The Abdus Salam
International Centre
for Theoretical Physics

United Nations
Educational, Scientific and
Cultural Organization

IAEA
International Atomic Energy Agency

2549-3

ADGLASS Winter School on Advanced Molecular Dynamics Simulations

18 - 21 February 2013

Advanced Free Energy Calculations at the Solid-Liquid-Interface: Phase Space Sampling with Replica Exchange Simulations

Julian Schneider

Theoretical Chemistry
Technical University Munich
Germany
and
Hybrid Materials Interfaces Group
BCCMS
University of Bremen
Germany

Strada Costiera, 11 - 34151 - Trieste - Italy • Tel. +39 0402240111 • Fax. +39 040224163 • sci_info@ictp.it • www.ictp.it
ICTP is governed by UNESCO, IAEA, and Italy, and it is a UNESCO Category 1 Institute

Advanced Free Energy Calculations at the Solid-Liquid-Interface:

Phase Space Sampling with Replica Exchange Simulations

Julian Schneider
Theoretical Chemistry, Technical University Munich
And
Hybrid Materials Interfaces Group, BCCMS, University of Bremen

ADGLASS School on Advanced Molecular Dynamics Simulations
Trieste 2013

OUTLINE:

Part I

- Experimental context:
  Reaction coordinates, dilution, and standard states.
- Weak binding:
  Surface hydrophilicity vs .adsorption free energy
- Strong binding: Metadynamics

Part II

- Complex Molecules and Surfaces:
  Conformation sampling with Replica exchange techniques
- Analysis beyond Experiments:
  Microscopic Mechanisms of Specific Material Binding

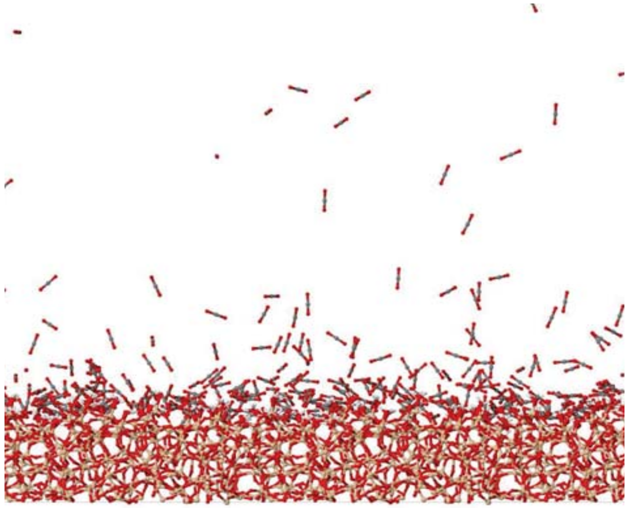
Introduction

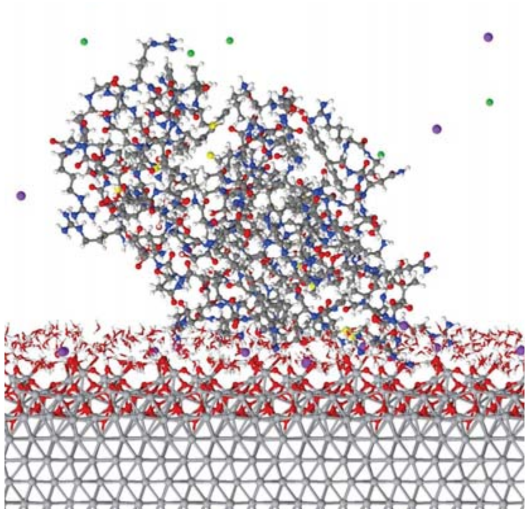
Solid/liquid-interface properties are determined by adsorbed molecules

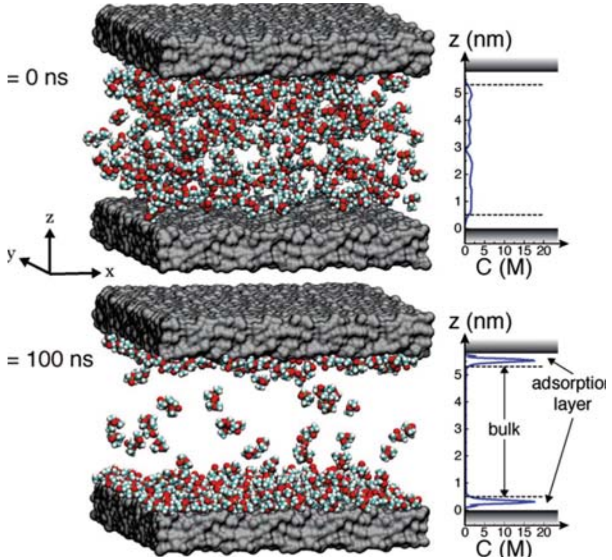
May change functionality of molecules and surface

Free energy change is the driving force for adsorption or desorption

Experimentally accessible observable.







R. Carr et al, J. Phys. Chem. Lett. 2, 1804 (2011)

Free Energy Definitions: The Driving Force at Constant *T*

Thermodynamic definition:

Gibbs free energy $G = H - TS$ (NPT ensemble)

Helmholtz free energy $G = U - TS$ (NVT ensemble)

→ Entropy *S* not an output observable of our simulations!!

How can we then simulate free energies??

Free Energy Definitions: The Driving Force at Constant *T*

Thermodynamic definition:

Gibbs free energy $G = H - T\,S$ (NPT ensemble)

Helmholtz free energy $G = U - T\,S$ (NVT ensemble)

Statistical mechanics definition:

Logarithm of partition function:

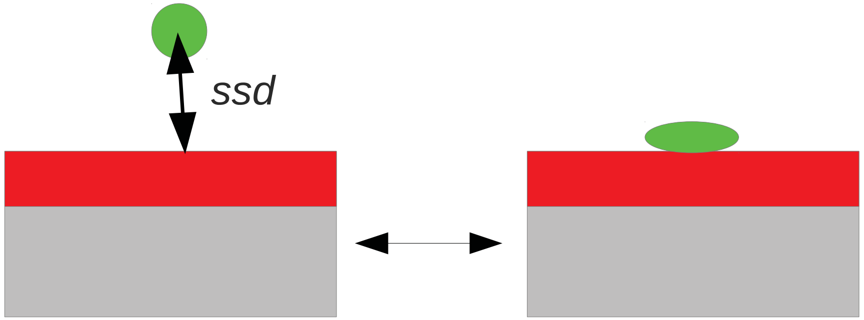
$$G = -k_B T \ln(Z) \qquad \text{where} \qquad Z = \int d\vec{R}\, d\vec{V}\, e^{-\beta H(\vec{R},\vec{V})}$$

Free energy along *reaction coordinate* s(***R***)*:*

$$\boxed{e^{-\beta G(s)} = \frac{1}{Z} \int d\vec{R}\, e^{-\beta V(\vec{R})} \delta(s - s(\vec{R})) \; = \; P(s)}$$

Adsorption Free Energy

Free energy difference between molecule in solution and molecule adsorbed at a solid surface $\Delta G = G_{ads} - G_{solution}$



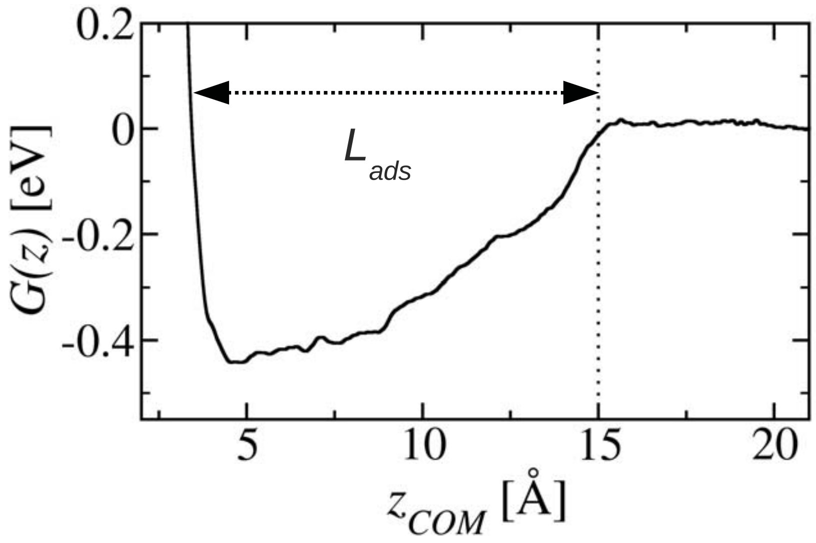
Suitable reaction coordinate to describe ad- and desorption:

- Discriminate between initial and final state
- Not necessarily retrace the exact process (*only for kinetic modelling/transition state theory*)

Adsorption/Desorption can be described by: **Surface separation distance (SSD)**

Adsorption Free Energy

Typical free energy profile: Define border between ads. region and bulk solution



Local probability density :

$$P(s) = e^{-\beta G(s)} \quad \text{with} \quad P_{solution} = e^{-\beta G_{solution}}$$

Average probability density at the surface:

$$\bar{P}_{ads} = \frac{1}{L_{ads}} \int_{z_{min}}^{z_{min}+L_{ads}} dz\, e^{-\beta G(z)}$$

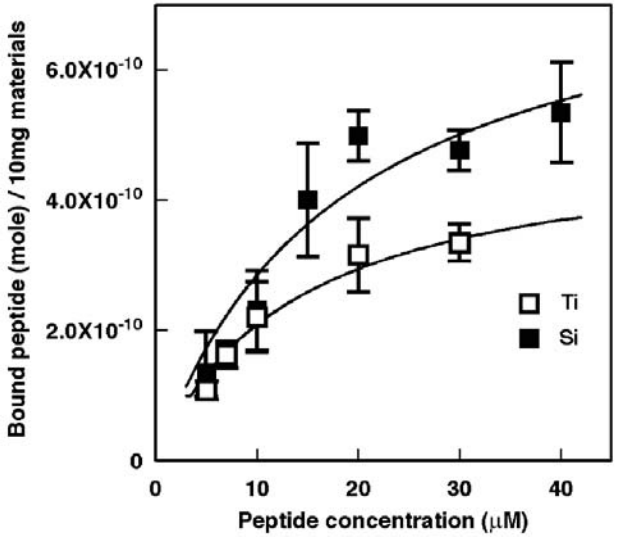
Single molecule equilibrium constant between adsorbed region and bulk solution:

$$K = \frac{\bar{P}_{ads}}{P_{solution}} \longrightarrow \Delta G = -k_B T \ln(K)$$

