The PLUMED plugin and free energy methods in electronic-structure-based molecular dynamics

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Outline

- What is free energy and why is important
- Traditional QC approach
- Explicit sampling
- Enhanced sampling
- PLUMED plugin for free energy calculations

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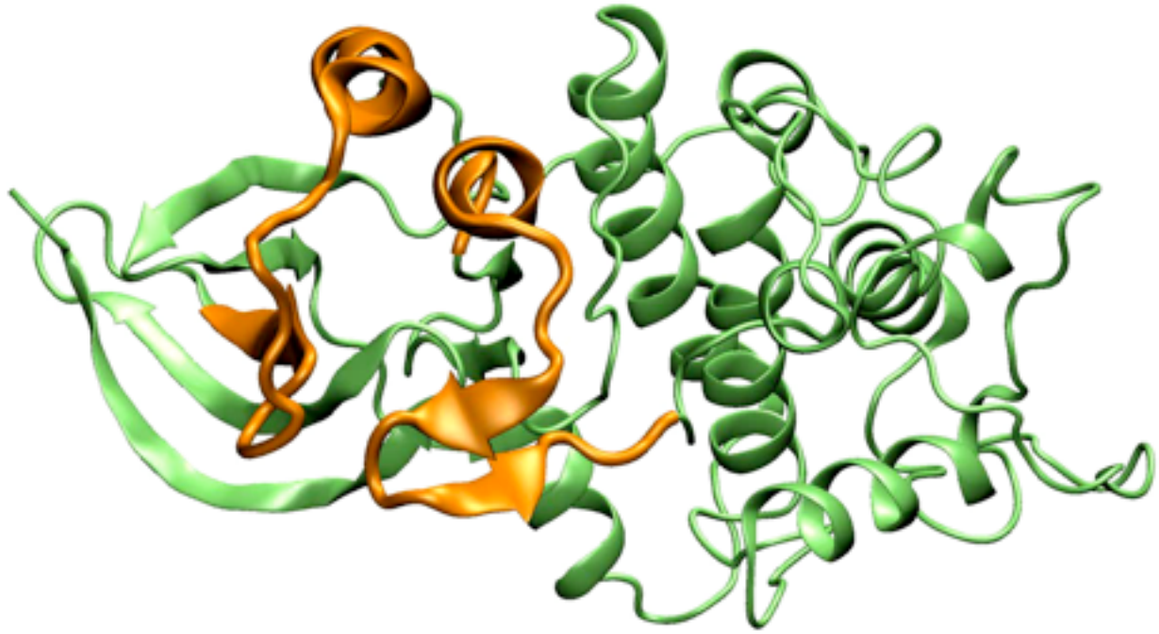
What is free energy and why is important

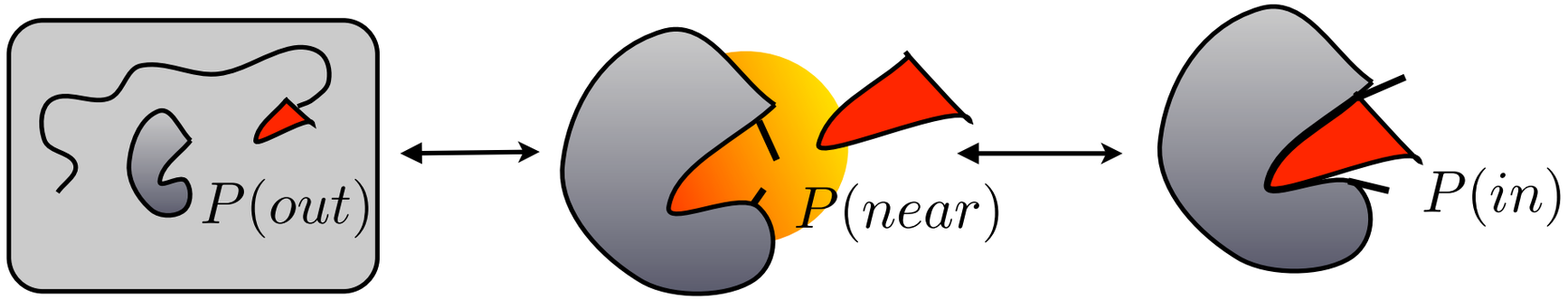
$$F(s) = -k_B T \ln P(s)$$

s= state descriptor (bound/unbound, reactant/products, phaseA/phaseB)

$$P(s) = \frac{\int e^{-\frac{V(x)}{k_b T}} \delta(s'(x) - s) dx}{Q}$$

* conformational transitions and equilibria
* ligand binding
* mechanism of transporters or channels
* chemical reactions and catalysis
* phase transitions
* .....





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Traditional QC approach

* Rigid rotor/ harmonic approximation is well known [1]

$$F(s) = H(s) - TS(s)$$

$$S(s) = R + R\ln\boxed{(q_t(s)q_e(s)q_r(s)q_v(s))} + RT\left(\frac{\partial \ln \boxed{q_t(s)q_e(s)q_r(s)q_v(s)}}{\partial T}\right)$$

trasl, elect, rot, vib partition functions

where the partition functions are obtained from the calculated vibrational spectrum (Hessian), moments of inertia, electronic structure

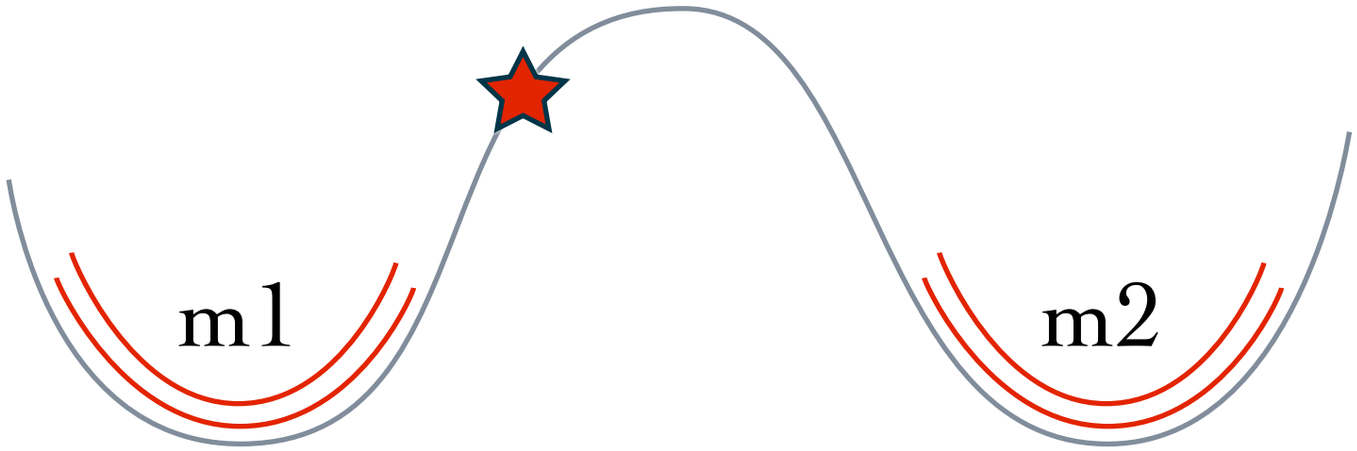
$$H(s) = H_{el}(s) + H_t(s) + H_v(s) + H_r(s)$$

* It requires electronic structure and Hessian in the local minima and transition states: 1 single conformation per state.

[1] McQuarrie, Simon “Physical Chemistry, a molecular approach”

Finding the RC (I)

- Static approach: look for saddle points by using chemical intuition and TS optimization.



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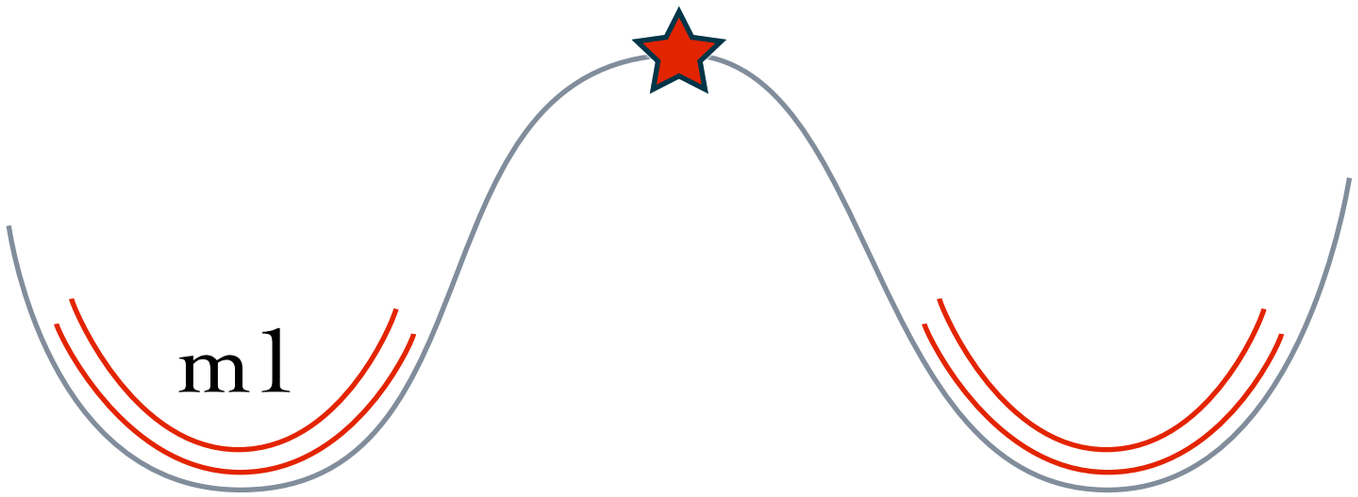

- Verify then by IRC: move forward and backward to verify to end in minima.

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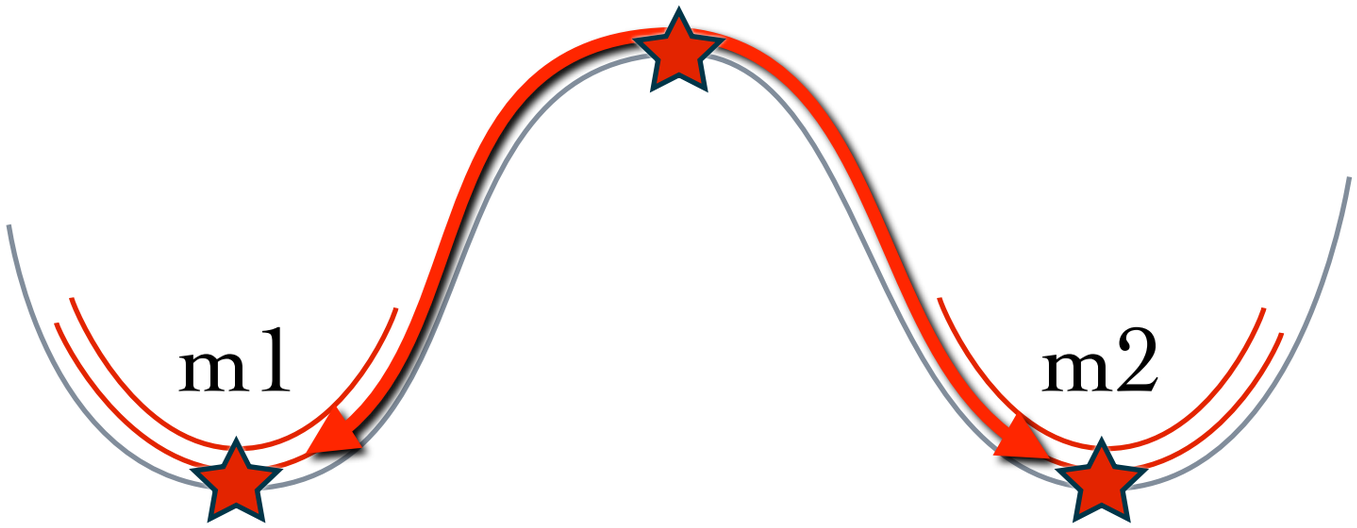

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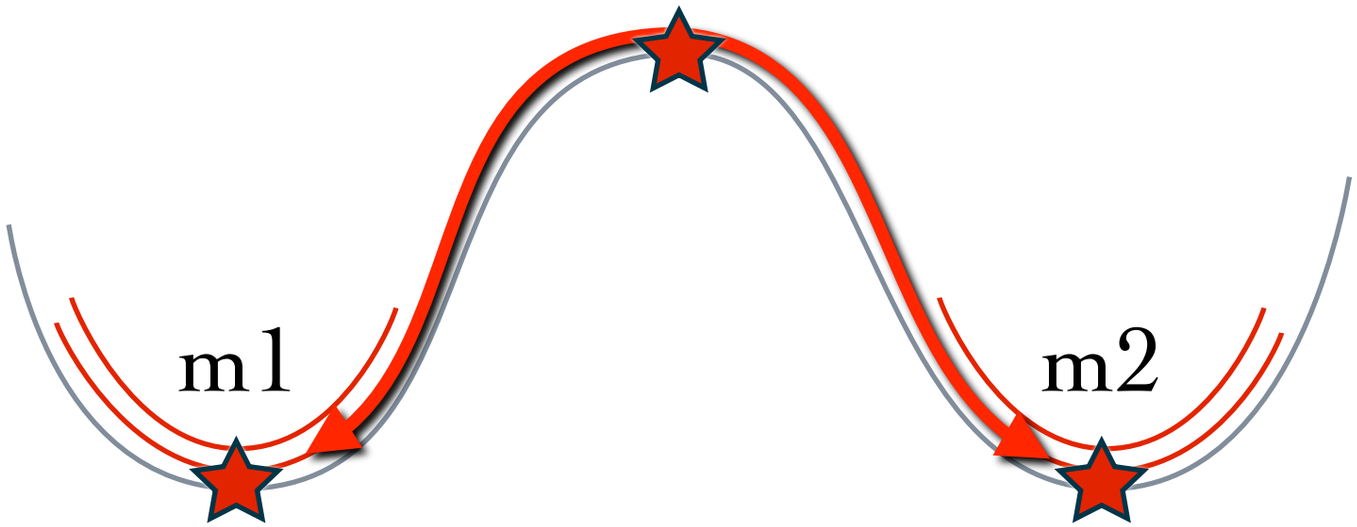


- Verify then by IRC: move forward and backward to verify to end in minima.

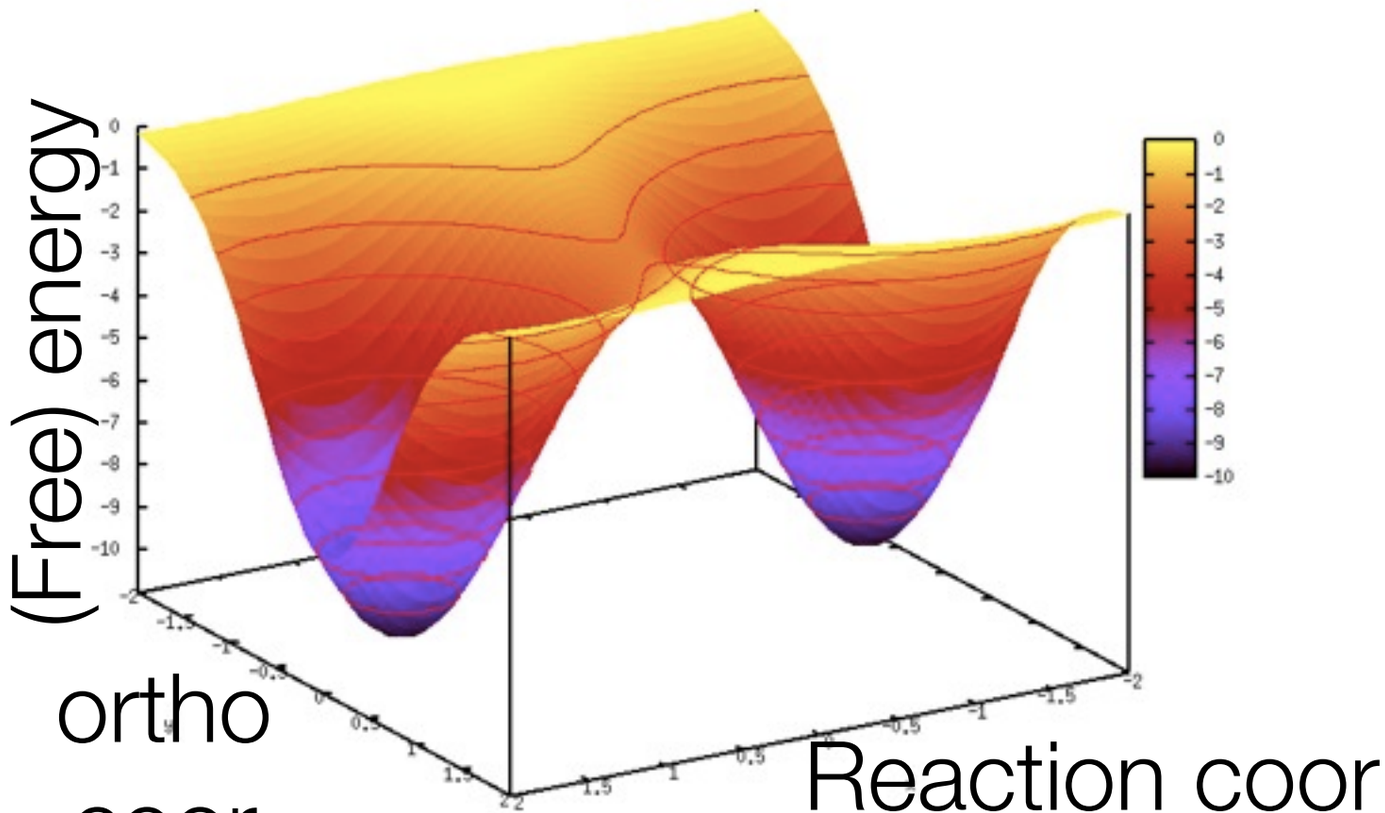
$$\Delta^{\ddagger}G = \Delta^{\ddagger}H - T\Delta^{\ddagger}S$$

- Rates may be derived from Eyring equation[2]: $k(T) = \frac{k_b T}{hc^0} e^{-\Delta^{\ddagger}G/RT}$

[2] Eyring, Chem. Rev. 1935 vol. 17 pp 65

Traditional QC approach

* PRO: one calculation per point (3 single points calculations per rate and free energy differences)
* CONS: optimizing TS is not trivial (redundant coordinates), the landscape must be very simple



Problems with traditional QC approach

* Many problems are not smooth as before: many parallel valleys (conformers), solvent induced roughness

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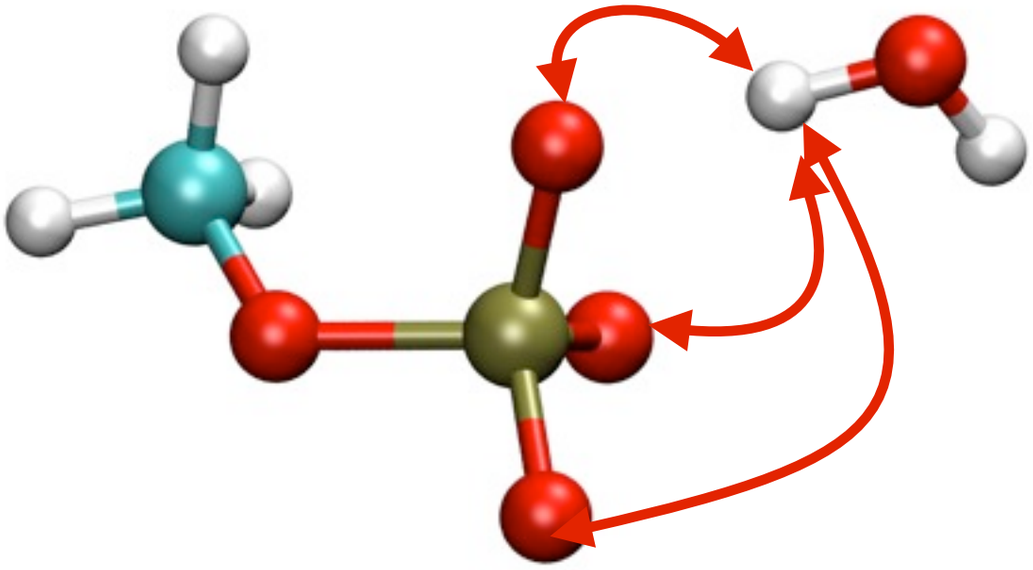

