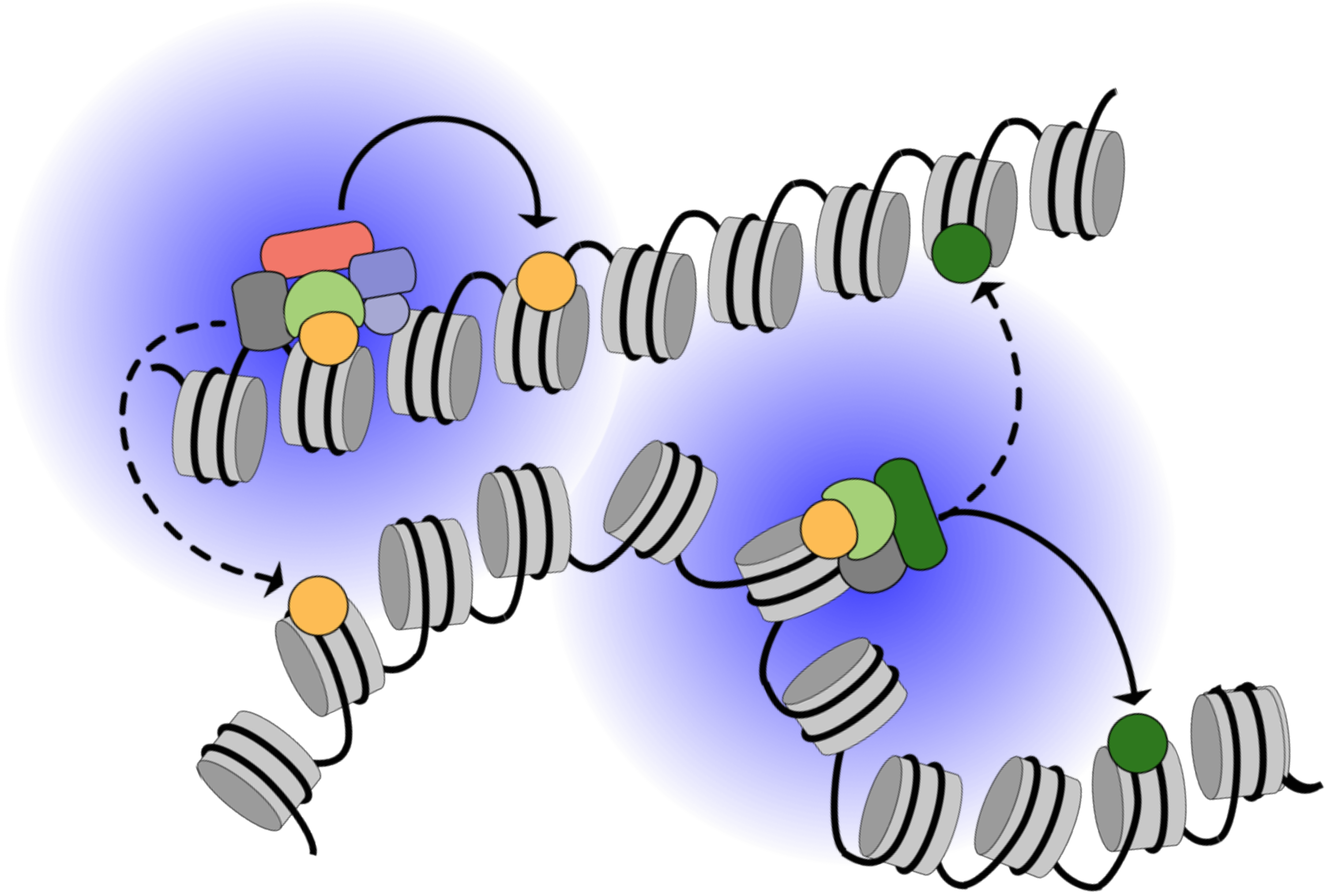
WS 24/25: Interactions of Proteins and Nucleic Acids: Biophysical Concepts and Theoretical Descriptions

Thursday 14.15-15.45, Bioquant SR 41 (unless noted otherwise)



Karsten Rippe

Division of Chromatin Networks
DKFZ & Bioquant

dkfz.

50 Years – Research for
A Life Without Cancer

BioQuant
MODEL base of LIFE

Coordinates for the seminar

Karsten Rippe
Division of Chromatin Networks
Bioquant, Room 645, 6th floor
Telefon: 54-51376
e-mail: Karsten.Rippe@bioquant.uni-heidelberg.de or Karsten.Rippe@dkfz.de

Overview on my Biophysics/Systems Biology teaching:
http://malone.bioquant.uni-heidelberg.de/teaching/index_teaching.html

Material for the lecture: Biophysical concepts and theoretical descriptions

http://malone.bioquant.uni-heidelberg.de/teaching/BPC_lectures/BPC_1+2.html
Username: teaching
Password: nonukes

Winter term 2024/25
Interactions of Proteins and Nucleic Acids: Biophysical Concepts and Theoretical Descriptions

Summer term 2025
Physico-chemical methods in systems biology within the Major Systems Biology (contact me for registration if you want to attend)

Literature

C. Cantor und P. Schimmel, Biophysical Chemistry, Vol I, II und III, Freeman Press, 1980

P. Nelson, Biological Physics, Freeman, 2004.

K. E. van Holde, W. C. Johnson, & S. P. Ho, Principles of Physical Biochemistry, Prentice-Hall, 1998; 2nd edition 2005

R. Philipps & R. Milo, Cell Biology by the Numbers, Garland Science, 2016

Research articles, book chapters and web links: see lecture web site:
http://malone.bioquant.uni-heidelberg.de/teaching/BPC_lectures/BPC_1+2.html

Computer programs

Viewing 3D protein and DNA structures: VMD (Visual Molecular Dynamics)
http://www.ks.uiuc.edu/Research/vmd

Kinetic simulations: Copasi (is being developed by the group of Ursula Kummer in the BioQuant)
http://www.copasi.org

Calculations and plotting: e. g. Maple, Mathematica, Excel, Origin, Kaleidagraph, R etc.

AI (LLM, large language models): perplexity.ai, chatgpt.com, claude.ai

Grades for “benotete Scheine”: 6 problem sets (biweekly)

Problem sets

- There will be problem sets every 2 weeks (6 in total)
- To be returned the following Thursday by mail to me before 14:15 hour (Karsten.Rippe@bioquant.uni-heidelberg.de, include BPC2024 in subject line)
- We will discuss the answers to the problem sets, as well as any issues you encountered. The corrected problem sets will be returned the next Thursday, ideally.
- To receive credit, you must obtain at least 50% of the possible points. Only the 5 highest-graded problem sets will be considered for your final grade, so you can still achieve 100% even if one problem set is missing.
- You are welcome to work in groups to complete the problem sets; however, each student must submit their own individual answers.
- Problem set #1, handed out today (October 17), is due on October 31.

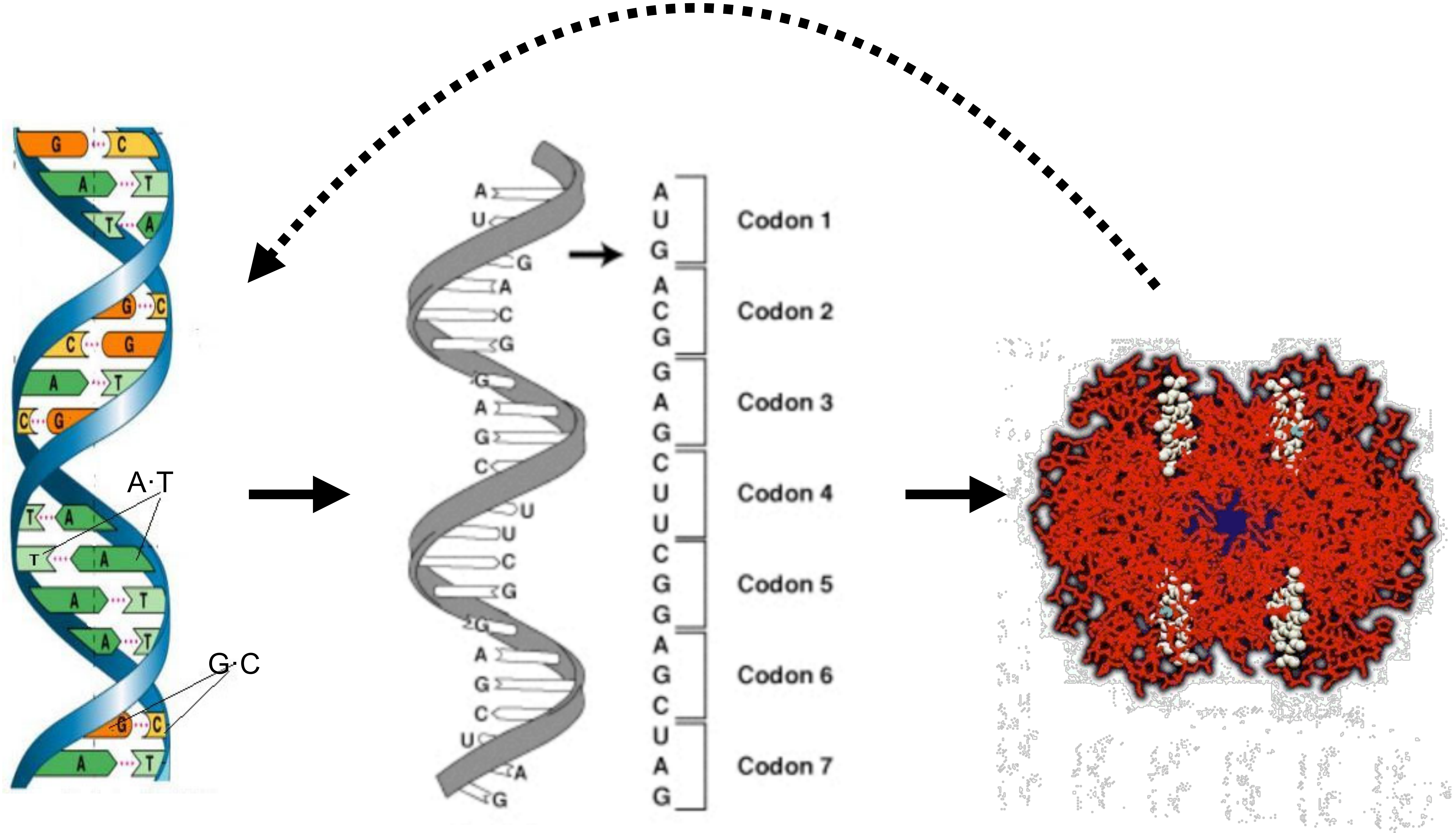
Lead questions of the seminar

- What drives binding of proteins to DNA and chromatin and target them to certain sites?
- How does the environment of the cell shape these interactions?
- How can we measure protein binding to DNA/chromatin in vitro and in living cells?
- What mechanisms partition the genome into active or silenced subcompartments?
- How is transcription regulated in bacteria vs. eukaryotes via macromolecular interactions?

