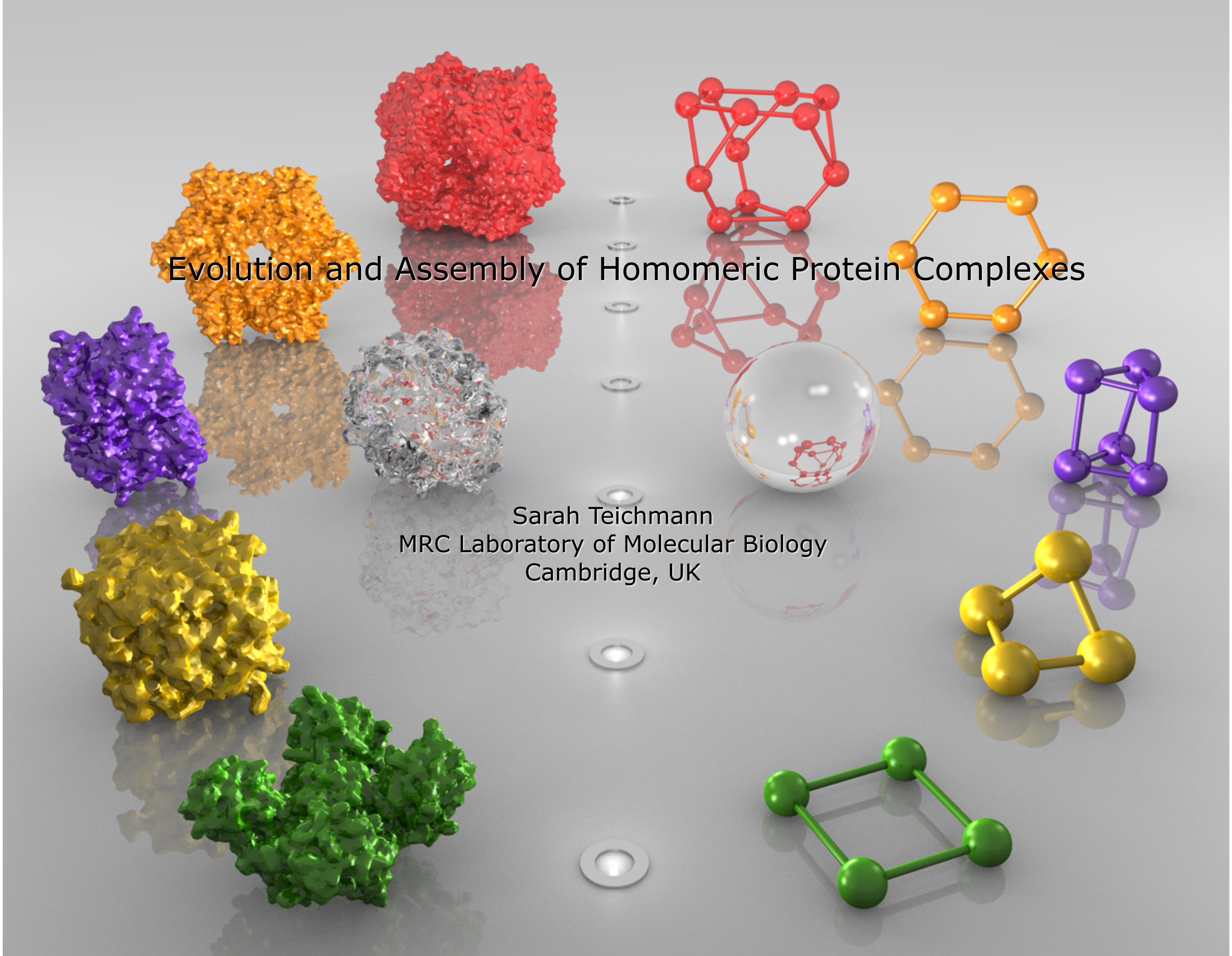
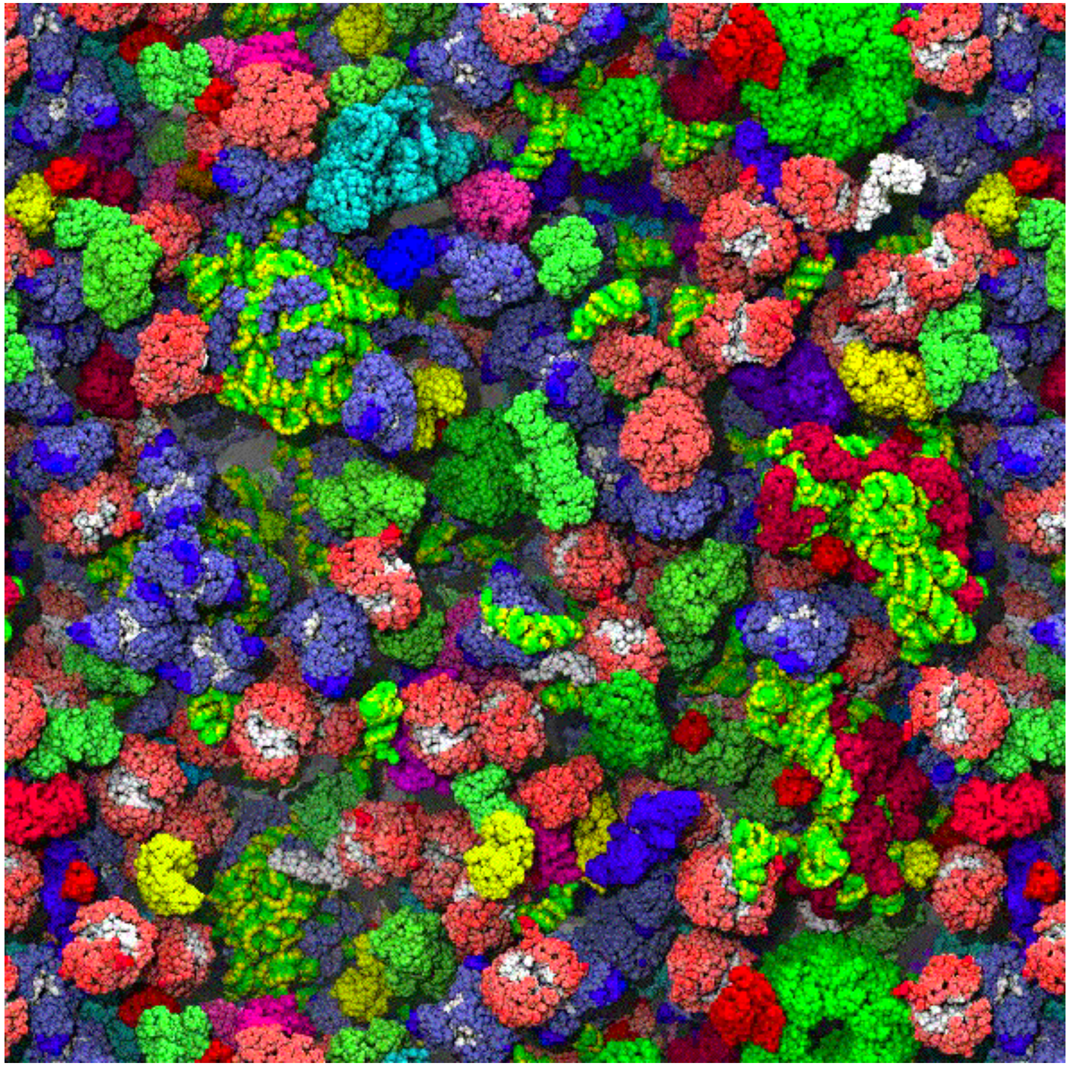
Evolution and Assembly of Homomeric Protein Complexes



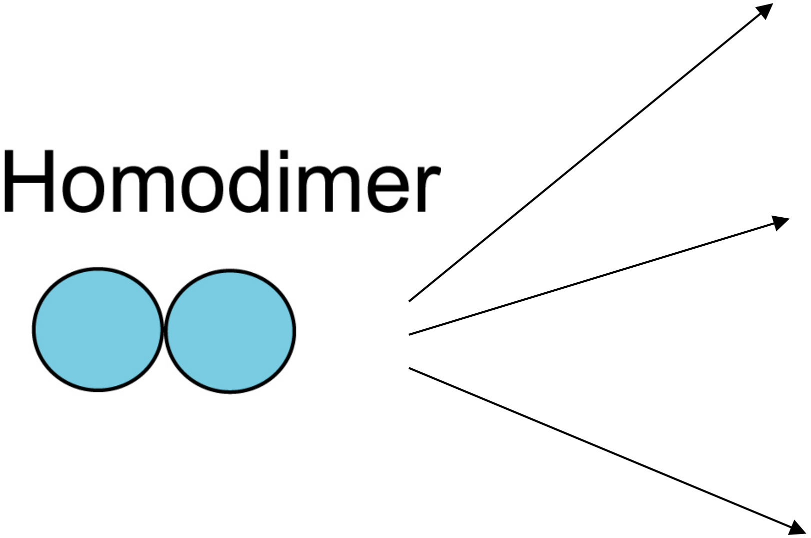
Sarah Teichmann
MRC Laboratory of Molecular Biology
Cambridge, UK

