The interaction between nanoparticles and membranes: from cytotoxicity to drug delivery

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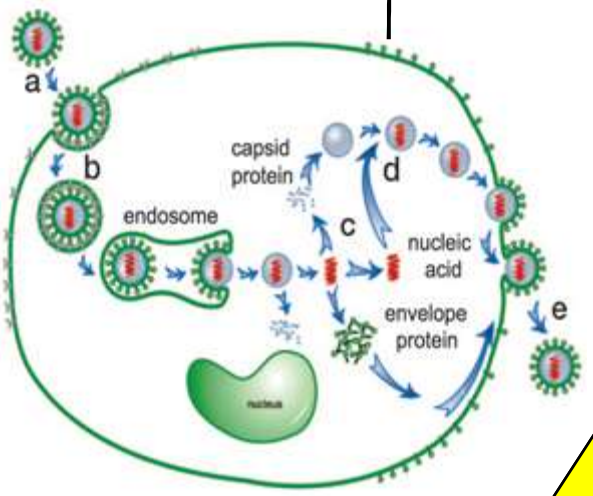
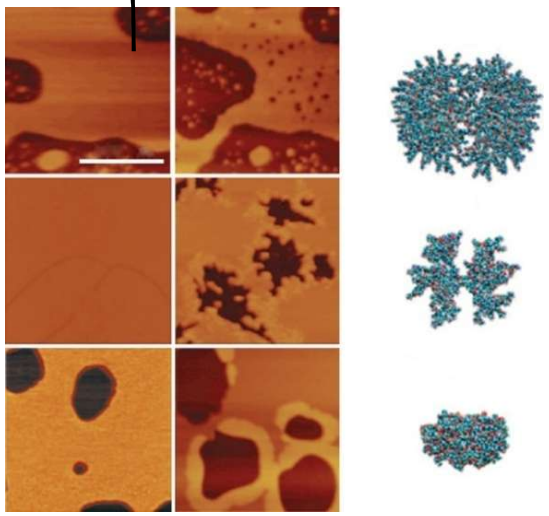
Nanomaterials could induce adverse biological effects, with the potential to create cytotoxicity.

Nanotechnology Present a Janus Face!



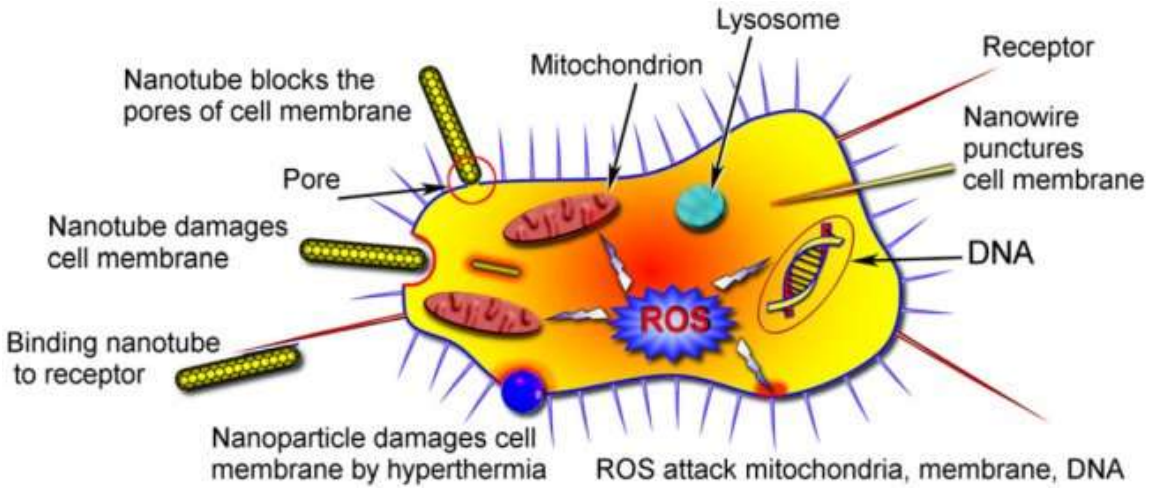


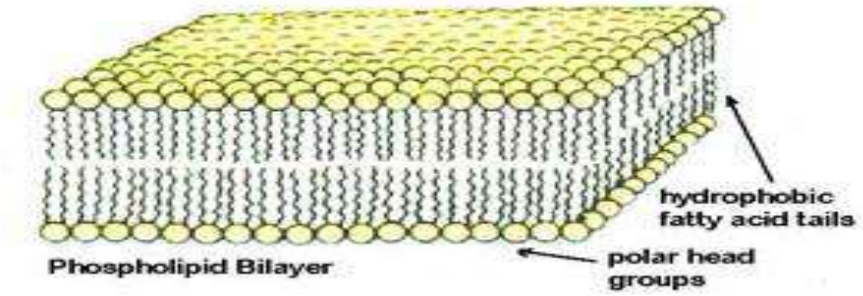
Balance between the role as carriers for drug delivery and their cytotoxicity?

Huajian Gao et al, PNAS (2005)

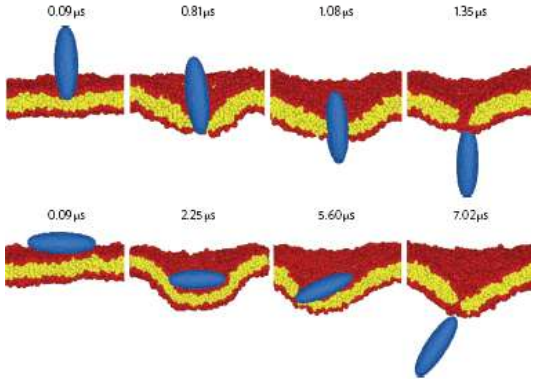
McNerny et al. *Nanomed. and Nanobio.* (2010)

Cytotoxicity





Membrane model



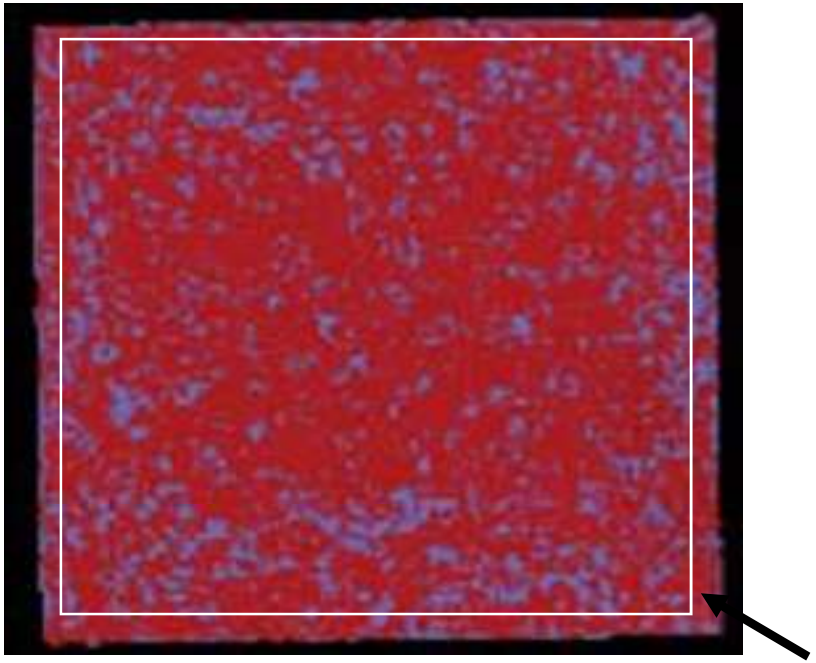
Yang et al. Nat. Nano.(2010)

Key question: the interaction between nanoparticles (NPs) and membranes

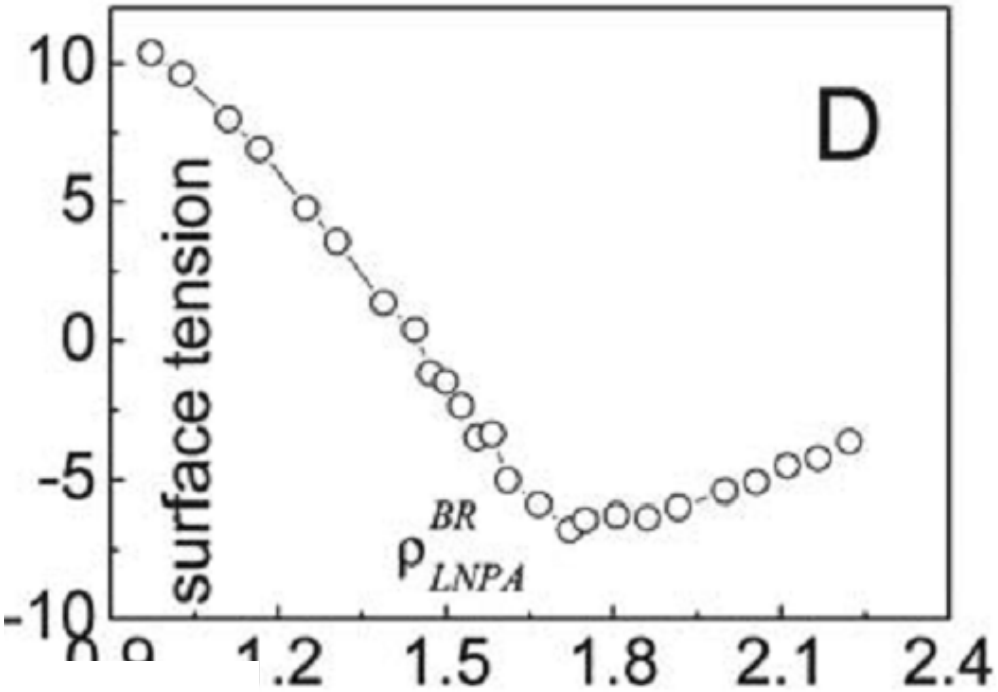
----With Dissipative particle dynamics

N-varied DPD: Standard DPD + lipid addition/deletion moves.

A variant of DPD version especially for controlling membrane tension



boundary region

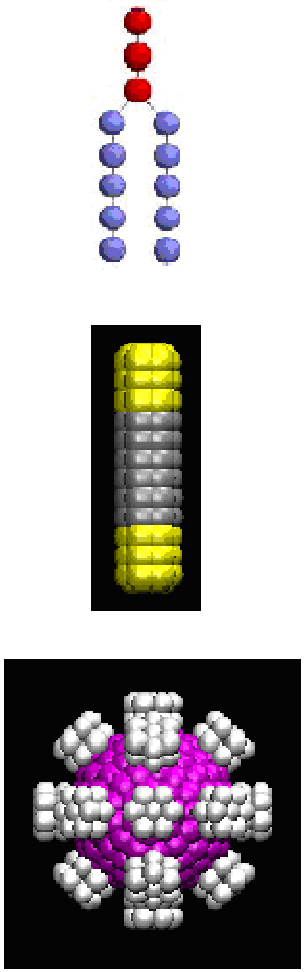


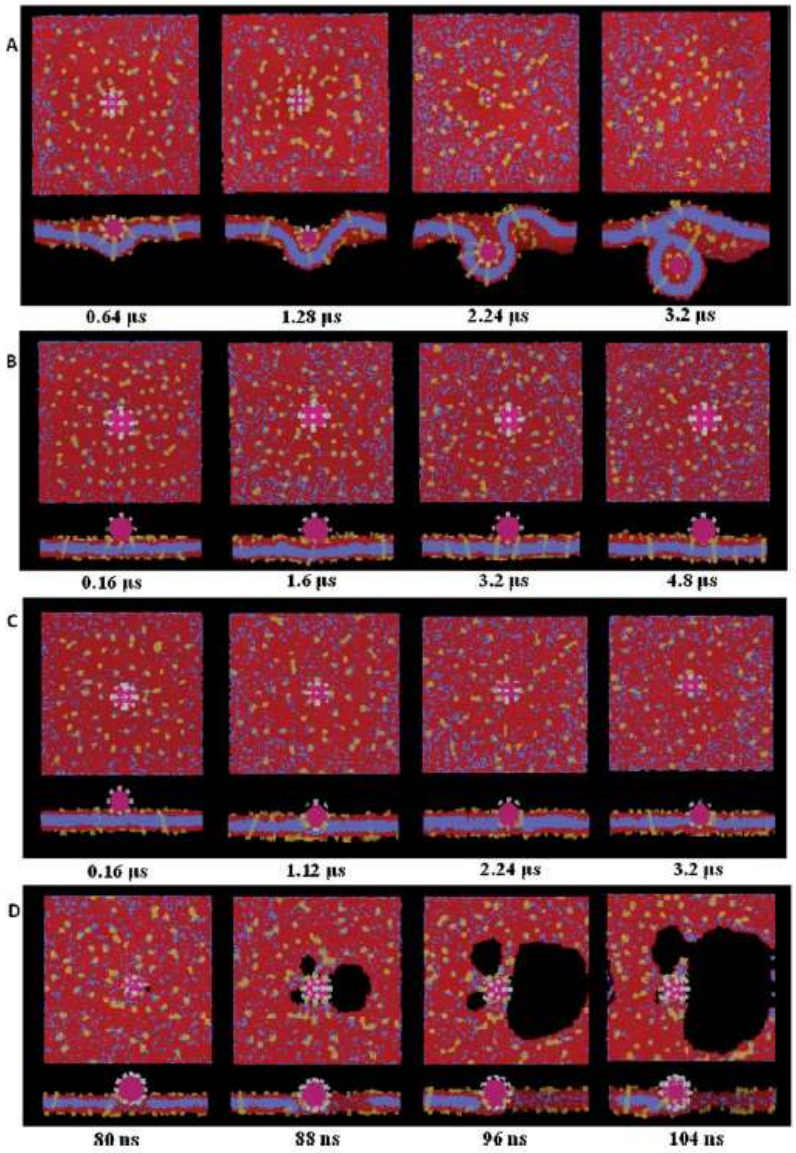
By addition/deletion moves of lipids in the boundary region per 200-1000 DPD time steps, the number of lipids in the boundary region is kept at the target value.

In the N-varied DPD method, the boundary region plays a role as a reservoir of lipids.

Receptor-mediated Membrane Responses to Ligand-coated Nanoparticles （NPs）

--- Four different membrane responses





Receptor-induced endocytosis

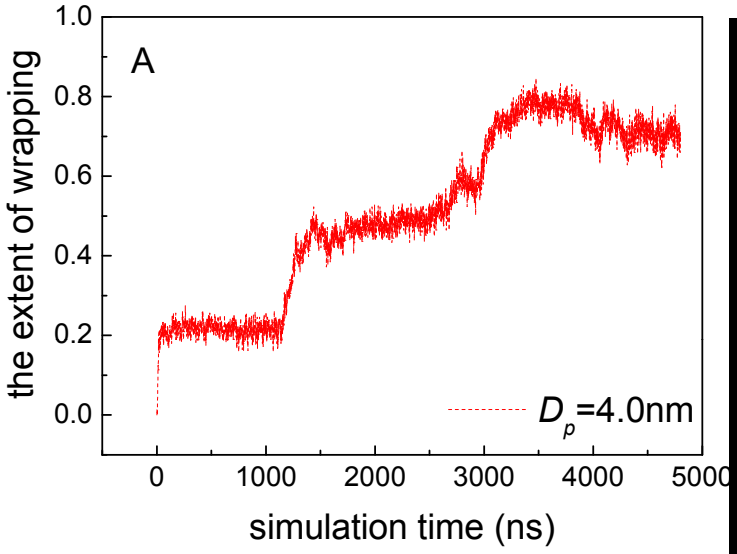
NP adhesion

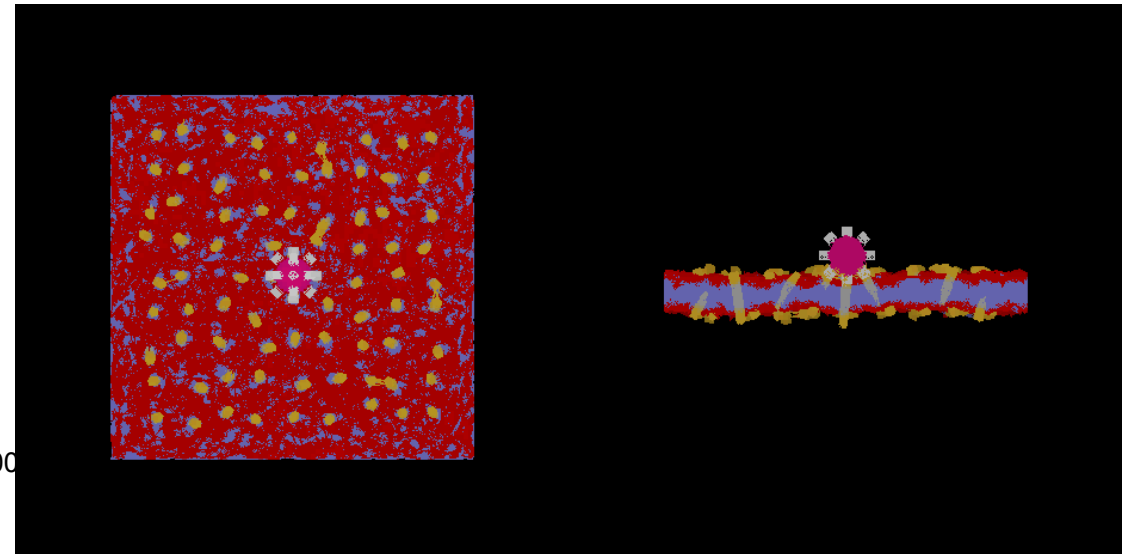
NP penetration

Membrane rupture

Yue and Zhang, **Soft Matter**, 2011, 7, 9104

Receptor-induced endocytosis (movie)



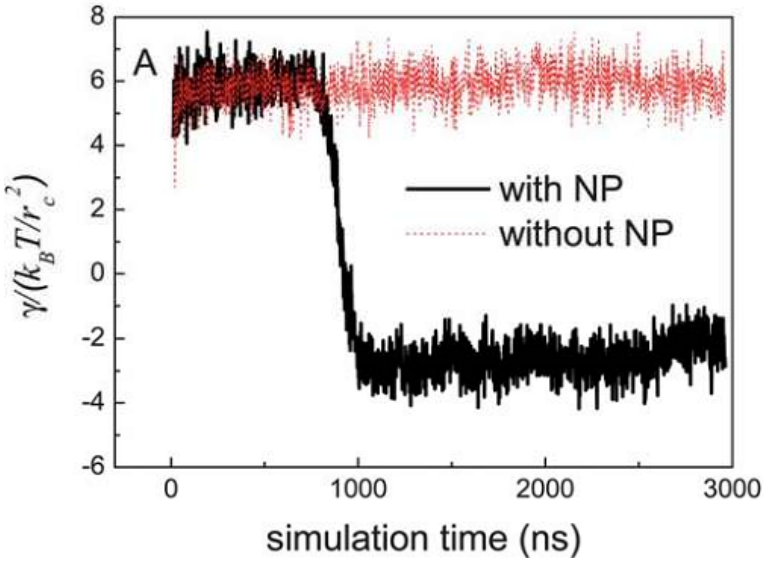


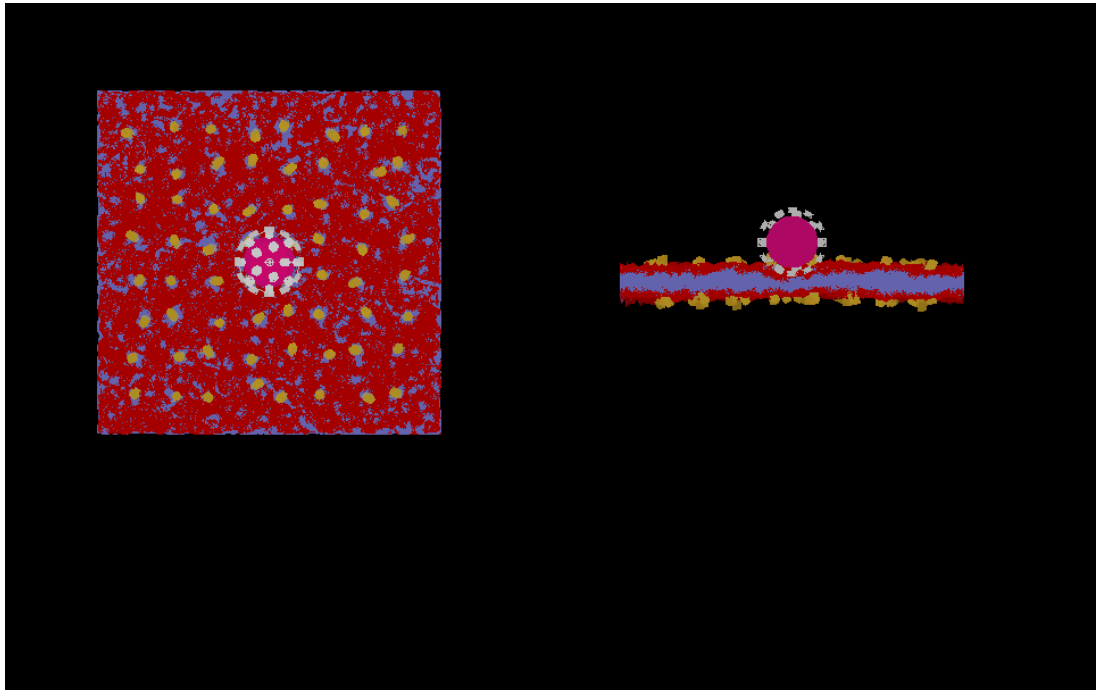
The process is controlled by the competition between the membrane bending energy and the receptor-ligand binding energy.

