Strategies to Stabilize Proteins on Surfaces from Improved Modeling of Protein-Surface Interactions

Thomas Knotts [C, S]
Department of Chemical Engineering, Brigham Young University, Provo, UT, U.S.A.
thomas.knotts@byu.edu

The interaction of proteins with surfaces is a central phenomenon in many applications in medicine, biotechnology, and proteomics. Understanding protein/surface interactions is key to improving these technologies, but current understanding of the behavior of proteins on surfaces is lacking. One of the challenges is that little is known about the biophysics involved in protein-surface interactions. Traditional experimental techniques used to determine protein structure—NMR and X-ray crystallography—are bulk techniques that are not amenable to surface-bound proteins, so simulation has emerged as the primary method to investigate the relevant phenomena. This talk explains how coarse-grain models have been developed and used to understand the thermodynamic stability of proteins on surfaces. We first show that by measuring stabilization using melting temperatures (obtained from heat capacity curves) and the Gibbs energies of folding, that the stability of small proteins tethered to surfaces can be correlated to the type of loop region where the tether is placed. We also show that any destabilization that occurs because of the surface is an enthalpic effect and that surfaces always stabilize proteins entropically. Second, we show how surfaces can drastically change the folding behavior of proteins on surfaces and how selecting correct tether positions, including using multiple tethers, can remove unstable intermediates and improve stability of enzymes. Finally, we demonstrate a new coarse-grain, protein-surface model that overcomes many previous limitations and how this model has been extended to antibodies and antibody fragments. Results will be presented that show: 1) the thermal stability of antibodies and antibody fragments is mostly a function of surface type and is less dependent on the orientation of the immobilized molecule on the surface and 2) that surfaces destabilize antibody-antigen binding. As a whole, the results offer hope that rational design of technologies involving protein-surface interactions, including protein arrays, is possible.