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Development of Multi-Level Biomolecular Simulation Protocols for Aptamer Engineering for Biomedical Applications

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Biomolecular simulations have long been an important part of the drug discovery and development process, with techniques such as docking, virtual screening, molecular dynamics and quantum mechanics being routinely used in the study of the interaction and selection of small molecular drugs with their target proteins or enzymes.
More recently, the application of these techniques in aptamer selection and aptamer engineering has algo become a reality. Such methods can help to understand aptamer-target interaction and to rationally introduce modifications in selected aptamers to modulate their affinity, specificity or ability to carry other molecules.
Here, we present a computational protocol developed by us for the selection of specific aptamers for protein recognition and for an atomic-level understanding of target-aptamer interaction. The protocol takes advantage of HPC resources and GPUs and combines protein-DNA/RNA docking, atomistic molecular dynamics simulations and free energy calculations, including the conformation variability of the protein and aptamer in the selection process.
This is illustrated with the identification and experimental confirmation of a novel aptamer for Cathepsin B, a predictive prostate cancer biomarker [1], and by atomic level clarification of the mode of action of an aptamer-RNA conjugate that targets the human transferrin receptor [2].

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References:
[1] Pereira, AC et al. - Identification of novel aptamers targeting cathepsin B-overexpressing prostate cancer cells - Molecular Systems Design & Engineering (2022) DOI: 10.1039/D2ME00022A

[2] Vasconcelos et al. -In silico analysis of aptamer-RNA conjugate interactions with human transferrin receptor - Biophysical Chemistry 314 (2024, DOI: 10.1016/j.bpc.2024.107308

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