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

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### Molecular Hydrophobicity Potential

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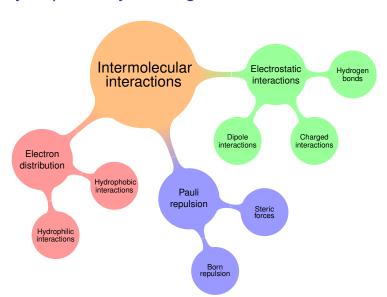
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# Hydrophobicity and log P



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# 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

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### Definition

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- Can be measured at an ionized or unionized state

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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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<sup>&</sup>lt;sup>1</sup>Ghose 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) compounds<sup>1</sup>, 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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<sup>&</sup>lt;sup>1</sup>Ghose et al, J. Phys. Chem. A 1998, 102, 3762-3772 ← ■ → → → → →

# What is Molecular Hydrophobicity Potential (MHP)?

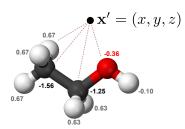
- ▶ By measuring the  $\log P$  of many (ca. 30,000) compounds<sup>1</sup>, single atoms can be assigned local "force" values.
- Combining these values with a distance-depended decay function, a potential can be constructed.
- ightharpoonup This potential predicts the local  $\log P$  behaviour of fragments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

Molecular Hydrophobicity Potential

Pelg Bar Sapir

What is it?

<sup>&</sup>lt;sup>1</sup>Ghose 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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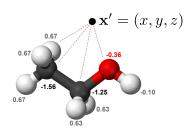
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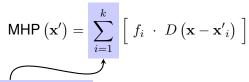
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Summing over all atoms

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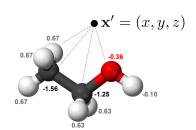
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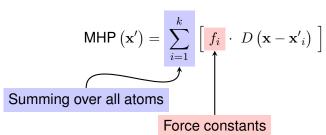
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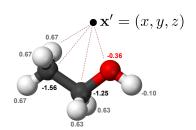


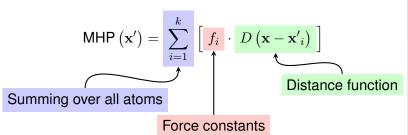
### Molecular Hydrophobicity Potential

### Pelg Bar Sapir

### General form







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# Force Constants - Carbon

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# **Carbon** atom contribution to hydrophobicity<sup>2</sup>

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

<sup>&</sup>lt;sup>2</sup>Source: Ghose et al, J. Phys. Chem. A 1998, 102, 3762-3772

# Force Constants - Hydrogen

# **Hydrogen** atom contribution to hydrophobicity<sup>3</sup>

Type	Description	$f_i$ value
	Hydrogen attached to:	
46	$\overline{\mathrm{C_{sp^3}}$ , no $\mathrm{X}$ 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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<sup>&</sup>lt;sup>3</sup>Source: Ghose et al, J. Phys. Chem. A 1998, 102, 3762-3772



# Force Constants - Oxygen

# **Oxygen** atom contribution to hydrophobicity<sup>4</sup>

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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<sup>&</sup>lt;sup>4</sup>Source: Ghose et al, J. Phys. Chem. A 1998, 102, 3762-3772



## Force Constants - Various

# **Various** atom contribution to hydrophobicity<sup>5</sup>

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

### Molecular Hydrophobicity Potential

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Force Constants

<sup>&</sup>lt;sup>5</sup>Source: Ghose et al, J. Phys. Chem. A 1998, 102, 3762-3772



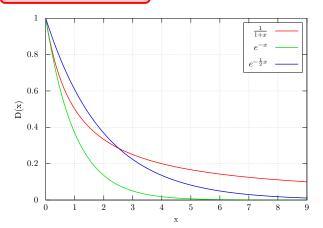
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# Audry form

# 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

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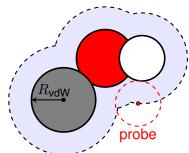
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# Solvent Accesible Surface

