

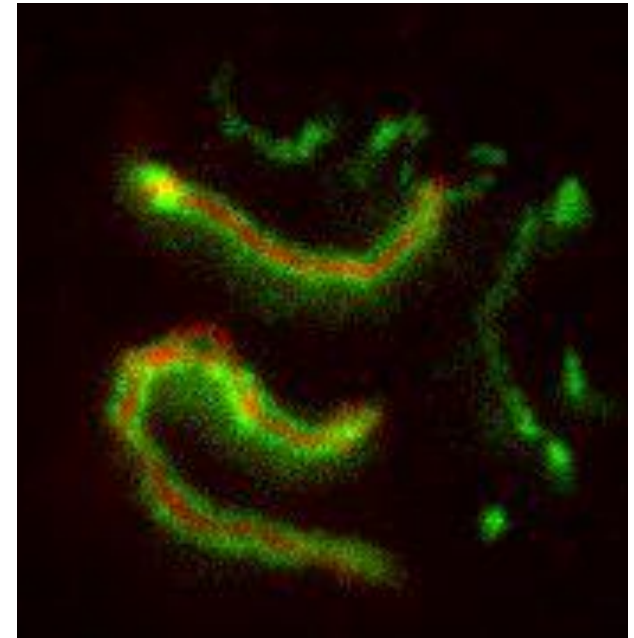
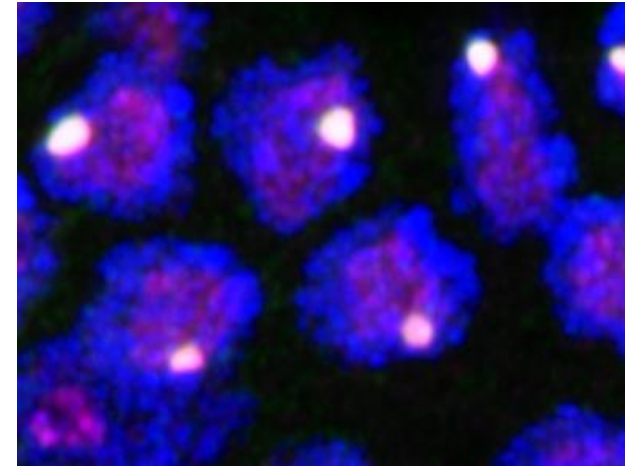
Smart Condensates and Droplets Symposium
6 September 2024, Cambridge, UK

The **synaptonemal complex** assembles
between **meiotic chromosomes** by wetting

Chiu Fan Lee

Department of Bioengineering, Imperial College London, UK

IMPERIAL



Plan

1. Meiosis in *C. elegans*
2. Synaptonemal complex (SC) as a glue to enable genetic crossover
3. Perturbations of SC to probe molecular mechanism of SC assembly
4. Physics of SC assembly
5. Summary & outlook

Acknowledgement



Dr Gordon Spencer



Prof Ofer Rog



Ref: S. Gordon, C.F. Lee, and O Rog (2024)
The synaptonemal complex assembles between meiotic
chromosomes by wetting
bioRxiv 2024.08.07.607092



The Leverhulme Trust

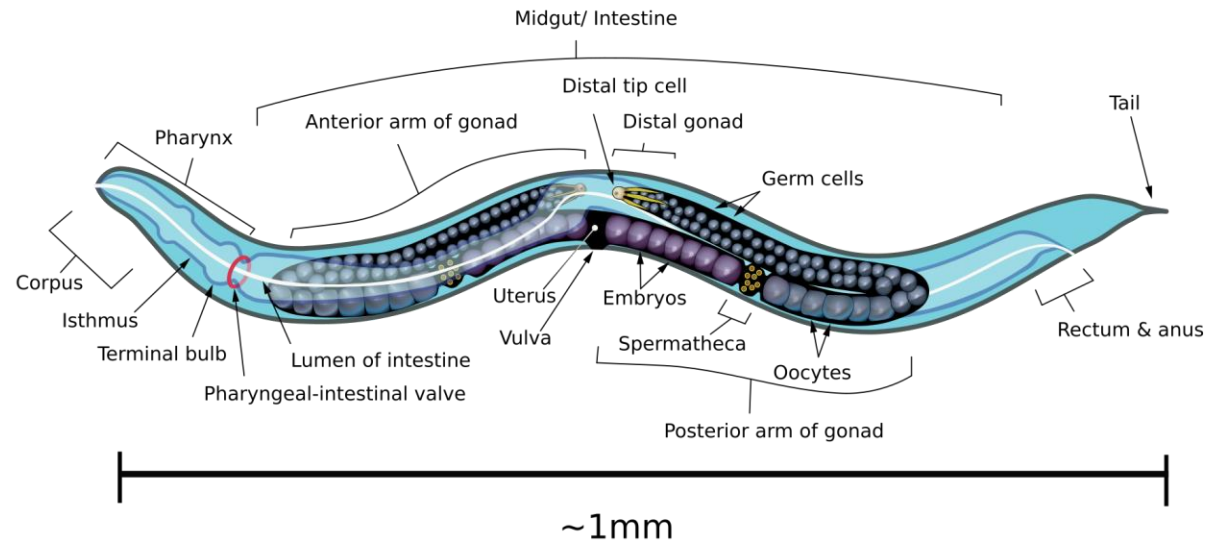


NIHR | Imperial Biomedical Research Centre

THE ROYAL SOCIETY

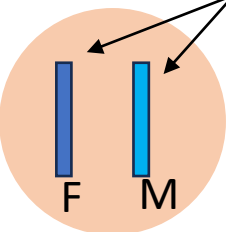


1. Meiosis in *C. elegans*

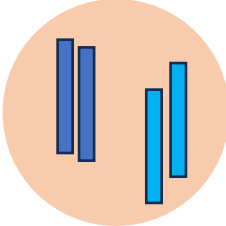


Mitosis

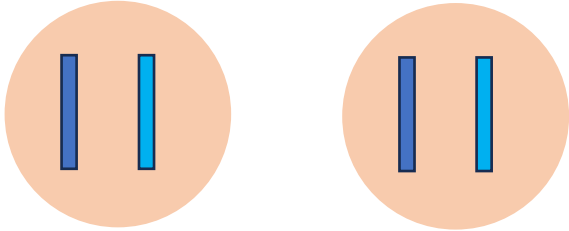
Homologous chromosomes
(only 1 pair shown for simplicity)



