

# Supplementary Material

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We have examined the convergence of the PMF's and reliability of the WHAM analysis using the umbrella sampling data from the first PMF's in Fig. 2 (top, solid and dashed lines) as an example (similar results are found for the other PMF's). To show how the PMF's converge with the accumulated data, we have constructed 5 PMF's using 0-100, 0-200, 0-300, 0-400, and 0-500 ps of data as shown in the figures below. It is seen that the PMF's rapidly converge to the final PMF as the 100 ps blocks of data are included. It is also clear from these plots that using 100 ps of data is not sufficient for convergence but 500 ps seems adequate (PMF's for the 400 and 500 ps blocks almost overlap).

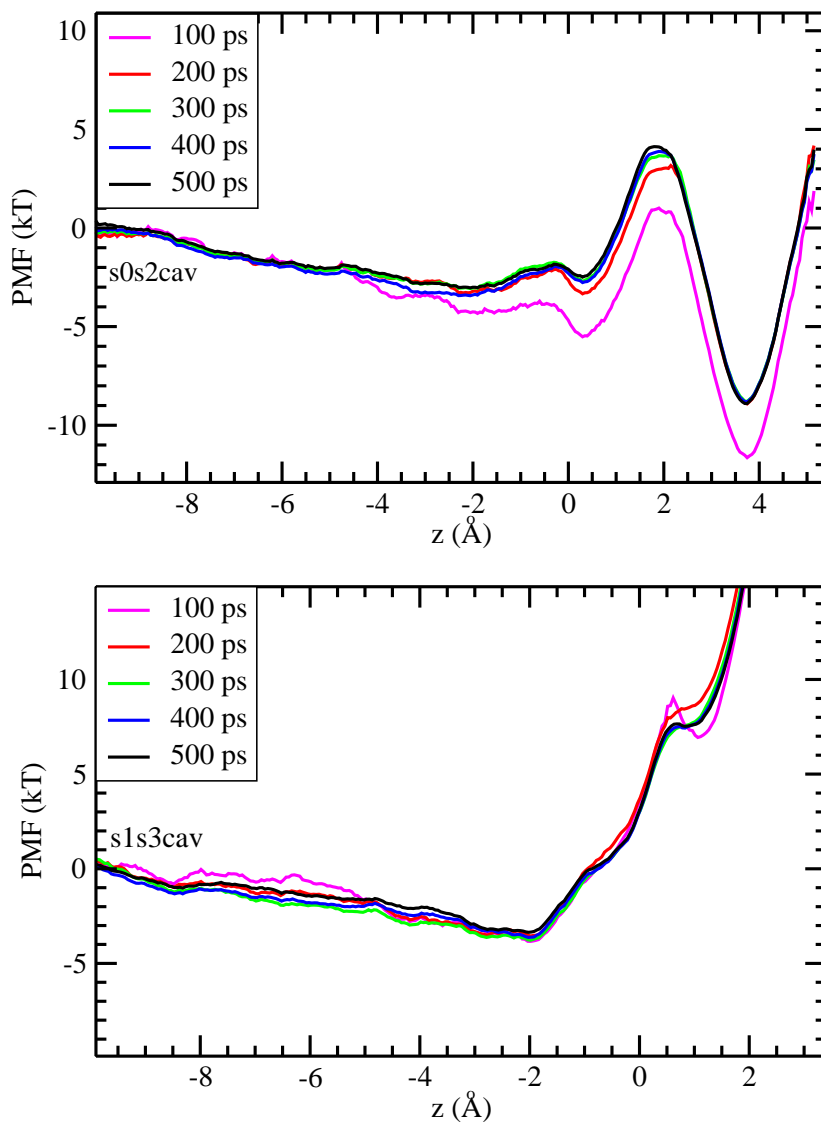


Figure 1: Convergence of the PMF's with the accumulated data.

To obtain a robust PMF from the WHAM analysis, it is essential that there is sufficient overlap of densities between the neighboring PMF windows. An overlap of  $> 5\%$  is usually sufficient to obtain a robust PMF. In the supplementary figure below, we show the densities for each umbrella window and the percentage overlap between the neighboring windows for the top PMF in the previous page. It is seen that there is more than adequate overlap among the neighboring windows.

