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Structural and molecular dynamics analysis of the super secondary motifs from TIM barrel proteins: Implications for folding and engineering of foldable building blocks for the assembly of TIMS

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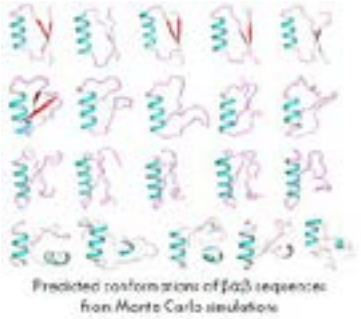
Statement of the Problem: The acquired complex three-dimensional structure of proteins is a culmination of simple structural fragments like α—α, β—β, α—β and β—α units. Thus, tertiary structures can be seen as a combination of basic building block motifs implying that all complex protein structures have evolved from the assembly of small independently folding super secondary structures. The TIM barrel proteins are made up of a regular repeating βαβ motif resulting in the strands and helices in an alternating repetitive pattern. Experimental and theoretical studies have revealed that βαβ unit acts as a minimal unit of stability. The success of designing super secondary motifs that fold in isolation underscores the prospects of designing and or identification of independently folding motifs from the existing protein structures. However, intriguingly, naturally occurring βαβ sequences from proteins that fold independently have not been identified. In our attempts, we addressed the finding of 'needles in hay stick' scenario by an exhaustive sequence and structural space search of the βαβ units from the TIM barrels.

Methodology & Theoretical Orientation: The search approach implemented in this work considered features such as alpha helical propensity, loop length, loop dynamics, residue preferences in loops, long range side chain main chain interactions etc., to shortlist βαβ units with strong propensity to fold in isolation. The prospective βαβ candidates thus shortlisted from the TIM barrels have been further subjected to structure forming tendency employing a combination of Monte Carlo and Molecular dynamics simulations to assess their foldability and stability.

Conclusion & Significance: The prediction of some independently folding βαβ candidates from TIMs are enabling us to experimentally asses their folding and stability. The identification and analysis of independently folding βαβ units that exist naturally will not only provide substantial information on nature's design strategies and evolution of protein conformations but also help to design/engineer novel proteins.



Predicted conformations of βαβ sequences from Monte Carlo simulations

Biography

Ramakrishna Vadrevu received his Master's degree in Physical Chemistry and his PhD degree in Biophysical Chemistry. He spent few years at the Pennsylvania State University and later at University of Massachusetts Medical School as a Postdoctoral Fellow with Prof. C. Robert Mathews. Since 2008 he has been a faculty at the Birla Institute of Technology and Science-Pilani, Hyderabad Campus in the department of Biological Sciences. His research focuses on understanding the role cellular environment on protein stability and folding. His research interests include: protein design and engineering, amyloid material and its applications.

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