Structural Dynamics of Non-Ribosomal Peptide Synthetases

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Non-ribosomal peptide synthetases (NRPS) are multi-domain modular enzymes that catalyze the synthesis of small molecules using amino acids or non-proteinogenic amino acid substrates. Each module consists of 3 core domains which are condensation, adenylation, and the peptidyl carrier protein. With the exception of the terminating module containing an additional thioesterase domain which is responsible for releasing the small molecule from the assembly line. The adenylation domain serves to activate the loaded substrate which is then transported by the peptidyl carrier protein to either the condensation or other catalytic domains which serve to modify the substrate. This occurs in an assembly line process until a functional molecule is formed and completely constructed. The structures of each domain have been isolated and solved which characterized their catalytic activity. Multidomain structures have also been solved in hopes of elucidating the functional interaction between the multiple domains. Although structures of each domain and multidomain complexes exist, there is no tangible evidence for how these modular enzymes are dynamically functioning. Using small angle x-ray scattering (SAXS) on these highly dynamic modules will allow us to see differences in the scattering profile of the varying conformational states that they can adopt. Then using DENSS, a standalone software which calculates electron density from scattering profiles, we will be able to visualize these changes. However, there is a need for a version of this software that will be able to construct an ensemble of states that will be present in SAXS data which I will develop. Coupling this with the crystal structures of the complex we are performing SAXS with will allow us to clearly visualize conformational changes in theoretically high resolution and see exactly how these modular enzymes assemble these important peptide products.