Imperial College London

SmartNanoTox
Smart Tools for Gauging Nano Hazards

Changjiang Professor

Free energy of adsorption of supported lipid bilayers from molecular dynamics simulation

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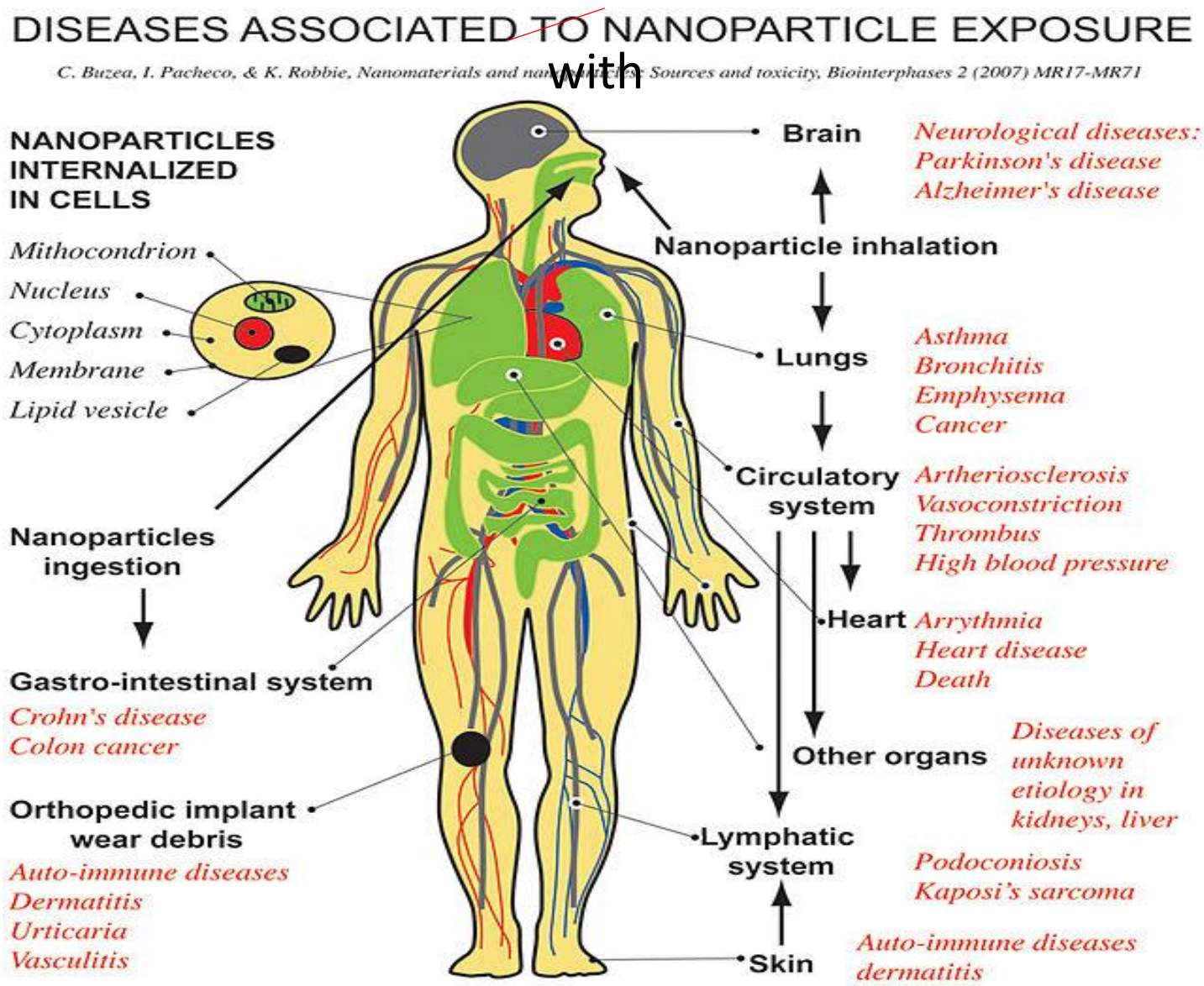
Background