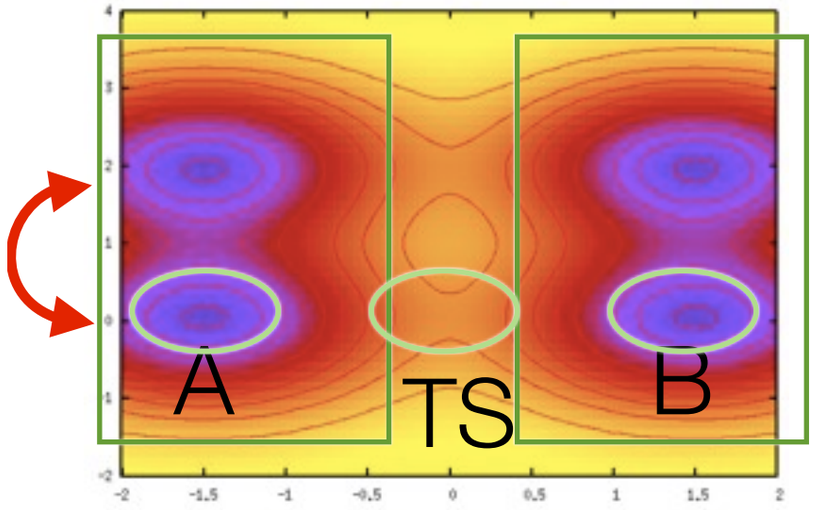

Perfectly parallel basins,
Not too bad
(small correction over
static approaches).
Typical case of symmetry
in a reaction

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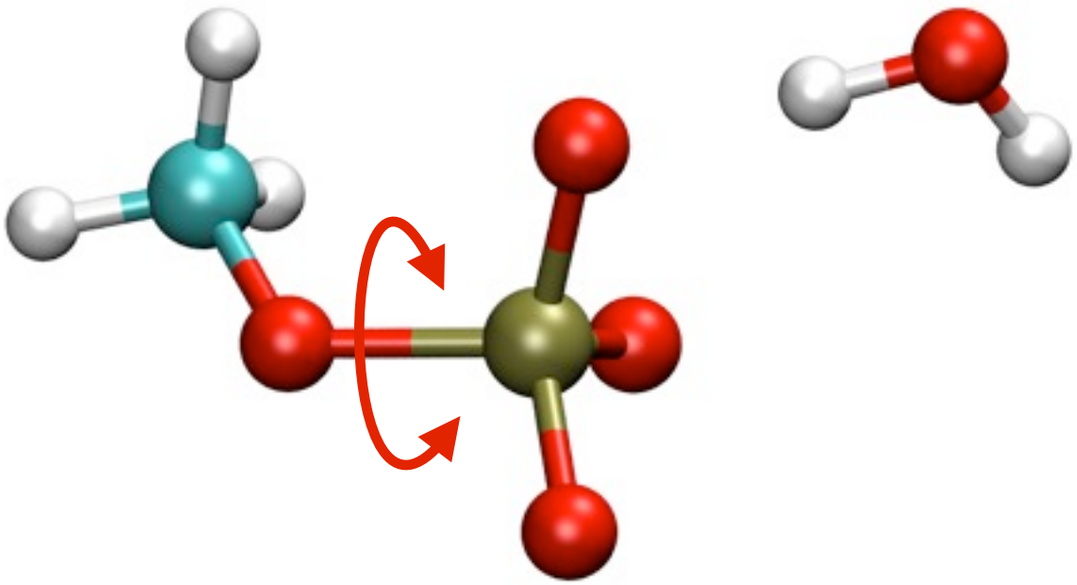

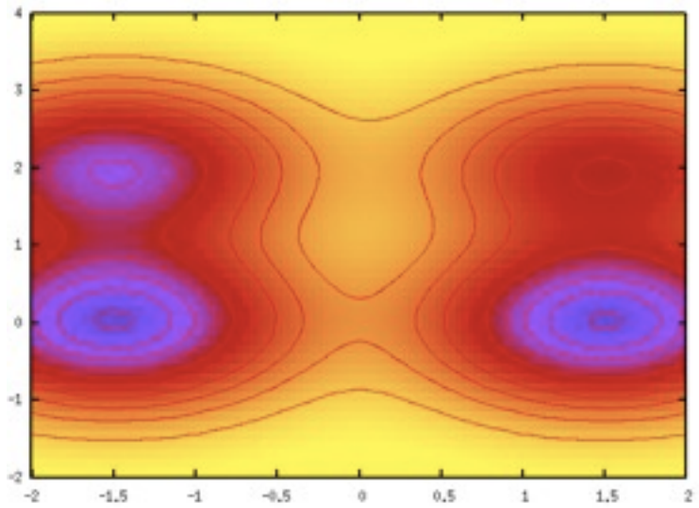

Perfectly parallel basins but energetically asymmetric,
Can be done with static QC but need to sample all the paths

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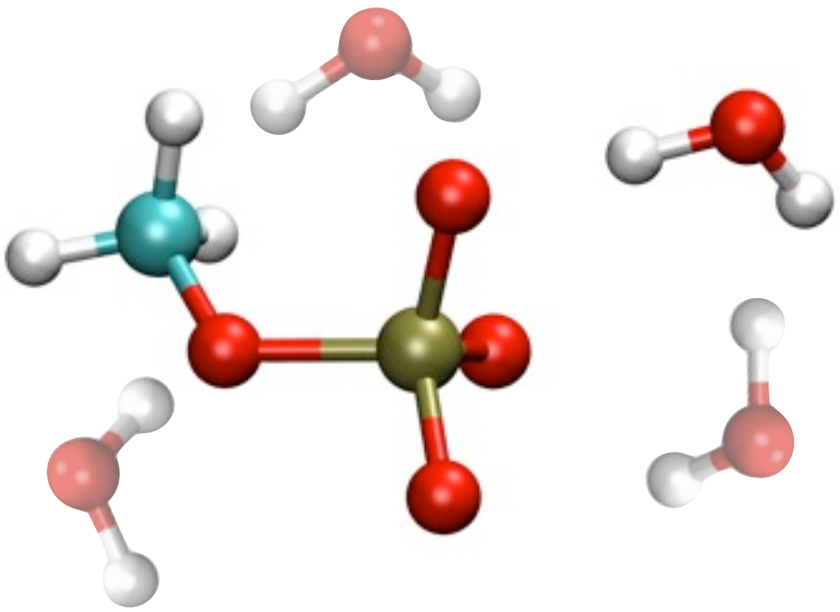

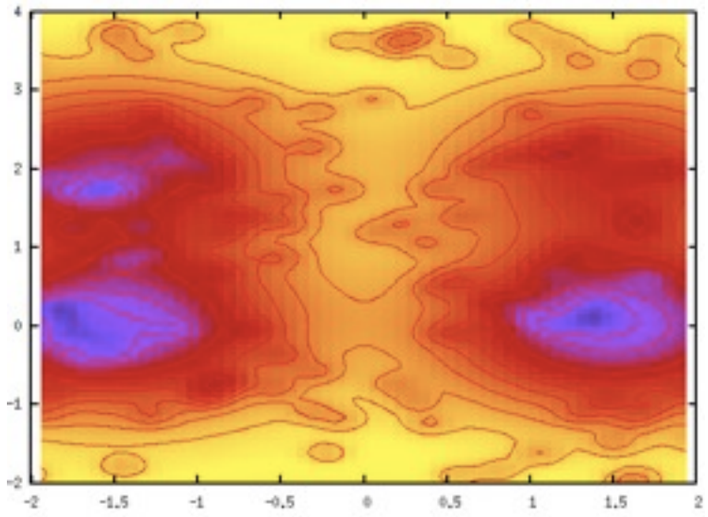

Rough paths: vibrations are meaningless, paths from IRC are not representative of reactions:

USE MD BASED METHODS

Problems with traditional QC approach

* Many problems are not smooth as before: many parallel valleys (conformers), solvent induced roughness

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- **Explicit sampling**
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The ingredients of the probability picture

* Free energy is connected to the probability of a given state to occur in a single measurement

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

Probability

$$P(s) = \frac{\int e^{-\frac{V(x)}{k_B T}} \delta(s'(x) - s) dx}{\int e^{-\frac{V(x)}{k_B T}} dx}$$

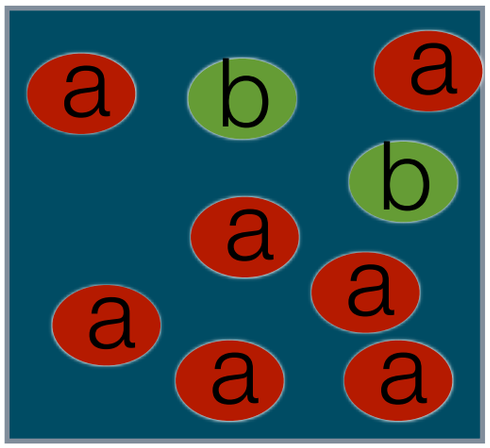
State descriptor

(bond length, folded/ unfolded descr., liquid/ crystal/amorphous)

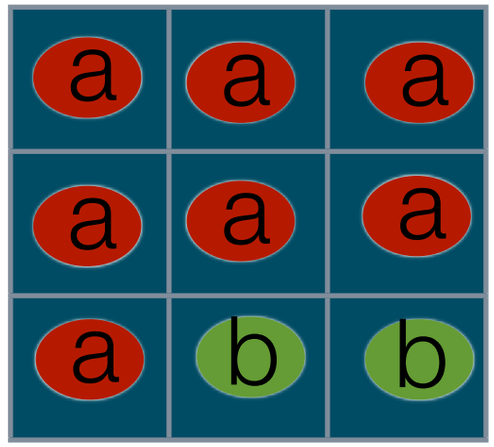
Explicit sampling via molecular dynamics

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

a real system (cuvette)

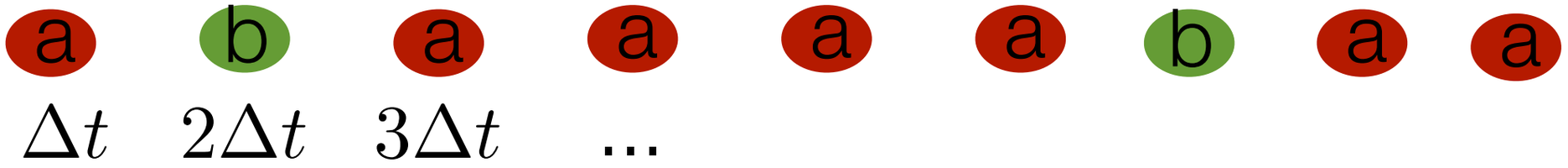


a set of independent objects (ensemble)



MD: evolve in time with Newton's eq. of motion

use ergodic hypothesis

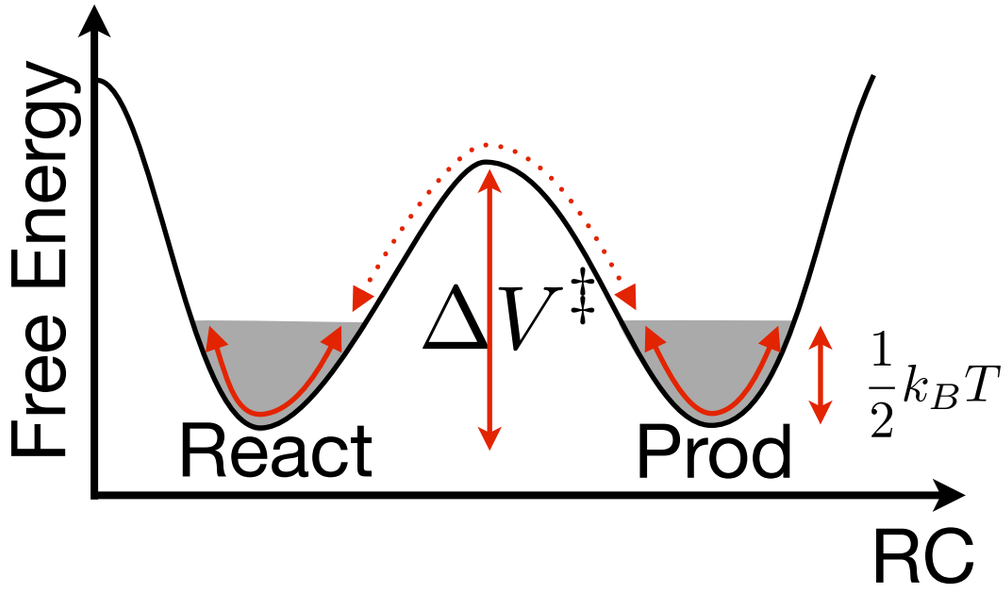


$P(s)$

all the available states can be sampled with t->infinite

Limitations

* Transition of 8 kcal/mol can take up to milliseconds at 300K



$$\nu = \nu_0 \exp\left(-\beta \Delta V^{\ddagger}\right)$$

$$\nu_0 = 5\ 10^9 s^{-1}$$

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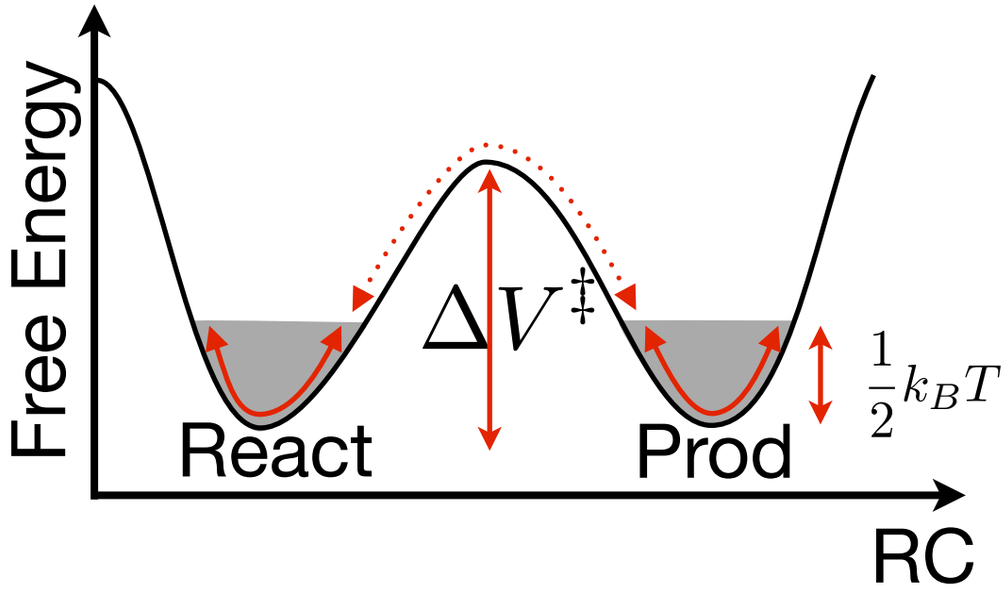

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* MD (DFT) can reach hundreds of ps.
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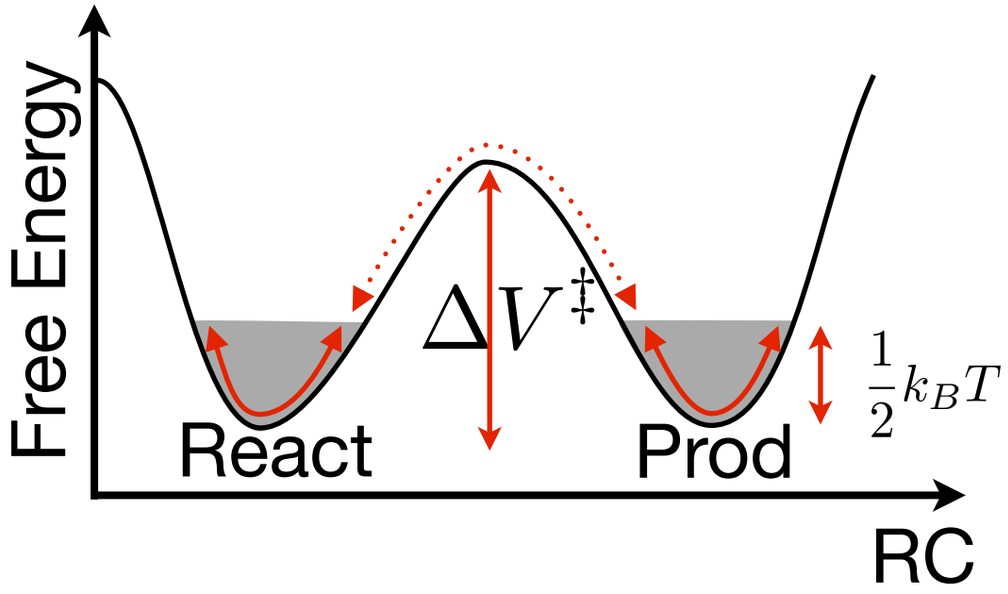

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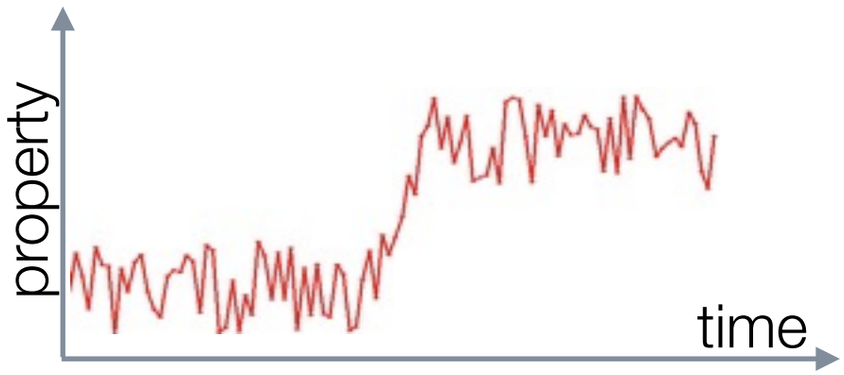

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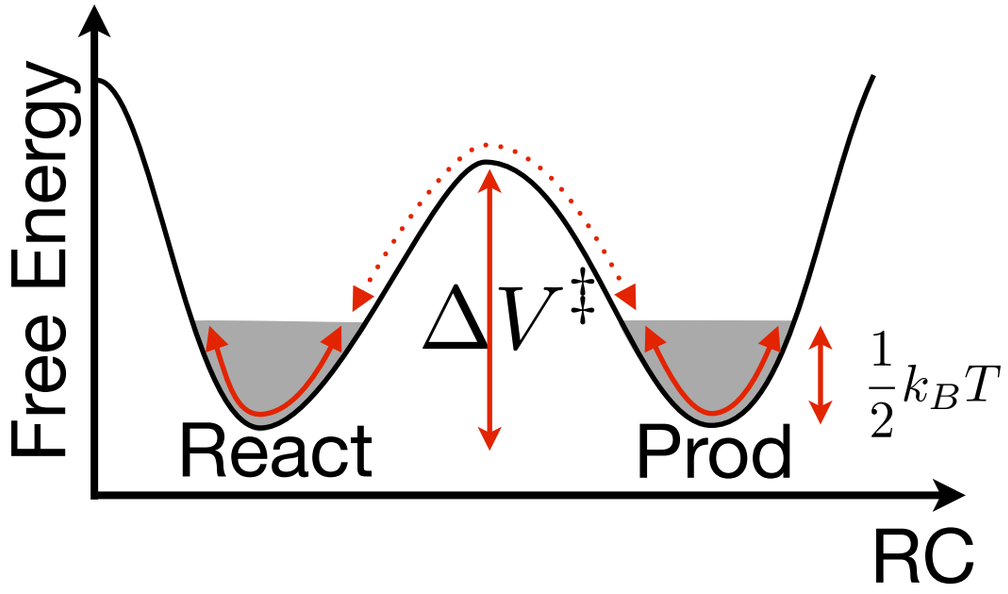

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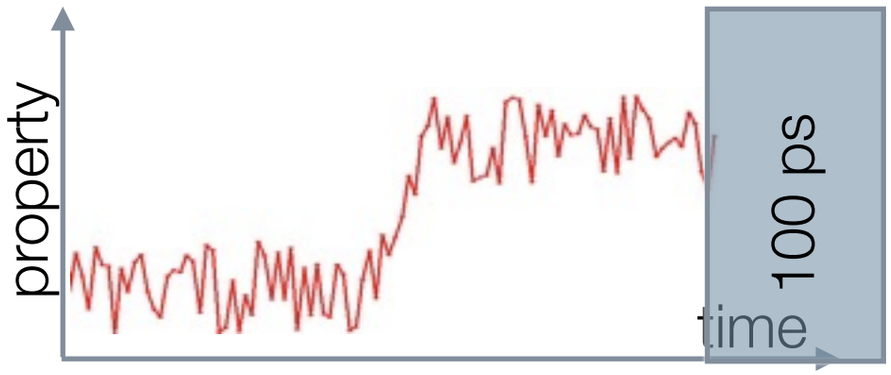

