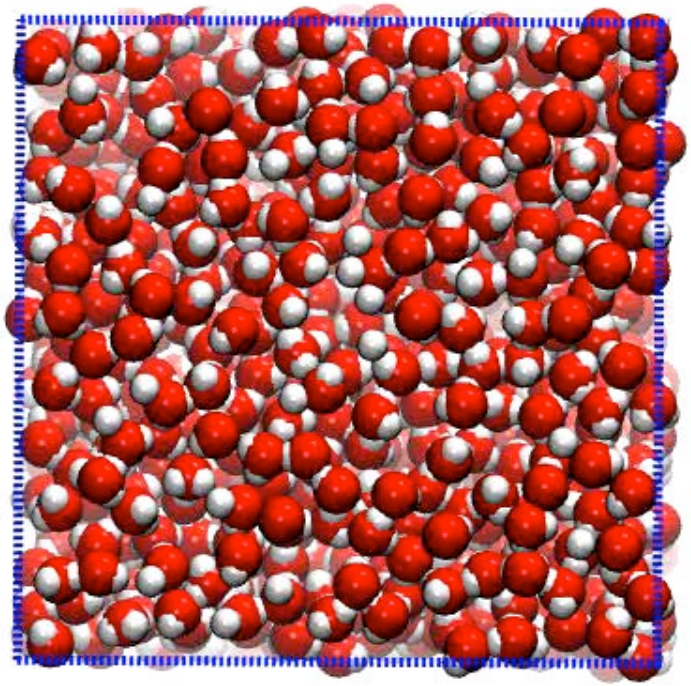
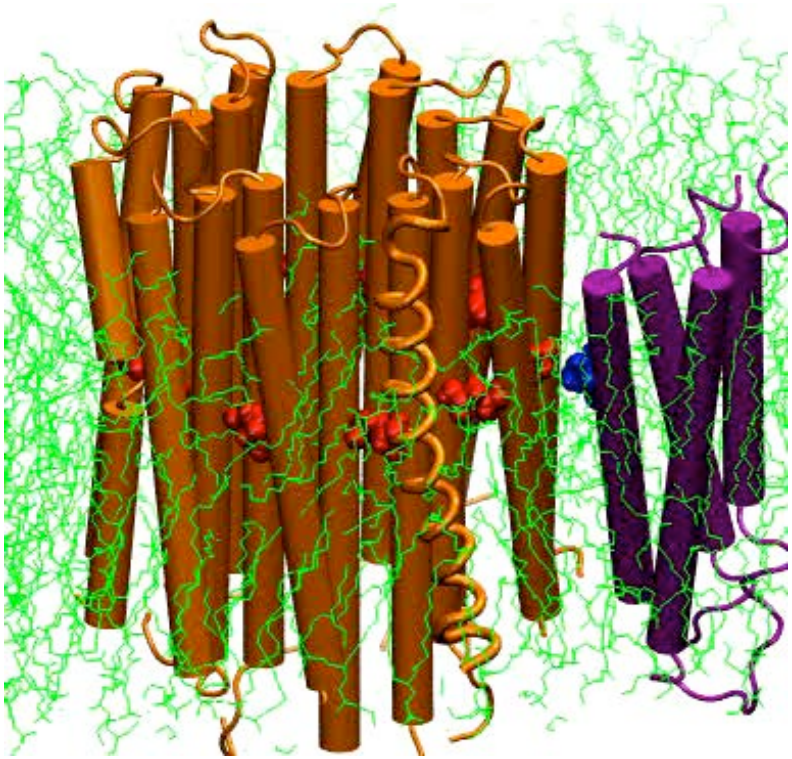
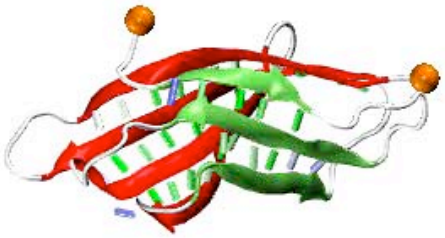
# External Forces in NAMD

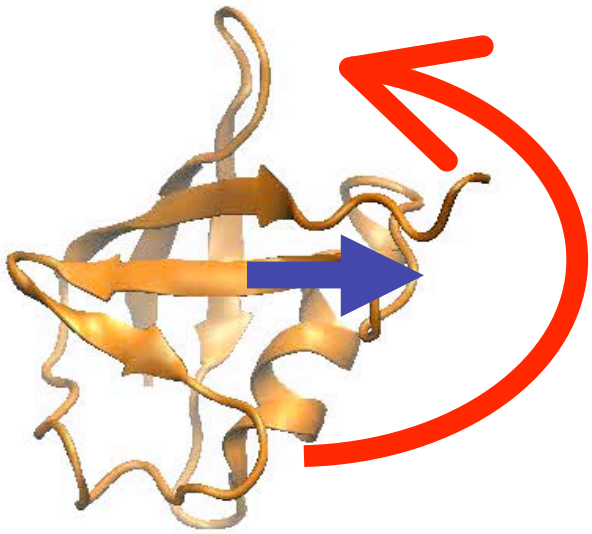




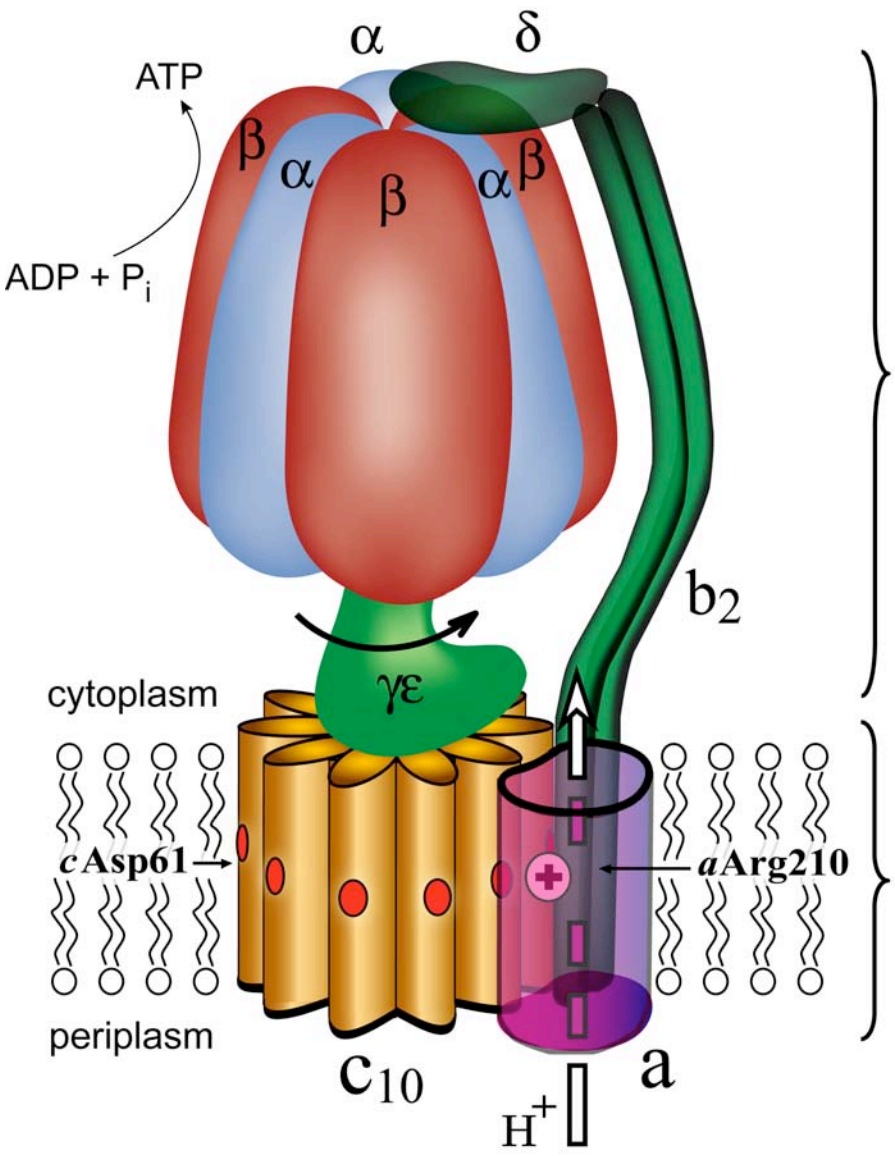
# Standard protocols are limited



SMD, moving (or rotating) constraints, constant foce



# F-ATP synthase

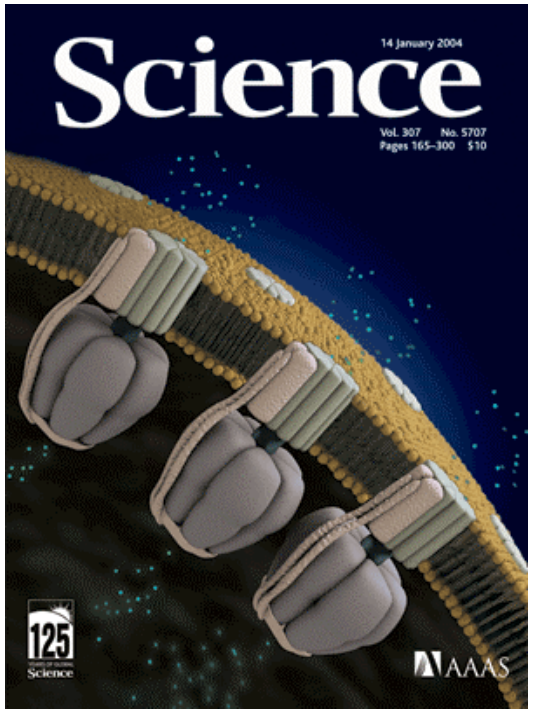



Rotary catalysis: Two protein motors coupled via common central stalk γδ

Solvent exposed $F_1$ unit ($\alpha_3\beta_3\gamma\delta\varepsilon$): central stalk rotation causes conformational changes in catalytic sites, driving ATP synthesis

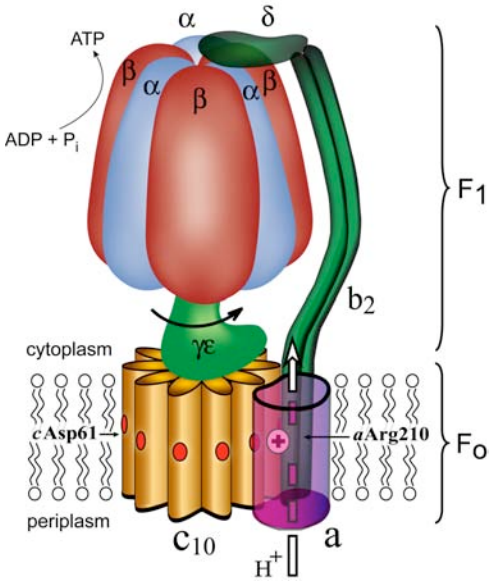
Transmembrane $F_o$ unit ($ab_2c_{10}$): converts proton motive force into mechanical rotation of central stalk

# Challenges




Atomic details matter: Displacing three atoms in F-ATP synthase can kill the cell

Multiple time and length scales make modeling difficult




Milliseconds: (rotation of the central stalk driving ATP synthesis)

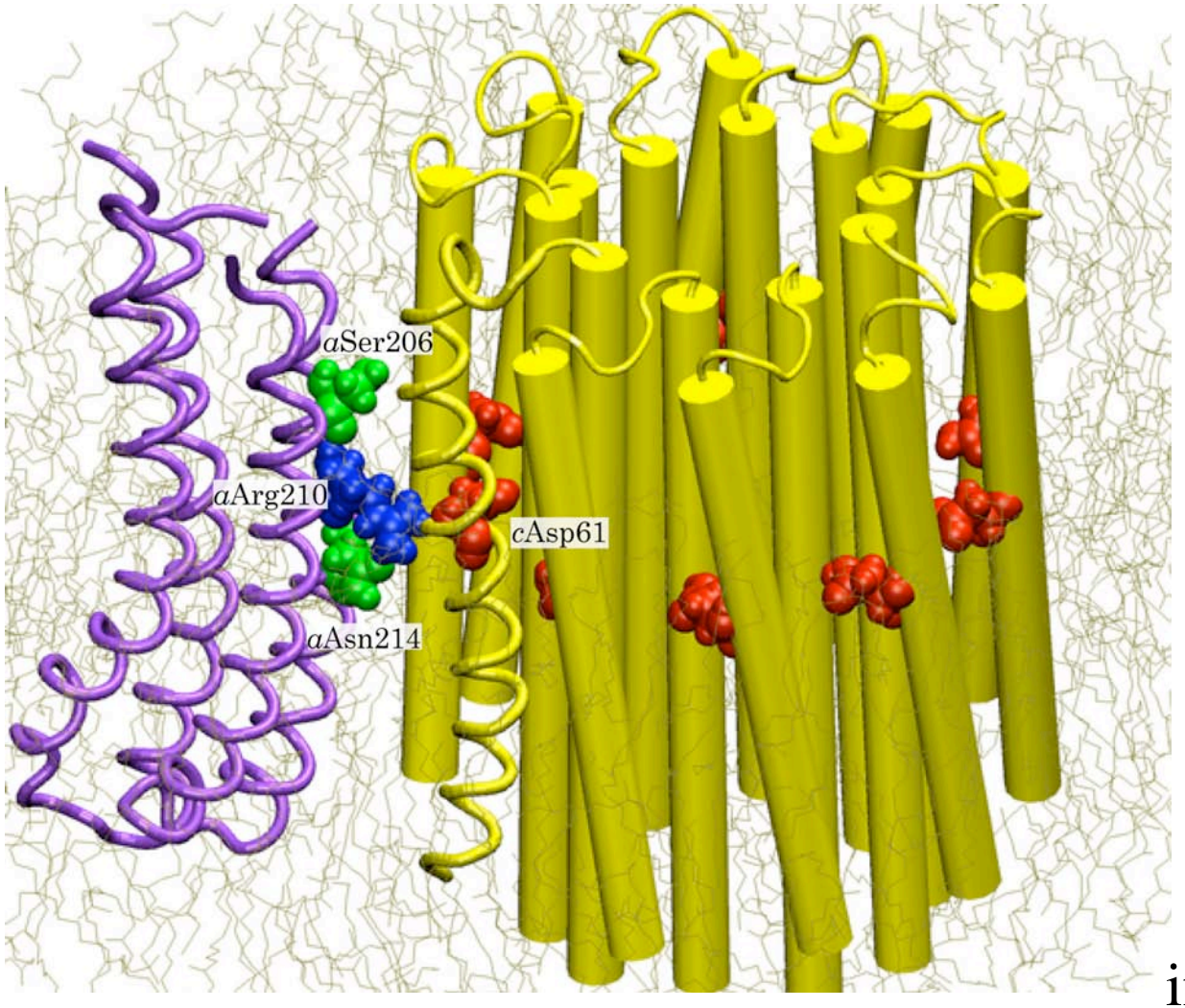
↑

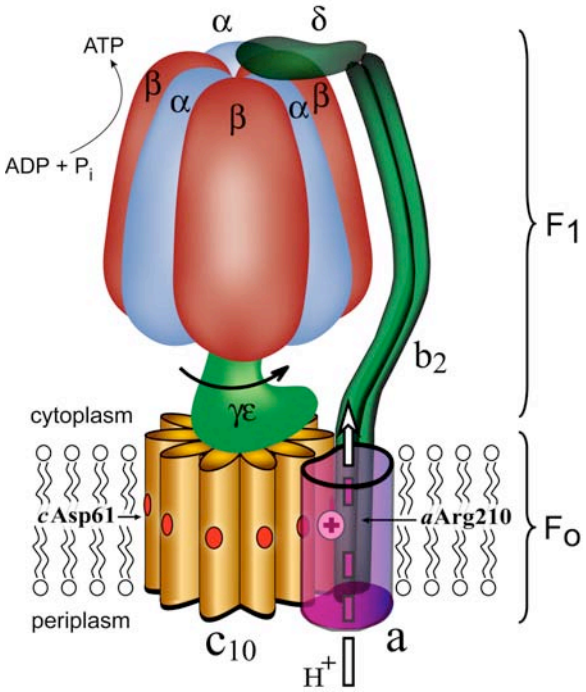
**$10^9$ gap**

↑

Picoseconds: (proton hopping required to fuel the rotation)

