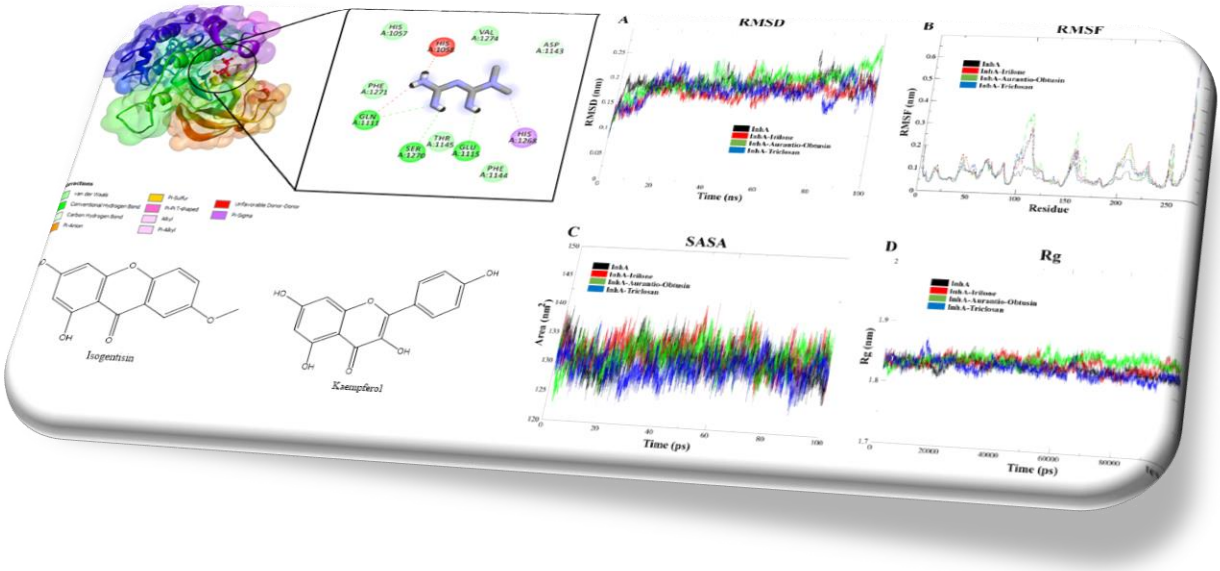
SEVEN-DAY BIOINFORMATICS SKILL DEVELOPMENT TRAINING PROGRAM ON



Ligand-Protein Interaction through Molecular Docking, MD Simulation & PCA in Determining Essential Dynamics

DEC. 7-14, 2023

Sponsored by:

Council of Scientific & Industrial Research, New Delhi (Govt. of India)

Organized by:

CSIR-Central Institute of Medicinal & Aromatic Plants, Lucknow

Training Program Contents

- *Introduction to Molecular Docking*
- *Molecular Docking Types & Scoring algorithms*
- *Introduction to Molecular Dynamics Simulation*
- *RMSD & RMSF Parameters in MDS*
- *SASA and Rg Parameters in MDS*
- *Interaction energy calculation*
- *Energy Minimization (Steepest Descent)*
- *Equilibration, Restraints to ligand*
- *Temperature coupling groups, NVT & NPT*
- *MD simulation Production (10 ns)*
- *PCA & its use in determining protein dynamics*

Convener
Dr. Feroz Khan

Coordinator
Dr. Laiq-Ur Rahman

Chairman
Dr. Prabodh K. Trivedi
Director, CSIR-CIMAP, Lucknow

About CSIR-CIMAP, Lucknow

CSIR-Central Institute of Medicinal & Aromatic Plants (CSIR-CIMAP) is a premiear multidisciplinary research institute of Council of Scientific & Industrial Research (CSIR), New Delhi, India with its major focus on exploiting the potential of medicinal and aromatic plants (MAPs) by cultivation, bioprospection, chemical characterization, extraction, and formulation of bioactive phytomolecules. With a strenght of 100 scientists, 162 technical officers, 129 support staff and nearly 300 doctoral and post-doc scholars at its head-quarter in Lucknow and research centers at Bengalure, Hyderabad, Pantnagar, and Purara. CSIR-CIMAP has played a key role in positioning India as a global leader in production of mints, vetiver and other aromatic grasses, and in ensuring indigenous production of artemisinin – a WHO approved antimalarial. CSIR-CIMAP houses a National Gene Bank on MAPs, which is one of the three of its kind in India. CSIR-CIMAP has played a key role in successfully commercializing an ayurvedic herbs based antidiabetic formulation, which has now benefitted millions. The institute is presently accredited by ICS-UNIDO and Indian-Ocean Rim Association (IORA) as a focal point for research and training on Medicinal Plants among 21 participating member countries. For more details please see the CSIR-CIMAP website www.cimap.res.in

About Bioinformatics Skill Development Program

Molecular Docking and thermodynamic-based **Molecular Dynamics** (MD) simulations are important methods for *in-silico* drug discovery. Molecular docking is an approach, which employs the binding modes of small molecules or macromolecules in contact with protein receptors at the atomic level. MD simulation techniques provide a significant complementary association with that of docking. These approaches are favourable in assessing the structural features of a protein–ligand, protein–protein, protein–nucleic acid, and protein–peptide complex.

