Title: Molecular dynamics studies of Langmuir monolayers of cationic/PC lipids

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Abstract: Our research focuses on computer simulations of cationic and Phosphatidylcholine (PC) containing lipid monolayers and their potential applications in drug and gene delivery. The ultimate motivation is to unravel how cationic compounds such as CTAB function for encapsulating novel DNA based drugs and other drugs e.g. protein based drugs into a delivery system. The major advantage of these drugs over traditional chemical agents is their specificity and selectivity.We employed the Berger lipid model to model lipid molecules. The Berger lipid model is based on GROMOS96 53a6 force field which has strength for describing proteins but has weakness for describing the long alkane chains of lipid molecules. The Berger lipid model did the improvement by using the Rychaert-Bellemans proper dihedral potential. Knowledge about partial charges distribution of cationic lipid molecules was retrieved from HF/MP2 level quantum chemistry calculation with the Natural Population Analysis partial charge scheme. The most important properties and behaviors of Langmuir monolayers can be obtained from the surface tension-area isotherm of the system at a given temperature. Thus a series of NVT simulations of monolayer systems of systematically varied box sizes with various cationic lipids: PC lipids ratio were done to evaluate the surface tension-area isotherms from the simulated trajectory averages. Our current results show that the cationic lipids have a tendency to stabilize the monolayers especially when the systems are more densely packed. Further investigations are on the way to fully explore other properties and behaviors of Langmuir monolayers of cationic/PC lipids.

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Molecular Dynamics Studies of Cationic Lipid Monolayer for Drug Delivery

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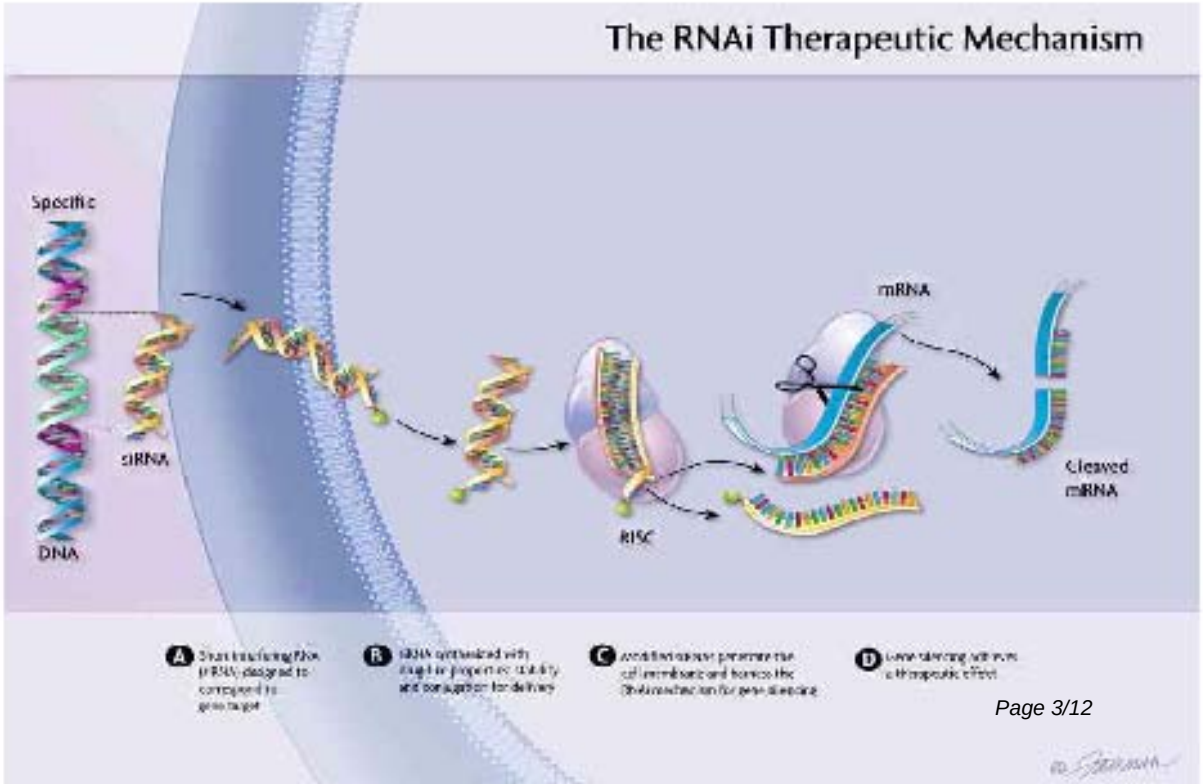
www.softsimu.net

