In silico Characterization of the Venus Flytrap Module of Venus Kinase Receptors from *Schistosoma japonicum*

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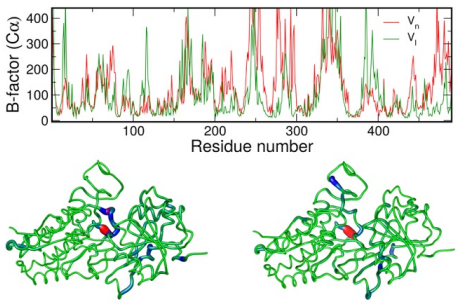
Abstract

Smart algorithms and advanced computing are the backbone of computational biochemistry. Molecular dynamics (MD) simulations of biomolecules in high performance computing (HPC) facilities are now a standard and an indespensable tool for characterization of protein-ligand interaction. Using the HPC of Advanced Science Technology Institute of DOST, we have performed various MD simulations of an important protein found in the blood fluke (*Schistosoma mansoni*) that causes schistosomiasis. The disease is characterized by the formation of mass granules in different organs caused by the interaction of worm eggs with the human immune system. We have performed 20 ns MD simulation of the extracellular binding domain, called the venus flytrap (VFT) module, liganded with different free amino acids (L-arginine, L-serine, and L-glycine) of the venus kinase receptor in *S. mansoni* using a parallel computing platform, i.e. 16 – 32 parallel CPUs. Our results show that, in general, ligand binding to the VFT module stabilizes the extracellular domain and causes it to assume a close conformation. It is theorized that VFT module activation in different proteins like the human metabotropic glutamate receptor and human gamma-aminobutyric acid receptor B is caused by closing of the VFT module subdomains. Characterization of these proteins in *S. mansoni* may lead to future development of anti-schistosomiasis therapuetics.

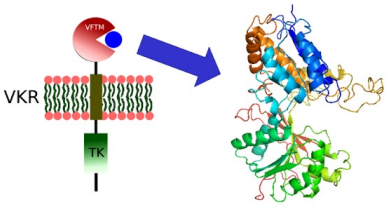
Methods

To date, no japonicum SjVKRs have been elucidated. Due to the presence of cloned and studied SmVKR, we use its cDNA to predict the putative sequence of SjVKR. The SjVKR cDNA sequence was searched using BLAST [1] in the GeneBD genomic sequence database (http://www.genedb.org) using SmVKR1 cDNA sequence (GenBank accession number AAL67949.1). The resulting cDNA of japonicum sequence was translated into its amino acid sequence. Limited by the VKR sequence found in the genome database, the sequence Sjp 0074540.1 (1262 amino acids) of the SjVKR Anhui isolate was used to obtain the apo 3D structures. To generate the initial coordinates of VFTM portion of SjVKR protein, the amino acid sequence spanning amino acid 503 to 994 was submitted to the I-TASSER server [2–4], an online protein structure prediction server.

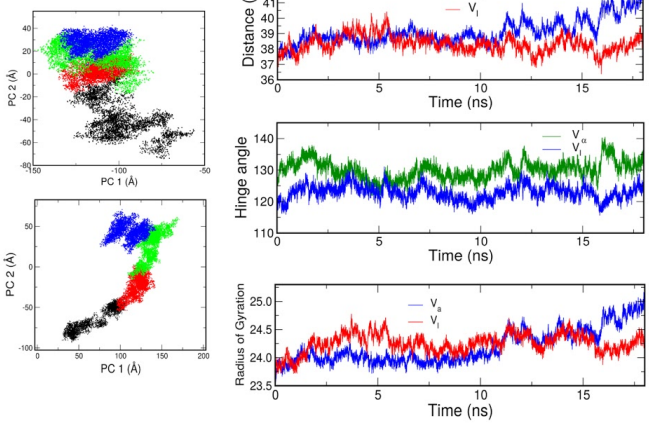
Minimization, heating, and equilibration was performed at constant pressure (NPT) of 1 atm. After, twenty nanoseconds (20 ns) constant volume (NVT) production runs at 300 K was performed. The temperature was regulated by Langevin thermostat [5]; bonds with hydrogen atoms was constrained using the SHAKE algorithm [6]; and the long range electrostatic interactions were evaluated using the Particle mesh Ewald method [7].



System of Interest



VFTM module of *Schistosoma japonicum*



Conclusion

We conclude that the apo and the liganded forms of the protein assume different (divergent) conformational states. The introduction of ligand to SjVFT leads to the formation of secondary structures like alpha helices and beta sheets and a subsequent decrease in the number of turns or loops, resulting in lower radius of gyration. In particular, bound calcium ion restricts the inter-domain opening of the VFTM section of the protein.

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