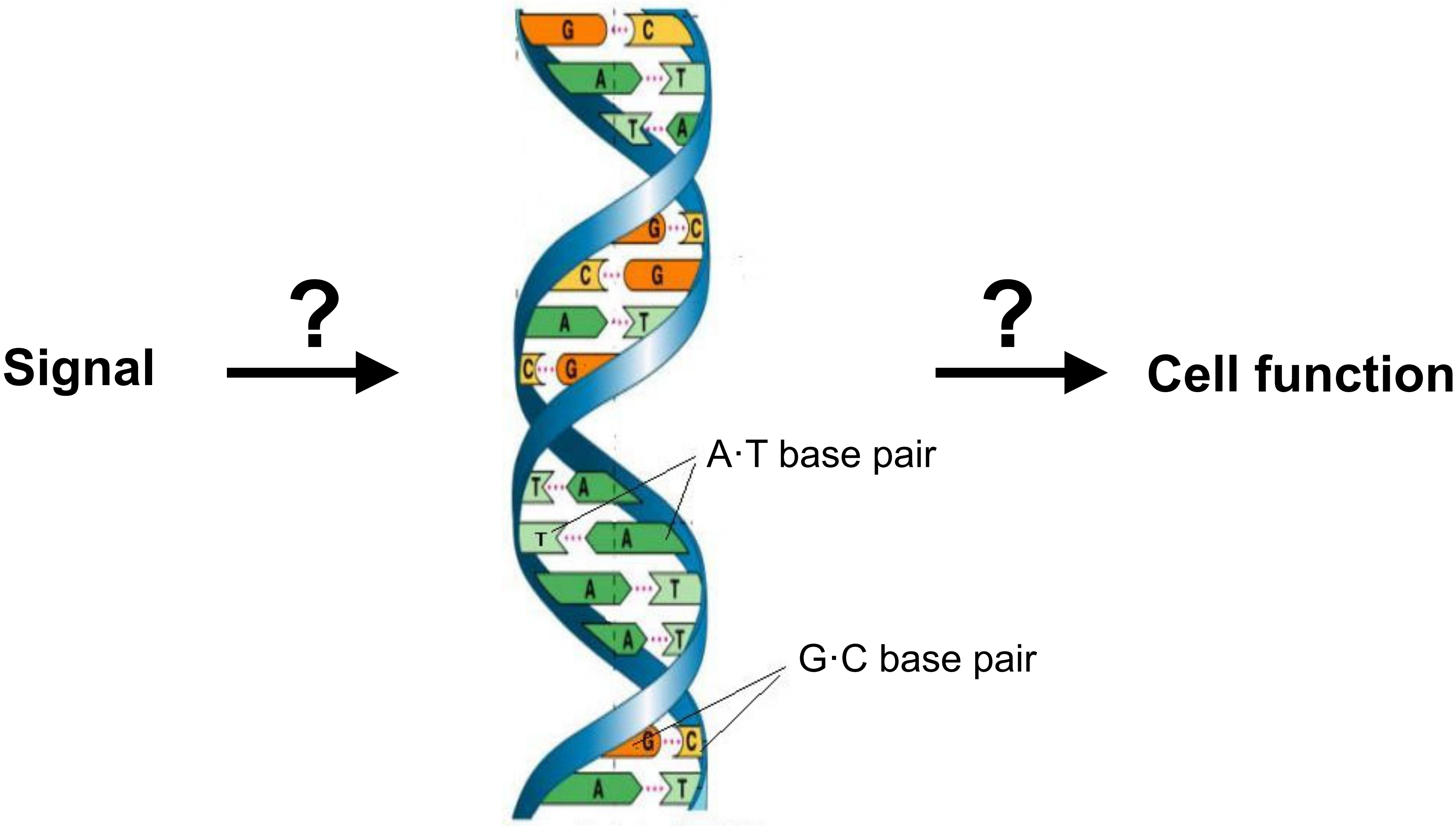
Translating genome information into cellular function



Human genome: $3 \cdot 10^9$ base pairs (**A**denine, **C**ytosine, **G**uanine or **T**hymine)

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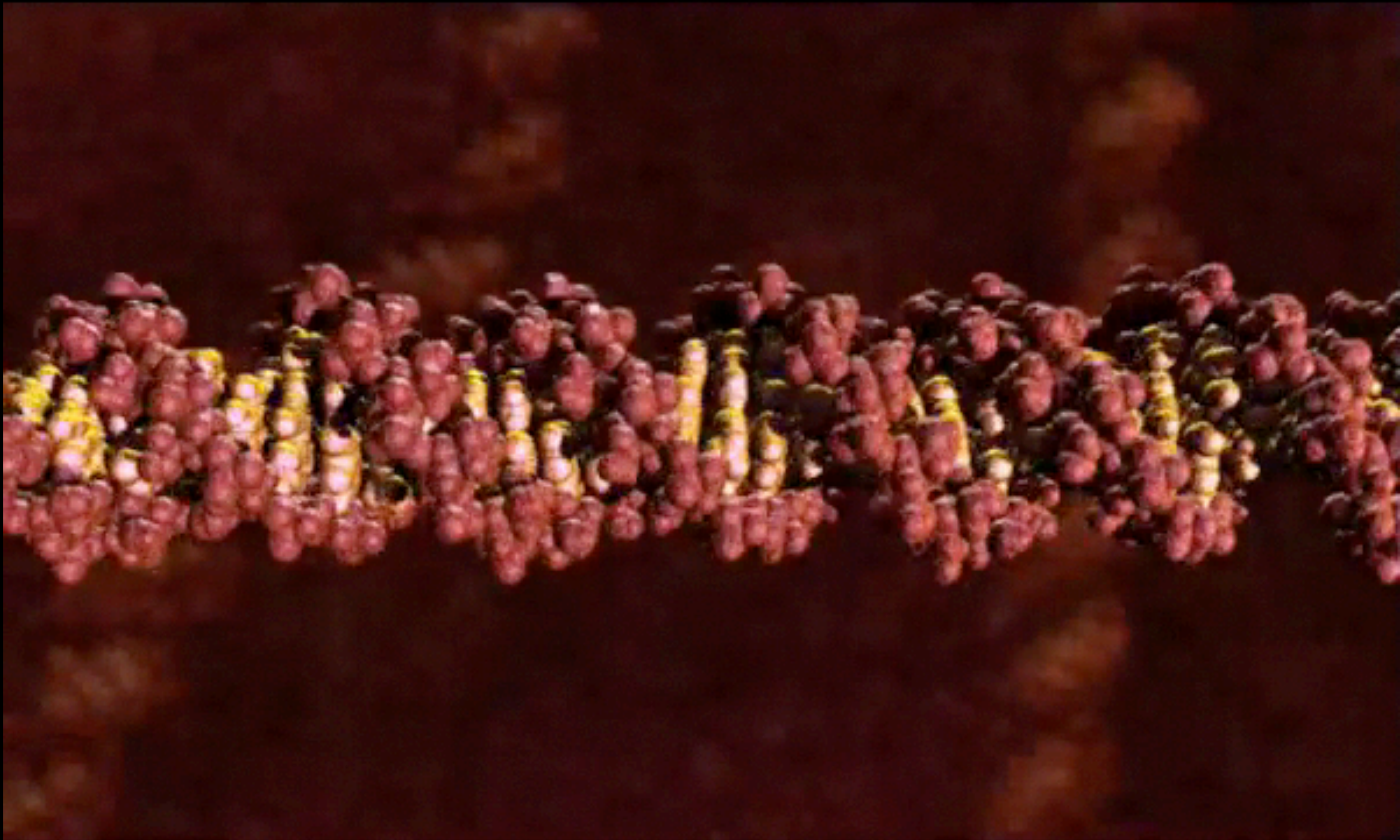
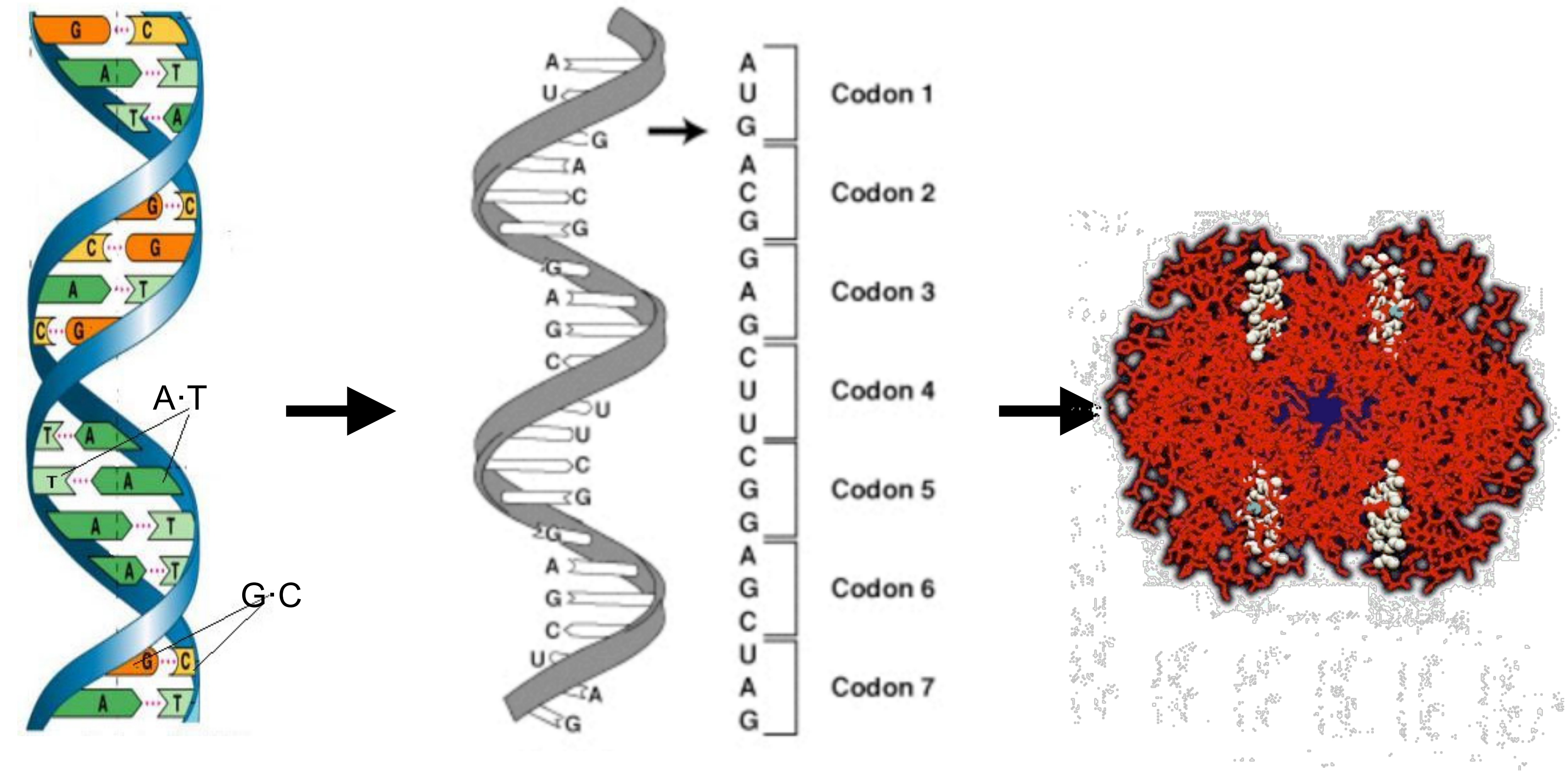


