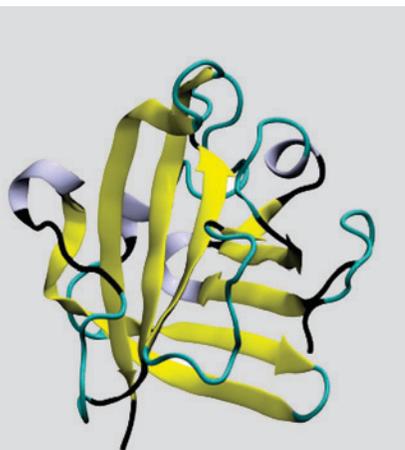


Molecular Dynamics Simulations of *Staphylococcus aureus* Sortase A

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The surfaces of Gram positive bacteria are decorated with a myriad of proteins that facilitate interaction with the environment. In the case of pathogenic bacteria, these proteins may enable evasion of immune response and elicit characteristic symptoms of infection. The mechanism by which surface proteins are anchored to the cell wall relies on the activity of sortase enzymes. These enzymes recognize a specific sorting sequence in proteins destined to be displayed on the surface of the bacteria, and catalyze the transpeptidation reaction that results in the attachment of the protein to a lipid II molecule. Due to the recent rise of antibiotic resistant strains of bacteria, there is interest in exploiting the link between sortase enzymes and bacterial virulence in the development of novel therapeutic drugs.

One of the most widely studied sortase enzymes is *Staphylococcus aureus* Sortase A (SrtA), which specifically cleaves its substrate at the LPXTG (X may be any amino acid) sorting signal and attaches it to a cell wall precursor molecule. We performed a study of *S. aureus* SrtA, utilizing both conventional and accelerated molecular dynamics simulations to simulate the enzyme in its apo state (top image, left) and bound to an LPATG sorting signal (middle image, left). Results support an induced fit binding mechanism and indicate that the sorting signal actively influences allosteric pathways connecting the sorting signal and lipid II binding sites. A potential allosteric pathway is shown as a surface on SrtA in the bottom, left image. Additionally, simulation results suggest that the sorting signal adopts multiple metastable binding conformations, which may provide insight into the binding of a longer peptide sequence. The three main conformations that were observed are shown in the images on the right. These results improve our understanding of the functioning of SrtA and will ultimately aid in the development of novel antibiotics.

