Coarse-Grained Modelling of Protein-Nanoparticle Interactions

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SmartNanoTox
Smart Tools for Gauging Nano Hazards

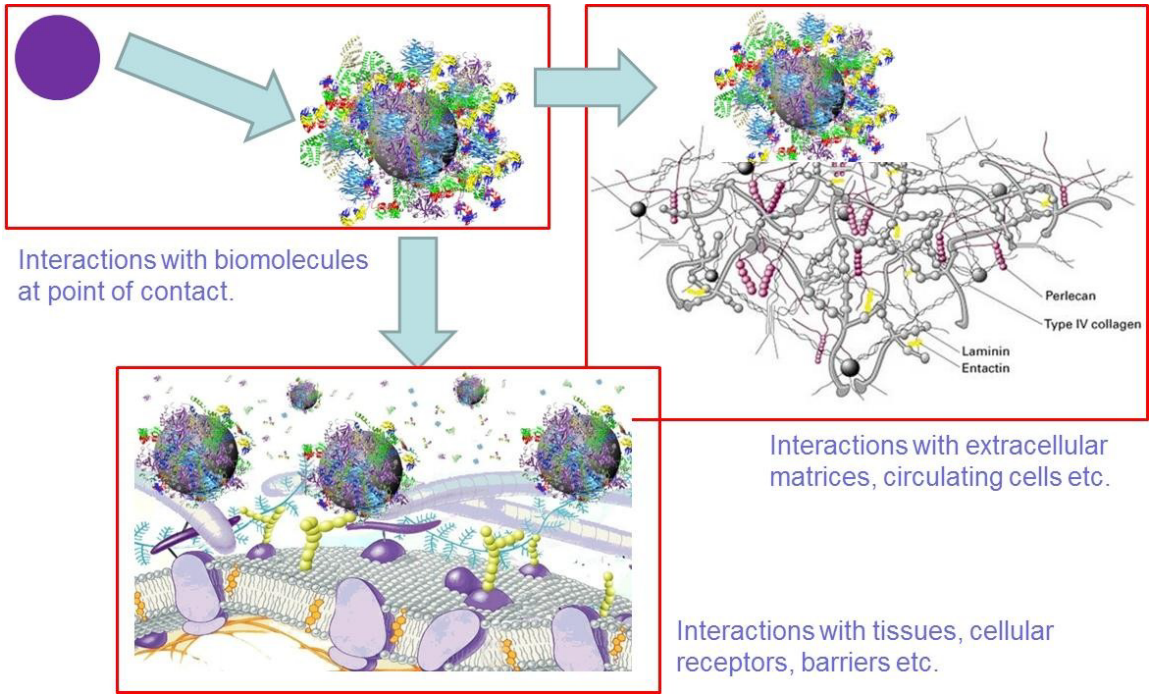
Horizon 2020
European Union funding
for Research & Innovation

Motivation

- Pathway based modelling/assessment

- Understanding of bionano interactions is needed to address Molecular Initiating Events

Nanoparticle Identity



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

The way forward

- 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

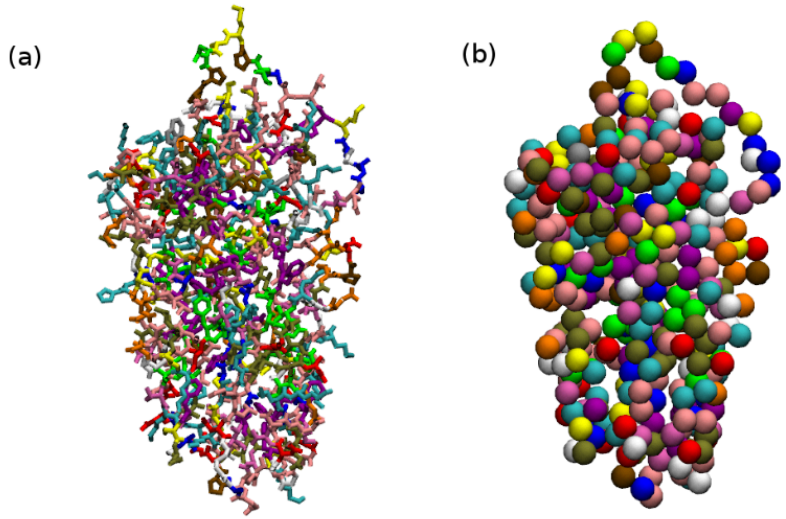
ALL BIOMOLECULES ARE BUILT FROM A SMALL NUMBER OF COMPONENTS!!!

