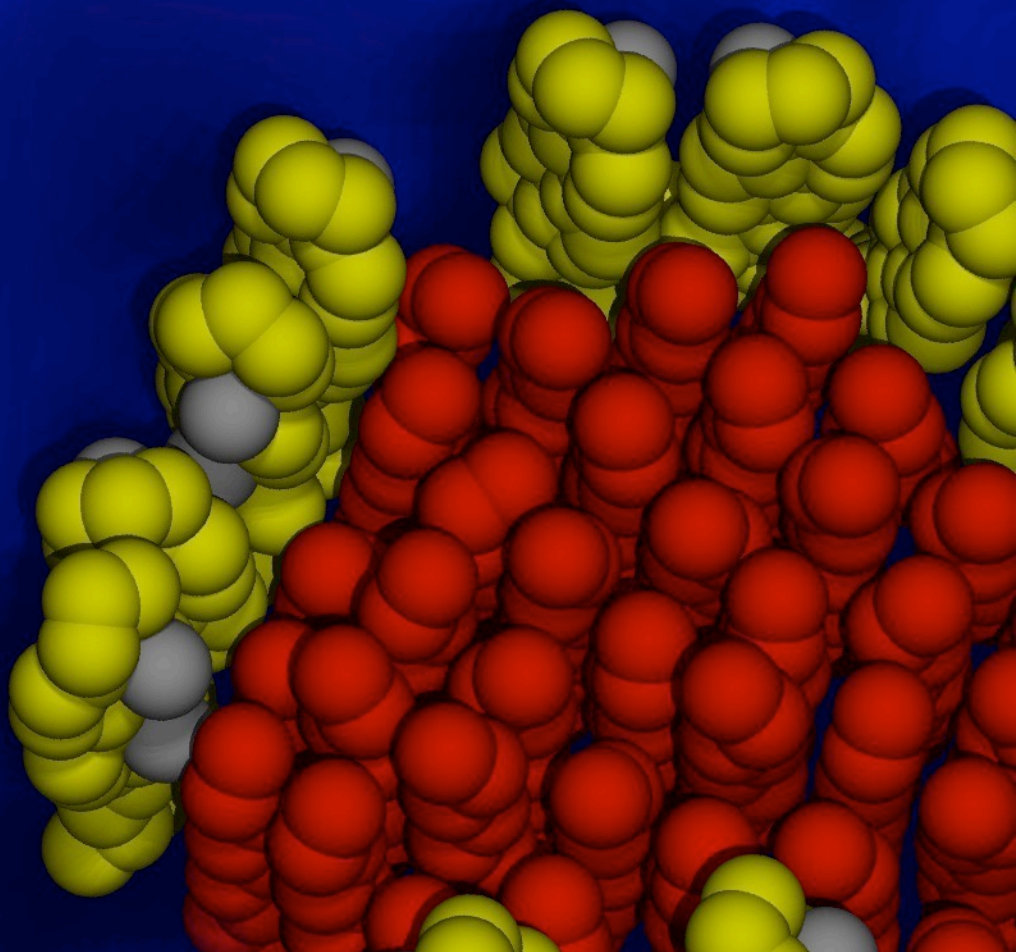
Surface viscosity and subdiffusion in membrane simulations

Ed Lyman

Dept of Physics and Astronomy and Dept of Chemistry and Biochemistry, Univ of Delaware

KITP FILMS21
June, 2021



Viscosity is a *fundamental concept* in membrane biology — Here's why!

Homeoviscous adaptation (Sinensky):[1]

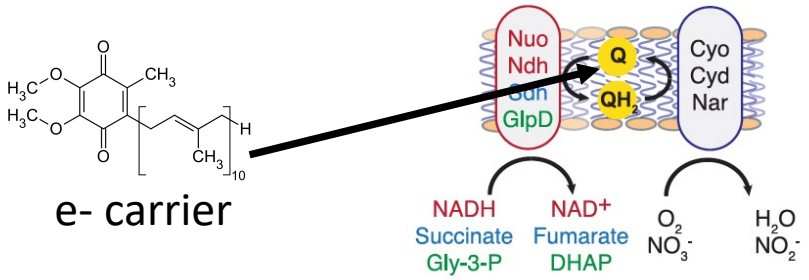
Cells actively regulate lipid *composition* in order to maintain membrane fluidity

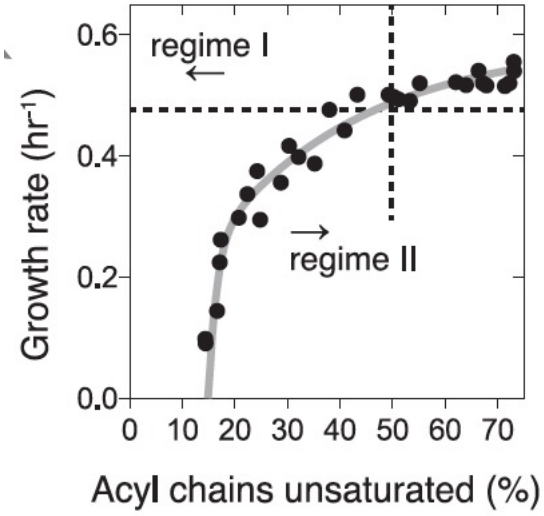
Why?

Viscosity controls the rates of events in membranes, such as diffusion of electron carriers in respiration[2]

TABLE 2. *The viscosity of E. coli lipid extracts from cells grown at different temperatures*

Temperature of growth (°C)	Temperature of measurement (°C)	τ (nsec)	η (poise)
15	15	2.8	1.8
30	30	2.7	1.9
37	37	2.6	1.8
43	43	2.7	2.0
43	15	13.8	15





[1] Sinensky *PNAS* 71:522(1974)
[2] Budin et al, *Science* 362:1186(2019)

Viscosity is a *fundamental concept* in membrane biology — Here's why!

Homeoviscous adaptation (Sinensky):[1]

Cells actively regulate lipid *composition* in order to maintain membra

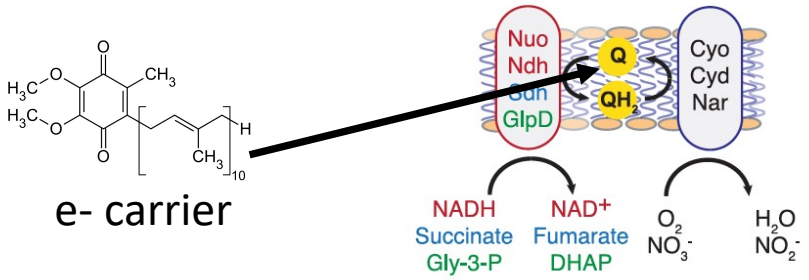
Increasing chain unsaturation

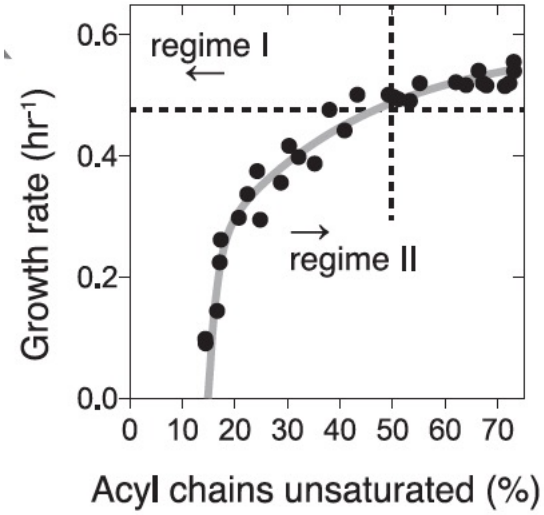
TABLE 2. *The viscosity of E. coli lipid extracts from cells grown at different temperatures*

Temperature of growth (°C)	Temperature of measurement (°C)	τ (nsec)	η (poise)
15	15	2.8	1.8
30	30	2.7	1.9
37	37	2.6	1.8
43	43	2.7	2.0
43	15	13.8	15

Why?

Viscosity controls the rates of events in membranes, such as diffusion of electron carriers in respiration[2]

