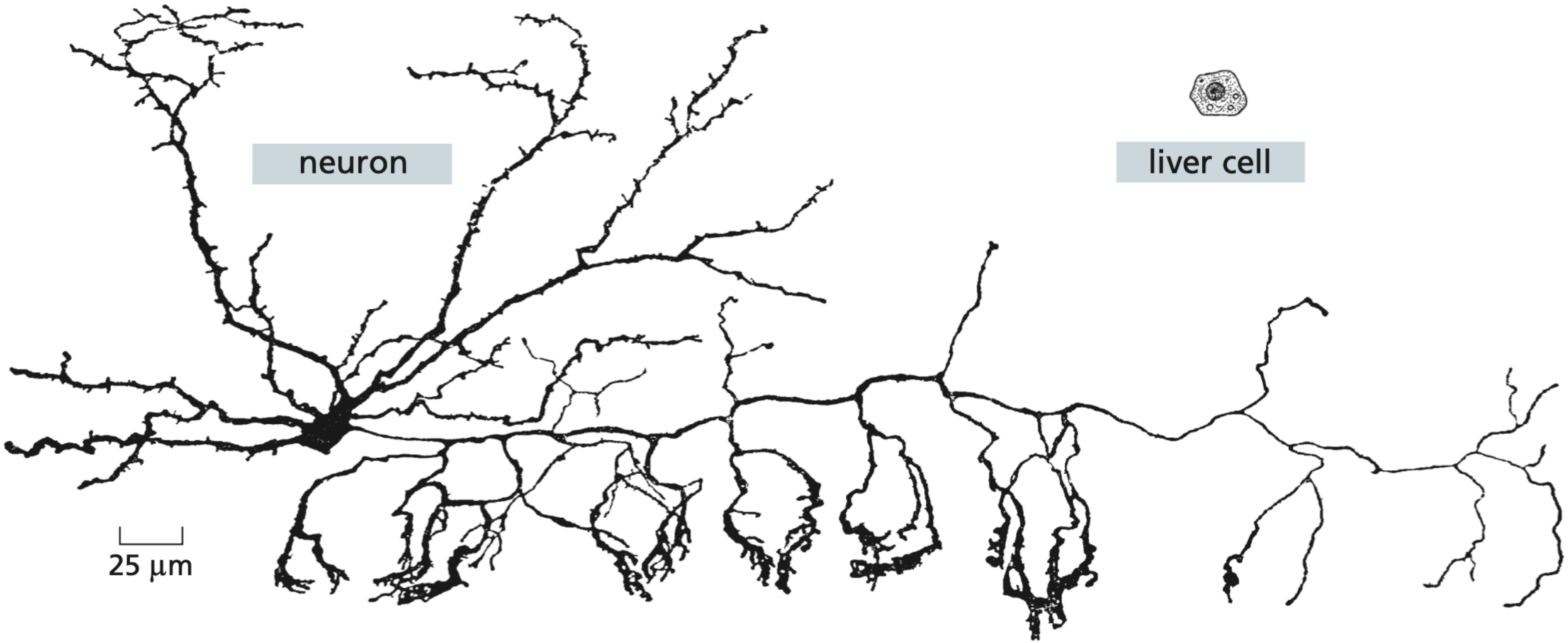
Simulating epigenetic chromatin states

Jan Fabio Nickels, AG Rippe

Outline

- Biological background
- Introduction to modeling epigenetic (bistable) chromatin
- Simulations (interactive)
- Wrap up

A neuron and a liver cell share the same genome



Alberts, B. (2022). Molecular biology of the cell, New York, NY: W. W. Norton & Company.

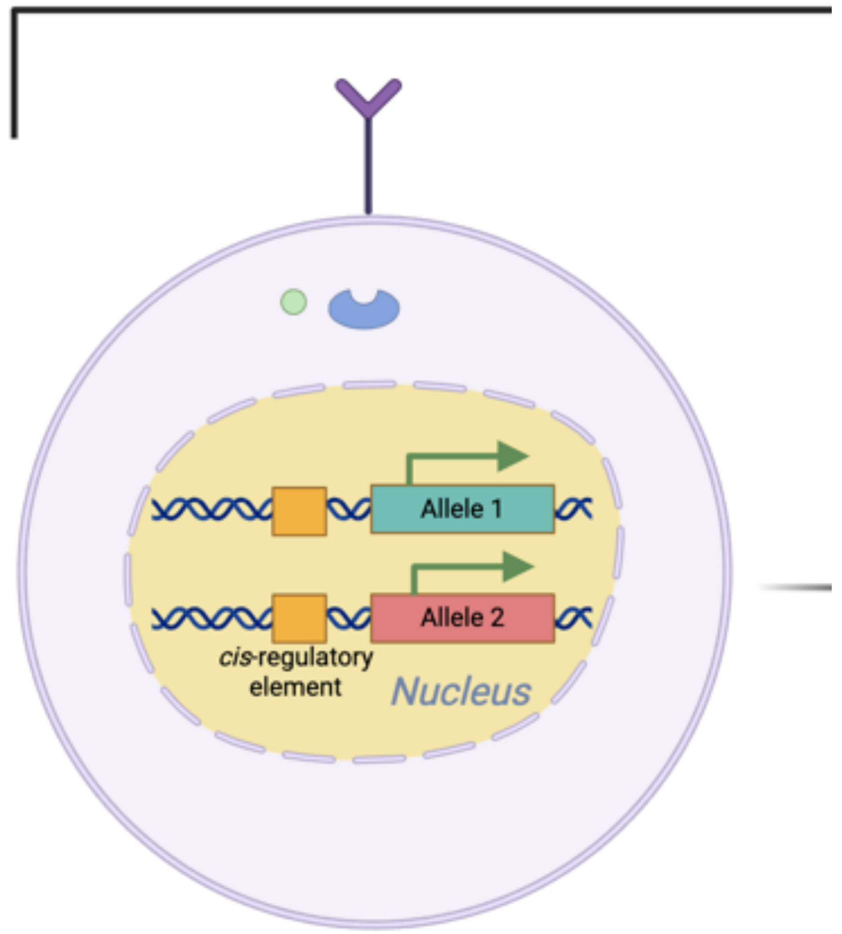
A definition of an epigenetic trait

An epigenetic trait is a **stably heritable** phenotype resulting from changes in a chromosome without alterations in the DNA sequence.

Berger et al. 2009, Genes & development

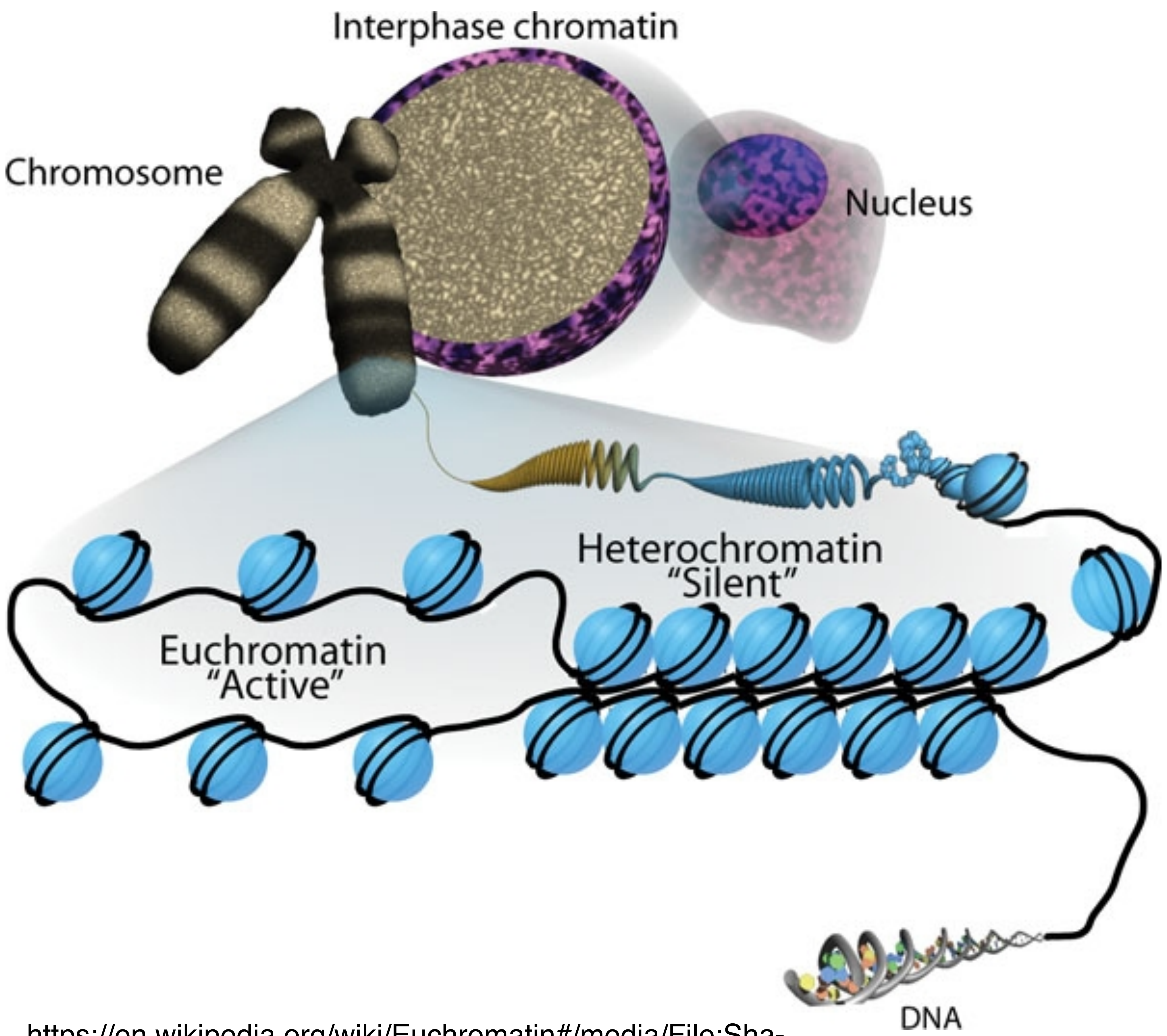
Epigenetic memory can be mediated in *trans* and in *cis*

