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

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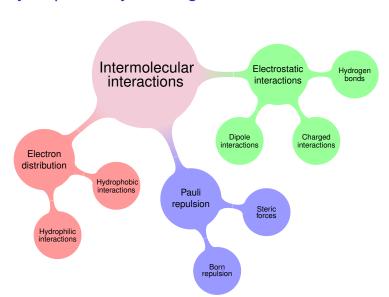
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Hydrophobicity and log P



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Hydrophobicity and log P

Hydrophilic/Hydrophobic Interactions

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Hydrophobicity and log P

Definition

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

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Definition

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

Commonly used: water and octanol

Molecular Hydrophobicity Potential

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Definition

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

- Commonly used: water and octanol
- Can be measured at an ionized or unionized state

Molecular Hydrophobicity Potential

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Molecular Hydrophobicity Potential

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Definition

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

- Commonly used: water and octanol
- Can be measured at an ionized or unionized state

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

ightharpoonup Hydrophobicity increases with the (common) $\log P$

Molecular Hydrophobicity Potential

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What is Molecular Hydrophobicity Potential (MHP)?

▶ By measuring the log P of many (ca. 30,000) compounds¹, single atoms can be assigned local "force" values.

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

What is Molecular Hydrophobicity Potential (MHP)?

- ▶ By measuring the log *P* of many (ca. 30,000) compounds¹, single atoms can be assigned local "force" values.
- Combining these values with a distance-depended decay function, a potential can be constructed.

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¹Ghose et al, J. Phys. Chem. A 1998, 102, 3762-3772 ← ■ → → → → →

What is Molecular Hydrophobicity Potential (MHP)?

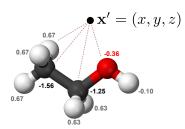
- ▶ By measuring the $\log P$ of many (ca. 30,000) compounds¹, single atoms can be assigned local "force" values.
- Combining these values with a distance-depended decay function, a potential can be constructed.
- ightharpoonup This potential predicts the local $\log P$ behaviour of fragments of a molecule.

Molecular Hydrophobicity Potential

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What is it?

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



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

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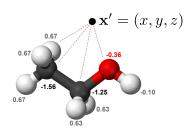
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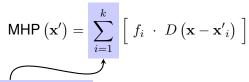
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Summing over all atoms

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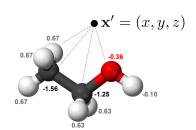
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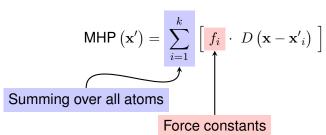
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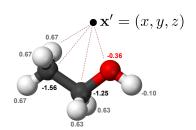


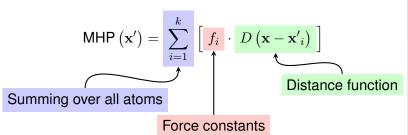
Molecular Hydrophobicity Potential

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General form







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Force Constants - Carbon

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Carbon atom contribution to hydrophobicity²

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

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

Force Constants - Hydrogen

Hydrogen atom contribution to hydrophobicity³

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	Heteroatom X	-0.1036
52	$\mathrm{C}_{\mathrm{sp}^3}$, 1 X in $lpha$	0.6666
54	$C_{\rm sp^3}$, 3 X in $lpha$	0.6338

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



Force Constants - Oxygen

Oxygen atom contribution to hydrophobicity⁴

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



Force Constants - Various

Various atom contribution to hydrophobicity⁵

Type	Description	f_i value
66	N in Primary amine	-0.5427
67	N in 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 in PR ₃ (phosphine)	-0.7941

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Force Constants

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



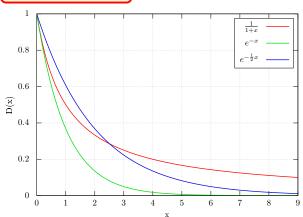
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Exponential decay form

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

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



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Solvent Accesible Surface

The surface around a molecule accesible to solvent molecules

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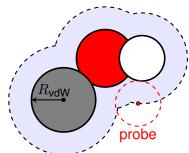
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Solvent Accesible Surface

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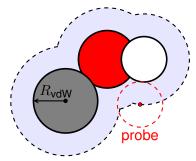
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Solvent Accesible Surface

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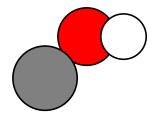
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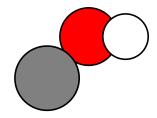
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- 1. Take all atoms with their vdW-radii
- 2. Create spheres around all atoms with $R^i = R^i_{\text{vdw}} + R_{\text{probe}}$

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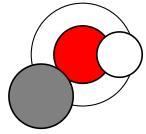
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- 1. Take all atoms with their vdW-radii
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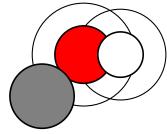
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- 1. Take all atoms with their vdW-radii
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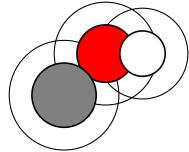
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- Take all atoms with their vdW-radii
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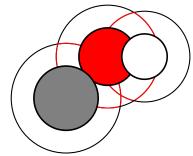
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- 1. Take all atoms with their vdW-radii
- 2. Create spheres around all atoms with $R^i = R^i_{
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 m probe}$
- 3. Delete all points that are "burried" in other extended spheres (i.e. $\Delta(p^i, c^j)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

