



# DNA can sense its neighbor's sequence

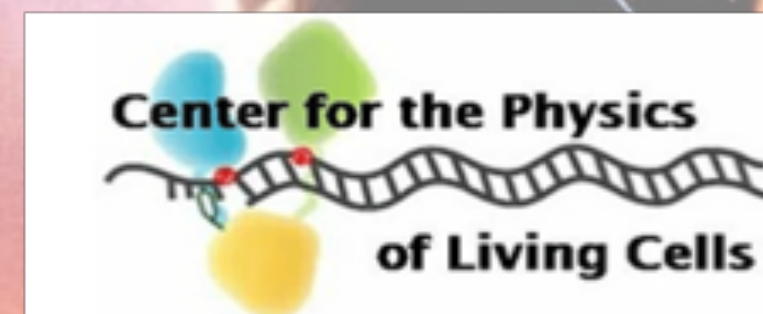
**Jejoong Yoo**

**Aleksei Aksimentiev group**

**In collaboration with Taekjip Ha group**

**University of Illinois at Urbana-Champaign**

**BLUE WATERS**  
SUSTAINED PETASCALE COMPUTING

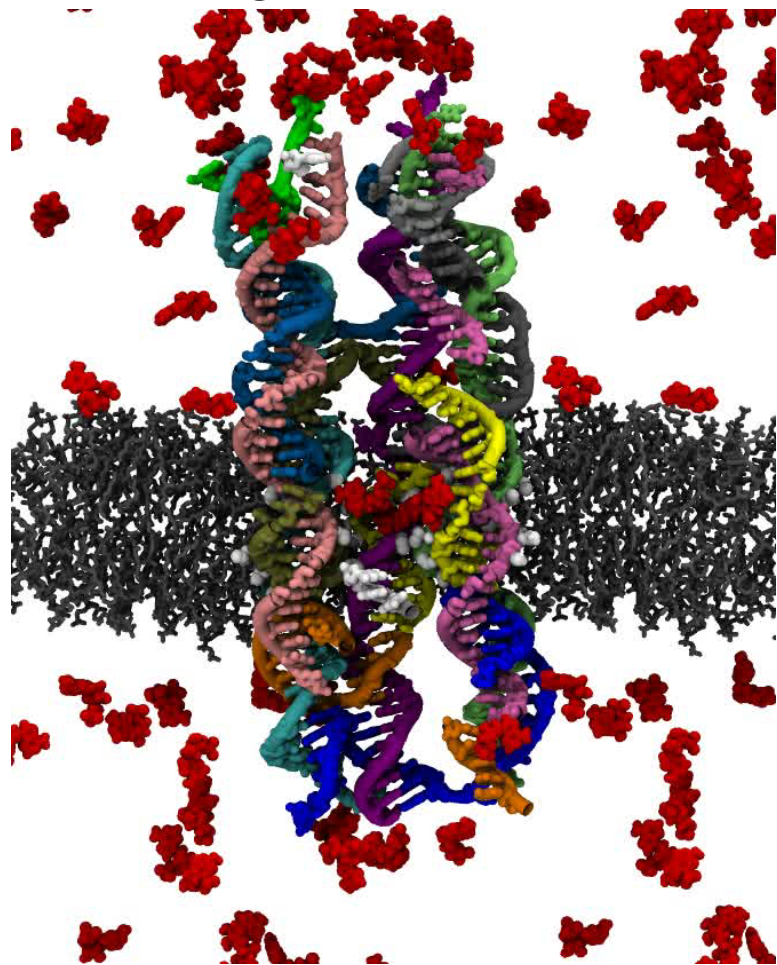




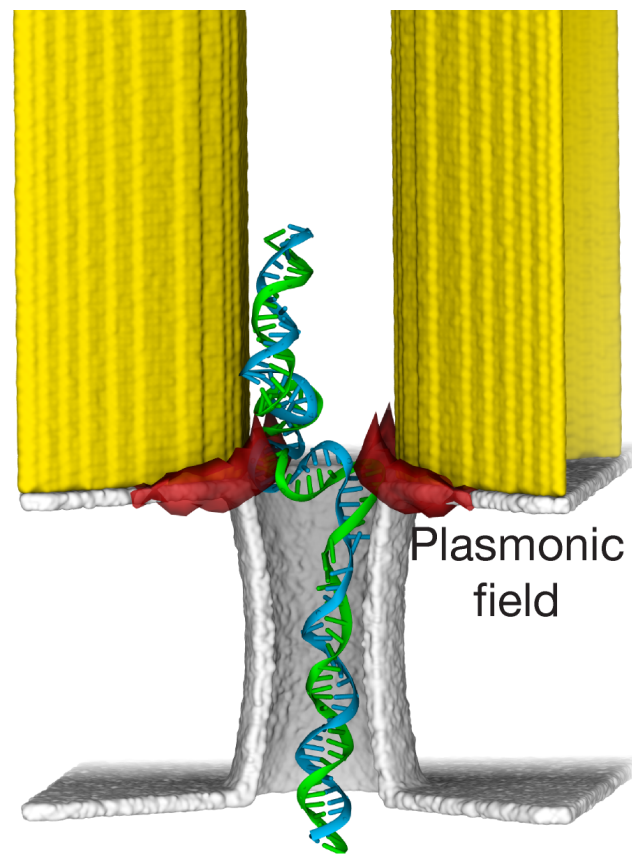
# Overview of Blue Waters projects

## Nanotechnology

DNA origami nanochannel



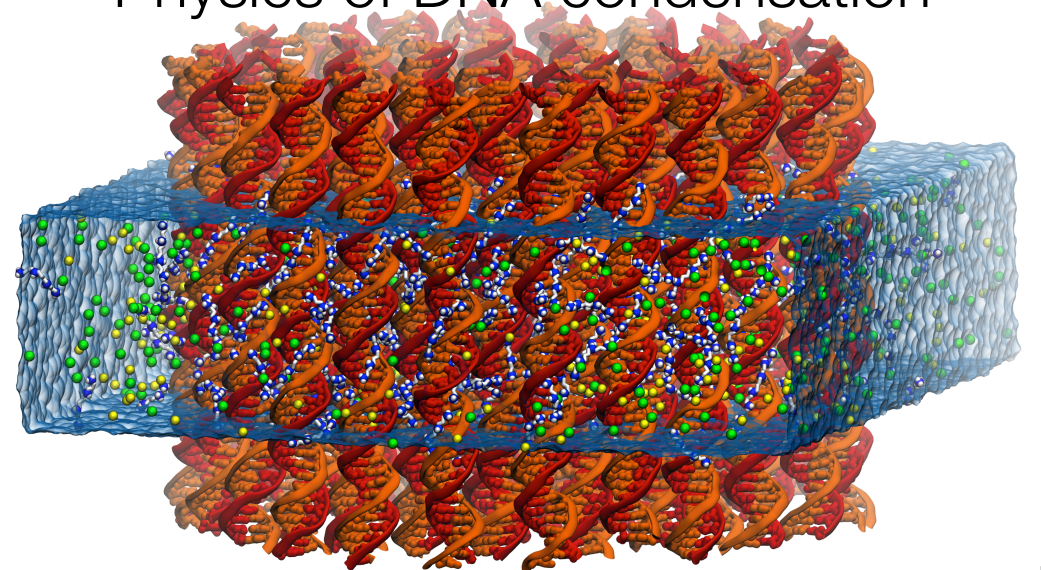
Plasmonic device for DNA sequencing



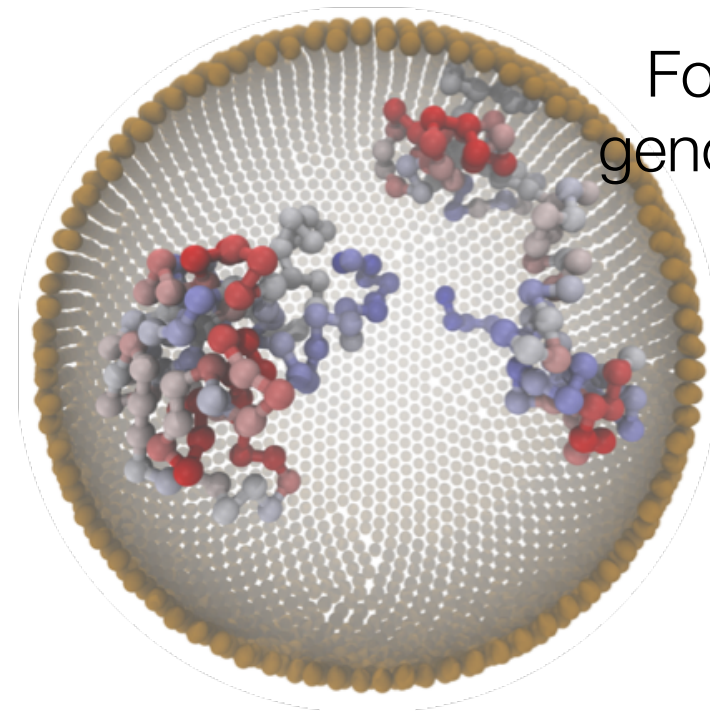
Maxim Belkin

## DNA/chromatin organization

Physics of DNA condensation



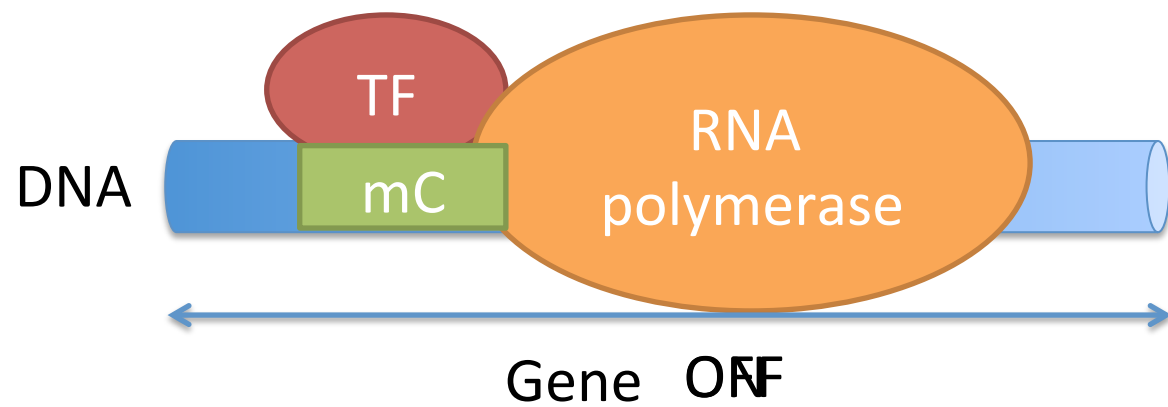
Folding of genomic DNA





# Epigenetic gene regulation mechanism

## Textbook mechanism

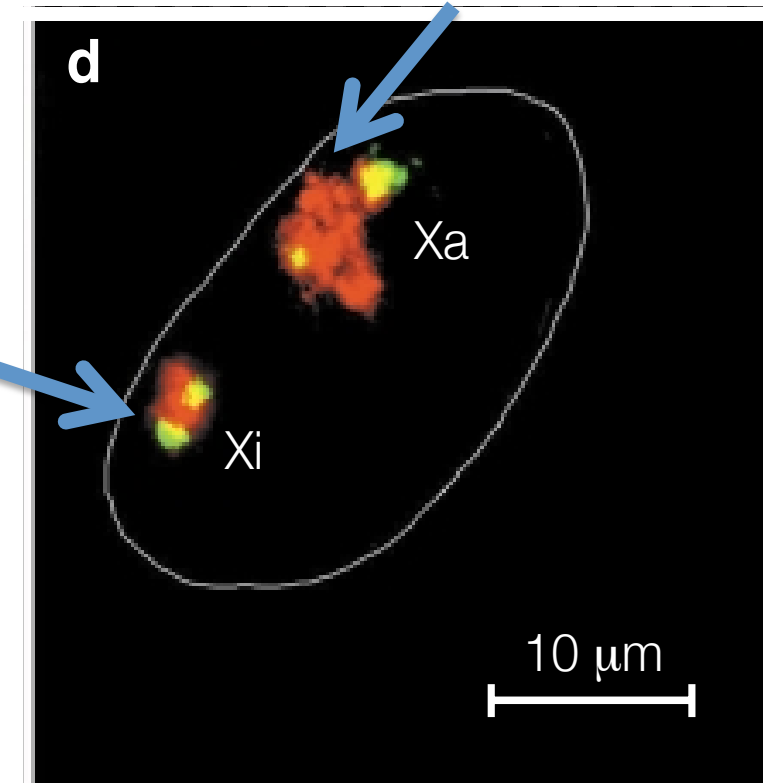


VS.

## Compaction level-based mechanism

Hypermethylation  
=> Compaction.  
=> Lower enzyme  
accessibility.  
=> Inactivation.

Higher enzyme  
accessibility



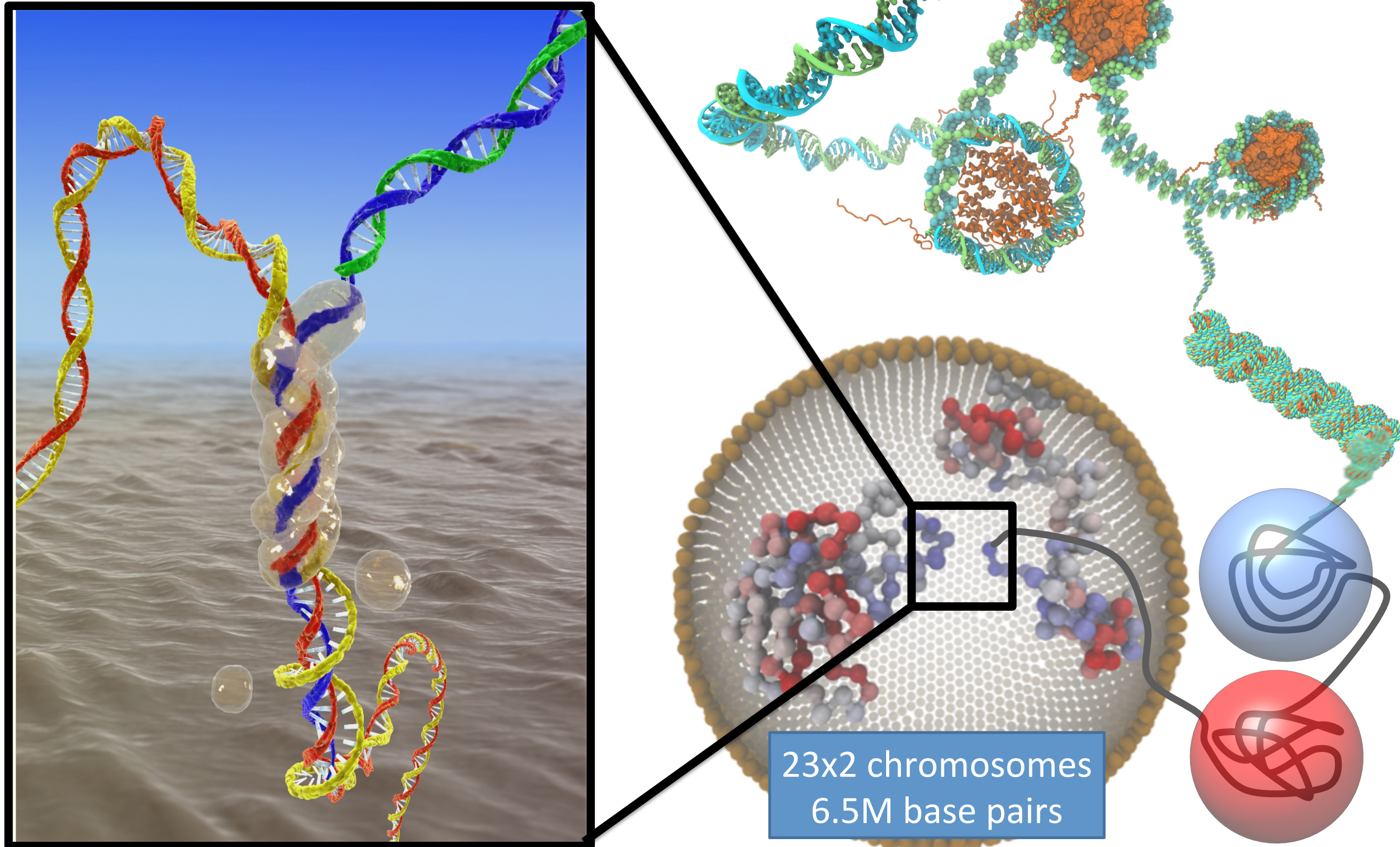
Cremer, T. & Cremer, C., 2001,, *Nat Rev Genet*, 2(4), pp. 292-301.

Compacted chromatin has  
no space for enzymes





# Homologous recombination: finding a needle in a haystack





# DNA telepathy (?!)

Your sequence I sense...

The homology I sense in you...



Leikin and Kornyshev  
Journal of Physical Chemistry B  
(2008)

DNA can recognize complementary sequence without any mediator protein

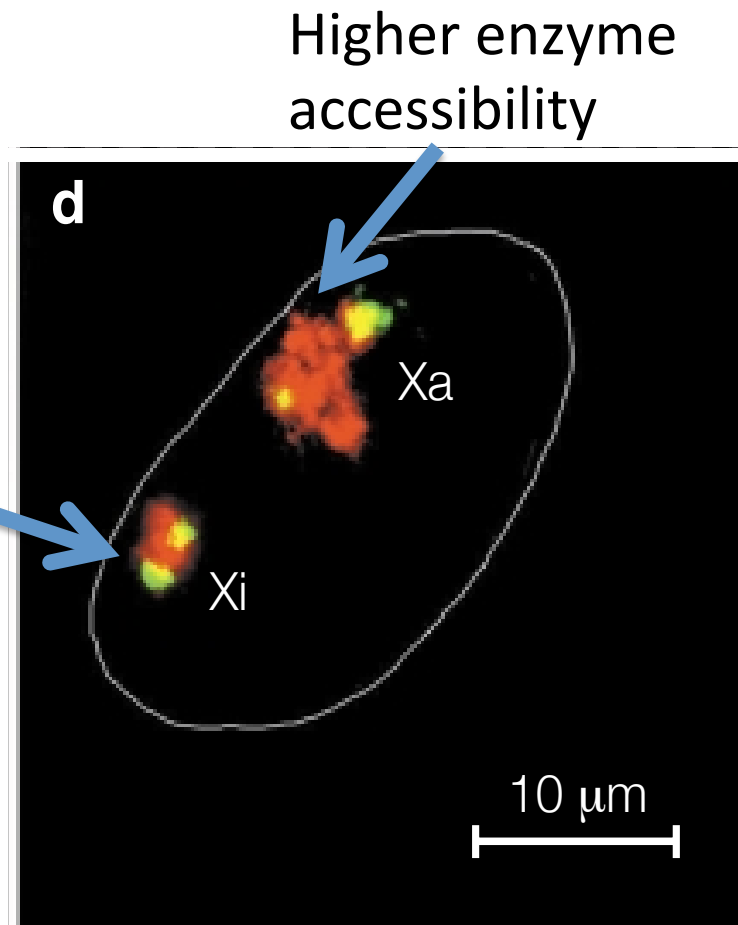
- **DNA telepathy** means sensing and colocalization of homology sequences.
- But, often debated due to lack of evidence.
- We validate this hypothesis.



