MM-PBSA as a potential tool for Structure-Based Drug Design

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MM-PBSA is one of many tools available to enable computational chemists to investigate the interaction of small organic molecules with their biological targets at the molecular level. There are hundreds of references citing the use of MM-PBSA using various protocols. Despite this large amount of available data, it is unclear when any of these protocols will be useful for Structure-Based Drug Design (SBDD). Our group has tested MM-PBSA calculations on several internal and external drug targets of interest with varying degrees of complexity. With these protein systems and their crystallographic ligands we examine the effects of water solvation models, the degree of sampling of the protein and ligand, and the potential added benefit of including entropy and conformational strain. With this work, we hope to gain a better understanding of the strengths and limitations of MM-PBSA and when it would most likely aid drug design.