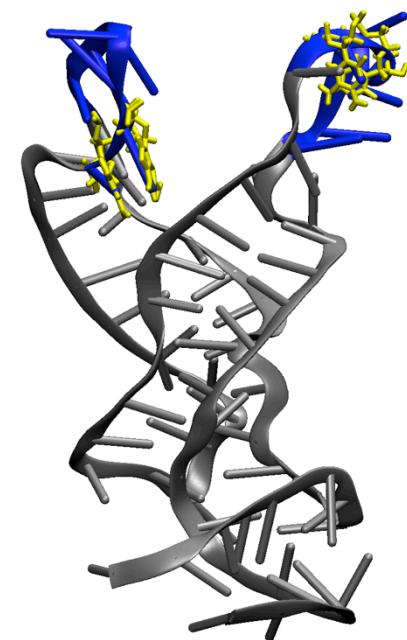
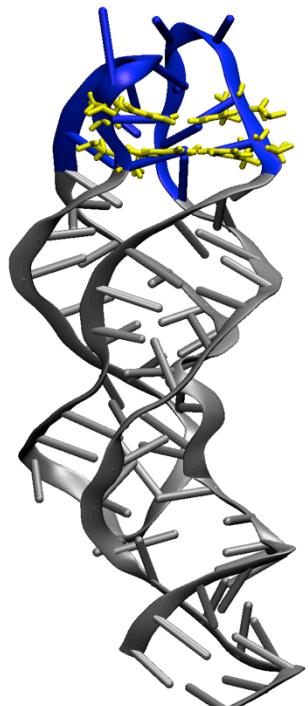


# Accelerated Weight Histogram method

Viveca Lindahl, Berk Hess

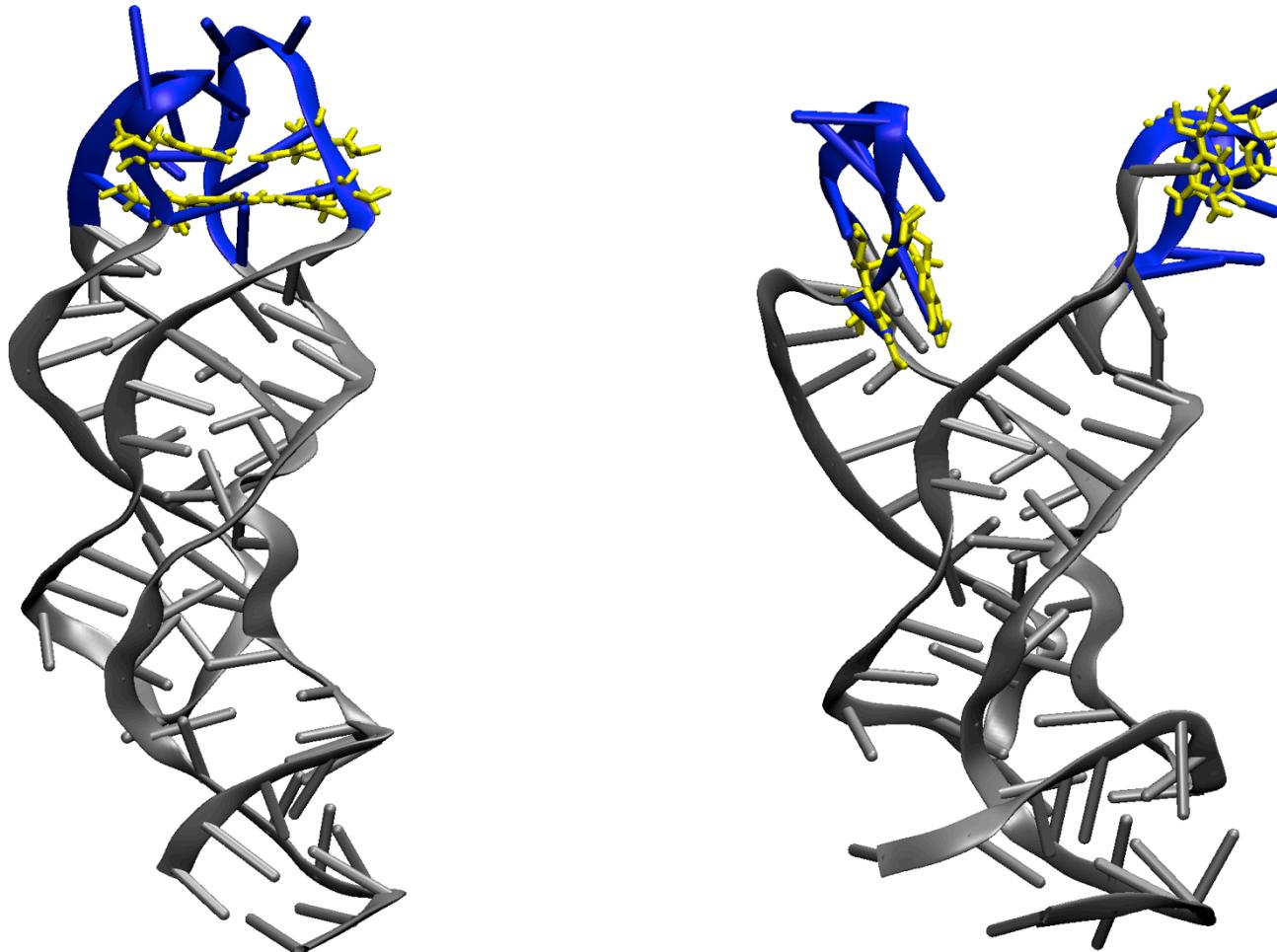
Theoretical and computational biophysics group  
KTH, Stockholm

