Welcome to CH-4114
Molecular Simulation

"Everything that living things do can be understood in terms of the jigglings and wigglings of atoms."

- Richard P. Feynman

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CH4114: Molecular Simulation
Teaching Plan

Weak1:Introduction to Molecular Simulations- a. History of development b. What is molecular simulation and introduction to Model building c. Introduction to physical/chemical/biological processes of different timescale and length scale, Introduction to Statistical Mechanics + Hands on set-up

Weak 2: Basic Statistical Mechanics- Microscopic and macroscopic parameters, Central Limit Theorem, Phase space and Ensembles, Fundamental Concepts and Postulates of Statistical Mechanics, Equilibrium and ergodicity + Hands on – Model Building

Weak 3: MD Initialization algorithm- Random Number Generation, velocity distribution, and hands-on sessions, Concept of Reduced Unit.

Weak 4: Implementation of Periodic boundary conditions, potential truncation, minimum image convention + Hands on – MD module code writing

Weak 5: Theory- Algorithms of different integrators: Velocity Verlet, Leapfrog algorithms + MD module code writing with integrator

Mid - Semester Exam: Evaluation: Small MD module code writing and plotting

Weak 6: Project Defining + Molecular dynamics of various Ensembles, MD at constant temperature; Berendsen, Andersen, and Nose-Hoover Thermostat.

Weak 7: MD at constant pressure: Berendsen, Andersen, and Parrinello-Rahman Barostat **+ GROMACS Implementation**

Weak 8: Molecular Simulation Analysis, Potential energy and Kinetic Energy Measurement of Lennard-Jones fluid, Algorithm of radial distribution function.

Weak 9: Calculation of diffusion, hands-on sessions + Project Discussion

Weak 10: Monte Carlo (MC) Simulations, Importance Sampling+ Project Discussion

Weak 11: The Metropolis method, Detailed Balance

Weak 12: Hands-on sessions on MC sampling

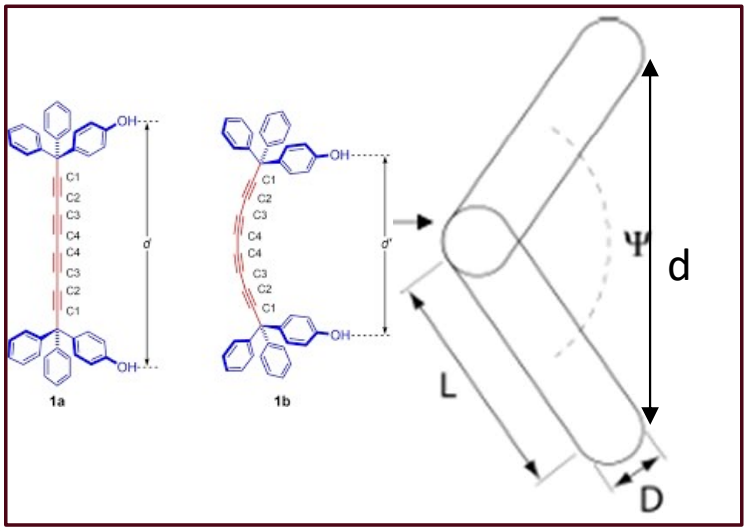
Weak 13: MC analysis **+** Hands-on sessions

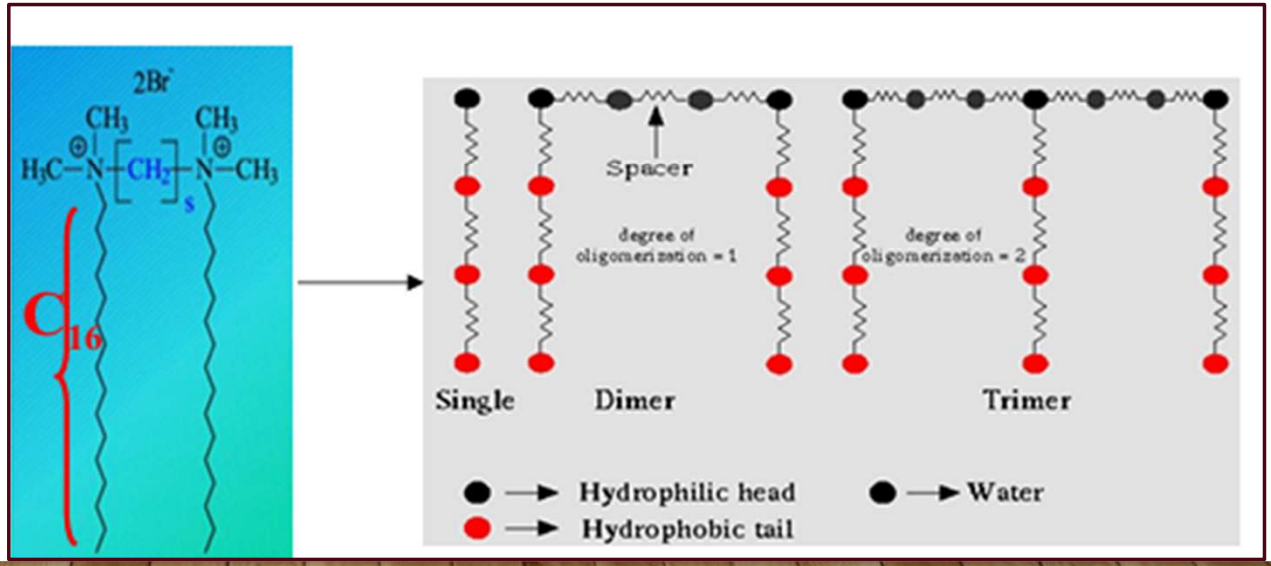
Endsem Evaluation: Project Evaluation + Presentation+ Code Writing Module

