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Minimum Free Energy Paths for a Nanoparticle Crossing the Lipid Membrane

Christina L. Ting*, Amalie Frischknecht
Sandia National Laboratories, *clting@sandia.gov

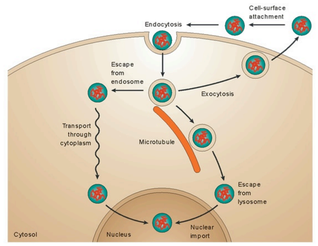
Zhen-Gang Wang
California Institute of Technology

Sandia National Laboratories

Caltech

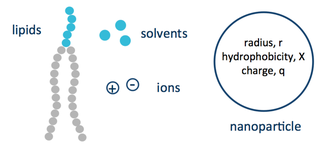
Abstract

The interaction of nanoparticles with lipid membranes is a common theme underlying a number of important topics in bionanotechnology, ranging from cytotoxicity to the delivery of therapeutics. Within self-consistent field theory, we develop an ''on-the-fly'' string method to compute the minimum free energy path (MFEP) for several activated processes involving a charged, solvophobic nanoparticle and a lipid membrane.



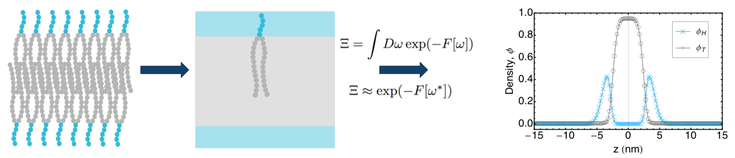
Under tensions well below the mechanical stability limit of the membrane, and in the regime where the event can occur on experimentally relevant time scales, our study suggests that there can be at least three competing pathways for crossing the membrane: (1) particle-assisted membrane rupture, (2) particle insertion into a metastable pore followed by translocation and membrane resealing, and (3) particle insertion into a metastable pore followed by membrane rupture.

Model, Theory and Method

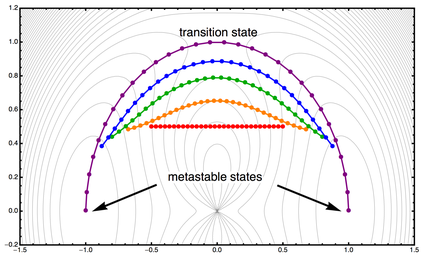


- Lipid chain connectivity
- Electrostatics at the Poisson Boltzmann level
- Excluded volume via strict incompressibility
- Local pairwise interactions

① Convert to a field based model using the *self-consistent field theory (SCFT)* and make a mean field approximation*:*



② Obtain activation *pathways*, using the string method[1]:

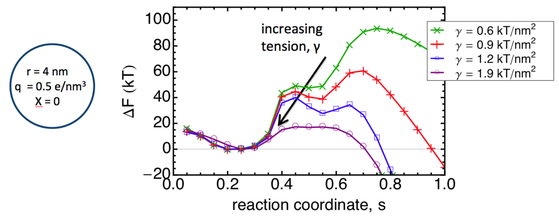


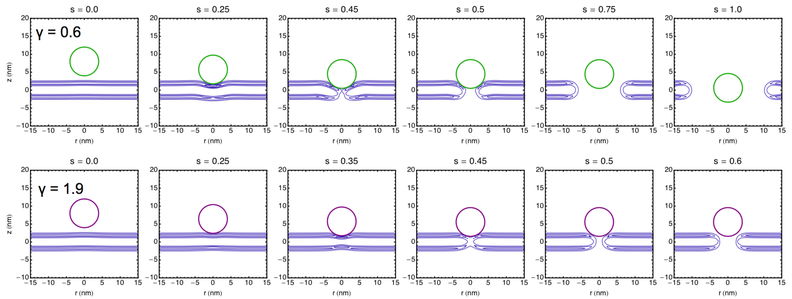
Evolve states according to a two step iterative procedure:

- Steepest descent dynamics of SCF eqns and particle position
- Equidistant *reparameterization* of states along the string

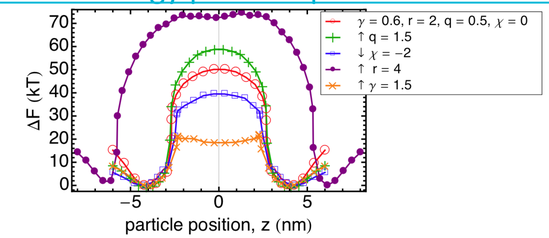
[1]W. E, W. Ren and E. Vanden-Eijnden, *J. Chem. Phys.*, 2007, **126**, 164103.