# Both sequence and methylation control chromatin compactness

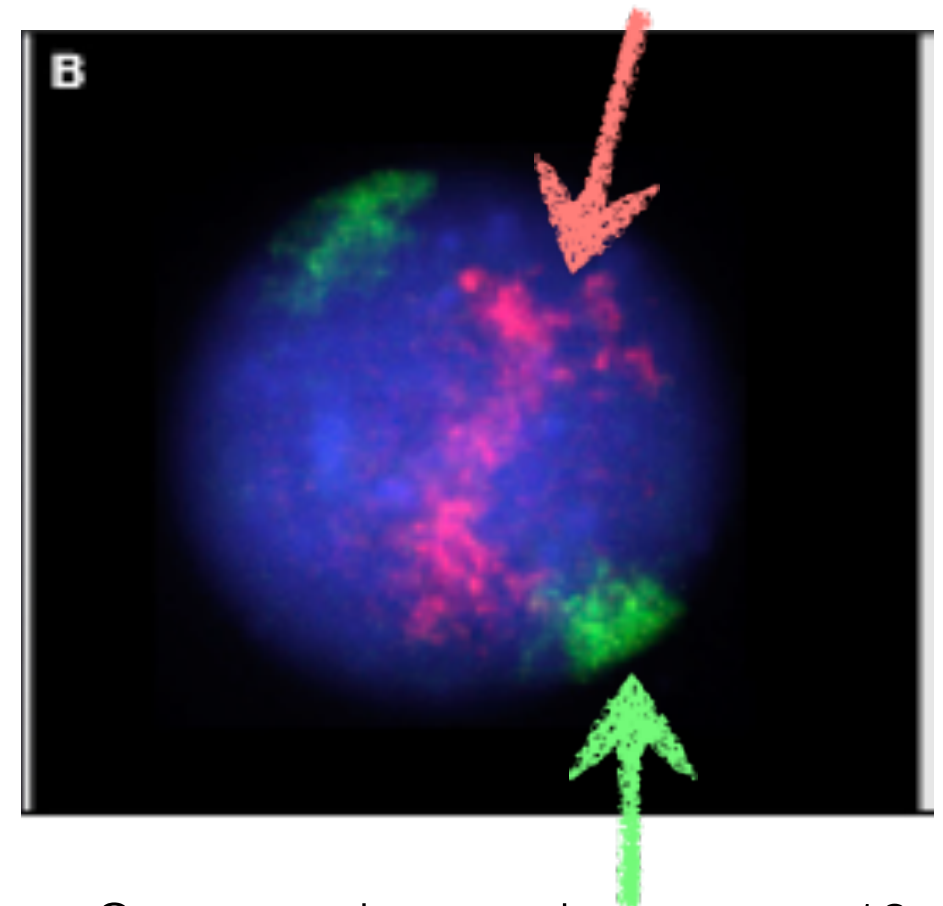
Methylation induces compaction

Hypermethylation  
=>Compaction.  
=> Lower enzyme  
accessibility.  
=> Inactivation.



High AT content induces compaction

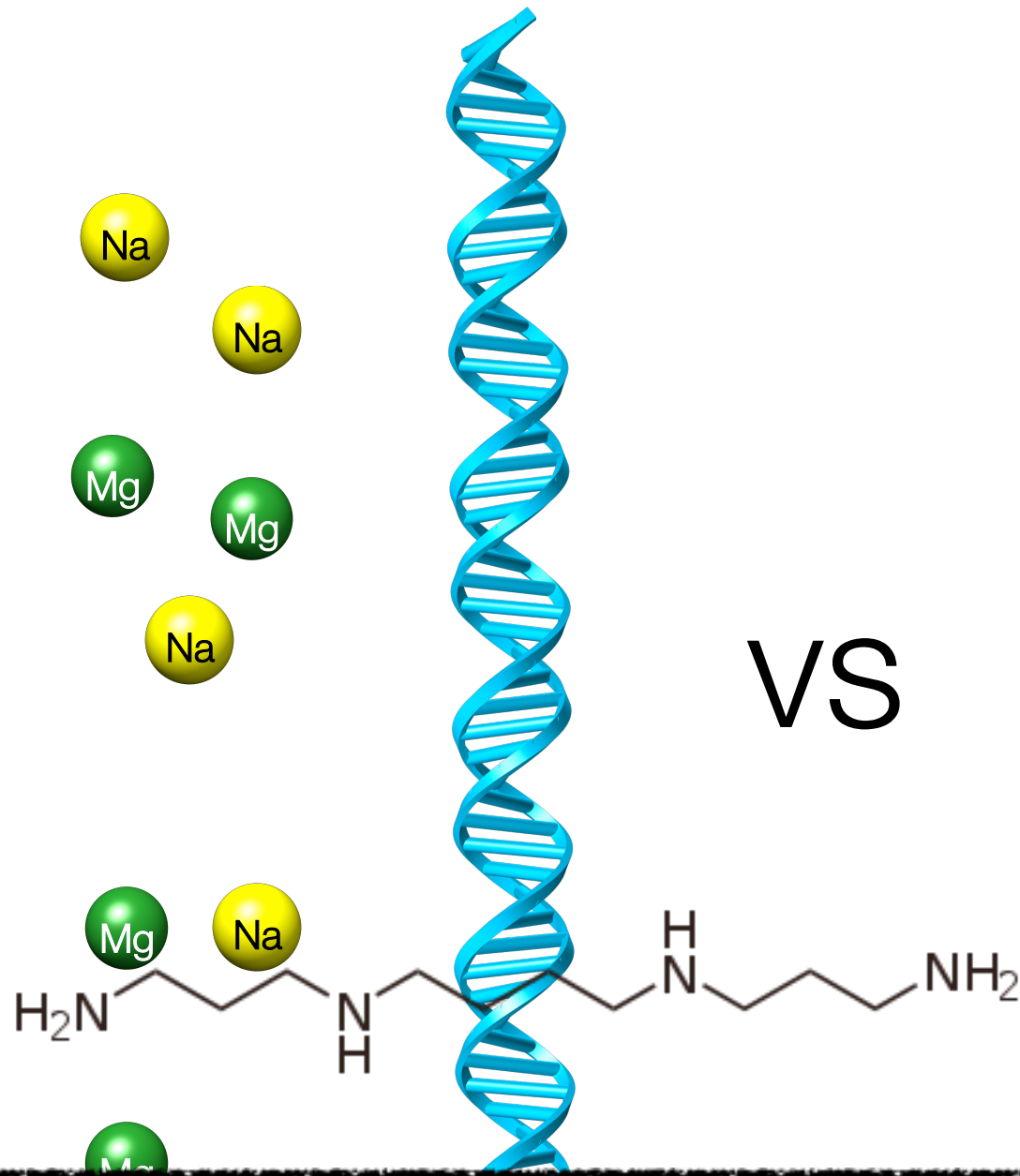
Gene-rich human chromosome  
19 (48% GC)



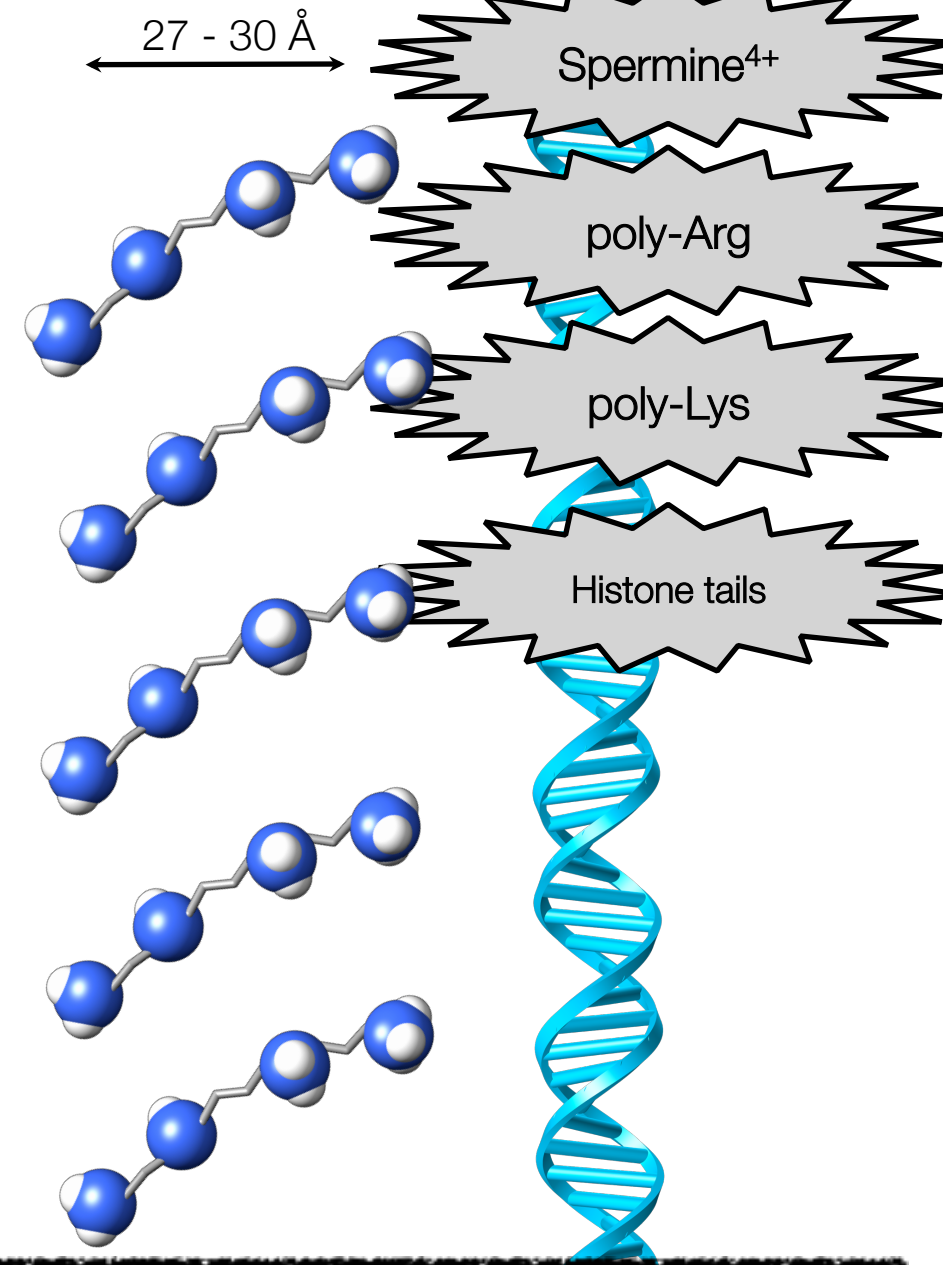
Gene-poor human chromosome 18  
(40% GC)



# Polyamines mediate inter-DNA attractions



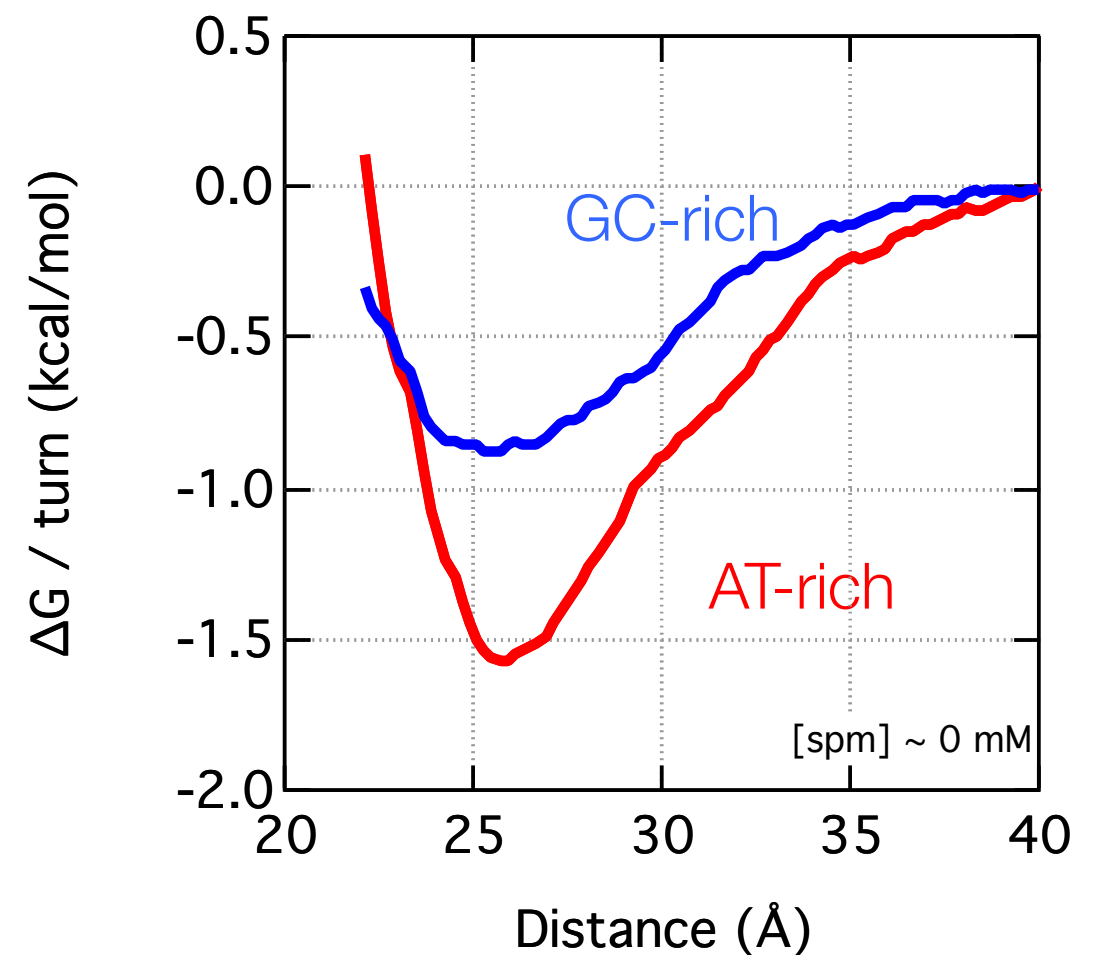
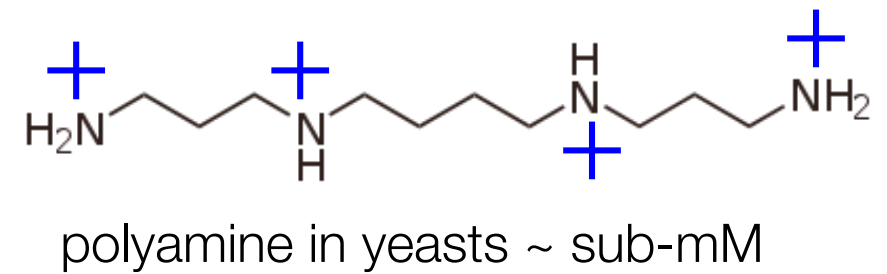
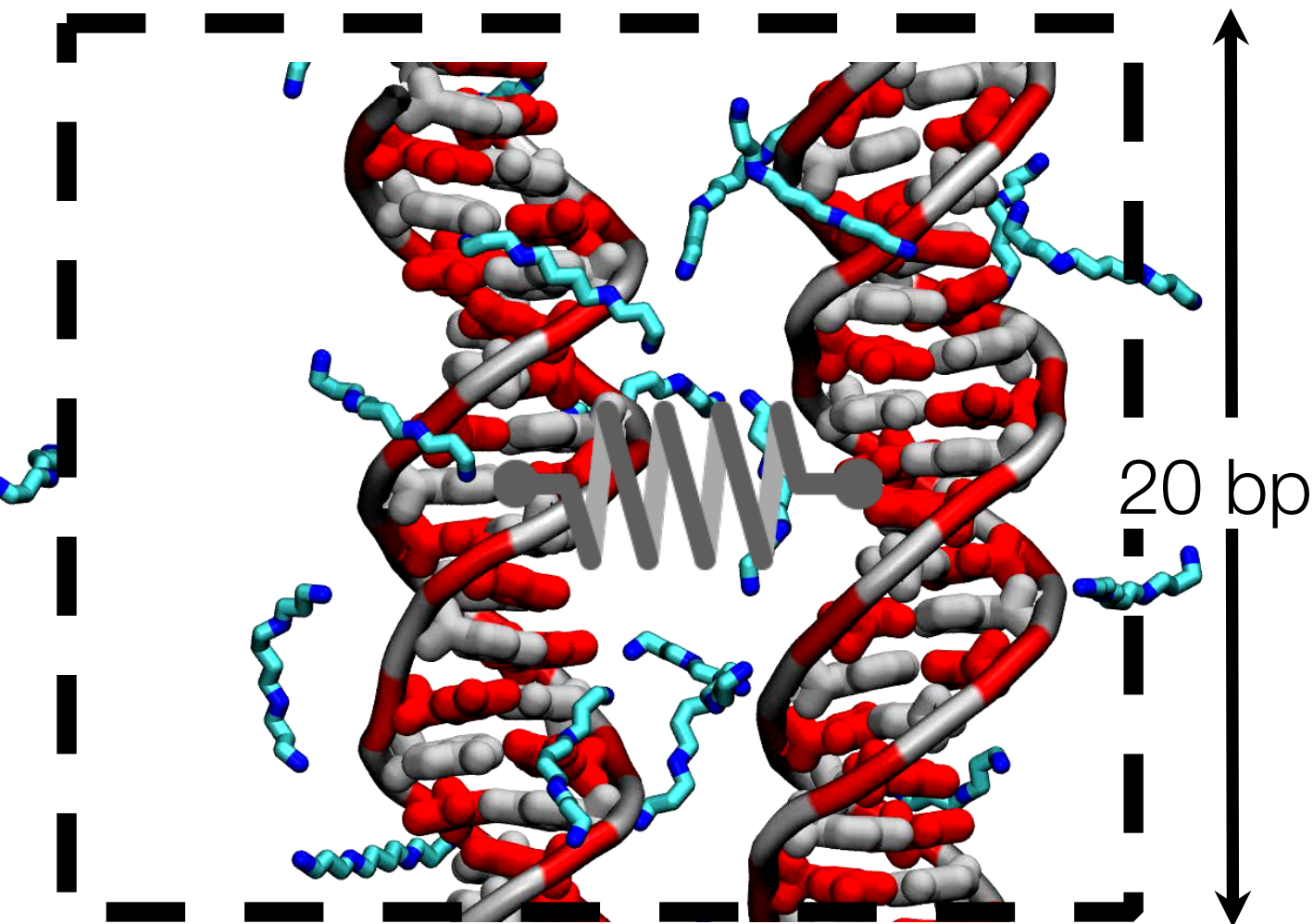
VS



=> Q. Does polyamine-mediated DNA-DNA attractions depend on DNA sequence?



