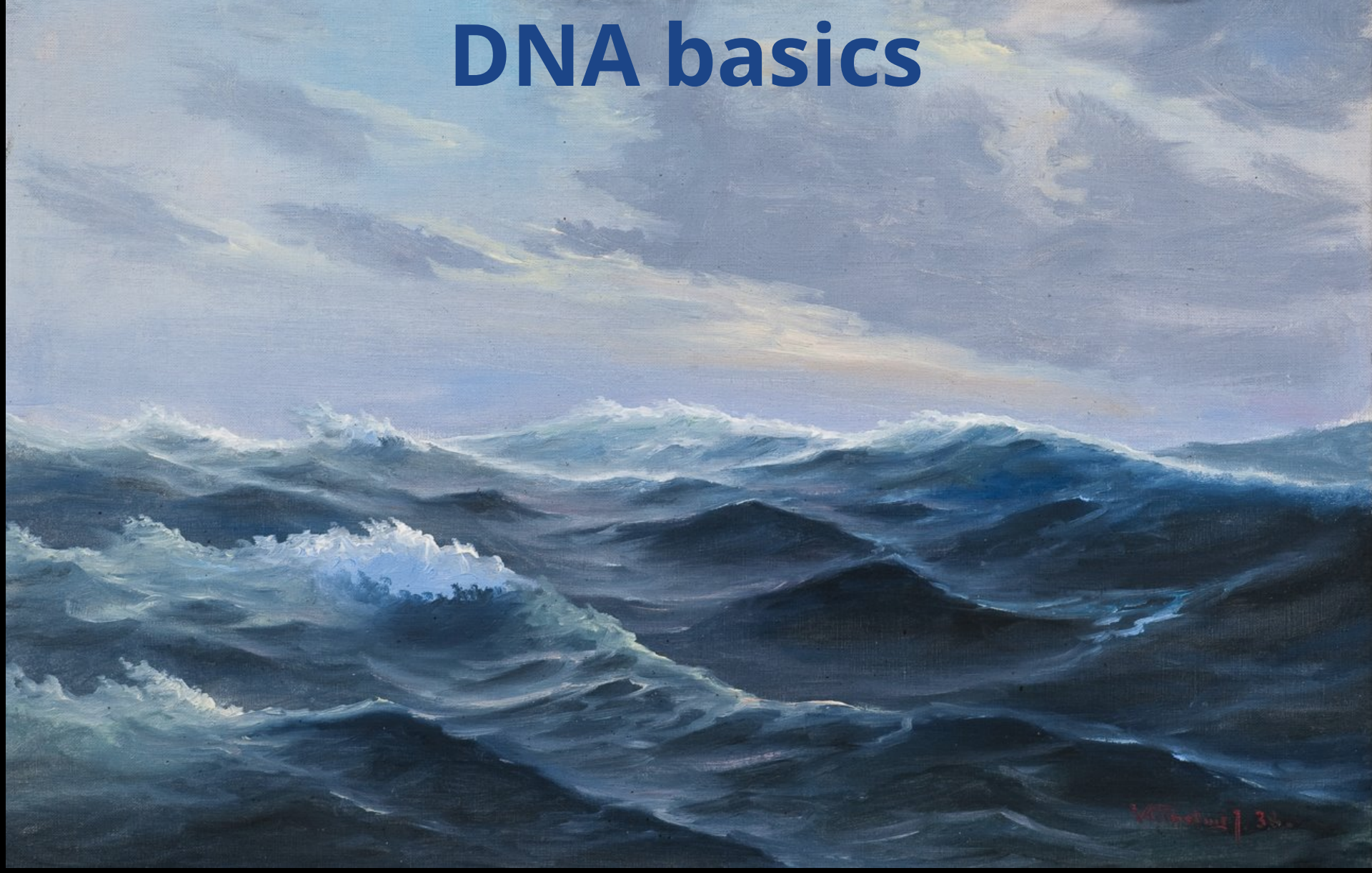
DNA basics



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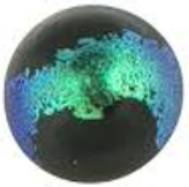
Chromosomes and DNA