Yue and Zhang, **Soft Matter**, 2011, 7, 9104

NP adsorption induced membrane rupture

movie

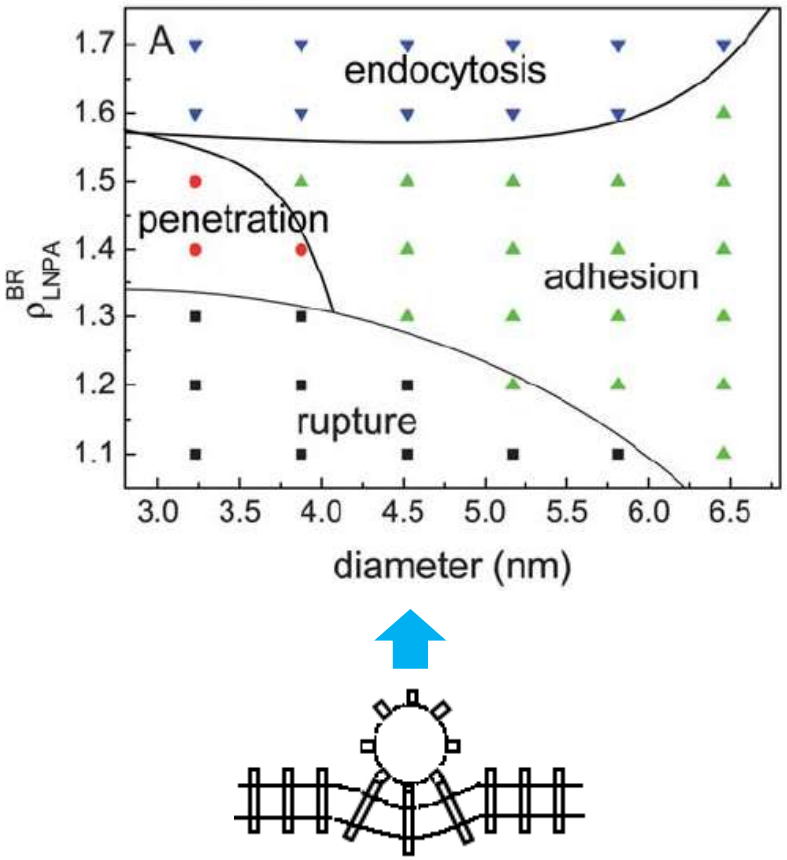


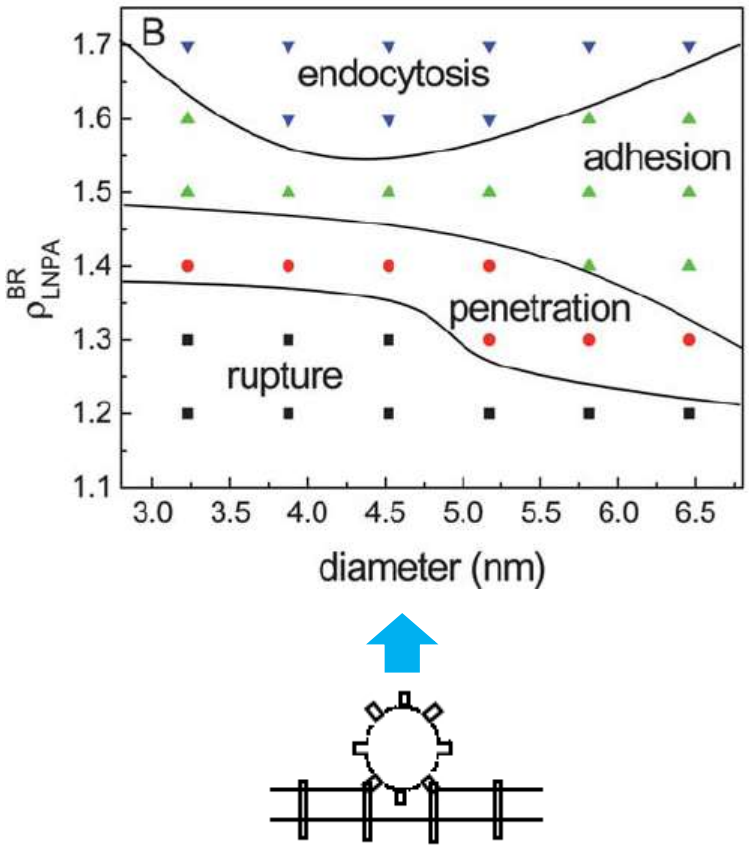


The process often takes place at large membrane.

Yue and Zhang, **Soft Matter**, 2011, 7, 9104

Phase diagram



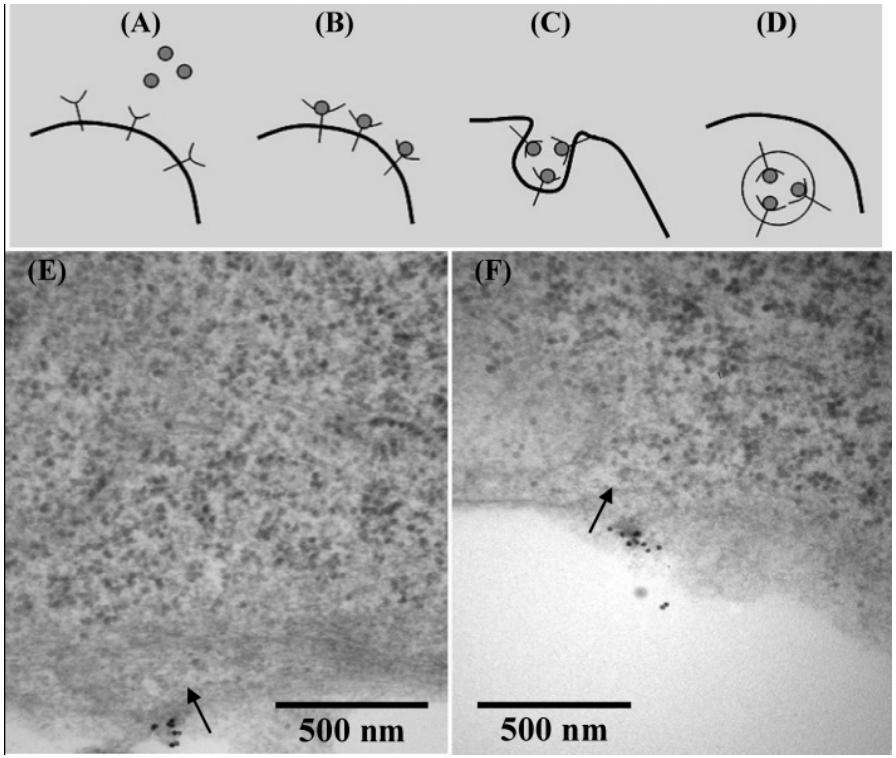


Factors affecting the membrane responses: Membrane tension, NP size and receptor-ligand binding mode.

Yue and Zhang, **Soft Matter**, 2011, 7, 9104

Cooperative Effect：

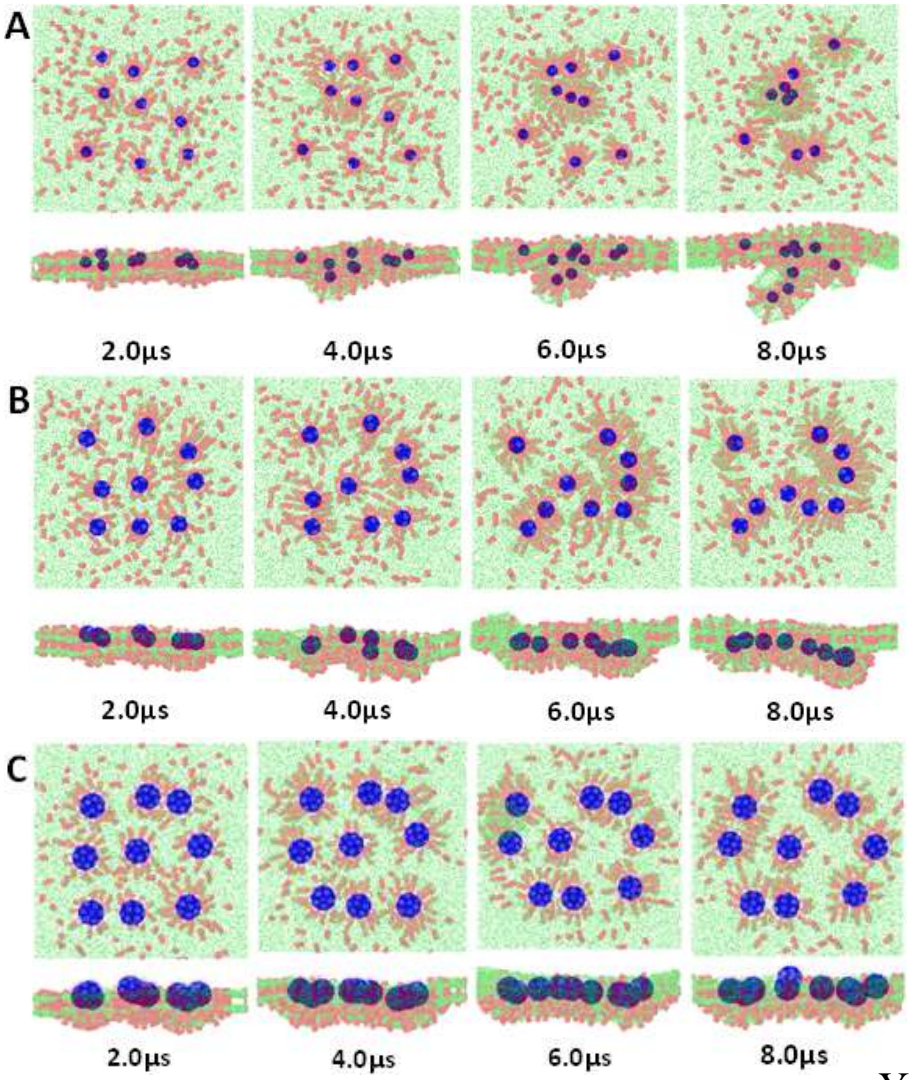
Receptor-Mediated Endocytosis of Multiple NPs



Endocytosis of multiple NPs in a cooperative manner?

Chithrani et al, Nano Lett. (2007)

Endocytosis of Multiple NPs



D_{NP}=2.5 nm, a closed packed aggregate

D_{NP}=4.0 nm, a linear pearl chain-like aggregate

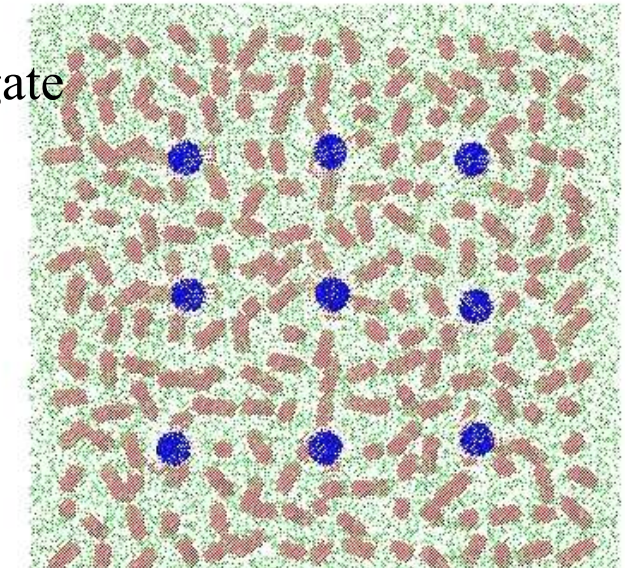
D_{NP}=6.0 nm, independent endocytosis

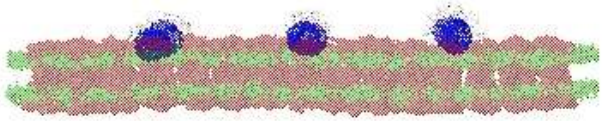
Yue and Zhang, **ACS Nano**, 2012, 6, 3196

Movie

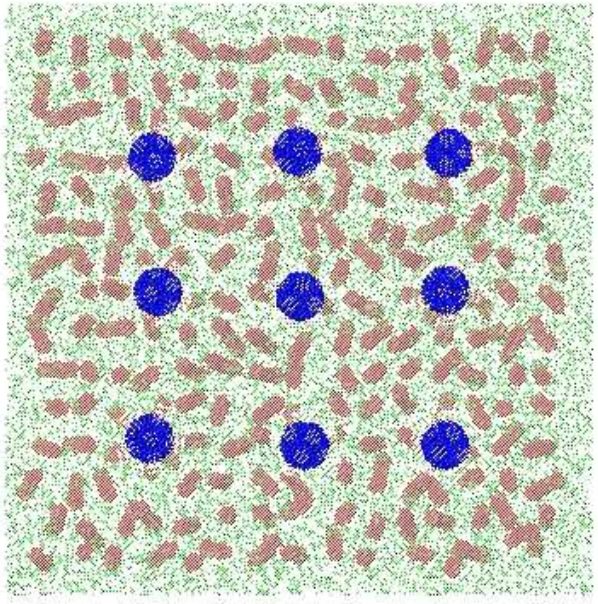
closed packed aggregate

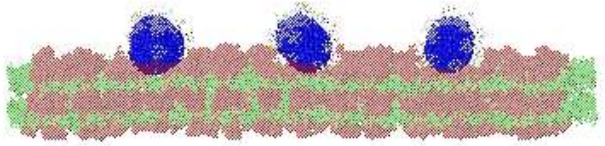
for small NP





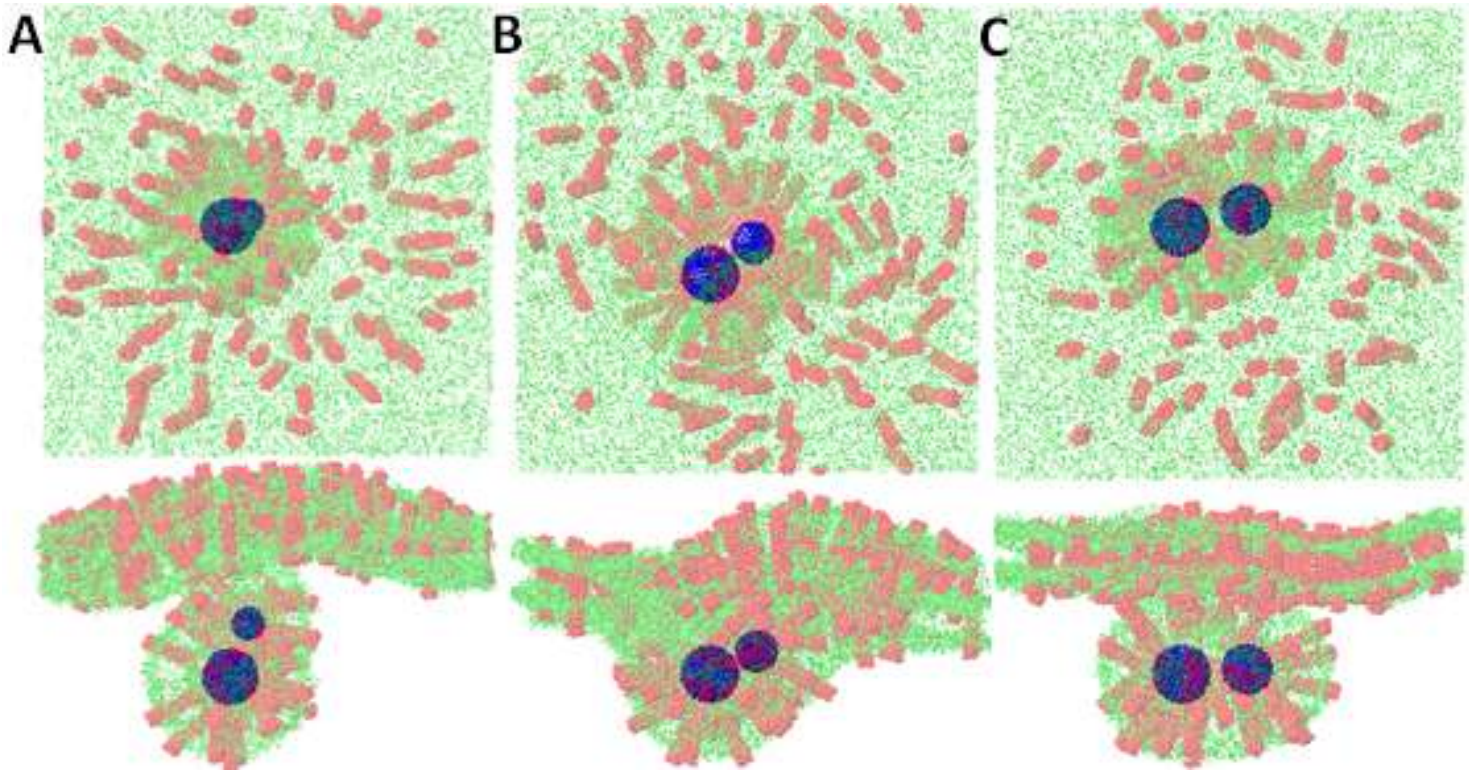
linear chain-like aggregate for NP of a size comparative to membrane thickness





Yue and Zhang, **ACS Nano**, 2012, 6, 3196

Internalization of Two NPs with Different Sizes:

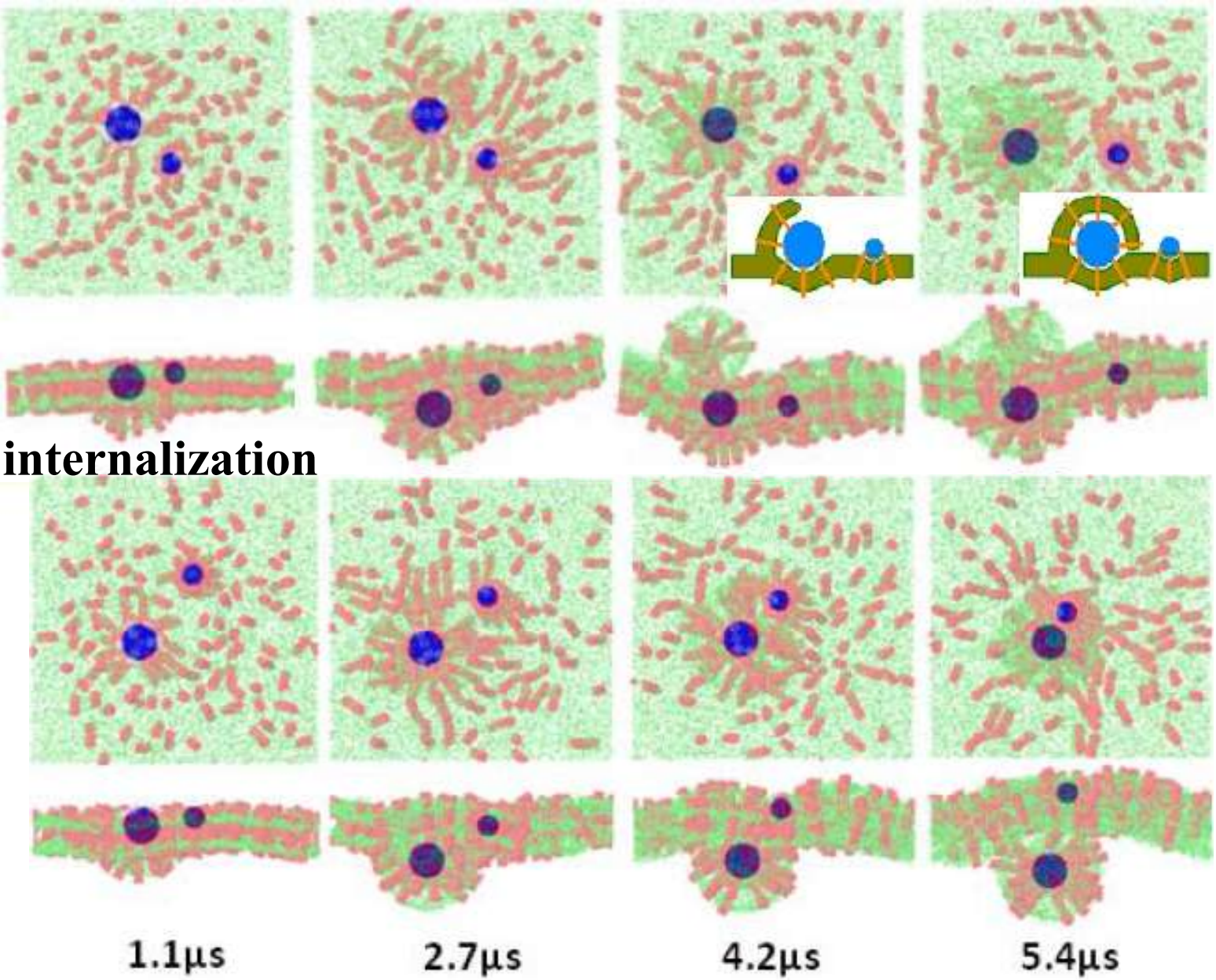


One NP's diameter is fixed to be 4.5nm, while the diameter of the other NP is (A) 2.5nm, (B) 3.3nm, (C) 4.0nm.

