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How Chemical Composition of Nanoparticles Affects the Interactions with Biological Systems

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Effect of Particles on biological systems: Correlations

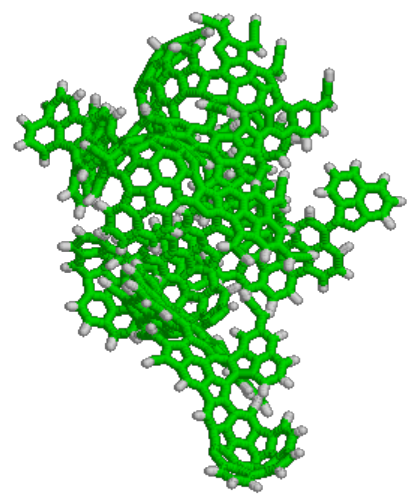
- NP deposition on the epithelial cells:
  - cell activation leading to **inflammation**;
  - production of **cytokines** (proteins) that stimulate the release of fibrinogens, which bind to platelets, contribute to their aggregation, and enhance their ability to clot; and
  - stimulation of **nerve cells** that leads to changes in the nervous system's control of breathing and heart rate. (Oberdörster G., et al. *Environ. Health Perspect*. ; HEI, *Health Effects Institute*, Special Report)

- Experiments show **translocation** of inhaled ^{13}C-carbon particles into the liver following whole body inhalation exposure of rats. (Oberdorster *et al, J. Toxicology and Env. Health)*

Objectives and Approach

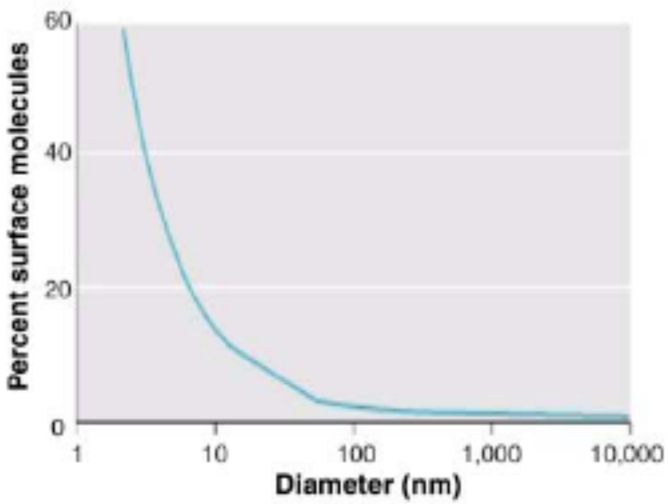
- Identify the molecular mechanisms of interactions of nanoparticles with cells
  - What are the mechanisms of **entry** into cells? Toxic effects depend on the uptake mechanism (differences in fate, i.e., being stored in intracellular vescicle)
  - How chemical and physical properties of nanoparticles affect the interactions?

- Atomistic simulations married to in vitro toxicology and biophysical studies



Characteristics of nanoparticles

- Size – falls in transitional zone between atoms and the corresponding bulk materials.



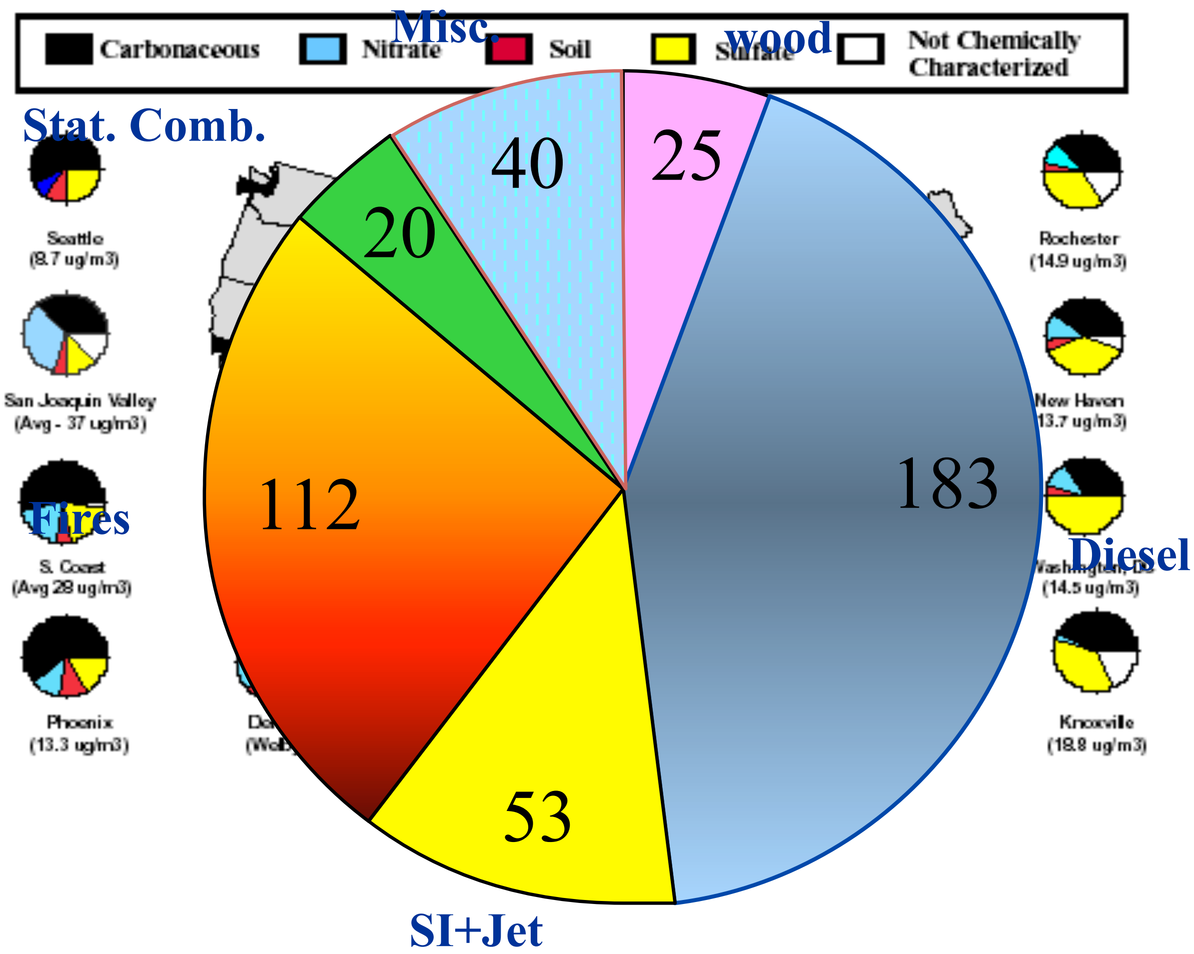
%molecules on surface to the total molecules increases exponentially when diameter decreases in range 1-100nm. *(Oberdorster, 2005)*

Atoms oriented on the surface rather than within the interior of the material.