Biophysical Concepts and Theoretical Descriptions

- Intro lecture and length and time coordinate system
- Interactions between molecules and associated energies
- Thermodynamics of protein-DNA interactions
- Equilibrium binding of proteins and nucleic acids
- Diffusion and protein transport
- Measuring protein-DNA/chromatin interactions in living cells
- Nuclear subcompartments - assembly mechanisms & functions
- Gene expression analysis in living cells
- Chromatin organization and remodeling
- Protein interactions mediated by DNA and chromatin looping (enhancers)
- Applying sequencing-based methods to study protein-DNA interactions
- Integrating sequencing and microcopy in spatially resolved “omics”

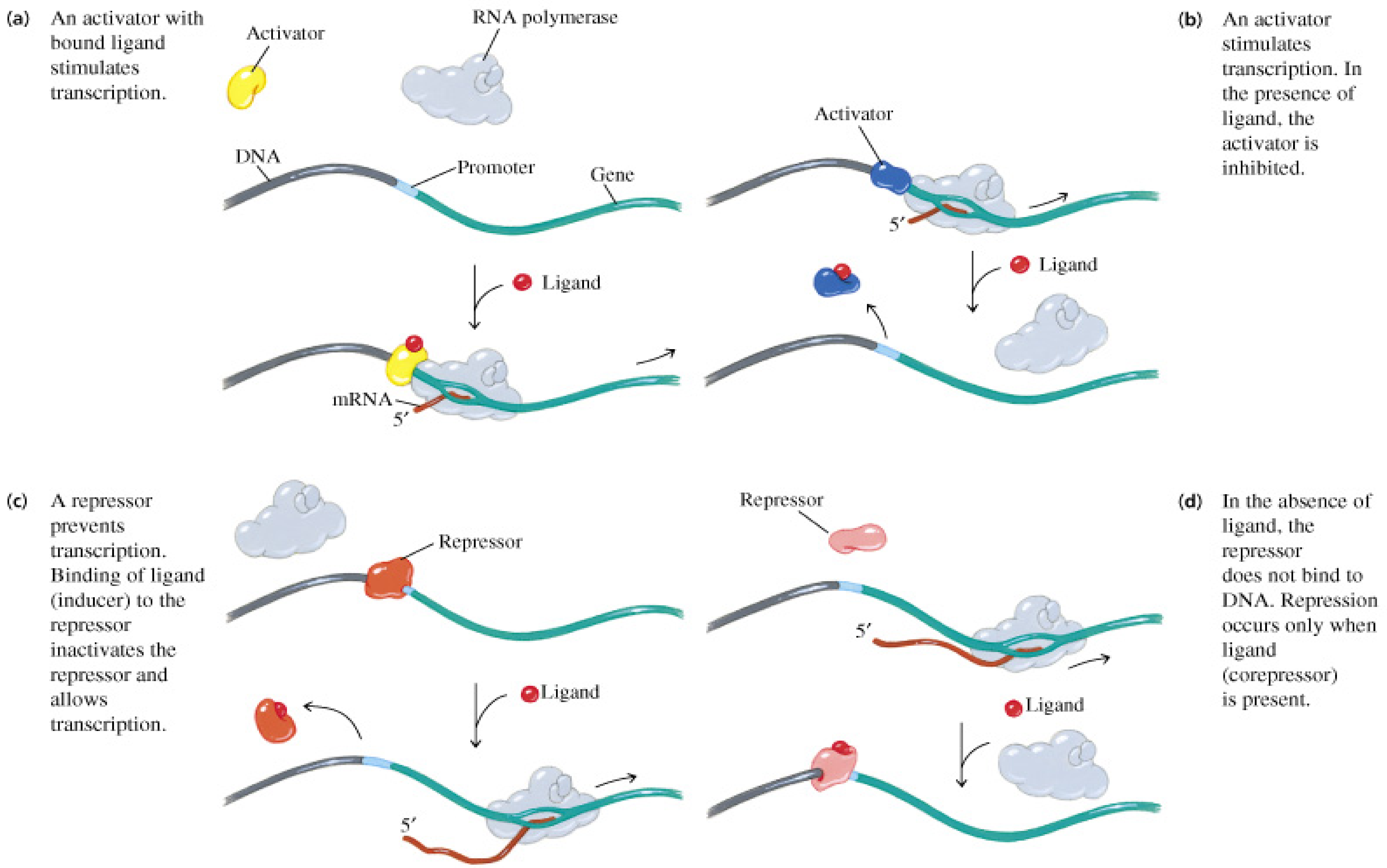
