MOLECULAR DYNAMICS SIMULATION STUDY OF PULMONARY SURFACTANT INTERACTING WITH NANOPARTICLES

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ABSTRACT

Dipalmitoylphosphatidylcholine (DPPC) a phospholipid, is the main component of the lung pulmonary surfactant. Components of pulmonary surfactant including dipalmitoylphosphatidic acid (DPPA), dipalmitoylphosphatidyl ethanolamine (DPPE), dimyristoylphosphatidylcholine (DMPC) and possibly lung pulmonary surfactant proteins are expected to play a significant role in the biological mechanism of defense against quartz cytotoxicity. Interactions of powder crystalline silica with biological systems cause cell damage, inflammation, and apoptosis. Unfortunately, mechanisms involved in these diseases are still unknown. Currently, molecular dynamics (MD) simulation of phospholipid bilayer are widely used to study the physicochemical properties of pure bilayers, composite bilayers, lipid rafts, cellular processes such as signaling and transport, permeation of water. Silica dust particles in the form of quartz (but not kaolin) have been hypothesized to promote pulmonary diseases such as silicosis. An exact mechanism of silica cytotoxicity at the molecular level is still unknown. It is known that silanol groups on crystalline silica are lethal while amorphous silica and silica in phyllosilicates (e.g., kaolinite) cause virtually no long-term adverse effects. Our 5ns MD simulation studies using NAMD of lipid bilayers supported on alpha-quartz (nanoparticles) and kaolinite with explicit water molecules will be presented to understand the physiochemical effects of nanoparticles on pulmonary surfactant.

INTRODUCTION

Lipid Bilayer:
Phospholipids generally refer as building blocks of most of the membranes that consist of glycerol phosphate-containing lipids. A primary function of most
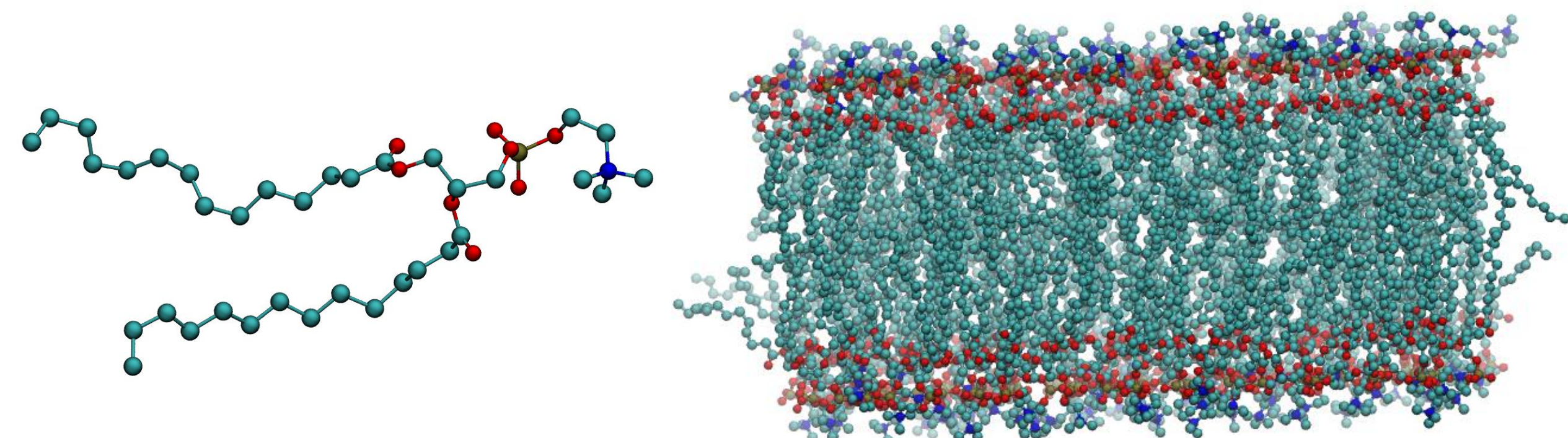
membrane lipids is to provide the permeability barrier of the cell. Lipid membranes have acquired much attention as well, with particular focus on membrane properties, including structural deformation, and electrostatic properties such as the interfacial dipole potential and dielectric constant variation with location in a bilayer. Interaction of these assemblies with synthetic substrates, including nano-structured materials has already exhibited potential in creating new biosynthetic architectures as well as in providing information about cellular responses to the non-biological world.