DNA

~1 m crystallographic length

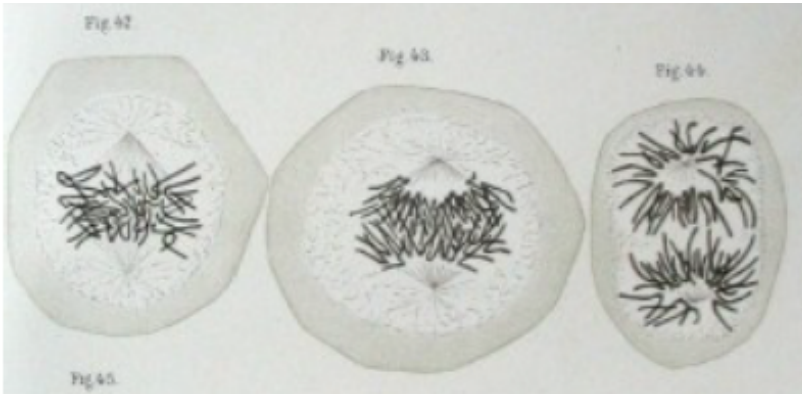
2 km

5 um nucleus



1 cm

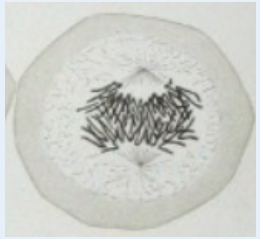
Walther Flemming



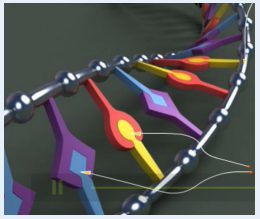
Chromosomes in mitotic cells, c.a. 1885

Multiscale chromosome organization

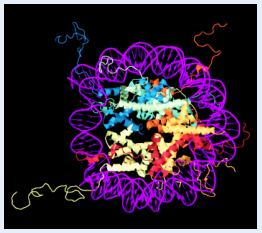
Mitotic chromosomes
Flemming, 1885



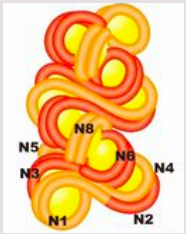
B-DNA
Watson & Crick, 1953
Franklin & Gosling, 1953