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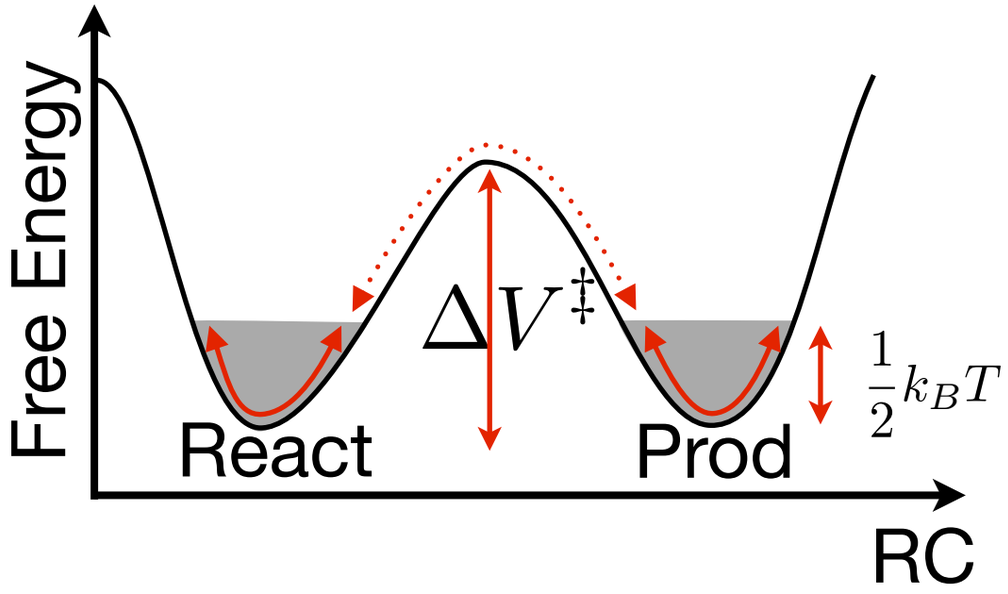

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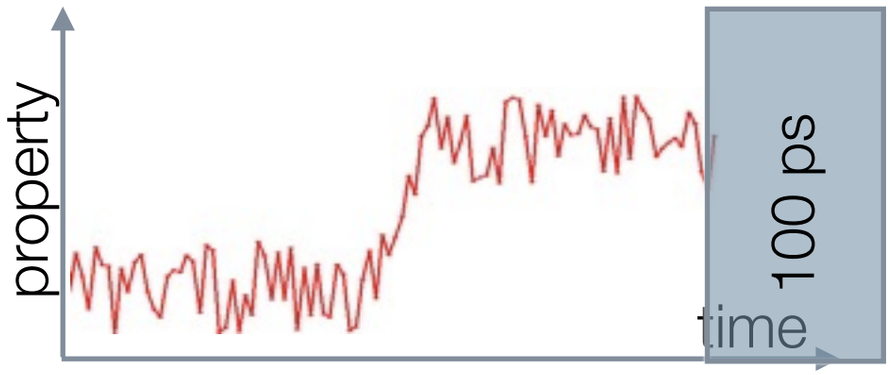

* If you want thermodynamics you must average over events

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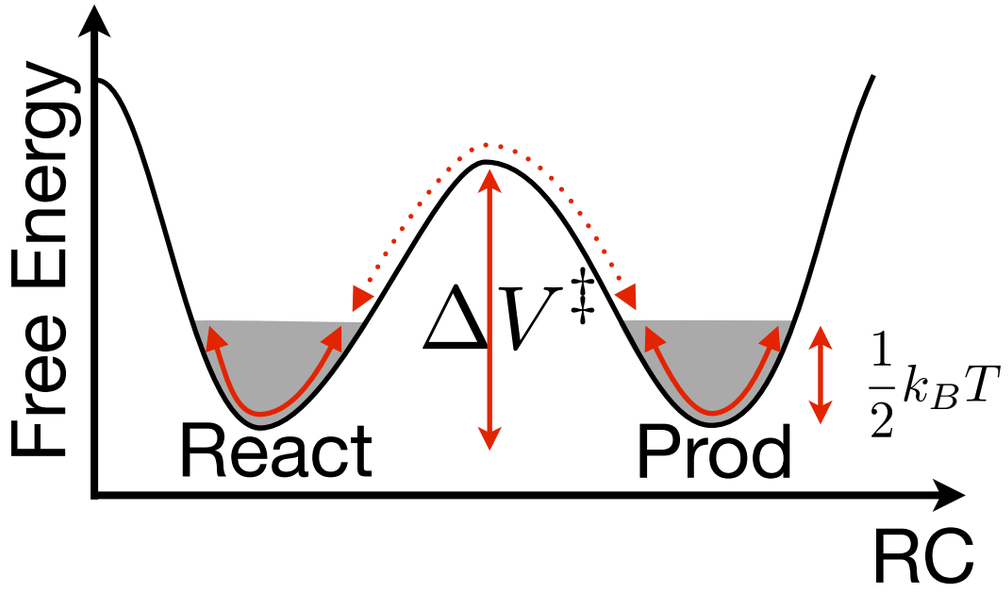

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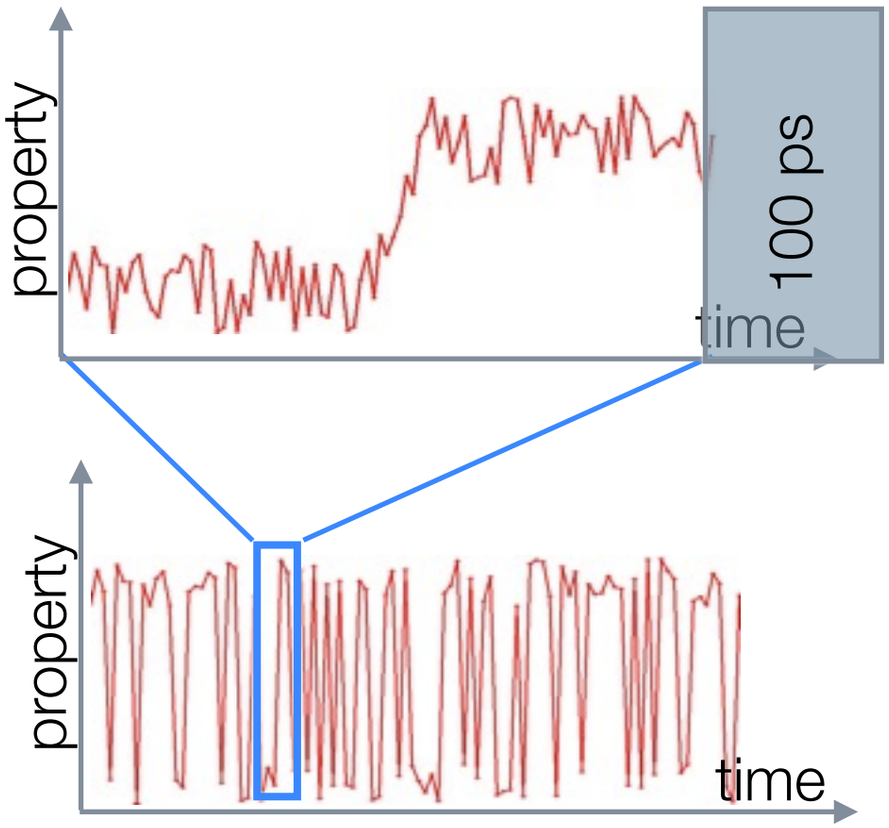

Limitations

* 300K

* M
  Lu

* If y
  m

This is not your solution

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- Traditional QM approach
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- **Enhanced sampling**
- PLUMED plugin for free energy calculations

The ancestor: Torrie & Valleau[3]

Free energy:

$$F(s_0) = -\frac{1}{\beta}\ln P(s_0)$$
$$= -\frac{1}{\beta}\ln \frac{\int e^{-\beta V(x)}\delta(s(x)-s_0)dx}{Q}$$

Free energy for a biased system:

$$F_b(s_0) = -\frac{1}{\beta}\ln P_b(s_0)$$
$$= -\frac{1}{\beta}\ln \frac{\int e^{-\beta(V(x)+V_b(s(x)))}\delta(s(x)-s_0)dx}{Q_b}$$
$$= V_b(s_0) - \frac{1}{\beta}\ln \frac{\int e^{-\beta V(x)}\delta(s(x)-s_0)dx}{Q_b}$$

use biasing potential to overcome barriers and retrieve free energies

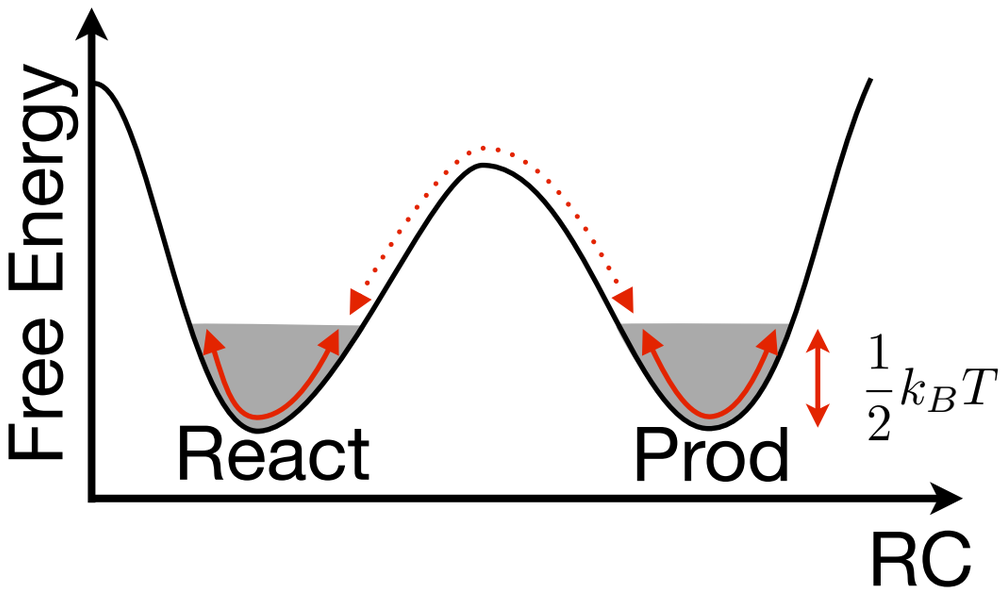
$$F_b(s_0) = V_b(s_0) - \frac{1}{\beta}\ln P(s)\frac{Q}{Q_b}$$

$$F(s_0) = F_b(s_0) - V_b(s_0) + C$$

[3] Torrie, Valleau J. Comp. Phys, 1977 vol. 23, pp 187

Lessons from Torrie & Valleau

Biasing potentials:



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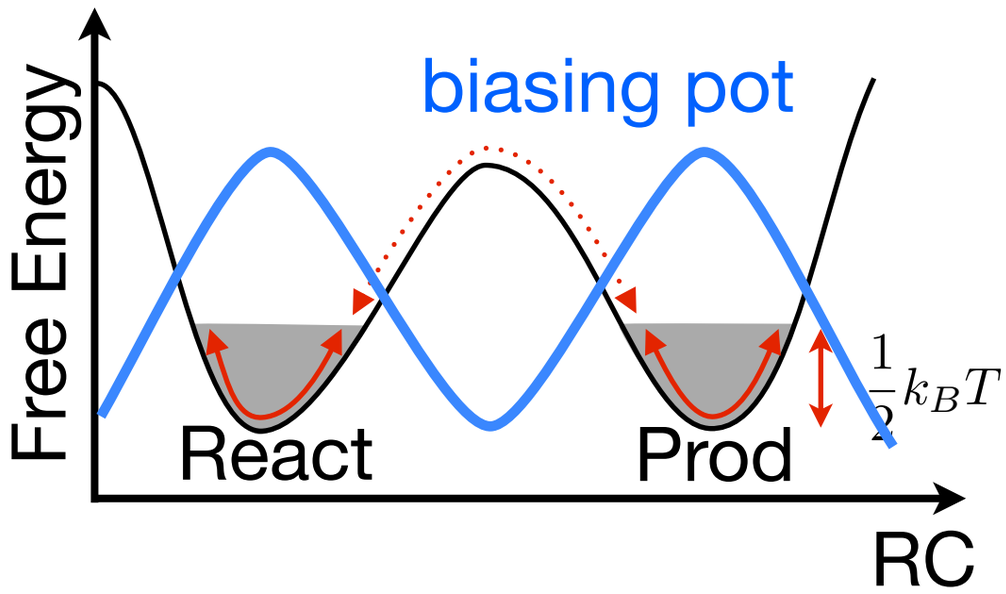

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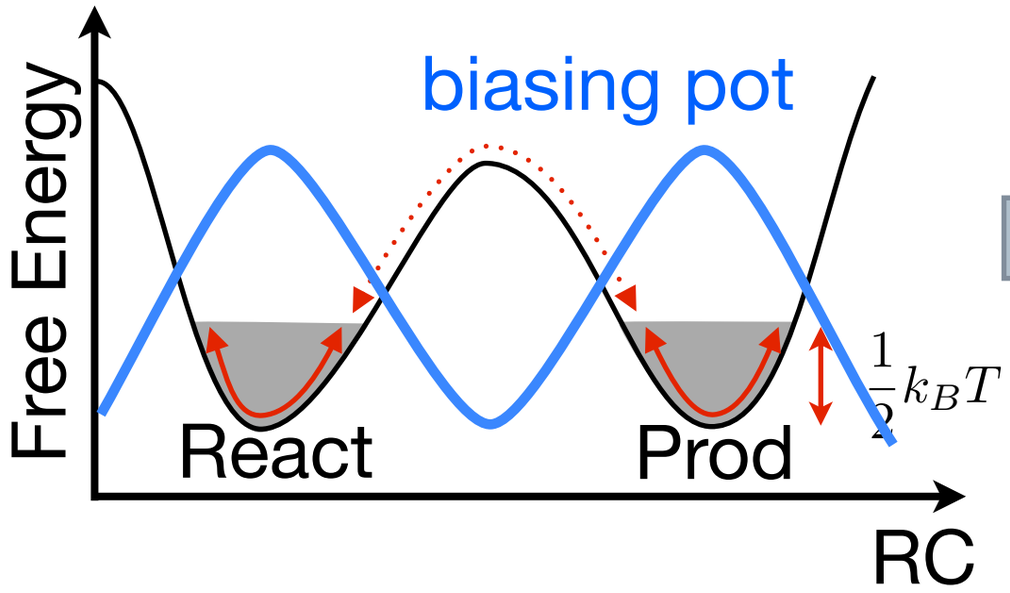
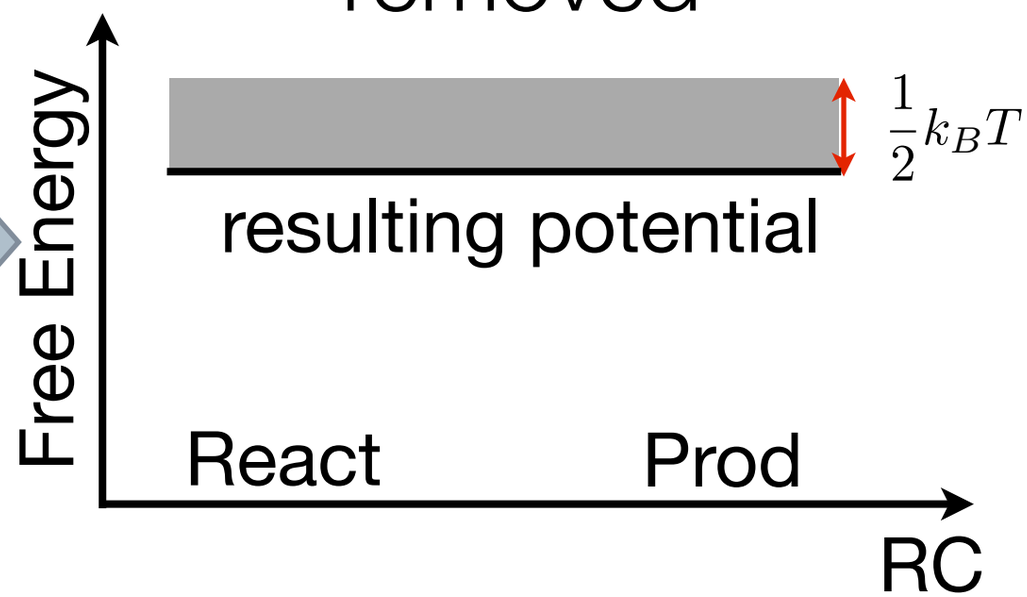


Metastabilities are removed



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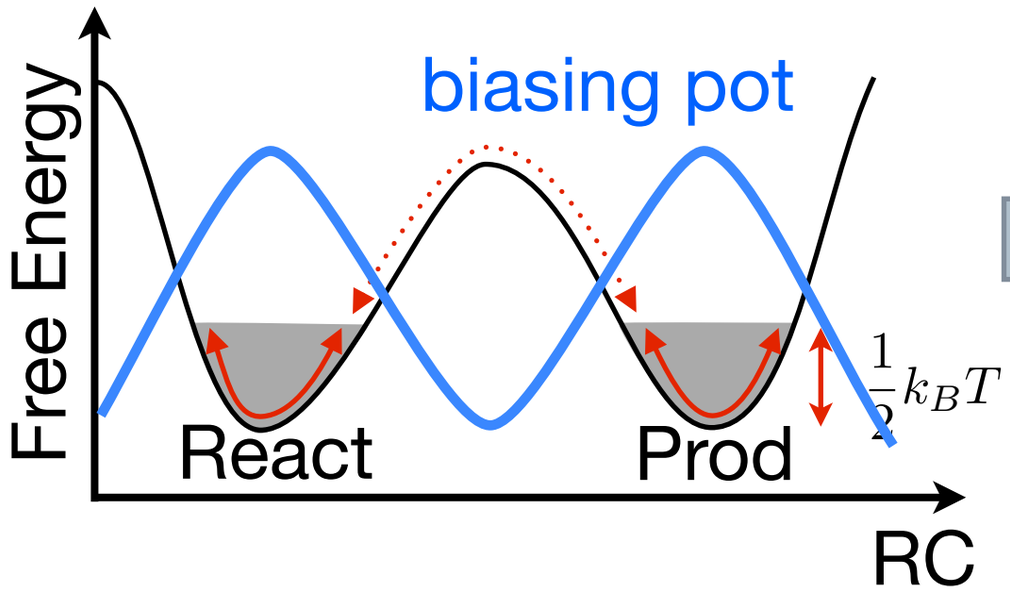

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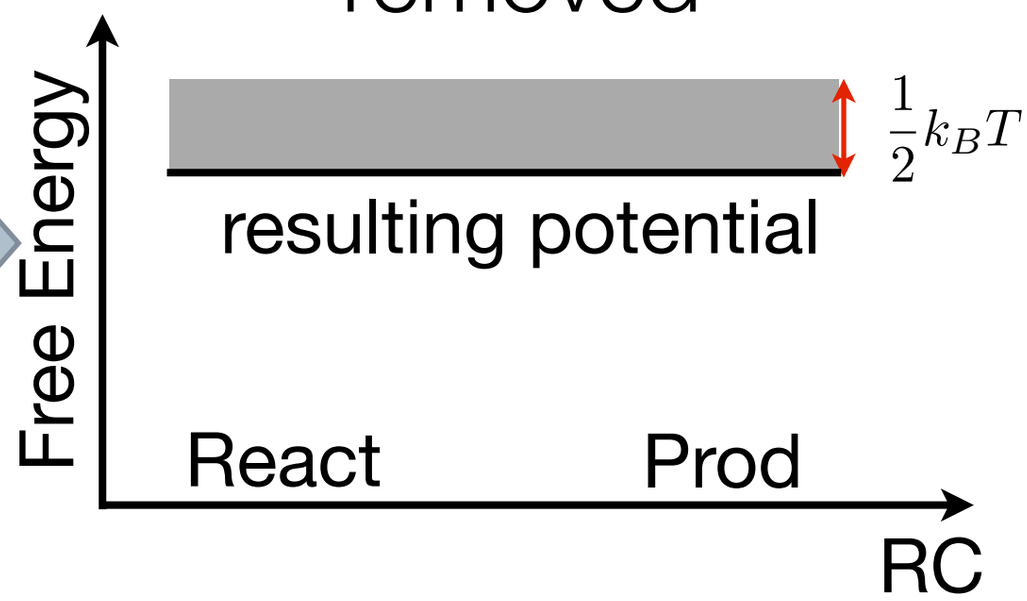


* allow to measure free energies: useful
* allow to overcome barriers: cheap
* need only an additional term to standard DFT forces: easy

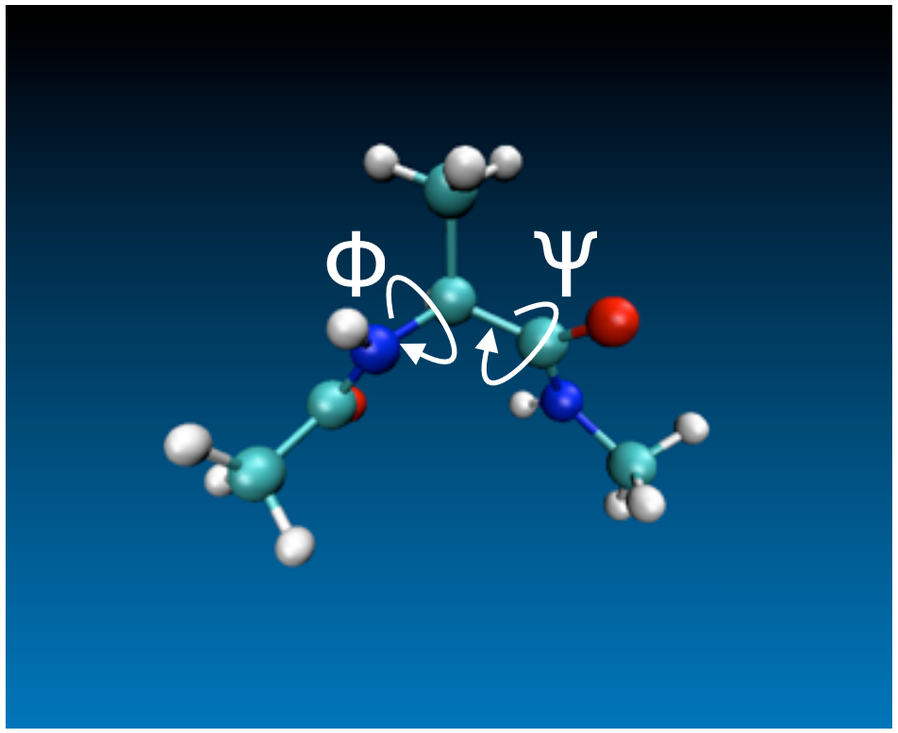
[3] Torrie, Valleau J. Comp. Phys, 1977 vol. 23, pp 187

Adaptive sampling methods

* Adaptive Biasing Force Darve & Pohorille, J. Chem. Phys. 2001, vol. 115, pp. 9169.
* Adaptive Umbrella Sampling Mezei, M. J Comput Phys 1987, vol. 68, pp. 237.
* Self Healing Umbrella Sampling Marsili et. al J. Chem. Phys. B vol. 110, pp. 14011.
* MetadynamicsLaio & Parrinello, PNAS 2002, vol. 20, pp. 12562.
* Conformational Flooding Grubmüller, Phys Rev E 1995, vol. 52, pp. 2893.
* ...

