Exercise_5 Molecular Dynamics Simulation

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1 Introduction

In this Exercise we are going to perform 6 different simulations of the A-DNA, stable conformations of Watson-Crick-base-paired DNA. The goal of the simulations is to investigate different Electrostatic interaction schemes, in particular we used: Particle Mesh Ewald (PME), a cut off with Potential-Shift-Verlet and a plain cut off. In molecular dynamics simulations, electrostatic interactions are long-range and decay slowly with distance as $1/r$, making them computationally expensive to evaluate directly.

- The **Particle Mesh Ewald (PME)** method is widely used to compute long-range electrostatics efficiently and accurately. PME is a variant of the classical **Ewald summation**, which splits the electrostatic potential into two parts:
  - A **short-range (real-space)** component computed directly in real space using a cutoff.
  - A **long-range (reciprocal-space)** component computed using Fourier transforms.

  In PME, the reciprocal-space contribution is evaluated using a fast Fourier transform (FFT) on a discrete grid, hence the name "Particle Mesh". The charges are interpolated onto this mesh using a smooth function, typically B-spline interpolation, and the Poisson equation is solved in Fourier space.

  The overall electrostatic potential energy can be expressed as:

  $$V_{\text{total}} = V_{\text{real}}(r < r_c) + V_{\text{reciprocal}} + V_{\text{self}} + V_{\text{correction}}$$

  PME provides $\mathcal{O}(N \log N)$ scaling, which is far more efficient than the $\mathcal{O}(N^2)$ cost of direct pairwise summation, while maintaining high accuracy. It is the default method in many molecular dynamics packages, including GROMACS, for periodic systems with long-range electrostatics.

  PME is particularly effective in systems using periodic boundary conditions, as it assumes periodicity to efficiently perform the reciprocal space calculation.

- The **cutoff method** approach involves introducing a *cutoff radius* r_c, beyond which interactions between particles are neglected. That is, only particle pairs separated by a distance $r \leq r_c$ contribute to the force and energy calculations. The cutoff method significantly reduces the computational cost to approximately $\mathcal{O}(N)$, making large-scale simulations feasible.

  Despite its efficiency, the cutoff method introduces approximations that may lead to artifacts, particularly in the treatment of long-range electrostatic interactions, which decay slowly with distance. Sudden truncation at r_c can cause discontinuities in the potential and forces, potentially affecting energy conservation and system stability.

  To mitigate such effects, various smoothing functions or switching schemes can be employed near the cutoff distance, and more accurate methods such as the Particle Mesh Ewald (PME) technique are often used for long-range electrostatics. Nevertheless, the cutoff method remains a fundamental concept and is often used for van der Waals interactions or in systems where long-range accuracy is less critical.

- One of the common challenges with using a simple cutoff method is the discontinuity introduced in the potential energy and force at the cutoff radius. This can lead to artifacts such as poor energy conservation and unphysical system behavior.

  To address this, GROMACS implements the **Potential-Shift Verlet** scheme, which provides a smooth and continuous potential function up to the cutoff. In this approach, the pairwise potential $V(r)$ is modified so that it smoothly goes to zero at the cutoff distance r_c. This is done by subtracting the value of the potential at r_c:

$$V_{\text{shift}}(r) = \begin{cases} V(r) - V(r_c) & \text{if } r < r_c \\ 0 & \text{if } r \geq r_c \end{cases}$$

  The shifted potential ensures continuity of the potential energy, though the force is not necessarily continuous unless additional smoothing is applied. However, when used in conjunction with the **Verlet cutoff scheme**, the algorithm ensures efficient neighbor list management and can be easily parallelized.

  The Verlet scheme is based on a buffered pair list, which allows for flexibility in force calculation frequency and minimizes the number of list updates. When combined with potential shifting, the resulting algorithm achieves a good balance between accuracy and computational performance, especially in large biomolecular simulations.

  This method is particularly suitable for van der Waals interactions and is the default in many GROMACS setups due to its robustness and efficiency.

2 Methods

To compare the effects of different simulation methods and cutoff radii on the structural and dynamical properties of the system, we employed two complementary analyses: the radial distribution function (RDF) and the root mean square deviation (RMSD).

The RDF, $g(r)$, provides insight into the local structural organization by measuring the probability of finding a particle at a distance r from a reference group, relative to an ideal gas at the same density. In our case, it was particularly useful for characterizing solvent organization around specific atomic groups of the DNA, such as the neutral phosphate oxygens.

The RMSD, on the other hand, quantifies the overall deviation of atomic positions over time with respect to a reference structure, typically the initial or minimized structure. This metric was used to monitor the structural stability and equilibration of the DNA under different cutoff schemes and interaction models.

Together, RDF and RMSD analyses allowed for a comprehensive assessment of how the simulation parameters influenced both the local solvation environment and the global conformational dynamics of the system.

