Implementing Molecular Hydrophobicity Potential Measurment for the Analysis of Dynamic Biomolecular Interactions

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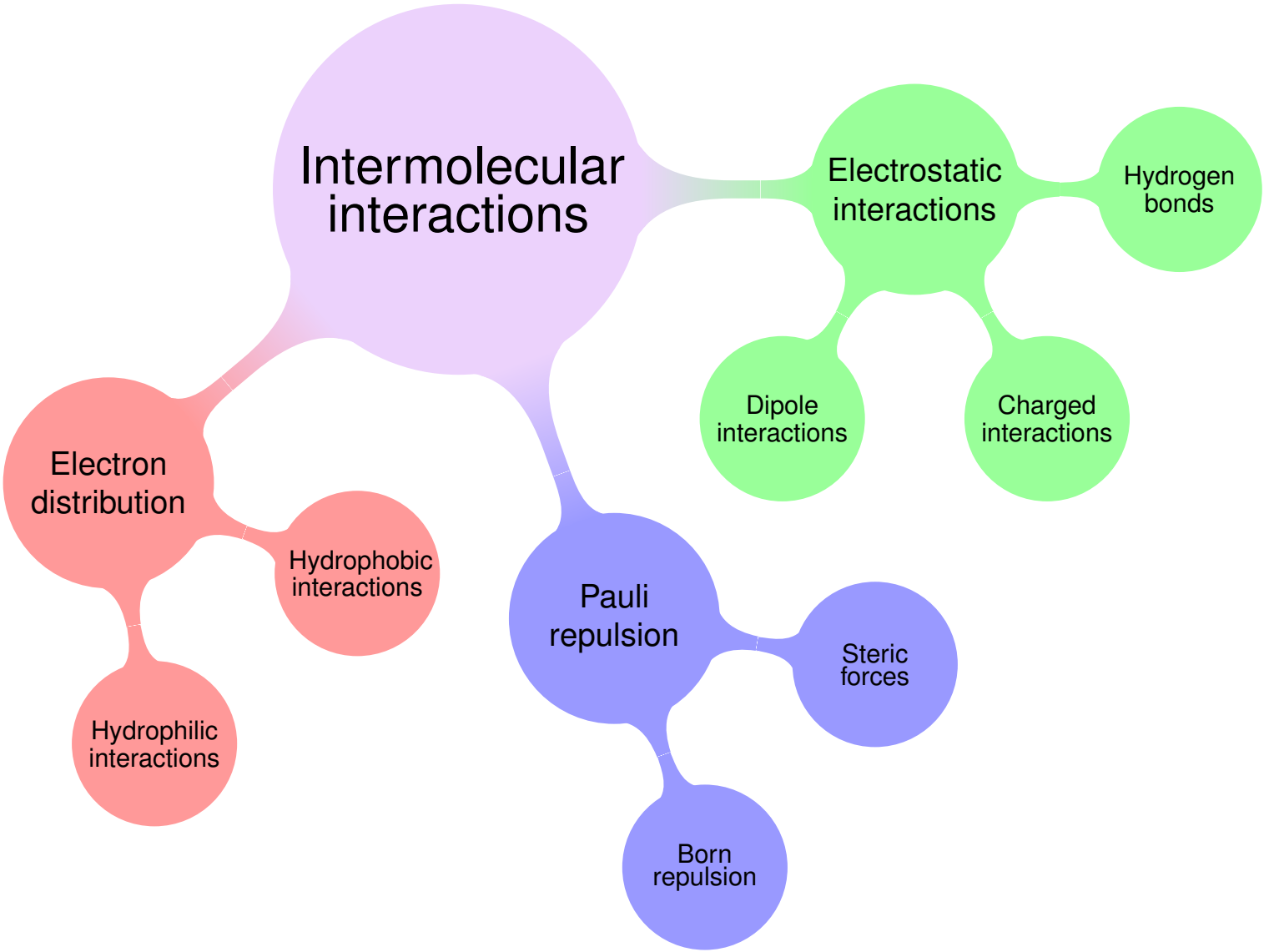
Hydrophobicity and log P



Hydrophilic/Hydrophobic Interactions

Partition Coefficient

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The ratio of concentrations of a compound in a mixture of two immiscible phases at equilibrium

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- $\log P_{\text{octanol/water}} = \log \left(\frac{[\text{solute}]_{\text{water}}}{[\text{solute}]_{\text{octanol}}} \right)$

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- Can be measured at an ionized or unionized state
- $\log P_{\text{octanol/water}} = \log \left(\frac{[\text{solute}]_{\text{water}}}{[\text{solute}]_{\text{octanol}}} \right)$
- Hydrophobicity increases with the (common) $\log P$

What is Molecular Hydrophobicity Potential (MHP)?

- By measuring the $\log P$ of many (ca. 30,000) compounds[1], single atoms can be assigned local "force" values.

[1] Ghose et al, J. Phys. Chem. A 1998, 102, 3762-3772

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- By measuring the $\log P$ of many (ca. 30,000) compounds[1], single atoms can be assigned local "force" values.
- Combining these values with a distance-depended decay function, a potential can be constructed.
- This potential predicts the local $\log P$ behaviour of fragments of a molecule.

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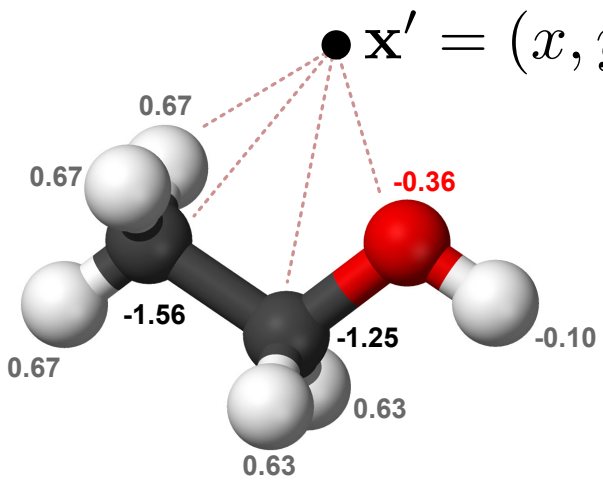
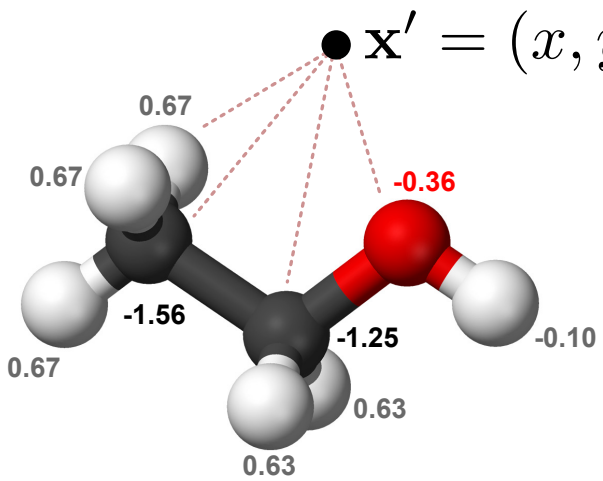
The MHP Formula



$$\text{MHP}\left(\mathbf{x}'\right) = \sum_{i=1}^{k} \left[f_i \cdot D\left(\mathbf{x} - \mathbf{x}'_i\right) \right]$$