V. Lindahl, J. Lidmar, B. Hess, JCP (2014) 141, 044110  
V. Lindahl, A. Villa, B. Hess, PLOS (2017), 13, e1005463



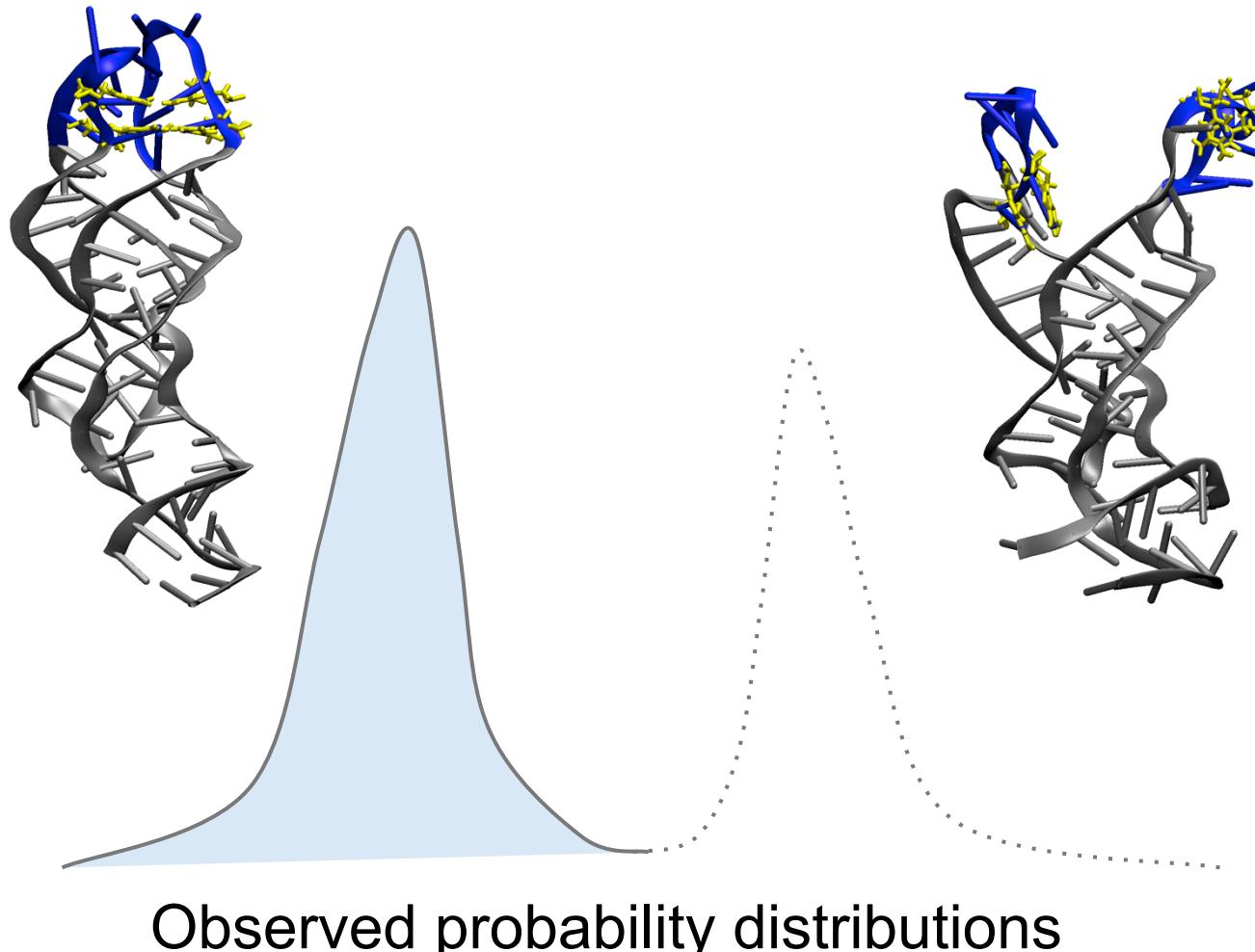
# Sampling rare events

Molecular dynamics – a powerful tool, but with limitations



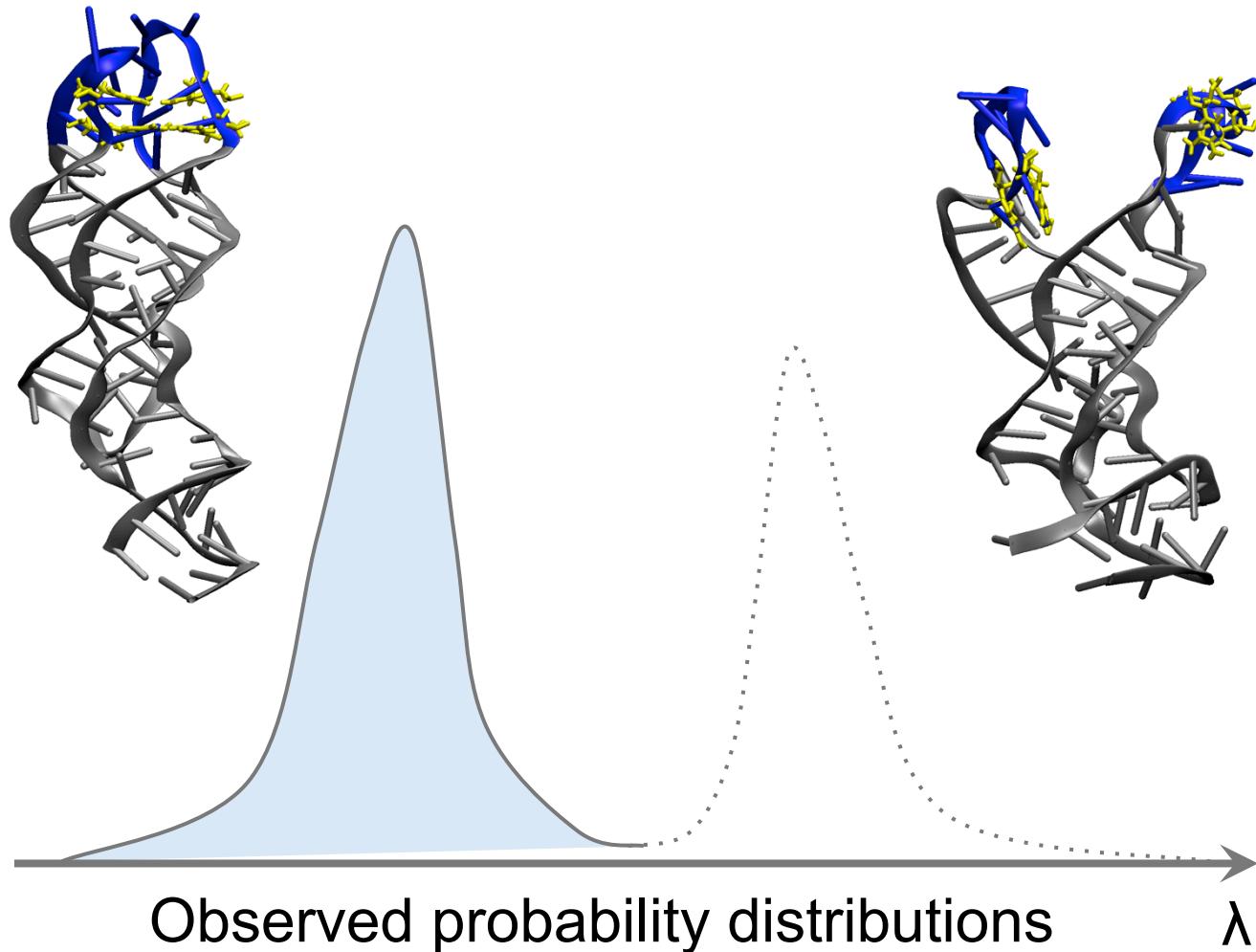
# Sampling rare events

Molecular dynamics – a powerful tool, but with limitations



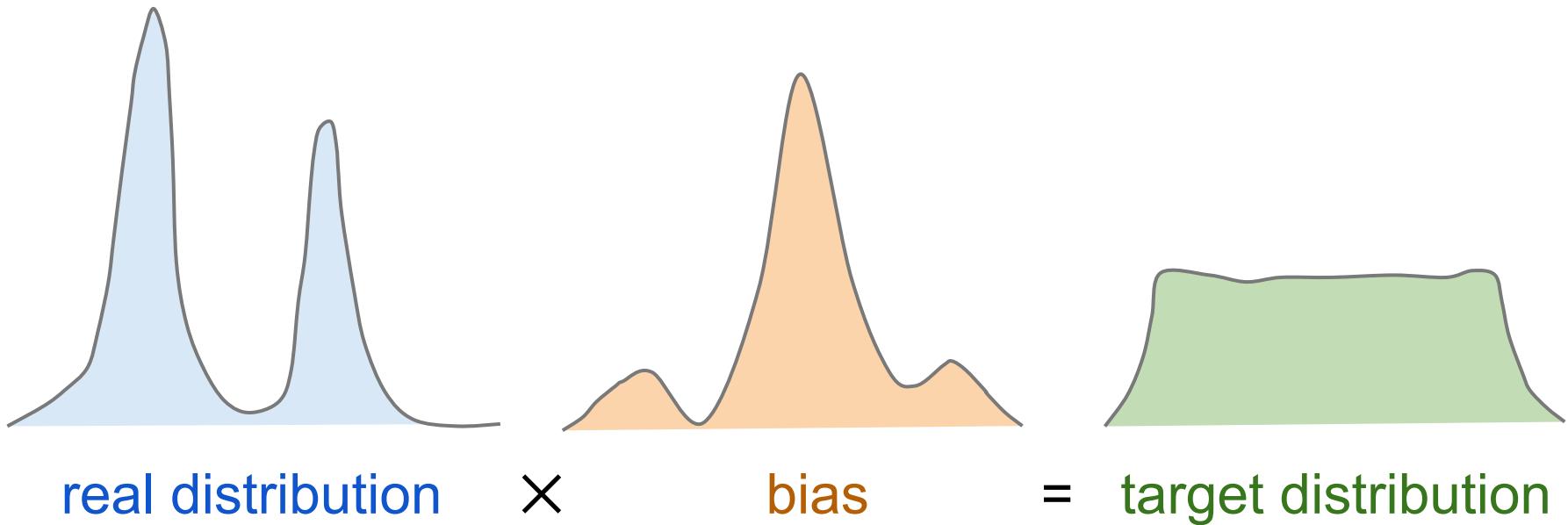
