Using Dedicated and Non Dedicated HPC Cluster and GPU *NVIDIA Tesla C2070* Cloud computing environment to simulate Molecular Dynamics of PfENR Enzyme with AMBER

[1,5] Heru Suhartanto, [2]Arry Yanuar, [3]Alhadi Bustamam, [1]T. Basaruddin,
[1]Aruni Yasmin Azizah, [1]Ari Wibisono, [1]M. H. Hilman, [1,4]Denny Hermawan
[1,] *Faculty of Computer Science Universitas Indonesia, heru@cs.ui.ac.id;chan@cs.ui.ac.id; ayazizah@gmail.com; ari.w@cs.ui.ac.id; h.hilman@cs.ui.ac.id*
[2,] *Faculy of Pharmacy Universitas Indonesia, arry.yanuar@gmail.com*
[3]*Faculty of Mathematics and Natural Sciences, alhadi@sci.ui.ac.id*
4 Faculty of Science and Technology, Al Azhar Indonesia University, dhermawan@gmail.com
[5]*Honorary Professor at School of ITEE, The University of Queensland*

Abstract

Molecular Dynamics (MD) is one of processes that requires High Performance Computing environments to complete its jobs. In the preparation of virtual screening experiments, MD is one of the important processes particularly for tropical countries in searching for anti-Malaria drugs. The search for anti-Malaria has previously conducted, for example by WISDOM project utilizing 1,700 CPUS. This computing infrastructure will be one of the limitation for country like Indonesia that also needs in silico anti malaria compounds searching from the country medical plants. Thus finding suitable and affordable computing environment is very important. Our previous works showed that our dedicated Cluster computing power with 16 cores performance better than those using fewer cores, however the GPU GTX family computing power is much better.

In this study, we investigate further our previous experiment in finding more suitable computing environment on much better hardware specification of non dedicated Cluster computing and GPU Tesla. We used two computing environments, the first one is Barrine HPC Cluster of The University of Queensland which has 384 compute nodes with 3144 computing cores. The second one is Delta Future Grid GPU Cluster which has 16 computing nodes with 192 computing cores, each nodes equipped with 2 NVIDIA Tesla C2070 GPU (448 cores). The results show that running the experiment on a dedicated computing power is much better than that on non dedicated ones, and the GPU performance is still much better than that of Cluster.

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Keywords: *Molecular Dynamic Simulation, GPU, Cluster*

1. Introduction

Drug design involves many disciplines, including chemistry, biology, pharmacy, and computer science. There have been some successful drug design activities based on computing-based drug design. Antiretroviral raltegravir for HIV-1 using AutoDock was produced by McCammon [1]. The product has been released after receiving approval by US FDA at Oct 12, 2007. Another success was done by Chen Yusong producing drugs schistomiasis using InvDock [2].

One important part that takes an important role in drug design activities is Molecular Dynamics (MD). The researchers conducted MD to study protein folding, and protein structural analysis, the structure and properties of molecules, [3, 4]. High Performance Computing infrastructures with multi-core system were used to do the MD[3], another special clusters used is the MD-Engine II [3,4], and a similar project is a quite popular volunteer distributed computing called Folding @ Home [5].

For countries that have plenty of medical plants have potentials to be the contributor in the era of new drug design using natural compounds from the plants. Indonesia is the world's centers of biodiversity, and is ranked the second richest in the world after Brazil. If marine life is taken into account, Indonesia ranks first in the richest biodiversity. On this earth, there are about 40,000 species of plants, 30,000 species which live in the country archipelago. Among the 30,000 species of plants that live in the country archipelago, it is known that there are at least 9600 species of medicinal plants.

Several compounds from natural sources have the potential to become a guide for model compounds that inhibit the action of a new enzyme, such as that of the HIV virus [6, 7]. A portal for medicinal plants database and three dimensional structure of chemical compounds from medicinal plants in Indonesia was proposed [8] for insilico screening the natural compounds. By using virtual screening, the usage of this database is needed to find inhibitors against enzymes such as those of HIV-1.

Activities on computing-based drug design have characteristics requiring large computing resources. To meet this needs, supercomputers as one of the high performance computing infrastructure are commonly used. For example, virtual screening for anti-malarial search conducted by WISDOM project uses grid infrastructure using 1700 CPUs of various infrastructure in 15 countries. [9]. Since this computing infrastructure can reduce the cost and time of in vitro and in vivo experiment, then in silico searching compounds from Indonesian natural materials can be potentials in searching for anti malarial using virtual screening methods [10].