Molecular Modeling

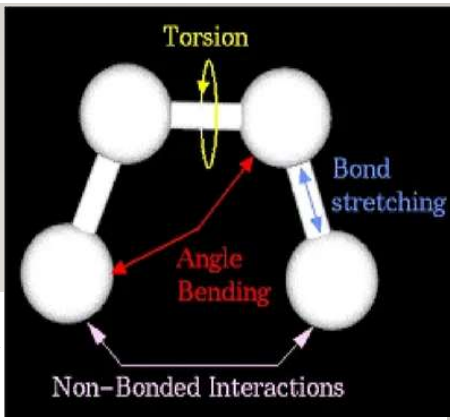
Molecular modeling is the science and art of studying molecular structure and function through model building and computation.

Model building could be as simple as representing molecule by hard/soft sphere (beads) , rigid rods, or other geometrical shape, sphere/beds connected through springs or molecule with full chemical details.





Molecular Simulation



Why "Molecular Simulation" techniques are so powerful ?

- Simply to understand, analyze and sometime to predict the connection between

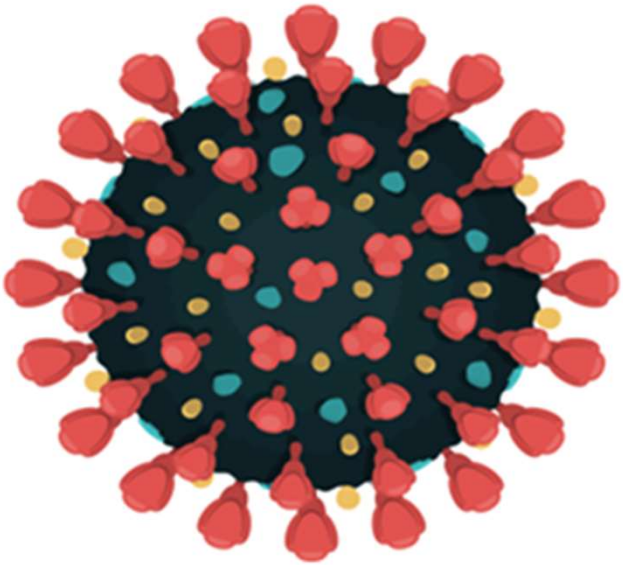
  Structure → Dynamics → Function

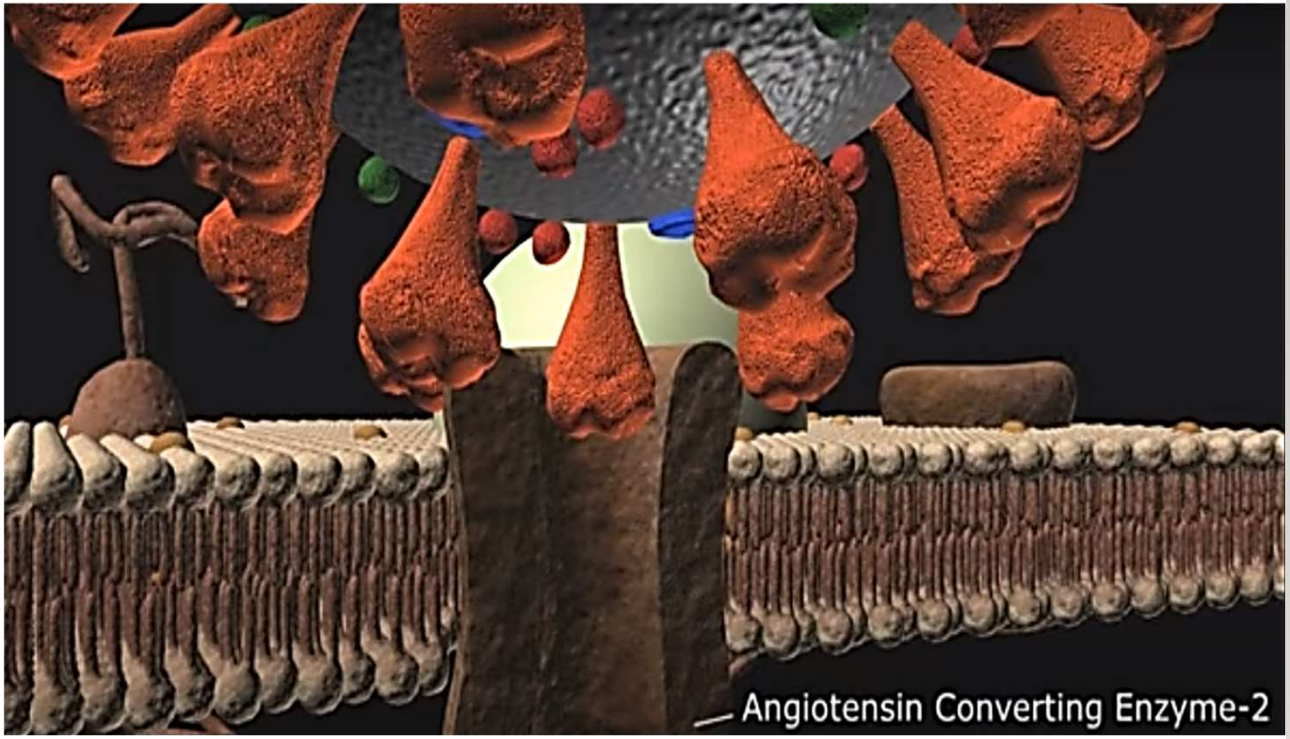
- Function follows structure: To perform a specific function, a molecule must adopt a defined structure.
- But, only dynamic structures can function: It is this flexibility and motion that enable molecules to perform their biological or chemical functions.
- Structures are not rigid: Under ambient conditions, molecular structures are not static. They fluctuate, access different degrees of freedom, and exhibit dynamic behavior.
- Molecular structures can be determined using experimental techniques such as X-ray diffraction (XRD) and cryo-electron microscopy (Cryo-EM), or predicted through computational modelling approaches like Density Functional Theory (DFT) for small molecules, and AlphaFold for biomacromolecules.
- Molecular simulation brings structures to life: But to go beyond static snapshots, molecular simulation emerges as a powerful technique, it breathes life into rigid structures, allowing us to observe their dynamics in action. Unlike experimental methods, molecular simulations let us visualize and analyze the trajectory of every atom over time, capturing the intricate choreography of molecular motion that underlies function.

