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RESEARCH ARTICLE

COARSE-GRAINED MOLECULAR DYNAMICS SIMULATION STUDY OF ASTN-2

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ABSTRACT

Membrane proteins have a pivotal role in cell biology. They are involved in supervising the cellular interactions and maintaining stability of the cell structure. Astrotactin-2 is a perfor in like protein, which has a crucial role in many neuro developmental brain disorders such as autism spectrum disorder, bipolar disorder, schizophrenia etc. Since transmembrane proteins are large in size, it is necessary to precisely orient the protein and thus coarse-grained simulation serves as the best option for computational studies of MPs. Coarse-grained models have been successfully used in studying proteins.Here in this study, MARTINI force field was used to run the coarse-grained simulation of ASTN-2.

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INTRODUCTION

Membrane proteins have a pivotal role in cell biology. They are involved in supervising the cellular interactions and maintaining stability of the cell structure (Sebastian Kmiecik *et al*., 2014). They help in transportation of biomolecules across plasma membrane (Sebastian Kmiecik *et al*., 2016). Since transmembrane proteins are large in size, it is necessary to precisely orient the protein and thus coarse-grained simulation serves as the best option for computational studies of MPs (Sebastian Kmiecik *et al*., 2016). It is a tedious task to experimentally determine the structure of MPs (Sebastian Kmiecik *et al*., 2016). Computational strategy of using coarse-grained models coupled with experimental data such as NMR, cryo-EM, X-ray seems to gives a better understanding of protein structures and their complexes (Sebastian Kmiecik *et al*., 2016). CG models are usually setup for implicit solvent environment, which accelerates the computations (Petr Stadlbauer *et al*., 2016).

Astrotactin is a newly cloned adhesion molecule for neuroglia-steered flow in cortical regions of brain (James *et al*., 1997). It is also an exceptionally good candidate for neuronal migration deformities in humans (James *et al*., 1997). The bonding between neurons and astroglia as a neuronal cell-surface antigen is achieved by astrotactin 1 (ASTN1), whereas, astrotactin 2 (ASTN2), regulates its expression on neuronal surface by interacting with ASTN1 in the neuronal membrane and, thereby intervening the formation and release of neuronal-glial adhesions during migration (Anath *et al*., 2014).

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Hatten *et al.* suggests that ASTN2 has a critical role in controlling surface membrane protein dynamics and endowment to neurodevelopmental brain disorders (Hourinaz Behesti *et al*., 2018). ASTN2 is associated with autism spectrum disorder, bipolar disorder, and schizophrenia (Christine *et al*., 2016).

MATERIALS AND METHODS

The coarse-grained molecular dynamics simulation of ASTN-2 was carried out using MERMAID server with MARTINI 22 force field. MARTINI force field is best suited to carry out the simulation of membrane proteins (Sebastian Kmiecik *et al*., 2016). MARTINI coarse-grained model for lipid membranes was first designed by Marrink group (Sebastian Kmiecik *et al*., 2016). In MARTINI force field four heavy atoms including associated hydrogens are portrayed by a single coarse-grained bead whereas, one coarse-grained water bead equals four water molecules (Sebastian Kmiecik *et al*., 2016). The non-bonded interactions are controlled by a Lennard-Jones (LJ) potential although electrostatic interactions are defined by the Coulombic energy function (Sebastian Kmiecik *et al*., 2016).

RESULTS AND DISCUSSION

Molecular dynamics (MD) simulations are being used to investigate the molecular details of the plastic flow, glassy response, pressure, and temperature dependence of polymeric systems (Amin Aramoon *et al*., 2016). Initially, atomistic simulations represent an ideal computational strategy to study the protein folding. However, closer inspection reveals that this

approach has noticeable drawbacks (Shoji Takada *et al*., 2015). Basically, the expenditure for atomistic simulations is high, which hinders the further analysis (Petr Stadlbauer *et al*., 2016). The practice of coarse grained (CG) models serves as an outstanding substitute to atomistic models, which grants simulations to be run on larger systems and longer time scales and yet present rational structural detailing (Siewert *et al*., 2007). Recognizing the protein folding mechanisms is certainly one of the main reasons for designing coarse-grained protein models (Sebastian Kmiecik *et al*., 2016). The first coarse-grained protein model was developed almost 40 years ago (Sebastian Kmiecik *et al*., 2016). Many coarse-grained models have been developed to evaluate the protein-folding, thermodynamics and kinetics of proteins (Siewert *et al*., 2007). Another productive area for coarse-grained modeling is protein structure prediction (Sebastian Kmiecik *et al*., 2016). The use of coarse-grained models now permits the simulations of membrane plots which encompasses ten thousands of lipids and various proteins up to millisecond time scales (Siewert *et al*., 2007). Coarse-grained models have been efficaciously adopted in studying protein folding with the aid of protein-like models or simulations of real proteins (Sebastian Kmiecik *et al*., 2016).

