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A Second Look at Canonical Sampling of Biomolecules Using Replica Exchange Simulation.

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Pages 1200−1202. Our recent Letter describing several factors which could limit the efficiency of the replica exchange (RE) approach, while mostly accurate to our knowledge, contains an important error of logic. When we correct our picture of the RE approach, our previous fairly negative assessment of RE must be amended to become more positive. We believe all our specific 'Observations,' except **Obs. V**, are correct, although the text following **Obs. III** and at the end of the table's caption are not correct.

Our Letter effectively equated sampling efficiency with 'speed' - - by which we meant the rate at which a simulation diffuses through configuration space. While our assessment of speed as such appears to have been correct, it does not properly reflect the true goal of canonical sampling: to sample all energy basins with the appropriate frequencies (probabilities). In RE, every level can sample new basins, which in turn can be 'transmitted' to the canonical ensemble desired for temperature T_0. Therefore, one can expect an overall *improvement* in canonical efficiency by a factor of

$$f < f_{\max} \sim (M+1)^{-1} \sum_{i=0}^{M} k_a(T_i)/k_a(T_0) \qquad (1)$$

where $k_a(T)$ is the Arrhenius rate for temperature T as defined in our recent Letter. This new relation accounts for the basin-hopping rates of all levels. Of course, inefficiencies in transmitting new basins to the T_0 ensemble will cause $f < f_{\max}$.

What is the overall outlook for biomolecular systems? The (fully correct) table entries from our Letter suggest $1 < f_{\max} < 10$ for barriers $\lesssim 6k_BT$ and maximum temperatures $T_M < 500$ K. By this analysis, assuming modest barriers and maximum temperatures for biomolecular systems, RE is clearly much more promising than suggested in our original Letter. Whether it is sufficient for canonical sampling of large biomolecular systems remains an open question, however. Additional discussion of this issue can be found at our Web site, http://www.ccbb.pitt.edu/Zuckerman/.

We would especially like to thank Paul Maragakis who brought eq 1 to our attention.

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