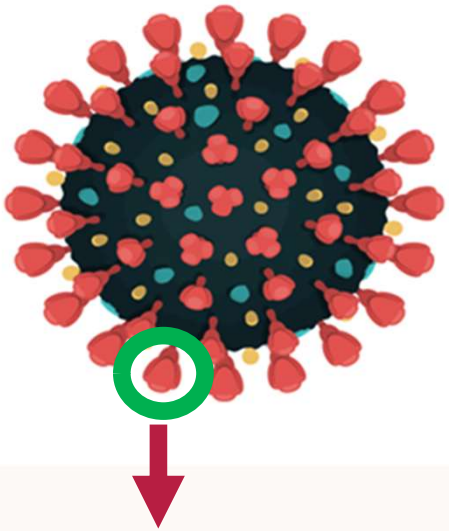
Structure → Dynamics→ Function

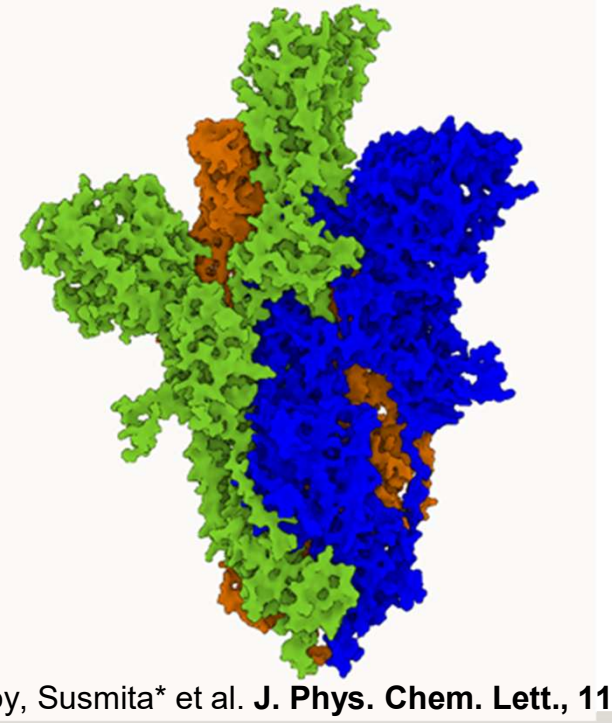
Practical Example:

The novel coronavirus spike protein is a smart molecular machine that instigates the entry of coronavirus to the host cell causing the COVID-19 pandemic.

