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Molecular Theory of Solvation Based Miltiscale Modeling of Biomolecular Systems and Functions

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The three-dimensional reference interaction site model with the Kovalenko-Hirata closure (3D-RISM-KH molecular theory of solvation) is Ornstein-Zernike type integral equation theory of liquids. Based on first principles of statistical mechanics, the 3D-RISM-KH theory consistently accounts for effect of chemical specificities of solvent, co-solvent, ions, and ligands on biomolecules solvation structure and thermodynamics, including steric forces, hydrophobicity, hydrogen bonding, and other effective interactions. It enables predictive modeling of complex chemical and biomolecular systems problematic or not feasible for molecular simulation or continuum solvation treatment:

• 3D-RISM-KH structural water detection and placement has been implemented in the Amber Tools and Molecular Operating Environment (MOE) packages. Structural water is critical in reproducing ligand binding modes and protein aggregation; case studies include the Maltose-Binding Protein, and HET-s prion and Aβ oligomer and fibril formation.

• 3D-RISM-KH supplemented with the partial molar volume correction (aka "Universal Correction") provides excellent agreement with experimental data on a large set of small compounds for solvation free energies in octanol and water, and so accurately predicts octanol-water partition coefficients.

• Treating flexible ligands decomposed into fragments as solution species, the 3D maps of potentials of mean force obtained from 3D-RISM-KH define scoring functions interfaced with the AutoDock package for automated ranking of docked conformations. The predicted location and residency times of the modes of binding of a flexible thiamine molecule to the prion protein at near-physiological conditions are in excellent agreement with experiment.

• 3D-RISM-KH reveals chemistry-driven nanoscale forces that control the resilient structure of plant cell walls formed by cellulose microfibrils in a matrix of hemicellulose and lignin, crucial for enzymatic and chemical deconstruction of biomass. It predicts effective interactions of cellulose nanocrystals (CNC) with pristine and functionalized surface in water, electrolyte solutions, organic solvents, and ionic liquids, so as to help design modified CNC with improved dispersion and preserved mechanical properties that can be effectively incorporated into nanocomposite materials.

• Multi-time-step MD of biomolecules steered with mean solvation forces obtained from 3D-RISM-KH at outer time steps and treated with generalized solvation force extrapolation (GSFE) at inner timesteps is efficiently stabilized with the optimized isokinetic Nosé-Hoover chain (OIN) thermostat and accurately reproduces conformational properties, as validated on hydrated alanine dipeptide, miniprotein 1L2Y, and protein G. This quasidynamics results in time scale compression of protein conformational changes coupled with solvent with respect to real time dynamics and provides up to 1000-fold effective speedup, compared to conventional MD with explicit solvent. This enables folding the miniprotein from a fully denatured state in 60 ns quasidynamics, cf. 4-9 μs physical folding time.

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