# Unsolved problems in ion channel dynamics: Trajectories of escape from potential and entropic traps

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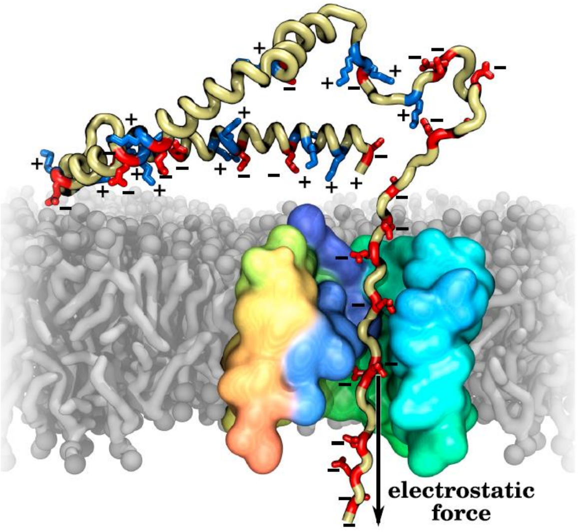
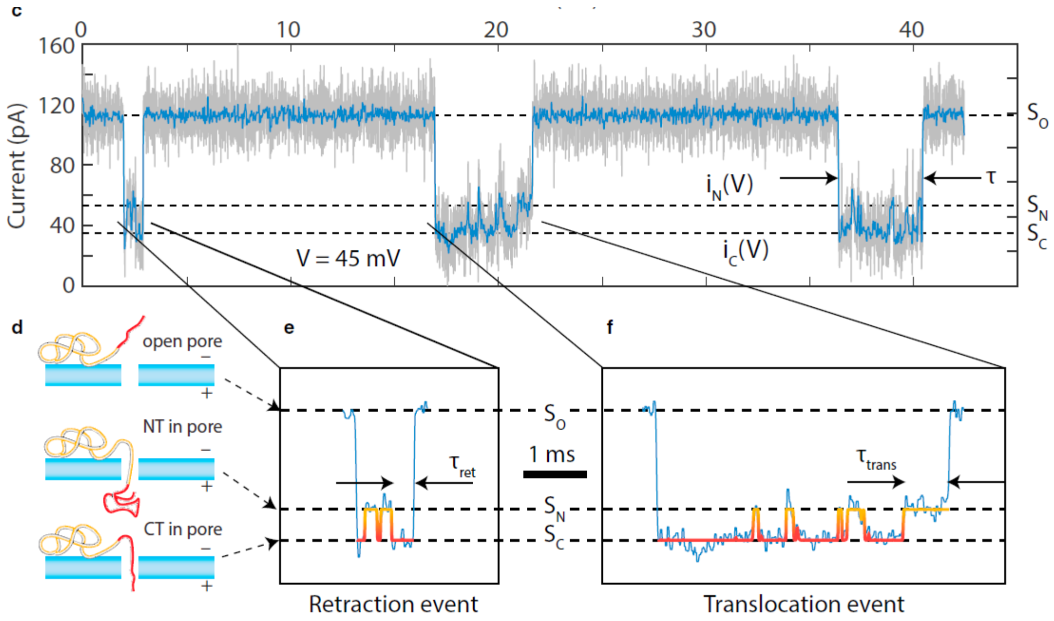
**Talk Outline:**

1. Why?
2. What?
3. Unsolved Problems

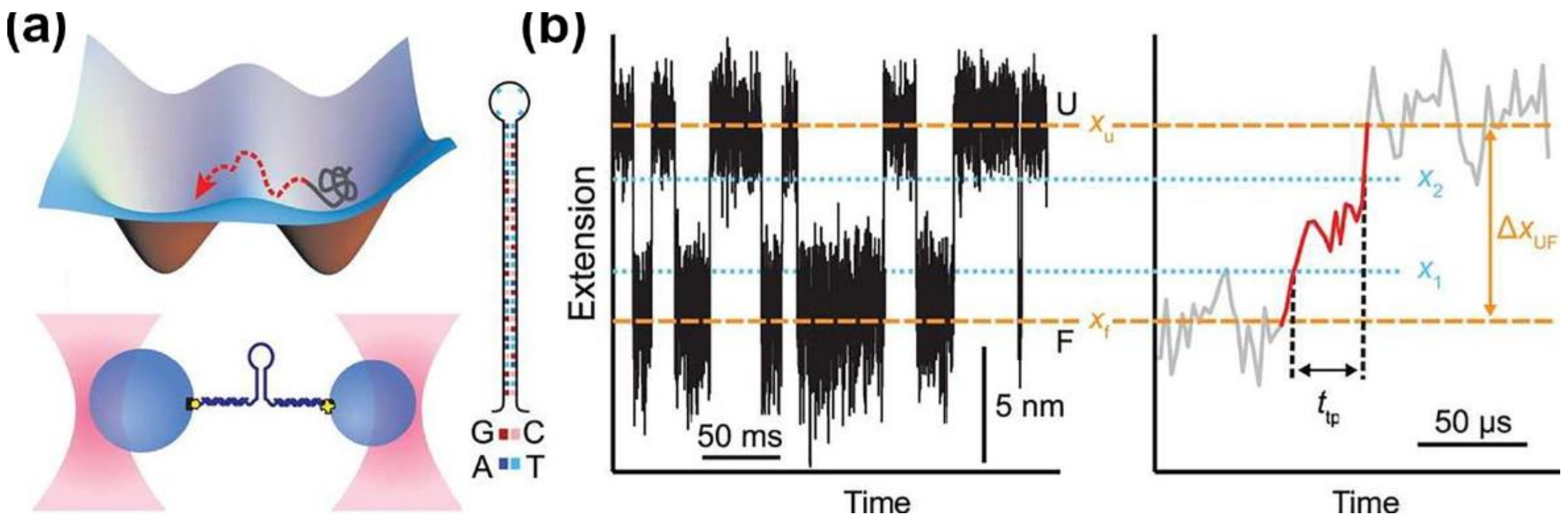
# <u>Motivation:</u> Single-molecule pore blockage by polymer



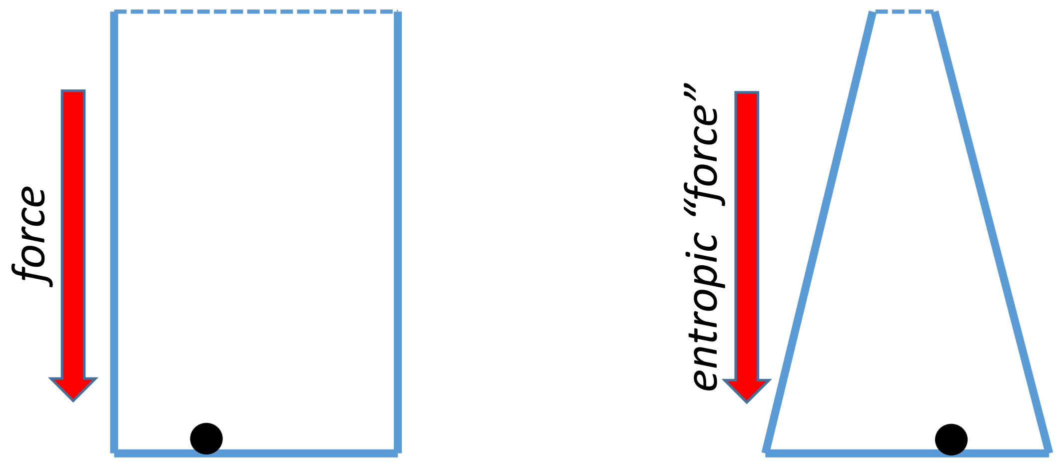

Hoogerheide, Gurnev, Rostovtseva, Bezrukov "Real-time nanopore-based recognition of protein translocation success", BJ 2018

