In Silico Screening of Bioactive Solutes using Molecular Integral Equation Theory

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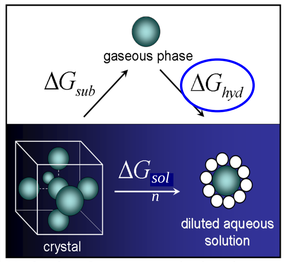
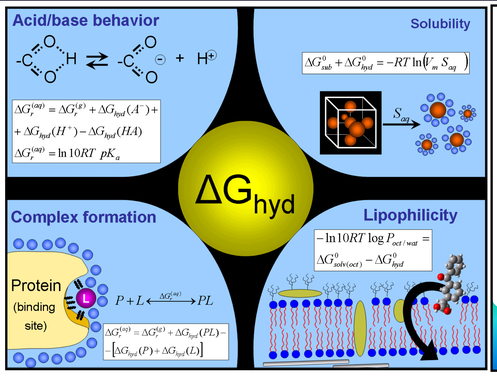
Field of interest:

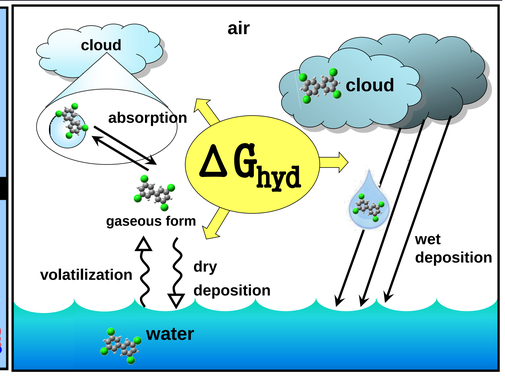


Hydration free energy is the change of the Gibbs free energy that accompanies the transfer of solute from gaseous phase to aqueous solution (under standardized conditions)

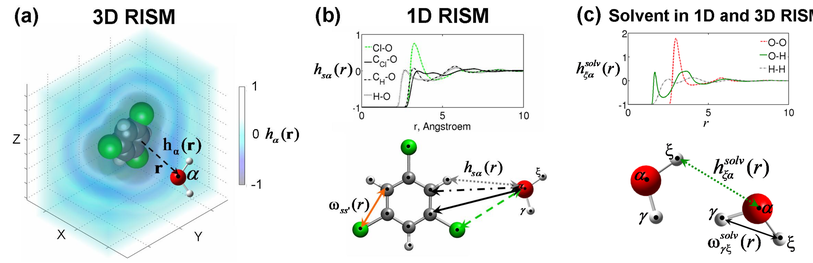
•***Fast and accurate*** prediction of the physicochemical properties of bioactive molecules is required in the ***agrochemical*** and ***pharmaceutical*** industries, but remains a significant challenge [1,2].

•We have developed two new free energy functionals (***3D RISM/UC, 3D RISM/SDC***) that allow the hydration free energies of bioactive molecules to be calculated accurately using Molecular Integral Equation Theory. Using ***3D RISM/UC,*** we demonstrate a first-principles approach to calculate the intrinsic aqueous solubility of crystalline druglike molecules.





1D and 3D Reference Interaction Site Model (RISM):

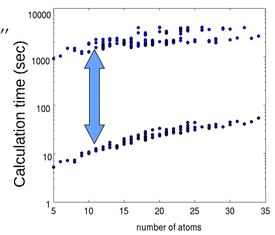


1D RISM equations: [2]

$$h_{s\alpha}(r) = \sum_{s'=1}^{N_{solute}} \sum_{\xi=1}^{N_{solvent}} \int_{R^3}\int_{R^3} \omega_{ss'}(|\mathbf{r}_1 - \mathbf{r}'|) c_{s'\xi}(|\mathbf{r}' - \mathbf{r}''|) \chi_{\xi\alpha}(|\mathbf{r}'' - \mathbf{r}_2|) d\mathbf{r}' d\mathbf{r}''$$

$$h_{s\alpha}(r) = \exp(-\beta u_{s\alpha}(r) + h_{s\alpha}(r) - c_{s\alpha}(r) + B_{s\alpha}(r)) - 1$$