Experimental Context: Langmuir model

Equilibrium reaction $A + S^* \longleftrightarrow AS$ with $\theta = \frac{n_{ads}}{n_{ads,max}}$

Equilibrium constant: $K_L = \frac{\theta}{(1-\theta)c_{solution}}$



Adsorption isotherm measurements:

$$\theta = \theta(c_{solution})$$

K.-I- Sano et al. Langmuir (2005)

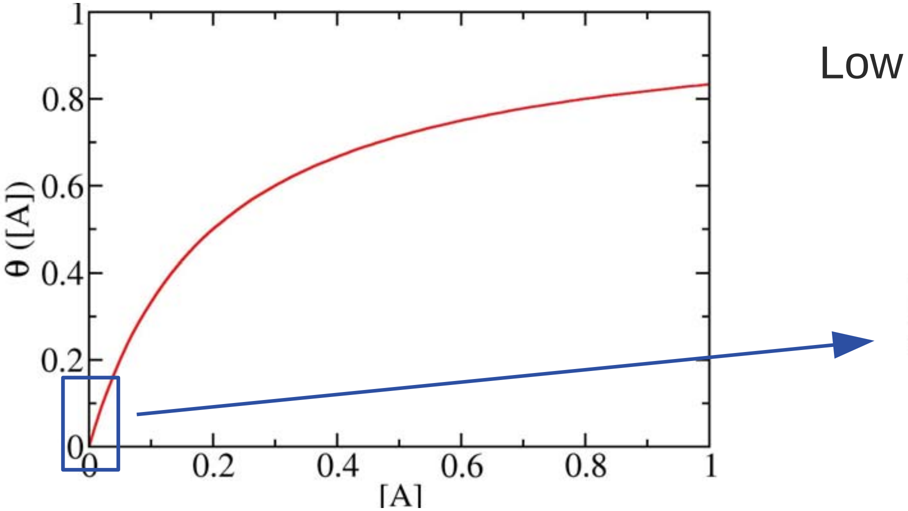
Equilibrium constant K_L obtained by fit to the Langmuir equation

$$\theta(c) = \frac{K_L c}{1 + K_L c} \longrightarrow K_L \longrightarrow \boxed{\Delta G = -RT\ln(K_L)}$$

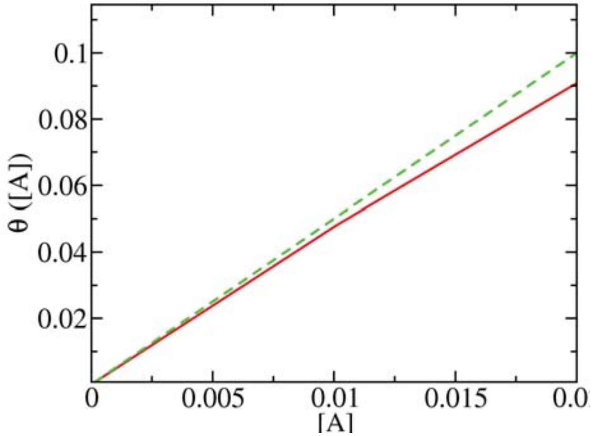
Comparing Experiments to Simulations: Finite vs. Infinite Dilution

We measure:

Surface density / coverage of adsorbed molecules at a *finite solution concentration*



Low concentration limit: $\theta(c) \simeq K_L c$



See also: R. Carr et al, J. Phys. Chem. Lett. 2, 1804 (2011)

We simulate:

Free energy difference ΔG between *one molecule* in solution and adsorbed at the surface

Comparing Experiments to Simulations: Standard State Conversion

We measure:

Standard states: Solution concentration in *mol/l* ⟷ Surface coverage

$$K^{\exp} = \frac{\theta}{c_{solution}}$$

We simulate:

Difference in (probability) densities at the surface and in solution:

Solution concentration (in *mol/l*) ⟷ Surface concentration *(in mol/l)*

$$K^{simul} = \frac{c_{surf}}{c_{solution}}$$

Standard state conversion necessary: $c_{surf} = \theta \frac{n_{ads}^{max}}{A_{surf} L_{ads}}$

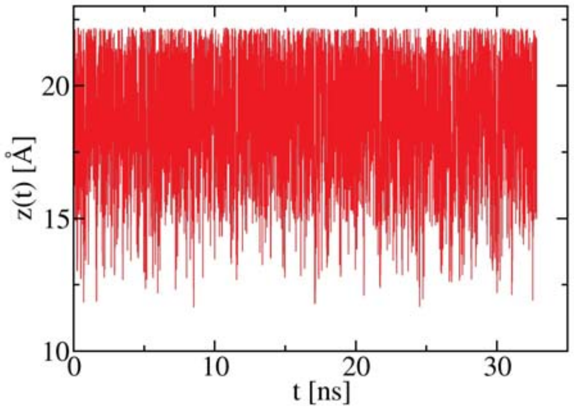
Strategies for the Calculation of Adsorption Free Energies

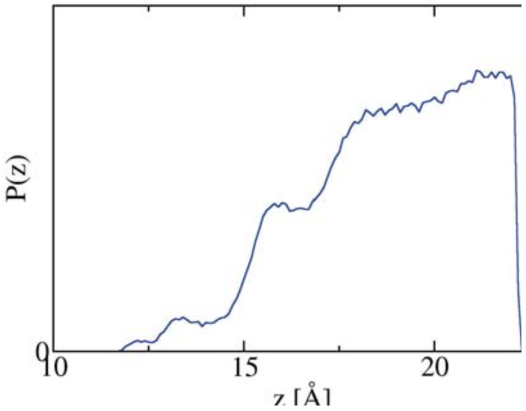
Using the probability/histogram method:

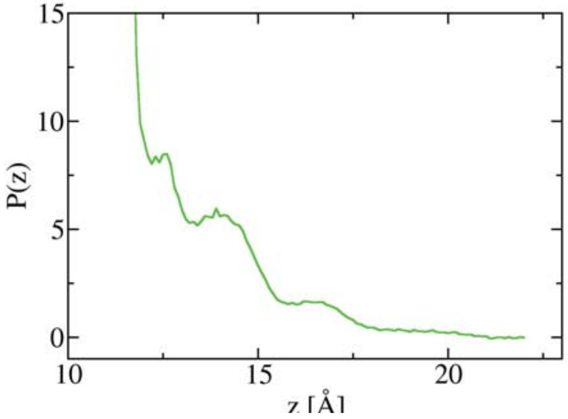
$$P(s) \sim \exp[-\beta G(s)] \quad \longleftrightarrow \quad \boxed{G(s) = -RT\ln(P(s)) + C}$$

Histogram measured in long equilibrium simulation

$$s(t) \rightarrow P(s) \rightarrow G(s)$$

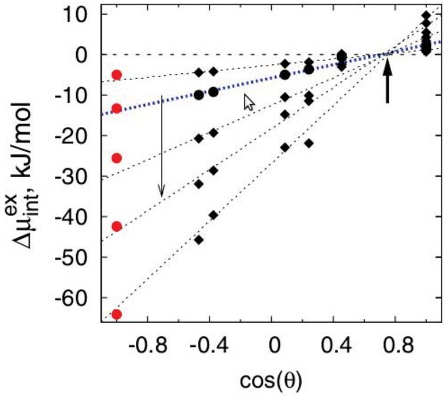






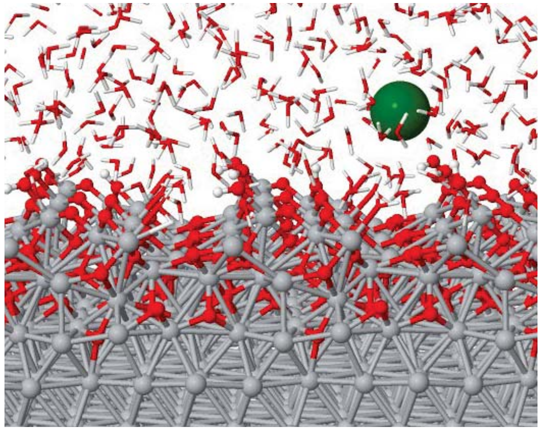
Works well for *weakly attractive* or *weakly repulsive* adsorbate-molecules-interactions

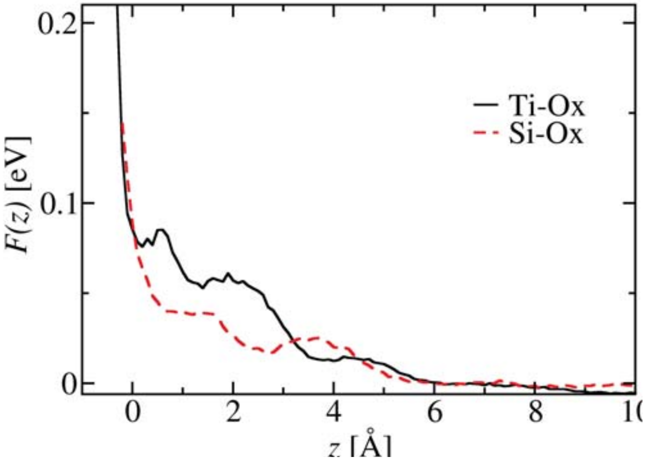
Example: Probing Local Hydrophilicity

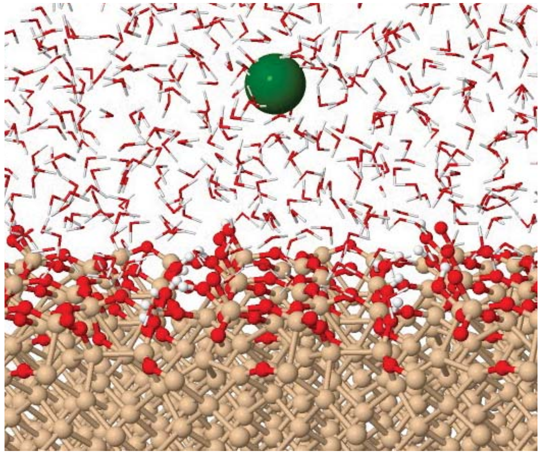


Adsorption free energy of a hydrophobic probe molecule is related to the water contact angle.

R. Godawat et al. PNAS 106, 15119 (2009).







Oxidized Titanium

Oxidized Silicon

Positive Δ*G* reveals hydrohilic character of oxidized surfaces.