# <u>Motivation:</u> Single-molecule pulling experiments




Chung “Transition path times measured by single-molecule spectroscopy”, JMB 2018
after Neupane, Foster, Dee, Yu, Wang, Woodside, 2016

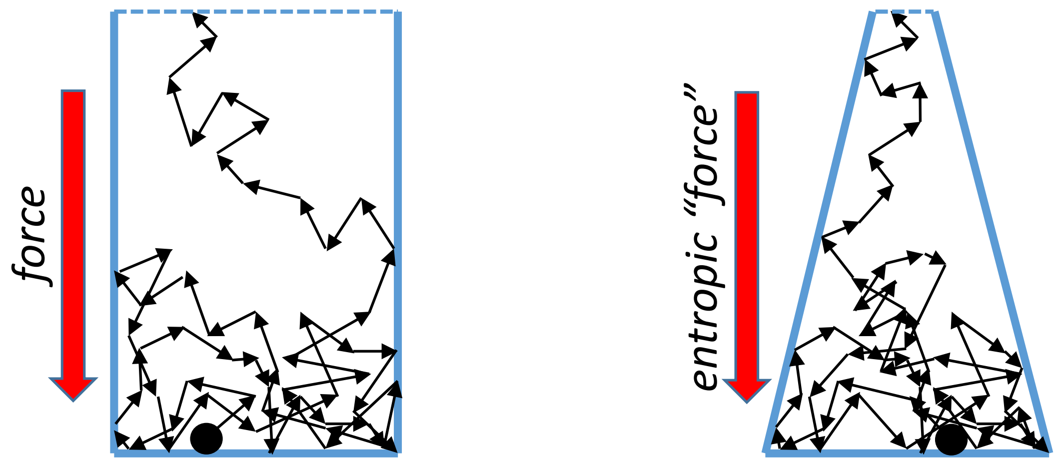
# <u>Model:</u> Escape of a Brownian particle from force-biased and entropic traps



# <u>Model:</u> Escape of a Brownian particle from force-biased and entropic traps

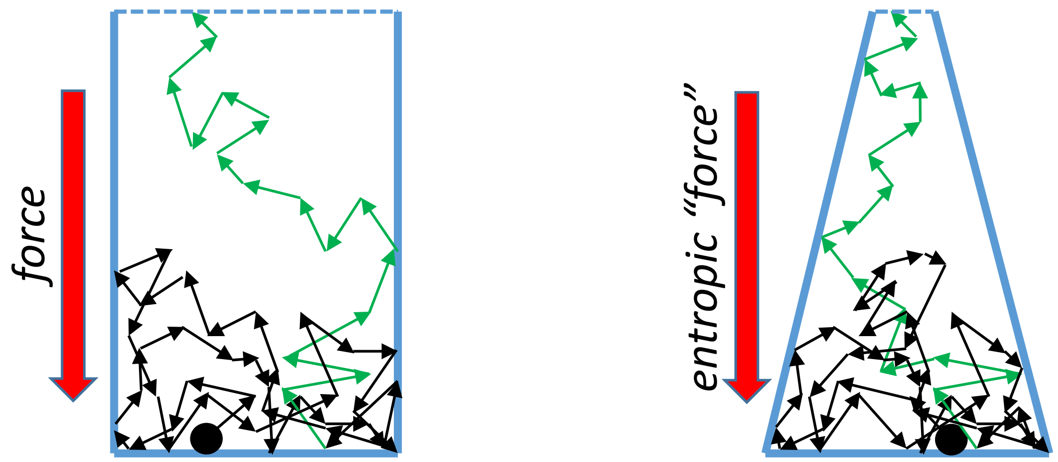
**We decided to analyze the "fine structure" of escape trajectories by dividing them into:**

## Looping and Direct Exit



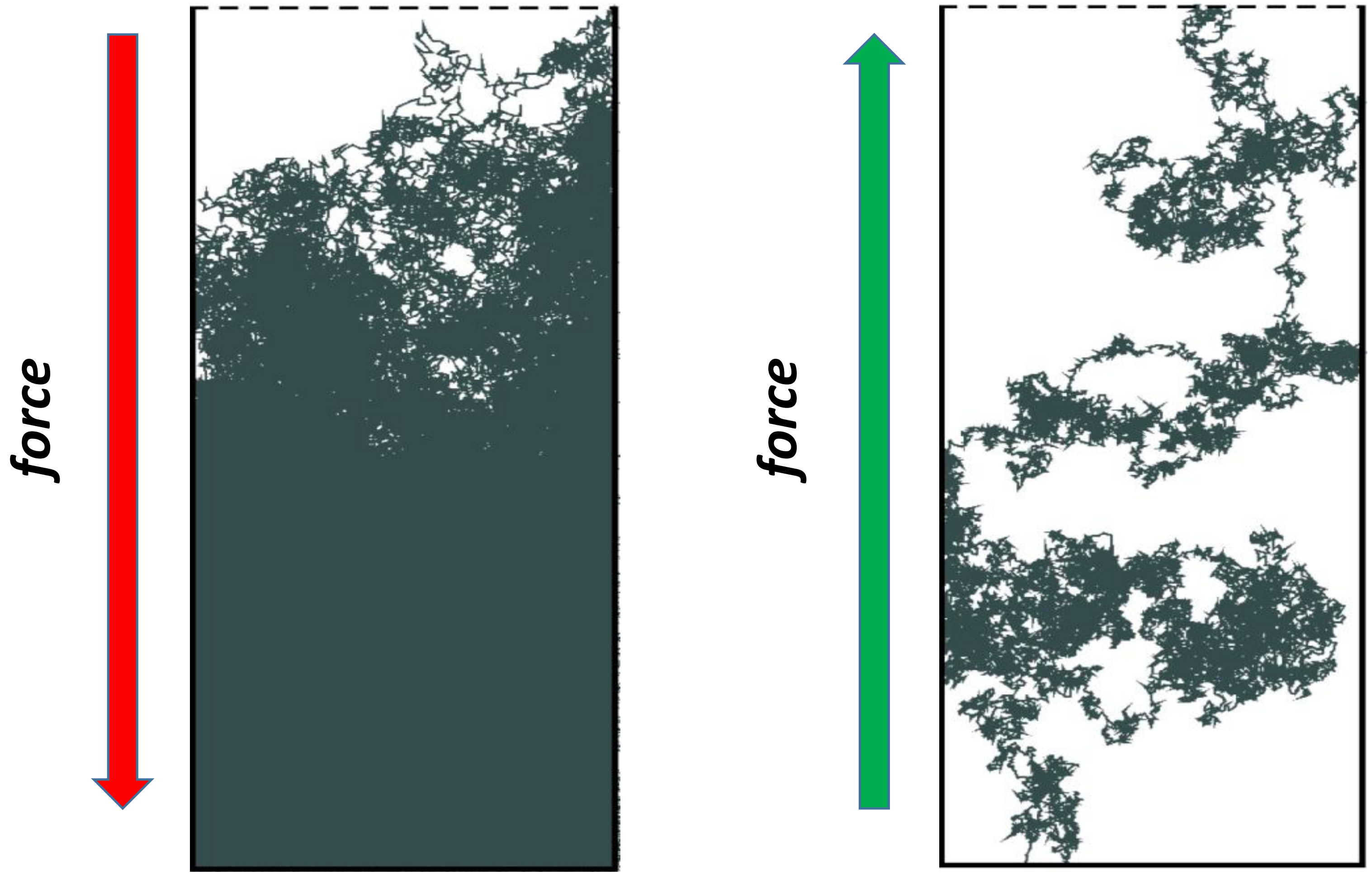
# <u>Model:</u> Escape of a Brownian particle from force-biased and entropic traps

