A Flexible and Scalable Package for Protein/Surface interactions

Stefano Poggio[1], David Power[1], Erick Brandt[2], Vladimir Lobaskin[1], Alexander Lyubartsev[2]

[1] School of Physics, University College Dublin, Dublin, Ireland
[2] Department of Materials and Environmental Chemistry, Stockholm University, Stockholm, Sweden

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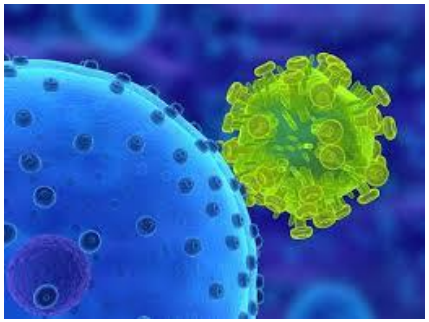
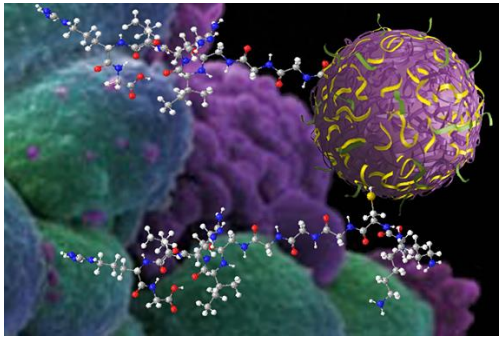
for Research & Innovation

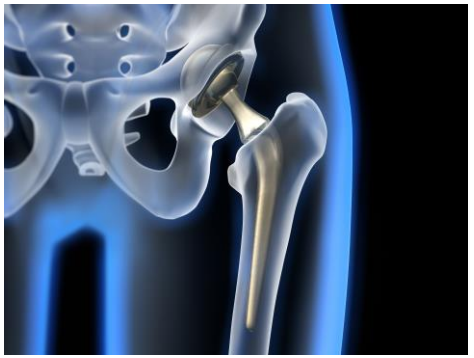
Outline

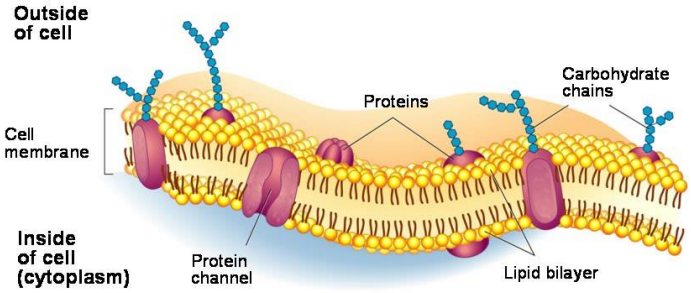
- Introduction and motivation for our code
- Modules we have developed so far.
- Results.
- Integration within ECAM project (flexibility, scalability and model improvement).

