Dynamic Coupling among Protein Binding, Sliding, and DNA Bending Revealed by Molecular Dynamics

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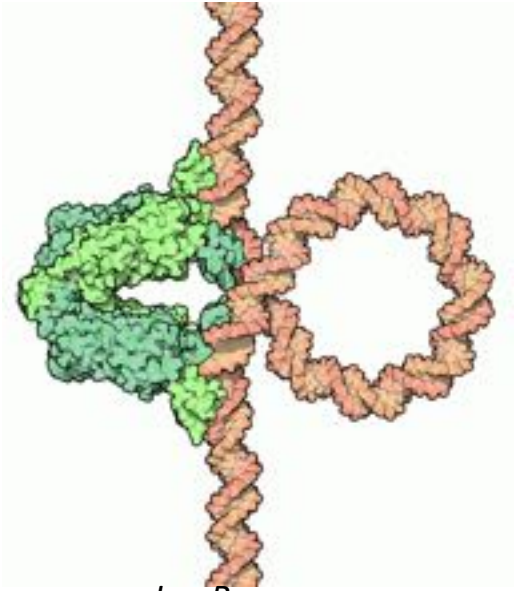
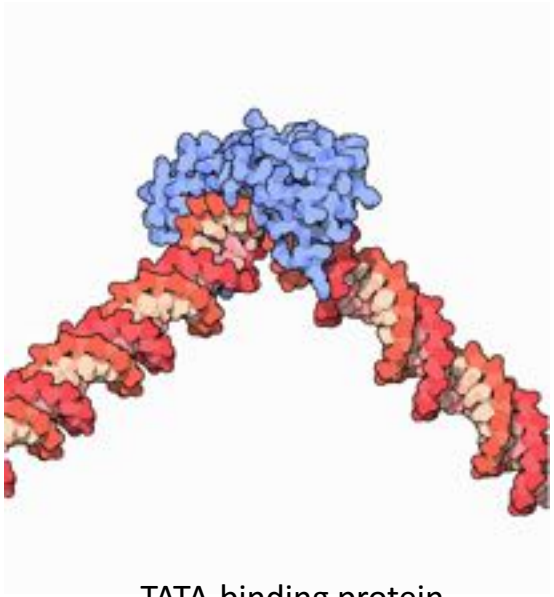
2017-03-15

Introduction

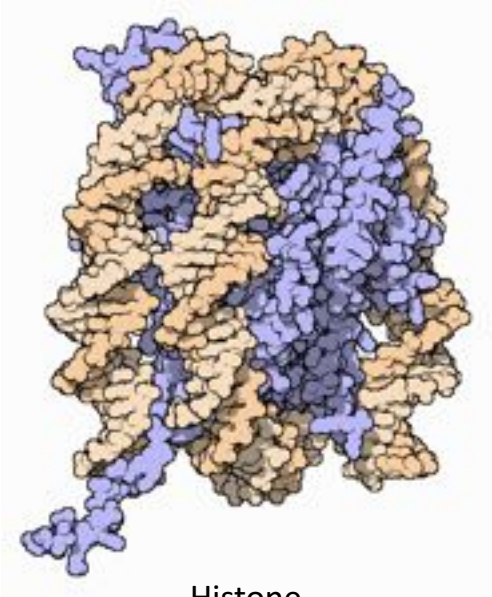
- Protein binding changes DNA shape.



