ACMM

Molecular simulation of biological systems: predicting mechanisms and free energies

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Winterschool Understanding Molecular Simulation
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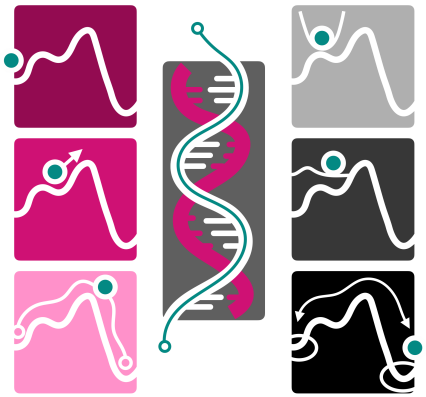
Biomolecular Simulation

Outline

Part 1: Simulating biomolecular systems

Part 2: Biased sampling

Part 3: Path sampling



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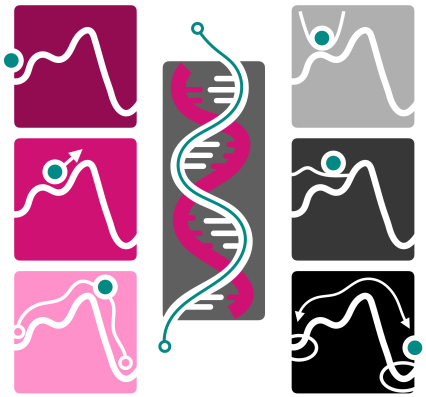
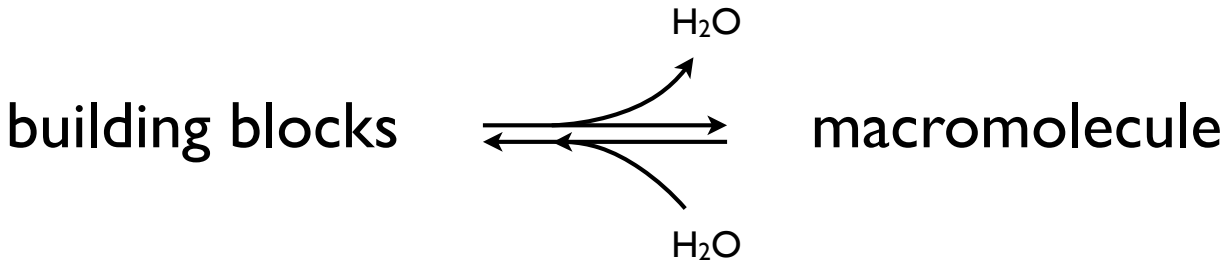
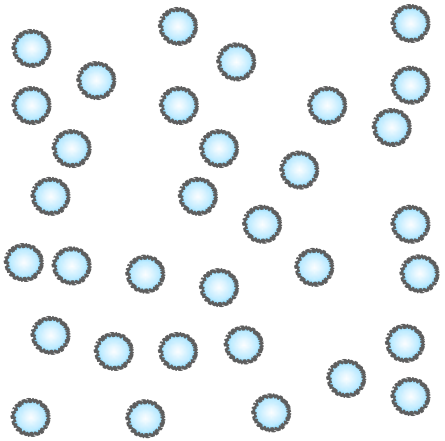


Biomolecules

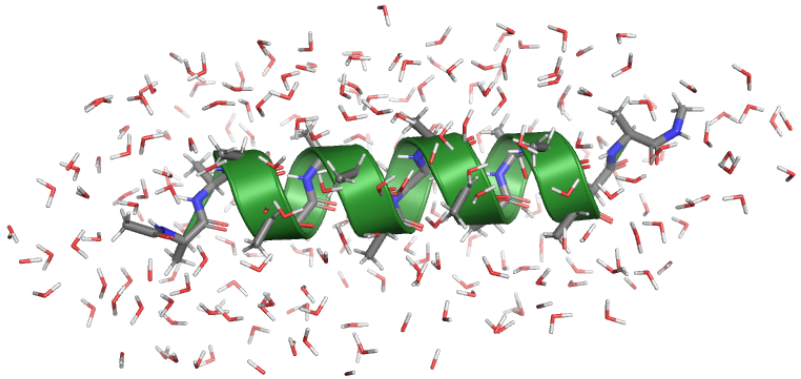


building block	**macromolecule**
amino acid	protein
nucleotide	nucleic acids
monosaccharide	cellulose, starch
lipid	membrane

Interactions in a biomolecular system



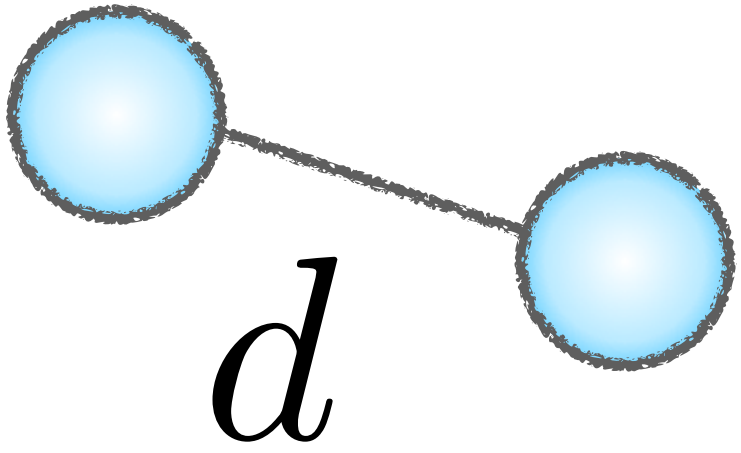
Lennard-Jones particles

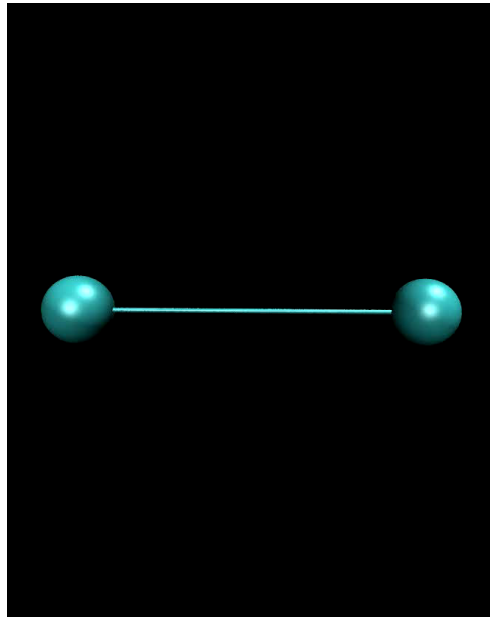


peptide in water

Bonded interactions

$$k_d(d - d_{eq})^2$$

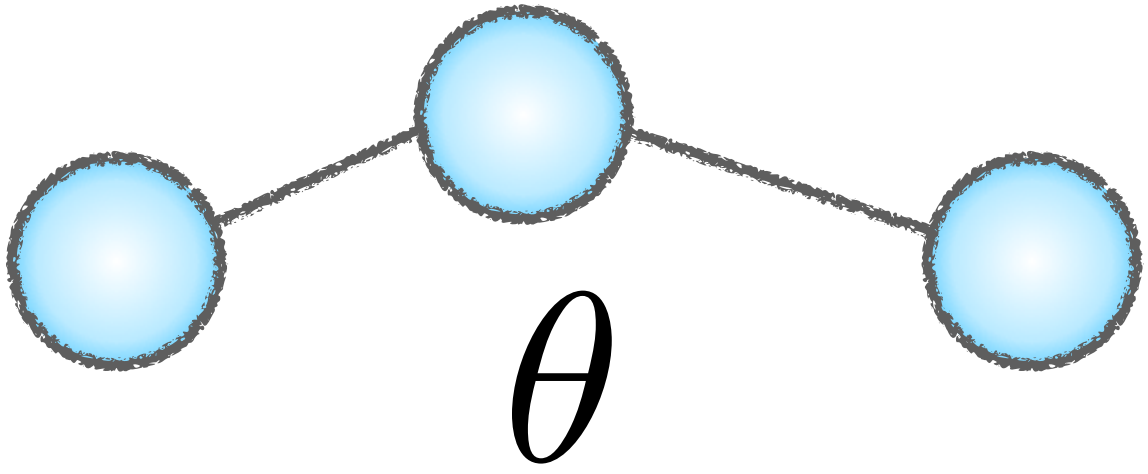


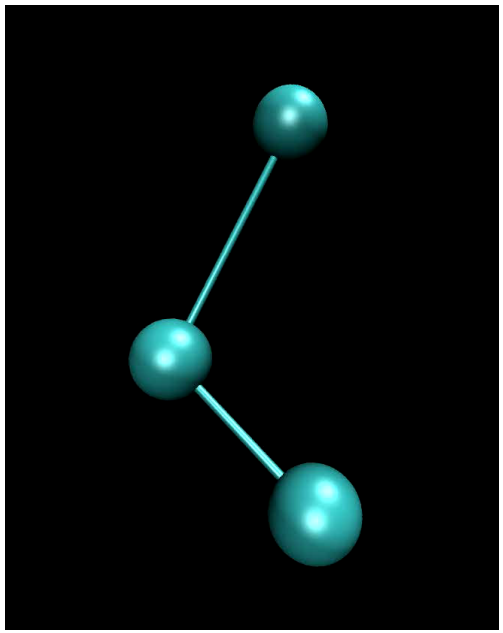


d bond distance
d_{eq} equilibrium bond distance
k_d force constant

Bonded interactions

$$k_\theta(\theta - \theta_{eq})^2$$





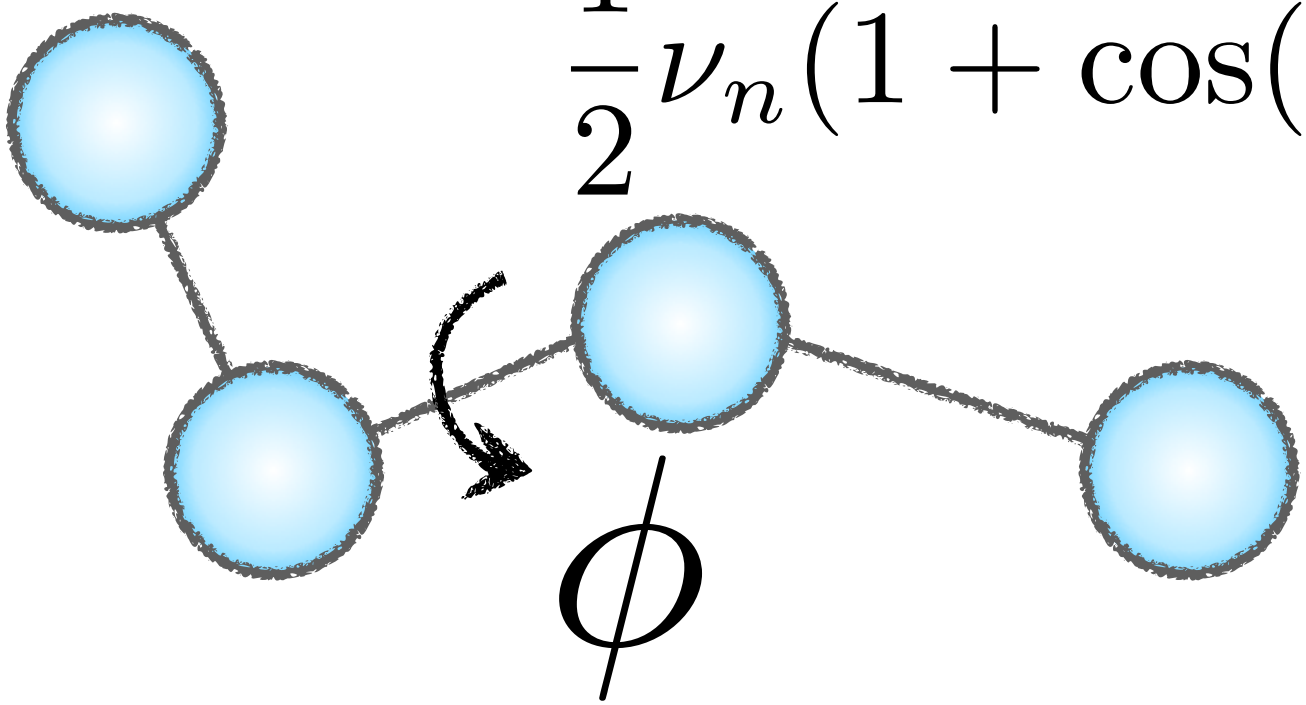
θ bond angle

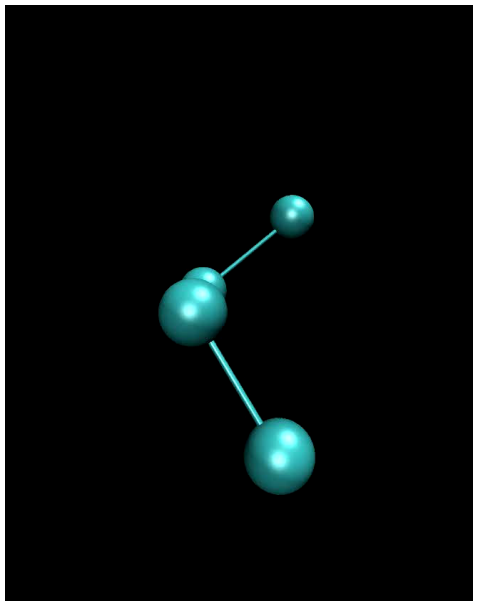
θ_{eq} equilibrium bond angle

k_θ force constant

Bonded interactions

$$\frac{1}{2}\nu_n(1+\cos(n\phi-\phi_0))$$





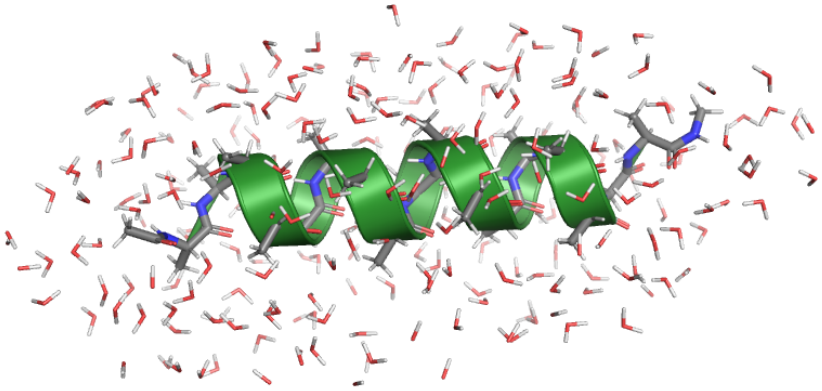
φ dihedral

φ_0 equilibrium dihedral

ν_n force constant

n periodicity

Bonded interactions



$$V(r) = \sum_{\text{bonds}} k_d(d - d_{eq})^2 +$$

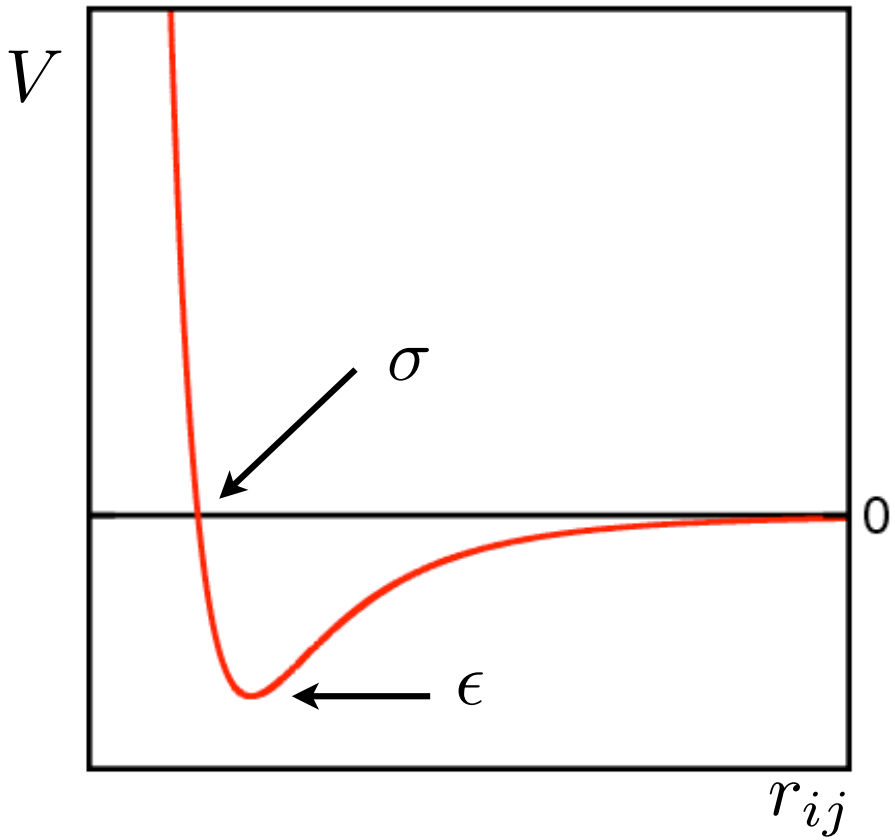
$$\sum_{\text{angles}} k_\theta(\theta - \theta_{eq})^2 +$$

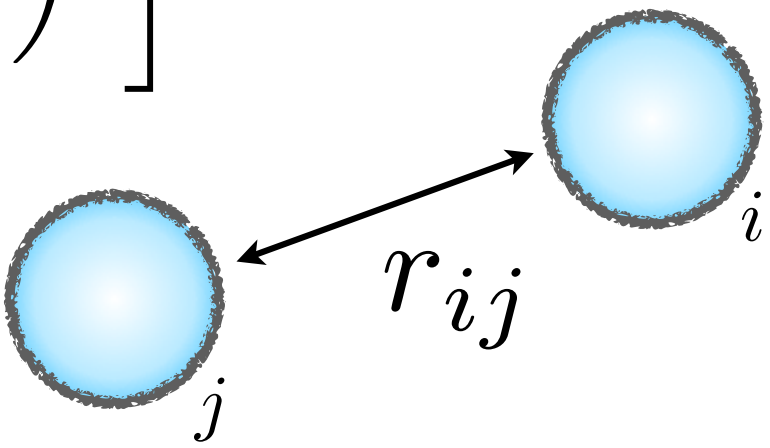
$$\sum_{\text{dihedrals}} \frac{1}{2}\nu_n(1 + \cos(n\phi - \phi_0))$$

V potential
r position

Non-bonded interactions

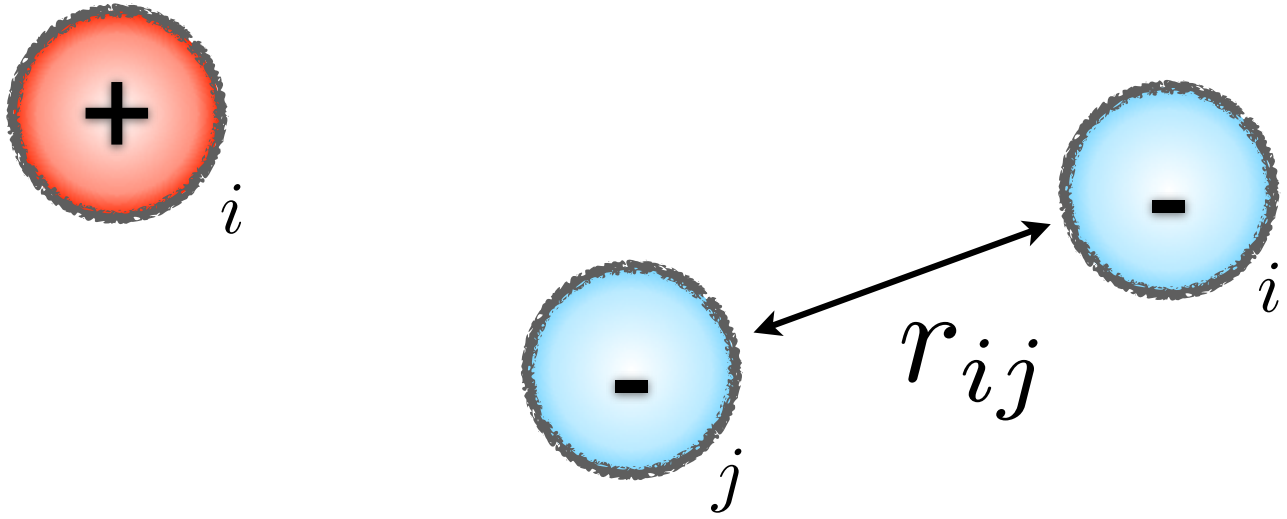
$$4\epsilon\left[\left(\frac{\sigma}{r_{ij}}\right)^{12}-\left(\frac{\sigma}{r_{ij}}\right)^{6}\right]$$





Lennard-Jones potential

Electrostatic interactions

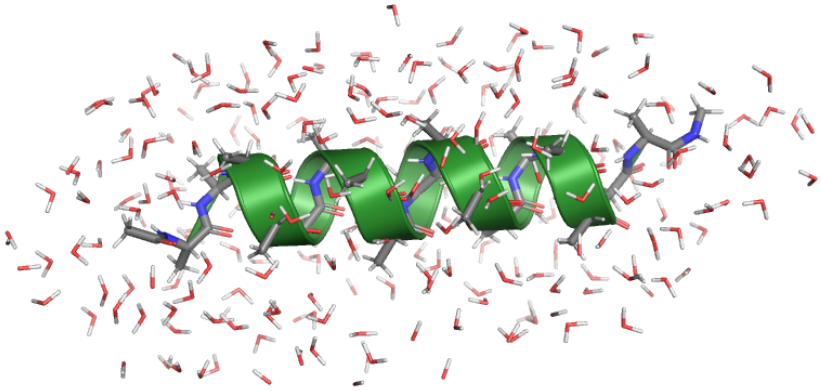


$$\frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}}$$

Coulomb's law

q charge
r_{ij} distance
ε_0 electric constant

Force field



$$V(r) = \sum_{\text{bonds}} k_d(d - d_{eq})^2 + \sum_{\text{angles}} k_\theta(\theta - \theta_{eq})^2 +$$

$$\sum_{\text{dihedrals}} \frac{1}{2}\nu_n(1 + \cos(n\phi - \phi_0)) +$$

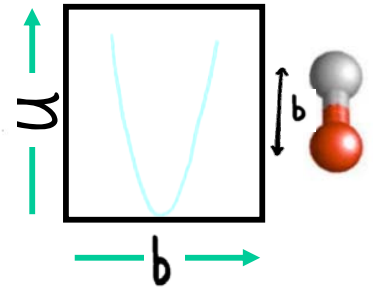
$$\sum_{i<j} \left(4\epsilon \left(\left(\frac{\sigma}{r_{ij}} \right)^{12} - \left(\frac{\sigma}{r_{ij}} \right)^{6} \right) + \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}} \right)$$

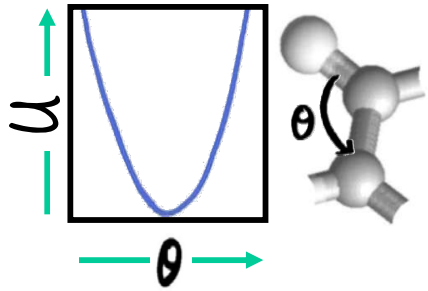
MOLECULAR POTENTIAL ENERGY

$$U = \sum \tfrac{1}{2} K_b (b - b_0)^2 + \sum \tfrac{1}{2} K_\theta (\theta - \theta_0)^2$$

All Bonds — All Angles

Hooke 1635

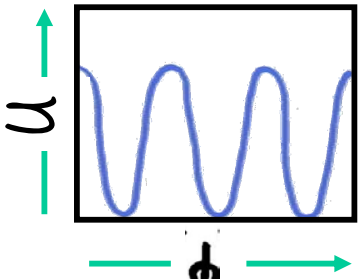


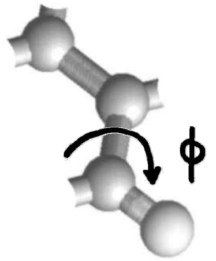


$$+ \sum K_\phi [1 - \cos(n\phi + \delta)]$$

All Torsion Angles

Fourier 1768

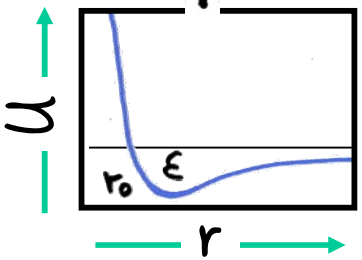


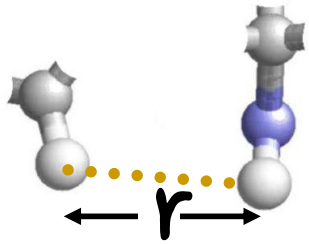


$$+ \sum \varepsilon \left[\left(r_0 / r \right)^{12} - 2 \left(r_0 / r \right)^{6} \right]$$

All Nonbonded pairs

Van der Waals 1837



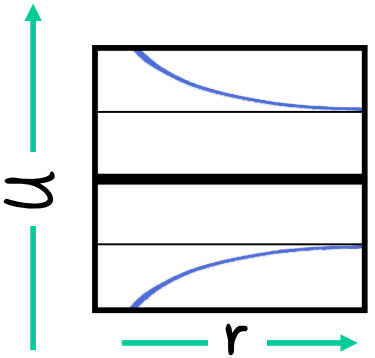


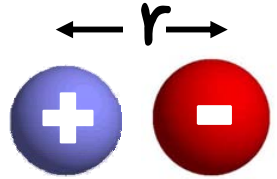
$$+ \sum 332 q_i q_j / r$$

All partial charges

Coulomb 1736

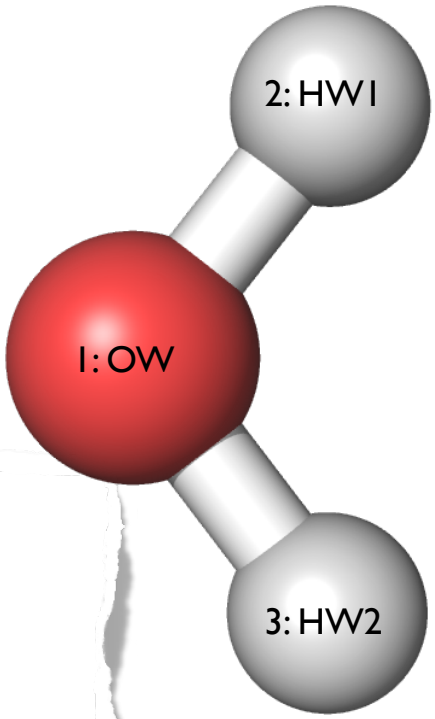
Simple sum over many terms





Topology

- List of atoms
- Connectivity

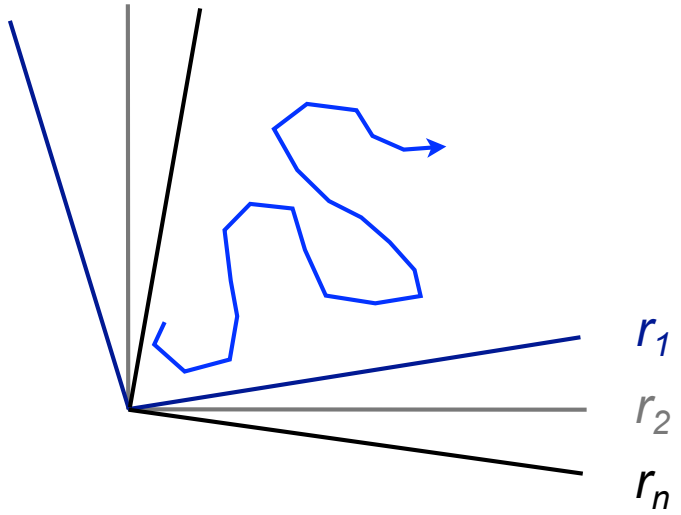



```
[ moleculetype ]
; molname       nrexcl
SOL             2

[ atoms ]
; id  at type     res nr  res name  at name  cg nr  charge    mass
  1   OW           1       SOL       OW       1      -0.834    16.00000
  2   HW           1       SOL       HW1      1       0.417     1.00800
  3   HW           1       SOL       HW2      1       0.417     1.00800

[ bonds ]
; i     j       funct   length  force_constant
1       2       1       0.09572 502416.0   0.09572         502416.0
1       3       1       0.09572 502416.0   0.09572         502416.0


[ angles ]
; i     j       k       funct   angle   force_constant
2       1       3       1       104.52  628.02      104.52  628.02
```

Sampling

Molecular dynamics:

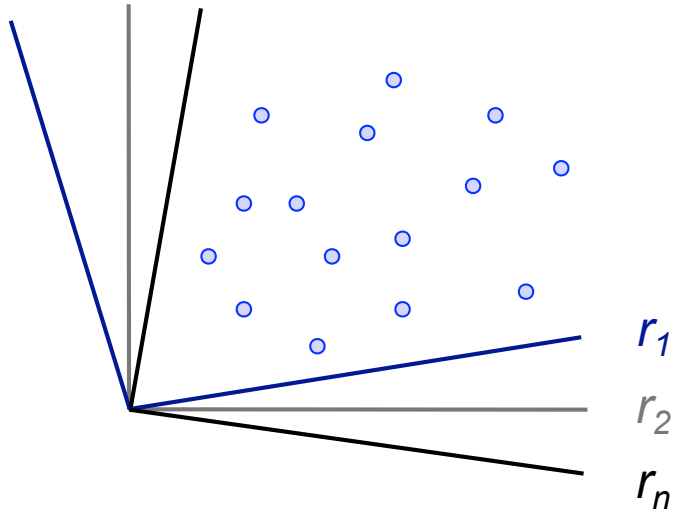
solve equations of motion



MD

Monte Carlo:

importance sampling

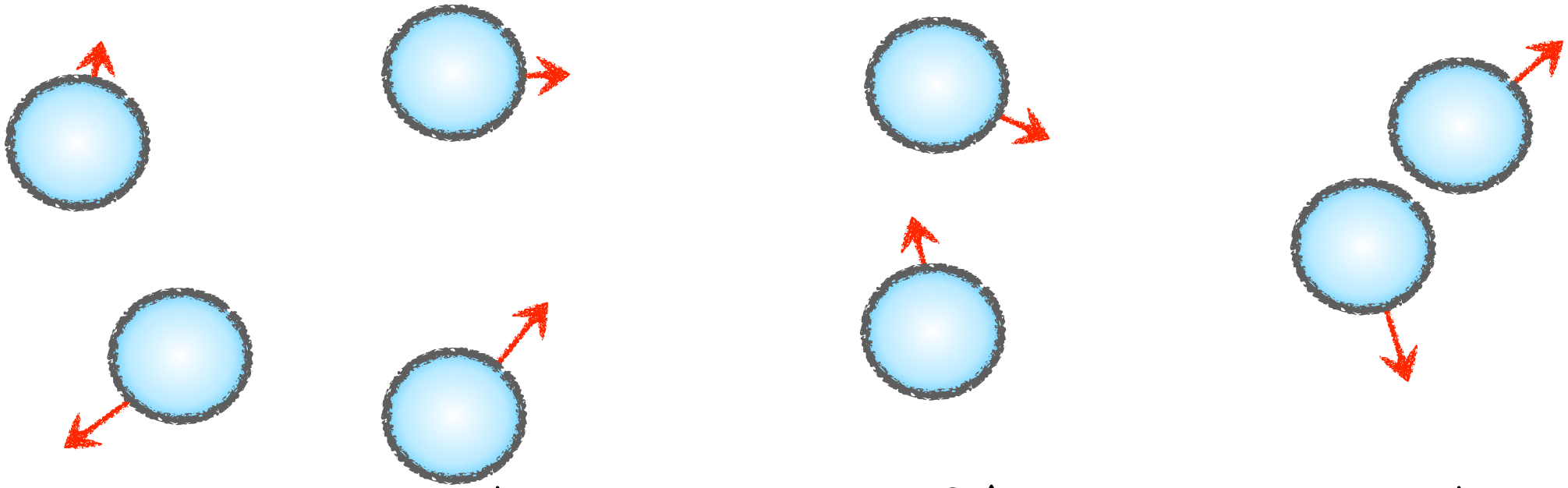


MC

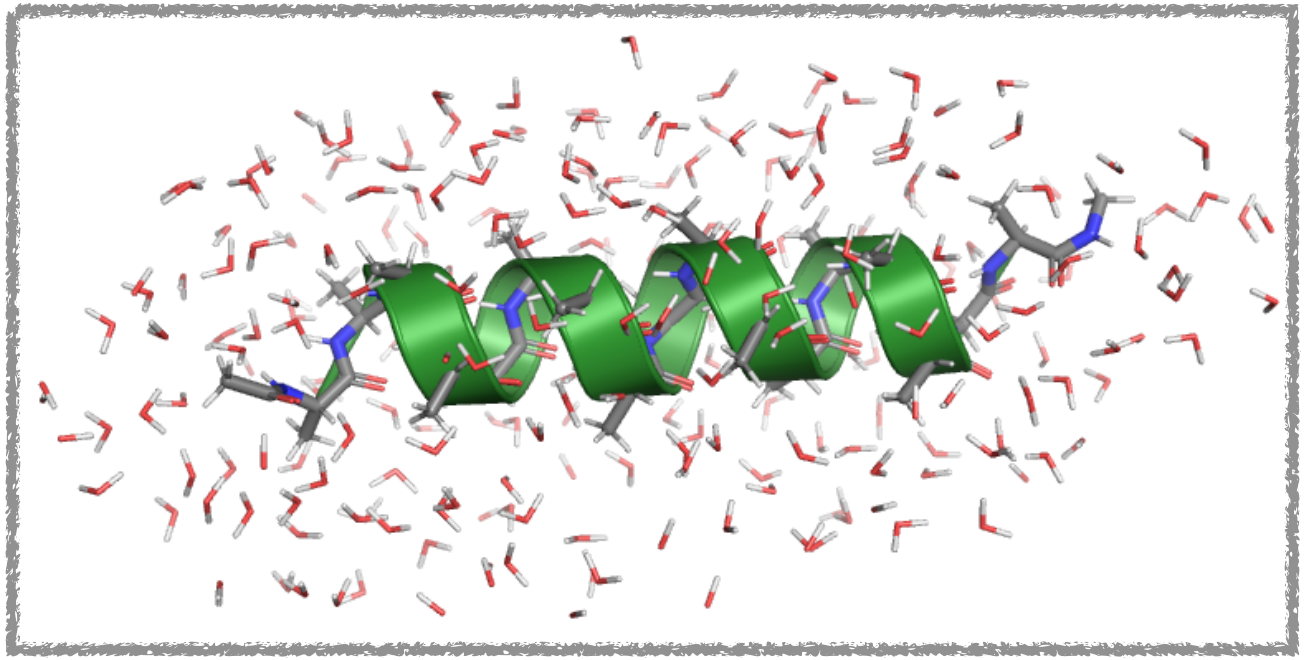
Molecular dynamics

- assign positions and velocities to particles
- compute forces on all particles
- integrate equations of motion
- measure properties
- stop

} repeat

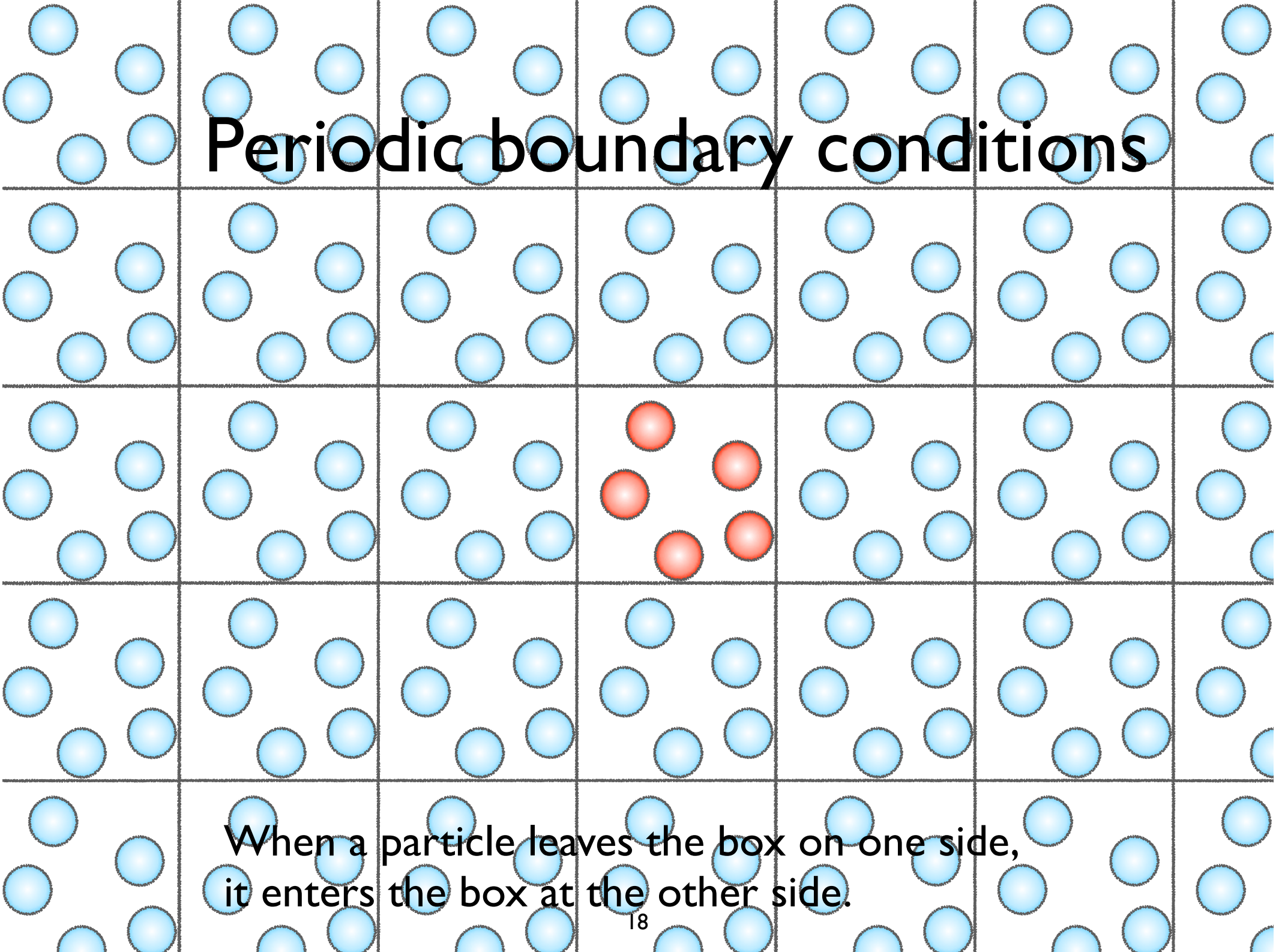


Simulating an alpha-helix



constant N, p, T

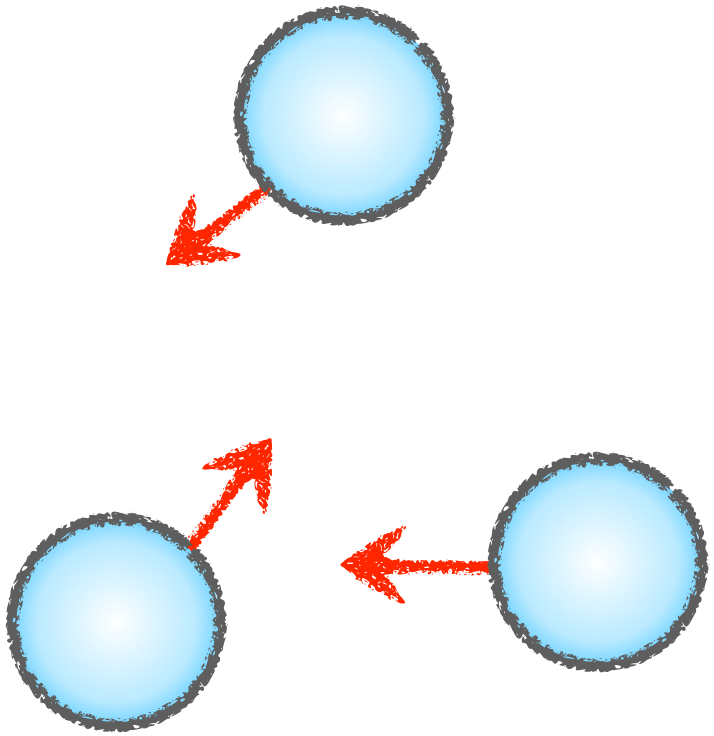
Periodic boundary conditions



When a particle leaves the box on one side,
it enters the box at the other side.

Thermostat

$$v^2 \backsim T$$



change velocities by

- scaling
  - Berendsen and Bussi thermostats
- stochastic forces
  - Andersen thermostat
- adding additional variable that modulates the kinetic energy
  - Nosé-Hoover thermostat

Barostat

$$\frac{1}{V} \sim p$$

change volume by

- scaling

  Berendsen barostat

- adding additional variable that modulates changes in volume

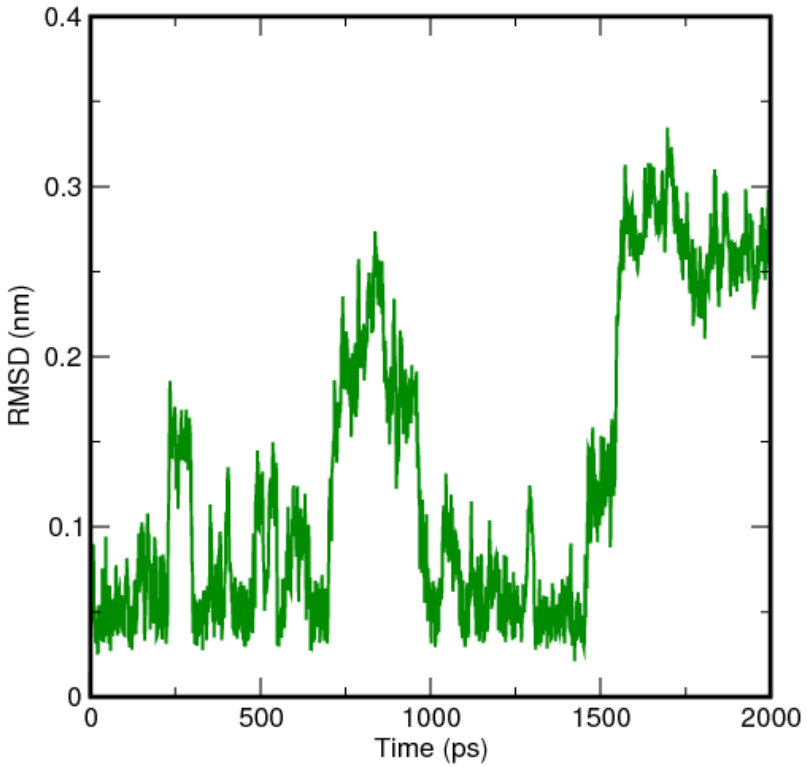
  Andersen barostat

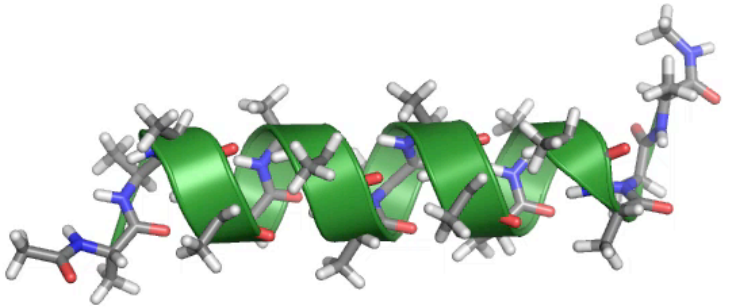
2 ns MD simulation of an alpha-helix

Root Mean Square Deviation
RMSD

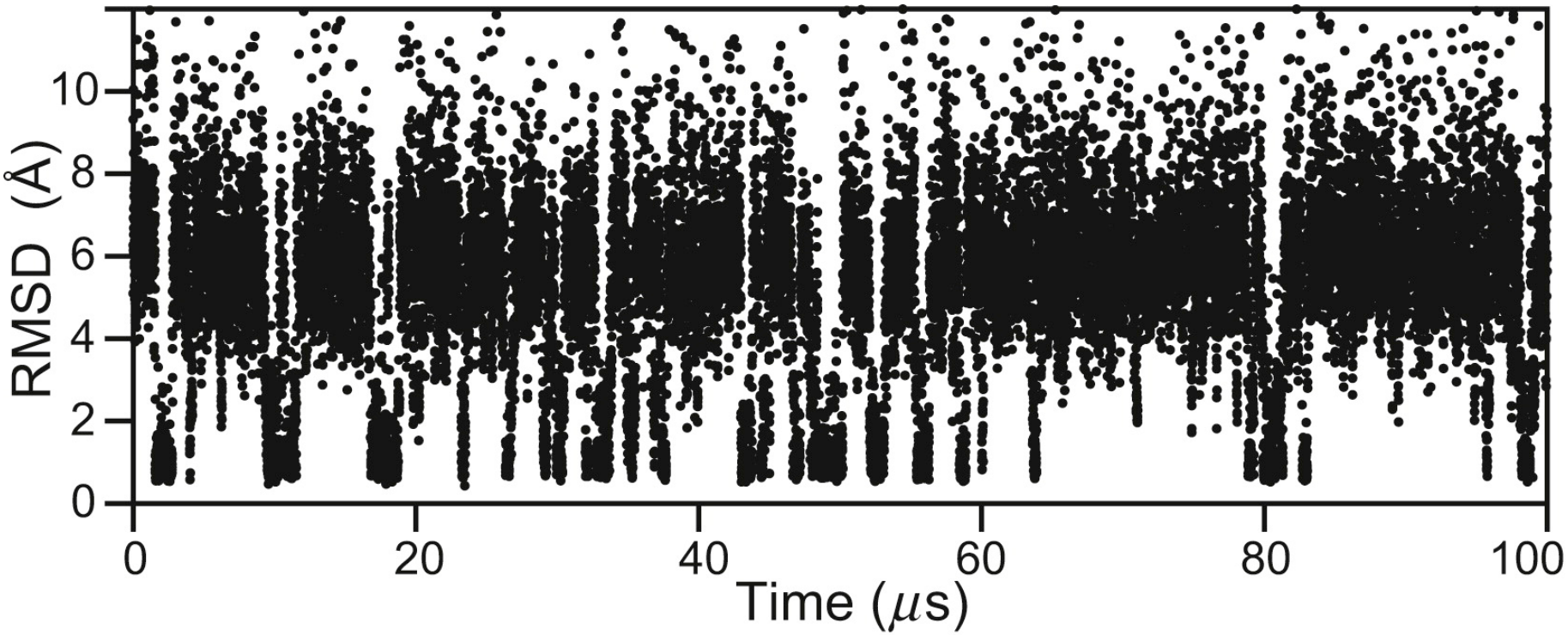
$$\sqrt{\frac{\sum_i^N (r_i - \hat{r}_i)^2}{N}}$$

N - number of atoms
i - atom index
r - position
$\hat{r}$ - reference position





Long MD simulation



Molecular dynamics

- assign positions and velocities to particles
- compute forces on all particles
- integrate equations of motion
- measure properties
- stop

} repeat

When?

