DATE: Day 11 Month May Year 2026

SUMMARY of
FY2025 RESEARCH RESULTS REPORT
For International Collaborative Research with IPR, The University of Osaka

Research Title		Elucidation of residue network working for allostery in *Bacillus subtilis* PyrR, using Molecular Dynamics, Thermodynamics and Machine Learning
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Summary: *Bacillus subtilis* PyrR is a regulatory protein that controls the expression of pyrimidine nucleotide biosynthesis (*pyr* genes) by binding to messenger RNA in bacteria. PyrR funcstions in a pyrimidine dependent way, and the level of which controls the equilibrium between the dimer and tretramer. This transition is the fundamental to this on/off mechanism of the pyrimidine synthesis is controlled allosterically by the nucleotide binding (GMP/UMP). Earlier, the alostery was investifgaed by Elastic Network Models (ENMs) it was shown by Perica et al. [Science. 2014;346(6216):1254346]. Our project at IPR, aimed to obtain an all atom based insights into the allosteric machinery using molecular dynamics simulations and more specifically we aimed to develop a pipeline to identify the allosteric hotspots in the structure using machine learning methods. Two objectives are the following: (i) Elucidate the intramolecular interaction network responsible for the long-ranged communications within a protein scaffold and mapping the allosteric hotspots and network hubs on the macromolecular structure, (ii) Develop a deep learning based protocol to automate such identification from an ensemble of conformations, generated from MD simulation based sampling. The project has established the initial computational framework to investigate the allosteric regulation mechanism of *the PyrR protein* at the atomic level. Through the construction and simulation of apo and GMP-bound tetrameric systems, we have demonstrated that nucleotide binding significantly alters the conformational landscape and dynamic behavior of PyrR. Preliminary PCA analyses indicate that GMP binding restricts large-scale collective motions and stabilizes specific conformational states, supporting the hypothesis that ligand-induced allosteric communication governs the functional switching mechanism of PyrR.

In parallel, substantial progress has been made toward the development and benchmarking of machine learning-based workflows for the automated identification of allosteric hotspots and communication networks from MD-derived conformational ensembles. Although the current MD trajectories already provide important preliminary insights, longer simulations and expanded datasets are required to fully capture the relevant timescales and conformational transitions associated with allosteric regulation.

***Deadline: May 11, 2026**
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