## Catalysis *in silico*

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Enzymes are superb biological catalysts capable of accelerating rates of chemical reactions by enormous factors. Despite decades of scientific advancement, a full and quantitative understanding of enzyme catalysis is still lacking, and there are still fundamental issues that are hotly debated. This is apparent from our inability to engineer efficient catalysts that match naturally evolved enzymes and by the many mechanistic puzzles uncovered over the years. To study mechanistic problems in complex enzyme-catalysed reactions with computational methods, a common challenge is to develop models that balance computational efficiency and accuracy.

Well-calibrated combined quantum mechanics and molecular mechanics (QM/MM) methods are now largely accepted as a valuable research tool in revealing mechanistic details and hold the potential for detailed atomic-level analyses of underlying mechanisms. We have been focusing on improving the robustness and applicability of the QM/MM techniques into enzymatic reactions where conformational transition plays an important role. Specifically, in the developed computational framework, a polarizable classical force field has been developed to include the polarization effect arising from the molecular environment (Yu *et al.*, 2010; Luo *et al.*, 2012); the long-range electrostatic is described by an efficient generalized solvent boundary condition and the approximate DFT method SCC-DFTB was further developed for biomolecular systems (Riccardi *et al.*, 2006).

Judicious combination of the developed QM/MM method with a range of theoretical and computational analyses helps to address some of the fundamental questions in myosin. We found that the hydrolysis of ATP is strongly dependent on the myosin structure beyond the active site and in this way myosin ensures that the chemistry step is tightly coupled to the dramatic swinging of the level arm more than 40 Å away (Yang *et al.*, 2008; Daily *et al.*, 2012).

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