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

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Molecular Hydrophobicity Potential

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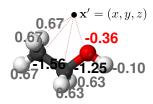
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$$\mathsf{MHP}\left(\mathbf{x}'\right) = \sum_{i=1}^{k} \left[f_i \cdot D\left(\mathbf{x} - \mathbf{x}'_i\right) \right]$$

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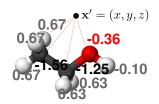
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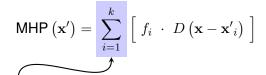
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Summing over all atoms

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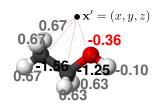
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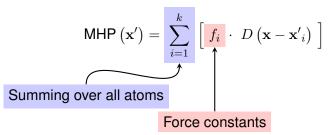
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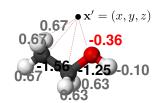
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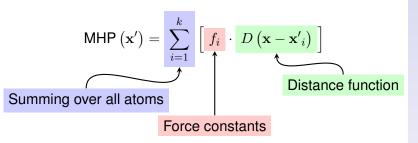
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Carbon atom contribution to hydrophobicity¹

| Type | Description | f_i value |
|------|--------------------|-------------|
| | Carbon in: | |
| 1 | $\mathrm{CH_{3}R}$ | -1.5603 |
| 3 | CHR_3 | -0.6681 |
| 7 | CH_2X_2 | -1.0305 |
| 13 | RCX_3 | 0.7894 |
| 17 | $=CR_2$ | 0.0383 |
| 24 | RCHR | -0.3251 |
| 25 | RCRR | 0.1492 |
| 26 | RCXR | 0.1539 |

¹Source: Ghose et al, J. Phys. Chem. A 1998, 102, 3762-3772

Force Constants - Hydrogen

Hydrogen atom contribution to hydrophobicity²

| Type | Description | f_i value |
|------|---|-------------|
| | Hydrogen attached to: | |
| 46 | $\overline{\mathrm{C_{sp^3}}$, no X in $lpha$ | 0.7341 |
| 47 | $ m C_{sp}^2$ | 0.6301 |
| 50 | X | -0.1036 |
| 52 | $\mathrm{C}_{\mathrm{sp}^3}$, 1 X in $lpha$ | 0.6666 |
| 54 | C_{sp^3} , 3 X in $lpha$ | 0.6338 |

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

Force Constants - Oxygen

Oxygen atom contribution to hydrophobicity³

| 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 |

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

Force Constants - Various

Various atom contribution to hydrophobicity4

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

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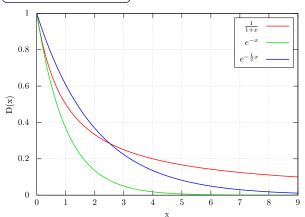
⁴Source: Ghose et al, J. Phys. Chem. A 1998, 102, 3762-3772

Audry form

Exponential decay form

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

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



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Solvent accesible surface

The surface around a molecule accesible to solvent molecules Molecular Hydrophobicity Potential

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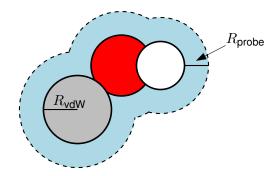
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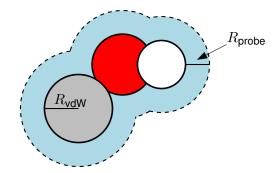
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Evenly distributed point

 The surface around a molecule accesible to solvent molecules



For water molecules usually $r=1.4~\c|\mbox{\AA}\c|$



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Take all atoms with their vdW-radii

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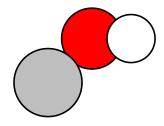
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1. Take all atoms with their vdW-radii

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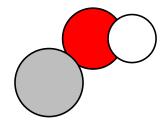
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- 1. Take all atoms with their vdW-radii
- 2. Create spheres around all atoms with $R^i = R^i_{\text{vdw}} + R_{\text{probe}}$

Molecular Hydrophobicity Potential

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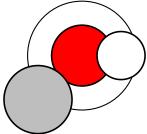
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- 1. Take all atoms with their vdW-radii
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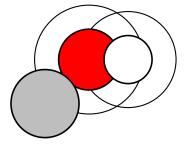
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- 1. Take all atoms with their vdW-radii
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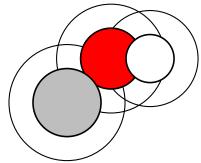
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- 1. Take all atoms with their vdW-radii
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$$R^i = R^i_{\text{vdw}} + R_{\text{probe}}$$