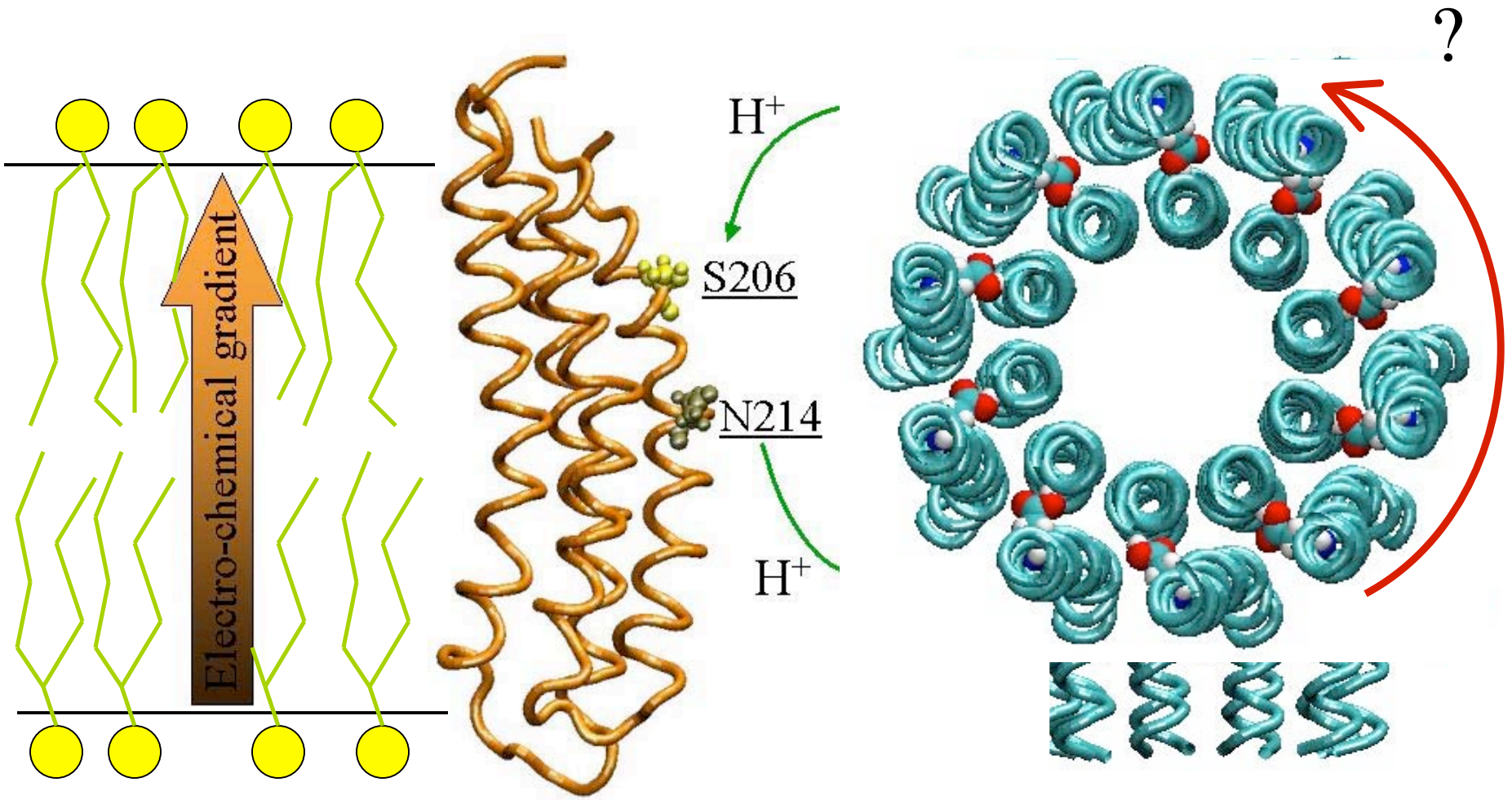
# Structure of the Fo unit




How proton flux induces rotation of $c_{10}$?

# Suggested Mechanism of Proton Translocation




(R.H. Fillingame, 2002)

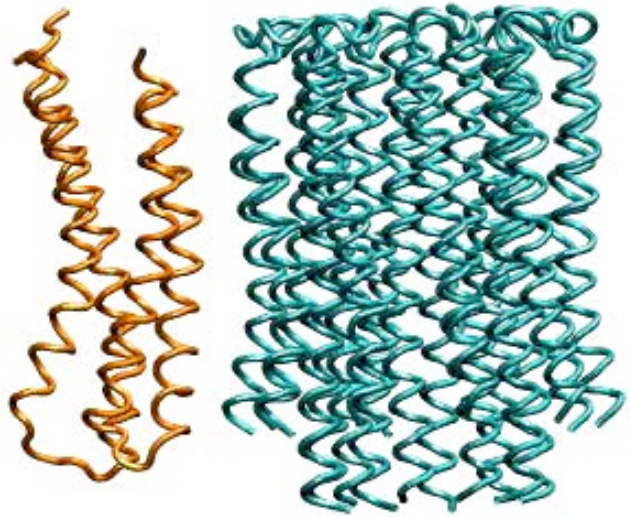
# Structural Model of *E. coli* $F_o$

$a_1c_{12}$ (Rastogi & Girvin, 1999, NMR)

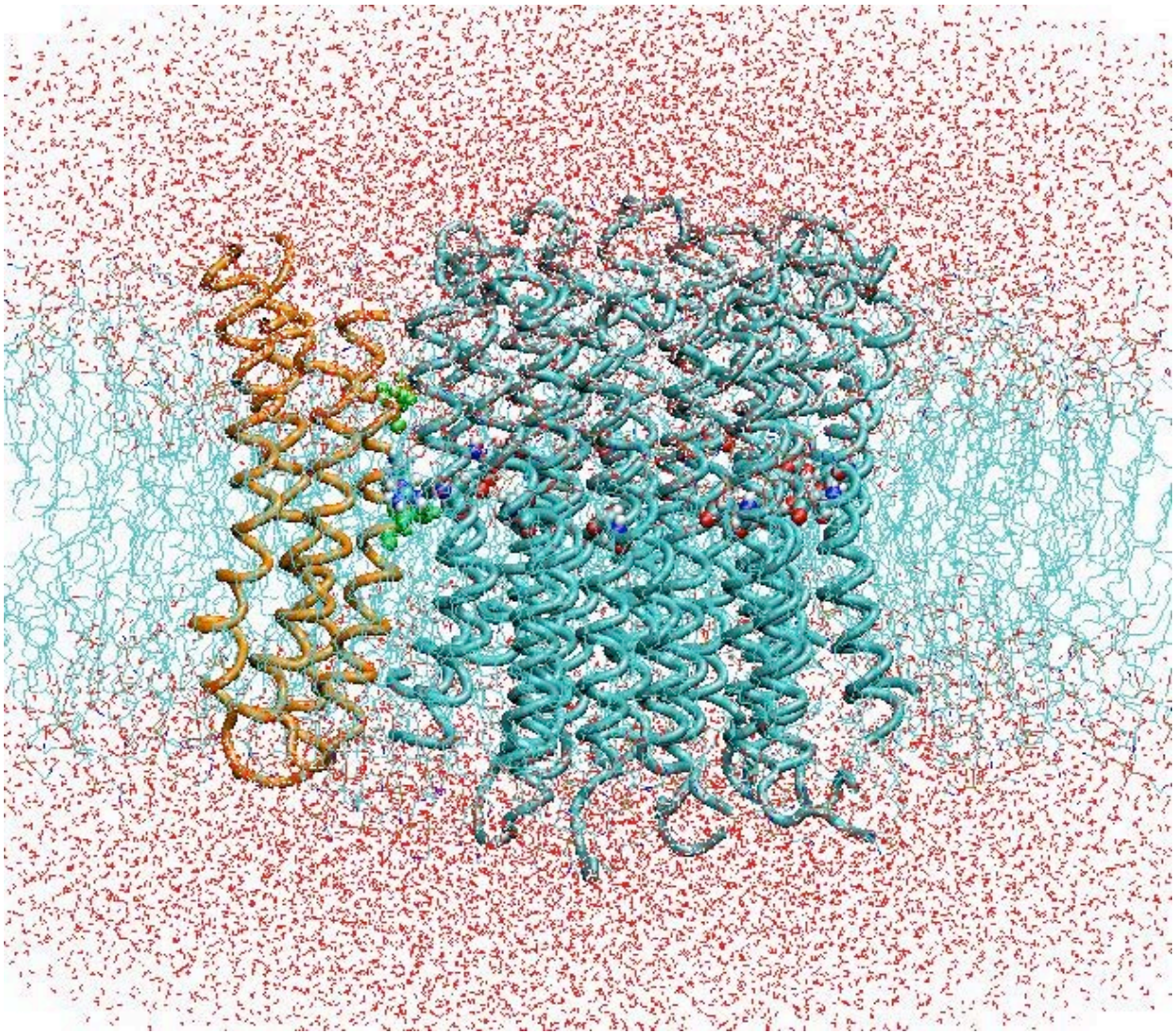
+

$c_{10}$ (Fillingame et al, 1999, NMR)

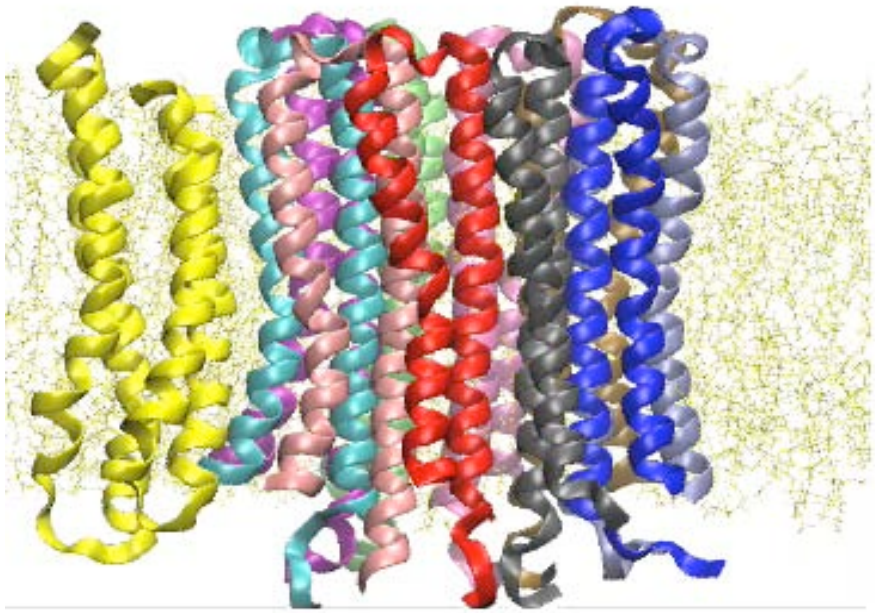
=



$a_1c_{10}$ (2001-2002, modeling)

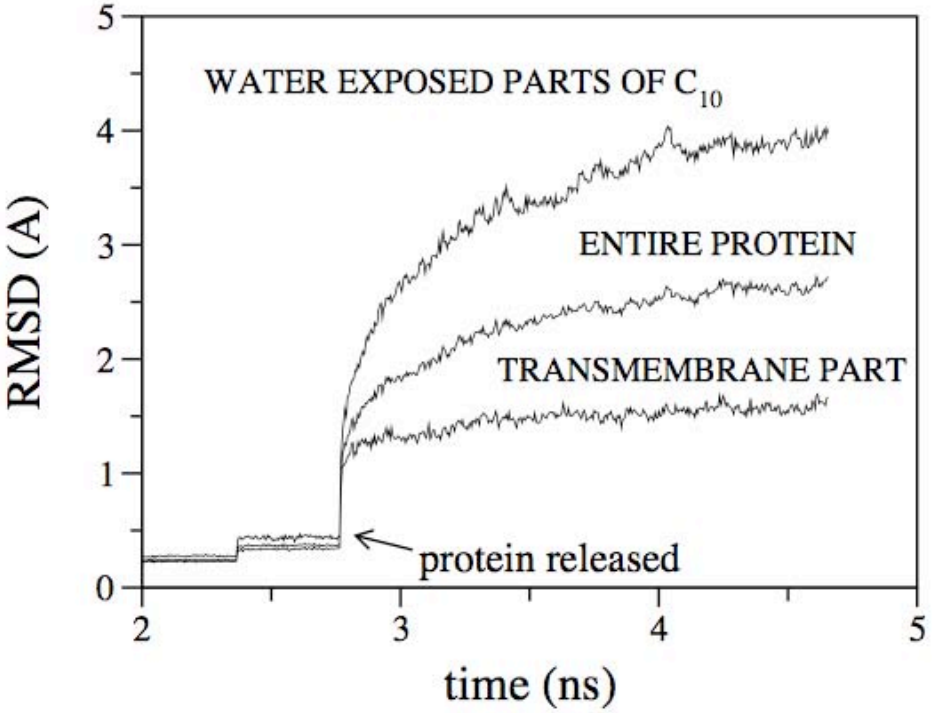


# Simulated Systems

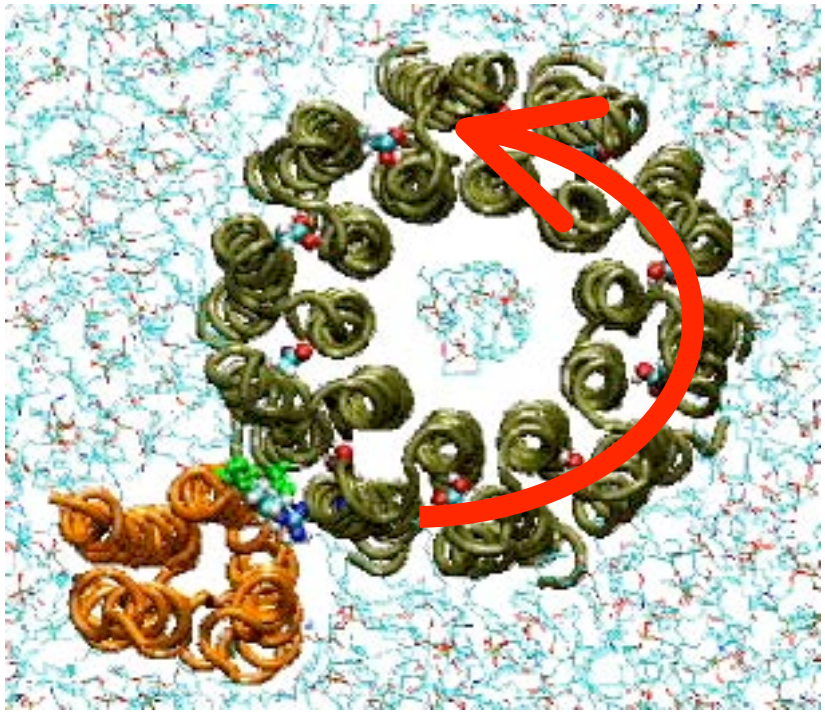


$a_1c_{10}$ + POPE + water
~112,000 atoms

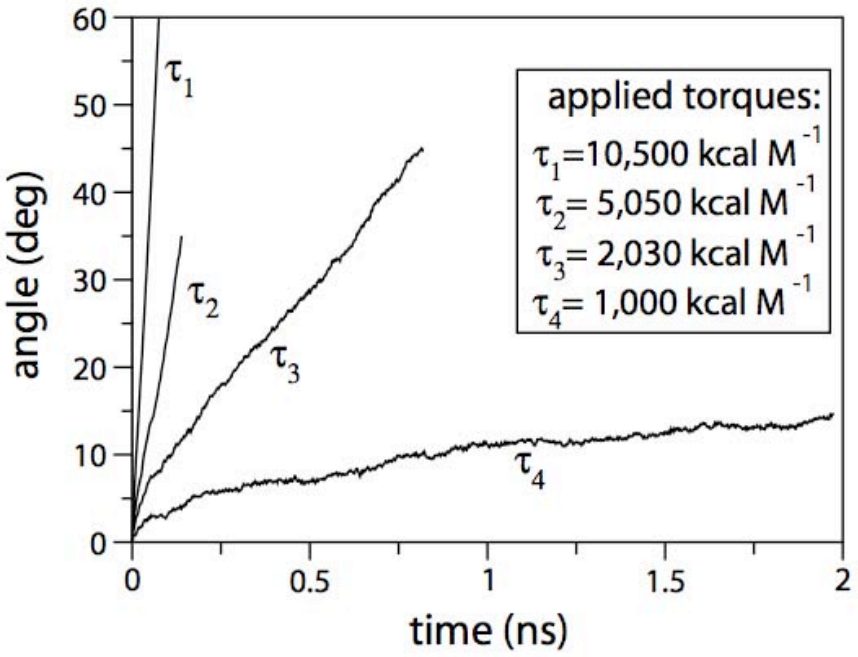
Water exposed parts of the $c_{10}$ oligomer alpha helices begun to unwind