Lac Repressor



TATA-binding protein

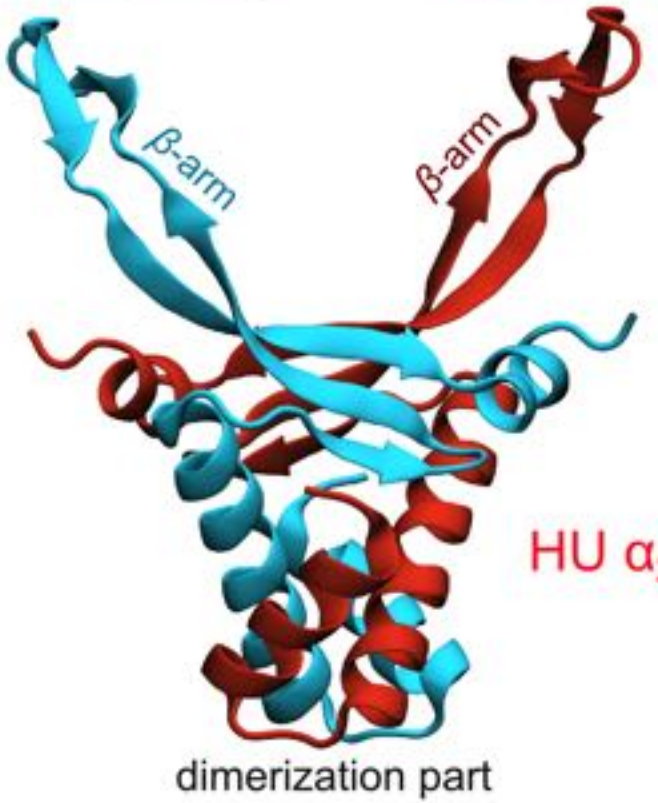


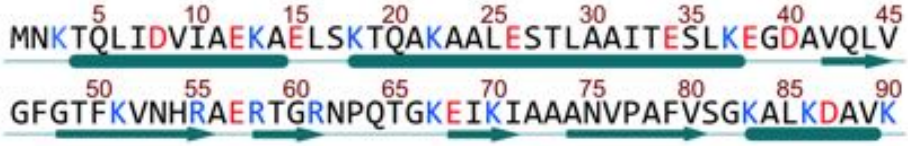
Histone

- (Local) DNA bending modulates protein diffusion?
  Focus: sequence-non-specific interactions between protein and DNA

Introduction

- HU: one of the most abundant "architectural" proteins

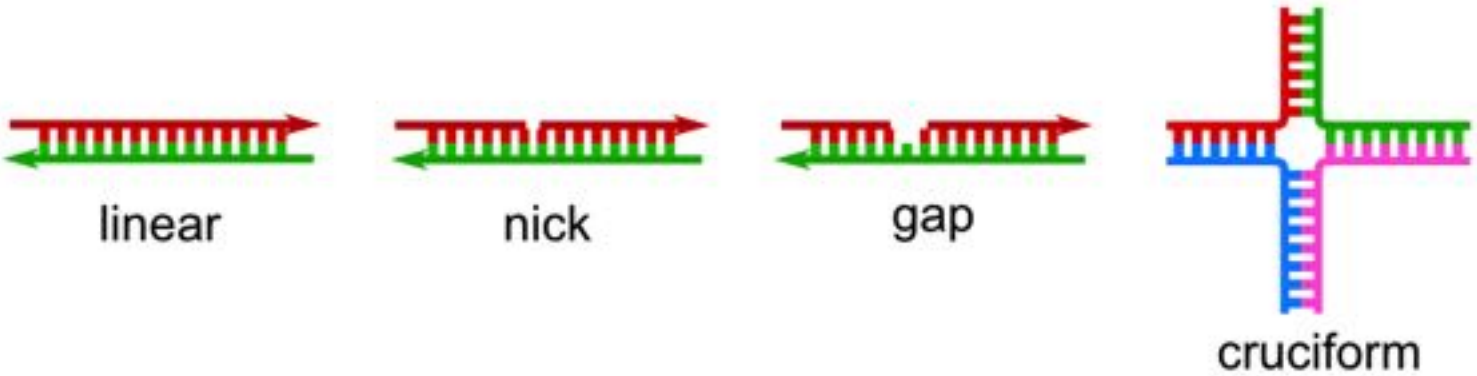




HU α_2 homodimer

Introduction

- HU-DNA binding specificity:
  Sequence: Slight preference for A/T-rich DNA.
  Structure: Strong preference for cruciform or gap/nick.

