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First passage times reveal underlying free energy landscapes

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Outline

1. Motivation: Biological membrane transport
2. Experiments: Colloidal model channel system with controlled potential landscapes
3. First passage time distributions in a colloidal system
4. First passage time distributions in molecular systems

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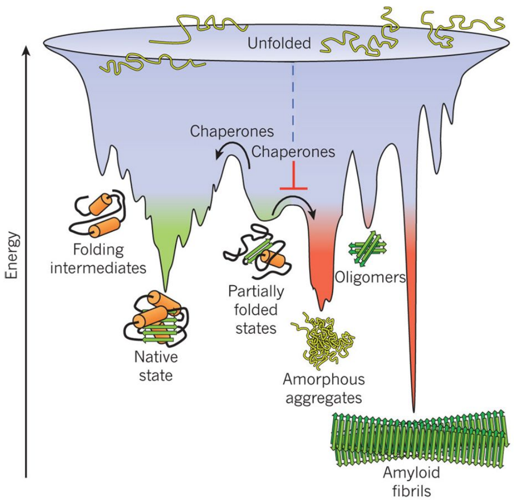
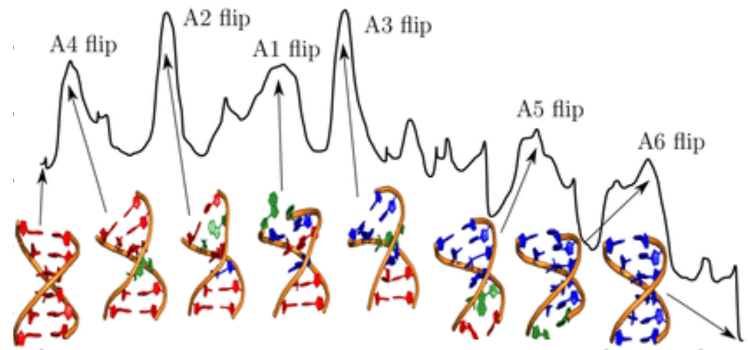
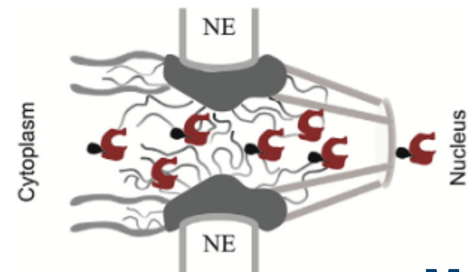
Free-energy landscapes govern biological phenomena

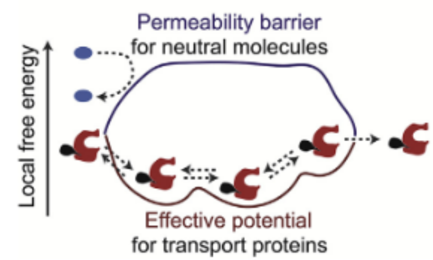




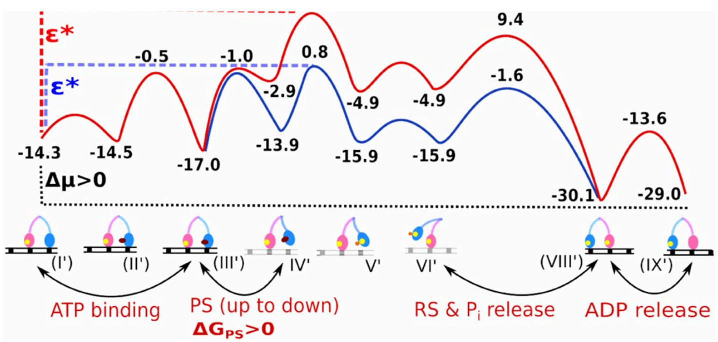
Protein/DNA/RNA folding



Membrane transport

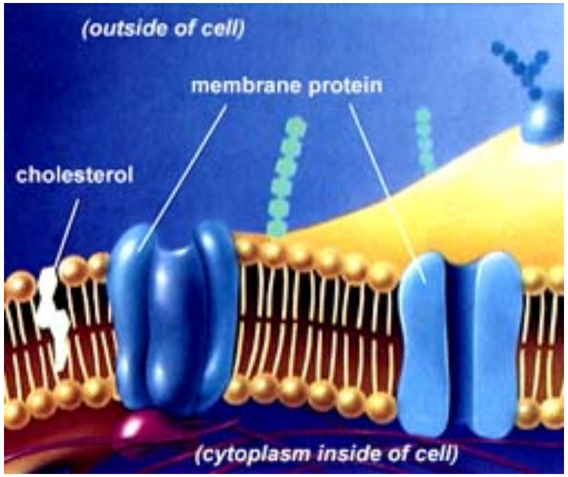


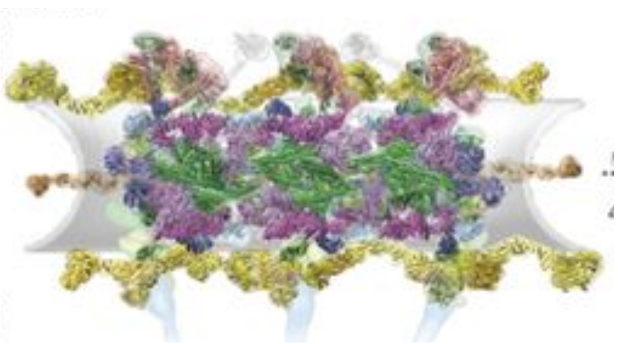
Molecular motors



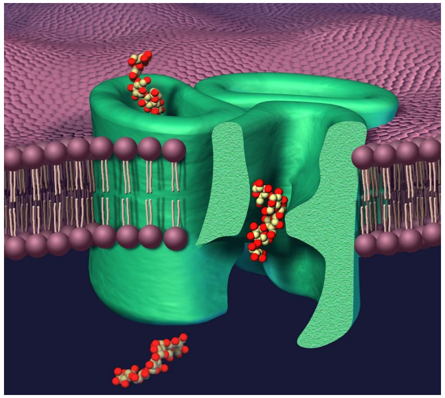
Example: Biological membrane transport

- Efficient and selective transport through a variety of pores and channels





Nuclear pore complex
~150 nm



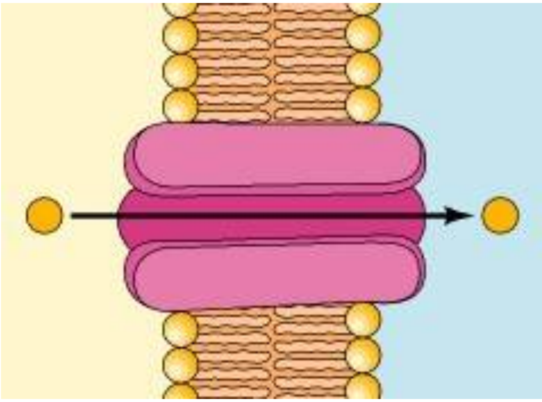
Maltoporin
~5 nm

- Mechanism of selective transport: size, shape, specific binding…?

