The molecular basis of meiotic chromosome synapsis by SYCP1

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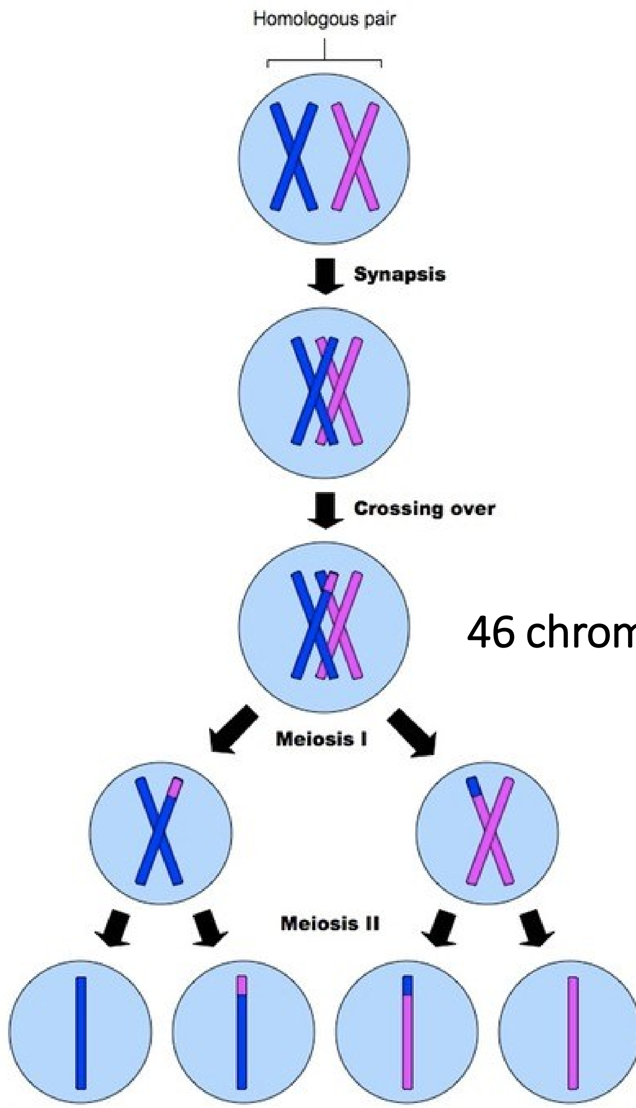
Meiotic cell division



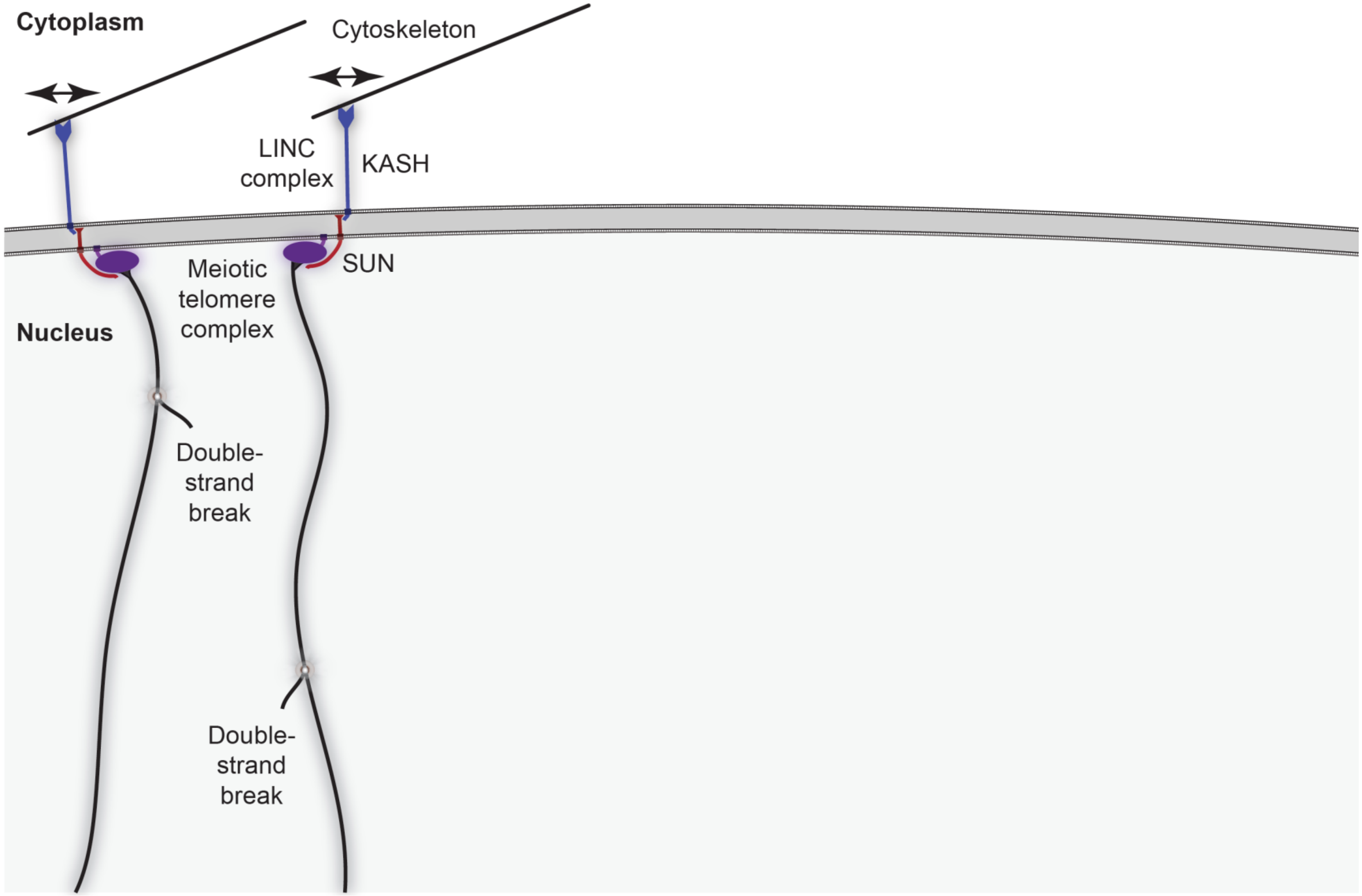
46 chromosomes

23 chromosomes

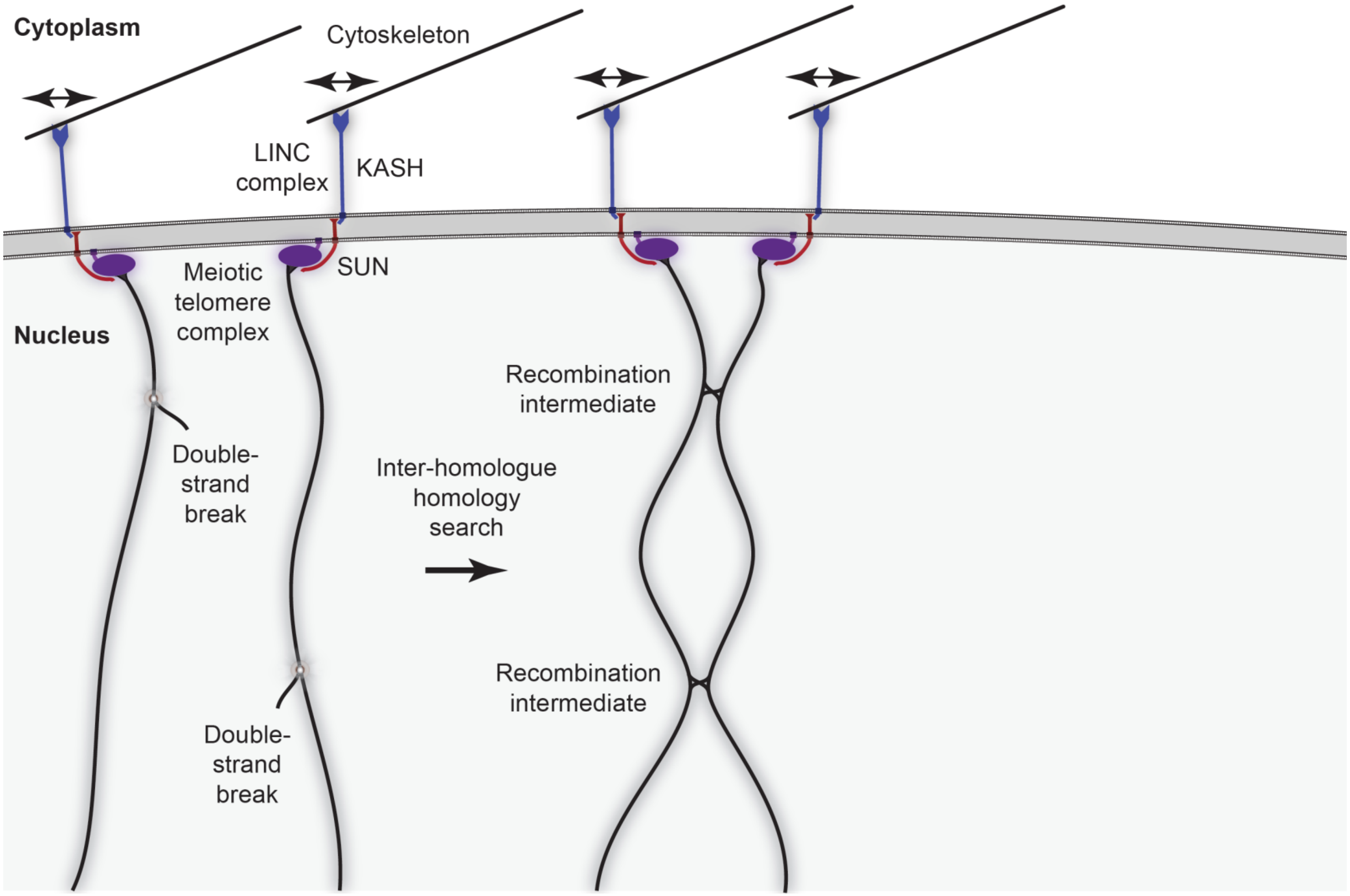
23 sister chromatids

Oocytes/spermatozoa

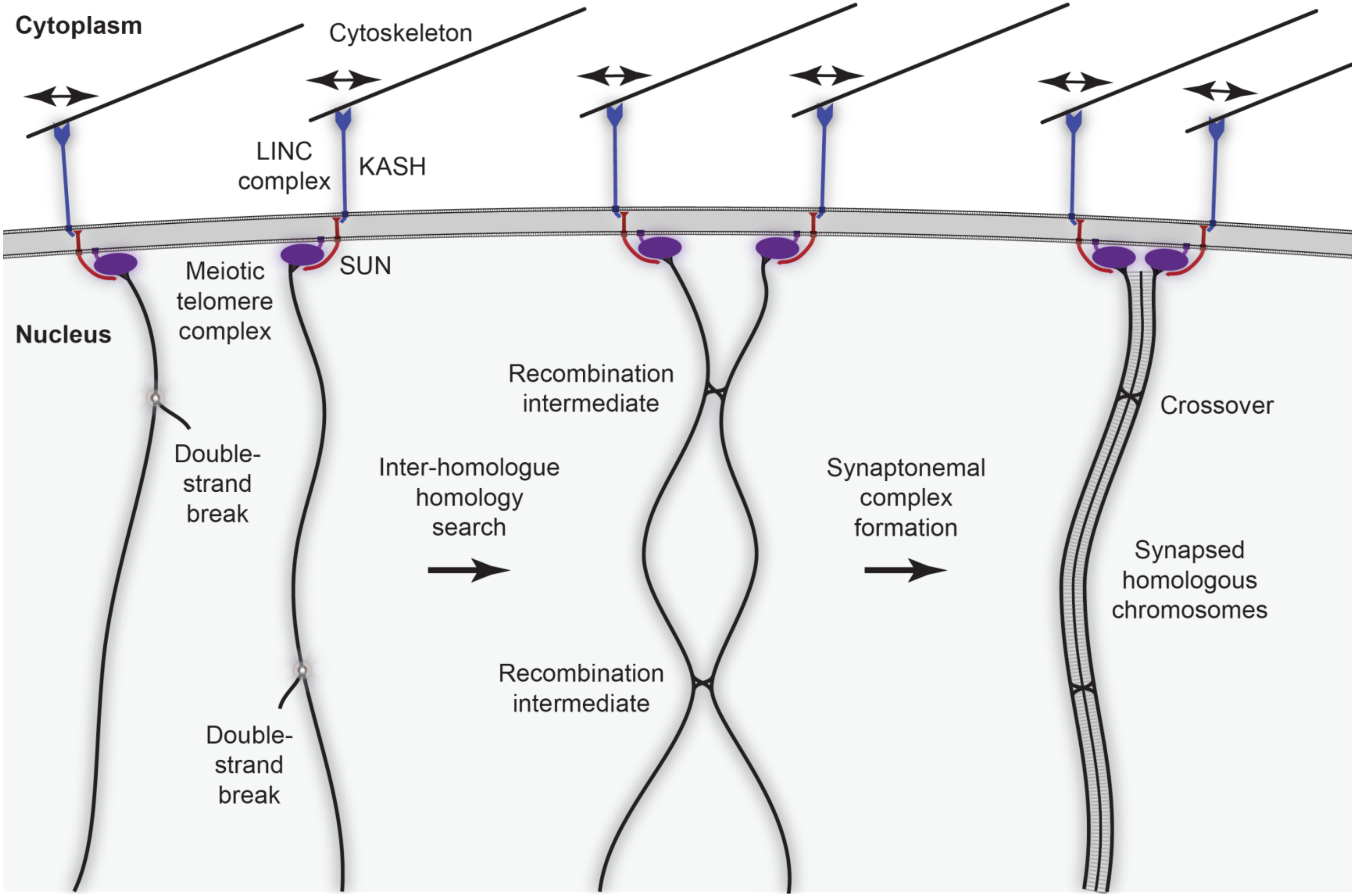
Establishment of homology pairs during mammalian meiosis



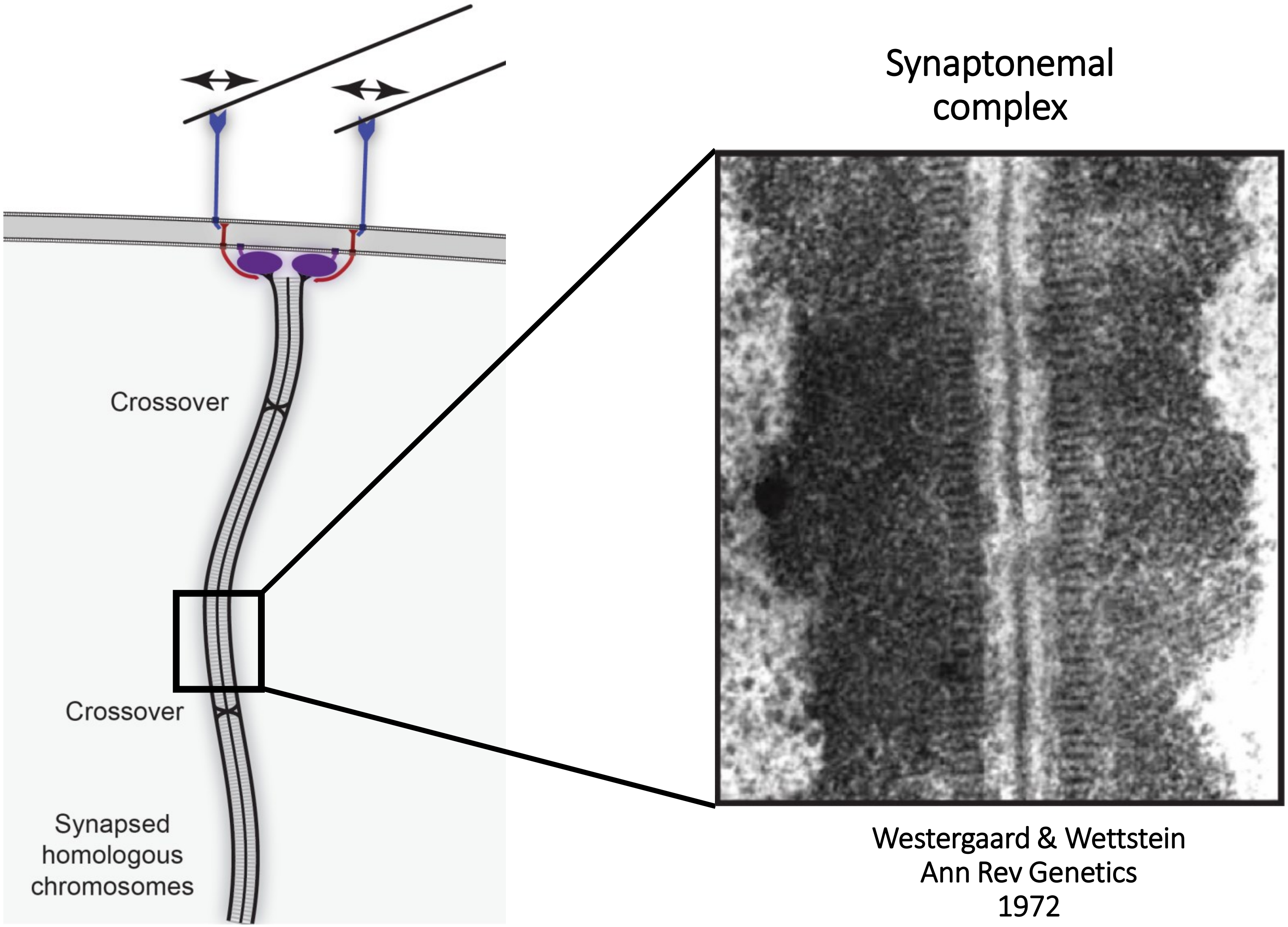
Establishment of homology pairs during mammalian meiosis



