

Title: Simulating the Capture and Translocation of Rigid fd Viruses through a Nanopore

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URL: <http://pirsa.org/14050036>

Abstract: <span>The passage of long biological molecules from one side of a membrane to the other through a nanoscale hole has been the subject of intense research in recent years. Motivated by the possibility of new sequencing technologies the focus of this work has been studying the translocation of DNA across biological and synthetic membranes. In this talk I will present results from a joint experimental-simulation study examining the translocation of rod-like fd viruses through a nanopore. While DNA is relatively flexible the fd virus has a persistence length that is over twice that of its contour length and is thus stiff. In principle translocation in this rod-like limit is much easier to model. However I will show that experimental results for the distribution of translocation times exhibit significant deviations from the expected result. I will present a model for fd translocation that was developed to probe these results. Simulations based on this model yield insight into previously unclear experimental results including i) details of how the polymer is captured by the pore at different external fields ii) a correlation between the translocation time and the conformation at capture and iii) sources for the increased dispersion in the translocation time distributions.</span>



Computational NanoBiophysics Lab  
University of Ontario Institute of Technology

# Translocation of Rigid, Filamentous Viruses through Nanopores

Hendrick W. de Haan, UOIT

Experimental Collaborators:

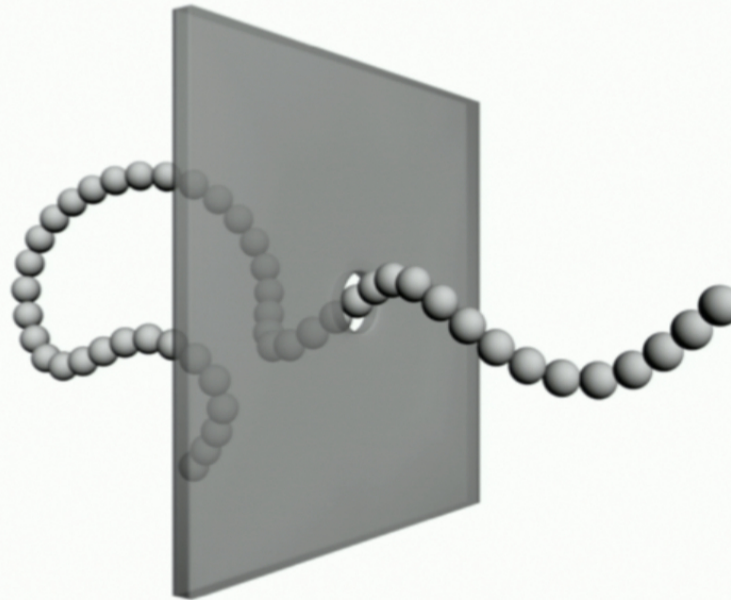
Angus McMullen, Jay X. Tang, Derek Stein  
Brown University

Compute Ontario  
Perimeter Institute  
May 7, 2014

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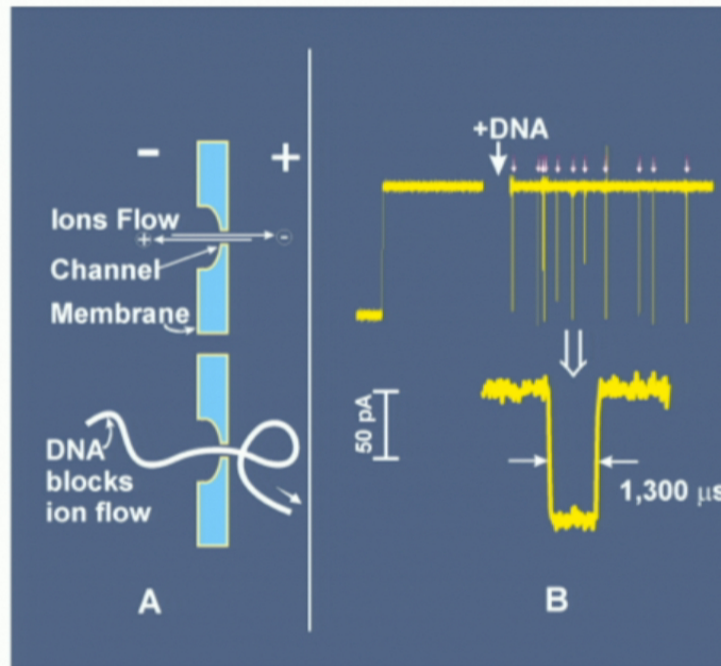
### Translocation through a Nanopore:

- biological object crossing a membrane through a nanoscale pore
- DNA
- RNA
- proteins



Nanotech Application: Detecting Molecules, Viruses

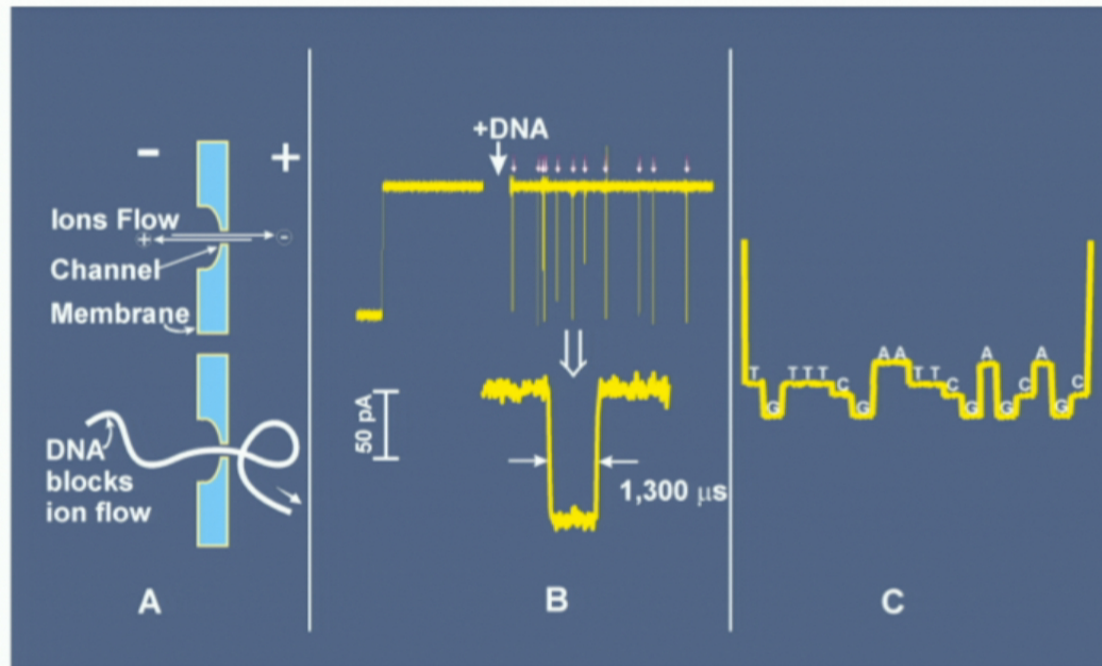
- device in water with ions and counter-ions
- substances passing through the pore reduce ionic current
  - ECD : Event Charge Deficit
- characteristic dips in the current traces