Pictures adapted from Pietzsch, *Nature* (2004), Kim et al. *Nature* (2018) , *Chemistry World* (Nov 2003),

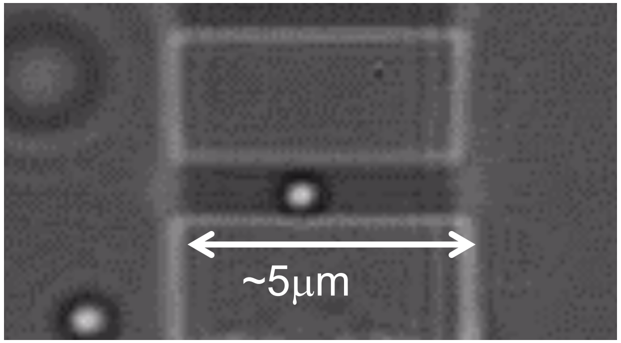
Our experimental model for membrane transport

Biological channels



Length scales~nm
Timescales~ ns

Microscale
Colloidal model channel



Length scales~μm
Timescales~ s

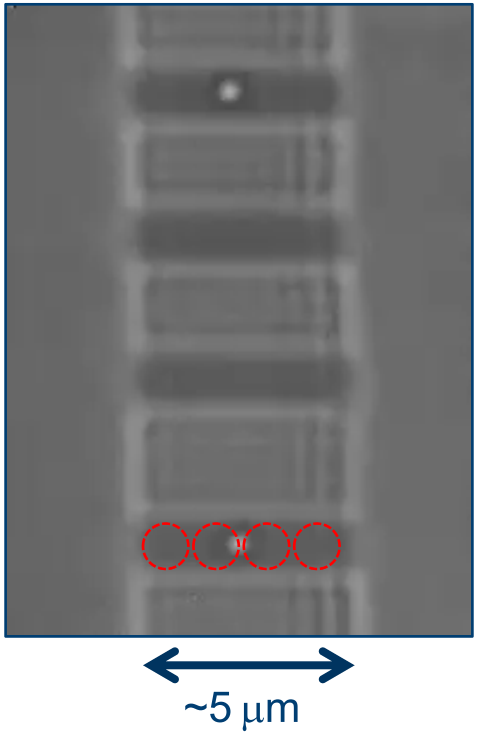
Molecular systems are difficult to visualise and directly manipulate…

…so consider a colloidal model system that is more experimentally accessible

Colloidal system offers full control over all key parameters

Experimental approach: colloids + microfluidics + optical tweezers

- Controlled channel **structure**
- Controlled **interactions**
- Resolved transport **dynamics**



→ Explore links between structure/interactions and dynamics

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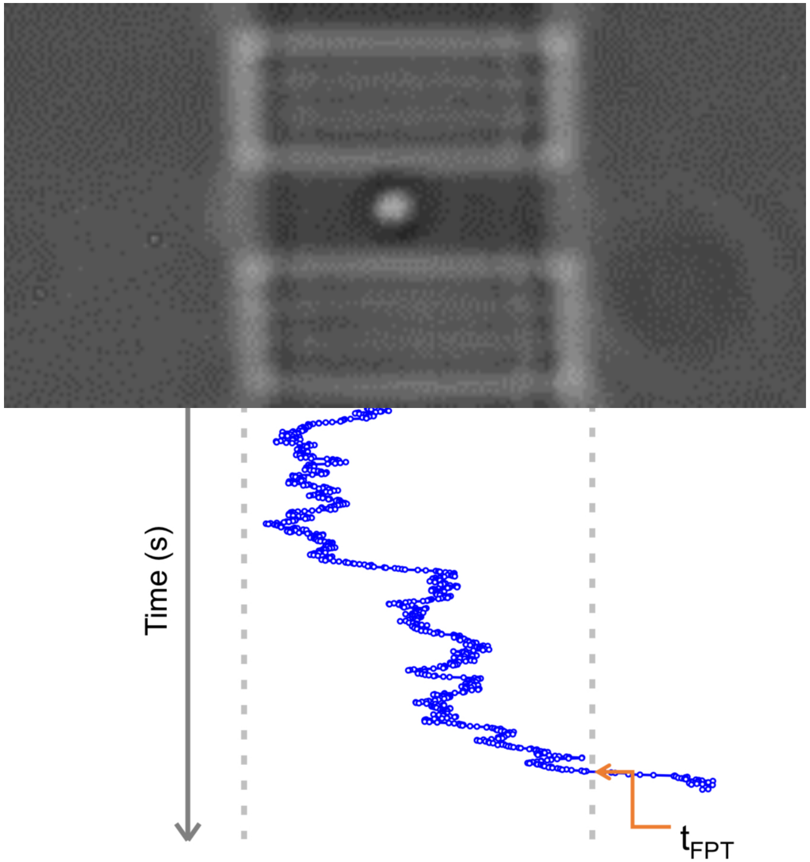
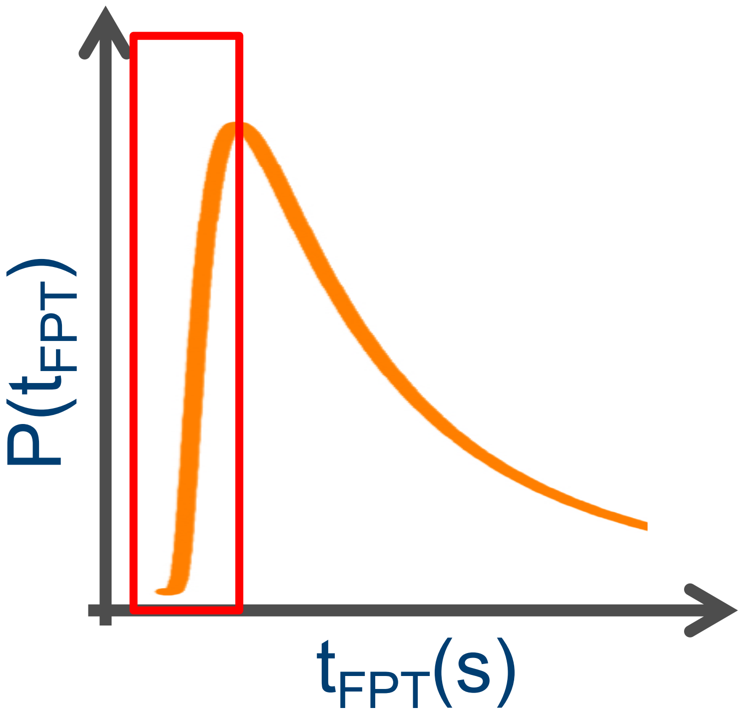
First passage times are easy to observe with colloids



- **First passage time** = time it takes for a process to attain a certain value *for the first time* i.e. how long does it take a particle to exit a channel

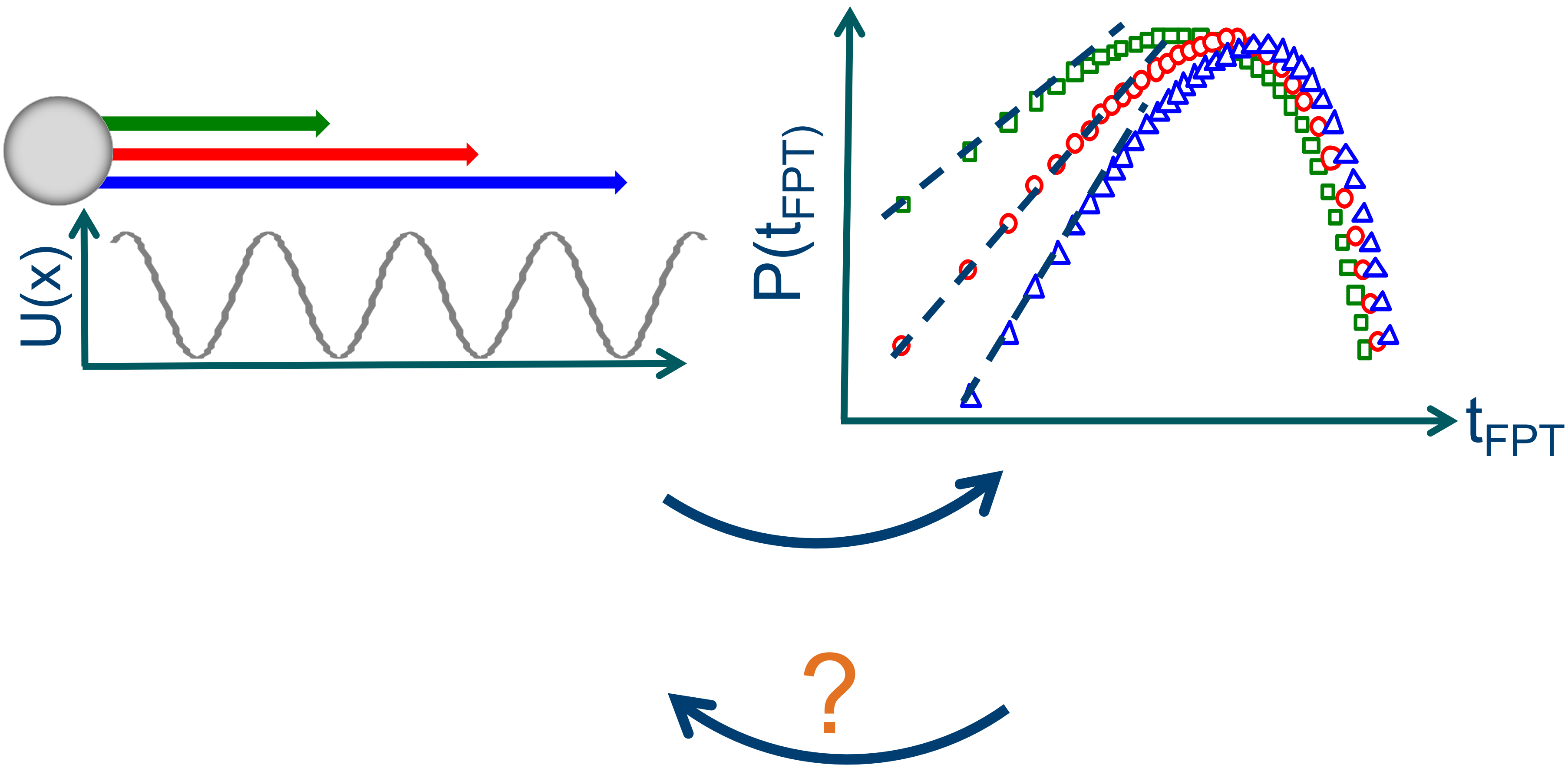
Full first passage time distributions can be measured