Establishment of homology pairs during mammalian meiosis

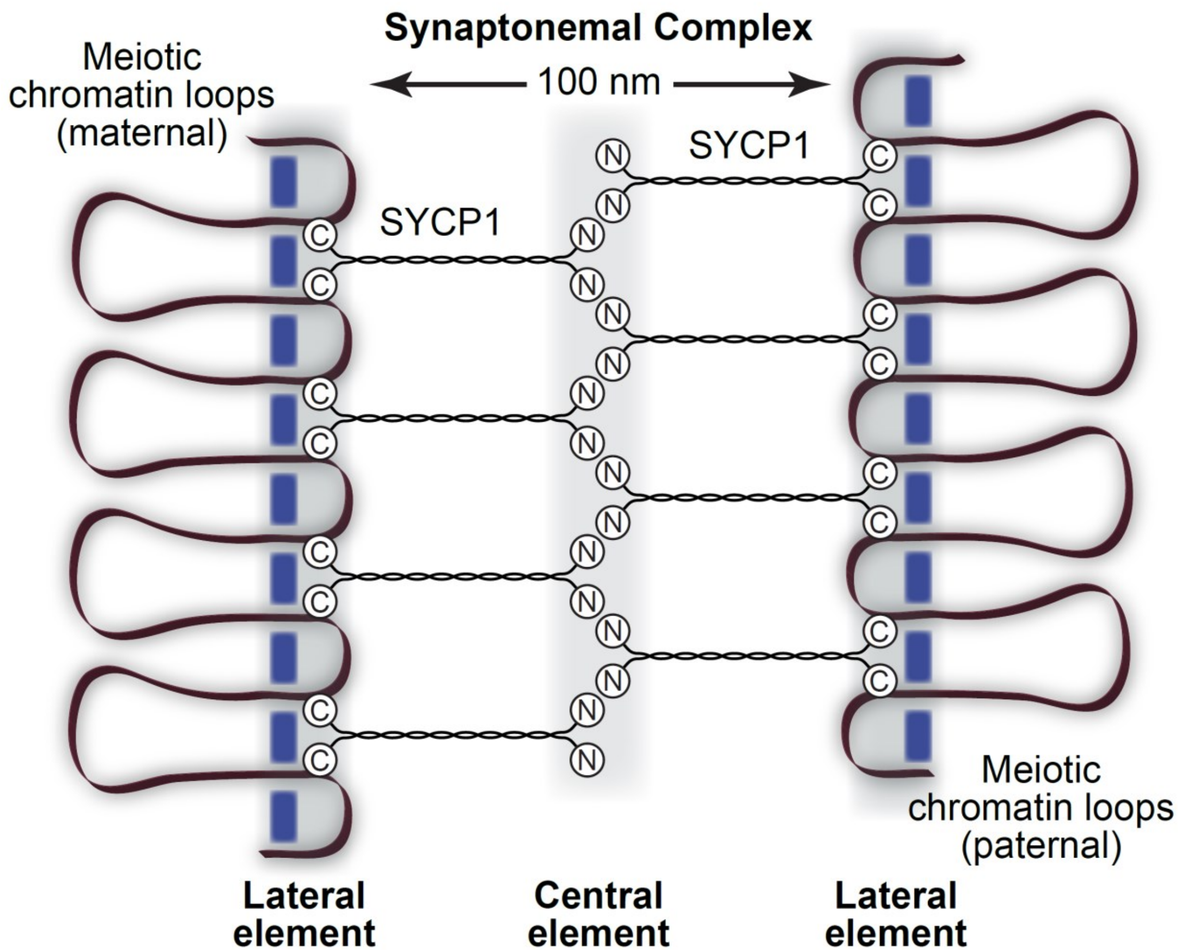


The synaptonemal complex



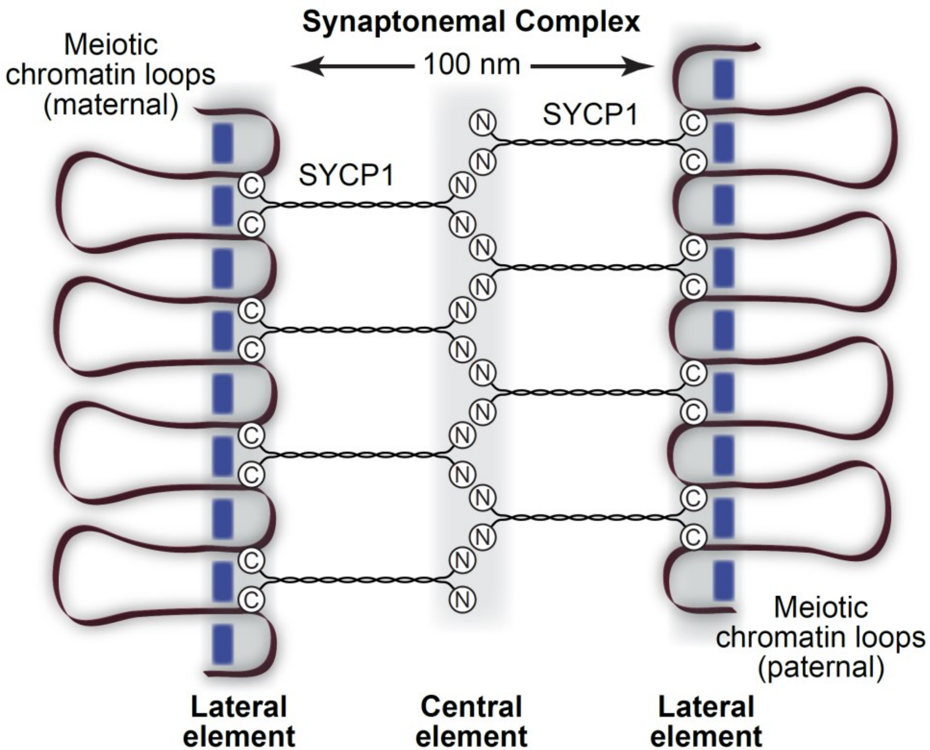
Westergaard & Wettstein
Ann Rev Genetics
1972

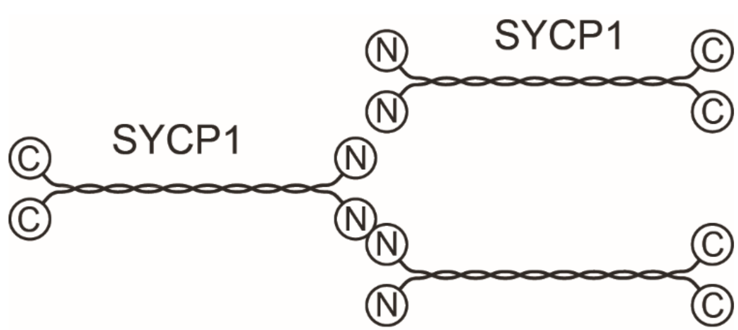
The structure of the mammalian synaptonemal complex (SC)



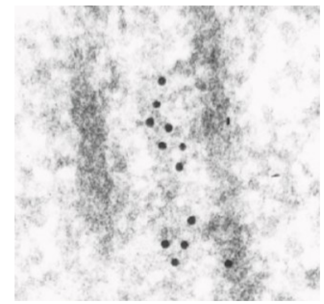
SYCP2	SYCE3	SYCP2
SYCP3	SYCE1-SIX6OS1	SYCP3
	SYCE2-TEX12	

Mammalian SYCP1

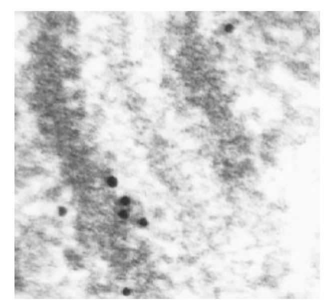




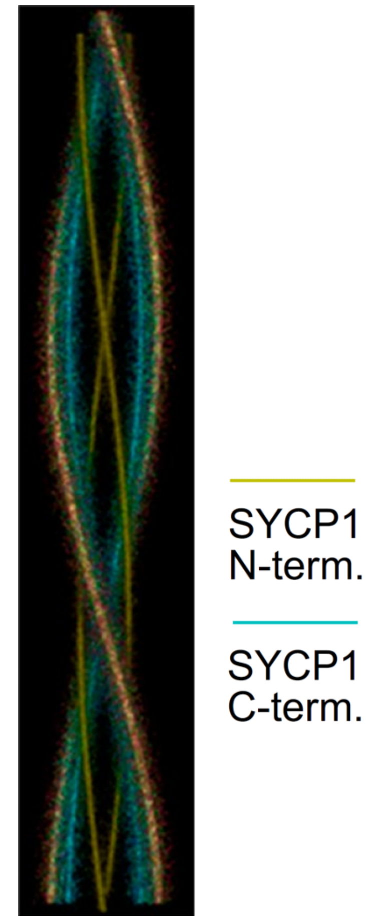
anti-SYCP1-N



anti-SYCP1-C

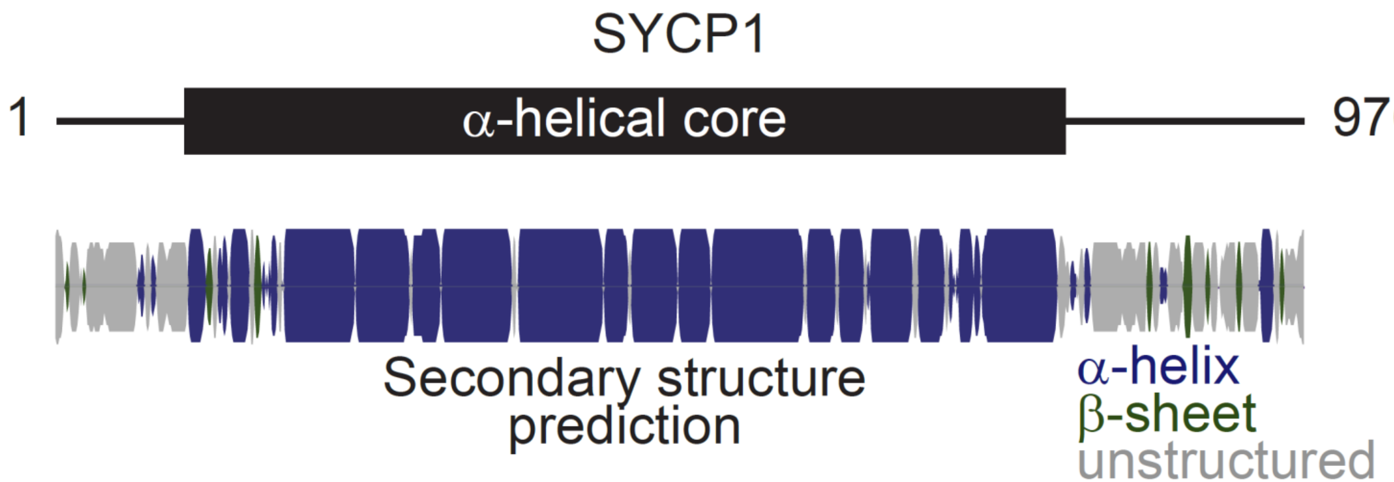


Schmekel *et al*
1996 *Exp Cell Res*

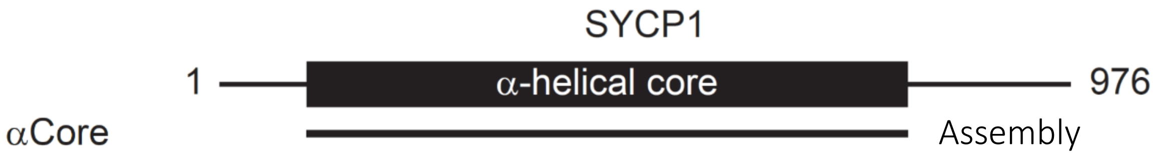


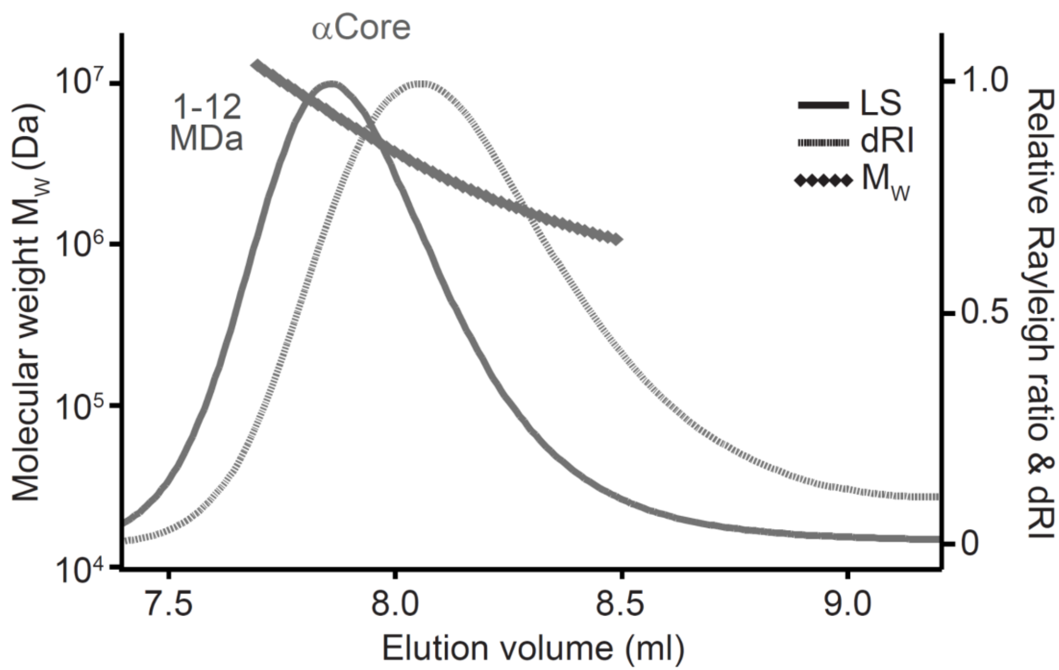
Schücker *et al*
2015 *PNAS*

Human SYCP1


SYCP1
1
α-helical core
976
Secondary structure prediction
α-helix
β-sheet
unstructured

