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EXPAND Mentor

HYBRID ENHANCED SAMPLING APPROACHES TO GAIN STRUCTURAL INSIGHTS INTO LEUCINE-RICH REPEAT KINASE 2 (LRRK2) PARKINSON'S DISEASE MUTATION

Rommie Amaro/Amaro Lab (October, 2022)

Parkinson's disease (PD) is a neurodegenerative disease affecting millions worldwide. A commonly mutated gene in PD is leucine-rich repeat kinase 2 (LRRK2), which contains multiple domains, including but not limited to kinase, ATPase, and GTPase. LRRK2 has been found to increase kinase activity and colocalize with microtubules. LRRK2 protein dynamics are affected by its conformation, regulating microtubule interactions and potentially enhancing intracellular trafficking. Despite recent advances in the structural insights of LRRK2, detailed studies on the effects of single-point mutations on the dynamics and conformations of LRRK2 are limited. Consequently, an all-atomistic molecular dynamics simulation is required to understand the allosteric and dynamical effects of single-point disease mutations in LRRK2, but it would be computationally expensive. We thereby employ enhanced molecular dynamics simulations to study single-point mutations in LRRK2, particularly the G2019S, R1441C, R1441G, R1441H, and Y1699C mutations. Our two-phase approach incorporates implementing Gaussian-accelerated molecular dynamics (GaMD) for enhanced sampling, followed by the weighted ensemble (WE) method. GaMD is an enhanced MD approach where a boost potential is added to the total potential energy of the system to accelerate the conformational search, while the WE method readjusts the weight of the simulation trajectories by frequent resampling to obtain the kinetic properties of interest accurately. Investigating the dynamics of such single-point mutations in LRRK2 could explain why specific mutations result in increased kinase activation and dynamicity of LRRK2. We expect our mentee to gain hands-on experience in running protein simulations and analyzing conformational pathways to understand the change in dynamics brought in by LRRK2 mutations.

Skills you will acquire

- Python programming
- Molecular modeling
- Machine learning
- Molecular dynamics