Yue and Zhang, **ACS Nano**, 2012, 6, 3196

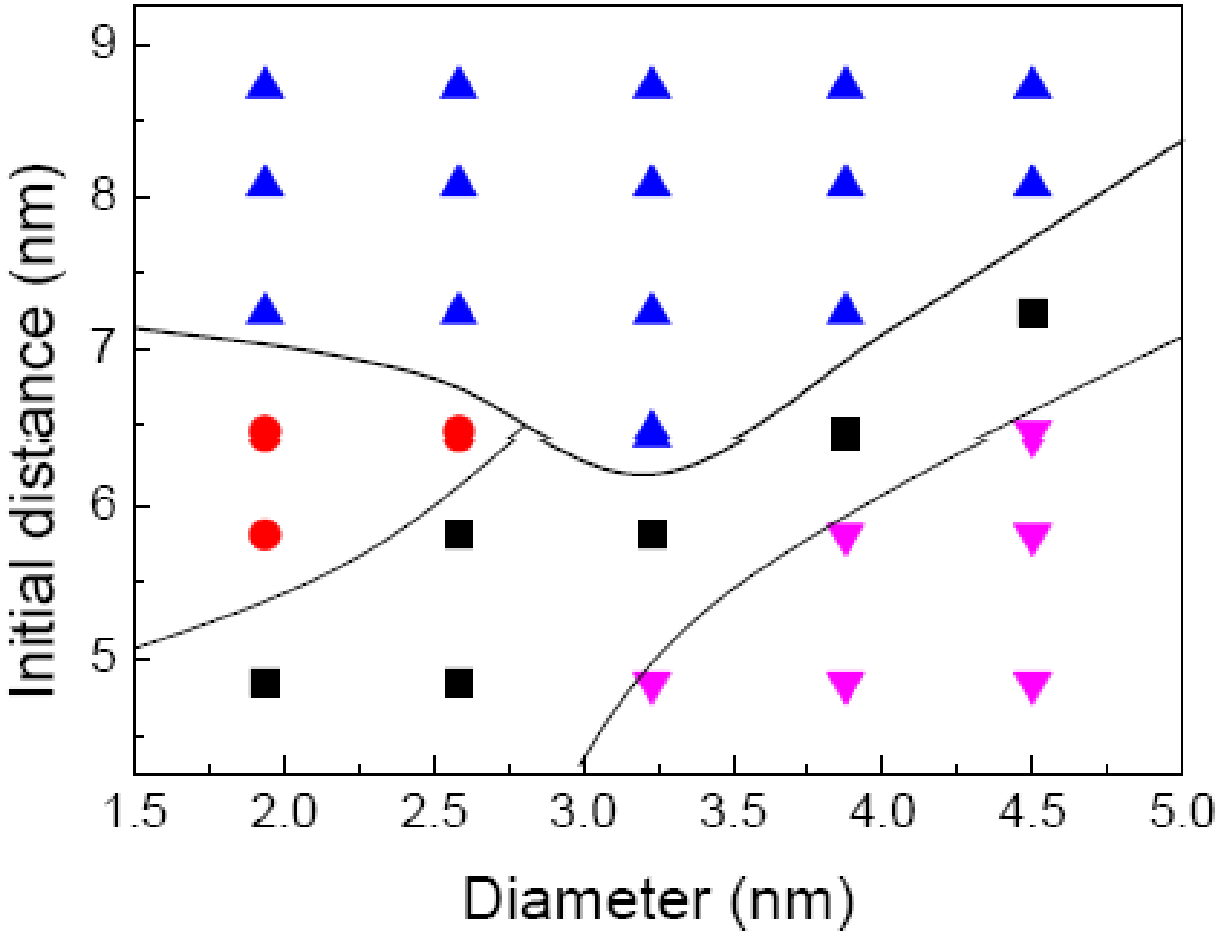
Pinocytosis-like internalization

Independent internalization



Yue and Zhang, **ACS Nano**, 2012, 6, 3196

Phase diagram

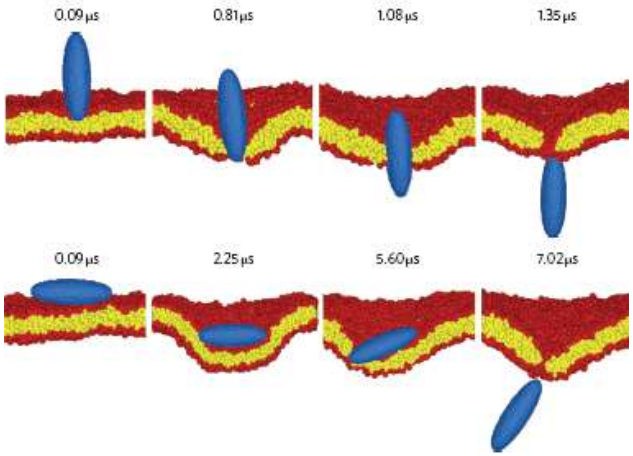


▲ independent internalization; ● pinocytosis-like internalization;

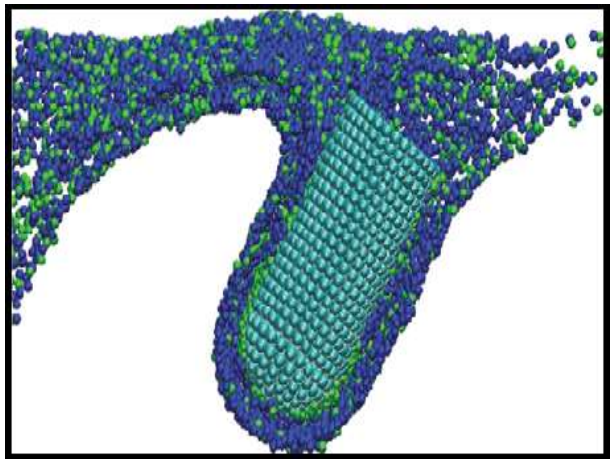
■ asynchronous internalization; ▼ synchronous internalization.

NP shape:

Relationship between NP shape anisotropy and endocytosis kinetics



K. Yang and Y. Ma, Nature Nanotech. (2010)

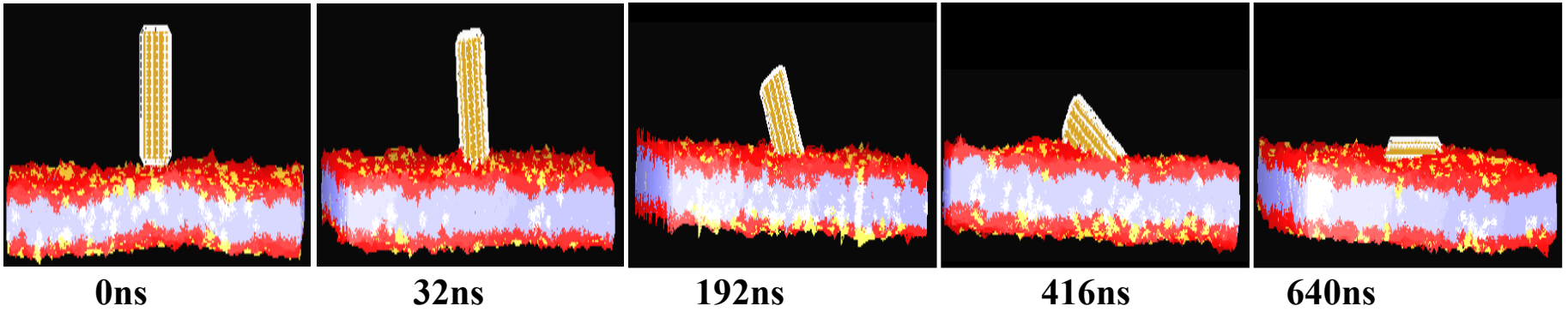


Xinghua Shi et al, Nature Nanotech.(2011)

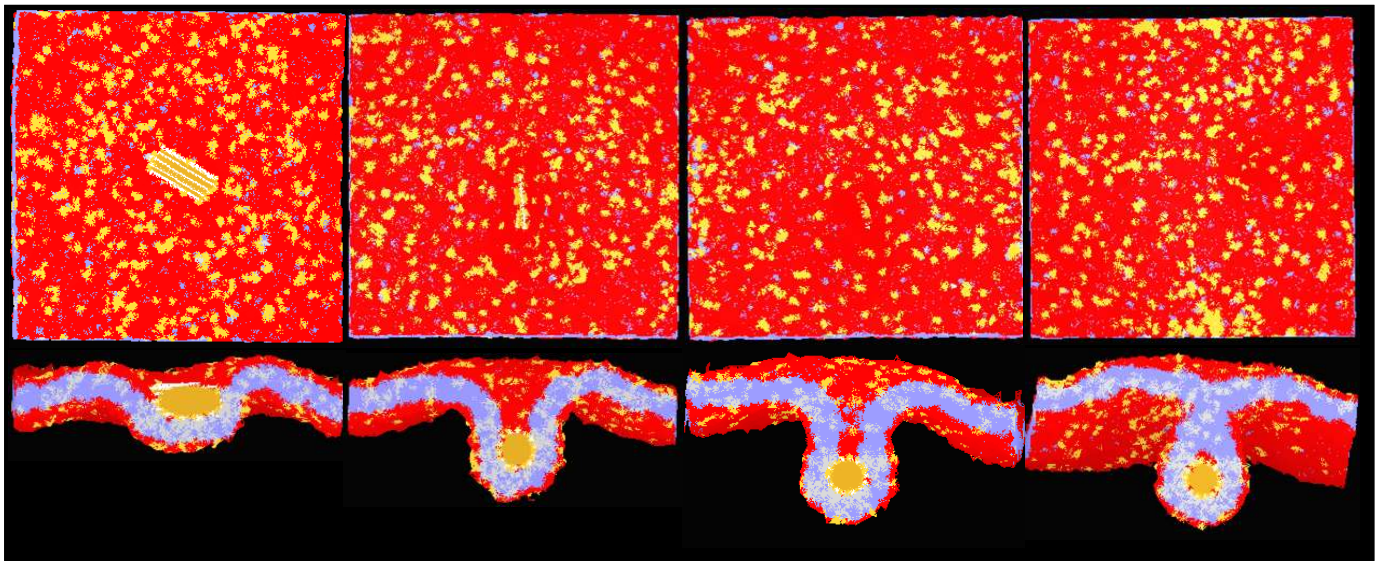
NP Rotation is one of the most important mechanisms:

rod-like NPs

Two stages: membrane invagination & nanoparticle wrapping



0ns 32ns 192ns 416ns 640ns



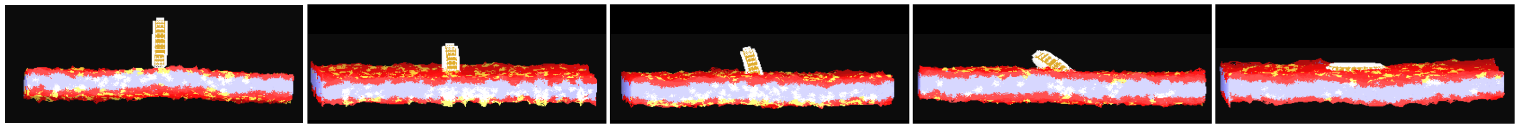
1440ns 2880ns 4000ns 4736ns

Li, Yue, Yang, Zhang. Biomaterials 2012, 33, 4965.

Rotation of Disk-shaped NPs.

To maximize NP-membrane contact

membrane invagination

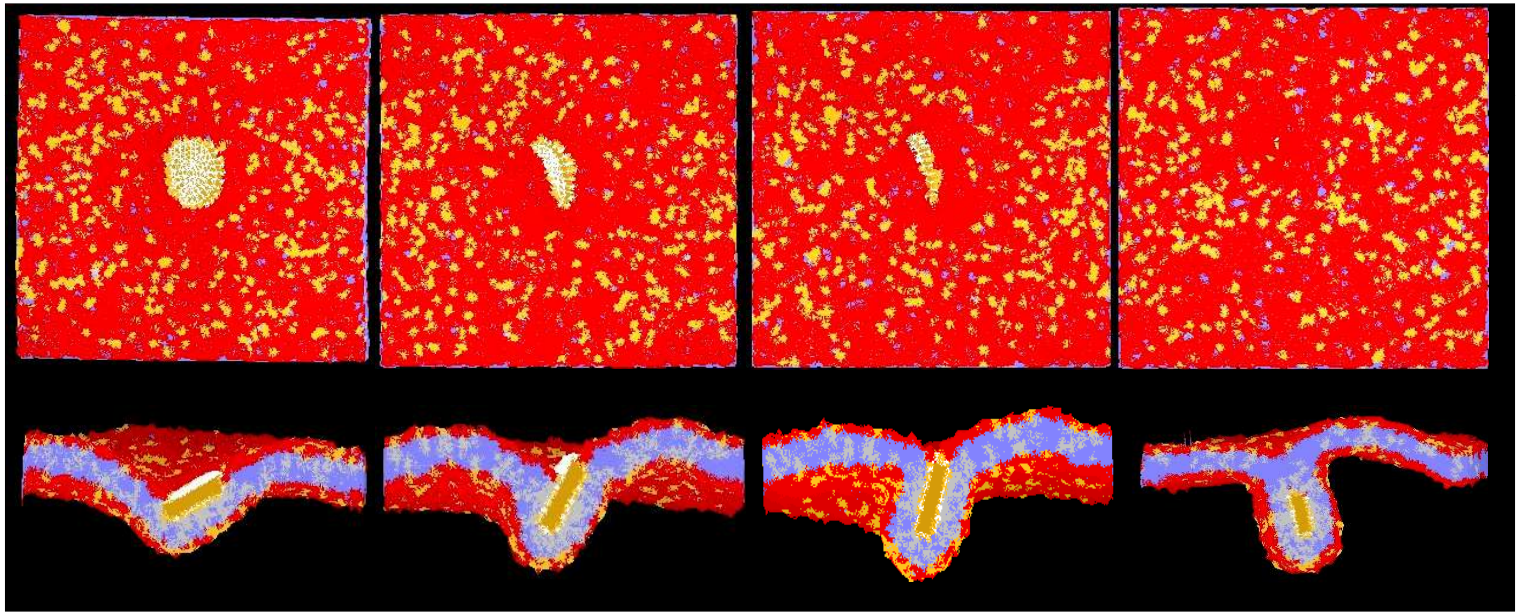


0ns 192ns 256ns 352ns 576ns

To minimize membrane bending:

The part of NPs with the largest local curvature

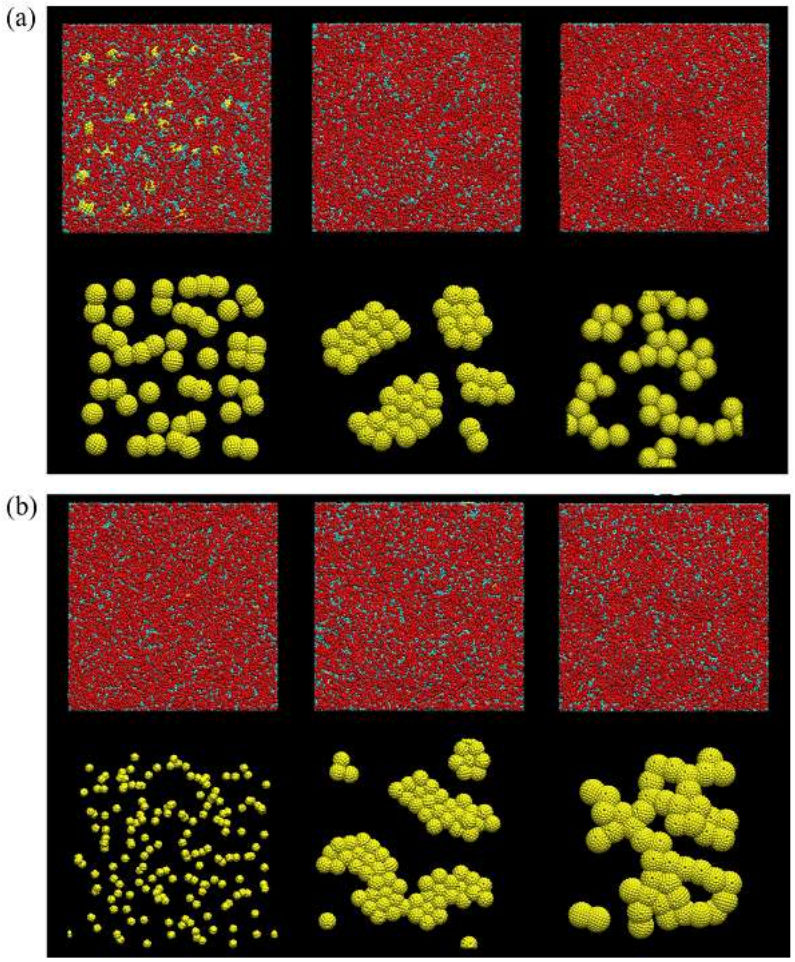
Nanoparticle wrapping

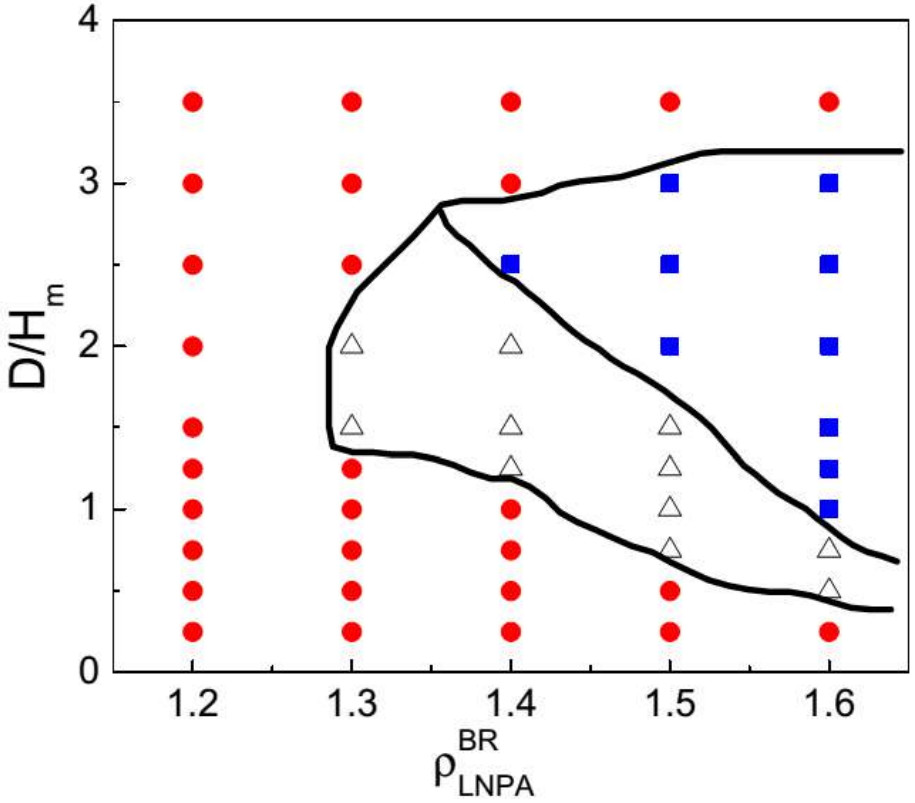


1920ns 2272ns 2240ns 4320ns

Li, Yue, Yang, Zhang. Biomaterials 2012, 33, 4965.