The inside of a cell



Adrian Elcock, U. Iowa

Molecular Narcissism



Homodimer

Structures

Evolution

Assembly in solution

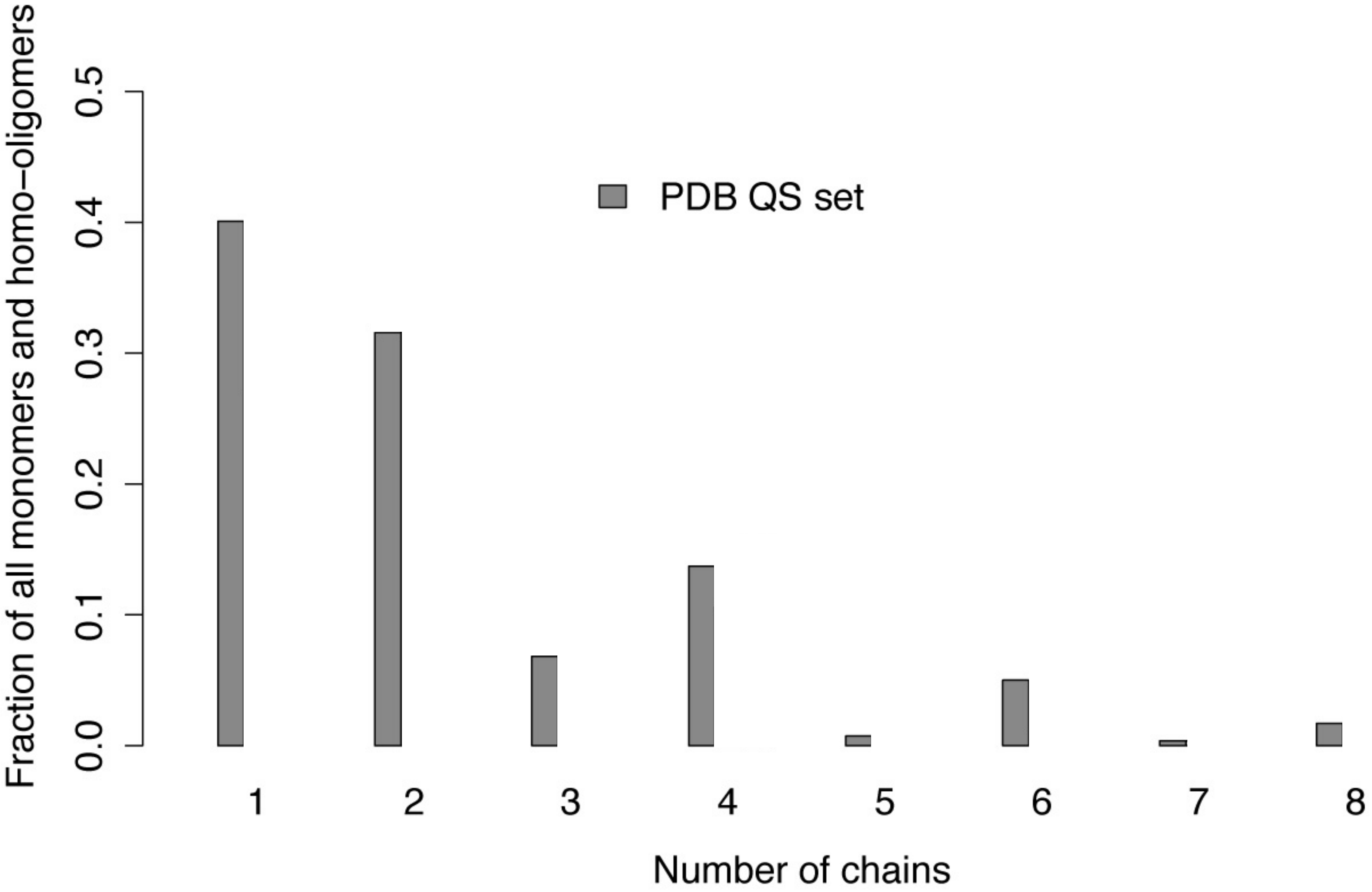
3Dcomplex.org - a hierarchical classification of complexes

Levy, E.D., Pereira-Leal, J., Chothia, C & Teichmann, S.A. (2006) 3DComplex: a structural classification of protein complexes. *PLoS Comp Biol*., **2**, e155.

www.PiQSi.org - a wiki for quaternary structure curation

Levy, E.D (2007) PiQSi: protein quaternary structure investigation. *Structure*, **15**, 1364-7.

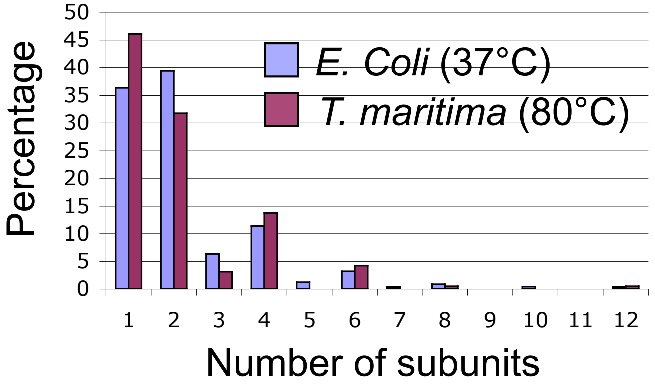
How frequent are homo-oligomers?



60% to 70% of proteins form homo-oligomers

Selective advantages of homo-oligomers

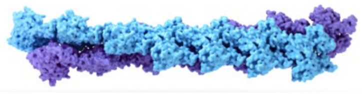
- Stability of the protein



- Functional advantages

Polymerisation

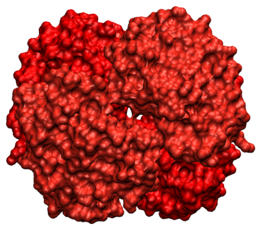
Actin



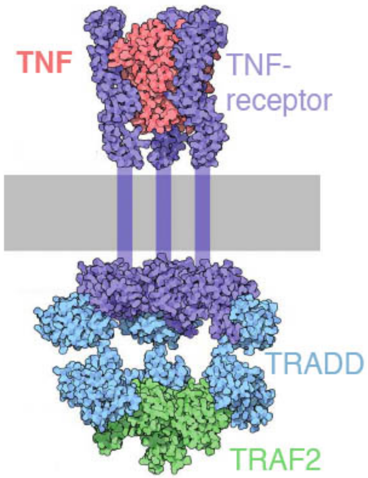
Tubulin

Cooperativity through allosteric changes

Hemoglobin

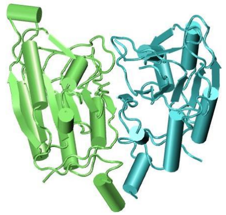


Template for assembly



Function regulation

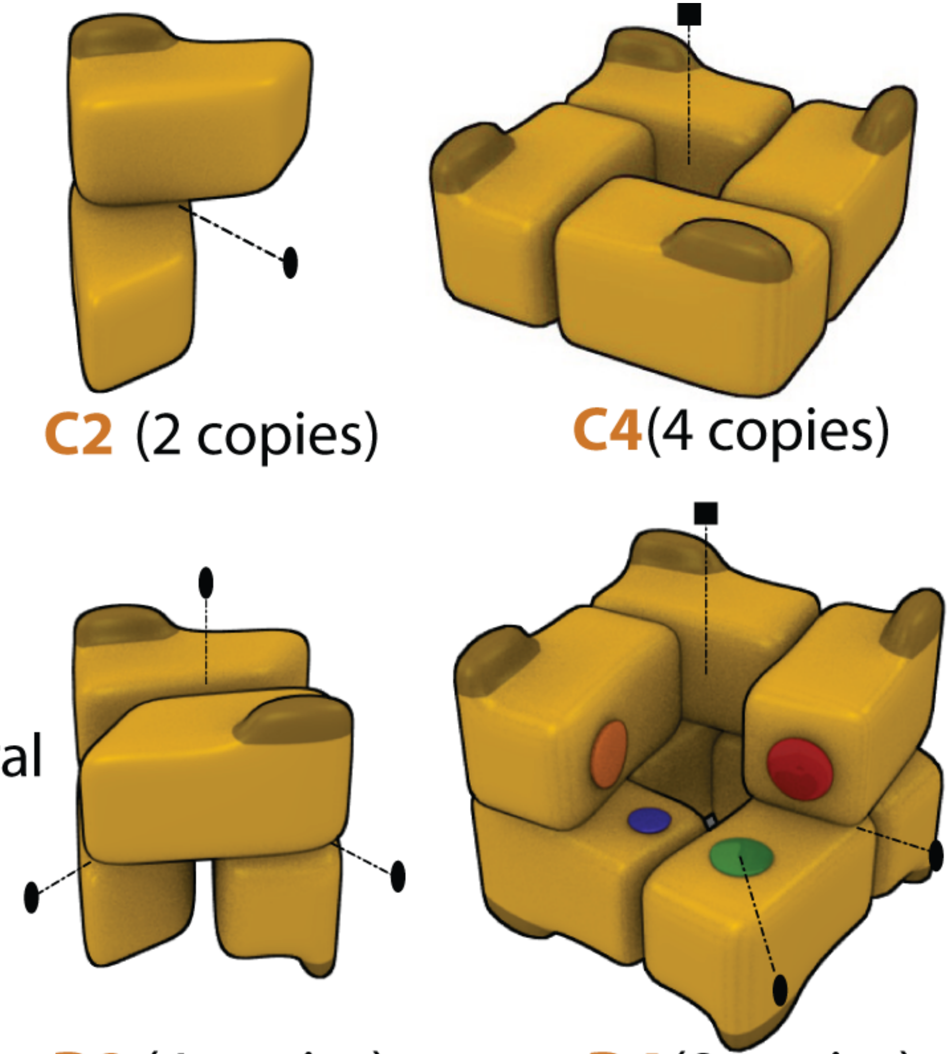
Caspase-9



↓

Apoptosis

Most proteins form symmetric “machines”



Cyclic

C2 (2 copies)

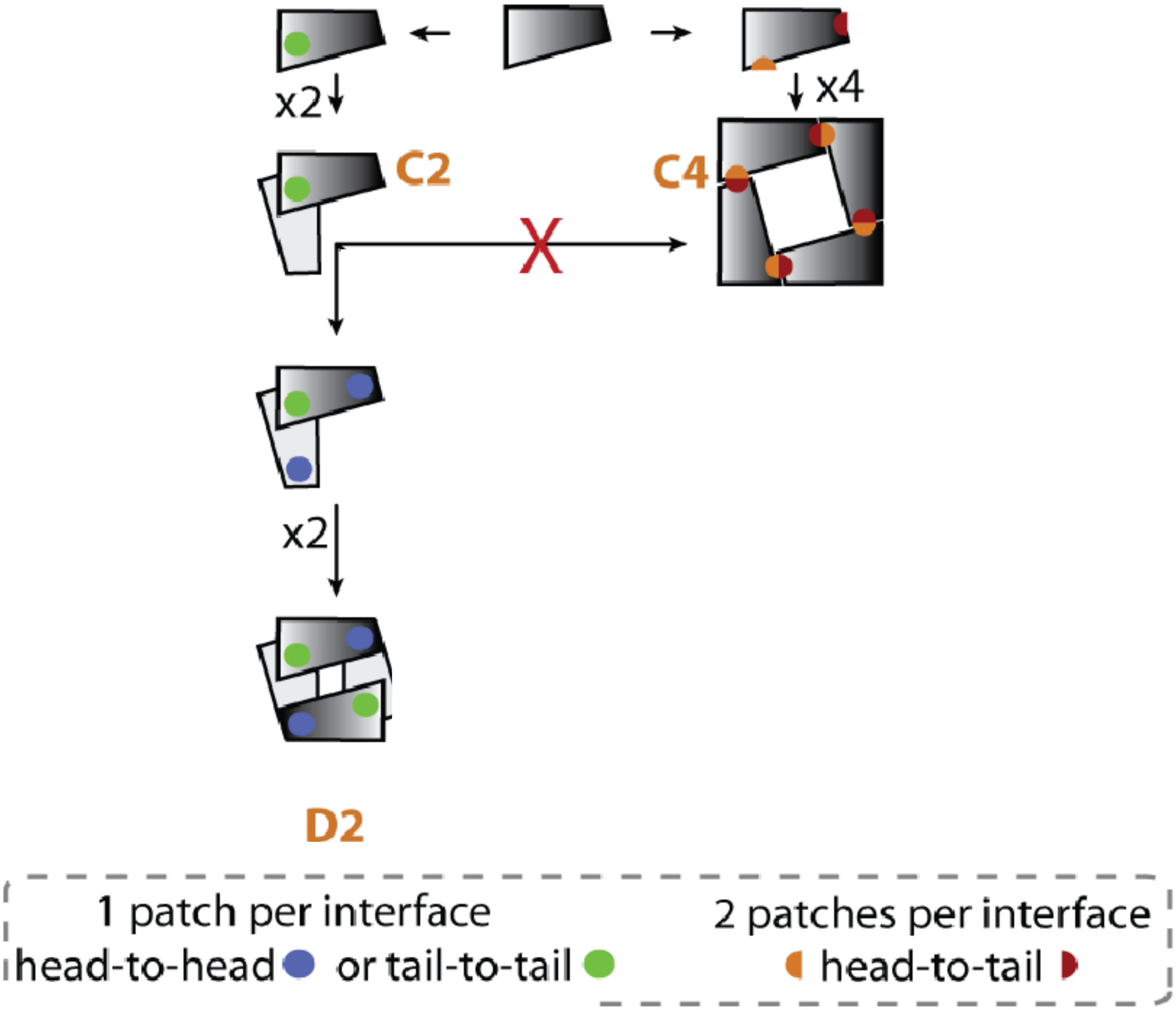
C4(4 copies)

