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

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SUPPORTING INFORMATION

Themis user guide

COMMAND LINE OPTIONS

Firstly, to display Themis help, one should use the command below

```
themis@linux:~$ themis --help
------------------------------------------------------------------------
                        Program THEMIS version beta
  STARTED AT: 26/09/2019 - 09:20:23
  COMMAND LINE READ: themis --help
------------------------------------------------------------------------
          Usage:  themis [RUNTYPE] [GRIDTYPE] [RADIUS|FILENAME]
------------------------------------------------------------------------
                               [RUNTYPE] options
            --run     Start new calculation.
          --rerun     Read energies from previous run. User must
                      give an energy.bin file (from Themis) or an
                      energy.log file (from external programs).
------------------------------------------------------------------------
                             [GRIDTYPE] options
          --shell     Translation moves will be performed on a
                      spherical shell grid generated on the run.
           --user     Translation moves will be performed on an
                      user-defined external grid.
------------------------------------------------------------------------
                               [RADIUS] value
           (real)     Scaling factor for the spherical grid
                      radius (in Angstrom)
                            [FILENAME] value
           (char)     XYZ file containing the user-defined
                      translation grid. It must be aligned
                      with molecule 1
------------------------------------------------------------------------
                                Other options
           --help     Display this help
        --version     Display the version
------------------------------------------------------------------------
themis@linux:~$
```

Also, to display Themis license information, one should use the following command

```
themis@linux:~$ themis --license
------------------------------------------------------------------------
                        Program THEMIS version beta
  STARTED AT: 26/09/2019 - 10:29:47
  COMMAND LINE READ: themis --license
------------------------------------------------------------------------
              Copyright (C) 2019 Felippe Mariano Colombari
                              License GPLv3+:
                        GNU GPL version 3 or later
                    see <http://gnu.org/license/gpl.html>
                             This is a free software
                  you are free to change it and redistributibe it
                There is NO WARRANTY, to the extent permited by law
                         Written by Felippe M. Colombari
                        E-mail: colombarifm@hotmail.com
------------------------------------------------------------------------
themis@linux:~$
```

To run a new simulation using a spherical translation grid of radius 4.0 Å, one should enter the following command

```
themis@linux:~$ themis --run --shell 4.0 > resume.log &
themis@linux:~$
```

On the other hand, the following command

```
themis@linux:~$ themis --run --user vdw.xyz > resume.log &
themis@linux:~$
```

will run a new simulation using a translation grid corresponding to the VdW surface of molecule 1 saved on “vdw.xyz”.

INPUT FILES

conf1.xyz and **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 an orientation vector along Z-axis, as shown below.

```
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:~$
```

parameters1 and **parameters2** are plain text files containing potential parameters used for energy calculations. Those files are read differently according to the potential used. For `potential : lj-coul` (eq. 1), TIP3P water parameters are given as follows:

$$U_{\mathrm{ljc}} = U_{\mathrm{lj}} + U_{\mathrm{coul}} = \sum_i \sum_{j<i} 4\epsilon_{ij} \left(\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^{6} \right) + \frac{1}{4\pi\epsilon_0} \sum_i \sum_{j<i} \frac{q_i q_j}{r_{ij}} \tag{1}$$

where $\epsilon_{ij} = (\epsilon_i \cdot \epsilon_j)^{\frac{1}{2}}$ and $\sigma_{ij} = (\sigma_i \cdot \sigma_j)^{\frac{1}{2}}$

```
  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 `potential : bh-coul` (eq. 2), MATSUI parameters for a TiO_2 unit must be provided as follows:

$$U_{\mathrm{bhc}} = U_{\mathrm{bh}} + U_{\mathrm{coul}} = \sum_i \sum_{j<i} \left\{ \left(\frac{-C_i C_j}{r_{ij}^6} \right) + f(B_i + B_j) \exp\left[\left(\frac{A_i + A_j - r_{ij}}{B_i + B_j} \right) \right] \right\} + \frac{1}{4\pi\epsilon_0} \sum_i \sum_{j<i} \frac{q_i q_j}{r_{ij}} \tag{2}$$

where the quantity f corresponds to a standard force of 4.184 kJ/mol/Å.

```
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.

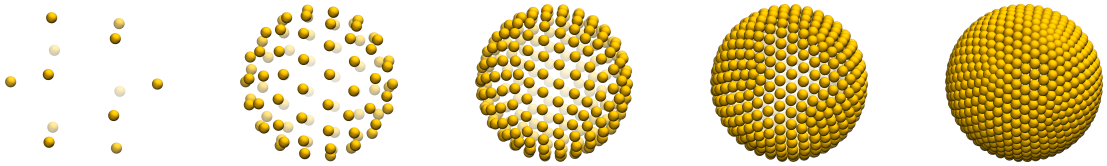
INPUT file: plain text file containing detailed intructions prior to calculation.

```
themis@linux:~$ cat INPUT

  reorientation_factor : 2                  # integer
  translation_factor : 2                    # integer
  gyration_factor :  36                     # integer
  gyration_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 : 20                    # integer
  write_frames : none                       # character. valid strings are: none, MOP or XYZ
  mopac_job :                               # character

themis@linux:~$
```

`reorientation_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 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).



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

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

`gyration_factor`: Corresponds to the number of gyration points around the rotation axis.

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

`temperature`: Absolute temperature (K).

`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 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.

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

inter_energy(g,r,t)   g       r       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, 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, r = 1, g = 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:~$ 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:~$ 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:~$
```

Umbrella Sampling calculations for the water dimer

The sampling along the OW-OW separation coordinate (ξ) was carried by running multiple independent simulations with a biased umbrella potential that restrains the water-water intermolecular distance. For each run, a short energy minimization was carried in order to remove repulsive contacts (especially for short intermolecular distances). The sampling was carried out in vacuum using a stochastic dynamics integrator (T = 300 K). Lennard-Jones and electrostatic interactions were computed in direct space without a cutoff. Bonds were constrained using LINCS allowing a time step of 2 fs. ξ_i was sampled from 2 Å to 15 Å in 0.5 Å intervals. An umbrella force constant of 10^4 kJ/mol/nm^2 was set for 3 Å $\leq \xi_i \leq$ 15 Å, and 2 $\times 10^4$ kJ/mol/nm^2 for 2 Å $\leq \xi_i <$ 3 Å.

Entropic and energetic contributions to the potential of mean force can be obtained by finite differences, considering simulations at different temperatures (here, 275 K and 325K).

$$\Delta S(\xi) = -\left(\frac{\partial \Delta A(\xi, T)}{\partial T}\right)$$

$$\Delta S(\xi) = -\frac{[\Delta A(\xi, T + \Delta T) - \Delta A(\xi, T - \Delta T]}{2\Delta T}$$

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

  reorientation_factor : 4
  translation_factor : 3
  gyration_factor :  36
  gyration_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 : none
  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
```