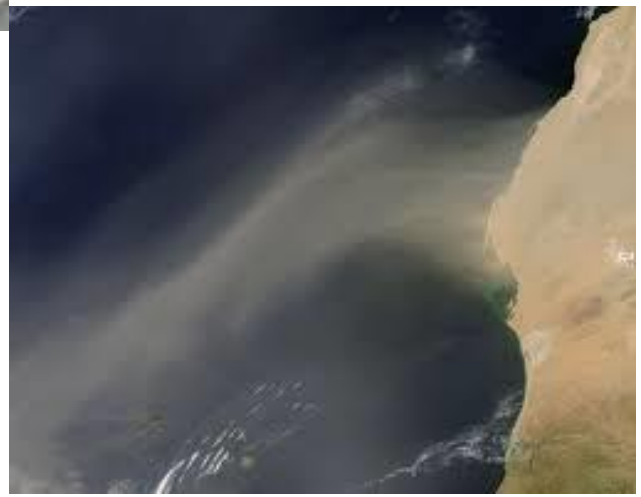
Nanoparticles

Risk- Nano - toxicity

Opportunity – drug/therapy delivery



Sources



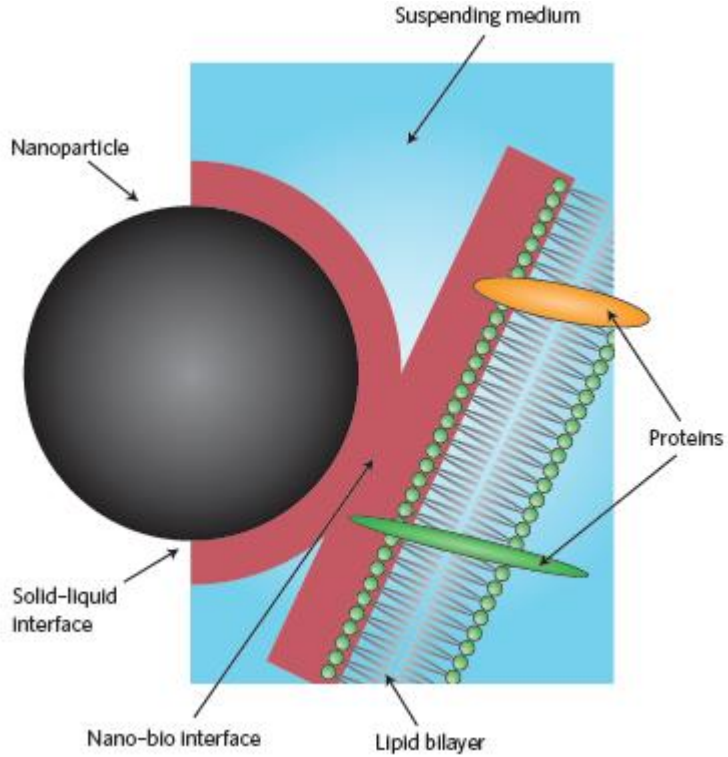
Nanoparticles in biological systems

Points of entry

- Lung
- Skin
- Stomach
- Blood

Proteins

Corona



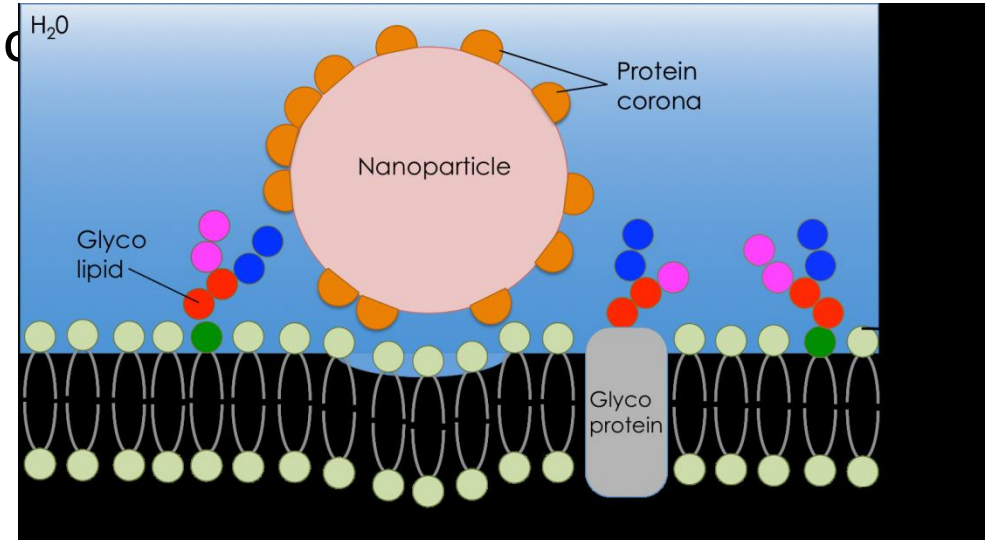
- Recent toxicology studies suggest that NANOPARTICLES can alter lung function, enter cells and *alter their functions*, and also cross the blood–brain barrier.

- Complex problem relevant to nanomedicine and nanotox

- **Understand using simulation?**

The principal challenges to modelling nanoparticle interactions with biological membranes

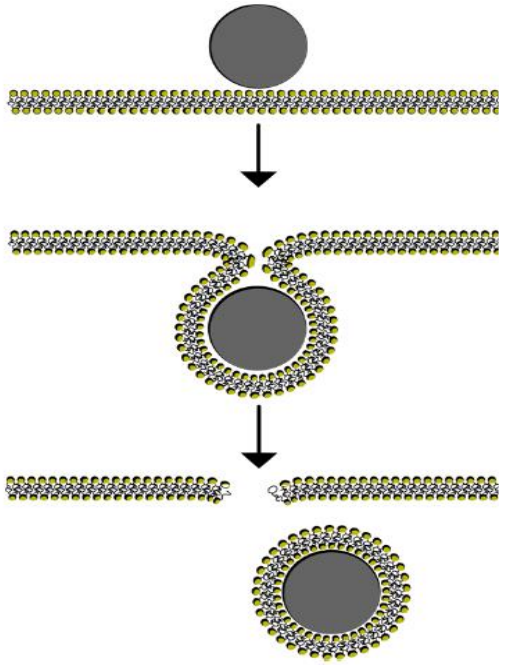
- NP coronas (cells do not see the NP?)
- Complexity of blood proteome (what adsorbs on the NP?)
- Complexity of the lung surfactant/cell membrane
- Dynamic composition of the coronas
- Time scale for sorption/desorption wrt typical MD timescale
- Role of water in NP and NP/protein interaction?
- Size of system required for realistic simulation?
- Passive or activated translocatic
- Role of charge?
- Calibrating potentials



Strategy: Towards a fundamental understanding of NP/membrane processes

- Simplify : use vesicles – one type of lipid
- Simplify: initially no corona

Q: What happens when a particle interacts with a vesicle?