The MHP Formula



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Summing over all atoms

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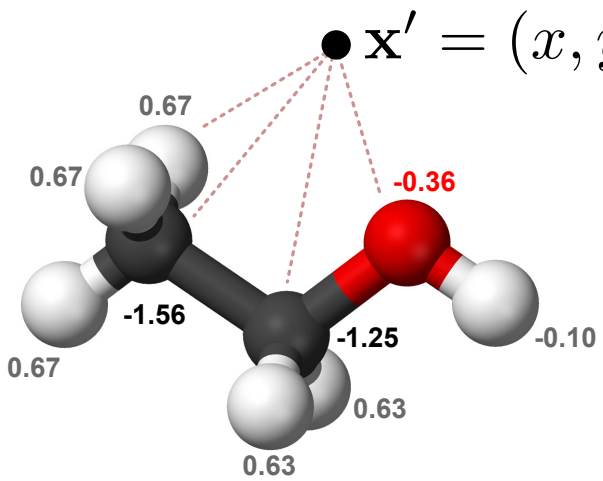

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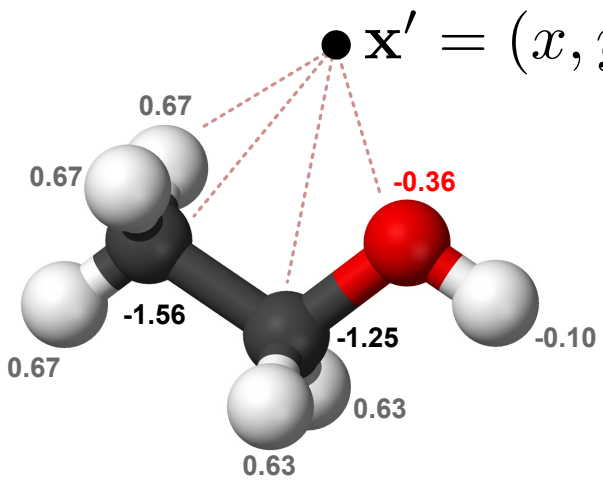
Force constants

The MHP Formula



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Summing over all atoms

Force constants

Distance function

Force Constants - Carbon

Carbon atom contribution to hydrophobicity[2]

Type	Description	f_i value
	Carbon in:	
1	CH_3R	-1.5603
3	CHR_3	-0.6681
7	CH_2X_2	-1.0305
13	RCX_3	0.7894
17	$=CR_2$	0.0383
24	$R--CH--R$	-0.3251
25	$R--CR--R$	0.1492
26	$R--CX--R$	0.1539

[2]Source: Ghose et al, J. Phys. Chem. A 1998, 102, 3762-3772

Force Constants - Hydrogen

Hydrogen atom contribution to hydrophobicity[3]

Type	Description	f_i value
	Hydrogen attached to:	
46	C_{sp^3}, no X in α	0.7341
47	C_{sp^2}	0.6301
50	X	-0.1036
52	C_{sp^3}, 1 X in α	0.6666
54	C_{sp^3}, 3 X in α	0.6338

[3] Source: Ghose et al, J. Phys. Chem. A 1998, 102, 3762-3772

Force Constants - Oxygen

Oxygen atom contribution to hydrophobicity[4]

Type	Description	f_i value
	Oxygen in:	
56	Alcohol	-0.3567
57	Phenol, enol, carboxyl OH	-0.0127
58	Ketone	-0.0233
61	Nitro, N-oxides	1.0520
62	O^-	-0.7941

[4] Source: Ghose et al, J. Phys. Chem. A 1998, 102, 3762-3772

Force Constants - Various

Various atom contribution to hydrophobicity[5]

Type	Description	f_i value
66	Primary amine	-0.5427
67	Secondary amine	-0.3168
81	F attached to $\mathrm{C_{sp^3}}$	0.4797
106	S in $\mathrm{R{-}SH}$ (thiol)	1.0520
119	P in $\mathrm{PR_3}$ (phosphine)	-0.7941

