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

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Molecular Hydrophobicity Potential

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Hydrophobicity and log P Partition Coefficient

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What is it?

General form

General Ionii

Distance function

Surface

Solvent Accesible Surface Evenly Distributed Points

Progra

What are we interested in

Result

Validation via Known log p

References

Outline

Introduction

Hydrophobicity and log P Partition Coefficient

Molecular Hydrophobicity Potential

What is it? Potential Surface

Program

What are we interested in? Program Specifications

Results

Validation via Known log p Values An Example System

Molecular Hydrophobicity Potential

Pelg Bar Sapir

troduction

Hydrophobicity and log P Partition Coefficient

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Potential

General form

Distance fund

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Result

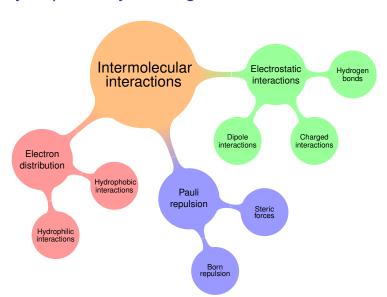
Validation via Known log p Values

All Example

References



Hydrophobicity and log P



Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P

Partition Coefficient

Molecular

Potential

otential

General form

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Solvent Accesible Surface Evenly Distributed Points

Program

What are we interested in?

Result

Validation via Known log p Values

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References

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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

Molecular Hydrophobicity Potential

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Introduction

vdrophobicity and log P

Partition Coefficient

Molecular

Molecular Hydrophobic Potential

What is it?

Potential

General form

Force Constants

urface

Solvent Accesible Surface Evenly Distributed Points

Progran

Vhat are we interested in?

Results

Validation via Known log p Values

References

Thankvou



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.

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

Molecular Hydrophobicity Potential

What is it?

Potential

General form

Distance fu

urface

Solvent Accesible Surface Evenly Distributed Points Integration

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/hat are we interested in? rogram Specifications

Results

Validation via Known log p Values

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References

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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.

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

> Molecular Hydrophobicity

What is it?

Potential

General form Force Constants

Distance iu Jurface

Solvent Accesible Surface Evenly Distributed Points

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Results

Validation via Known log p Values

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What is Molecular Hydrophobicity Potential (MHP)?

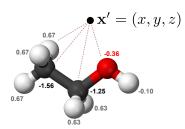
- ▶ By measuring the $\log P$ of many (ca. 30,000) compounds¹, single atoms can be assigned local "force" values.
- Combining these values with a distance-depended decay function, a potential can be constructed.
- ightharpoonup This potential predicts the local $\log P$ behaviour of fragments of a molecule.

Molecular Hydrophobicity Potential

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What is it?

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



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

Molecular Hydrophobicity Potential

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Introduction

Hydrophobicity and log F Partition Coefficient

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What is it?

General form

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Solvent Accesible Surface Evenly Distributed Points

Evenly Distributed Points Integration

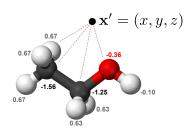
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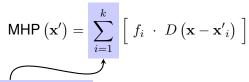
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Validation via Known log p Values

References





Summing over all atoms

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log F Partition Coefficient

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What is it?

General form

Force Constants

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Solvent Accesible Surface Evenly Distributed Points

Evenly Distributed Points Integration

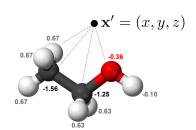
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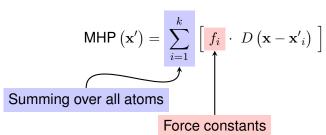
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Validation via Known log Values

References



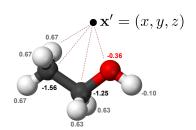


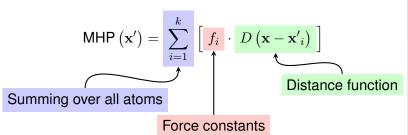
Molecular Hydrophobicity Potential

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General form







Molecular Hydrophobicity Potential

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Introduction

Hydrophobicity and log F Partition Coefficient

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What is it?

