Description for a problem studied at the UK Mathematics-in-Medicine Study Group Reading 2011
< http://www.maths-in-medicine.org/uk/2011/nanoparticles/ >

How do Manufactured Nanoparticles Enter Cells?

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Summary: The ever increasing production and use of manufactured nanoparticles in industry, research and medicine, has led to greater potential for incidental environmental exposure, as well as deliberate contact through products and therapeutics (1). However, the potential for cellular entry and toxicity of manufactured nanoparticles has only recently begun to be investigated. The extent of potential cellular affects following nanoparticle exposure would depend upon environmental conditions, cell type, nanoparticle dosage, composition, size, shape and surface chemistry. However, very little work in the field of mathematical modelling has been focused on the question of how manufactured nanoparticles enter cells. That being said, within each potential mechanism for cellular entry of nanoparticles there has been considerable quantitative analysis of the relevant pathways. Therefore, this represents a timely and "open" question which can be firmly grounded in previous analyses but for which no comparable overall models have been generated thus far.

Potential mechanisms of entry: The cell is bound by the plasma membrane, a lipid bilayer which contains opposing monolayers, or leaflets, of phospholipids with the hydrophilic head groups facing the extracellular and intracellular solutions, and the hydrophobic tails facing each other (Figure 1). Generally speaking three routes for nanoparticle entry into cells exist, each of which must be analysed independently before a comprehensive model can be formed (Figure 2).

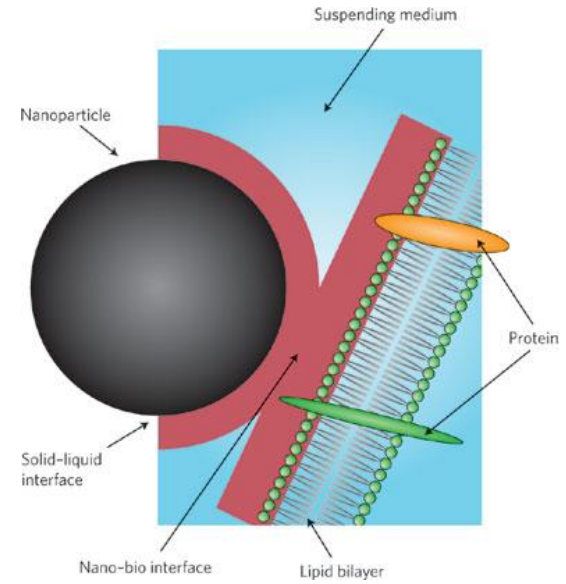

Figure 1. Representation of the interface between a nanoparticle and a lipid bilayer. (Figure and legend taken from Reference 3)

Mechanism 1: Direct diffusion of nanoparticles across the plasma membrane can occur and has been described in certain situations (2). Numerous variables could affect the ability of a nanoparticle to penetrate the lipid bilayer including size, charge, hydrophobicity, composition and shape. Furthermore, these parameters need to be considered within the different physical spaces involved, including the nanoparticle surface, the solid-liquid interface, and the nano-bio interface (3). This analysis would also need to include characterisation of the biological membrane including the lipid composition, fluidity and identities of membrane bound molecular species.

Importantly, some molecular dynamic simulations have already been generated to describe the potential diffusion of specific types of nanoparticles across biological membranes which could serve as a very useful starting point in further modelling of this process (4).

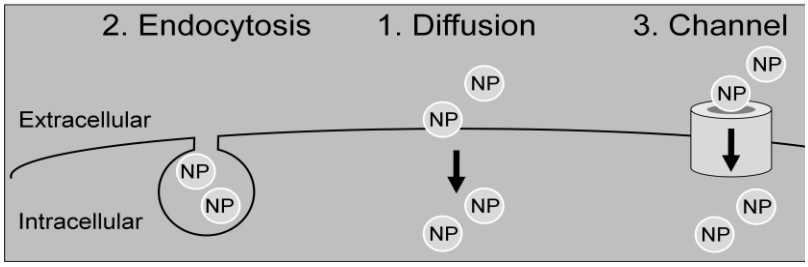

Figure 2. Potential mechanisms of nanoparticle entry into cells.

Mechanism 2: The second potential mechanism of nanoparticle entry is “endocytosis”. This involves wrapping the lipid bilayer around cargo substances that are being internalised. Subsequently a “fission” reaction occurs which pinches off a “vesicle”, a small membrane bound compartment, containing the cargo, permitting entry into the cell. Different endocytosis pathways exist and significant data suggests that nanoparticles can enter cells via this mechanism (5). Already, the data obtained in this relatively new field point to differences in potential for cellular uptake and mechanisms of endocytosis depending upon physical parameters (e.g. size) of the nanoparticles analysed (5). Endocytosis can either be “fluid phase” or “receptor mediated”. In the former water soluble substances diffuse into forming vesicles and enter through mass action, while in the latter cargo for endocytosis bind to a component of the cell surface which will in turn be internalised carrying the substrate along into the cell. The “receptor” can be a cargo specific membrane protein, or it can simply be any lipid, protein or carbohydrate entity to which cargo binds, and will undergo endocytosis.

Mechanism 3: Numerous ion channels and transporter proteins reside in the plasma membrane and function to mediate the translocation of specific substances into or out of the cell. These aqueous pores can permit rapid flux of molecules across the plasma membrane. However, the generally high level of selectivity, low open probability and extremely small average pore size (e.g. a few Angstrom units) suggest that for all but the smallest nanoparticles this potential pathway can most likely be disregarded.

Summary of current experiments: The focus on our work in this area is to determine the routes of nanoparticle entry into various model cell lines (e.g. cancer, pulmonary, neuronal). In particular we are focusing on the first two potential mechanisms for nanoparticle entry and are employing polystyrene beads as a model nanoparticle. One hypothesis we are testing is that at 37° C endocytosis should predominate as the mode of entry, while cooling cells down to 4° C, a temperature that eliminates endocytosis, should reveal the potential for direct diffusion across the plasma membrane. However, we are also developing *in vitro* systems employing synthetic lipid vesicles to test the potential for nanoparticles to pass through model membranes of various compositions at different temperatures. The polystyrene beads we are employing range in size (e.g. 20nm or 200nm) and charge (e.g. carboxylate, negative, or amine, positive, modified). Furthermore we are conjugating coatings to the nanoparticles to eliminate charge and increase hydrophobicity. Finally we are determining differences in cellular entry of nanoparticles depending on the presence/absence of serum proteins. Thus, the combination of previous published analyses and our data should provide rigorous quantitative values which could be employed in model generation.

Questions for the study group: 1) What are the relevant parameters that need to be considered regarding nanoparticle composition and the nano-bio interface? 2) Can a model for diffusion of nanoparticles across the plasma membrane be generated that is robust enough to account for all potential variables? 3) Can a model of nanoparticle endocytosis be generated that includes all potential trafficking pathways? 4) Can nanoparticle entry through plasma membrane channels and transporters truly be excluded? 5) Can an integrated model describing all potential means of nanoparticle entry into cells be produced?

References:

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