NP hydrophobicity: How hydrophobic NPs enter a cell --insertion and aggregation





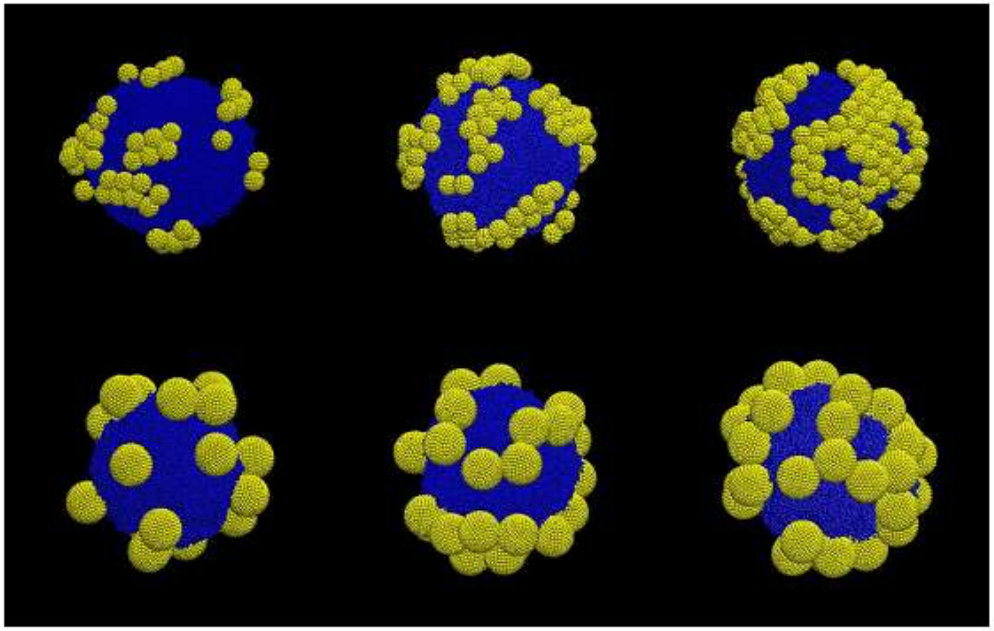
Circles: Gas-like state

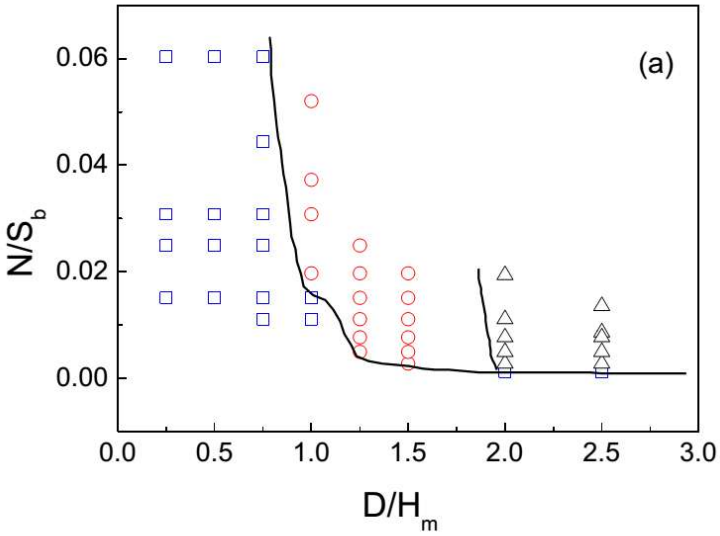
Triangles: patch-like structure

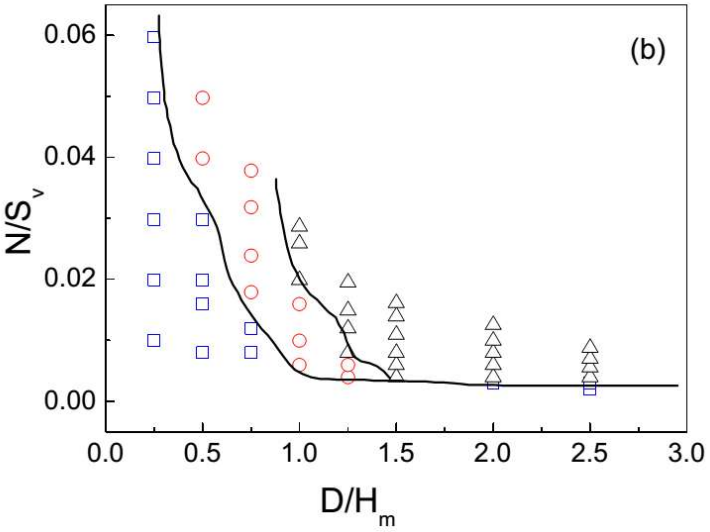
squares: chain-like structure.

Tian, Zhang, Dong, Phys. Rev. E, 2014, 90, 052701

NP hydrophobicity: How hydrophobic NPs enter a cell --insertion and aggregation







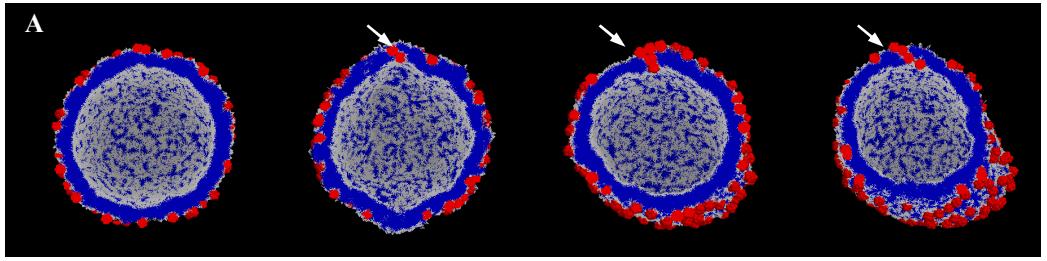
Phase diagram

Tian, Zhang, Dong, Phys. Rev. E, 2014, 90, 052701

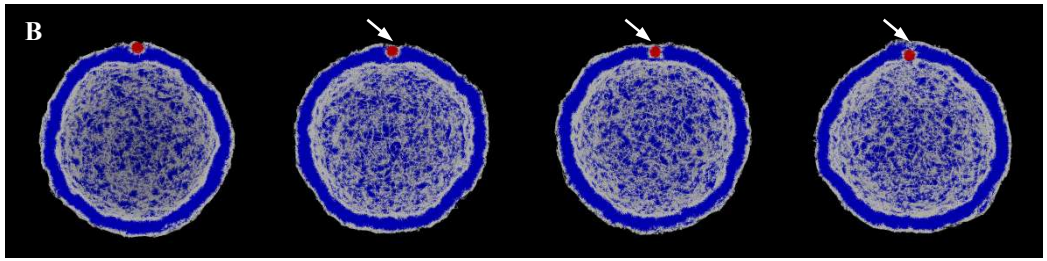
NP hydrophobicity: How hydrophilic NPs enter a cell

using vesicle as a model of cell, three pathways for NP penetration are identified

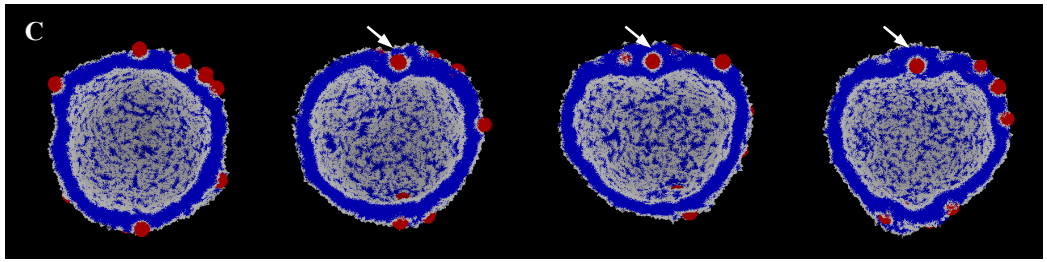
A) cooperative chain-like penetration (small NP)



B) direct penetration (intermediate NP size)

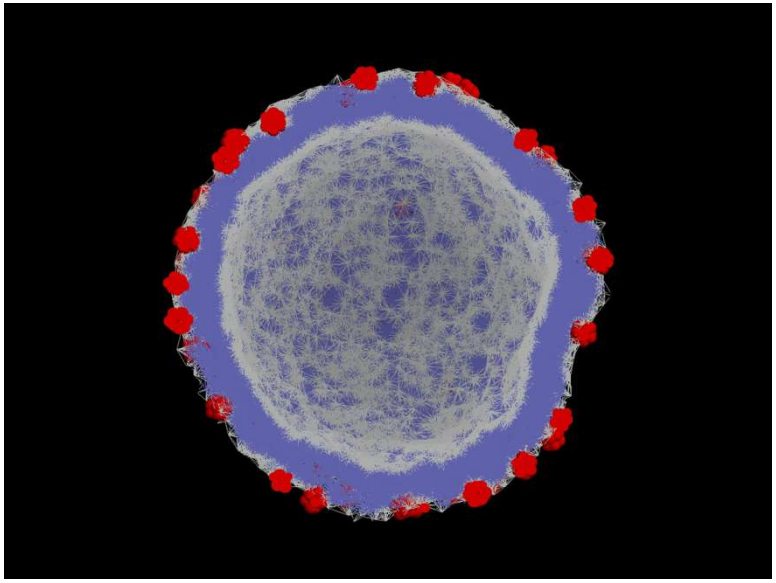


C) inverted micelle-like penetration (intermediate NP size)

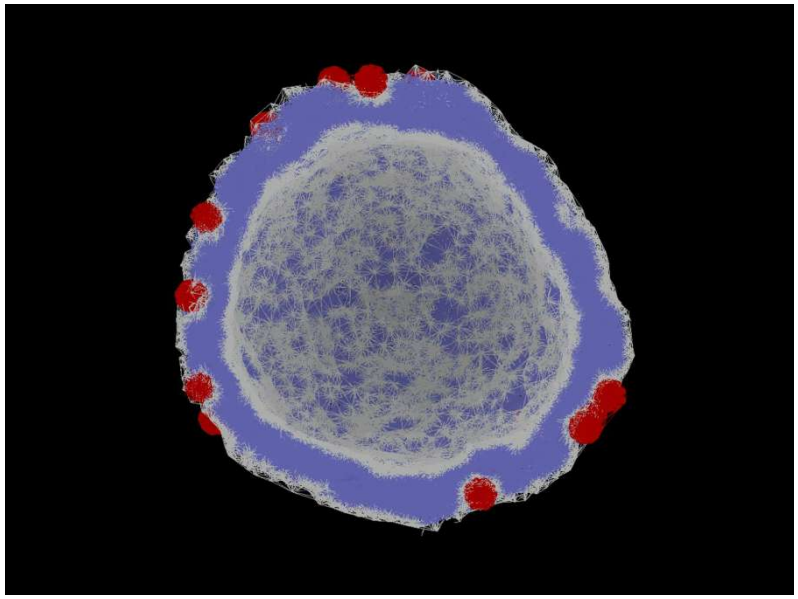


Chen, Tian, Zhang and Wang. Soft Matter 2013, 9, 7592.

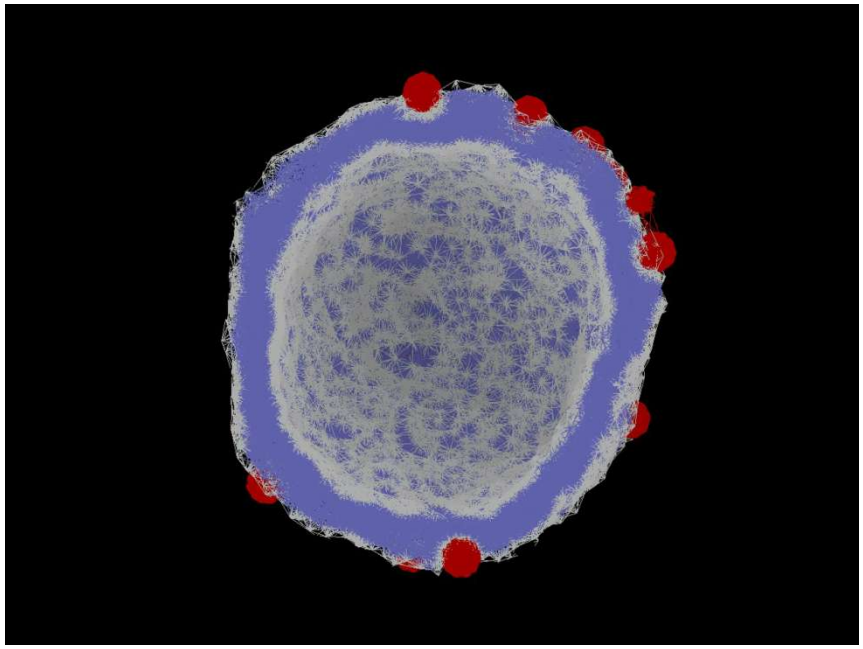
cooperative chain-like penetration



direct penetration

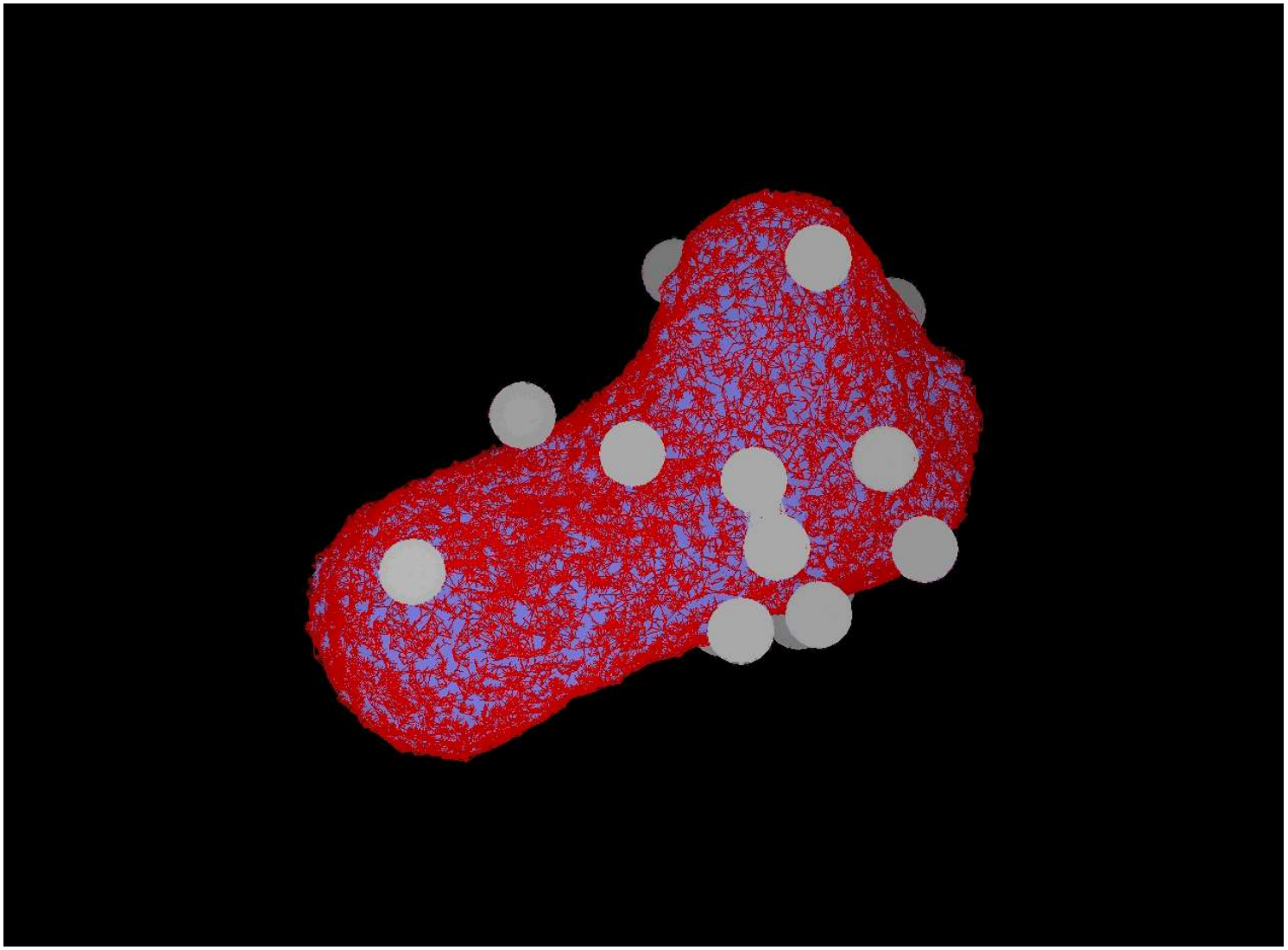


movie



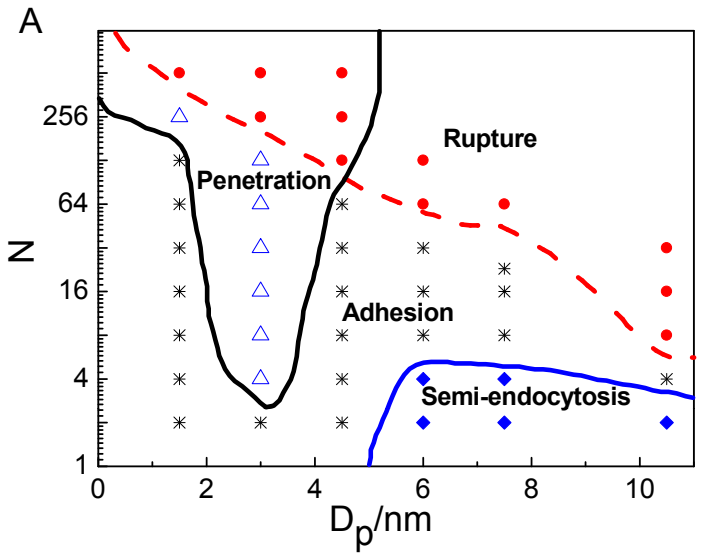
inverted micelle-like penetration

Endocytosis for large NP (movie)