Protein-surface interactions







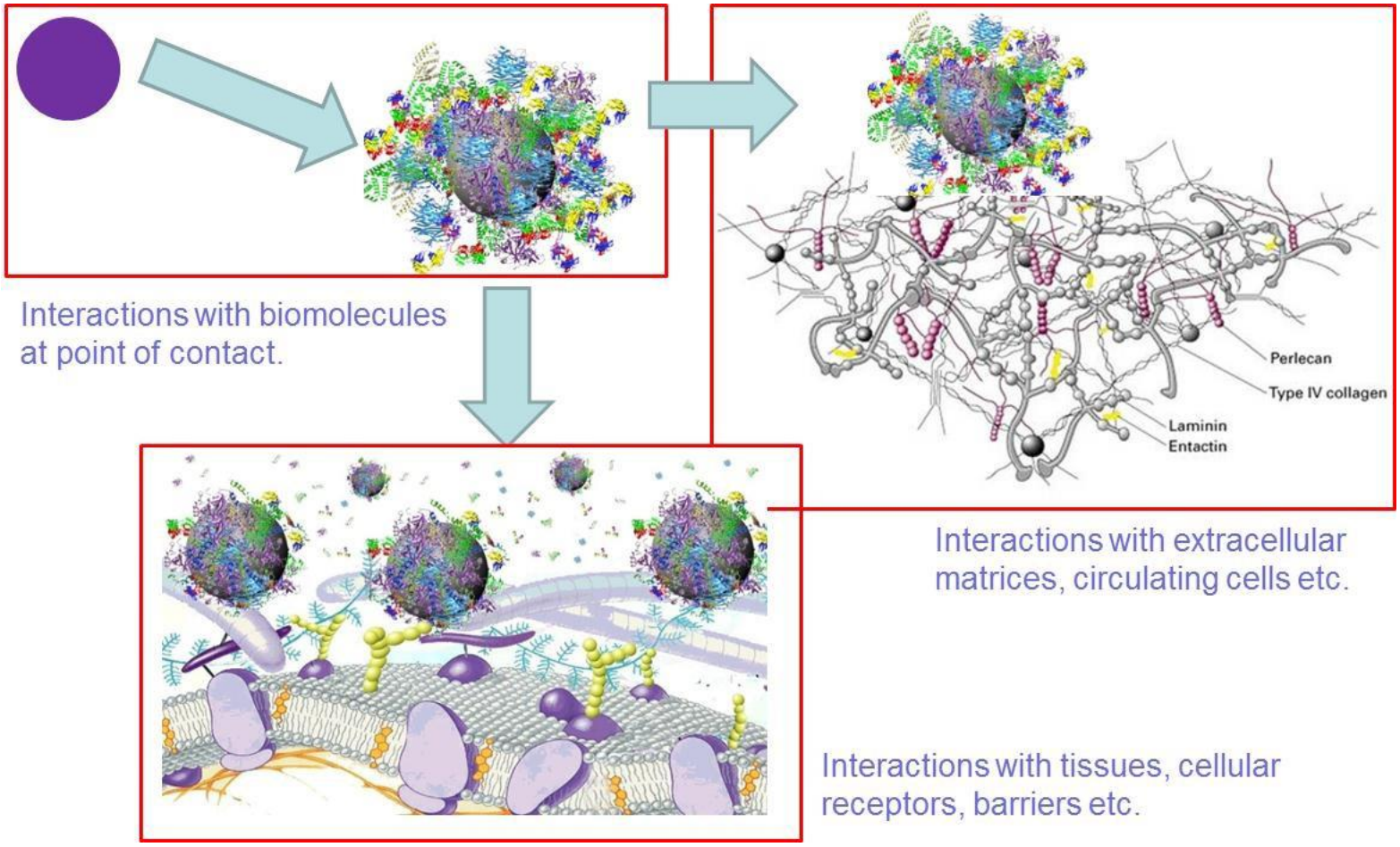


What our code is designed for (so far)

Pathway-based modelling / assessment:

Understanding of bionano interactions is needed to address Molecular Initiating Events, systemic transport

Nanoparticle Identity



M. P. Monopoli *et al. Nature Nanotechnology* **7,** 779-786 (2012)

The way forward

- Ab-initio (QM) methods (~ 20/30 atoms)
- Molecular Dynamics (~ 10^6 atoms)
- Need to model NPs of radius ~ 100nm or greater
- For a 100nm Au NP we need ~ 254,522,462 atoms, and this does not include biomolecules (proteins, lipids and sugars).
- Impossible task for any computer, need to find a path around it.

BUT

ALL BIOMOLECULES ARE BUILT FROM A SMALL NUMBER OF COMPONENTS!!!

Objectives & Methods

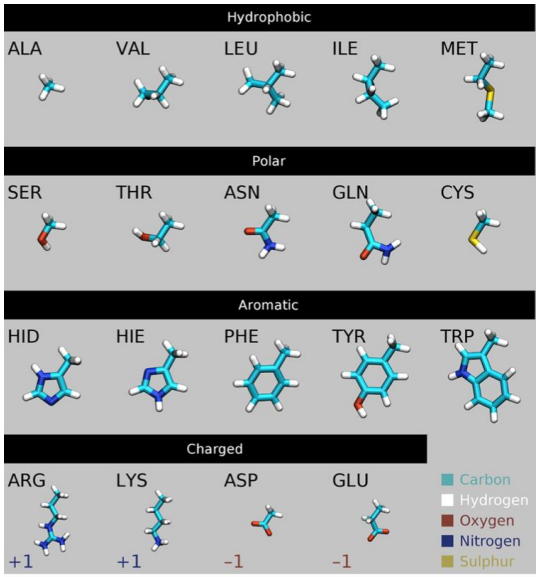
- Predict in silico the protein corona composition and find potential AOPs initiators.
- Build a scheme for fast calculation of protein/NP affinity.

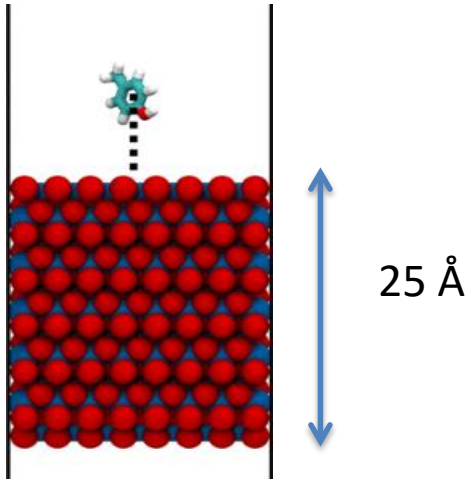
- Combine atomistic simulations of lipids (IC) and proteins (SU).
- Reduce the number of components in the system.

All atomistic simulations

Use metadynamics to calculate the Potential of Mean Force PMF for the fragments.

Any convenient MD engine is suitable.