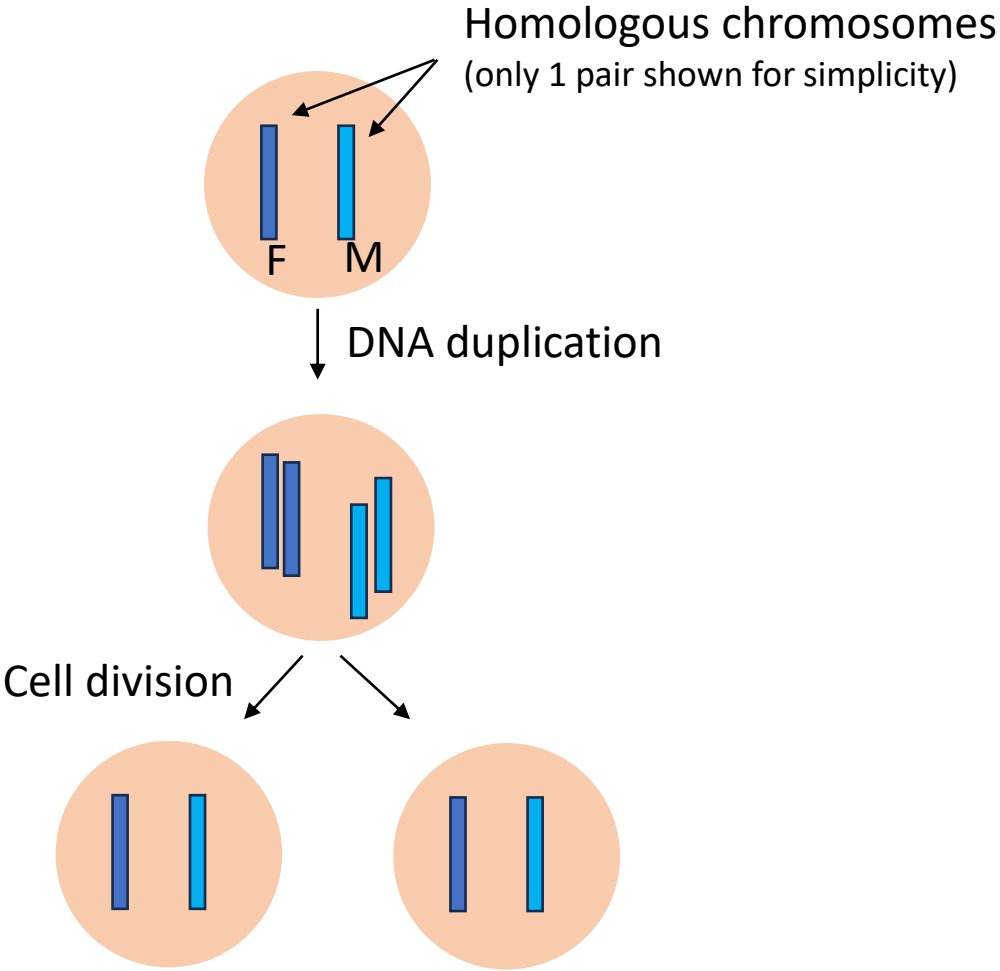
DNA duplication



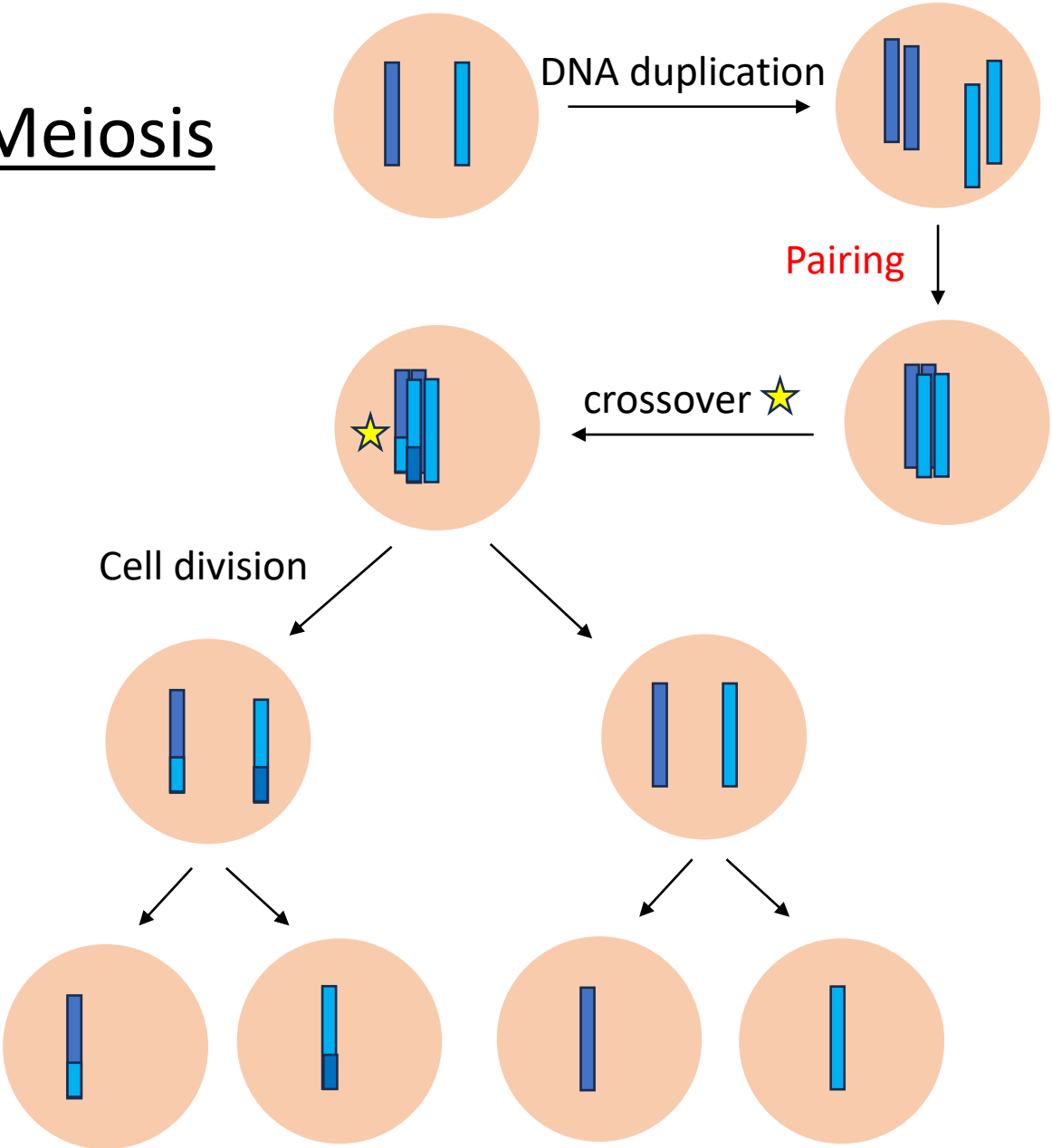
Cell division



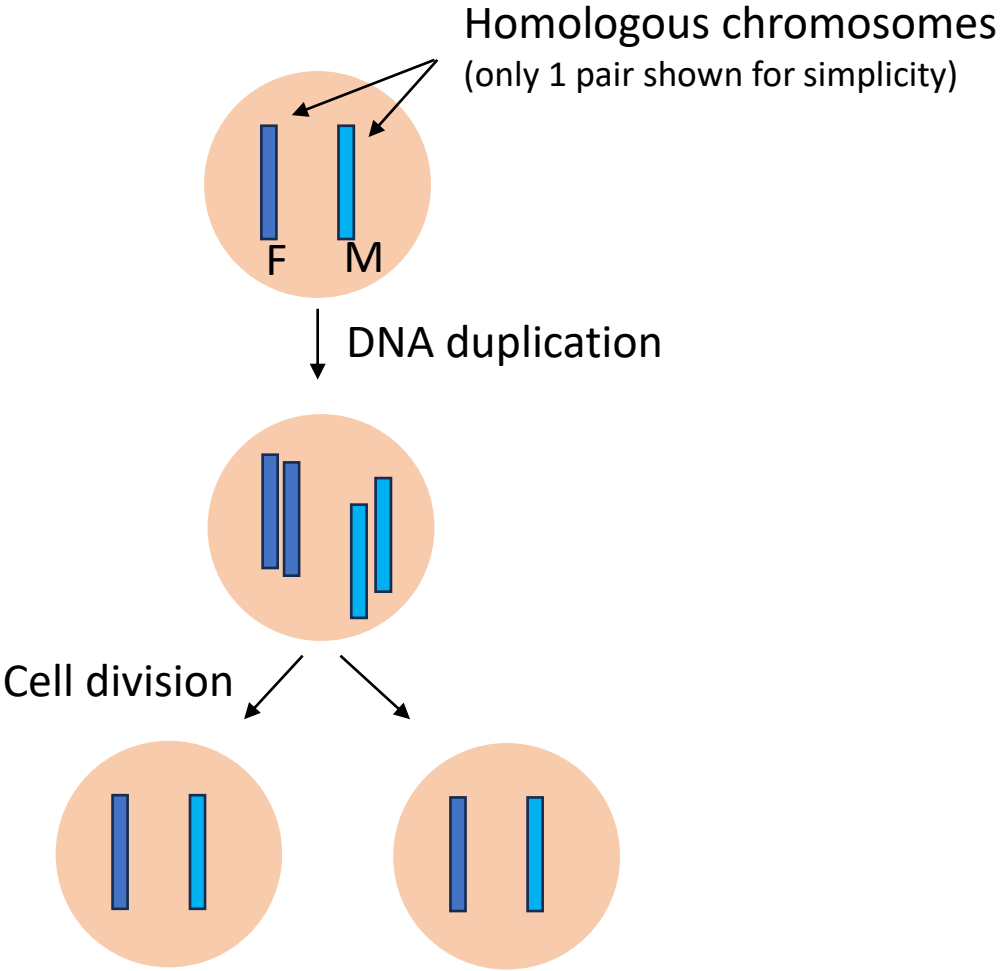
Mitosis



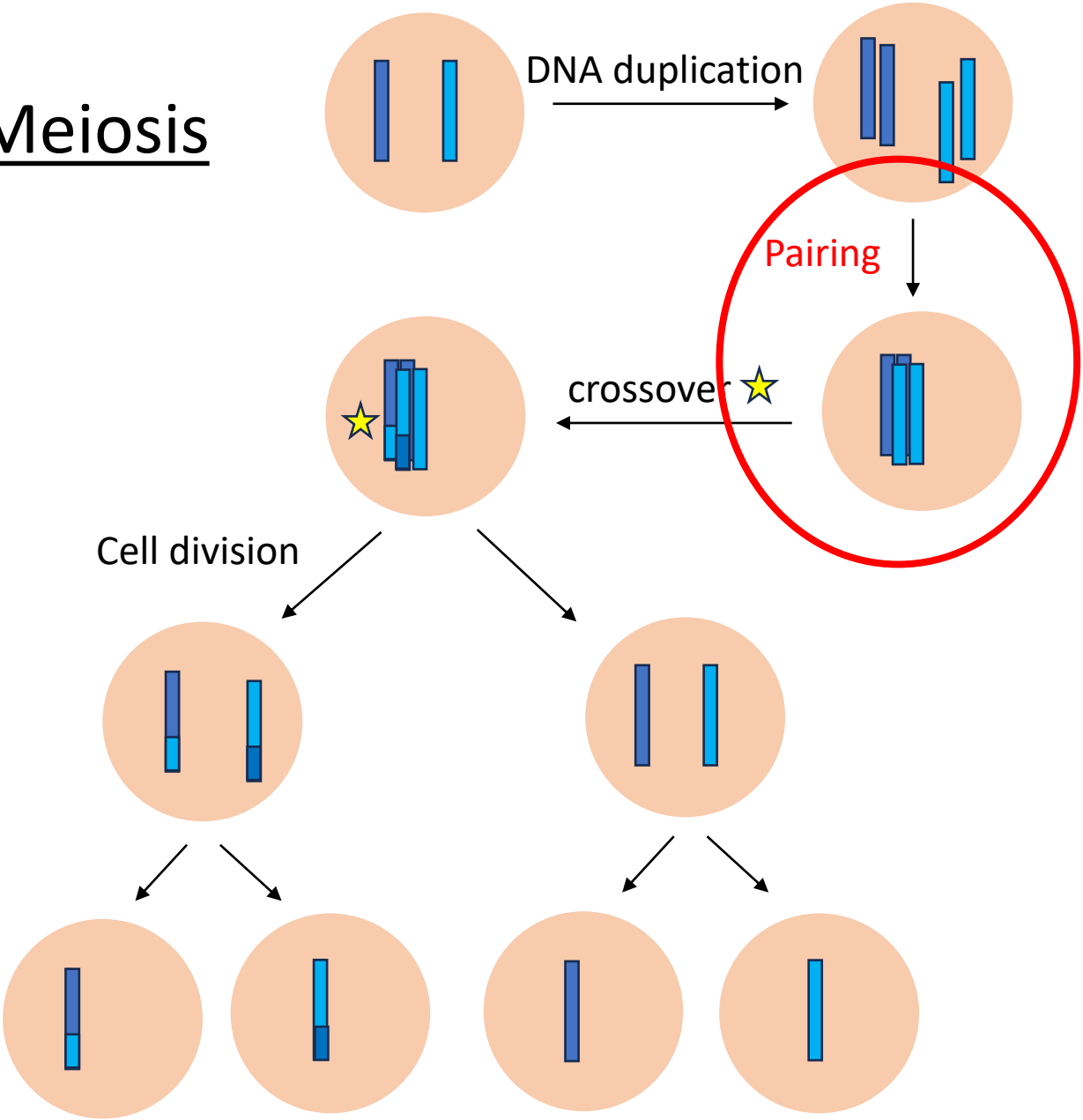