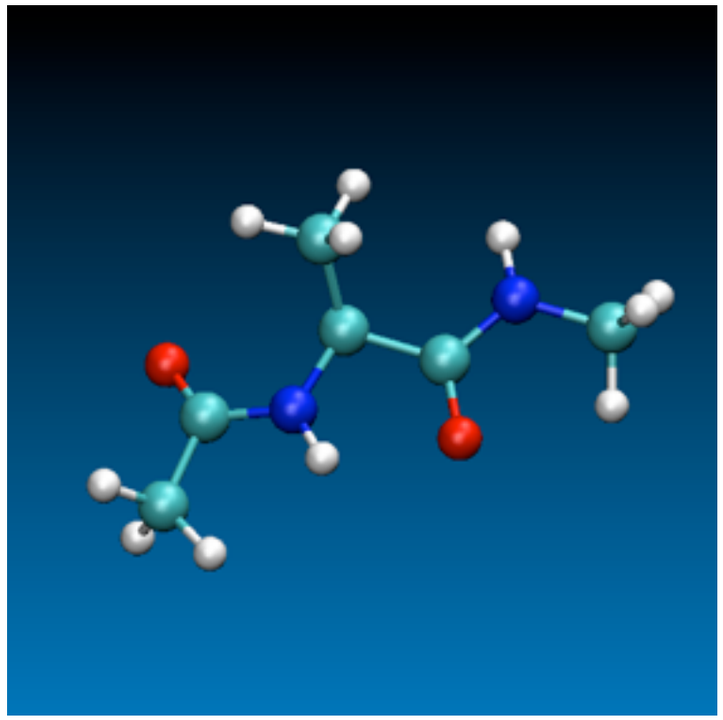
Adaptive sampling methods (e.g. metadynamics)

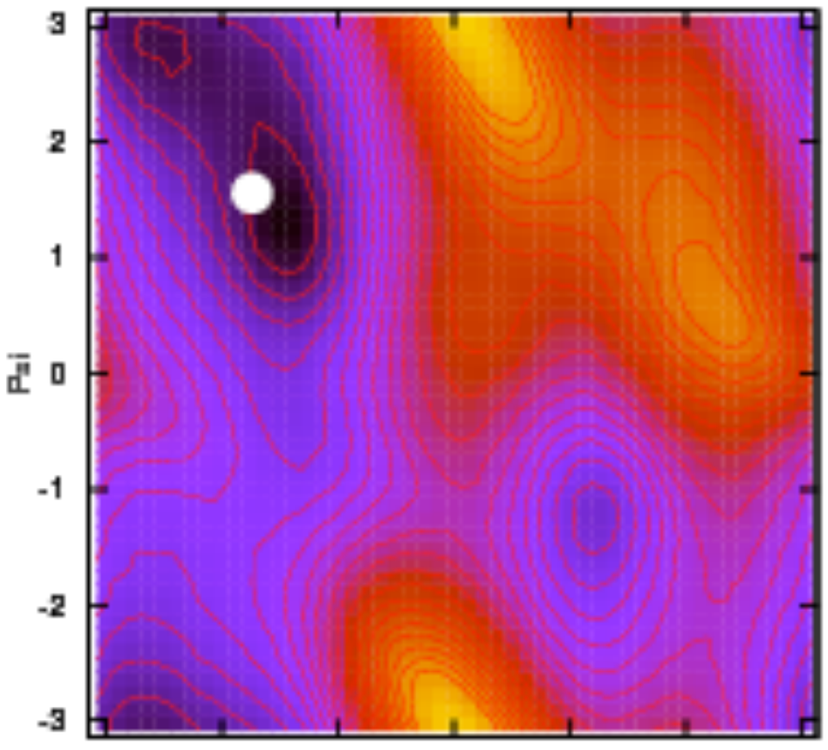
without ES



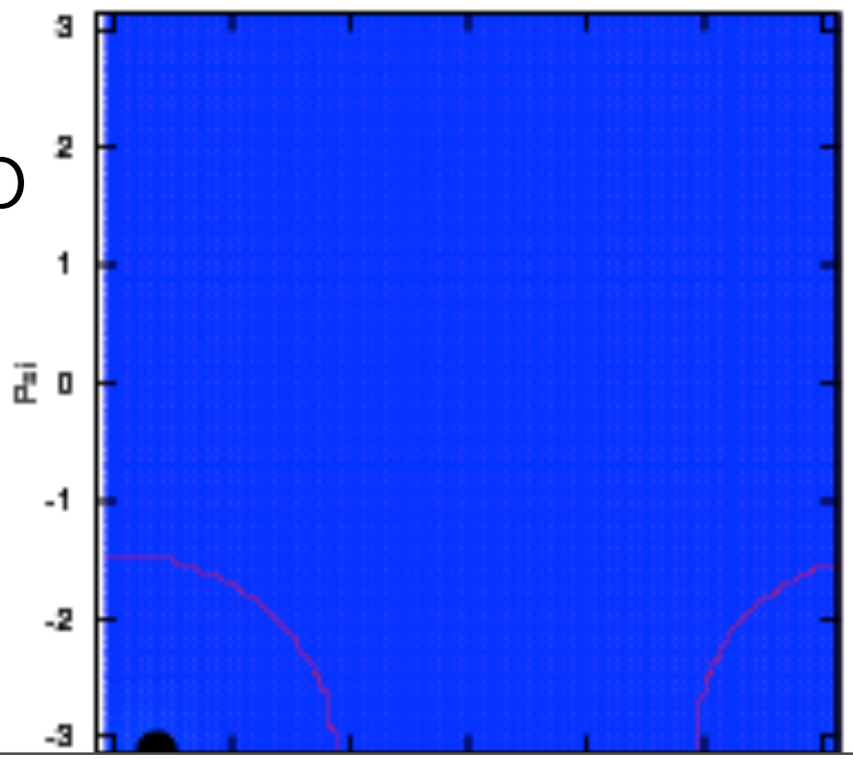
from milli secs...

with ES





to nano secs!



Thermodynamic-Integration-like approaches

* The ancestor is mean force calculation through harmonic potential

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

$$\left.\frac{\partial F(s)}{\partial s}\right|_{s_0} = -k_B T \frac{1}{\int e^{-\frac{V(x)}{k_B T}} \delta(s'(x) - s) dx} \frac{\partial}{\partial s} \int e^{-\frac{V(x)}{k_B T}} \delta(s'(x) - s) dx \Big|_{s_0}$$

* Dirac delta function ≈ Gaussian function (I like this trick!)

$$\left.\frac{\partial F(s)}{\partial s}\right|_{s_0} \simeq -k_B T \frac{1}{\int e^{-\frac{V(x)}{k_B T}} e^{-\frac{k}{2k_B T}(s'(x)-s)^2} dx} \frac{\partial}{\partial s} \int e^{-\frac{V(x)}{k_B T}} e^{-\frac{k}{2k_B T}(s'(x)-s)^2} dx \Big|_{s_0}$$

* It is an average of a biased simulation!

$$\left.\frac{\partial F(s)}{\partial s}\right|_{s_0} \simeq -\frac{1}{\int e^{-\frac{V(x)+k/2(s'(x)-s_0)^2}{k_B T}} dx} \int k(s'(x) - s_0) e^{-\frac{V(x)+k/2(s'(x)-s_0)^2}{k_B T}} dx$$

$$= -k\langle s'(x) - s_0 \rangle_{bias,s0}$$ (opposite of the “mean force”)

Thermodynamic Integration 101

* Make a constrained simulation (go over barrier!)
* Acquire mean force
* Integrate

Sloping, slatted, wooden platforms are preferable for sheep dragging.

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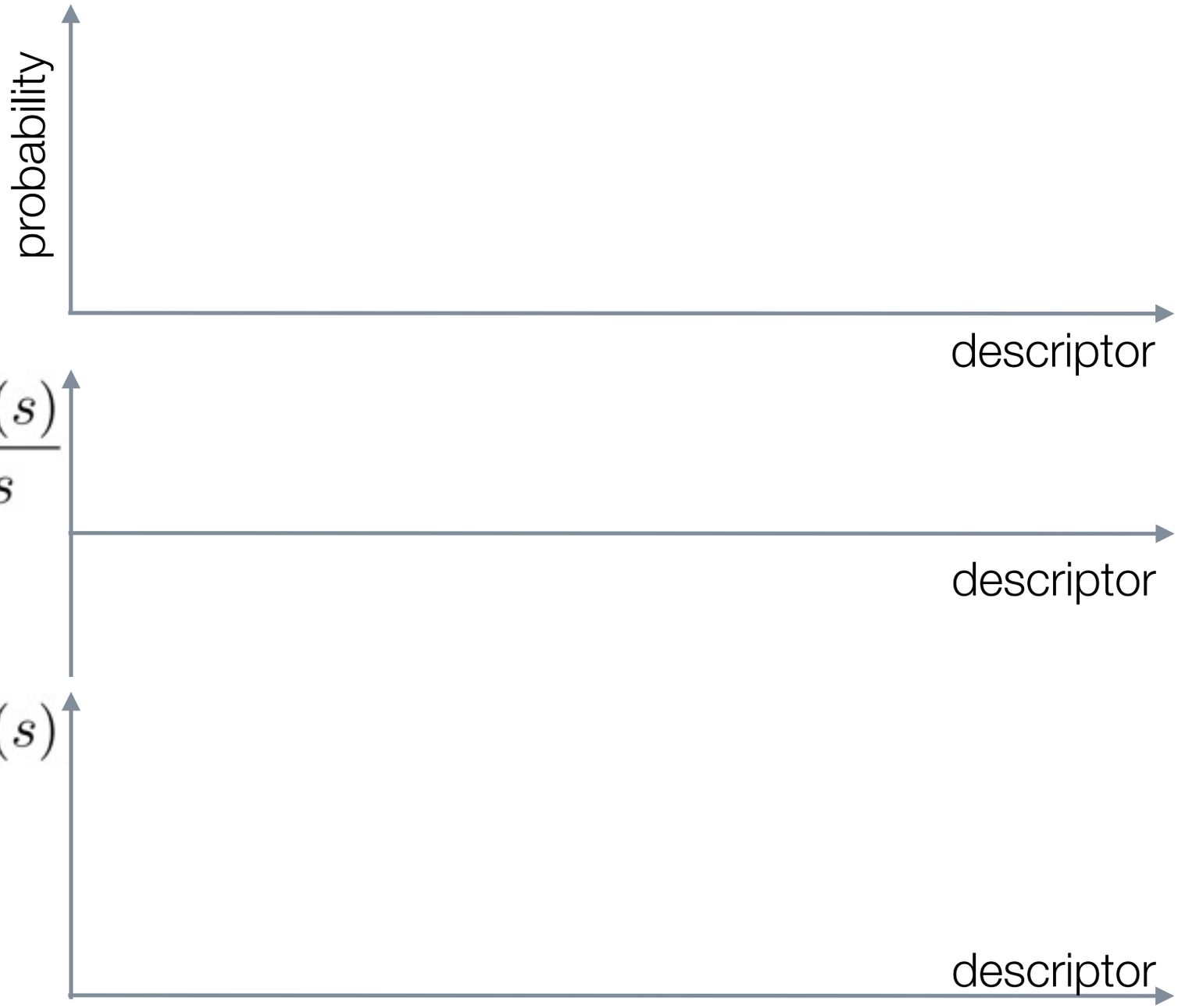

+WHAM etc...

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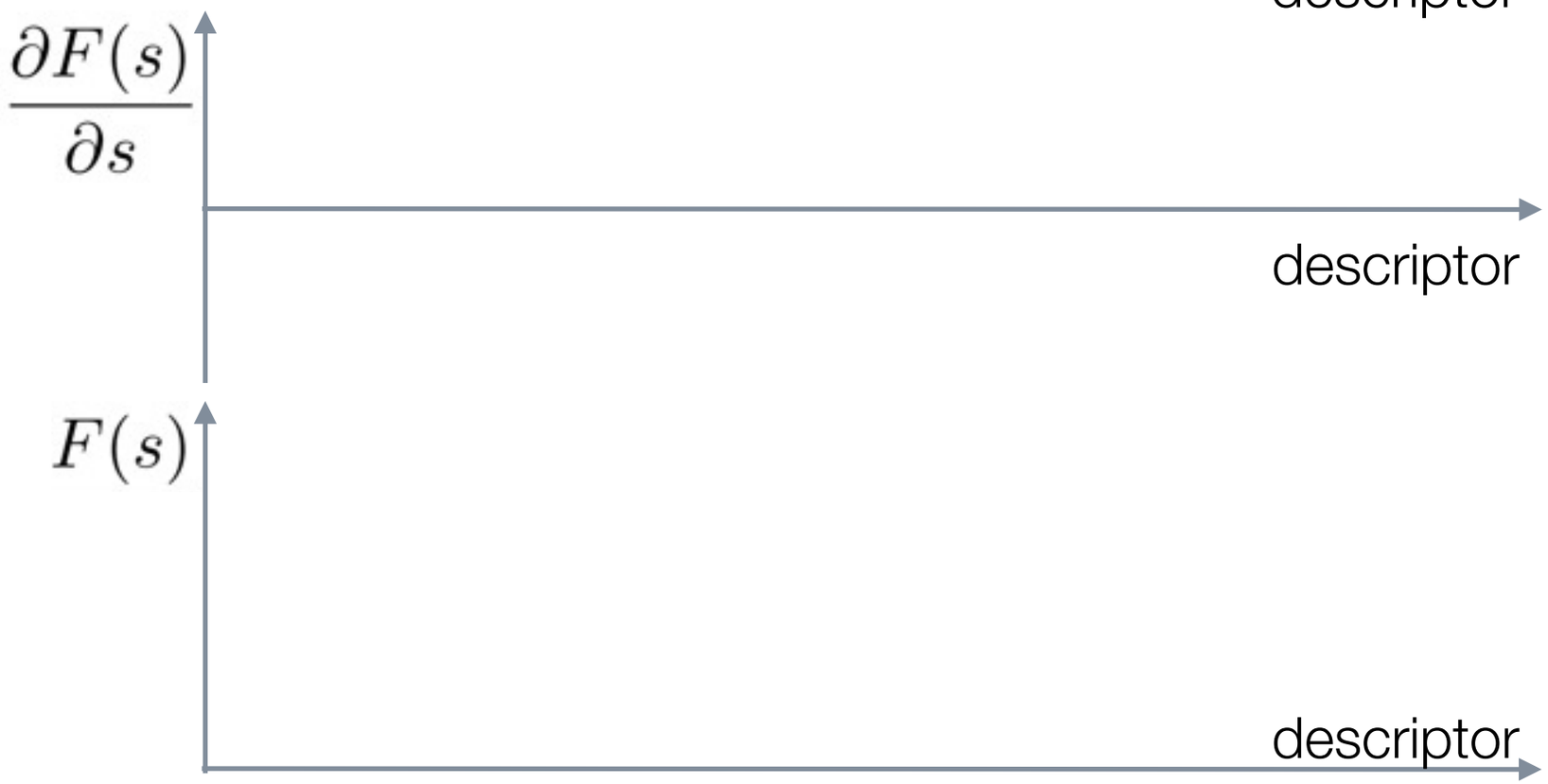

+WHAM etc...

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* Acquire mean force
* Integrate

Sloping, slatted, wooden platforms are preferable for sheep dragging.

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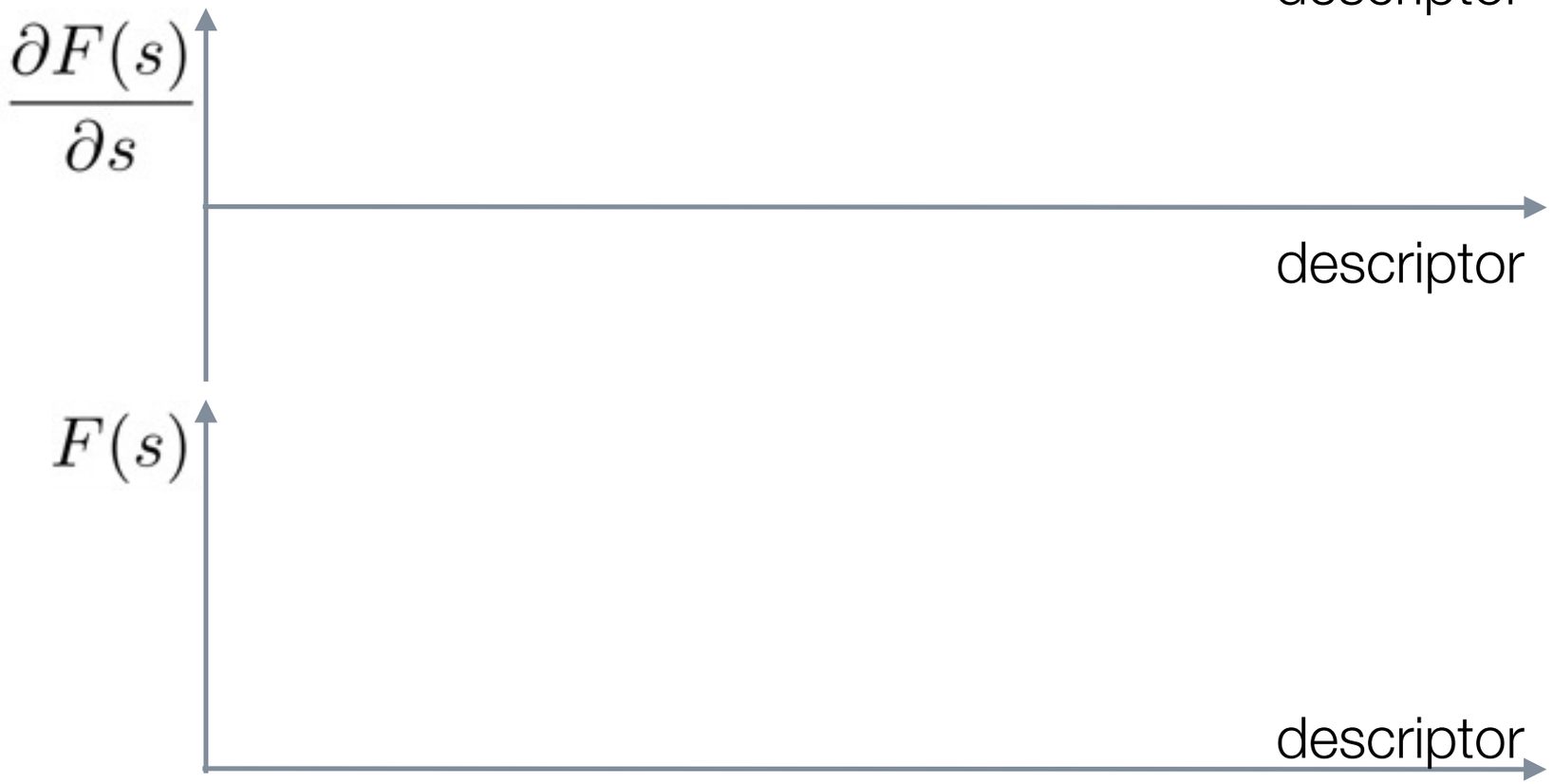