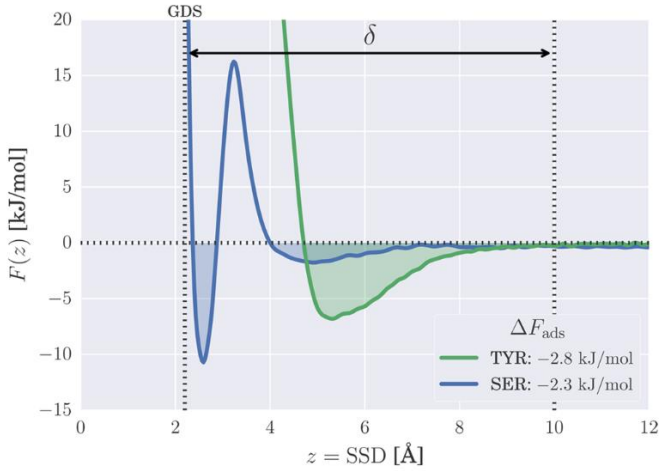


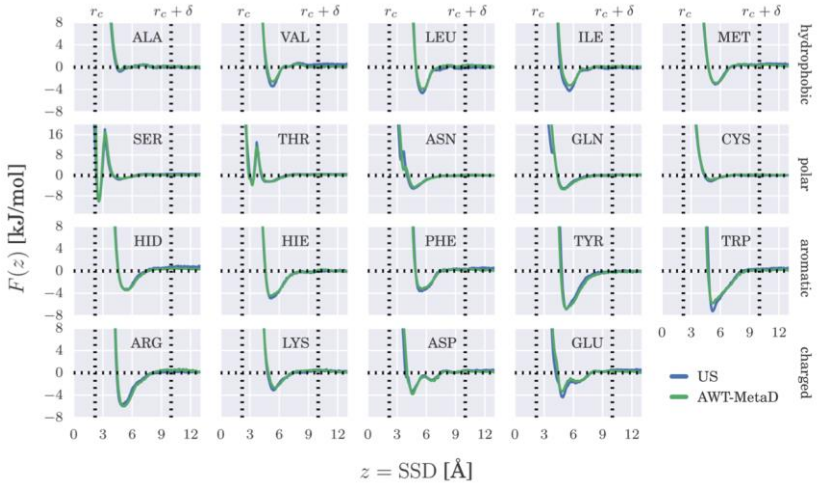
Brandt & Lyubartsev, JPC C, 18126, 119, 2015

AA fragments on a (100) TiO_2 surface

Ti-O force field reproduces ζ-potential and heat of immersion of TiO_2-water interface.

Umbrella sampling used to calculate the free energies (GROMACS 4.6.5)
1nm cutoff

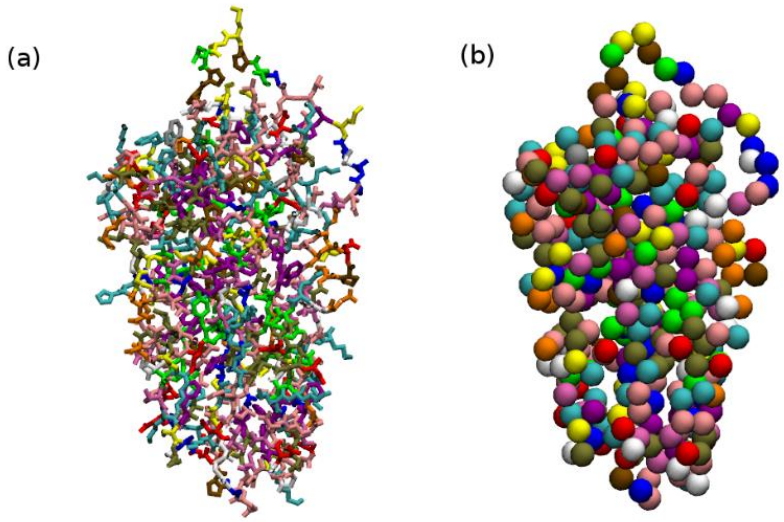


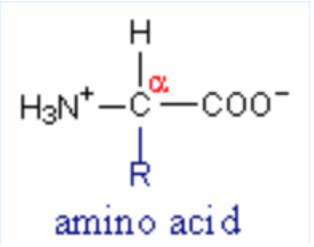


Brandt, E. G.; Lyubartsev, A. J. J. Phys. Chem. C 2015, DOI: 10.1021/acs.jpcc.5b02669

CG of proteins

- One bead per aminoacid.
- Center of bead placed at the pos. of α-carbon



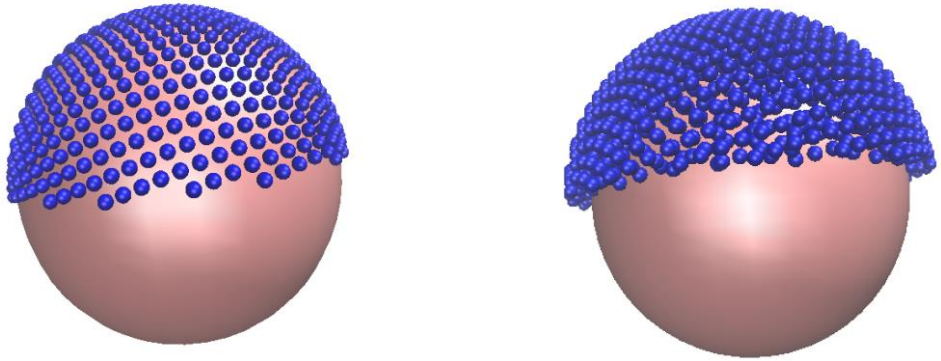


Lopez et al., JCP, 243138, 143, 2015

- Model preserves the shape and size of the protein.
- Protein is a rigid body.

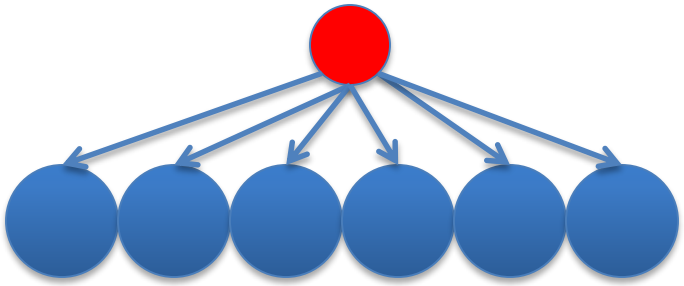
CG of Nanoparticles (1)