<http://www.mit.edu/~kardar/research/seminars/translocation/KITP/introduction.html>

Nanotech Application: Detecting Molecules, Viruses

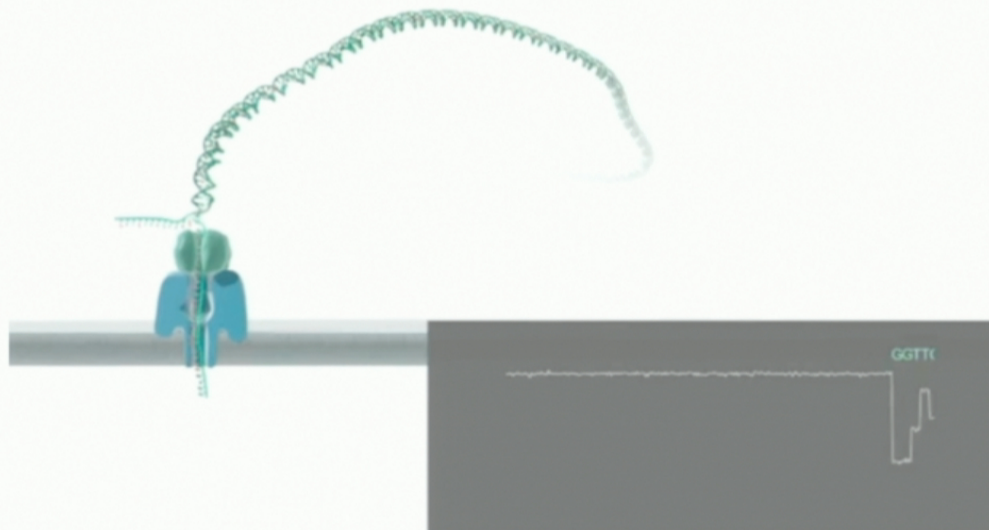
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## Nanotech Application: Sequencing DNA

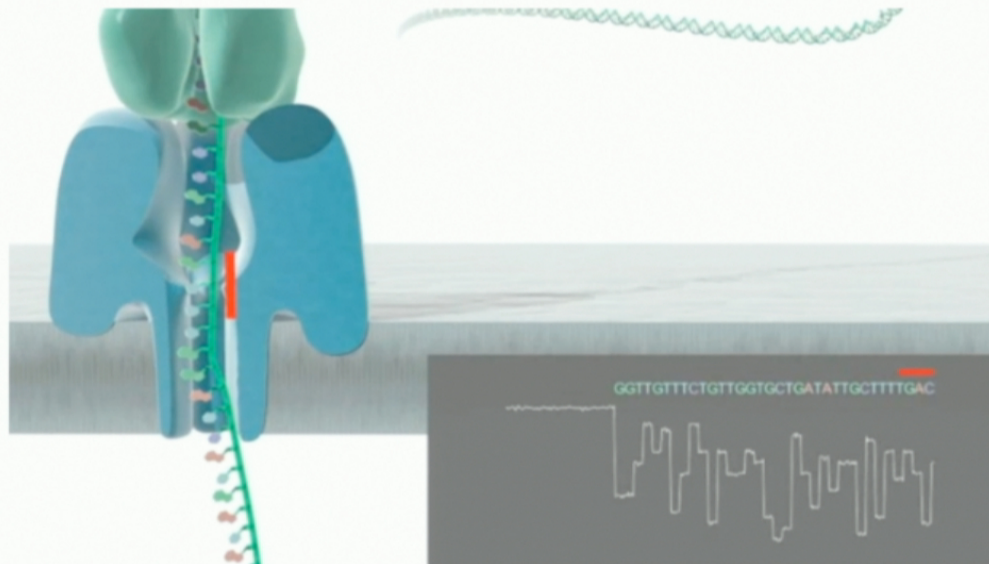
- read bases as pass through the pore



Oxford nanopores

Nanotech Application: Sequencing DNA

- read bases as pass through the pore



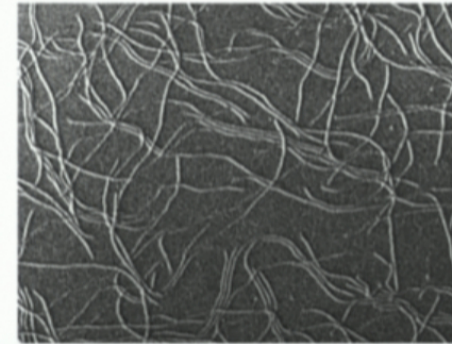
Oxford nanopores

**fd Virus:**

- bacteriophage
  - infects *E. coli*
  
- rigid, filamentous virus
  
- contour length: 880 nm
- persistence length: 2200 – 2800 nm
- diameter: 6.6 nm



<http://www.rowland.harvard.edu/rjf/dogic/fdvirus.php>



<http://www.brandeis.edu/departments/physics/complexfluids/fraden/research/LiqCryst/Virus.html>

**Applications:**

- nanotech:
  - building self-assembled nanostructures
  
- medical:
  - proxy for detecting *E. Coli*
  - similar to *Filoviridae* that causes Marburg and Ebola
  - engineered to be antigen delivery system in vaccination



*fd* Virus vs. dsDNA: Flexibility Matters!