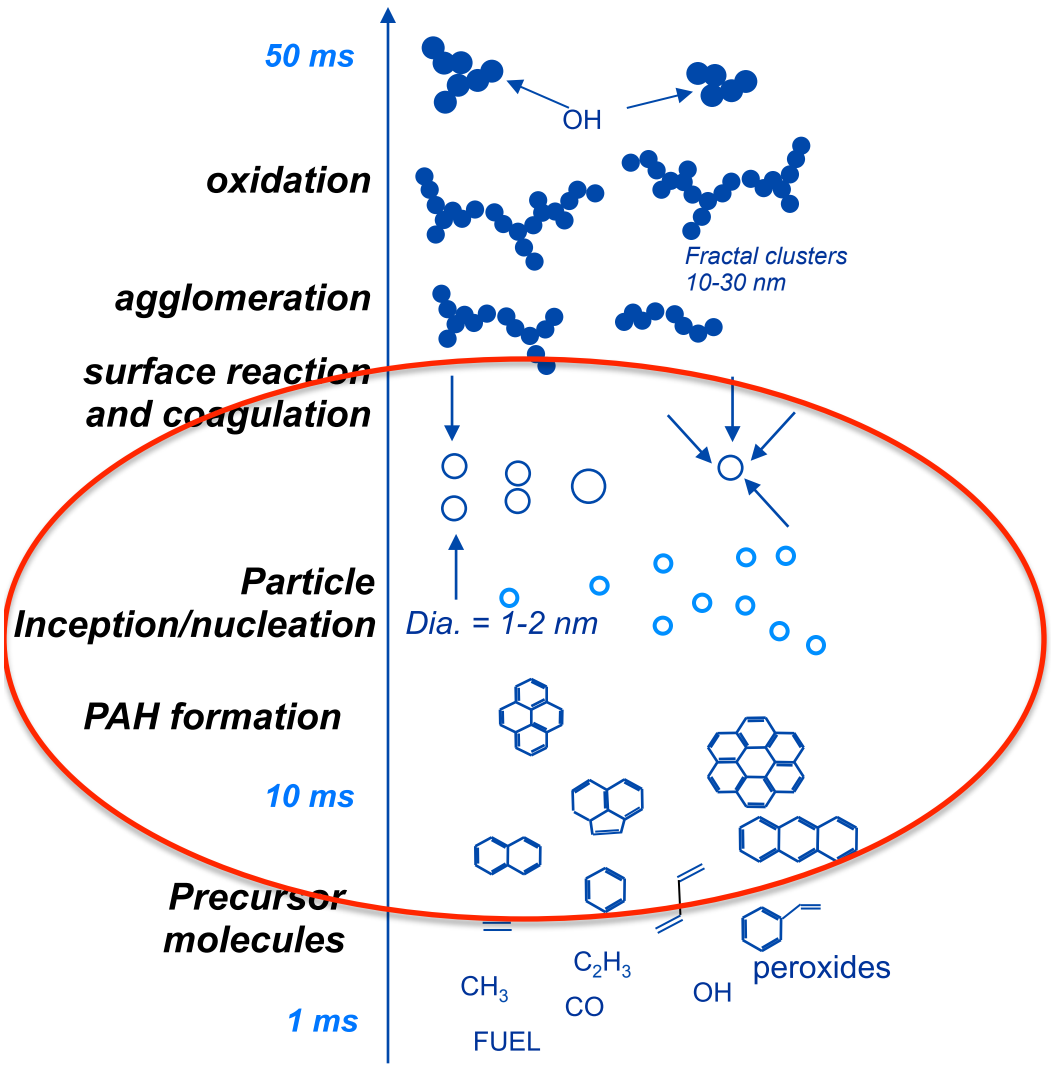
The surface-to-volume ratio determines the potential number of reactive groups.

Enhanced activities could be either beneficial (e.g., antioxidation, carrier capacity for drugs, increased uptake and interaction with biological tissues) or disadvantageous (e.g., toxicity, instability, induction of oxidative stress). Nel et al. 2006

Major classes of particulate matter: Carbonaceous particles dominate (Pace, EPA'05)



From fuels to Soot Particles



Violi et al. 2006

- Currently no accurate capability to predict combustion by-products
- Nanoparticle growth determines soot properties, i.e., morphology and composition.

Nanoparticles: Transition Regime

- **Kinetics of nanoparticles** nucleation control the number of nascent particles and the coagulation of these particles determine the evolution of particle number density.

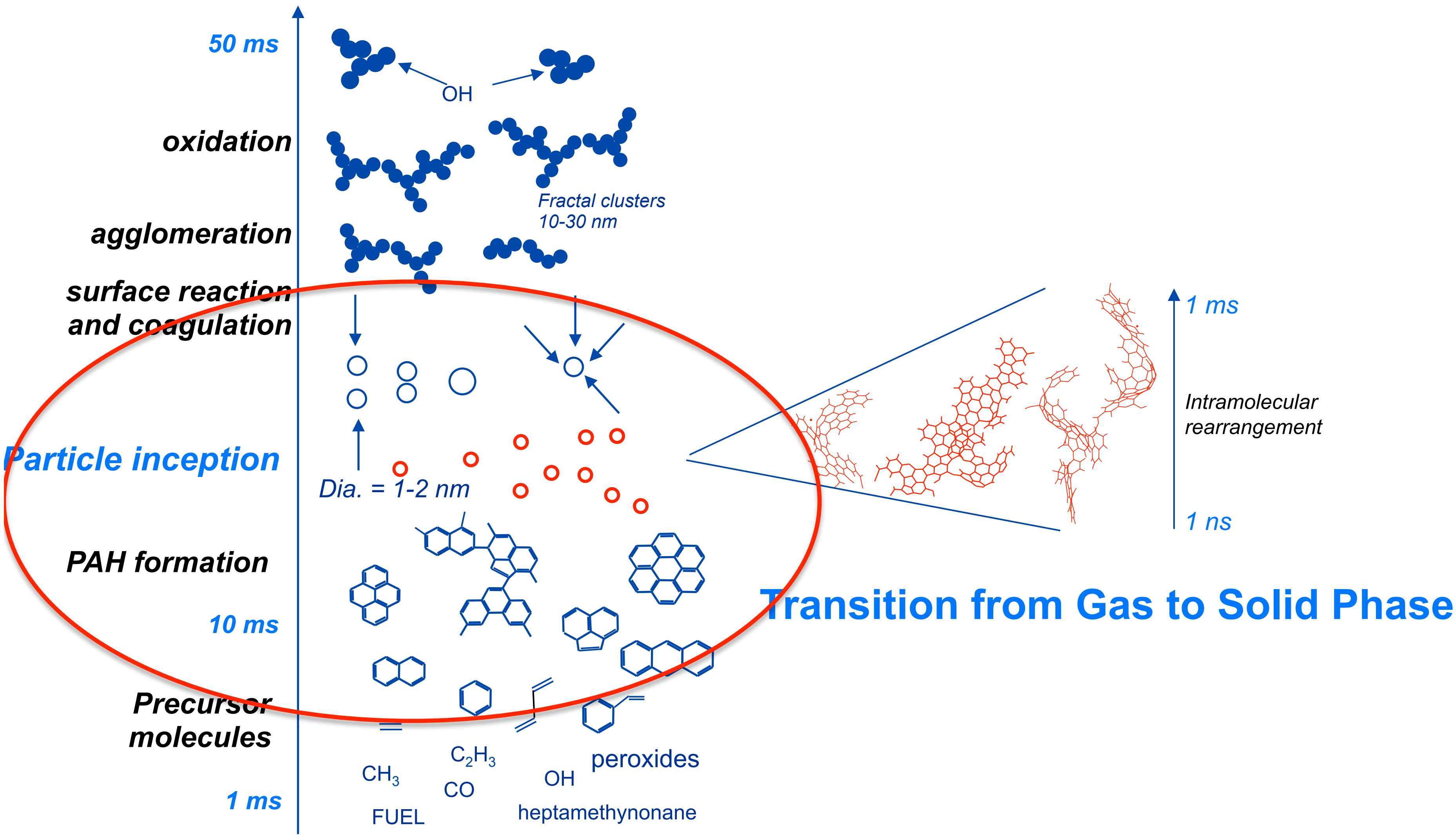
- **Shape** of the particle size distribution function of young and growing soot is highly sensitive to the nucleation rate as well as surface growth.

