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# Automating the GROMACS analysis tools on HPC systems

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# Introduction

- The GROMACS software package includes many programs.
  - An MD engine: `gmx mdrun`
  - Tools to prepare simulations: `pdb2gmx`, `grompp`, ...
  - Post-processing and analysis tools: `trjconv`, `rms`, `energy`, ...
- The MD engine is very well suited to HPC environments.
  - Highly optimised for parallel computations
  - Easy to use in scripts submitted to the job scheduler
- The GROMACS analysis tools are more challenging on HPC systems.
  - They ask for input interactively.
  - They typically do not work in parallel.
  - They are hard to script (no interface for languages such as Python).

# Introduction

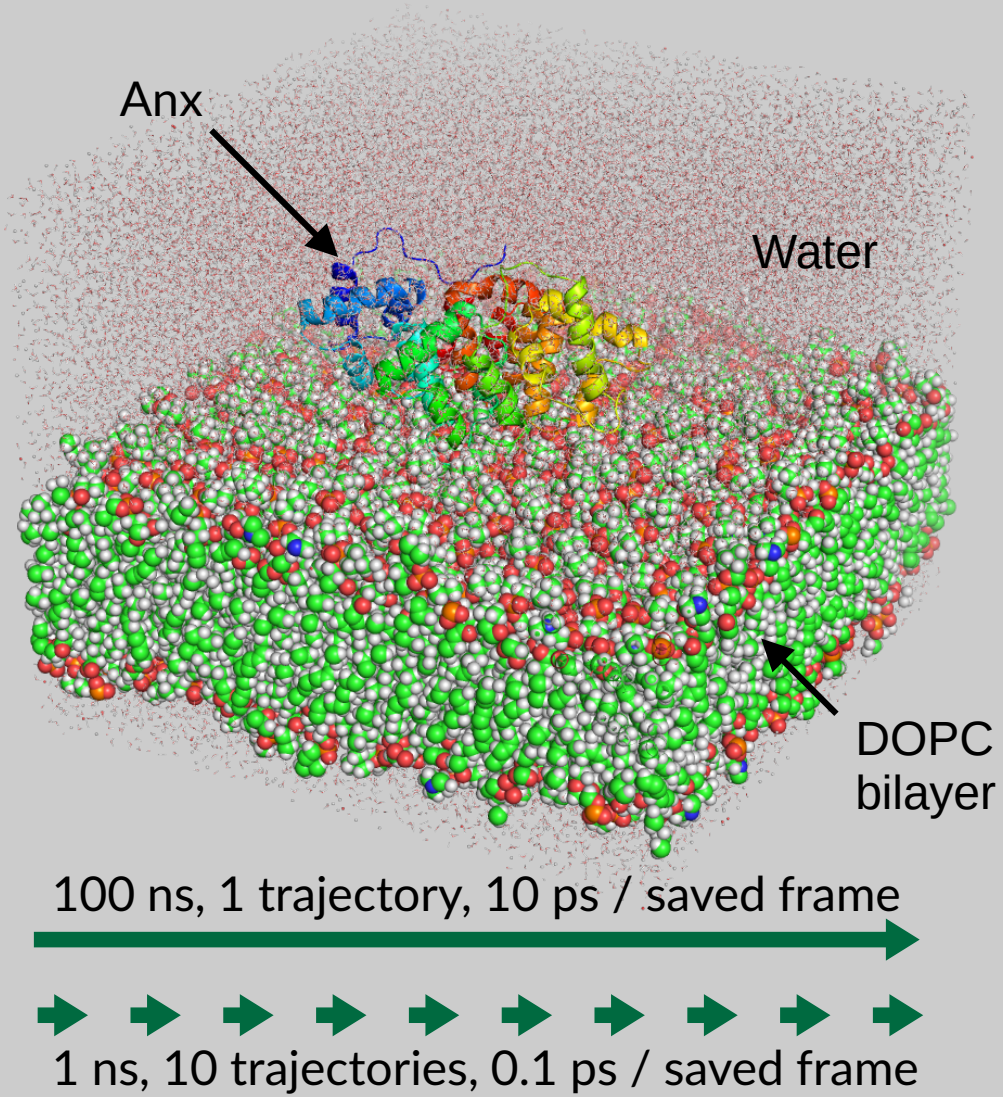
- The GROMACS analysis tools work well on a workstation.
  - Output files can be copied from the cluster to your PC.
  - This might be acceptable for small projects.
  - For large or numerous trajectories, this is limiting.
- Running the GROMACS analysis tools on the cluster is better.
  - No need to copy files back and forth
  - Access to much more processing power
- There are techniques to work around these limitations.

