Modelling of Bio-Nano Interactions for Predictive Toxicology

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Basel, November 2017

Horizon 2020
European Union funding
for Research & Innovation

SmartNanoTox

Smart Tools for Gauging Nano Hazards

Horizon 2020 RIA NMBP call “Increasing the capacity to perform nano-safety assessment”

SmartNanoTox: Smart Tools for Gauging Nano Hazards

Project consortium: 11 partners

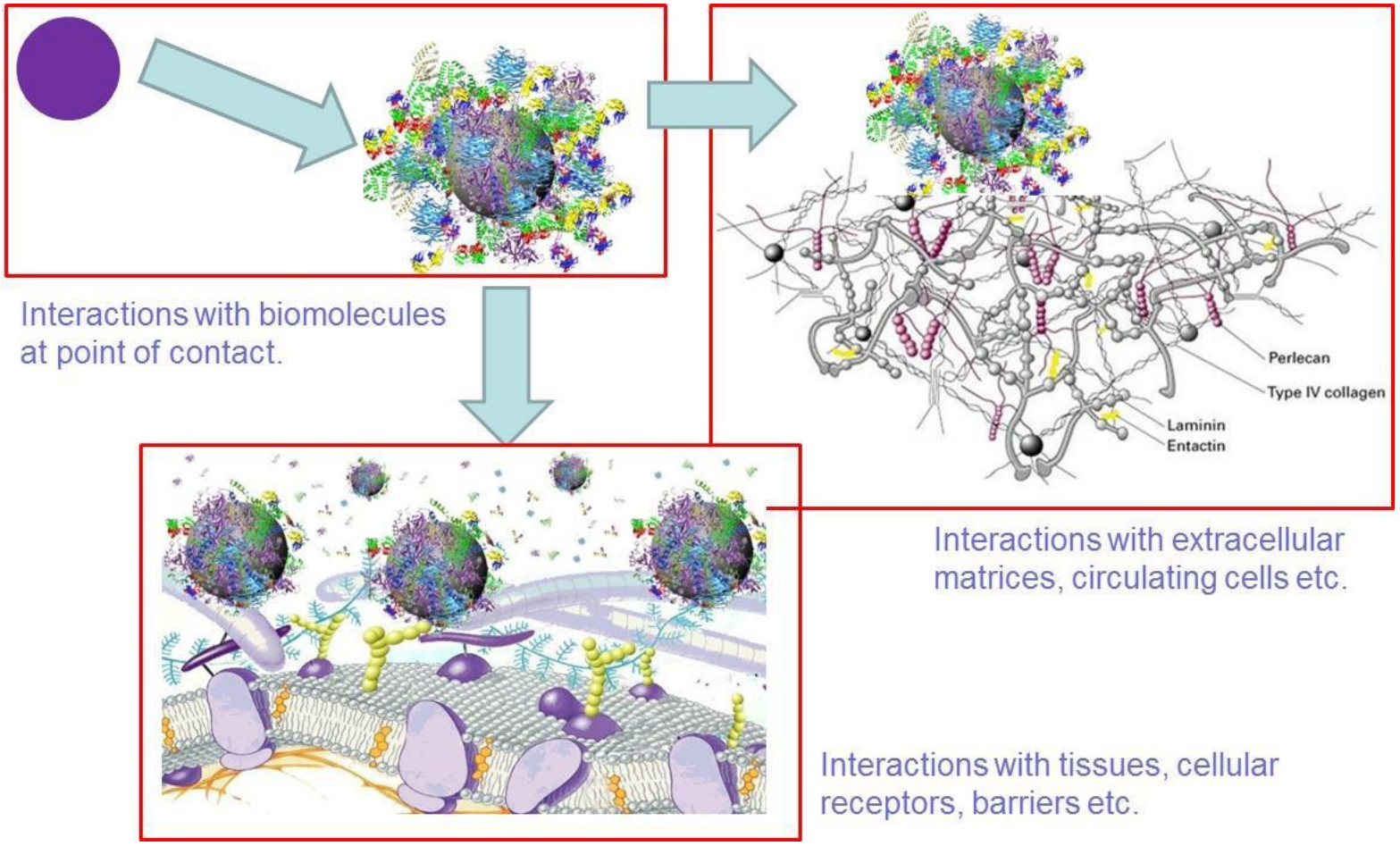
Coordinator: University College Dublin

This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grand agreement No. 686098