Why Nanoparticles

- *Importance – emissions, health effects, new materials, etc.*
- Environmental effects related to particle **morphology and composition**
  - Health concerns – amphiphillic character as biological systems
  - Correlation with cellular responses
  - Optical properties for atmospheric interactions

- Future emission regulations will consider these parameters

From few C to agglomerates of millions of C

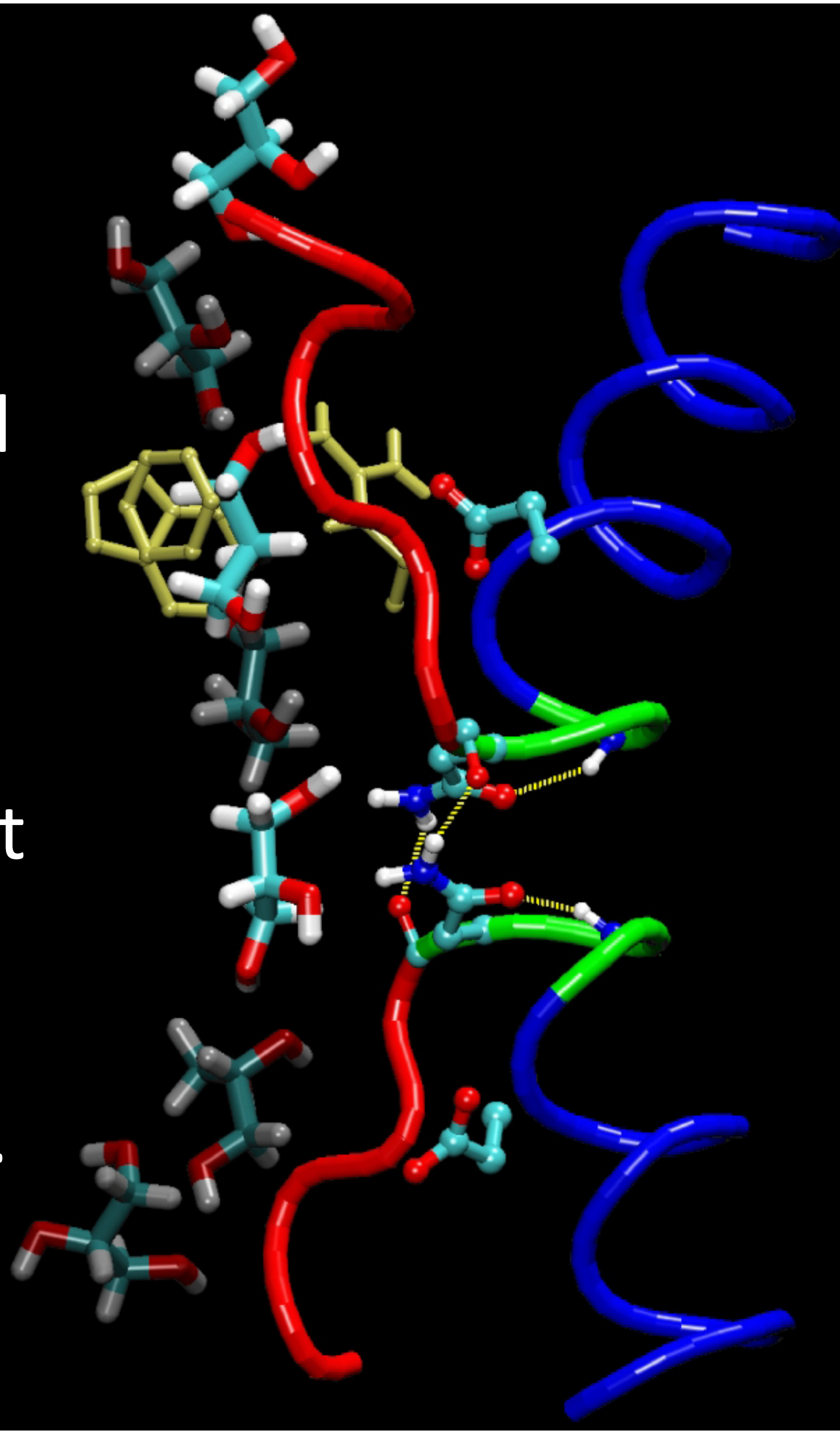


Violi, J. Chem. Theory Comput. 2006

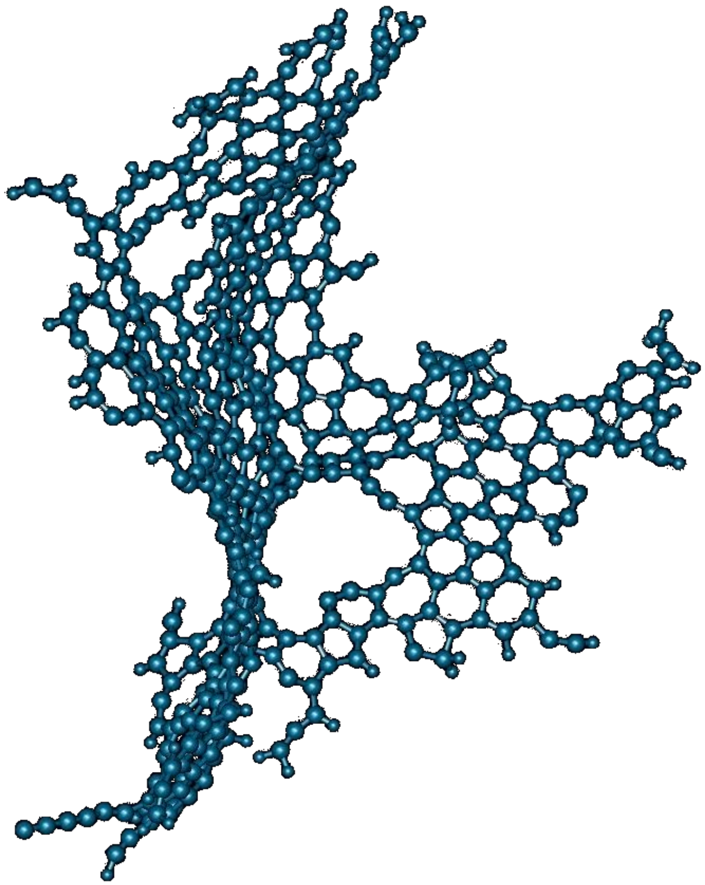
Molecular Dynamics

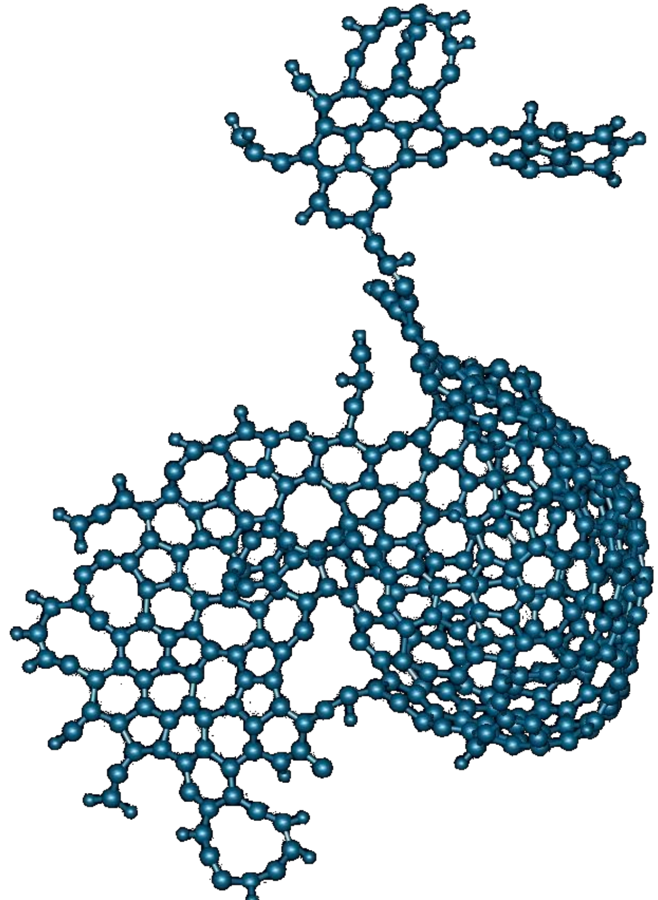
It investigates the physical movement of atoms and molecules.