1. Translocation Time

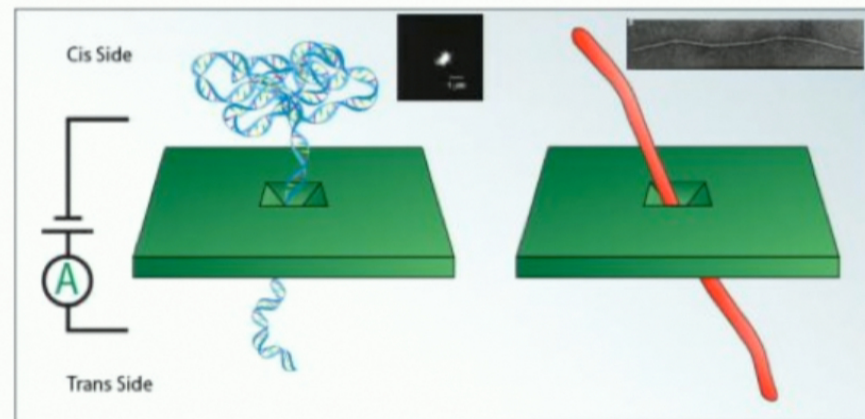
- dsDNA: initial configuration influences translocation time  $\tau$
- *fd* virus: possible conformations are much more limited

- in the rod like limit:

$$F(\tau) = \frac{L}{\sqrt{4\pi D_{\parallel} \tau^{\frac{3}{2}}}} \exp\left(-\frac{(L - v\tau)^2}{4D_{\parallel} \tau}\right)$$

L : length  
v : velocity  
D<sub>||</sub>: diffusion coefficient

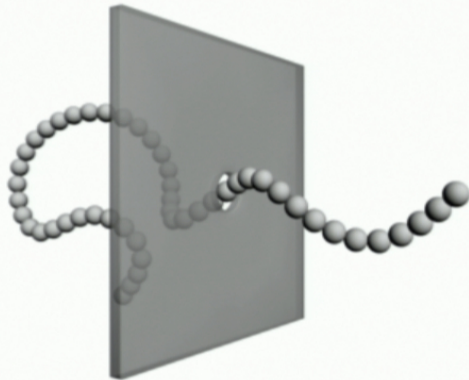
- distribution has a well defined width given by D<sub>||</sub>
- only depends on thermal noise
- narrow distribution
- identify *fd* with certainty



Model for the *fd* Virus:

Semi-flexible polymer made up of beads connected by springs

- diameter :  $1 \sigma$  (bead diameter)
- contour length :  $133 \sigma$
- persistence length :  $423 \sigma$

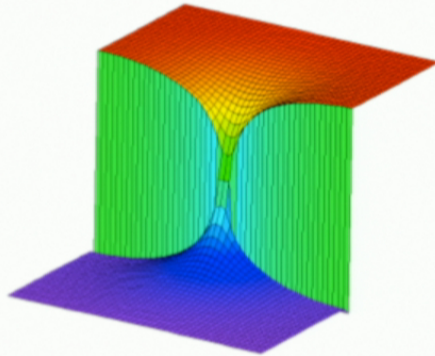


Nanopore containing membrane:

- pore diameter :  $5 \sigma$   
(30 nm)
- pore length :  $3 \sigma$   
(20 nm)

Forces: External Force

- calculate potential via finite difference method
- largest gradients (largest forces) near pore

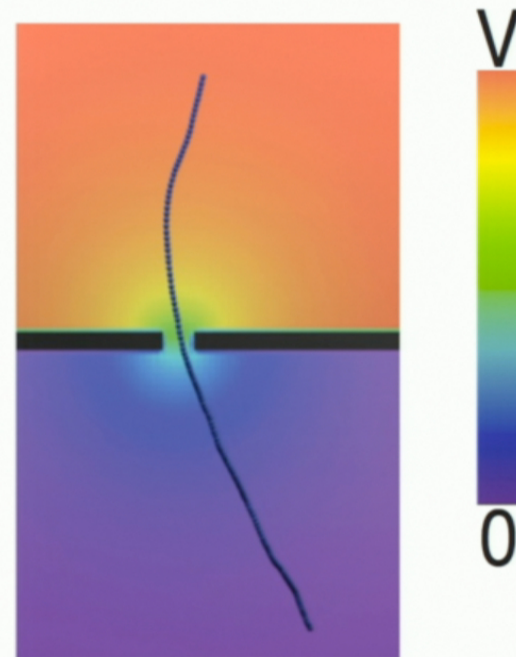


MD Simulation Method

- calculate force on each particle

$$\sum F = ma$$

- numerically integrate twice
- Langevin Dynamics: implicit fluid
  - drag term
  - thermal kick term