These integral transmembrane proteins with 2 transmembrane helices have a molecular weight of 150 Dalton (Tao Ni *et al*., 2017). The crystal structure of a broad section of ASTN2 imparts that C-terminal domain enclose three EGF-like domains, an MACPF domain, Fibronectin type-3 domain and Annexin like domain (Tao Ni *et al*., 2017). The pore-forming MACPF domain have two sets of TMHs with identical number of residues, but subjecting ASTNs, one of the TMHs is 30 residues lesser than the other so that it would not match it in forming the β-barrel (Tao Ni *et al*., 2017). The annexin-like domain of ASTNs is unlike human annexin sequence, which is remarkably homologous to the annexin repeat fold (Tao Ni et al., 2017). The MACPF-Fn (III)-annexin complex crop up into a folded solid unit, with a pervasive intermolecular interface between the MACPF domain and Fn (III) domain. ASTN2 link with inositol diphosphate and inositol triphosphate (Tao Ni *et al*., 2017). The N-terminal domain and cytosolic domain play an important role in ASTN activity (Tao Ni *et al*., 2017). Hatten et al suggests that, ASTN2 is probably entangled in many phases of endo-lysosomal trafficking and not just the surface membrane (Hourinaz Behesti *et al*., 2018).

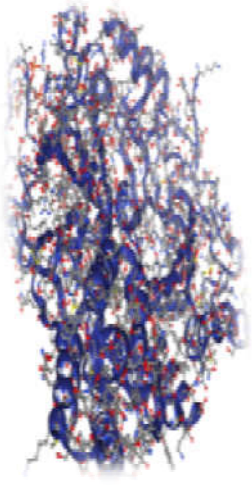

Figure 1. Structure of protein

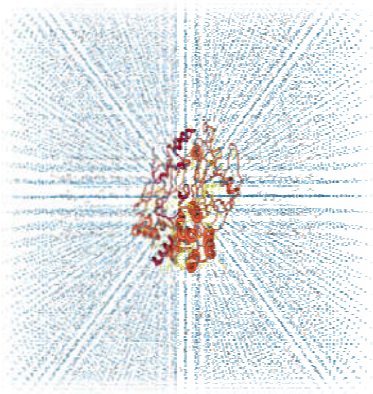

Figure 2. Initial CG structure

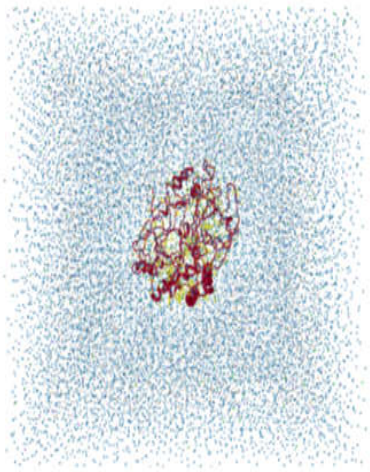

Figure 3. Minimized CG structure

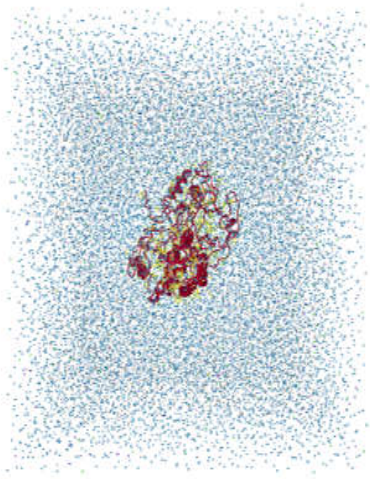

Figure 4. Production CG structure

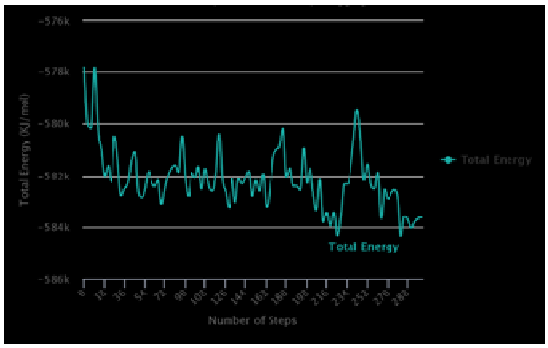

Figure 5. Total Energy Graph

Figure 6. Production-Temperature Graph

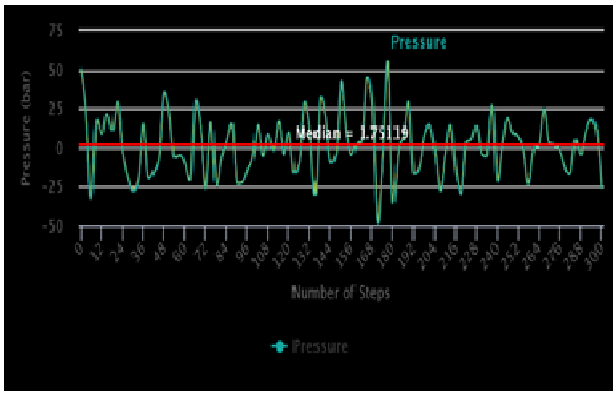

Figure 7. Production-Pressure Graph

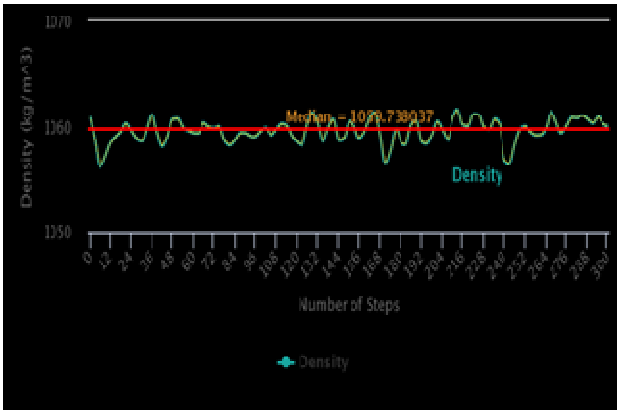

Figure 8. Production-Density Graph

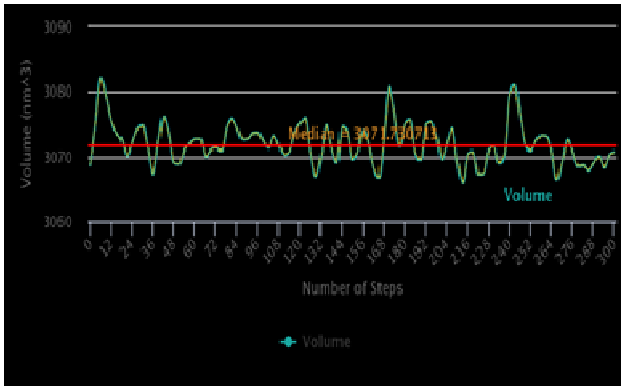

