<u>**Marks Distribution:**</u>

Core theme coverage: 60

(Presentation 1: Introduction +Literature survey+ Understanding the Goal of your MD Project): Marks: 10

Presentation 2: Simulation Model Implementation: Marks: 20

Presentation 3: Result discussion & Overall Summary: 20

Challenging part coverage (as denoted below): 10

**1. Phase transition in simple Lennard-Jones nano-confined fluids**

**(Challenge: Nanoconfinement creation and tipping point identification)**

LAMMPS Tutorial:

A. https://www.youtube.com/watch?v=7RtRerwJqQw

https://www.sciencedirect.com/science/article/pii/S0378381220300418

2. **Thermal Conductivity via Green-Kubo Method**

(Challenge: comparison between crystalline vs amorphous systems.)

Recommendation to read : https://pubs.acs.org/doi/10.1021/ja983581p

(Use MD trajectories to compute thermal conductivity from heat current autocorrelation; **Calculate** Transport properties using nonequilibrium statistical mechanics; Then compare crystalline vs amorphous systems.

3. Assessing **DNA-pepide/drug binding and solvent-mediated interaction using Free energy Perturbation Method (FEP)**

(Run short MD of a nucleic acids system in explicit water and measure secondary structure stability; Analyze biomolecular interactions, hydrogen bonding, solvation effects measuring free energy of solvation.

Read: http://www.mdtutorials.com/gmx/free_energy/index.html

**4. A nucleic acids tetraloop folding landscape analysis**

**(challenge: Correct order parameter identification with GPT analysis)**

(Run long simulation, AI-guided clustering/weighted ensemble analysis and use interpretable AI

## 5. Heat Capacity measurement via Energy Fluctuations (Challenge: AI-based fitting using ML regression)

(**System:** Argon across temperatures (NVT ensemble); **MD:** Run multiple T, compute energy fluctuations → Cv(T); **AI/ML analysis:**Fit Cv vs T data to Debye or Einstein models using ML regression. GPT interprets deviations from simple models (e.g., "enhanced Cp near melting due to anharmonic phonons).

## 6. RNA base flipping simulation and free energy analysis from trajectories (Challenge: Appropriate thermodynamic reaction coordinate identification with ML)

## 7. Find allosteric communication simulating a small biomolecule using Dijkstra's Algorithm of signal transduction from source to sink.

**Challenging part: Brainstorm to include ML.**

## 8. Simulate and analyze Drug-DNA intercalation.

**Identification allosteric rewiring comparing before and after intercalation using Dijkstra's Algorithm of signal transduction from source to sink. (Challenging part: Brainstorm to include ML.)**

## 9. *How does solvation structure change around a hydrophobic vs. hydrophilic nanoparticle? (*MD part: Simulate spherical solutes (LJ spheres with different ε) in water; compute RDFs, hydration numbers.

**Brainstorm to include ML)**

## 10. Calculate Preferential Interaction Coefficient of salt around a polyelectrolyte.

**(Compare various salt and their preferential interaction coefficient.**

**Challenge: Compare with available experiments and order them in a Hoffmeister series)**

**11. Simulate a binary mixture of water and any electrolyte sampling various concentration and calculate any collgigative property (such, as osmotic pressure).**

**(Challenging part: Brainstorm to connect to McMillan-Mayer theory of solutions)**

# Brainstorming Session-1

## *Project 1 (Harish):*

*Read this paper: Examination of the phase transition behavior of nano-confined Lennard-Jones fluids* (J. Chem. Phys., 2015).

**Though Process:**

We want to study how classic LJ fluid phase behavior (gas ⟷ liquid, layering, capillary condensation) changes under nanoconfinement and to identify *tipping points* — parameter values where the system abruptly changes state (e.g., sudden adsorption, layering-to-bulk transition, loss of metastability). Goals:

- Create slit-pore and cylindrical nano-confinements with tunable wall-fluid interactions.

- Map phase behavior vs temperature (T), density ( ρ), and confinement size (pore width H or radius R).

- Detect tipping points robustly (statistical signatures, order parameters, hysteresis).

Units: LJ reduced units (σ = 1, ε = 1, m = 1). Time unit τ = σ√(m/ε).

Fluid–fluid: standard 12–6 Lennard-Jones
$U_{ff}(r) = 4\varepsilon[(\sigma/r)^{12} - (\sigma/r)^6]$, cutoff rc = 2.5σ (shifted).