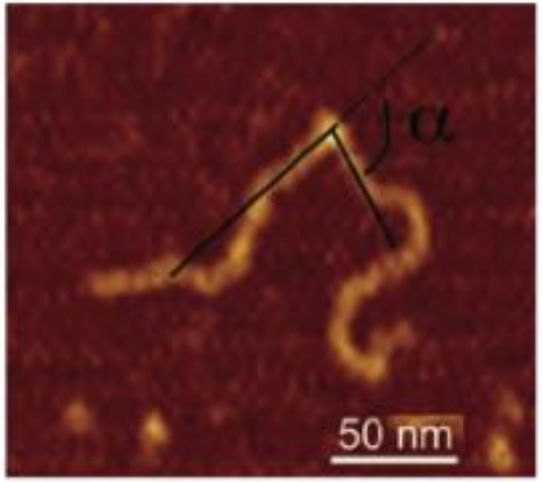


	linear	nick	gap	cruciform
K_d (nM)	9000	40.0	11.0	25.0

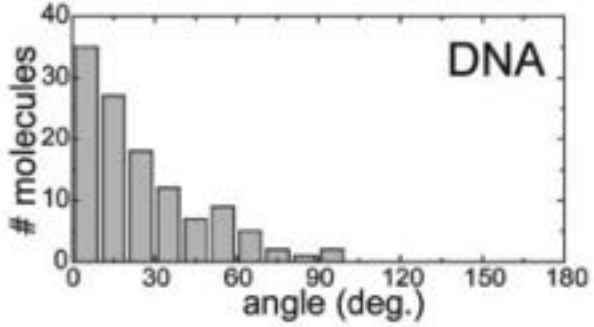
Prieto, A. I. *et al.* (2012) *Nucleic Acids Res.* **40**, 3524.
Pinson, V. *et al.* (1999) *J. Mol. Biol.* **287**, 485.

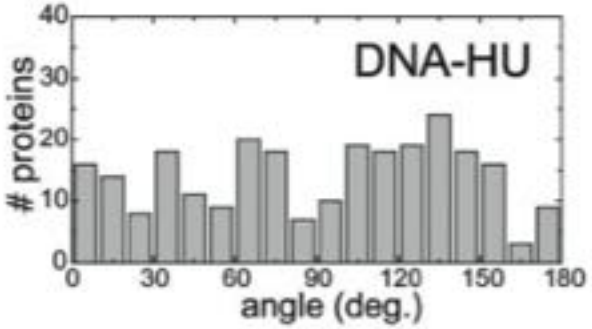
Introduction

- HU enhances DNA bending (AFM experiment)



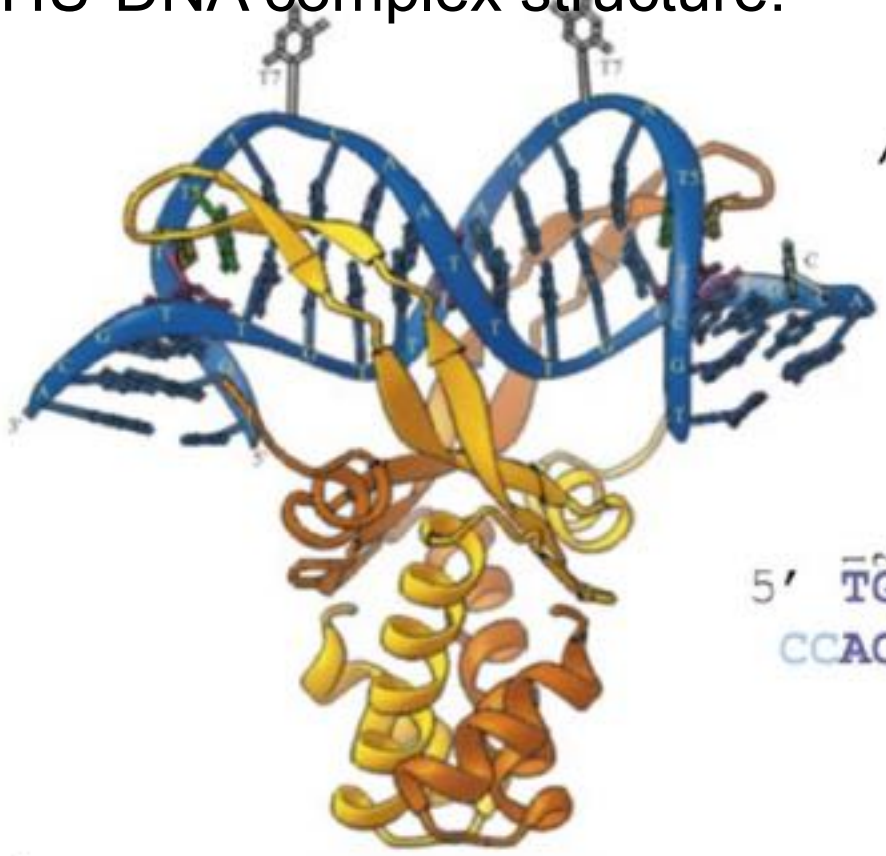
van Noort, J. *et al.* (2004)
Proc. Natl. Acad. Sci. **101**, 6969.





