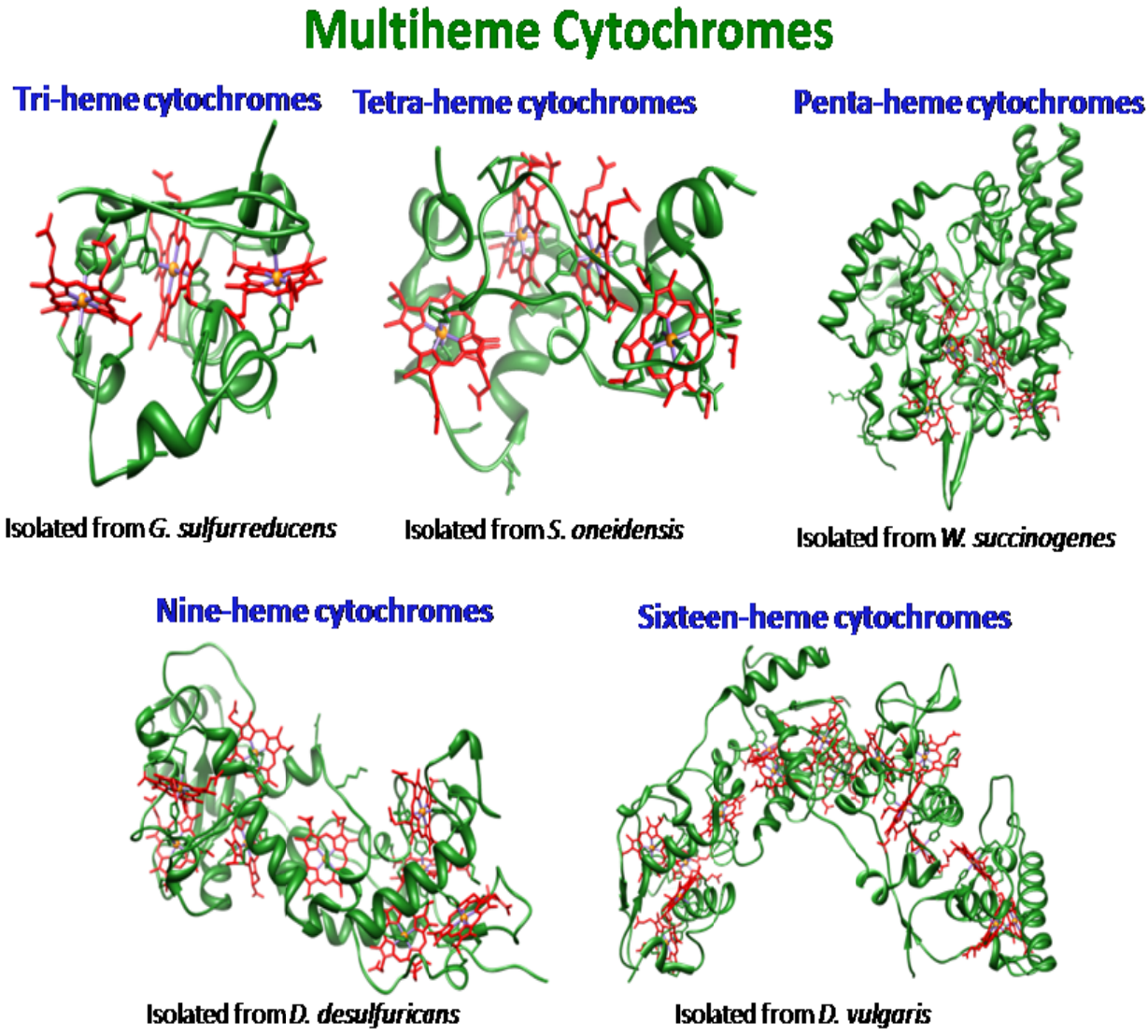
Unfolding Mystery of Multi-Heme Proteins