Wall geometry:

- **Slit pore**: two parallel atomistic or implicit walls separated by H (in σ).

- **Cylindrical pore**: cylinder of radius R.

Wall–fluid interactions:

- Atomistic wall: LJ sites arranged in lattice, use LJ parameters (ε_wf, σ_wf).

- Implicit wall: 9–3 LJ integrated wall potential (good & efficient for smooth walls):
$U_w(z) = \frac{2\pi\rho_w\epsilon_{wf}\sigma_{wf}^3}{3}[\frac{2}{15}(\frac{\sigma_{wf}}{z})^9 - (\frac{\sigma_{wf}}{z})^3]$(z = distance to wall).

- Tune $\varepsilon_{wf}/\varepsilon$ to be hydrophilic (strongly attractive, $\varepsilon_{wf} \geq \varepsilon$) or hydrophobic (weakly attractive, $\varepsilon_{wf} < \varepsilon$).

Typical parameter sweep:

- H = 2σ, 3σ, 4σ, 6σ, 10σ (ultra-confined → quasi-bulk)

- T* = 0.6 → 1.4 (coexistence region for LJ around T* ≈ 1.1 critical)

- Bulk reduced densities ρ* = 0.01 → 0.9 (for canonical/μVT comparisons)

- $\varepsilon_{wf}/\varepsilon$ = 0.2, 0.5, 1.0, 2.0

Boundary conditions: Periodic in directions parallel to walls (x,y); non-periodic along confinement normal for slit (or periodic with large vacuum buffer). For cylinder use periodic along cylinder axis.

Ensemble:

- For phase mapping: grand-canonical (μVT) is ideal (adsorption isotherms), but can be computationally heavy.

- Canonical (NVT) or isothermal–isobaric (NPT) with careful density scans + hysteresis loops can work. For MD, use NVT or NVT + insertion/evaporation MC if needed.

Thermostat/barostat: Nosé–Hoover thermostat (time constant 0.1–1.0 τ). If using NPT, barostat only on directions parallel to walls.

Simulation length: equilibration 200k–1M steps; production 1–5M steps depending on size. (Tune by convergence of energies and density profiles.).

Ensemble: NVT

Thermostat/barostat: Nosé–Hoover thermostat (time constant 0.1–1.0 τ). If using NPT, barostat only on directions parallel to walls.

Simulation length: equilibration 200k–1M steps; production 1–5M steps depending on size. (Tune by convergence of energies and density profiles.)

LAMMPS will be easier to implement the codes. LAMMPS Tutorial:

A. https://www.youtube.com/watch?v=7RtRerwJqQw

## Project 2: Thermal Conductivity via Green-Kubo Method (Debanjan)

Reading Material: Green–Kubo and transport theory: *D. J. Evans & G. P. Morriss, Statistical Mechanics of Nonequilibrium Liquids.*

NEMD & Müller–Plathe: *F. Müller-Plathe, J. Chem. Phys. 1997 (Reverse NEMD method).*

***Müller–Plathe (RNEMD)***

- *Exchange kinetic energy between hottest particle in cold slab and coldest in hot slab — creates a flux without thermostats in the slabs.*

- *LAMMPS: fix thermal/conductivity implements Müller–Plathe (reverse non-equilibrium MD).*

- *Measure steady heat flux J from total energy exchanged per time and the resulting temperature gradient ∇T from spatially binned temperature profile. Use linear region excluding thermostatted slabs to compute ∇T.*

- **Compute heat current time series J**$(t)$ during production run — sample frequently (every 1–10 timesteps depending on property).

- **Compute HCACF**

$$C_{\alpha\beta}(t) = \langle J_\alpha(0) J_\beta(t) \rangle$$

  - Use block averaging: break trajectory into M blocks, compute HCACF in each block and average to get mean + error.
  - Use FFT-based convolution to compute autocorrelation efficiently for long data sets.

- **Integrate to get κ**

$$\kappa_{\alpha\beta}(t_{\text{int}}) = \frac{1}{k_B T^2 V} \int_0^{t_{\text{int}}} C_{\alpha\beta}(t)\, dt$$

  - Plot running integral vs $t_{\text{int}}$. Look for a plateau — take plateau value as κ. In practice noise causes drift; choose plateau region before noise dominates.
  - Use multiple independent runs and block bootstrap to estimate mean ± uncertainty.

