

Graph-theoretical prediction of biological modules in quaternary structures of large protein complexes

Florian J Gisdon, Mariella Zunker, Jan Niclas Wolf, Kai Prüfer,
Jörg Ackermann, Christoph Welsch, Ina Koch

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Gökçe Uludoğan

PhD Candidate

LifeLU Reading Group | 26 September 2024

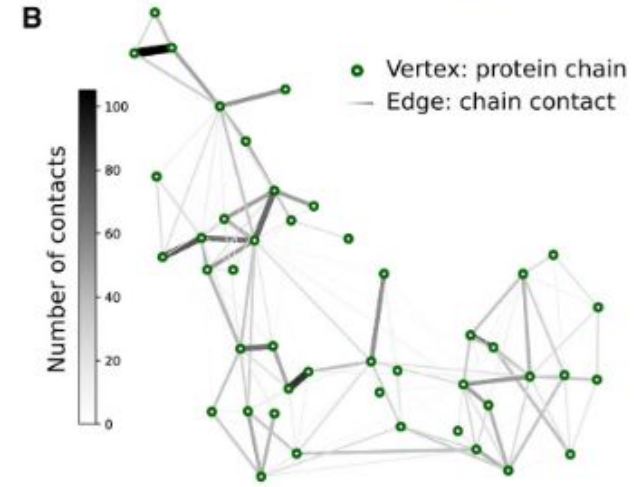
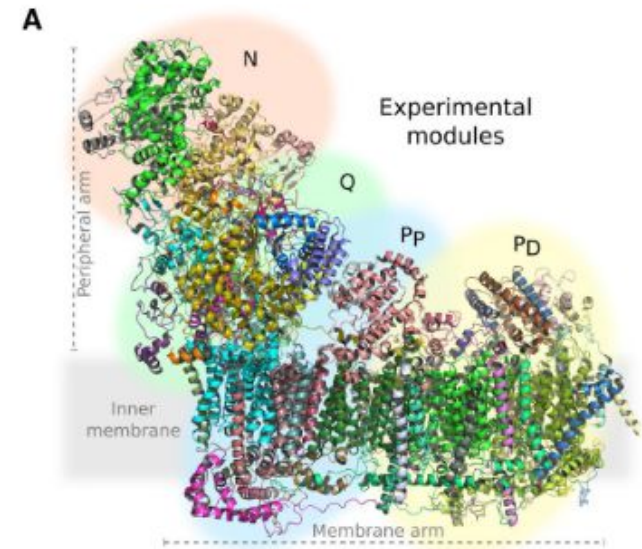
Motivation

- PDB Update in 2023
 - Released ~1300 entries with >10 chains
 - ~13% of total entries that year
- Protein complex analysis
 - Challenging
 - Need computational tools for structural and functional characterization
- Complex graph representation & graph-theoretical approaches

Hypothesis: Partitioning of the protein complex graph by graph theoretical methods gives functional, biological modules.

Complex Graph

- Nodes
 - Chains
- Edges
 - Inter-chain residue-residue contacts
- Edge weight
 - # residue-residue contacts
- Contact
 - A sphere model for atoms
 - Atom contact: sphere overlap.
 - Residue contact: at least one atom-atom contact
 - Chain contact: at least one residue residue contact.