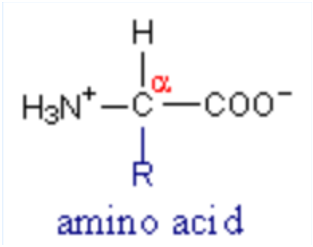
Objectives & Methods

- 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 and proteins.
- Reduce the number of components in the system.

Coarse Graining the protein

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

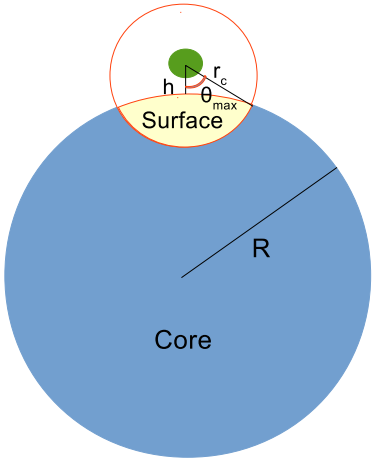




Lopez et al., JCP, 243138, 143, 2015

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

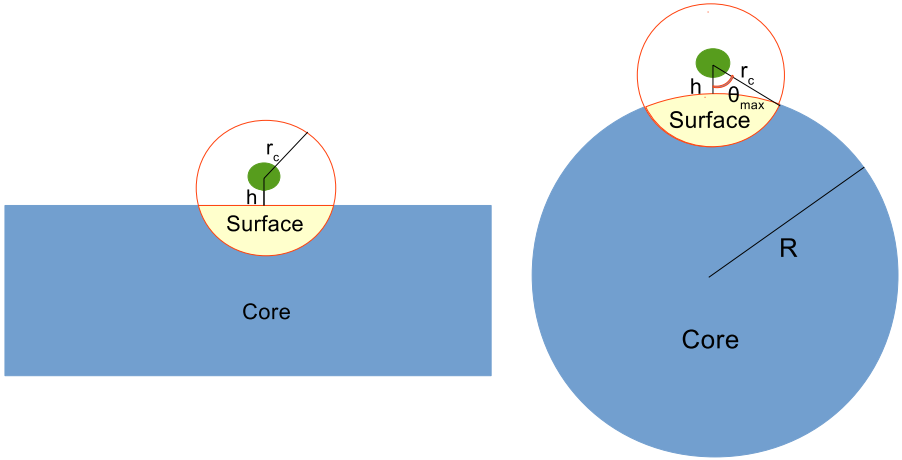
CG of Nanoparticles



- Separate the surface from the core contribution, r_c = 1.6nm
- Surface layer includes solvent effects.
- Core interacts only with long-range interactions − continuum description is sufficient.
- Core size equal to NP of radius R minus volume of surface lens.

Surface pair potential

- Calculate all-atomistic PMFs for AAs.
- Pairwise additivity & r^{-6} interaction.
- Volume inside cutoff of sphere < Volume of surface, correct by distance dependent factor *f*(h).



$$U_R(h) = U_{PMF}(h) f(h)$$

The *f* factor

$$E_{sph}(h,R) = \varepsilon \int_{r=h}^{r_c} \int_{\theta=0}^{\theta_{\max}} \int_{\phi=0}^{2\pi} \frac{r^2 \sin\theta}{r^6} d\phi\, d\theta dr$$