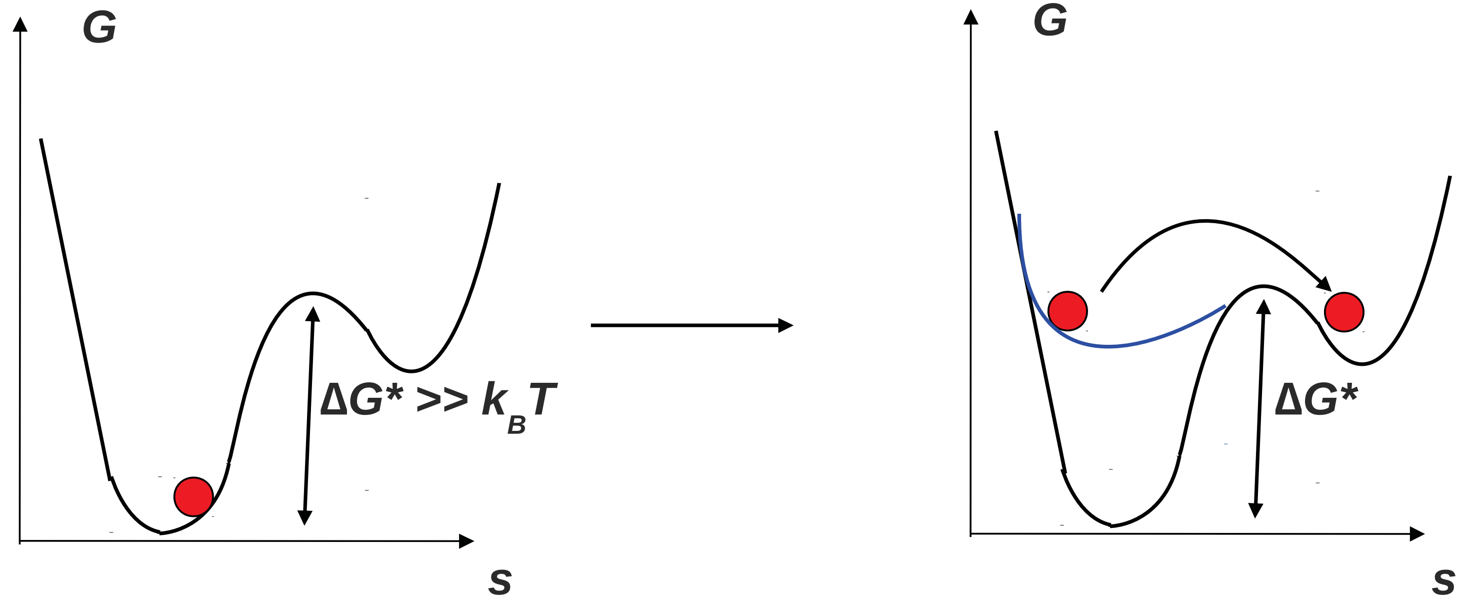
Ti-Ox more hydrophilic compared to Si-Ox.

J. Schneider and L. Colombi Ciacchi, JACS 134, 2407(2012

Strong Binding to the Surface:
The Sampling Problem **(Part I)**

The reaction coordinate is trapped in a free energy minimum:
No spontaneous desorption!

Adding a ***bias potential V_{bias}*** to push the RC out of the valley**.**



Reweighting to recover the original system:

To recover the original *free energy landscape*: ***Well-tempered Metadynamics, Umbrella sampling + WHAM, ...***

To recover the original *dynamics*: ***Hyperdynamics***

Metadynamics: Constructing the Bias-Potential on-the-Fly!

Adaptive time dependent bias-potential to repel the RC from previously visited values:

$$V_{bias}(\vec{R},t)=\sum_{t'=t_0}^{t} W_0\, e^{-V_{bias}(s(t'),t')/\Delta T} \exp\left[\frac{-(s(\vec{R})-s(\vec{R}(t')))^2}{2\sigma^2}\right]$$

Sum over RC values visited during simulation

Adaptive height, depending on the current bias potential

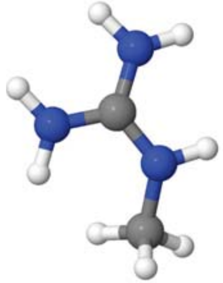
Gaussian hill centered at the current RC value

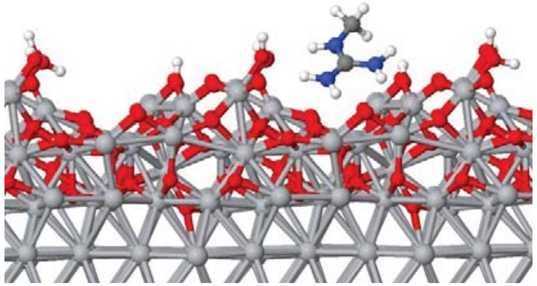
Converged bias potential can be related to the unbiased free energy profile *G(s)* via

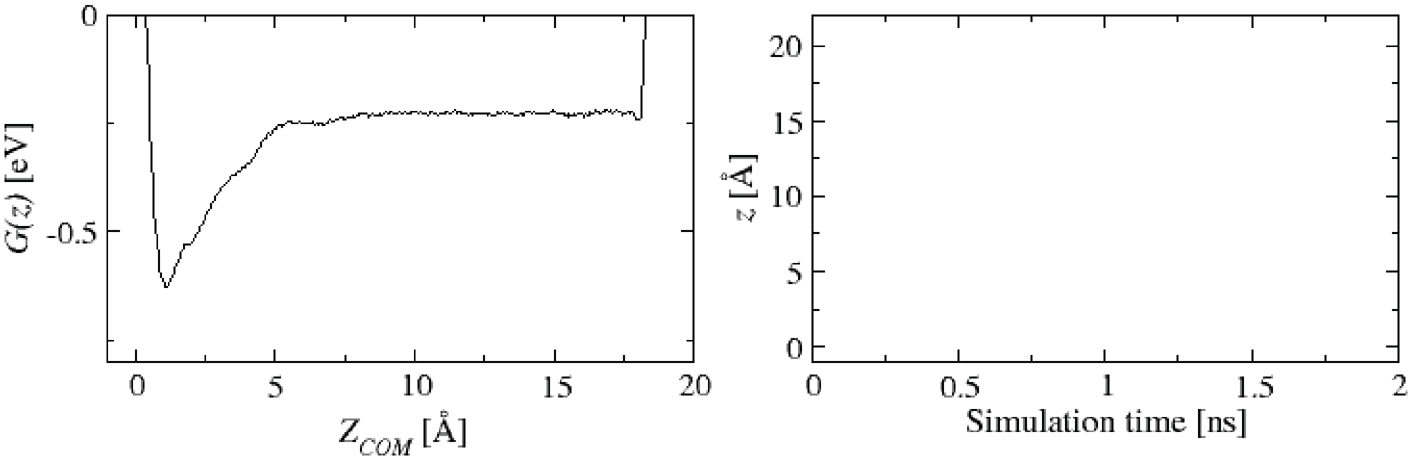
$$\boxed{\lim_{t\to\infty} V_{bias}(s,t)=-\frac{\Delta T}{T+\Delta T}G(s)}$$

A. Barducci at al, Phys.Rev. Lett. 100, 20603 (2008)

Example: End Group of Arginine on Ti-Ox in Water



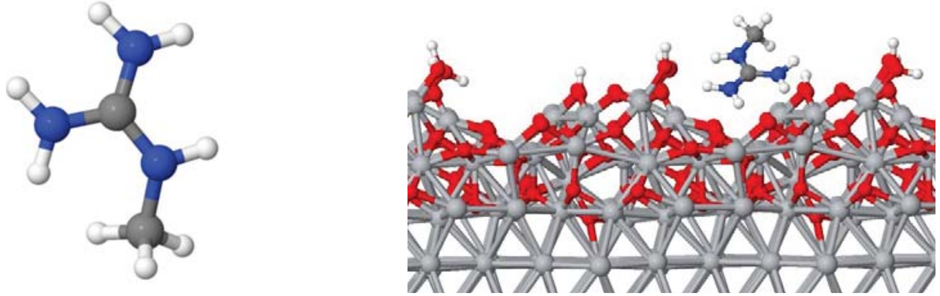




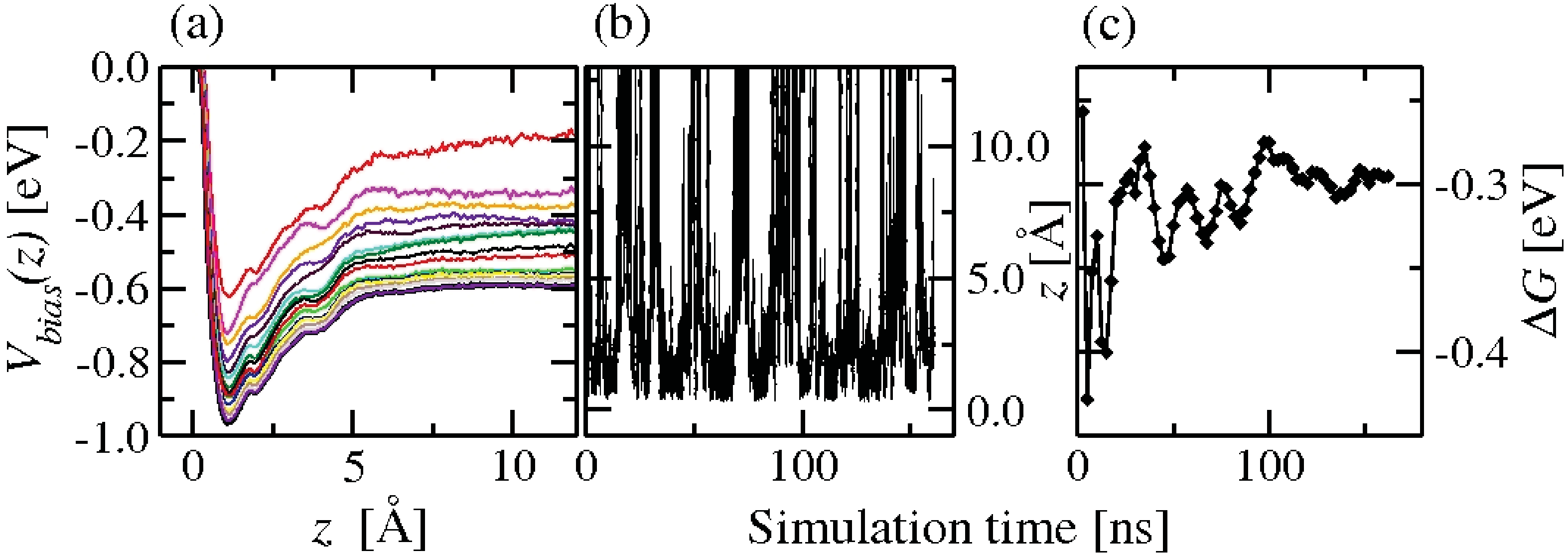
Julian Schneider
Theoretical Chemistry, TU Munich

Department Chemie

Example: End Group of Arginine on Ti-Ox in Water



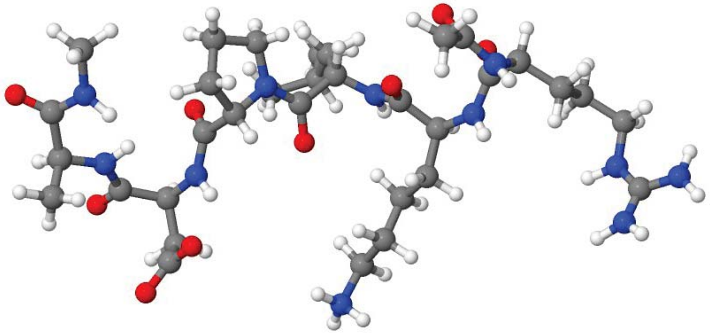
Good convergence!

