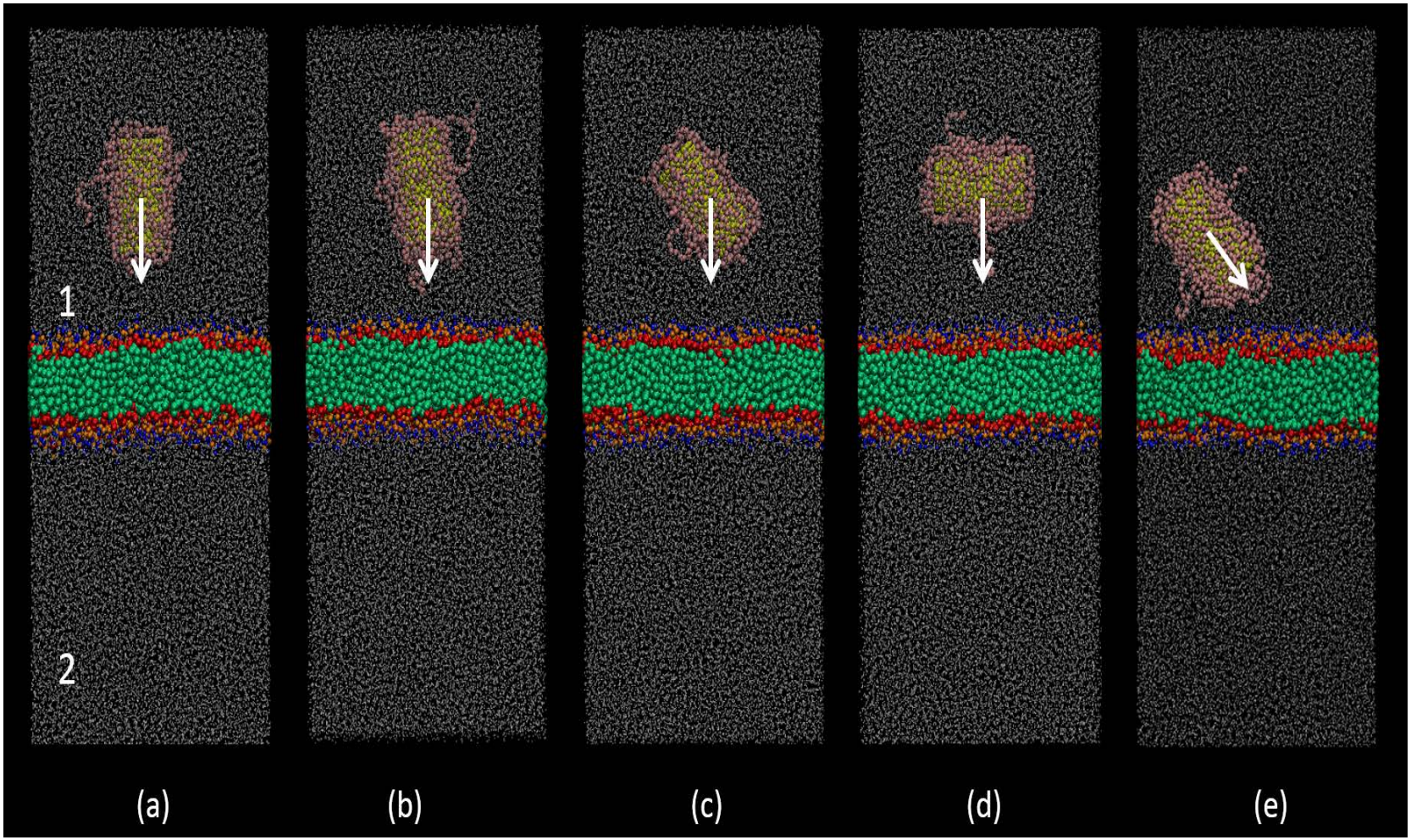
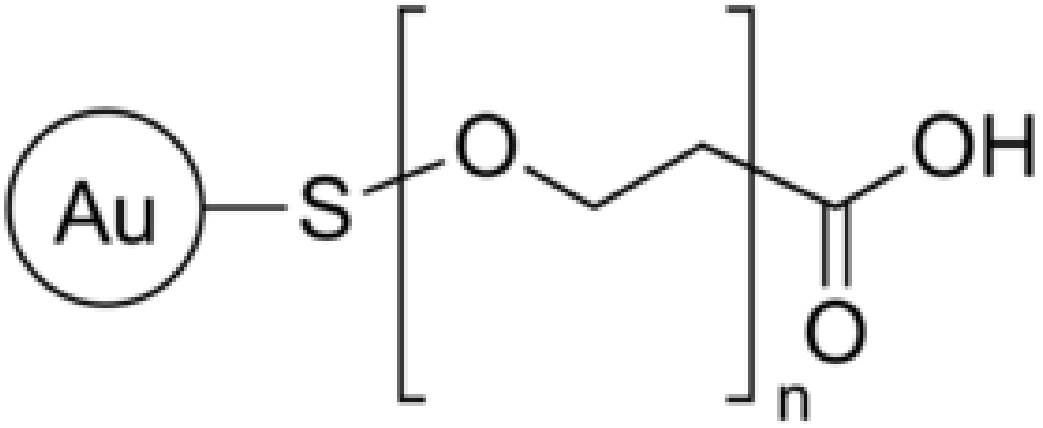
PEGylated Au nanoparticles permeate a lipid membrane



Priyanka Oroskar, Cynthia J Jameson and Sohail Murad

PEG ligand on gold

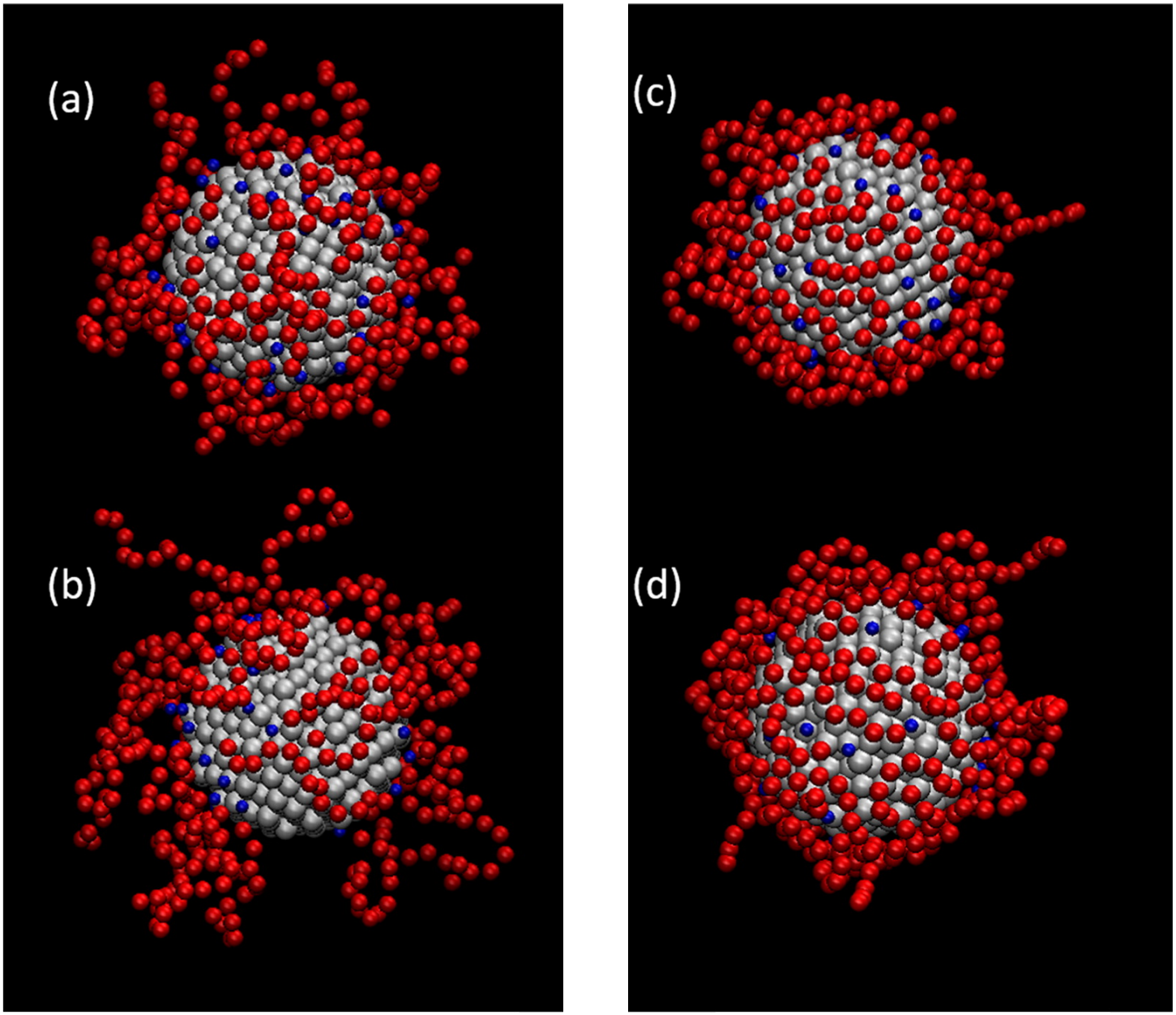


Our simulations use the methyl derivative
Coarse-grained model based on Lee, de Vries, Marrink & Pastor (2009) J Phys Chem B, 113, 13186.

