Supporting Information: Determining Free Energy Differences Through Variational Intermediates

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Table 1: Mean squared errors (MSE) as a function of total simulation time for the electrostatic decoupling of solvated butanol. All MSEs are given in units of $[(k_BT)^2]$. The linear intermediates are compared to three variants of VI. Firstly, with an exact initial estimate of the free energy difference, secondly, with an estimate that is 1 k_BT smaller than the exact reference value, and, thirdly, with an estimate of 0 k_BT, i.e., 8.708 k_BT smaller than the reference value. For the latter two variants see continuation in Table 2.

sim. time [ps]	linear	VI, C exact
20	$(6.46 \pm 0.04)\cdot10^{-1}$	$(3.89 \pm 0.04)\cdot10^{-1}$
40	$(3.50 \pm 0.03)\cdot10^{-1}$	$(2.22 \pm 0.04)\cdot10^{-1}$
100	$(1.49 \pm 0.02\cdot10^{-1}$	$(7.3 \pm 0.2)\cdot10^{-2}$
200	$(7.7 \pm 0.2)\cdot10^{-2}$	$(3.40 \pm 0.08)\cdot10^{-2}$
400	$(3.8 \pm 0.1)\cdot10^{-2}$	$(1.57 \pm 0.04)\cdot10^{-2}$
1000	$(1.5 \pm 0.1)\cdot10^{-2}$	$(6.6 \pm 0.3)\cdot10^{-3}$
2000	$(7.5 \pm 0.5)\cdot10^{-3}$	$(3.4 \pm 0.2)\cdot10^{-3}$
4000	$(3.7 \pm 0.3)\cdot10^{-3}$	$(1.8 \pm 0.2)\cdot10^{-3}$
10000	$(1.4 \pm 0.1)\cdot10^{-3}$	$(8 \pm 1)\cdot10^{-4}$

Table 2: Continuation of Table 1

sim. time [ps]	VI, $\Delta C = 1\mathrm{k_B T}$	VI, $C = 0$
20	$(4.2 \pm 0.1)\cdot 10^{-1}$	14.61 ± 0.06
40	$(2.6 \pm 0.1)\cdot 10^{-1}$	8.36 ± 0.06
100	$(8.2 \pm 0.4)\cdot 10^{-2}$	4.05 ± 0.05
200	$(4.1 \pm 0.2)\cdot 10^{-2}$	2.82 ± 0.05
400	$(2.0 \pm 0.1)\cdot 10^{-2}$	2.43 ± 0.06
1000	$(1.0 \pm 0.1)\cdot 10^{-2}$	2.50 ± 0.09
2000	$(5.9 \pm 0.9)\cdot 10^{-3}$	2.75 ± 0.14
4000	$(3.5 \pm 0.7)\cdot 10^{-3}$	2.82 ± 0.08
10000	$(1.9 \pm 0.6)\cdot 10^{-3}$	3.21 ± 0.21