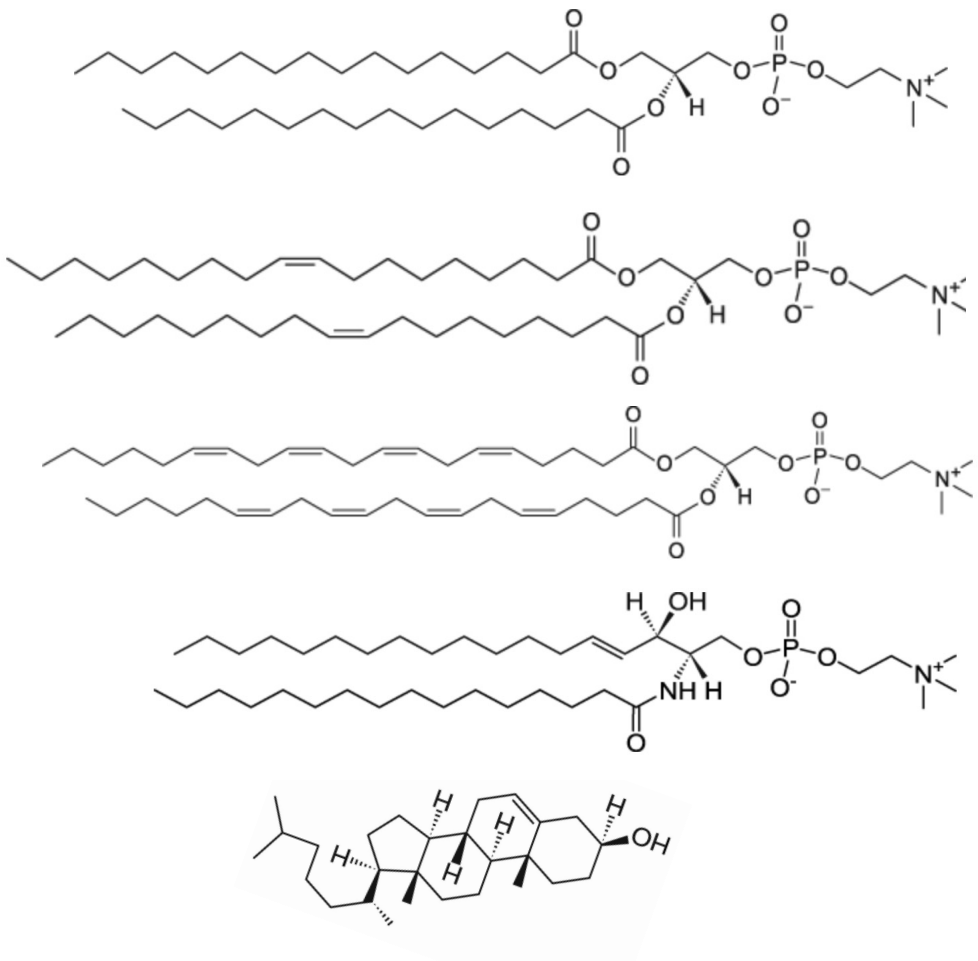




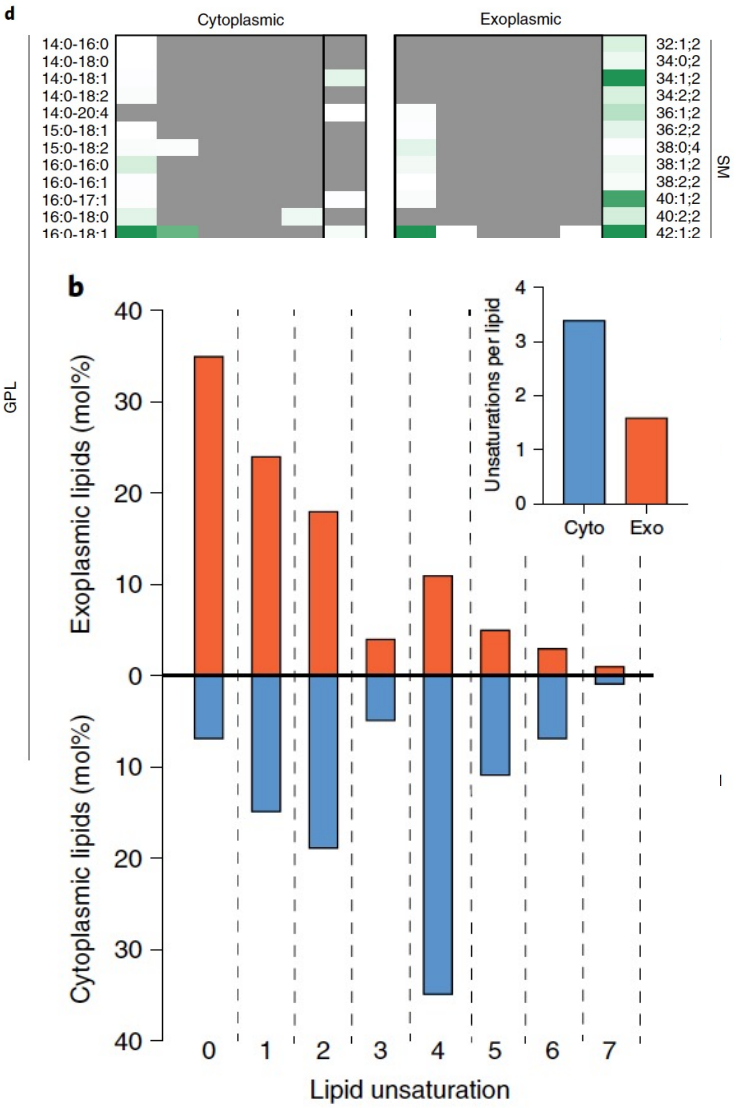
[1] Sinensky *PNAS* 71:522(1974)
[2] Budin et al, *Science* 362:1186(2019)

Essential lipid chemistry, and the lipidomic revolution

Some “common” lipids



There are hundreds of lipids in our membranes!

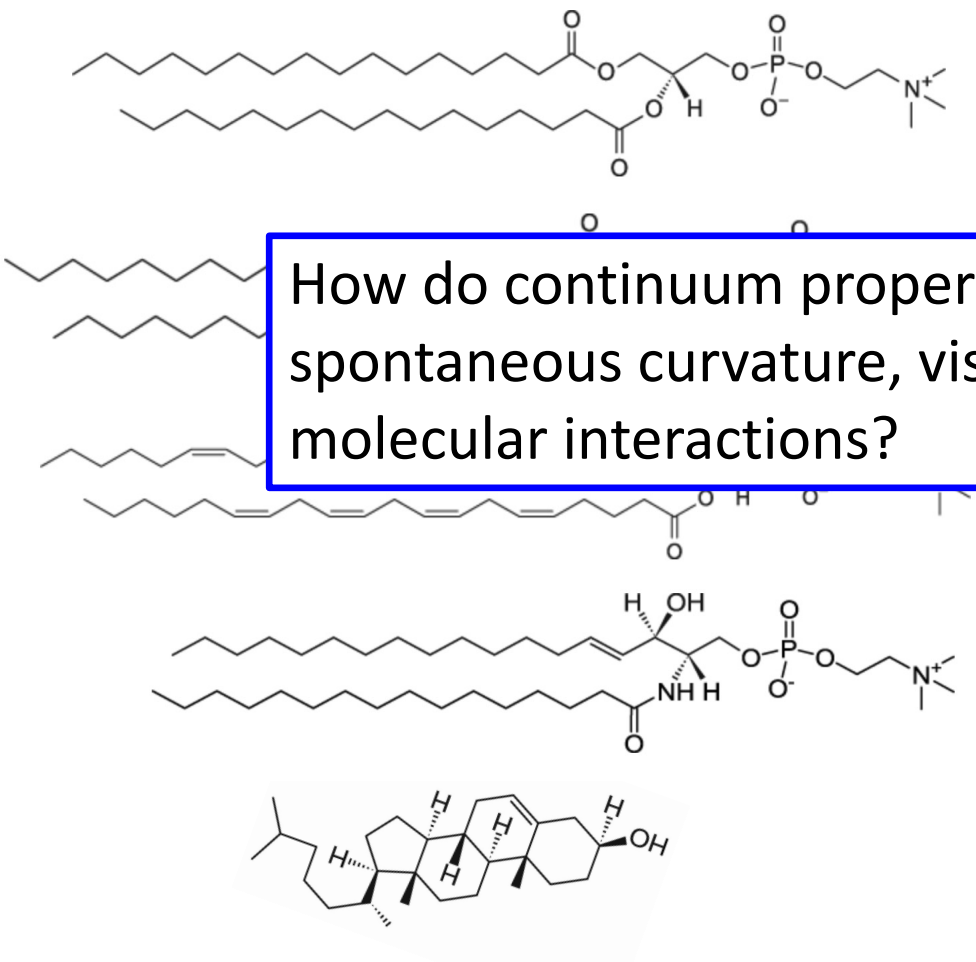


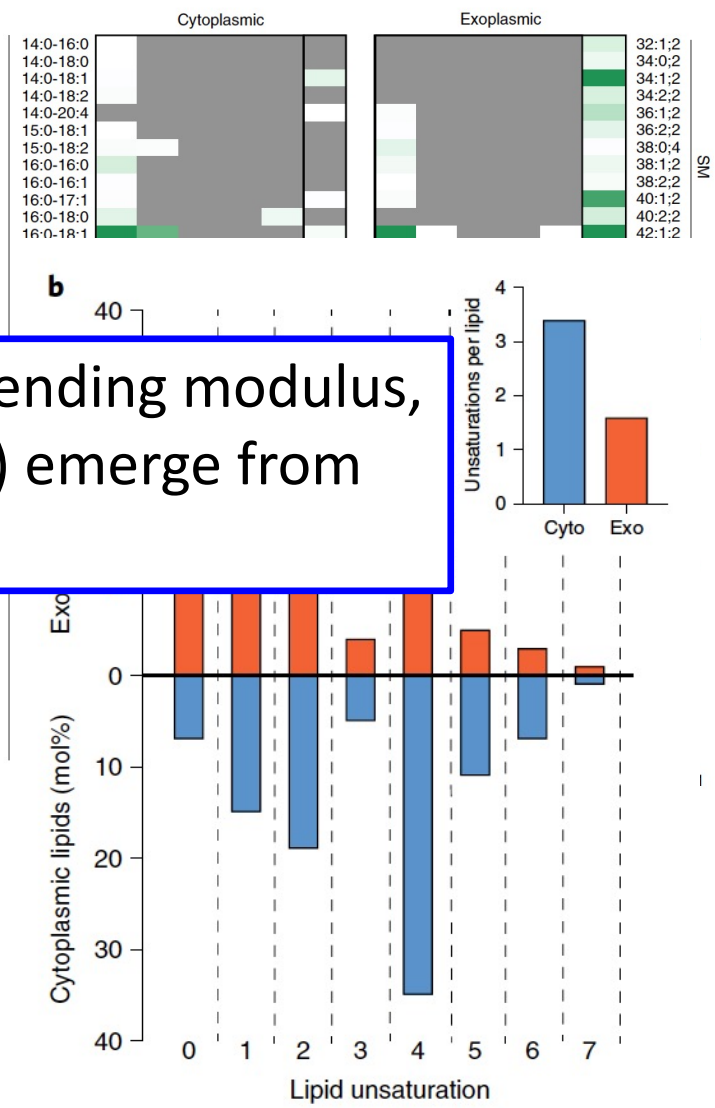
Levental et al *Nat Chem Biol* 16:644 2020

Essential lipid chemistry, and the lipidomic revolution

There are hundreds of lipids in our membranes!

Some “common” lipids





How do continuum properties (bending modulus, spontaneous curvature, viscosity) emerge from molecular interactions?

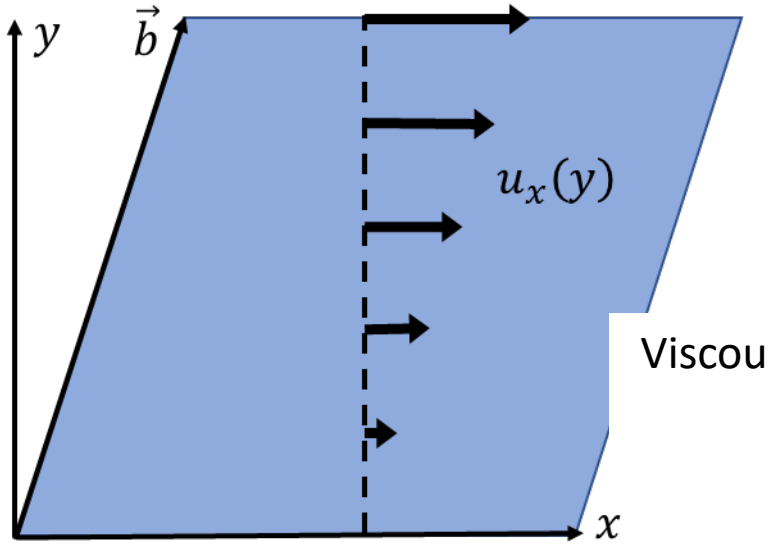
Levental et al *Nat Chem Biol* 16:644 2020

Outline

- Lipid viscosities obtained by a nonequilibrium method, non-Newtonian behavior at high shear
- (Lots of) viscosities obtained from equilibrium fluctuations
- Subdiffusion in the Lo phase, and some rampant speculation

Shear viscosity: Definition and units

Consider a simple fluid subjected to a shearing deformation, resulting in a velocity gradient:



$$\sigma_{xy} = \eta\left(\frac{\partial u_x}{\partial y} + \frac{\partial u_y}{\partial x}\right) = \eta\dot{\varepsilon}$$

(Newtonian assumption)

Viscous stress tensor

viscosity

Shear rate

Units:

$$[\dot{\varepsilon}] = [time]^{-1}$$

In 3D: $[\sigma_{xy}] = \frac{[\text{Force}]}{[\text{area}]} \Rightarrow [\eta] = \frac{[\text{force}][\text{time}]}{[\text{area}]}$

In 2D: $[\sigma_{xy}] = \frac{[\text{Force}]}{[\text{distance}]} \Rightarrow [\eta] = \frac{[\text{force}][\text{time}]}{[\text{distance}]}$

Shear viscosity of some alkanes and aliphatic alcohols

Carbons	Alkanes	Alcohols
4		2.5*
6	0.2*	
8	0.386	3.5*
10	0.5*	
12	1.06	9.0*
14	1.0*	
16	2.1	9 or 27

- Units are cP
- Aliphatic alcohols are about 9x more viscous than the corresponding alkane
- Hexadecanol comparison is complicated by higher melting temp (50 C) and inconsistency in the literature. One source says 53 cP at 75 C. Another says 9 cP at 53 C.

