Supporting information for: Extension of the Highly Mobile Membrane Mimetic to Transmembrane Systems Through Customized in silico Solvents

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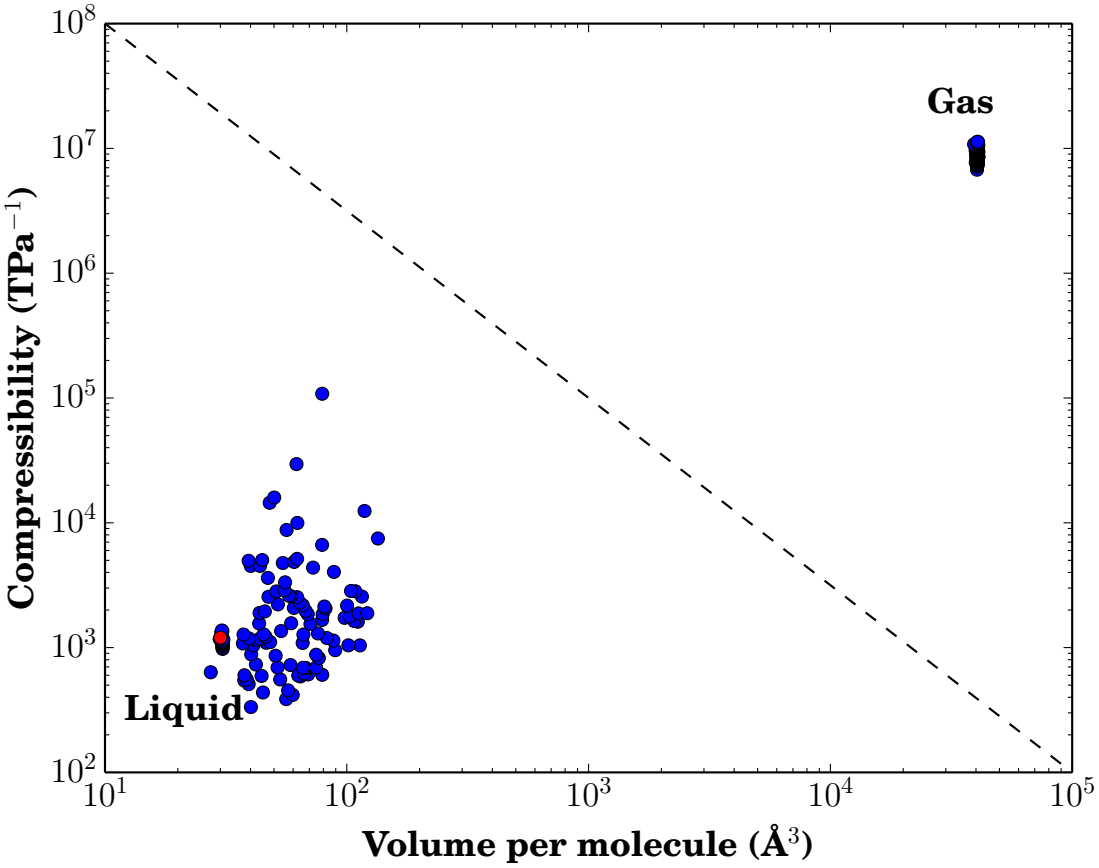

Figure S1: Accessible compressibility and volume values. The red point is the target value of cyclohexane, and blue are observed points from attempted parameters.

