Nulaka Srinivasu, M. Naresh Babu, Allam Appa Rao / International Journal of Engineering Research and Applications (IJERA) ISSN: 2248-9622 www.ijera.com
Vol. 2, Issue 5, September- October 2012, pp.1884-1887

Energy Minimization of CDK2 bound ligands: A Computational Approach

Nulaka Srinivasu*, M. Naresh Babu, Allam Appa Rao*****

*(Department of Computer Science (MCA), KGRL College, Bhimavaram.)
** (Assistant Professor, C R Rao AIMSCS, UoH Campus, Hyderabad)
*** (Director, C R Rao AIMSCS, UoH Campus, Hyderabad)

ABSTRACT

Cell proliferation is a consequence of positive signals which promote cell division and negative signals which suppress the process. Key factors in this signaling cascade are a series of cyclin dependent kinases (CDKs). It has been identified experimentally that CDK enzymes are highly flexible and the ligand binding orientations are primarily influenced by side chain torsions of amino acids in active site region. Ligands internal energy needs to be minimized before performing docking experiments. Energy needs to be minimized for high stability. Energy can be minimized efficiently by using molecular mechanics and molecular dynamics techniques. Two different co-crystallized ligands of 1H1S and 1OIT (CDK2 Proteins) are selected to find their minimum energy states using molecular mechanics and molecular dynamics algorithms reveals minimum energy state of these ligands can obtained using fletcher reeves algorithm of MM+ force-field.

Keywords: CDK, Molecular Mechanics, Molecular Dynamics, Energy Minimization, computational drug discovery

I. INTRODUCTION

Molecular dynamics (MD) is a form of computer simulation wherein atoms and molecules are allowed to interact for a period of time under known laws of physics, giving a view of the motion of the atoms. Because molecular systems generally consist of a vast number of particles, it is impossible to find the properties of such complex systems analytically; MD simulation circumvents this problem by using numerical methods. It represents an interface between laboratory experiments and theory, and can be understood as a "virtual experiment" [1] [2].

Molecular dynamics is a multidisciplinary method. Its laws and theories stem from mathematics, physics, and chemistry, and it employs algorithms from computer science and information theory. MD allows studying the dynamics of large macromolecules, including biological systems such as proteins, nucleic acids (DNA, RNA), membranes. Dynamical events may play a key role in controlling processes which affect functional properties of the biomolecule [3][4].

However, long MD simulations are mathematically ill-conditioned, generating cumulative errors in numerical integration that can be minimized with proper selection of algorithms and parameters, but not eliminated entirely.

The term molecular mechanics (MM) refers to the use of Newtonian mechanics to model molecular systems. The potential energy of all systems in molecular mechanics is calculated using force fields. Molecular mechanics can be used to study small molecules as well as large biological systems or material assemblies with many thousands to millions of atoms.

The great computational speed of molecular mechanics allows for its use in procedures such as molecular dynamics, conformational energy searching, and docking that require large numbers of energy evaluations.

Molecular mechanics methods are based on the following principles:

- Nuclei and electrons are lumped into atom-like particles.
- Atom-like particles are spherical (radii obtained from measurements or theory) and have a net charge (obtained from theory).
- Interactions are based on springs and classical potentials.
- Interactions must be pre assigned to specific sets of atoms.
- Interactions determine the spatial distribution of atom-like particles and their energies.[5]

II. MATERIALS AND METHODS

HYPERCHEM SOFTWARE:

HyperChem (http://www.hyper.com/) software is a molecular modeling and computational chemistry system for constructing molecular structures, computing their electronic energies, optimum geometries and for simulating their vibrational motion including chemical reactions. Molecules can readily be built and displayed on the computer's monitor by making selections from the system's menus with the computer's mouse. When constructing a molecule in this way the system checks that the normal valence of each element is not exceeded, but the user may disable this checking

in order to create other valence states or to build charged structures such as ionic complexes. After sketching the structure of the molecule, the user selects "build" and the system adjusts the bond lengths and angles to standard values, and at the same time converts the 2-dimensional sketch into a 3-dimensional structure.