For performing the simulation we created a box for the solvent, than we equilibrated the system solvent with DNA coupled with temperature and then with pressure. In the end we run a preproduction and a production useful to analyse trajectories and gain the desired properties of the system. We run in total 6 simulations: three with cut off of length 0.8, 1.2 and 1.8. Two with cutoff 0.8 and 1.2 but with the potential-shift-Verlet method and one with PME.

3 Results

From the simulation we extracted the $g(r)$, the $RMSD$ and the timings that are *Core time* (The sum of the time spent by all CPU cores), *Wall Time* (The actual time taken by the simulation, as perceived by the user) and *Perfomance* (How fast the simulation progresses in terms of nanoseconds of simulated time per day of real time). It is notable that for the TR8 we had to use a $timestep = 0.001$ becuase if not the simulation crashed, so we doubled the number of steps. In the following images Fig 1 and Fig 2 are plotted the results for the $g(r)$ and $RMSD$ respectively. As notable, the PME method is the only method coherent with the experimental peaks for the $g(r)$ and with a corrected $RMSD$ stable that fluctuates around a mean value.The only other simulation that perfom correcly the $g(r)$ function is the TR18 becouse of the big cutoff

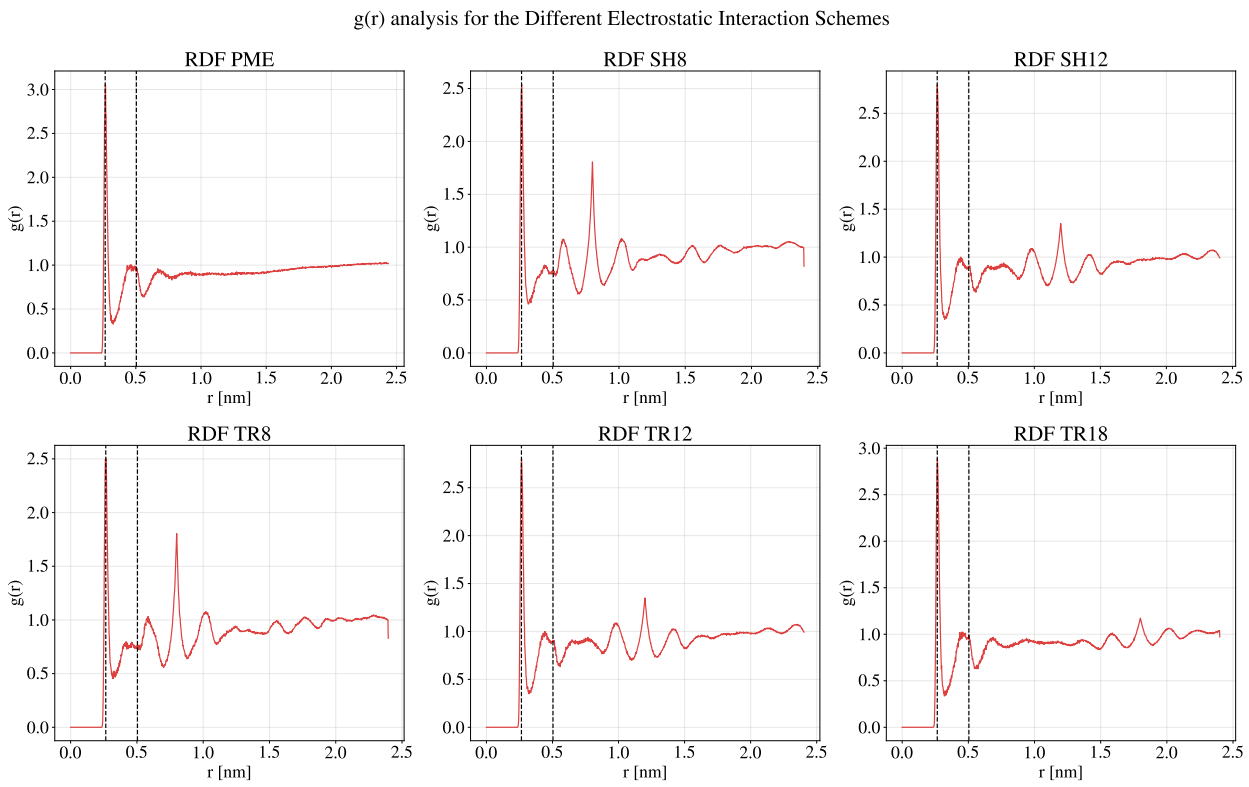

Figure 1: $g(r)$ distribution for the all 6 simulations performed with different electrostatic interaction methods. The purple verticla lines are the expected values.

radius but the $RMSD$ grows too much along time because of the accumulation of the long range interaction not treated properly. We notice that the $RMSD$ of the shifted Verlet method are slightly better than the raw cutoff.

From the performance results summarized in Table **??**, we observe significant differences in computational efficiency and structural stability across the tested methods. Among all, the TR8 method exhibits the best time performance, reaching nearly 50 ns/day with the lowest wall-clock time. On the other hand, TR18 is the most computationally expensive configuration, taking more than 9 hours to simulate a single nanosecond.

