ABSTRACT

Title of Dissertation: BILAYER MEMBRANE ELECTROSTATICS AND CHARGE-REGULATED MEMBRANE-NANOPARTICLE INTERACTIONS

Shayandev Sinha

Dissertation directed by: Dr. Siddhartha Das
Department of Mechanical Engineering

Nanoparticle (NP) driven targeted drug delivery and NP driven imaging of cells, tumors etc. have been one of the most investigated areas in interfacial and biomedical engineering in recent years involving a massive amount interdisciplinary efforts cutting across disciplines like physics, chemistry, material science, biology, pharmaceutics, and engineering. Drug delivery or imaging with the NPs invariably require the NPs to first adhere to the surface of a cell, which is bound by a cell membrane (also known as plasma membrane or PM). All of these processes occur in an electrolyte medium as the fluids present inside and outside the cell have ions inside them. There have been significant amount of studies on adhesion of nanoparticles but until today, there has been very less number of investigations on the role of the ionic environment on such systems of adhesion. The ions present in the intracellular and the extracellular space produce an electric double layer (EDL) on both sides of the PM. The PM is also a semipermeable membrane i.e it does not let all kinds of ions to pass through it. The moieties that it lets to pass through it is completely dependent on the ion channels present across it and such semi-permeable action dictates the ion distribution around the PM, which in turn would regulate the NP-PM interactions.

The main aim of this dissertation is to look into the influence of this ionic environment and the role that it can play on adhesion of NPs. In order to look deeply we first look into the electrostatics of the PMs. We develop a continuum model to investigate the role of the ionic environment or the EDL on the electrostatics present across the membrane. This investigation led us to a very important aspect of membrane electrostatics. We found out charge-inversion (CI) like characteristics on the cytosol side (fluids present inside the cell) of the membrane. There has been no previous reports of such CI like characteristics in either the PM electrostatics or more importantly, in a system consisting of only monovalent electrolyte ions (as is the case we consider). In the next step, we looked into the role of the the surface charge density of the membrane and the concentration of the ions in influencing this PM electrostatics. This led to more interesting results. We found out that for biologically relevant conditions and for standard membrane surface charges, there is a possibility of having the location of CI on the surface of the membrane itself. This is a most remarkable result establishing a positive zeta potential on the surface of the negatively charged PM and we explored the phase-space where such situation of opposite signs of membrane zeta potential and membrane surface charge persists.

This electrostatics definitely influences various measurable properties of the membrane. One such very important measurable property of a membrane is the membrane capacitance. It has been widely reported that the ionic environment does not influence the capacitance much. However, with exploration of this phase-space through our continuum simulations we were able to pinpoint a domain where the capacitance can be influenced by as much as 15%. This also stems from the fact that the electrostatics of the system is itself very interesting to study under various conditions.

We then move on to explore the effect of this electrostatics on the adhesion of NP on

the membranes. Most of these adhesive processes occur through the receptor-ligand (R-L) mechanism. Therefore, until and unless a ligand is able to physically influence a receptor and can get bonded to it, the process of adhesion will never begin. The electrostatics can cause a hindrance to this phenomenon. The main reason is the electrostatic osmotic or disjoining pressure, which causes a repulsion between the ligand-bearing NP and the receptor-bearing cell membrane, and forbids the NP to come to significant proximity of the PM for ensuring that the ligands start to interact with the receptors. Through our analysis, we calculated such repulsion and calculated the distance up to which this repulsion remains strong and can overcome the influence of other attractive effects (e.g., van der Waals forces or thermal forces) that drive the NP closer to the PM. We hypothesize that if the length of the ligand-receptor complex is not larger than this distance up to which the electrostatic repulsion effects remain dominant then the process of adhesion will not even begin.

Next, we study what is the role of this ionic environment for the case where the NP adhere to the PMs non-specifically. Such non-specific adhesion (NSA) refers to the adhesion of the NP to the PM by actual physical attachment without involving R-L interactions. Understanding such NSA is vital to gauge the side effects of the NP-based drug delivery – the dug carrying NP will invariably adhere (non-specifically) to the healthy cells causing damages to the healthy cells. Therefore the current practice necessitates uses of those NPs that demonstrate least cytotoxicity post adhesion and internalization in healthy cells. We show that when metallic NPs non-specifically adhere to the PMs, the resulting destruction of the surface charge effects of PMs would lead to a favorable energy change, which in turn drives the NP NSA to even stiffer membranes (e.g., cell membranes rich in cholesterol).

Subsequently, we show that one can use biomimetic NPs (namely NPs encapsulated in PM-derived lipid bilayers) to ensure that electrostatic interactions between the biomimetic NPs and the PM can usher in the most coveted scenario where one can simultaneously ensure the promotion of specific adhesion and prevention of NSA.

Finally we address the future directions of this work and how this work can start the discussion about the role of other kinds on nanoparticles in drug delivery and therapy.