PEGylated AuNP in PEG *or in water*

PEG6 AuNP

PEG12 AuNP

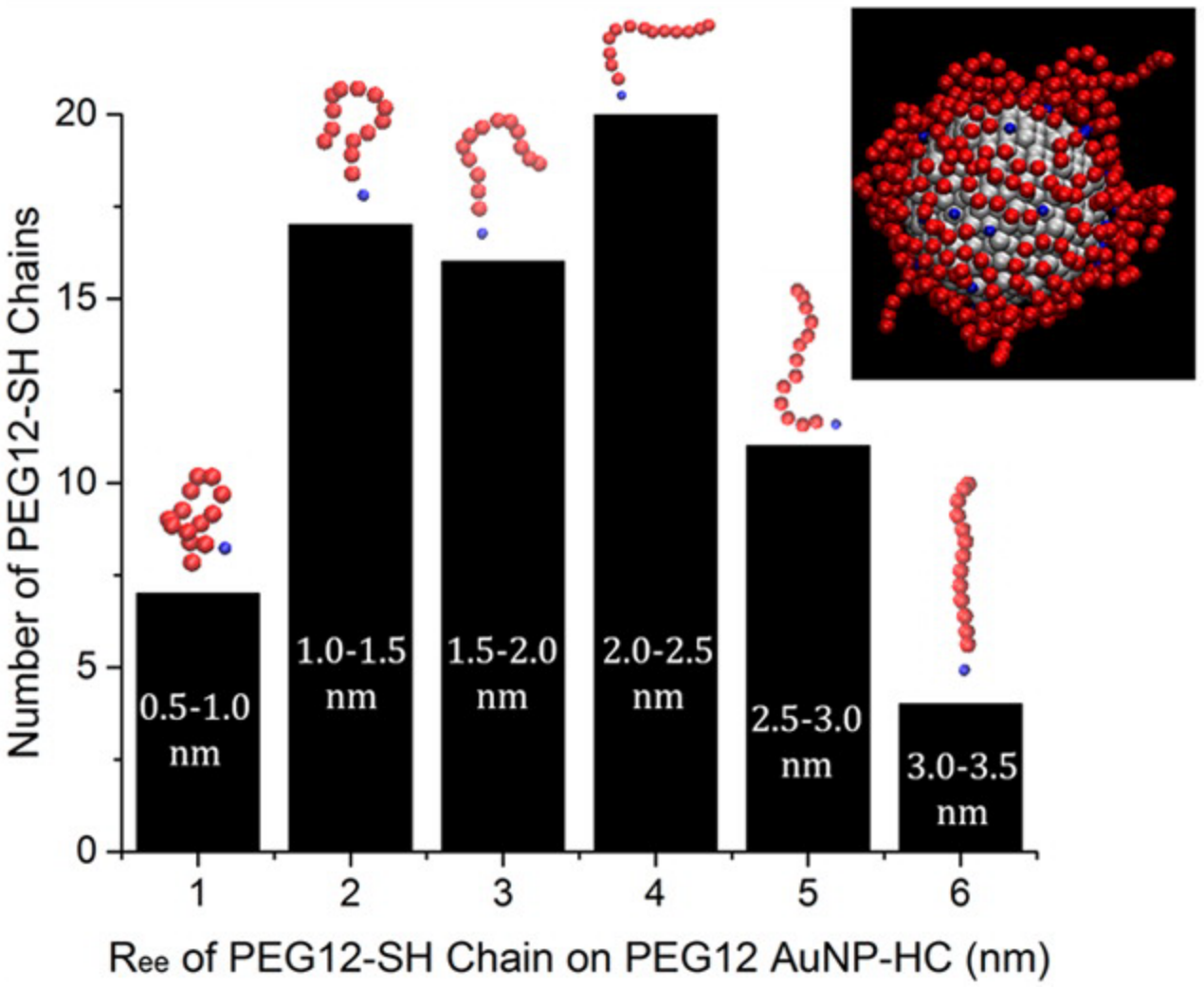


For clarity, solvent molecules are not shown.

“Mushroom” vs “Brush”

Mushroom and Brush descriptions of PEGylated AuNPs in water at low and high surface coverage actually correspond to a distribution of ligand configurations.

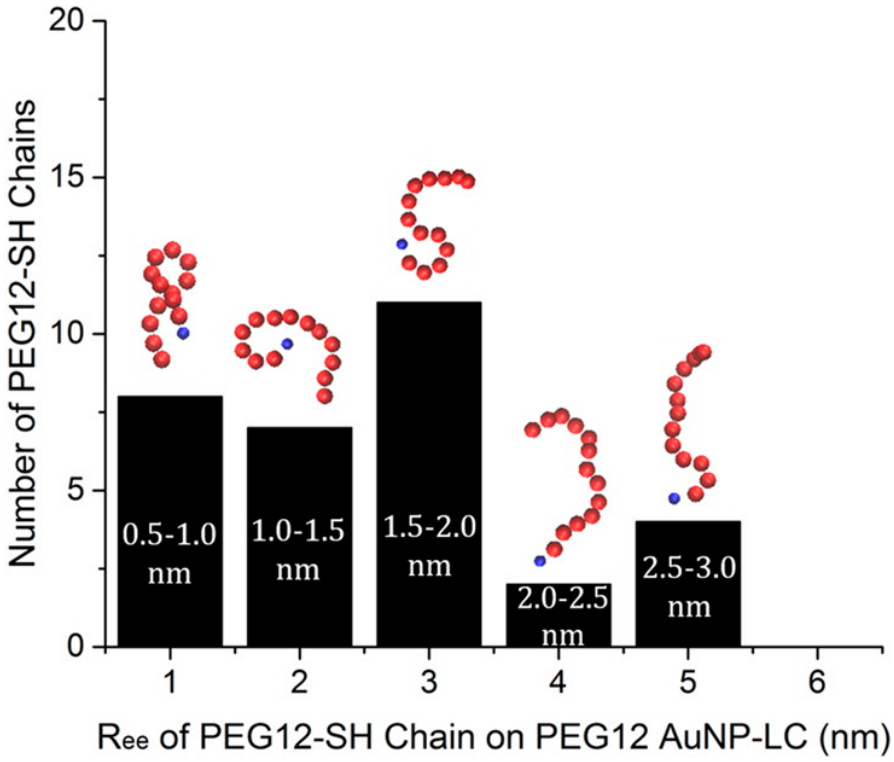
Conformations of ligands at High Coverage on PEGylated AuNP