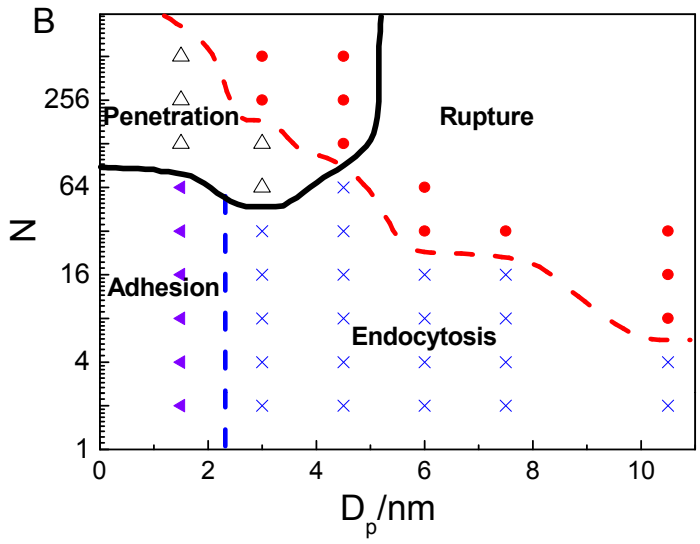


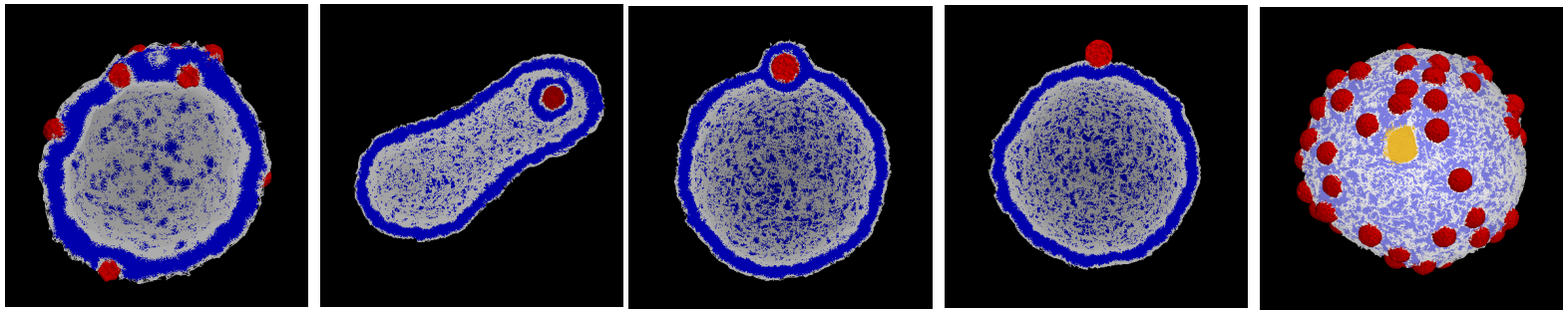
Phase diagram

Spherical vesicle



Tubular vesicle





Penetration endocytosis semi-endocytosis Adhesion rupture

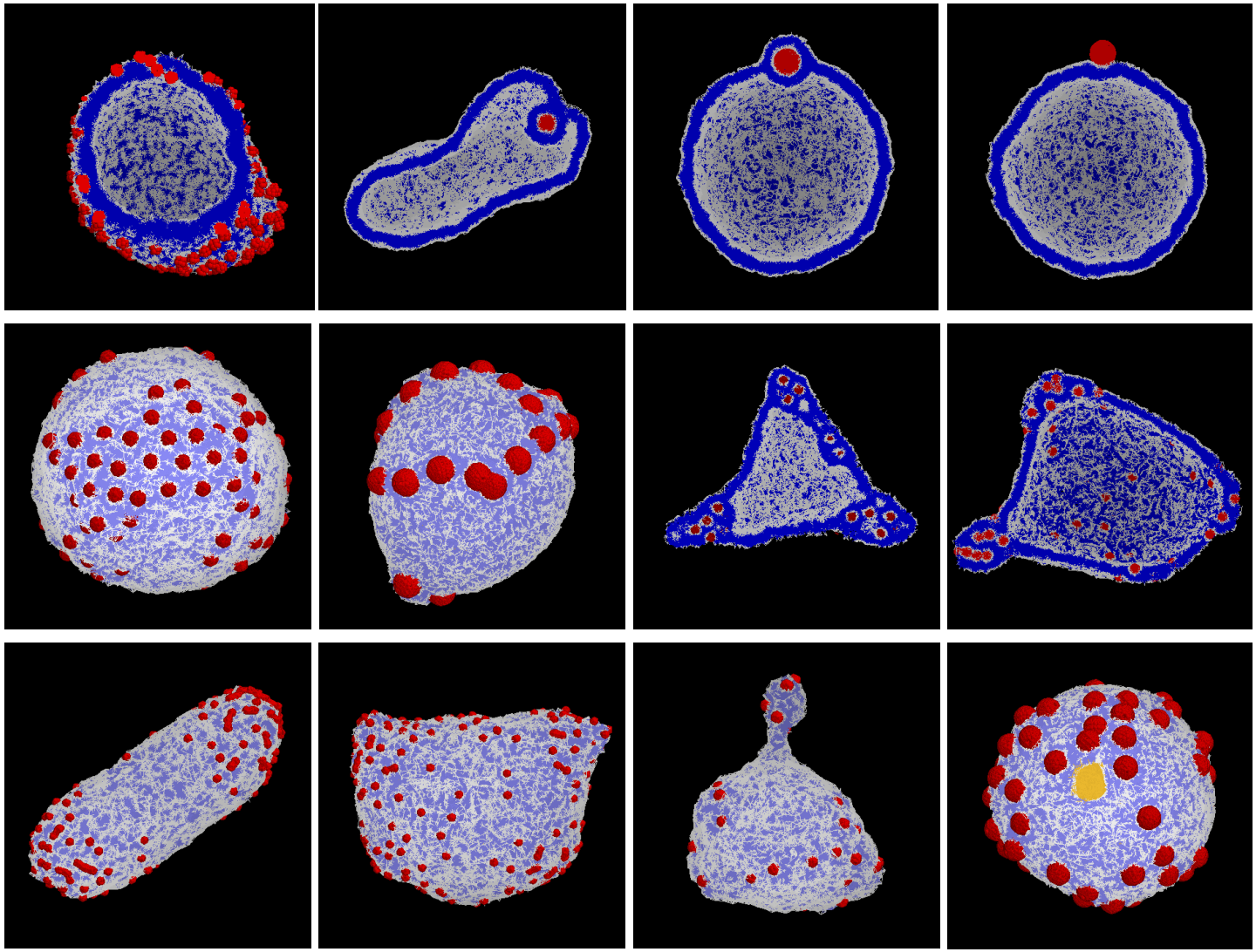
Chen, Tian, Zhang and Wang. Soft Matter 2013, 9, 7592.

NP hydrophobicity: How hydrophilic NPs enter a cell

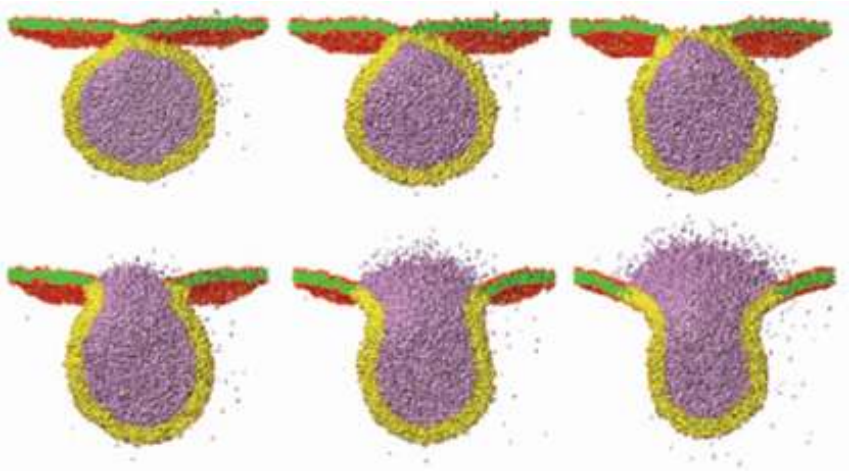
Pathways

Clustering

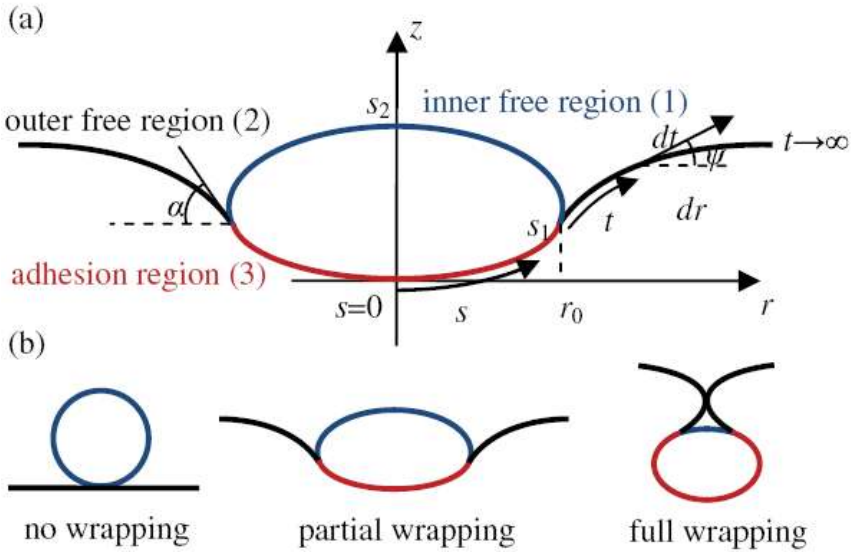
Responses



Soft NPs: Interaction between vesicle and membrane



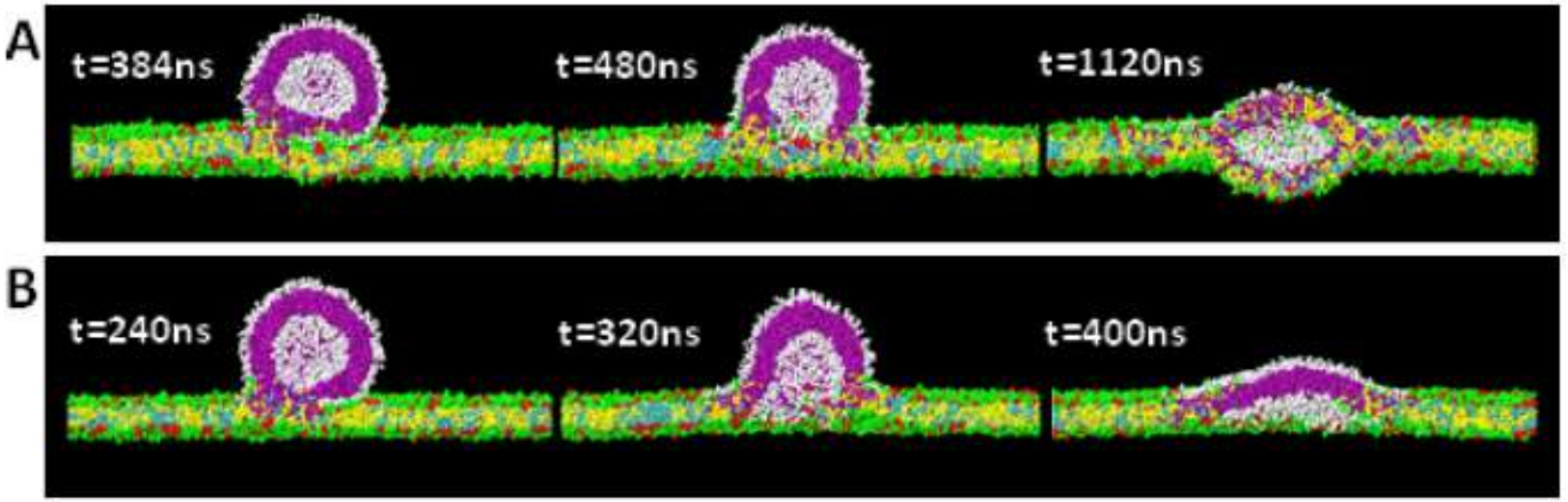
Shillcock et al, Nature Mater. (2005)



Yi et al, Phys. Rev. Lett. (2011)

Five different responses

vesicle fusion and vesicle hemi-fusion

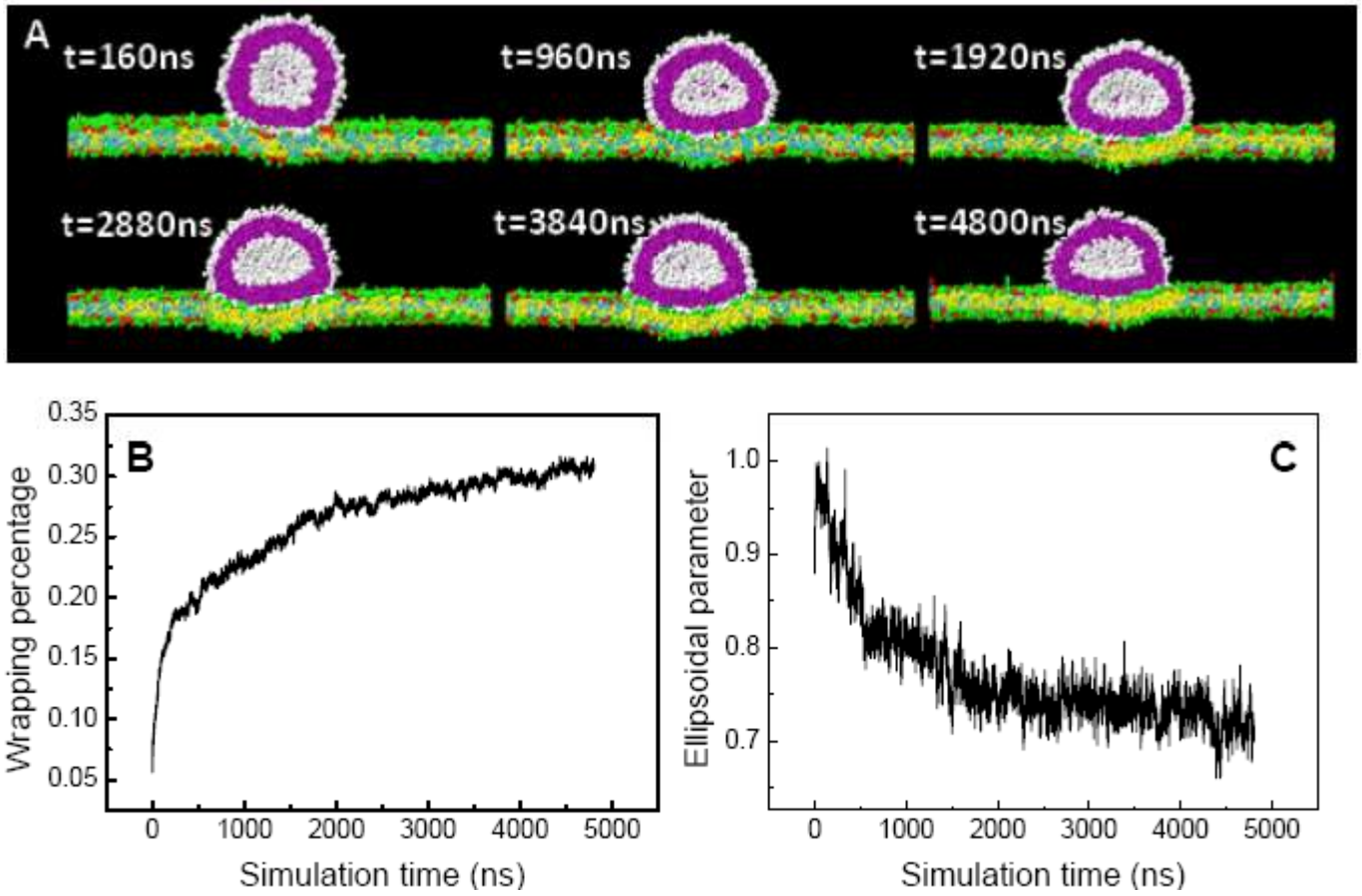


vesicle fusion and vesicle hemi-fusion is determined by membrane tension.

Yue and Zhang, Soft Matter 2013, 9, 559.

Five different responses

vesicle adhesion

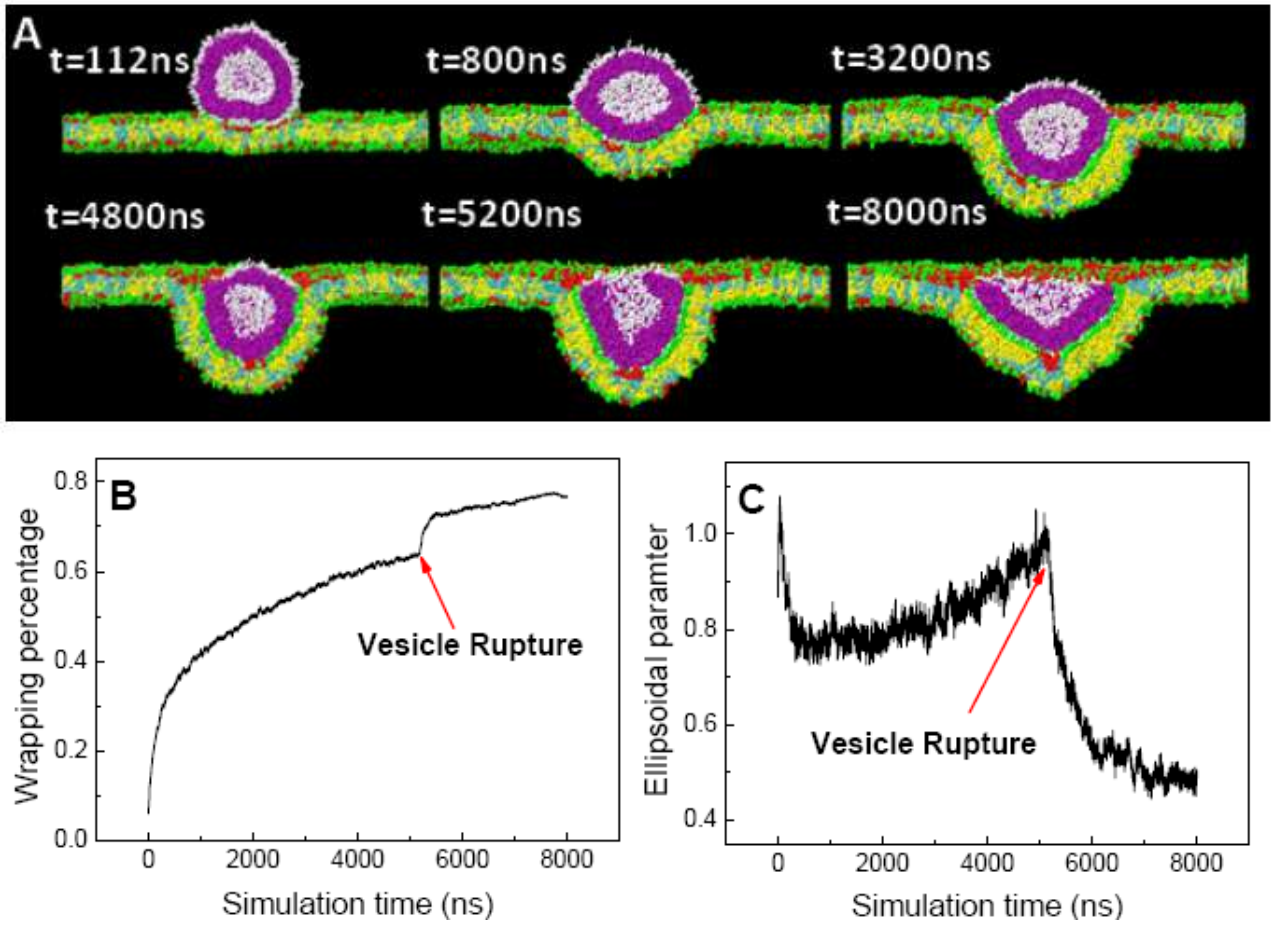


Vesicle adhesion often takes place on a lipid membrane with a relatively high surface tension.