The central dogma in molecular biology



DNA **RNA** **Protein**

… with some feedback loops

Strategies for transcription regulation in bacteria

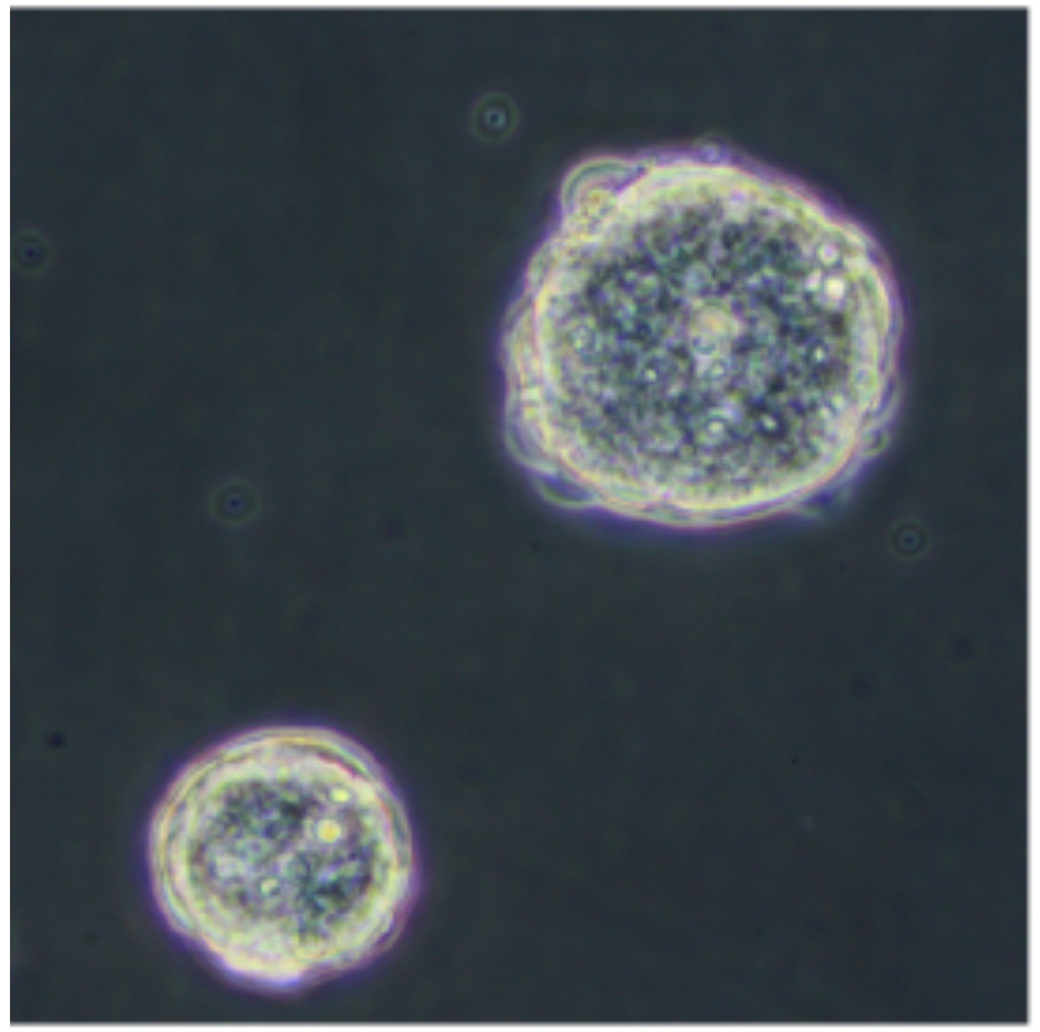


Epigenetic differences determine gene expression programs in higher eukaryotes

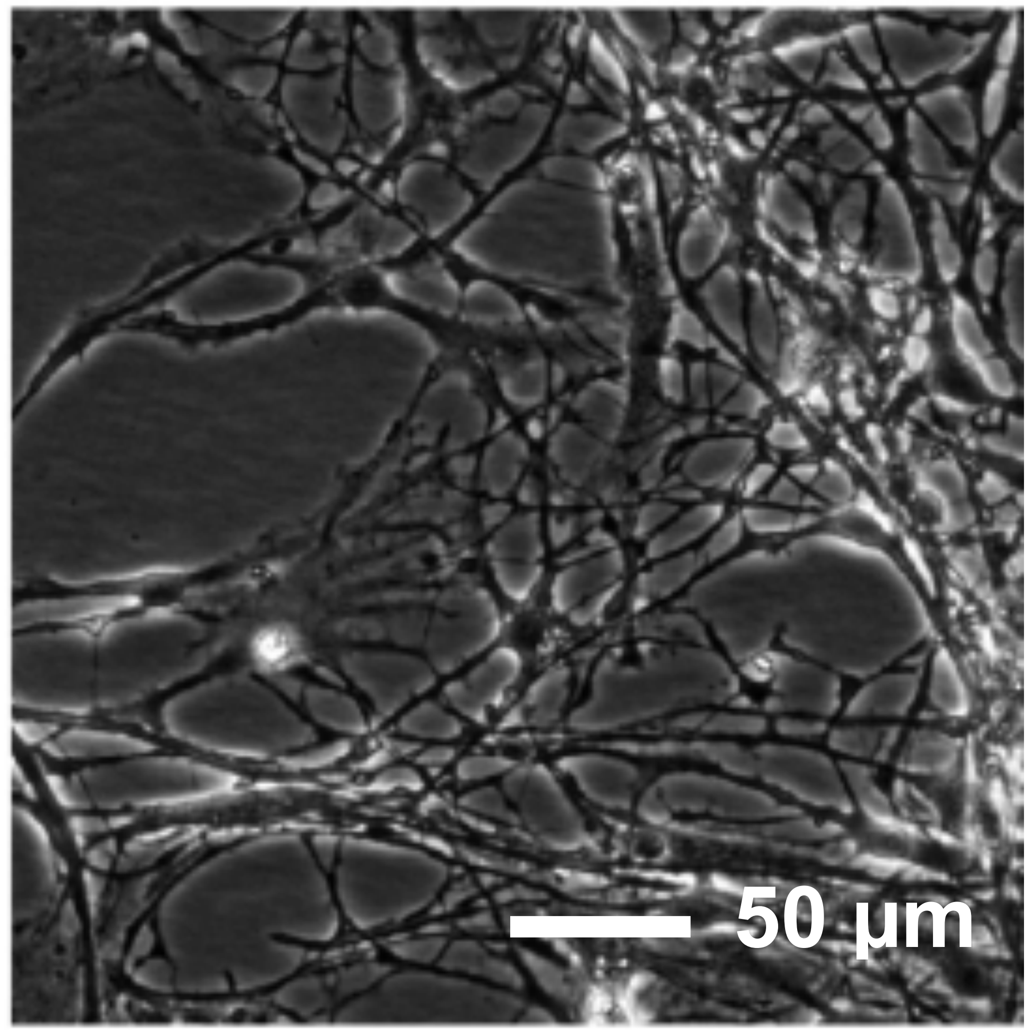
1% genomic differences

Image: James Balog Getty Images

Embryonic stem cells

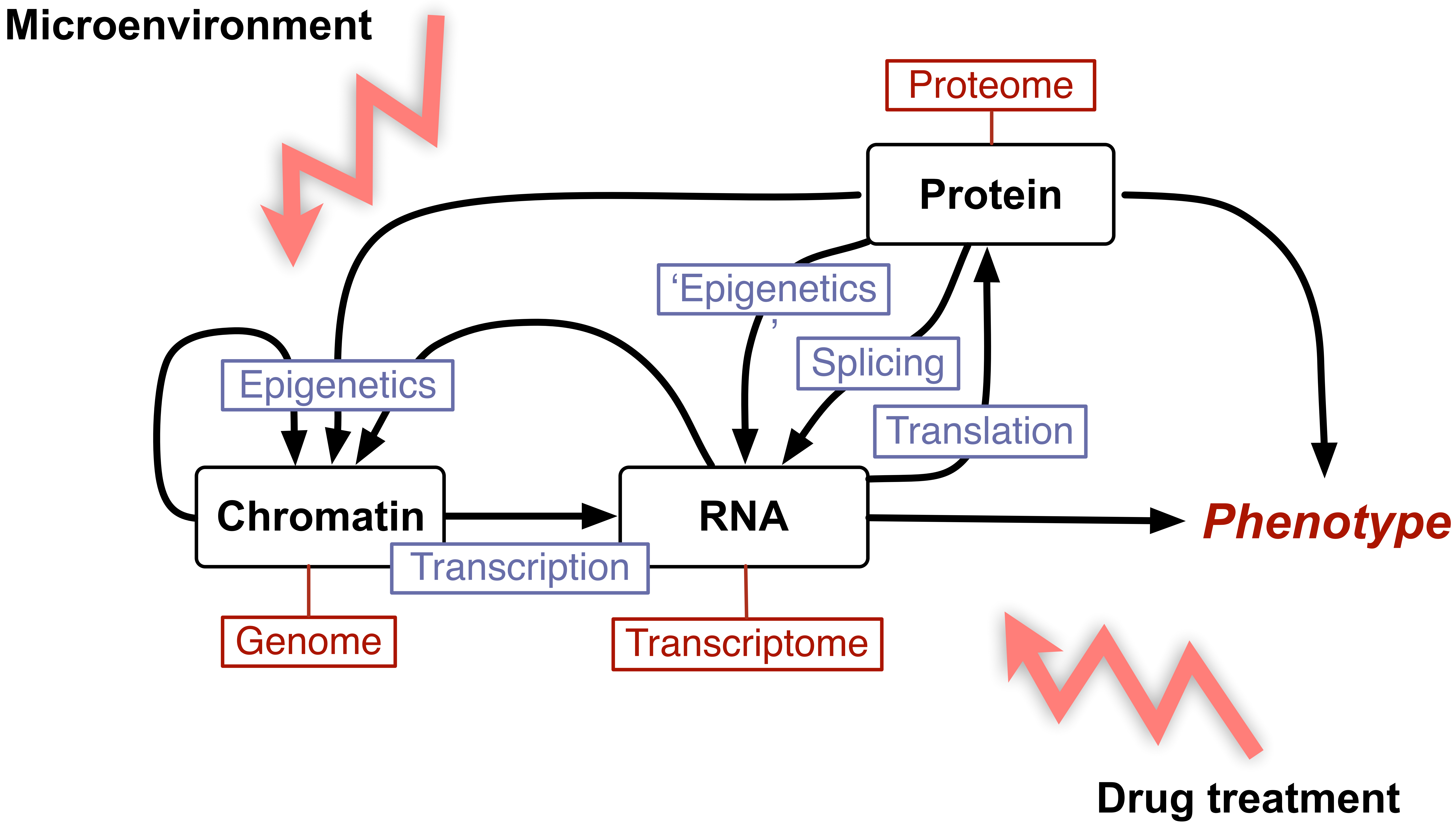


Neural cells

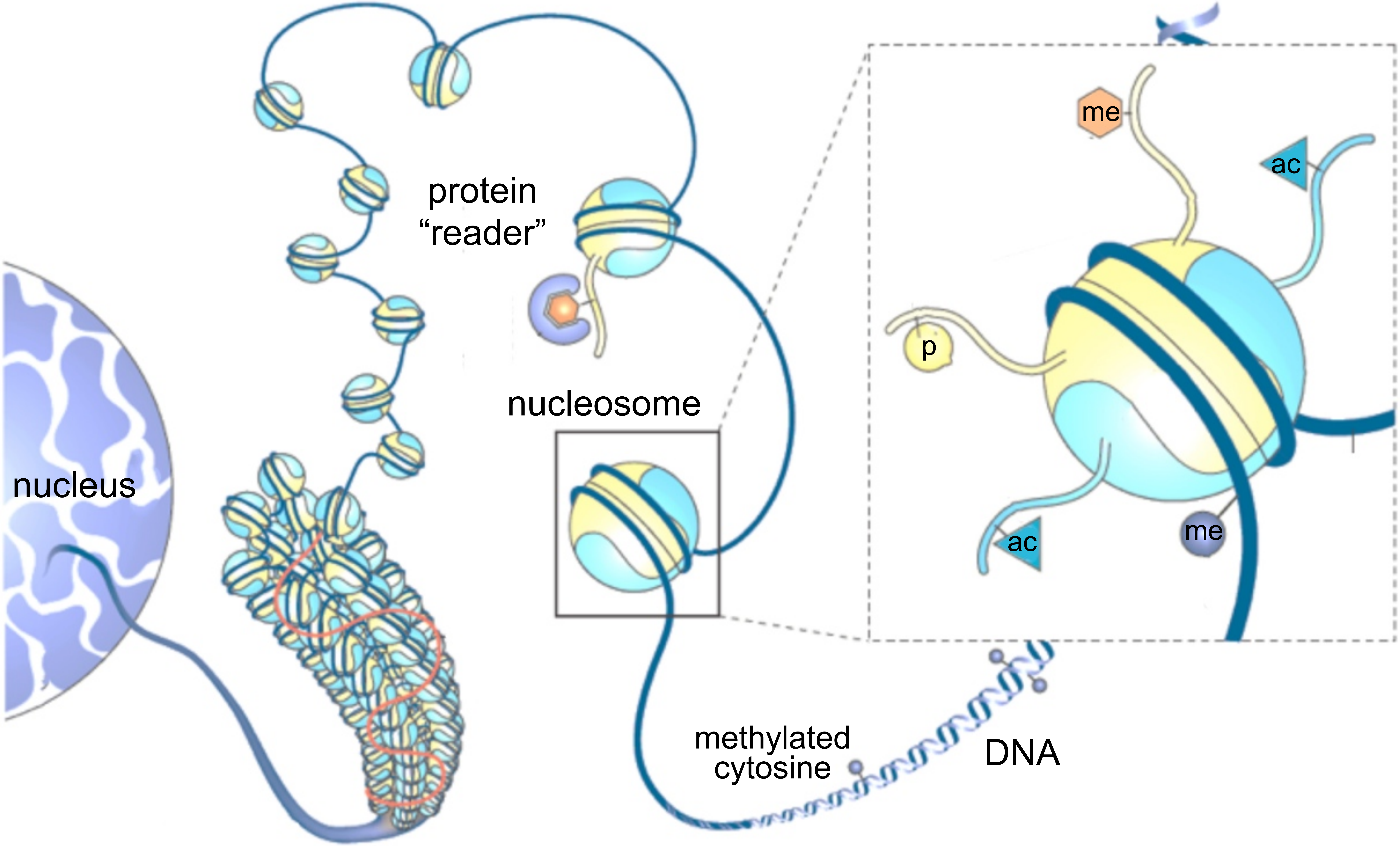


No genomic differences

A complex network links DNA to phenotype in eukaryotes

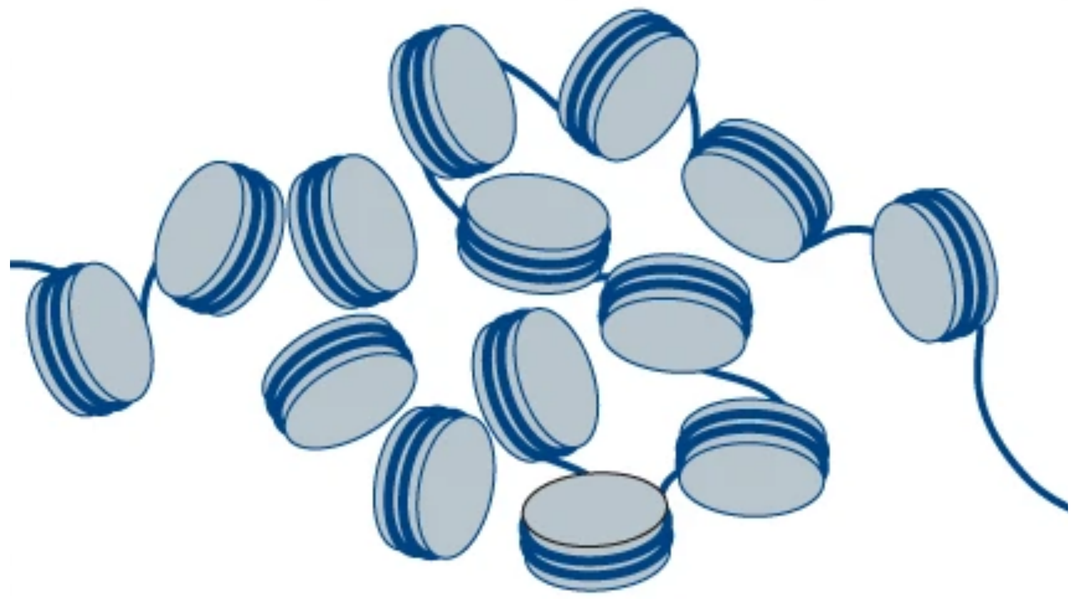


Epigenetic signals define access to the DNA genome and cell type specific chromatin state patterns

