[P7] Molecular dynamics studies of the variability of ZN-coordination sphere in metallo-β-lactamases

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Antibiotic resistance is a worldwide public health issue whose exponential increase is threatening the quality and the security of medical care. This resistance is mainly due to β-lactamases, which are enzymes able to cancel the antibiotic effect of β-lactam compounds by hydrolyzing them. This phenomenon is especially worrying with the emergence of new bacteria producing β-lactamases active on all classes of β-lactams (even the carbapenems that are only used as last resort treatment in intensive care units) and leading to therapeutic failure. Some of these were recently classified in a global priority pathogens list. [1]

We are currently interested in the study of the interaction of metallo-β-lactamases (MBLs) with substrates and inhibitors. Molecular dynamics simulations are required to take into account the flexibility of this important class of enzymes. In this context, we developed OPLS-AA force field parameters for the residues coordinating the zinc ions. [2]

In this work, we studied the variability of Zn-coordination sphere in MBLs using sequence alignments and molecular dynamics simulations. We focused on MBLs showing an unusual Zn-coordination pattern, e.g. GOB-18 and LRA-12 that have a glutamine Zn-coordinating residue. The parametrization of this residue in OPLS-AA force field and subsequent simulations of natural and *in silico* mutants evidenced the influence of these mutations on the overall stability and flexibility of these enzymes.

This information will be a valuable asset for the evaluation of selectivity of existing substrates and inhibitors towards new MBLs.

Bibliography:

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