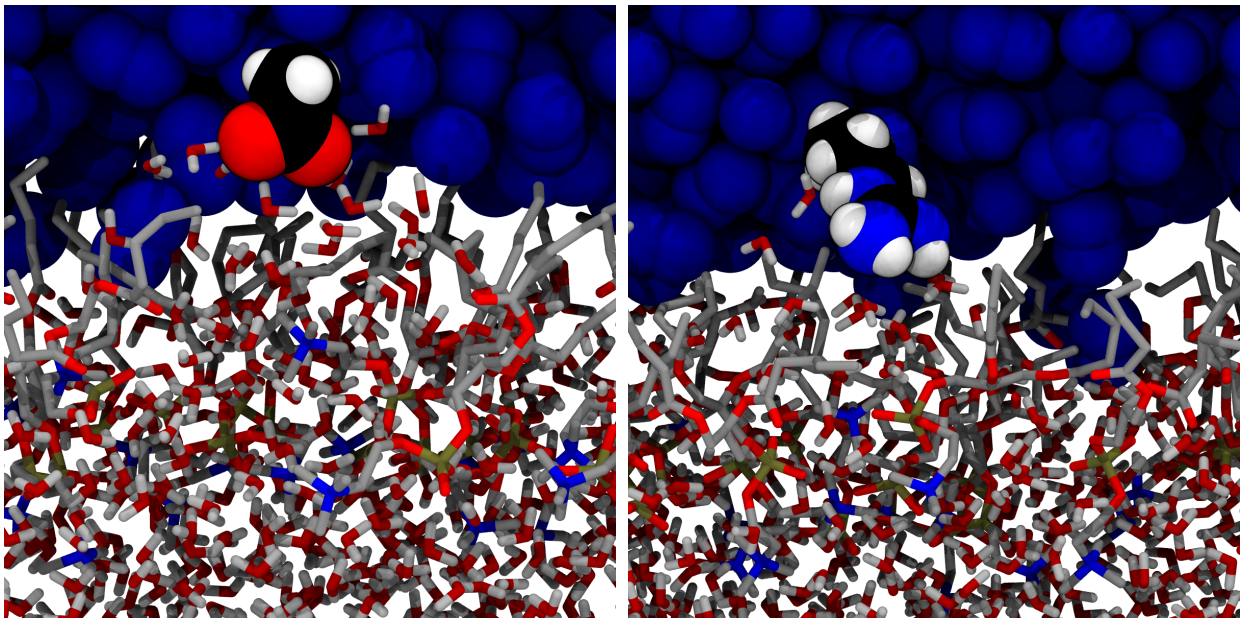

Figure S2: Example water defects formed during simulation with aspartate (left) and arginine (right) analogs. Here, water molecules (stick representation) interact so strongly with the charged species (sphere representation with black carbons) that they intercalate below the short lipids (stick representation with grey carbons) to the interface with the SCSE (background blue spheres).

