

# Using Stochastic Modeling to Predict Long Timescale Transport Behavior of Solutes in an $H_{II}$ Phase Lyotropic Liquid Crystal Membrane

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## 1 Introduction

We need highly selective membranes in order to perform efficient separations.

Amphiphilic molecules are capable of self-assembling into ordered nanostructures.

Lyotropic liquid crystals are a class of amphiphilic molecules that can be cross-linked into mechanically strong membranes.

- $H_{II}$  phase lyotropic liquid crystals have densely packed, uniform sized pores and have the potential to disrupt conventional membrane separation techniques by being selective based not only on size and charge, but on chemical functionality as well.
- $Q_I$  phase LLCs consist of a tortuous network of 3D interconnected pores.

We can only learn so much from experiment. MD can give us mechanistic insights with atomistic resolution so that we can intelligently design new membranes for solute-specific separations.

In our previous work, we studied the transport of 20 small polar molecules in an  $H_{II}$  phase LLC membrane.

Unfortunately, the timescales that we can simulate with MD are insufficient to be able to predict well-converged predictions of macroscopic transport properties traditionally used to characterize membranes in the lab.

In this work, we explore two approaches to modeling the dynamic behavior of a subset of solutes that we studied in our previous work.

- First is based on the anomalous diffusion literature
- Our second approach to modeling solute transport groups solute behavior into different dynamical states.

## 2 Methods

We ran all MD simulations and energy minimizations using GROMACS 2018. We performed all post-simulation trajectory using python scripts which are available online at <https://github.com/shirtsgroup/LLC.Membranes>.

### 2.1 Molecular Dynamics Simulations

We studied transport of solutes in the  $H_{II}$  phase using an atomistic molecular model of four pores in a monoclinic unit cell with 10 % water by weight.

- Approximately one third of the water molecules occupy the tail region with the rest near the pore center.
- We chose to study the 10 wt % water system because solutes move significantly faster than in the 5 wt % system studied previously.

- Appropriate stochastic modeling requires that solutes explore as much structural space as possible.

We chose to study a subset of 4 of the fastest moving solutes from our previous work: methanol, acetic acid, urea and ethylene glycol.

- In addition to exploring membrane structural space the most, these solutes have a relatively diverse set of chemical functionality.
- For each solute we created a separate system and to each system we added 6 solutes per pore for a total of 24 solutes.
- This number of solutes per pore provides a balance of a low degree of interaction between solutes and sufficient amount of data from which to generate statistics on the time scales which we simulate.
- Further details on the setup and equilibration of these systems can be found in our previous work.[1]

We extended the 1  $\mu$ s simulations of our previous work to 5  $\mu$ s in order to collect ample data.

- We simulated the system with a time step of 2 fs at a pressure of 1 bar and 300 K controlled by the Parinello-Rahman barostat and the v-rescale thermostat respectively.

## 2.2 Modeling subdiffusion

Solutes in our H<sub>II</sub> LLC membrane system exhibit subdiffusive behavior, a type of anomalous diffusion.

- During an anomalous diffusion process, the mean squared displacement (MSD) does not grow linearly with time, rather it is of the form:

$$\langle x^2(t) \rangle = K_\alpha t^\alpha \quad (1)$$

where  $\alpha$  is the anomalous exponent and  $K_\alpha$  is the generalized diffusion coefficient.

- A value of  $\alpha < 1$  indicates a subdiffusive process, while values of  $\alpha = 1$  and  $\alpha > 0$  are characteristic of Brownian and superdiffusive motion respectively.

We analyzed both the ensemble-averaged and time-averaged MSDs of the simulated trajectories.

- The ensemble-averaged MSD measures the displacement of a particle from its initial position [2] and can be written as

$$\langle x^2(t) \rangle = \langle x(t) - x(0) \rangle \quad (2)$$

- The time-averaged MSD measures the displacement between all possible time lags and can be written as

$$\overline{x^2(\tau)} = \frac{1}{T - \tau} \int_0^{T - \tau} (x(t + \tau) - x(t))^2 dt \quad (3)$$

where  $\tau$  is the time lag and T is the length of the trajectory [2].