Quartz Particles:
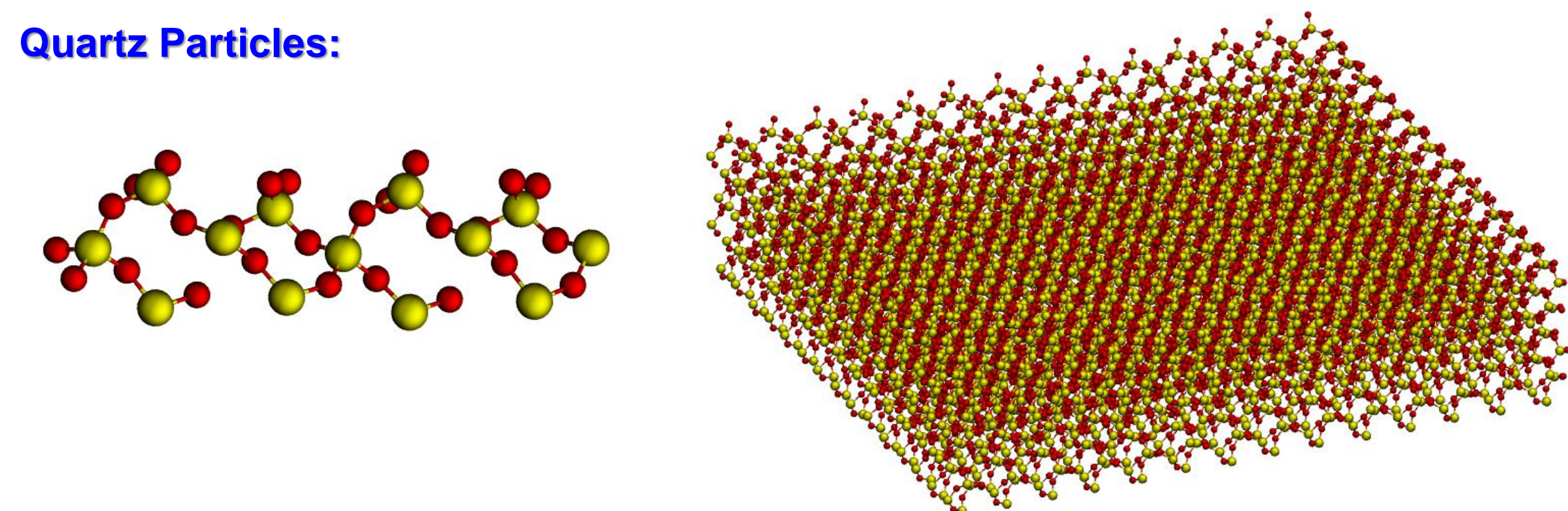
Interactions of pulverized crystalline silica with biological systems, including the lungs, cause cell damage, inflammation, and apoptosis. An exact mechanism of silica cytotoxicity at the molecular level is still unknown. It is known that silanol groups on crystalline silica are lethal. Amorphous silica and silica in phyllosilicates (e.g., kaolinite) cause virtually no long-term adverse effects. Protein function is influenced by specific protein-lipid interactions that are dependent on the chemical and structural features anatomy of lipids (head group, backbone, and alkyl chain length, degree of unsaturation, chirality, ionization and chelating properties). However, protein function is also influenced by the unique self-association properties of lipids that result from the collective properties (fluidity, thickness, shape, and packing properties) of the lipids organized into membrane structures.