Ensemble averages

For properties that only depend on the configurational part, the probability P($\mathbf{\Gamma}$) to find a configuration $\mathbf{\Gamma} = \{\mathbf{r}_1, \mathbf{r}_2, \ldots, \mathbf{r}_N\}$ is

$$P(\mathbf{\Gamma}) = \frac{1}{Q} \exp[-\beta U(\mathbf{\Gamma})]$$

with Q the partition function, U the internal energy and $\beta = 1/k_B T$.

The ensemble average of a property A is

$$\langle A \rangle = \int P(\mathbf{\Gamma}) A(\mathbf{\Gamma}) d\mathbf{\Gamma}$$

$$\langle A \rangle = \frac{1}{Q} \exp[-\beta U(\mathbf{\Gamma})] A(\mathbf{\Gamma}) d\mathbf{\Gamma}$$

Ergodicity theorem

Suppose we have an ensemble average of a system defined by U(**Γ**) obtained by MC.

$$\langle A \rangle = \frac{1}{Q} \exp[-\beta U(\mathbf{\Gamma})] A(\mathbf{\Gamma}) d\mathbf{\Gamma}$$

Now suppose we have an NVT molecular dynamics trajectory for the same system.

A time average over the trajectory is simply:

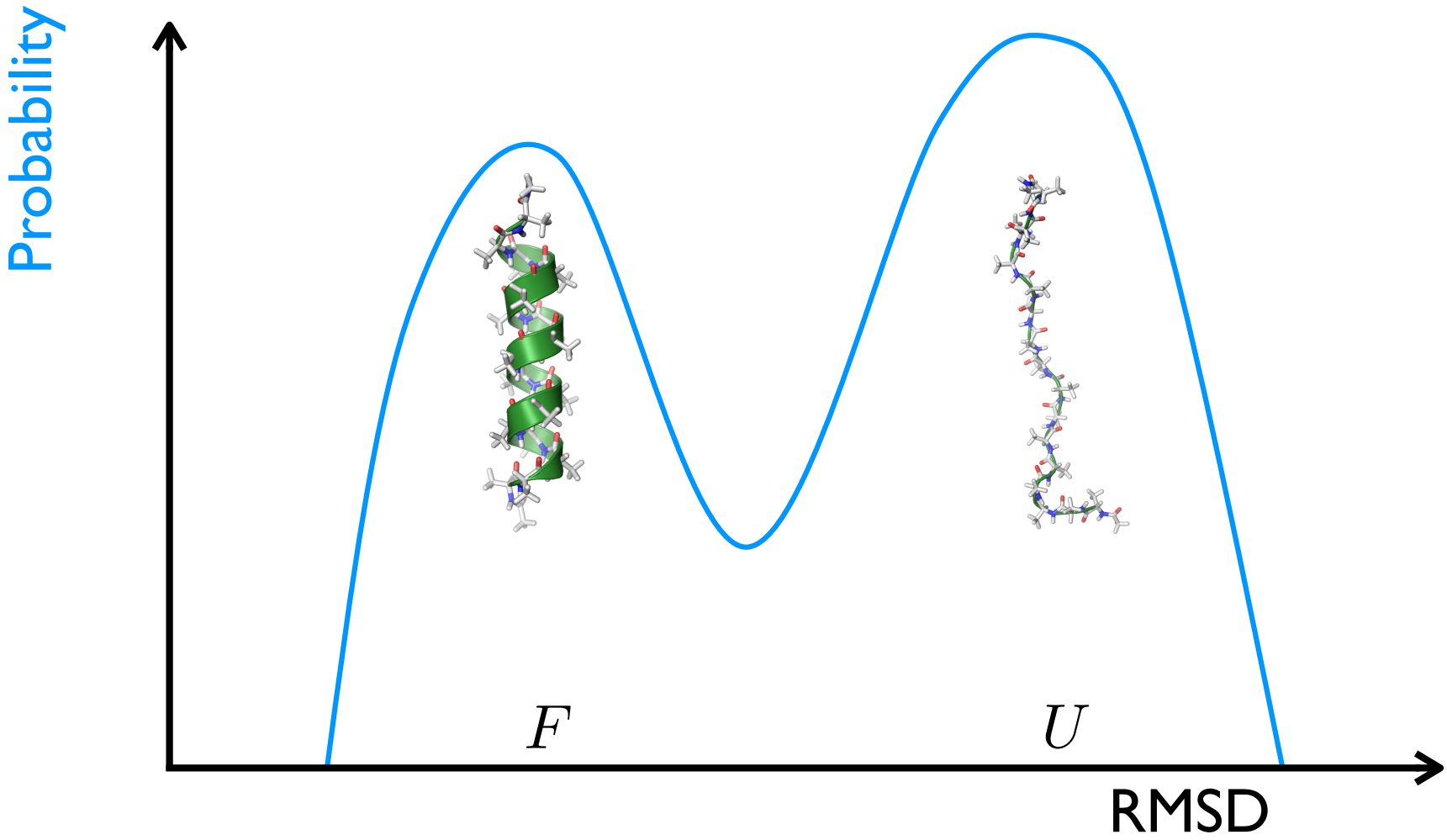
$$\bar{A} = \frac{1}{\mathcal{T}} \int_0^{\mathcal{T}} A(t) dt$$

The ergodicity theorem states that for an 'ergodic system',
the time average is equal to the ensemble average.

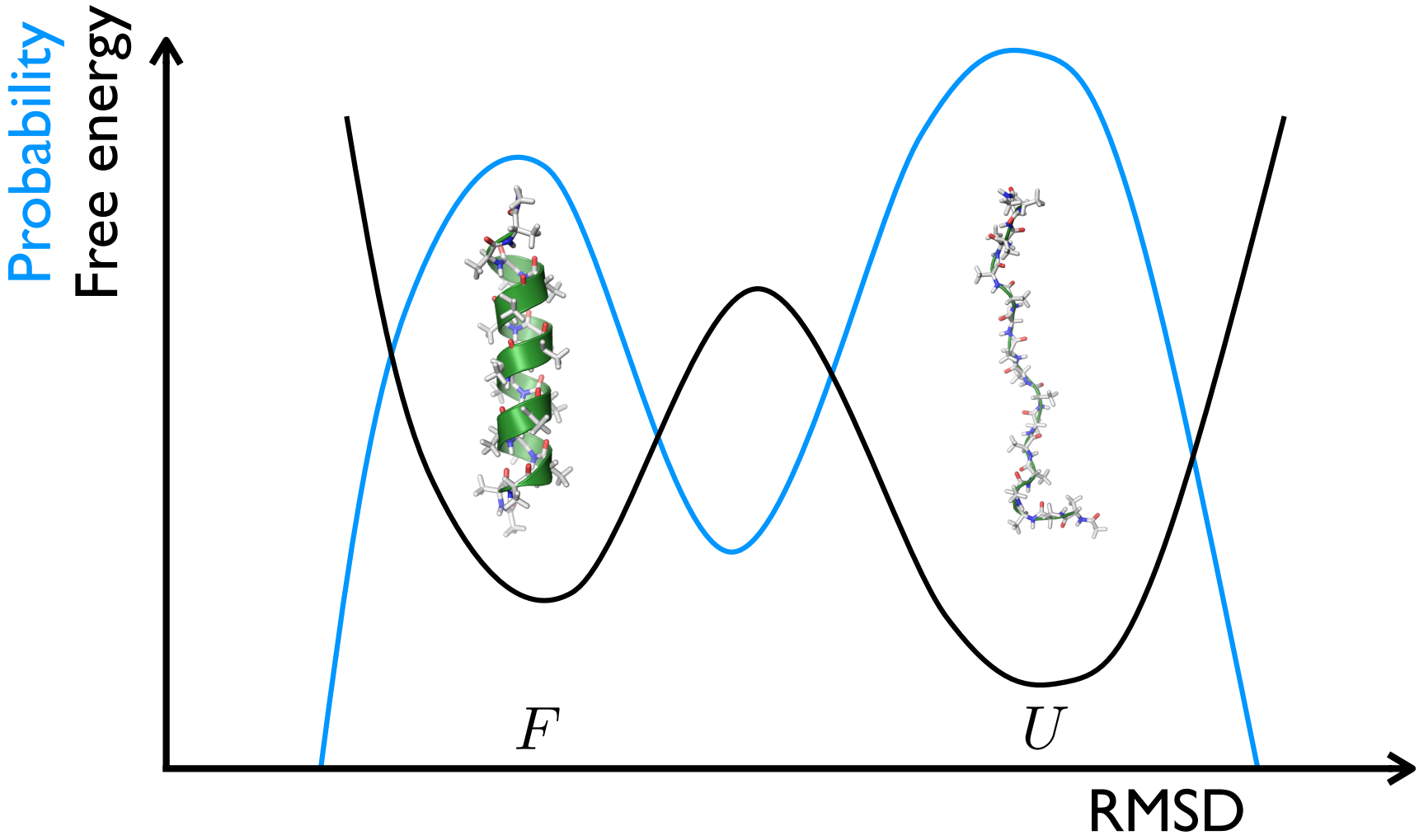
$$\bar{A} = \langle A \rangle$$ MC and MD give the same averages!

An MD simulation is done when the probability distribution no longer changes.

Probability histogram

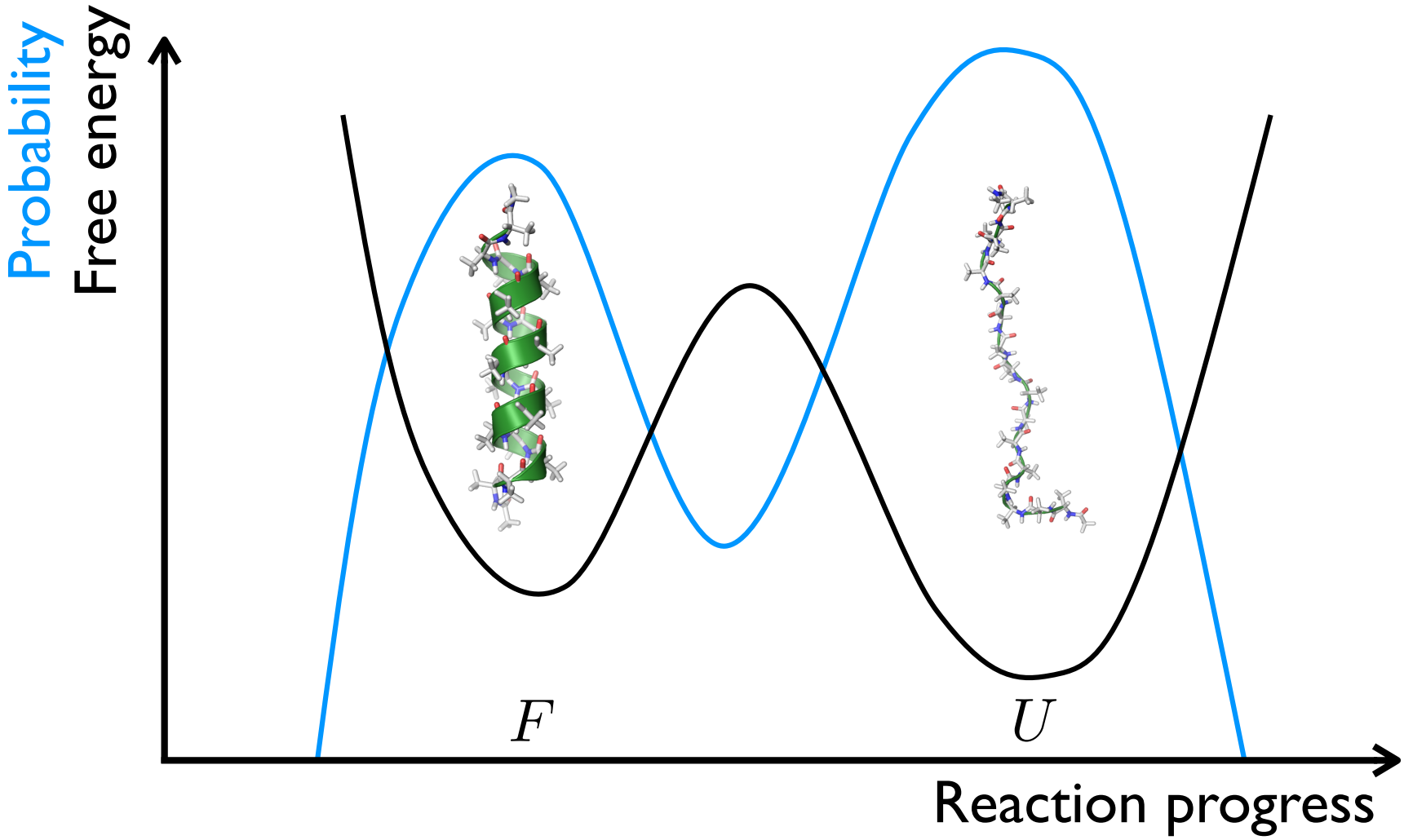


Free energy profile



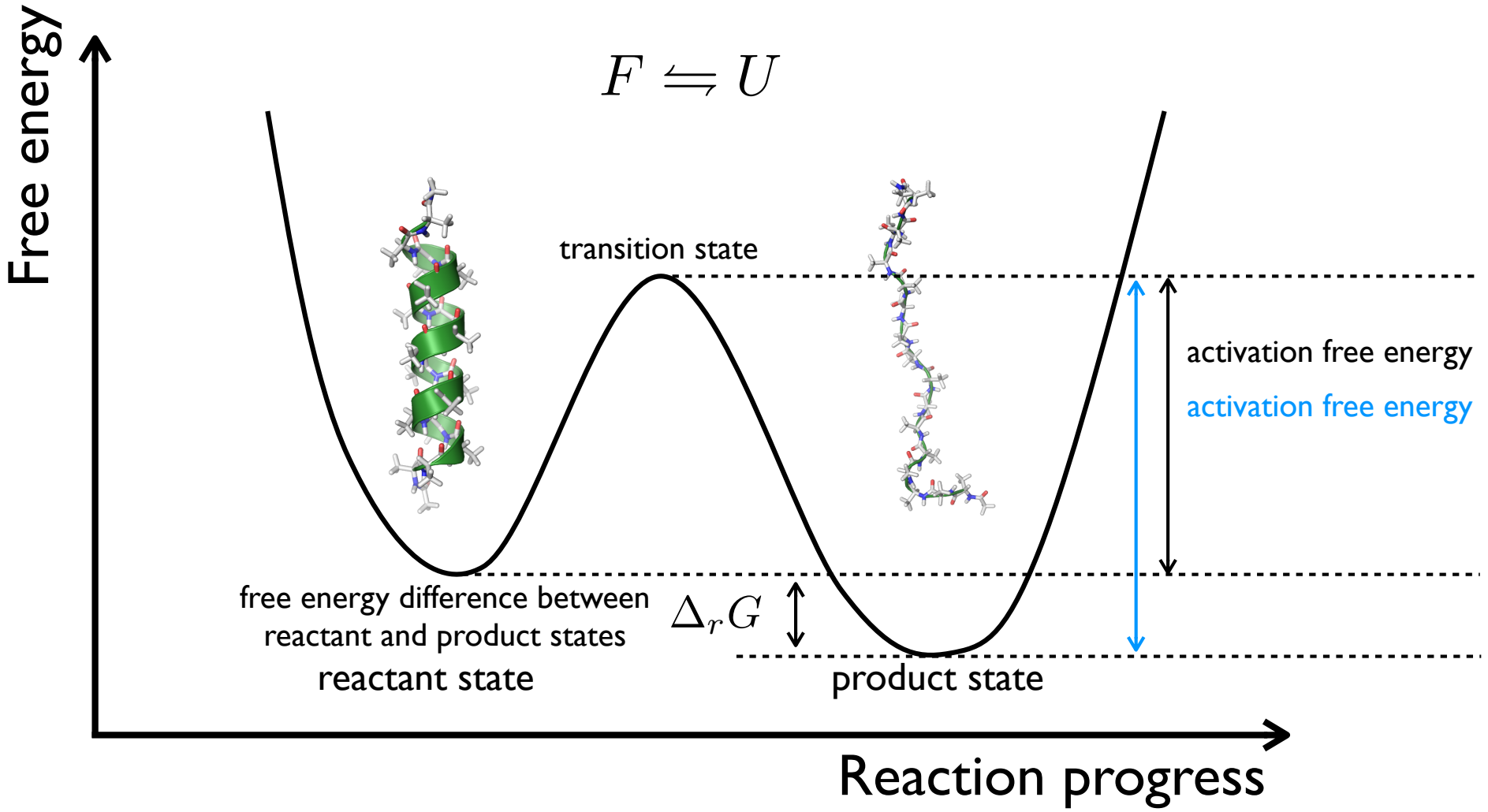
Free energy = -ln(Probability) in units of k_BT

Free energy profile



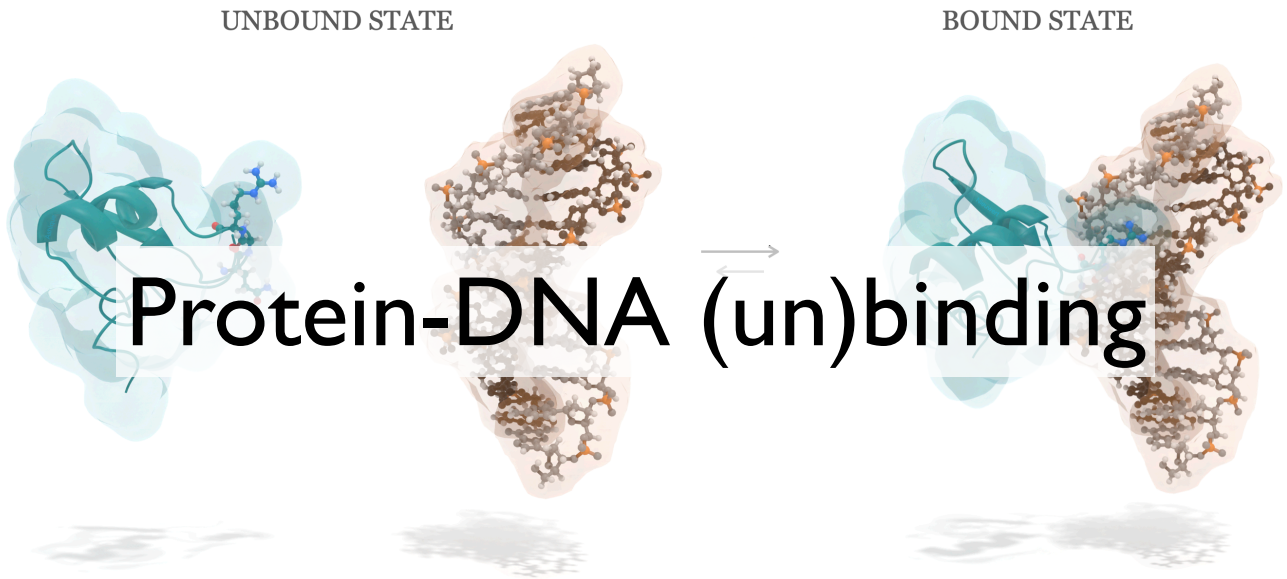
Free energy = -ln(Probability) in units of k_BT

Free energy profile



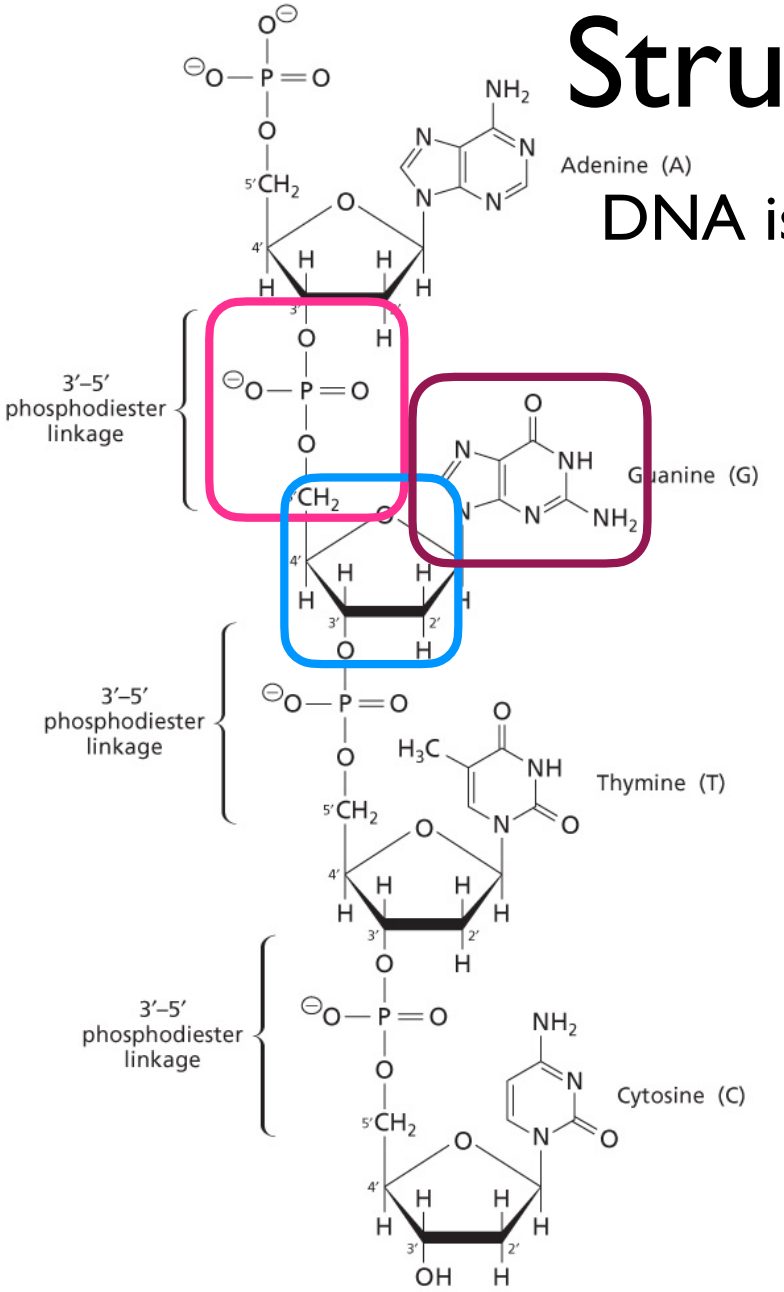
Biomolecular processes in this lecture

Conformational transitions in DNA



Protein-DNA (un)binding

Structure of DNA



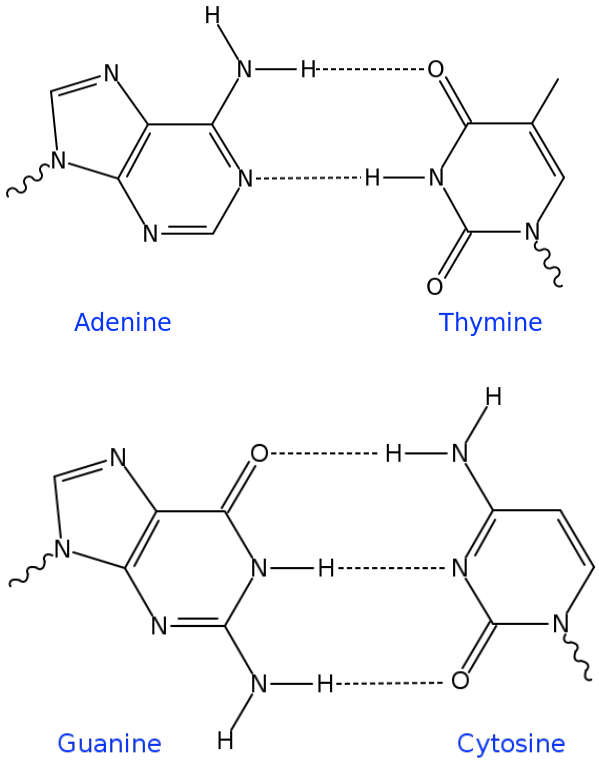
DNA is a polymer of nucleotides.

A nucleotide consists of:

-phosphate

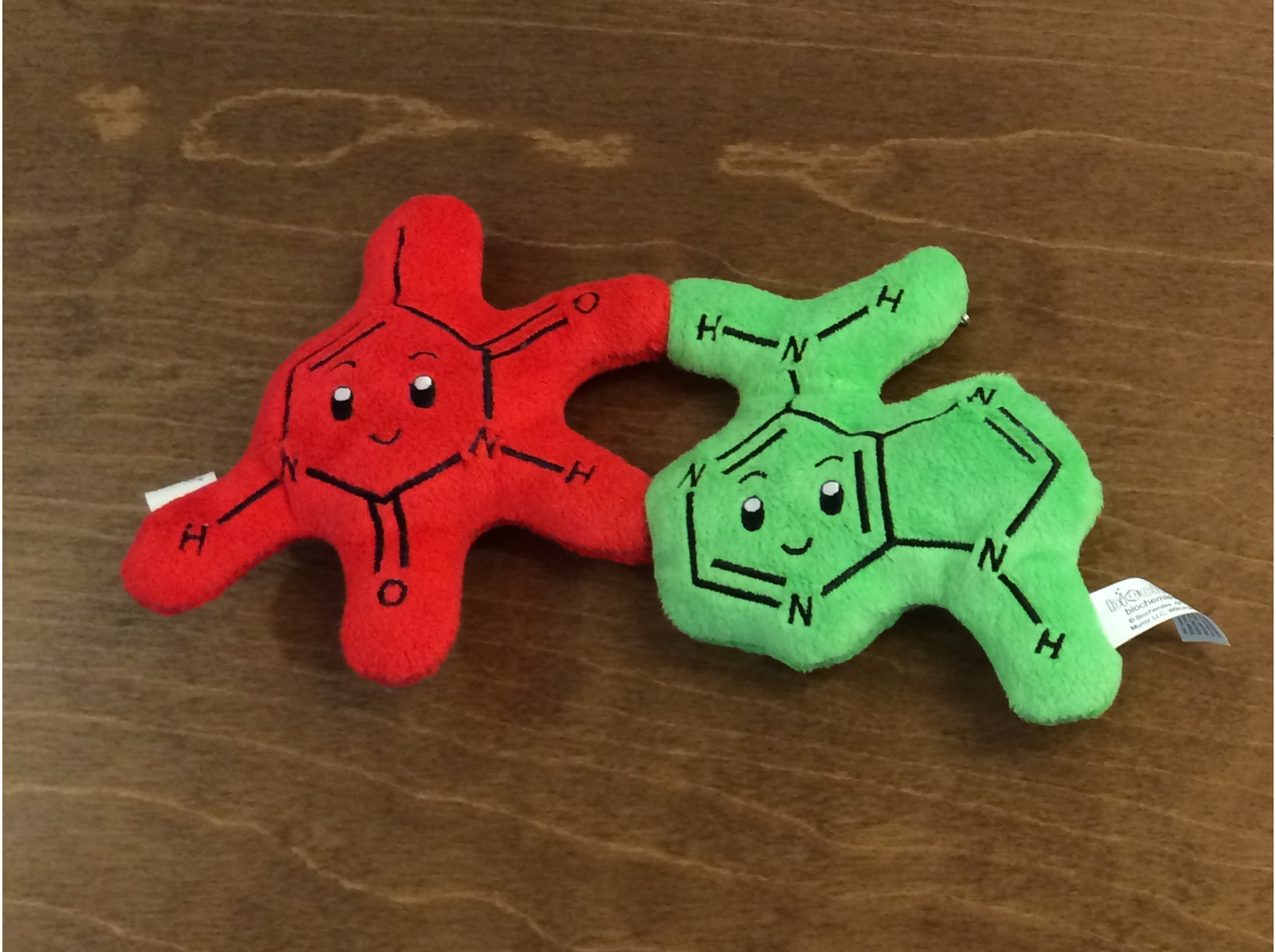
-deoxyribose

-nucleobase

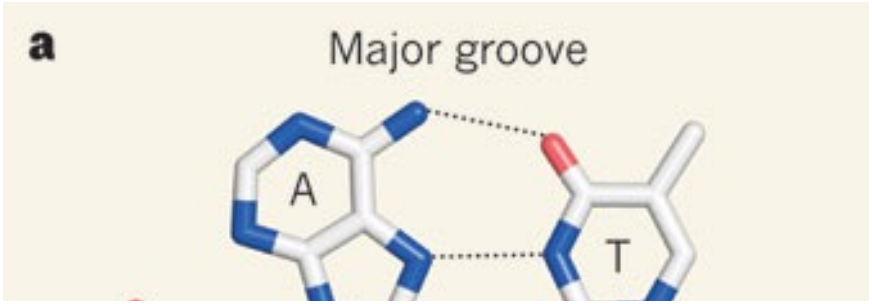


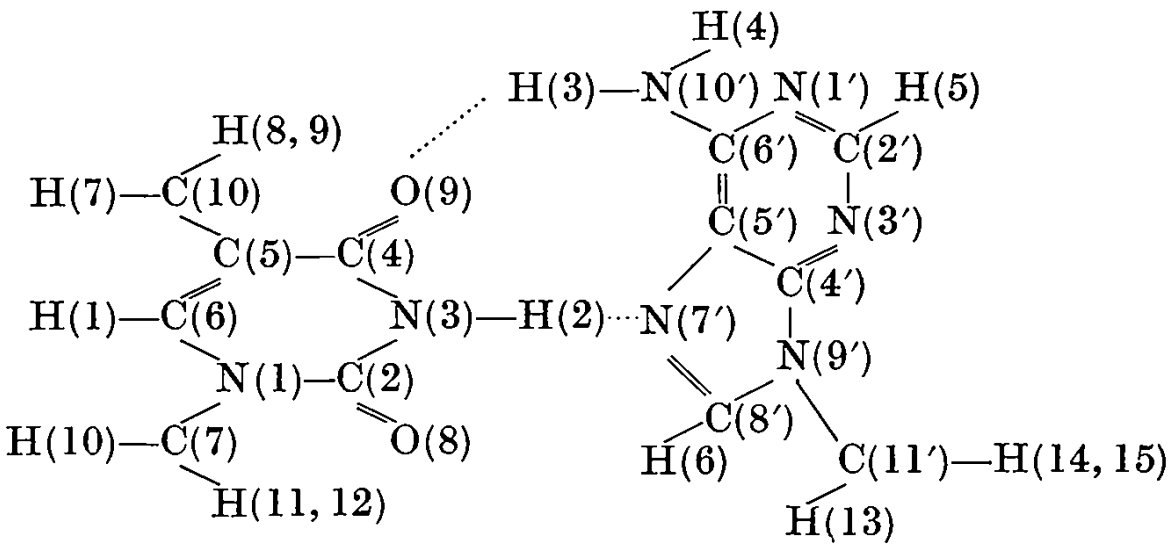
Franklin & Gosling *Nature* 1953 v. 171 p. 740

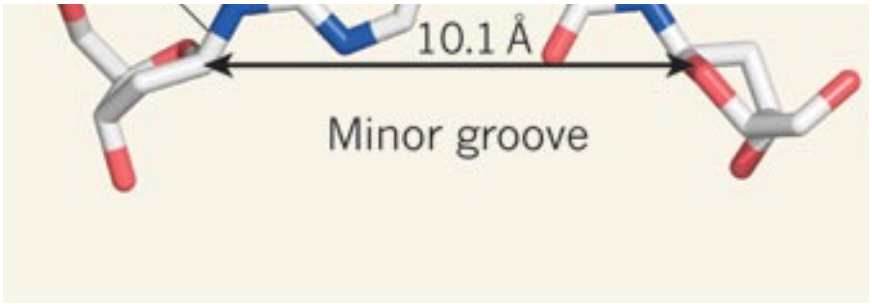
Watson & Crick *Nature* 1953 v. 171 p. 737


O
N
H
H
O
H
N
H
N
N
N
N
H

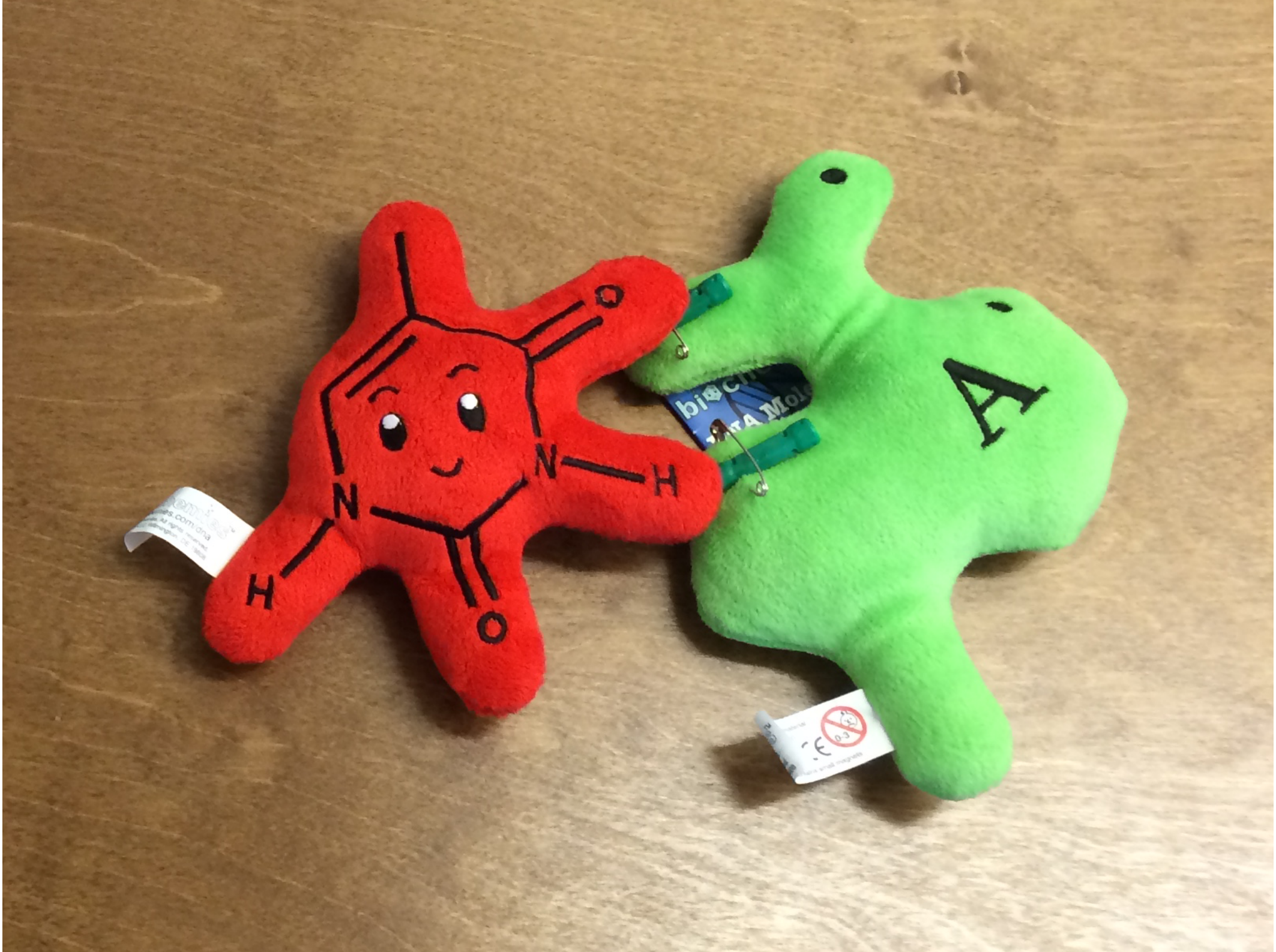
Hoogsteen basepairing



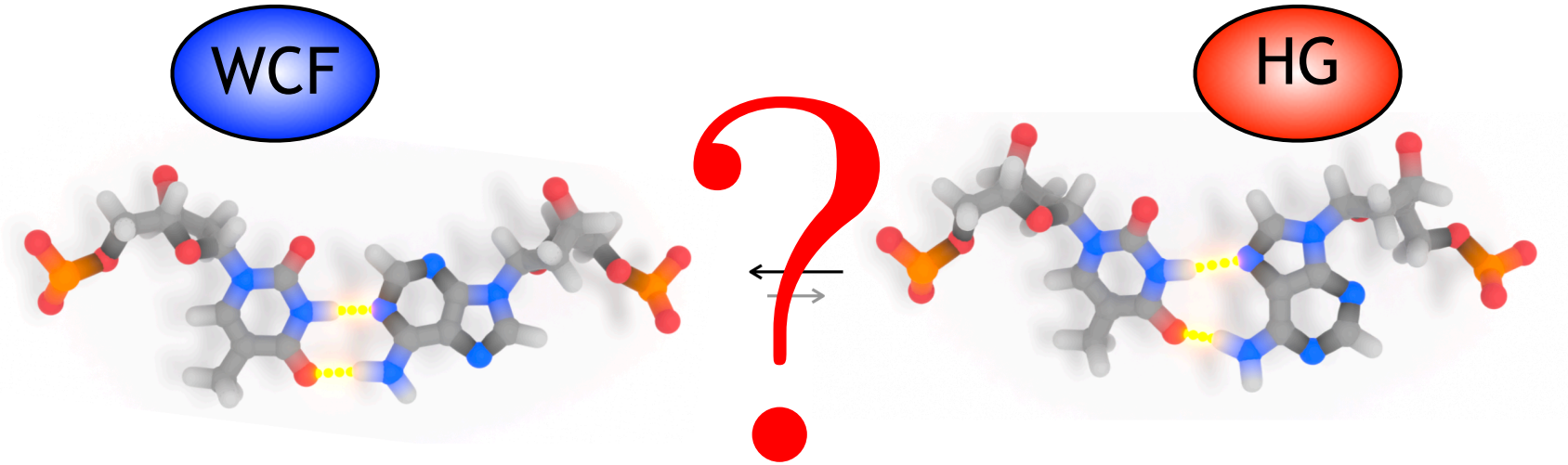


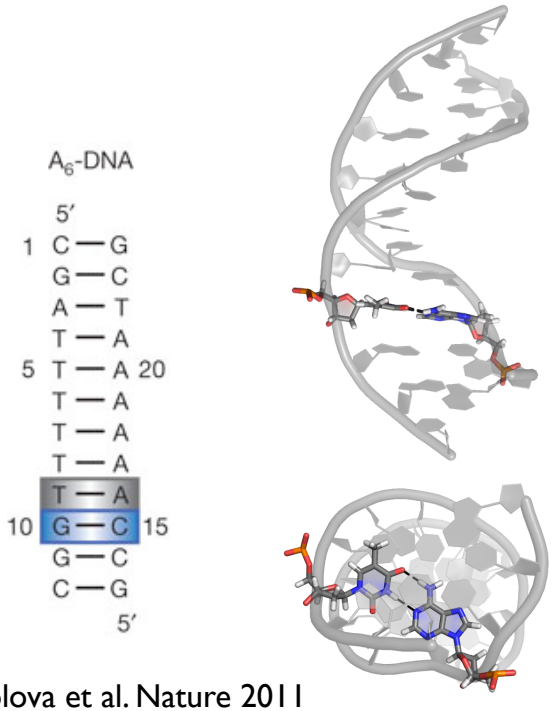


Hoogsteen *Acta Cryst.* 1963
Honig & Rohs *Nature* 2011


O
N
H
N
H
O
A

What is the mechanism?



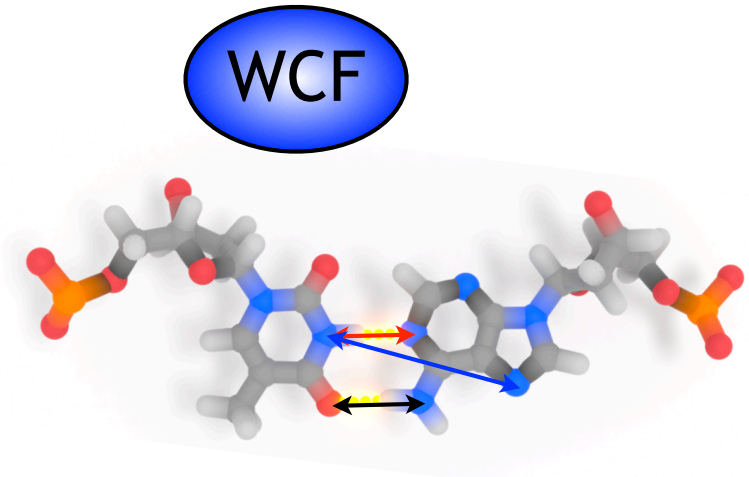


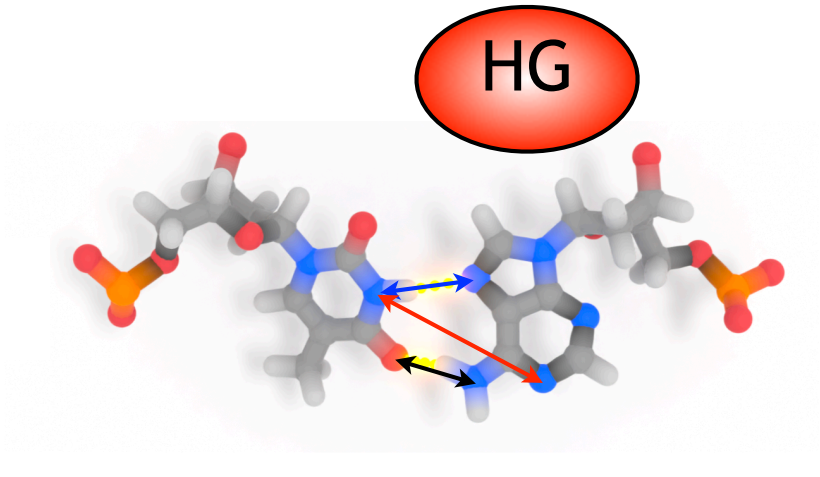
Molecular Dynamics:
5′–GGATTTTTTGGC–3′
3′–CCTAAAAAACCG–5′
AMBER03 force field
TIP3P water + 25 mM NaCl
NpT ensemble, T = 300 K
20868 atoms
gromacs v4.6.1

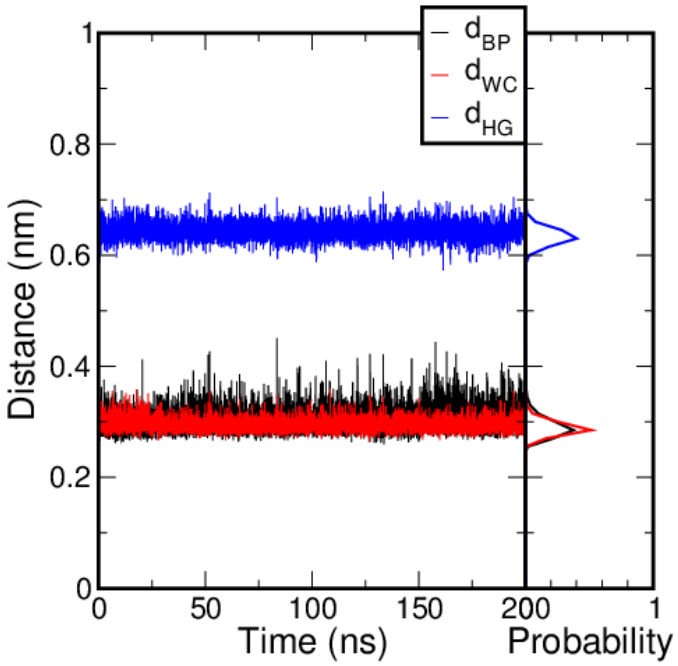
Nikolova et al. Nature 2011

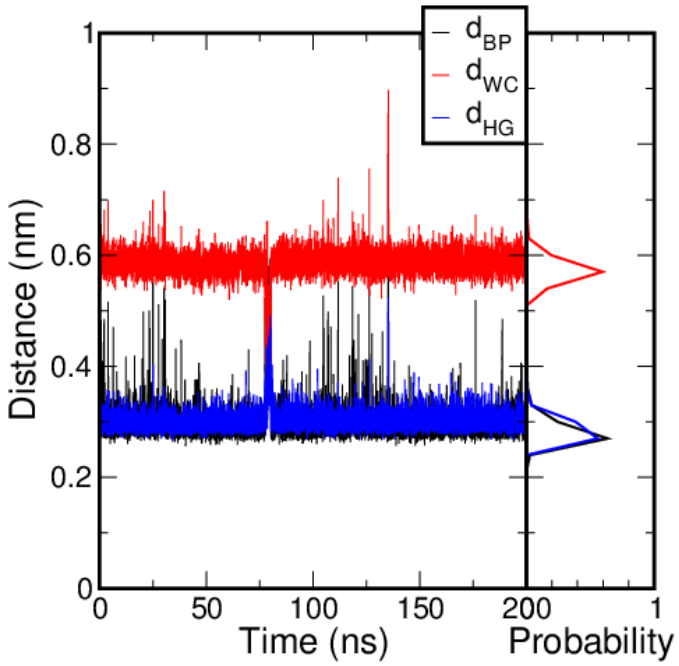
Vreede, Pérez de Alba Ortíz, Bolhuis & Swenson, NAR 2019

The transition between WC and HG does not occur within 200 ns.