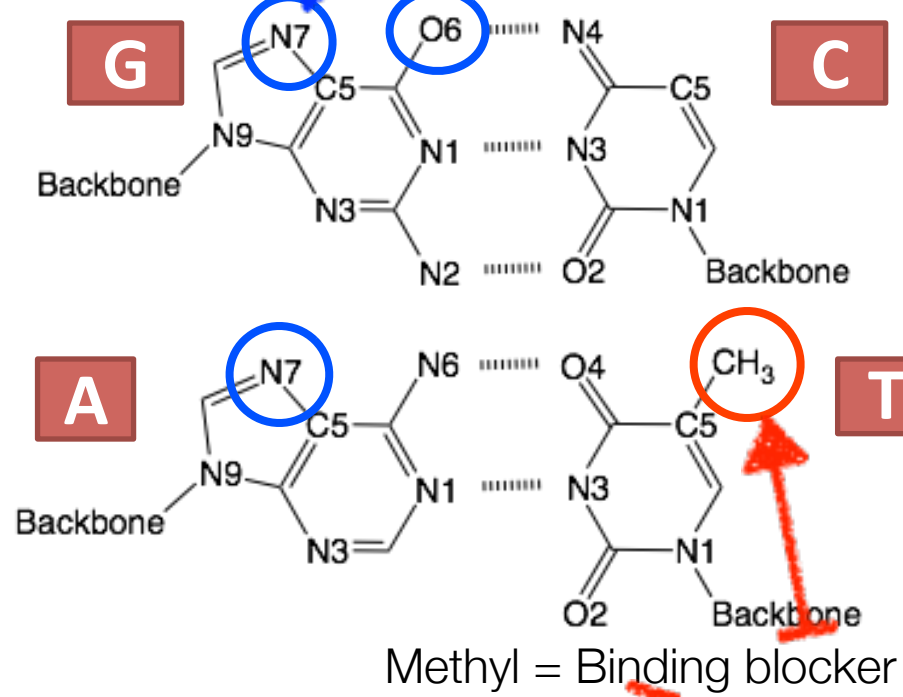
# Free energy calculations predict **stronger attraction** by polyamine for **higher AT-contents** DNA molecules



- AMBER99bsc0 force field with custom refinement of amine-phosphate interactions.
- Sub-mM level of spermine; just enough to neutralize DNA.
- Fully atomistic including explicit water.
- Umbrella sampling.

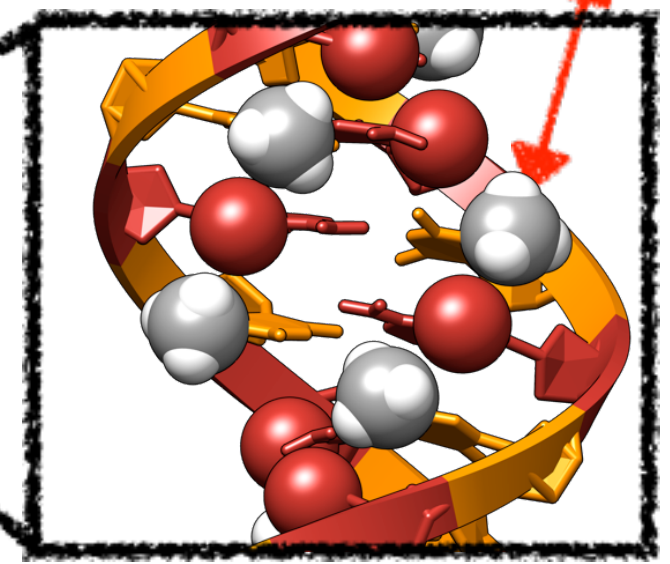
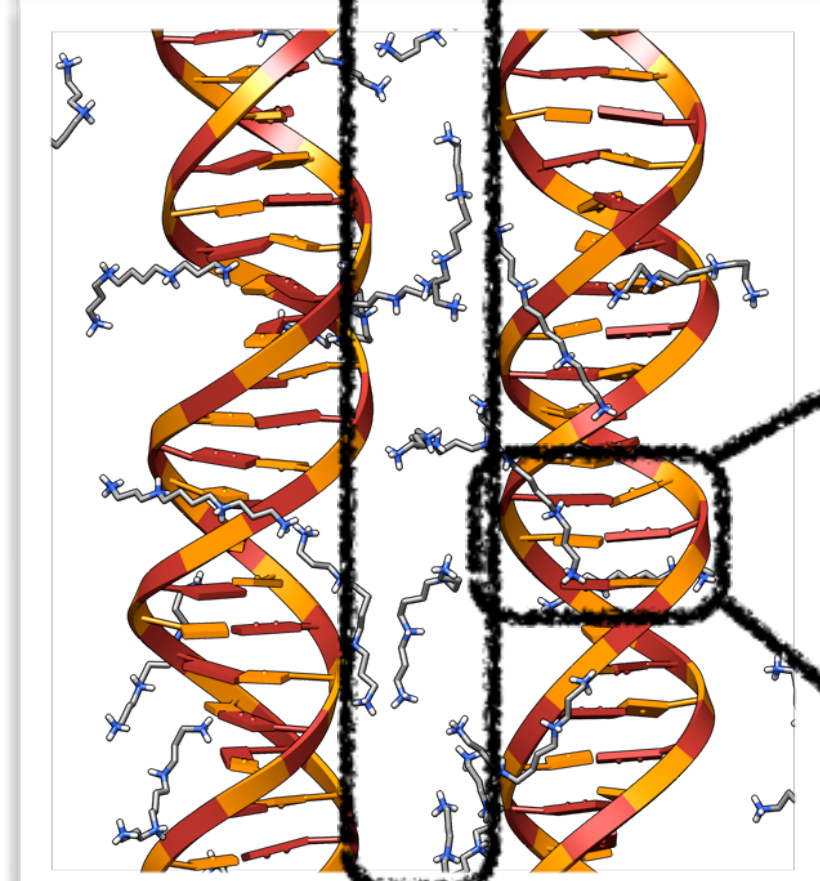
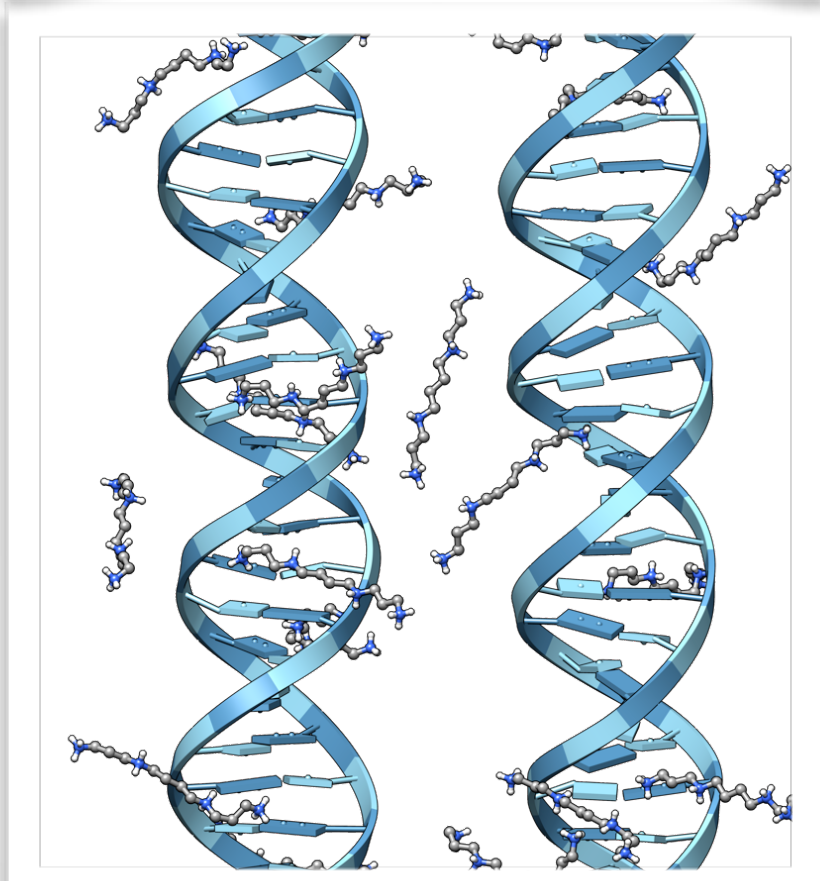
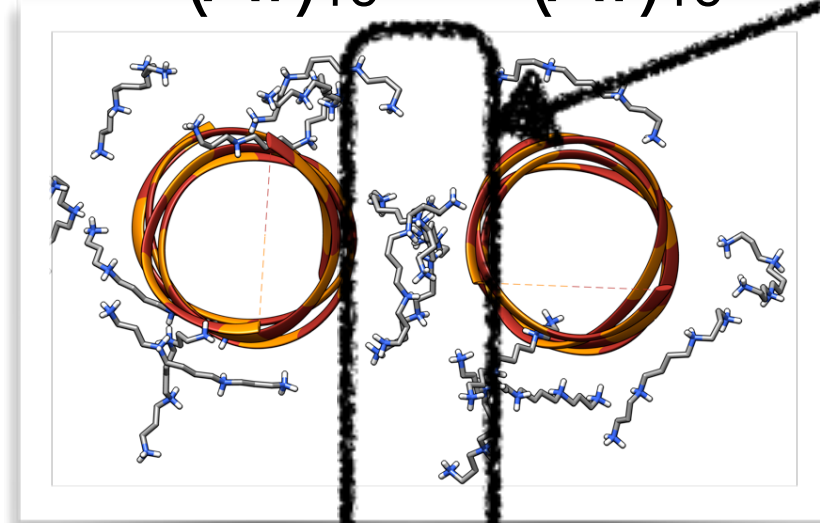
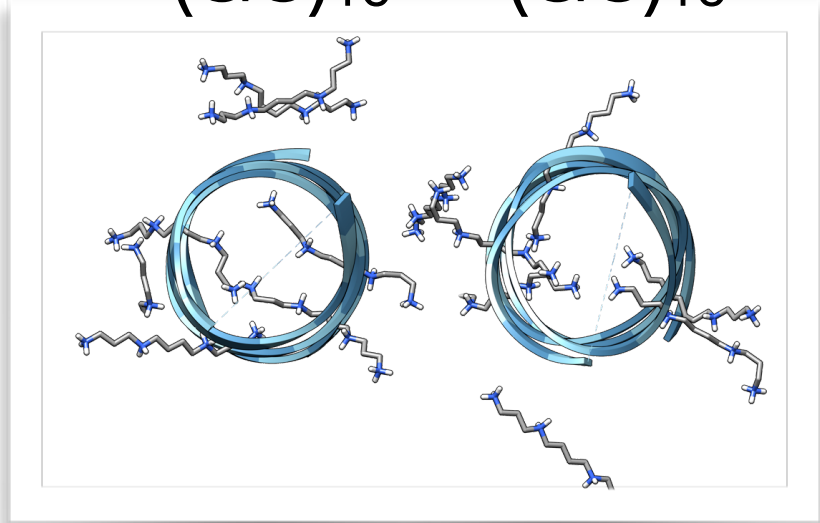
# AT-rich segments form **clusters** better because they **share** polyamines with neighbors

“Bridging” polyamines  
Polyamine binding site



(GC)<sub>10</sub> (GC)<sub>10</sub>

(AT)<sub>10</sub> (AT)<sub>10</sub>

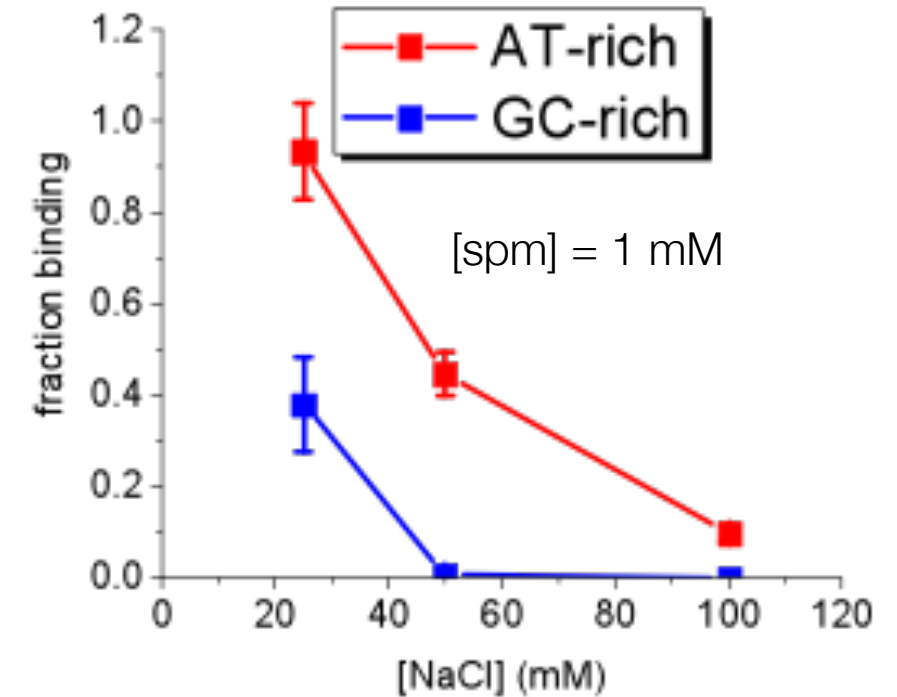
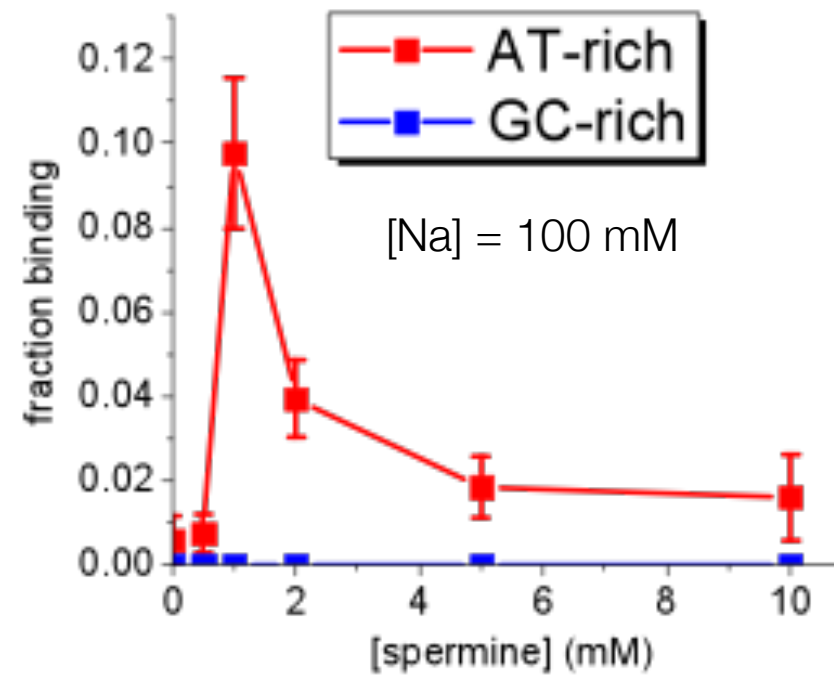
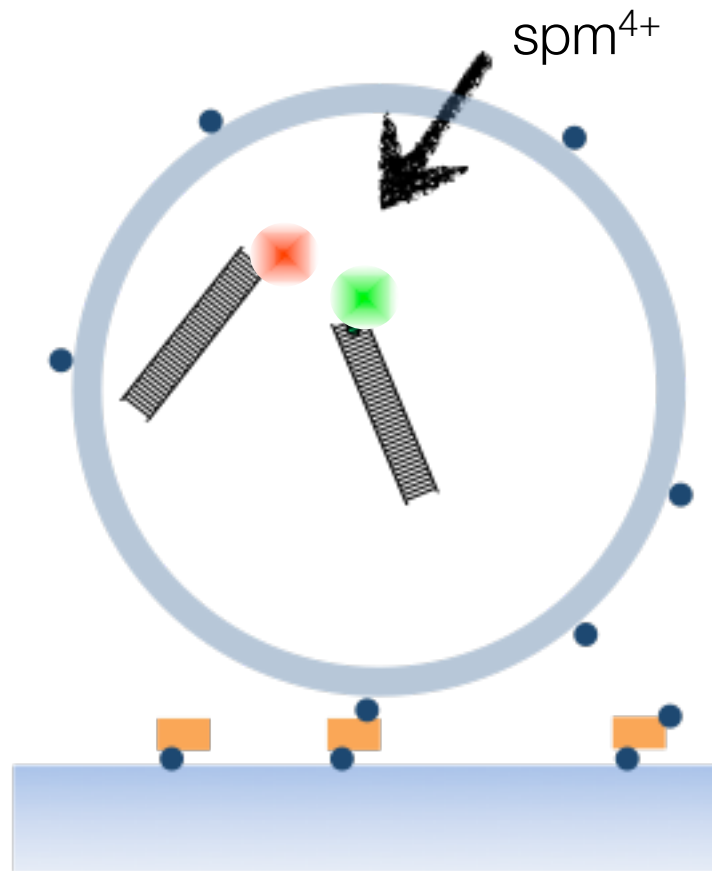




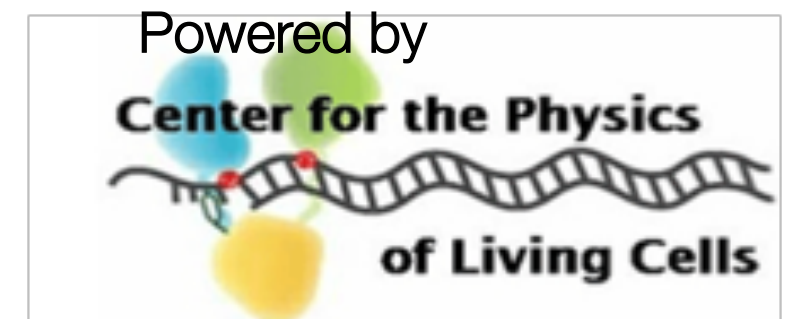
# FRET experiments confirm MD predictions