Phospholipase A2 (PLA2):
The phospholipase A2 (PLA2) family imparts a well studied example of membrane surface-active enzymes that hydrolyze phospholipids of cell membranes. It therefore provides a good test case for developing computational approaches to understand the interactions of membrane-bound enzyme with the bilayer surface.
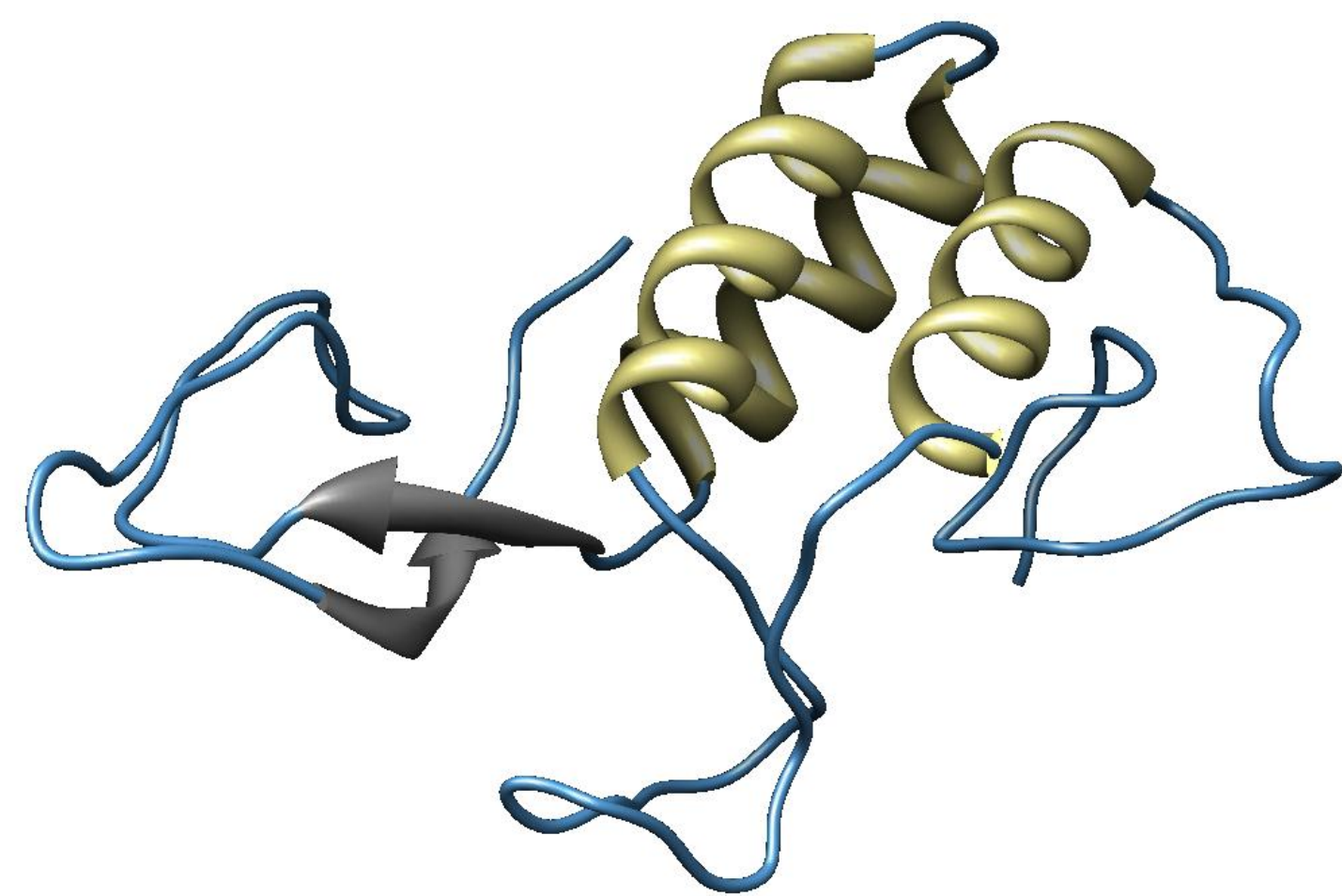