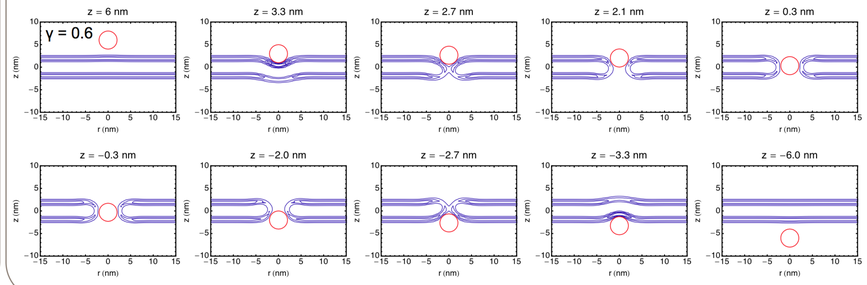
Minimum free energy path for membrane rupture





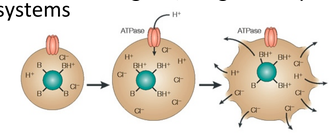
Minimum free energy path for particle translocation





Conclusions

- Multiple competing pathways for a nanoparticle to cross the membrane
- Nanoparticle can *directly* lower the activation barrier for rupture or translocation
- Membrane tension is critical for achieving activation barriers surmountable on realistic time scales
- Implications for endosomal escape mechanism in gene/drug delivery systems



- Methodology can be used to study activated events in soft matter systems beyond membranes, e.g. polymer-nanoparticle composites

Acknowledgements

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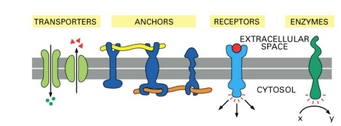
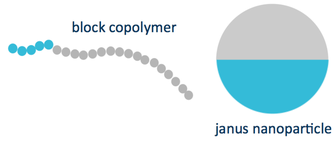
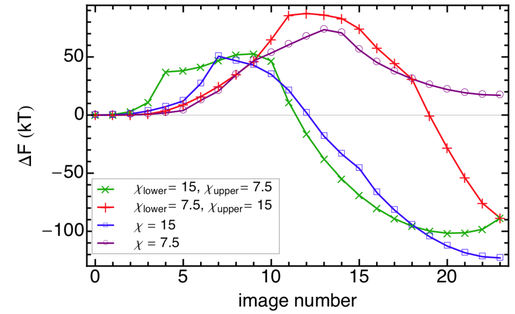
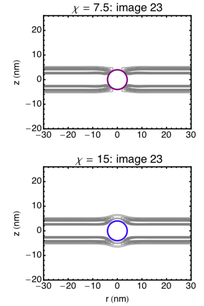
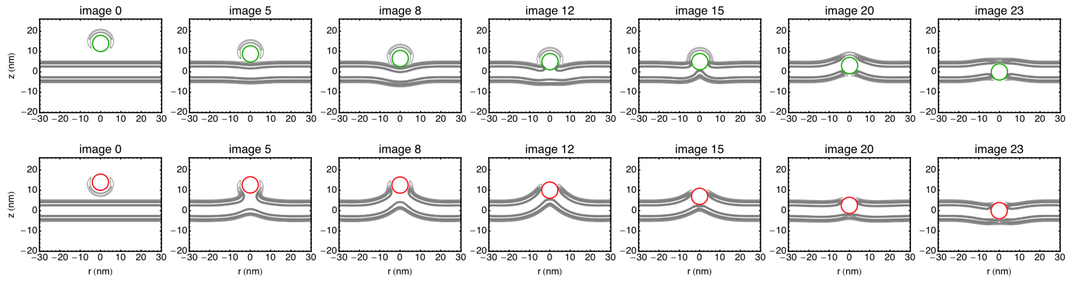
Ongoing: the directed insertion of *asymmetric* nanoparticles into polymersomes











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