# Forced Rotation of the $c_{10}$ Subunit



Forces were applied to all backbone atoms of $c_{10}$

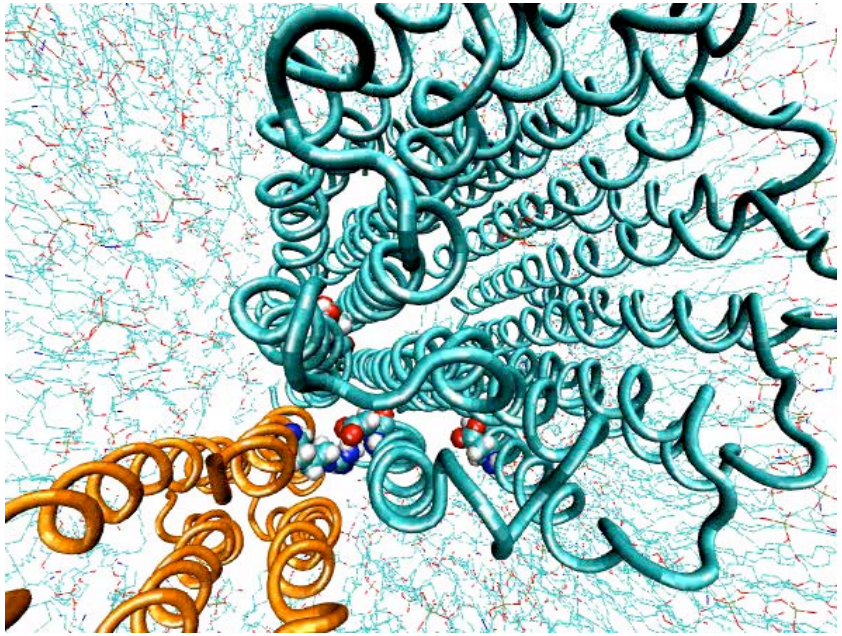



Estimated friction coefficient $\zeta \sim 10^5$ kcal/(M sec)

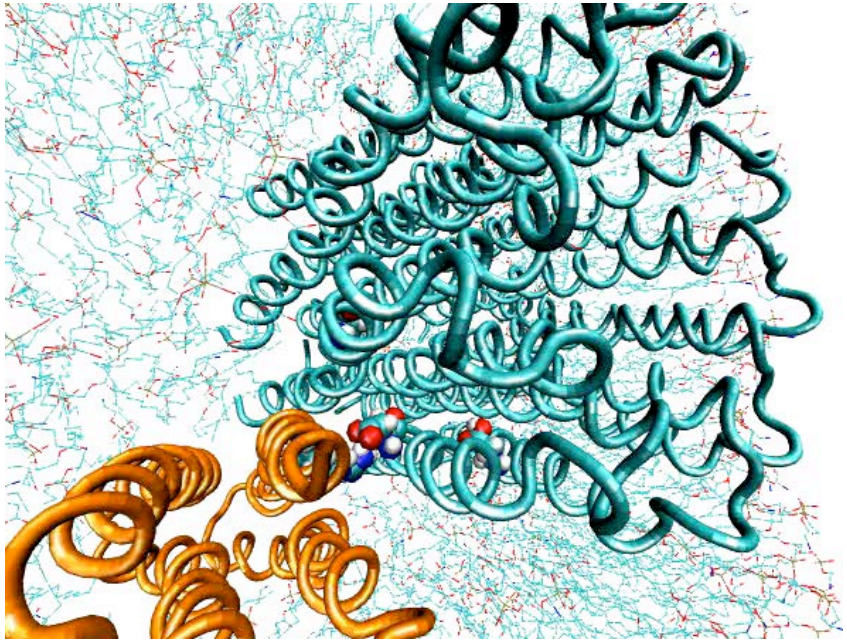
# Salt Bridge $Arg_{210}$-$Asp_{61}$ is Formed

**With only one $Asp_{61}$ residue deprotonated, SMD rotation of $c_{10}$ breaks the structure apart.**

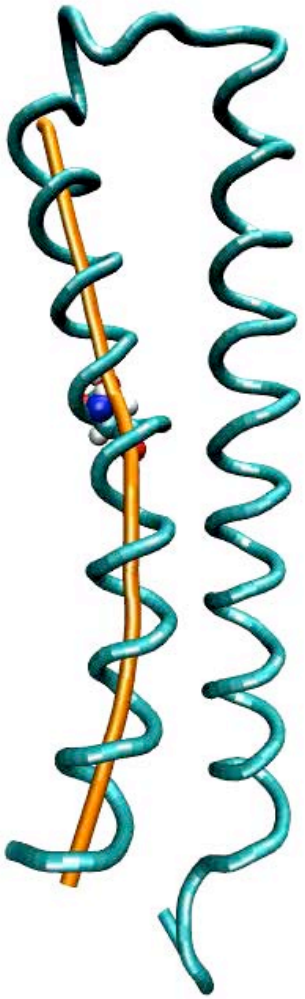
No restraints

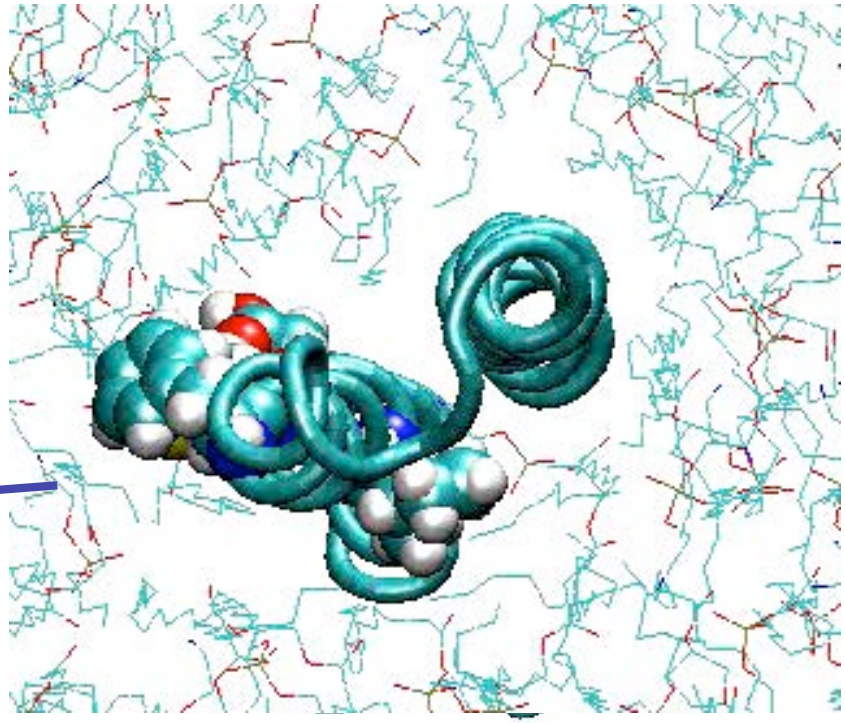


Subunit *a* is restrained



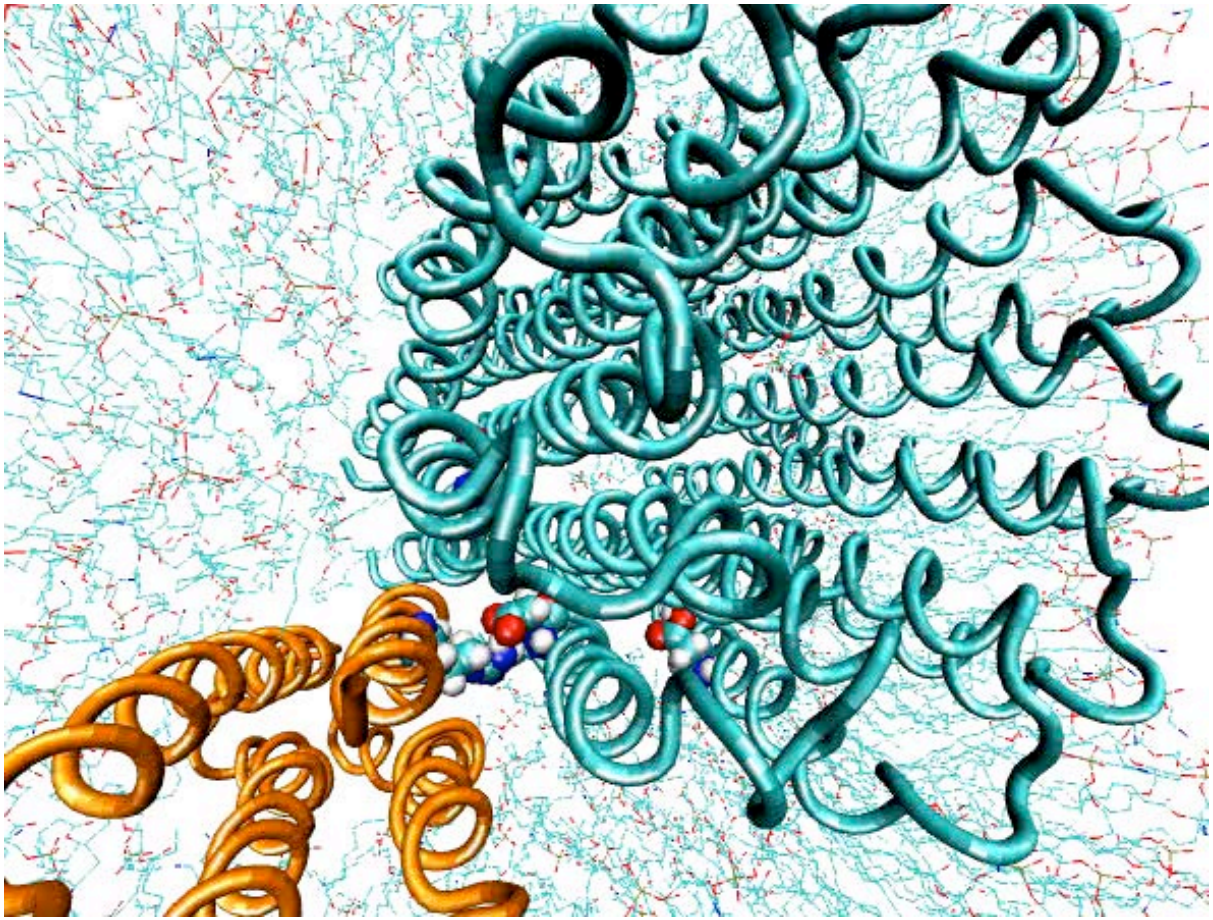
# Single Helix Rotation





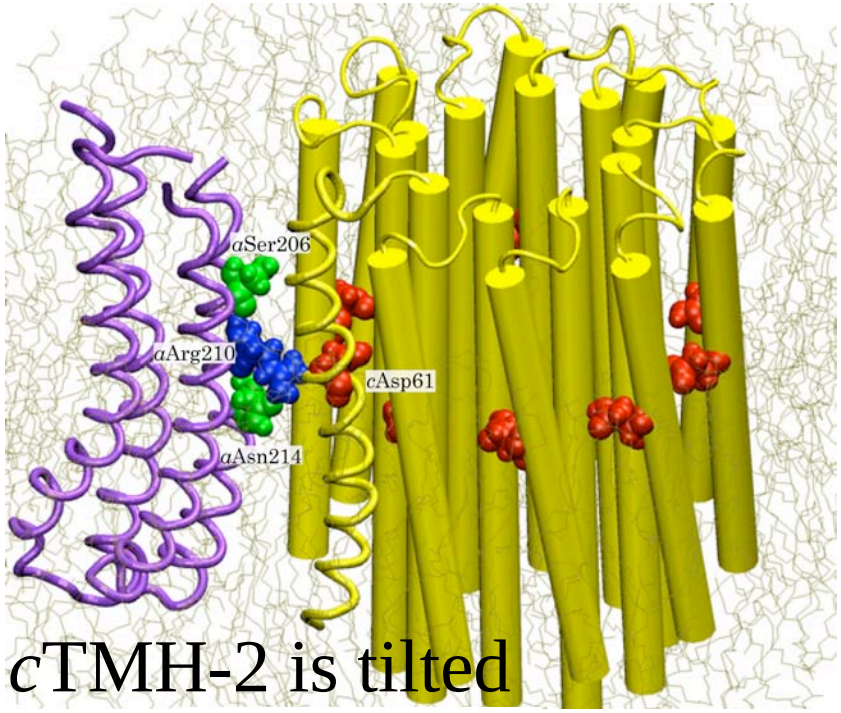
To minimize steric hindrance (critical on nanosecond time scale), helix was forced to rotate in a reptation tube (local pivot points and directors).

# Salt Bridge Can Be Transfered

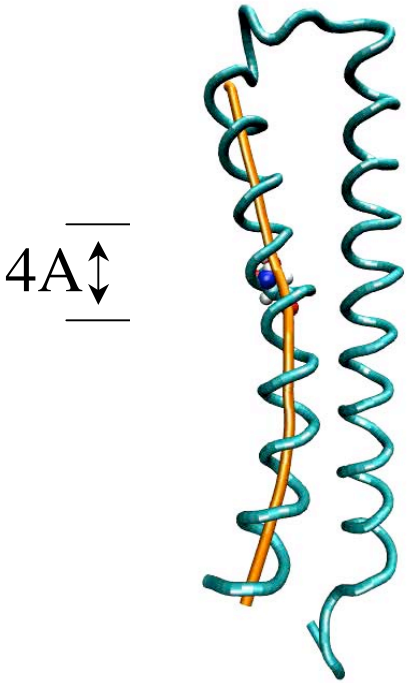


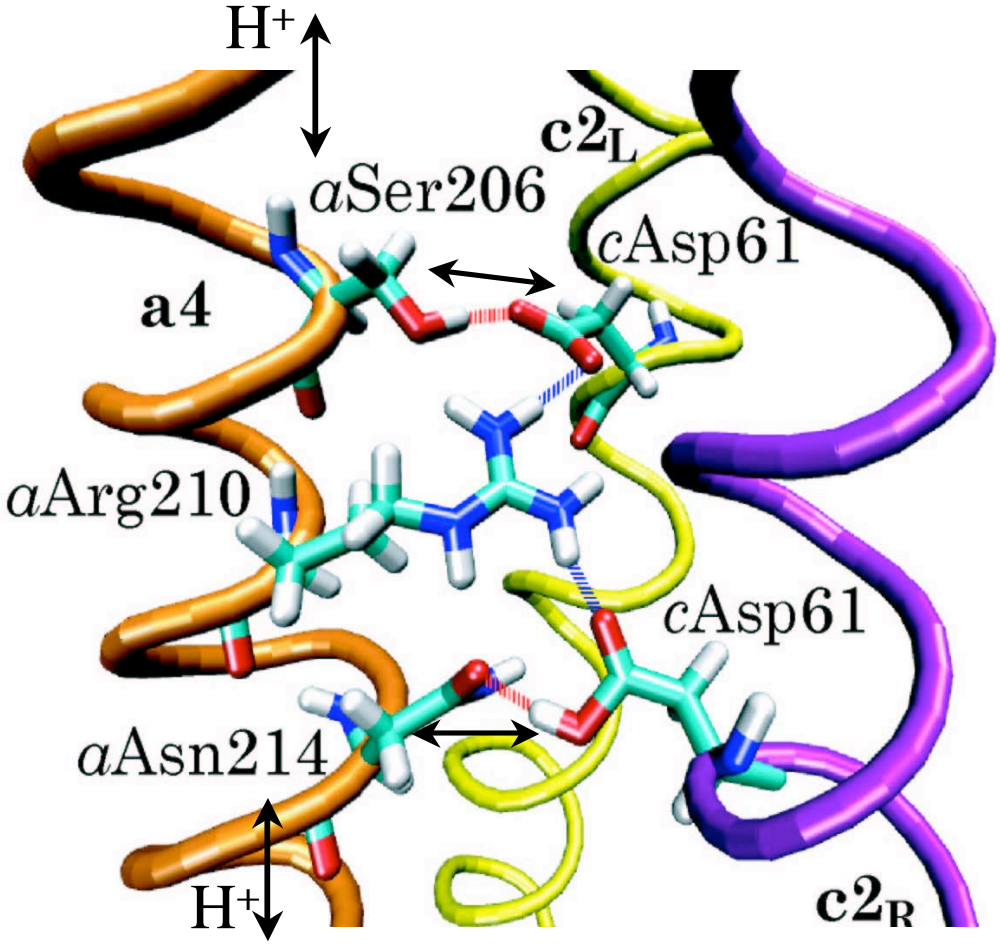
The salt bridge can be transferred by the concerted rotation of the $c_{10}$ complex and the outer TMH of subunit *c*