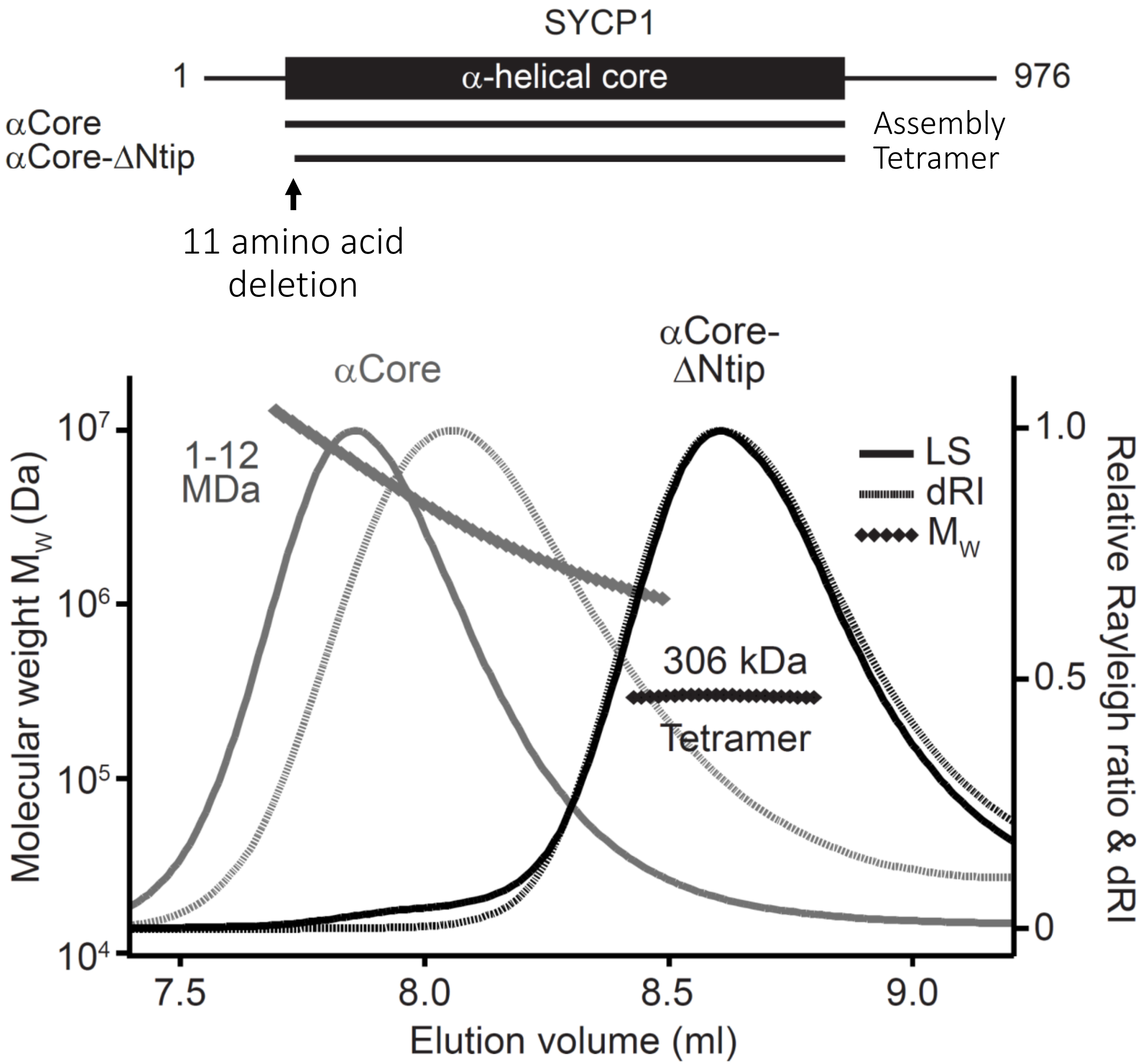
SYCP1 core undergoes self-assembly





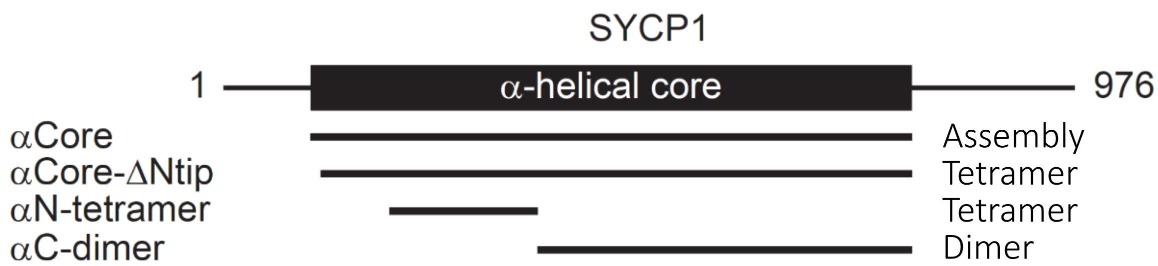
Size-exclusion chromatography
multi-angle light scattering
(SEC-MALS)

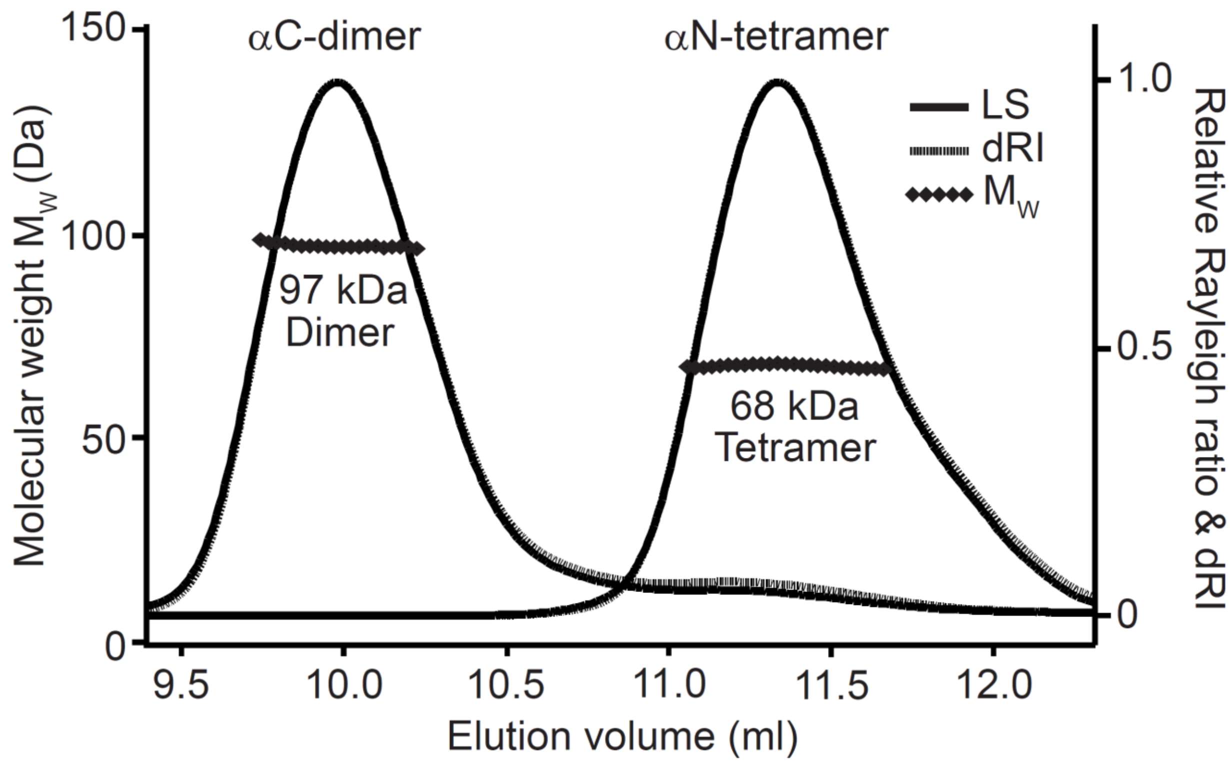
SYCP1 is an obligate tetramer



SEC-MALS

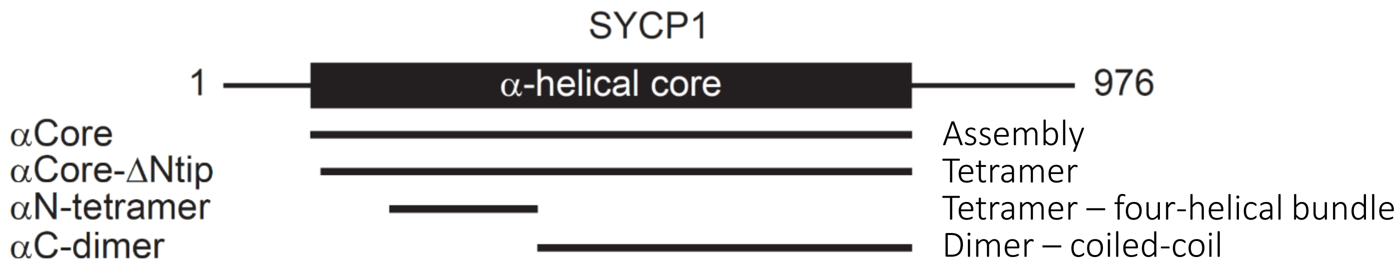
SYCP1 core consists of an αN-tetramer and αC-dimers

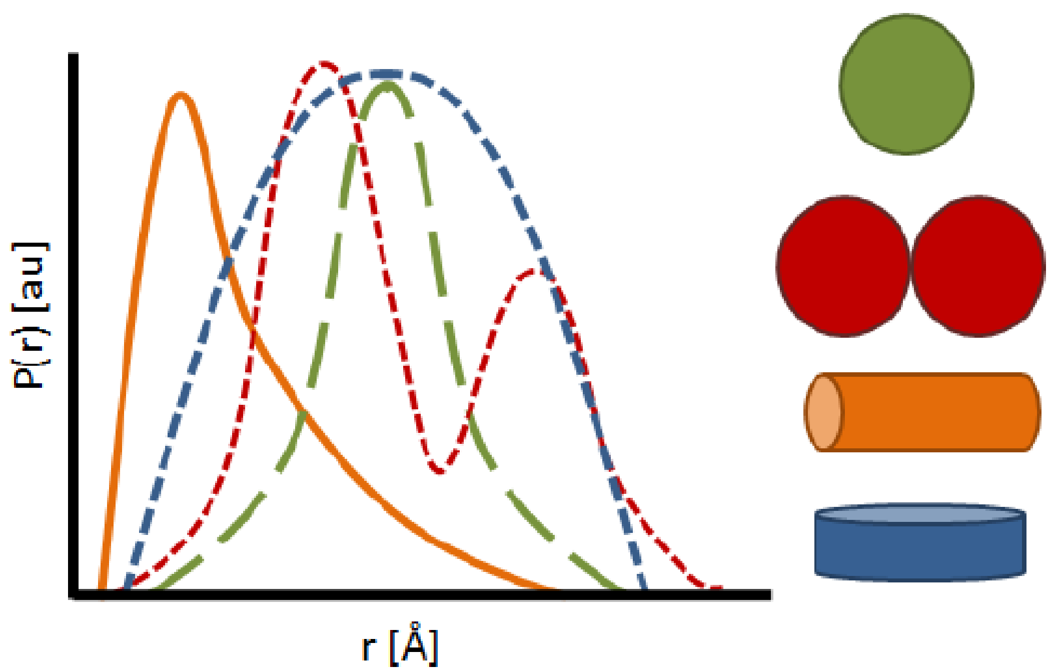




SEC-MALS

SAXS analysis of the SYCP1 αN-tetramer and αC-dimer



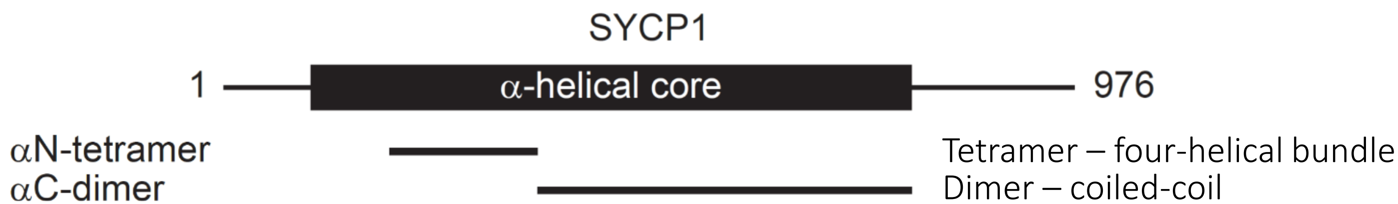


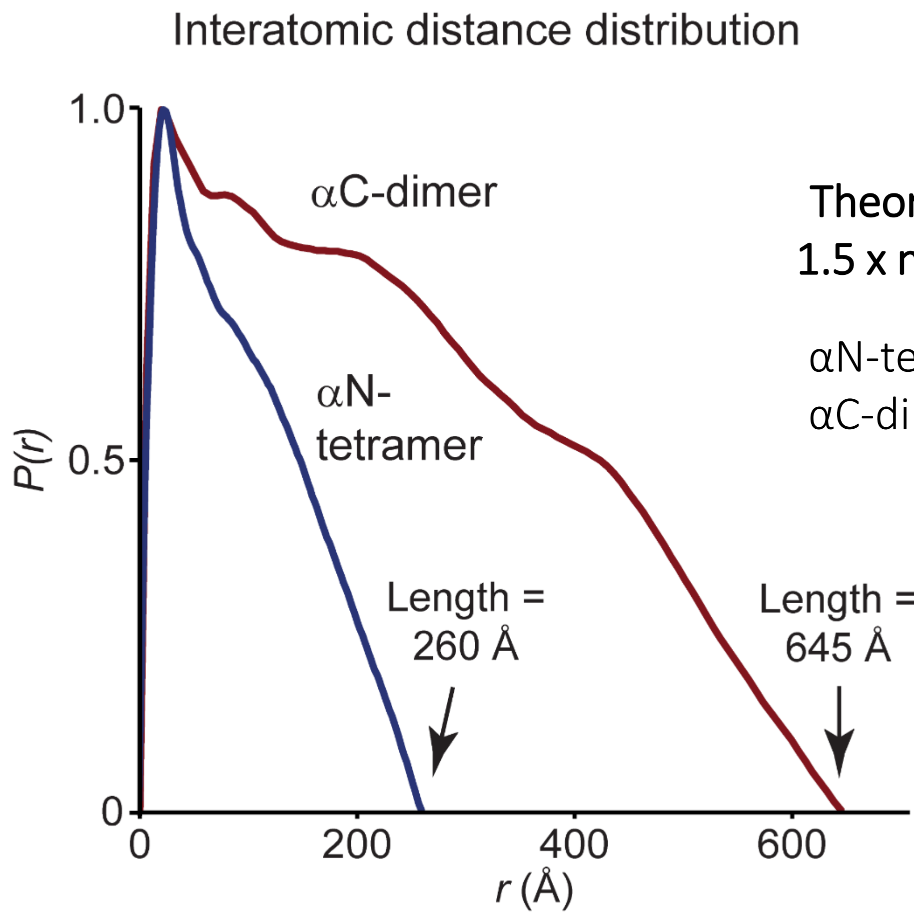
Small-angle X-ray scattering (SAXS)

P(r) Interatomic distance distribution

SAXS analysis of the SYCP1 αN-tetramer and αC-dimer

P(r) Dmax reveals coiled-coil length





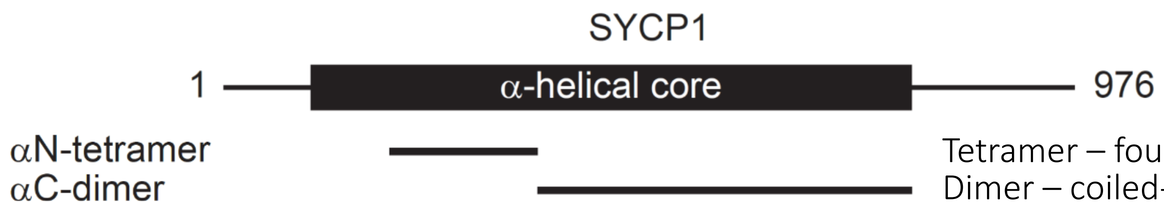
Theoretical coiled-coil length = 1.5 x number of amino-acids (Å)