www.smartnanotox.eu

Horizon 2020
European Union funding
for Research & Innovation

Nanoparticle Identity

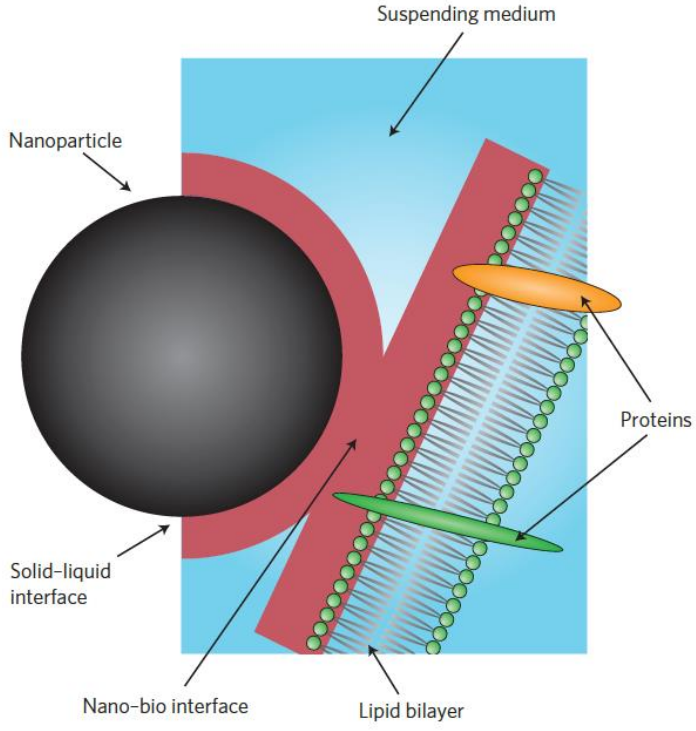


M. P. Monopoli *et al. Nature Nanotechnology* **7,** 779-786 (2012)

Relevant Interactions

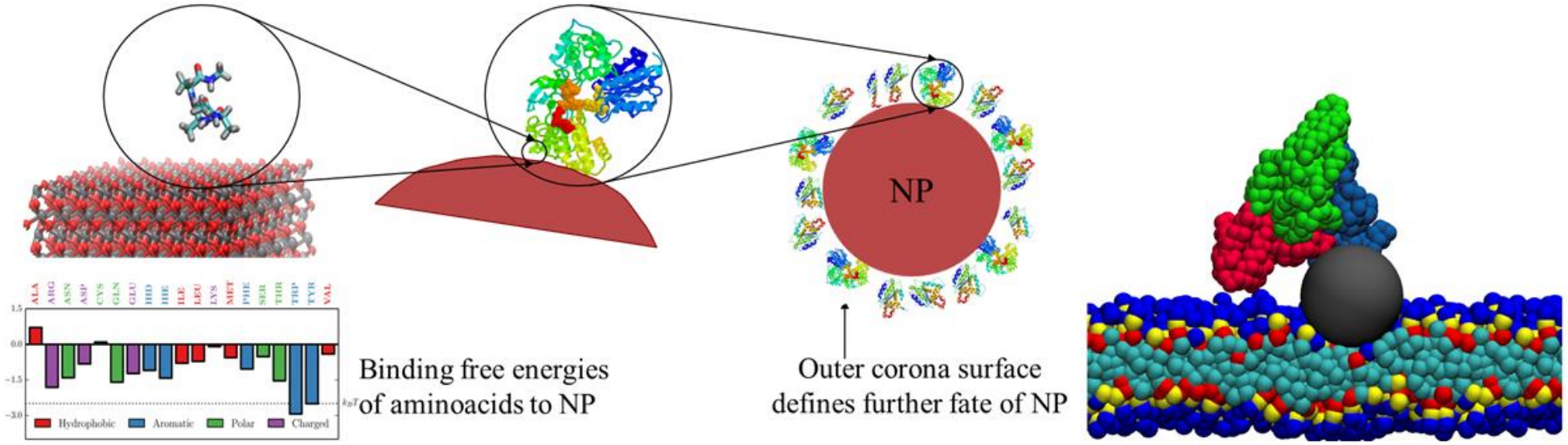
At different stages of systemic NP distribution we can observe

- NP – protein, NP – lipid interaction
- NP – NP and NPB – NPB (NPB – biomolecule complex)
- NP – membrane and NPB – membrane
- NP – DNA / RNA
- NP – glycans



Nel et al. Nature Materials, 2009

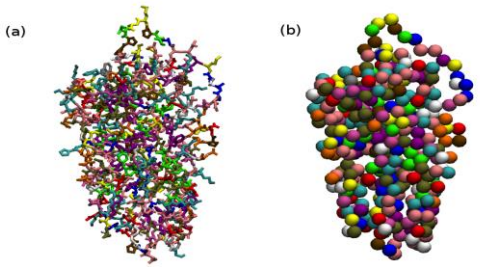
Multiscale Modelling Approach



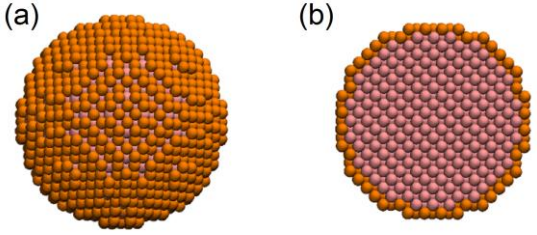
FP7 MembraneNanoPart (2013-15)
H2020 SmartNanoTox (2016-20)

Multiscale Modelling Approach

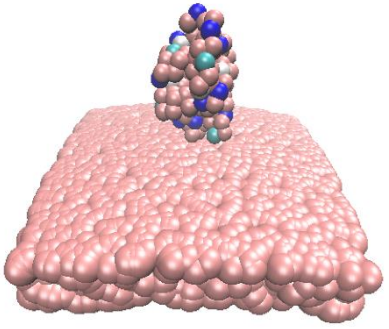
Attempt to model protein corona formation



