A Tutorial for TIPSI, and How to Assemble Paths

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Introduction

Who am I?

- Dylan Goldsborough
- Student at the computational science master
- Attended the course on biomolecular simulation
- Enjoyed figuring out TIPSI in class
- Did a project to write a tutorial that introduces TIPSI over the past months!

Outline

In this presentation I will:

- Give a brief recap of TPS
- Outline my contribution
- Discuss both the examples the tutorial offers
- Discuss the additional documentation

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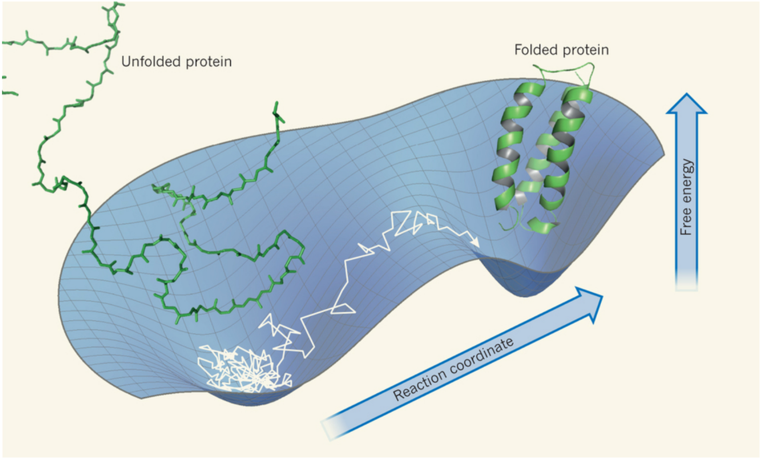
What is TPS?

Find trajectories of rare transitions:



(Chung and Eaton, 2013)

What is TPS?

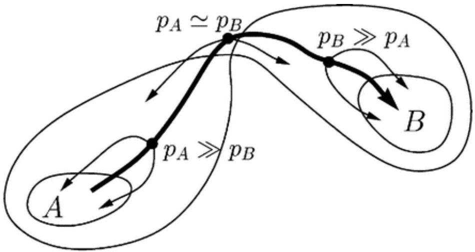
Algorithm:

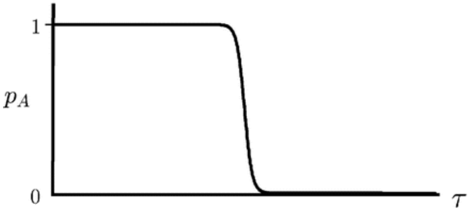
- Take existing path
- Choose random time slice t
- Change momenta slightly at t
- Integrate forward or backward in time to create new path
- Accept if state A or B is reached, otherwise reject and retain old path

Important: we assume that both states are stable, and that we have a transition trajectory ready!

What is TPS?

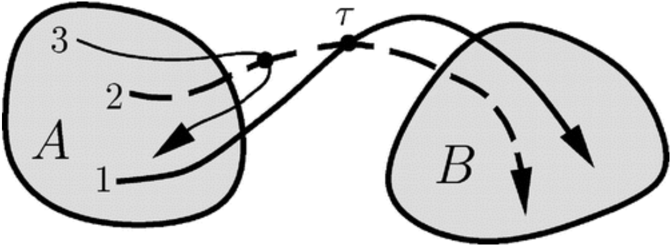
Committor probability:





What is TPS?

Shooting move:



Accepted if state *A* or *B* is reached.
(Bolhuis, 2002)

What is TIPSI?

