A Novel Physics-based Ensemble Modeling Approach that Utilizes Crystal Packing to Predict Aqueous Thermodynamic Solubility

Rajni Miglani Bhardwaj*, Richard S. Hong, Nathan Abraham, Alessandra Mattei and Ahmad Y. Sheikh

Process Research & Development, AbbVie Inc., 1 N Waukegan Road, North Chicago, IL 60064, United States

rajni.bhardwaj@abbvie.com

Pharmaceutical industries have witnessed an increasing trend towards poor aqueous solubility and according to a report 75% of the marketed drugs belong to BCS class II or IV. Efforts to improve aqueous solubility by modifying the chemical structures are carried out during lead optimization in early drug discovery stage while trying to maintain desired potency and ADME properties. However, experimental aqueous solubility assays available during lead optimization are prone to overestimate solubility to a variable extent. This overprediction of aqueous solubility can result in overly optimistic view of developability with negative implications for compounds differentiation and candidate selection for development. On the other hand, failure to improve aqueous solubility could lead to inadequate evaluation of safety and efficacy profile of candidates and resource intensive formulation approaches. With the advancement of computations as well as due to immense pressure to shorten development timelines, in-silico approaches to predict aqueous thermodynamic solubility are of greater importance. In this presentation a physics-based ensemble modeling approach consisting of high-fidelity cloud-based crystal structure prediction (CSP) methodology optimized for computational cost and a novel free energy perturbation (FEP+) workflow is discussed to predict aqueous thermodynamic crystalline solubility of chemically structurally related compounds during lead optimization stage using just the 2-D structure as an input.

Keywords: crystal structure prediction, property prediction, aqueous thermodynamic solubility, pharmaceuticals, free energy perturbation