# Outline

1. Avoiding interactivity using input redirection
2. Running analyses in parallel with job arrays
3. Using job arrays with multi-dimensional input
4. Multiple short analyses in a single job with GNU parallel
5. Speeding up analyses using trajectory post-processing
6. MDAnalysis for GROMACS structures and trajectories
7. Generating GROMACS index groups with MDAnalysis

# Molecular system used for all examples

- O. Fisette, C. Päslack, R. Barnes, J. M. Isas, R. Langen, M. Heyden, S. Han, L. V. Schäfer. *Hydration Dynamics of a Peripheral Membrane Protein*. JACS, 2016, 138, 36, 11526–11535. doi: *10.1021/jacs.6b07005*.
- Water diffusion is slowed down in the vicinity of a peripherical membrane protein, annexin B12.
- 14 annexin residues were used as probes in MD and NMR to measure water retardation.



# Following and repeating these examples

- All examples will be done on a cluster (Plato at USask) similar to Alliance clusters.
- All interactive commands are given in the slides.
- Pre-written scripts will be discussed extensively.
- All scripts are available in an archive.
  - WestDRI webinar page
  - *https://asteria.feralhosting.com/ribosome/gmxtools.tar.gz*
- The trajectories are not included in the script archive.
- These slides are available as a PDF.
  - WestDRI webinar page
  - Included in the script archive

# Avoiding interactivity with input redirection

- We compute backbone RMSD, after a minimising fit to alpha carbons, for a short portion of an Anx trajectory.
- Using the GROMACS tools in an interactive session

```
ssh plato
salloc
cd ~/Anx_on_DOPC/simulations/2_MD
ls
module spider gromacs
module spider gromacs/2022.3
module load StdEnv/2020 gcc/9.3.0 openmpi/4.0.3
module load gromacs/2022.3
gmx rms -f traj_comp.xtc \
    -o Anx_backbone_RMSD_fit_to_Ca.xvg -e 5 -tu ns
3
4
...
exit
```

# Avoiding interactivity with input redirection

- The problem with scripts and interactivity

```
mkdir -p ~/Anx_on_DOPC/analysis/RMSD
cd ~/Anx_on_DOPC/analysis/RMSD
cp ~/gmxtools/01_RMSD.sh RMSD.sh
less RMSD.sh
sbatch --wait RMSD.sh
less slurm_RMSD.out
```

- The `gmx msd` program requested input interactively and stopped with an error because that input was not provided.

# Avoiding interactivity with input redirection

- We can use a separate text file to select the index groups.
- The text file is passed to `gmx rms` using the < redirection operator.

```
cp ~/gmxtools/02_selected_groups.txt selected_groups.txt
cp ~/gmxtools/03_RMSD.sh RMSD.sh
cat selected_groups.txt
less RMSD.sh
sbatch --wait RMSD.sh
less slurm_RMSD.out
(head; tail) < Anx_backbone_RMSD_fit_to_Ca.xvg
```

- The < redirection operator copies the contents of a file to the standard input channel of a program.

# Avoiding interactivity with input redirection

- Using numbers to select the index groups is not clear.
- Fortunately, the GROMACS tools also accept index group names.

```
cp ~/gmxtools/04_selected_groups.txt selected_groups.txt
cat selected_groups.txt
sbatch --wait RMSD.sh
less slurm_RMSD.out
```

# Avoiding interactivity with input redirection

- Having a separate file to select the index groups is a little confusing.
- We can use a Bash “here-document” to inline the index groups selection in the script.

```
cp ~/gmxtools/05_RMSD.sh RMSD.sh
less RMSD.sh
sbatch --wait RMSD.sh
less slurm_RMSD.out
```

- The `<<` and `<<-` redirection operators start a here-document.
  - They are followed by an arbitrary token (e.g. `EOF`) that is repeated at the end of the here-document.
  - The text between the two tokens is the here-document. It is copied to the standard input channel of a program.
  - The `<<-` operator ignores tab characters at the start of lines. This allows indenting the text to make it more readable.