Vreede, Pérez de Alba Ortíz, Bolhuis & Swenson, NAR 2019

Protein-DNA interactions

- Electrostatics

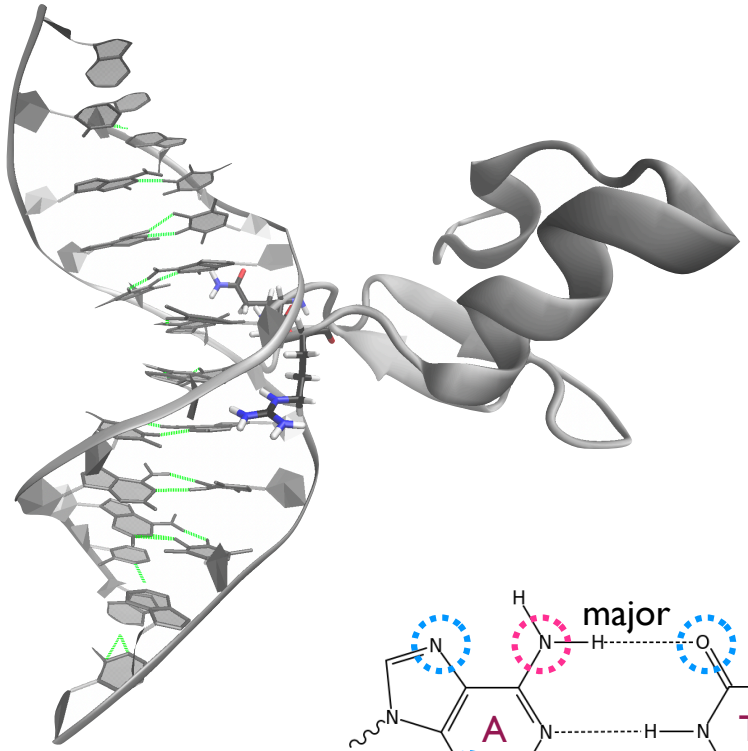
negatively charged phosphate backbone
positive charges on the protein

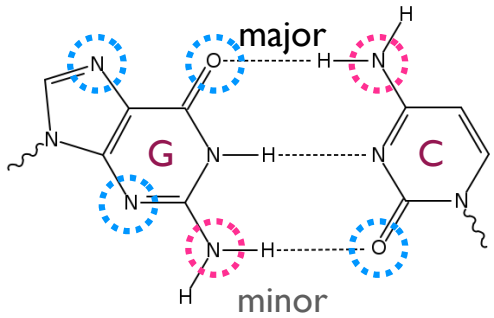
- Hydrogen bonds

AT has 2 hydrogen bonds, GC 3 hydrogen bonds
Recognition of groove or nucleotide sequence

- Steric considerations

width of major/minor groove
curvature





Riccardi, *et al.* PLoS Comput. Biol. 2019
van Heesch, Bolhuis, Vreede, Nucleic Acids Res. 2023

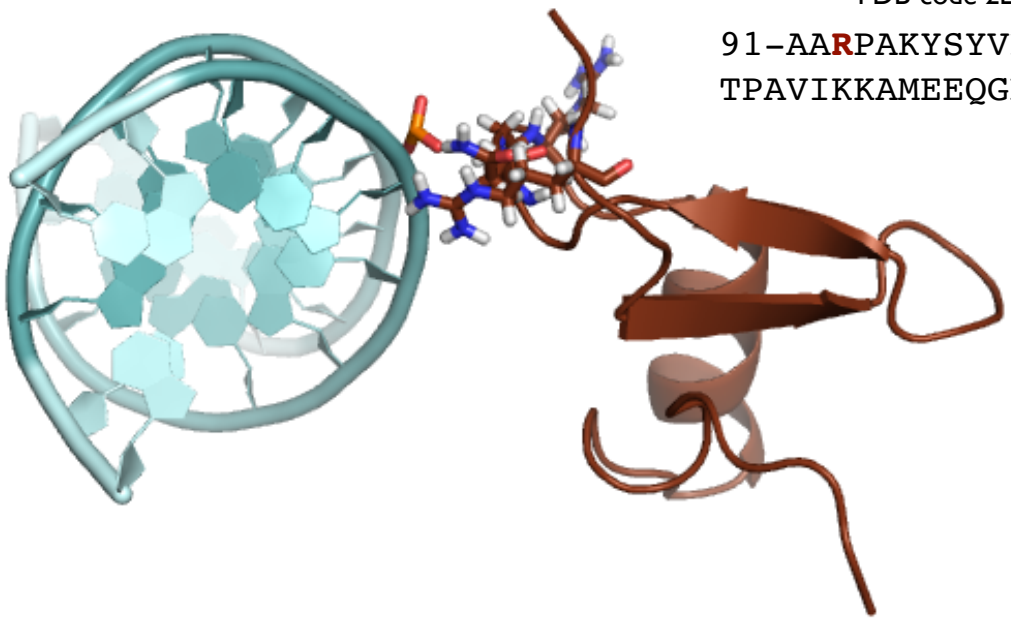
Protein-DNA complex
Molecular dynamics simulation

AMBER14 force field
TIP3P water + 150 mM NaCl
NpT ensemble, T = 300 K
gromacs

H-NS binding domain (from *Salmonella typhimurium*)
PDB-code 2L93, Gordon *et al.* PNAS 2011

91–AA**R**PAKYSYVDENGETKTWTG**QGR**
TPAVIKKAMEEQGKQLEDFLIKELE–139

high affinity sequence
CG**AATATATT**GC
GC**TTATATAA**CG



Once the protein is bound to the DNA, it stays bound for the rest of the μs simulation.

All-atom force field molecular dynamics of biomolecular systems

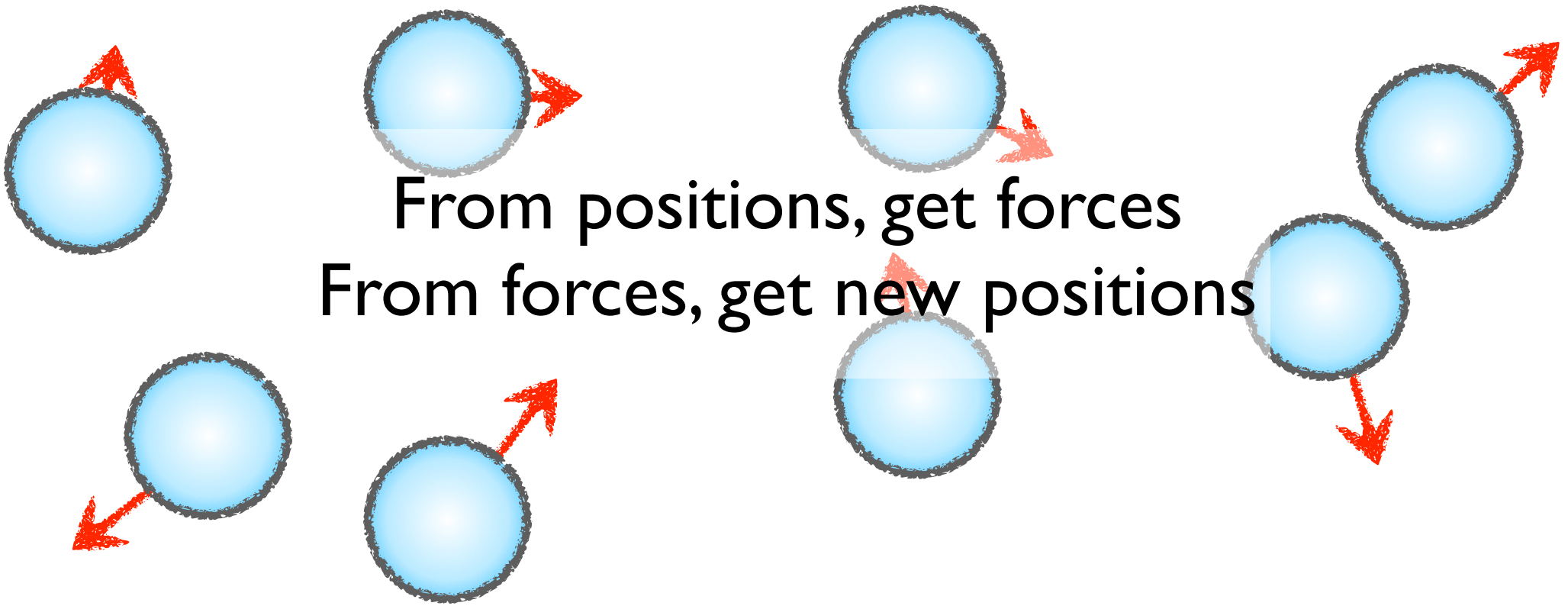
$$F = m\frac{d^2r}{dt^2} = ma$$

$$F = -\frac{dV(r)}{dr}$$

Given the potential, one can numerically integrate the trajectory of the whole system as a function of time.

numerically

The force F is given by the gradient of the potential *V(r)*.



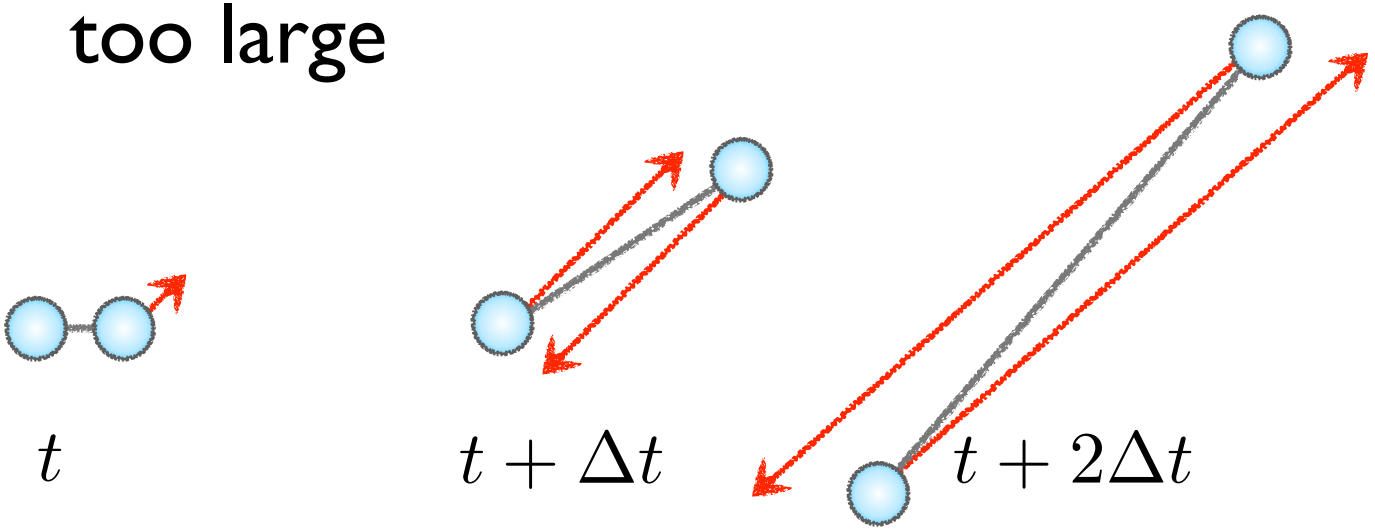
From positions, get forces

From forces, get new positions

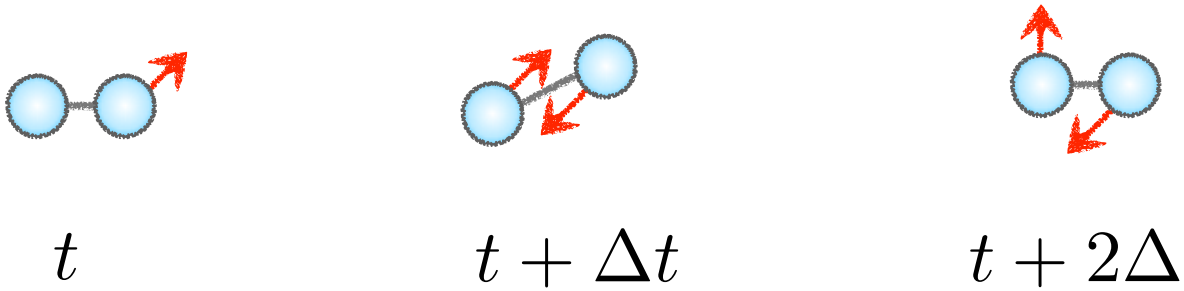
t $t + \Delta t$ $t + 2\Delta t$ $t + 3\Delta t$

Choosing the time step

Δt too large

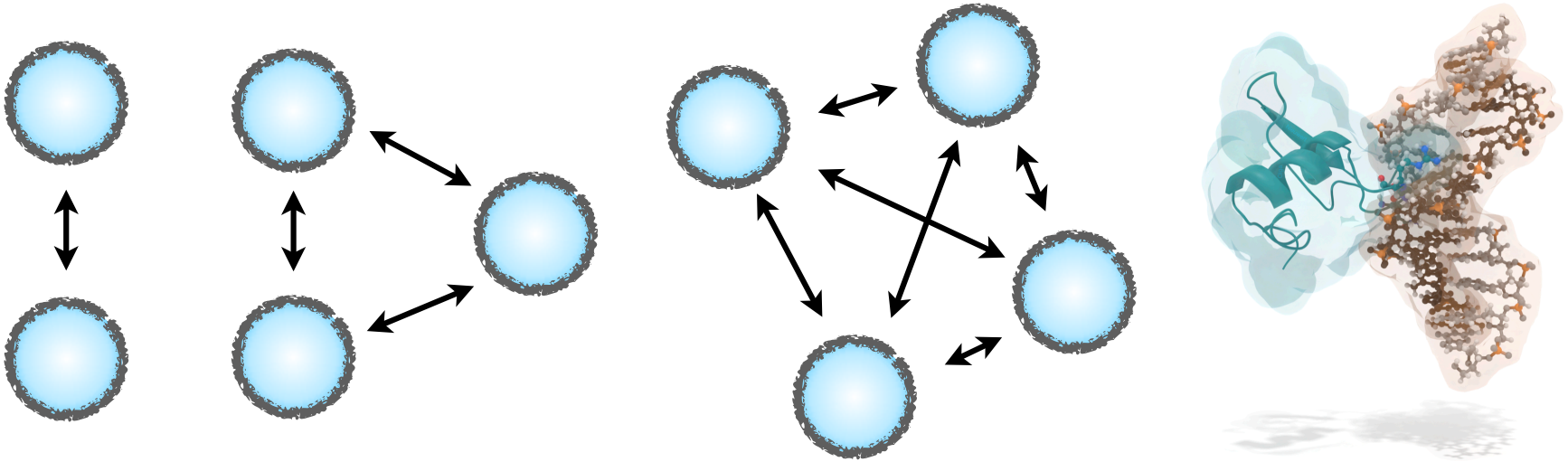


Δt just fine (2 fs for all-atom force field MD)



Force computations

Assumption: pairwise interactions



system				
number of force computations	1	3	6	N(N-1)/2

A system of N particles requires N(N-1)/2 force computations.

N number of atoms

$\Delta t = 2\ \mathrm{fs} = 2 \cdot 10^{-15}\ \mathrm{s} = 0.000000000000002\ \mathrm{s}$

A time step(Δt) takes about 0.0026 seconds = 2.6 ms on a supercomputer.

$1\ \mathrm{ns} = 10^{-9}\ \mathrm{s}$

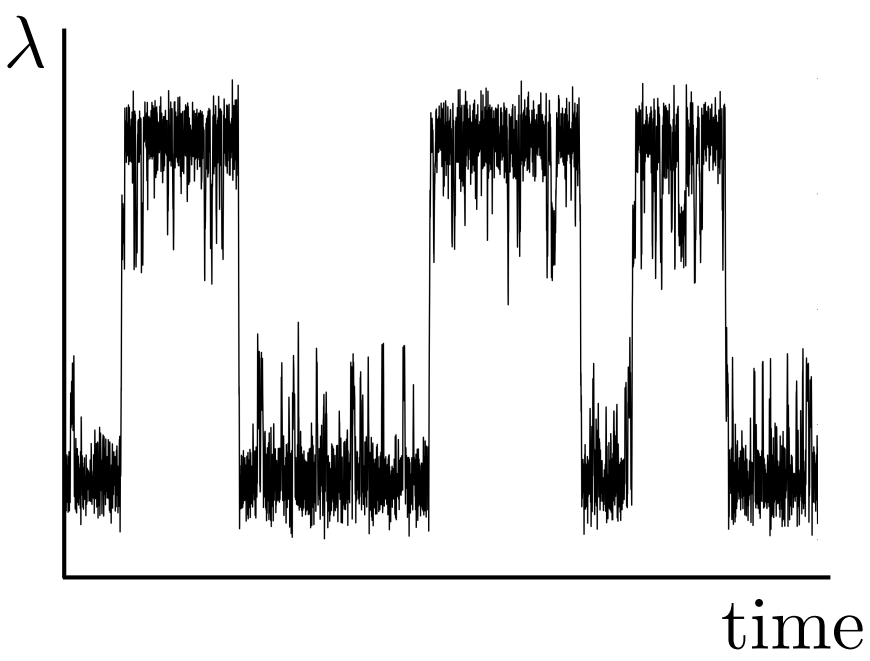
1 ns = 500.000 steps = 13.00 s ≈ 22 minutes

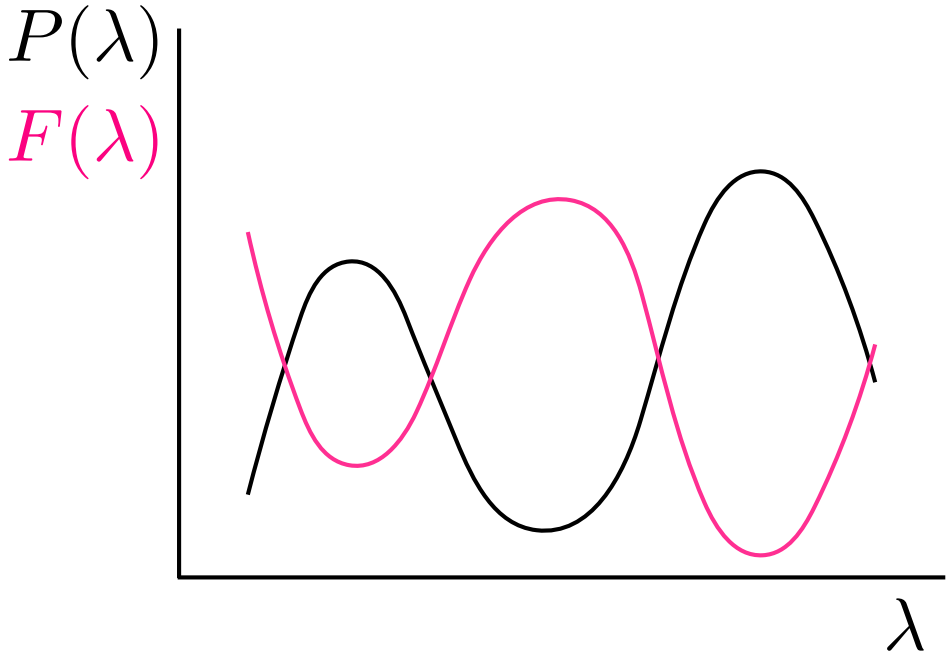
1 s = 500.000.000.000.000 steps
≈ 42.000 year

A protein-DNA complex in water

How long does it take to calculate the movements of the complex for 1 s?

Computing a free energy profile from a molecular dynamics simulation



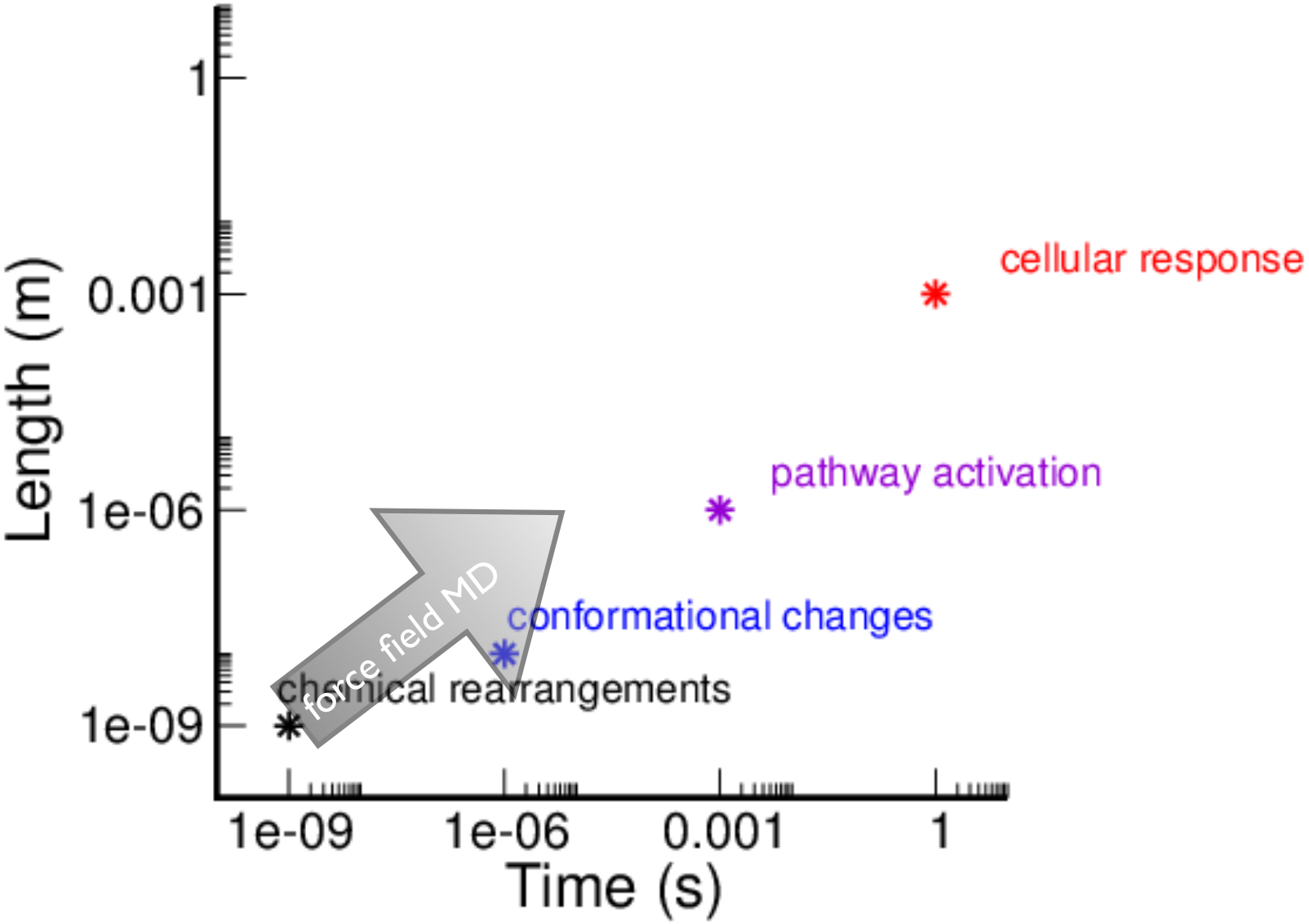


$$F(\lambda) = -k_B T \ln(P(\lambda))$$

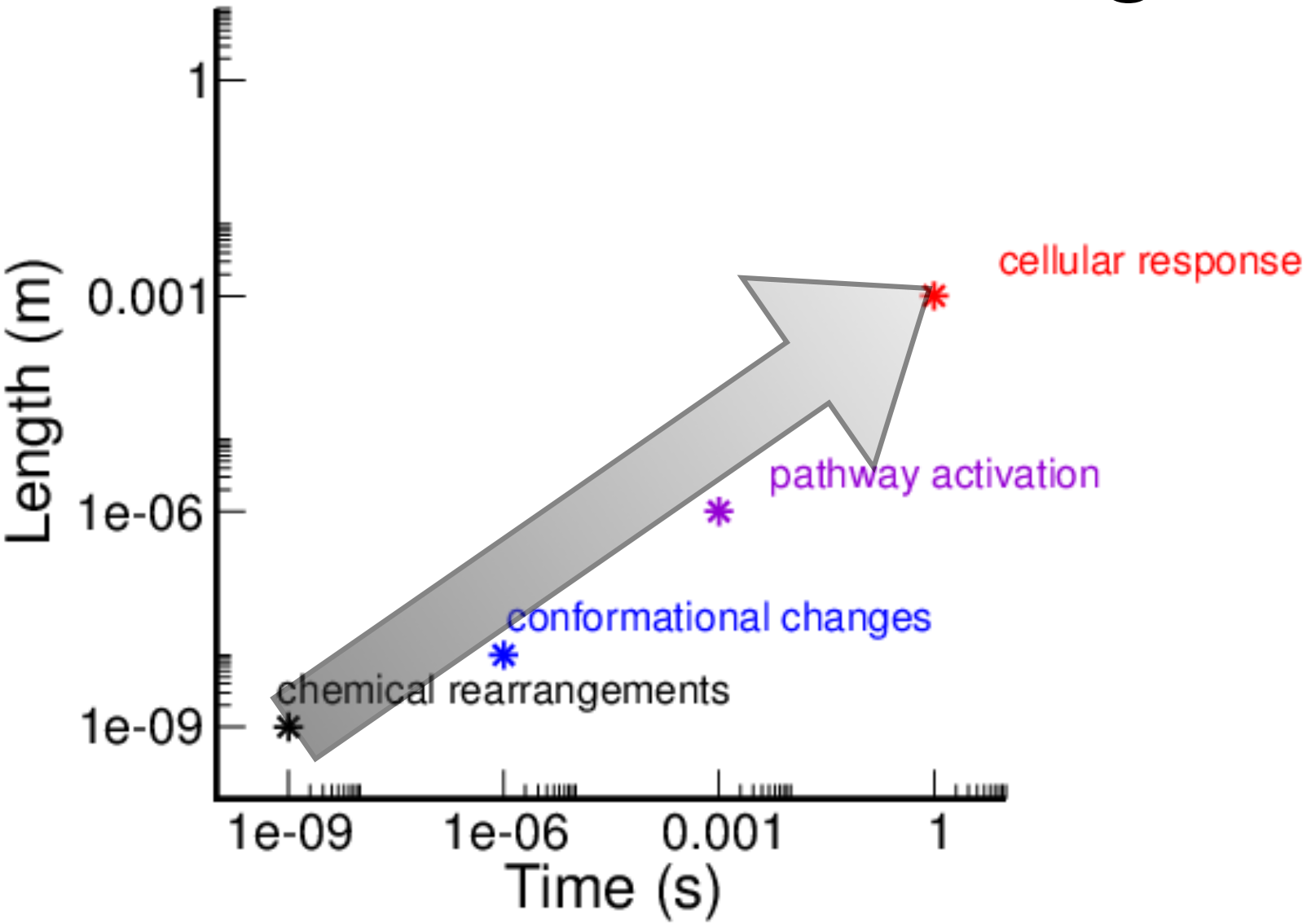
Problem: no sampling except in minima of F(λ)

F free energy
k_B Boltzmann's constant
T temperature
P probability
λ coordinate describing reaction progress

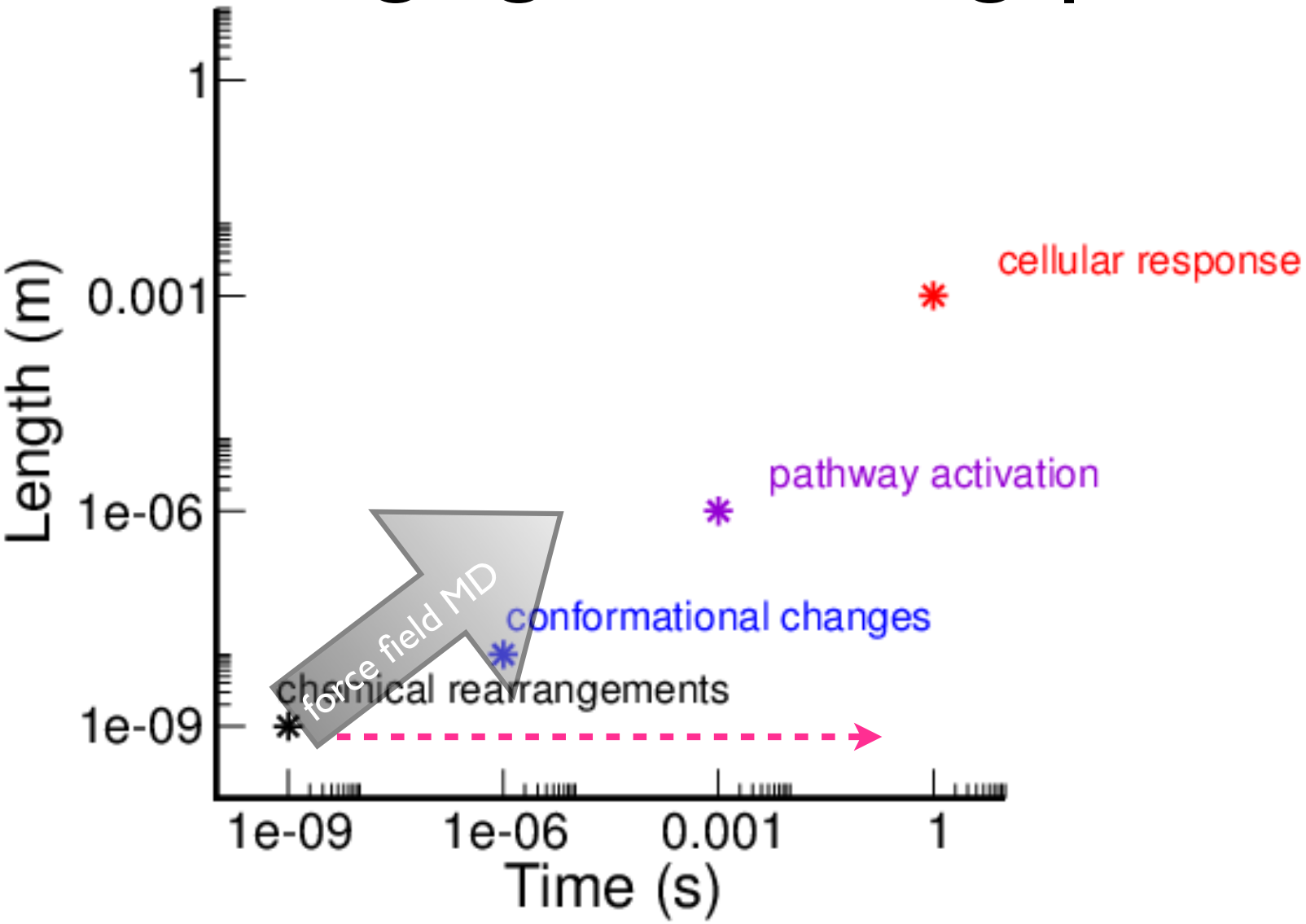
Where we are…


Length (m)
1
0.001
1e-06
1e-09
1e-09
1e-06
0.001
1
Time (s)
cellular response
pathway activation
conformational changes
chemical rearrangements
force field MD

And where we want to go!



Bridging the time gap



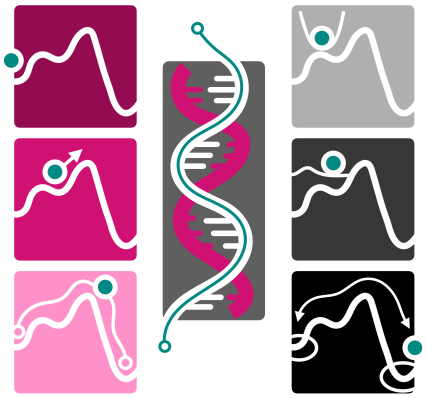
Biomolecular Simulation

Outline

Part 1: Simulating biomolecular systems

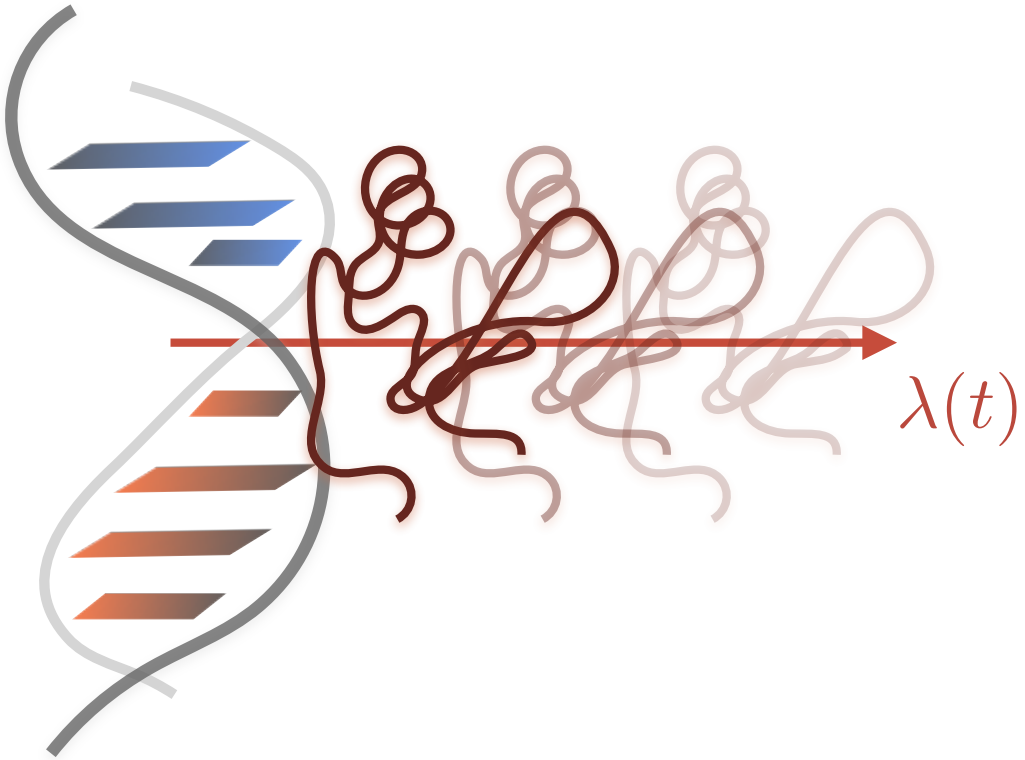
Part 2: Biased sampling

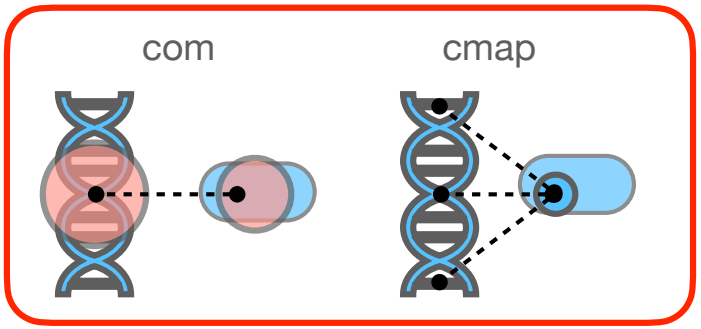
Part 3: Path sampling



Jarzynski Phys. Rev. Lett. 1997
Park & Schulten J. Chem. Phys. 2007
van Heesch, Bolhuis & Vreede Nucleic Acids Res. 2023

Steered molecular dynamics





Pull the protein off the DNA at constant velocity

$$U_\lambda(x,t) = \frac{k}{2}(s(x) - \lambda(t))^2$$

$$\lambda(t) = s_0 + vt$$

$$U_\lambda(x,t) = \frac{k}{2}(s(x) - s_0 - vt)^2$$

Measure the force

$$F(x,t) = -\frac{dU_\lambda}{ds(x)} = -k(s(x) - s_0 - vt)$$

Measure the work

$$w_{0\to t} = \int_0^t F(x,t)dt = kv\int_0^t (s(x) - s_0 - vt)dt$$

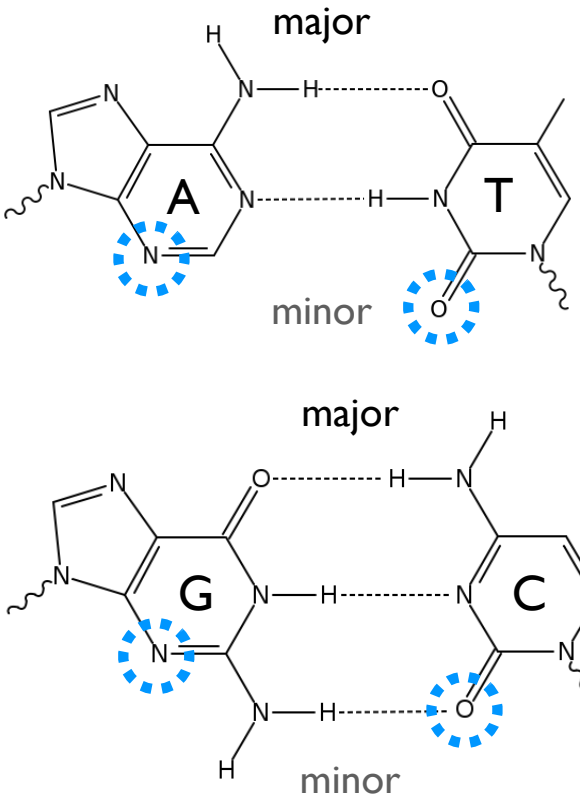
Average over several runs

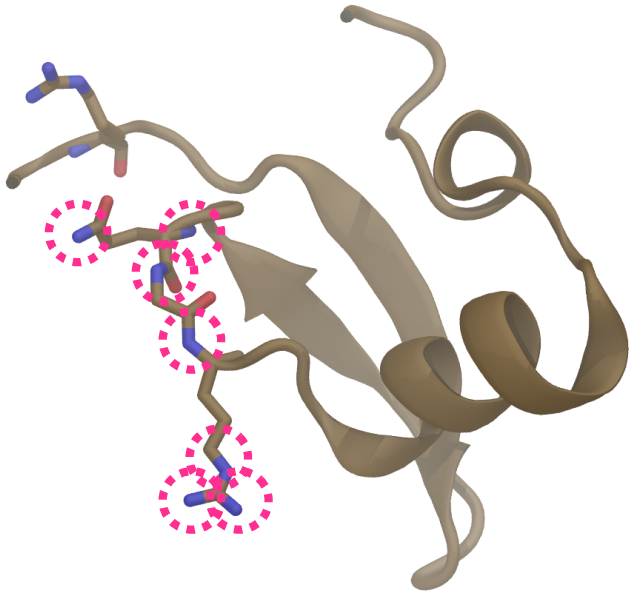
$$\langle \exp(-\beta w)\rangle = \exp(-\beta \Delta G)$$

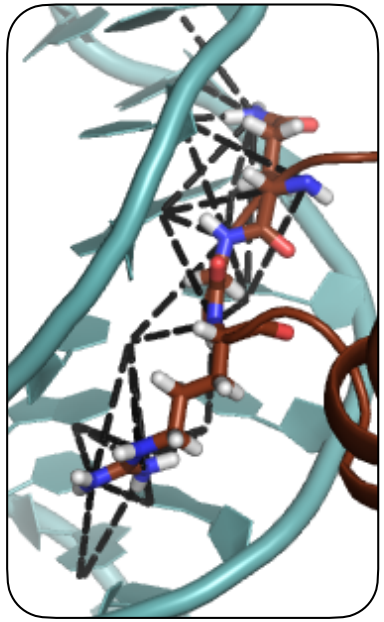
Contact map

Count contacts between protein and DNA

$$c_{\text{protein}-\text{DNA}} = \sum_{i \in \text{protein}} \sum_{j \in \text{DNA}} s_{ij} \qquad s_{ij} = \frac{1 - \left(\frac{r_{ij} - d_0}{r_0}\right)^2}{1 - \left(\frac{r_{ij} - d_0}{r_0}\right)^4}$$





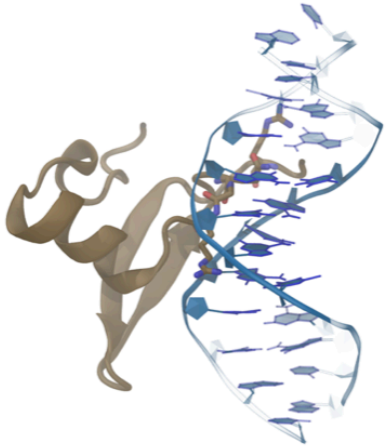


Riccardi, van Mastbergen, Navarre, Vreede, PLoS Comput. Biol. 2019
van Heesch, Bolhuis & Vreede Nucleic Acids Res. 2023

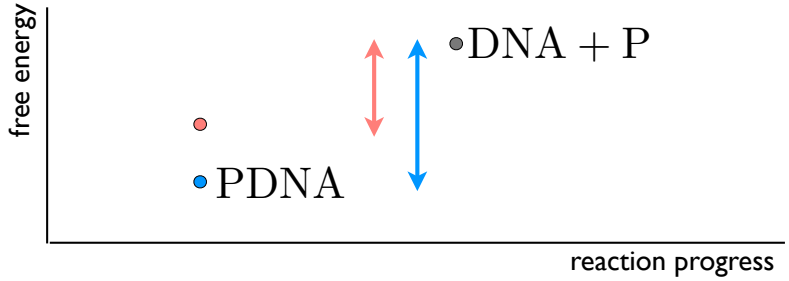
van Heesch, Bolhuis & Vreede Nucleic Acids Res. 2023

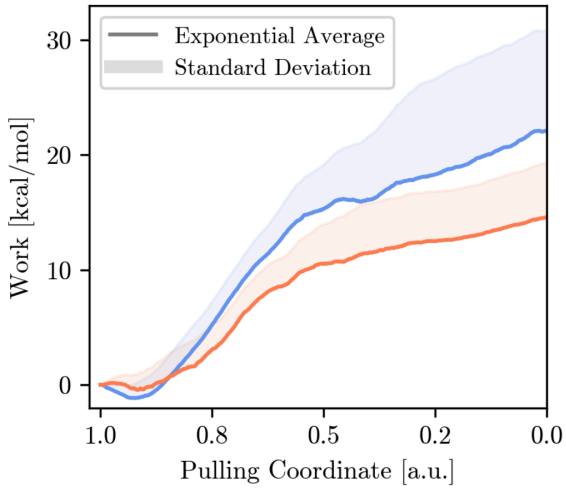
minor groove binder

Histone-like nucleoid structuring protein



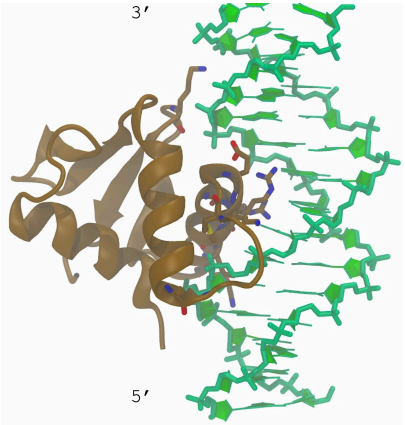
high affinity 5’–GCAATATATTGC–3’
GC–analogue – 5’–GCGGCGCGCCCG–3’