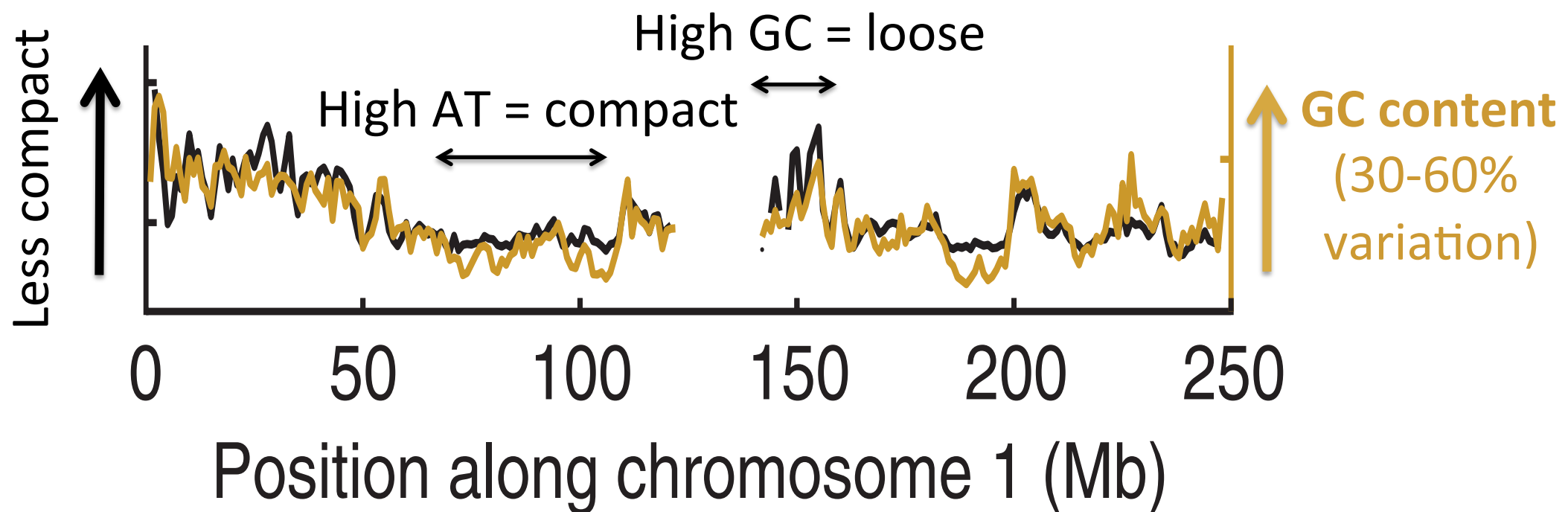
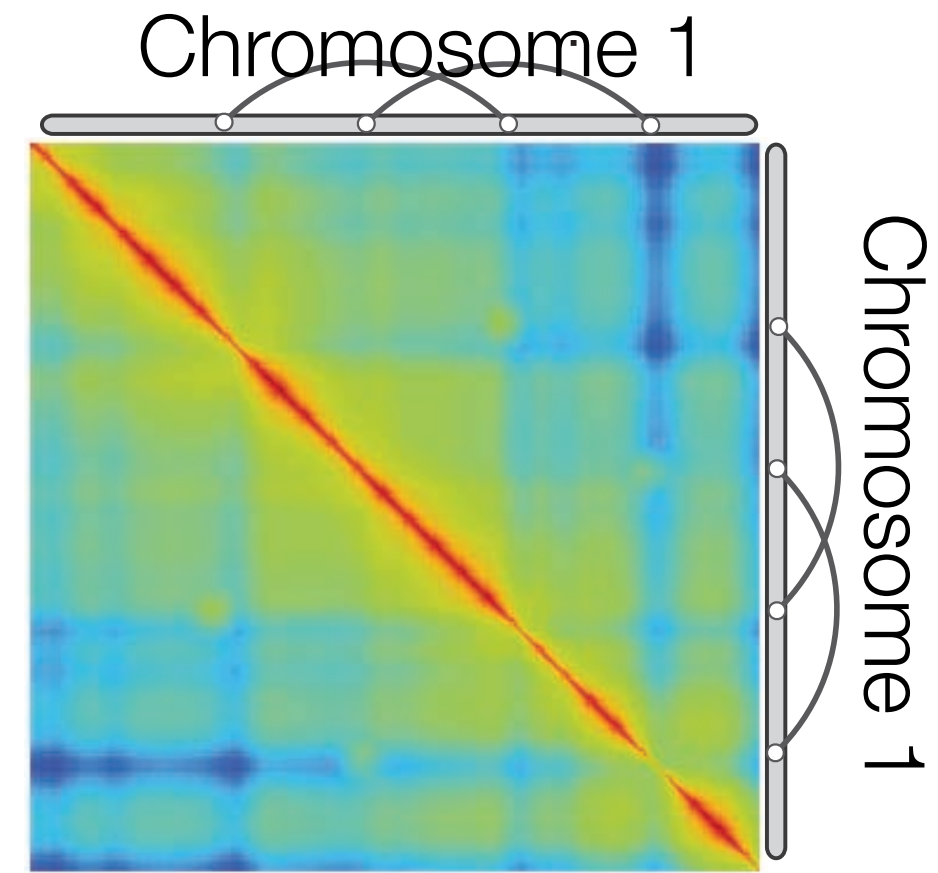
Hajin Kim (Ha group)



- To our best knowledge, the **first direct evidence** of sequence sensing w/o WC pairings!
- Carefully designed MD simulations have **prediction power**.
- Huge implications to chromatin **folding & gene regulations**.

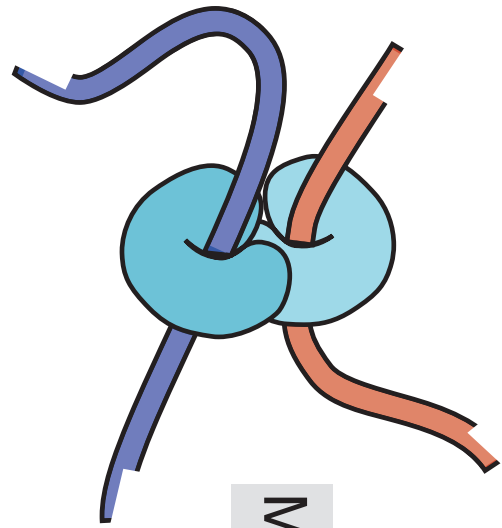


Experimental chromatin interaction map indicates more compact AT-rich segments for all chromosomes

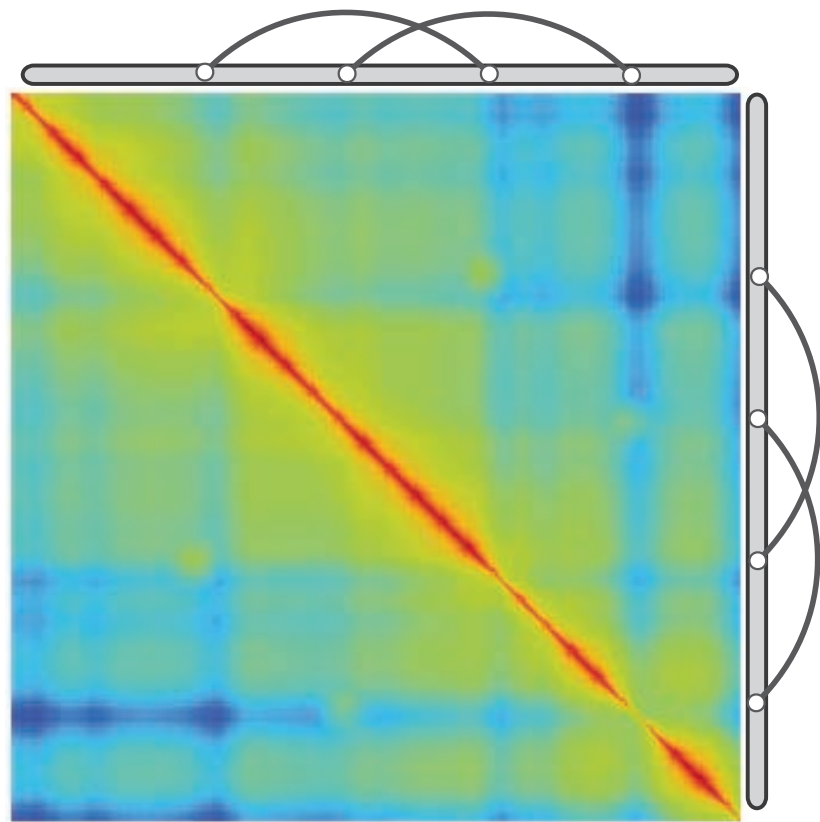




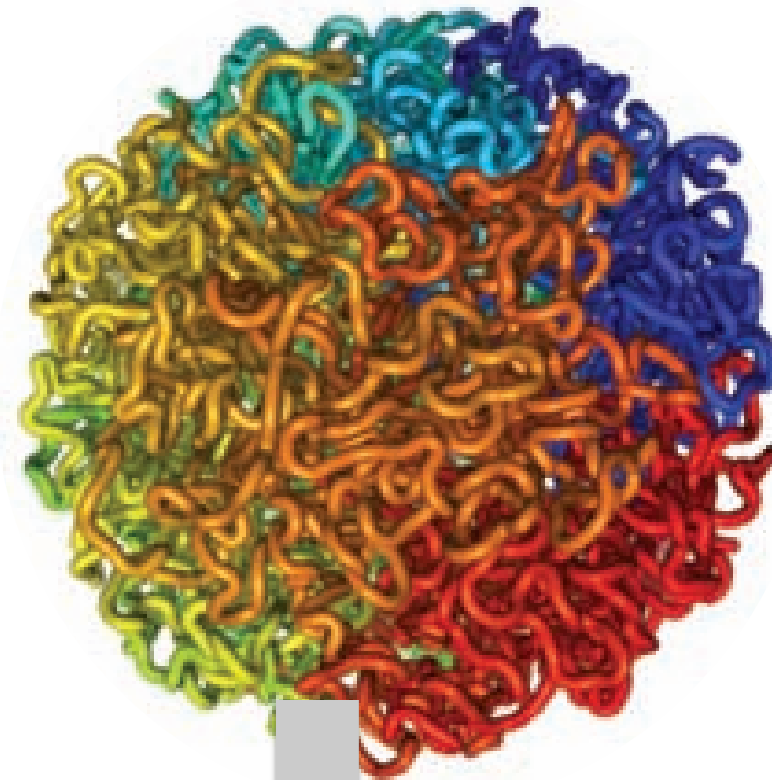
Hi-C interactions



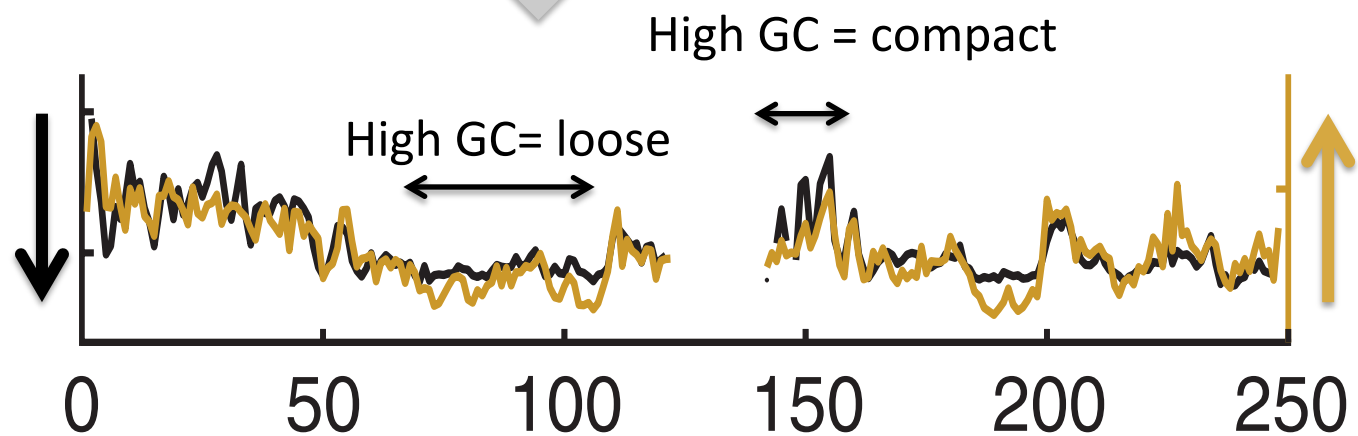
Mapping



High-throughput chromatin interaction (Hi-C) map indicates more compact AT-rich segments for all chromatins.



Compactness



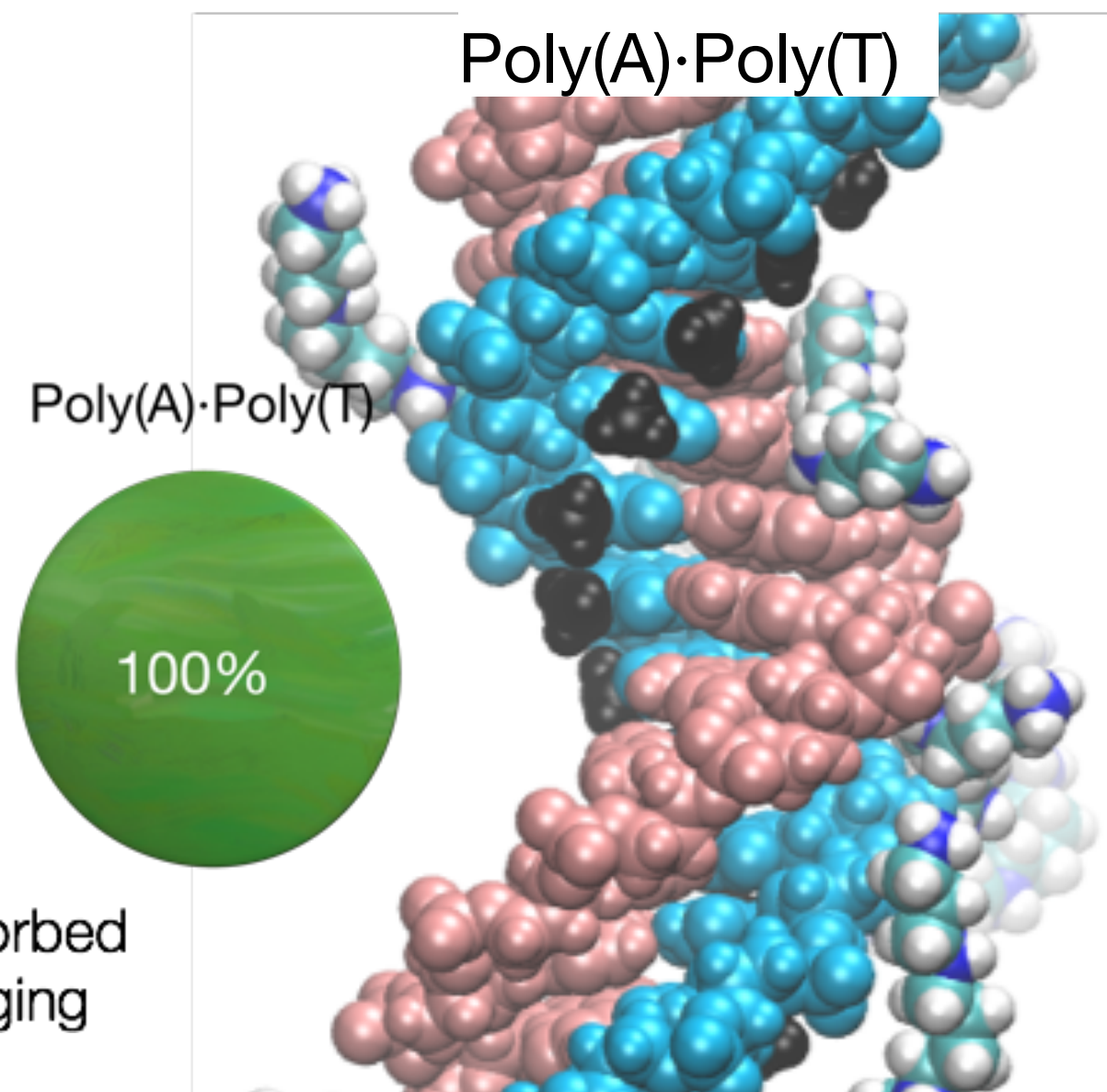
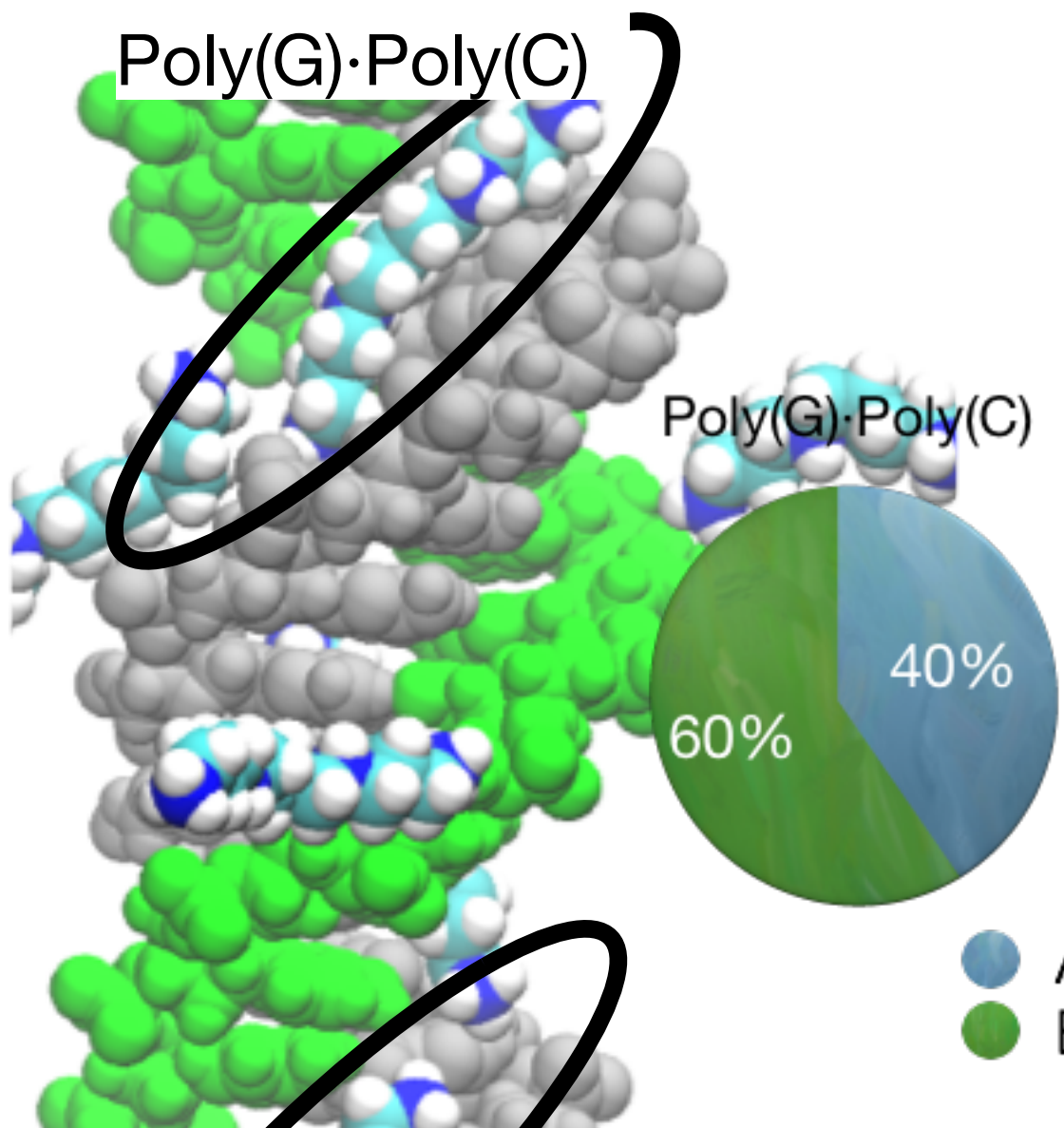
GC content (30-60% variation)

