

2023 Buck Summer Scholar: Will Nickols



Will Nickols is a rising fourth-year at Harvard College where he studies chemical and physical biology and statistics. At Harvard, he works in the Curtis Huttenhower lab building biostatistical and computational biology tools for working with 'omics data. In particular, his work currently focuses on developing software to better understand the links between particular microbial species and metagenome-associated diseases, such as inflammatory bowel disease and colorectal cancer. After seeing the impact age can have on many of these diseases, Will became interested in studying the fundamental mechanisms of aging and elucidating how underlying processes can simultaneously increase someone's risk for many age-related diseases. At the Buck Institute, Will was part of the Chuankai Zhou lab, which studies mitochondrial aging and proteostasis in

budding yeast. In particular, Will supported computational work on a variety of projects, including computational modeling of proton movement in mitochondria and mitochondrial ribosome structure analysis.

Mitochondria are primarily known as the energy producers of eukaryotic cells, where they cycle protons between the mitochondrial matrix and the intermembrane space to generate ATP. Mitochondrial dysfunction is a hallmark of aging, and it has been implicated in a variety of age-associated diseases including non-alcoholic fatty liver disease, type II diabetes, and Alzheimer's disease. As cells age, the proton gradient between the mitochondrial matrix and intermembrane space tends to decrease, and protons might leak from mitochondria into the cytoplasm. To better understand this phenomenon, one of Will's projects involved quantifying the proportion of protons that leave their normal cycling in mitochondria and are shed to the cytoplasm.

To this end, Will developed a 3D modeling system in Python to quantify the fates of protons exported to the mitochondrial intermembrane space. When a proton is pumped through the electron transport chain to the mitochondrial intermembrane space, it travels pseudo-randomly before returning to the mitochondrial matrix through ATP synthase or exiting the intermembrane space through membrane pores. This model incorporated previously published biological parameters in yeast and estimated that approximately 1% of protons leak from mitochondria into the cytoplasm. Since this proportion is quite dependent on a few key modeling parameters, obtaining more accurate estimates for those parameters will be an important next step.

In a separate project, Will also worked on analyzing the structure of mitochondrial ribosomes, complexes of rRNA and proteins that translate mRNA from mitochondrial genes into proteins. Ribosomes are made of two subunits held together by bridges that consist of proteins and rRNA. These bridges differ in composition and location across different ribosomes and ribosome conformations, but the degree to which each bridge contributes to ribosome stability is not understood quantitatively. To understand these contributions, another of Will's projects involved modeling the free energy of association for individual bridges under a variety of physical assumptions. By determining the relative strength of these bridges, this project helped elucidate the interplay between ribosome structure and function and will help identify future drug targets.



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