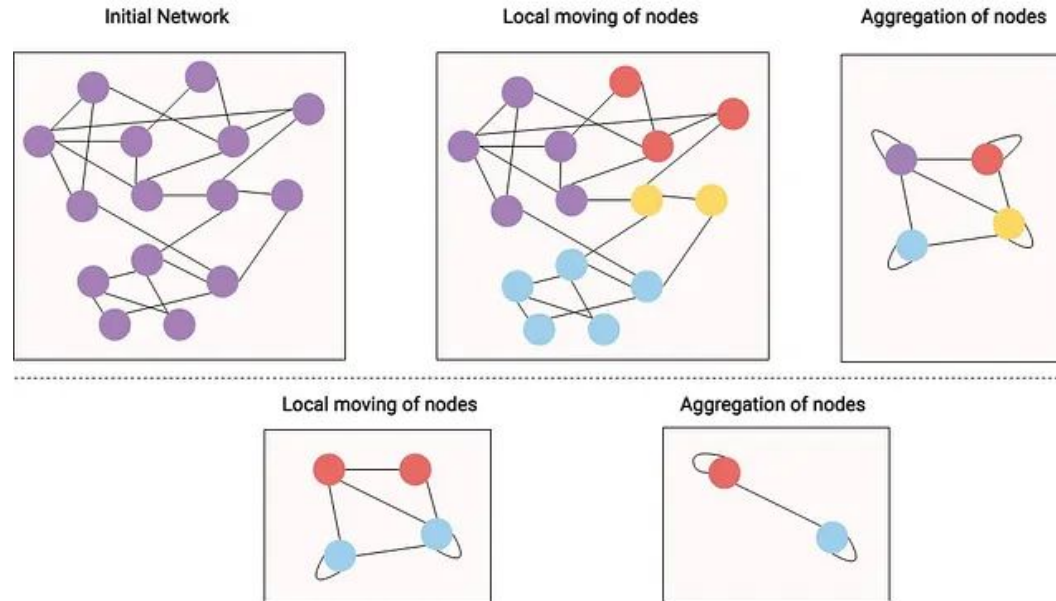


Community Detection - Louvain Algorithm

Based on modularity, a measure of how well a network has been partitioned into clusters.

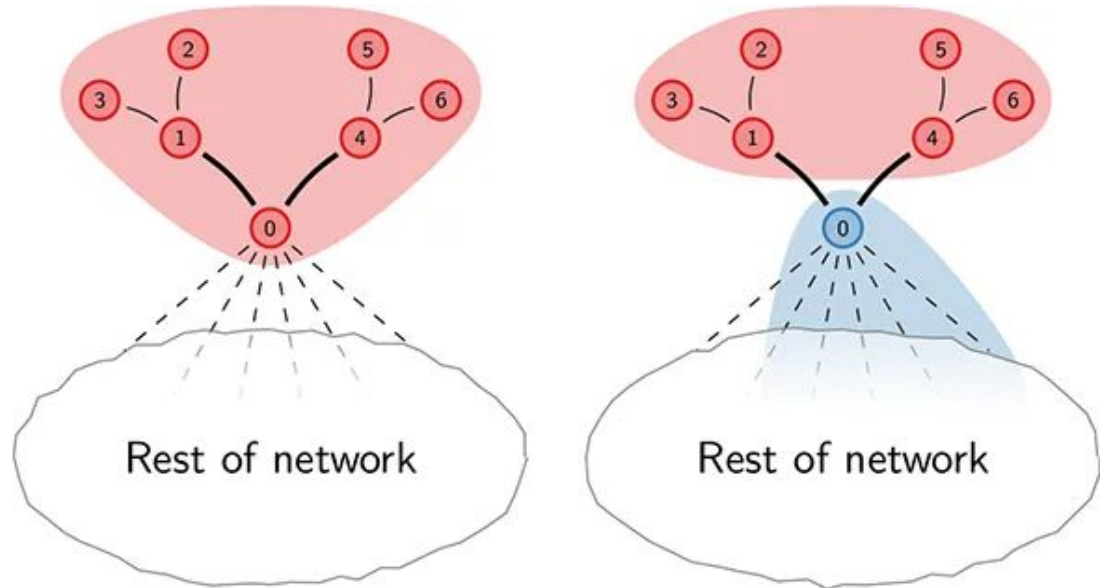
Two steps:

- local moving of nodes
- aggregation of nodes.

