Investigating chromosome folding during mitosis

Giada Forte







From interphase to mitosis

Interphase



Earnshaw et Laemmli, JCB, 1983

Internal structure of mitotic chromosomes

Late 70s: Lemmli investigates the internal structure of mitotic chromosomes.



Marsden et al, Cell, 1979

Mitotic chromosomes are organised as bottlebrush polymers.

Recent Hi-C experiments provide genomic contact probability



Naumova et al, Science, 2013

Key elements for mitotic compaction



Watson, Molecular biology of the gene.

Kalitsis et al, Chromosome Research, 2017

Condensin active loop extrusion



Goloborodko et al, eLife, 2016

Issue: loop extrusion can explain only compaction during the early stage of mitosis.

Our model for chromosome compaction



Loop size

Two parameters:

Topoisomerase activity (strength of repulsion among non bonded chromatin beads)

Forte et al, Journal of Cell Biology, 2024

Our model for chromosome compaction



Comparison with experiments

Simulated contact probability is in line with experiments.

Experiments **10**-5 **10**-6 P(s) ~ s^{-0.5} **10**⁻¹ P(s) (s) 10⁻⁷ chr17 10⁻² 10-8 chr21 10⁻³∟____ 10³ 10⁻⁹ **10**⁵ **10**⁷ **10**⁴ **10**⁶ Genomic distance s (bp)



Elasticity of mitotic chromosomes





Claussen et al, Cytogenet. Genet. Res., 1994

Forte et al, Journal of Cell Biology, 2024

Investigating common fragile sites

Common fragile sites (CMFs) are unstable chromatin regions which appear under replication stress conditions.

CFSs are prone to show faulty folding during mitosis and are often associated to cancer onset.







CMFs have been associated to faulty condensin loading.

Control





Conclusions and future directions



- New pathway to explain mitotic chromosome compaction;
- Simulation of CFSs

And now? how are loop extrusion and bridging activity regulated? Which is the relationship between CFSs and supercoiling?

Acknowledgements

Davide Marenduzzo (UoE)Lora Boteva (UoE)Nick Gilbert (UoE)Filippo Conforto (UoE)Peter Cook (Oxford University)

Thank you for your attention!