Meiosis

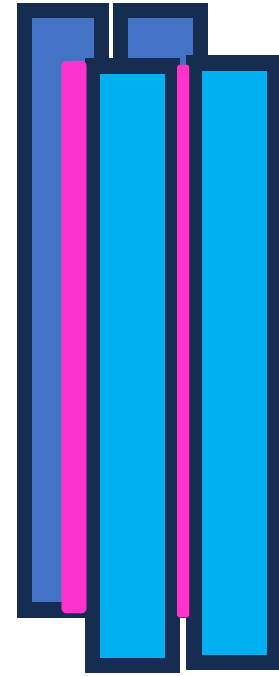


Mitosis



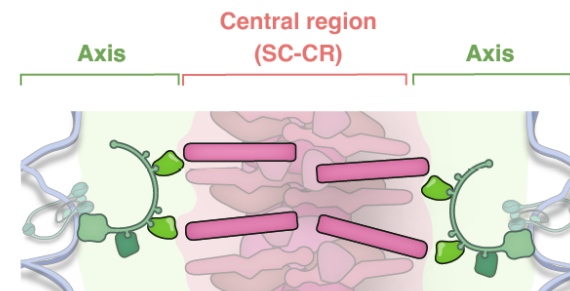
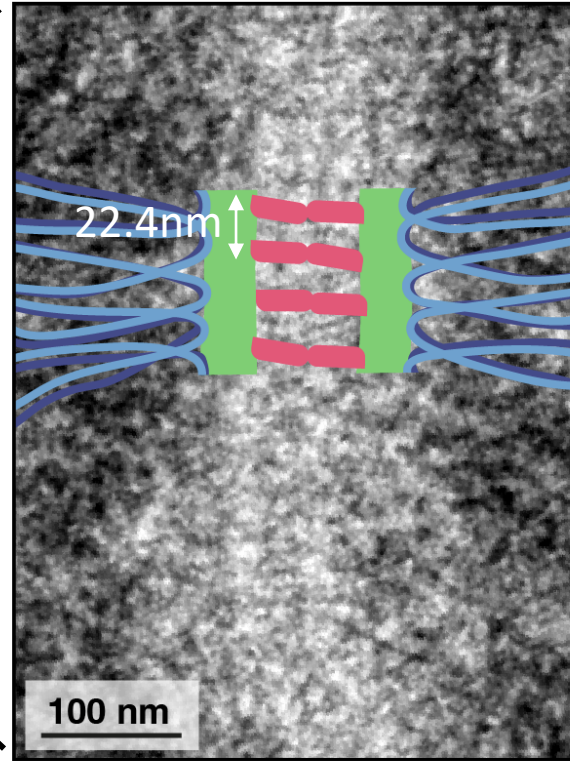
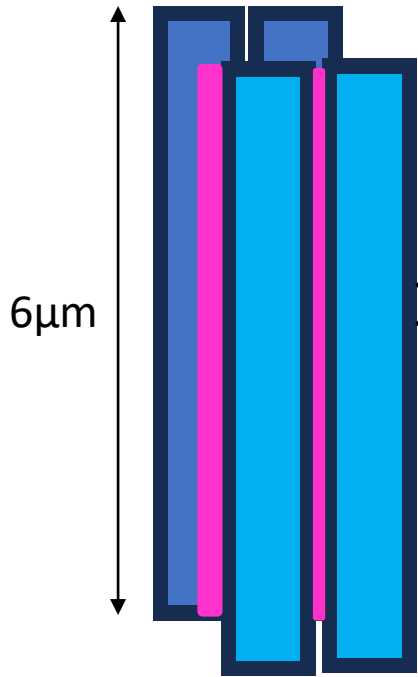
Meiosis