# Molecular mechanism for unidirectional rotation

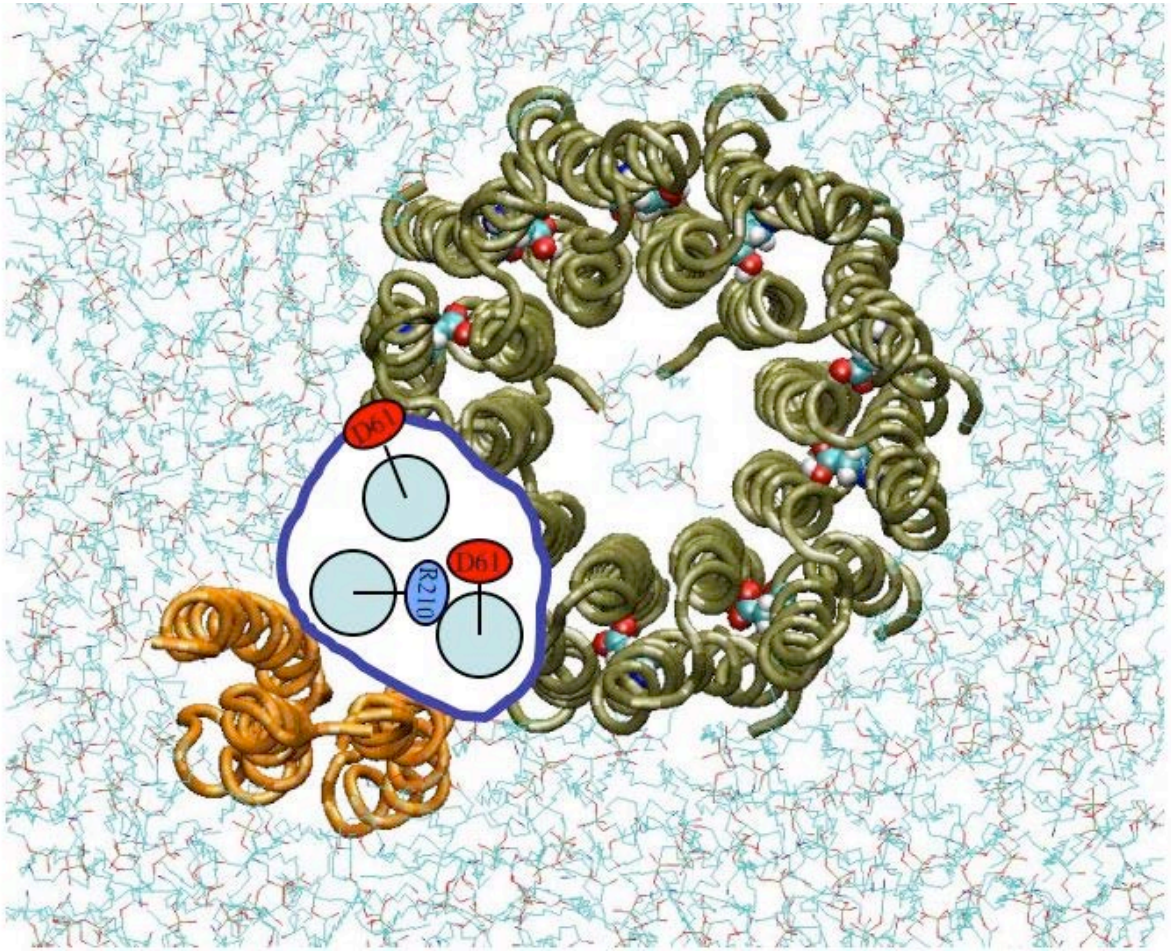



*c*TMH-2 is tilted



# Stochastic model




Microscopic model

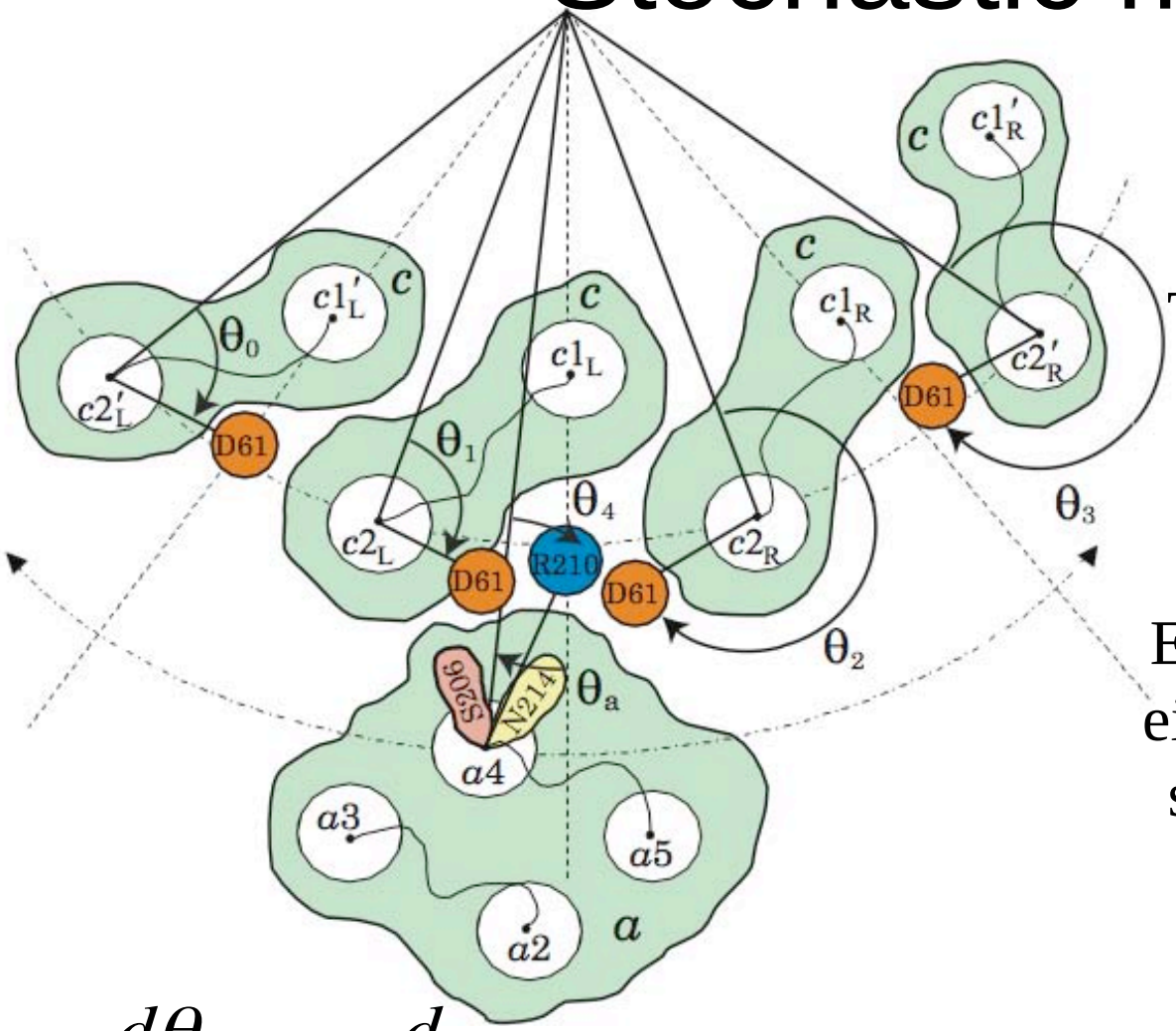
↓

Reduced system

↓

Principle degrees of freedom

# Stochastic model

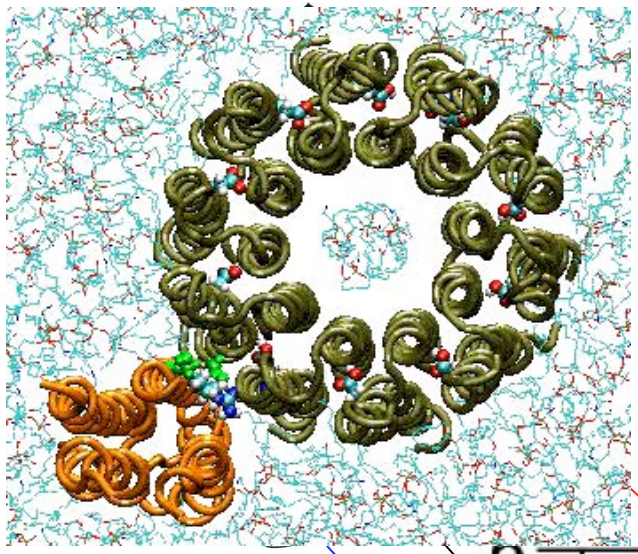


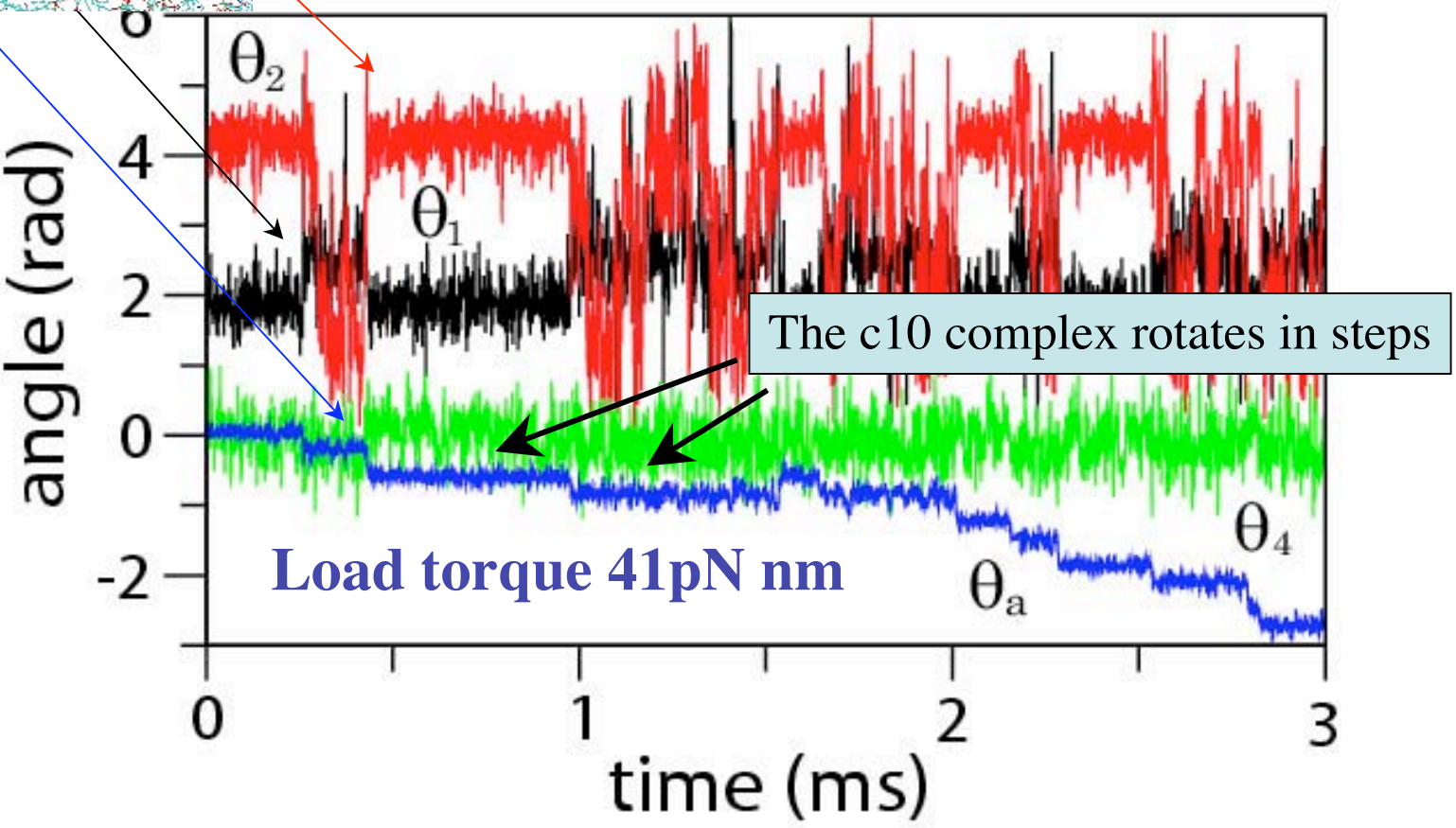

6 degrees of freedom: $\theta_0$, $\theta_1$, $\theta_2$, $\theta_3$, $\theta_4$ are TMH rotation angles; $\theta_A$ - position of the *a* subunit

Each Asp61 can be in either of two chemical states (protonated or deprotonated).

$$\zeta_i \frac{d\theta_i}{dt} = -\frac{d}{d\theta_i}[\mathrm{U}_{\mathrm{group}} + \mathrm{U}_{\mathrm{hydroph.}} + \mathrm{U}_{\mathrm{internal}} - \tau\theta_a] + \eta_i(t)$$

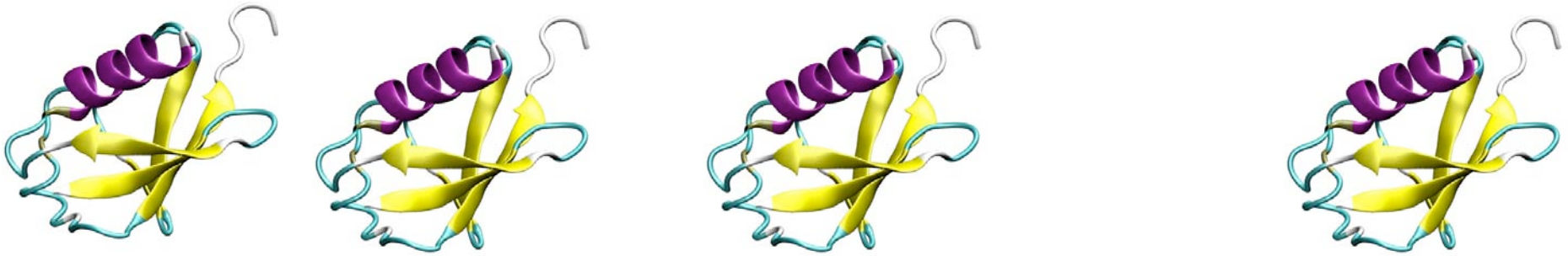
# Stochastic Simulations of $F_o$ Operation





# TclForces

Constant force to all atoms



t=0 t=1 t=2 t=3

$x = a\,t^2\,/2$

$F = ma \longrightarrow a = F\,/m$

# Exemplary script

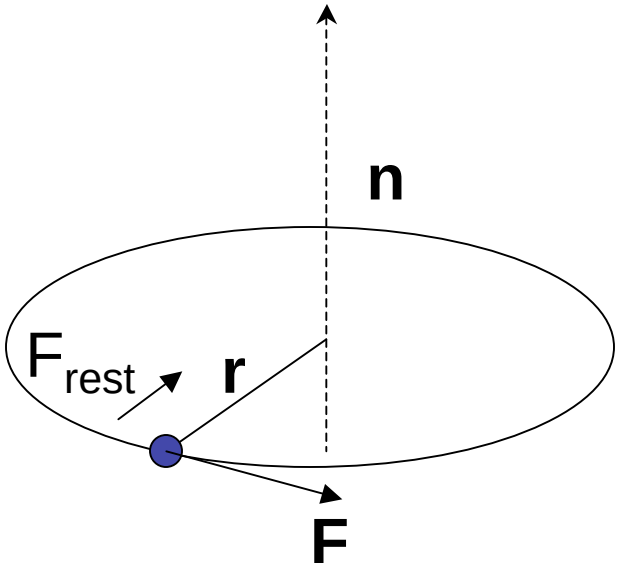
NAMD config file

```
tclforces         on
set linaccel      "30 0 0"
tclforcesscript   push.tcl
```