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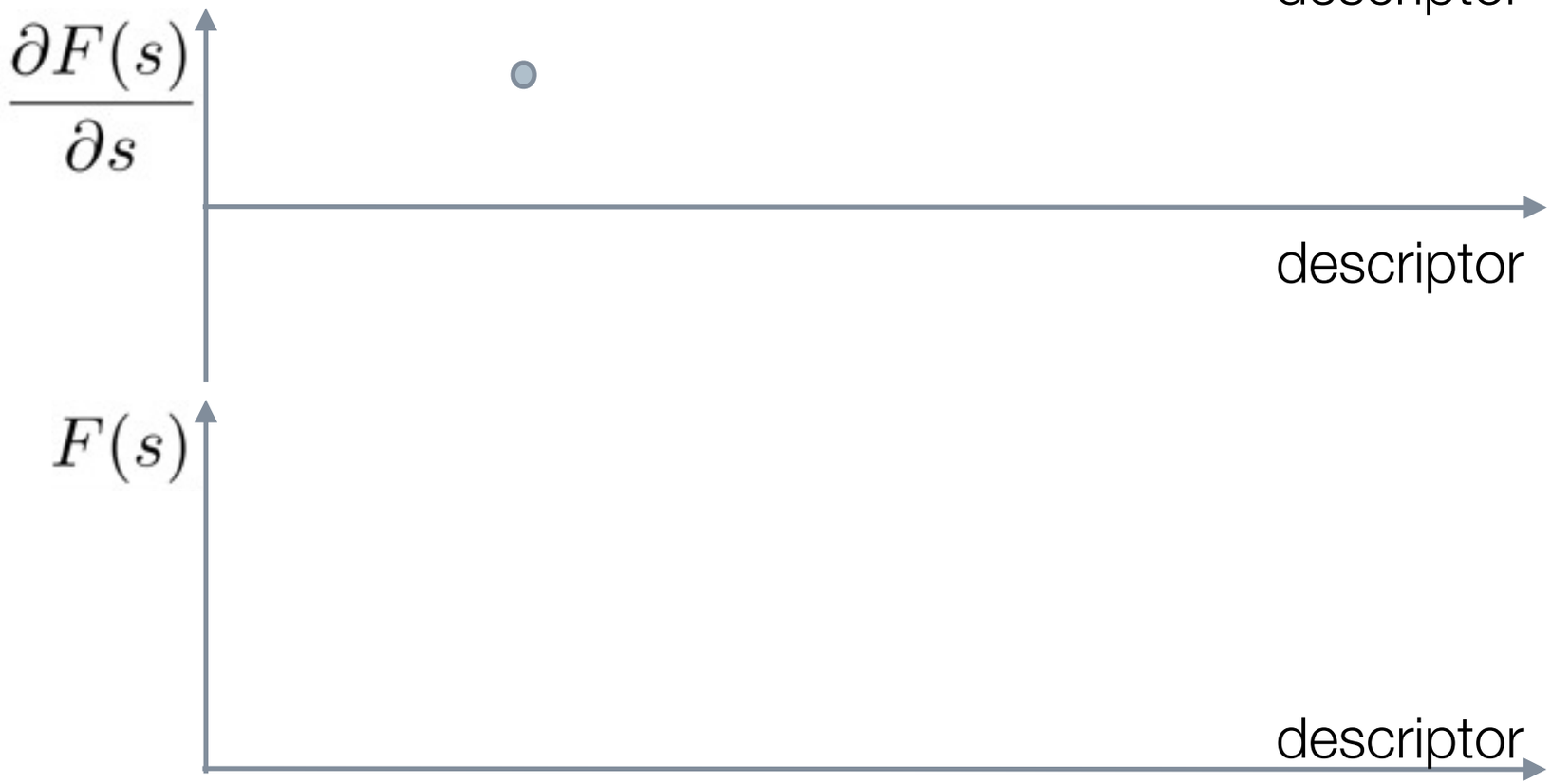

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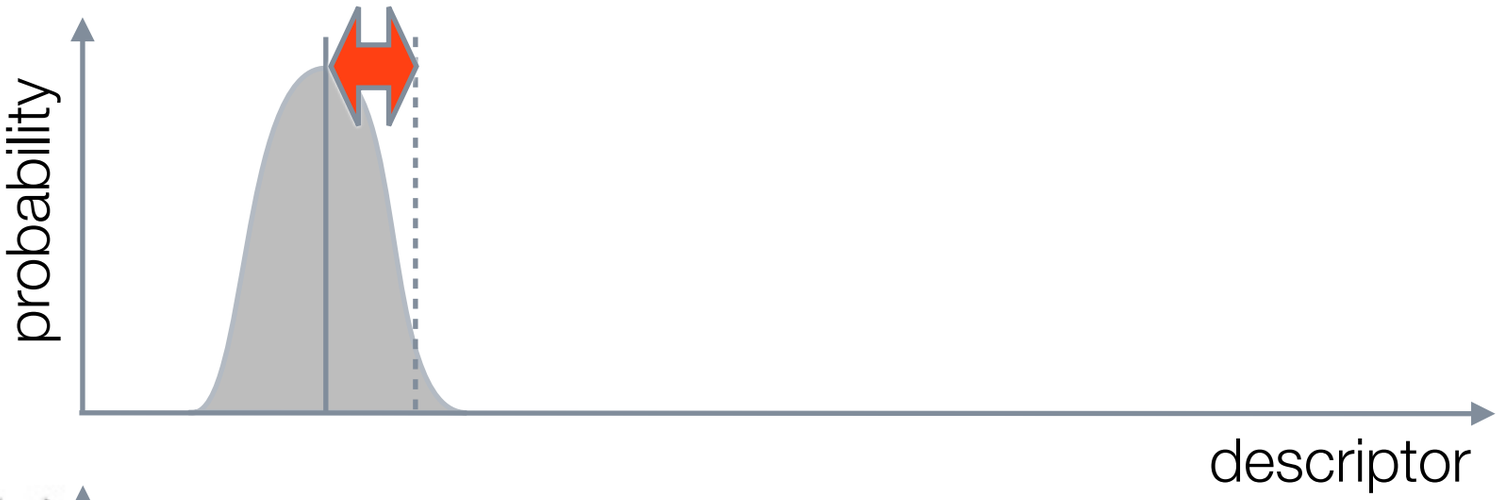

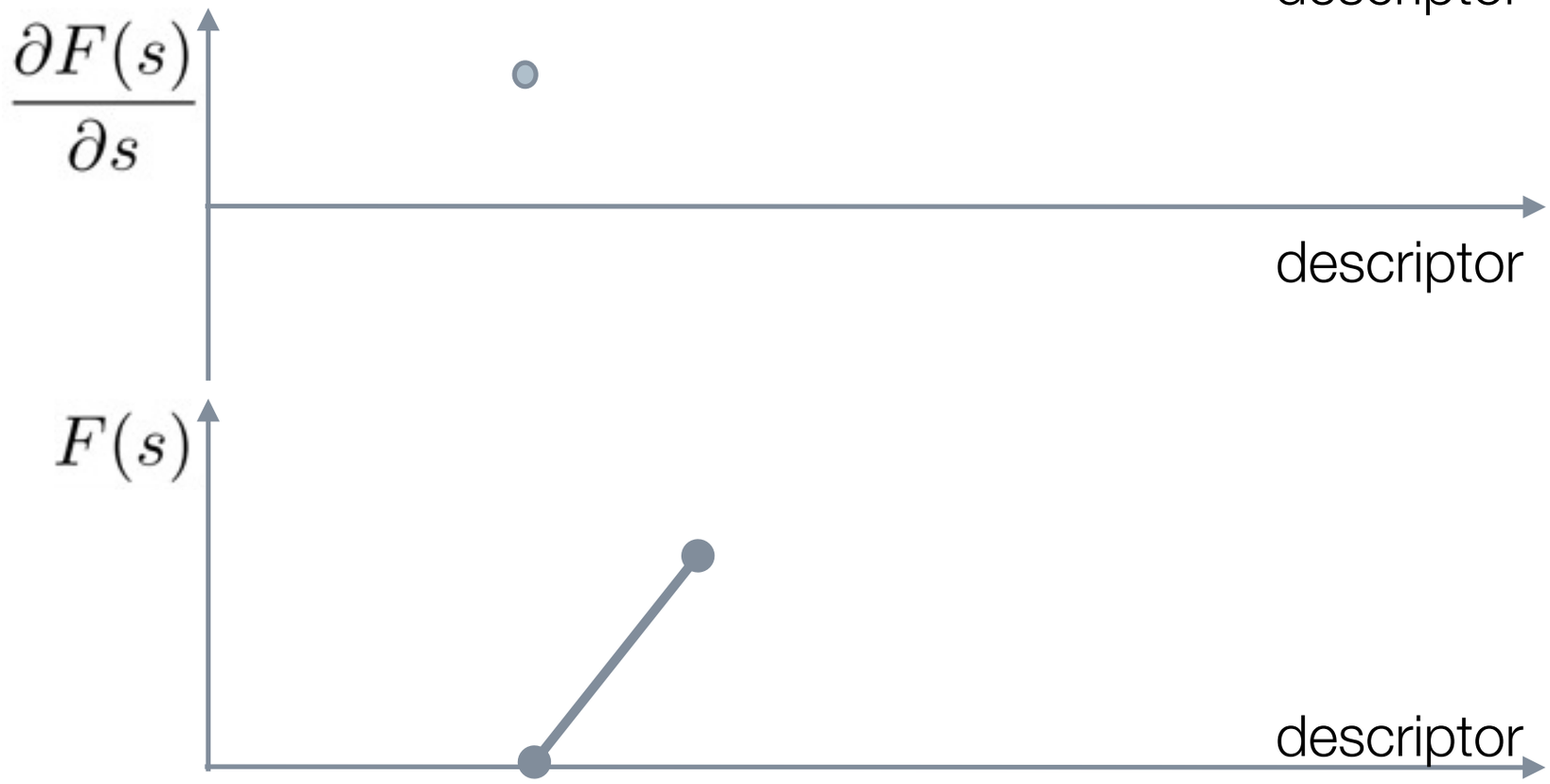

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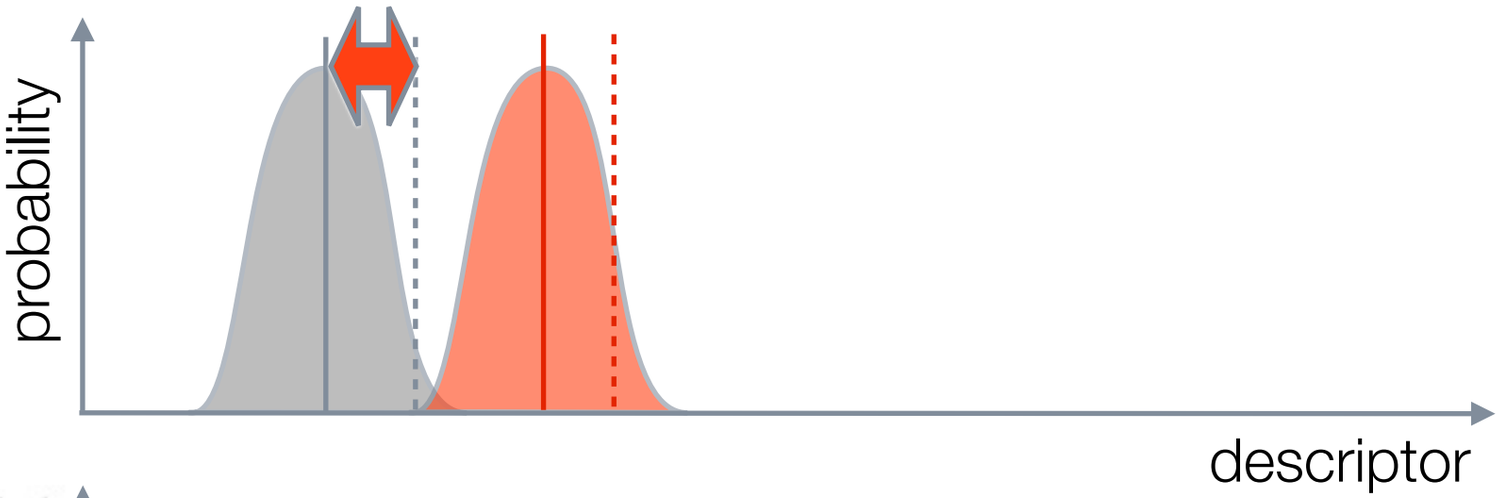

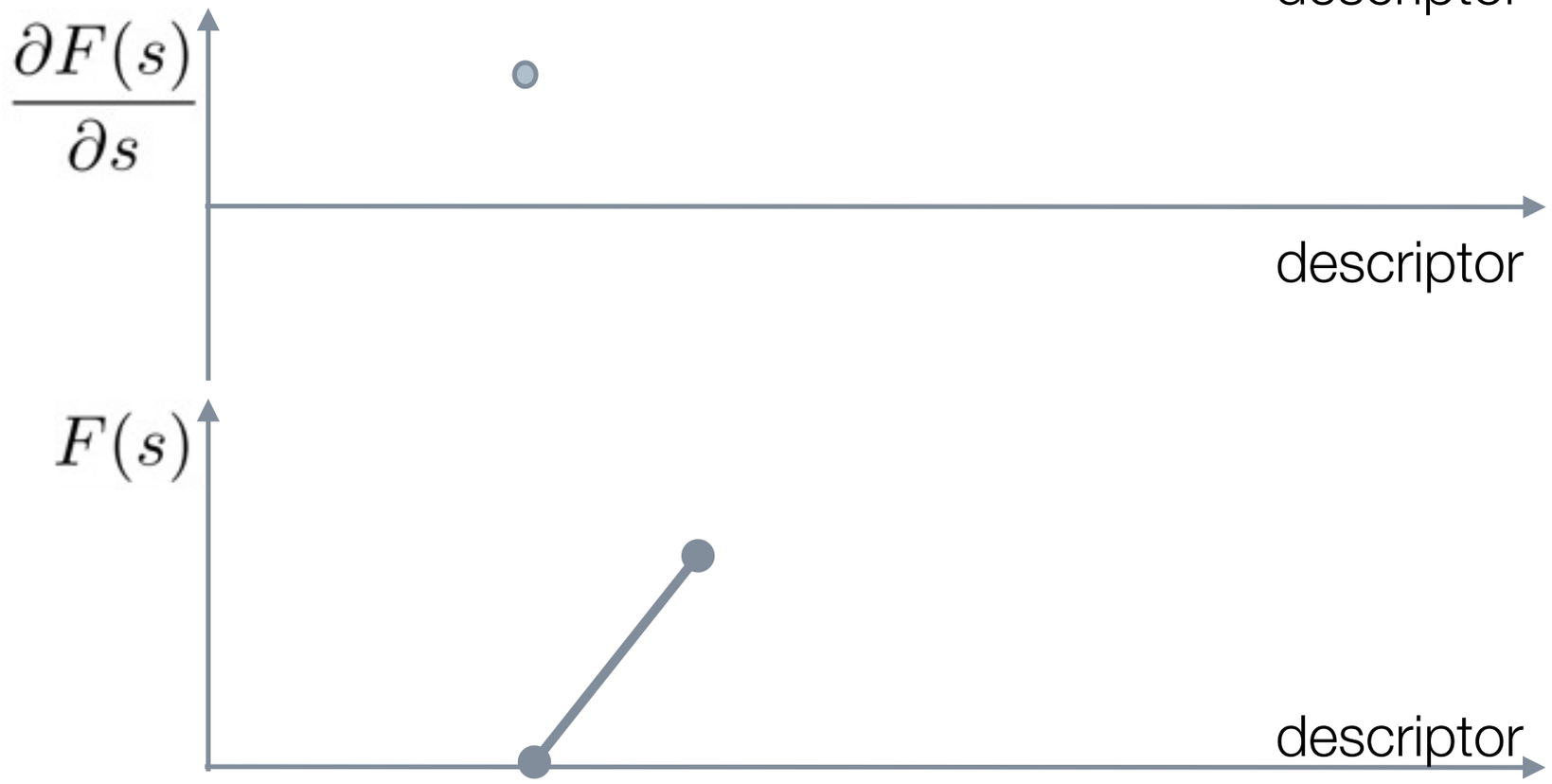

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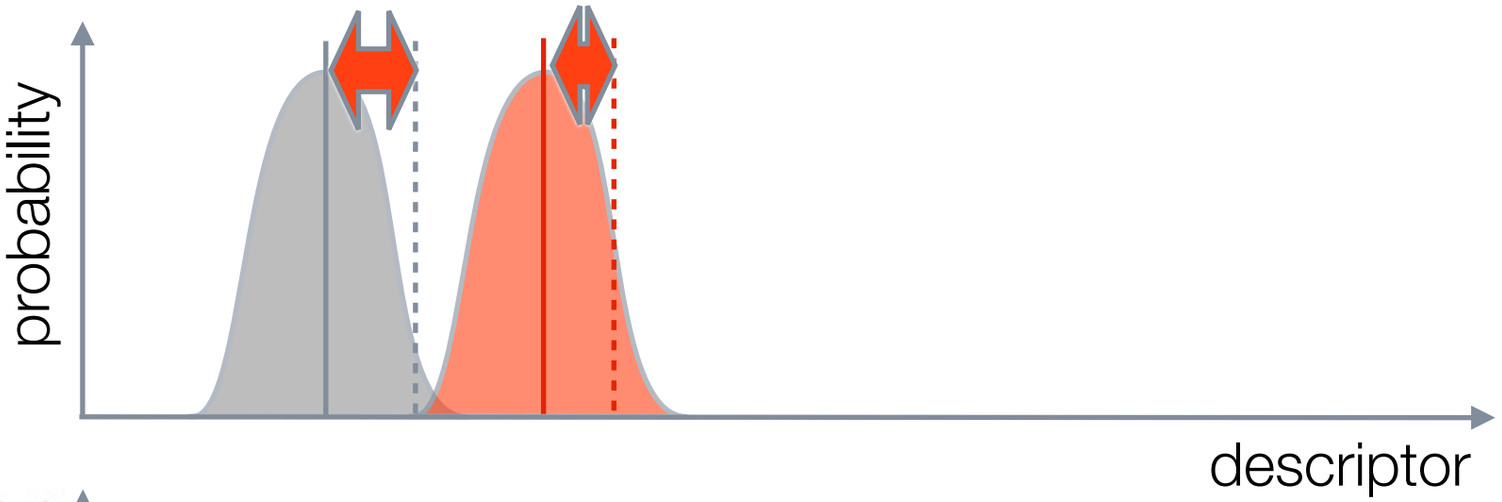

