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

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Molecular Hydrophobicity Potential

Pelg Bar Sapir

ntroduction

Hydrophobicity and log P Partition Coefficient

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What is it?

Potential

General form

Porce Constants

Surface

Solvent Accesible Surface Evenly Distributed Points

Progra

Vhat are we interested in?

Result

Validation via Known log p

An Example

Bibliography

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

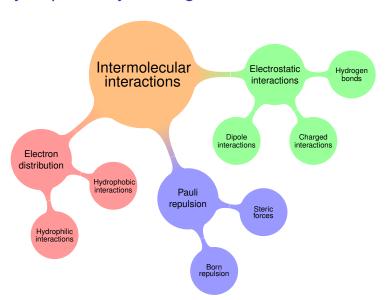
Validation via Known log p Values An Example System

Molecular Hydrophobicity Potential

Pelg Bar Sapir



Hydrophobicity and log P



Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P

Partition Coefficien

Molecular

Potential

hat is it?

General form

General form

Dietance function

urface

Solvent Accesible Surface

Evenly Distributed Poi

Integration

Progran

What are we interested in? Program Specifications

Resul

Validation via Known log p Values

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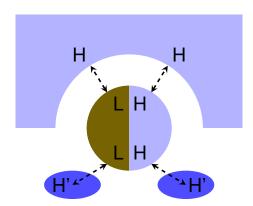
Bibliography

References

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Hydrophilic/Hydrophobic Interactions

In short: like interacts best with like¹.



Molecular Hydrophobicity Potential

Pelg Bar Sapir

ntroduction

Hydrophobicity and log P

Molecular Hydrophobicity

> /hat is it? otential

General form

Force Constants
Distance function

Surface

Evenly Distributed Points Integration

Progran

What are we interested in? Program Specifications

Resul

Validation via Known log p Values

Ribliography

Bibliography

References

Гhankyou

¹Figure based on [1]

Definition

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

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

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

Pelg Bar Sapir



Definition

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Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P

Partition Coefficient

Molecular

Hydrophobic Potential

What is it?

General form

Force Constants

Distance fund

ırface

Solvent Accesible Surface Evenly Distributed Points Integration

Progra

Vhat are we interested in? Program Specifications

Result

Validation via Known log p Values

741 Example O

Bibliography

References



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) compounds[3]

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

> olecular ydrophobicity

What is it?

Potential

General form

Force Constants

urface

Solvent Accesible Surface Evenly Distributed Points Integration

rogram

Vhat are we interested in?

Result

Validation via Known log p Values

An Example

Bibliography

References

What is Molecular Hydrophobicity Potential (MHP)?

- ▶ By measuring the $\log P$ of many (ca. 30,000) compounds[3]
- Combining these values with a distance-depended decay function, a potential can be constructed.

Molecular Hydrophobicity Potential

Pelg Bar Sapir

ntroduction

Hydrophobicity and log P Partition Coefficient

> olecular /drophobicity otential

What is it?

Potential

General form

Distance funct

urface

Solvent Accesible Surface Evenly Distributed Points

rogram

nat are we interested in?

Results

Validation via Known log p Values

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Bibliography

References



What is Molecular Hydrophobicity Potential (MHP)?

- ▶ By measuring the $\log P$ of many (ca. 30,000) compounds[3]
- Combining these values with a distance-depended decay function, a potential can be constructed.
- ▶ This potential predicts the local $\log P$ behaviour of fragments of a molecule.

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 1

Surface

Solvent Accesible Surface Evenly Distributed Points Integration

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nat are we interested in?

Results

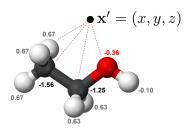
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Bibliography

References





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

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log F Partition Coefficient

Molecular Hydrophobic

What is it?