TclBC custom script

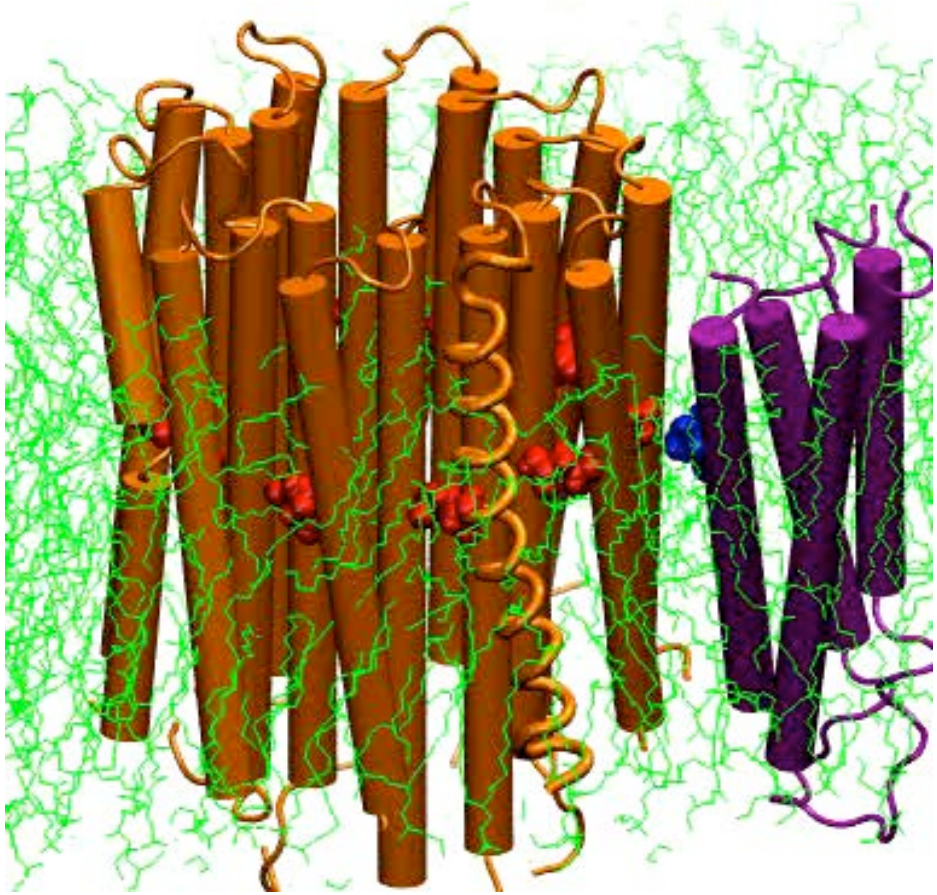
```
set numatoms 1231

set atoms {}
for { set i 1 } { $i <= $numatoms } { incr i } {
    lappend atoms $i
}

foreach atom $atoms {
    addatom $atom
}

# Convert input to NAMD units: kcal/(mol*Ang*amu)
set linaccel_namd [vecscale [expr 1.0/418.68] $linaccel]

print "Linear acceleration applied: ($linaccel) Ang*ps^-2"

proc calcforces { } {
    global atoms numatoms linaccel_namd

    loadcoords coords
    loadmasses masses

    set comsum "0 0 0"
    set totalmass 0
    foreach atom $atoms {
        # Take force vector from NAMD config file
        set force [vecscale $masses($atom) $linaccel_namd]
        addforce $atom $force
        set comsum [vecadd $comsum [vecscale $masses($atom) $coords
($atom)]]
        set totalmass [expr $totalmass + $masses($atom)]
    }
    print "Center of mass = [vecscale [expr 1.0/$totalmass] $comsum]"
}
```

# Rotation of the c-ring

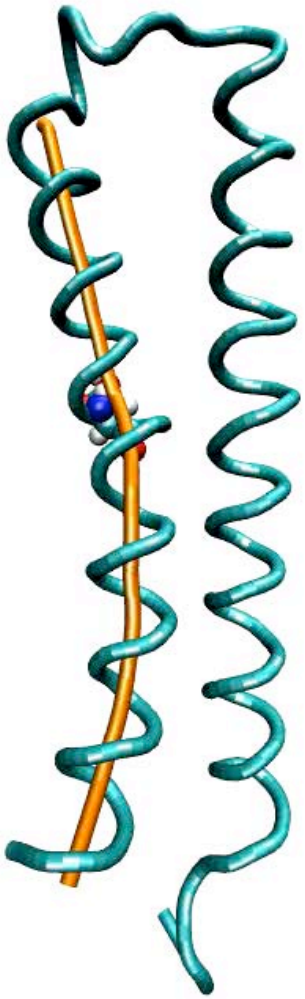


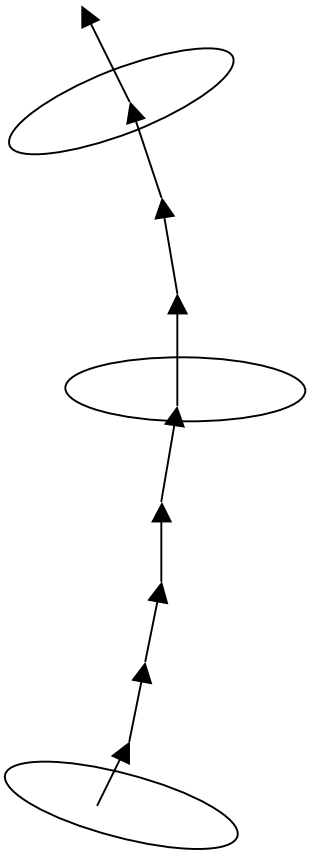

$\mathbf{F} = C\,\rho(z)\,[\mathbf{r} \times \mathbf{n}]$

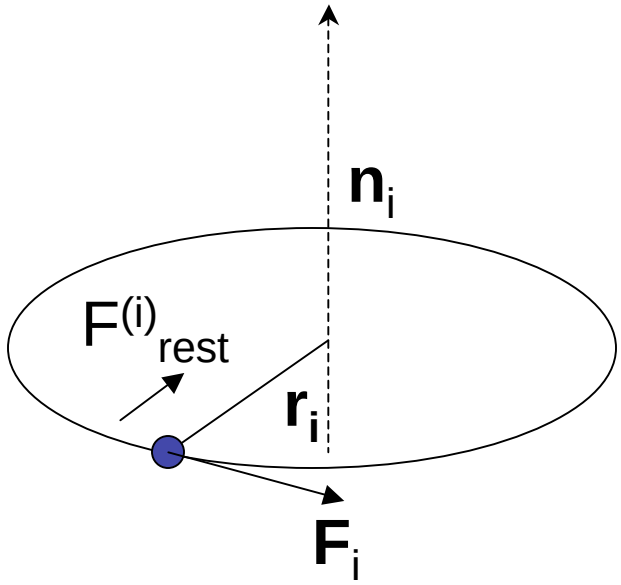
$\mathbf{F}_{rest} = k\,(\mathbf{r}-\mathbf{r}_0)$



# Single Helix Rotation





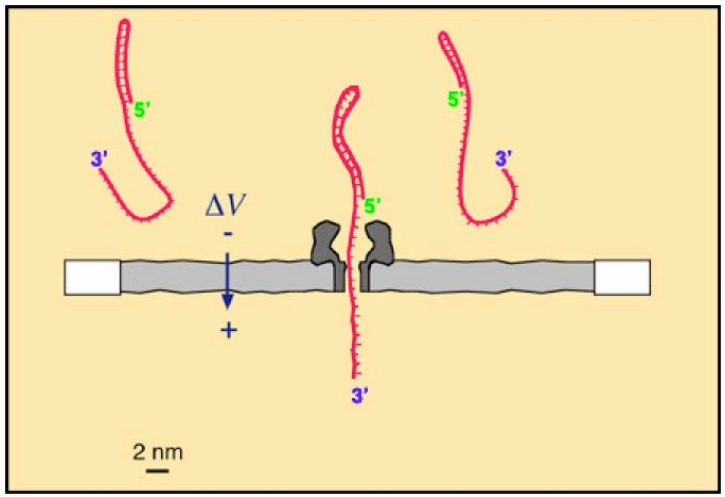


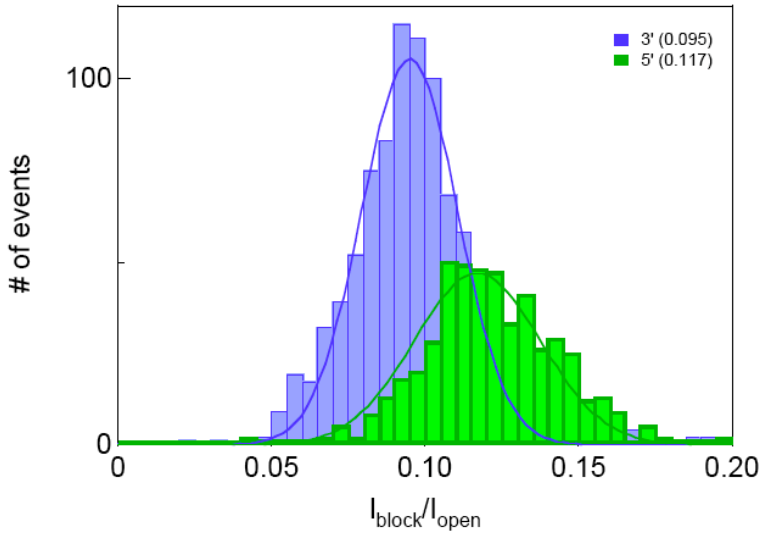

$$\mathbf{F}_i = C\,[\mathbf{r}_i \times \mathbf{n}_i]$$

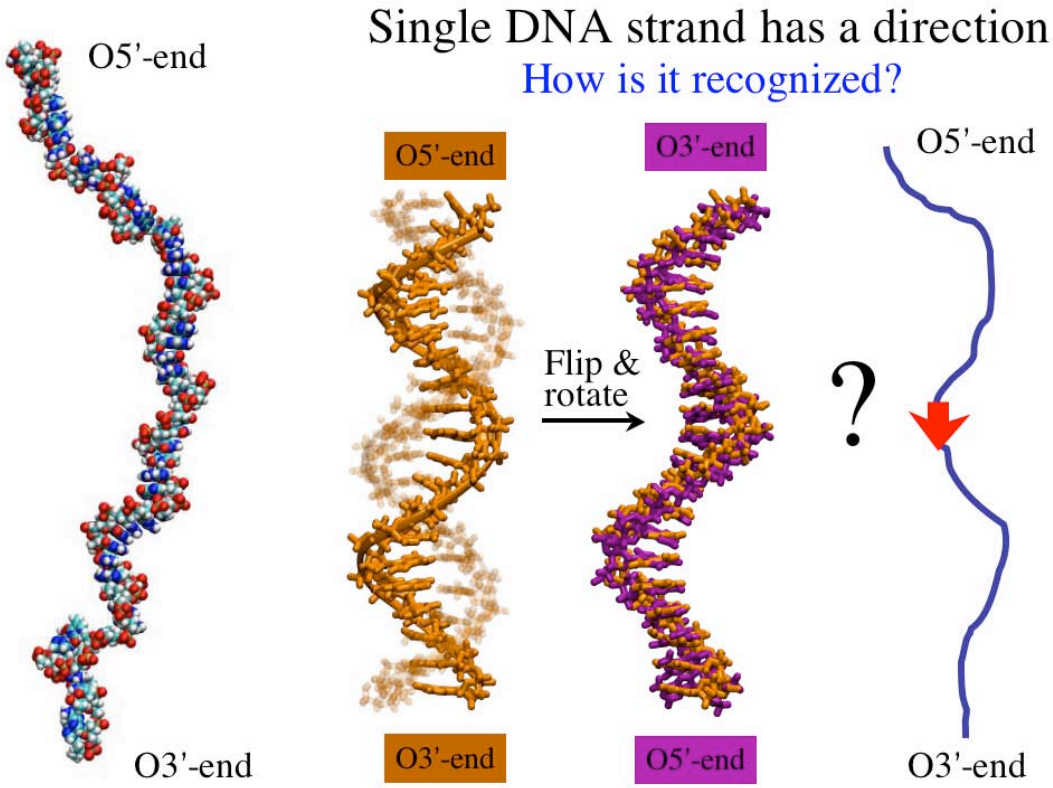
$$\mathbf{F}^{(i)}_{rest} = k\,(\mathbf{r}_i - \mathbf{r}^{(i)}_0)$$

Local directors and pivot points for rotation

# Translocation of DNA through alpha-hemolysin

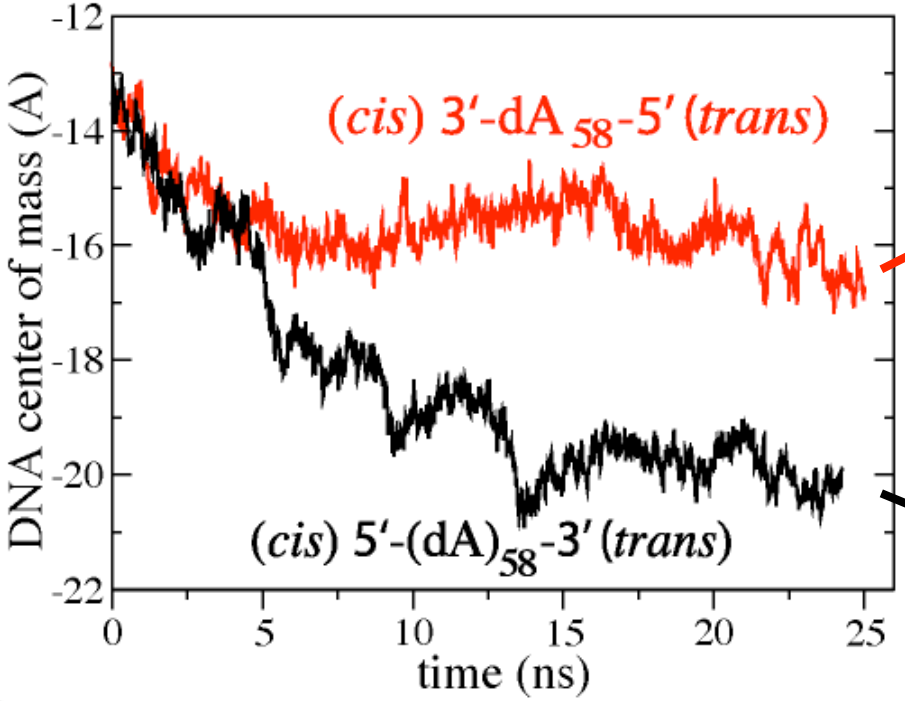


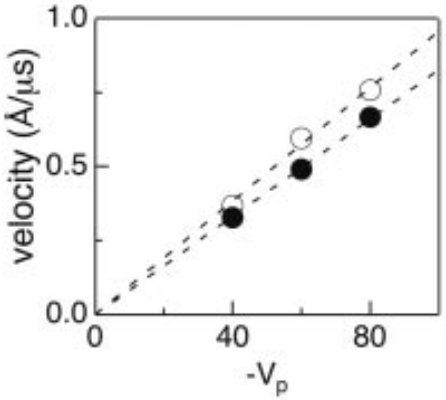



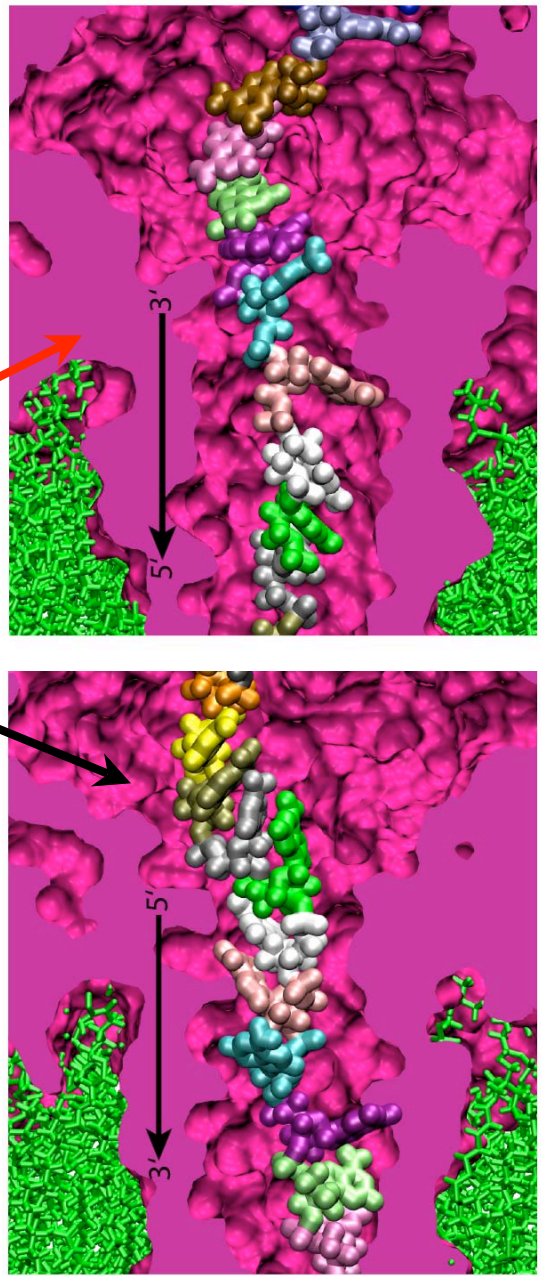

Experiment: Jerome Mathe and Amit Meller

Pushing a DNA strand through a pore is …
like bringing a X-mass three through a door