Dihedral

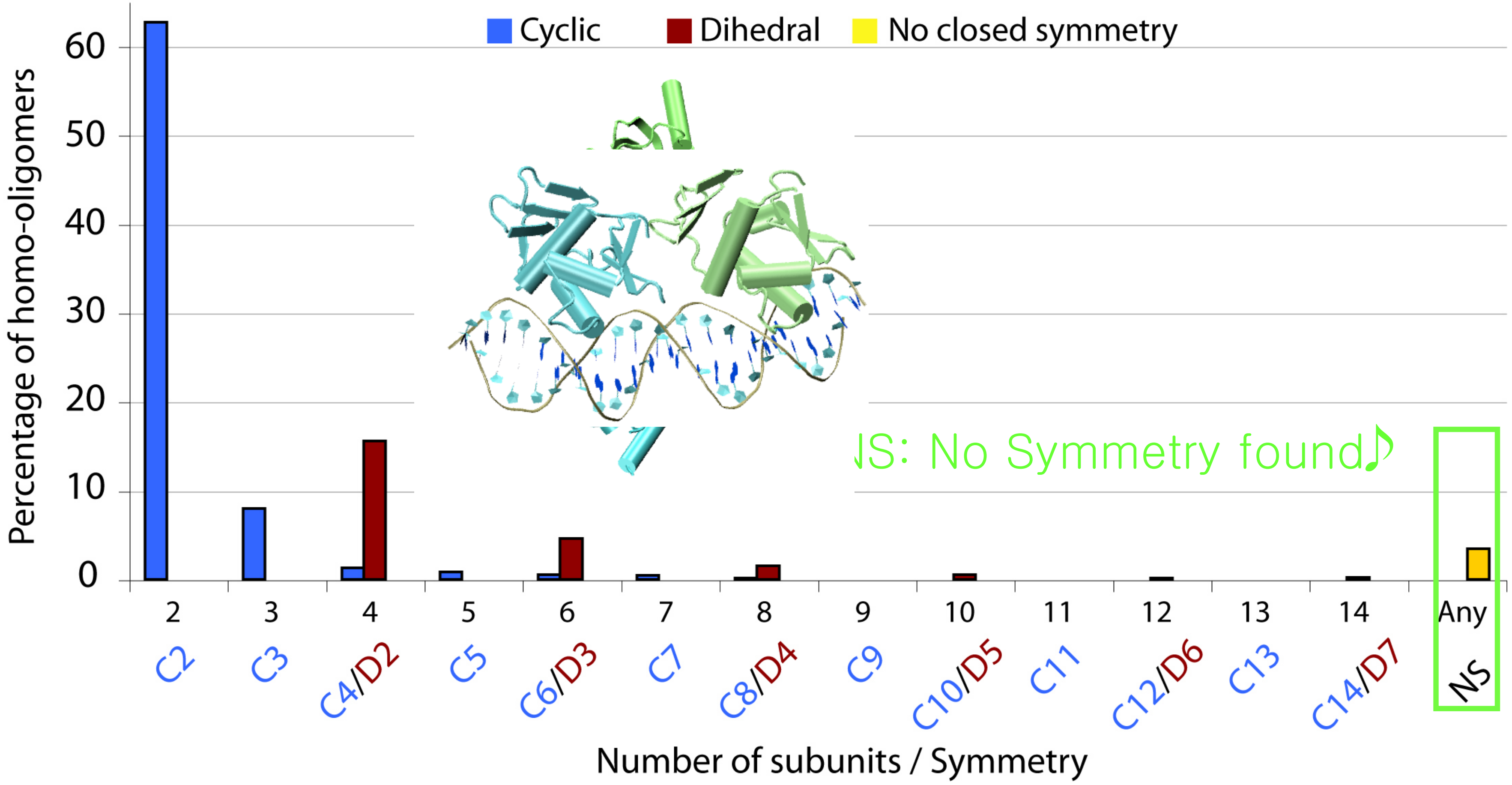
D2 (4 copies)

D4(8 copies)

