Themis user guide

Version 1.0.0

Themis: a Software to Assess Association Free Energies Via Direct Estimative of Partition Functions

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1. ABOUT

Themis is a statistichal mechanics software designed to obtain the association thermodynamics of two structures (ions, molecules, crystals, nanoparticles, etc). It generates a configurational partition function by systematically sampling the phase space using discrete grids to perform translations and rotations of one structure around another. Interaction energy for each microstate can be obtained by one of the potentials implemented or by using external softwares.

Themis is a free software written in Fortran 2003 language, being available at `http://www.lqt.dq.ufscar.br/lqt/lqt_software-pt.html` under the GPLv3+ License. It runs under Linux environment with gfortran/gcc 5.4+ compilers. Since it was written in modules, new potential functions and analysis routines can be easily implemented.

2. OBTAINING A COPY AND COMPILING

3. COMMAND LINE OPTIONS

Themis usage is done via Linux command line as follows:

```
themis [RUNTYPE] [GRID]
```

[RUNTYPE] options are:

`--run` to start a new calculation.

`--rerun` to calculated properties from interaction energies obtained previously. In this case, an `energy.bin` file will be read if these energy values were obtained with Themis of an `energy.log` file will be read if these energy values were obtained externally. While ther former is useful in order to obtain thermodynamic properties using a different temperature from a previous calculation, the latter is useful in order to obtain thermodynamic properties using quantum chemistry interaction energies.

[GRID] options are:

`--shell <radius>` indicates that translation moves will be performed on a spherical shell around the reference molecule (generated on the run). The real argument <radius> is the scaling factor for the radius (in Angstrom).

`--user <file.xyz>` indicates that translation moves will be performed on an user-defined grid read from <file.xyz>. It must be aligned with molecule 1 and can be generated using the `sas_grid` utility.

This description can be seen using the `--help` flag.

4. INPUT FILES

conf1.xyz, **conf2.xyz**

Standard XYZ files containing the coordinates of both structures. For the water dimer mentioned in the previous sections, a dummy site (X) corresponding to water center of mass was used to define the rotation axis of MOL1.

```
themis@linux:~$ cat conf1.xyz

  4
  *blank line*
  OW       0.00000      0.06682      0.00000
  HW      -0.76677     -0.53032      0.00000
  HW       0.76677     -0.53032      0.00000
  X        0.00000      0.00000      0.00000

themis@linux:~$
```

```
themis@linux:~$ cat conf2.xyz

  4
  *blank line*
  OW       0.00000      0.06682      0.00000
  HW      -0.76677     -0.53032      0.00000
  HW       0.76677     -0.53032      0.00000
  X        0.00000      0.00000      0.00000

themis@linux:~$
```

INPUT

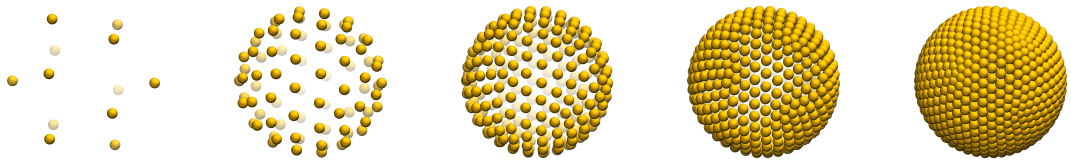
Plain text file containing detailed intructions prior to calculation. It must contain the following keywords:

```
themis@linux:~$ cat INPUT

  rot1_factor : 2                    # integer
  translation_factor : 2             # integer
  rot2_factor :  36                  # integer
  rot2_range : 360.0                 # real
  temperature : 300.0                # real
  potential : lj-coul                # character. valid strings are: none, lj-coul our bh-coul
  ref_mol1 : 1                       # integer
  rot_ref_mol1 : 4                   # integer
  ref_mol2 : 1                       # integer
  rot_ref_mol2 : 2                   # integer
  shortest_distance : 0.8            # real
  write_xtc : no                     # character. valid strings are: no, F, yes or T
  lowest_structures : 2              # integer
  write_frames : none                # character. valid strings are: none, MOP or XYZ
  mopac_job :                        # character

themis@linux:~$
```

rot1_factor : Parameter (p) used to generate the spherical grid used for reorientation moves. The number of points (n) obtained along the sphere surface by dodecahedron tessellation (Figure 4.1) is given by $n = 12 + 10 \times 3 \times (p-1) + 10 \times (p-2) \times (p-1)$. If one uses $p = 0$, the reorientation move will correspond to align molecule 2 along Z-axis (1 reorientational move).