# Structural genetics

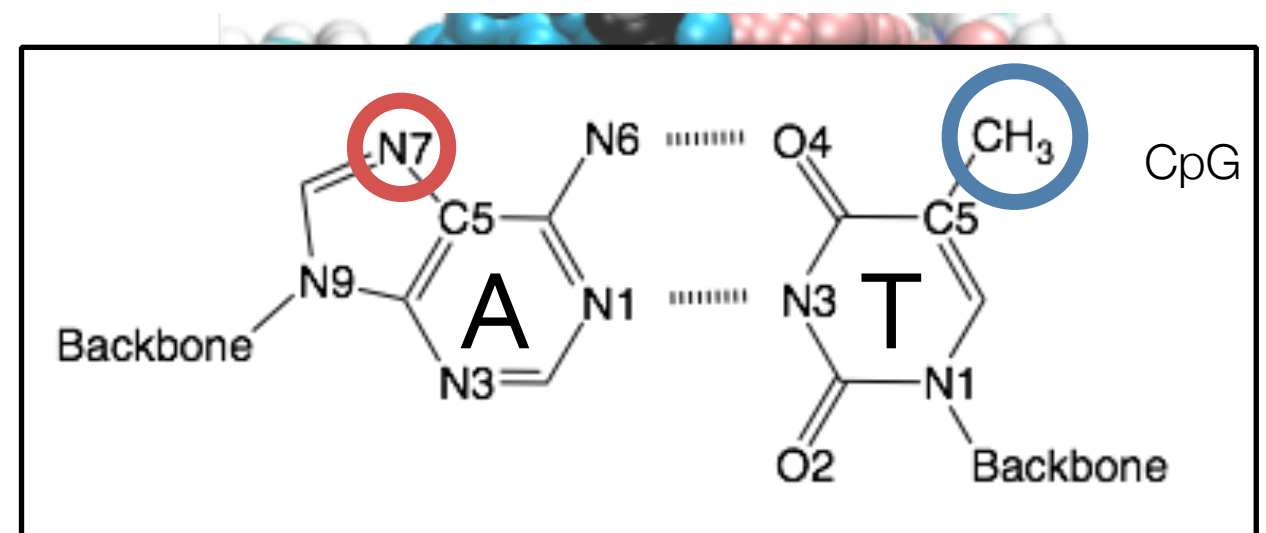
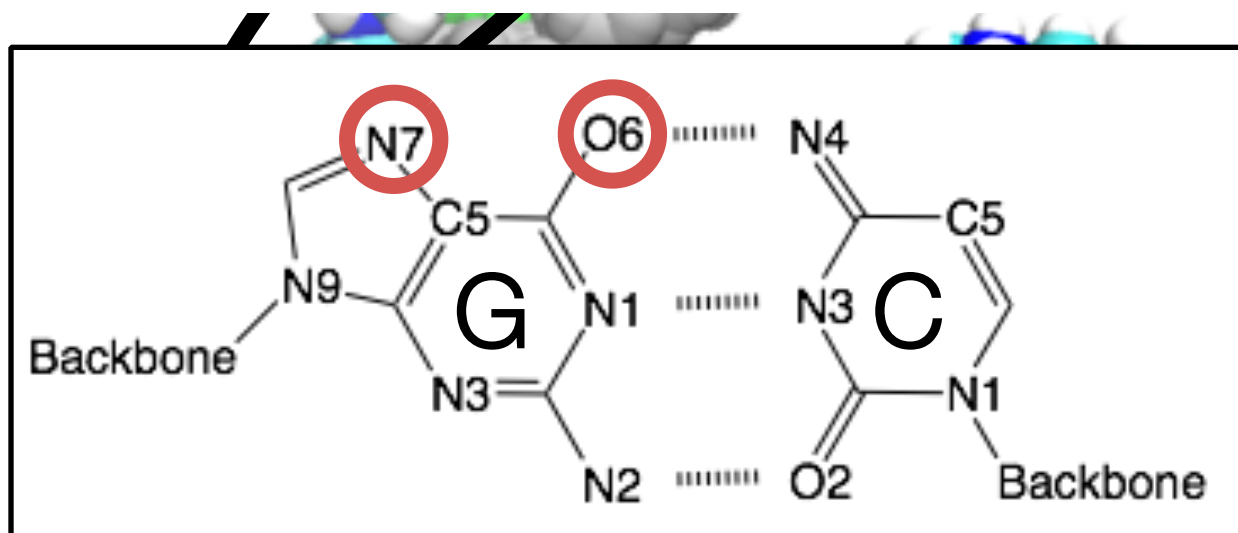
- Chromatin is not a random polymer.
- Chromatin folds into a 3D conformation depending on sequence.
- Chromatin conformation regulates expression.

Q. Is sequence everything in genetics?





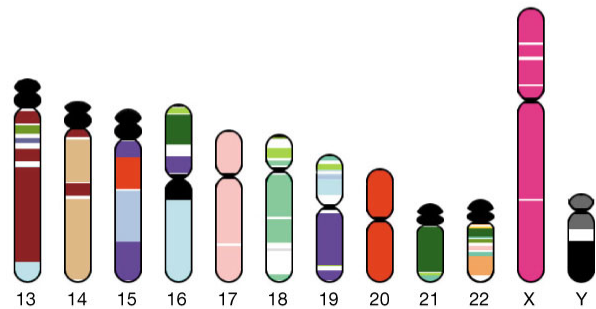
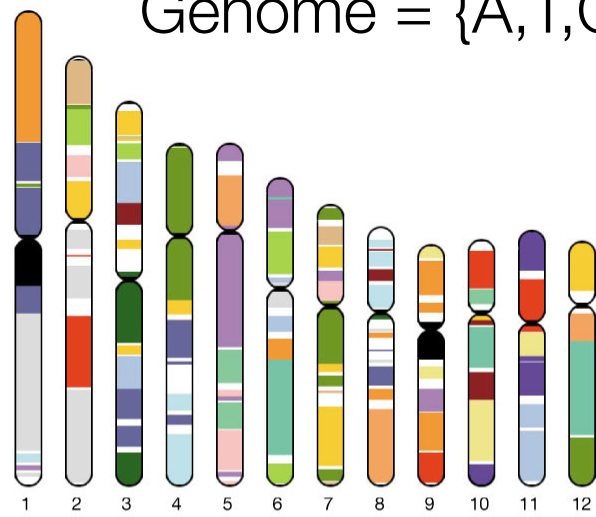
- AT-rich and methylation-rich segments attract each other by sharing bridging polyamines.



h HR

# Epigenetics

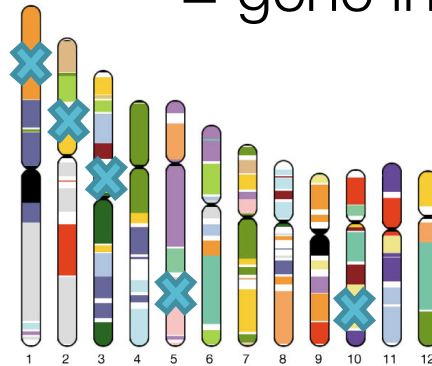
Genome = {A,T,G,C}



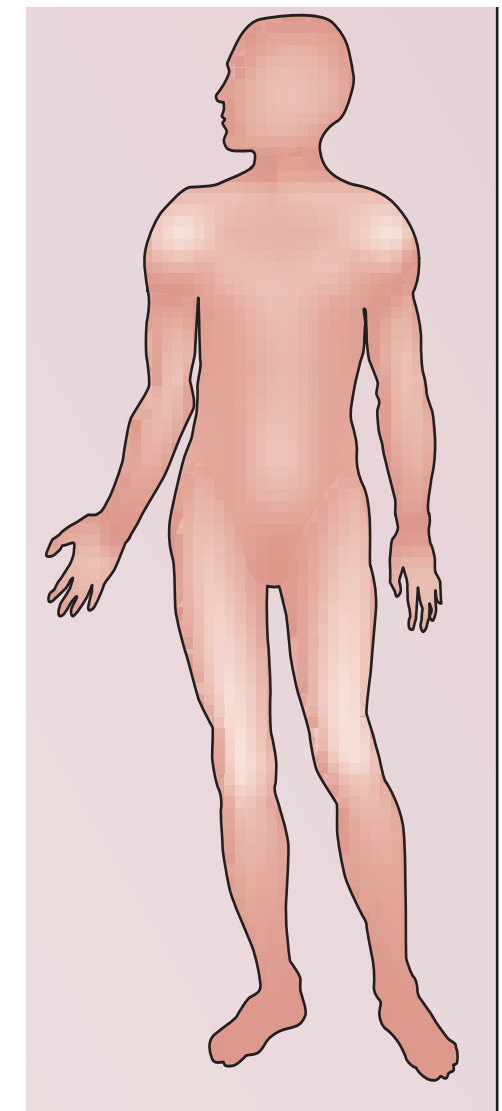
Genetics



✕ = methylation of C (mC)  
= gene inactivation



Epigenetics

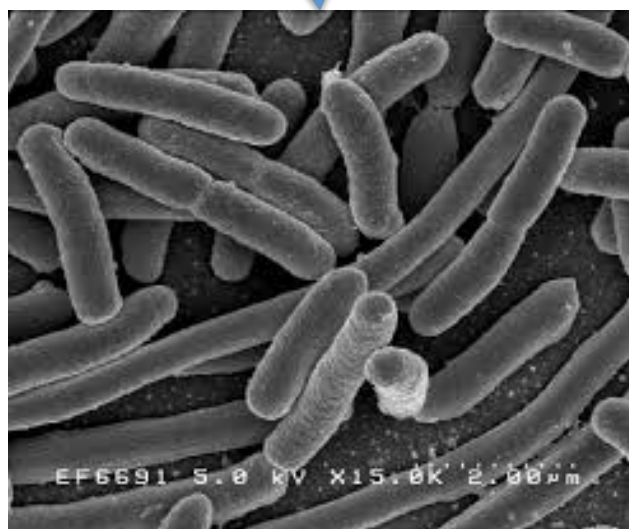


~20k genes

Gene regulation  
= Turning on/off specific genes.

No methylation. Just gene on/off

- Same genome, different fate, depending on epigenetic markers.
- How epigenetic markers determine tissue types and cancer?



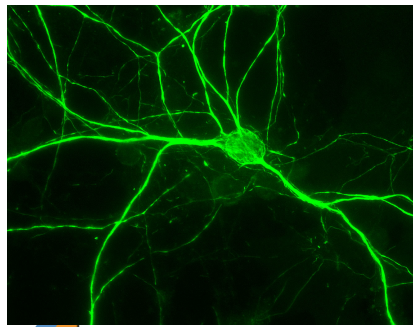
~4k genes



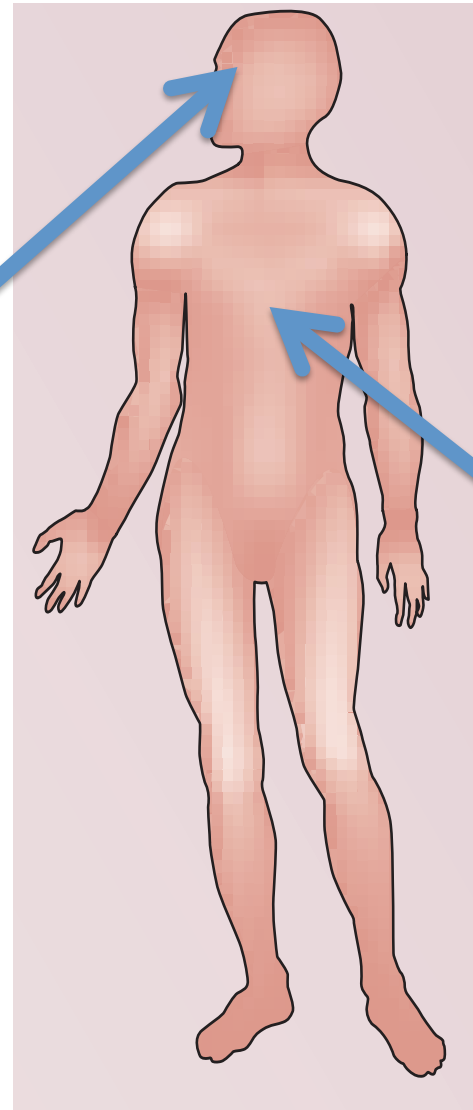
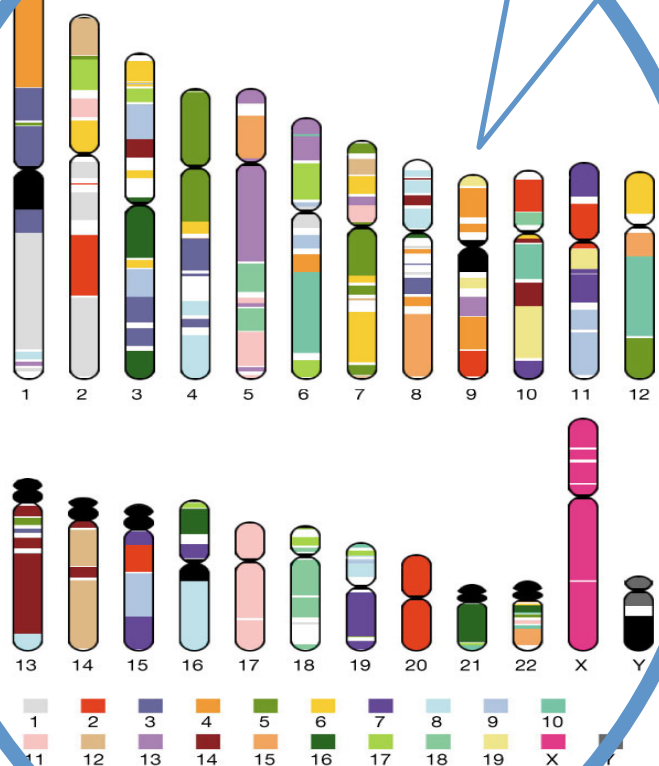
~15k genes



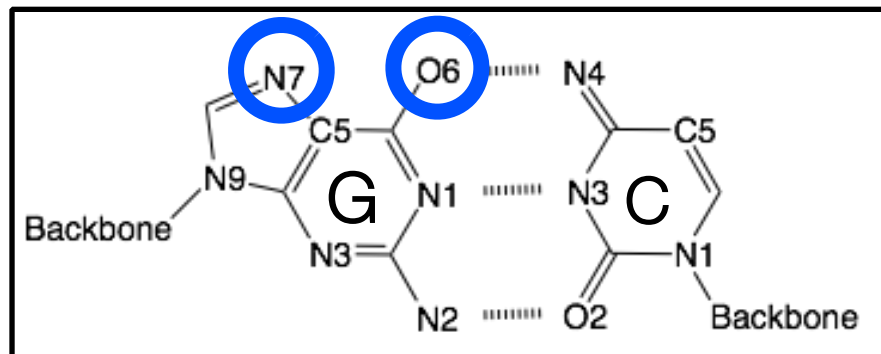
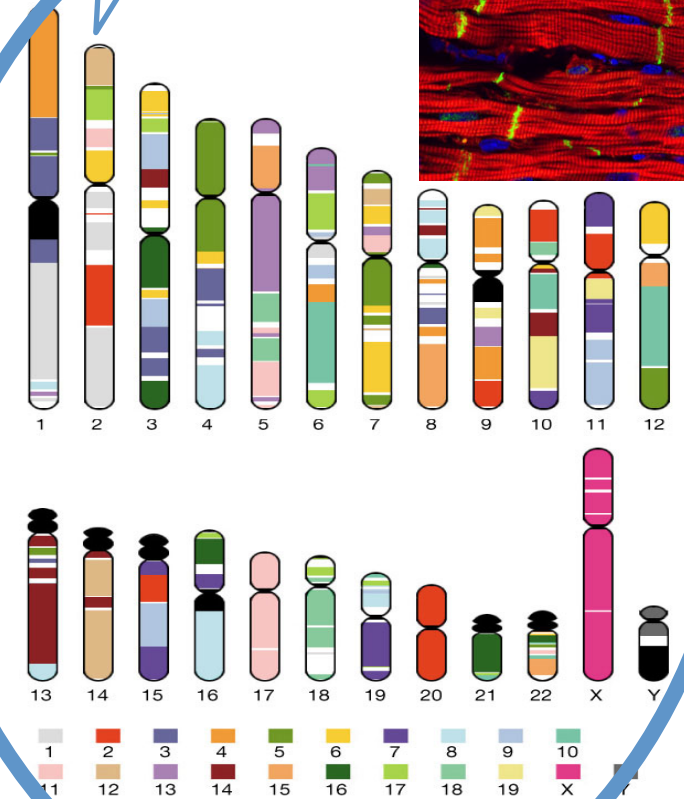
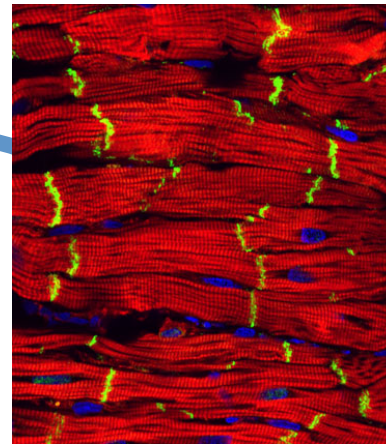
# Genome in every cell is identical



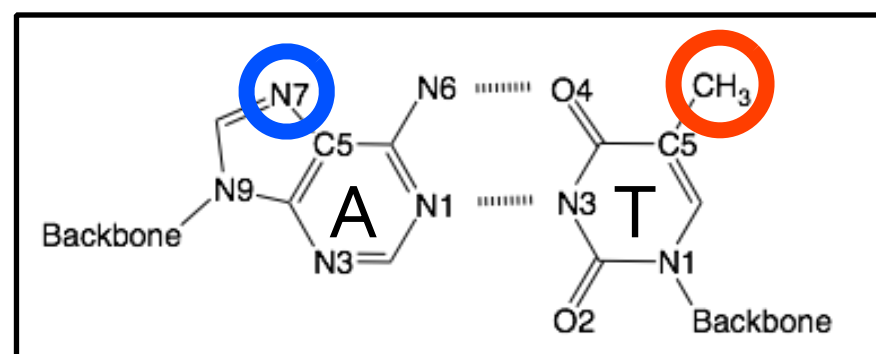
ATGCGCTTAT  
ATGGCC...



