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## MEETING ABSTRACTS

# DIMERIZATION INTERFACE OF CHOLINESTERASES: ANALYSIS OF CRYSTAL STRUCTURES, FREE ENERGY MOLECULAR DYNAMICS CALCULATIONS,AND *IN SILICO* ALANINE SCREENING

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For acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), several oligomeric forms are known. *In vivo*, the monomers in dimers are covalently bound by a C-terminal disulfide bond formed after association of the monomers. Available crystal structures were obtained for truncated forms without disulfide bonds and serve as good models for describing the role of non-covalent interactions in the dimerization of cholinesterases before linking by disulfide bonds.

Here, we analyze the formation of the four-alpha-helix bundle in cholinesterases and differences between AChE and BChE dimers. To identify interactions stabilizing the four-alpha-helix bundle, we counted hydrophobic interactions, solvent accessible surface (SASA), and hydrogen bonds between monomers and estimated electrostatic contributions to dimerization. To reveal the contribution of amino acids in the area of contact to dimerization, we performed free energy perturbation (FEP) alanine screening. Potential of mean force (PMF) calculations of dimerization revealed a difference between acetylcholinesterase and butyrylcholinesterase in the dimerization process and stability of non-covalent dimers.

According to replica exchange molecular dynamics umbrella sampling (REMD-US) calculations, the free energy of BChE dimerization is 20 kcal/mol, which is 15 kcal/mol less than the free energy of hAChE dimerization. BChE has less hydrophobic contacts than hAChE. Electrostatic contribution to oligomerization energy is almost the same for hAChE, mAChE, tcAChE, and BChE. In the case of BChE, contribution from the loops surrounding the helices forming bundles is less significant than that from the helices, whereas in all AChEs, vice versa. The *in silico* alanine screening showed that hydrophobic interactions between the helices are most important for dimerization with stabilization by charged amino acids, mostly lying on surrounding loops.

*Keywords: acetylcholinesterase; butyrylcholinesterase; free energy perturbation; in silico alanine screening; replica exchange*

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