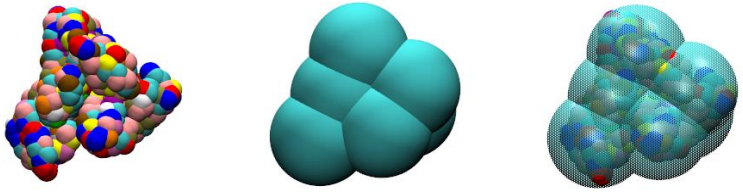
1. CG protein



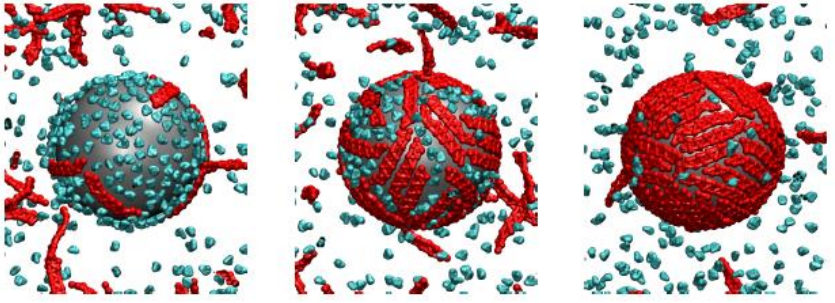
2. CG NP



3. Interaction



4. Further coarse-graining

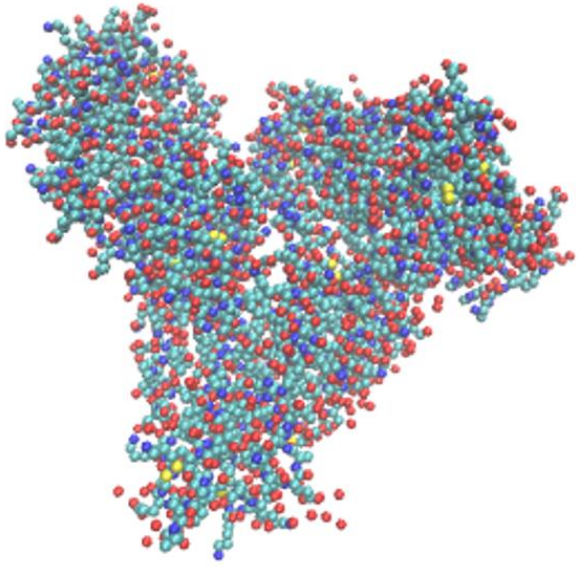


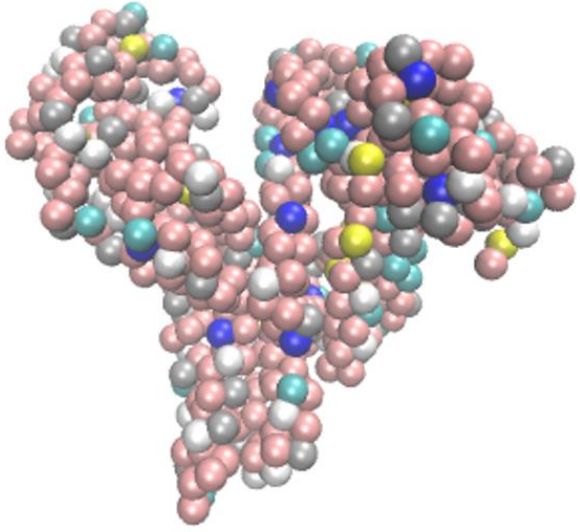
5. Competitive adsorption

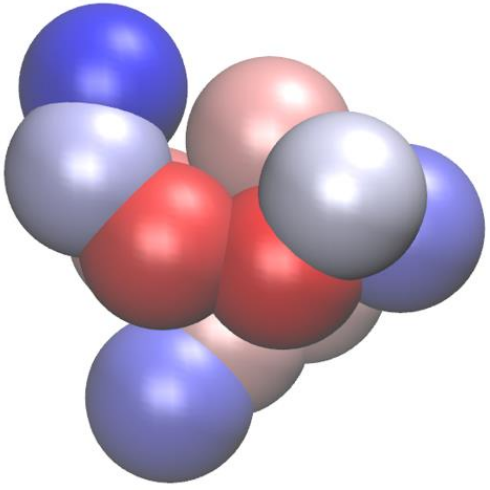
Model of protein globule

Native structure from Protein Data Bank (PDB) $\rightarrow$1N5U

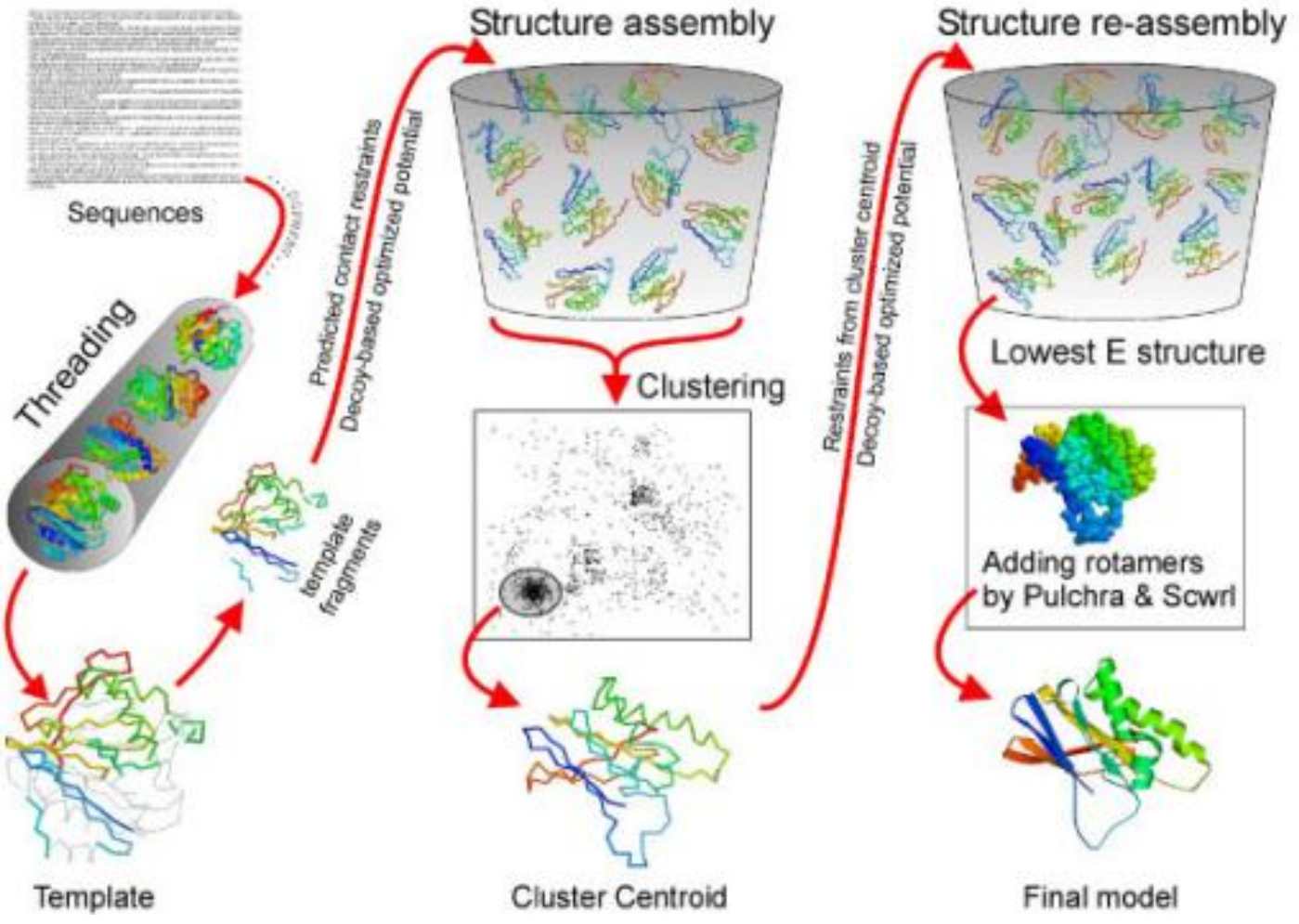
CG HSA $\rightarrow$ one bead per residue at the alpha carbon $\rightarrow$ 11-bead model