Background

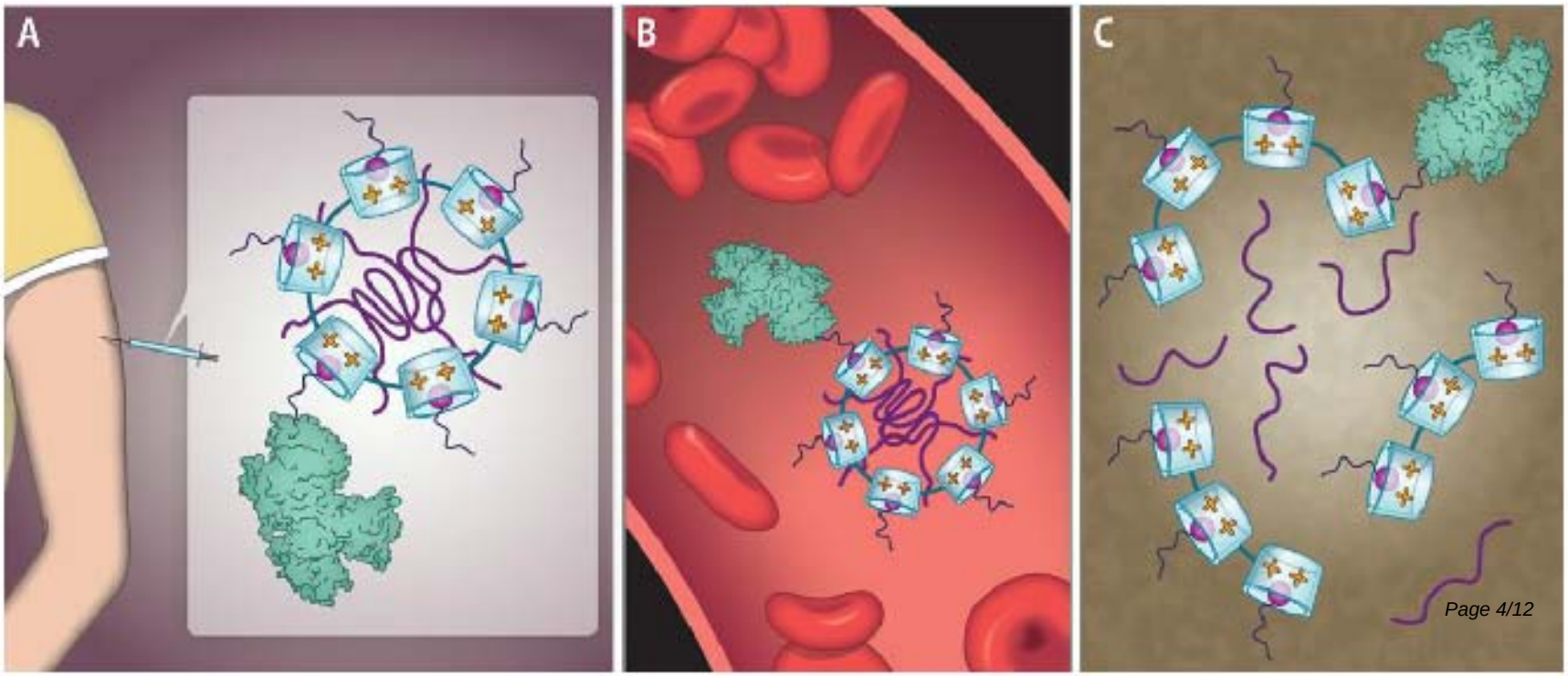
- siRNA: small interfering RNA
  - → Emerging novel drug for treatment of cancers
  - → Double stranded RNA
- Physicochemical property of siRNA:
  - → high molecular weight
  - → anionic charge
  - → Hydrophilicity
- siRNA based drugs requires delivery carriers to penetrate plasma membranes.