$p = 1$	$p = 3$	$p = 5$	$p = 7$	$p = 9$
$n = 12$	$n = 92$	$n = 252$	$n = 492$	$n = 812$

Figure 4.1: Spherical grids obtained by Tessellation.

translation_factor : Same as `rot1_factor` if a spherical translation shell is used.

rot2_factor : Corresponds to the number of rotation moves around the rotation axis.

rot2_range : Corresponds to the maximum rotation angle (in degrees).

temperature : Absolute temperature (K) used to calculate all thermodynamic properties.

potential : Potential energy function selection. Options are "none", "lj-coul", "bh-coul".

write_frames : Selects the format in which all valid frames will be written: "XYZ", "MOP" and "none". If "MOP" is selected, the optional character variable containing the first line of MOPAC input (**mopac_job**) is read.

ref_mol1 : Site of molecule 1 used for centering, according to **conf1.xyz** file.

rot_ref_mol1 : Site of molecule 1 that will build its rotation vector, according to **conf1.xyz** file.

ref_mol2 : Site of molecule 2 used for centering, according to **conf2.xyz** file.

rot_ref_mol2 : Site of molecule 2 that will build its rotation vector, according to **conf2.xyz** file.

shortest_distance : Corresponds to the lowest intermolecular distance to consider the configuration as a valid one. Below such value (in Angstrom), molecular contacts are considered strongly repulsive and an interaction energy value of 10^{10} kJ/mol is attributed to such configuration. This is useful to avoid spending time calculating energies for unphisical configurations since the energy loop is skipped.

write_xtc : Flag to enable the writting of all configurations to a XTC file. WARNING: very large files can be generated ;)

lowest_structures : Selects the number of lowest energy/highest probability structures to write after the run.

mopac_job : String containing the header for mopac calculations. Enabled when "write_frames : MOP" is selected.

parameters1, **parameters2**

Plain text files containing potential parameters used for energy calculations. Those files are read differently according to the potential used. For Lennard-Jones + Coulomb interaction potential (invoked by `potential:lj-coul`), one should provide q_i, σ_i and ϵ_i parameters, according to Equation 4.1

$$U_{\mathrm{ljc}} = \sum_i \sum_{j<i} 4\epsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^{6} \right] + \frac{1}{4\pi\varepsilon_0} \sum_i \sum_{j<i} \frac{q_i q_j}{r_{ij}} \tag{4.1}$$

where $\epsilon_{ij} = (\epsilon_i \cdot \epsilon_j)^{\frac{1}{2}}$ and $\sigma_{ij} = (\sigma_i \cdot \sigma_j)^{\frac{1}{2}}$. TIP3P parameter files for water are read as follows:

```
themis@linux:~$ cat parameters1

#   q          sig (A)     eps (kJ/mol)
OW  -0.834     3.15061     0.636386
HW  +0.417     0.00000     0.000000
HW  +0.417     0.00000     0.000000
X    0.000     0.00000     0.000000

themis@linux:~$
```

```
themis@linux:~$ cat parameters2

#   q          sig (A)     eps (kJ/mol)
OW  -0.834     3.15061     0.636386
HW  +0.417     0.00000     0.000000
HW  +0.417     0.00000     0.000000
X    0.000     0.00000     0.000000

themis@linux:~$
```