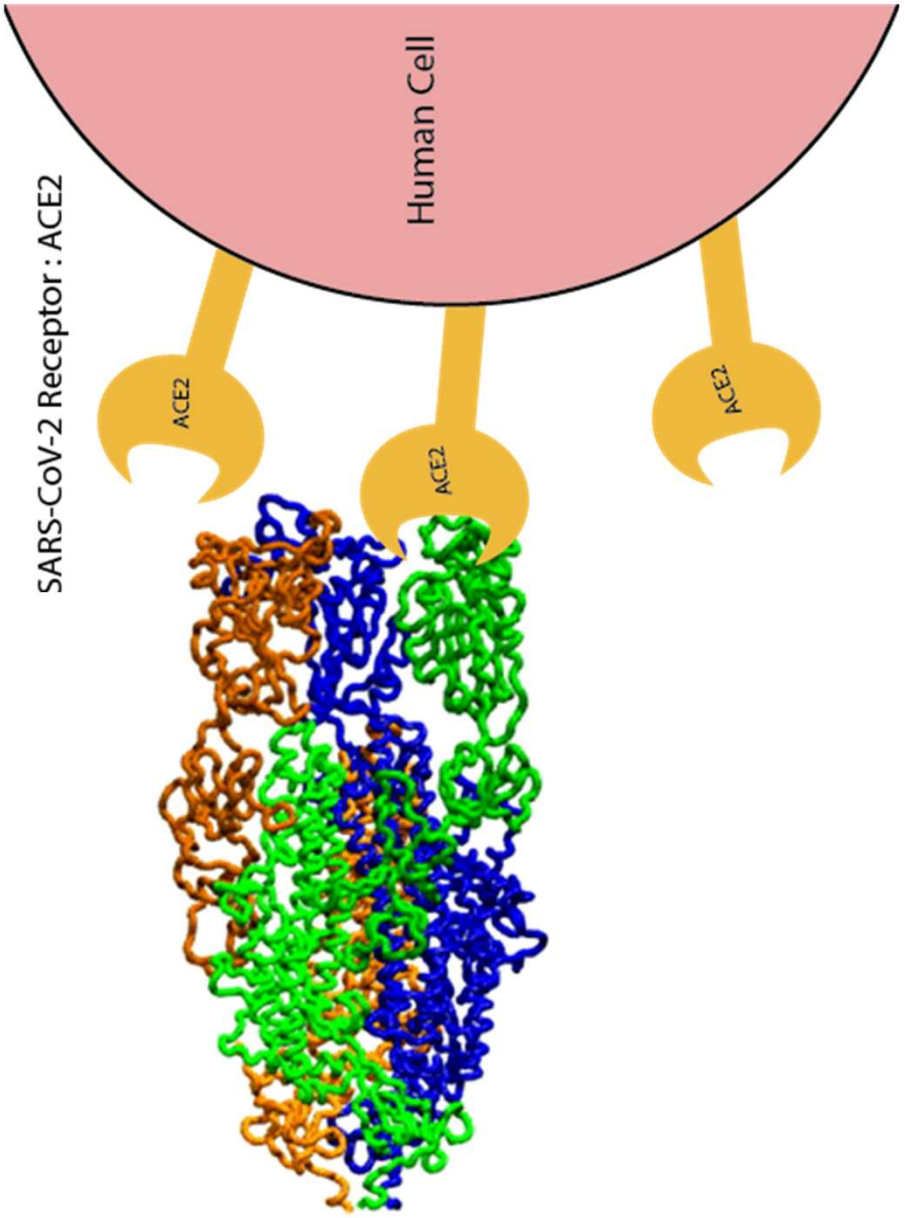








Roy, Susmita* et al. **J. Phys. Chem. Lett., 11, 7021-7027**

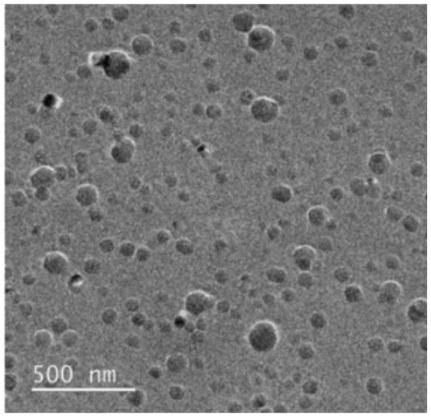


Viral Envelope

Transmission electron microscopy (TEM) Image

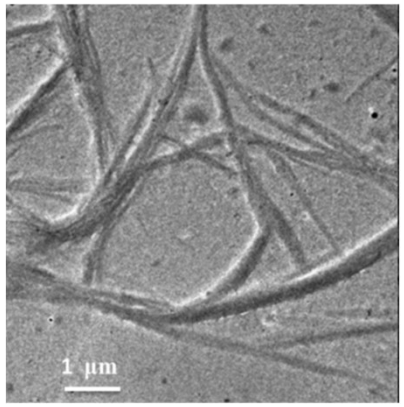
Monovalent

K^+ Induced Change in Morphology



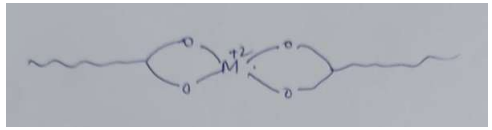
Divalent

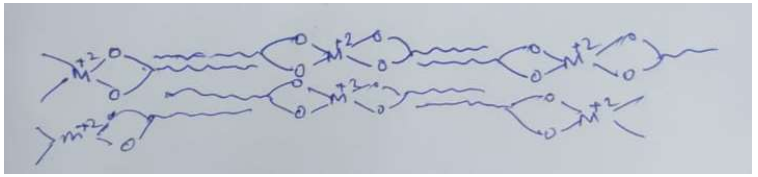
Sr^{2+} Metal Ions Induced Shrinking



Micelle

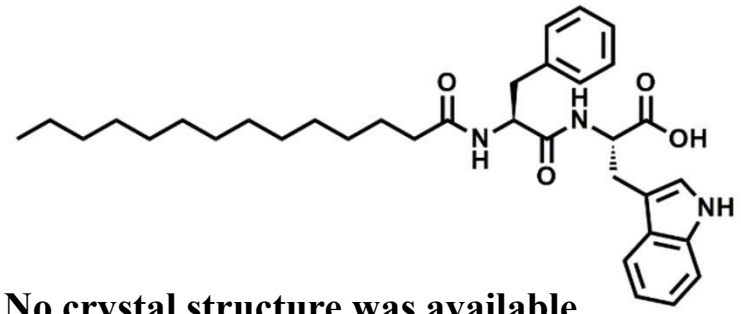
Nano-rod



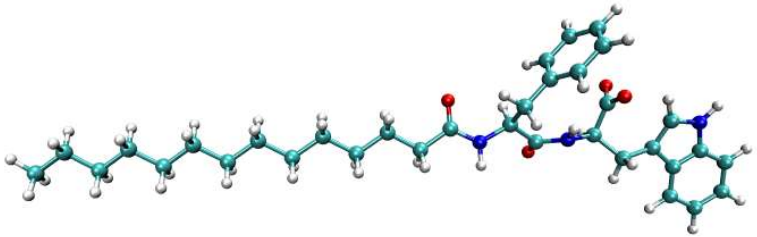


Minimum gelation concentration (MGC) of gelator G1 in presence of metal ion (1.05 Mm) =2.1 mM in 1 ml phosphate buffer pH=7.46.