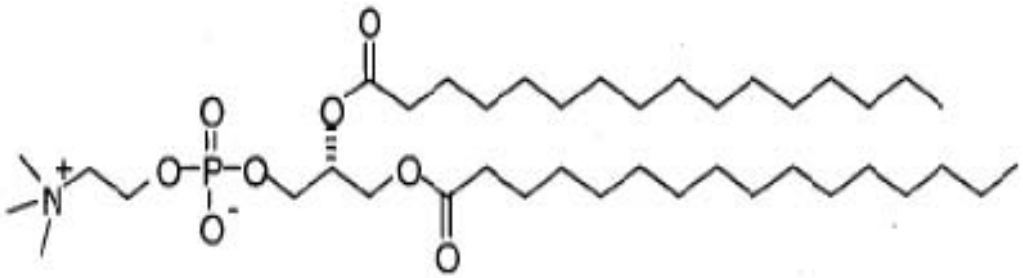
Background

Cationic lipid monolayers as nanocarriers for siRNA based drug delivery

- Neutrally charged together with siRNA
- Monolayers wrap into inverted micelles to protect siRNA during blood circulation
- Carriers dissolve at the targeted cell (cancer cell) membrane
- siRNA released into the cytoplasma



The DPPC/CTAB monolayer model systems

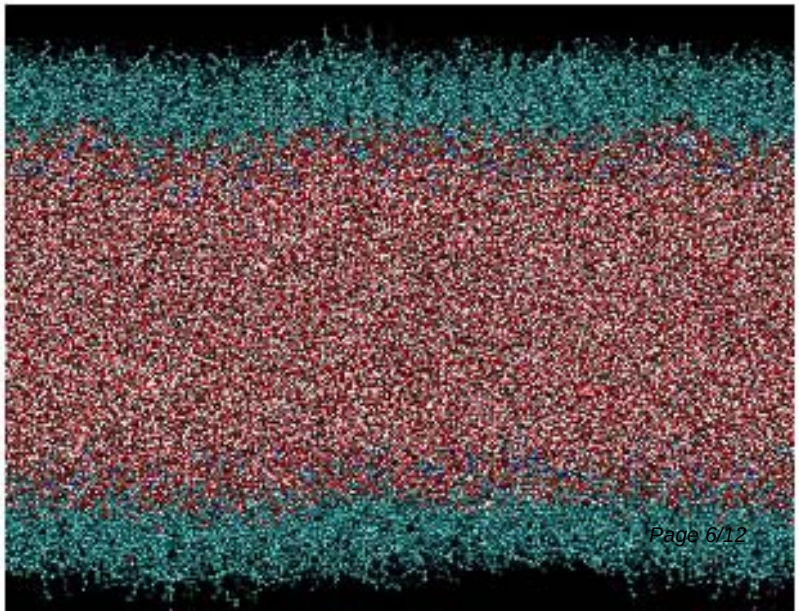


DPPC:
- Zwitterionic
- Amphiphilic
- A common surfactant
- Well studied both by experiment and by simulation

CTAB:
- Cationic
- Amphiphilic
- Also a surfactant

Simulated system setup

- Pure DPPC monolayer system
  - Baseline system for comparison between simulation and experiments
- DPPC/CTAB mixtures with various composition
  - 80% DPPC and 20% CTAB
  - 70% DPPC and 30% CTAB
  - 60% DPPC and 40% CTAB
  - 50% DPPC and 50% CTAB
- Symmetric simulation box
  - Two monolayers per simulation box
  - Decoupled by a thick water slab
  - 128 lipids per monolayer

