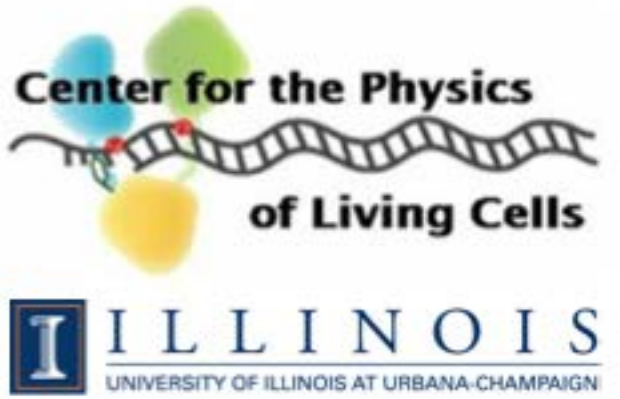
Improved Molecular Dynamics Model Suggests Novel Epigenetic Mechanisms

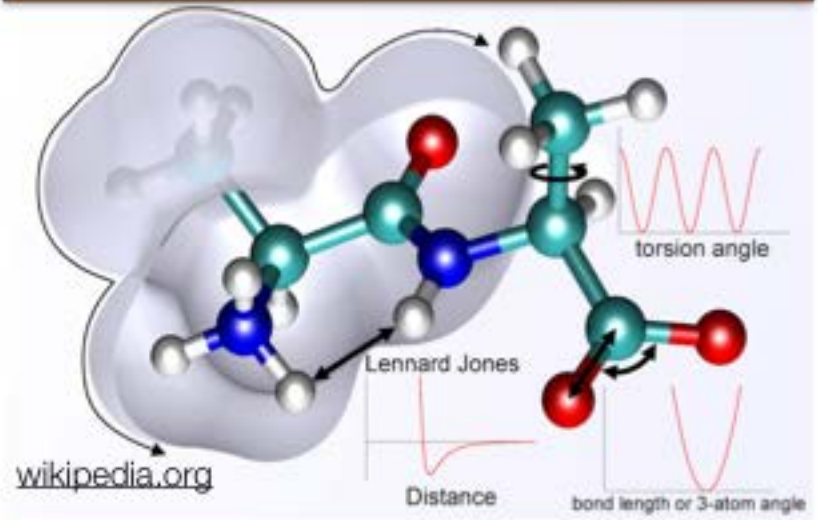
Jejoong Yoo (Aksimentiev group)
Center for the Physics of Living Cells
University of Illinois at Urbana-Champaign



Blue Waters Symposium
Jun 13, 2016

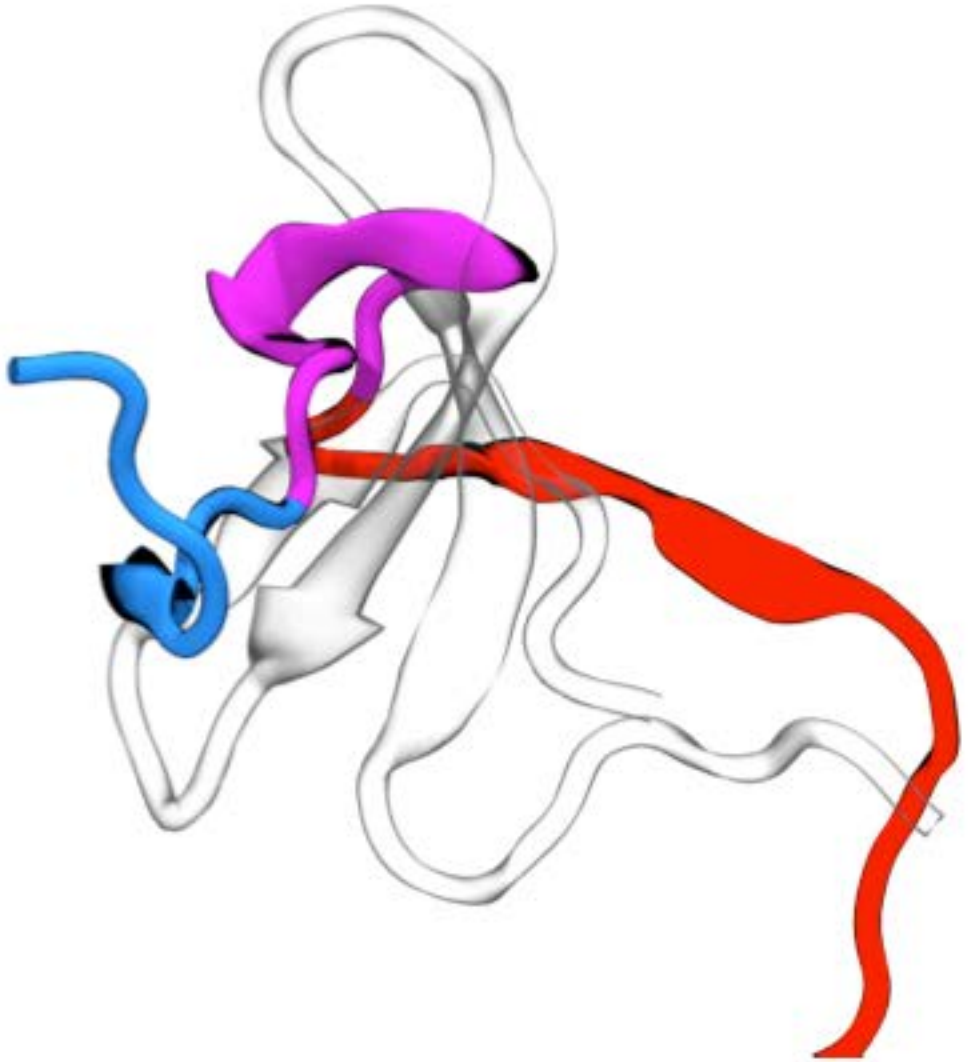
Molecular Dynamics (MD) Simulation

Define $F(x) = -\nabla U(x)$:
Force Field such as AMBER & CHARMM

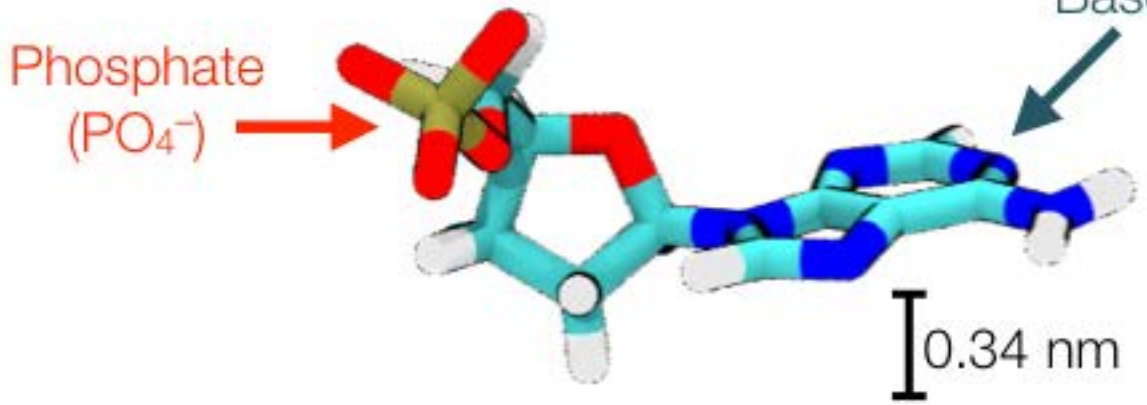


Solve $F(x) = ma$
Gromacs, NAMD, CHARMM etc

Folding of Fip35 WW domain (35 residues)
3 μs x 56 replicas using ~120 K node hours on BW