Chemical Structure of the Gelator molecule

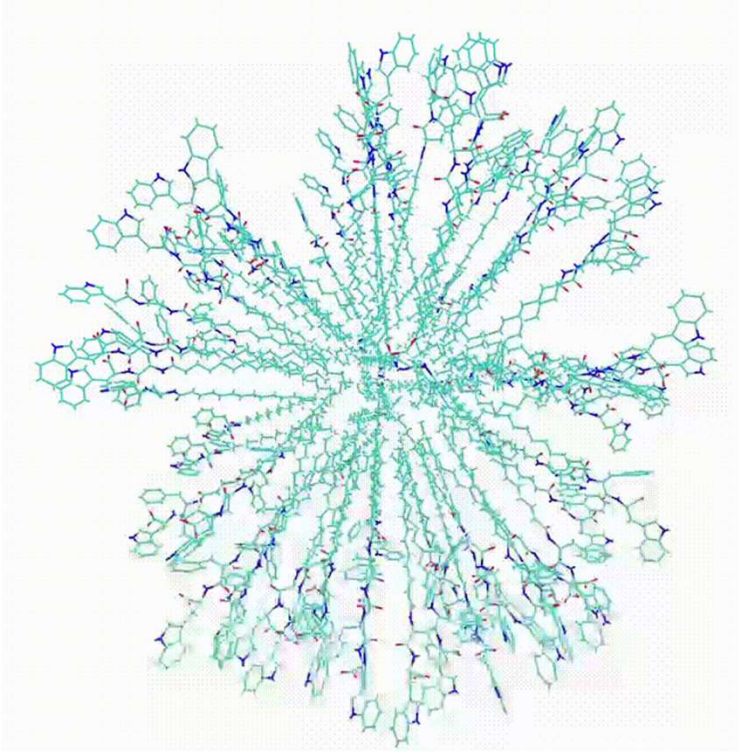


No crystal structure was available.