## Looping and Direct Exit

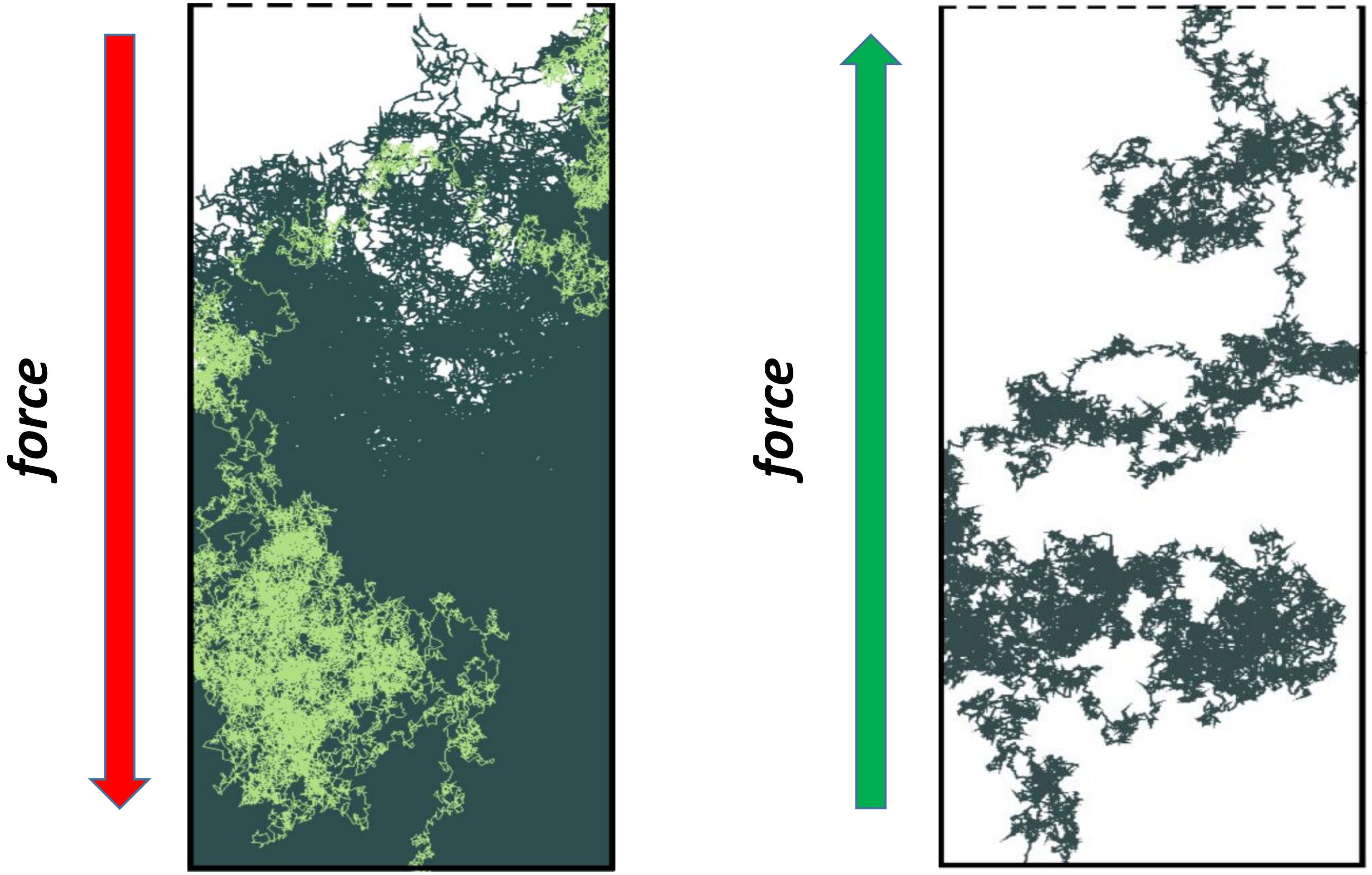



$$t_{FP} = t_l + t_{dtr}$$

# Simulations: Escape of a Brownian particle from force-biased traps



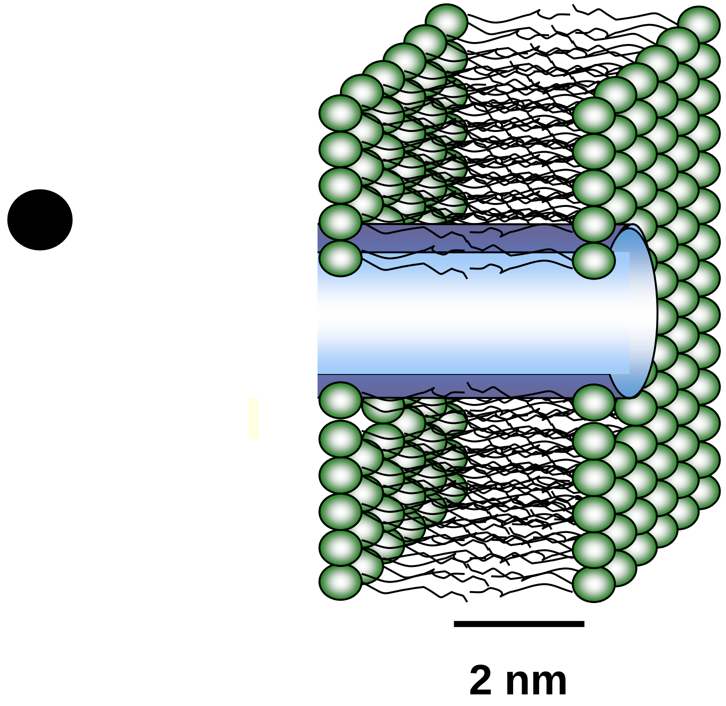
## <u>Simulations:</u> Escape of a Brownian particle from force-biased traps