ATGCGCTTAT  
ATGGCC...

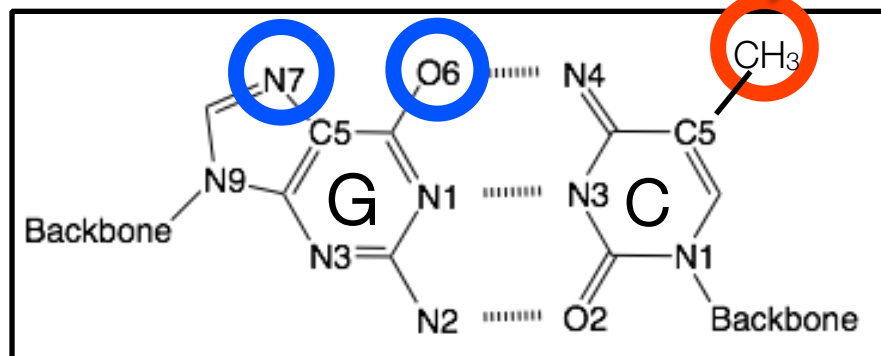
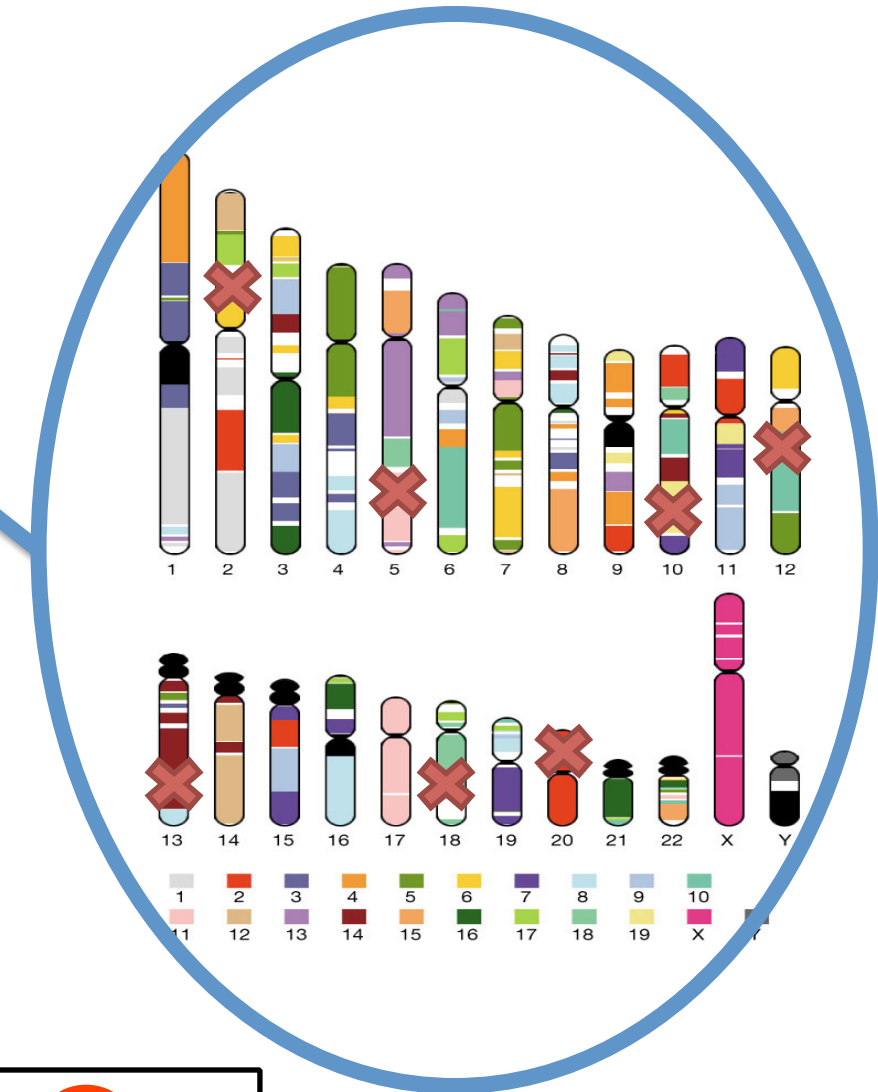
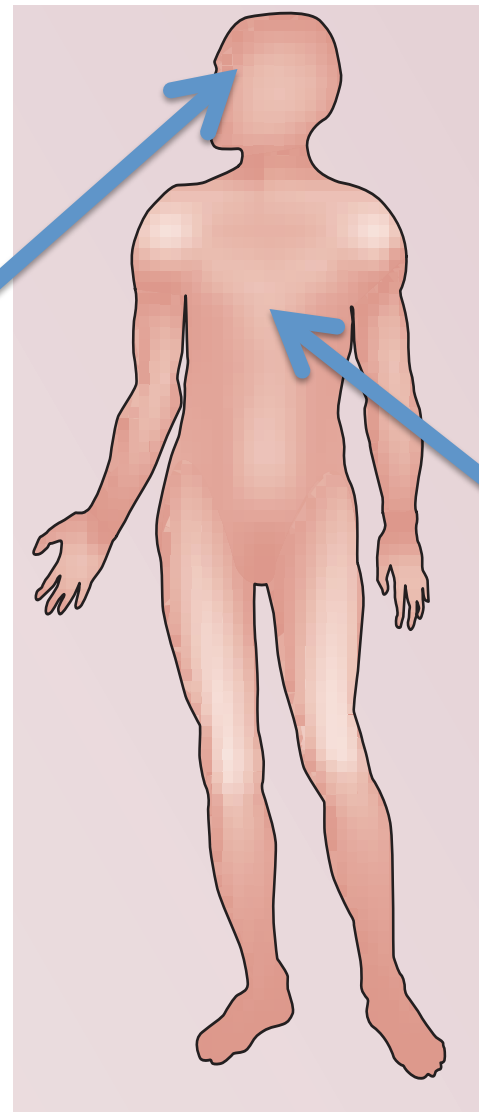
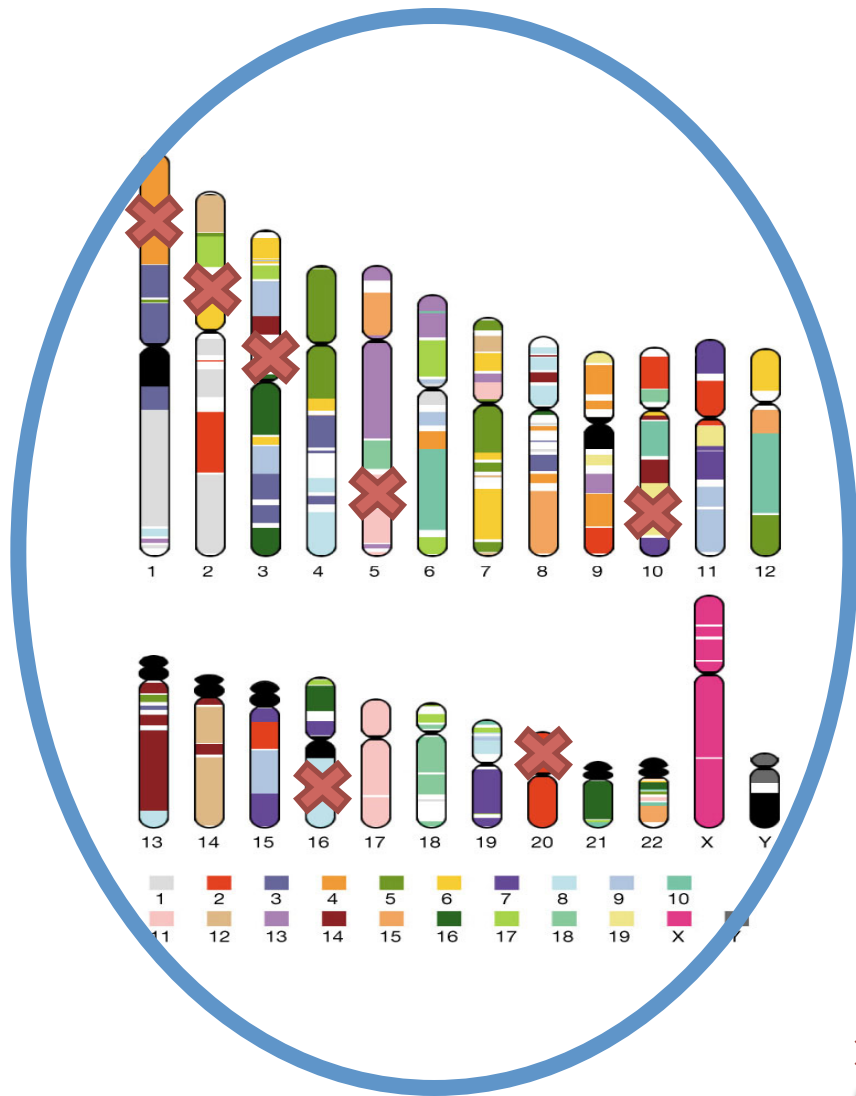


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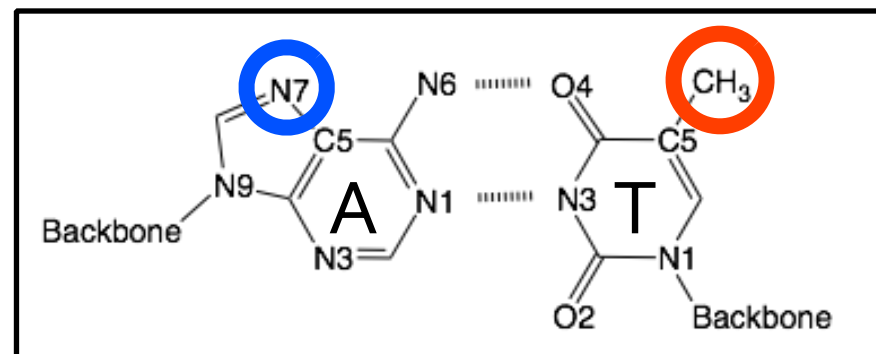


# Methylation makes difference

✗ = methylation of C (mC)  
= gene inactivation

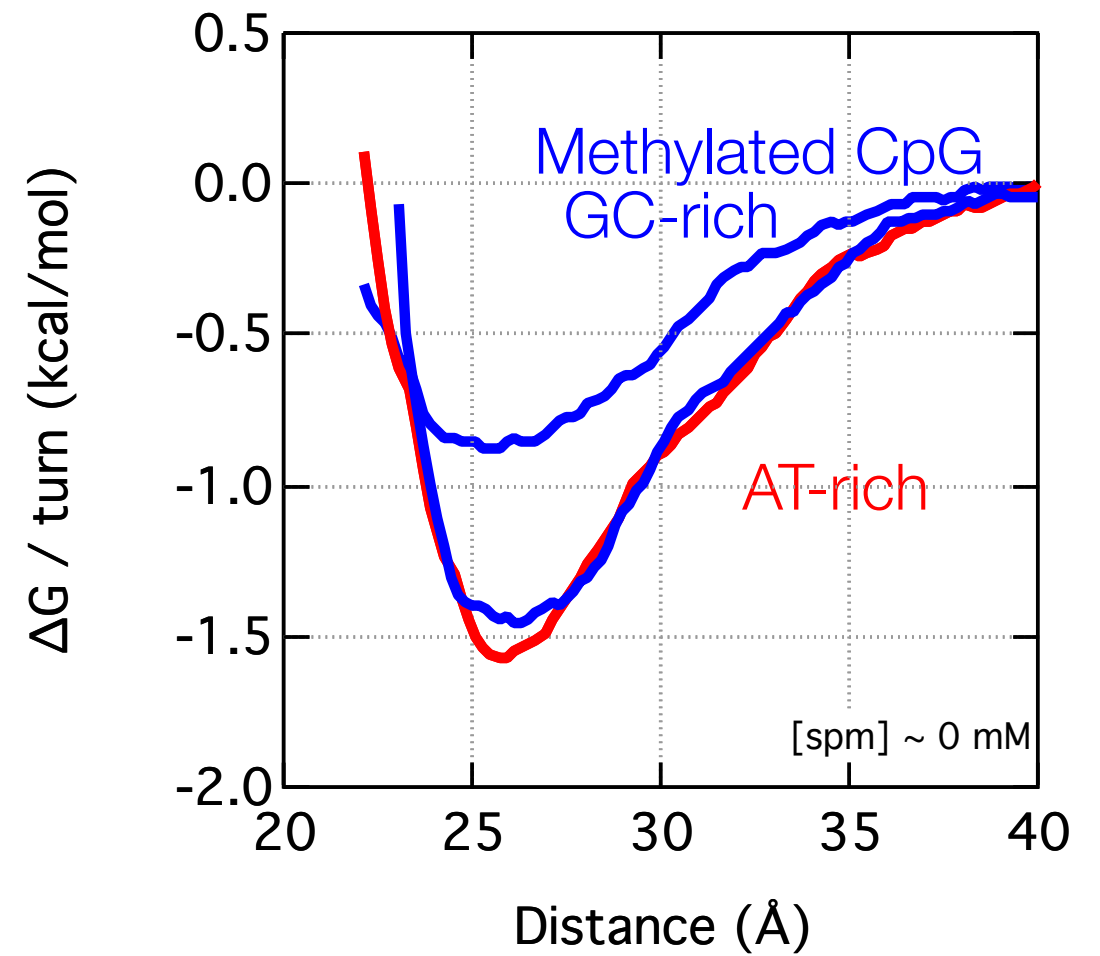
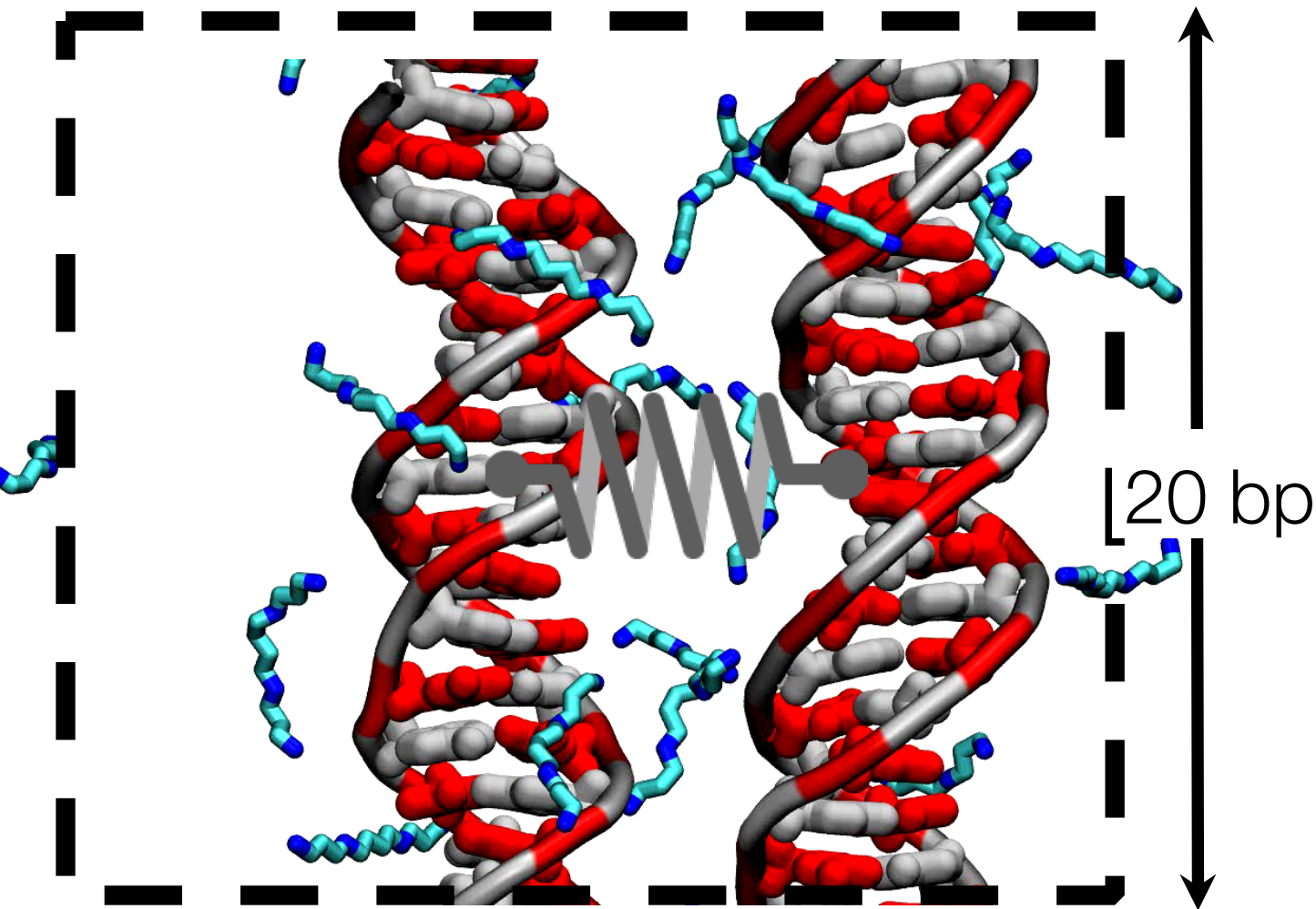


