

Supporting Information: Modeling Monomer Interactions with Molecular Dynamics

October 14, 2019

We used an atomistic molecular model and molecular dynamics simulations in order to quantify the number of acid-base reactions that would occur in a real system as a pure consequence of proximity. We ran all MD simulations and energy minimizations using GROMACS 2018. [1, 2, 3, 4] We built and equilibrated initial configurations and performed post-simulation trajectory analysis using python scripts which are available online at https://github.com/shirtsgroup/LLC_Membranes. Table S1 provides more detail about specific scripts used for each task.

Script	Purpose
<code>/setup/build.py</code>	Build initial configuration
<code>/setup/equil.py</code>	Energy minimize and equilibrate initial configurations
<code>/analysis/hbonds.py</code>	Identify hydrogen bond interactions based on angle and distance cut-off criteria.
<code>/analysis/hbond_reactions.py</code>	Track cumulative number of reacted acid-base pairs using hydrogen bonds as a reaction surrogate

Table S1: The first column provides the names of the python scripts available in the `LLC_Membranes` GitHub repository that were used for system setup and post-simulation trajectory analysis. Paths preceding script names are relative to the `LLC_Membranes/LLC_Membranes` directory. The second column provides a brief description of the purpose of each script.

We constructed four independent simulation unit cells on which to collect data. The monoclinic unit cells consist of four pores, each made of 5 columns of 20 monomers stacked on top of each other 3.7 Å apart in a parallel displaced configuration (see Figure S1). We randomly distributed the acidic and basic monomers among the columns. The parallel displaced $\pi - \pi$ stacking configuration is more stable than the sandwiched configuration where monomers stack directly on top of each other. [5] In previous work with a similar monomer, we also found that systems built in the parallel displaced configuration as described above provide the closest match to experimental structural data. [6]

We equilibrated the unit cells using the same procedure as our previous work. [6] All steps of the following procedure are implemented in `LLC_Membranes/setup/equil.py` (see Table S1):

1. Build initial configuration
2. Energy minimize initial configuration with high ($1e6 \frac{kJ}{mol \cdot nm^2}$) position restraints on head group heavy atoms.
3. Run 50 ps NVT simulation with same position restraints.
4. Repeat steps 2 and 3, gradually reducing the force constant on head group heavy atoms according to the sequence 3162, 56, 8, 3, 2, 1, 0 $\frac{kJ}{mol \cdot nm^2}$.
5. Run 5 ns unrestrained NPT simulation with semi-isotropic pressure coupling controlled by the Berendsen barostat and temperature controlled by the v-rescale thermostat.