Nucleosomes
Luger, 1997



Chromatin fibers, loops, etc



Chromosome Territories
Bolzer, 2005

size

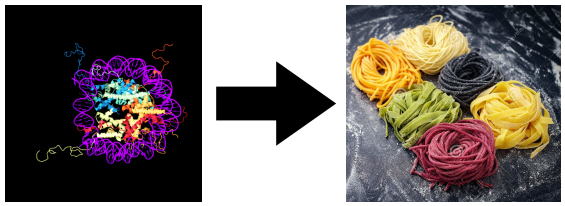
2nm

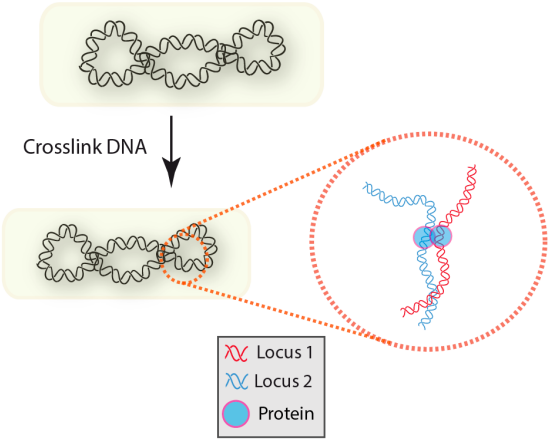
~10nm, 180bp

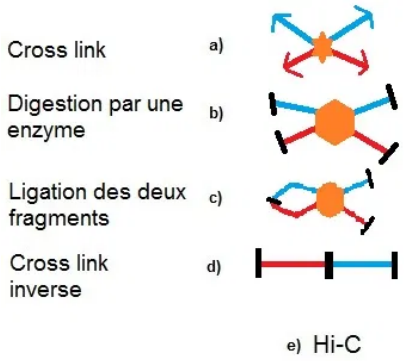
~200nm, >100kb

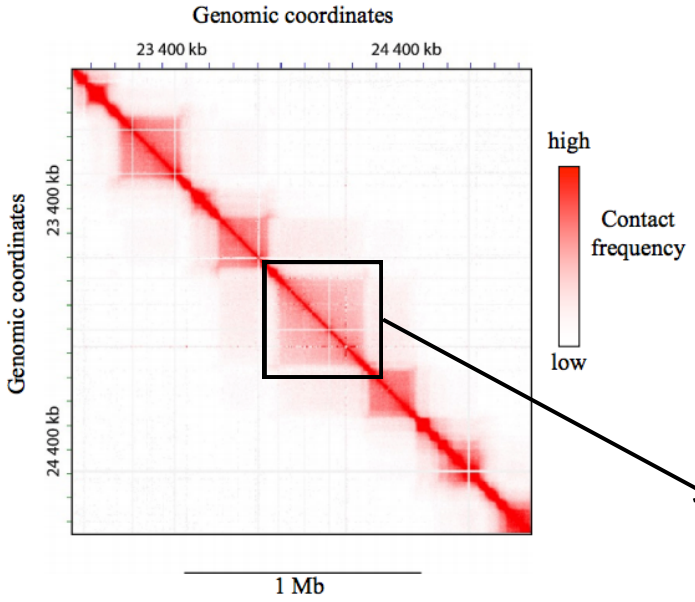
~1um, >10Mbp

Sequencing-based technologies









High-throughput sequencing

GAAGTGCGGTTCAACACCCTCCG

chromosome conformation capture
(3C-seq, **Hi-C**, etc)

TAD: Topological Associating Domains

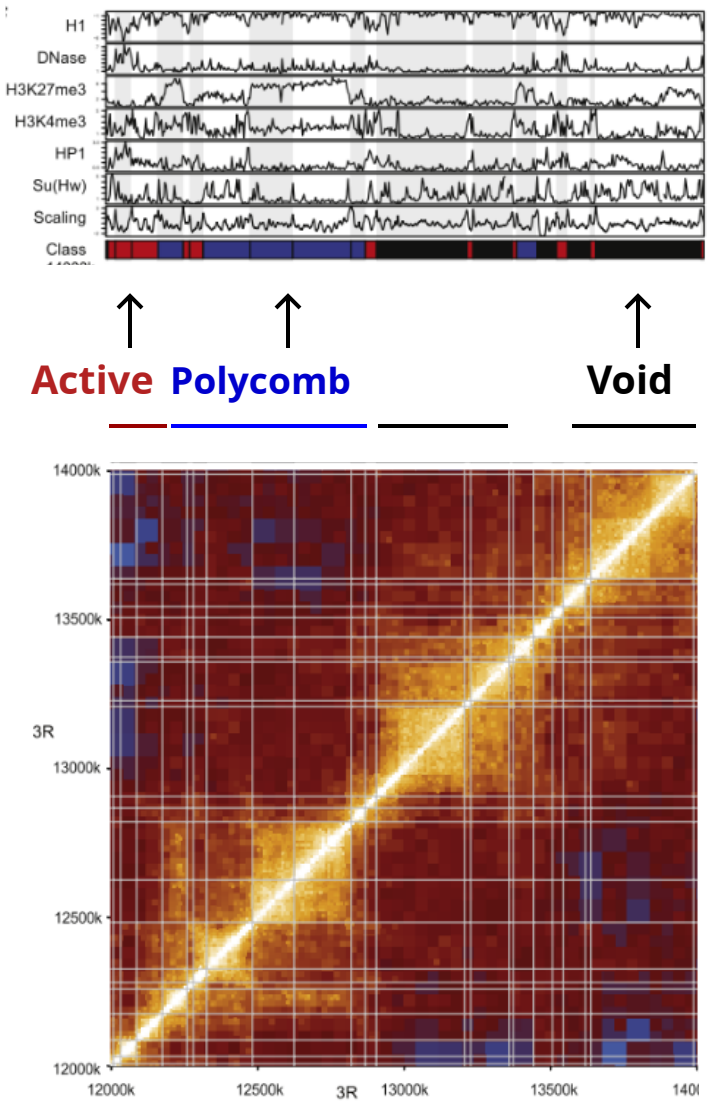
(Sexton, 2012, Dixon, 2012; Nora, 2012)

epigenetic domains and TADs

NGS: chromatin immuno-precipitation (ChIP)

epigenetic domains

Filion (2011)