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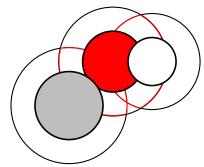
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- 1. Take all atoms with their vdW-radii
- 2. Create spheres around all atoms with $R^i = R^i_{\text{vdw}} + R_{\text{probe}}$
- 3. Delete all points that are "burried" in other extended spheres (i.e. $\Delta(p^i, c^j) \leq R^j + R_{\text{probe}}$)

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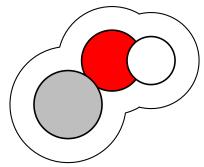
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- 1. Take all atoms with their vdW-radii
- 2. Create spheres around all atoms with $R^i = R^i_{\text{vdw}} + R_{\text{probe}}$
- 3. Delete all points that are "burried" in other extended spheres (i.e. $\Delta\left(p^i,c^j\right)\leq R^j+R_{\text{probe}}$)
- The remaining surface is the solvent-accesible surface of the molecule

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Molecular Hydrophobicity Potential

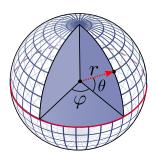
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How to distribute N points on a surface of a sphere?



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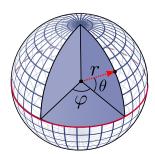
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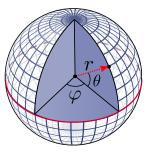
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How to distribute N points on a surface of a sphere?

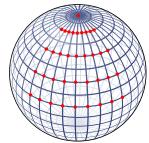


$$\varphi_i = i \cdot \frac{2\pi}{N}$$
$$\theta_j = j \cdot \frac{\pi}{N}$$

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



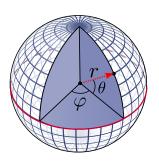




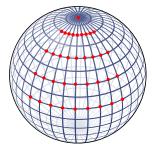
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How to distribute N points on a surface of a sphere?

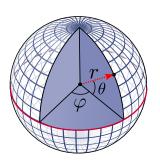




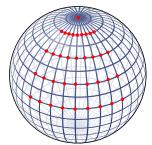


 $\varphi_i = i \cdot \frac{2\pi}{N}$ $\theta_j = j \cdot \frac{\pi}{N}$

Points are not evenly distributed How to distribute N points on a surface of a sphere?







- $\varphi_i = i \cdot \frac{2\pi}{N}$ $\theta_j = j \cdot \frac{\pi}{N}$

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

Solution: Vogel's method

In 2 dimensions:

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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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Solution: Vogel's method

In 2 dimensions:

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Solution: Vogel's method

In 2 dimensions:

- ▶ Distances: $r_i = \sqrt{\frac{i}{N}}$
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In 3 dimensions (cylindrical coordinates):

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In 2 dimensions:

▶ Distances:
$$r_i = \sqrt{\frac{i}{N}}$$

• Angle:
$$\theta_i = \varphi i$$

(φ is the golden ratio!)

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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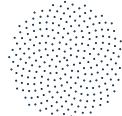
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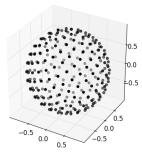
In 2 dimensions:

- ▶ Distances: $r_i = \sqrt{\frac{i}{N}}$
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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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Integration

Each atom's total surface area:

$$V^a = 4\pi \left(R_{\text{vdW}}^a + R_{\text{probe}} \right)^2$$

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Integration

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 $V^a = 4\pi \left(R_{\text{vdW}}^a + R_{\text{probe}}\right)^2$

▶ The surface is represented by *N* points

► Each atom's total surface area:

 $V^a = 4\pi \left(R_{\text{vdW}}^a + R_{\text{probe}}\right)^2$

lacktriangle The surface is represented by N points

▶ Meaning: each point has $V_j^a = \frac{4\pi}{N} \left(R_{\text{vdW}}^i + R_{\text{probe}} \right)^2$

► Each atom's total surface area:

$$V^a = 4\pi \left(R_{\text{vdW}}^a + R_{\text{probe}} \right)^2$$

- lacktriangle The surface is represented by N points
- ▶ Meaning: each point has $V_j^a = \frac{4\pi}{N} \left(R_{\text{vdW}}^i + R_{\text{probe}} \right)^2$
- ▶ In addition, each point has: MHP_j^a

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

▶ The surface is represented by N points

In addition, each point has: MHP^a_i

Therefore, each atom has a total MHP of:

▶ Meaning: each point has $V_j^a = \frac{4\pi}{N} \left(R_{\text{vdW}}^i + R_{\text{probe}} \right)^2$

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