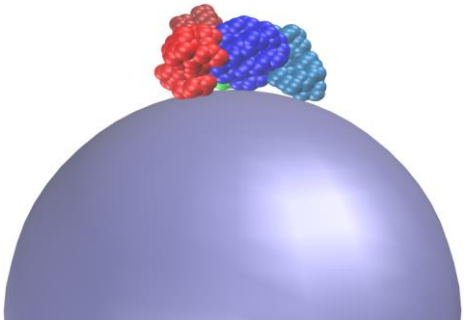


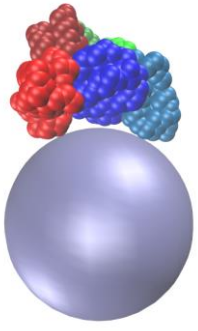
Protein structure prediction



Simulation settings

- All simulations → ESPResSo
- Unit of Energy: k_BT (T=310 K)
- Unit of length: nm
- Ionic strength: 100 mM
- Angle grid every 5°: 36x72=2592 points
- NP charge: 0, –0.05 C/m^2
- NP radii between 5 nm and 500 nm
- Residue charges: LYS and ARG +e, ASP and GLU –e and HIS +0.5e (physiological conditions)



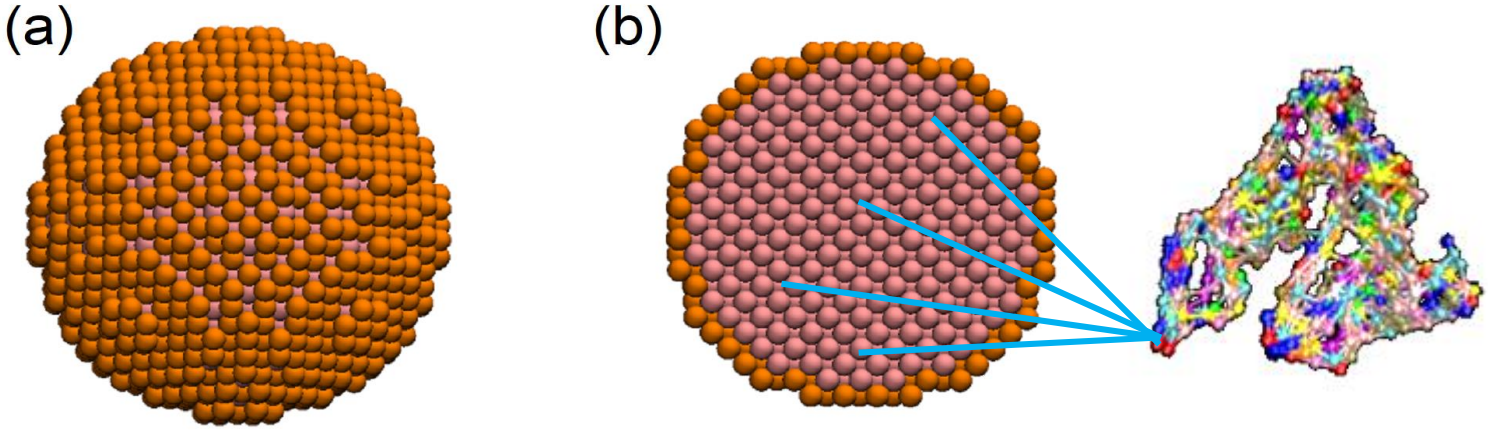


powered by ESPResSo

http://www.espressomd.org

Model of a Nanoparticle

Two-layer model: surface beads and bulk are treated differently



Bulk beads: van der Waals interaction (Hamaker procedure)

$$U_{bi}^{vdW}(r) = -\frac{A}{12k_BT}\left[\frac{4R_1R_2}{r^2-(R_1+R_2)^2}+\frac{4R_1R_2}{r^2-(R_1-R_2)^2}+2\ln\frac{r^2-(R_1-R_2)^2}{r^2-(R_1+R_2)^2}\right]$$

1 – NM, 3 – AA,

2 - water

$$A = \frac{3}{4}kT\left(\frac{\epsilon_1-\epsilon_2}{\epsilon_1+\epsilon_2}\right)\left(\frac{\epsilon_2-\epsilon_3}{\epsilon_2+\epsilon_3}\right) + \frac{3h\nu_e}{8\sqrt{2}}\frac{(n_1^2-n_3^2)(n_1^2-n_3^2)}{(n_1^2+n_3^2)^{1/2}(n_2^2+n_3^2)^{1/2}\{(n_1^2+n_3^2)^{1/2}+(n_2^2+n_3^2)^{1/2}\}}$$

Dispersion forces

Hamaker constants NM-water-AA, 10^{-20} J

ARG	HIS	LYS	ASP	GLU	SER	THR	ASN	GLN	CYS
4.70	5.40	3.23	5.42	4.36	4.21	3.70	5.04	4.40	28.88
GLY	PRO	ALA	VAL	ILE	LEU	MET	PHE	TYR	TRP
4.28	3.12	3.29	2.82	2.79	2.70	4.25	5.20	5.26	6.49

AA - gold

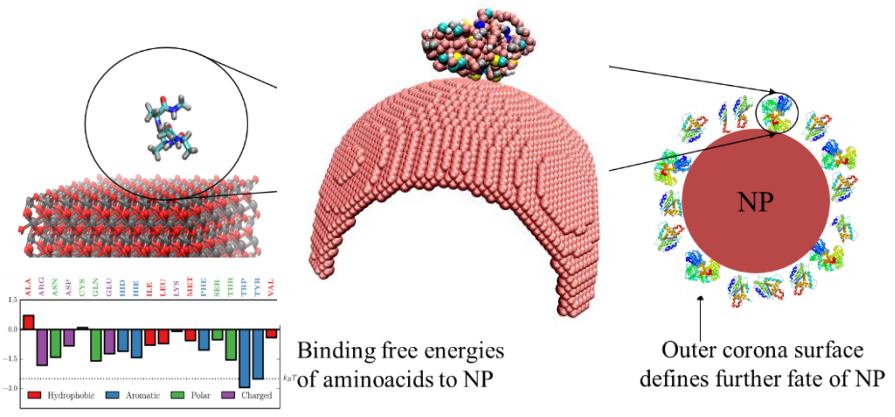
ARG	HIS	LYS	ASP	GLU	SER	THR	ASN	GLN	CYS
7.34	8.13	5.53	8.16	6.92	6.75	6.12	7.73	6.98	31.74
GLY	PRO	ALA	VAL	ILE	LEU	MET	PHE	TYR	TRP
6.83	5.40	5.61	5.00	4.97	4.84	6.79	7.91	8.43	9.37