General form

orce Constants

Distance function

Surface

Solvent Accesible Surface Evenly Distributed Points Integration

Progra

What are we interested in? Program Specifications

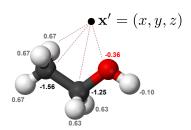
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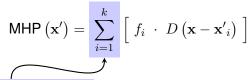
Validation via Known log p Values

Dibliography

Bibliography

References





Summing over all atoms

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log F Partition Coefficient

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/hat is it?

General form

orce Constants

Distance funct

Surface

Evenly Distributed Points Integration

Prograi

Program Specifications

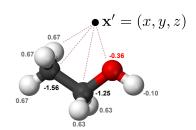
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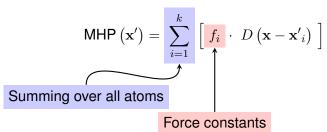
Validation via Known log p Values

Dibliograph

Bibliography

References





Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log F Partition Coefficient

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Vhat is it?

General form

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Distance 1

Surface

Solvent Accesible Surface Evenly Distributed Points Integration

Prograi

What are we interested in: Program Specifications

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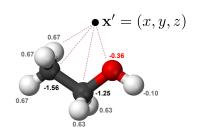
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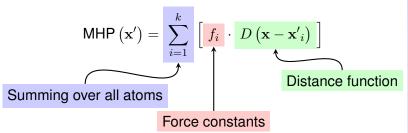
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Bibliograph

References







Molecular Hydrophobicity Potential

Pelg Bar Sapir

General form

Force Constants - Carbon

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Force Constants

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	$C_{\rm sp^2}$	0.6301
50	Heteroatom X	-0.1036
52	$\mathrm{C}_{\mathrm{sp}^3}$, 1 X in $lpha$	0.6666
54	C_{sp^3} , 3 X in $lpha$	0.6338

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

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General form Force Constants

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rface olvent Accesible Surf

Evenly Distributed F Integration

rogram

ogram Specifications

Result

Validation via Known log p Values

ibliography

References

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

Force Constants

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	$P \text{ in } PR_3 \text{ (phosphine)}$	-0.7941

Molecular Hydrophobicity Potential

Pelg Bar Sapir

ntroduction

Hydrophobicity and log P Partition Coefficient

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Force Constants
Distance function

Surface

Solvent Accesible Surface Evenly Distributed Point Integration

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What are we interested in

Result

Validation via Known log p Values

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Bibliography

References

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

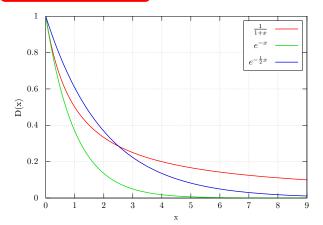
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Audry form

Exponential decay form

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

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



Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

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otential

otential

orce Constants

Distance function

Surface

Solvent Accesible Surface Evenly Distributed Points

Progran

Vhat are we interested in? Program Specifications

Result

Validation via Known log p Values

An Example

Bibliography

References

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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 Hydrophob

Potential

What is it?
Potential

Conoral for

orce Constants

Distance function

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Solvent Accesible Surface

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Progran

What are we interested in? Program Specifications

Results

Validation via Known log p Values

An Example 3

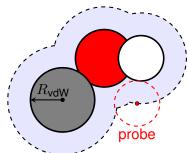
Bibliography

References



Solvent Accesible Surface

The surface around a molecule accesible to solvent molecules



Molecular Hydrophobicity Potential

Pelg Bar Sapir

ntroduction

Hydrophobicity and log P Partition Coefficient

Molecular

lydropho otential

Vhat is it?

General form

Force Constants

Surface

Solvent Accesible Surface

Evenly Distributed Points

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What are we interested in: Program Specifications

Result

Validation via Known log p

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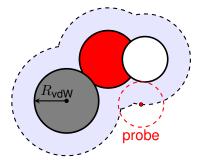
Bibliography

References



Solvent Accesible Surface

 The surface around a molecule accesible to solvent molecules



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

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P

Molecular

lydropho otential

Vhat 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

An Example

Bibliography

References





Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

Molecular Hydrophobicity Potential

Vhat 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

Bibliography

References





1. Take all atoms with their vdW-radii

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

Molecular Hydrophobicity Potential

What is it?

