Analysis of molecular aspects of proteins regulation considering water molecules as a potential mediator in intermolecular interactions

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Abstract

The doctoral dissertation presents the results of several works related to modelling the dynamics of water molecules in biological systems, resulting from the use of dedicated software and computational methods. Results presented in this thesis are related to the analysis of the various functions performed by water molecules in proteins. Specifically, they concern three areas of application: drug design, protein regulation and engineering, as well as studying enzymatic reaction.

As concerns the application of water molecules in drug design – I presented how, by using a combination of small-molecule tracking and local-distribution approaches, it is possible to describe the variations in the dynamics of the internal pockets within the macromolecules and identify novel potential sites for ligand binding. Such analyses were performed for different molecular targets, particularly for SARS-CoV-2 main protease (SARS-CoV-2 Mpro) and human soluble epoxide hydrolase (hsEH). Also, the above-mentioned approach was used during evaluating the potential risk of off-target for SARS-CoV-2 Mpro and a panel of various proteases. For the application in protein regulation and engineering – I showed that, by tracking of water molecules during molecular dynamics simulations, it is possible to describe in details tunnel networks and the transportation phenomena in proteins. Such an analysis was performed for enzymes from the soluble epoxide hydrolase subfamily (sEH). For these enzymes, it was possible to establish the relationship between their structure and their tunnel network but also conduct an evolutionary analysis of the identified tunnels. Also, the small-molecule tracking methods was compared to the geometry-based approach for detecting and analysing tunnels in proteins. As for the enzymatic reaction – I presented that the combination of small-molecule tracking and local-distribution approaches can reveal different roles of water molecules during

particular reaction cycle. This analysis was performed during the investigation of the proteolytic cleavage of the Z-loop in TLR8 by furin protease. In addition to the basic role of water, which is the catalytic function, additional roles have been proposed, in particular related to the stabilisation for certain intermolecular interactions or as a mediator, either during the transfer of a proton or in the dissociation process.

The results of the works included in the doctoral thesis were published in nine peer-reviewed journals and as one preprint sent for the revision.