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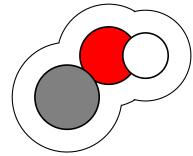
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- 1. Take all atoms with their vdW-radii
- 2. Create spheres around all atoms with $R^i = R^i_{\text{vdw}} + R_{\text{probe}}$
- 3. Delete all points that are "burried" in other extended spheres (i.e. $\Delta(p^i, c^j) \leq R^j + R_{\text{probe}}$)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

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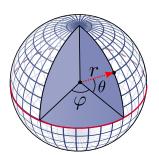
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Evenly Distributed Points

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



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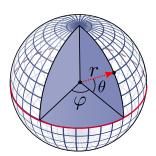
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Evenly Distributed Points

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



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

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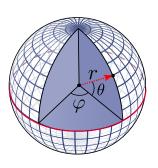
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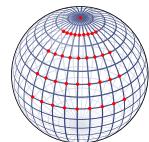
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Evenly Distributed Points

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







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

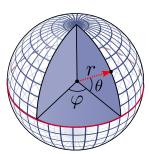
$$\theta_j = j \cdot \frac{\pi}{N}$$

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Evenly Distributed Points

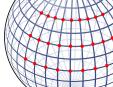
How to distribute N points on a surface of a sphere?





$$\theta_j = j \cdot \frac{\pi}{N}$$





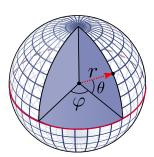
Points are not evenly distributed

Molecular Hydrophobicity Potential

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Evenly Distributed Points

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

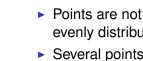


$$\varphi_i = i \cdot \frac{2\pi}{N}$$

$$\theta_j = j \cdot \frac{\pi}{N}$$







Several points overlap at poles

evenly distributed

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Evenly Distributed Points

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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In 2 dimensions:

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In 3 dimensions (cylindrical coordinates):

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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!)

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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Solution: Vogel's method

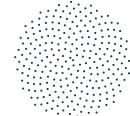
In 2 dimensions:

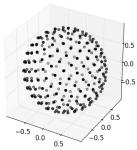
▶ Distances:
$$r_i = \sqrt{\frac{i}{N}}$$

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





0.5 Image source: Marmakoide's Blog

Molecular Hydrophobicity Potential

Pelg Bar Sapir

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

$$V^a = 4\pi \left(R_{
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Molecular Hydrophobicity Potential

Pelg Bar Sapir

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

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

▶ The surface is represented by N points

Molecular Hydrophobicity Potential

Pelg Bar Sapir

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

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

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

Molecular Hydrophobicity Potential

Pelg Bar Sapir

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

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

- ▶ 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^a_i

Molecular Hydrophobicity Potential

Pelg Bar Sapir



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

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

- ▶ 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^a_i

Therefore, each atom has a total MHP of:

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

Molecular Hydrophobicity Potential

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Written in Python3, utylizing ProDy

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- Written in Python3, utylizing ProDy
- Heavy calculation written in Cython

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- Written in Python3, utylizing ProDy
- Heavy calculation written in Cython
- Uses neighbor cells implementation for faster calculation

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References



- Written in Python3, utylizing ProDy
- Heavy calculation written in Cython
- Uses neighbor cells implementation for faster calculation
- ▶ Uses PSF, PDB and DCD files

Molecular Hydrophobicity Potential

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References



- Written in Python3, utylizing ProDy
- Heavy calculation written in Cython
- Uses neighbor cells implementation for faster calculation
- Uses PSF, PDB and DCD files
- Generates a PDB output, MHP values in beta column

Molecular Hydrophobicity Potential

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► Input: PSF + PDB or DCD

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- Input: PSF + PDB or DCD
- Subselection (optional): Atomic selection (like vmd)

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- ► Input: PSF + PDB or DCD
- Subselection (optional): Atomic selection (like vmd)
- ▶ Number of points per atom (default: 64)

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References



- ► Input: PSF + PDB or DCD
- Subselection (optional): Atomic selection (like vmd)
- ▶ Number of points per atom (default: 64)
- ► Solvent probe radius (defalt: 1.4Å)

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References



- ► Input: PSF + PDB or DCD
- Subselection (optional): Atomic selection (like vmd)
- Number of points per atom (default: 64)
- ► Solvent probe radius (defalt: 1.4Å)
- ► Cutoff distance for distance function (default: 4Å)

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- ► Input: PSF + PDB or DCD
- Subselection (optional): Atomic selection (like vmd)
- ▶ Number of points per atom (default: 64)
- ► Solvent probe radius (defalt: 1.4Å)
- ► Cutoff distance for distance function (default: 4Å)
- ► Frame range (if DCD)

Molecular Hydrophobicity Potential

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▶ By integrating and comparing to known $\log P$ values, a correlation can be measured.