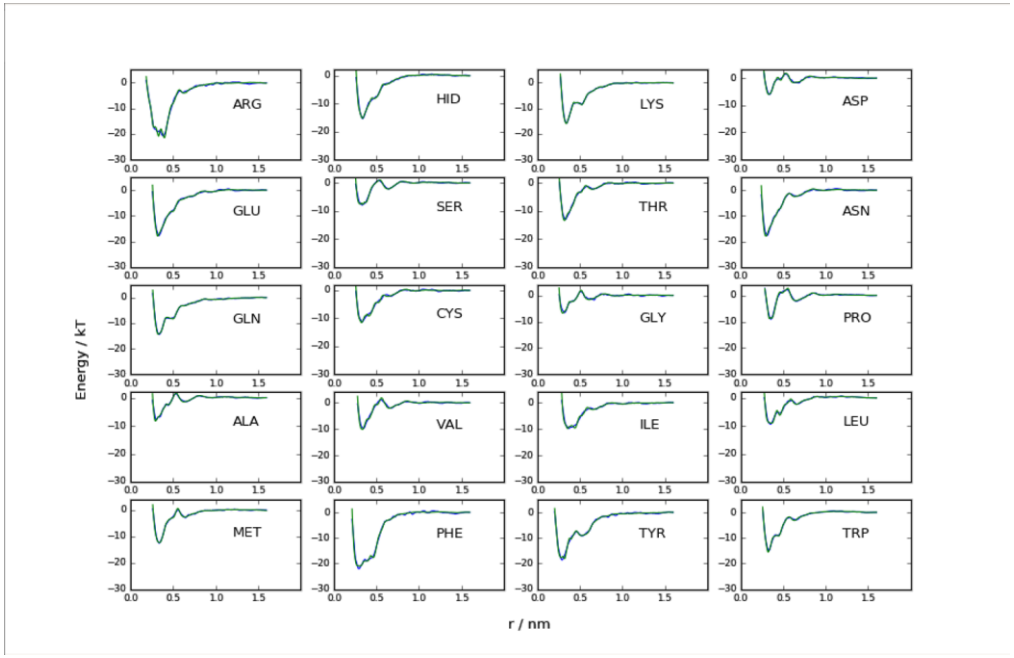
AA - TiO_2

Model of interaction

Two-layer model.

Surface beads: R = 0.5 nm



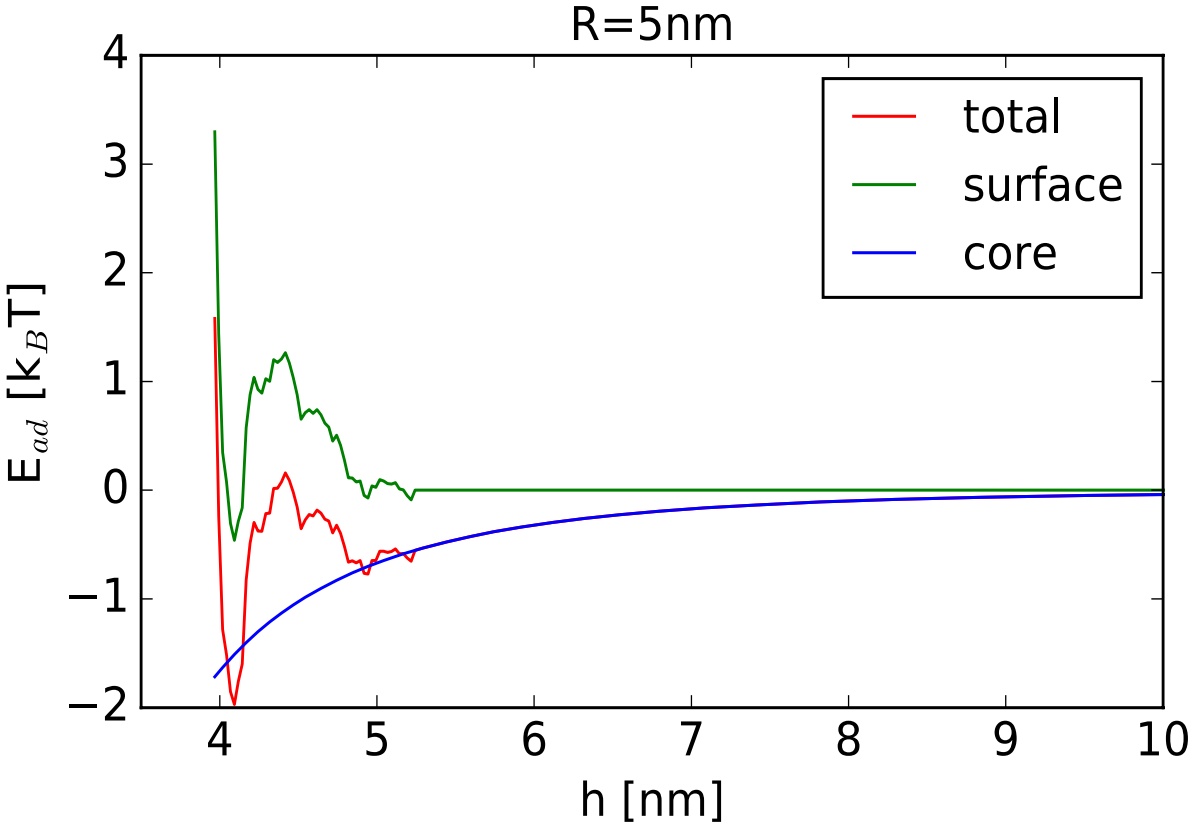


CG PMF vs All-atom MD PMF

Gold—AA, TiO_2 – AA potentials (Brandt, Lyubartsev, 2016)