Step 1: Adhesion

Step 2: Engulfment

Step 3: Fission

This is a simple biomimetic system where the bilayer serves a model of the cell membrane

We need to understand this system before we can make sense of real systems

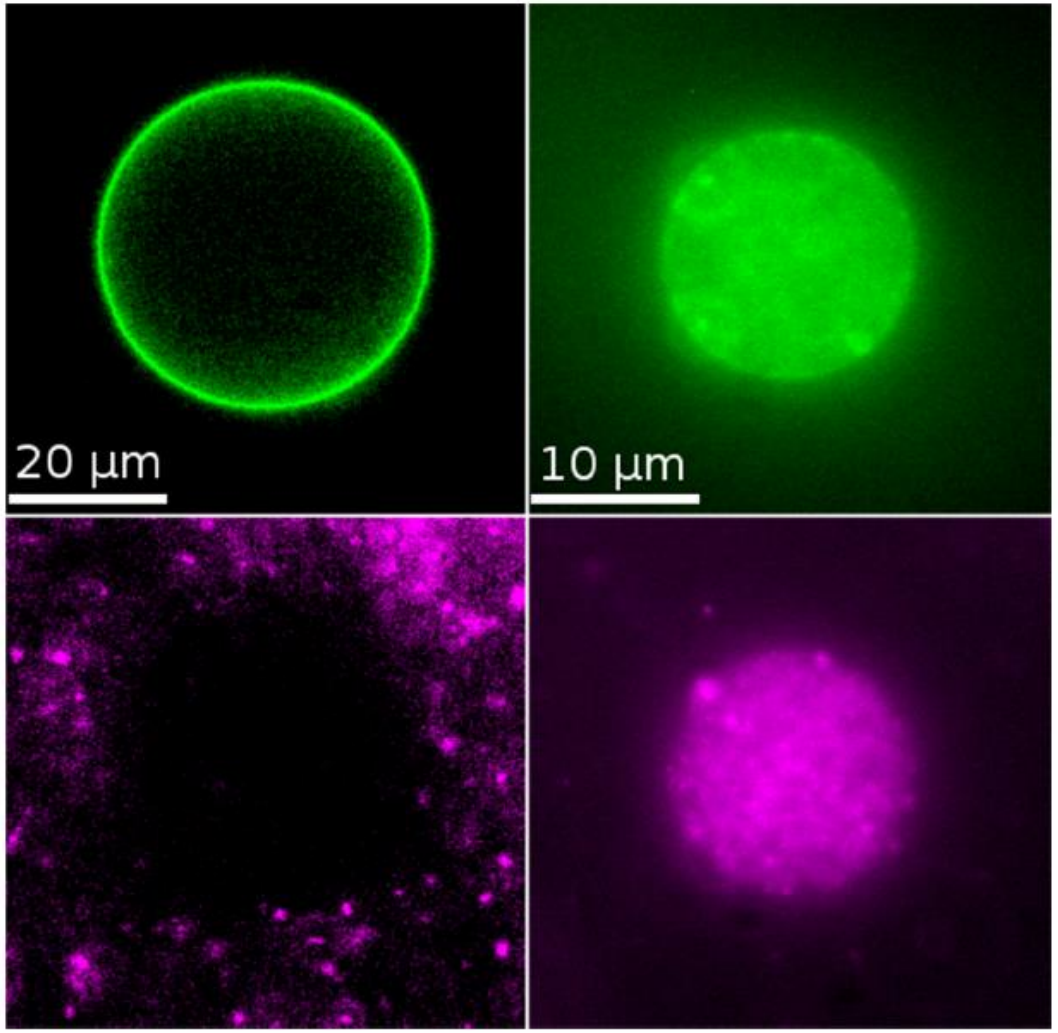
Experiment?

Strobl et al 2014: Flourescence microscopy

DOPC vesicles

SiO_2
r = 123 nm

SiO_2
r = 42 nm



1 minute after incubation
Fluid phase

1 minute

10 minutes after incubation
Gel phase

10 minutes

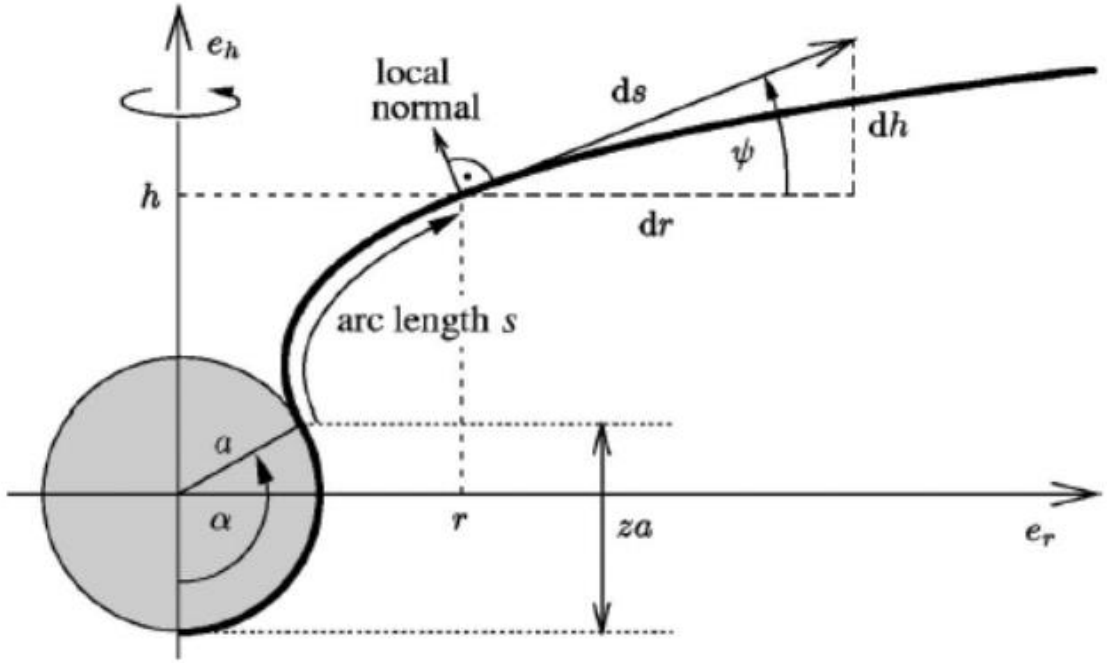
Here we observe that 123 nm particles are not taken up by vesicle in the fluid phase

However, they found that these particles are taken up in the gel phase

In contrast 42 nm particles are taken up
by the vesicle at all times

What's important?

