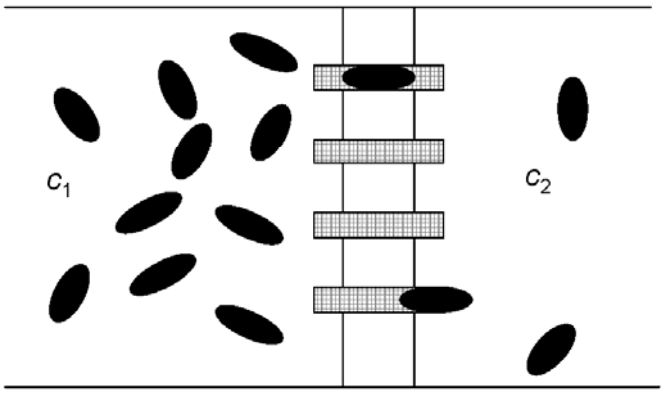
Channel may be occupied by only one particle (single occupation approximation = SO)

A simple approximation of the **inter**particle interaction in the channel



Bauer WR & Nadler W. PNAS, August 2006|Vol. 103|Issue 31|pp.11446-11451

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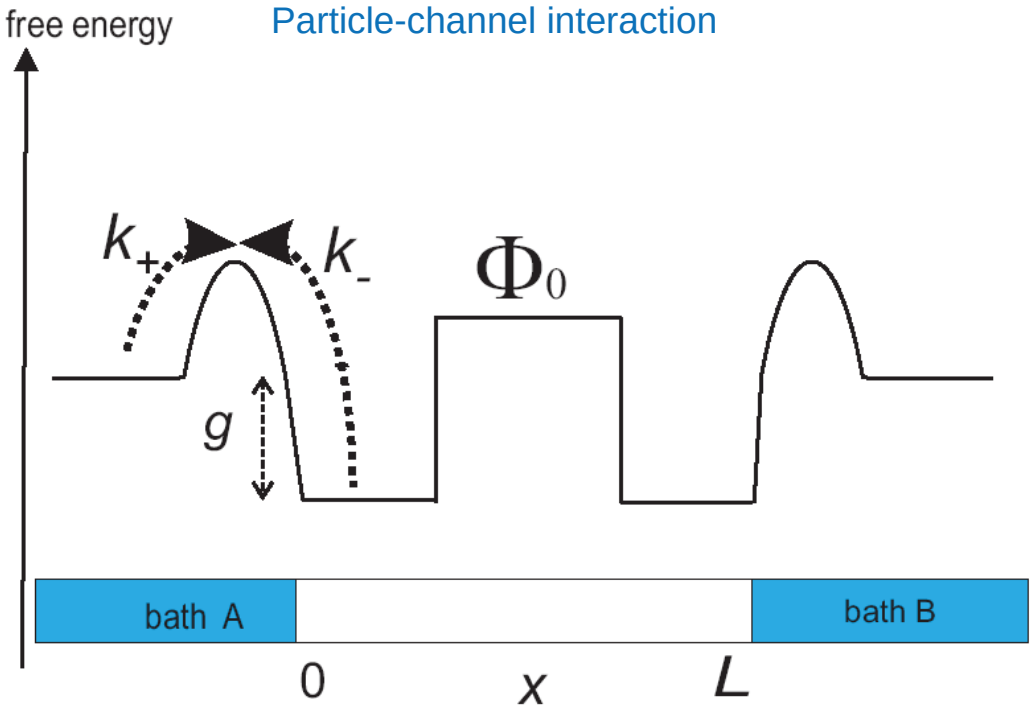
Free energy profile within the channel



Bauer WR & Nadler W. PlosOne, December 2010 | Volume 5 | Issue 12 | e15160

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How to obtain channel flow?

$$\partial_t \rho(x) = -\partial_x j_c(x)$$

$$j_c(x) = D(x)(\partial_x + \partial_x \Phi(x))\rho(x)$$ In the channel:Smoluchowski Eq.

