

## 4.5: Nanoparticle Spontaneous Penetration and Assembly in and Through Membranes

Nanomaterial science is a rapidly evolving field of study to approach many scientific questions across fields. From sensors, drug delivery systems, cellular augmentation, and probes to highlight a handful of uses. However, these particles across application often come into contact with lipid membranes and can interact with the berries in a verity of ways. Nanoparticles (NPs) have been shown to restructure lipid membranes to penetrate or embed themselves into the lipids spontaneously. How they are achieved this, and the effectiveness of these NP relies on an on a variety of tunable factors. These elements have been studied in detail, allowing for the ability to design one's nanomaterial not only to accomplish its task but to predict its interaction with the membranes in question[1]. This article will introduce the elements that determine different lipid interactions, primarily focusing on NPs spontaneous passage through the membrane along with modeling tools to predict interactions. NPs can use cellular channels or adhere to membranes; however, these prove too large a topic to cover though information can be found [2, 3]. However, there are still other ways to approach the topic of NP interaction with cell membranes, or model membranes. I have chosen here to explore a central concept of spontaneous penetration and the surrounding concept that supports this interaction and its study. With the ever-growing field and applications of NPs, their involvement and our exposures to them in our everyday life bring concerns of toxicity which is often a focus of NP membrane interactions and how best to disperse the embedded or passage of the NP across the membranes. [4-7].

### A Brief Understanding of Functionalized Nanoparticles

One fundamental concept of most applications of NPs is that they are functionalized by an introduction of impurity that often disrupts its natural shape, charge, size, etc. For example, if you were to functionalize a single-walled carbon nanotube (SWNT), you would decorate it with another polymer, i.e., DNA, Pd, etc. In this example, the functionalizing unit can either completely or partially associate with the core SWNT. This is only one, rather, specific case example of functionalization of SWNT particles. However, many other types of NP can be functionalized for a variety of means and can be explored in more depth across a variety of topic applications from imaging, medical, and living plant systems [4-7].

### Spontaneous Penetration and Assembly in and Through Membranes

NPs can spontaneously move through bio-lipid double membranes, however, due to their particle material, size, shape, surface, charge, corona, and other factors the efficiencies and how they remodel the membranes can vary (fig 1B) [1, 8]. NPs can move fully through the membrane or get trapped/ encapsulated, wrapped while passing or translocated through gaps, all based on the characteristics of the particle in question and can be predicted. Through this process, the NPs can also form pores in a variety of ways (Fig 1A). Below we will explore how these physical properties change the relationship of the passive spontaneous passage of NPs across both biological and model membranes. However, the physical properties of the particle are not the only factors to be considered as the environment, and the membrane characteristics itself need to be considered. In this page, we will focus on the particle characteristics governing the relationship with membrane penetration; however, for a more holistic overview of this topic refer to the following citation [9].

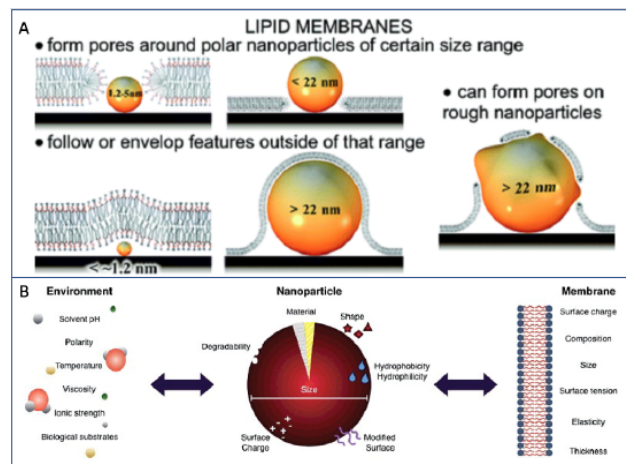


Figure 4.5.1. Figure taken from [10]. A. Nanoscale range of surface feature curvatures where lipid membranes lose integrity and form pores has been found experimentally. The pores were experimentally observed in the 1- $\alpha$ -dimyristoyl phosphatidylcholine membrane around 1.2–22 nm polar nanoparticles deposited on mica surface. Lipid bilayer envelops or closely follows surface features with the curvatures outside of that region. This finding provides essential information for the understanding of nanoparticle–lipid membrane interaction, cytotoxicity, preparation of biomolecular templates and supported lipid membranes on rough and patterned surfaces. Properties that influence NP-membrane interaction. The intrinsic characteristics of a NP, the surrounding environment and the biological substrate that influences the interaction between NPs and biological membranes[9].

### Wrapping Translocation Vs Embedding

NP can pass through or embed in membranes in two different ways. One method is when the membranes bend to maximize the number of contact interaction with the NP; this is called wrapping and induces positive curvature[11]. The head groups of the membrane form vesicles around the nanoparticle and depending on the charge can become stuck to the outer surface of the NP, discussed further below. Wrapping resembles an absorption process. This is fundamentally different than particles that become embedded as the embedding process has minimal disruption to the membrane structure in contrast to wrapping.