For Buckingham + Coulomb interaction potential, according to Matsui [**?**], one should invoke `potential:bh-coul` and provide A_i, B_i and C_i parameters according to (eq. 4.2)

$$U_{\mathrm{bhc}} = \sum_i \sum_{j<i} \left\{ \left(\frac{-C_i C_j}{r_{ij}^6} \right) + f(B_i + B_j) \exp\left[\left(\frac{A_i + A_j - r_{ij}}{B_i + B_j} \right) \right] \right\} + \frac{1}{4\pi\epsilon_0} \sum_i \sum_{j<i} \frac{q_i q_j}{r_{ij}} \tag{4.2}$$

where the quantity f corresponds to a standard force of 4.184 kJ/mol/Å. Parameters for a TiO_2 unit must be provided as follows:

```
themis@linux:~$ cat parameters1

#   q          A(A)       B (A)      C(A**3 kJ/mol)
Ti   2.1960    1.18230    0.07700    22.5000
O   -1.0980    1.63390    0.11700    54.0000
O   -1.0980    1.63390    0.11700    54.0000
X    0.0000    0.00000    0.00000    0.00000

themis@linux:~$
```

```
themis@linux:~$ cat parameters2

#   q          A(A)       B (A)      C(A**3 kJ/mol)
Ti  2.1960    1.18230    0.07700    22.5000
O  -1.0980    1.63390    0.11700    54.0000
O  -1.0980    1.63390    0.11700    54.0000
X   0.0000    0.00000    0.00000    0.00000

themis@linux:~$
```

NOTE: It is important to highlight that atoms described in both `parameters1` and `parameters2` files must be in the same order as they appear in both `conf1.xyz` and `conf2.xyz` files. Parameters file must contain a header followed by one line for each atom descrived in structure files.

5. OUTPUT FILES

energy.bin

Binary file containing interaction energy values for all microstates. Since all entries are written in the right loop sequence, they can be read using the `rerun` feature.

energy-sort.log

Contains interaction energy values and probabilities for the N most probable structures. By running Themis with the input files presented below, and considering a spherical grid with radius = 2.8 Å, one obtains

```
themis@linux:~$ cat energy-sort.log

#int_energy(r2,r1,t) r2      r1       t        prob.     sum prob.
  -2.83500E+001       1      10       3     6.704E-004  6.704E-004
  -2.83500E+001       1       4       9     6.704E-004  1.341E-003
  -2.83453E+001       2       4       9     6.692E-004  2.010E-003
  -2.83453E+001       2      10       3     6.692E-004  2.679E-003
  -2.83453E+001     120       4       9     6.692E-004  3.348E-003
  -2.83453E+001     120      10       3     6.692E-004  4.017E-003
  -2.83312E+001       3      10       3     6.654E-004  4.683E-003
  -2.83312E+001     119      10       3     6.654E-004  5.348E-003
  -2.83312E+001       3       4       9     6.654E-004  6.014E-003
  -2.83312E+001     119       4       9     6.654E-004  6.679E-003
  -2.83078E+001     118      10       3     6.592E-004  7.338E-003
  -2.83078E+001     118       4       9     6.592E-004  7.997E-003
  -2.83078E+001       4      10       3     6.592E-004  8.657E-003
  -2.83078E+001       4       4       9     6.592E-004  9.316E-003
  -2.82751E+001     117       4       9     6.506E-004  9.966E-003
  -2.82751E+001     117      10       3     6.506E-004  1.062E-002
  -2.82751E+001       5      10       3     6.506E-004  1.127E-002
  -2.82751E+001       5       4       9     6.506E-004  1.192E-002
  -2.82333E+001     116      10       3     6.398E-004  1.256E-002
  -2.82333E+001       6      10       3     6.398E-004  1.320E-002

themis@linux:~$
```

