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Simulating the effects of charged lipids on bilayer area compressibility

Harrie Ha

Mentors: James “Shea” Fitzgerald and Elizabeth Kelley

Membranes Define Boundaries

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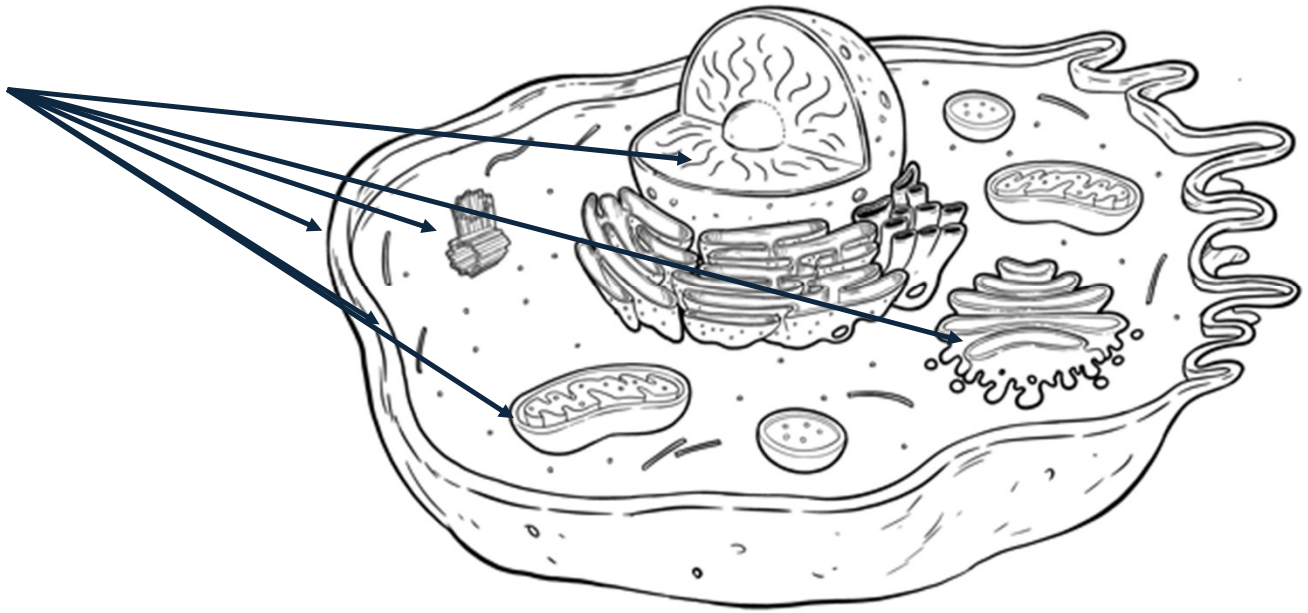
Anything you see here that has a boundary has a lipid membrane!



The core purpose of the membrane is to define boundaries and keep the cell functional.

Balancing Flexibility and Rigidity

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Membranes are vital to cell processes like cell division and diffusion. However, these processes must still occur **while** maintaining a strong boundary EX: Blood cells need to be flexible enough to flow, but not break!

Q: How do membranes achieve this?

Balancing Flexibility and Rigidity

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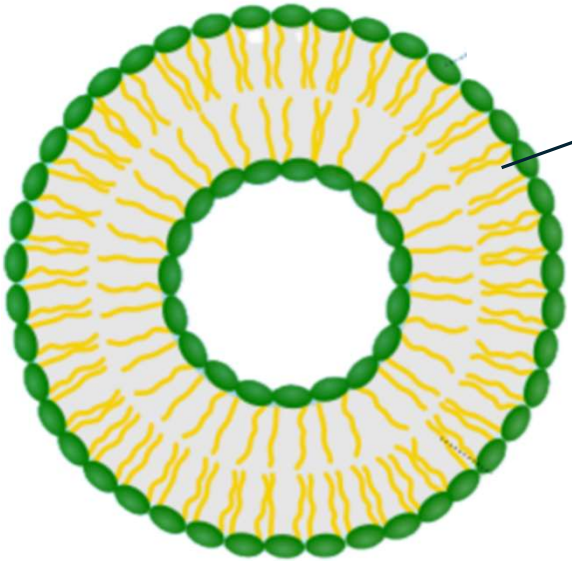
Membranes are vital to cell processes like cell division and diffusion. However, these processes must still occur **while** maintaining a strong boundary EX: Blood cells need to be flexible enough to flow, but not break!

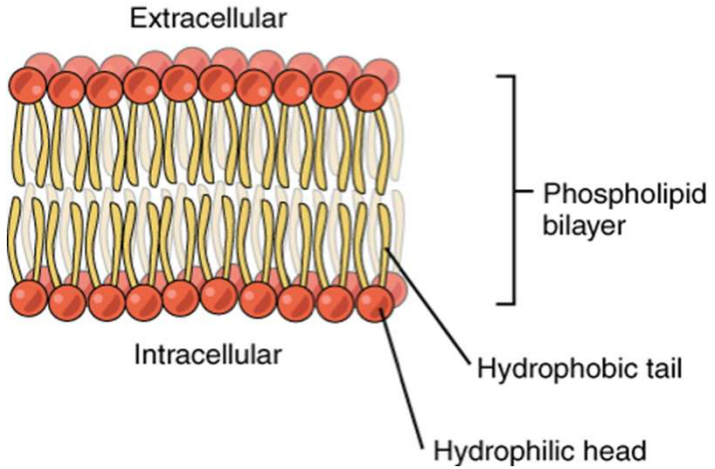
Q: How do membranes achieve this?

A: Lipids!

Cross Section of a Membrane



By SuperManu - Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=2918850



Clark, M. A., Douglas, M., & Choi, J. (2018). Lipids. In *Biology 2e*. Houston, Texas: OpenStax. Retrieved from https://openstax.org/books/biology-2e/pages/3-3-lipids

Biomembranes adjust their mechanical properties by changing their lipid composition

Biologically Common Lipids

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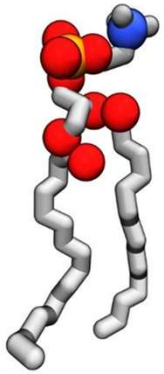
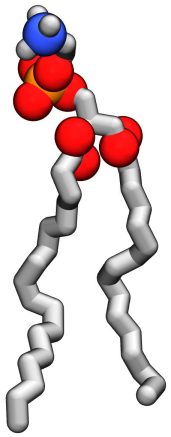
Neutral



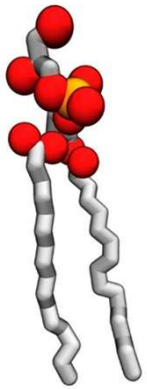
DPPC

Tails Headgroup

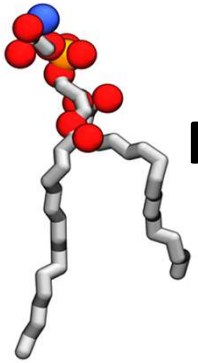


POPC

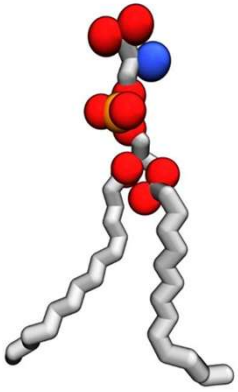
Charged



DPPG



POPS



DPPS

Area Compressibility (K_A)