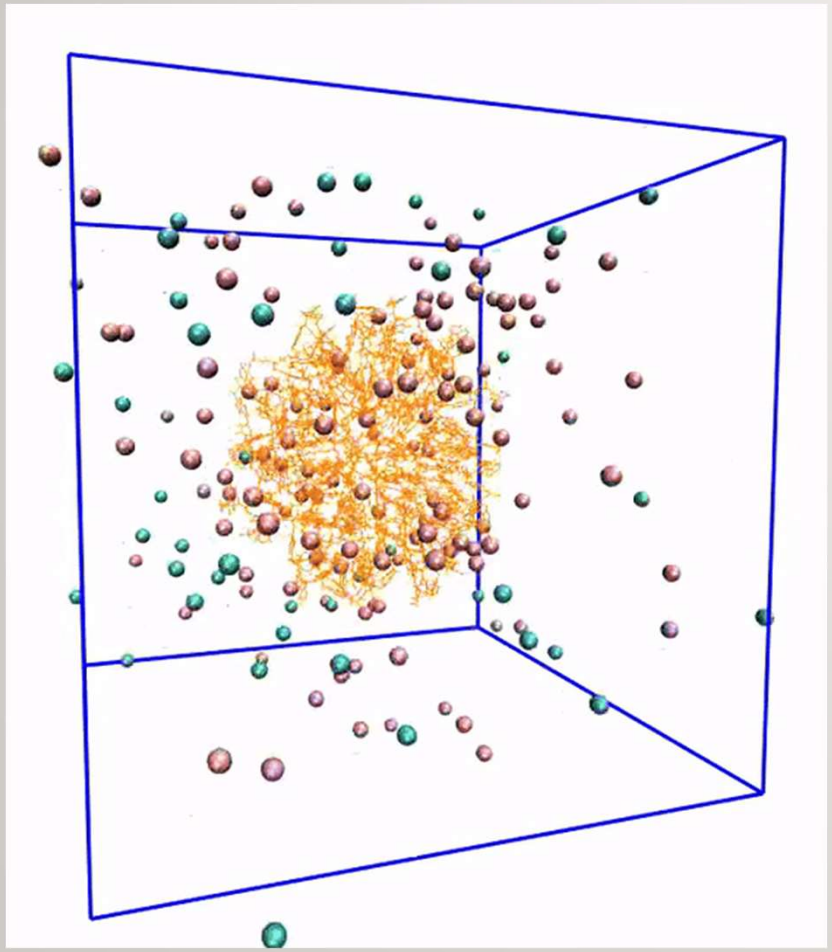


Energetically optimized generated structure of the Gelator

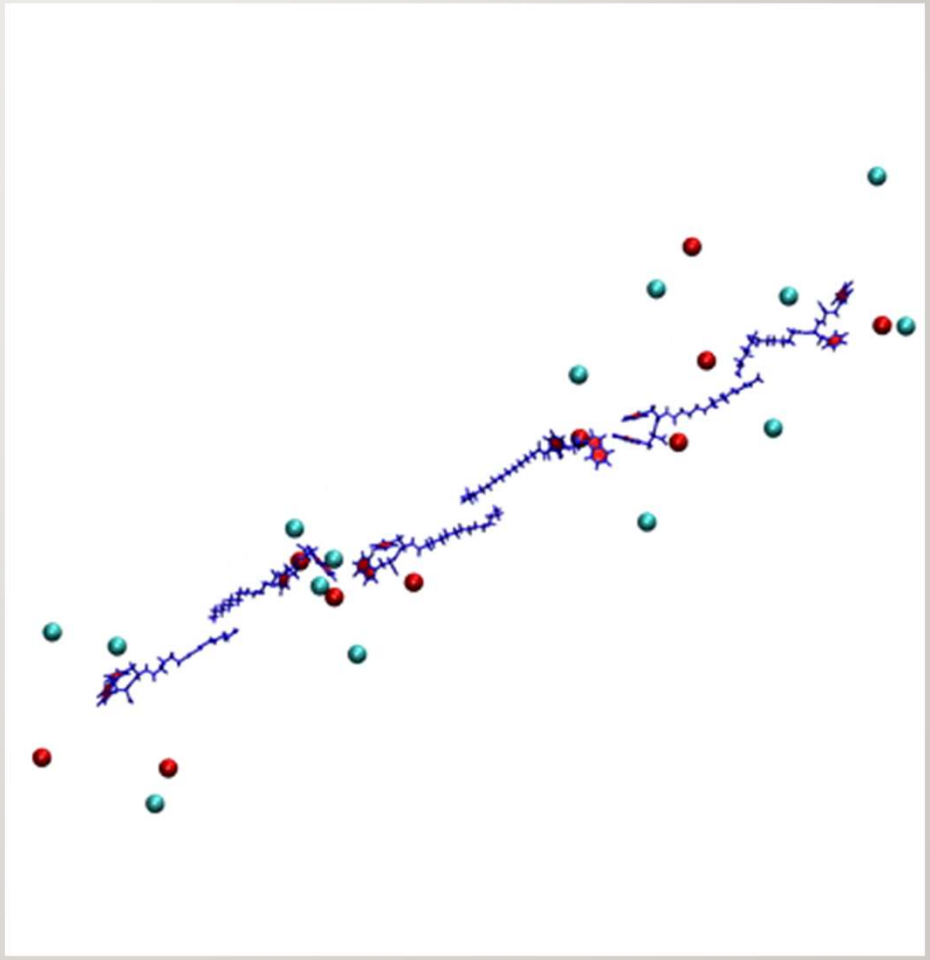
A micelle structure has been built with GEL1 molecules, keeping the hydrophobic parts in the core and the hydrophilic head in the outside direction



To study the stabilization of this micellar structure in a Monovalent and a Trivalent salt environment, we adopted the classical Molecular Dynamic Simulation.

