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13. ABSTRACT *(Maximum 200 words)*

The overall goal of the proposed research is to pursue realistic molecular modeling studies of the stability, dynamics, structure, function, and folding of proteins and protein-based biomaterials in solution. Simulations of elastin-based polymers will investigate the driving forces and mechanism for the unusual temperature-dependent conformational changes, knowledge that will assist in redesign of this system for specific applications and the design of other such molecules. Studies of the stabilities of cyclic peptides and their multimers (nanotubes) to both environment and peptide substitutions will be addressed, as well as their mechanism of transport, selectivity, and gating. Methods are being developed for identifying and optimizing small, robust scaffolds for use as novel receptors, or biosensors. Functional optimization (typically binding) will also be explored.

14. SUBJECT TERMS
biomaterial, molecular dynamics, modeling, biosensor

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FINAL REPORT

Grant #: N00014-99-1-0245

PRINCIPAL INVESTIGATOR: Valerie Daggett

INSTITUTION: University of Washington

GRANT TITLE: Simulation of Protein- and Peptide-Based Biomaterials

AWARD PERIOD: 1 January 1999 - 31 December 2001

OBJECTIVE: To pursue realistic molecular modeling studies of the stability, dynamics, structure, function, and folding of proteins and protein/peptide-based biomaterials in solution.

APPROACH: Simulations of elastin-based polymers are being performed to investigate the driving forces and mechanism for the unusual temperature-dependent conformational changes, knowledge that will assist in redesign of this system for specific applications and the design of other such molecules. This effect is also modulated by the solvent environment and realistic representations of the solvent are necessary to capture these effects.

ACCOMPLISHMENTS: We have been able to reproduce the inverse temperature transition observed with elastin-based peptides. We have performed single-molecular 'pulling' simulations to characterize the molecular basis of elasticity. We have performed 10-ns simulations of a 90-mer of elastin in water at 7 different temperatures. Below the transition temperature the molecule remains expanded, but it does not retain Urry's precise β-spiral structure in water---as has also been observed experimentally. At higher temperatures the molecule undergoes hydrophobically driven collapse with an associated expulsion of hydration waters from its surface. This is the first time this type of behavior has been simulated, and we hope to obtain a molecular explanation for elasticity. To this end we have performed single-molecule 'pulling' simulations of elastin both above and below its transition temperature from different starting conformations. Removal of the pulling force (like what a protein would experience in AFM pulling experiments) leads to rapid contraction of elastin, particularly at the higher temperatures. We have found that its elasticity is due to the same fundamental forces that are responsible for its inverse temperature transition. For comparison, we also simulated the pulling of barnase, whose folding behavior in solution has been mapped in detail through a collaboration involving my lab and Alan Fersht's. The pulling simulations

were done in parallel with AFM experiments by Jane Clarke (Cambridge).

We are characterizing the conformational behavior of the elastin-based biopolymers in solvent and, in particular, investigating the molecular basis of elasticity. We have performed numerous all-atom molecular dynamics simulations of an elastin peptide. We are now extending those studies to investigate how changes in the sequence and length of the peptide affect its conformational behavior. We have also been inserting small portions of a small globular protein to investigate their ability to act as temperature-controlled switches of stability. We have a couple of very promising designs in which an elastin switch that has been introduced into chymotrypsin inhibitor 2 stabilizes the structure to thermal denaturation. In addition, since the behavior of elastin can also be modulated by solvent and our work in this area is an extension of our solvent-development studies, we continue to explore the effects of different solvents on peptide and protein structure and dynamics.

SIGNIFICANCE: The proposed research has bearing on ONR biosensor and biomaterial development. An understanding of the conformational behavior of biomaterials and how they interact with other molecules and solvent will aid in their design and optimization for Navy uses. The proposed research should aid in the design of biomaterials and biosensors with specific functional attributes tailored to the conformational behavior.

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