DNA

If you know the DNA sequence it is all very simple...



DNA **RNA** **Protein**

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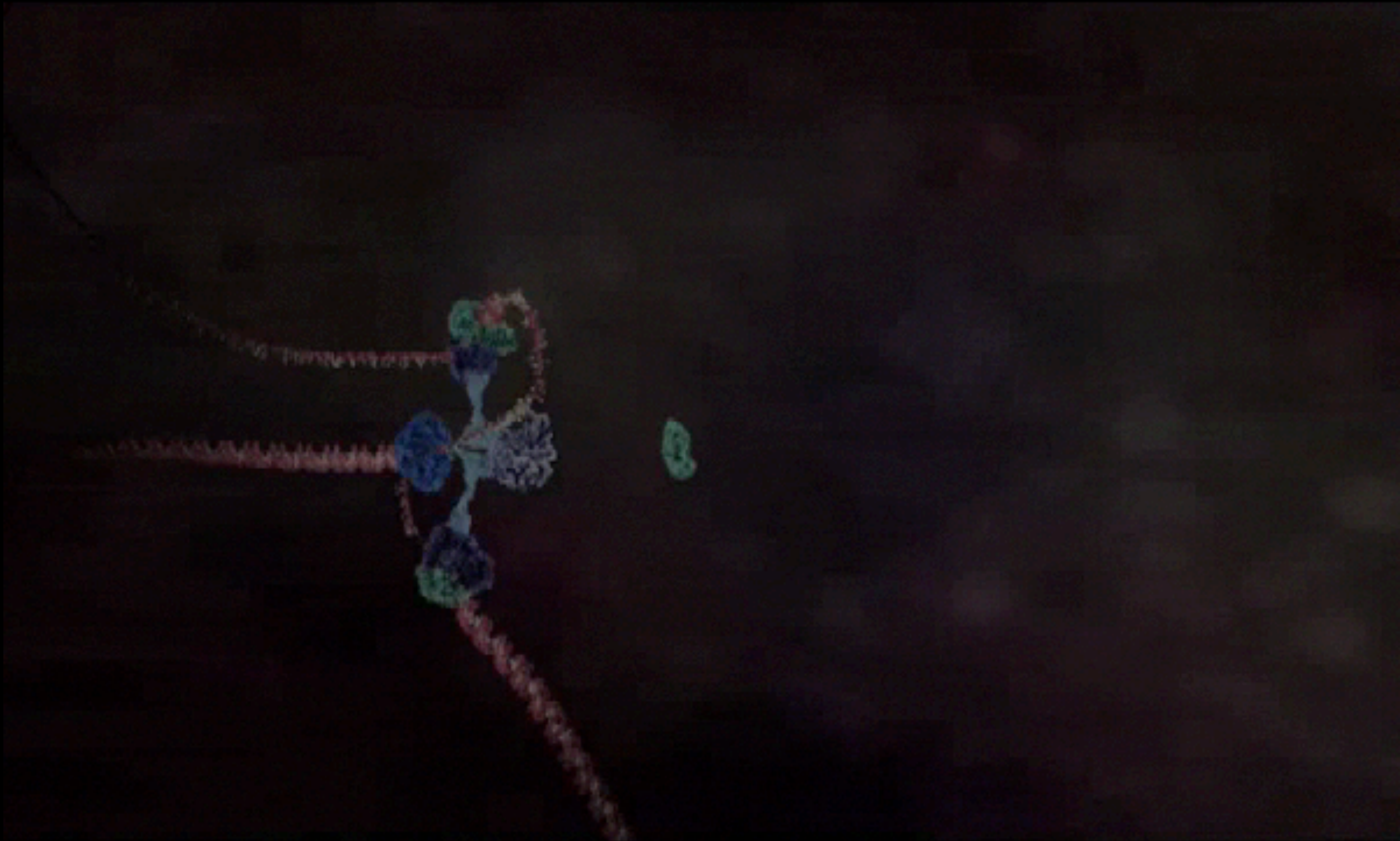
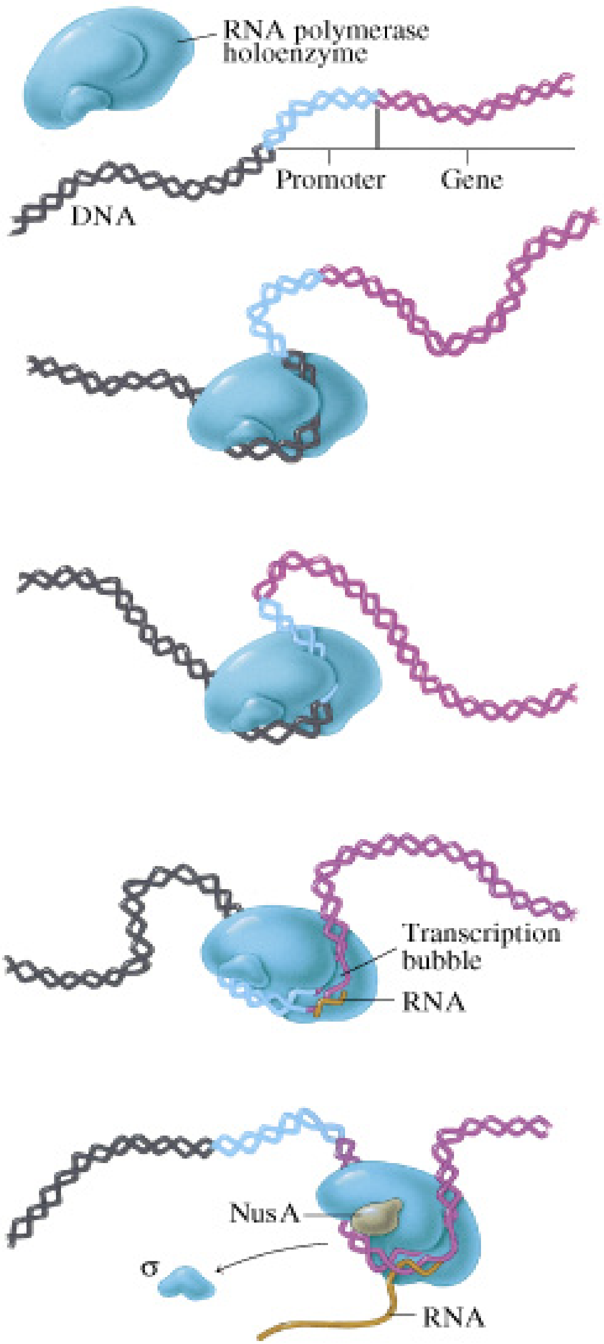


Initiation of transcription in the bacterium E. coli



(a) RNA polymerase holoenzyme binds nonspecifically to DNA.