output.log

Contains thermodynamic data for all translation grid points, and also for the overall ensemble. Written in an extended XYZ format containing extra field values for each grid point (probability, free energy, energy and entropic penalty).

```
themis@linux:~$ cat output.log

        42
 #      X (A)     Y (A)     Z (A)  point          PROB      A (kJ/mol)    -TS (kJ/mol)      E (kJ/mol)
 X    2.38182   1.47205   0.00000      1   2.98845E-003   -1.08134E+001    6.75915E+000   -1.75725E+001
 X    2.38182  -1.47205   0.00000      2   2.98845E-003   -1.08134E+001    6.75915E+000   -1.75725E+001
 X    1.47205   0.00000   2.38182      3   5.85172E-002   -1.82330E+001    6.84167E+000   -2.50746E+001
 X    1.47205   0.00000  -2.38182      4   1.34004E-003   -8.81280E+000    4.19575E+000   -1.30086E+001
 X    0.00000   2.38182   1.47205      5   1.00969E-002   -1.38502E+001    6.78551E+000   -2.06357E+001
 X    0.00000   2.38182  -1.47205      6   1.74725E-001   -2.09615E+001    4.32032E+000   -2.52818E+001
 X    0.00000  -2.38182   1.47205      7   1.00969E-002   -1.38502E+001    6.78551E+000   -2.06357E+001
 X    0.00000  -2.38182  -1.47205      8   1.74725E-001   -2.09615E+001    4.32032E+000   -2.52818E+001
 ...
 X   -2.26525   0.86525  -1.40000     40   9.83462E-004   -8.04111E+000    5.57165E+000   -1.36128E+001
 X   -2.26525  -0.86525  -1.40000     41   9.83462E-004   -8.04111E+000    5.57165E+000   -1.36128E+001
 X   -2.80000   0.00000   0.00000     42   2.97201E-003   -1.07996E+001    6.97190E+000   -1.77715E+001
 ---------------------------------------------------------------------------------------------------------
 TOTAL OVER TRANSLATIONAL GRID            1.00000E+000   -1.59900E+001    7.67496E+000   -2.36649E+001

themis@linux:~$
```

output-sort.log

Same as `output.log` but ordered from most probable point to the least probable point.

```
themis@linux:~$ cat output-sort.log

        42
 #      X (A)     Y (A)     Z (A)  point          PROB      A (kJ/mol)    -TS (kJ/mol)      E (kJ/mol)
 X    0.00000  -2.38182  -1.47205      8   1.74725E-001   -2.09615E+001    4.32032E+000   -2.52818E+001
 X    0.00000   2.38182  -1.47205      6   1.74725E-001   -2.09615E+001    4.32032E+000   -2.52818E+001
 X    0.00000   0.00000   2.80000     24   8.68520E-002   -1.92179E+001    6.43659E+000   -2.56545E+001
 X    1.47205   0.00000   2.38182      3   5.85172E-002   -1.82330E+001    6.84167E+000   -2.50746E+001
 X   -1.47205   0.00000   2.38182      9   5.85172E-002   -1.82330E+001    6.84167E+000   -2.50746E+001
 X    0.86525   1.40000   2.26525     22   4.04675E-002   -1.73130E+001    7.12969E+000   -2.44427E+001
 X   -0.86525   1.40000   2.26525     29   4.04675E-002   -1.73130E+001    7.12969E+000   -2.44427E+001
 X    0.86525  -1.40000   2.26525     23   4.04675E-002   -1.73130E+001    7.12969E+000   -2.44427E+001
 ...
 X   -2.26525   0.86525  -1.40000     40   9.83462E-004   -8.04111E+000    5.57165E+000   -1.36128E+001
 X    2.26525  -0.86525  -1.40000     19   9.83462E-004   -8.04111E+000    5.57165E+000   -1.36128E+001
 X   -2.26525  -0.86525  -1.40000     41   9.83462E-004   -8.04111E+000    5.57165E+000   -1.36128E+001
 ------------------------------------------------------------------------------------------------------
 TOTAL OVER TRANSLATIONAL GRID            1.00000E+000   -1.59900E+001    7.67496E+000   -2.36649E+001

themis@linux:~$
```

surf_free-energy.vmd, surf_energy.vmd, surf_entropic-penalty.vmd

Contains a VMD script for reading the thermodynamic data along the translation grid from file `output.log`.

lowest_0001.xyz

XYZ coordinates for the most probable structure from the whole ensemble. The number of lowest structure files is defined by the user in the `INPUT` file.

```
themis@linux:~$ cat lowest_0001.xyz

          8
 Energy =  -2.8350000E+01
 O       0.0000     0.0000     0.0000
 H      -0.0000    -0.7668    -0.5971
 H      -0.0000     0.7668    -0.5971
 X      -0.0000    -0.0000    -0.0668
 O       1.4720     0.0000     2.3818
 H       0.9611     0.0000     1.5551
 H       0.7957     0.0000     3.0797
 X       1.4056     0.0000     2.3746

themis@linux:~$
```

grid_log.log

File containing informations of each translation grid point: point number, number of rejected structures (due to atomic clashes), spent time.

```
themis@linux:~$ cat grid_log.log

 t point   rejected structures   time (s)
       1         0 of    5040      0.020
       2         0 of    5040      0.012
       3         0 of    5040      0.012
       4         0 of    5040      0.013
     ...
      38         0 of    5040      0.024
      39         0 of    5040      0.013
      40         0 of    5040      0.013
      41         0 of    5040      0.012
      42         0 of    5040      0.014

themis@linux:~$
```

full_ensemble.xtc

XTC trajectory file containing the whole ensemble. Written if INPUT option `write_xtc` is enabled.