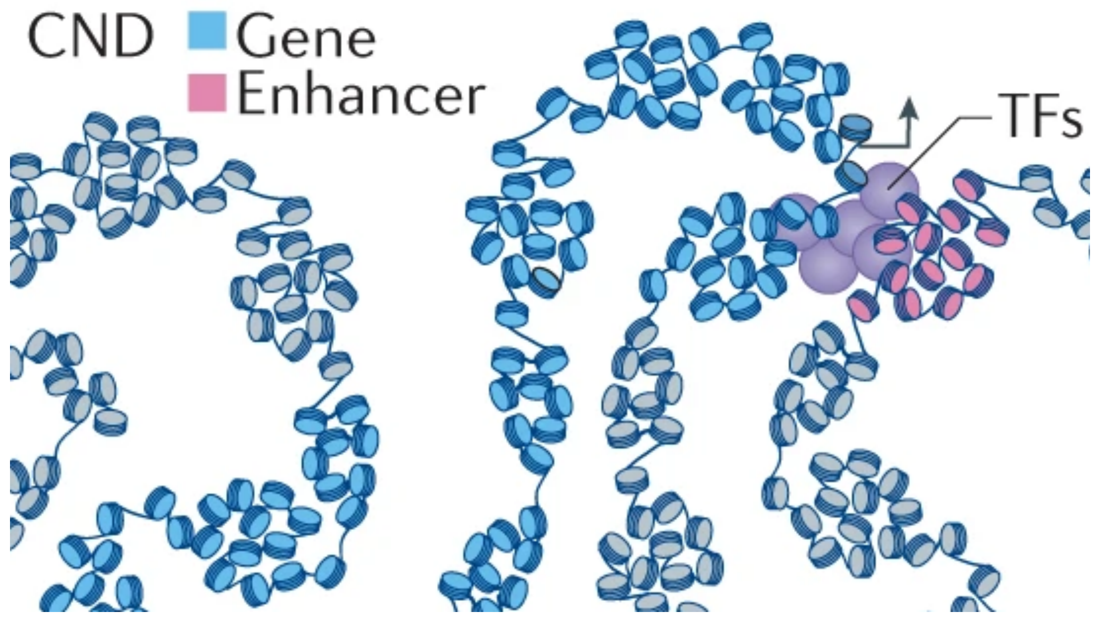


Probst, Nat Rev Mol Cell Biol

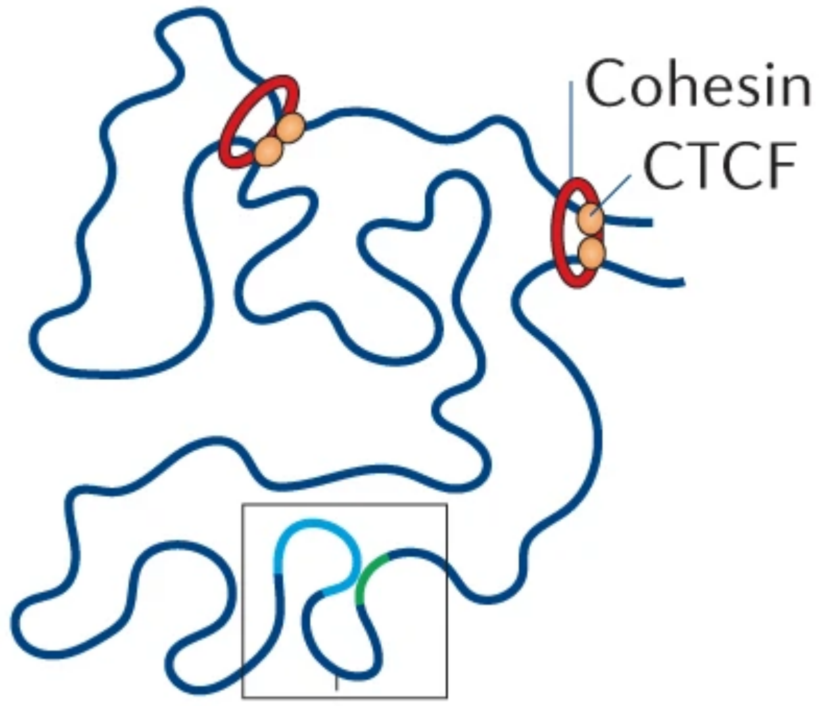
Chromatin organization on different length scales