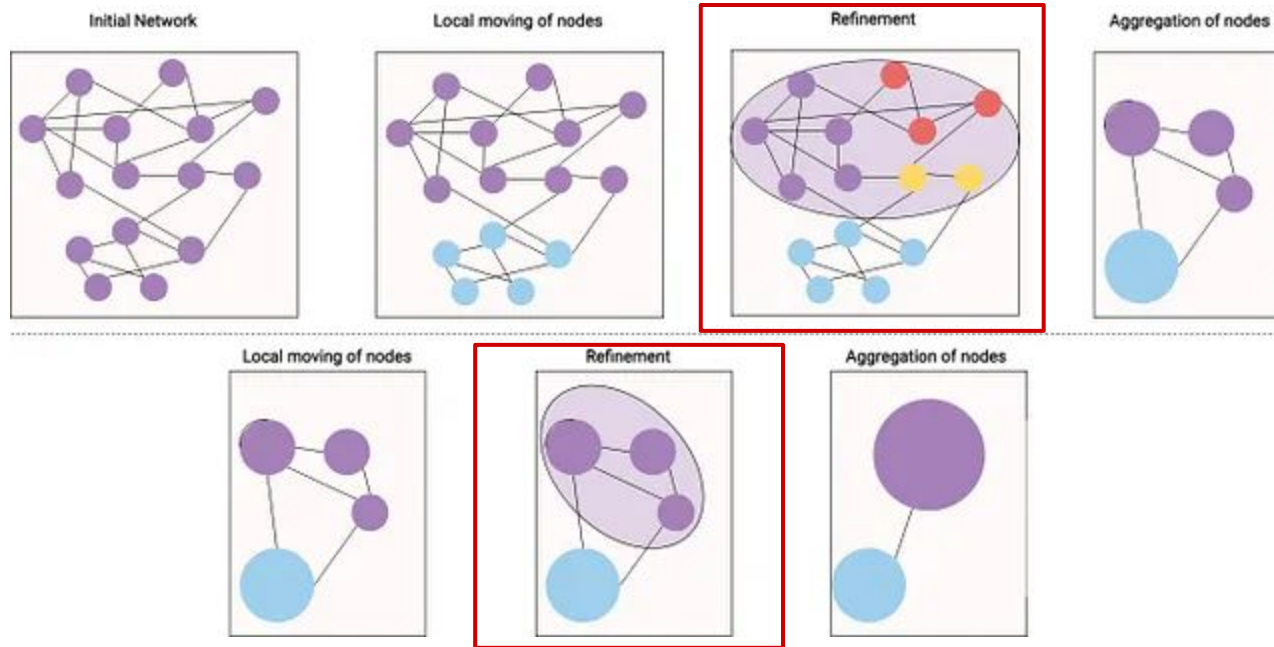


Community Detection - Louvain Algorithm

internally disconnected
communities



Community Detection - Leiden Algorithm

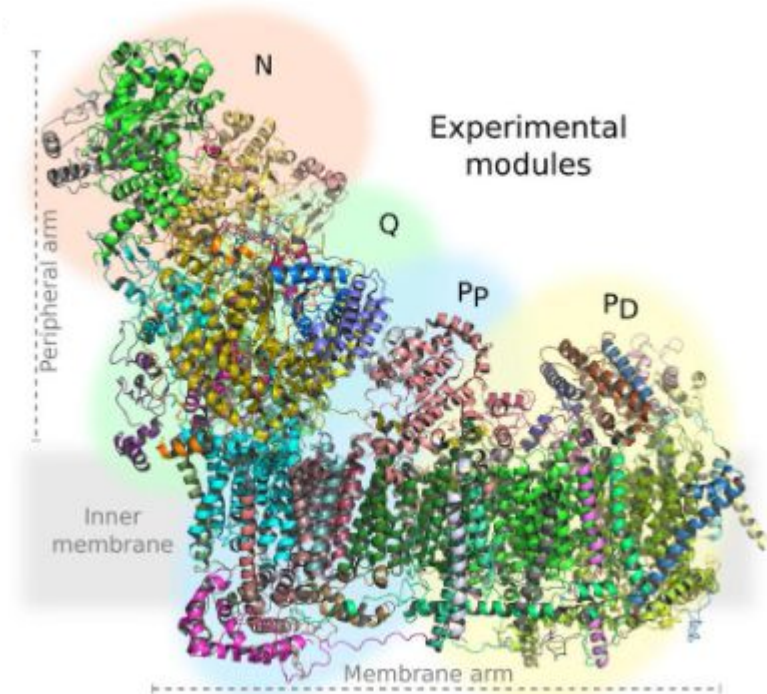


Case studies

- human respiratory complex I
 - Assigned functional modules
 - Proton gradient across the membrane
 - 45 chains (44 unique)

