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USE OF GRID COMPUTING INFRASTRUCTURES FOR IN-SILICO DRUG DISCOVERY AND DRUG DESIGN : A REVIEW

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ABSTRACT

The development of new drugs with potential therapeutic applications is one of the most complex and difficult in the discovery of new drugs. Discovery new drug candidate compounds also require millions of dollars and takes many years to become a new drug that is ready to be marketed. One of the main challenges facing researchers in drug discovery is the need for data access and the need for massive computing power in a collaborative environment. Grid techniques can present an architectural framework that aims to provide access to heterogeneous resources in a way that is secure, reliable and scalable. Computer grid technology provides innovative infrastructure for the application of scientific and industrial complex in the field of search research and drug design. In this review, we discuss the application of computer grid technology for drug discovery, which is accompanied by an overview of computer grid architecture for drug discovery.

Keyword: *Virtual screening, Docking molecule, Cluster computer, Drug discovery.*

I. INTRODUCTION

The initial step discovery of new drug compounds usually begins with the identification of compounds suitable drug targets, such as receptors, enzymes and ion channels. Then continued to stage initial target validation which normally use testing in vitro and in animal models, to final validation remain with human clinical trials, conducted after all the initial target validation has been obtained (Terstappen, G.C., Reggiani, A., 2001).

In the period of the last decade of search and computer-aided drug design has become a trend among researchers of medicinal chemistry. Rational drug design with the help of a computer such as molecular modeling, docking, virtual screening, etc. With the help of computers, analysis and identification of candidate drug compounds would be easier, saving time and cost without the need to synthesize compounds advance drug candidates (Sliwoski, G., Kothiwale, S., Meiler, J., Lowe, E.W., 2013).

The starting point of the start of the search trends and computer-assisted drug design, starting around 1950, the beginning of the development of computational chemistry, which changes the description of a chemical system between experiment and theory. In computational chemistry experiments, calculations are performed using an algorithm written in a programming language, using theoretical models of experts. By using the methods and algorithms, allows the calculation of molecular properties of drug compounds, complex calculations can be done with the results correlated significantly with experimentation (Jensen, F., 2007).

The rapid developments computational chemistry and application of modern computational techniques in the pharmaceutical industry, especially in the search for new drug compounds, has placed high demands on computing resources in the search for and discovery of new drug compounds. Coupled with the drive to improve

efficiency greater cost. One way in which the big pharmaceutical companies are using grid computing to obtain efficient levels higher than on a desktop. The term grid computing has evolved which refers to the three main types of grid namely compute grids, grids of data and knowledge grid. In this paper the term refers to a grid computing infrastructure more compute grids (Konagaya, A., 2006).

II. GRID COMPUTING

The concept of grid technology was first described by Foster and Kesselman in 1998. The definition of grid computing by Foster and Kesselman (1998), A computational grid is a hardware and software infrastructure that Provides dependable, consistent, pervasive, and inexpensive access to high-end computational facilities. In 2001, Foster, Kesselman, and Tuecke to revise the definition of Grid be coordinated resource sharing and problem-solving in dynamic, multi-institutional virtual organization (Foster, I., Kesselman, C.,1999; Foster, I.,2001). So the grid is the infrastructure that appeared to distributed computing that provides a mechanism that is secure, scalable, using remote software and data resources.

Grid computing is based on many ideas such as utility computing, shared computing and so on. There are four layers in a grid architecture: the network, resource layer, middleware layer and application layer. To connect the Grid resources we need the network layer and this layer is the lowest layer in the architecture Grid. Resource layer lies just above the network layer where all grid resources are present such as storage systems, sensors and so on that connects to the network. Above lies the resource layer middleware layer that enables the elements to Participate in the grid. This middleware layer is Recognized as the "brain" behind grid computing. After middleware layer, the highest layer is the application layer the which helps users to interact with (Sohal, S.K., Sidhu, H.S., 2015).

The concept of grid computing is often described with an analogy as an electric power grids, where users can consume computer resources simply insert their electrical devices into any outlet and get the power from the collective. Examples of computing Grids are EGEE, NASA IPG, the World Wide Grid, and the NSF TeraGrid. The range of applications includes high-energy physics, particle physics, chemical engineering, and biomedical applications such as homology modeling, molecular docking, and molecular dynamics simulations (Kasam, V.K., 2009).

Biomedical applications utilizing distributed computing and grid computing is still relatively new, the development and research using grid computing is a new trend in the past 10 years (Rosenthal, A., Mork, P., Li, M.H., Stanford, J., et al., 2010).

III. CHARACTERISTICS OF GRID

Ian Foster defines the main characteristics of a grid as follows:

Decentralized control : In a computer grid system, allowing decentralized control of resources, which enables different administrative policies and management systems locally.

Open technology: A grid should use of open protocols and standards.

High-quality service : A grid provides high quality of service in terms of performance, availability, and security (Foster, I., Kesselman, C., Tuecke, S. 2002).

