Single molecule dynamics of enzyme catalysis for thermoadaptation and design

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Project description:

This project combines single molecule experiments with simulations to investigate enzyme catalysis and dynamics. It will test new theories of how evolution adapts enzymes to different temperatures, and use this knowledge to design their properties. This project has potential impact ranging from developing new biocatalysts to understanding how organisms respond to climate change. The project will provide excellent training in state-of-the-art biophysical methods and molecular dynamics simulations, in a collaborative project, with strong links in New Zealand.

This project is a close collaboration between computation and experiments: simulations will inform experiments and vice versa, to reveal the dynamics of enzyme catalysis in atomic detail, and use that information to design and engineer biocatalysts. Optoplasmonic nanoscale sensors, using 'Whispering-gallery modes,' can detect the movements of single proteins with high sensitivity. In this project, this technique will be applied to investigate the conformational changes of individual enzyme molecules during catalytic turnover. Simulations will provide the essential atomic-level analysis to interpret single-molecule measurements, to reveal the dynamics of enzyme catalysis and thermoadaptation.

The project will also investigate how enzymes are adapted to work at different temperatures. Enzymes have an optimum temperature at which they are most catalytically active. Above that temperature, they become less active. The textbook explanation that enzymes unfold at higher temperatures does not explain this, most obviously for cold-adapted enzymes which are stable, but less active, above their optimum temperature. In contrast to simple 'chemical' catalysts, they become less active at higher temperatures even though they maintain their functional shape. Instead, a basic physical property - the heat capacity - explains and predicts the temperature dependence of enzymes. The heat capacity changes during the reaction and is 'tuned' by the enzyme's dynamics to give the optimal temperature. The theory that describes this - macromolecular rate theory, (MMRT) - applies to all enzymes, and so has a critical role in predicting metabolic activity as a function of temperature. Experiments are revealing characteristics of MMRT at the level of cells, whole organisms, embryogenesis and even ecosystems. This means that it is important in understanding the response of biological systems to temperature changes, for example, how ecosystems will respond to climate change.

This project will use simulations and experiments to reveal how enzyme dynamics are tuned to determine optimum temperatures of catalysis. It will analyse and predict effects of mutations and identify novel principles of enzyme engineering (Bunzel et al. Nature Chemistry 2021).