[5] Source: Ghose et al, J. Phys. Chem. A 1998, 102, 3762-3772

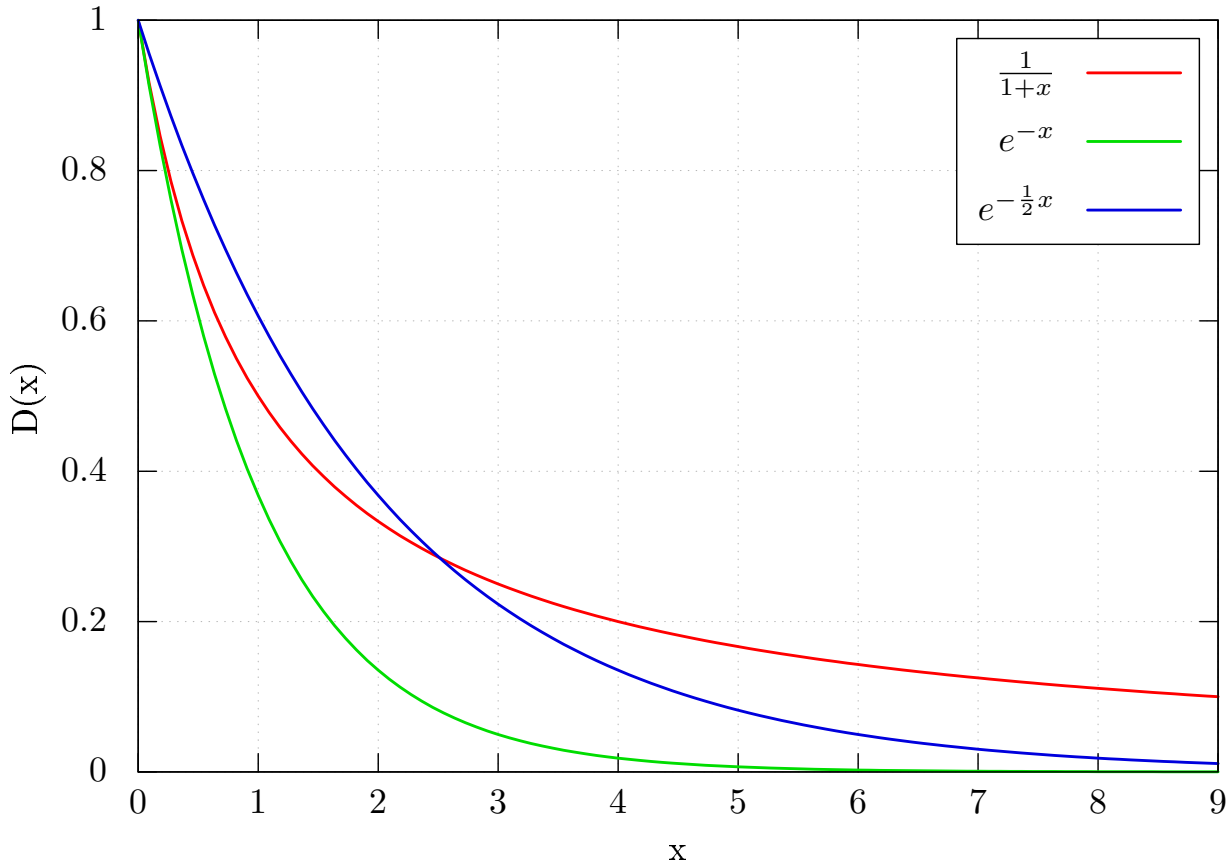
Distance function

Audry form

$$D(x) = \frac{1}{1+x}$$

Exponential decay form

$$D(x) = e^{-\alpha x}$$



Solvent accesible surface

- The surface around a molecule accesible to solvent molecules

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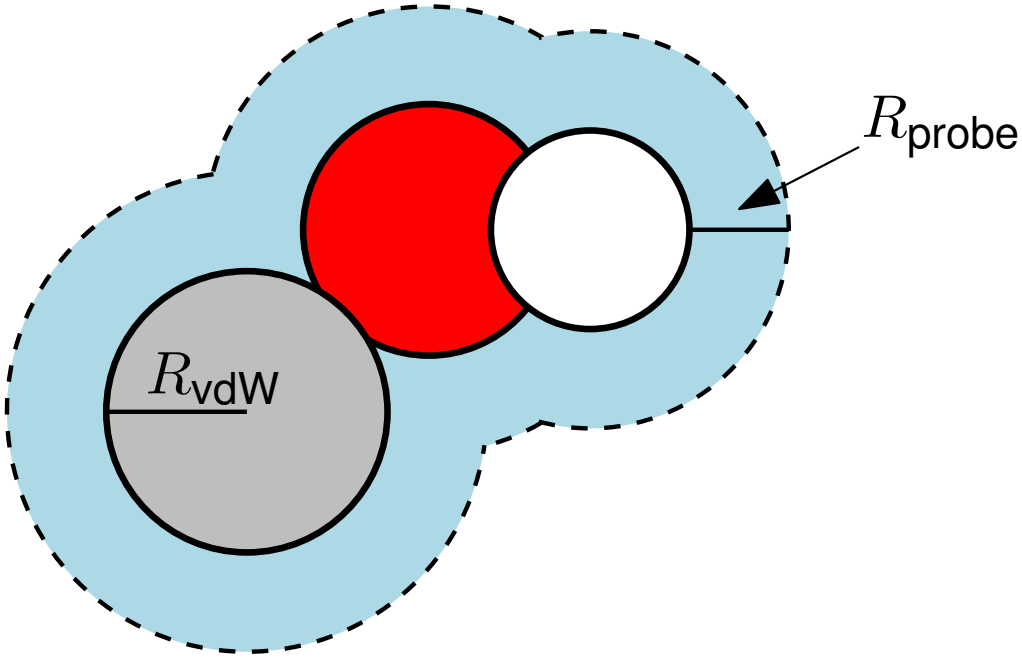

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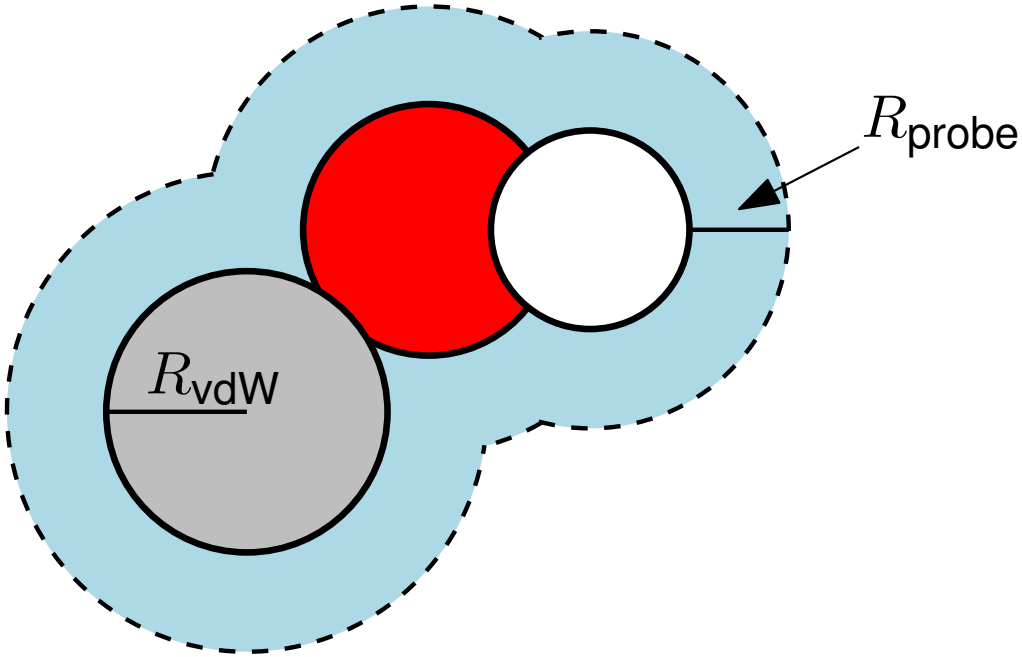
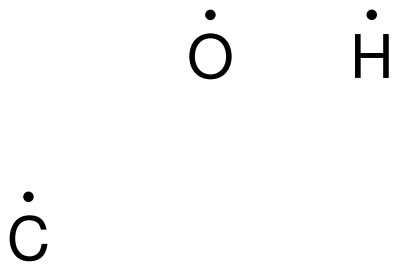


- For water molecules usually $r = 1.4\,[\text{Å}]$

How to Create the Solvent Accesible Surface?



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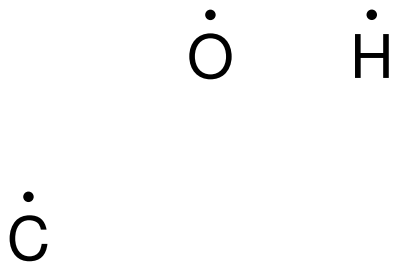

1. Take all atoms with their vdW-radii

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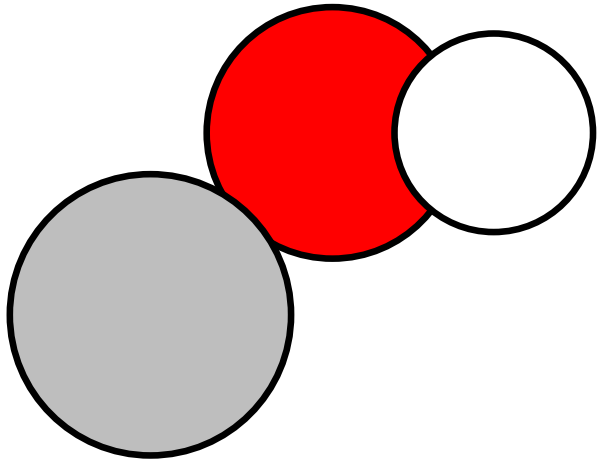

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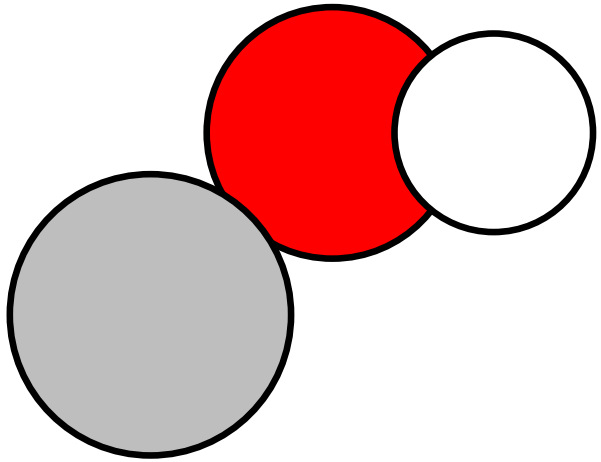

1. Take all atoms with their vdW-radii
2. Create spheres around all atoms with $R^i = R^i_{\text{vdw}} + R_{\text{probe}}$

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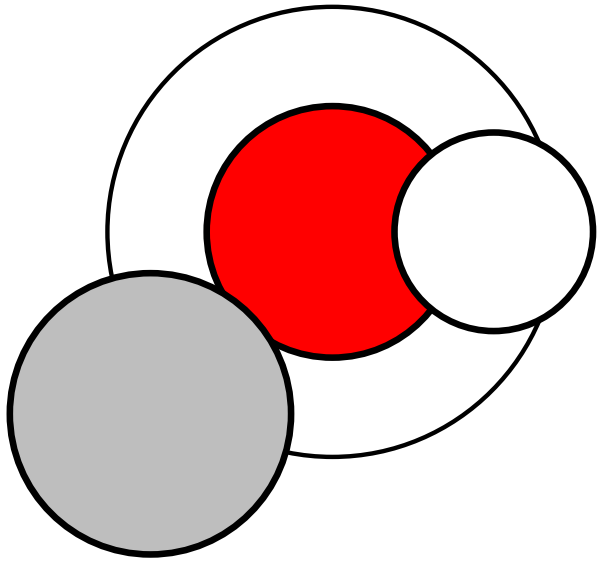