Deserno 2004
Continuum Elastic Model
Full numerical solution of free profile



$$E_{total} = E_{ad} + E_{be} + E_{te} + E_{free}$$

$E_{ad} = -2\pi a^2 z w_\infty$ adsorption

$E_{be} = 4\pi z \kappa$ bending

$E_{te} = \pi a^2 z^2 \sigma$ membrane tension

$z = 1 - \cos(\alpha)$

z = 0 for non adhesion
z = 2 for complete engulfment

Low tension limit:
Free membrane adopts catenoid profile
Mean curvature is everywhere zero
We can neglect E_{free}

High tension limit:
$E_{te} >>> E_{free}$
We can neglect E_{free}

M. Deserno, 'Elastic deformation of a fluid membrane upon colloid binding', *Physical Review E*, vol. 69, no. 3, Mar. 2004.

Ignore free membrane

$$\tilde{w} := \frac{2wa^2}{\kappa}, \quad \tilde{\sigma} := \frac{\sigma a^2}{\kappa}$$

High Tension limit:
For complete engulfment (z=2)

$$E_{ad} + E_{be} < E_{te}$$

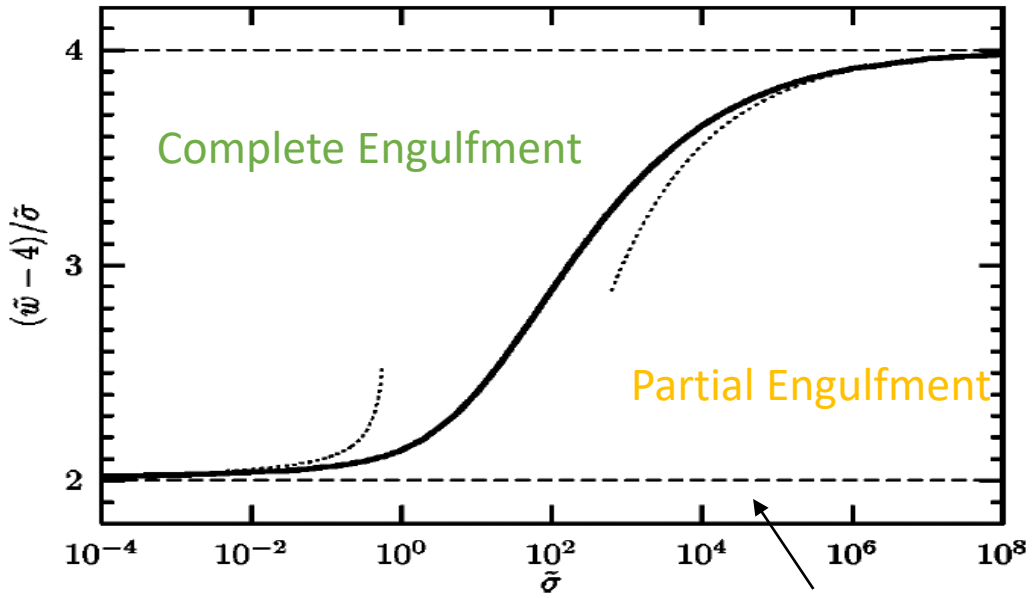
$$r \geq r_{crit} = \sqrt{\frac{2\kappa}{w_\infty - \sigma}}$$

Low tension limit:
For adhesion to occur

$$E_{ad} + E_{be} < 0$$

$$r \geq r_{crit} = \sqrt{\frac{2\kappa}{w_\infty}}$$

adhesion must be strong enough to pay bending cost



- This assumes that the bending modulus of the bilayer is unchanged upon adsorption: Does this assumption hold for thick membranes?
- If σ≈ w then particles never completely engulfed , or not adsorbed. Strobl suggests large particles increase vesicle tension and prevent further engulfment

Direct MD Simulation?

Problem I: lack of validated potentials

- Quantitative predictions of MD simulations are only as accurate as the interaction potentials employed. A great deal of effort has been expended to optimise lipid-lipid and lipid-water interaction potentials by calibration against empirically determined macroscale properties.

- Similarly, interaction potentials between water with inorganic surfaces are typically calibrated to reproduce interfacial properties determined by experiment.
- Lipid-substrate interactions, on the other hand, are usually generated by cross averaging using geometric or arithmetic averages.
- In order to conduct realistic and predictive simulations lipid-substrate interactions should also be calibrated using experimental data.

- The obvious choice for such data is the free energy of adsorption and a prerequisite for using these data is a simulation method that can accurately predict the adsorption energy for a given set of potentials.

The relative strength of the lipid/NP and water/NP interactions controls the NP/membrane outcome