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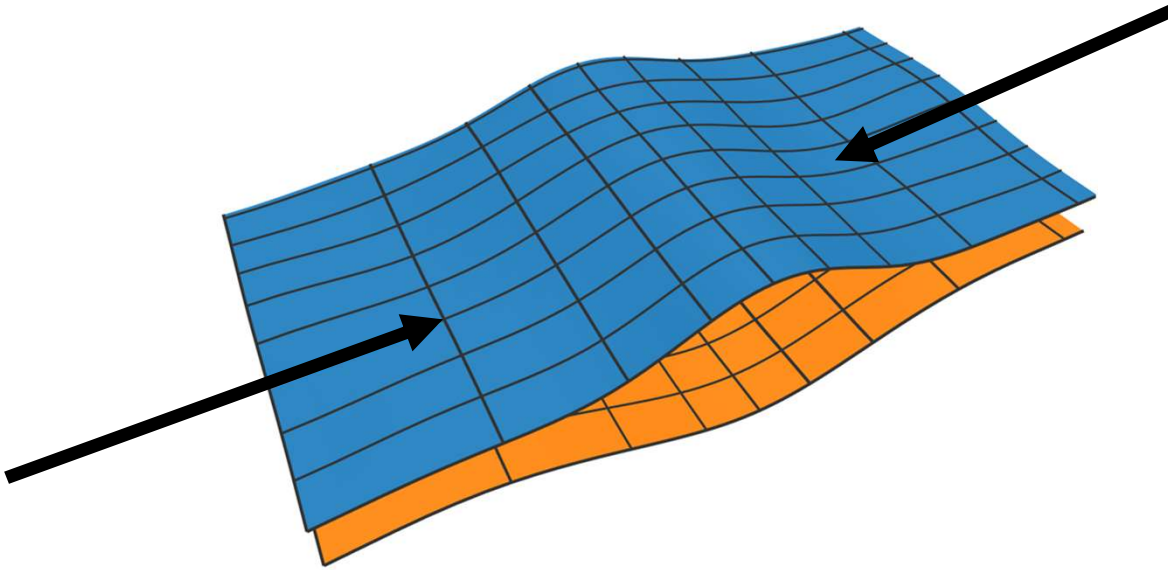
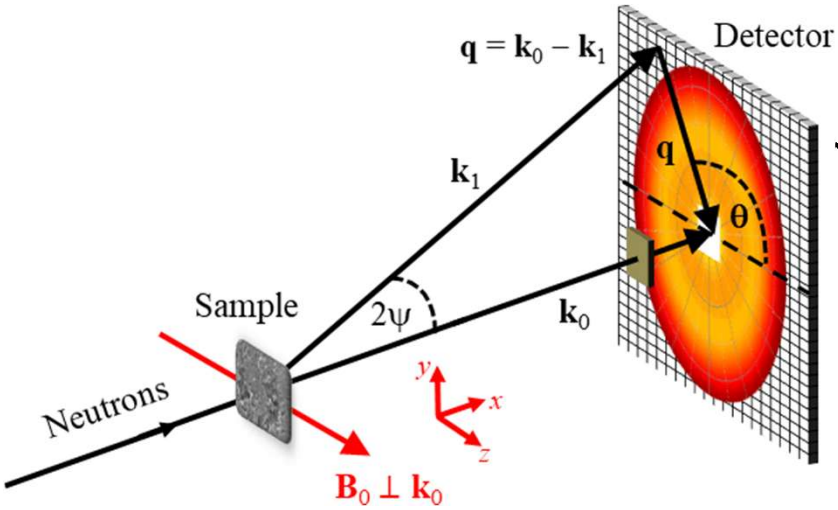
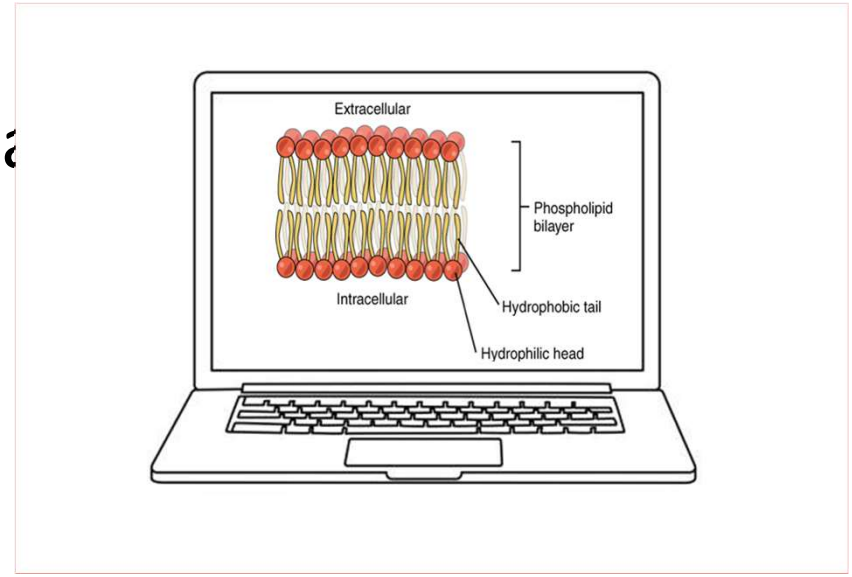
The bilayer's resistance to mechanical compression



Combining Scattering and Simulation



ne mecha



Magnetic neutron scattering from spherical nanoparticles with Neel surface anisotropy: Atomistic simulations - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Sketch-of-the-neutron-scattering-geometry-The-applied-magnetic-field-B-0-e-z-is_fig1_360640775

Neutron Scattering Analysis Is Hard!

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$$S(q,t) \sim \exp\left[-\frac{k_B T q^2 R^2}{4\pi} \sum_{\ell=2}^{\lfloor \pi R/\delta \rceil} (2\ell+1) \frac{(1-Q_{11})e^{-\gamma_1 t} + Q_{11} e^{-\gamma_2 t}}{(\ell(\ell+1)-2)(\ell(\ell+1)\kappa)}\right]$$

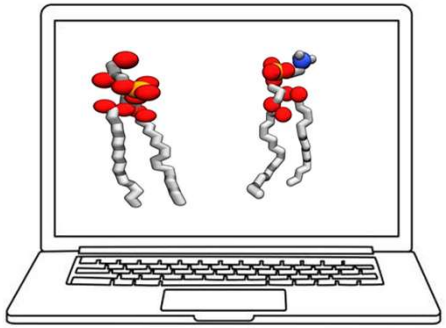
Vlahovska, Petia M., and Rony Granek. "Equilibrium Fluctuations of a Quasi-Spherical Vesicle: Role of the Membrane Dissipation." *Soft Matter*, 2026, 10.1039.D6SM00156D. https://doi.org/10.1039/D6SM00156D.

$$Q_{11} = \frac{1}{2} + 2\frac{\begin{array}{l}\ell^6(\lambda^2-\alpha)\chi_s + \ell^5(\lambda^2-\alpha)(3\chi_s+2) \\ +\ell^4\left[(\lambda^2-\alpha)(2\beta+5) - 2\lambda^2\chi_s\right] \\ +\ell^3\left[\lambda^2(-9\chi_s+4\beta-4) + 4\alpha^2 + \alpha(-4\beta+5\chi_s)\right] \\ +\ell^2\left[-\lambda^2(6\beta+11) + 3\alpha\lambda + \alpha(5+6\alpha+2\beta)\right] \\ +\ell\left[4\lambda^2(1-2\beta) + \alpha(2+4\beta+3\lambda) + \chi_s(8\lambda+4\alpha^2-2\alpha)\right] \\ +4\lambda^2(2\beta+1) - 6\lambda\alpha - \alpha^2 - 4\chi_s(2\alpha^2+\lambda)\end{array}}{2\alpha\sqrt{\begin{array}{l}\left[2\alpha\left(-4\left(\ell^2+\ell-2\right)\chi_s - 2(2\ell+3)\ell^2+1\right)\right. \\ \left.+2(\ell-1)\ell(\ell+1)(\ell+2)\left(2\beta+\left(\ell^2+\ell-1\right)\chi_s+2\ell+1\right)\right]^2 \\ -4(1-\ell)(\ell+2)\left(-\lambda+4\lambda\left(\ell^2+\ell-2\right)\chi_s + \ell(\ell(\lambda(4\ell+6)+3)+3)\right) \\ \cdot\left(6\alpha+2\lambda(\ell-1)(\ell+2)\left(2\beta+\left(\ell^2+\ell-1\right)\chi_s+2\ell+1\right)\right)\end{array}}}$$