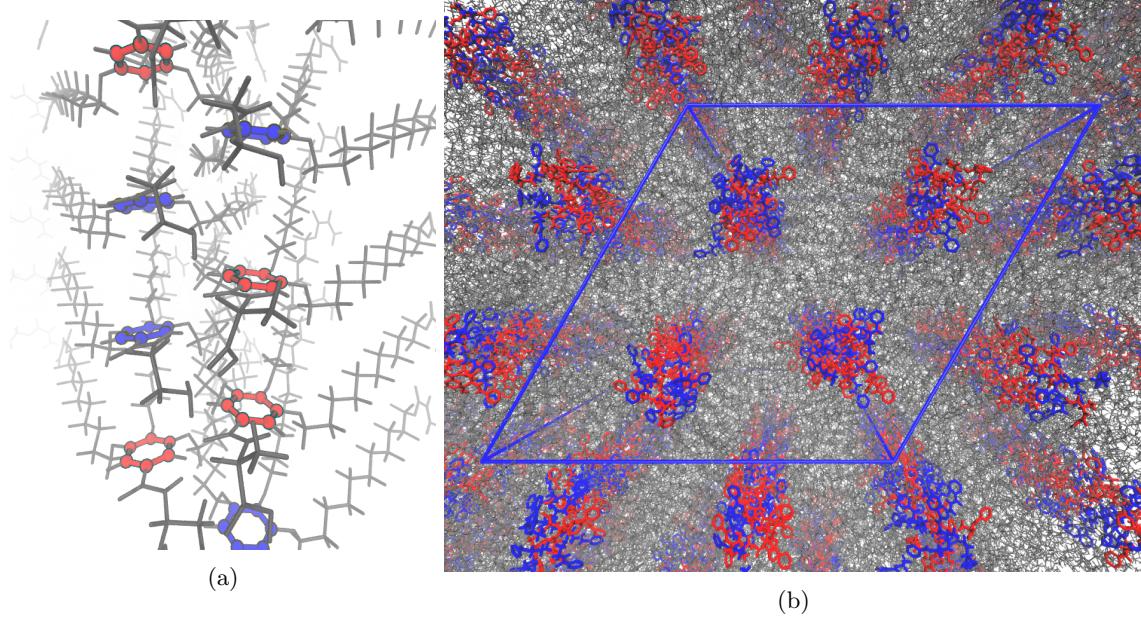


Figure S1: (a) We randomly chose a total of 20 acidic (red) and basic (blue) monomers and stacked the aromatic head groups in a parallel displaced configuration on top of each other to form columns. (b) We created 4 pores, each consisting of 5 columns, and placed them in a monoclinic unit cell (represented by the blue box) which is the smallest unit cell that preserves hexagonal symmetry when the system is extended periodically. The pore centers are highlighted by the colored monomer head groups.

6. Run long ($> 400\text{ ns}$) NPT simulations with semi-isotropic pressure coupling controlled by the Parinello-Rahman barostat and temperature controlled by the v-rescale thermostat.

Because MD simulations typically do not involve reactions, we used hydrogen bonding as a surrogate for the acid-base reaction that would deactivate catalytic monomers. We considered a reaction to occur if a COOH group of monomer **1** donated its hydrogen to the NH₂ group of monomer **2**. A study of hydrogen bonding patterns among thousands of structures in the Cambridge Structural Database suggests that this type of hydrogen bond does not exist [7]. This is likely because proton transfer is immediate and nearly irreversible.

We predicted the percentage of unreacted monomers present in bulk film by counting the number of unique acid-base “reactions” as a function of time in our MD simulations. In our search for hydrogen bonds, we considered each new hydrogen bonded pair to be “reacted” and excluded both monomers from the rest of the search. We ran our simulations until the percentage of reacted monomers plateaued for at least 100 ns.

The exact percentage of unreacted monomers predicted from our simulations is a function of the geometric criteria that we chose to use for identifying hydrogen bonds. There is no consensus in the simulation literature as to the proper way of identifying a hydrogen bond. [8] In our previous work, we defined a hydrogen bond to exist if the distance, d , between the donor (D) and acceptor (A) atoms was less than 3.5 Å and the D-H \cdots A angle, θ , was less than 30°(see Figure S2). [9] However, most of the hydrogen bonds were of the type O-H \cdots O whereas we are interested in O-H \cdots N. Studies of structurally similar hydrogen bonds show a range of behavior with d between 2.75 and 3.12 and θ up to 90°. [10, 11] In the main text we chose to use $d=3.0$ and $\theta=30^\circ$. We tested the sensitivity of our conclusions to these criteria in Figure S3. The plateau in the percentage reacted monomers is well below 100% indicating that our conclusions hold with even the most lenient criteria.

We extrapolated the final number of reacted catalytic groups by fitting a plateauing function of the form:

$$f(x) = M(1 - x^{-a}) \quad (1)$$

where M and a are the asymptotic maximum function value and the rate of decay respectively. We believe

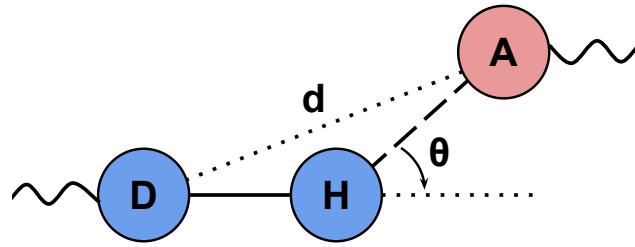


Figure S2: We identify hydrogen bonds using geometric criteria based on the distance, d , between the donor (D) and acceptor (A) atoms as well as the angle, θ , between the \vec{DH} and \vec{HA} vectors (where H is the hydrogen atom)