Active: RNA polymerase

Polycomb: H3K27me3

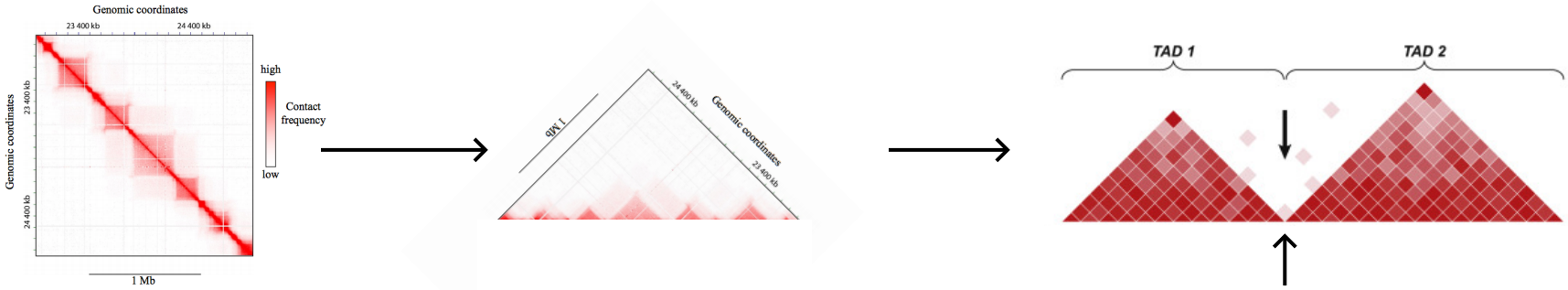
NGS: Hi-C

TADs

(**Sexton, 2012**; Dixon, 2012; Nora, 2012)

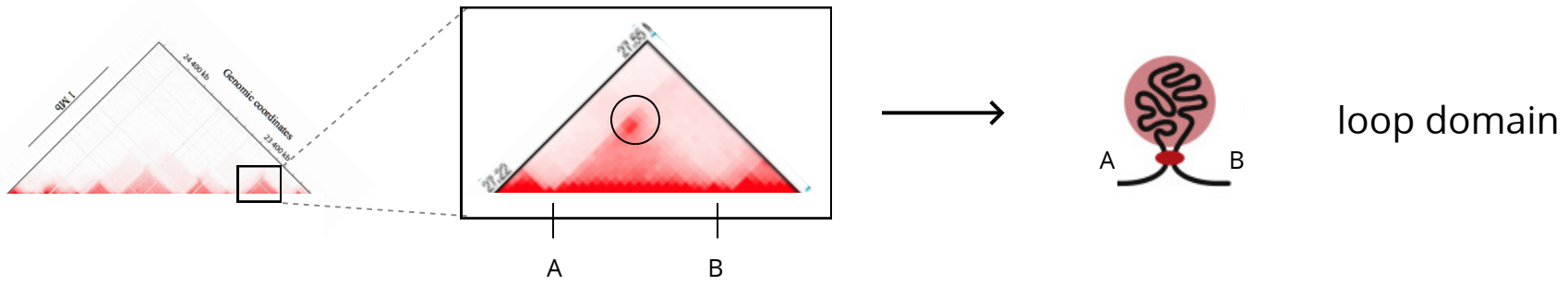
TADs: structural features

Domain borders



housekeeping genes
RNApol2
H3K4me1
chromatin insulators (e.g. CTCF)

