HelmholtzZentrum münchen
German Research Center for Environmental Health
Institute of Structural Biology

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Introduction to the Reference Interaction Site Model (RISM)

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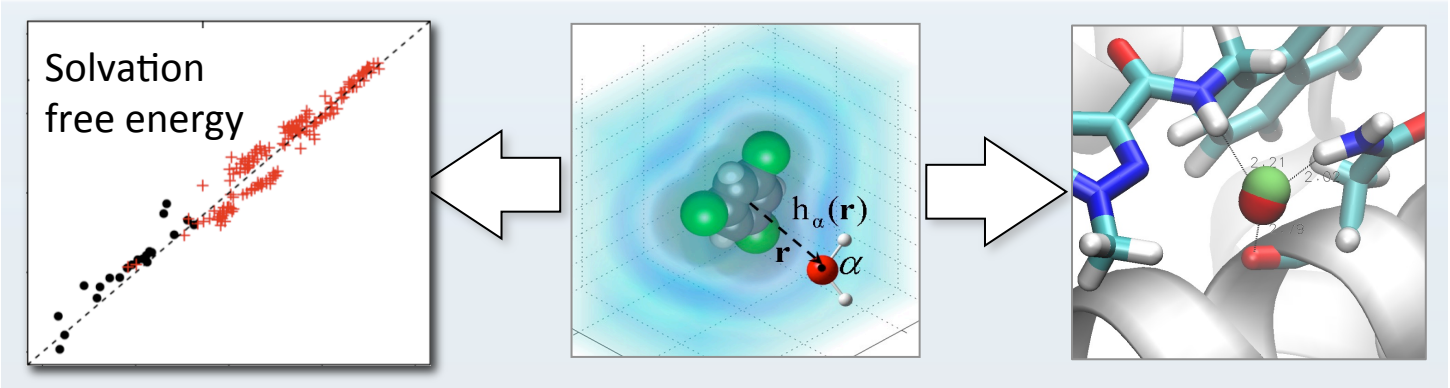


"BigChem" seminar / 22.03.2017

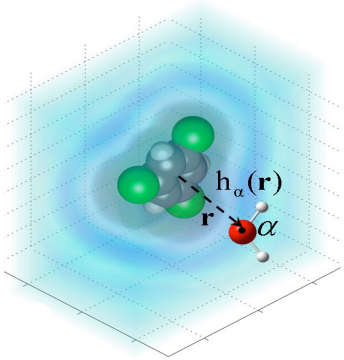
Outline

1. Integral Equations Theory (IET) of Molecular Liquids

a. Ornstein-Zernike (OZ) equation

b. Molecular OZ equation

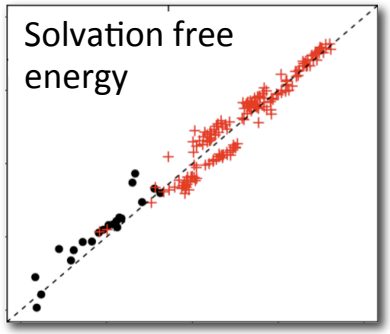
c. Reference Interaction Site Model (RISM)



2. Solvation thermodynamics from RISM approximations

a. Solvation Free Energy

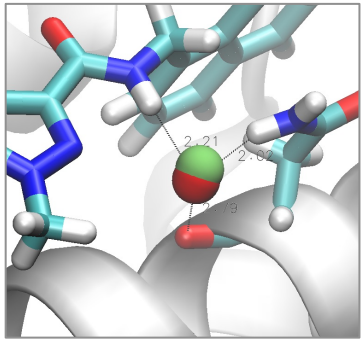
b. Partial Molar Volume



3. Systems structure predictions

a. Principal Hydration Sites

b. Fragments placement



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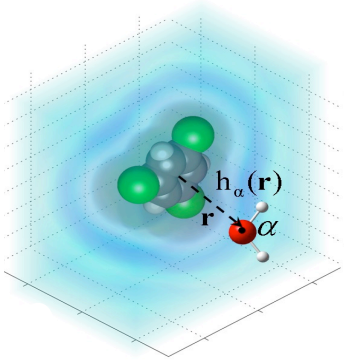

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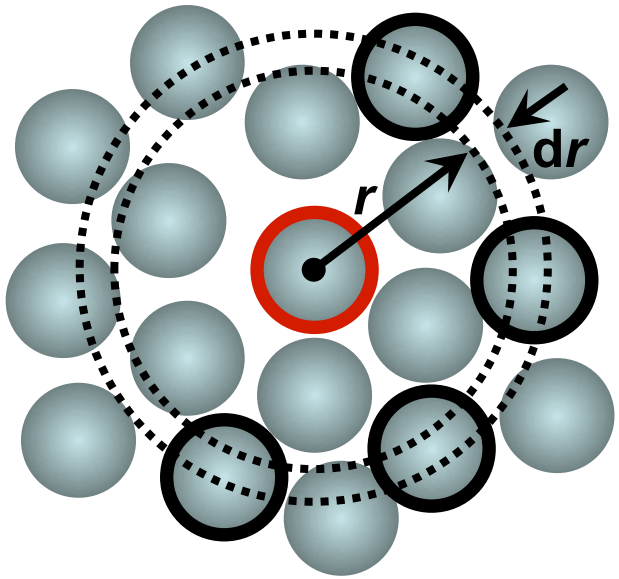
Radial Distribution Function (RDF)



$$g(r) = \left\langle \frac{\rho_{segment}(r)}{\rho_{bulk}} \right\rangle$$

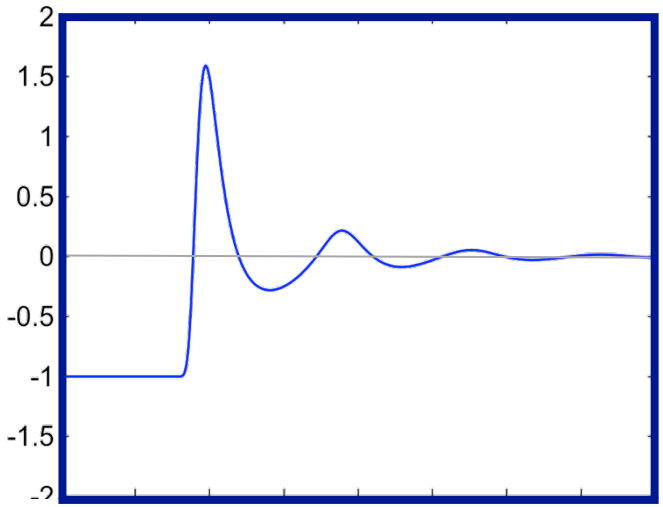
segment number density

bulk number density

$$\boxed{\mathrm{h}(r)} = \mathrm{g}(r)\text{-}1$$

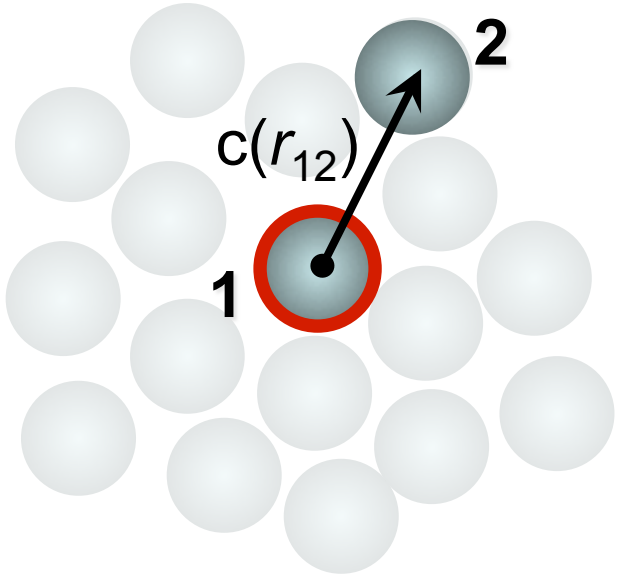
total

correlation function



Frisch, H. & Lebowitz J.L. The Equilibrium Theory of Classical Fluids (New York: Benjamin, 1964)

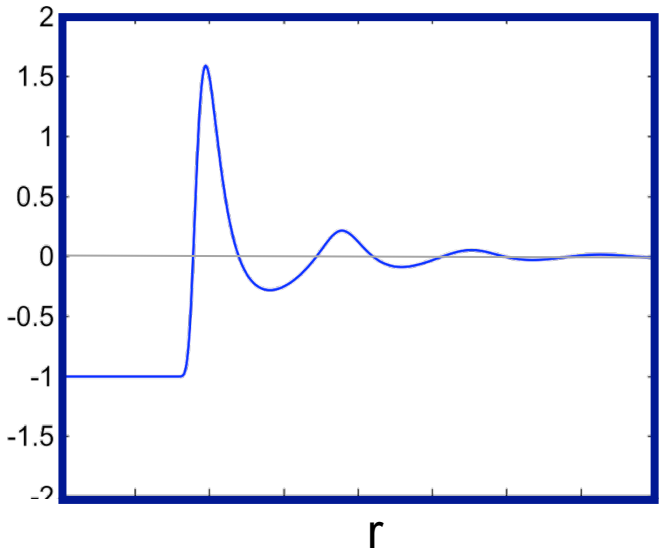
Direct correlation function

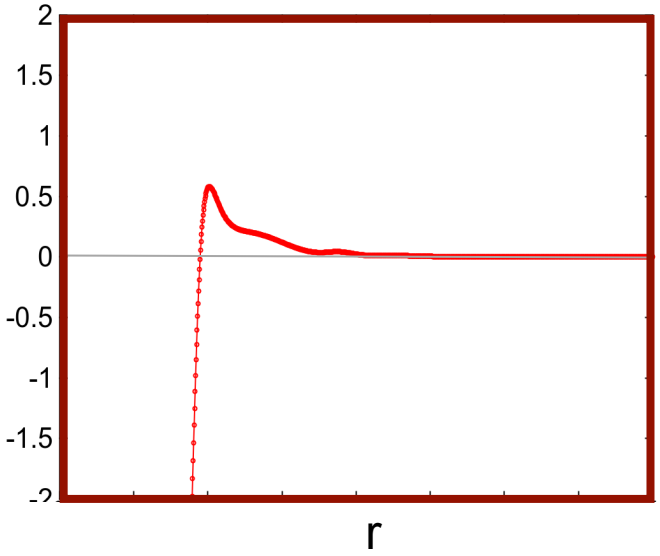


$$h(r_{12}) = c(r_{12}) + \gamma(r_{12})$$

total ***direct*** ***indirect***

correlation function

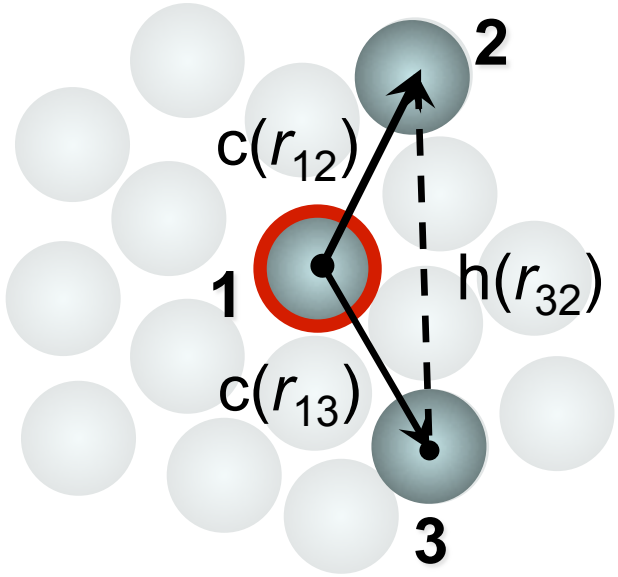




It is not physically intuitive but it has a simple structure

Ornstein, L. S. and Zernike, F. *Proc. Acad. Sci*. Amsterdam **1914**, 17, 793-806