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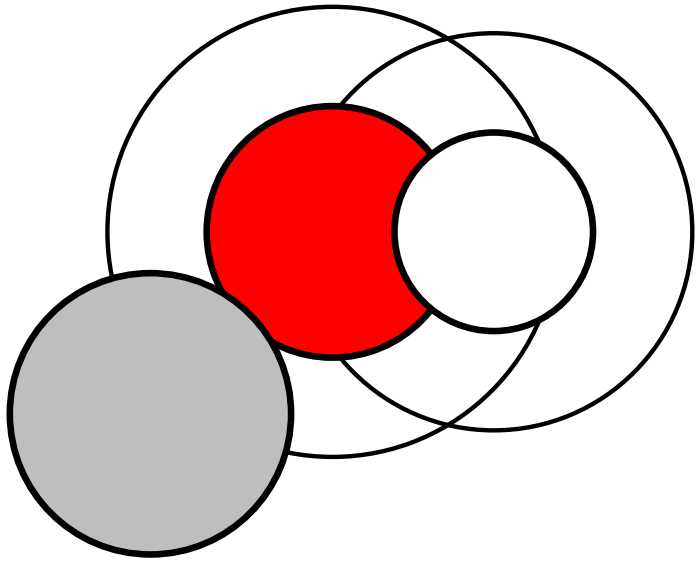

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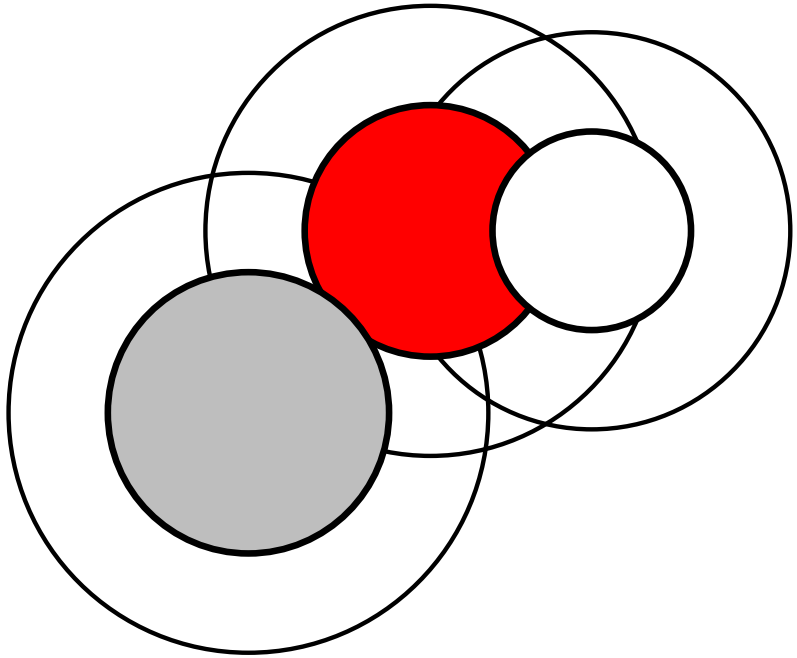

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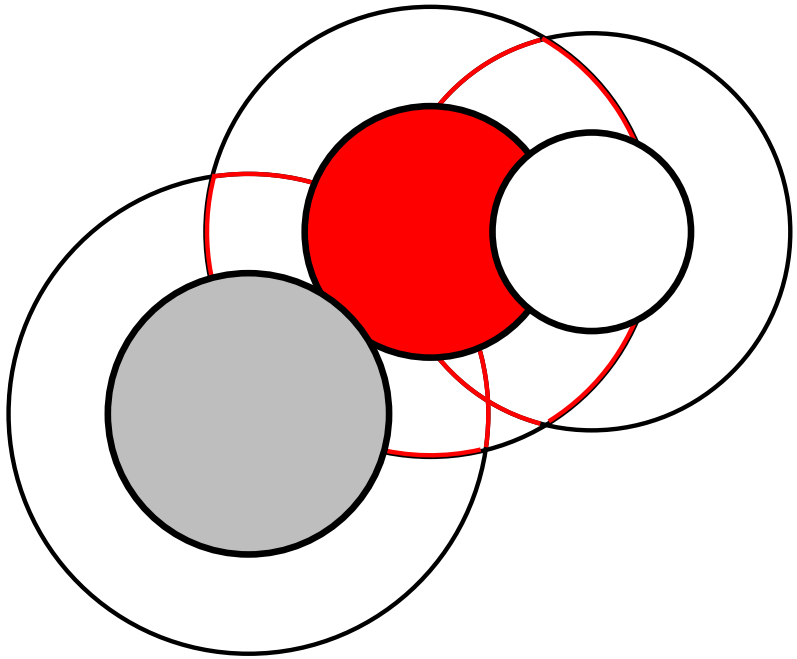

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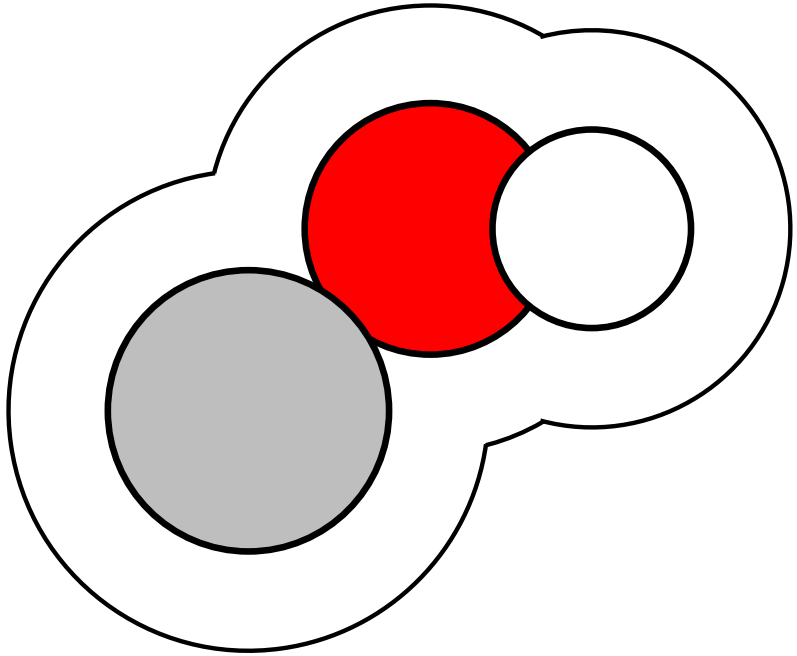
2. Create spheres around all atoms with $R^i = R^i_{\text{vdw}} + R_{\text{probe}}$
3. Delete all points that are "burried" in other extended spheres (i.e. $\Delta\left(p^i, c^j\right) \leq R^j + R_{\text{probe}}$)

How to Create the Solvent Accesible Surface?