Consider a thin (4-5 nm) slab of 16 carbon chains: $(h) \times (\eta_{hex}) = \eta_m$

This would give a surface viscosity for DPPC of $4.5 \times (10)^{-11}$ Pa-m-sec

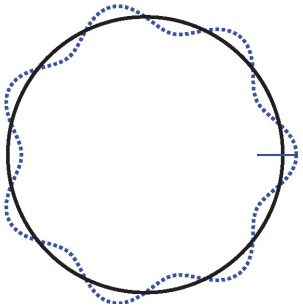
(Multiply by 10^3 to get P-cm)

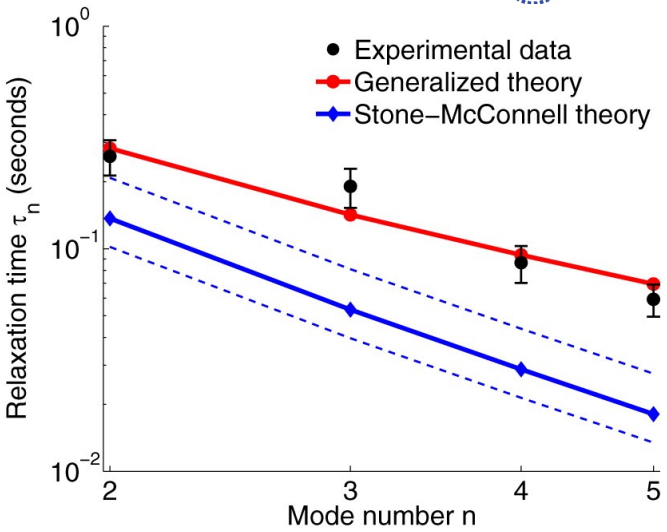
*from Yamaguchi, *JCP* 146:094511(2017) at 25 C
*from (sources cited in) Venable, Krämer, Pastor *Chem Rev* 119:5954(2019)

Membrane viscosity: Some experimental numbers

Domain flicker spectroscopy:

DPPC:DiPhy:chol

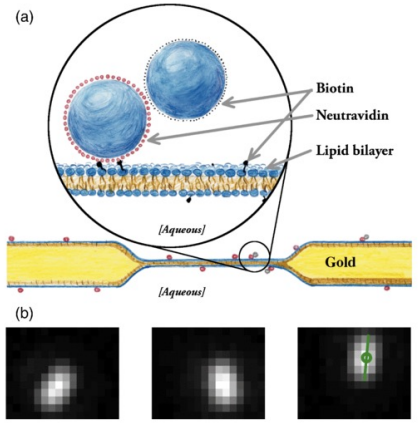


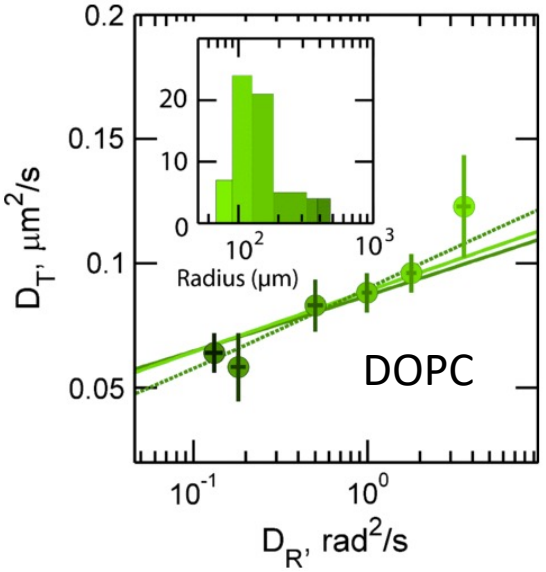


$$\eta = 4\times10^{-9}\ \mathrm{Pa\cdot m\cdot sec}$$

Camley et al Biophys J 99:L44(2010)

Fits to SDHPW:





[a]BLM, DOPC:

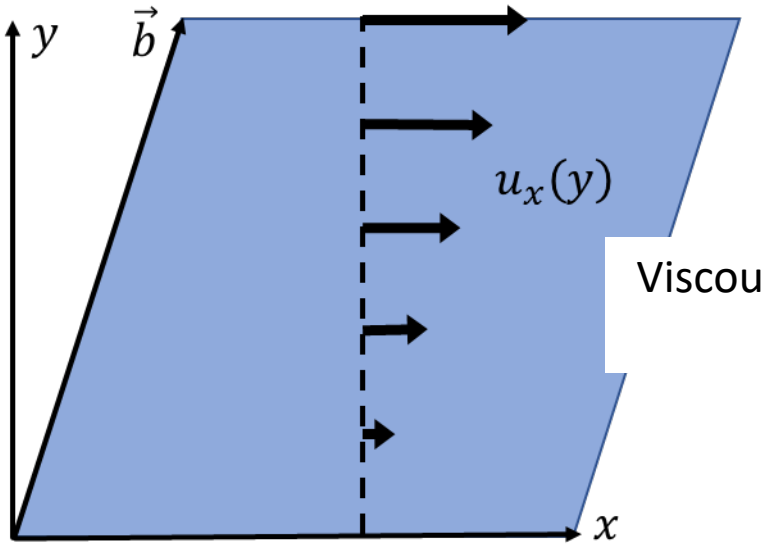
$$\eta = (15.9\ \pm 2.3)\times10^{-9}\ \mathrm{Pa\cdot m\cdot sec}$$

[b]GUV, L_o phase:

$$\eta = (\ 5 - 10)\times10^{-9}\ \mathrm{Pa\cdot m\cdot sec}$$

[a]Hormel…Parthasarathy PRL 112:188101(2014)
[b]Cicuta, Keller, Veatch J Phys Chem B 111:3328(2007)

Measuring surface viscosity of lipid forcefields: NE box deformation protocol



$$\sigma_{xy} = \eta\left(\frac{\partial u_x}{\partial y} + \frac{\partial u_y}{\partial x}\right) = \eta\dot{\varepsilon}$$

(Newtonian assumption)

Viscous stress tensor

viscosity

Shear rate

The protocol for surface viscosity:

- Apply a box deformation to achieve diff shear rates
- Average P_{xy}

Stress tensor obtained from pressure (virial) tensor

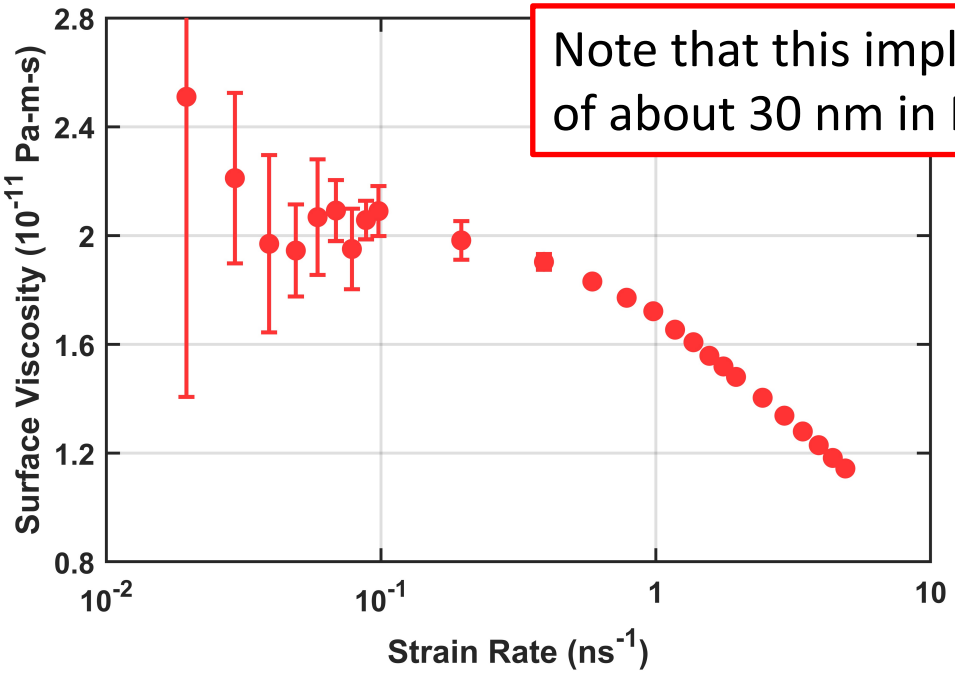
$$\sigma_{xy} = -\langle P_{xy} \rangle$$

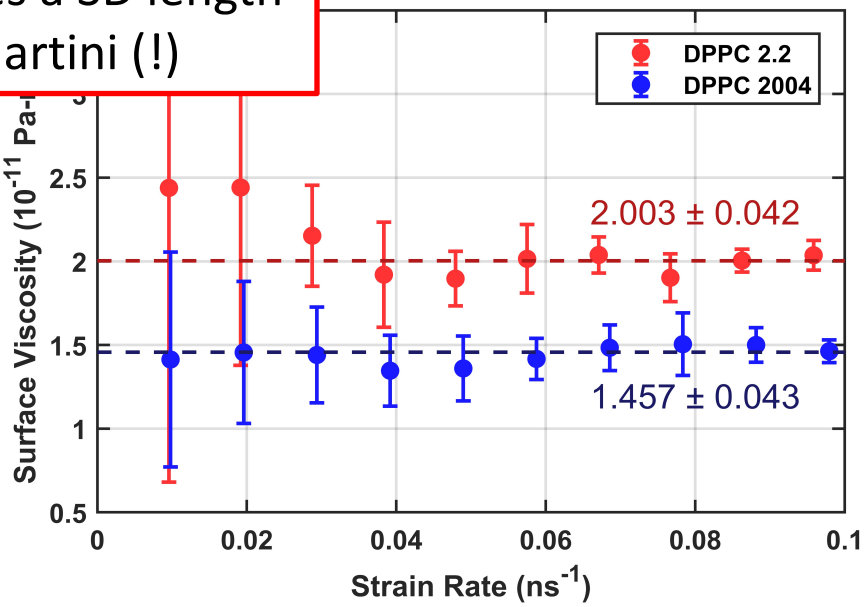
Martini DPPC Shear Viscosity

Andrew Zgorski

- Surface viscosity depends on Martini version
- Values are (nearly) in agreement with earlier report by den Otter (1.2×10^{-11}) for v. 2004
- Value for v.2.2 is in agreement with ind calc using Einstein relation: $(2.23 +/- 0.21) \times 10^{-11}$

Note that this implies a SD length of about 30 nm in Martini (!)