epigenetic memory in *trans*

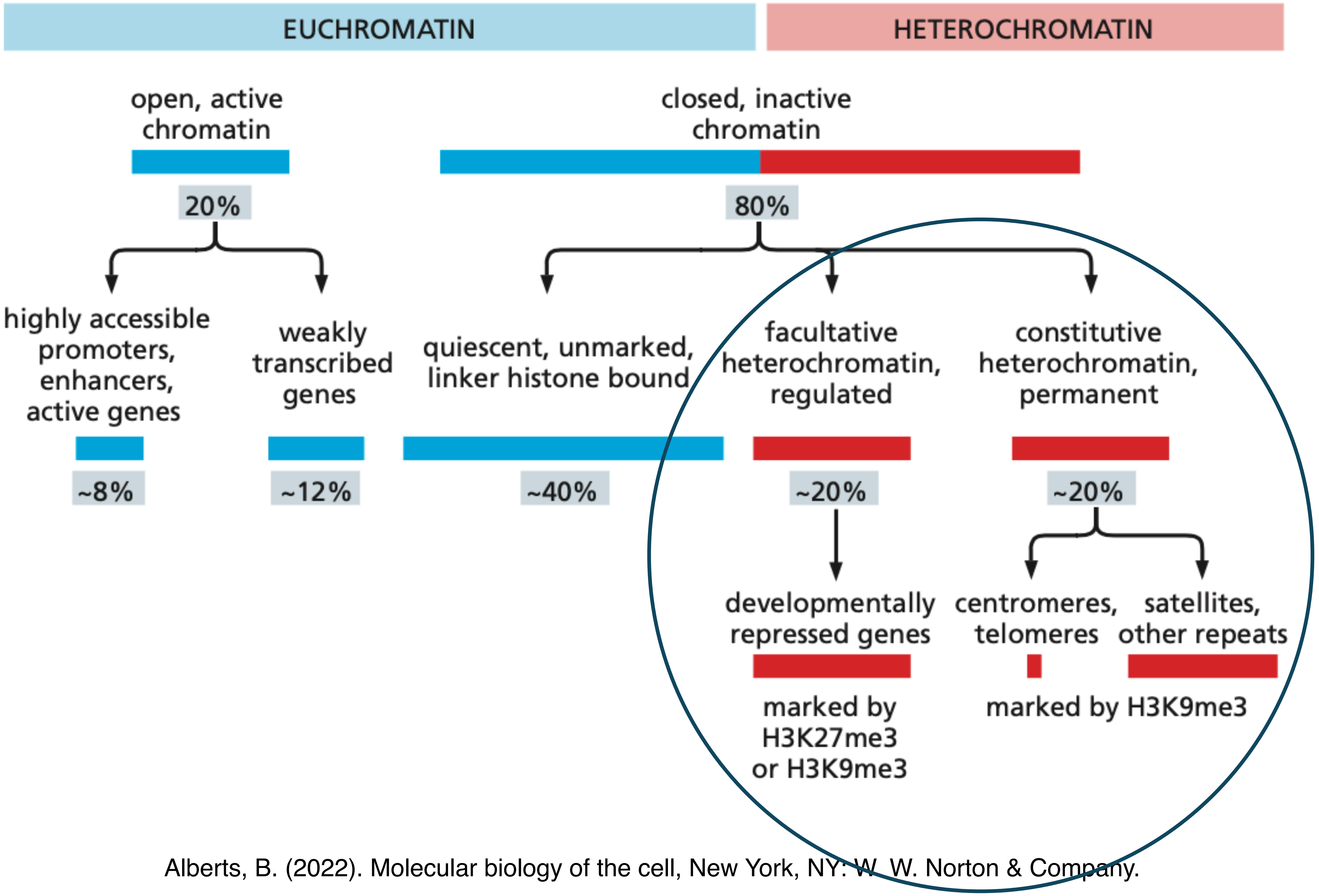


epigenetic memory in *cis*

Heterochromatin and Euchromatin



https://en.wikipedia.org/wiki/Euchromatin#/media/File:Sha-Boyer-Fig1-CCBy3.0.jpg



EUCHROMATIN

HETEROCHROMATIN

open, active chromatin

20%

closed, inactive chromatin

80%

highly accessible promoters, enhancers, active genes

~8%

weakly transcribed genes

~12%

quiescent, unmarked, linker histone bound

~40%

facultative heterochromatin, regulated

~20%

constitutive heterochromatin, permanent

~20%

developmentally repressed genes

marked by H3K27me3 or H3K9me3

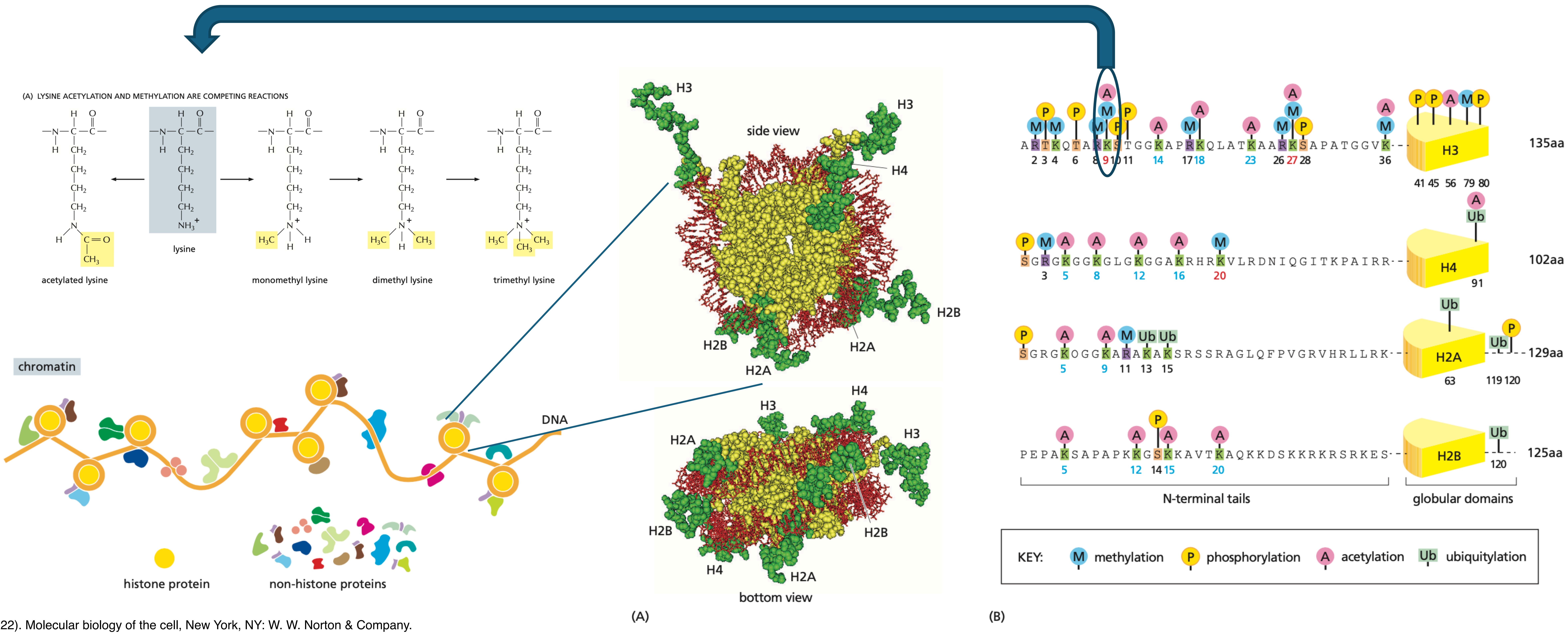
centromeres, telomeres

satellites, other repeats

marked by H3K9me3

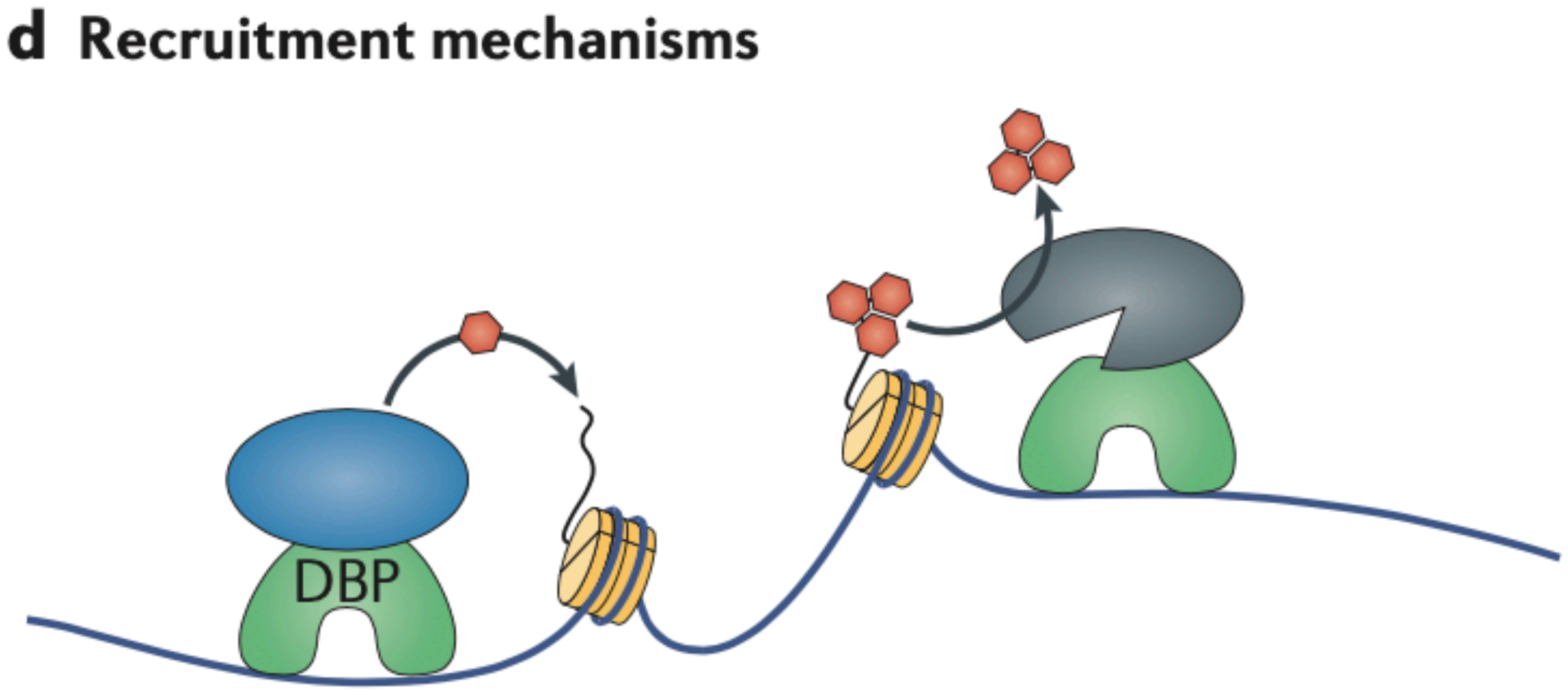
Alberts, B. (2022). Molecular biology of the cell, New York, NY: W. W. Norton & Company.

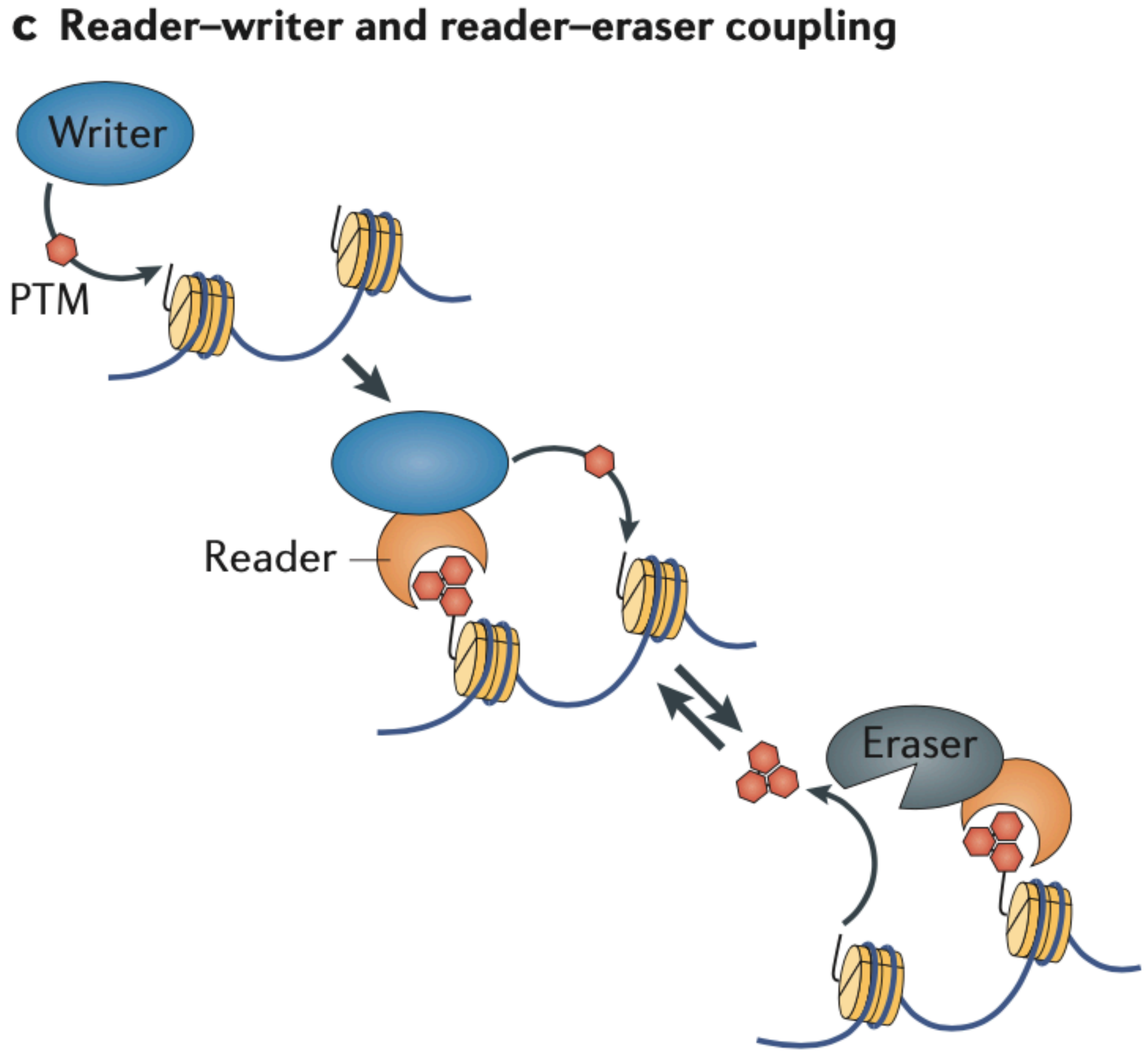
Histones can be modified at different positions on their tails