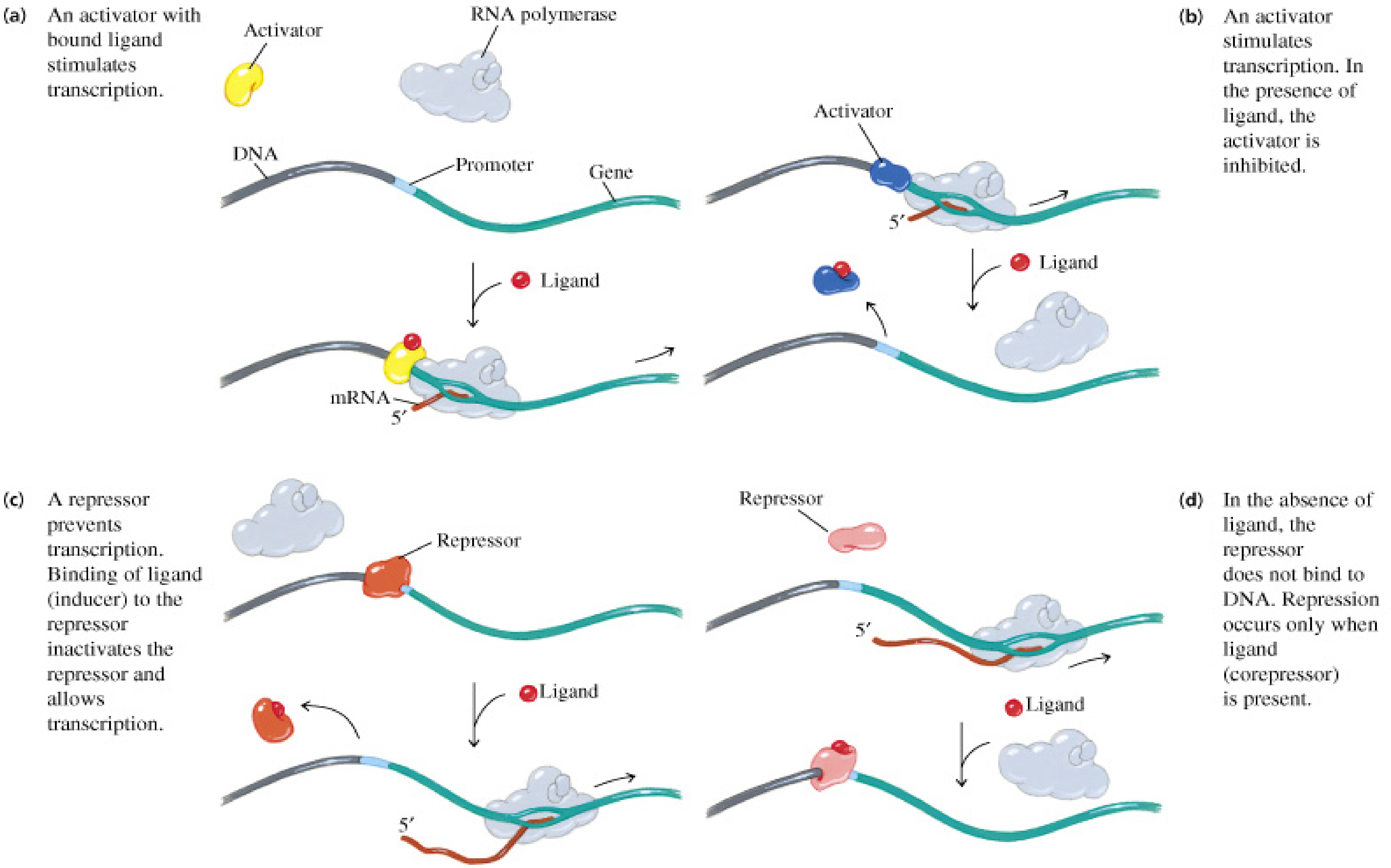
(b) The holoenzyme conducts a one-dimensional search for a promoter.

(c) When a promoter is found, the holoenzyme and the promoter form a closed complex.

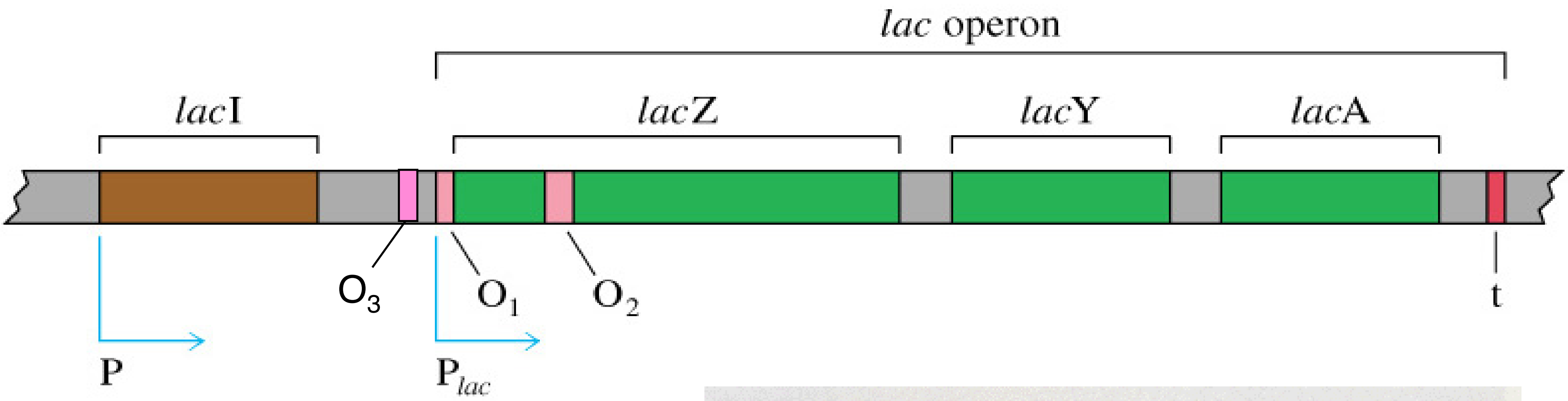
(d) A conformational change from the closed complex to an open complex produces a transcription bubble at the initiation site. A short stretch of RNA is then synthesized.

(e) The σ subunit dissociates from the core enzyme, and RNA polymerase clears the promoter. Accessory proteins, including NusA, bind to the polymerase.

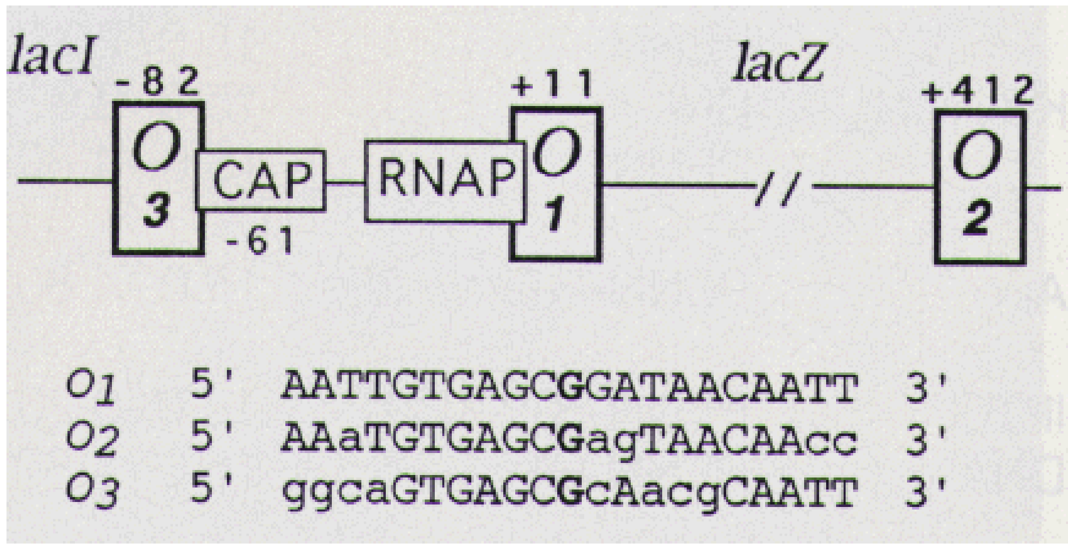
Strategies for transcription regulation in bacteria



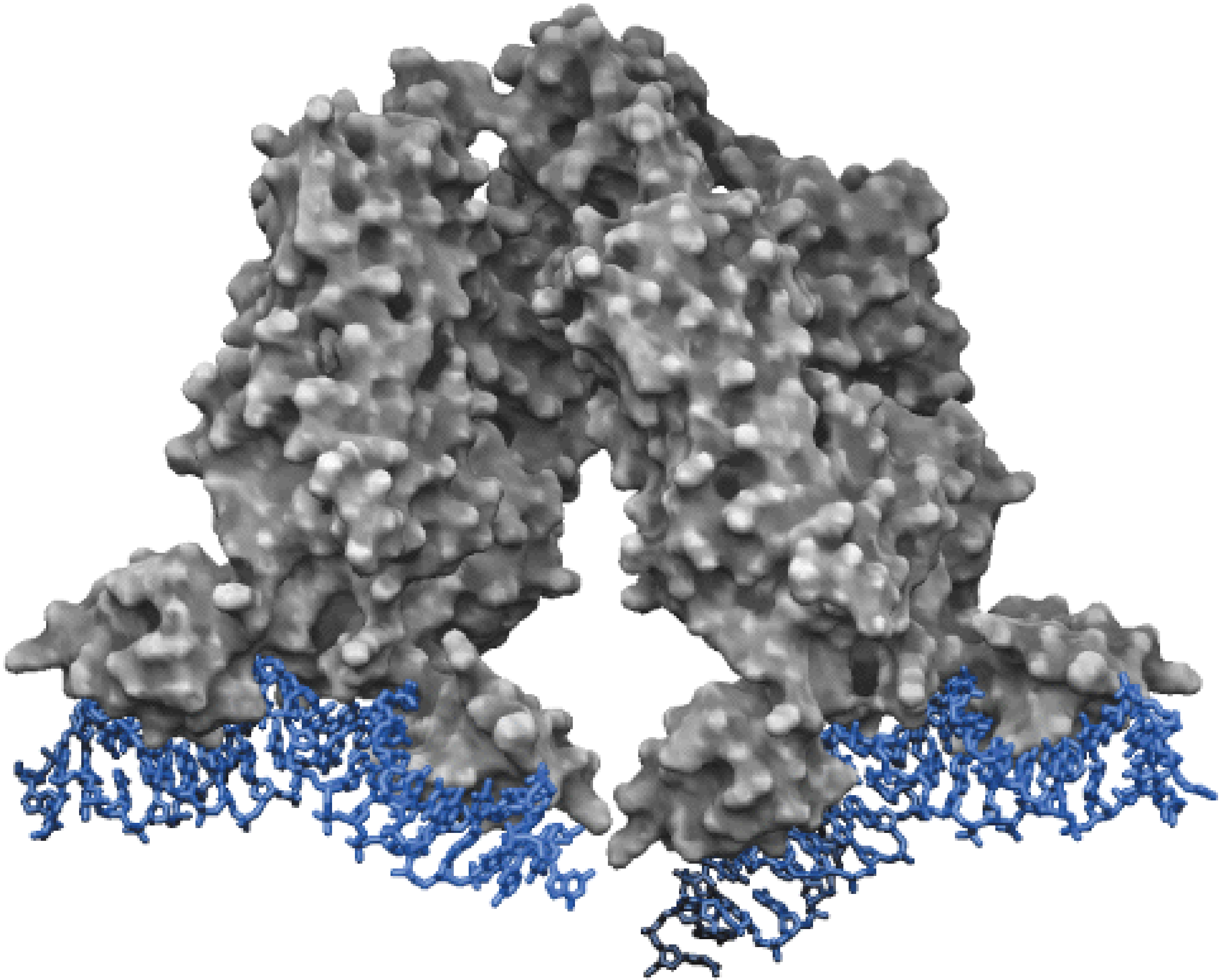
Organization of the genes regulated by Lac repressor, a transcription repressor protein in the bacterium E. coli