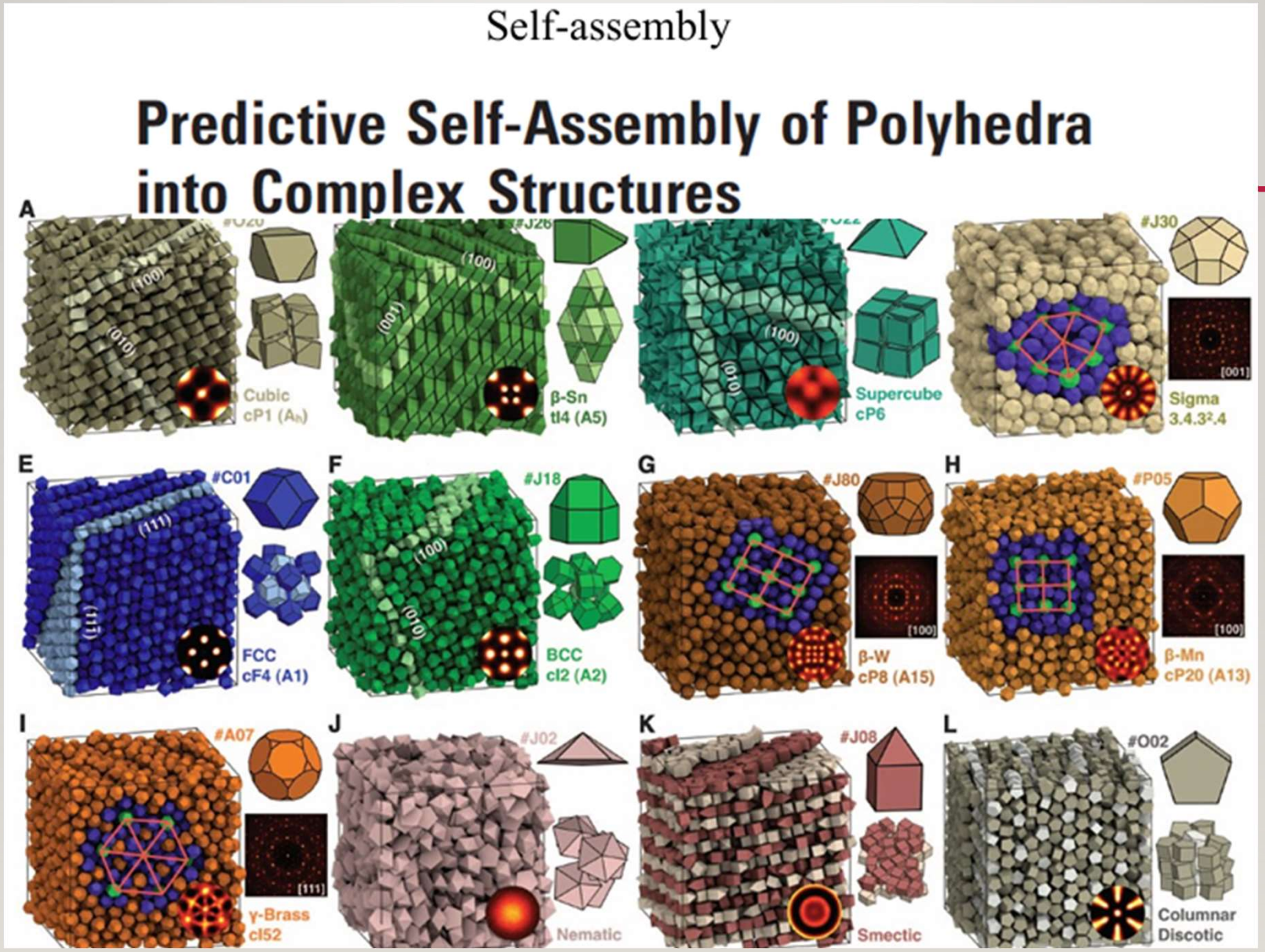


K^+ Induced Change in Morphology

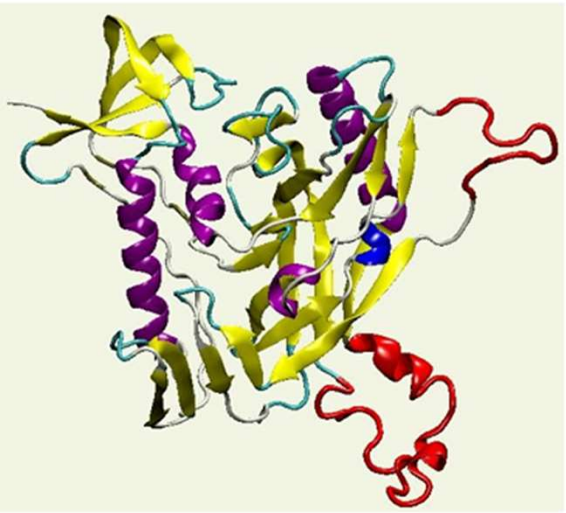


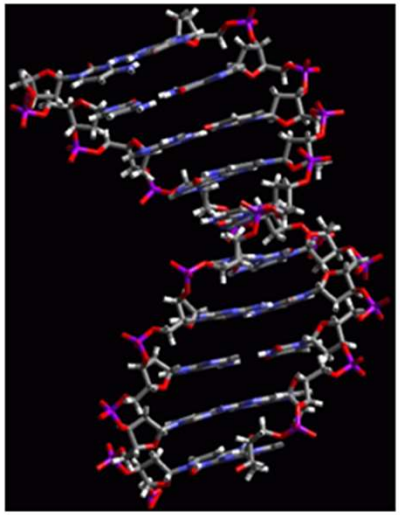
Sr^{2+} Metal Ions Induced Shrinking

Endless Scopes

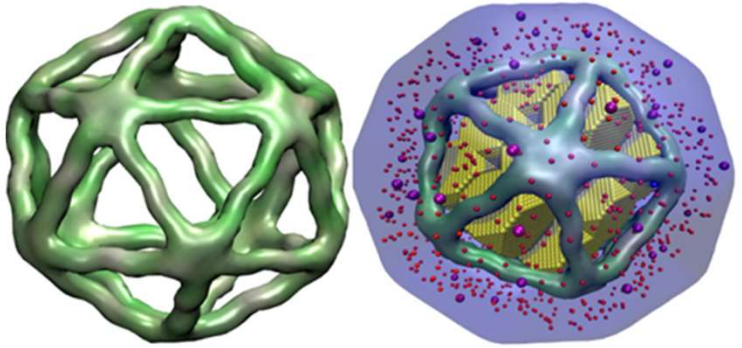


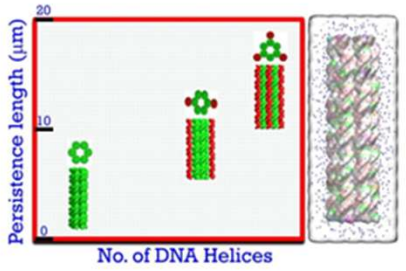
Molecular model of bio-molecules





DNA nanotechnology





Historical development of Molecular Simulation

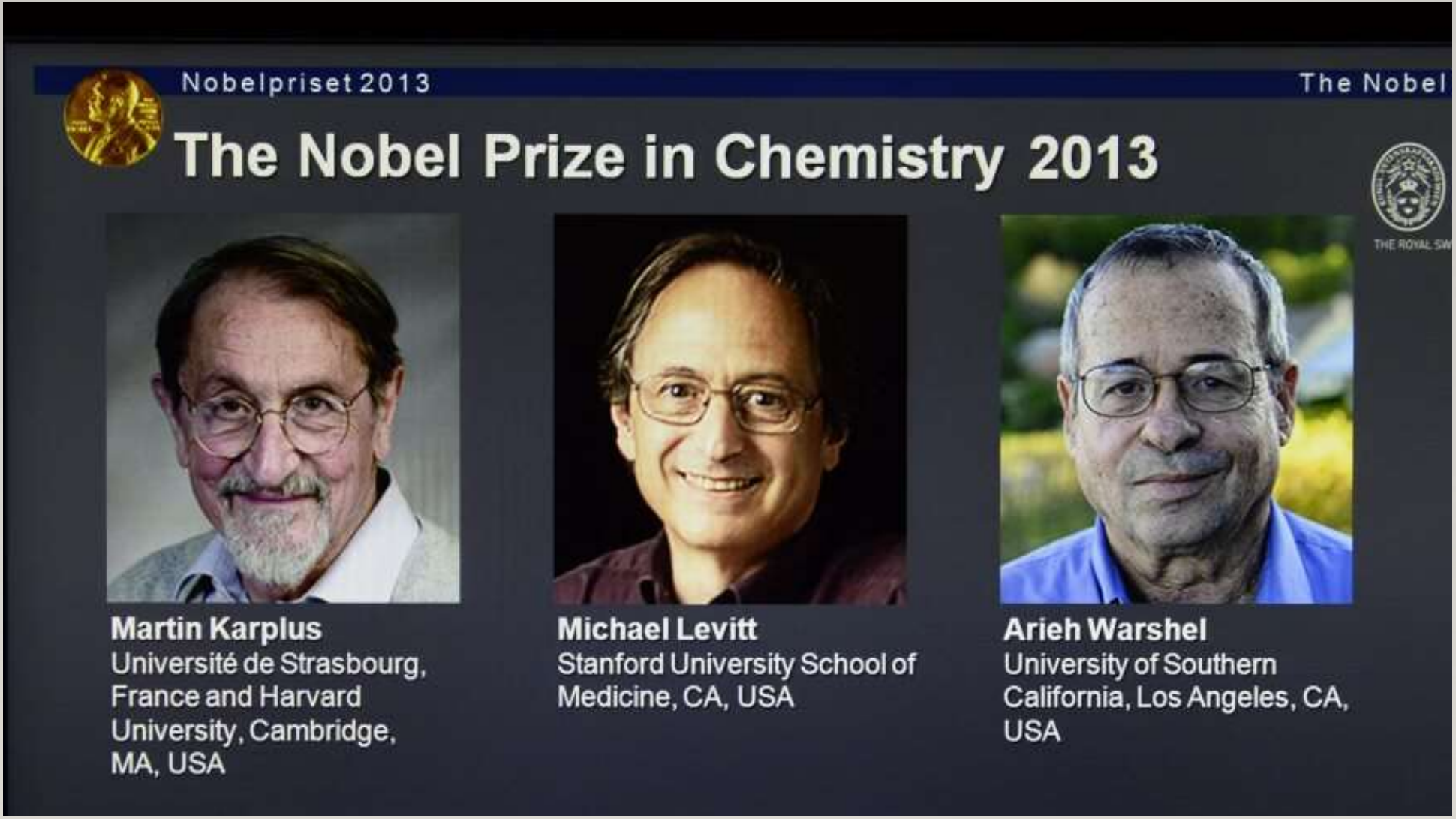
- The journey of molecular simulation began in the aftermath of World War II, when computing machines-originally developed for wartime code-breaking and ballistics (by **Alan Turing** and his team)- were repurposed to explore problems in physics and chemistry.
- One of the earliest such machines, the **MANIAC** (Mathematical Analyzer, Numerical Integrator, and Computer) built in **1952 at Los Alamos**, was soon employed for pioneering simulations.
- A landmark moment came in **1953**, when **Metropolis, Rosenbluth, and Teller** introduced the **Metropolis Monte Carlo method**, establishing a probabilistic approach to sampling molecular configurations. This marked the birth of computational statistical mechanics.
- Shortly after, **Alder and Wainwright** at **Livermore National Lab** (1956–1957) performed the first molecular dynamics simulations, modeling the behavior of **hard spheres** to understand fluid properties, an approach that shifted simulations from static snapshots to real-time dynamics.
- In **1959–60**, **Vineyard** at **Brookhaven** explored the **dynamics of radiation damage** in copper, extending simulations into materials science.