Three common mathematical models for modeling anomalous subdiffusion processes include continuous time random walks (CTRW), fractional Brownian motion (FBM) and random walks on fractals (RWF).[2]

- FBM is common in crowded, viscoelastic environments where each step comes from a Gaussian distribution but is anti-correlated to its previous step. [3, 4, 5]
- A CTRW is characterized by a distribution of hop lengths and dwell times, where each step is characterized by independent random draws from each distribution.[6, 7]
- An RWF is imposed by a system's geometry. Systems with tortuous pathways and dead ends cause anti-correlated motion.[2, 8]
- The processes described above can happen alone or in combination.

We believe that solutes in the system studied here exhibit subordinated fractional Brownian motion (sFBM) where the parent process is FBM and the leading process is a CTRW.

- The ensemble-averaged MSD differs from the time-averaged MSD, which is indicative of non-ergodicity, a trait inherent to CTRWs but not FBM or RWFs. [9]
- We also observe non-stationary  $z$ -coordinate traces of each solute's center of mass (COM).
- For a pure CTRW, the time-averaged MSD should be linear. [8, 10]
- However, a typical time-averaged solute MSD is sublinear (see supporting information), which suggests that there is another underlying subdiffusive mechanism.
- The hop lengths recorded after each dwell period are anti-correlated (See supporting information)
- Given the viscoelastic nature of the monomers in our system, we believe the hop lengths can be modeled with FBM.
- For subordinated FBM, it can be shown that

$$\langle x^2(t) \rangle \simeq t^{\alpha\beta} \quad (4)$$

where  $\alpha$  is the anomalous exponent characteristic of the leading CTRW process and  $\beta$  is the anomalous exponent characteristic of the parent FBM process.

We can characterize a CTRW process using the parameters which describe its dwell time and hop length distribution.

- We used the `ruptures` python package in order to identify changepoints in solute trajectories.[11] (See Supporting Information for more details on chosen parameters. i.e. type of cost function, cost function penalty tolerance, number of dimensions used)
- We used the corresponding hop lengths and dwell times between break points to construct empirical distributions.

For solutes in our system, the distribution of hop lengths appears to be well-represented by a Gaussian distribution. [12, 13, 14]

- We are most interested in the standard deviation,  $\sigma$ , of the hop length distribution.

The distribution of dwell times is expected to fit a power law (or heavy-tailed) distribution proportional to  $t^{-1-\alpha}$ . [2]

- Because we are limited to taking measurements at discrete values dictated by the output frequency of our simulation trajectories, we fit the empirical dwell times to a discrete power law distribution whose maximum likelihood  $\alpha$  parameter we calculated by maximizing the following likelihood function:

$$\mathcal{L}(\beta) = -n \ln \zeta(\beta, x_{min}) - \beta \sum_{i=1}^n \ln x_i \quad (5)$$

where  $\beta = 1 + \alpha$ ,  $x_i$  are collected dwell time data points,  $n$  the total number of data points, and  $\zeta$  is the Hurwitz zeta function where  $x_{min}$  is the smallest measured value of  $x_i$ . [15]

- We obtained distributions of the hop length standard deviations,  $\sigma$ , and  $\alpha$  using statistical bootstrapping.[16]

FBM processes can be described using the Hurst parameter,  $H$ , where  $H = \beta/2$ .

- Brownian motion is recovered for  $H = 0.5$

- The autocovariance function of hop lengths has the analytical form: [3]

$$\gamma(k) = \frac{1}{2} \left[ |k-1|^{2H} - 2|k|^{2H} + |k+1|^{2H} \right] \quad (6)$$

where  $k$  is the number of increments between hops.

- We obtained  $H$  by performing a least squares fit of Equation 6 to the empirically measured autocovariance function.
- We used statistical bootstrapping to generate a distribution of  $H$  values.

In general, we observe different dynamical behavior when solutes move inside the pore versus in the tail region.

- Therefore, we created 2 sets of parameters based on the solute's radial location.
- Solutes in the pore region are located less than 0.75 nm from the pore center and all else are in the tail region.
- We determined this cut-off and described how we calculated radial distance from the pore center in our previous work [1]

For each solute, we simulated 10000 5  $\mu$ s sFBM trajectories.

- We constructed trajectories by simulating sequences of dwell times and correlated hop lengths generated based on parameters randomly chosen from our bootstrapped parameter distributions.
- We propagated each trajectory until the total time reached 1  $\mu$ s, and truncated the last data point so that the total time exactly equaled 5  $\mu$ s.
- Valid comparisons are only possible between fixed length sFBM simulations. The power law dwell time behavior gives rise to the aging phenomenon, embodied by a decrease in MSD with measurement time. [8, 13]
- We reported the MSD after 5  $\mu$ s with corresponding 95 % intervals

## 2.3 The Infinite State Hidden Markov Model

Hidden Markov models (HMMs) are a useful and widely used technique for modeling sequences of observations where the probability of the next observation in a sequence depends only on a previous unobserved, or hidden, state. [?]