Probability distribution of first passage times, $P(t_{FPT})$ = probability an event will happen for the first time after a certain elapsed time

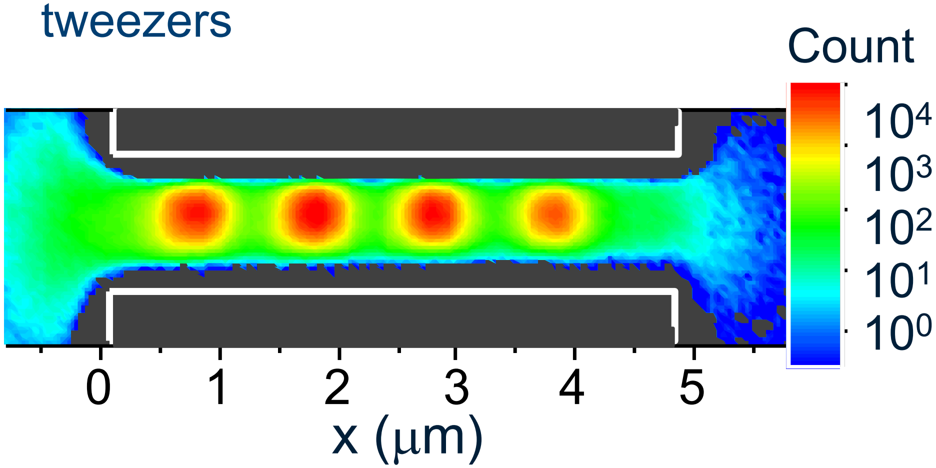
Crucially,
$P(t_{FPT})$ sensitively linked to underlying free energy landscape

Does the shape of the first passage time distribution reveal details of the potential landscape?