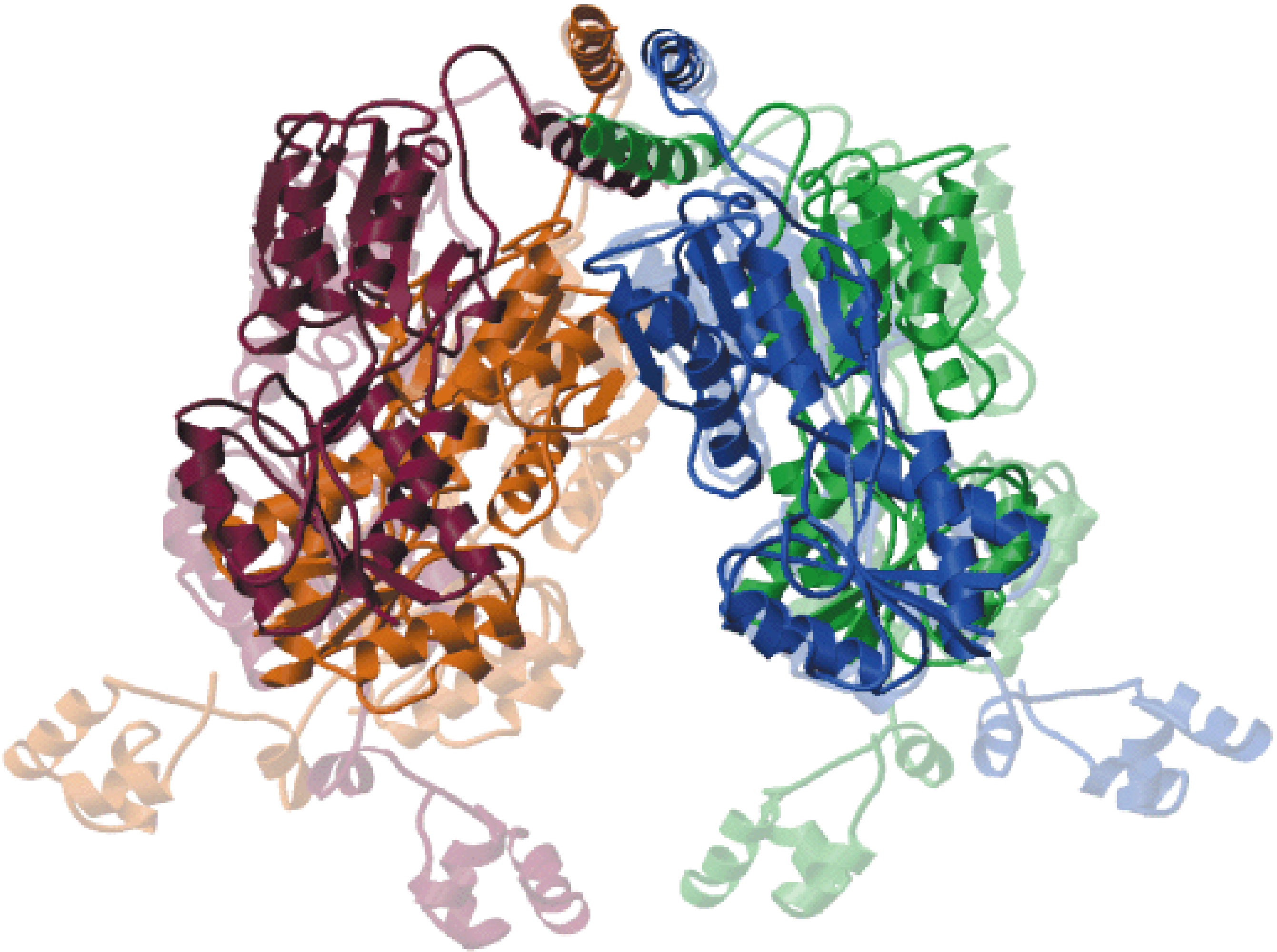
Lac repressor binds to the operators O_1, O_2 and O_3



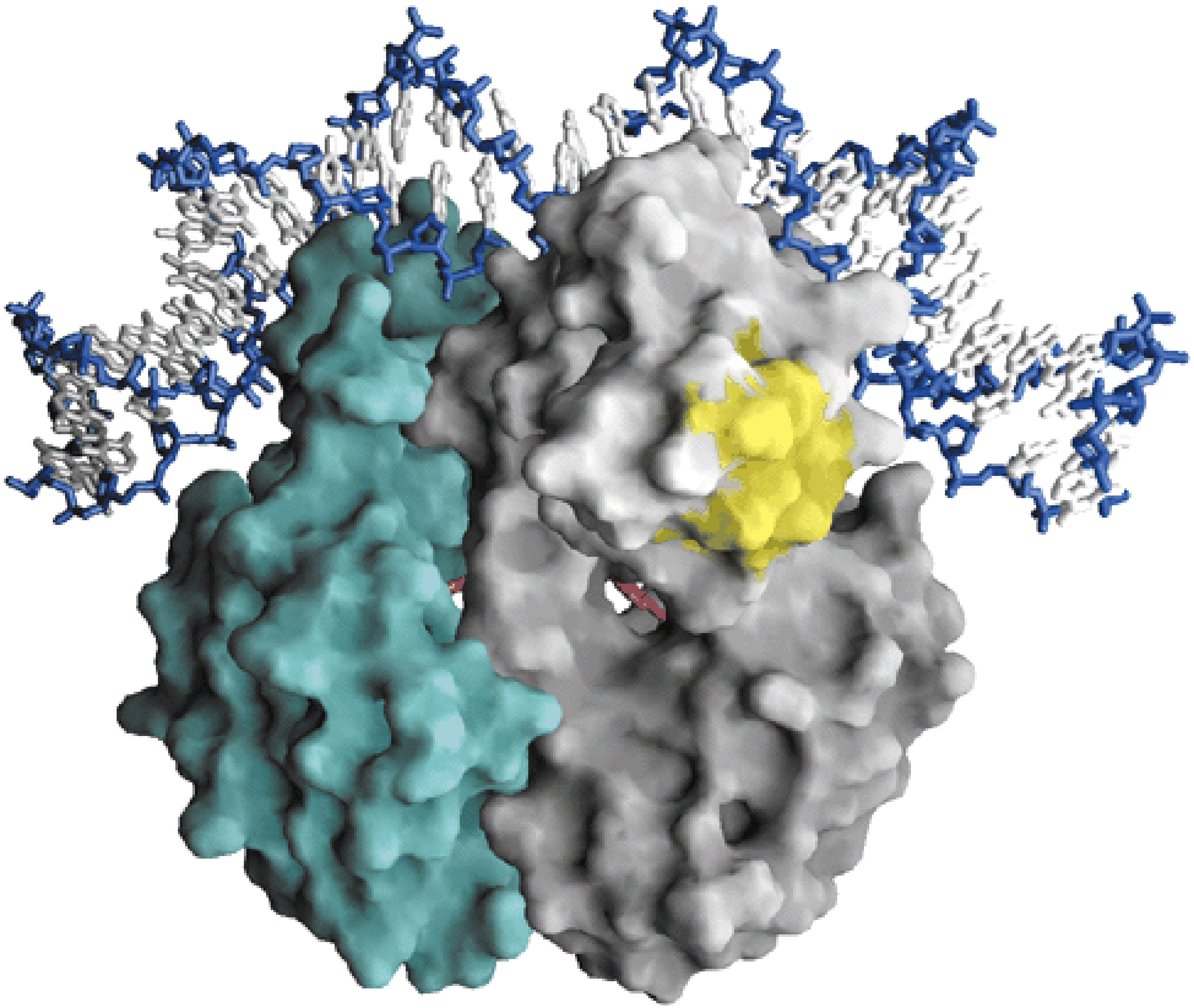
Molecular structure of E. coli lac repressor



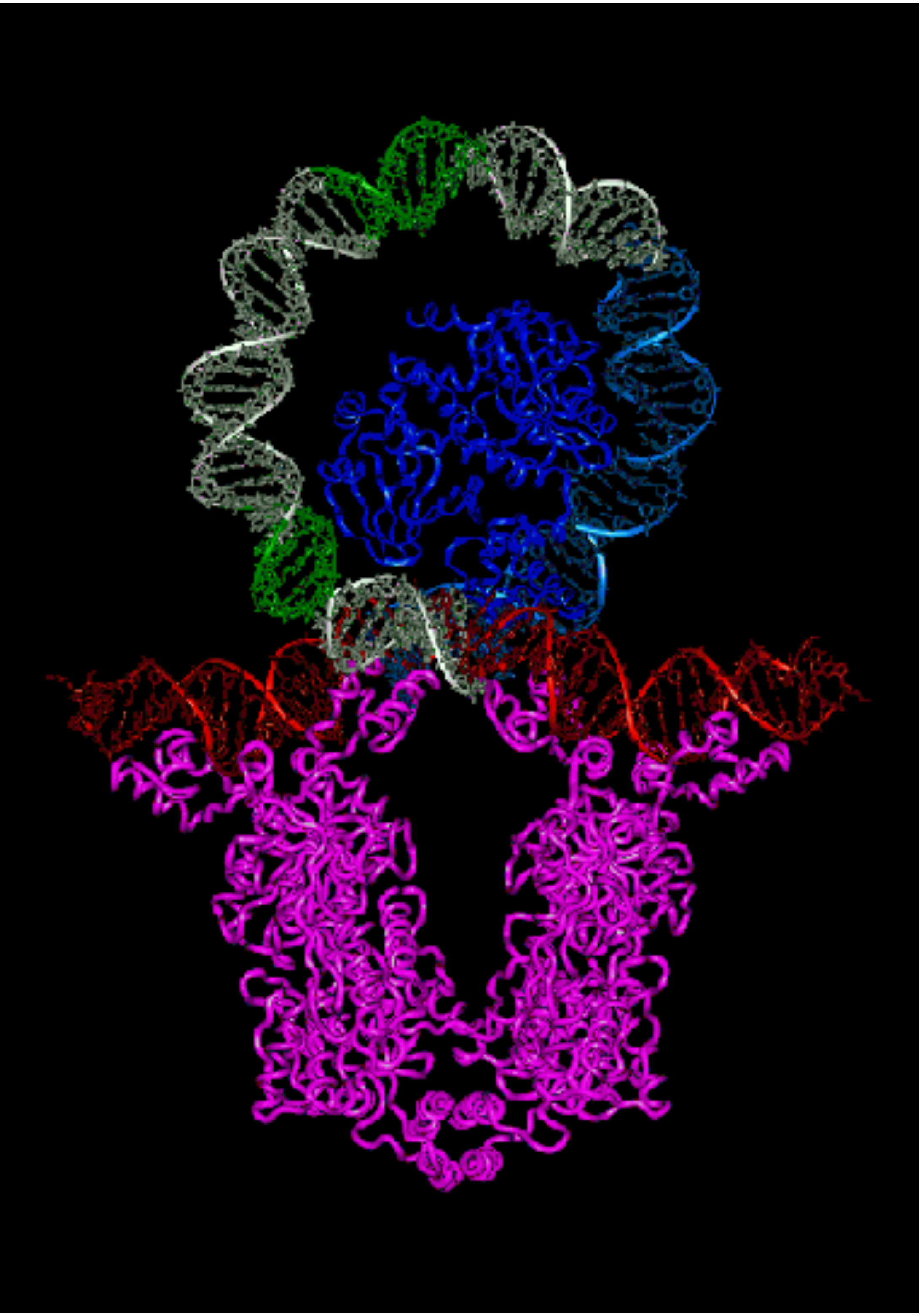
E. coli lac repressor + ligand allolactose that signals the presence of lactose in the medium and reduces DNA binding