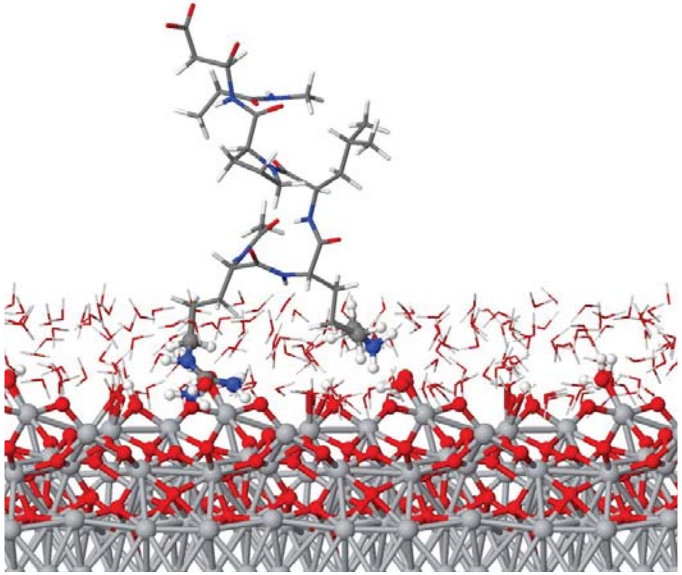


Can we apply the same recipe to a larger Molecule?

The model system:
The minimum titanium-binding peptide motif min-TBP-1, built by the amino acid sequence RKLPDA.

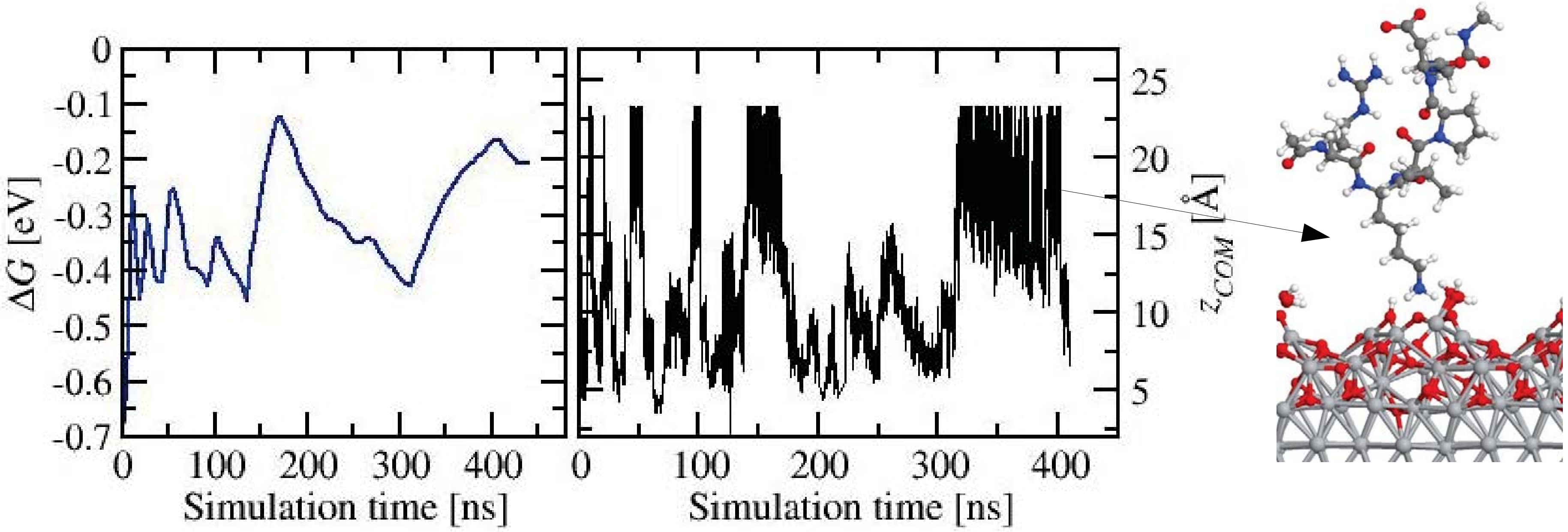
K.-I. Sano et al.,JACS (2003)





Can we apply the same recipe to a larger Molecule?

Metadynamics to sample along the z-component of the COM of minTBP-1



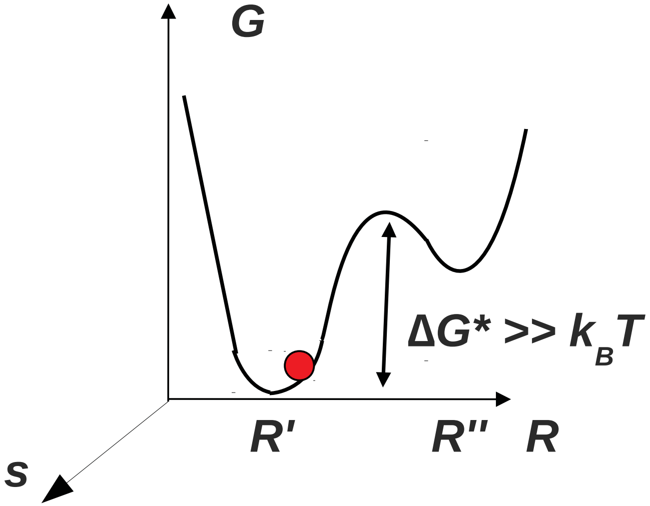
Have we captured all relevant peptide conformations and adsorption sites with the correct statistical weight ??

The Sampling Problem, Part II

Sampling the slow transverse degrees of freedom, i.e. all conformations ***R*** associated with the RC value *s:*

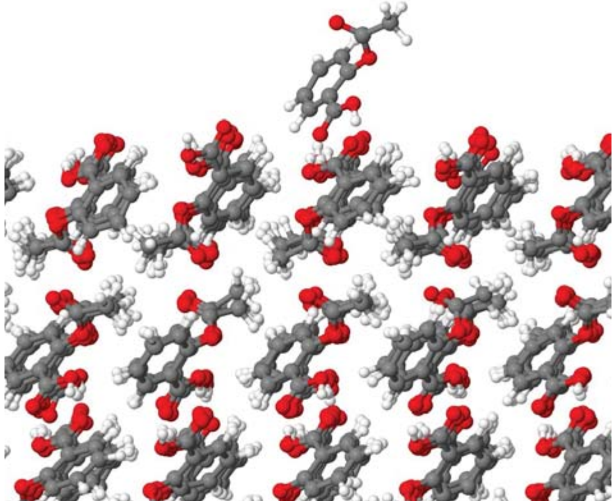
$$e^{-\beta G(s)} = \frac{1}{Z} \int d\vec{R}\, e^{-\beta V(\vec{R})}\, \delta(s(\vec{R}) - s) \approx \frac{1}{\tau_{simul}} \int_0^{\tau_{simul}} dt\, \delta(s(\vec{R}) - s)$$

The problem: Different conformations ***R'*** and ***R''*** might be separated by large barriers!



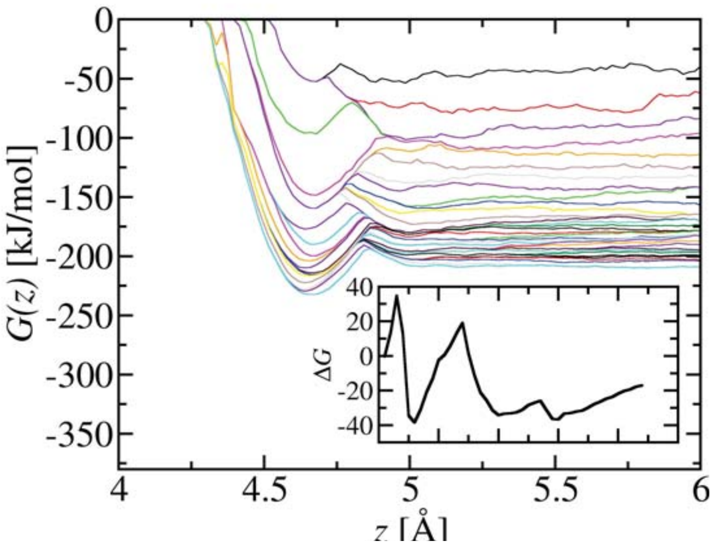
Pathologic case: Aspirin Adsorption and Desorption

One aspirin ad-molecule on a perfect crystal (100)/water interface:



Constrained to move only vertically, no rotation.

Z_{COM} as CV.



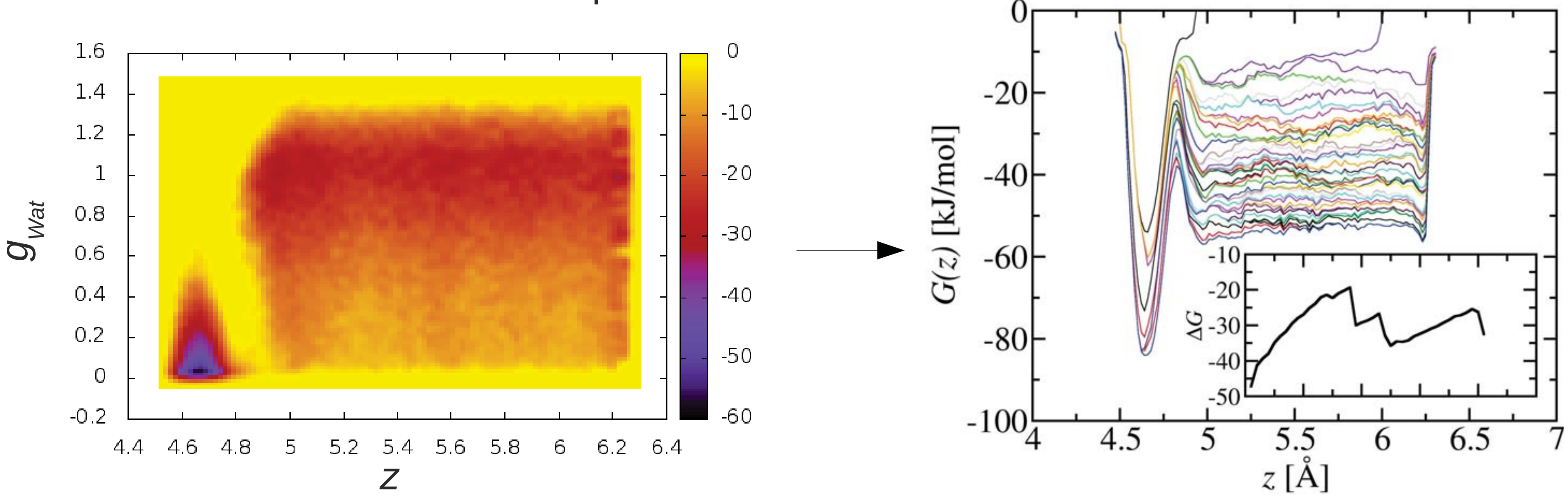
Where does the bad convergence behaviour come from?