# Sampling rare events

Molecular dynamics – a powerful tool, but with limitations



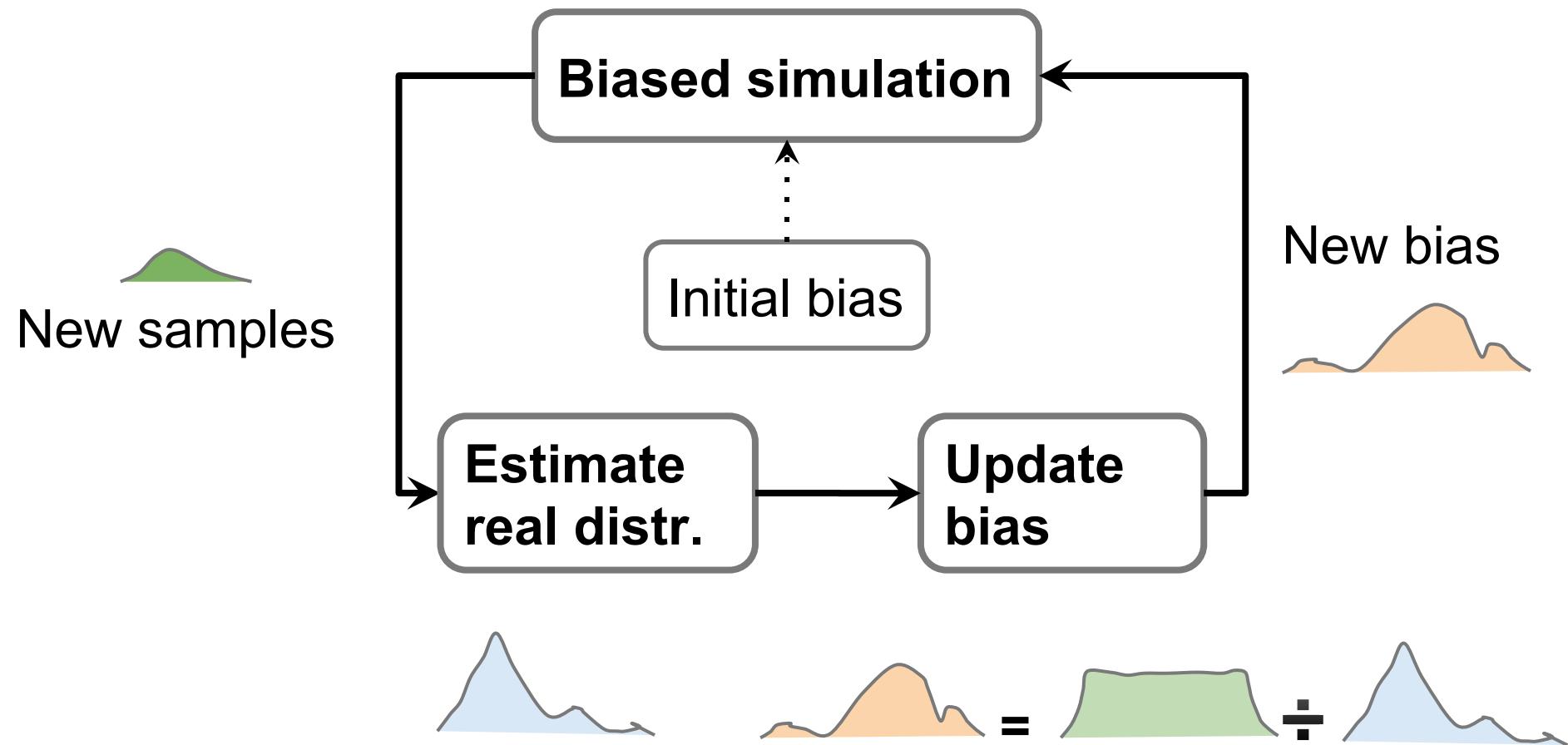
# Biasing simulations

Add sampling to important regions

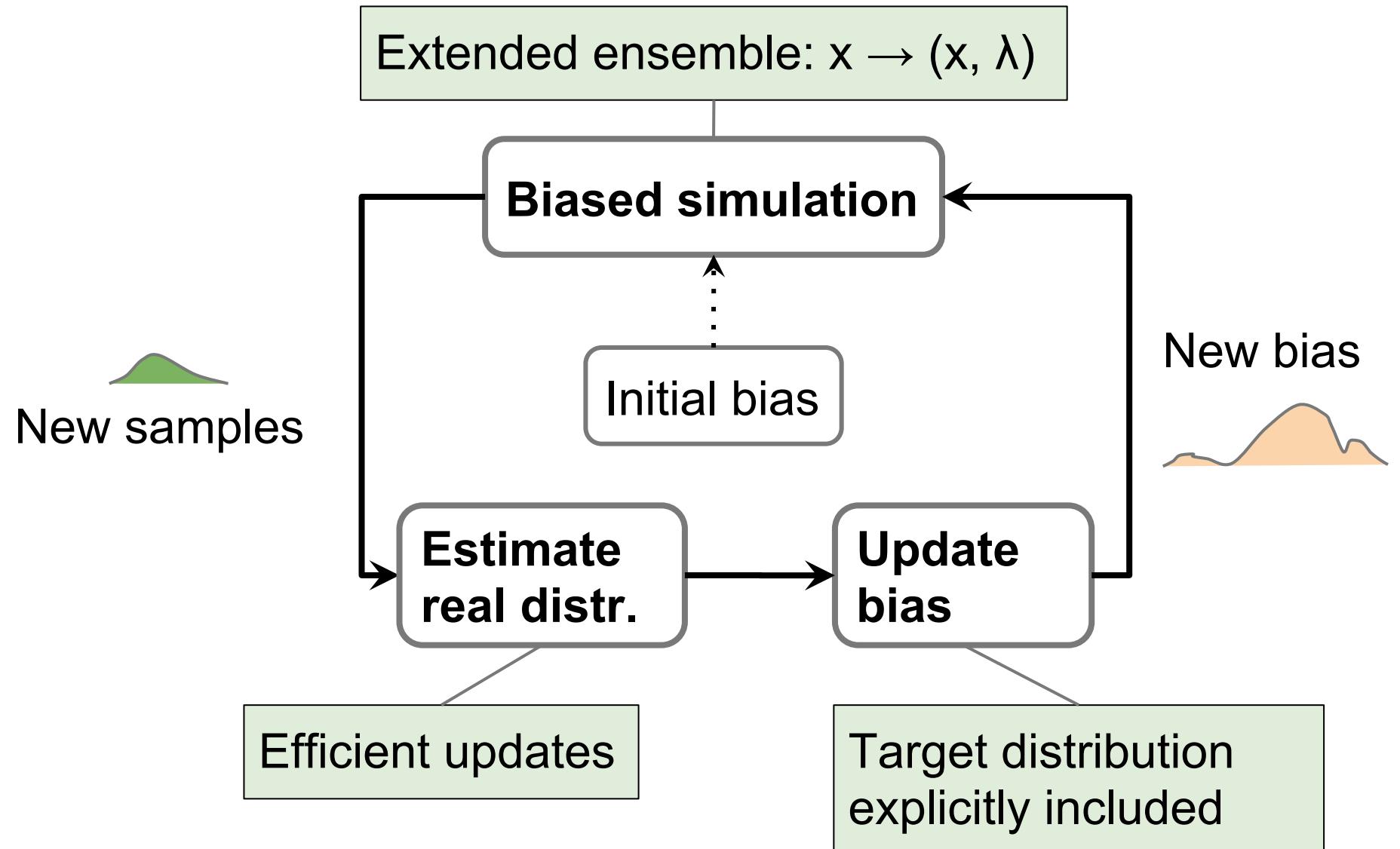


# Adaptive biasing

The general procedure:



# AWH: the accelerated weight histogram method



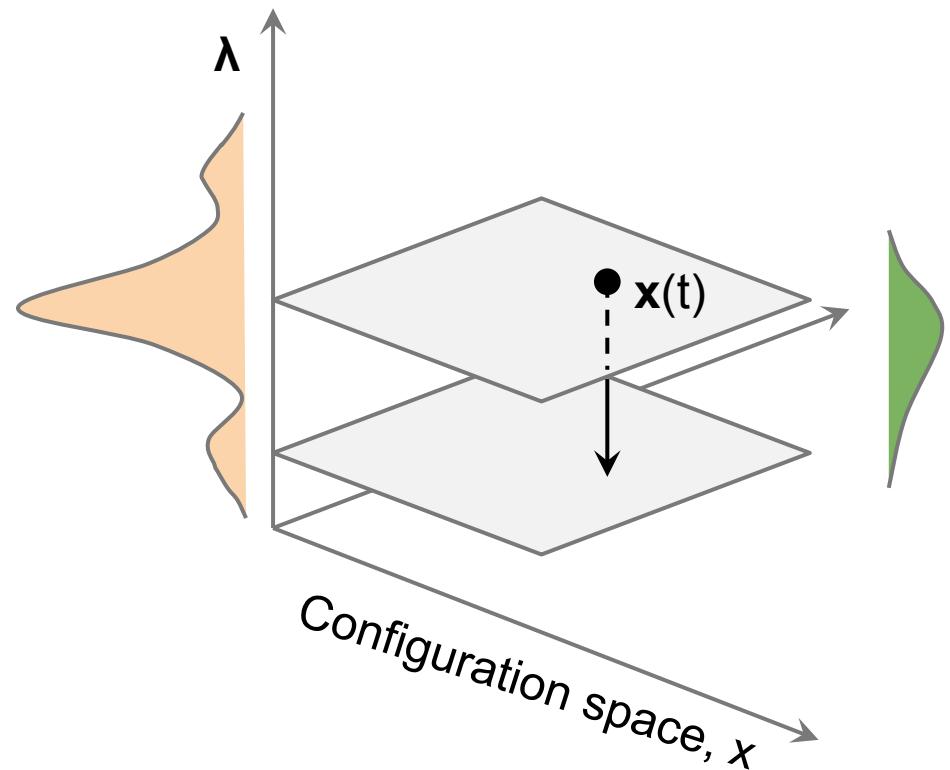
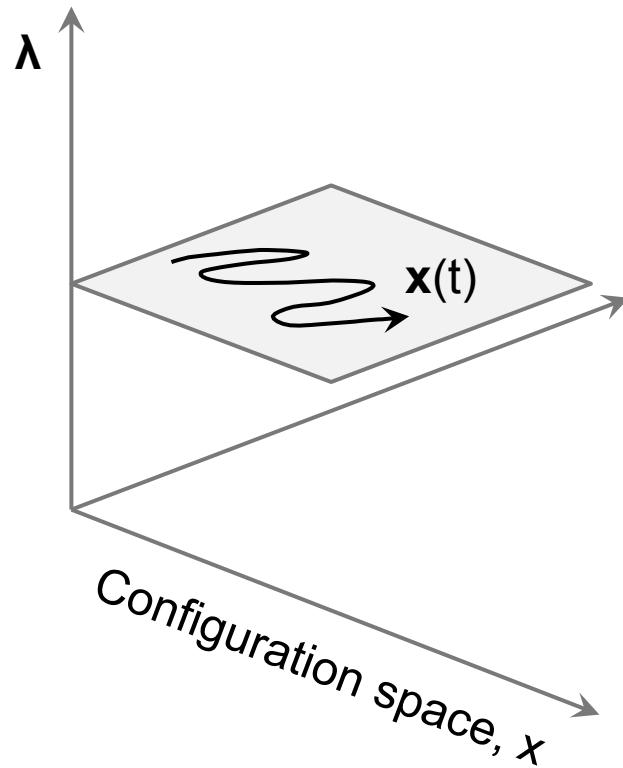
# AWH: the accelerated weight histogram method