DNA is a highly *negatively charged* polymer that forms human genome



2 nm

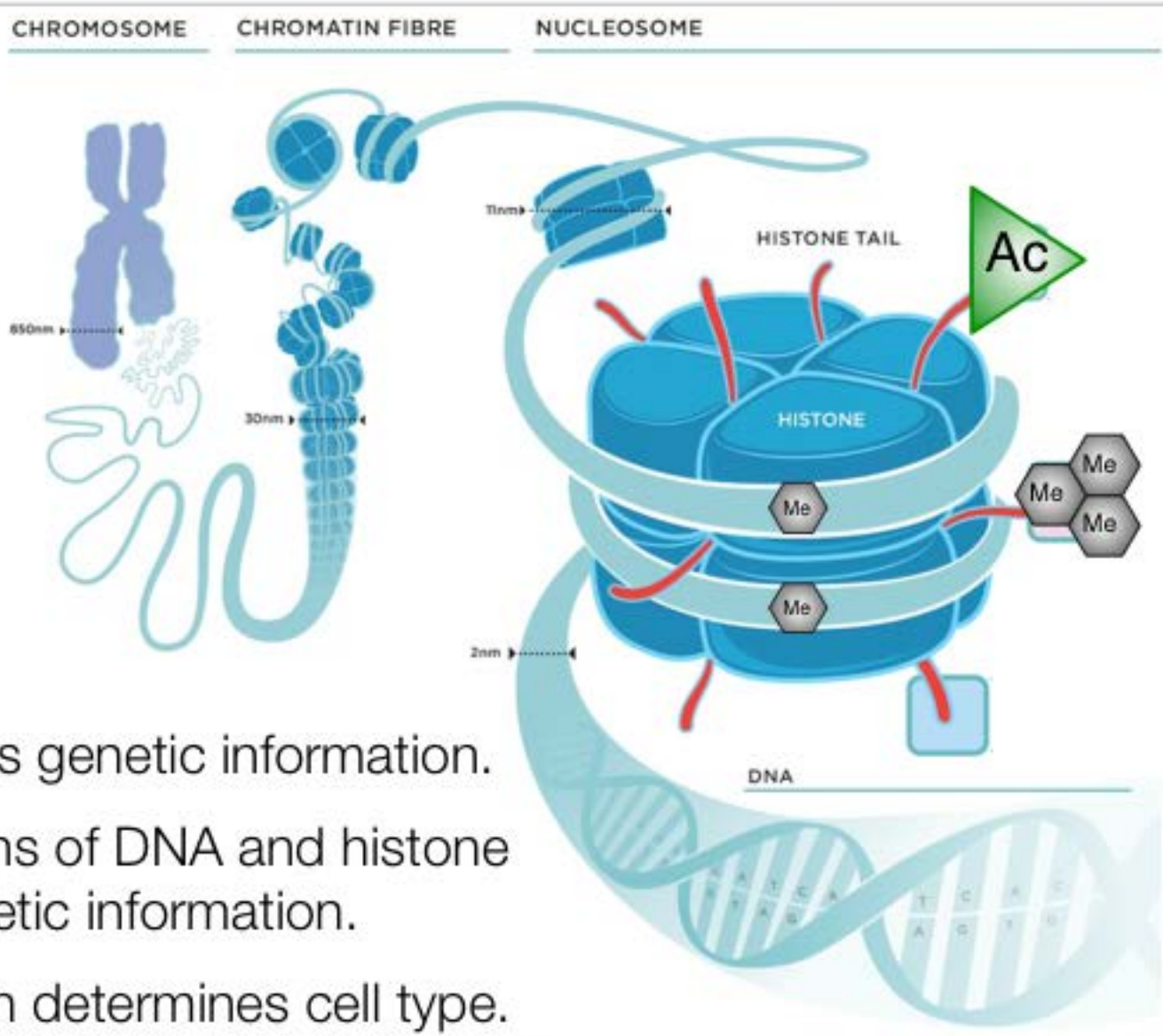
23x2 chromosomes of 12 billion DNA are **highly condensed** and **highly bent**.

Animation by Chris

Lieberman-Aiden et al., Science (2009)

Beyond DNA sequence: Epigenetic regulation

http://roadmapepigenomics.org

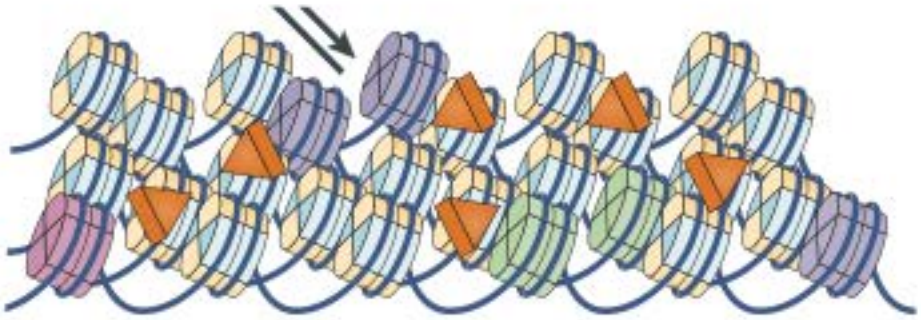


- DNA sequence carries genetic information.
- Chemical modifications of DNA and histone proteins carry epigenetic information.
- Epigenetic information determines cell type.

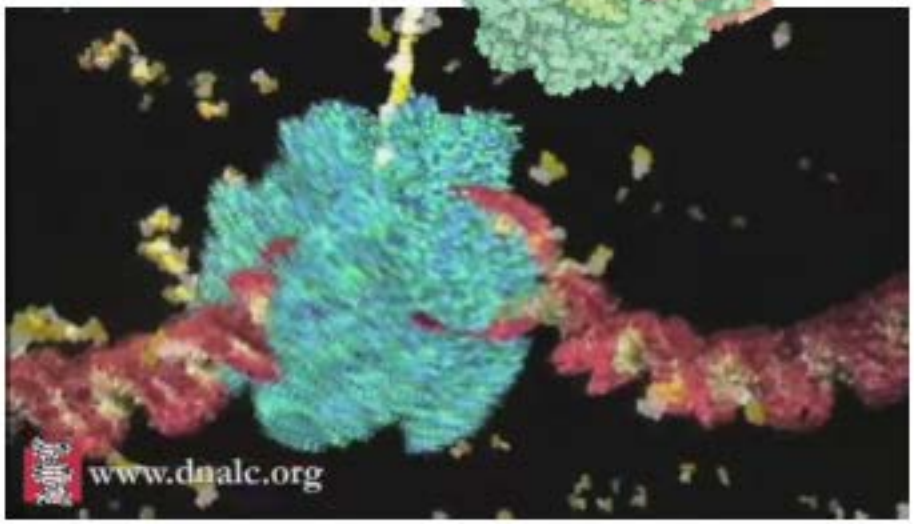
http://www.resverlogix.com/programs/rvx-208-moa/epigenetics

RNA pol.

Two-step gene-regulation mechanism



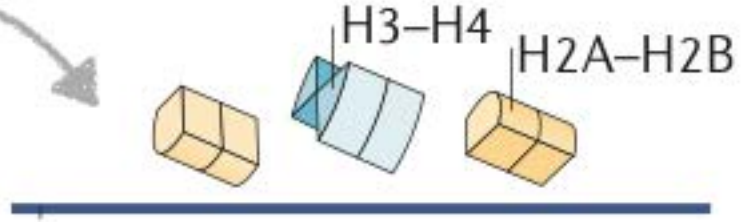
Higher-order chromatin fibre (tertiary chromatin structure)



Decondensation (global)

Unwrapping (local)

10 nm fibre (primary chromatin structure)

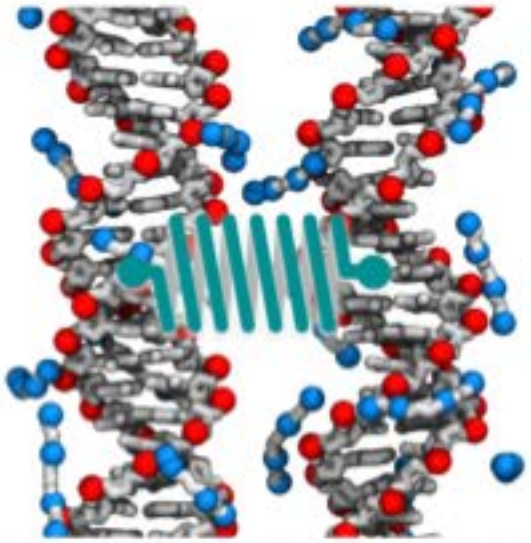


- At the fundamental level, physics of DNA (condensation and flexibility) affects gene regulation.

Luger, K. et al. (2012). *Nature Reviews. Molecular Cell Biology*, *13*(7), 436-47.

Two fundamental problems of epigenetics

Two fundamental problems of epigenetics



How epigenetic modifications control **DNA–DNA condensation**?

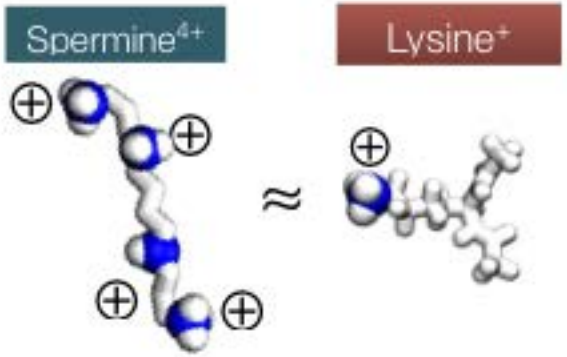
- **JY***, Kim*, Aksimentiev & Ha, *Nature Communications* (2016)

How epigenetic modifications control **flexibility of DNA**?