Molecular Dynamics (MD) Simulations:
Molecular dynamics (MD) simulations are widely used as computational tools to study the conformational dynamics of surface proteins and their interactions with lipids. MD protocols discussed in the methodology section were set for the lipid/water system and water/lipid/quartz systems depicted below. The aim of this study was to characterize the structure and dynamics of lipid bilayer with and without quartz particles.
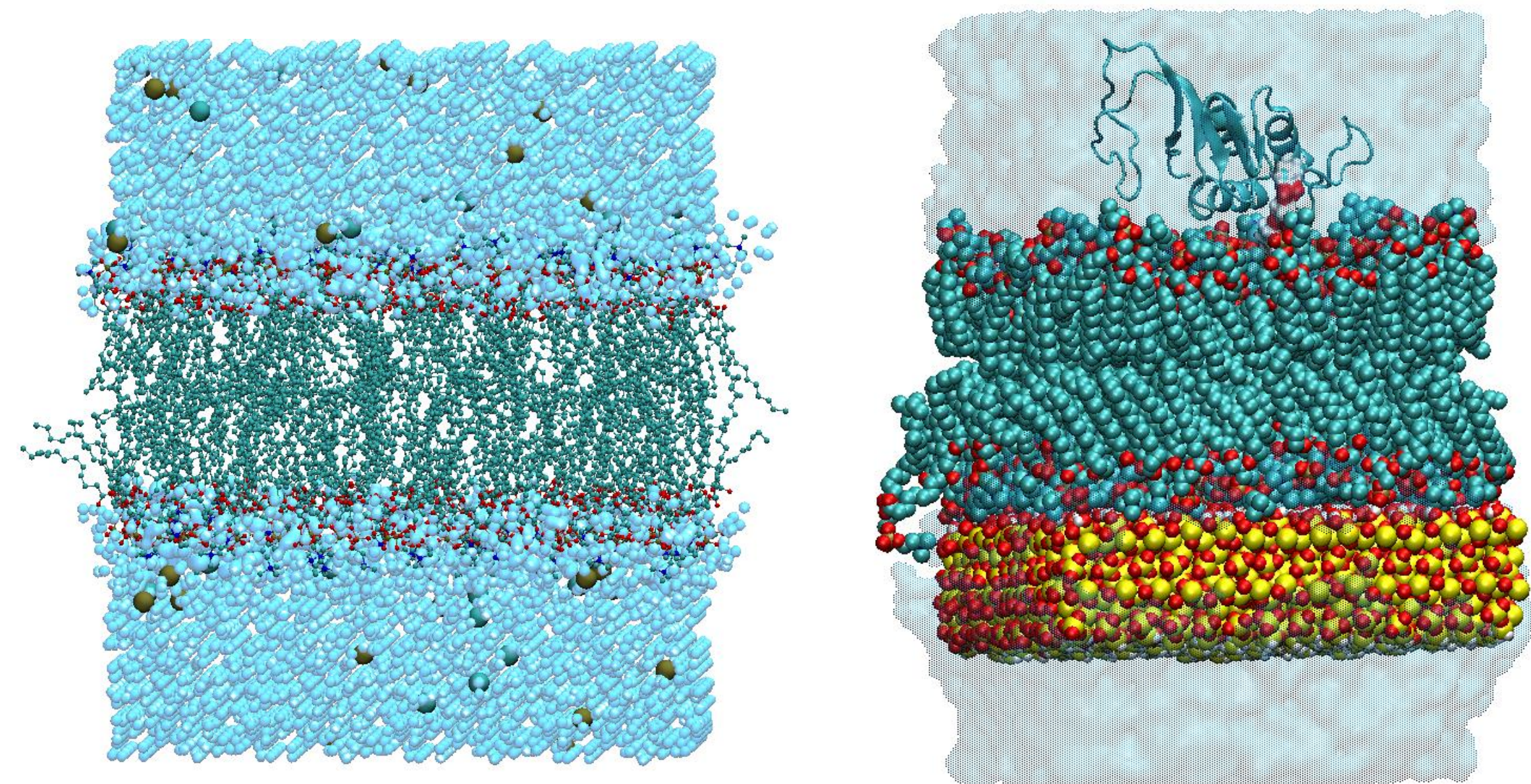
METHODOLOGY