αN-tetramer = 160 amino-acids

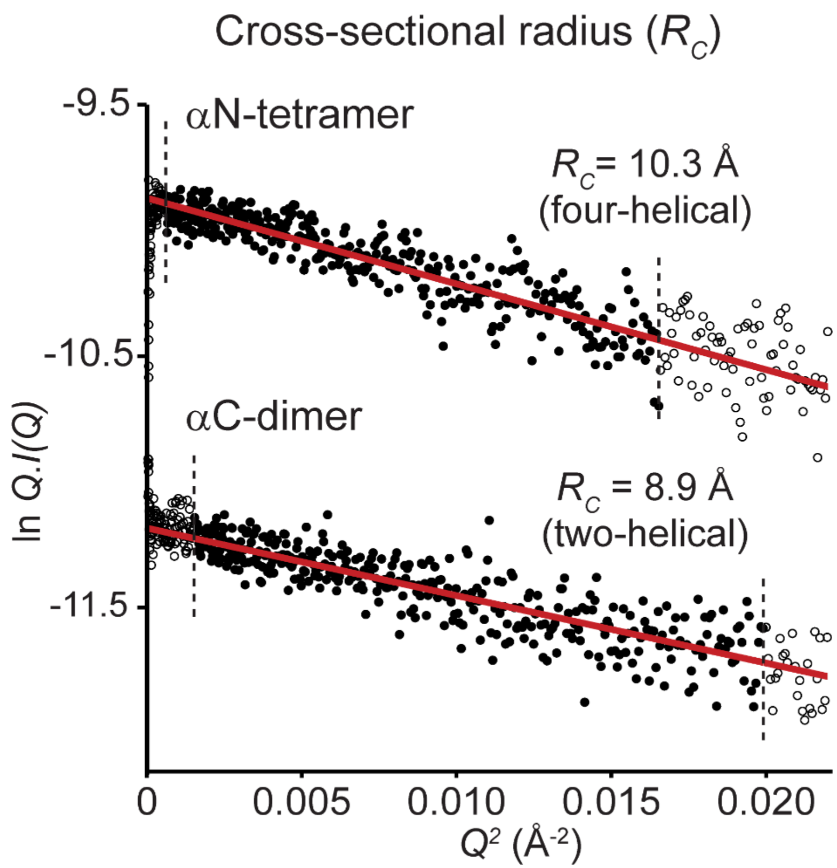
αC-dimer = 430 amino-acids

SAXS analysis of the SYCP1 αN-tetramer and αC-dimer

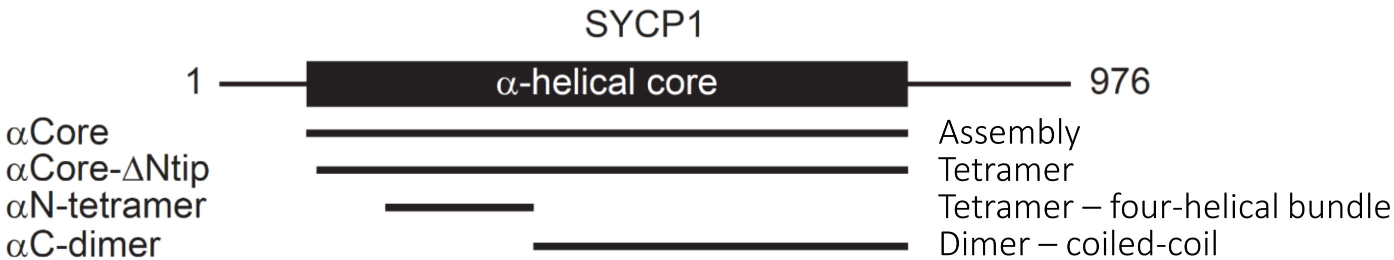
Cross-sectional Rg reveals coiled-coil width

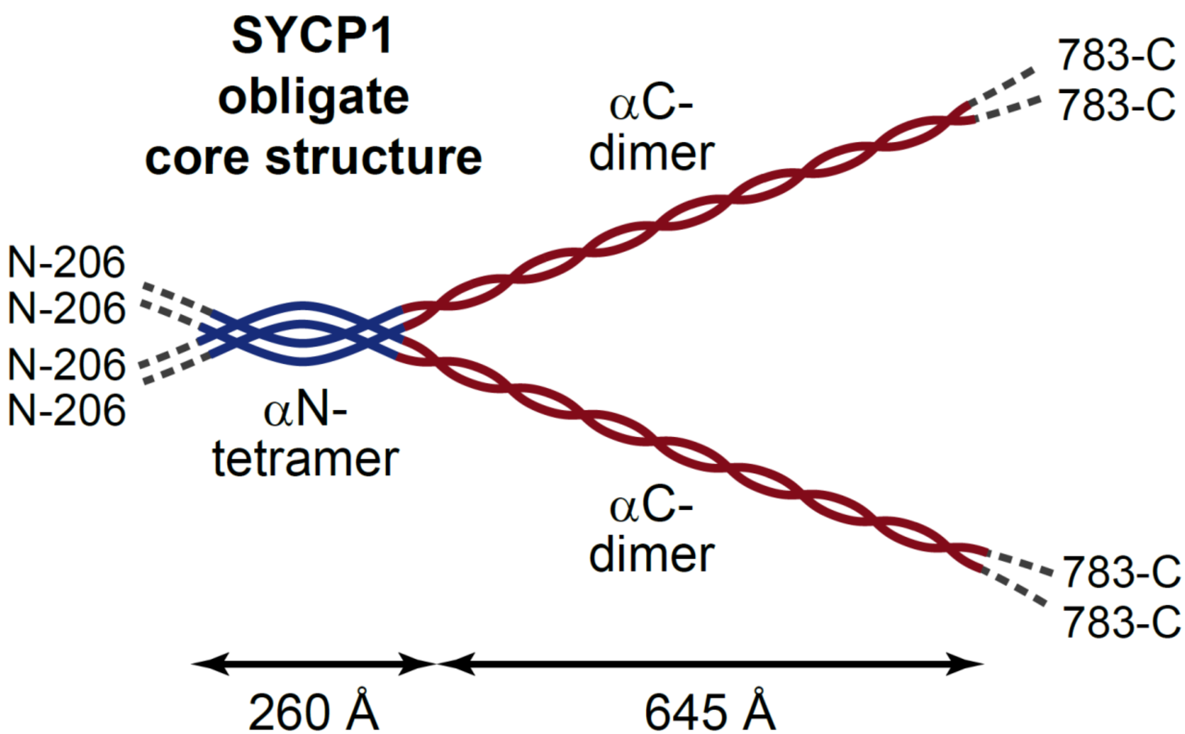


Tetramer – four-helical bundle
Dimer – coiled-coil

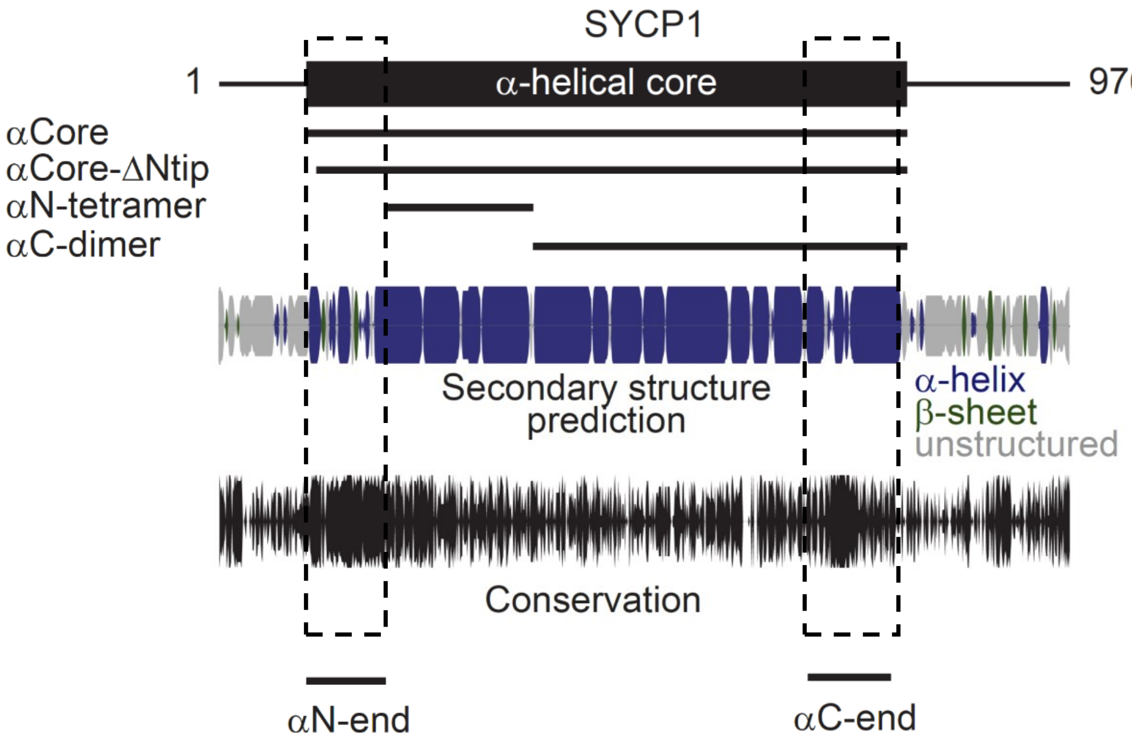


The obligate structure of the SYCP1 core





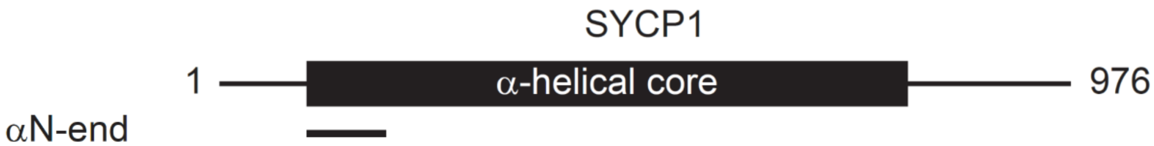
How does SYCP1 core self-assemble?

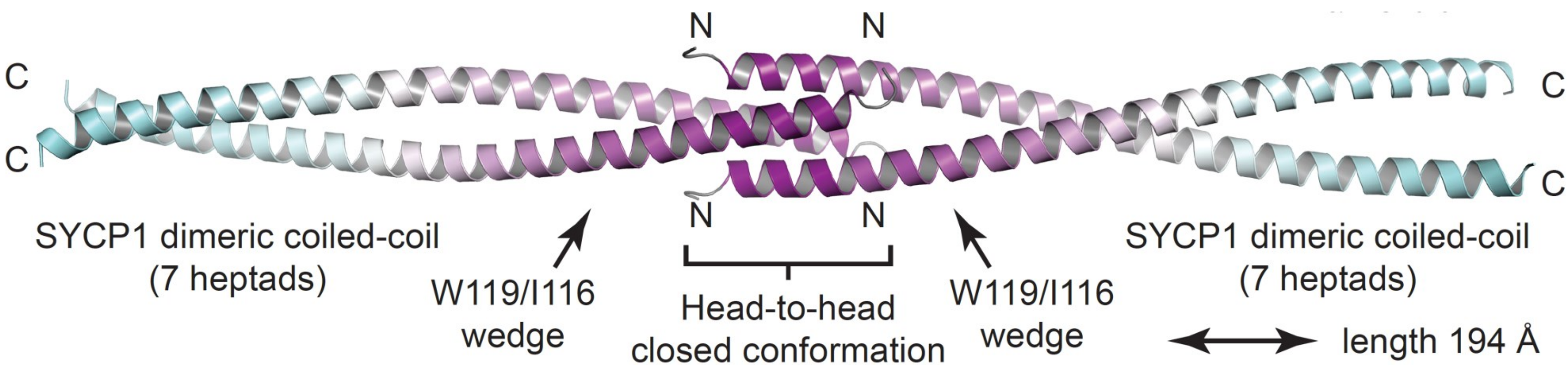


N-terminal self-assembly?

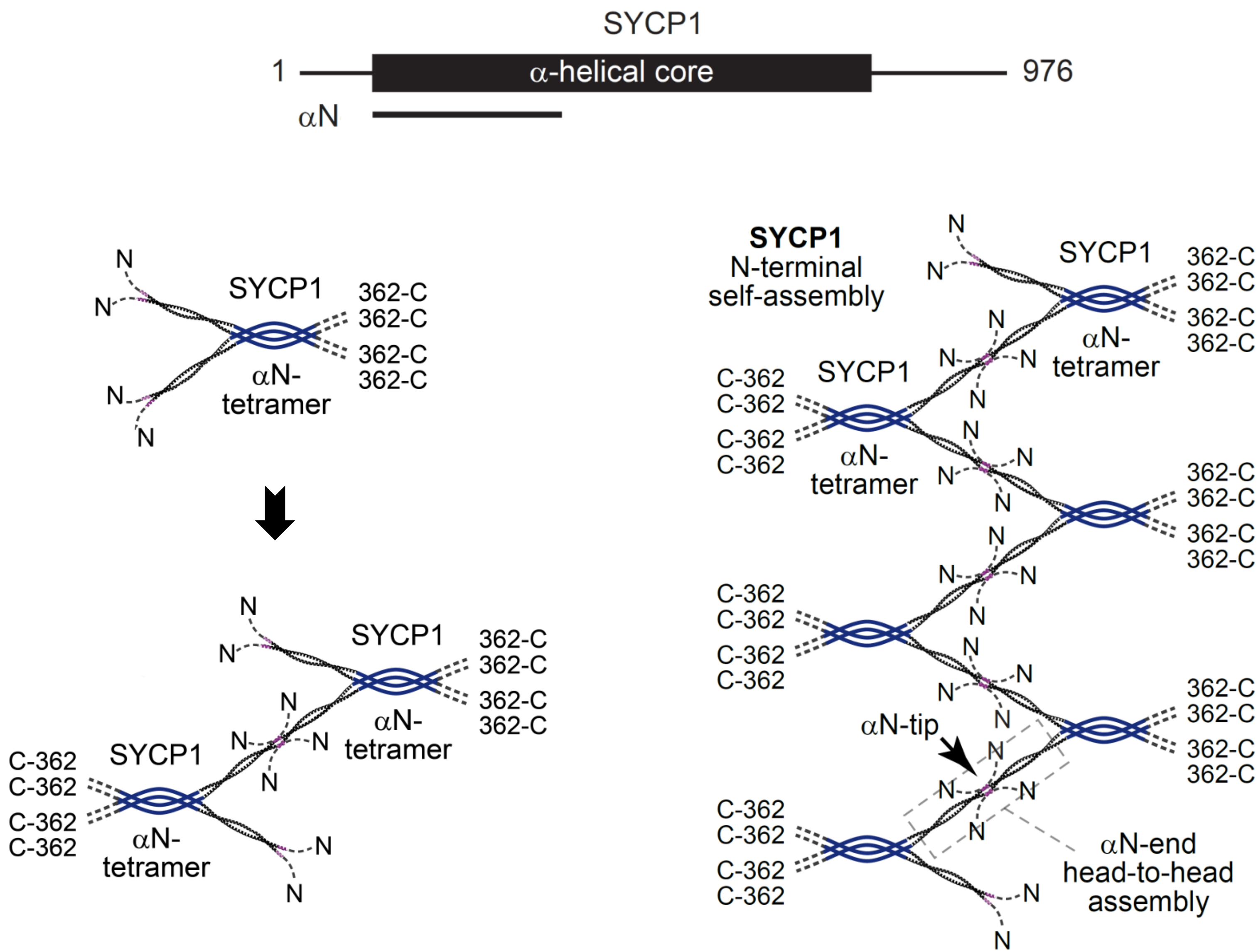
C-terminal self-assembly?