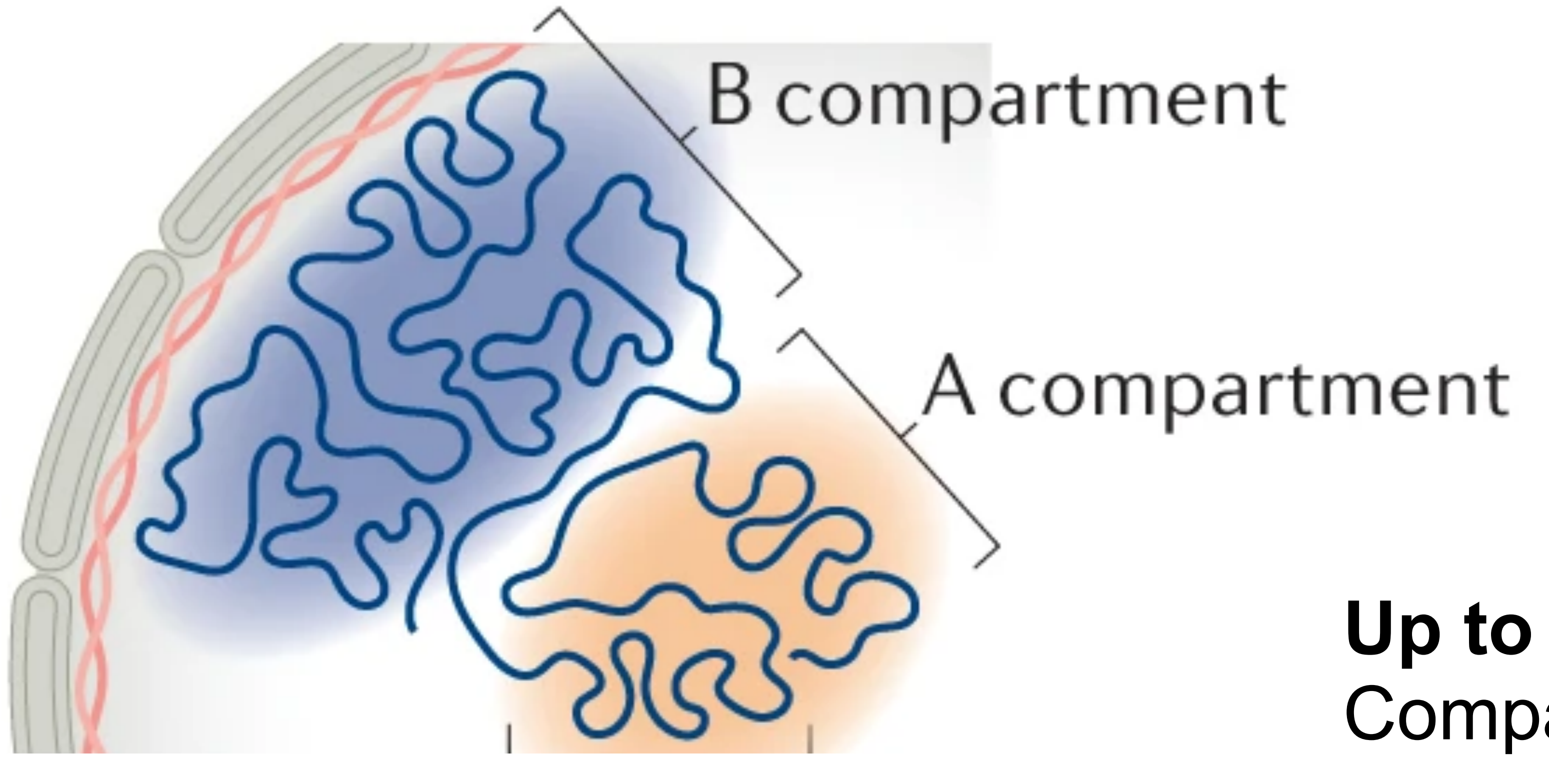
1-2 kb: Nucleosome clutches



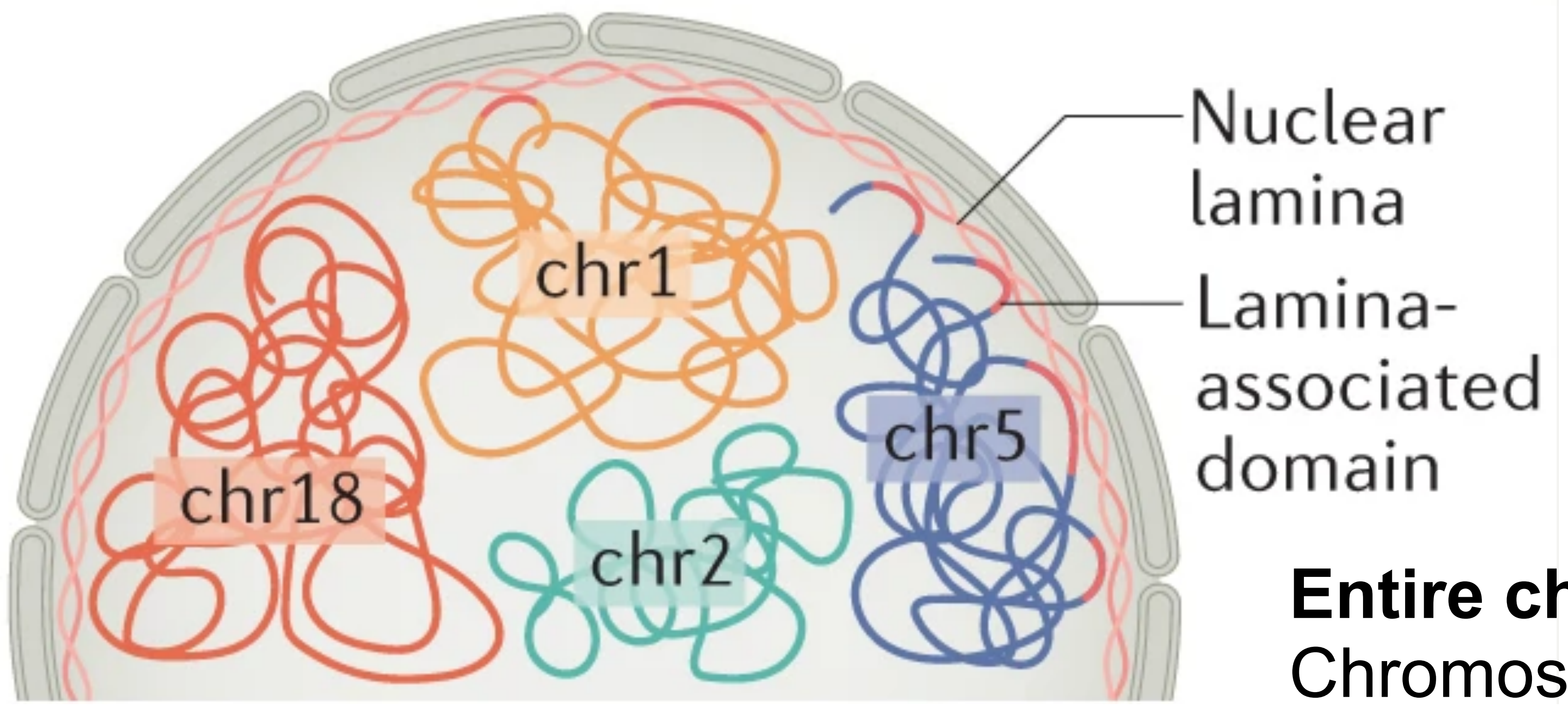
10-100 kb: Chromatin domains and functional loops (enhancer-promoter contacts)



100 kb to a few Mb: Chromatin loops and topologically associating domains (TADs)



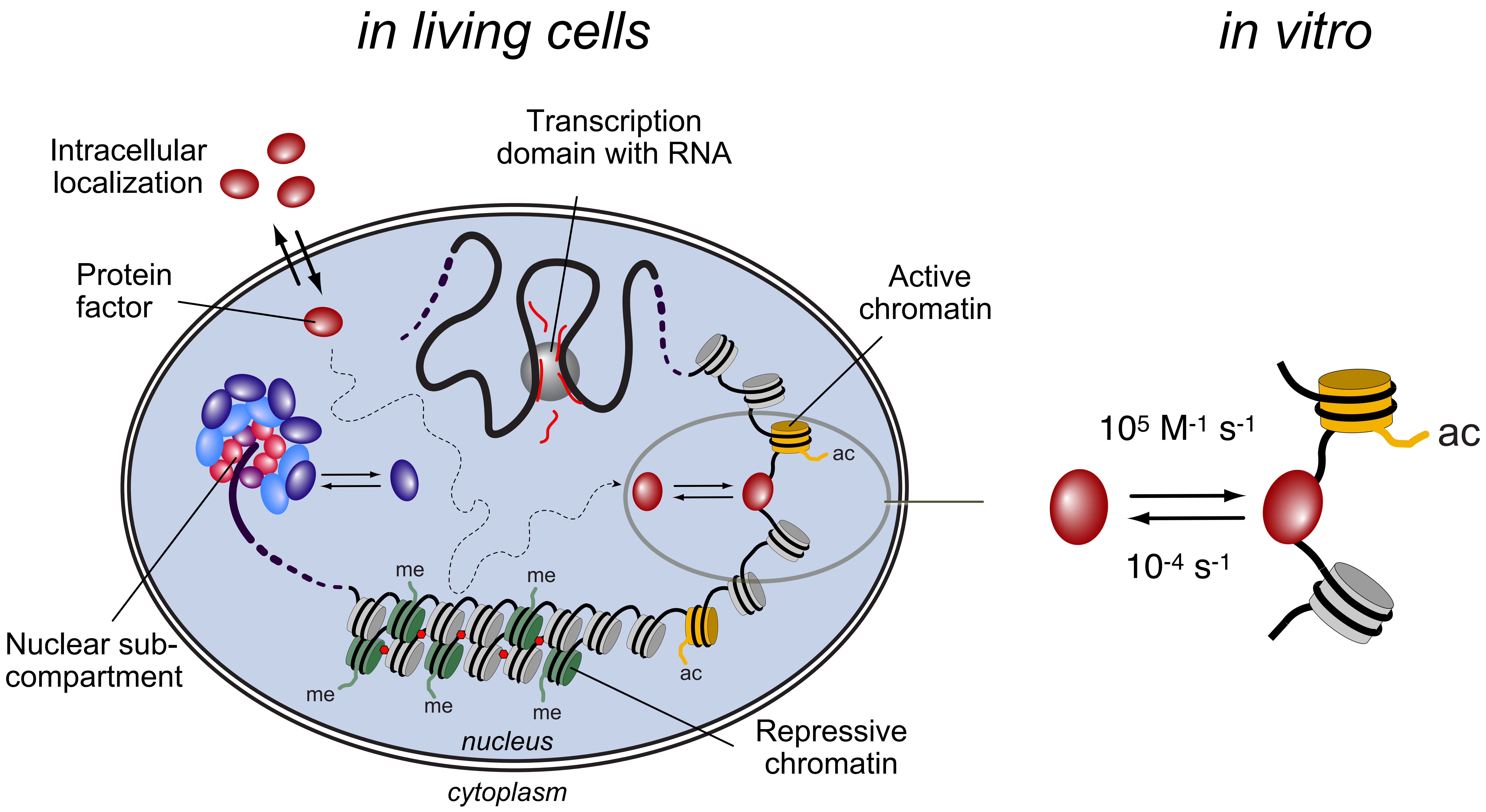
Up to 100s of Mb: Compartments and hubs



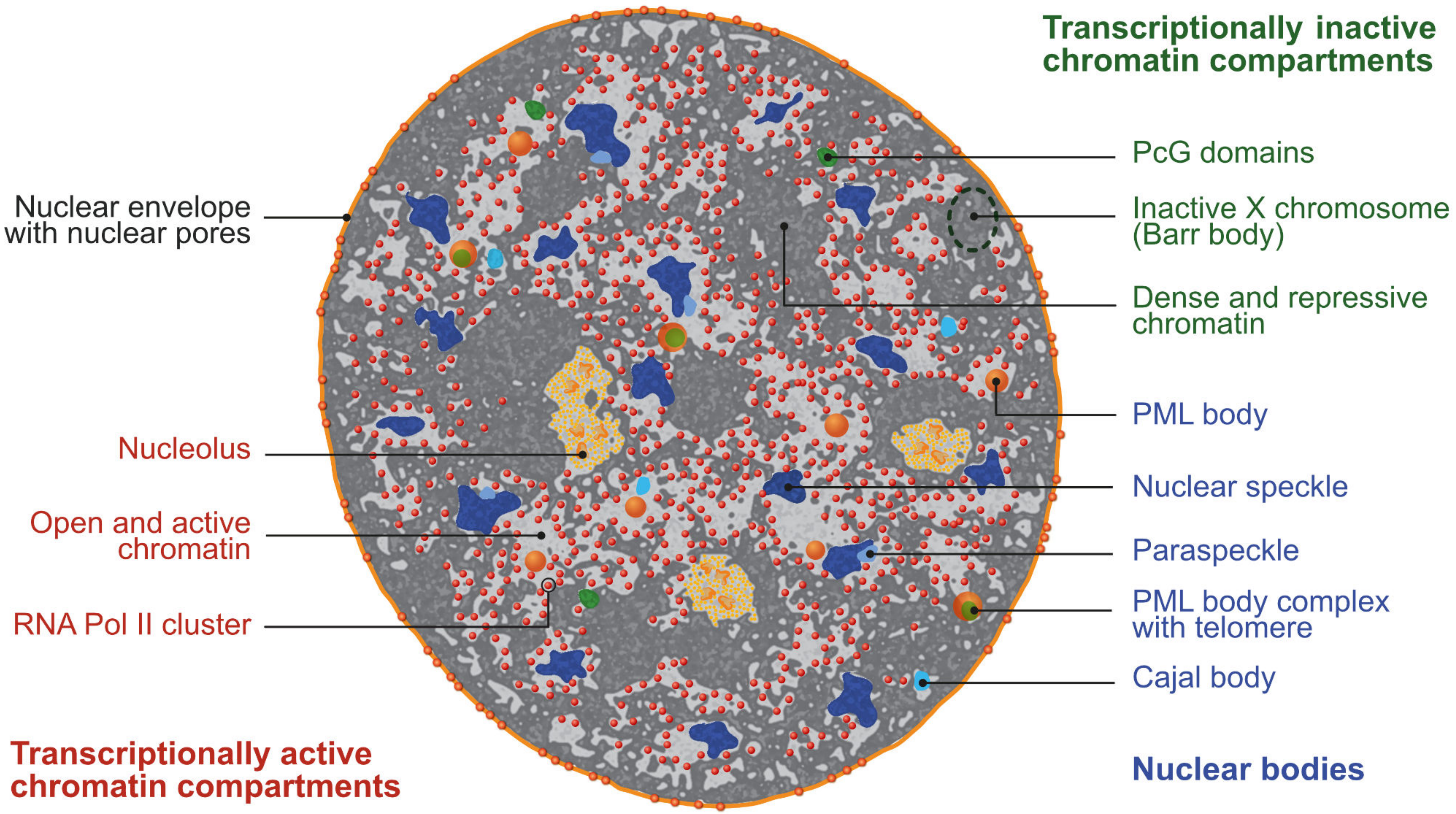
Entire chromosomes: Chromosome territories