IV. GRID ARCHITECTURE MODEL

Availability of computer grid technology enables architectural framework with high performance and can provide an interconnection access to heterogeneous resources in a way that is secure, reliable and scalable with different levels of access restrictions (Venugopal, S., Buyya, R.,

Ramamohanarao, K., 2006). Accessibility of the applications is an important issue in Grid computing. A need has emerged for communities to have standards and a standards-based architecture that would facilitate better interoperability among various grid middleware systems and Grid-enabled applications. In the ideal grid infrastructure, the physical locations of resources do not matter anymore as the applications and data have logical references to these redundant distributed locations (Saltz, J., Hastings, S., Langella, S., Oster, S., et al., 2008). Basic Grid architecture consists of four layers: Application layer, User-level Middleware layer, Core Middleware layer, Grid fabric layer (Foster, I., Kesselman, C., 1999; Jiang, Z., Lu, F., Zhang, J., 2006; Sild, S., Maran, U., Lomaka, A., Karelson, M., 2006; Venugopal, S., Buyya, R., Ramamohanarao, K., 2006; Foster, I., 2007; Lu, B., 2008; Sohal, S.K., Sidhu, H.S.,2015;)

Table 1. List Grid projects for drug discovery

Project Title	**Website**	**Description**
World Community Grid	http://www.worldcommunity Grid.org/	Public computing Grid, runs FIGHTAIDS@HOME and Discovering Dengue Drugs-Together
ViroLab	http://www.virolab.org/	Individualized HIV treatment optimization; molecular dynamics
SIMDAT	http://www.simdat.org	Pharma activity with data integration; distributed workflow tasks
OpenMolGRID	http://www.openmolGrid.org/	Speed up drug-design, ADME filtering, QSAR
GridLab	http://www.Gridlab.org	Data management and visualization
GEMSS	http://www.it.neclab.eu/gemss/	Grid enabled medical simulation services
EuroGrid	http://www.euroGrid.org/	Bio-Grid: Biomolecular simulations, structural analysis
EUMed-Grid	http://www.eumedGrid.org/	Empowering e-Science across the Mediterranean, several bioinformatic tools
EMBRACE	http://www.embraceGrid.info	Integration of major databases and software tools in bioinformatics
DEISA	http://www.deisa.eu/	Bio-molecular simulations, molecular docking
DataMiningGrid	http://www.dataminingGrid.org/	Data mining applications on standards compliant Grid service infrastructures; Grid-assisted re-engineering of gene regulatory networks and analysis of proteins using computational simulations
D2OL	http://www.d2ol.com/	The Drug Design and Optimization Lab (D2OL)™ works to discover drug candidates against Anthrax, Smallpox, Ebola, SARS and other potentially devastating infectious diseases
Cardioworkbench	http://www.cardioworkbench.eu/	Drug Design for Cardiovascular Diseases: Integration of *in silico* and in Vitro Analyses
CancerGrid (UK)	http://www.cancerGrid.org	Anti-cancer drug design
caBIG	https://cabig.nci.nih.gov/	The cancer Biomedical Informatics Grid (caBIG) connects individuals and institutions to enable the sharing of data and tools for worldwide cancer research
BRIDGE	http://www.bridge-Grid.eu/	Drug design scenario: virtual screening by several molecular docking tools
BioSapiens	http://www.biosapiens.info/	Integrated Genome Annotation
BIG GRID	http://www.nikhef.nl/Grid/BIG	The Dutch e-Science Grid
@neurIST	http://www.aneurist.org	Integrated biomedical informatics; individualized patient risk assessment

AIDS@home	http://www.fightaidsathome.org	Compute against AIDS
Asia Pacific BioGrid	http://www.apbionet.org/apbioGrid	Asia pacific bioGrid Initiative
ProGenGrid	http://datadog.unile.it/progen	Proteomics and genomics grid
Virtual laboratory project	http://www.Gridbus.org/vlab	Molecular modeling for drug design
WISDOM	http://wisdom.eu-egee.fr	Initiative projects for grid-enabled drug discovery
ThaiGrid project	http://www.thaiGrid.net	Drug design grid project
Smallpox research grid	http://www.Grid.org	Compute against smallpox
Predictor@home	http://predictor.scripps.edu	Predict protein structure
Breast cancer grid	http://www.ediamond.ox.ac.uk	Compute against breast cancer
HealthGrid project	http://www.healthGrid.org	Health grid project
DDGrid	http://www.ddGrid.ac.cn	Drug discovery grid in CHINA
DiaDexus	http://www.diadexus.com	Identify disease-associated molecular targets