$$t_{FP} = t_l + t_{dtr}$$

# Analytics: Channel-facilitated transport

Particle and Channel

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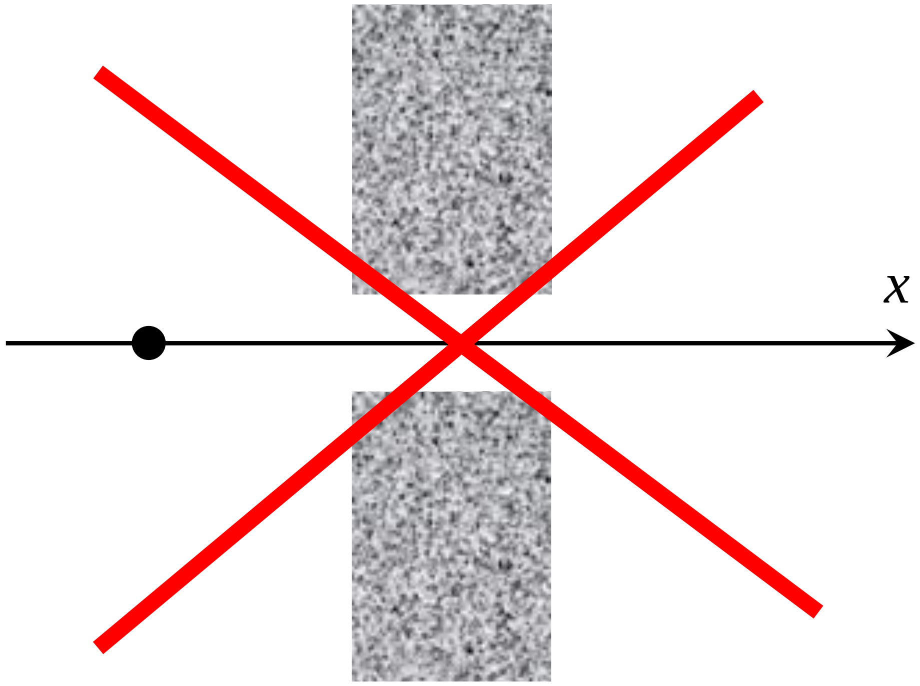
# **Analytics:** Channel-facilitated transport

It is tempting to start with the Smoluchowski equation

$$\frac{\partial p(x,t;x_0)}{\partial t} = \frac{\partial}{\partial x}\left\{D(x)e^{-\beta U(x)}\frac{\partial}{\partial x}\left[p(x,t;x_0)e^{\beta U(x)}\right]\right\}$$



# Analytics: Channel-facilitated transport

We **do** start with the Smoluchowski equation

$$\frac{\partial p(x,t;x_0)}{\partial t} = \frac{\partial}{\partial x}\left\{D(x)e^{-\beta U(x)}\frac{\partial}{\partial x}\left[p(x,t;x_0)e^{\beta U(x)}\right]\right\}$$

# <u>Analytics:</u> Escape of a Brownian particle from force-biased and entropic traps

$$\bar{t}\,(0 \to L) = \frac{\int_0^L \left(1 + \kappa_0 e^{-\beta U(0)} \int_0^x e^{\beta U(y)} \frac{dy}{D(y)}\right)\left(1 + \kappa_L e^{-\beta U(L)} \int_x^L e^{\beta U(y)} \frac{dy}{D(y)}\right) e^{-\beta U(x)} dx}{\kappa_0 e^{-\beta U(0)} + \kappa_L e^{-\beta U(L)} + \kappa_0 \kappa_L e^{-\beta(U(0)+U(L))} \int_0^L e^{\beta U(x)} \frac{dx}{D(x)}}$$

It is clear that the mean direct transit time (*dtr*) corresponds to the case of $\kappa_0, \kappa_L \to \infty$

$$\bar{t}_{dtr}(0 \to L) = \frac{\int_0^L \left(\int_0^x e^{\beta U(y)} \frac{dy}{D(y)}\right)\left(\int_x^L e^{\beta U(y)} \frac{dy}{D(y)}\right) e^{-\beta U(x)} dx}{\int_0^L e^{\beta U(x)} \frac{dx}{D(x)}}$$

# Analytics: Escape of a Brownian particle from force-biased and entropic traps

**Constant force:** $\beta U_{ent}(x) = Fx$ $\qquad$ $t_{FP} = t_l + t_{dtr}$

**Allows for simple algebraic expressions:**

$$\tilde{F} = \beta F L \qquad \langle t_{FP} \rangle = \frac{L^2}{D}\left(\tilde{F} - 1 + e^{-\tilde{F}}\right)\Big/\tilde{F}^2$$

$$\langle t_{dtr} \rangle = \frac{L^2}{2D}\left[\left(\tilde{F}/2\right)\coth\left(\tilde{F}/2\right) - 1\right]\Big/\left(\tilde{F}/2\right)^2$$

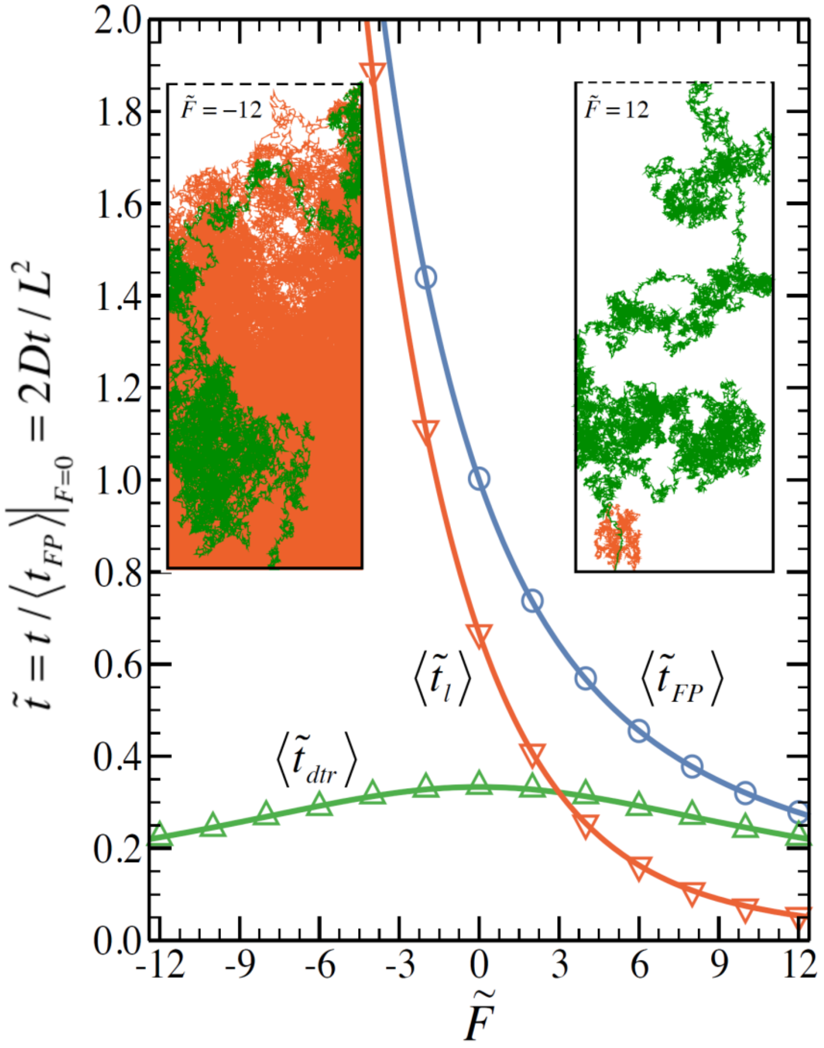
$$\langle t_l \rangle = \langle t_{FP} \rangle - \langle t_{dtr} \rangle$$