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References



- ▶ By integrating and comparing to known $\log P$ values, a correlation can be measured.
- A groups of amino acids of varying hydrophobicity where simulated and their MHP calculated

Molecular Hydrophobicity Potential

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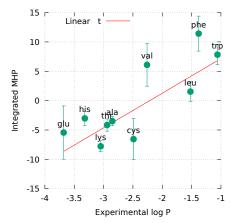
Validation via Known log p Values

7 til Example Oyl

References

Thankyou

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

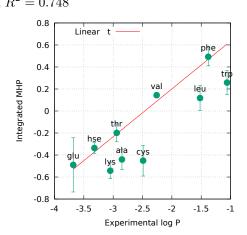


⁶MD simulation using NAMD, performed by Dr Tillmann Utesch ∽ac

Hydrophobicity Potential Pelg Bar Sapir

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



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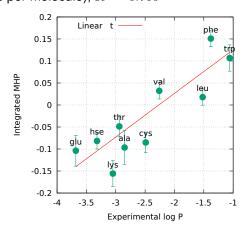
References

Hydrophobicity Potential Pelg Bar Sapir

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



Molecular Hydrophobicity Potential

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- The validation shows a reasonable qualitative correlation to real data.
- Performed in water (with structural optimization), the results became more accurate.

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- The validation shows a reasonable qualitative correlation to real data.
- Performed in water (with structural optimization), the results became more accurate.
- ► The environment did not match experiments, which could affect the accuracy.

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- The validation shows a reasonable qualitative correlation to real data.
- Performed in water (with structural optimization), the results became more accurate.
- ► The environment did not match experiments, which could affect the accuracy.
- Amino acids are small molecules, each error becomes more significant.

Molecular Hydrophobicity Potential

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Molecular Hydrophobicity Potential

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An Example System

An existing trajectory (100 frames) of a protein-membrane system⁷ was analazyed.

The peptide: OP-145, a Cathelicidin derivative with improved properties.

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An Example System

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Trajectory provided by Dr. Alejandra de Miguel Catalina

An Example System

An existing trajectory (100 frames) of a protein-membrane system⁷ was analazyed.

- ► The peptide: OP-145, a Cathelicidin derivative with improved properties.
- ► The interaction mechanism pathway was studied by means of all-atom simulation.

Molecular Hydrophobicity Potential

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⁷Trajectory provided by Dr. Alejandra de Miguel Catalina

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An Example System

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Γhankyou

An existing trajectory (100 frames) of a protein-membrane system⁷ was analazyed.

- ► The peptide: OP-145, a Cathelicidin derivative with improved properties.
- The interaction mechanism pathway was studied by means of all-atom simulation.
- The membrane used for the study consists of a mixture of two lipids, PG and PE, in agreement with experimental measurements.

⁷Trajectory provided by Dr. Alejandra de Miguel Catalina → → → → → →

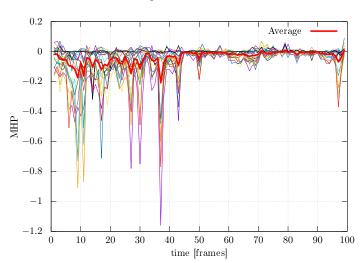
A video of the system

Molecular Hydrophobicity Potential

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An Example System

MHP change over time for ARG-7



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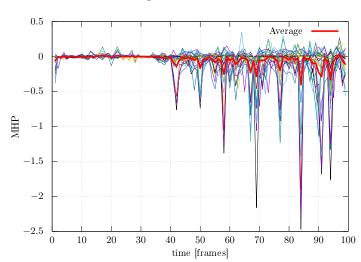
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MHP change over time for ARG-24



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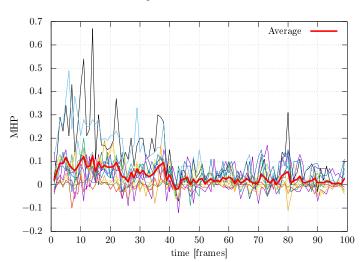
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MHP change over time for PRO-22



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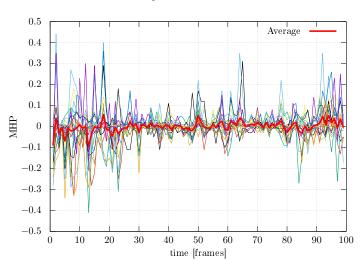
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MHP change over time for LYS-3



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- The validation shows a reasonable qualitative correlation to real data.
- Performed in water (with structural optimization), the results became more accurate.

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- The validation shows a reasonable qualitative correlation to real data.
- Performed in water (with structural optimization), the results became more accurate.
- ► The environment did not match experiments, which could affect the accuracy.

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- The validation shows a reasonable qualitative correlation to real data.
- Performed in water (with structural optimization), the results became more accurate.
- ► The environment did not match experiments, which could affect the accuracy.
- Amino acids are small molecules, each error becomes more significant.

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- The validation shows a reasonable qualitative correlation to real data.
- Performed in water (with structural optimization), the results became more accurate.
- ► The environment did not match experiments, which could affect the accuracy.
- Amino acids are small molecules, each error becomes more significant.
- Larger trajectories will sample conformational space better.

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