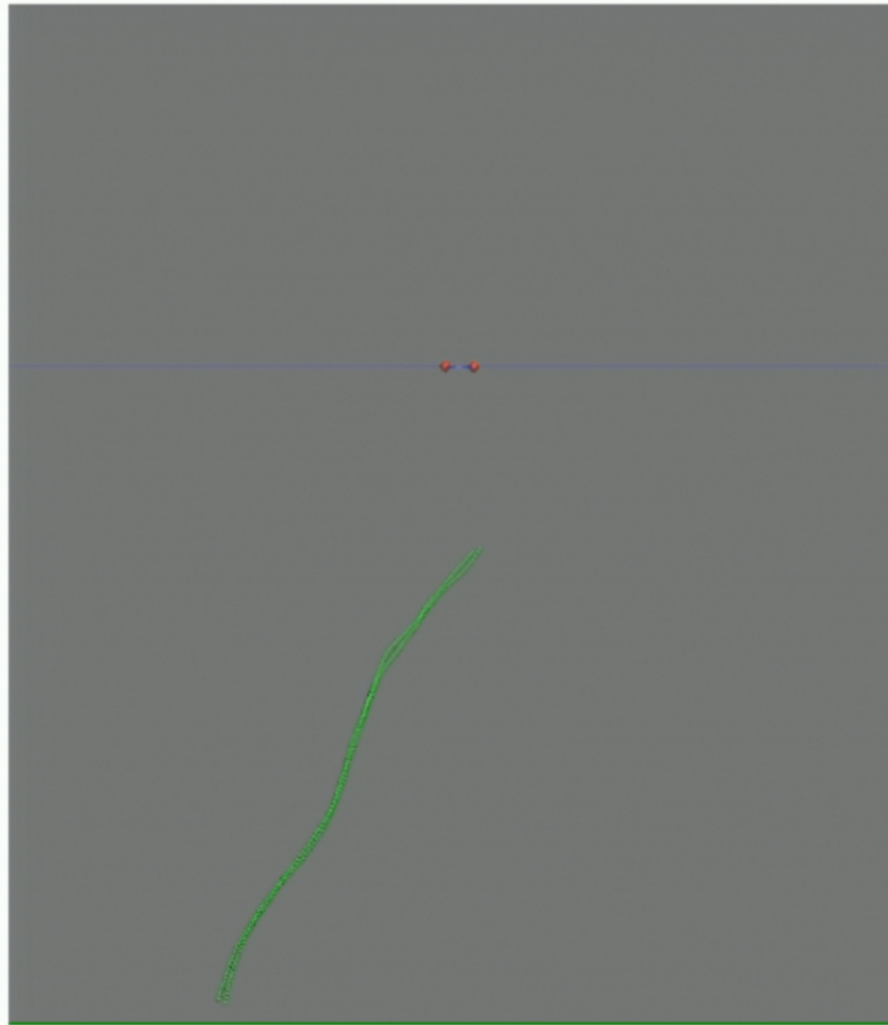


**Simulation:**

- equilibrate far from pore
- transport closer
- capture via:
  - diffusion
  - drift

**Measure:**

- details that can't be resolved in experiment
- state at capture
  - monomer index
  - orientation

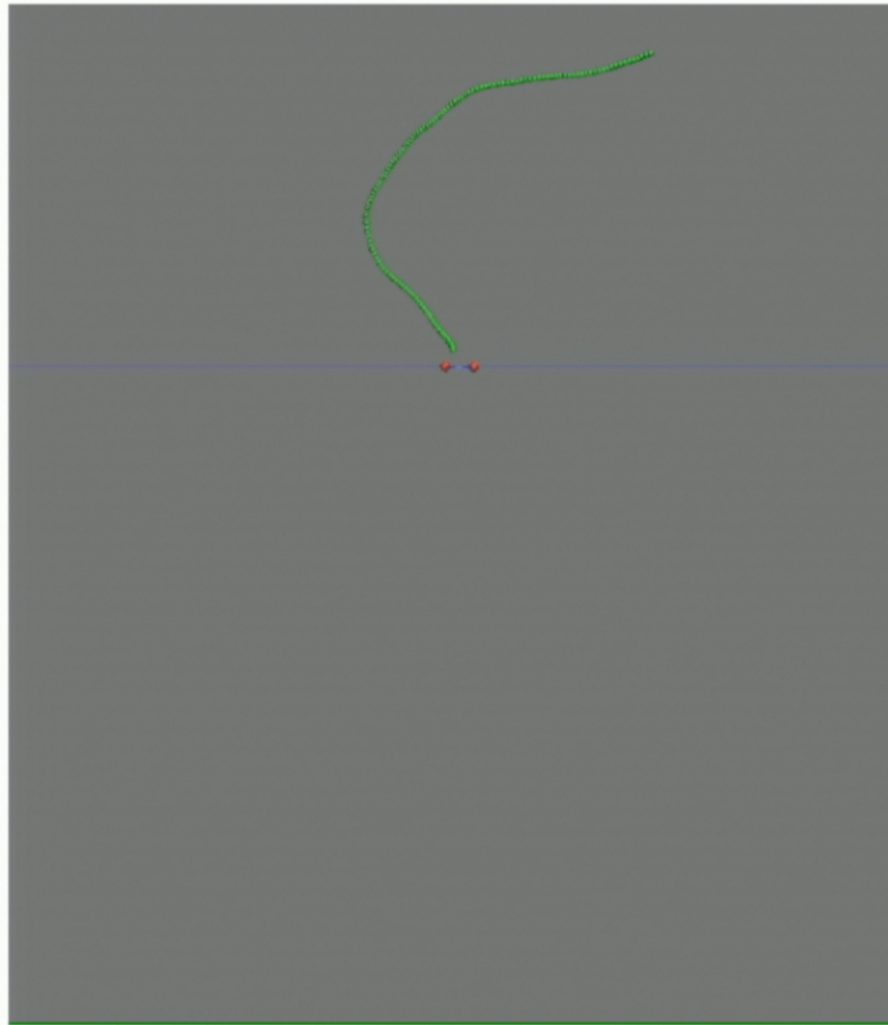


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## HPC : SHARCNET

- very efficient parallelization ...
  - perfectly parallel
  - (embarrassingly parallel?)

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## Serial Computing!