# Analytics vs. Brownian Dynamics: Escape of a particle from force-biased traps

$$t_{FP} = t_l + t_{dtr}$$

$$\langle t_{dtr}(0 \to L) \rangle \Big|_{|F| \to \infty} = L \Big/ \left( D\beta |F| \right) = L/v$$

$$\langle t_{dtr}(0 \to L) \rangle \Big|_{|F| \to 0} = \frac{1}{3} \langle t_{FP} \rangle = \frac{L^2}{6D_\lambda}$$

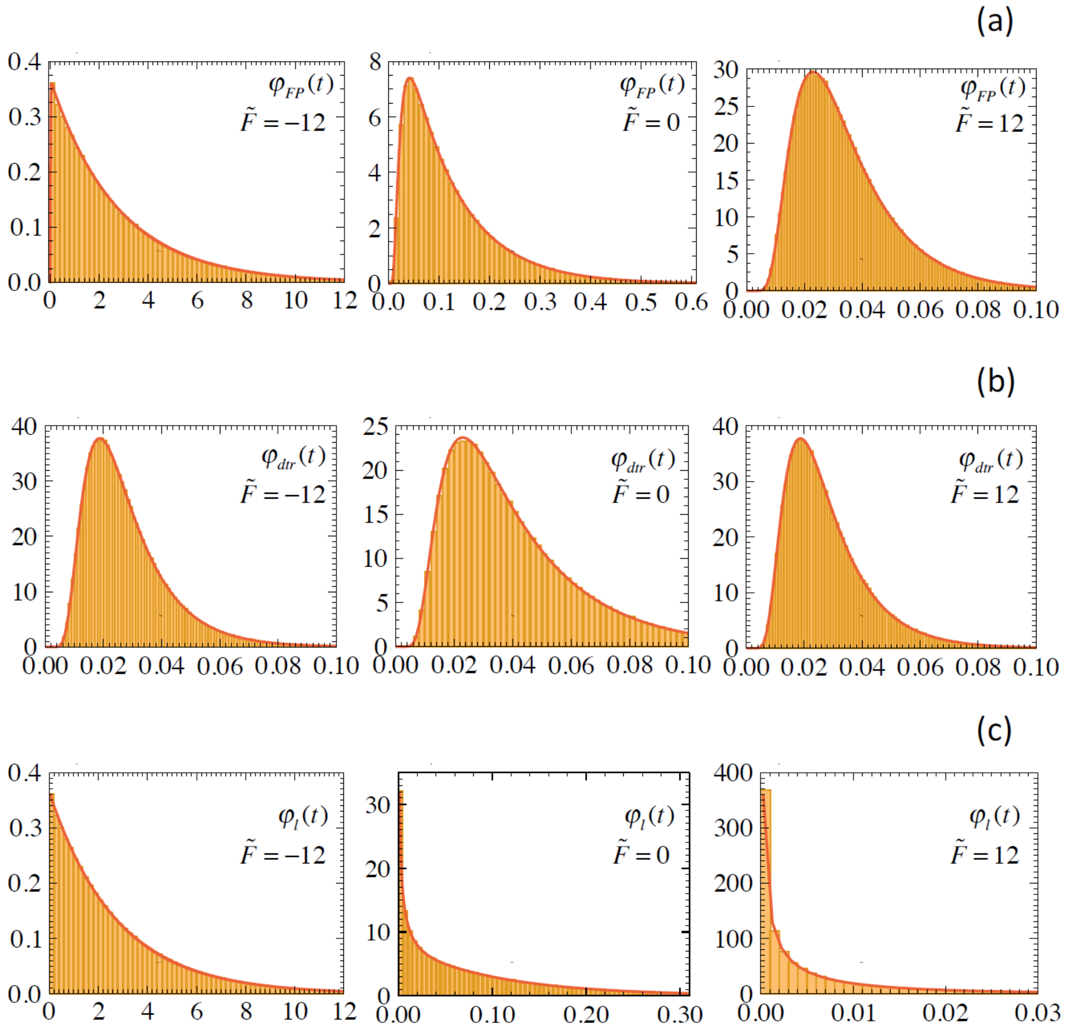


# Analytics vs. Brownian Dynamics: Escape of a particle from force-biased and traps

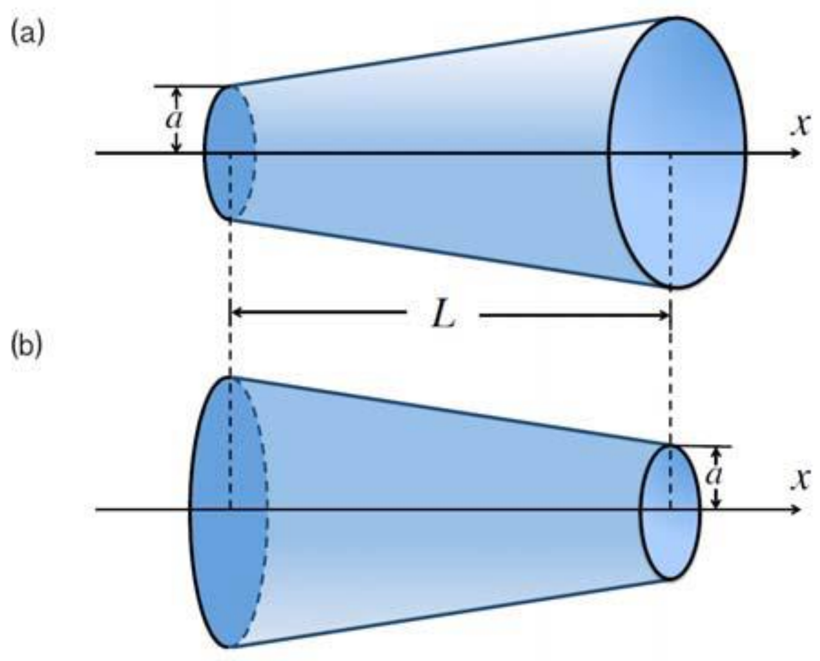
**First-Passage Time**

**Direct-Transit Time**

**Looping Time**



## **Analytics:** Escape of a Brownian particle from entropic traps

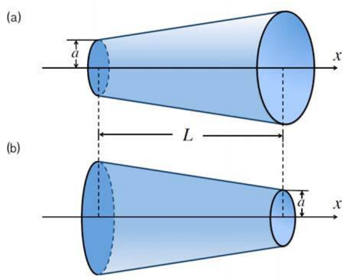



$$r(x) = a + \lambda x$$

$$A(x) = \pi r^2(x)$$

$$\beta U_{ent}(x) = -\ln\left(A(x)/A(0)\right) = -2\ln\left(r(x)/a\right) = -2\ln\left(1 + \lambda x/a\right)$$