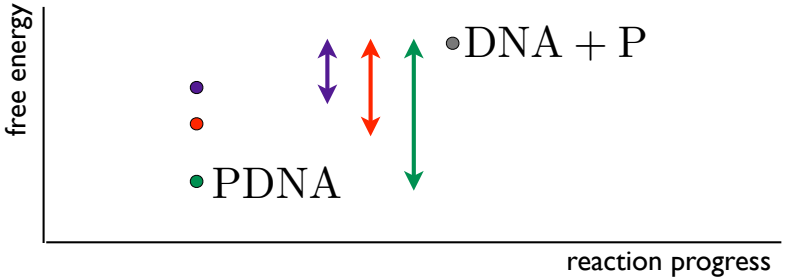


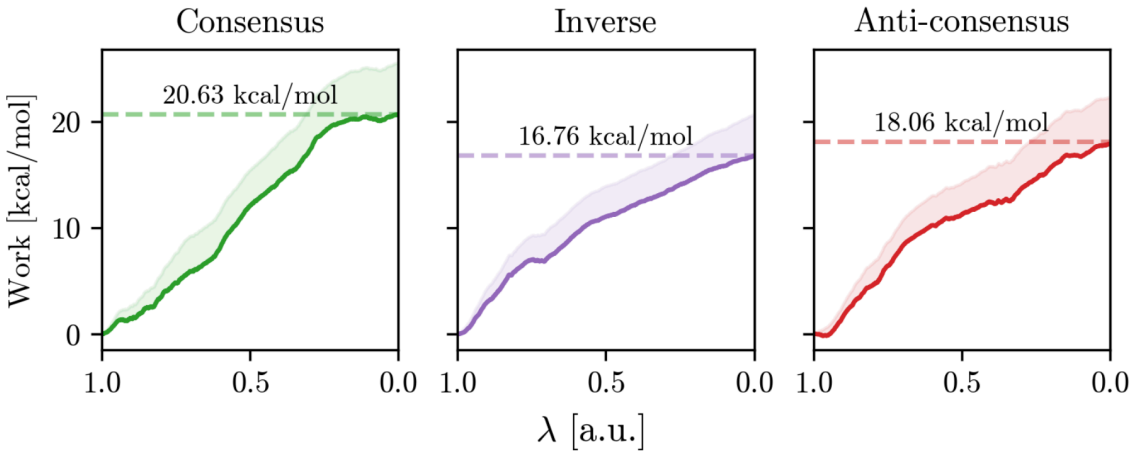
major groove binder

ETS domain from Pu.1 transcription factor

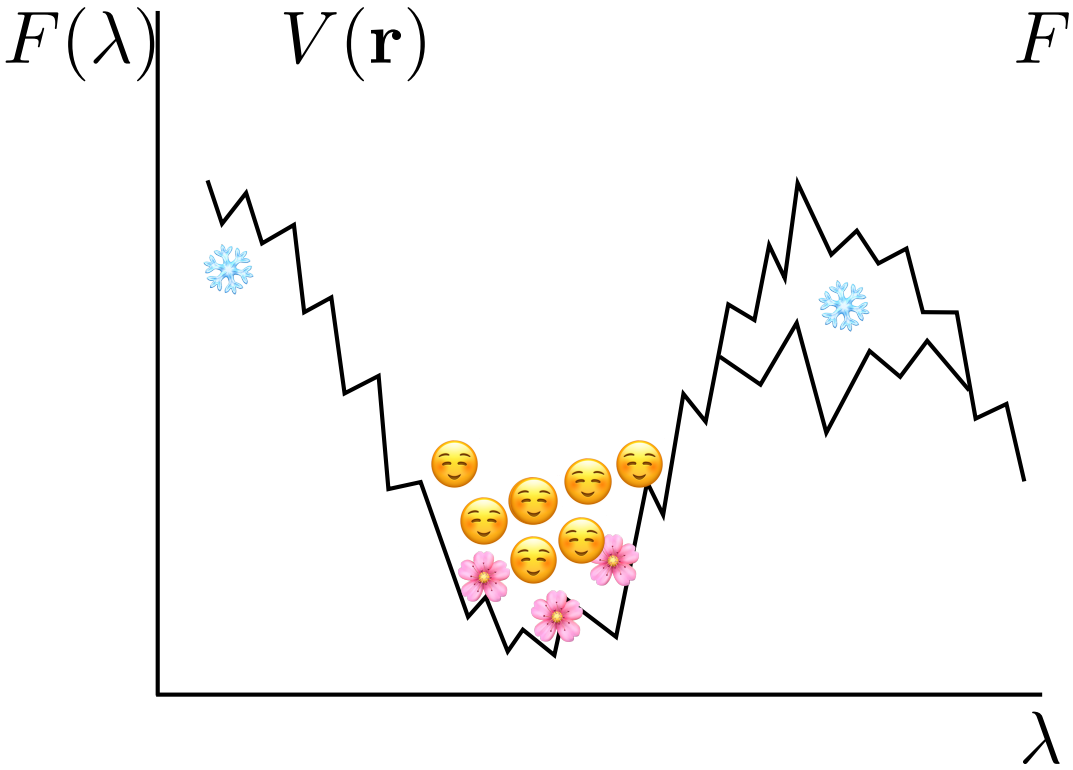


consensus 5’–AAAAGGGGAAGTGGG–3’
inverted 5’–CCCCTTTTCCTGAAA–3’
anti–consensus 5’–AAAA**AA**GGAAG**GT**GG–3’

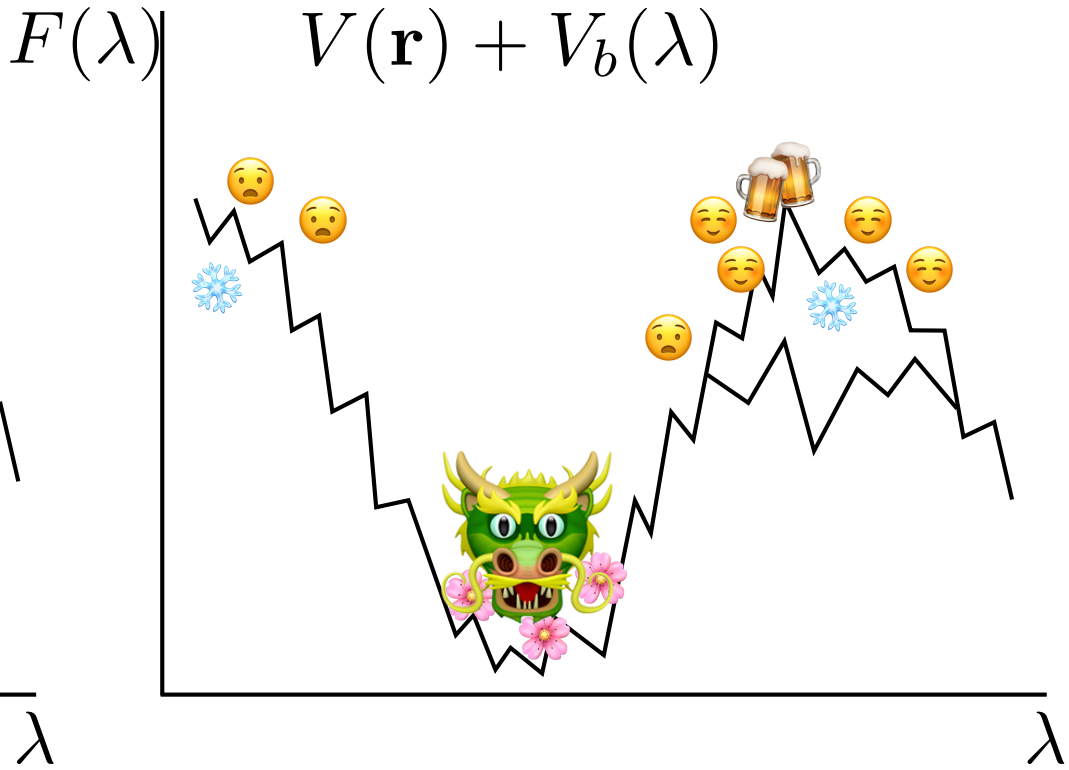




Biased sampling



Straightforward MD



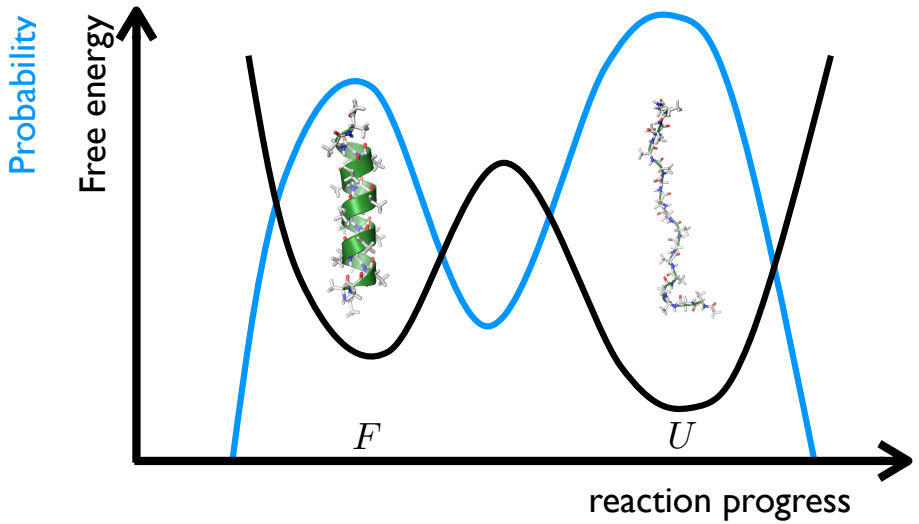
Biased sampling

Biasing coordinate

A collective variable (CV) is a function λ of the 3N-dimensional configuration **r**.
λ maps **r** onto an M-dimensional space **z**.
M << 3N

$$P(\mathbf{z}) = \langle \delta[\lambda(\mathbf{r}) - \mathbf{z}] \rangle$$

$$F(\mathbf{z}) = -k_B T \ln \langle \delta[\lambda(\mathbf{r}) - \mathbf{z}] \rangle$$



Biased sampling

$$V_{total} = V(\mathbf{r}) + V_b(\mathbf{r})$$

$V(\mathbf{r})$ interatomic potential, dependent on positions **r**

$V_b(\mathbf{r})$ bias potential, dependent on **r**

Biased sampling

Derive statistics on a system with different energetics from the energetics used to perform the sampling

potential

$$V_{total} = V(\mathbf{r}) + V_b(\mathbf{r})$$

$V(\mathbf{r})$ interatomic potential, dependent on positions **r**

$V_b(\mathbf{r})$ bias potential, dependent on **r**

distribution

$$P_b(\mathbf{z}) = \frac{\int d\mathbf{r} \exp(-\beta V(\mathbf{r})) \exp(-\beta V_b(\mathbf{r})) \delta(\lambda(\mathbf{r}) - \mathbf{z})}{\int d\mathbf{r} \exp(-\beta V(\mathbf{r})) \exp(-\beta V_b(\mathbf{r}))}$$

mulitply by 1

$$\frac{\int d\mathbf{r} \exp(-\beta V(\mathbf{r})) \exp(-\beta V_b(\mathbf{r})) \delta(\lambda(\mathbf{r}) - \mathbf{z})}{\int d\mathbf{r} \exp(-\beta V(\mathbf{r}))} \frac{\int d\mathbf{r} \exp(-\beta V(\mathbf{r}))}{\int d\mathbf{r} \exp(-\beta V(\mathbf{r})) \exp(-\beta V_b(\mathbf{r}))}$$

$$= \frac{\langle \exp(-\beta V_b(\mathbf{r})) \delta(\lambda(\mathbf{r}) - \mathbf{z}) \rangle}{\langle \exp(-\beta V_b(\mathbf{r})) \rangle}$$

ensemble averaged on interatomic potential V(**r**)

z - reaction coordinate space

λ - collective variable

Biased sampling

$$P_b(\mathbf{z}) = \frac{\langle \exp(-\beta V_b(\mathbf{r}))\delta(\lambda(\mathbf{r}) - \mathbf{z})\rangle}{\langle \exp(-\beta V_b(\mathbf{r}))\rangle}$$

bias $V_b(\mathbf{r})$ is function of the collective variables $\lambda(\mathbf{r})$

$$P_b(\mathbf{z}) = \frac{\exp(-\beta V_b(\mathbf{z}))\,\langle \delta(\lambda(\mathbf{r}) - \mathbf{z})\rangle}{\langle \exp(-\beta V_b(\lambda(\mathbf{r})))\rangle}$$

unbiased statistics $P(\mathbf{z}) = \langle \delta(\lambda(\mathbf{r}) - \mathbf{z})\rangle$

$$P(\mathbf{z}) = P_b(\mathbf{z}) \exp(\beta V_b(\mathbf{z}))\,\langle \exp(-\beta V_b(\lambda(\mathbf{r})))\rangle$$

An ergodic MD simulation on V_b can provide the statistics of λ as if generated with the unbiased potential V.

Biased sampling

The closer the bias potential is to the negative free energy $-F(z)$ the more uniform the sampling of λ will be.

if $V_b(\lambda(\mathbf{r})) = -F(\lambda(\mathbf{r}))$

then $\exp(\beta V_b(\mathbf{z})) = \exp(-\beta F(\mathbf{z})) = P(\mathbf{z})$

$$P(\mathbf{z}) = P_b(\mathbf{z}) \exp(\beta V_b(\mathbf{z})) \langle \exp(-\beta V_b(\lambda(\mathbf{r}))) \rangle$$

$$P_b(\mathbf{z}) = \frac{1}{\langle \exp(\beta F(\mathbf{z}) \rangle} = \frac{1}{\int d\mathbf{z} \exp(-\beta F) \exp(\beta F)}$$

$$= \frac{1}{\int d\mathbf{z}} \quad \langle \exp(\beta F(\mathbf{z}) \rangle = \int d\mathbf{z} P(\mathbf{z}) \exp(\beta F)$$

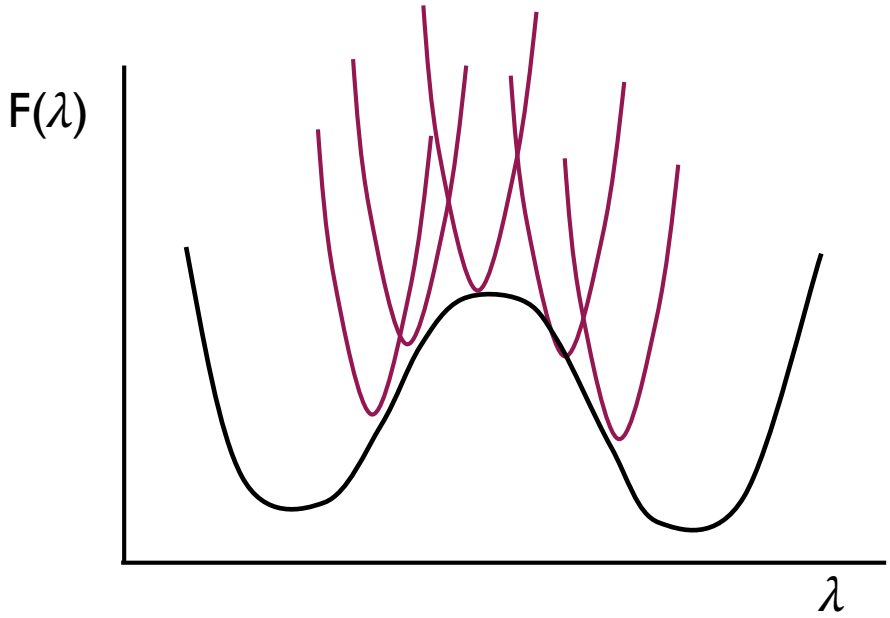
All states z become equiprobable

Umbrella sampling

Harmonic spring keeps the trajectory close to z_i

$$V_b(\mathbf{r}) = \frac{1}{2} k \left[\lambda(\mathbf{r}) - \mathbf{z}_i\right]$$

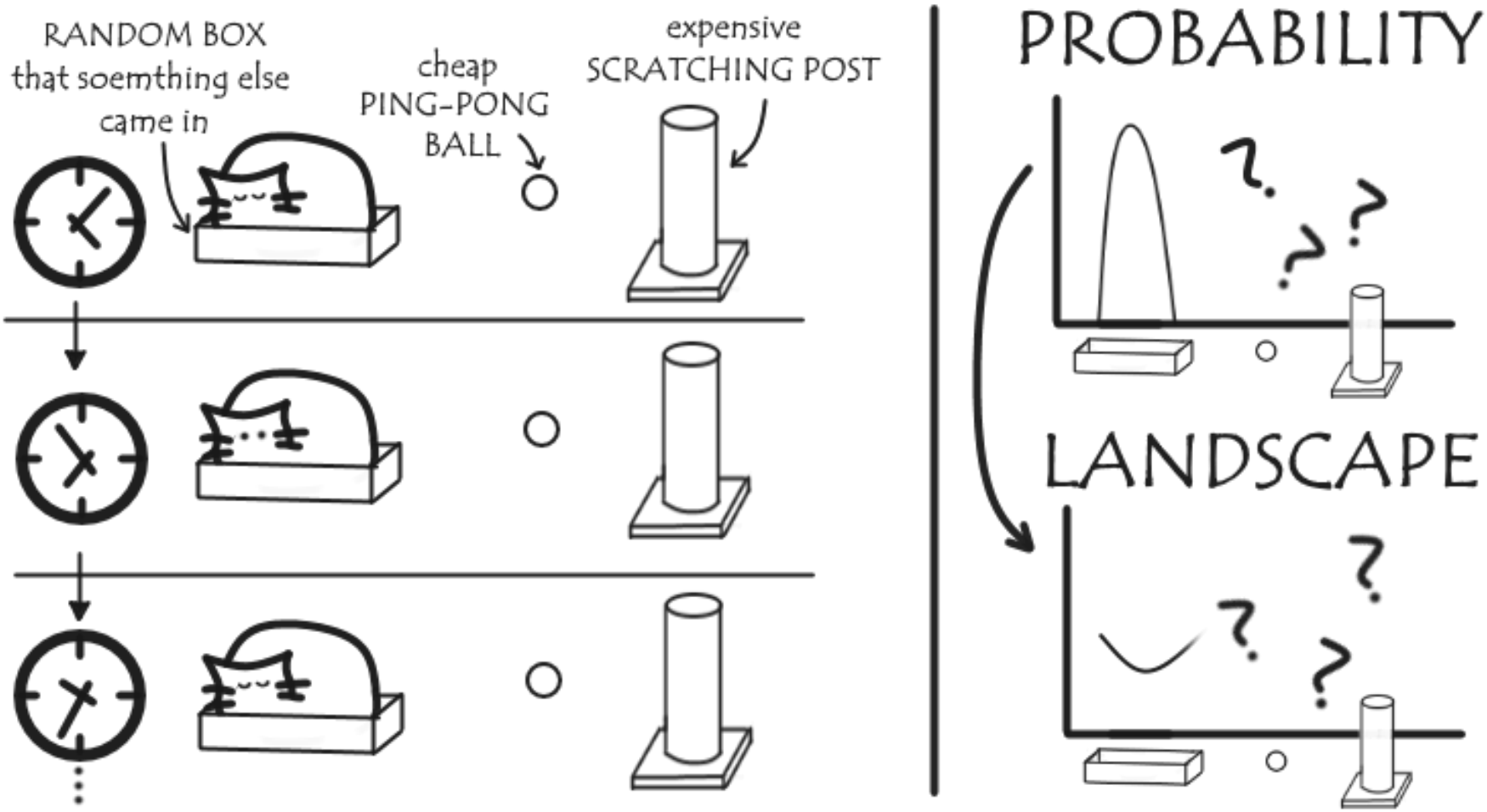
The points $\mathbf{z}_i$ and the value of k must be chosen such that $\lambda(\mathbf{r}(t))$ makes excursions into the window of its neighbor.



$$P(\mathbf{z}) = P_b(\mathbf{z}) \exp(\beta V_b(\mathbf{z})) \left\langle \exp(-\beta V_b(\lambda(\mathbf{r}))) \right\rangle$$

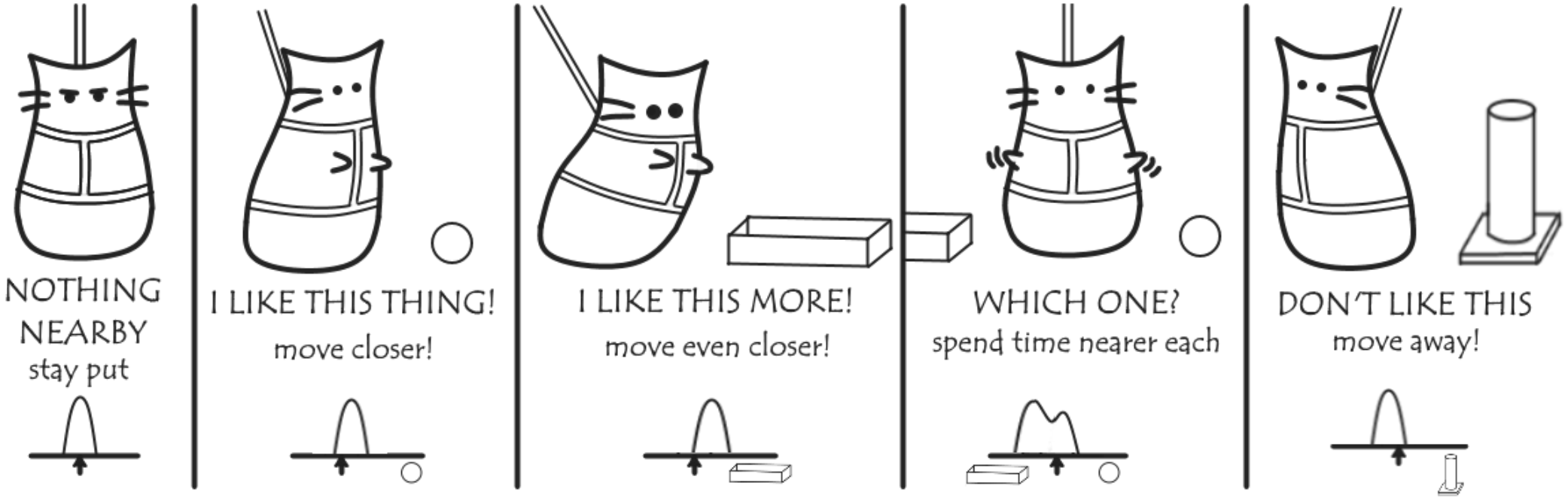
$$P_i(\mathbf{z}) = P_{b,i}(\mathbf{z}) \exp(\frac{1}{2}\beta k |\mathbf{z} - \mathbf{z}_i|^2 \left\langle \exp(-\beta \frac{1}{2} k |\lambda(\mathbf{r}) - \mathbf{z}_i|^2) \right\rangle$$

Molecular dynamics simulation of a cat

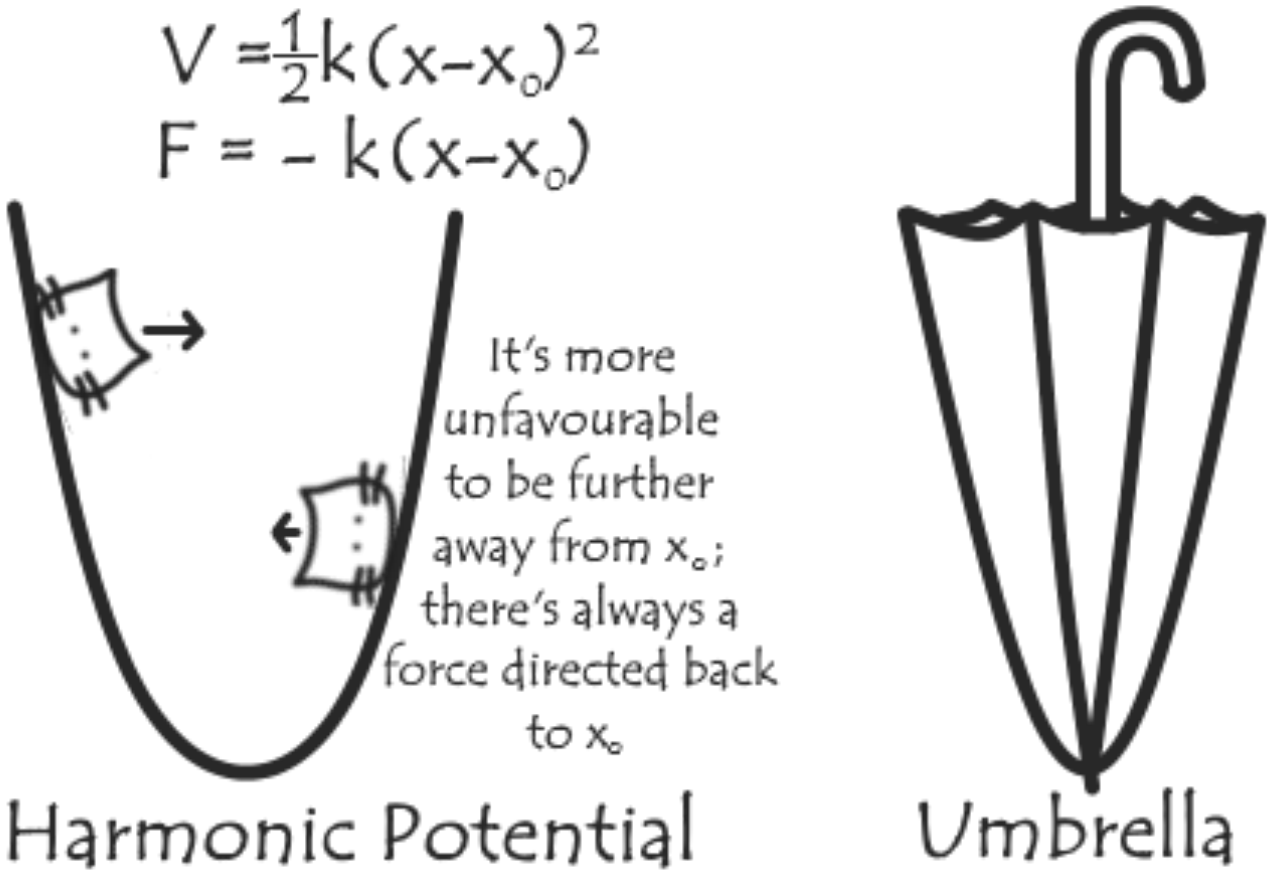


http://fiona-naughton.github.io/blog/2016/05/25/What-is-this-MD-thing-anyway

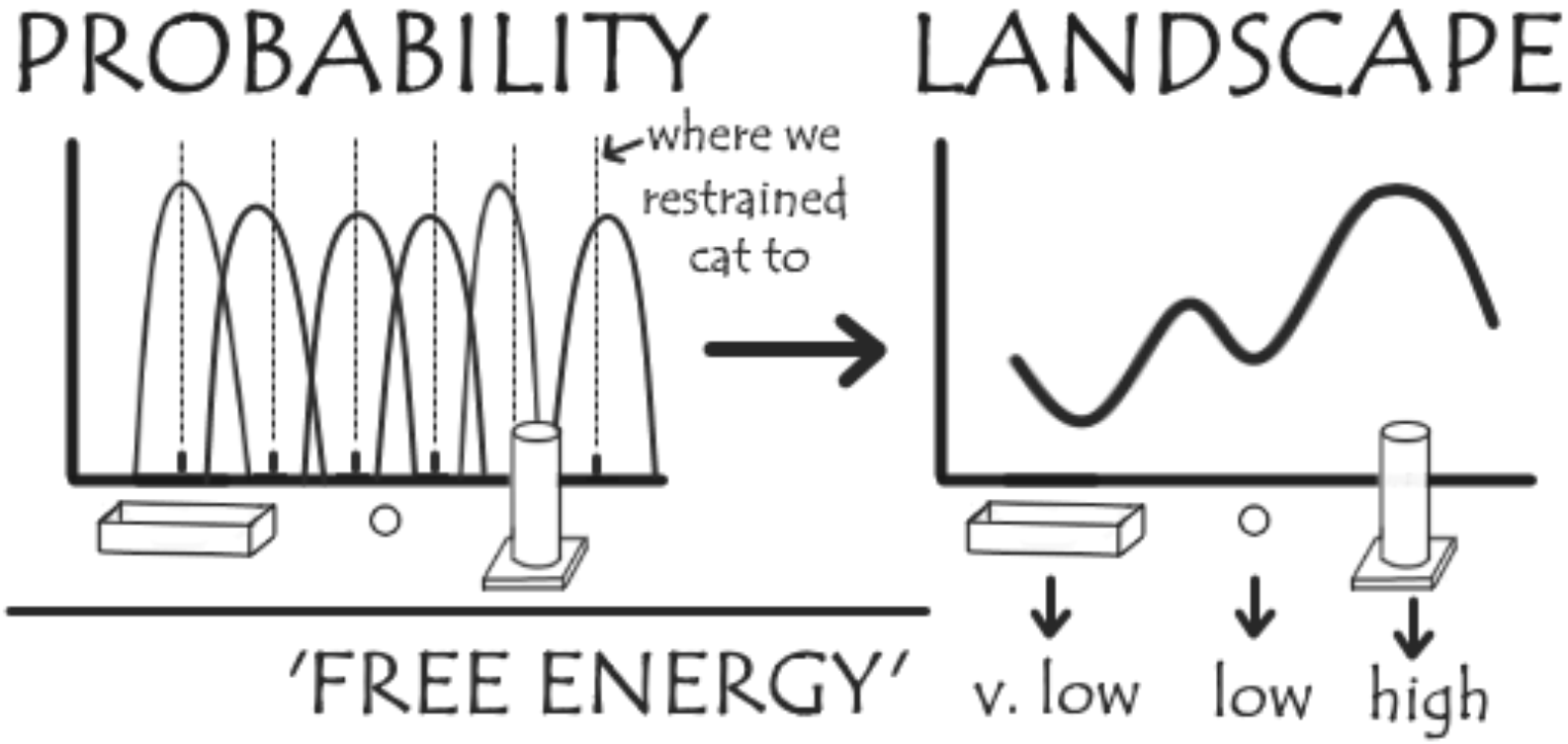
Umbrella sampling of a cat



Umbrella sampling

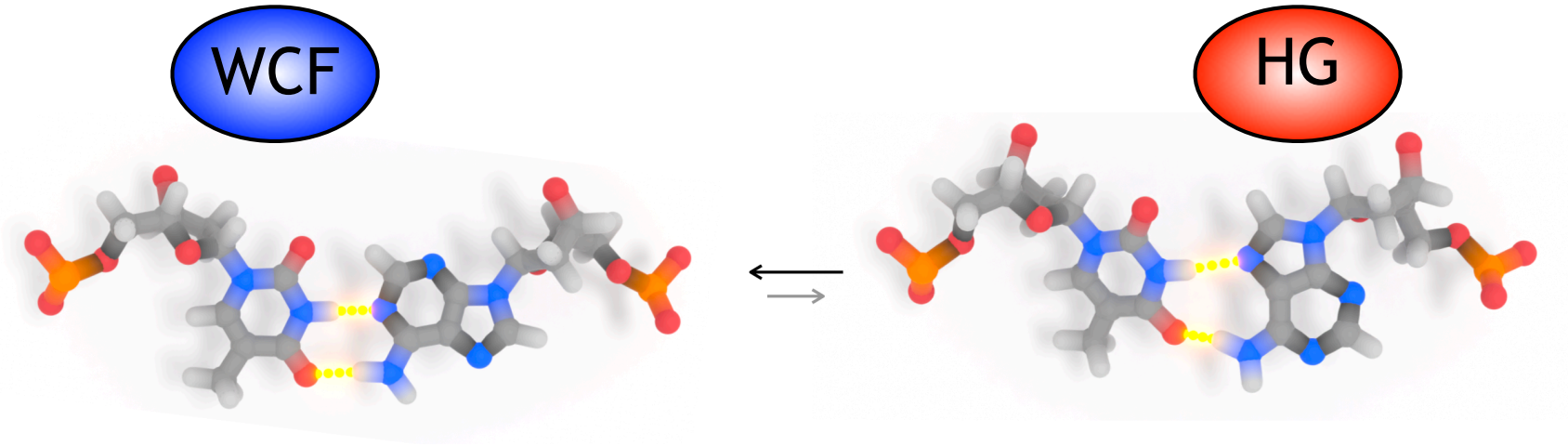


Umbrella sampling

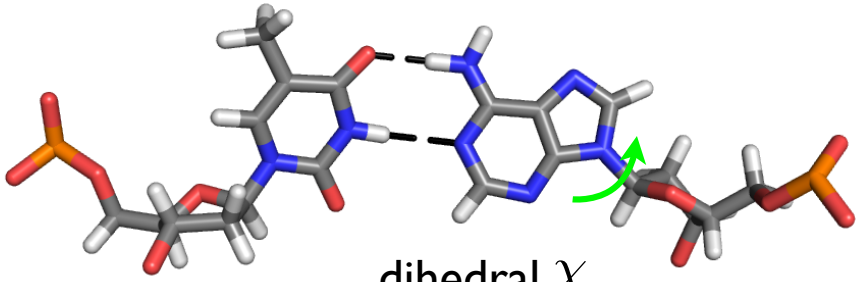


http://fiona-naughton.github.io/blog/2016/05/25/What-is-this-MD-thing-anyway

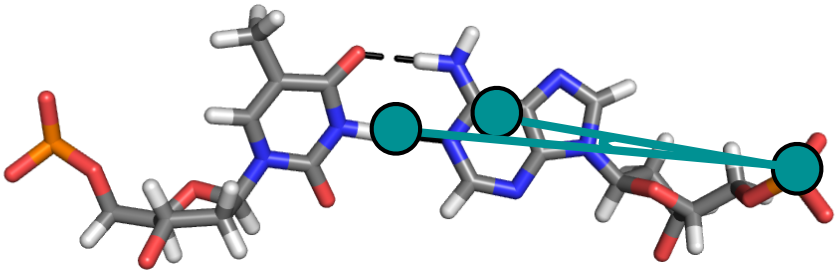
Umbrella sampling of the WCF to HG transition



Umbrella sampling of the WCF to HG transition

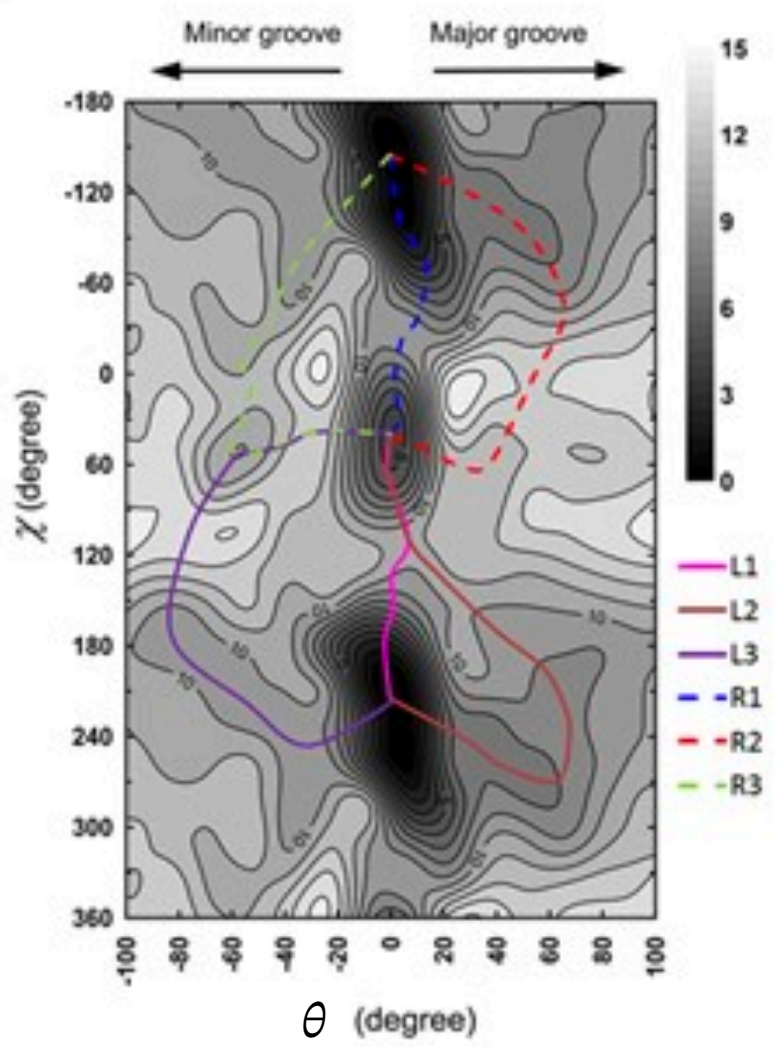


dihedral χ



base flipping angle θ

13x24 windows
20 ns per window
>6μs simulation time



Biased sampling

$$V_{total} = V(\mathbf{r}) + V_b(\mathbf{r})$$

$V(\mathbf{r})$ interatomic potential, dependent on positions **r**

$V_b(\mathbf{r})$ bias potential, dependent on **r**

- What is the bias?

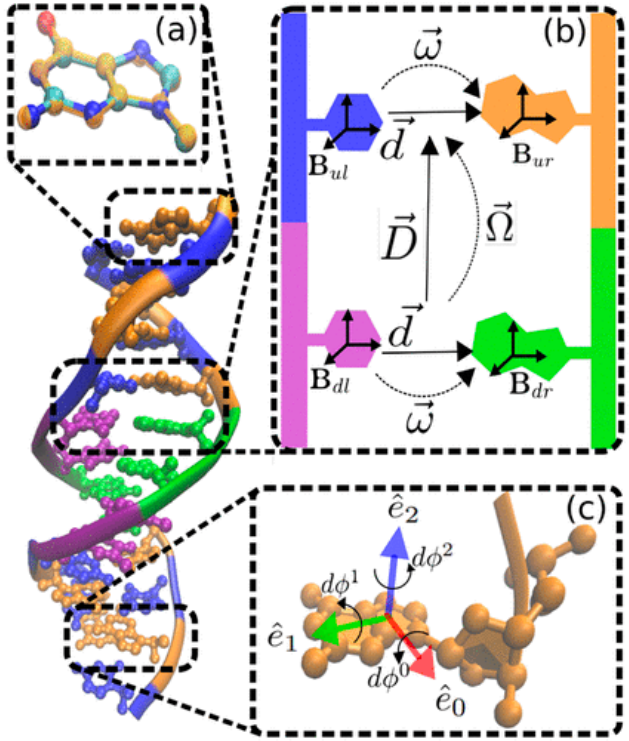
System dependent, should be close to free energy profile

- How is the bias applied?

steered MD, umbrella sampling, metadynamics, …

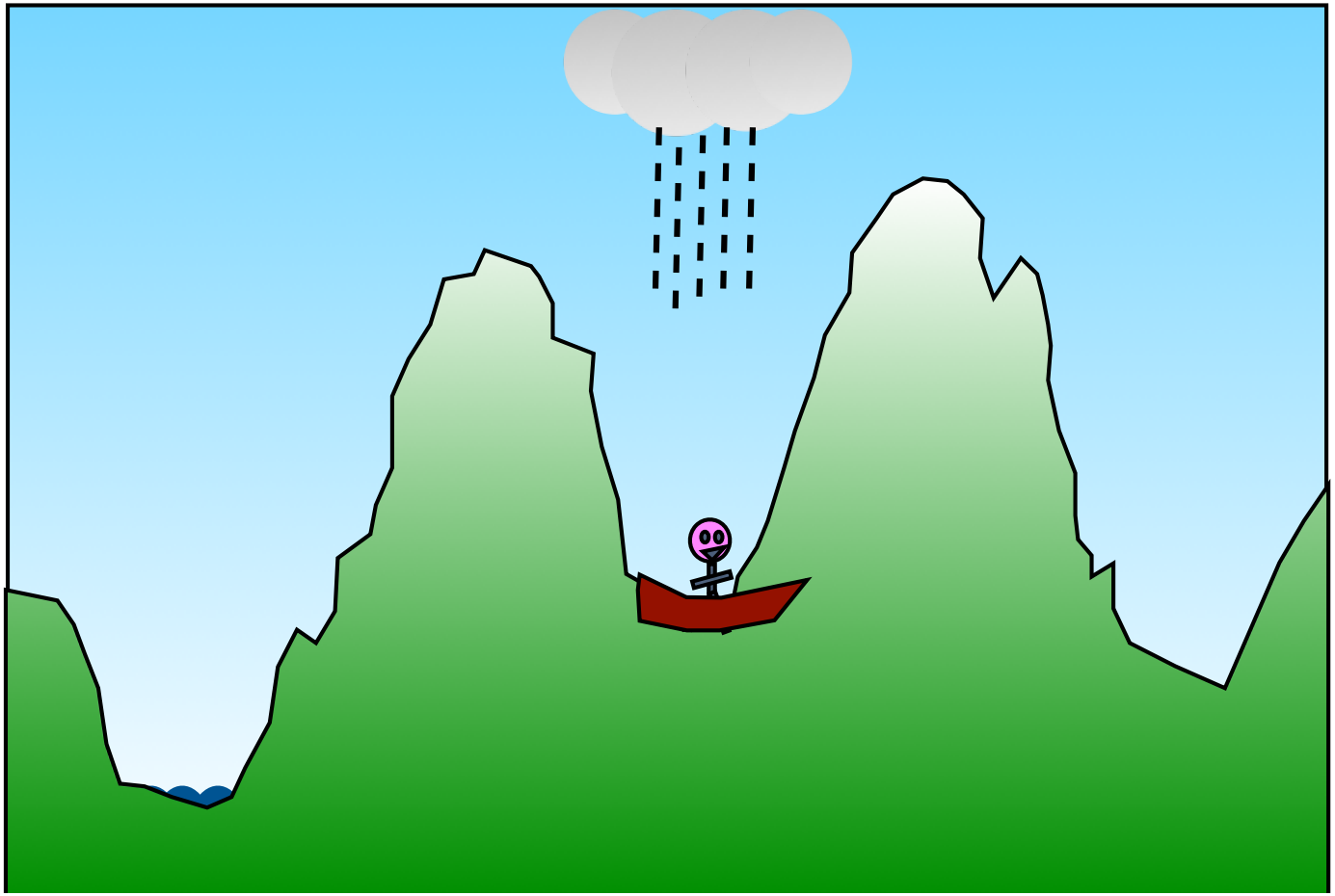
Choosing V_b

The closer the bias potential is to the negative free energy, the more uniform the sampling of λ will be.



Voorspoels, Vreede & Carlon, JCTC 2023

Metadynamics



Animation by Bernd Ensing
Laio and Parrinello, PNAS (2002)

Metadynamics

$$V_{total} = V(\mathbf{r}) + V_b(\lambda(\mathbf{r}), t)$$

force field bias potential

The bias potential acts on collective variables λ, which approximate the reaction coordinate.

$$V_b(\lambda(\mathbf{r}), t) = w \sum_{t'<t} \exp\left(-\frac{|\lambda(\mathbf{r}(t) - \mathbf{r}(t'))|^2}{2\delta\lambda^2}\right)$$

$$t' = \tau_G, 2\tau_G, ...$$

w height of the Gaussian
τ_G time interval between depositions
$\delta\lambda$ Gaussian width

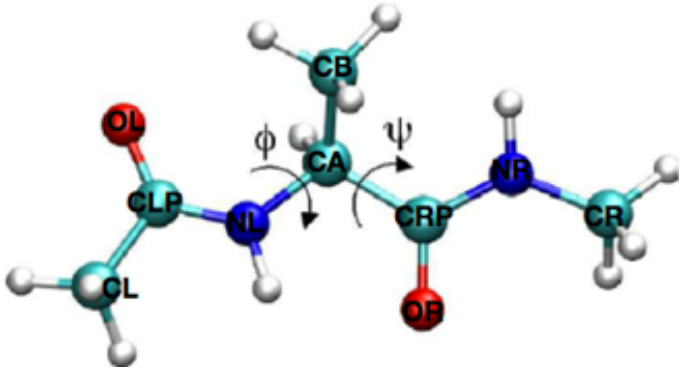
The bias is built as a sum of repulsive Gaussian functions, centered on the points in collective variable space already visited.

$$F = -\lim_{t\to\infty} V_b(\lambda(\mathbf{r}), t)$$

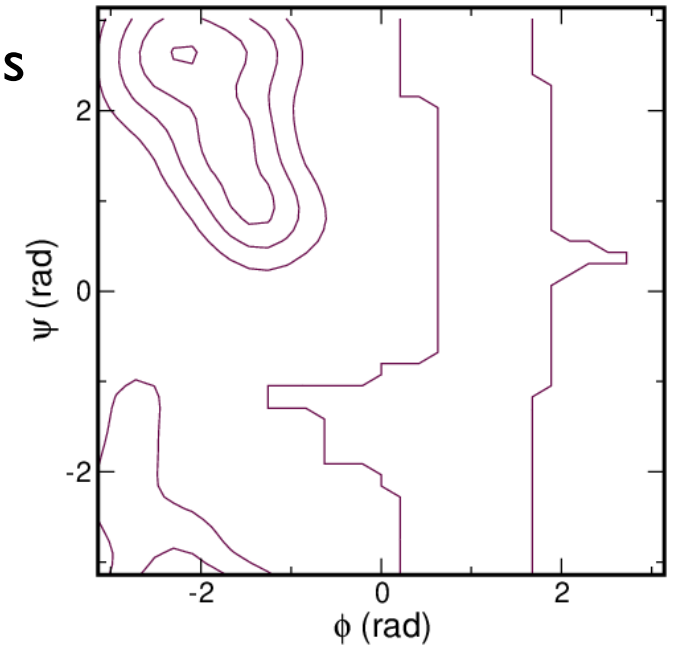
The bias potential becomes the negative free energy when simulated long enough.