Evolutionary pathways of complex assembly

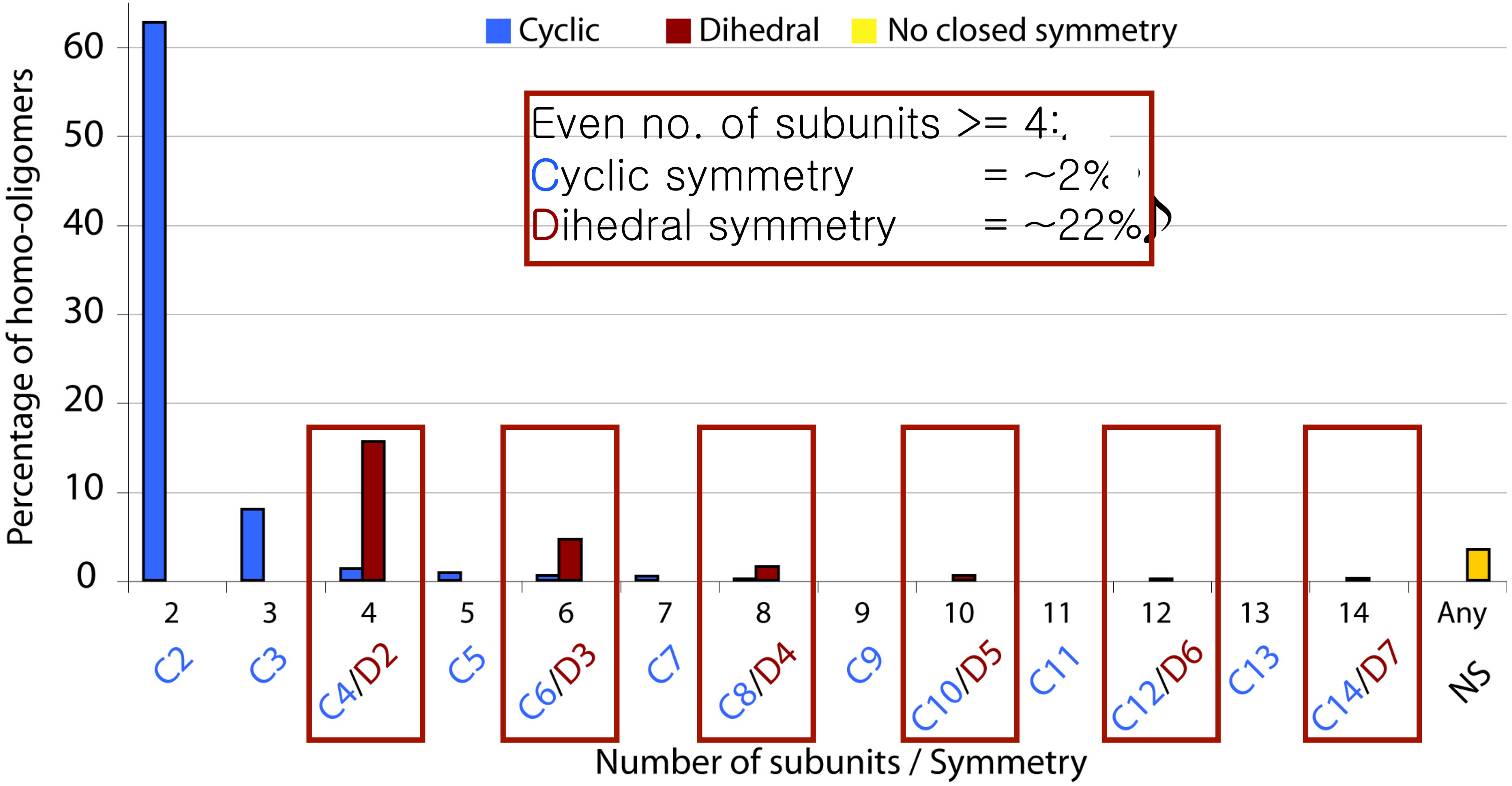


Symmetries found in a non-redundant set of ~2500 complexes



S: No Symmetry found♪

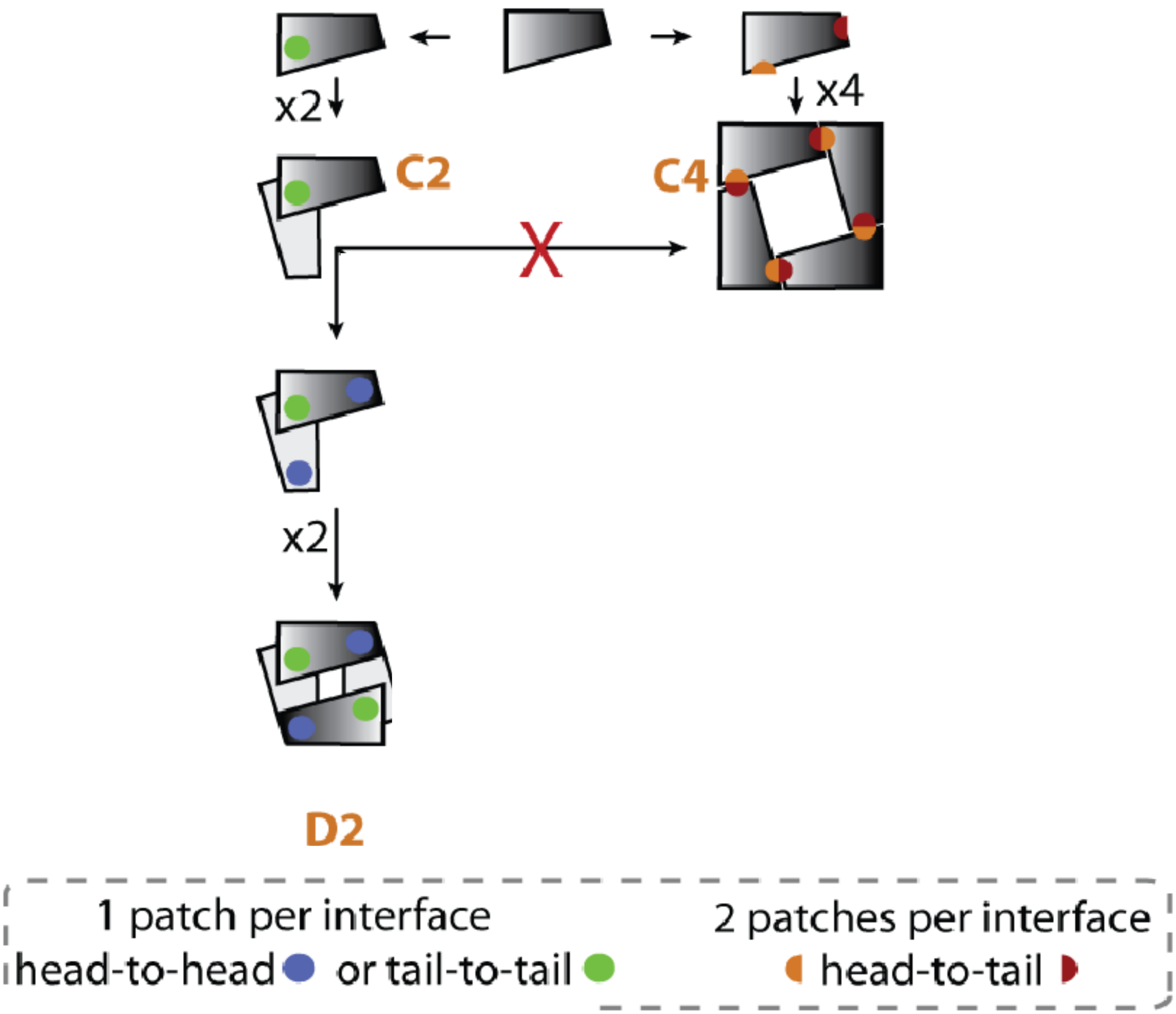
Symmetries found in a non-redundant set of ~2500 complexes



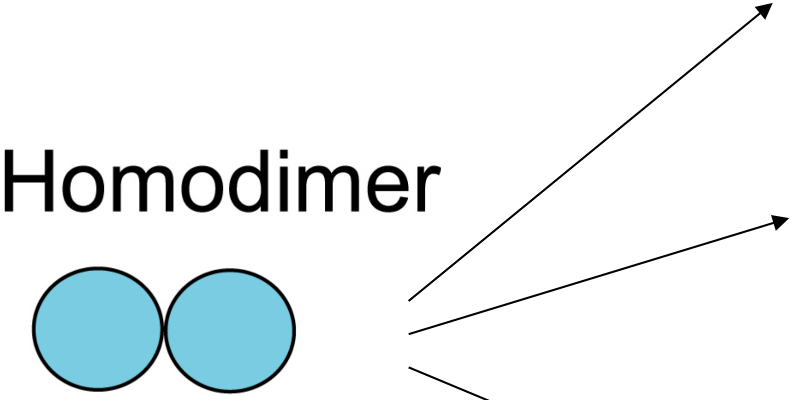
Even no. of subunits >= 4:
Cyclic symmetry = ~2%
Dihedral symmetry = ~22%

When there is a choice, dihedral favoured and ~10x more frequent than cyclic

Evolutionary pathways of complex assembly



Homodimer



Structures 2/3 of proteins homomers

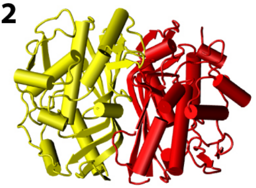
Evolution

Assembly in solution

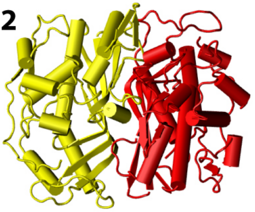
Conservation of Quaternary Structure - Examples

