Computational Imaging Project Proposal
Blind Source Separation in DNA Dehybriziation Kinetics Imaging
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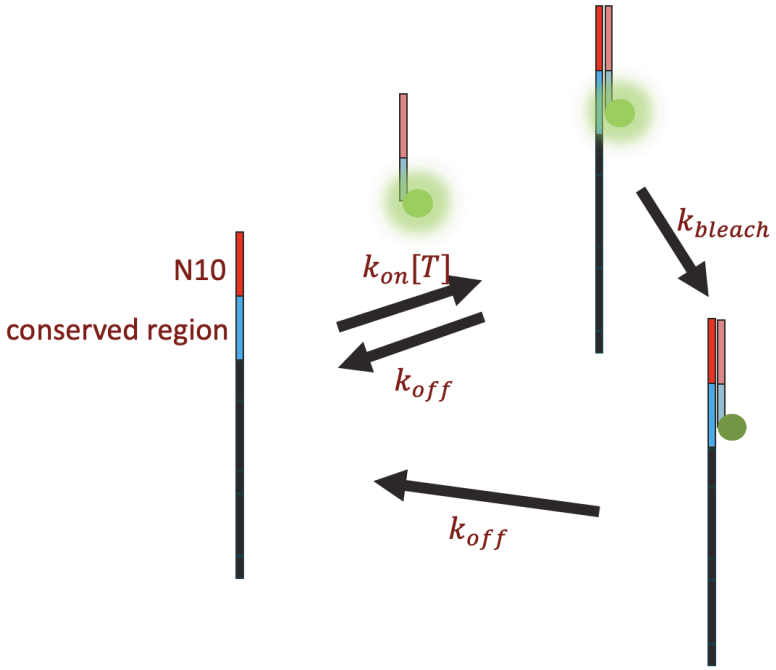
Background:
Complementary DNA/RNA sequences hybridization is a fundamental molecular mechanism which is of significant importance in natural biological processes as well as analytic biotechnologies with applications ranging from forensics to therapeutics. The characterization of this transition, i.e. going from separate single strands to the final hybrid form, can be investigated both in long run (steady-state) or transient state. The former, i.e. thermodynamics of hybridization, has been extensively studied and efficient general-purpose methods are available now. Nearest neighbor model based models of nucleic acid thermodynamics have been proposed and calibrated from experimental data over decades. However, the existing methods kinetics properties have been shown to be slow and inaccurate.[1, 2]

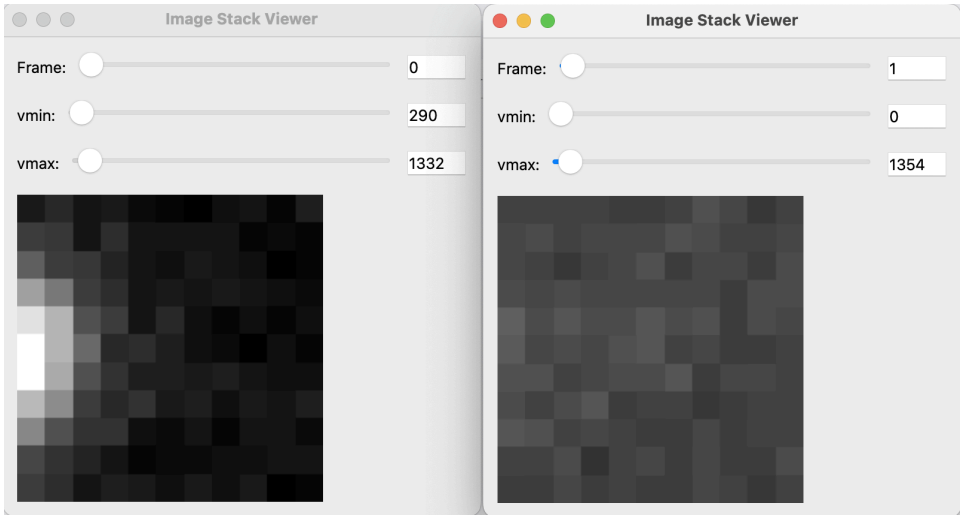
To investigate the kinetic properties, fluorescence imaging is utilized. Several clusters of DNA strands, each with many copies of a specific sequence, are adhered to the surface of a flowcell, and then a solution including a secondary DNA strand is introduced to the flowcell.

Each cluster then goes through hybridization and dehybridization overtime as various basepair in each strand attach to each other according to Chargaff's rule. Using fluorescence imaging, various images are taken from the flowcell overtime and the time constant of the (de)hybridization is approximated from the intensity of the light emitted from each cluster overtime.



However, a big challenge here is that the flowcell can sometimes be out of focus (depending on the camera used for imaging), and also some clusters might happen to be so close to each other that the actual light emission intensity cannot be separated efficiently by just selecting the intensity of the pixels near each cluster.

Therefore, in this project, I aim to use blind source separation [3] methods in order to efficiently locate the exact location and also the exact intensity of light emitted from each of the clusters which in turn would result in approximating the kinetics of each (de)hybridization more accurately.



References:
1- Zhang, J.X., Yordanov, B., Gaunt, A. et al. A deep learning model for predicting next-generation sequencing depth from DNA sequence. Nat Commun 12, 4387 (2021). https://doi.org/10.1038/s41467-021-24497-8
2- Zhang, J., Fang, J., Duan, W. et al. Predicting DNA hybridization kinetics from sequence. Nature Chem 10, 91–98 (2018). https://doi.org/10.1038/nchem.2877
3- Neher RA, Mitkovski M, Kirchhoff F, Neher E, Theis FJ, Zeug A. Blind source separation techniques for the decomposition of multiply labeled fluorescence images. Biophys J. 2009 May 6;96(9):3791-800. doi: 10.1016/j.bpj.2008.10.068. PMID: 19413985; PMCID: PMC2711419.