Simulation and Generalized Langevin Equation Study of Lipid Subdiffusion in Biomembrane Phases

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Background

Membranes show anomalous (often sub-diffusive) lipid motion on ps–ns scales.
Classic hydrodynamics is insufficient; frequency-/memory-based probes capture viscoelastic effects.
We need a **phase-resolved** short-time picture across gel, ripple-like, fluid.

Significance—Clinical: Quantifying ps-ns membrane caging via VACF-derived κ(t) refines biophysical readouts (FRAP/NMR/IR), supporting more reliable diffusion estimates in complex or diseased membranes and informing assay interpretation for membrane-active therapeutics.

Significance—Biological: Phase-dependent transient caging (gel > ripple-like > fluid) links local viscoelastic memory to lipid mobility, offering a mechanistic basis for how packing and hydration modulate subdiffusion in cell-like membranes.

Simulation Details

System (Different Temperatures)	324, 316 (fluid), 290, 288 (ripple), 268, 248 K (gel)
Force field (All atom)	CHARMM36 [128 DMPC lipids]
Water Model	TIP4P/2005
Annealing Rate	0.01 K/ps
Sampling for Analysis	NVT (Dynamic analysis): saving frequency 0.01 ps; 30 ns; 4 independent sets NPT (Structure analysis): saving frequency 10 ps; ~100 ns; 4 independent sets
Constraints	Equilibration: H-bonds Production: None
Analysis	Used inhouse code in python

Microscopic Memory → Macroscopic Transport

Equations connecting ps memory to diffusivity (D)

MSD scaling : $W(t) = \left\langle \left(\boldsymbol{x}(t) - \boldsymbol{x}(0)\right)^2 \right\rangle \overset{(t\to\infty)}{\sim} 2dD_\alpha t^\alpha$

VACF to MSD (exact link): $W(t) = 2\int_0^t d\tau (t-\tau) c(\tau)$

Subdiffusive VACF tail: $c(t) \sim D_\alpha \alpha(\alpha-1)t^{\alpha-2}$, as $t \to \infty$

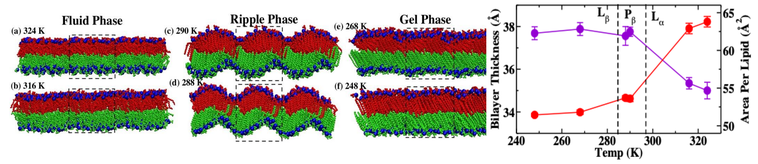
VACF correlation time: $\tau_{VACF} = \left(\frac{D_\alpha}{\langle v^2 \rangle}\right)^{\frac{1}{2-\alpha}}$

Generalized Langevin (memory kernel): $\frac{\partial c(t)}{\partial t} = -\int_0^t \kappa(t-t')c(t')\,dt'$

Effective cage size from short-time κ(t): $\kappa(t) \overset{t\to\infty}{\sim} \frac{\langle v^2 \rangle}{\langle u^2 \rangle}$ for $\alpha \to 0$, cage size $(\sqrt{< \boldsymbol{u}^2 >})$

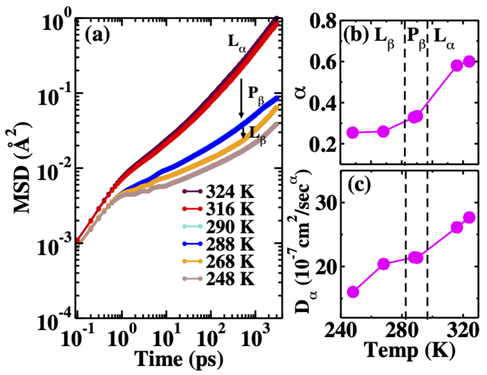
Results and Discussion

Bilayer Structural Properties: Area per Lipid and Bilayer Thickness

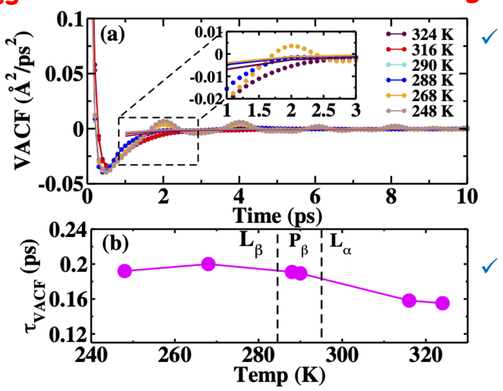


Area per lipid (APL) decreases and **thickness** increases with cooling → tighter packing → reduced mobility