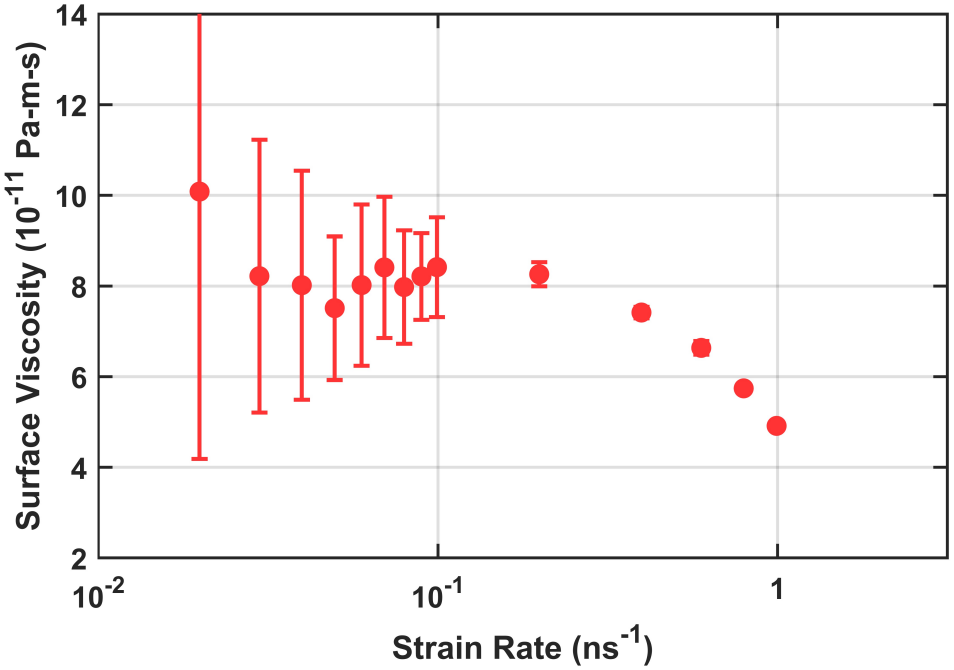


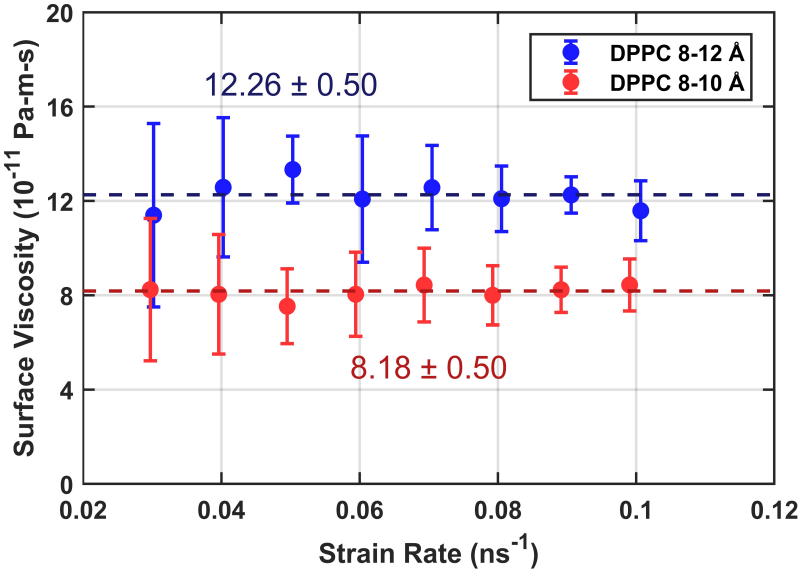
- 10 x 10 nm membranes, 10 replicas run for 10 usec in NPT, then system rescaled to the average box size and equilibrated under NVT
- 820 nsec production runs, 3 runs at each strain rate

A Zgorski, R Pastor, EL *JCTC* 15:6471(2019)

C36 (all-atom) DPPC Shear Viscosity

- Surface viscosity depends on LJ cutoff (ca. 50% difference)
- Simulated values (8-12 x 10^{-11} P-cm) are below expt. values by a factor of 200 or so. (oi)





- 10 x 10 nm membranes, relaxed and rescaled to the average box size and equilibrated under NVT for 10 nsec
- <P_{xy}> converged to < 1.5 bar after 20 nsec
- 5 x 25 nsec production runs to obtain visc at ea. strain rate

A Zgorski, R Pastor, EL *JCTC* 15:6471(2019)

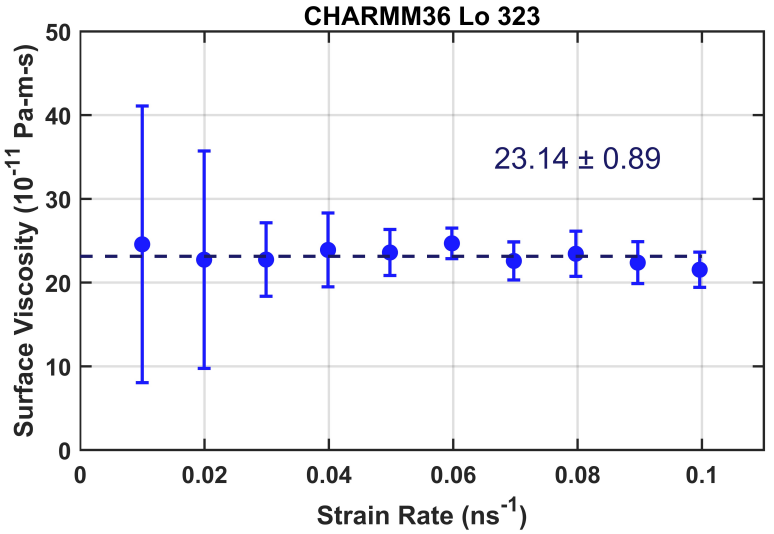
All-atom lipids: A surprise for cholesterol rich membranes

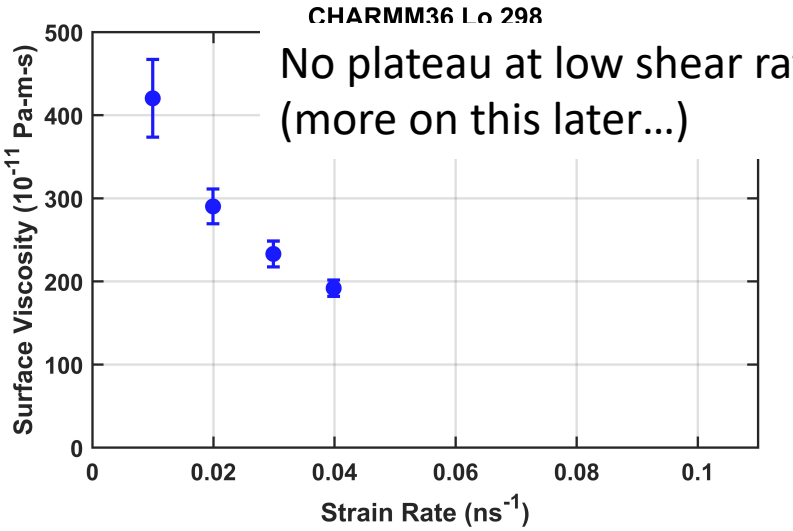
Membrane Composition	Surface Viscosity (10^{-11} Pa-m-s) = (10^{-8} P*cm)
DPPC (8-10)	8.18 ± 0.50
DPPC (8-12)	12.26 ± 0.50
DOPC (8-12)	19.68 ± 0.69
PSM (8-12)	48.8 ± 1.2
L_o (8-12)	23.83 ± 0.92 (T = 323K)
L_o (8-12)	??? (T = 298K)
L_d (8-12)	9.39 ± 0.47 (T = 323K)
L_d (8-12)	40.6 ± 1.0

T_{sim} = 323

T_{sim} = 303

T_{sim} = 323





No plateau at low shear rate!
(more on this later…)

A Zgorski, R Pastor, EL *JCTC* 15:6471(2019)

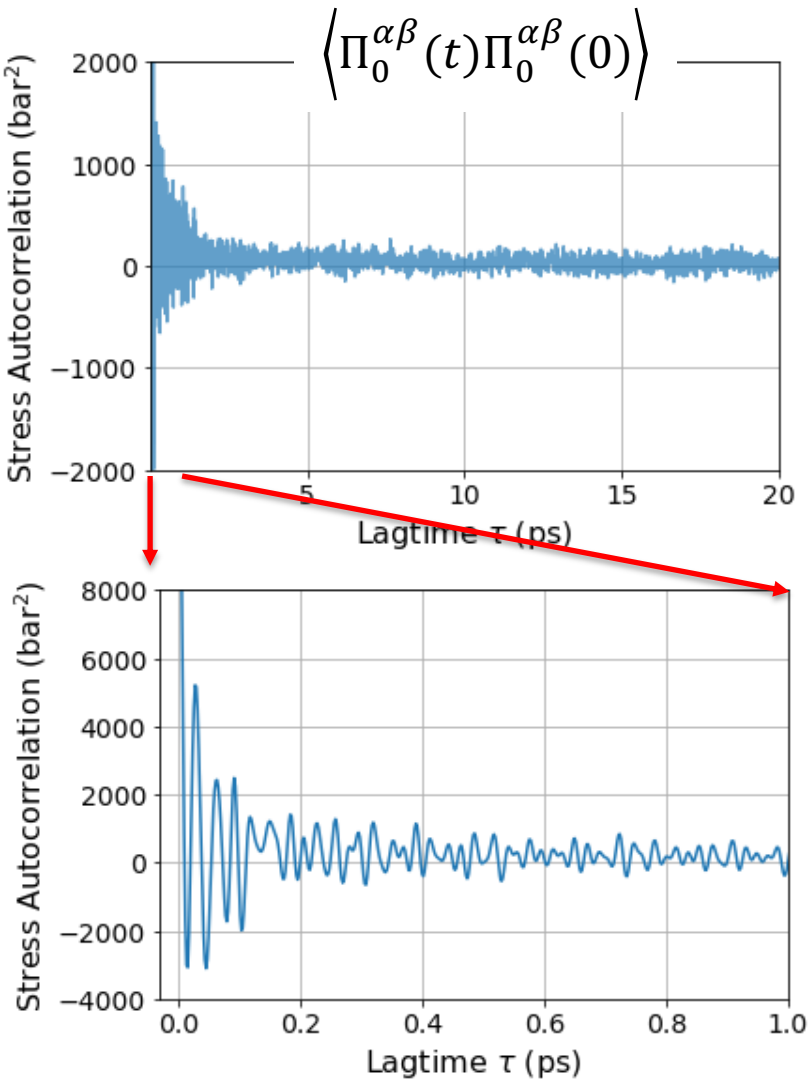
An equilibrium protocol. Or, how to blow a bunch of cycles chasing a number

A Green-Kubo relation for shear viscosity:

$$\eta = \frac{\beta}{V}\int_0^\infty \left\langle \Pi_0^{\alpha\beta}(t)\Pi_0^{\alpha\beta}(0)\right\rangle dt$$

Notes:

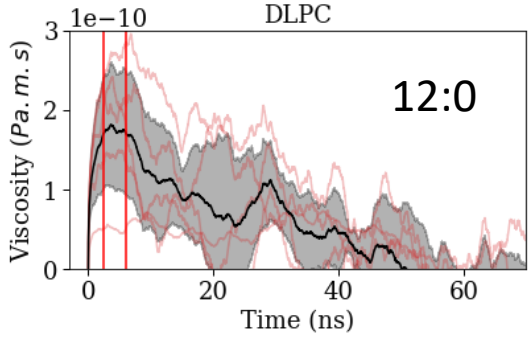
- "0" subscript reminds us that we have taken a k→0 limit
- $\Pi_0^{\alpha\beta}$ is the atomic stress tensor here. We use NVT conditions to avoid artifacts
- To get membrane surface viscosity, α, β in the plane and $\alpha \neq \beta$.
- We get $\Pi_0^{\alpha\beta}$ from the pressure tensor, so from G-K we get the system viscosity (membrane + water)

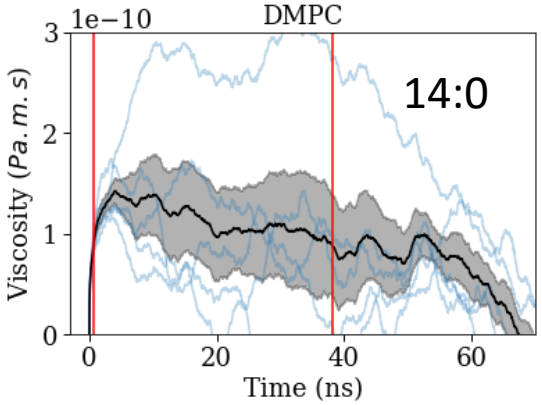


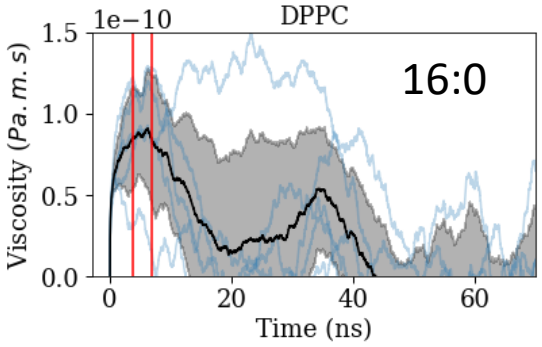
Shea Fitzgerald and EL, unpublished

G-K integrals

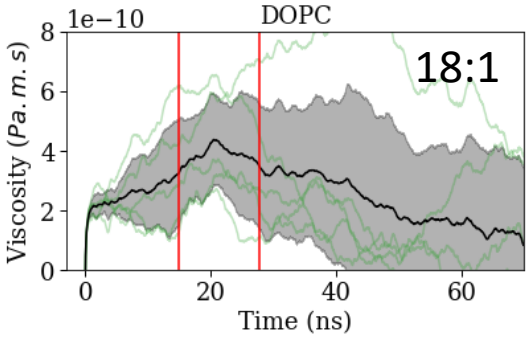
Chain length



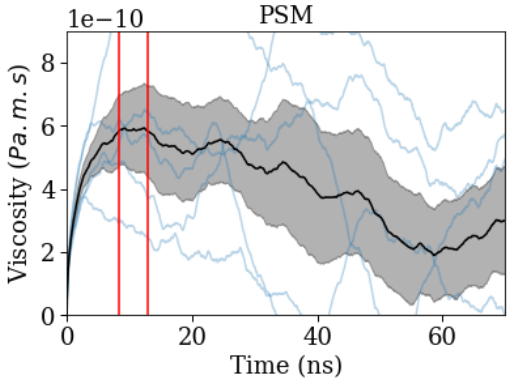




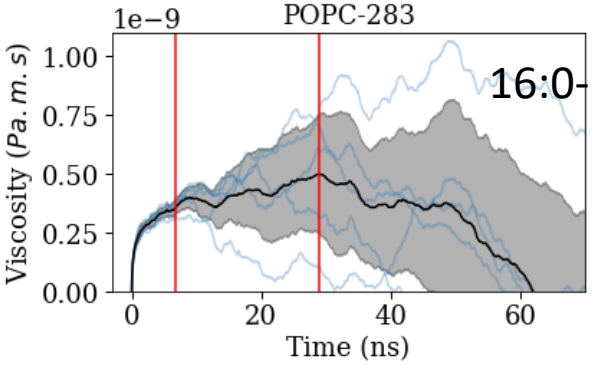
Unsaturation

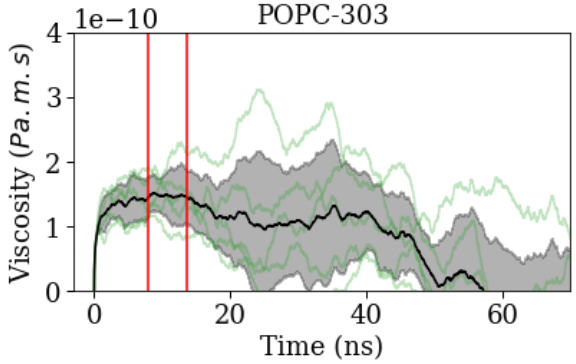


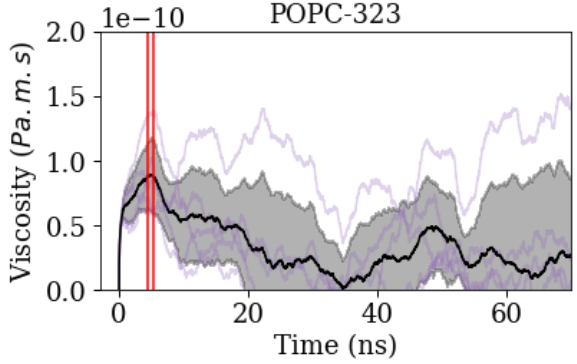
Sphingolipid



Temperature

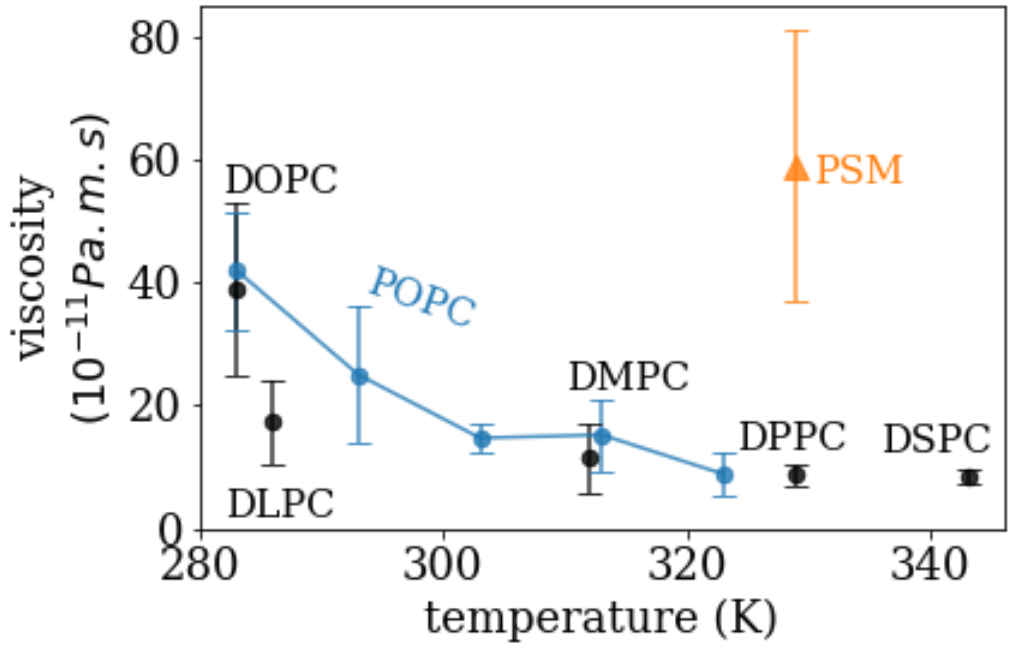






Shea Fitzgerald and EL, unpublished

Equilibrium viscosity results, summary



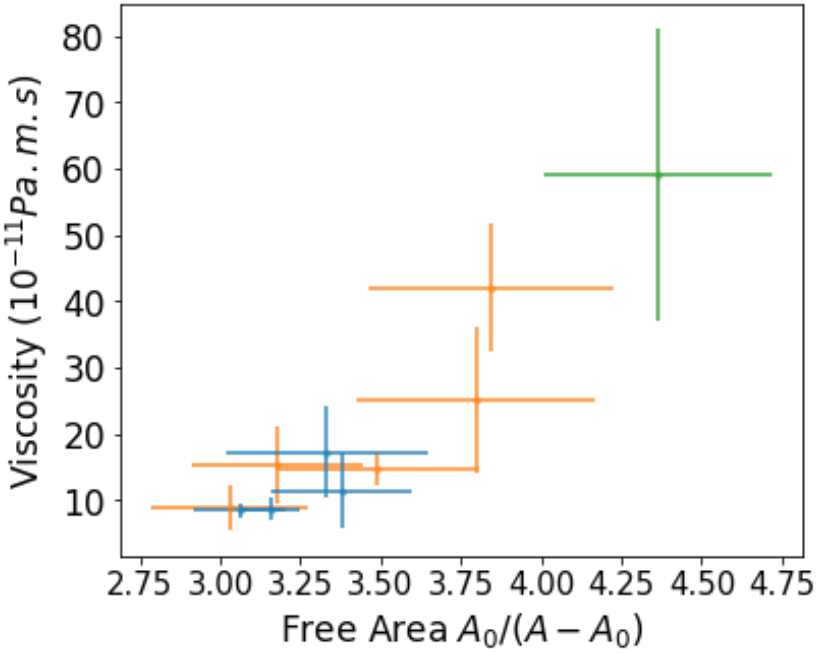
Lipid	T_m	T_{sim}	η (10^{-11}) Pa-m-sec
DLPC 12:0	271	286	17.3 ± 6.8
DMPC 14:0	297	312	11.4 ± 5.7
DPPC 16:0	314	329	8.7 ± 1.7
DSPC 18:0	327	343	8.5 ± 1.1
DOPC 18:1	256	283	39 ± 14
PSM	314	329	59 ± 22
POPC 16:0-18:1	271	283	42.0 ± 9.6
POPC 16:0-18:1	271	293	25 ± 11
POPC 16:0-18:1	271	303	14.7 ± 2.5
POPC 16:0-18:1	271	313	15.2 ± 5.8
POPC 16:0-18:1	271	323	8.8 ± 3.4

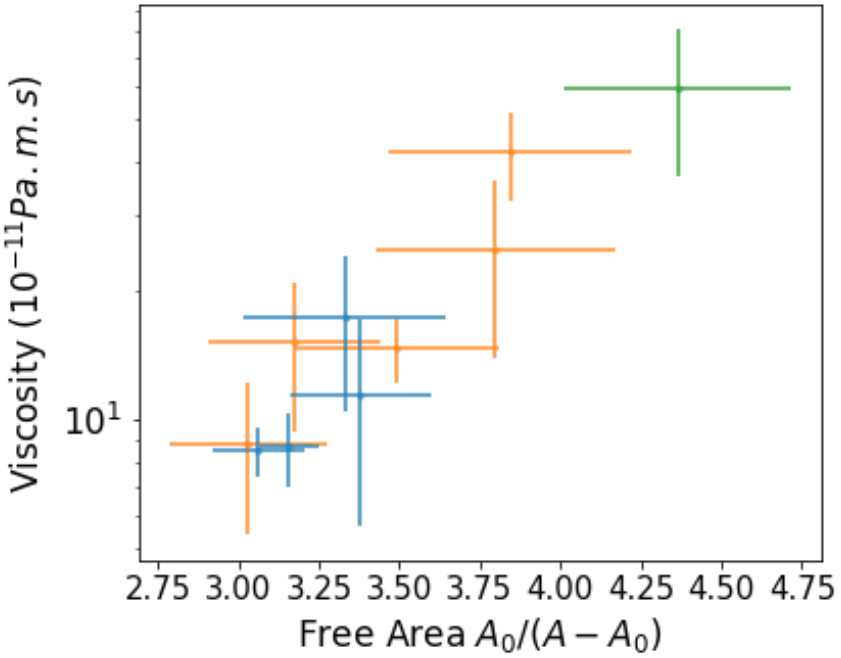
Non Equil results:
DPPC @ 323: 12.26 +/- 0.5
PSM @ 323: 48.8 +/- 1.2

Shea Fitzgerald and EL, unpublished

Does “free area” explain membrane viscosity?