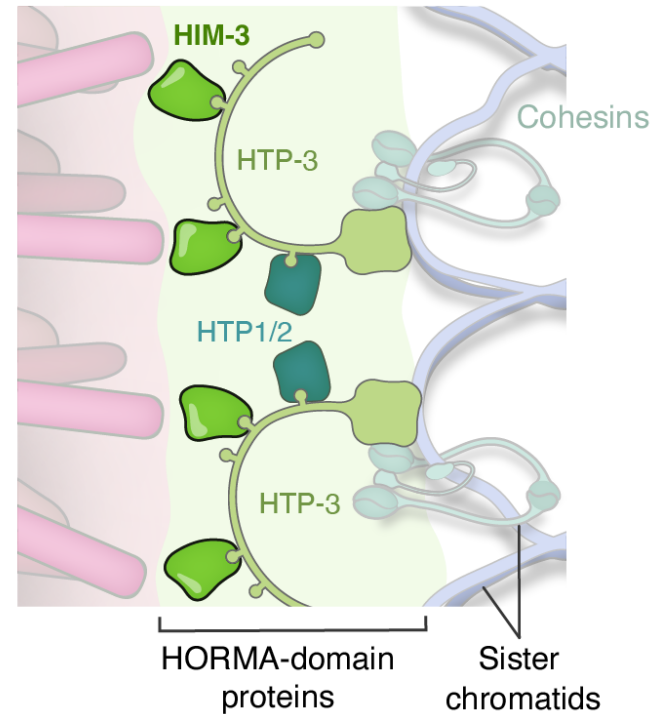
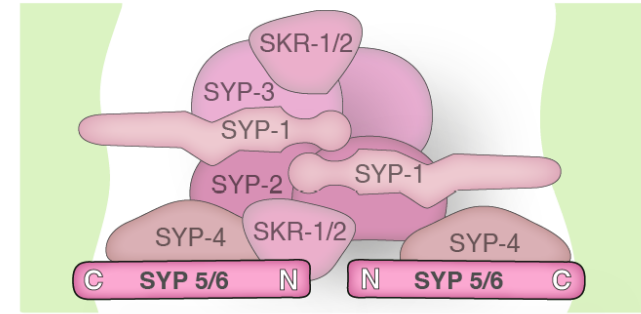


2. **Synaptonemal complex (SC)** as a glue to enable genetic crossover

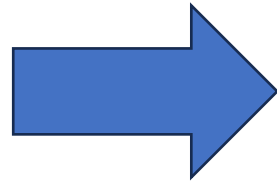
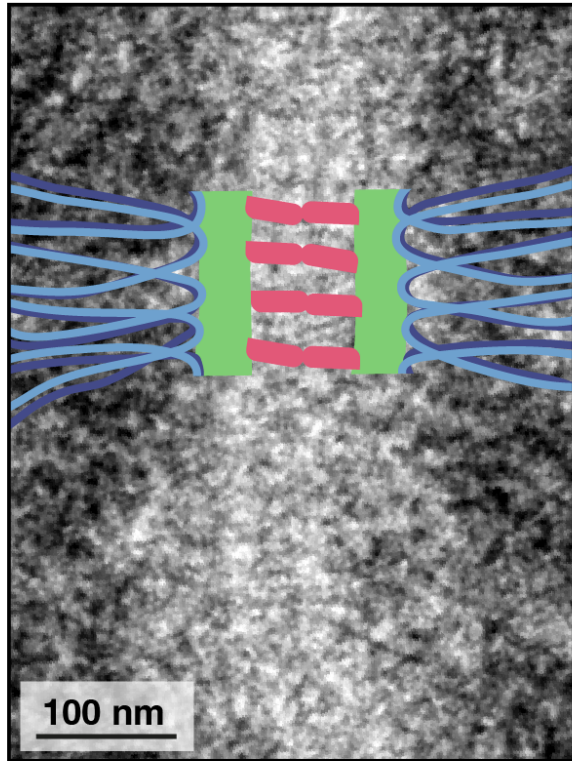
SC composition



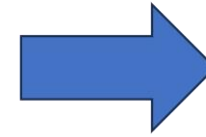
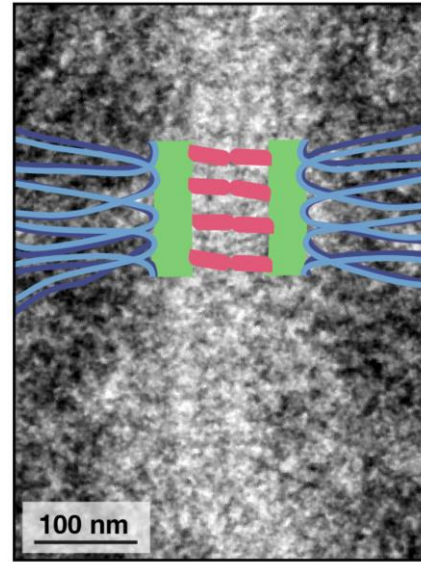
SC-CR



Like a zipper?



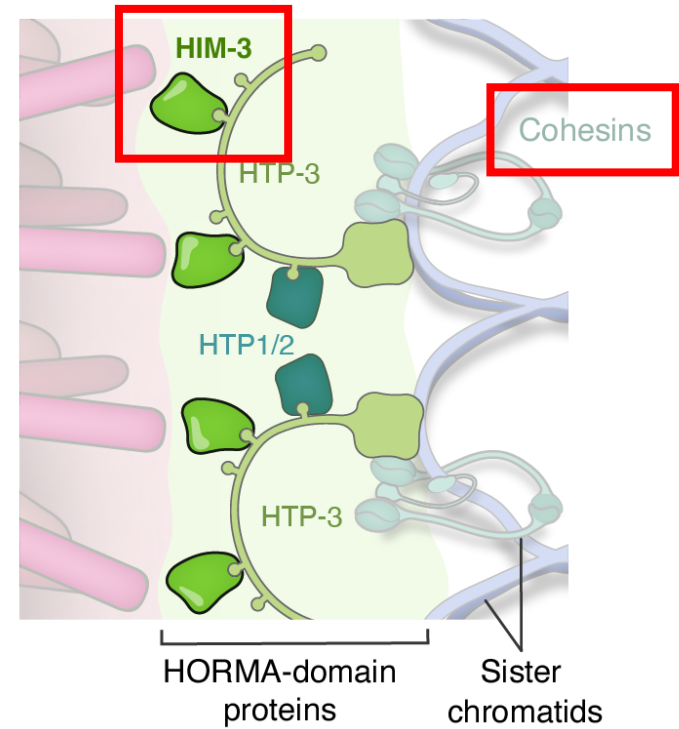
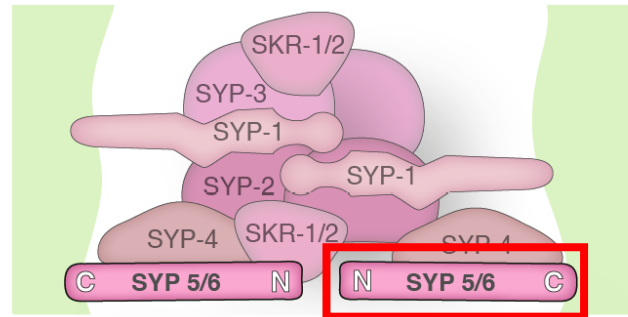
What does it mean?