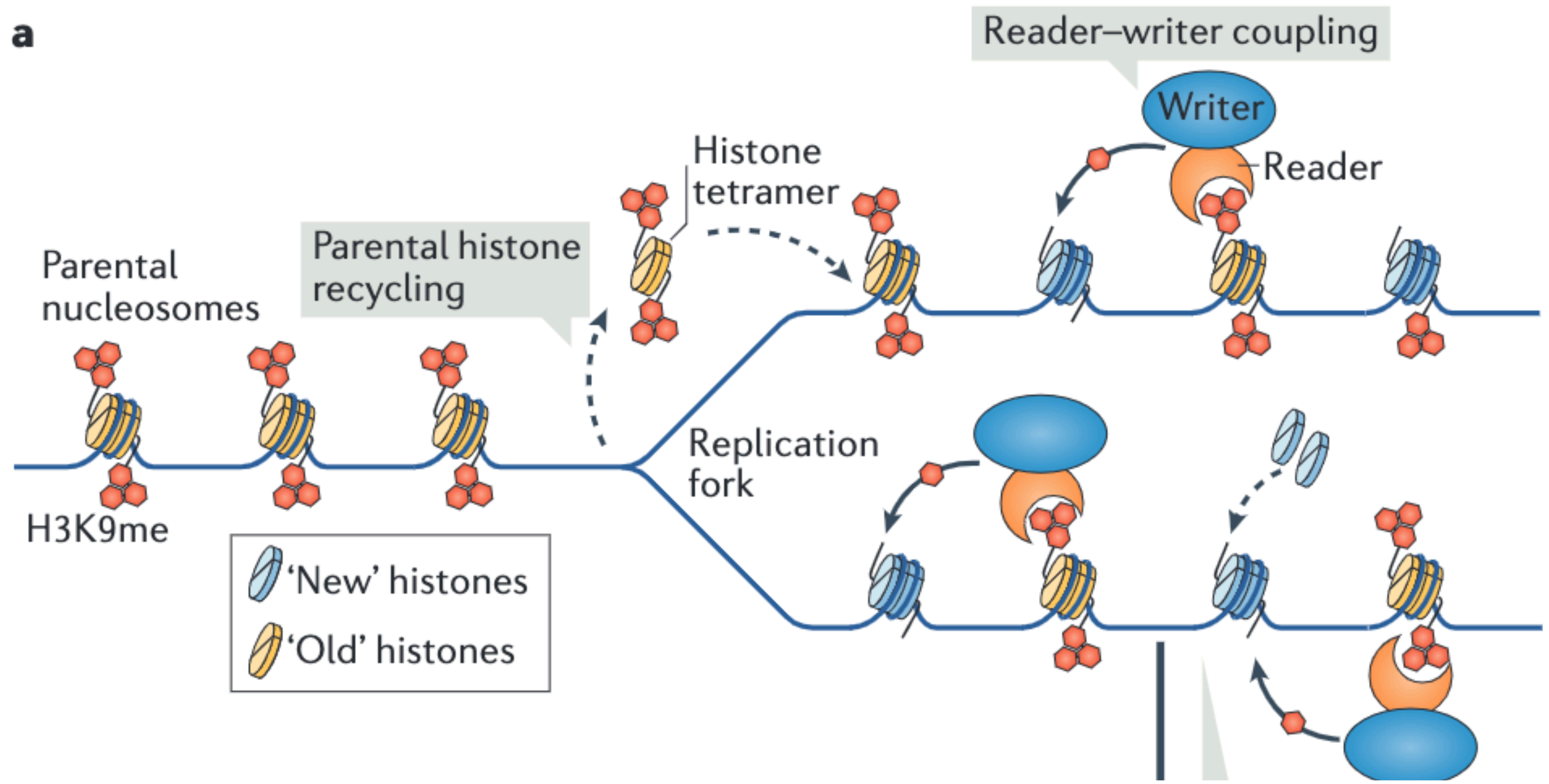
Alberts, B. (2022). Molecular biology of the cell, New York, NY: W. W. Norton & Company.

Histone modifications can spread from nucleation site





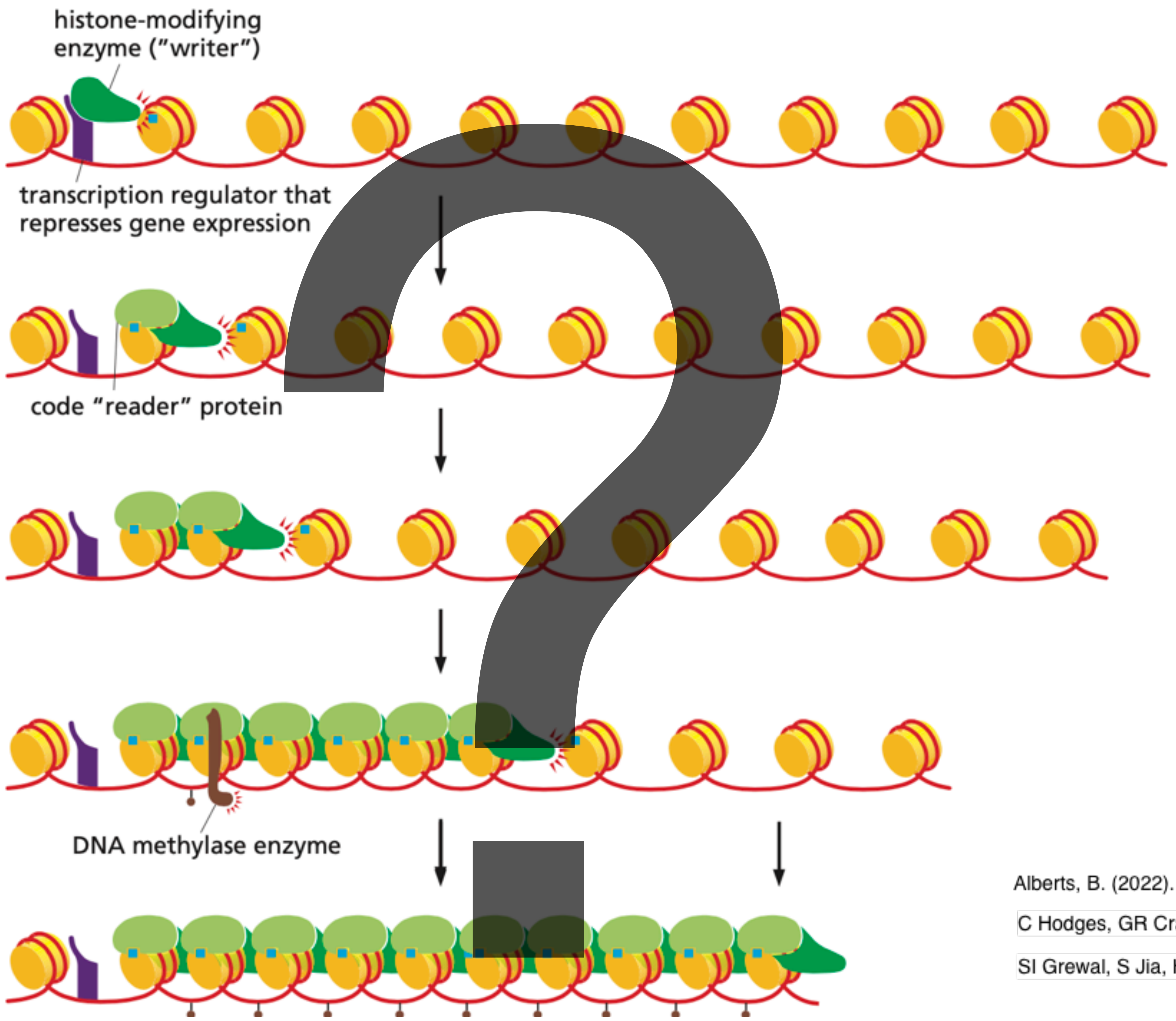
Allshire, R., Madhani, H. Ten principles of heterochromatin formation and function. *Nat Rev Mol Cell Biol* **19**, 229–244 (2018). https://doi.org/10.1038/nrm.2017.119



Histone modifications can be maintained through cell division

Allshire, R., Madhani, H. Ten principles of heterochromatin formation and function. *Nat Rev Mol Cell Biol* **19**, 229–244 (2018). https://doi.org/10.1038/nrm.2017.119

Does H3K9me2/3 spread linearly along DNA?

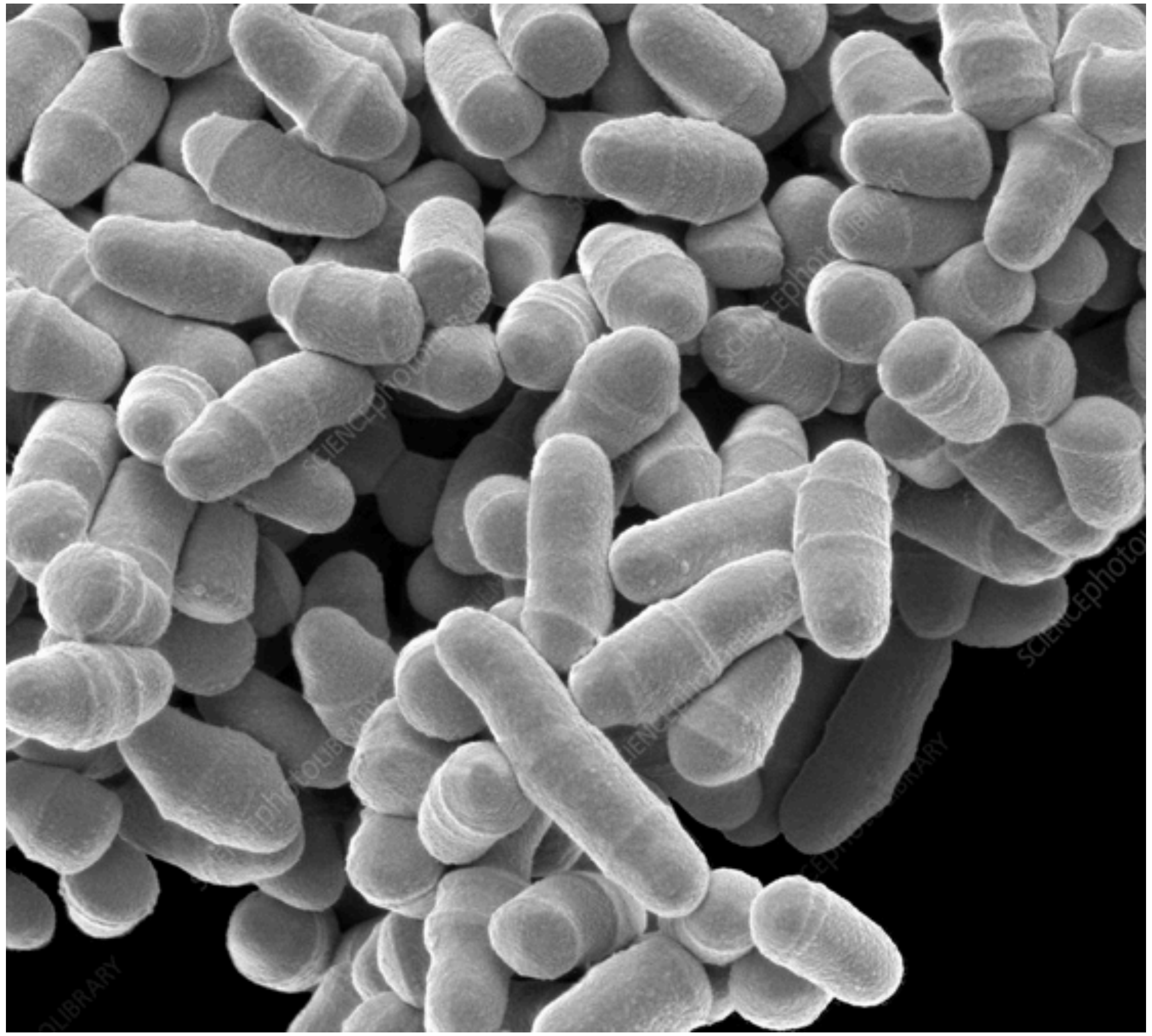


Alberts, B. (2022). Molecular biology of the cell, New York, NY: W. W. Norton & Company.

