Signal Transduction: The Effect of Mutations and Modified Inducers on TetR

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Tim Clark is a world leader in computational chemistry from small molecule high-end calculations to large molecule (enzyme) based calculations. His talk in Wollongong is

Abstract
Molecular-dynamics simulations have been used to characterize the mechanism of induction of the tetracycline repressor protein (TetR), which has become the archetypical system for signal transduction induced by small molecules.

Initial work on the wild-type TetR(BD) using tetracycline (Tc) and 5,6-anhydrotetracycline (ATc) as inducers revealed the role of the so-called flexible loop (which is not resolved in TetR X-ray structures) in the induction mechanism. The mechanism was analyzed and identified by a number of techniques including low-frequency normal-mode (LFNM) analysis, interatomic distance plots and energy decompositions. This work also resulted in a detailed pharmacophore for TetR induction by Tc-like molecules (i.e. those that induce as a complex with a magnesium ion).

One remarkable feature of TetR is that point mutations can lead to the reverse phenotype (i.e. a TetR-variant that is induced ion the absence of tetracyclines, but not in their presence). Further molecular-dynamics simulations showed that this effect is caused by a change in the geometry of the free TetR such that the distance between the DNA-binding heads is too short to bind DNA efficiently.3 Docking a tetracycline inducer causes an increase in the inter-head distance (exactly as in the wild type) so that DNA binding is now efficient. The same movement in the wild type weakens DNA-binding because the inter-head distance becomes too large.

More recently, a peptide inducer of TetR (Tip) has been discovered.4 The X-ray structure of TetR complexed to Tip5 proves to be that of a non-induced form, even though Tip is an inducer. This serendipitous discovery has allowed us to observe induction directly in several different MD-simulations using different force fields. The implications of these calculations will be discussed.