Surface viscosity and subdiffusion in membrane simulations

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

Homeoviscous adaptation (Sinensky):

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

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

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<tr>
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<th>$\tau$ (nsec)</th>
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<td>1.9</td>
</tr>
<tr>
<td>37</td>
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<td>2.6</td>
<td>1.8</td>
</tr>
<tr>
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<td>2.7</td>
<td>2.0</td>
</tr>
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Some “common” lipids

There are hundreds of lipids in our membranes!

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

There are hundreds of lipids in our membranes!

• 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

Shear rate

Units:

In 3D: \[ \sigma_{xy} = \frac{[\text{Force}]}{[\text{area}]} \]  

\[ \eta = \frac{[\text{force}][\text{time}]}{[\text{area}]} \]

In 2D: \[ \sigma_{xy} = \frac{[\text{Force}]}{[\text{distance}]} \]  

\[ \eta = \frac{[\text{force}][\text{time}]}{[\text{distance}]} \]
Shear viscosity of some alkanes and aliphatic alcohols

<table>
<thead>
<tr>
<th>Carbons</th>
<th>Alkanes</th>
<th>Alcohols</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td></td>
<td>2.5*</td>
</tr>
<tr>
<td>6</td>
<td>0.2*</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>0.386</td>
<td>3.5*</td>
</tr>
<tr>
<td>10</td>
<td>0.5*</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>1.06</td>
<td>9.0*</td>
</tr>
<tr>
<td>14</td>
<td>1.0*</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>2.1</td>
<td>9 or 27</td>
</tr>
</tbody>
</table>

- 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: \((h) \times (\eta_{\text{hex}}) = \eta_m\)

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
Membrane viscosity: Some experimental numbers

Domain flicker spectroscopy:

DPPC:DiPhy:cho

Fits to SDHPW:

\( \eta = (15.9 \pm 2.3) \times 10^{-9} \text{ Pa} \cdot \text{m} \cdot \text{sec} \)

\( \eta = (5 - 10) \times 10^{-9} \text{ Pa} \cdot \text{m} \cdot \text{sec} \)


[a]Hormel...Parthasarathy PRL 112:188101(2014)
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

Shear rate

viscosity

The protocol for surface viscosity:

- Apply a box deformation to achieve different shear rates
- Average \( P_{xy} \)

Stress tensor obtained from pressure (virial) tensor

\[ \sigma_{xy} = -\langle P_{xy} \rangle \]
Martini DPPC Shear Viscosity

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

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)

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

<table>
<thead>
<tr>
<th>Membrane Composition</th>
<th>Surface Viscosity $(10^{-11} \text{ Pa-m-s}) = (10^{-8} \text{ P*cm})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPPC (8-10)</td>
<td>$8.18 \pm 0.50$</td>
</tr>
<tr>
<td>DPPC (8-12)</td>
<td>$12.26 \pm 0.50$</td>
</tr>
<tr>
<td>DOPC (8-12)</td>
<td>$19.68 \pm 0.69$</td>
</tr>
<tr>
<td>PSM (8-12)</td>
<td>$48.8 \pm 1.2$</td>
</tr>
<tr>
<td>$L_o$ (8-12)</td>
<td>$23.83 \pm 0.92 \text{ (T = 323K)}$</td>
</tr>
<tr>
<td>$L_o$ (8-12)</td>
<td>$?? \text{ (T = 298K)}$</td>
</tr>
<tr>
<td>$L_d$ (8-12)</td>
<td>$9.39 \pm 0.47 \text{ (T = 323K)}$</td>
</tr>
<tr>
<td>$L_d$ (8-12)</td>
<td>$40.6 \pm 1.0$</td>
</tr>
</tbody>
</table>

$T_{\text{sim}} = 323$

$T_{\text{sim}} = 303$

$T_{\text{sim}} = 323$

No plateau at low shear rate!
(more on this later...)
An equilibrium protocol. Or, how to blow a bunch of cycles chasing a number

A Green-Kubo relation for shear viscosity:

\[ \eta = \frac{\beta}{V} \int_0^\infty \langle \Pi_0^{\alpha\beta}(t)\Pi_0^{\alpha\beta}(0) \rangle \, dt \]

Notes:

- “0” subscript reminds us that we have taken a \( k \rightarrow 0 \) limit
- \( \Pi_0^{\alpha\beta} \) is the atomic stress tensor here. We use NVT conditions to avoid artifacts
- To get membrane surface viscosity, \( \alpha, \beta \) 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