Multi-heme constitutes a widespread class of proteins with essential functions in electron transfer and enzymatic catalysis and been emerged as a very important research area today. Recent discoveries of newer proteins in large numbers and their involvement in various biological processes have raised two immediate questions: what are the selective advantages of containing so many redox co-factors in a single polypeptide, and why did the spatial distribution of the co-factors evolve to be the way it is? The functional properties of such important and widely distributed family are largely determined by the arrangement and interaction of their multiple heme cofactors. Understanding the significance of these motifs is crucial for the elucidation of the highly optimized properties of multiheme cytochromes *c*, but their spectroscopic investigation is often restricted by the presence of a large number and efficient coupling of the individual centers. Although, mono heme protein/enzyme and their model compounds have already been studied extensively, only a few in vivo studies are reported with multiheme. These attractive features have prompted us to investigate on the biomimetic models of multi-heme proteins as a part of our ongoing research activities.

Interaction between heme centers has been smartly implemented by Nature in order to regulate different properties of multiheme cytochromes, thereby allowing them to perform a wide variety of functions. Our broad interest lies in unmasking the role played by heme-heme interaction in modulating different properties *viz.*, metal spin state, redox potential etc., of

the individual heme centers using ethane-bridged porphyrin dimer as a synthetic model of dihemes. The large differences in the structure and properties of the diheme complexes, as compared to the monoheme analogs, provide an unequivocal evidence of the role played by heme-heme interaction in the dihemes.



