Supporting Information – Mathematical steps to obtain Eq 7 and 8

The hydration free energy can be decomposed into an electrostatic and non-polar components

$$\Delta G = \Delta G_{ele} + \Delta G_{np}$$

It is well known that components of the free energy can be path or process dependent. We follow a well-defined, widely used process for our decomposition. In simulations as well as liquid state theories, the non-polar component can be computed by setting all the solute atomic partial charges to zero, keeping the solute Lennard-Jones potential and solving the integral equation numerically. Then ΔG_{ele} is computed by subtracting ΔG_{np} from ΔG. These hydration free energies here are calculated with the analytical chemical potential formula for the KH closure of 3D-RISM defined as

$$\Delta G = k_B T \sum_{\alpha=O,H} \int_V d\vec{r}^3 \left[\frac{\Delta \rho_\alpha(\vec{r})^2}{2\rho_\alpha} \theta(-\Delta \rho_\alpha(\vec{r})) - c_\alpha(\vec{r}) \left[\rho_\alpha + \frac{\Delta \rho_\alpha(\vec{r})}{2} \right] \right]$$

where k_B is the Boltzmann constant, T is the temperature in Kelvin, α is the solvent particle label, ρ_α is the bulk density of solvent particle α, $c_\alpha(\vec{r})$ is the direct correlation function, the $\Delta \rho_\alpha(\vec{r})$ is the excess solvent density compared to bulk and is defined as $\Delta \rho_\alpha(\vec{r}) = \rho_\alpha(\vec{r}) - \rho_\alpha$ with $\rho_\alpha(\vec{r})$ the density of solvent particle α, $\theta(-\Delta \rho_\alpha(\vec{r}))$ is a step function that is zero when the solvent density is below bulk density and V is the overall volume of integration.

Now, we define a new free energy functional for which the non-polar direct correlation function is scaled by a constant γ but only within the solvent exclusion volume

$$\Delta G^{\gamma} = \Delta G_{ele} + k_B T \sum_{\alpha} \int_V d\bar{r}^3 \left[\frac{\Delta \rho_{\alpha}^{np}(\bar{r})^2}{2\rho_{\alpha}} \theta(-\Delta \rho_{\alpha}^{np}(\bar{r})) - c_{\alpha}^{np}(\bar{r}) \left[\rho_{\alpha} + \frac{\Delta \rho_{\alpha}^{np}(\bar{r})}{2} \right] \right]$$

$$= \Delta G_{ele} + k_B T \sum_{\alpha} \int_{Vext} d\bar{r}^3 \left[\frac{\Delta \rho_{\alpha}^{np}(\bar{r})^2}{2\rho_{\alpha}} \theta(-\Delta \rho_{\alpha}^{np}(\bar{r})) - c_{\alpha}^{np}(\bar{r}) \left[\rho_{\alpha} + \frac{\Delta \rho_{\alpha}^{np}(\bar{r})}{2} \right] \right]$$

$$+ k_B T \sum_{\alpha} \int_{Vin} d\bar{r}^3 \left[\frac{\Delta \rho_{\alpha}^{np}(\bar{r})^2}{2\rho_{\alpha}} \theta(-\Delta \rho_{\alpha}^{np}(\bar{r})) - \gamma \cdot c_{\alpha}^{np}(\bar{r}) \left[\rho_{\alpha} + \frac{\Delta \rho_{\alpha}^{np}(\bar{r})}{2} \right] \right]$$

In this new integral, we have partitioned the integration domain into the solvent exclusion domain V_{in} and the external volume V_{ext}. We can now use the following identity $\gamma \cdot c_{\alpha}^{np}(\bar{r}) = c_{\alpha}^{np}(\bar{r}) - (1-\gamma) \cdot c_{\alpha}^{np}(\bar{r})$

to rewrite the above equation in order to simplify the equations

$$\Delta G^{\gamma} = \Delta G_{ele} + k_B T \sum_{\alpha} \int_{Vext} d\bar{r}^3 \left[\frac{\Delta \rho_{\alpha}^{np}(\bar{r})^2}{2\rho_{\alpha}} \theta(-\Delta \rho_{\alpha}^{np}(\bar{r})) - c_{\alpha}^{np}(\bar{r}) \left[\rho_{\alpha} + \frac{\Delta \rho_{\alpha}^{np}(\bar{r})}{2} \right] \right]$$

