Computational and Experimental Evaluation of Drug Interactions with Hosts

It has been shown that certain antioxidant naturally occurring products, such as curcumin (found in the Turmeric Spice), have remarkable anti-tumor and potential for treatment of Alzheimer’s.¹ ² Such natural products, however, are not very water soluble, and in fact struggle to cross the blood brain barrier to carry out their defensive and preventative function. Sugar based gels made from cyclodextrins (glucose units connected in a ring- see Figure 1), have been used in drug delivery systems as encapsulators of drugs that are otherwise insoluble in water and/or blood.³ Cyclodextrins are powerful at solubilizing hydrophobic molecules due to their hydrophobic cavity within two hydrophilic rims (see Figure 1).

An important aspect of designing such binding and solubilizing hosts is the measurement of their binding interactions with specific drugs and ligand models. Curcumin has been shown to bind into β-cyclodextrin (which harbors 7 glucose units and is biologically as harmless as starch).⁴ ⁵ We hereby propose to use Computational Molecular Modeling tools (using Spartan Software- already available at Florida Tech) to compare the binding energies of varying ligands into a single cyclodextrin host with a novel experimental approach using STM and AFM. The initial focus will be to use STM to anchor model compounds and potential drugs to the STM tip and measure the HOMO and LUMO energies of the surfaces. This will be a collaborative effort, which Professor Joel A. Olson who has already established novel means to study such interactions with molecules self assembled on gold surfaces.⁶ ⁷
Nesnas and Olson were the first to use Direct Analysis in Real Time Mass Spec to identify Self-Assembled Monolayers (SAMs), which will be critical in this study.\(^8\)

We will engage one undergraduate student and one graduate student in this project. One student will undertake the modeling of cyclodextrins and various ligands and compare energies. This will also be compared with experimentally reported values (such as those obtained from calorimetry and fluorescence). The other student will prepare a perthiolated cyclodextrin (the one with 7 Sulfur atoms), and lay it down on the gold surface. Only three sulfurs need to attach to anchor the host. We will initially image the surface and report the first images of cyclodextrin face up on Gold surfaces. Then we will anchor varying ligand molecules (such as the ones modeled, see Figure 2) to STM tip and measure the HOMO and LUMO energies. We will compare the computational trends to the single molecular trends and relate them to known binding values established by other methods.

This work will have significant impact in drug delivery techniques. This research has not been done in either Nesnas lab or in Olson’s lab. We will pursue this area further using AFM (atomic force microscopy, with Professor B. B. Akhremitchev) to measure the force of pulling these drugs out of their hosts. Preliminary results will lead at least one publications co-authored with an undergraduate and a graduate student, and potentially pave the way to submit an NSF and an NIH grant (R01).