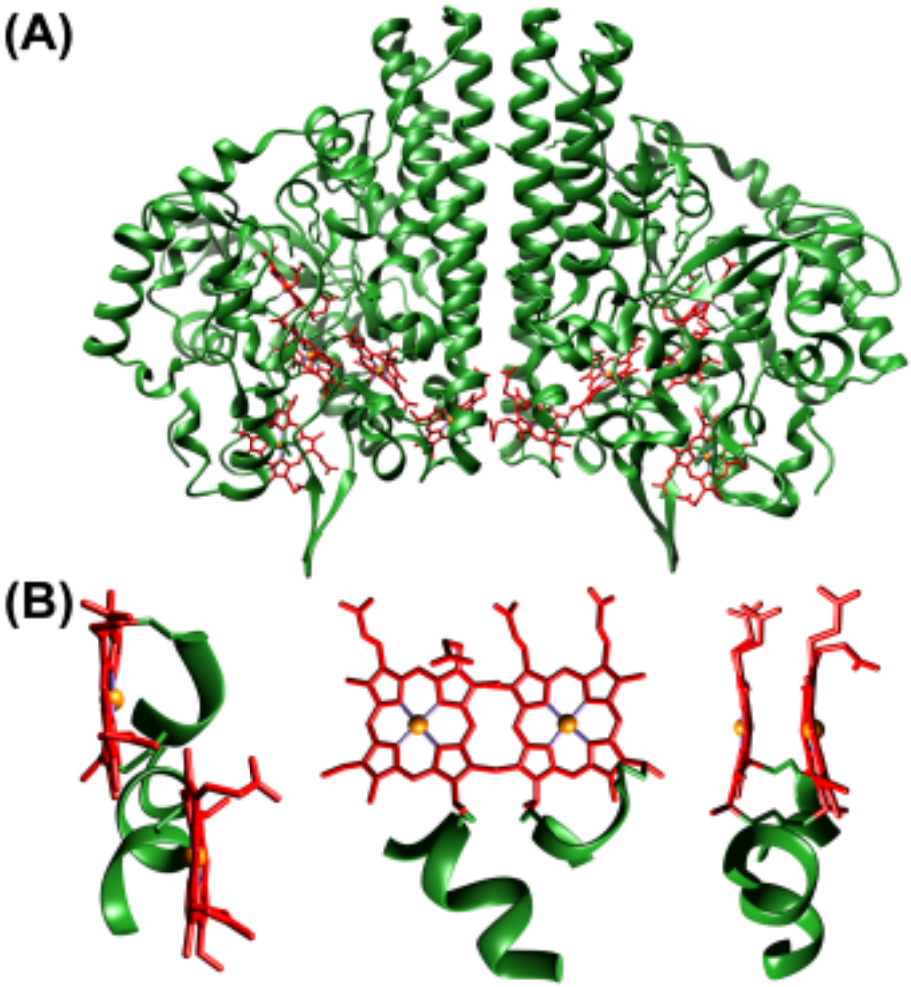


Fig. 1. (A) Structure of cytochrome c nitrite reductase (PDB code 1QDB) in which the protein chain and the heme groups have been colored green and red, respectively. (B) Different views of the diheme motif formed by heme 3 and heme 4 in the nitrite reductase.