Flows at the channel ends

$$j_{end,1} = k_+ c_1 - k_- \rho(0)$$

$$j_{end.2} = k_- \rho(L) - k_+ c_2$$

$$J \equiv j_c(x)$$

$$J \equiv j_{end,1}$$

$$J \equiv j_{end,2}$$

In the steady state: flow is constant

$$\int_0^L \rho(x)dx + P_0 = 1$$

P_0 Probability of an open channel

Conservation of probability

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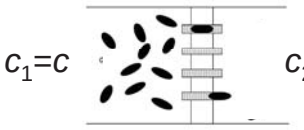
Unidirectional transport: bath A -> B



$$J = k_+ c \cdot P_0 \cdot p_{x=0 \to x=B}$$

$k_+ c$ Number of particles impinging to the channel entrance

P_0 Probability that channel (entrance) is empty

$p_{x=0 \to x=B}$ Conditional probability: particle at the channel entrance reaches the oppositely bath = translocation probability

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Unidirectional transport: bath A -> B in symmetric channel

$$J = k_+ c \cdot P_0 \cdot p_{x=0 \to x=B}$$

$$P_0 = \frac{1}{1 + \frac{cL}{2}\left\langle e^{-g-\Delta\Phi(x)} \right\rangle}$$

Decreases for: - high concentrations c
- strong binding

$$p_{x=0 \to x=B} = \frac{D}{k_+ L\left\langle e^{g+\Delta\Phi(x)} \right\rangle + 2D}$$

Increases with binding strength
Independent of concentration

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Unidirectional transport: bath A -> B in asymmetric channel

$$J = k_+ c \cdot P_0 \cdot p_{x=0 \to x=B}$$

$$P_0 = \frac{1}{1 + \frac{cL}{2}\left\langle e^{-g-\Delta\Phi(x)} \right\rangle \pm c\Delta n}$$

Asymmetry term

Translocation probability
- independent of permutations of Φ
- Characteristically for SO model

$$p_{x=0 \to x=B} = \frac{D}{k_+ L\left\langle e^{g+\Delta\Phi(x)} \right\rangle + 2D}$$

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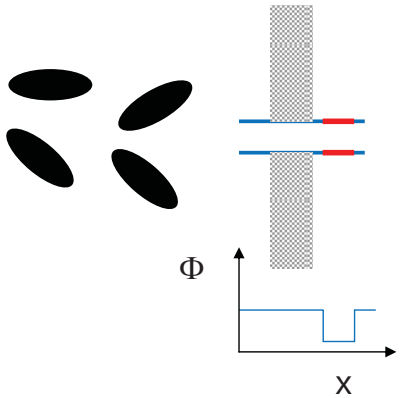
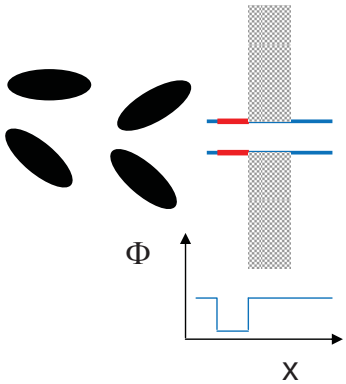
Asymmetry of flow in an asymmetric channel



Binding site in trans position



Binding site in cis position

Probability of an open channel $P_{0,T} > P_{0,C}$

Translocation $p_{translocation,T} = p_{translocation,C}$

Flow $J_T = k_+ c P_{0,T}\, p_{translocation} > J_C = k_+ c P_{0,C}\, p_{translocation}$