# Analytics: Escape of a Brownian particle from entropic traps




$$\bar{t}_{dtr}(0 \to L) = \frac{\int_0^L \left( \int_0^x e^{\beta U(y)} \frac{dy}{D(y)} \right) \left( \int_x^L e^{\beta U(y)} \frac{dy}{D(y)} \right) e^{-\beta U(x)} dx}{\int_0^L e^{\beta U(x)} \frac{dx}{D(x)}}$$

$$\beta U_{ent}(x) = -\ln\left( A(x)/A(0) \right) \quad \Rightarrow$$

$$\bar{t}_{dtr}(0 \to L) = \frac{\int_0^L \left( \int_0^x \frac{dy}{D(y)A(y)} \right) \left( \int_x^L \frac{dy}{D(y)A(y)} \right) A(x)\, dx}{D_\lambda \int_0^L \frac{dy}{D(y)A(y)}}$$

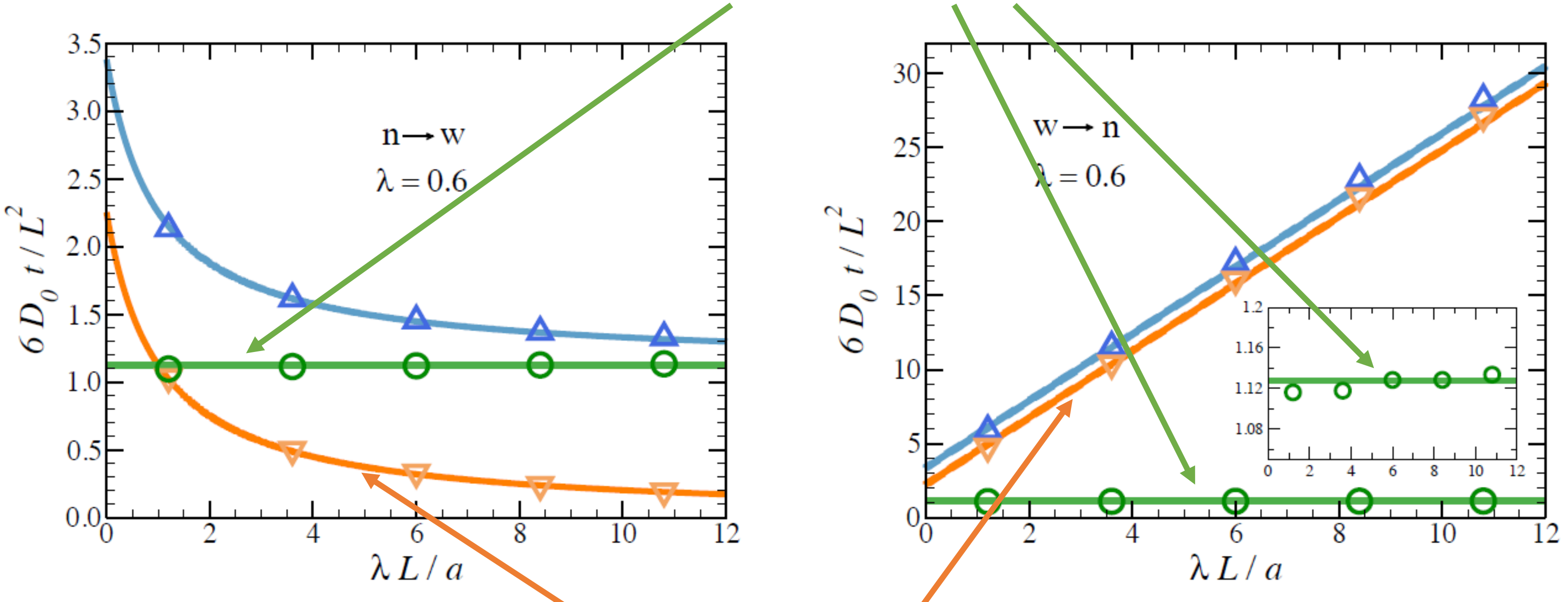
$$A(x) = \pi \left( a + \lambda x \right)^2 \quad \Rightarrow$$

$$\bar{t}_{dtr}(0 \to L) = \bar{t}_{dtr}(L \to 0) = \frac{L^2}{6D_\lambda}$$

!