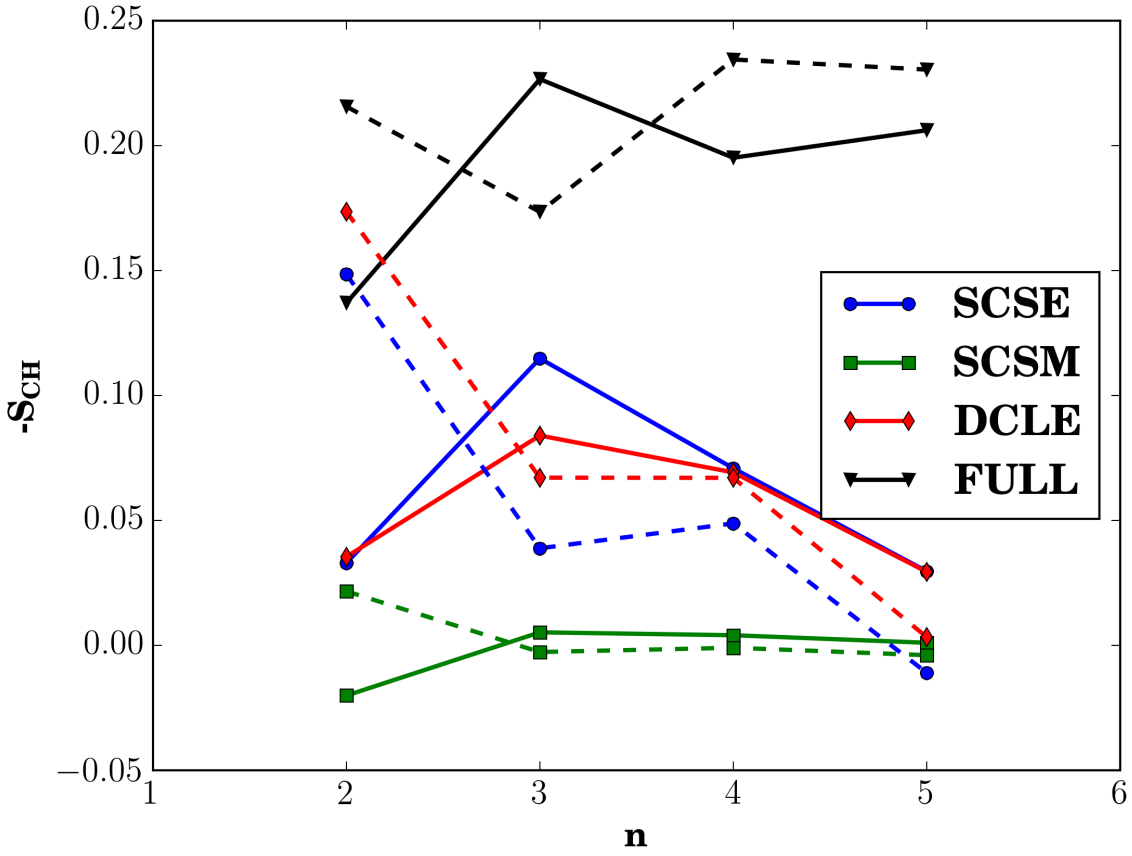

Figure S3: Order parameter S_{CH} calculated for lipid tail components without constraints from C2 to C5. Points connected by solid lines correspond to the tail attached to C2 of the glycerol, while dashed lines connect points that correspond to the tail attached to C3 of the glycerol.

Intercalation Counting Algorithm

Counting intercalated atoms is difficult. Conceptually, we are searching for a particle that is mostly surrounded by protein. While it is easy to point out deeply intercalated atoms which are surrounded on all sides by protein, edge cases also exist that are not as clearcut. Our evaluation criteria is to consider every potentially intercalating atom, and calculate an effective protein density at the position of the potential intercalant. The protein density (ρ) contributions at each potential intercalant i is calculated as follows:

$$\rho\left(i\right) = \sum_{j \in \mathrm{H}} \exp\left(\frac{-\left|R_j - R_i\right|^2}{2 r_j \sigma}\right)$$

Where r_j is the radius of atom j, σ is a scaling factor, R_x are the atomic coordinates of atom x, and H is the set composed of all protein heavy atoms close to intercalant i to contribute significantly to the sum. To reduce the computational cost, elements of H were chosen such that:

$$\left|R_j - R_i\right| \leq \xi\sigma$$

Where ξ serves to cutoff the extent of the gaussian. Utilizing this formalism, we can assign a ρ-value to every potential intercalant within the bounding-box of the protein, and dictate that atoms are only intercalated if $\rho \geq threshold$ (Fig. S4).

There are effectively three free parameters to determine if a particle is intercalated: ξ, σ, and the threshold value. After some experimentation, we found that $\xi = 1.5$, $\sigma = 7.0$ and threshold=125 was close to the optimal for the proteins tested, closely matching our intuition for what qualifies as an "intercalated" atom without too many false positives (Fig. S5). For practical implementations, the product $\xi\sigma$ should be comparable to the nonbonded cutoff used in the simulation to avoid including too many atoms in H for efficient computation. Large σ values are useful for capturing intercalants trapped on three sides but which are still partially exposed to the membrane, but this is an analytical measurement that needs refinement specific to each system.