Human Respiratory Complex I

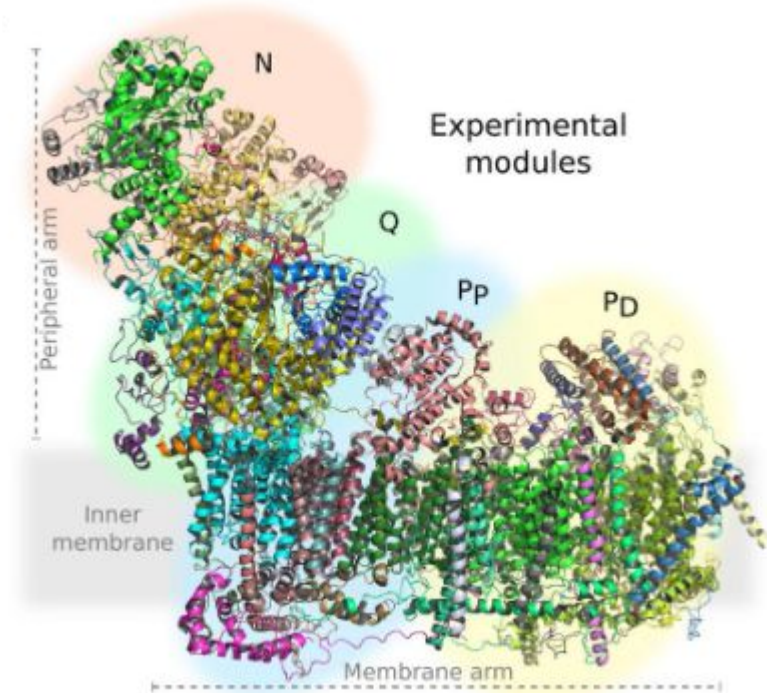
- Peripheral arm
 - N-module
 - oxidation of NADH takes place under the release of two electrons.
 - Q-module
 - ubiquinone is bound onto which the electrons are transferred
- The membrane arm (P-module)
 - Proximal and a distal part, P_P and P_D
 - The proton translocation across the membrane involves three antiporter-like subunits.
 - ND4 and ND5 in P_D
 - ND2 in P_P



Human Respiratory Complex I

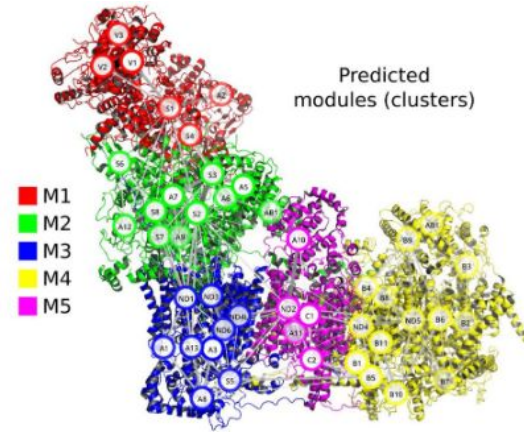
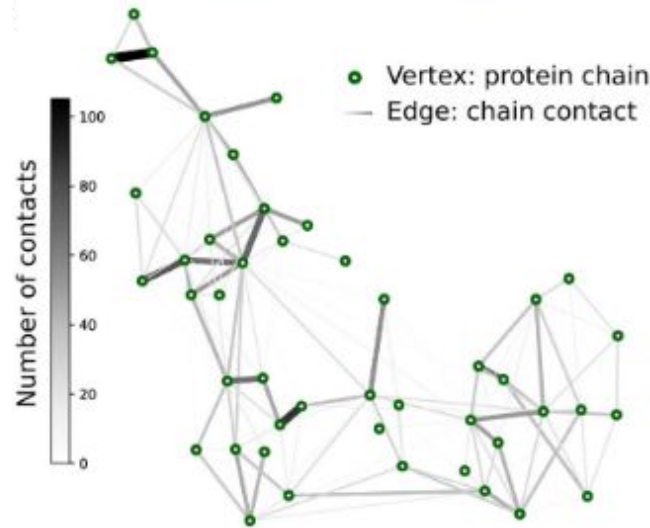
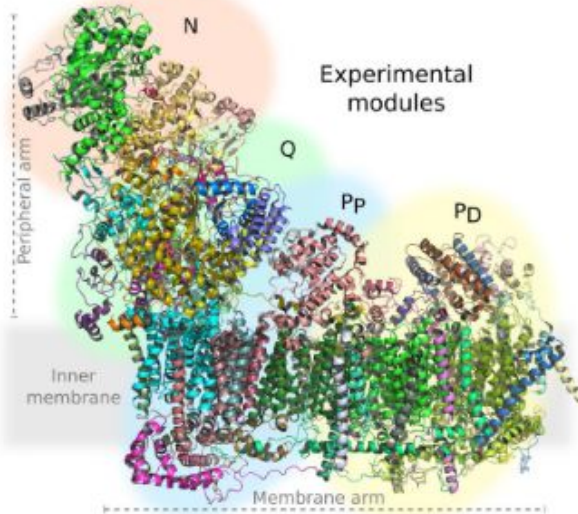
An antiporter is an integral membrane protein that is involved in the active transport of two or more different molecules or ions across a phospholipid membrane .