Crystal structure of SYCP1 αN-end

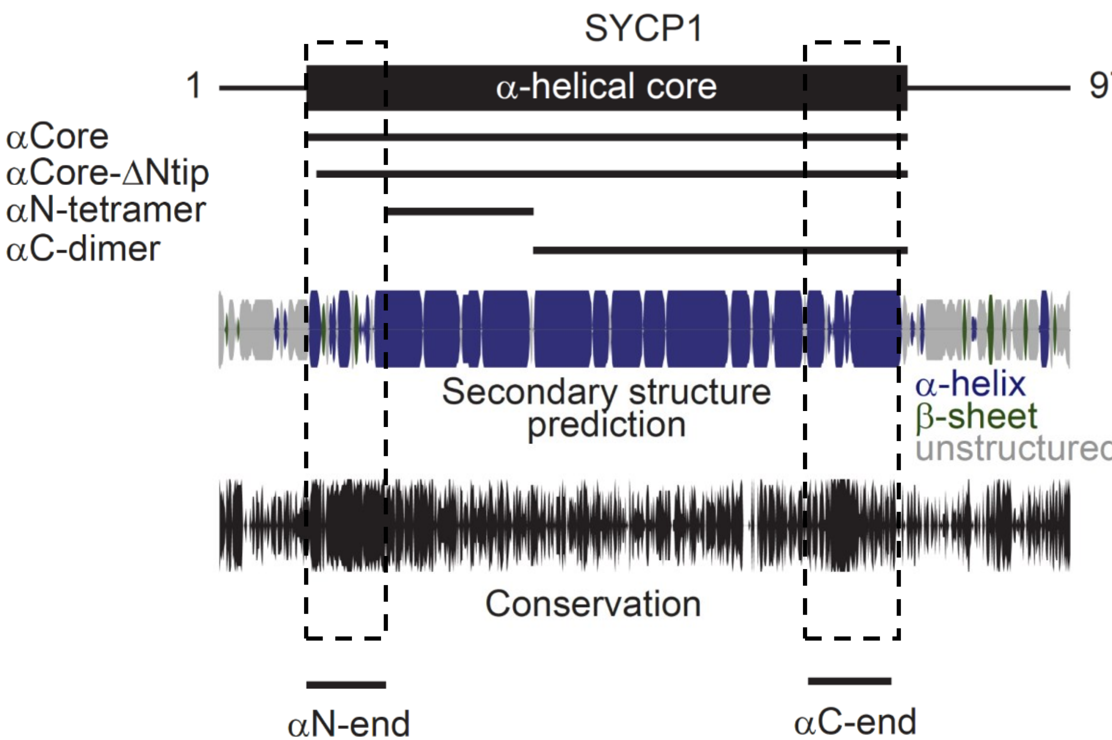




SYCP1 N-terminal self-assembly



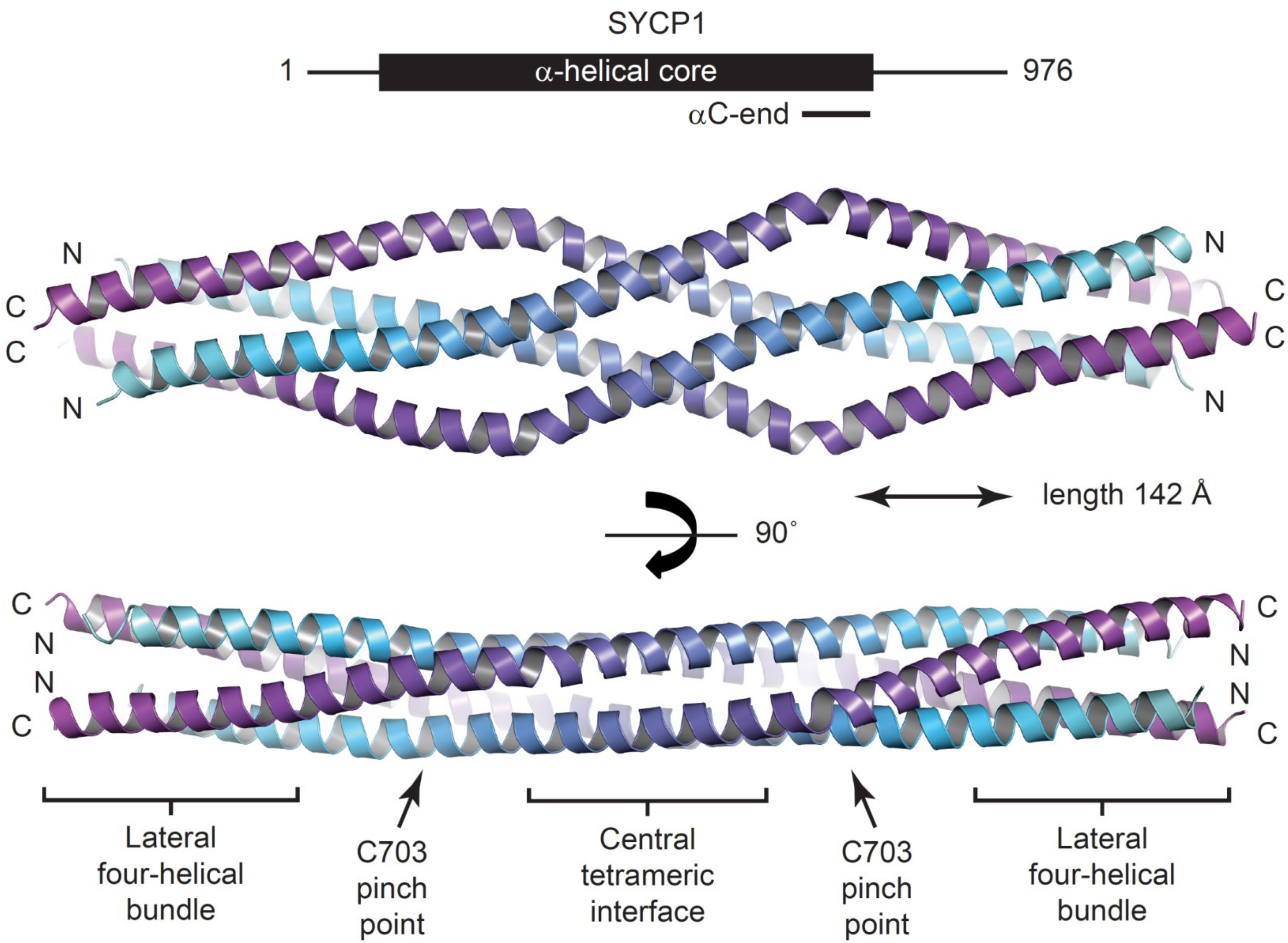
How does SYCP1 core self-assemble?



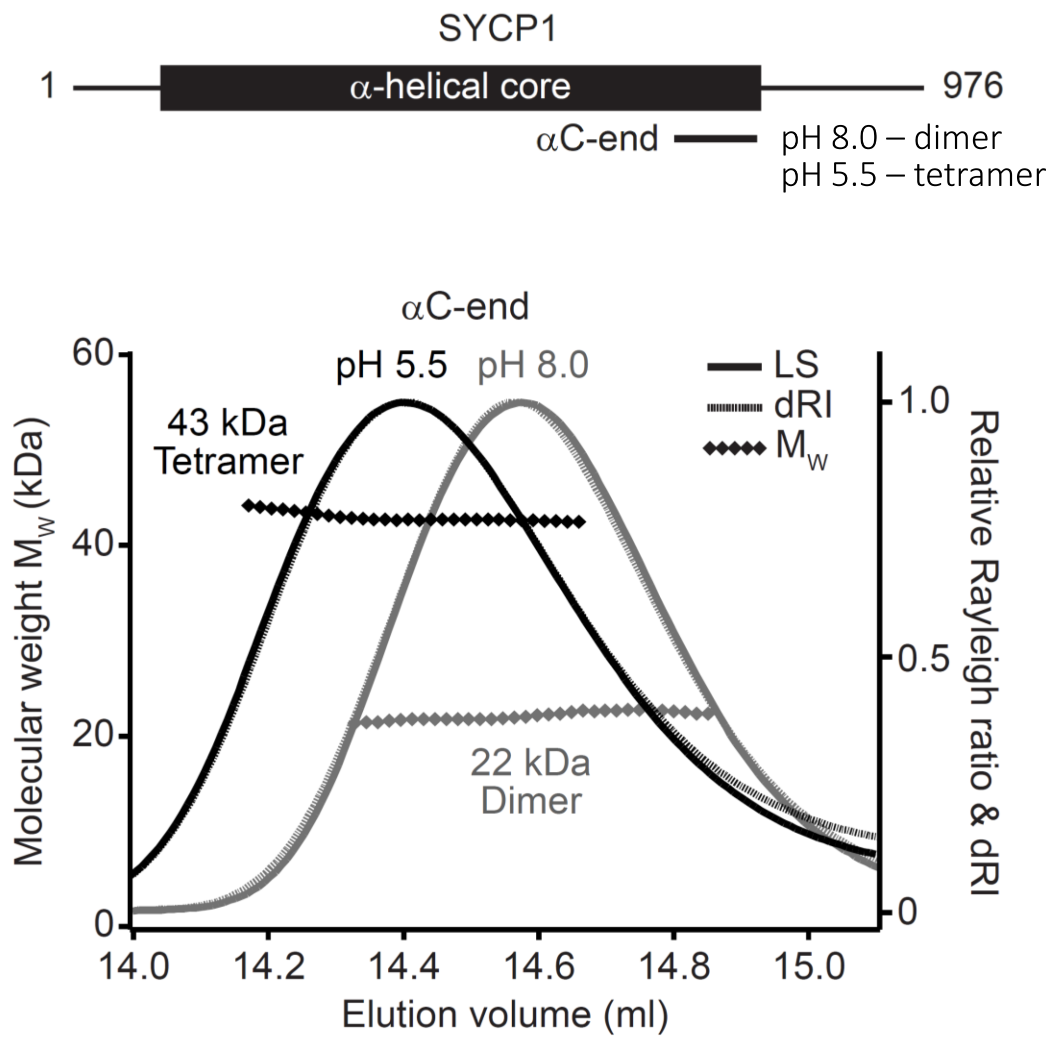
N-terminal self-assembly?

C-terminal self-assembly?

Crystal structure of SYCP1 αC-end



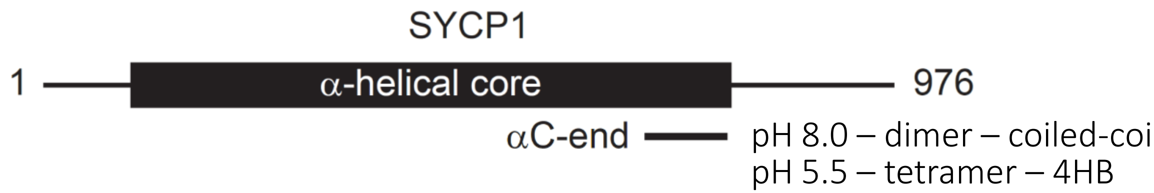
SYCP1 αC-end undergoes pH-induced tetrameric assembly