- DLPC
- DMPC
- DPPC

Unsaturation

- DOPC
- PSM

Sphingolipid

- POPC-283
- POPC-303
- POPC-323

Temperature

- 16:0-18:1

Shea Fitzgerald and EL, unpublished
Equilibrium viscosity results, summary

<table>
<thead>
<tr>
<th>Lipid</th>
<th>$T_m$</th>
<th>$T_{sim}$</th>
<th>$\eta \times 10^{-11}$ Pa-m-sec</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLPC 12:0</td>
<td>271</td>
<td>286</td>
<td>17.3 ± 6.8</td>
</tr>
<tr>
<td>DMPC 14:0</td>
<td>297</td>
<td>312</td>
<td>11.4 ± 5.7</td>
</tr>
<tr>
<td>DPPC 16:0</td>
<td>314</td>
<td>329</td>
<td>8.7 ± 1.7</td>
</tr>
<tr>
<td>DSPC 18:0</td>
<td>327</td>
<td>343</td>
<td>8.5 ± 1.1</td>
</tr>
<tr>
<td>DOPC 18:1</td>
<td>256</td>
<td>283</td>
<td>39 ± 14</td>
</tr>
<tr>
<td>PSM</td>
<td>314</td>
<td>329</td>
<td>59 ± 22</td>
</tr>
<tr>
<td>POPC 16:0-18:1</td>
<td>271</td>
<td>283</td>
<td>42.0 ± 9.6</td>
</tr>
<tr>
<td>POPC 16:0-18:1</td>
<td>271</td>
<td>293</td>
<td>25 ± 11</td>
</tr>
<tr>
<td>POPC 16:0-18:1</td>
<td>271</td>
<td>303</td>
<td>14.7 ± 2.5</td>
</tr>
<tr>
<td>POPC 16:0-18:1</td>
<td>271</td>
<td>313</td>
<td>15.2 ± 5.8</td>
</tr>
<tr>
<td>POPC 16:0-18:1</td>
<td>271</td>
<td>323</td>
<td>8.8 ± 3.4</td>
</tr>
</tbody>
</table>

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 L₀ Phase

DPPC/DOPC/Chol 0.55/0.15/0.30

Top view, one leaflet
L₀ phase composition

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

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?

The turnover to Newtonian behavior: Some rampant speculation

$\text{MSD} \equiv \left\langle |\Delta \mathbf{r}(t)|^2 \right\rangle \propto t^\alpha$

$\alpha = 1.0$

$\alpha = 0.65$

1 µsec $L_d$ trajectory

5 µsec $L_o$ trajectory

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 $L_0$ phase: iSCAT SPT

Chia-Lung Hsieh, Academia

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
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- Shea Fitzgerald
- Miguel Joya

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- Cassie O’Quinn

Collaborators

Rich Pastor (NHLBI)
Alex Sodt (NICHD)
Ilya Levental (UT Health Sciences)
Itay Budin (UCSD)
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\(^1\)

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

\[ \delta r^2(t) = \int [r(t)]^2 P(r,t) \, d^2r \]

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

- Fractional Brownian Motion (FBM)
  - Memory
  - Viscoelastic Stuff
- Continuous Time Random Walk (CTRW)
  - Long-tailed waiting time distribution
  - Binding to “traps”
- Laplace Process
  - Fractal support
  - Crowding
Displacement statistics distinguish FBM and CTRW\textsuperscript{1}

\[
\frac{\langle |\Delta r(t)|^4 \rangle}{\langle |\Delta r(t)|^2 \rangle^2} = 2 \text{ for FBM (in 2D)} \\
> 2 \text{ for CTRW} \\
< 2 \text{ for Laplace}
\]

\[
\frac{\langle |\Delta r_{\text{max}}(t)|^4 \rangle}{\langle |\Delta r_{\text{max}}(t)|^2 \rangle^2} < 1.49 \text{ for FBM} \\
> 1.49 \text{ for CTRW} \\
< 2 \text{ for Laplace}
\]

We think that FBM is a signature of the L\textsubscript{o} phase\textsuperscript{2} (on 20 nm lengthscales)

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: \[ L_{SD} = \frac{2 \times 10^{-8} \text{P cm}}{0.69 \text{ cP}} \approx 30 \text{ nm} \]
• For c36: \[ L_{SD} = \frac{20 \times 10^{-8} \text{P cm}}{0.3 \text{ cP}} \approx 660 \text{ nm} \]
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From Dynamics to Membrane Organization: Experimental Breakthroughs Occasion a “Modeling Manifesto”

Edward Lyman, Chia-Lung Hsieh, and Christian Eggeling

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

Hydrodynamics for membranes:
• Low Re number $\rightarrow$ 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)