Computational screening and selection of cyclic peptide hairpin mimetics by molecular simulation and kinetic network models

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Abstract

Designing peptidomimetic compounds to have pre-organized structure in solution is highly non-trivial. Simulation-based approaches can help speed this process. Here, we present an extensive simulation study of designed cyclic peptide mimics of a hairpin from bacterial protein LadP involved in a protein-protein interaction (PPI) pertinent to bacterial biofilm formation. We used replica-exchange molecular dynamics (REMD) simulation to screen twenty covalently cross-linked designs with varying stereochemistry, and selected the most favorable of these for massively parallel simulation on FoldingHome in explicit solvent. Using Markov State Models (MSMs) we identified a key steric interaction between a methyl substituent and a valine sidechain that acts to allosterically shift population between native and near-native states, which could be exploited in experimental design rounds. Visualization of this mechanism is aided considerably by the iCAMS method, which identifies degrees of freedom most important in slow conformational transitions. The combination of quantitative detail and human comprehension provided by iCAMS suggests such approaches will be increasingly useful for design.

Introduction

A biofilm is any group of microorganisms in which cells stick to each other on a surface
Biofilm hazards: Dental plaques, Infectious kidney stones, Water pollution, etc
Mechanism of biofilm growth: first Microorganisms stick to a surface, then they reproduce and cover more surface area until they reach a point that the surface is no longer large enough to hold all the microorganisms. At this point the colony bursts and microorganisms propagate and cover new surface area.

Folding Home simulation results confirm REMD results. Qualitative agreement between REMD and Fjord results is obtained by comparing free energy of cyclic hairpin designs. This confirm reliability of implicit REMD simulations and the fact that designs 1, 2, 9, and 10 are the most promising, see concluding figures.

Markov State Models of Cyclic Hairpin Designs Reveal a Stacking Mechanism for Stability of Methylylated D-VaI. Free energy landscape of designs 1, 2, 9, and 10 show two distinct basins below 1.2 kcal/mol one at 1.4 kcal/mol (near-native) and one at 0.7 kcal/mol (native). Design 10 (methylylated D-VaI-) shows higher stability in near native basin compared to design 9 (unmethylated D-VaI). To see conformational differences of native and near-native basins we projected the simulation data on iCAMS space (a newly developed landscape analysis technique that identifies the slowest reaction coordinates in a system). MSM built on iCAMS landscape is capable of distinguishing native and near-native states: the native state has Val and methyl facing opposite to each other, while in the near-native conformations, the Val and methyl are facing close to each other, which causes steric clash between them and increases free energy of the near-native conformations. MSMs built on conventional free energy landscapes like RMSD-RC cannot identify native and near-native basins since there is no clear boundary between these states (Fig. 5). iCAMS components (eigenvectors of a time-lagged covariance matrix normalized with the covariance matrix) reveal that the value is playing dimensional role in controlling the kinetics of the system (Fig. 4) as well as governing the thermodynamics through allosteric interactions with the turn region.

For the L-VaI design, the native backbone conformation has the valine side chain above the hairpin plane; the additional methyl group destabilizes this configuration. The opposite is true for the D-VaI designs; in that case, the additional methyl destabilizes non-native backbone configurations having the valine side chain below the plane. One lesson from our work here is that the problem of rational designing conformational constraints can be highly nontrivial. We showed here that some subtle changes in one end of a cyclic hairpin can allosterically effect conformation on the turn region leading to significant stabilization or destabilization of a target structure.

Conclusion


References