Indirect correlation function



$$h(r_{12}) = c(r_{12}) + \gamma(r_{12})$$

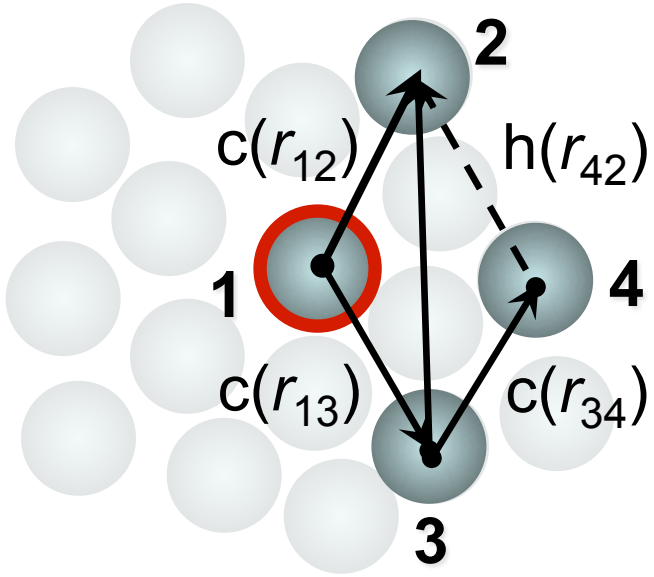
indirect
correlation function

The indirect influence can be described with ***direct*** influence of particle **1** on **any** particle **3**, which, in turn, influences ***indirectly*** particle **2**

$$h(r_{12}) = c(r_{12}) + \rho \int c(r_{13}) h(r_{32}) dr_3$$

Ornstein, L. S. and Zernike, F. *Proc. Acad. Sci*. Amsterdam **1914**, 17, 793-806

Ornstein-Zernike (OZ) equation



Ornstein-Zernike equation

for homogeneous fluid
of spherical particles

$$h(r_{12}) = c(r_{12}) + \rho \int c(r_{13}) h(r_{32}) dr_3$$

$$h(r_{12}) = c(r_{12}) + \rho \int c(r_{13}) c(r_{32}) dr_3 + \rho^2 \int\int c(r_{13}) c(r_{34}) c(r_{42}) dr_3 dr_4 + \ldots$$

Ornstein, L. S. and Zernike, F. *Proc. Acad. Sci*. Amsterdam **1914**, 17, 793-806

Closure relation

$$h(r_{12}) = c(r_{12}) + \rho \int c(r_{13}) h(r_{32}) dr_3$$

two unknown functions

Closure relation

$$\begin{cases} h(r_{12}) = c(r_{12}) + \rho \int c(r_{13}) h(r_{32}) dr_3 \\ h(r_{12}) - 1 = e^{-\beta U(r_{12}) + h(r_{12}) - c(r_{12}) + B(r_{12})} \end{cases}$$

bridge functional

Hyper-Netted Chain Closure (HNC)

$$B(r) = 0$$

$$h(r)-1 = \exp[\Xi(r)]$$

Problem with convergence!

$$\Xi(r) = -\beta U(r) + h(r) - c(r)$$

Partial linearization of HNC closure:

$$h(r)-1 = \begin{cases} \exp[\Xi(r)] & \text{when } \Xi(r) \le 0 \\ \sum_{i=0}^{n} \Xi^i(r)/i! & \text{when } \Xi(r) > 0 \end{cases}$$

(KH closure: i=1)

J.P. Hansen, I.R. McDonald, *Theory of Simple Liquids* 4th ed., Elsevier Academic Press, Amsterdam, The Netherlands, **2000**

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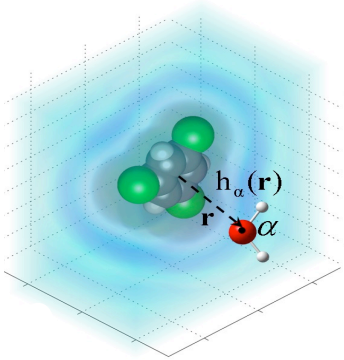

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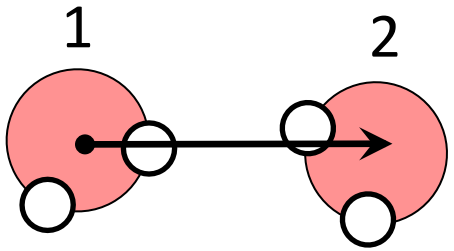
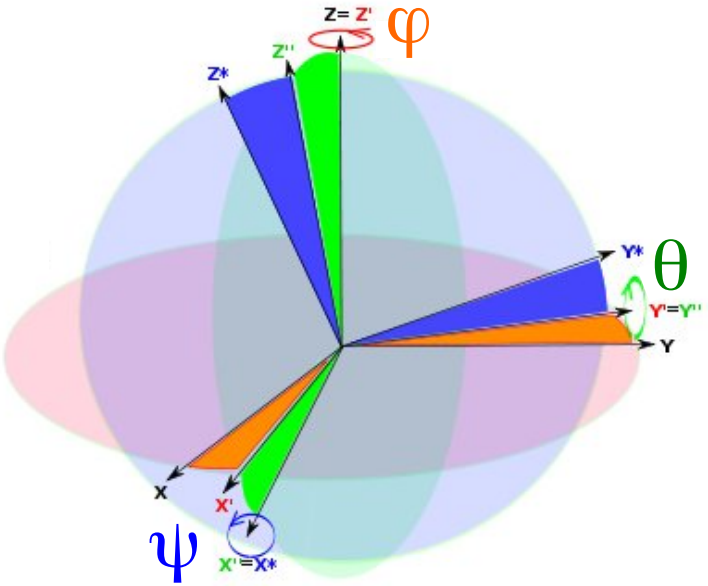
MOZ equation



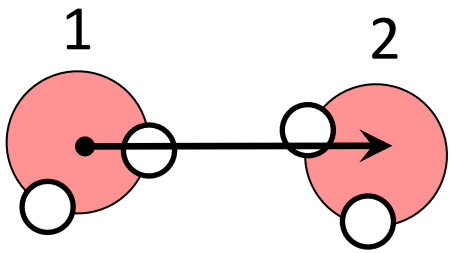
$$h(\Gamma_{12}) = c(\Gamma_{12}) + \frac{\rho}{8\pi^2} \int_R \int_\Omega c(\Gamma_{13}) h(\Gamma_{32}) d\mathbf{r}_3 d\boldsymbol{\Theta}_3$$

$$\left.\begin{aligned} r_{12} &= \mathbf{r}_1 - \mathbf{r}_2 \\ \boldsymbol{\Theta}_1 &= (\psi_1, \theta_1, \varphi_1) \\ \boldsymbol{\Theta}_2 &= (\psi_2, \theta_2, \varphi_2) \end{aligned}\right\} \Gamma_{12}$$



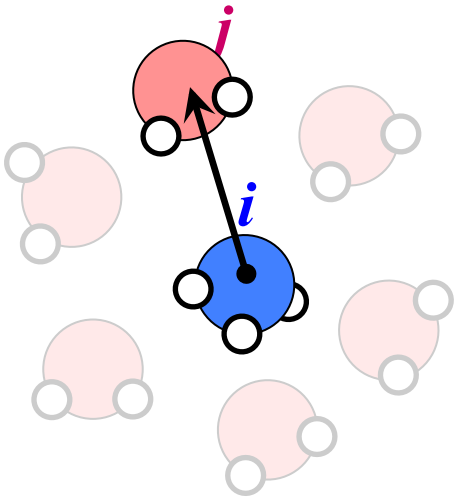
Ornstein, L. S. and Zernike, F. *Proc. Acad. Sci*. Amsterdam **1914**, 17, 793-806

MOZ equations



homogeneous fluid:

$$h(\Gamma_{12}) = c(\Gamma_{12}) + \frac{\rho}{8\pi^2} \int_R \int_\Omega c(\Gamma_{13}) h(\Gamma_{32}) d\mathbf{r}_3 d\Theta_3$$



heterogeneous fluid:

$$h(\Gamma_{ij}) = c(\Gamma_{ij}) + \sum_{m=1}^{M} \frac{\rho_m}{8\pi^2} \int_R \int_\Omega c(\Gamma_{im}) h(\Gamma_{mj}) d\mathbf{r}_m d\Theta_m$$

6D integrals over positional and orientational coordinates

Necessary to introduce some ***approximations*** to make the MOZ equations solvable for systems of chemical interest

Ornstein, L. S. and Zernike, F. *Proc. Acad. Sci*. Amsterdam **1914**, 17, 793-806

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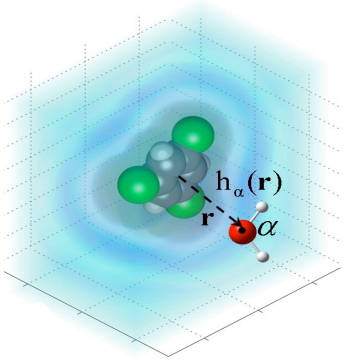