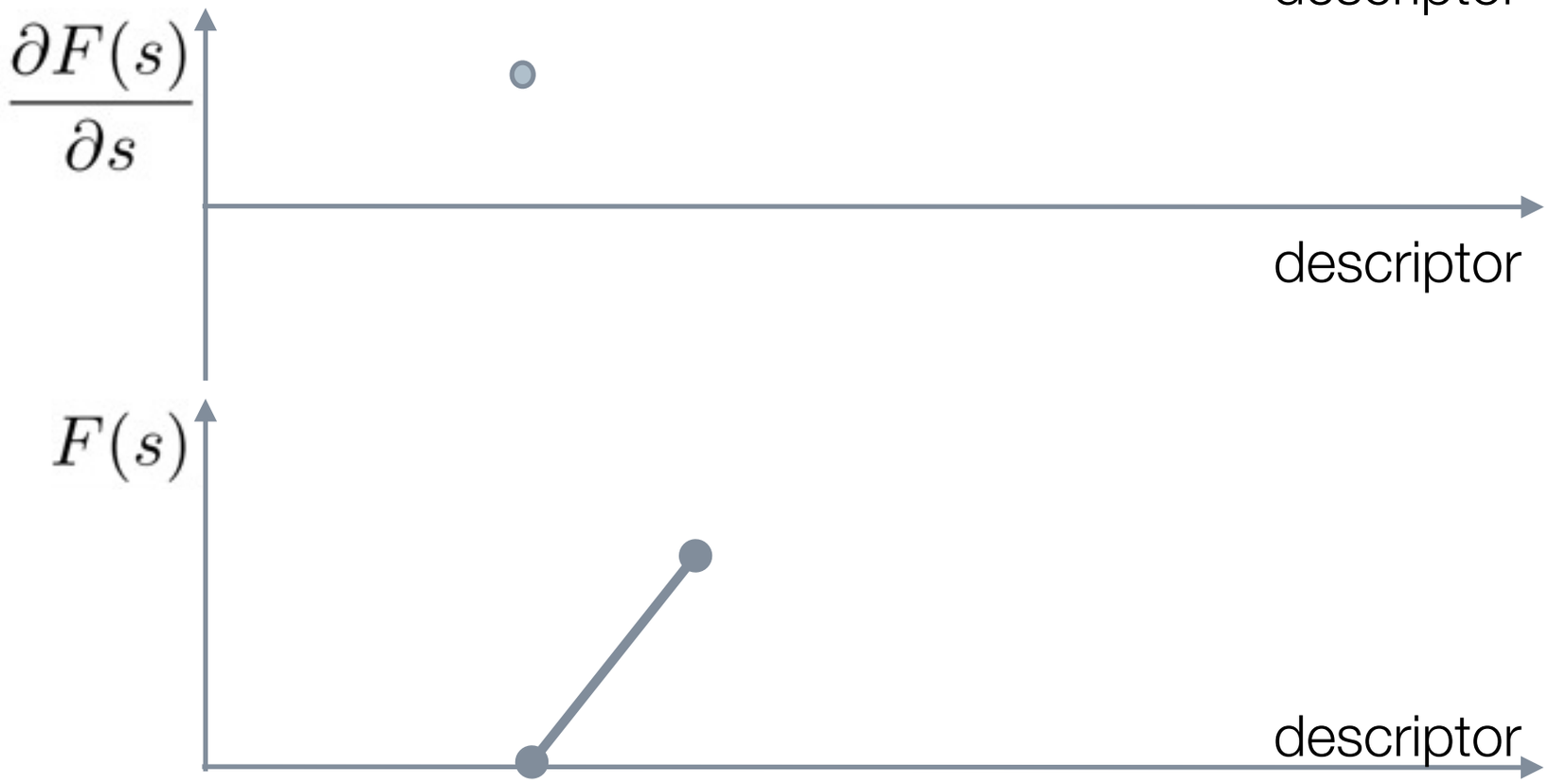

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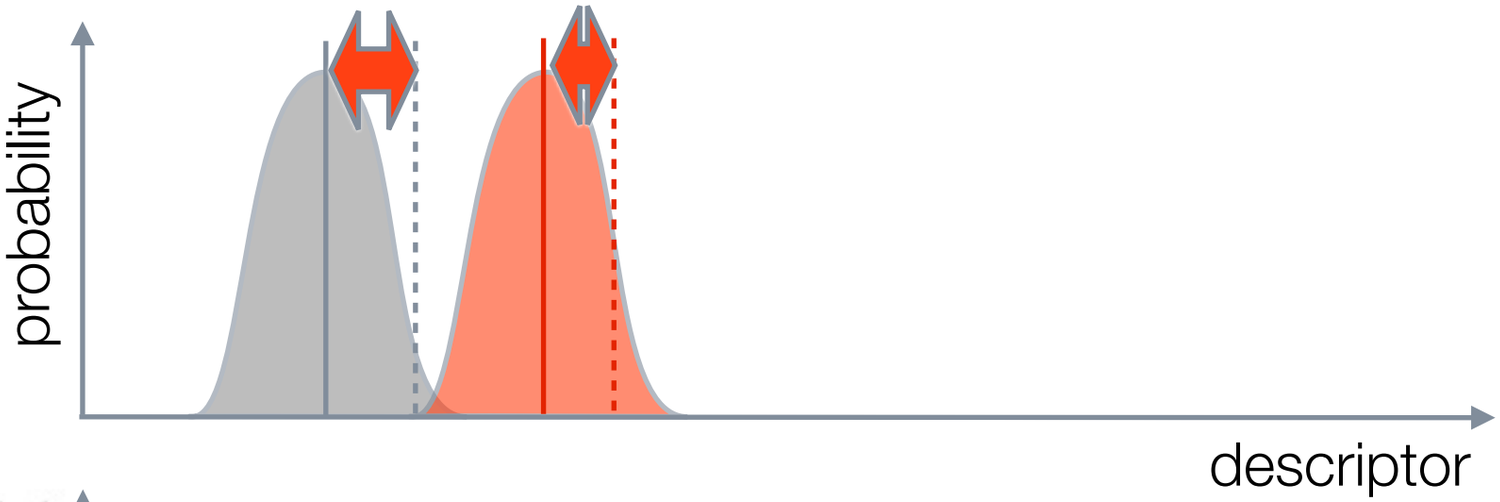

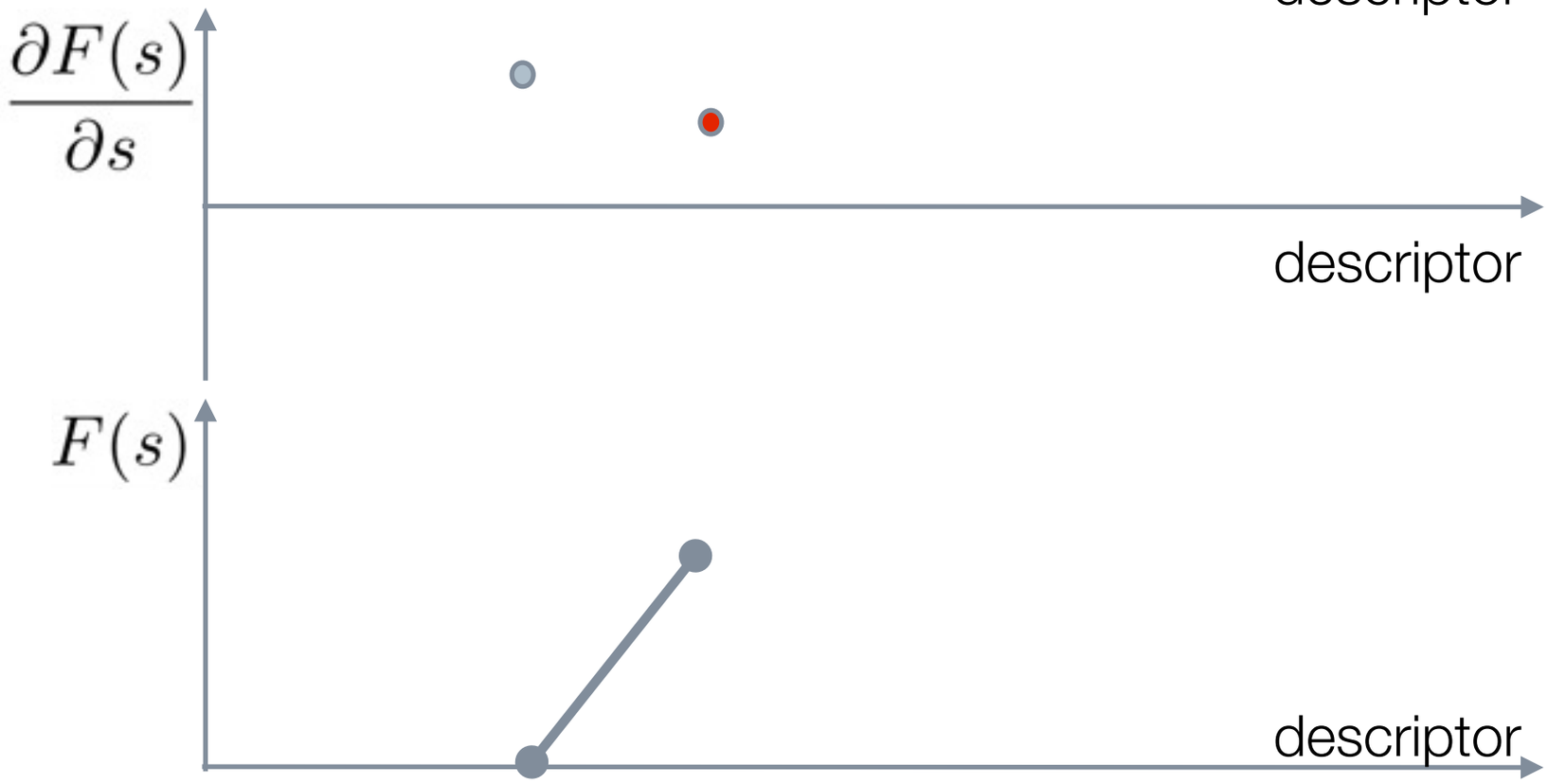

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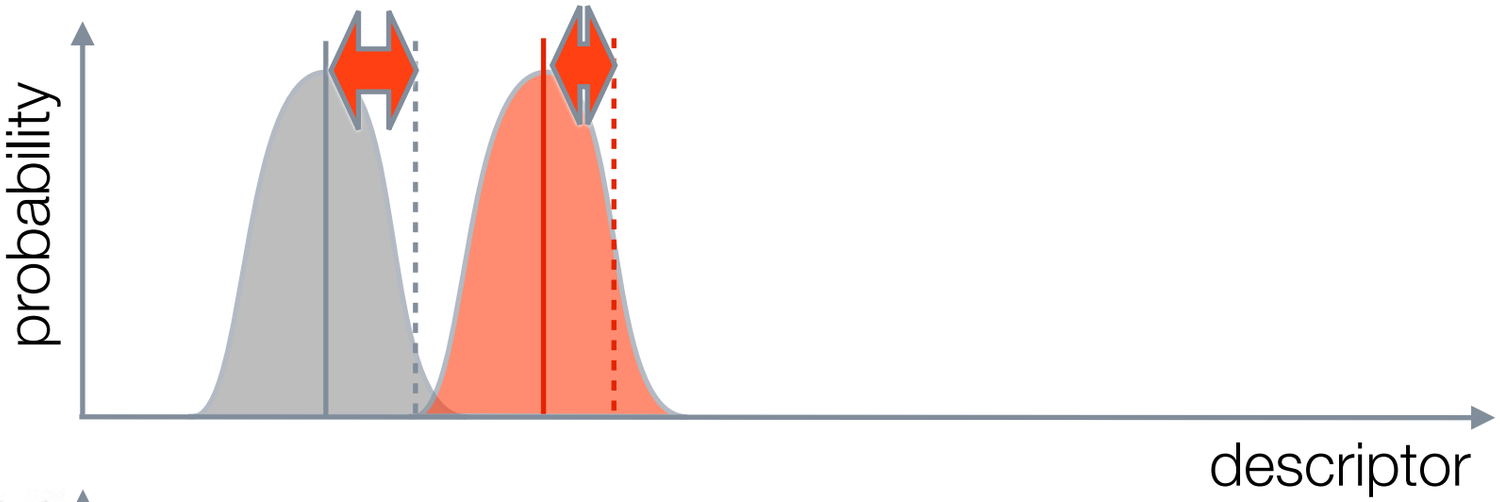

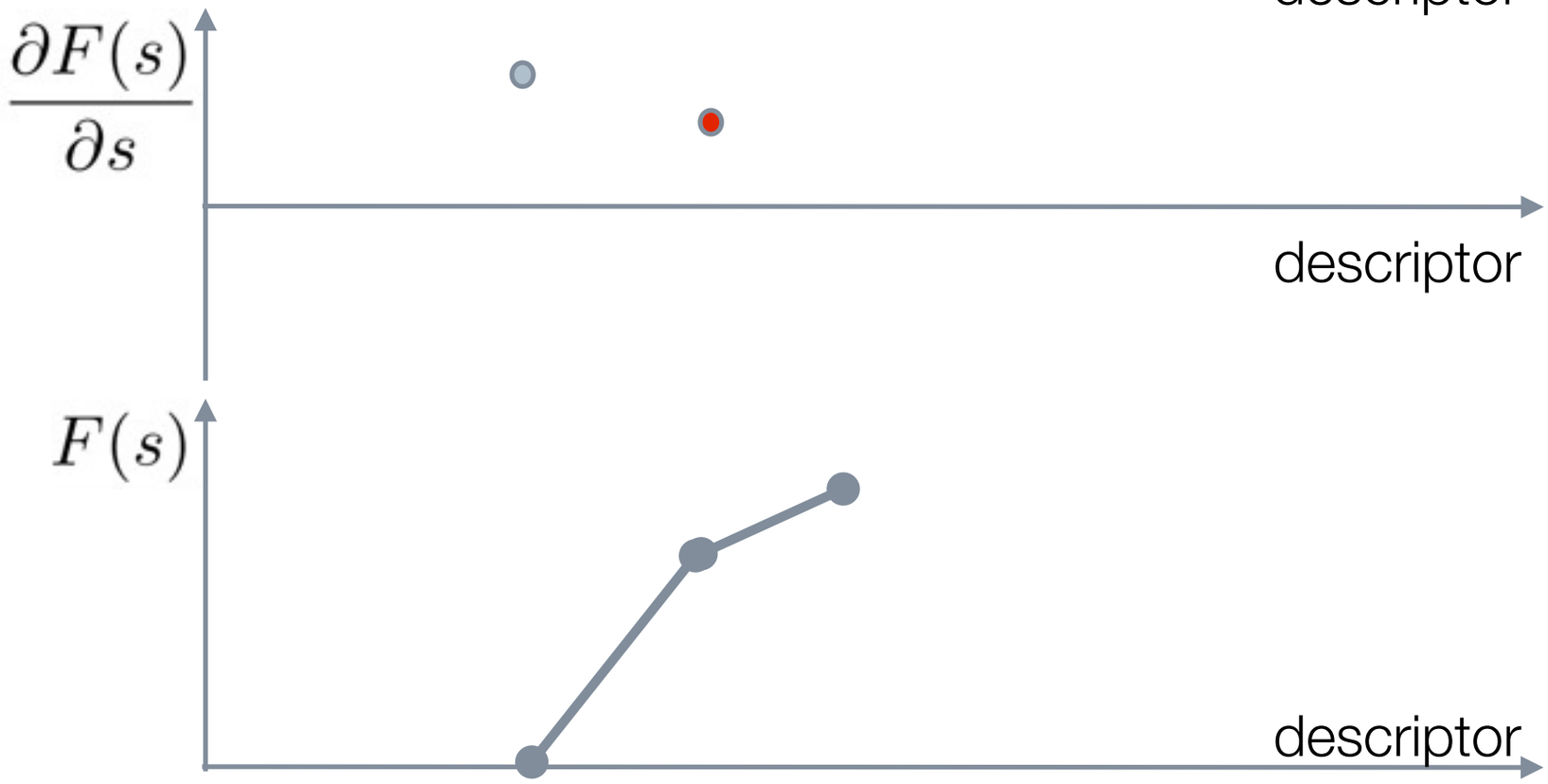

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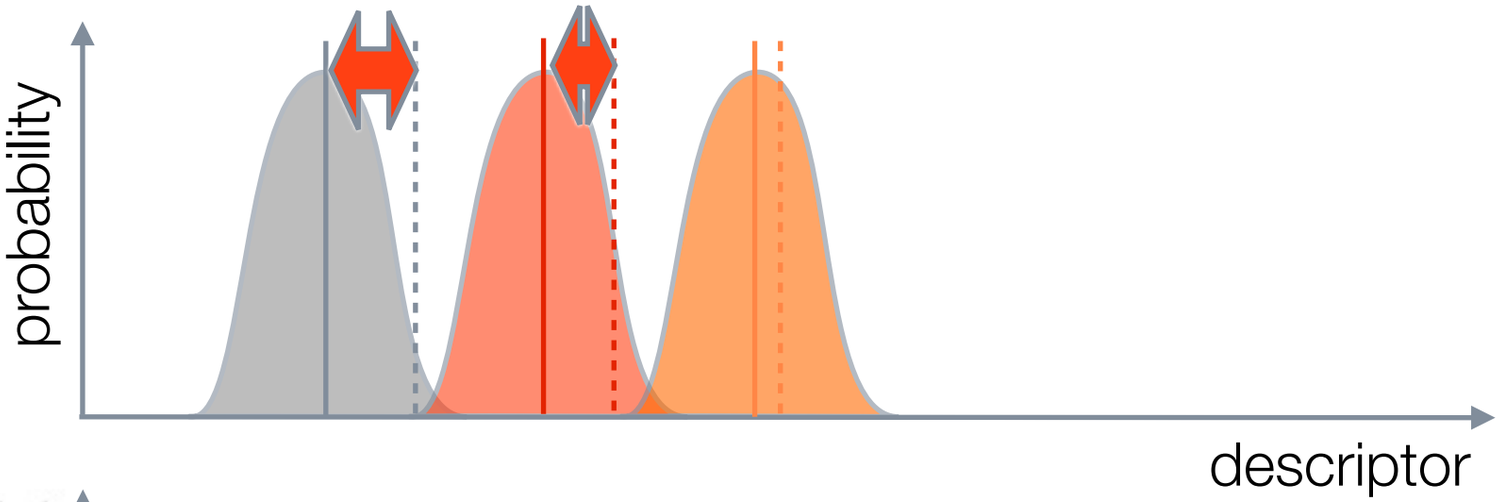

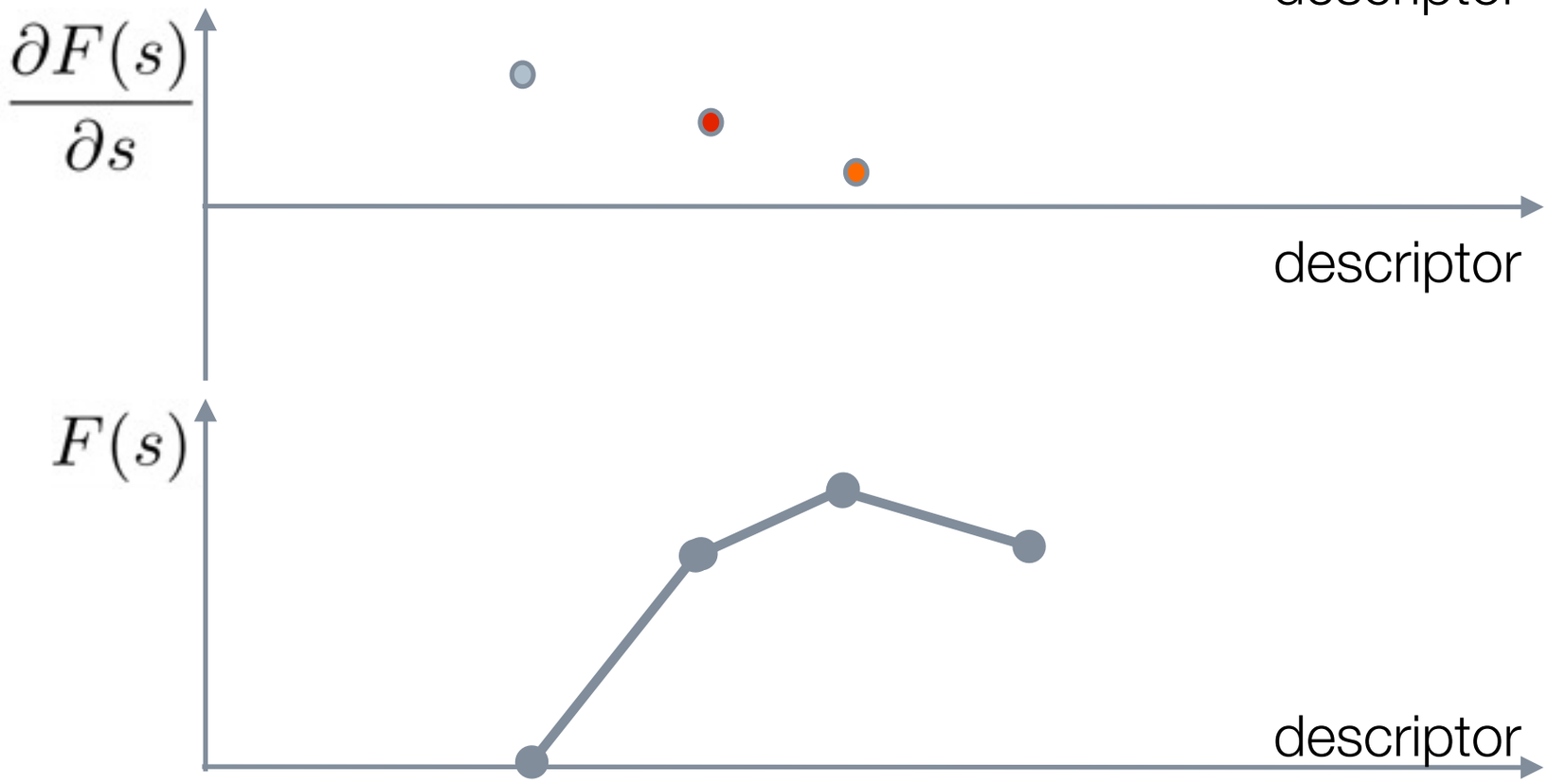

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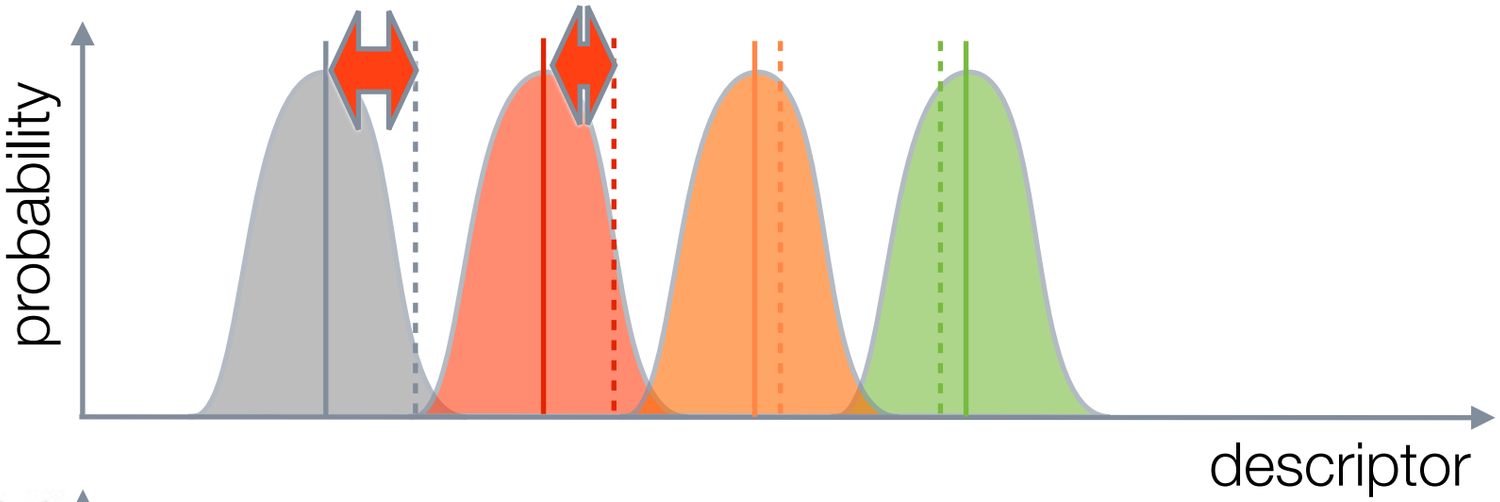