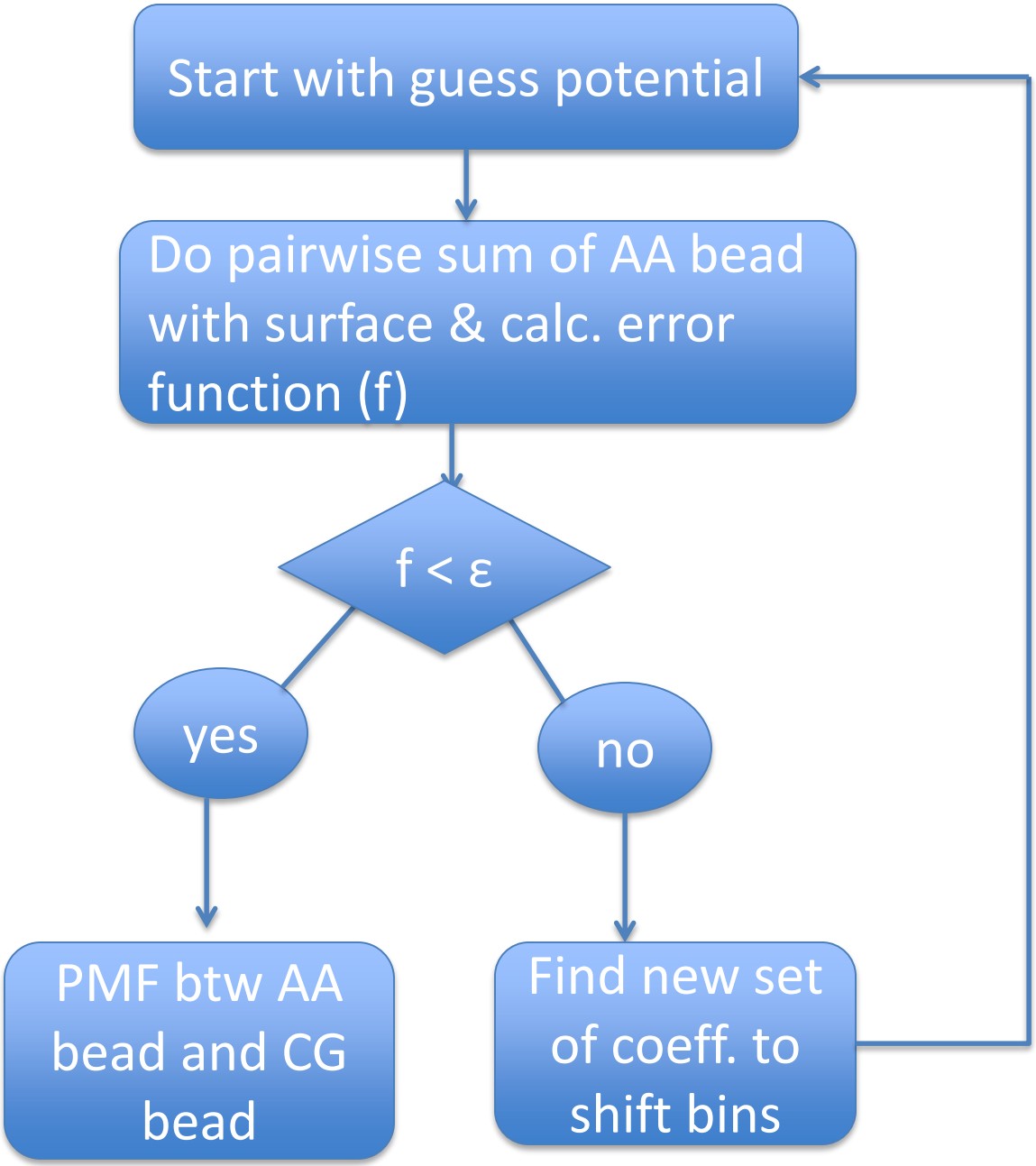
- Divided the NP in 2 parts: surface (in contact w solvent) and core.
- Surface beads interact directly w protein and solvent. Need to be atomistic.
- Core bead is not in contact with protein (too big for all-atomistic) simulations.