**\*\* Ionic diffusion and conductivity: Nernst–Einstein vs actual conductivity (Debanjan)**

Goal: compute ionic diffusion coefficients and use Nernst–Einstein relation to estimate conductivity; measure ionic correlations that cause deviations.
Why: links microscopic diffusion to macroscopic ionic conductivity — important in batteries, electrolytes.
Recipe:

- System: simple salt (NaCl) in water or organic solvent; run at several concentrations.
- Observables:
  - Self-diffusion D_i from MSD.
  - Nernst–Einstein conductivity $\sigma_{NE} = \frac{e^2}{k_B T V} \sum_i \ z_i^2 N_i D_i$.

- Compute ionic current autocorrelation (Green–Kubo) to get exact conductivity and compare with σ_NE — difference shows ion pairing/correlations.
- Ion-pair lifetimes, RDF g_{Na-Cl}(r).
  **Deliverables:** D_i vs concentration, σ_NE vs GK σ, explanation of deviations and ion correlations.

**Ref:** Estimates of Electrical Conductivity from Molecular Dynamics Simulations: How to Invest the Computational Effort.

**Ref:** DOI: [10.1039/D1MA00572C](10.1039/D1MA00572C) - They discuss how the Nernst–Einstein approach **overestimates** conductivity compared to the correlated conductivity (Green–Kubo).

## Project 3: Assessing DNA-pepide/drug binding and solvent-mediated interaction using Free energy Perturbation Method (FEP) (Mugil)

(Run short MD of a nucleic acids system in explicit water and measure secondary structure stability; Analyze biomolecular interactions, hydrogen bonding, solvation effects measuring free energy of solvation.

Read: http://www.mdtutorials.com/gmx/free_energy/index.html

**Read** *J. Am. Chem. Soc.* 2008, 130, 30, 9747–9755

## Project 4: Calculation of Preferential Interaction Coefficient of Salt Around a Polyelectrolyte (Sayan)

**Ref:** **https://pmc.ncbi.nlm.nih.gov/articles/PMC8988897/**

experimental papers to compare with

1. **Yu Bai, Max Greenfeld, et al., "Quantitative and comprehensive decomposition of the ion atmosphere around nucleic acids."** *J. Am. Chem. Soc.* 2007.

   - Method: buffer-exchange + atomic emission spectroscopy (BE-AES) / ion counting.
   - Why useful: one of the first rigorous, quantitative ion-counting studies for short DNA duplexes — provides excess ion numbers you can directly compare to Γ from MD.

**Project 5: A Nucleic Acids Tetraloop Folding Landscape Analysis (**Rupendra**)**

Kinetics and barrier characterization (Ansari et al., PNAS 2001; Biophys J 2002)

Reading material: https://pmc.ncbi.nlm.nih.gov/articles/PMC4914146/

Experimental Evidence: Ultrafast *laser temperature-jump (T-jump)* fluorescence spectroscopy.
Findings:

- Measured folding/unfolding rates over temperature range.
- Determined *folding barrier* $\Delta G\ddagger \approx 6–8$ kcal mol$^{-1}$.
- Folding time ($\tau\_f$) $\approx 10–50$ µs; unfolding $\approx 0.1–1$ ms.
- Single-exponential kinetics → two-state folding.

Experimental Refs:

- Ansari, A., Kuznetsov, S. V., Shen, Y. (2001). *"Configurational diffusion down a folding funnel describes the dynamics of DNA hairpins."* Proc. Natl. Acad. Sci. USA, 98, 7771–7776.
  (Although nominally DNA, same group later extended to RNA UUCG.)
- Ma, H., Proctor, D. J., Kierzek, R., Kierzek, E., Bevilacqua, P. C., Gruebele, M. (2006). *"Exploring the energy landscape of a small RNA hairpin."* Proc. Natl. Acad. Sci. USA, 103(19):7268–7273.
  → RNA UUCG hairpin directly, microsecond folding kinetics measured.

