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

Peleg Bar Sapir¹

Under supervision of Prof. Maria Andrea Mroginski²

¹Freie Universität Berlin ²Techniche Universität Berlin

February 19, 2018

Molecular Hydrophobicity Potential

Pelg Bar Sapir

ntroduction

Hydrophobicity and log P Partition Coefficient

lydrophobi otential

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

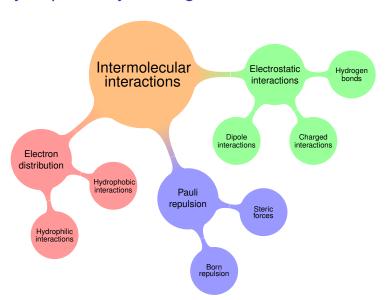
Validation via Known log p Values An Example System

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

. .

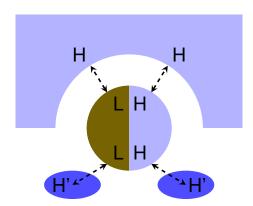
Bibliography

References

The section 1.

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

Pelg Bar Sapir



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

Pelg Bar Sapir



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

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

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

Pelg Bar Sapir

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

i ii Exampio oyo

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

> lolecular ydrophobicity otential

What is it?

Potential

General form
Force Constants

Distance 1

Surface

Solvent Accesible Surface Evenly Distributed Points Integration

rogran

nat are we interested in?

Results

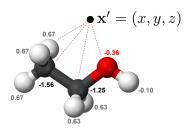
Validation via Known log p

i ii Exampio oyo

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

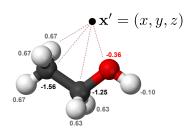
Resul

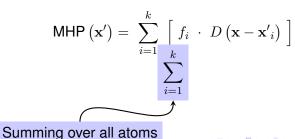
Validation via Known log p Values

Dibliography

Bibliography

References





Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log F Partition Coefficient

Aolecular Aydrophobic

/hat is it?

General form

orce Constants

Distance functio

Surface

Evenly Distributed Points Integration

Progra

What are we interested in? Program Specifications

Resu

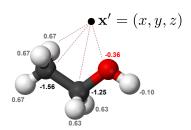
Validation via Known log | Values

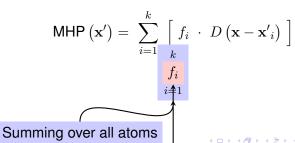
_

Bibliograph

Reference





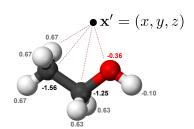


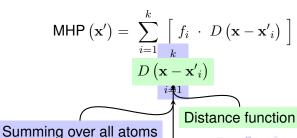
Molecular Hydrophobicity Potential

Pelg Bar Sapir

General form







Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introductio

Hydrophobicity and log F Partition Coefficient

Molecular Hydrophol

otential

Vhat is it?

General form

oroo Constants

Force Constants

Curfoso

Solvent Accesible Surfa

Evenly Distributed Points Integration

Progra

Program Specifications

Resu

Validation via Known log p Values

An Example

Bibliograph

References

hankyou

4 D > 4 D > 4 D > 4 D > 4 D >

Force Constants - Carbon

Molecular Hydrophobicity Potential

Pelg Bar Sapir

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

1olecular

rophobicit ential

otential

General form Force Constants

nce funct

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

olecular drophobicity

/hat is it?

eneral form

Force Constants
Distance function

Surface

Solvent Accesible Surface Evenly Distributed Point Integration

rogran

What are we interested in

Result

Validation via Known log p Values

libliography

Bibliography

References

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

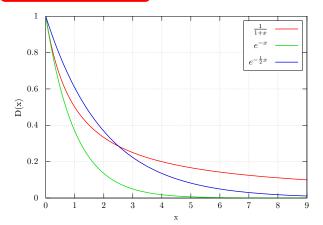
Distance function

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

lolecular ydrophobicity

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

Thankyou

◆ロト ◆御 ト ◆ 恵 ト ◆ 恵 ・ 夕 ○ ○

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

Ounace "LL O (

Solvent Accesible Surface

ntegration

Progran

What are we interested in? Program Specifications

Results

Validation via Known log p Values

An Example 3

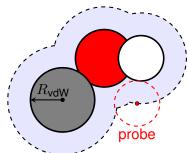
Bibliography

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

D....

What are we interested in: Program Specifications

Result

Validation via Known log p

. .

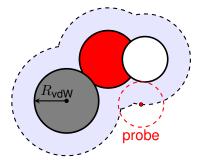
Bibliography

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

Resul

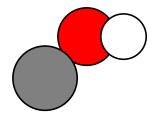
Validation via Known log p Values

An Example

Bibliography

References





1. Take all atoms with their vdW-radii

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

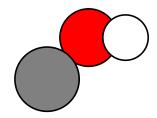
Validation via Known log p

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 P Partition Coefficient

lolecular ydrophobicity otential

hat is it?