C Hodges, GR Crabtree, Dynamics of inherently bounded histone modification domains. *Proc Natl Acad Sci USA* **109**, 13296–13301 (2012).

SI Grewal, S Jia, Heterochromatin revisited. *Nat Rev Genet* **8**, 35–46 (2007)

Many insights on heterochromatin dynamics have been gained using fission yeast



https://www.offset.com/photos/close-up-of-schizosaccharomyces-pombe-yeast-197768

- Simple eukaryote
- Conserved heterochromatin components
- Short generation time
- Little redundancy (e.g. Clr4 is sole HMT in fission yeast)

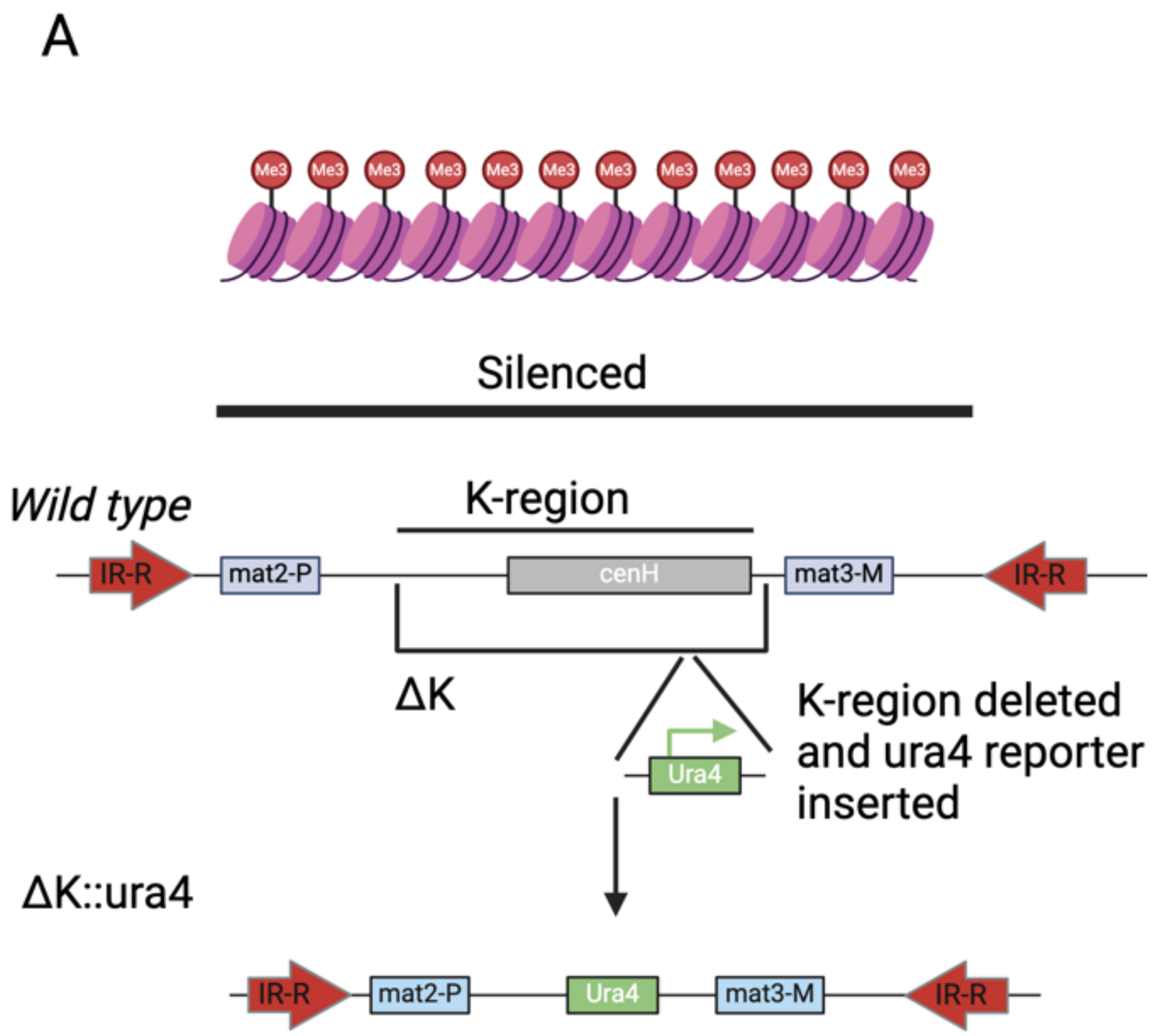
Theory

Cell

Theoretical Analysis of Epigenetic Cell Memory by Nucleosome Modification

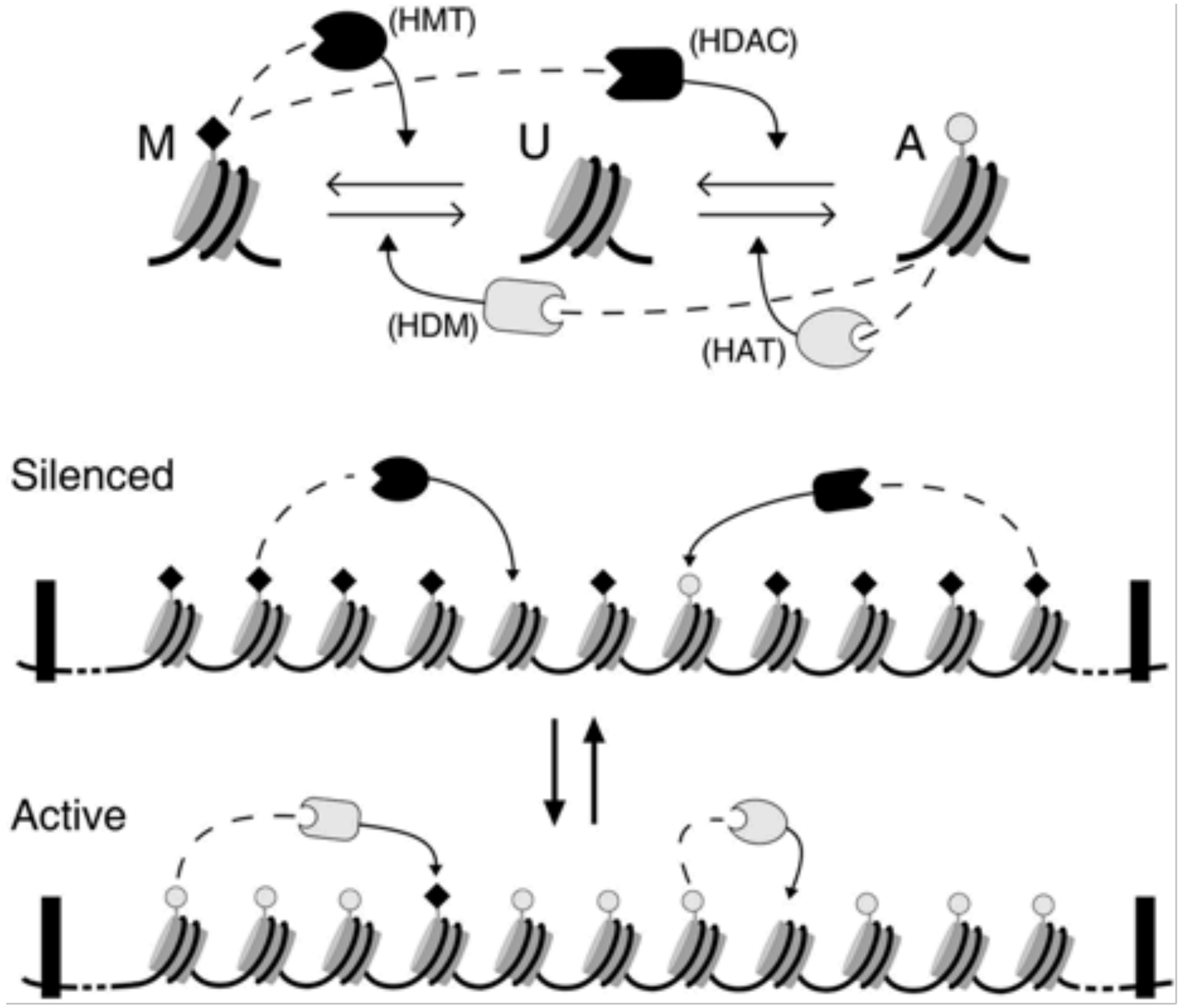
Ian B. Dodd,[1,2] Mille A. Micheelsen,[1] Kim Sneppen,[1,*] and Geneviève Thon[3]
[1] Center for Models of Life, Niels Bohr Institute, Blegdamsvej 17, DK-2100, Copenhagen Ø, Denmark
[2] Department of Molecular and Biomedical Sciences (Biochemistry), University of Adelaide SA 5005, Australia
[3] Department of Molecular Biology, University of Copenhagen Biocenter, Ole Maaløes Vej 5, DK-2200 Copenhagen N, Denmark
*Correspondence: sneppen@nbi.dk
DOI 10.1016/j.cell.2007.02.053

