Abstract

In the present work, we have investigated ligand conformational diversity and studied its relation to ligand flexibility and sequence similarity. In general, our preliminary analysis suggested that ligand tends to show diverse conformation with increase in its flexibility. However, diversity is limited due to binding site volume available for ligand binding in protein. Another interesting observation is that ligands adopt similar conformation when binds to sequences with higher sequence identity than to non-homologous proteins. The results could be useful in molecular docking simulations, for example one could limit conformation search space for flexible ligand based on number of rotatable bonds; sequence homology could exploited to find similar ligand conformations from PDB. Moreover, in case of ligand modeling for non-homologous sequences the conformation search space need to be search extensively relative to modeling of ligand in homologous sequences. These will be used to develop method for ligand modeling. A systematic structural analysis of conservation in G-motif showed that unliganded structures show less structural conservation in comparison to ligand bound structures (GDP/GTP bound). Among different motifs, G-3 motif shows remarkable structural conservation in GTP bound structures across sequence diverged members of Gproteins. This could partially be explained by the fact that this motif is involved in binding γ-phosphate and possible different structures should adopt similar conformations in binding site to accommodate this ligand. Moreover, it has been observed that in completely sequence genomes, there is relatively less number of GAP encoding genes than GEFs, which indicates that a single GAP can activate GTP hydrolysis of proteins classified in different subfamilies of G-proteins. However, GEF has evolved different to be specific for different subfamilies.