- In the context of our simulations, the observations correspond to the center of mass coordinates of the solutes versus time, and the states correspond to the dynamical behavior which giving rise to those types of observations.
- Unfortunately, HMMs require the number of hidden states to be known a priori.

The infinite-state HMM overcomes this drawback using a hierarchical Dirichlet process (HDP).

- Using some base probability distribution,  $H$ , a Dirichlet process (DP) generates distributions over a countably infinite number of probability measures:

$$G_0 = \sum_{k=1}^{\infty} \beta_k \delta_{\theta_k} \quad \theta_k \sim H \quad (7)$$

## 3 Results and Discussion

### 3.1 Governing Mechanisms

The mechanisms which govern transport of small polar solutes in this system can be broadly described based on a solute’s size, shape, and polarity.

- In general, solutes can move fastest in the pore center, where there is comparatively little resistance to diffusion.
- The well-established trend of decreasing solute mobility with size is not defied here, however we observe small solutes with lower-than-expected MSDs because they spend time trapped between monomer head groups.
- Additionally, planar molecules are prone to exhibiting similar trapping behavior, even for large molecules whose similar sized, but flexible counterparts exhibit faster diffusion.
- The polarity of solutes also influences a solute’s ability to stay in the pore center. Highly polar molecules tend to spend more time in the pore center, while those with hydrophobic character tend to spend more time in the head group region.
- Finally, the ability to hydrogen bond offers a second trapping mechanism. Solute that are hydrogen bond donors can donate hydrogen atoms to any of the 5 oxygen atoms located on the monomer head groups. Increasing the number of hydrogen bond donating groups increases the solute’s polarity causing solutes to spend more time in the pore centers, but the effect can be countered by excessive trapping if there many hydrogen bonds are being formed.
- Overall solutes exhibit some degree of trapping, by one or a combination of the above mechanisms, with anticorrelated hops between each period of immobility due to obstructions.

We will explore these factors in greater detail in the context of specific groups of molecules in the discussion that follows.

### 3.2 MSD Predictions

We calculated the MSD of each solute in the set over the course of  $1\mu\text{s}$  MD simulations.

- We extracted values of  $\sigma$ ,  $\alpha$  and  $H$  for each solute and then simulated 10000 sFBM trajectories of the same length as our MD simulations, as described in Section ?? of the Methods.
- The final MSDs of the sFBM trajectories are compared to those calculated directly from MD simulations in Figure 1.
- The three sFBM parameters, calculated based on MD solute trajectories are presented in Table 1.
- We would like to emphasize that we rely on the MD MSD values in order to define trends in the total MSD, while the sFBM trajectories and parameter values allow us to speculate as to the reasons for the observed trends.
- There is a non-negligible amount of error in the calculation of each parameter which prevents us from reliably portraying our sFBM MSDs as reduced uncertainty MD MSDs.

Our simulated sFBM MSDs qualitatively reproduce the MD trends.

- sFBM generally lower
- There are a few noticeable discrepancies.
- We will discuss reasons for these as we proceed with the discussion.

In most cases, it is easy to relate  $\sigma$ ,  $\alpha$  and  $H$  to the simulated MSD values presented in Table 1.

