Modelling of Bio-Nano Interactions for Predictive Toxicology

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SmartNanoTox: Smart Tools for Gauging Nano Hazards

Project consortium: 11 partners

Coordinator: University College Dublin

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www.smartnanotox.eu
Nanoparticle Identity

Interactions with biomolecules at point of contact.

Interactions with extracellular matrices, circulating cells etc.

Interactions with tissues, cellular receptors, barriers etc.

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

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) → 1N5U
CG HSA → one bead per residue at the alpha carbon →
11-bead model
Protein structure prediction

Not all 3D structures are available from PDB.
Simulation settings

- All simulations → ESPResSo
- Unit of Energy: $k_B T$ ($T=310$ K)
- Unit of length: nm
- Ionic strength: 100 mM
- Angle grid every 5°: $36 \times 72 = 2592$ 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)

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)

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

1 – NM, 3 – AA, 2 - water
Dispersion forces

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

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AA - gold

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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

![Graph showing adsorption energy $E_{ad}$ vs. distance $R$. The graph displays a trend where $E_{ad}$ decreases sharply as $R$ increases, approaching a horizontal line labeled as flat.](image-url)
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

R = 50 nm

Preferred protein orientation: HSA
## Ranking proteins by adsorption energy

### Increasing affinity

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<th>NP Radius, nm</th>
<th>Rank 1</th>
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**Large** and **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
From united-atom to united aminoacid model:

Optimisation of the model using a genetic algorithm

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