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Study of membrane permeability for various peptides by steered molecular dynamics

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Motivation and Aim: Natural membranes are involved in the regulation of many processes, so the composition and ratio of their molecular components are diverse. The membranes are based on phospholipid molecules, and one of the most common components is cholesterol, which has a significant effect on the physicochemical properties of the lipid matrix. Membrane active peptides serve many important functions in nature as they act as antimicrobials, channels, transporters or hormones. There is still no answer to the mechanism of penetration of antimicrobial peptides through the membrane bilayer. Several mechanisms for such a process have been proposed. It is necessary to understand whether it is possible by the steered molecular dynamics method to determine the ability of peptides of different composition and length to pass through a membrane bilayer. The purpose of the work is to find out which peptides most easily penetrate the cell membrane.

Methods and Algorithms: The PUMA [1-3] and PUMA-CUDA software packages were used as a molecular dynamics simulation program. AMBER force field was used as well as the TIP3P water model. Due to the support of periodic boundary conditions, an infinite cell membrane in an aqueous environment is simulated. The passage of peptides through the membrane at a constant rate of 0.1, 0.05 and 0.01 Å/ps was studied due to the force applied to the center of mass of the peptide or its terminal atom. The possibility of exerting force on two subsystems was added to the PUMA-CUDA software package. One subsystem, the cell membrane, was fixed at the center of mass. The second system, the peptide, was subjected to a force effect, leading to movement through the cell membrane at a constant speed. The force action was applied to the center of mass, as well as to the atom.

Results: In this work, we developed a technique for constructing bilayers of arbitrary dimensions, hydration under periodic boundary conditions, adding peptides of a given sequence to them, and force pulling the peptide through the resulting bilayer. 656 steered molecular dynamics calculations were carried out for pulling seven amyloidogenic peptides with antimicrobial potential and monopeptides (homo-repeats consisting of 10 residues of the same amino acid: Poly(Ala), Poly(Leu), Poly(Met), Poly(Arg), Poly(Glu)) with various sequences through the membrane. Among the 15 studied peptides, the peptides exhibiting the least force resistance when passing through the bilayer were found, and the maximum reaction occurs at the boundary of the membrane bilayer entry.

Conclusion: The pulling force per atom is always lower than the force applied to the center of mass, due to the fact that when pulling out the atom, the peptide is pulled into a line, thereby the area of resistance to the peptide is smaller. Also, analysis of datasets in [3] would suggest that simultaneous duplication of several domains underlies the formation of repetitive regions, while duplication of a single domain is rare. This fact may explain the predominance of four- and six-domain ribosomal S1 proteins. At the same time, the parts of *rpsA* genes encoding adjacent domains are more identical what correlates with the data suggesting that duplication occurs mainly in the middle of the protein chain between other repeats. The maximum resistance force depends at least on two reasons: 1) partial charges of atoms; 2) amino acid resistance area. The best correlation between the maximum reaction force of the membrane and the calculated parameters corresponds to the instability index.

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