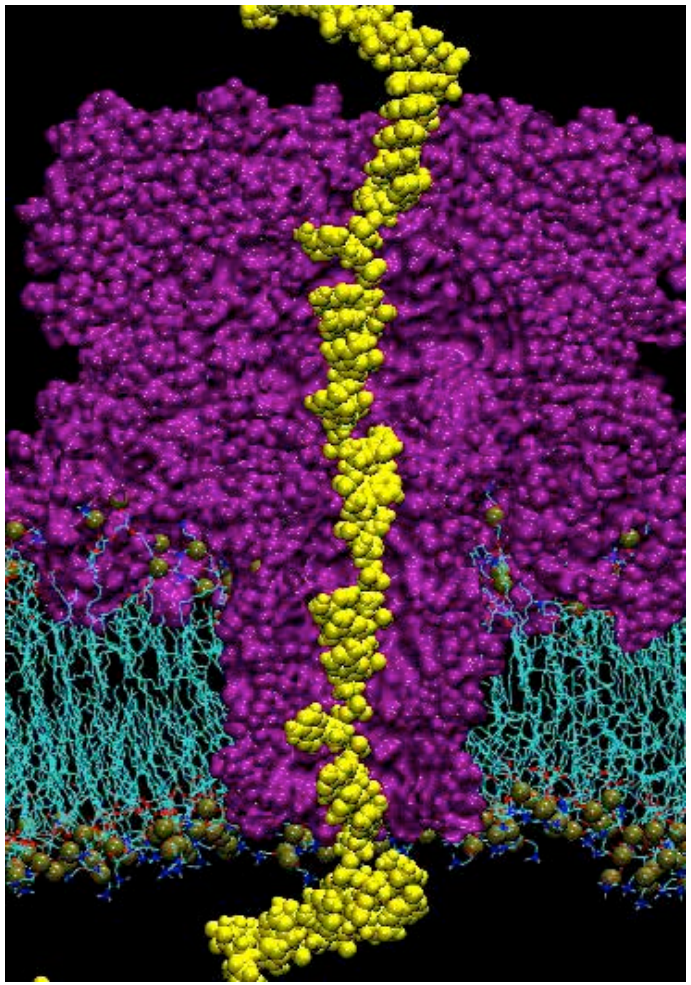


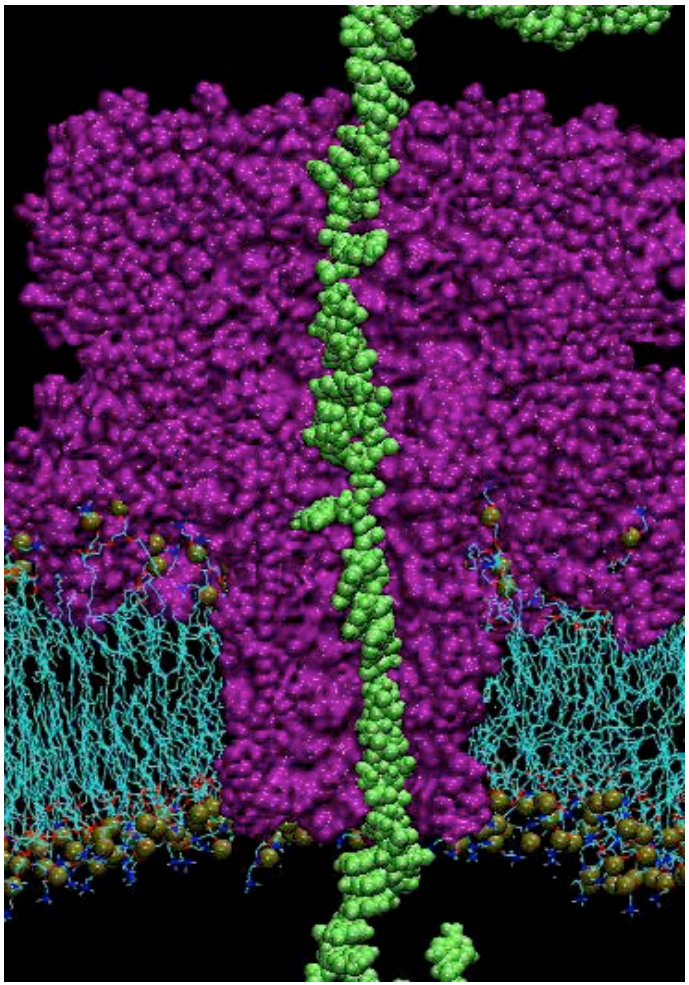

Experiment:
J. Mathe *et al*
PNAS 2005



# SMD simulation of DNA translocation through α-hemolysin

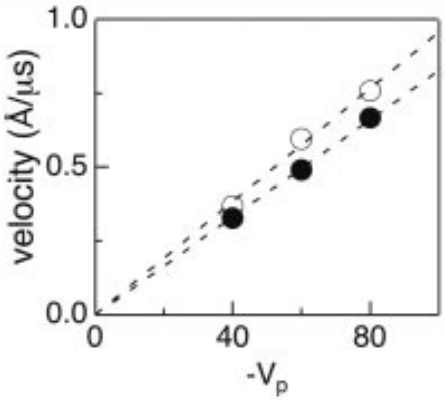


3’-end first



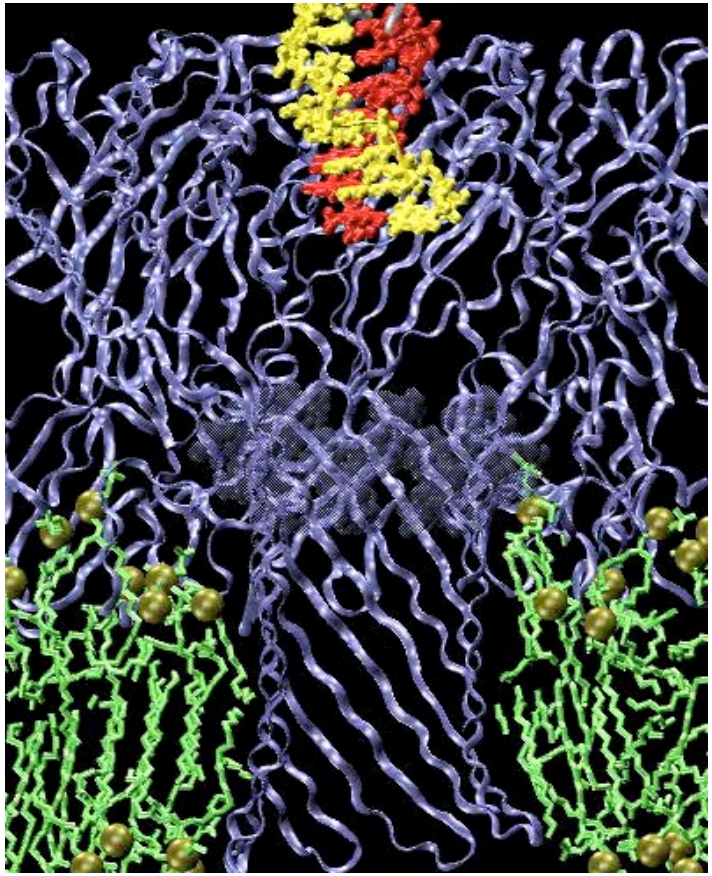
5’-end first

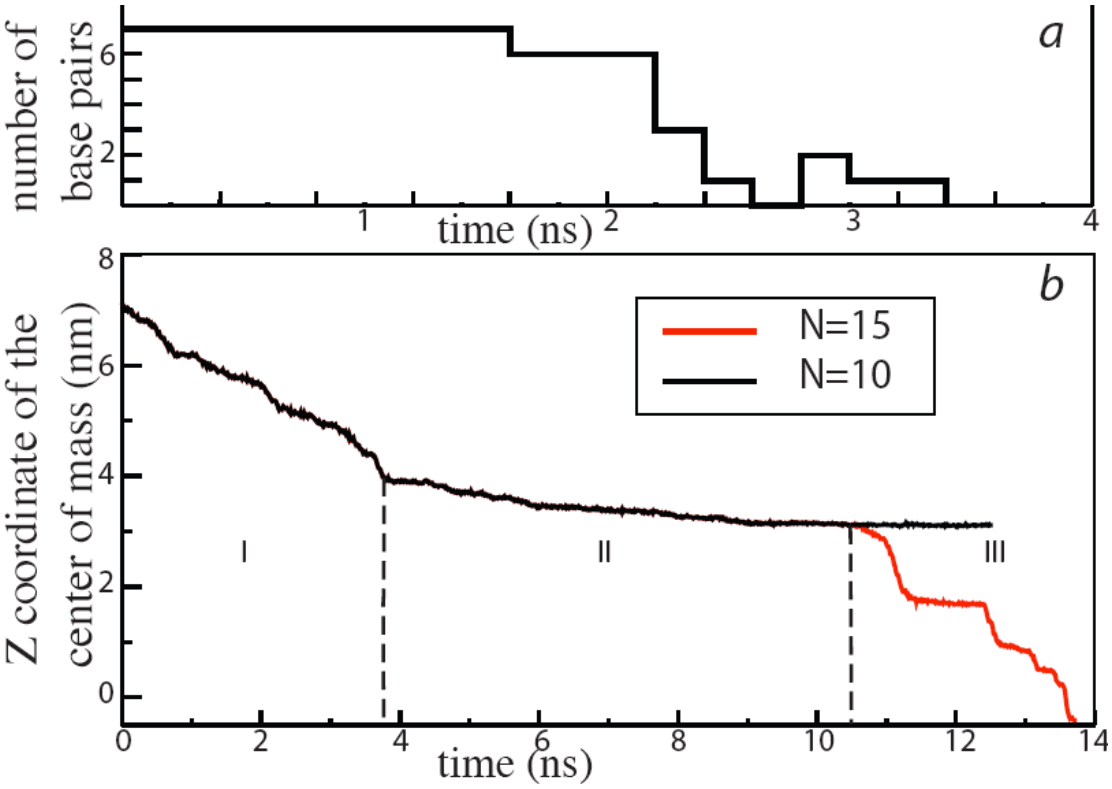
**3’-end-first translocation is about 10% faster**