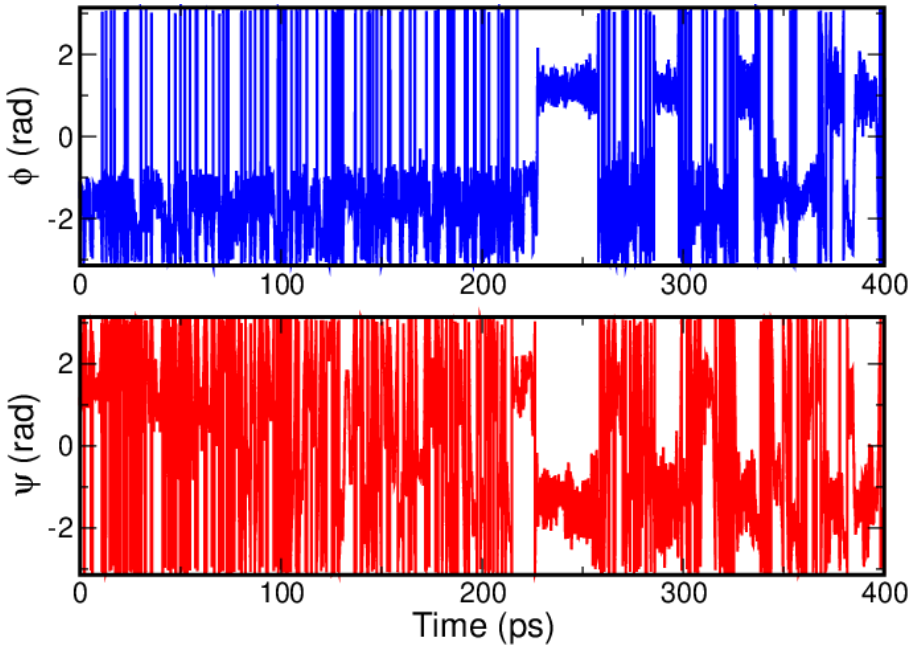
Laio & Parrinello *Proc. Natl. Acad. Sci USA* 2002

Alanine dipeptide in vacuum

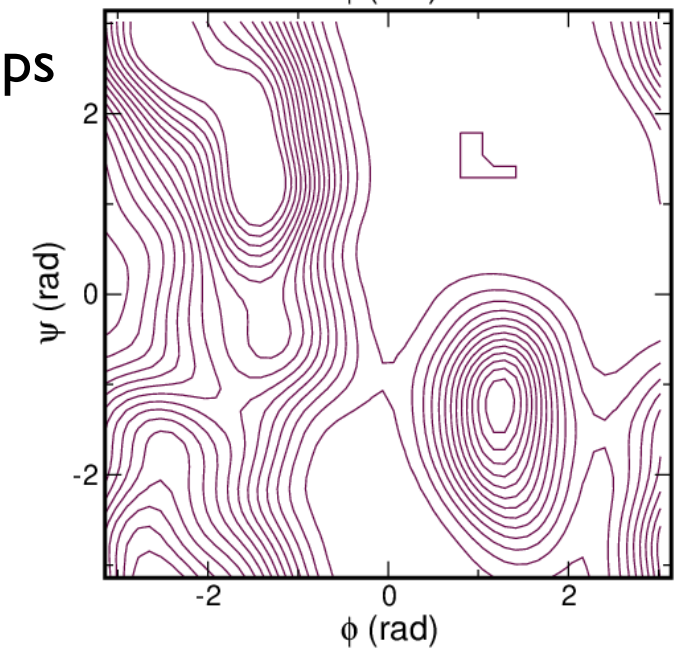


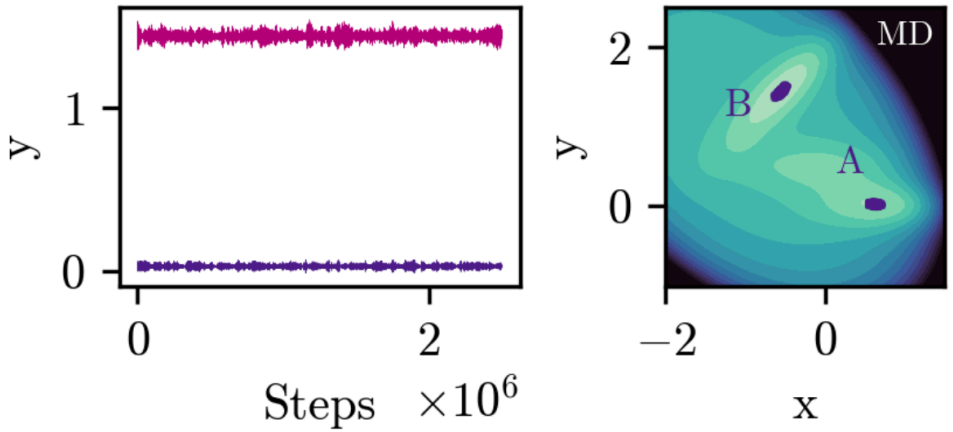
40ps





400ps



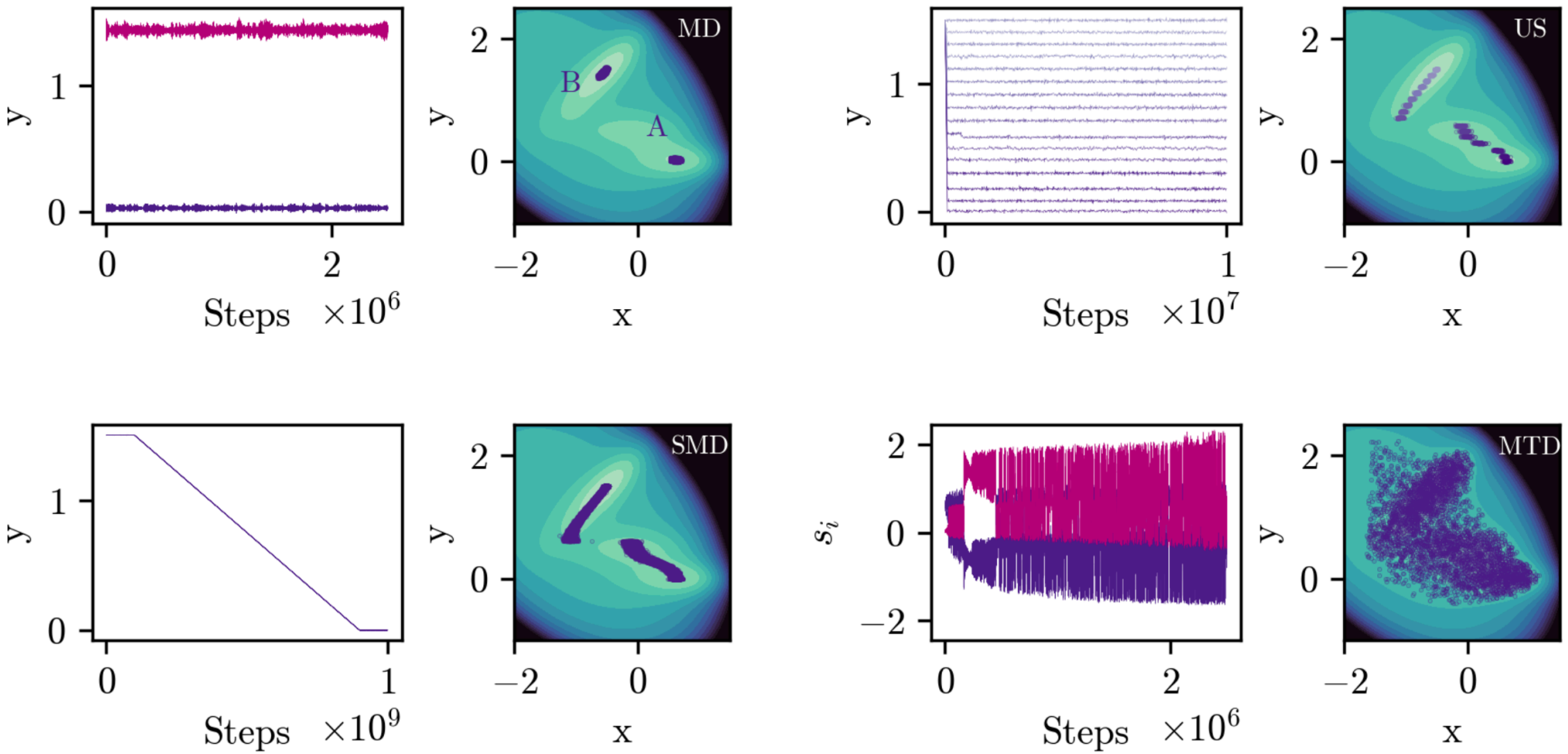


Müller-Brown potential

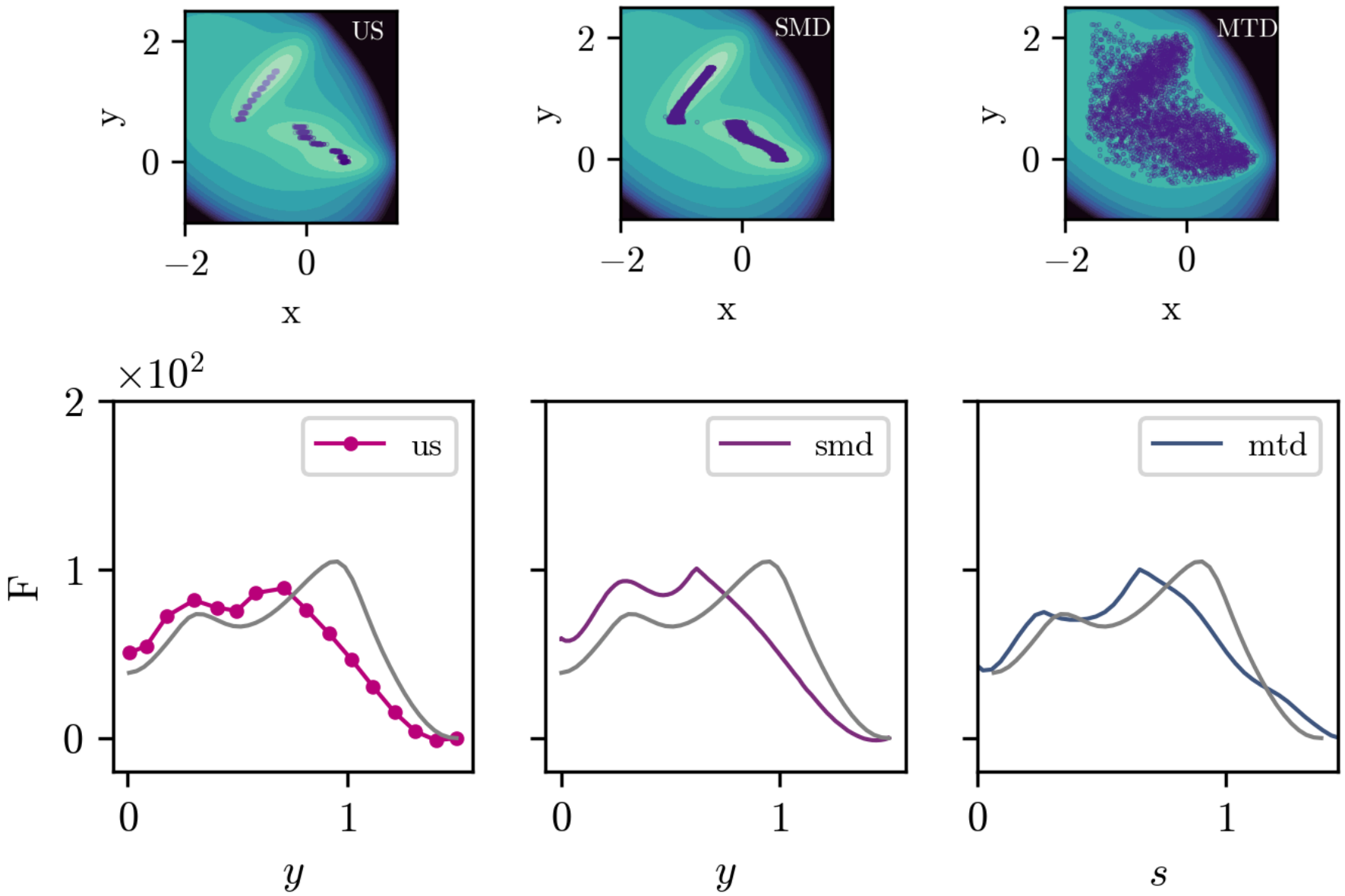
$$V(x,y) = \sum_{k=1}^{4} A_k \exp(a_k(x - x_k^0)^2 + a_k(x - x_k^0)(y - y_k^0) + c_k(y - y_k^0)^2)$$

Müller & Brown Theoretica Chimica Acta 1979

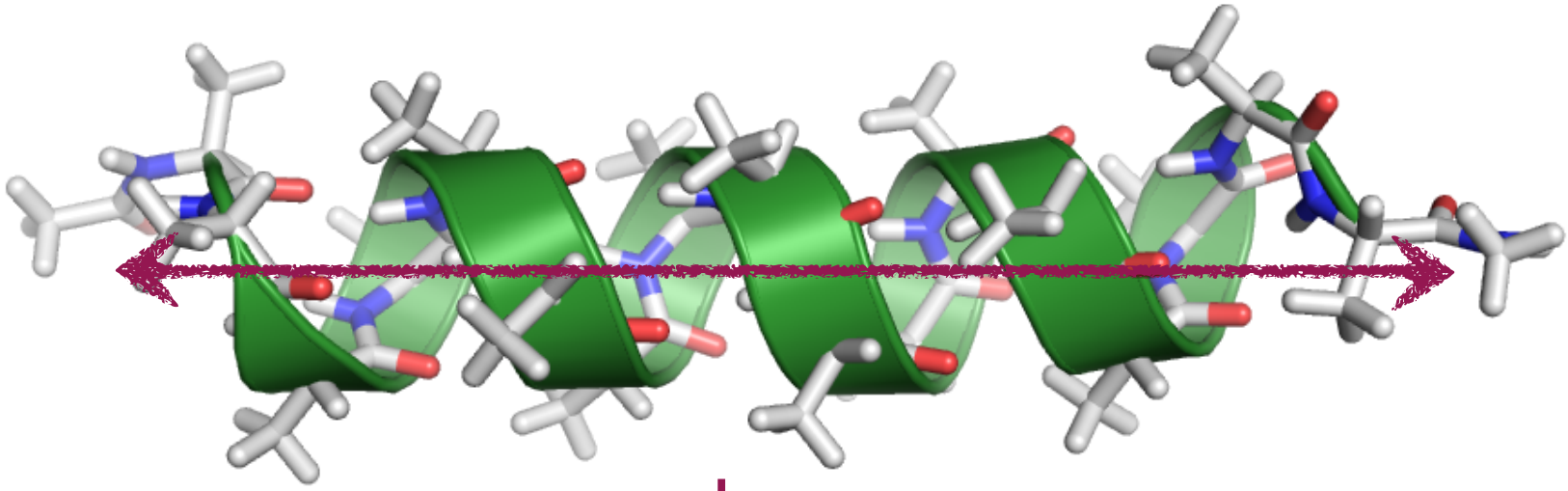
Mohr, van Heesch, Pérez de Alba Ortíz, Vreede, WIREs Molecular Computational Science, in revision



Mohr, van Heesch, Pérez de Alba Ortíz, Vreede, WIREs Molecular Computational Science, in revision



Setup of a metadynamics simulation

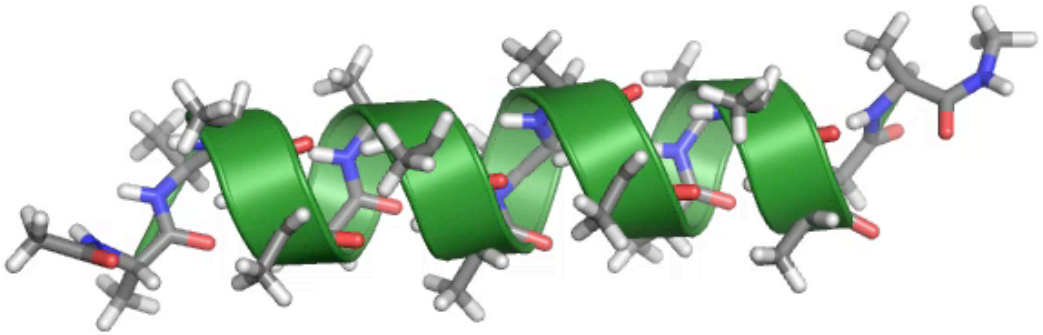


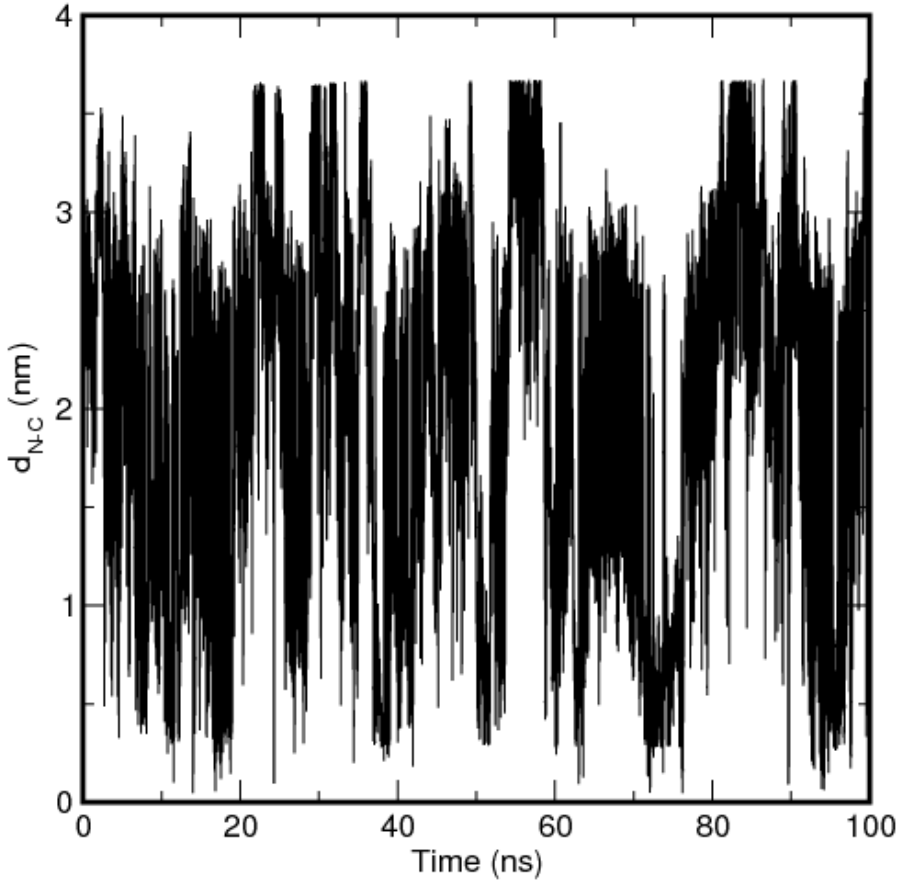
$d_{N\text{-}C}$

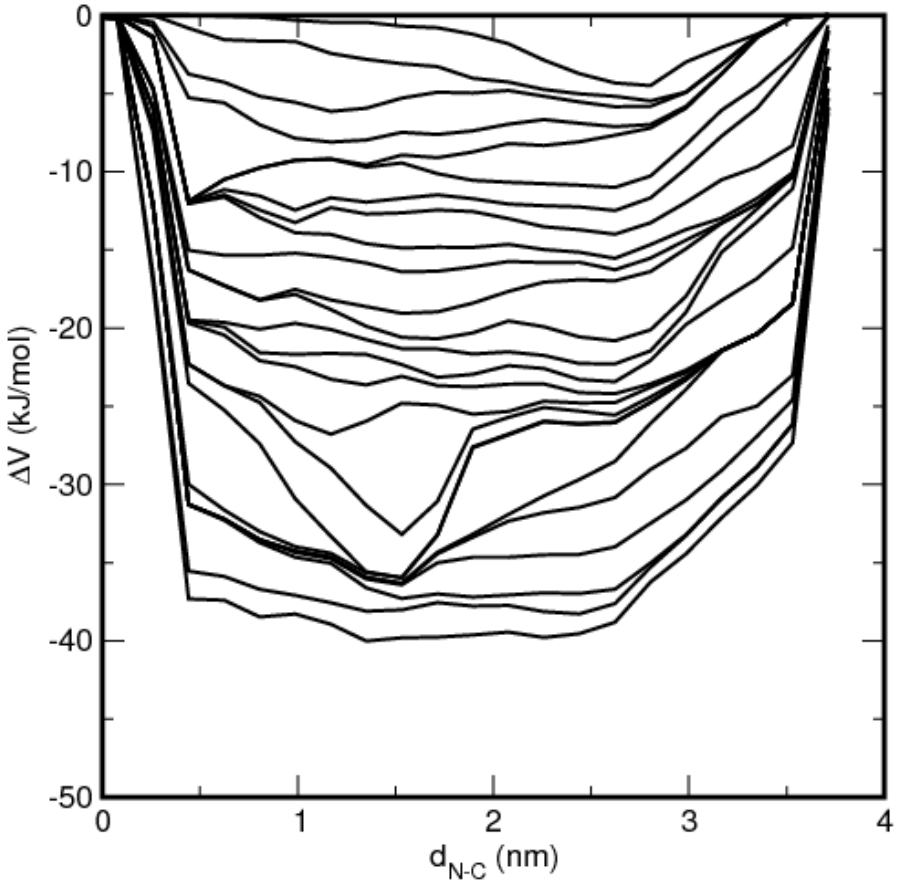
$$V_b(\lambda(\mathbf{r}),t) = w \sum_{t'<t} \exp\left(-\frac{|\lambda(\mathbf{r}(t)-\mathbf{r}(t'))|^2}{2\delta\lambda^2}\right)$$

$$t' = \tau_G, 2\tau_G, \ldots$$

w height of the Gaussian
τ_G time interval between depositions
$\delta\lambda$ Gaussian width

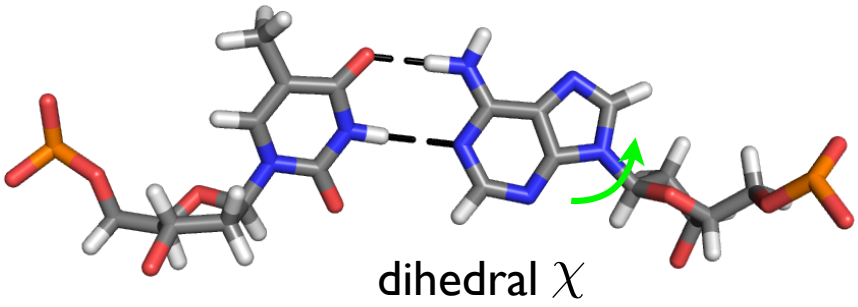



4
3
2
1
0
0
20
40
60
80
100
Time (ns)
d_{N-C} (nm)

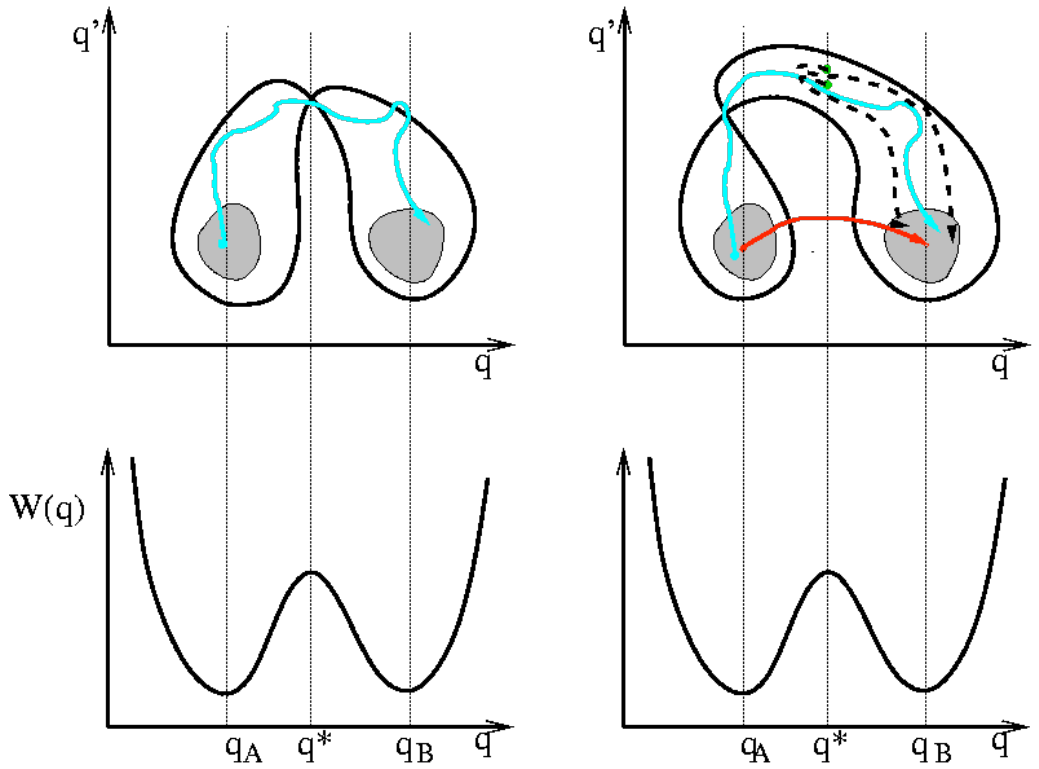

0
-10
-20
-30
-40
-50
0
1
2
3
4
ΔV (kJ/mol)
d_{N-C} (nm)

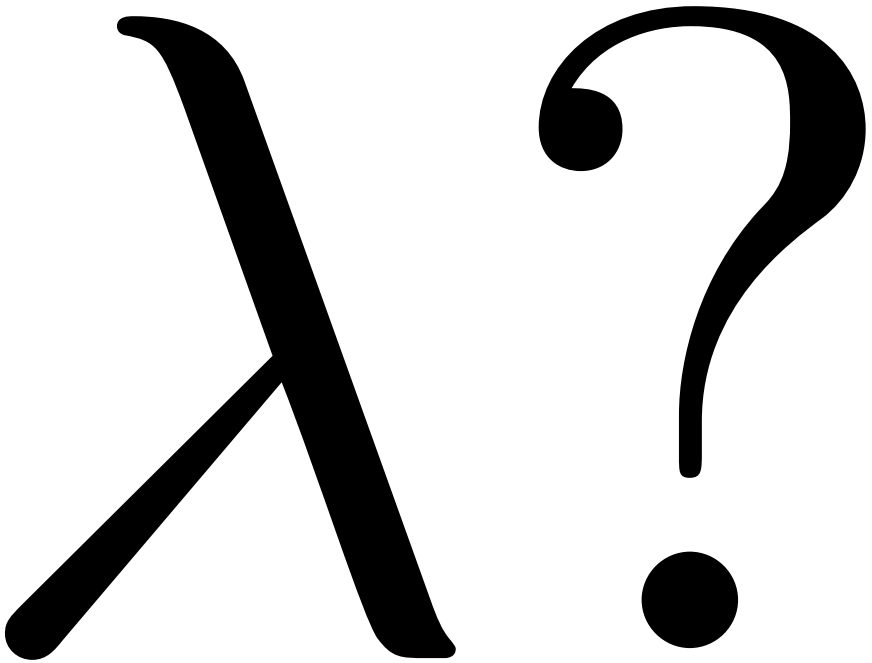
Metadynamics of the WCF to HG transition

No convergence
Instead, distortion and unfolding of the DNA fragment
These metadynamics attempts failed...



The reaction coordinate problem





Metadynamics of the WCF to HG transition

No convergence
Instead, distortion and unfolding
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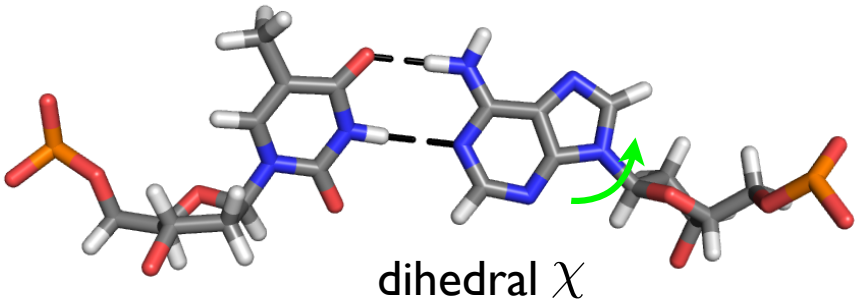
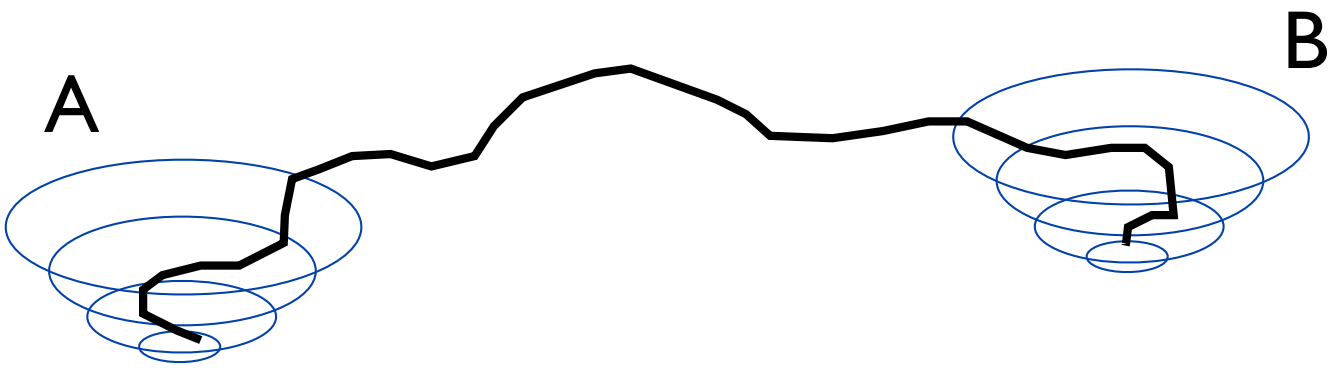


… instead, use the adaptive path collective variable (path cv)
- a function of other collective variables
- bias potential works on the path cv
- adapts during the simulation

path-metadynamics

Diaz Leines & Ensing *Phys Rev Lett* 2012
Pérez de Alba Ortíz, Vreede & Ensing, Methods in Molecular Biology 2019

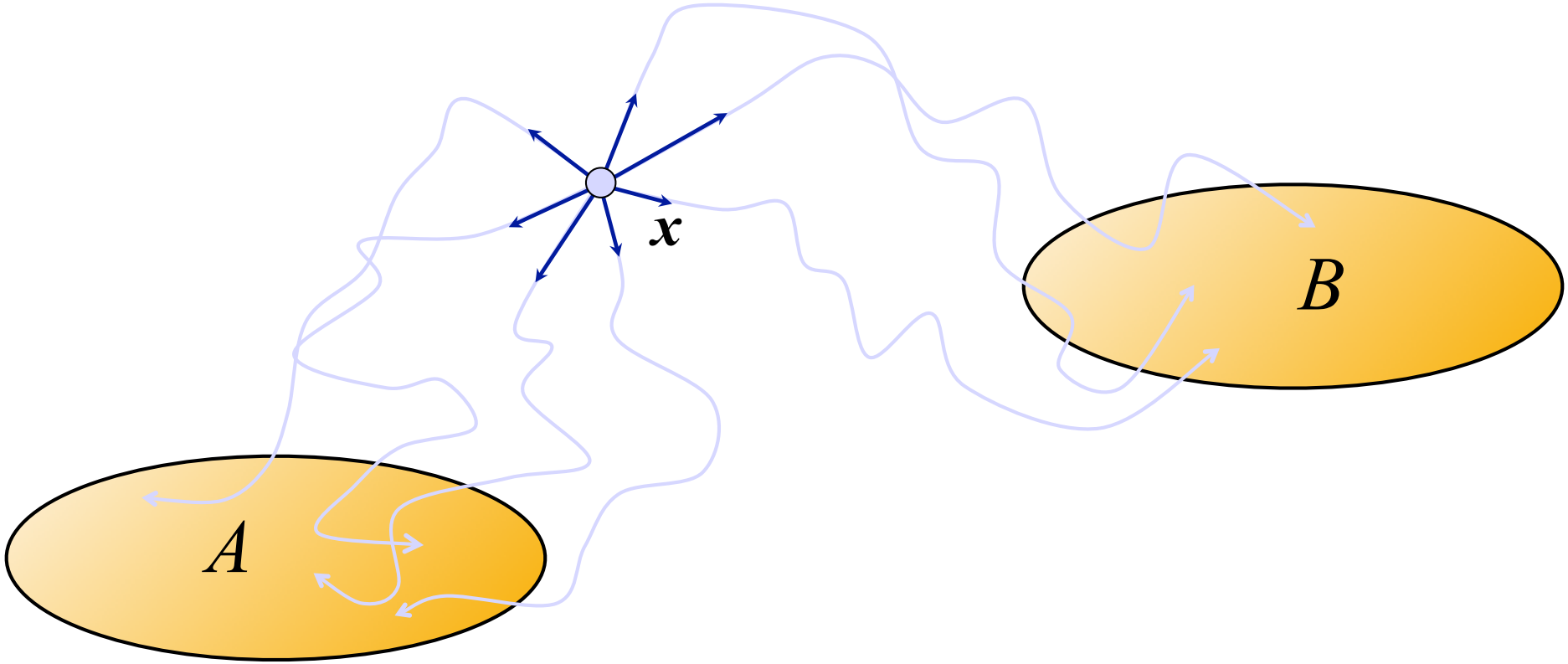
Two state system in a CV space



σ - path in CV space

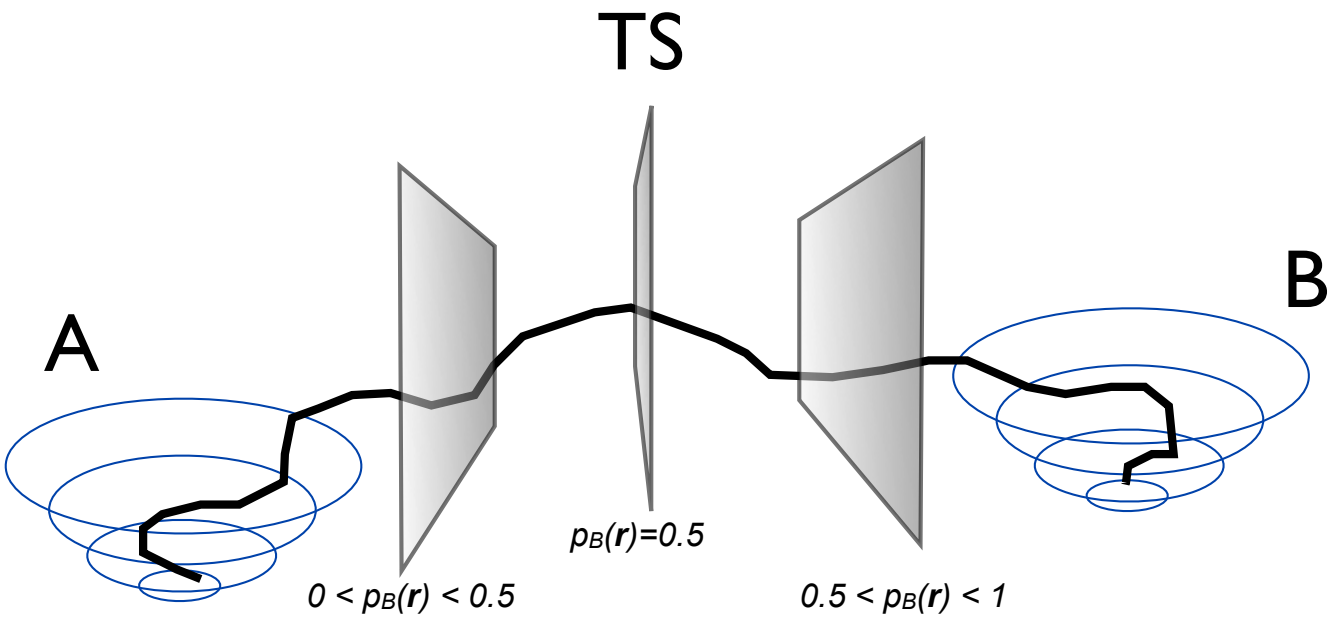
Diaz Leines & Ensing *Phys Rev Lett* 2012

Committor probability p_B



Probability that a trajectory initiated at *x* (random velocities) ends in state *B*

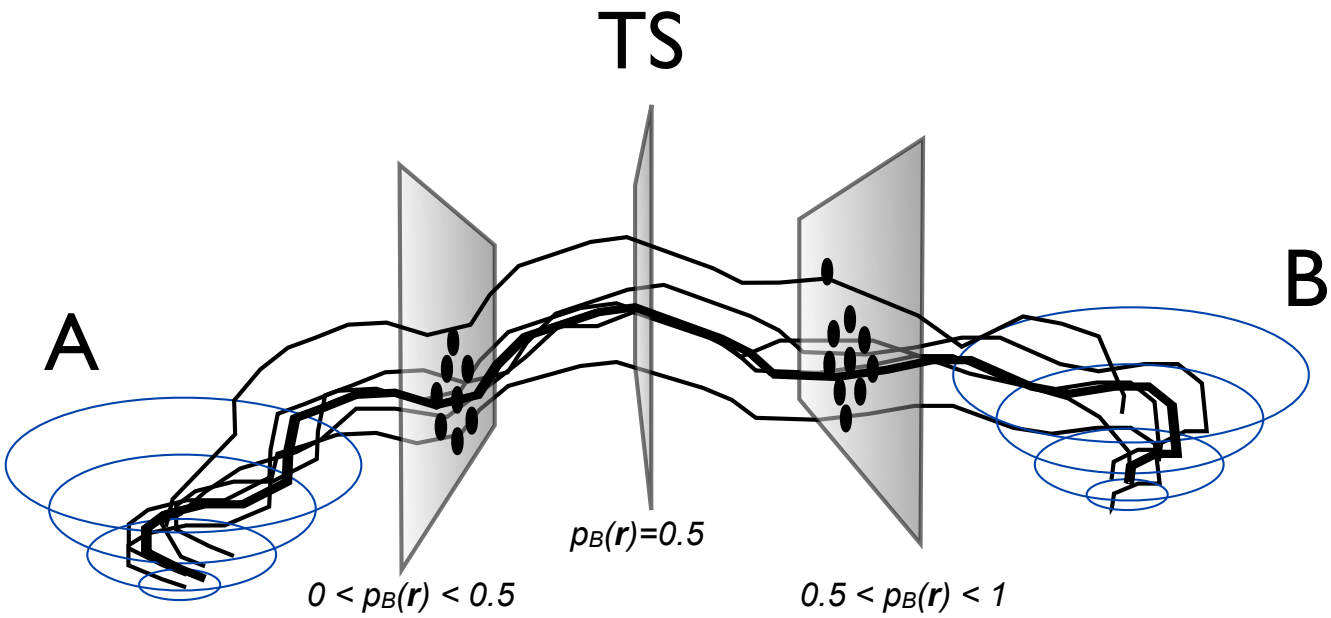
Iso-committor surfaces



σ - path in CV space

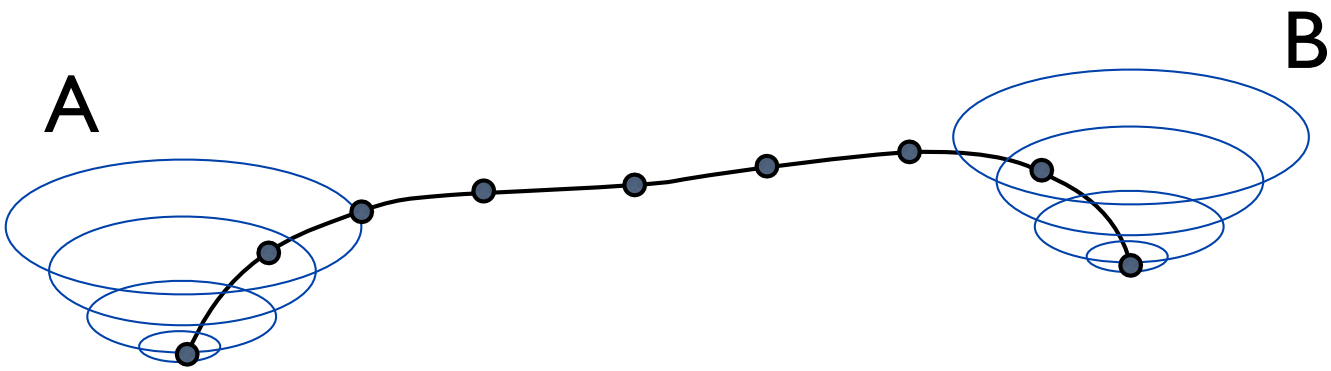
Diaz Leines & Ensing *Phys Rev Lett* 2012

The average transition pathway



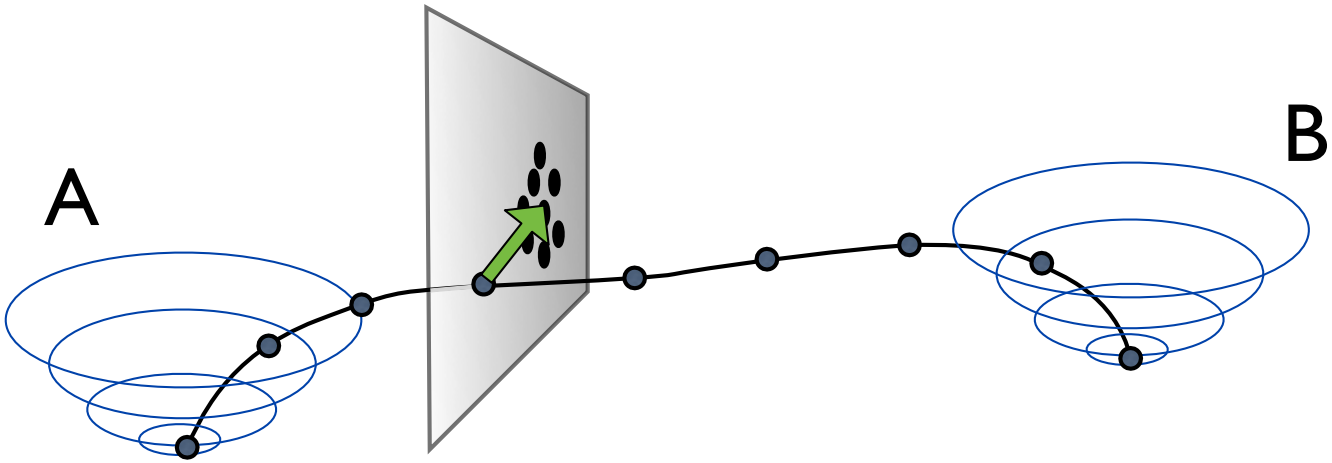
Diaz Leines & Ensing *Phys Rev Lett* 2012

Path metadynamics (i)



construct a path in CV space by placing nodes
perform metadynamics along the path

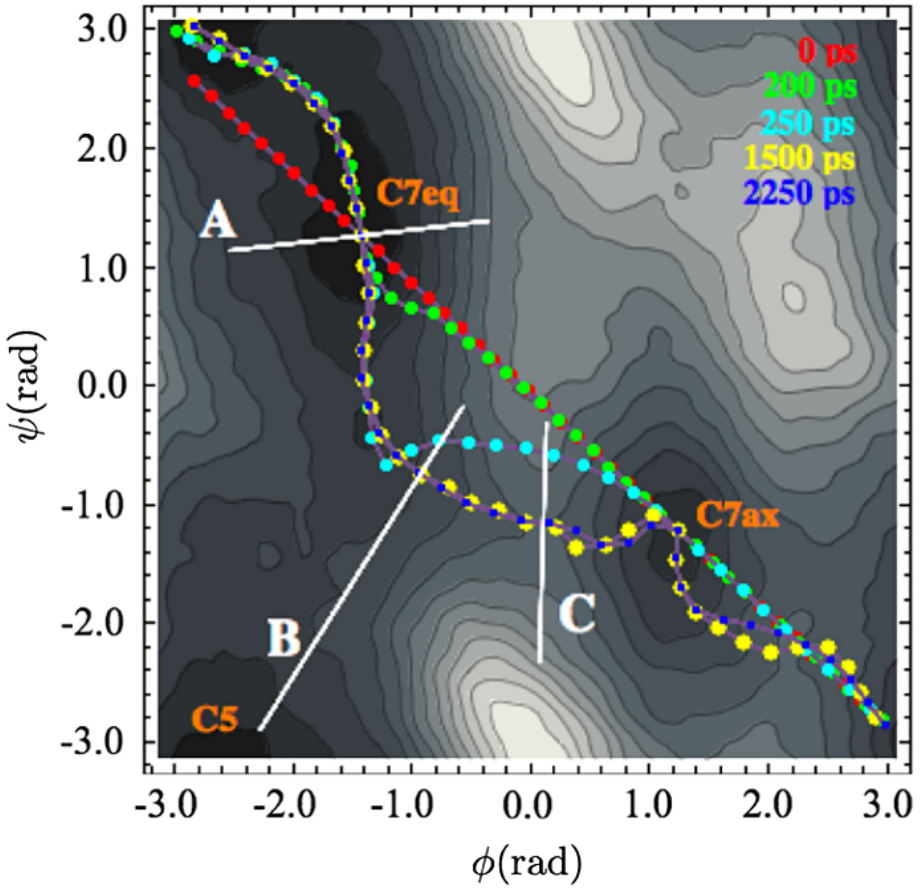
Path-metadynamics (ii)