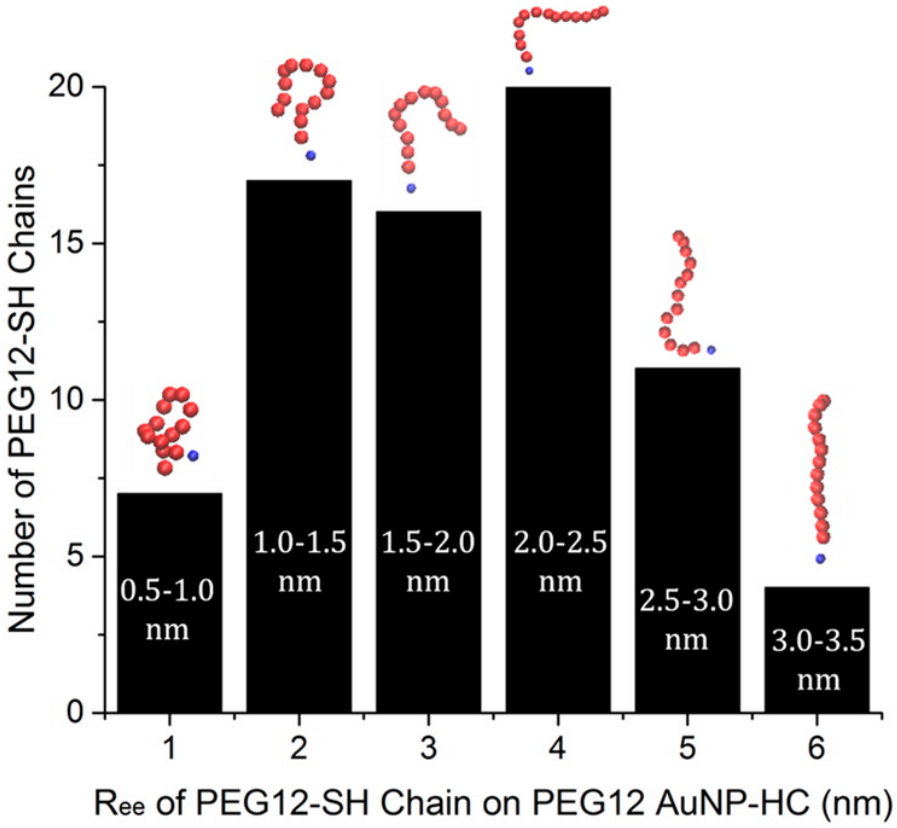
in water

R_{ee} = average end-to-end distance

Distribution of ligands, LOW vs HIGH Coverage



LOW Coverage



HIGH Coverage

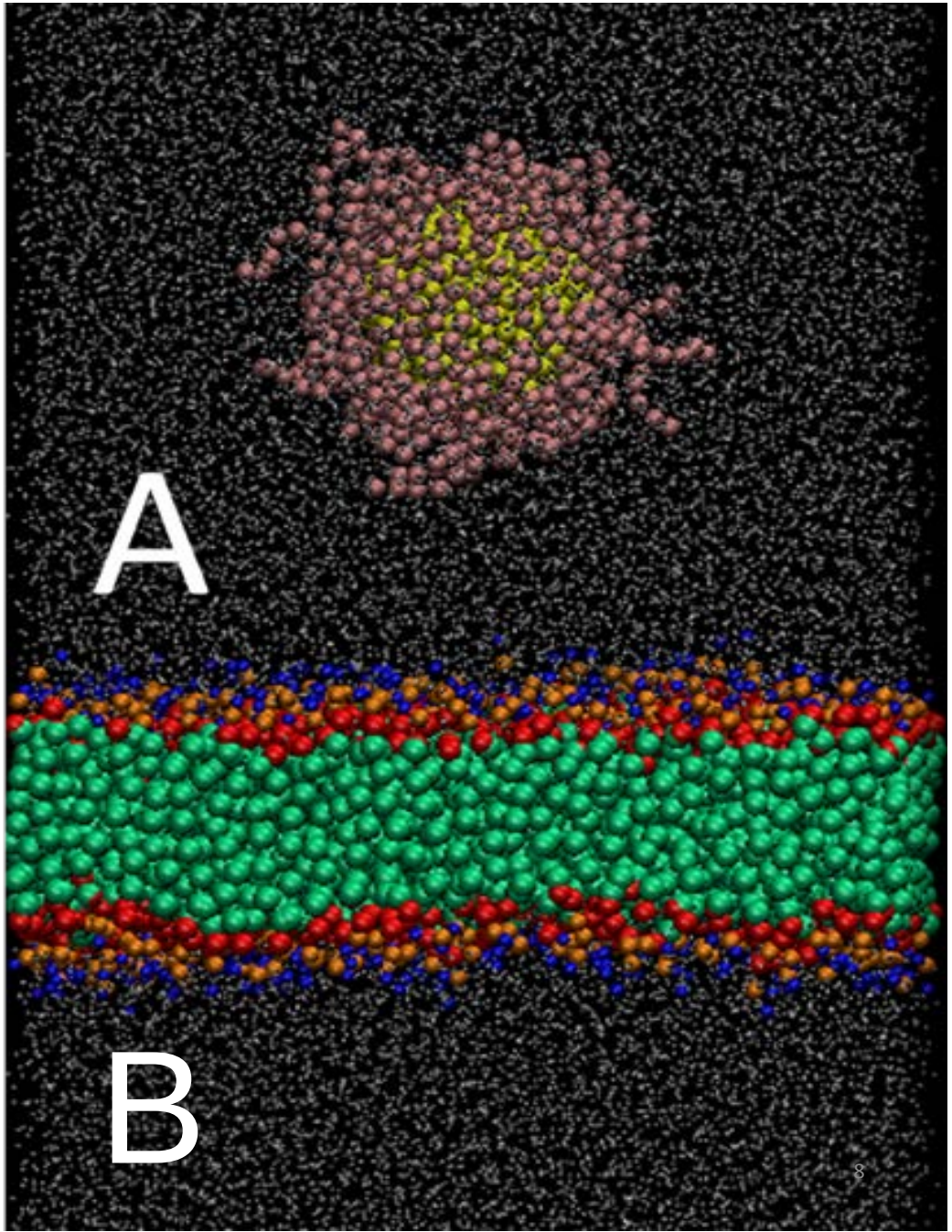
A distribution of conformations occurs at all coverages.
Coiled conformations (mushroom-type) dominate at low coverage while extended conformations (brush-type) appear at high coverage.

CONCLUSIONS about ligand configurations

Molecular – level behavior of PEG ligands on gold nanoparticles in water in our MD simulations reveal that contrary to limiting descriptions such as “brush” or “mushroom” for high and low coverage situations, there is always a distribution of ligand configurations ranging from laying flat, highly coiled, curled, to stretched.

A distribution of ligand configurations occurs at any coverage, only the proportions of configurations change.

Simulation box for PEGylated nanoparticle with DPPC membrane

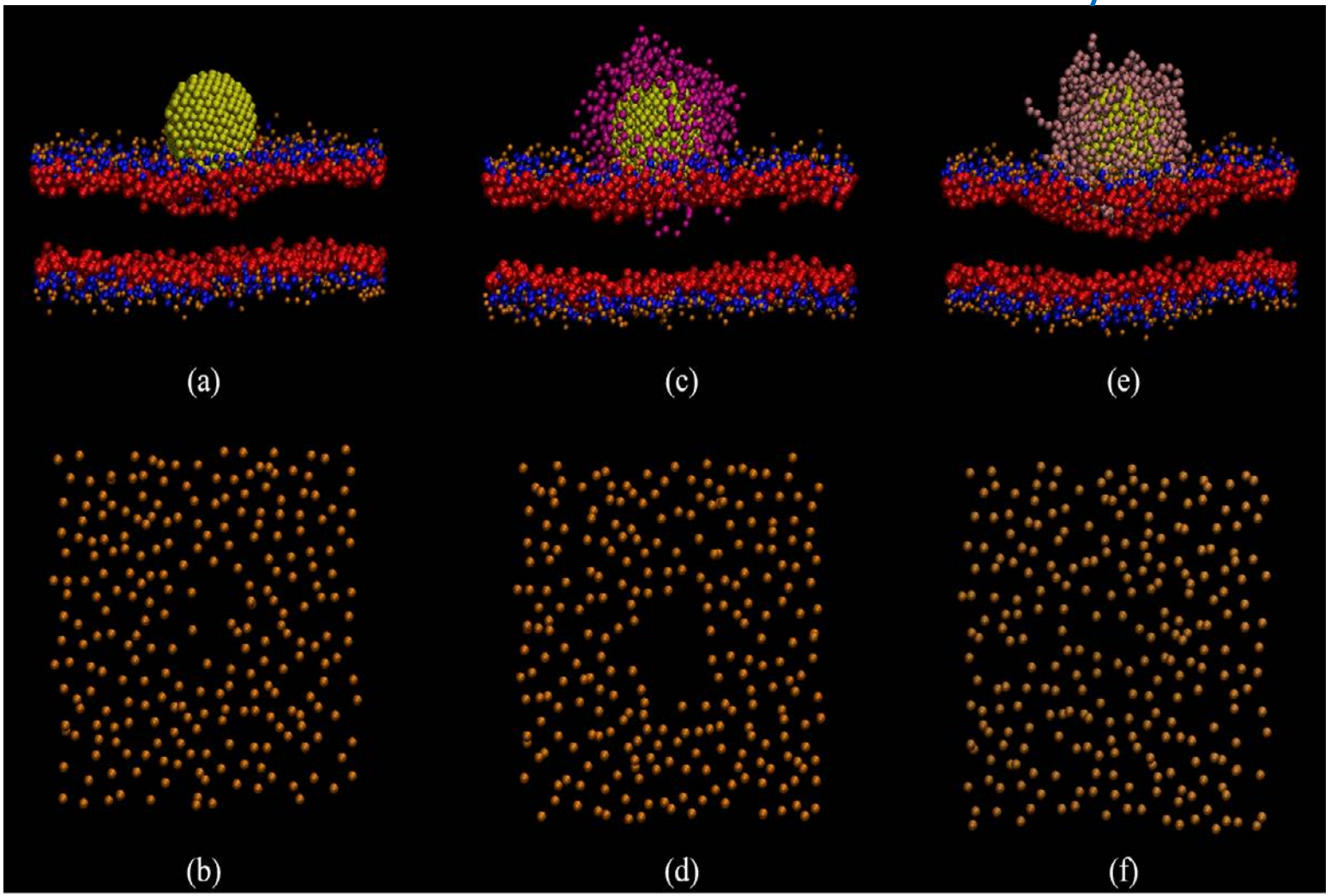


Comparison of membrane penetration characteristics of spherical-core nanoparticles:

- *bare Au*
- *alkane thiol Au*
- *PEGylated Au*

At the top leaflet of the membrane

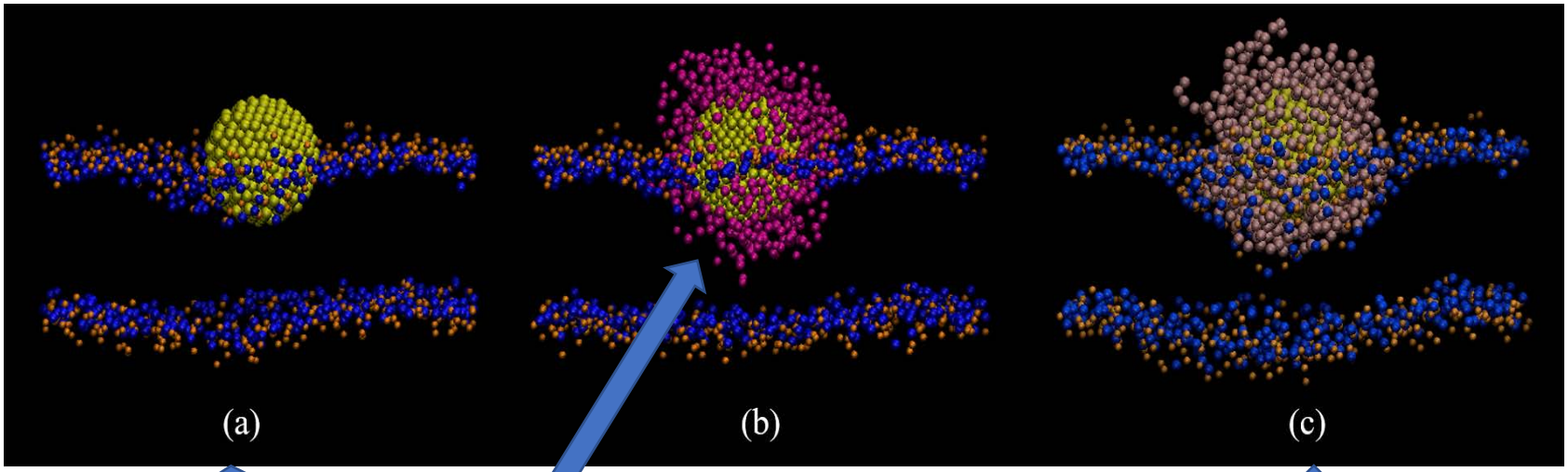
Bare Au Alkane thiol Au PEGylated Au



Top view of choline headgroups, compare **hole formation**

Penetration of the top leaflet of the membrane

Bare Au | Alkane thiol Au | PEGylated Au



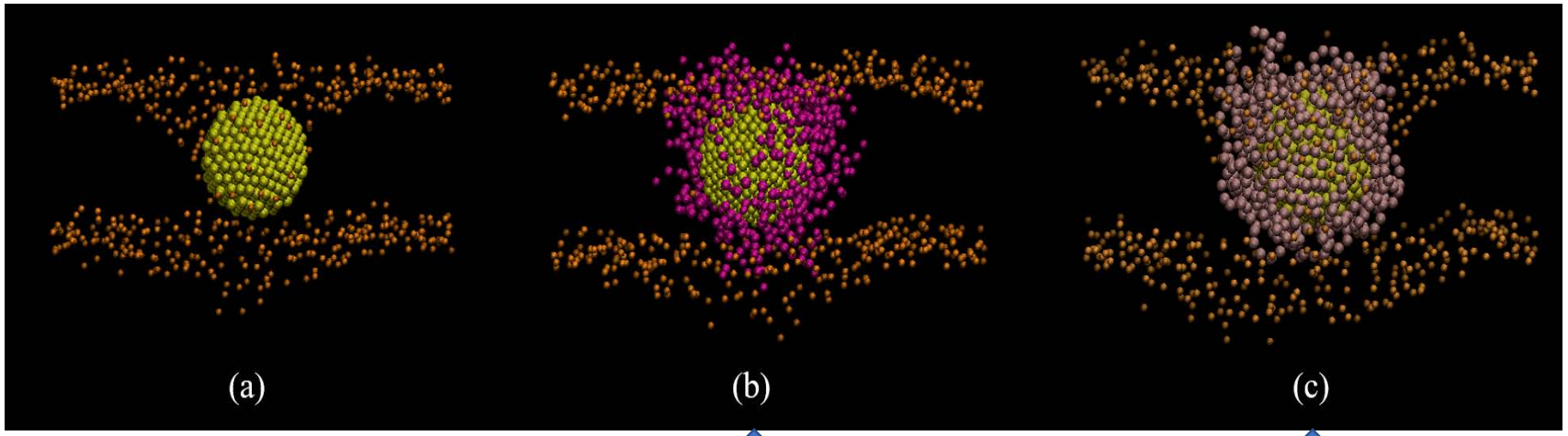
Bare nanocrystal is pushing apart the lipid head groups to permeate the membrane

Alkane ligands stretch and interact with lipid tails

Significant curvature of the membrane where phosphate & choline lipid head groups surround the PEGylated NP

In the middle of the membrane

Bare Au | Alkane thiol Au | PEGylated Au



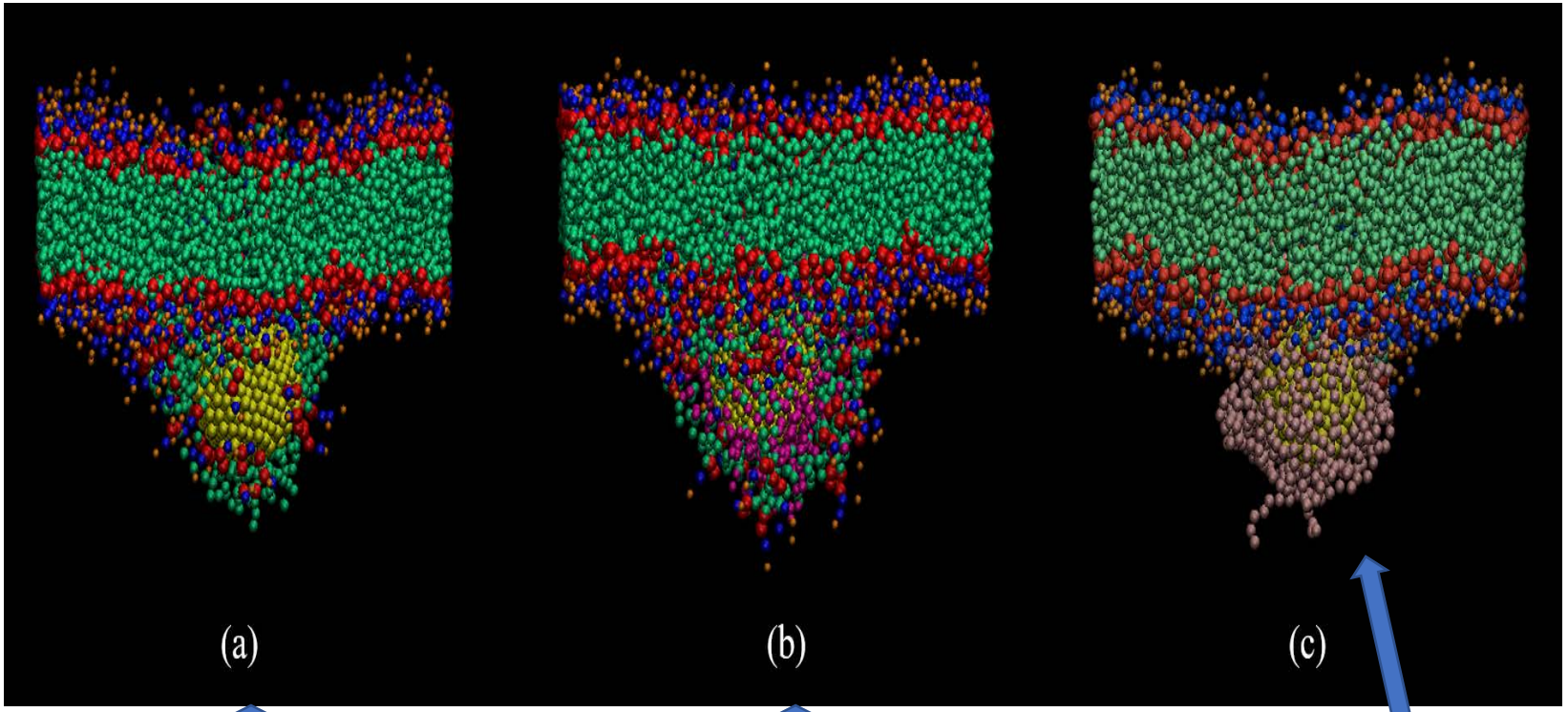
Lipids attracted to bare Au

Ligands of the alkanethiol-coated Au NP are stretched and interacting with surrounding lipid tails