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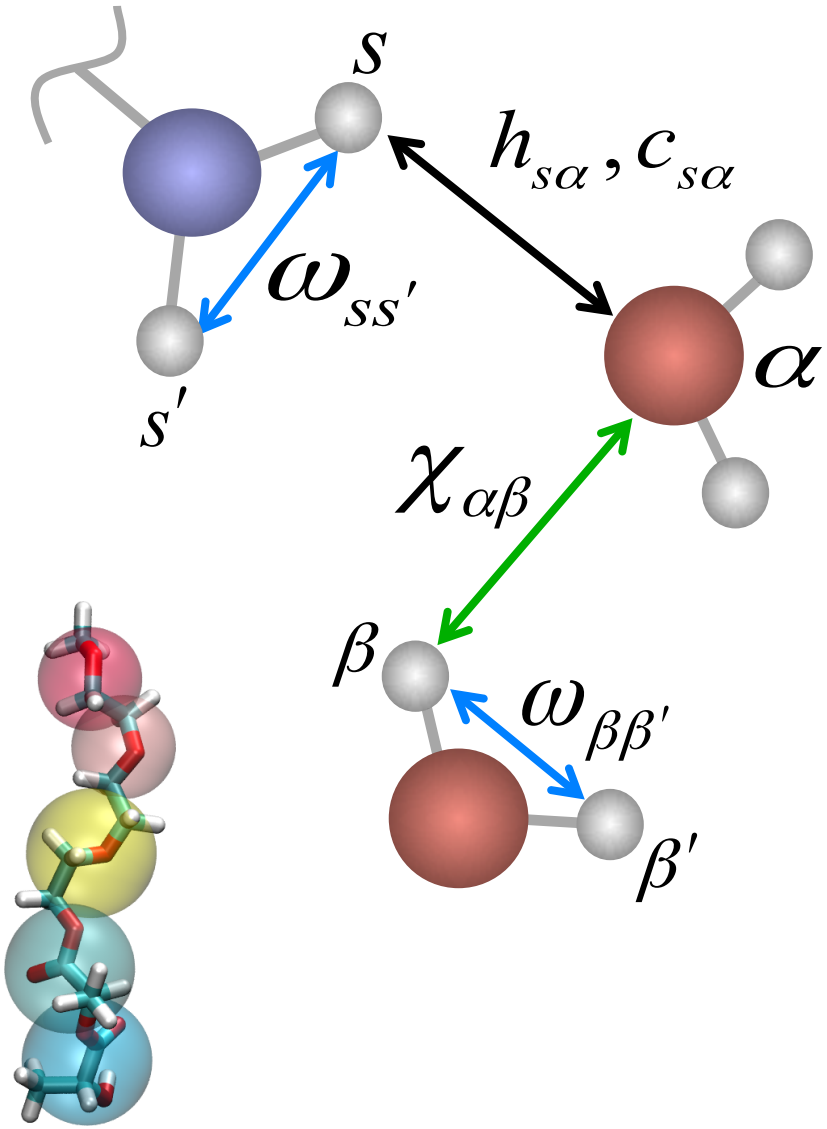
Site-site approximation



Molecules are modeled as *sets of* ***sites*** (atoms, groups).

Intramolecular correlation functions:

$$\omega_{ss'}(r) = \frac{\delta(r - r_{ss'})}{4\pi r_{ss'}^2}$$

Bulk solvent susceptibility:

$$\chi_{\alpha\beta} = \omega_{\beta\beta'}(r) + \rho h_{\alpha\beta}(r)$$

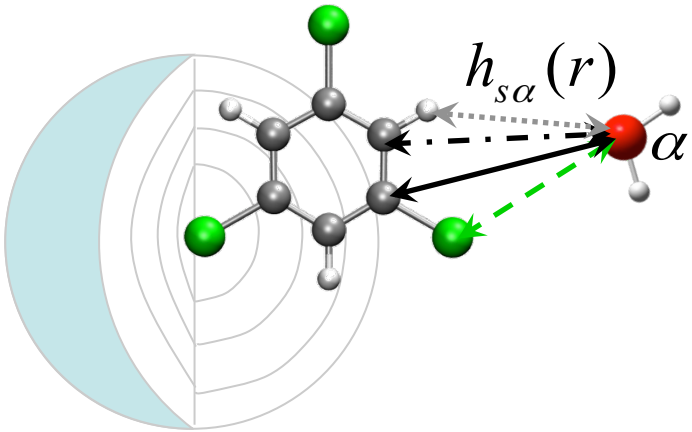
Assumption:

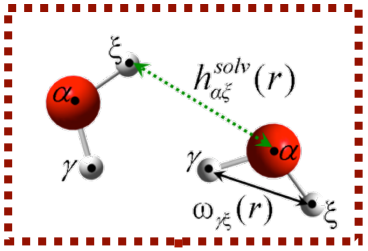
$$\mathrm{c}(r_{ij}, \boldsymbol{\Theta}_i, \boldsymbol{\Theta}_j) = \sum_{s\alpha} \mathrm{c}_{s\alpha}(r)$$

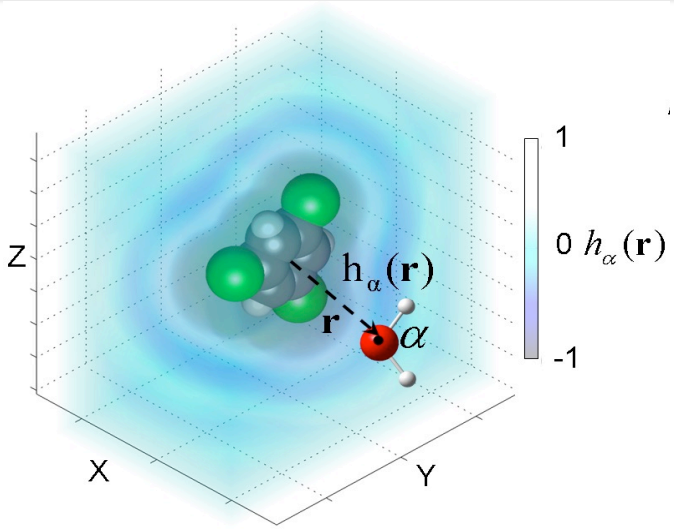
$$\mathrm{h}_{s\alpha}(r) = \frac{1}{8\pi^2} \int_{\Omega} \mathrm{h}(r_{ij}, \boldsymbol{\Theta}_i, \boldsymbol{\Theta}_j) \mathrm{d}\boldsymbol{\Theta}_i \mathrm{d}\boldsymbol{\Theta}_j$$

D. Chandler, H.C. Andersen, *J. Chem. Phys.*, **1972**, 57, 1930-1937

1D and 3D versions of RISM







site – site functions

$$h_{s\alpha}(r) = \sum_{s'=1}^{N} \sum_{\alpha'=1}^{M} \int_R \int_R \omega_{ss'}(r)\, c_{s'\alpha'}(r)\, \chi_{\alpha'\alpha}(r)\, d\mathbf{r}_{s'} d\mathbf{r}_{\alpha'}$$

$$h_{s\alpha}(r) = \exp\left[-\beta u_{s\alpha}(r) + h_{s\alpha}(r) - c_{s\alpha}(r) + B_{s\alpha}(r)\right] - 1,$$

D. Chandler, H.C. Andersen, *J. Chem. Phys.*, **1972**, 57, 1930;

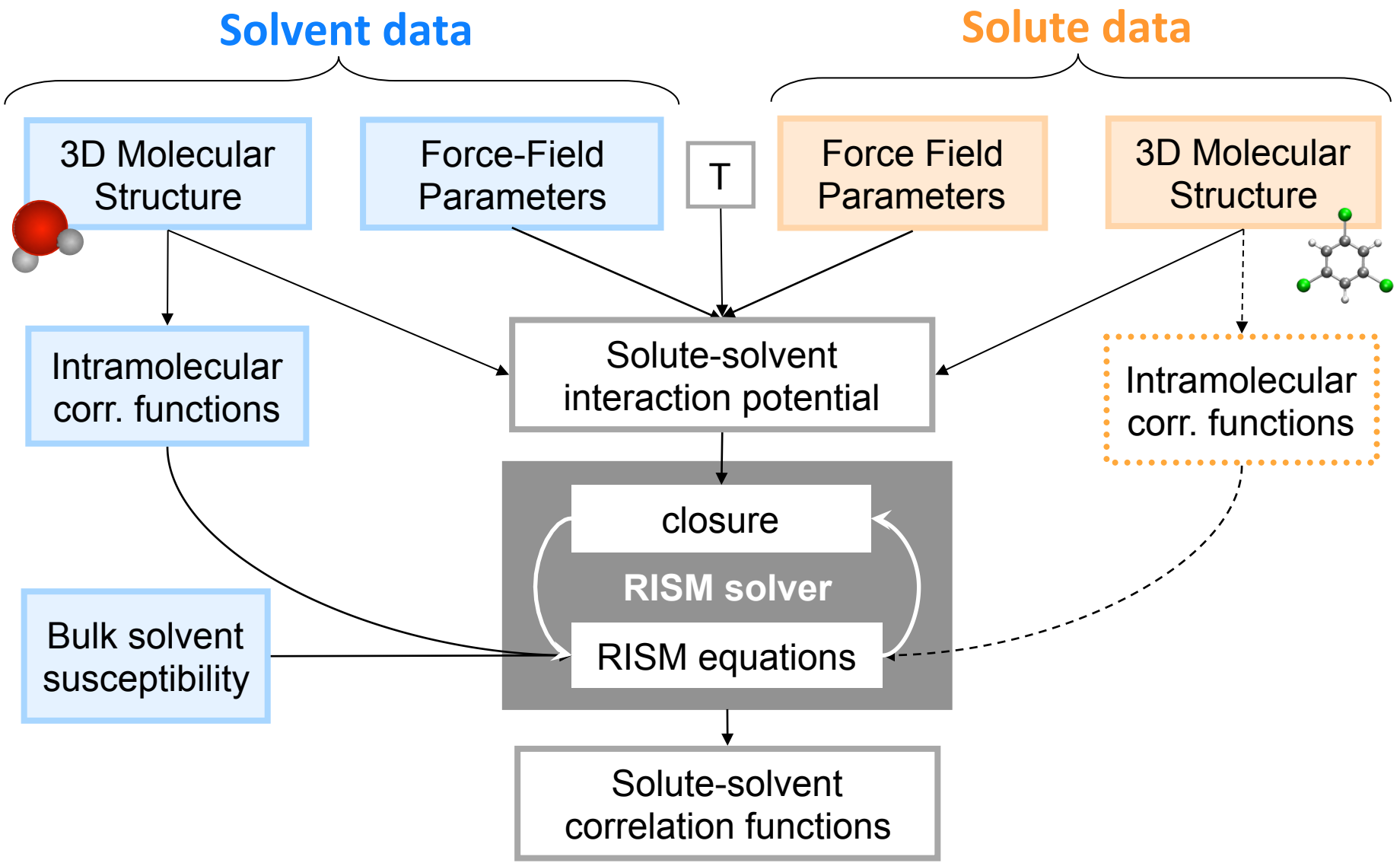
molecule – site functions

$$h_\alpha(\mathbf{r}) = \sum_{\alpha'=1}^{M} \int_R c_{\alpha'}(r)\, \chi_{\alpha'\alpha}(r)\, d\mathbf{r}_{\alpha'}$$

$$h_\alpha(r) = \exp\left[-\beta u_\alpha(r) + h_\alpha(r) - c_\alpha(r) + B_\alpha(r)\right] - 1$$