Thymidylate Synthase

C2 *E. coli*



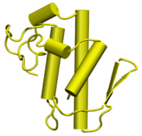
C2 *B. subtilis*



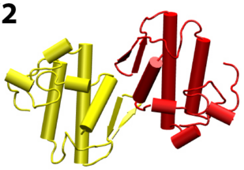
C2 *H. sapiens*

Phospholipase A2

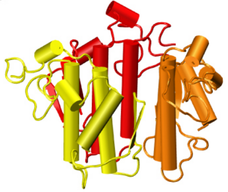
C1 *A. contortrix*



C2 *B. pirajai*



C3 *B. caeruleus*

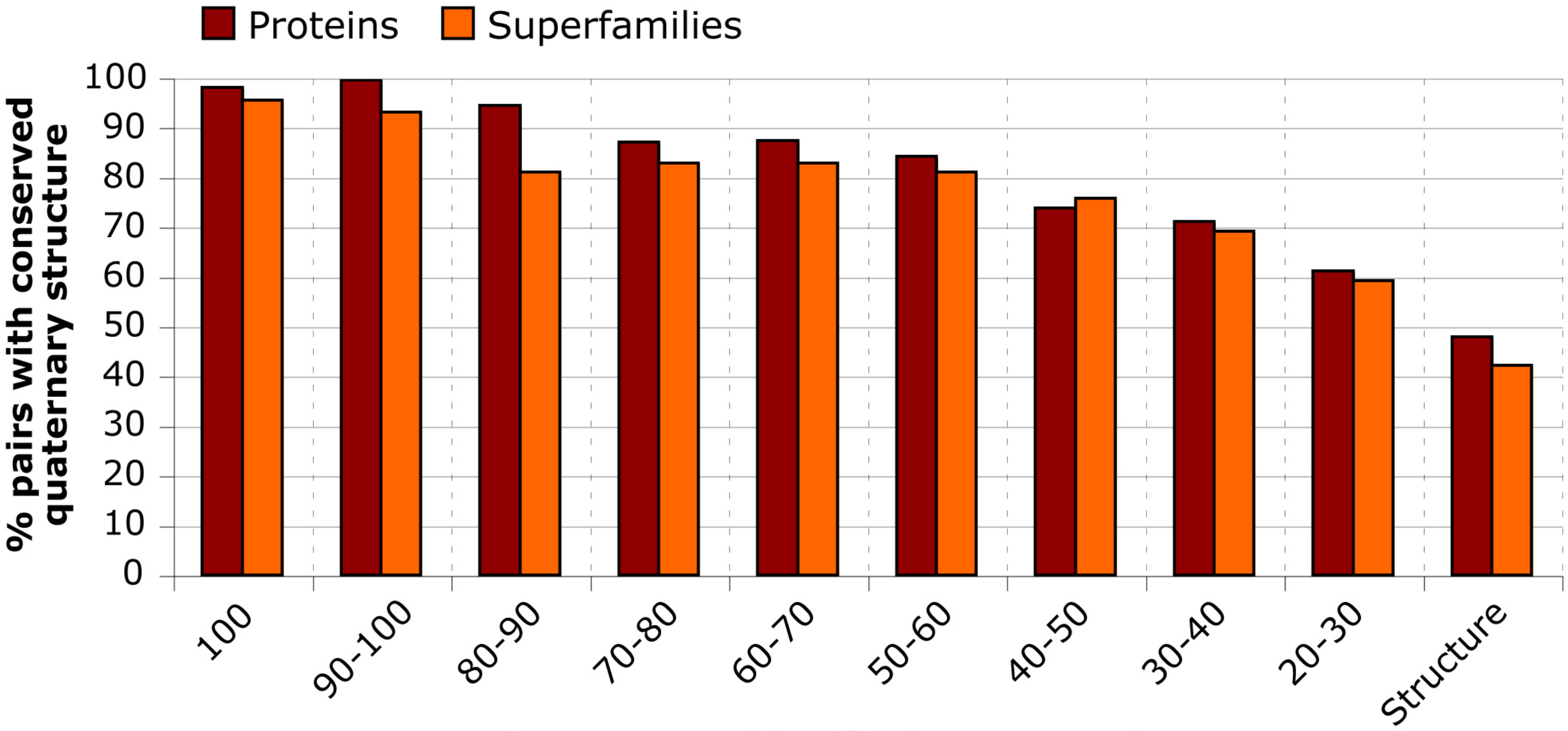


High **Low**

Conservation of Quaternary Structure

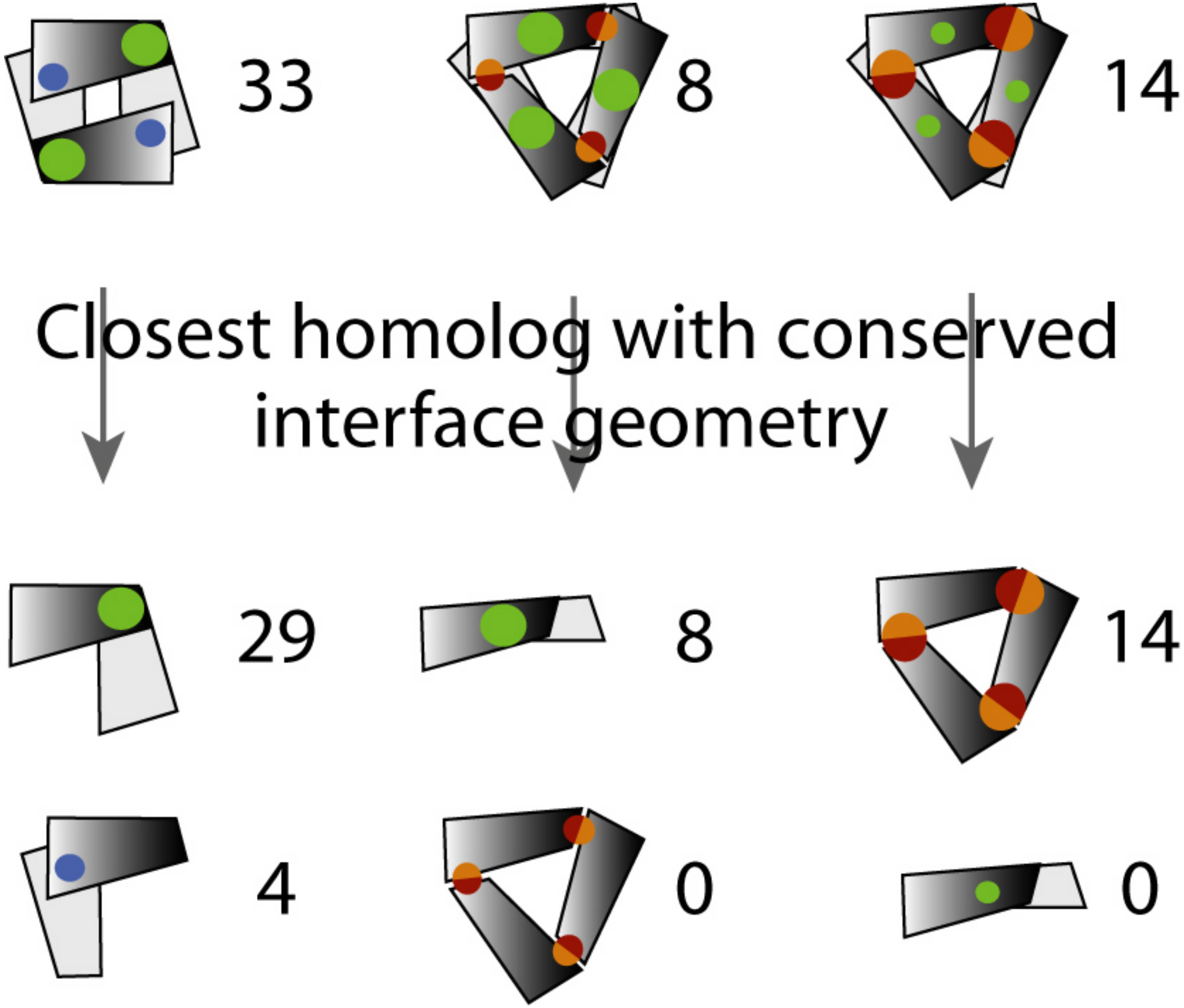
Where do most protein stand on this spectrum?

Conservation of the Quaternary Structure



At 30% sequence identity, 70% of protein pairs conserve quaternary structure

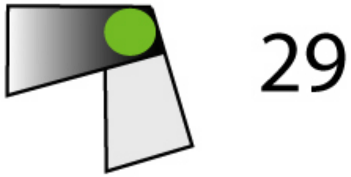
Homology to the largest interface is common

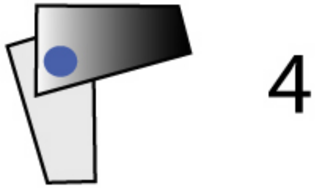


Closest homolog with conserved interface geometry

Levy, E.D., Erba, E.B., Robinson, C.V. & Teichmann, S.A. (2008)
Assembly reflects evolution of protein complexes. *Nature*, 453, 1262-5.

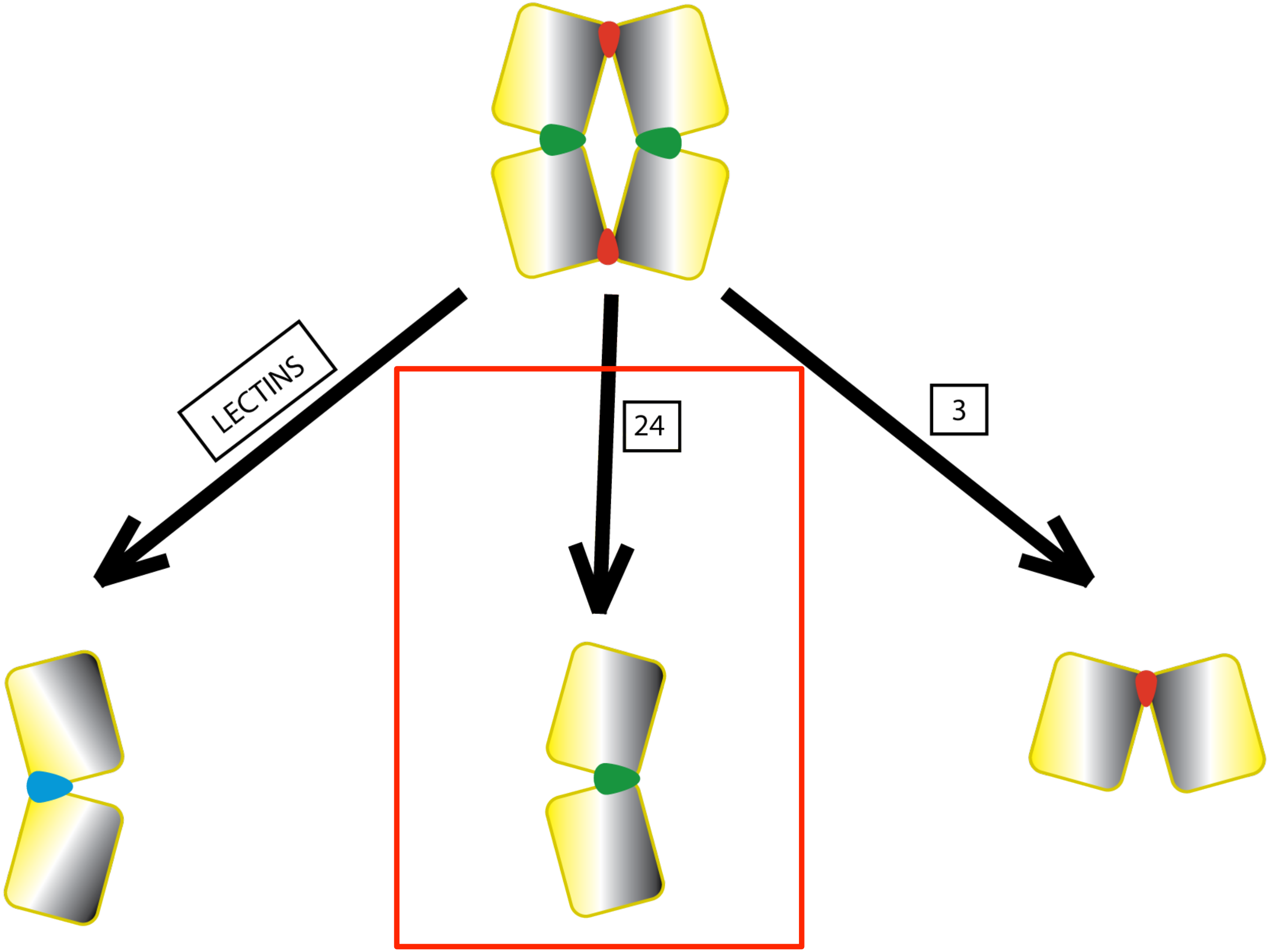
Homology to the largest interface is common