The surface around a molecule accesible to solvent molecules



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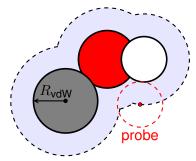
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# Solvent Accesible Surface

 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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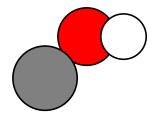
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Take all atoms with their vdW-radii

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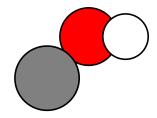
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- Take all atoms with their vdW-radii
- 2. Create spheres around all atoms with  $R^i = R^i_{\text{vdw}} + R_{\text{probe}}$

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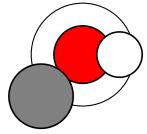
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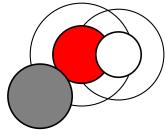
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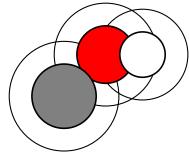
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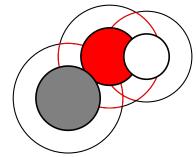
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- Take all atoms with their vdW-radii
- 2. Create spheres around all atoms with  $R^i = R^i_{\text{vdw}} + R_{\text{probe}}$
- 3. Delete all points that are "burried" in other extended spheres (i.e.  $\Delta(p^i, c^j) \leq R^j + R_{\text{probe}}$ )

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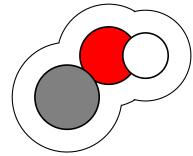
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- 1. Take all atoms with their vdW-radii
- 2. Create spheres around all atoms with  $R^i = R^i_{\text{vdw}} + R_{\text{probe}}$
- 3. Delete all points that are "burried" in other extended spheres (i.e.  $\Delta(p^i, c^j) \leq R^j + R_{\text{probe}}$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

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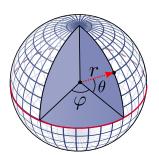
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# **Evenly Distributed Points**

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



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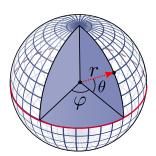
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# **Evenly Distributed Points**

## 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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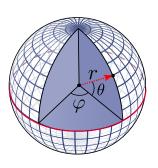
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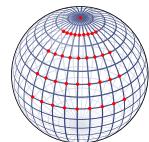
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# **Evenly Distributed Points**

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







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

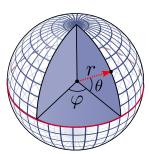
$$\theta_j = j \cdot \frac{\pi}{N}$$

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**Evenly Distributed Points** 

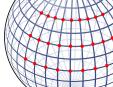
How to distribute N points on a surface of a sphere?





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





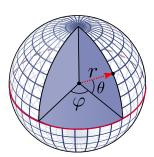
Points are not evenly distributed

Molecular Hydrophobicity Potential

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**Evenly Distributed Points** 

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

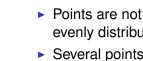


$$\varphi_i = i \cdot \frac{2\pi}{N}$$

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







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:  $\theta_i = \varphi i$ 

( $\varphi$  is the golden ratio!)

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Solution: Vogel's method

### In 2 dimensions:

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

• Angle:  $\theta_i = \varphi i$ ( $\varphi$  is the golden ratio!)

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Solution: Vogel's method

### In 2 dimensions:

- ▶ Distances:  $r_i = \sqrt{\frac{i}{N}}$
- Angle:  $\theta_i = \varphi i$  ( $\varphi$  is the golden ratio!)