- Unidirectional?
- Driven by nonequilibrium forces (e.g., via ATP-hydrolysis)?
- How does the zipper get on the chromosomes?

Visual similarity does not answer these questions

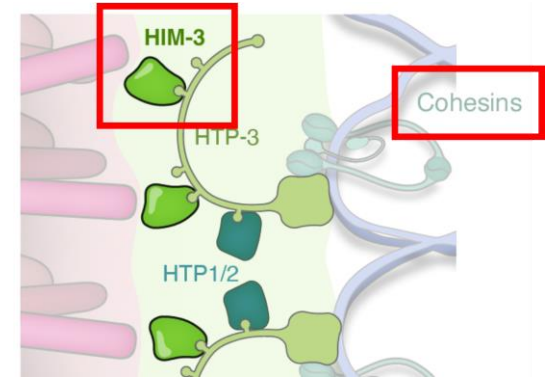
SC-CR



3. Perturbations of SC to probe molecular mechanism of SC assembly

Getting rid of cohesins

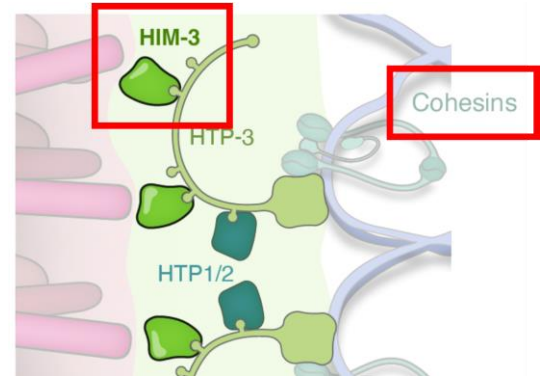
Do we get linear aggregates of SC-CR (e.g., six zipped-up rods)?



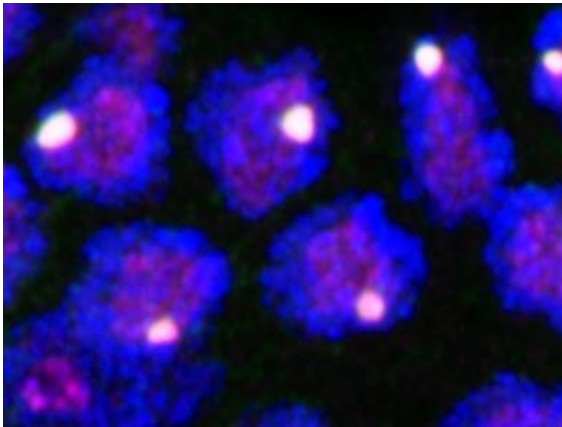
Getting rid of cohesins

Do we get linear aggregates of SC-CR (e.g., six zipped-up rods)?

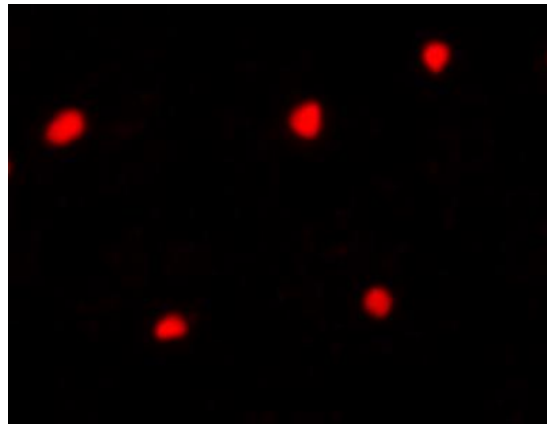
No, we get spherical condensates!



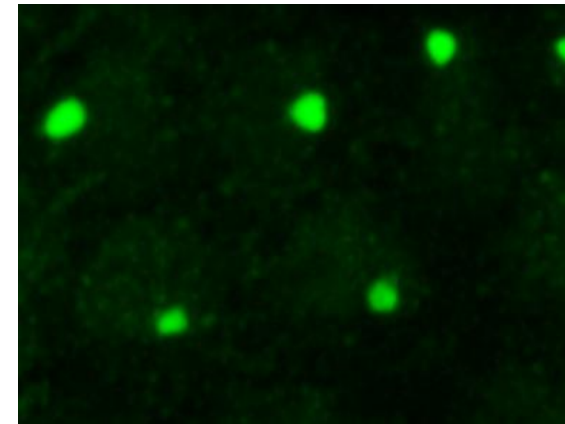
DAPI (merge)



SYP-5



HIM-3

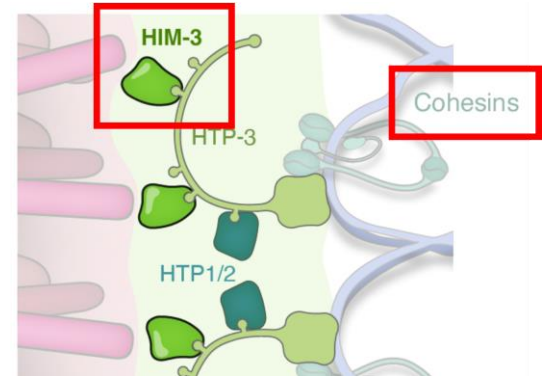


→ SC-CR interactions is not 'entirely' directional

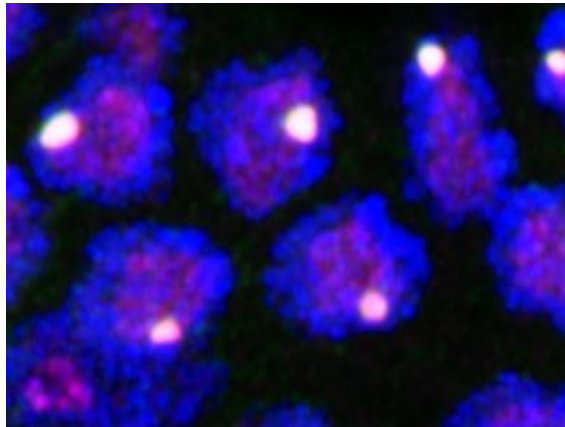
Getting rid of cohesins

Do we get linear aggregates of SC-CR (e.g., six zipped-up rods)?