# Avoiding interactivity with input redirection

- Here-documents are the best way to select index groups in scripts.
- Some GROMACS tools have command-line options for selections.

```
gmx msd -sel [...]
gmx sasa -surface [...] -output [...]
```

- Most tools have no such options!

# Running analyses in parallel using job arrays

- We compute minimum distance time series between 14 Anx residues and the DOPC bilayer. (These residues were used as probes in NMR.)
- We have not one but 14 calculations to perform.
- We do these calculations in parallel.
- The first step is to prepare index groups for the 14 residues and the DOPC bilayer.
  - This step can be done on the login node.
  - We use a here-document with `gmx select`.

```
mkdir -p ~/Anx_on_DOPC/analysis/bilayer_aa_mindist
cd ~/Anx_on_DOPC/analysis/bilayer_aa_mindist
cp ~/gmxtools/06_make_mindist_index.sh make_mindist_index.sh
less make_mindist_index.sh
bash make_mindist_index.sh
less groups.ndx
```

# Running analyses in parallel using job arrays

- We start with a naive serial script.

```
cp ~/gmxtools/07_mindist.sh mindist.sh
less mindist.sh
sbatch mindist.sh
...
ls
...
scancel ...
```

- Analyses are done one at a time.
- This approach is much too slow.

# Running analyses in parallel using job arrays

- Our second attempt is a loop that submits multiple jobs.
  - This is an example of what not to do!
- We have two scripts.
  - One is run on the login node to loop over the residues and submit a job for each.
  - One job script to perform a mindist calculation for a given residue.

```
rm *.{sh,out,xvg}
cp ~/gmxtools/08_submit_mindist.sh submit_mindist.sh
cp ~/gmxtools/09_mindist.sh mindist.sh
less submit_mindist.sh
less mindist.sh
bash submit_mindist.sh
...
```

# Running analyses in parallel using job arrays

- Using a loop to submit jobs sounds like a good idea at first.
- It is problematic on clusters.
  - Each call to sbatch sends a remote call to the job scheduler.
  - A large number of calls can make the scheduler unresponsive (denial of service).
- It also has other disadvantages.
  - There is no match between the input and the SLURM output filenames.
  - Rerunning one crashed calculation is easy, but what about a subset of the calculations?
- Do not use loops to submit multiple jobs.

# Running analyses in parallel using job arrays

- Job arrays are a SLURM feature to submit multiple similar jobs efficiently.
- In a job array, all jobs use the same batch script.

```
rm *.{out,sh,xvg}
cp ~/gmxtools/10_mindist.sh mindist.sh
less mindist.sh
sbatch mindist.sh; sq
...
```

- The `--array` option submits a job array.
- The `SLURM_ARRAY_TASK_ID` variable is set to the array step by the job scheduler.

# Running analyses in parallel using job arrays

- Job arrays can span ranges.

```
--array=1-10,15
```

- A maximum number of concurrent running jobs can be set.

```
--array=1-100%10
```

  - Useful to avoid overloading a filesystem

- You can run new array steps or rerun past steps.

```
sbatch --array=12,252 mindist.sh
```

  - Useful to rerun crashed calculation

- Output filenames match array steps.

```
ls slurm-*.out
```

# Using job arrays with multi-dimensional input

- We compute the mean-square displacement (MSD) of water molecules in the vicinity of 14 Anx residues (NMR probes) in 10 trajectories.
- We have 140 (14 × 10) calculations to perform.
  - Residues: 12, 16, 104, 112, 117, 121, 124, 128, 137, 141, 144, 162, 180, 260
  - Trajectories: 01, 02, 03, 04, 05, 06, 07, 08, 09, 10
- SLURM job arrays are one-dimensional.
  - Each step is a positive integer: 0, 1, 2, ...
  - This does not match our two input variables.
  - How do we convert between multiple input variables and a linear job step?

