The well-tempered ensemble

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In order to alleviate the sampling problem in complex systems characterized by metastable states separated by large barriers we introduce the well-tempered ensemble defined by the partition function $Z_\gamma = \int dU\ [e^{-\beta U} N(U)]^{1/\gamma}$ where U is the potential energy and $N(U)$ the density of states. As γ is varied, Z_γ spans the range from the canonical ($\gamma = 1$) to the multicanonical ($\gamma = \infty$) ensemble. We show that, to a first approximation, at intermediate values of γ the average energy is close to its canonical value while its fluctuations are strongly enhanced. These properties can be used to enhance sampling especially in combination with parallel tempering. We show that Z_γ is the ensemble sampled in a well-tempered metadynamics run [A. Barducci, G. Bussi, and M. Parrinello, Phys. Rev. Lett. **100,** 020603 (2008)] that uses the energy as a collective variable. Canonical ensemble averages are then recovered by applying a recently developed reweighing scheme [M. Bonomi, A. Barducci, and M. Parrinello, J. Comput. Chem. **30**, 1615 (2009)]. In a series of applications as varied as the Ising model, a Go-like model for HIV protease and the freezing of a Lennard Jones liquid we demonstrate orders of magnitude gain in sampling efficiency.