Performing advanced MD simulations with ORAC

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2011, march 22
Cycle “Modélisation de Macromolécules Biologiques”
Université di Cergy-Pontoise (FR)

last update: May 10, 2011

ORAC

ORAC rel 5.1

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Home Page

Home page:

http://www.chim.unifi.it/orac

References

[1] P. Procacci, E. Paci, T. Darden, and M. Marchi. ORAC: A Molecular Dynamics Program to Simulate Complex Molecular Systems with Realistic Electrostatic Interactions. *J. Comput. Chem.*, 18:1848–1862, 1997.

[2] S. Marsili, G. F. Signorini, R. Chelli, M. Marchi, and P. Procacci. ORAC: A molecular dynamics simulation program to explore free energy surfaces in biomolecular systems at the atomistic level. *J. Comput. Chem.*, 31:1106–1116, 2010.

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In practice

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    - Intel
    - IBM xlf family
    - . . .

(see file BUILDING)

Anatomy of a distribution


```
  orac.5_1_1.rev257/
|-- BUILDING
|-- COPYRIGHT_NOTICE
|-- Makefile
|-- README
|-- RELEASE
|-- doc/
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|-- pdb/
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Look for README files in each directory for help!

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$ cd orac-5_1_x
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   default
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   Intel
   IBM
   ...
   PARALLEL
   gfortran_PARALLEL
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   ...
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   gfortran_PARALLEL
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   ...
```

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   default
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   Intel
   IBM
   ...
   PARALLEL
   gfortran_PARALLEL
   Intel_PARALLEL
   IBM_PARALLEL
   ...
```

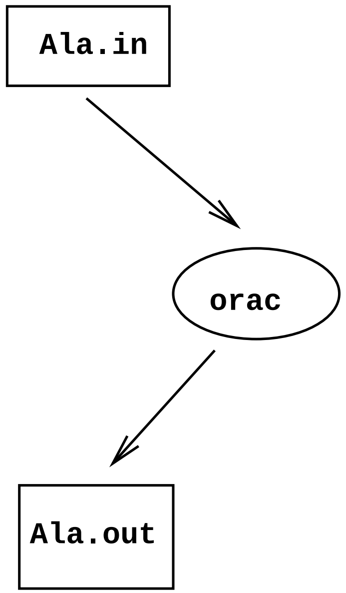
- to create the executable `orac_XXXXX` in directory `src/default`:

```
$ make default
```

- edit `src/config.H` and recompile, to change maximum array dimensions

Input and Output files

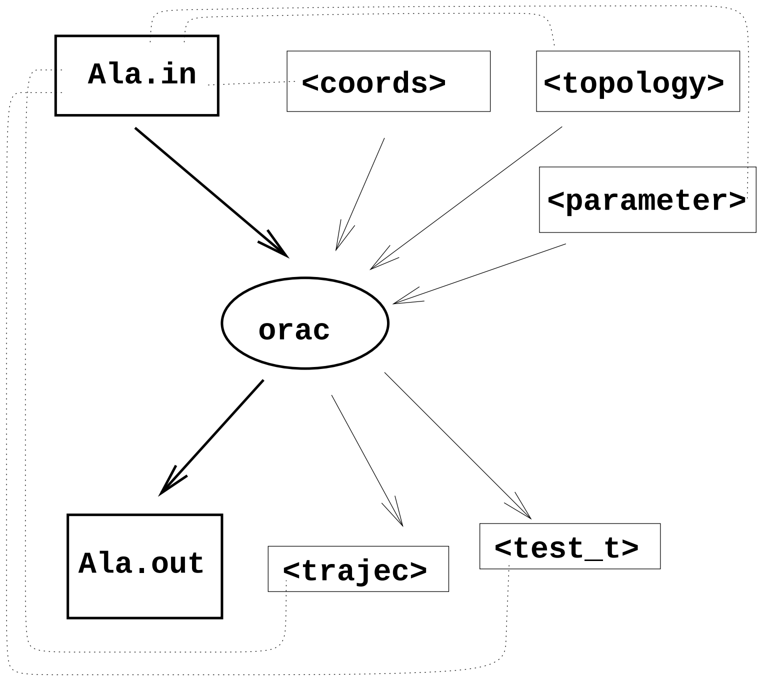
- Standard input and standard output:




```
orac < Ala.in > Ala.out
```

Input and Output files

- Auxiliary files whose names are defined in main input:

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The main input file

- The main input file has a block structure
  - each block begins with &KEYWORD and ends with &END

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  - each block begins with &KEYWORD and ends with &END
- Block order does not matter
  All the input is read first; then the required computations are started

The main input file (2)


```
&SETUP
   CRYSTAL  62.0 62.0 62.0 90.0 90.0 90.0
   READ_PDB ../../pdb/glc.pdb
&END
```

The main input file (2)


```
&SETUP
  CRYSTAL 62.0 62.0 62.0 90.0 90.0 90.0
  READ_PDB ../../pdb/glc.pdb
&END

&PARAMETERS
  READ_TPG_ASCII ../../lib/amber03.tpg
  READ_PRM_ASCII ../../lib/amber03.prm
  JOIN SOLUTE
    glc
  END
&END
```

The main input file (2)


```
&SETUP
   CRYSTAL  62.0 62.0 62.0 90.0 90.0 90.0
   READ_PDB ../../pdb/glc.pdb
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&PARAMETERS
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   JOIN SOLUTE
     glc
   END
&END

&POTENTIAL
   CUTOFF 12.0
   STRETCHING
   UPDATE 10.0 2.0
&END

&SIMULATION
   MINIMIZE
     CG 0.00001
   END
   FREQUENCIES
     print OPEN glc.frq
   END
&END

&RUN
  PRINT 10.0
  TIME 1000.0
&END
```

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     print OPEN glc.frq
   END
&END

&RUN
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```

- See section “Input to ORAC” in the manual for detailed description of input

The main output file

1. a copy of the input

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2. output from startup operations (reading files, setup box, ...)

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3. intermediate simulation results:

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3. intermediate simulation results:

```
      Tstep  =      60.0 Total =  -2889.889 TotPot = -8624.839
      Coulomb = -14817.630 Recipr = -8874.305 NonBond = -15058.432
      Ener14 =   1285.083 Bonded = 6433.593 Stretch = 2125.946
      Angle  =   1728.847 I-Tors =  88.797 P-Tors = 2490.003
      TotTemp =  328.854 Hoover =    54.3 ResTemp = 323.494
      TraTemp =  367.831

<------ Dumping Restart File ------->

Neighbor Lists Dimensions *neighbor( 36855)*



      Tstep  =      72.0 Total =  -2918.812 TotPot = -8891.027
      Coulomb = -15052.095 Recipr = -9031.840 NonBond = -15282.772
      Ener14 =   1264.188 Bonded = 6391.744 Stretch = 2014.560
      Angle  =   1780.318 I-Tors = 107.506 P-Tors = 2489.360
      TotTemp =  342.152 Hoover =   157.6 ResTemp = 333.165
      TraTemp =  407.513