Introduction

- HU-DNA complex structure:



crystal structure of
Anabaena HU bound to DNA

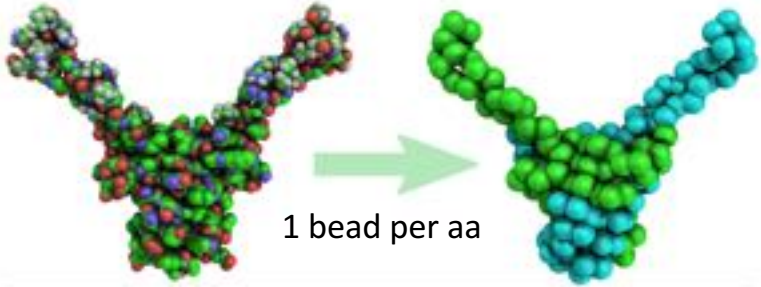
PDB: 1P71

Motivation

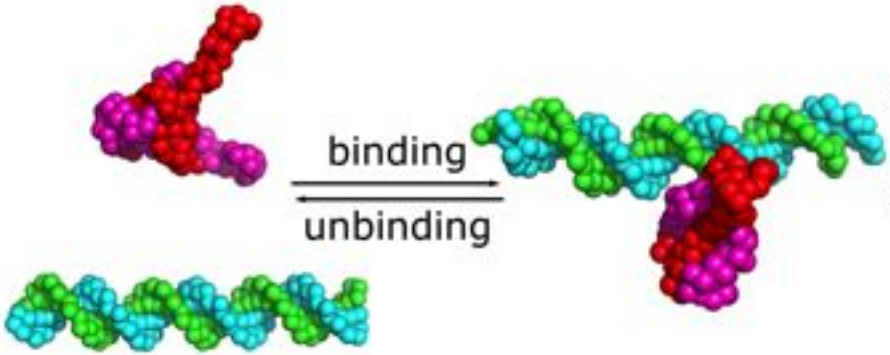
- Q1: How does HU bind to and slide on DNA?
- Q2: How does DNA conformation change in response to HU binding?
- Q3: What's the relationship between HU binding and DNA conformational change?

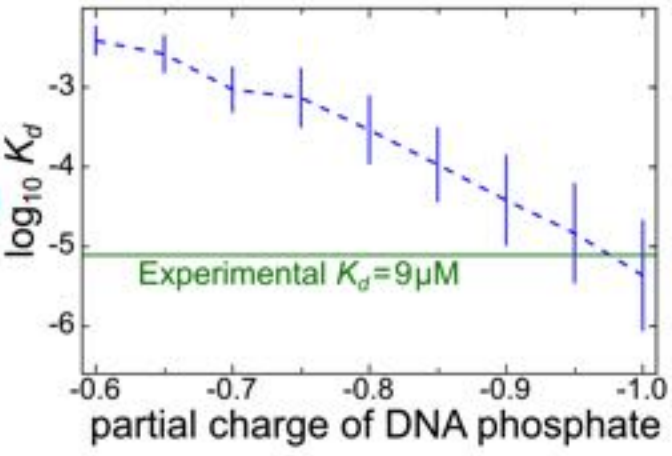
Coarse-Grained Models and Methods

- CG Protein: AICG2+
  W. Li *et al.* (2014) *PNAS*.
- DNA: 3SPN.2C
  Sequence dependent properties
  G. Freeman *et al.* (2014) *JCP*.