Simulating in the extended ensemble

Update  $(x, \lambda)$ . Alternate:

1) molecular dynamics in  $x$

2) biased Monte-Carlo in  $\lambda$



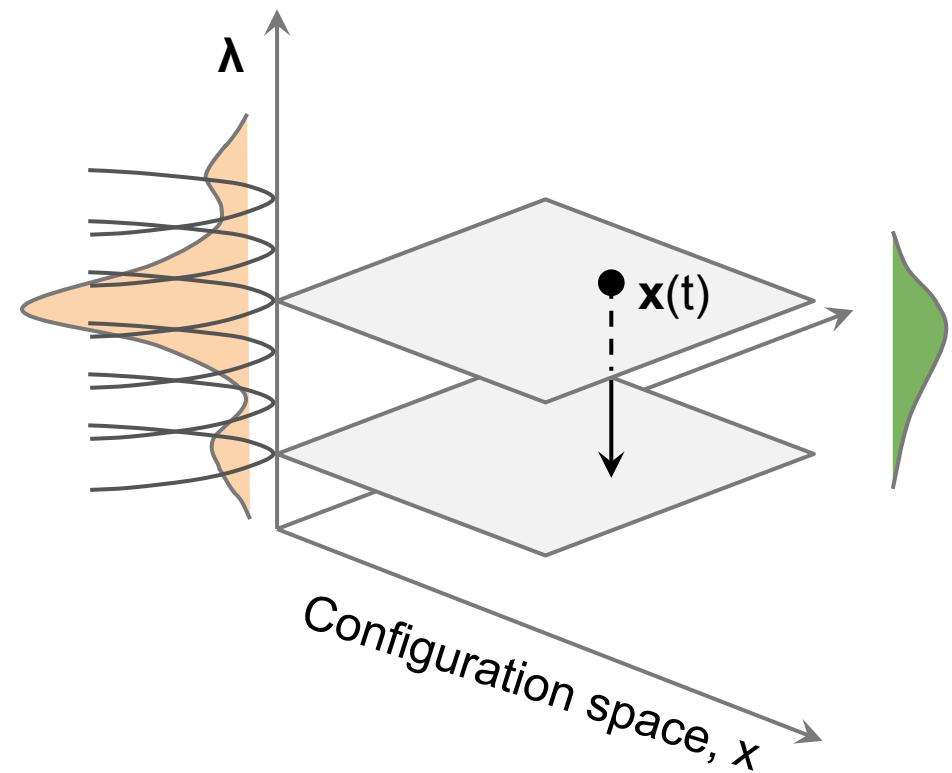
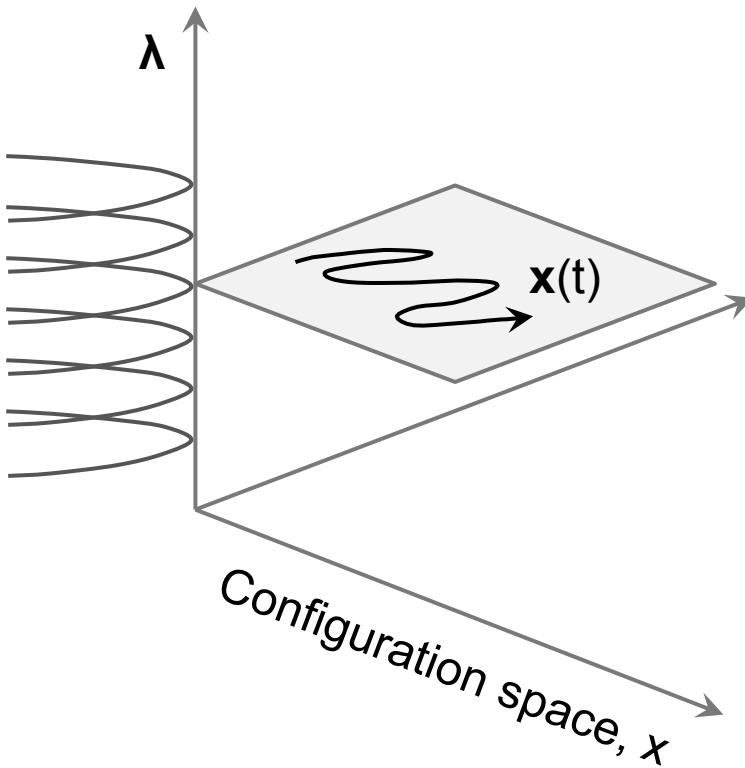
# AWH: the accelerated weight histogram method

Reaction coordinate case

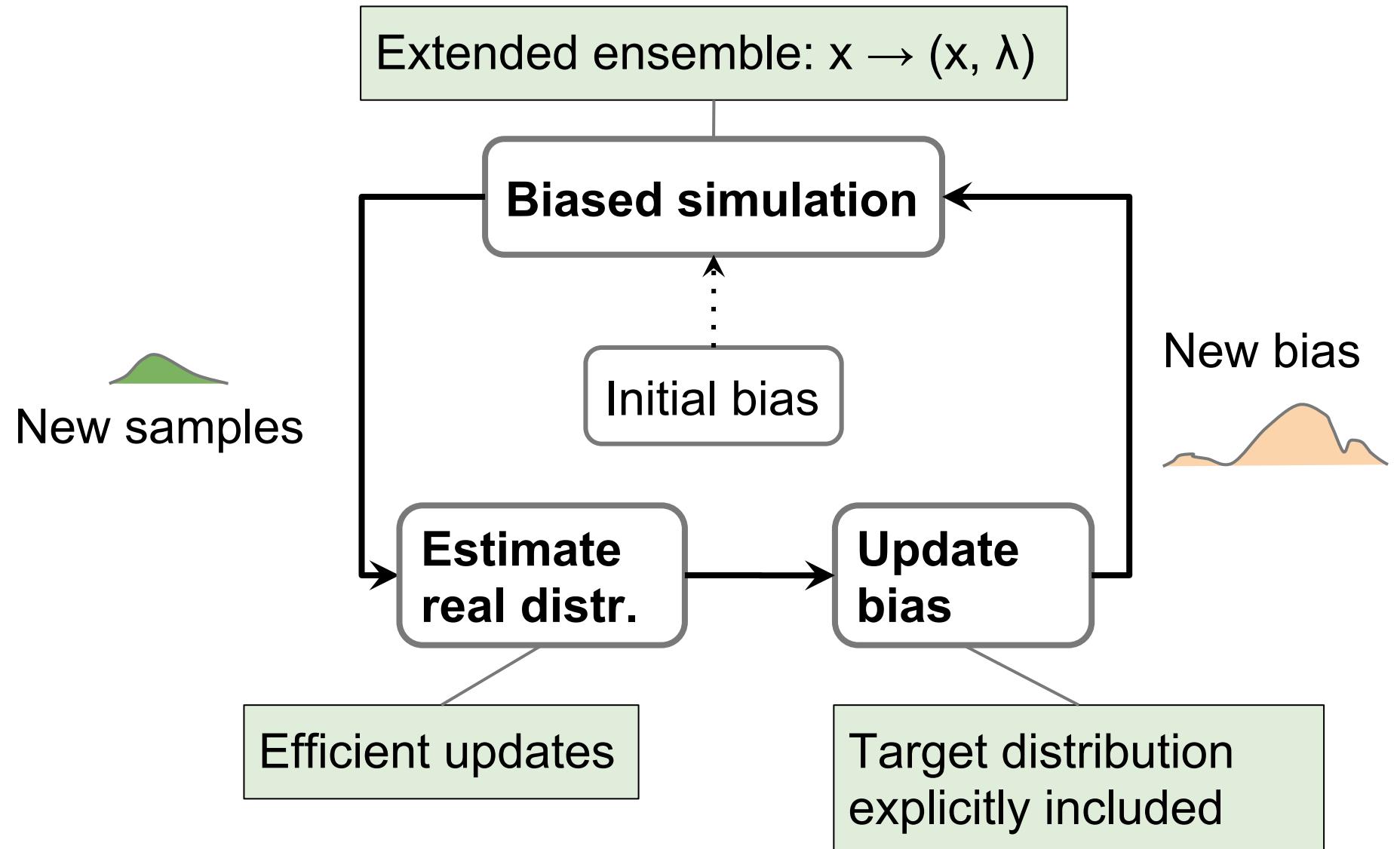
Updating  $\lambda \Leftrightarrow$  **pulling** reaction coordinate

...but not with constant rate!