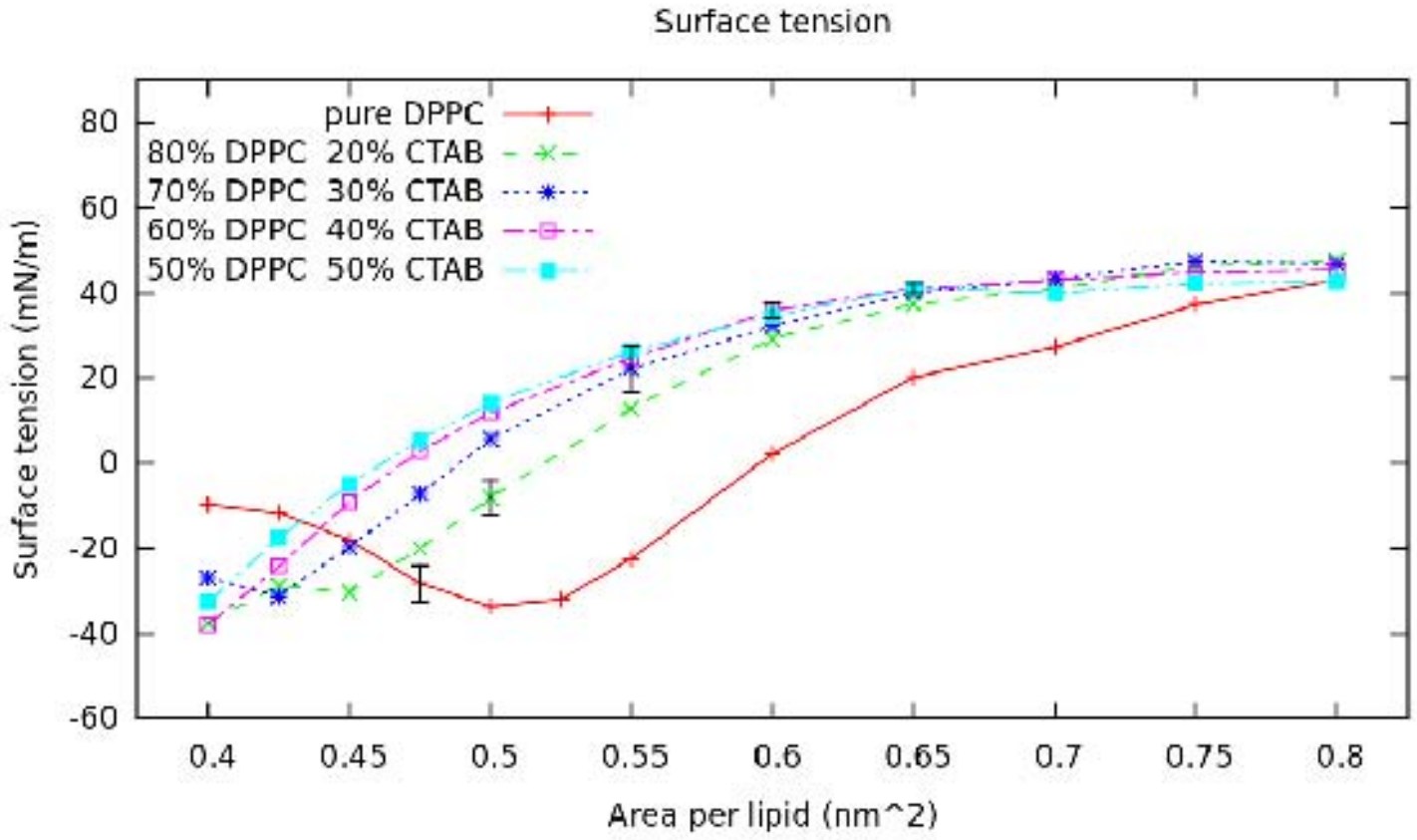


Simulation approaches

- DPPC parametrization work done by Prof. Tieleman's group
- CTAB parametrization based on Berger lipids model
  - → GROMOS96 53a6 force field
  - → Natural Population Analysis (NPA) partial charge scheme
- GROMACS 4.5.5
- SPC water model
- NVT simulations at 323.15K
- 1 μs simulation length (first 100ns for stabilizing systems)