Supercomputer requirement as the main resource of high performance computing poses a special problem in the research community, especially for those research institutes with limited budget particularly in some third world countries. Mostly they do not have an adequate budget for their research on national income and expenditure budgets. One alternative is to use the cluster, grid and GPU computing environment. This technology is one of the best alternatives for every researcher in providing high- performance computing resources need for drug design experiments.

We did several simulations using a simple compounds or molecules taken from literature and our medical plants database portal in our previous works. Initially, we have conducted simulation using the GROMACS on our cluster computing environment that gain significant speed up results in experiments with five nodes [11]. Another MD simulation with GROMACS using cluster computing environments, named Cluster05 which are also equipped with a GPU (Graphics Processing Unit). The GPU simulation gained speed up to 11-12 times those of Cluster [12]. However, our preliminary experiments performed using the MD with AMBER on cluster even though showed a speed - up but it is not too significant [13]. Thus , we intent to improve the performance of MD simulations using the AMBER in GPU computing environment for processing the conformational ensemble of PfENR which is an important enzyme in Plasmodium falciparum seeking to build a drug candidate for malaria.

Caused by parasites that are transmitted to humans through the bite of an infected female Anopheles mosquito or through blood transfusions, malaria is a life-threatening disease. Antimalarial drugs are widely used in Indonesia, among others, quinine, primaquine, chloroquine, pyrimethamine - sulfadoxine. Quinine is an alkaloid class of antimalarial drugs that are skizontosid kinkona blood in humans and Plasmodium vivax and gametosid on Plasmodium malariae. This drug is an antimalarial drug alternative to radical treatment without resistance Plasmodium falciparum to chloroquine and pyrimethamine - sulfadoxine (multi- drug) [14]. Currently, most of Plasmodium falciparum is resistant to the existing antimalarial drugs. This situation is caused by the occurrence of spontaneous mutations on the structure and activity of drug targets in malaria parasites.

Thus is very important to search for antimalaria drugs that work specific to the target parasites such as PfENR (Plasmodium falciparum Enoyl acyl Carrier Protein Reductase) , PM (plasmepsin) and FTase (farnesyl transferase) . In the past decade, there was a finding of a potential target for antimalarial. This target is a path of type II fatty acid biosynthesis that is known to take place also in Plasmodium falciparum with specific target ie Plasmodium falciparum Enoyl acyl Carrier Protein Reductase (PfENR) [15] . PfENR is an enzyme that plays an important role in type II fatty acid biosynthesis that occurs in Plasmodium falciparum. PfENR catalyzes the final step in the elongation cycle of fatty acid biosynthesis. PfENR works by reducing carbon double bond in enoil covalently bound to the acyl carrier protein [16].

In the era of designing new drugs, the availability of Indonesian Medicinal Plants database will become the basis for further investigation, particularly in the search for anti- malarial with the target PfENR enzyme. The use of a cluster or grid computing is the best solution in terms of increasing the speed of screening process, however, since the limited infrastructure and high operational costs it is necessary to find alternatives such as the technology of Graphical Processing Unit (GPU).

2. Related works

The bandwidth and computation power are approximately 10 times of the CPU capability that makes the GPU system is a very fast one. The micro benchmark performance is very convincing, the elementary mathematics instruction reaches 472 GFLOPS on 8800 Ultra GPU and 1581 types GFLOPS on a new generation GPU GTX 580. While the basic memory bandwidth performance is 86 GB per second for Tesla C870 GPU , and 144 GB per second for a new generation Tesla C2050 . Some applications may proceed more rapidly, for example, the N - body computation can achieve 240 GFLOPS which means 12 billion interactions per second. Case studies have been done on the issue of Molecular Dynamics (MD) and Seismic data processing. The power of GPU computing environment has also been demonstrated in the process of protein to protein interactions [17].