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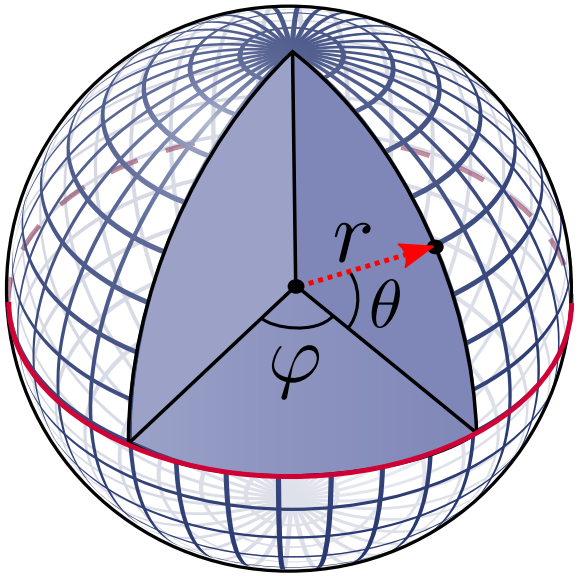
3. Delete all points that are "burried" in other extended spheres (i.e. $\Delta\left(p^i, c^j\right) \leq R^j + R_{\text{probe}}$)
4. The remaining surface is the solvent-accesible surface of the molecule

Evenly distributed points

How to distribute N points on a surface of a sphere?



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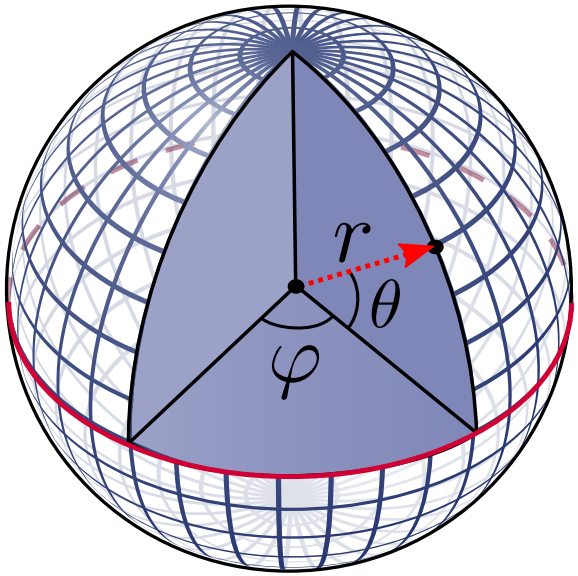

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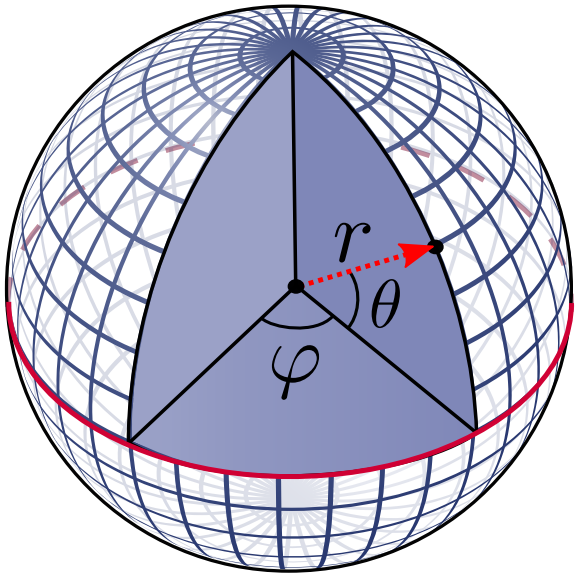

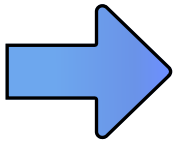

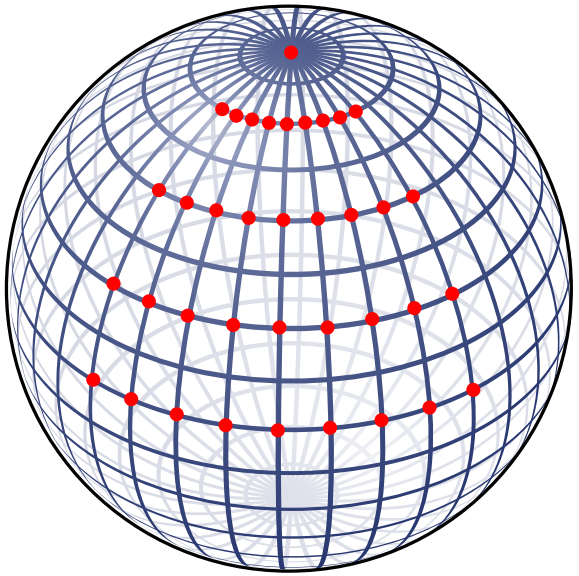

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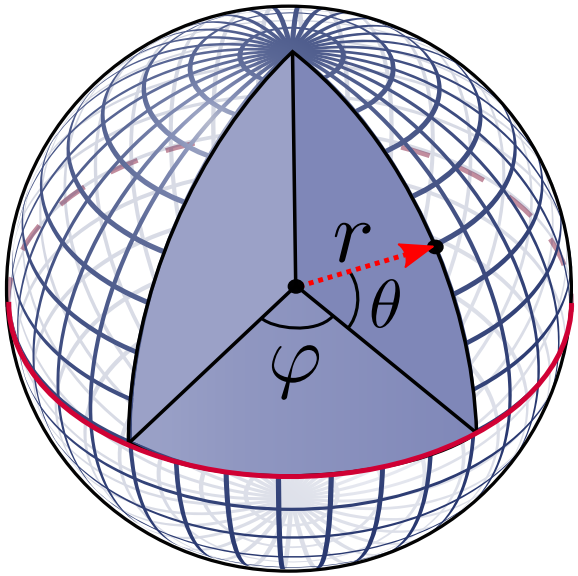

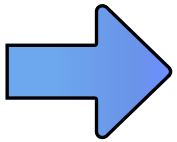

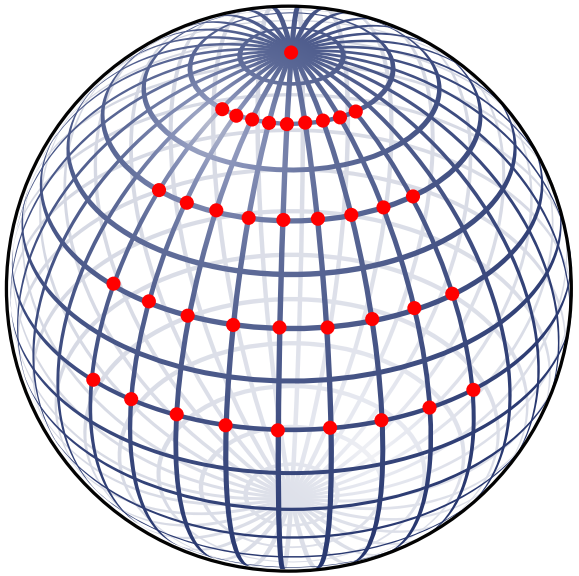

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- Points are not evenly distributed

Evenly distributed points

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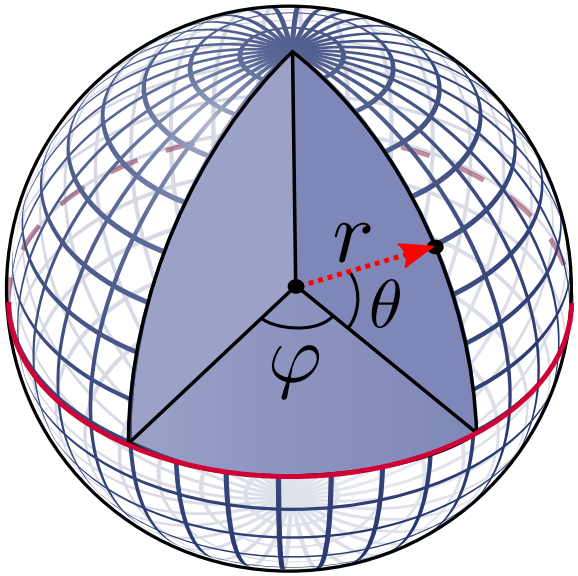