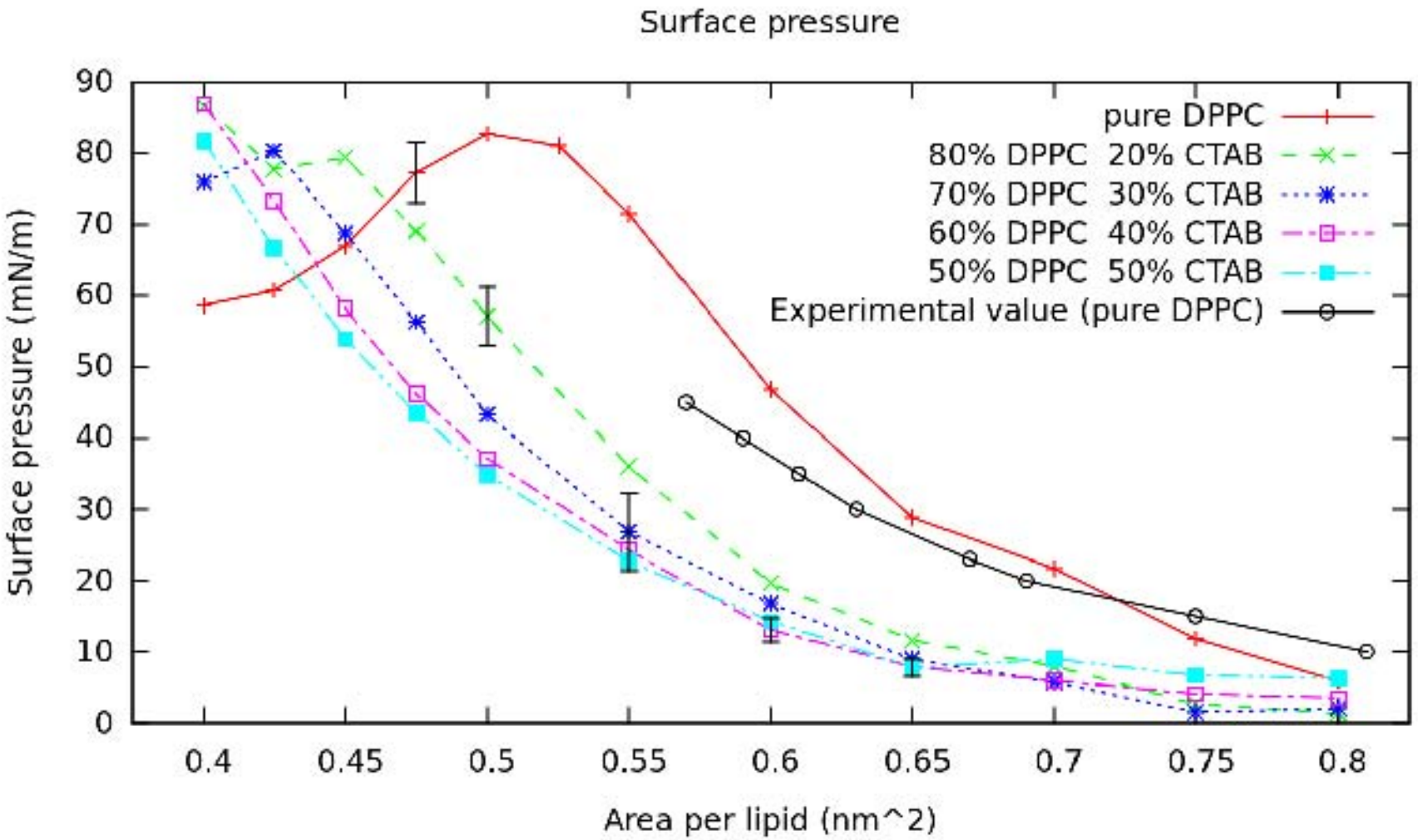
Simulation Results and Analysis

Surface tension-area per lipid isotherms



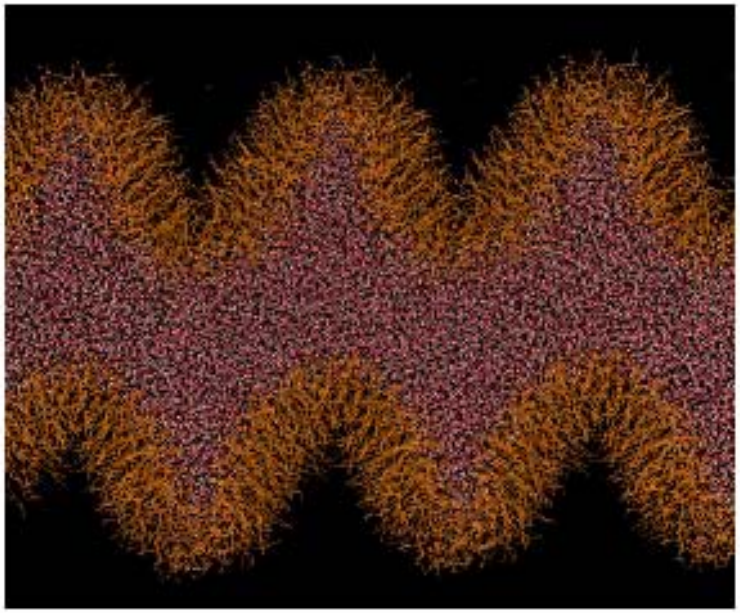
$$\Gamma = \left\langle P_{zz} - \frac{1}{2}(P_{xx} + P_{yy}) \right\rangle * \frac{L_z}{2}$$

