Unveiling Mutation Effects on the Structural Dynamics of the Main Protease from SARS-CoV-2 with Hybrid Simulation Methods

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Abstract

The main protease of SARS-CoV-2 (called Mpro or 3CLpro) is essential for processing polyproteins encoded by viral RNA. Macromolecules adopt several favored conformations in solution depending on their structure and shape, determining their dynamics and function. Integrated methods combining the lowest-frequency movements obtained by Normal Mode Analysis (NMA), and the faster movements from Molecular Dynamics (MD), and data from biophysical techniques, are necessary to establish the correlation between complex structural dynamics of macromolecules and their function. In this article, we used a hybrid simulation method to sample the conformational space to characterize the structural dynamics and global motions of WT SARS-CoV-2 Mpro and 48 mutants, including several mutations that appear in P.1, B.1.1.7, B.1.351, B.1.525 and B.1.429+B.1.427 variants. Integrated Hybrid methods combining NMA and MD have been useful to study the correlation between the complex structural dynamics of macromolecules and their functioning mechanisms. Here, we applied this hybrid approach to elucidate the effects of mutation in the structural dynamics of SARS-CoV-2 Mpro, considering their flexibility, solvent accessible surface area analyses, global movements, and catalytic dyad distance. Furthermore, some mutants showed significant changes in their structural dynamics and conformation, which could lead to distinct functional properties.

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