Transverse DOF: One water molecule jumps in and out of the binding site!

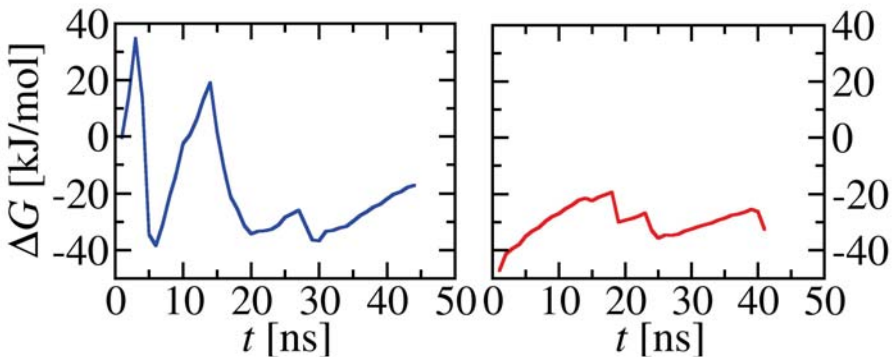
→ Hysteresis!

One transverse CV: Aspirin Adsorption and Desorption

Additional CV: Coordination number g_{Wat} of water molecules
Around the COOH H-bond receptor.

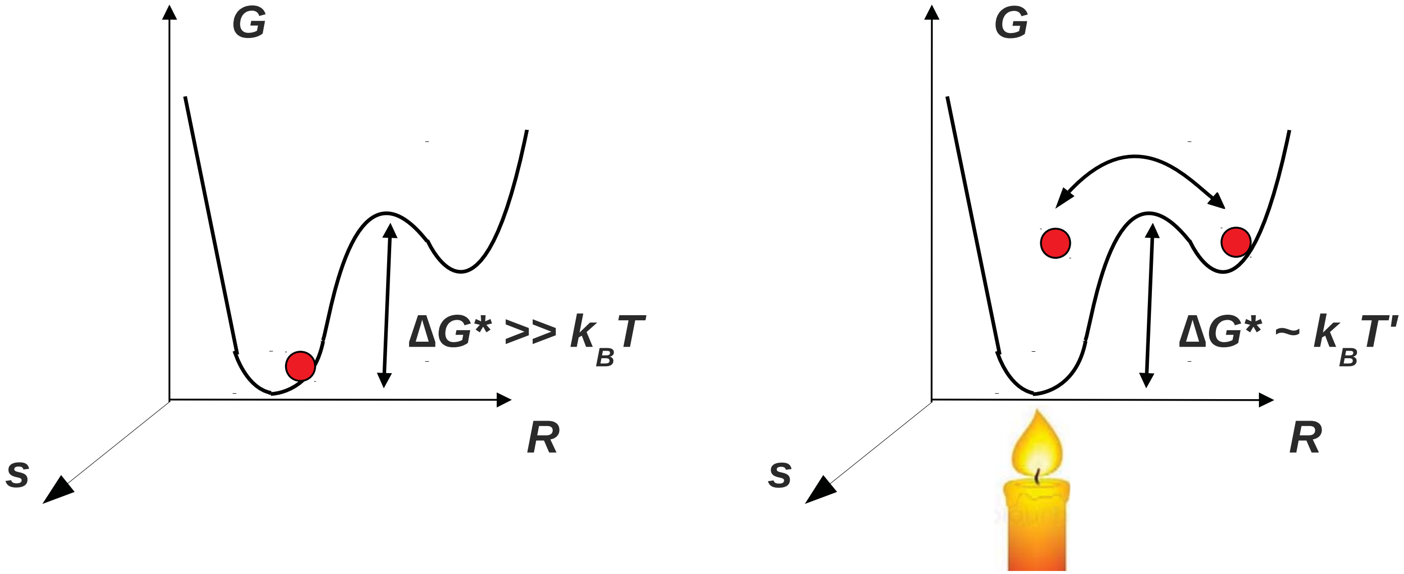


Convergence behaviour significantly improved!



The Sampling Problem, Part II

We need a *secondary sampling engine* which takes care of the transverse phase space!



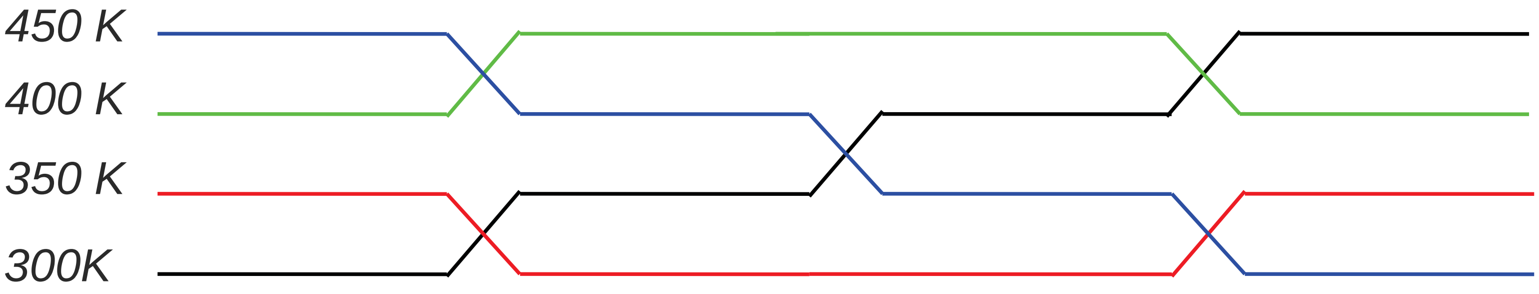
We can increase the temperature to overcome barriers!

BUT: We want to sample our free energy profile at room temperature..

→ **Replica Exchange !**

Replica Exchange Molecular Dynamics (REMD)

Several replicas of the system are simulated at different temperatures.
Exchange of temperatures is attempted with a certain frequency.



Exchange criterion obeys *detailed balance*:

$$P(i \rightarrow j) = \exp\left[-(\beta_i - \beta_j)(E_j - E_i)\right]$$

to ensure sampling from a canonical ensemble.

High-T-replicas can easily overcome intramolecular barriers.
Conformations are sampled from the RT replica.

BUT: Low probability states are still rarely sampled!

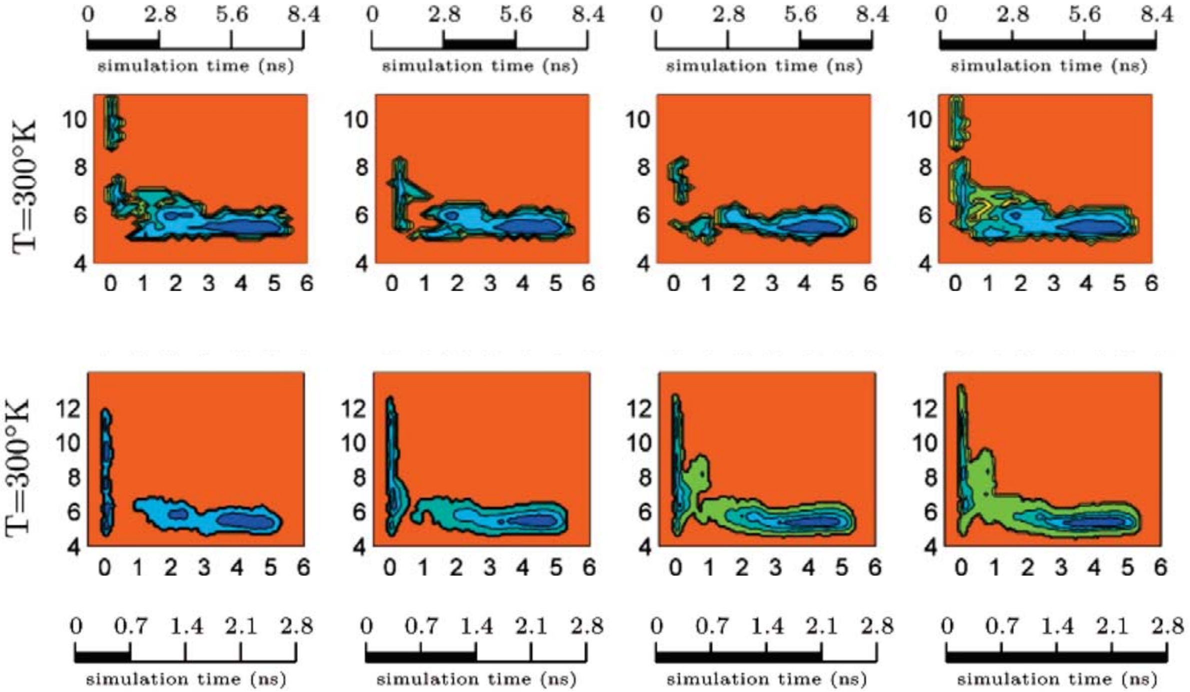
Combination of Metadynamics and REMD

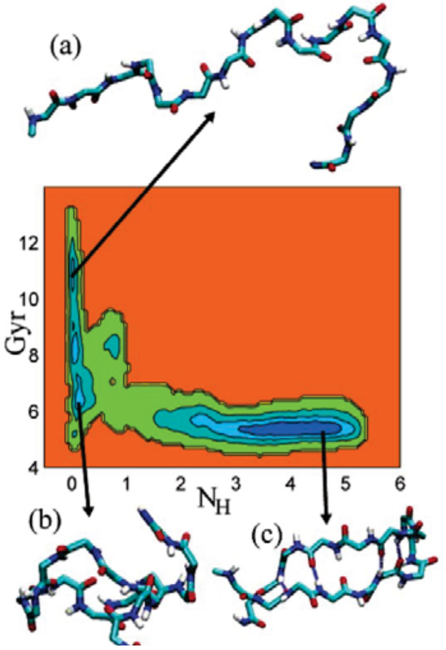
Metadynamics as primary method to sample along the RC combined with REMD to enhance conformational sampling:

Example: Folding of a hairpin peptide consisting 16 amino acids
64 Replicas spanning temperature range 270 – 695 K

MetaD

MetaD
+
REMD





G. Bussi et al, JACS 128, 13441 (2006)

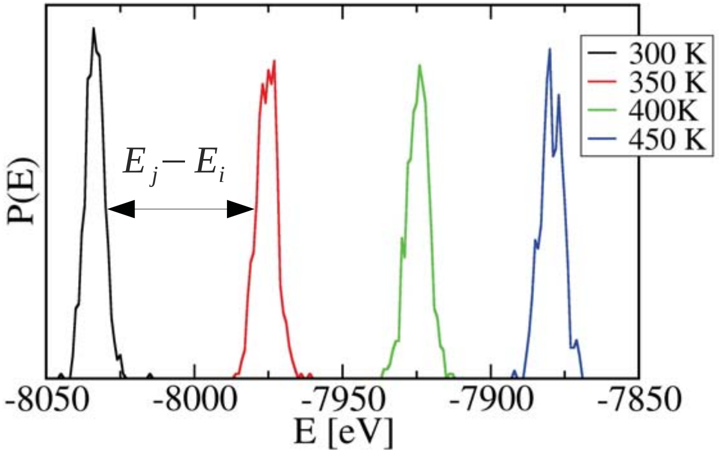
Back to the Adsorption problem:

Timescale ~100 ns, 10000 Atoms, 8 Processors per Replica.

With 64 replicas ──► 512 CPUs several hundreds of ns

Can we afford that?

Why can't we use only 4 replicas?



$$P(i \rightarrow j) = \exp\left[-(\beta_i - \beta_j)(E_j - E_i)\right]$$

Sufficient *overlap* of the energy distributions is required for exchange between neighboring replicas!

──► **Large number of replicas!**

How can we decrease the numbers of replicas?

We heat up mostly *water*, while we primarily want to overcome barriers in the *adsorbate molecule's degrees of freedom*...

So why not anneal only these degrees of freedom?

Replica Exchange with Solute Tempering (REST)[1]

Selective tempering of the solute molecule at temperature T_i is achieved by rescaling the potential energy surface:[2]

$$\boxed{E(\vec{R}, T_i) = \frac{T_0}{T_i} E_{pp}(\vec{R}) + \sqrt{\frac{T_0}{T_i}} E_{pw}(\vec{R}) + E_{ww}(\vec{R})}$$

All replicas are simulated at a physical temperature T_0.
The replicas exchange their Hamiltonians rather than their temperatures:

→ **Hamiltonian Replica Exchange (HREX)**

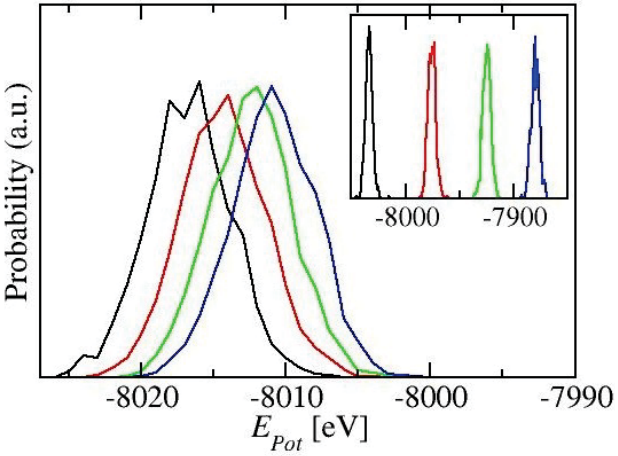
$$P(i \rightarrow j) = \exp\left[-\beta[U_j(\vec{R}_i) - U_i(\vec{R}_i) + U_i(\vec{R}_j) - U_j(\vec{R}_j)]\right]$$

---

[1]: *P. Liu et al, PNAS 102, 13749 (2005)*
[2]: *L. Wang et al. J. Phys. Chem. B 115, 9431 (2011)*

Replica Exchange with Solute Tempering

Improved overlap of energy distributions → Enhanced exchange probability!

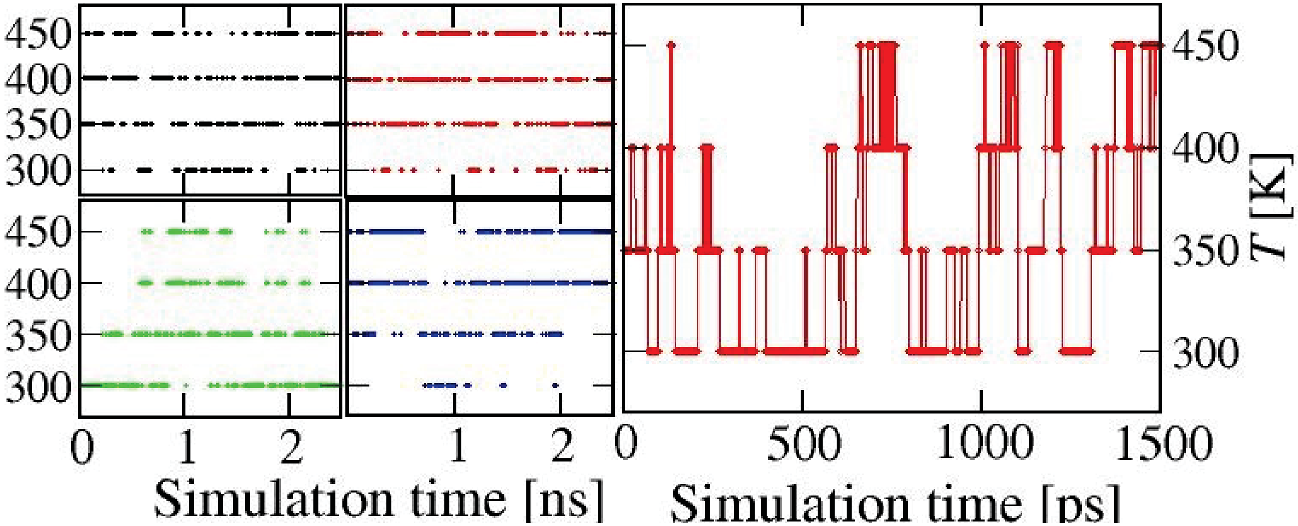


- ✓The system obeys detailed balance.
- ✓The conformations are sampled from a canonical ensemble.
- ✓Only the base replica has a physical meaning.
- ✓The diffusion between bottom and top temperature is much faster.

Caution:

- ✗ Separation of replicas may be encountered
- ✗ Barriers associated with the solvent confirmation are not tackled.

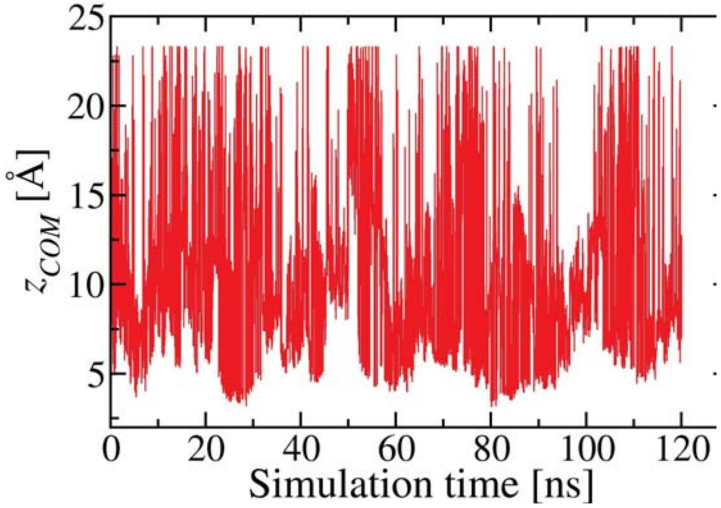
Application to Ti-Ox + minTBP-1



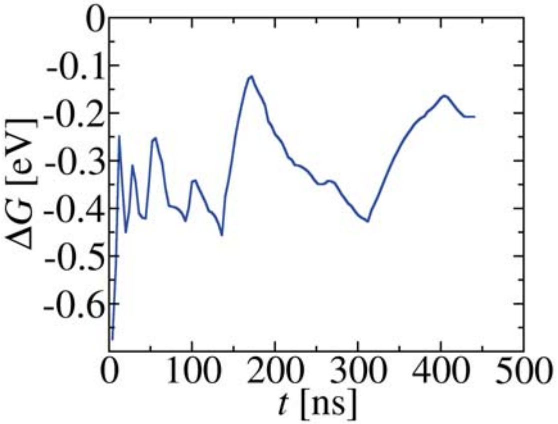
- ✓ All replicas visit all temperatures
- ✓ The diffusion of a replica from bottom to top takes place in ~1ns.