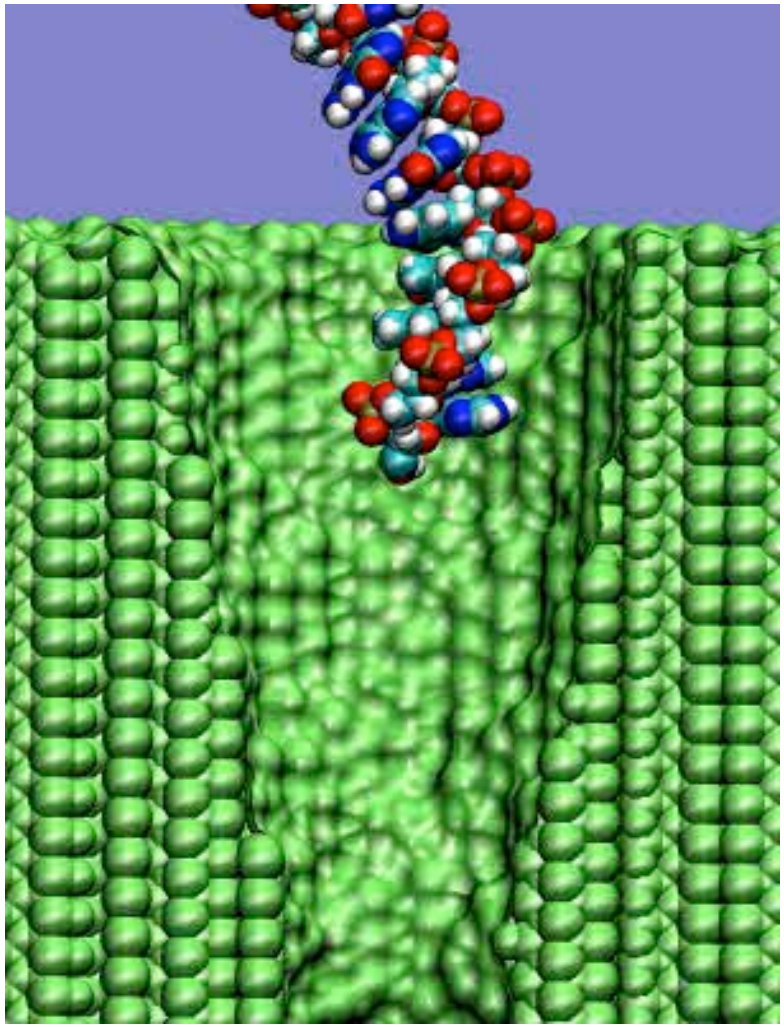

J. Mathe *et al*
PNAS 2005

# SMD simulations of DNA hairpin permeation through a-hemolysin





# Translocation of single-stranded DNA

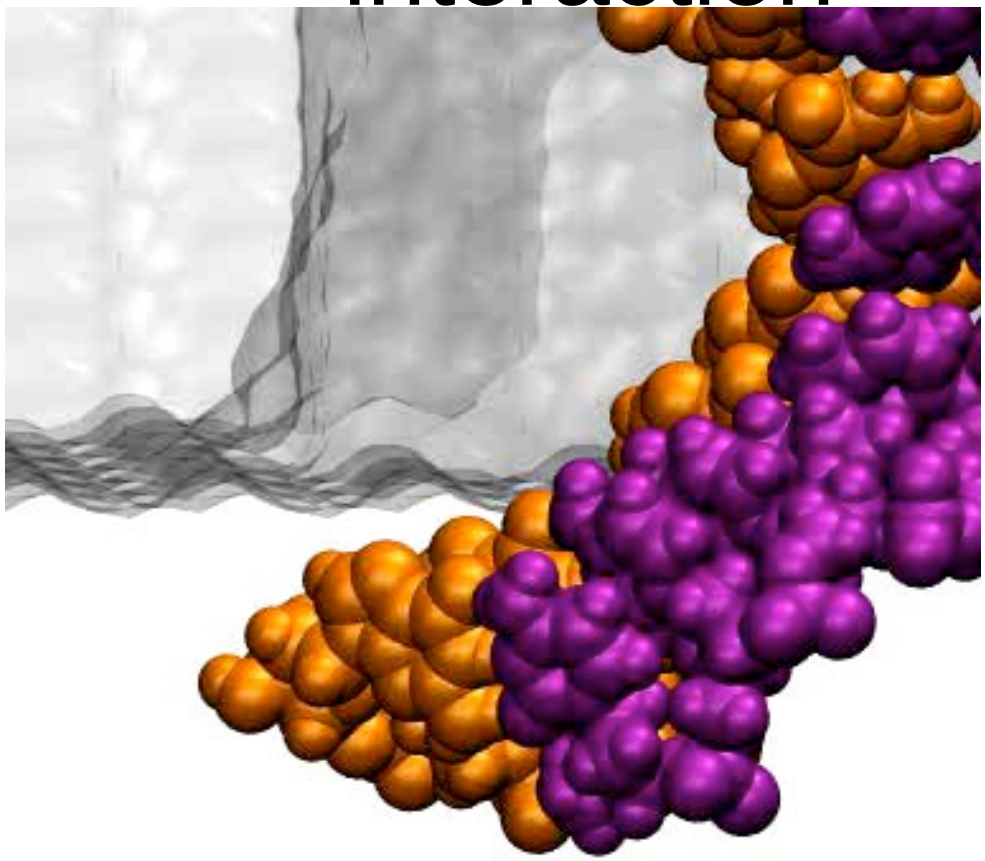


MD simulation of single stranded DNA translocation through 1.5-nm-diameter pore

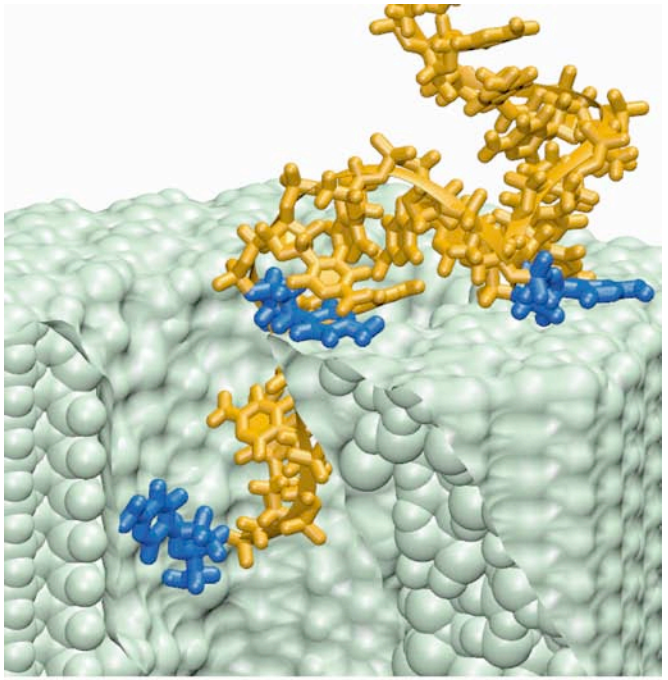
1.3 V / 10 nm;
Time: 17.5ns

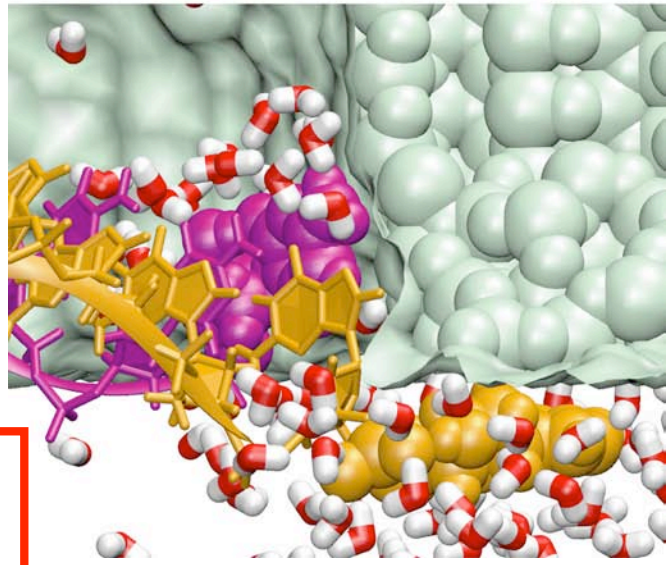
The translocation halts b/c the DNA sticks to the wall!

# DNA - nanopore interaction



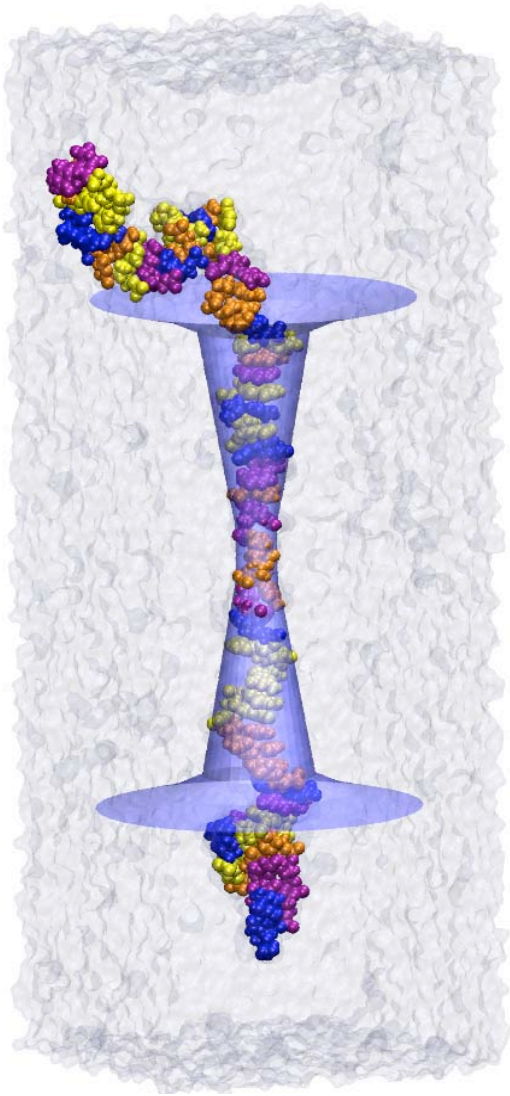
140mV bias, 26 ns total simulation time





Hydrophobic adhesion of DNA bases to the pore wall slows down DNA translocation

# Pruning DNA-nanopore interaction with phantom pores

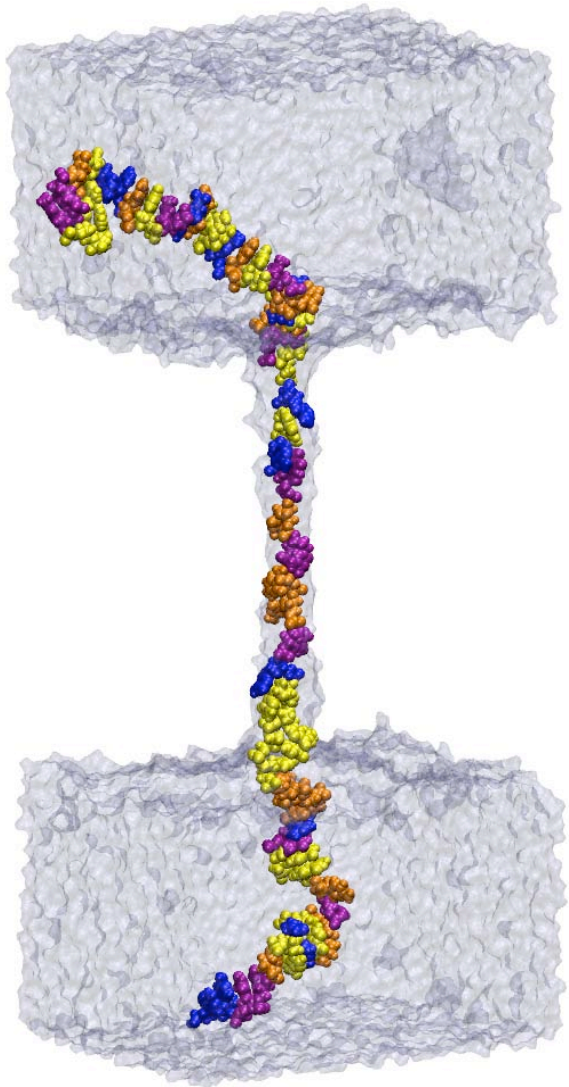


Steric friction between DNA and the pore

←

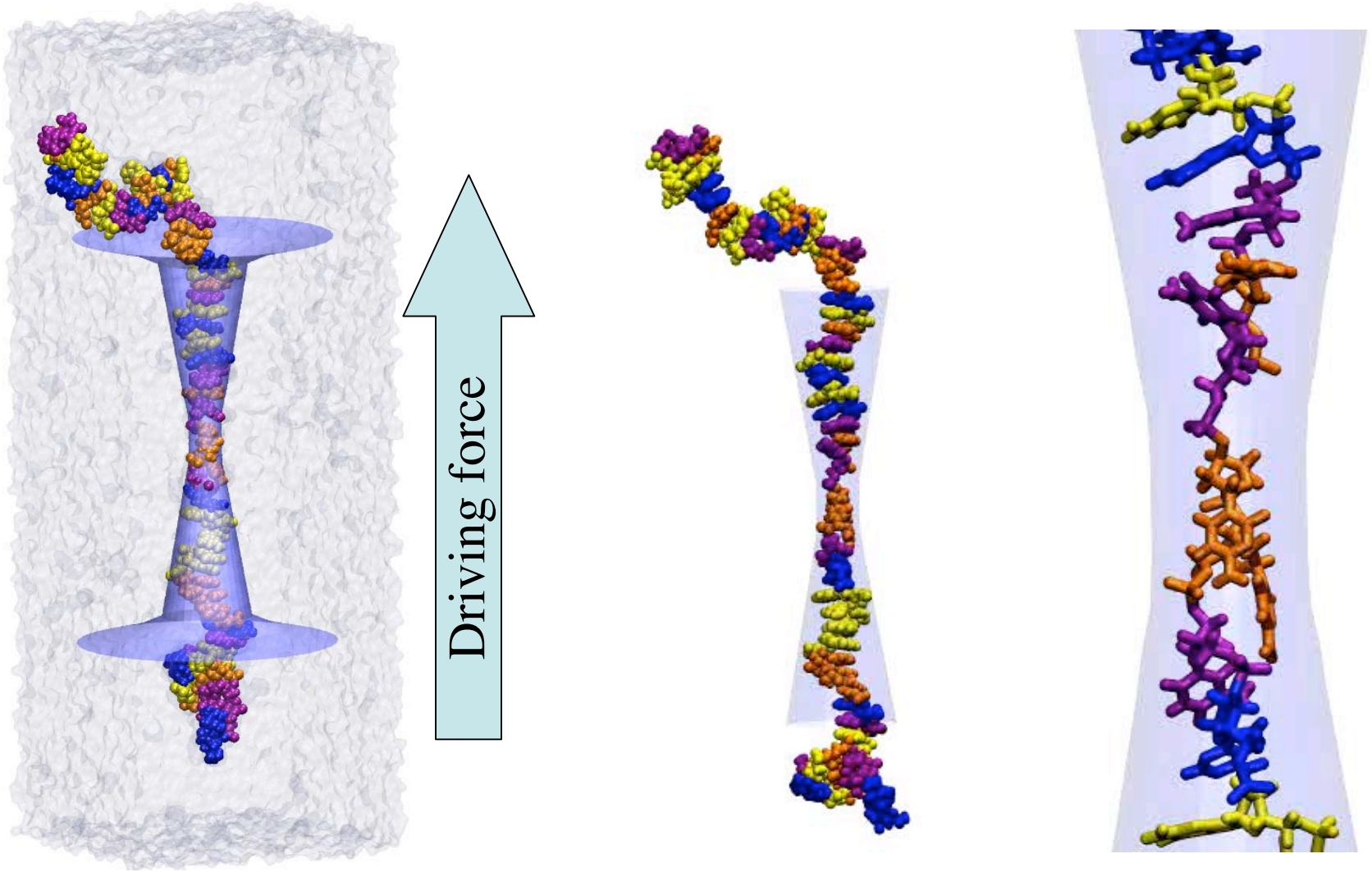
Steric friction and screening of the DNA charge by counter ions

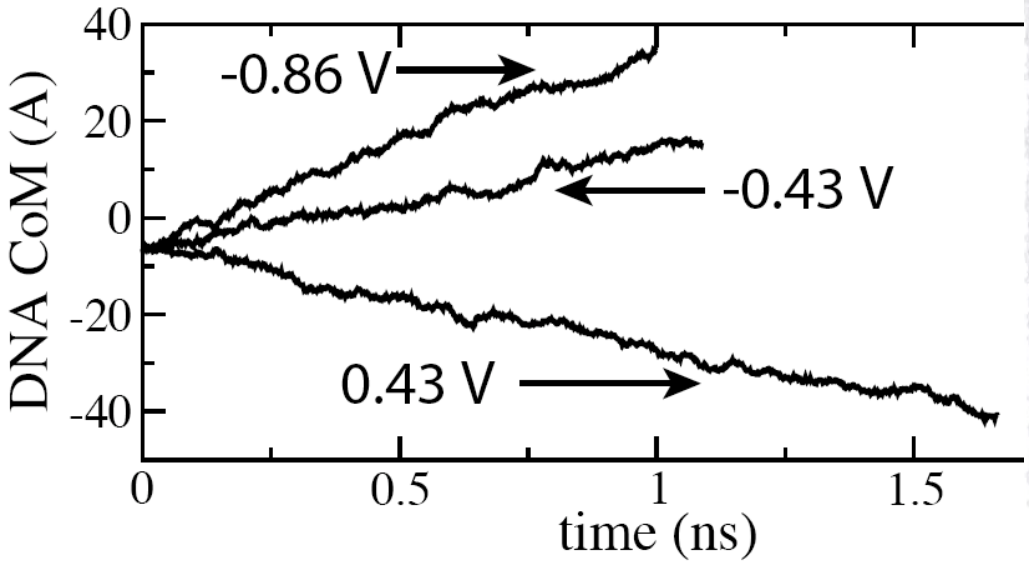
→

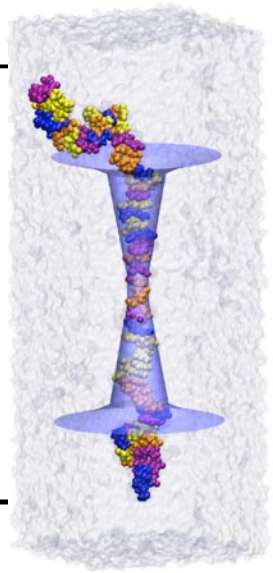


**Mathematical surface confines DNA**

# Translocation of single-stranded DNA through a phantom pore

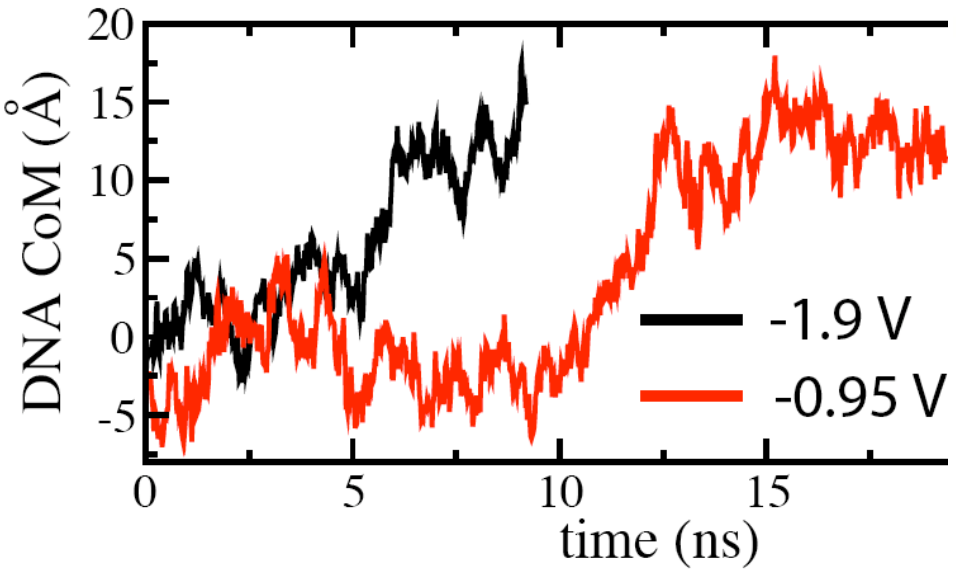


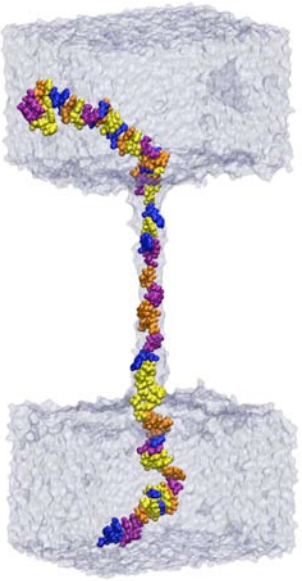


- steric friction
- no screening by counter-ions
- no surface adhesion

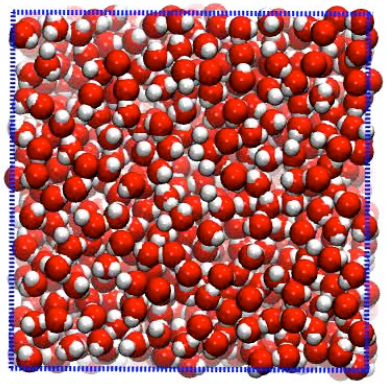
- steric friction
- screening by counter-ions
- no surface adhesion

