# Conformational variability of the p53 core domain

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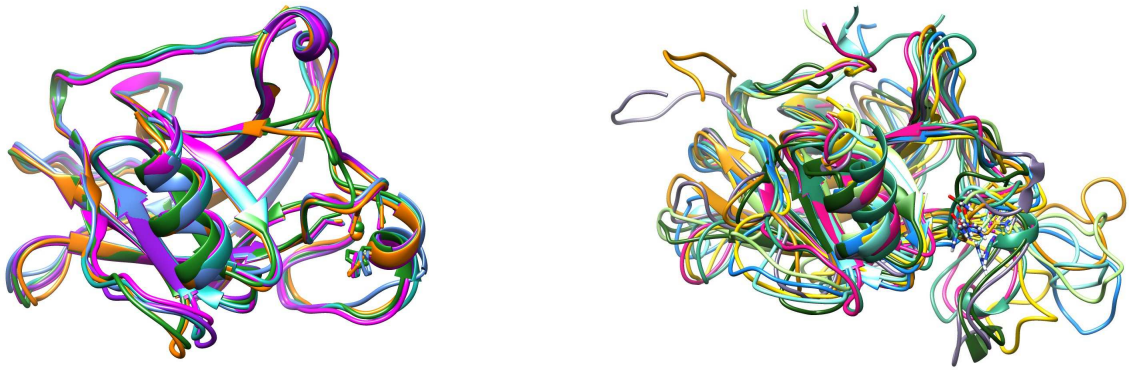
The tumor suppressor protein p53 has been widely studied because of its high mutation rate in human cancer cell lines. When intact, it acts as a transcription factor within a complex protein-signaling network, to control DNA damage repair, senescence and apoptosis. P53 has N-terminal and C-terminal unstructured regions to facilitate interaction with many different molecules, whereas the DNA binding domain is intrinsically ordered.

Many crystal structures are available for the p53 DNA binding domain in isolated form and in complex with a variety of other macromolecules [1-6]. From different crystal structures, six molecular-dynamics simulations were started and run for several microseconds each.



Compared with the different crystal structure starting points (overlay in left picture), a much greater structural variety is observed during the simulations (overlay in right picture). By analyzing the flexible regions of the protein domain separately with cluster analysis techniques, numerous intermittently stable conformations can be found. The structures of some flexible regions reappear during the simulations, whilst the vast majority of structures for other regions are formed only once. It is assumed that a larger part of the conformational space was sampled for flexible regions with reappearing structures, compared to regions without reappearing structures. However, the existence of additional conformations is considered very likely for each of the flexible regions.

In summary, there are several regions within the DNA-binding domain of p53 that have a much higher flexibility than can be seen in crystal structures. During their movement, they still form intermittently stable conformations.

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