Potential

General form

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Distance fun

Surface

Solvent Accesible Surface Evenly Distributed Points Integration

Progran

Vhat are we interested in? Program Specifications

Results

Validation via Known log p Values

Reference

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Force Constants - Carbon

Molecular Hydrophobicity Potential

Pelg Bar Sapir

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Hydrophobicity and log P Partition Coefficient

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General form Force Constants

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Surface

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Results

Validation via Known log p Values

References

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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

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

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General form
Force Constants

Constants

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Solvent Accesible Surfa Evenly Distributed Point Integration

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Result

Validation via Known log p Values

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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

Molecular Hydrophobicity Potential

Pelg Bar Sapir

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Hydrophobicity and log P Partition Coefficient

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Force Constants

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Solvent Accesible Surfa Evenly Distributed Point Integration

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Validation via Known log p Values

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References

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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



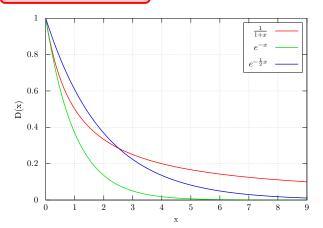
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Exponential decay form

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

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



Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

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otential General form

Force Constants

Distance function

Surface

Solvent Accesible Surface Evenly Distributed Points Integration

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Validation via Known log p Values

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Reference

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Solvent Accesible Surface

The surface around a molecule accesible to solvent molecules

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

Molecular Hydrophobi

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/hat is it?

Potential

General form

Force Constants

Distance function

Surface

Solvent Accesible Surface

Evenly Distributed Points Integration

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What are we interested in? Program Specifications

Results

Validation via Known log p Values

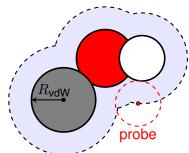
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References



Solvent Accesible Surface

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Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

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What is it?

Potential

General form

Force Constants

Distance function

Solvent Accesible Surface

Evenly Distributed Points

Program

What are we interested in Program Specifications

Result

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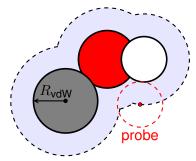
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Solvent Accesible Surface

 The surface around a molecule accesible to solvent molecules



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

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P

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Potential
General form

Force Constants

Surface

Solvent Accesible Surface

Evenly Distributed Points Integration

Progra

What are we interested in Program Specifications

Result

Validation via Known log p Values

An Example

Reference

Thankvou



Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

Molecular Hydrophobicity Potential

What is it?

Potential

General form

Force Constants

Surface

Solvent Accesible Surface

Evenly Distributed Points

Progran

What are we interested in? Program Specifications

Resul

Validation via Known log Values

References



Take all atoms with their vdW-radii

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

Molecular Hydrophobicity

What is it?

Potential

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Force Constants

Distance func

Solvent Accesible Surface

Evenly Distributed Points

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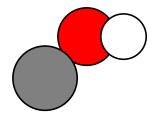
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Molecular Hydrophobicity Potential

Pelg Bar Sapir

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Hydrophobicity and log P Partition Coefficient

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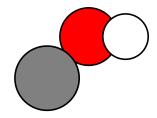
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Result

Validation via Known log p Values

References





- 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

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

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What is it?

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Force Constants

Distance function

Solvent Accesible Surface

Evenly Distributed Points

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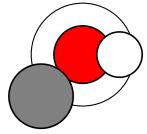
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Validation via Known log

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Molecular Hydrophobicity Potential

Pelg Bar Sapir

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Hydrophobicity and log P Partition Coefficient

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Force Constants

Distance function

Surface

Solvent Accesible Surface

Evenly Distributed Points Integration

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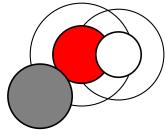
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Validation via Known log p

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Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

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Force Constants

Distance function

Solvent Accesible Surface

Evenly Distributed Points

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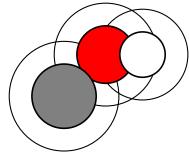
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Validation via Known log p

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Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

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General form

Force Constants

Distance function

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Evenly Distributed Points Integration

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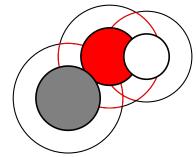
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Validation via Known log p

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References



- 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. $\Delta(p^i, c^j) \leq R^j + R_{\text{probe}}$)

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

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What is it?

General for

Force Constants

Distance function

Solvent Accesible Surface

Evenly Distributed Points

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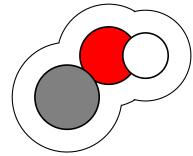
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Result

Validation via Known log p

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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

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

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What is it?