The time evolution of a set of interacting atoms is followed by integrating their equations of motion.



Different morphologies and chemical compositions

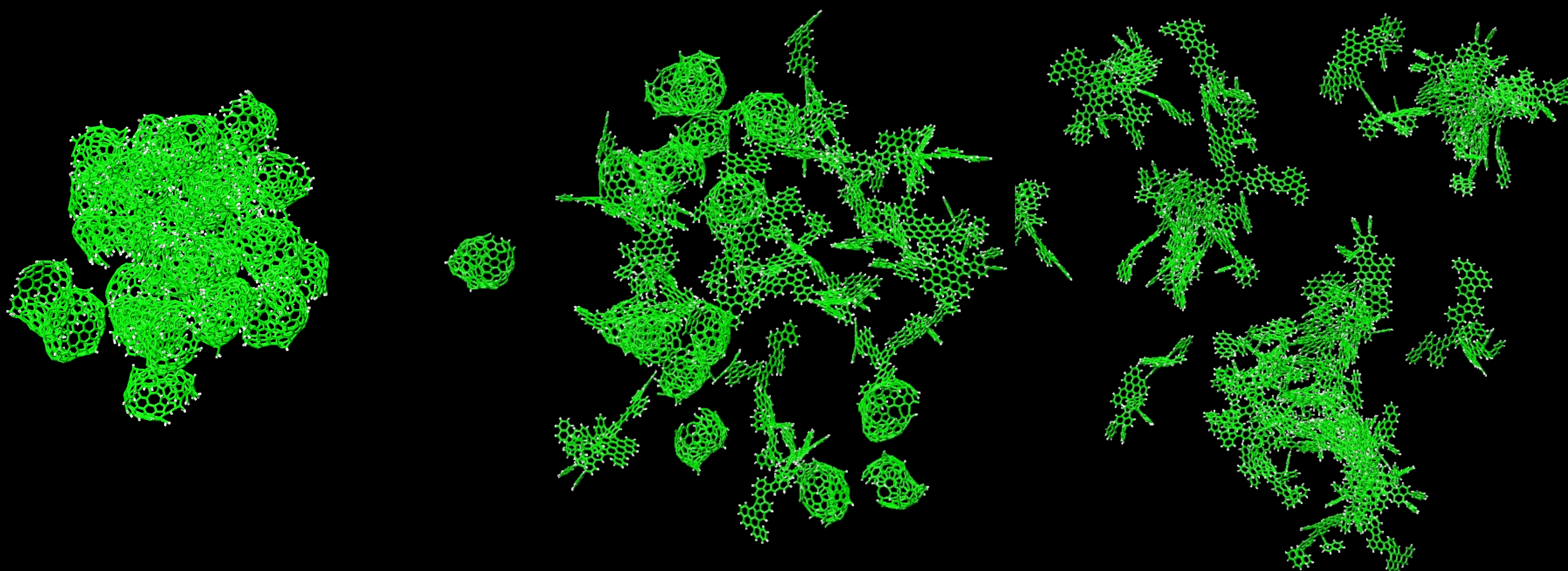




Different fuels lead to particles of different morphology and chemical composition

Chung, Violi J. P.ys. Chem. 2010
Chung, Violi CARBON 2008
Violi and Venkanathan, J. Chem. Phys 2006

Importance of Morphology



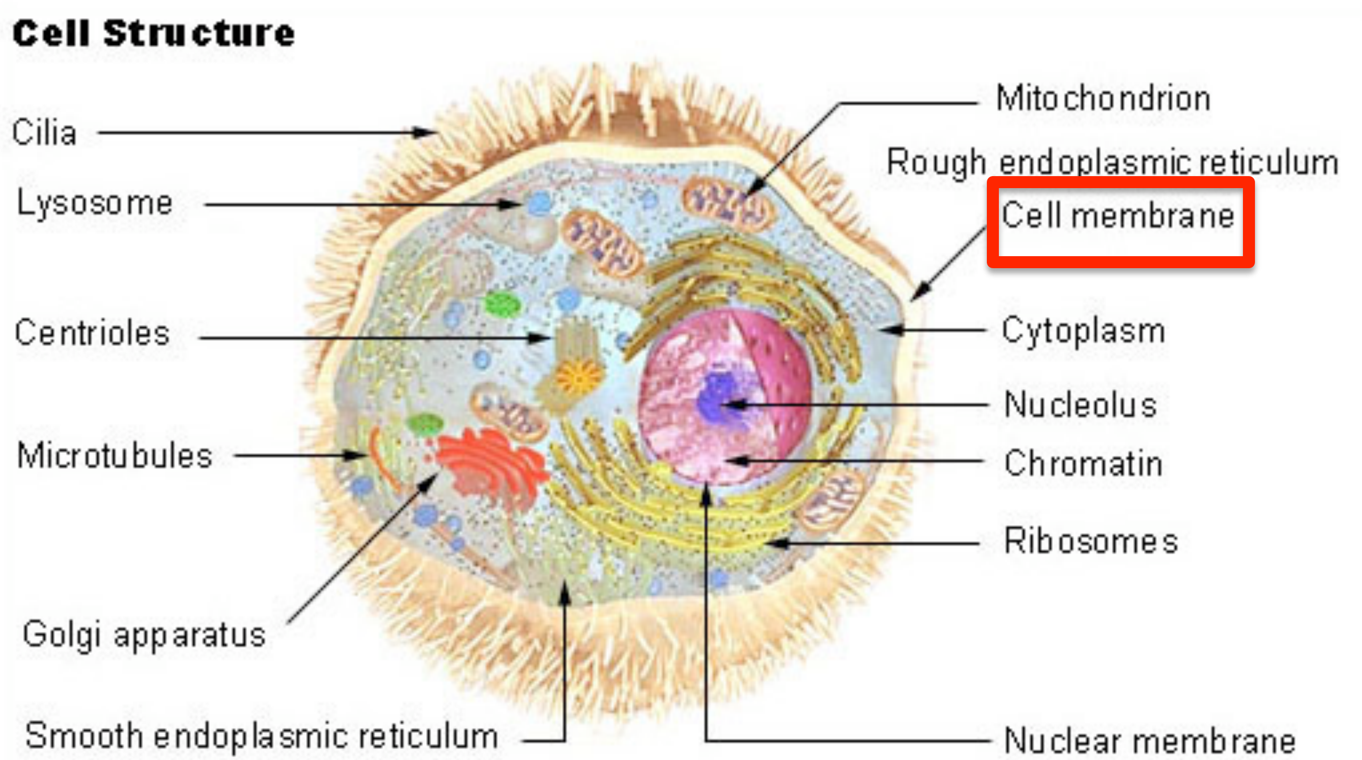
Izvekov, Violi *J. Chem. Theory Comput. 2(3), 504-512 (2006).*

Interactions of Carbonaceous Nanoparticles with Biological Systems

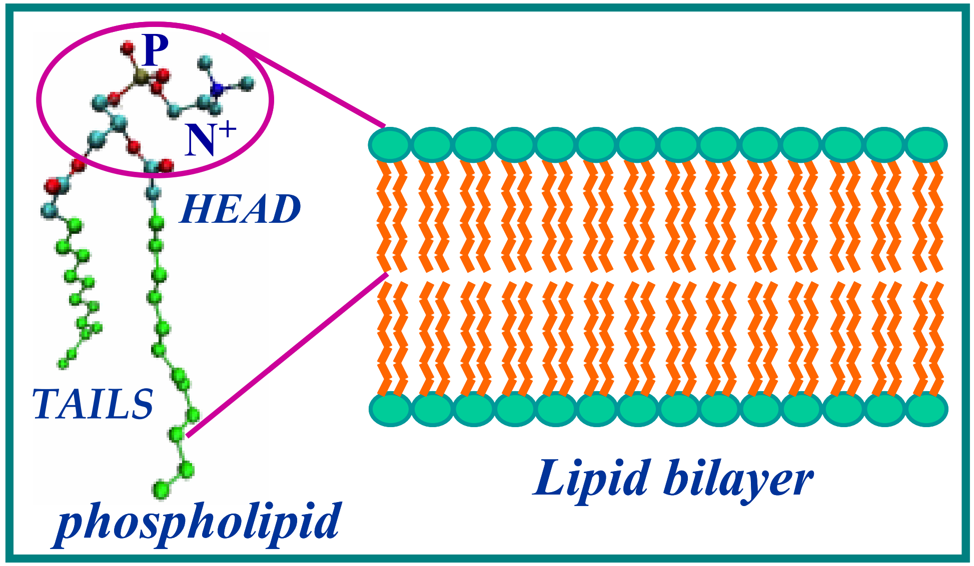
- Cellular membranes and Lipid
- Lung

Cell: smallest unit of living organisms

- There are many different types of cells in the body. However, they all contain three parts: the cell membrane, the nucleus, and the cytoplasm.