Yue and Zhang, Soft Matter 2013, 9, 559.

Five different responses

Vesicle rupture

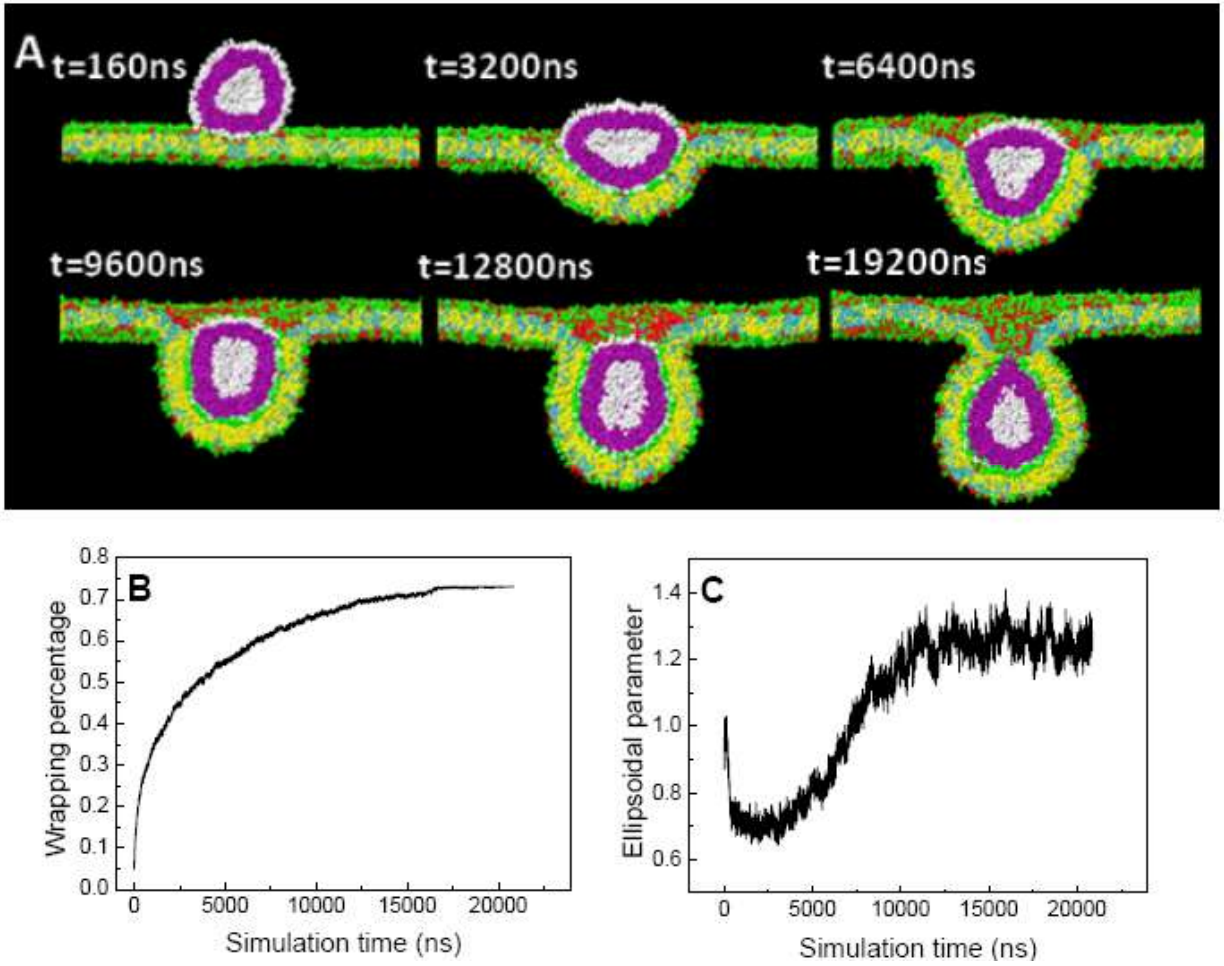


The vesicle rupture is mainly induced by the strong ligand-receptor interaction and high membrane tension.

Yue and Zhang, Soft Matter 2013, 9, 559.

Five different responses

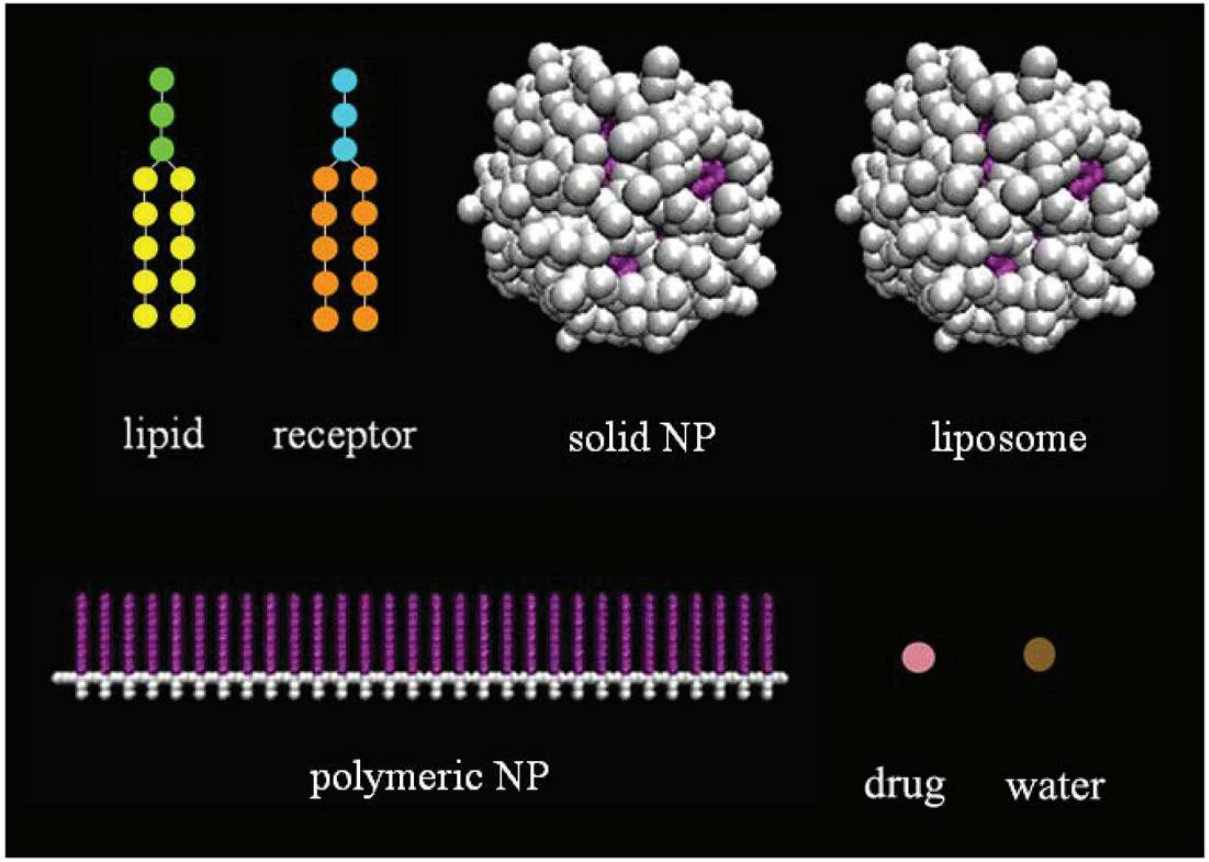
receptor-mediated endocytosis (seldomly observed)



The self-adjustment of vesicle shape is common mechanism for he endocytosis of soft nanoparticles.

Yue and Zhang, Soft Matter 2013, 9, 559.

NP hardness: Interaction between NPs and membrane



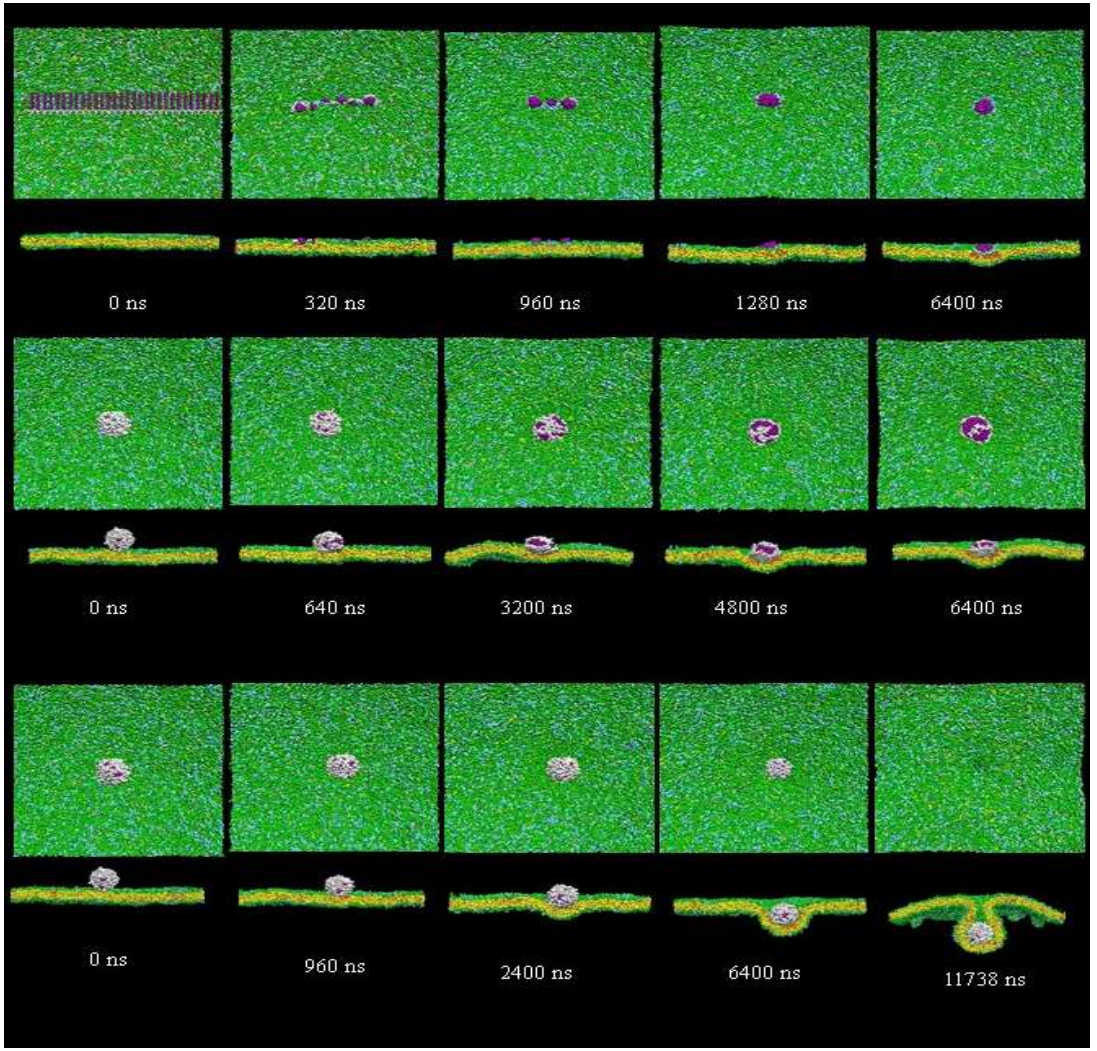
Li, Zhang, Cao. *Nanoscale* 2015, 7 , 2758

Two factors affecting successful endocytosis of soft NPs: ligand depletion and shape deformation

Polymeric NP

liposome

Solid NP

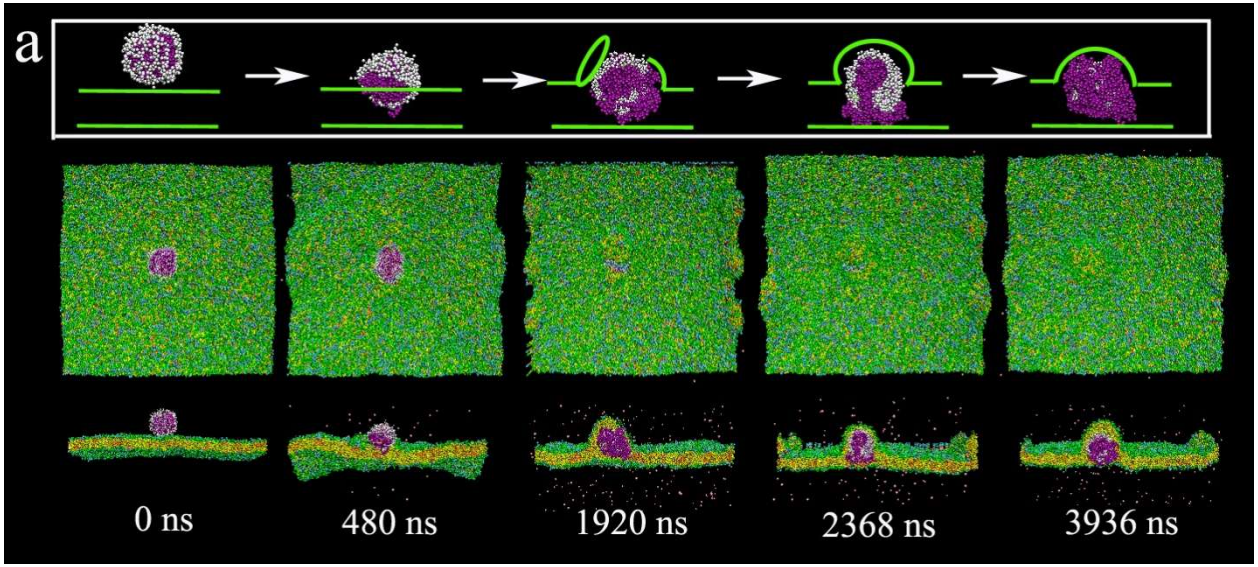


Increasing hardness

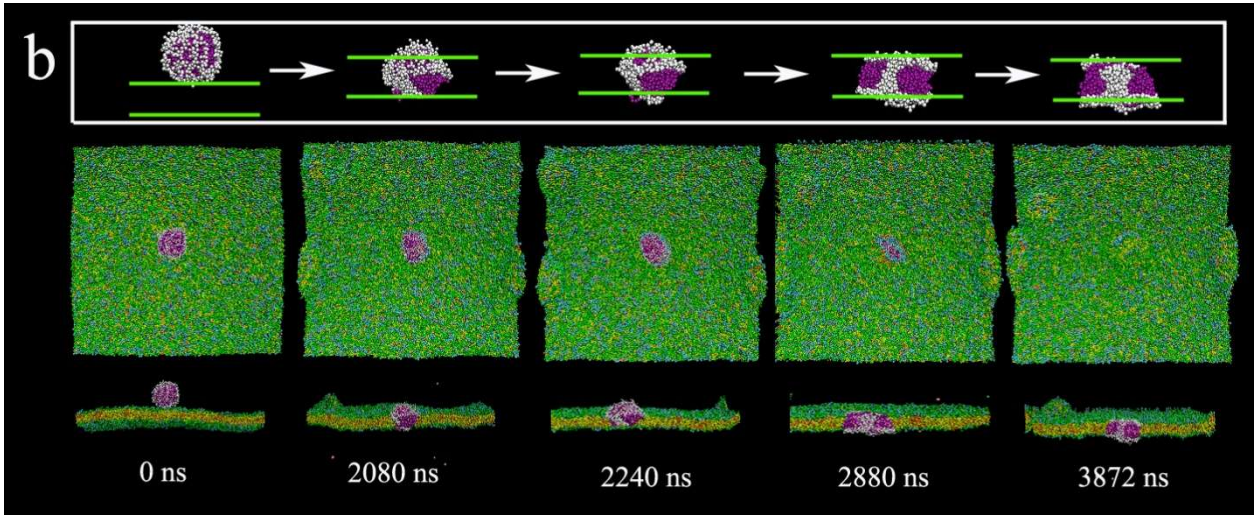
Hard NP can be endocytosed, but soft NP almost can not

Soft NPs often adopts the penetration pathway.

fusion–wrapping–switch



fusion–penetration–rearrangement

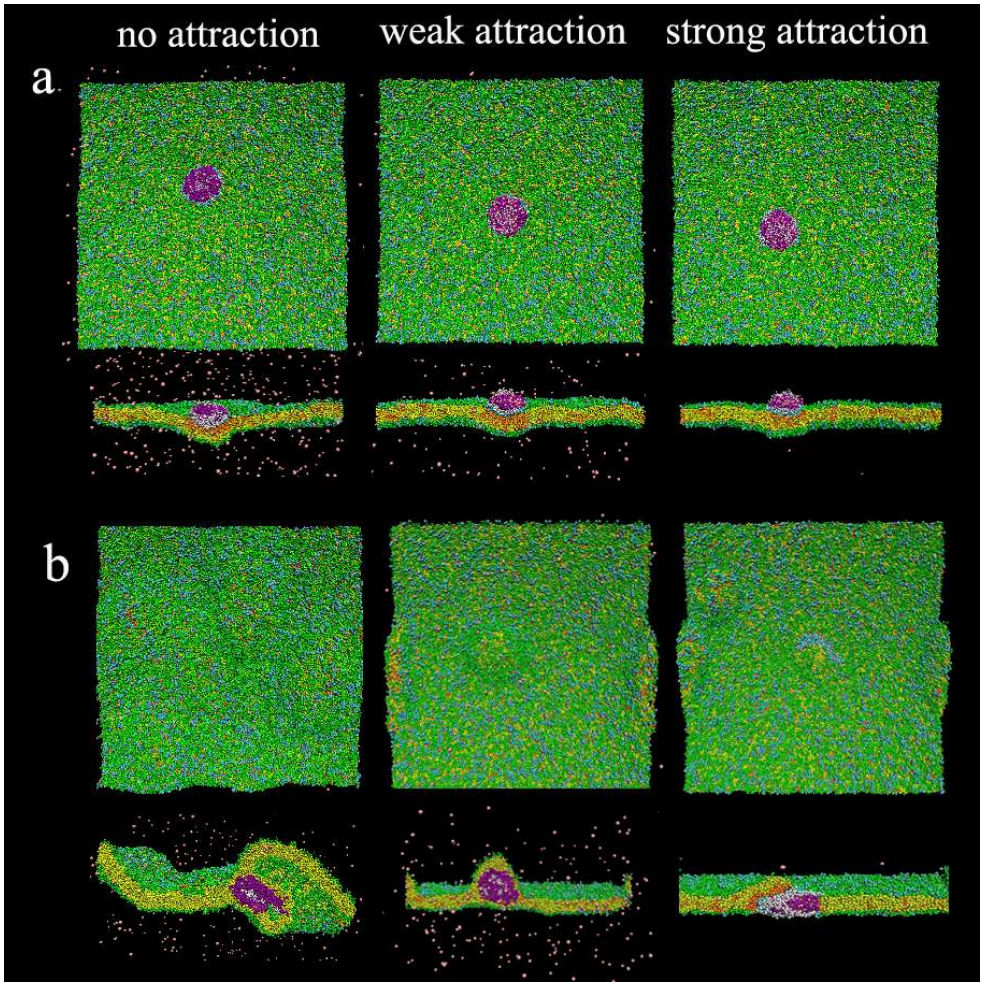


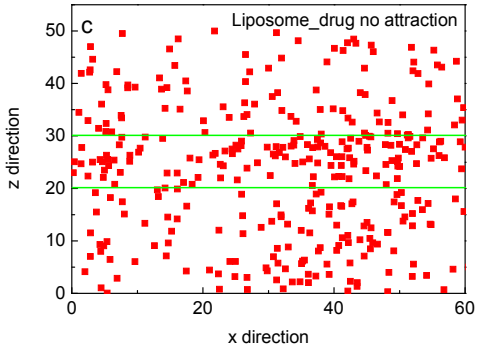
Li, Zhang, Cao. *Nanoscale* **2015, 7 , 2758**