- Intermolecular interactions:
  electrostatic + excluded volume





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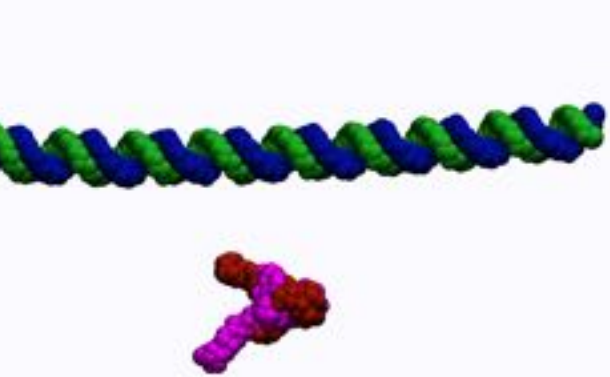
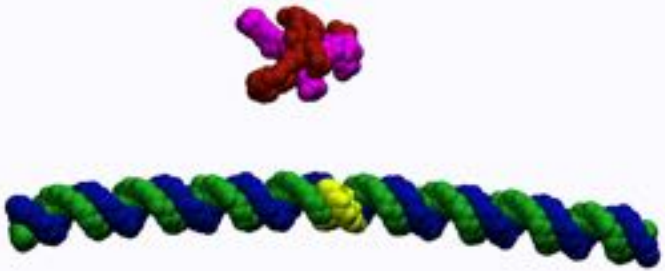
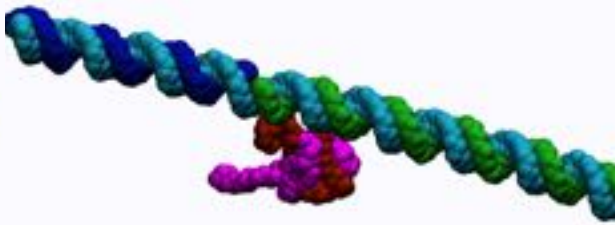
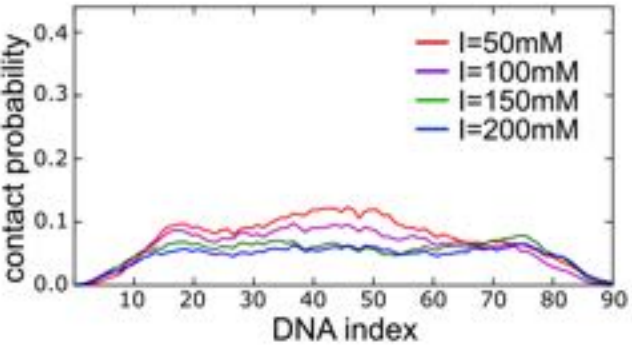
HU Prefers A/T Rich and Gapped Region

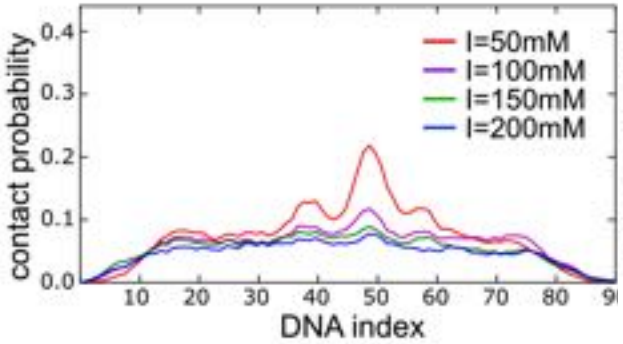
- Purely C/G
- A/T region at center
- Gap at index 36