Potential

Force Constants

Distance function

Solvent Accesible Surface

Evenly Distributed Points

Progra

hat are we interested in?

Resu

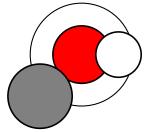
Validation via Known log p

7 III Example 0 y

Bibliography

References





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

Molecular Hydrophobicity Potential

Pelg Bar Sapir

ntroduction

Hydrophobicity and log P Partition Coefficient

Molecular lydrophobicit

hat is it?

Potential

General form

Distance function

Solvent Accesible Surface

Solvent Accesible Surface

Evenly Distributed Points Integration

Progra

hat are we interested in:

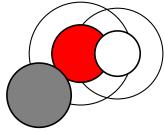
Resu

Validation via Known log p

Bibliography

References





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

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

> olecular odrophobicity otential

What is it's Potential

General form

Force Constants

Distance function

Solvent Accesible Surface

Evenly Distributed Points

Integration

Progra

hat are we interested in?

Resu

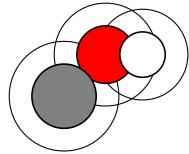
Validation via Known log p

. . . _ ,

Bibliography

References





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

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

> olecular drophobicity tential

Potential

General form

Distance function

Surface Solvent Accesible Surface

Evenly Distributed Points

Evenly Distributed Points Integration

Progra

What are we interested in Program Specifications

Resu

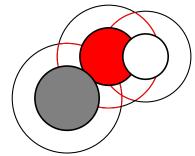
Validation via Known log p

D.1. 11

Bibliography

References





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

olecular drophobicity tential

What is it?

Potential General fo

Force Constants

Distance function

Solvent Accesible Surface

Evenly Distributed Points

Progra

What are we interested in Program Specifications

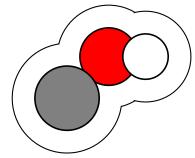
Result

Validation via Known log p

An Example S

Bibliography

References



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

hat is it?

General form

Force Constants
Distance function

Surface Solvent Accesible Surface

Evenly Distributed Points

Program

What are we interested in Program Specifications

Result

Validation via Known log p

An Example S

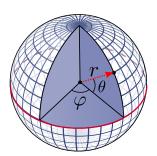
Bibliography

References



Evenly Distributed Points

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



Molecular Hydrophobicity Potential

Pelg Bar Sapir

ntroduction

Hydrophobicity and log F Partition Coefficient

Molecula Hydropho

Potential
What is it?

Potential

General for

Force Constants

Surface

Solvent Accesible Surface

Evenly Distributed Points

Progra

What are we interested in?

Result

Validation via Known log p Values

Ribliograph

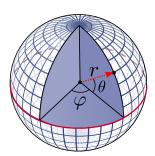
Dibliograph

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

troduction

Hydrophobicity and log F Partition Coefficient

Molecular

otential

Potential

General for

Force Constants

Distance fi

Surface

Solvent Accesible Surface Evenly Distributed Points

Integration

What are we interested in

Results

Validation via Known log p Values

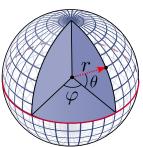
. .

Bibliography

References

Evenly Distributed Points

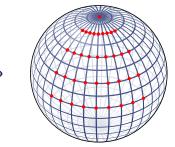
How to distribute N points on a surface of a sphere?





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

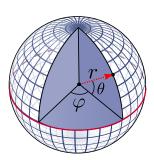
$$\theta_j = j \cdot \frac{\pi}{N}$$



Pelg Bar Sapir

Evenly Distributed Points

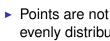
How to distribute N points on a surface of a sphere?



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

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





evenly distributed

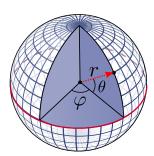
Molecular Hydrophobicity Potential

Pelg Bar Sapir

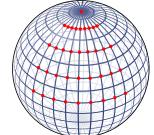
Evenly Distributed Points



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

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 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

Barr I

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

lolecular ydrophobicity

otential That is it?

Potential

General form

Force Constants

Distance

Surface

Solvent Accesible Surfac Evenly Distributed Points

Program

nat are we interested in ogram Specifications

Result

Validation via Known lo Values

Bibliography

References

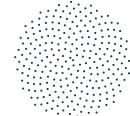
Solution: Vogel's method

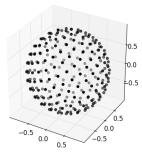
In 2 dimensions:

- ▶ 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

Pelg Bar Sapi

Introductio

Hydrophobicity and log F Partition Coefficient

lolecular ydrophobio

otential /hat is it?