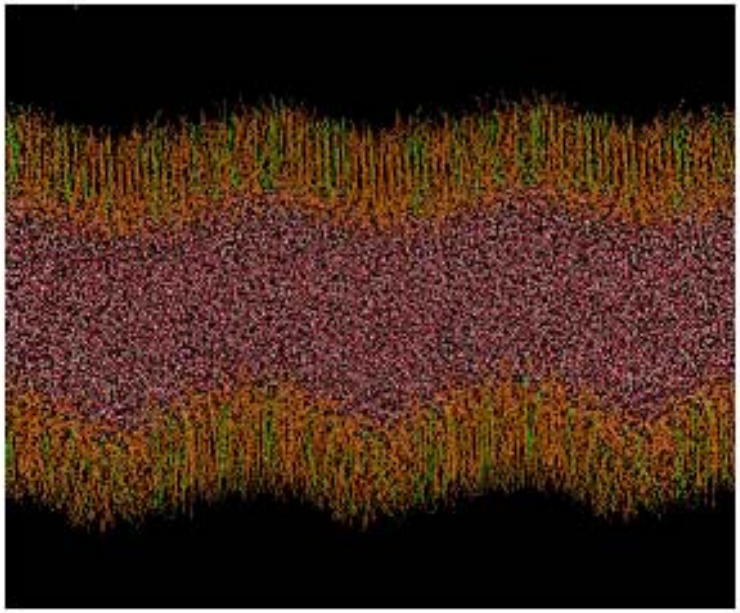
Surface pressure-area per lipid isotherms



Crane, J. M., G. Putz, and S. B. Hall. 1999. *Persistence of phase coexistence in disaturated phosphatidylcholine monolayers at high surface pressure*. Biophys. J. 77:3134–3143