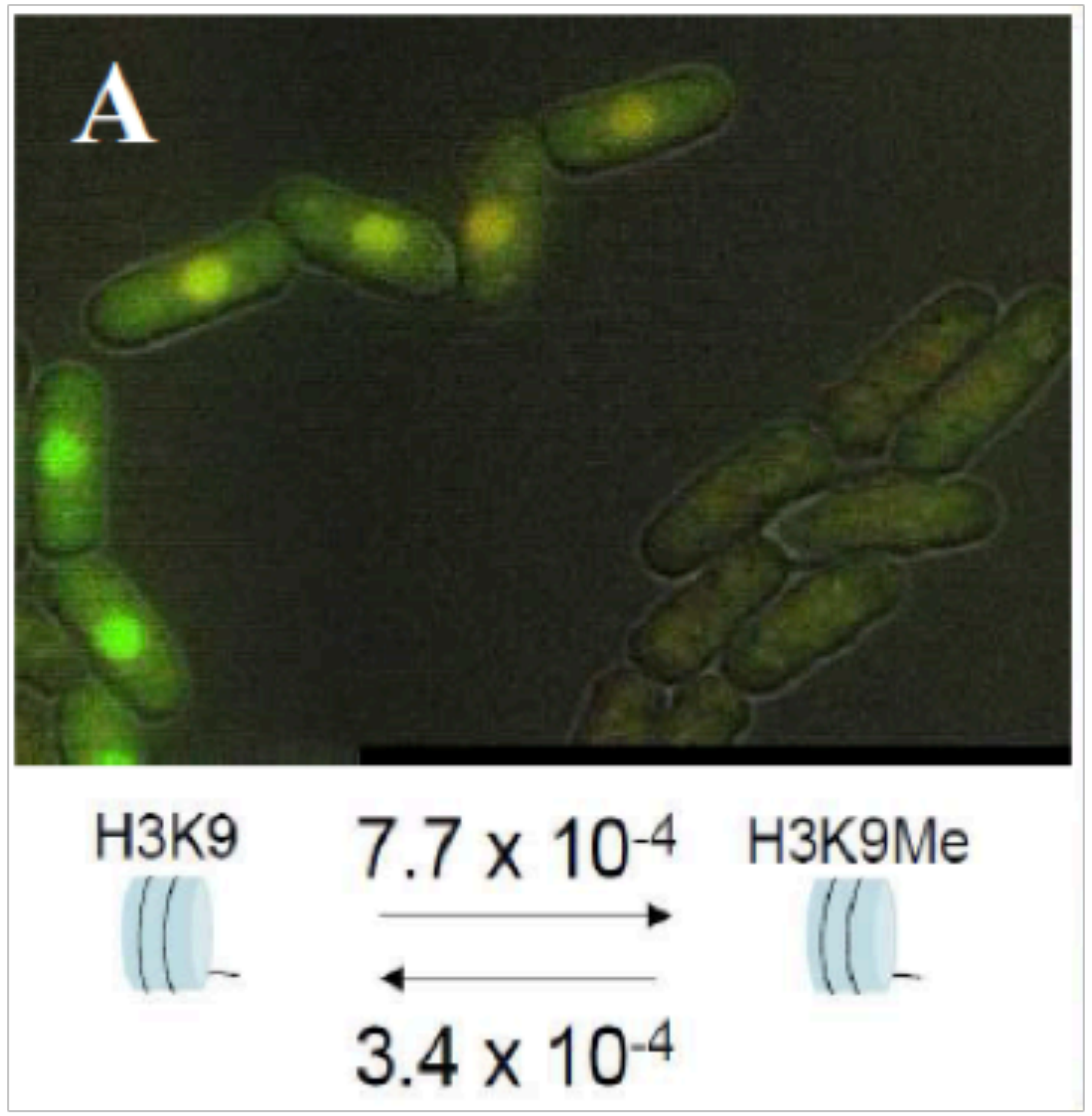
Mutants with shortened mating-type region show bistable chromatin- and gene expression states



How to model bistable chromatin states?

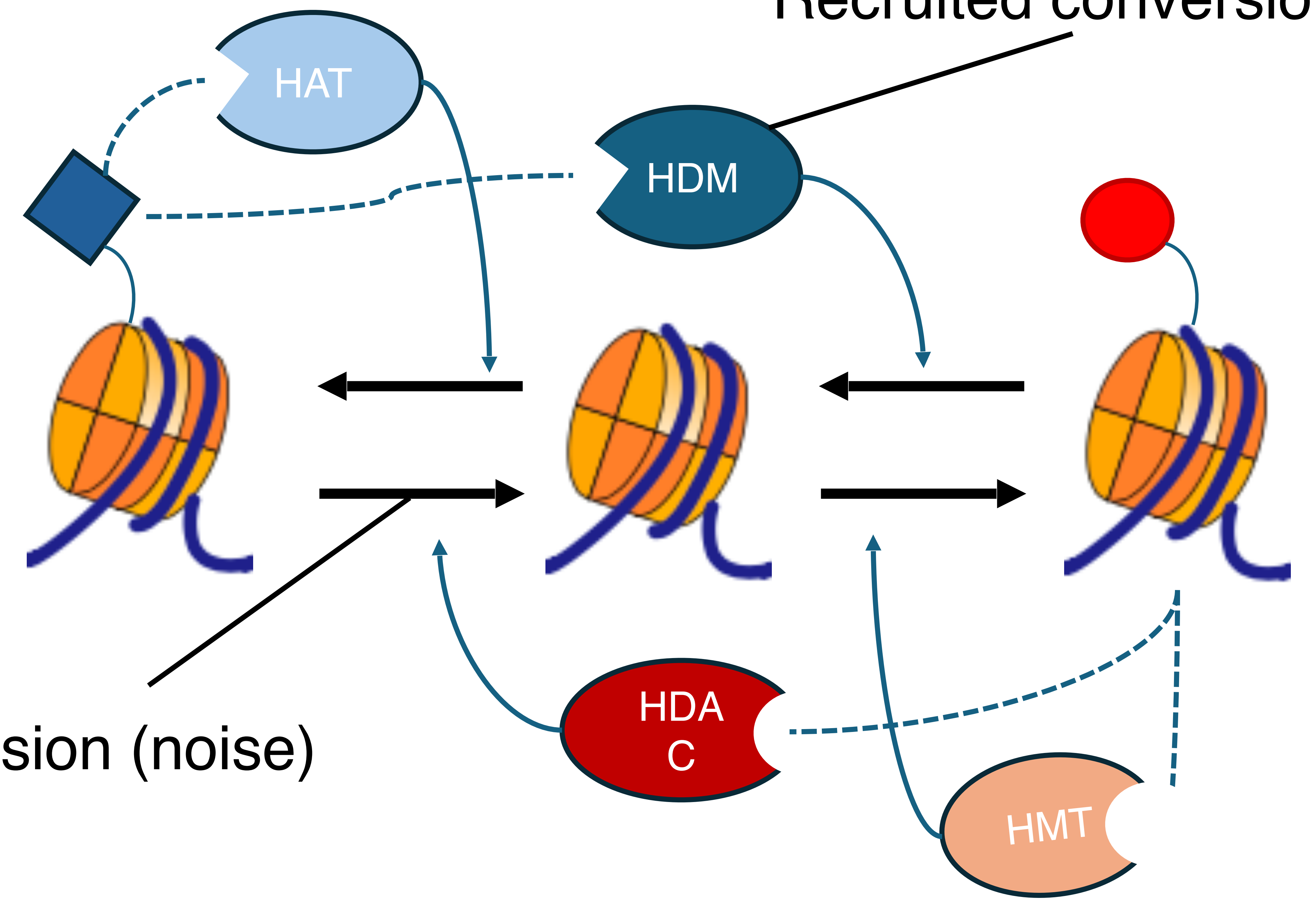
Modeling bistable and heritable chromatin states





Dodd, I. B., Micheelsen, M. A., Sneppen, K. & Thon, G., Theoretical analysis of epigenetic cell memory by nucleosome modification. Cell 129, 813-822 (2007).

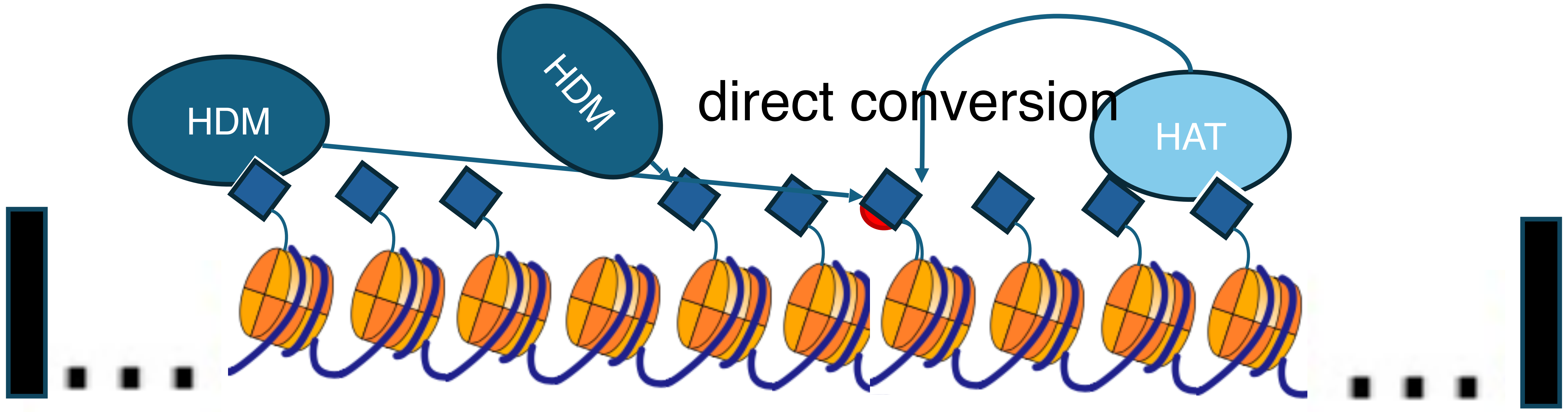
Recruited conversion (feedback)



Direct conversion (noise)

Recruited conversion Recruited conversion

direct conversion

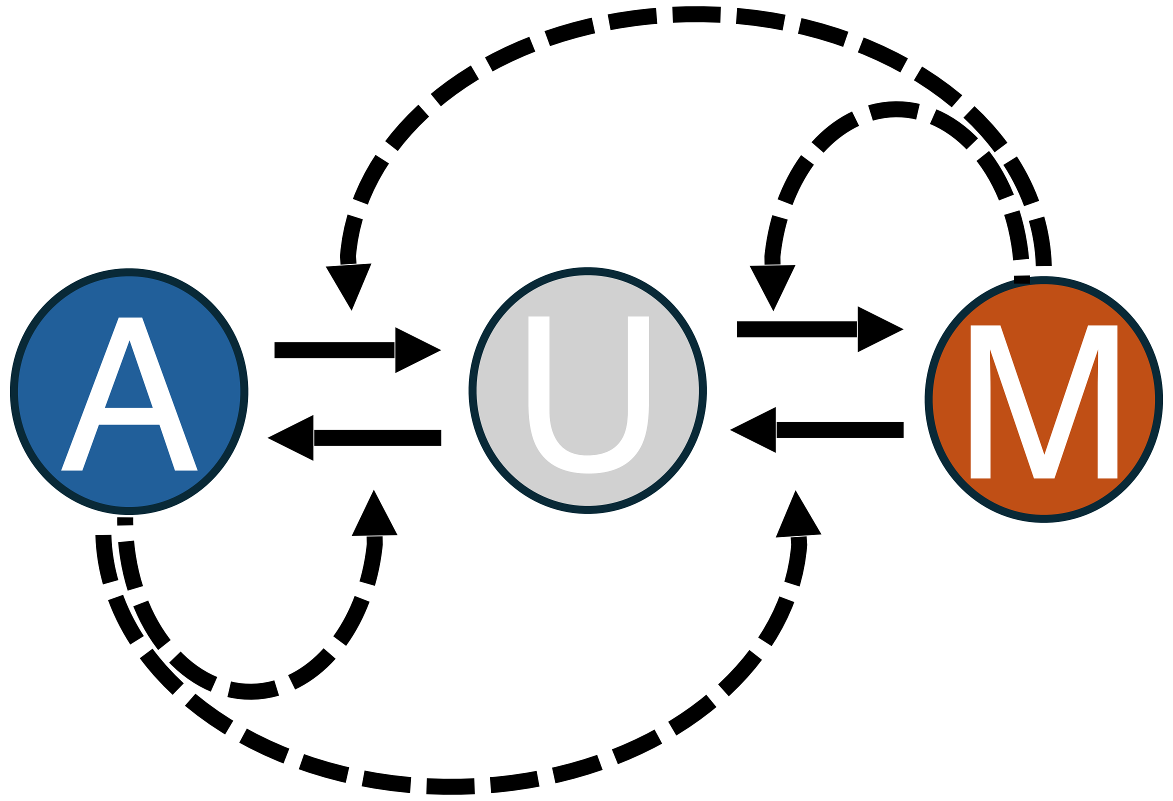


Basic algorithm of the bistable chromatin model

1. **Choose parameter value**: feedback (α) → $F = \dfrac{\alpha}{1 - \alpha}$
2. **Do feedback attempt with probability α:**
    - Select a random recruiting nucleosome **n1**
    - Select a random substrate nucleosome **n2**
    - If **n1** is in state **A or M**, change the state of **n2** one step towards **n1**
3. **Do noise attempt with probability $1 - \alpha$:**
    - Select a random nucleosome and state one step toward the opposing state (e.g. A to U)
4. **Mimic DNA replication** after certain intervals:
    - Convert each nucleosome in the system to the U state with 50% chance