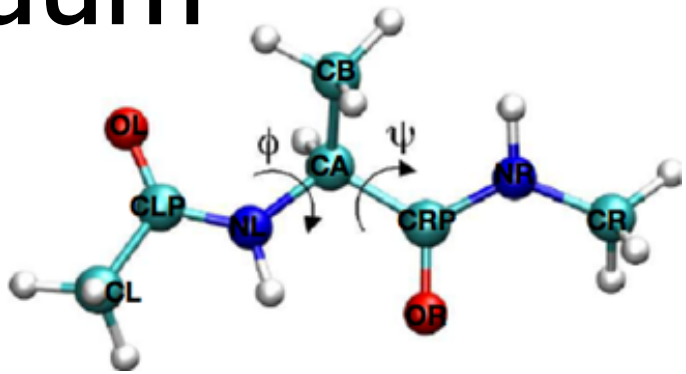


determine distance to mean density
move nodes to mean density

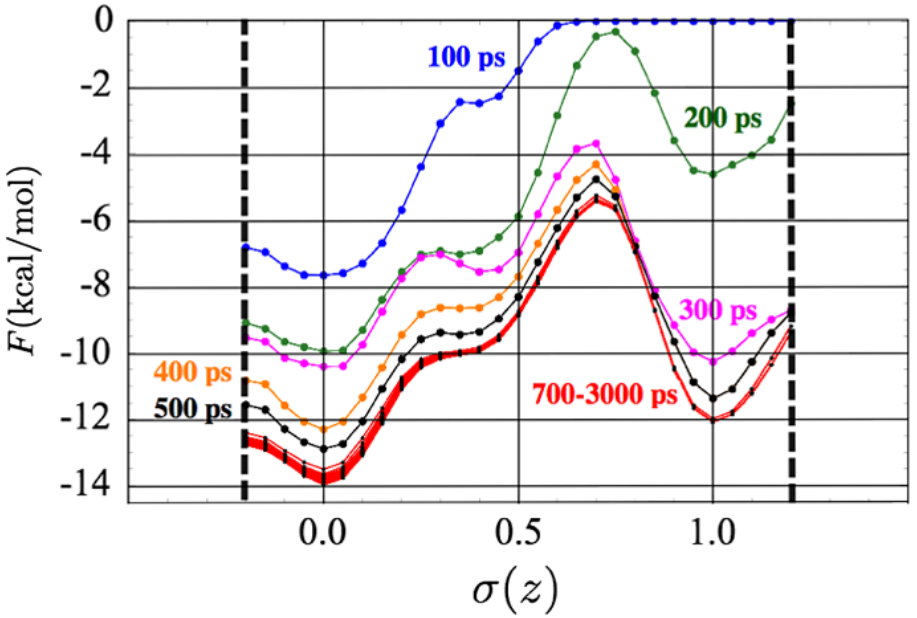
Path-metadynamics of alanine dipeptide in vacuum

path in cv space



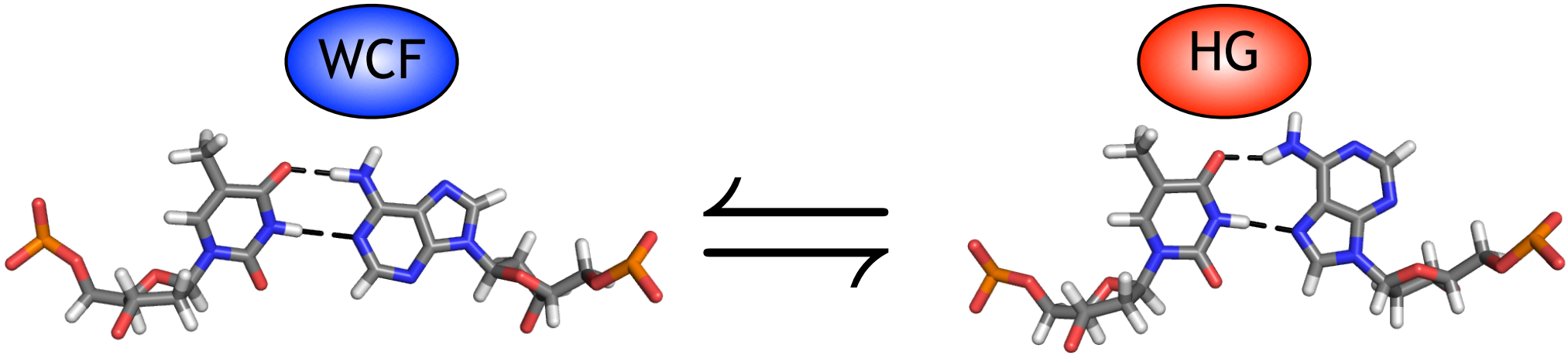


free energy along the path

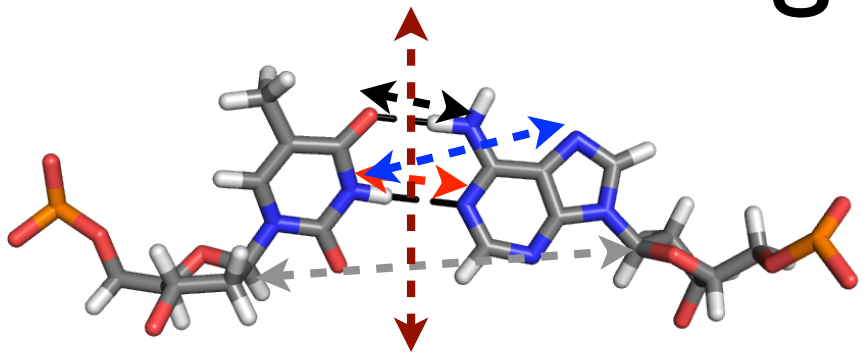


Diaz Leines & Ensing *Phys Rev Lett* 2012

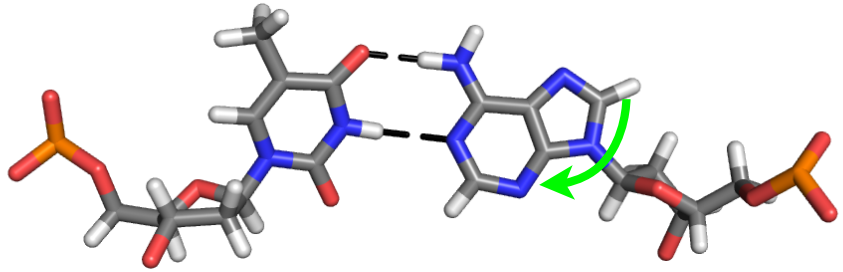
Back to DNA baserolling



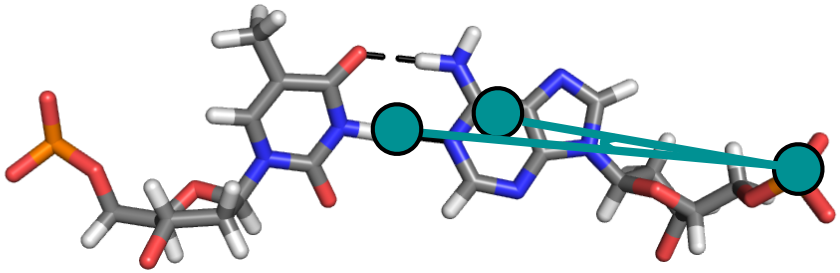
Biasing DNA baserolling defining CVs



distances:
d_{WC}, d_{HG}, d_{HB}, d_{CC}, d_{NB}



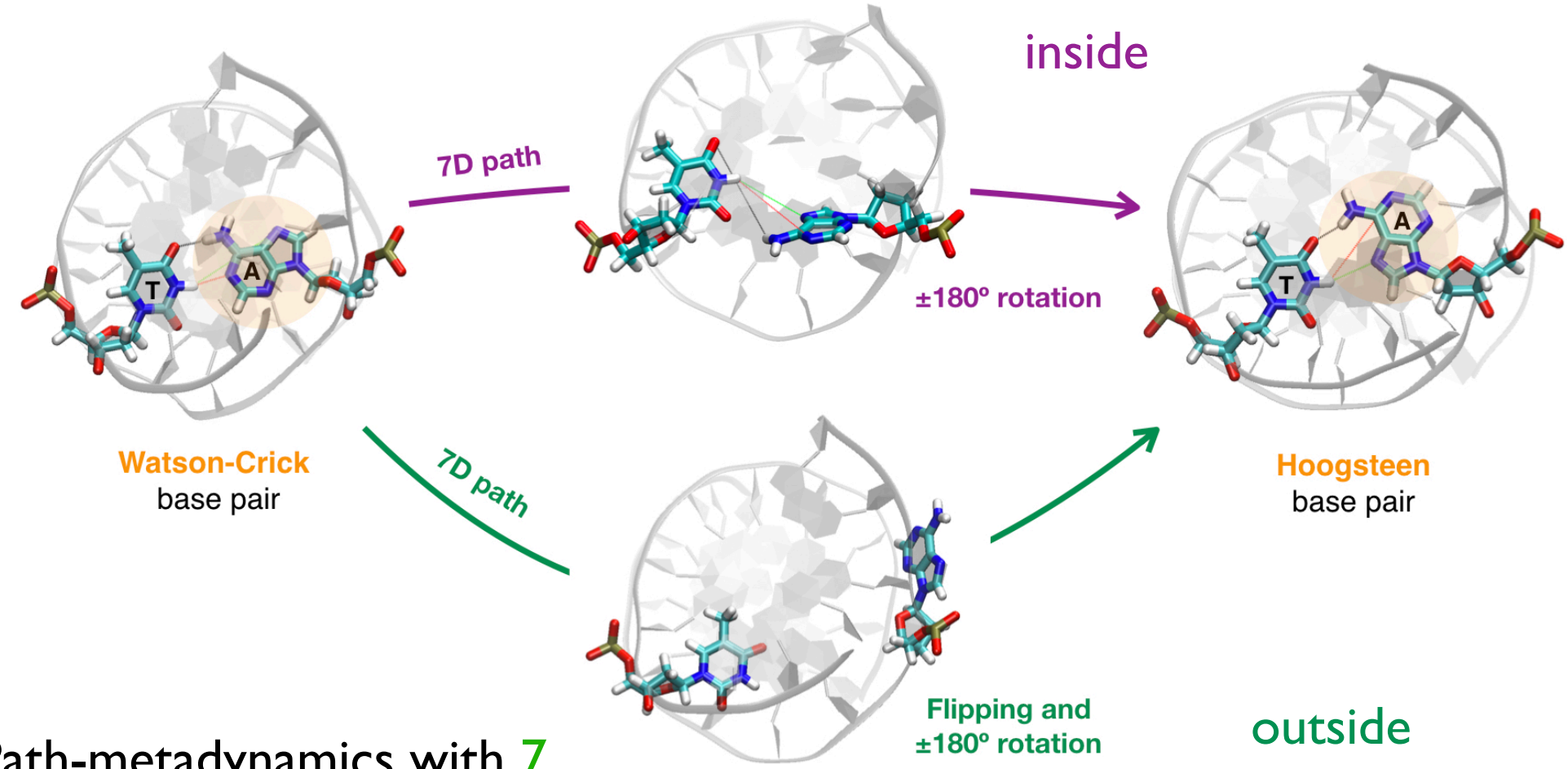
base rolling angle



base opening angle

Path-metadynamics with 7 CVs including H-bonding, rolling, base opening and breathing.

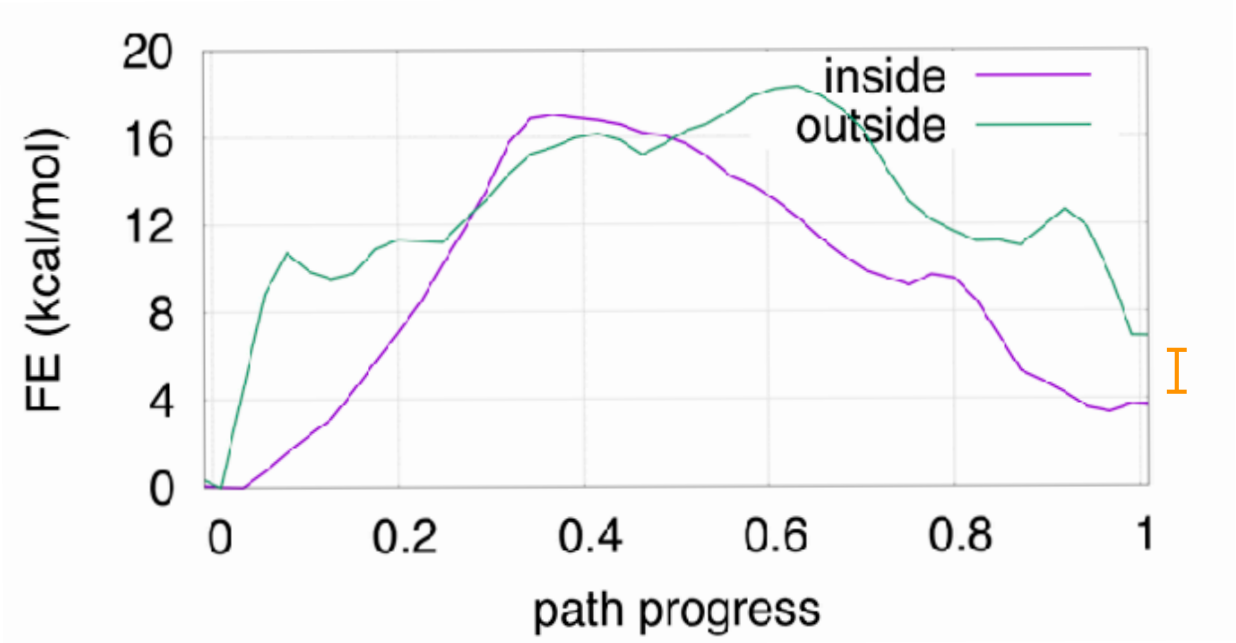
Two mechanisms



Path-metadynamics with 7 CVs including H-bonding, rolling, flipping, breathing...

Pérez de Alba Ortíz, Vreede & Ensing, Methods in Molecular Biology 2019

Free energy profiles

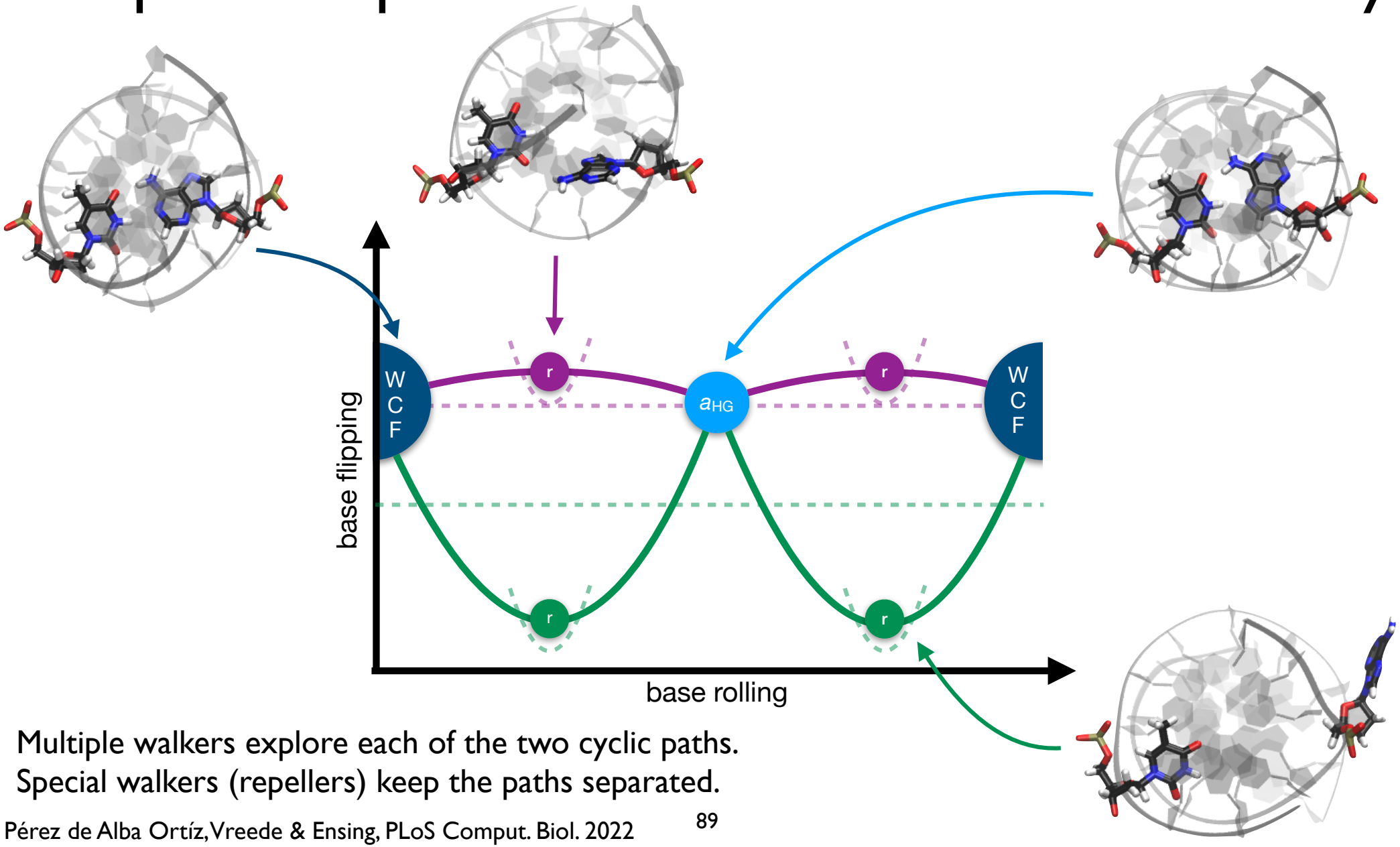


- Path-metadynamics with 7 CVs including H-bonding, rolling, flipping, breathing.
- No clear preference for **inside** or **outside**

- **Lessons in path-metadynamics:**
  - Difficulty in capturing one out of several competing mechanisms
  - Entropic penalty due to the tube potential acting in unnecessary CVs

Pérez de Alba Ortíz, Vreede & Ensing, Methods in Molecular Biology 2019

Multi-path-metadynamics: sample multiple reaction channels simultaneously

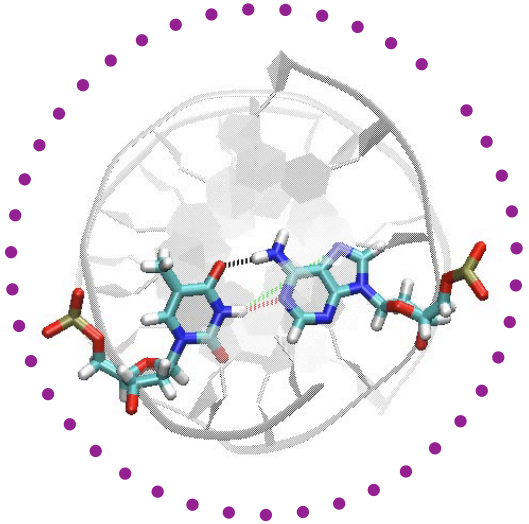


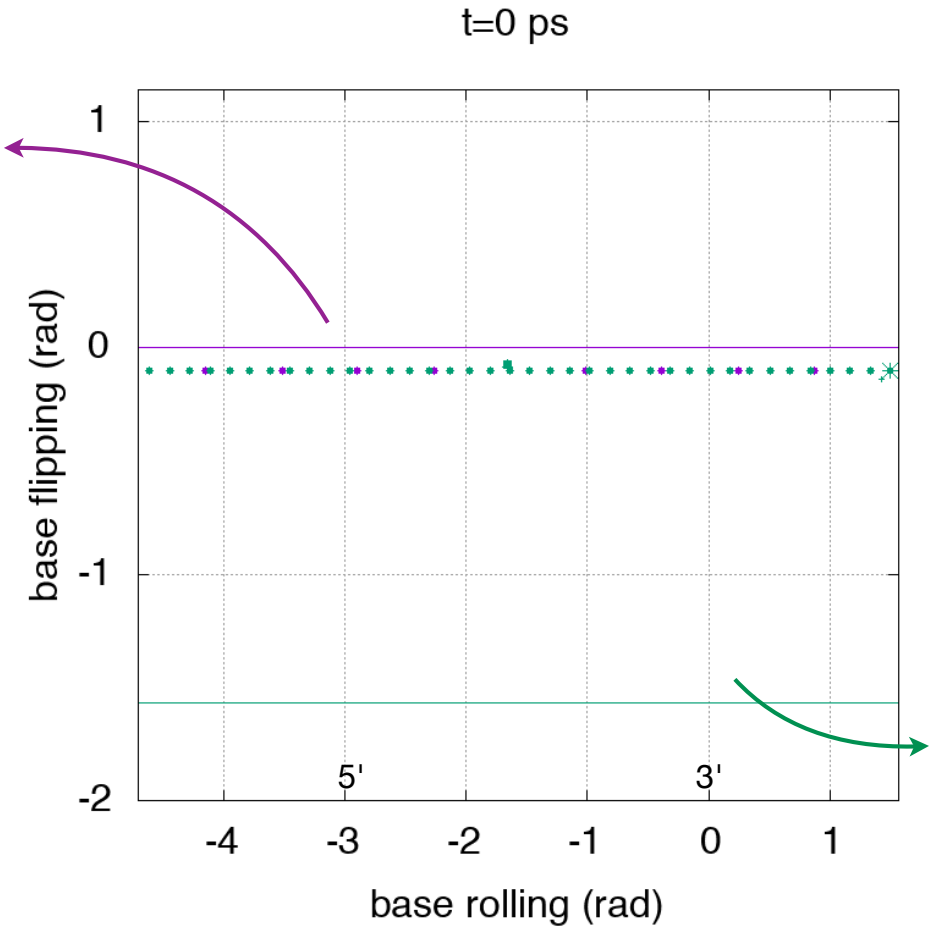
Multiple walkers explore each of the two cyclic paths.
Special walkers (repellers) keep the paths separated.

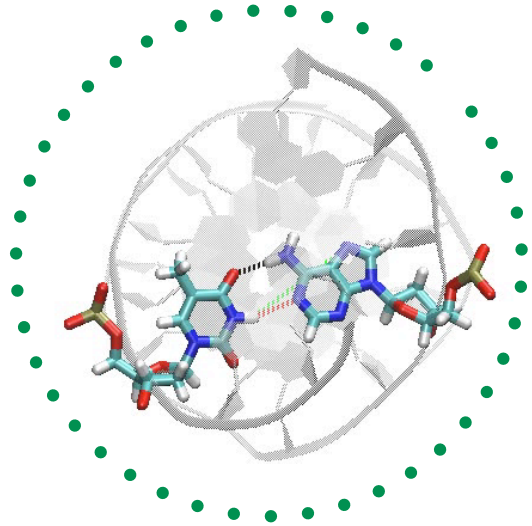
Pérez de Alba Ortíz, Vreede & Ensing, PLoS Comput. Biol. 2022

DNA base rolling with PMD

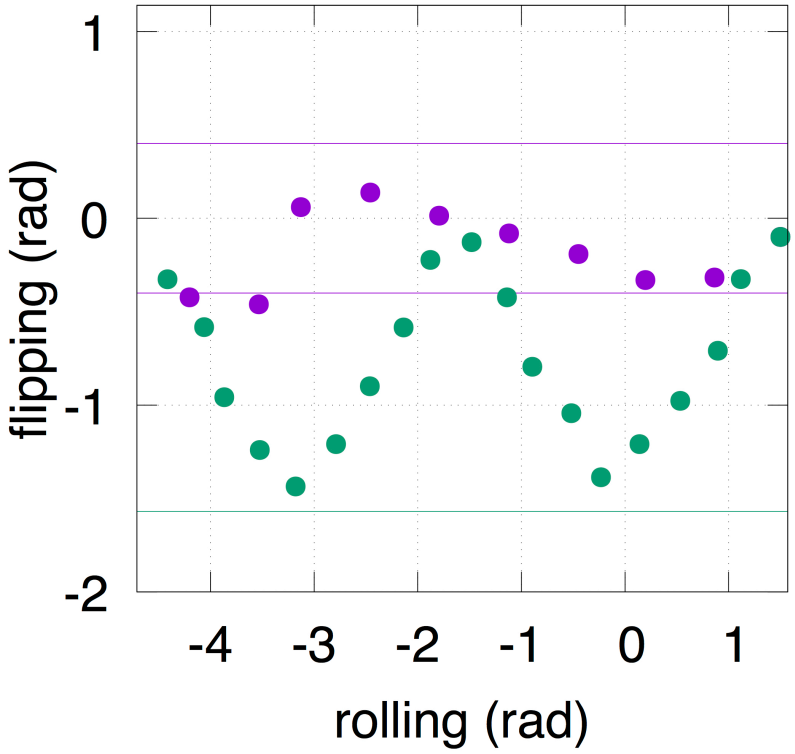
The paths diverge after 2 ns.
Sampling continues until 10 ns.

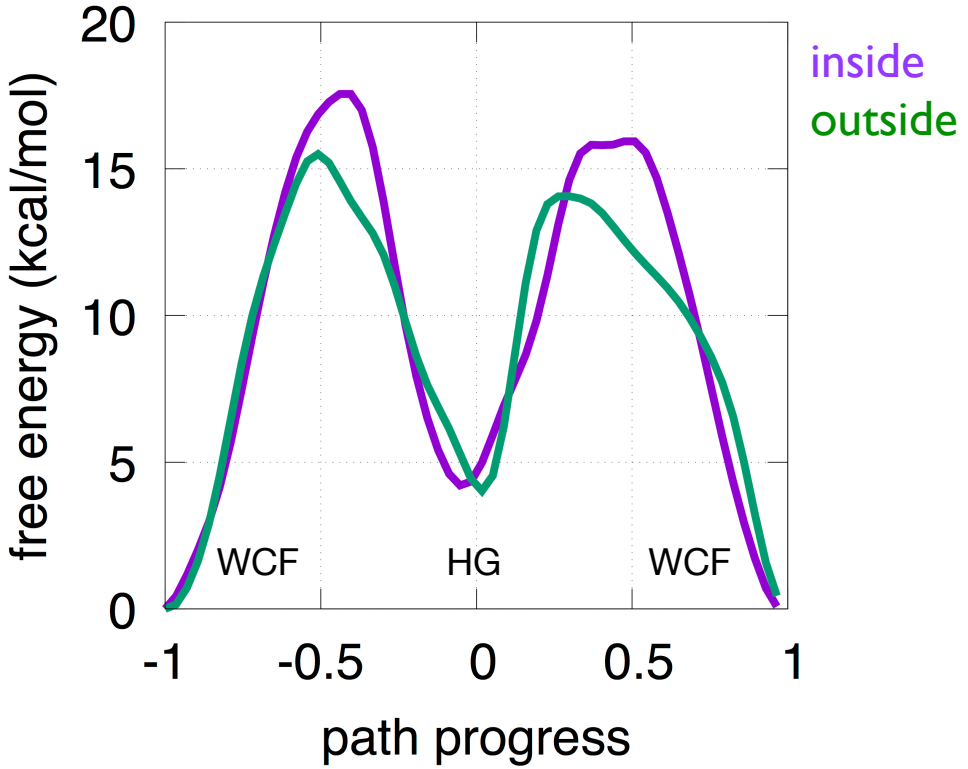






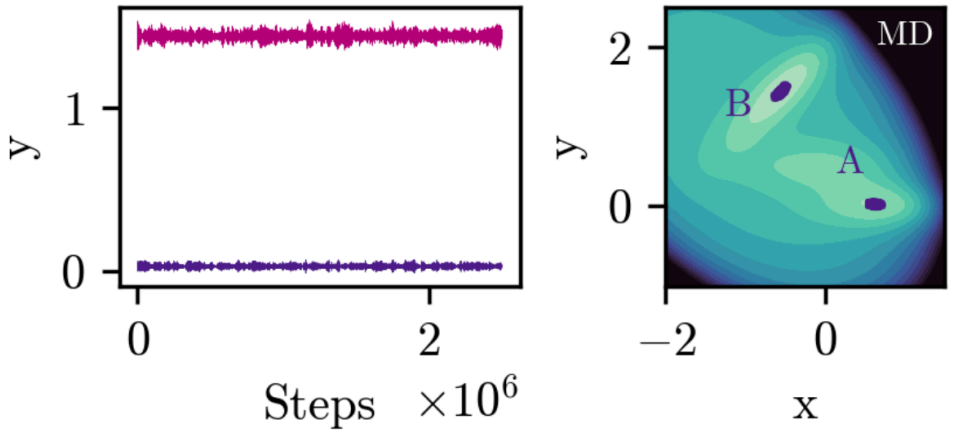
DNA baserolling with path-metadynamics





Free energy difference between WCF and HG close to experimental value.
Outside path has lower barriers.

Pérez de Alba Ortíz, Vreede & Ensing, Methods in Molecular Biology 2019
Pérez de Alba Ortíz, Vreede & Ensing, PLoS Comput. Biol. 2022



Müller-Brown potential

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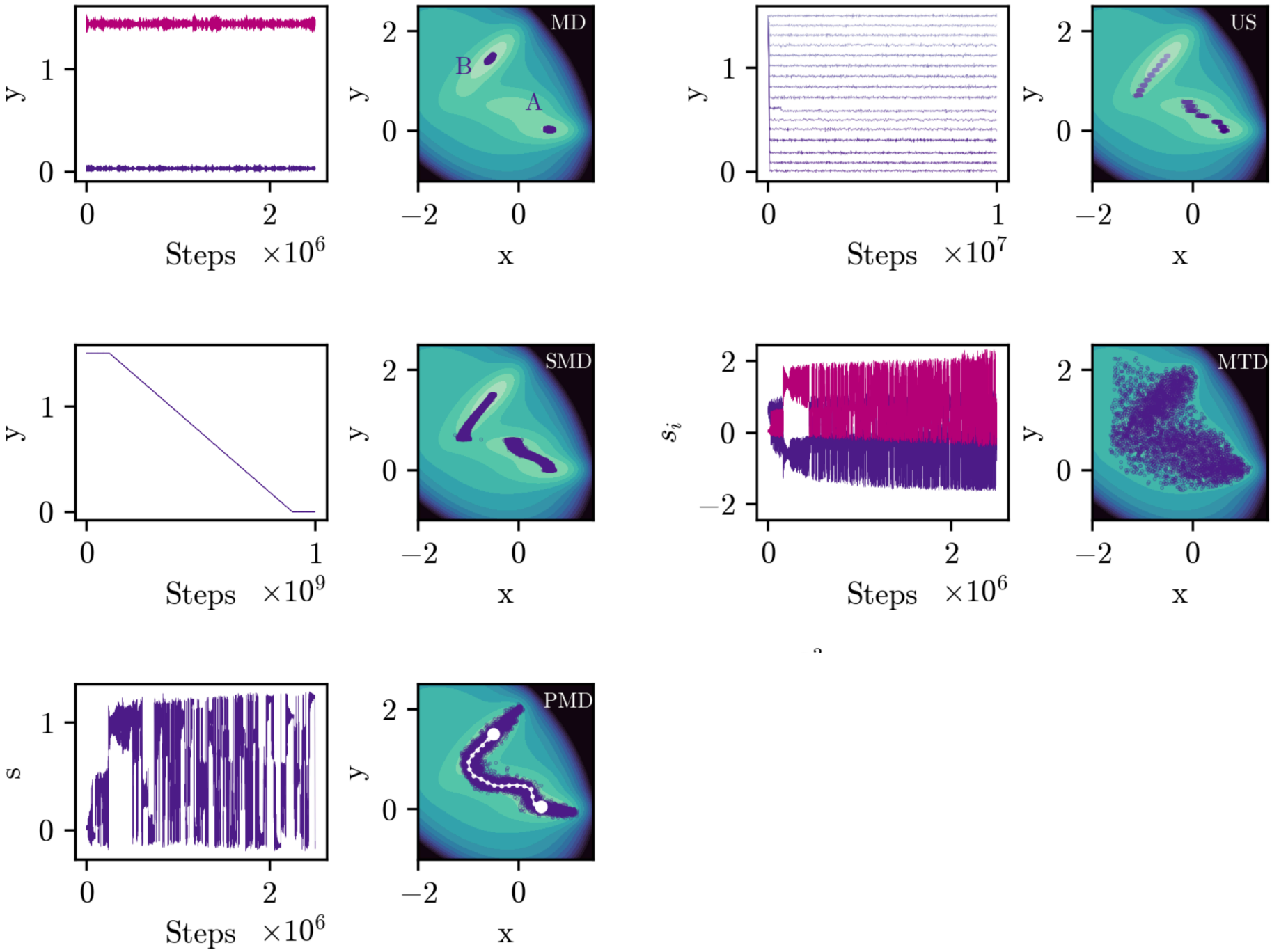
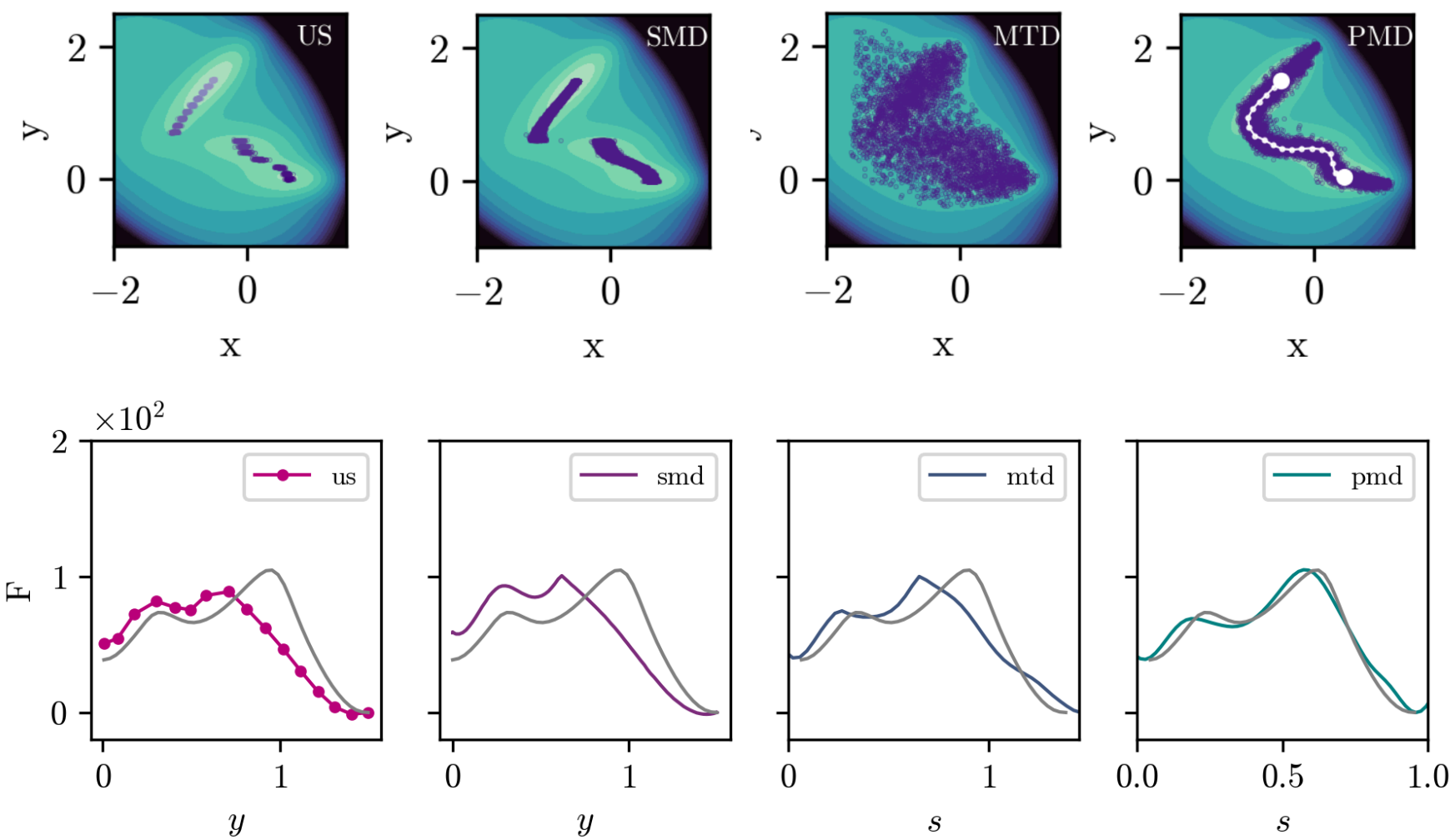
Mohr, van Heesch, Pérez de Alba Ortíz, Vreede, WIREs Molecular Computational Science, in revision

Mohr, van Heesch, Pérez de Alba Ortíz, Vreede, WIREs Molecular Computational Science, in revision




US
SMD
MTD
PMD
x
y
−2
0
2
$\times 10^2$
F
us
smd
mtd
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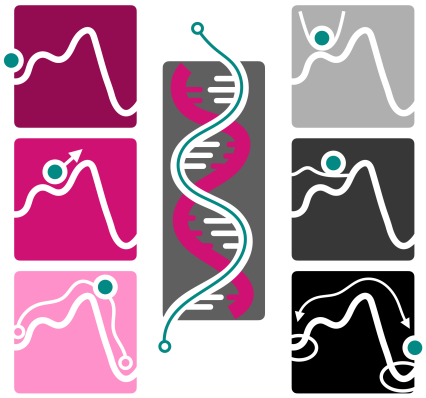
Biomolecular Simulation

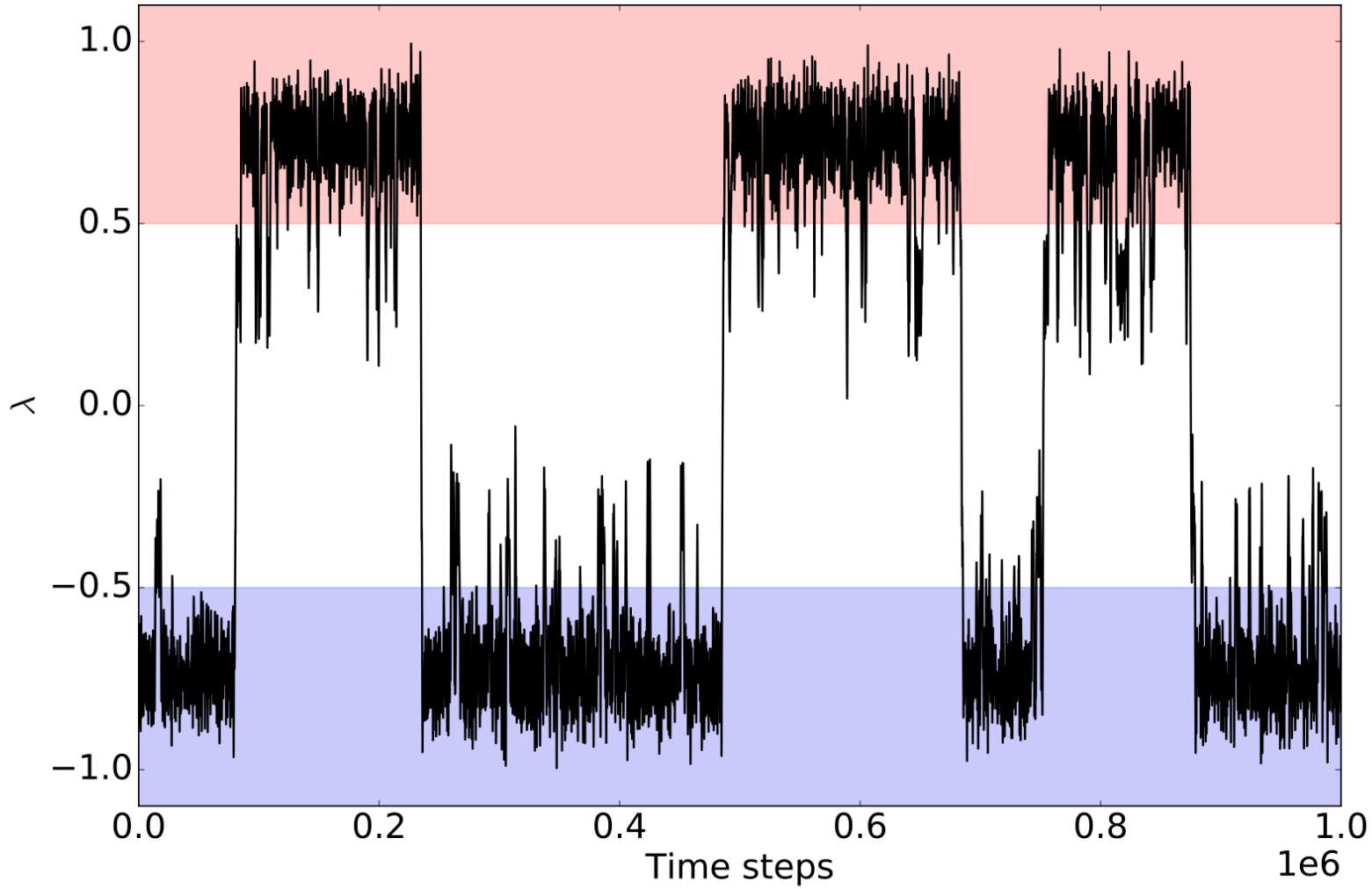
Outline

Part 1: Simulating biomolecular systems

Part 2: Biased sampling

Part 3: Path sampling

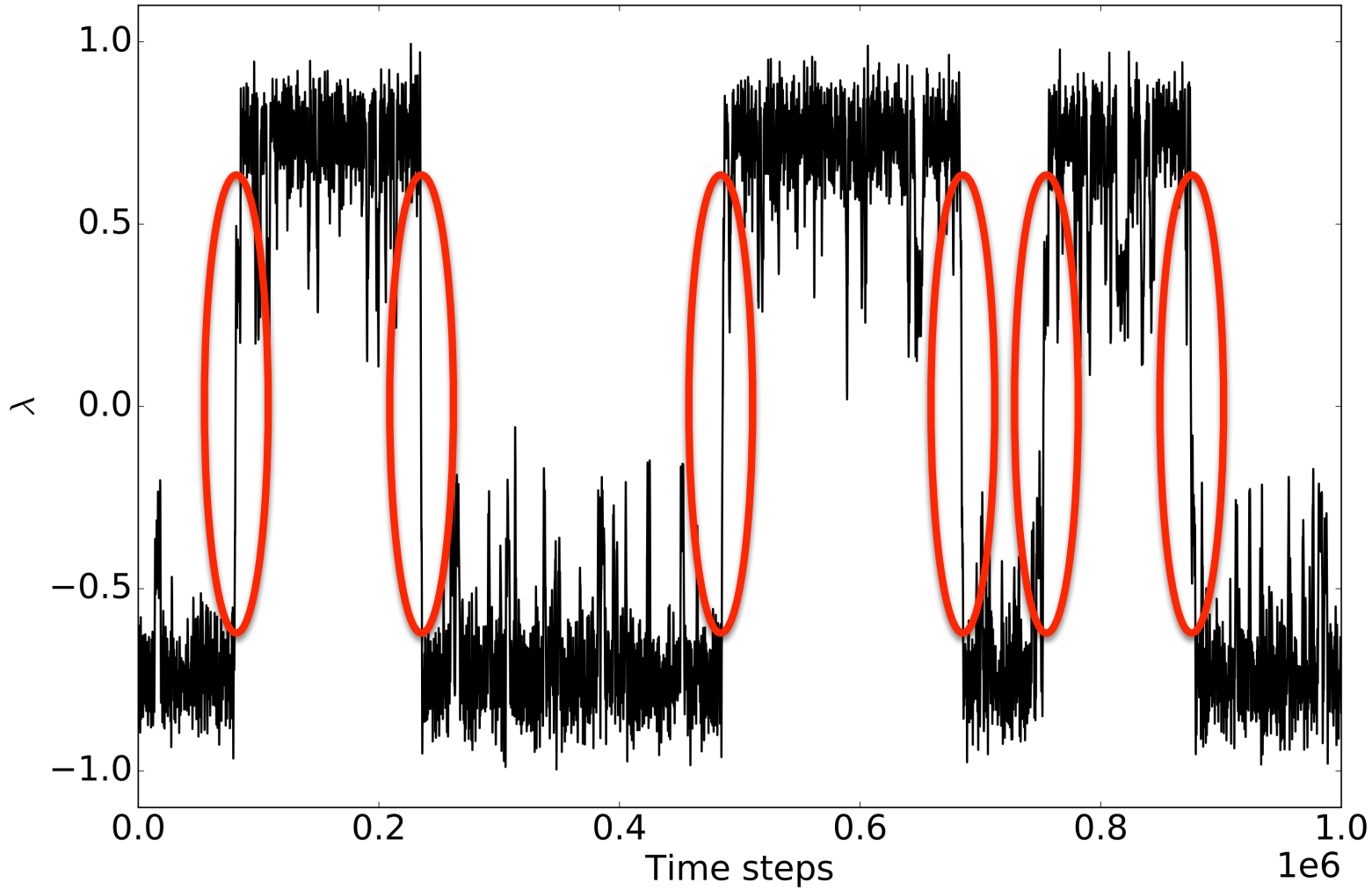




Separation of time scales: fundamental time scale vs. frequency of event

Slide by David Swenson

Path sampling



Focus on the transition regions

Monte Carlo in path space

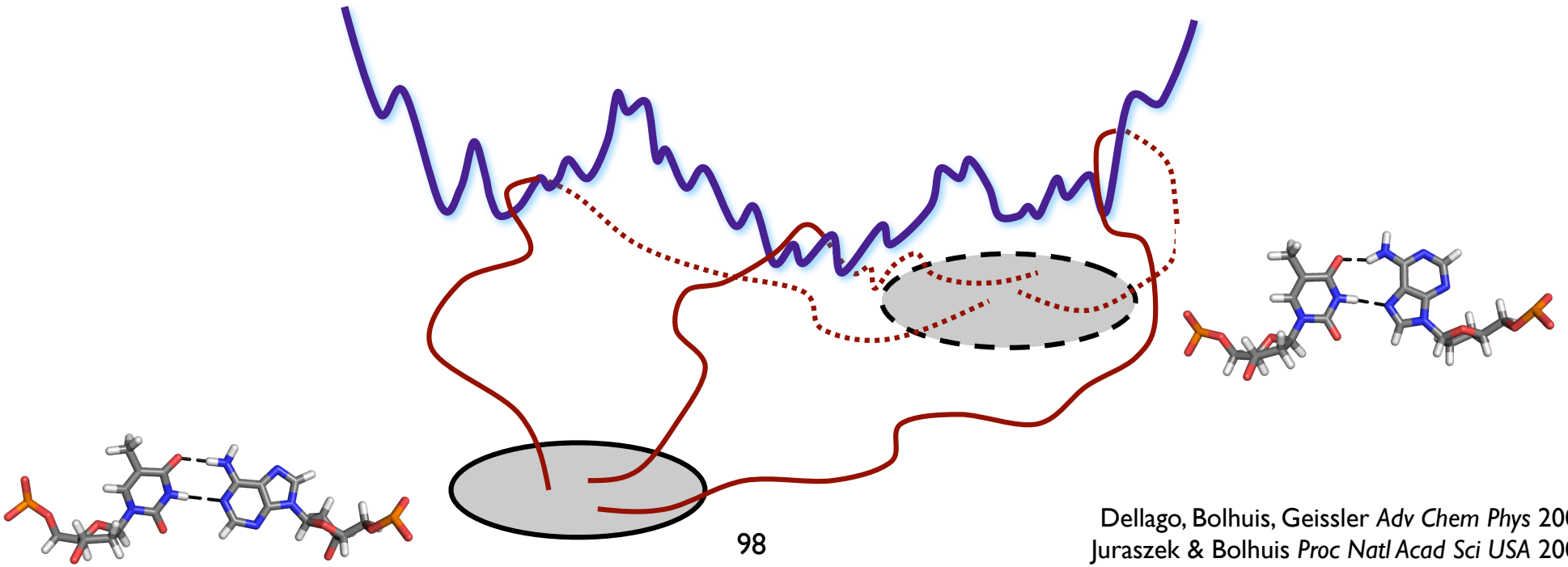
Slide by David Swenson

Sampling rare events: transition path sampling

Input

Result: ensemble of transition paths

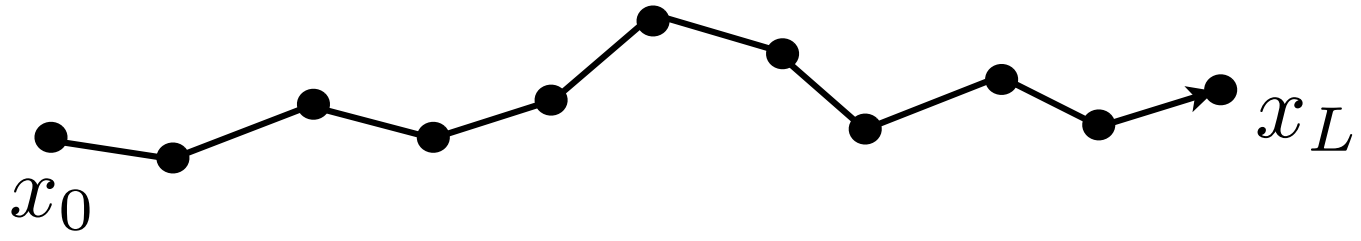
Algorithm



Dellago, Bolhuis, Geissler *Adv Chem Phys* 2002
Juraszek & Bolhuis *Proc Natl Acad Sci USA* 2006