HyperChem has several alternative algorithms for finding the optimum geometry. This minimum-energy, equilibrium geometry is of primary interest to the structure of stable molecules. HyperChem offers several different quantum mechanical methods to characterize and predict the structure and stability of chemical systems, to estimate energy differences between different states, and to explain reaction pathways and mechanism (nuclear motion) at the atomic level These calculations require much CPU time, and in practice the choice of method is usually a compromise between the time required for the calculation and the accuracy obtained.

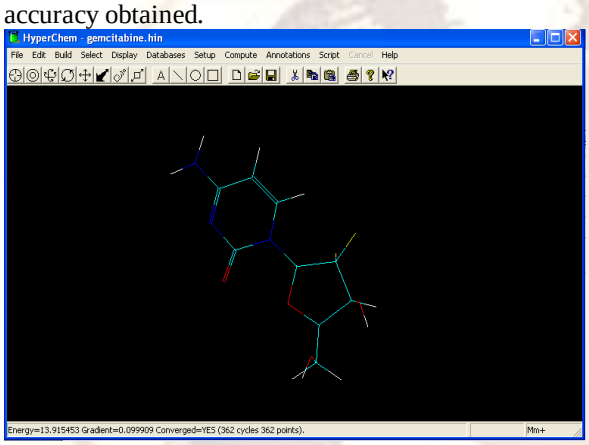

Fig 1: Generation of 3dimensional structure of gemcitabine using HyperChem software.

The geometry of these generated 3D models are optimized to get minimum energy state using various molecular mechanics optimization algorithms like Steepest descent, Fletcher –Reeves (conjugate gradient), Polak-Ribiere (conjugate gradient) under molecular mechanics force fields like MM+, AMBER, BIOCHARMM and OPLS.

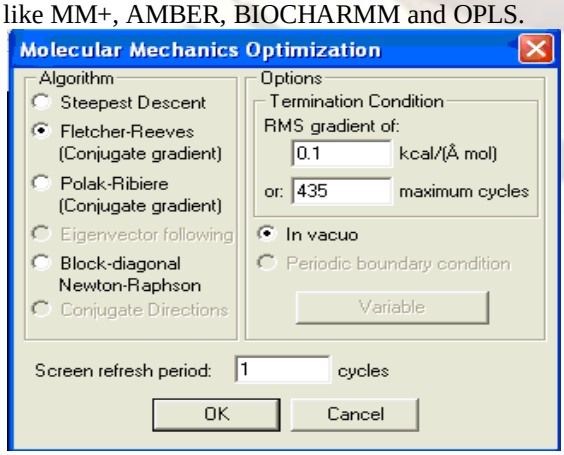

Fig 2: Image showing various molecular mechanics algorithms applied on ligands

Energy Minimization using Molecular Mechanics

Therefore, hyperchem software was employed to perform the task and the results are given below. In the given example, two bound ligands are selected to analyze or test the ability of few algorithms to reduce the energy states of ligands under default conditions.

The geometry of these generated 3D models are optimized to get minimum energy state using various molecular mechanics optimization algorithms like Steepest descent, Fletcher –Reeves (conjugate gradient), Polak-Ribiere (conjugate gradient) under molecular mechanics force fields like MM+, AMBER, BIOCHARMM and OPLS.

