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Supplementary Material



Figure S1. Radial distribution functions between the nitrogen atom from the amino moiety and the oxygen from the water molecules as a function of the distance. The solid blue curve represents the radial distribution for the deprotonated lysine analog (neutral) and the solid red curve for the protonated lysine analog (charged). The switching function used for the calculation of the second collective variable namely the coordination (or hydration) of the lysine analog is plotted as a dark dashed line. Inset: Number integral of the g(r). Same legend as for the radial distribution.



Figure S2. 1D Free energy profiles along the normal to the bilayer for the charged and deprotonated lysine analogs crossing the POPC lipid Bilayer (snapshot on the right side) and estimates of the pKa. Adapted from [17]. The grey area highlights the lipid/water interfacial region, and the arrow represents the 10.7 shift in pKa.



Convergence of the free energy surfaces

The convergence of the free energy profiles has been evaluate in agreement with ref [30] by determining the local error appropriate to compare the FES estimators. The latter is defined as:

$$\varepsilon_{local} = \Delta \phi = \frac{1}{N} \sum_{i} |\phi(i) - \phi^{last}(i)|$$

where $\phi(i)$ is the free energy estimated at a given bin in the CV space at time t and $\phi^{last}(i)$ the free energy at the end of the sampling time, the summation beeing limited to a specific well sampled region (indicated by the black and red squares in Figure xxx x)

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Figure S3. Right: Evolution of the local error on the Free energy surfaces as a function of the simulation time for the charged lysine. Left: Sampled areas defining the local region



Figure S4. Histogram corresponding to the sampling of the collective variable relative to the distance between the center of mass of the charged lysine with the center of mass of the membrane. Histograms are plotted with different ton of red for every 200 ns of sampling. Those samplings correspond to the last µs depicted on the RMSD on Fig. S3.



Figure S5. Histogram corresponding to the sampling of the collective variable relative to the distance between the center of mass of the neutral lysine with the center of mass of the membrane. Histograms are plotted with different ton of red for every 200 ns of sampling. Those samplings correspond to the last μ s depicted on the RMSD on Fig. S5.

Adiabatic temperature



Figure S6. Configurational temperature for each CV of the protonated lysine using equation (4).