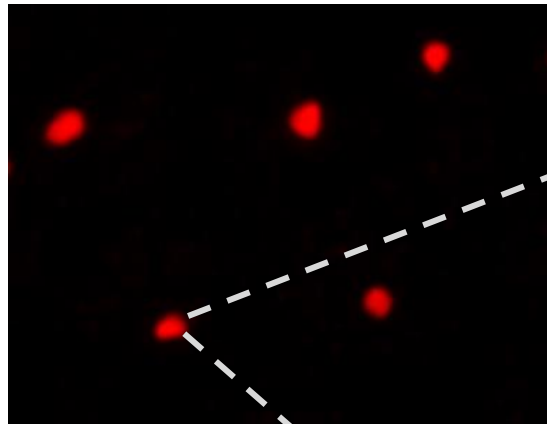
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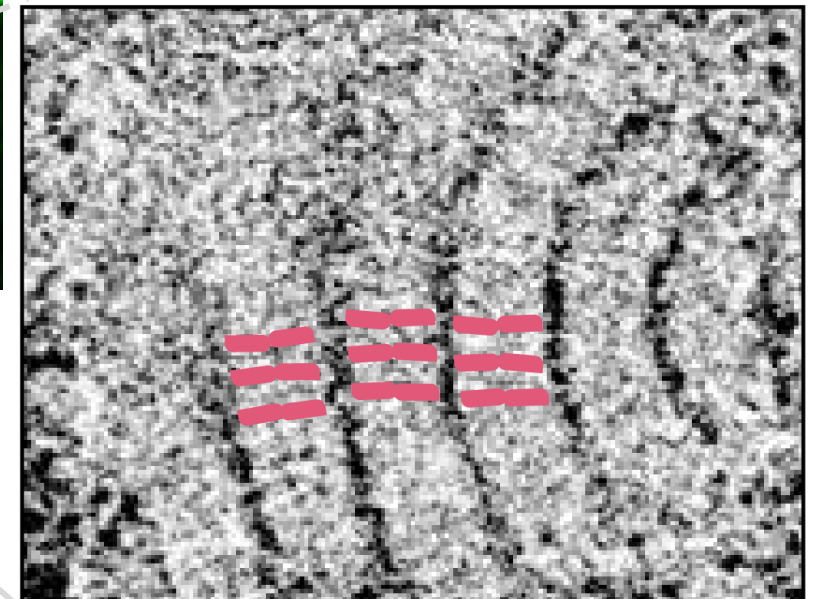
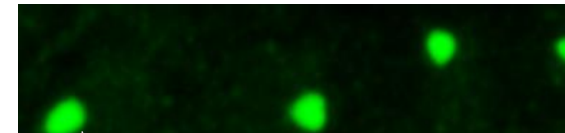
DAPI (merge)



SYP-5



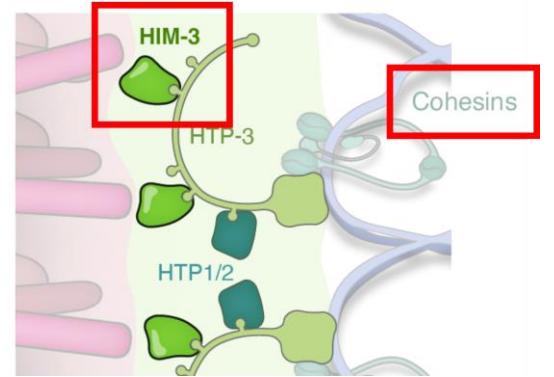
HIM-3



→ SC-CR interactions is not 'entirely' directional

Weakening HIM-SYP interactions

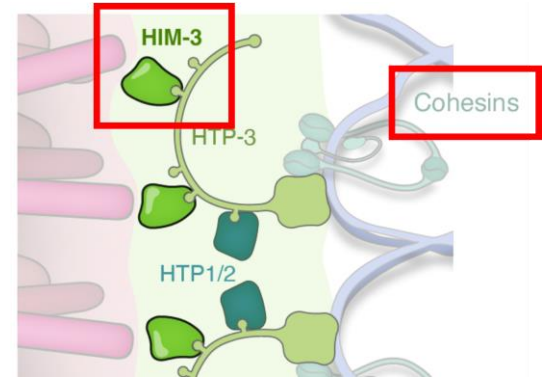
Do we get 6 partially zipped up chromosome pairs?



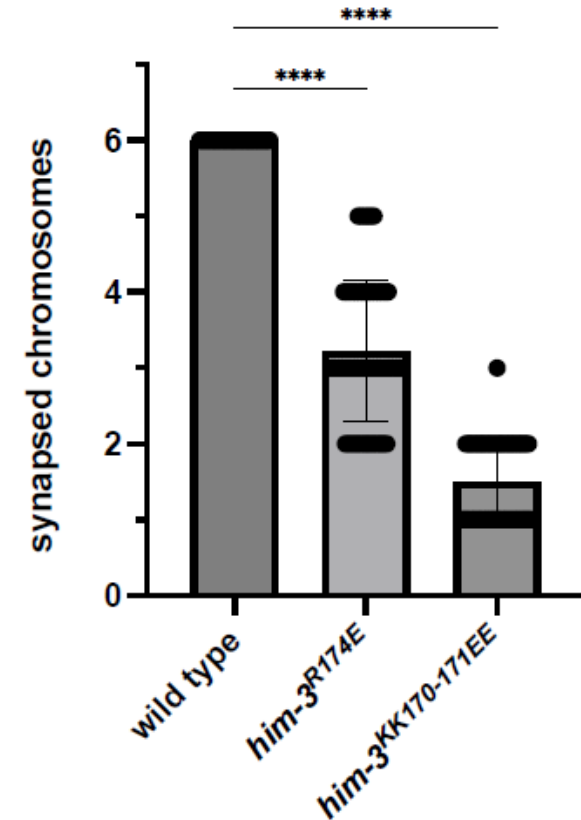
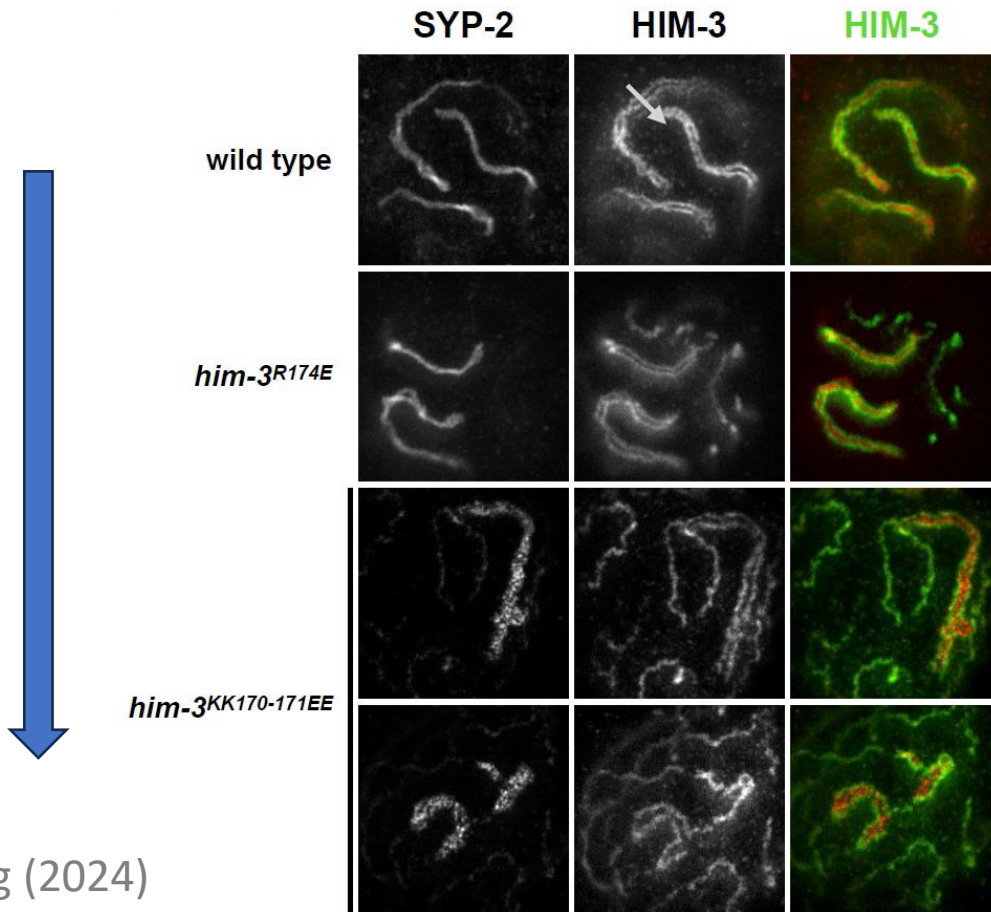
Weakening HIM-SYP interactions

Do we get 6 partially zipped up chromosome pairs?