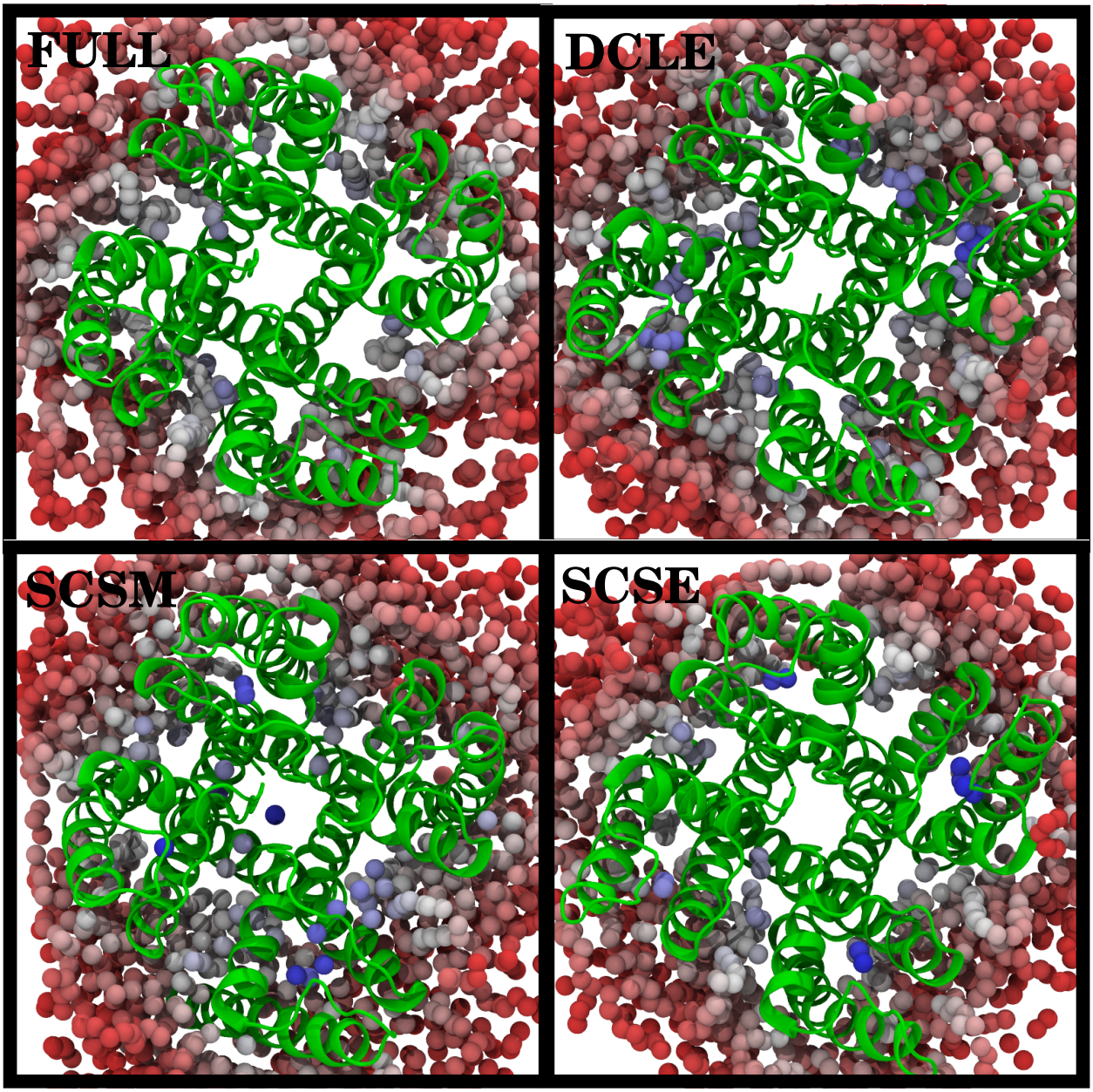

Figure S4: Final structures after 20 ns for each simulation, where membrane components with nonzero ρ values are shown in addition to KcsA (green). The different colors of the membrane components represent the ρ value. Large ρ are blue, small ρ are red, and intermediate ρ are white.