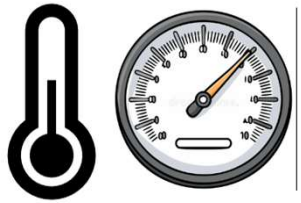
and

$$\gamma_{1,2} = \ell(\ell+1)\frac{\begin{pmatrix}-(\ell-1)\ell(\ell+1)(\ell+2)\left(2\beta+\left(\ell^2+\ell-1\right)\chi_s+2\ell+1\right) + \alpha\left(-4\left(\ell^2+\ell-2\right)\chi_s - 4\ell^3 - 6\ell^2+1\right) - 3\lambda(\ell-1)(\ell+2) \\ \mp\frac{1}{2}\sqrt{\begin{array}{l}\left(2(\ell-1)\ell(\ell+1)(\ell+2)\left(2\beta+\left(\ell^2+\ell-1\right)\chi_s+2\ell+1\right) + 2\alpha\left(-4\left(\ell^2+\ell-2\right)\chi_s - 4\ell^3-6\ell^2+1\right)\right)^2 \\ -4(1-\ell)(\ell+2)\left(-\lambda+4\lambda\left(\ell^2+\ell-2\right)\chi_s + 4\lambda\ell^3 + (6\lambda+3)\ell^2 + 3\ell\right) \\ \cdot 6\alpha + 2\lambda(\ell-1)(\ell+2)\left(2\beta+\left(\ell^2+\ell-1\right)\chi_s+2\ell+1\right)\end{array}}\end{pmatrix}}{9+(1-6\ell^2-4\ell^3-4(-2+\ell+\ell^2)\chi_s)(2+4\ell+4\beta+2(-1+\ell+\ell^2)\chi_s)}$$

Getting K_A Through Simulation

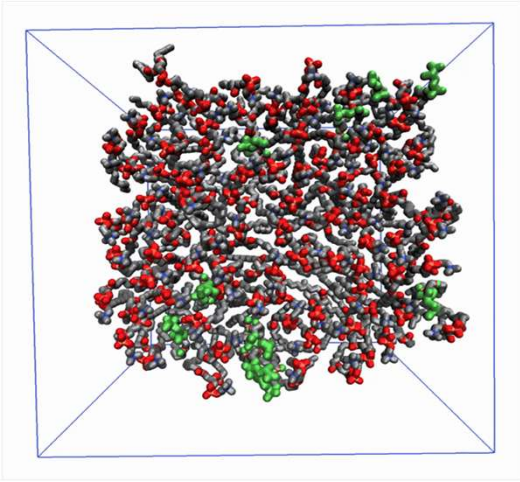


Select lipid composition

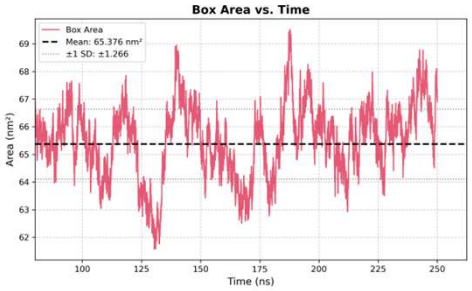


Select temperature & pressure

$$K_A = \frac{k_B T \langle A \rangle}{\langle \delta A^2 \rangle}$$



Extract box size

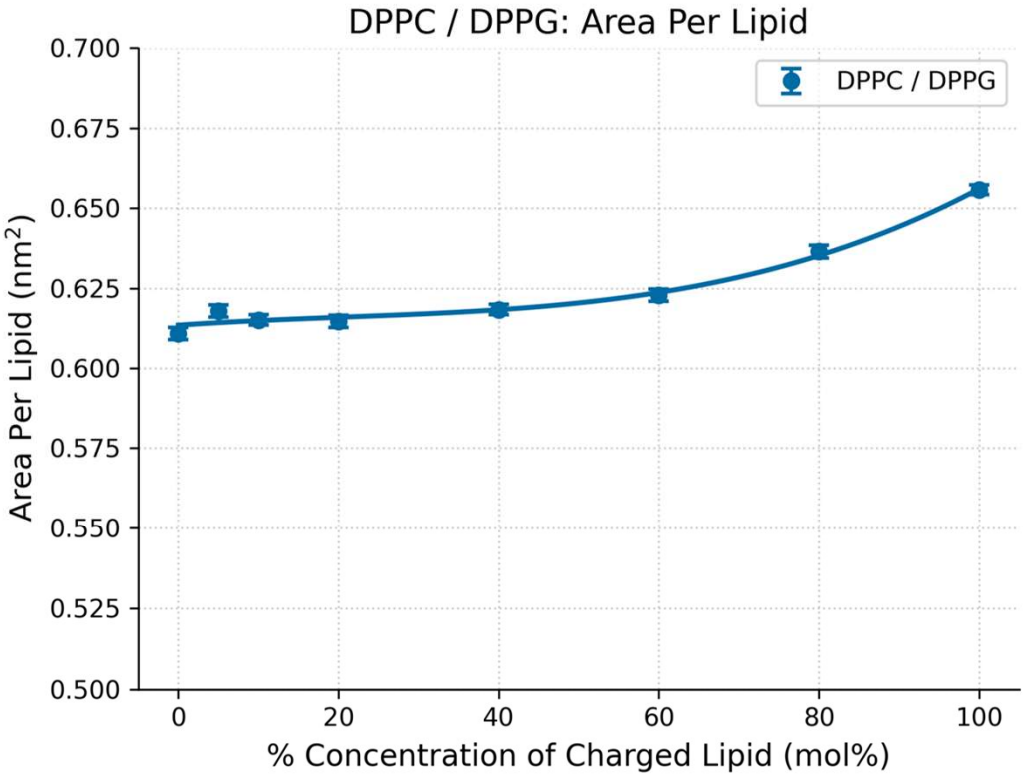


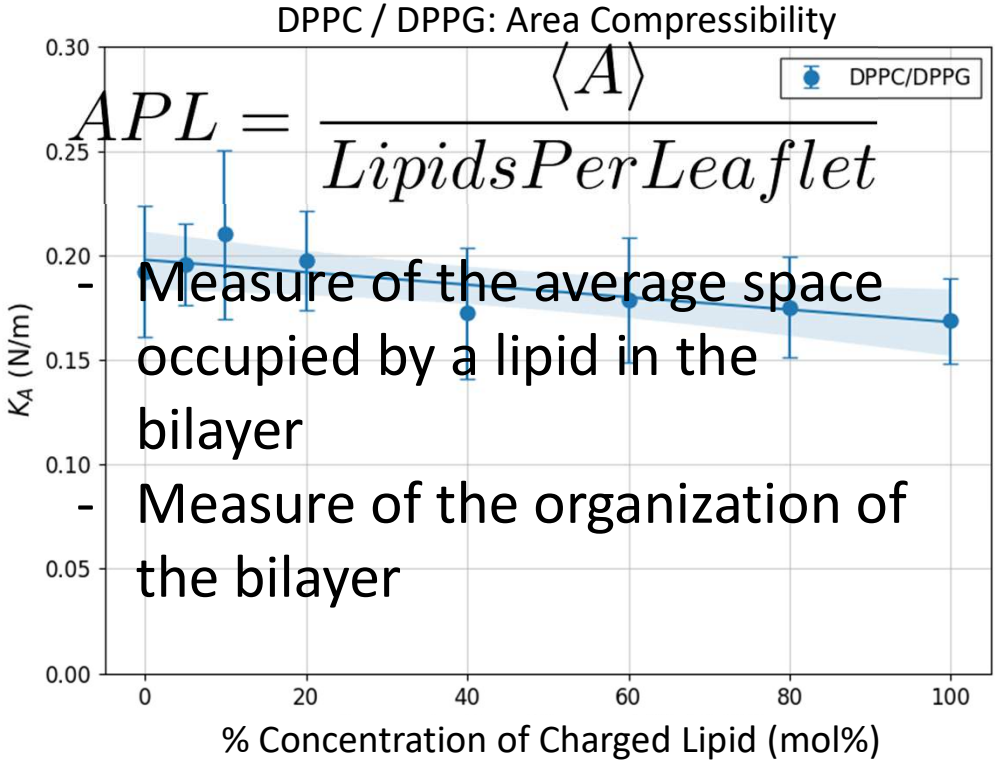
Analyze!

Venable, R. M., Brown, F. L. H., & Pastor, R. W. (2015). Mechanical properties of lipid bilayers from molecular dynamics simulation. *Chem. Phys. Lipids*, 192, 60–74. https://doi.org/10.1016/j.chemphyslip.2015.07.014

How do charged lipids affect area compressibility?

APL Increase, K_A (Nearly) Unchanged

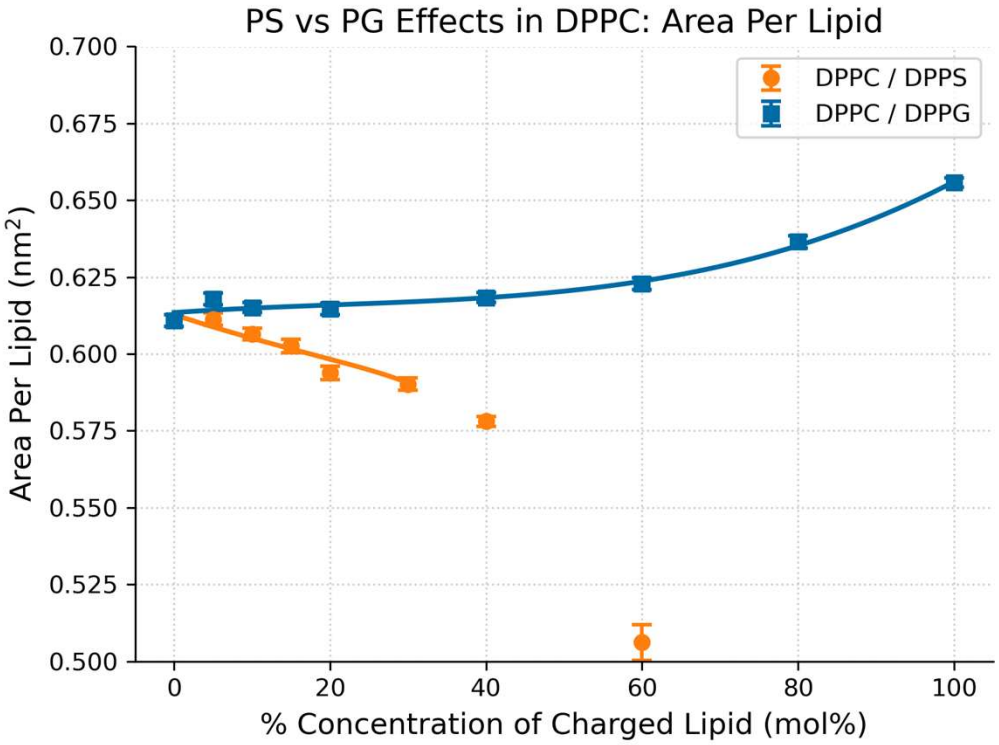


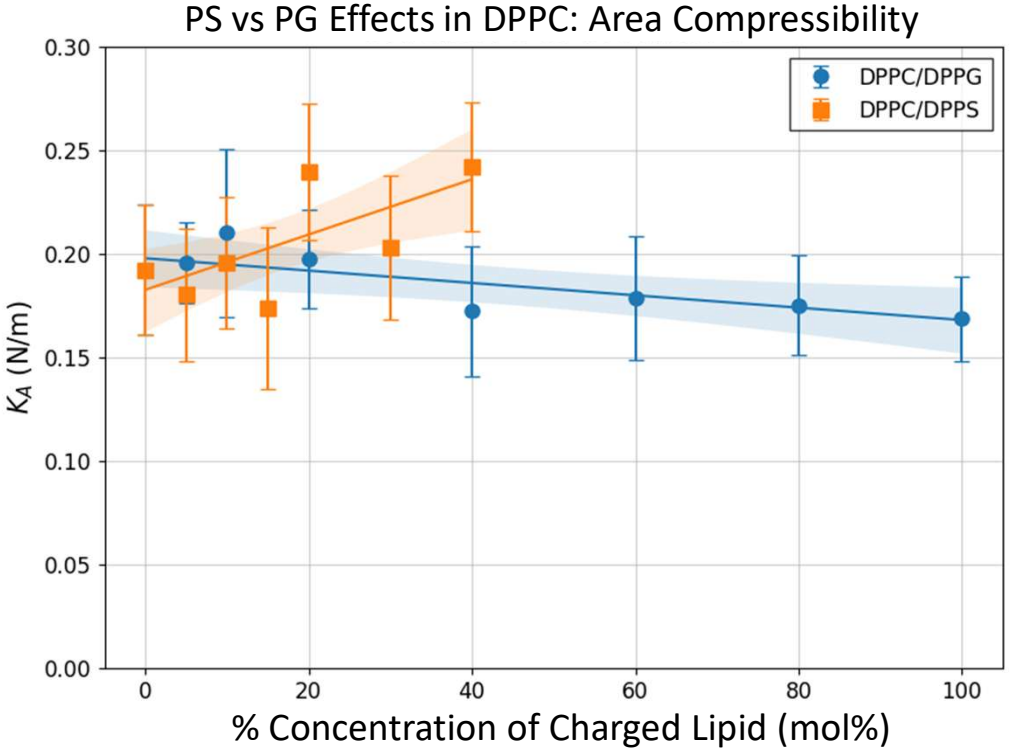


$$APL = \frac{\langle A \rangle}{LipidsPerLeaflet}$$

- Measure of the average space occupied by a lipid in the bilayer
- Measure of the organization of the bilayer

DPPC/DPPS: Very Different Behavior!





4:6 DPPC:DPPS Becoming Gel

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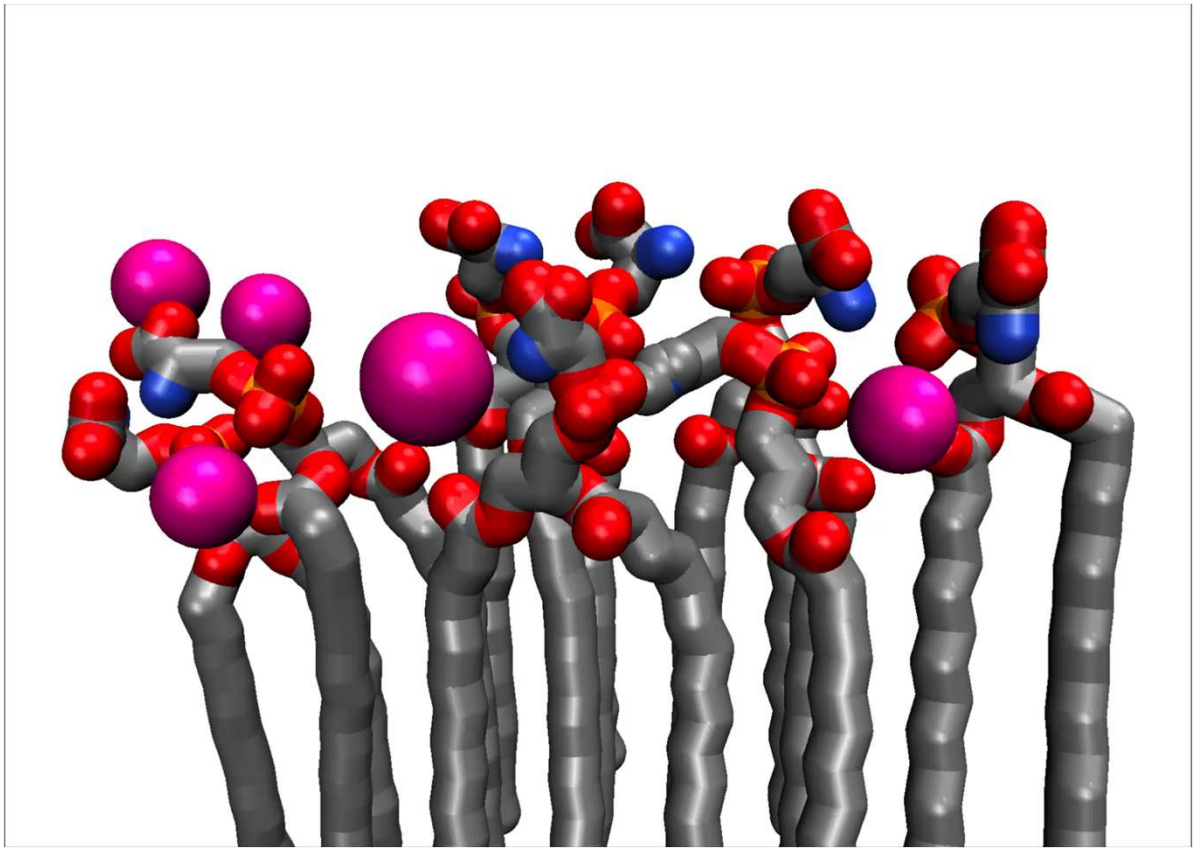
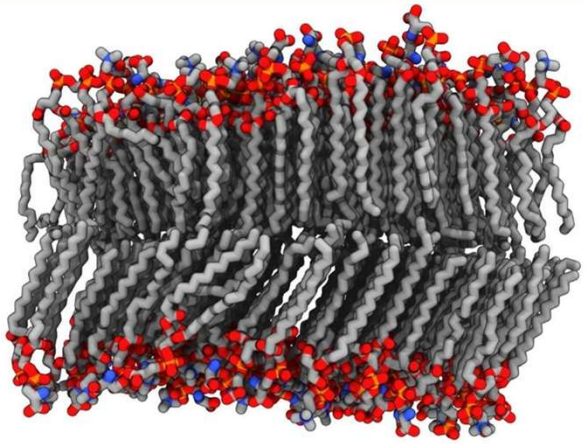
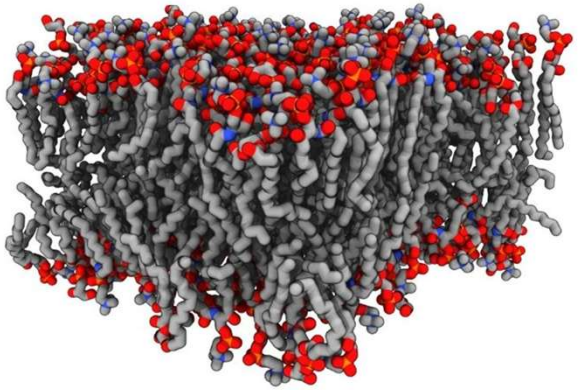