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- Importance of channel transport in biology: e.g. nuclear pores
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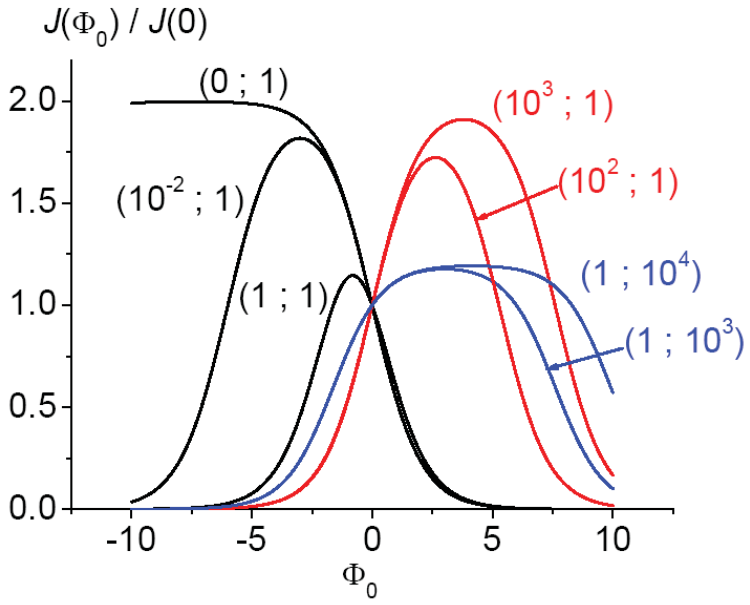
Maximal flow: tradeoff between “empty channel” and translocation

active concentration ; access time to channel

$$Lce^{-g}; \tau_e / \tau_0 = (1/k_+ c)/(L^2/2D)$$



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Which in-channel-interaction provides maximal flow?

Optimal interaction depends on concentration and access time

-the higher the concentration
-The slower access dynamics at the end

} the weaker must be the optimum binding site

Which conditions imply attractive / repulsive interactions for maximum channel flow?

$$\tfrac{1}{2}(Lce^{-g})^2\left(\tau_e/\tau_0\right)\begin{cases}<1 \rightarrow \Phi_{max}<0\\ =1 \rightarrow \Phi_{max}=0\\ >1 \rightarrow \Phi_{max}>0\end{cases}$$

Repulsive interaction

- Importance of channel transport in biology
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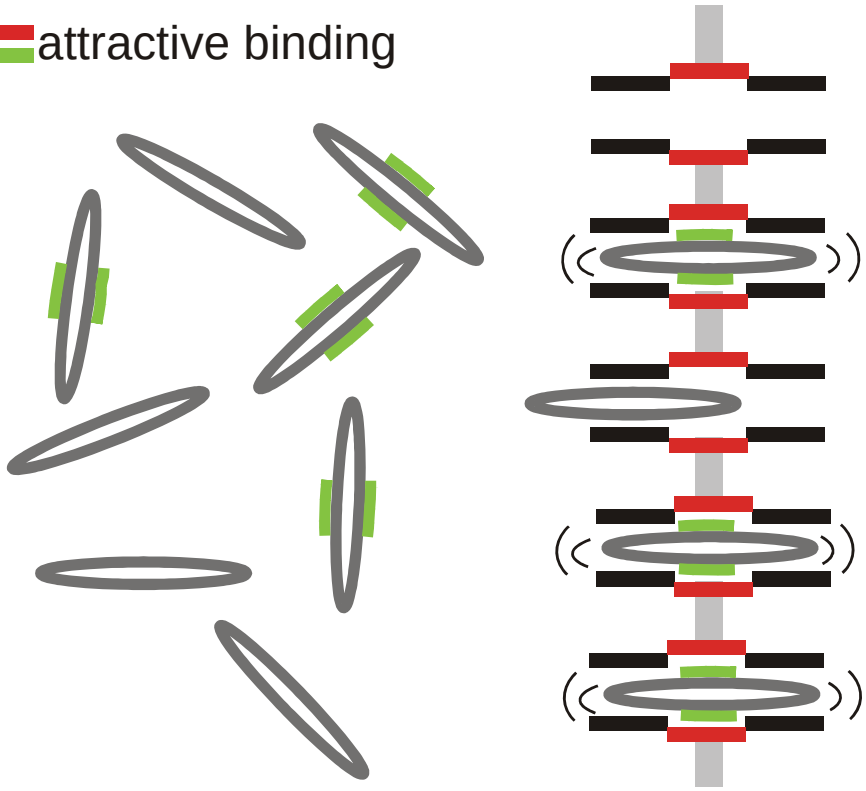
Competition of 2 species: binding and non-binding