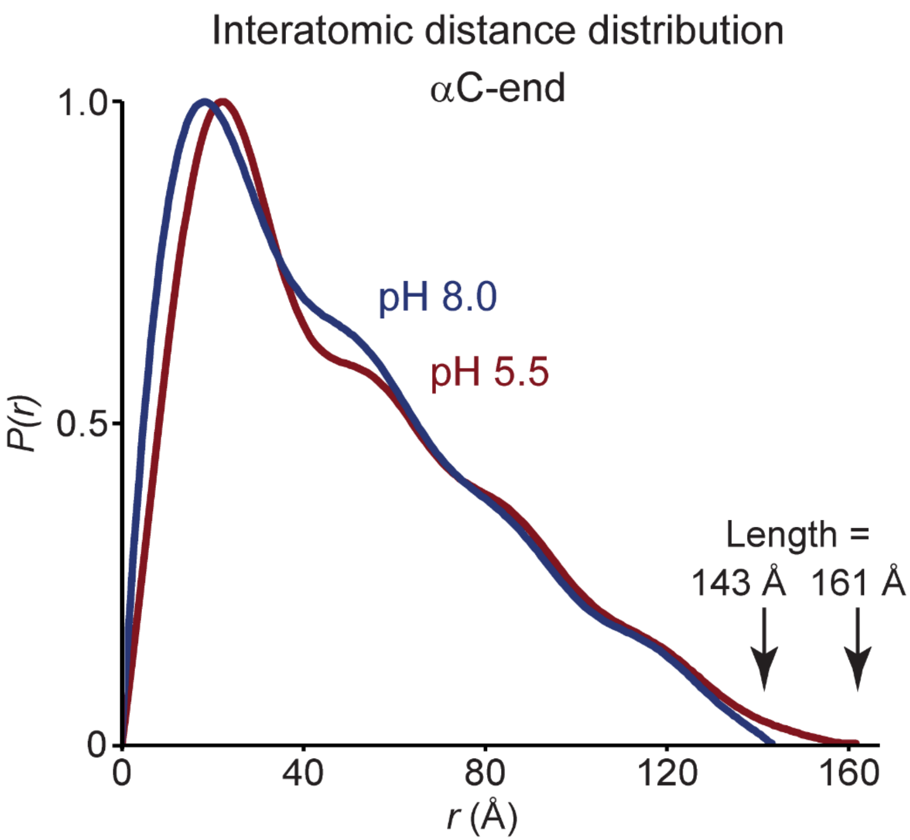


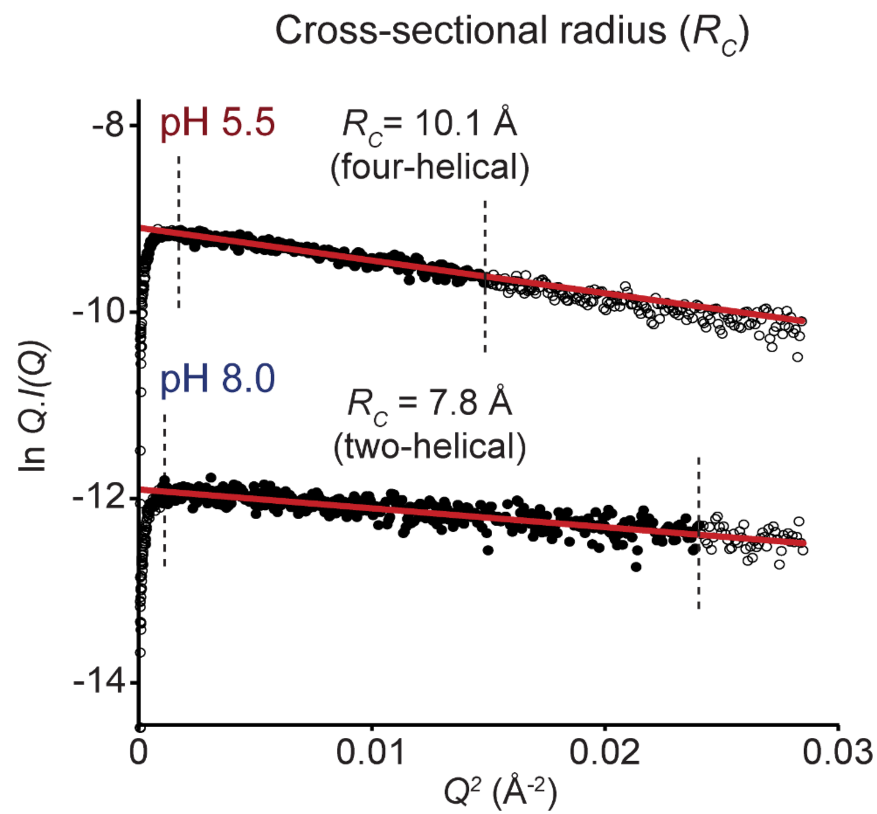
SEC-MALS

SAXS analysis of SYCP1 αC-end dimers and tetramers

P(r) and cross-sectional Rg analysis

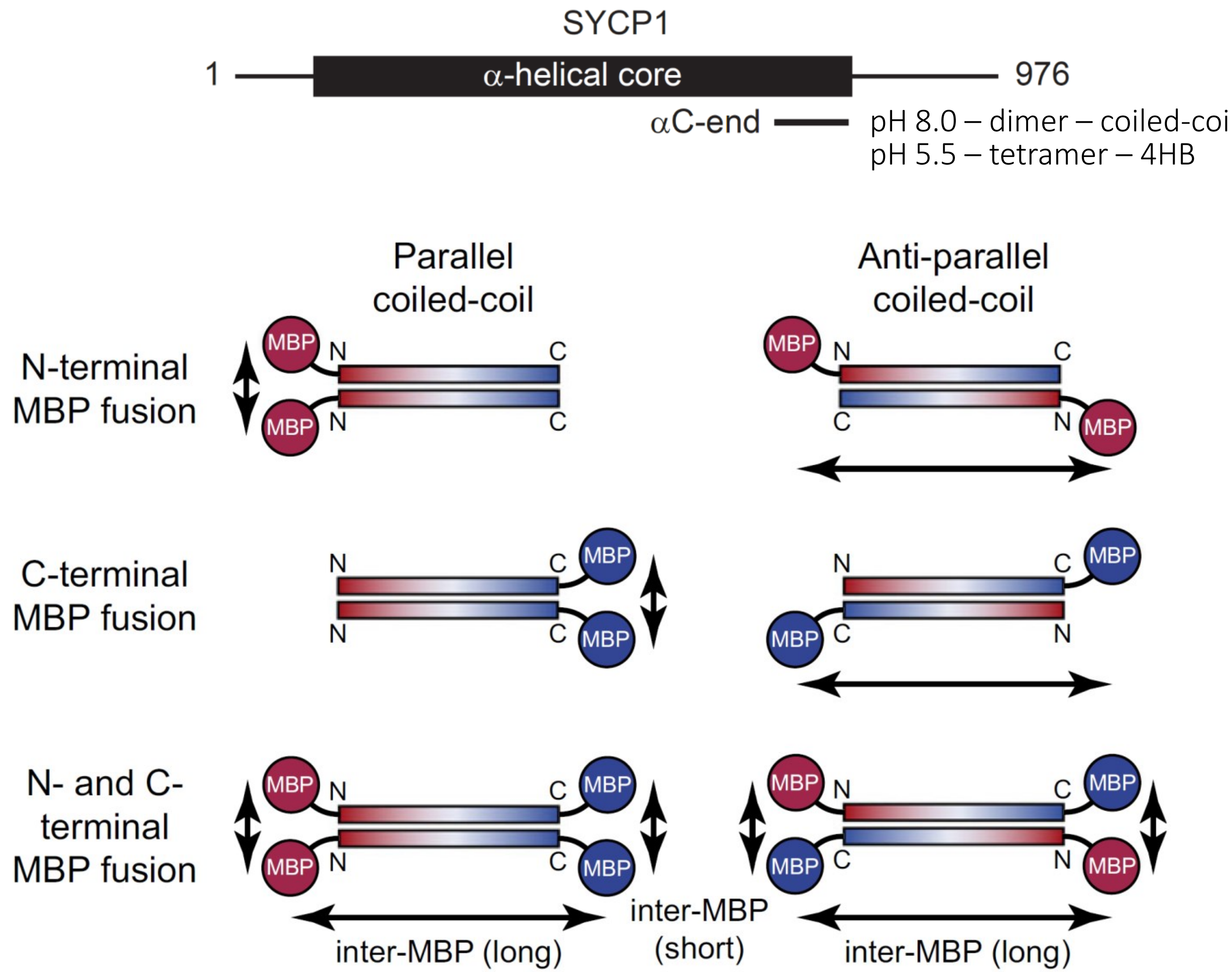






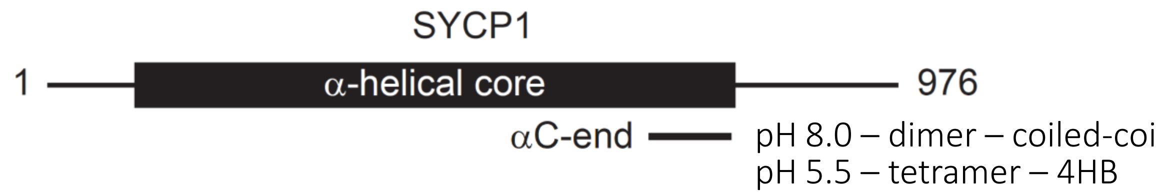
SAXS analysis of SYCP1 αC-end dimers and tetramers

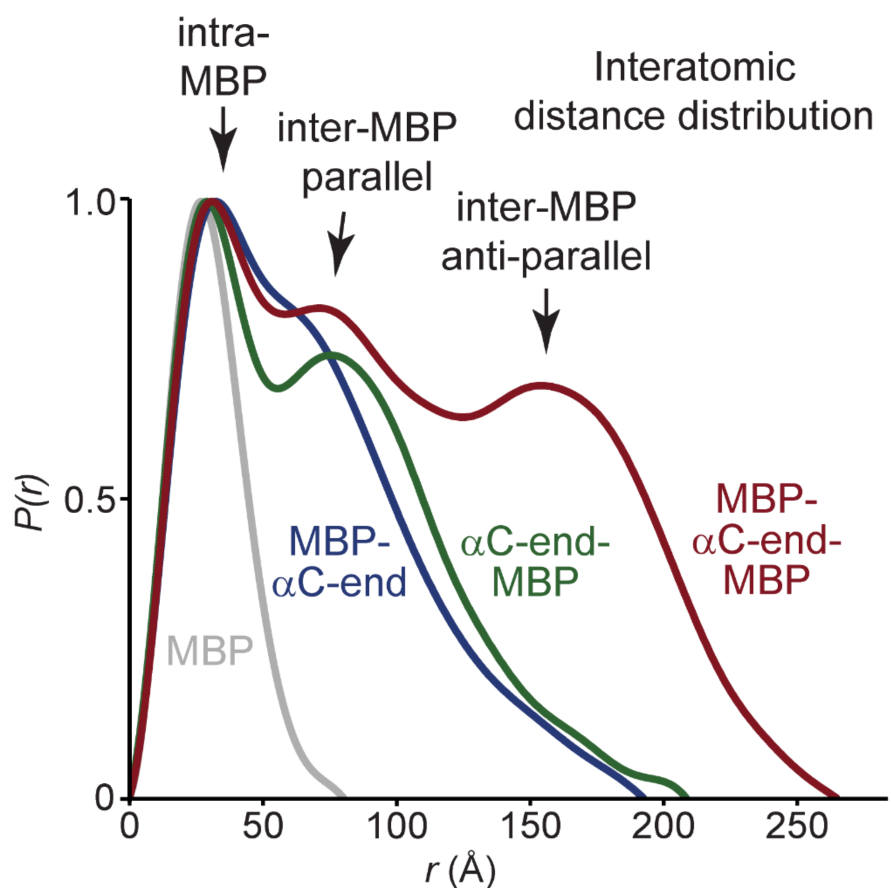
Using MBP fusions to determine helical orientation

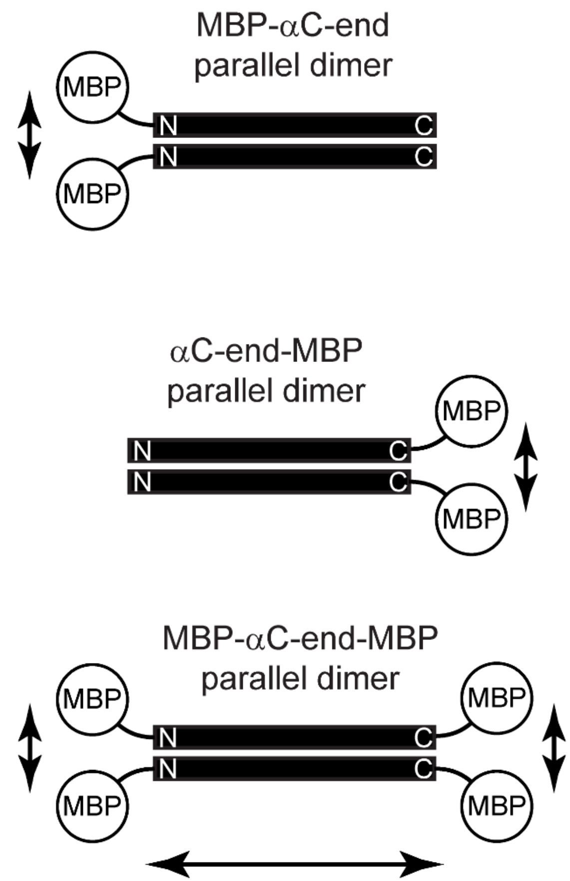


SAXS analysis of SYCP1 αC-end dimers and tetramers

Using MBP fusions to determine helical orientation

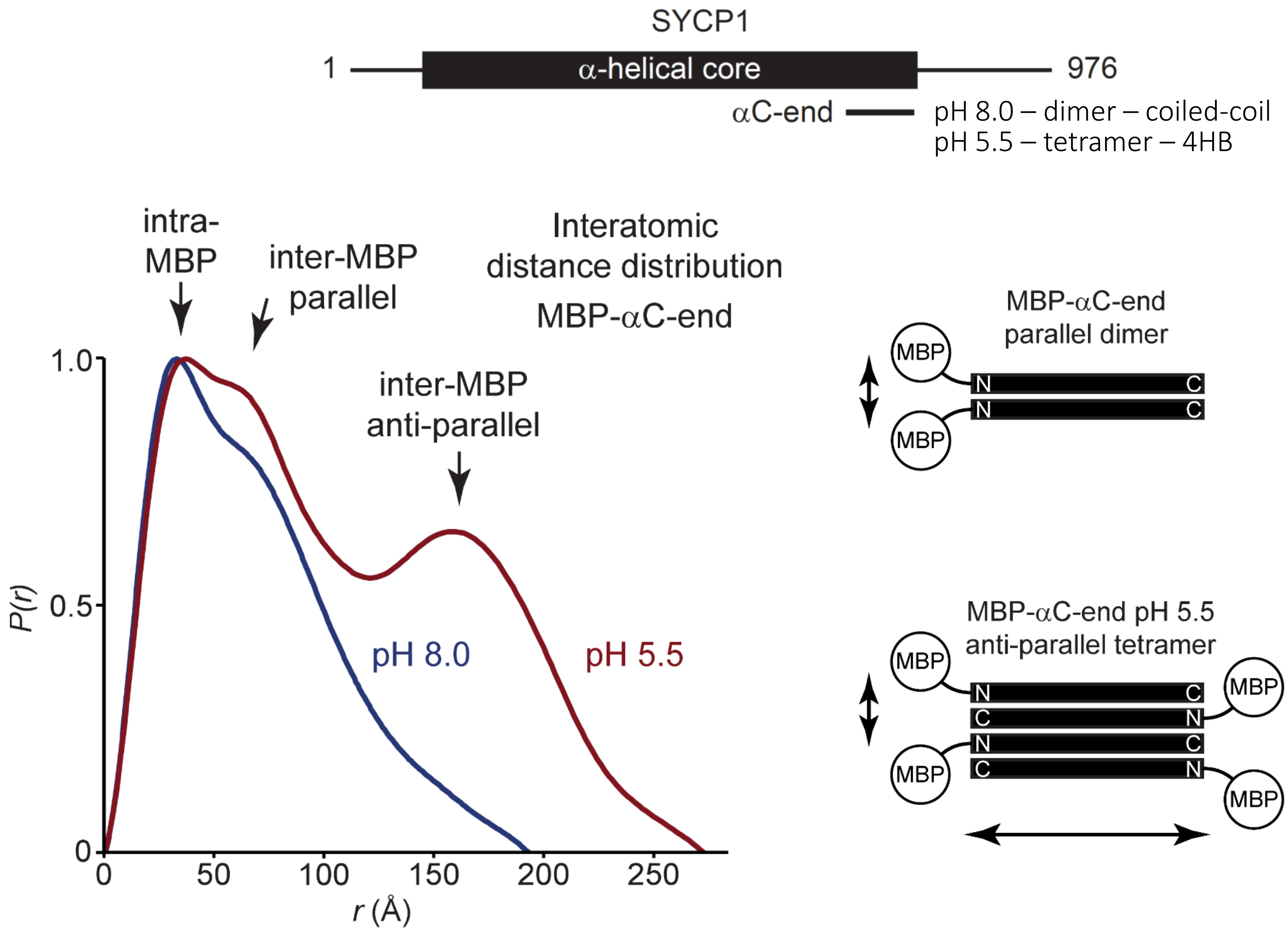






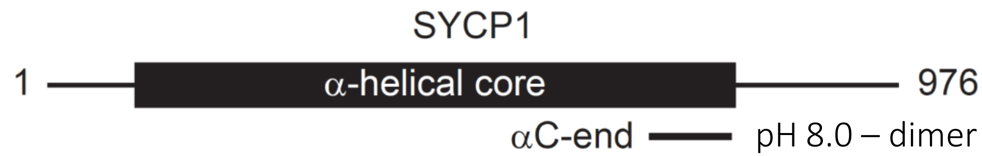
SAXS analysis of SYCP1 αC-end dimers and tetramers

Using MBP fusions to determine helical orientation

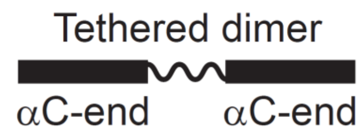


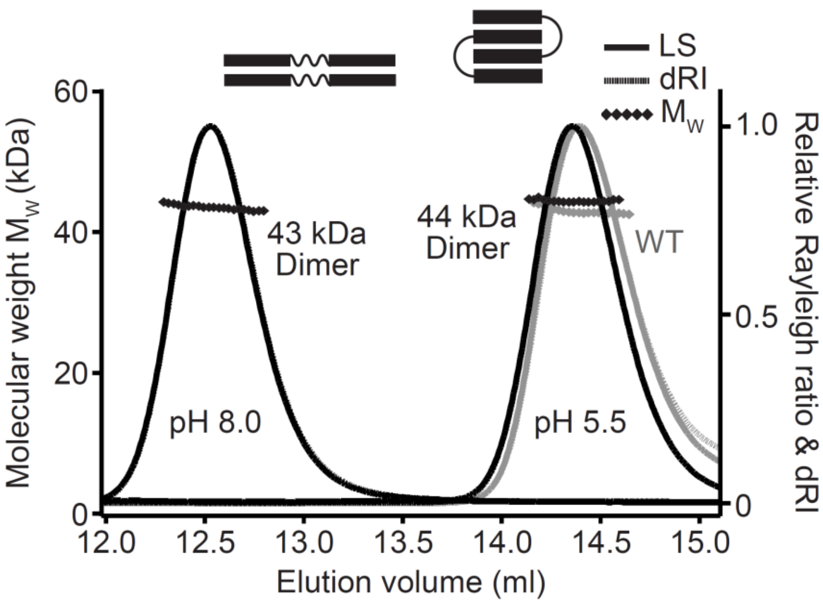
SAXS analysis of SYCP1 αC-end dimers and tetramers