Molecular Dynamics (MD) Simulations was performed by using NAMD and trajectory analysis was carried out by VMD Graphical User Interface (GUI). Simulation protocols involve several steps represented by the flow chart.
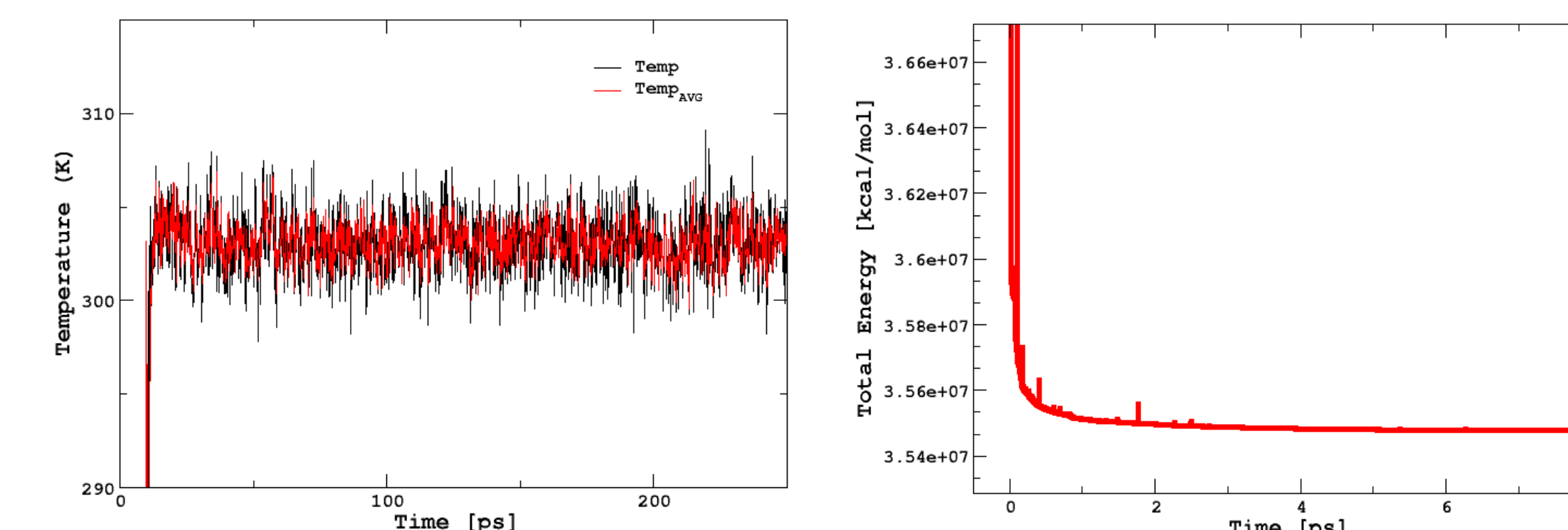
MD Protocols:
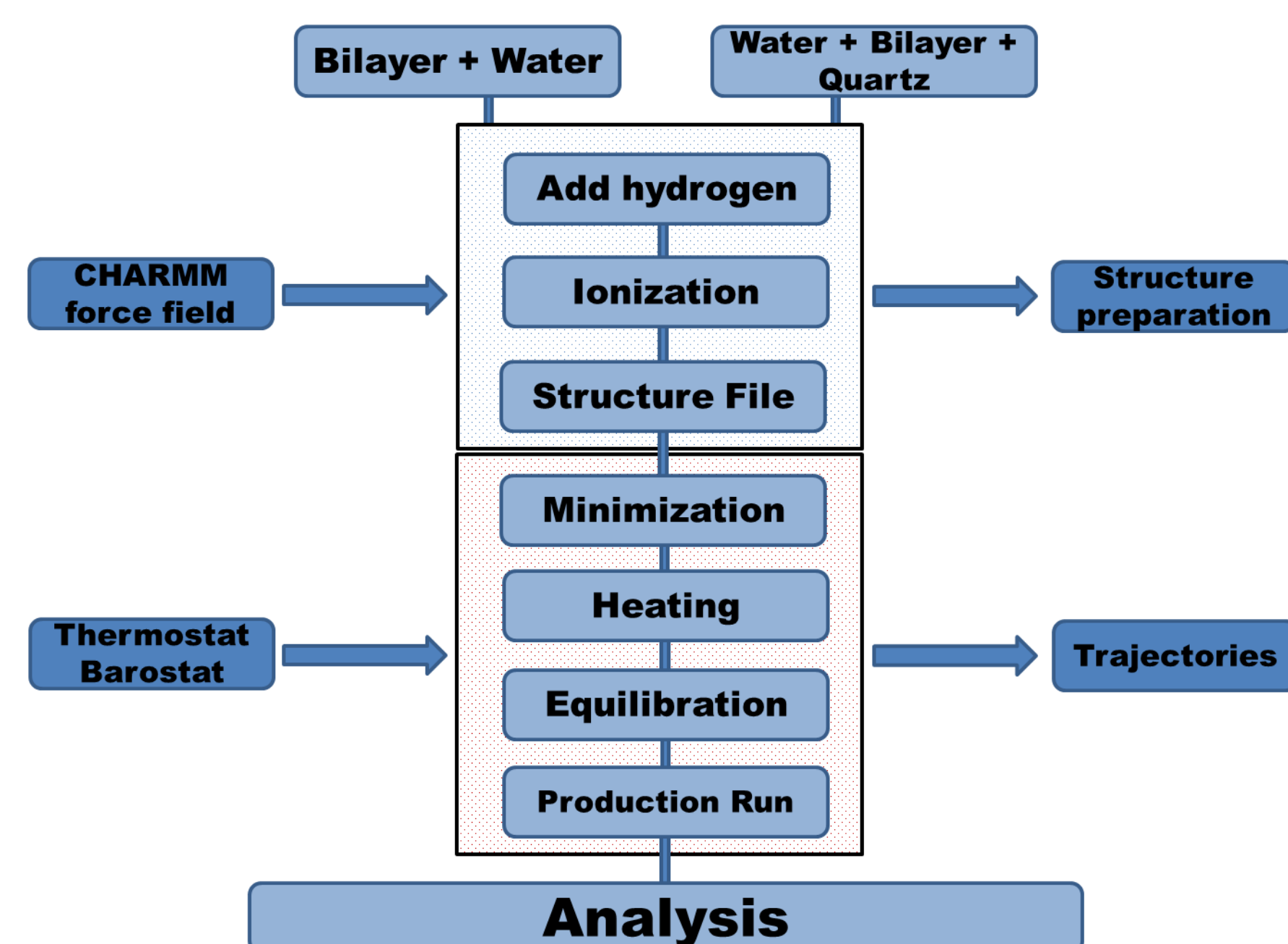
RESULTS & DISCUSSION