Adsorption energies

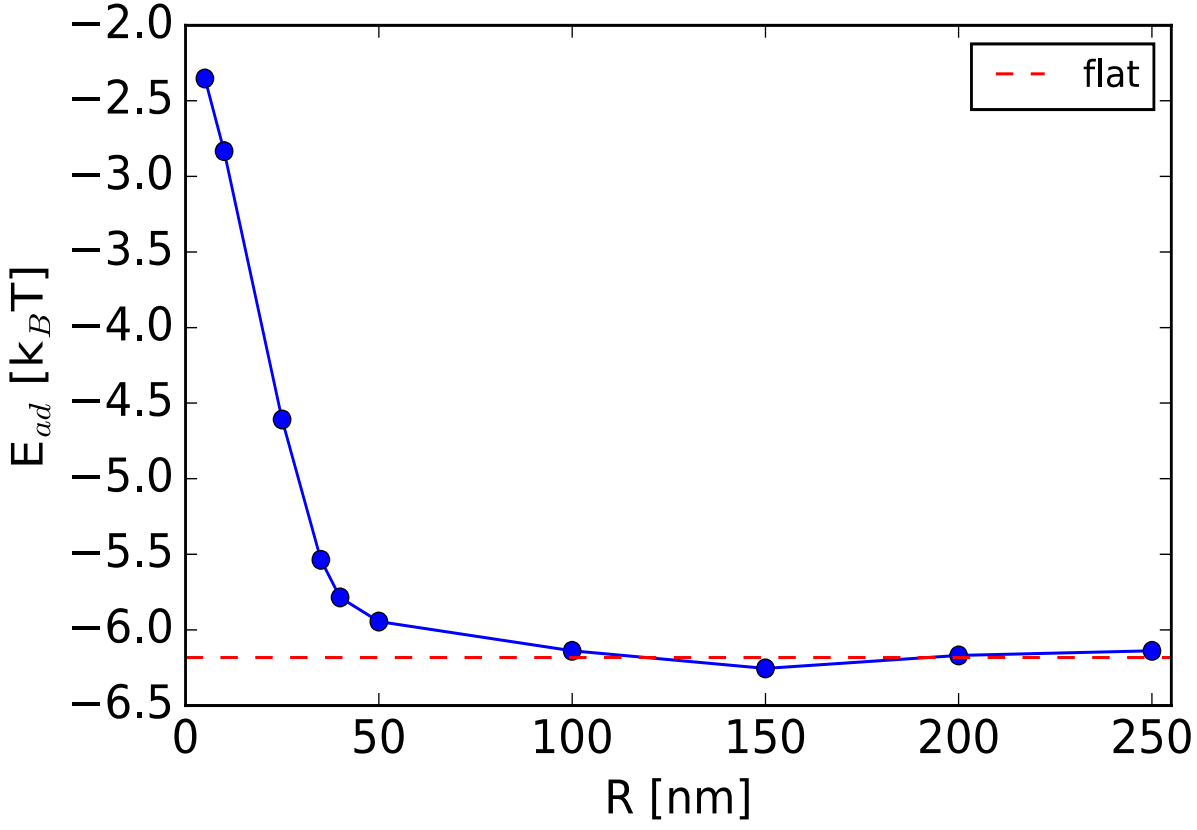
HSA: single orientation, R = 5 nm, rutile TiO_2