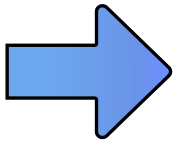

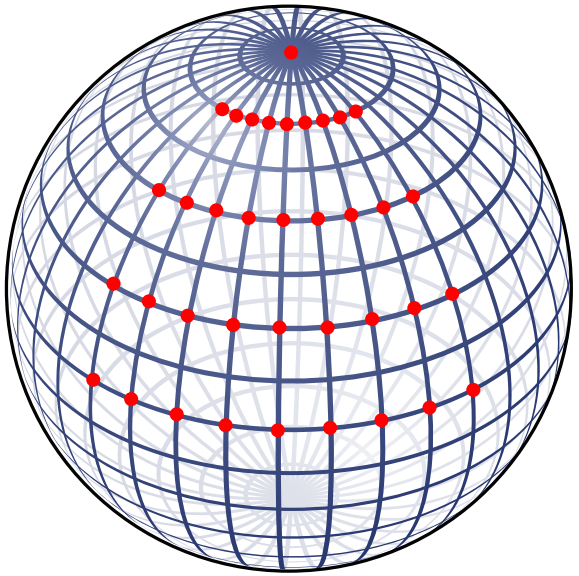

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- Points are not evenly distributed
- Several points overlap at poles

Evenly distributed points

Solution: Vogel's method

In 2 dimensions:

Evenly distributed points

Solution: Vogel's method

In 2 dimensions:

- Distances: $r_i = \sqrt{\frac{i}{N}}$
- Angle: $\theta_i = \varphi i$

  (φ is the golden ratio!)

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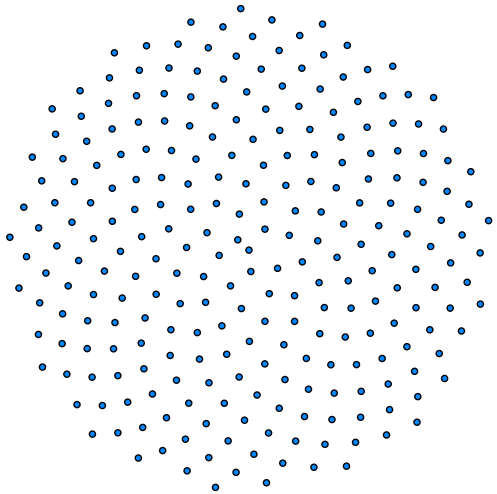

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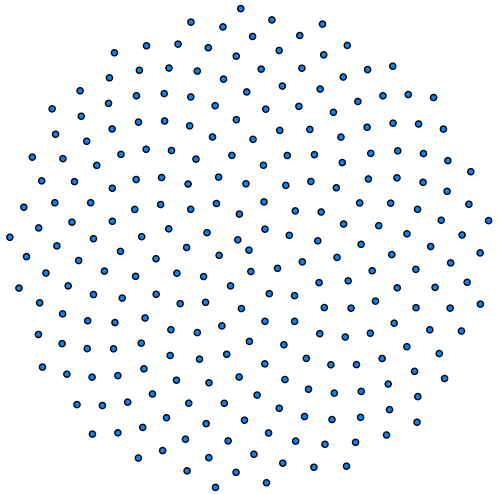

In 3 dimensions (cylindrical coordinates):

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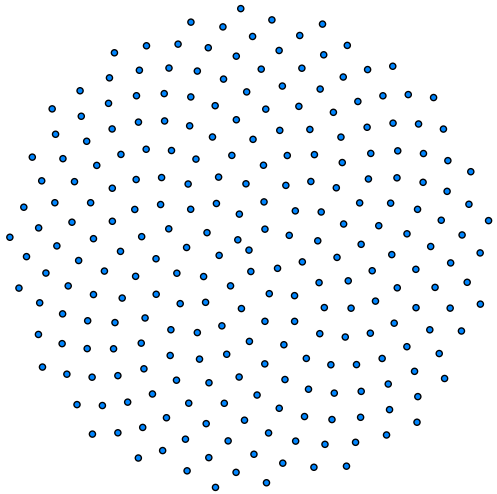

In 3 dimensions (cylindrical coordinates):

- Distances: $z_i = \left(1 - \frac{1}{N}\right)\left(1 - \frac{2i}{N-1}\right)$
- Angles:

  $\theta_i = \varphi i,\ \rho_i = \sqrt{1 - z_i^2}$

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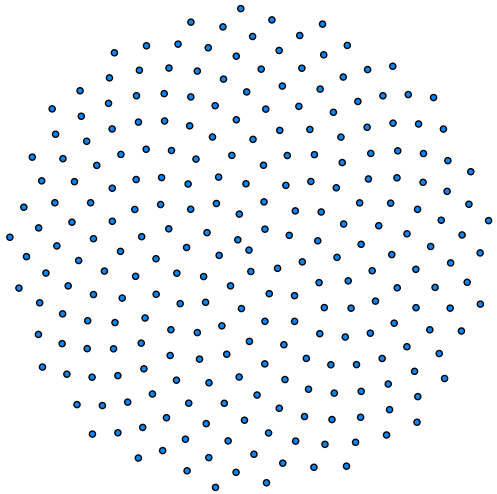

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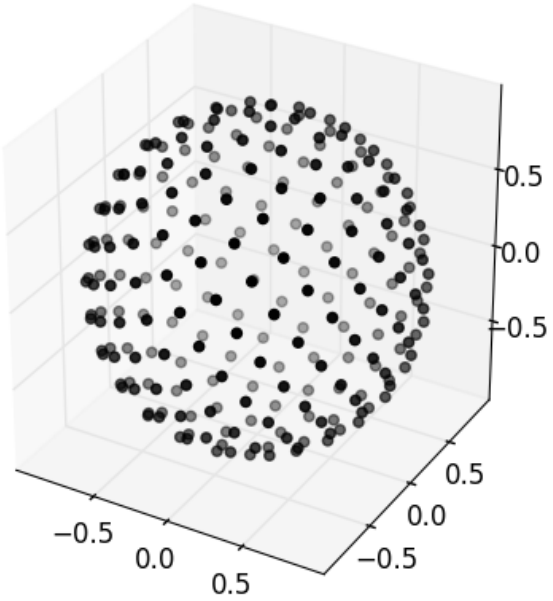

Image source: Marmakoide's Blog

Integration

- Each atom's total surface area:
  $V^a = 4\pi \left(R^a_{\text{vdW}} + R_{\text{probe}}\right)^2$