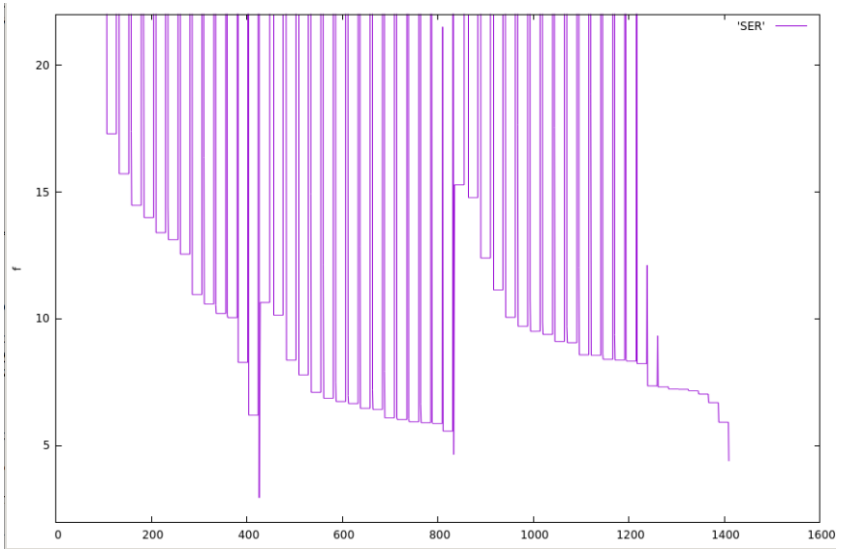


Potential parameterization

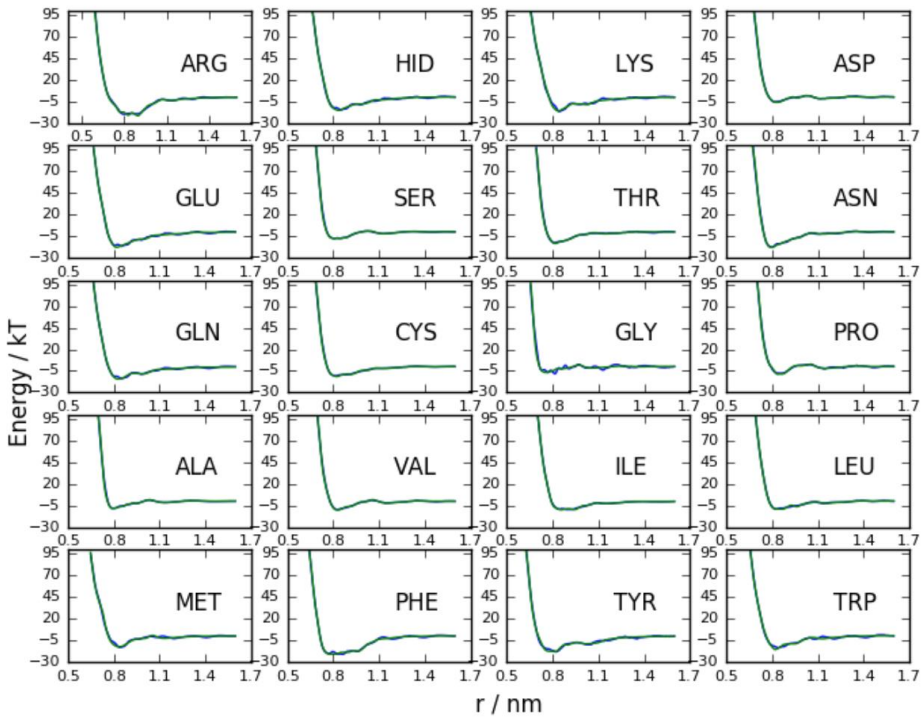
- Potential Mean Force of AA's on a flat surface (slab) for several materials.
- PMF tables for each AA as function of distance from the surface. Reference potential.
- One bead per AA and surface "superatoms".
- Pairwise summation of energies.




Start with guess potential
Do pairwise sum of AA bead with surface & calc. error function (f)
f < ε
yes
no
PMF btw AA bead and CG bead
Find new set of coeff. to shift bins



PMF minimization of SER



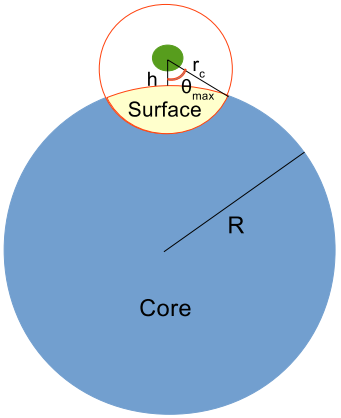
AA's PMFs with Au surface

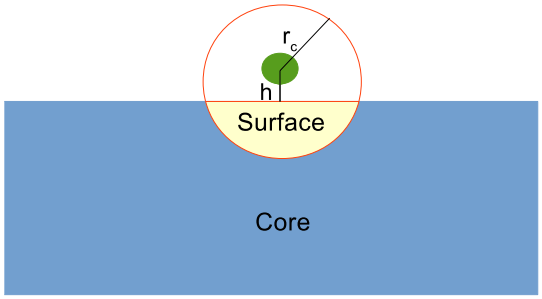
R_{bead} = 0.5nm

≈ 1:40 atom ratio but can chose "any" ratio.

Brandt & Lyubartsev, JPC C, 18126, 119, 2015

CG of Nanoparticles (2)





$$E_{sph}(h,R) = e\int_{r=h}^{r_c}\int_{q=0}^{q_{max}}\int_{f=0}^{2p}\frac{r^2\sin q}{r^6}\,df\,dq\,dr$$

$$E_{sph}(h,R) = -\frac{pe}{h+R}\left(\frac{h-2R}{12h^3}+\frac{-6r_c^2+8r_c(h+R)-3h(h+2R)}{12r_c^4}\right)$$

$$R\to\infty$$

$$E_{flat}(h) = pe\left(\frac{1}{6h^3}-\frac{2}{3r_c^3}+\frac{h}{2r_c^4}\right)$$

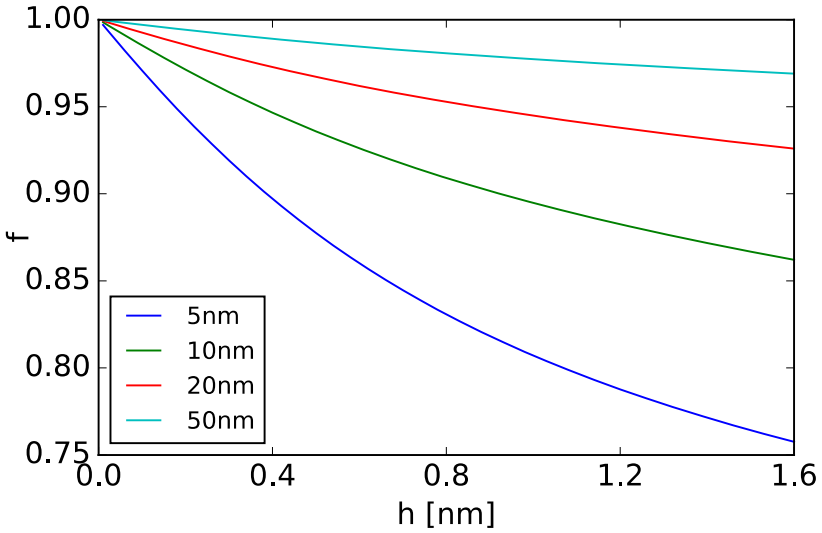
$$f = \frac{E_{sph}(h,R)}{E_{flat}(h)} = -\frac{r_c^2(h-2R)+2r_ch(h-2R)-3h^2(h+2R)}{2\left(r_c^2+2r_ch+3h^2\right)(h+R)}$$

The *f* factor

The correction becomes less important as the NP radius increases and the particle is closer to the surface.

