[P33] Diverse applications of free energy calculations in drug discovery

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Successful applications of free energy calculations in drug discovery projects are beginning to emerge, as a result of progress in science (improvements to force fields), technology (sufficient conformational sampling via GPUs), and ease-of-use (interfaces and workflows that make FEP accessible to a broader population). Here, we describe the free energy perturbation approach as implemented in FEP+ and highlight the accuracy through extensive retrospective and prospective applications. We show a wide range of application areas, such as protein-ligand binding, protein-protein binding, antibody optimization, protein stability, fragment-based design, selectivity, drug resistance, and small molecule solubility. We demonstrate that the use FEP+ can lead to a measurable and significant acceleration of drug discovery projects in prospective applications. Finally, we demonstrate that FEP+ can be applied to homology models, which has significant implications regarding the domain of applicability of free energy methods.