PEG ligands are held more closely to the gold core

Exiting the membrane at the bottom leaflet

Bare Au | Alkane thiol Au | PEGylated Au

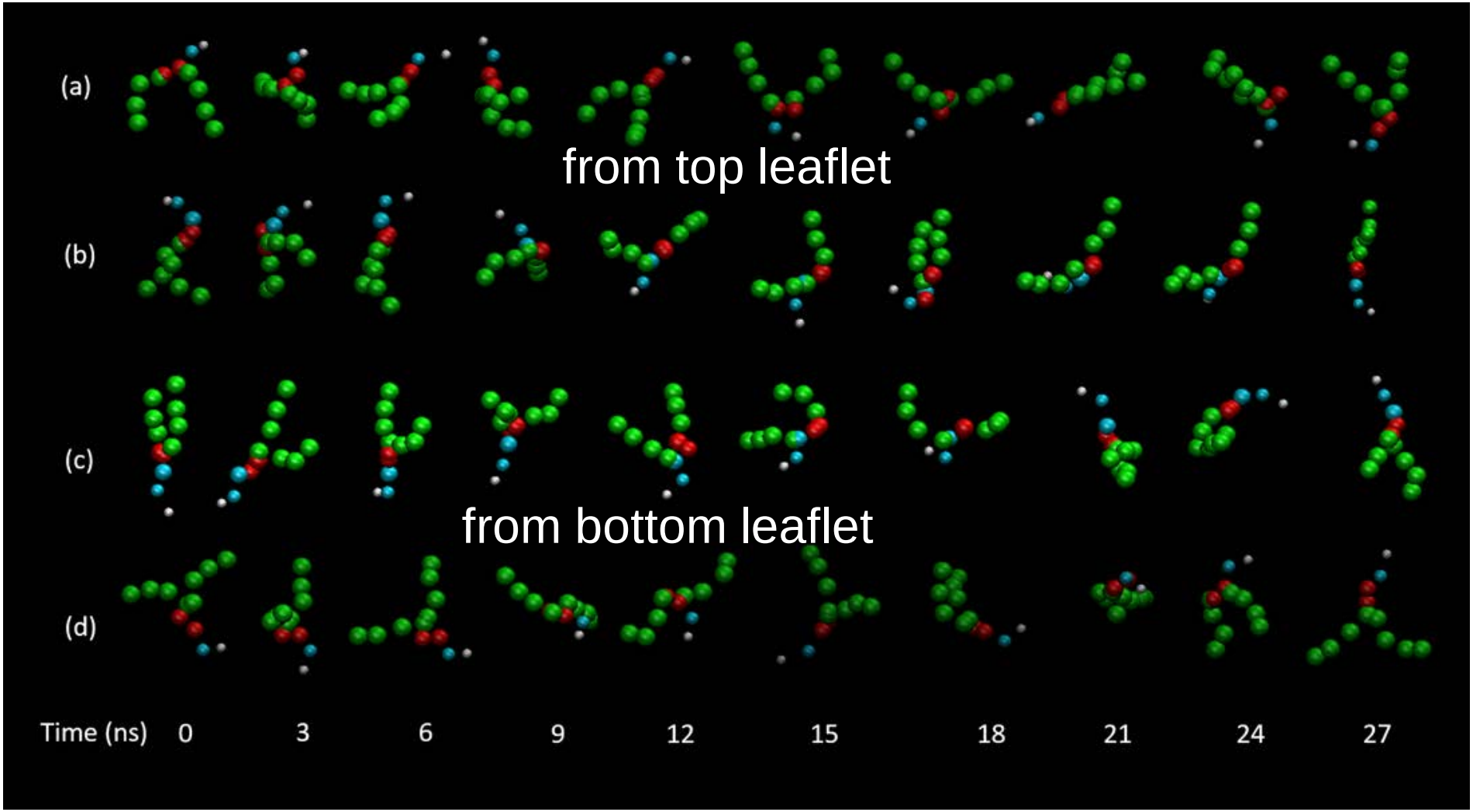


Lipid molecules surround the bare nanocrystal and alkanethiol-coated nanoparticle upon exit

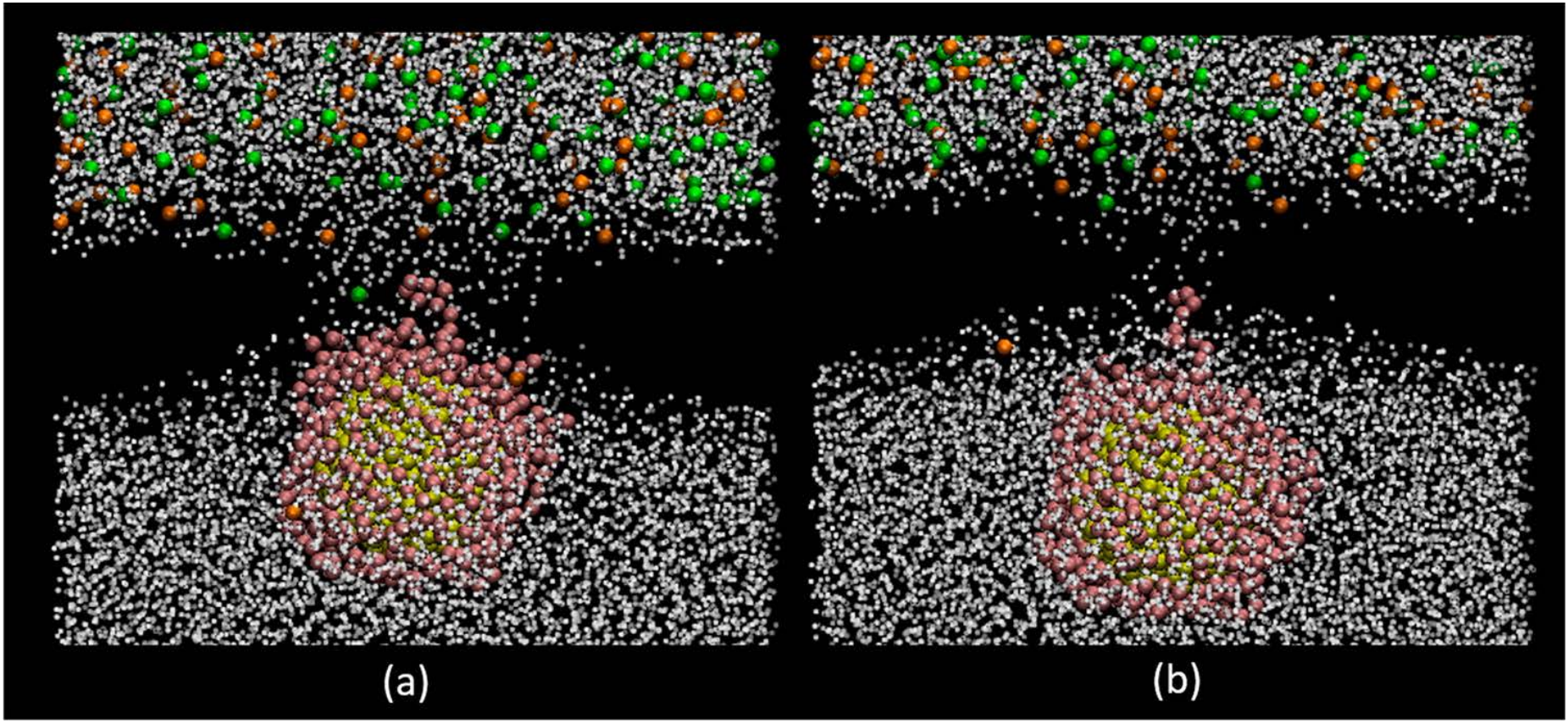
Alkanethiol-coated gold NP drags many lipid molecules into the bulk solution upon exit

PEGylated AuNP does not

Lipid flip-flop events induced by PEGylated nanoparticle with high coverage



Formation of water column by PEG12-AuNP as it leaves bottom leaflet of membrane



Membrane not shown for clarity, Na^+(orange) and Cl^-(green) ions in top compartment

Comparison PEGylated AuNP vs alkane thiol-coated AuNP (same Au core): water

Unlike the alkane-thiol-coated AuNP,
PEG AuNP leads to a short-lived water column.

As soon as the nanoparticle crosses the second membrane leaflet, the lipid membrane begins to recover and water molecules return to the bulk solution. This too drives ions to return to the interfacial and phospholipid head group region

Comparison PEGylated AuNP vs alkane thiol-coated AuNP: membrane recovery

Unlike the alkane-thiol-coated AuNP, PEG AuNP leads to hardly any lipid displacement from the membrane; the overall disturbance to the membrane is minimal since the lipid molecules are not dragged by the PEGAuNP and the membrane is allowed to recover immediately after permeation.

Induced water penetration is minimal for PEG AuNP

Ion transport does not occur; recovery of the membrane as the NP passes the second leaflet drives ions to return to the interfacial region.

INFERENCES about cytotoxicity

Molecular – level behavior of PEGylated Au nanoparticles in our MD simulations reveal the basis for their very low cytotoxicity. Their permeation of a bilayer membrane leads to short-lived water columns, no ion penetration and no displacement of lipids from the membrane. Membrane recovery begins even as the particle is leaving the second leaflet, unlike the case of AuNPs coated with hydrophobic ligands such as alkane thiols.