Multiply the all atomistic PMFs by the cutoff and distance dependent *f*-factor.

f-factor can be calculated for any geometry by taking the appropriate limits

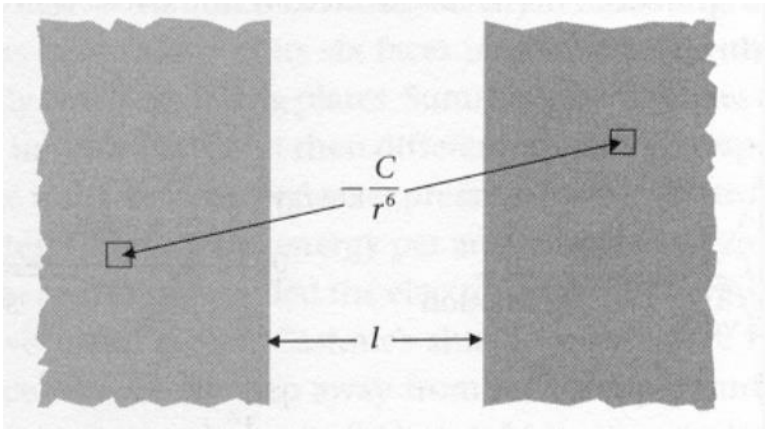


for r_c= 1.6nm

Limit of aa PMF calculations.

Core pair potential

$$U_{12}(D) = \frac{-A_{123}}{12}\left(\frac{4R_1R_2}{D^2 - (R_1+R_2)^2} + \frac{4R_1R_2}{D^2 - (R_1 - R_2)^2} + 2\ln\left(\frac{D^2 - (R_1 - R_2)^2}{D^2 - (R_1+R_2)^2}\right)\right)$$

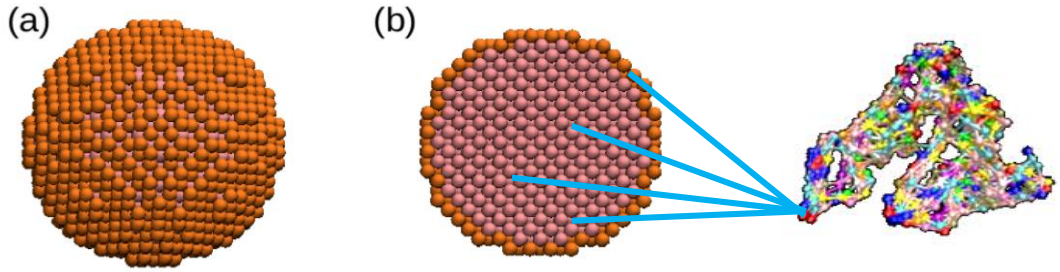


$$A_{123} = \frac{3}{4}k_BT\left(\frac{e_1 - e_3}{e_1+e_3}\right)\left(\frac{e_2 - e_3}{e_2+e_3}\right) + \frac{3hn_e}{8\sqrt{2}}\left(\frac{\left(n_1^2 - n_3^2\right)\left(n_2^2 - n_3^2\right)}{\left(n_1^2+n_3^2\right)^{1/2}\left(n_2^2+n_3^2\right)^{1/2}\left\{\left(n_1^2+n_3^2\right)^{1/2} + \left(n_2^2+n_3^2\right)^{1/2}\right\}}\right)$$

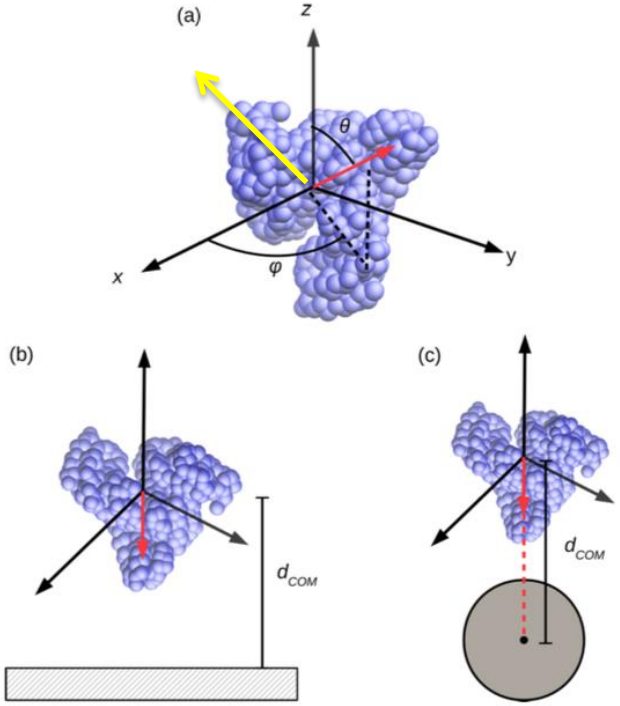
The only material dependent property is A_{123} , at the moment we need literature values.

Calculate directly on the fly from ab-initio/MD

Protein-NP interaction



Pairwise summation between protein beads with NP beads.
Protein treated as rigid body.