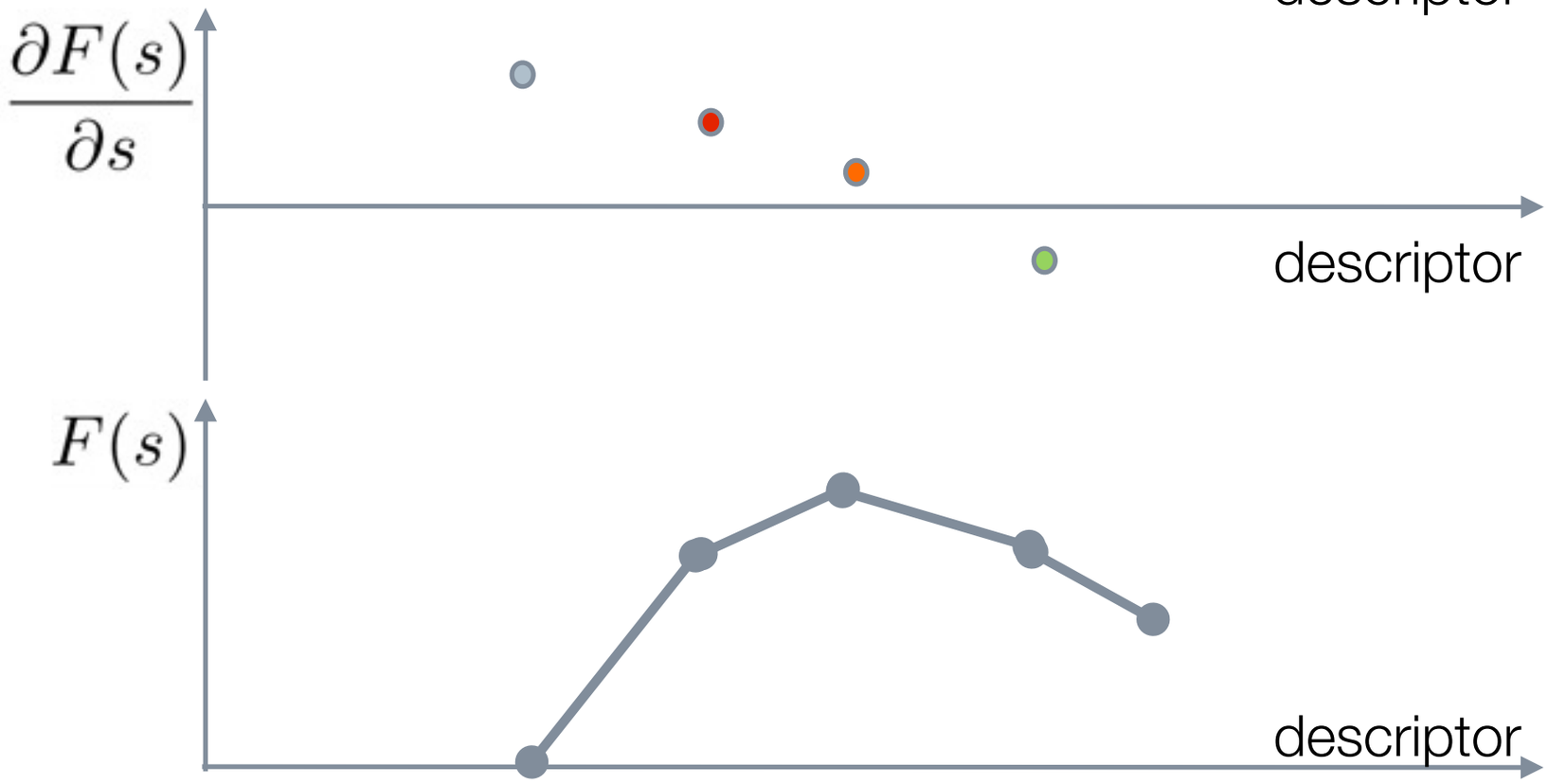

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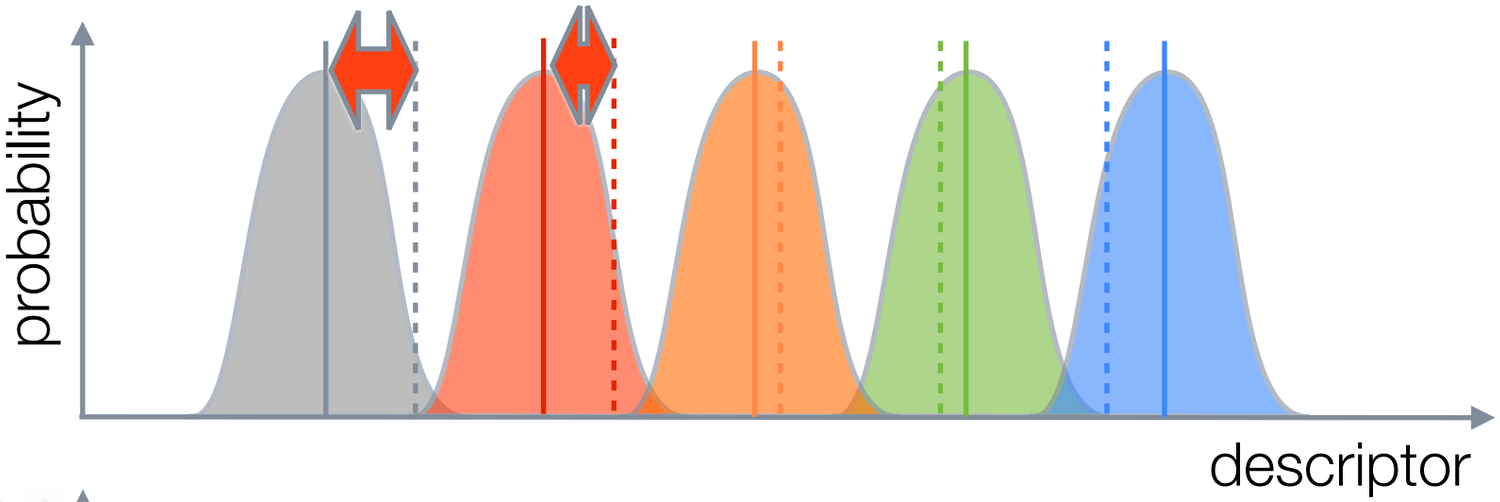
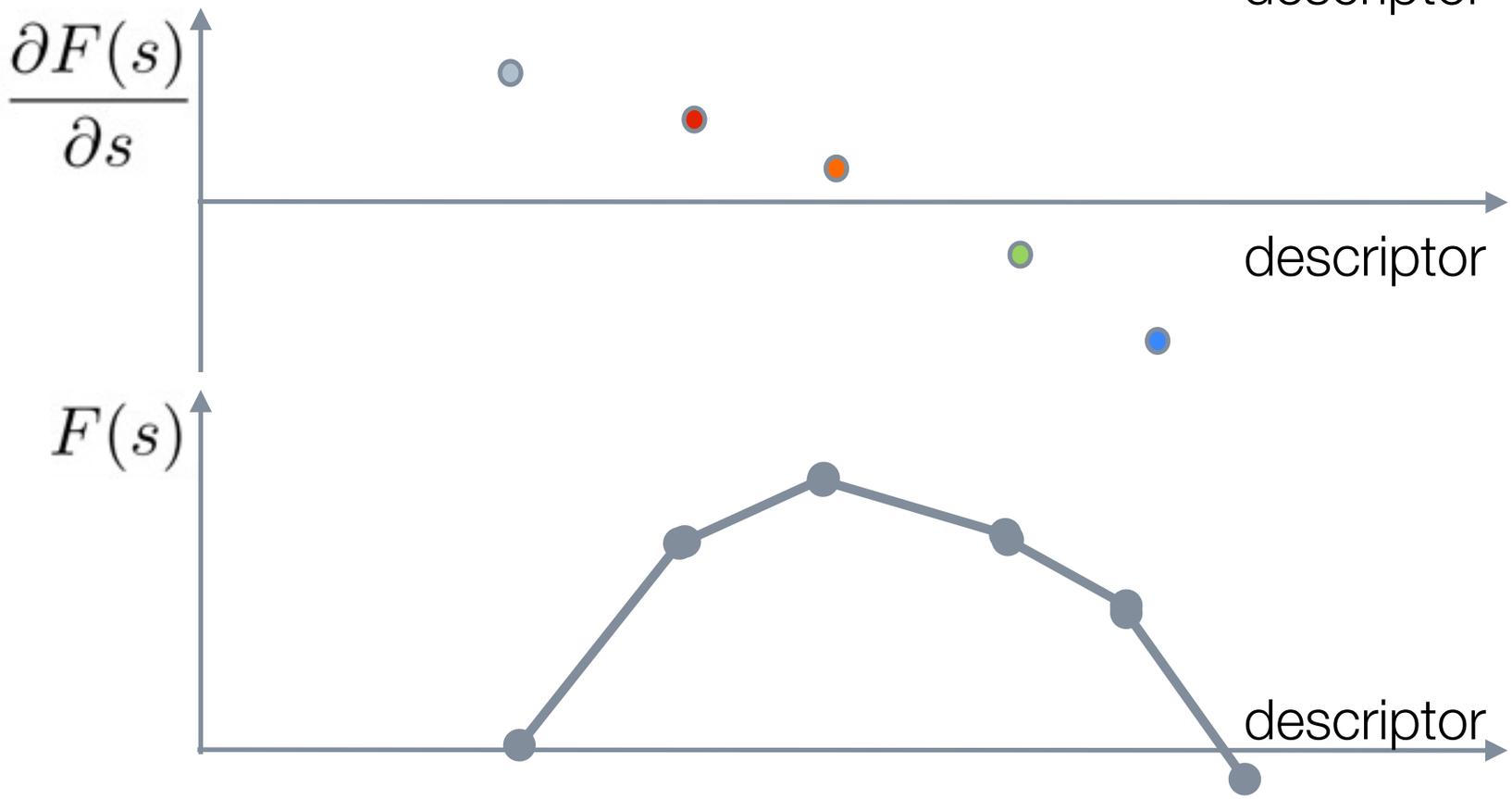
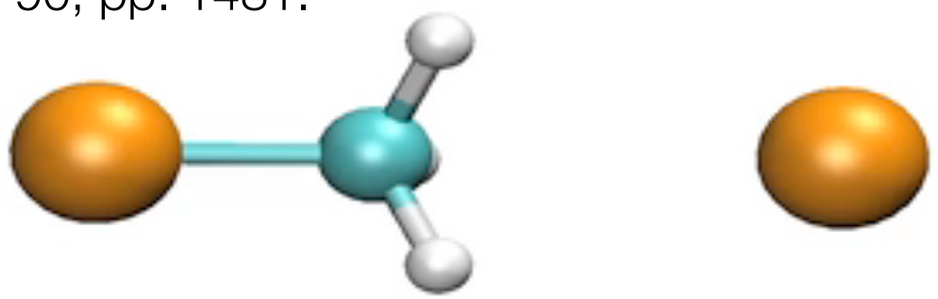




+WHAM etc...

Thermodynamic-Integration-like approaches

* Thermodynamic integration Beveridge, DiCapua, Annu Rev Biophys Biophys Chem 1989, vol 18, pp. 431.
* WHAM Roux, Comp Phys Comm 1995, vol. 91, pp. 275.
* Free energy perturbation Beveridge, DiCapua, Annu Rev Biophys Biophys Chem 1989, vol 18, pp. 431.
* Jarzynski-equation based approaches (steered-MD) Jarzynski Phys Rev Lett 1997, vol. 78, pp. 2690.
* Crooks-equation based approaches (two directions steered-MD)
  Crooks J Stat Phys 1998, vol. 90, pp. 1481.



SN2 reaction: if you like this movie come to the tutorial to see how to make it!

Adaptive sampling vs TI-like methods

Adaptive sampling:

* The problem is multidimensional but probably the accessible phase space is limited: they explore only what you need
* The free energy landscape has competitive, parallel reactive paths (solvent degrees of freedom, rotations) that can be overcome at some point

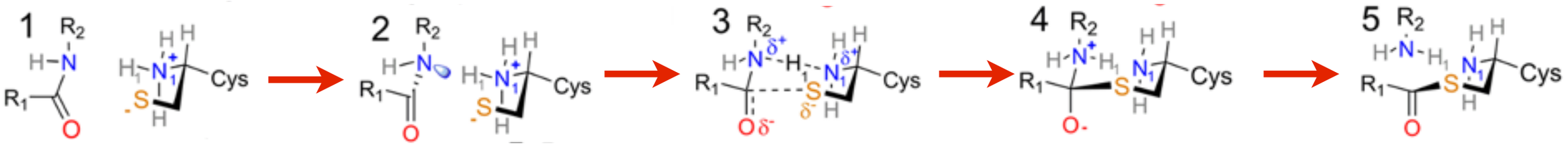
TI-like:

* In 1-d (max 2-d, via WHAM or, better in DFT, rbf fitting schemes) very effective
* Sometimes trivially parallel (many umbrellas at same time)

The problem of the descriptors

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

* A multidimensional landscape: turn into monodimensional



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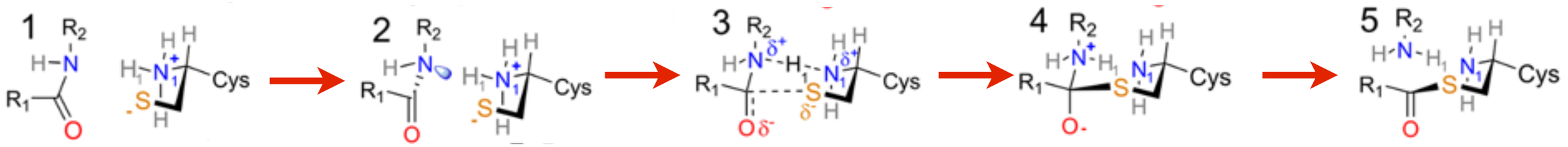

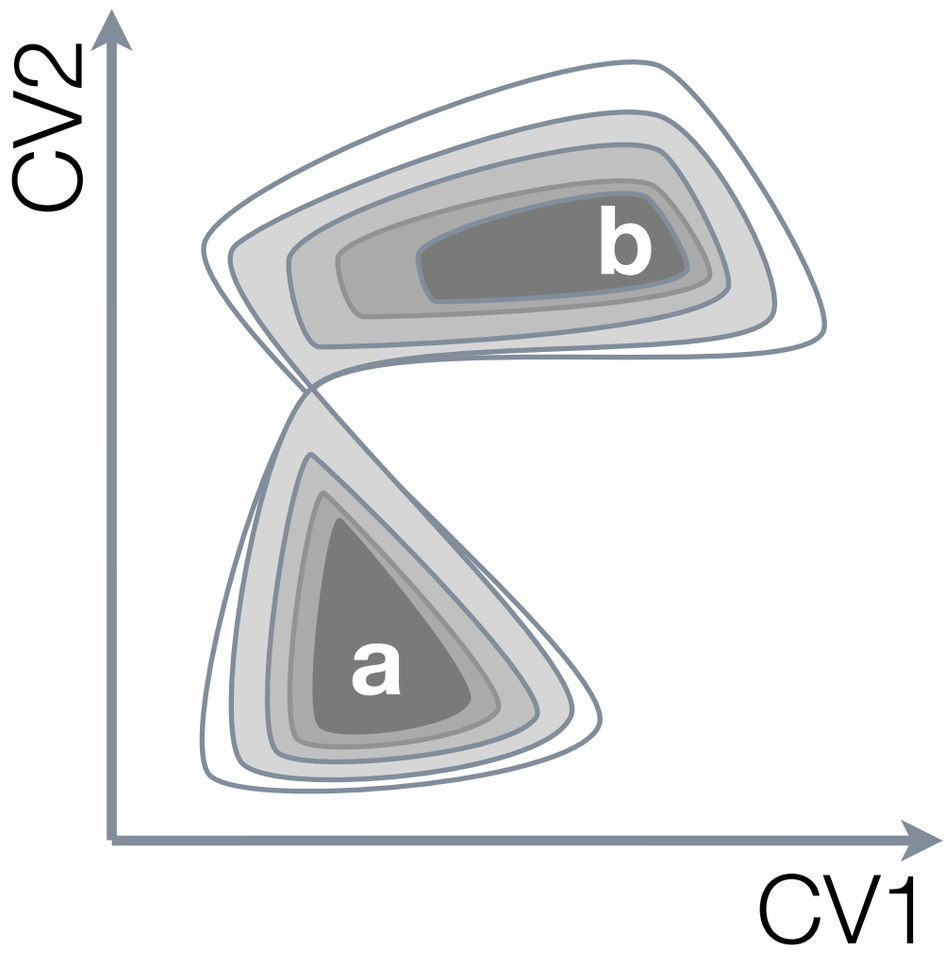

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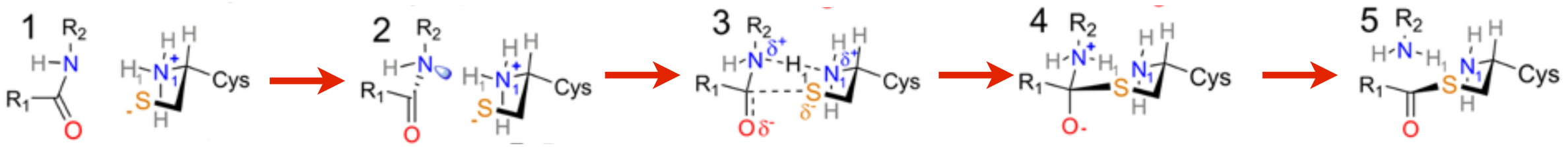

