Intermolecular energy calculation in LAMMPS applied to calculation of pharmaceutical solubility

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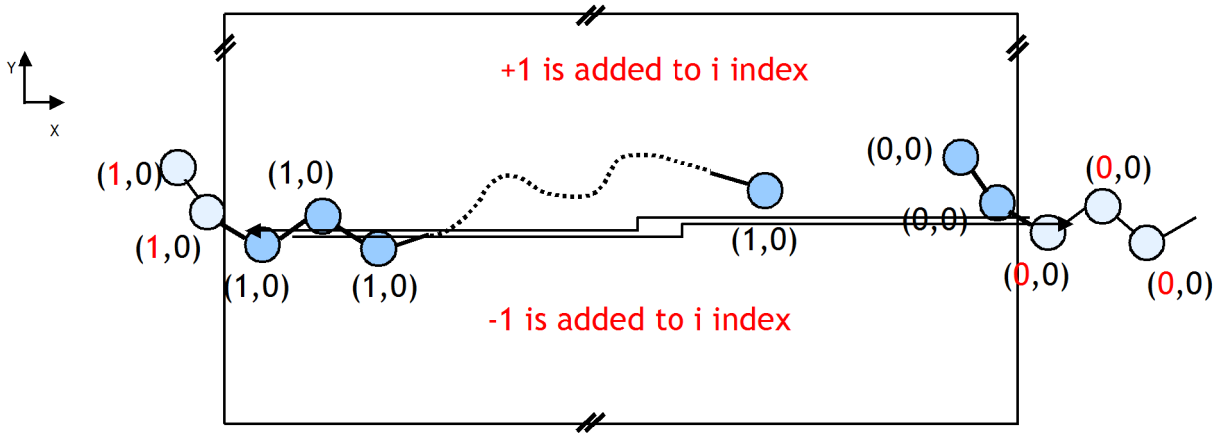
Scienomics 9th August 2011

Calculating intermolecular energy -1

- specify if an interaction is intermolecular. Use continuity indexes to distinguish the images of the same parent molecule
- separate Van der Waals and electrostatic parts of the interaction



D. Theodorou, T. D. Boone, L. R. Dodd, K. F. Mansfield, , Macromolecules. Chem., Theory Simul., 2, 191-238 (1993)

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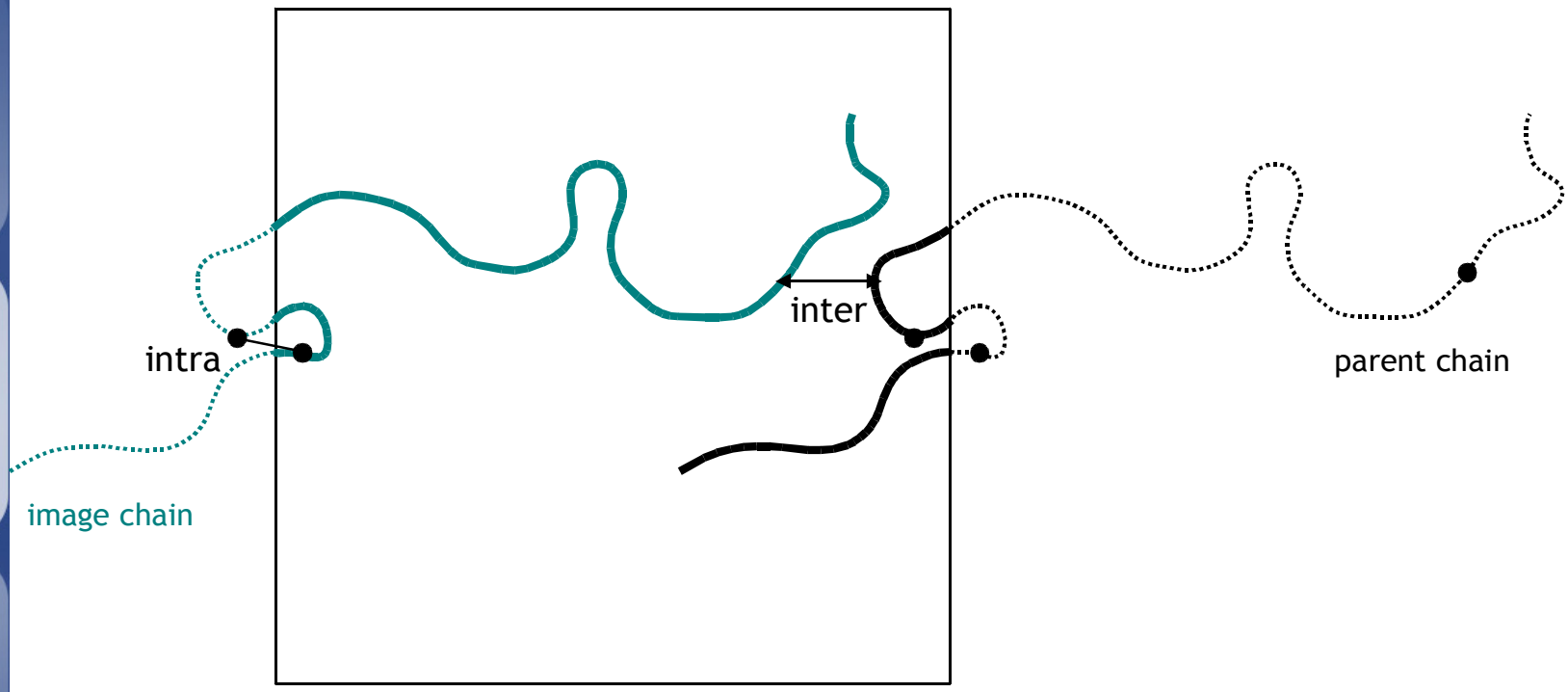
Calculating intermolecular energy -2