or alternatively convolve all umbrella (Gaussians like metaD)



# AWH: the accelerated weight histogram method



# Exponential-linear weight decrease or automated time tuning

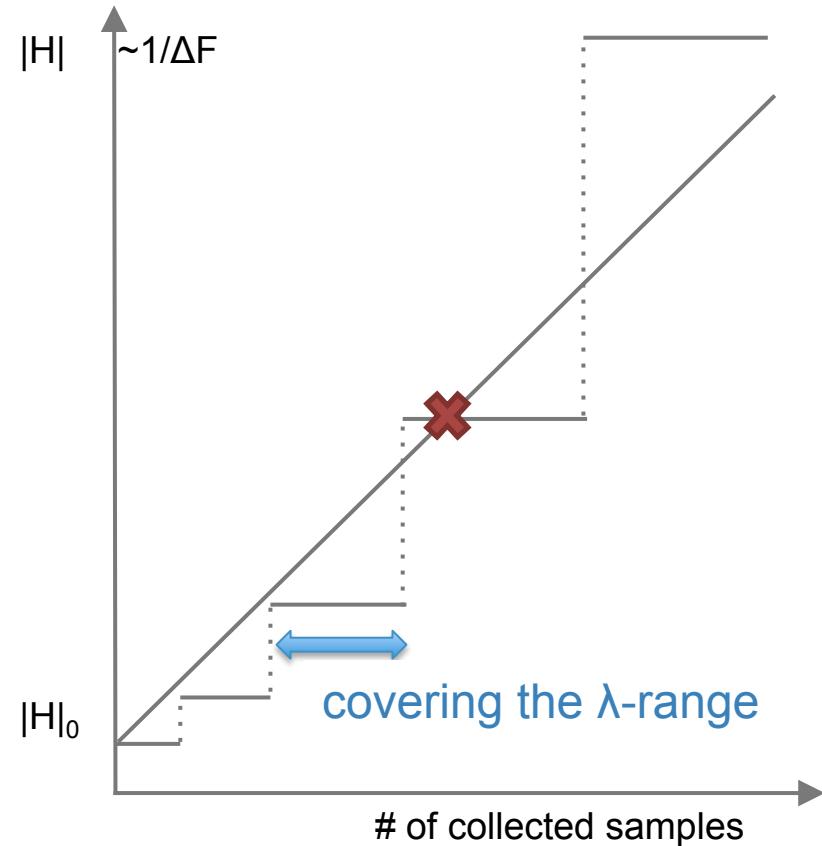
Initial phase:

- Constant update size
- When range covered, halve the update size (Wang-Landau)

Final phase:

- Update size  $1/\# \text{samples}$

Switch when weight (in samples) crosses the real collected samples



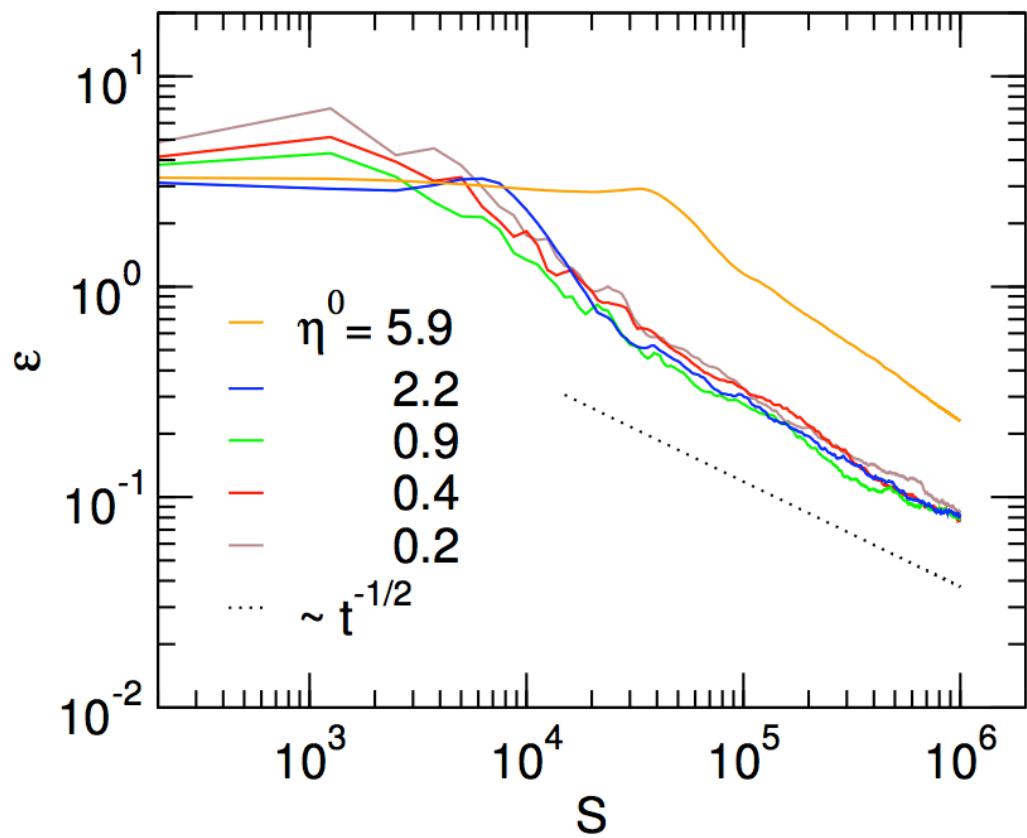
# Convergence

Only one parameter:  
the initial update size  
or equiv. initial weight

We set this using two physical parameters:

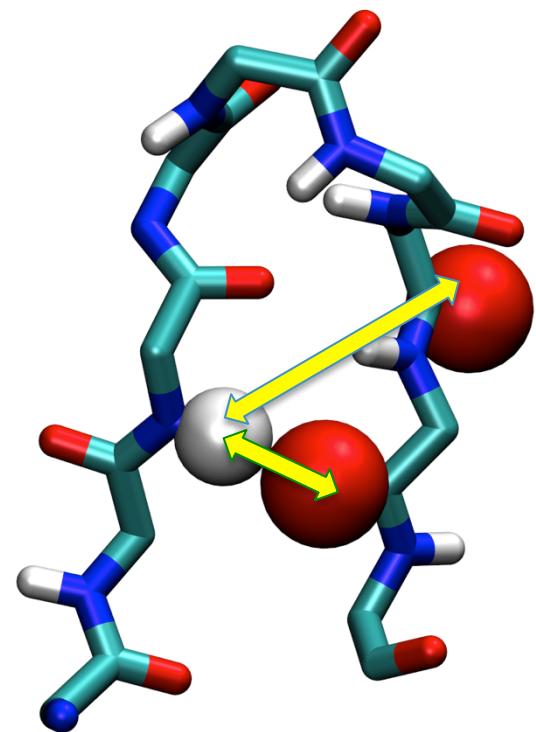
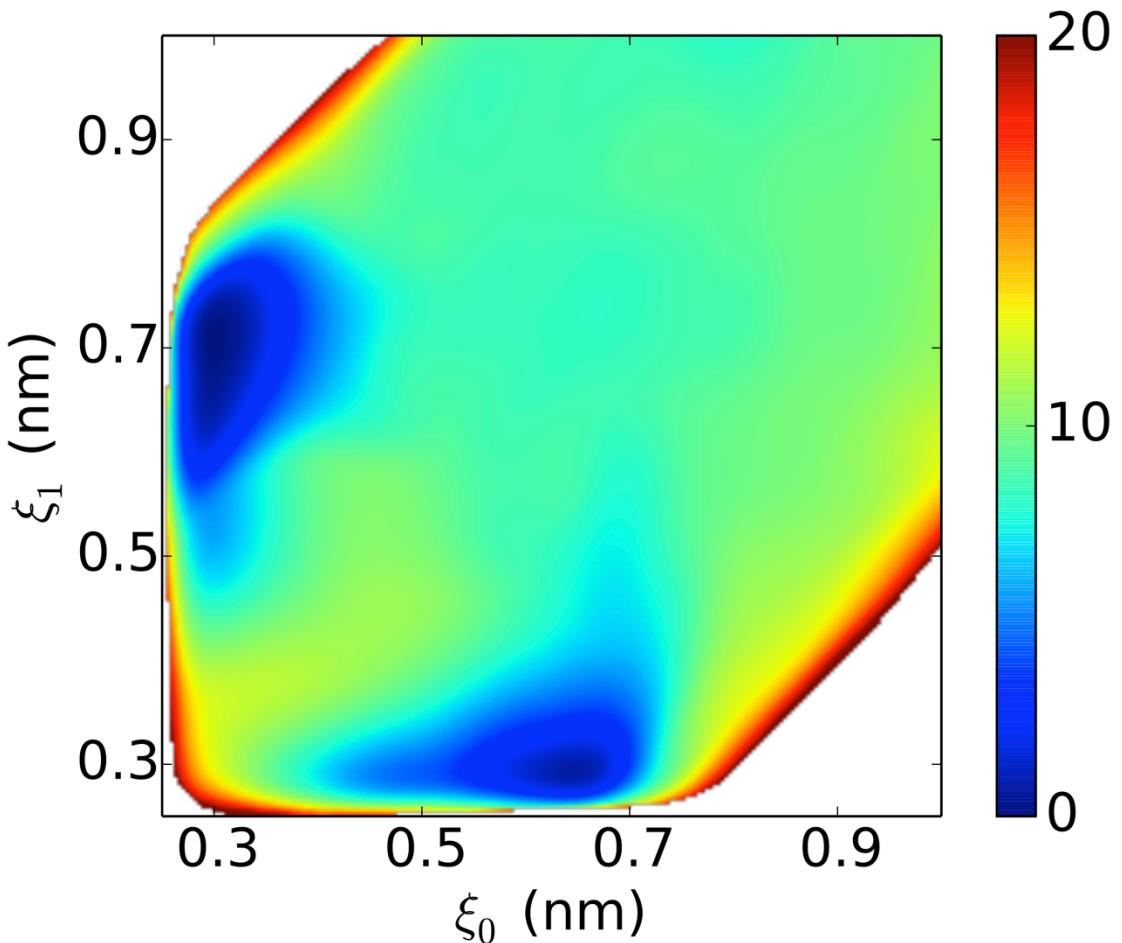
- the initial error
- the diffusion coeff.