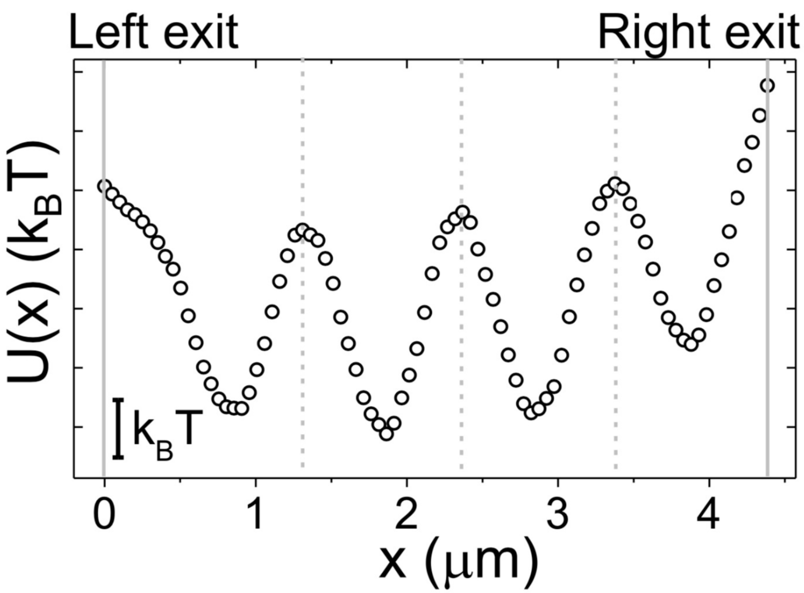


Model channel system with four states

Potential landscapes with multiple minima imposed with optical tweezers



2D histogram of particle positions

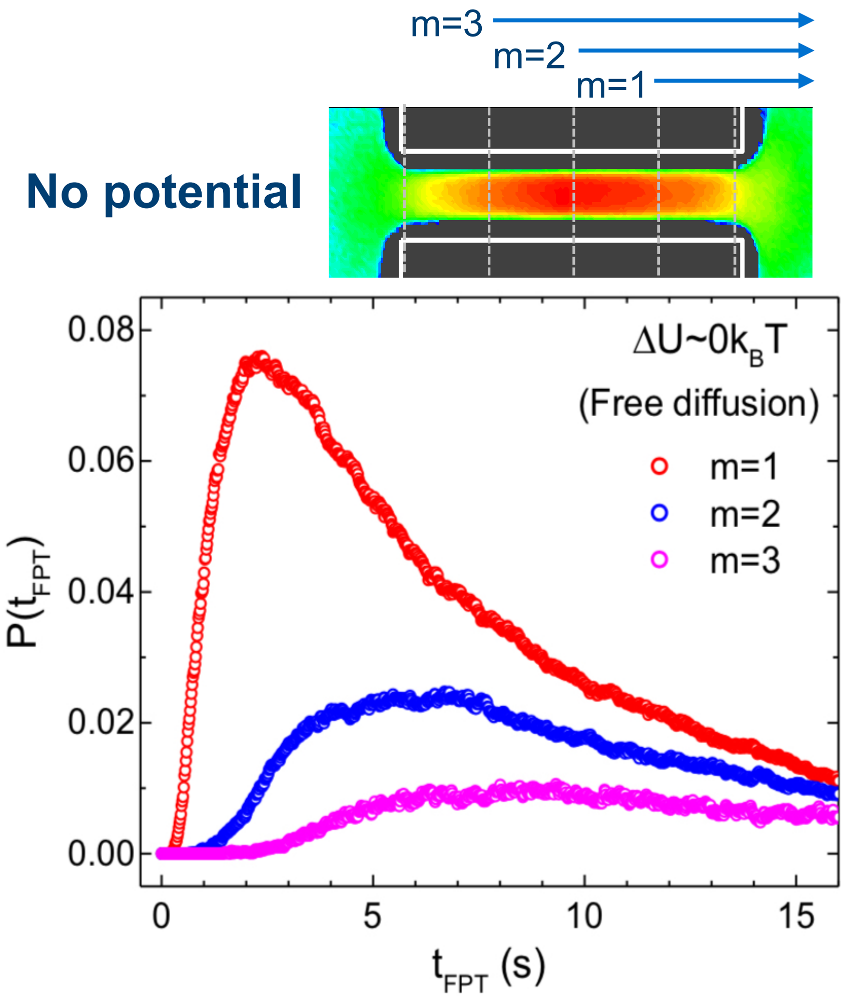


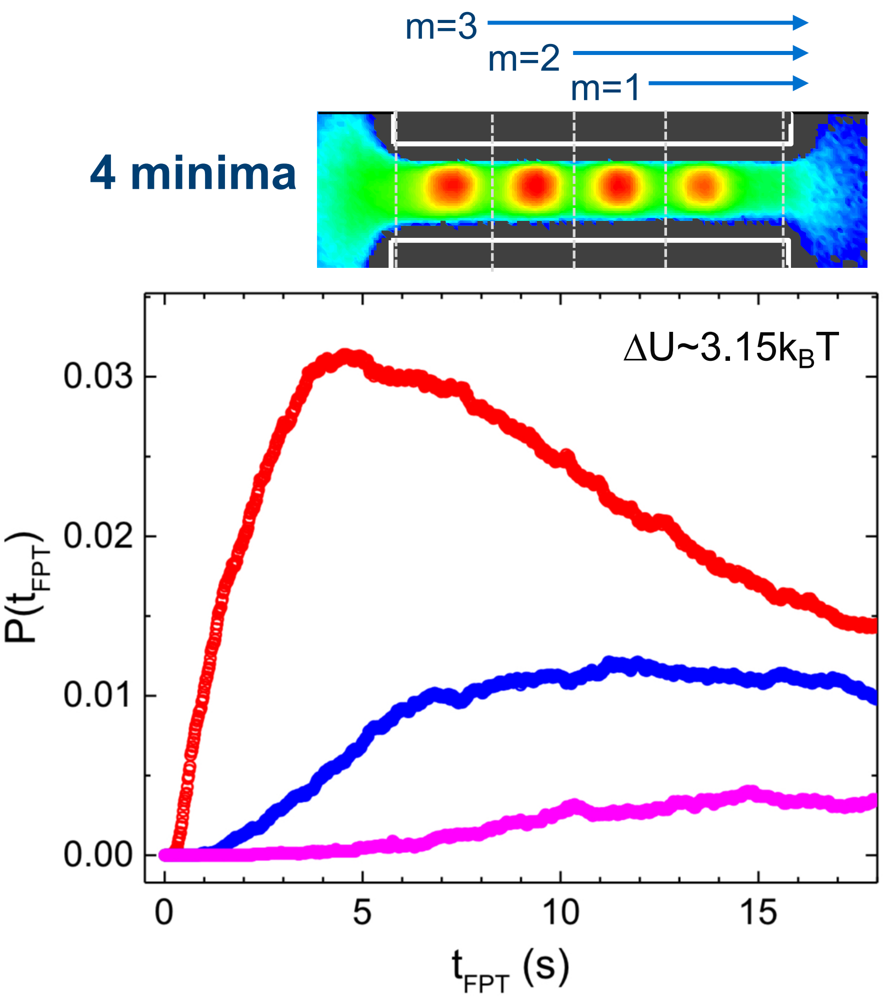
Potential landscape,

$$U(x) \sim -\ln(P(x))$$

with P(x) the probability distribution of particle positions

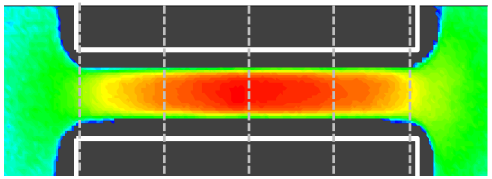
First passage distributions on a linear scale appear similar…



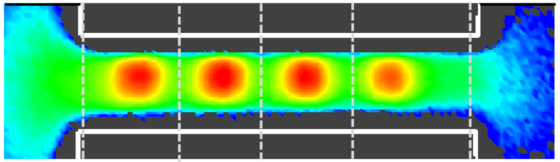


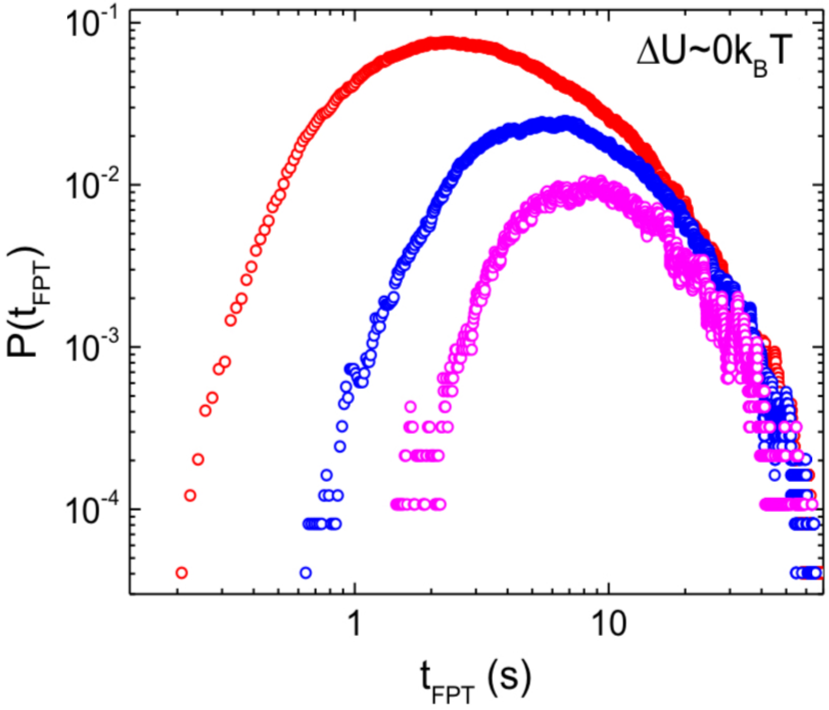
…but potential minima qualitatively change distributions