- Van der Wals: accurate with small cutoff = 2.5 sigma
- electrostatic: needs larger cutoff, optionally use kspace

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Calculating intermolecular energy -3

compute approach, **inter** keyword

e.g

- Define groups corresponding to molecular types:

```
group       H2O molecule <> 1 500
group       C3H8 molecule 501
```

- Use compute:

```
compute     1 all inter  H2O C3H8
```

current status

- the compute works for all the atoms i.e. all atoms should be assigned to groups which identify the molecular types
- calculates the interaction with all the molecular types i.e molecule of type A with all the other molecular types A included.
- planning to refine the split i.e. for a system with molecular types A, B, C … to calculate A-A , A-B, A-C … interactions

Intermolecular energies for one conformation

Properties viewer [Conformation]

Attribute	Value
Angle energy	937.416900
Annotation	(Not set)
Bond energy	785.185200
Coulomb energy	805.354000
Electrostatic energy	805.354000
ID	cnf72293
Inter C21H26N4O2 Coulomb energy	-90.006400
Inter C21H26N4O2 VDW energy	-38.950100
Inter C21H26N4O2 energy	-128.956500
Inter CH4O Coulomb energy	-1396.752500
Inter CH4O VDW energy	-936.177400
Inter CH4O energy	-2332.929900
Kinetic energy	2706.837800
Long-range energy	0.000000
Name	50.000 ps
Out-of-plane energy	1.056700
Potential energy	1863.907500
Pressure	4765.355300
Temperature	297.538700
Time step	50.000000
Torsion energy	131.835800
Total energy	4570.745300
Van der Waals energy	-796.941100

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Calculate pharmaceutical solubility using classical simulation tools

- We propose a scheme for the calculation of the solubility of any organic molecule in any pure solvent.
The proposed scheme is based on a simplification of the Particle Deletion Method (J. Chem. Phys. 2001, *115*, 8231).

The proposed scheme compares the energy and accessible volume of two systems:

1) Pharmaceutical molecule + water
2) Pharmaceutical molecule + any other solvent

- No experimental data are required for this calculation except for the solubility of the molecule in water, which is used as the reference point for any solubility calculation.