Sub-Diffusive Behavior and Fractional Diffusion Across Membrane Phases

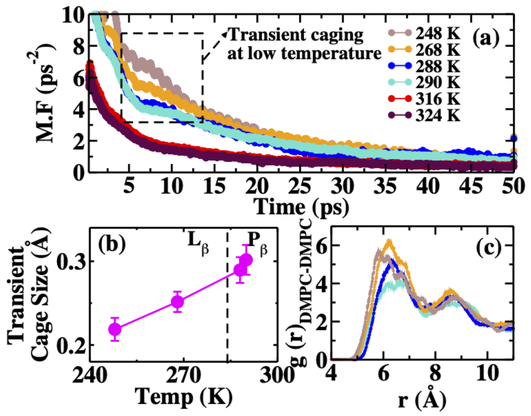


Velocity Autocorrelation Function and Molecular Caging



- Low-T phases show **deeper negative dips** and **longer positive tails**, indicating **transient caging** and subdiffusion.
- The **correlation time** τ_{VACF} grows as temperature decreases / order increase

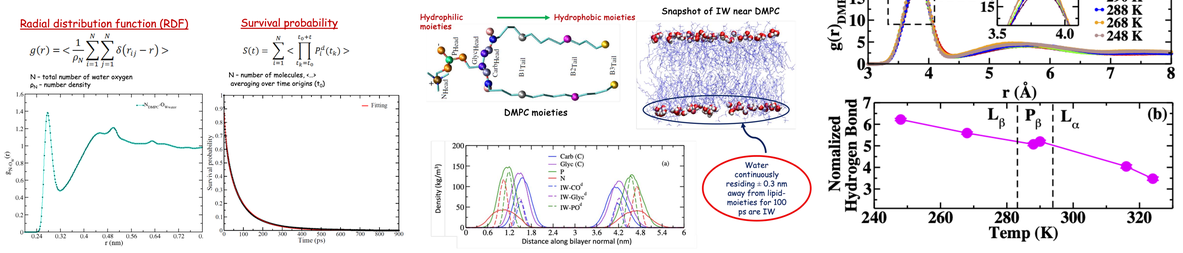
Memory Effects in Lipid Diffusion : Insights from the Generalized Langevin Equation



- **Memory function (κ(t), model-free GLE).** Inversion of VACF yields a **positive long-time tail** with a **5–10 ps hump** at lower T/greater order—hallmarks of **transient molecular caging.**
- Short-time κ(t) gives an **effective cage scale** $\sqrt{\langle u^2 \rangle}$,which **decreases** as ordering increases.

Interfacial Water (IW) and Hydrogen Bonding Effects on Lipid Transient Caging

Identification of interface water (IW)



Limitations

- ✓ **Finite size:** 128-lipid box → use **"ripple-like"**; cannot resolve full ripple periodicity/conformer spectrum.
- ✓ **Timescale:** Analysis is **ps–ns**; does **not** target long-time hydrodynamic D.
- ✓ **Model choices:** Force field, water model, thermostat can shift absolute values; relative trends are robust.
- ✓ **Uncertainty:** Report fit windows/SEMs for **α**, D_{alpha}, , τ_{VACF} , κ(t)

Conclusions

- ✓ Phase-dependent subdiffusion quantified via MSD, VACF, and **κ(t)**; τ_{VACF} and cage size track order.
- ✓ κ(t) plateau/positive tail is a **dynamical fingerprint** of caging.
- ✓ Framework links ps memory to slower transport; extendable to mixtures/proteins

Future Directions and Questions

- ✓ **Scale up systems**; apply **hydrodynamic corrections** to link ps–ns memory to long-time **D**.
- ✓ **Method upgrade:** more robust **VACF → κ(t)** inversion with **uncertainty** estimates.
- ✓ **Experiment bridge:** predict **FRAP, PFG-NMR, QENS** directly from **κ(t)**.
- ✓ **ML screening:** learn mapping **structure → (α, τ_{VACF}, κ-tail)** for fast design.

Scan for code and poster PDF

References

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