Velocities have been rescaled ---->
```

Analysis of results

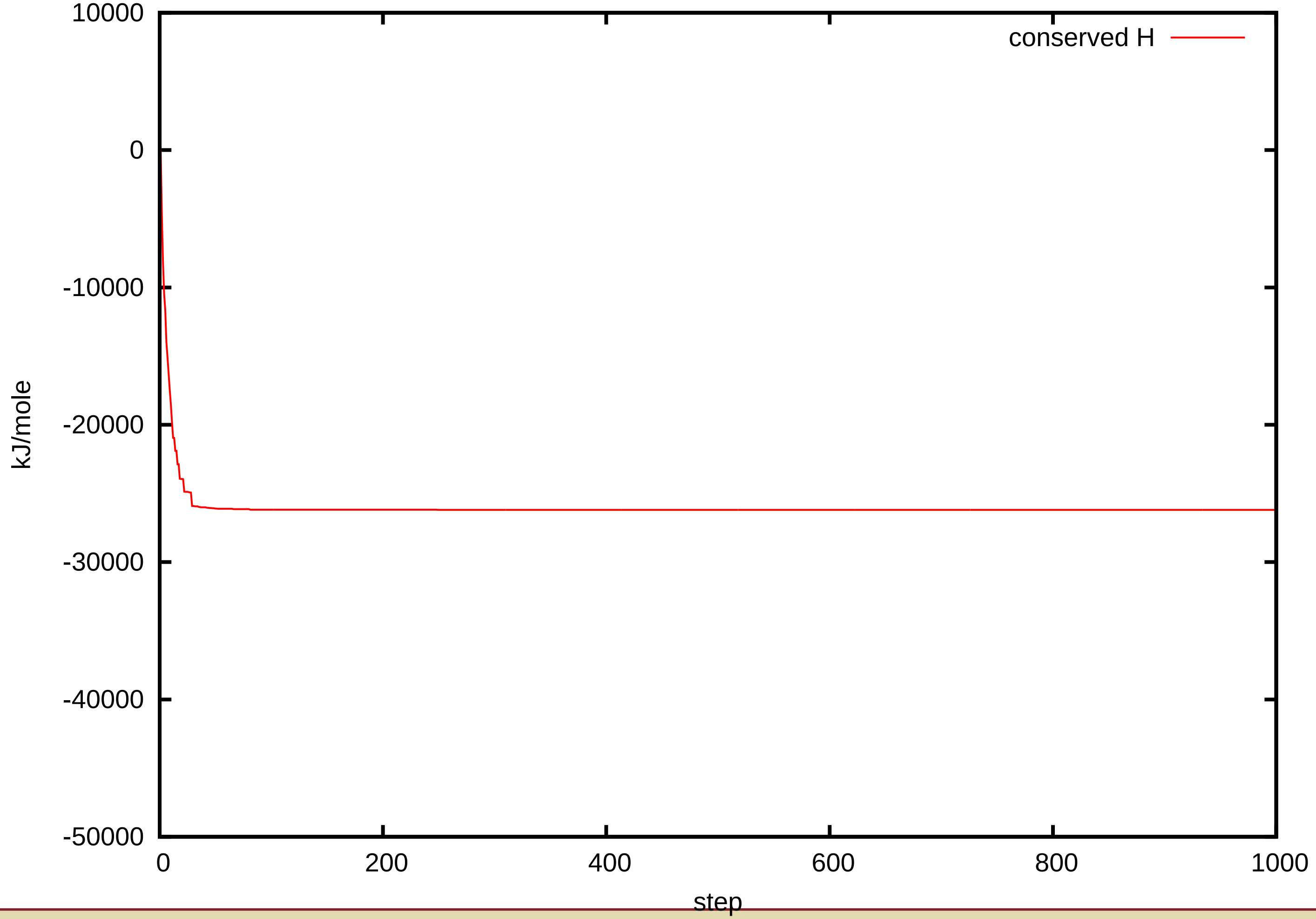
- use tools:
  - orac-post-proc
  - analysis
  - rmsd90

Examples

A basic example

NpT simulation of a small protein in water, with initial equilibration

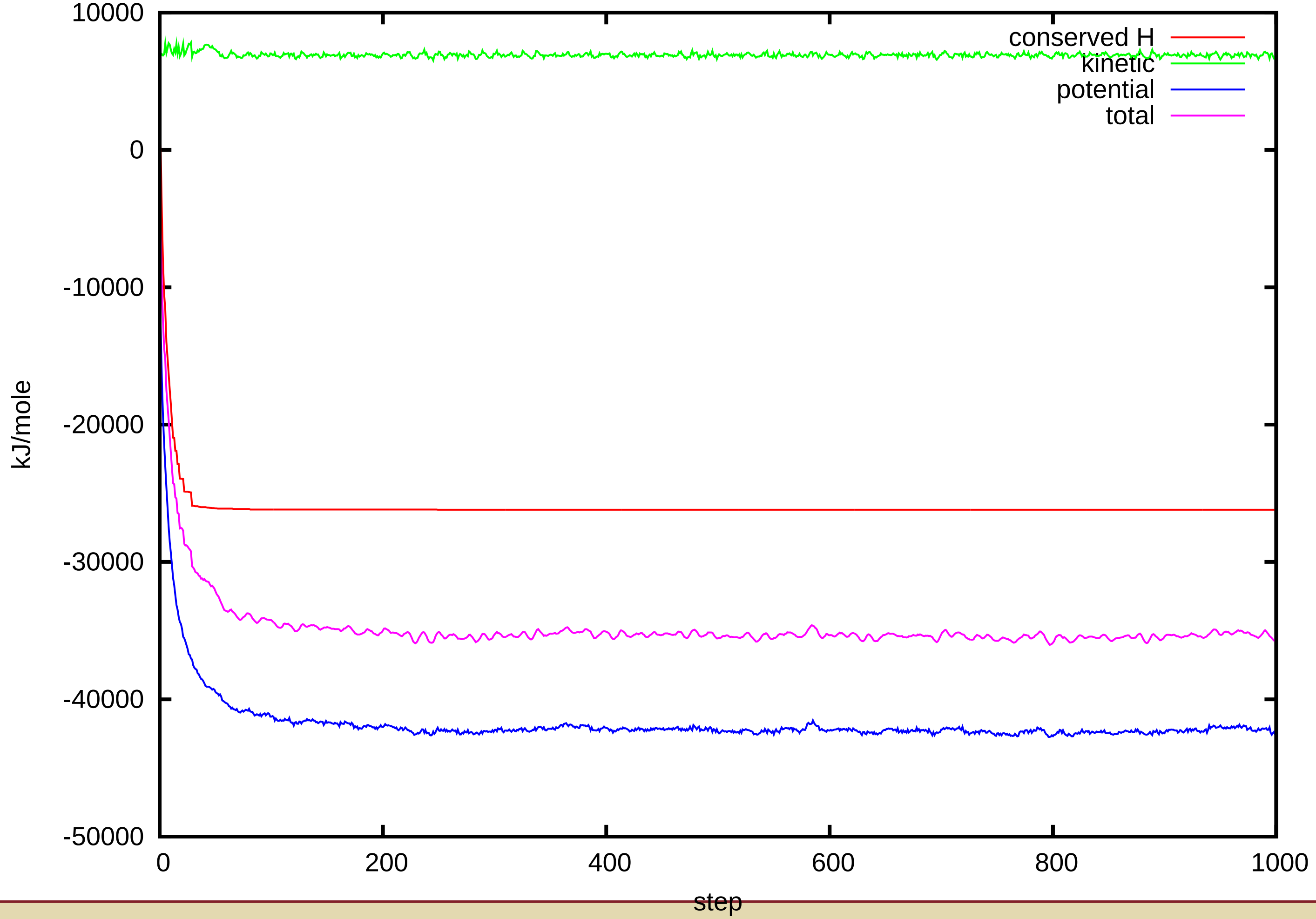
- Conservation of Hamiltonian:



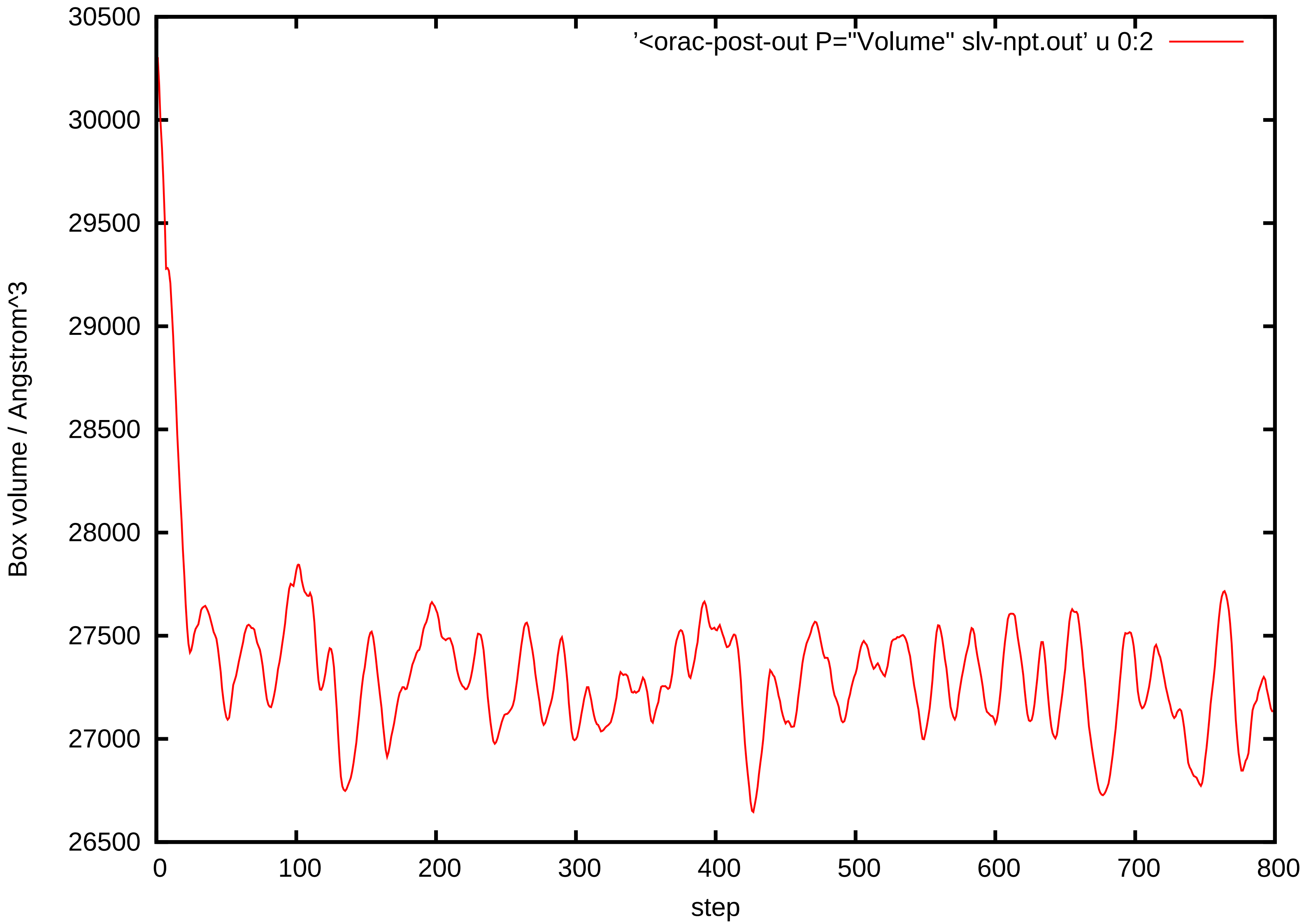
A basic example

NpT simulation of a small protein in water, with initial equilibration

- Energies of the real system:



plot selected properties from output



compute structural properties with `analysis`

`analysis` is a small, extensible auxiliary program to compute structural properties from PDB trajectory:

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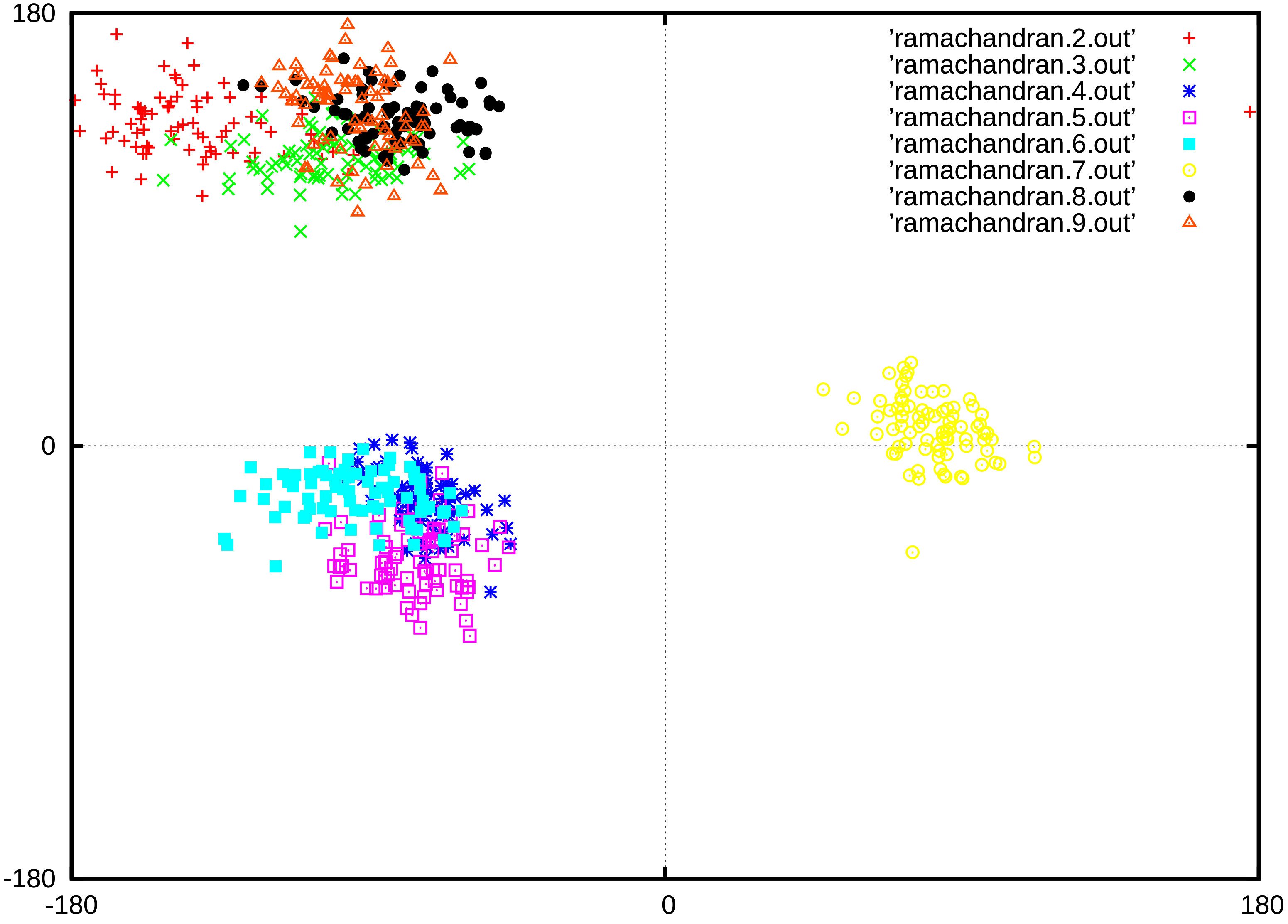
The file `ana.in` looks like the following:

```
   # name of the PDB file to analize:
slv.pdb
   #
& ramachandran 1
& ramachandran 2
& ramachandran 3
& ramachandran 4
& ramachandran 5
& ramachandran 6
& ramachandran 7
& ramachandran 8
& ramachandran 9
```

compute structural properties with `analysis` (2)



Tests

ORAC tests

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Tests are designed to be very short! no real-world calculation!

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   then configure it

   (see README_PARALLEL files, and `http://www.mcs.anl.gov/research/projects/mpich2`)

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   ```

   then configure it

   (see README_PARALLEL files, and `http://www.mcs.anl.gov/research/projects/mpich2`)

2. to build the parallel version of the program, e.g.:

   ```
   $ cd orac-5_1_x/
   $ make PARALLEL
   ```

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- at the end of each test, you may find that the output is different from the reference data listed in the package

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  - the evolution of a REM simulation, or of a steered MD trajectory, depend critically on random number generators, that may work differently in your hw/sw environment, soon driving your simulation away from the reference one.

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- this is not necessarily an error:
  - the evolution of a REM simulation, or of a steered MD trajectory, depend critically on random number generators, that may work differently in your hw/sw environment, soon driving your simulation away from the reference one.
  - just check that results are *reasonable and similar* to what is expected

REM Tests

Hamiltonian REM

Hamiltonian Replica Exchange MD is implemented in ORAC

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$$c_1 = 1, c2, \ldots, c_N$$

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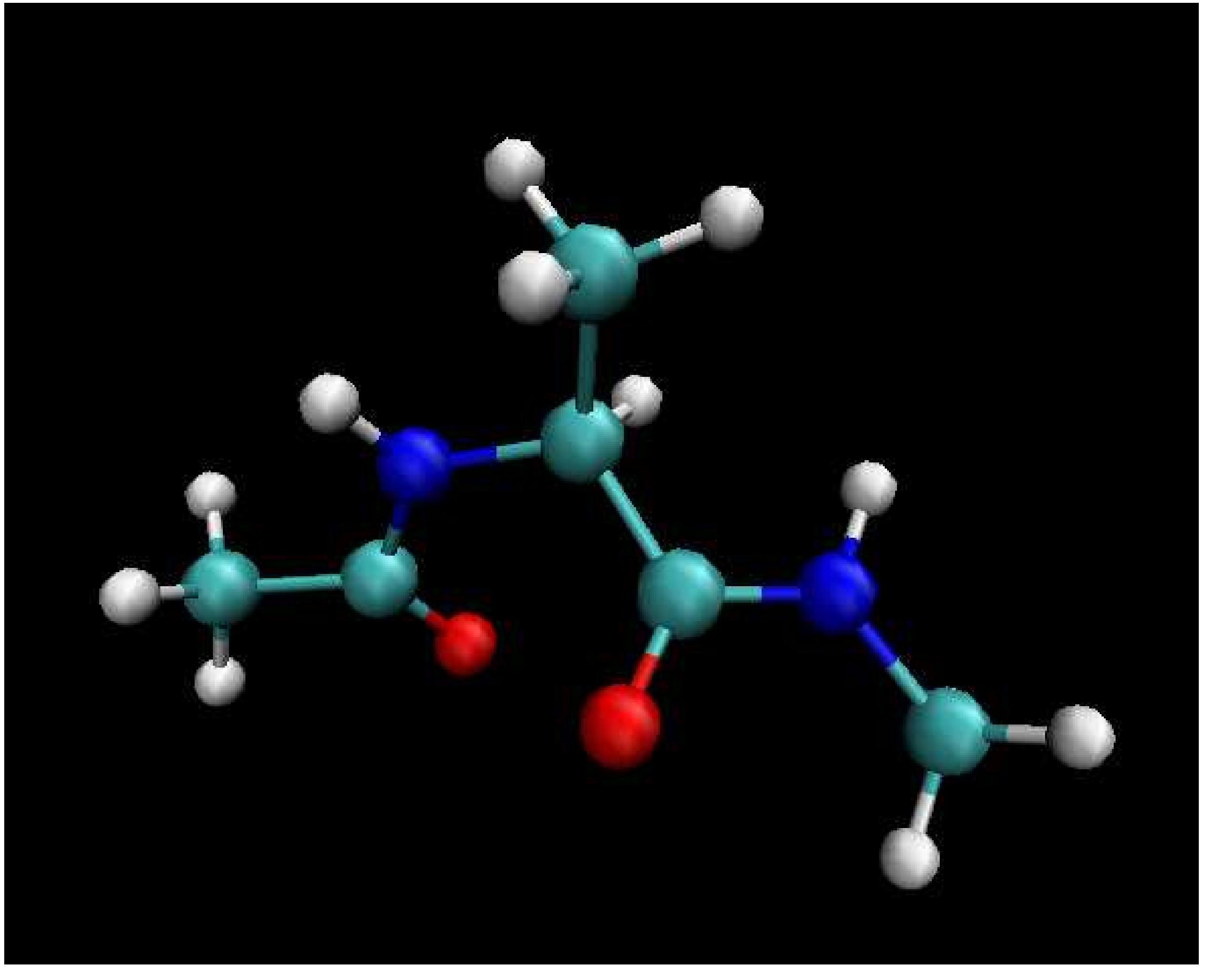
- N copies of the system are simulated, with potential scaling coefficients

$$c_1 = 1, c2, \ldots, c_N$$

  and exchanges between adjacent copies are attempted at definite intervals
- In what follows:
  - "replica" or "temperature" designates one value of the scaled potential
  - "trajectory" designates one simulation:
    "one *trajectory* explores different *temperatures*"

A simple REM example

Figure 1: Alanine dipeptide



input file `1.in`

- REM Test n.1: run a cold start of Alanine dipeptide, on 8 processors.

```
&REM
   SETUP 0.75 1
   STEP 5.
   PRINT 1000.
&END
```

- This will run a REMD simulation with replicas having a scaling coefficient going from 1 to 0.75, (equivalent to temperature going from T to $\frac{T}{0.75}$), attempting a swap every $5.fs$

Run the test

(Before actually running the tests, you may need some tweaking of the Makefile in that directory, e.g. setting `O_BIN_P` to a different path for the parallel executable).

```
$ cd orac-5_1_x/tests/REM_tests
```

Run the test

(Before actually running the tests, you may need some tweaking of the Makefile in that directory, e.g. setting `O_BIN_P` to a different path for the parallel executable).

