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Comparison of GPU-accelerated Molecular Dynamics Simulation Efficiency for the Acetylcholinesterase-Huprine X Complex using YASARA, GROMACS, and AMBER

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ABSTRACT

Molecular dynamics simulations are a valuable tool to identify potential acetylcholinesterase inhibitors for Alzheimer's disease therapy. Recent advancements in hardware and software, particularly the implementation of graphics processing units (GPUs), have significantly improved the efficiency of MD simulations. This study aims to compare GPU-accelerated molecular dynamics (MD) simulations of the acetylcholinesterase-Huprine X complex using YASARA, GROMACS, and AMBER. The complex was obtained from the Protein Data bank with code 1E66 and was prepared with the same conditions. MD simulations were performed for 50 ns with three repetitions per software. GROMACS exhibited the shortest average simulation duration (45,104 seconds), followed by AMBER (48,884 seconds) and YASARA (649,208 seconds). RMSD analysis of protein backbone and ligand movement indicated stable simulations across all platforms. Interaction analysis at 25 ns and 35 ns of YASARA's run revealed that Huprine X maintained key aromatic interactions within the AChE binding pocket, despite undergoing a 180° rotation. YASARA proved more efficient in MD preparation and produced more precise results, while GROMACS was the most efficient in simulation runtime. The study highlights the trade-offs between ease of use, simulation speed, and result consistency among these software packages for AChE-HUX MD simulations.

INTRODUCTION

The development of Acetylcholinesterase inhibitor (AChEI) has become a potential target for Alzheimer's diseases therapy (El Khatabi *et al.*, 2021). Inhibiting the activity of acetylcholinesterase (AChE) can prevent acetylcholine (ACh) degradation, which will increase the level of ACh in the brain and improve the condition of brain cholinergic neurotransmission (Marucci *et al.*, 2021). The molecular dynamics (MD) study itself is a method that can help identify a potent AChEI compound (Prasasty and Istyastono, 2020). Huprine X (HUX) is one of the AChEI compounds and can be used as a reference for MD study (Waskitha *et al.*, 2023).

In the last decades, improvements in computational hardware and algorithms as well as software have been done to make the MD process efficient. One of the improvements is the implementing the graphics processing unit (GPU) (Hollingsworth and Dror, 2018). GPU is a highly parallel co-processor that can operate separately (Rapaport, 2022). It has been proven that implementing GPU has improved the efficiency of MD simulations (Loukatou *et al.*, 2014).

Some of the software capable of MD simulations and having implemented the use of GPU are YASARA, GROMACS, and AMBER. YASARA MD algorithm was accelerated by GPU to calculate the nonbonded interactions, while the

rest (such as Particle Mesh Ewald (PME), bonded interaction, and Nuclear Magnetic Resonance (NMR) charge) was done by CPU (Krieger and Vriend, 2015). GROMACS is more focused on efficient parallelization by using GPU acceleration in calculating short-range non-bonded interaction and PME (Abraham *et al*., 2023). While AMBER had three models in implementing GPU, which is single precision single floating-point arithmetic but accumulated in double precision (SPDP), everything else is computed in single precision (SPSP) or double precision (DPDP) (Götz *et al*., 2012). This study aims to compare the efficiency and results of AChE-HUX MD simulations by implementing GPU on YASARA, GROMACS, and AMBER. This study is expected to serve as a reference source regarding the use of GPUs in modeling the molecular dynamics of protein-ligand systems.

METHODS

Materials and Instrumentations

The crystal structure complex of AChE-HUX (1E66) was obtained from the Protein Data Bank (PDB). The MD simulations were performed using server from CAD3BNP (Computer-aided Drug Design & Discovery of Bioactive Natural Products) research group (Server specification: Intel Xeon E-2286G 6 Core 4.0 GHz, RAM 64GB, Nvidia RTX A2000 12 GB), with Ubuntu Linux 20.04 as the operating system, with YASARA-Structure 23.9.29, GROMACS 22023.2, AmberTools23, Amber22 and PyPLIF-HIPPOS 0.2.0. Additionally, a personal laptop operating Windows 11 is used as the operating system.

Procedures

The preparation and docking procedure of HUX on AChE were followed the procedure provided (Waskitha *et al*., 2023). The best docking based on the RMSD value was used as the input for the MD simulation. The preparation and docking procedure were performed using a personal computer, while the MD simulation was performed using the server.

The MD simulations in YASARA-Structure were performed in two steps using two macro files that define the parameters of the simulations. The first macro file YAS-eq.mcr was prepared by modifying the default macro md_run.mcr. It was done to perform 5 ns MD simulations that will act as the equilibrium run. The equilibrium run was stored in a directory named "EQ", which was replicated thrice and used as the starting point for production run. The production run itself was performed by a macro file YAS-pr.mcr, modified from the default macro md_run.mcr. The production run continues by 50 ns from the last equilibrium run snapshot. Both macros have snapshots taken every 100 ps at 310K, in water density of 0.993 g/mL, AMBER03 was set as the forcefield, and run on 1 CPU thread and 1 GPU.

The input file for AMBER needs to be modified first to generate the topology for the ligand (HUX) and the complex of AChE-HUX. This was done by saving the PDB file of HUX molecule and the complex with the hydrogen molecule deleted from the system separately. The hydrogen atom was then added using the reduce program. The PDB of HUX was then converted to MOL2 using antechamber. Parmchk2 program was also employed to add the missing parameter which generated a "hux.frcmod" file. The topology and coordinates of HUX were then generated by the LEaP program with a general AMBER force field (GAFF) that was set as the force field. The topology was then loaded to the complex of AChE-HUX to generate the complex's coordinates and topology using the Leap program with ff03 (reference) set as the force field. The complex was then solvated with TIP3PFBOX and added with 53 Na+ molecules and 40 Cl- molecules. The solvated complex ran a short minimization, 500 ps of heating and 500 ps of density equilibration, followed by 2 ns of constant pressure equilibration at 310 K. The production run ran a total of 50 ns using pmemd.cuda program and coordinates that are recorded every 100 ps. This process was repeated thrice continued from the equilibrated state as the starting point.

ACYPYPE program was employed to generate the.gro and topology files with the complex's topology and coordinates before solvated from AMBER as the reference. The topology was then manually modified to include amber03.ff as the forcefield. The complex was then solvated, and Na+ and Cl- ions were also added. The solvated complex ran a short minimization using the steepest descent, followed by 500 ps of NVT at 310 K and 500 ps of NPT equilibration at 1 bar, and followed by energy minimization for 2 ns. The production ran a total of 50 ns, which was run on 1 CPU threads and 1 GPU. This process was be repeated three times continued from the equilibrated state as the starting point.

Analysis

The duration for production run from the three programs was noted and calculated the duration in seconds. The first 5 ns were

considered an equilibrium run, while the subsequent 50 ns were considered as the production run for YASARA MD. The resulting snapshots were analyzed using the default macro "md_analyze.mcr". For AMBER's production run, the RMSD of backbone and ligand move were analyzed using the CPPTRAJ program referring to complex_unsolvated.pdb. For GROMACS's production run, the RMSD of backbone and ligand move were analyzed using the "gmx trjconv" command. The files were copied to the computer client for further analysis. The stability of the systems was analyzed by following the suggestions provided by (Liu *et al*., 2017).

The trajectory of YASARA's MD was converted to PDB format using modified macro from "md_convert.mcr" which excluded the water object. The specific pose of 25 ns and 35 ns was used as the input for PyPLIFF-HIPPOS.

RESULTS AND DISCUSSION

The molecular docking validation showed that all 100 docked native ligands had an RMSD value ≤ 2.000 Å with a maximum RMSD value of 0.3123 Å. The results also showed that all redocked HUX had similar docked conformation and binding energy, ranging from -13.062 to -13.211 kcal/mol. This indicated that the molecular docking procedure was valid and reliable because the RMSD value of redocking poses was ≤ 2.000 Å.

To reduce interfering variables in MD simulations using YASARA, GROMACS, and AMBER, efforts were made to ensure that they ran in the same settings, including the starting point, temperature, and pH, and simulations were run using 1 CPU thread. The procedure for YASARA's MD simulations was more easily done as it only needed to modify the default macro. The AMBER's procedure was a bit complicated as the ligand had to be parameterized separately before the topology for the complex could be generated. The salt molarity also had to be calculated manually to have the same pH condition using the suggested formula (Machado and Pantano, 2020).

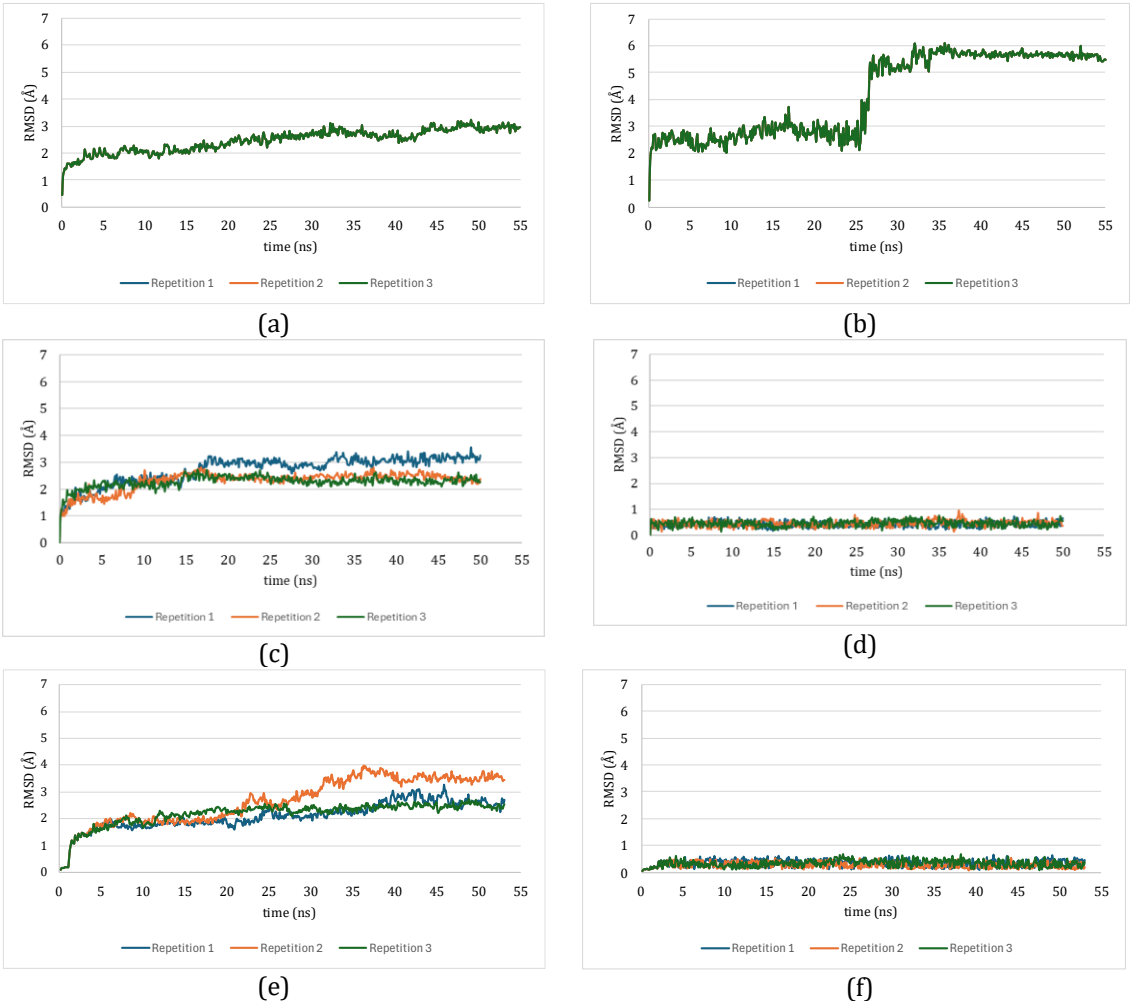

Figure 1. The RMSD values of AChE backbone atoms of MD simulations (a. YASARA, c. GROMACS, and e. AMBER) and RMSD values of HUX movement of MD simulations (b. YASARA, d. GROMACS, and f. AMBER)

Table 1. MD simulations duration (seconds)

Repetition	YASARA-Structure	GROMACS	AMBER
1	659239	45049	48556
2	642384	45130	49248
3	646002	45134	48849
Average	649208	45104	48884
SD	8873.17	47.96	347.35
CV	1.37	0.11	0.71

Table 2. Interaction analysis of AChE-HUX at 25 ns and 35 ns

RESIDUE	INTERACTION TYPE	25 ns	35 ns
TRP84	Aromatic face-to-face	✓	-
TRP84	Aromatic edge-to-face	✓	✓
TYR121	Aromatic edge-to-face	-	✓
TYR334	Aromatic edge-to-face	✓	✓
TYR442	Aromatic edge-to-face	✓	-

The GROMACS's procedure is more challenging as the topology had to be manually modified and the wrong step in the procedure could result in restoring the previous topology.

The details of the duration required for each production run simulation for 50 ns are shown in Table 1. The average duration of MD simulations for YASARA, GROMACS, and AMBER in sequence is 649208, 45104, and 48884 seconds. YASARA requires 13-14 times longer compared to GROMACS and AMBER. GROMACS provides the shortest duration and consistent, based on the CV value. The duration can be ordered from the shortest one, which is GROMACS, followed by AMBER, and YASARA, respectively.

The stability of the simulation from 3 repetitions on three programs is shown in Figure 1. YASARA shows 3 identical replicates of the simulation for 55 ns in both RMSD backbone (RMSDBb), and ligand move (RMSDLigMove) in Figures 1.a and 1.b. On the RMSDBb production run, the system runs stably despite experiencing a constant increase in RMSD values. On the other hand, the RMSDLigMove after the equilibrium run shows HUX ligand stability up to 25 ns and a high RMSD increase, followed by stabilization at 35 ns. The analysis of RMSDBb and RMSDLigMove on the production was run using GROMACS and AMBER did not provide identical results like YASARA for each replicate. However, RMSDBb values from YASARA, GROMACS, and AMBER all give results below 4.000 Å. Unlike RMSDBb, RMSDLigMove from GROMACS and AMBER provides more identical results for each replicate. RMSDLigMove also shows differences from YASARA results, where there is no significant increase in RMSD during the simulation duration.

According to (Liu *et al*., 2017), a protein-ligand simulation can be considered stable if the ΔRMSD value from the last 5 ns is ≤ 2.000 Å. The average ΔRMSDBb values for YASARA, GROMACS, and AMBER in sequence are 0.490; 0.503; and 0.534 Å, respectively, while the average ΔRMSDLigMove values are 0.586; 0.491; and 0.418 Å, respectively. Both ΔRMSDBb and ΔRMSDLigMove show stable protein-ligand simulation values ≤ 2.000 Å. The best results are shown by YASARA with identical ΔRMSD values, followed by AMBER with CV ΔRMSDBb 22.854% and ΔRMSDLigMove 9.855%, and finally GROMACS with CV ΔRMSDBb 23.012% and ΔRMSDLigMove 20.863%.

In Figure 1.b, the RMSDLigMove value increases from 25 ns to 35 ns. Analysis of fingerprint interactions except hydrophobic interactions is shown in Table 2. Both poses at 25 ns and 35 ns have aromatic interactions with TRP84 and TYR334. This indicates that HUX is still within its binding pocket, particularly that HUX still forms aromatic interactions with -

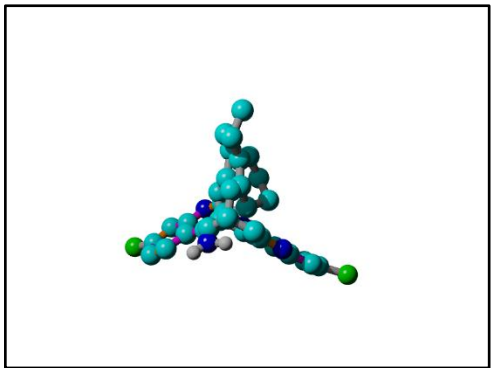

Figure 2. Superimposition of 25 ns and 35 ns from YASARA production run

TRP84 which is an important amino acid at the anionic sub-site of AChE (Xu *et al*., 2017). The visual superimposition of the two poses (Fig. 2) shows that HUX undergoes a 180° rotation, which causes the RMSDLigMove of HUX to increase.

CONCLUSIONS

The present study shows that YASARA is more efficient in preparing the MD simulations. GROMACS is more efficient in MD simulations than YASARA and AMBER, but YASARA's MD simulation results are more precise. Further study is needed to examine the MM/PBSA analysis for more precise results.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in this study.

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