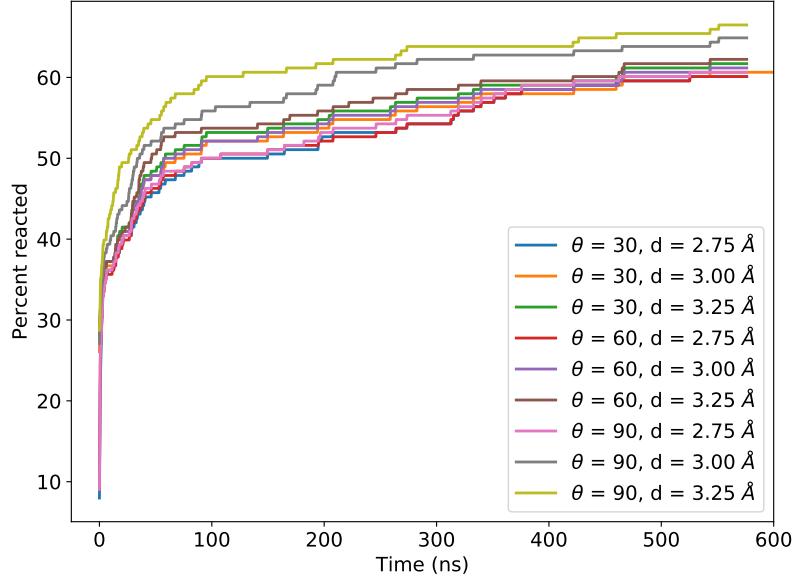


Figure S3: We tested the sensitivity of our conclusions to hydrogen bond geometric identification criteria. As our conditions become more lenient (higher d and θ), the percentage of reacted monomers increases but still plateaus well below 100%.

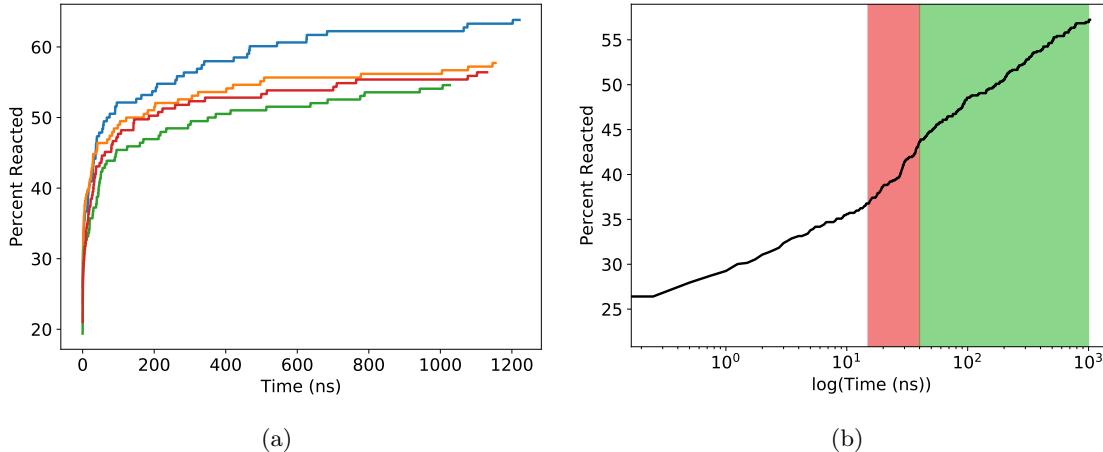


Figure S4: (a) Although the growth rate of total surrogate reactions decreases with time, it is likely that the curves will not fully plateau on a time scale that we can reasonably simulate. (b) The growth rate appears to enter at least three distinct regimes shown approximately by the different colored regions. We fit Equation 1 to the last (green) regime.

this type of fit is necessary because the number of hydrogen bond "reactions" continues to grow slowly over time even after long plateaus (see Figure S4a).

There are multiple regimes of growth in the number of hydrogen bond surrogate reactions. Since we are interested in the asymptotic value, M , of the plateau, we fit Equation 1 to the average growth curve starting after 40 ns where the percent reacted head groups versus the log of time becomes consistently linear (see Figure S4b).

We used bootstrapping to determine the mean value of M with its associated uncertainty. The procedure is as follows:

1. Randomly choose, with replacement, 4 of the curves in Figure S4a.
2. Fit Equation 1 to the mean of the 4 curves to get the value of M .
3. Repeat 200 times to generate a distribution of M values.
4. Report mean and standard error of M distribution.

Note that this procedure is best performed with many more than 4 curves, however it should still yield a more realistic uncertainty than the typically very small error returned by the single non-linear least squares fit to the average.

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