Cellular Membrane

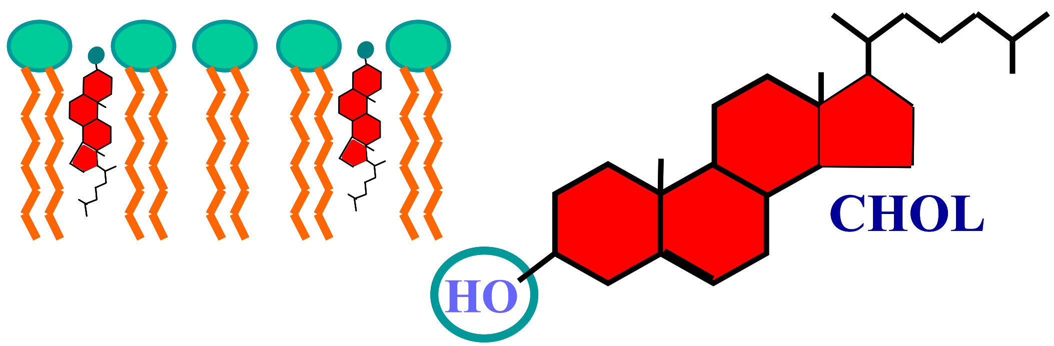


The membranes of eukaryotic cells contain three major classes of lipids: glycerophospholipids (GP), sphingolipids and cholesterol.

GP: polar headgroup and 2 nonpolar fatty acyl chains. Headgroup attached via a phosphate moiety PO_4 to glycerol backbone CH_2-CH_2-$N(CH_3)_3$

The fatty acyl chains usually have an even number of carbon atoms (between 16 and 20 in total) with one hydrocarbon chain being saturated and the other unsaturated.

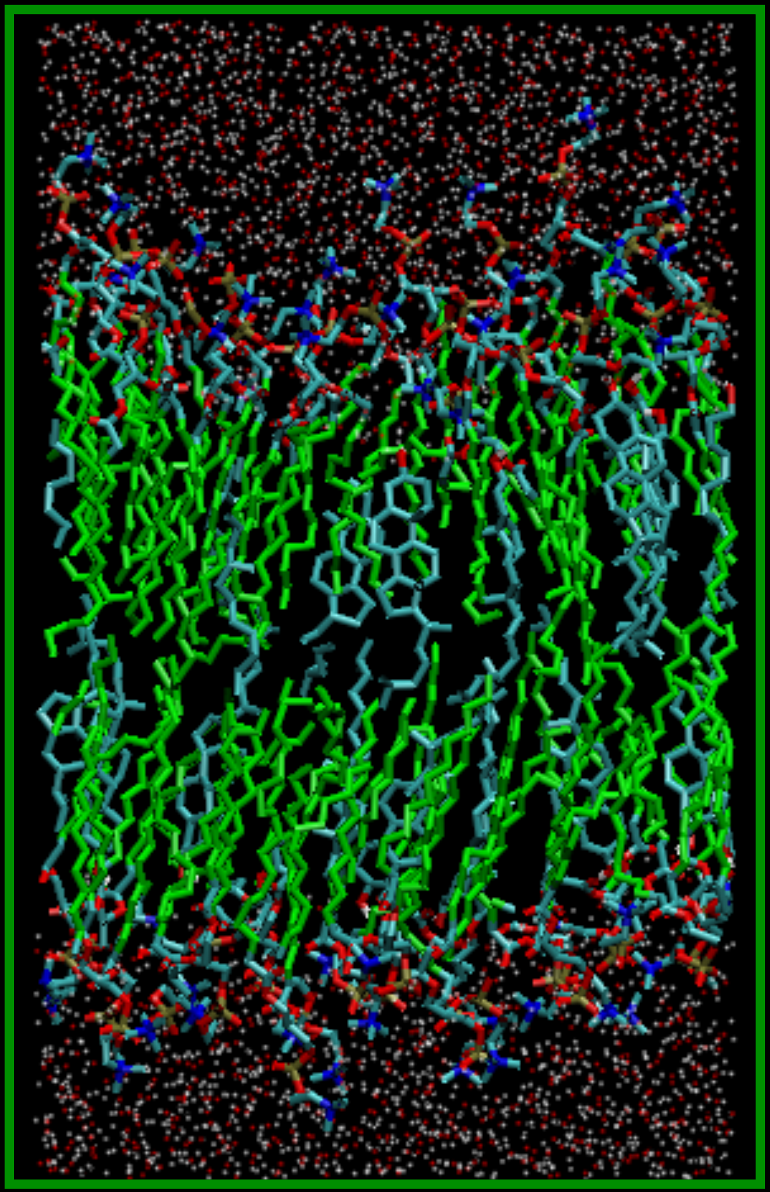
Cholesterol



When the hydroxyl group is next to the phospholipid ester carbonyl, the rigid body of cholesterol is situated alongside the fatty-acid tails of neighboring phospholipids and can help to order these tails (.