D. Beglov, B. Roux, *J. Phys. Chem.*, **1997**, 101, 7821-7826

RISM calculations: *workflow*

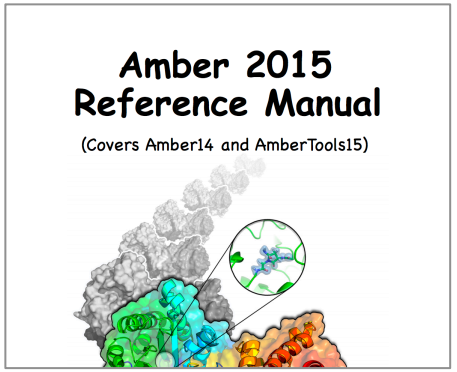


RISM calculations: *software*

AmberTools http://ambermd.org

http://ambermd.org/tutorials/

***TUTORIAL A14**: Using 3D-RISM to place waters (Dan Sindhikara)*



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MOE

https://www.chemcomp.com

ADF® molecular modeling suite

www.scm.com/adf-modeling-suite

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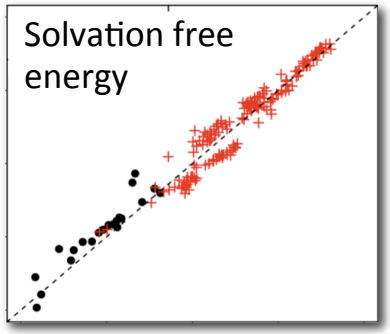

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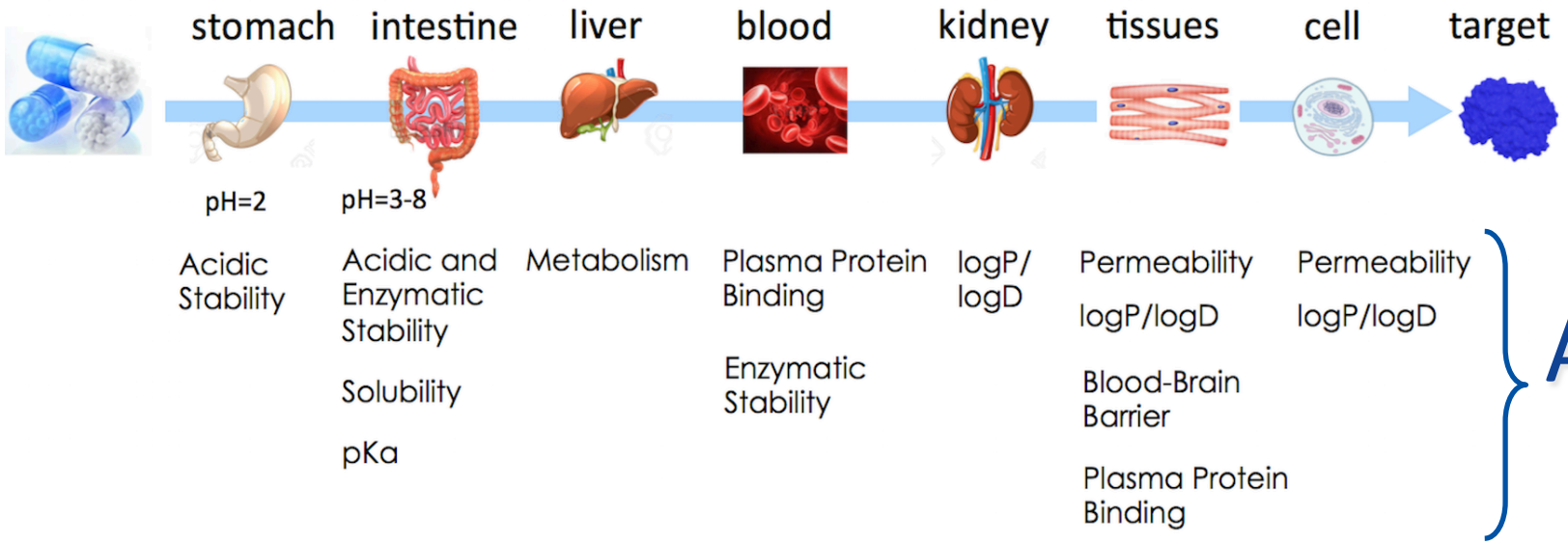
Physico-chemical properties in Drug Design



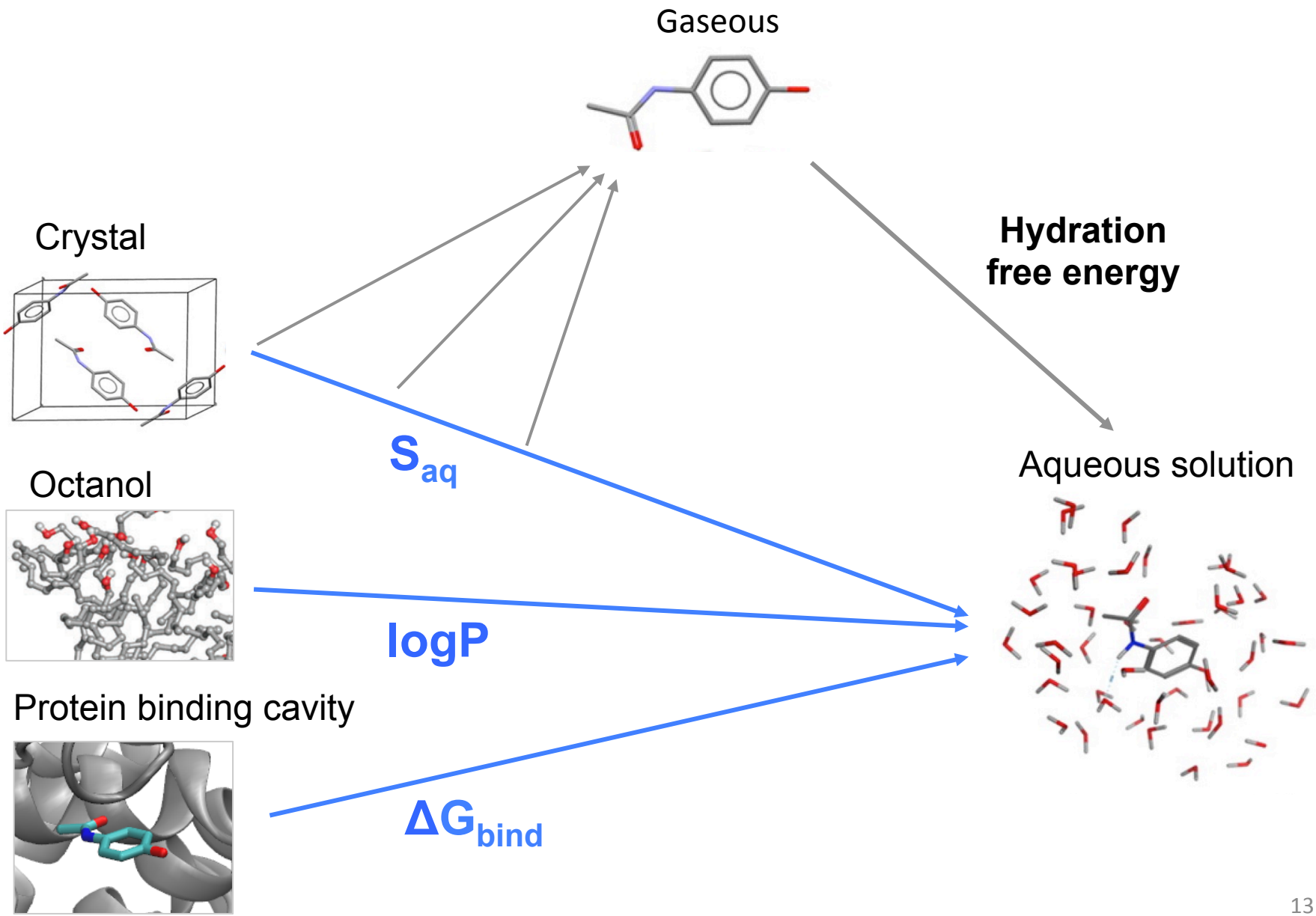
Early stage Drug Design:

- Hit-to-lead
- Lead optimization

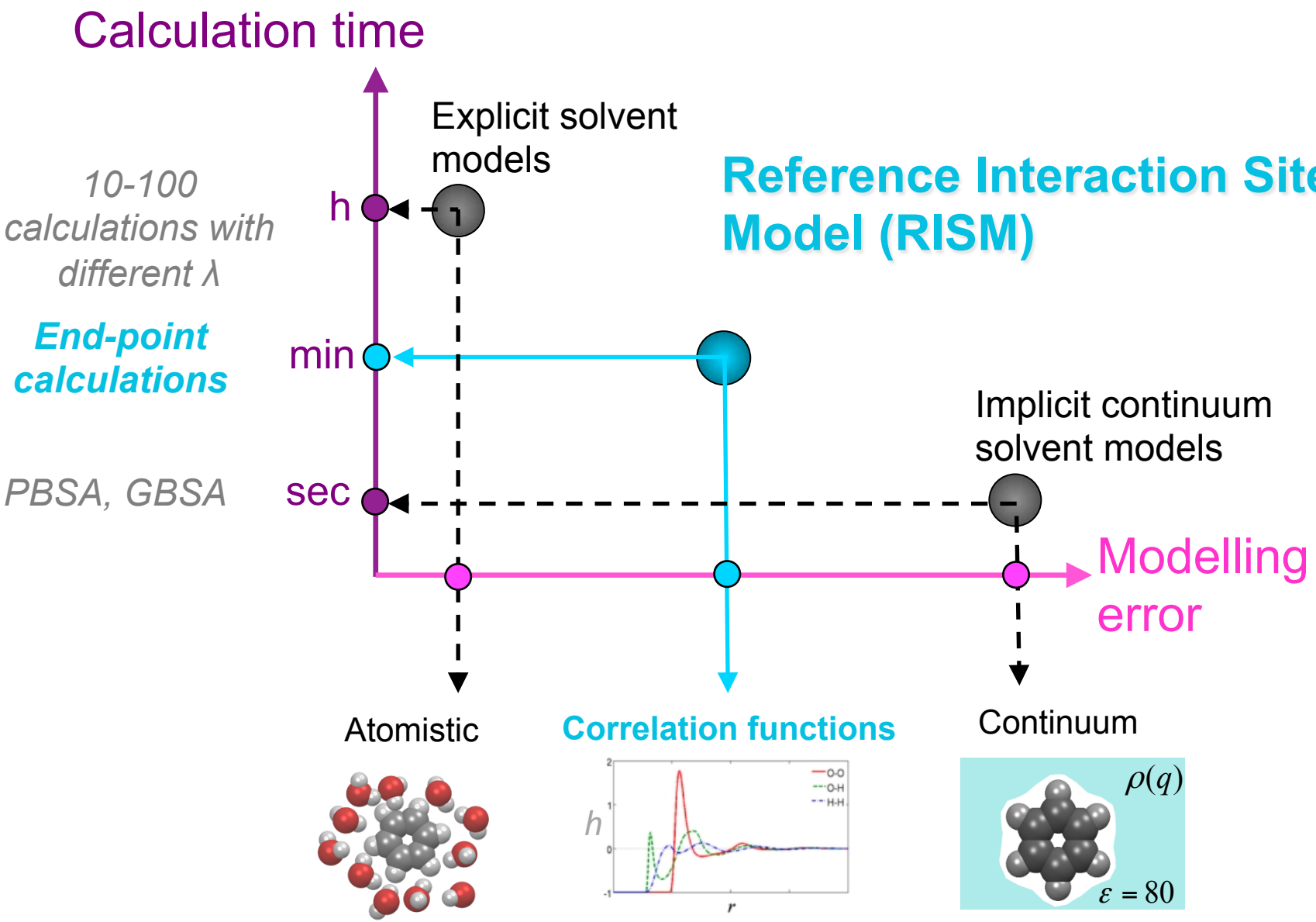
(filtering, ranking, and analysis of compounds)

Kerns, E. H.; Di, L., Pharmaceutical profiling in drug discovery. *Drug Discov. Today* **2003**, *8*, 316-323

Partitioning and hydration free energy



Models for hydration free energy calculation

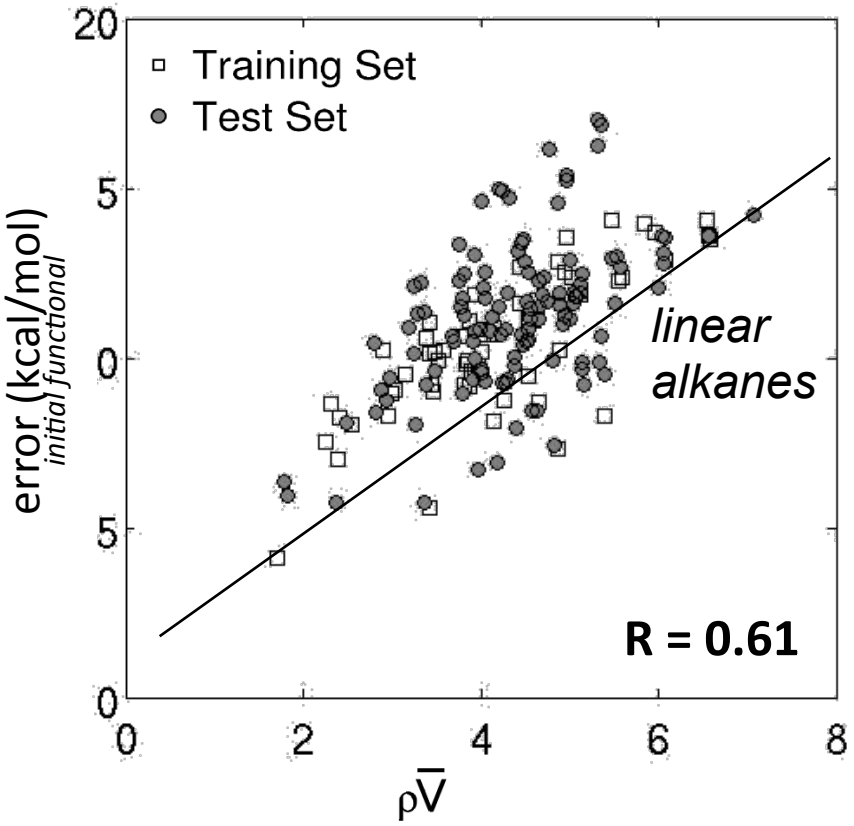


Hydration free energy from RISM

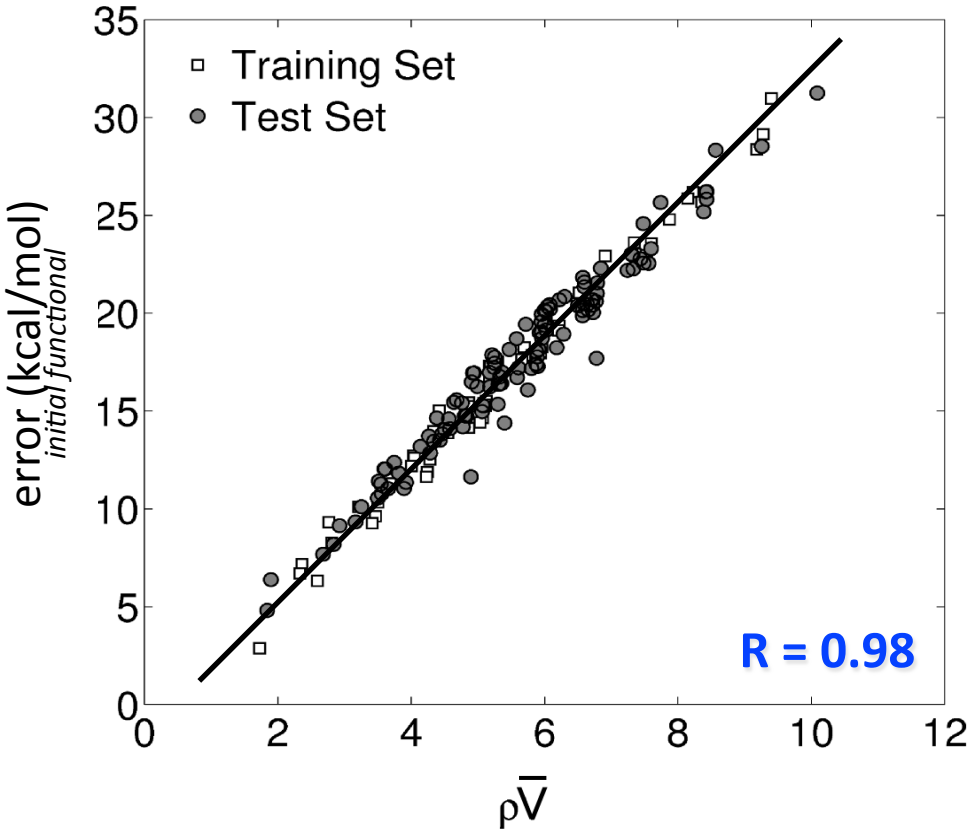
Universal correction (UC):

$$\Delta G_{hyd}^{UC} = \Delta G_{hyd}^{RISM} + a_1 \rho\bar{V} + a_0$$

1D RISM

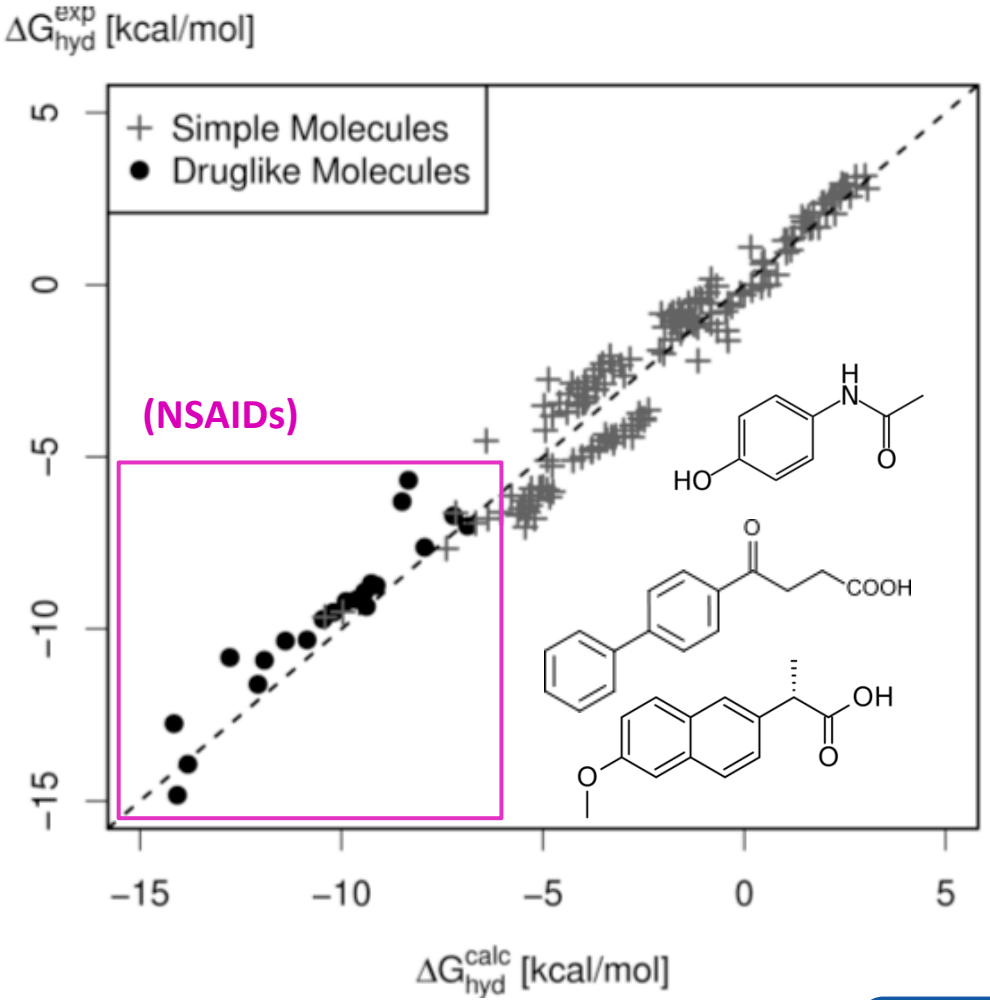


3D RISM



D.S. Palmer, A.I. Frolov, **E.L. Ratkova,** M.V. Fedorov, *J. Phys. Cond. Matt.*, **2010**, 22, 492101

