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Molecular Dynamics (SS2025)
Exercise 4

Pressure and Temperature Coupling in MD Simulations

Report Tasks

1. For all 12 simulations, list σ_V^2 and κ_T tabularly and plot E_{tot}, V and P as a function of time. Discuss differences and similarities between barostats and choices of τ_P.
2. Calculate κ_T for TIP4P and SPC/E Water and compare to the experimental value.
3. Briefly, describe the differences in E_{kin}, E_{pot}, ρ, H and E_{tot} for the standard and non-standard simulation. Try to explain said differences and propose an MD-based method to verify your explanation.

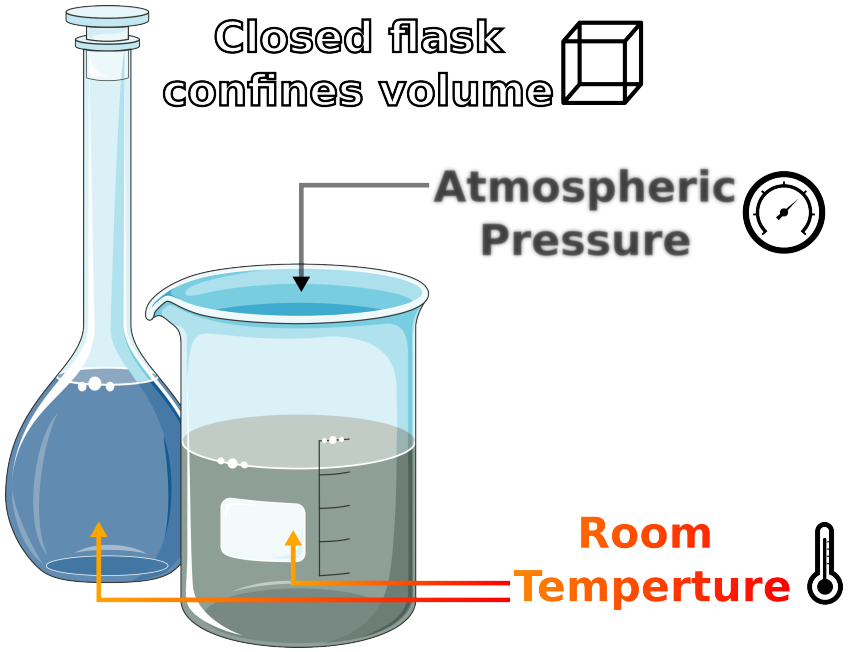

Figure 1: The application of a thermodynamic ensemble (NVT, NPT) is required to mimic the physical conditions in the wet lab. High accuracy algorithms for barostatting and thermostatting are crucial to yield realistic results from an MD simulation.[1]

The Choice of the Coupling Constant Matters

After last week's tutorial about temperature coupling, everything in this tutorial is centered around pressure coupling and the isothermic-isobaric ensemble. The final goal is to calculate

[1] Flask images were taken from `https://smart.servier.com/` (CC-BY 3.0)

the isothermal compressibility κ_T which depends on the volume fluctuations of the simulation. Thus, if the simulation does not reproduce accurate volume fluctuations, as a result of pressure coupling, κ_T will be erroneous.
Just like in temperature coupling, a barostat can be tuned by adjusting its coupling parameter τ_P. This parameter defines how tight the system's pressure is coupled. For a thorough comparative analysis, six different coupling constants τ_P and two barostats (Berendsen and Parrinello-Rahman) should be tested in simulations of a TIP3P water box. The `MDP` files can be found in the download repository, with missing values for the τ_P-option and the barostat in the NPT input files. The values to be screened are listed in table 1.
In the previous three exercises, the input files were usually pre-made and ready to use. In this exercise, creating the `GRO` and `TOP` file is part of the task.[2] A good starting point would be the command `gmx solvate`. This command offers a variety of options to solvate systems or create them from scratch. Since the command is quite versatile, it is recommended to read the `GROMACS` documentation[3] to figure out the crucial flags and options. Set the box dimensions to $2.504 \times 2.504 \times 2.504\,\mathrm{nm}^3$ and even though we use TIP3P water, spc216 needs to be specified for the `-cs` flag. In `GROMACS` spc216 is the standard 3-Point water model `GRO` file, also representing the coordinates of the TIP3P model and all other 3-point water models. The same rationale holds true for 4-Point and 5-Point water models as well.
Unfortunately, `gmx solvate` regularly fails to squeeze the requested amount of solvent into the simulation box. Hence, the `-maxsol` flag should be set to 1 so that we can use the resulting one-water `GRO` file as input for `gmx insert-molecules`[4]. This command fills a given box with the required number of water molecules (523) and unlike `gmx solvate` it tries to meet the specifications as many times as given in `-try`. The generated single-water `GRO` file should be used for the `-ci` flag. Finally, `gmx pdb2gmx` creates the respective `TOP` file, herein with the TIP3P water model and the Amber99sb-ildn forcefield. An exemplary workflow for creating the aqueous system is shown below.

```
gmx solvate -cs spc216 -box 2.504 2.504 2.504 -maxsol 1 -o tip3p.gro
gmx insert-molecules -ci tip3p.gro -box 2.504 2.504 2.504 -nmol 523 -try 10000 -o choice_tauP.gro
gmx pdb2gmx -f choice_tauP.gro -p choice_tauP.top -water tip3p -o trash.gro # UI prompted after
    execution
```

As a reminder, you should make sure to keep directories and naming conventions within your projects clean and consistent. Thus, names should be kept as short as possible and as informative as necessary in order to maintain a good overview. Anyhow, the simulation sequence consists of a minimisation, followed by an NVT Simulation and then by the NPT-Ensemble. The values for τ_P can be found in the following table. For certain τ_P values adjusting the `-maxwarn` flag of `gmx grompp` might be necessary.