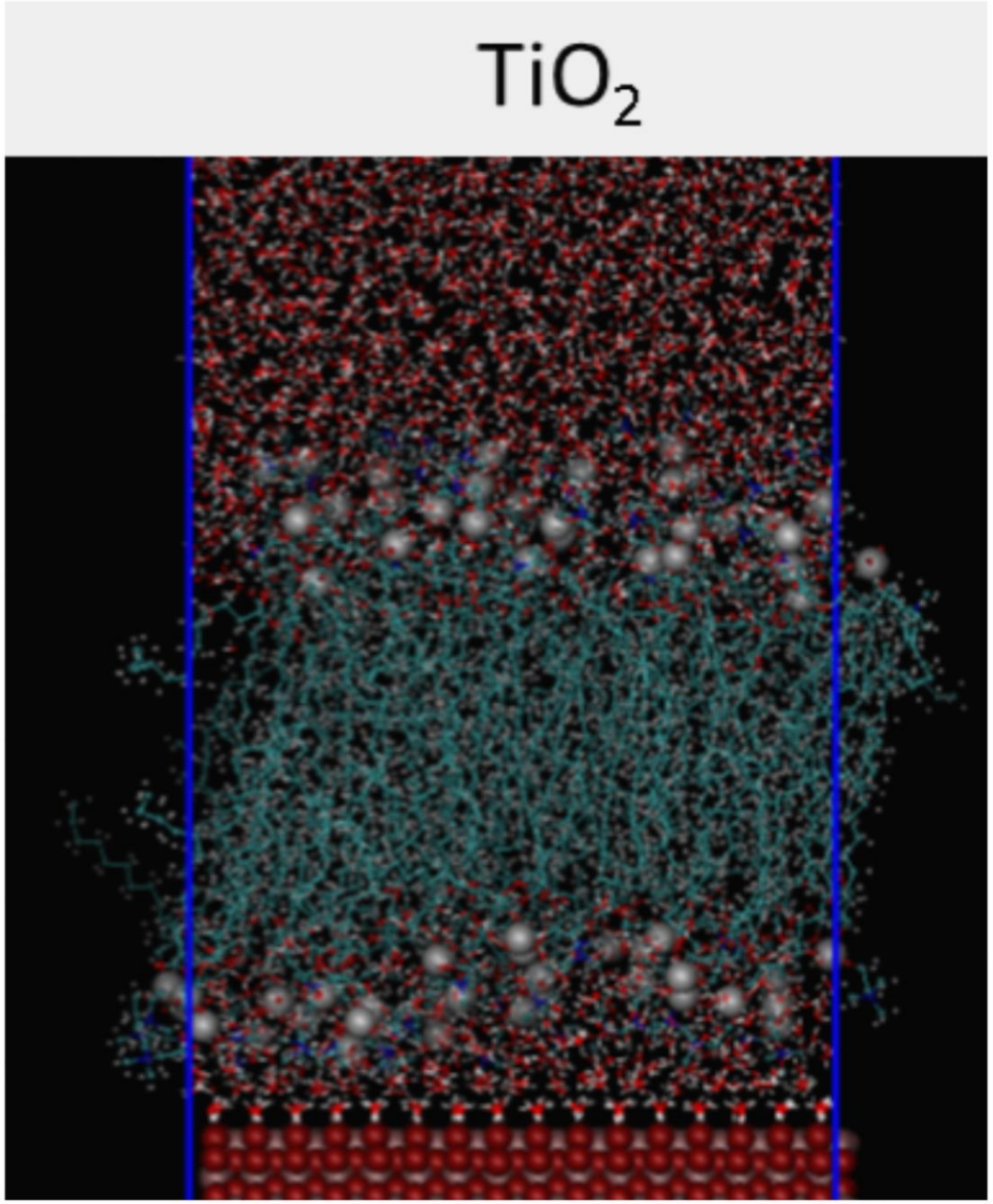
Problem II: MD methodology

- Simulations of *free* bilayers are typically conducted in the canonical ensemble with a periodic membrane spanning the simulation cell under tension that is controlled by an anisotropic barostat.

- **When a periodic solid surface is introduced to the simulation cell in this geometry the water between the surface and bilayer is unable to exchange molecules with the bulk water phase and spontaneous adsorption will not occur.**

- Heine and coworkers /bilayers on silica surfaces,/is to manually vary the amount of intervening water and measure the total energy of the system.-does not give the free energy of adsorption, only the separation between surface and bilayer at the total energy minimum.

- Pertsin and Grunze /DLPE bilayers on mica/ intervening water was equilibrated using a GCMC procedure, and they measured the force between the surface and bilayer as a function of separation. uncertainty in the force measurement was too large to allow an accurate estimate of the adhesion energy



Problem III: lack of experimental data

- Almost no experimental data for lipid/nanoparticle heats of adsorption
  - Initiating an experimental nano-calorimetry programme through smartnanotox in collaboration with UCL

- We have one data point for DMPC on gold*:– 40 $mN.m^{-1}$

* Lipkowski: et al obtained the adhesion energy from integration of the difference between charge density curves obtained from chronocoulometry in the presence and the absence of the bilayer,: Sarah L. Horswell, Vlad Zamlynny, Hong-Qiang Li, A. Rod Merrill and Jacek Lipkowski: Faraday Discuss., 2002, 121, 405–422

Model Validation: gold nanoparticles at DMPC bilayer

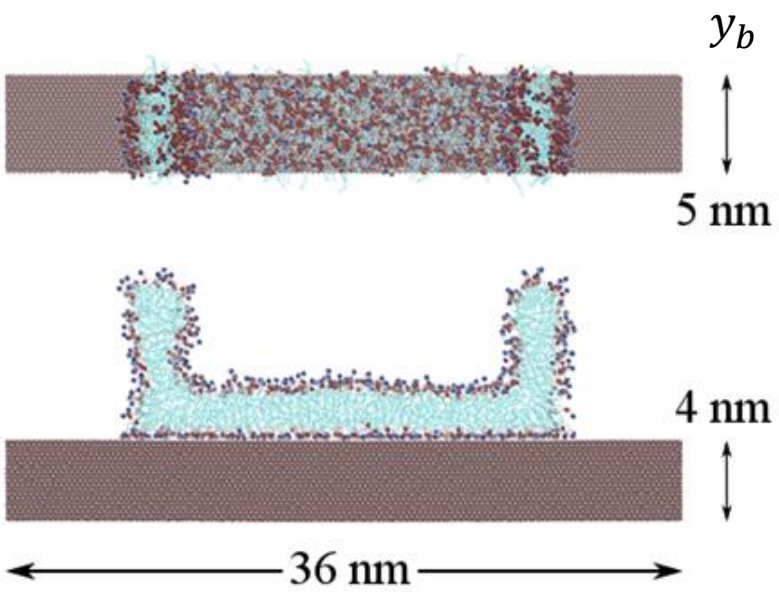
DMPC	Slipids 118 site all-atom model with partial charges Reproduces: areas and volumes per lipid bending and compressibility modulus	Jämbeck and Lyubartsev
Gold	Modelled with only LJ potential Reproduces: density, interfacial energies with vacuum and water	Heinz, Vaia, Farmer and Naik
Water	Tip3p with 1 LJ site and 3 partial charges Reproduces: density, surface tension	Jorgensen, Chandrasekhar, Madura, Impey and Klein