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Therefore, each atom has a total MHP of:

$$\text{MHP}^a = \frac{4\pi}{N} \sum_{j=0}^{M} \text{MHP}^a_j$$

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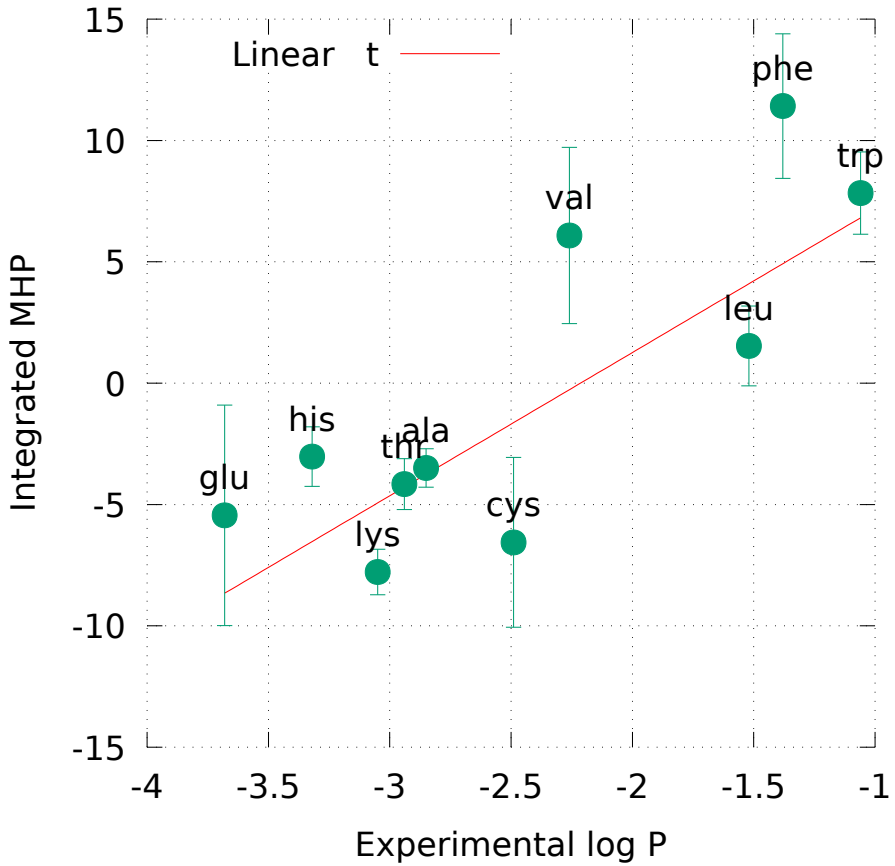
- A groups of amino acids of varying hydrophobicity where simulated and their MHP calculated.

Validation via Known $\log P$ Values

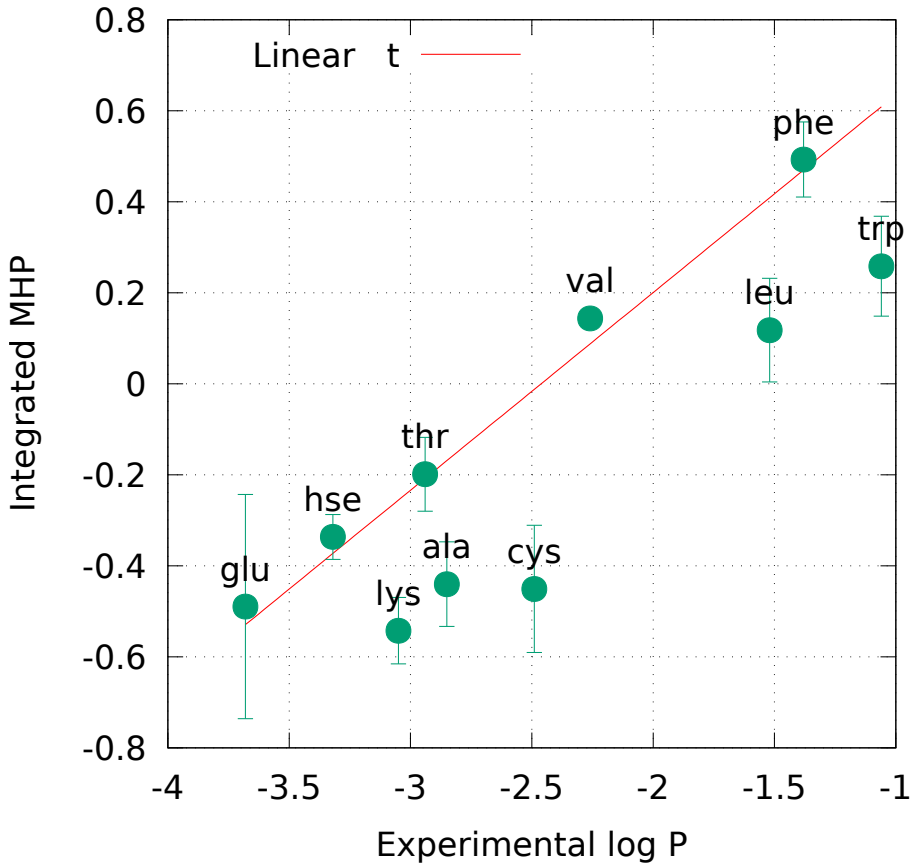
Validation in vacuum (5 frames per molecule)[6], $R^2 = 0.668$



[6]MD simulation using NAMD, performed by Dr. Tillmann Utesch

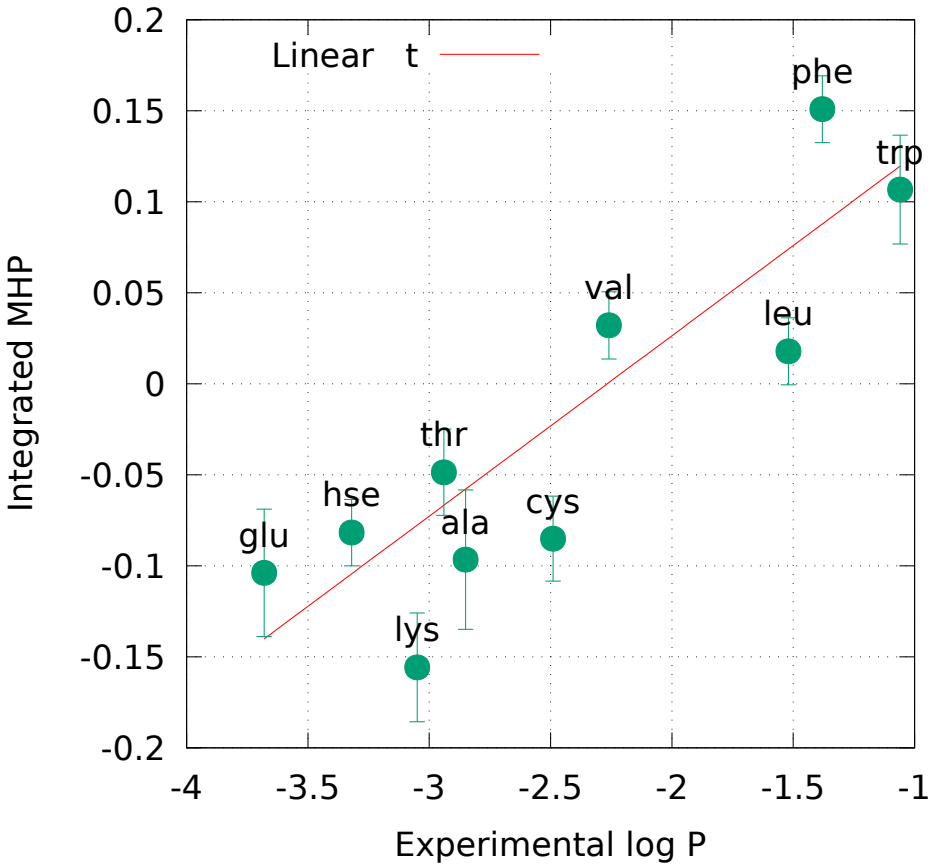
Validation via Known $\log P$ Values

Validation in water + structural optimization (10 frames per molecule), $R^2 = 0.748$



Validation via Known $\log P$ Values

Validation in water + structural optimization + SAS normalization (10 frames per molecule), $R^2 = 0.760$



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- The membrane used for the study consists of a mixture of two lipids, PG and PE, in agreement with experimental measurements.