- Ngo, **JY**, et al., *Nature Communications* (2016)

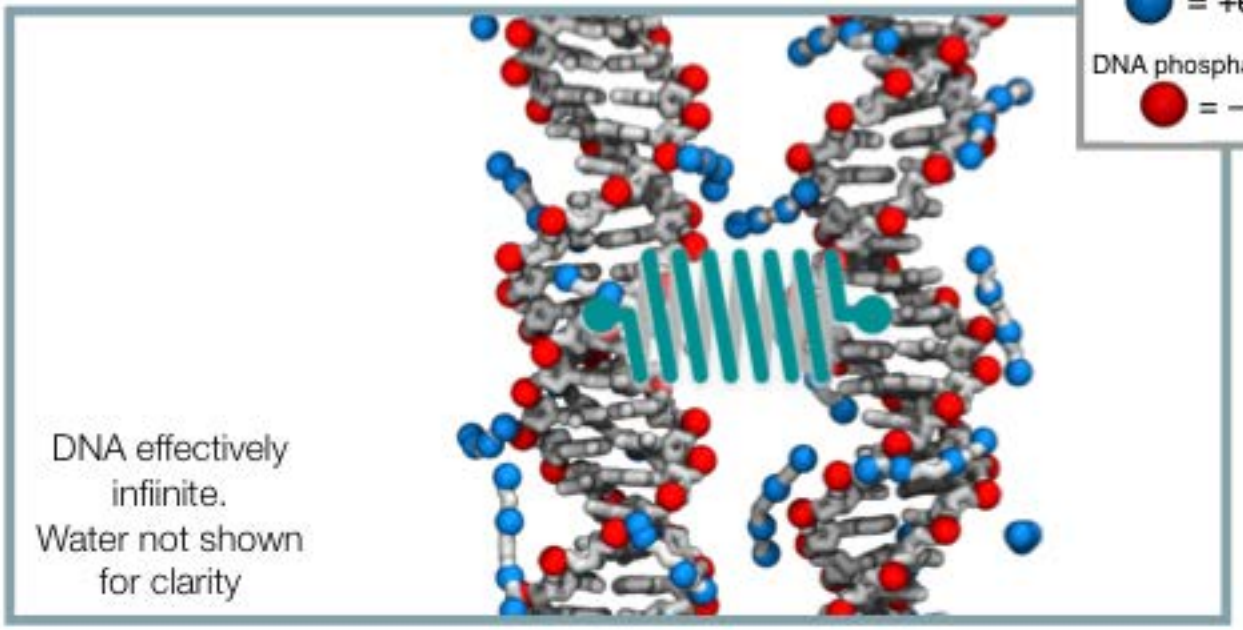
Computation of polyamine-mediated DNA–DNA interaction free energy using quasi-static pulling simulations (>100 ns per 1 Å)

using quasi-static pulling simulations (>100 ns per 1 Å)



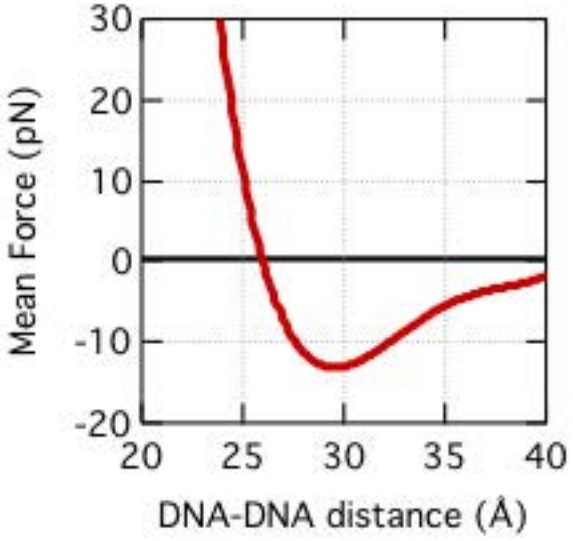
Polyamine:

- abundant in cells (~mM)
- analogous to Lys residues
- induces DNA condensation.



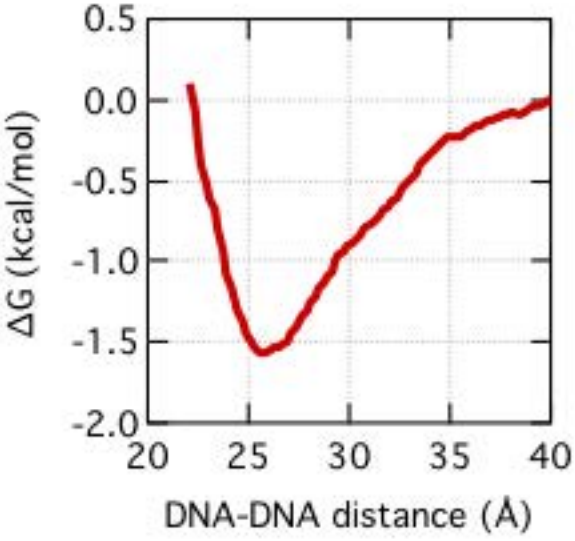
$\langle F(r) \rangle$

Compute Mean Force



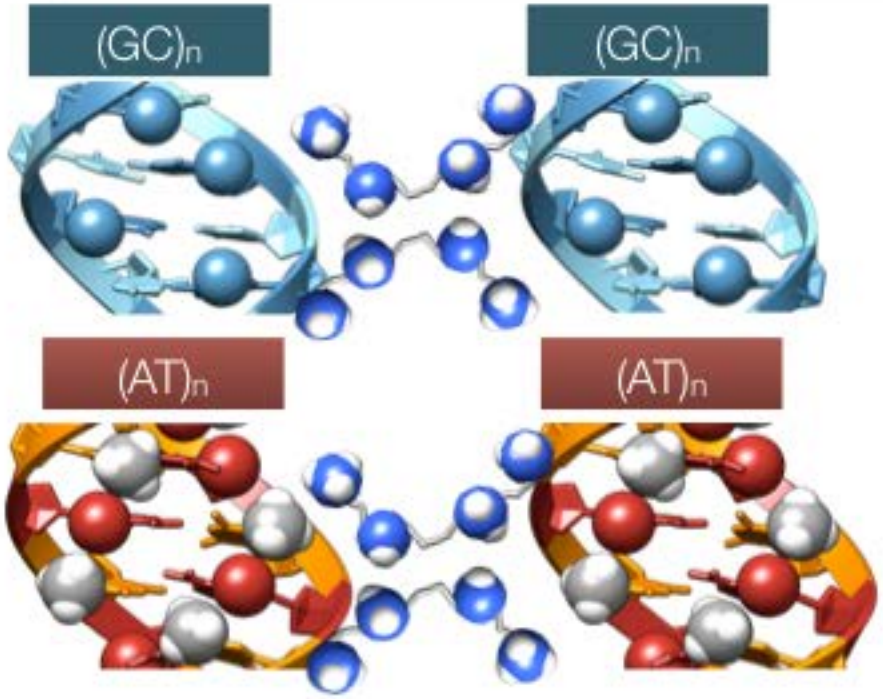
Potential of Mean Force

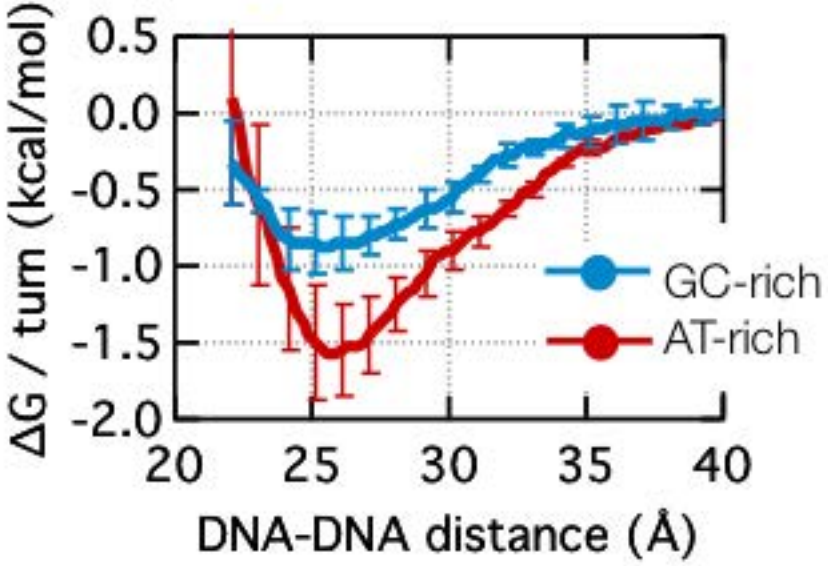
$$\langle F(r) \rangle = -\frac{d\Delta G}{dr}$$



