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Molecular Dynamics Simulation of Shiga Toxin

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To develop a drug against infection by Shiga toxin (Stx)-producing *Escherichia coli* O157:H7 [1], this study investigates docking of Stx2 B subunit (Stx2 B) and a peptide neutralizer, using molecular dynamics simulations.
The used software is Generalized-Ensemble Molecular Biophysics (GEMB) [2]. The PDB code 1R4P is employed for the initial structure of Stx2 B, and the amino acid sequence of the neutralizer is MAPPPRRRRA. The number of residues of Stx2 B is 350, so that the required number of water molecules is estimated to be about 20,000. The force field is AMBER99SB for Stx2 B and TIP3P for water molecules.
Several simulations have shown that Arg's included in the neutralizer are attracted to Asp's and Glu's located at the binding sites of Stx2 B. In a representative result, among the amino acids in the sequence R9-R8-R7-R6-P5-P4-P3 of the neutralizer, R9 and R8 have electrostatic interactions with E15 and D16 of Stx2 B, respectively; R7 and P4 are thought to have small effects on the binding because they are directed towards the outside of Stx2 B from its inside; although R6 interacts with W33 through its alkyl part, this interaction is not electrostatic; P5 is located at the foot of R6 and not participating the binding; it is possible that P3 interacts with alkyl of R32, but the distance between them may be large. It can be suggested that two effects are important in simulations considering water molecules: screening of electrostatic interactions between basic and acidic residues; existence of hydrophobic residues in the neutralizer.

[1] Nishikawa, K., Watanabe, M., Kita, E., Igai, K., Omata, K., Yaffe, M.B., and Natori, Y., A multivalent peptide library approach identifies a novel Shiga toxin inhibitor that induces aberrant cellular transport of the toxin, *The FASEB Journal*, 20:2597-9, 2006.
[2] Okumura, H., Temperature and pressure denaturation of chignolin: Folding and unfolding simulation by multibaric-multithermal molecular dynamics method, *Proteins*, 80: 2397-2416, 2012.