Adapted from Fitz-James & Cavalli 2022 *Nat Rev Genet*

Protein interactions with DNA and RNA



The mammalian nucleus organizes genome functions in subcompartments



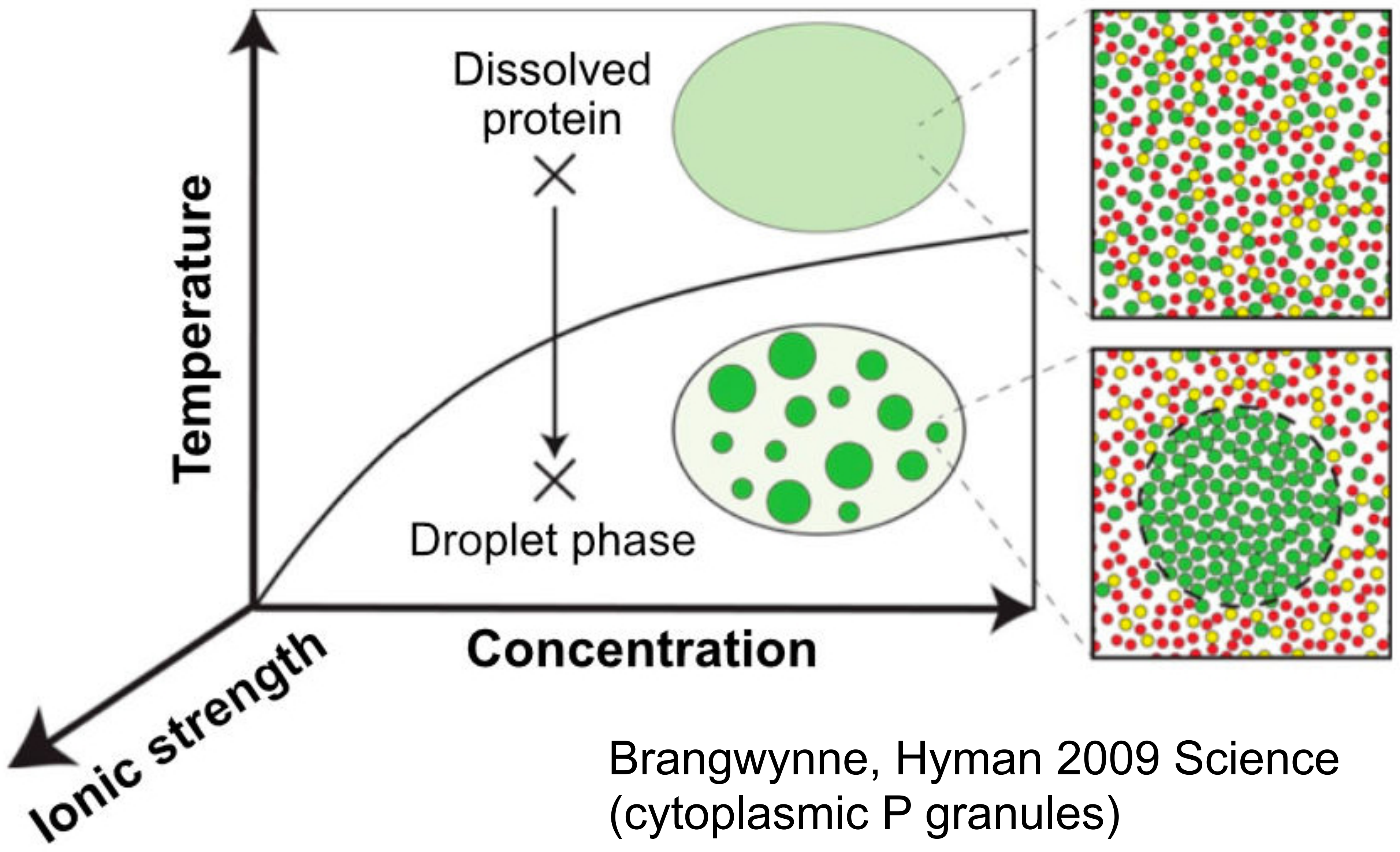
Caudron-Herger & Rippe 2012 *Curr Opin Genet Dev*

On the 10 μm length scale of the nucleus proteins mix fast by diffusion

… and gravitation is irrelevant for proteins

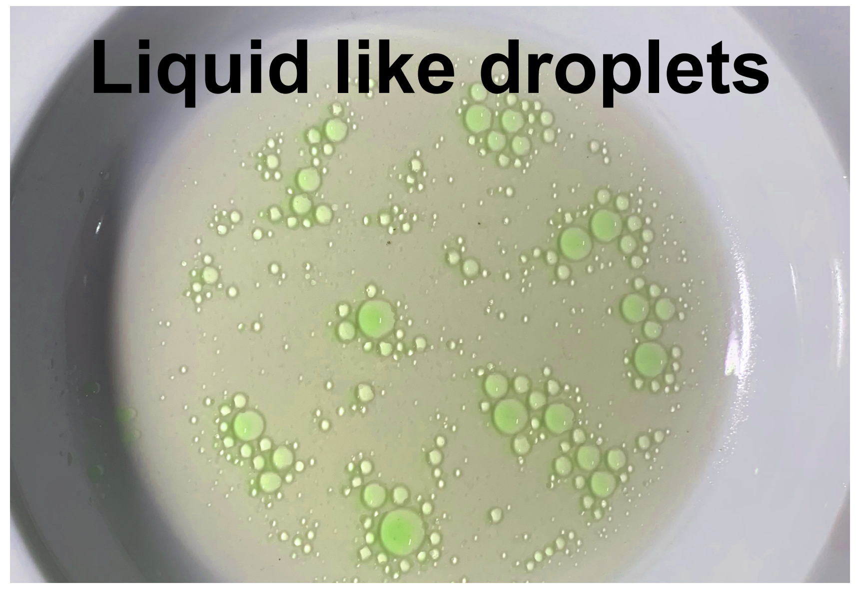
- Thermal energy at 25 ºC: $k \cdot T = 4 \cdot 10^{-21}$ J
- GFP translocation in 1 sec (D = 30 μm^2 s^{-1}): 13 μm
- Gravitational energy *PEG* GFP (27 kDa, 10 μm): $4 \cdot 10^{-27}$ J or 0.000001 kT

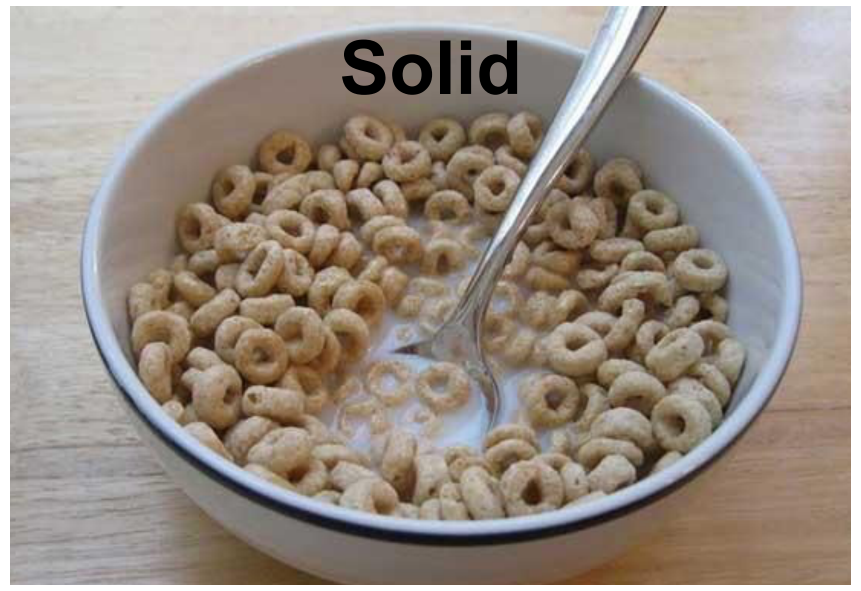
Liquid-liquid phase separation (LLPS) to form cellular subcompartments



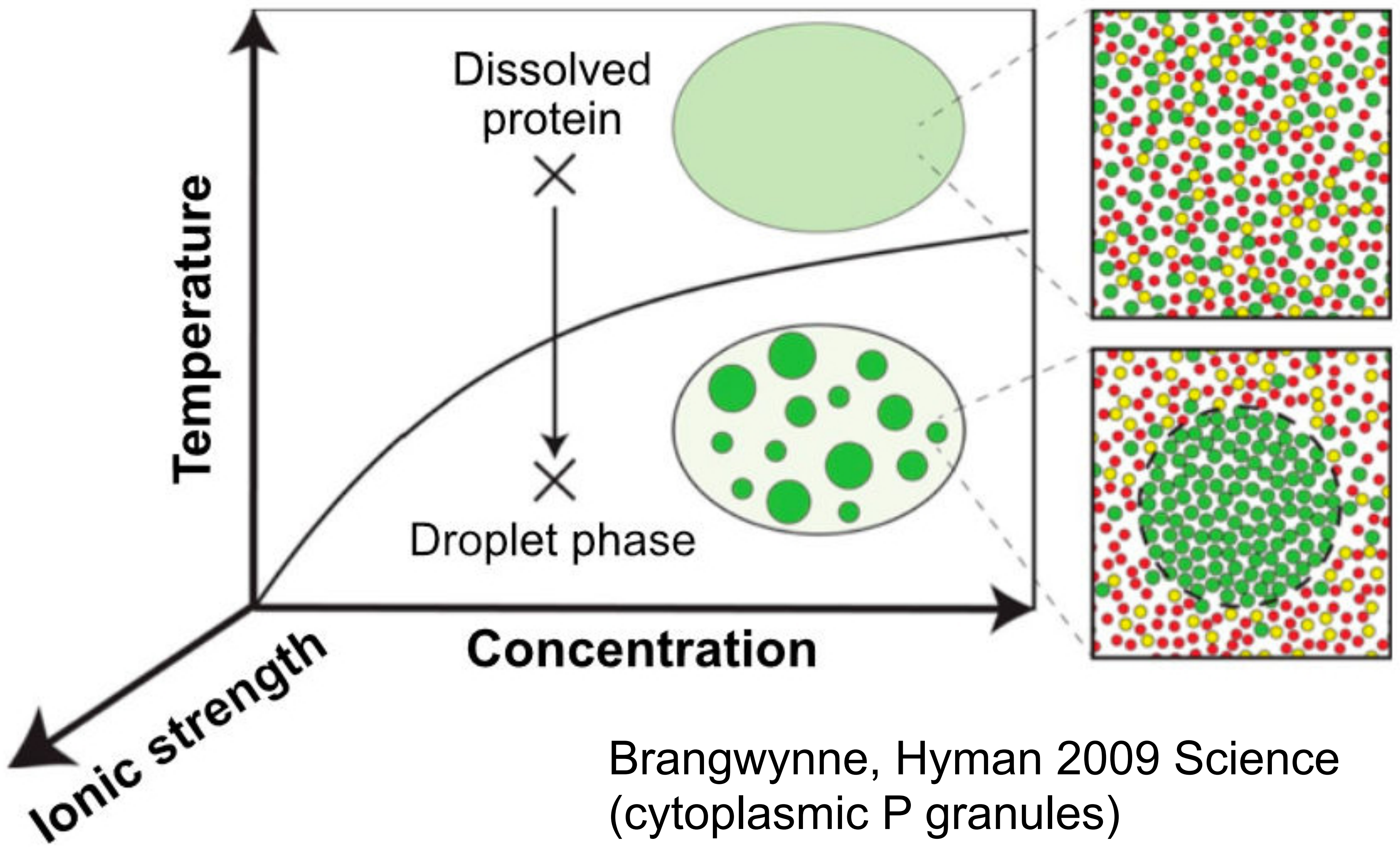
Brangwynne, Hyman 2009 Science
(cytoplasmic P granules)

or phase transitions to other states?