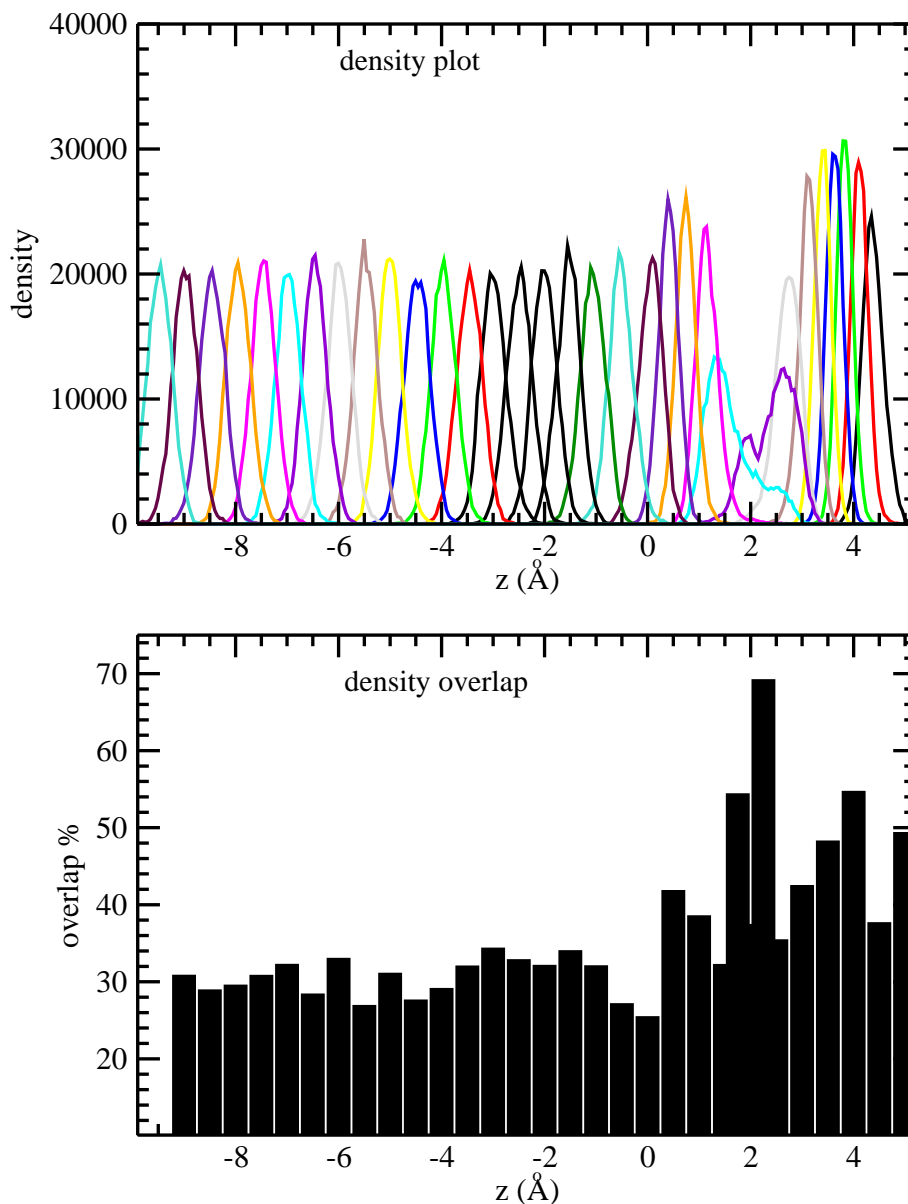


Figure 2: Density plots for the umbrella windows used in the construction of the PMF shown in the previous page and the percentage overlap between the neighboring windows.