Monolayers under high surface pressure

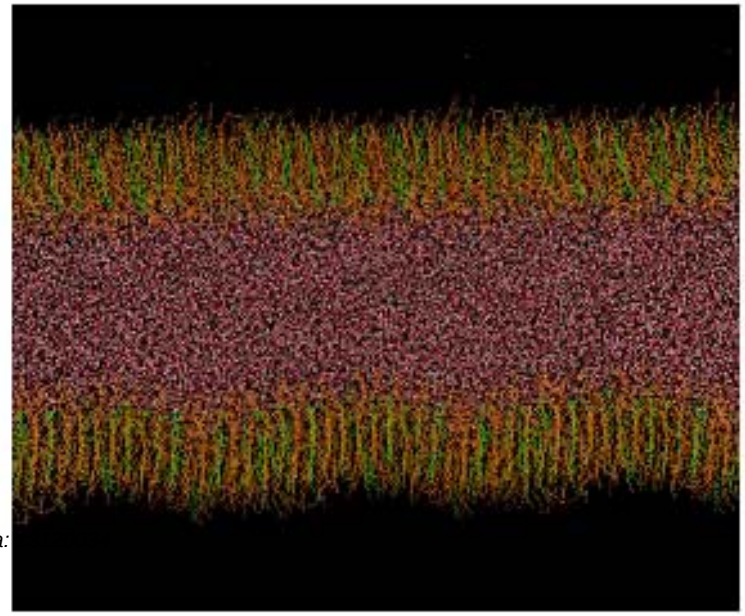


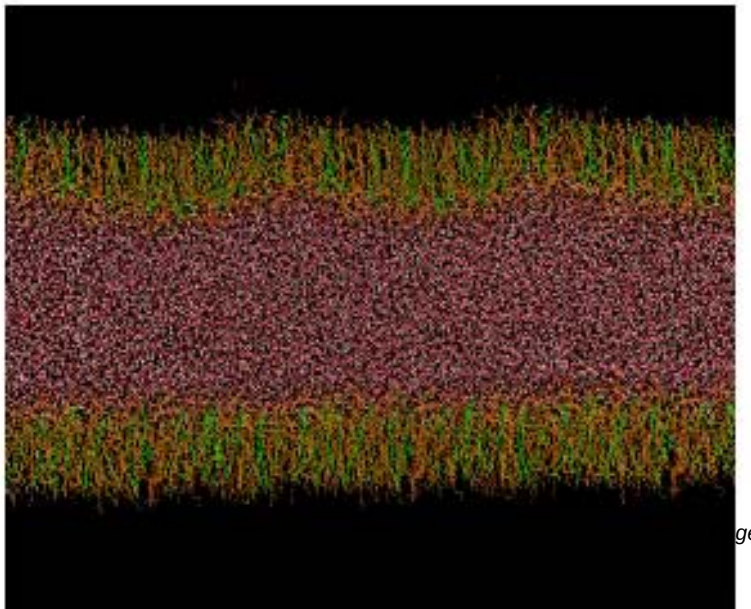


Pure DPPC

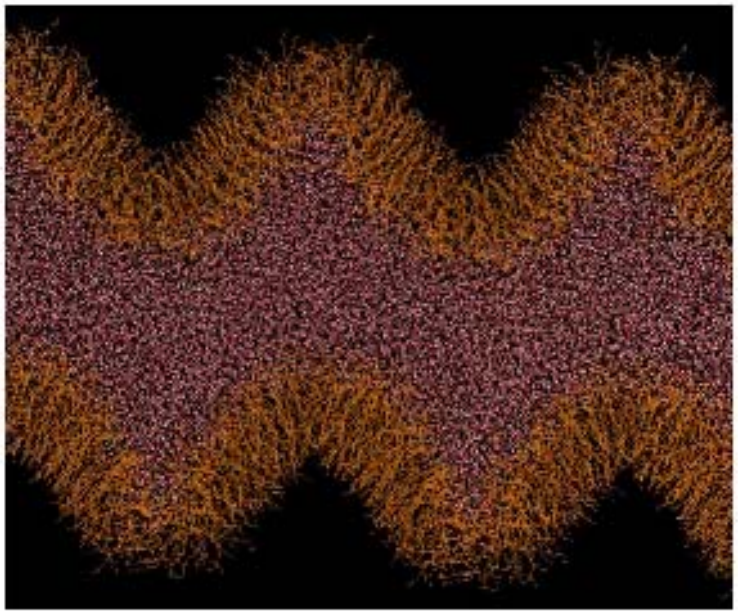
Area per lipid: 0.4 nm^2

20% CTAB

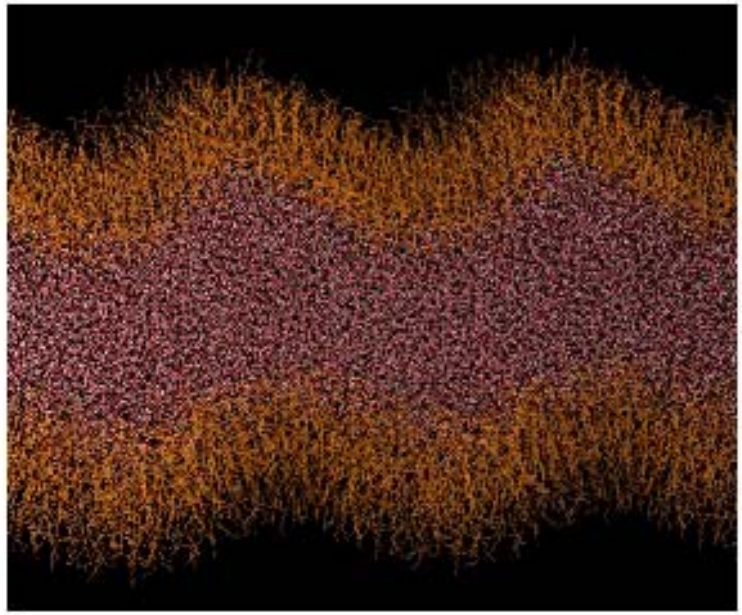