Error insensitive to initial update size, if not too small



# Choosing the target distribution

Avoid “unphysical” regions (very high free energy)

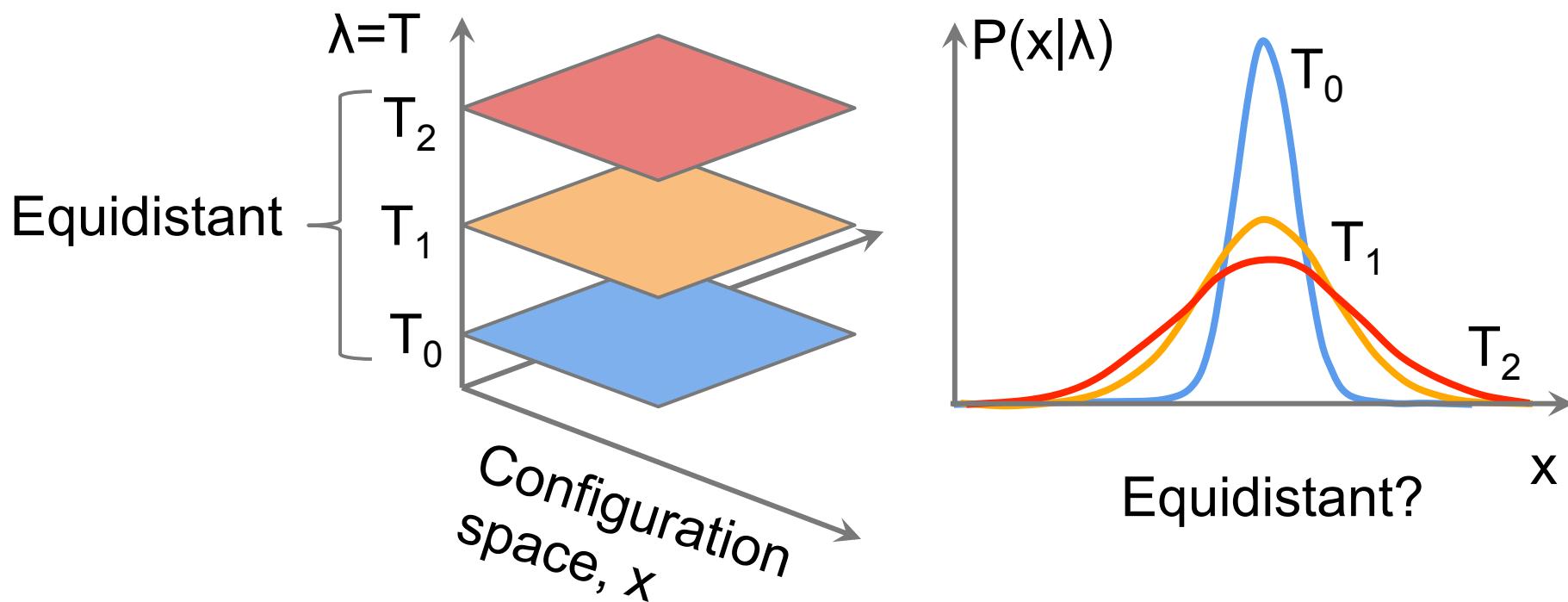


# Choosing the target distribution

Uniform distribution is generally not optimal

Would like sample more in regions where:

- $P(x|\lambda)$  changes a lot with  $\lambda$  (small overlap)
- $\lambda$  diffuses slowly (dynamic bottleneck)



# Choosing the target distribution

Our suggestion for measuring importance in  $\lambda$  space

The friction tensor  $g(\lambda)$ :

Conjugate force to  $\lambda = -dE/d\lambda$

$$g_{ij}(\lambda) = \beta \int_0^\infty \langle \delta \mathcal{F}_i(\tau) \delta \mathcal{F}_j(0) \rangle_\lambda d\tau$$

is a proper thermodynamic metric<sup>1</sup>.

# Choosing the target distribution

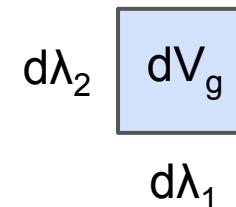
Our suggestion for measuring importance in  $\lambda$  space

The friction tensor  $g(\lambda)$ :

Conjugate force to  $\lambda = -dE/d\lambda$

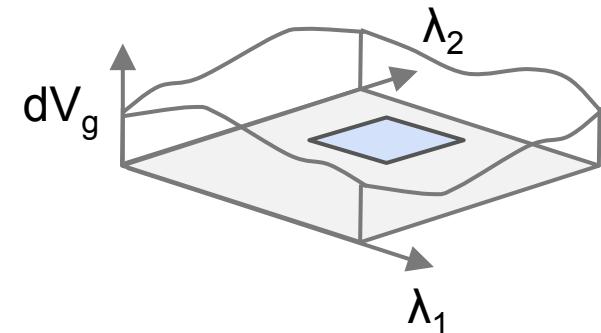
$$g_{ij}(\lambda) = \beta \int_0^\infty \langle \delta \mathcal{F}_i(\tau) \delta \mathcal{F}_j(0) \rangle_\lambda d\tau$$

is a proper thermodynamic metric<sup>1</sup>.



Uniform distribution with this metric:

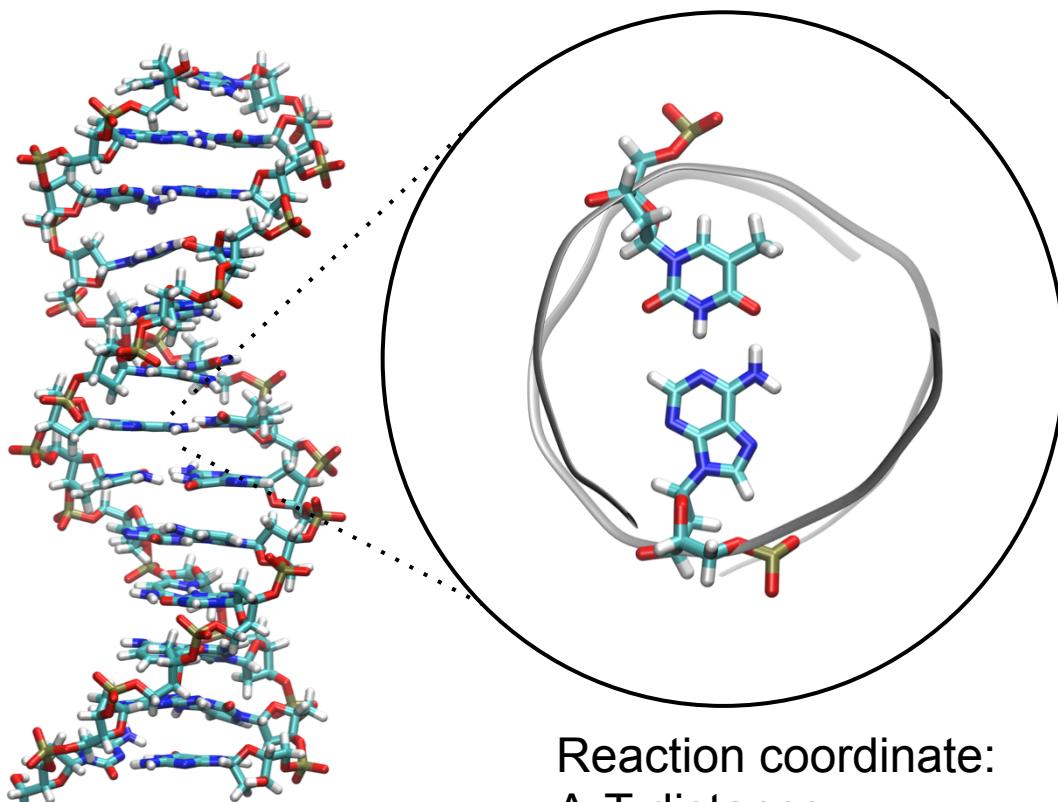
$$\rho_{\text{target}}(\lambda) = \sqrt{\det g(\lambda)}$$