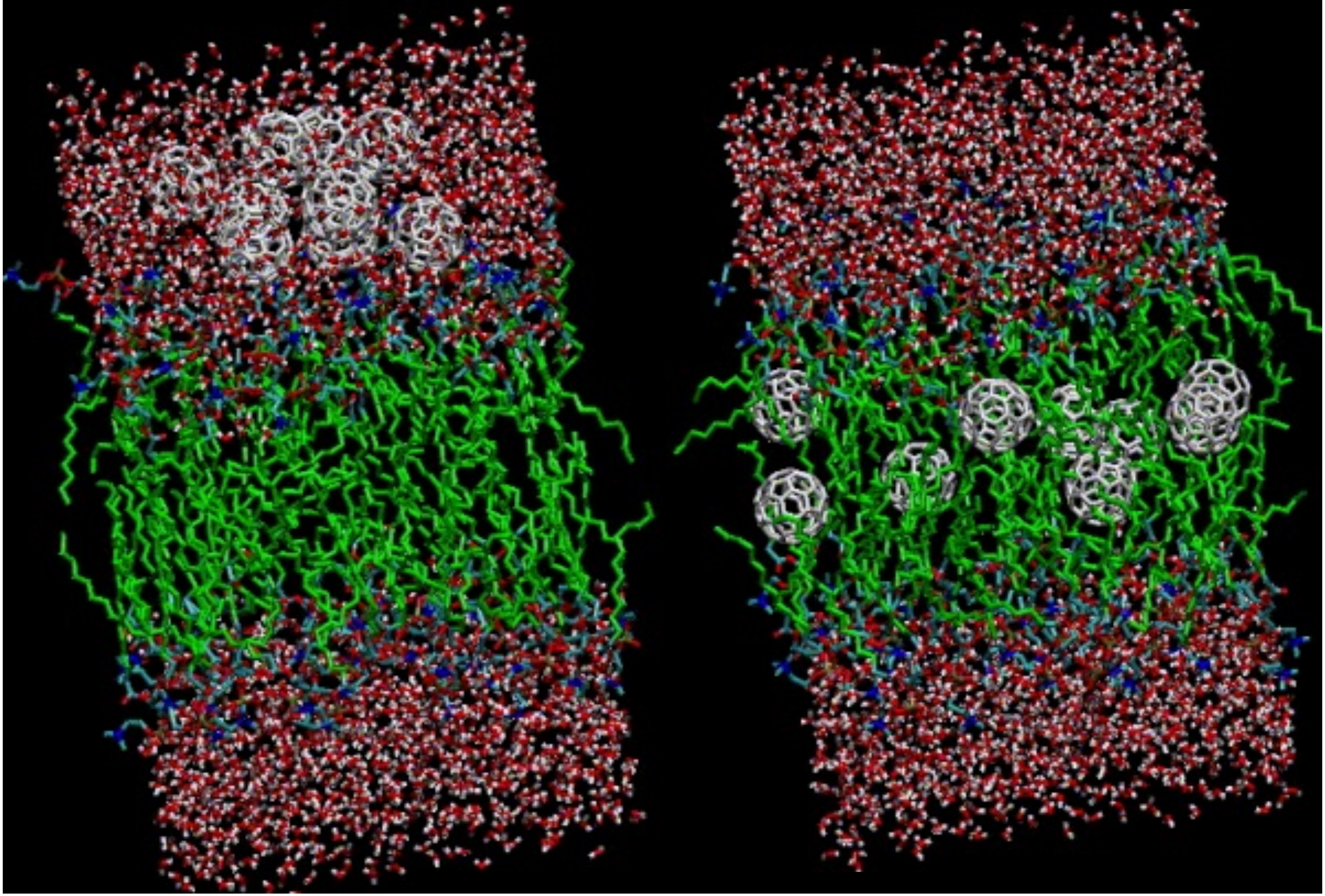
CHOL consists of a series of fused rings, which make this part of the molecule quite rigid. CHOL, like other membrane lipids, has both hydrophilic and hydrophobic poles that determine its positioning within the lipid bilayer (30-40%).

Lipid Bilayer

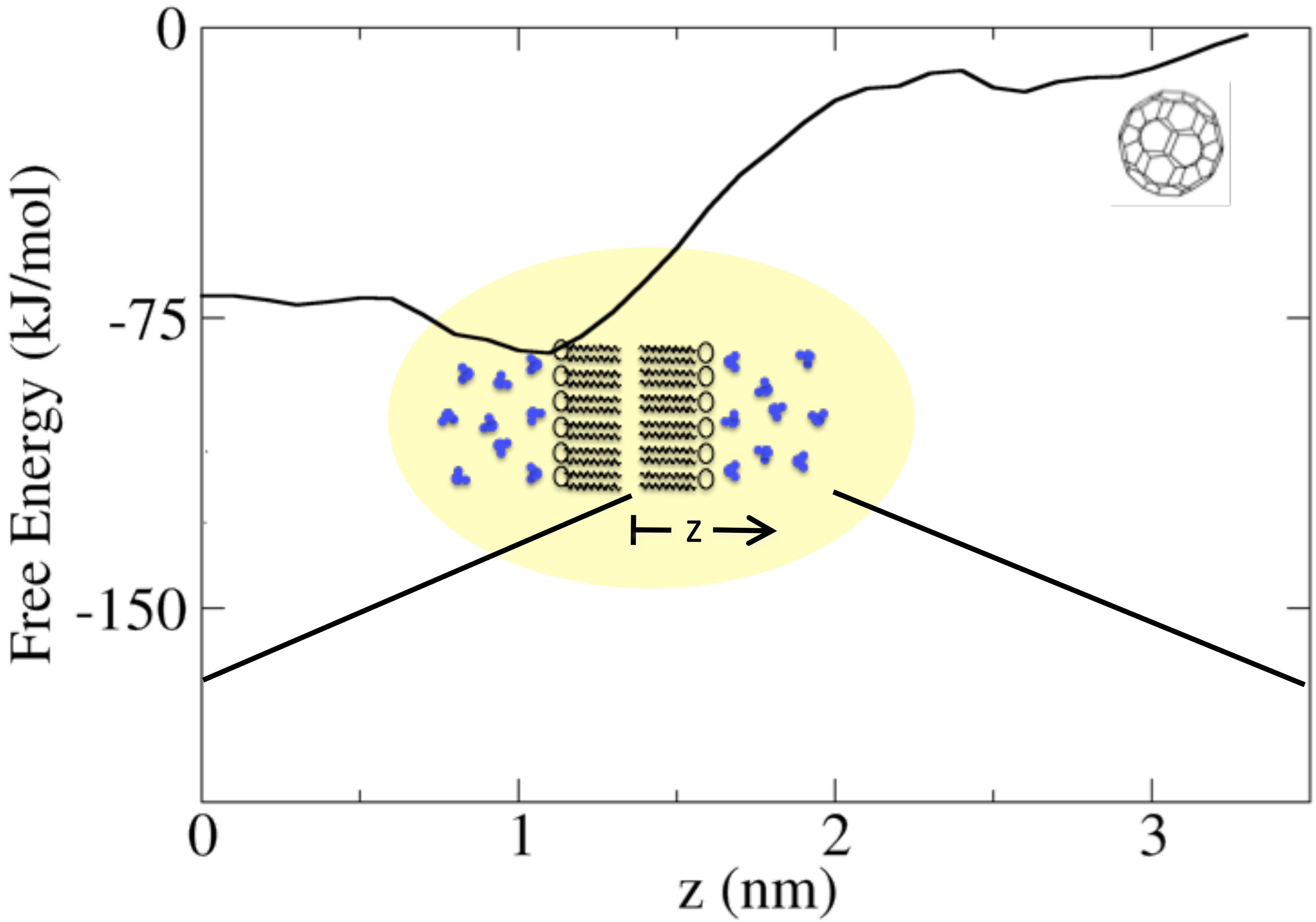


LB display large gradients in free volume, density, and polarity on very small length scales, making it difficult to determine free energy profiles experimentally.

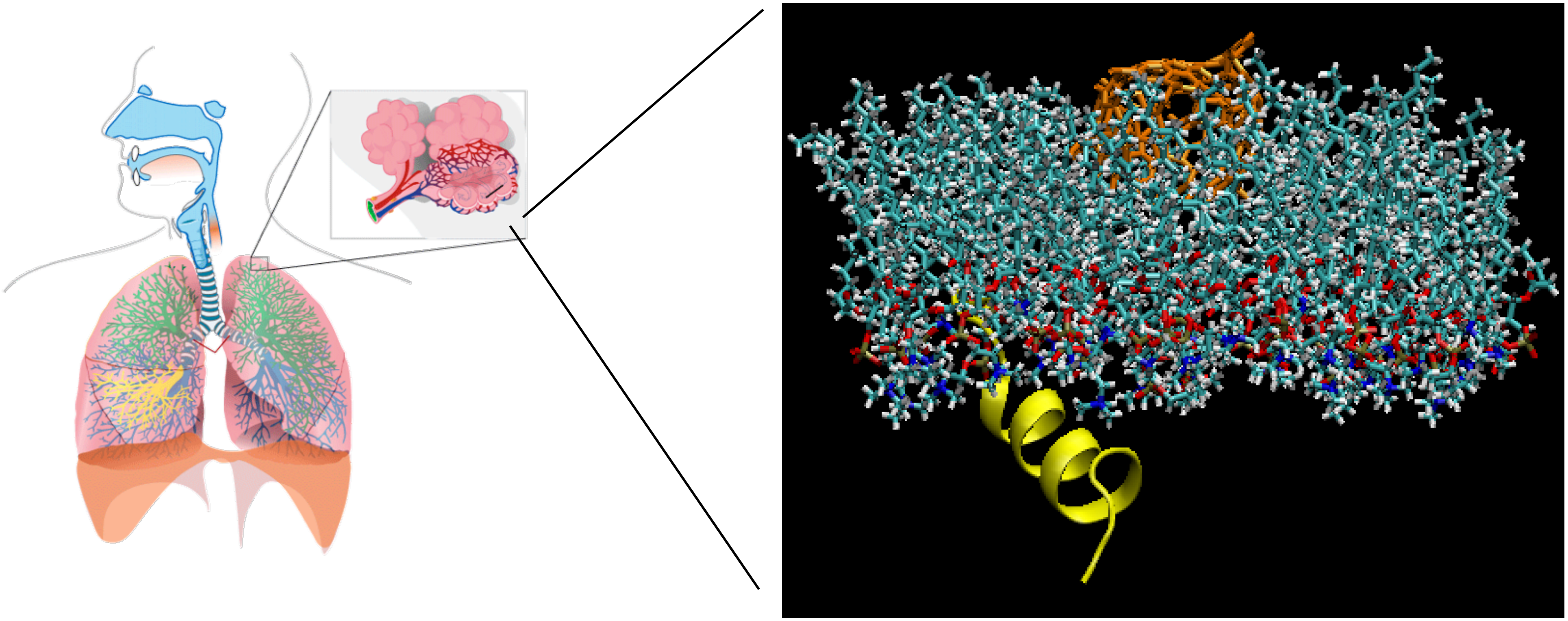
Lipid Bilayers and Engineered Nanoparticles C60