General Purpose Programming on GPUs (GPGPU) is a common non graphical application development process on the GPU. Initially, this technique is quite complicated. The issue to be faced should be considered as a problem related to graphics. Data must be mapped into the image (texture maps) and algorithms must be adapted to image synthesis [18]. Further development of GPGPU grow more rapidly again into GPU computing , after the launch of the programming tools Compute Unified Device Architechture (CUDA) by NVIDIA in 2007 . CUDA allows the leap very significant computational performance by moving the computational processes that run in series from the CPU into massively parallel computing using thousands of threads in the hundreds or even thousands of cores on the GPU. With the continuously strong support from NVIDIA and the cost of installation of the system is much cheaper than machines supercomputers and clusters, GPU computing via CUDA development continues to increase rapidly to almost all areas requiring high-performance computing.

Libraries are developed and provided in a programming language to facilitate the use subprograms within an application program where the programmer does not need to make these subprograms repeatedly. The programmer simply uses the pre-defined subprograms in a library. Many libraries have been built as a collection based on CUDA such as CUBLAS (Basic Linear Algebra Subprograms in CUDA) and CUFFT (Fast Fourier Transform in CUDA) [19].

Some applications running on the GPU have been developed by researchers such as in medicine and other research applications. Another example is the implementation and use of GPU computing has succeeded in improving the performance of the Markov clustering algorithm for inter- protein interaction networks [20]. Meanwhile, the ability of a machine to produce images with very detailed (highly detailed) in a very fast time unit is needed in the process of scanning breast cancer. TechniScan, a developer of automated ultrasound imaging system, has transferred the CPU -based implementation into CUDA ™ and NVIDIA ® Tesla ™ GPUs [21].

We have done some simulations using a simple compounds or molecules that are taken from literature and our portal. Initially, we have conducted research using the GROMACS on cluster computing environments that provide significant results in five trials nodes [22]. We have also done using the GROMAC in another cluster computing environments, named Cluster05 and computing facilities are equipped with the GPU (graphics processing unit) that provides speed up to 11-12 times [12]. However, preliminary experiments using the AMBER on cluster computing showed not too significant a speed – up [13]. Thus, in this activity, we want to improve the performance of MD simulations using the AMBER on GPU computing environment for manufacturing PfENR conformational ensemble. Given the conformational ensemble, we will further conduct virtual drug screening to find candidate anti-malarial using molecules from Indonesian Medicinal Plants Database [8].

PfENR is located in the apicoplast, the organelle which is the site of several metabolism in Plasmodium falciparum one of which fatty acid biosynthesis. The biosynthesis of fatty acids is essential for living organisms. As a major component of cell membranes, fatty acids are essential for energy needs. In Plasmodium falciparum, fatty acid biosynthesis is also required for cell growth, cell division and homeostasis. Biosynthesis of fatty acids increased during the phase of erythrocytes, where parasites grow and divide very quickly [15].

The biosynthesis of fatty acids that occur in Plasmodium falciparum is a type II fatty acid biosynthesis. One of the enzymes involved in this process is PfENR. It is becoming a key enzyme in the biosynthesis pathway of type II fatty acid [23]. This enzyme is involved in the extension of the final reduction step of fatty acid biosynthesis. It has a unique advantage because it does not exist in humans,

only in a few specific bacteria and protozoa. Therefore, this target is a good target to do the virtual screening process [24].

Virtual screening is an analog computing system or in silico biology screening. The purpose of virtual screening is to look for value, rank or filter a set of one or more structures using computational procedures. Virtual screening is used to help determine the compound to be screened or to help the process of synthesis [25]. Virtual screening project for anti- malarial conducted by WISDOM project uses grid infrastructure using 1700 CPUs of various infrastructure in 15 countries [9].

Virtual screening based on a collection (ensemble) of conformational structure of the protein conformational ensemble refers to the use of the crystal structure, NMR studies or molecular dynamics simulations give better results [10]. Conformational ensemble is necessary because the protein is flexible, can undergo folding - unfolding thermodynamically [26], so that the virtual screening process with the shape of the structure is not enough.

This work aims are part of our target to develop affordable HPC technology competencies to support simulation that processes large amounts of data and long processing time in MD. In addition to obtain the conformational ensemble with molecular dynamics simulations Plasmodium falciparum Enoyl acyl Carrier Protein Reductase (PfENR) by maximizing the use of the GPU as a computing environment. Information on plant species or potential drug-containing compounds guiding inhibitors on Plasmodium falciparum PfENR is very urgent to be known. Virtual screening protocols are established based on the target molecule conformational ensemble processed on the GPU.