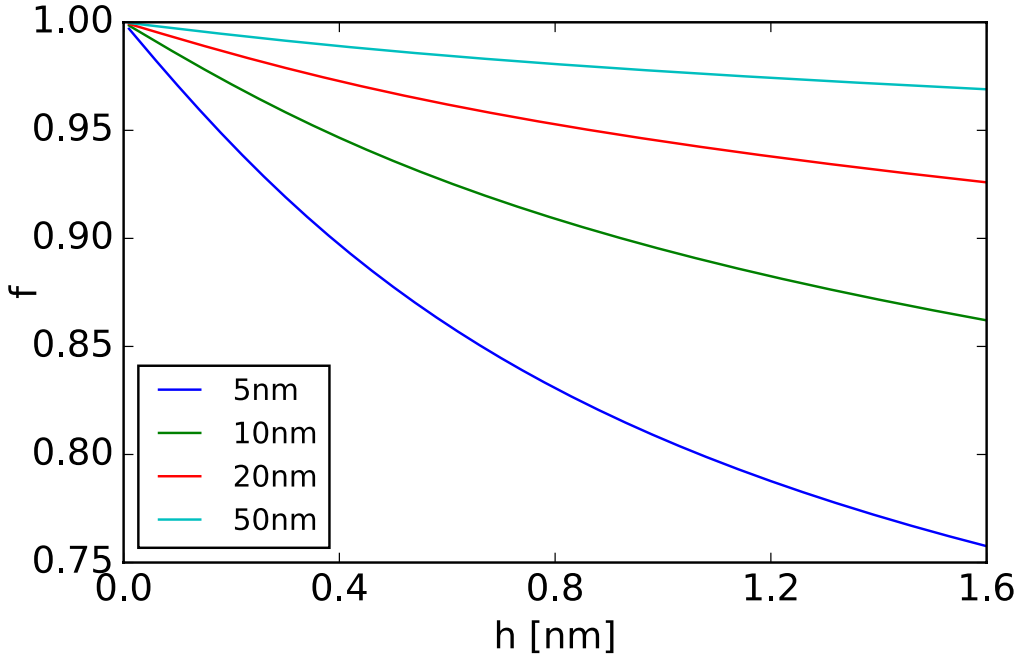
$$\theta_{\max} = \cos^{-1}\left(\frac{r^2 - R^2 + (R+h)^2}{2r(R+h)}\right)$$

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

$$R \to \infty, E_{sph} \to E_{flat}$$

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

The *f* factor



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

Core pair potential

For 2 spherical particles of radii R_1 and R_2 integrate the r^{-6} VdW over volumes and obtain for a separation D:

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

$$A_{123} = \frac{3}{4}k_BT\left(\frac{\varepsilon_1-\varepsilon_3}{\varepsilon_1+\varepsilon_3}\right)\left(\frac{\varepsilon_2-\varepsilon_3}{\varepsilon_2+\varepsilon_3}\right) + \frac{3h\nu_e}{8\sqrt{2}}\left(\frac{\left(n_1^2-n_3^2\right)\left(n_2^2-n_3^2\right)}{\left(n_1^2+n_3^2\right)^{1/2}\left(n_2^2+n_3^2\right)^{1/2}\left\{\left(n_1^2+n_3^2\right)^{1/2}+\left(n_2^2+n_3^2\right)^{1/2}\right\}}\right)$$

Absorption energy

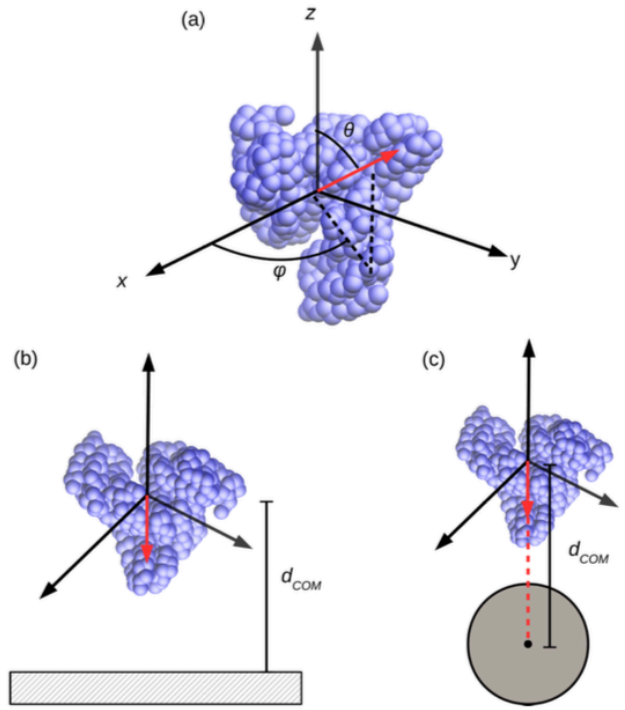
- Boltzmann average over configurational space.
- Proteins assumed to be rigid.