Molecular structure of E. coli CRP (also called CAP for catabolite gene activator protein)



Model for the complex of CAP and LacI at the lac operator

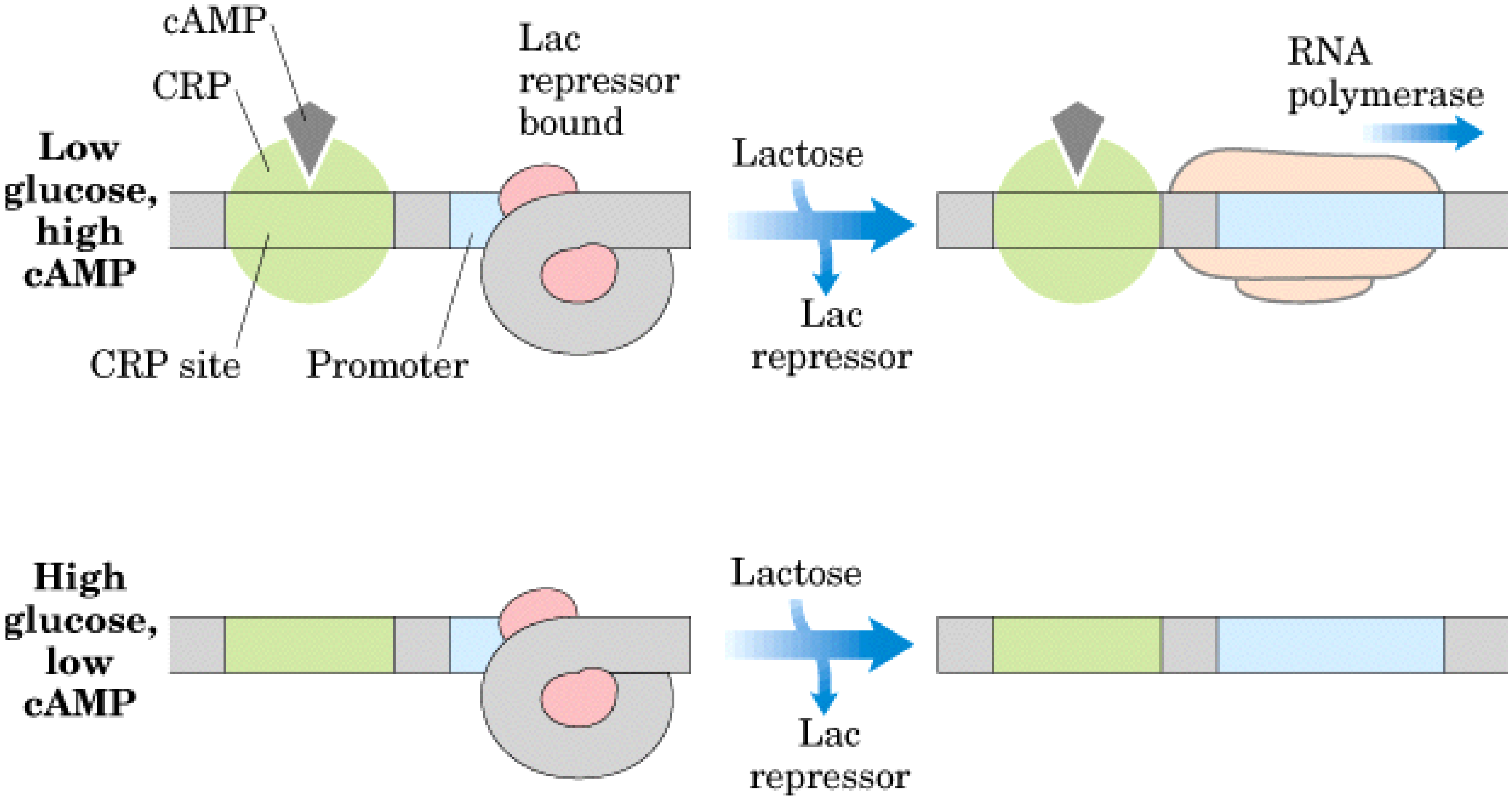


CAP

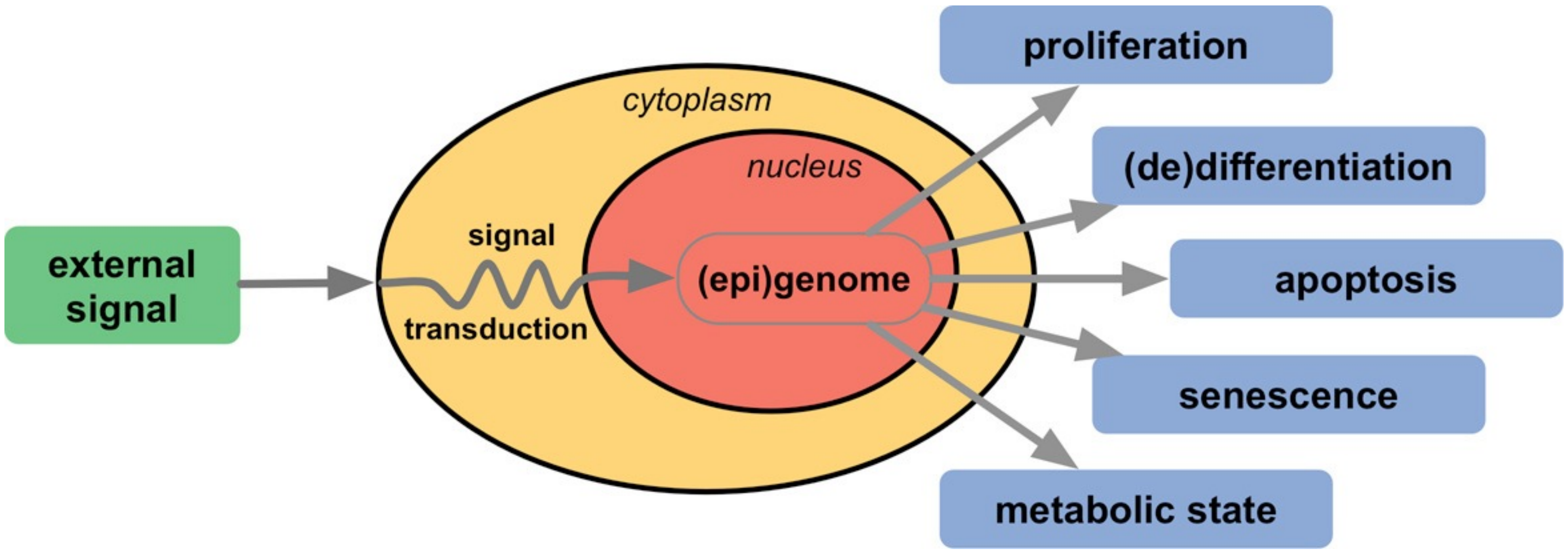
low glucose and low lactose
=> both CAP and LacI bound
=> repression