Prediction of HFE for drugs



Test Set (N=120) *Small Molecules*

rmse = 1.0 kcal/mol

No re-parameterization

Validation Set (N=21): ***Drugs***

method	RMSE (kcal/mol)
3D RISM/UC	1.06
HF/6-31G(d) PCM	1.12
MO6 2X/6-31G(d) SM8	0.82
MO6 2X/6-31G(d) SM6	1.16

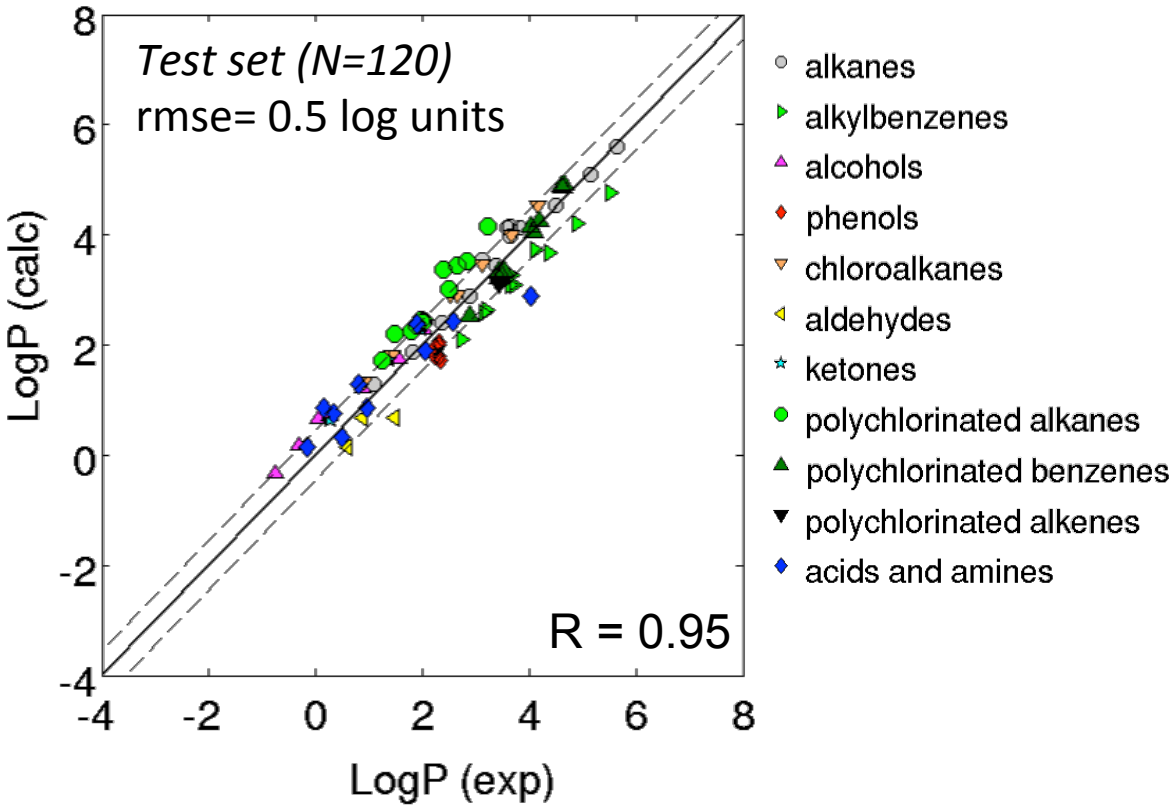
It has been a challenge for over 40 years

D.S. Palmer, A.I. Frolov, **E.L. Ratkova,** M.V. Fedorov, *Mol. Pharmaceutics* **2011**, 8, 1423-1429

logP predictions

$$\log P_{oct/wat} = \frac{1}{-RT(\ln 10)}\left(\Delta G^{UC}_{solv(oct)} - \Delta G^{UC}_{solv(wat)}\right)$$

$$\Delta G^{UC}_{solv} = \Delta G^{RISM}_{solv} + a_1 \rho \bar{V} + a_0$$



Small molecules:

- there are as efficient predictive models

Larger molecules:

- problem with site-site representation of solvent
- problems with convergence

Ratkova, Frolov, Fedorov (to be published)

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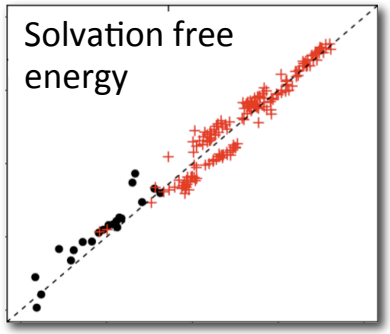

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Partial Molar Volume (PMV)

Partial Molar Volume characterizes the change in the volume when an infinitesimal amount of substance is added to water at constant T, P, and amount of solvent.

$$\overline{V}_A = \left(\frac{\partial V}{\partial n_A} \right)_{T,P,n_{B \neq A}}$$

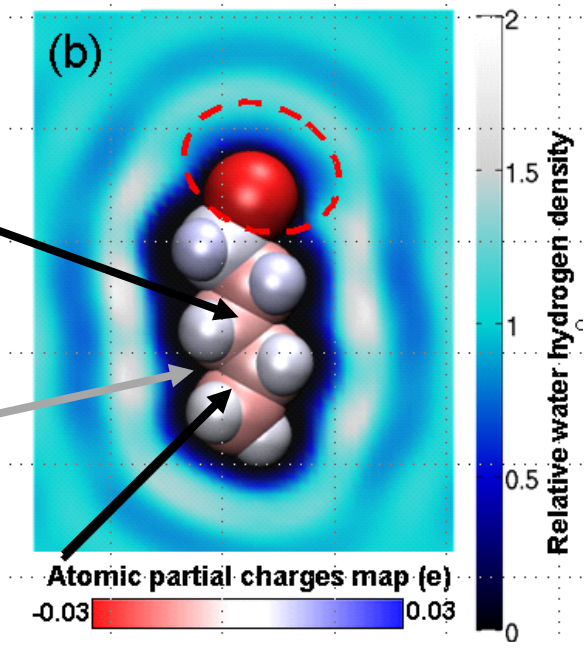
$$\overline{V} = \underbrace{V_W + V_T}_{V_C} + V_I + V_V + k_B T \chi_T$$

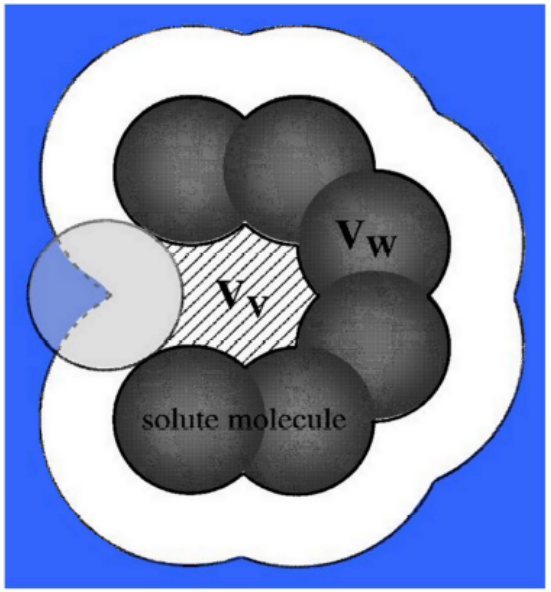
interaction volume

Cavity volume:

V_W molecular volume

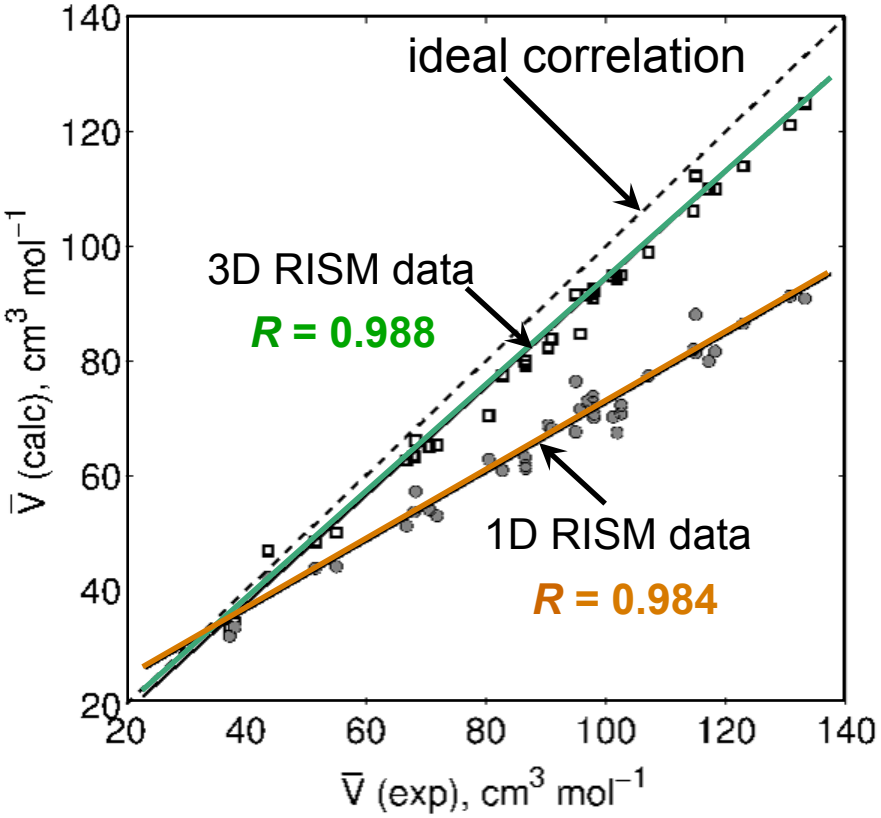
V_T thermal volume

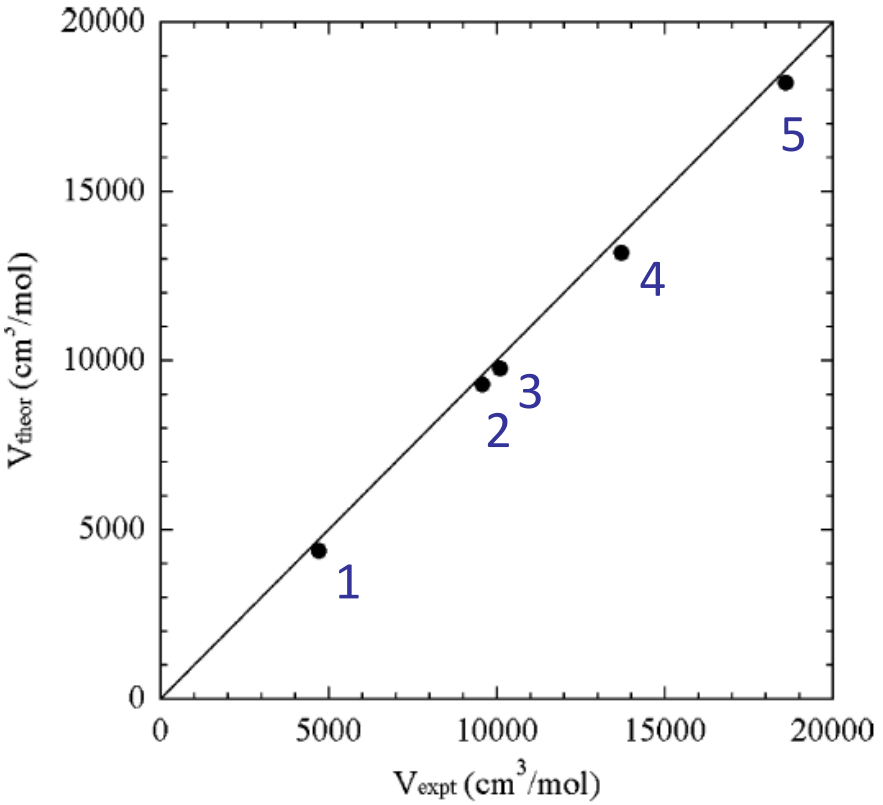


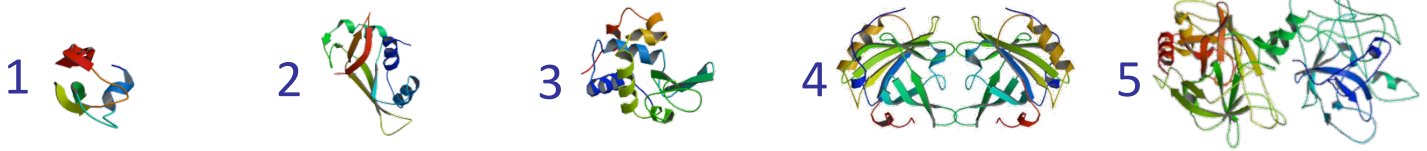


T. Imai; *et al. Protein Sci.* **2007**, *16*, 1927.
T.V. Chalikian; K.J. Breslauer. *Biopolymers* **1996**, *39*, 619.

PMV predictions with RISM







1 Bovine Pancreatic Trypsin Inhibitor

2 Bovine Pancreatic Ribonuclease A

3 hen egg-white lysozyme

4 bovine milk β-lactoglobin A

5 Bovine pancreatic a-chymotrypsinogen A

Ratkova E.L. (**2011**). *PhD Thesis*. University of Duisburg-Essen, Germany

T. Imai; *et al. Chem, Phys. Lett.* **2004**, *395*, 1.

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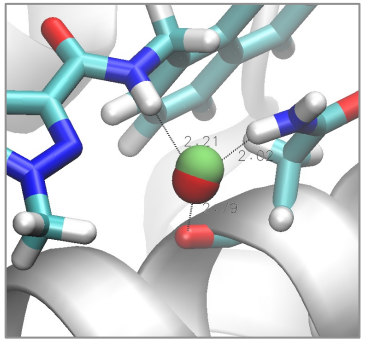
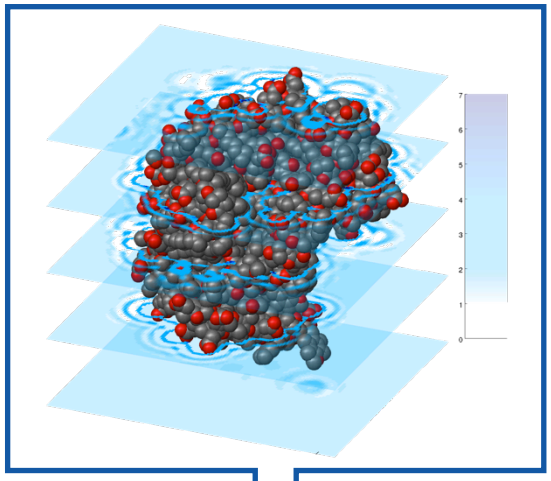
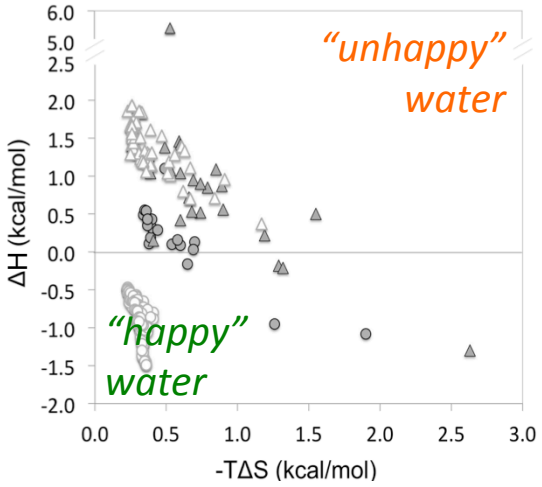


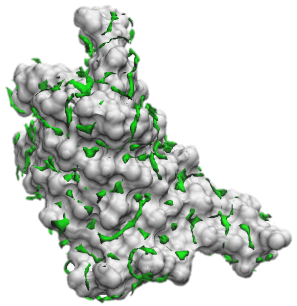
Water analysis: *workflow*



3D-RISM distribution functions



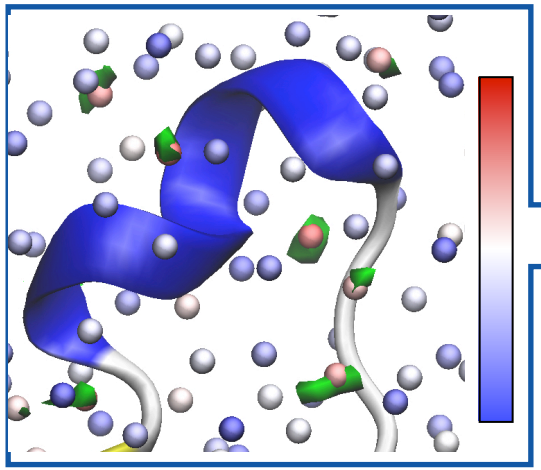
$g_O(r)$ > cut-off



$g_O(r)$ > 4

highly probable binding modes

population analysis



most probable binding modes

IST

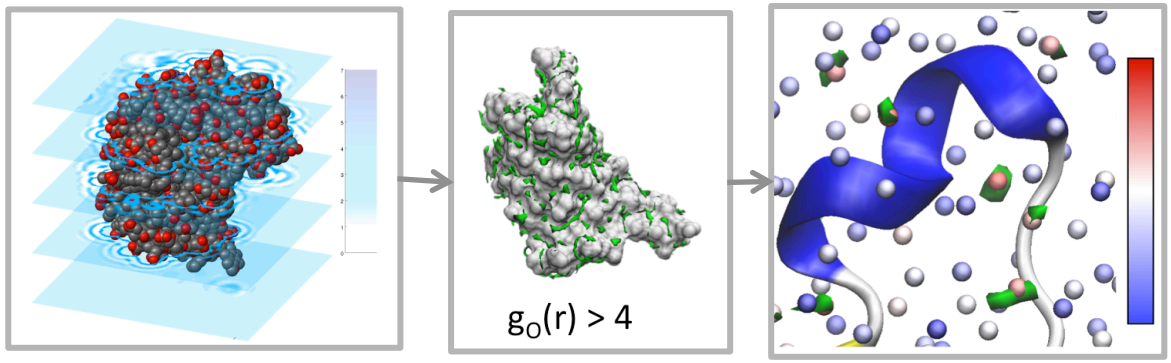
binding modes ranking:

- $g_O(r)$
- ΔG
- ΔH
- -TΔS

(IST = Inhomogeneous Solvation Theory)

Water analysis: *software*

1) Explicit positions of water molecules

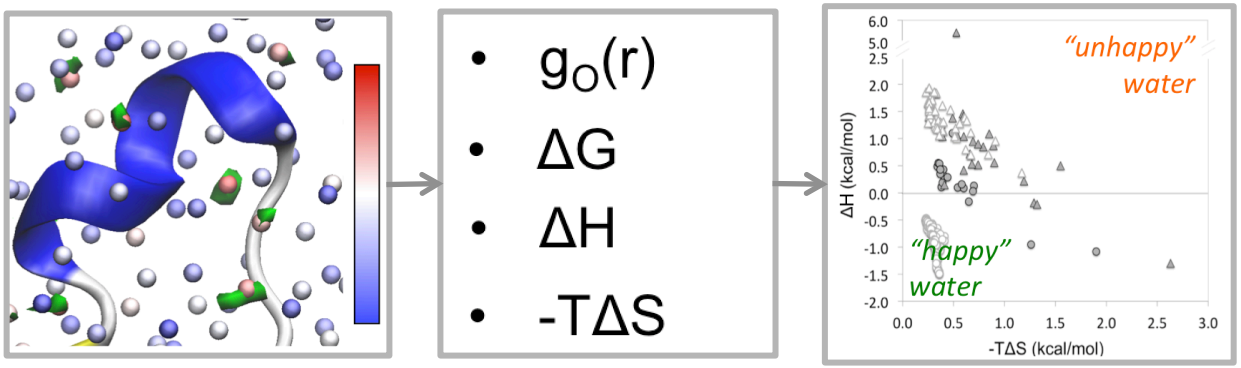


Software "Placevent" *(free)*

http://ambermd.org/tutorials/

TUTORIAL A14

2) Thermodynamic parameters of water molecules

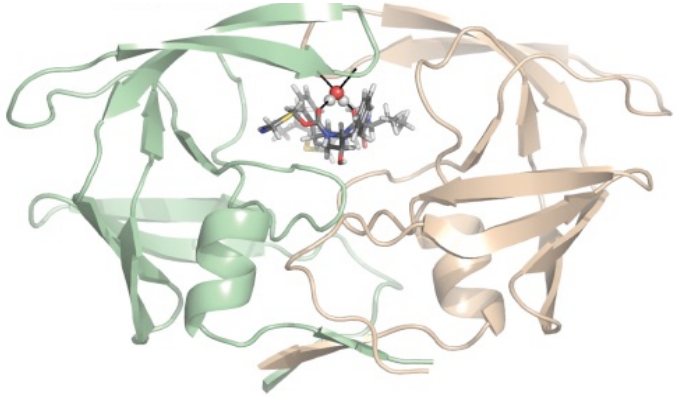


Software "SolutionMap"

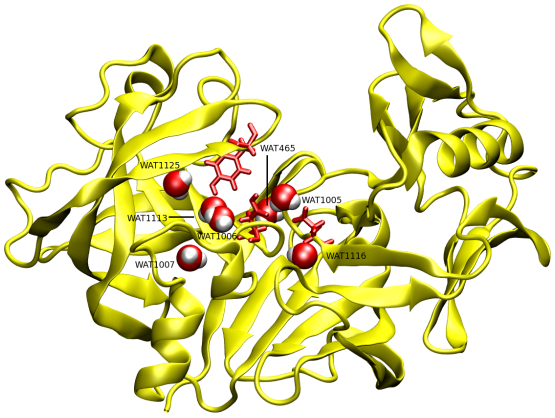
(Molecular Design Frontier Co. Ltd.)