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Human Respiratory Complex I

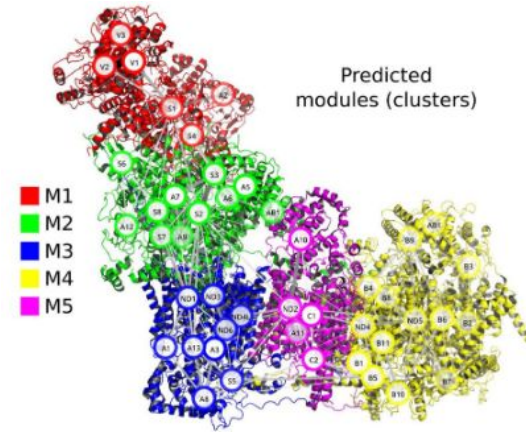
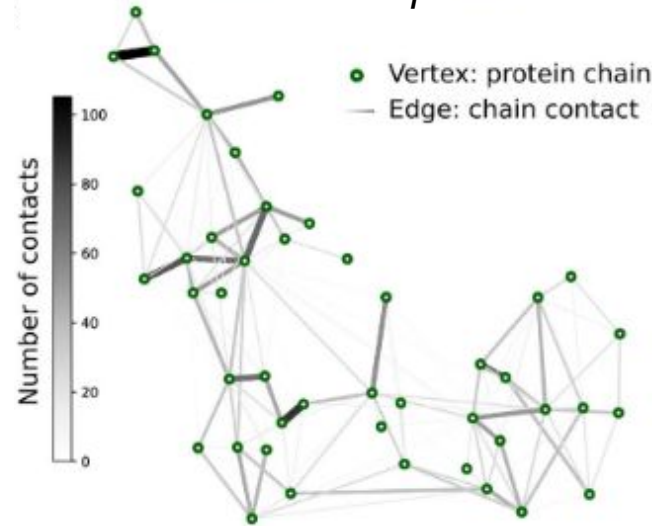
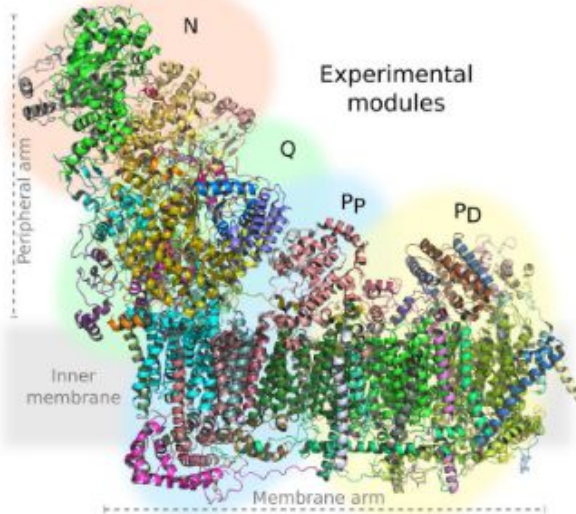
The structural modules are in accordance with the well-connected regions in the complex graph and correlated with experimental findings.



Human Respiratory Complex I

Structural modules were rather rigid but between the modules, higher flexibility is expected.