attractive binding



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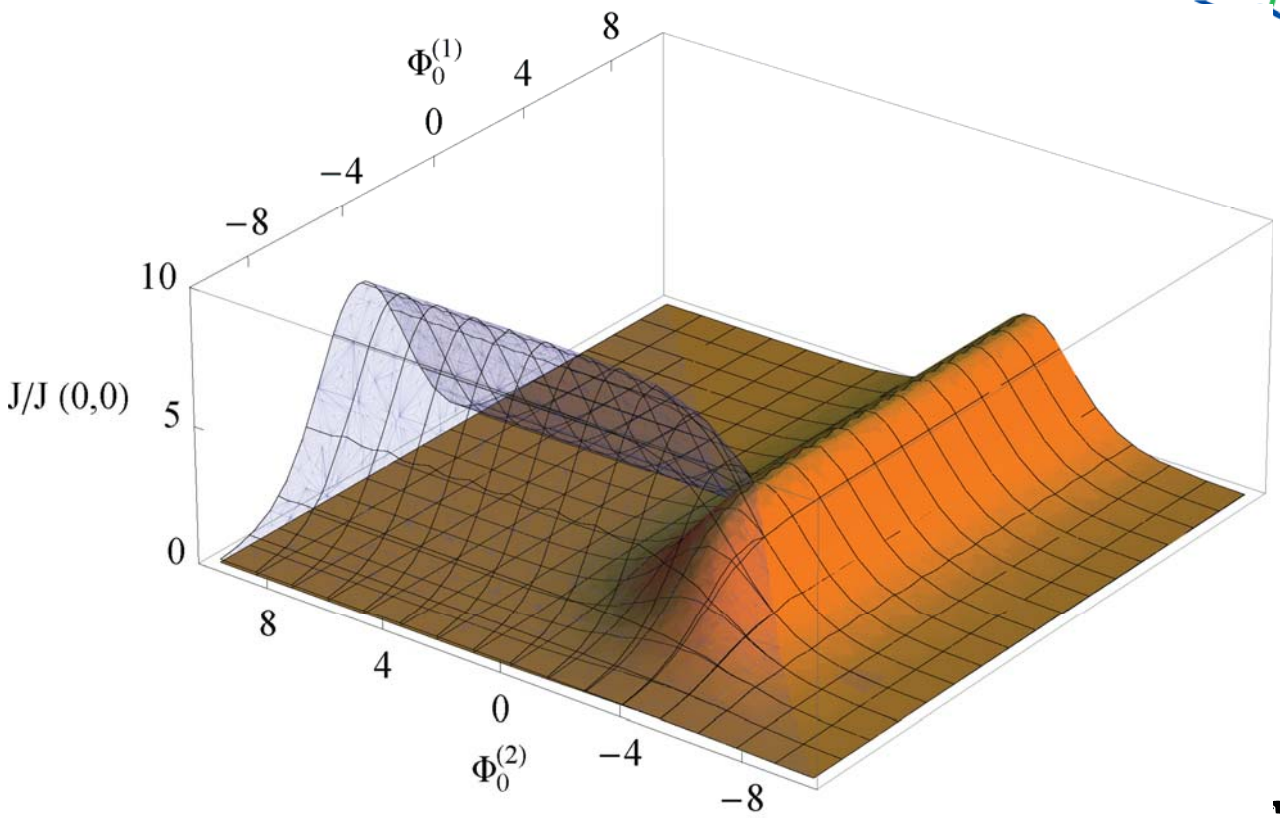
Blue (1) vs. Brown (2) ratio of concentrations 1:9