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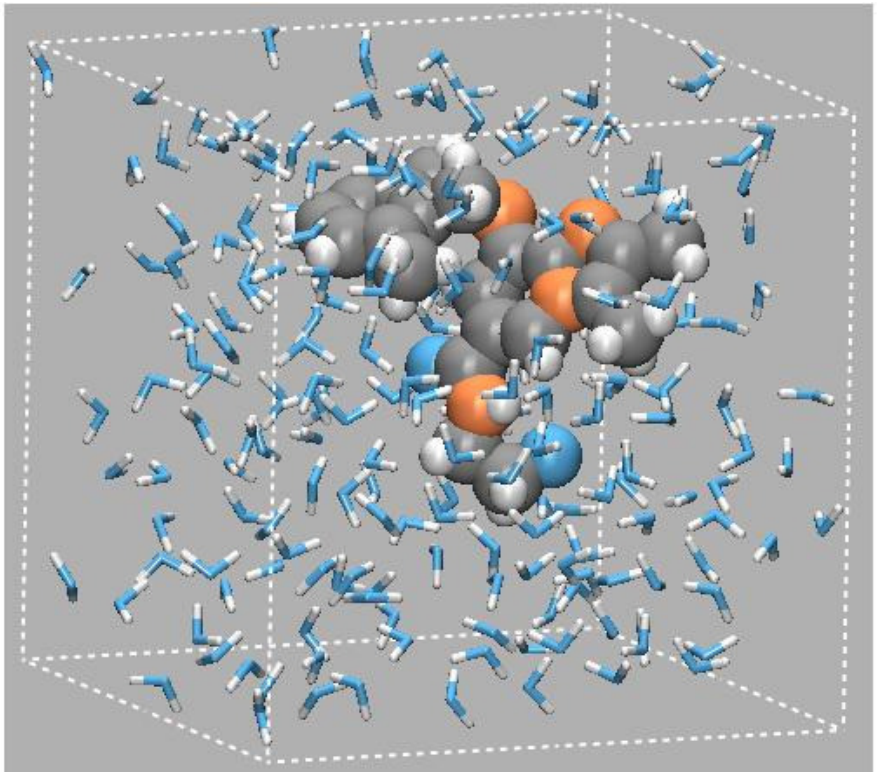
Calculate the solubility of a molecule relative to its solubility in water: Visualization of the procedure

STEP 1 : Simulate the organic molecule immersed in water



Perform an NVT MD simulation using the LAMMPS engine.

Calculate intermolecular energy of interaction (E_1) and accessible volume ($Vacc_1$) using the analysis tools of MAPS.

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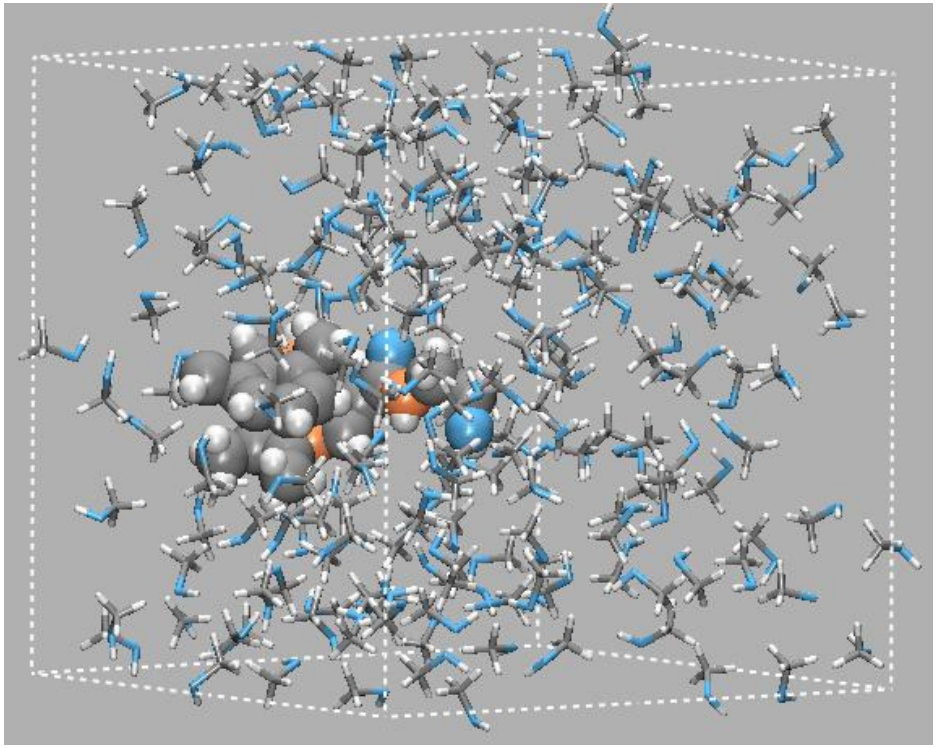
STEP 2 : Simulate the organic molecule immersed in one solvent