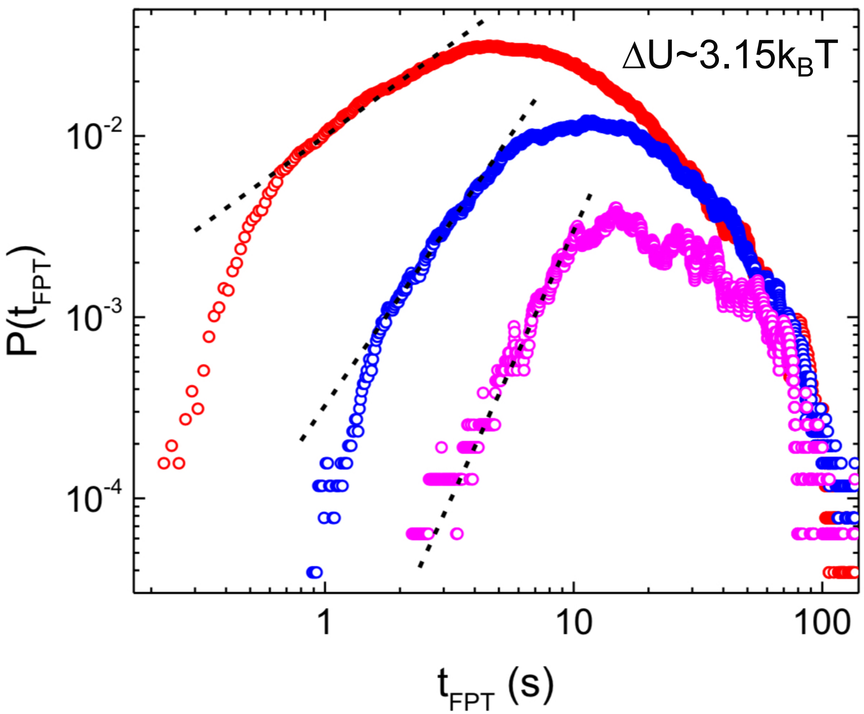
No potential



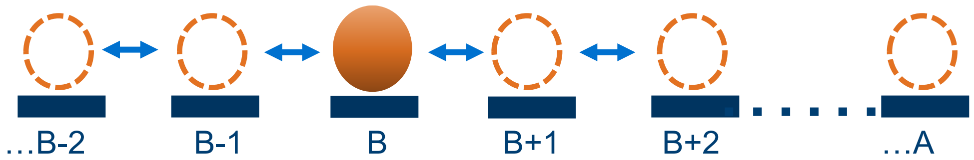
4 minima





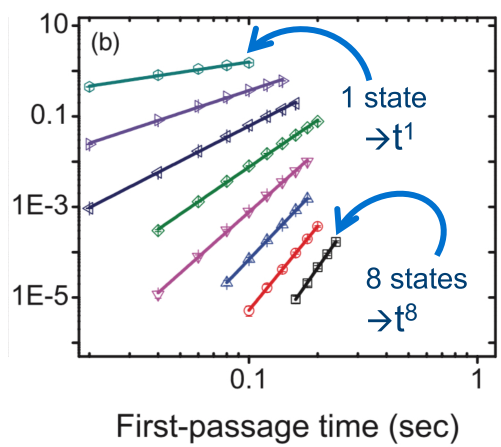


First passage time distributions in a 1D network



Short-time regime: $$\ln P(t_{FPT}) \simeq (A - B - 1)\ln t + C$$

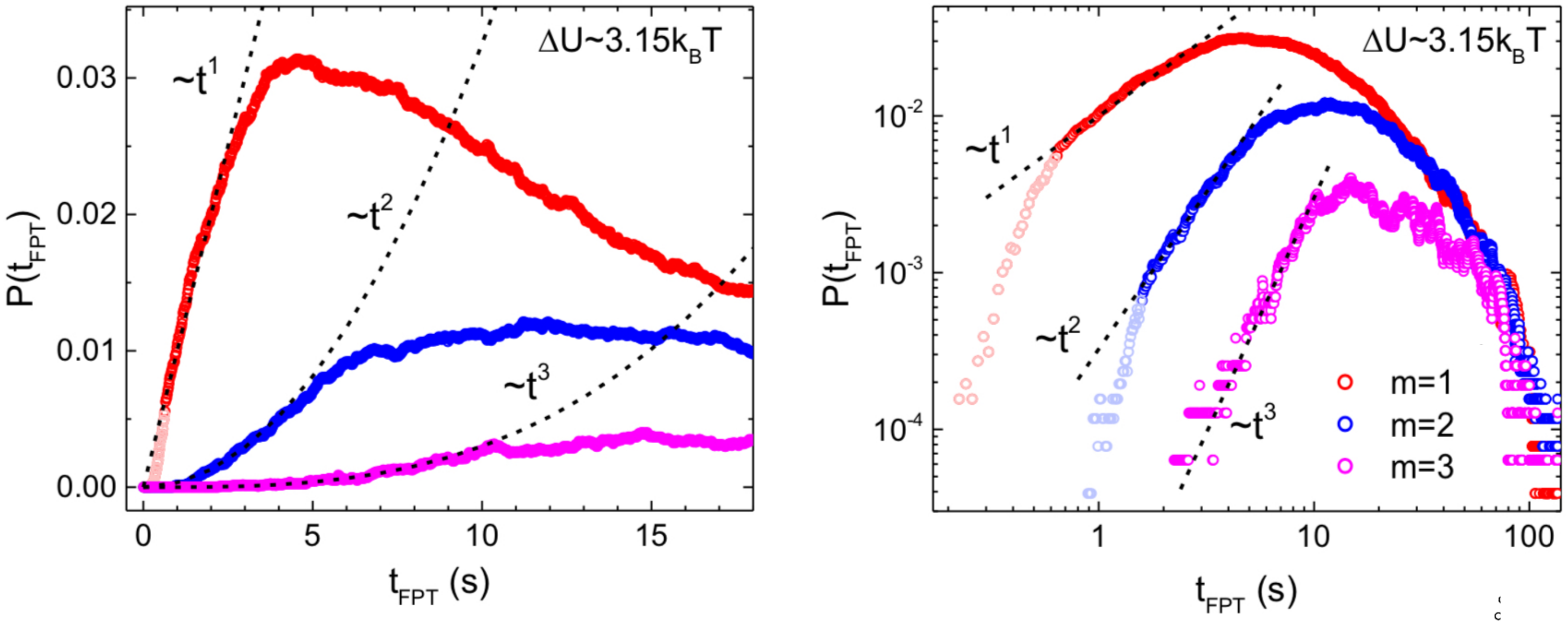
Simulation results:



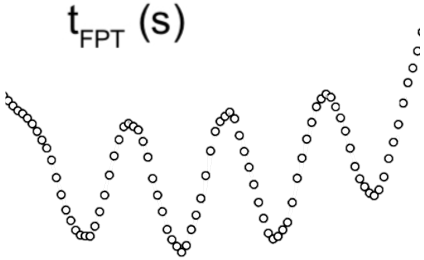
Measurement of $P(t_{FPT})$ at short times→ number of states that must be crossed to exit

Li and Kolomeisky, J. Chem. Phys, (2013)

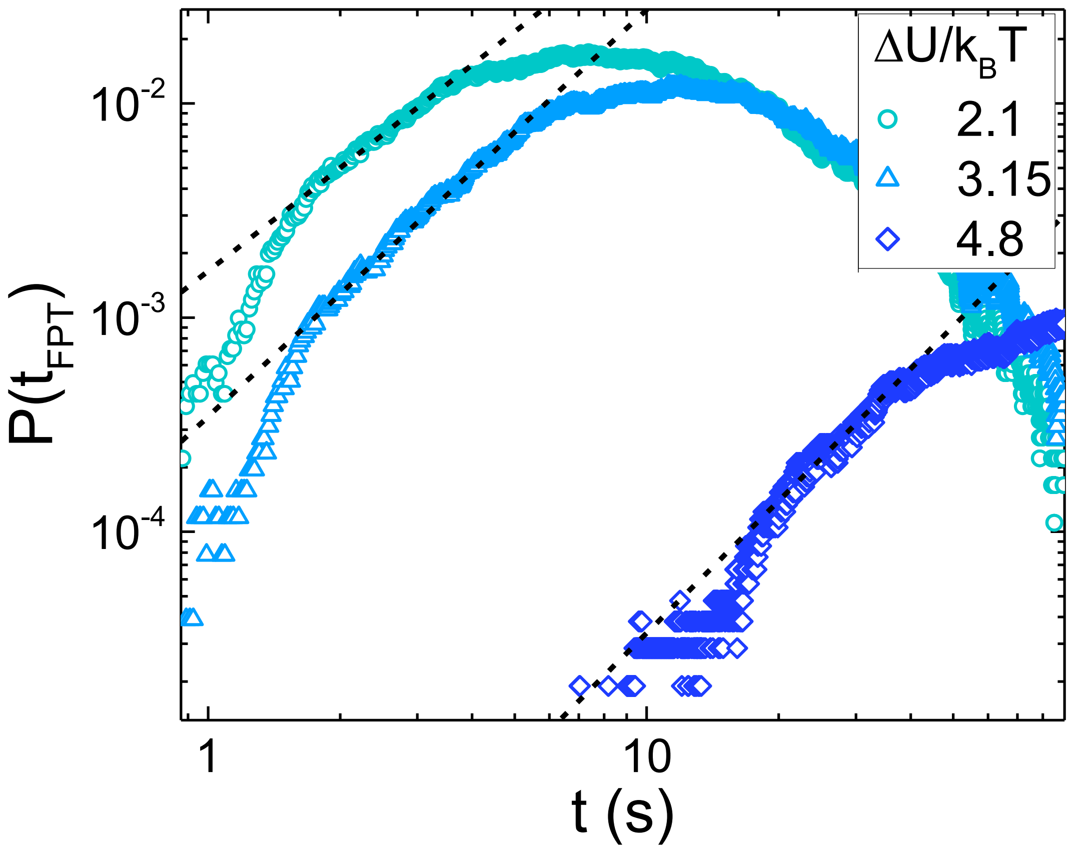
Short-time regime reflects number of potential minima