```
$ cd orac-5_1_x/tests/REM_tests
$  # possibly edit Makefile
```

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```
$ cd orac-5_1_x/tests/REM_tests
$  # possibly edit Makefile
$ make test1
```

Run the test

(Before actually running the tests, you may need some tweaking of the Makefile in that directory, e.g. setting `O_BIN_P` to a different path for the parallel executable).

```
$ cd orac-5_1_x/tests/REM_tests
$  # possibly edit Makefile
$ make test1
Starting test 1...
mpiexec -n 8 ../../src/PARALLEL/orac_Linux < 1.in
```

Run the test

(Before actually running the tests, you may need some tweaking of the Makefile in that directory, e.g. setting `O_BIN_P` to a different path for the parallel executable).

```
$ cd orac-5_1_x/tests/REM_tests
$  # possibly edit Makefile
$ make test1
Starting test 1...
mpiexec -n 8 ../../src/PARALLEL/orac_Linux < 1.in
```

NOTE that the number of processes is given as argument to `mpiexec`

Run the test

(Before actually running the tests, you may need some tweaking of the Makefile in that directory, e.g. setting `O_BIN_P` to a different path for the parallel executable).

```
$ cd orac-5_1_x/tests/REM_tests
$  # possibly edit Makefile
$ make test1
Starting test 1...
mpiexec -n 8 ../../src/PARALLEL/orac_Linux < 1.in
```

NOTE that the number of processes is given as argument to `mpiexec`
Each trajectory (process) outputs to a separate directory:

```
REM_tests/
|-- PAR0000/
|-- PAR0001/
|-- PAR0002/
|-- PAR0003/
|-- PAR0004/
|-- PAR0005/
|-- PAR0006/
`-- PAR0007/
```

What's in a PARxxxx

In each subdirectory one finds output from one trajectory.
A useful file is REM_DIAGNOSTICS:

```
Time(fs) Ens.Index Etot Ekin  Epot     Unscaled_Epot(1) Unscaled_Epot(2) Unscaled_Epot(3)
   0.000       1 -15798.591 3975.097 -20294.758 36.86108963 66.27519055 -20397.89417554
   9.000       1 -15799.197 3941.835 -20268.162 48.33958736 69.89173141 -20386.39351932
  18.000       1 -15799.348 3849.030 -20180.790 36.61301332 64.85898411 -20282.26240292
  27.000       1 -15799.181 3885.160 -20221.080 59.92605948 76.18079698 -20357.18730765
...
1350.000       1 -15810.839 3921.483 -20032.673 44.99945318 71.23901455 -20148.91159616
1359.000       1 -15810.624 3863.698 -19971.024 55.31566941 65.84458965 -20092.18387400
1368.000       2 -15005.928 3832.054 -19934.166 46.66017953 64.12593199 -20044.95241986
1377.000       2 -15008.400 3910.391 -20015.584 55.69435608 66.28114096 -20137.55997783
1386.000       1 -15812.089 3905.204 -20005.686 39.16567754 64.59704046 -20109.44839358
1926.000       2 -15013.292 3673.233 -19566.784 71.44607447 65.80181736 -19704.03189459
1935.000       2 -15013.742 3753.891 -19648.255 48.80251814 72.37553816 -19769.43267586
2475.000       2 -15017.244 3886.572 -19709.729 65.61279004 59.80027938 -19835.14226040
2484.000       2 -15015.418 3799.623 -19619.400 46.35157101 59.93559335 -19725.68686377
2493.000       3 -14258.520 3823.324 -19648.693 66.39847825 60.42549336 -19775.51746544
2502.000       3 -14257.609 3846.527 -19674.834 47.17524086 60.32764207 -19782.33721673
8892.000       5 -12883.864 4017.228 -18906.366 85.57769971 63.23855096 -19055.18207049
8901.000       4 -13556.068 3933.928 -18804.655 67.43223259 61.38770229 -18933.47506054
8910.000       4 -13556.754 3912.949 -18776.002 84.37418764 73.93300859 -18934.30906146
8919.000       5 -12887.471 3860.507 -18708.009 84.38999028 69.17496051 -18861.57386744
```

- column 2 is the replica (=”temperature”) index applied to that trajectory at that time

output to terminal

Standard output reports program progression, and the exchange ratio between couples of replicas.

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```
==== current simulation time = 900.0
```

output to terminal

Standard output reports program progression, and the exchange ratio between couples of replicas.

```
==== current simulation time = 900.0
==== current simulation time = 1800.0
```

output to terminal

Standard output reports program progression, and the exchange ratio between couples of replicas.

```
==== current simulation time = 900.0
==== current simulation time = 1800.0
   Exchange number:    112
   1 < = >  2 Nacc/N% 0.000
   2 < = >  3 Nacc/N% 14.286
   3 < = >  4 Nacc/N% 0.000
   4 < = >  5 Nacc/N% 37.500
   5 < = >  6 Nacc/N% 0.000
   6 < = >  7 Nacc/N% 7.143
   7 < = >  8 Nacc/N% 0.000
```

output to terminal

Standard output reports program progression, and the exchange ratio between couples of replicas.

```
==== current simulation time = 900.0
==== current simulation time = 1800.0
   Exchange number:    112
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   2 < = >  3 Nacc/N% 14.286
   3 < = >  4 Nacc/N% 0.000
   4 < = >  5 Nacc/N% 37.500
   5 < = >  6 Nacc/N% 0.000
   6 < = >  7 Nacc/N% 7.143
   7 < = >  8 Nacc/N% 0.000
==== current simulation time = 2700.0
```

output to terminal

Standard output reports program progression, and the exchange ratio between couples of replicas.

```
           ==== current simulation time = 900.0
           ==== current simulation time = 1800.0
              Exchange number:    112
              1 < = >  2 Nacc/N% 0.000
              2 < = >  3 Nacc/N% 14.286
              3 < = >  4 Nacc/N% 0.000
              4 < = >  5 Nacc/N% 37.500
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           ==== current simulation time = 2700.0
 ...
```

output to terminal

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When program ends, you will probably want to check whether

- the exchanges are efficient ($\geq 20\%$)

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              7 < = >  8 Nacc/N% 0.000
           ==== current simulation time = 2700.0
 ...
```
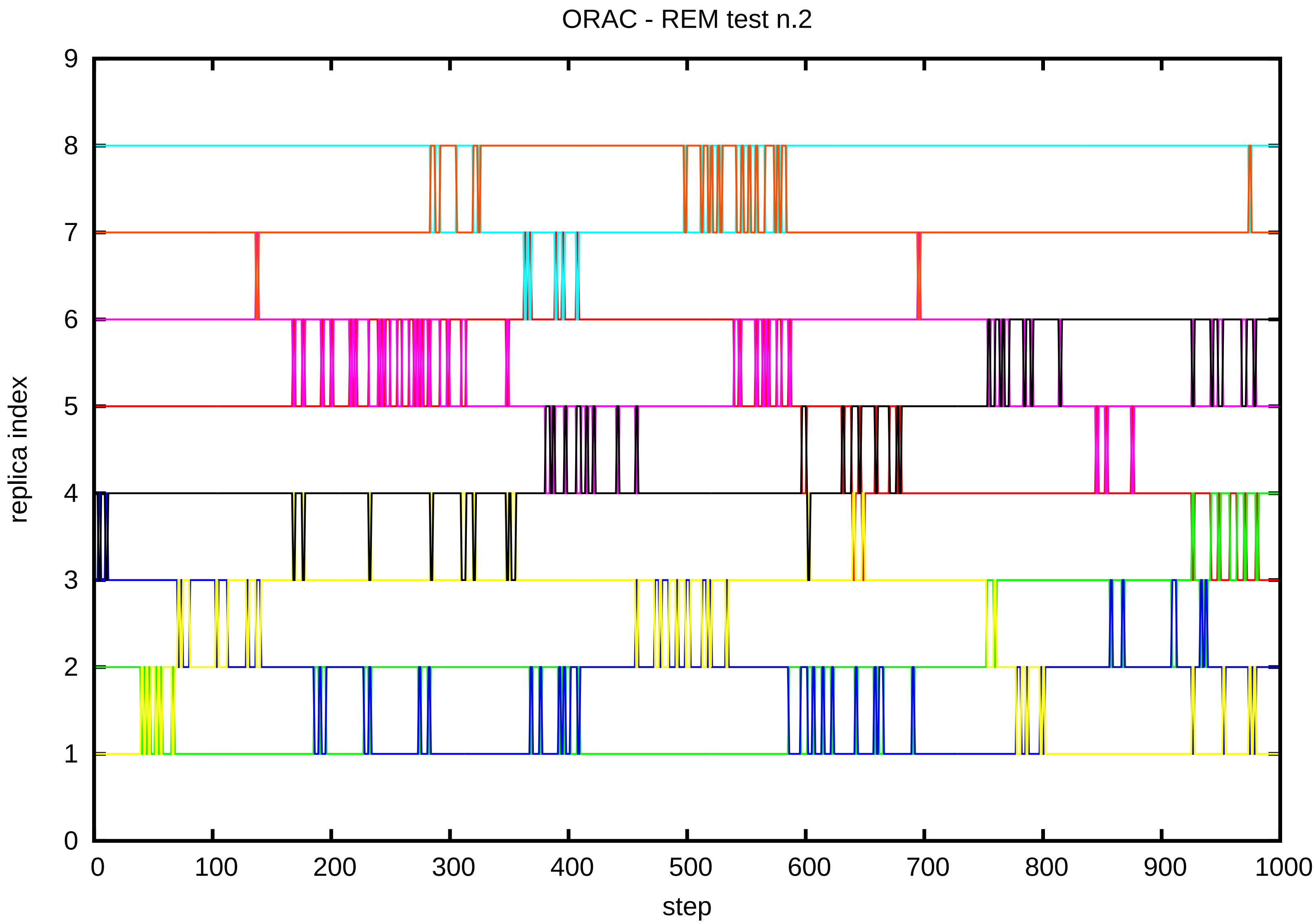

