Contribution ID: **120** Type: **Poster (Chemistry SIG)**

Towards allosteric modulation of Hsp72: Molecular modeling and network analysis

Discovery of new compounds active against human cancers is vital for the ongoing battle against the disease. Structure-based drug design could be used to identify high quality leads. Even though current drugs provide significant therapeutic effects, tumor heterogeneity and resistance often render them ineffective. That is why we need highly potent inhibitors against reliable targets that can precisely subdue tumor survival mechanisms. Human heat shock proteins, Hsp72 and Hsc70, have been strongly implicated in modulation of cell-signaling pathways critical in tumor development and progression. In this study, both proteins were screened against 623 indigenous South African natural compounds from the South African Natural Compound Database (SANCDB) for antitumor drug discovery strategy. High throughput virtual screening was performed on entire protein surfaces using AutoDock Vina, while implementing gnu parallel on a single node with 24 cores and 24 MPI ranks. Aiming at allosteric pockets located at the substrate binding domain, a potential hit yielding low binding energy scores was identified. All atom molecular dynamics simulations (MDs) performed on protein-inhibitor complexes using MPI-enabled GROMACS 5.1.2 simulation tool revealed stable biomolecular associations. In total, 16 MDs, including duplicates, were performed. Each system, consisting of nearly 160,000 atoms, utilized 20 nodes during simulation, with 24 cpu cores and 8 MPI ranks per node for optimal performance. This translated to approximately 50 hours of wall-time. Computation of binding free energies yielded promising results indicative of robust protein-inhibitor interactions. Finally, we demonstrate using dynamic residue network analysis that the identified hit possesses the capability of allosteric inhibition via disruption of cross-domain communication. All experiments were performed at the Centre for High Performance Computing (CHPC), Capetown, SA. Challenges were encountered with parallelization of binding free energy calculations while using g_mmpbsa tool, since the available module was not compiled with external Adaptive Poisson-Boltzmann Solver (APBS).

Presenter Biography

Arnold Amusengeri is a PhD Bioinformatics student studying at Rhodes University under the supervision of Prof. Ozlem Tastan Bishop. He holds an MSc Bioinformatics degree from the same institution, and pursued Biochemistry in undergraduate. His research interests include structural bioinformatics and drug discovery.

Primary authors: Mr AMUSENGERI, Arnold (Rhodes University); TASTAN BISHOP, Ozlem (Rhodes University)

Presenter: Mr AMUSENGERI, Arnold (Rhodes University)

Session Classification: Chemistry and Material Science SIG Seminar

Track Classification: Chemistry and Material Science SIG Seminar