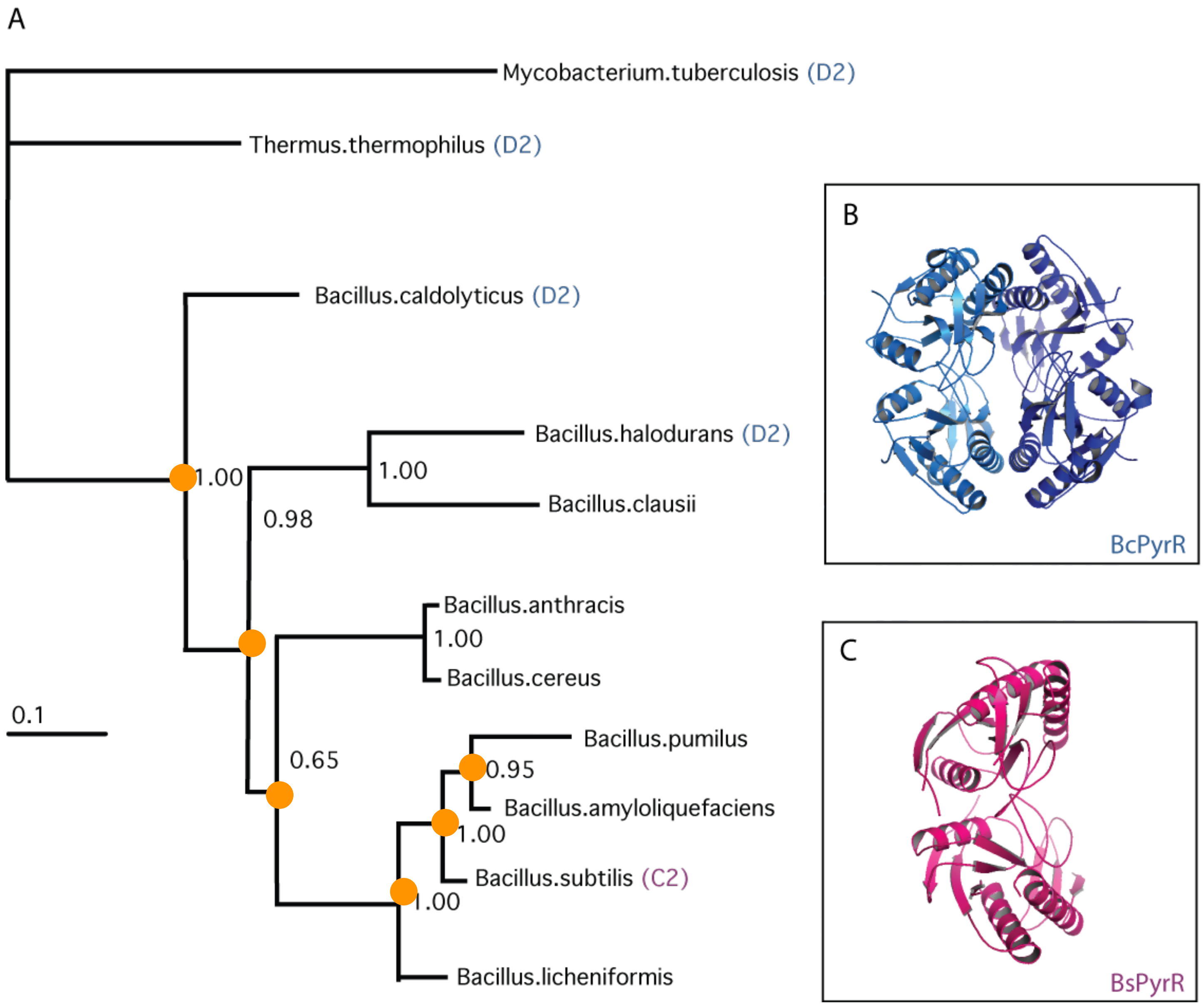


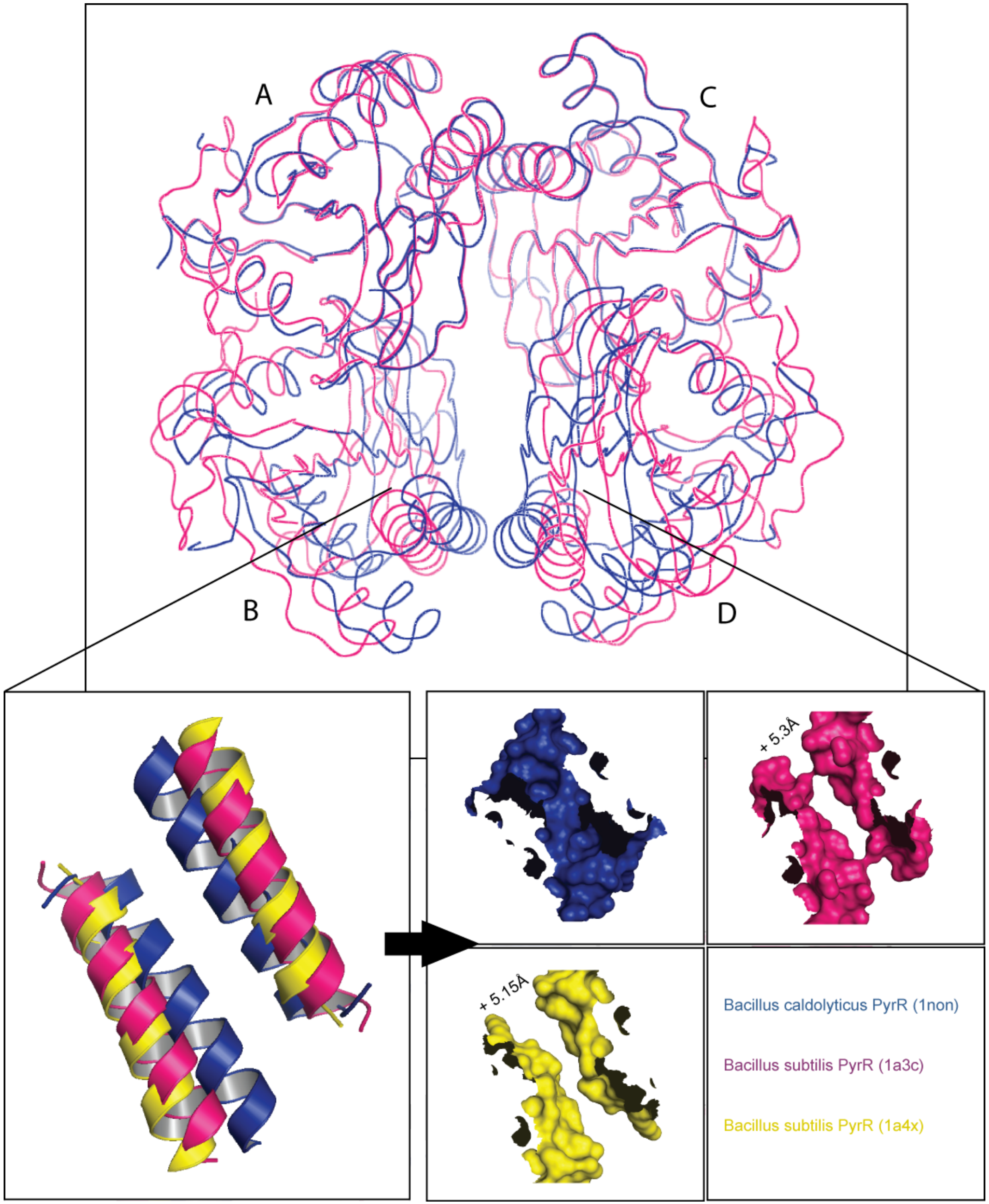
Which mutations change quaternary structures?

Tetramer-dimer pairs with >40% sequence similarity



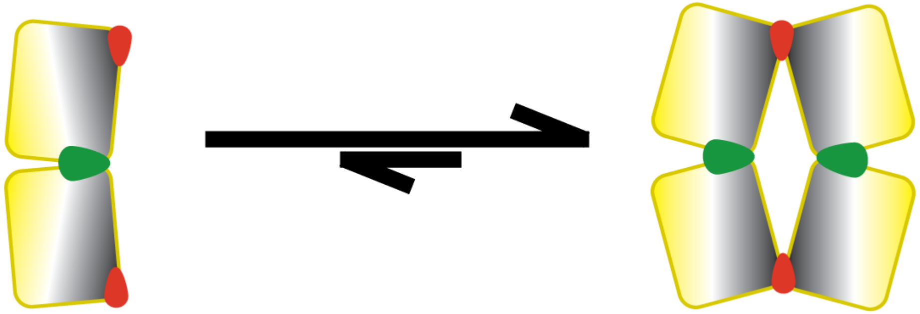
PyrR: Evolvability of Quaternary Structure



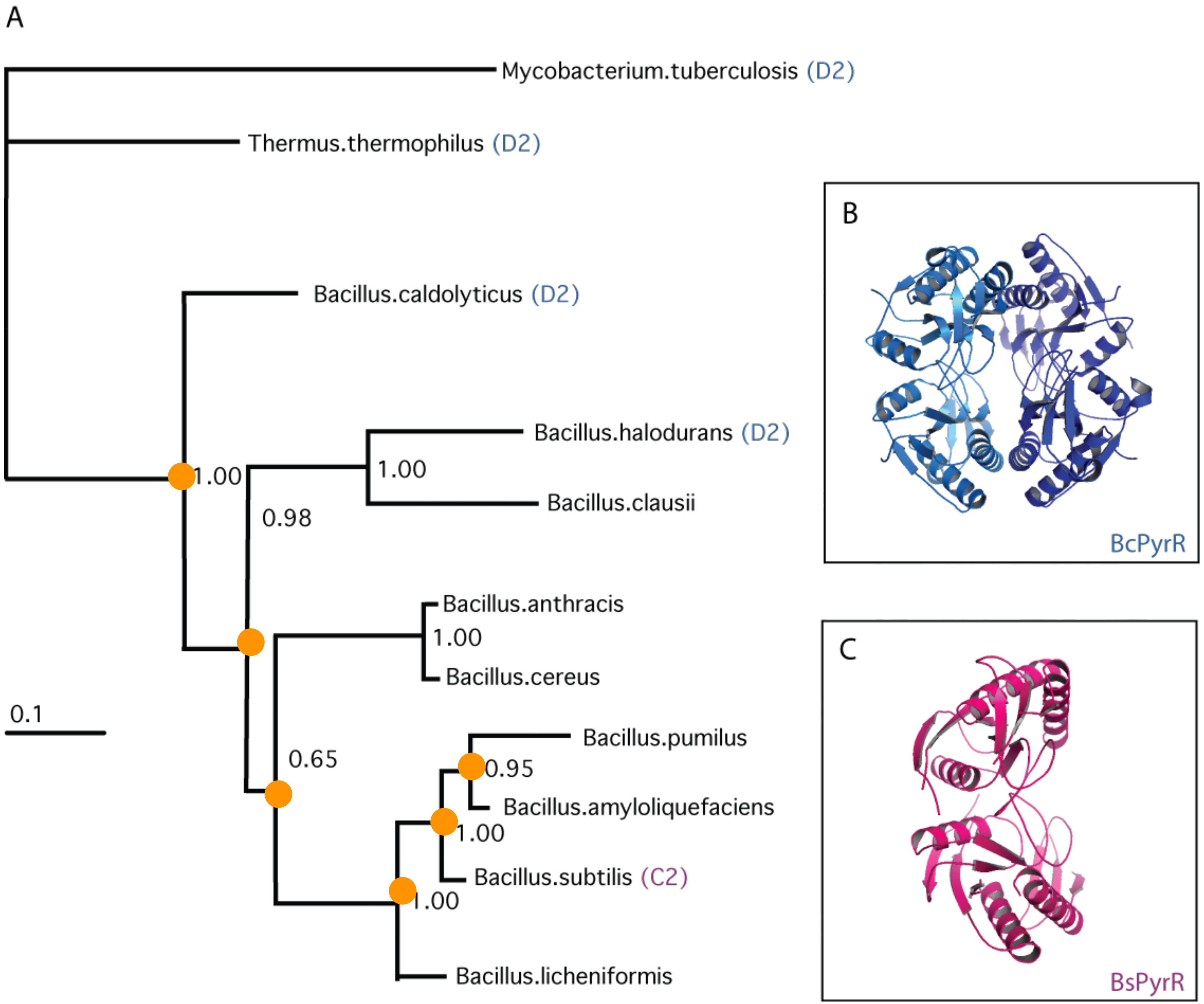

A
C
B
D
+ 5.3Å
+ 5.15Å
Bacillus caldolyticus PyrR (1non)
Bacillus subtilis PyrR (1a3c)
Bacillus subtilis PyrR (1a4x)