Major short-range contribution comes from surface interactions

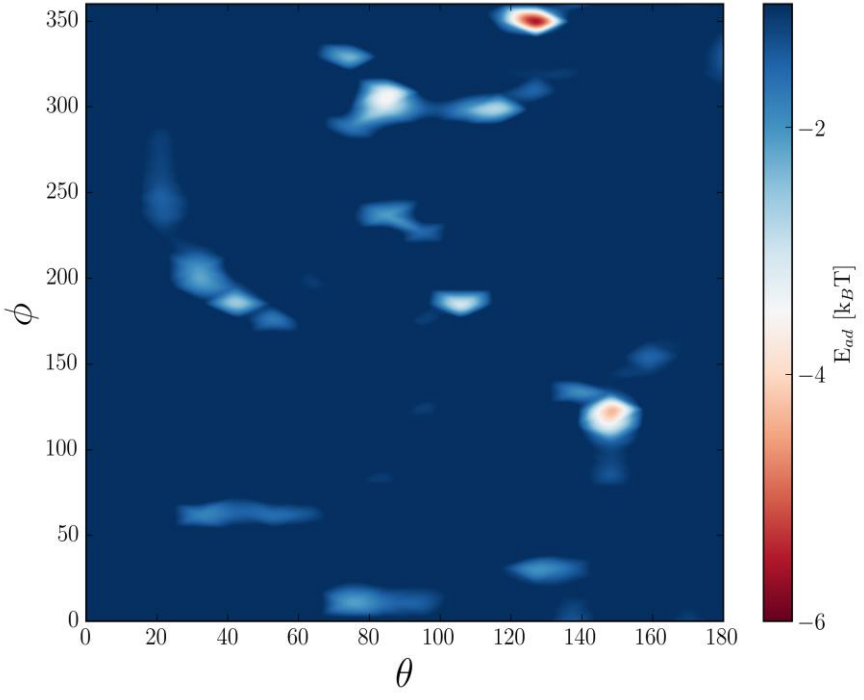
Adsorption energies

HSA on Rutile TiO_2 NP

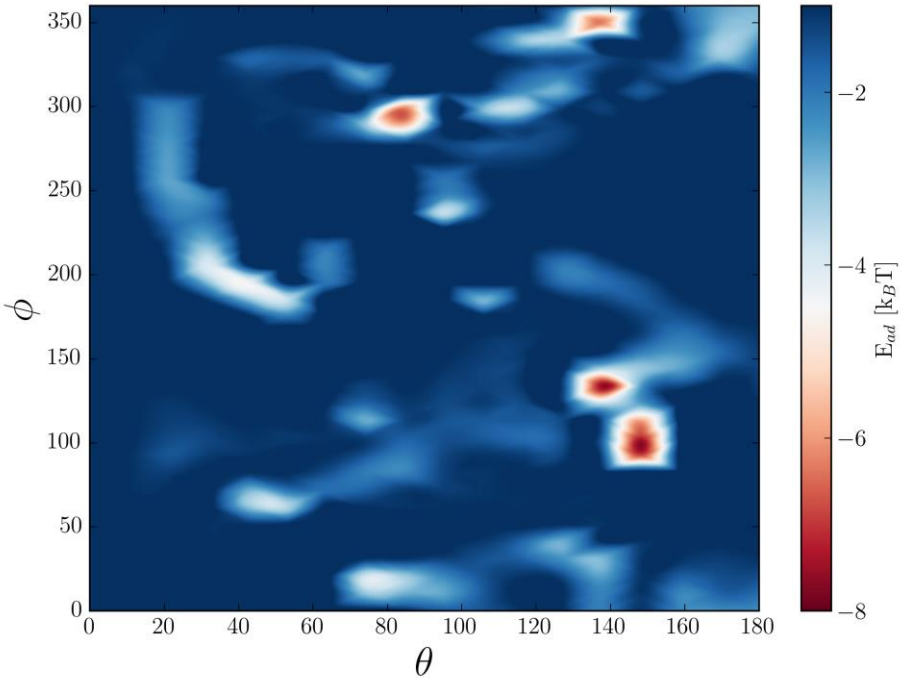


Preferred protein orientation: HSA

R= 5 nm



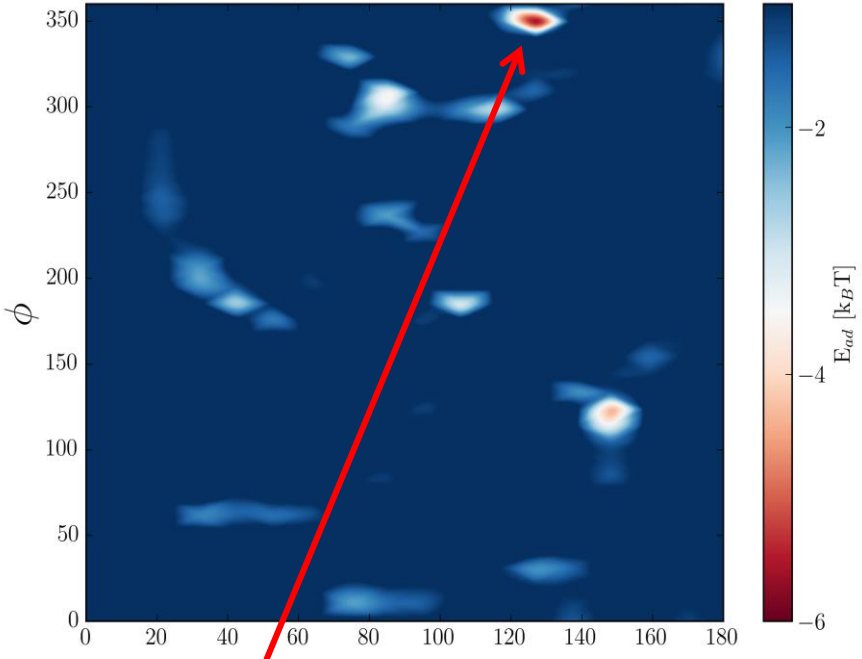
R= 50 nm

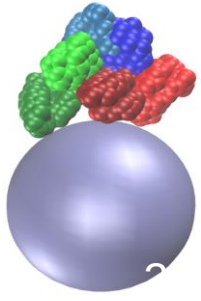


Maps do not vary much for different charges but depend on NP size

Preferred protein orientation: HSA

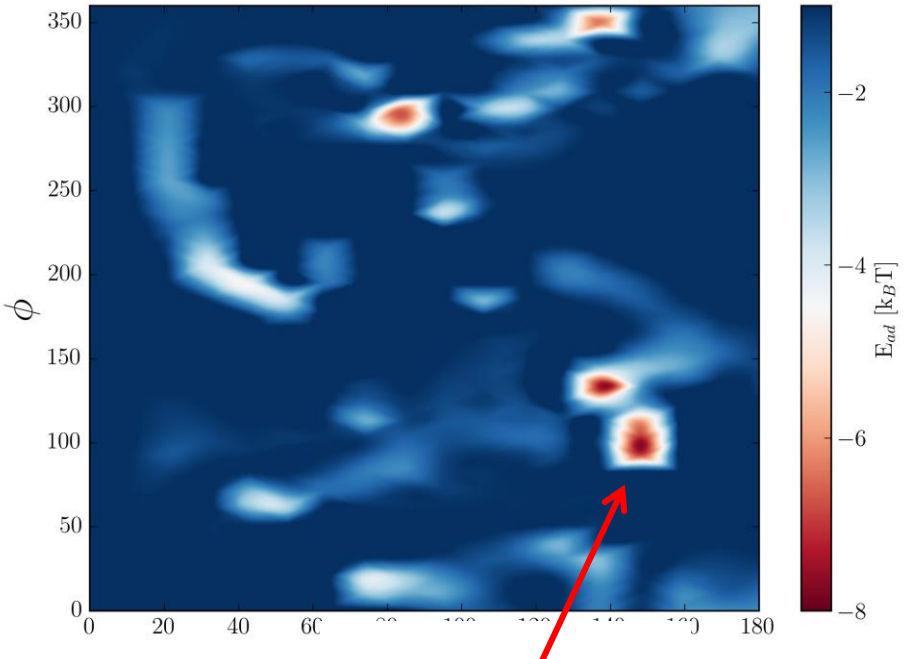
R = 5 nm

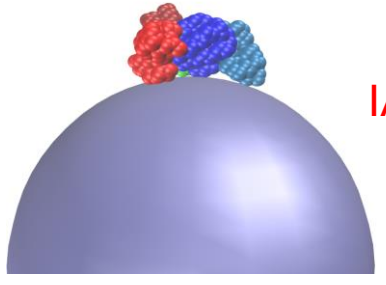




IA IB IIIB

R=50 nm





IA IIA IIB IIIA

Ranking proteins by adsorption energy

Increasing affinity ←

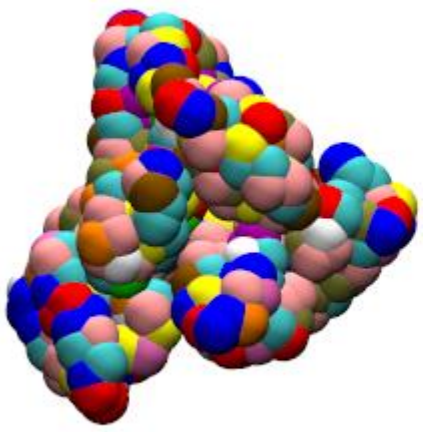
NP Radius, nm	Rank					
	1	2	3	4	5	6
5	A2M	IgG	Fib	Tra	A1A	HSA
20	Fib	A2M	IgG	Tra	A1a	HSA
50	Fib	A2M	IgG	Tra	A1A	HSA
100	Fib	IgG	A2M	Tra	A1A	HSA
500	Fib	IgG	A2M	Tra	A1A	HSA
	Fib	A2M	IgG	A1A	Tra	HSA