In 3 dimensions (cylindrical coordinates):

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Solution: Vogel's method

### In 2 dimensions:

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

Solution: Vogel's method

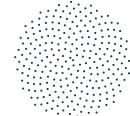
### In 2 dimensions:

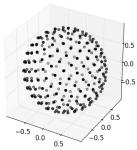
▶ Distances: 
$$r_i = \sqrt{\frac{i}{N}}$$

• Angle:  $\theta_i = \varphi i$ ( $\varphi$  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

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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

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

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

▶ 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<sup>a</sup><sub>i</sub>

#### 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<sup>a</sup><sub>i</sub>

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

### Pelg Bar Sapir

Written in Python3, utylizing ProDy

#### Molecular Hydrophobicity Potential

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

#### Molecular Hydrophobicity Potential

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

#### 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

#### 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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#### References



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

#### Molecular Hydrophobicity Potential

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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)

#### Molecular Hydrophobicity Potential

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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)

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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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- ▶ 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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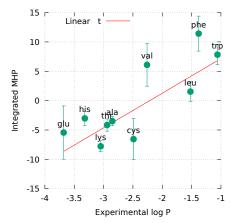
Validation via Known log p Values

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Thankyou

## Validation in vacuum (5 frames per molecule)<sup>6</sup>, $R^2 = 0.668$

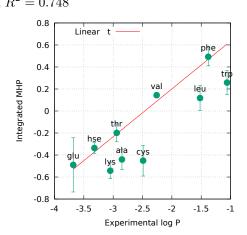


<sup>&</sup>lt;sup>6</sup>MD simulation using NAMD, performed by Dr Tillmann Utesch ∽ac

### 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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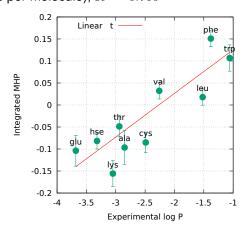
#### References

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.

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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.

#### 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.
- ► 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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- The validation shows a reasonable qualitative correlation to real data.
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- ► The environment did not match experiments, which could affect the accuracy.
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# An Example System

An existing trajectory (100 frames) of a protein-membrane system<sup>7</sup> was analazyed.

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

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### An Example System

References

Trajectory provided by Dr. Alejandra de Miguel Catalina

# An Example System

An existing trajectory (100 frames) of a protein-membrane system<sup>7</sup> was analazyed.

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

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<sup>&</sup>lt;sup>7</sup>Trajectory provided by Dr. Alejandra de Miguel Catalina

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Γhankyou

An existing trajectory (100 frames) of a protein-membrane system<sup>7</sup> 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.

<sup>&</sup>lt;sup>7</sup>Trajectory provided by Dr. Alejandra de Miguel Catalina → → → → → →

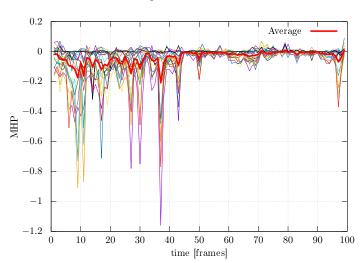
# A video of the system

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An Example System

## MHP change over time for ARG-7



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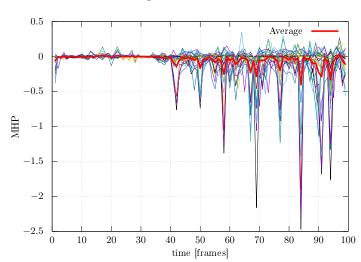
#### Result

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## MHP change over time for ARG-24



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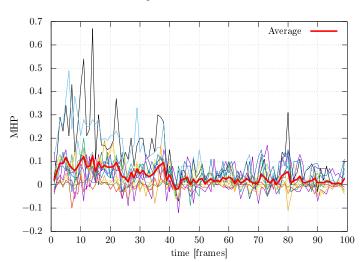
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## MHP change over time for PRO-22



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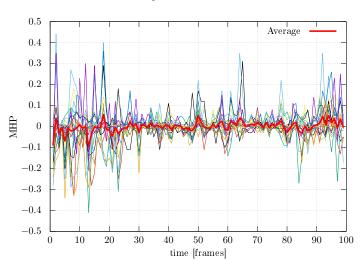
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## MHP change over time for LYS-3



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The validation shows a reasonable qualitative correlation to real data.

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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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- 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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## Thank You for Your Attention!

Molecular Hydrophobicity Potential

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