Transition Path

A path (MD trajectory) is
a sequence of discrete
time snapshots



Path probability:

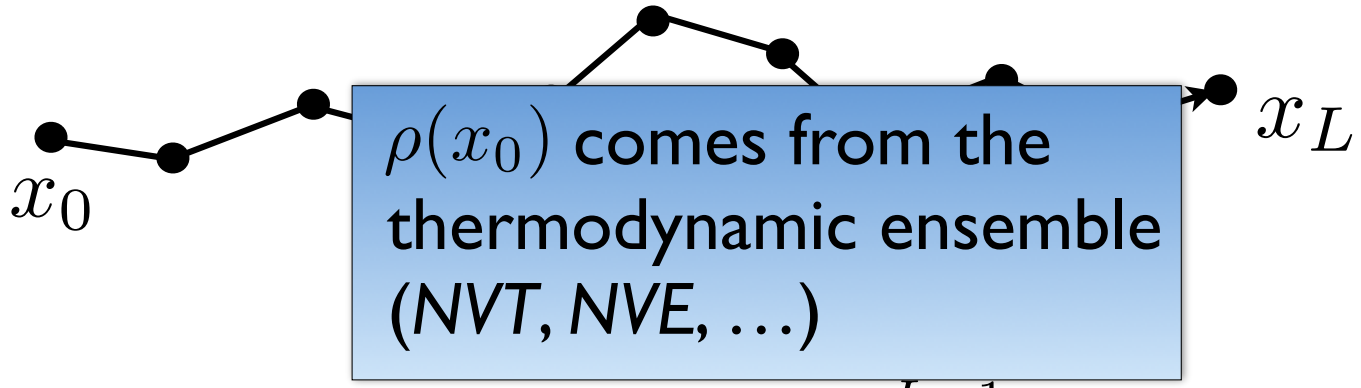
$$\mathcal{P}[\mathbf{x}] = \rho(x_0) \prod_{i=0}^{L-1} P(x_i \to x_{i+1}) / Z(L)$$

normalization constant
(partition function)

$$Z(L) = \int \mathcal{D}\mathbf{x}\, \mathcal{P}[\mathbf{x}(L)] Z(L)$$

Transition Path

A path (MD trajectory) is a sequence of discrete time snapshots



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Transition Path

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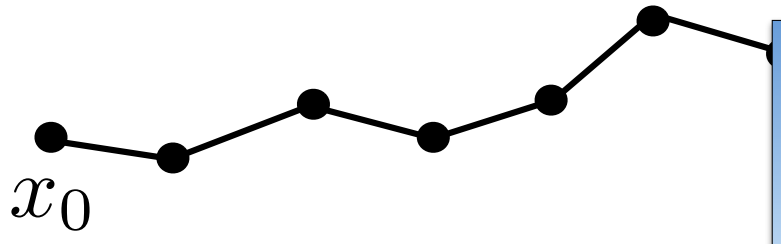


$P(x_i \to x_{i+1})$ comes from the molecular dynamics algorithm (integrator)

Path probability:

$$\mathcal{P}[\mathbf{x}] = \rho(x_0) \prod_{i=0}^{L-1} P(x_i \to x_{i+1}) / Z(L)$$

normalization constant (partition function)

$$Z(L) = \int \mathcal{D}\mathbf{x}\, \mathcal{P}[\mathbf{x}(L)] Z(L)$$

Detailed Balance (Paths)

$$\mathcal{P}[\mathbf{x}^{(o)}]\ \pi\left(\mathbf{x}^{(o)} \to \mathbf{x}^{(n)}\right) = \mathcal{P}[\mathbf{x}^{(n)}]\ \pi\left(\mathbf{x}^{(n)} \to \mathbf{x}^{(o)}\right)$$

prob. of old state

prob of moving old → new

prob. of new state

prob of moving new → old

$$\pi\left(\mathbf{x}^{(o)} \to \mathbf{x}^{(n)}\right) = P_{\text{gen}}\left(\mathbf{x}^{(o)} \to \mathbf{x}^{(n)}\right)\ P_{\text{acc}}\left(\mathbf{x}^{(o)} \to \mathbf{x}^{(n)}\right)$$

transition probability

generation probability

acceptance probability

$$P_{\text{acc}}(\mathbf{x}^{(o)} \to \mathbf{x}^{(n)}) = \min\left(1, \frac{\mathcal{P}[\mathbf{x}^{(n)}] P_{\text{gen}}\left(\mathbf{x}^{(n)} \to \mathbf{x}^{(o)}\right)}{\mathcal{P}[\mathbf{x}^{(o)}] P_{\text{gen}}\left(\mathbf{x}^{(o)} \to \mathbf{x}^{(n)}\right)}\right)$$

Slide by David Swenson

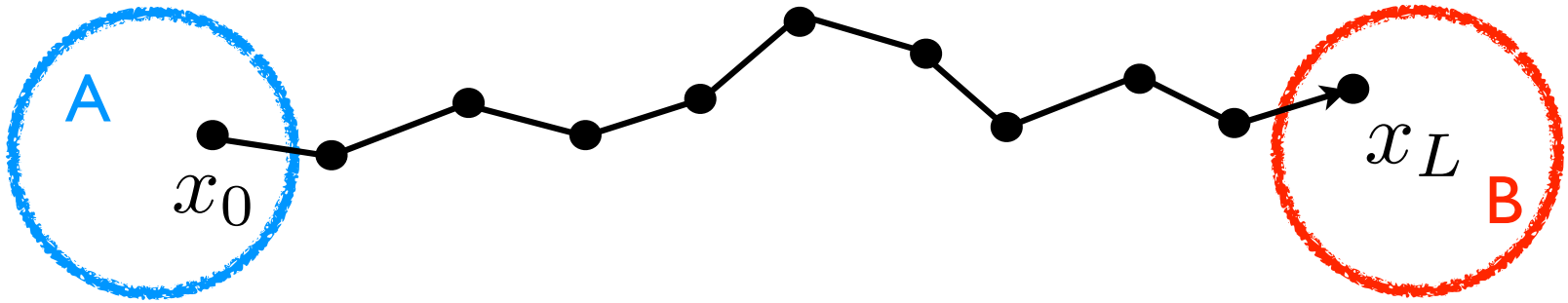
Transition Path

How do we focus on the transition region?

Indicator Function

$$h_A(x) = \begin{cases} 1 & \text{if } x \in A \\ 0 & \text{if } x \notin A \end{cases}$$

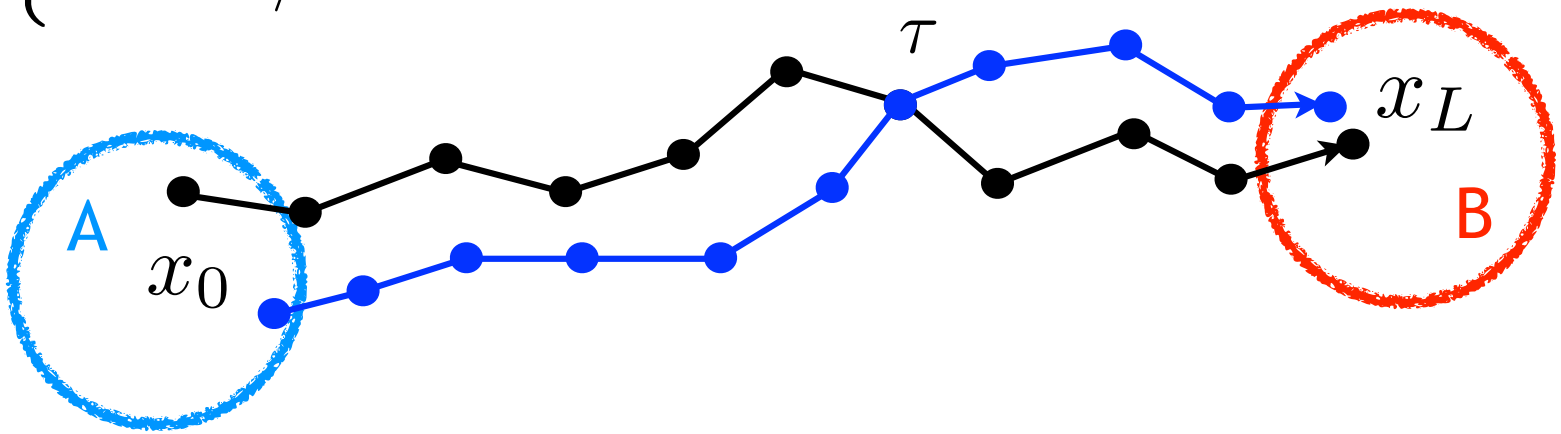
Note: $h_A(x) + h_B(x) \neq 1$!



$$\mathcal{P}_{AB}[\mathbf{x}(L)] = h_A(x_0)\, h_B(x_L)\, \mathcal{P}[\mathbf{x}(L)]/Z_{AB}(L)$$

Change the path

$$h_A(x) = \begin{cases} 1 & \text{if } x \in A \\ 0 & \text{if } x \notin A \end{cases}$$



1. Select a point to "shoot" from (frame τ)
2. Modify the velocities at that point
3. Run forward (from τ to *T*) and backward (from τ to 0)

$$P_{\text{gen}}^{\text{shoot}}\left(\mathbf{x}^{(o)} \to \mathbf{x}^{(n)}\right) = P_{\text{sel}}(x_\tau^{(o)}; \mathbf{x}^{(o)}) P_{\text{mod}}(x_\tau^{(o)} \to x_\tau^{(n)}) P_{\text{fwd}}(\mathbf{x}_{\tau \ldots L}^{(n)}) P_{\text{bkwd}}(\mathbf{x}_{0 \ldots \tau}^{(n)})$$

Shooting Algorithm: Detailed Balance

$$P_{\text{gen}}^{\text{shoot}}\left(\mathbf{x}^{(o)} \to \mathbf{x}^{(n)}\right) = P_{\text{sel}}(x_\tau^{(o)}; \mathbf{x}^{(o)}) P_{\text{mod}}(x_\tau^{(o)} \to x_\tau^{(n)}) P_{\text{fwd}}(\mathbf{x}_{\tau\ldots L}^{(n)}) P_{\text{bkwd}}(\mathbf{x}_{0\ldots\tau}^{(n)})$$

$$P_{\text{sel}}(x_\tau^{(o)}; \mathbf{x}^{(o)}) = 1/(L^{(o)} - 1) \quad \text{select shooting point}$$

$$P_{\text{mod}}(x_\tau^{(o)} \to x_\tau^{(n)}) = P_{\text{mod}}(x_\tau^{(n)} \to x_\tau^{(o)}) \quad \text{modify it (symmetric!)}$$

$$P_{\text{fwd}}(\mathbf{x}_{\tau\ldots L}^{(n)}) = \prod_{i=\tau}^{L-1} P(x_i \to x_{i+1}) \quad \text{make forward segment}$$

$$P_{\text{bkwd}}(\mathbf{x}_{0\ldots\tau}^{(n)}) = \prod_{t=1}^{\tau} \bar{P}(x_i \to x_{i-1}) \quad \text{make backward segment}$$

Slide by David Swenson

Shooting Move Acceptance

$$P_{\text{acc}}(\mathbf{x}^{(o)} \to \mathbf{x}^{(n)}) = \min\left(1, \frac{\mathcal{P}_{AB}\left(\mathbf{x}^{(n)}\right) P_{\text{gen}}^{\text{shoot}}\left(\mathbf{x}^{(n)} \to \mathbf{x}^{(o)}\right)}{\mathcal{P}_{AB}\left(\mathbf{x}^{(o)}\right) P_{\text{gen}}^{\text{shoot}}\left(\mathbf{x}^{(o)} \to \mathbf{x}^{(n)}\right)}\right)$$

$$\frac{P_{\text{gen}}^{\text{shoot}}\left(\mathbf{x}^{(n)} \to \mathbf{x}^{(o)}\right)}{P_{\text{gen}}^{\text{shoot}}\left(\mathbf{x}^{(o)} \to \mathbf{x}^{(n)}\right)} = \frac{P_{\text{sel}}(x_\tau^{(n)}; \mathbf{x}^{(n)})}{P_{\text{sel}}(x_\tau^{(o)}; \mathbf{x}^{(o)})} \frac{P_{\text{mod}}(x_\tau^{(n)} \to x_\tau^{(o)})}{P_{\text{mod}}(x_\tau^{(o)} \to x_\tau^{(n)})} \frac{P_{\text{fwd}}(\mathbf{x}_{\tau\ldots L}^{(o)}) P_{\text{bkwd}}(\mathbf{x}_{0\ldots\tau}^{(o)})}{P_{\text{fwd}}(\mathbf{x}_{\tau\ldots L}^{(n)}) P_{\text{bkwd}}(\mathbf{x}_{0\ldots\tau}^{(n)})}$$

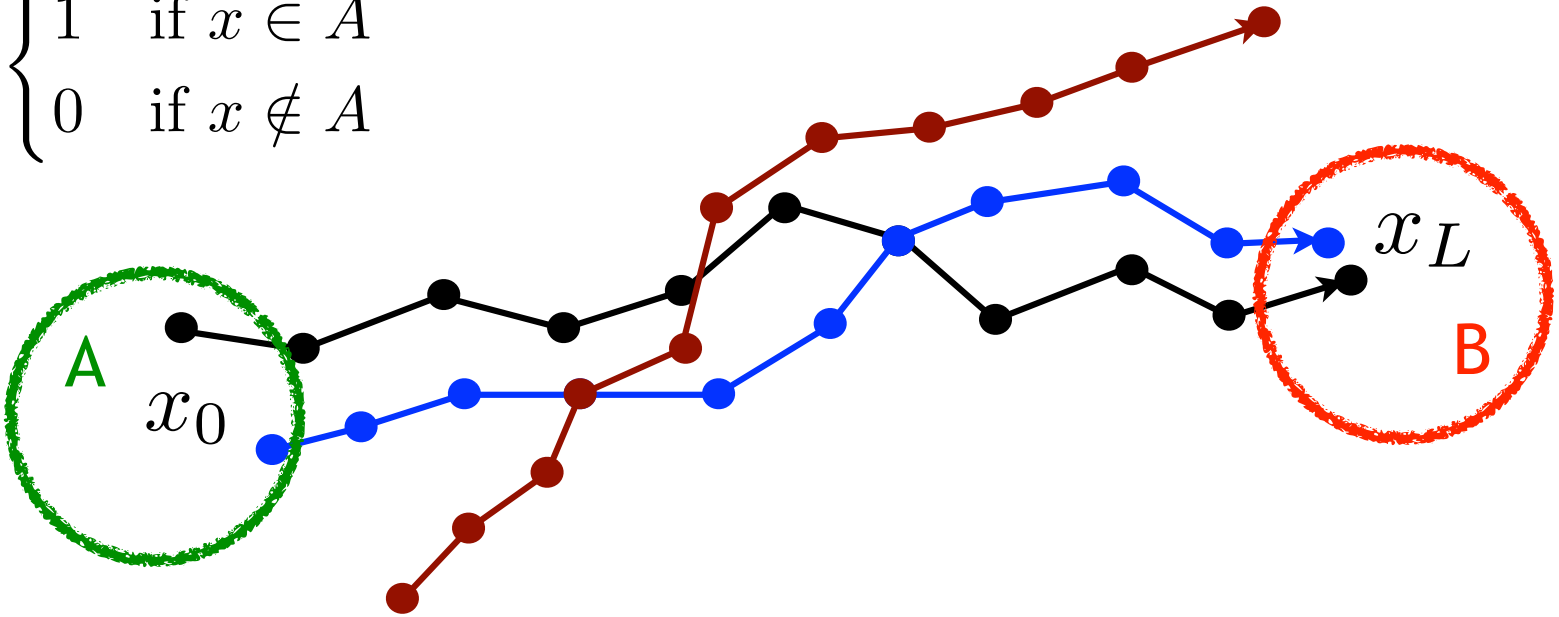
Assumptions:

- symmetric, distribution-preserving modification of the shooting point
- reversible (and distribution-preserving) dynamics
- fixed number of frames in each trajectory, equal probability of selecting any as a shooting point

$$P_{\text{acc}}(\mathbf{x}^{(o)} \to \mathbf{x}^{(n)}) = h_A\left(x_0^{(n)}\right)\ h_B\left(x_L^{(n)}\right)$$

Transition Path Sampling

$$h_A(x) = \begin{cases} 1 & \text{if } x \in A \\ 0 & \text{if } x \notin A \end{cases}$$



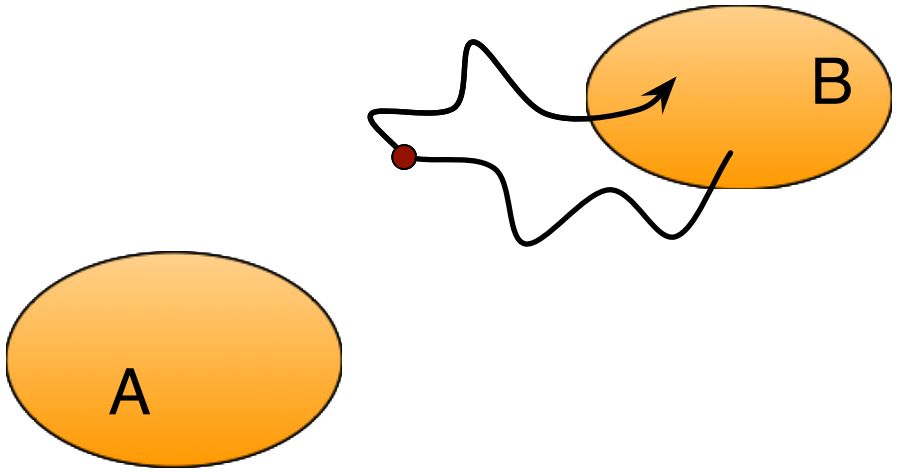
1. Select a point to "shoot" from (frame τ)
2. Modify the velocities at that point
3. Run forward (from τ to *T*) and backward (from τ to 0)
4. Accept/reject

$$P_{\text{acc}}(\mathbf{x}^{(o)} \to \mathbf{x}^{(n)}) = h_A\left(x_0^{(n)}\right)\ h_B\left(x_L^{(n)}\right)$$

What if the modification didn't matter?

Velocity is randomized after ~1ps in biomolecules.

Start with a shooting point at the transition state.



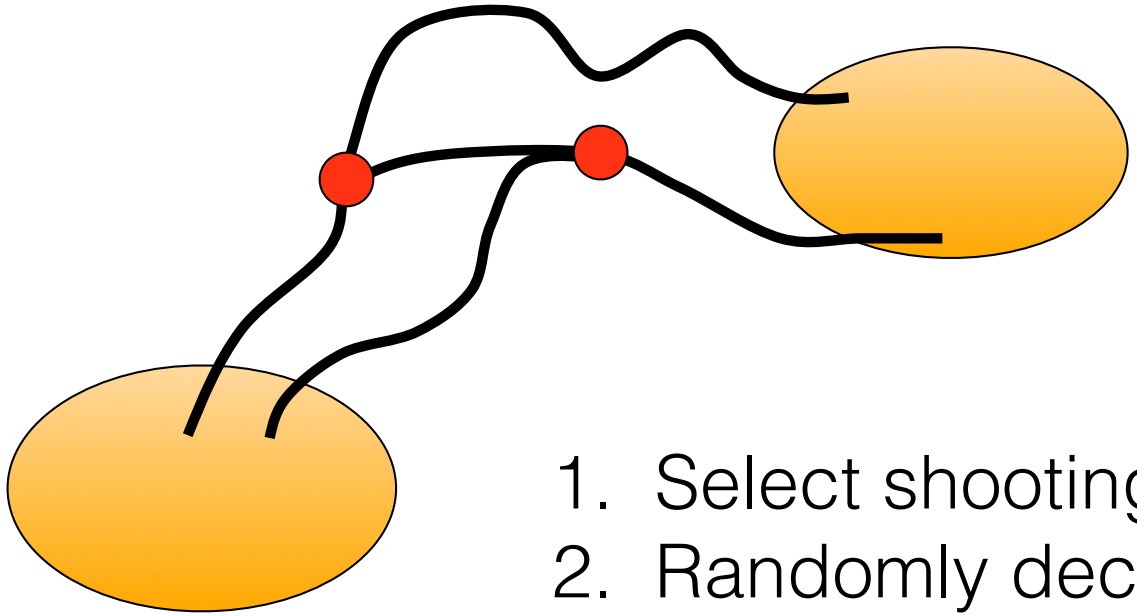
Prob. forward path hits B: 50%

Prob. backward path hits A: 50%

Best acceptance: 25%. Can we do better?

If we only run one direction, we don't have a physical path …
… unless we use a stochastic integrator!

Stochastic (One-Way) Shooting



1. Select shooting point
2. Randomly decide to shoot either forward or backward
3. The new trajectory has some frames from the old trajectory

No modification of the selected snapshot!

Flexible-Length Shooting

The time spent in the barrier region has a wide variance. The average time can be 1/5 as long as the time of the longest 1% of trajectories. If you always have to go to the longest time, you end up doing 5 times as much work.

Let's design a shooting move that stops as soon as it enters the state. Accepted paths will have one frame in each state (first frame and last frame), and no other frames will be in any state. The path length will be allowed to vary.

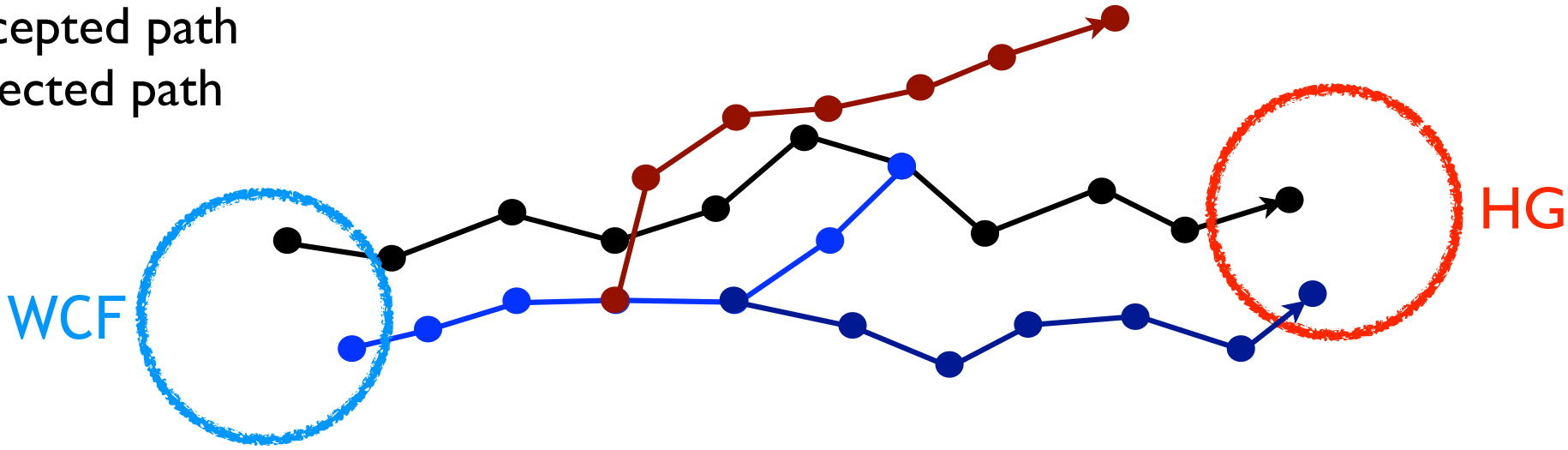
$$P_{\text{sel}}(x_\tau; \mathbf{x}^{(o)}(L^{(o)})) = 1/(L^{(o)} - 1)$$

$$\frac{P_{\text{sel}}(x_\tau; \mathbf{x}^{(n)}(L^{(n)}))}{P_{\text{sel}}(x_\tau; \mathbf{x}^{(o)}(L^{(o)}))} = \frac{1/(L^{(n)} - 1)}{1/(L^{(o)} - 1)} = \frac{L^{(o)} - 1}{L^{(n)} - 1}$$

$$P_{\text{acc}}(\mathbf{x}^{(o)} \to \mathbf{x}^{(n)}) = h_A(x_0^{(n)})\, h_B(x_L^{(n)}) \min\left(1, \frac{L^{(o)} - 1}{L^{(n)} - 1}\right)$$

Transition Path Sampling optimised for biomolecular systems

- initial trajectory
- accepted path
- rejected path



1. Select a point to "shoot" from
2. Randomly decide to shoot forward or backward
3. Run molecular dynamics with stochastic integrator until reaching the state, or reaching maximum length
4. Trial path consists of old and new frames
5. Decide
   a. accept if trial path connects both states
   b. reject if trial path does not connect both states

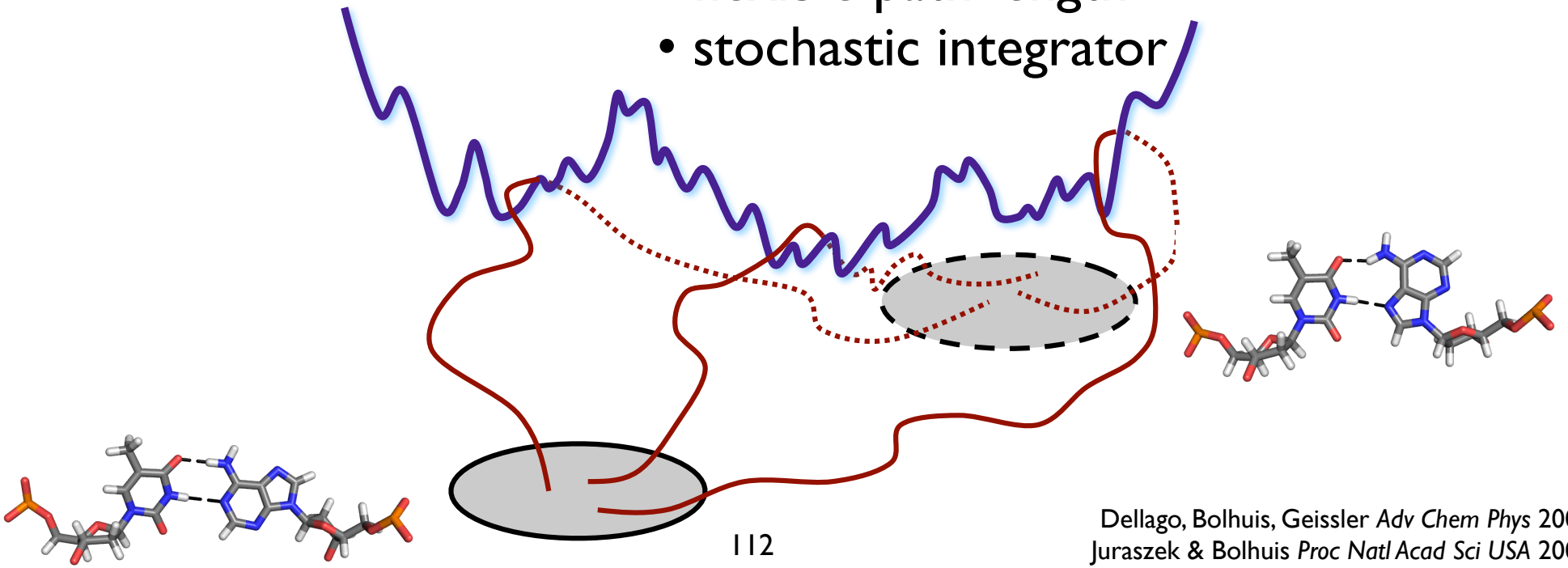
Sampling rare events: transition path sampling

Input

Result: ensemble of transition paths

Algorithm

- one way shooting
- flexible path length
- stochastic integrator

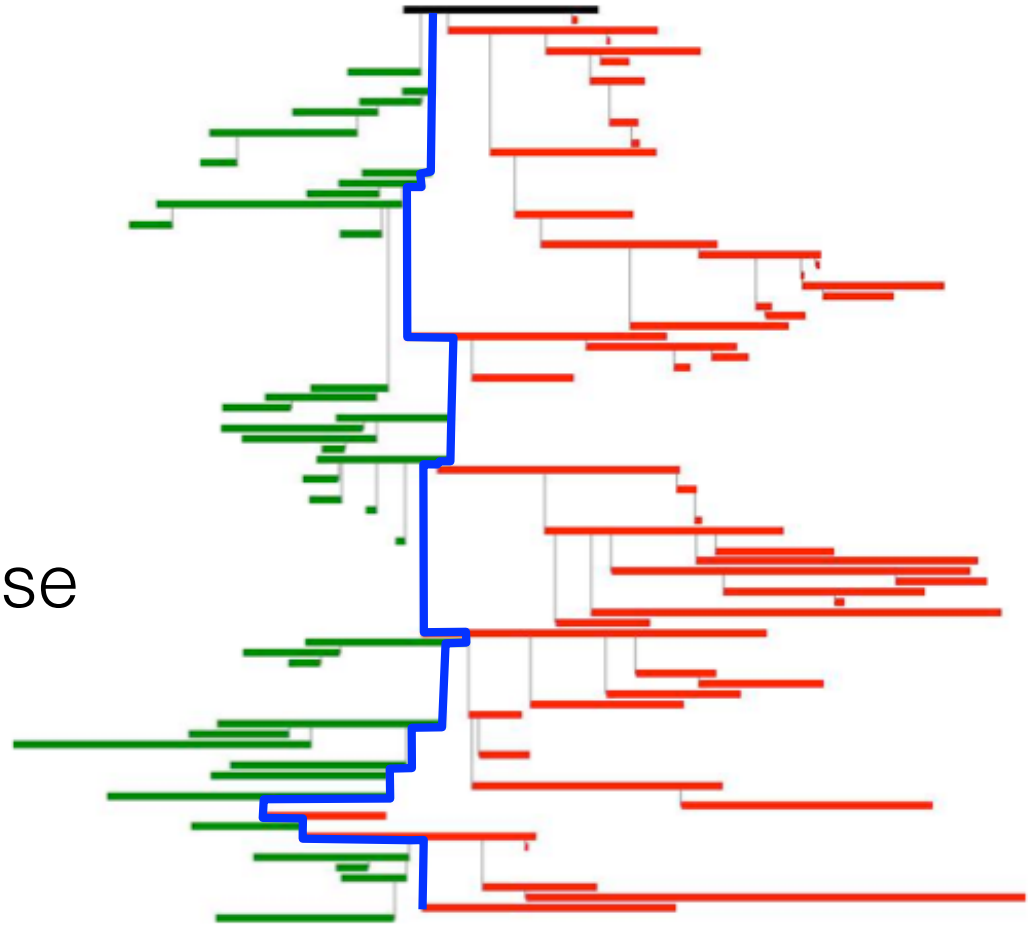


Dellago, Bolhuis, Geissler *Adv Chem Phys* 2002
Juraszek & Bolhuis *Proc Natl Acad Sci USA* 2006

Path Trees and Transition Region

Path tree is a check of good behavior in simulation:

- Both forward and backward shots accepted with similar frequency
- See decorrelated paths: those with no frames in common



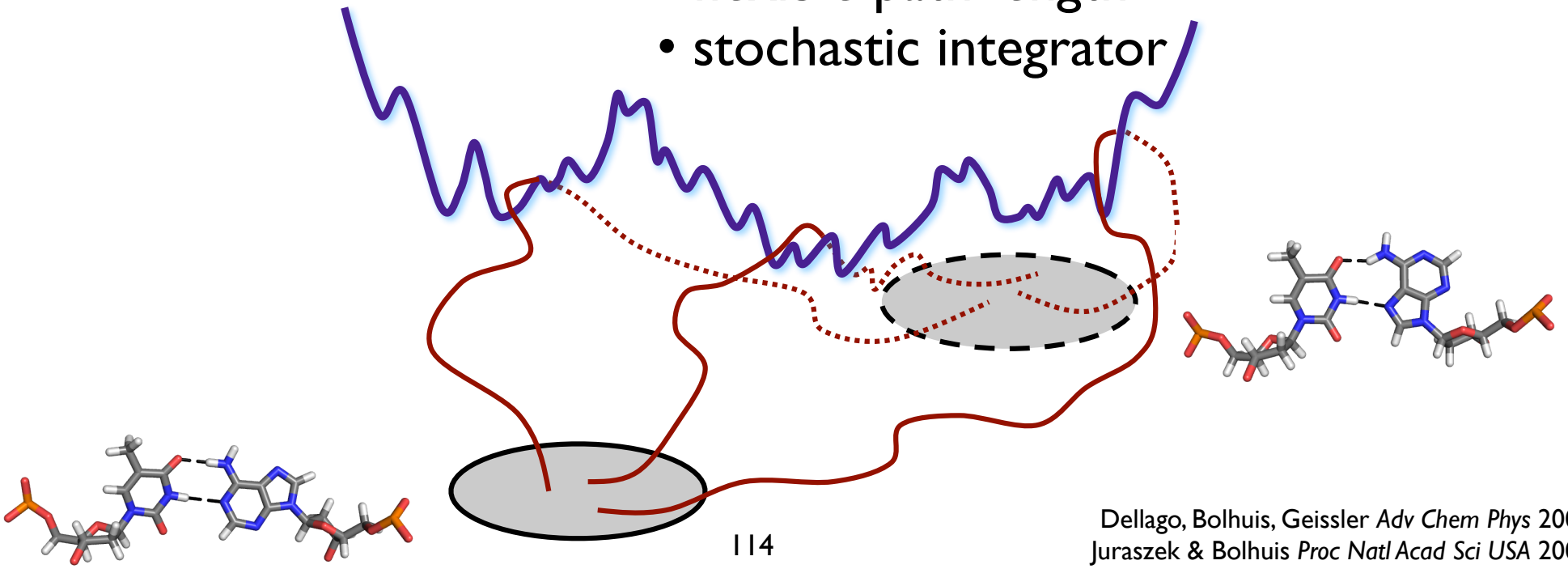
Least-changed path: Stays near top of barrier; Approximation of transition state ensemble

Sampling rare events: transition path sampling

Input
- initial reactive path
- definitions of stable states

Result: ensemble of transition paths

Algorithm
- one way shooting
- flexible path length
- stochastic integrator



Dellago, Bolhuis, Geissler *Adv Chem Phys* 2002
Juraszek & Bolhuis *Proc Natl Acad Sci USA* 2006

How do we define states?

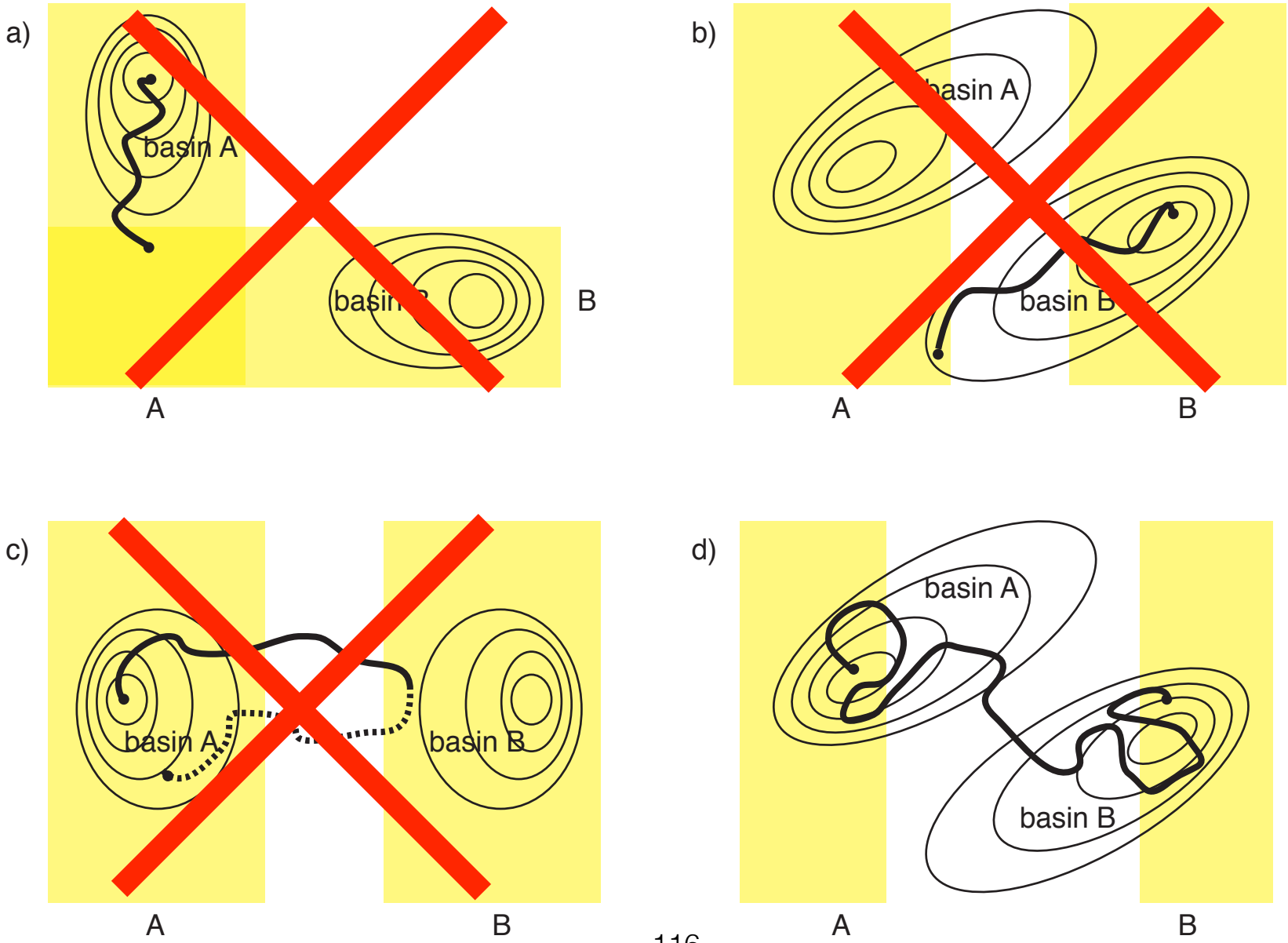
Take something that you can measure (distance, dihedral angle) and say it has to be within some range of values.

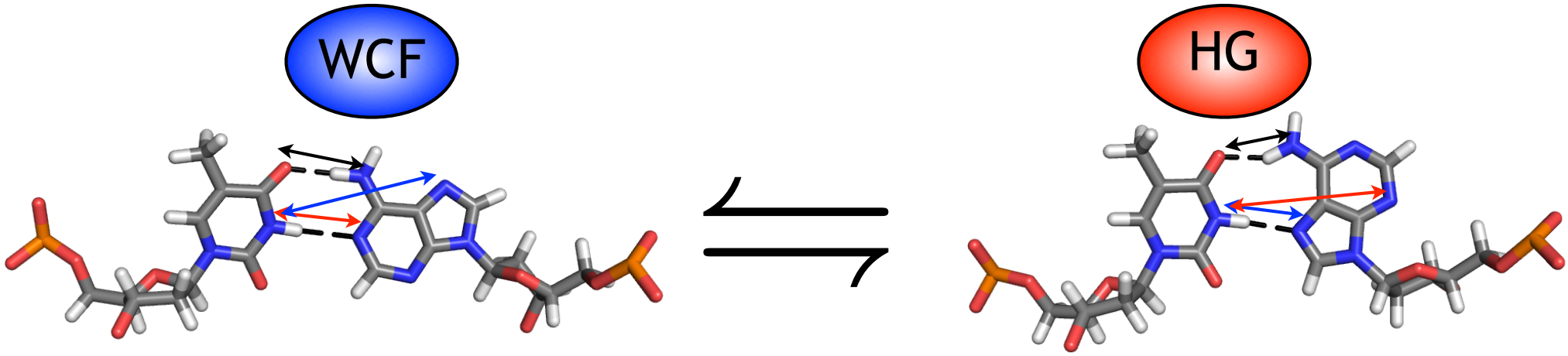
Examples:

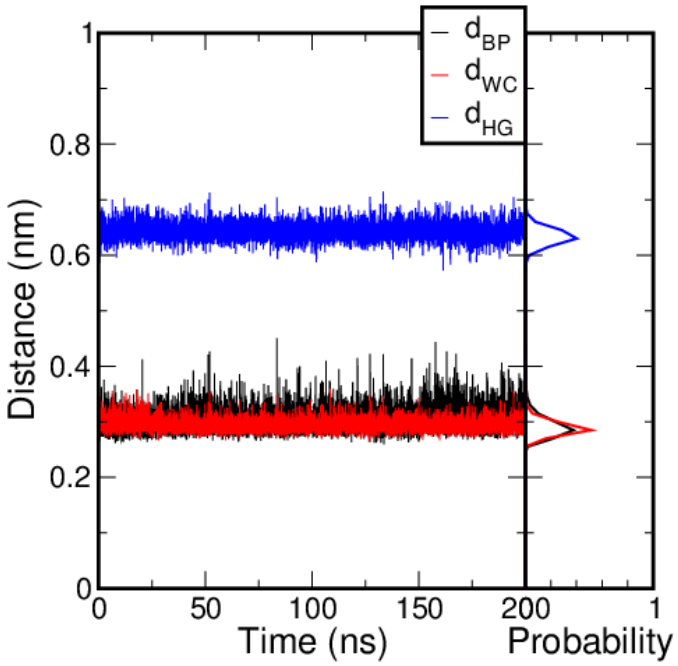
- Hydrogen bond formed ($d_{donor\text{-}acceptor} < 3.5$ Å)
- Specific value of (several) dihedral angles

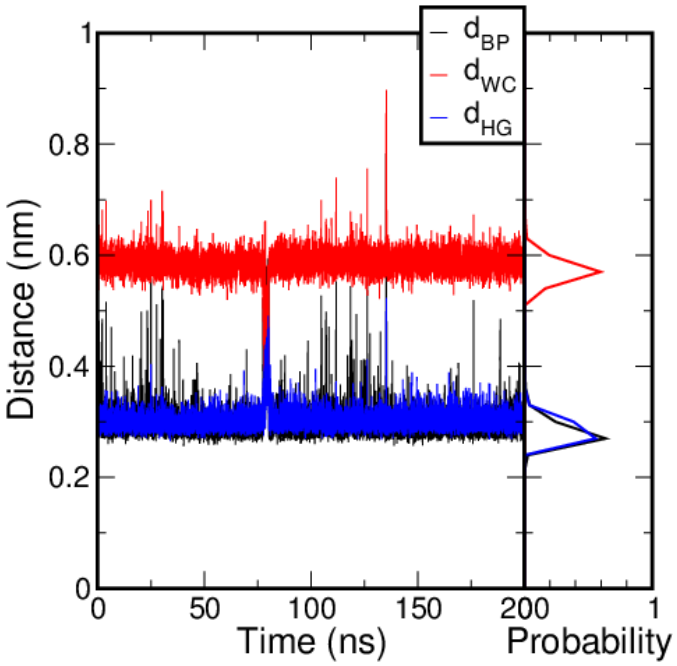
What makes a good definition?