Coupling of Interfaces

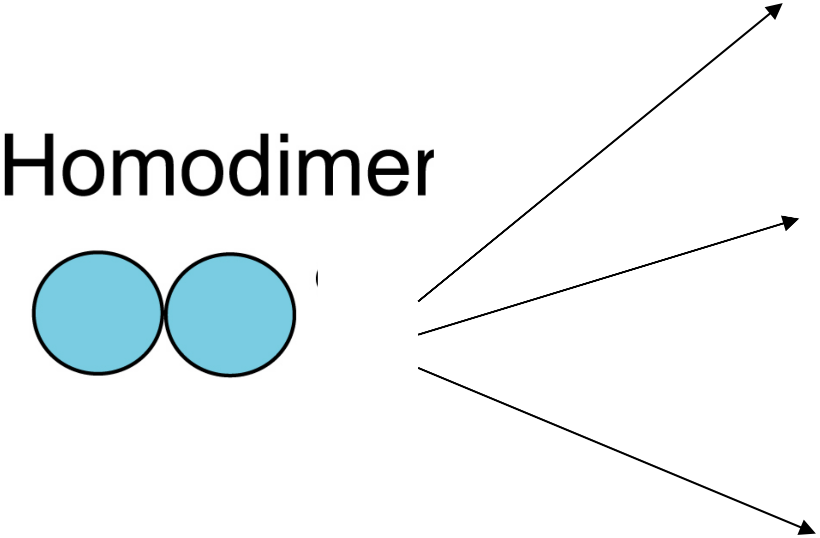
Tetramer



PyrR: Evolvability of Quaternary Structure



Homodimer

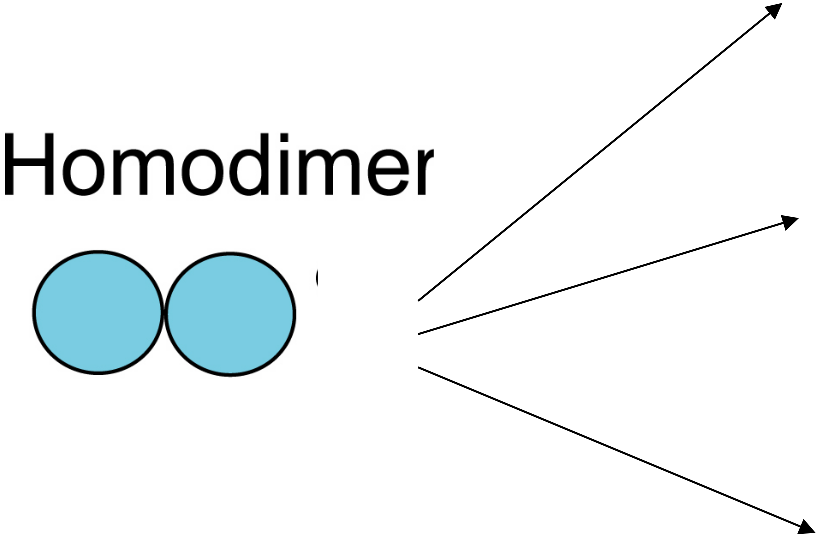


Structures 2/3 of proteins homomers

Evolution
Conservation 4° struc/seq
Cons. of large interfaces
Change in angle - rewiring

Assembly in solution

Homodimer



Structures 2/3 of proteins homomers

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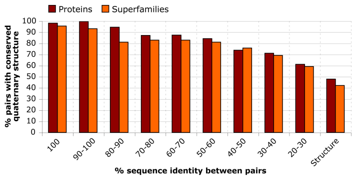
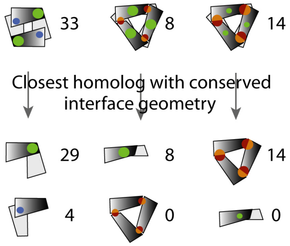
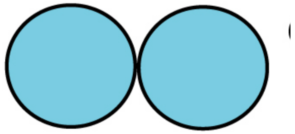




- •Predict quaternary structure by homology
- •Predict interface geometry for divergent homologues