Sampling and Convergence of MetaD+REST

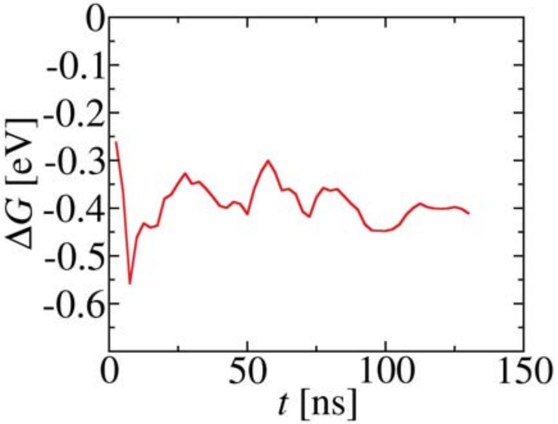
RC sampling with MetaD+REST



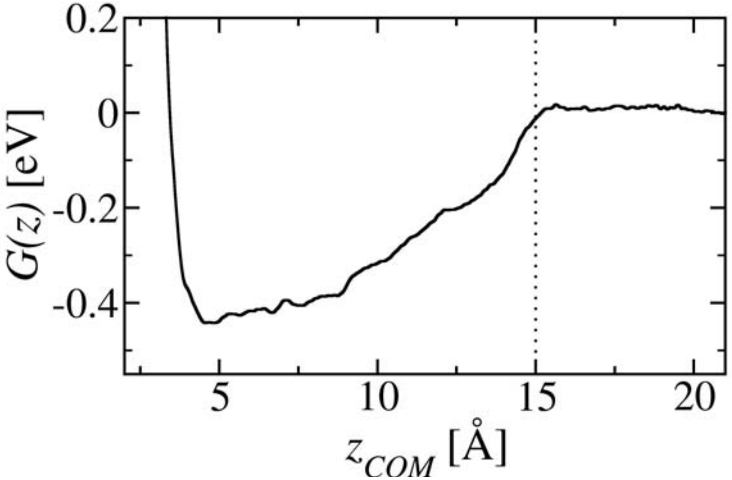
Metadynamics alone



Metadynamics + REST



Converged Adsorption Free Energy Profile

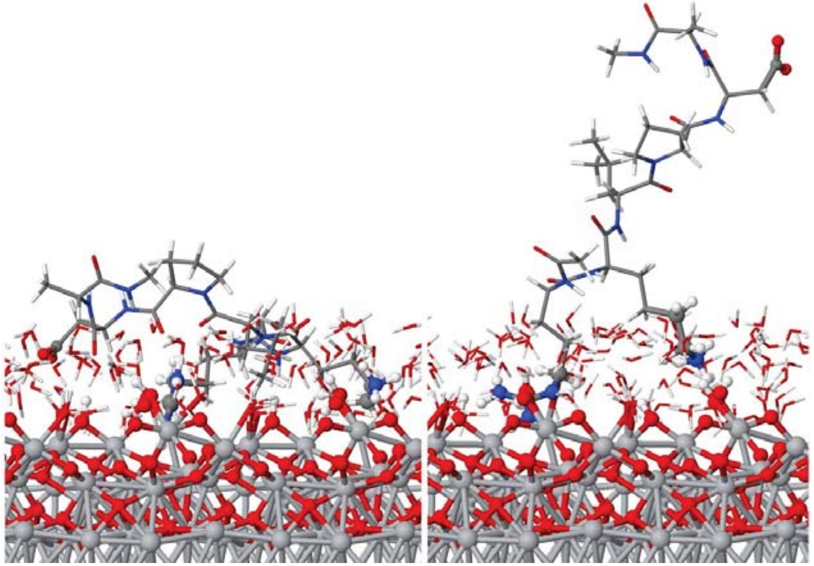


$$\Delta G^\circ = -k_B T \ln\left(c_{surf}/c_{solution}\right)$$

$$\boxed{\Delta G_{ads} = -0.4 \pm 0.04\ eV}$$

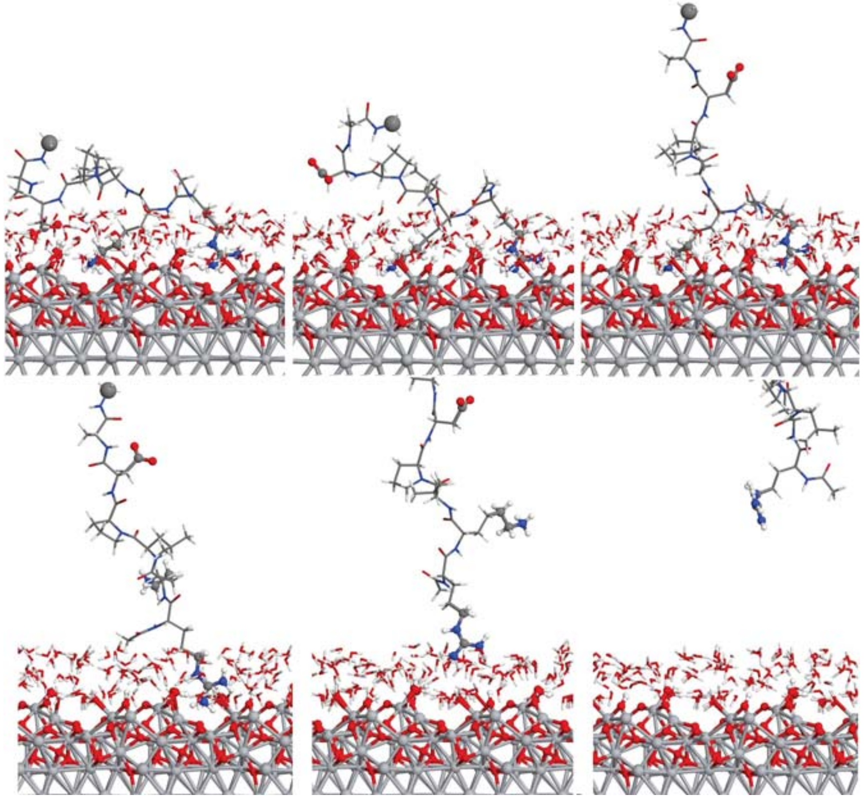
- ✓ Good agreement with experiments!

2 main adsorbed conformations
Identified from MetaD+REST trajectory

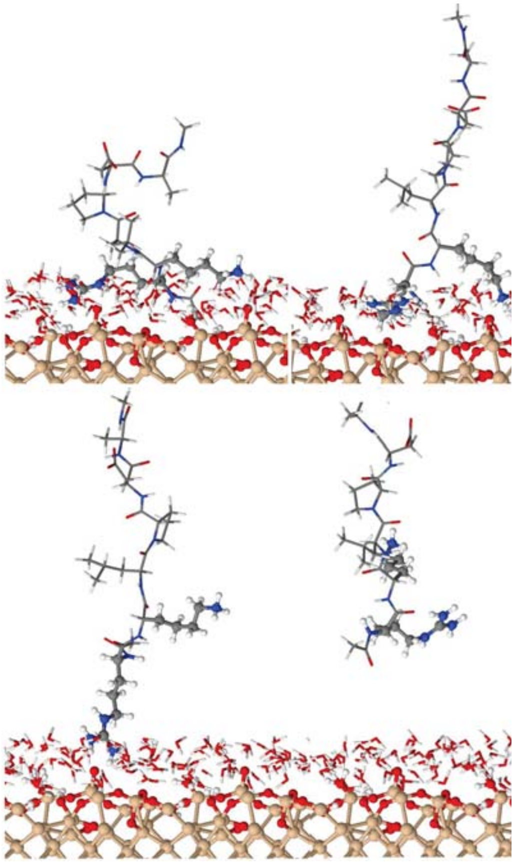


J. Schneider and L. Colombi Ciacchi, JACS 134, 2407(2012)

Comparison of Ti and Si Adhesion



Titanium



Silicon

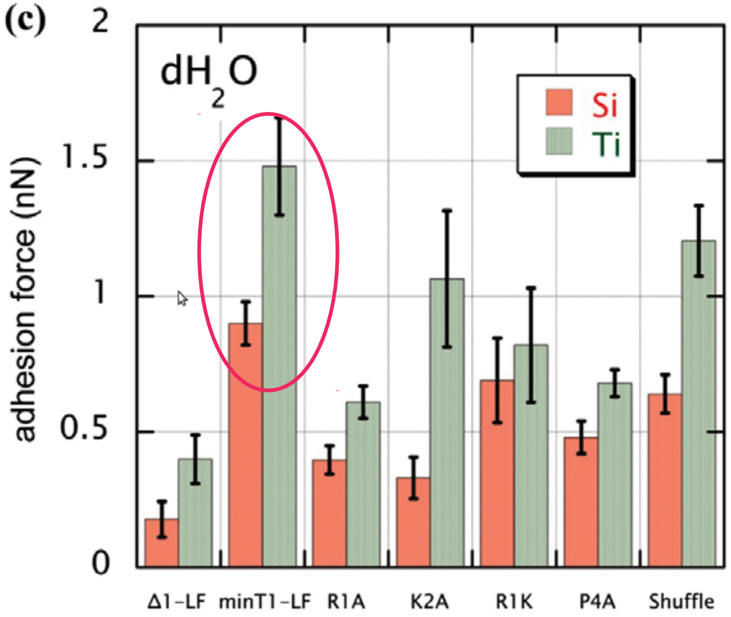
→ **Very similar detachment behaviour!**

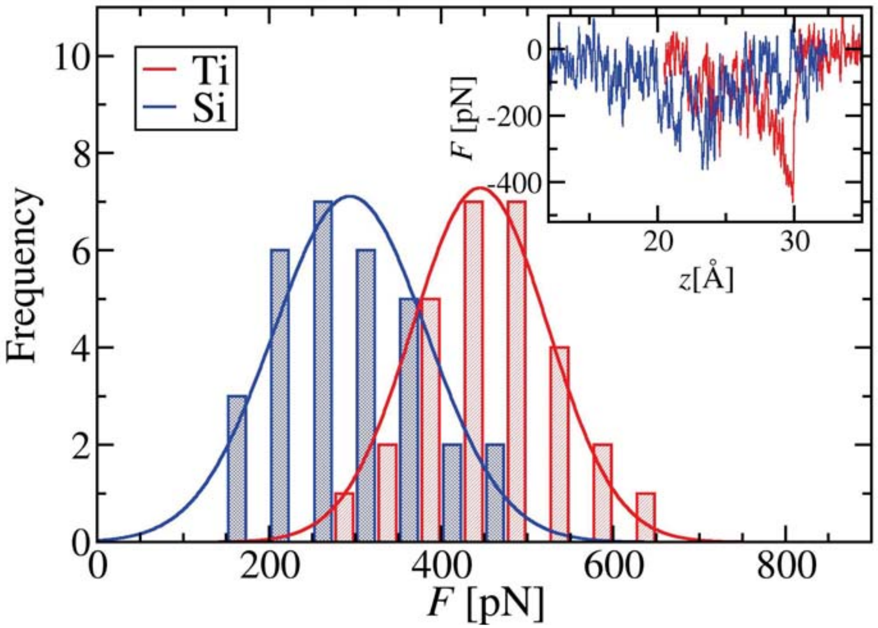
Comparison of Ti and Si Adhesion

Force-displacement-curves and histogram of peak forces

Average experimental AFM forces[1]

Simulations





Ratio of average force between Ti and Si of 1.5:1 agrees well with experiments.