How do we define states?









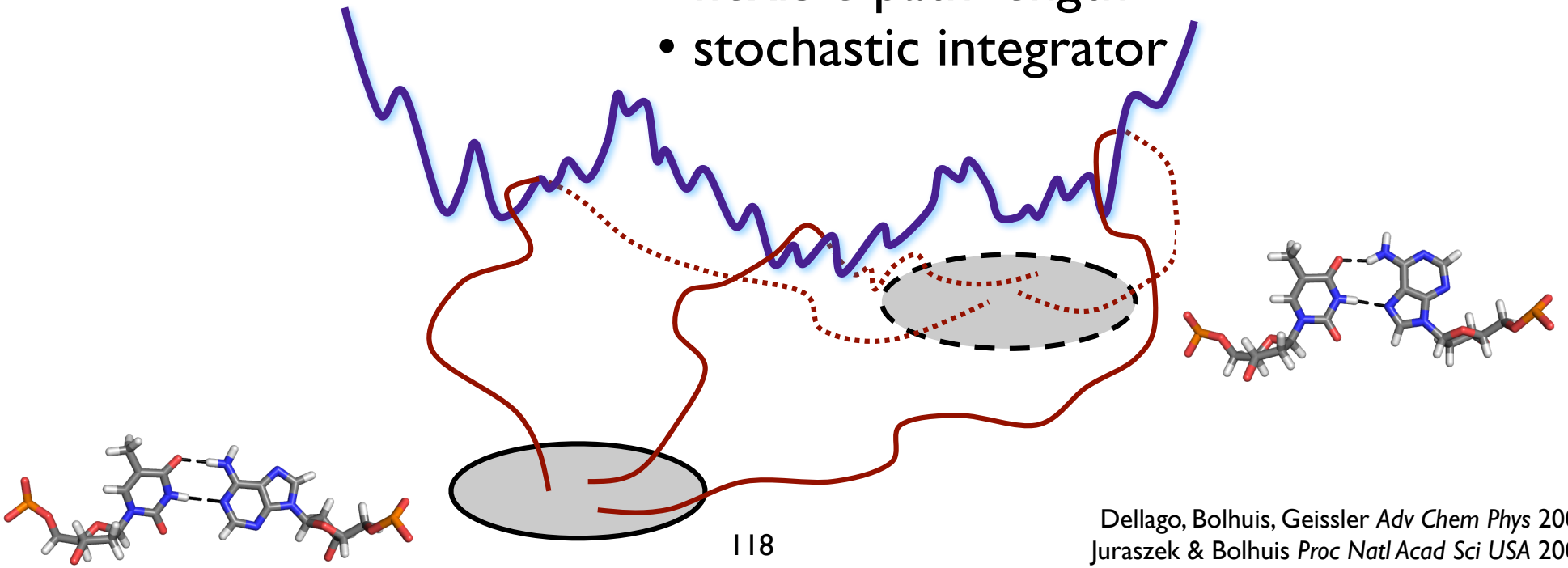
Vreede, Pérez de Alba Ortíz, Bolhuis & Swenson, NAR 2019

Sampling rare events: transition path sampling

Input
- initial reactive path
- definitions of stable states

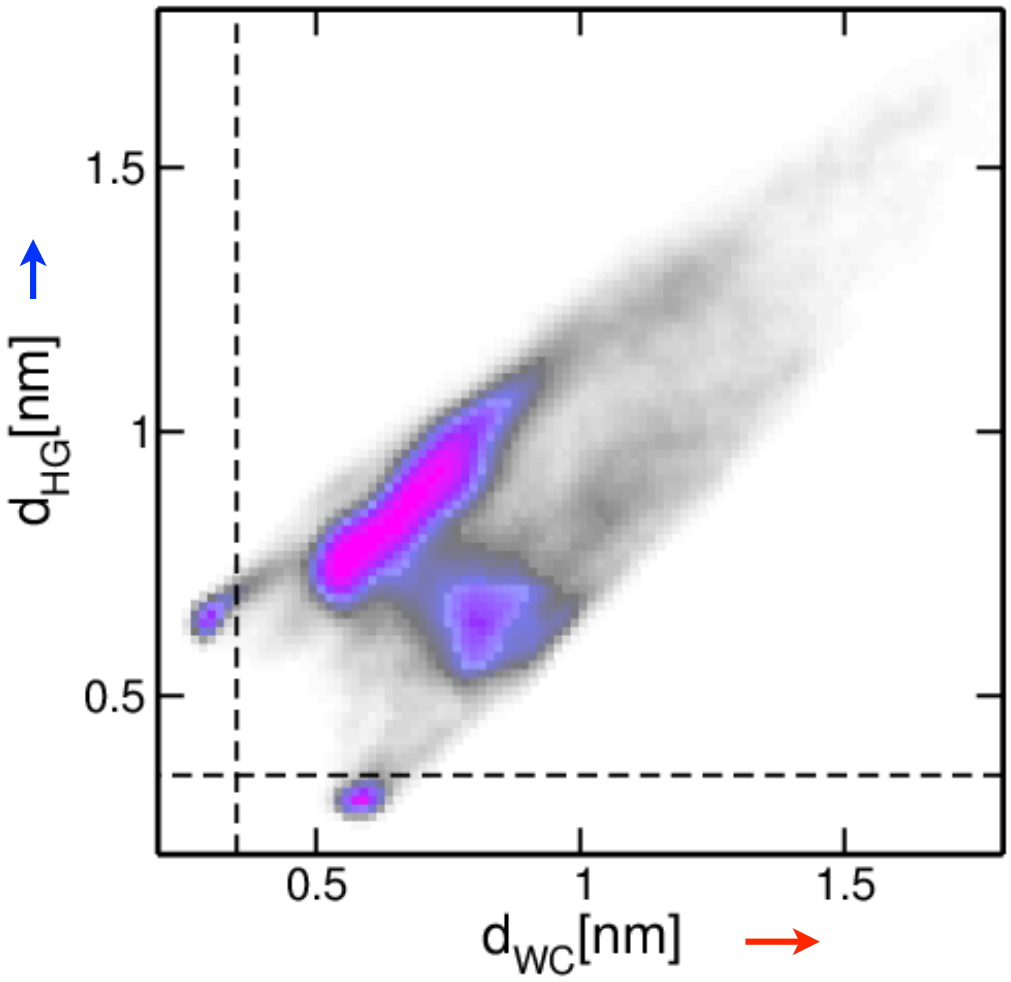
Result: ensemble of transition paths
- mechanism
- relevant reaction coordinates

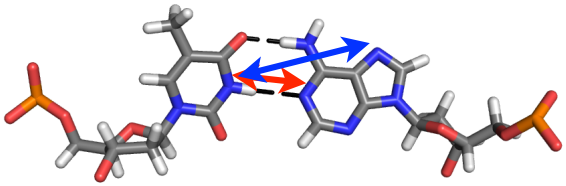
Algorithm
- one way shooting
- flexible path length
- stochastic integrator



Dellago, Bolhuis, Geissler *Adv Chem Phys* 2002
Juraszek & Bolhuis *Proc Natl Acad Sci USA* 2006

Generate reactive trajectories using transition path sampling





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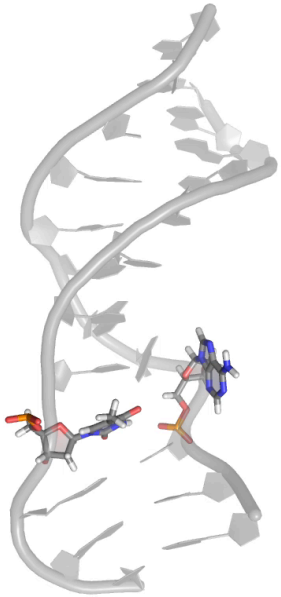
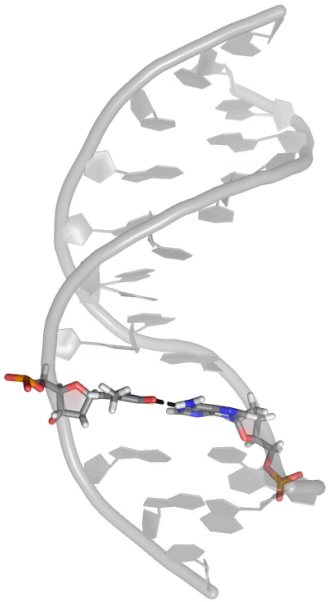
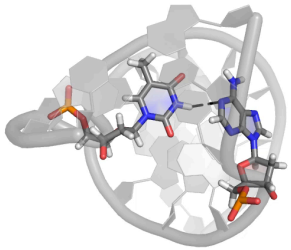
Two types of transitions

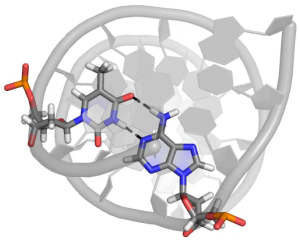


outside

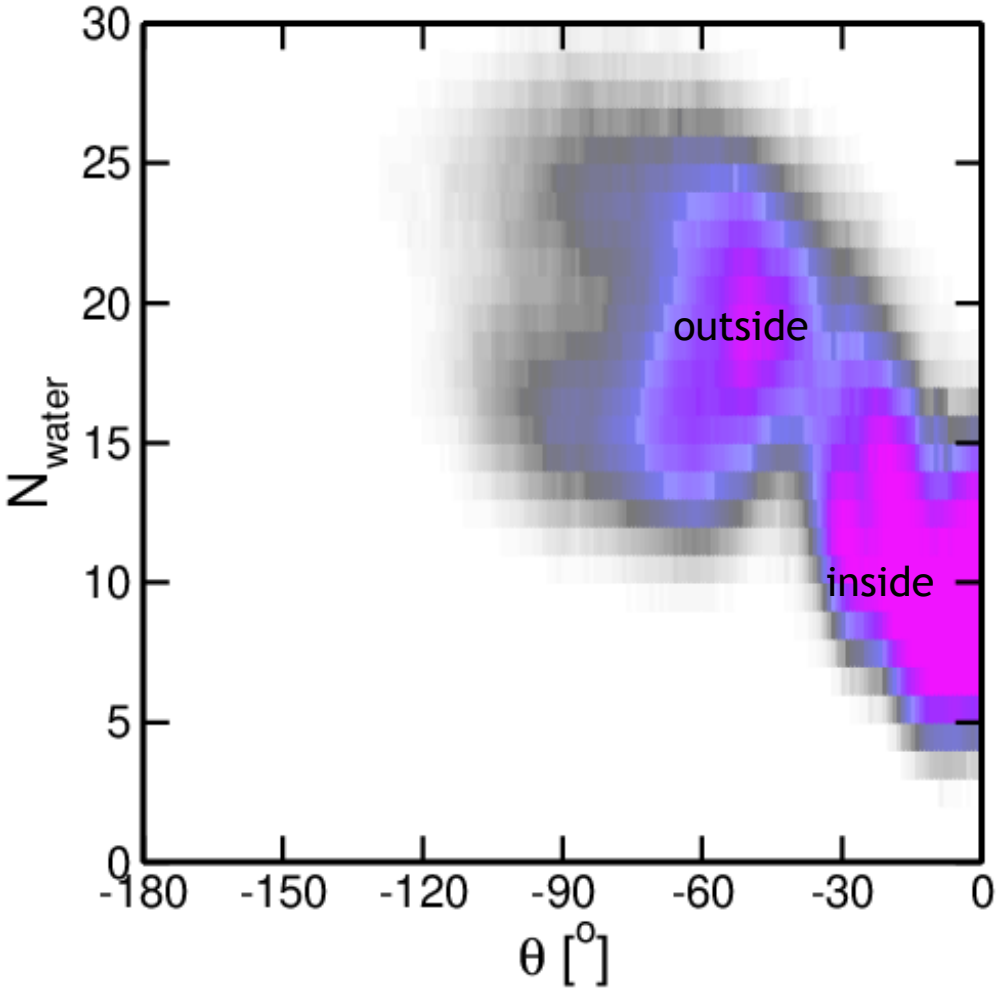


inside

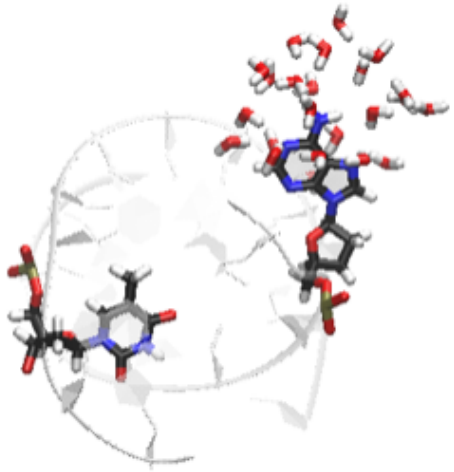




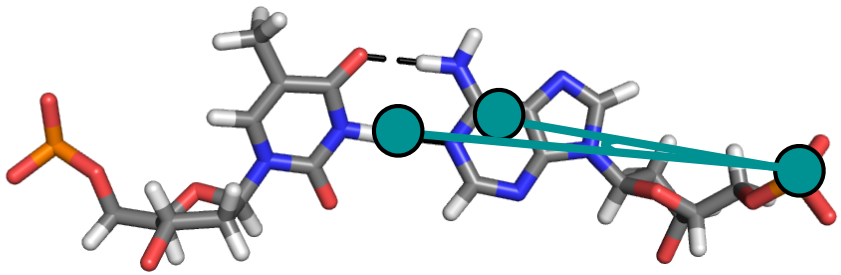
Two reaction channels: inside and outside



N_{water}



θ base flipping angle



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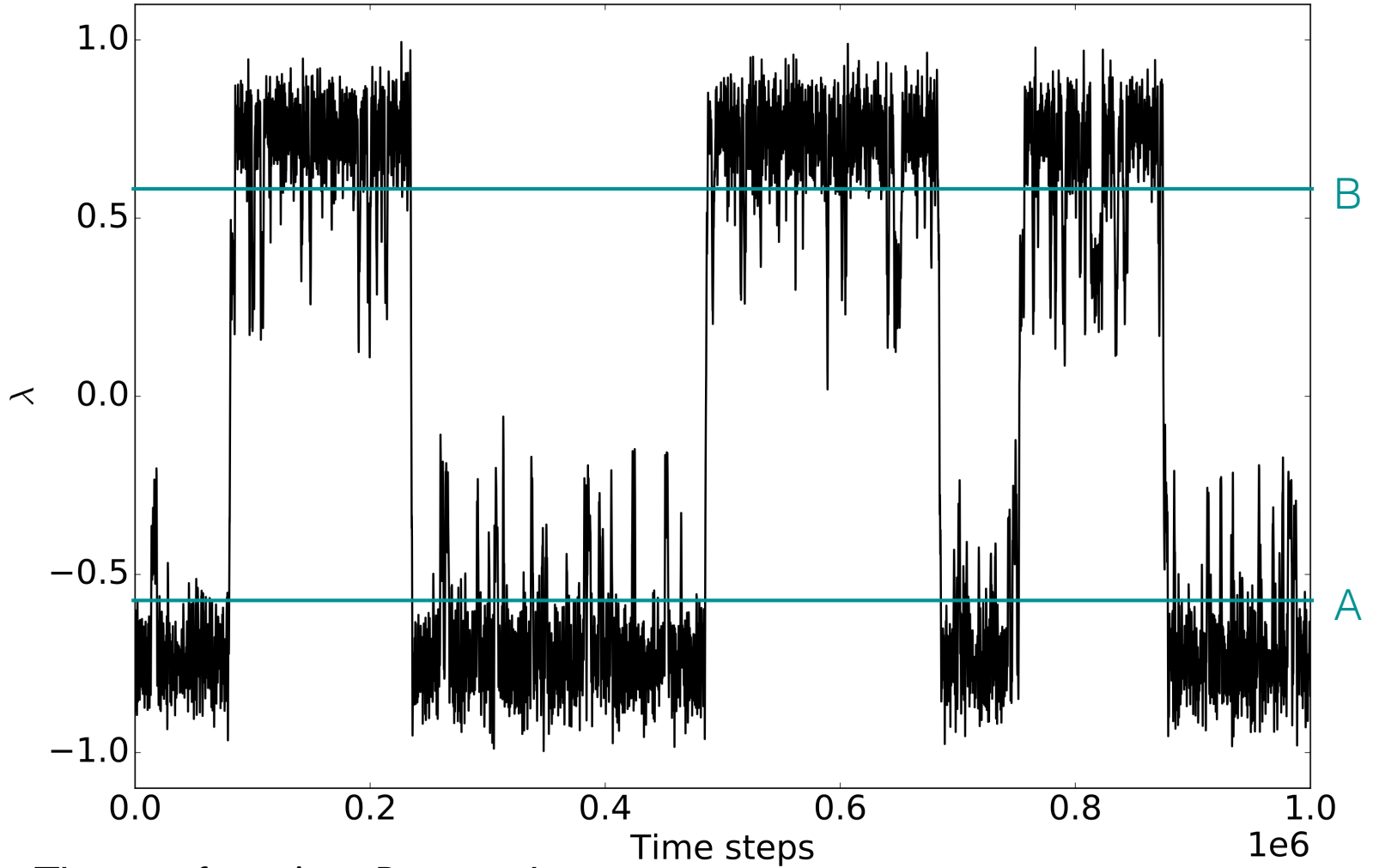
Calculate the rate



The rate from A to B is equal to

the number of transitions per time unit

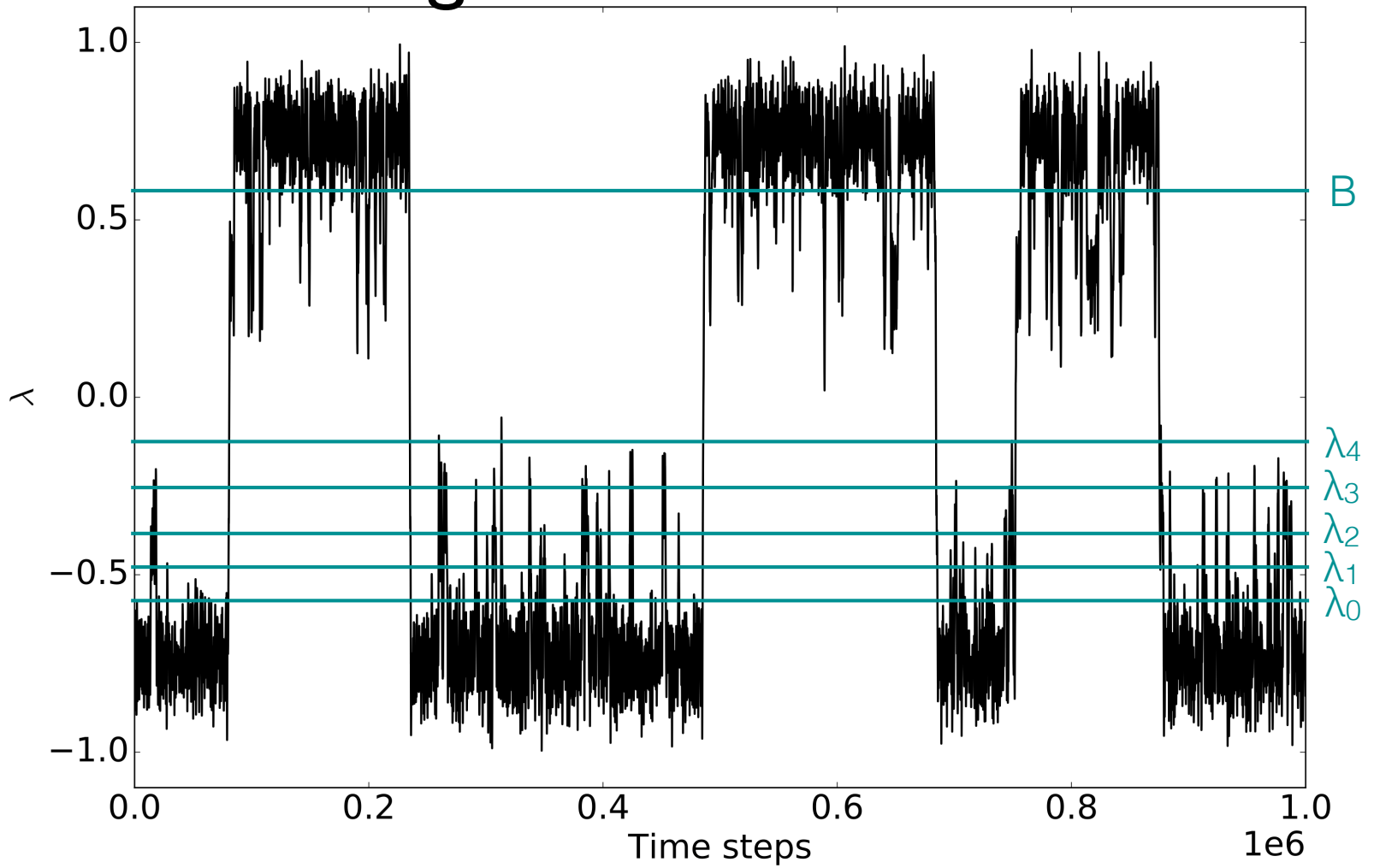
divided by the time spent in state A

$$k_{AB} = \lim_{\mathcal{T}\to\infty} \frac{N_{A\to B}(\mathcal{T})}{t^A_{tot}(\mathcal{T})}$$

Slide design by David Swenson

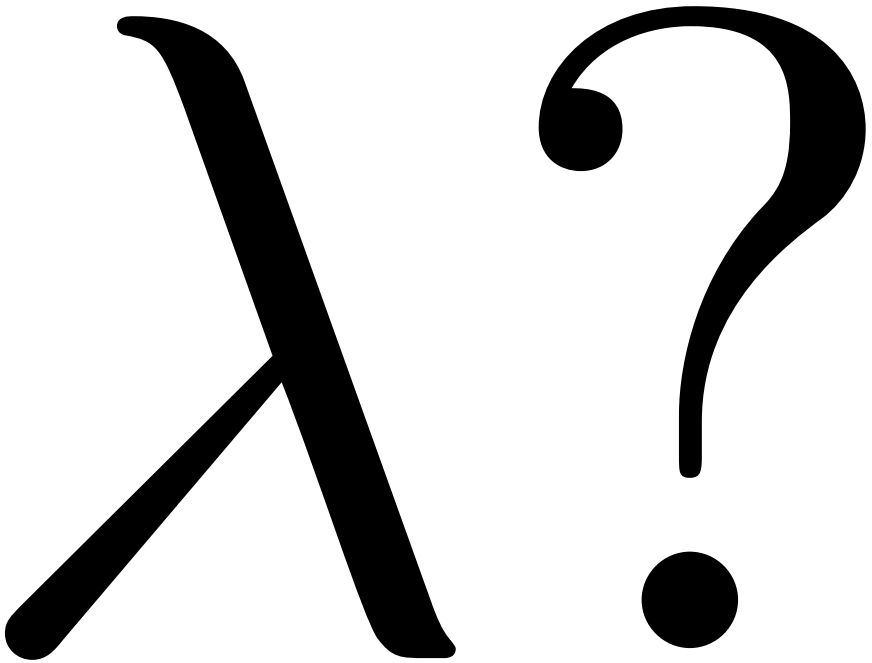
van Erp et al. J. Chem. Phys 2003

Transition Interface Sampling: calculating the rate with interfaces

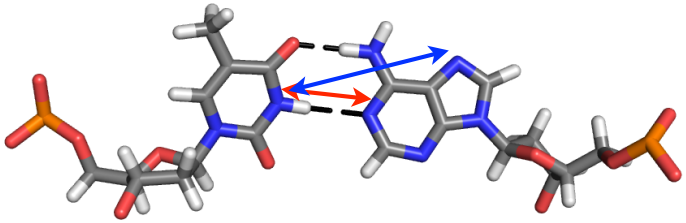


$$k_{AB} = \phi_{A,0} P(B|\lambda_m) \prod_{i=0}^{m-1} P(\lambda_{i+1}|\lambda_i)$$

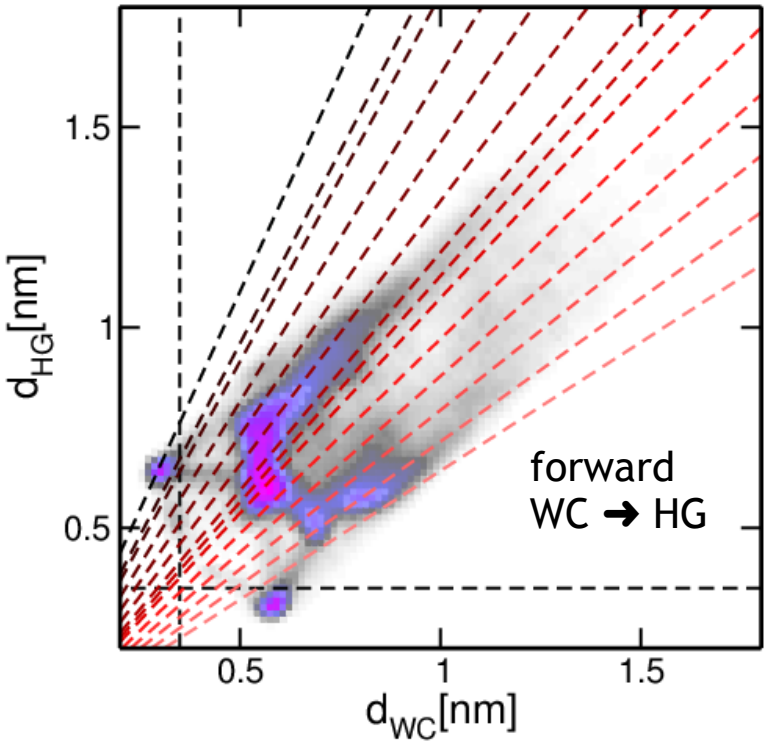
Slide design by David Swenson
van Erp et al. J. Chem. Phys 2003

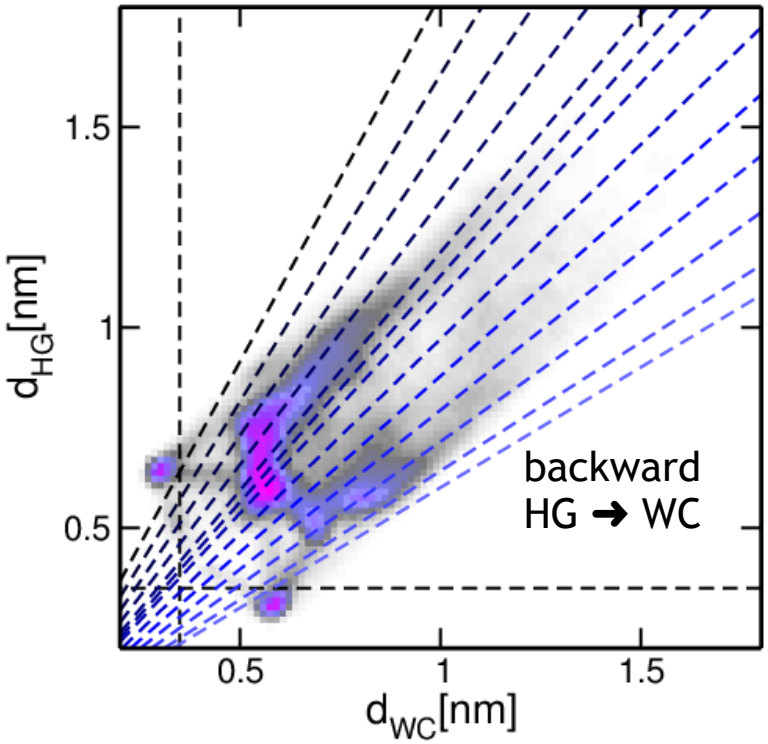


Interfaces



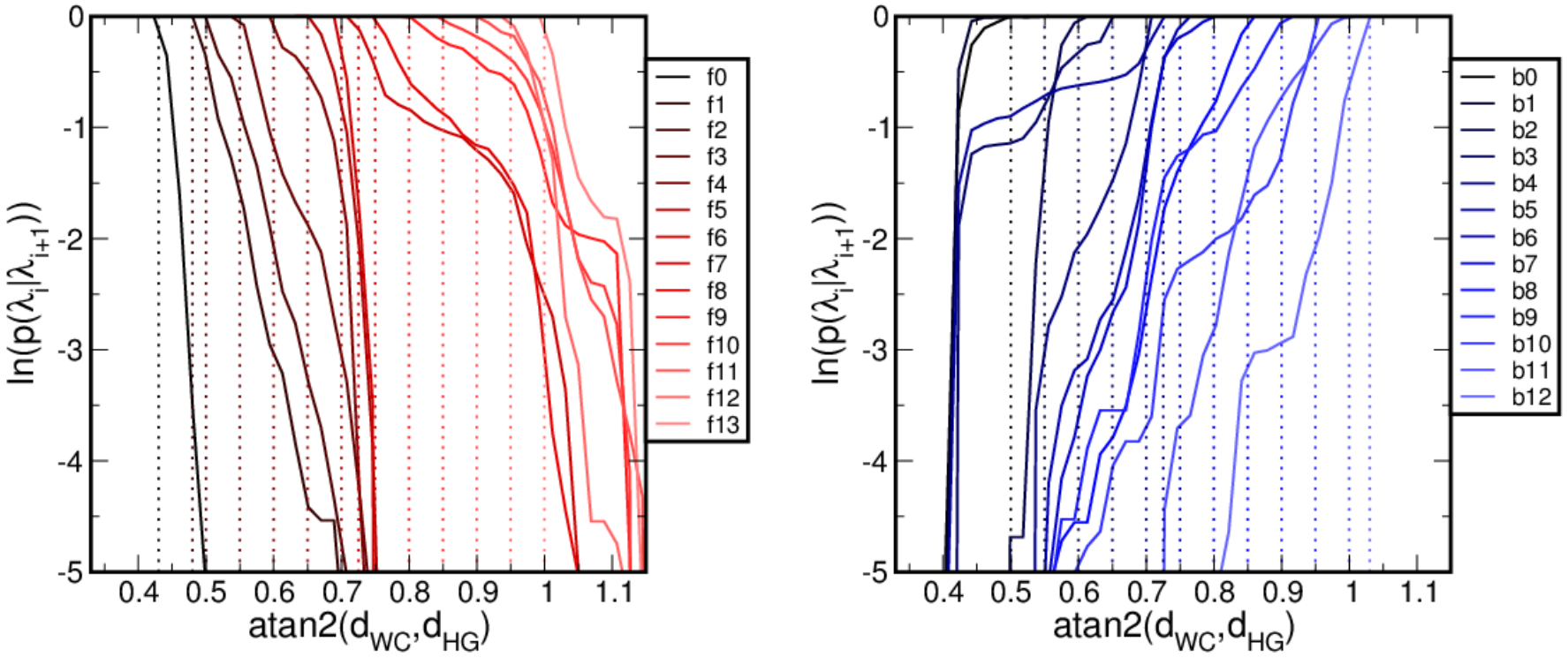
$$\lambda = \arctan(d_{WC}, d_{HG})$$





Vreede, Pérez de Alba Ortíz, Bolhuis & Swenson, NAR 2019

Crossing probabilities



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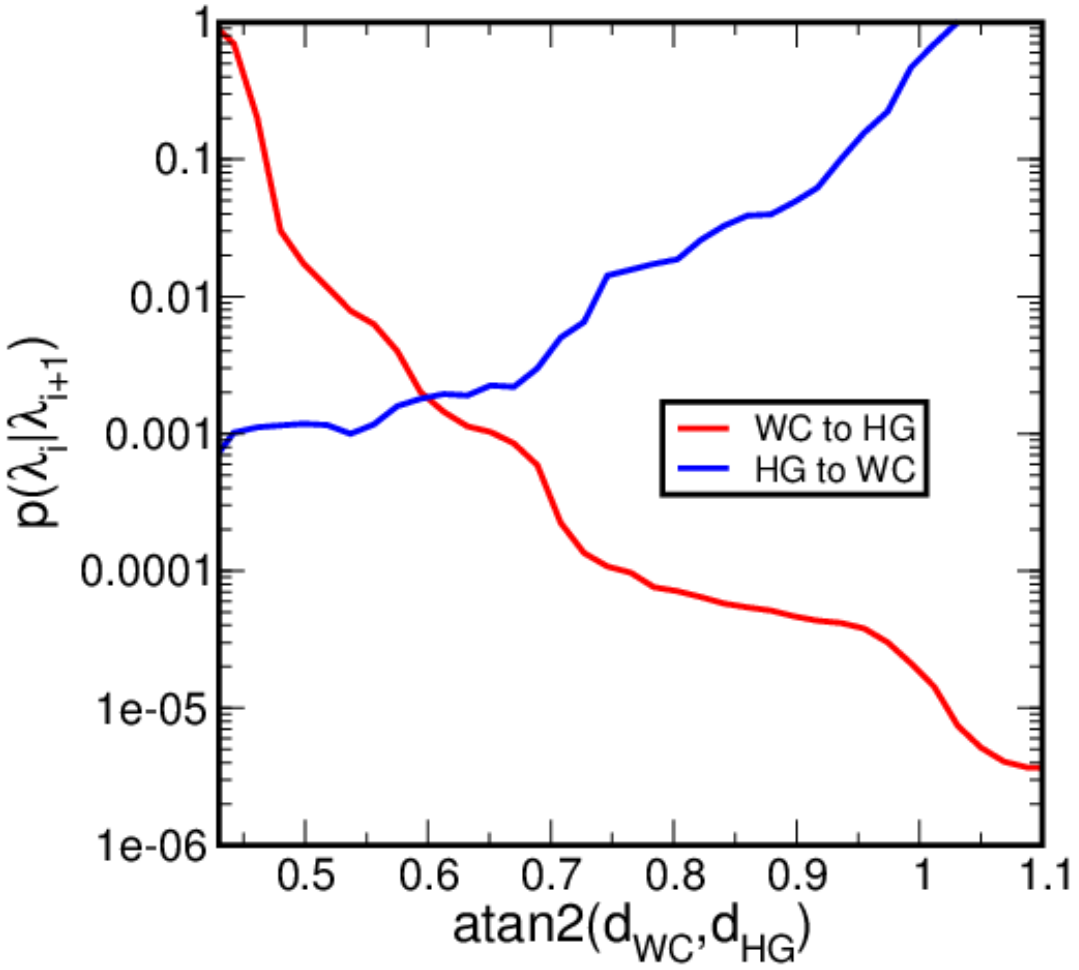
Crossing probabilities



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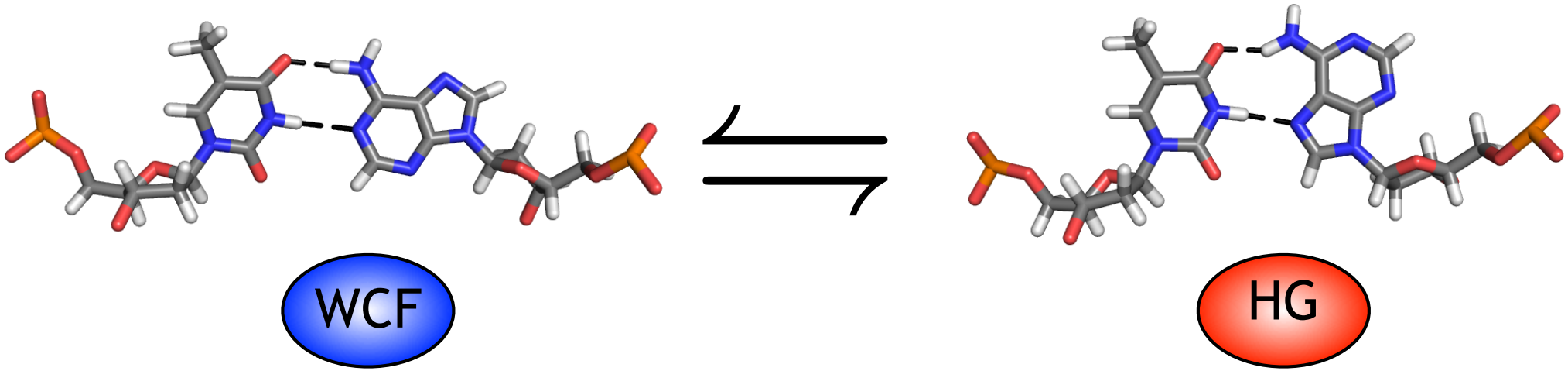
Rates



	expt*	TIS**
$k_{WC \to HG}$ (s^{-1})	14.2 ± 1.03	742
$k_{HG \to WC}$ (s^{-1})	3670 ± 200	$1.6 \cdot 10^5$
ΔG ($k_B T$)	5.5	5.4
	at 26.0°C	at 300K

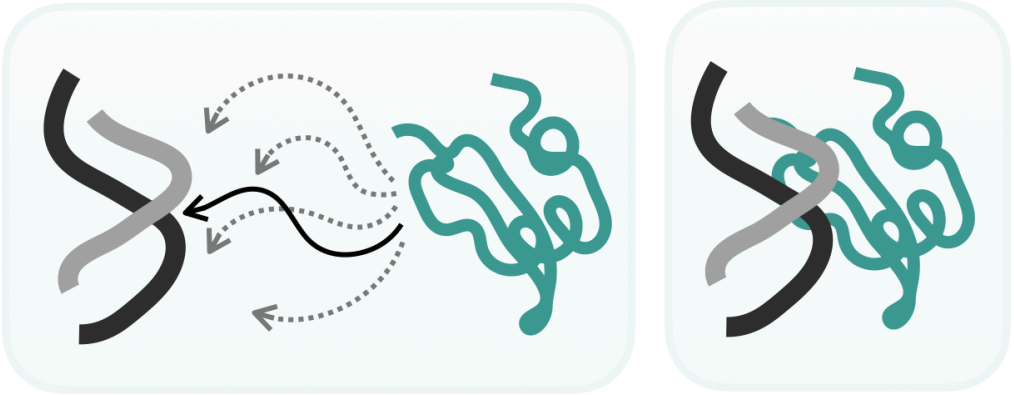
TIS:
one-way shooting
flexible path length
500 accepted paths per interface
13 interfaces

*Nikolova, Kim, Wise, O'Brien, Andricioaei and Al-Hashimi Nature 2011 v. 470, p. 498

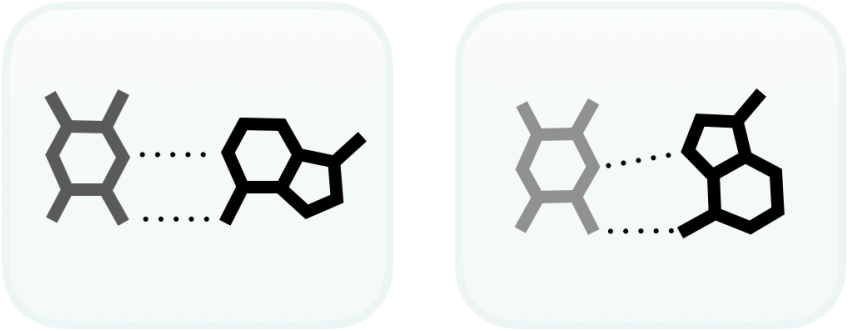
**Vreede, Ortiz de Alba Perez, Bolhuis & Swenson, NAR 2019

$$\Delta G = -\ln \frac{k_{WC \to HG}}{k_{HG \to WC}}$$

Characterise States with MD

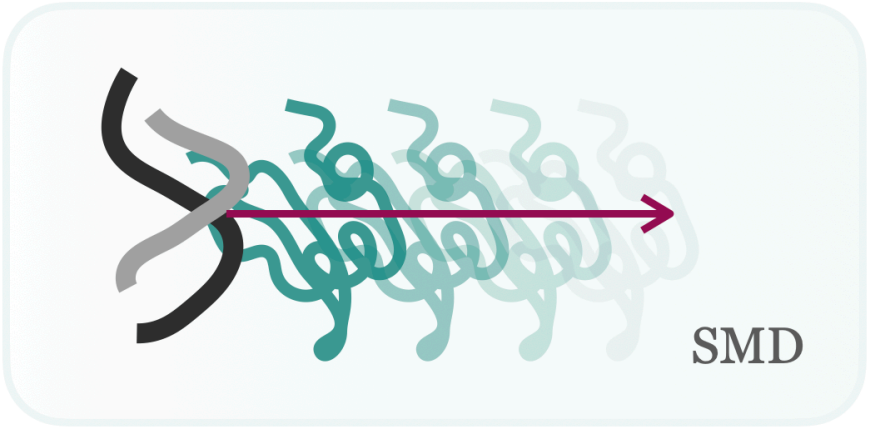


Identify Bound States

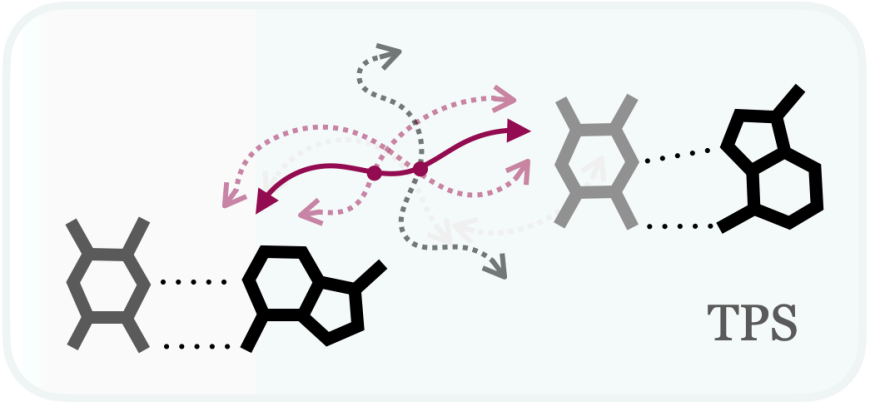


WCF *HG*

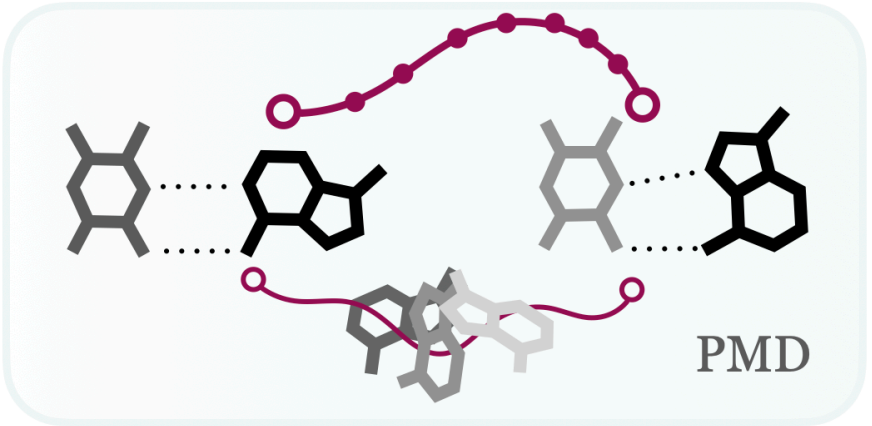
Free Energy Differences



Mechanistic Insights



Free Energy Profiles



Ambient conditions

- temperature $\left\langle \frac{1}{2}mv^2 \right\rangle = \frac{3}{2}k_B T$

- pressure $p = \rho k_B T + \frac{1}{V}\left\langle \sum_{i<j} F(r_{ij}) \cdot r_{ij} \right\rangle$

m mass
v velocity
k_B Boltzmann's constant
T temperature
p pressure
ρ density
V volume
F force
r distance between i and j