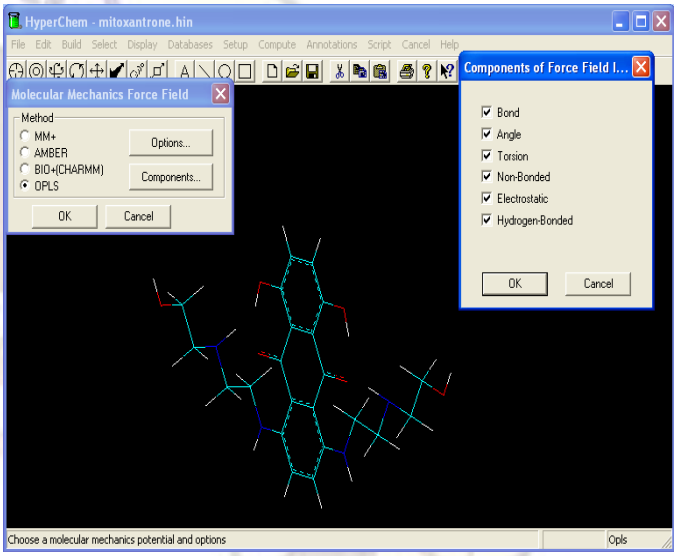

Fig3: Image showing various molecular mechanics force fields applied on ligands

Energy minimization using Molecular Dynamics:

A file was opened in HyperChem software, which is the output of energy minimization using molecular mechanics methods, is considered as the input for the molecular dynamics run. For example all the ligands has shown the lowest energy value in the fletcher reeves algorithm of MM+ force-field and this was subjected to molecular dynamic run providing the various parameters like Heat time - 0.2ps, Runtime- 1 ps, Cool time- 0.2ps, starting temperature-0K, simulation time-500K, final temperature-0K, temperature step-10K. The averages of the potential energy, kinetic energy and the total energy graph were obtained simultaneously along with the energy value in molecular dynamics by proceeding further. Thus the molecular dynamics was performed likewise for all the 4 molecules, changing the run time from 1-5 picoseconds and keeping all the other parameters constant

III. RESULTS AND DISCUSSIONS

Ligands internal energy needs to be minimized before docking experiments, such energy minimization can be carried out efficiently by employing molecular mechanics and molecular

dynamics techniques using HyperChem software. Two different co-crystallized ligands of 1H1S and 1OIT (taken from PDB) are selected to find there minimum energy states using molecular mechanics and molecular dynamics algorithms.

Energy minimization using Molecular Mechanics:

The minimum energies states obtained for the two selected ligands in molecular mechanics method are tabulated in Table 1and Table 2.

Energy differences between various force-fields and algorithms suggest that the minimum energy state of 1H1S_ligand can obtained using fletcher reeves algorithm of MM+ force-field (34.3235kcal/mol).

Energy differences between various force-fields and algorithms suggest that the minimum energy state of 1H1S_ligand can obtained using fletcher reeves algorithm with MM+ force-field (47.9043kcal/mol).

From the above data obtained by performing energy minimization using various molecular mechanics optimization methods , we can infer that MM+ molecular mechanics force field with Fletcher reeves algorithm gives better optimization of ligands than others.

Energy minimization using Molecular Dynamics:

1H1S_ligand:

1H1S_ligand was subjected to molecular dynamics, changing the run time from 1-5 picoseconds and keeping all the other parameters constant, the lowest energy value was obtained for the run time 5 ps (35.8976 kcal/mol) as shown in Table 3.

Table 3: Molecular dynamics run of 1H1S_ligand using various run times

liagand	Runtime (pS)	Energy(kcal/ mol)
1H1S_ligand	1	38.9995
	2	42.1432
	3	39.7106
	4	40.9952
	5	**35.8976**

1OIT_ligand:

1OIT_ligand was subjected to molecular dynamics, changing the run time from 1-5 picoseconds and keeping all the other parameters constant, the lowest energy value was obtained for the run time 2ps (53.6117 kcal/mol) as listed in Table 4.

Table 4: Molecular dynamics run of 1OIT_ligand using various run times.

Liagand	Runtime (pS)	Energy(kcal/ mol)
1OIT_ligand	1	56.2851
	2	**53.6117**
	3	56.6788
	4	54.0676
	5	55.1931

Following the above analysis, remaining all ligands bound to CDK-2 are energy minimized using Flectcher-reeves algorithm and further taken up for docking analysis.