Gold nanorods

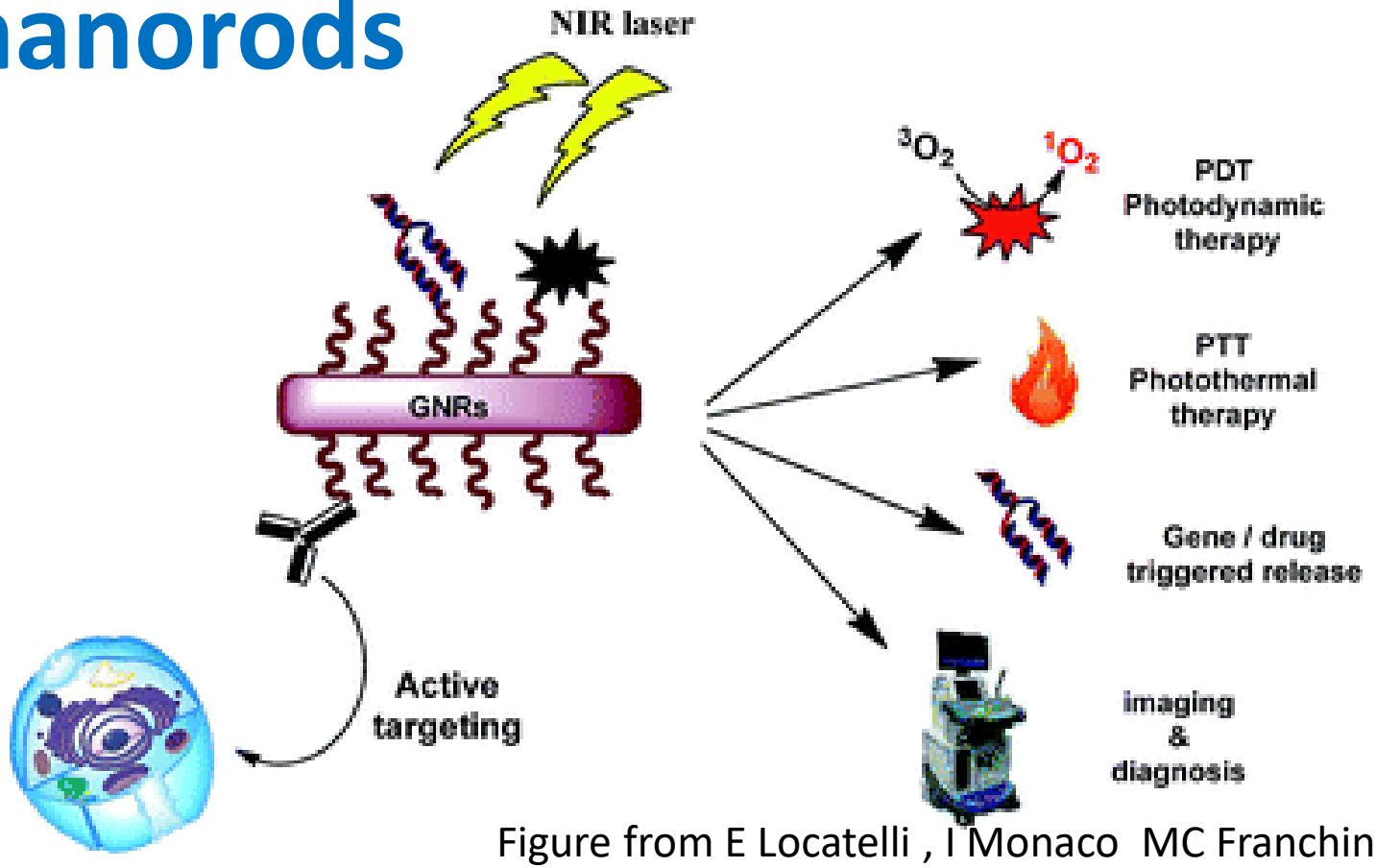
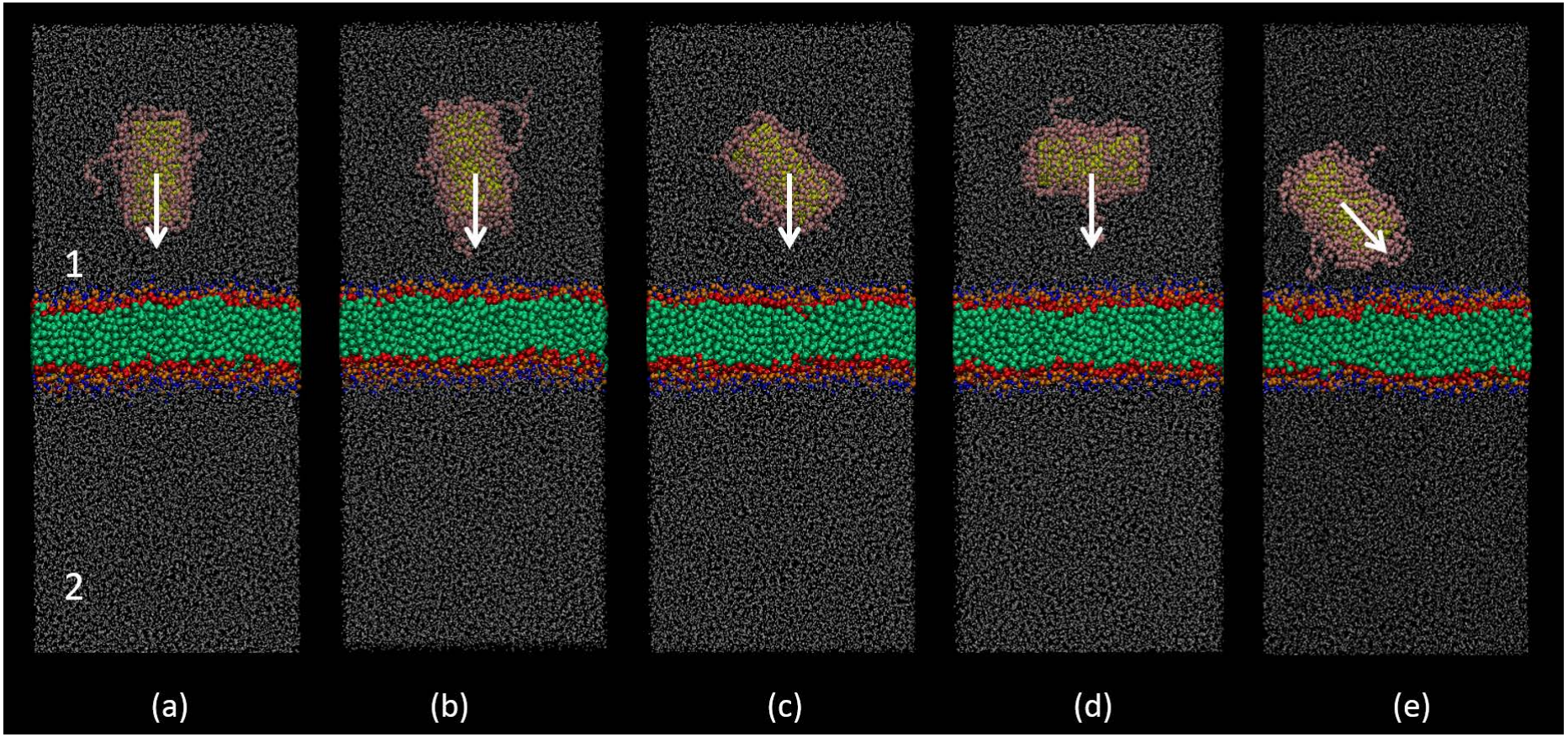


Figure from E Locatelli , I Monaco MC Franchini, RSC Adv., 2015, 5, 21681-21699

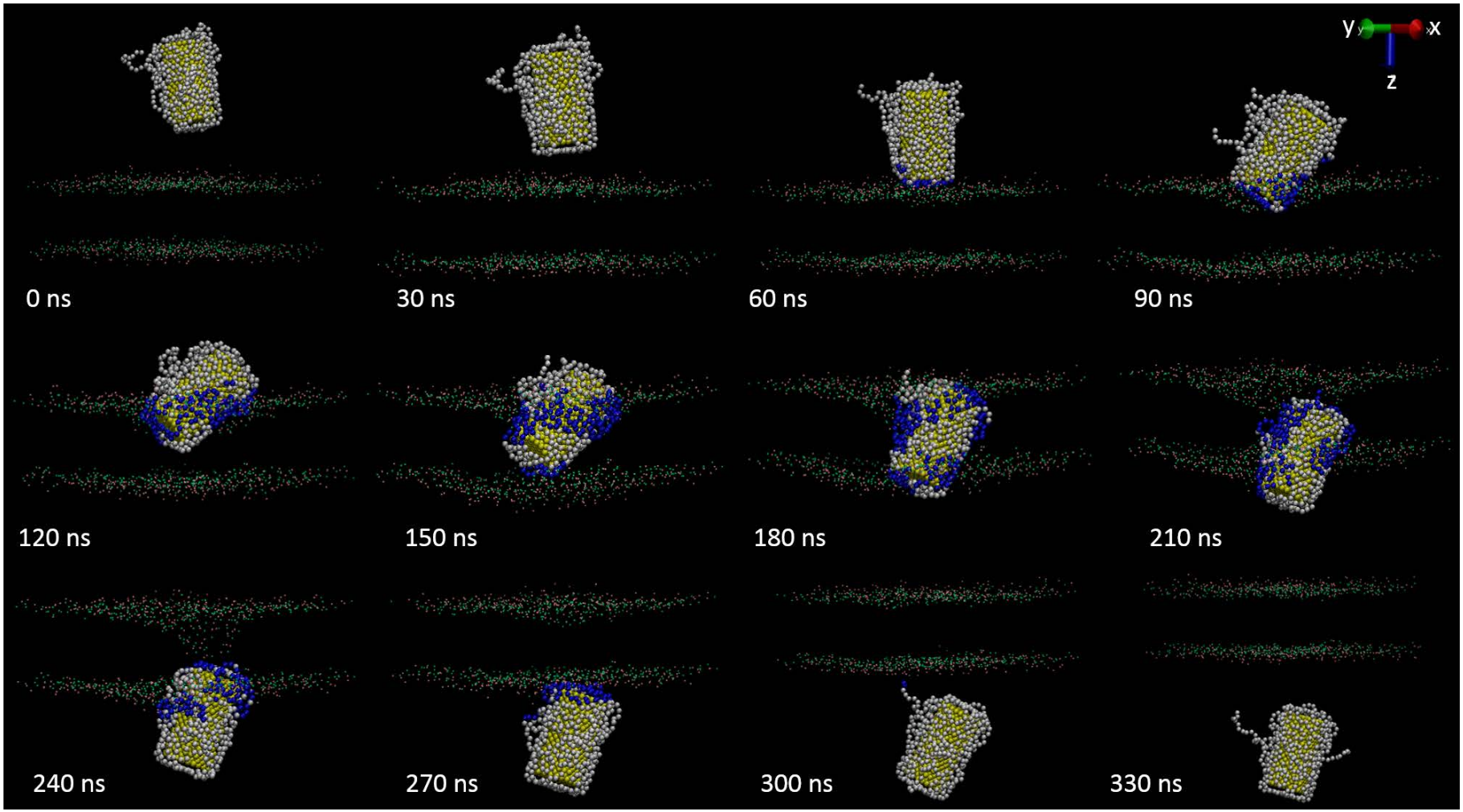
Look into mechanism of permeation

Permeation of PEG18-nanorod in the lipid bilayer membrane (at various initial angles)