TIPSI is a script by Tsjerk Wassenaar, which:

- Adaptation of a Perl script by Jarek Juraszek
- Written in Python
- It relies on GROMACS version 4.5.4 (a molecular dynamics engine)
- Does random shooting moves forward and backward
- Reverses time for backward shooting
- A "molecular calculator"

Contributions

I made several minor contributions to this project:

- Bash implementation to assemble paths
- Python script to analyze the paths
- Tutorial with a Python tool

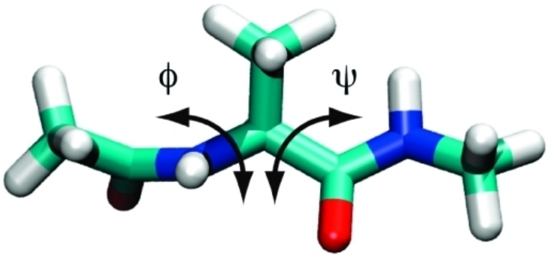
Resulted in some surprises that had to be dealt with...

Alanine Dipeptide

Our first example is **alanine dipeptide**:

- Extremely fast to run
- Very simple to understand, with simple order parameters (dihedrals)
- Has a nice transition between two distinct states
- Common example to use

Alanine Dipeptide



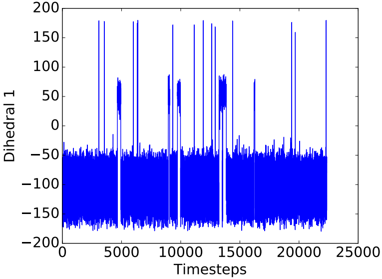
Preparing for TIPSI

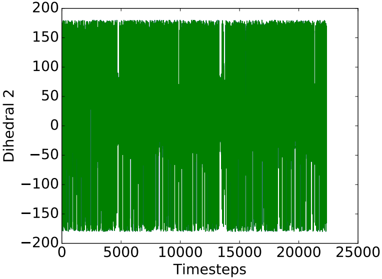
In this example we do everything from scratch:

- Start with pdb-file (defines the structure) and MD settings
- We prepare a periodic system, add a solvent
- We do energy minimization followed by a constrained MD run
- We do runs at room temperature and high temperature

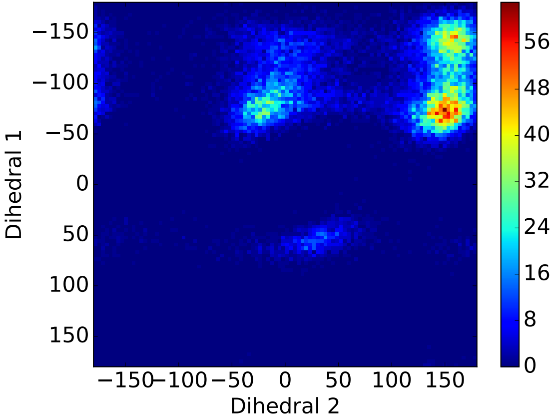
We look at the order parameters in the run using a Python script and GROMACS commands.

Defining the stable states





Defining the stable states



Running TIPSI

```
maxframes  = 2000

par dh1  = dihdeg(frame$Dihedral1)
par dh2  = dihdeg(frame$Dihedral2)

state A = (-150 < dh1 & dh1 < -50
        & 120 < dh2 & dh2 < 180)
state B = (-100 < dh1 & dh1 < -50
        & -50 < dh2 & dh2 < 20)

interface I = (!A) & (!B)
```

Assembling paths

TIPSI only saves the shooting moves to save space, so to view and analyze the transitions we need to assemble them.

The problem:

- TIPSI outputs shooting moves only
- Instructions on how the paths are made in `dat`-files
- Backward shooting moves are the wrong way around
- Negative timestamps

Result: assembling the paths is a minor nightmare...

