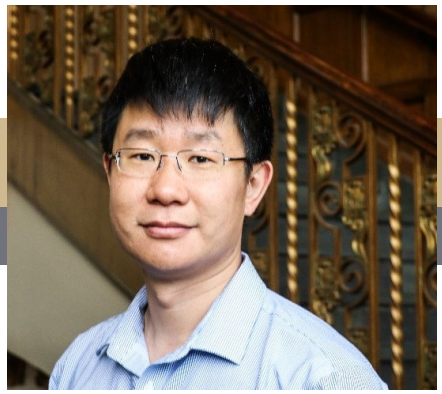
BIOCHEMISTRY SEMINAR

Catalysis in Motion: Large-Scale Domain Alternations Activate the Adenosylcobalamin Cofactor

Shiliang Tian

Assistant Professor of Chemistry, Purdue University



Abstract: Substrate binding often triggers conformational changes in proteins, enhancing their catalytic efficiency—a common theme in enzymatic processes essential for diverse biological functions. While many enzymes experience only modest conformational adjustments, with catalytic residues shifting less than 1 Å, some enzymes display substantial movement, particularly in surface loops. Understanding how large-scale conformational motions couple with the catalytic cycle to facilitate substrate binding, activation, product release, and protection of transient reaction intermediates remains a key question in enzyme catalysis dynamics. In this seminar, I will present cryo-electron microscopy (cryo-EM) structures of adenosylcobalamin (AdoCbl)-dependent enzymes captured in both their inactive "Open" (substrate-free) and active "Closed" (substrate-bound) states. Our findings reveal that substrate binding induces a significant conformational shift, including a more than 50-degree rotation of the Rossmann domain. This rearrangement repositions the AdoCbl cofactor by over 20 Å, activating the Co(III)-C bond to generate the adenosyl radical, positioning it precisely near the substrate. A surrounding hydrogen bond network constrains the reactive adenosyl radical, ensuring selective interaction with specific C-H bonds on the substrate. This complex interplay of protein conformational shifts, Co(III)-C activation, and targeted substrate engagement underscores the sophistication, efficiency, and precision of nature's catalytic machinery.

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PURDUE UNIVERSITY | James Tarpo Jr. and Margaret Tarpo Department of Chemistry