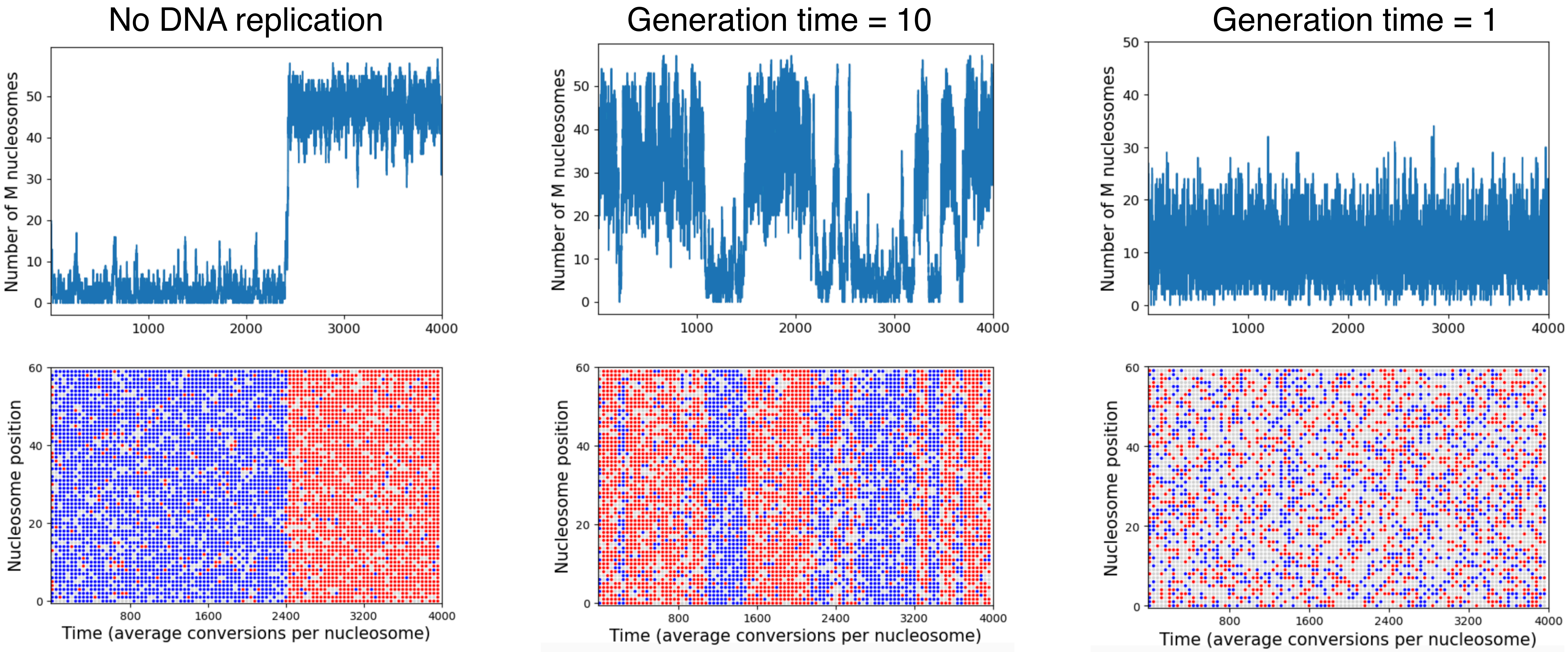
Simulations (practice)

1. How does DNA replication influence the simulations? What is the dependence on generation time?
2. What happens when there are only two states?
3. What happens if recruited conversions can only occur between nearest-neighbors?
4. Does doubling/halving the system size influence Bistability? If so, how?