If the error bars are big enough --- sure!





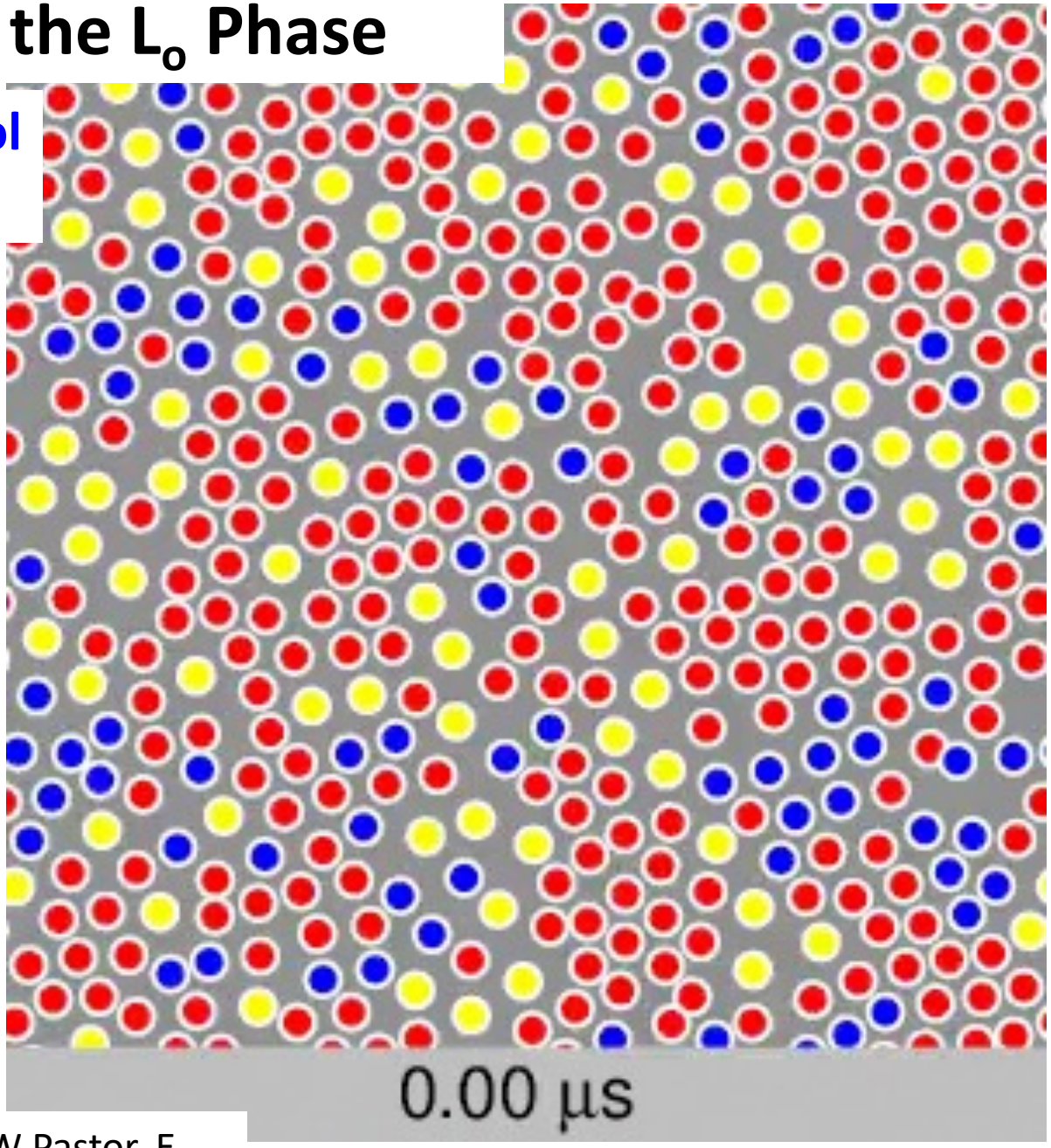
Shea Fitzgerald and EL, unpublished

Dynamics of the L_o Phase

DPPC/DOPC/Chol
0.55/0.15/0.30

Top view, one leaflet
L_o phase composition

- **Yellow: CHOL**
- **Blue: DOPC chain**
- **Red: DPPC chain**



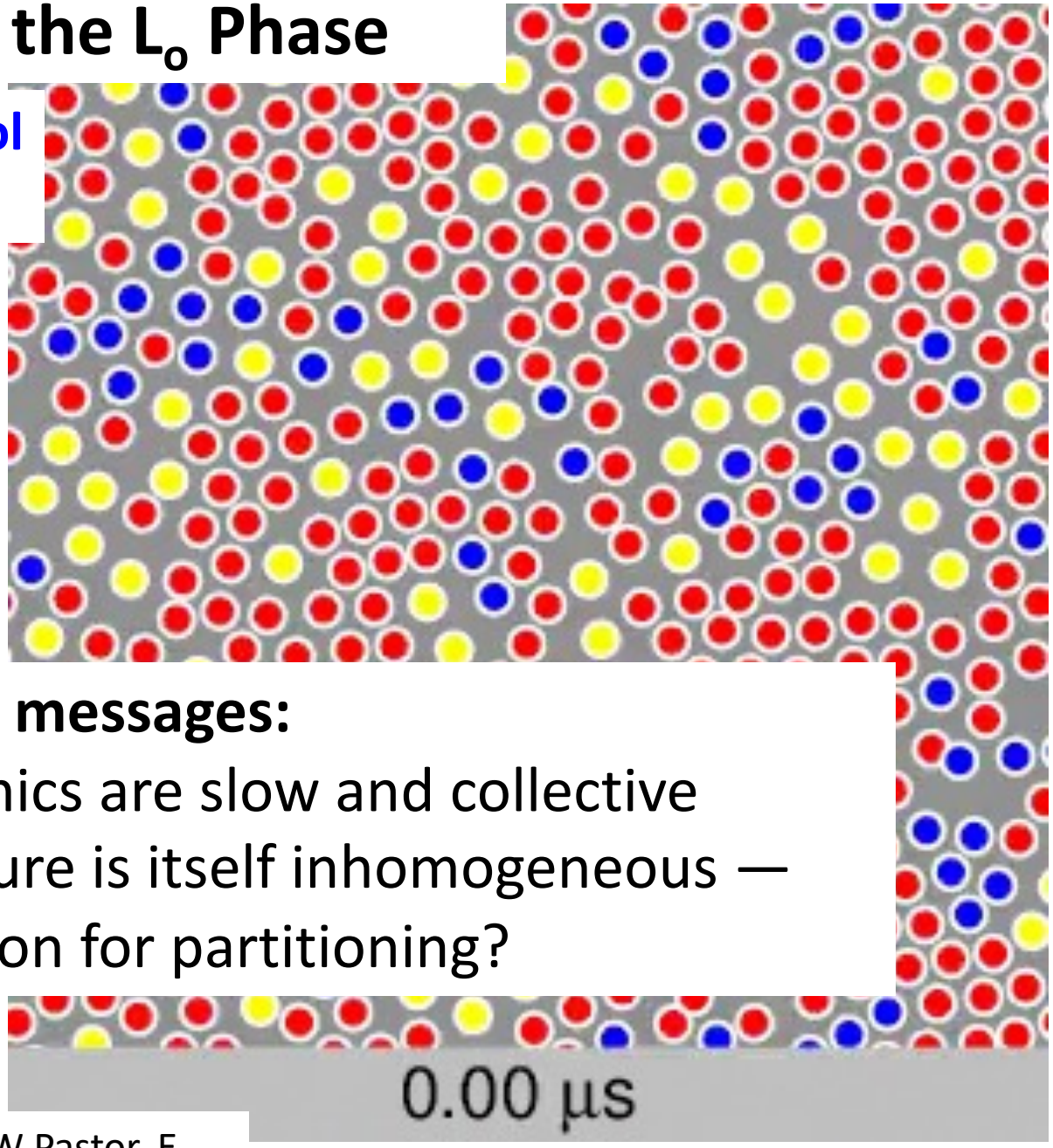
A Sodt, ML Sandar, K Gawrisch, RW Pastor, E Lyman *J Am Chem Soc* 136:725(2013)