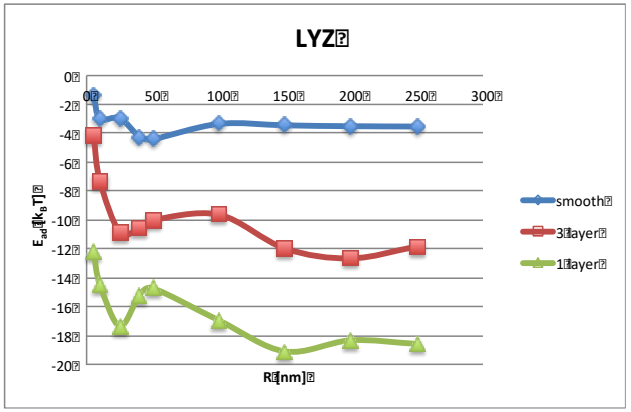
3 angles of rotation θ, φ, ζ
10x10x20 grid interval = 11,664 points

2 angles of rotation for smooth surface = 648 points

Lopez et al., JCP, 243138, 143, 2015

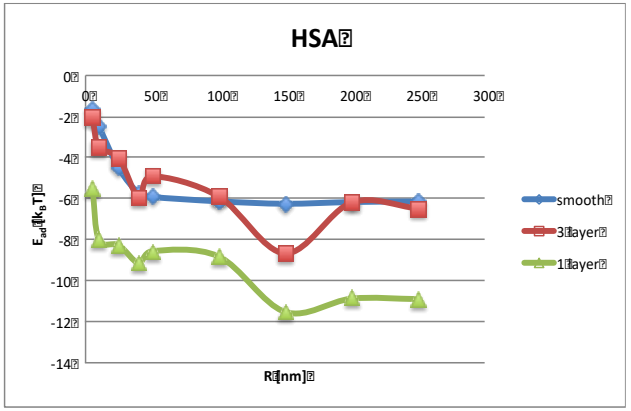
Results

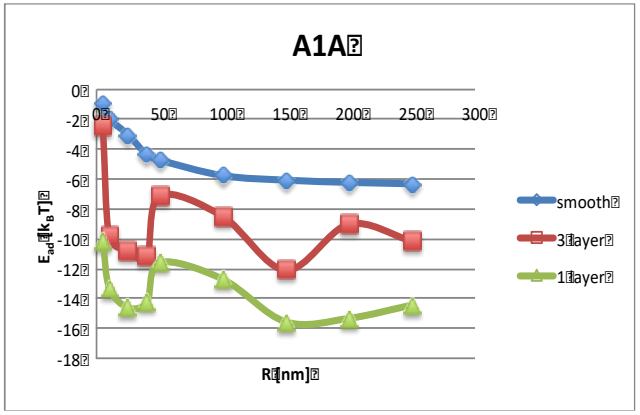
Protein absorption on NP at physiological conditions (pH = 7 and T = 300K)



Smooth surface is the one with lowest E_{ad} but has the smoother trend.

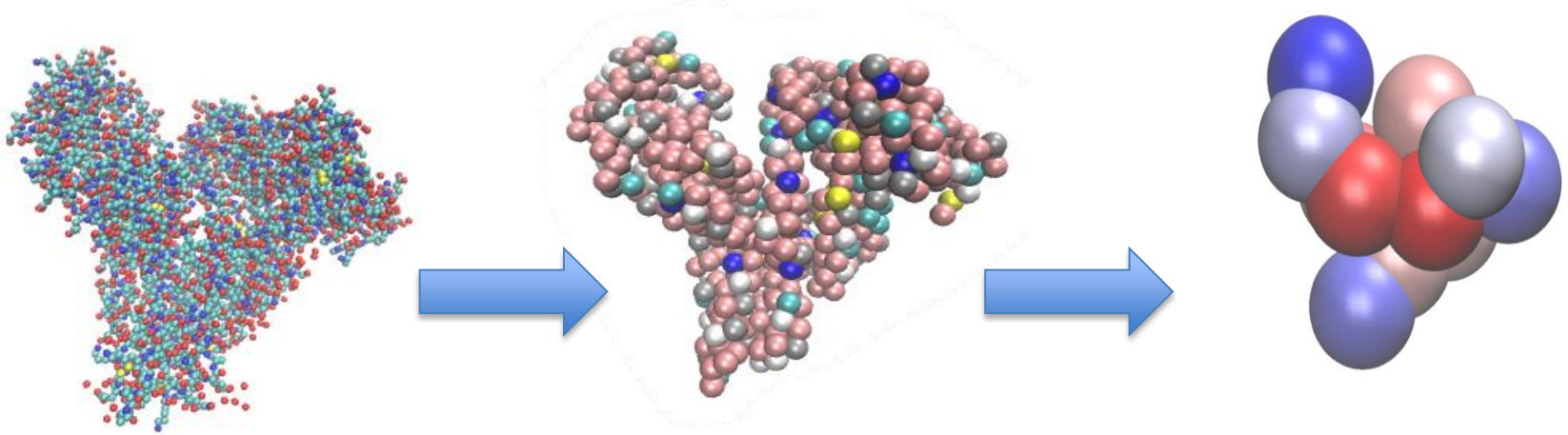
E_{ad} depends on the size of the CG bead but as it decreases the E_{ad} gets closer to perfectly smooth surface.





Further CG

From united-atom to united aminoacid description



All-atoms

United-atoms (UA)

United-aminoacids (UAA)

Protein is reduced to minimum number of beads that preserve the shape.