No, we tend to fully zipped up chromosome pairs or completely unzipped pairs!



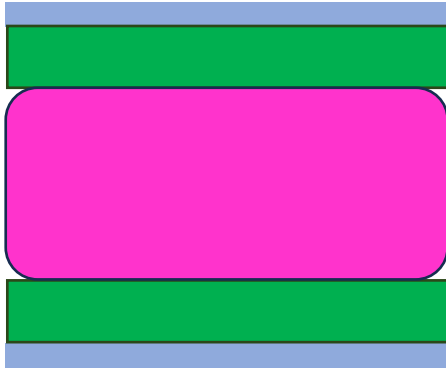
Progressive
weakening of
HIM-SYP
interactions



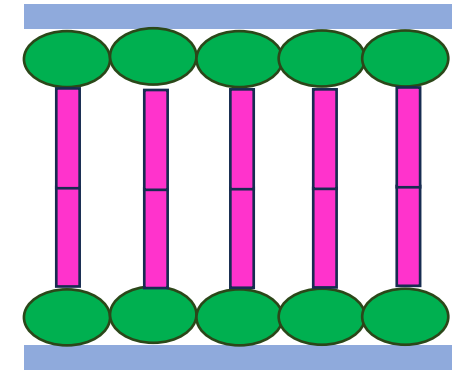
So what is going on?

We need to inject some physics!

Condensate wetting



Adsorption (molecular binding)



4. Physics of SC assembly

A thermodynamic model

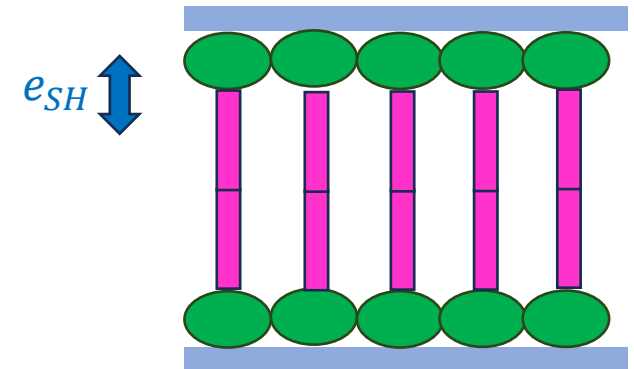
- Free energy includes 2 ingredients
 1. Interfacial free energy (continuum picture)
 2. Bindings between HIM & SYP (molecular picture)

$$F_{tot} = e_{SH} \times [\# \text{ HIM-SYP bonds}] + F_{interface}$$

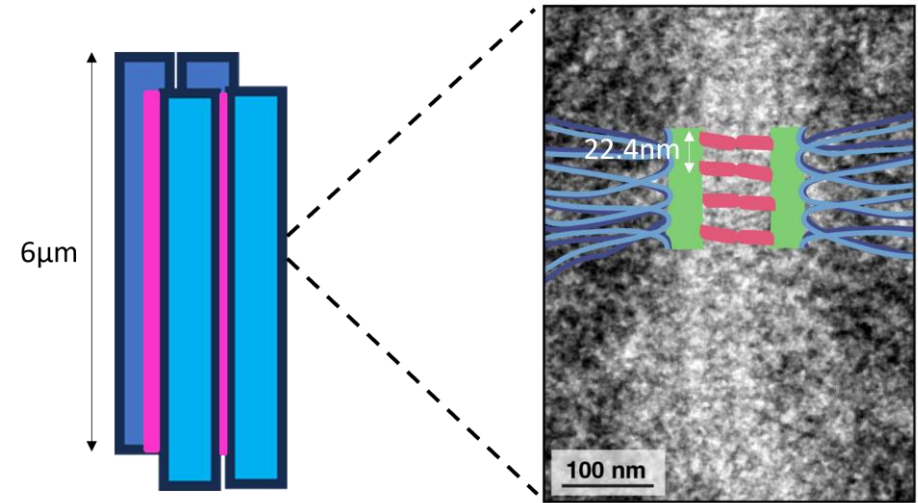
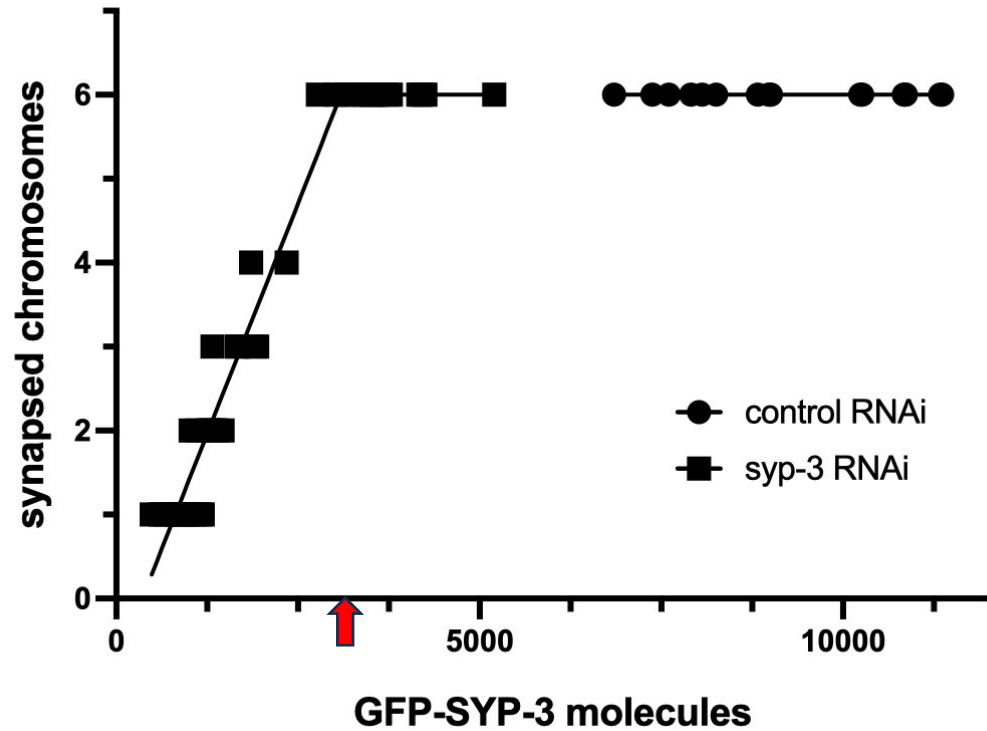
Condensate wetting



Adsorption (molecular binding)



Why ingredient 2 (molecular binding)?



Around 540 binding sites per chromosome pair
→ a total of ~3200 binding sites (↑)

→ Every binding site is bound until there isn't enough SYP-5 around!