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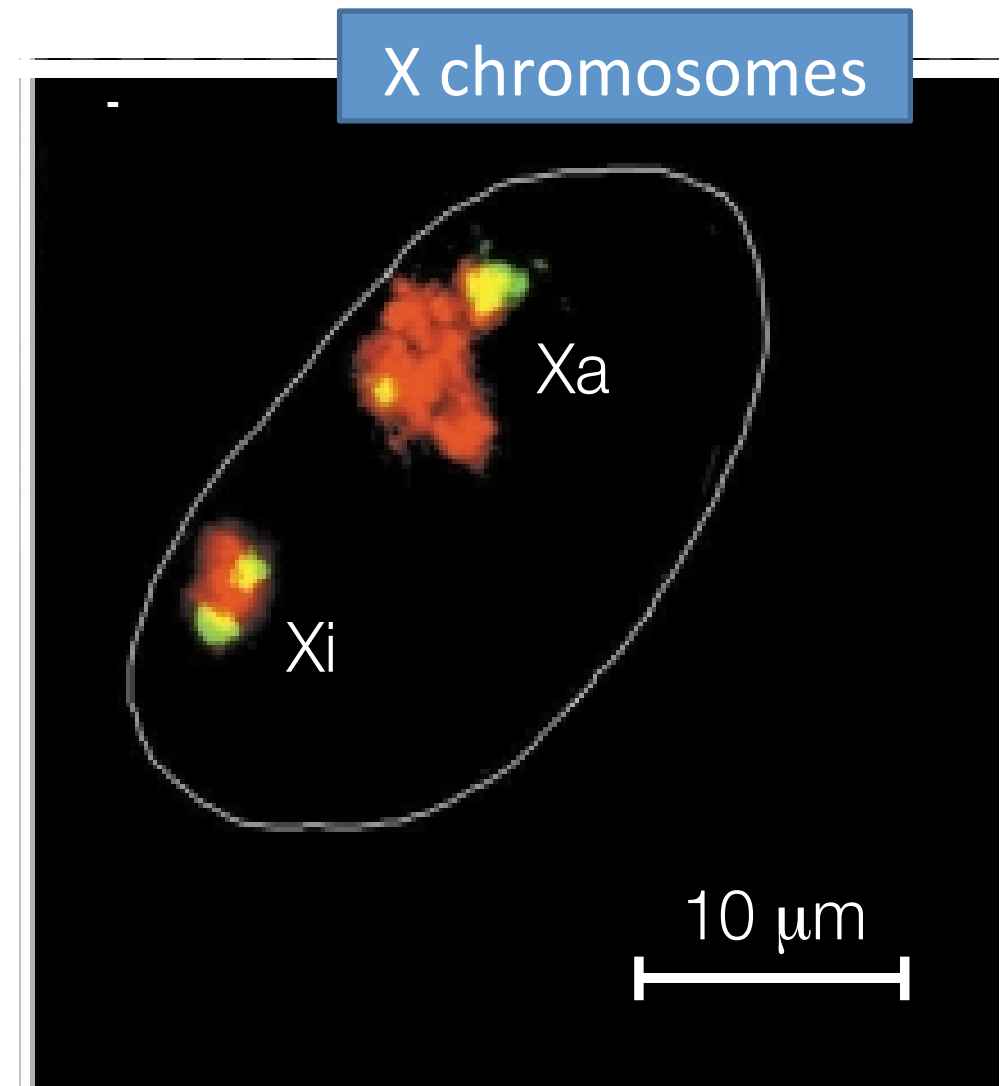
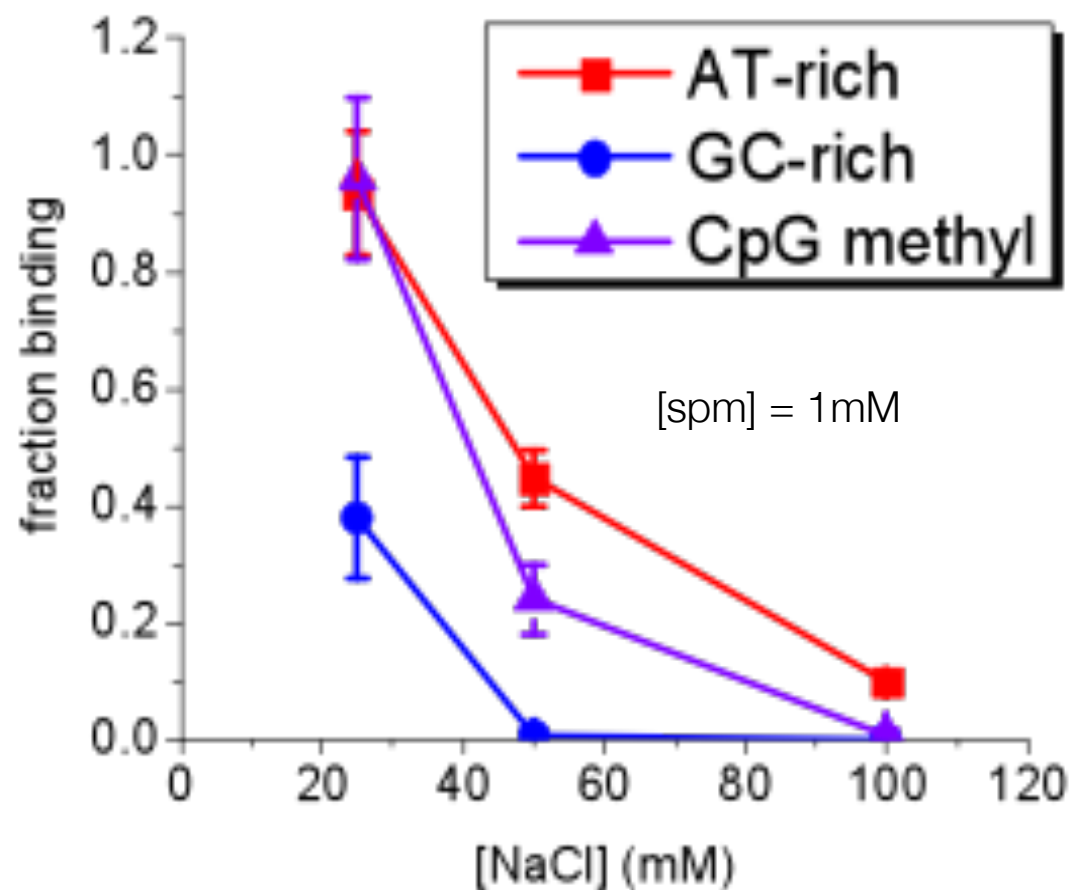




# Methylated CpG is as attractive as AT



# Methylated CpG is as attractive as AT



- Hypermethylation
- => Compaction.
- => Lower enzyme accessibility.
- => Inactivation.

*Nat Rev Genet*, 2(4), pp. 292-301.



# Take-home message: dsDNA bonds by sharing polyamines

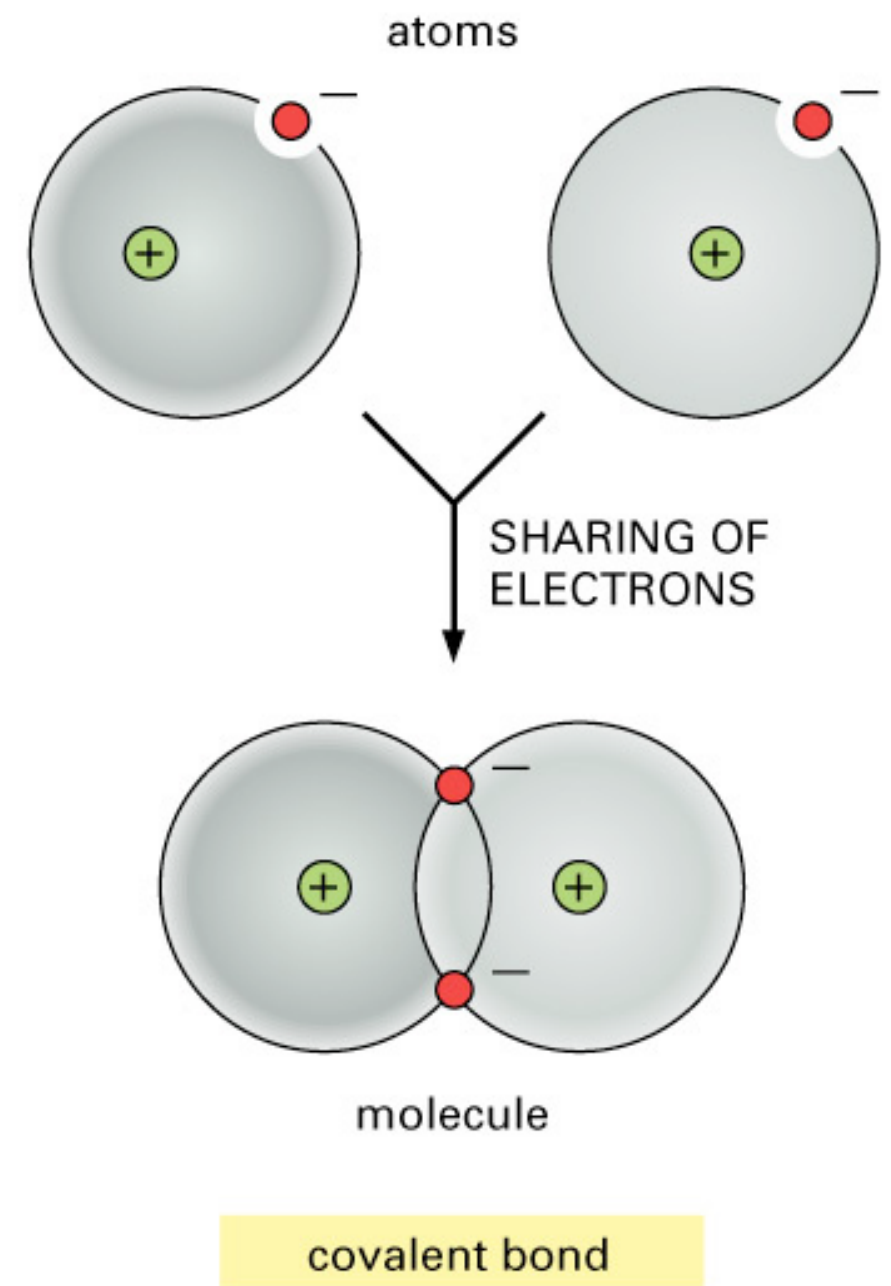
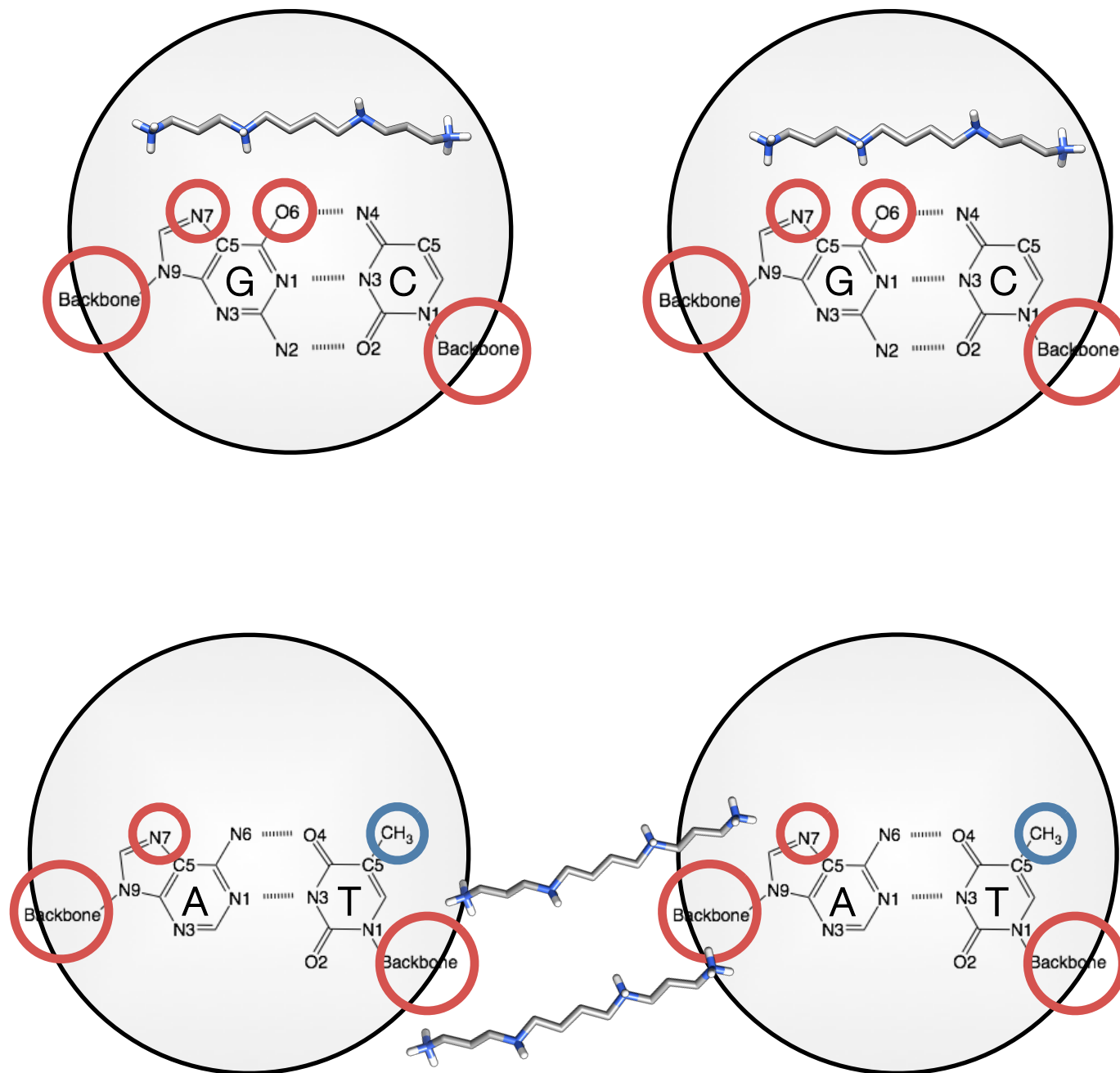
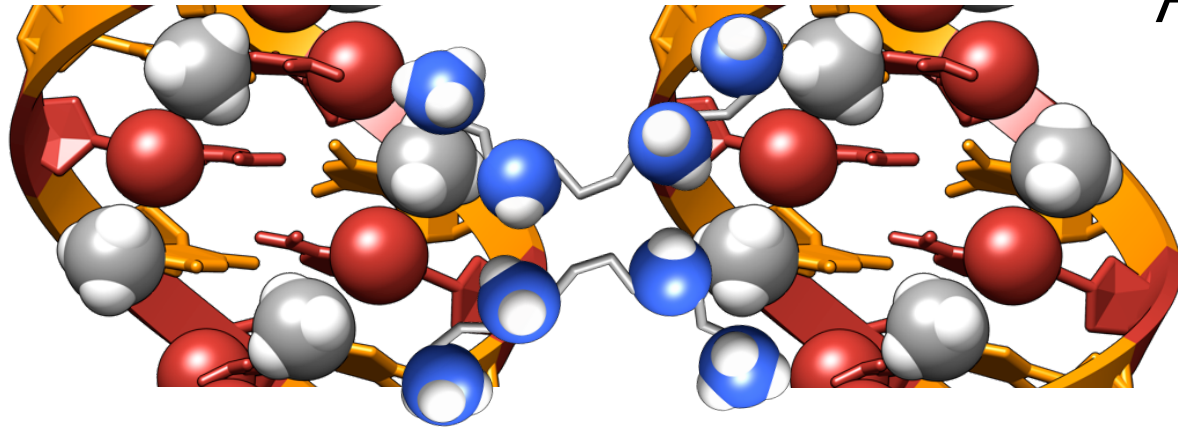


Figure 2.6 Essential Cell Biology, 2/e. (© 2004 Garland Science)

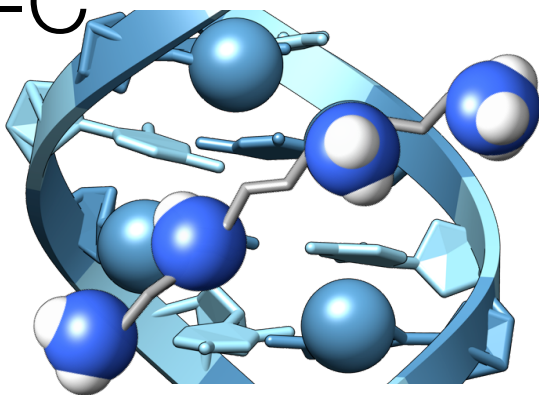
# Take-home message: dsDNA bonds by sharing polyamines

A-T



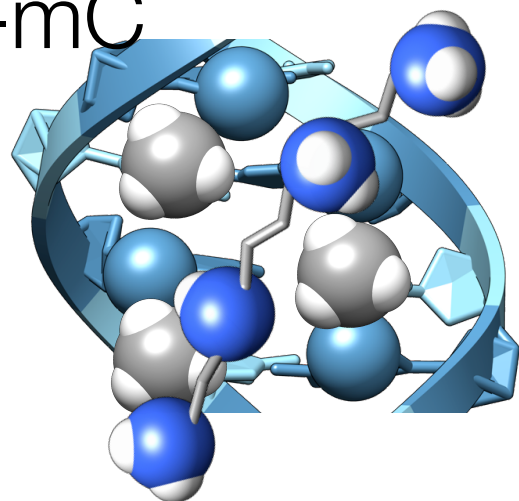
A-T

G-C



G-C

G-mC



G-mC

Analogy to chemical bond

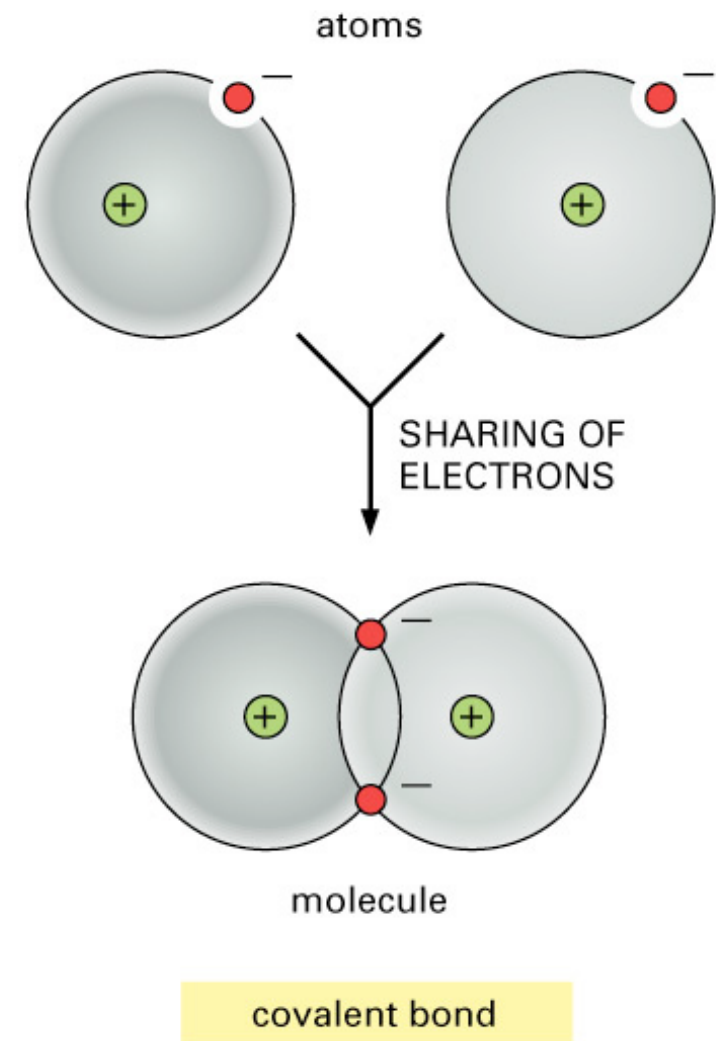
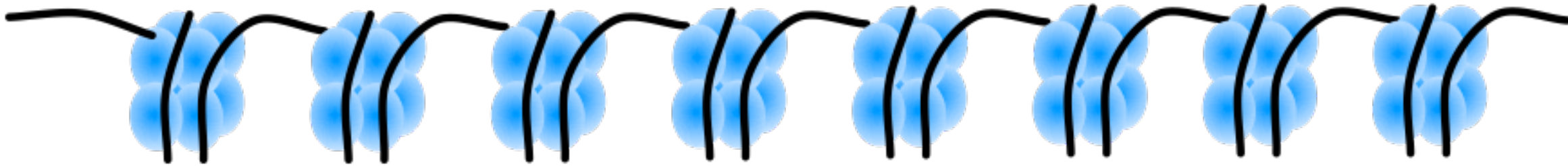