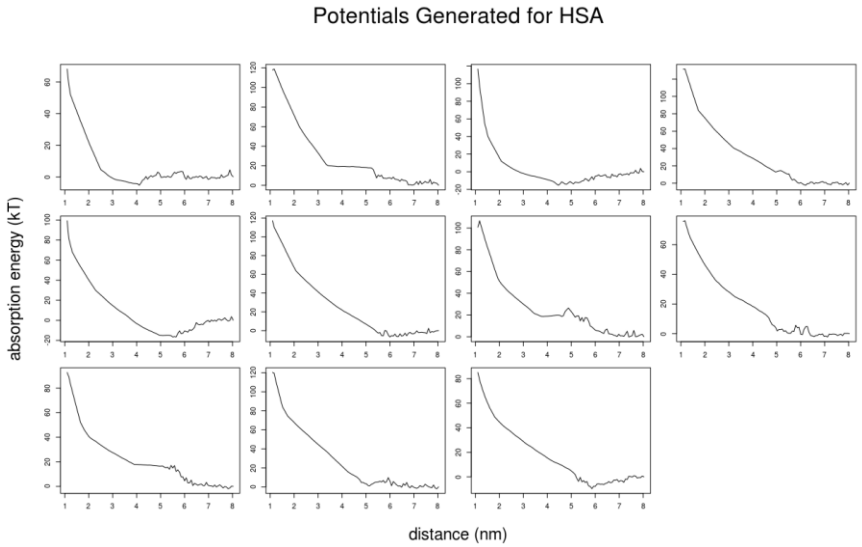
For Human Serum Albumin 11 beads.

Genetic Algorithm maps the adsorption energy of UA protein into unique bead-potentials for each UAA bead.

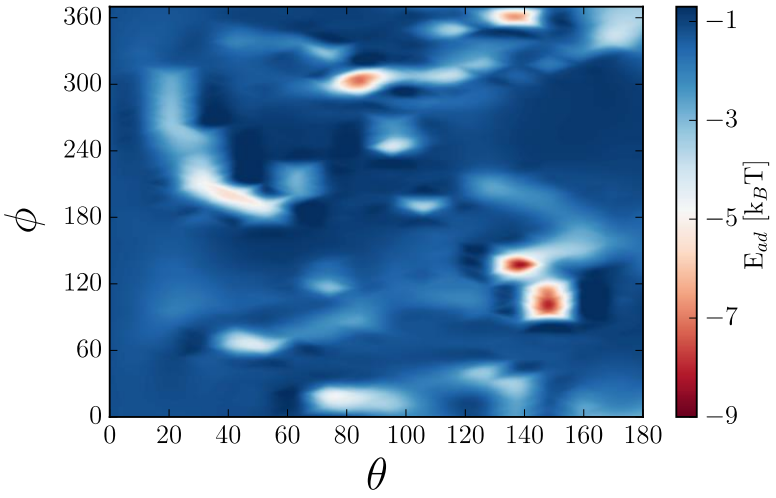
10,000 generations.

GA potential overestimate the width of minimum, although it is less deep.

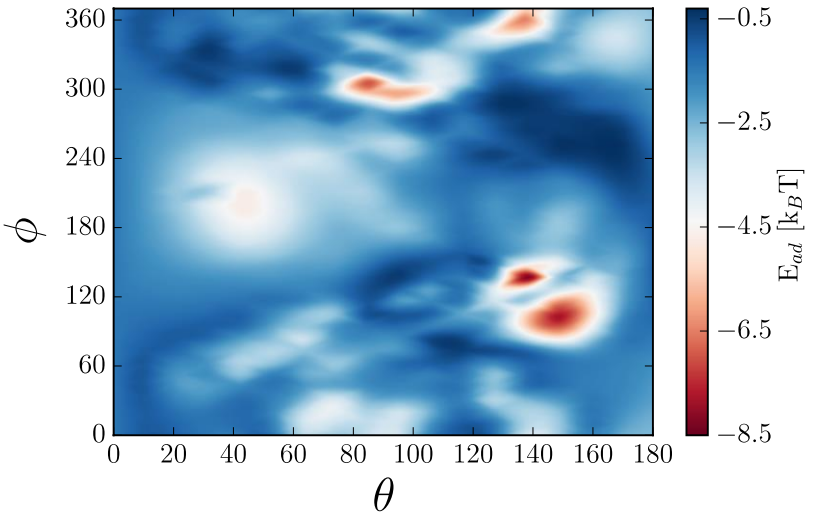
GA capable of reproducing the main attraction geometries of the protein.



UA HSA, on 50nm TiO_2 NP



UAA HSA, on 50nm TiO_2 NP



- All atomistic PMF calculation of AA fragments with inorganic surfaces:
  - Metadynamics, GROMACS, AMBER FF.
  - Code is open and freely accessible.

Outcome

PMFs for molecular fragments with an inorganic flat surface

- Define the level of coarse graining and generate a UA system:
  - Python script using SciPy libraries.
  - Integration and correction wrt flat surface for simple geometries.

Outcome

Absorption energies for proteins on an inorganic surface (EsPREssO)

- Generate a (super)UA description of the system:
  - GA algorithm (written in C++) mathces PMFs with UA.

Outcome

For HSA we go from 4635 atoms to just 11 and still preserved the essential features!!

What we hope to do

Combine the three modules into a single, robust and scalable package.

The user needs only to specify the level of coarse graining and the coordinates of the inorganic surface + some physical parameters.

How we are planning to do it

UA algorithm can be re-written in C/C++ and made it parallelizable.

Abs. energies for the UA model can be calculated using GROMACS or any convenient MD engine (now they are written in Tcl)

Once the package is well parallelized, the CG level of the surface can be reduced with no cost in computer time.

The PRO's

- This code is highly flexible.
- They modeling level follows the updates of the main MD engines.
- It would be possible to integrate it with any suitable MD engine.
- Can re-run all calculations if a new and better model for describing interactions has been found.
- UA model can be extended to allow a more accurate description of proteins.
- Any macromolecule can be modeled