Lac repressor bound to operator sites O1 and O3

“On” and “off” states of the E. coli lac repressor



Eukaryotes: Decisions on the cell's fate made in the nucleus

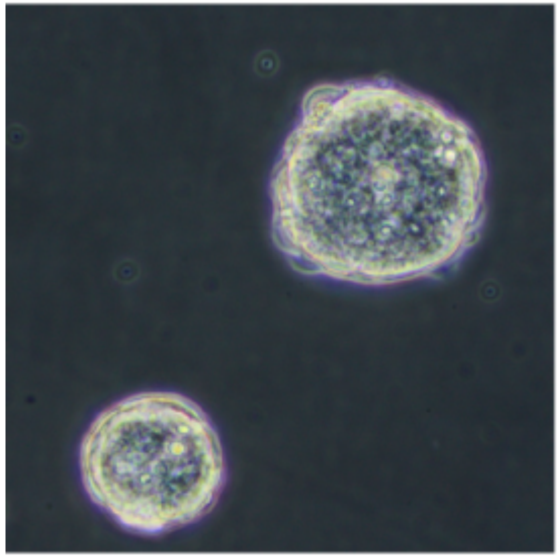


About genomic and epigenomic differences

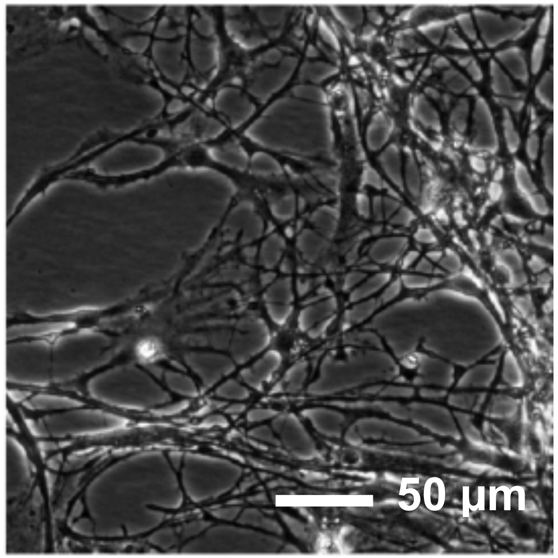
1% genomic differences

Image: James Balog Getty Images

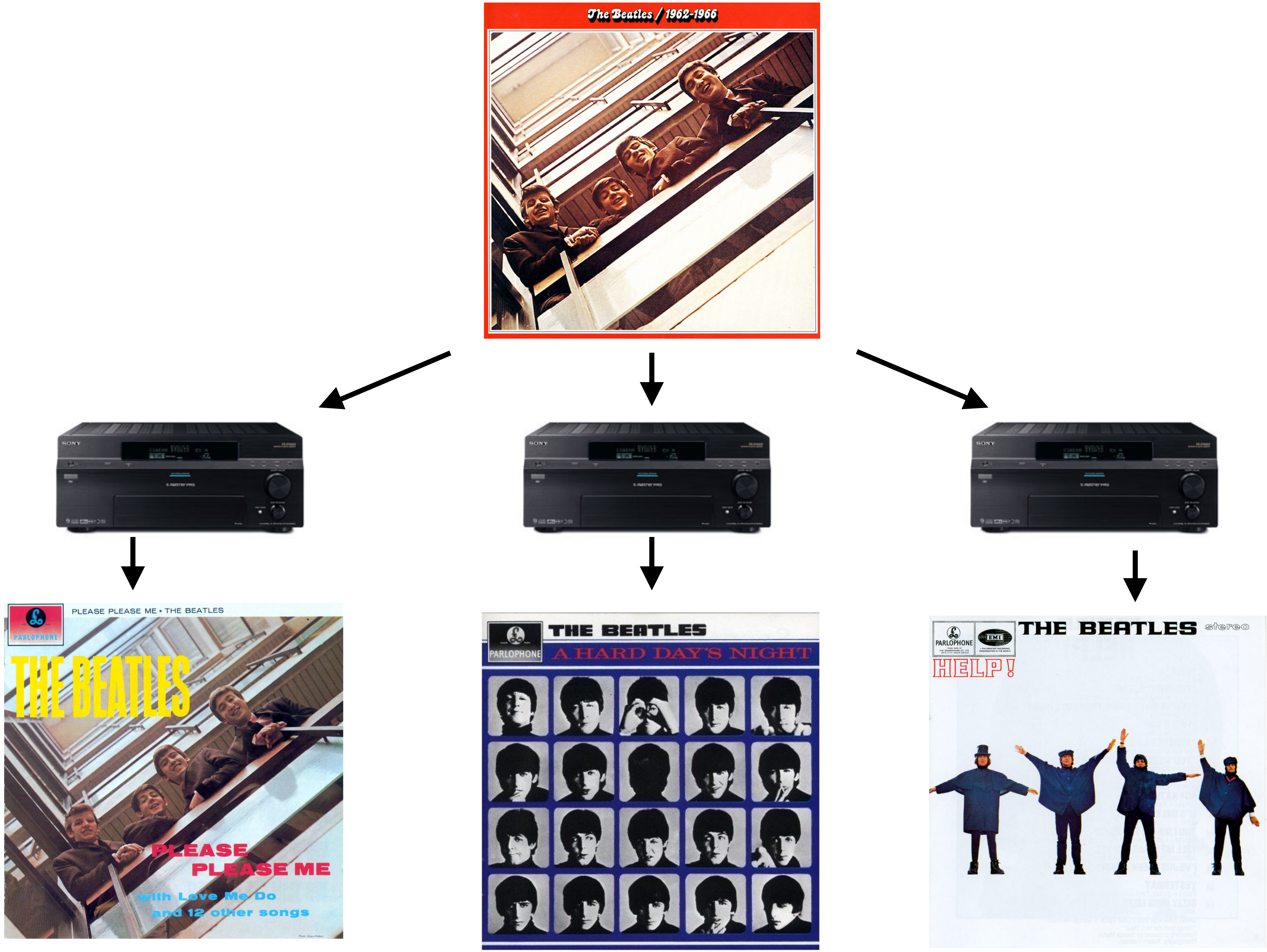
Embryonic stem cells



Neural cells

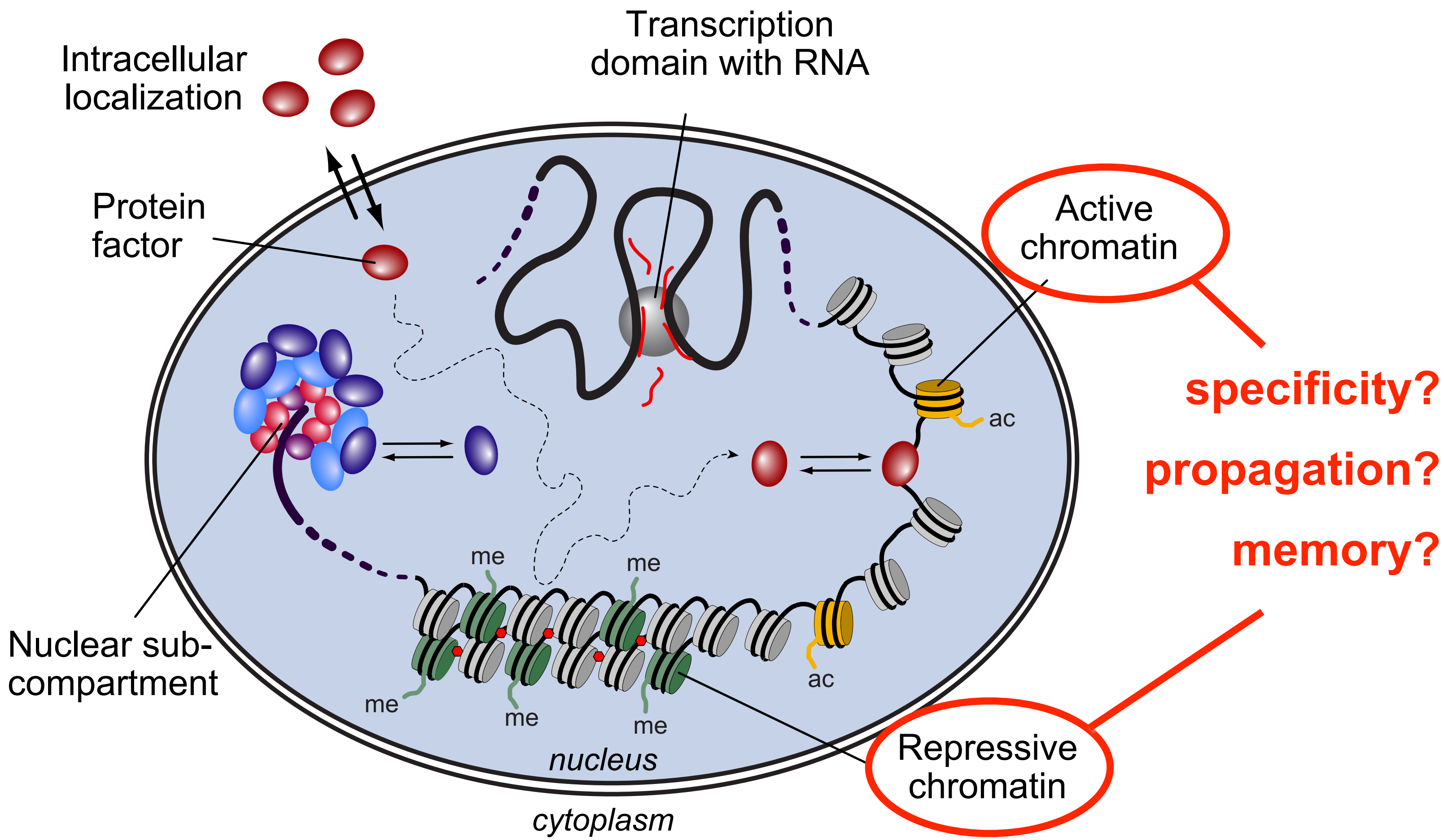


no genomic differences

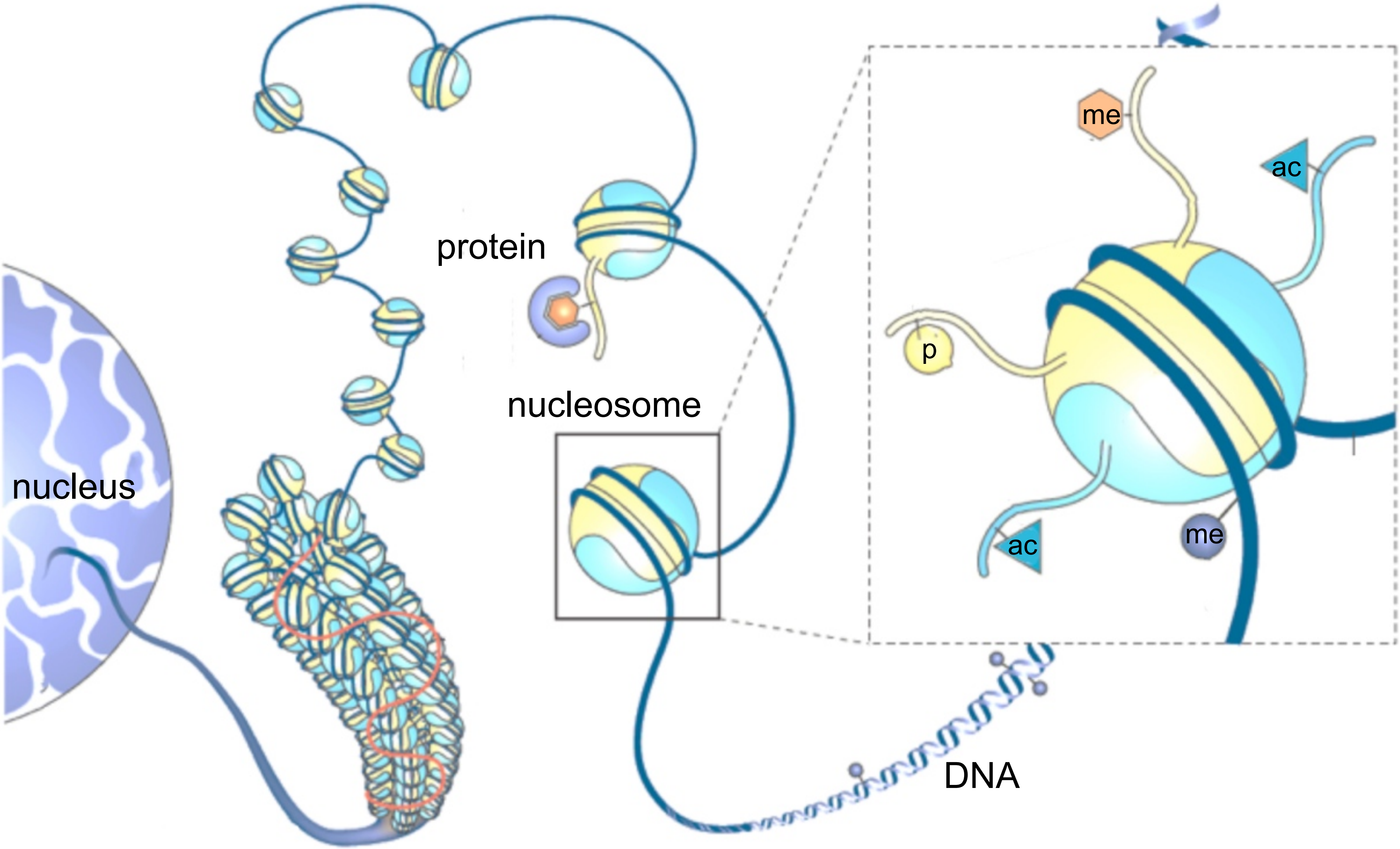


The Beatles / 1962-1966
PLEASE PLEASE ME • THE BEATLES
