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# Interaction energy model of SARS-CoV-2 $M^{pro}$ with peptides in cleavage sites

Kadtsyn E.D.[1, 2, 3]*, Kolybalov D.S.[1, 2], Zubavichus Y.V.[1, 2]

[1] *SRF "SKIF", Koltsovo, Russia*

[2] *Novosibirsk State University, Novosibirsk, Russia*

[3] *Voevodsky Institute of Chemical Kinetics and Combustion, SB RAS, Novosibirsk, Russia*

* *e.kadtsyn@g.nsu.ru*

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*Motivation and Aim*: SARS-CoV-2 main protease ($M^{pro}$) is a common target for design of anti-COVID drugs due to its high conservativity, difference from human proteases and critical role in virus lifecycle. A tempting strategy for viral protease inhibition is a use of peptidomimetics. To design a peptidomimetic with high inhibition constant an information about peptide-enzyme complex structure and interaction energy is highly desirable. It is difficult to obtain crystallographic structure of such complexes due to their metastability. Despite that recently a crystal structures of 11 $M^{pro}$-peptide complexes were registered, each of peptides consist of 6 residues after the cleavage position with one mutation heightening its stability in complex. Being inspired by that work we carried out a molecular dynamic (MD) simulation of these 11 hexapeptides without mutations as well as of 11 hexapeptides consisted of 3 residues before cleavage position and 3 residues after it. Obtained models were used to estimation of peptide-protease interaction energy and decompose them to energies of each residue. The data were used then to check correlation between energies for different residues and built energy model of interaction.

*Methods and Algorithms*: Crystallographic structure of $M^{pro}$ was taken from PBD database (7NG6), starting configurations of peptides were generated by AmberTools package from known sequence. 100ns MD simulation of peptides in aqueous solution were carried out to relax the structures, then using cluster analysis the most represented structures were extracted and docking was used to obtain structures of complexes. 500ns MD simulation of each complex were carried out. RMSD, $R_g$ and SASA values were calculated to check an enzyme stability during simulation and influence of peptide to protease. MMPBSA approach was used to estimate interaction energies and per-residue contributions. H-bonds were analyzed to explain energy results.

*Results*: RMSD, $R_g$ and SASA values for all systems show that complex is stable during the simulation in each case, no notable differences between pure protease and complexes were detected proving no influence of peptide to protease structure. Interaction energies and their contributions were determined. For interaction energies sets of the same amino acids in the same positions *t*-tests and *F*-tests were carried out, no statistically notable differences were shown, independent residue model hence can be applied to calculate peptide energy. Per-residue values for all amino acids presented in studied peptides were collected. From the data the most interacting peptide sequence was hypothesized.

*Conclusion*: From the model data of amino acid energy contributions one can construct the structure of highly-interacting peptide as well as highly-interacting peptidomimetic. Data of H-bonds between each peptides residue and protease was used to explain results.

The data obtained should be used in future to rationally design peptidomimetic drugs suitable for anti-COVID therapy.

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