Explaining protein-protein interfaces in protease recognition with local dynamics and local interaction potentials

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Proteases are enzymes that catalyze the cleavage of peptide bonds and are important in numerous fundamental cellular processes, ranging from food digestion over blood coagulation to apoptosis. Proteases also account for 1-5% of the genome of infectious organisms such as bacteria, parasites and viruses [1].

While proteases involved in cellular signaling pathways such as the blood coagulation pathway or the apoptosis pathway show high specificity, proteases involved in processes such as the digestion of food proteins show rather low specificity. The specificity of a series of proteases has recently been quantified by Fuchs et al. through calculation of the so-called cleavage entropy as a sub-pocket-wise and overall specificity score [2] based on cleavage data from the MEROPS database [3].

To understand the mechanism of protease recognition, we will present a quantitative correlation between the local dynamics at the binding site of a series of homologous serine proteases with Trypsin-like fold obtained from molecular dynamics simulations and the specificity of the investigated proteases. In addition, we will present GRID [4] analyses for molecular dynamics trajectory snapshots to give a view of local interaction potentials at different conformational states of the proteases using selected probes. Through combination of thermodynamic data from the GRID analyses with the flexibility data obtained from molecular dynamics simulations, we want to give more insight into the interactions at protein-protein interfaces in protease recognition and discuss the contributions of enthalpic and entropic factors to protease substrate recognition.

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[4] Goodford, P. J. "A computational procedure for determining energetically favorable binding sites on biologically important macromolecules." *Journal of medicinal chemistry* 28.7 **1985**, 849-857.