$$E\left(\phi_i,\theta_j\right)=$$

$$-k_BT\ln\left[\frac{3}{\left(R+a\left(\phi_i,\theta_j\right)\right)^3-R^3}\int_R^{R+a\left(\phi_i,\theta_j\right)}D^2\exp\left(\frac{-U\left(D,\phi_i,\theta_j\right)}{k_BT}\right)dD\right]$$

$$E_{ad}=\frac{\sum_i\sum_j P_{ij}E\left(\phi_i,\theta_j\right)}{\sum_i\sum_j P_{ij}}$$

$$P_{ij}=\sin\left(\theta_j\right)\exp\left(\frac{-E\left(\phi_i,\theta_j\right)}{k_BT}\right)$$



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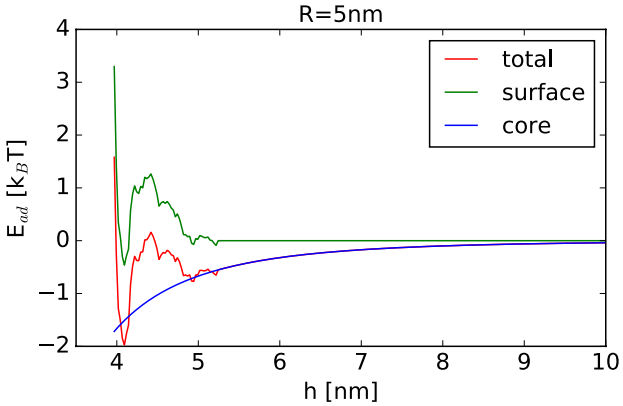
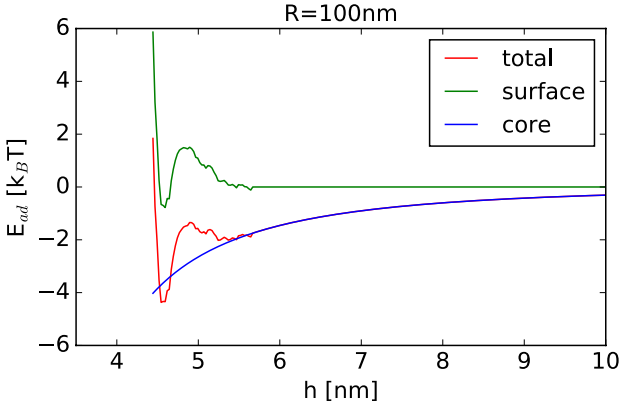
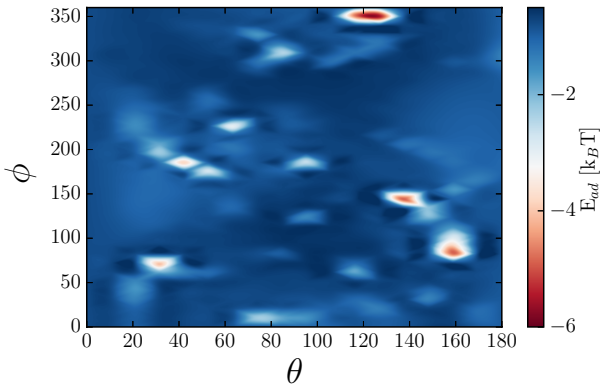
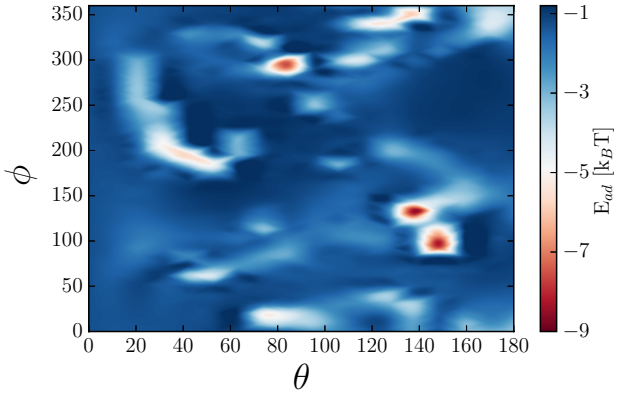
Human Serum Albumin on TiO_2