3. The methodology

Our work is done with a combination of literary studies, GPU computing environment preparation, compound preparation, simulations and molecular modeling.

Preparation the GPU computing environments

While the Cluster computing environment is already established, performing molecular dynamics simulations of proteins with GPU-based computing environment requires some hardware that are able to accommodate the use of the GPU card. The supporting Softwares are CUDA toolkit, CUDA SDK, OpenMM, and Amber 11 [27, 28]. For Hardware needs, then the match will be investigated by the variation of the motherboard with suitable GPU available in local market. Our previous experience showed that excellent GPU type is not yet available in our local market and must be imported, but we have the opportunity to run in https://portal.futuregrid.org/ (currently it is now stopped running). For software needs, especially the AMBER11 parameters and CUDA parameters should be adjusted with suitable grid size and the number of threads.

Searchs and Downloads of Protein Structure

Macromolecular structures of PfENR targets were sought in the website of PDB (Protein Data Bank). Macromolecules were selected based on inclusion criteria such as wild-type macromolecule or nonmutan and related to the ligand. The Exclusion criteria are resolution which is greater than 2.5 Å and the incomplete chain. The Macromolecules was downloaded in text format then in Pdb format for further processing.

4. Experiment results

We conducted the simulation on several computing environment. First is the Barrine system which is a HPC cluster of 378 compute nodes managed by a PBSPro batch system. It is managed and built by the University of Queensland. There are 4 node types, the majority having 24GB of memory and 8 cpus based on Intel L5520 (2.27GHz). Three nodes are available with 1TB memory, 32 cpu (Intel X7550 2.0GHz). Computation is support by an Infiniband fabric connecting to 90TB of Panasas parallel filesystem and to other storage including 2PB of offline storage. Table 1 is the specifications of Barrine HPC Cluster,

Table 1. Barrine HPC Cluster Specification

- 384 compute nodes (3144 cores)
  - Mostly 8 cpu and RAM 24 GB per node
  - Some equipped by 8 cpu with bigger RAM/disk/GHz
  - 3 nodes have 32 cpu and RAM 1024 GB per node
- Attached storage
  - 250 GB local disk per node
  - 90 TB shared disk
  - 2.5 PB scale
- Operating environment
  - Linux OS (SuSE SLES VII)
  - Batch system (Altair PBS Pro VII)
  - Software development (Intel & TotalView tools)

Next, we also use Future Grid that has several clusters for high performance computing for free use by researchers who are already approved the project. The hardware owned by Future Grid can be seen in http://manual.futuregrid.org/hardware.html. There are computing resources such as foxtrot (IBM iDataPlex at UF), hotels (IBM iDataPlex at U Chicago), India (IBM iDataPlex at IU), sierra (IBM iDataPlex at SDSC), bravo (large memory machine at IU), and delta (GPU Cloud). The machine that will run a molecular dynamics simulation experiments are based GPU Cloud delta machine.

Delta Machine (delta.futuregrid.org), is a GPU cluster with 16 nodes with 32 CPU and a total of 192 cores running Red Hat Linux, with TORQUE (also called PBS) and Moab for task management, and a module to simplify the application and configuration. Delta consists of 16 nodes with two Intel X5560 6-core 2.8 GHz, 192 GB of DDR3 memory, and 15TB RAID5 disk storage. Each node contains two NVIDIA Tesla C2070 GPU with 448 cores.

Table 2. Delta Future Grid with Tesla C2070 Specification

- 16 compute nodes (192 cores)
  - Each node consist of 2 Intel X5560 6-core 2.8 GHz processor
  - 192 GB DDR3 RAM
- Graphic Processing Unit
  - Each node equipped with 2 NVIDIA Tesla C2070 GPU (448 cores
- Operating environment
  - Red Hat Linux
  - Batch System TORQUE/PBS

Table 2 is a specification Delta Future Grid with Tesla C2070. Prior to these, we also used our own Cluster, named as Cluster05 [29, 30] . It has 16 computing nodes whose specification is provided in Table 3. Comparing this with the other computing environment, ours has the weakest hardware specification, however it is a dedicated cluster for running this simulation.