(a-la "WaterMap")

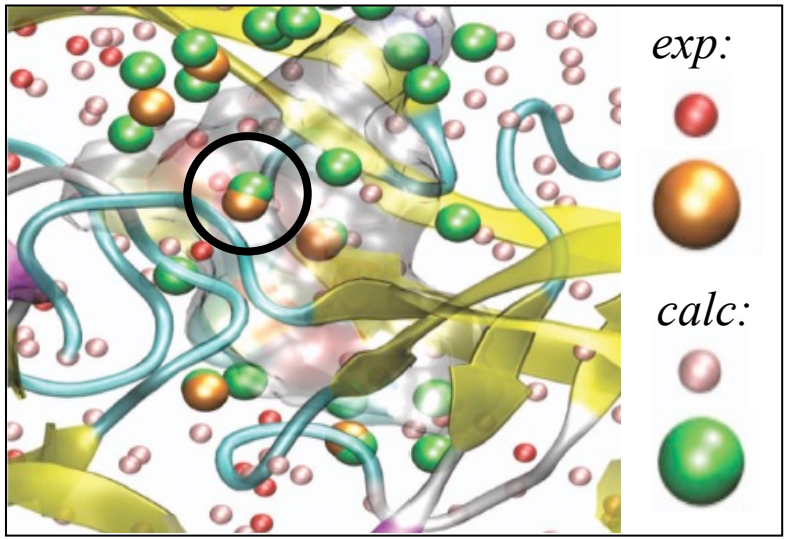
Principle hydration sites

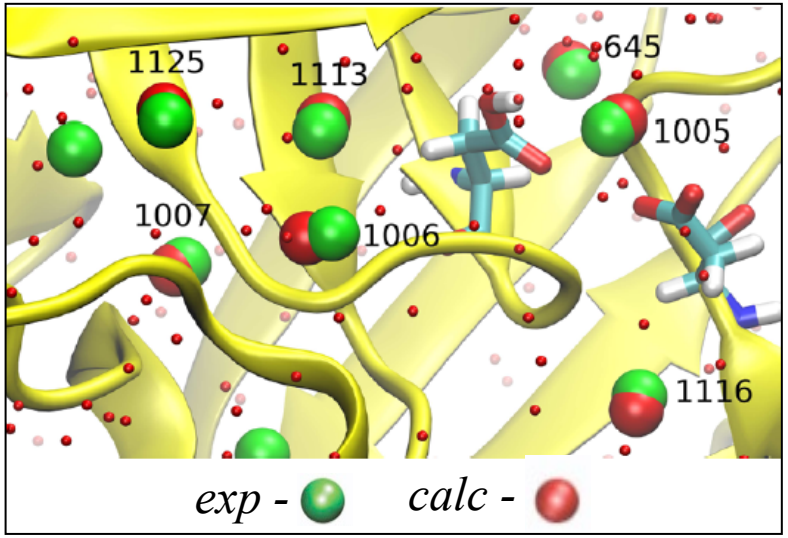


HIV-1 protease has 1 conserved H_2O in binding pocket [1]



Bovine chymosin has 7 conserved H_2O in binding pocket [2]





[1] D.J. Sindhikara, N. Yoshida, F. Hirata, *J. Comp. Chem.* **2012**, 133, 1536

[2] Palmer et al., *J. Comp. Theor. Chem.* **2013**, 9, 5706

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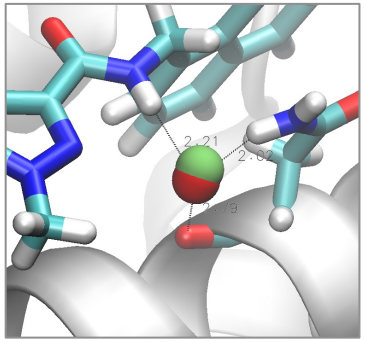
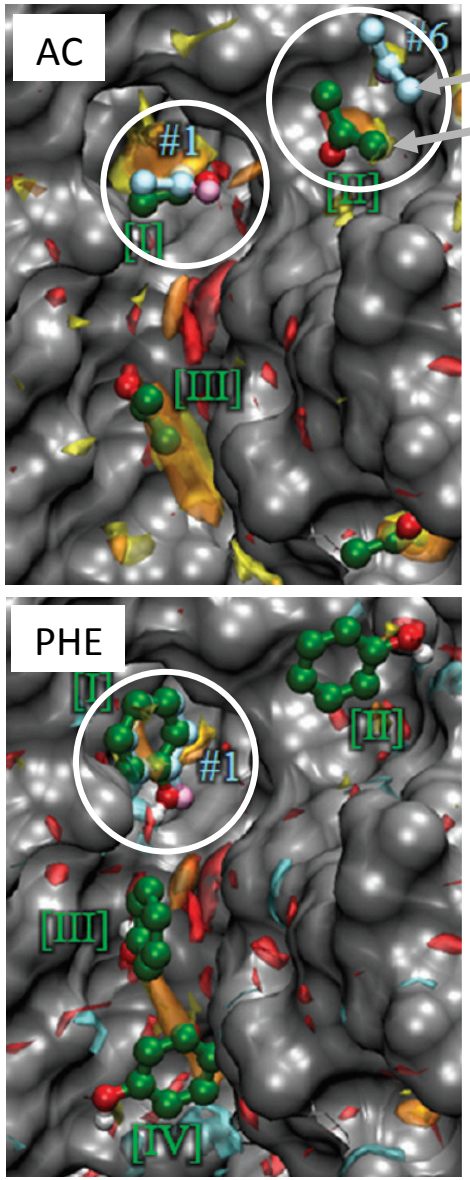
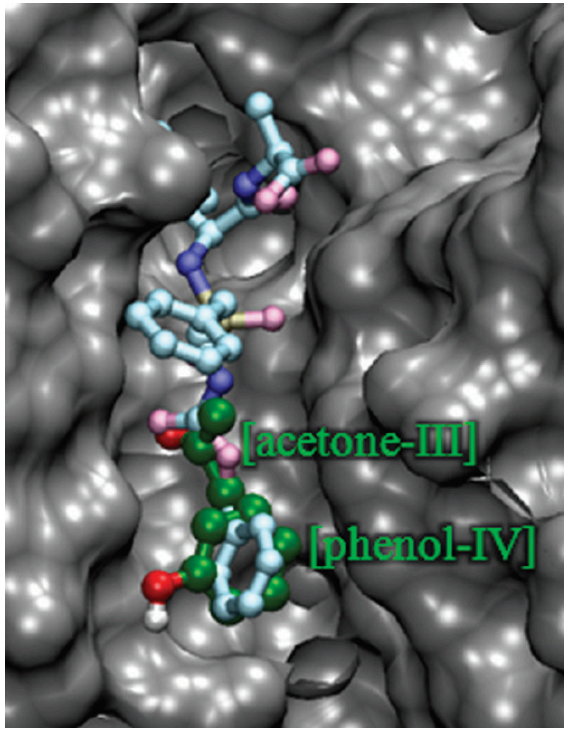


Mixed solvent for fragment placement in *de-novo* design

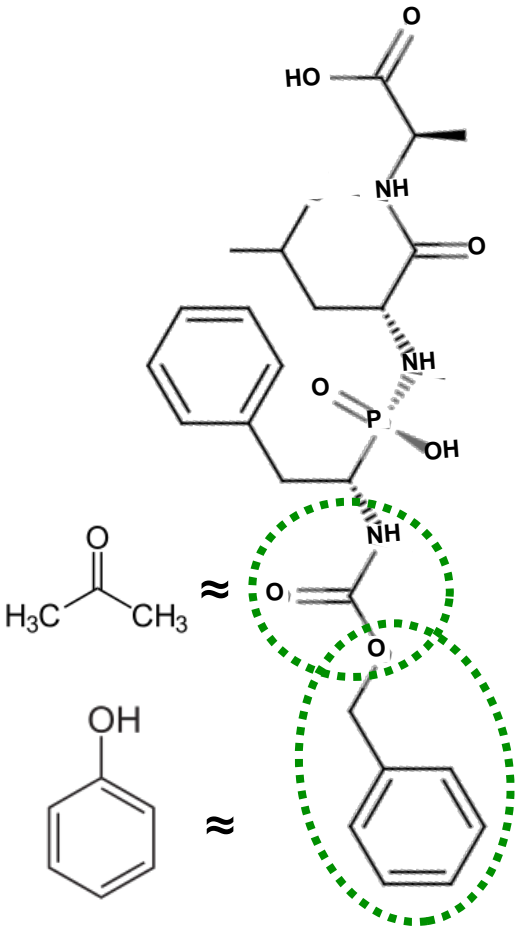


X-ray data

3D RISM results



X-ray structure of ZF^{P}LA complex with *thermolysin*



T. Imai et al, *JACS* **2009**, 131, 12430

MDFT (6D-MOZ): G. Jeanmairet et.al, *J Phys Chem Lett* **2013**, 4, 619–624

Take-home messages

RISM is a **theory**, not a computer experiment

- ✓ Significantly **less computationally expensive** than molecular simulation
- ✓ Allows **specific solute-solvent effects** to be studied (*unlike continuum solvent models*)
- ✓ 1D and 3D versions allow choose between **speed** and **accuracy**
- ✓ Allows calculations at **different parameters** (T, concentration, etc.)

Phys/chem properties predictions

RISM  **Chemo-informatics**

Solvent = **water** (ΔG_{hydr}, PMV)

- ✓ high accuracy for small compounds
- ✓ applicable for larger molecules

Solvent = **octanol** ($\log P_{o/w}$)

- ✓ high accuracy for small compounds
- • problems for larger molecules

Structure predictions

Solvent = **water**

- ✓ Correct principal hydration sites
- ✓ Analysis of thermodynamics
- ✓ Developed software

Solvent = **water** + **fragments**

- • there is a proof-of-concept
- • non-trivial replacement
- • under development

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