**Project 6:** Find allosteric communication simulating a small biomolecule using Dijkstra's Algorithm of signal transduction from source to sink. (Gourab)

**Graph Theory Approaches for Molecular Dynamics**

**Simulations:** doi: 10.1017/S0033583524000143

Experimental Ref on ADK's allosteric site:
https://pmc.ncbi.nlm.nih.gov/articles/PMC10160949/

**Project 7:** **Simulate a binary mixture of water and any electrolyte sampling various concentration and calculate any collgigative property (such, as osmotic pressure).**

**(Challenging part: Brainstorm to connect to McMillan-Mayer theory of solutions)**

**(Avik)**

**Thought Process:**

## Compute virial expansion using MM effective potentials (PMFs) → Π(c)

- Compute effective solute–solute PMFs w_ij(r) in solvent (e.g., ion-ion PMFs) via umbrella sampling or from g_ij(r):
$$w_{ij}(r) = -k_B T \ln\, g_{ij}(r)$$
(valid if g is the solute–solute RDF in presence of solvent).
- Compute second virial coefficient B₂ from w(r):
$$B_2 = -\frac{1}{2} \int (e^{-\beta w(r)} - 1) d\mathbf{r}$$
- Build MM virial expansion for osmotic pressure (solute-only ensemble):
$$\Pi = k_B T c + k_B T B_2 c^2 + k_B T B_3 c^3 + \cdots$$
where c is solute number density (for symmetric electrolytes special counting applies — see below).
- Pros: directly connects MD observables to McMillan–Mayer, MM theory; conceptually clean. Cons: requires accurate PMFs and evaluation of higher virial coefficients for mid/high concentrations; long-range electrostatics complicate integrals.

## System choices (recommended)

- Electrolyte: NaCl (1:1) — simplest. Alternatives: KCl, CsCl or MgCl₂ (divalent but adds complications).
- Water model: TIP4P-Ew or OPC (better dielectric properties than TIP3P). Use ion parameters compatible with chosen water model (e.g., Joung & Cheatham or Li & Merz tuned for TIP4P).
- Box size: For RDF/PMF and KB integrals want large boxes; start with ~4–6 nm cubic box containing ~4000–10000 water molecules depending on concentration.
- Concentrations: 0.0, 0.1, 0.5, 1.0, 2.0 M (convert molarity → number of ion pairs given box volume).
- Ensemble: NPT (1 atm, 300 K) for equilibration; for production NVT is fine if comparing concentrations (but NPT recommended to capture density changes).

- Electrostatics: PME with appropriate real-space cutoff (e.g., 1.0 nm), dispersion correction for energy/pressure.
- Integration: 2 fs timestep with constraints on bonds (LINCS/SHAKE).

Software: GROMACS (recommended).

**From PMF → B₂ → Π (detailed)**

For a symmetric 1:1 electrolyte you need to treat all pair types (cation–cation, cation–anion, anion–anion). In MM formalism solute species are ions; but because of charge neutrality, effective interactions include long-range Coulomb screened by solvent — PMFs will reflect that.

- Compute $B_2$ for each pair type:
$$B_2^{ij} = -\frac{1}{2}\int_0^\infty 4\pi r^2 (e^{-\beta w_{ij}(r)} - 1)dr.$$

- For mixture, the net second-virial contribution to osmotic pressure depends on species concentrations; for electroneutral electrolytes ($c_+ = c_- = c$), the leading term is ideal: $\Pi\_ideal = kT (c_+ + c_-) = 2 kT c$ for number density of particles. But in MM osmotic pressure is defined relative to solvent — standard formula often uses moles of solute pairs (see careful counting). For 1:1 electrolyte it's conventional to treat osmotic pressure per formula unit: $\Pi \approx kT v c + kT B\_2' c^2$ ... where v is number of solute particles per formula unit (v=2). Be explicit in your bookkeeping so you compare to experimental osmotic coefficients correctly.

- Numerically integrate w(r) → $B_2$ (cutoff r_max must be large; include tail correction or extrapolate).

- Build virial series:
$$\Pi = k_B T v c + k_B T B_2^{\text{eff}} c^2 + \cdots$$

For moderate-to-high c (>0.5 M) higher virial terms become important; you may need $B_3$ which can be estimated via three-body PMFs (expensive) or using empirical corrections.

Plan you could try: Take an example PMF (or a sample g(r)) and show the full pipeline: compute w(r) → $B_2$ (with Debye-tail correction) → Π(c) and overlay experimental points from Hamer & Wu / Pitzer (DoI: https://doi.org/10.1063/1.3253108).

8. **Project 8 (Subham)**

***How does solvation structure change around a hydrophobic vs. hydrophilic nanoparticle? (*MD part: Simulate spherical solutes**

(i) Ref to read: *Water's structure around hydrophobic solutes and the hydrophobic effect*.

DoI:

(ii) Experimental paper to benchmark model: Water Content in Nanoparticles Determined by Small-Angle Neutron Scattering and Light Scattering