Figure 9. Production-Volume Graph

The protein was placed in a hexagonal box with dimensions 15cm x 15cm x 15cm in x, y and z axes. The lipids POPC, POPE, CHOC, POPS, POPI, POSM and DPGI were added to the system (Table 1). 1- ns MD simulations were done using MERMAID server with a coupling time constant of 0.03 fs. MARTINI 22 force field was used for energy minimization. The solvent molecules were equilibrated with the stable protein. The temperature of the system quickly reaches the target value (K) and remains stable over the reminder of equilibration. Over the course of production, the average value of temperature is 299.631958 K. The pressure value fluctuates widely over the course of production phase. The average value of pressure is 1.75119 bar. The median value of density & volume in production phase is 1059.738037 kg/m^3 and 3071.730713kg/m^3 respectively. The total energy of system was found to be approximately -582.2 Joule.

Table 1. Lipid Concentration

CHOL	POPC	POPE	POPS	POPI	POSM	DPG1
20	20	18	7	3	18	3

Conclusion

I have performed an intensive computational study of Astrotactin-2, a membrane protein involved in human neuronal development using MD simulation**.**ASTN2 has a critical role in controlling surface membrane protein dynamics and endowment to neurodevelopmental brain disorders. Coarse grained simulation was opted as the strategy to study this perforin like protein. I observed that, the temperature of the system quickly reaches the target value (K) and remains stable over the reminder of equilibration. The other parameters such as pressure, volume and density also fluctuates widely over the course of production phase. The total energy of system was found to be approximately -582.2 Joule.

Conflict of Interests: The author declares no conflict of interest.

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