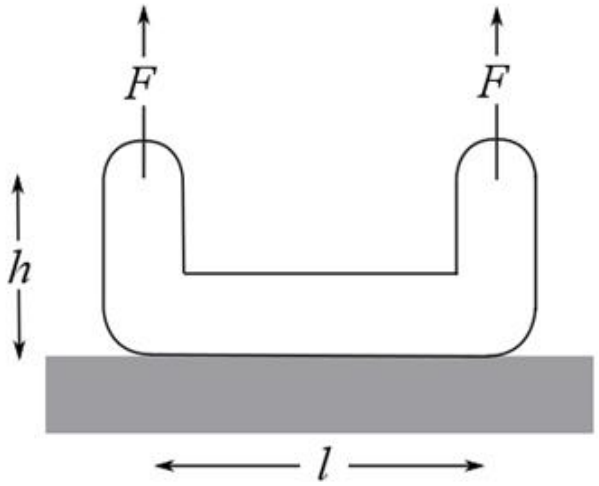
The DMPC-gold interaction potential has never been validated

Use flat interfaces in the first instance and then extend to curved interfaces

Calibration of the gold-lipid interaction

scaling the epsilon value of the LJ cross interactions to match the adhesion energy





The 18 lipids at each end of the ribbon form 2 pull groups

A harmonic restraint is placed between each pull group and the gold surface

The pull groups are recalculated periodically (0.5 ns) to allow migration of lipids between leaflets

This ensures that the bilayer is symmetrical and therefore the spontaneous curvature C_0 is zero.

≈ 160,000 atoms

We need to know the lipid specific area in the adsorbed bilayer and in the free membrane

$$w_\infty = F\frac{dh}{dA} = -F\frac{a_{fm}(F)}{y_b a_{slb}}$$

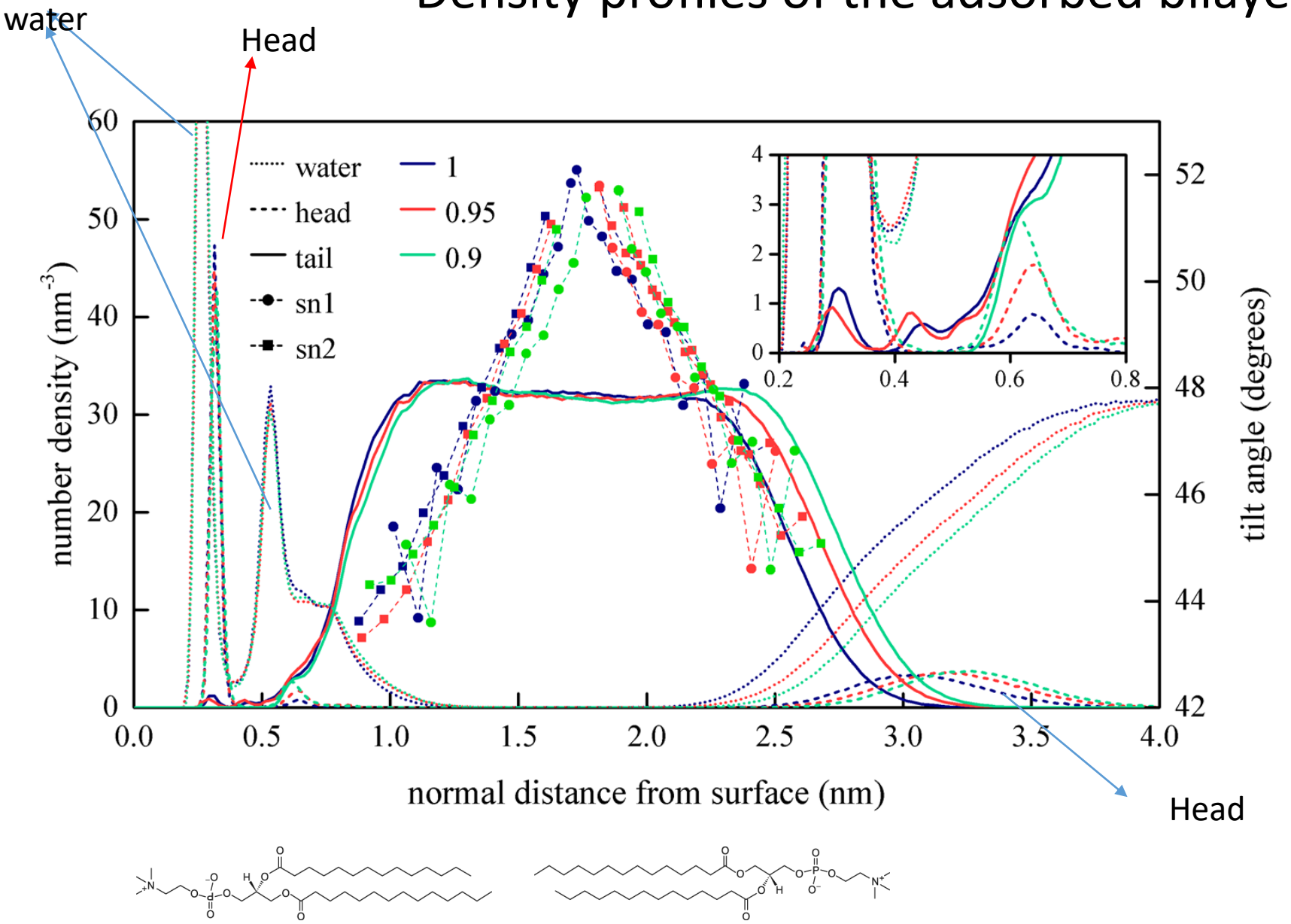
M. Schneemilch, N. Quirke, Chemical Physics Letters 664 (2016) 199–204