When program ends, you will probably want to check whether

- the exchanges are efficient ($\geq 20\%$)
- each trajectory explores all "temperatures"

exchange chart

ORAC REM test n.2. Exchanges between replicas



total energy

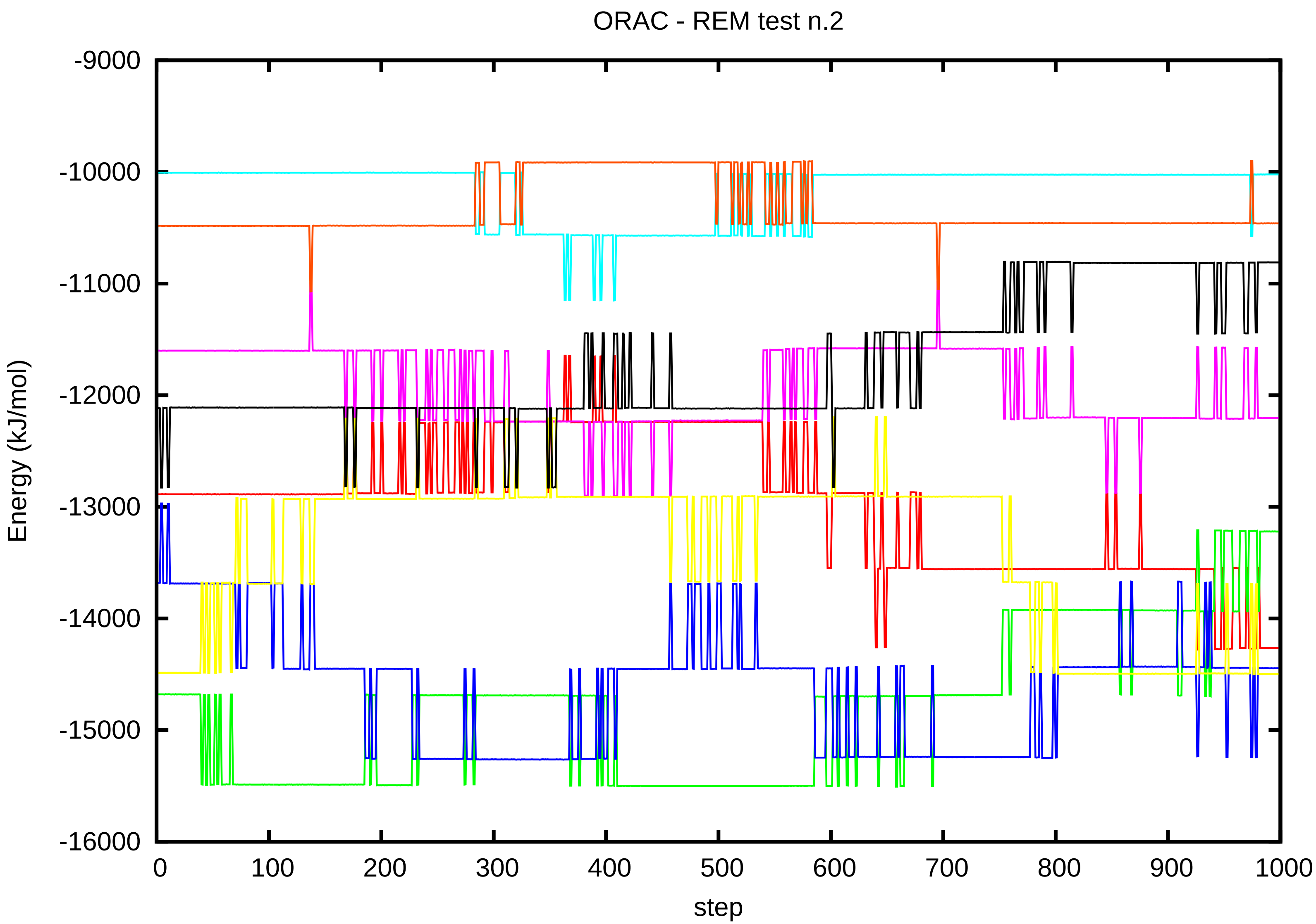


Figure 2: ORAC REM test n.2. Energy of trajectories

collecting data for the target potential

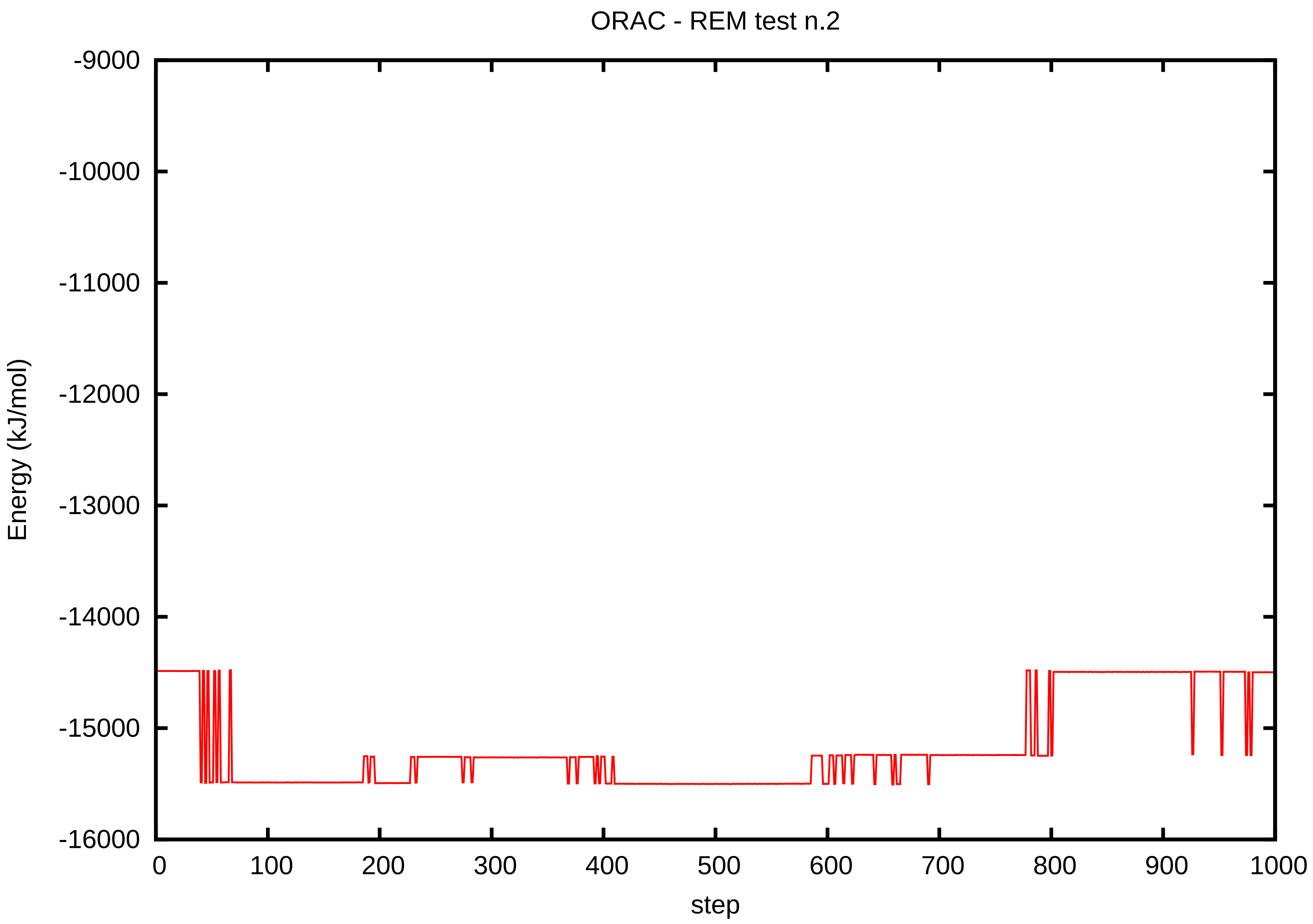


Figure 3: ORAC REM test n.2. Energy of target potential (replica 1)

how to reorder data by replica

using `order.sh`, energy and structural data can be reordered by replica:

```
$ cd orac-5_1_x/tests/REM_tests
$ make test2
```

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```

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$ cd orac-5_1_x/tests/REM_tests
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$ ./order.sh 2.pdb REM_DIAGNOSTICS
$ ls
```

how to reorder data by replica

using `order.sh`, energy and structural data can be reordered by replica:

```
$ cd orac-5_1_x/tests/REM_tests
$ make test2
$ ./order.sh 2.pdb REM_DIAGNOSTICS
$ ls
2-0001.pdb # data from PAR????/2.pdb, replica=1
2-0002.pdb #                          replica=2
2-0003.pdb
2-0004.pdb
2-0005.pdb
2-0006.pdb
2-0007.pdb
2-0008.pdb
REM_DIAGNOSTIC-0001 # data from PAR????/REM_DIAGNOSTIC, replica=1
REM_DIAGNOSTIC-0002
REM_DIAGNOSTIC-0003
REM_DIAGNOSTIC-0004
REM_DIAGNOSTIC-0005
REM_DIAGNOSTIC-0006
REM_DIAGNOSTIC-0007
REM_DIAGNOSTIC-0008
$
```

REM efficiency

- The program provides a default set of scaling coefficients, with equal spacing between adjacent temperatures (this set gives optimal overlap in a harmonic oscillator collection)

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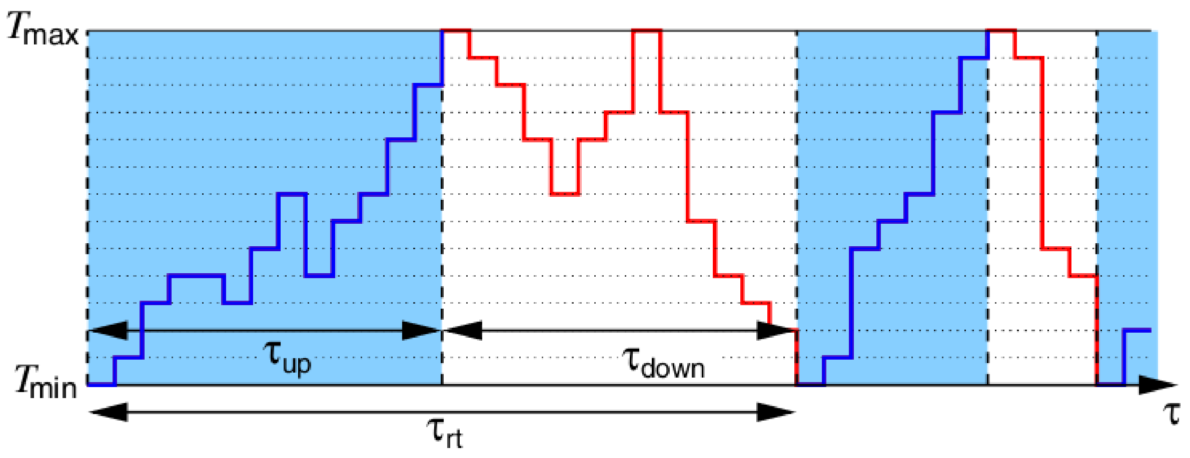
- If replica exchange is not effective, you can
  - increase the number of replicas
  - set the coefficients manually, decreasing the spacing between replicas that don't exchange well

monitoring trajectory flow



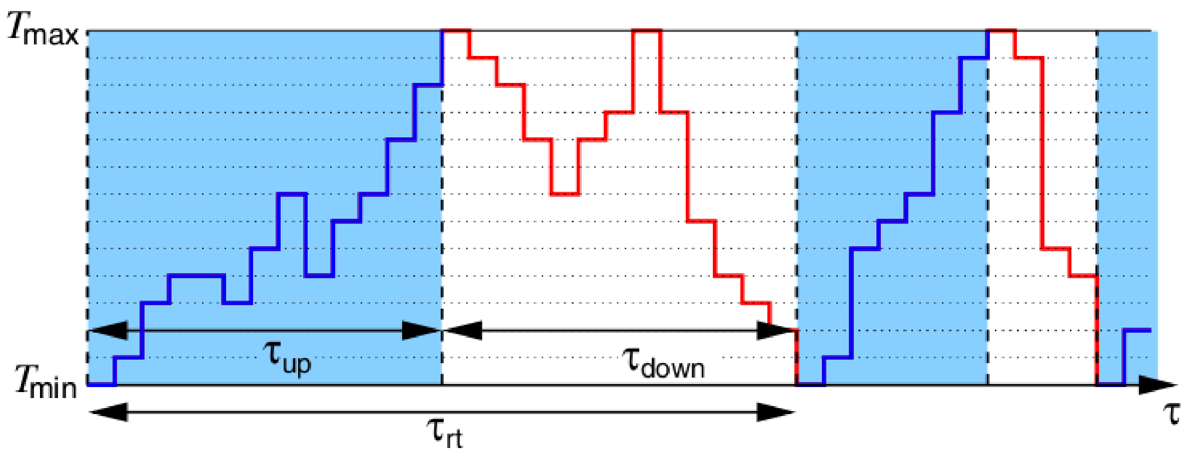
fraction of trajectories that are travelling "up" at replica i:

$$f_i^{up} = \frac{n_i^{up}}{n_i^{up} + n_i^{down}}$$

diffusivity at replica i:

$$D_i = \frac{\Delta T}{df/dT}$$

monitoring trajectory flow



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diffusivity at replica i:

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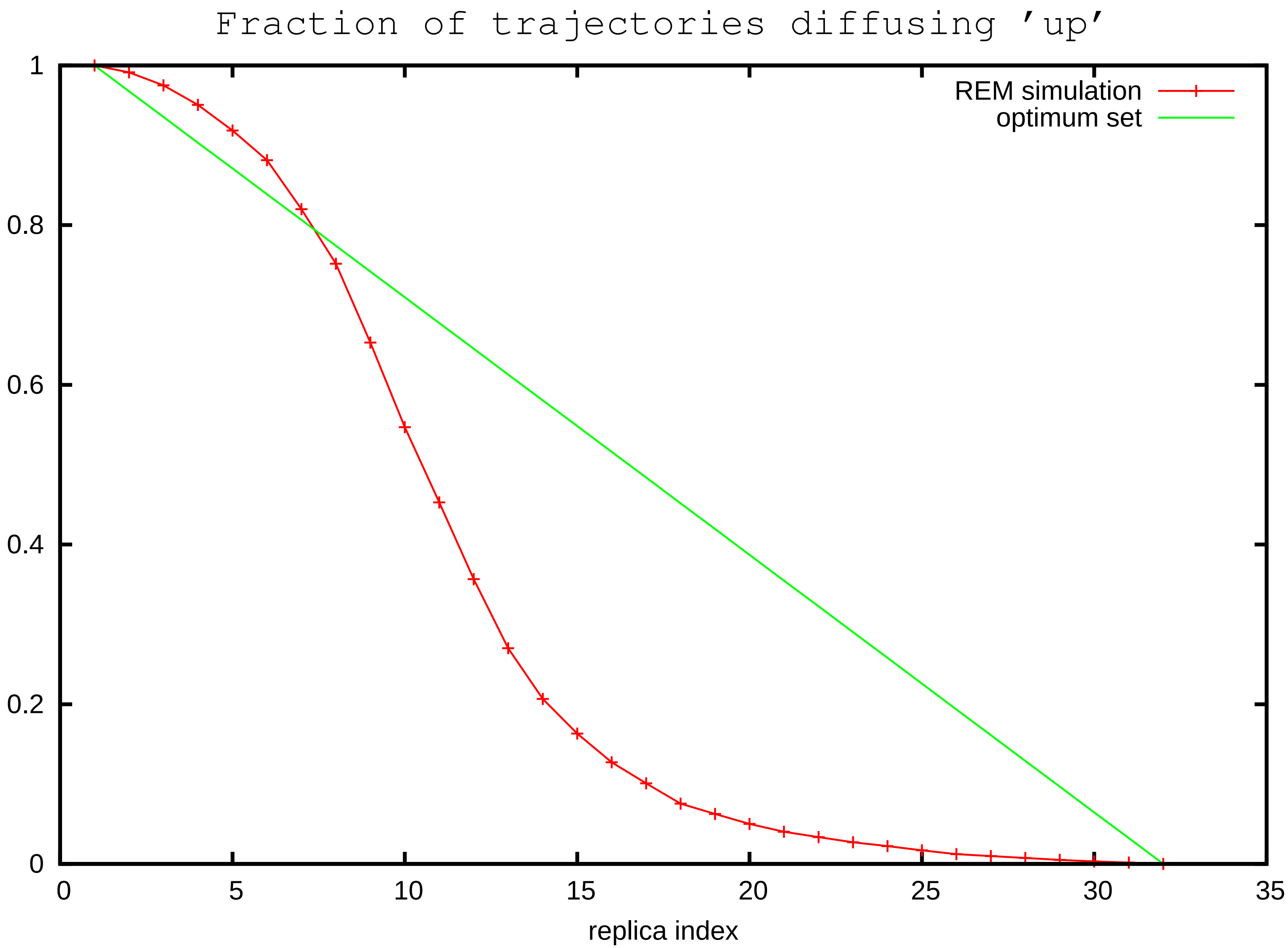
optimal: constant diffusivity

monitoring trajectory flow (2)



HREM with potential partitioning

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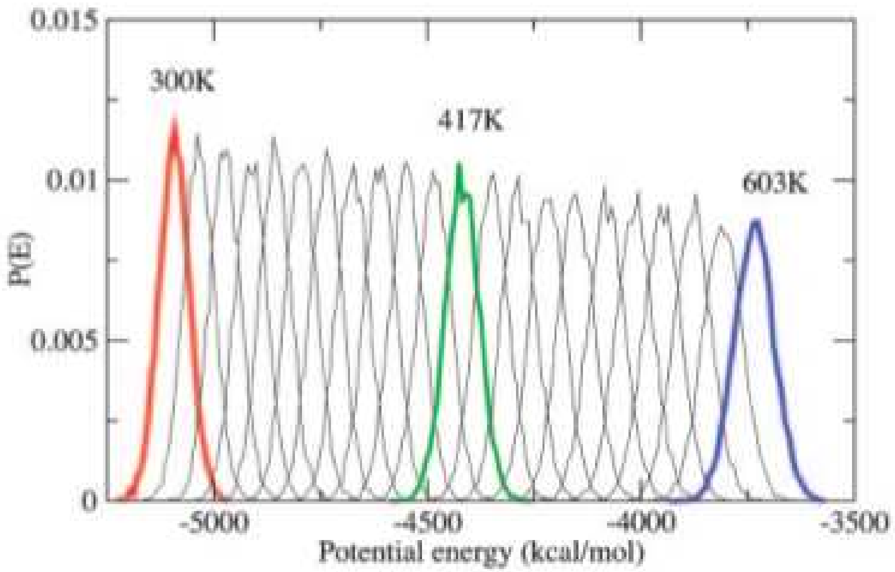
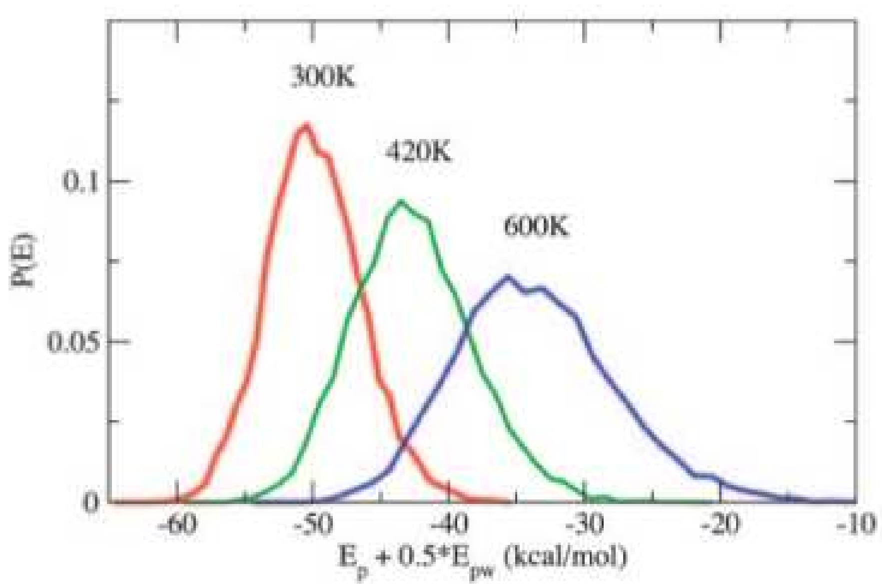
normal REM



REM with pot. partitioning



HREM with potential partitioning (2)

- In ORAC, different scaling can be applied to different parts of the potential

max. scaling	interaction
c_1	stretching and bending
c_2	torsion and 1-4 interaction
c_3	non-bonded

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c_1	stretching and bending
c_2	torsion and 1-4 interaction
c_3	non-bonded

- Here is how this is implemented in REM test 3:

```
&REM
#       bend+bond torsion+1-4 nonbonded
  SETUP  1.0       0.20      0.75      1
  STEP 5.
  PRINT 1000.
&END
```

Solute Tempering extension

- It is also useful to partition the system in a "solute" and a "solvent".

"solute" $\longrightarrow$ any portion of the system $\longrightarrow$ "Segment"
"solvent" $\longrightarrow$ the rest $\longrightarrow$ "Environment"

interaction	S	S-E	E-E
stretching and bending	1	1	1
torsion and 1-4	c_2	c_2	1
non-bonded	c_3 (or 1)	1 (or c_3)	1

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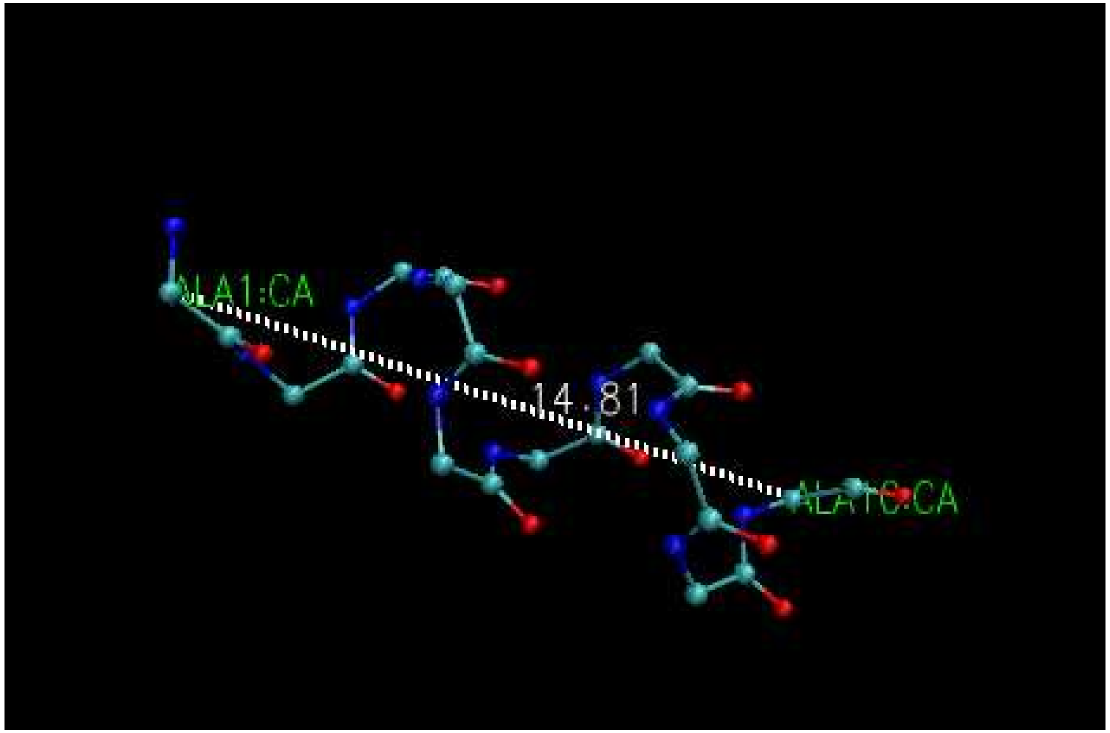
interaction	S	S-E	E-E
stretching and bending	1	1	1
torsion and 1-4	c_2	c_2	1
non-bonded	c_3 (or 1)	1 (or c_3)	1

- Here is how this is implemented in REM test 5:

```
&REM
#        bend+bond torsion +1-4 n-bonded
   SETUP  1.0        0.20       0.20      1
   SEGMENT
     define 1 22
     kind intra
   END
   ...
&END
```

Steered MD Tests

Deca-Alanine



SMD additional potential: $V' = \frac{1}{2}k\left(d - (d_0 + v \cdot t)\right)^2$

- end-to-end distance $d = |C_1^\alpha - C_{10}^\alpha|$
- state A: $d = 15.5$ (α-helix)
- state B: $d = 31.5$

Flow chart

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or other "bidirectional" methods that can estimate the free energy profile along the whole path $A \longrightarrow B$

(*) Step 2 can be performed in parallel

step 1: prepare canonical distributions


```
$ cd orac-5_1_x/tests/jarzynski_tests
$ mpiexec -n 1 ../../src/PARALLEL/orac_Linux < 2Pa.in
$ mpiexec -n 1 ../../src/PARALLEL/orac_Linux < 2Pb.in
```

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- These commands create configuration files corresponding to a canonical distribution of state A and state B in directories RESTART_A/ and RESTART_B/, respectively.

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- These commands create configuration files corresponding to a canonical distribution of state A and state B in directories RESTART_A/ and RESTART_B/, respectively.
- The parallell version of ORAC is used (on 1 processor) only for compatibility with step 2
- this is how this is implemented in test 2Pa:

```
&INOUT
  RESTART
    write 250.0 SAVE_ALL_FILES ../RESTART_A/ala10_A
  END
&END
```

step 2: run SMD in parallel


```
$ cd orac-5_1_x/tests/jarzynski_tests
```

step 2: run SMD in parallel


```
$ cd orac-5_1_x/tests/jarzynski_tests
$ mpiexec -n 4 ../../src/PARALLEL/orac_Linux < 3a.in
$ mpiexec -n 4 ../../src/PARALLEL/orac_Linux < 3b.in
```

- These commands start 4 parallel processes in directories PAR0000 ... PAR0003 creating workfunction files WRKa.1 and WRKb.1 in each directory

step 2: run SMD in parallel


```
$ cd orac-5_1_x/tests/jarzynski_tests
$ mpiexec -n 4 ../../src/PARALLEL/orac_Linux < 3a.in
$ mpiexec -n 4 ../../src/PARALLEL/orac_Linux < 3b.in
```

- These commands start 4 parallel processes in directories PAR0000 ... PAR0003 creating workfunction files WRKa.1 and WRKb.1 in each directory

```
# The bending inolving dum atom with large mass is required
# in order to stretch 10-alanine along the z-coordinate
&POTENTIAL
  ADD_STR_BONDS 1 102 400.0 15.5 31.5
  ADD_STR_BENDS 102 1 105 600.0 180.0
  ...
&END
# Unfolding of 10-ala occurs in 10000 fs.
&RUN
  CONTROL              2
  REJECT           0.0
  STEER      0.0   9900.0
  TIME             9900.0
  MAXRUN           9900.0
&END