Table 1: τ_P values to be selected for simulations.

τ_P/ps^{-1}	0.05	0.1	0.5	1	5	10

For the Parrinello-Rahman barostat and τ_P values above $0.1\,\mathrm{ps}^{-1}$, the option `nstpcouple = 1` must be deleted in the respective `MDP` files. For each NPT-simulation, plot the Volume V and Pressure P against time and calculate the variance of the volume σ_V^2 over the course of

[2] The manual creation of the two missing files is an optional sub-task. If time is limited, this task may be skipped by using `tip3pbox.gro` and `tip3p.top` from last weeks exercise.
[3] `https://manual.gromacs.org/documentation/2018/user-guide/cmdline.html`
[4] `https://manual.gromacs.org/documentation/2018/user-guide/cmdline.html`

the simulation. Concerning the plots, the first few frames may be excluded, if they are not representative for an equilibrated system by using `gmx energy -b <FRAME>`. σ_V^2 represents the volume fluctuations which are linked to the isothermal compressibility κ_T to be calculated for each τ_P as well. Tabulate the various values of σ_V^2 and κ_T and feature the plots in the report. Additionally, discuss which of the τ_P and barostats delivers results comparable to the literature[5] value of $\kappa_T^{TIP3P} = 6.3 \times 10^{-5}\,\mathrm{bar}^{-1}$ and why others may fail. The command `gmx energy` is highly recommended to conduct the result collection. The formula GROMACS uses to calculate κ_T comprises the volume fluctuations RMSD(V), the temperature T, the Boltzmann constant k_B and the average volume $\langle V \rangle$.[6]

$$\kappa_T = \frac{\mathrm{MSD}(V)}{k_B T \langle V \rangle} \tag{1}$$

The command is analogous to the one used in the prior exercise to obtain the isochoric heat capacity. The *energetic* properties, that you need to pick from the interactive menu can be deduced from the formula above.

```
gmx energy -f <ENERGYFILE> -o <OUTPUTFILE> -fluct_props -nmol <NUMBER>
```

Influence of the Water Model on the Isothermal Compressibility

In this task, two water models should be simulated in order to investigate the influence of different water models on κ_T. Optimally, the experimental value[7] $\kappa_T^{exp} = 4.52 \times 10^{-5}\,\mathrm{bar}^{-1}$ for 298.15 K is retained from the simulation runs. The water models in question are the SPC/E and TIP4P water model. This time, the simulation procedure includes an energy minimisation, an NVT- and NPT-equilibration, conlcuded by the preproduction and production run. It is common practice to use the Berendsen thermostat and barostat for the NVT- and NPT-equilibrations since it is robust and computationally inexpensive. The pre-production and production runs are usually simulated with the Nose-Hoover and Parrinello-Rahman algorithms for high fidelity production data. The pre-production run facilitates the system adjusting itself to the enhanced algorithms. As shown in last week's tutorial, some algorithms sample a certain ensemble more reliably which implies the introduction of physical changes that the system has to adapt to. The transition time necessary for this adaptation should not be included in the analysis since it is not representative of the thermodynamic equilibrium. The data for result computation should stem only from the fully equilibrated production run.
In order to save time, `nsteps` in the `MDP` files can be adjusted based on the MD runs from the first task. Simulations should be long enough to collect sufficient data to compute results, but not longer (feel free to play around with the `nsteps` option).
All necessary `MDP` files are given or can be repurposed and the `TOP` and `GRO` files can be obtained via the aforementioned workflow. `SPC/E` is a three-site water model and `TIP4P` is a four-site water model, thus the correct option for the `-cs` flag must be ensured.

```
gmx solvate [...] | gmx insert-molecules [...] | gmx pdb2gmx [...] # Procedure of obtaining GRO
    and TOP file
```

Once the simulations have finished, `gmx energy` is recommended to evaluate which of the water models performs better with respect to κ_T.

[5] https://doi.org/10.1063/5.0020514
[6] Allen M., Tildesley D. Computer Simulations of Liquids. Oxford. Clarendon Press. 1987. p.53
[7] https://doi.org/10.1063/5.0050841

Simulation Behaviour for Large τ_T Values

In the preceding tasks, strengths and weaknesses between algorithms were uncovered and parameter choices for τ_P were examined as well as the feasibility of different water models. Thus, our thoughts revolved mostly around the pressure coupling aspect within MD simulations. This last task, serves as a reminder that a simulation consists of a delicate interplay of various algorithms and their settings.
Therefore, two simulation setups shall be compared with each other. One features a relatively tight pressure coupling and a high τ_T value, corresponding to infrequent corrections to the temperature. Meanwhile, the τ_T and τ_P values of the other setup can be considered standard. The system itself is exactly the same as in the second task. Therefore, the only differences lie in the `MDP` files deposited in the moodle directory. Said files, `standard.mdp` and `non_standard.mdp`, should be used to simulate the NVT-equilibrated SPC/E system from the second task. Once the simulation is done, use `gmx energy` to calculate and plot the kinetic energy E_{kin}, the potential energy E_{pot}, the density ρ, the enthalpy H and the total energy E_{tot} of the two simulations.
Include your plots in the report and discuss differences in their appearances. Try to come up with an explanation for your observations and propose a simulation related way to test your hypothesis.