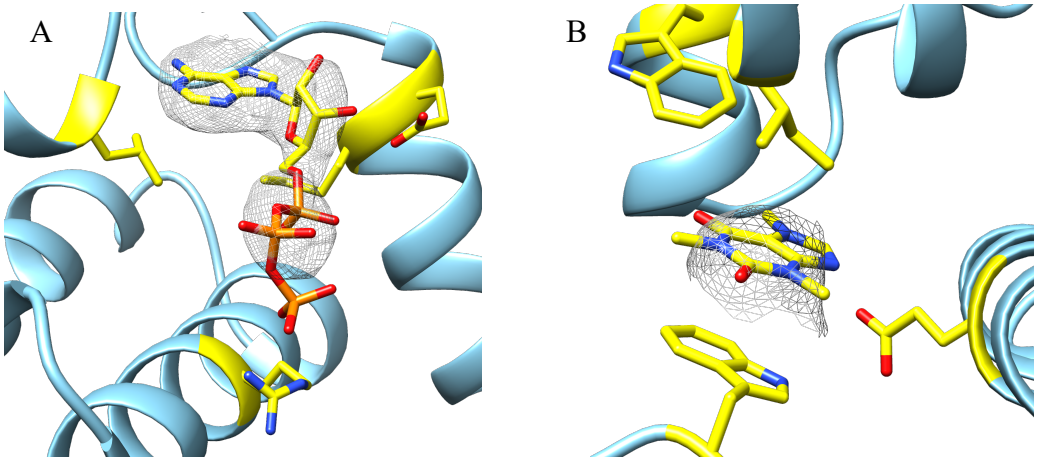

Figure 1. Cryo-EM structures of RyR1 complexed with (A) ATP or (B) Caffeine. Density for ligands is shown as grey mesh.

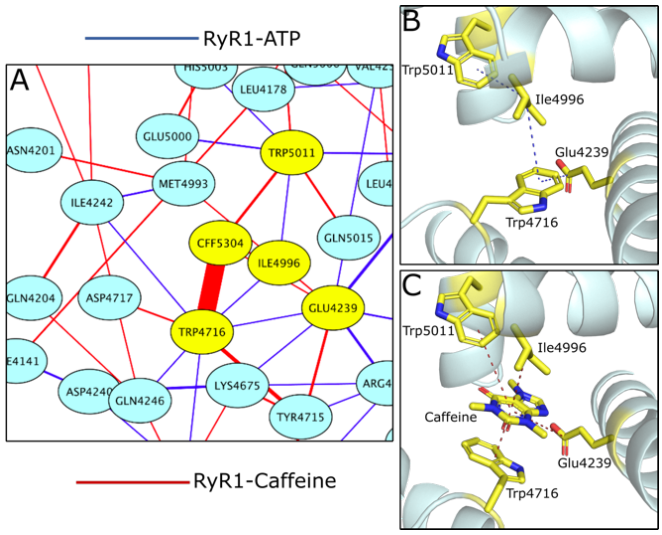

Figure 2. Analysis of 3D RyR1 structures using 2D residue interaction networks (RINs) with amino acids represented as labeled nodes and non-covalent interactions between them depicted as edges. (A) Difference network depicting contacts gained and lost at caffeine binding site (yellow nodes) in RyR1 structure complexed with ATP (blue edges) or Caffeine (red edges). **(B)** In caffeine unbound structure of RyR1, residue Trp4716 interacts directly with residues Ile4996, Glu4239 and indirectly with Trp5011 through Ile4996 (blue edges in RyR1-ATP network). **(C)** Binding of caffeine to RyR1 perturbs the network wherein caffeine takes over the contacts formed by Trp4716 in (B) by interacting with Trp4716, Ile4996, Glu4239 and Trp5011 (red edges in RyR1-Caffeine network).