# Using job arrays with multi-dimensional input

- One way to convert between multiple input variables and a linear job step is to put all variable combinations in a file.

```
12 01
12 02
...
12 10
16 01
16 02
...
260 09
260 10
```

- The line number of a given variable combination becomes its array step.
- The total number of lines is the number of array steps.

# Using job arrays with multi-dimensional input

- We start by generating the file for the array step variables.

```
mkdir -p ~/Anx_on_DOPC/analysis/MSD
cd ~/Anx_on_DOPC/analysis/MSD
cp ~/gmxtools/11_make_MSD_vars.sh make_MSD_vars.sh
less make_MSD_vars.sh
bash make_MSD_vars.sh
(head; tail) < MSD_vars.txt
wc -l MSD_vars.txt
```

- We then use a job array.

```
cp ~/gmxtools/12_MSD.sh MSD.sh
less MSD.sh
sbatch MSD.sh; sq
...
```

# Multiple short analyses in a single job with GNU parallel

- Some calculations require only a minute or even a few seconds.
- In such cases, a job array is not an appropriate approach.
  - Each array step is a full-fledged job.
  - It takes (at least) a few seconds to set up when a step starts.
  - It takes (at least) a few seconds to clean up after a step completes.
  - When steps very are short, this overhead becomes significant.
- Very short calculations should be packed together in a single job.
- However, we want to retain the ability to run calculations in parallel.

# Multiple short analyses in a single job with GNU parallel

- GNU parallel is a great tool to run multiple calculations in parallel inside a single SLURM job.
- GNU parallel dispatches calculations efficiently on one or more CPU cores.
- Example: You have 800 calculations to perform and submit a job requesting one full 40-core node.
  - GNU parallel starts 40 calculations when the job starts.
  - As soon as a calculation ends, GNU parallel starts another.
  - The 40 cores stay busy until there are no more calculations to start.
  - On average, each core performs 20 calculations (800 / 40).

# Multiple short analyses in a single job with GNU parallel

- We repeat the previous example, computing the MSD of water around 14 Anx residues in 10 trajectories.
- We use two scripts.
  - One is a batch job script that runs GNU parallel to repeat an MSD calculation over 14 residues and 10 trajectories.
  - The other performs an MSD calculation for the water in the vicinity of a given residue, for a given trajectory.

```
cd ~/Anx_on_DOPC/analysis/MSD
rm *
cp ~/gmxtools/13_gnupar_MSD.sh gnupar_MSD.sh
cp ~/gmxtools/14_MSD.sh MSD.sh
less gnupar_MSD.sh
less MSD.sh
sbatch gnupar_MSD.sh
...
less slurm_MSD.out
```

# Multiple short analyses in a single job with GNU parallel

- In the previous example, the output from all calculations is collated in one SLURM output file.
- We can separate the output for each calculation using `--results`.

```
rm *.{ndx,out,xvg}
cp ~/gmxtools/15_gnupar_MSD.sh gnupar_MSD.sh
less gnupar_MSD.sh
sbatch --wait gnupar_MSD.sh
tree output | less
less output/i/12/j/01/stderr
```

# Speeding up analyses using trajectory post-processing

- Some trajectory analyses are IO-limited (input-output).
  - Usually by the rate at which the trajectory can be read from disk
  - This is frequent for simple analyses such as extracting positions.
- Trajectory compression (e.g. XTC format) slows down analyses.
  - Frames must be decompressed to read coordinates
- Appropriate trajectory post-processing can speed up analyses
  - Removing atoms not used during analysis (typically the solvent)
  - Using an uncompressed format (e.g. TRR)
  - Post-processed trajectories can be stored in `/scratch`.
    - Better for intensive read/write operations on large files
    - These are temporary files for which no backup is needed.
    - Remember that inactive files are regularly purged from `/scratch`.
  - Post-processing compressed trajectories and outputing another compressed trajectory can lead to loss of precision (e.g. XTC → XTC).