Competition between HIM-SYP binding & interfacial energy

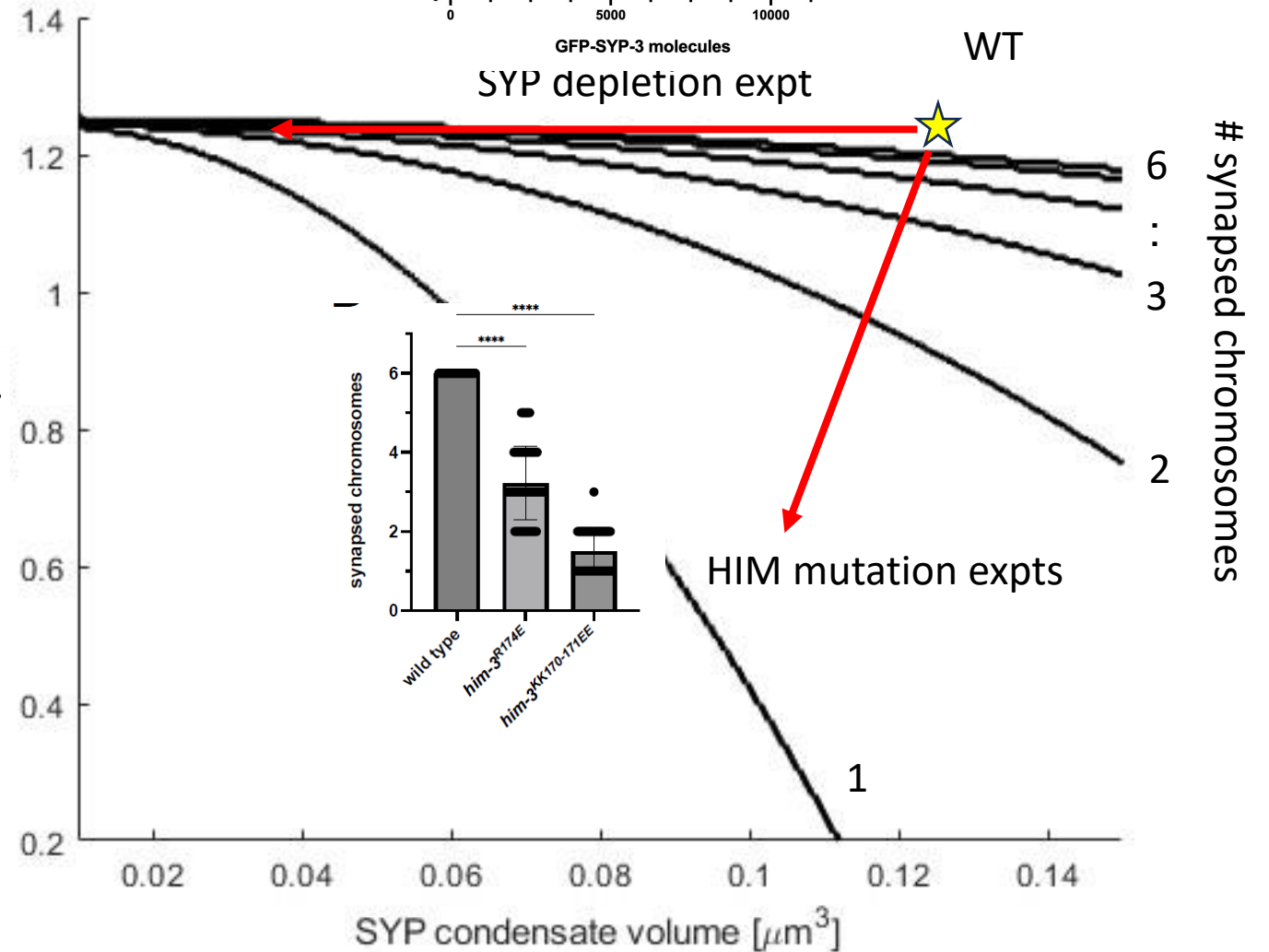
$$F_{tot} = e_{SH} \times [\# \text{ HIM-SYP bonds}] + F_{interface}$$

- If HIM-SYP binding dominates \rightarrow all six chromosome pairs are synapsed
- Conversely, as interfacial energy increases, fewer synapsed chromosomes (fewer condensates = less surface area)

'Phase' diagram

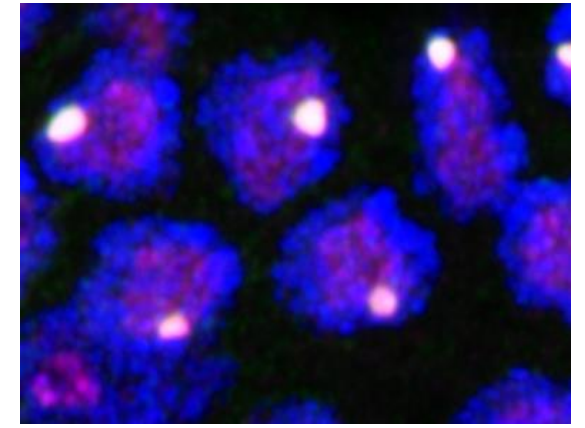
Other perturbations
(temperature/SYP mutations)
can also be explained by this
phase diagram

$$\frac{e_{SYP-HIM}}{e_{SYP-SYP}}$$

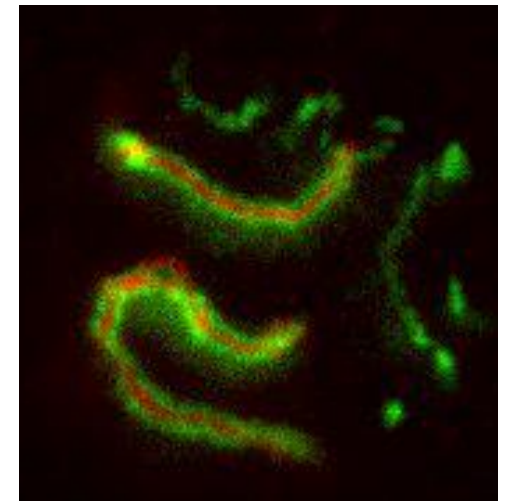


Summary

- A minimal, thermodynamic model explains all salient experimental observations of SC assembly
- Key mechanisms
 1. HIM-SYP binding at the molecular level
 2. Condensate wetting at the mesoscopic level

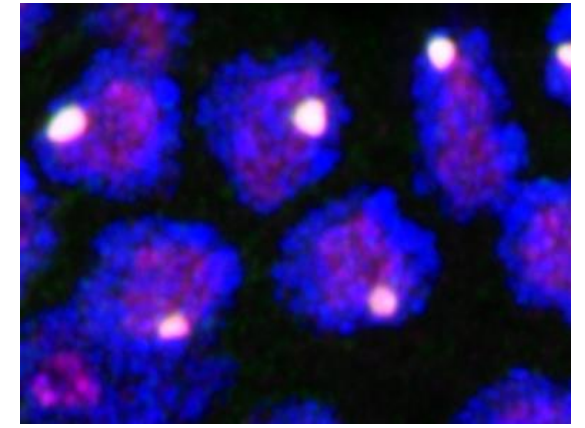


molecular binding
+
wetting

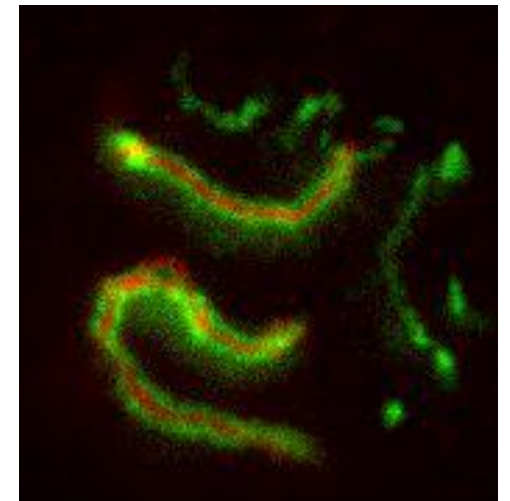


Outlook

- Only static pictures so far, but thermodynamics does dictate how system evolves and provides interesting predictions
- Why the need of condensate? To speed up chromosome synapsis?



molecular binding
+
wetting



Thank you for your attention