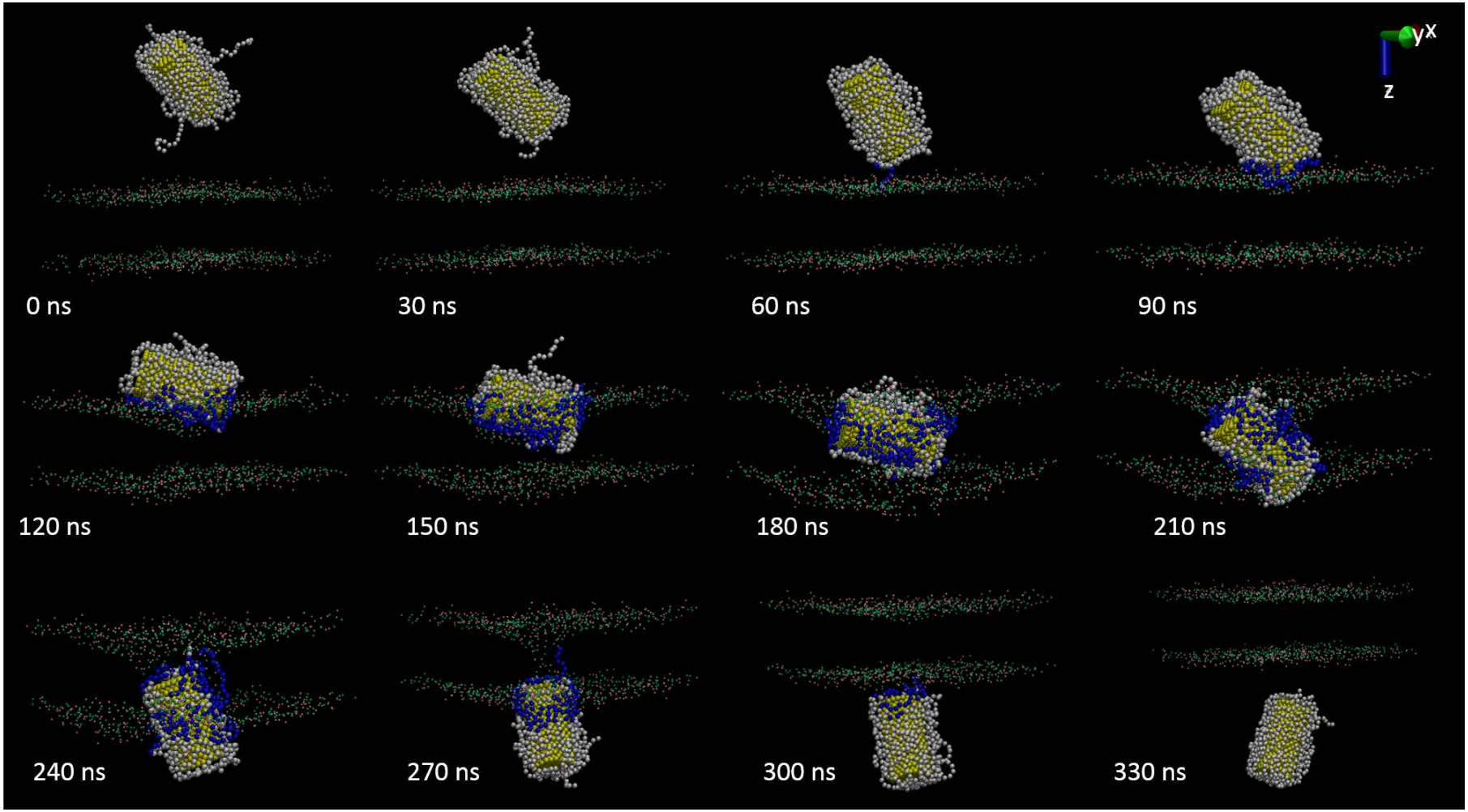
Arrow indicates direction of minimal pulling velocity

Permeation of PEG18-nanorod in the lipid bilayer membrane (initial angle 10°)



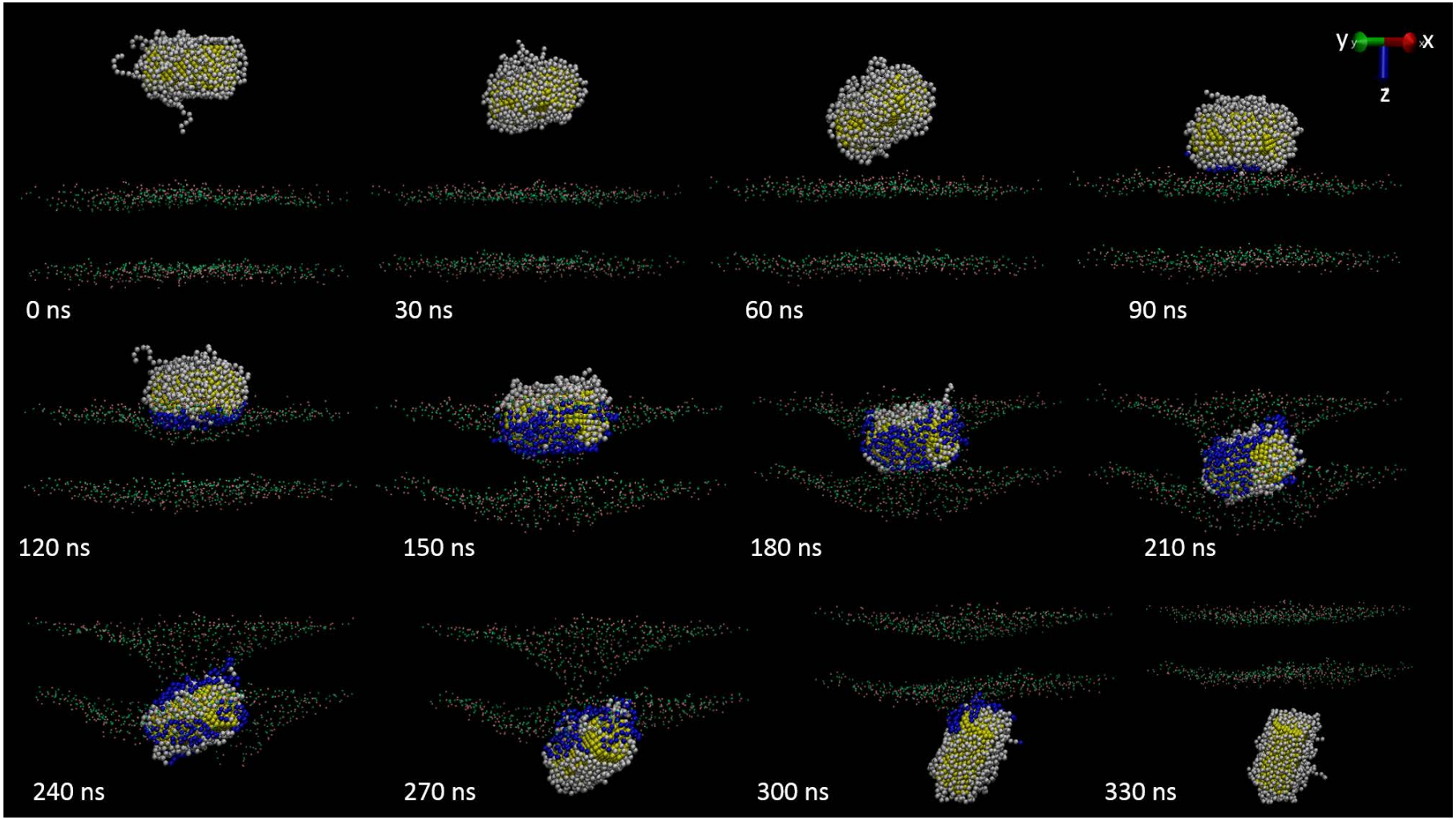
highlighted in blue: interactions sites on the nanorod within 1 nm of the choline and/or phosphate groups

Permeation of PEG18-nanorod in the lipid bilayer membrane (initial angle 45°)