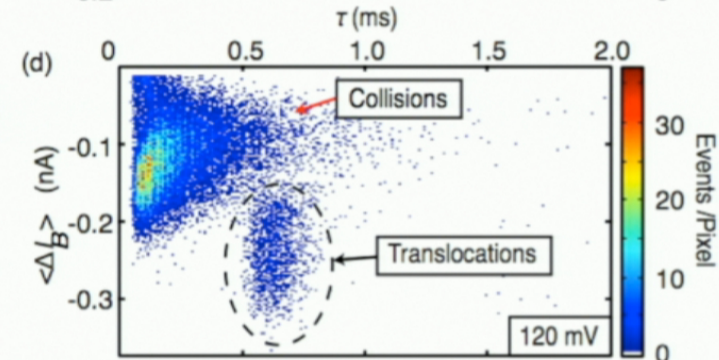
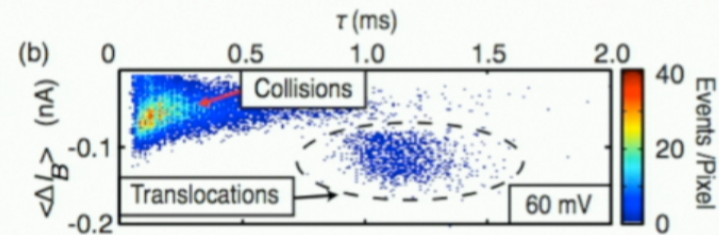
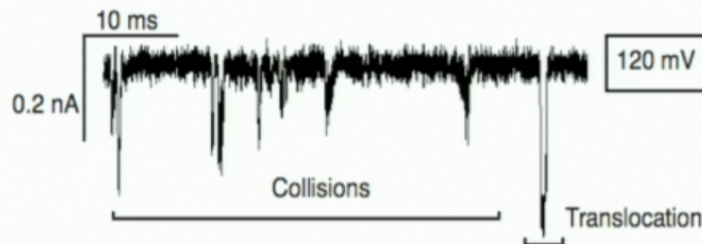
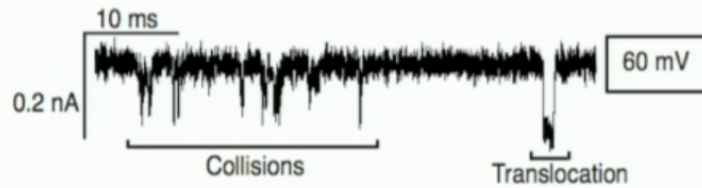
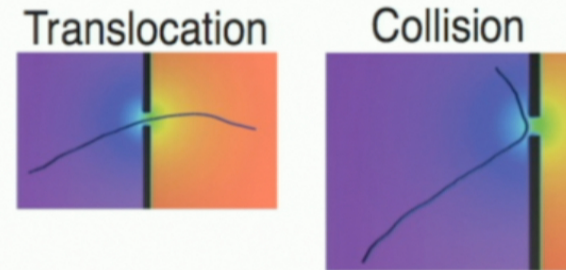
- launch many independent runs across 200+ cores
- generate proper ensemble averages, distributions quickly
- explore phase space efficiently
- excellent bang for the buck!

Experimental: Current Traces

Two types of events

- collisions: short duration, small ECD
- translocations: long duration, large ECD

Harder to distinguish as voltage is increased



McMullen, de Haan, Tang, Stein, *Nature Comm.*, in press

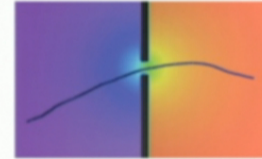


Simulation: Translocation vs. Stuck

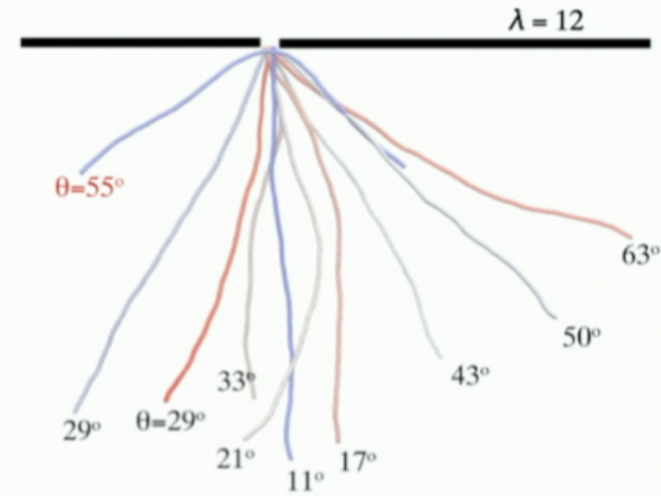
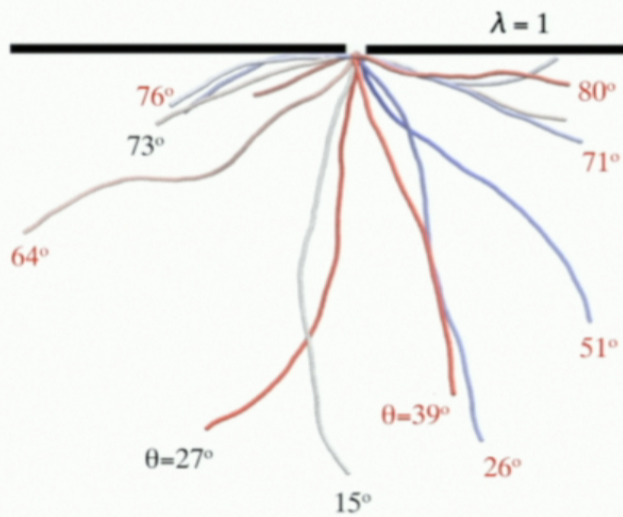
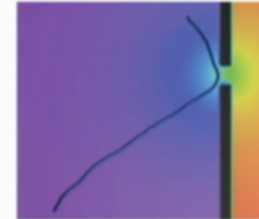
What differentiates events?