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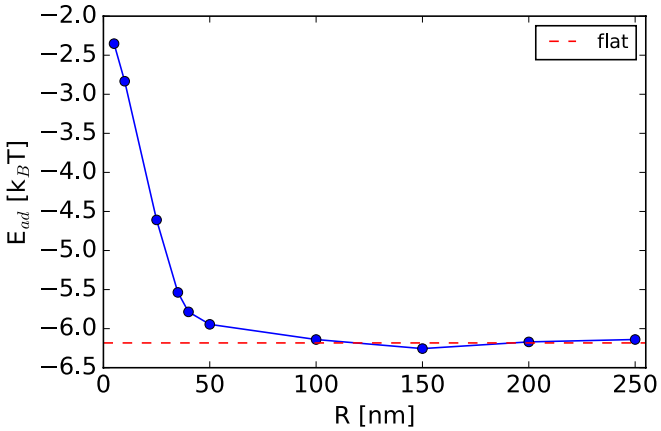
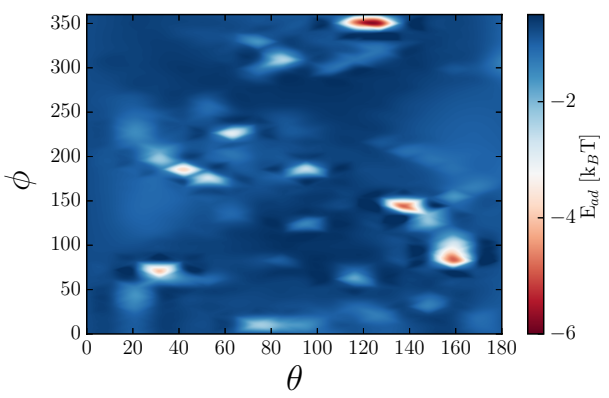
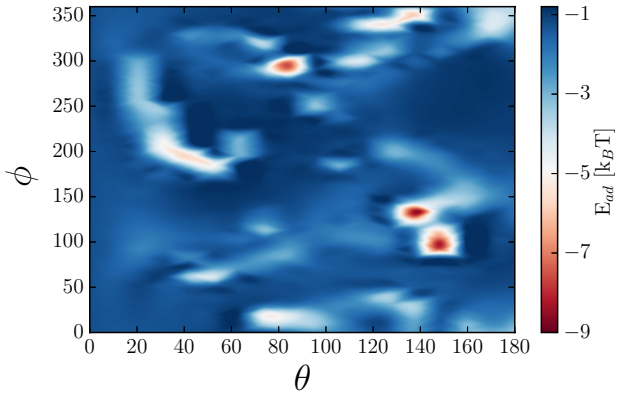
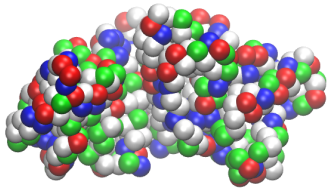
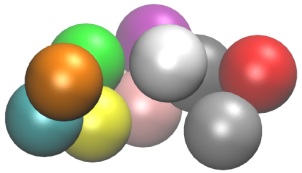