Interestingly, time performance appears to be inversely correlated with structural stability as measured by the RMSD. For instance, PME, which is generally considered accurate for electrostatics, shows a relatively big RMSD fluctuations compared to methods like SH8 and TR12.

Furthermore, the large increase in RMSD observed for TR8 and PME methods indicates that higher cutoff radii can lead to less stable trajectories, possibly due to the inclusion of long-range interactions without appropriate damping or smoothing corrections. This emphasizes the importance of balancing computational cost with physical accuracy, and highlights how medium-range cutoff methods with potential shifting (e.g., SH8, SH12) can provide both efficient and physically stable simulations.

In conclusion, the analysis shows that carefully tuning the electrostatics method and cutoff radius is crucial not only for performance optimization but also for maintaining structural integrity during molecular dynamics simulations. The PME is the best method taking accout all the parameters.

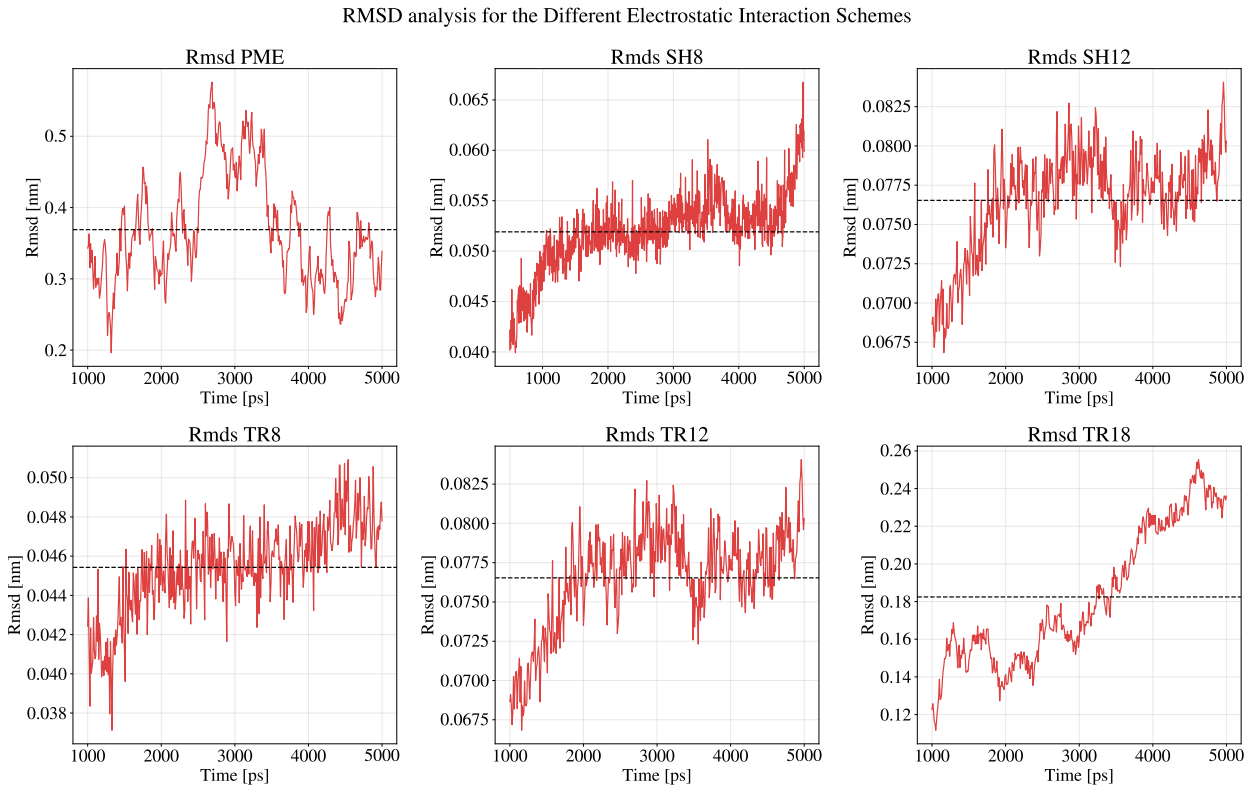

Figure 2: RMSD computed for all the 6 simulations. As notable there is a drift for some simulations and a significantly different variance for different methods.

Table 1: Performance and structural stability comparison of different electrostatics and cut-off methods.

Method	**Core Time (s)**	**Wall Time (h:mm:ss)**	**Performance (ns/day)**	$\langle RMSD \rangle$	σ_{RMSD}
PME	79193.30	2:44:59	43.640	0.3690	0.0768
SH8	136820.34	4:45:02	25.259	0.0454	0.0023
SH12	150846.65	5:14:15	22.911	0.0765	0.0032
TR8	69314.82	2:24:24	49.859	0.1825	0.0361
TR12	175409.42	6:05:26	19.702	0.0519	0.0038
TR18	277535.11	9:38:11	12.452	0.0765	0.0032