# Analytics vs. Brownian Dynamics: Escape of a particle from entropic traps

Direct Transit



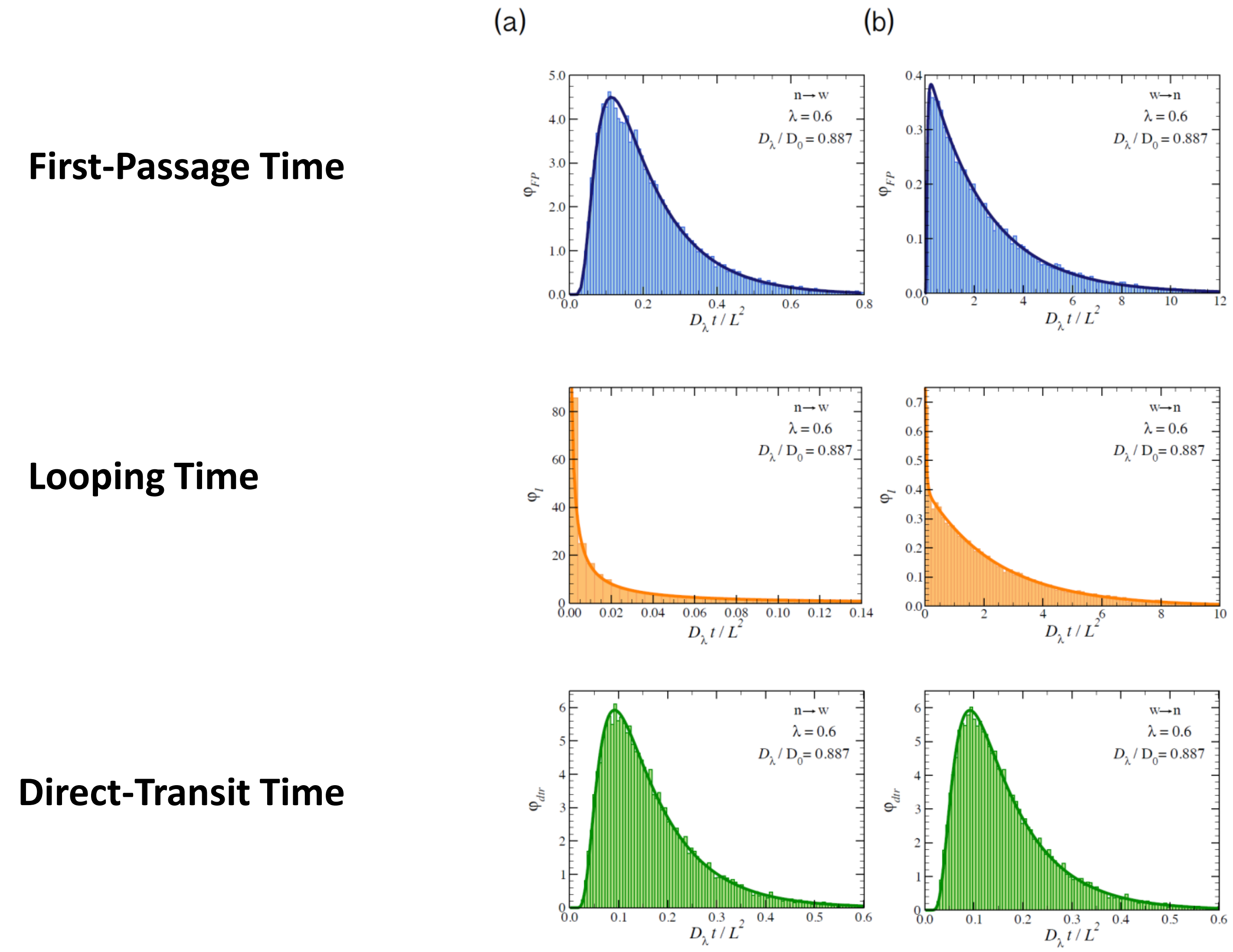

$$\bar{t}_{dtr}^{n\to w} = \bar{t}_{dtr}^{w\to n} = \frac{L^2}{6D_\lambda}$$

Looping

$$D_\lambda = \frac{D_0}{\sqrt{1+\lambda^2}}, \quad \lambda \equiv \frac{dR(x)}{dx}$$

D Reguera and JM Rubi, 2001

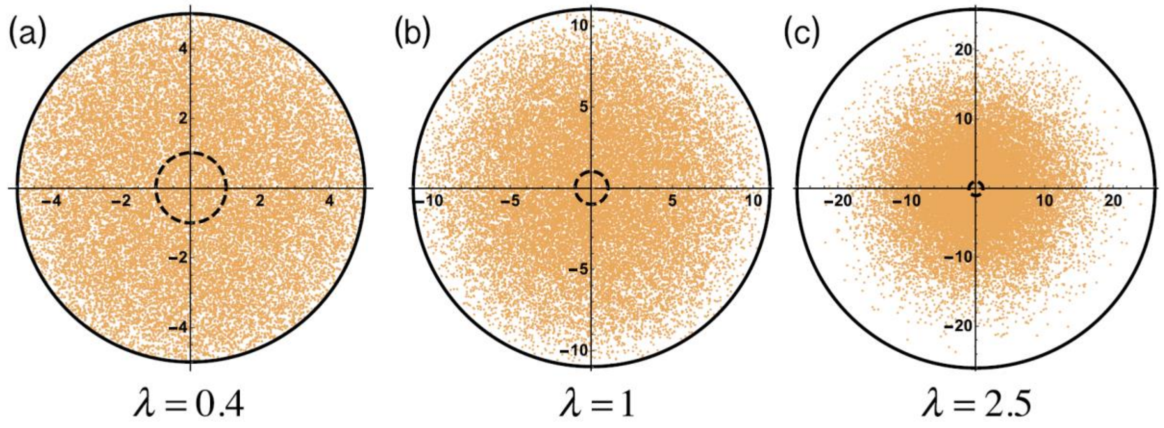
# Analytics vs. Brownian Dynamics: Escape of a particle from entropic traps



# Conclusions:

Exploration of the "fine structure" of escape trajectories by dividing them into the looping and direct-transit segments leads to the following findings:

I. Mean looping time is sensitive to both direction and magnitude of the applied (or entropic) force;
II. Mean direct-transit time, in case of *bona fide* applied force is sensitive to its magnitude, but not its direction;
III. Mean direct-transit time, in case of "entropic force" of a 3D cone is not sensitive to the force at all.



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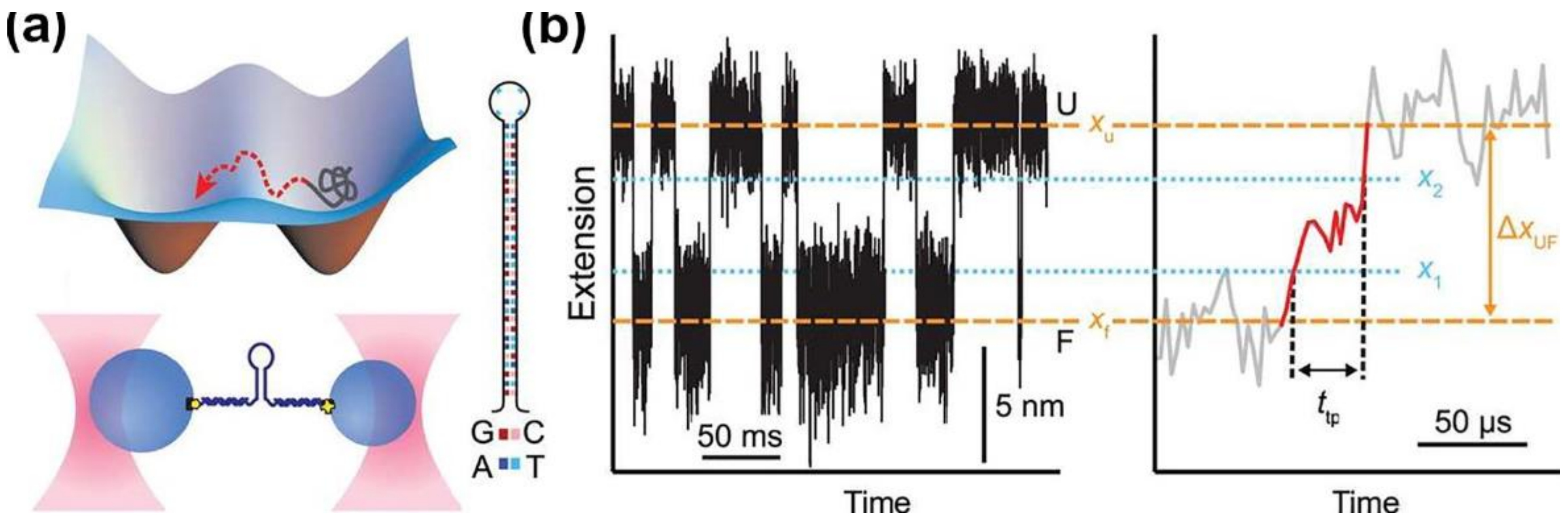
**Why bother?**