Gel 4:6 DPPC:DPPS



Liquid Bilayer

Charge Distribution of DPPG & DPPS

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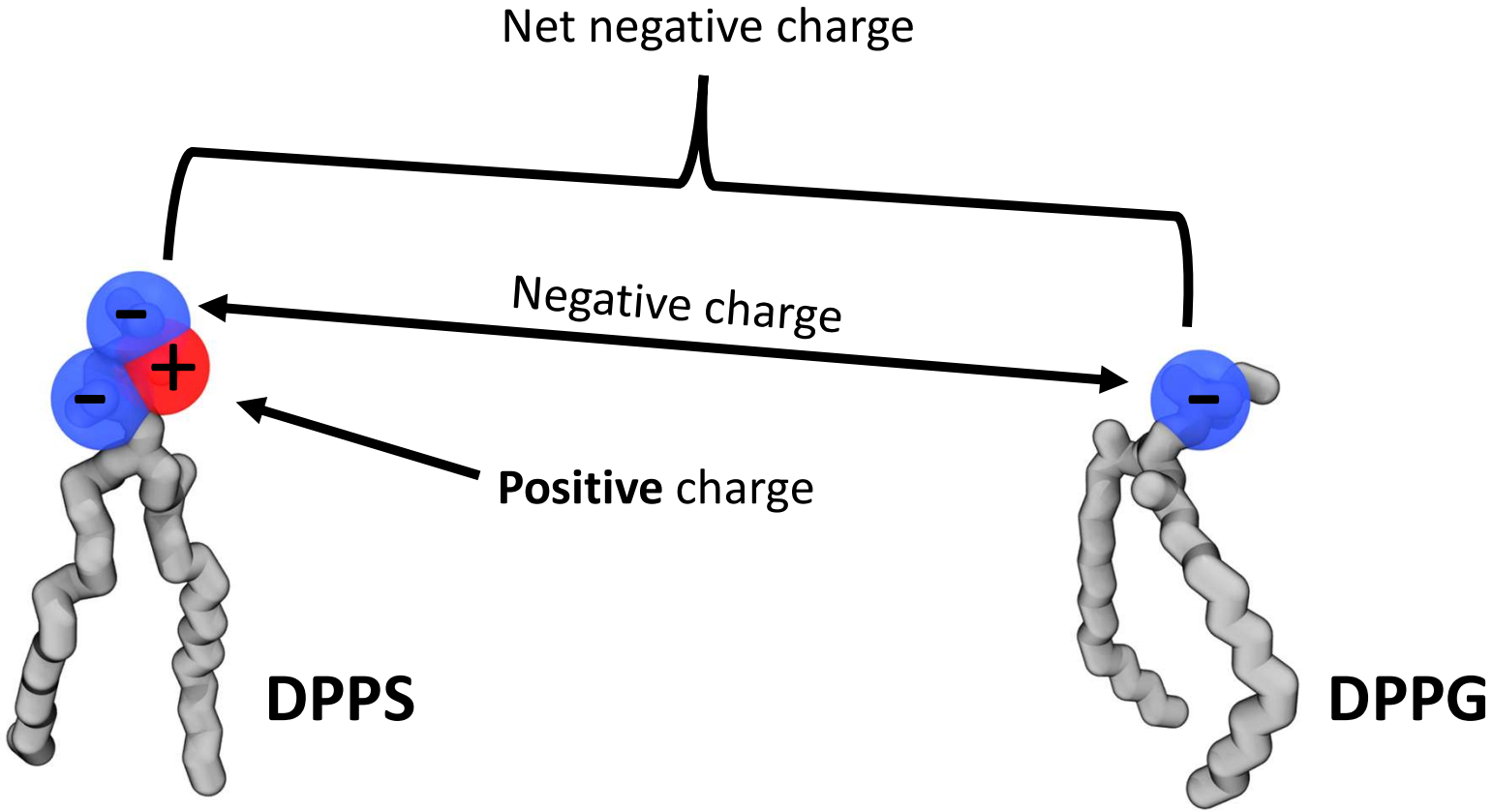

Charge Distribution of PS vs PG

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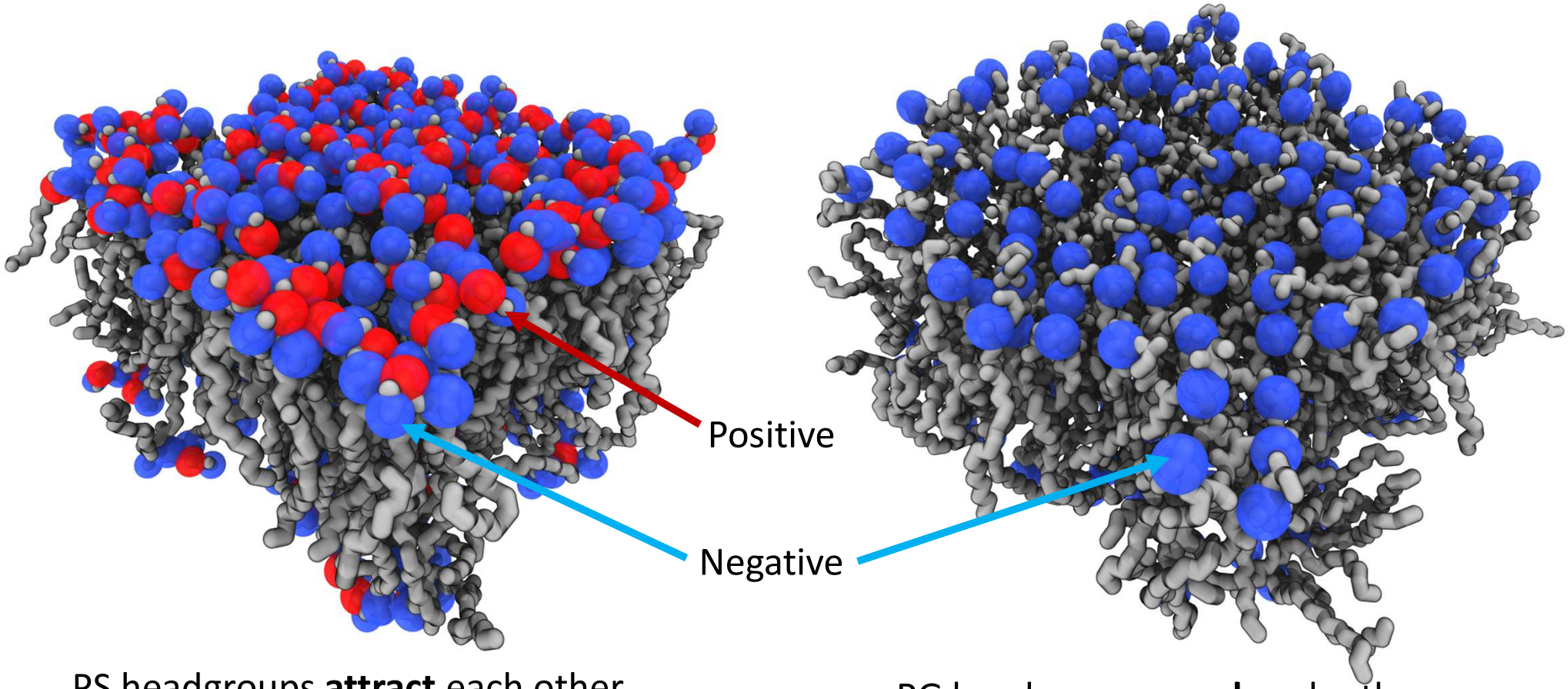