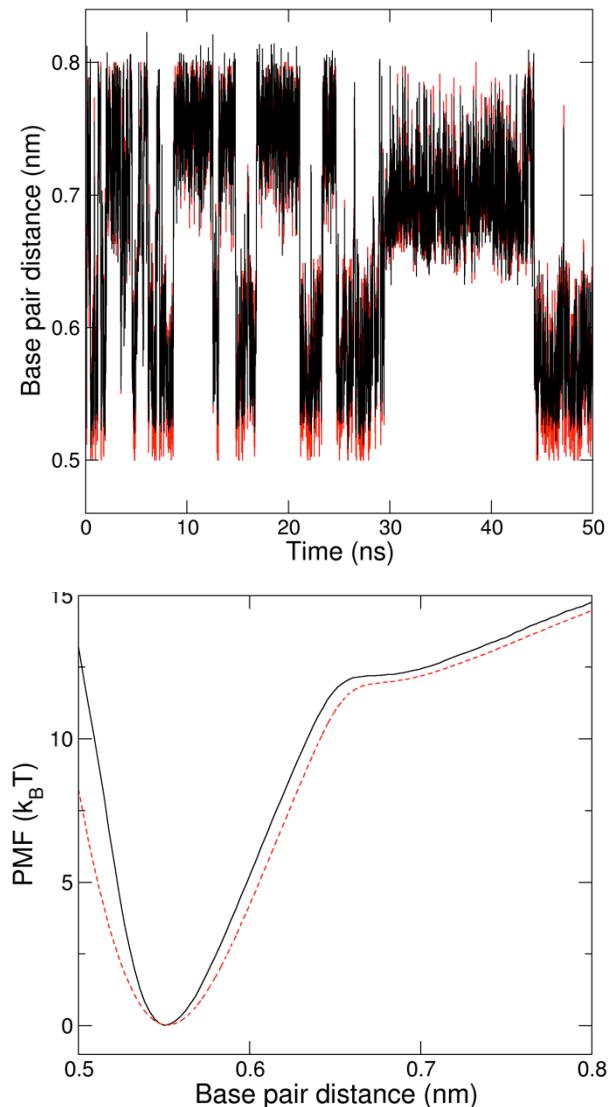
# Ex: DNA base pair flipping with AWH

Flat target distribution

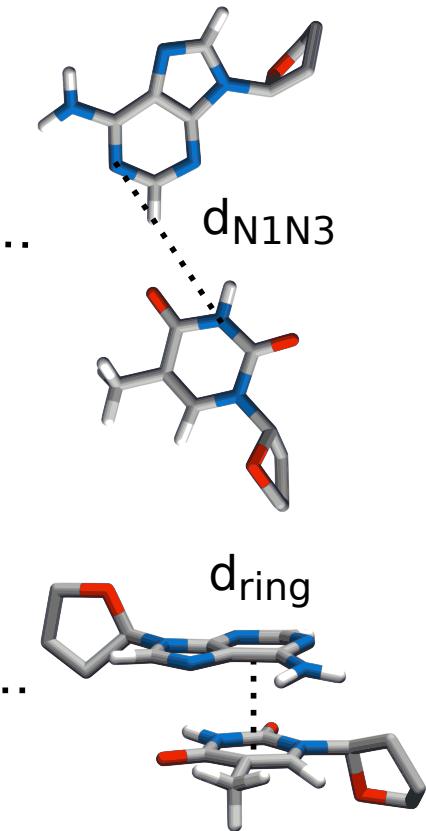
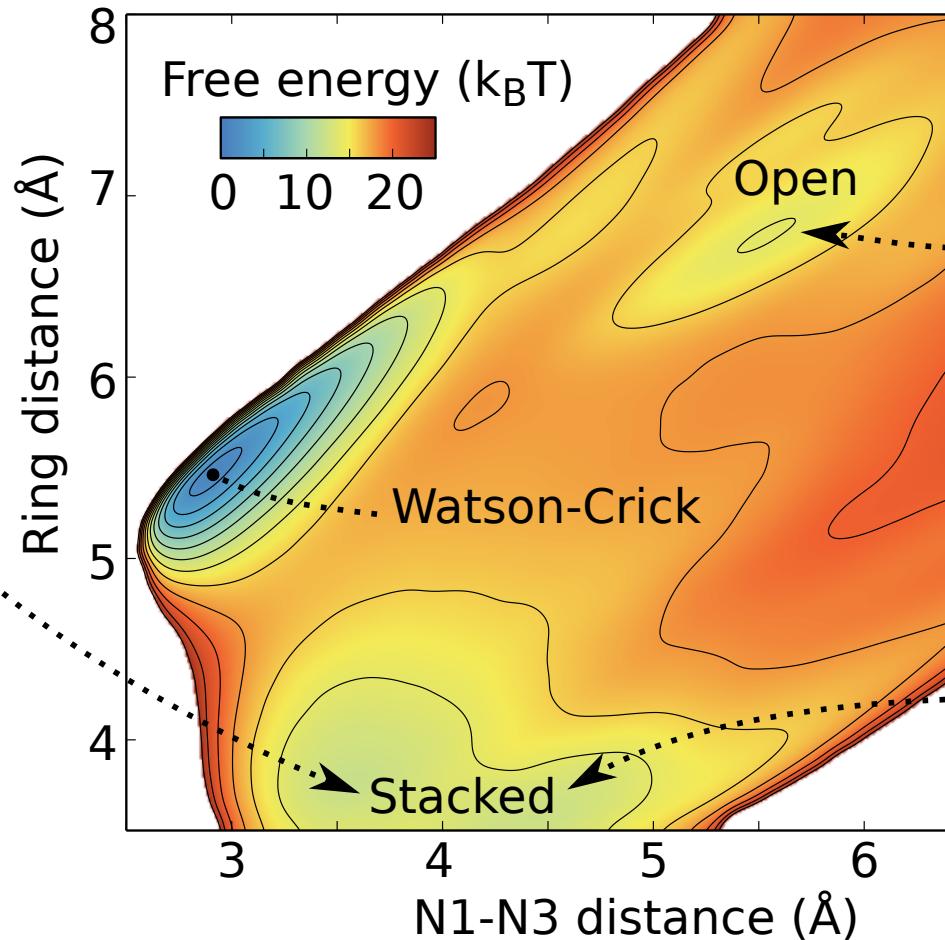
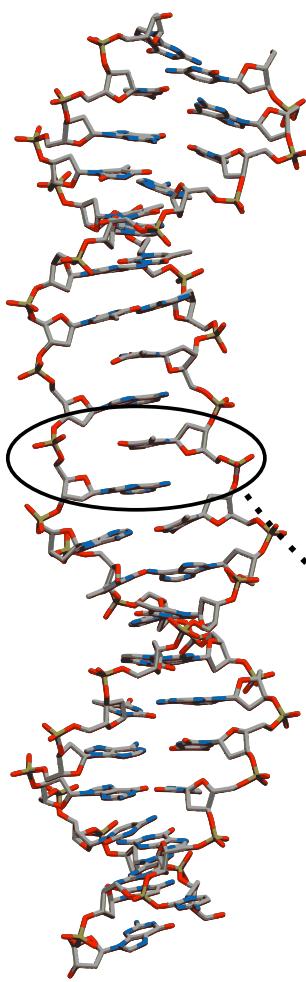
How does sequence affect  
base-pair flipping?



Reaction coordinate:  
A-T distance



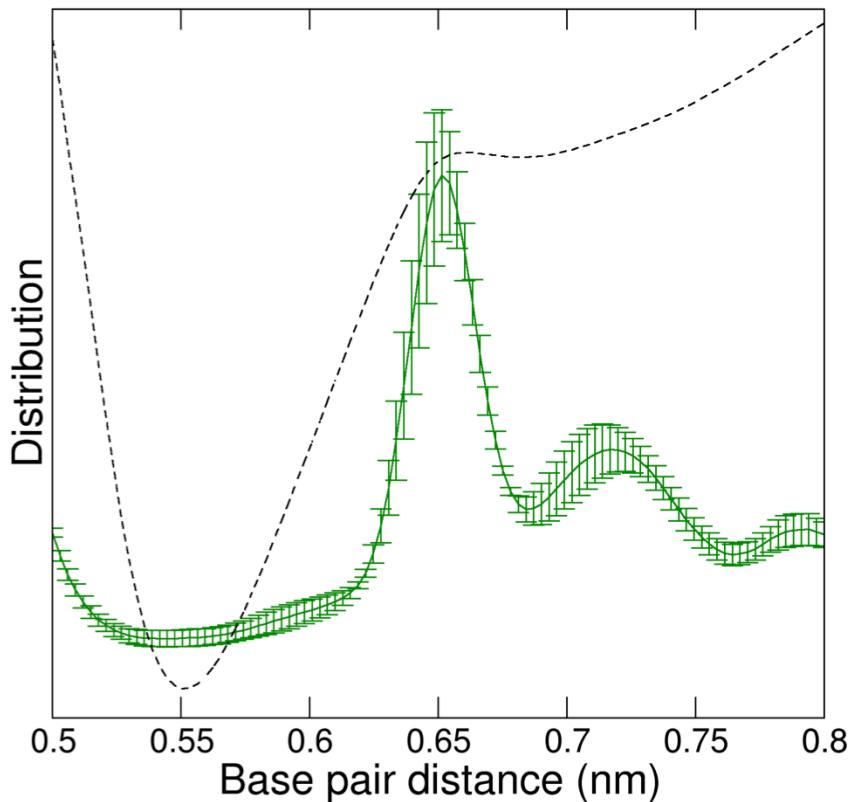
# 2D reaction coordinate



# Ex: DNA base pair flipping with AWH

Friction optimized target distribution – is it useful?