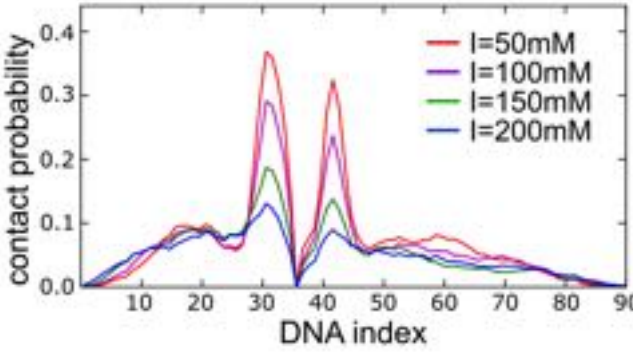












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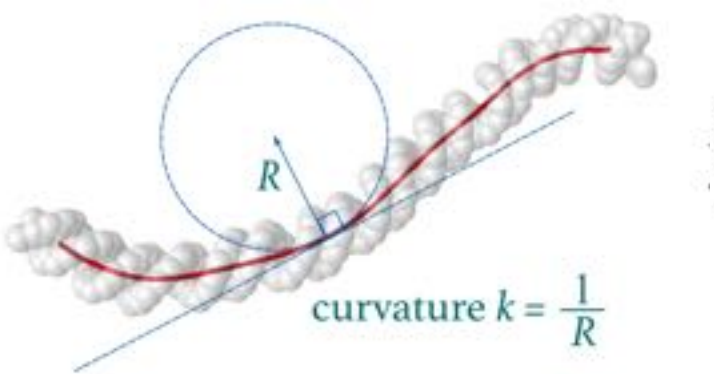
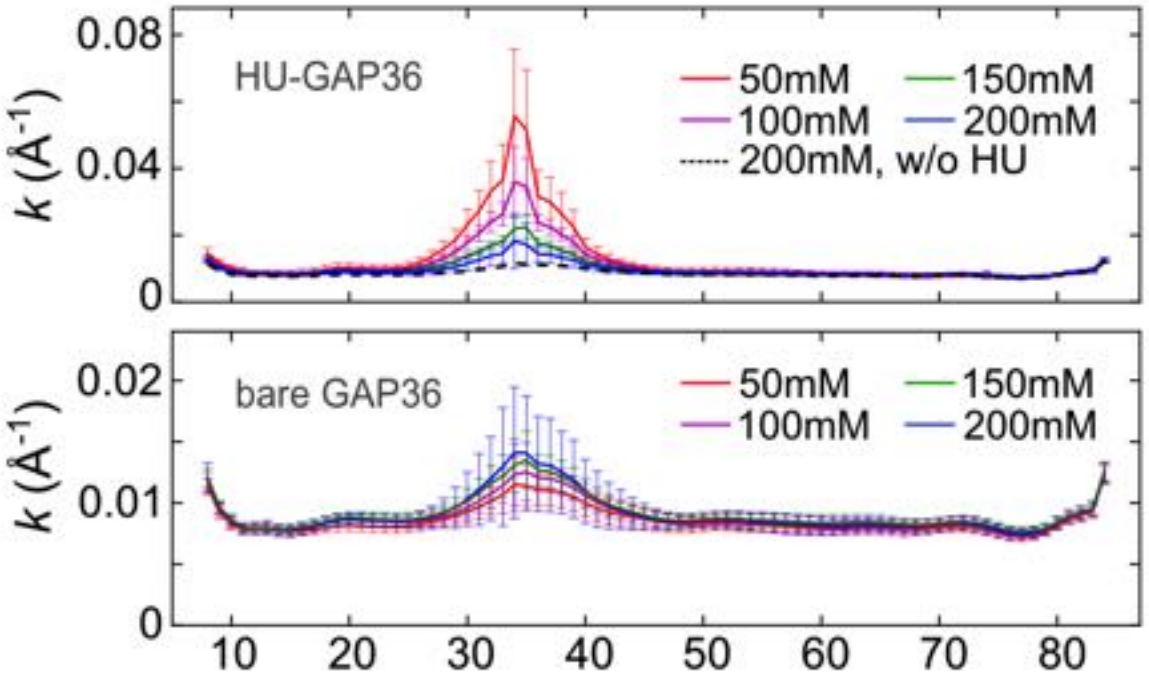
HU Enhances Bending of Gapped DNA





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HU Binding & DNA Bending

- Q1: How does HU bind to and slide on DNA?
  - A1: HU prefers more bendable DNA structure
- Q2: How does DNA conformation change in response to HU binding?
  - A2: HU binding statistically facilitates DNA bending
- Q3: What's the relationship between HU binding and DNA conformational change?