# Speeding up analyses using trajectory post-processing

- We perform the same backbone RMSD calculation on two trajectories.
  - The original XTC resulting from the simulation.
  - A post-processed TRR containing only the protein.
- We compare calculation times.

```
mkdir -p ~/Anx_on_DOPC/analysis/traj_post_process
cd ~/Anx_on_DOPC/analysis/traj_post_process
cp ~/gmxtools/16_extract_protein.sh extract_protein.sh
less extract_protein.sh
sbatch --wait extract_protein.sh
ls -l ~/Anx_on_DOPC/simulations/2_MD/traj_comp.xtc \
    traj_protein.trr
cp ~/gmxtools/17_timed_RMSD.sh timed_RMSD.sh
less timed_RMSD.sh
sbatch --wait timed_RMSD.sh
grep real slurm_RMSD.out
```

# MDAnalysis for GROMACS structures and trajectories

- The GROMACS tools are command-line programs and can be automated using Bash scripts.
- They support a variety of options that make them very powerful.
- However, they are not flexible beyond their built-in options.
- There is no programming language interface (e.g. Python) to control or customise the tools.
- If you want to program something that the GROMACS tools cannot do, one solution is to a library for a programming language you are familiar with.
- Examples (this list is not exhaustive):
  - bio3D (R)
  - MDAnalysis (Python, MD trajectory analysis)
  - MDtraj (Python, MD trajectory analysis)
  - pytraj (Python, front-end for `cpptraj` from the Amber Tools)

# MDAnalysis for GROMACS structures and trajectories

- MDAnalysis is a Python library for the analysis of MD trajectories.
- It supports reading and writing structures and trajectories in the file formats typically used with GROMACS.
  - PDB, GRO, XTC, TRR
- MDAnalysis gives you direct access to atom coordinates and other properties through NumPy arrays.
- It comes with an extensive analysis submodule.
  - Distances, contacts, H-bonds, membranes, nucleic acids
- This provides a very flexible analysis framework.
- You can develop your own analysis routines by accessing atom properties and reusing existing analysis routines.

# MDAnalysis for GROMACS structures and trajectories

- We repeat the previous distance calculations between 14 Anx residues (NMR probes) and the DOPC bilayer, using MDAnalysis instead of the GROMACS tools.
- This time, instead of minimum distance, we want time series of ΔZ between the centre of mass of the residues and the average position of the phosphates in the upper leaflet of the bilayer.
- We start by installing MDAnalysis in a Python virtual environment.

```
module purge
module load python/3.8
virtualenv ~/MDA_env
source ~/MDA_env/bin/activate
avail_wheels MDAnalysis --all-versions
pip install --no-index MDAnalysis
deactivate
```

# MDAnalysis for GROMACS structures and trajectories

- We use two scripts.
  - One is a batch job script that activates our virtual environment and calls the other script.
  - The other is a Python script that uses MDAnalysis to compute all 14 timeseries in a single pass over the trajectory.

```
mkdir -p ~/Anx_on_DOPC/analysis/bilayer_aa_comdist
cd ~/Anx_on_DOPC/analysis/bilayer_aa_comdist
cp ~/gmxtools/18_comdist_job.sh comdist_job.sh
cp ~/gmxtools/19_comdist.py comdist.py
less comdist_job.sh
less comdist.py
sbatch --wait comdist_job.sh
...
```

# Generating GROMACS index groups with MDAnalysis

- MDAnalysis can be used to generate index groups for usage with the GROMACS tools.
- We repeat the atom selections done in the previous example, but save them to an NDX file instead of calculating distances in MDAnalysis.
- This script can be run on the login node.

```
cp ~/gmxtools/20_make_comdist_index.py make_comdist_index.py
less make_comdist_index.py
source ~/MDA_env/bin/activate
python make_comdist_index.py
deactivate
less groups.ndx
```

# References

- GROMACS: *https://www.gromacs.org/*
  - Manual: *https://manual.gromacs.org/*
- Anx article in JACS: *https://pubs.acs.org/doi/10.1021/jacs.6b07005*
- SLURM: *https://slurm.schedmd.com/*
  - Job arrays: *https://slurm.schedmd.com/job_array.html*
- GNU parallel: *https://www.gnu.org/software/parallel/*
  - Manual: *https://www.gnu.org/software/parallel/man.html*
- MDAnalysis: *https://www.mdanalysis.org/*
  - Documentation: *https://docs.mdanalysis.org/*