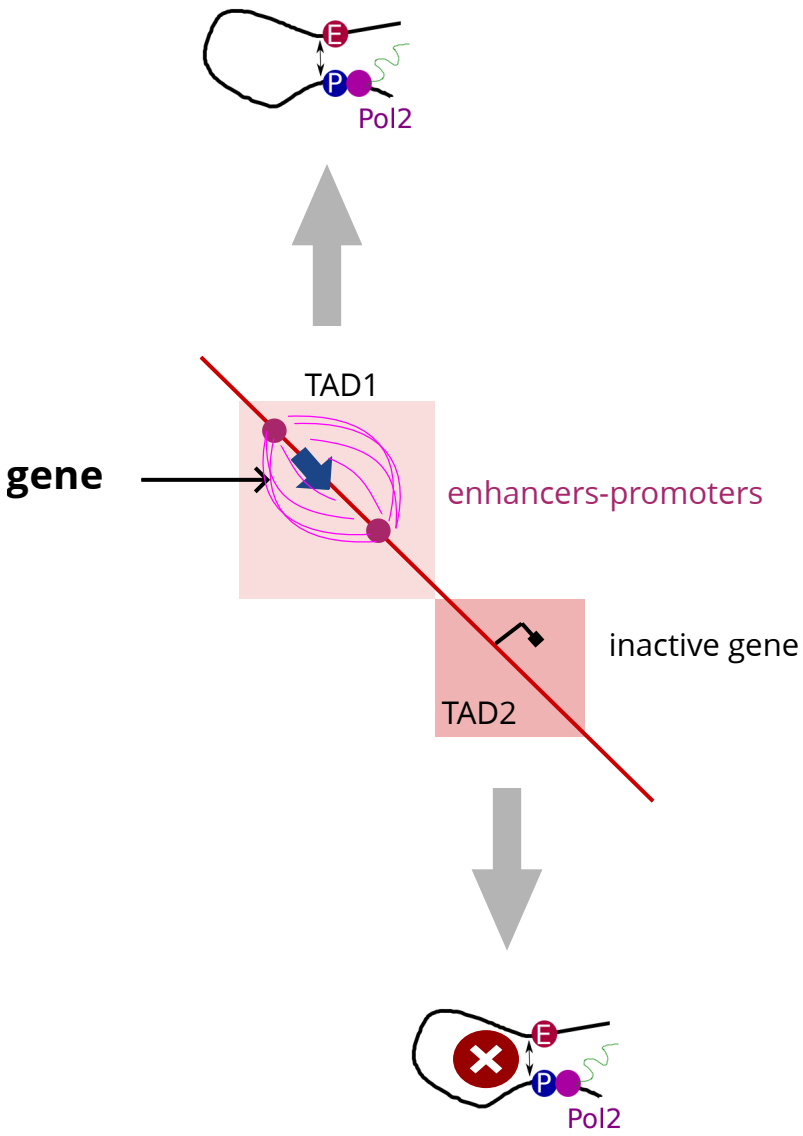
Border Loop



loop domain

Rao (2015)

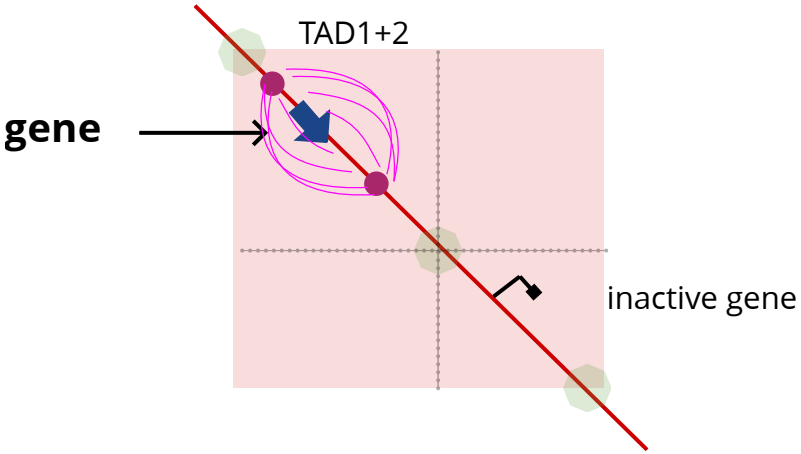
Do TADs have a functional role?



- TADs are conserved among species (Dixon, 2012)
- Internal structure of TADs changes between cell types (Phillips-Cremins, 2013)
- removal of border leads to ectopic expression and developmental defects and to cancers (Lupiañez, 2015; Norhcott, 2014)

TADs are functional units of chromosome organization

Genetic manipulation: are TADs correlated to function **?**



- Loss of TAD insulation lead to small effect in global transcription (Nora, 2017; Schwarzer, 2017; Rao, 2017; Despang, 2017).
- Fusion of TADs may not change gene expression (Rodriguez-Carballo, 2019; Williamson, 2019).
- Large TAD rearrangements lead to small changes in gene expression (Ghavi-Helm, 2019).
- Enhancers can communicate across TAD boundaries (Galupa, 2020)

Do TADs play major roles in transcriptional regulation ?