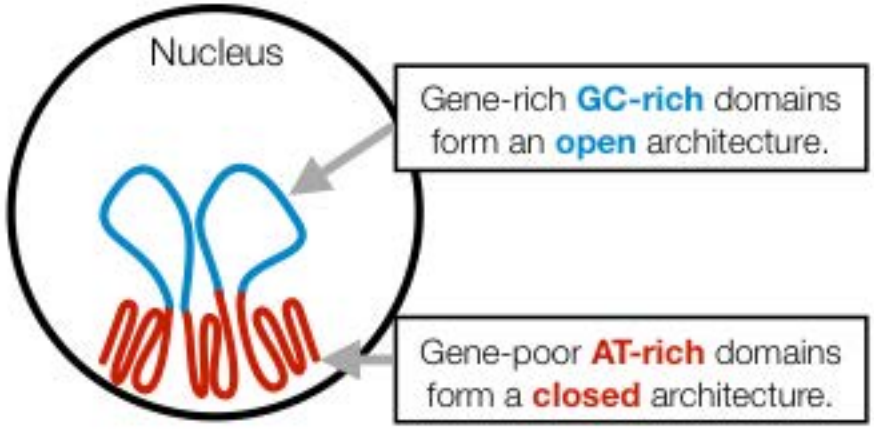
CUFIX: **JY** & Aksimentiev, JCTC (2016)

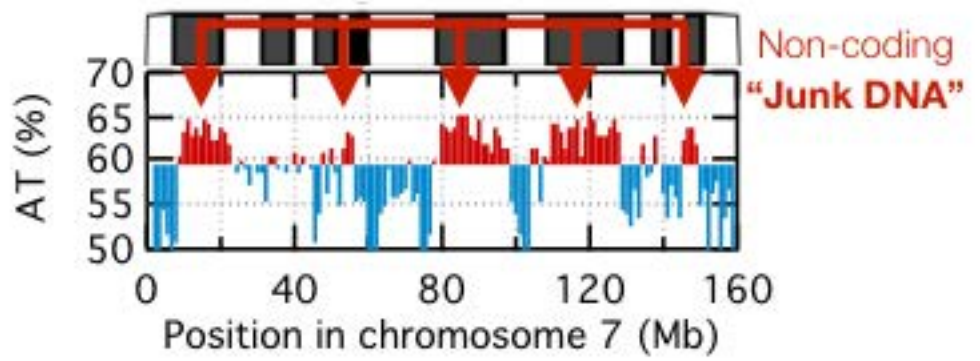
The higher AT content, the stronger condensation

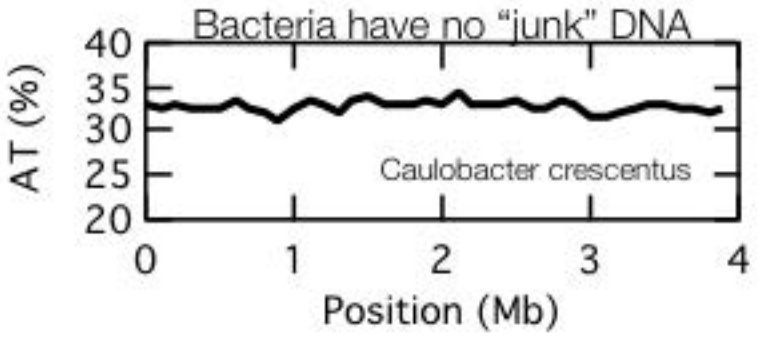




Not "junk DNA", but "architectural" DNA!

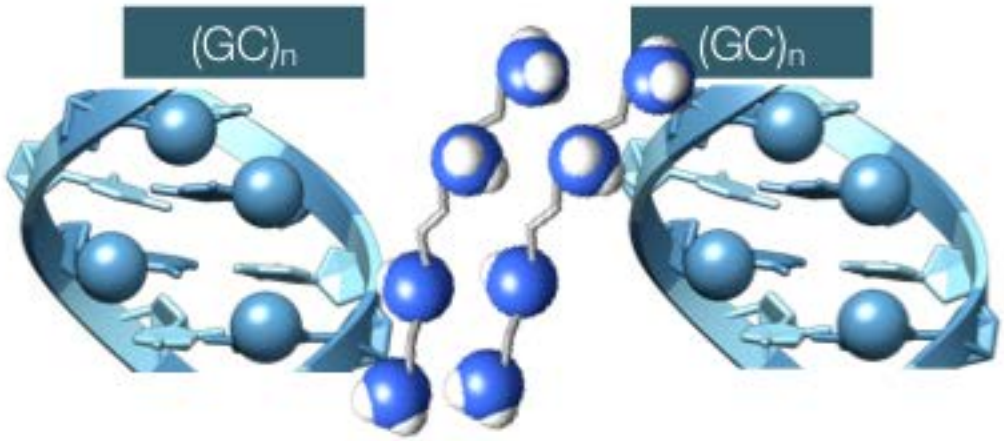


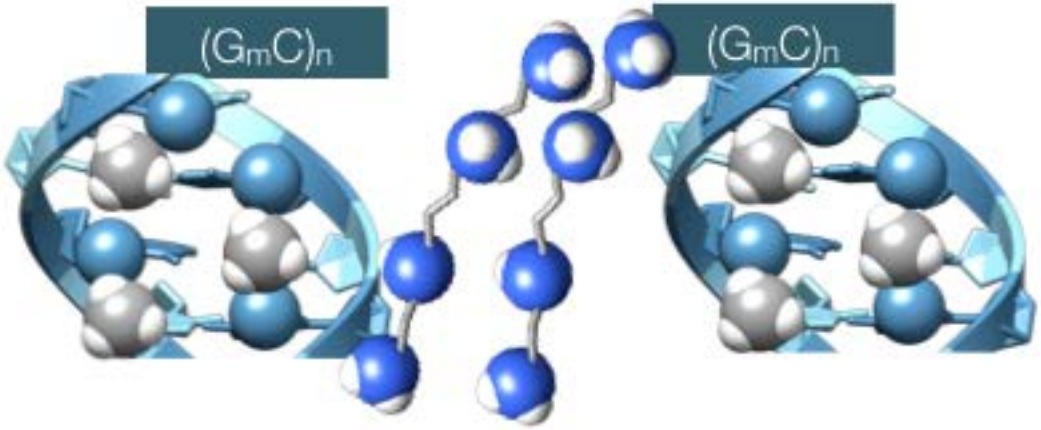


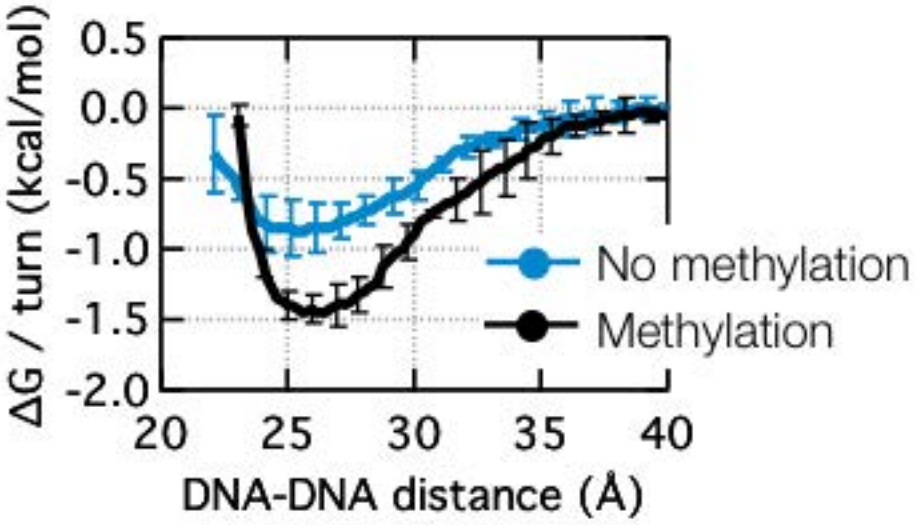


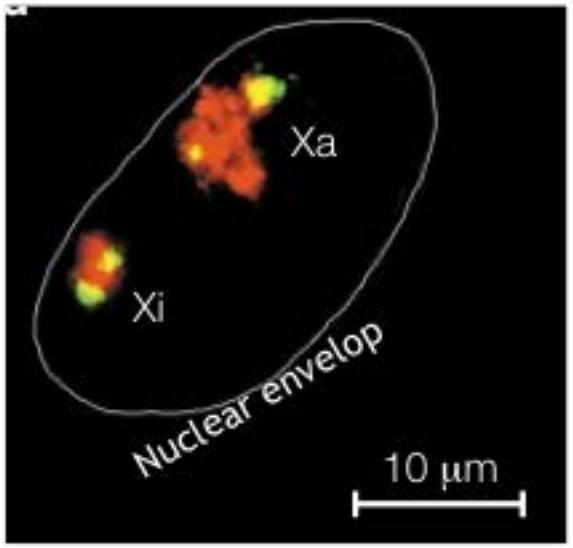
Dekker and coworkers, Science (2009), Bickmore & van Steensel, Cell (2013)