- Then, in **1964**, **Rahman** at **Argonne** performed the first realistic molecular dynamics simulation of **liquid argon**, laying the groundwork for simulating real liquids.
- The **1970s** saw the extension of these methods to **more complex fluids**, including early attempts to model **liquid water**, one of the most challenging systems due to its hydrogen bonding.

Historical development of Molecular Simulation

- A major breakthrough came in **1985** when **Car and Parrinello** introduced **ab initio molecular dynamics**, uniting quantum mechanics and classical molecular motion in a single framework-greatly expanding the scope and accuracy of molecular simulations.

- From the **1980s** onward, researchers like **Karplus** and **Goddard** began applying these tools to **biomolecules**, such as **proteins and polymers**, leading to insights into folding, function, and dynamics. These efforts later contributed to Karplus sharing the **2013 Nobel Prize in Chemistry**.

- By the **mid-1990s to 2000**, simulations were increasingly applied to **fracture mechanics** and **engineering systems**, including **nanotechnology**, **carbon nanotubes (CNTs)**, and **nanowires**, showcasing the growing relevance of molecular simulations in both materials science and industry.
- Today, molecular simulation stands as a cornerstone of theoretical and computational science-bridging disciplines, unraveling complexity, and operating across the vast **length and time scales** that define the natural world.



“For the development of multiscale models for complex chemical systems”