The solvent in the picture is MeOH.

Perform an NPT MD simulation using the LAMMPS engine.

Similarly, calculate intermolecular energy of interaction (E_2) and accessible volume ($Vacc_2$).

Calculate solubility in MeOH by an expression of the type:

$$S_{MeOH} = S_{H2O} \times \exp\left(1/kT \times \Delta E - \ln\frac{V_{acc2}}{V_{acc1}}\right)$$

where S_{H2O} is the solubility of the molecule in water

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Comparison between calculated and experimental data of the solubility of a tentative set of molecules in MeOH

API	Calculated solubility (Mole fr.)	Experimental solubility (Mole fr.)	Relative error
Paracetamol	0.0630	0.0950	0.34
Naproxen	0.0296	0.0120	1.47
Trimethoprim	0.0011	0.0017	0.35
Temazepam	0.0100	0.0055	0.83
Butylparaben	0.0413	0.3360	0.88
Diclofenac	0.0008	0.0059	0.86
Carbamazepine	0.0130	0.0130	0.00
Flurbiprofen	0.0278	0.0480	0.42
Salicylamide	0.0374	0.0410	0.09
AZD0865	0.0050	0.0014	2.46
AZD8330	0.0050	0.0023	1.15

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Comparison between calculated and experimental data of the solubility of a tentative set of molecules in acetone

API	Calculated solubility (Mole fr.)	Experimental solubility (Mole fr.)	Relative error
Paracetamol	0.0390	0.0370	0.05
Naproxen	0.0440	0.0500	0.12
Trimethoprim	0.0160	0.0009	16.78
Temazepam	0.0207	0.0207	0.00
Butylparaben	0.1070	NA	
Diclofenac	0.0184	0.0302	0.39
Carbamazepine	0.0216	0.0037	4.84
Flurbiprofen	0.1250	0.1250	0.00
Salicylamide	0.0530	0.1290	0.59
AZD0865	0.0017	0.00018	8.55

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- The proposed scheme can be a valuable tool for pharmaceutical solubility predictions.

- It can be used as a supplementary tool to SciTherm equation of state calculations.

Experimental datasets – sharing and viewing

> "A disincentive to sharing data is that there is often grunt work involved in exporting, cleaning and documenting the dataset"

MAPS enables researchers to share the definition and results of a LAMMPS experiment within a single file. Reviewers can view and analyse the results and attach annotations at any level.

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Experimental datasets – MAPS file format

```
<cml>
  <experiment title="LAMMPS MD calculation" >

    <expParamSet type="LAMMPS" version="21Oct10">
      <scalar title="startTemperature" dataType="xsd:string">298.15</scalar>
       any number of experimental setup parameters...

    <expResult title="Result for API-water" >
      <molecule title="API-water" type="input">
       any number of molecule-level properties...
       complete set of bonds...

       INITIAL conformation definition = unitcell, other conformation-level properties
                                         and complete set of atoms with coordinates

      <molecule title="API-water" type="output">
       any number of GENERATED molecule-level properties...
       complete set of bonds...

       1..n GENERATED conformation definitions "0.000 ps" to "50.000 ps"
                      = GENERATED conformation-level properties
                        and complete set of atoms with coordinates

      <propertyList title="Data files">
       files relating to this Experimental Result
```

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