Table 3. Cluster05 computing nodes specification [30]

Hardware (4 Buah *Computing Node*)
• Quad Core, 2.8GHz, 8MB Cache, Socket LGA1156 • 2x 2GB, DDR3, PC-12800 • Socket LGA1156, Intel P55 Chipset, DDR3 Dual Channel, 2x PCIe 16x 2.0, SATA III, USB 3.0, 2.0, Audio • 607W, Active PFC, Triple Rail +12V • Internal DVD-RW, SATA, Black, 2MB, 22x DVD+R Write • VC3430SNA, Middle Tower, No PSU • 640GB, 7200RPM, SATA II, 64MB Cache, 3.5", include SATA cables and mounting screws • NVIDIA GeForce GTX 465 (1 buah), NVIDIA GeForce GTX 470 (2 buah), NVIDIA Quaddro 4000 (1 buah)

4.1. Performance Analysis for PfENR protein

We have simulated PfENR in Barrine HPC Cluster and Delta Future Grid with Tesla C2070 with a few time step scenarios. It can be seen from Figure 1 that the amount of execution time decrease slightly between 4 and 8 processors. But the amount of execution time increase significantly when the number of processors are 16 and 32. For example when we use 4 processors and the number of time steps is 100ps, it took about 1.56 hours, however, it took only 0.88 hour when we use 8 processors to complete the task. The amount of execution time increases slightly between 8, 16, and 32 processors, namely 0.88 hr, 6.03 hr, 17.5 hr, respectively. The simulation on Delta Future Grid with Tesla C2070 shows greater result, it only took 0.29 hours for time step 100 ps.

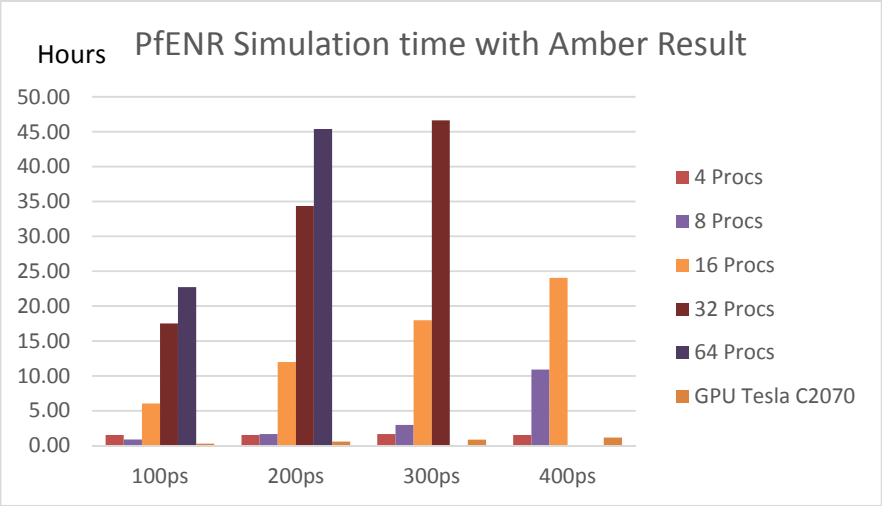


Figure 1. Amber PfENR Simulation Execution Time on Barrine HPC Cluster and Delta Future Grid with Tesla C2070

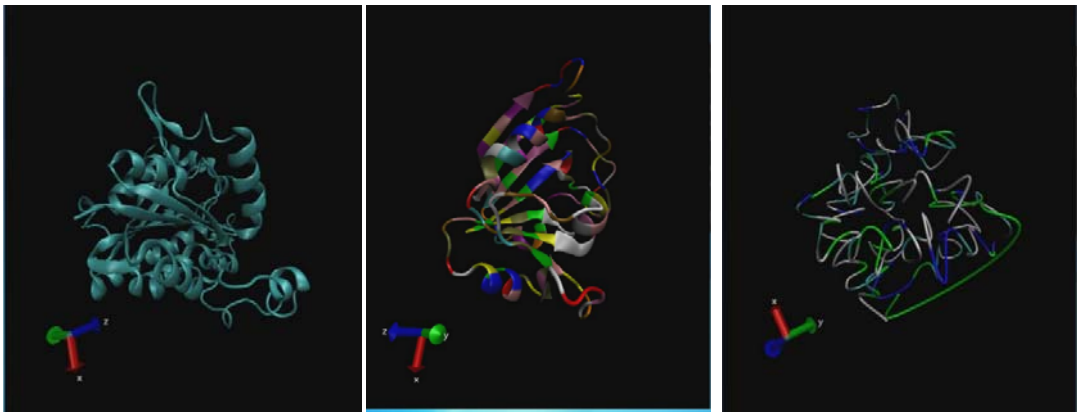
We have also run the simulation with a different time steps, 100ps, 200ps, 300ps, and 400ps. The experiments show that the amount of execution time for each time step decreases slightly between 4