$445 \pm 79\, pN$ on Ti

$294 \pm 89\, pN$ on Si

[1]: *T. Hayashi et al. Langmuir (2009)*

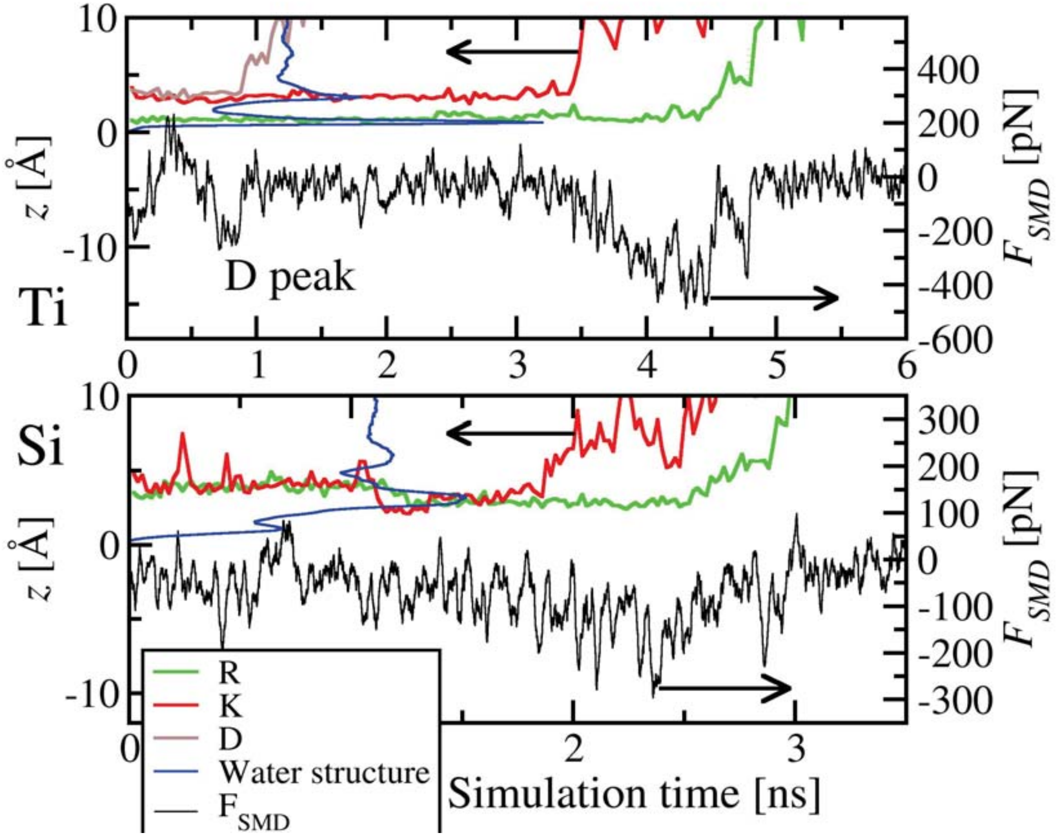
J. Schneider and L. Colombi Ciacchi, JACS 134, 2407(2012)

Comparison of Ti and Si Adhesion

What is the origin of the specific adsorption?

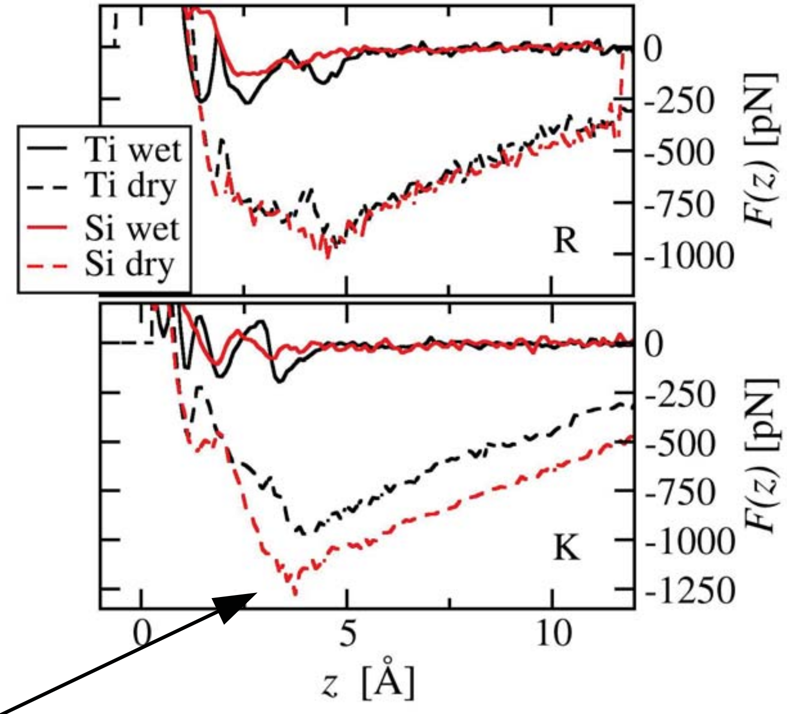
Comparison of Ti and Si Adhesion

Correlation of significant events in the side chain trajectories with peaks in the FD curve



Adhesion of Amino Acid End Groups

Force profiles on ARG and LYS end groups with and without including water mediated Interactions:

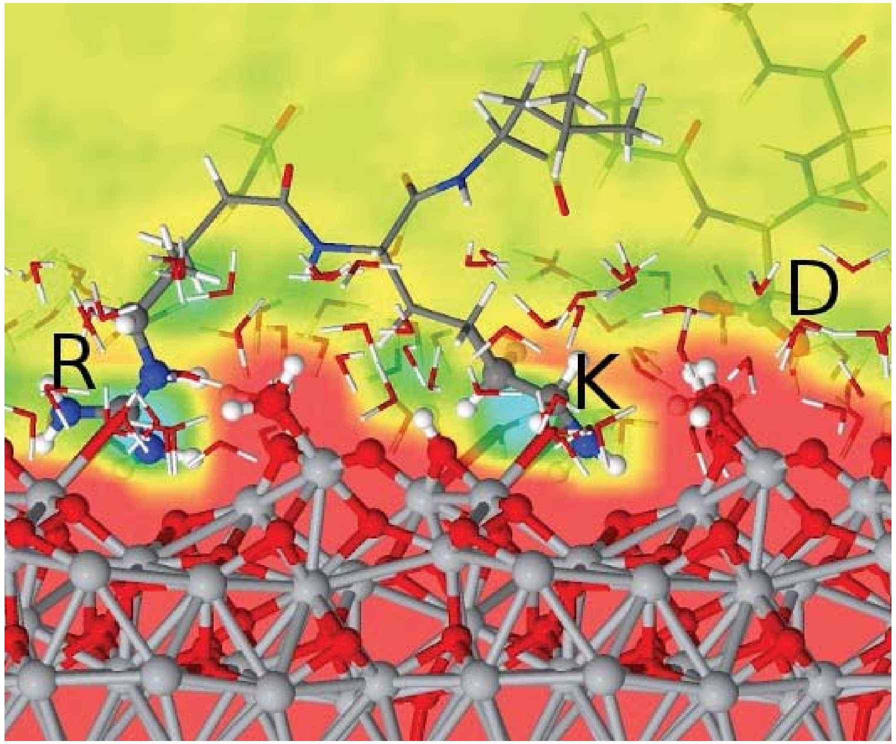


Dry forces stronger on Si !!

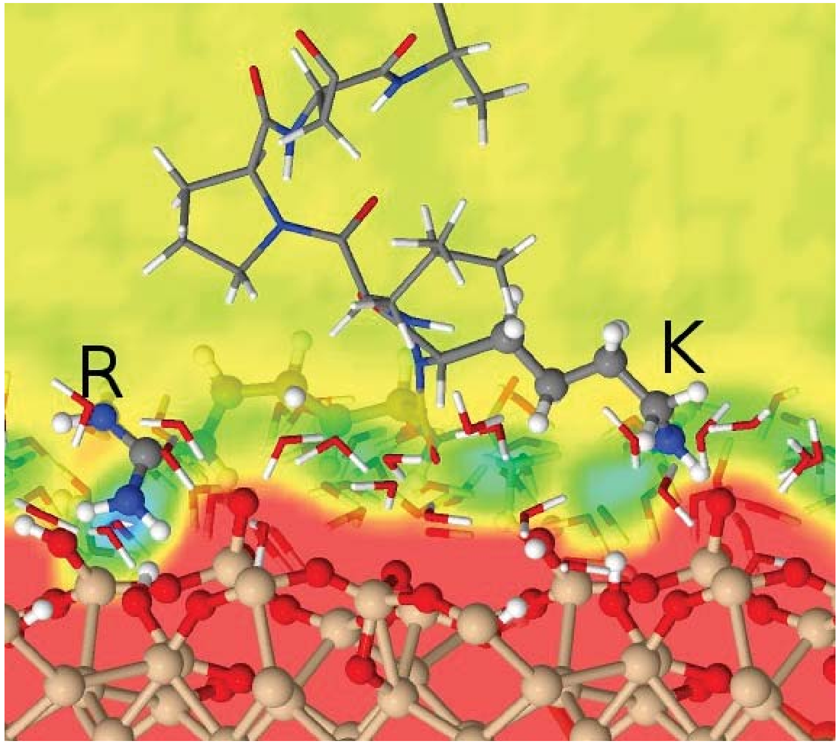
Equalization or inversion of specificity!

Interplay with Water Structure

Different water structure above the two surfaces:



Localized spots on Ti..



...contiguous patches on Si.

Peptide recognizes patterns in the water structure similar to *biological recognition.*

Summary:

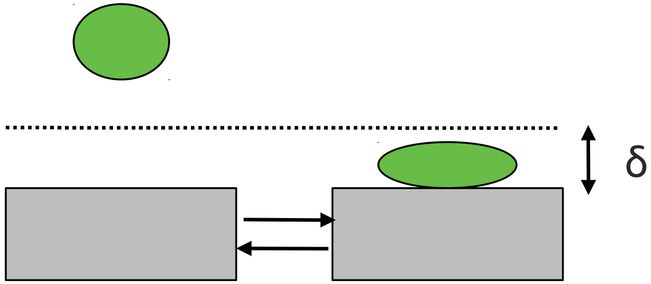
Guidelines to calculate reliable free energies:

- Use a suitable reaction coordinate!
- Use an appropriate/efficient method to sample *along the RC!*
- Make sure that you sample sufficiently *perpendicular to the RC!*
- When comparing to experiments take care of the standard states!

- Use clever ways to analyze your simulations to understand the microscopic mechanisms!
- Exploit your advantage of having atomic resolution!

Free energy is the driving force in the canonical ensemble

$$\boxed{G = \mu N}$$



In equilibrium: $\mu_b = \mu_a$

with $\mu = \mu^0 + RT \ln\left(c / c^0\right)$

$$0 = \mu_a^0 - \mu_b^0 + RT \ln\left(c_a / c_s\right)$$

$$\boxed{\Delta G_{ads}^0 = \Delta \mu^0 = -RT \ln\left(c_s / c_a\right)}$$