Optimized target distribution



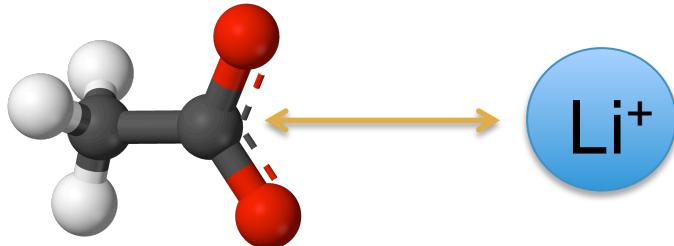
Sampling enhancement

	<b>Round-trips (1/ns)</b>	<b>PMF error (<math>k_B T</math>)</b>
<b>Flat</b>	$0.9 \pm 0.3$	0.9
<b>Optim.</b>	$1.5 \pm 0.3$	0.3
<b>Ratios</b>	~2	~3

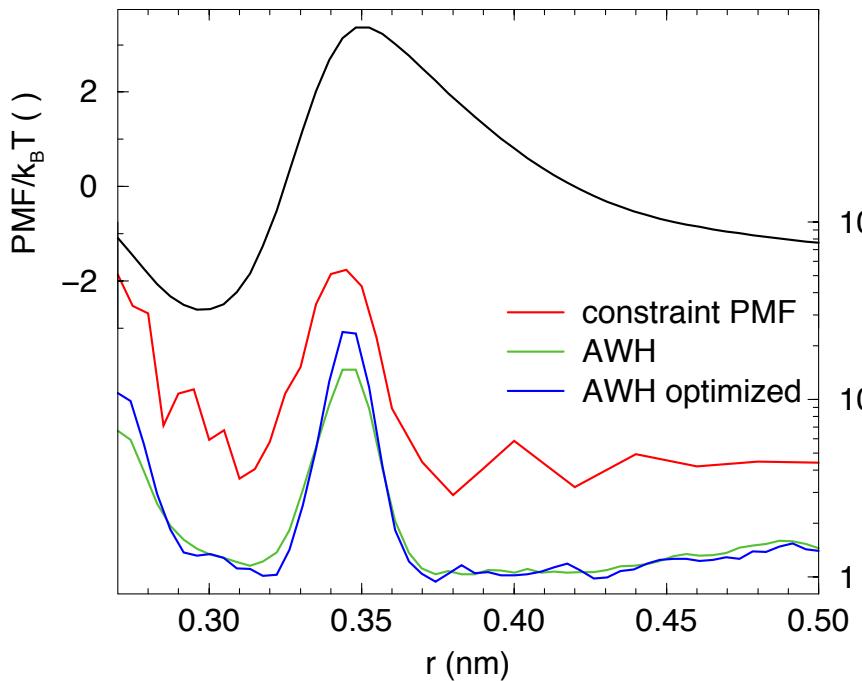
16 seeds x 50 ns

# Compare constraint/umbrella - AWH

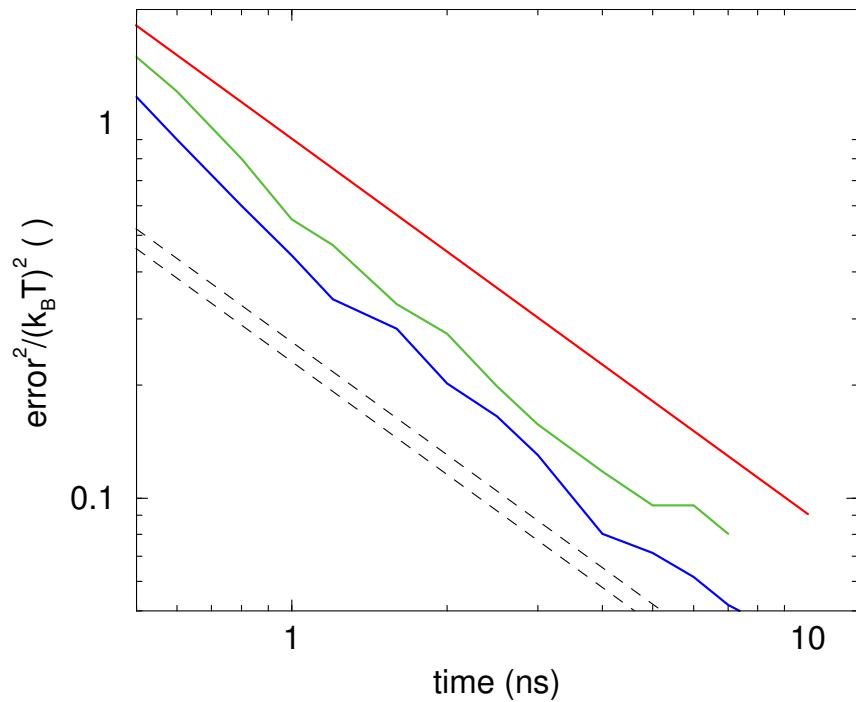
Distance  $\text{Li}^+ - \text{Ace}^-$



PMF & force autocorrelation



Accuracy comparison



# How to set it up?

```
pull                      = yes
pull_ngroups               = 2
pull_ncoords                = 1
pull-group1-name            = Li
pull-group2-name            = Cl
pull-coord1-groups          = 1 2
pull-coord1-type             = external-potential
pull-coord1-potential-provider = AWH
pull-coord1-geometry          = distance
pull-coord1-k                  = 128000

awh                      = yes
awh1-ndim                 = 1
awh1-dim1-pull-coord        = 1
awh1-dim1-start              = 0.27
awh1-dim1-end                  = 0.50
awh1-dim1-diffusion           = 2e-4
awh1-error-init                = 2.0
```

# Conclusions and outlook

**AWH:** an extended ensemble method adaptively “pulling”  
along a system parameter or reaction coordinate

A flat target distribution is non-optimal

The **friction metric optimized target distribution** can  
improve sampling

# Acknowledgements

Dr. Berk Hess, KTH

Dr. Jack Lidmar, KTH

Prof. Erik Lindahl, KTH

Dr. Alessandra Villa, KI

# **Try it out!**

AWH is branched from GROMACS

Later: official GROMACS release

Now: development code available at:

[bitbucket.org:vivecalindahl/awh-gromacs-open.git](https://bitbucket.org/vivecalindahl/awh-gromacs-open.git)

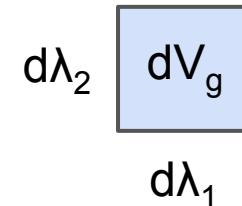
# **Thank you for listening!**

# Choosing the target distribution

How should we measure distances in  $\lambda$  space?

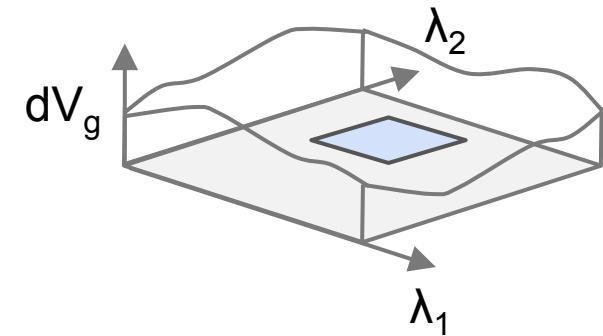
We can now measure probabilities (integrate)

$$dP(\lambda) = \rho_g(\lambda) dV_g(\lambda) = \rho(\lambda) d\lambda_1 \dots d\lambda_n$$



Volume element:

$$dV_g(\lambda) = \sqrt{\det g(\lambda)} d\lambda_1 \dots d\lambda_n$$



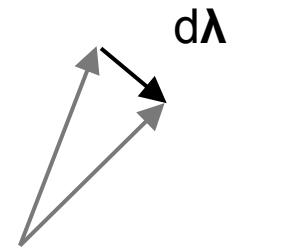
Flat target distribution with respect to this metric  $\Leftrightarrow$

$$\rho(\lambda) \propto \sqrt{\det g(\lambda)} = \sqrt{\text{friction}(\lambda)}$$

# Choosing the target distribution

How should we measure distances in  $\lambda$  space?

- A local measure of “resistance” (friction) to changes  $\lambda$
- Closely related to the Fisher information metric
- Includes dynamics


$$ds^2 = g_{ij} d\lambda_i d\lambda_j$$