General form

Force Constants
Distance function

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Evenly Distributed Points

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What are we interested in Program Specifications

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Validation via Known log p

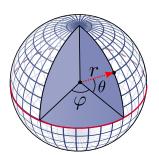
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Evenly Distributed Points

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



Molecular Hydrophobicity Potential

Pelg Bar Sapir

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Hydrophobicity and log F Partition Coefficient

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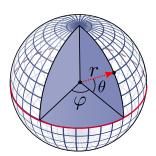
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Evenly Distributed Points

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



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

Molecular Hydrophobicity Potential

Pelg Bar Sapir

troduction

Hydrophobicity and log F Partition Coefficient

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General form

Force Constants

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Solvent Accesible Surface Evenly Distributed Points

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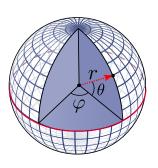
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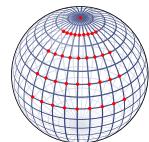
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Evenly Distributed Points

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

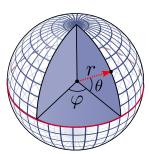
$$\theta_j = j \cdot \frac{\pi}{N}$$

Molecular Hydrophobicity Potential

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Evenly Distributed Points

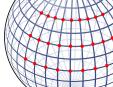
How to distribute N points on a surface of a sphere?





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





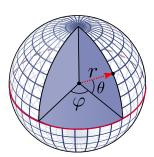
Points are not evenly distributed

Molecular Hydrophobicity Potential

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Evenly Distributed Points

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

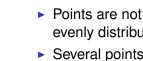


$$\varphi_i = i \cdot \frac{2\pi}{N}$$

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







Several points overlap at poles

evenly distributed

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Evenly Distributed Points

Solution: Vogel's method

In 2 dimensions:

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

> Molecular Hydrophobicity Potential

What is it?
Potential

General f

General form

Distance fund

Surface

Solvent Accesible Surface Evenly Distributed Points

Progra

What are we interested in

Result

Validation via Known log Values

An Example

Reference

Thankvou

Solution: Vogel's method

In 2 dimensions:

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

• Angle: $\theta_i = \varphi i$

(φ is the golden ratio!)

Molecular Hydrophobicity Potential

Pelg Bar Sapir

ntroduction

Hydrophobicity and log F Partition Coefficient

> Molecular Hydrophobicity Potential

What is it?

Potential

General form

Distance fund

Surface

Solvent Accesible Surface Evenly Distributed Points

Prograi

What are we interested in Program Specifications

Result

Validation via Known log | Values

An Example

Reference

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Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

Molecular Hydrophobicity

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Potential

General form

Force Constants

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Solvent Accesible Surface Evenly Distributed Points

Prograi

Vhat are we interested in?

Results

Validation via Known log p Values

An Example

Reference

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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):

Molecular Hydrophobicity Potential

Pelg Bar Sapir

ntroduction

Hydrophobicity and log P Partition Coefficient

Molecular Hydrophobicity

What is it?

Potential

General form

Force Constants

Distance

Surface

Solvent Accesible Surface Evenly Distributed Points

Integration

Progra

/hat are we interested in? rogram Specifications

Results

Validation via Known log p Values

An Example

Reference

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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Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

Molecular lydrophobicity

hat is it?

Potential

General form

Distance fun

Surface

Solvent Accesible Surfac

Evenly Distributed Points Integration

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Validation via Known lo Values

References

Solution: Vogel's method

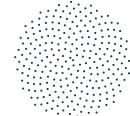
In 2 dimensions:

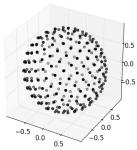
▶ Distances:
$$r_i = \sqrt{\frac{i}{N}}$$

• 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

Introductio

Hydrophobicity and log F Partition Coefficient

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What is it?

General form

Force Constants

Surface

Solvent Accesible Surface
Evenly Distributed Points

Program

What are we interested in Program Specifications

Result

Validation via Known log p Values

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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

Pelg Bar Sapir

Written in Python3, utylizing ProDy

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

Molecular Hydrophobicity Potential

Vhat is it?

Potential

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Distance fund

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Solvent Accesible Surface Evenly Distributed Points Integration

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Program Specifications

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Validation via Known log p

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References



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

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

Molecular lydrophobicity

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What is it?

General form

Force Constants

Distance fun

urface

Solvent Accesible Surface Evenly Distributed Points Integration

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hat are we interested

Program Specifications

Result

Validation via Known log p Values

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References



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

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

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What is it?

