Computational Analysis of the Dynamics in Single-Chain FV Fragments of the Anti-lymphotoxin-ß Receptor Antibody upon Various Amino Acid Mutations

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The focus of this research was to computationally elucidate the change in dynamics in single-chain FV fragments (scFV) of the anti-lymphotoxin-ß receptor antibody upon various amino acid mutations. The mutants examined within this study included two point mutations, a double, triple and quadruple mutations relative to the wild type protein (referenced as WT). These protein fragments were selected from the scientific literature, where they were engineered in such a way that all the mutations are stabilizing relative to the WT, but share approximately the same activity. This work represents an extension to previous results that characterized the mechanisms underlying thermodynamic stability and intrinsic flexibility. Protein function is intimately related to its dynamical properties. The pharmaceutical industry routinely attempts to piece together parts of naturally occurring proteins, and redesign them through mutation to arrive at a protein therapeutic. The challenge that researchers face is that the dynamics is hard to control, and hence engineering function is difficult. Much of the success in protein design is from experimental high throughput screening using combination chemistry and directed evolution methods. However, it is appreciated that this blind empirical approach is inefficient, and the success rate can be increased with rational design. The first step toward this goal is to characterize the dynamics, and to quantify differences between mutants. Necessities for the experimental methods of this project included the use of a computer with a Unix

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