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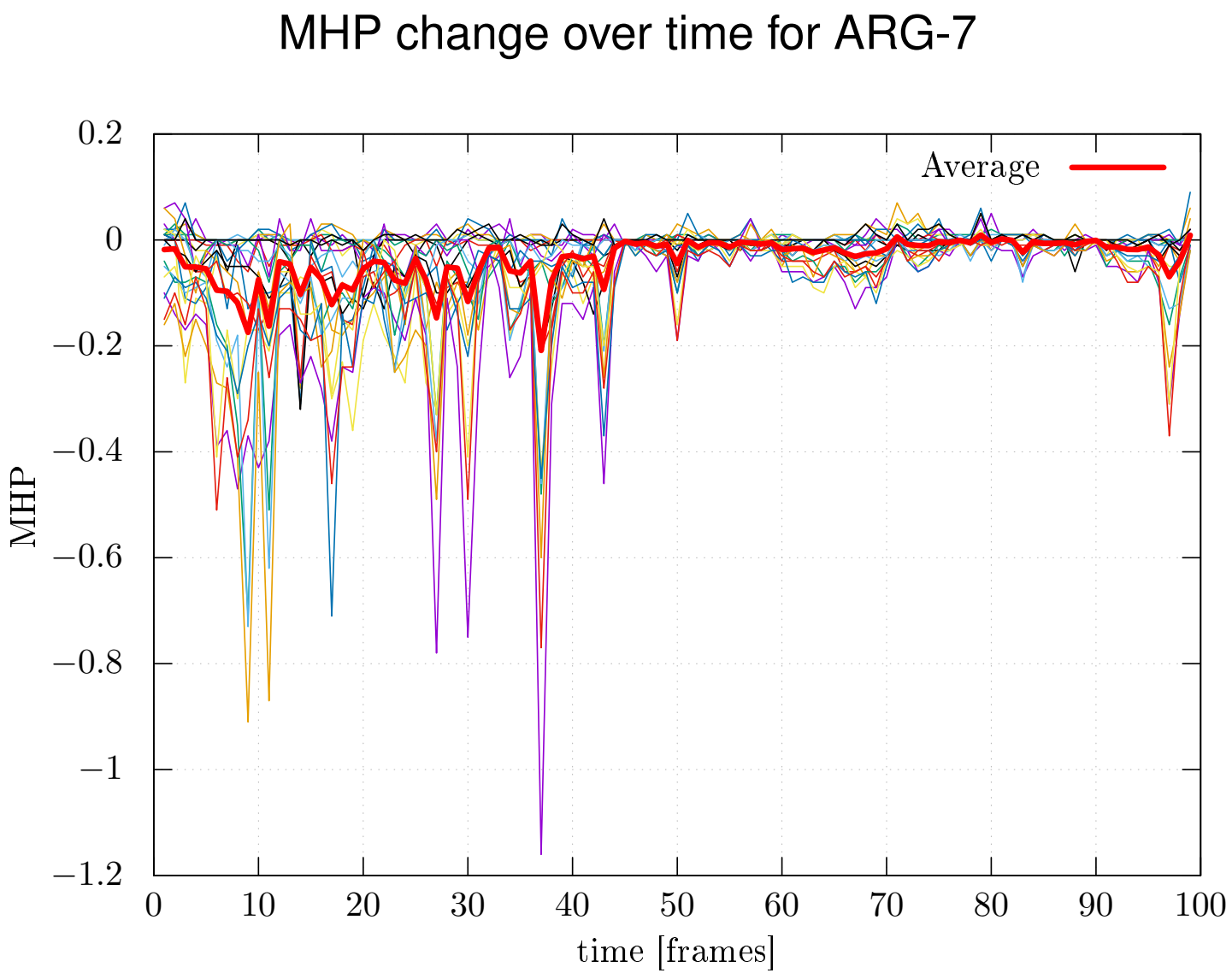
A picture of the system

MHP Change Over Time



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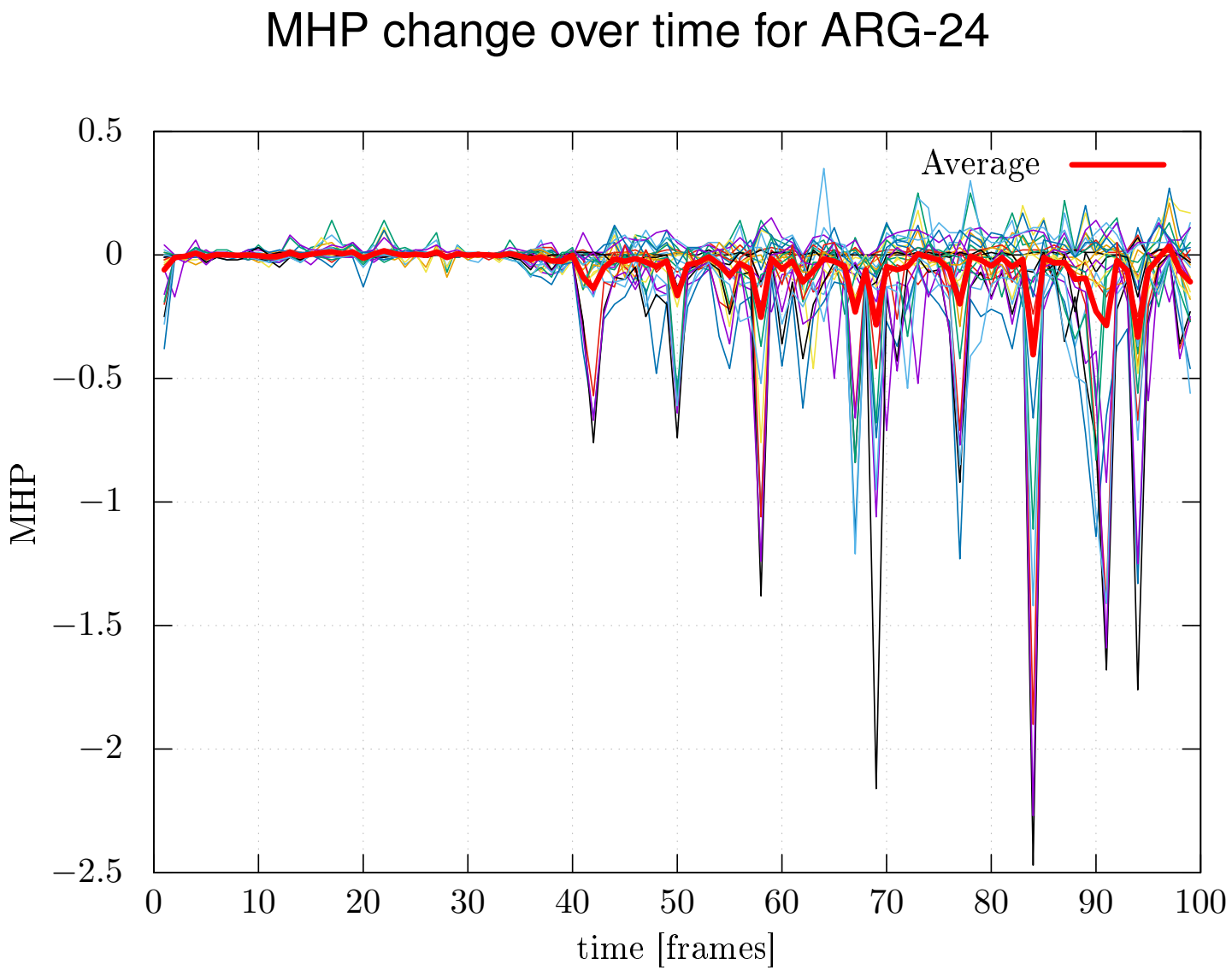

MHP Change Over Time