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Understanding cooperativity and dynamic disorder in fluctuating enzymes at the single molecule level

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Single molecule techniques allow researchers to study not only the average reaction rates but also the statistics of single molecule transitions in the context of enzymatic reactions. Such measurements show that the slow fluctuation between enzyme conformers can lead to fluctuations in the rate constants of the reaction, a phenomenon known as dynamic disorder [1]. The most accessible characteristics of reactivity fluctuations in individual enzyme molecules relate to the second moment of turnover time statistics and is defined by the randomness parameter. Measurement of this quantity can serve as an indicator for dynamic disorder in the catalytic step of the reaction. Such enzymatic fluctuations can also lead to deviation in Michaelis- Menten behavior of the reaction rates and the emergence of dynamic cooperativity in single enzymes. In this talk I will discuss about a few such biologically relevant enzyme reaction schemes with multiple binding sites and slow fluctuations between the binding sites. I will propose a simple analytical model based on the first passage time distribution between successive catalytic turnover events that can be used to calculate the average reaction rate and obtain closed-form analytical expressions of the randomness parameter in terms of constant parameters [2, 3]. Our results confirm that slow fluctuations between the free enzyme conformers can lead to dynamic cooperativity whereas dynamic disorder at high substrate concentration is determined only by the slow fluctuations between the enzyme – substrate conformers [4]. Our theoretical findings are well supported by comparison with experimental data on the single enzyme beta-galactosidase [5].

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