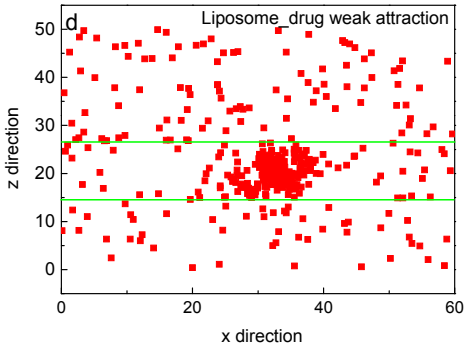
Penetration pathways for soft NPs carrying drug molecules

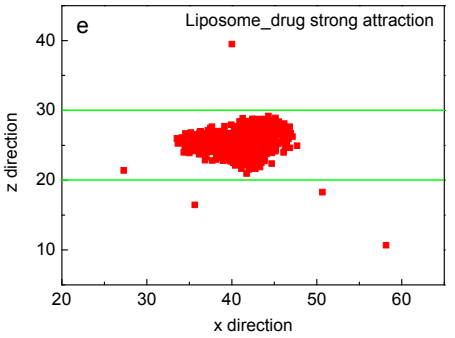
Wrapping

penetration



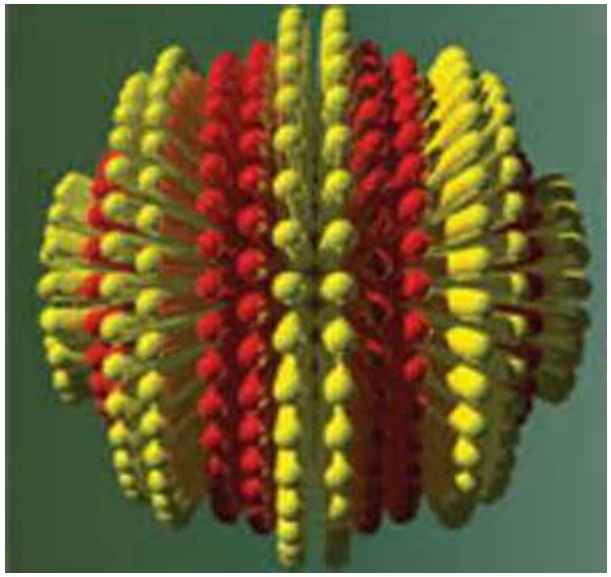


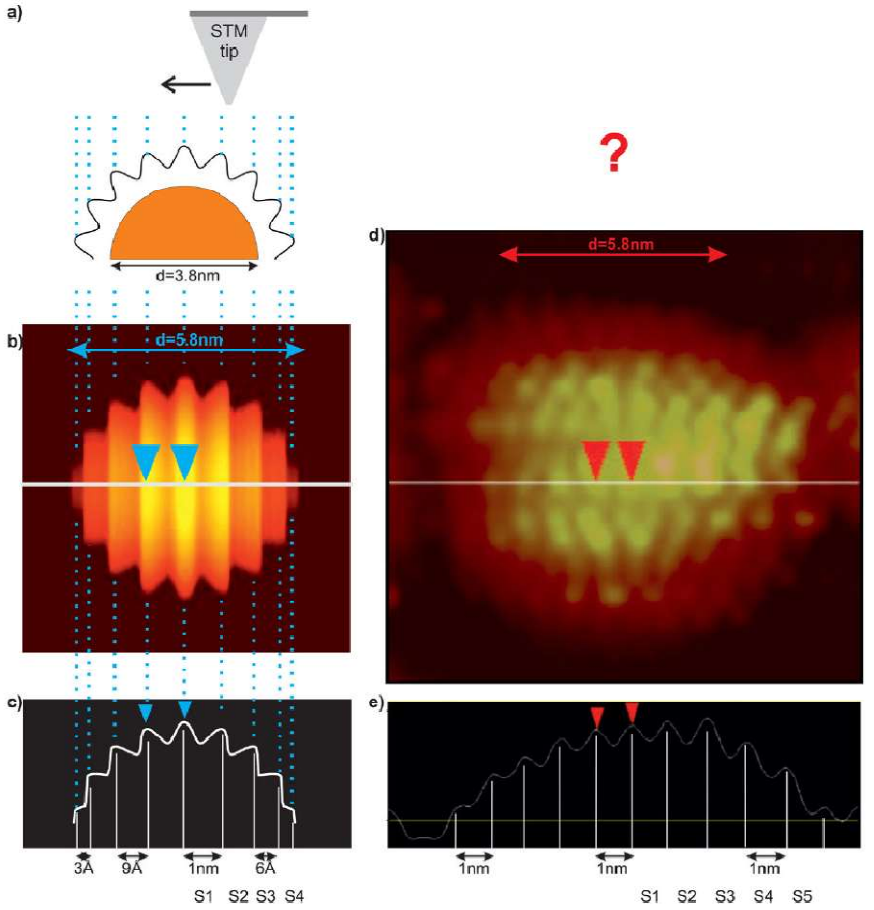




Drug-NP interaction is also important for drug delivery

Patterned NPs: How do patterned NPs enter a vesicle?



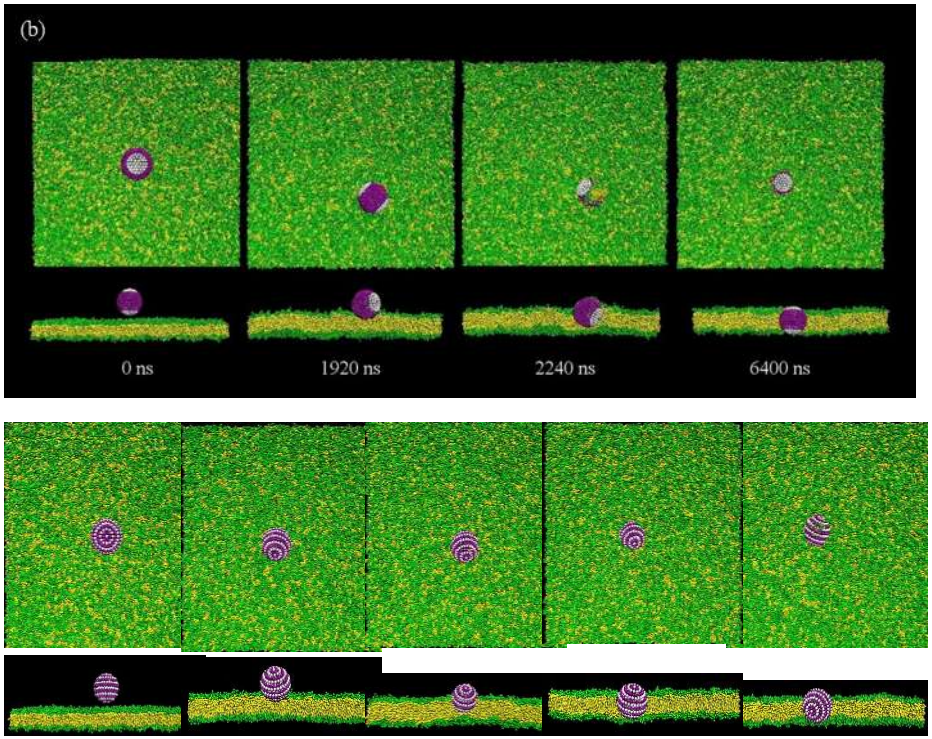


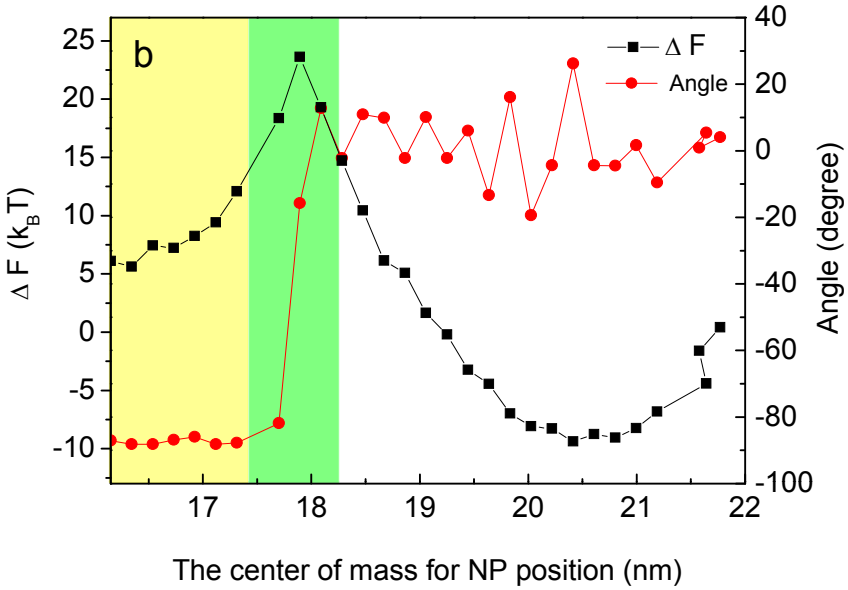
Verma et al. *Nat. Mater.* **2008** , *7* , 588

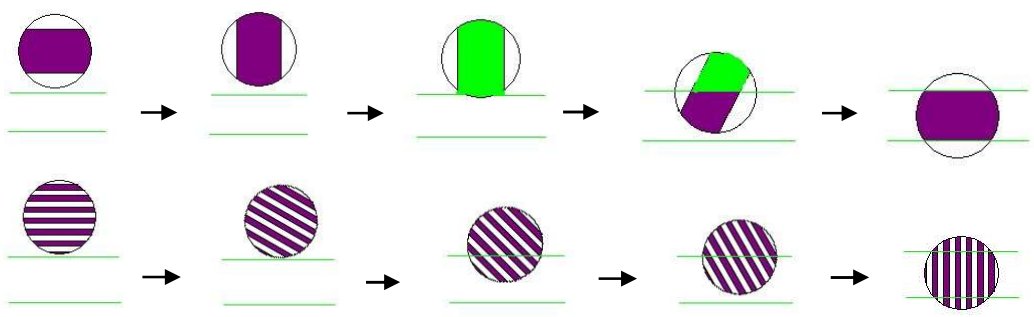
Cesbron et al. *small, 2012,* DOI: 10.1002/smll.201001465

Gold NPs coated with stripes of anionic and hydrophobic ligands could penetrate the cell membrane without bilayer disruption

Patterned NPs: How patterned NPs enter a vesicle



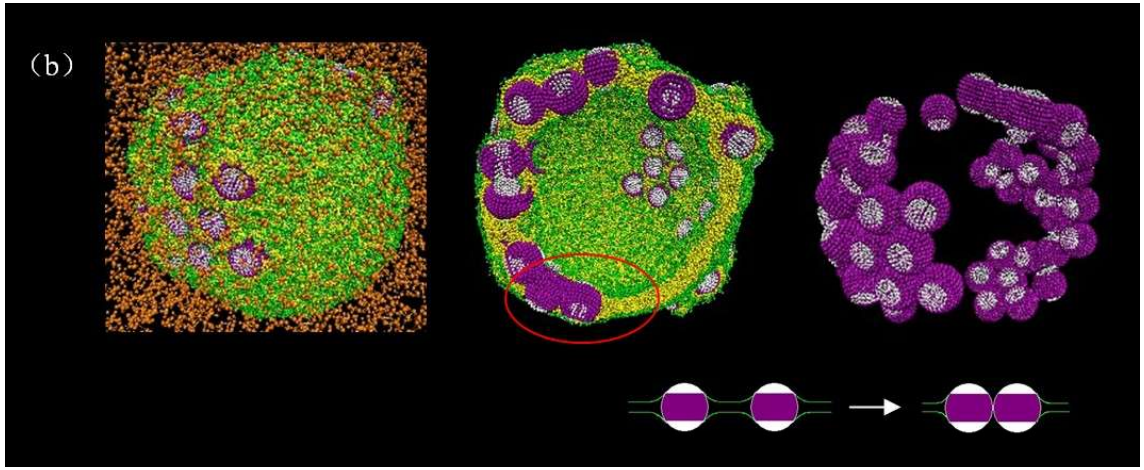


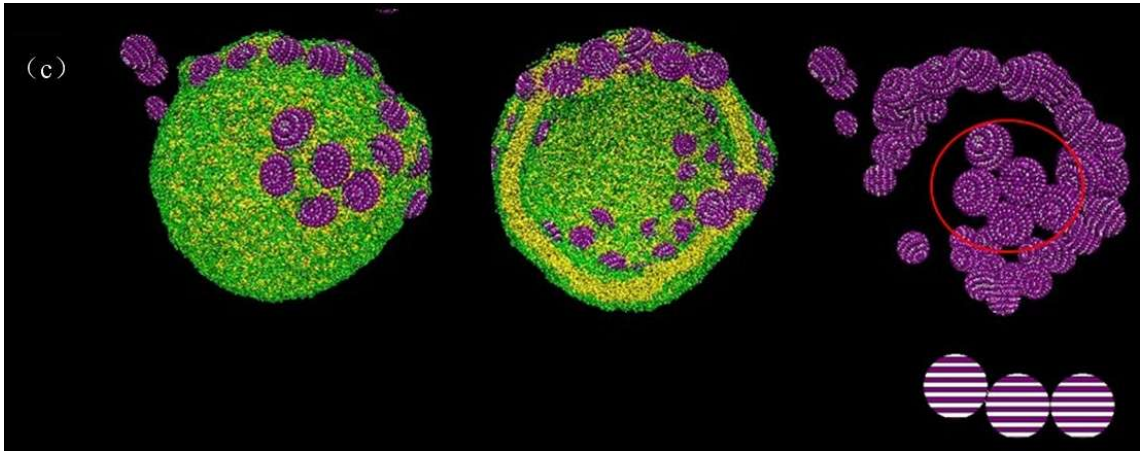


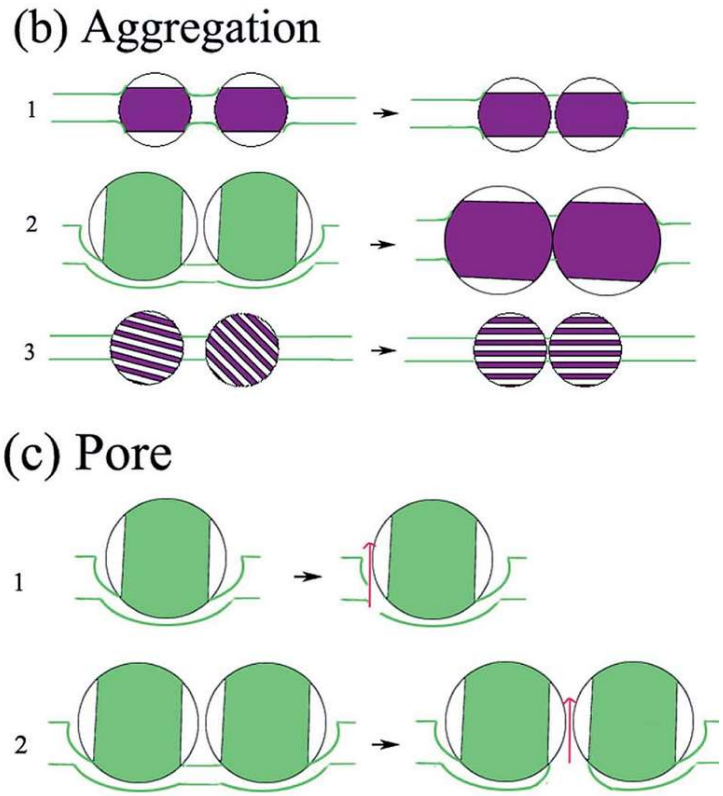
3-SNP spontaneously uptake with an insertion-rotation mechanism

Li, Zhang & Cao, Soft Matter, 2014, 10, 6844.

Internalized stripy NPs aggregate and induce membrane pore

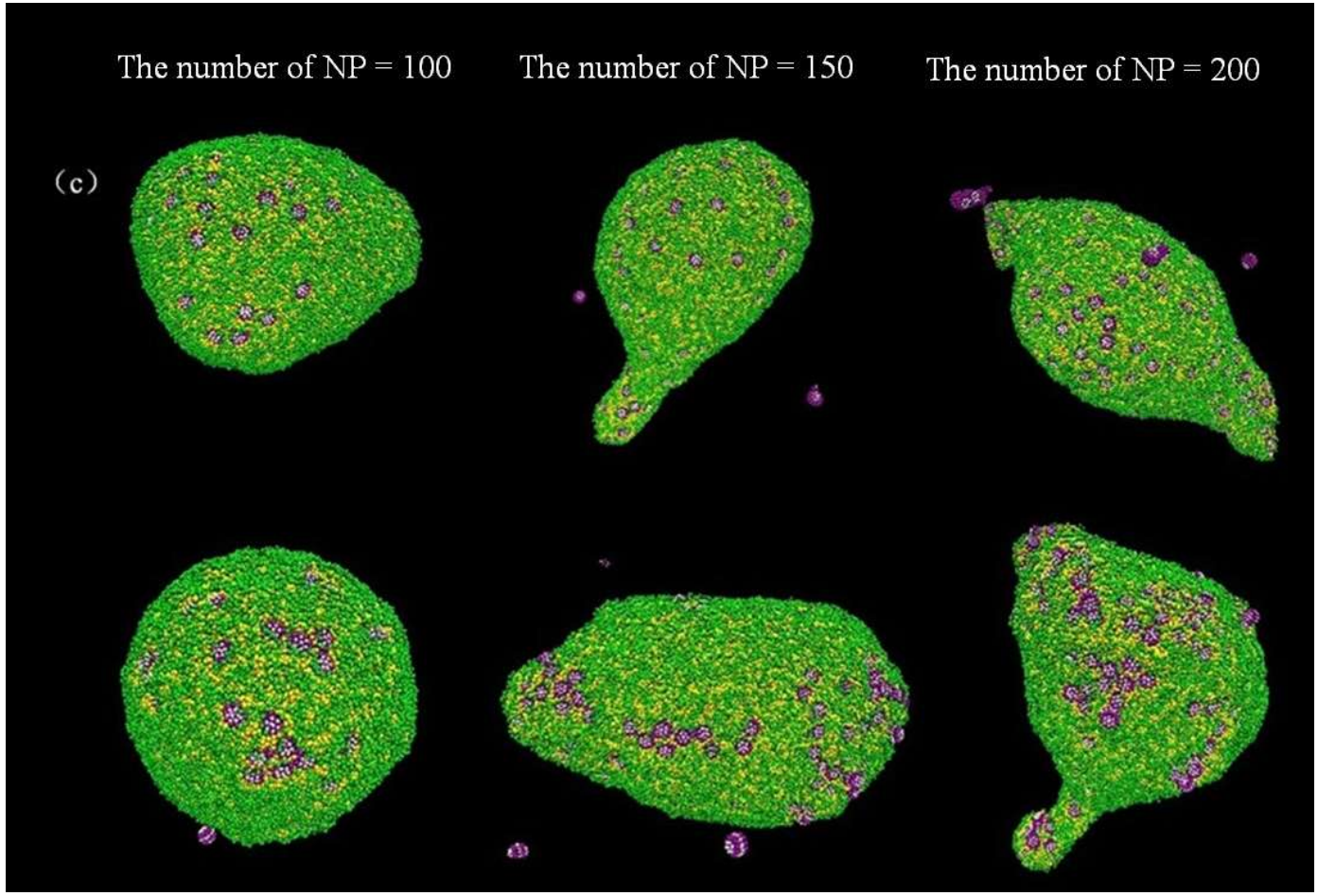






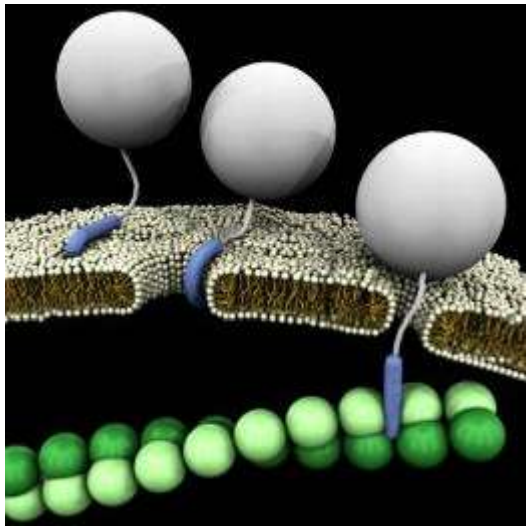
Li, Zhang & Cao, Soft Matter, 2014, 10, 6844.