The molecular docking method used to model the molecular interaction between a small molecule (phytomolecules & its derivatives) and a target protein (enzymes) or receptor at the atomic level, which elucidate the behaviour of small molecules in the binding site of target proteins as well as to elucidate fundamental biochemical processes. The docking process involves two basic steps: prediction of the ligand conformation as well as its position and orientation within these sites (referred as pose) and assessment of the binding affinity. These two steps are related to sampling methods and scoring schemes, respectively. Proteins active sites may be predicted through online servers, e.g., GRID, POCKET, SurfNet, PASS and MMC. Considering the limitation of computer resources, docking mostly performed with a flexible ligand and a rigid receptor, either with known binding/active site information or with blind docking approach (if no binding site known). Still flexible receptor based docking a challenging problem. Most commonly used docking softwares are: AutoDock, AutoDock Vina, DOCK, FLOG, DS LibDock, CDOCKER, SANDOCK, FlexX, ICM, GOLD, GLIDE, SCIGRESS, SYBYL Surflex Dock, etc.

Molecular dynamics (MD) is a computational simulation method for analyzing the physical movements of atoms and molecules. Atoms and molecules are allowed to interact for a fixed period of time, giving a view of the dynamic "evolution" of the system. The trajectories of atoms and molecules are determined by numerically solving Newton's equations of motion for a system of interacting particles, where forces between the particles and their potential energies are often calculated using interatomic potentials or molecular mechanics force fields. The first MD simulation of a biomolecule was accomplished in 1977 with 9.2 ps simulation on 58 residues

long Bovine Pancreatic Trypsin Inhibitor (BPTI) (McCammon et al., 1977). Now, MD simulations have evolved into a mature technique that can be used effectively to understand macromolecular structure-to-function relationships and protein-ligand binding stability. Most commonly used softwares for MD simulation are GROMACS, CHARMM, AMBER, NAMD and LAMMPS.

PCA in MD Simulation Studies

Principal component analysis (PCA) of MD simulations is a popular method to account for the essential dynamics of the system (protein complex) on a low-dimensional free energy landscape. PCA is a common linear dimensionality reduction technique that maps the coordinates in each frame of trajectory to a linear combination of orthogonal vectors. The vectors are called principal components and they are ordered such that the first principal component accounts for the most variance in the original data (i.e. the largest uncorrelated motion in trajectory), and each successive component accounts for less and less variance. The frame-by-frame conformational fluctuation can be considered a linear combination of the essential dynamics yielded by the PCA. Trajectory coordinates can be transformed onto a lower-dimensional space constructed from these principal components in order to compare conformations. It is now common approach to employ PCA to reveal the most important motions in proteins and to make inferences about the essential dynamics of a protein without having desired amount of samples. Here, protein dynamics means a change in protein molecular structure or conformation as a function of time. The MD simulation generate the trajectories of conformations, which ultimately, lead to better understand how proteins perform biological functions.

Keeping in mind the importance of MD simulation, in this bioinformatics skill development training program, we will describe the key steps of molecular docking and protein MD simulation, protein-ligand (drug/phytochemicals) MD simulation & role of PCA in MD simulation. Through this training participants may know how to perform (i) 3D structure preparation of target protein and small molecule, (ii) Molecular docking and Energy plot generation for potential energy, pressure, temperature and density for NVT, NPT during MD simulation experiments, (iii) RMSD (Root-Mean Square Displacement) analysis will be performed to study stability based on atoms position, (iv) RMSF (Root-Mean Square Fluctuation) analysis will be performed to understand overall flexibility detection of protein and complex. It will also help to detect the most flexible residue in the system (docked complex), (v) Radius of Gyration (Rg) analysis will be performed to assess the stability based on compactness, it will give answer whether target protein is in sphere form or not?

