COSMOomic for biomembrane systems – combination with molecular dynamics simulations

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Methods

Molecular dynamics:
• Atomistic resolution
• Time-based

COSMOomic:
• Extension of COSMO-RS for micelles and bilayers
• Less detailed

\[ P = \frac{c_{\text{vesicle solute}}}{c_{\text{water solute}}} \]

free energy profile

efficient (screening possible)

computationally demanding

I. COSMOmic input from MD simulations

II. Comparison of COSMOmic with MD
COSMOmic (COSMO-RS for micelles) is an extension of COSMO-RS for anisotropic systems.

How do we get atomic resolution information about the composition of the anisotropic system?

Connection MD - COSMOmic

**Point of departure:**
COSMOmic needs one lipid conformer and one system (bilayer/water) configuration.

**Requirements:**
The structures (conformer and system) should be representative for the conditions studied: advantageous to take it from MD simulations.

**Problem:**
MD simulations produce a vast amount of lipid conformers and system configurations. For example: A MD simulation with 128 lipids running for 40 ns and writing output every 10 ps:

\[ 128 \times 40/0.01 = 512,000 \text{ lipid conformers and 4000 system configurations} \]

**Question:**
Which one should be used? Lipid conformer: one out of hundred thousands - System configuration: one out of thousands

Atomic distribution

Averaged atomic distribution

- COSMOmic robust against system snapshot (at least for the simulation set up used here)
- better to use averaged distributions (more physically sound)

\[
\text{RMSE} = \sqrt{\frac{1}{n} \sum_{i=1}^{n} (\log P_{i,\text{calc}} - \log P_{i,\text{exp}})^2}
\]

Lipid conformer influence

66 DMPC/water partition coefficients

52 POPC/water partition coefficients

\[
\text{RMSE} = \sqrt{\frac{1}{n} \sum_{i=1}^{n} (\log P_{i,\text{calc}} - \log P_{i,\text{exp}})^2}
\]

Work flow

MD simulation of a lipid bilayer

Chose one representative lipid conformer (e.g., having a SAS equal to the average SAS)

DFT geometry optimization

Databank of lipid conformers

Calculate average atomic distribution

Databank of depth-dependent membrane composition

Databank of solute conformers

COSMOmic

Results:
- partition coefficients
- free energy profiles
- solute orientation
- etc.

Databank for COSMOmic input

http://www.tuhh.de/v8/downloads/membranesmicelles.html

<table>
<thead>
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<th>System</th>
<th>Properties</th>
<th>Files</th>
<th>Comments</th>
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</table>
| DMPC/water | • water/lipid = 30.6  
• Nlipids=128  
• T=303 K  
• simulation time 80 ns  
• force field: CHARMM36 | • averaged atomic distribution (no of layers = 30)  
• system snapshot (pdb)  
• lipid conformer (pdb) | please cite DOI: 10.1002/icc.23262 |
| POPC/water | • water/lipid = 31.6  
• Nlipids=128  
• T=303 K  
• simulation time 30 ns  
• force field: CHARMM36 | • averaged atomic distribution (no of layers = 30)  
• system snapshot (pdb)  
• lipid conformer (pdb) | please cite DOI: 10.1002/icc.23262 |
| DOPC/water | • water/lipid = 41.9  
• Nlipids=128  
• T=298 K  
• simulation time 30 ns  
• force field: CHARMM36 | • averaged atomic distribution (no of layers = 30)  
• system snapshot (pdb)  
• lipid conformer (pdb) | please cite DOI: 10.1002/icc.23262  
• it was used in DOI: 10.1063/1.4890877 |

- Currently, data for lipid bilayers
- Data for micelles will be added soon
Comparison of free energy profiles

COSMOmic

Free energy profile

Partition coefficient

MD simulation

Free energy profile

Partition coefficient

No experimental data, comparison of the two methods

Experimental partition coefficients are available
Free energy profiles of solutes

- Details about the partitioning behavior
- Experimentally not accessible
- Partition coefficients can be calculated from these profiles, these coefficients can be measured experimentally

\[
P_i^{\alpha\beta} = \frac{c_i^\alpha}{c_i^\beta}
\]

- Molecular Dynamics
- COSMOmic

distance from bilayer center

partition coefficients
Calculation of free energy profiles with MD simulations

For MD simulations the sampling of regions with high free energies will be very poor.

**Biased MD simulations necessary**

**Umbrella sampling**: the solute is free to move in the xy-plane but is restrained in the z-direction.

**Weighted histogram analysis method** (WHAM): unbiased free energy profile

**Problem**: Computationally very demanding

**Example**: For one half of the bilayer 32 simulations of 100 ns (in total 3.2 µs) are necessary. On a single CPU this would take ca. 15 years!

Highly **parallel calculations** are necessary (most results shown here were calculated on 160 cores).
Uncharged solutes

4-ethylphenol

propanol

5-phenylvaleric acid
dibenz[a,h]anthracene
Free energy profiles

a) 4-ethylphenol

b) propanol

c) 5-phenylvaleric acid

d) dibenz[a,h]anthracene

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Influence of headgroup?

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Solute orientations in lipid bilayers

a) 4-ethylphenol in SOPC

b) propanol in DMPC

c) 5-phenylvaleric acid in DOPC

d) dibenz[a,h]anthracene in POPC

dotted lines: COSMOMic mean orientation
colour plot: MD angle distribution

Free energy profiles COSMOmic 15 FINE

a) 4-ethylphenol

b) propanol

c) 5-phenylvaleric acid

d) dibenz[a,h]anthracene
Summary

• Input for COSMOmic can be obtained from MD simulations.
• Input is provided on our homepage.
• Partition coefficients from COSMOmic and MD are in good agreement with experimental results.
• Free energy profiles and orientations from MD simulations and COSMOmic are in good agreement.
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http://www.tuhh.de/v8

More information: