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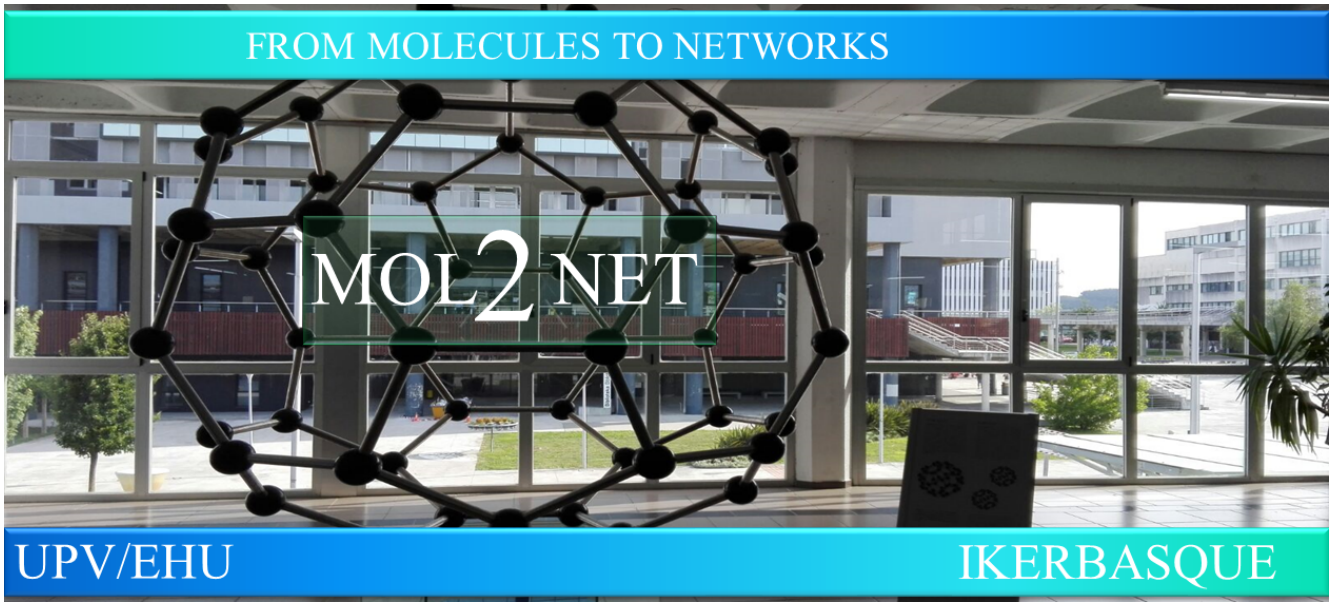

Engineering protein fragments via evolutionary and protein-protein interaction algorithms: *De novo* design of peptide inhibitors for F_OF_1-ATP synthase

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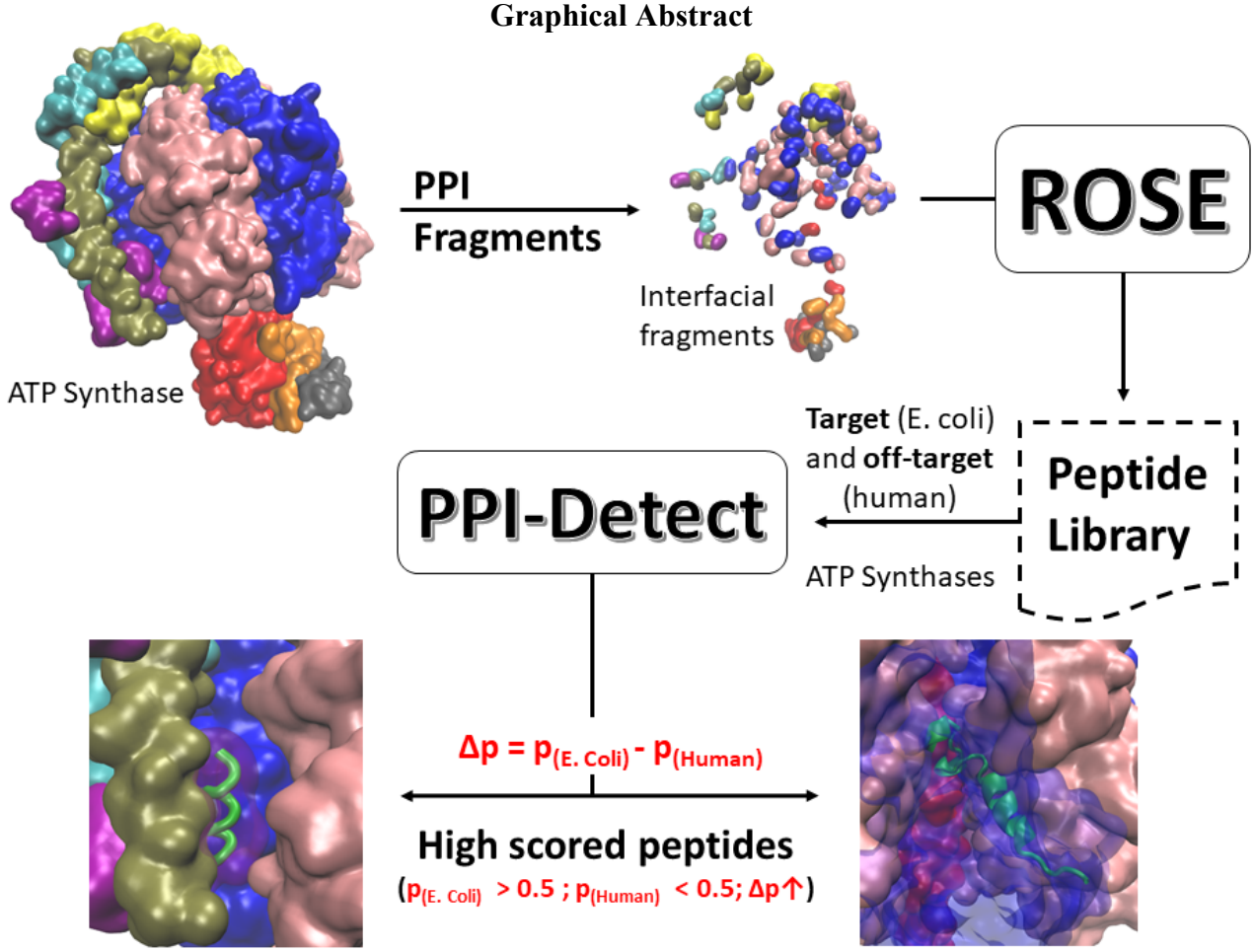
Graphical Abstract



Abstract: Enzyme's subunits interfaces have remarkable potential in drug design as both target and scaffold for their own inhibitors. We show an evolution-driven strategy for the *de novo* design of peptide inhibitors targeting interfaces of the *E. coli's* FoF1-ATP synthase as a case study. The evolutionary algorithm ROSE is applied to generate diversity-oriented peptide libraries by engineering peptide fragments from ATP synthase interfaces. The resulting peptides are scored with PPI-Detect, a sequence-based predictor of protein-protein interactions. Two selected peptides were confirmed by *in vitro* inhibition and binding tests. The proposed methodology can be widely applied to design peptides targeting relevant interfaces of enzymatic complexes (https://doi.org/10.1002/1873-3468.13988).

The main bibliographic sources used in this paper are listed below [1-10].

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