The sharp rise in the S1-S3-cavity PMF (Fig. 2, top) as the  $K^+$  ion approaches the S4 site is attributed to the Coulomb repulsion between the ions, which is 186 kT at a distance of 3 Å. To demonstrate that this is not caused by discontinuities in the sampled positions of ion and water or trapping of a water molecule between the ions, we show the densities of the ions involved and the water molecule in between in the following figure. The cavity ion's position changes continuously as it passes near the water molecule. Note that the water molecule occupies the lower S4 site ( $z = 2.3$  Å), where the filter opens to the cavity and is wide enough to allow simultaneous occupation by the ion and water. The density plot for the cavity ion correlates well with the PMF in Fig. 2. The window positions are slightly shifted backwards between  $z = -1.5$  and  $0.5$  Å corresponding to the initial rise in the PMF. There is no shift at  $z = 1$  Å where there is a shoulder in the PMF. Thereafter the shift becomes increasingly larger due to the unscreened Coulomb repulsion between the ions leading to the sharp rise observed in the PMF.

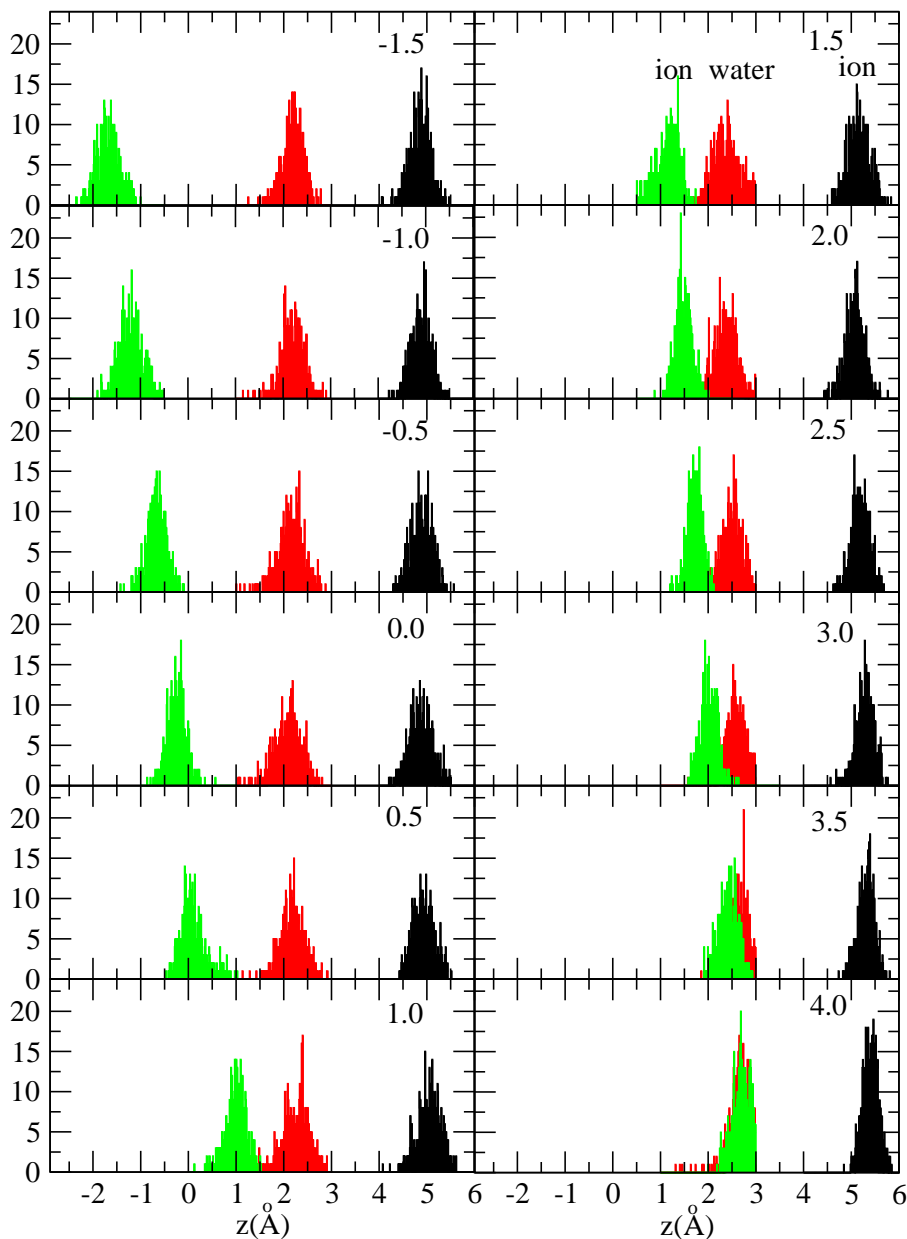


Figure 3: Distribution of the ion and water positions for the S1-S3-cavity PMF (Figure 2, top), as the cavity ion (green) is moved towards S4. The window positions (in Å) are indicated on the figures.