Experimental adhesion energy of DMPC on gold – 40 $mN.m^{-1}$

Scaling factor	1	0.95	0.9
a_0^{bot} (nm^{-2})	0.91 ± 0.02	0.83 ± 0.03	0.817 ± 0.003
a_0^{top} (nm^{-2})	0.873 ± 0.004	0.84 ± 0.01	0.835 ± 0.002
a_0^{comb} (nm^{-2})	0.89 ± 0.01	0.84 ± 0.01	0.83 ± 0.01
Thickness (nm)	2.72 ± 0.01	2.83 ± 0.04	2.87 ± 0.03
Separation (nm)	0.33 ± 0.01	0.36 ± 0.01	0.36 ± 0.01
Tension ($mN.m^{-1}$)	49.2 ± 1.8	41.5 ± 1.8	38 ± 0.8
a_0^{free} (nm^{-2})	0.93 ± 0.02	0.85 ± 0.02	0.82 ± 0.02
W ($mN.m^{-1}$)	-51.1 ± 2.8	-42.2 ± 2.0	-37.9 ± 1.2

Best fit scaling factor =0.925

Density profiles of the adsorbed bilayer

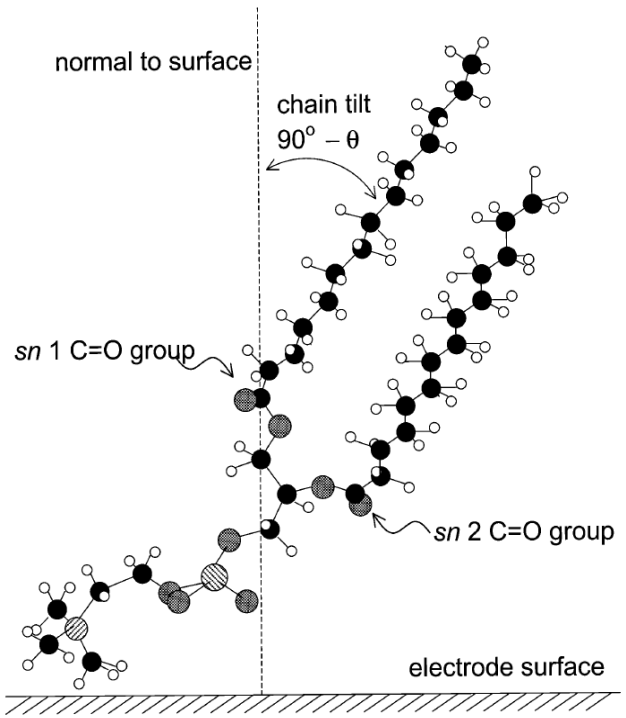


The specific lipid area in the SLB is determined from the average density profile in the middle of the ribbon.

We have examined 3 scaling factors: 1, 0.95 and 0.9

The outer leaflet is very similar to a free membrane.