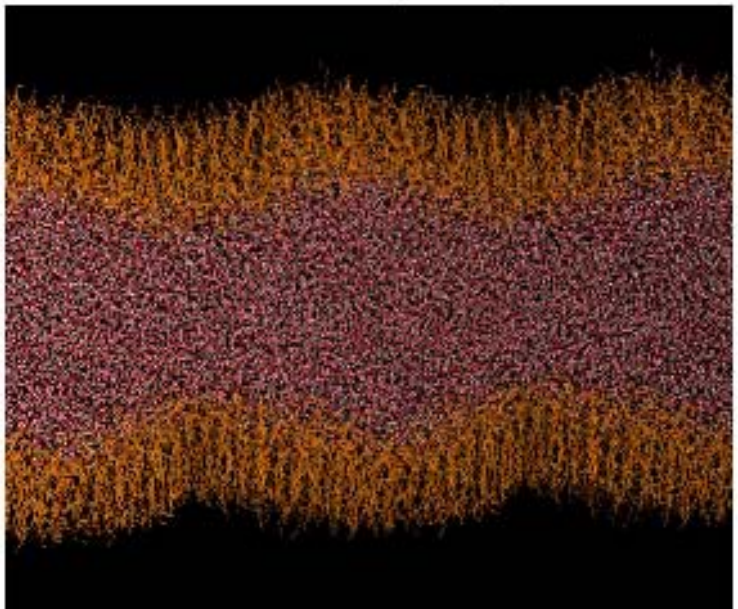
Pure DPPC monolayers

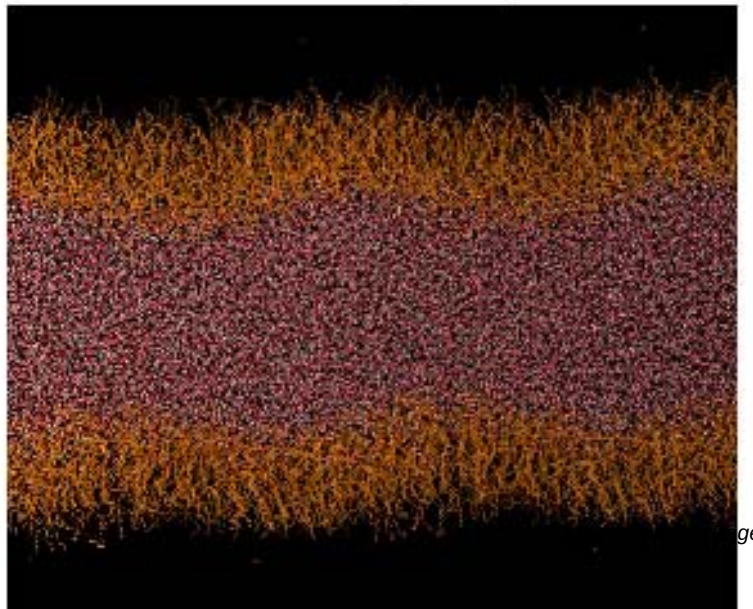


0.45nm^2 per lipid



0.5nm^2 per lipid





Acknowledgements

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