1. How does DNA replication influence the simulations? What is the dependence on

$$F = 2$$

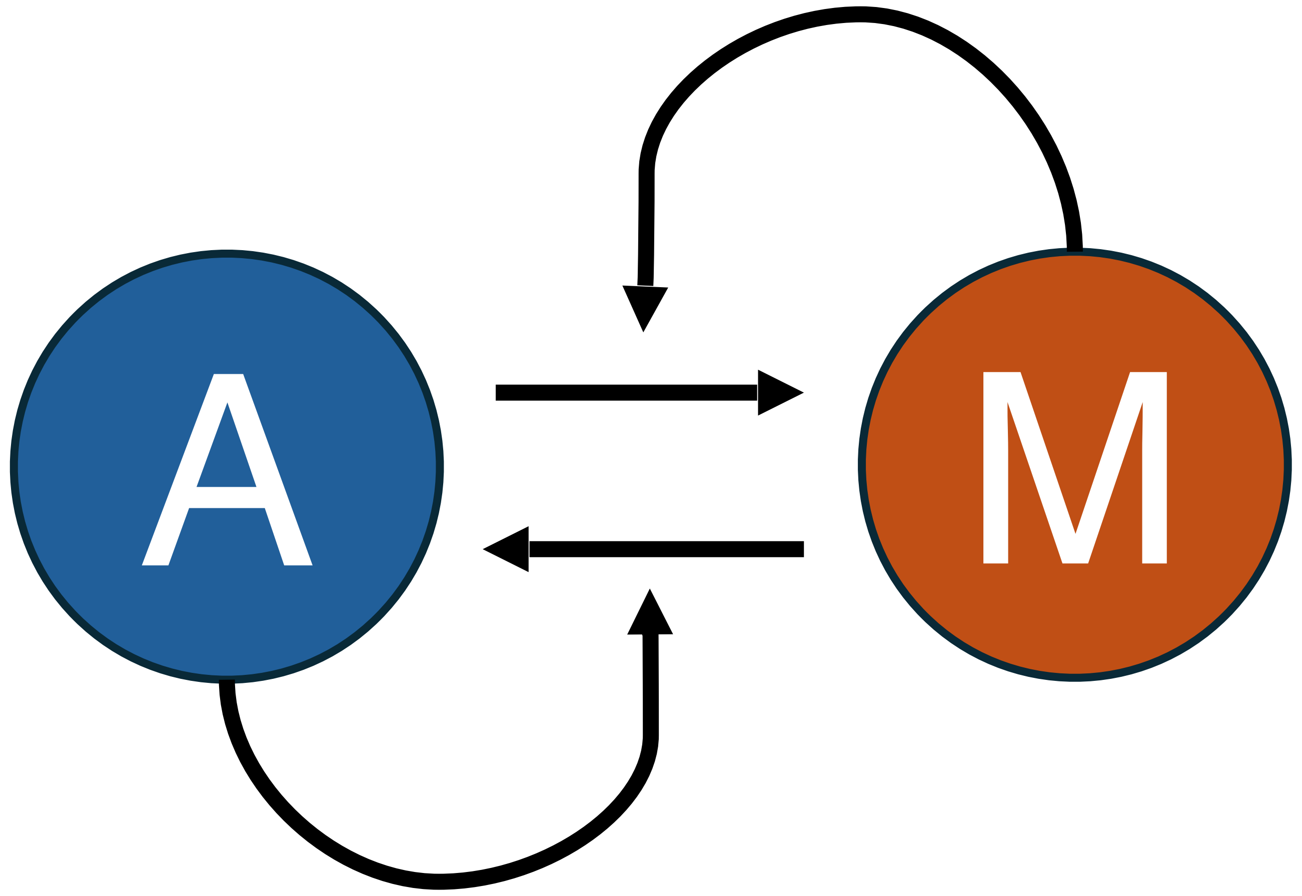


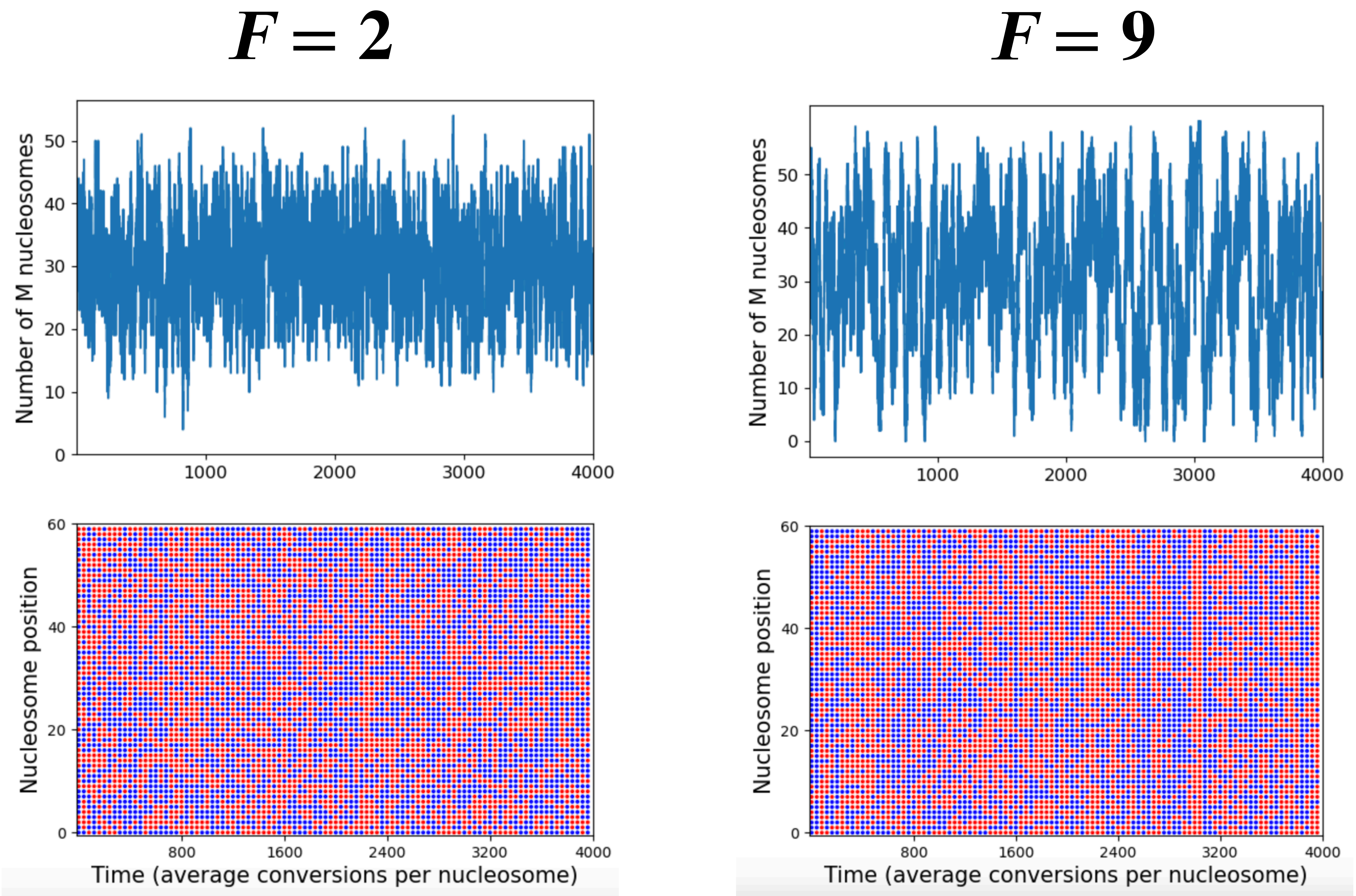
No DNA replication

Generation time = 10

Generation time = 1

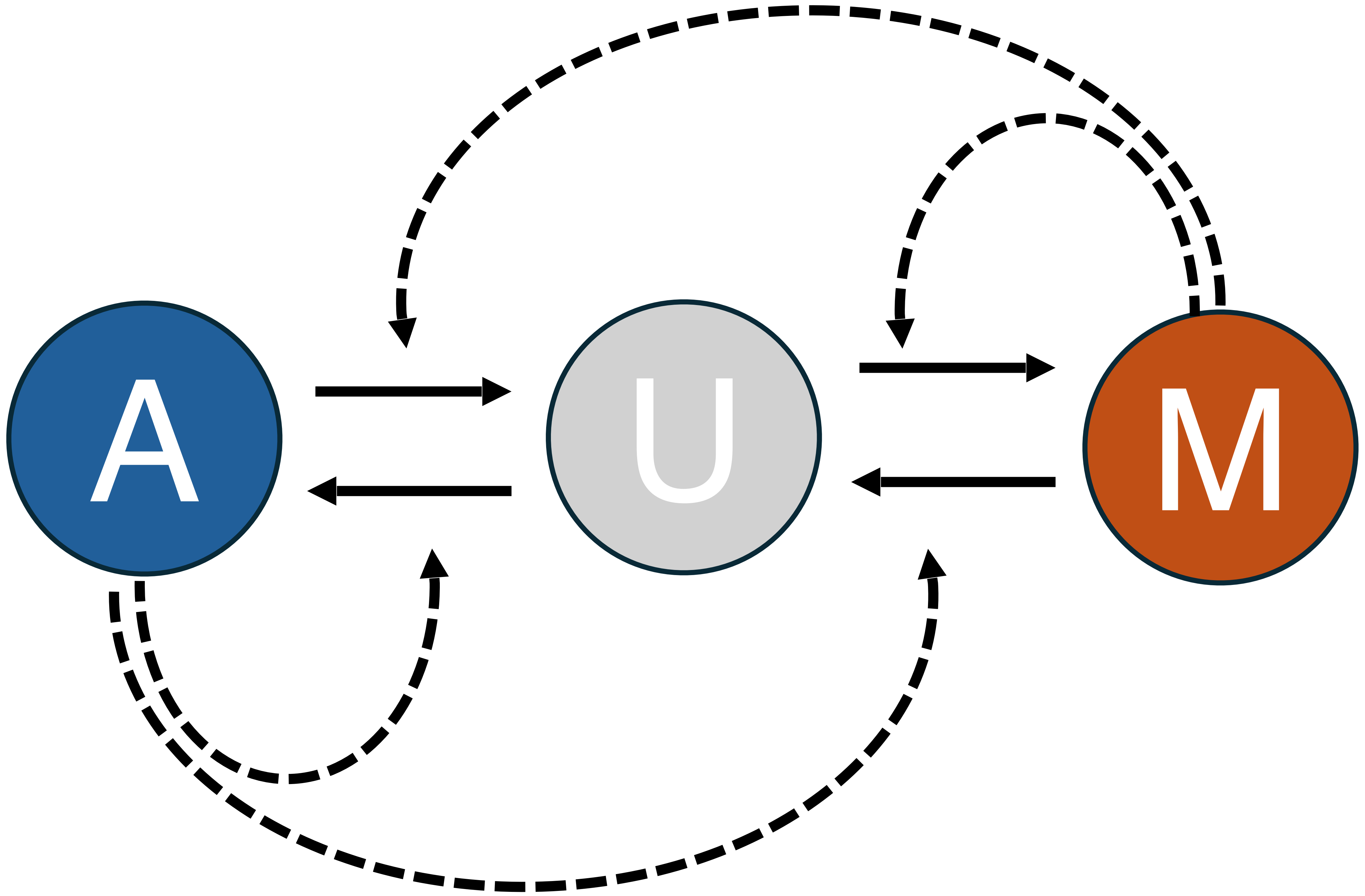
2. What happens when there are only two states?



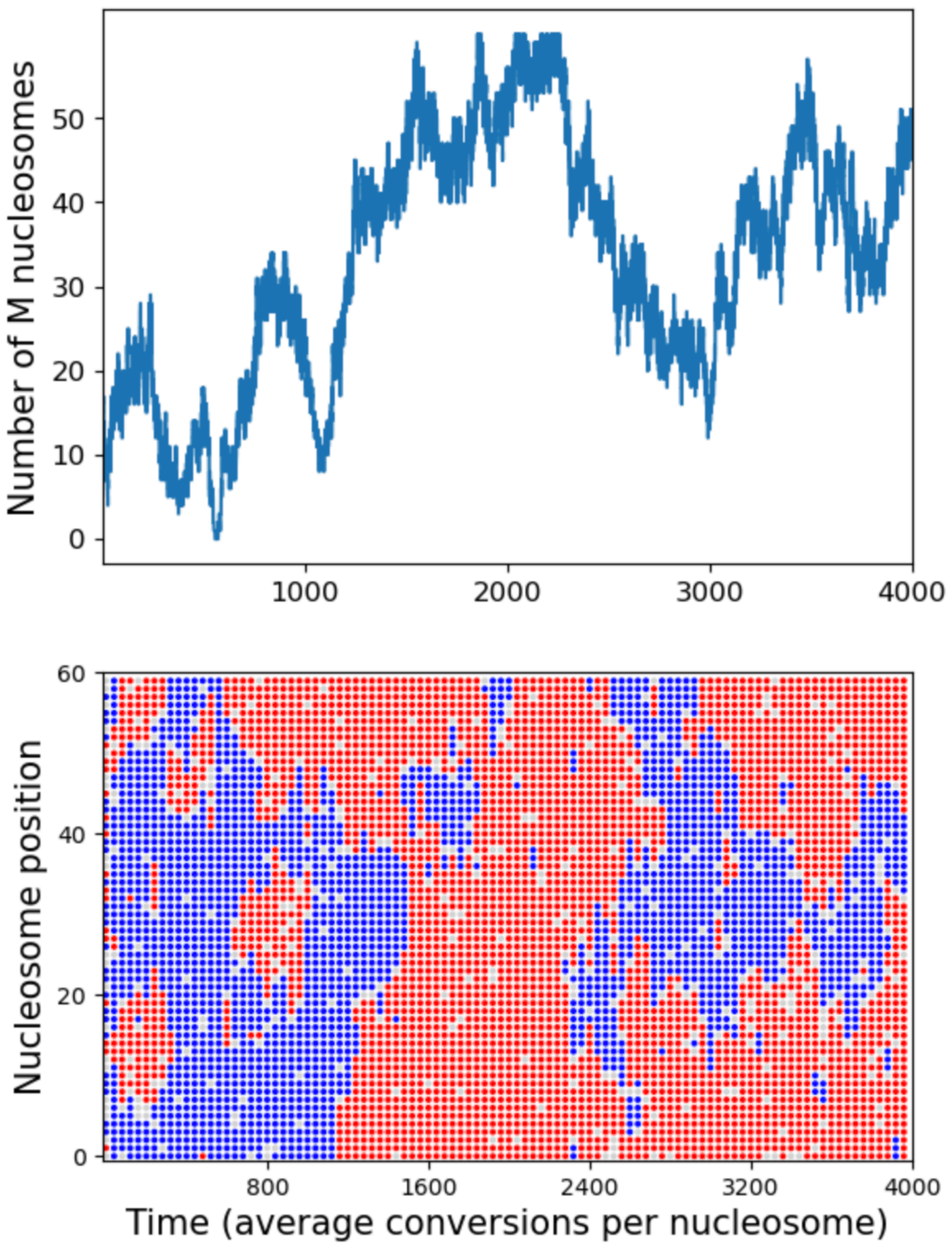

$F = 2$

$F = 9$

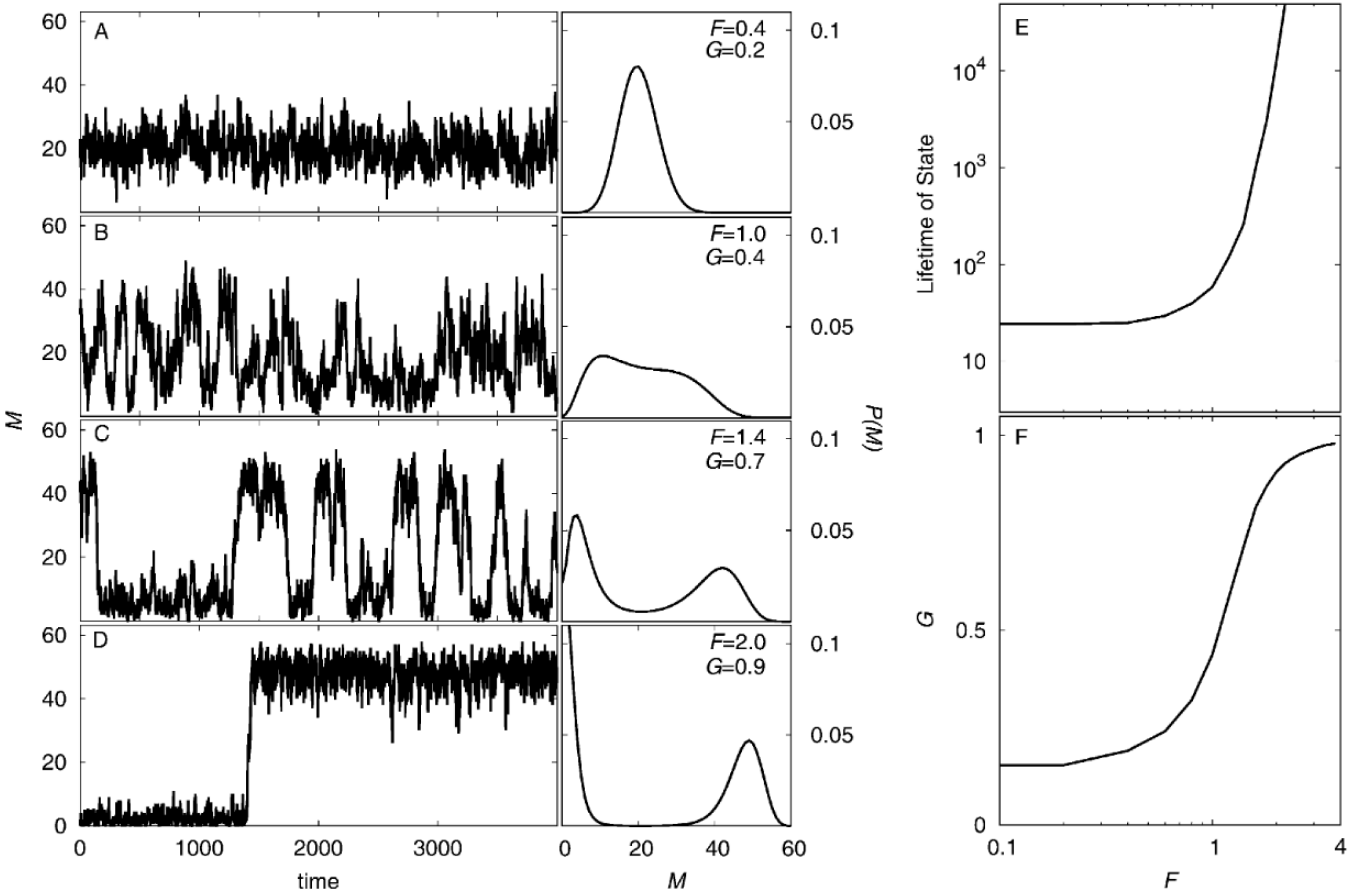
3. What happens if recruited conversions can only occur between nearest-neighbors?



