

## **The dynamical properties of a metastable protein studied by molecular dynamics simulations and normal mode analysis**

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Serpins are an unusual class of protease inhibitors that initially fold to a metastable structure and undergo a remarkable conformational change to a stable form when they inhibit their protease targets. Alpha-1 antitrypsin (A<sub>1</sub>AT) is the most abundant serpin in human plasma, and a point mutation in A<sub>1</sub>AT carried by ~200,000 people in the United States causes a structural change which leads to misfolding and polymerization and, ultimately, to serious diseases including liver cirrhosis and emphysema. Our laboratory studies the conformational dynamics of A<sub>1</sub>AT and its major pathological mutant both experimentally using hydrogen/deuterium exchange, and computationally using all atom molecular dynamics simulations and coarse grained normal mode analysis. NMA has revealed that the structure of A<sub>1</sub>AT can be divided into regions of significant mobility that are separated by low mobility “hinge” regions. These hinge regions correspond to regions of high sequence conservation, and the majority of the hinge residues cluster in a region of the structure that has previously been identified as playing a critical role in the conformational change. Molecular dynamics simulations have been employed to probe the dynamics of both Wild Type A<sub>1</sub>AT and the pathological mutant. Principal component analysis of the MD simulations has characterized the major modes of motion and exhibits both similarities and differences with the motions identified by NMA. Simulations reveal differences in the dynamical behavior of Wild Type and mutant A<sub>1</sub>AT. In particular, the dynamics of the mutant suggest a possible mechanism for conversion to a polymerization prone conformation. The relationship of these computational results to experimental hydrogen exchange data will be discussed.