Liquid-liquid phase separation (LLPS) to form chromatin subcompartments



Brangwynne, Hyman 2009 Science
(cytoplasmic P granules)

Nucleolus
Brangwynne 2011 *PNAS*
Feric 2016 *Cell*
Caragine 2019 *eLife*
Frottin 2019 *Science*
Riback 2020 *Nature*

(Peri)centromeres/ heterochromatin
Larson 2017 *Nature*
Strom 2017 *Nature*
Cerase 2019 *NSMB*
Wang 2019 *Mol Cell*
Trivedi 2019 *Nat Cell Biol*
Huo 2020 *Mol Cell*

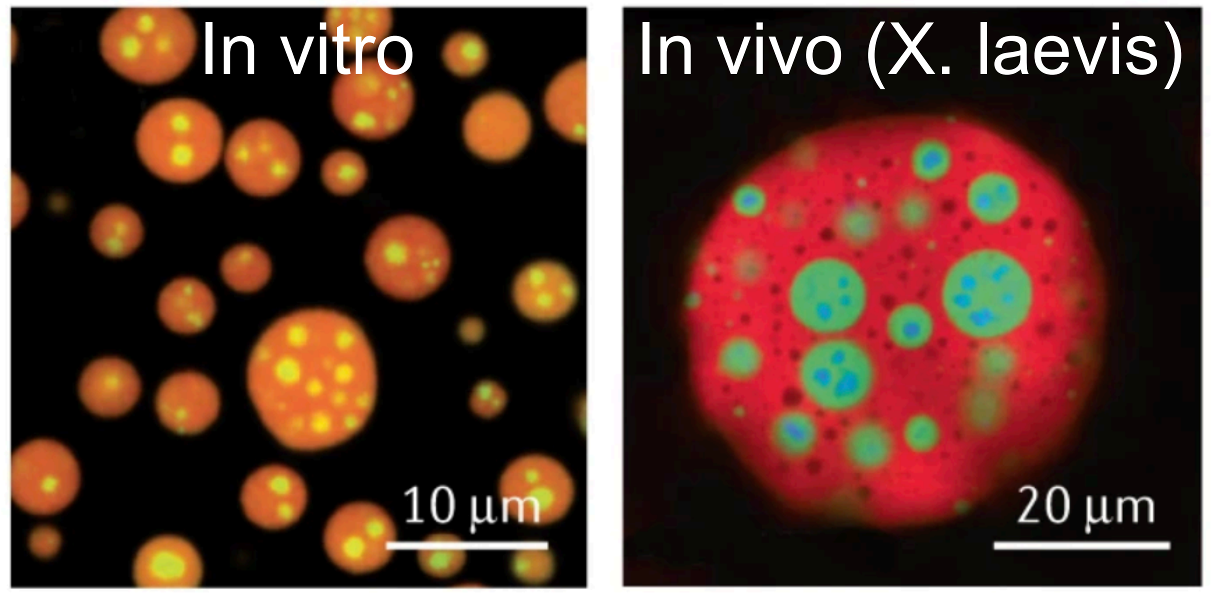
Telomeres
Shin 2018 *Cell*
Min 2019 *Genes Dev*
Jack 2022 *Dev Cell*

DNA repair sites
Kilic 2019 *EMBO J*
Pessina 2019 *Nat Cell Biol*

"Transcriptional condensates"
Hnisz 2017 *Cell*
Sabari 2018 *Science*
Boija 2018 *Cell*
Boehning 2018 *NSMB*
Cho 2018 *Science*
Lu 2018 *Nature*
Chong 2018 *Science*
Shrinivas 2019 *Mol Cell*
Zamudio 2019 *Mol Cell*
Klein 2020 *Science*
Wei 2020 *Nat Cell Biol*
Lu 2020 *Nat Cell Biol*
Liu 2020 *Nat Cell Biol*
Henninger 2020 *Cell*
Ma 2021 *Mol Cell*

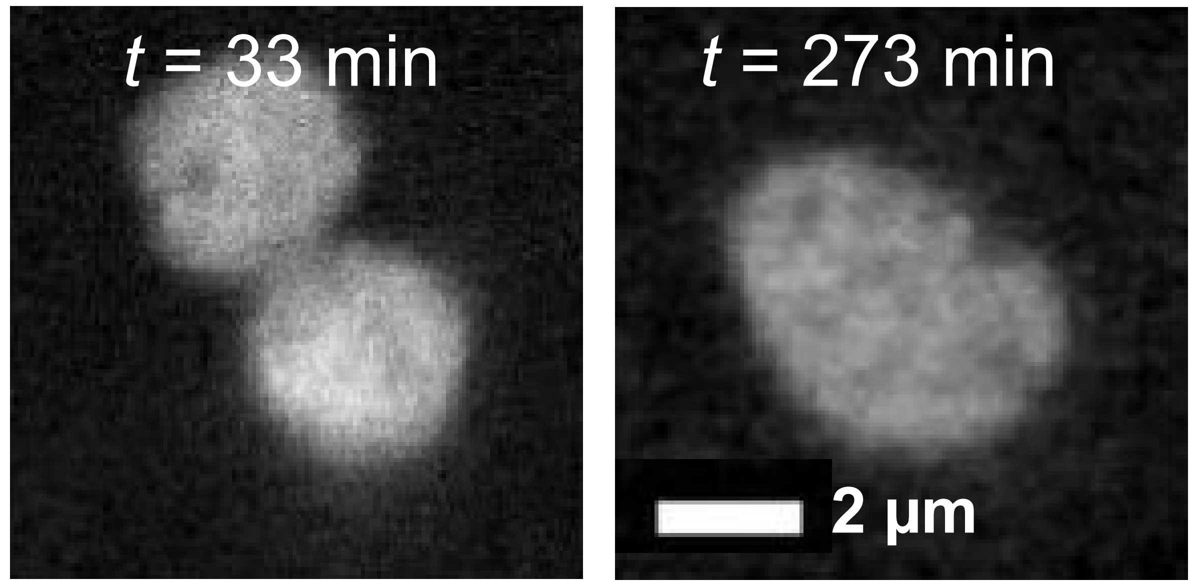
Chromatin
Gibson 2019 *Cell*
Gallego 2020 *Nature*