$F = 9$



Bistability is a function of noise

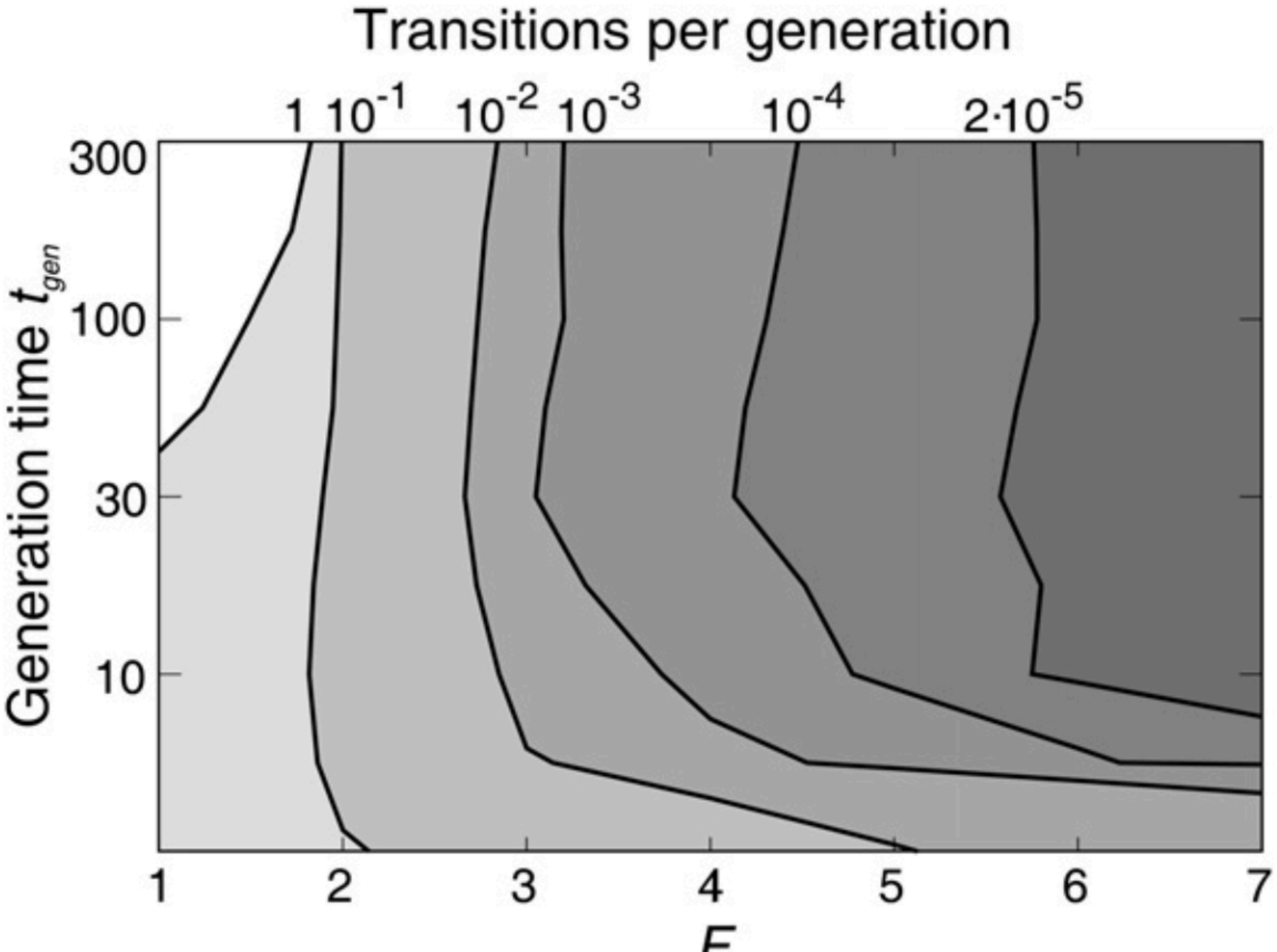


$$High\ A\ state: A > M$$
$$High\ M\ state: M > A$$

Transition to the high-M state is scored when M > 1.5A

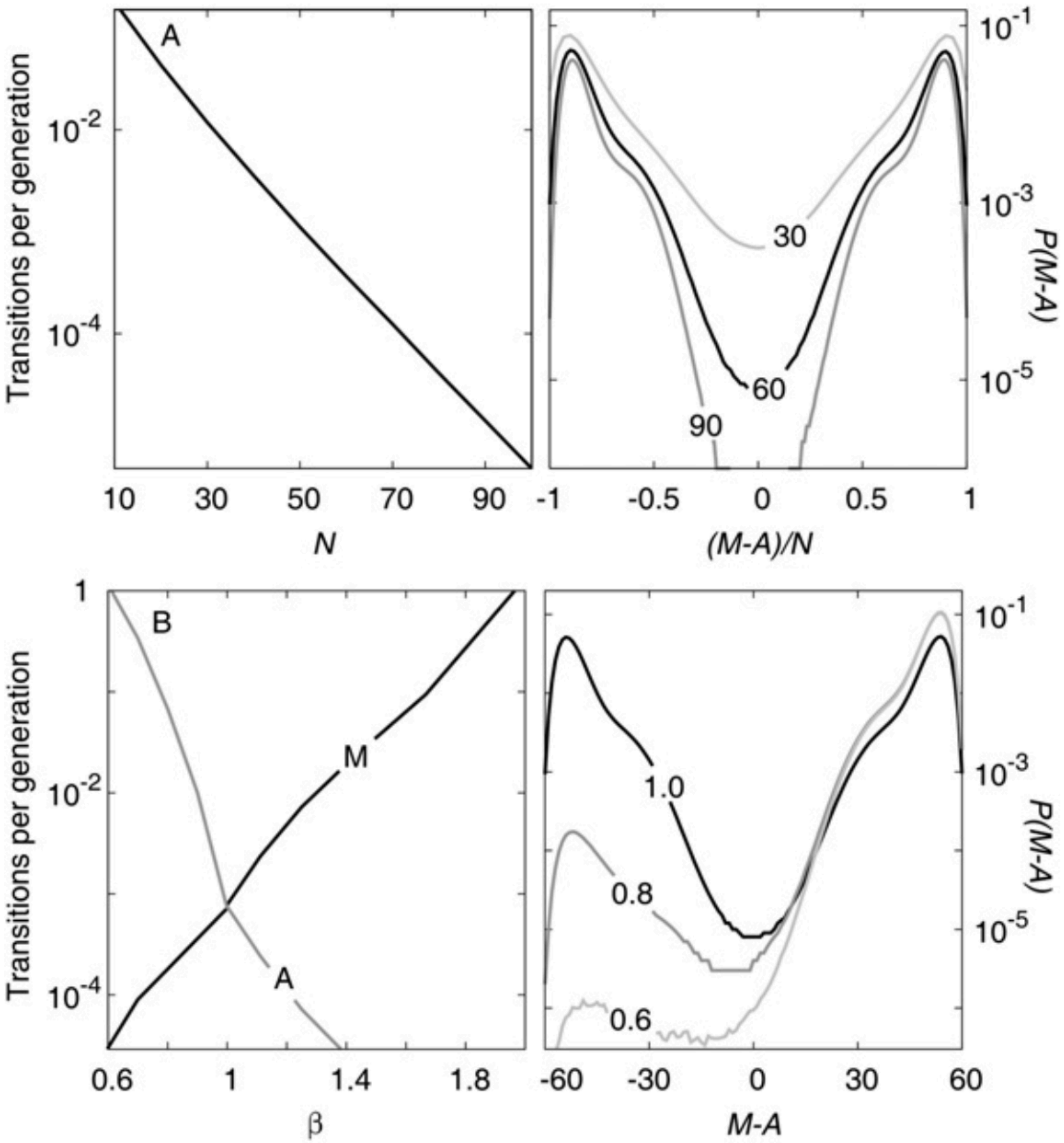
$$G = average\left(\frac{\left|M - A\right|}{\left|M + A\right|}\right)$$

Inheritance of the Epigenetic States



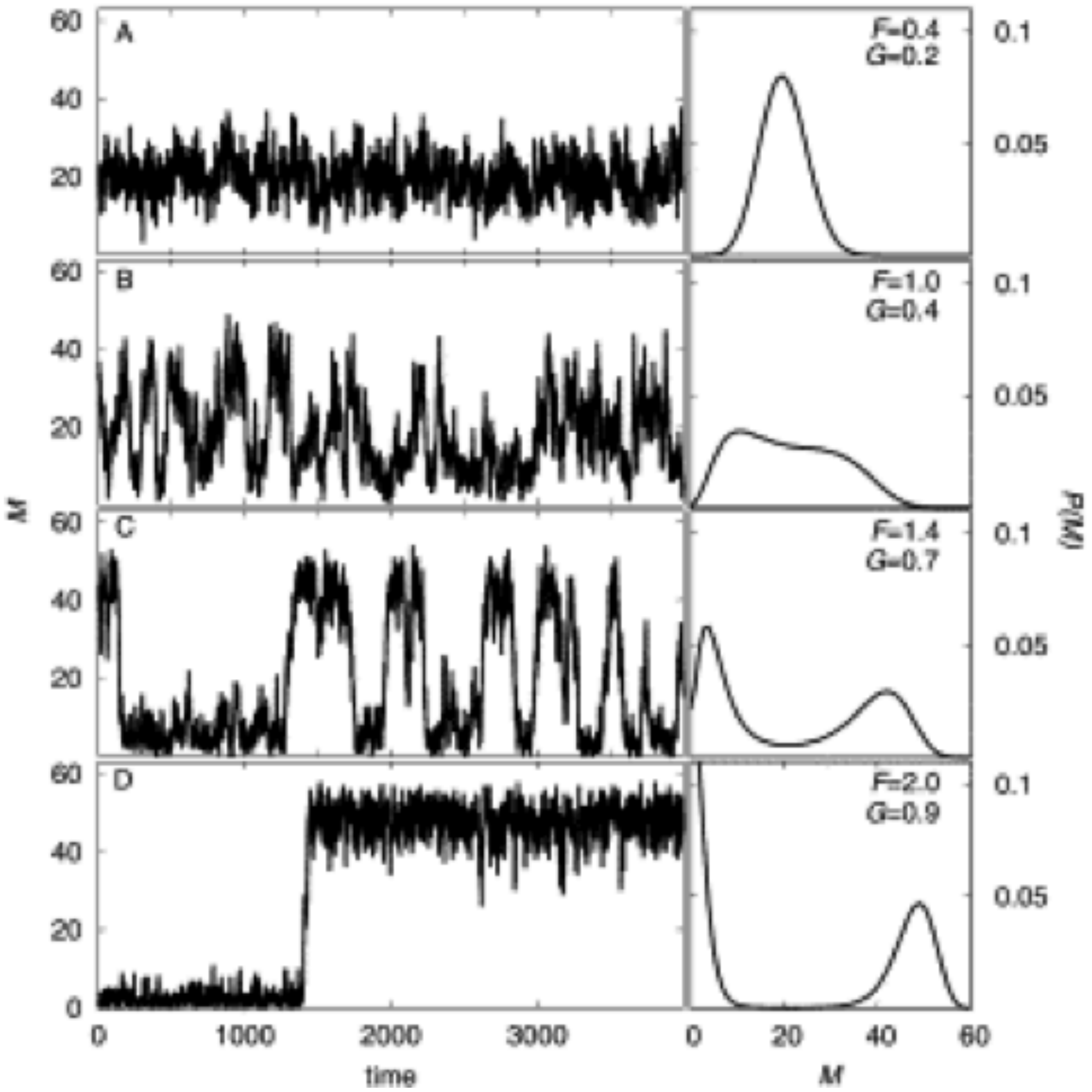
Can you think of experimentally testable predictions of the model?

Effect of system size and modification asymmetry on bistability



Summary of the results

- Nucleosome-mediated epigenetic cell memory is a **dynamic** and stochastic process.
- Positive **feedback, long-range interactions**, and **cooperativity** are essential for robust bistability and heritability.
- **Histone modifications don’t spread linearly from nucleation sites**



Homework

1. If two recruiting nucleosomes are chosen instead of only one, how does this change bistability of the two-state and the three-state model? Generate plots for at least three different F values for both models and discuss briefly what you see.

Do feedback attempt with probability α:

- Select two random recruiting nucleosomes **n1 and n2**
- Select a random substrate nucleosome **n3**
- If **n1 and n2 are both** in state **A/M**, change the state of **n2** one step towards **n1**