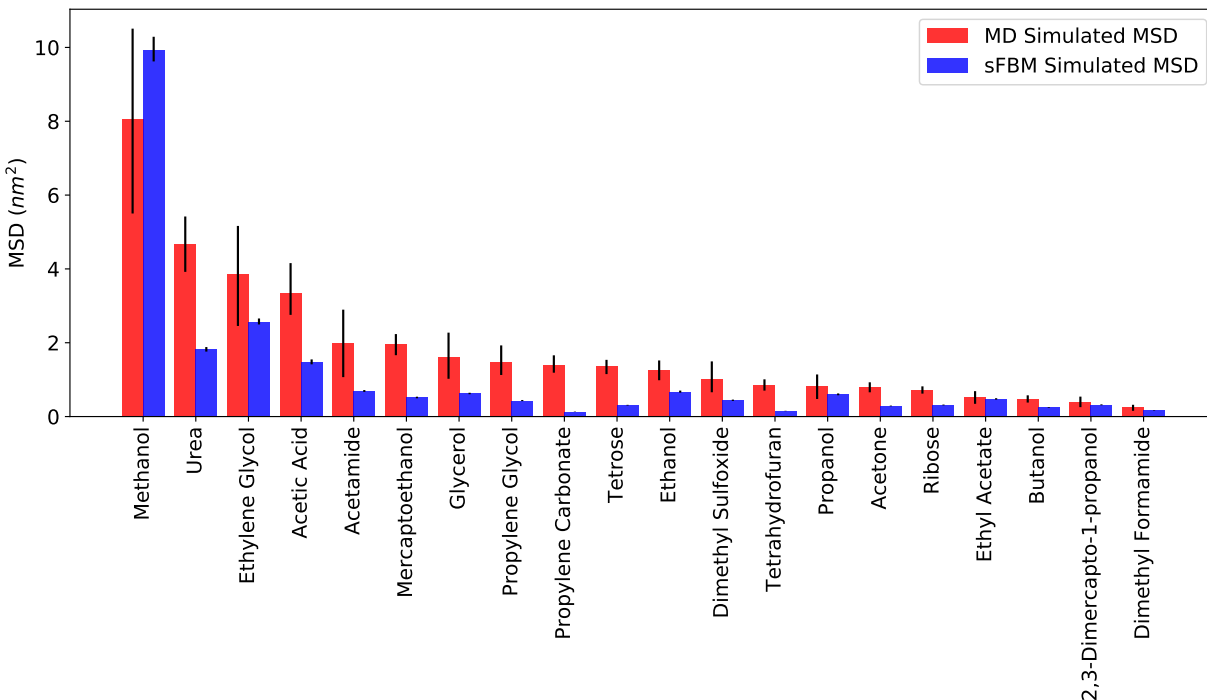


Figure 1

- Higher values of  $\sigma$  indicate larger average hop lengths.
- Higher values of  $\alpha$  mean that there will be less sampling of long dwell times.
- Values of  $H$  near the Brownian limit of 0.5, indicate a lower degree of anti-correlation.
- All of which contribute to an overall increase in the simulated MSD

We fit a CTRW model (see Section ??) to these trajectories and predicted macroscopic diffusion coefficients which are presented in Table TBD.

- We confirmed that our molecules exhibit anomalous diffusion by fitting a power law to the MSD curve. The exponent is less than 1, indicative of anomalous subdiffusion.
- We used the decision making process given by Meroz and Sokolov in order to identify the appropriate subdiffusion model to use based on our time series (See Section S-TBD of the Supporting info for more details).
- The motion of the solutes is non-ergodic and the steps are uncorrelated which tells us the system is likely well-described by a CTRW.

### The Influence of Water Content on Macroscopic Diffusion Coefficients

Solutes in systems with lower water content exhibit lower diffusion coefficients.

- Pores are more crowded when there is less water (show RDFs of each)
- Not a linear function of pore size - radius increase by  $x$ ,  $D$  increases by  $y$
- Larger influence on bigger molecules

System	$\sigma$ (nm)	$\alpha$	$H$
Methanol	0.46	0.85	0.40
Urea	0.33	0.64	0.40
Ethylene Glycol	0.35	0.64	0.36
Acetic Acid	0.28	0.51	0.44
Mercaptoethanol	0.30	0.54	0.26
Ethanol	0.32	0.55	0.25
Propylene Glycol	0.26	0.48	0.35
Glycerol	0.23	0.46	0.37
Acetamide	0.28	0.52	0.26
Propanol	0.25	0.41	0.35
Acetone	0.23	0.44	0.34
Ethyl Acetate	0.21	0.41	0.37
Dimethyl Sulfoxide	0.26	0.48	0.26
Tetrose	0.24	0.43	0.30
Butanol	0.19	0.41	0.33
Dimethyl Formamide	0.20	0.39	0.32
2,3-Dimercapto-1-propanol	0.20	0.37	0.35
Ribose	0.20	0.40	0.27
Propylene Carbonate	0.19	0.38	0.29
Tetrahydrofuran	0.24	0.39	0.16

Table 1: We calculated values  $\sigma$ ,  $\alpha$  and  $H$  from MD simulation trajectories and then computed the average ensemble-averaged MSD of 10000 simulated trajectories.