Homodimer

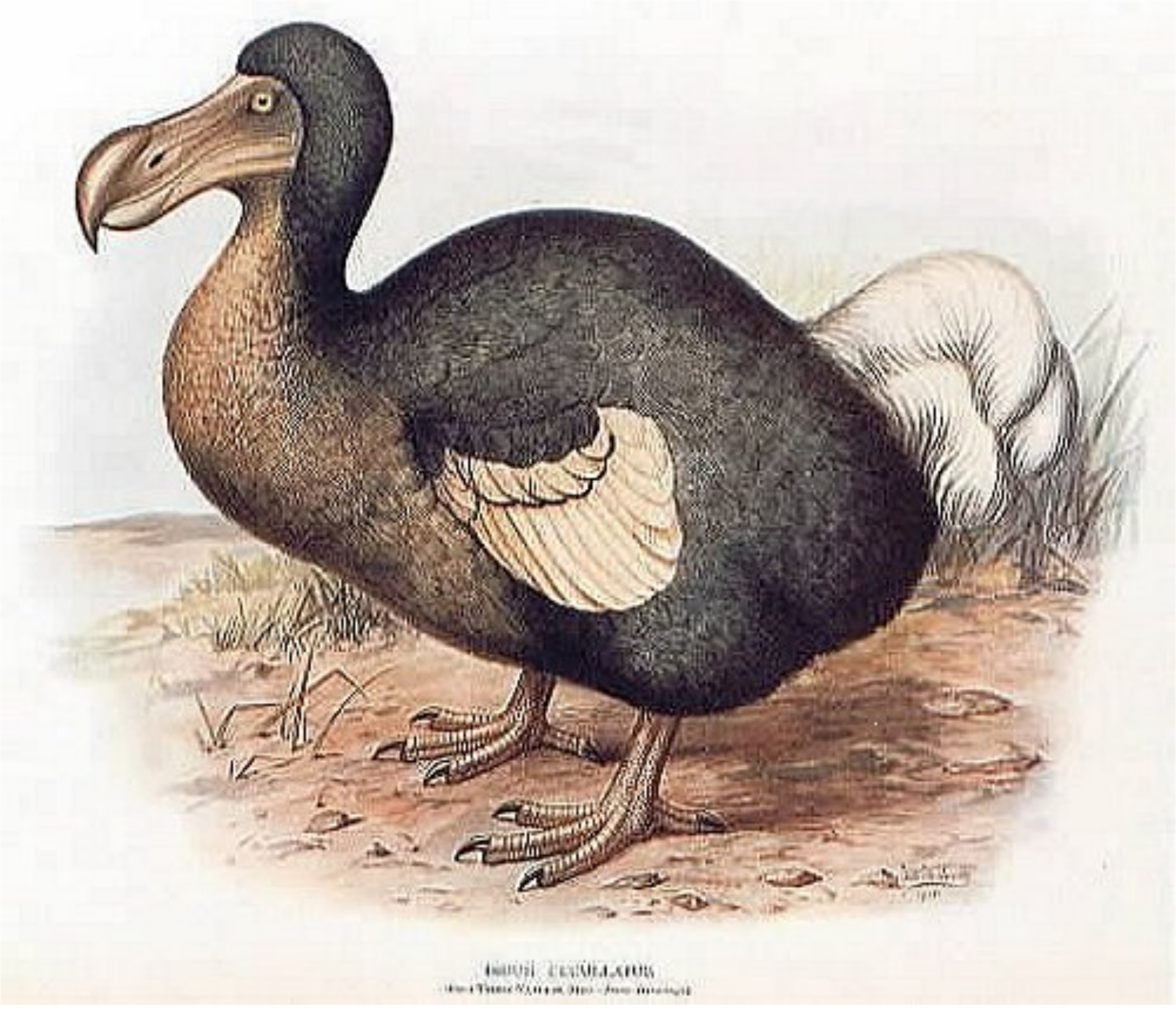


Structures 2/3 of proteins homomers

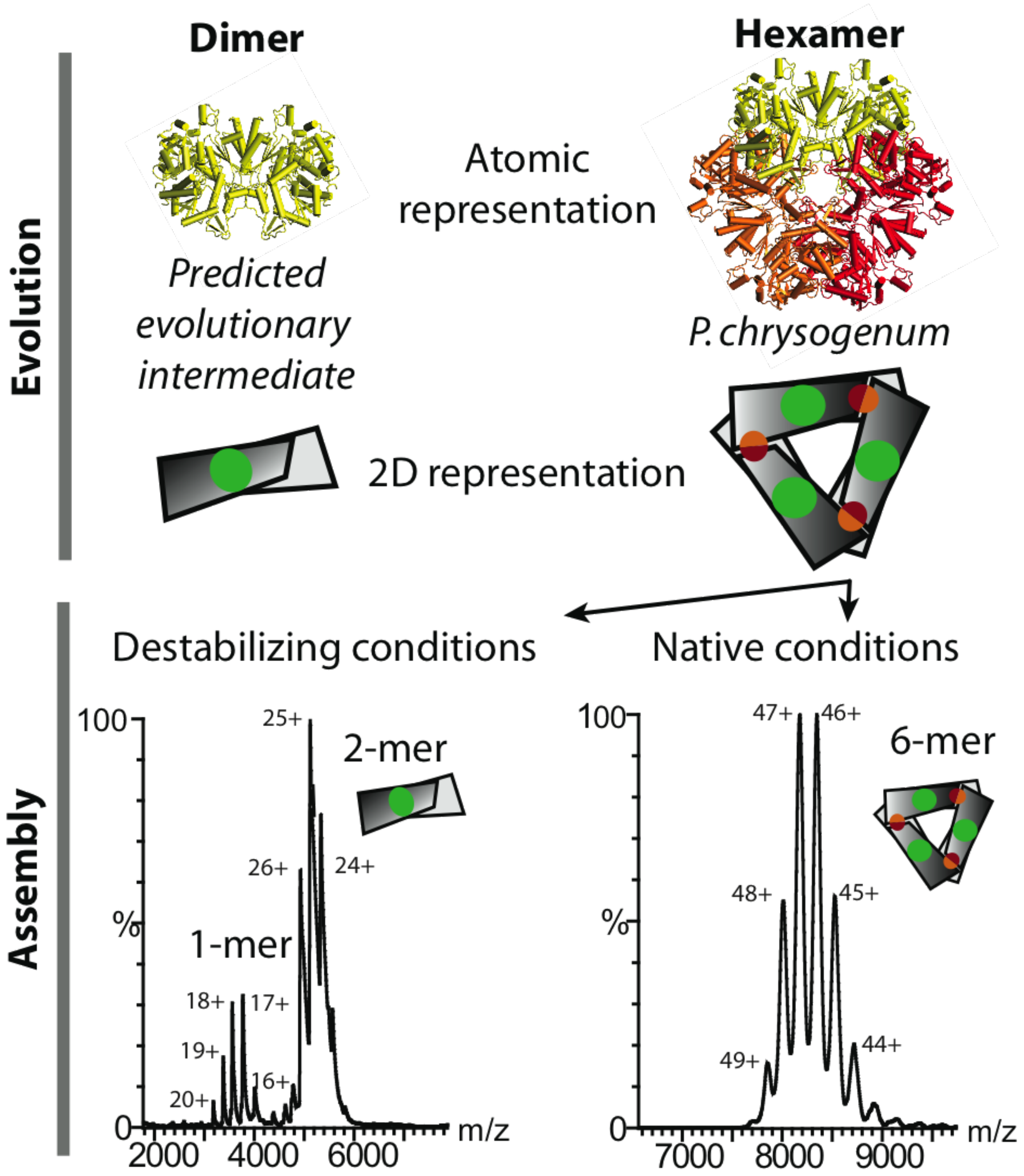
Evolution **Cons. of large interfaces**

Assembly in solution

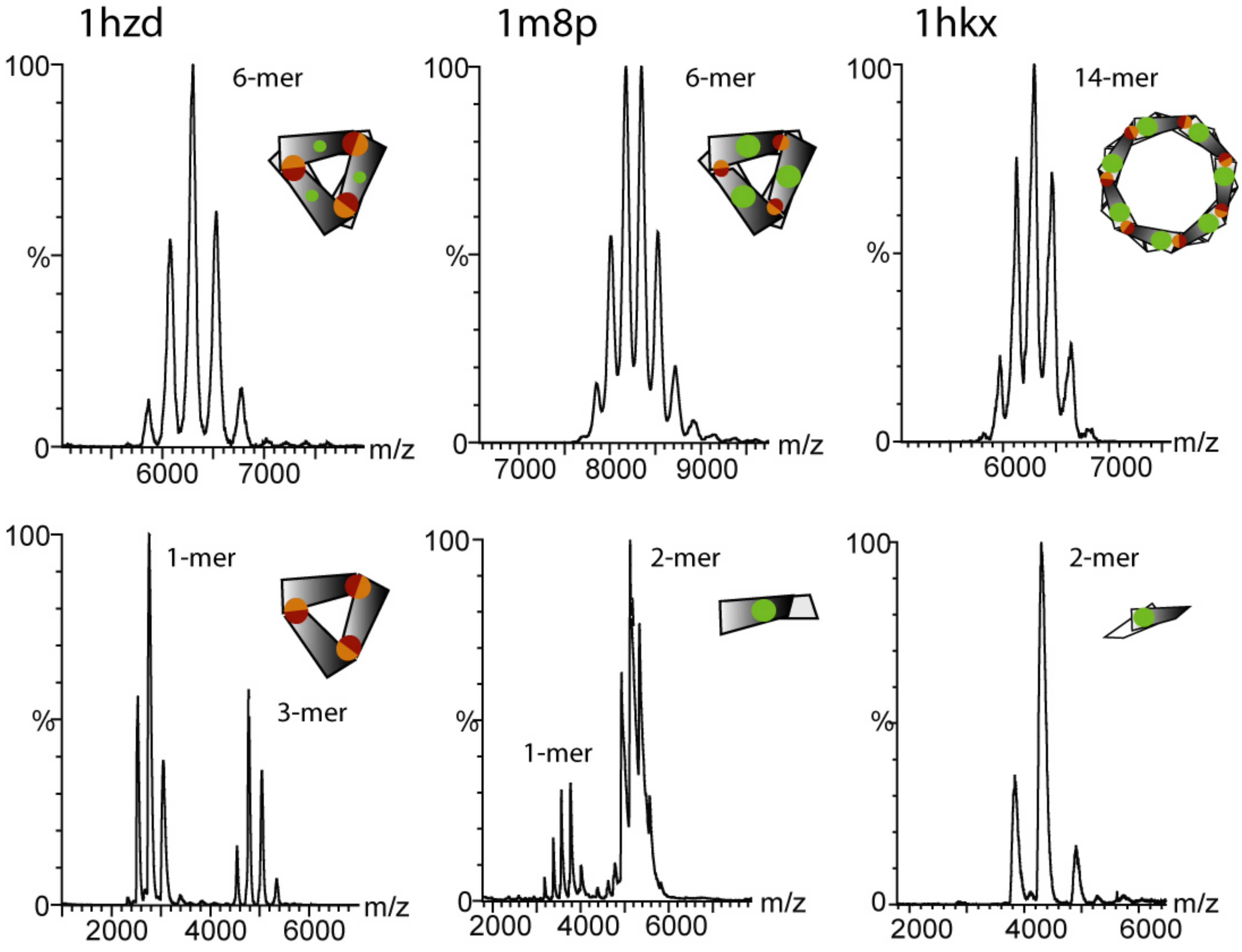
Conservation of largest interface – An evolutionary relic?



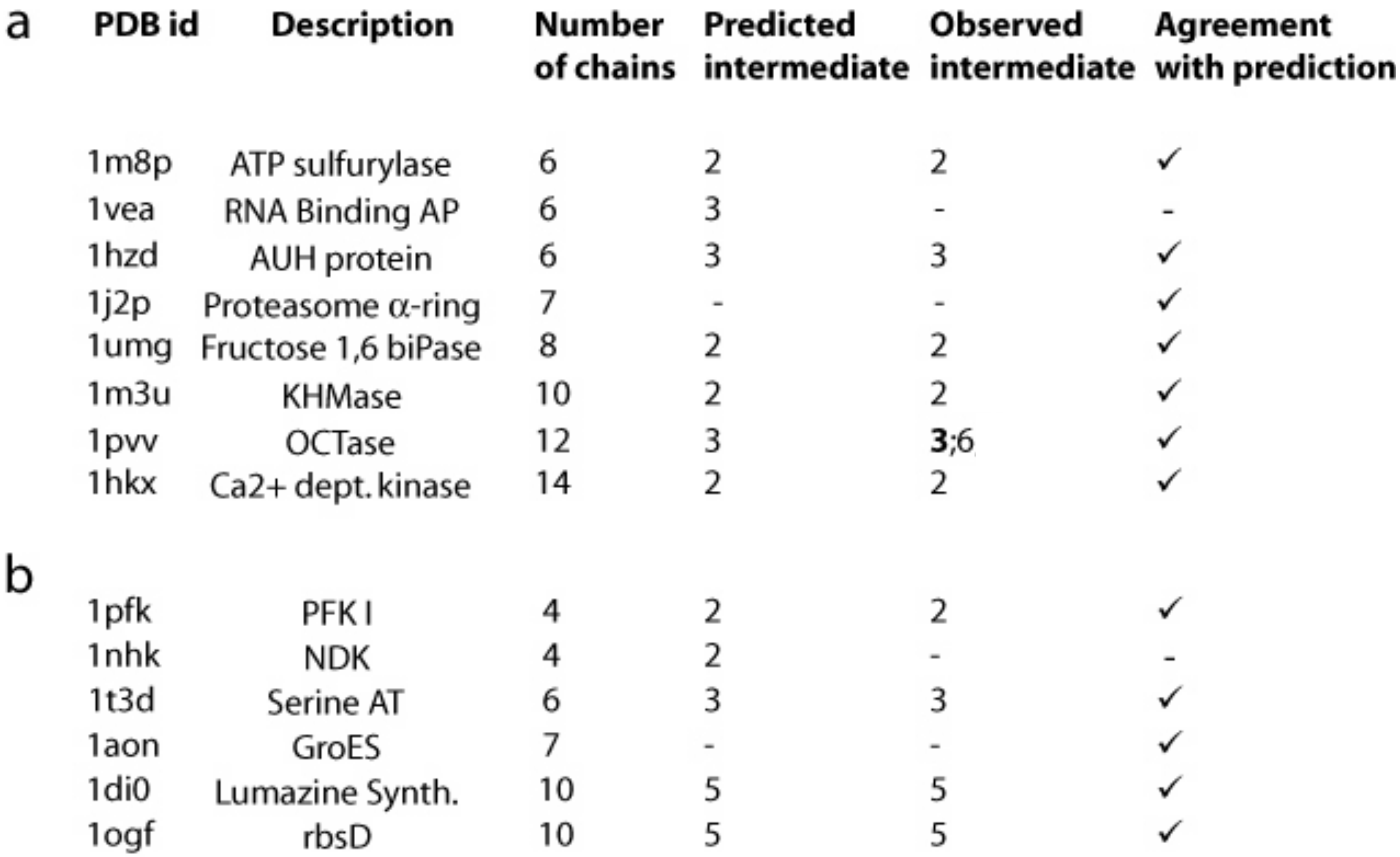
Evolution predicts assembly pathway



Macromolecular mass spectrometry (E.B. Erba & C.V. Robinson)



Complexes with characterised assembly pathways - agreement with predictions

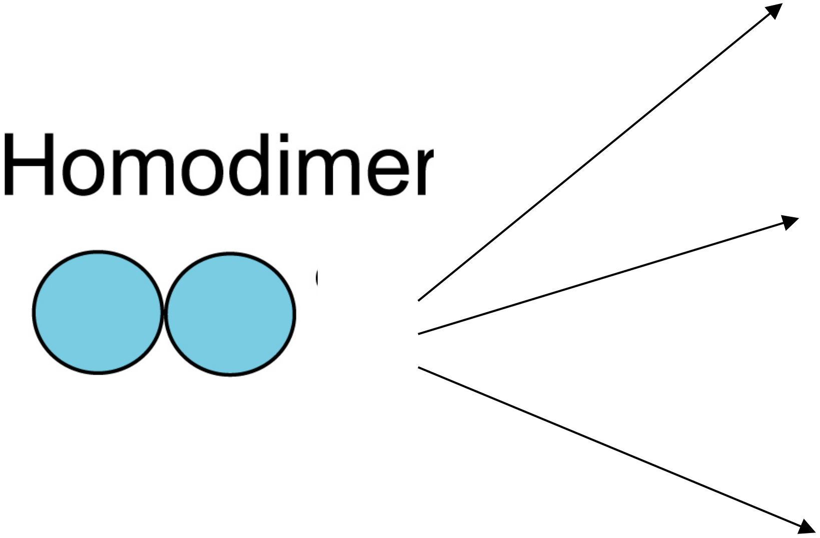


a	PDB id	Description	Number of chains	Predicted intermediate	Observed intermediate	Agreement with prediction
	1m8p	ATP sulfurylase	6	2	2	✓
	1vea	RNA Binding AP	6	3	-	-
	1hzd	AUH protein	6	3	3	✓
	1j2p	Proteasome α-ring	7	-	-	✓
	1umg	Fructose 1,6 biPase	8	2	2	✓
	1m3u	KHMase	10	2	2	✓
	1pvv	OCTase	12	3	**3**;6	✓
	1hkx	Ca2+ dept. kinase	14	2	2	✓
b						
	1pfk	PFK I	4	2	2	✓
	1nhk	NDK	4	2	-	-
	1t3d	Serine AT	6	3	3	✓
	1aon	GroES	7	-	-	✓
	1di0	Lumazine Synth.	10	5	5	✓
	1ogf	rbsD	10	5	5	✓

Levy, E.D., Erba, E.B., Robinson, C.V. & Teichmann, S.A. (2008)

Assembly reflects evolution of protein complexes. *Nature*, 453, 1262-5.

Homodimer



Structures 2/3 of proteins homomers

Evolution Cons. of large interfaces

Assembly in solution via conserved intermediates

Interface size as unifying principle of evolution & assembly

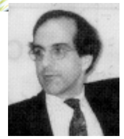
Acknowledgements

- **Jose B. Pereira-Leal,Gulbenkian Insitute, Lisbon**

- **Emmanuel D. Levy, MRC-LMB**

- **Tina Perica, MRC-LMB**

- **Cyrus Chothia, MRC-LMB**



- Carol Robinson, Dept Chemistry, Oxford,

- Elisabetta Boeri Erba, Dept Chemistry, Cambridge

A brief reminder of symmetry