and 8 processor and increase significantly when the number of processor are 16 and 32. The experiments also shows that the simulation in ns/day increases when the number of processors between 4 and 8, but it decreases significantly when the number of processors are 16 and 32 while the performance of Delta Future Grid with Tesla C2070 is consistent for any time steps scenario. The detailed result is available in Table 4 below.

Table 4. Amber PfENR Simulation Execution Time on Barrine HPC Cluster and Delta Future Grid with Tesla C2070

Timesteps	Barrine HPC Cluster										Delta Future Grid	
	4		8		16		32		64		GPU Tesla C2070	
	ns/day	time (hr)	ns/day	time (hr)	ns/day	time (hr)	ns/day	time (hr)	ns/day	time (hr)	ns/day	time (hr)
100ps	1.53	1.56	2.74	0.88	0.40	6.03	0.14	17.50	0.11	22.73	8.27	0.29
200ps	1.54	3.11	2.88	1.67	0.40	11.98	0.14	34.36	0.05	45.40	8.26	0.58
300ps	1.66	4.33	2.43	2.97	0.40	17.98	0.14	46.63	n/a	n/a	8.29	0.86
400ps	1.54	6.23	0.75	10.90	0.40	24.05	0.14	67.14	n/a	n/a	8.27	1.15

We have also run protein JAC_DHFR and myoglobin, the result of the test scenario is showed in Table 5. The simulation was performed using a timestep 100ps, 200ps, and 300PS. We have also test the time step with different size of processors (8, 16, 32, 64, and 128).



(a) (b) (c)

Figure 2. Protein Visualization of (a) PfENR-NAD, (b) JAC_DHFR, and (c) Myoglobin

We can see from Table 5. Simulation time shows that the shortest time when simulated using 8 processors is with timestep 100ps (4.37 hours PfENR-Nad). For the simulation using 32 processors, it produces the longest simulation time (290.4 hours) of estimation results.

Table 5. Amber Simulation Execution Time on Barrine HPC Cluster
(Protein Pfner-nad, jac_dhfr, myoglobin)

Protein									
	100ps			**200ps**			**300ps**		
	no of processors			**no of processors**			**no of processors**		
	8	16	32	8	16	32	8	16	32
PfENR-nad	4.37	6.03	17.50	8.75	11.98	34.36	9.06	17.98	51.82
jac_dhfr	4.48	11.68	31.23	8.89	21.89	31.34	13.09	33.48	85.98
myoglobin	8.01	20.66	94.92	4.19	48.14	95.55	5.97	67.23	290.94

Note that we did similar **jac_dhfr** and **myoglobin** simulation on Cluster05 with 100ps timesteps using 8 and 16 processors [29, 30]. The results of **jac_dhfr** is 6.33 and 6.23 hours respectively. While the results of **myoglobin** is 3.15 and 2.52 hours respectively. It is obvious that the Barrince HPC cluster with 8 cores performes worse compared that with 16 cores. But different phenomena is shown in Cluster05 where the simulation time using 16 cores improved the 8 cores simulation. The Cluster05 on this particular example also show much better performance than the Barrine HPC Cluster. A dedicated usage of the computing power is one of the reasons, Cluster05 is fully dedicated and allocated for running this simulation whereas the Barrine HPC Cluster are shared among heavy load jobs requesting many cores owned by many users at the same period of time.

5. Conclusion

The Barrine HPC Cluster does not scale up from 8 to 16 and then to 32 processors. The communication among the processors dominated the processes. The heavy load jobs submitted by many users affected the worst performance compared with Cluster05 which is a dedicated cluster running this experiment. The much better hardware specification does not guarantee providing much better performance. As in the previous works [30], The GPU performance is much better than that on cluster.

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