&INOUT
  RESTART
    rmr ../RESTART_A/ala10_A 0
  END
  PLOT STEER_ANALYTIC 300.0 OPEN WRKa.1
&END
```

step 2: (2) work paths

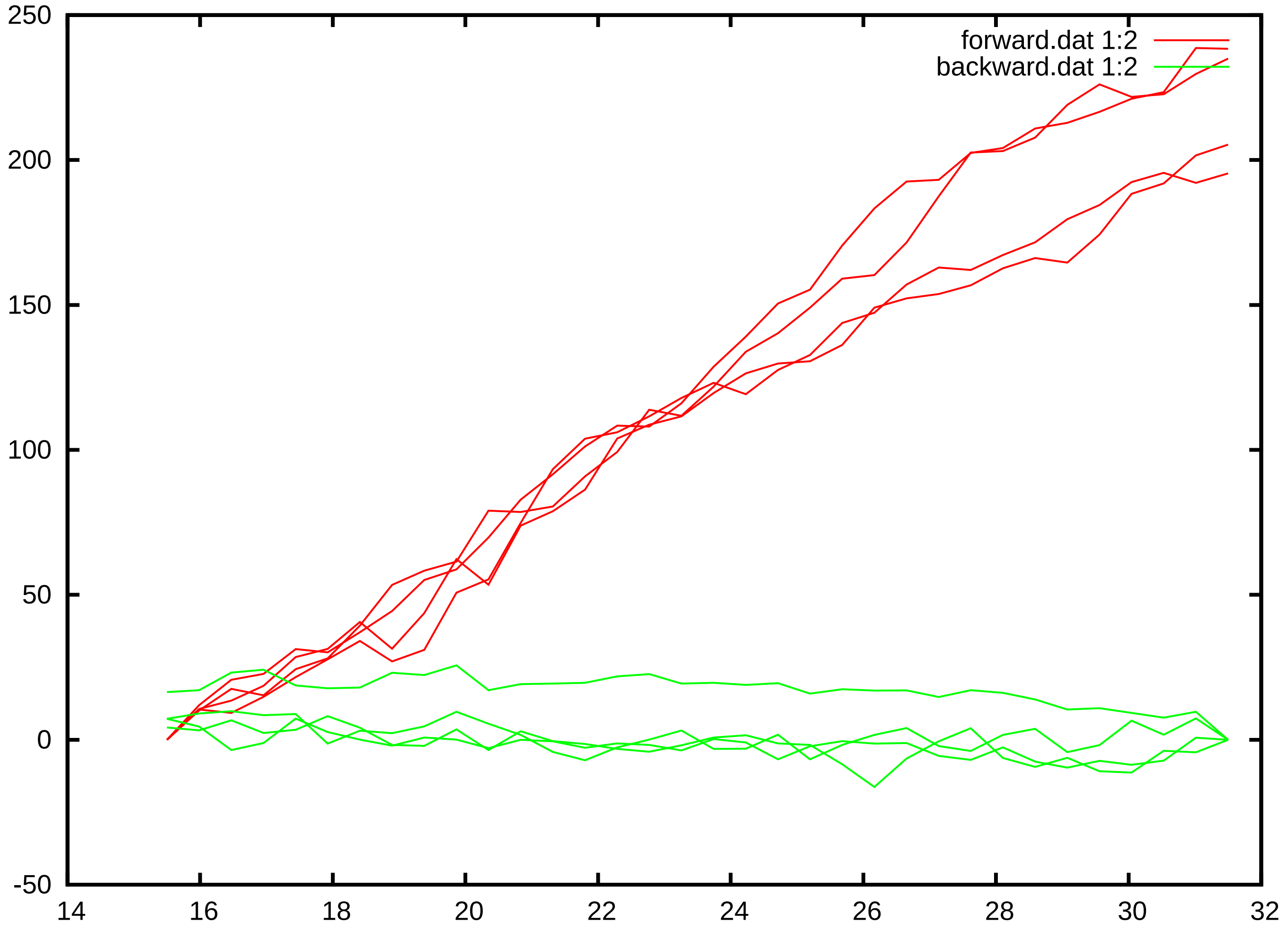

Figure 4: Jarzynski test 2P

how it looks in real SMD simulations

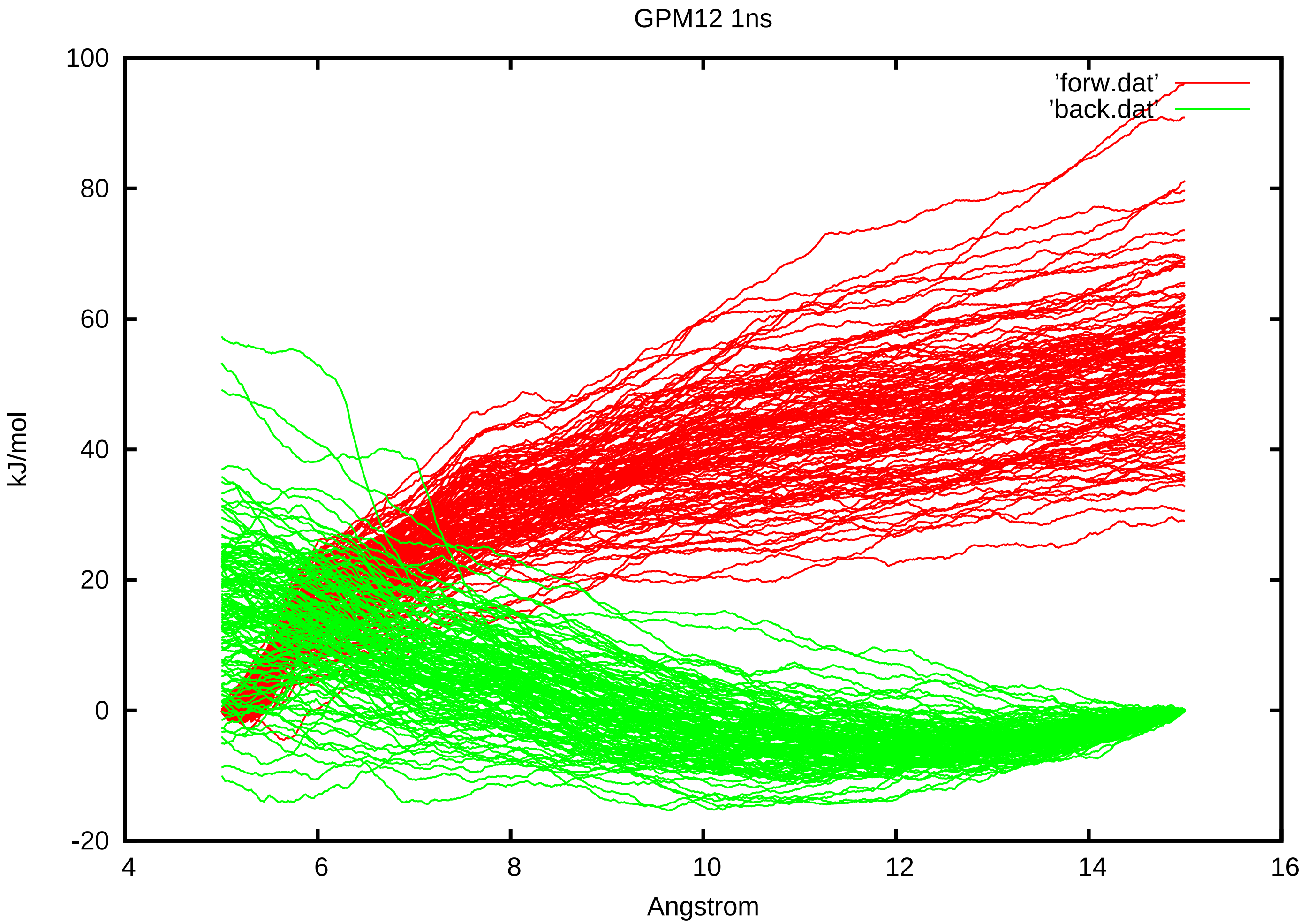

Figure 5: real-world example

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- these are *experimentally* implemented in the auxiliary program `fes`, which currently uses fixed names for input files

```
$ cd orac-5_1_x/tests/jarzynski_tests
```

step 3: estimate Free Energy Profile

- the most accurate results are obtained with bidirectional methods
- these are *experimentally* implemented in the auxiliary program `fes`, which currently uses fixed names for input files

```
$ cd orac-5_1_x/tests/jarzynski_tests
$ make fes
```

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- the most accurate results are obtained with bidirectional methods
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```
$ cd orac-5_1_x/tests/jarzynski_tests
$ make fes
$ for i in ‘ls -d PAR*‘; do mv $i/WRKa.1 FORWARD/WRKa.$i; done
$ for i in ‘ls -d PAR*‘; do mv $i/WRKb.1 REVERSE/WRKb.$i; done
```

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```
$ cd orac-5_1_x/tests/jarzynski_tests
$ make fes
$ for i in ‘ls -d PAR*‘; do mv $i/WRKa.1 FORWARD/WRKa.$i; done
$ for i in ‘ls -d PAR*‘; do mv $i/WRKb.1 REVERSE/WRKb.$i; done
$ echo 4 | ./fes
```

step 3: estimate Free Energy Profile (2)

- the last command produces the following output:

```
# position, DF_AQ_EQ8, DF_AQ_EQ9, DF_AQ_EQ16, DF_AQ_MINH, DF_AQ_PMFA, DF_AQ_J, DF_BQ_J
 15.9848500  5.3572   5.3496   5.3572  10.6992   0.0000  10.6992   6.5107
 16.4697000  5.6583   5.5398   5.6583  12.1777   1.4786  12.1777   5.4125
 16.9545500  4.5535   4.8978   4.5535  16.4513   5.7521  16.4513  -0.1450
 17.4393900  9.7112   9.7197   9.7112  24.1973  13.4981  24.1973   1.7528
 ...
 31.0151500 92.3263  93.6842  93.6842  91.7988  81.0997 195.5132  -4.3500
 31.5000000 95.5277  97.2839  97.2839  94.9066  84.2075 198.8083  -1.2422
```

step 3: estimate Free Energy Profile (2)

- the last command produces the following output:

```
# position, DF_AQ_EQ8, DF_AQ_EQ9, DF_AQ_EQ16, DF_AQ_MINH, DF_AQ_PMFA, DF_AQ_J, DF_BQ_J
 15.9848500  5.3572   5.3496   5.3572  10.6992   0.0000  10.6992   6.5107
 16.4697000  5.6583   5.5398   5.6583  12.1777   1.4786  12.1777   5.4125
 16.9545500  4.5535   4.8978   4.5535  16.4513   5.7521  16.4513  -0.1450
 17.4393900  9.7112   9.7197   9.7112  24.1973  13.4981  24.1973   1.7528
 ...
 31.0151500 92.3263  93.6842  93.6842  91.7988  81.0997 195.5132  -4.3500
 31.5000000 95.5277  97.2839  97.2839  94.9066  84.2075 198.8083  -1.2422
```

columns 2-6 report the FEP (with different methods), while the last two columns give Jarzynski estimate for the forward and backward transformation