The higher methylation, the stronger condensation





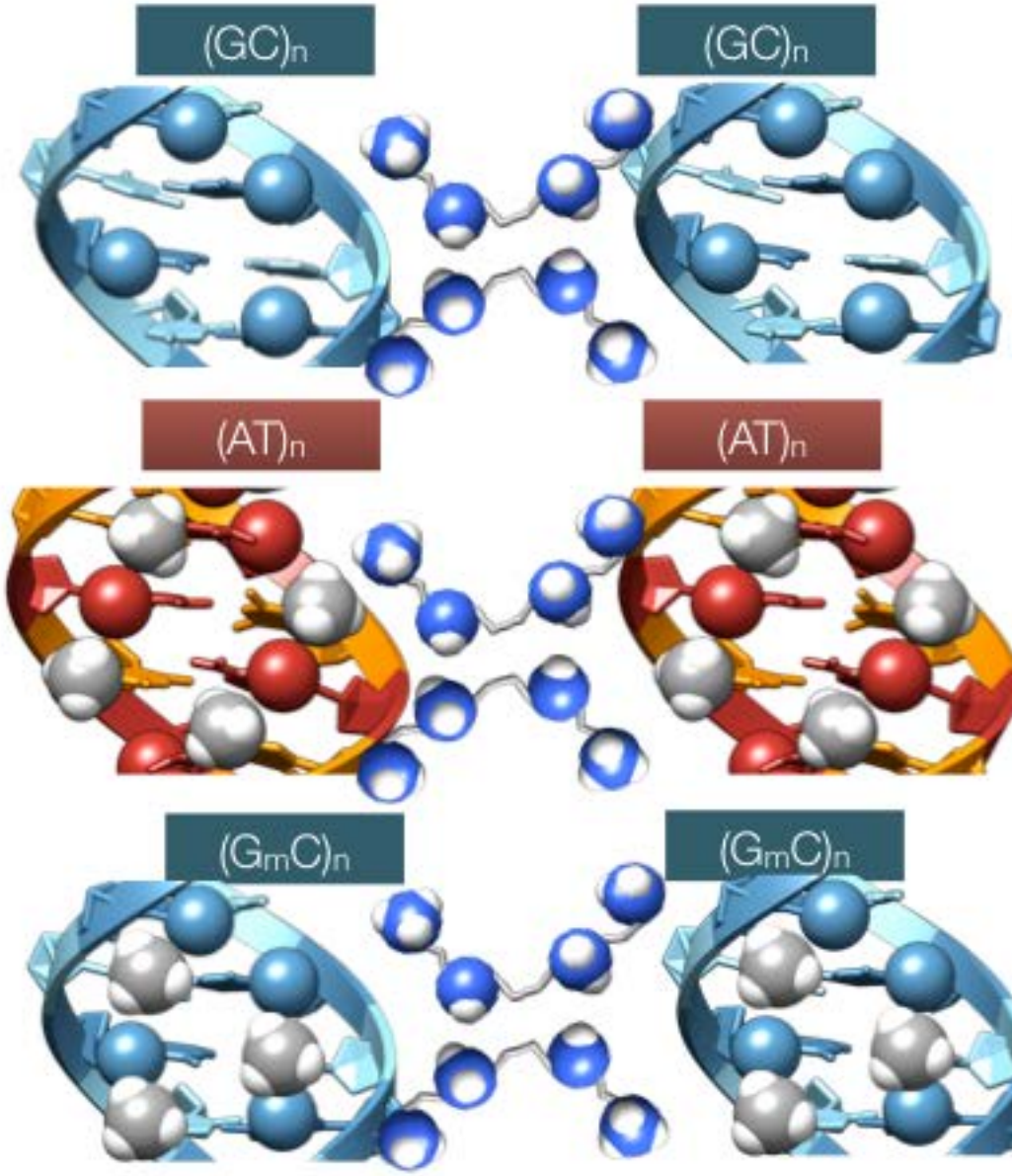




Highly methylated inactive X (Xi) chromosome is more compact than active X (Xa).

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

DNA molecules unite by **sharing** polyamine



Less sharing, less attraction

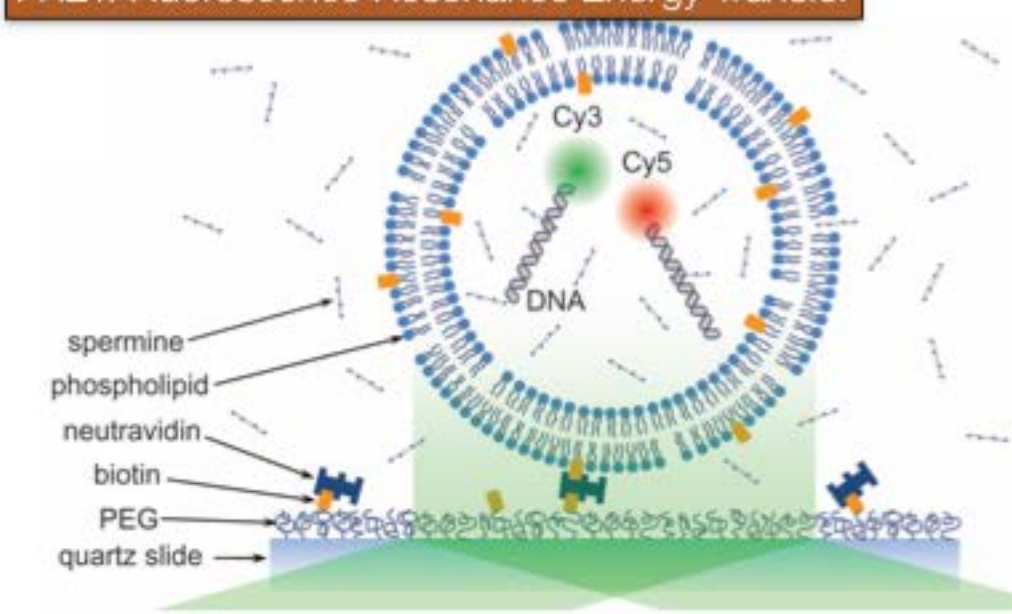
Attraction by sharing

Attraction by sharing

JY*, Kim*, Aksimentiev & Ha, *Nature Communications* (2016)

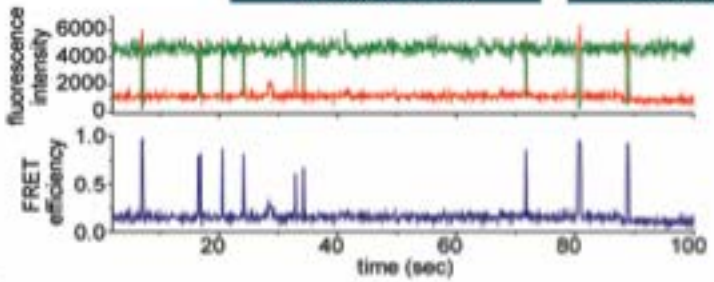
FRET experiment confirms the prediction

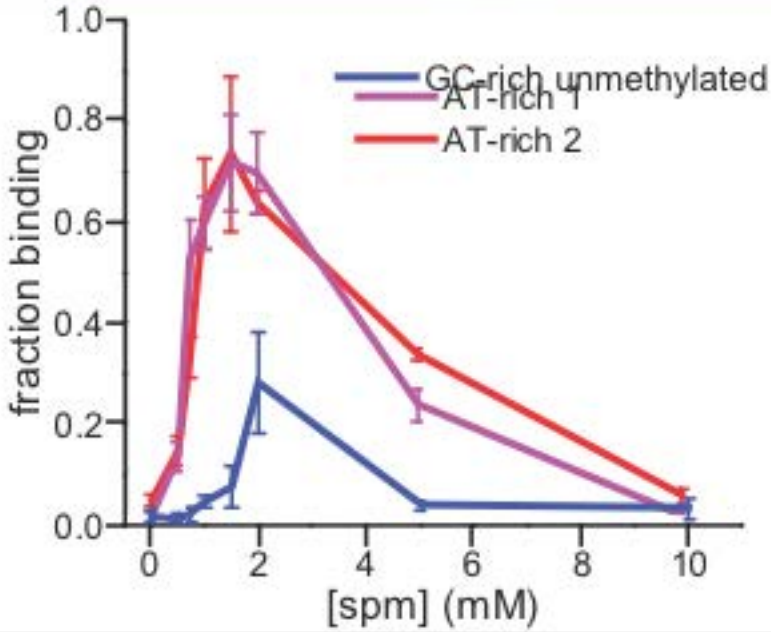
FRET: Fluorescence Resonance Energy Transfer