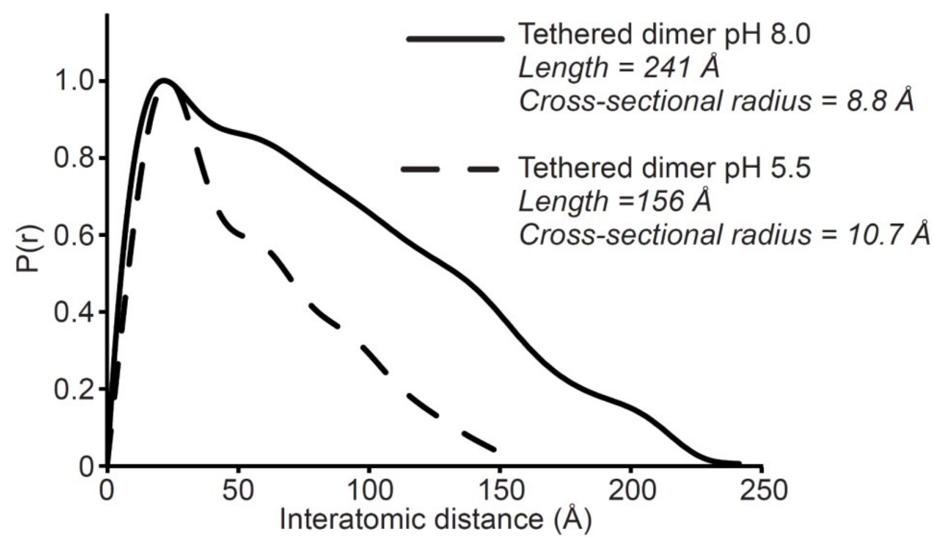
Using a tethered dimer to determine helical orientation



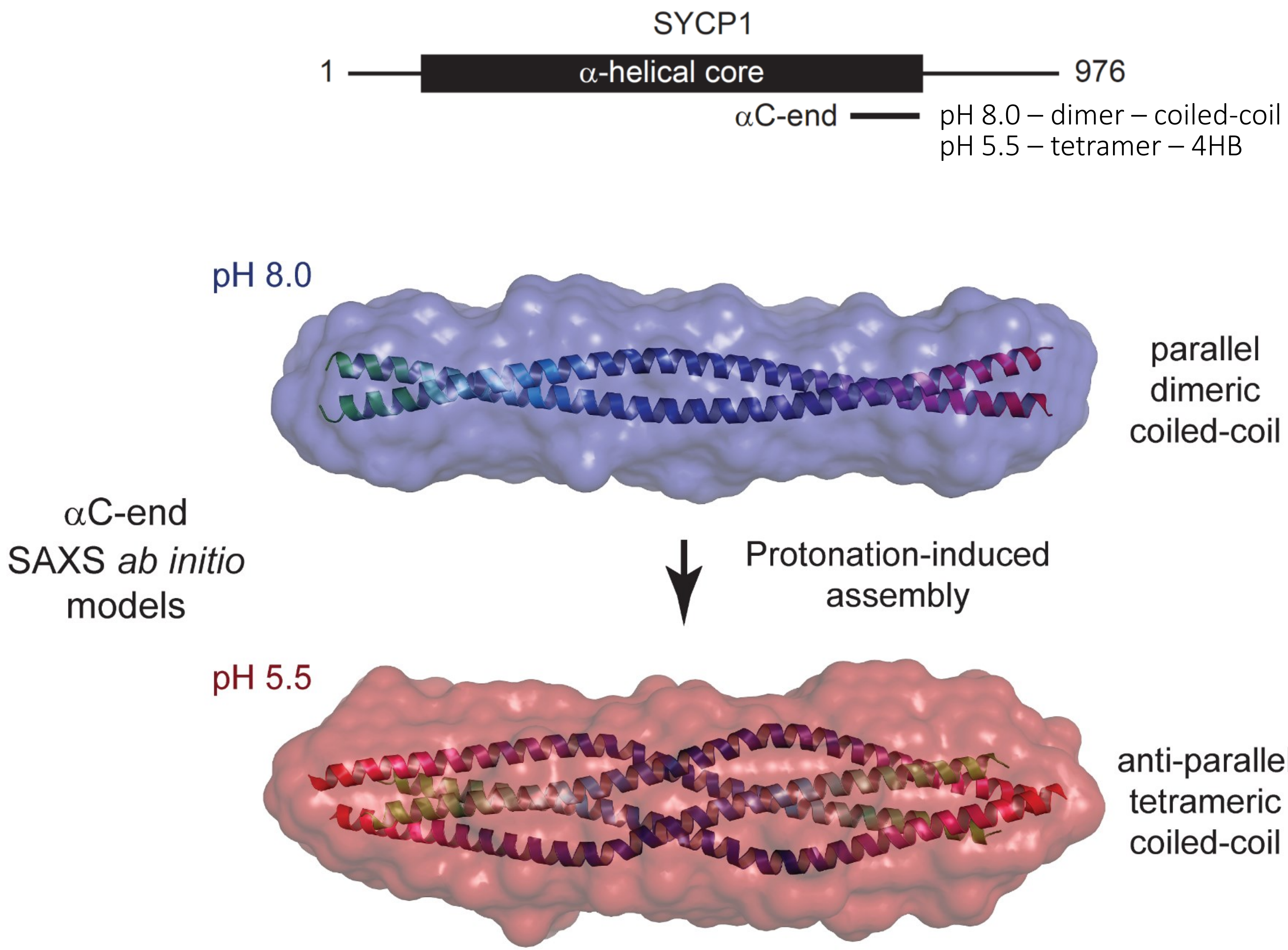
pH 8.0 – dimer – coiled-coil
pH 5.5 – tetramer – 4HB