### 3.2.1 Experimental Measurements

## 3.3 Transport Mechanisms

In order to truly understand the molecular origins of the macroscopic diffusion coefficients in Section ??, we studied the microscopic interactions between solutes and the membrane that lead to the observed dwell time and hop distributions.

- We studied the radial distribution functions of solutes as a function of distance from the pore center
- We looked at hydrogen bonding patterns
- Coordination numbers
- Order parameters

The radial distribution function of each solute studied is shown in Figure TBD.

### Transport of Water

All water molecules exhibit hop diffusion.

Even in the center of the pore, where the density of water molecules is highest, individual water molecules exhibit hop diffusion as they create a tight hydrogen bond network.

- Water sticks to pore walls
- Dwell times are short
- Water tumbles across pore for a while until it sticks again.
- Water gets caught in h-bonds with other water molecules away from pore center.

In this confined environment, the diffusion constant is x times lower than expected bulk diffusion coefficient of tip3p water.

## Transport of Alcohols

The hydroxyl functional group of alcohol molecules is a hydrogen bond donor and prefers to donate it's hydrogen to more strongly polarized carboxylate head groups.

As alcohol groups increase in hydrophobic character, they are more inclined to stick to the outside edges of the pore.

- The alkane tails prefer to stay at the edges of the pore.
- Radial distribution functions show peaks at pore edges, however smaller alcohols have high densities near the pore center.
- They tend to get trapped between monomers and closer to the tail region.
- The entrapment is further stabilized by hydrogen bonds with ether oxygens connecting the monomer's alkane tails to the head groups.

The diffusion coefficient of simple alcohols increases as the length of the alkane chain increases.

- The dwell times increase as the oily tails become more entrapped in monomer tails.

Ethylene glycol, a diol, has two hydrogen bond donor groups.

- Can hydrogen bond with same moiety.
- Can hydrogen bond with different moieties in the same vicinity.
- Dwell times tend to be shorter. If one hydroxyl group is bound with a hydrogen bond, the other unbound hydroxyl group may form a hydrogen bond elsewhere and effectively pull the other bound hydroxyl group along with it.

## Transport of Acetone

The carbonyl group of Acetone is a hydrogen bond acceptor and therefore only form hydrogen bonds with water molecules in the pore.

The hydrophobic character of the two methyl groups on acetone causes the methyl groups to gravitate towards the outside of the pore, while the carbonyl group reaches towards the pore center in order to hydrogen bond with water molecules.

- Order parameter defined between vector along carbonyl and vector extending from acetone COM to pore center is non-zero.

## Transport of Acetic Acid

Acetic acid, since we modeled it solely in its protonated state, has hydrogen bond donor and acceptor groups.

## Transport of Ions

Sodium ions also exhibit hop diffusion because polarized water and carboxylate head groups both work to neutralize its charge.

- Ions get trapped in oxygen 'cages' composed of combinations of water molecules, carboxylate head groups and ether oxygens connecting the head groups to their tails.
- Interesting coordination number data
- Dwell time proportional to surrounding charge within coordination shell

## Remarks

Overwhelming amount of water in 10 wt% system makes hydrogen bonding competitive between head groups and water.



### 3.4 Design Suggestions

Water content affects pore size. Experiments to understand this could be useful.

Separate polar molecules by creating monomers with more hydrophilic head group components. More incentive to dwell on walls.

Make ions move faster by placing charges in sterically inaccessible places.

## 4 Conclusion

We have examined the transport characteristics of a series of small polar molecules in our model of the  $H_{II}$  phase formed by Na-GA3C11.

We calculated the macroscopic diffusion coefficients of each solute as approximated by a CTRW model and validated our estimates using experimental DOSY NMR measurements.

We have studied the influence of water content on the diffusion coefficients.

We showed that hydrogen bonding between solutes and Na-GA3C11 monomers plays a major role in mechanism by which molecules traverse the nanopores.

We can use this intuition in order to modify our monomers for a specific separation.

- Increase number of h-bond sites to increase selectivity towards water over polar molecules
- Also separate acetone (things with only h-bond accepting groups) in this way

## Supporting Information

Detailed explanations and expansions upon the results and procedures mentioned in the main text are described in the Supporting Information. This information is available free of charge via the Internet at <http://pubs.acs.org>.

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## TOC Graphic