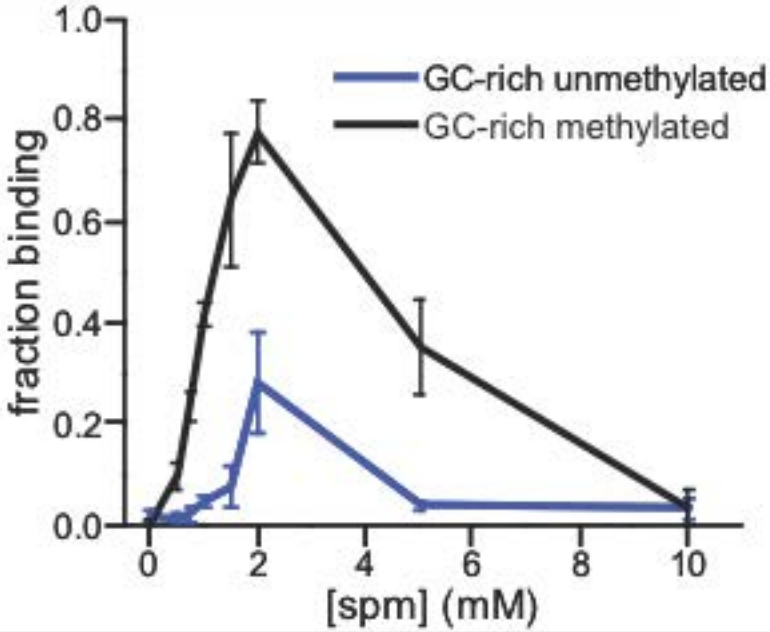


Hajin Kim

Taekjip Ha





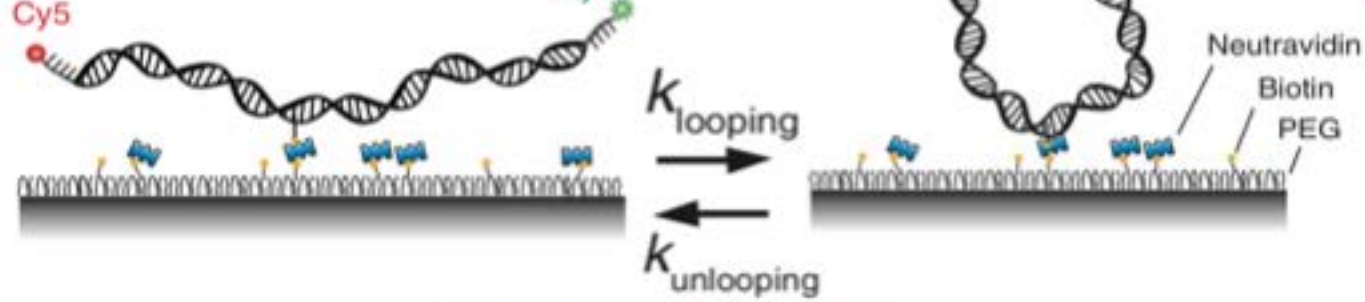


Cytosine modifications can increase or decrease DNA flexibility depending on modification types

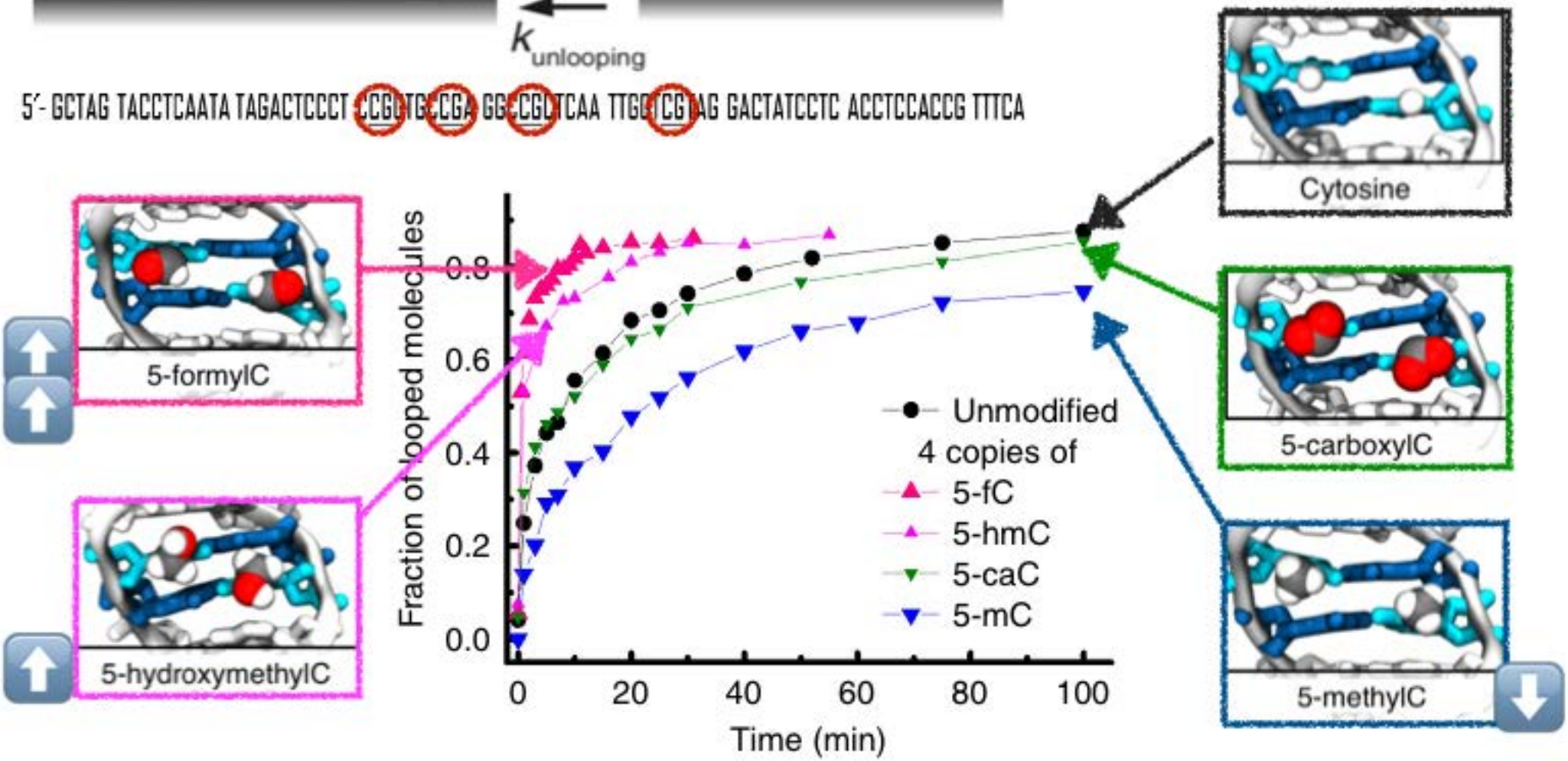
Thuy Ngo

Taekjip Ha

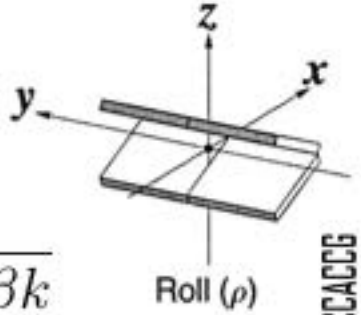
Thuy Ngo | Taekjip Ha



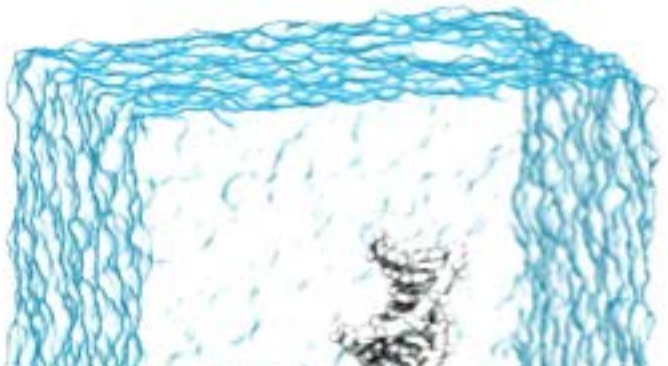
5′- GCTAG TACCTCAATA TAGACTCCCT CCGCTGCCGA GGCCGCGTCAA TTGGTCGTAG GACTATCCTC ACCTCCACCG TTTCA