The leaflet next to the surface displays considerable deformation



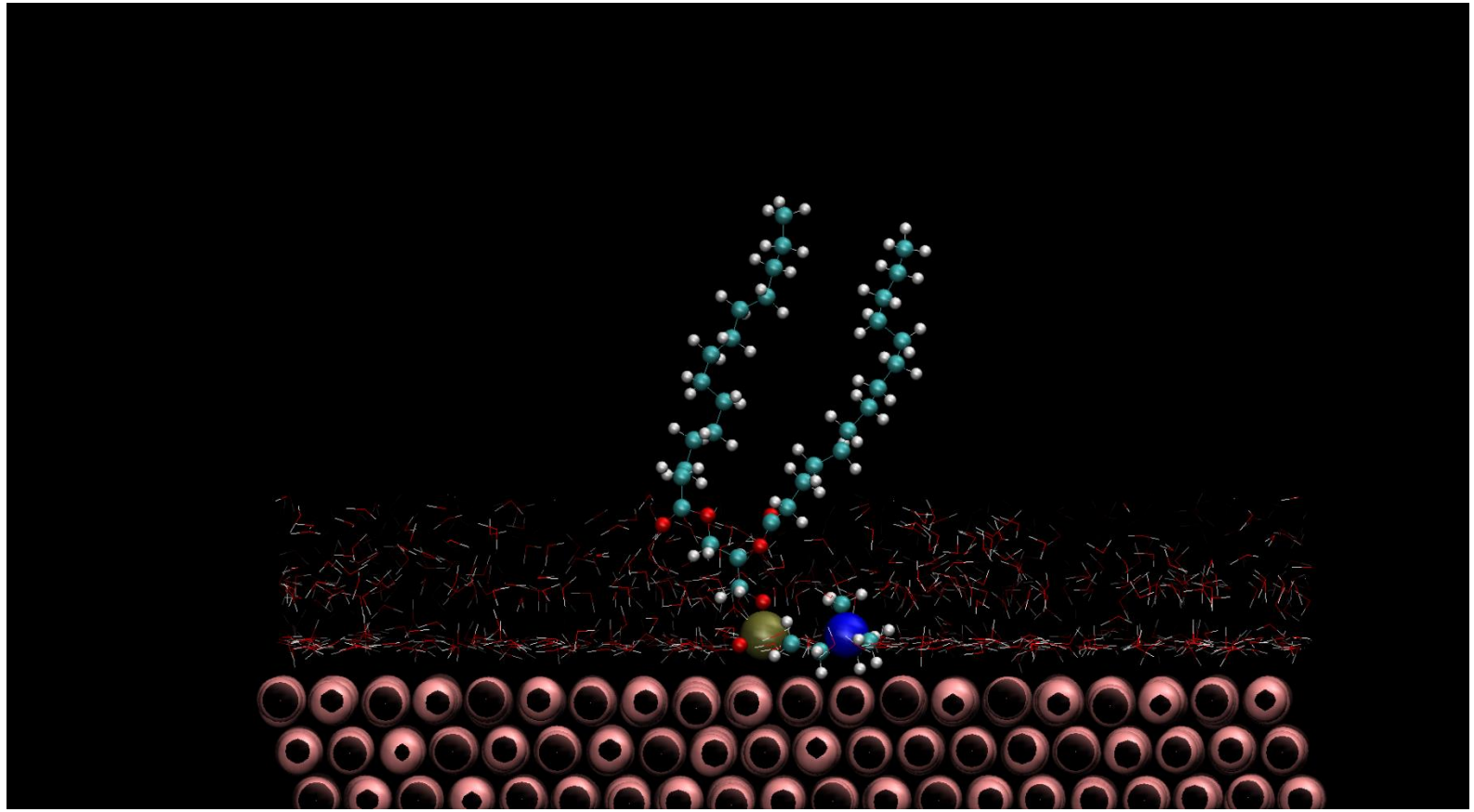


Fig. 1 Schematic diagram of DMPC molecule adsorbed on the electrode surface. The angle θ is t
between the transition dipole of CH_2 band and the surface normal. Adapted from ref. 38.

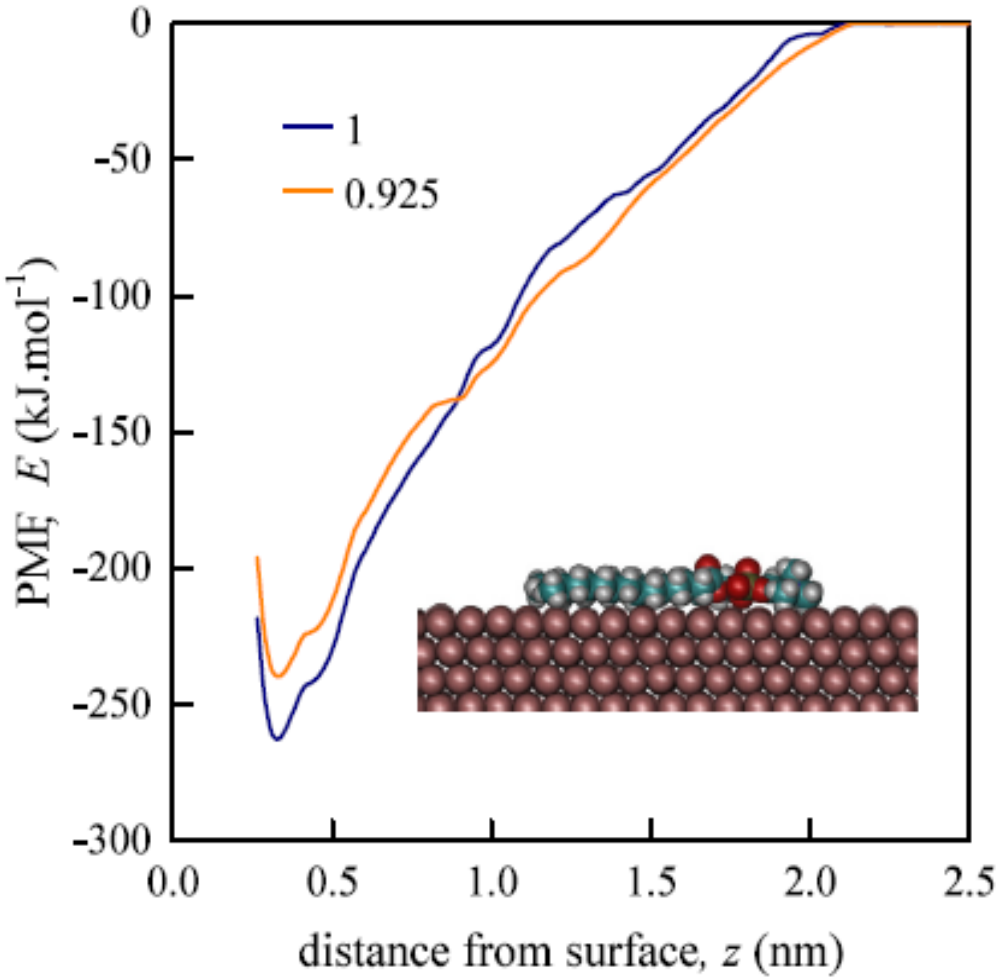


Fig. 4. The potential of mean force for a single lipid adsorbing on the gold surface. The inset shows the lipid in the minimum energy configuration. Colours denote the scaling factor for the gold-lipid potential. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Single molecule PMF

- Scaled potential ≈ unscaled
- Adsorption energy 10* the bilayer

It is well established that the mechanism of vesicle fusion of DMPC on gold involves an intermediate step where the molecules released by vesicle rupture adsorb flat onto the surface to form an ordered monolayer

Simulation consistent with the AFM experiments (Lipkowski)

Next steps

Extend to curved interfaces

Extend to silica/other materials

Measure heats and calibrate potentials

All atom simulations of NP engulfment by lipid bilayers (non PBC/flip flop or CG vesicles)

Refine theory based on simulations: use to predict outcomes for NP classes

Introduce the corona and membrane complexity