Supporting Information for: Multiple free energy calculations from single state point Continuous Fractional Component Monte Carlo simulation using umbrella sampling

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1 Umbrella Sampling

The partition function in the NPT ensemble, expanded with a fractional molecule[1–3] equals:

$$
\begin{aligned}
Q_{\mathrm{CFC}NPT} = & \beta P \left[\prod_{i=1}^{S} \frac{1}{\Lambda_i^{3N_i} N_i!}\right] \times \frac{1}{\Lambda^3} \int_0^1 \mathrm{d}\lambda' \int \mathrm{d}V V^{N+1} \exp\left[-\beta PV\right] \\
& \times \int \mathrm{d}s^N \exp[-\beta U(s^N, V)] \int \mathrm{d}s_{\mathrm{frac}} \exp[-\beta U_{\mathrm{frac}}(s_{\mathrm{frac}}, s^N, \lambda', V)]
\end{aligned}
\tag{S1}
$$

The probability of $\lambda' = \lambda$ is written as

$$
\begin{aligned}
\left\langle \delta\left(\lambda - \lambda'\right)\right\rangle_\beta = & \frac{\beta P}{Q_{\mathrm{CFC}NPT}} \prod_{i=1}^{S} \frac{1/\Lambda^3}{\Lambda_i^{3N_i} N_i!} \int \mathrm{d}V V^{N+1} \exp[-\beta PV] \\
& \times \int_0^1 \mathrm{d}\lambda' \int \mathrm{d}s^N \exp[-\beta U_{\mathrm{total}}\left(s^N, s_{\mathrm{frac}}, \lambda', V\right)] \delta\left(\lambda - \lambda'\right)
\end{aligned}
\tag{S2}
$$

where $U_{\mathrm{total}}\left(s^N, s_{\mathrm{frac}}, \lambda', V\right)$ is the total interaction potential between the molecules including the fractional molecule. Multiplying and dividing the integrand on the right hand side of Eq. S2 by a biasing factor proportional to the Boltzmann factor of total enthalpy of the system at $T^\star$, $\exp[-\beta^\star\left(U_{\mathrm{total}} + PV\right)]$, leads to

$$
\begin{aligned}
\left\langle \delta\left(\lambda - \lambda'\right)\right\rangle_\beta = & \frac{\beta P}{Q_{\mathrm{CFC}NPT}} \prod_{i=1}^{S} \frac{1/\Lambda^3}{\Lambda_i^{3N_i} N_i!} \int \mathrm{d}V V^{N+1} \exp[\Delta\beta PV] \\
& \times \int_0^1 \mathrm{d}\lambda' \exp[-\beta^\star PV] \int \mathrm{d}s^N \exp[\Delta\beta U_{\mathrm{total}}\left(s^N, s_{\mathrm{frac}}, \lambda', V\right)] \\
& \times \exp[-\beta U_{\mathrm{total}}\left(s^N, s_{\mathrm{frac}}, \lambda', V\right)] \delta\left(\lambda - \lambda'\right)
\end{aligned}
\tag{S3}
$$

where $\Delta\beta = \beta^\star - \beta$. Rearranging Eq. S3 leads to

$$
\begin{aligned}
\left\langle \delta\left(\lambda - \lambda'\right)\right\rangle_\beta = & \frac{\beta P}{Q_{\mathrm{CFC}NPT}} \prod_{i=1}^{S} \frac{1/\Lambda^3}{\Lambda_i^{3N_i} N_i!} \int \mathrm{d}V V^{N+1} \\
& \times \int_0^1 \mathrm{d}\lambda' \left(\delta\left(\lambda - \lambda'\right) \exp\left[\Delta\beta H_{\mathrm{total}}\left(s^N, s_{\mathrm{frac}}, \lambda', V\right)\right]\right) \\
& \times \exp[-\beta^\star PV] \int \mathrm{d}s^N \exp[-\beta^\star U_{\mathrm{total}}\left(s^N, s_{\mathrm{frac}}, \lambda', V\right)]
\end{aligned}
\tag{S4}
$$

which means that the distribution $p(\lambda)$ in the CFCNPT ensemble can be sampled by performing a simulation in the CFC$NPT^{\star}$ ensemble. Eq. S4 can be written as

$$p\left(\lambda\right)\big|_{\beta} = c \cdot \left\langle \delta(\lambda^{'} - \lambda) \exp\left[\left(\beta^{\star} - \beta\right) H\right] \right\rangle_{\beta^{\star}} \tag{S5}$$

where c is a normalization constant. In a similar manner, one can calculate other ensemble averages, such as the density, in the CFCNPT ensemble by performing a simulation in the CFC$NPT^{\star}$ ensemble. To compute the distribution $p(\lambda)$ at a different pressure, one can simply multiply and divide the right hand side of equation Eq. S2 by $\exp[-\beta P^{\star} V]$ leading to

$$\begin{aligned}\left\langle \delta\left(\lambda - \lambda'\right)\right\rangle_{P} = \frac{\beta P}{Q_{\mathrm{CFC}NPT}} \prod_{i=1}^{S} \frac{1/\Lambda^{3}}{\Lambda_{i}^{3N_i} N_i!} \int \mathrm{d}V V^{N+1} \exp[\beta V \Delta P] \\ \times \int_{0}^{1} \mathrm{d}\lambda' \exp[-\beta P^{\star} V] \int \mathrm{d}s^{N} \exp[-\beta U_{\mathrm{total}}\left(s^{N}, s_{\mathrm{frac}}, \lambda', V\right)] \delta\left(\lambda - \lambda'\right)\end{aligned} \tag{S6}$$

where $\Delta P = P^{\star} - P$. Rearranding Eq. S6 leads to

$$\begin{aligned}\left\langle \delta\left(\lambda - \lambda'\right)\right\rangle_{P} = \frac{\beta P}{Q_{\mathrm{CFC}NPT}} \prod_{i=1}^{S} \frac{1/\Lambda^{3}}{\Lambda_{i}^{3N_i} N_i!} \int \mathrm{d}V V^{N+1} \\ \times \int_{0}^{1} \mathrm{d}\lambda' \left(\delta\left(\lambda - \lambda'\right) \exp\left[\beta V \Delta P\right]\right) \exp[\beta P^{\star} V] \\ \times \int \mathrm{d}s^{N} \exp[-\beta U_{\mathrm{total}}\left(s^{N}, s_{\mathrm{frac}}, \lambda', V\right)]\end{aligned} \tag{S7}$$

which means that the distribution $p(\lambda)$ in the CFCNPT ensemble can be sampled by performing a simulation in the CFC$NP^{\star}T$ ensemble. Eq. S7 can be written as

$$p\left(\lambda\right)\big|_{P} = c \cdot \left\langle \delta(\lambda^{'} - \lambda) \exp\left[\beta V \left(P^{\star} - P\right)\right] \right\rangle_{P^{\star}} \tag{S8}$$

In a similar, manner, one can calculate other ensemble averages, such as the density, in the CFCNPT ensemble by running a simulation in the CFC$NP^{\star}T$ ensemble.

References

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