Potential

General for

Force Constants

Distance fur

Solvent Accesible Surface

Evenly Distributed Points Integration

Progra

What are we interested in? Program Specifications

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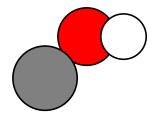
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An Example

Bibliography

References





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Molecular Hydrophobicity Potential

Pelg Bar Sapir

ntroduction

Hydrophobicity and log P Partition Coefficient

Molecular Hydrophobicity Potential

hat is it?

Potential

Force Constants

Distance function

Solvent Accesible Surface

Evenly Distributed Points

Integration

What are we interested in?

Result

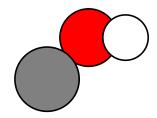
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All Example 5

Bibliography

References





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

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log F Partition Coefficient

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Vhat is it? Potential

General for

Force Constants

Distance function

Solvent Accesible Surface

Evenly Distributed Points

Progra

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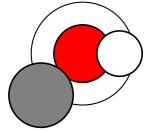
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Validation via Known log p Values

Bibliography

References





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Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

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hat is it?

Potential

General form

Distance function

Solvent Accesible Surface

Evenly Distributed Points

Prograi

What are we interested in

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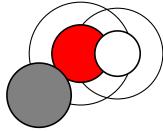
Validation via Known log p

7 III Example 0 y

Bibliography

References





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 m probe}$

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

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Vhat is it? otential

General for

Force Constants

Distance function

Solvent Accesible Surface

Evenly Distributed Points Integration

Progra

What are we interested in Program Specifications

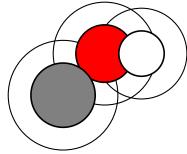
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Validation via Known log p Values

Bibliography

References





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- 2. Create spheres around all atoms with $R^i = R^i_{
 m vrlw} + R_{
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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

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Force Constants

Distance function

Solvent Accesible Surface

Evenly Distributed Points

Prograi

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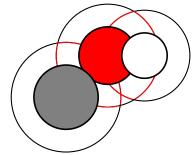
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Bibliography

References

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

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

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Potential General fo

Force Constants

Surface function

Solvent Accesible Surface

Evenly Distributed Points

Prograi

hat are we interested in?

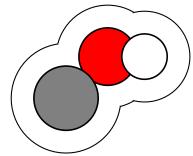
Result

Validation via Known log p

An Example S

Bibliography

References



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

> olecular odrophobicity

What is it?

General form

Force Constants
Distance function

Solvent Accesible Surface

Evenly Distributed Points

Integration

What are we interested in

Results

Validation via Known log p

An Example S

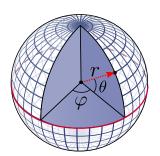
Bibliography

References



Evenly Distributed Points

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



Molecular Hydrophobicity Potential

Pelg Bar Sapir

troduction

Hydrophobicity and log F Partition Coefficient

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Potential
What is it?

Potential

General for

Force Constants

Distance

Surface

Solvent Accesible Surface Evenly Distributed Points

Program

What are we interested in?

Result

Validation via Known log p Values

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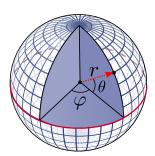
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References



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

ntroduction

Hydrophobicity and log F Partition Coefficient

Molecular Hydropho

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What is it?

General for

Force Constants

Distance fi

Surface

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Evenly Distributed Points

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Result

Validation via Known log p Values

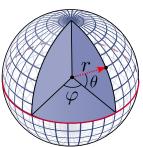
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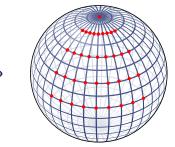
How to distribute N points on a surface of a sphere?





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

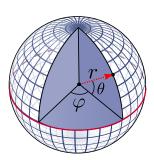
$$\theta_j = j \cdot \frac{\pi}{N}$$



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Evenly Distributed Points

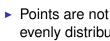
How to distribute N points on a surface of a sphere?



