

S4 Figure. Sequence-position mapping for the DHFR protein family

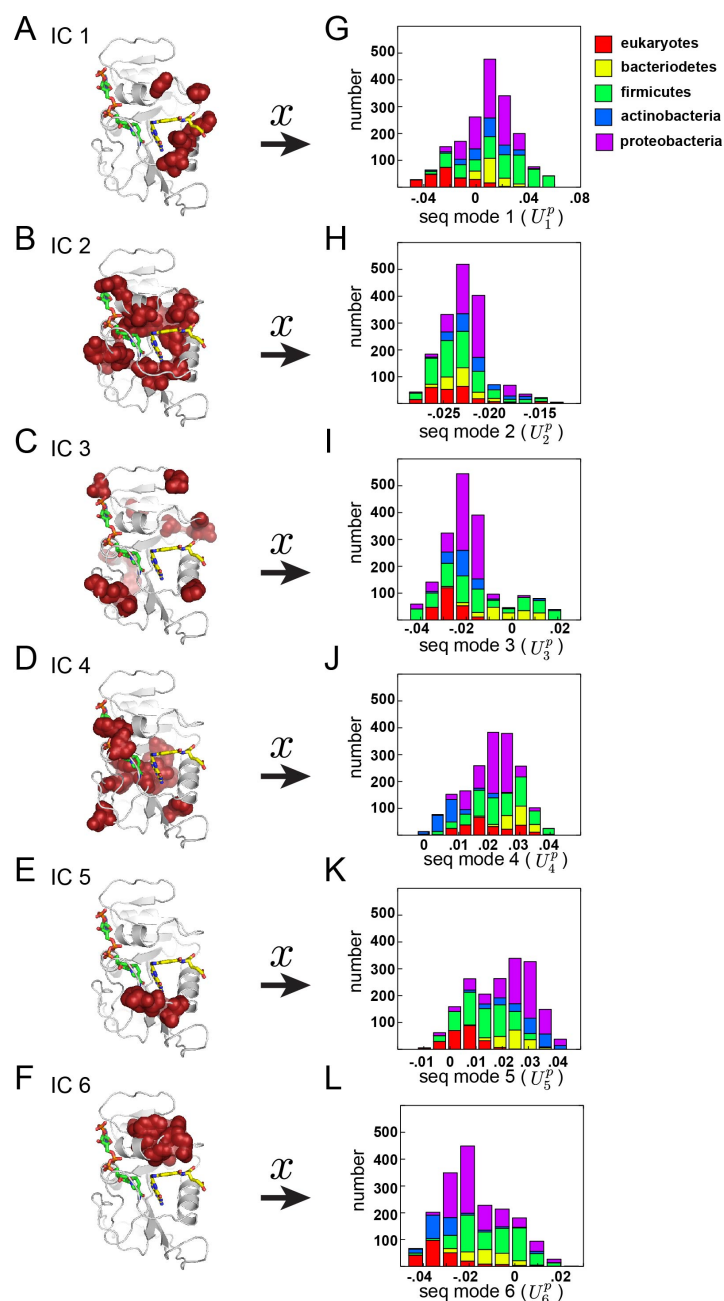


FIG. 4 **Sequence-position mapping for the DHFR protein family.** A-F show the positions comprising the six ICs of the SCA coevolution matrix (Fig. S3A), respectively, as colored spheres on the structure of *E. coli* DHFR (PDB 1RX2), and G-L show stacked histograms of the corresponding sequence space colored by phylogenetic annotation. The data show that ICs 1, 5, and 6 roughly separate eukaryotic and prokaryotic sequences and that the remainder are more homogeneous with regard to phylogenetic divergence. The significance of these apparent heterogeneities will require further investigation, but prior work demonstrates functional and mechanistic differences between the eukaryotic and prokaryotic members of this protein family (?).