Dynamics of the L_o Phase

DPPC/DOPC/Chol
0.55/0.15/0.30

Top view, one leaflet
L_o phase composition

- **Yellow: CHOL**
- **Blue: DOPC chain**
- **Red: DPPC chain**

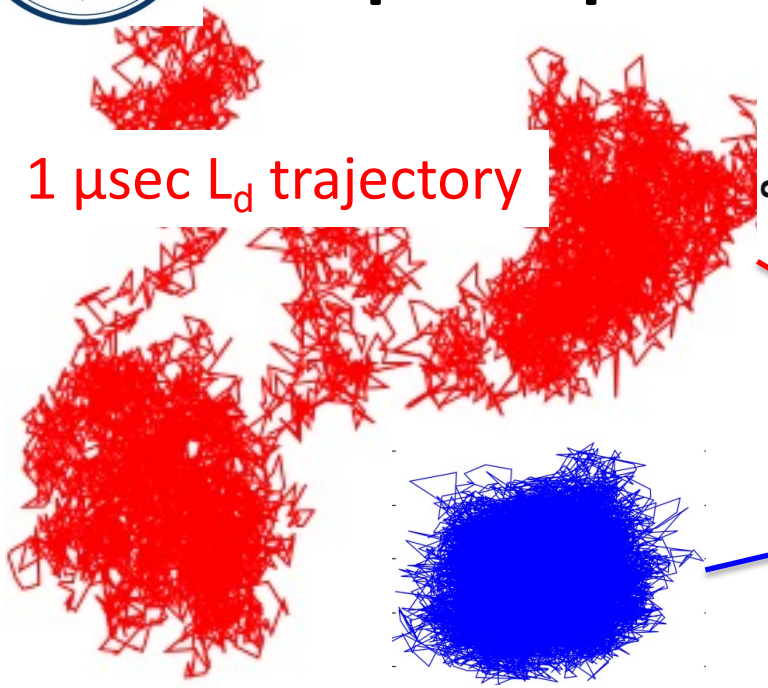


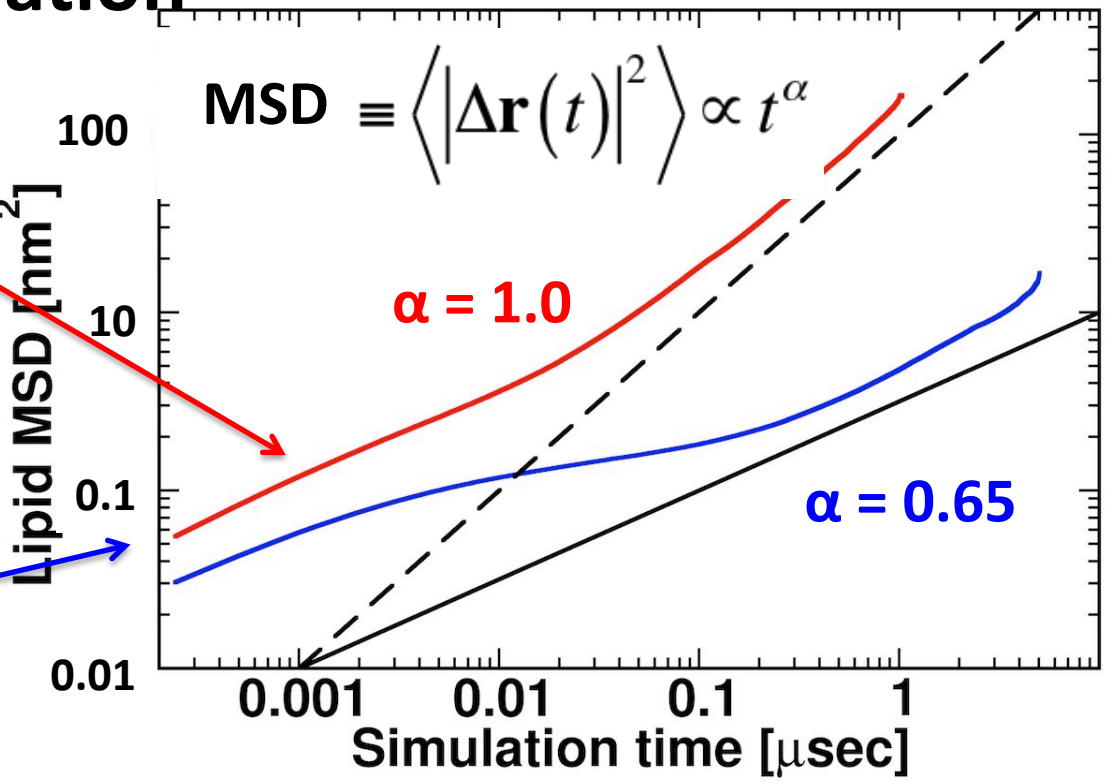
Take home messages:

- L_o dynamics are slow and collective
- L_o structure is itself inhomogeneous — Implication for partitioning?

A Sodt, ML Sandar, K Gawrisch, RW Pastor, E Lyman *J Am Chem Soc* 136:725(2013)

The turnover to Newtonian behavior: Some rampant speculation



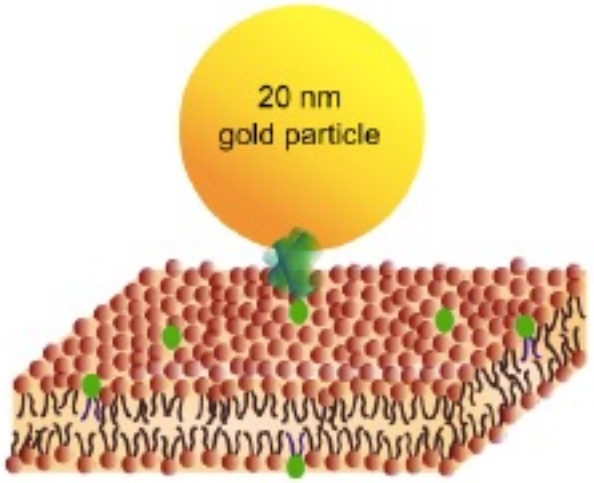


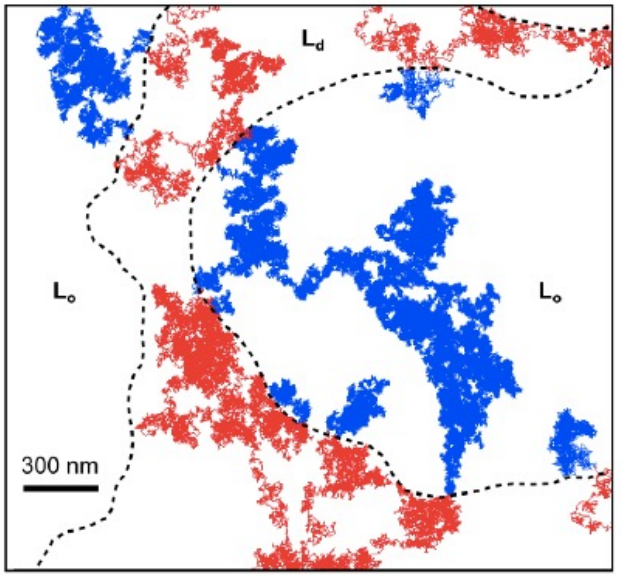
iSCAT SPT of a lipid moving **from L_d to L_o**

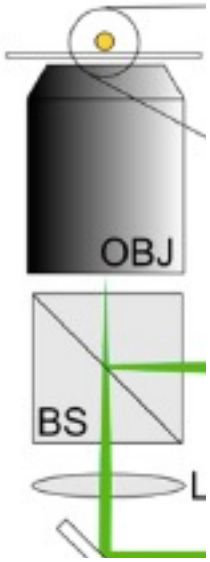
Hsieh et al Optics in the Life Sciences (2015)

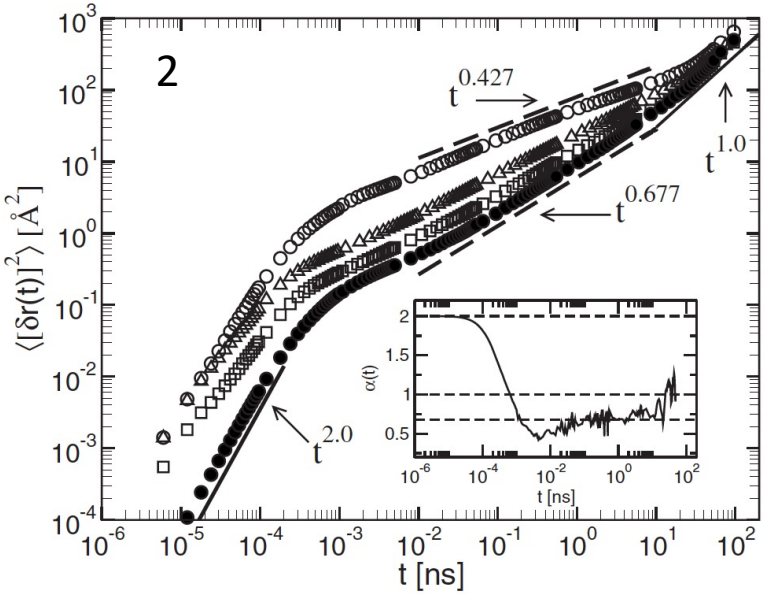
Lipid subdiffusion in the L_o phase: iSCAT SPT

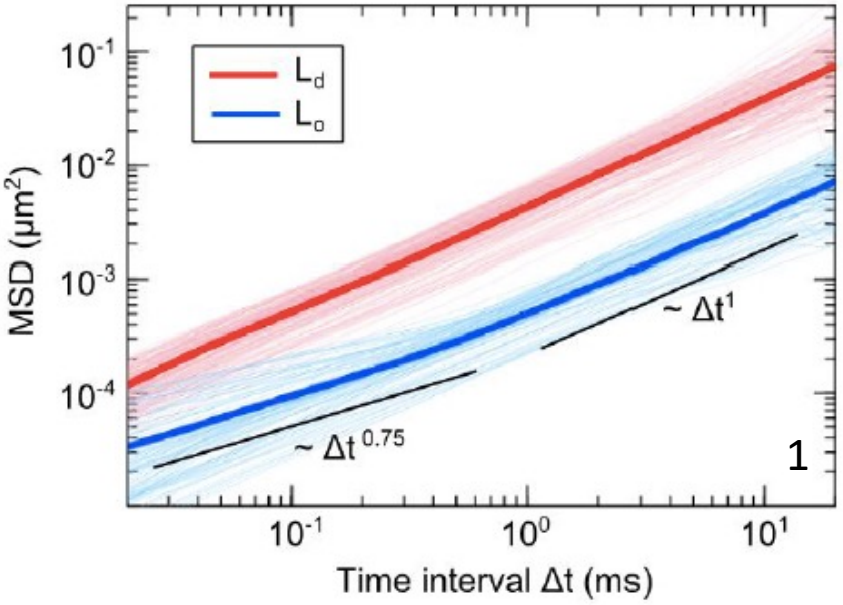
Chia-Lung Hsieh,
Academia











[1] Wu, …Chia-Lung Hsieh **Sci Rep** 2016
[2] Flenner et al, PRE 79:011907(2009)

Summary

- Surface viscosities in all-atom simulations are at least 10x lower than experimental measurements --- Why?
- The DPPC/DOPC/Chol L_o phase at 295 does not plateau at accessible shearing rates — is this a signature of longer timescale elastic to viscous crossover?
- Interpreting lipid diffusion with the PSD yields a lipid hydrodynamic radius of 0.15 nm

Acknowledgements

Funding:

- NIH P20GM104316, R01-GM120351
- Univ of Delaware Research Foundation
- National Resource for Biomedical Supercomputing at the Pittsburgh Supercomputing Center
- Oak Ridge Affiliated Universities Program

Lyman Group @Udel

Post docs:

- Alison Leonard
- Liam Sharp

Grad Students:

- Long Chen
- John Melkumov
- Shea Fitzgerald
- Miguel Joya

Undergrad Students:

- Cassie O'Quinn

Collaborators

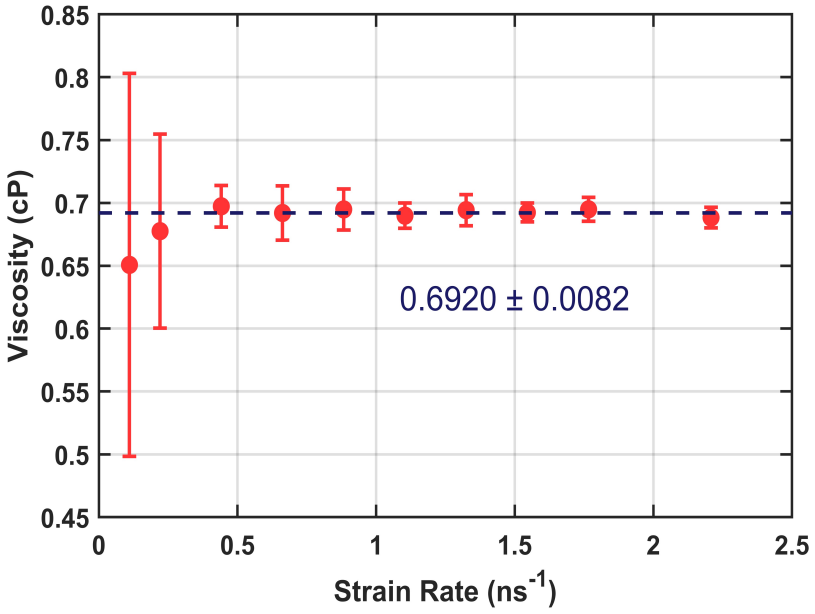
Rich Pastor (NHLBI)
Alex Sodt (NICHD)
Ilya Levental (UT Health Sciences)
Itay Budin (UCSD)