TIPSI output

Example of Tipsi output:

```
DIR: tipsi-tutorial/output/jobname/DATA/9/1

9-1-BW.cpt   9-1-BW.out   9-1-BW.xtc   DONE
9-1-BW.dat   9-1-BW.top   9-1.dat      md-prod.mdp
9-1-BW.edr   9-1-BW.tpr   ACCEPTED     PARENT
9-1-BW.err   9-1-BW.trr   CMD          parent.dat
```

TIPSI output

```
REGEX: '[A-I]\s+(\S+)\s+[F-T][a-z]+\s+(\S+)\s+'

state    time     stop    file
A        -1325.0  True    ../../9/1/9-1-BW.trr
I        -1305.0  False   ../../9/1/9-1-BW.trr
I        -1285.0  False   ../../9/1/9-1-BW.trr
I        -1265.0  False   ../../9/1/9-1-BW.trr
...
I        465.0    False   ../../6/4/6-4-FW.trr
I        485.0    False   ../../6/4/6-4-FW.trr
I        505.0    False   ../../6/4/6-4-FW.trr
B        525.0    True    ../../6/4/6-4-FW.trr
```

Assembling paths

The solution:

- Bashscript that searches for directories with `ACCEPTED`-file
- Scans `dat`-file using regular expressions
- Overwrites timestamps
- Creates each path by dumping and appending single frames
- Stores some metainformation in a `csv`-file

Takes a while to dump frames for long trajectories...

Metainformation paths

We can do some nice things with the metainformation, I wrote a script that:

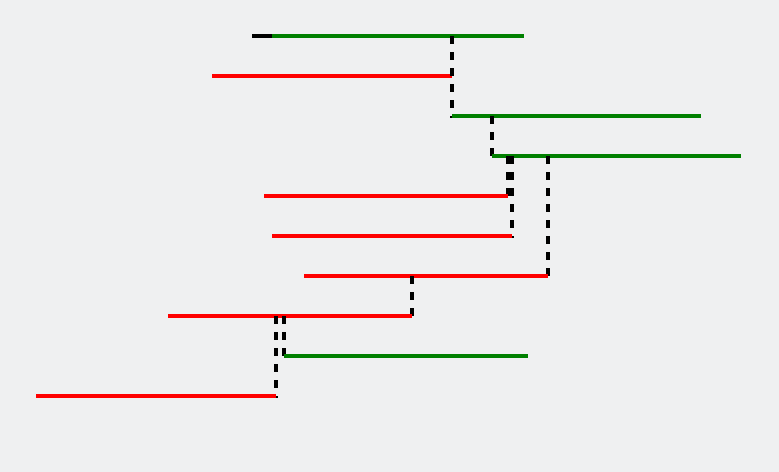
- Finds the average path length
- Finds the number of decorrelated groups of paths
- Ratio of FW:BW shooting moves
- Draws a tree of all shooting moves

Analyzing TIPSI

I appended the bashscript to the end of the job, so that it puts all paths and the metadata in the `output/DATA` directory, now we can take a look at the trajectory in VMD!
We find that:

- Average length is 136.4 frames
- FW/BW ratio is 0.4
- Number of decorrelated groups of paths is 2

Analyzing TIPSI



We visualize path 9 in VMD.

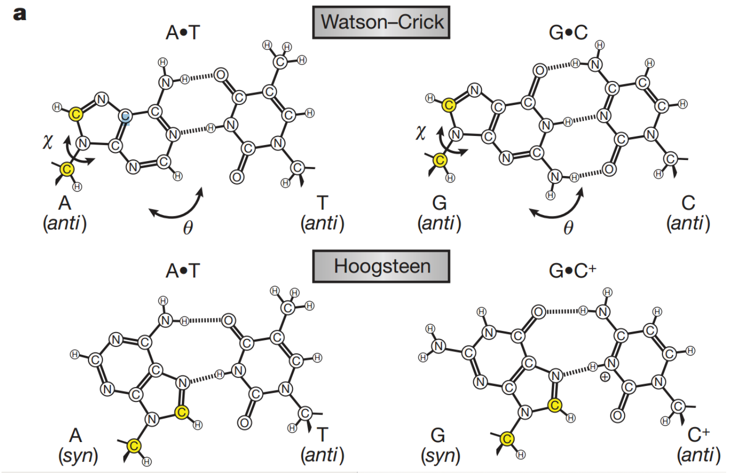
DNA baseroll

Second example is the DNA baseroll:

- Project by Jocelyne Vreede and David Swenson
- Concerns the transition from the WC- to the HG-pairing
- An actual rare event (microsecond range), unlike example 1

Metadynamics simulation has been done, so there is a trajectory available that contains the transition!