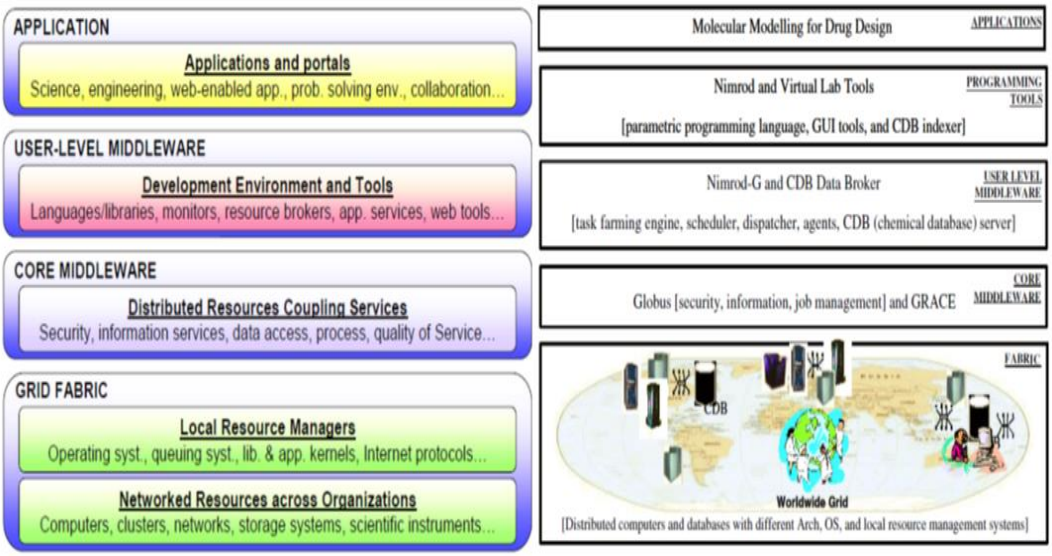

Figure 1. Layered architecture of grid computer for In-silico drug discovery and drug design (Buyya, R., Branson, K., Giddy, J., Abramson, D., 2003; Jacq, N., 2006).

a. Grid Middleware

Grid system develops very fast, now has available a lot of different options for grid middleware. Among these, the grid system the most mature and well-known that Unicore, Globus, Condor, and commercial products such as GridMP and Entropia.

Grid middleware can usually be divided into two layers: user-level middleware and the core middleware. The core middleware layer offers services to abstract the complexity and the heterogeneity of the resource level. The user-level middleware layer Provides higher-level abstractions and services.

Grid middleware usually very specific to the infrastructure of the grid. It could be said grid middleware is the key technology of computer grid, because the grid middleware has a duty to take care of the distribution of jobs, security, and checks the status of jobs in the computer grid system (Foster, I., Kesselman, C., 1999; Li, M., 2006; Sohal, S.K., Sidhu, H.S., 2015).

b. Application

When this has provided many chemical applications for structural analysis of drug candidate compounds. These applications are available now available in the system different grid middleware (Sild, S., Maran, U., Lomaka, A., Karelson, M., 2016).

c. Over Grid Computer Docking

Grid computer enables the prediction of the molecular target of the compound. Research in chemistry and drug design requires a lot of software, databases, and file format that is different (Buyya, R., Branson, K., Giddy, J., Abramson, D., 2003). With a computer grid, all of which can be easily integrated and implemented together in a single workflow (Buyya, R., Branson, K., Giddy, J., Abramson, D., 2001). This creates a virtual organization that joins with the expertise and resources of different agencies and groups. Installation of the system can be made more specific to the organization either in small or large scale. For example, predictive QSAR models for 3D geometric datasets compounds created from 2D coordinate conversion, followed by quantum chemical calculations and the calculation of molecular descriptors, everything can be set up in an automated workflow (Cherkasov, A., Muratov, E.N., Fourches, D., Varnek, A., et al., 2014).

Table 2. Different types of grid middleware, molecular modeling and grid application framework for grid system (Sild, S., Maran, U., Lomaka, A., Karelson, M., 2016).

Middleware	Molecular modeling application	Grid application framework
UNICORE	CPMD	
	Gausian98	BioGRID
	Gamess	BioGRID
	Amber	BioGRID
	PDB database	BioGRID
	Entrez database	OpenMolGRID
	MOLGEO	OpenMolGRID
	MOPAC 7	OpenMolGRID
	CODESSA Pro/MDC	OpenMolGRID
	CODESSA Pro/MDA	OpenMolGRID
	NTP database	OpenMolGRID
	ECOTOX database	OpenMolGRID
Condor	MOPAC 2003	WWMM
GridMP	THINK	Screensaver Lifesaver Project
	LigandFit	Screensaver Lifesaver Project
Globus	DOCK	VLAB, Nimrod/G
	GAMES	Nimrod/G
	Autodock	WISDOM
	FLEXX	WISDOM
	Gausian98	QC Grid
	WIEN2k	ASKALON, CoG
	NAMD	BioCoRe
Entropia	Autodock	AIDS@HOME

V. CONCLUSION

The development and implementation of grid computing can shorten the analysis of hundreds or even thousands of drug candidate compounds. With a computer grid method provides various other advantages such as the analysis cheaper, faster, more efficient in terms of computer hardware, software and human resources, shorten time, improve productivity and increase efficiency to identify the most promising protein targets. With a computer grid, the workflow can be set-up and reused easily, so that the reproducibility and higher

labor productivity. Just needs a little time spent to install different programs in architecture and environment apart and scattered in several locations. With a computer grid system also allows the database processing for docking and screening compounds more effectively, thus further facilitate the prediction of the nature of the target drug compounds.

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