point_0001_0001_0001.xyz

XYZ file containing the structure of the microstate t = 1, r1 = 1, r2 = 1. Files are numbered according to the loop position. Written if INPUT option `write_frames = XYZ` is set. Microstates with

intermolecular distances below the one defined by `shortest_distance` are skipped. WARNING: this option will create a very large number of files in the directory. ;)

```
themis@linux:~$ cat point_0001_0001_0001.xyz

       8
 Energy =   0.0000000E+00
 O       0.0000     0.0000     0.0000
 H      -0.0000    -0.7668    -0.5971
 H      -0.0000     0.7668    -0.5971
 X      -0.0000    -0.0000    -0.0668
 O       2.3818     1.4720     0.0000
 H       3.2085     1.9830    -0.0000
 H       2.1793     1.3469     0.9423
 X       2.4167     1.4936     0.0527

themis@linux:~$
```

point_0001_0001_0001.mop

Same as before, but in MOPAC format, containing the header defined by `mopac_job`. Written if INPUT options `write_frames = MOP` is set. Microstates with intermolecular distances below the one defined by `shortest_distance` are skipped. WARNING: this option will create a very large number of files in the directory. ;)

```
themis@linux:~$ cat point_0001_0001_0001.mop

 PM7 1SCF CHARGE=0 THREADS=1 OUTPUT
 *blank line*
 *blank line*
 O       0.0000  0   0.0000  0   0.0000  0
 H      -0.0000  1  -0.7668  1  -0.5971  1
 H      -0.0000  1   0.7668  1  -0.5971  1
 X      -0.0000  0  -0.0000  0  -0.0668  0
 O       2.3818  0   1.4720  0   0.0000  0
 H       3.2085  0   1.9830  0  -0.0000  0
 H       2.1793  1   1.3469  1   0.9423  1
 X       2.4167  1   1.4936  1   0.0527  1

themis@linux:~$
```

Workflow for MOPAC calculations of biphenyl dimers

Calculations using Themis + MOPAC were performed in multiple steps. For each intermolecular distance

i) Write MOPAC input files for all configurations using the following INPUT options:

```
themis@linux:~$ cat INPUT

  rot1_factor : 4
  translation_factor : 3
  rot2_factor :  36
  rot2_range : 360.0
  temperature : 300.0
  potential : none
  ref_mol1 : 23
  rot_ref_mol1 : 1
  ref_mol2 : 23
  rot_ref_mol2 : 1
  shortest_distance : 1.2
  write_xtc : no
  lowest_structures : 10
  write_frames : MOP
  mopac_job : MOP PM7 1scf output threads=1 shift=1.0 itry=150

themis@linux:~$
```

ii) Run the single-point calculation for every `.mop` file. This can be done more efficiently using the GNU Parallel tool. [**?**]

iii) Once finished, a python script was used to extract the final heat of formation of every output file and generate a `energy.log` file containing all interaction energies.

iv) Themis `-rerun` option was used to read all required files, calculate all thermodynamic properties and search for the most stable structures.

For excited state calculations, we used the following MOPAC header:

```
mopac_job : MOP PM7 1scf output threads=1 shift=1.0 itry=150 CIS C.I.=4 MECI ROOT=2 SINGLET geo-ok
```

PERFORMANCE BENCHMARK

In order to analyze the effect of grid coarseness on both computation time and thermodynamic results, the association thermodynamics for (L)-CYS dimer was obtained using different grids for translation and rot_{point}. Considering $nr_2 = 120$ and 167 separation distances, the number of microstates of the whole ensemble ranges from $\approx 3.5 \times 10^7$ (grid factors = 2) to $\approx 2.0 \times 10^{10}$ (grid factors = 10). This large difference results in wall-times ranging from ≈ 6 min to ≈ 2 days (Fig. 5.1, top-left), which requires a compromise between computational cost and accuracy.