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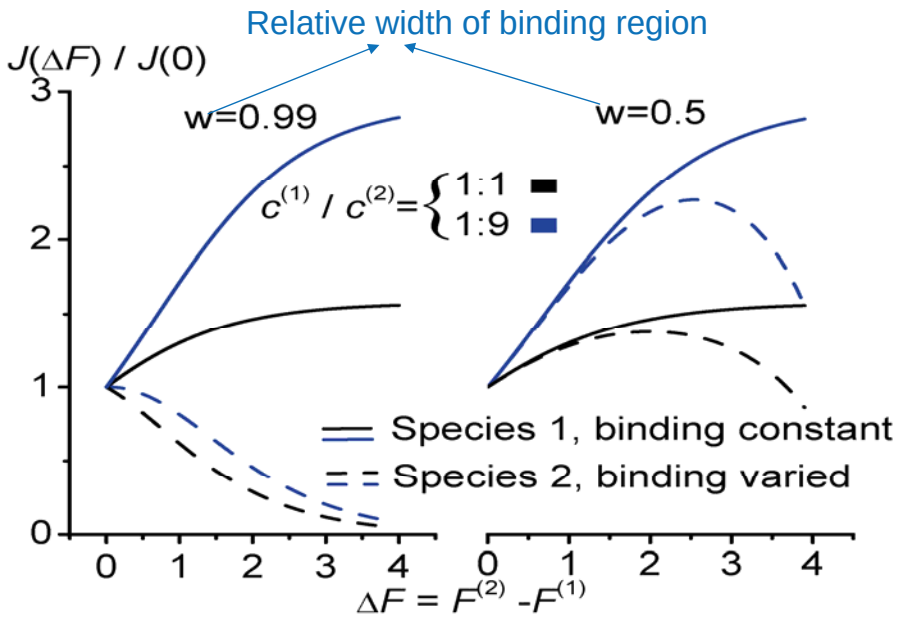
Decreasing binding strength of species 2 favors flow of binding species 1

Initial situation: same binding strength $F = -\ln\left\langle e^{-g-\Delta\Phi(x)}\right\rangle$ $F_1 = F_2 = -4$

Binding strength of species 2 is decreased, i.e. $\Delta F = F_2 - F_1$ increases



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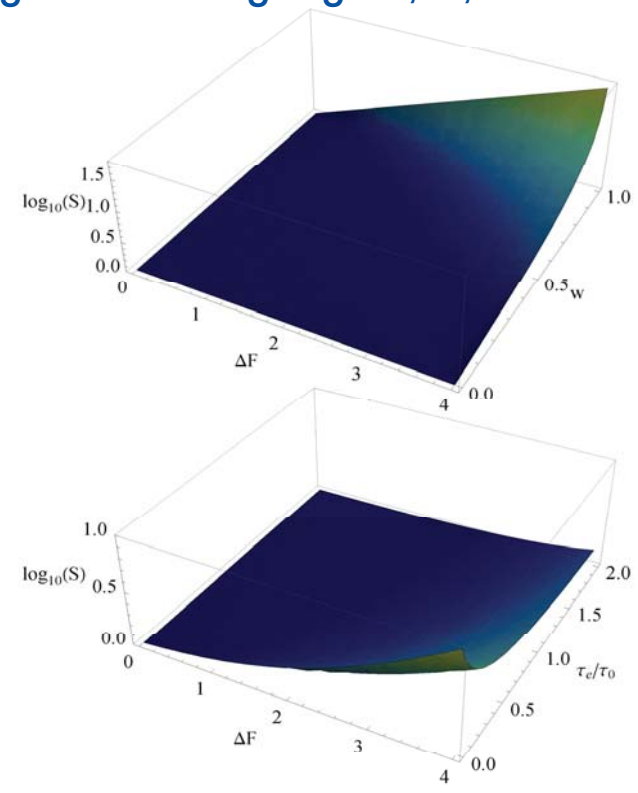
Selectivity of transport: influence of length of binding region, w, and access dynamics