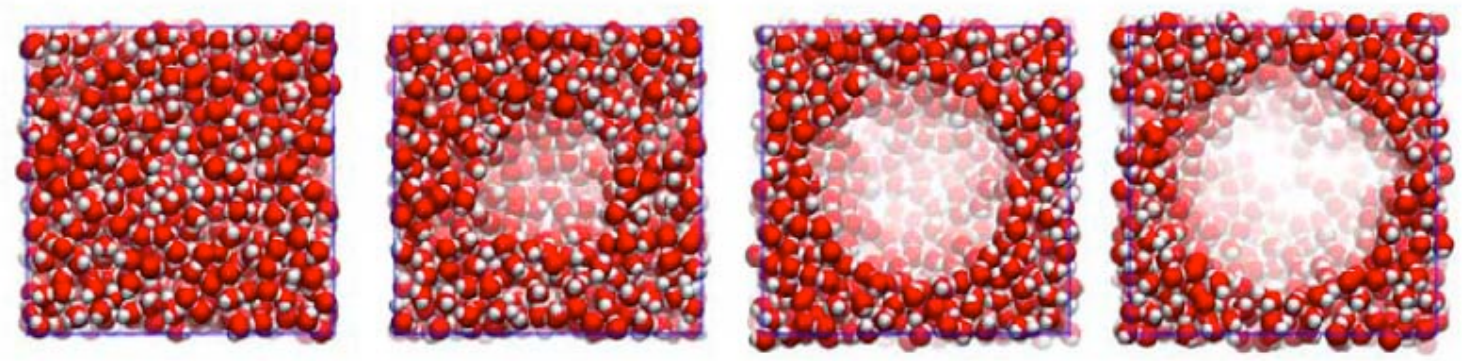


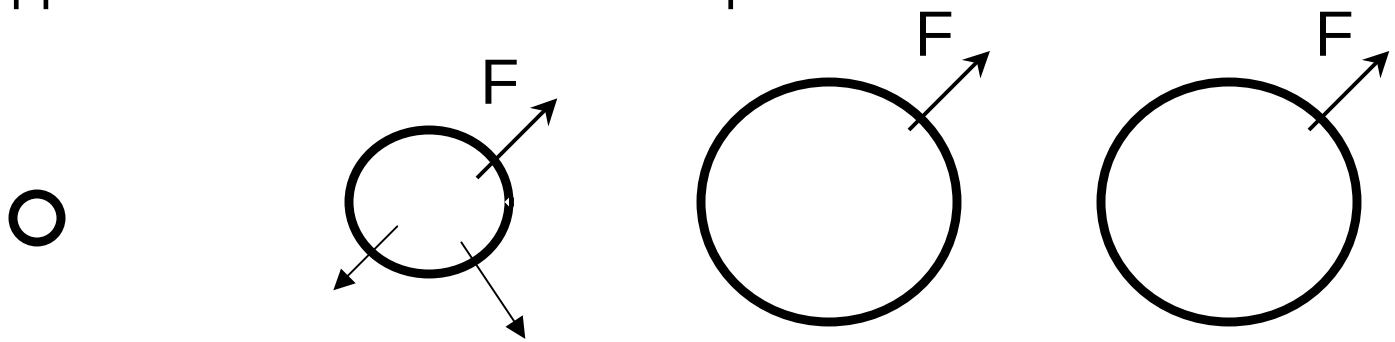
**Screening by counter-ions dominates over steric friction in narrow (~1-nm-diameter) pores**

# Making bubble with TclBC





Force is applied to all atoms inside the sphere



# Exemplary script

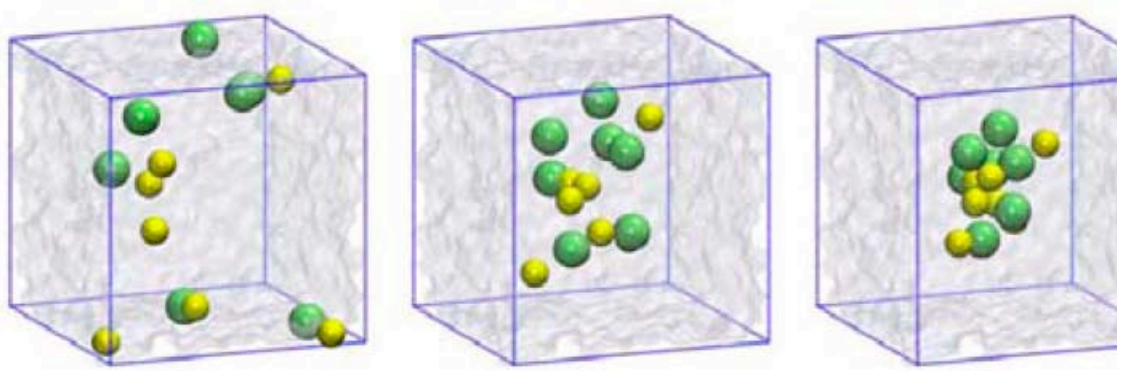
NAMD config file

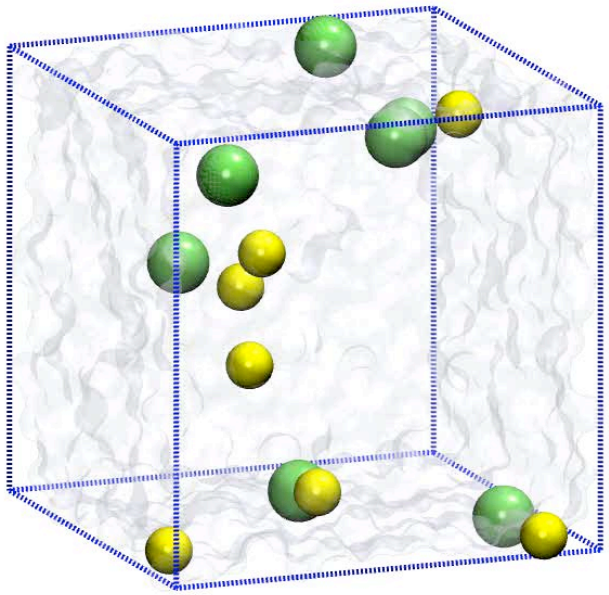
```
tclBC on
tclBCScript {
  set bubbleCenter    "0.0  0.0  0.0"
  set tclBCScript     < your working directory >/bubble.tcl
  source $tclBCScript
}
tclBCArgs {0. 15. 0.01 5.}
```

TclBC custom script

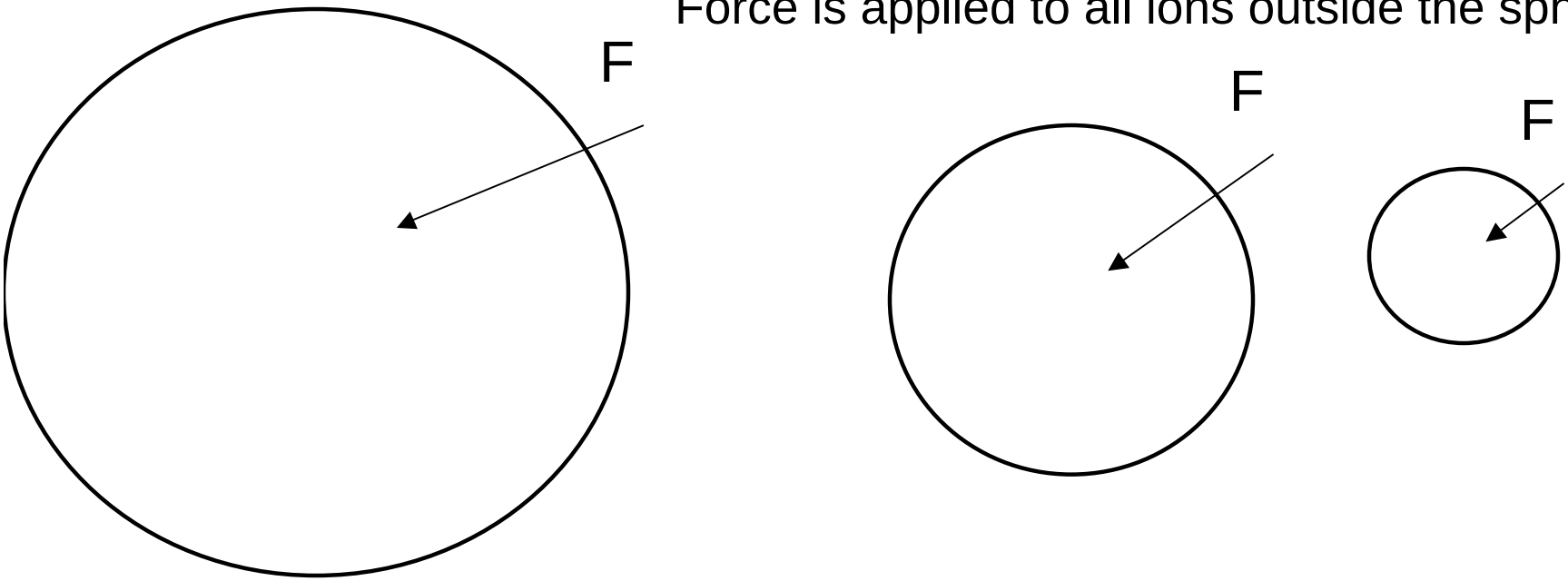
```
proc calcforces {step unique Rstart Rtarget Rrate K} {

  global bubbleCenter ;# defined in tclBCScript{ ... }

  # increase R, starting from $Rstart, by $Rrate at each step,
  # until it reaches $Rtarget; then keep it constant

  set R [expr $Rstart + $Rrate * $step]
  if { $R > $Rtarget } { set R $Rtarget }

  # let only the main processor print the output

  if { $unique } {
```

# Condensing ions with TclBC

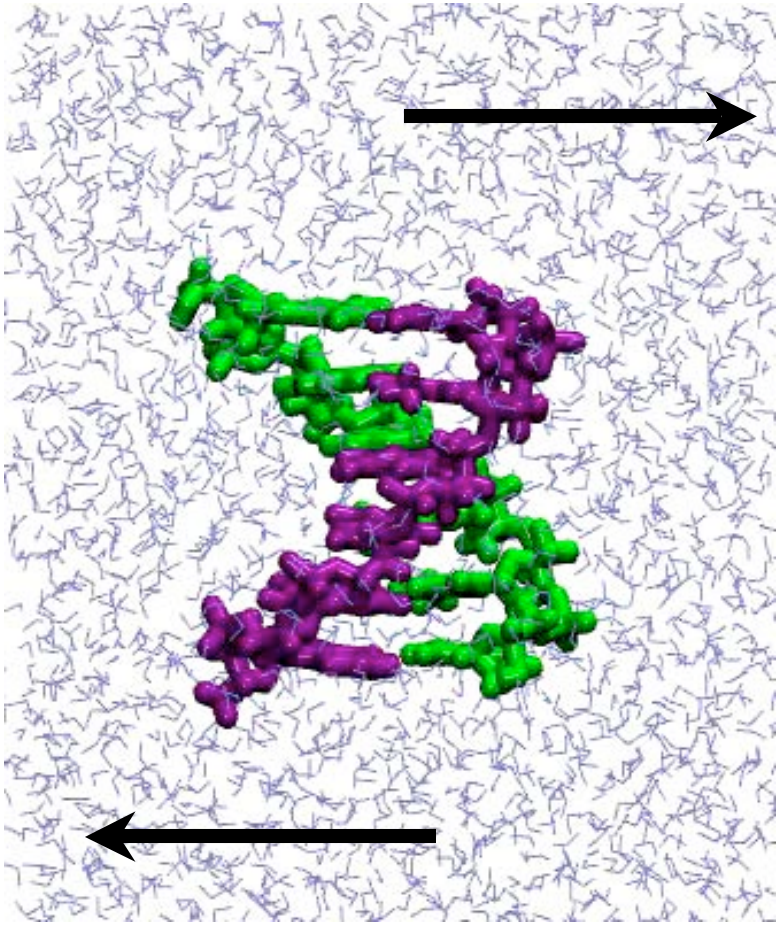


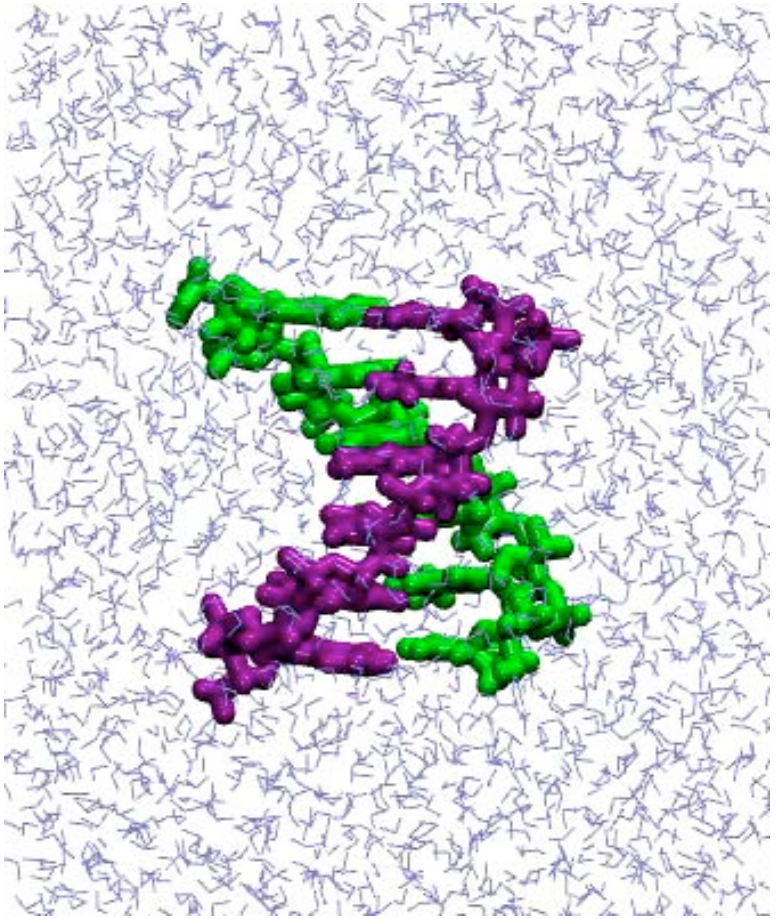


Force is applied to all ions outside the sphere



# Simulating shear flow with TclBC





# Summary

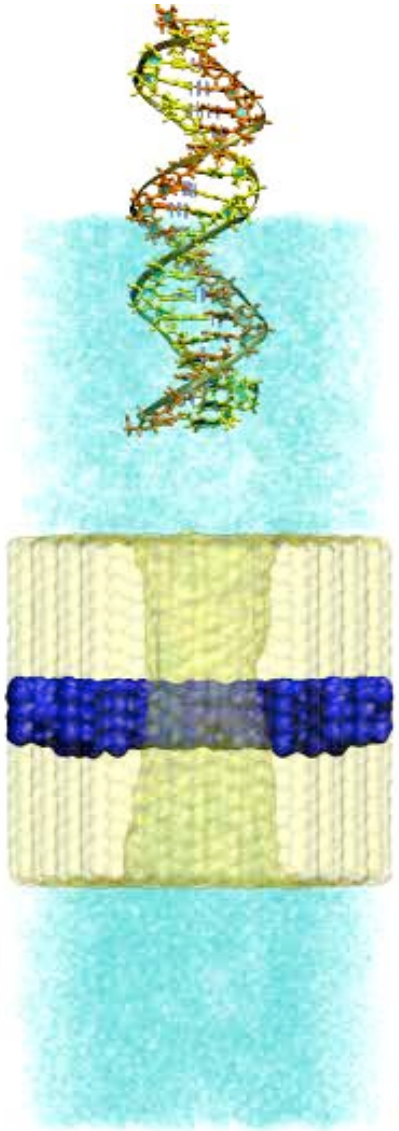
TclForces:

- Executed only on one (master) processor
- Many commands exists
- Can be made efficient if applied to a smal number of atoms

TclBC:

- Executed on each processor
- Few commands exists
- More efficient when applied to a large number of atoms

# Pulling DNA with Constant Force



Constant force was applied to all heavy (non-hydrogen) atoms of the DNA molecule (about 100 pN for per atom)

Fixed atoms