Statistical Inference of Transport Mechanisms and Long Time Scale Behavior from Time Series of Solute Trajectories in Nanostructured Membranes.

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1 Introduction

There is a need for highly selective membranes in order to perform efficient separations of components of complex aqueous streams.

- Organic micropollutants
- Desalination and boric acid removal from seawater.
- While many researchers focus on membrane permeability, we may be able to reduce costs of commercial nanofiltration and reverse osmosis with higher selectivity. [1]

Lyotropic liquid crystals (LLC) are a class of amphiphilic molecules whose ordered phases can be cross-linked into mechanically strong membranes capable of highly selective separations.

- The shape of the LLC monomers and water content dictates the ordered phase that they form. There are two phases of particular interest for membrane applications.
- H_{II} phase lyotropic liquid crystals are characterized by hexagonally packed, straight, pores while the Q_I phase consists of a tortuous network of 3D interconnected pores.
- In both cases the pores are uniform in size with radii on the order of 1 nm giving them a very strict molecular weight cut-off.
- Additionally, they 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.
- Their pores are lined with LLC monomer functional groups which can potentially be designed to interact with solutes in a chemically-specific manner

There are limits to what we can learn from experiment about LLC membrane design.

- Experimental observables like permeability and selectivity allow us to speculate about the molecular origins of separation processes.
- This drives an empirical design approach which can potentially neglect key interactions which influence selectivity.
- LLC membranes have been shown to exhibit selectivities which cannot be fully explained by relatively simple macroscopic models.

Molecular Dynamics (MD) simulations 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 built a detailed atomistic model which we used to understand the nanoscopic structure of an LLC Membrane. [2]
- We also used the model in order to gain a qualitative understanding of trapping mechanisms which lead to subdiffusive transport behavior. [3]

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

- However, if we use descriptive stochastic models that can capture solute dynamics, then we could project long timescale behavior in addition to gaining a deeper understanding of solute behavior on short timescales.

In our previous work, we designed two different approaches which used solute time series in order to parameterize stochastic models that could be used to project transport on much longer timescales.

- In our first approach we modeled solute trajectories as subordinated fractional Brownian and Lévy motion, called the anomalous diffusion (AD) model.
- We generated solute trajectories by generating a series of anti-correlated hops separated by random periods of entrapment drawn from a power law distribution.
- Our second approach treated solute motion as a Markov state model with state-dependent dynamics, called the Markov state-dependent dynamical model (MSDDM).
- We parameterized the state transition probabilities between each of eight discrete states as well as the solute dynamics within each of these states. We generated stochastic trajectory realizations by drawing a state sequence based on the transition probability matrix and incorporating the state dynamics while solutes were trapped in each state.

Although both models had reasonable success at predicting solute mean squared displacements (MSDs) on MD simulation timescales, they had shortcomings.

- The MSDDM failed to reproduce the hopping and trapping behavior that characterizes solute center-of-mass trajectories in our MD simulations.
- The AD model did not suffer this qualitative shortcoming, but the persistent curvature of the predicted MSD curves suggested that the model might underestimate MSDs on long timescales.
- The formulation of both models required careful examination and characterization of the interactions and dynamics exhibit by MD trajectories which required considerable human effort.

In this work, we apply the infinite hidden markov model (IHMM), a modeling approach that is agnostic to the source of time series data, in order to automatically detect and infer the parameters of an unknown number of latent autoregressive (AR) modes present in solute center-of-mass time series.

- In addition to AR parameters for each state, the IHMM estimates the state transition probability matrix.
- The model helps simultaneously uncover underlying transport mechanisms which give rise to dynamical behavior and project that behavior on longer timescales so that we can estimate macroscopic transport observables.

We use the parameters of the states identified by the IHMM in order to infer dominant solute-membrane interactions and transport mechanisms.

- We compare the inferred mechanisms to those which we manually identified in our previous work.
- Some kind of conclusion here. Did we find more or less states. Any new states/ subdivisions of states?

We can also use the IHMM to generate stochastic trajectory realizations that share the same dynamical characteristics as solute trajectories observed in our MD simulations.

- The trajectories are qualitatively similar, showing expected hopping and trapping behavior.
- They are quantitatively similar in that they reproduce the MSDs measured in MD.

Finally, we use the stochastic trajectory realizations in order to compute the macroscopic flux of each solute and selectivity of the LLC membranes studied towards each solute.

- We relate these macroscopic properties to our nanoscopic model by simulating mean first passage time (MFPT).
- Some kind of conclusion. This membrane is selective towards solutes with this functionality.
- Does the conclusion agree with our previous work? Any length dependence? (I think not)

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 sample the accessible mechanisms with representative probability.

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.[3]

We extended the 1 μs simulations of our previous work to 5 μs 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.
- We recorded frames every 0.5 ns

2.2 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, latent or hidden, state. [4]

- 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 give rise to those types of observations.
- Unfortunately, standard HMMs require the number of hidden states to be known a priori.
- One can partially overcome this by testing a range of numbers of hidden states and determining which is the best representation of the data.

The infinite-state HMM overcomes this drawback by placing a hierarchical Dirichlet process (HDP) prior on the transition probabilities.

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

$$G_0 = \sum_{k=1}^{\infty} \beta_k \delta_{\theta_k} \quad \theta_k \sim H, \beta \sim GEM(\gamma) \tag{1}$$

  where the θ_k are values drawn from the base distribution and the weights β_k come from a stick-breaking process parameterized by the concentration parameter γ (equivalently referred to as GEM(γ)).