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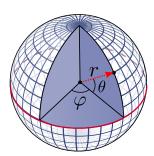
Molecular Hydrophobicity Potential

Pelg Bar Sapir

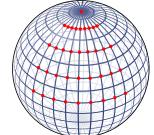
Evenly Distributed Points



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







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



Points are not evenly distributed

 Several points overlap at poles Molecular Hydrophobicity Potential

Pelg Bar Sapir

ntroduction

Hydrophobicity and log F Partition Coefficient

> olecular odrophobicity otential

Vhat is it?

General form Force Constants

Distance function

Surface

Solvent Accesible Surface Evenly Distributed Points Integration

Progra

What are we interested in Program Specifications

Results

Validation via Known log p Values

Ribliography

Bibliography

References

Solution: Vogel's method

In 2 dimensions:

Molecular Hydrophobicity Potential

Pelg Bar Sapir

ntroduction

Hydrophobicity and log P
Partition Coefficient

Molecular Hydrophobicity Potential

What is it

Potential

Seneral form

Distance f

urface

Solvent Accesible Surface Evenly Distributed Points

Integration

rogram What are we interest

Program Specifications

Resul

Validation via Known log p Values

An Example \$

Bibliography

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!)

Molecular Hydrophobicity Potential

Pelg Bar Sapir

ntroduction

Hydrophobicity and log F Partition Coefficient

> Molecular Hydrophobicity Potential

What is it?

Potential

General form

Force Constants

urface

Solvent Accesible Surface Evenly Distributed Points

Evenly Distributed Point ntegration

rogram

What are we interested in Program Specifications

Result

Validation via Known log p Values

An Example

Bibliography

References

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Molecular Hydrophobicity Potential

Pelg Bar Sapir

ntroduction

Hydrophobicity and log P Partition Coefficient

Molecular Hydrophobicit

otential

Potential

General form

Force Constants

Distance 1

Surface Solvent Accesible Surfac

Evenly Distributed Points

Prograi

Vhat are we interested in

Result

Validation via Known log p Values

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Bibliography

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):

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Evenly Distributed Points

Solution: Vogel's method

In 2 dimensions:

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

In 3 dimensions (cylindrical coordinates):

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

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

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

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Potential

General form

Force Constants

Distance

Surface

Solvent Accesible Surfac Evenly Distributed Points

Program

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Result

Validation via Known lo Values

Bibliography

References

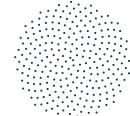
Solution: Vogel's method

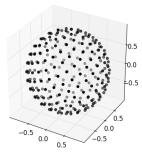
In 2 dimensions:

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





Molecular Hydrophobicity Potential Pelg Bar Sapir

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Introductio

Hydrophobicity and log F Partition Coefficient

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Potential

Force Constants

Distance

Surface

Solvent Accesible Surface Evenly Distributed Points

Program

What are we interested in Program Specifications

Resul

Validation via Known log p Values

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Dibliography

References

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

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Molecular Hydrophobicity Potential

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

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

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

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

- ▶ 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

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



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

Molecular Hydrophobicity Potential

Pelg Bar Sapir

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

Molecular Hydrophobicity Potential

Pelg Bar Sapir



- 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 P Partition Coefficient

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Potential
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General form

Distance fun

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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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Bibliography

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

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Hydrophobicity and log P Partition Coefficient

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Potential

General form

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Distance function

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Solvent Accesible Surface Evenly Distributed Points

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Program Specifications

Results

Validation via Known log p

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Bibliography

References



► Input: PSF + PDB or DCD

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

Molecular Hydrophobicity Potential

What is it?

Potential

General form

Porce Constants

urface

Solvent Accesible Surface Evenly Distributed Points

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What are we interested in

Program Specifications

Result

Validation via Known log Values

An Example

Bibliography

References

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

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

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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

An Example

Bibliography

Reference

- ► 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

Force Constants

Distance

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Validation via Known log p Values

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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)

Molecular Hydrophobicity Potential

Pelg Bar Sapir



- 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



▶ 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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What is it?