Free Energy Profile from MD simulations



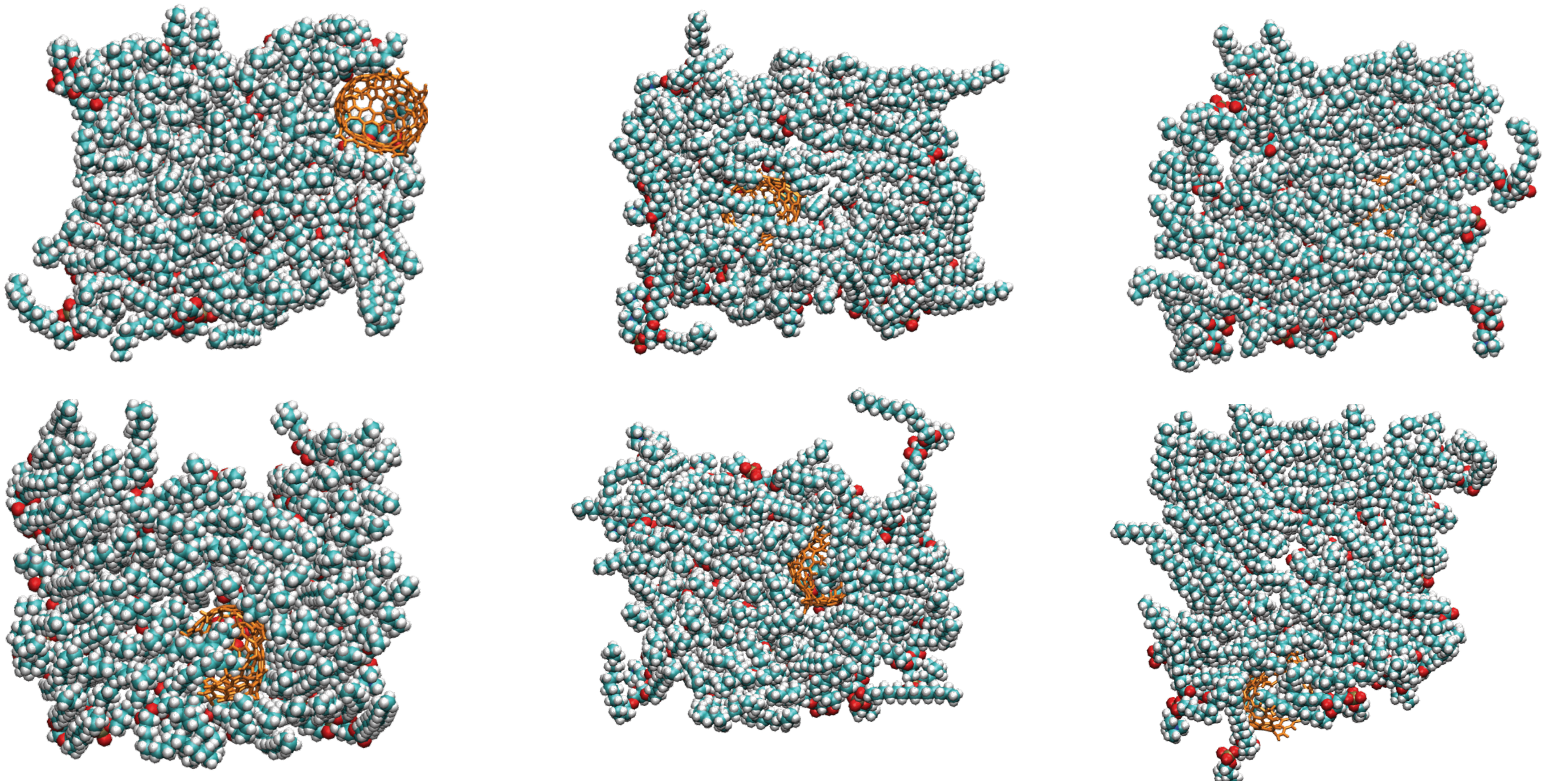
Surfactant



45 DPPC, SP-$B_{1\text{-}25}$, $C_{188}H_{53}$, 5500 H_20, Cl^-

S. Choe, R. Chang, J. Jeon, A. Violi, Biophysical Journal, 2008

Nanoparticle in Lung Surfactant



A B C

- Lipids wrap around the nanoparticle and that by the end of the simulations the cavity is filled with lipids.

Nanoparticle-Lung Surfactant Main Results

- Nanoparticle orientation influences lipid chain order.
- **<u>Nanoparticle and SP-B1-25 repel each other (initial angle 45^{o} – final 31± 5^{o}</u>**
- Carbon nanoparticles strongly adsorb in the tail region of the LS (free energy)

S. Choe, R. Chang, J. Jeon, A. Violi, Biophysical Journal, 2008

Standardized Protocols for Health Effects

- International Alliance for NanoEHS Harmonization to evaluate potential health effects of nanoscale materials. It is designed to standardize toxicological testing protocols. (Science, October 2008)