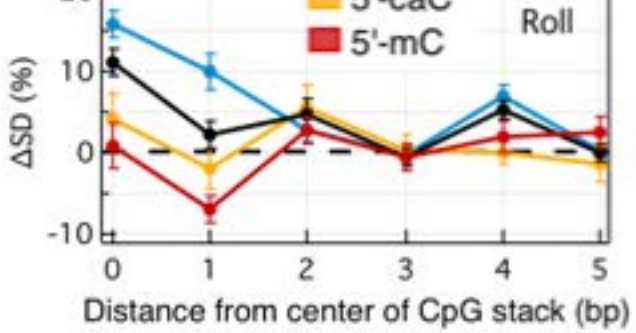


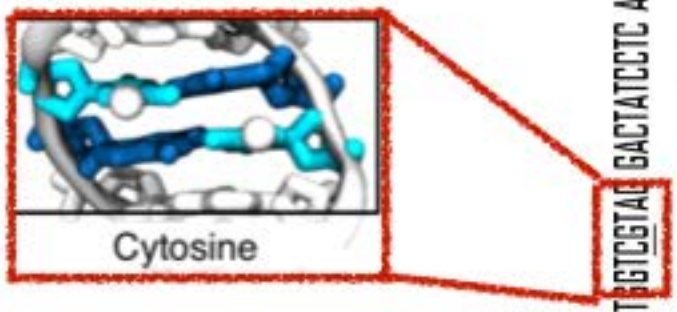
CYT modifications change local flexibility of DNA

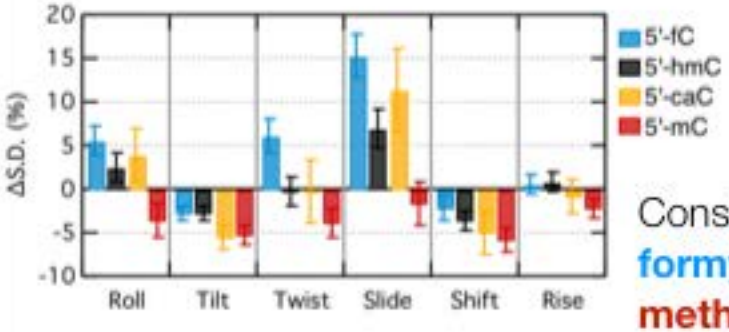


$$\mathrm{SD} = 1/\sqrt{\beta k}$$

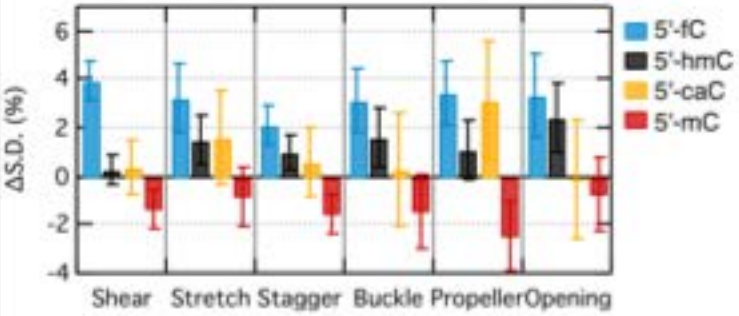


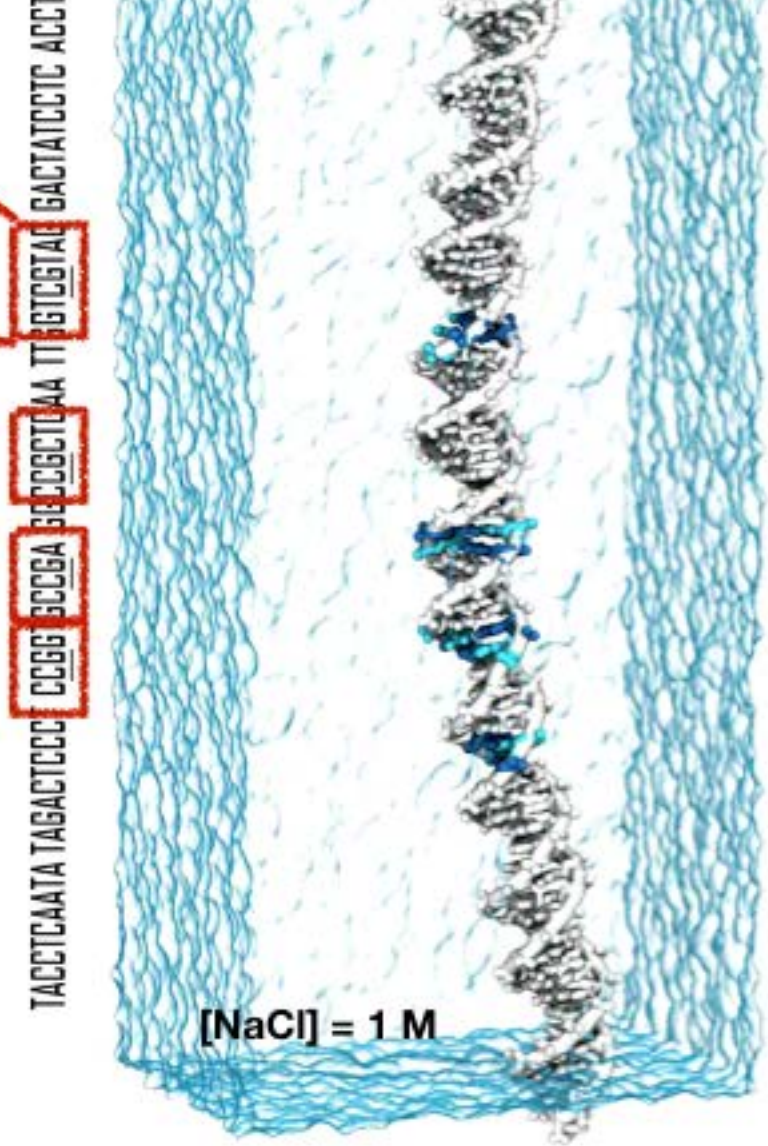






Consistent with the experiment,
formylC & **hmC** enhances flexibility
methylC reduces flexibility





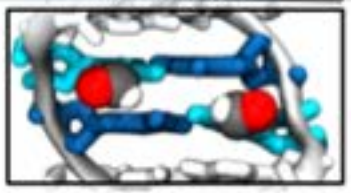
http://nar.oxfordjournals.org/content/31/17/5108/F1.large.jpg