PS headgroups **attract** each other

PG headgroups **repel** each other

Charge Distribution of DPPG & DPPS

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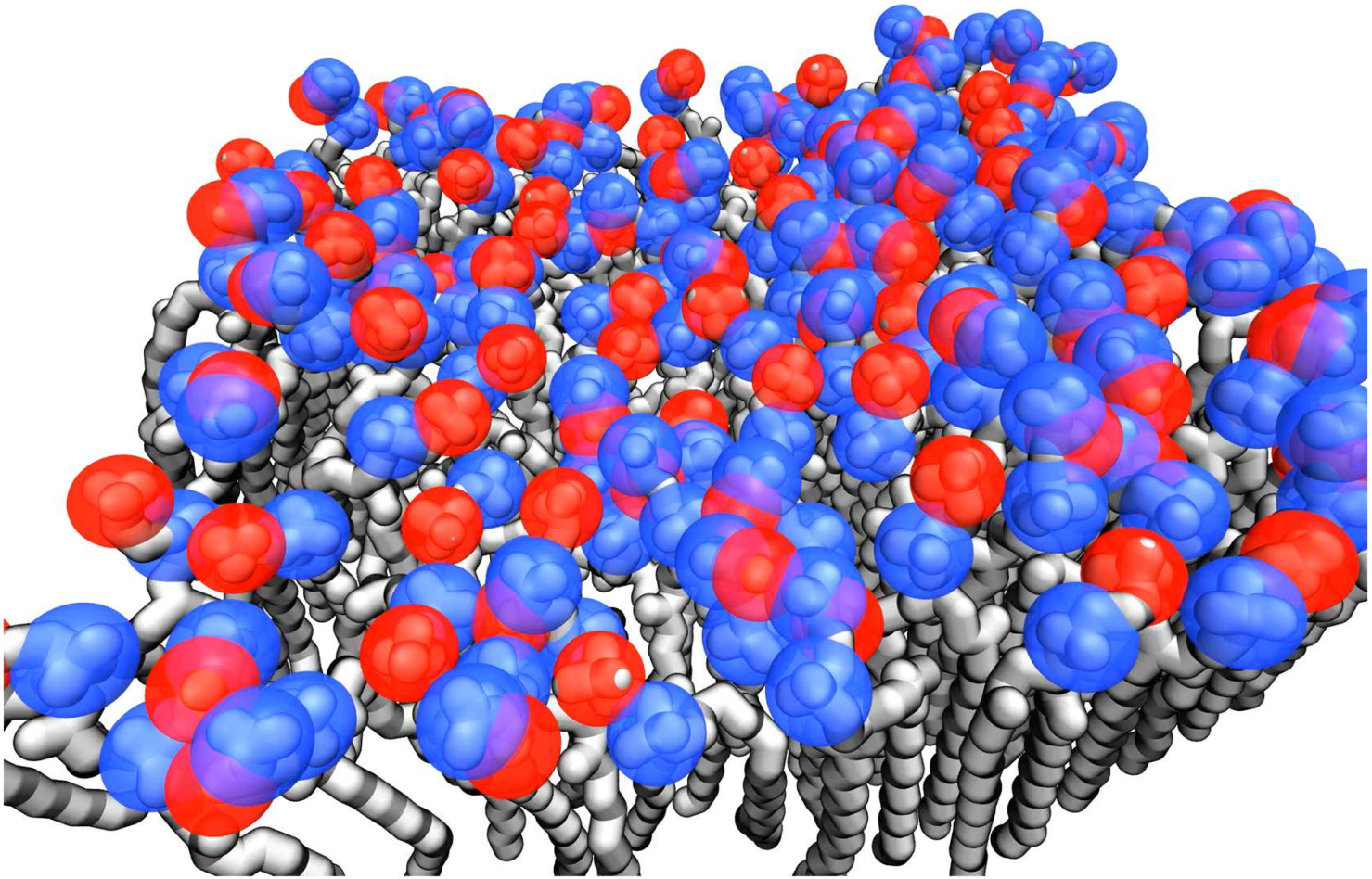
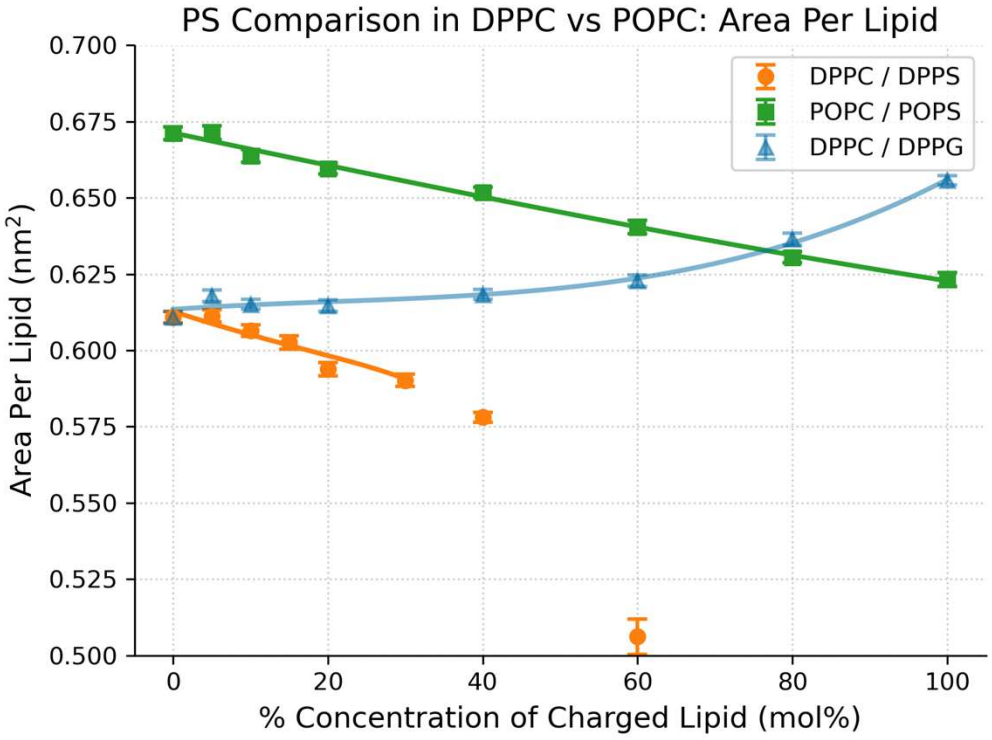
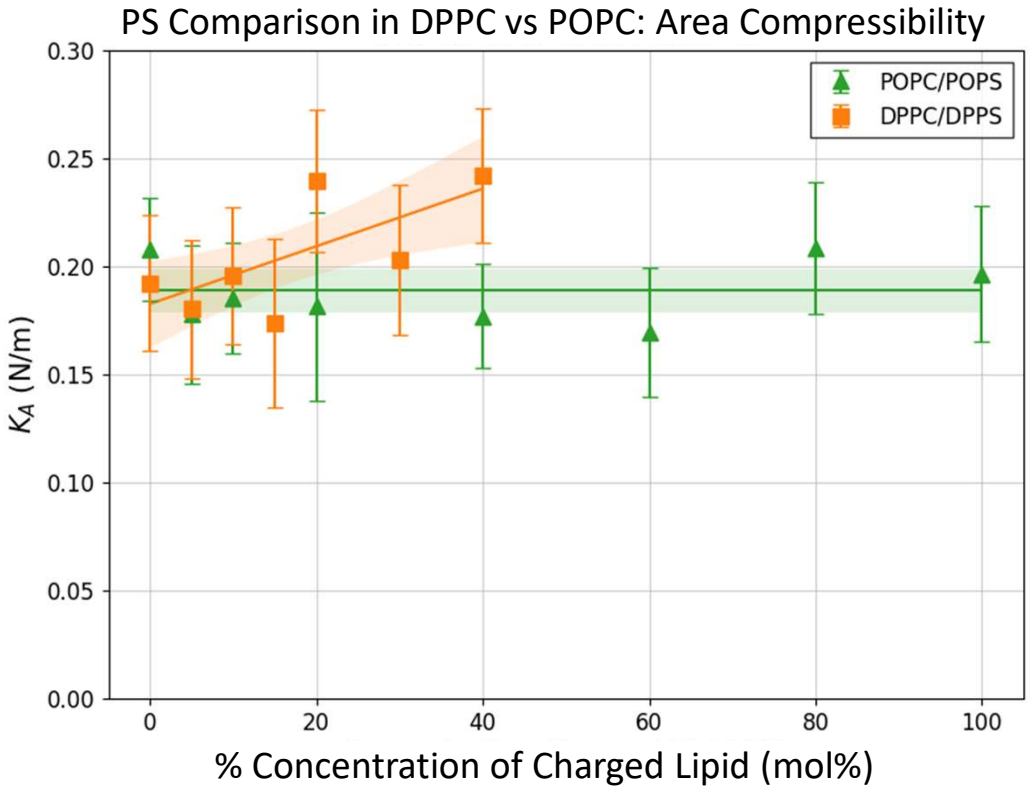