- alignment at capture
- monomer that hits the pore
- depends on the field

Translocation



Collision

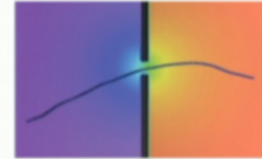


Simulation: Translocation vs. Stuck

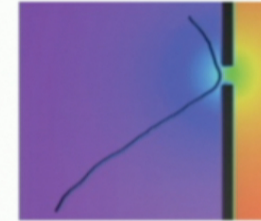
Alignment

- lower angle means more aligned with the pore

Translocation

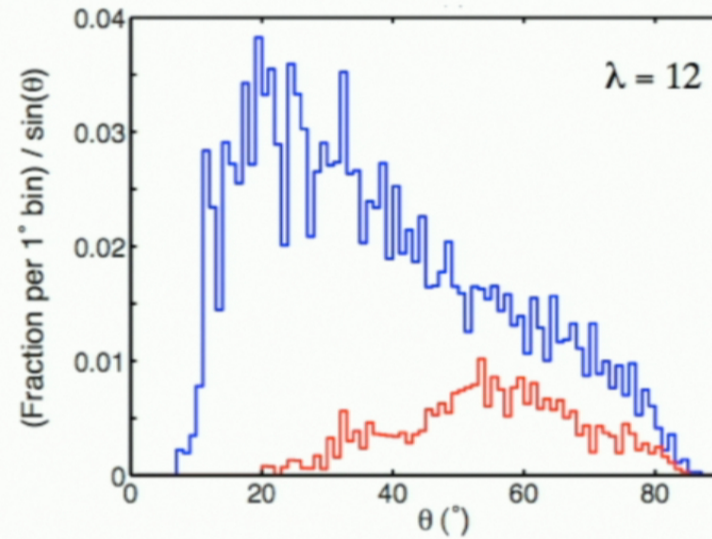
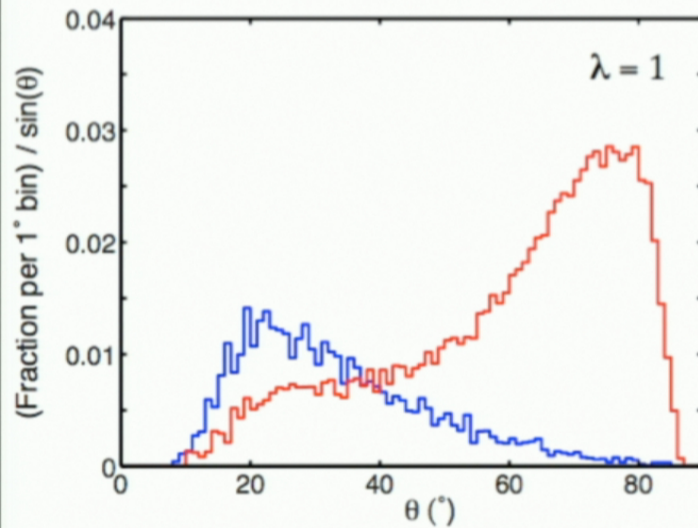


Collision



Low field: not aligned

High field: aligned



McMullen, de Haan, Tang, Stein, *Nature Comm.*, in press

Simulation: Translocation vs. Stuck

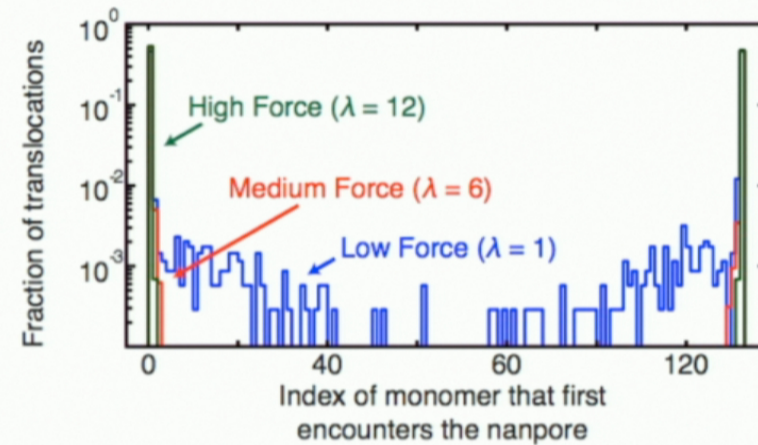
What monomer hits the pore first?

Low field:

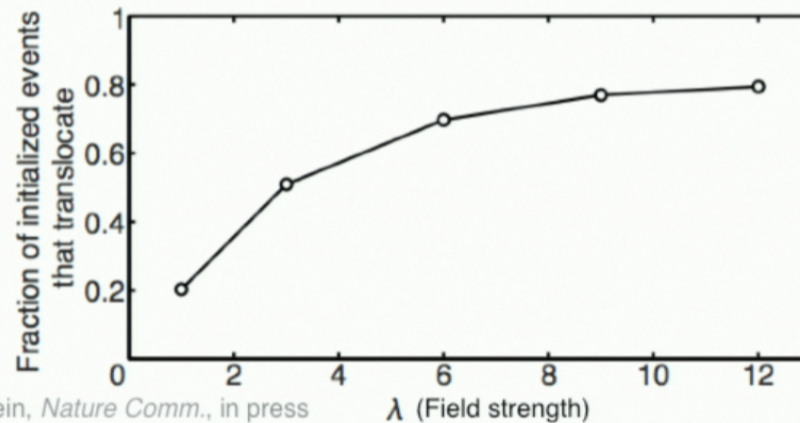
- less likely by an end
- possible to rearrange and translocate

High field:

- likely to be aligned
- if not, stuck against the pore



Overall: probability of translocation increases with field



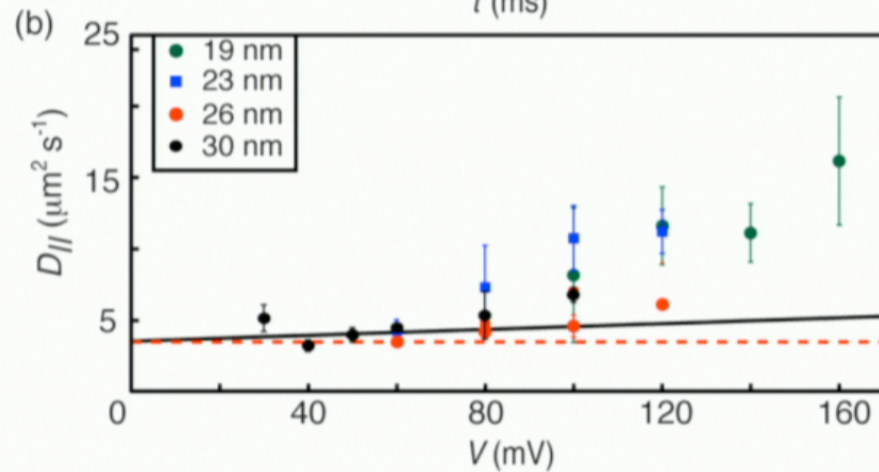
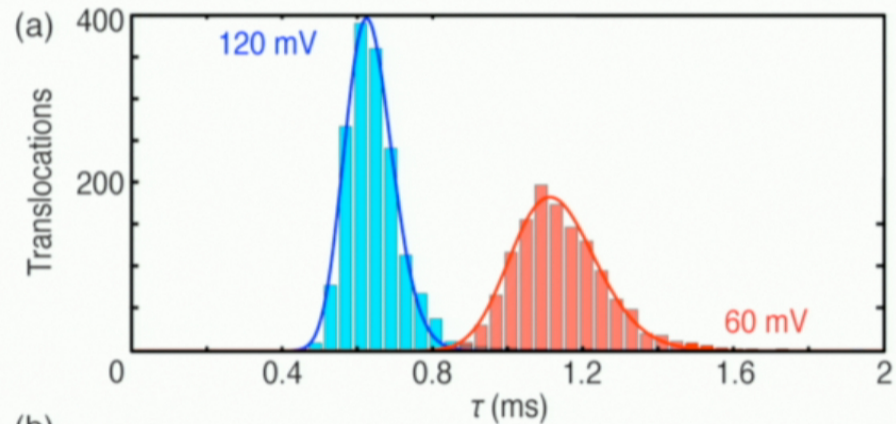
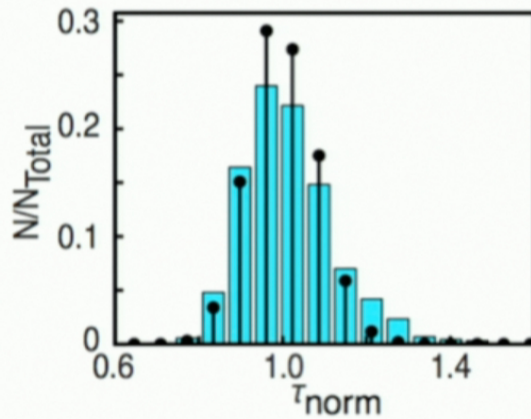
McMullen, de Haan, Tang, Stein, *Nature Comm.*, in press

Experimental: Translocation Time

- distributions wider than predicted
- extra source of dispersion
- deviation increase with  $V$
- what is the source?

Simulation: Translocation Time

- also increased dispersion



McMullen, de Haan, Tang, Stein, *Nature Comm.*, in press

## Simulations: Translocation Time

### Angle on threading

- do oblique viruses translocate slower?
- simulations find no correlation

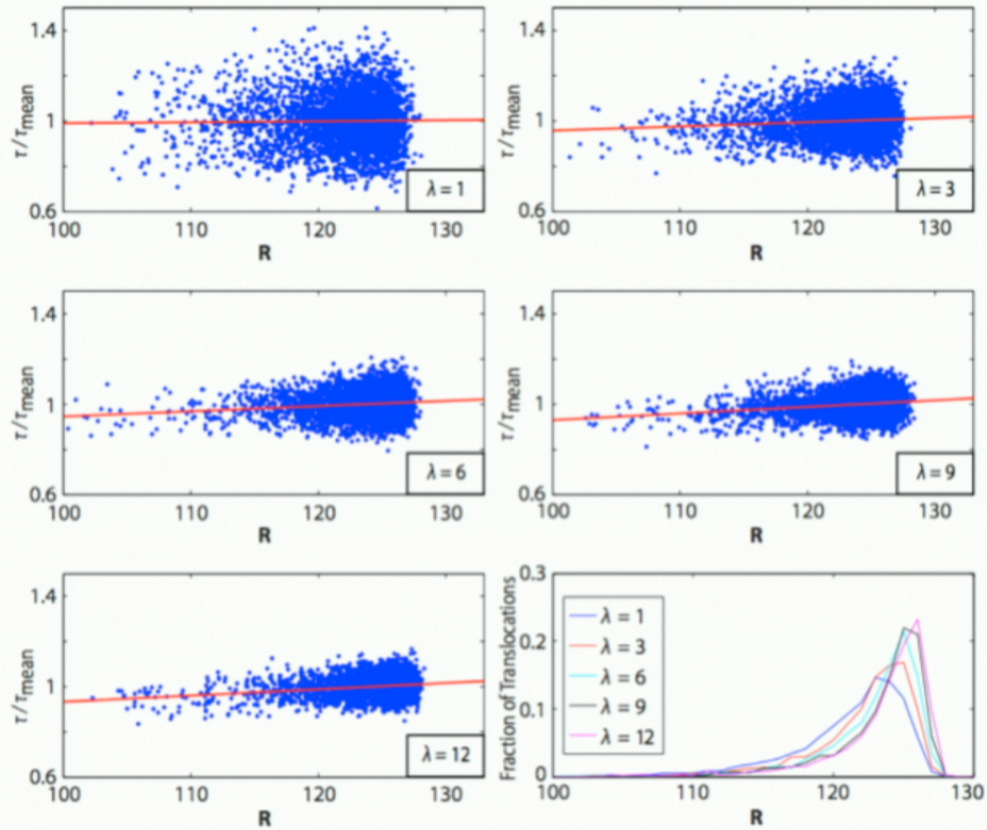
### Lateral placement in pore

- faster if virus near the center?
- faster if virus near the edge?
- simulations find no correlation