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

Piblicarophy

Dibliography

References

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

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

Molecular Hydrophobicity Potential

Pelg Bar Sapir

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

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

▶ 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

> olecular ydrophobicity

hat is it?

Potential
Conoral form

General form

Distance fun

ırface

Solvent Accesible Surface Evenly Distributed Points Integration

ogram

hat are we interested i

Program Specifications

D - - - - 18 -

Validation via Known log p Values

7 til Example Oyl

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

ntroduction

Hydrophobicity and log P Partition Coefficient

olecular drophobicity

otential

Potential

General form

Control Control

Distance function

ırface

Solvent Accesible Surface Evenly Distributed Points

ogram

hat are we interested

Program Specifications

Results

Validation via Known log p

. .

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

rogram

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

olecular ydrophobicity

tential

Potential

General form

Force Constants

rface

Solvent Accesible Surface Evenly Distributed Points

ogram

Vhat are we interested in

Program Specifications

Resu

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

olecular drophobicity

tential

Potential

General form

Force Constants

Distance

urface Solvent Acces

olvent Accesible Su venly Distributed Po Itegration

rogram /hat ara wa intercate

Program Specifications

_ .

Resu

Validation via Known log p Values

An Example S

Bibliography

Poforonoos

- 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



- 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

lolecular ydrophobicity otential

What is it?

General form

General form

Dietance function

urface

Solvent Accesible Surface Evenly Distributed Points Integration

Progran

/hat are we interested in?

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

lolecular ydrophobicity otential

What is it?

Potential

General form

Distance

Solvent Accesible Surface Evenly Distributed Points

Prograi

hat are we interested in

Results

Validation via Known log p

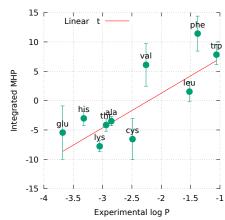
An Example S

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

aerierarioriii

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

Evenly Distributed Poin Integration

Program

rnat are we interested it rogram Specifications

Resul

Validation via Known log p Values

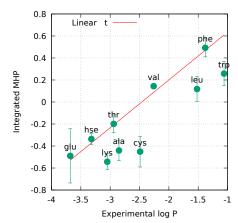
An Example S

Bibliography

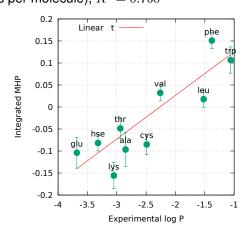
References

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

ntroduction

Hydrophobicity and log P Partition Coefficient

/lolecular

otential

/hat is it?

General form

General form

Dietance function

Surface

Solvent Accesible Surface Evenly Distributed Points

Program

What are we interested in

Resul

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

hat is it?

Potential

General form

Distance function

urface

Solvent Accesible Surface Evenly Distributed Points Integration

Progran

Vhat are we interested in? Program Specifications

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

ntroduction

Hydrophobicity and log P Partition Coefficient

ydrophol otential

Otential
What is it?

Potential

General form

Distance fun

urface

Solvent Accesible Surface Evenly Distributed Points Integration

rogram

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

> olecular drophobici tential

Vhat is it?

Potential
General form

Force Constants

ırface

Solvent Accesible Surface Evenly Distributed Points

rogram

nat 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.
- Amino acids are small molecules, each error becomes more significant.

Molecular Hydrophobicity Potential

Pelg Bar Sapir

ntroduction

Hydrophobicity and log P Partition Coefficient

olecular /drophobicity

What is it?

Potential

General form

Distance f

urface

Solvent Accesible Surface Evenly Distributed Points Integration

Program

hat are we interested in rogram Specifications

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

olecular /drophobi

tential

Potential

General form

Force Constants

Distance iu

пасе

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

Moleculai Avdropho

drophobio tential

What is it?
Potential

General form

Force Constants

. .

urface

Solvent Accesible Surface Evenly Distributed Points

rogram

nat are we interested in ogram 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.
- 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

olecular ydrophobi

Votential

What is it?

Potential

General form

orce Constants

urface

Solvent Accesible Su

Evenly Distributed Po Integration

What are we interested in

Program Specification

Results

/alidation via Known log p

An Example System

ibliography

References

A video of the system

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

Molecular Hydrophobicity Potential

What is it

Potential

General form

Force Constant

Duefooo

Surface

Solvent Accesible Surface Evenly Distributed Point

Progra

What are we interested in? Program Specifications

Resu

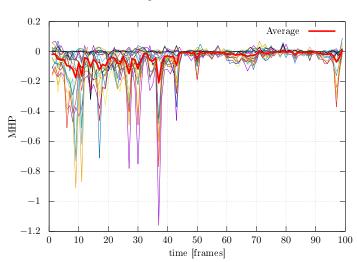
Validation via Known log p

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

lydropho otential

/hat is it?