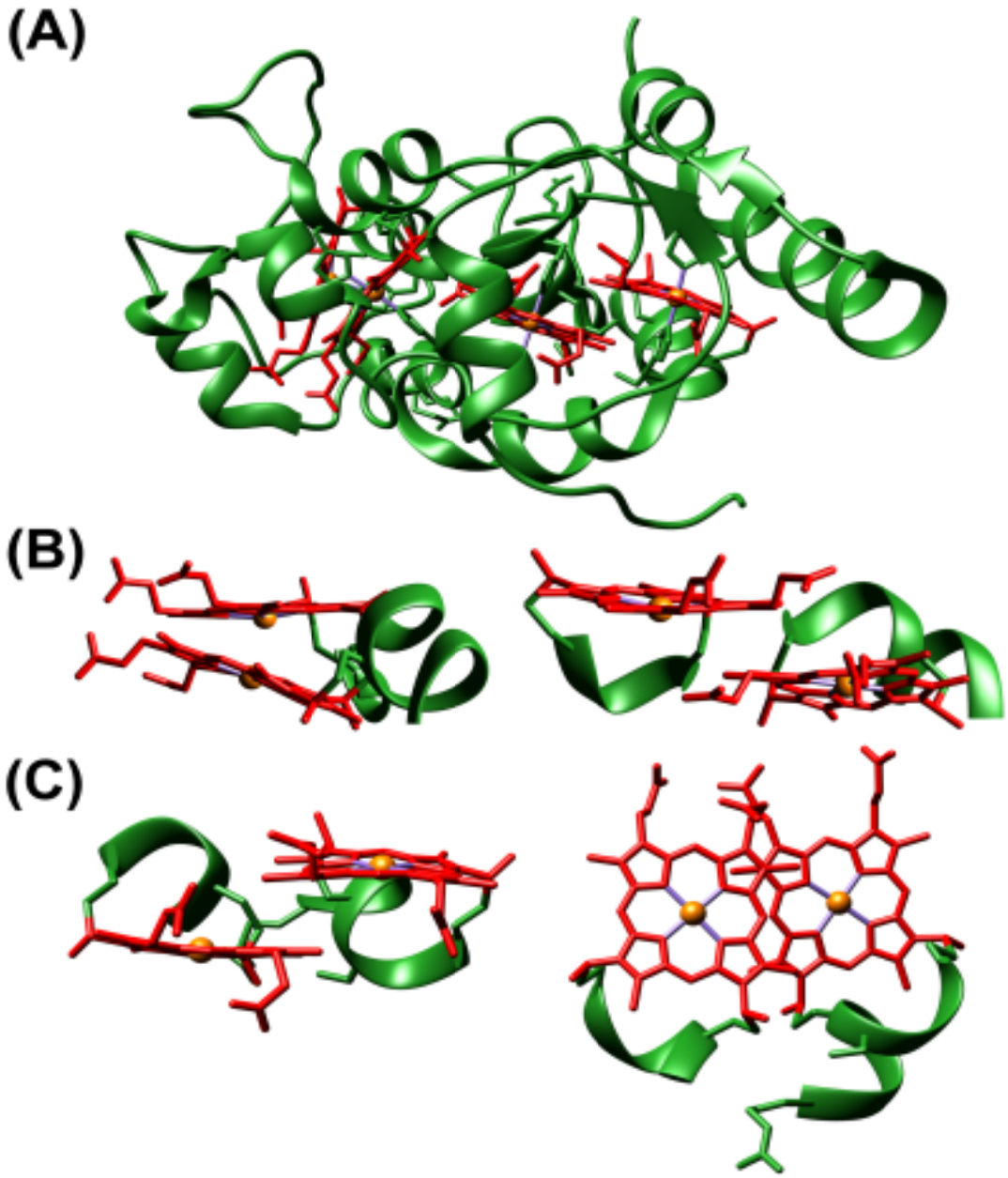


Fig. 2. (A) Structure of the oxidized state of tetraheme cytochrome c554 from *Nitrosomonas europaea* (PDB code 1FT5). The protein chain and the heme groups have been colored green and red, respectively. Different views of the diheme motifs formed by (B) hemes I and III and (C) hemes II and IV.