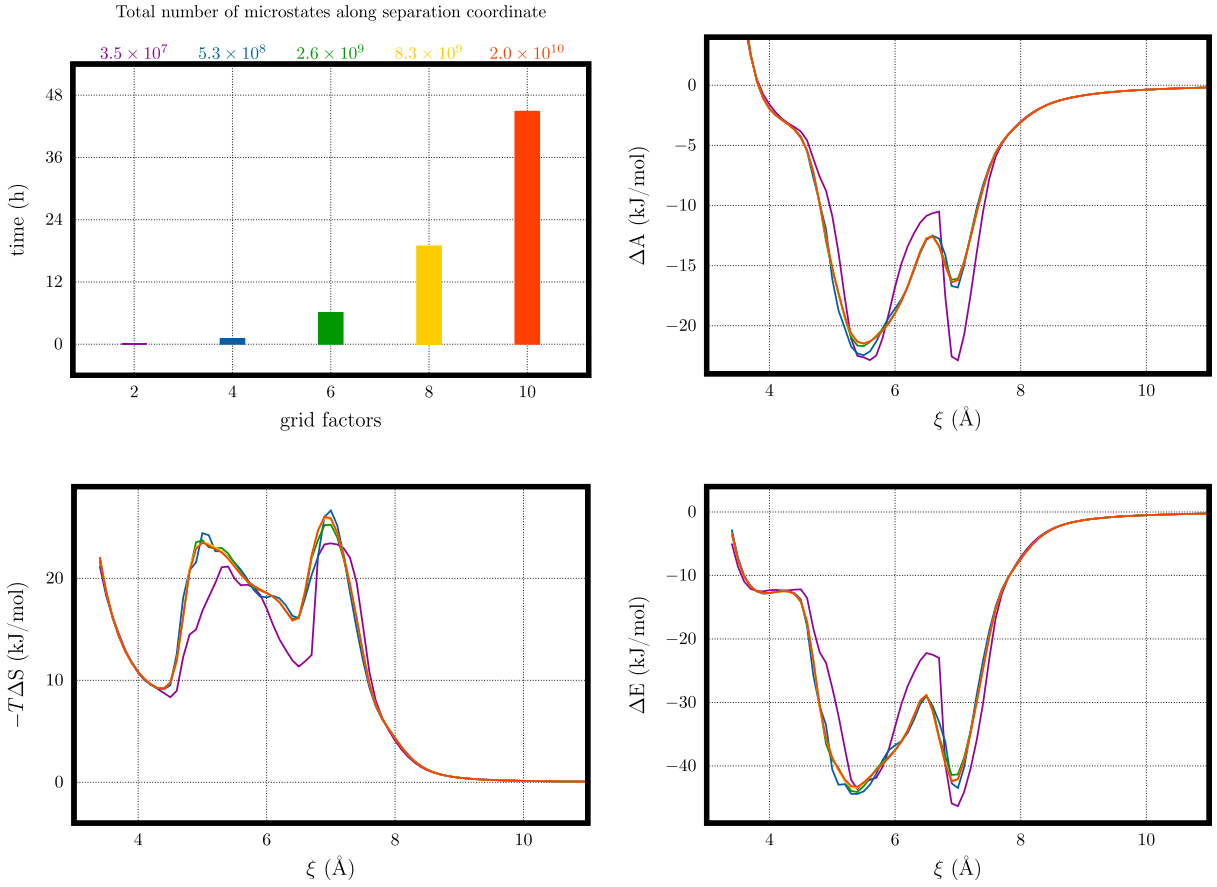


Figure 5.1: Comparison of calculation wall-time (in hours) and thermodynamic properties as a function of the grid coarseness for the association of (L)-CYS dimers.

As one can notice, the cheapest calculation (grid factor = 2, purple curves) resulted in thermodynamic profiles considerably different, due to poorly sampling phase space regions with higher entropic loss. For grid factor = 4 (blue curves), although results are improved, one can still observe noticeable differences in comparison to the more costly calculations. On the other hand, for grid factor >= 6, only small differences are observed, indicating a good convergence for all thermodynamic profiles.