The PMF's in Figures 4 and 5 are constructed using the center of mass of the ions as the reaction coordinate. Because the ions are in a single file in the filter buffered with water molecules on either side, their relative distances are severely restricted. To demonstrate this point, we show in the figure below the distributions of the ion-ion distances ( $z_2-z_1$ ) for the two-ion PMF in Figure 4 for several windows along the reaction coordinate. As expected, they exhibit sharply peaked Gaussians with half widths of about 0.5 Å. Thus the ions move together as if they are connected with an effective spring with a constant  $k \sim 10$  kcal/mol/Å<sup>2</sup>. Note that as the ions move through the filter, the ion-ion distance changes, which is a direct result of the unequal distances between the binding sites.

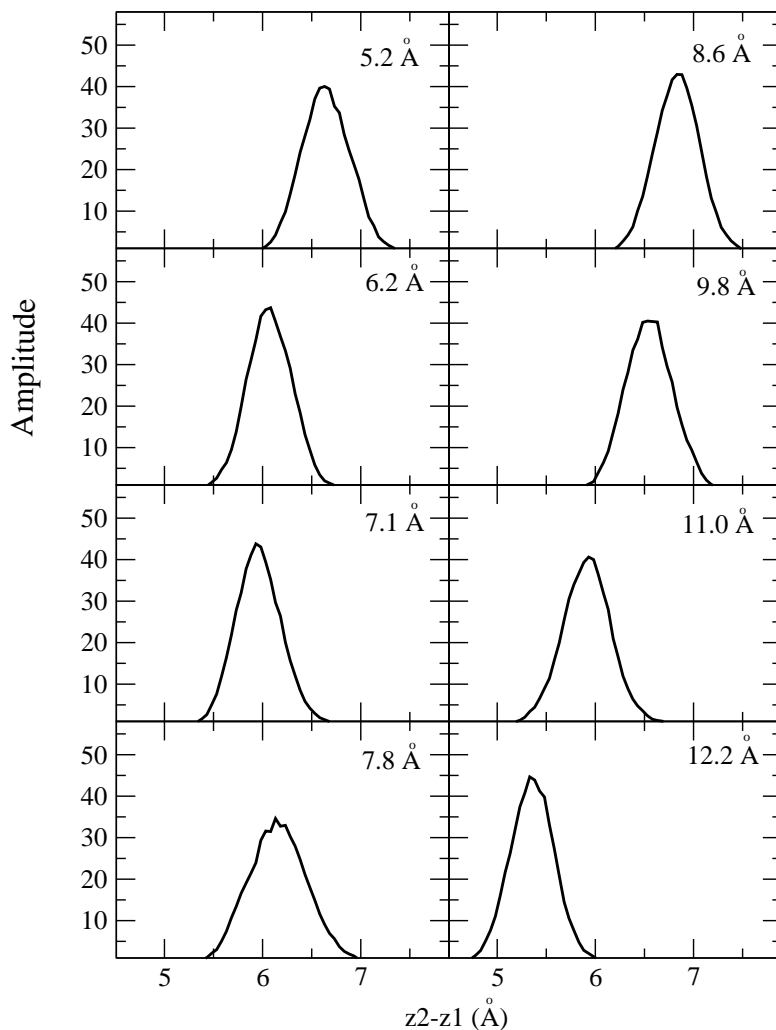


Figure 4: Distribution of the ion-ion distances ( $z_2-z_1$ ) for the two-ion PMF. Window positions are chosen at about 1 Å intervals (indicated on the figures)