Using modeling prediction with informed biological studies researches can understand the impact of the size of the NP on the lipids. Hydrophilic NPs of 20Å become wrapped while those smaller and closer to 10Å become embedded in the bilayer interacting with the hydrophilic headgroups as it is encapsulated as shown in Figure 4.5.2a. Hydrophobic NP regardless of their size even up to 60Å, do not become wrapped by the lipids and instead penetrate the membranes to embed into the hydrophobic core (fig 2 c) [12]. However, here they have only modeled one type of membrane, and as tunable, the NPs can be it has also been shown that lipid head groups and tail lengths play a significant role in the interactions of the two [11]. In the case of wrapping passages, the strength of the head groups wrapping ability and connection was shown to be inhibited by hydrophobic interactions of longer hydrophilic PEG chains allowing the NP to more easily pass through the rapping and come out the other side of the membrane. Because the NP is disordering the membranes upon entering the leaflets, the wrappings positive curvature can be modulated by the length of overhanging tails of the functionalizing unit along the NPs. The overall shape of these structures, i.e., rod vs. spherical, can also play a role in how they pass through the membranes[11, 13].

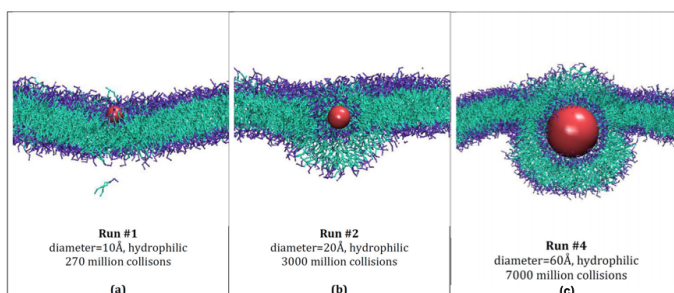


Figure 4.5.2. Adapted Figure from [7]. Snapshots of final configurations for simulations run on LIME systems containing hydrophilic NPs of different sizes and a DPPC bilayer membrane. The color scheme is purple (DPPC choline entity), orange (DPPC phosphate group), red (DPPC ester groups), cyan (DPPC alkyl tail groups), red (NPs). Also See Figure 4.5.6 for shape dependence [13]

### Charges Can Lead to Membrane Reconstruction

It has been shown that NPs can pass through phospholipid membranes spontaneously, which is one of the many factors making them ideal for drug delivery and sensor creation. NPs can only pass through phospholipid membranes spontaneously when they are charged either in the positive or negative direction (fig. 3). Where the negatively charged particles elicit local gelation in otherwise fluid bilayers while positively charged particles gain passage by targeting gelled membranes to fluidize locally[8]. These charges cause phase transitions that deviate from nominal phase transition temperature by tens of degrees but were shown across lipid types DOPC (dioleoyl phosphocholine (PC)), DLPC (dilauryl PC), and DPPC (dipalmitoyl PC), with differing gel-to-fluid phase transition temperature ( $T_m$ ) of approximately  $-20\text{ }^{\circ}\text{C}$ ,  $-1\text{ }^{\circ}\text{C}$ , and  $+40\text{ }^{\circ}\text{C}$ , respectively. Both charges absorbed to the PC group of phospholipids and showed that the liposomes penetrated by the NPs could maintain their integrity with minimal shrinkage by the negatively charged NPs. The physical rigidity of these particles is thought to allow for this unique interaction with the phospholipid membranes, whereas DNA, an Anionic particle, does not elicit the same membrane reconstruction as similarly charged anionic NPs[8]. This phenomenon is novel in the fact that a foreign nonbiological object has caused these alterations as the membranes are often passing through these different states to allow ions and natural membrane remodeling to occur. Coupled with the fact that this process is not classified as endocytosis but a passage through the membranes when disruptions as lipids bind to the particle itself (fig. 4)

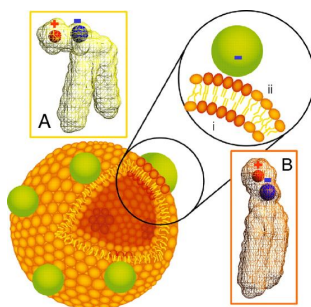


Figure 4.5.3. Taken from [8]. Schematic diagram of a phospholipid bilayer vesicle with bound NP. Binding of anionic NPs to a leaflet in the fluid phase causes the NP to template a gel phase in the place where the NPs binds. Binding-induced reorientation of the PC head group causes lipids in the fluid phase to have a lower density (A) than in the gel phase (B). In the PC head group,  $P^-$  and  $N^+$  are denoted by blue and red, respectively.