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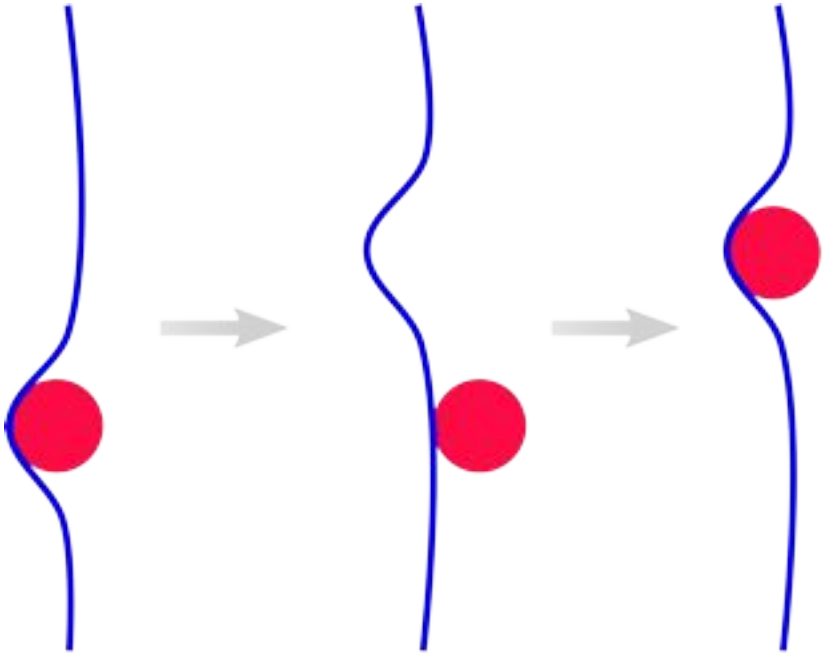
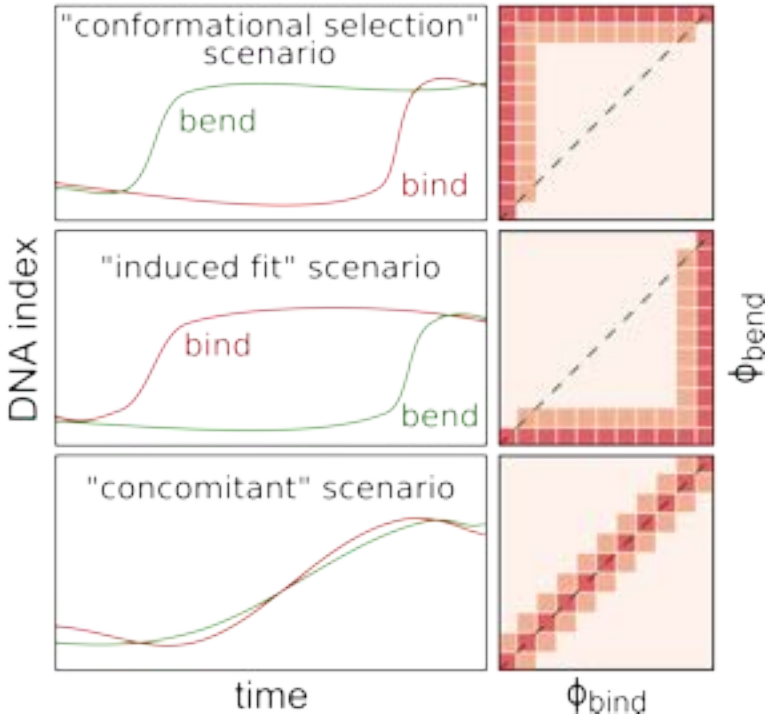
Scenarios of Different Mechanism



“Conformational selection”