POPS: APL Still Decreases





Summary & Future Work

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Summary

- PS and PG lipids have different effects on the membrane despite having the same charge
- Area per lipid is fairly impacted but not the area compressibility

Future Work

- Evaluating Polymer brush model (a well-known theory in bilayer studies)

$$K_A \propto A_L^2 \kappa$$

- Applications to experimental/material design

- Applications to analysis on NSE data of bilayers (recently collected at ILL, soon to be collected at NCNR!)

Rawicz ... Evans. *Biophysical Journal* 79, 1 (2000): 328-39

Acknowledgements

I would like to thank my mentors, James Fitzgerald and Elizabeth Kelley, for their guidance and support throughout this project.

Also to the SURF organizers: Cara O'Malley, Julie Borchers, Kelsi Rehmann, and Susana Teixeira

RCHPC (Research Computing and High Performance Computing at NIST)

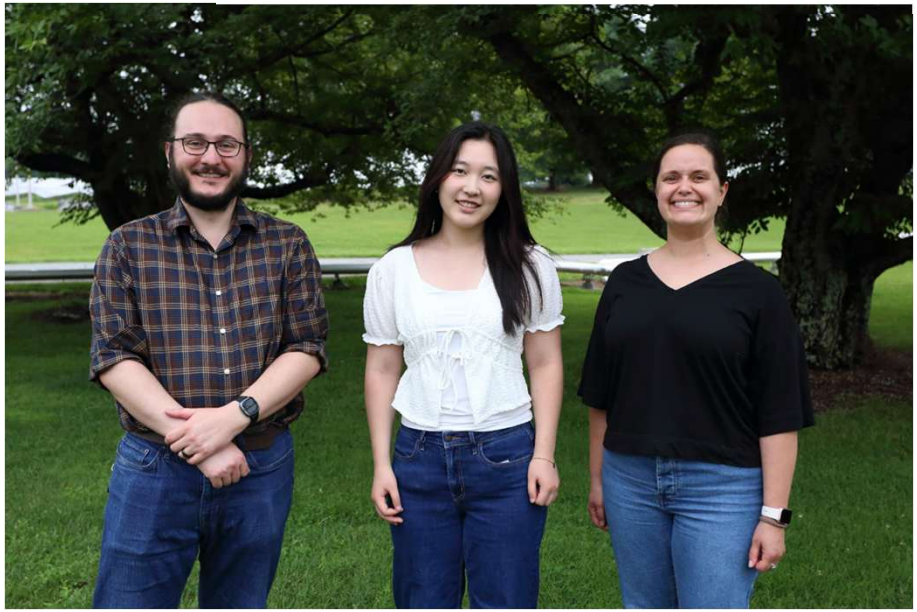

Image by Yiming Qiu

Supplementary: Lipid Phase Transitions

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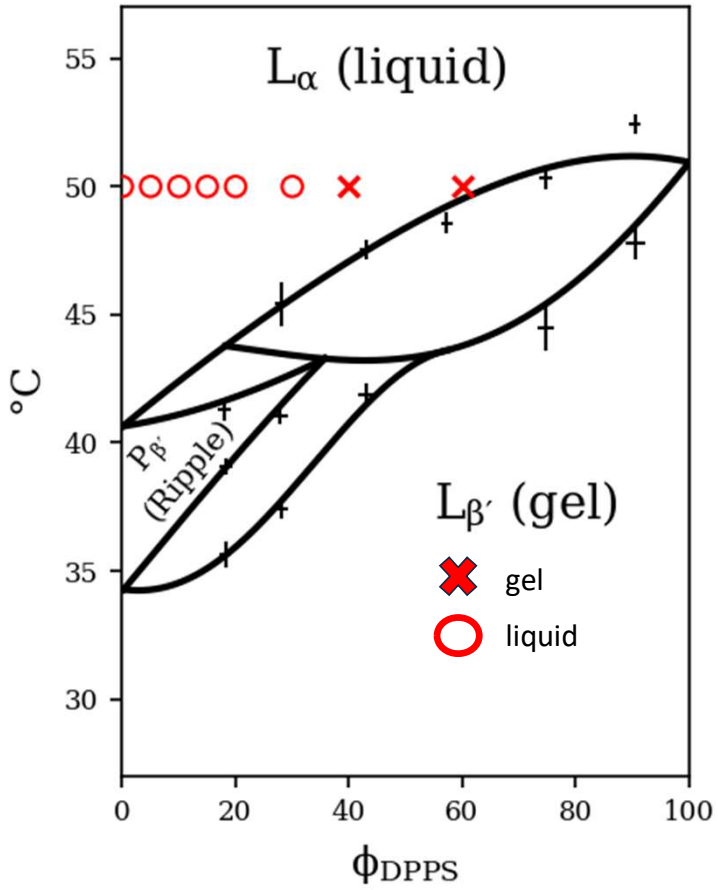
lipid	Tails	T_m (°C)	T_{sim}(°C)
EggSM	16:0	38.3	50
DPPC	16:0	41	50
DPPG (-)	16:0	41	50
DPPS (-)	16:0	54	50
POPC	16:0-18:1	-2	25
POPS (-)	16:0-18:1	14	25

Z., González-Ramírez, E.J., Goñi, F.M., Tristram-Nagle, S., & Nagle, J.F. (2018). Phase behavior of palmitoyl and egg sphingomyelin. Chemistry and Physics of Lipids, 213, 102-110. https://doi.org/10.1016/j.chemphyslip.2018.03.



Luna, Elizabeth J., and Harden M. McConnell. "Lateral Phase Separations in Binary Mixtures of Phospholipids Having Different Charges and Different Crystalline Structures." *Biochimica et Biophysica Acta (BBA) - Biomembranes* 470, no. 2 (1977): 303–16. https://doi.org/10.1016/0005-2736(77)90108-0.