## Why bother:

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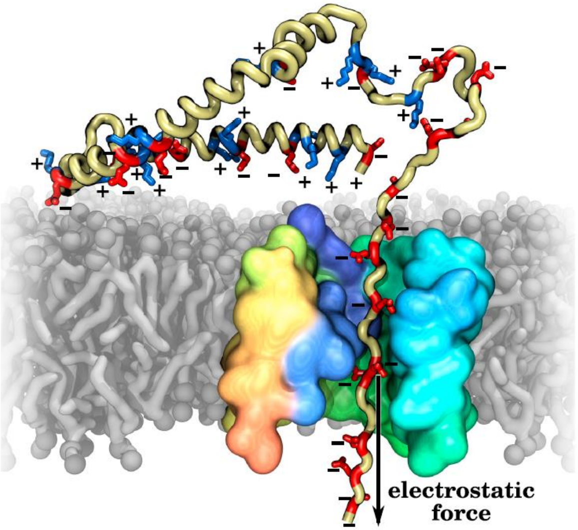


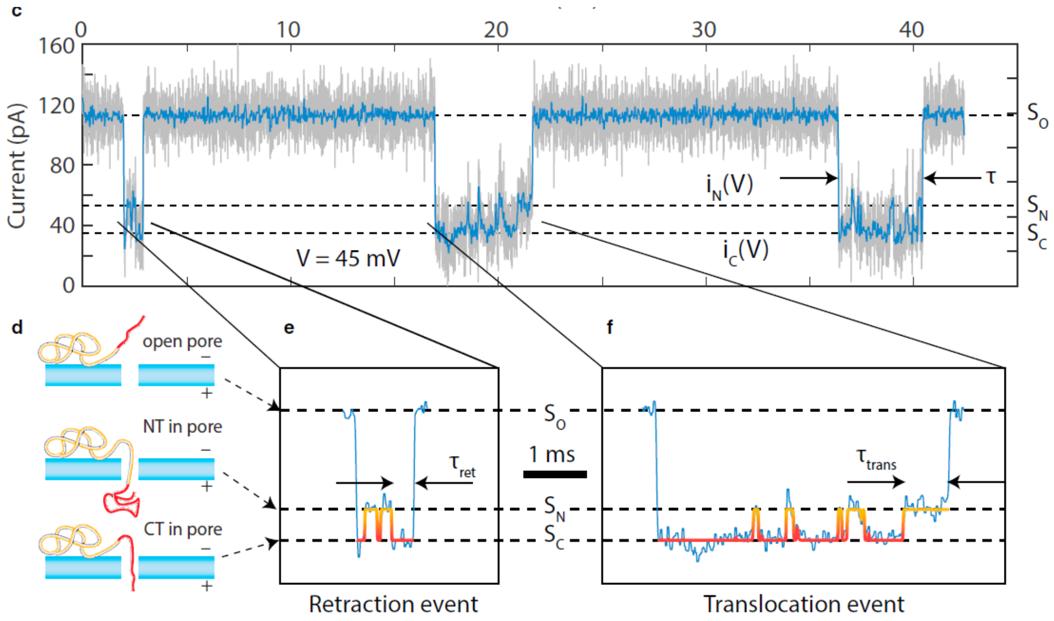


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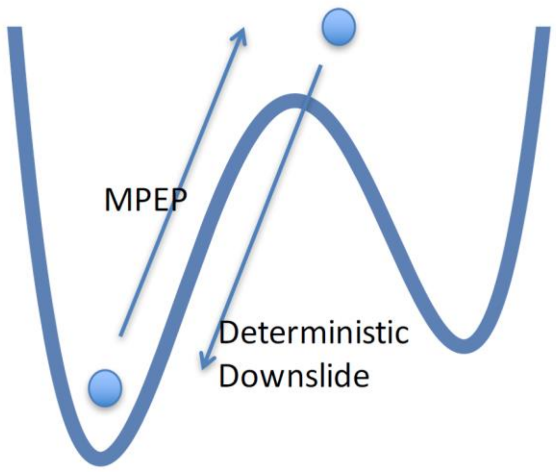
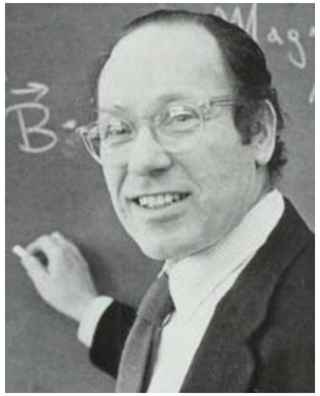
# Old news?




The Most Probable Escape Path (MPEP) over the barrier is the reverse of the Deterministic Downslide

The MPEP is driven by many consequent properly oriented Brownian kicks

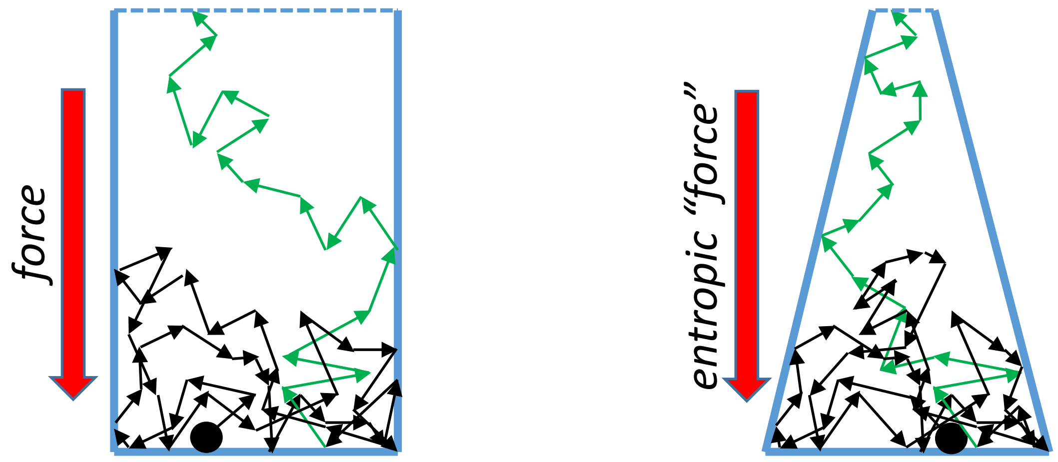
Lars Onsager and Stefan Machlup, *Phys. Rev.*, 1953



And, later, explored by many other fine scientists in terms of “optimal path”, “anomalous (giant) fluctuation”, etc.:
PVE McClintock, MI Dykman, P Hanggi, M Shlesinger, R Mannella, NG Stocks, DG Luchinsky, M Bier, W Eaton, G Hummer, R Elber, E Vanden-Eijnden, DE Makarov …

# Escape of a Brownian particle from force-biased and entropic traps

## Looping and Direct Exit




**Our approach provides general analytic results, very often in the form of simple algebraic expressions, which allow for critical evaluation of different free energy components, leading to unexpected conclusions and new (unsolved) problems**

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