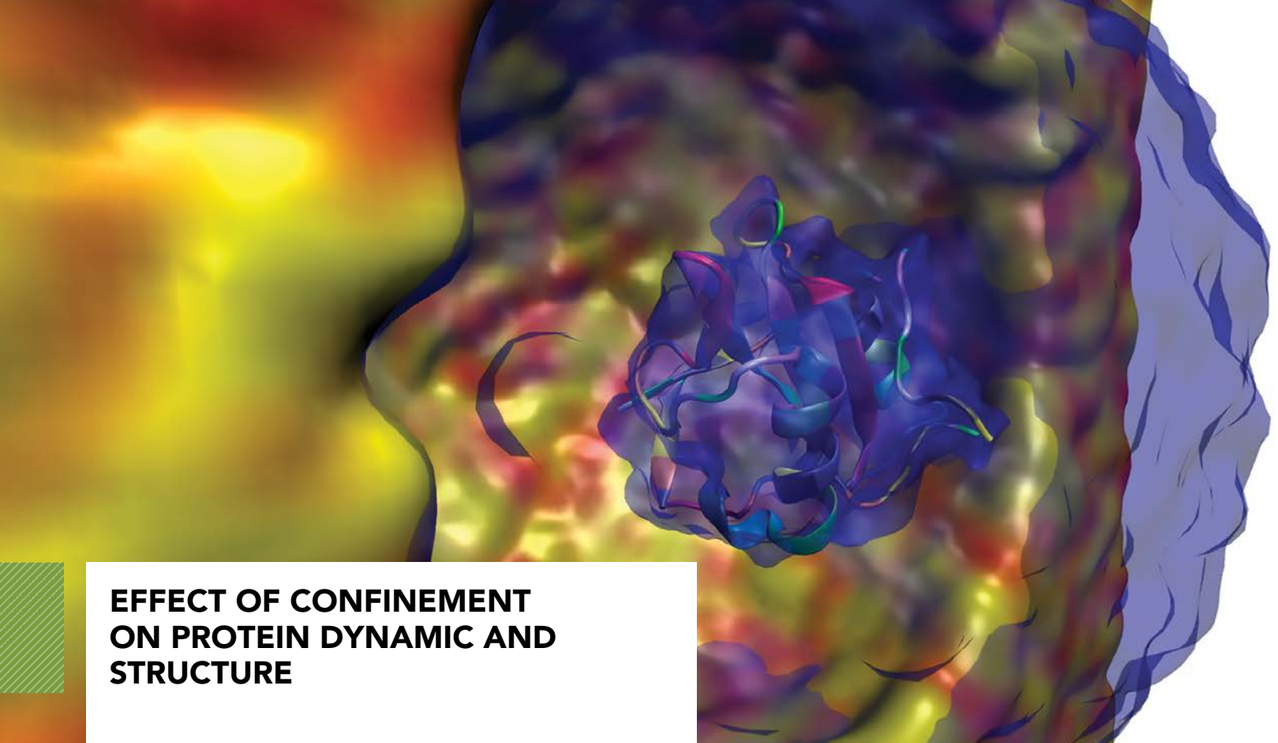

EFFECT OF CONFINEMENT ON PROTEIN DYNAMIC AND STRUCTURE

Allocation: Illinois/0.29 Mnh
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EXECUTIVE SUMMARY:

Understanding structure function relationships of proteins is a major goal of biology, biomedicine, and biotechnology. For soluble proteins, simulations have been done in an aqueous environment, essentially assuming that the molecules are in a bath of infinite size. However, proteins in cells function in a confined environment. We believe this is a factor in the many observations that protein interactions in cells differ from the same interactions in solution. In our work we confined water and proteins in silica cavities to explore the effects of the confinement on structure and dynamics. Specifically, we observed a large influence of confinement on water, bovine pancreatic trypsin inhibitor (BPTI), and on the signaling protein SHP2. For water we saw ordered ice-like structures induced at a physiological temperature where bulk water is fluid. For proteins we saw significant structural modifications and reduction in flexibility, even when the cavity was substantially larger than the largest protein dimension.

INTRODUCTION

Proteins are essential components of living cells. One of the limiting factors in our understanding of proteins is a failure, so far, to replicate the environment of the cellular interior. For soluble proteins, dynamic simulations have been done in an aqueous environment, effectively assuming that the molecules are in a bath of infinite size. However in living cells the motions of reactive proteins are constrained by surrounding molecular scaffolds. Possibly as a result of such constraints, the kinetics of soluble protein reactions in cells (*in vivo*) is often significantly different from that in aqueous environment (*in vitro*). It may be that structures are somewhat different as well.

To shed light on the structure and dynamics of proteins, we confined pure water and the proteins (BPTI, SHP2) in silica-bounded cavities.

Because of its relatively small size, biological importance (as a protease inhibitor), and ready availability, bovine pancreatic trypsin inhibitor (BPTI) has for decades served as a model system for exploring issues of protein structure and dynamics, for example the subject of the very first molecular dynamics simulation of a protein in 1977 [1].

The choice of the larger protein SHP2 for the next part of our study was due to the fact that large biologically important protein conformational changes monitored in this molecule by FRET have much more rapid kinetics *in vivo* than *in vitro* [2]. We will seek to understand this computationally.

We expect this work to make a large contribution towards bridging the gap between structure and dynamics of proteins *in vivo* and *in vitro*.

METHODS & RESULTS

In the current study we explored a native and mutant BPTI in which the mutation confers added flexibility to the protein [3]. We confirmed that our molecular dynamics in bulk replicates the reported experimental results in solution, and then explored the effects of confinement on both the native and the mutant strains.

Confinement (encapsulation in silica cavity) has a large effect on the dynamics of BPTI. The mutant of BPTI (G37A) exhibits large flexibility compared to its wild type. Both wild type and mutant BPTI 's RMSD drops when placed in confinement. The water structure is dramatically changed due to confinements and density layering is observed near silica wall. The peak density of water in density layering is augmented due to the overlap of the protein hydration shell and near-wall ordering.

WHY BLUE WATERS

Our largest simulations so far involve just under 100,000 atoms and all our simulations involve much conformational sampling because we are interested in significant deviations from crystal structure. In the next stage of the project, the systems involving the complete SHP2 protein, including fluorescent probes, will be significantly larger. These expensive computations are not possible to perform in reasonable time without a petascale supercomputer.

PUBLICATIONS

B. Farimani, N. R. Aluru, Eric Jakobsson, Effect of confinement on protein dynamic and Structure, Biophysical Society Meeting, Baltimore, MD, (2015).

FIGURE 1 (BACKGROUND): BPTI in a smaller amount of water confined in a silica cavity . The image (which is a cutaway section view) shows the protein confined in a cavity, which emulates the crowding in a cell.