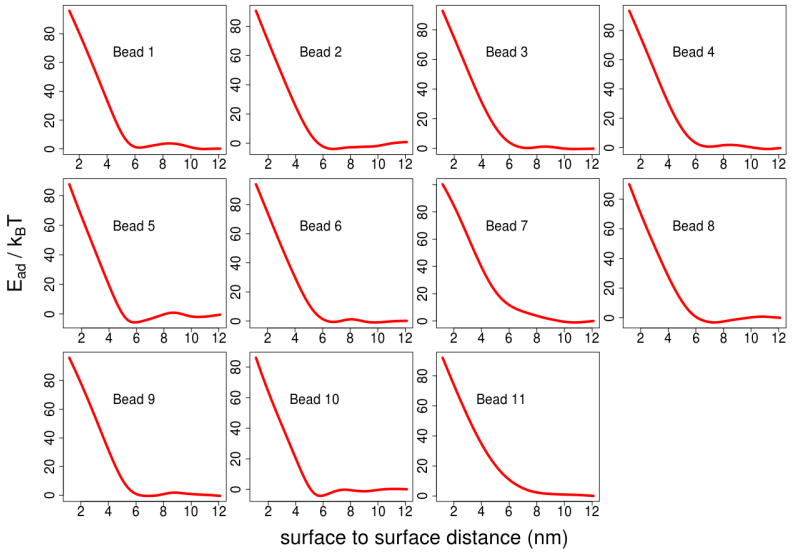




From united-atom to united-aminoacids







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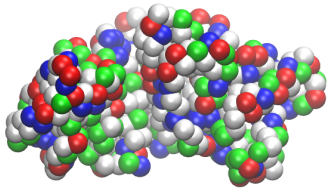
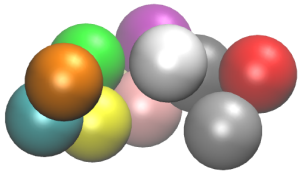
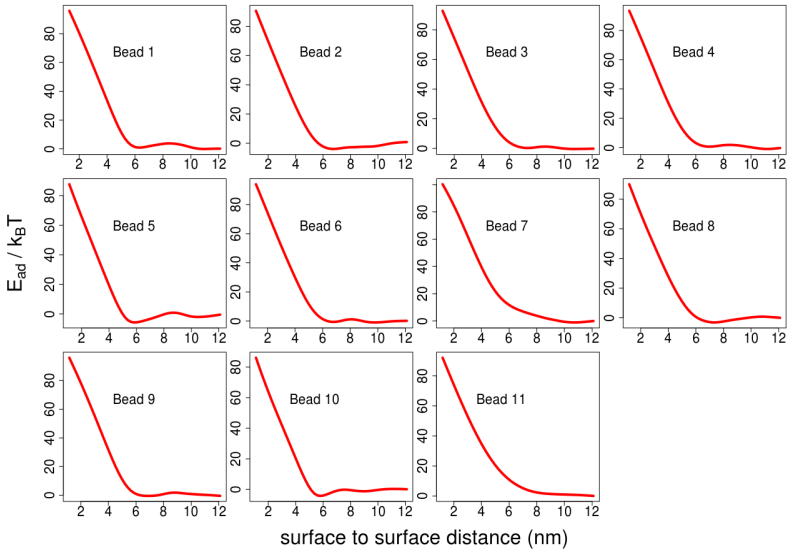
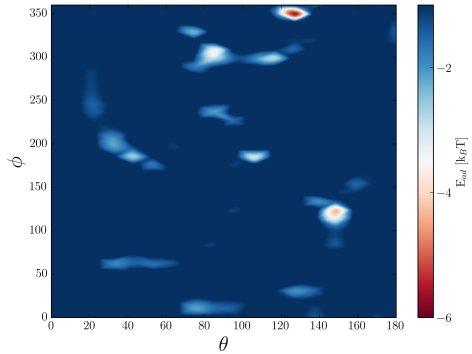


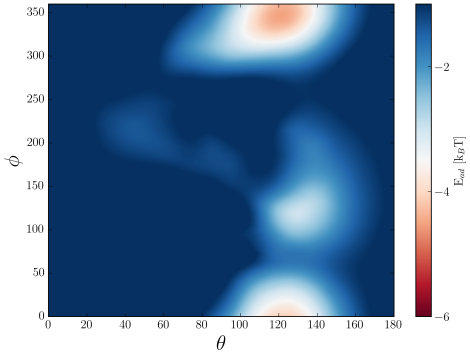




HSA on 10nm TiO_2



United-atoms



United-aminoacids

Conclusion

- We have developed a CG model of proteins-NP interactions starting from atomistic calculations.
- Can extend to lipids and sugars.
- The core and surface of NP have been treated differently.
- Use Abs Energies to predict corona composition (QSAR) − unique fingerprint.
- Rank abs energy for a large number of proteins.
- Process can be completely automated.

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