DNA baseroll



Preparing for TIPSI

In this example we start with a trajectory and state definitions:

- We import the custom topology
- We create a `tpr`-file (containing the simulation settings) to suit our MD-needs
- We set up a parameter file that include the state definitions (H-bonds)
- We run TIPSI with this `tpr` and the provided trajectory

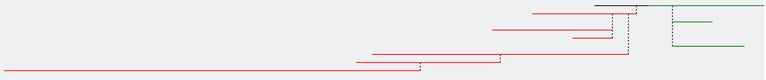
Analyzing TIPSI

We find that:

- Average length is 723.88 frames
- FW/BW ratio is 0.33
- Number of decorrelated groups of paths is 1

Analyzing TIPSI

Not very balanced tree:



We visualize path 9 in VMD.

Cheatsheets

As an appendix, I included:

- A Linux cheatsheet, for students who are unfamiliar
- A GROMACS cheatsheet (which I caught myself use often too)
- A TIPSI cheatsheet

The last adresses the documentation problem with TIPSI.

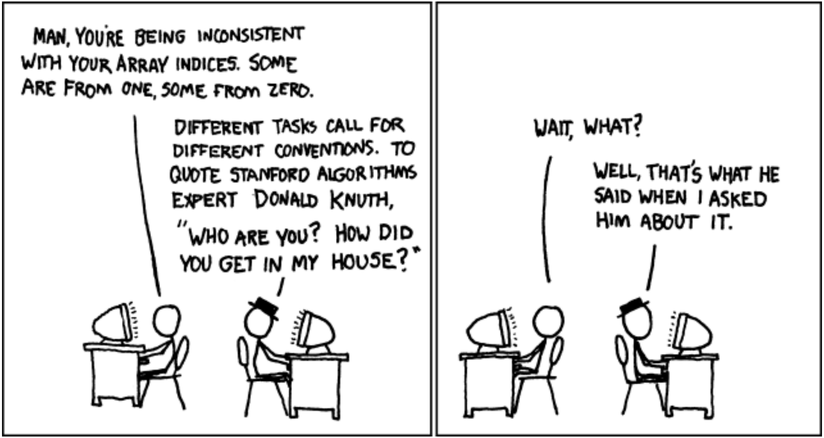
Cheatsheets

TIPSI cheatsheet includes:

- How to set up a parameter file
- All calculator options
- Several ways to define groups of atoms
  - Numpy arrays
  - Groups from GROMACS `ndx`-files (defines groups of atoms by their number)

There are **indexing problems**...

Relevant XKCD



Running TIPSI

Calculator options are:

- `com`: center of mass
- `dist`: distance (several options)
- `angle`: angle of 3 atoms
- `dihrad`/`dihdeg`: dihedral in rads/degrees
- `rgyr`: radius of gyration, incompatible with GROMACS
- `rmsd`: root-mean-square-deviation
- `hbonds`: number of hydrogen bonds, specific or non-specific

Summary

- I wrote a tutorial for students/people interested in TIPSI with a fast but not so rare example, and a more computationally demanding but actually interesting example
- Added a bash script that finishes the output to make it fit for further analysis
- Added a basic script that helps understand the shooting moves made
- Compiled all calculator options, and how to set up a parameter file for TIPSI

Future changes?

There might be some things to change down the line:

- Include OPS as an analysis tool (no time now, and still being developed)
- Append to the possibilities in the parameter file (non-calculator options)
- Any other changes...

The project is on GIT and should be public:
`https://github.com/dgoldsb/tipsitutorial.git`