$$S = \frac{J^{(1)}(\Delta F)/J^{(1)}(0)}{J^{(2)}(\Delta F)/J^{(2)}(0)}$$

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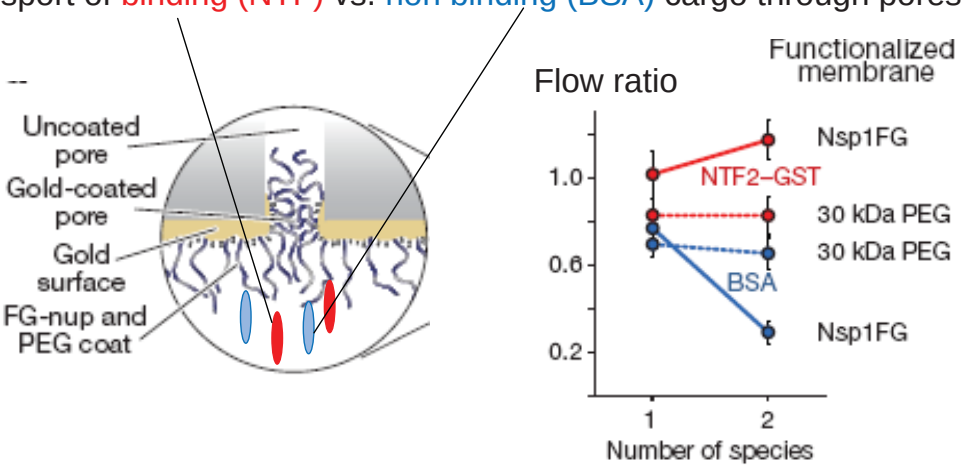
Competition in artificial nuclear pores

Transport of binding (NTF) vs. non binding (BSA) cargo through pores



Modified from Jovanovic-Talisman et al., Nature 2009

- Binding may enhance transport
- Competition: the binding species is favored on cost of the non-binding

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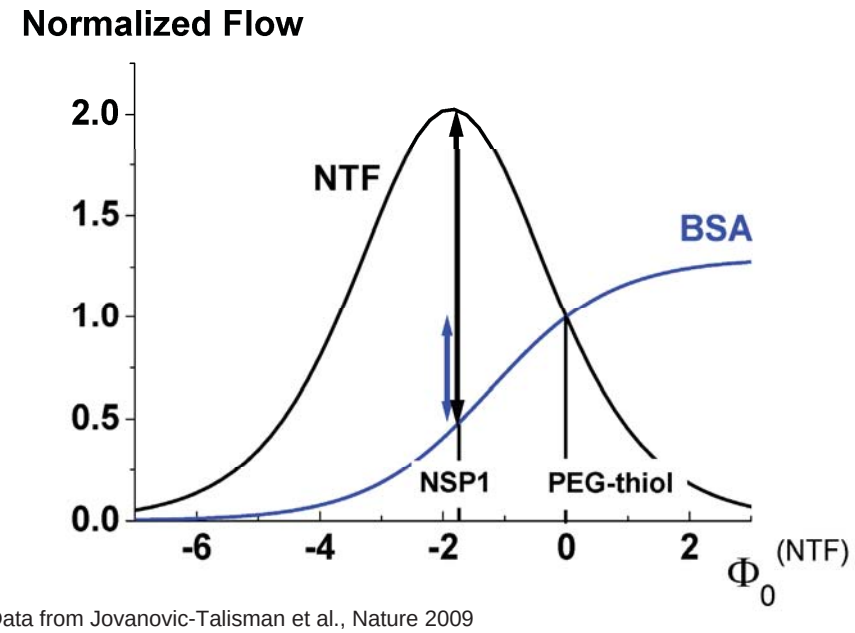
Comparison with experimental data