General form

General form

Dietance function

urface

Solvent Accesible Surface Evenly Distributed Points Integration

Progran

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Results

Validation via Known log p Values

An Example S

Bibliography

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

Introduction

Hydrophobicity and log P Partition Coefficient

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What is it?

Potential

General form

Distance

Solvent Accesible Surface Evenly Distributed Points

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Results

Validation via Known log p

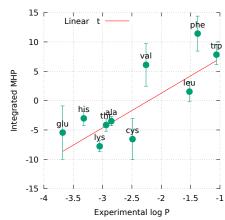
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Bibliography

References



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



Molecular Hydrophobicity Potential

Pelg Bar Sapir

ntroduction

Hydrophobicity and log P Partition Coefficient

Molecular

Potential

What is it?

General form

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Distance funct

Surface

Solvent Accesible Surface Evenly Distributed Points

Prograi

What are we interested in?

Resu

Validation via Known log p Values

7 til Example Oye

Bibliography

References

⁶MD simulation using NAMD, performed by Dr. Tillmann Utesch 200

Potential Pelg Bar Sapir

Molecular

Hydrophobicity

Introduction

Partition Coefficient

Hydrophob Potential

Potential

General form

Force Constants

Distance

Solvent Accesible Surface Evenly Distributed Points

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Program

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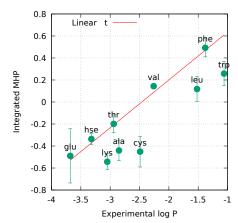
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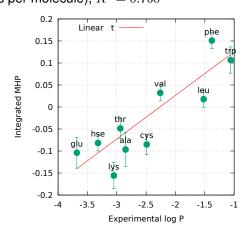
References

Thankyou

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



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



Molecular Hydrophobicity Potential

Pelg Bar Sapir

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Hydrophobicity and log P Partition Coefficient

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General form

General form

Dietance function

Surface

Solvent Accesible Surface Evenly Distributed Points

Program

What are we interested in

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Validation via Known log p Values

7 ar Example Oye

Bibliography

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

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Potential

General form

Distance function

urface

Solvent Accesible Surface Evenly Distributed Points Integration

Progran

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Result

Validation via Known log p Values

An Example 9

Bibliography

References



- 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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Hydrophobicity and log P Partition Coefficient

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What is it?

Potential

General form

Distance fun

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Solvent Accesible Surface Evenly Distributed Points Integration

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Vhat are we interested in?

Results

Validation via Known log p Values

An Example S

Bibliography

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.

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

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Vhat is it?

Potential
General form

Force Constants

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Solvent Accesible Surface Evenly Distributed Points

rogram

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Results

Validation via Known log p Values

An Example S

Bibliography

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.

Molecular Hydrophobicity Potential

Pelg Bar Sapir

ntroduction

Hydrophobicity and log P Partition Coefficient

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What is it?

Potential

General form

Distance f

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Solvent Accesible Surface Evenly Distributed Points Integration

Program

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Results

Validation via Known log p Values

An Example Sy

Bibliography

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

Validation via Known log p Values

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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Potential

General form

Force Constants

Distance iu

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Solvent Accesible Surface Evenly Distributed Points Integration

rogram

Vhat are we interested in? Program Specifications

Results

Validation via Known log p Values

An Example System

Bibliography

References

⁷Trajectory 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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What is it?
Potential

General form

Force Constants

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urface

Solvent Accesible Surface Evenly Distributed Points

rogram

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Results

Validation via Known log p Values

An Example System

Bibliography

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⁷Trajectory 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.
- The membrane used for the study consists of a mixture of two lipids, PG and PE, in agreement with experimental measurements.

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

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What is it?