Distributions exhibit a short-time power law regime with $P(t_{FPT}) \sim t^m$ scaling consistent with theory

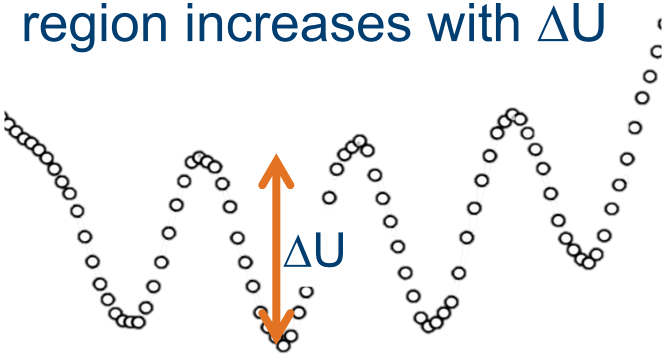


Length of power law regime increases with ΔU



Short-time regime for m=2 distributions

- All distributions exhibit a power-law regime, t^m, with m~2
- Length of power-law (linear) region increases with ΔU



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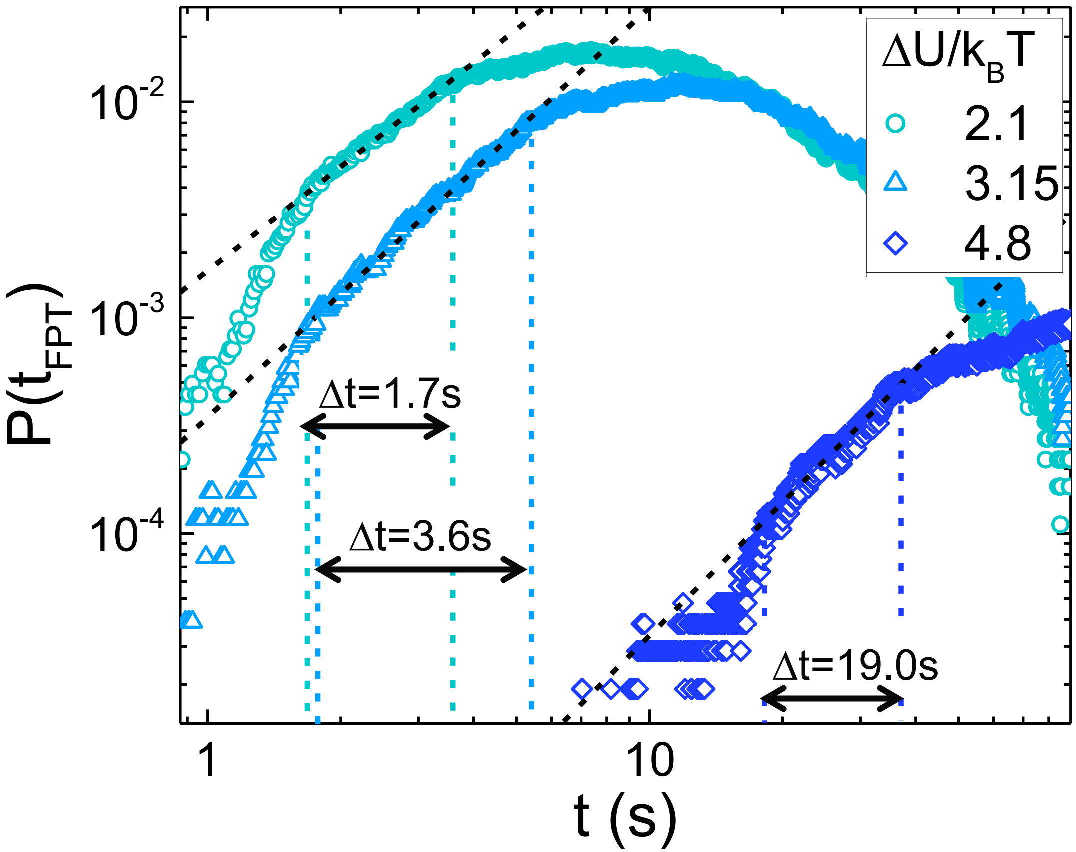
Length of power law regime increases with ΔU



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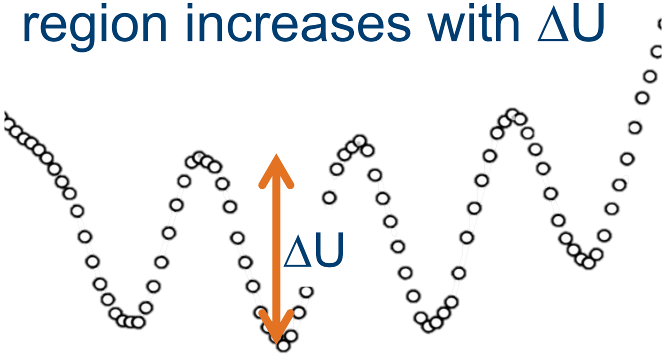
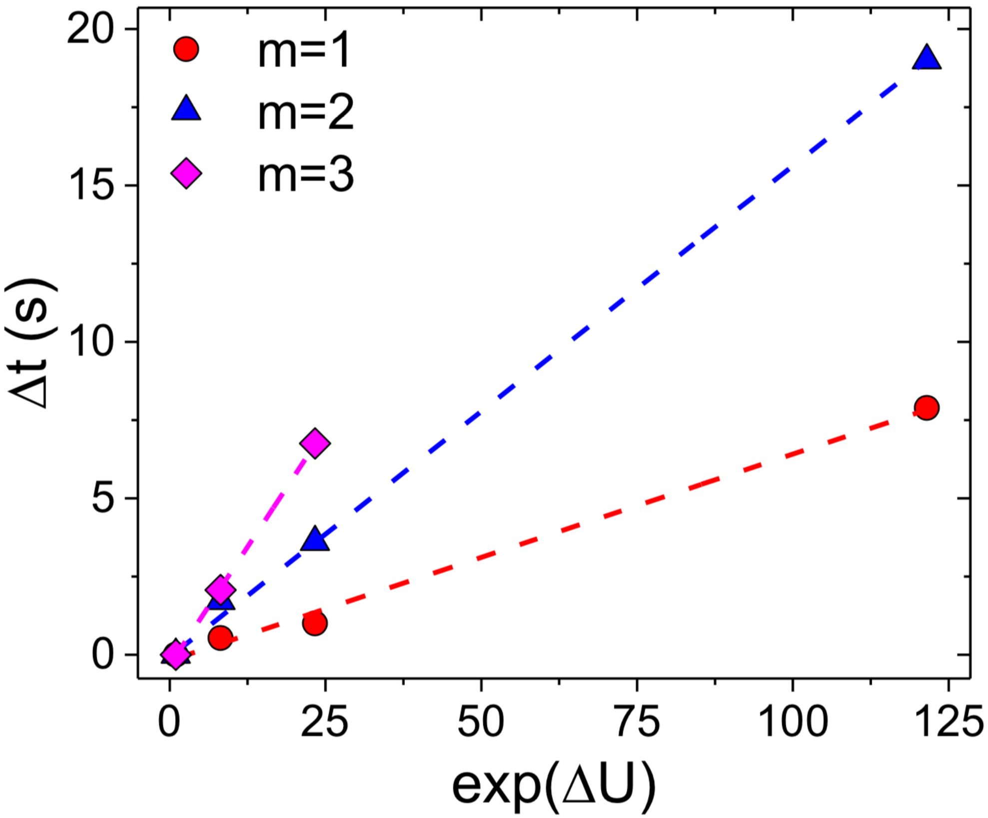


