# Computational analysis of aptamer-protein complex between cubane modified aptamer and PvLDH

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## Abstract

Aptamer-protein interaction has long been a hot topic in biological research. Aptamers are short DNA or RNA sequences with high affinity and specific binding ability toward their targets. SOMAmer (Slow Off-rate Modified Aptamer) are aptamers with specifically modified nucleotides, which are known to show an extraordinary binding efficiency toward specified targets. This project aims to computational analyze a newly developed cubane modified DNA aptamer to present potential properties in interacting with its target protein, Plasmodium vivaxlactate dehydrogenase (PvLDH). Moreover, we collected a set of data from various papers concerning aptamer-protein complexes to reveal the relationship between dissociation constant (Kd) and interface area and observe if our aptamer fits. We adopt biomolecular analyzing computer software and data source websites to generate our analysis. We show that the aptamer bind to the target ligand via three different kind of interaction, including hydrogen bond, polar interaction and hydrophobic interaction. Besides, we did not find a strong association between the general trend of multiple aptamer-protein complexes. One possible reason might be that the aptamer goes through one step counterselection against a similar protein PfLDH, therefore high specific aptamer instead of high affinity aptamer was eluted. We believe that this project will give us a better understanding of the crystal structure of cubane modified aptamers and their interacting properties.

## Tools & Methods

*PyMOL*
PyMOL is a user-sponsored molecular visualization system on an open-source foundation. The most impressive feature of PyMOL is the ability to generate high-quality 3D images of small molecules and macromolecules

*LigPlus*
LigPlus is a software created for automatic generation of 2D ligand-protein interaction diagrams. we can acquire a better comprehension of the interaction between selected chain/molecule and their surrounding chain/molecule with this tool.

*PDBePISA*
PDBePISA is an interactive tool for the exploration of macromolecular interaction. It can list all the possible interactions (Hydrogen/Disulphide bond/Salt bridge/covalent link) and interfacing residues. In this project, we mainly use this site to reveal possible interactions and calculate the interface area.

## Results

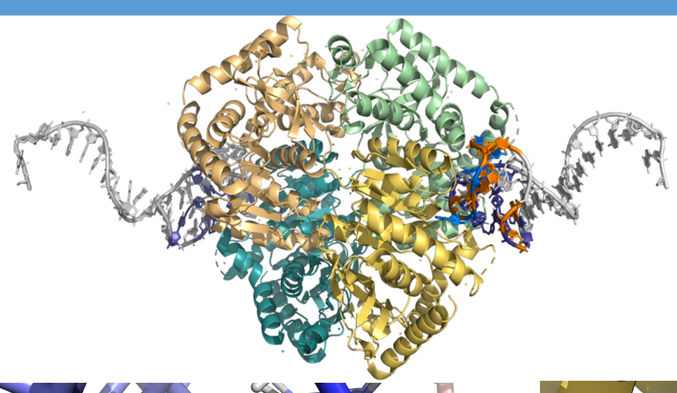


**Fig.1** An overview of the aptamer-protein complex. (A) shows the four subunits of PvLDH were colored in light green, yellow, wheat and deepteal. The two aptamers were colored in grey and the cubane modifications are colored in deepblue.

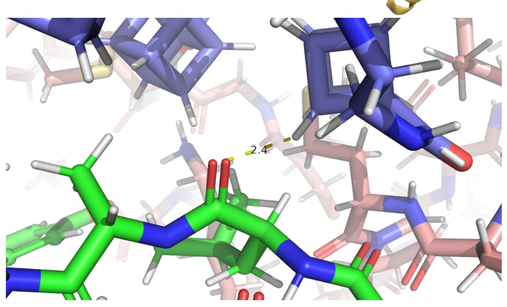


**Fig.2** We also discover a CH—O hydrogen bond between cubane and PvLDH subunit B. The formation of hydrogen bond may also contribute to the binding.