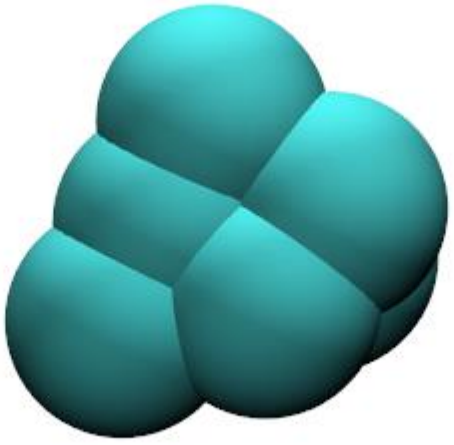
Large Small

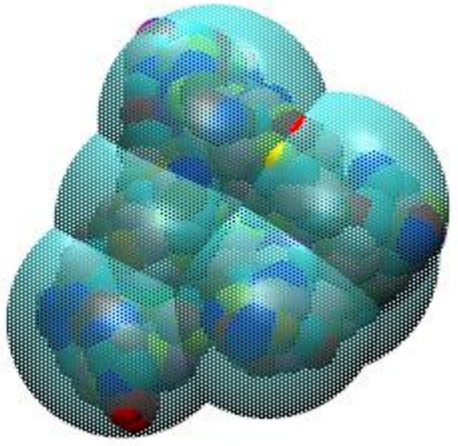
Agrees with measured affinity of HSA, Fib and γ−globulins to Gold NPs. De Paoli *et al.* [*ACS Nano*, **4**, 365 (2010)] – Vroman effect.

Second coarse-graining

From united-atom to united-aminoacid model
HSA: 11 beads. PMF protein bead – NP calculated by minimising differences to whole protein PMF



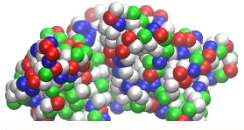


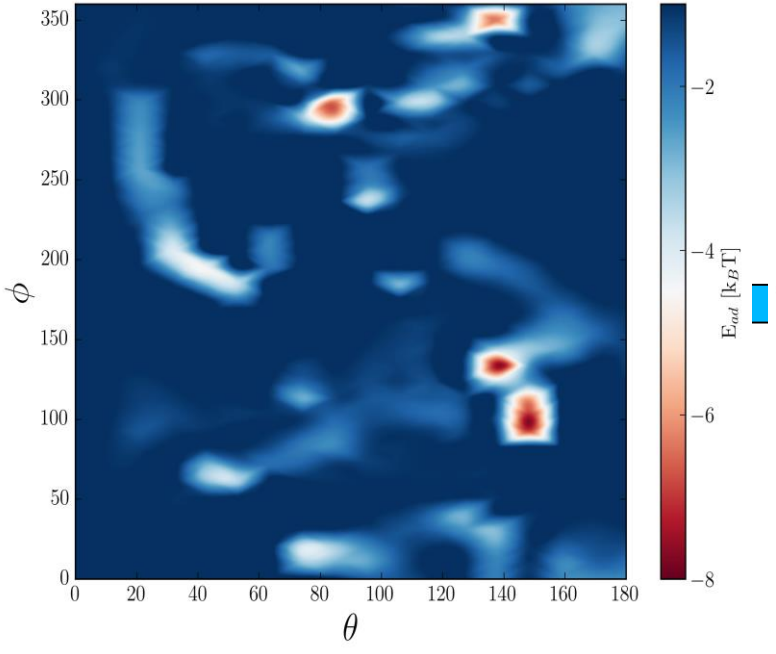


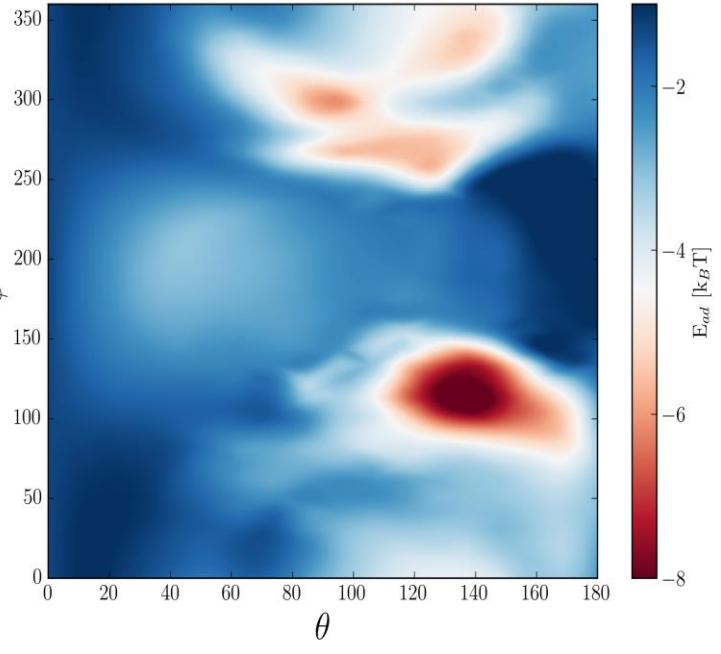
Second coarse-graining

From united-atom to united aminoacid model:
Optimisation of the model using a genetic algorithm

Fitness: $S = \Sigma_{i,j} \left(E_{i,test}(\theta_i, \phi_j) - E_{i,test}(\theta_i, \phi_j) \right)^2$







NP-protein interactions

Attraction depends on the NP density/dielectric properties:

NP adsorption affinity ranking with HSA:

$$E_{ad}^{Au} > E_{ad}^{TiO_2} > E_{ad}^{CdSe} > E_{ad}^{SiO_2} > E_{ad}^{CNT}$$

Protein descriptors

Intrinsic descriptors

- Sequence descriptors: e.g. number of acidic groups, mass
- Structure descriptors: size, aspect ratio, solvent accessible area, van der Waals energy

Extrinsic descriptors

- Charge
- Dipole moment
- Protein-protein interactions

Nanoparticle descriptors

Intrinsic descriptors

- Chemical composition: core, shell
- Bandgap
- Dielectric permittivity
- Hamaker constant
- Ionisation potential
- Molecular mass, crystalline structure, size, shape

Extrinsic descriptors

- Charge
- Dipole moment
- Hydration energy
- Dissolution rate

Descriptors of bionano interaction

Extrinsic descriptors

- Binding energy for molecular groups: aminoacids, glucose, alkyl groups
- Binding energy for biomolecules: proteins, lipids, sugars, DNA
- Ranking by binding energy
- Ranking by cell association / uptake
- Ranking by direct damage: membrane, protein
- Corona content: total protein adsorbed
- …

Summary

- Understanding bionano interface is key to progress in mechanistic understanding of biological action of NPs
- Protein binding can be reversible (light materials, small proteins, small NPs) or irreversible
- Evaluation of descriptors can be automated (work for NanoCommons)
- Need to identify NP and protein descriptors for relevant for interactions