1D RISM is ~ 100 time faster

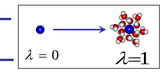


3D RISM equations: [2]

$$h_{\alpha}(\mathbf{r}) = \sum_{\xi=1}^{N_{solvent}} \int_{R^3} c_{\xi}(\mathbf{r} - \mathbf{r}') \chi_{\xi\alpha}(|\mathbf{r}'|) d\mathbf{r}',$$

$$h_{\alpha}(\mathbf{r}) = \exp(-\beta u_{\alpha}(\mathbf{r}) + h_{\alpha}(\mathbf{r}) - c_{\alpha}(\mathbf{r}) + B_{\alpha}(\mathbf{r})) - 1$$

Hydration free energy: end-point calculations [8]



3D-RISM-KH-GF: $$\Delta G_{hyd}^{GF} = k_B T \sum_{\alpha=1}^{N_{solvent}} \rho_{\alpha} \int_{R^3} \left[-c_{\alpha}(\mathbf{r}) - \frac{1}{2} c_{\alpha}(\mathbf{r}) h_{\alpha}(\mathbf{r}) \right] d\mathbf{r}$$

An alternative to thermodynamic integration.

Partial Molar Volume: [8]

$$V = k_B T \eta (1 - \rho_{\alpha} \sum_{\alpha=1}^{N_{solvent}} \int_{R^3} c_{\alpha}(\mathbf{r})\, d\mathbf{r})$$

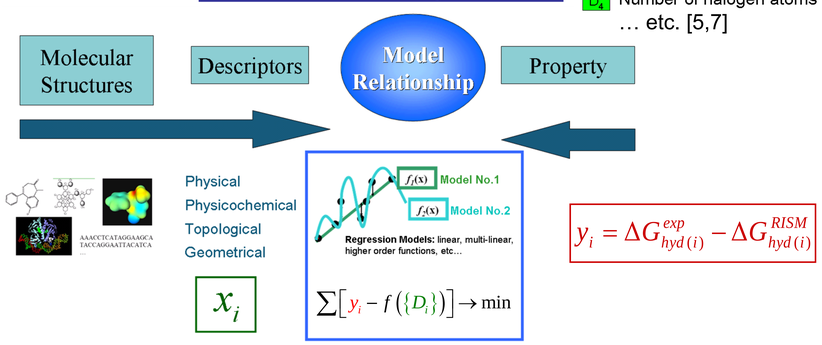
Computational Details:
- *Amber11 and AmberTools1.5* [5]
- *AM1 / BCC atomic partial charges*
- *Amber GAFF L-J parameters*
- *Kovalenko-Hirata (KH) Closure*

Structural Descriptors Correction (SDC) model:

RISM-data **Cheminformatics**

$$\Delta G_{hyd}^{SDC} = \Delta G_{hyd}^{RISM} + \sum_i a_i D_i + a_0$$

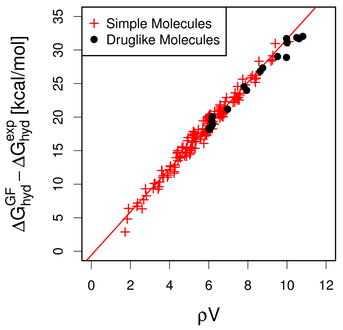
D_1 Partial molar volume
D_2 Number of branches
D_3 Number of benzene rings
D_4 Number of halogen atoms
… etc. [5,7]



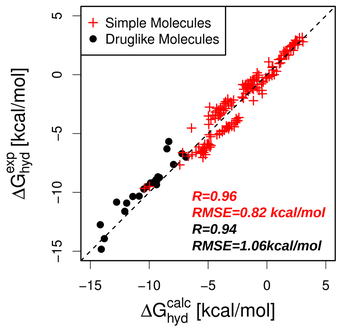
Results:

3D RISM/UC

Hydration Free Energy Calculation



The error in hydration free energy calculated using the 3D-RISM-KH-GF theory is strongly correlated with 3D-RISM calculated partial molar volume (*V*) [3,4]



•Two coefficients in the 3D-RISM/UC model are transferable between different chemical classes [3,4]

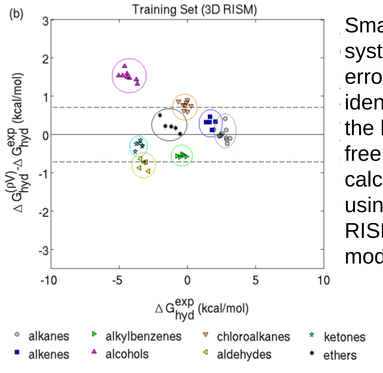
•***Training Set: 163 simple organic molecules***

•***Test Set: 21 druglike molecules***

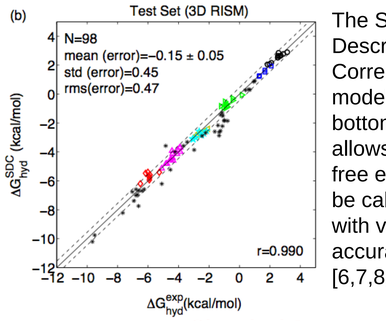
3D-RISM/UC: $$\Delta G_{hyd}^{3DRISM/UC} = \Delta G_{hyd}^{3DRISM/GF} + 3.2217 \rho V + 0.5783$$

3D RISM/SDC

Hydration Free Energy Calculation



Small systematic errors can be identified in the hydration free energies calculated using the 3D-RISM/UC model.[6]



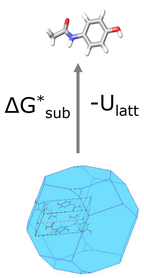
The Structural Descriptor Correction model (SDC, see bottom right) allows hydration free energies to be calculated with very high accuracy. [6,7,8,9]

Chemical Accuracy!

There is a shortage of accurate experimental thermodynamic data for druglike molecules

Calculation of the Aqueous Solubility of the Neutral Form of Crystalline Druglike Molecules

Sublimation Free Energy (ΔG_{sub})



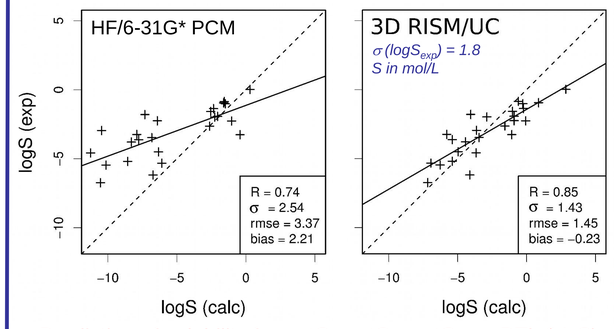
$\Delta G_{sub} = \Delta H_{sub} - T\Delta S_{sub}$

$\Delta H_{sub} \approx -U_{latt} - 2RT$

$\Delta S_{sub} = S_{trans,gas} + S_{rot,gas} - S_{ext\ vib,crystal}$

- Lattice energy (U_{latt}) calculated in DMACRYS: [10,11]
  - *Electrostatic contribution:*
    - *Distributed Multipoles (MP2/6-31G**)*
  - *Repulsion-Dispersion contribution:*
    - *Buckingham potential (FIT parameters)*
- Intermolecular vibrational entropy of crystal ($S_{ext,crystal}$) calculated from phonon modes
- Translational and rotational entropy of gas ($S_{trans,gas}$, $S_{rot,gas}$) estimated assuming an ideal gas.
- Minimised x-ray crystal structures (rigid monomer)

Intrinsic Aqueous Solubility (S)



Prediction of solubility from $\Delta G_{sol}=\Delta G_{sub}+\Delta G_{hyd}=-RT\ln(V_m S)$ without direct parameterization against solubility data (i.e. not QSPR!) [12]

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