Supplementary: POPC/POPS

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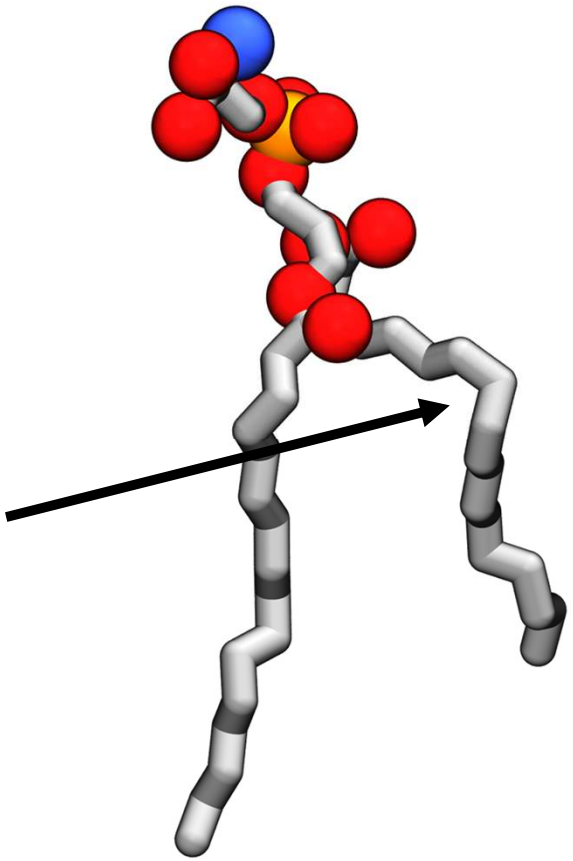
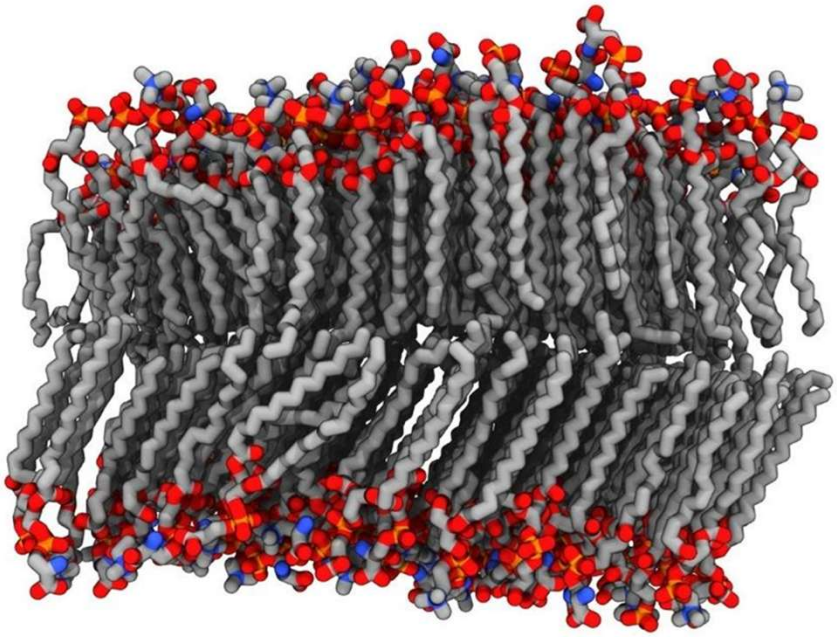
Q: Why does POPC/POPS start at a higher APL than DPPC/DPPS?

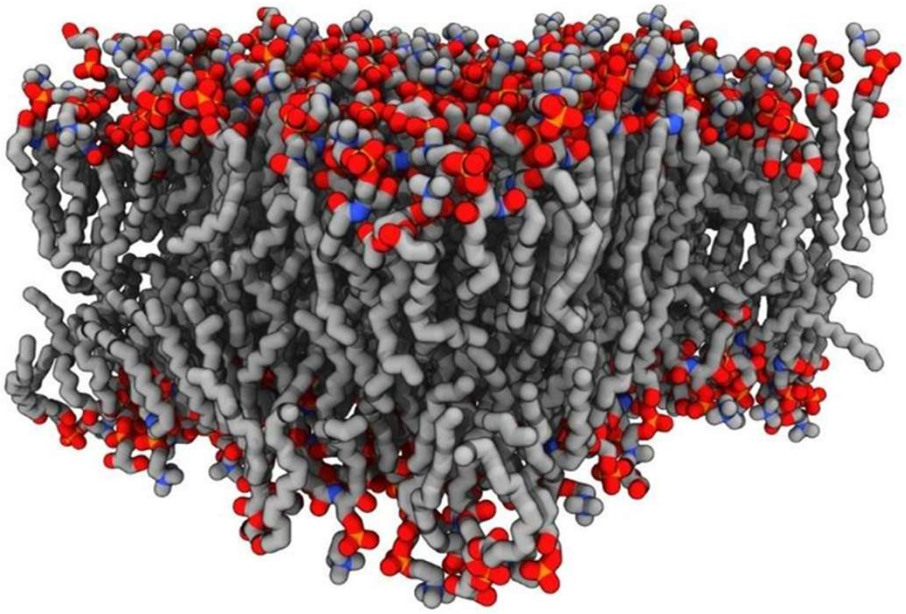
A: Due to having an extra bend in the tail, the POPS takes up more space than the DPPS, resulting in more APL.



Supplementary: Gel vs Liquid



Gel 4:6
DPPC:DPPS



Liquid ESM

Supplementary: DPPS/DPPC

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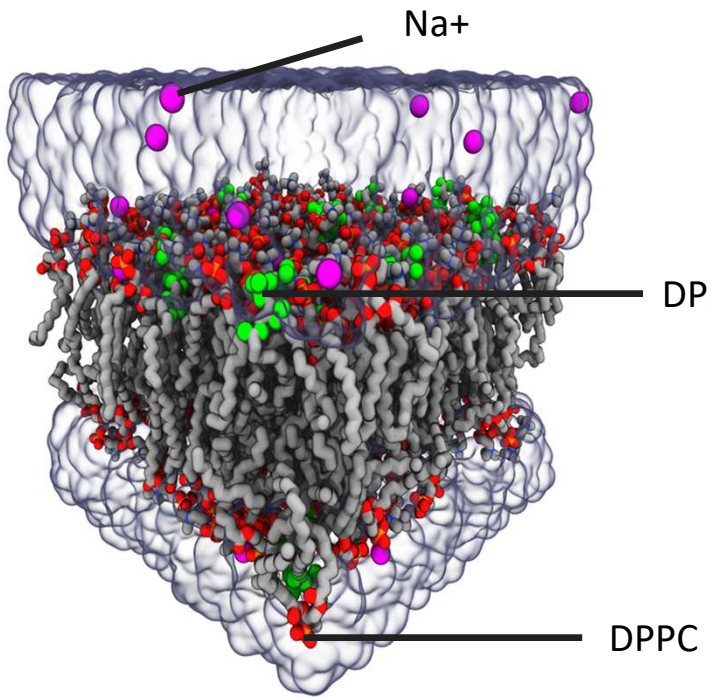
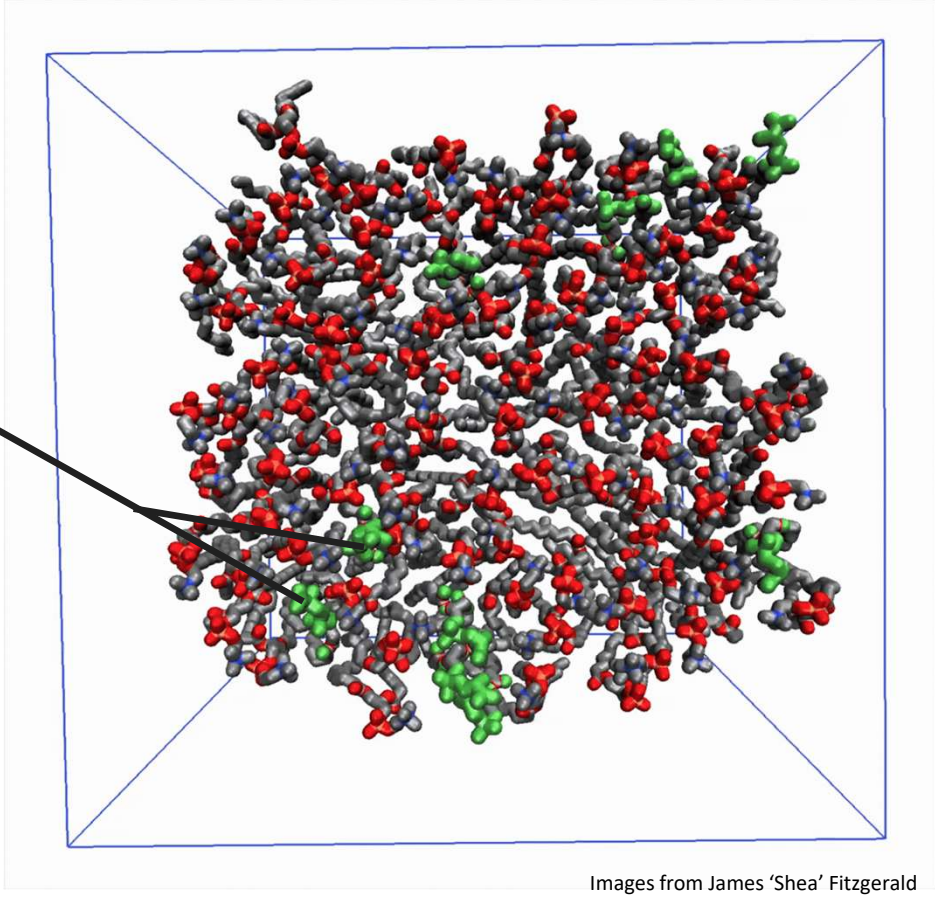
1:9 DPPS:DPPC

All-atom MD, CHARMM36 FF





Images from James 'Shea' Fitzgerald

Supplementary: 4:6 DPPC:DPPS

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