Shea Fitzgerald

Alison Leonard

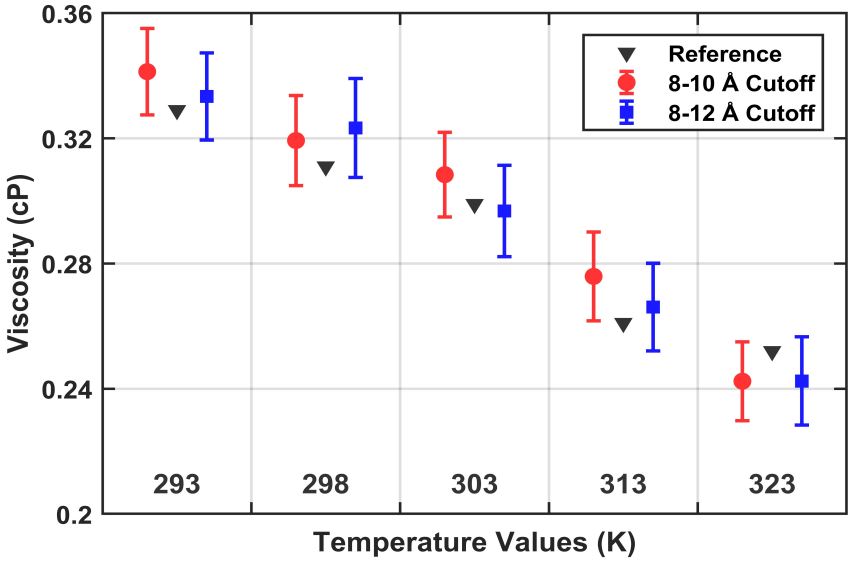
Testing the box deformation protocol

Martini "water"



- 3 independent replicas (420 nsec ea) at each strain rate
- 6100 vdW particles
- Agrees w/ ind. Measurement obtained from Green-Kubo

Tip3p



- 5 independent replicas 12 nsec ea) at each strain rate (0.2-4 nsec^{-1})
- 4074 waters
- Agrees w/ ind. Measurement obtained from Green-Kubo[1]

[1]Venable et al J Phys Chem B 114:12501 (2010)
A Zgorski, R Pastor, EL *JCTC* 15:6471(2019)

α < 1 … let me count the ways

The MSD does not fully characterize the probability distribution

$$\delta r^2(t) \equiv \int \left[\mathbf{r}(t)\right]^2 P(\mathbf{r},t)\, d^2 r$$

There are **at least three** distinct microscopic processes relevant to biology that all yield α < 1 !!

Fractional Brownian Motion (FBM)	Continuous Time Random Walk (CTRW)	Laplace Process
↓	↓	↓
Memory	Long-tailed waiting time distribution	Fractal support
↓	↓	↓
Viscoelastic Stuff	Binding to “traps”	Crowding

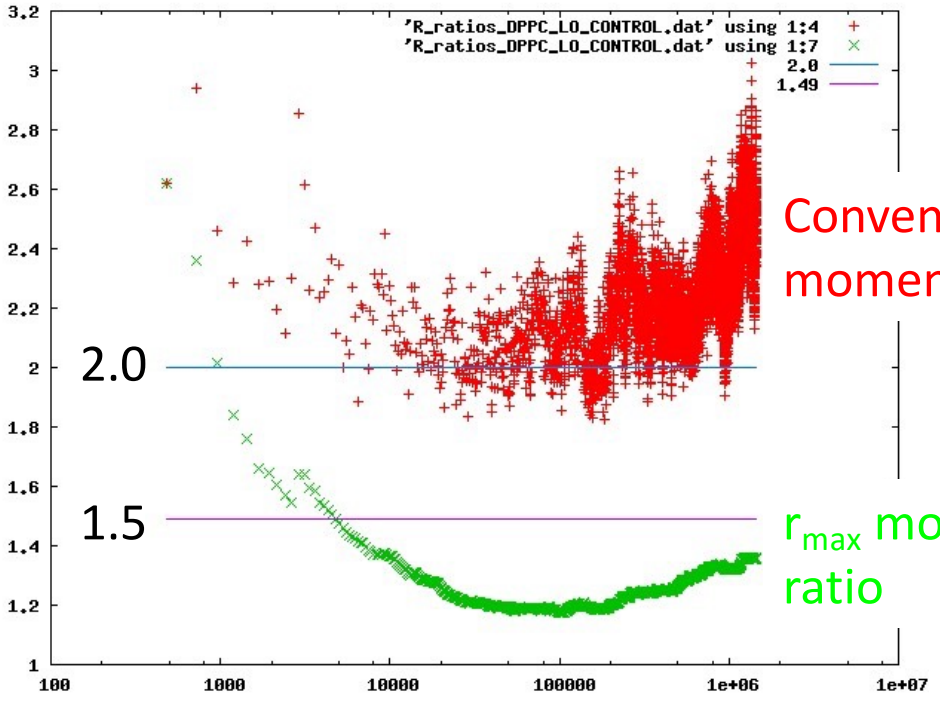
Displacement statistics distinguish FBM and CTRW[1]

$$\frac{\left\langle \left|\Delta \mathbf{r}(t)\right|^4 \right\rangle}{\left\langle \left|\Delta \mathbf{r}(t)\right|^2 \right\rangle^2}$$

= 2 for FBM (in 2D)
> 2 for CTRW
< 2 for Laplace

$$\frac{\left\langle \left|\Delta \mathbf{r}_{\max}(t)\right|^4 \right\rangle}{\left\langle \left|\Delta \mathbf{r}_{\max}(t)\right|^2 \right\rangle^2}$$

< 1.49 for FBM
> 1.49 for CTRW
< 2 for Laplace



Conventional moment ratio

r_{max} moment ratio

We think that FBM is a signature of the L_o phase[2] (on 20 nm lengthscales)

[1] Tejedor et al *Biophys J* **98**:1364(2010)
[2] Jeon et al PRL 109:188103(2012)

What criteria must a simulation fulfill? A manifesto

A molecular simulation approach should:

- Retain sufficient chemical detail to resolve lipids and membrane proteins
- Be tractable for actin compartment spatiotemporal scales
- Be faithful to the dynamics of membrane lateral transport

How big is big enough?

- For Martini 2.2: $\mathrm{L}_{SD} = \frac{2\times10^{-8}\,\mathrm{P\cdot cm}}{0.69\ \mathrm{cP}} \cong 30\ \mathrm{nm}$
- For c36: $\mathrm{L}_{SD} = \frac{20\times10^{-8}\,\mathrm{P\cdot cm}}{0.3\ \mathrm{cP}} \cong 660\ \mathrm{nm}$

What criteria must a simulation fulfill? A manifesto

A molecular simulation approach should:

Biophysical Journal

Biophysical Perspective

Biophysical Society

From Dynamics to Membrane Organization: Experimental Breakthroughs Occasion a "Modeling Manifesto"

Edward Lyman,[1,2,*] Chia-Lung Hsieh,[3] and Christian Eggeling[4,5,6]

How big is big enough?

- For Martini 2.2: $L_{SD} = \frac{2 \times 10^{-8}\,\mathrm{P \cdot cm}}{0.69\ \mathrm{cP}} \cong 30\ \mathrm{nm}$
- For c36: $L_{SD} = \frac{20 \times 10^{-8}\,\mathrm{P \cdot cm}}{0.3\ \mathrm{cP}} \cong 660\ \mathrm{nm}$

Saffman-Delbruck and q2D hydrodynamics: Long ranged and counter-intuitive

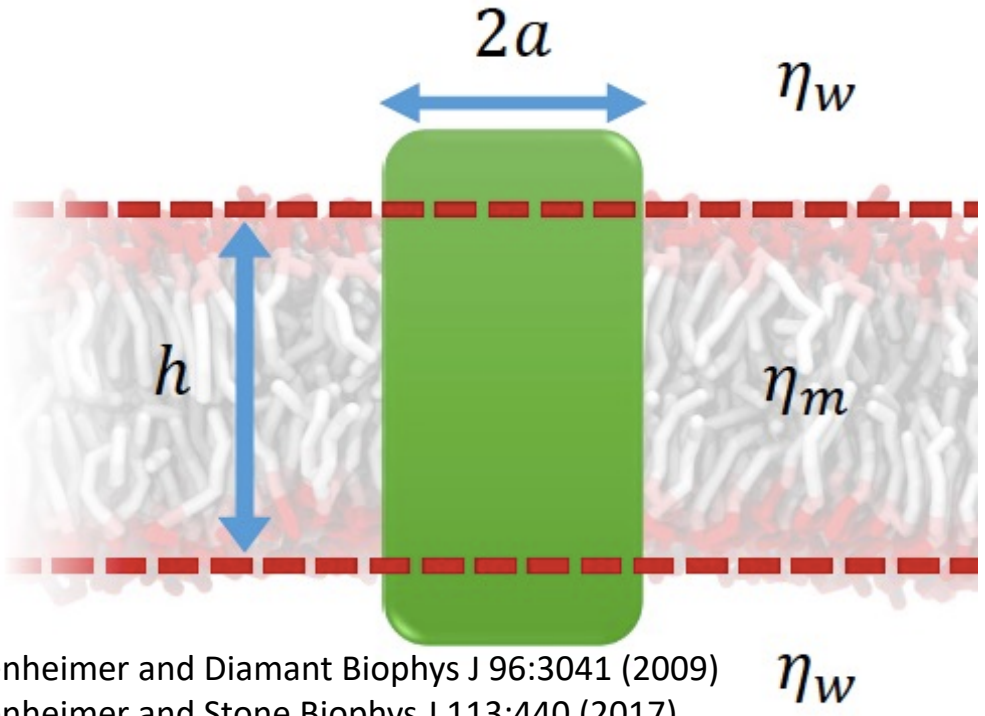
Hydrodynamics for membranes:

- Low Re number → Navier-Stokes linearize
- Incompressible (both membrane and water)
- 2D fluid coupled to 3D bulk, $\eta_m \sim 1000 \times \eta_w$

A new length scale appears: $L_{SD} = h\frac{\eta_m}{\eta_w}$

Mobility scales with log radius:

$$\mu = \frac{1}{4\pi h \eta_m}\left(\ln\left(\frac{2L_{SD}}{a}\right) - \gamma\right)$$



Saffman and Delbruck, J Fluid Mech 1976
Oppenheimer and Diamant PRL 258102(2011)

Oppenheimer and Diamant Biophys J 96:3041 (2009)
Oppenheimer and Stone Biophys J 113:440 (2017)