$$+ k_B T \sum_{\alpha} \int_{Vin} d\bar{r}^3 \left[\frac{\Delta \rho_{\alpha}^{np}(\bar{r})^2}{2\rho_{\alpha}} \theta(-\Delta \rho_{\alpha}^{np}(\bar{r})) - (c_{\alpha}^{np}(\bar{r}) - (1-\gamma) \cdot c_{\alpha}^{np}(\bar{r})) \cdot \left[\rho_{\alpha} + \frac{\Delta \rho_{\alpha}^{np}(\bar{r})}{2} \right] \right]$$

$$= \Delta G_{ele} + k_B T \sum_{\alpha} \int_{Vext} d\bar{r}^3 \left[\frac{\Delta \rho_{\alpha}^{np}(\bar{r})^2}{2\rho_{\alpha}} \theta(-\Delta \rho_{\alpha}^{np}(\bar{r})) - c_{\alpha}^{np}(\bar{r}) \left[\rho_{\alpha} + \frac{\Delta \rho_{\alpha}^{np}(\bar{r})}{2} \right] \right]$$

$$+ k_B T \sum_{\alpha} \int_{Vin} d\bar{r}^3 \left[\frac{\Delta \rho_{\alpha}^{np}(\bar{r})^2}{2\rho_{\alpha}} \theta(-\Delta \rho_{\alpha}^{np}(\bar{r})) - c_{\alpha}^{np}(\bar{r}) \left[\rho_{\alpha} + \frac{\Delta \rho_{\alpha}^{np}(\bar{r})}{2} \right] \right]$$

$$+ k_B T \sum_{\alpha} \int_{Vin} d\bar{r}^3 \left[(1-\gamma) \cdot c_{\alpha}^{np}(\bar{r})) \cdot \left[\rho_{\alpha} + \frac{\Delta \rho_{\alpha}^{np}(\bar{r})}{2} \right] \right]$$

$$= \Delta G_{ele} + \Delta G_{np} + k_B T (1-\gamma) \sum_{\alpha} \rho_{\alpha} \int_{Vin} d\bar{r}^3 \left[c_{\alpha}^{np}(\bar{r})) \cdot \left[1 + \frac{\Delta \rho_{\alpha}^{np}(\bar{r})}{2\rho_{\alpha}} \right] \right]$$

This is eq 7 of the main text. In the development above, we have reassembled the

V_{in} and V_{ext} components to recover the ΔG plus a correction term that depends on the

constant γ. Since the domain of V_{in} is by definition a region of negligible solvent density,

it is reasonable to set the non-polar solvent density to zero. This simplifies the rightmost

term of above equation to ½ given that density excess is minus the bulk density

$$\rho_\alpha^{np}(\vec{r}) = 0 \Rightarrow 1 + \frac{\Delta\rho_\alpha^{np}(\vec{r})}{2\rho_\alpha} = 1 + \frac{-\rho_\alpha}{2\rho_\alpha} = \frac{1}{2}$$

and we directly find that ΔG^γ is given by

$$\Delta G^\gamma = \Delta G_{ele} + \Delta G_{np} + \frac{k_B T}{2}(1-\gamma)\sum_\alpha \rho_\alpha \int_{Vin} d\vec{r}^{\,3} c_\alpha^{np}(\vec{r})$$

$$= \Delta G_{KH} + \frac{k_B T}{2}(1-\gamma)\sum_\alpha \rho_\alpha \int_{Vin} d\vec{r}^{\,3} c_\alpha^{np}(\vec{r})$$

Applying the idea that the water oxygen particle mostly define the exclusion volume since this is the largest atom at the center of the molecule, one finds equation 8 from the main text

$$\Delta G^c = \Delta G_{KH} + \frac{k_B T \rho_O}{2}(1-\gamma)\int_{Vin} d\vec{r}^{\,3} c_O^{np}(\vec{r})$$

We note that in this form, the correction has the functional form in the KH 3D-RISM free energy of a bridge function-like correction on the interior of the solute.