Coarse-Grained Modelling of Protein-Nanoparticle Interactions

Stefano Poggio
University College Dublin

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Motivation

- Pathway based modelling/assessment

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

Interactions with biomolecules at point of contact.

Interactions with extracellular matrices, circulating cells etc.

Interactions with tissues, cellular receptors, barriers etc.

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, $r_c = 1.6\text{nm}$
- 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 dependent factor $f(h)$.

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

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

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

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

\[ R \to \infty, E_{sph} \to E_{flat} \]

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

\[
f = \frac{E_{\text{sph}}(h,R)}{E_{\text{flat}}(h)} = -\frac{r_c^2(h - 2R) + 2r_c h(h - 2R) - 3h^2(h + 2R)}{2(r_c^2 + 2r_c h + 3h^2)(h + R)}
\]
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 $D$:

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

$$A_{123} = \frac{3}{4} k_B T \left( \frac{\varepsilon_1 - \varepsilon_3}{\varepsilon_1 + \varepsilon_3} \right) \left( \frac{\varepsilon_2 - \varepsilon_3}{\varepsilon_2 + \varepsilon_3} \right) + \frac{3\hbar \nu_{\text{e}}}{8\sqrt{2}} \left( \frac{n_1^2 - n_3^2}{(n_1^2 + n_3^2)^{1/2}} \right) \left( \frac{n_2^2 - n_3^2}{(n_2^2 + n_3^2)^{1/2}} \right) \left\{ \left( \frac{n_1^2 + n_3^2}{2} \right)^{1/2} + \left( \frac{n_2^2 + n_3^2}{2} \right)^{1/2} \right\}$$
Absorption energy

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

\[ E(\phi_i, \theta_j) = -k_B T \ln \left[ \frac{3}{(R + a(\phi_i, \theta_j))^3} \right] - R^3 \int_{R}^{R+a(\phi_i, \theta_j)} D^2 \exp \left( -\frac{U(D, \phi_i, \theta_j)}{k_B T} \right) dD \]

\[ E_{ad} = \sum_i \sum_j P_{ij} E(\phi_i, \theta_j) \]

\[ P_{ij} = \sin(\theta_j) \exp \left( -\frac{E(\phi_i, \theta_j)}{k_B T} \right) \]

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Human Serum Albumin on TiO$_2$
Human Serum Albumin on TiO$_2$

![Graph showing the relationship between E$_{ad}$ and R (nm).]

![Images of φ and E$_{ad}$ heat maps for θ and φ.]

20/10/2017
From united-atom to united-aminoacids
From united-atom to united-aminoacids

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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