The Aim of Bioinformatics Skill Development Training Program

To familiarize students/researchers/academicians/industry experts with the basics of molecular docking and molecular dynamics simulation methods. Also to highlight the types of molecular docking methods and scoring algorithms with software used presently. In parallel, practical exercises/example demo for technical skill development will be scheduled after introductory lectures. Participants need to follow the instructions and perform the different steps during Hands-On training. Live trouble shooting will assist the participants in smooth learning of tools and techniques. The training program will cover an expert lecture, a training program related routine lecture and a demo presentation for practical exercise sessions. The training program would cover the following aspects:

- Introduction to Molecular docking
- Installation and setup of required software and packages
- Molecular Docking Types and Scoring Algorithms
- Introduction to Molecular Dynamics (MD) Simulation Study
- Generate Topology - Prepare the protein topology & Prepare the ligand topology – (AMBER/CHARMM/OPLS force field may be used) (GROMACS)
- Define box and Solvate –Defining the Unit Cell and Adding Solvent (GROMACS)
- Add Ions – Neutralize the system (GROMACS)
- Energy Minimization – Steepest Descent method use, calculate Potential energy, Maximum force and Normalized force (GROMACS)
- Equilibration – applying restraints to the ligand, treatment of temperature coupling groups, NVT equilibration, and NPT equilibration (GROMACS)
- Production of MD simulation – run 10 ns MD simulation of protein (control) and Protein crystallographic complex/docked sample (GROMACS)
- Analysis – Recentering and Rewrapping coordinates, Analyzing protein-ligand interactions, Ligand Dynamics, and Protein-Ligand Interaction Energy
- Key parameters of MD simulations- RMSD, RMSF, Rg, SASA analysis (GROMACS)
- Interaction energy calculation
- Hydrogen Bonds Analysis
- Introduction to PCA with example
- Role of PCA in protein dynamics study
- Example exercise/Hands-On – Molecular Docking, MD simulation and PCA

The skill development training gained through this program may help in making the career in Biotechnology, Bioinformatics, Structural Bioinformatics, Structure-Function Relationship domain, Molecular Modeling, Medicinal Chemistry, Biomedical informatics, Cheminformatics, Computer-Aided Drug & Discovery (CADD), and Artificial Intelligence/Machine Learning methods application in Biological/Chemical/Biomedical/Pharmaceutical Sciences.

Eligibility

UG/PG students of Science/Engg./Pharmacy (Bioinformatics/ Biotechnology/ Pharmacy/ Biochemistry/ Microbiology/ Life Sciences/ Medicinal Chemistry/ Botany/ Zoology/ Plant Sciences/ BioMedical/Medical Sciences; Ph.D. fellows/ Post-Doc scholars/ RA/ Scientist fellows/ Technical Officers; Project fellows/ Industry Professionals/ Entrepreneurs/ Academicians/ Faculty can attend. Basic knowledge of Biology, Chemistry, Biochemistry, Statistics, and working experience of Windows/Linux OS are required. For fresher's, tutorial will be provided for basics commands of Linux during MD simulation studies through GROMACS and PCA based protein dynamics calculations.

Certification
Training program's participants will receive a digital certificate of participation from the CSIR-CIMAP, Lucknow after successful completion of the skill development program. The digital certificate will be emailed after the successful completion of training program.

Feedback
After training program, participants may be asked to submit the given feed-back form. Participants may be asked to express their training experiences and suggestions for further improvement.

Training mode: Offline & Online hybrid mode. Online mode training will be done through MS Team/Google Meet or similar online apps.

Registration Fee: **Rs.5,000/-** for each (without accommodation & dinner) and **Rs.10,000/-** for each (with accommodation (twin shared basis), dinner included).

The registration fee includes Registration kit which includes a bag, tea (morning & evening time), lunch, training brochure, program schedule, stationary items in folder including pen & sketch pen/marker, tutorials, practical exercise, feed-back form, group photo (digital copy) and a certificate (digital copy will be emailed, however participants may collect the hard copy) after successful completion of the training.

Registration fee can be pay through online mode (Net/Mobile Banking) to:
SBI bank A/c No. 00000030267691783, SBI Main branch, Hazratganj, Lucknow (IFSC code: SBIN0000125) or through Demand Draft in favor of '**Director, CIMAP**', payable to Lucknow.

Deadline: Complete registration form along with the fee details should send to us by email (f.khan@cimap.res.in) or post before deadline i.e., **Dec. 05, 2023 up to 5:00 PM**.

Selection Criteria: Registration to the skill development training program will be on 'First-come-First-serve' basis. Seats are limited.

For any query related to this skill development training program, kindly contact:

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For any further details please contact:

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E-mail: director@cimap.res.in , Website: www.cimap.res.in

Application/Registration Form

Applicant's Full Name: _____

Designation/Position: _____

Affiliation (Institute/Univ. Name):_____

Affiliation Address:_____

Locality Type (Urban/Rural):_____

Category (Gen/OBC/SC/ST):_____

Gender (Male/Female):_____

Area of Interest: _____

E-mail: _____

Contact No.: (+91) _____

Registration Fee Payment Details:

Registration Fee: Rs. _____

Mode of Payment (NEFT/DD/UPI-Paytm/PhonePe/GPay etc.): _____

Net/Mobile banking/UPI Transaction/DD No._____Date _____

Bank Name, Branch & City: _____

Applicant's Signature_____