Molecular Dynamics Investigation of Cooperative Binding Within the KIX Domain

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It has been established, that flexibility plays a crucial role for a variety of biochemical processes.[1] Molecular Dynamics (MD) computer simulations are a suitable technique to study biomolecular dynamics at atomic resolution.[2] We present a method to derive backbone torsional entropies for various complexes of the KIX domain[3] with the transcription factors MLL and cMyb. From states sampled by MD simulations, we obtain a continuous probability density function of state space by Kernel Density Estimation.[4] Subsequent numerical integration over $S = p(t) \ln p(t)$ directly yields entropy in where p denotes the probability density function of the state vector t.[5] We predict changes in the backbone conformational ensemble upon transcription factor binding and conclude that the stabilization induced by formation of a binary KIX-ligand complex is on the same order of magnitude than required to form a ternary complex.
Based on the PDB structure 2AGH 100 ns MD Simulations for various KIX complexes where obtained using the AMBER force field ff99SB. From these simulations, backbone torsional entropies were calculated. The holo structure shows a significantly higher flexibility, whereas each binary complex, either with MLL or cMyb induces stabilization. This stabilization is on the order of magnitude of the ternary complex.
Therefore we conclude that the cooperative binding effect observed for the KIX domain is caused by a global stabilization of the KIX secondary structure induced by the formation of any binary complex.

References

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