This phenomenon has also been characterized in plants with a verity of different NPs. Here the Lipid Exchange Envelope Penetration or “LEEP” model show that the cargo the particles are doped with can have an effect on spontaneous penetration and localization within the cell down to single organellar, such as the chloroplast[14, 15]. In Figure 4.5.4 Shows the ability to penetrate the cell and internal compartments based off of the charge as illustrated through zeta potential (the energy difference existing between the surface of a solid particle immersed in a conducting liquid (e.g. water) and the bulk of the liquid) to take into account the aqueous environment that is the cell. As stated above in A Brief Understanding of Functionalized Nanoparticles the doping or cargo of a particle can have a significant effect on the dynamics of the particles in regards to shape, size, charge, and other vital characteristics.

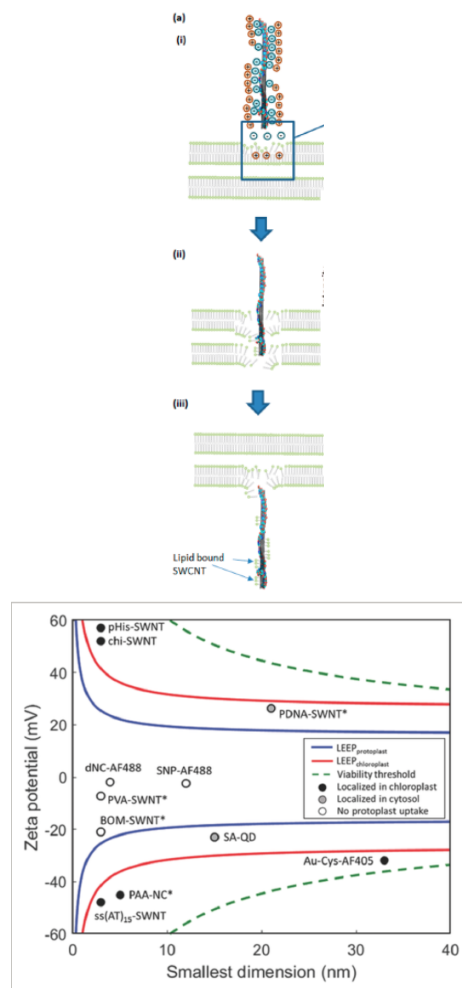


Figure 4.5.4. Adapted from [14,15]. A. (i) SWNT NP with high zeta potential approach the outer membrane that is similarly negatively charged. This induces image charges on the lipid bilayer and leads to membrane expansion and softening. (ii) Glycerolipids wrap around SWNT as they interact with the membrane. Interaction between lipids and SWNT is confirmed by the solvchromatic shift observed upon addition of dipalmitoylphosphatidylcholine (DPPC) to SWNT. (iii) The lipid-bound SWNT enters and binds to the interior. The lipid membrane of the membrane heals. B. LEEP model explains the entry and distribution of NPs inside protoplasts. LEEP model for protoplasts and chloroplasts are indicated by blue and red lines, respectively, while the threshold to maintain protoplast viability is shown by the dashed green lines. The LEEP model can not only explain the experimental observations in this study, but also NPs investigated in previous studies (denoted by \*).

### Models Used for Prediction

There is an ever-growing library of different types of NP polymers functionalized with a verity of differing decorations all influencing the overall characteristics of the NP as a whole. It would be impossible to test the viability and dynamics of all different polymers that can be created with the different combinations of backbones and decorations. Therefore, many modules have been created to predict and simulate their dynamics based on the information gathered by the portion of the library studied both in vivo and in vitro[12]. The models used for prediction of the type of interaction can fall into two types of categories, High- resolution or atomistic and low resolution or coarse-grained models giving different perspectives and output times on the information. See Table 1 for a summary.

High- resolution or atomistic models can give a representative picture of the geometry and energetics of all the molecules that are typically accounted for in the motion of every atom, including every solvent atom. These are often used to study the passive transport of NP through lipid membranes. One such study was conducted by Bedrov et al. to understand the passive motion of C60fullerenes into lipid di-myristoly-phosphatidylcholine (DMPC)[16].

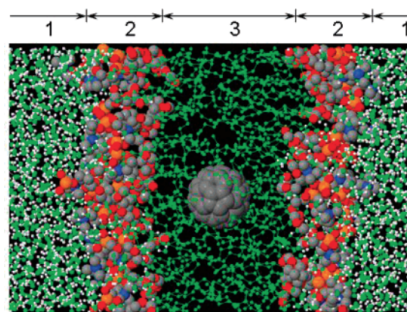


Figure 4.5.6. Adapted from [16]. Illustrated is the system configuration with a snapshot of the hydrated DMPC membrane containing a C60 fullerene and illustrates three well-defined regions: (1) bulk water outside of lipid bilayer, (2) dense layer of lipid hydrophilic head groups, and (3) hydrophobic region of lipidic tails. Hydrogen atoms associated with lipid tail are not shown. Fullerene carbon atoms are shown in dark gray, water oxygen atoms in green, and hydrogen atoms in white. In the DMPC molecule: tail backbone carbon atoms are dark lime, nitrogens dark blue, phosphorus atoms orange, and oxygen atoms red.