Internalized stripy NPs induce vesicle shape change



Li, Zhang & Cao, Soft Matter, 2014, 10, 6844.

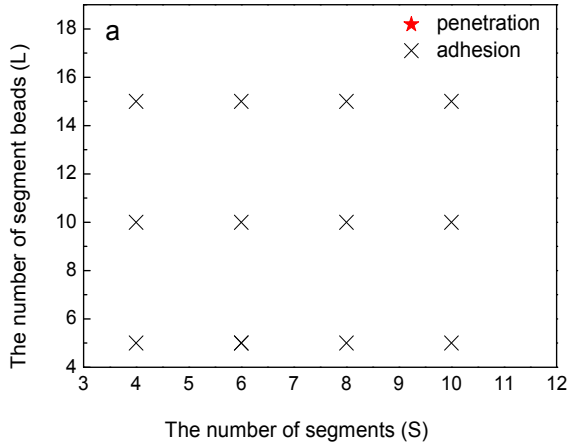
Designing cell-penetrating copolymer (CPC) for drug delivery



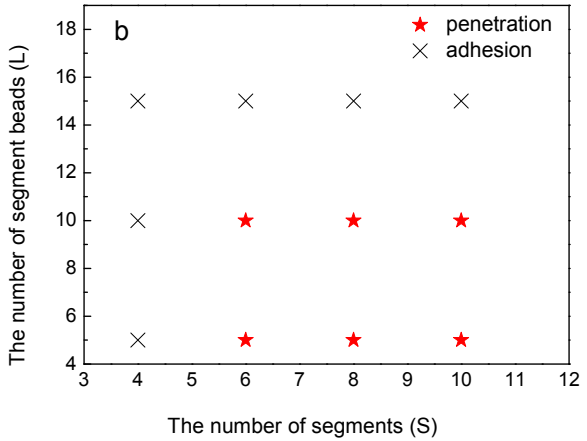
the idea comes from cell-penetrating peptides (CPP) that have both hydrophilic and hydrophobic residues and are capable of penetrating membranes without inducing membrane disruption

Li, Feng, Zhang, Cao. *Biomaterials,* 2015,52,171

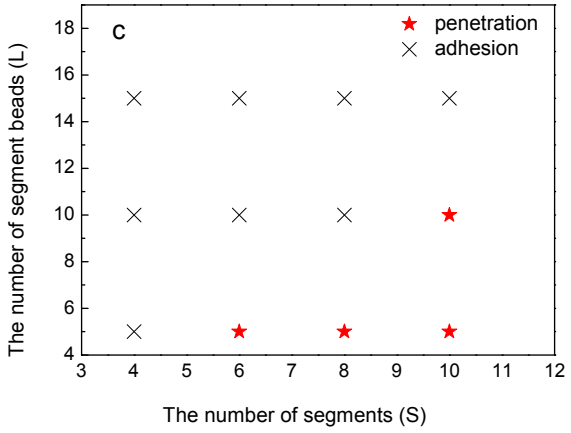
Designing CPC for drug delivery: Optimizing structure



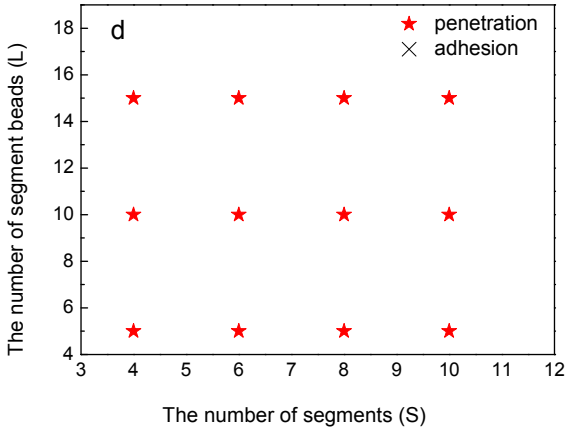
$a_{HP_H} = 15, a_{P_H P_H} = 25$



$a_{HP_H} = 15, a_{P_H P_H} = 15$



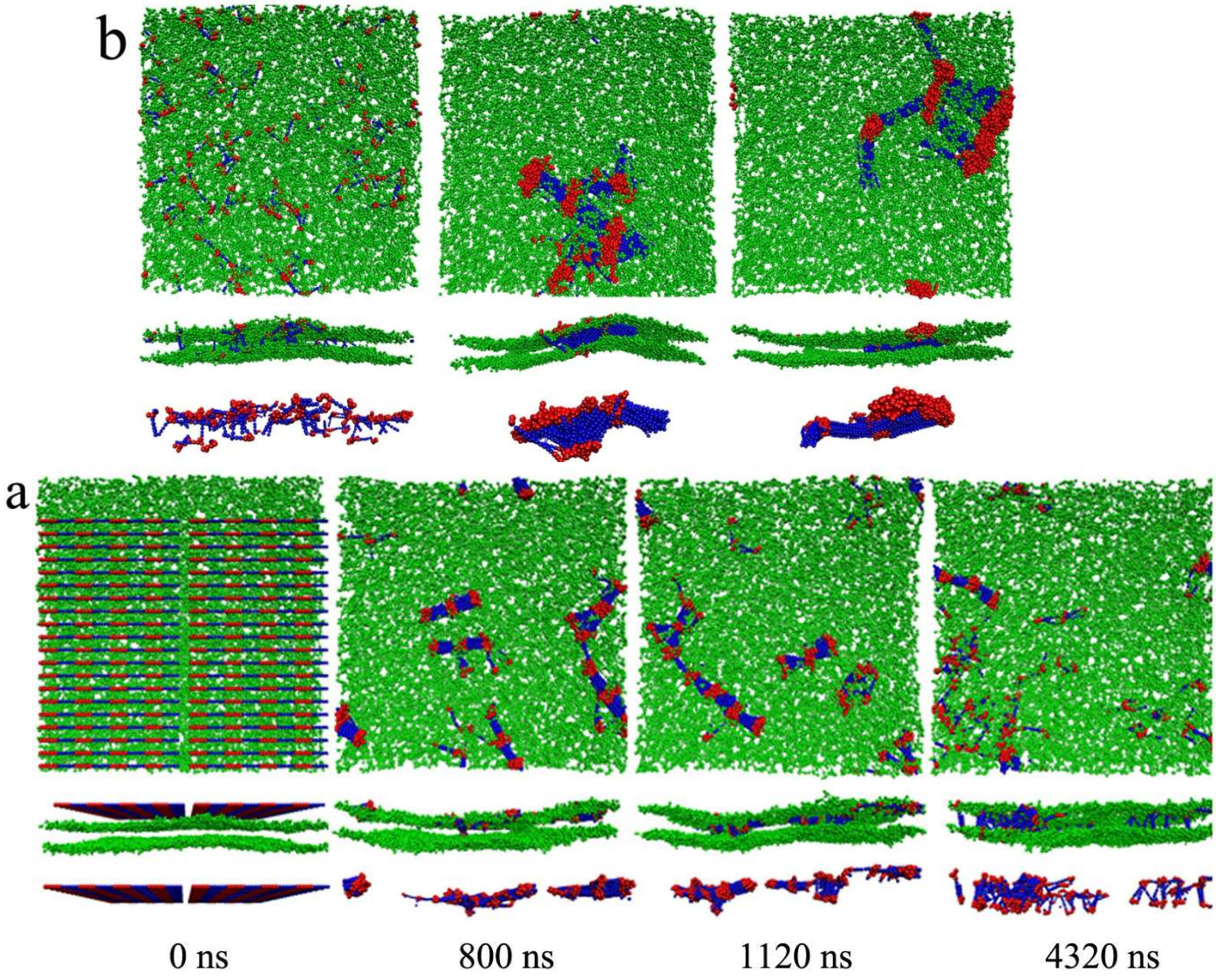
$a_{TP_T} = 15, a_{P_H P_H} = 25$



$a_{TP_T} = 15, a_{P_H P_H} = 15$

CPC of high efficiency: multiple number of hydrophobic segments with a length comparable to membrane thickness

Typical CPC penetration processes

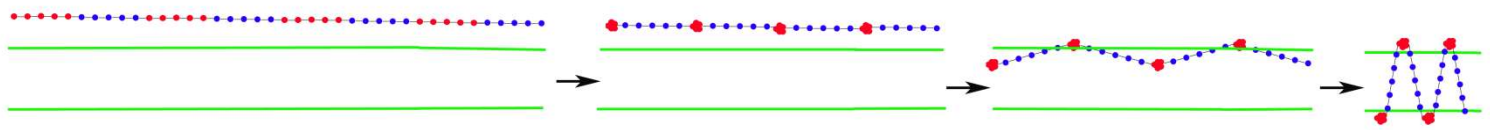


Li, Feng, Zhang, Cao. *Biomaterials,* 2015,52,171

Mechanism for CPC penetration

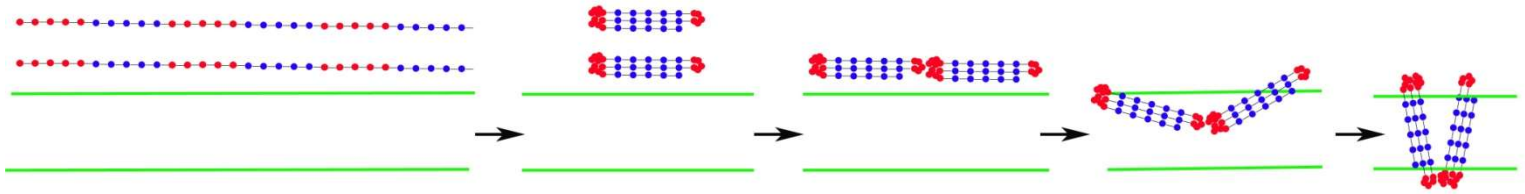
Zipper-like mechanism

a



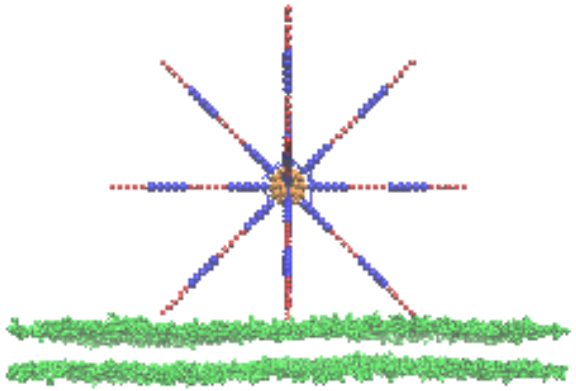
Cooperative mechanism

b



Li, Feng, Zhang, Cao. ***Biomaterials,*** **2015,52,171**

Movie： penetrating process for CPC carrying drug

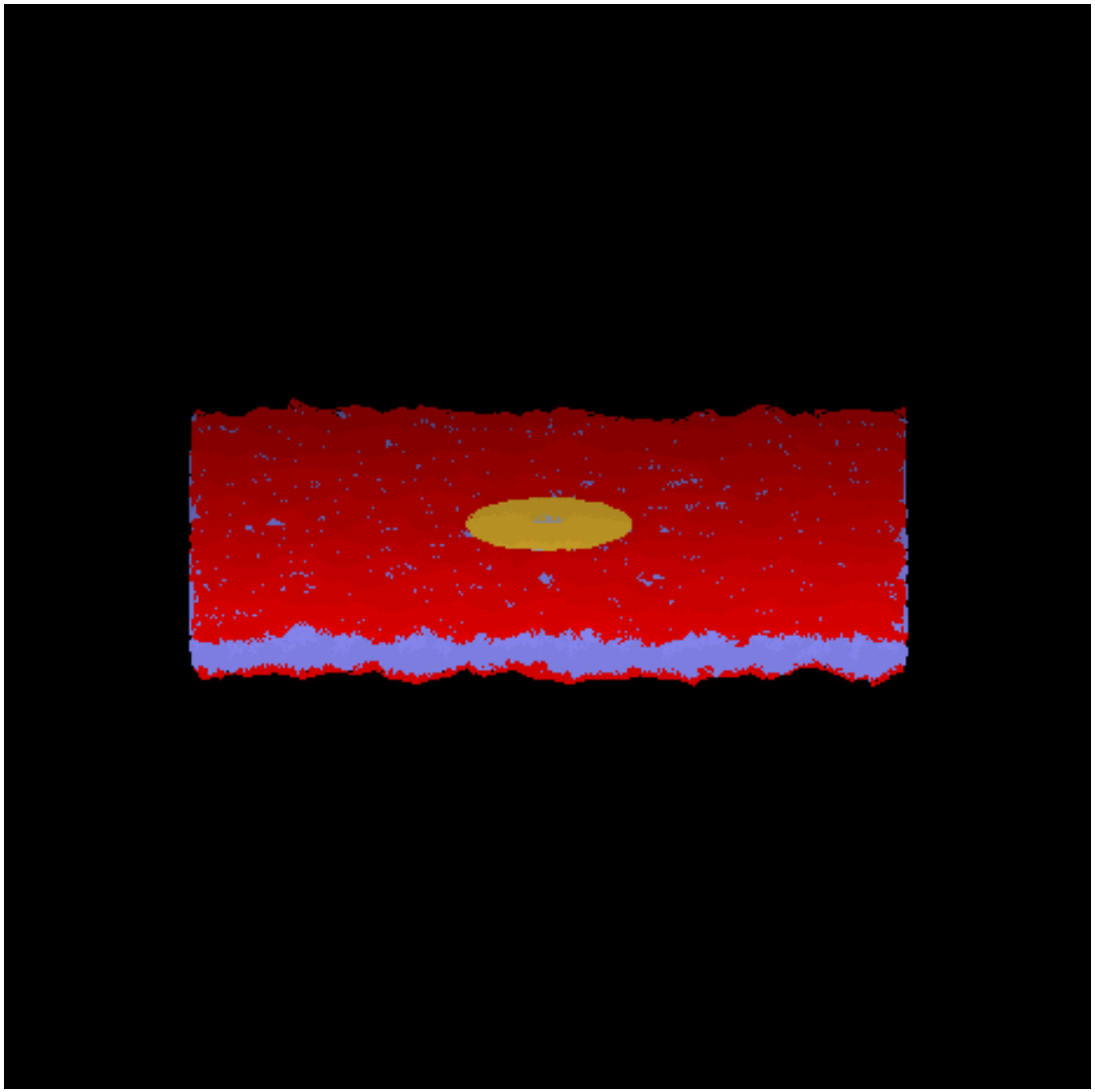


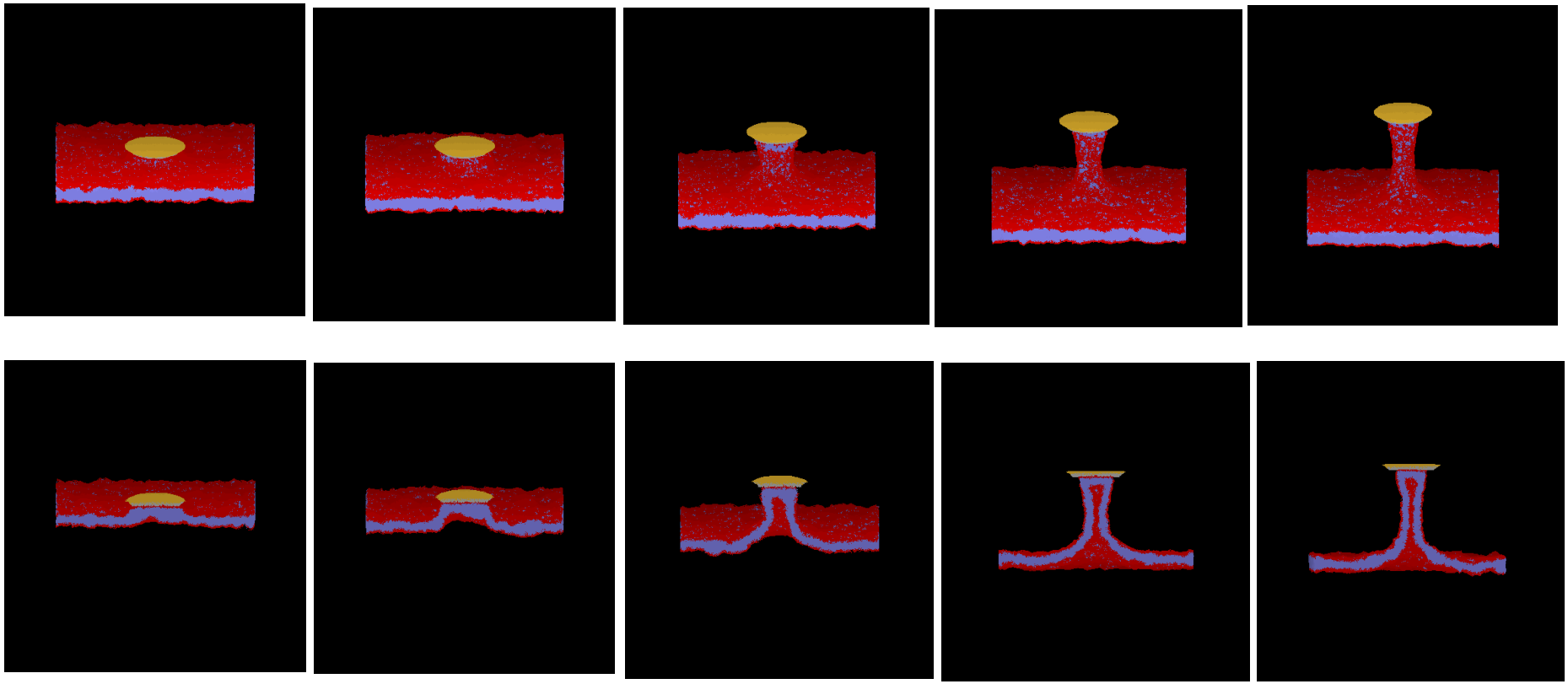
High penetration efficiency for CPCs conjugating drug

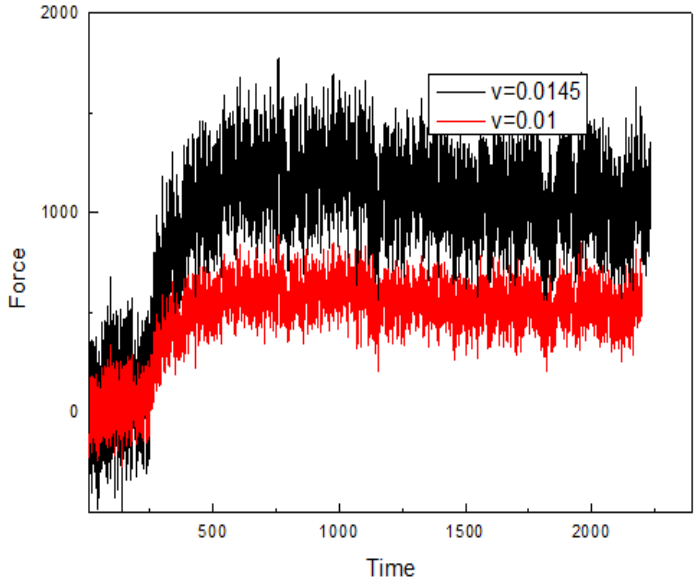
NP motion induced membrane tube

---competition between thermodynamics and kinetics

movie






2000
1000
0
Force
500
1000
1500
2000
Time
v=0.0145
v=0.01

Summary

We studied the interaction between NPs and membrane, considering the effect of NP size, shape, rigidity, and surface pattern. Different pathways for NP internalization and membrane responses were observed.

Due to the complex cellular environment, the direct comparison of simulated results to their *in vivo* experimental counterparts is at most qualitative.

NPs may *in vivo* be immediately covered with proteins and other biomolecules, and the formation of the layer of proteins changes the NP properties by simply lowering the surface free energy, and affects significantly the NP-membrane interaction.

Acknowledgement

The simulations were performed by Dr. Tongtao Yue

and by PhD students Falin Tian, and Ye Li

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Thank You

DPD workshop, Shanghai, 2015. 09. 22