Droplets of nucleolar proteins



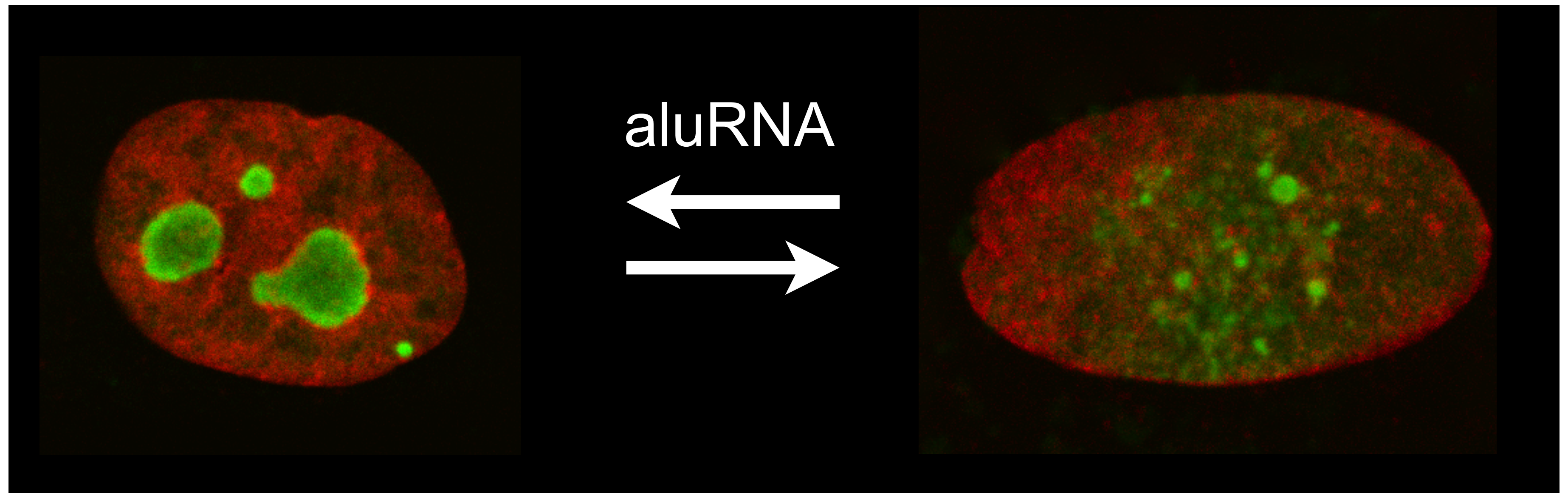
Lafontaine 2020 *Nat Rev Mol Bio*

Nucleoli fusion



Caragine 2019 *eLife*

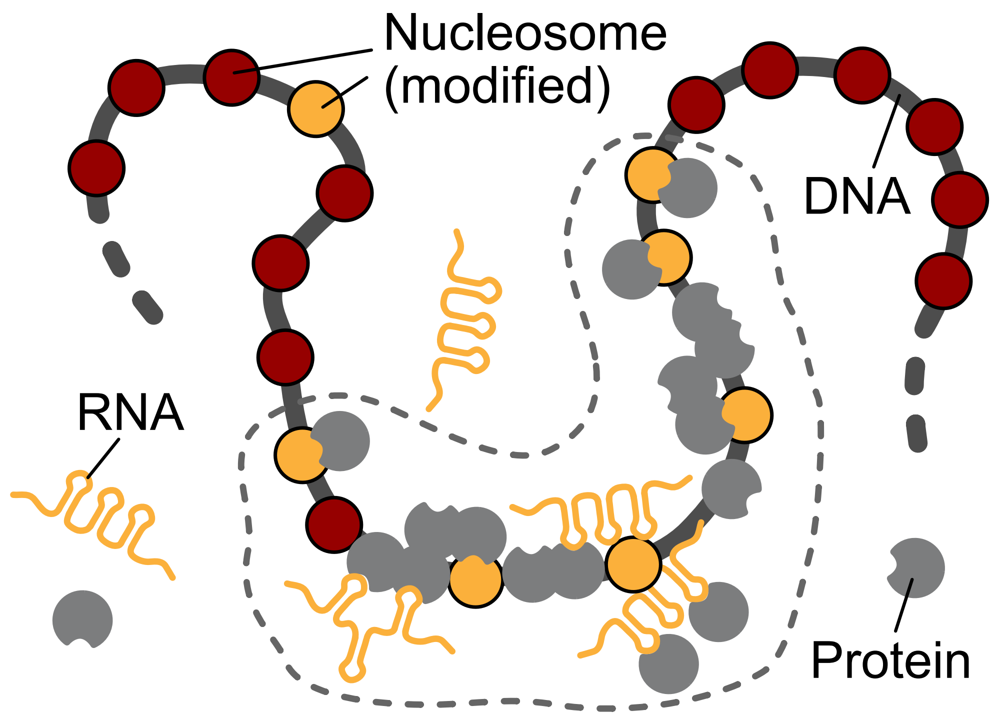
RNA dependent dispersion of nucleoli



Caudron-Herger 2015 *EMBO J; 2016 Nucleus*

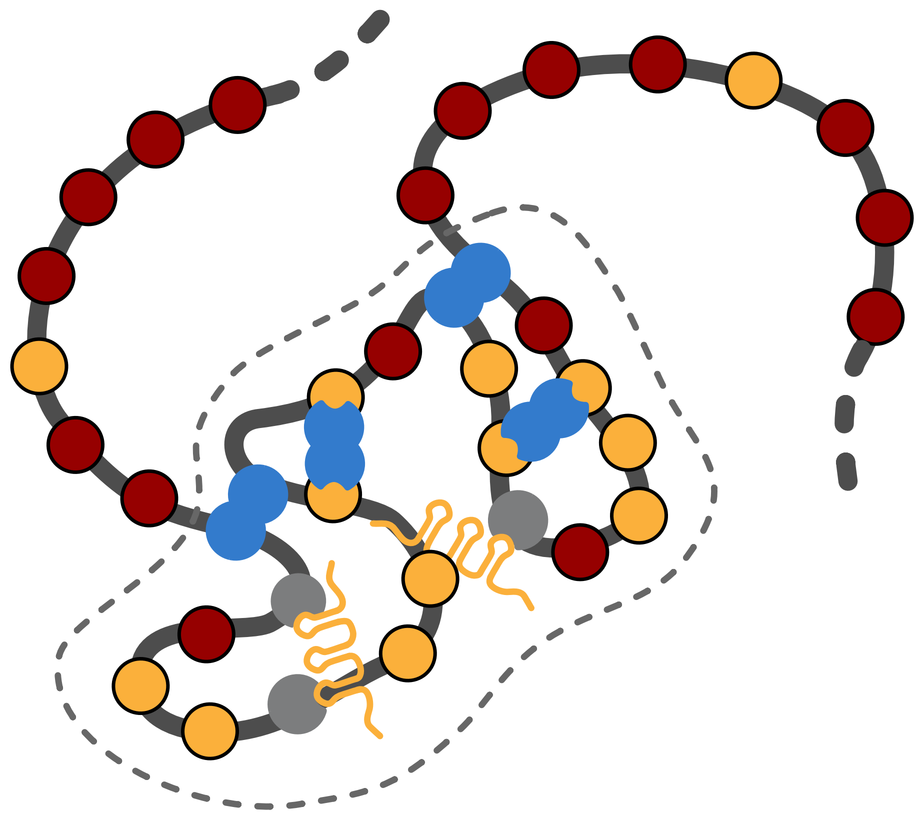
Different mechanisms to form chromatin subcompartments

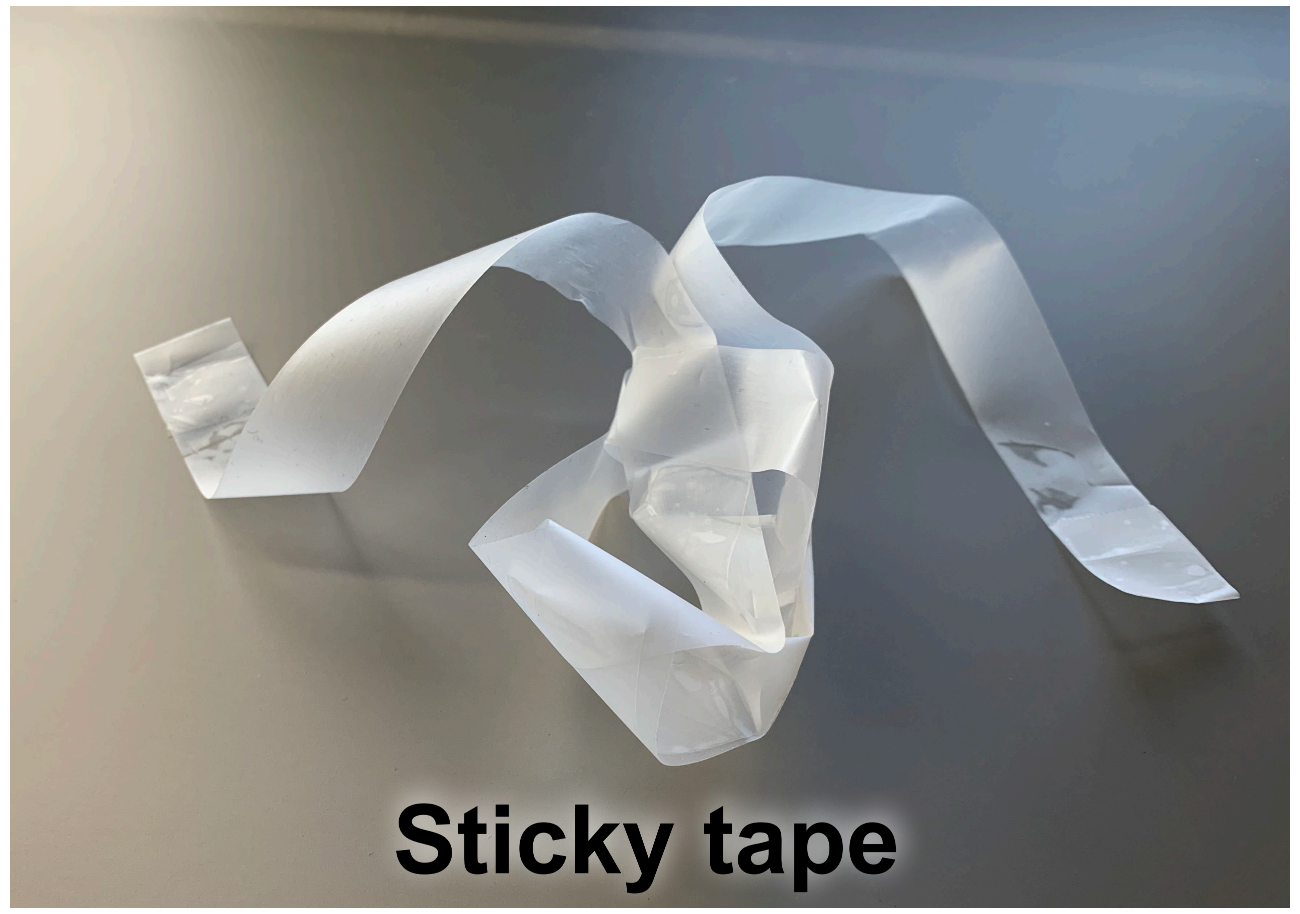
Binding site cluster



Original image by Sean McGrath

Chromatin bridging interactions





Liquid-liquid phase separation

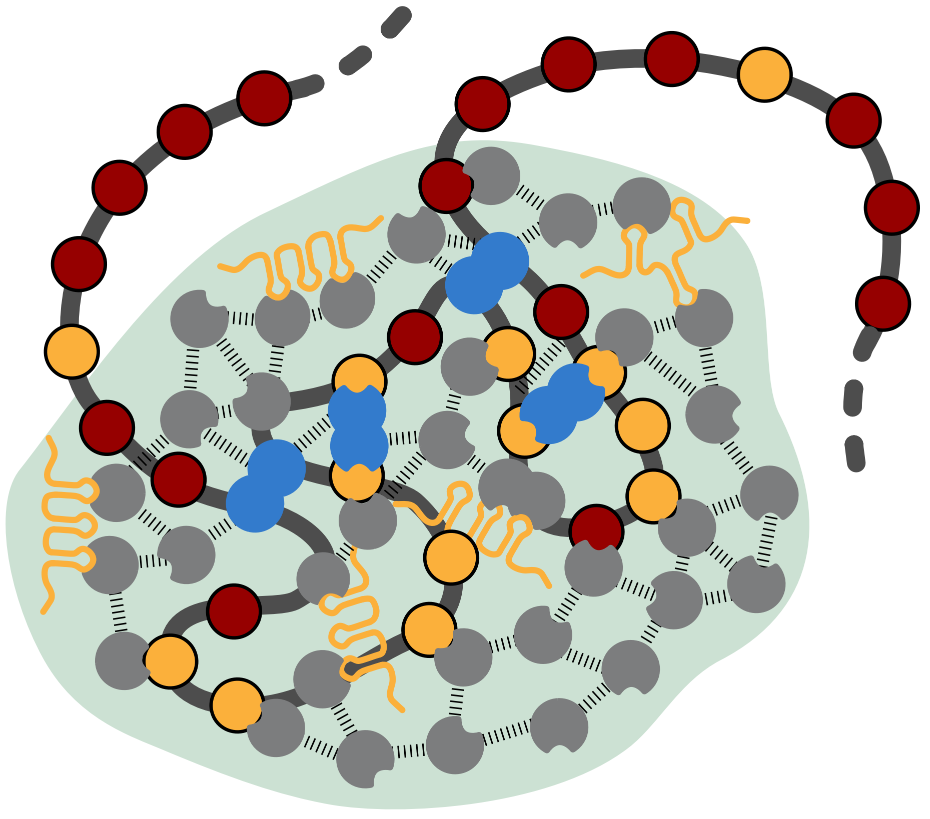


Image by Mathew Spolin

Erdel & Rippe 2018 *Biophys J;* Frank & Rippe 2020 *J Mol Biol;* Rippe 2022 *Cold Spring Harb Perspect Biol*