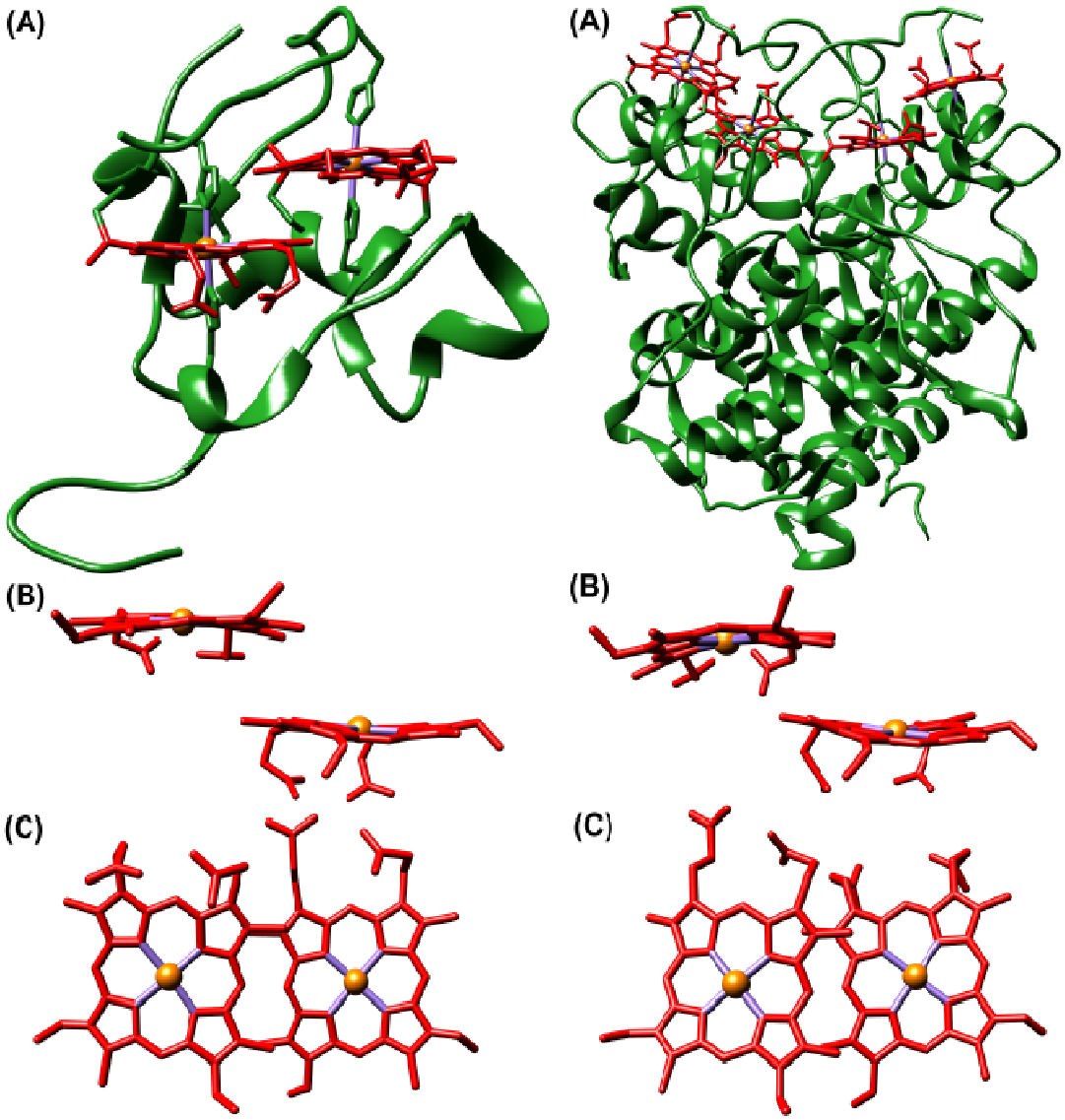


Fig. 4. *Left*, (A) structure of the diheme cytochrome c, NapB, from *Haemophilus influenzae* (PDB code 1JNI); (B) side and (C) top views of diheme motifs therein. *Right*, (A) structure of the aerobic form of the split-Soret diheme cytochrome *c* from *Desulfovibrio desulfuricans* ATCC 27774 (PDB code 1H21); (B) side and (C) top views of diheme motifs therein. The protein chain and the heme groups have been colored green and red, respectively.

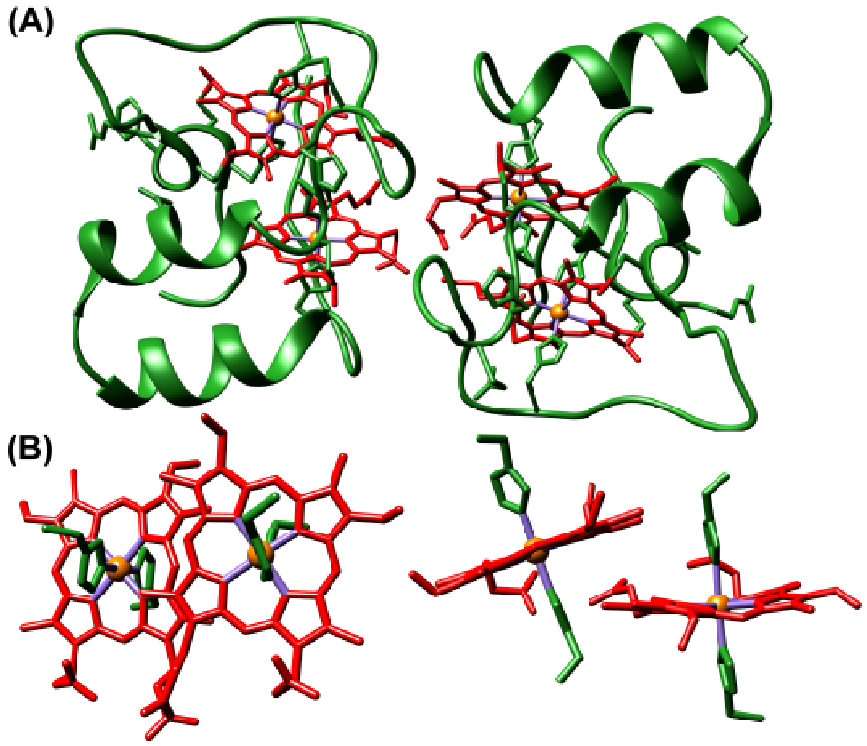


Fig. 3. (A) Structure of the diheme cytochrome c, DHC2, from *Geobacter sulfurreducens* (PDB code 2CZS) containing 2 monomer per asymmetric unit. Each monomer has two heme groups covalently attached to the protein chain. The protein chain and the heme groups have been colored green and red, respectively. (B) Different views of structural arrangements of the heme groups.

Representative Publication:

1. **Ethane-bridged Porphyrin Dimer as Model of Di-heme Proteins: Inorganic and Bioinorganic Perspectives and Consequences of Heme-Heme Interactions**

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