Potential

General form

Force Constants

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Solvent Accesible Surface Evenly Distributed Points

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Program Specifications

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Validation via Known log p Values

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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

Pelg Bar Sapir

Introduction

Hydrophobicity and log F Partition Coefficient

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Potential

General form

Force Constants

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Evenly Distributed Points Integration

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Program Specifications

Results

Validation via Known log p Values

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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

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

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General form

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Solvent Accesible Surface Evenly Distributed Points Integration

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Program Specifications

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Validation via Known log p Values

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References



► Input: PSF + PDB or DCD

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log I Partition Coefficient

Molecular Hydrophobicity Potential

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Solvent Accesible Surface Evenly Distributed Points

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What are we interested

Program Specifications

Results

Validation via Known log Values

An Example

References



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

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log F Partition Coefficient

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General form

Force Constants

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Solvent Accesible Surface Evenly Distributed Points

Evenly Distributed Points Integration

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Validation via Known log | Values

An Example

References



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

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

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Potential

General form

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Solvent Accesible Surface Evenly Distributed Points Integration

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Program Specifications

Results

Validation via Known log p Values

An Example

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)

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log F Partition Coefficient

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Force Constants

Distance function

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Solvent Accesible Surface Evenly Distributed Points

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Result

Validation via Known log p Values

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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)

Molecular Hydrophobicity Potential

Pelg Bar Sapir

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Hydrophobicity and log P Partition Coefficient

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General form

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Solvent Accesible Surface Evenly Distributed Points

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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

Pelg Bar Sapir

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Hydrophobicity and log P Partition Coefficient

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What is it?

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General form

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Solvent Accesible Surface Evenly Distributed Points Integration

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Program Specifications

Result

Validation via Known log p

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References

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

Molecular Hydrophobicity Potential

What is i

Potential

General form

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Solvent Accesible Surface Evenly Distributed Points

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What are we interested in

Result

Validation via Known log p Values

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

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

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Solvent Accesible Surface Evenly Distributed Points Integration

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Validation via Known log p Values

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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

Pelg Bar Sapir

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What is it?

General form

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Results

Validation via Known log p

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Hydrophobicity Potential Pelg Bar Sapir

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Hydrophobicity and log P Partition Coefficient

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Evenly Distributed Points Integration

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What are we interested in? Program Specifications

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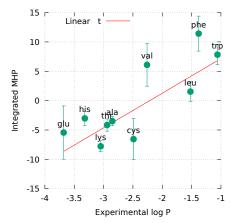
Validation via Known log p Values

7 til Example Oyl

References

Thankyou

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

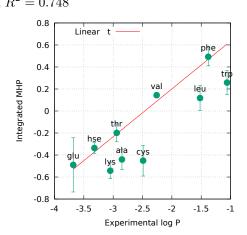


⁶MD simulation using NAMD, performed by Dr Tillmann Utesch ∽ac

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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Hydrophobicity and log P Partition Coefficient

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Solvent Accesible Surface Evenly Distributed Points

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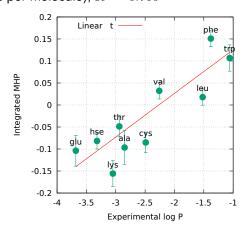
References

Hydrophobicity Potential Pelg Bar Sapir

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Validation via Known log p Values

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



Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

Molecular Hydrophobicity Potential

What is it

Potential

General form

Force Constants

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Surface

Solvent Accesible Surface Evenly Distributed Points

Prograi

What are we interested in? Program Specifications

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Validation via Known log p Values

An Example System

References

The validation shows a reasonable qualitative correlation to real data.

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

Molecular Hydrophobicity Potential

Vhat is it?

Potential

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Distance function

Surface

Solvent Accesible Surface Evenly Distributed Points Integration

Prograi

What are we interested in? Program Specifications

Result

Validation via Known log p Values

An Example Syste

Reference

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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.

Molecular Hydrophobicity Potential

Pelg Bar Sapir

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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

Pelg Bar Sapir

Introduction

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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

Pelg Bar Sapir

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Hydrophobicity and log P Partition Coefficient

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Solvent Accesible Surface Evenly Distributed Points Integration

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References



- 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.

Molecular Hydrophobicity Potential

Pelg Bar Sapir

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Hydrophobicity and log P Partition Coefficient

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What is it?

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General form

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Solvent Accesible Surface Evenly Distributed Points Integration

Prograi

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Results

Validation via Known log p Values

An Example Syste

References



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.

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log F Partition Coefficient

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What is it?