PARLOPHONE
THE BEATLES
PLEASE
PLEASE ME
with Love Me Do
and 12 other songs
THE BEATLES
PARLOPHONE
A HARD DAY'S NIGHT
PARLOPHONE
EMI
THE BEATLES
stereo
HELP!

The dynamic organization of the nucleus and of chromatin control genome function



Epigenetic signals



Probst et al. 2009, Nat Rev Mol Cell Biol

A complex network of proteins sets and removes a variety of histone modifications at multiple sites

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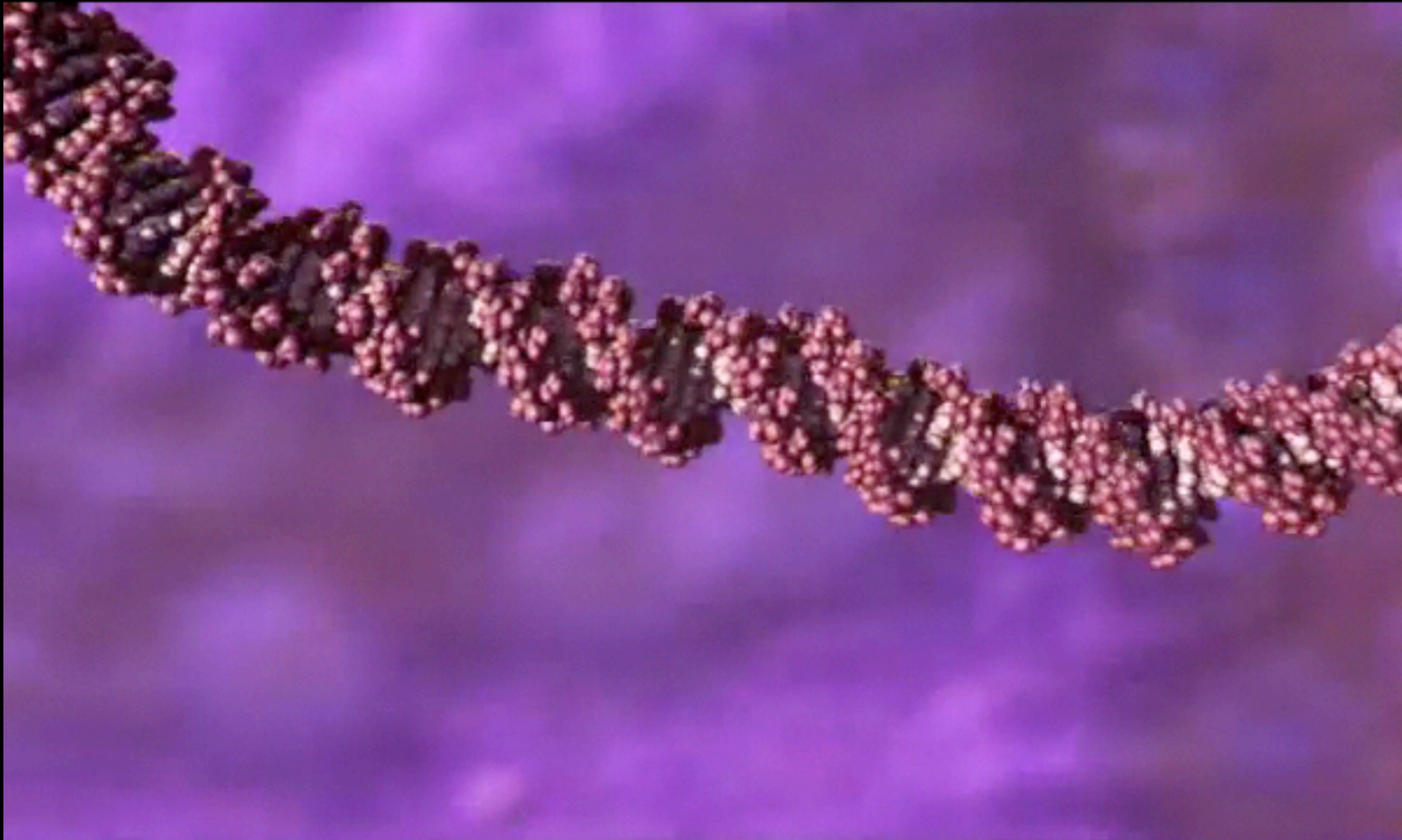
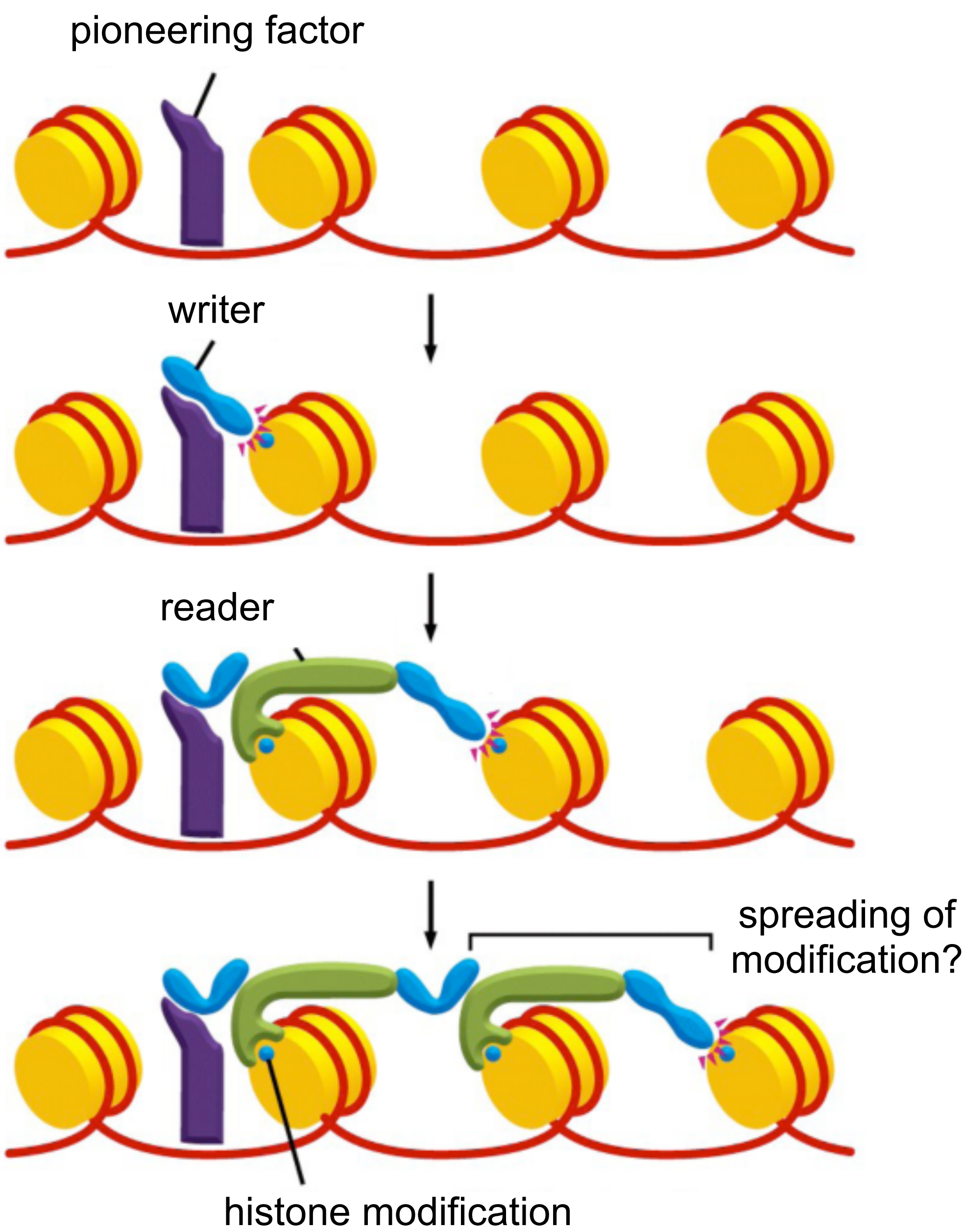
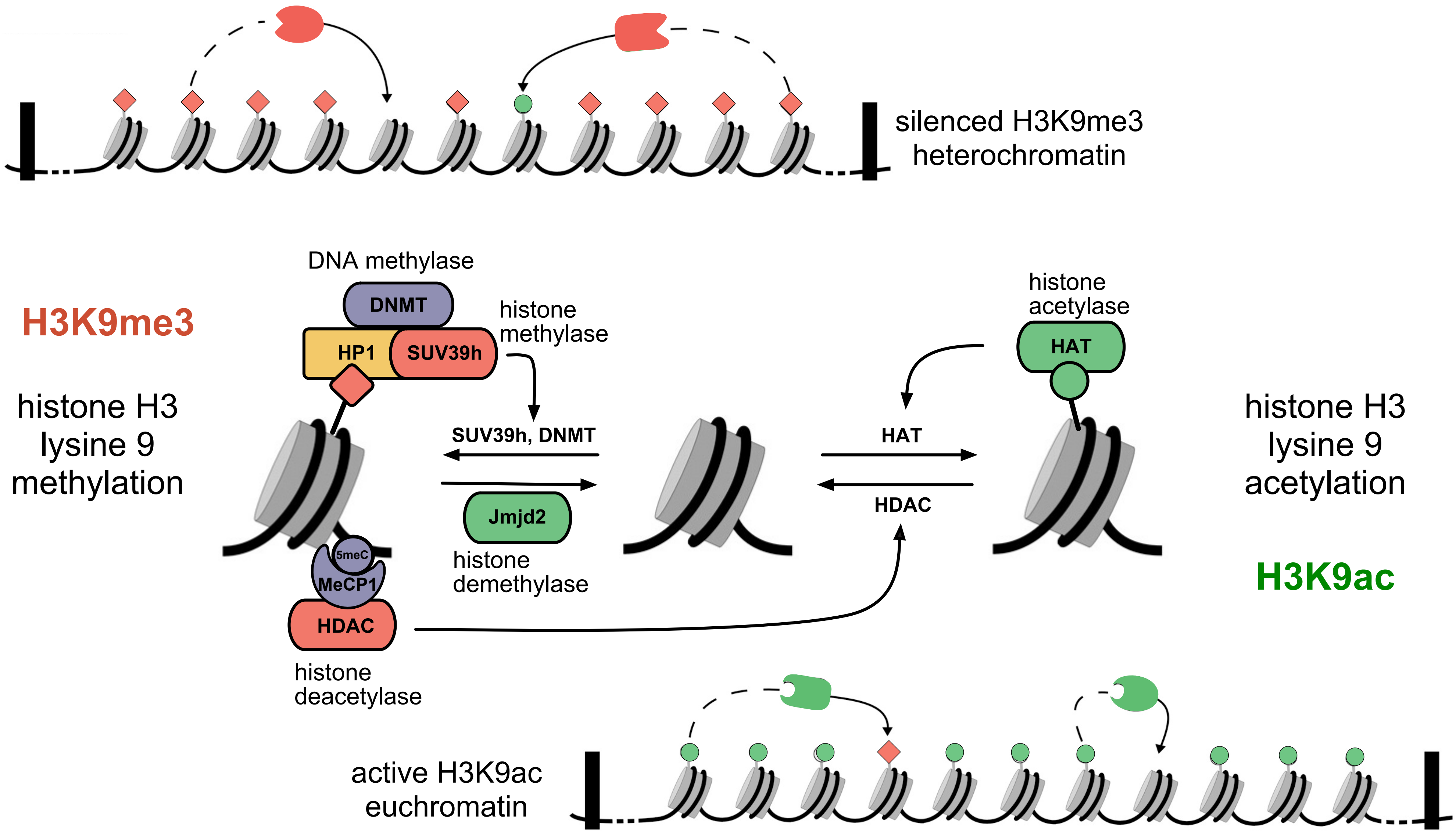