Physico-chemical Properties:
Temperature and Total energy of the simulation systems were monitored as a function of time as well as other physico-chemical properties such as pressure, density etc. must be also be monitored to get knowledge about the stability of the simulation.

Structure and Dynamics:
Radial Distribution Function (RDF)
RDF between atoms of head group of bilayer (Nitrogen and Phosphorus) and water molecules as well as between atoms of head group of bilayer and quartz particles will be evaluated.
It is the most fundamental analysis performed to elucidate the structural characteristics of solutions. This property is a dimensionless quantity represented as g_r which gives the probability of finding a particle (an atom or molecule) j at a distance r from another particle i compared to the ideal distribution.

$$g(r_{ij}) = \frac{V}{N_i \cdot N_j} \left\langle \sum_{i=1}^{N_i} \sum_{j=1}^{N_j} \delta(r - ||r_{ij}||) \right\rangle$$

Probability/Angular Distribution Function
Probability distribution function of angle of the lipid head group P–N vector and the vector pointing away from the middle of the bilayer will be plotted. Changing angle of water molecules near the lipid head group are also analyzed, thus, it is helpful to describe effects of quartz interacting with lipid bilayer.

Principal Component Analysis (PCA)
PCA will be performed to explore the correlated motions of group of atoms of lipid bilayer in the presence and absence of quartz particles. PCA can be briefly described as higher frequency fluctuations filtered out by diagonalization of atomic positional fluctuations covariance matrix calculated during the production run, and the corresponding eigen vectors and eigen values are used to describe large amplitude motions.

The elements of the correlation analysis (C_{ij}) are compared as:

$$C_{ij} = \frac{\langle \Delta r_i . \Delta r_j \rangle}{\left(\sqrt{\langle \Delta r_i^2 \rangle} \sqrt{\langle \Delta r_j^2 \rangle} \right)}$$

Where Δr_i is the displacement from the mean position of the ith atom and the $\langle \ \rangle$ represents the limit average over the whole trajectory.

Positive C_{ij} values represent a correlated motion between residues i and j (i.e., the residues move in the same direction).

Negative values of C_{ij} represent an anti-correlated motion between residues i and j (i.e., the residues move in opposite direction).

Cumulative positive and cumulative negative correlations were computed by adding separately the positive and negative terms.

LIMITATIONS

1. The large size of the system consisting of ~67164 atoms require sophisticated computer hardware facilities that render difficulties to run simulation of this size.
2. Presence of high performance computing is therefore, necessary which will definitely help to increase the computing power to study properties such as large bio-macromolecular systems.
3. The cluster computer installed at PCMD has following specifications:

Number of Processors: 60
Number of Nodes: 10 (5 Quad Core and 5 Dual Core)
Memory: 2 GB in each Node
Total Space: 80Gb in each Node

Total simulation time: just 5 ns

FUTURE DIRECTIONS

Other information related to dynamics of lipid bilayer will also be explored:

Lipid mobility will also be computed from mean square displacement (MSD) of the lipid center of mass projected into the x-y plane, the plane of the bilayer surface.

Water dynamics: Diffusion coefficient for water will also be calculated to explore the dynamics of solvent.

Free energy calculations associated with removing a phospholipid molecule from the top leaflet of the bilayer by using employing potential of mean force.

CONCLUDING REMARKS

In short, we propose to develop and explore computational models to study silica pulmonary cytotoxicity which is due to the interaction of lung pulmonary surfactant with the mineral particles. We first plan to investigate the influence of a mineral on a lipid bilayer, specifically the bilayer leaflet opposite the mineral surface. The next step will be to study the direct interaction between the mineral surface and the lipid. These first two steps will provide data on the exchange of lipids between the bilayer and solution. The final step is to investigate the degradation of free lipids in the presence of small nanocrystal mineral fragments and compare the results of important interactions between nanosized crystals of silica and kaolinite and a phospholipid head group in the gas phase that we have identified using quantum chemical methods. The results from these calculations will be compared to the hypotheses derived from NMR as well as other experimental data.

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ACKNOWLEDGEMENT