Modification type	Hydrophobic ⬇	Polarity ⬆	⊖ Charge ⬇	Overall
	Yes ⬇⬇	N/A		⬇⬇

5-methylC

Yes ⬇⬇

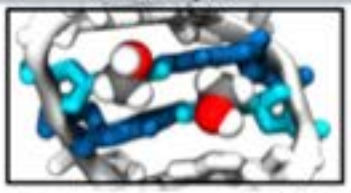
N/A



5-formylC

Yes ⬆⬆

N/A

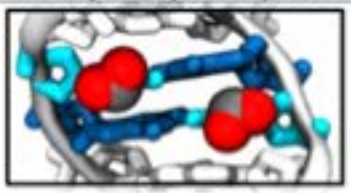


5-hydroxymethylC

Yes ⬇

Yes ⬆⬆

N/A

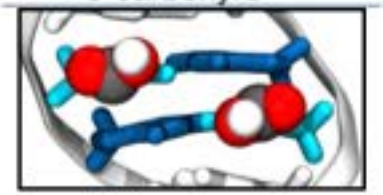


5-carboxylC

Yes ⬆⬆

⬇⬇

Cancel out



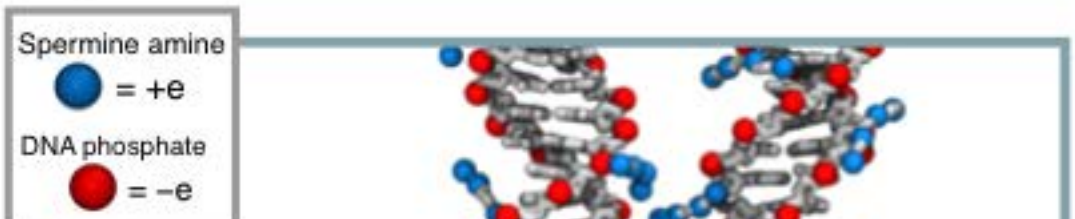
5-HcarboxylC

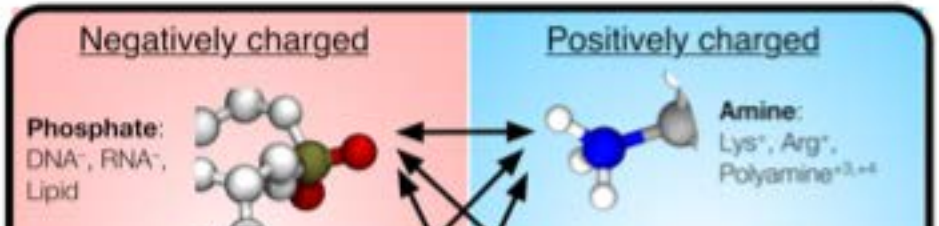
Yes ⬆⬆

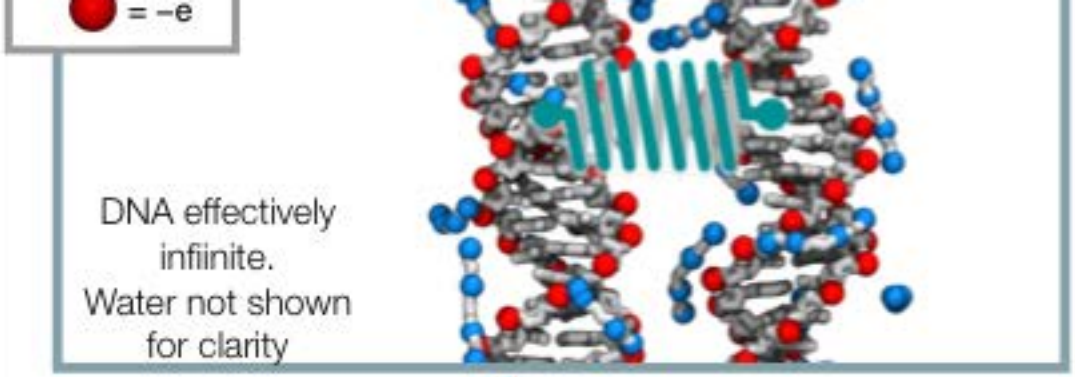
N/A

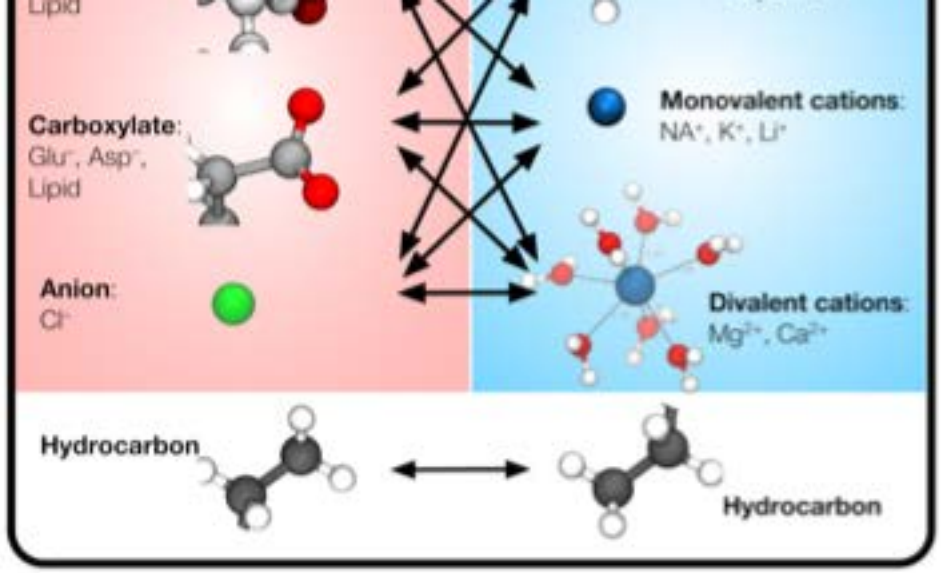
CUFIX: Champaign-Urbana nonbonded FIX for CHARMM and AMBER

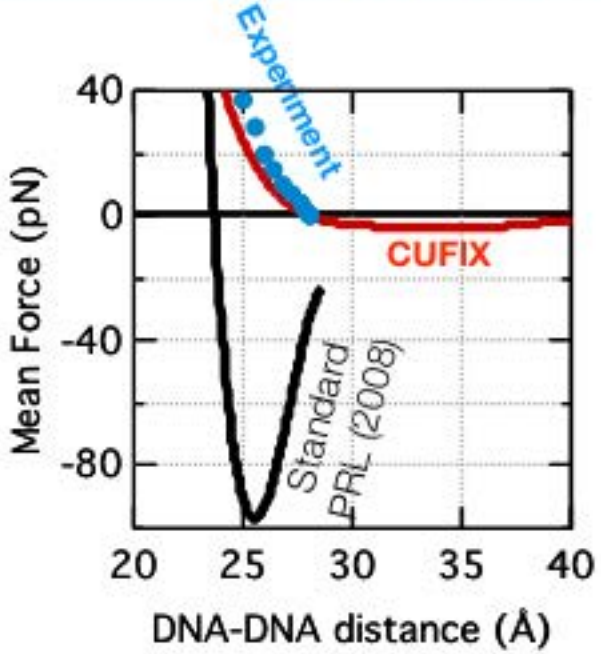
http://bionano.physics.illinois.edu/CUFIX











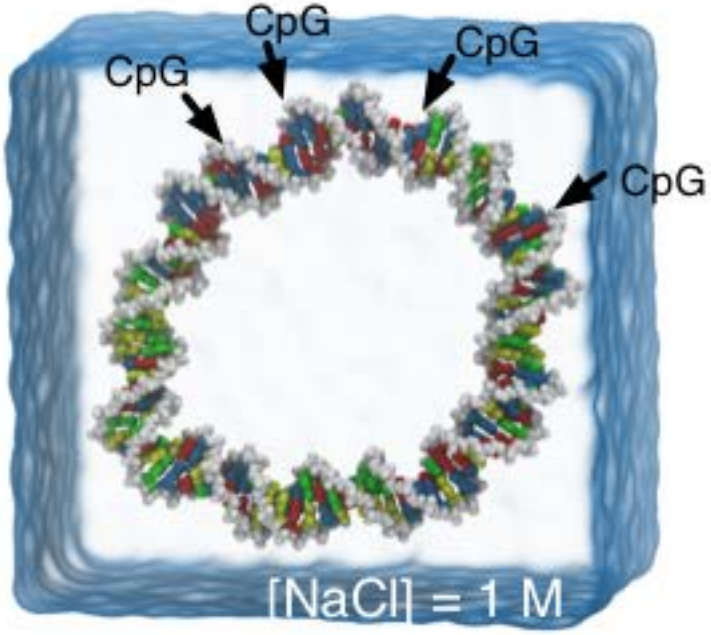
- **CUFIX** improves MD simulations:
  - Protein folding
  - DNA–protein interactions
  - Lipid–protein interactions etc.
- Extensive validations using BW revealed **only improvements**.

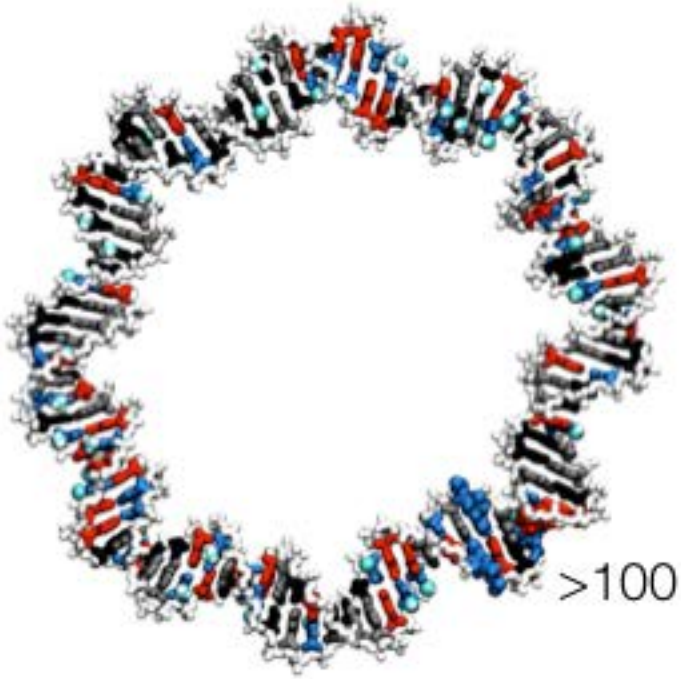
CUFIX: **JY** & Aksimentiev, JCTC (2016) & NAR (2016)

Why Blue Waters?

- By combining the state-of-the-art model and the power of Blue Waters, we could predict previously unknown mechanisms of DNA–DNA attraction and DNA flexibility.

- Extensive validation using Blue Waters helped us develop the improved model for the community.
- Using Blue Waters, we are computing the genome-wide profile of DNA flexibility.





>100 different sequences
~10 μs each

Acknowledgements

- Funding through CPLC

NSF

Center for the Physics of Living Cells

of Living Cells

- Computations

BLUE WATERS
SUSTAINED PETASCALE COMPUTING

XSEDE
Extreme Science and Engineering Discovery Environment

- Prof. Taekjip Ha at JHU & collaborators


Taekjip Ha


Hajin Kim


Thuy Ngo

- Prof. Aleksei Aksimentiev & his group members at UIUC


Aleksei Aksimentiev


Chris Maffeo