Writing, reading and transmitting epigenetic signals

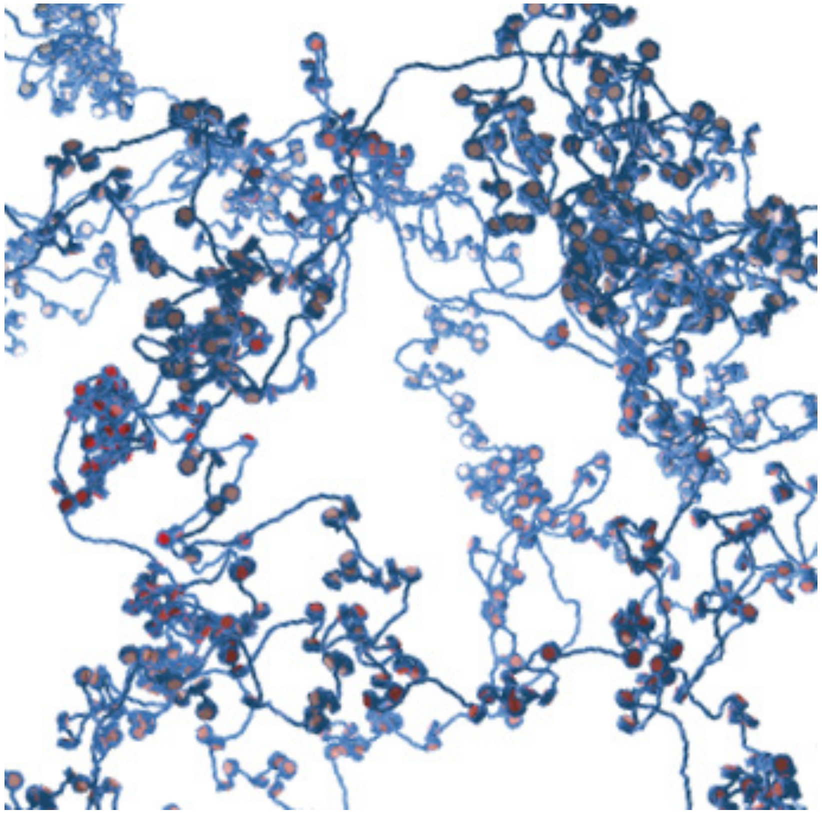


from Molecular Biology of the Cell

Distinct chromatin states can be established and maintained via interlinked feedback loops



The domino cascade model for spreading histone modifications along the DNA - what about 3D?



average distance between nucleosomes

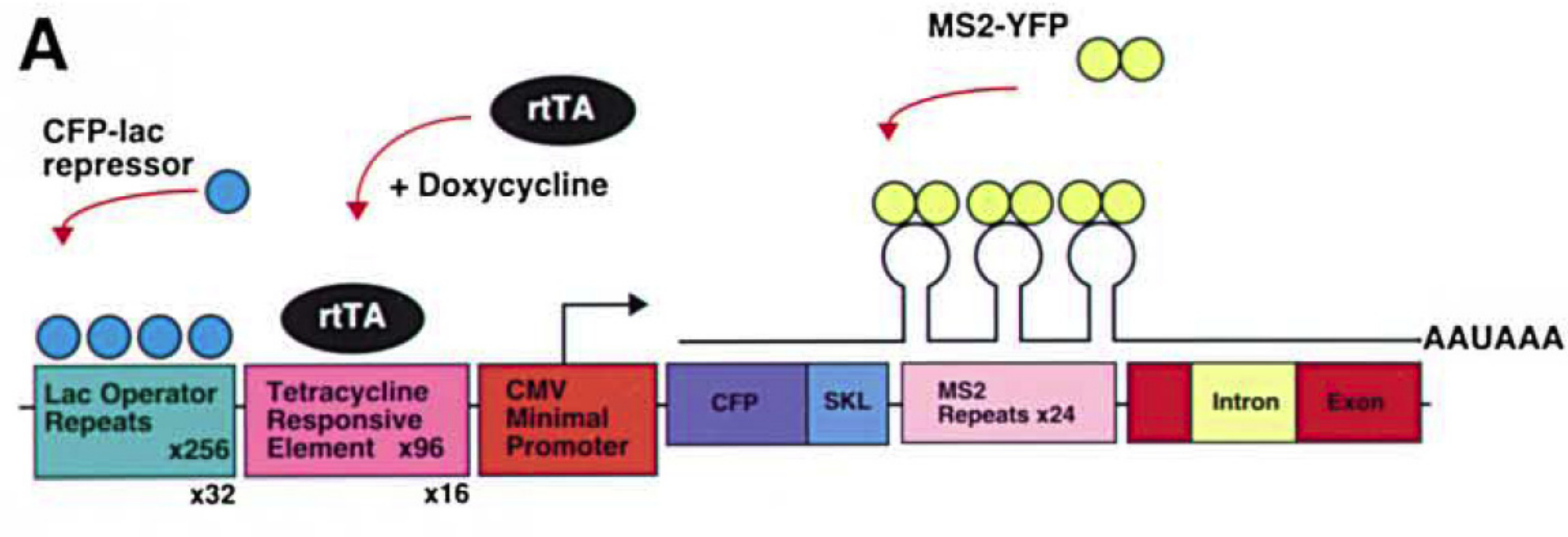
in 1D: ~25 nm
(extended chain)

in 3D: ~28 nm
("sea of nucleosomes")

3D constructions with dominos are very fragile…

from Annodomino2007 on Youtube

Following gene expression in living cells



Janicki, S. M., Tsukamoto, T., Salghetti, S. E., Tansey, W. P., Sachidanandam, R., Prasanth, K. V., Ried, T., Shav-Tal, Y., Bertrand, E., Singer, R. H., and Spector, D. L. (2004). From silencing to gene expression: real-time analysis in single cells. Cell 116, 683-698.

CFP-LacI (chromatin)
CFP (translated protein)

MS2-YFP (RNA)