Low resolution or coarse-grained models still account for both the lipids and NP but are a simplified representation of the molecular geometry and energies. Here instead of taking into account the whole system, a single interaction site is used to represent a group of several atoms. Because of this, the seed of the calculation is quicker as the total number of sites is decreased. Again, passive transport can be studied using this model type. In one informative biological study, the passive endocytosis of ligand-coated NP was studied based on different geometries of size, shape coverage, and membrane-binding strength [13]. The phospholipid molecules were modeled by three spheres; one for the hydrophilic head group, and two for the hydrophobic tails. Similarly, the NP was simply expressed as spheres of the same size as the tail groups. Though simplistic, the group was able to show that the model was sufficient enough to show that larger spherical particles endocytosis easier than smaller particles as a result of favorable energies for bending rigidity and surface adhesion while also illustrating the favorable energies for spherocylindrical NP to normal spherical particles.

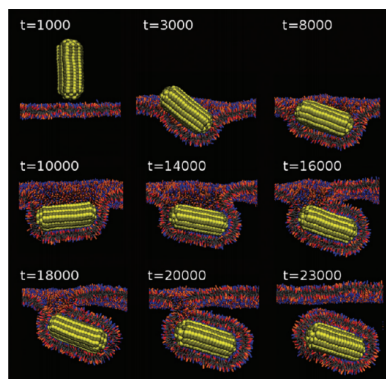


Figure 4.5.6. Taken from [13] A representation of the generated model of spherocylinder endocytosis. The spherocylinder is initially oriented perpendicular to the membrane. It changes orientation and becomes parallel upon binding to the membrane ( $t = 10\,000$ ); then it rotates and gets encapsulated further. Detachment from the membrane takes place at the end of spherocylinder. The particle surface is composed of 50% of ligands that interact by 5.0 kT with 50% of lipid headgroups representing membrane receptors. A cut through the membrane at the particle position is depicted for clarity. Color coding: nanoparticle, yellow beads are ligands and gray beads are purely repulsive; membrane, blue beads are membrane receptors, orange are headgroups, and gray and orange are tail beads.

Recently an intermediate- resolution model has been developed for describing the implicit-solvent for lipid molecules or LIME[12]. A boon of this is a better resolution than a true coarse-grained model but also more time efficient than an atomic high-resolution models' prediction. The increase in speed is due to the use of discontinuous molecular dynamics. So far, this model has been used to capture the interaction between the hydrophilic and hydrophobic NPs and DPPC bilayer membranes, taking into account both the membrane and the NPS geometric and energetic parameters. However, like the other model types, there are drawbacks. Figure 4.5.2 is generated using the LIME model.

Table 1.

	Advantages	Disadvantages	Common uses
High resolution / atomistic models	<ul style="list-style-type: none"> <li>Visualization of geometry and energetics of all the molecules</li> <li>motion of every atom captured</li> <li>solvent atom dynamics</li> <li>account the whole system</li> </ul>	<ul style="list-style-type: none"> <li>Takes a lot of computing power</li> <li>Long output time</li> <li>Cannot examine large conformational changes</li> </ul>	<ul style="list-style-type: none"> <li>study the passive transport of NP through lipid membranes.</li> <li>Bedrov et al. [16]</li> </ul>
Low resolution/ coarse-grained	<ul style="list-style-type: none"> <li>Accounts a single interaction site</li> <li>Fast output time</li> <li>Less computing power needed</li> </ul>	<ul style="list-style-type: none"> <li>simplified representation of both lipids and NP</li> </ul>	<ul style="list-style-type: none"> <li>Particles endocytosis</li> <li>Passive transport</li> <li>Vacha, R., F.J. Martinez-Veracoechea, and D. Frenkel, [13]</li> </ul>
Intermediate-resolution / LIME	<ul style="list-style-type: none"> <li>Better resolution than a true coarse-grained</li> <li>More time efficient than an atomic high-resolution</li> </ul>	<ul style="list-style-type: none"> <li>Discontinuous molecular dynamics</li> <li>Electrostatics is not represented explicitly</li> <li>Diffusion and hydrodynamics are not well represented</li> <li>A direct correlation between reduced temperature and real temperature can only be made at which LIME was parameterized</li> </ul>	<ul style="list-style-type: none"> <li>Capture the interaction between the hydrophilic and hydrophobic NPs and Membranes</li> <li>Curtis, E.M., et al., [12]</li> </ul>

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