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Free energy versus potential energy landscapes of drug-like molecules[1] YONAS ABRAHAM, Wake Forest University, REBECCA HARRIS, PHILIP S. HAMMOND, JEFFREY D. SCHMITT, Targacept Inc — To gain information about molecular shape tendencies, the life science community has traditionally focused primarily on conformational search methodologies that explore the Potential Energy Surface (PES). The output of these methods is a collation of so-called minimum energy conformers. In our effort to gain more insight into molecular shape and overall behavior, we have used both PES conformational search techniques and *ab initio* molecular dynamics to study a set of neuronal nicotinic receptor (NNR) ligands that possess a non-trivial structure-affinity relationship. This latter method, properly executed, provides the free energy landscape. In this poster we show the sometimes dramatic difference in predicted behavior between these two methods. Significantly, conformers predicted to be highly populated in one method are disallowed in the other method. This work constitutes our first exploration into the use of an *ab initio* derived free energy landscape to better understand small molecules of biological interest.

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