- The concentration parameter expresses one's confidence in H relative to the posterior and is closely related to the number of data observations.
- Each row, G_j, of the transition matrix is produced by drawing from a DP specified using the β vector as a discrete base distribution and a separate concentration parameter, α.

$$G_j = \sum_{k=1}^{\infty} \pi_{jk} \delta_{\theta_k} \quad \pi_j \sim DP(\alpha, \beta) \tag{2}$$

- This hierarchical specification ensures that the transition probabilities in each row share the same support points $\{\theta_1, ..., \theta_k\}$.
- Once the model has converged only a finite number of states will have significant sampling.

We describe the dynamics of each state using a vector autoregressive (VAR) model.

- A VAR(r) process is characterized by a vector of observations in a time series that are linearly dependent on r previous values of the time series vector:

$$\mathbf{y}_t = \mathbf{c} + \sum_{i=1}^{r} A_i \mathbf{y}_{t-i} + \mathbf{e}_t \qquad \mathbf{e}_t \sim N(0, \Sigma) \tag{3}$$

  Previous observations are weighted by coefficient matrices A_i. The VAR(r) process is further characterized by a shift in the mean of each dimension by the vector $\mathbf{c}$ and a white noise term $\mathbf{e}_t$. [5]

- We assumed multivariate Gaussian noise, with mean zero and covariance, Σ.
- We limited our analysis to an autoregressive order of $r = 1$.
- We used a conjugate matrix-normal inverse-Wishart prior on parameters A and Σ and a conjugate Gaussian prior on $\mathbf{c}$ in order to analytically draw from the posterior. [6]

Using the IHMM framework, we estimated the most likely number and sequence of hidden states while simultaneously estimating VAR(1) parameters for each state and the overall state transition probability matrix, T.

- We created a python implementation of this process which we heavily adapted from the MATLAB code of Fox et al. [7]
- Parameter estimation is iterative. Therefore, we looked for convergence as shown in SI.
- We refer the interested reader to much more extensive descriptions of this process and its implementation. [4, 8, 9, 6, 10]

We applied the IHMM algorithm to the radial and axial coordinates of each solute center-of-mass trajectory.

- We measured the radial coordinate as the distance from the closest pore center.
- Because the pores are somewhat tortuous, we approximated the pore center as a spline. See previous work.

We clustered like parameter sets in order to reduce the state space to a more easily interpretable size.

- Since the mean vector, $\mathbf{c}$ of each state can take on continuous values, the IHMM algorithm tends to find a large number of states, with very few states revisited.
- However, $\mathbf{A_i}$ and $\mathbf{\Sigma}$ tend to share similarities with independently identified states. Therefore, we clustered based on $\mathbf{A_i}$ and $\mathbf{\Sigma}$, ignoring the mean.
- Since we do not know the number of similar states beforehand, we used a non-parametric Bayesian Gaussian mixture model
- We used the clustered parameters in order to relabel states in the estimated state sequences and to recalculate the state transition probability matrix.

We generated stochastic trajectory realizations by drawing state sequences based on the rows of T.

- While in a given state, we simulated motion according to the VAR(1) parameterization of that state.
- We set the unconditional mean of each state based on the position before the state transition occurred.

2.3 Estimating Flux and Selectivity

We calculate first passage times by propagating stochastic trajectories until they reach distance L.

We determine the mean first passage time (MFPT) using the following equation: [11]

$$P(t) = -\frac{1}{\sqrt{\pi}} e^{-(L-vt)^2/(4Dt)} \left(-\frac{D(L-vt)}{4(Dt)^{3/2}} - \frac{v}{2\sqrt{Dt}} \right) \tag{4}$$

Flux, J, is simply 1 / MFPT by the Hill relation. [12]

In our previous work, we showed that, in the absence of convective solute flux, selectivity towards solute i versus solute j can be calculated by:

$$S_{ij} = \frac{J_i/\Delta C_i}{J_j/\Delta C_j} \tag{5}$$

where ΔC_j is the trans-membrane concentration difference.

3 Results and Discussion

3.1 Inferring Solute Transport Mechanisms

Clustering parameters sets results in X distinct dynamical modes.

- In the figure below, we show time series simulations that qualitatively illustrate the difference in dynamical behavior between modes.

We can relate the identified states back to transport mechanisms.

- More detailed discussion of identified states
- How size of fluctuations, autoregressive parameters are influenced by trapping mechanisms
- How do these states compare to those identified in our previous work?
- Any new states?

3.2 Reproducing MD Trajectories and MSDs with the IHMM

Trajectory realizations qualitatively match MD simulation trajectories.

- Look for hopping and trapping behavior

MSDs generated from stochastic trajectories match those from MD.

- Look at curvature and 1-σ confidence intervals

3.3 Estimating Solute Flux and Selectivity

We can predict macroscopic flux and selectivity.

- Flux as function of pore length
- Selectivity as function of pore length (if flux scaling is length-dependent)

4 Conclusion

We have shown that the IHMM can be used to parameterize solute time series with an unknown number of latent dynamical modes.

We can use the IHMM to help identify mechanisms by relating the latent states to observed solute behavior.

We can use the IHMM to predict macroscopic transport properties.

The IHMM is not limited to the H_{II} phase.

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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