Figure 2.6 Essential Cell Biology, 2/e. (© 2004 Garland Science)



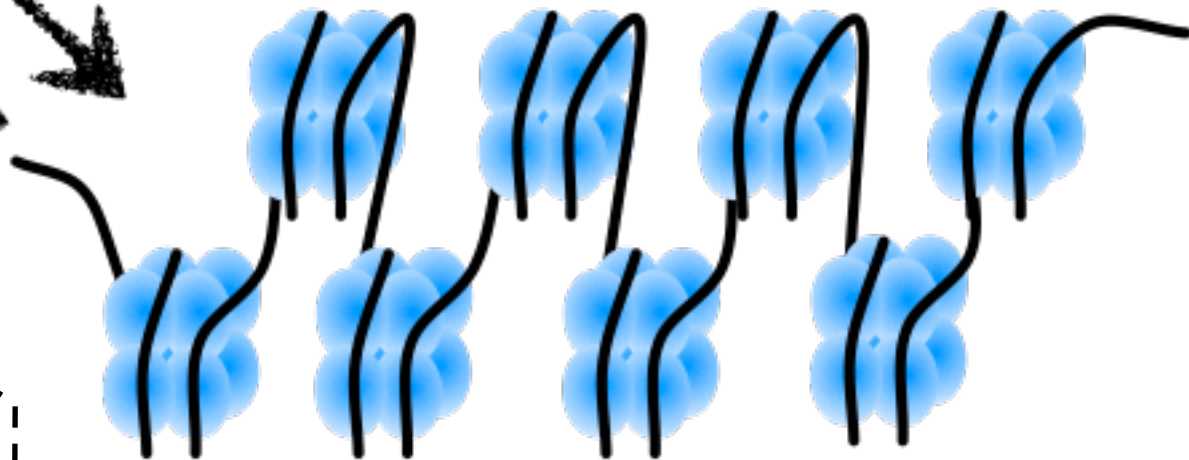
# Chromatin folding might follow the same mechanism

GC-rich domains are actively expressed.

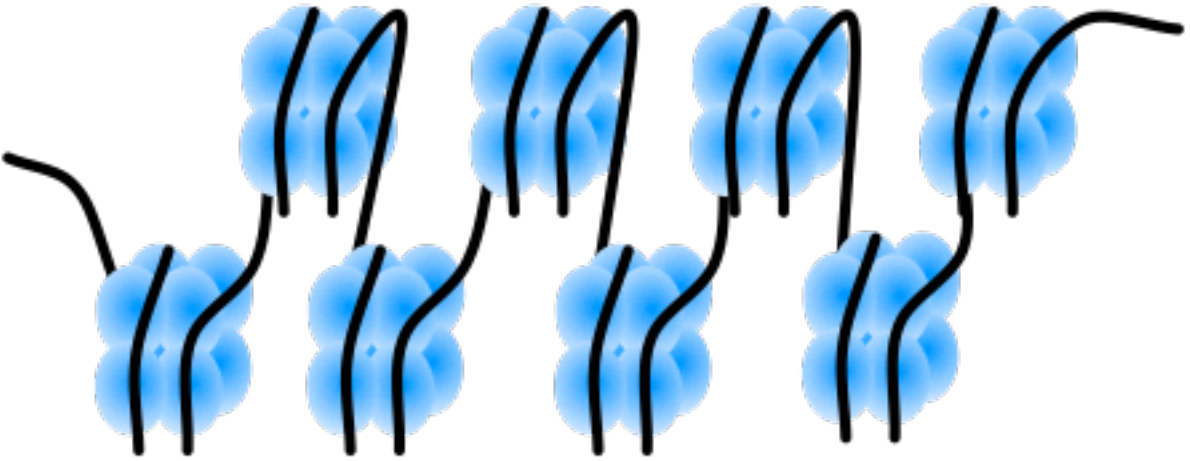


Methylation

Demethylation

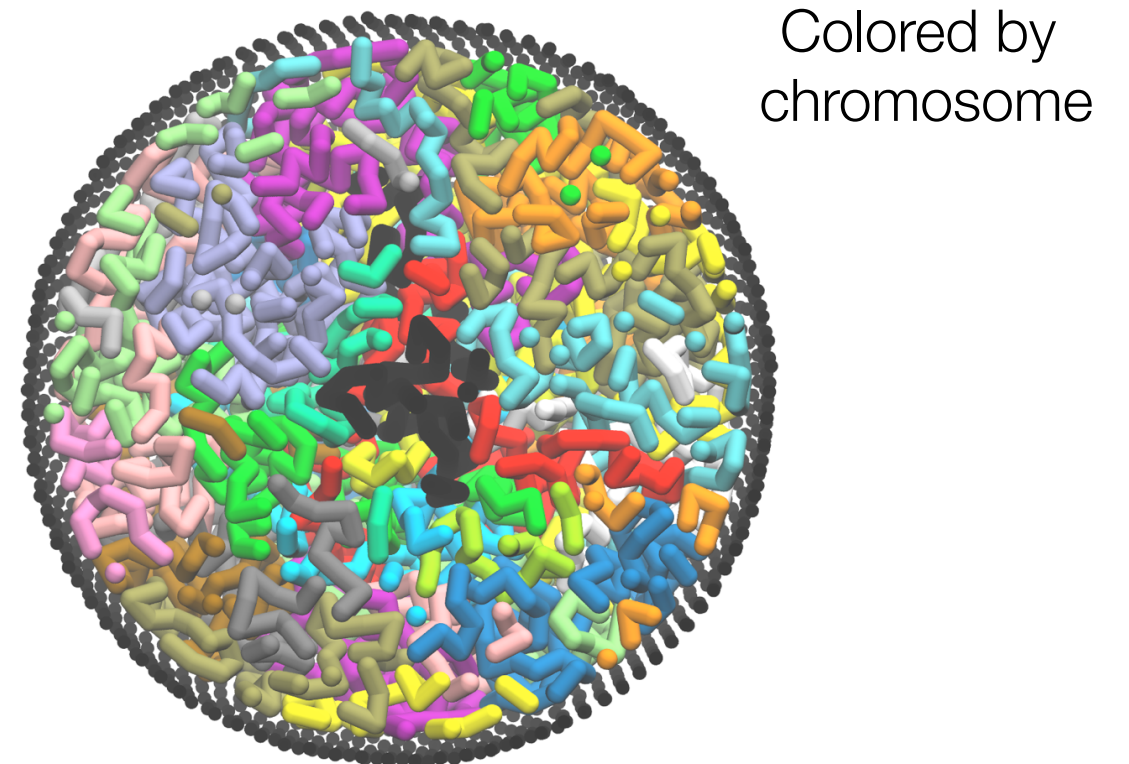
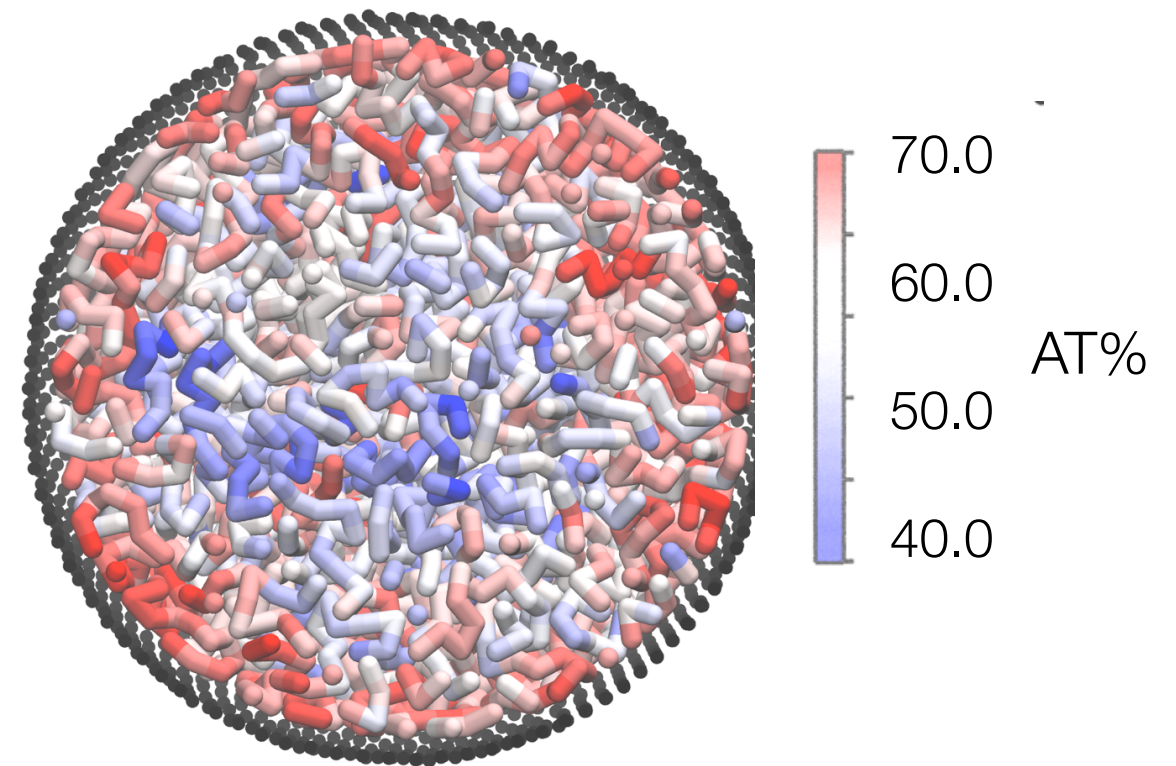
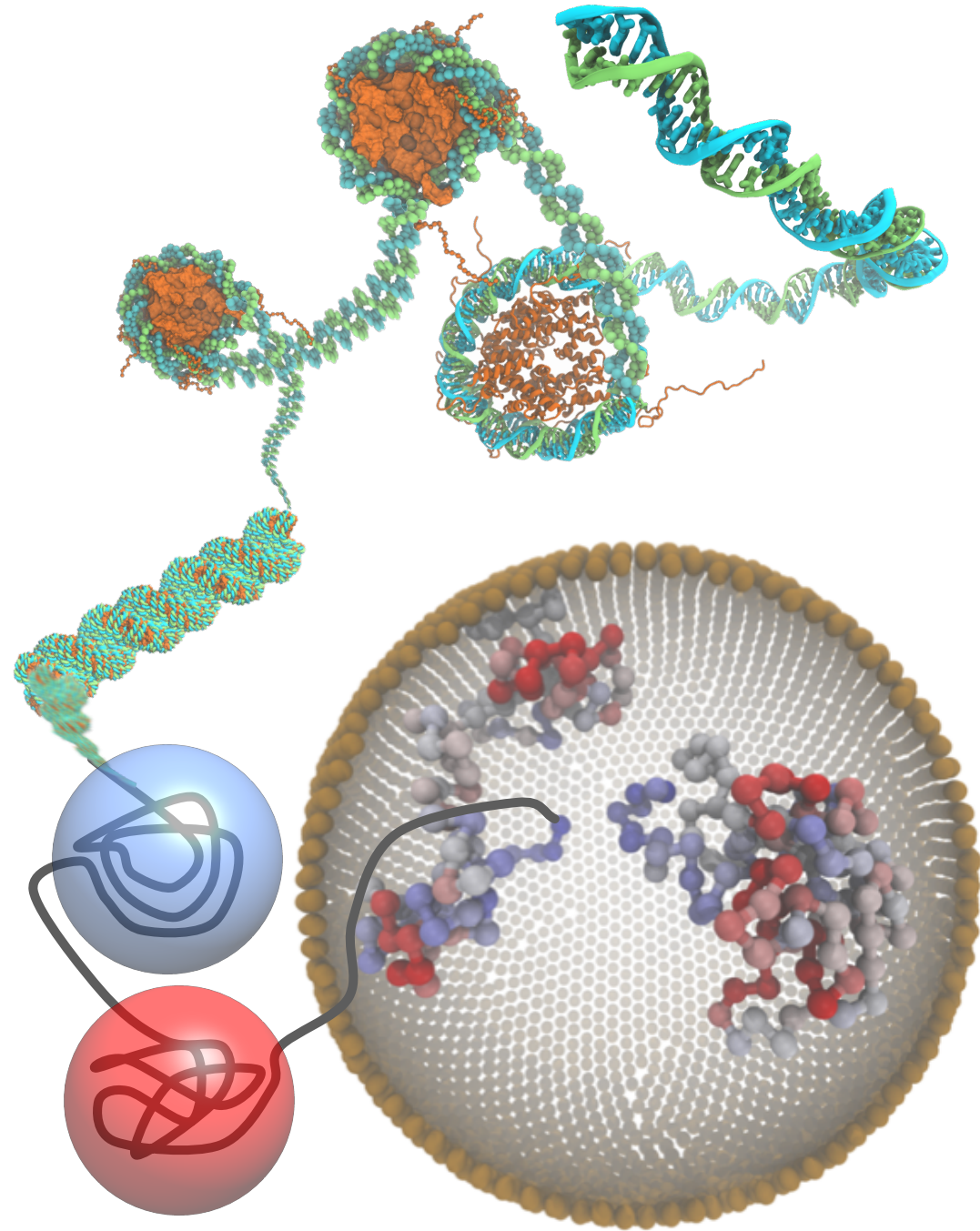


Gene-poor AT-rich domains are condensed permanently.



Methylation turns off GC-rich domains by compaction.

# Developing story on Blue Waters – whole-nucleus simulation



- Inter-bead interactions depend on AT-content.



# Conclusion & outlook

- We hypothesized a physical principle that might govern global organization of chromatin.
- And we proved it using MD simulations & FRET experiments.
- Our hypothesis is consistent with well known facts such as
  - AT-content-dependent compaction of chromatin.
  - Methylation-induced compaction
- Further, we need to prove our hypothesis for more realistic chromatin fiber & in the presence of nuclear envelope *in vivo*.

# Acknowledgements

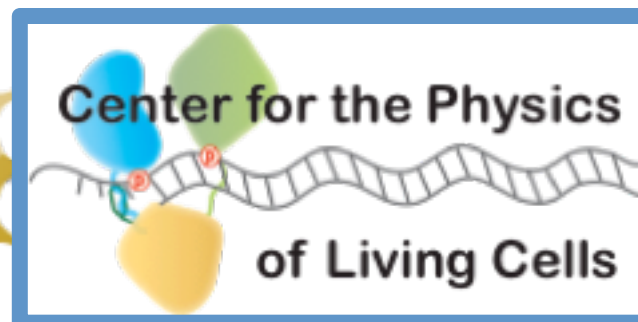
Prof. Aleksei Aksimentiev



Prof. Taekjip Ha



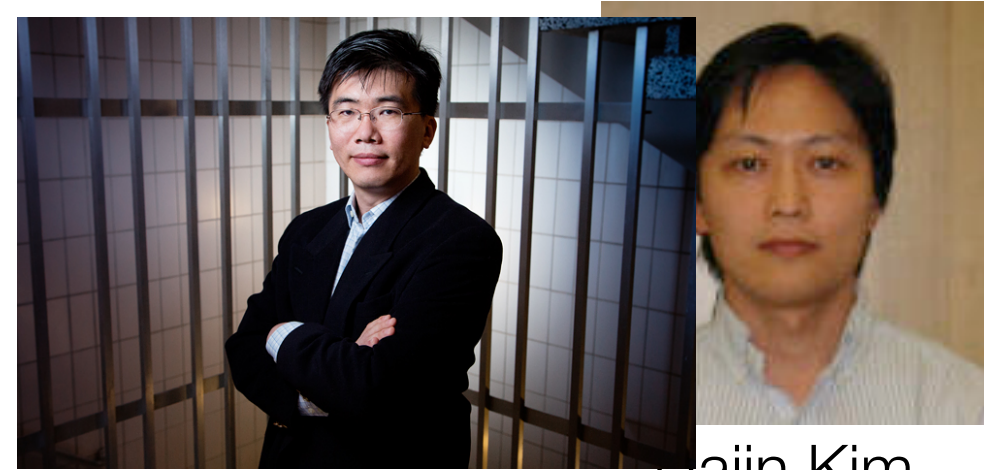
Dr. Hajin Kim



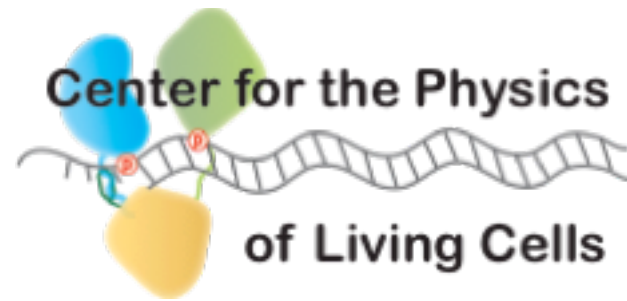
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Chen-Yu Li  
Derek van Damm  
Dmitrii Kochkov  
Karl Decker



# Acknowledgements



Hajin Kim



VMD and NAMD



TeraGrid