M3 & M5 flexibility - ND1 and ND6 subunits
conformational movements in open and closed forms

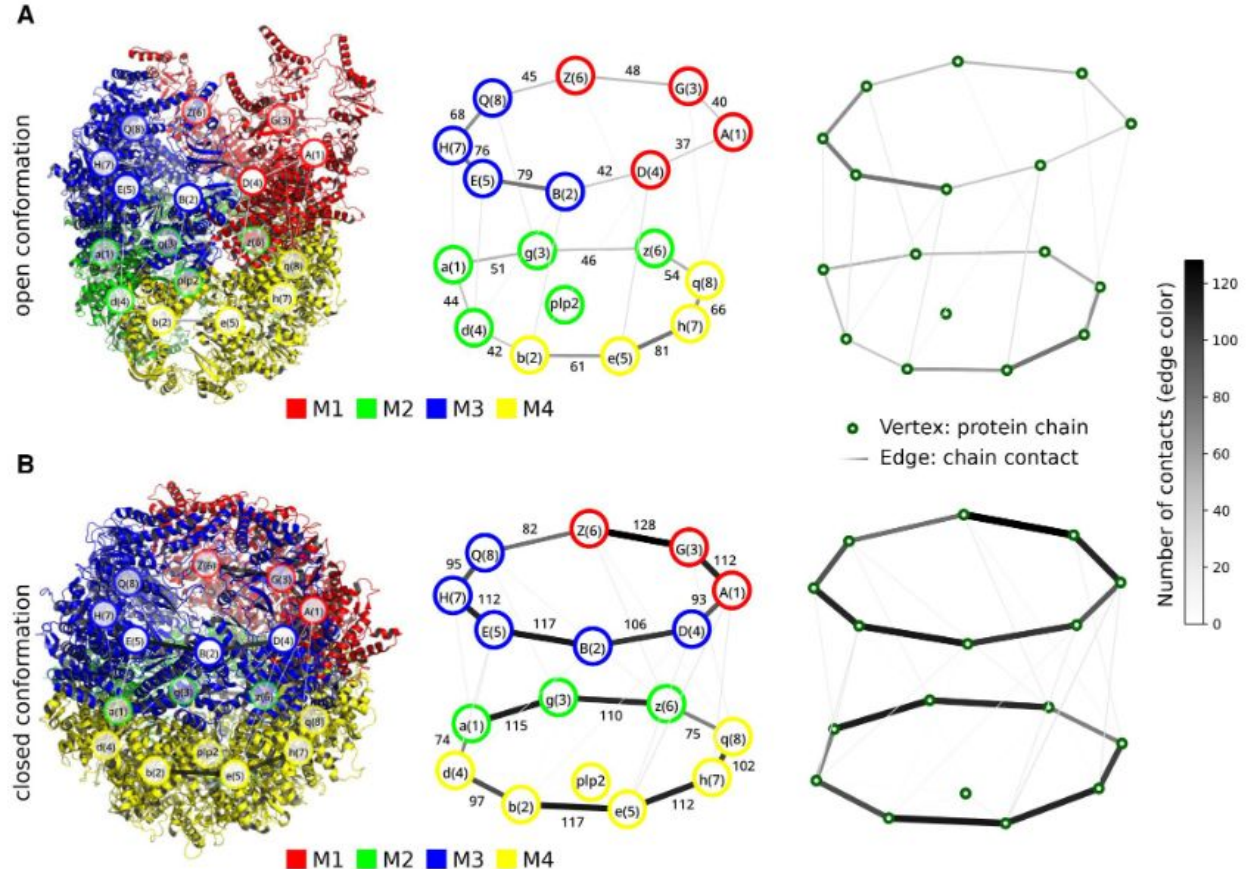


Case studies

- human respiratory complex I
 - Assigned functional modules
 - Proton gradient across the membrane
 - 45 chains (44 unique)
- the group II chaperonin TRiC/CCT
 - group II chaperonin TCP-1 ring complex/chaperonin containing TCP-1 (TRiC/CCT) from yeast with co-chaperon plp2
 - Open conformation (ATP binding)
 - Closed conformation (ATP hydrolysis)
 - Folding of the cytoskeletal proteins actin and tubulin
 - Asymmetrical
 - 17 chains (9 unique)