Potential

errer Constants

Distance fu

Solvent Accesible Surface

Evenly Distributed Points Integration

Prograi

nat are we interested in? ogram Specifications

Result

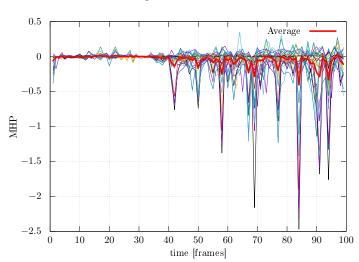
Validation via Known log p

An Example System

Bibliography

References

MHP change over time for ARG-24



Molecular Hydrophobicity Potential

Pelg Bar Sapir

ntroduction

Hydrophobicity and log P Partition Coefficient

olecular ydrophobici

What is it?

Potential

General form

Distance fur

Surface

Solvent Accesible Surface Evenly Distributed Points

Progran

at are we interested in? ogram Specifications

Result

Validation via Known log p

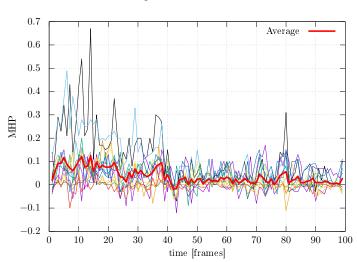
An Example System

Bibliography

References



MHP change over time for PRO-22



Molecular Hydrophobicity Potential

Pelg Bar Sapir

ntroduction

Hydrophobicity and log F Partition Coefficient

lydropho otential

What is it?

Potential

Force Constants

urfooo

Solvent Accesible Surface Evenly Distributed Points

Prograi

/hat are we interested in?

Resul

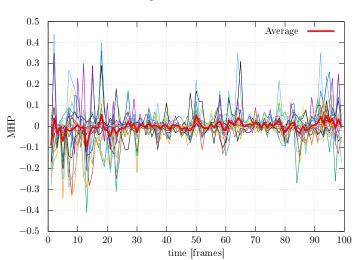
Validation via Known log p

An Example System

Bibliography

References

MHP change over time for LYS-3



Molecular Hydrophobicity Potential

Pelg Bar Sapir

ntroduction

Hydrophobicity and log F Partition Coefficient

lolecula lydropho

otential What is it?

Potential

Jeneral form

Distance i

Solvent Accesible Surface

Evenly Distributed Points Integration

Prograi

nat are we interested in? ogram Specifications

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

orce Constants

Distance fun

urface

Solvent Accesible Surface Evenly Distributed Points Integration

rogram

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

,

urface

Solvent Accesible Surface Evenly Distributed Points Integration

rogram

hat are we interested in?

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

Oterilia

What is it?

Potential

General form

Force Constant

Distance

Surface

Solvent Accesible Surface Evenly Distributed Points Integration

rogram

at are we interested in?

Results

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

Molecular Hydrophobicity Potential

Pelg Bar Sapir

An Example System



Bibliography

- [1] Timothy V. Pyrkovand Anton O. Chugunovand Nikolay A. Krylovand Dmitry E. Noldeand Roman G. Efremov. "PLATINUM: a web tool for analysis of hydrophobic/hydrophilic organization of biomolecular complexes". In: *Bioinformatics* 25.9 (2009), pp. 1201–1202.
- [2] Patrick Gaillard, Pierre-Alain Carrupff, and Alain Boudon Bernard Testa. "Molecular Lipophilicity Potential, a tool in 3D QSAR: Method and applications". In: Journal of Computer-Aided Molecular Design 8.235 (1994), pp. 83–96.
- [3] Arup K. Ghose, Vellarkad N. Viswanadhan, and John J. Wendoloski. "Prediction of Hydrophobic (Lipophilic) Properties of Small Organic Molecules Using Fragmental Methods: An Analysis of ALOGP and CLOGP Methods". In: The Journal of Physical Chemistry A 102 (1998), pp. 3762–3772.
- [4] Vladimir PliSka, Bernard Testa, and Han van de Waterbeemd. Lipophilicity in Drug Action and Toxicology. VCH Verlagsgesellschaft mbH, 1996.

Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introduction

Hydrophobicity and log P Partition Coefficient

> lecular drophobicity

tential nat is it?

otential

General form Force Constants

urface

urtace Polyopt Ao

Evenly Distributed Points Integration

rograr

Vhat are we interested in? Program Specifications

Result

Validation via Known log p Values

Bibliography

References

Thankvou

Thank You for Your Attention!



Molecular Hydrophobicity Potential

Pelg Bar Sapir

Introductio

Hydrophobicity and log I Partition Coefficient

Molecular Hydrophobicity Potential

/hat is it?

Potential

General form

Pirtue Constants

Surface

Solvent Accesible Surface Evenly Distributed Points Integration

Progran

What are we interested in?
Program Specifications

Results

Validation via Known log p Values

. .

Bibliography