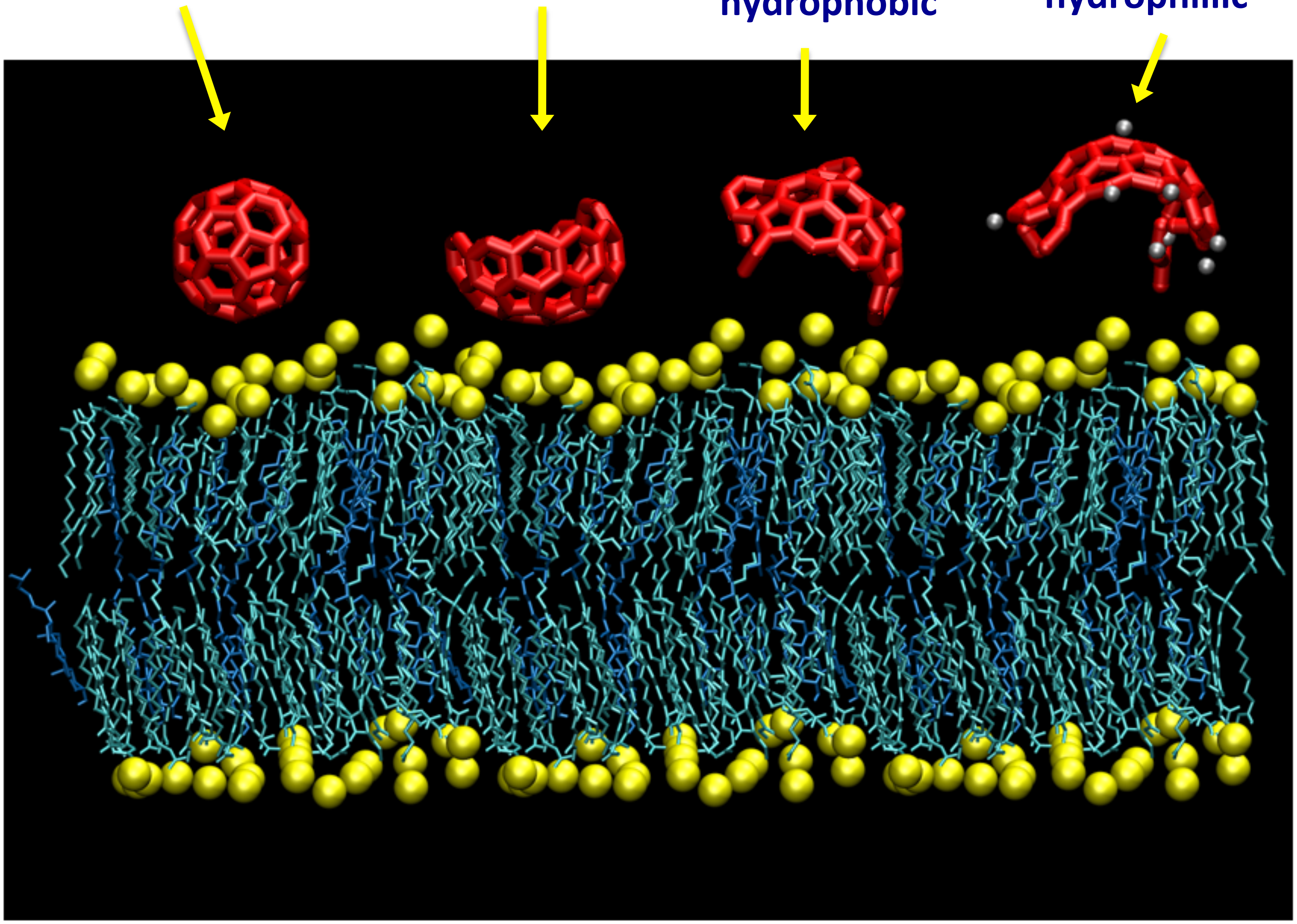
- In the set of 14 substances, carbonaceous particles in the size range of 0.5 - 1.5 nm are represented **by only** **C60 fullerenes** and potentially very short single and multiple-walled carbon nanotubes.

fullerene

Open fullerene

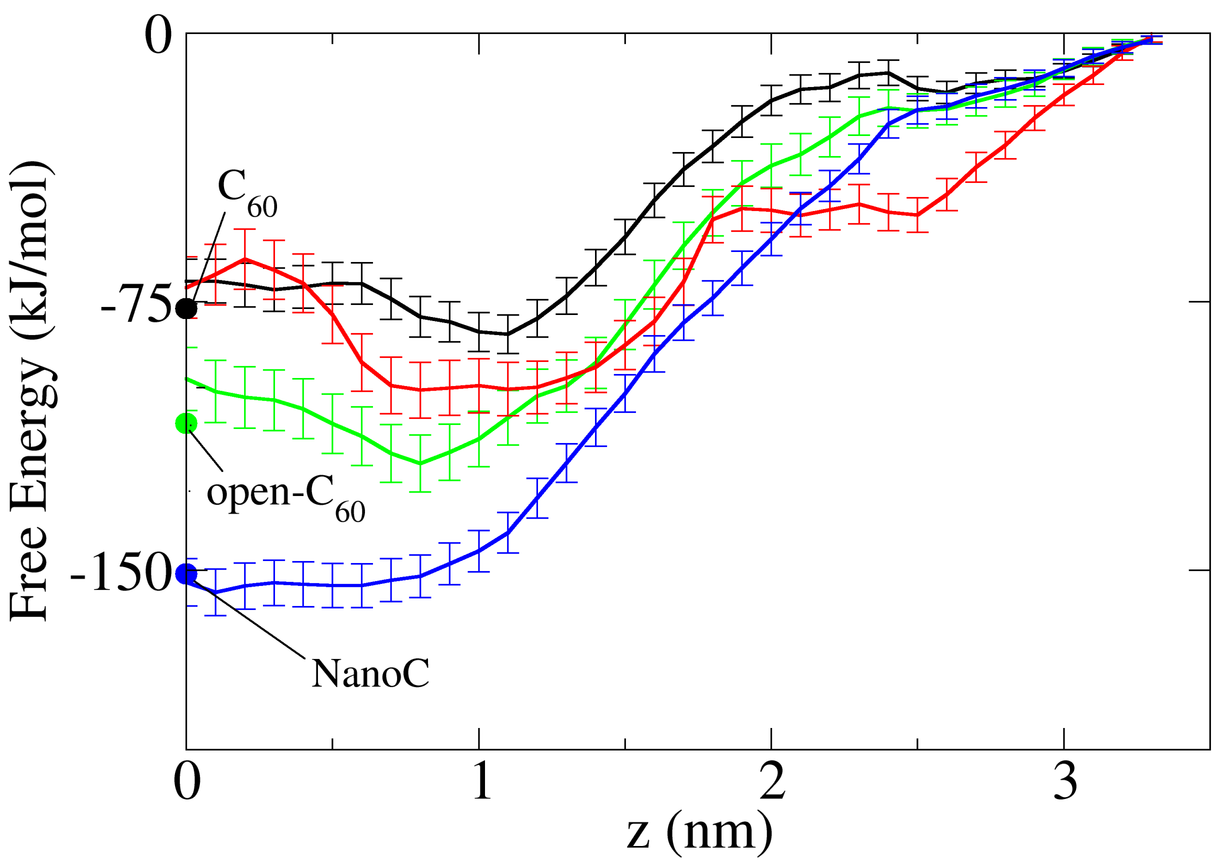
Combustion NP
hydrophobic

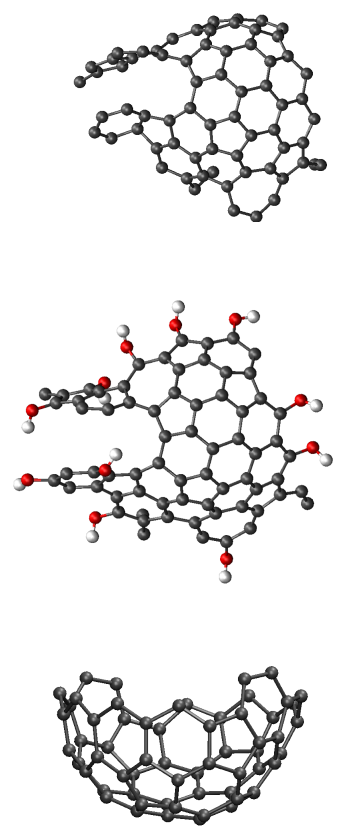
Combustion NP
hydrophillic



Fiedler and Violi, Biophysical Journal 99: 144-152 *(2010)*

Free Energy Calculations





Open-C60 binding depth 120 kJ/mol, 1.4 larger than C60 and 0.8 less than nanoC
Nano-OH great binding at lipid/water

Fiedler and Violi, Biophysical Journal 99: 144-152 *(2010)*

Need for extended set of parameters

- Surface area appears to be the size parameter of the greatest influence on the permeation process.
- C60 is limited in its ability to generically represent the toxicity of similarly sized nanoparticles.
- To adequately assess the health effects of anthropogenic carbonaceous nanomaterials, an expanded and inclusive set of representative systems should be considered.