Species 1: Nuclear transport factor (**NTF**)
non-binding to PEG thiol channel
binding to nuclear porin channel (NSP1)

Species 2: Bovine serum albumin (**BSA**)
non-binding in any channel modification (PEG Thiol, nuclear porin NSP1)



Data from Jovanovic-Talisman et al., Nature 2009

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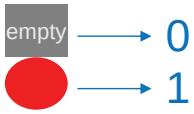
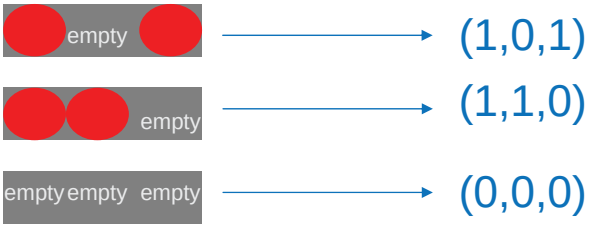
Outlook: more than one particle in the channel

Discretization of space in the channel, e.g. 3

state variable σ

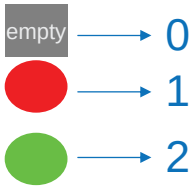
Single species





Binary code

Two species



Ternary code

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Dynamics of channel transport

Dimension of state space: $(m+1)^n$

m Number of species

n Spatial discretization of channel
=channel length /size of molecule

Markov dynamics between states

$$\sigma = (1,1,0,\ldots) \underset{\mu}{\overset{\lambda}{\rightleftharpoons}} \sigma' = (1,0,1,\ldots)$$

Rates: 0 if final spatial position in is occupied
otherwise dependent on channel particle interactions in respective states
(detailed balance)

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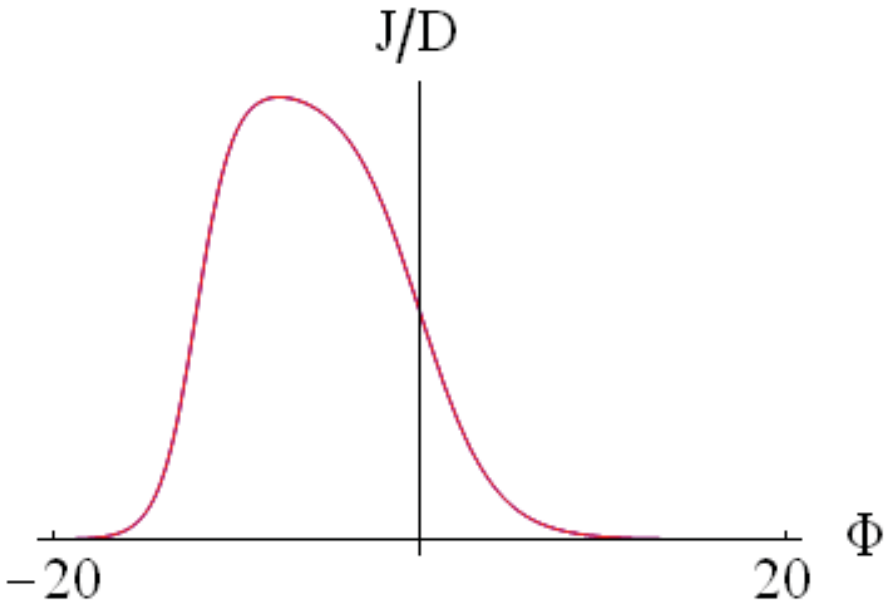
Comparison of models: dependence of flow on particle channel interaction

Concentration is varied: 10^{-5} -> 10^{2}

Single occupation approximation
Exact model with 3 spatial states



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- Single occupation approximation model
  - *is a generic analytical model for channel transport*
  - *employs relevant parameters*
  - *explains mechanisms how to optimize transport*
  - *gives insight how selectivity is achieved for different competing species*
- Single occupation model has its limitations
  - *in the high concentration limit*
- The exact description is future work

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Thank you!

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