Do All Pieces Make a Whole?

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The partitioning of the free energy into additive contributions originating from groups of atoms or force field terms has a potential to provide free energy based relationships between structure and biological activity of molecules and has been used as a background for many new methods of Bioinformatics like scoring functions, QSAR, or linear response approximations. Whether such decomposition is justified has been a subject of vigorous debate in the molecular modeling society with thermodynamic integration serving as a key theoretical tool. We will address this question in terms of the free energy perturbation (FEP) method, which represents the most robust methodology for calculations of the free energy differences.

The starting point is the standard Zwanzig expression for the calculation of the free energy difference by FEP:

$$\Delta G_{i\to i+1} = -\beta^{-1} \ln\left\langle \exp\left(-\beta \Delta E\right)\right\rangle_i , \qquad (1)$$

where $\Delta G_{i\to i+1}$ denotes the free energy difference between states i and i+1. $\Delta E = E_{i+1} - E_i$ represents corresponding potential energy difference. $\beta^{-1} = k_B T$, where k_B stands for the Boltzmann constant, and T is the thermodynamic temperature. Notation $\langle \cdots \rangle_i$ indicates averaging over the ensemble of configurations generated by a MD simulation on the potential energy surface of the state i. If we expand exponential function into a Taylor series we obtain:

$$\Delta G_{i\to i+1} = -\beta^{-1} \ln\left(1 - \beta \langle \Delta E \rangle_i + \frac{\beta^2}{2} \langle \Delta E^2 \rangle_i - \cdots \right) \qquad (2)$$

The series expansion of the logarithmic function gives us a double power series, which reordered in increasing powers of β forms:

$$\Delta G_{i\to i+1} = \sum_{n=1}^{\infty} \frac{\kappa_n}{n!} \left(-\beta\right)^{n-1} \qquad (3)$$

The coefficients κ_n are the so called *Thiele cumulants*. We will express these cumulants in the form of potential energy differences, which generally originate from different groups of atoms or force field terms. We will show that every dissecting into the corresponding free energy contributions possesses an inherent nonadditivity error arising from mixing potential energy terms in Thiele cumulants of second and higher orders. Fortunately, these cumulants increasingly loose importance as states i and i+1 become more alike. It is, therefore, in the limit of a small perturbation step possible to adequately represent the total free energy as a sum of all constituent free energy components.