Length of power law regime scales linearly with ΔU



Length of power law regime scales with potential depth

→Residence time important
→Route to infer potential depth

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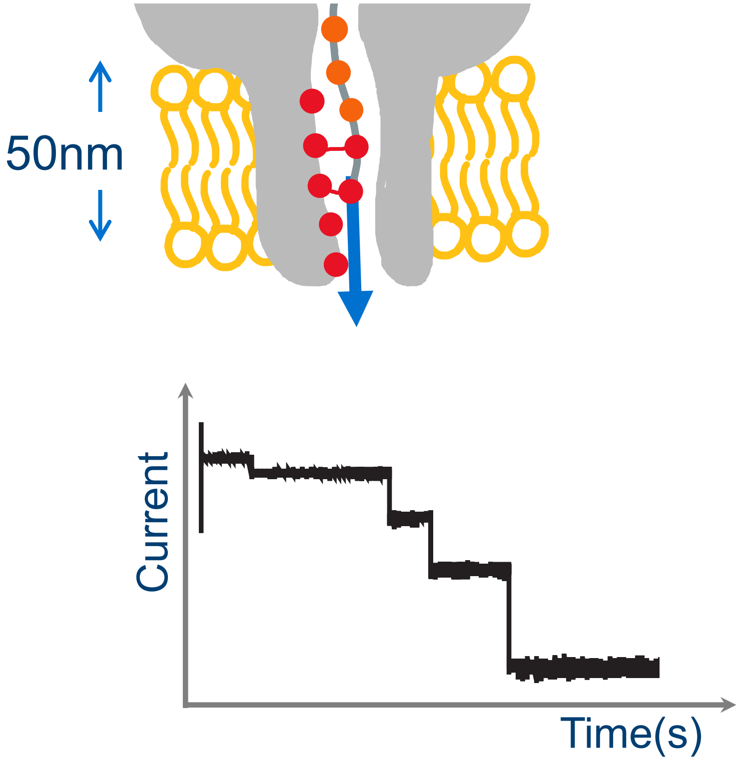
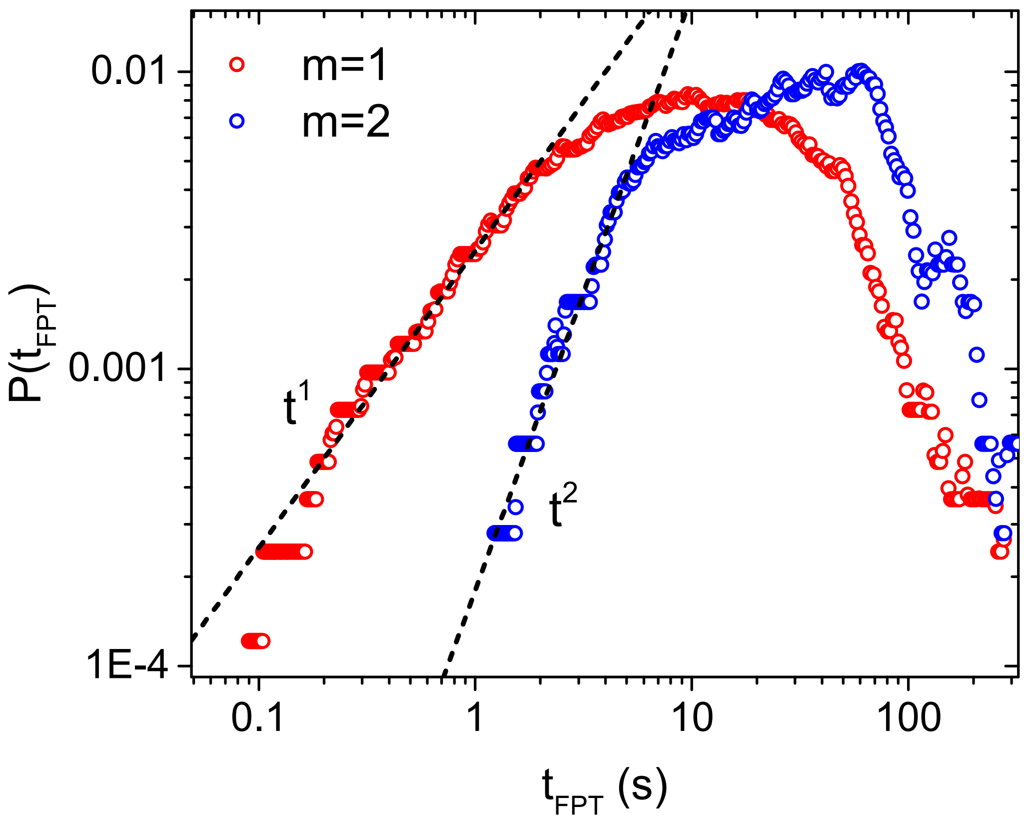
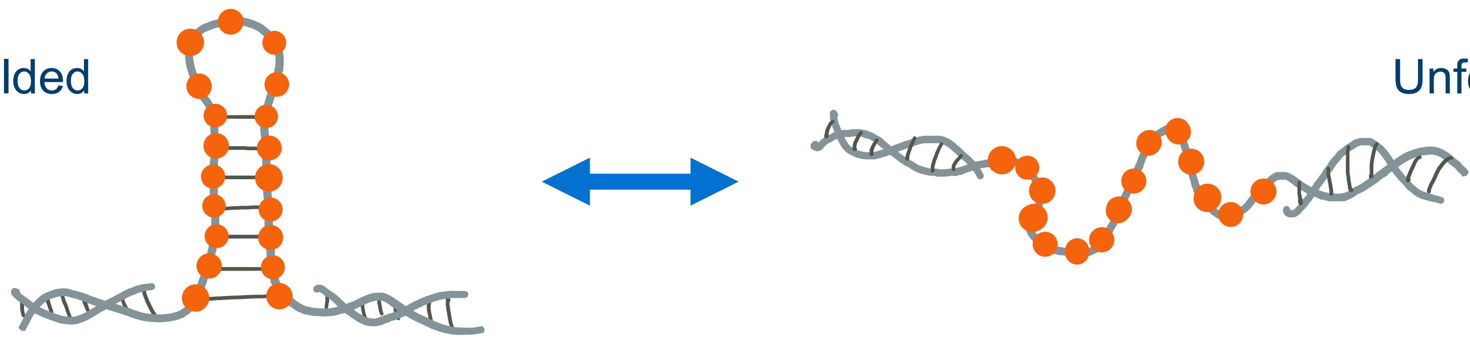
Molecular example 1: biological pore transport

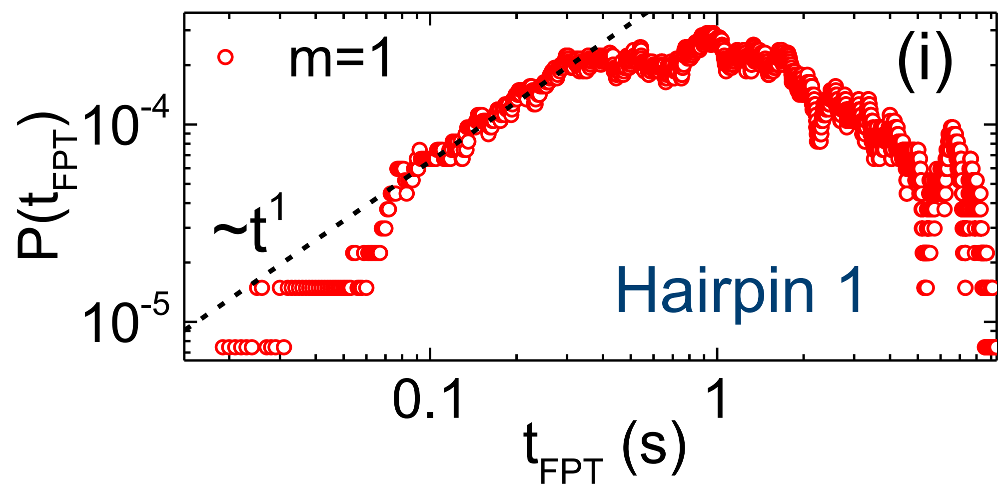




Data from Bayley group, University of Oxford
Qing et al, Science (2018)