IV. CONCLUSIONS AND FUTURE SCOPE

Ligands internal energy needs to be minimized before docking experiments. A molecular mechanics and dynamics approach was employed to evaluate the importance of algorithms in minimizing the energy of ligands (1H1S_ligand and 1OIT_ligand). Energy optimization using molecular mechanics approach resulted in Flecher-Revees algorithm under MM+ force field as better optimization method. Molecular dynamics run in vacuum conditions show lowest energies for gemcitabine at 3ps (16.74 kcal/mol), mitoxanthrona at 2ps (23.22 kcal/mol), 1H1S_ligand at 5ps (35.89 kcal/mol) and 1OIT_ligand at 2ps (53.61 kcal/mol) respectively. The minimized energy for 1H1S_ligand is 34.3235 kcal/mol and for 1OIT_ligand is 47.9034 kcal/mol. Further remaining all ligands bound to CDK-2 proteins are energy minimized using Flectcher-reeves algorithm and further taken up for docking analysis.

V. ACKNOWLEDGMENTS

Dr. Allam Appa Rao and Dr. M. Naresh Babu would like to thank the Dept. of Science and Technology for their financial support (DST-CMS GoI Project No.SR/S4/MS:516/07 Dated 21.04.2008)

REFERENCES

[1] D. Frenkel, et. al; "Understanding Molecular Simulation: From Algorithms to Applications"(2001)
[2] D. C. Rapaport; "The Art of Molecular Dynamics Simulations" (2004)
[3] H. J. C. Berendsen, Molecular Dynamics Simulation of Stadistical-Mechanical Systems, p. 496. North-Holland, 1986. G. Ciccotti and W. G. Hoover (Editors).
[4] H. J. C. Berendsen Comp. Phys. Commun., no. 44, p. 233, 1987
[5] http://biochem-vivek.tripod.com/id26.html

ANNEXURE

1H1S_ligand: (4-[[6-(cyclohexylmethoxy)-9H-purin-2- yl] amino]benzenesulfonamide)

Table 1: Energy minimized data of 1H1S_ligand molecule using various Molecular Mechanics algorithms.

Force-field	Geometry optimization	Energy (kcal/mol)
MM+	STEEPEST DESCENT	35.8962
	FLETCHER REEVES	**34.3235**
	POLAK-RIBIERE	34.3631
	NEWTON-RAPSON	34.0952
AMBER	STEEPEST DESCENT	51.9762
	FLETCHER REEVES	51.0968
	POLAK RIBIERE	51.1408
BIOCHARMM	STEEPEST DESCENT	100.5240
	FLETCHER REEVES	99.5412
	POLAK RIBIERE	99.4335
OPLS	STEEPEST DESCENT	39.6702
	FLETCHER REEVES	38.8010
	POLK RIBIERE	38.7903

10IT_ligand: (4-[(4-imidazo[3,2-a]pyridin-3-ylpyrimidin-2-yl)amino]benzenesulfonamide*)*

Table 2: Energy minimized data of 1OIT_ligand molecule using various Molecular Mechanics algorithms.

Force-field	Geometry optimization	Energy (kcal/mol)
MM+	STEEPEST DESCENT	48.3266
MM+	FLETCHER REEVES	**47.9034**
	POLAK RIBIERE	47.9652
AMBER	STEEPEST DESCENT	65.1429
	FLETCHER REEVES	63.2049
	POLAK RIBIERE	63.2717
BIOCHARMM	STEEPEST DESCENT	74.9808
	FLETCHER REEVES	73.9558
	POLAK RIBIERE	73.8895
OPLS	STEEPEST DESCENT	50.0360
	FLETCHER REEVES	48.9933
	POLAK RIBIERE	48.8810