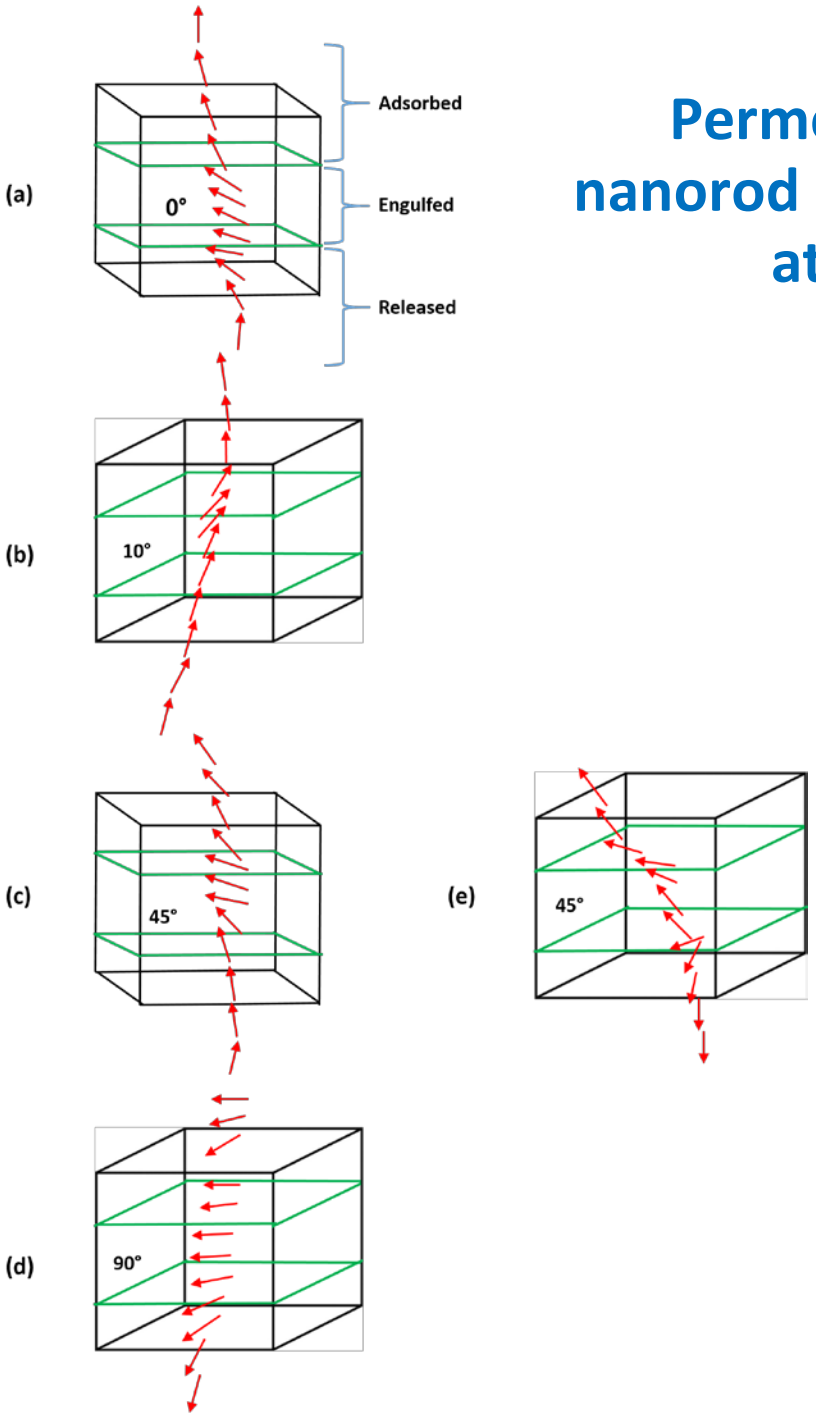


highlighted in blue: interactions sites on the nanorod within 1 nm of the choline and/or phosphate groups

Permeation of PEG18-nanorod in the lipid bilayer membrane (initially parallel)



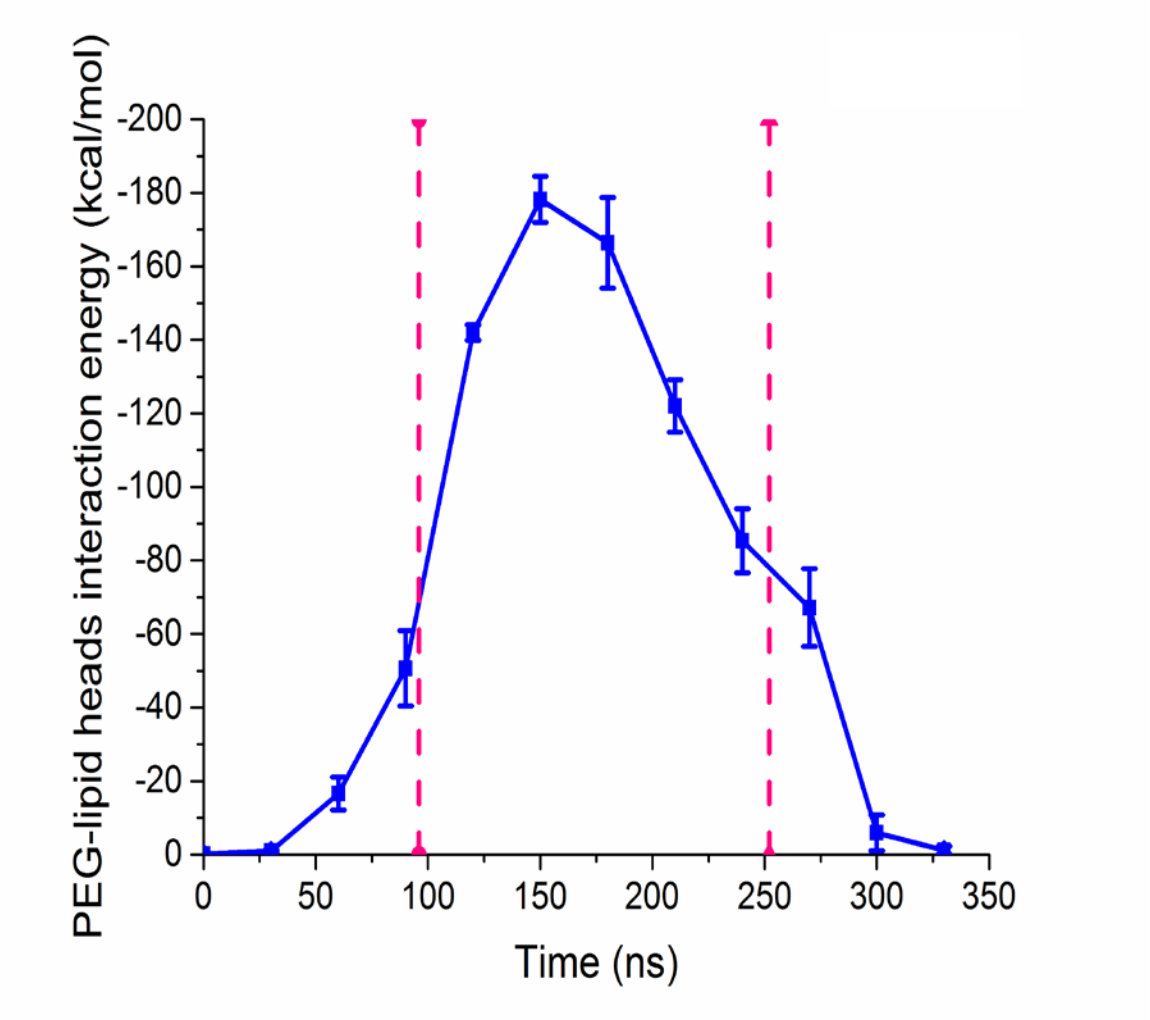
highlighted in blue: interactions sites on the nanorod within 1 nm of the choline and/or phosphate groups



Permeation pathway of PEG18-nanorod in the lipid bilayer membrane at various initial angles.

In every case: nanorod begins to tilt toward the membrane surface even before permeating the first bilayer leaflet, rotates as it lies down, and straightens out before exiting the second leaflet

Interaction energy between all PEG beads and phosphate and choline lipid head groups along the course of nanorod permeation for initial angle 10°



Similarly for all other entry angles

CONCLUSIONS about mechanism of permeation of PEGylated AuNR: undergoes a rotational motion, passing through a lying down orientation, straightening up on exit

- Tilting occurs immediately when the leading PEG ligands begin to interact with the lipid head groups in the first membrane leaflet. The tilting behavior of the nanorod occurs to maximize favorable hydrophilic interactions between lipid head groups and PEG ligands, thus overcoming the energetic barrier to permeation.
- These favorable interactions drive the nanorod to lie in a Particular way (lying down) that maximizes this interaction.
- PEG ligands in the torso retract away from lipid tails & present a slimmer projectile passing through the lipid tail regions. Keeping the trailing end in touch with the lower leaflet head groups as it exits permits the final bit of favorable interactions, and so of course exit has to be in a straightened up orientation to facilitate all these.

REFERENCES

- Simulated Permeation and Characterization of PEGylated Gold Nanoparticles in a Lipid Bilayer System, P A Oroskar, C J Jameson, and S Murad, **Langmuir** 32, 7541−7555 (2016).
- Rotational behavior of PEGylated gold nanorods in a lipid bilayer system," P A Oroskar, C J Jameson, and S Murad, ***Mol. Phys.*** xx, xxx-xxx (2016).
- Molecular dynamics simulations reveal how characteristics of surface and permeant affect permeation events at the surface of soft matter," P A Oroskar, C J Jameson, and S Murad, ***Molec. Simul.*** xx, xxx-xxx (2016)

Acknowledgments:

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