Molecular example 2: (un)folding of a DNA hairpin





Data from Ritort group, University of Barcelona
Forns et al, Phys. Rev. Lett. (2009), Rico-Pasto, J. Chem. Phys. (2018)

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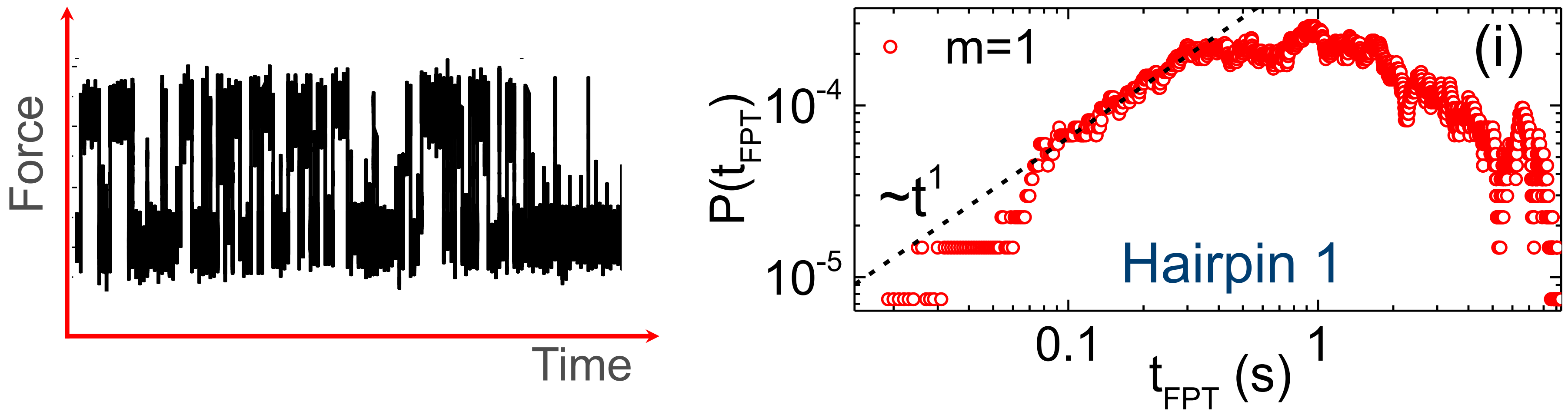

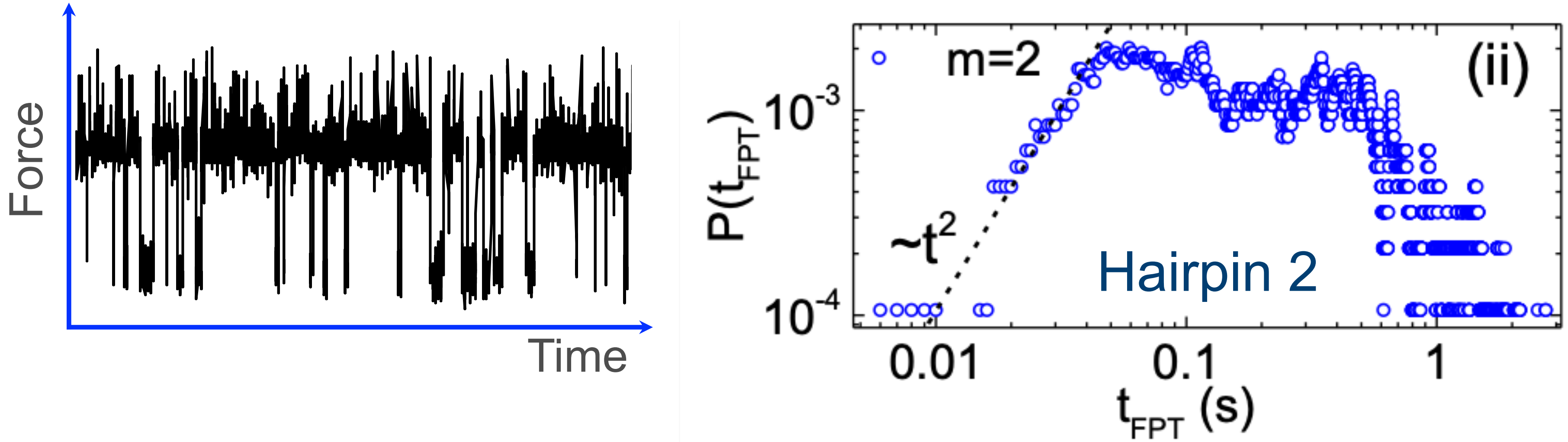

Data from Ritort group, University of Barcelona
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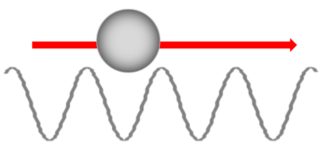
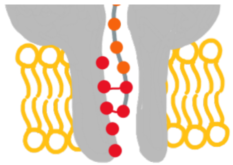
Universal behaviour of the FPT distribution

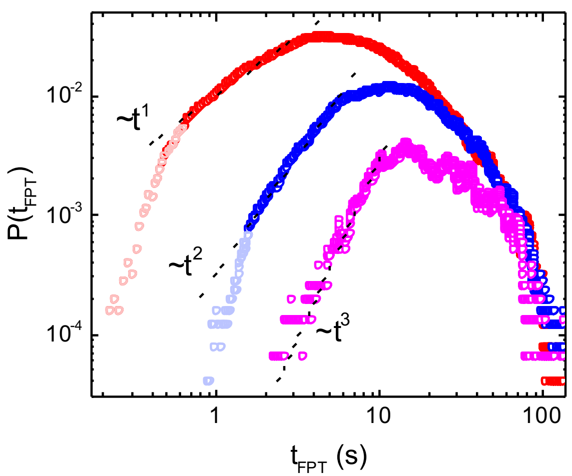
Colloidal channel

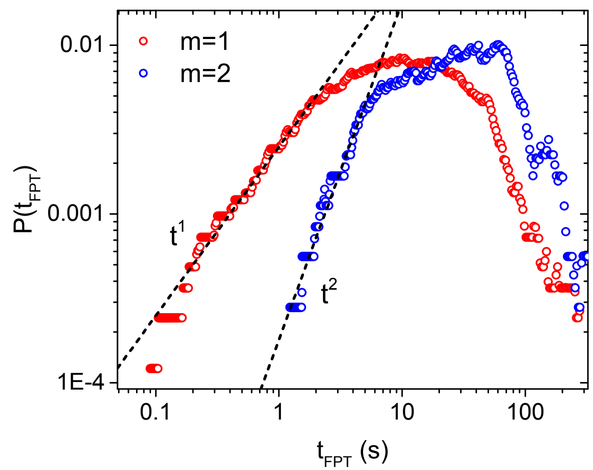


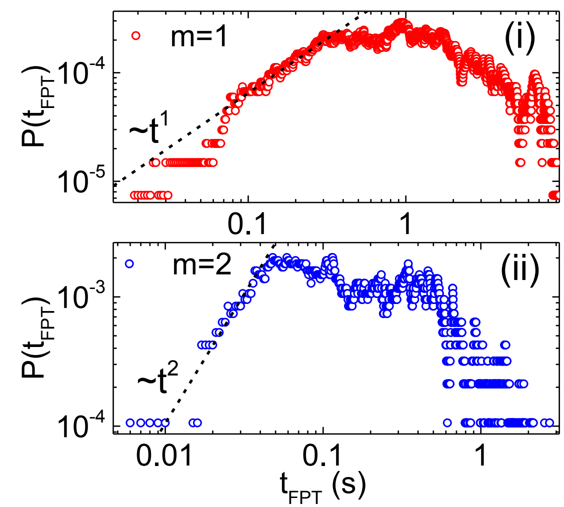
Biological pore



DNA Hairpin







Mesoscale

Microscale

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KeyserLab

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