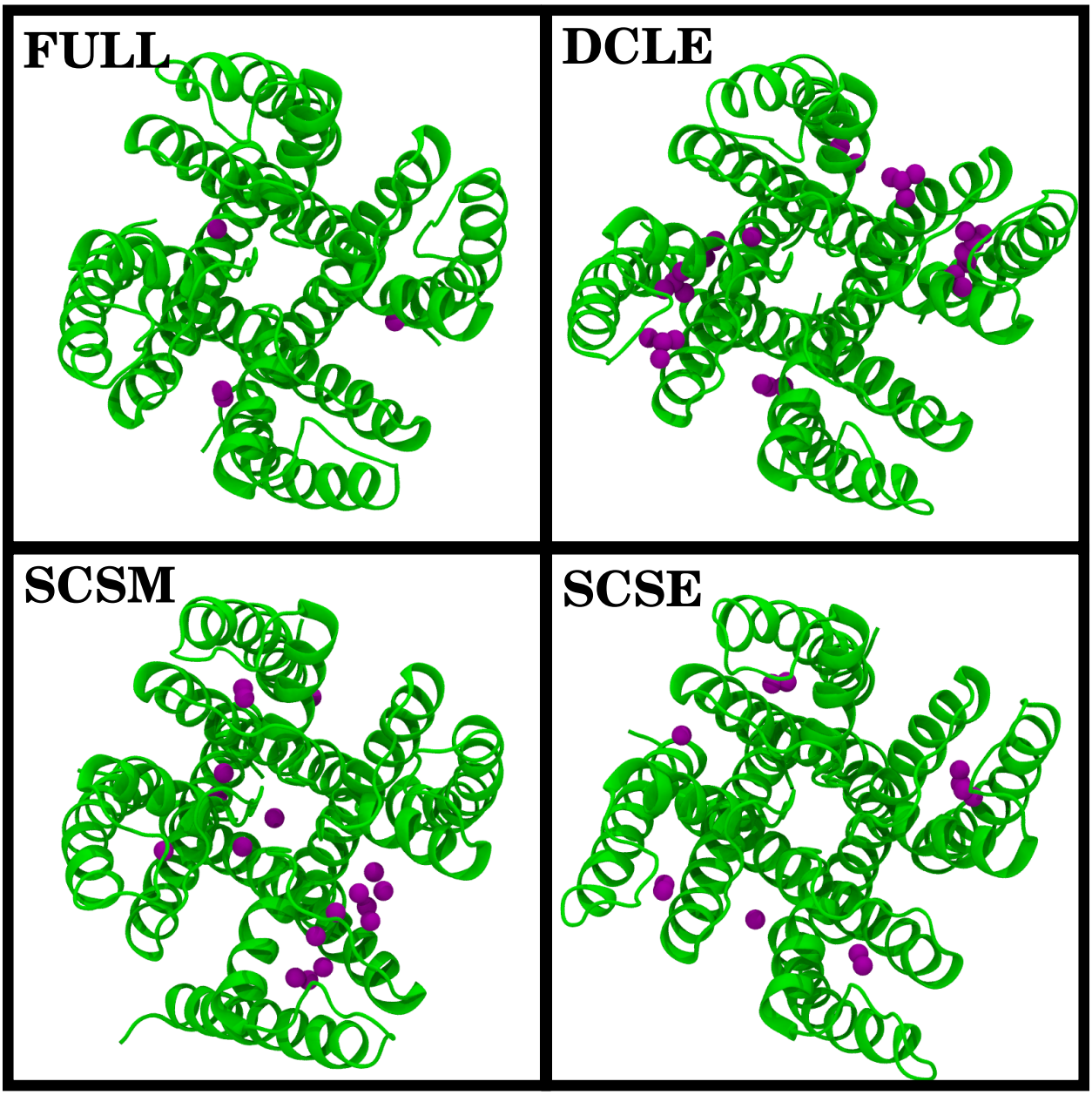

Figure S5: Final structures after 20 ns for each simulation, where membrane components where $\rho > 125$ (purple) are shown in addition to KcsA (green). There are only four false positives for the full membrane case, but substantial intercalation in the other cases.