Potential

General form

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Solvent Accesible Su

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What are we interested in

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Results

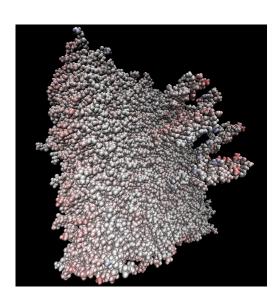
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An Example System

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References

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Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log I Partition Coefficient

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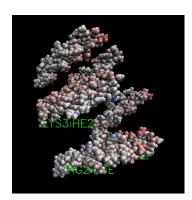
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Bibliography

References

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Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log F Partition Coefficient

Molecular Hydrophobic

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What is it?

Potentia

General form

Force Constants

Distance function

Surface

Solvent Accesible Surfa Evenly Distributed Point

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Program

What are we interested in

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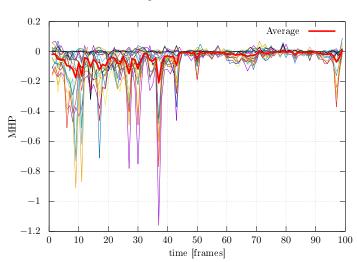
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An Example System

Bibliography

References

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

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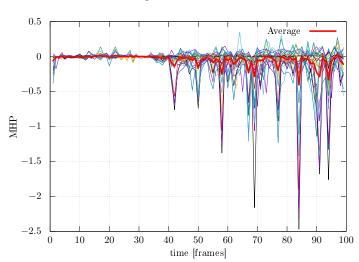
Validation via Known log p

An Example System

Bibliography

References

MHP change over time for ARG-24



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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Validation via Known log p

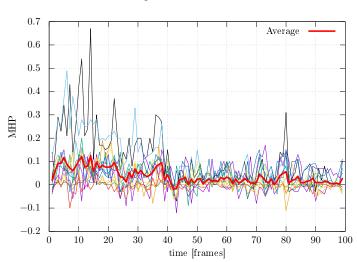
An Example System

Bibliography

References



MHP change over time for PRO-22



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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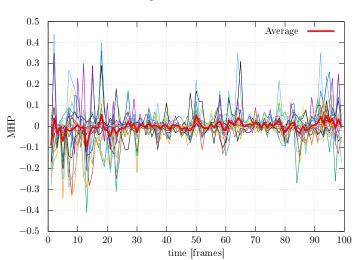
Validation via Known log p

An Example System

Bibliography

References

MHP change over time for LYS-3



Molecular Hydrophobicity Potential

Pelg Bar Sapir

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Hydrophobicity and log F Partition Coefficient

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Potential

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Solvent Accesible Surface

Evenly Distributed Points Integration

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Results

Validation via Known log p

An Example System

Bibliography

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 Hydrophob

Potential

Potential

General form

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Distance fun

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Solvent Accesible Surface Evenly Distributed Points Integration

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Vhat are we interested in? Program Specifications

Result

Validation via Known log p Values

An Example System

Bibliography

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 Goefficient

Hydrophol

Vhat is it?

Potential

General form

Force Constants

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urface

Solvent Accesible Surface Evenly Distributed Points Integration

rogram

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Result

Validation via Known log p

An Example System

Bibliography

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

Introduction

Hydrophobicity and log F Partition Coefficient

Hydropho Potential

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What is it?

Potential

General form

Force Constant

Distance

Surface

Solvent Accesible Surface Evenly Distributed Points Integration

rogram

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Results

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An Example System

Bibliography

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.
- More systems could (and should!) be analyzed using this method

Molecular Hydrophobicity Potential

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An Example System



Bibliography

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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

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Evenly Distributed Points Integration

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Vhat are we interested in? Program Specifications

Result

Validation via Known log p Values

Bibliography

References

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Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introductio

Hydrophobicity and log I Partition Coefficient

Molecular Hydrophobicity Potential

hat is it?

Potential

General form

Force Constants

Surface

Solvent Accesible Surface Evenly Distributed Points Integration

Prograi

What are we interested in Program Specifications

Result

Validation via Known log p Values

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Bibliography