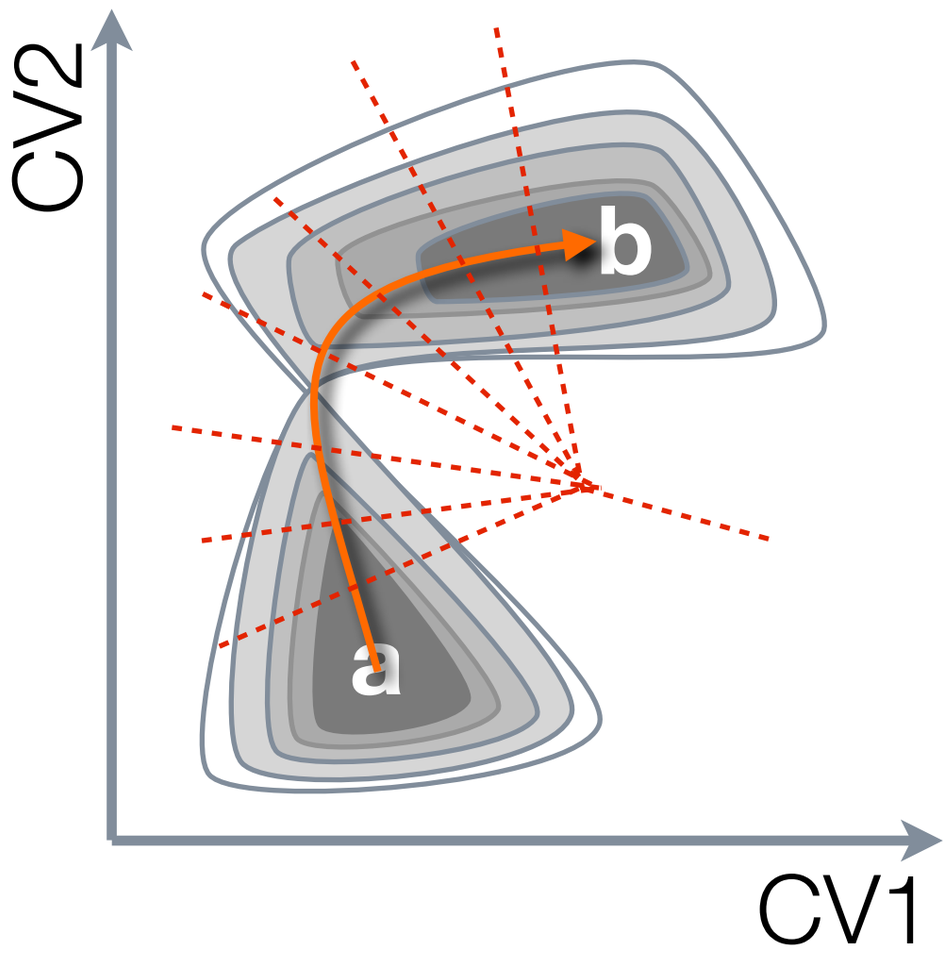

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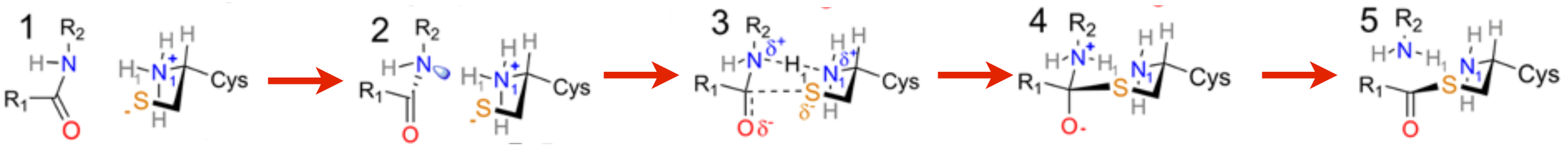
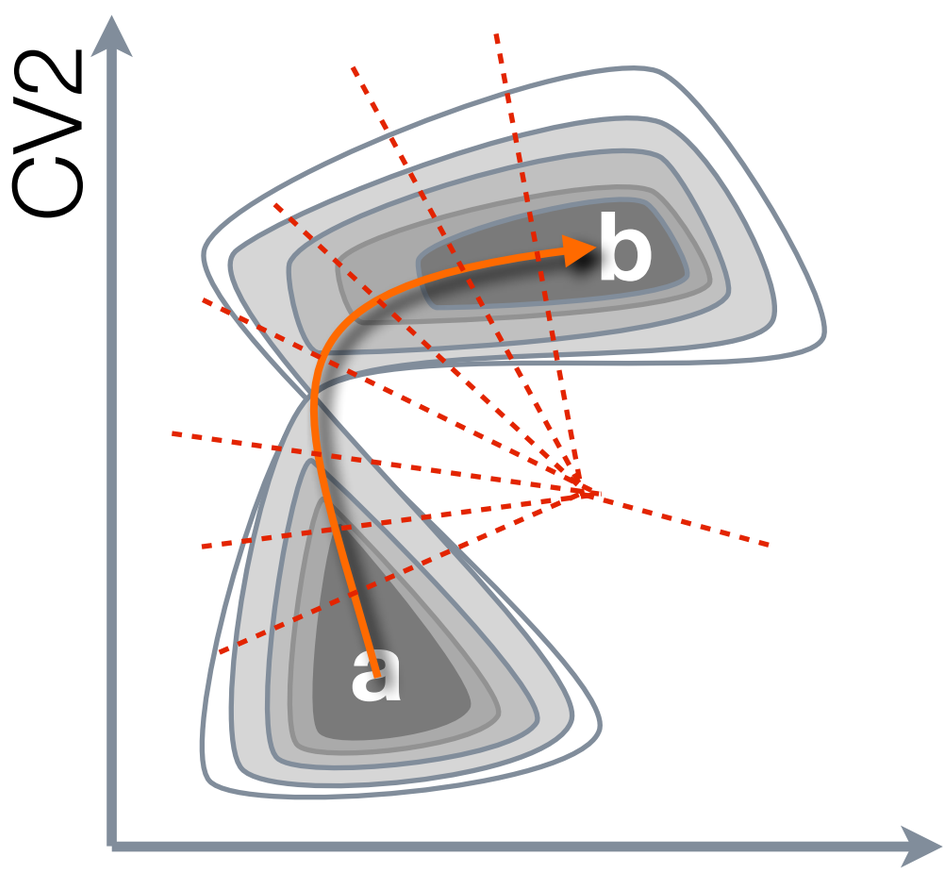
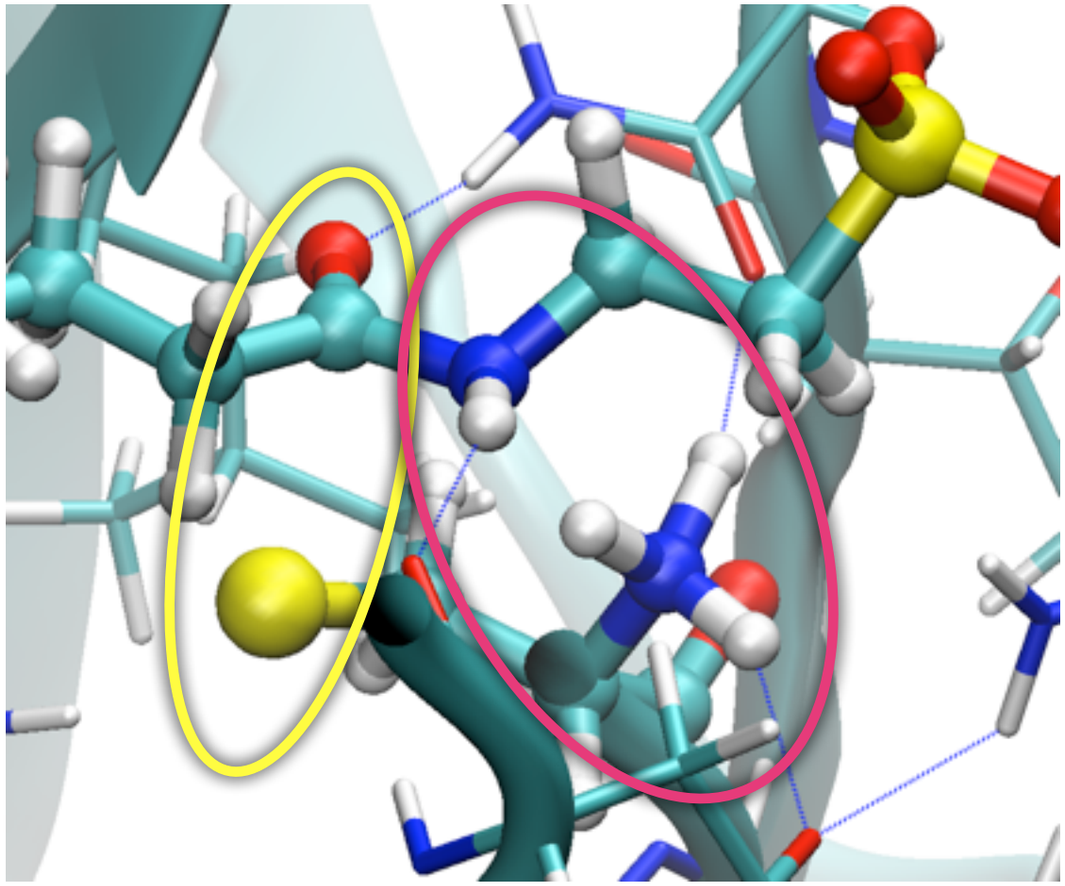


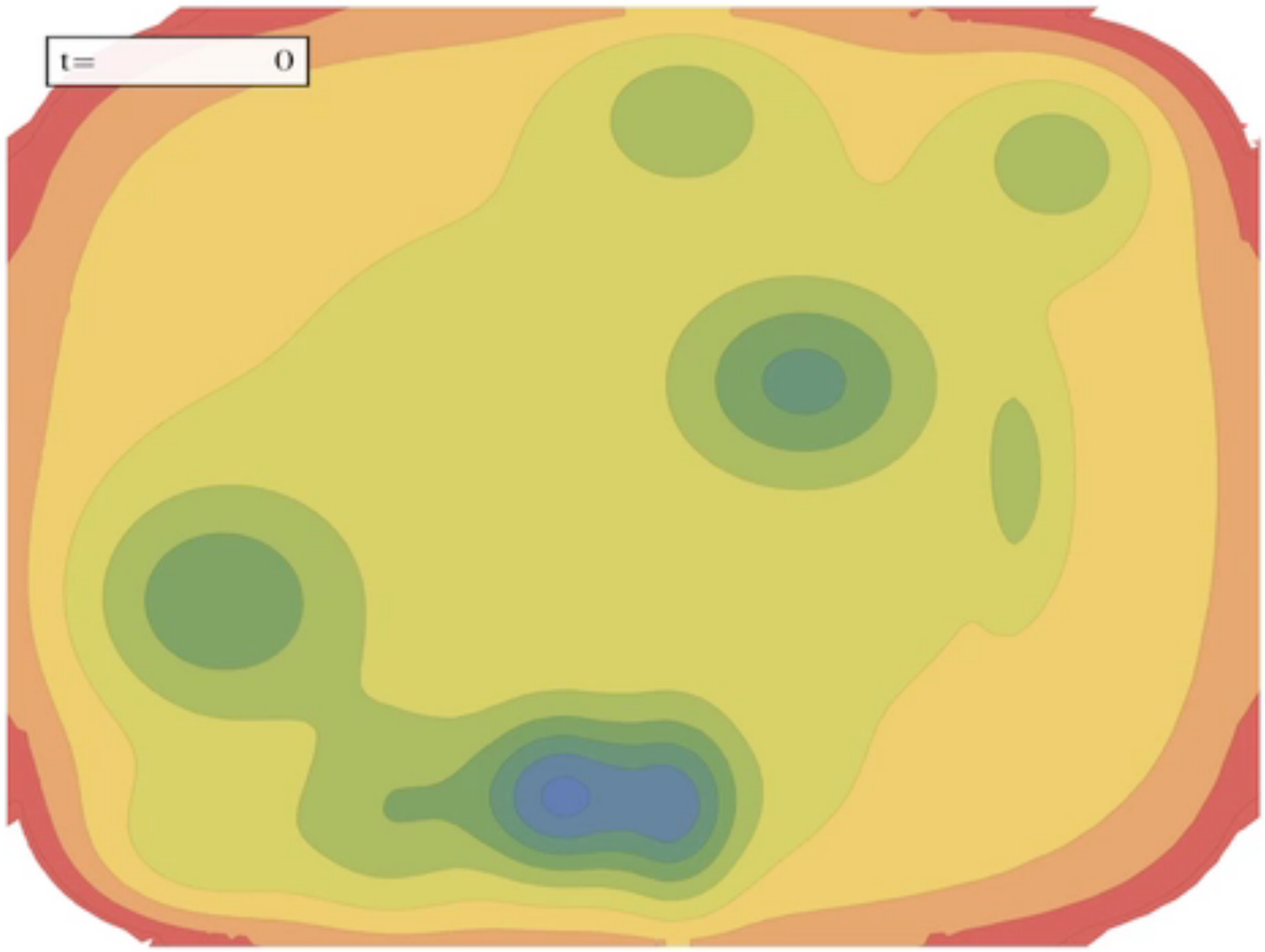




Lodola, Branduardi, De Vivo, Capoferri, Mor, Piomelli, Cavalli, PlosOne, 2012, vol 7, pp. e32397

The problem of the descriptors

* Use machine learning approaches Tribello et. al. PNAS 2010, vol. 107, pp. 17509.

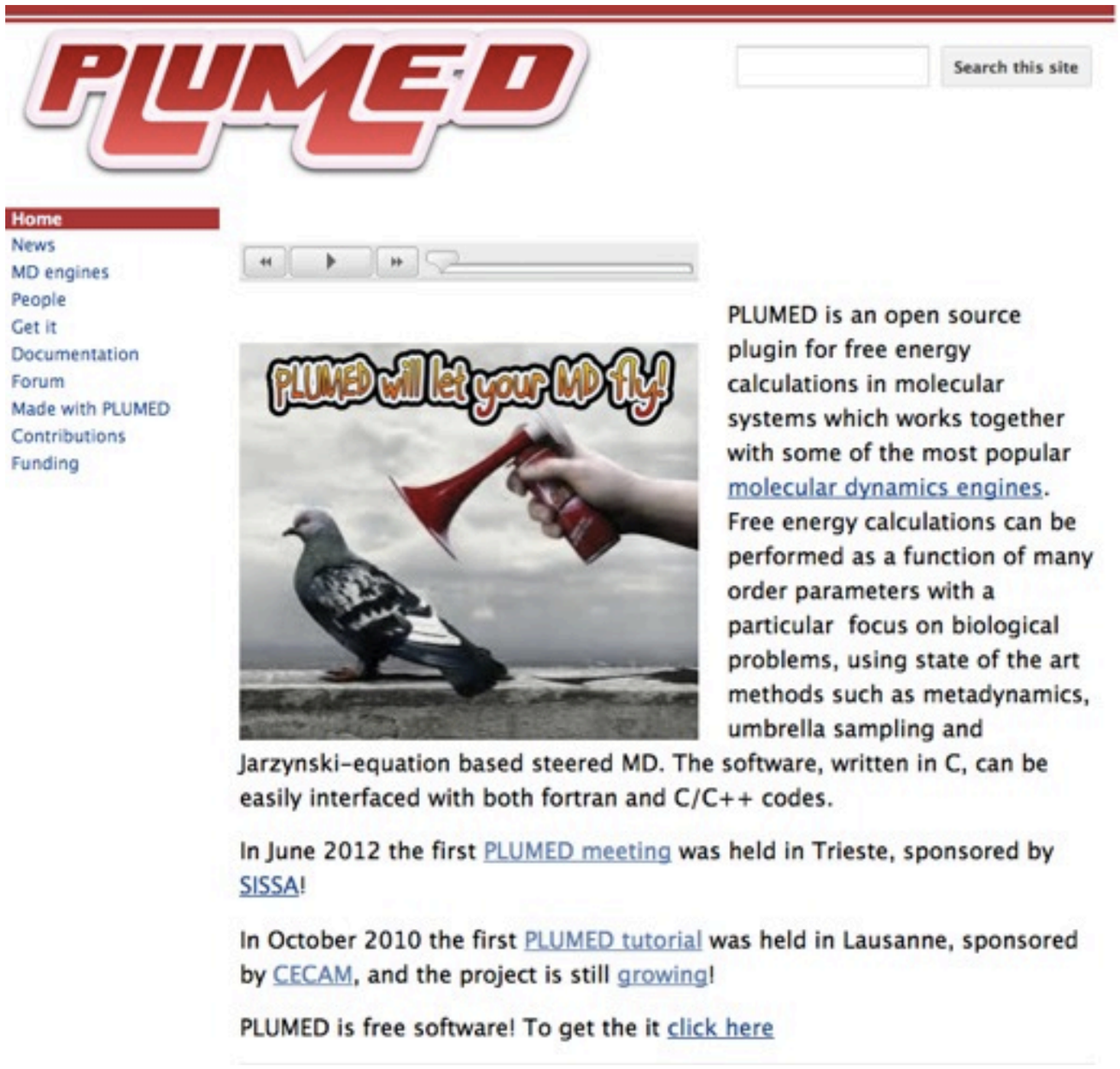


Outline

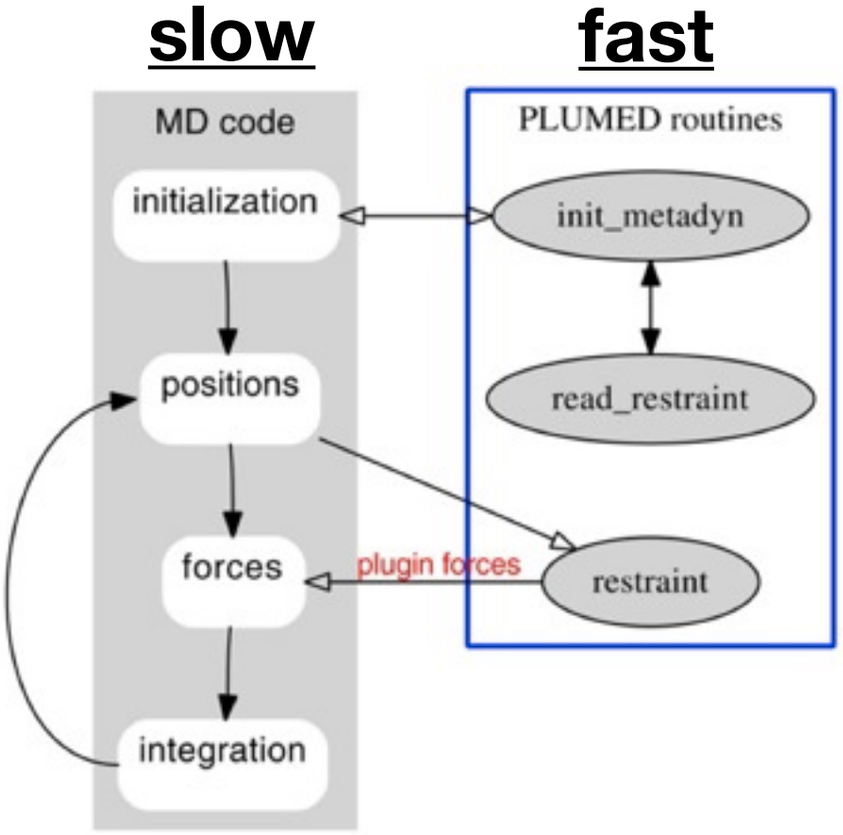
- What is free energy and why is important
- Traditional QM approach
- Explicit sampling
- Enhanced sampling
- **PLUMED plugin for free energy calculations**

The PLUMED plugin: www.plumed-code.org

Bonomi, Branduardi et al., Comp. Phys. Comm. 2009 vol. 180 pp.1961



small connection with MD code



Already in many classical MD codes (LAMMPS, DLPOLY, SANDER, GROMACS, NAMD) **now in FHI-aims**!

PLUMED: what it contains

Methods

- Constrained relaxation
- Umbrella sampling
- Metadynamics (well-tempered)
- d-AFED
- Steered MD
- Harmonic walls
- Ratcheting
- Reweighting schemes
- String method

Descriptors (with der.)

- Distances, angles, dihedrals
- Coordination numbers
- Contact maps
- Path collective variables
- Energy
- Function of variables
- SPRINT variables
- .....

+ MetaGUI analysis interface and PLUMED preparation GUI in VMD+analysis tools!

In FHI-aims

* compile separately: Makefile.meta

* in control.in

```
MD_run   500.0  NVT_parrinello 300 0.01
MD_time_step  0.002
MD_clean_rotations  .true.
MD_restart    .false.
output_level MD_light
MD_maxsteps -1
MD_MB_init  300
MD_RNG_seed 12345
plumed .true.
```

this enables PLUMED

* plumed.dat

```
DISTANCE LIST 1 <g1> SIGMA 0.11
g1->
3 4 5 6
g1<-
DISTANCE LIST 2 <g1> SIGMA 0.11
UWALL CV 1 LIMIT 7. KAPPA 0.5
UWALL CV 2 LIMIT 7. KAPPA 0.5
HILLS HEIGHT 0.00047 W_STRIDE 50
PRINT W_STRIDE 2
ENDMETA
```

set a distance as descriptor

set anotherdistance as descriptor

set repulsive boundaries

set metadynamics

Acknowledgements

* Luca Ghiringhelli (FHI, Berlin)
* The PLUMED developers (ETHZ, USILU, Cambridge, UCSF, SISSA, Mount Sinai, Curtin, EPFL, MPI-BP)
* Giovanni Bussi (SISSA, Triest)
* Michele Parrinello (ETHZ/USILU, Lugano)
* José Faraldo-Gómez (MPI-BP, Frankfurt/Main)

Thank you!