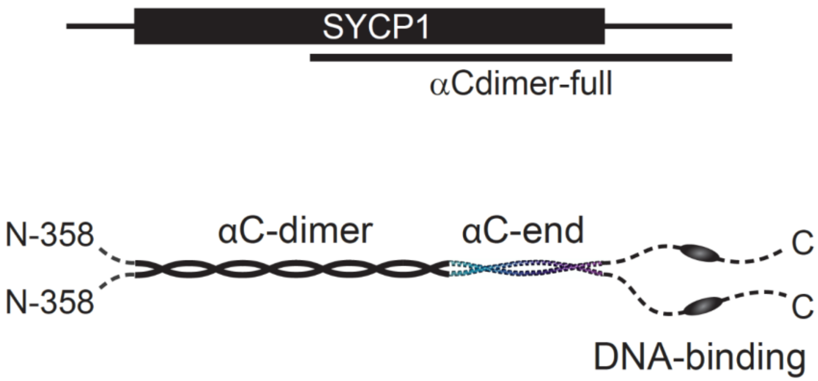


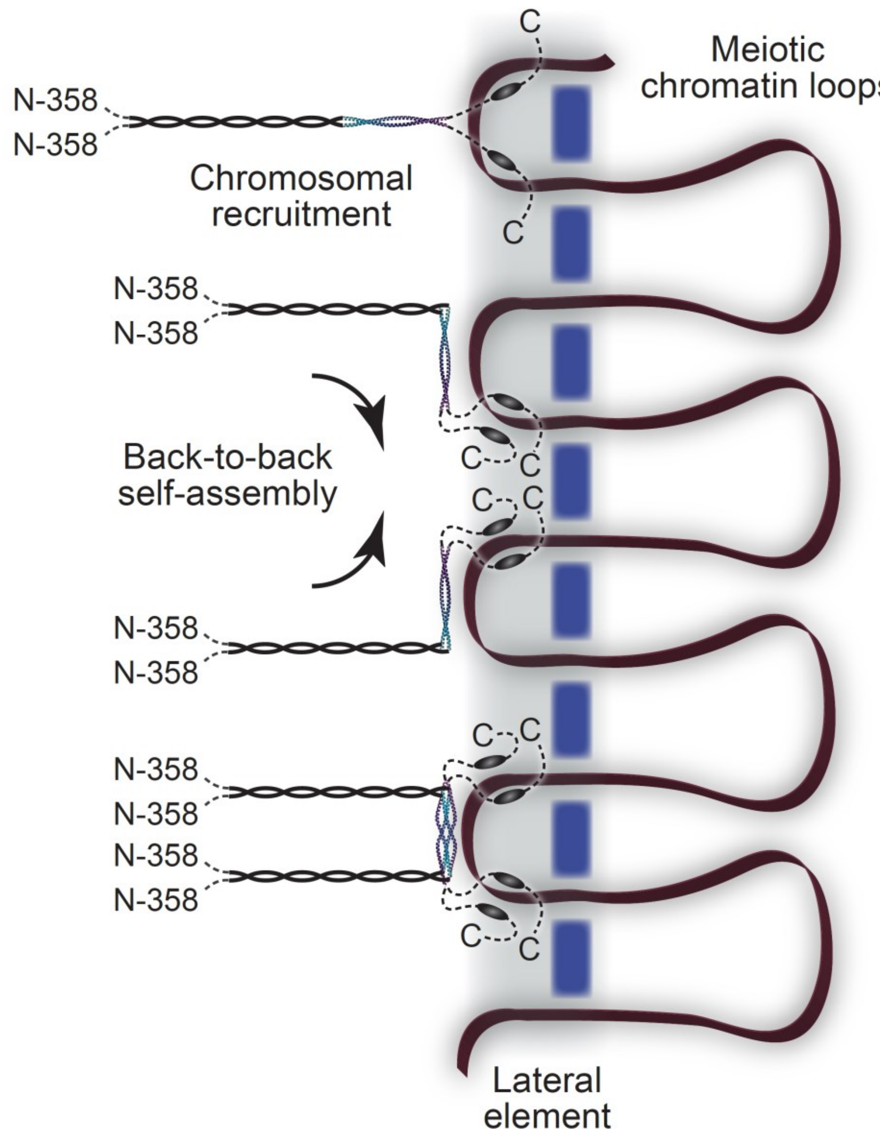


SYCP1 αC-end undergoes pH-induced tetrameric assembly

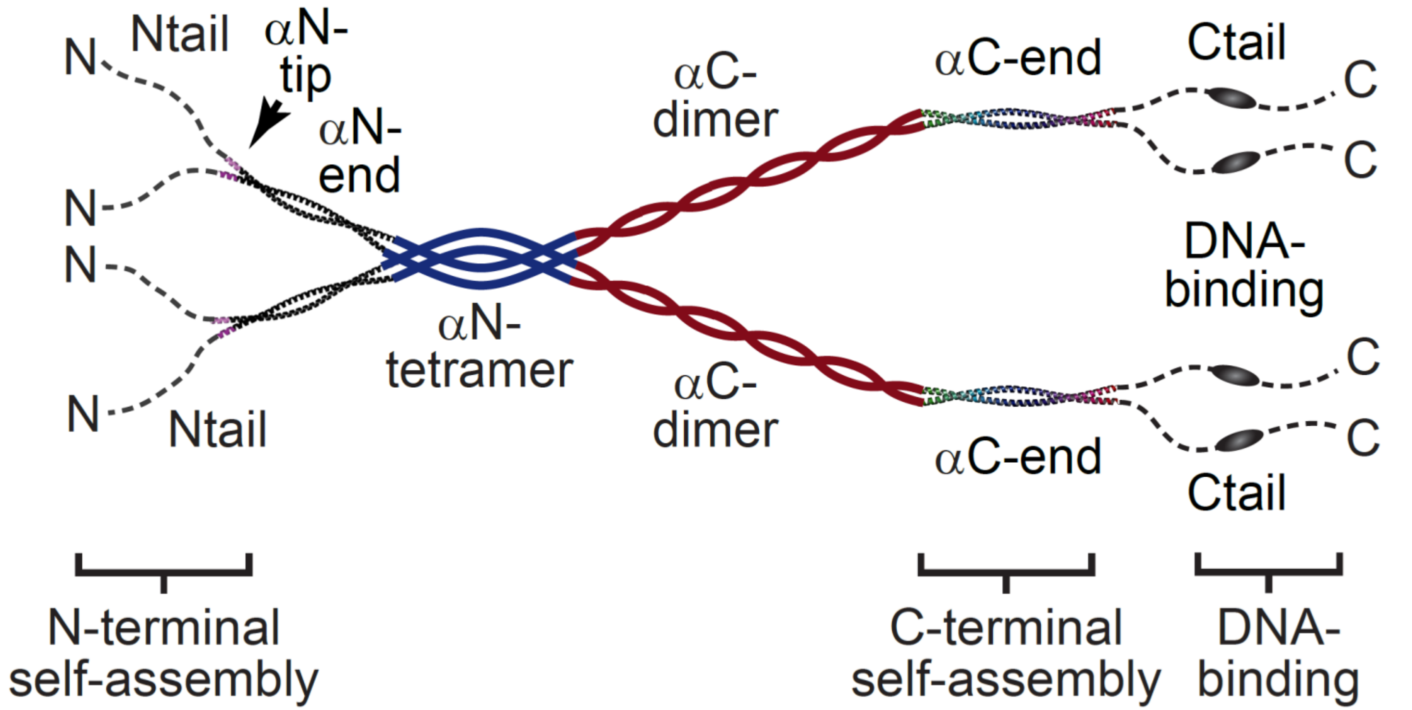


Chromosomal recruitment of SYCP1

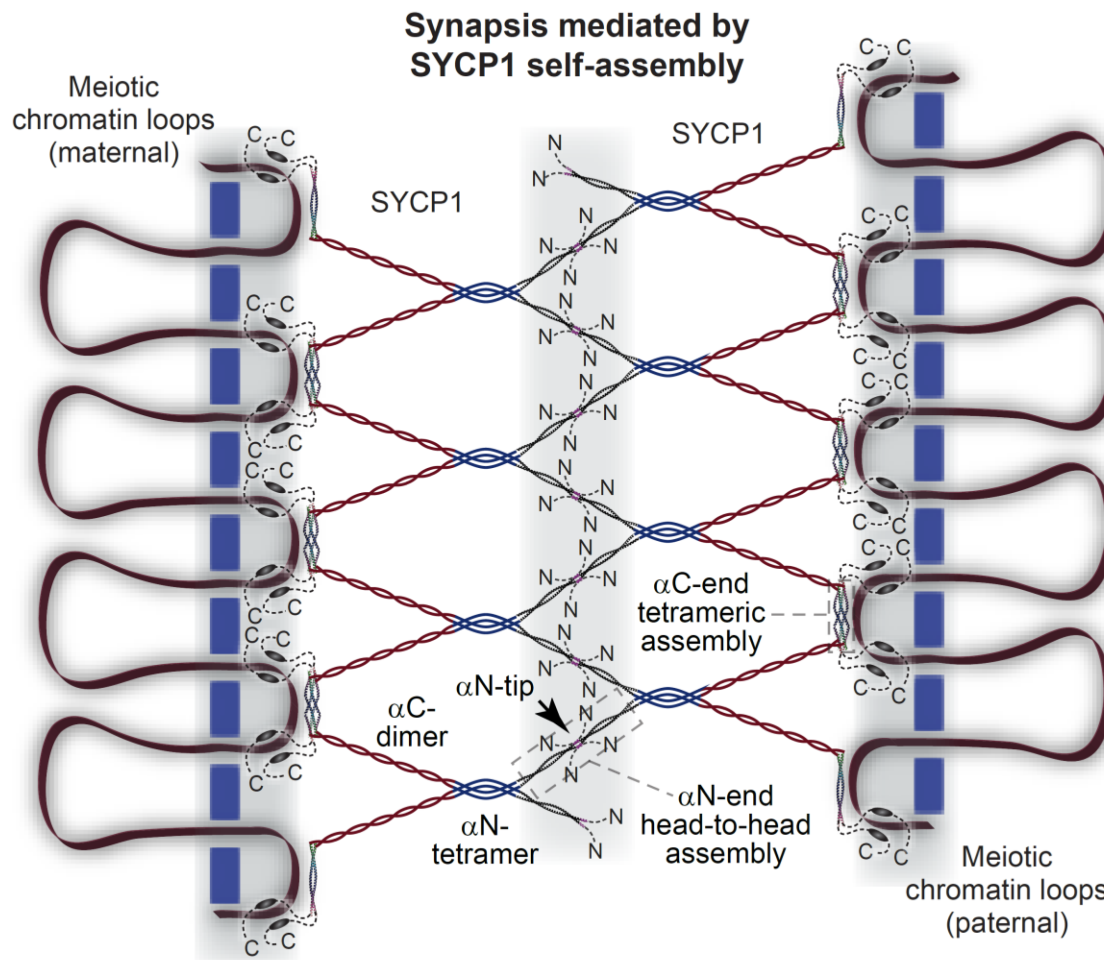




SYCP1 obligate structure



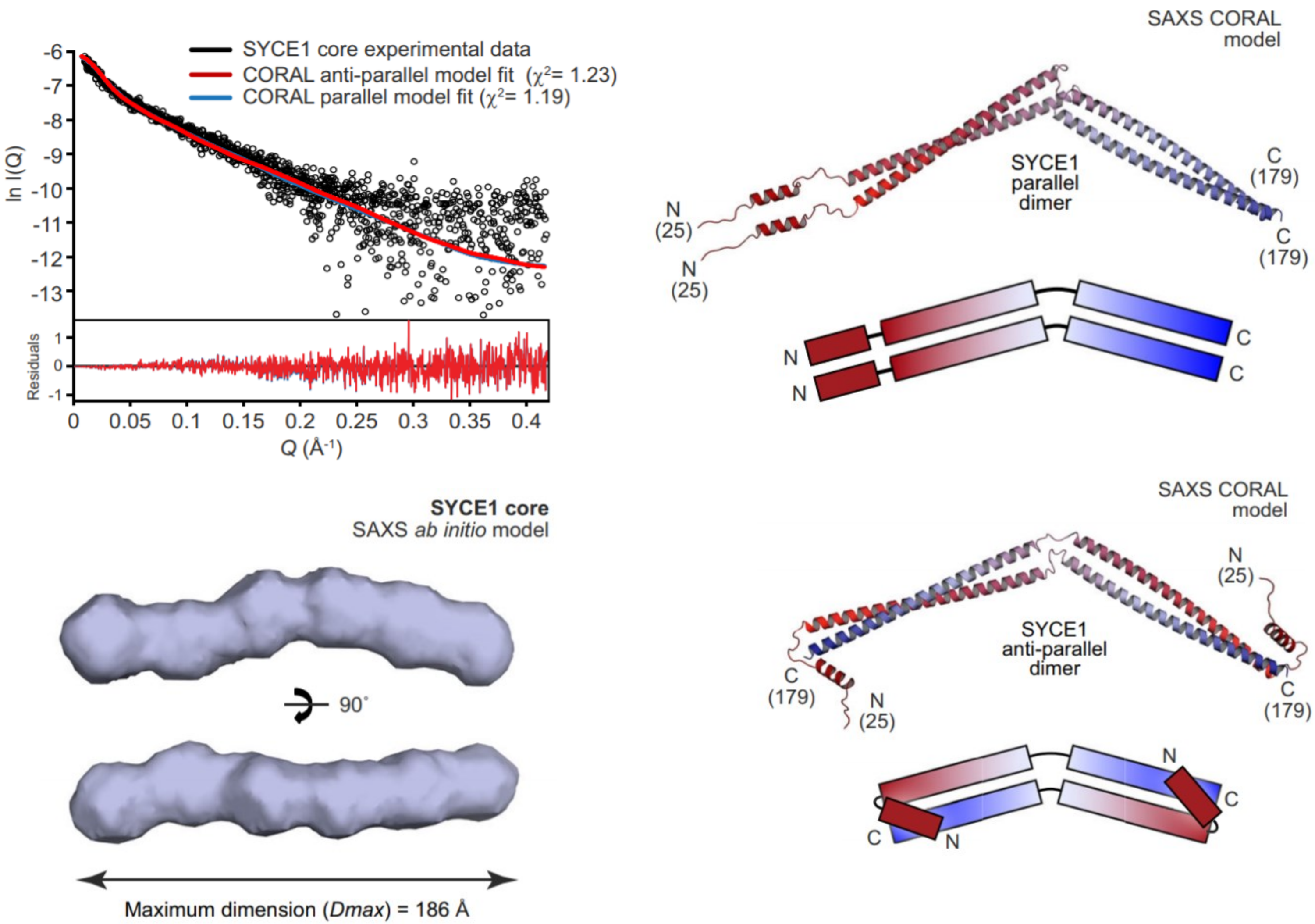
Self-assembly of SYCP1 into a supramolecular lattice



Dunce *et al* 2018 *Nature Structural & Molecular Biology*.

Another example – anti-parallel SYCE1 dimer

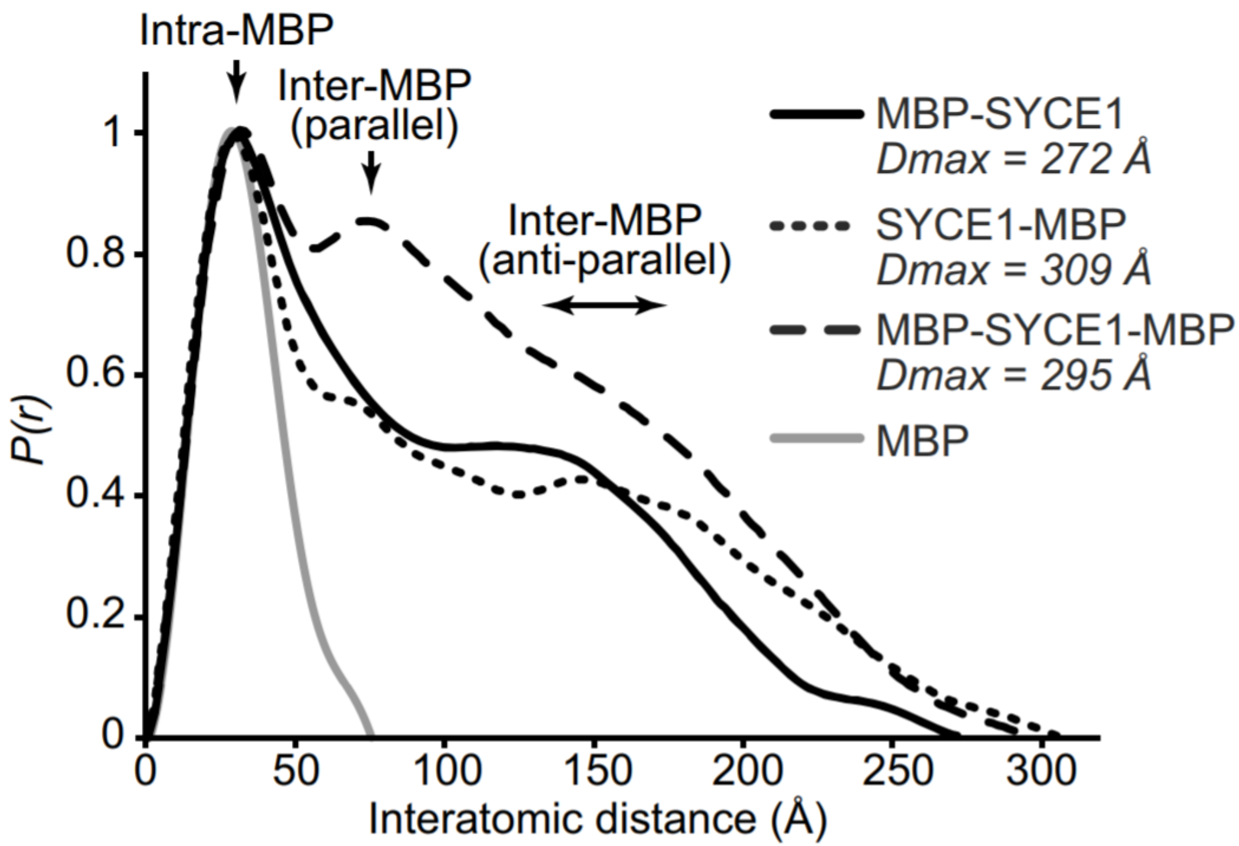
Direct modelling of coiled-coils



Dunne & Davies 2019 *Chromosoma*

Another example – anti-parallel SYCE1 dimer

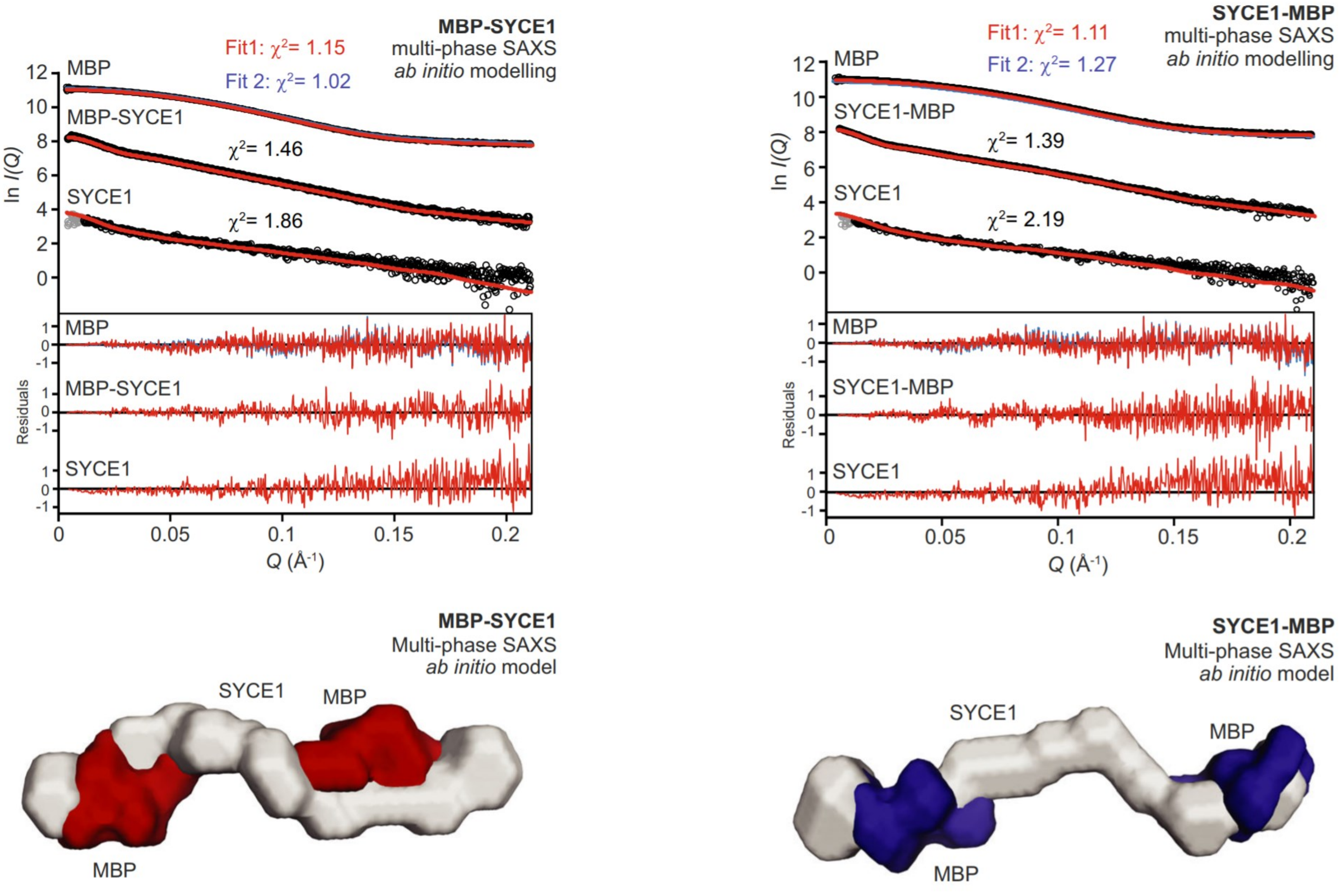
P(r) distributions of MBP fusions



Dunne & Davies 2019 *Chromosoma*

Another example – anti-parallel SYCE1 dimer

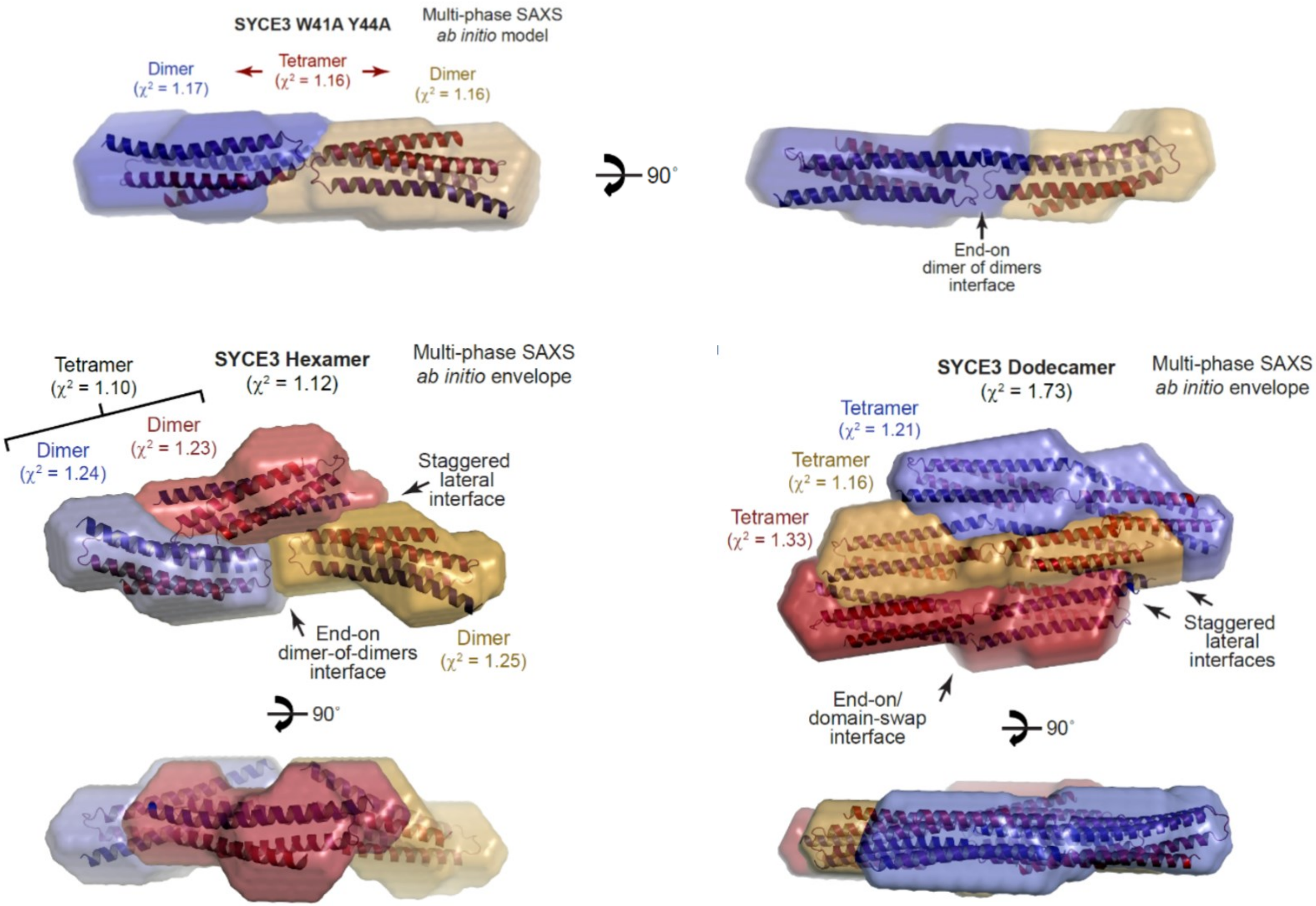
Multi-phase ab initio modelling of MBP fusions



Dunne & Davies 2019 *Chromosoma*

Another example – SYCE3 self-assembly

Multi-phase modelling of SYCE3 structures



Dunne & Davies 2019 *Journal of Biological Chemistry*

Acknowledgements

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Lucy Salmon
Chandni Ravindan (joint with Amy MacQueen)

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Matthew Ratcliff
Vincentius Aji Jatikusumo
Carmen Espejo Serrano
Omar Al-Jourani
Urszula McClurg

Arnaud Basle (X-ray manager)

All at Diamond Light Source beamline B21

wellcome trust Fellow

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