Simulations: Translocation Time

Initial Configuration

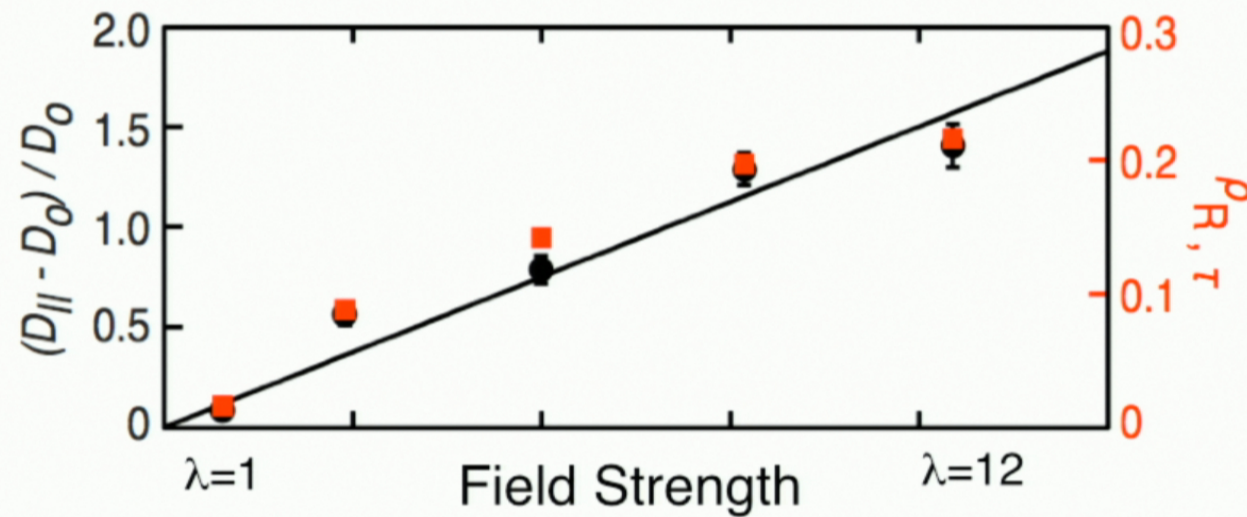
- although stiff,  $fd$  can bend
- R: end-to-end distance on thread
- correlation
  - lower R, shorter  $\tau$
  - more monomers in higher E
  - lower effective drag
- increases with E



### Simulations: Translocation Time

#### Initial configuration

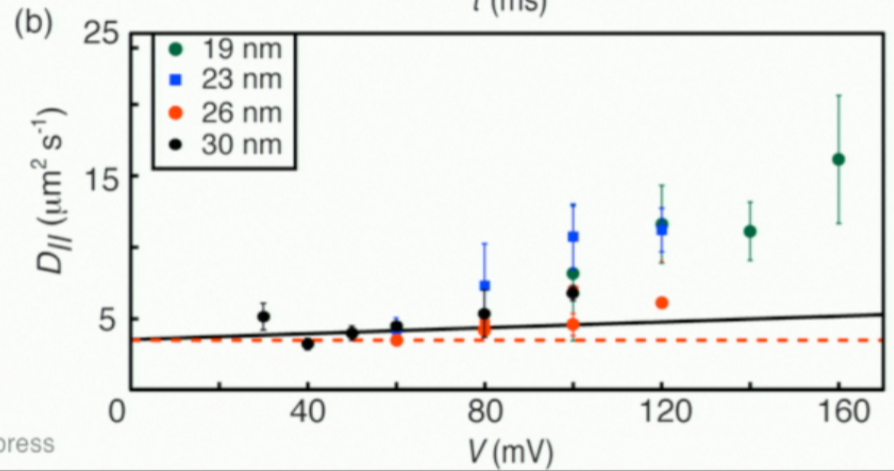
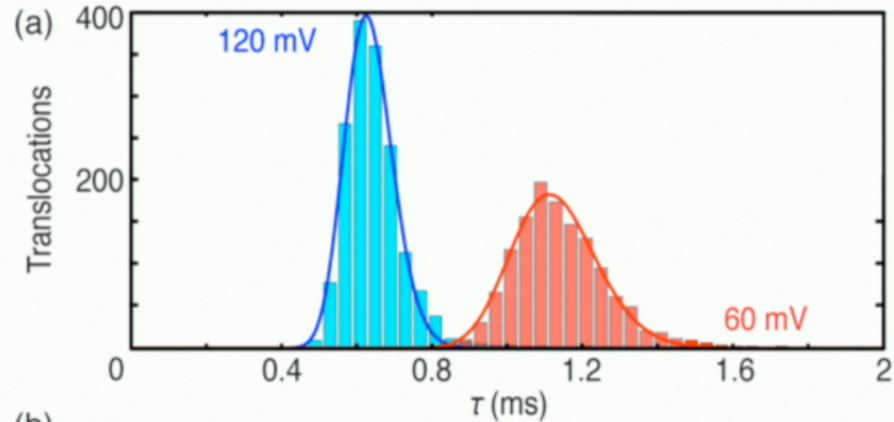
- increased dispersion in simulations explained by this correlation
- so initial configuration still matters!
- grows with field: IC washed out at lower fields where thermal effects play a larger role



Experimental and Simulation

- IC effect only explains a part of the increased dispersion

- still work to do!



McMullen, de Haan, Tang, Stein, *Nature Comm.*, in press



### Other Sources

- more complicated electric field profile
  - lead to lateral placement dependence?
- friction
  - any type of friction between the virus and the pore could greatly affect the results

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### Conclusions

- simulations reveal:
  - details of capture process: translocation vs. stuck  
dependence on field strength
  - source of extra dispersion: initial configuration  
???

### Future Work

- explore other sources of dispersion
- other effects:
  - persistence length
  - ionic strength
  - pore width

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## Graduate Positions Available

funding available  
these and other research projects

### Graduate Programs:

- Modelling and Computational Science
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