Potential

General form

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Solvent Accesible Surface Evenly Distributed Points Integration

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Vhat are we interested in? Program Specifications

Results

Validation via Known log p Values

An Example System

References

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

Pelg Bar Sapir

Introduction

Hydrophobicity and log F Partition Coefficient

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General form

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Surface

Solvent Accesible Surface Evenly Distributed Points Integration

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Results

Validation via Known log p

An Example System

References

⁷Trajectory provided by Dr. Alejandra de Miguel Catalina

What is it? Potential

General form

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Evenly Distributed Points Integration

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What are we interested in Program Specifications

Result

Validation via Known log p

An Example System

References

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 → → → → → →

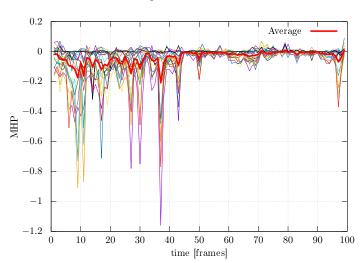
A video of the system

Molecular Hydrophobicity Potential

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An Example System

MHP change over time for ARG-7



Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log F Partition Coefficient

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Solvent Accesible Surface Evenly Distributed Points

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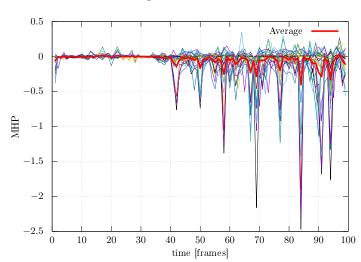
Result

Validation via Known log p

An Example System

Reference

MHP change over time for ARG-24



Molecular Hydrophobicity Potential

Pelg Bar Sapir

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Hydrophobicity and log F Partition Coefficient

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Solvent Accesible Surface Evenly Distributed Points

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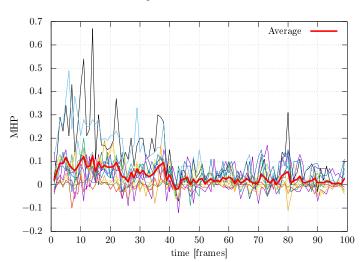
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Validation via Known log p

An Example System

References

MHP change over time for PRO-22



Molecular Hydrophobicity Potential

Pelg Bar Sapir

ntroduction

Hydrophobicity and log F Partition Coefficient

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Solvent Accesible Surface Evenly Distributed Points

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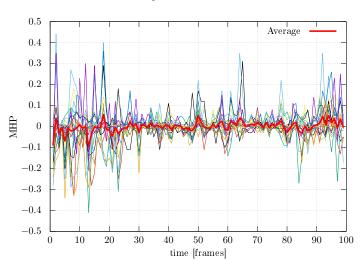
Validation via Known log p

An Example System

References



MHP change over time for LYS-3



Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log F Partition Coefficient

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Vhat is it?

General form

Force Constants

Surface

Solvent Accesible Surface Evenly Distributed Points

Prograi

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Results

Validation via Known log p

An Example System

References



Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

Molecular Hydrophobicity Potential

What is it

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General form

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Solvent Accesible Surface Evenly Distributed Points Integration

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What are we interested in? Program Specifications

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An Example System

References

We again get qualitative correlation to expected results (i.e. interior Hydrophobic).

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log F Partition Coefficient

Molecular Hydrophobici

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Potential

General form

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Solvent Accesible Surfac Evenly Distributed Points Integration

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Results

Validation via Known log p Values

An Example System

References



- We again get qualitative correlation to expected results (i.e. interior Hydrophobic).
- The amino acid residues have the correct hydrophobicity.

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log F Partition Coefficient

Molecular Hydrophob

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Potential

General form

Force Constants

Distance :

Surface

Solvent Accesible Surface Evenly Distributed Points Integration

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hat are we interested in?

Results

Validation via Known log p

An Example System

References

- We again get qualitative correlation to expected results (i.e. interior Hydrophobic).
- The amino acid residues have the correct hydrophobicity.
- Observing changes in MHP of fragments of interest is possible.

Molecular Hydrophobicity Potential

Pelg Bar Sapir

An Example System



- We again get qualitative correlation to expected results (i.e. interior Hydrophobic).
- The amino acid residues have the correct hydrophobicity.
- Observing changes in MHP of fragments of interest is possible.
- More systems could (and should!) be analyzed using this method

Molecular Hydrophobicity Potential

Pelg Bar Sapir

An Example System

References

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

Molecular Hydrophobicity Potential

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Potential

General form

Force Constants

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Surface

Solvent Accesible Surface Evenly Distributed Points

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What are we interested in? Program Specifications

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Validation via Known log p Values

An Example

References



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Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

Molecular Hydrophobicity Potential

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Surface

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What are we interested in? Program Specifications

Results

Validation via Known log p Values

Reference