Group II chaperonin TRiC/CCT

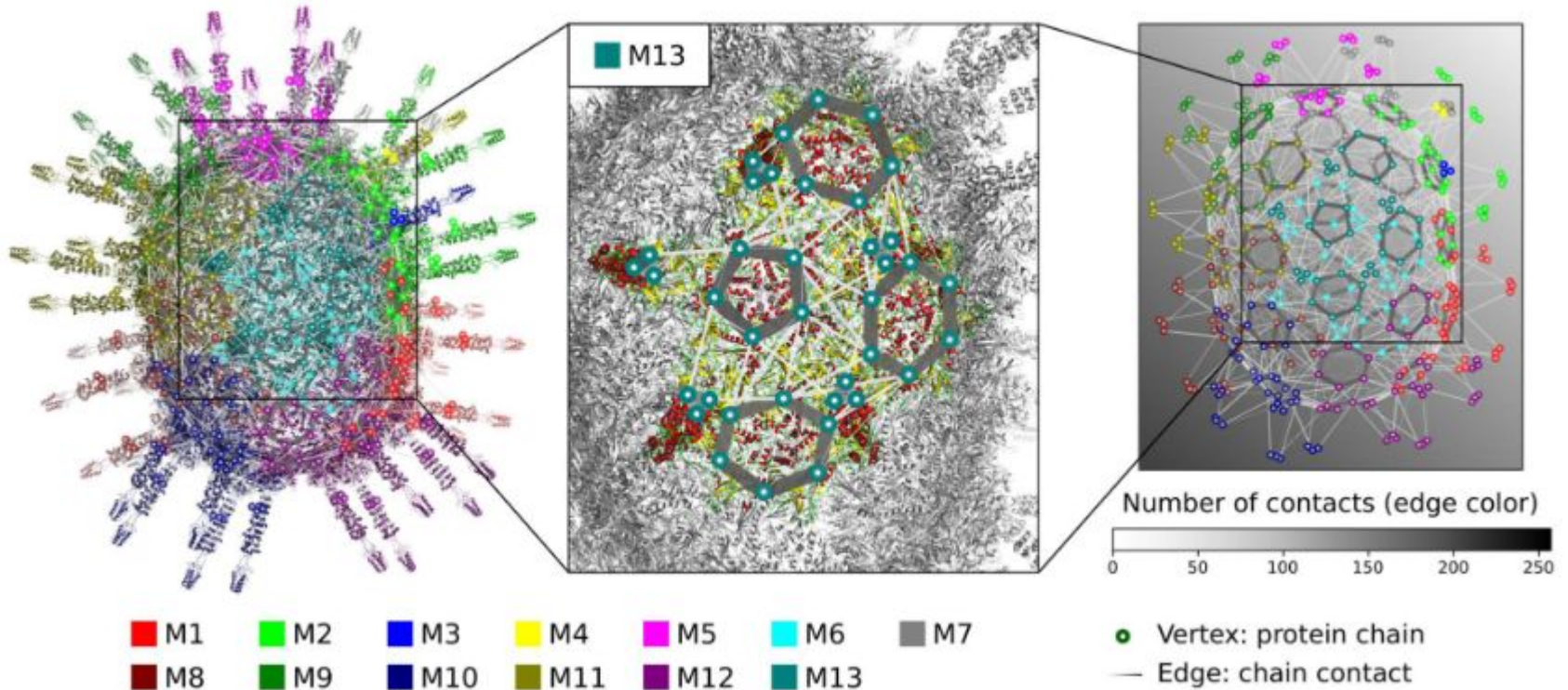
- Asymmetry in ring contacts
- pronounced intra-ring contacts
- 4 modules changing from the open to the closed conformation
- Two structural modules in each ring and a dynamic change in the module structure upon chamber closure



Case studies

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 - Open & Closed conformation (ATP hydrolysis)
 - Folding of the cytoskeletal proteins actin and tubulin
 - Asymmetrical
 - 17 chains (9 unique)
- the head of the bacteriophage $\Phi 29$
 - 400 chains (2 unique)
 - Very large protein complex with little variation in the individual components, which assemble into different structural units.

the head of the bacteriophage $\Phi 29$



Execution Time

- Complex graph
 - Bottleneck
 - 20s for complex I and TRiC/CCT
 - 1.5h for the bacteriophage Φ 29
- Graph partitioning
 - 2s