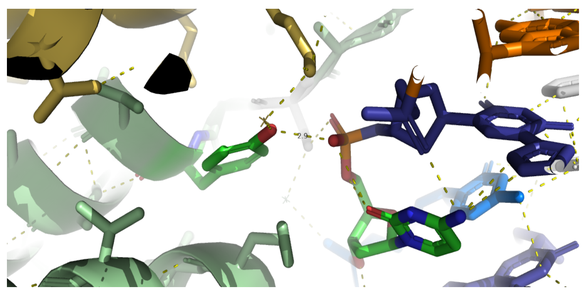


**Fig.3** The polar interactions and distance measurement between cubane modified aptamer and PvLDH.

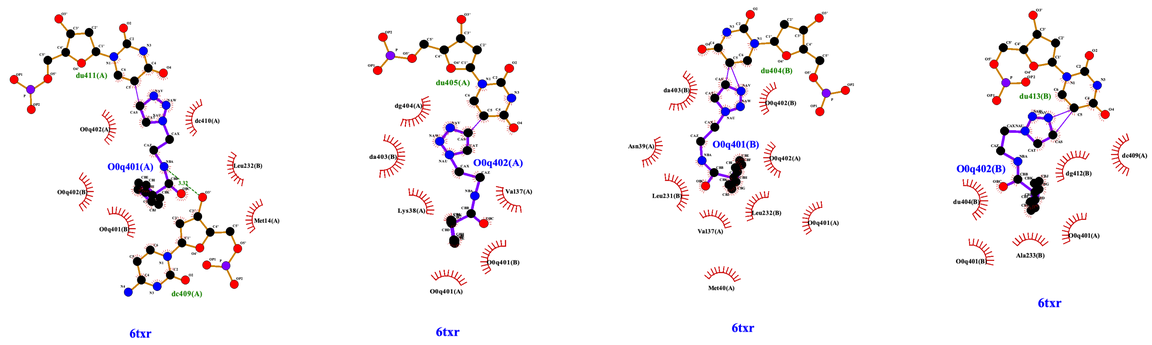
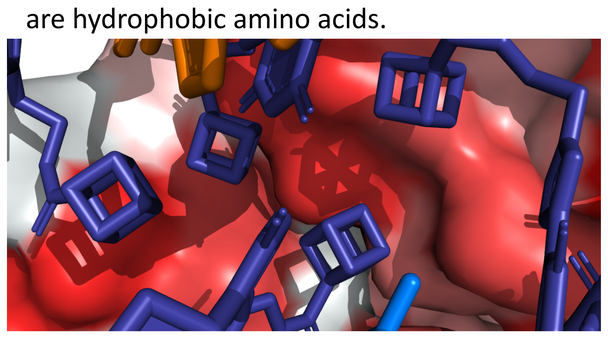



**Fig.4** The interaction map of four cubane modified nucleotides in one hydrophobic cluster generated with Ligplus. We can observe that most of the surrounding amino acids are hydrophobic amino acids.



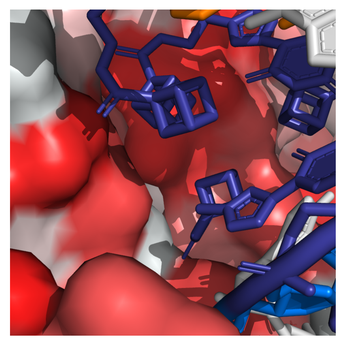


**Fig.5** The cubane modifications can form a hydrophobic cluster to interact with PvLDH on its hydrophobic surface. The molecules in deep blue is cubane modifications, while the surface in white and red is the hydrophobic surface of PvLDH. Red surface stands for hydrophobic molecules while white stands for hydrophilic molecules.

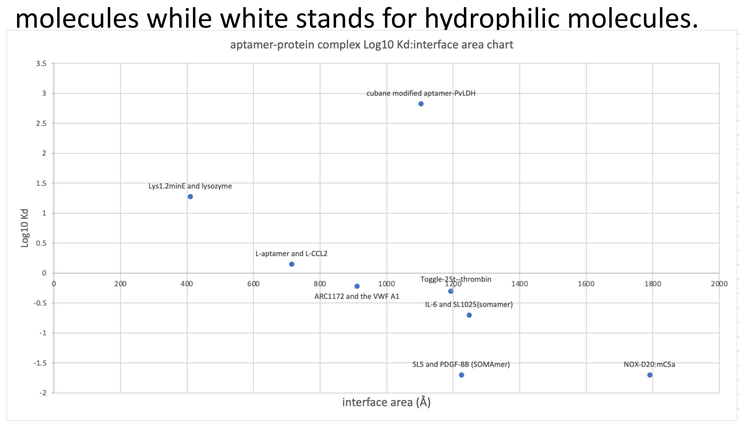



**Fig.6** The general complexes shows a clear trend that as the interface area increase the Kd value will decrease, but our cubane modified aptamer does not fit in this trend.

## Discussion

The uracil in this aptamer is modified with a cubane molecule, different from previously adopted benzyl modification. Therefore, we would like to know more about the unique binding mechanism and interactions of cubane moiety. We discovered a formation of a hydrophobic cluster with four cubane modified nucleotides (O0Q401 (A), O0Q402 (A), O0Q401 (B), O0Q402 (B)). The cluster is close to the target protein's hydrophobic surface, which proves that cubane moiety plays an active role in hydrophobic interaction with the target protein. The interaction map generated from Ligplus also supports the cluster formation and hydrophobic interaction with protein. We then use the PDBePISA server to calculate the interface area between this cluster. We only estimate the interface between cluster components and the protein, and the outcome is 1105.8 Å. In Fig.3, polar interactions can also be observed between cubane modified aptamer and PvLDH. Moreover, in Fig.2, a strong hydrogen bond is also presented. We can conclude that the cubane modified aptamer binds to the target protein via hydrophobic interaction, polar bonds, and hydrogen bonds. By observing the interface: Kd graph (Fig.6), we can find that for general aptamers, the Kd value will decrease as the interface area increase, this makes sense as more extensive interface indicate tight binding. However, our modified aptamer does not fit into this trend. We estimate the reason is that that the aptamer goes through a step of counterselection against a similar protein PfLDH. Therefore, high specific aptamer instead of a high-affinity aptamer was eluted. We can carry out further studies to find the actual reason.

## References

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