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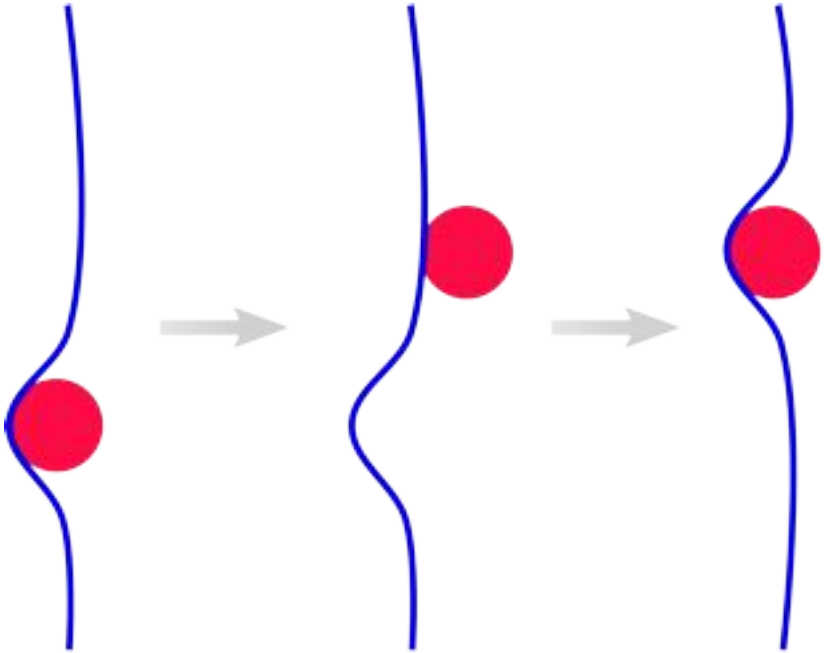
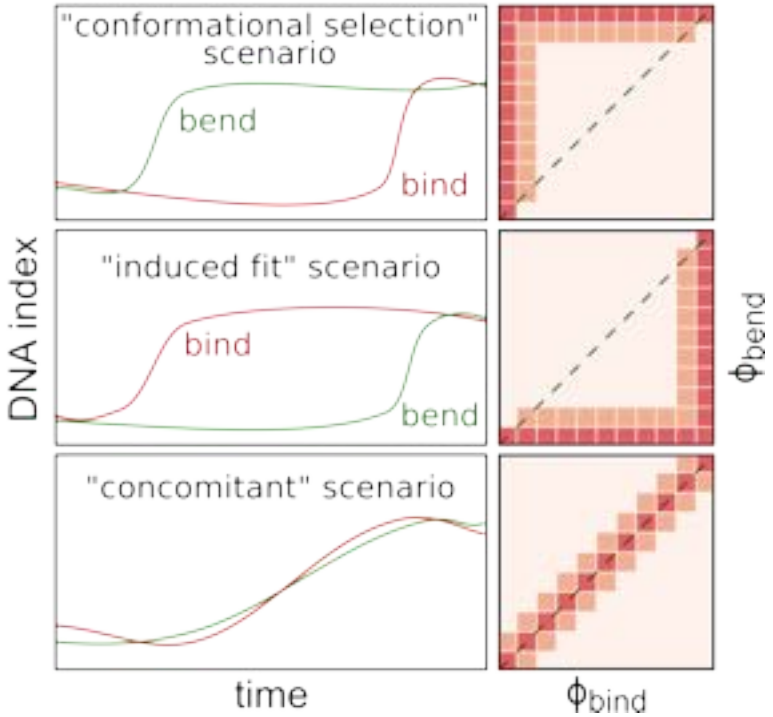
Scenarios of Different Mechanism



“Induced fit”



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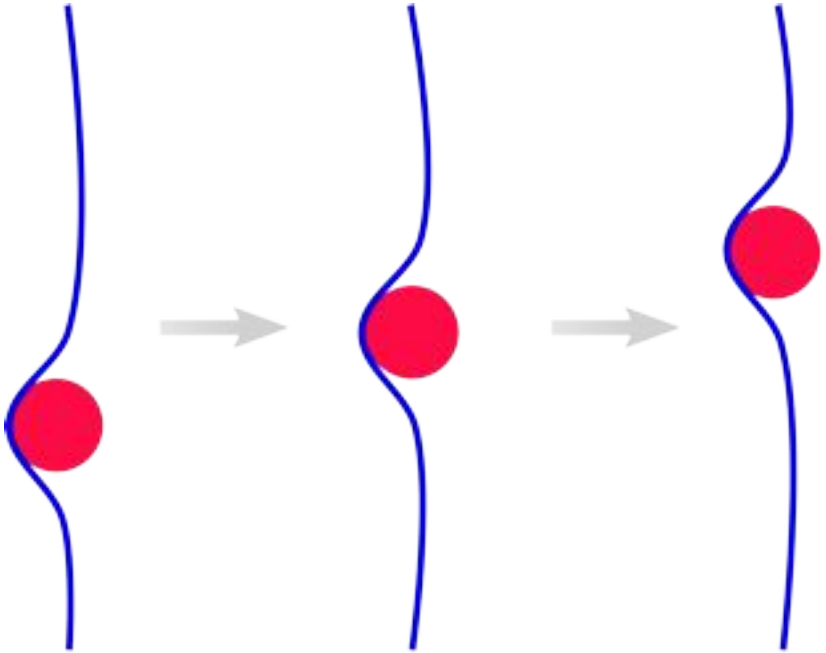
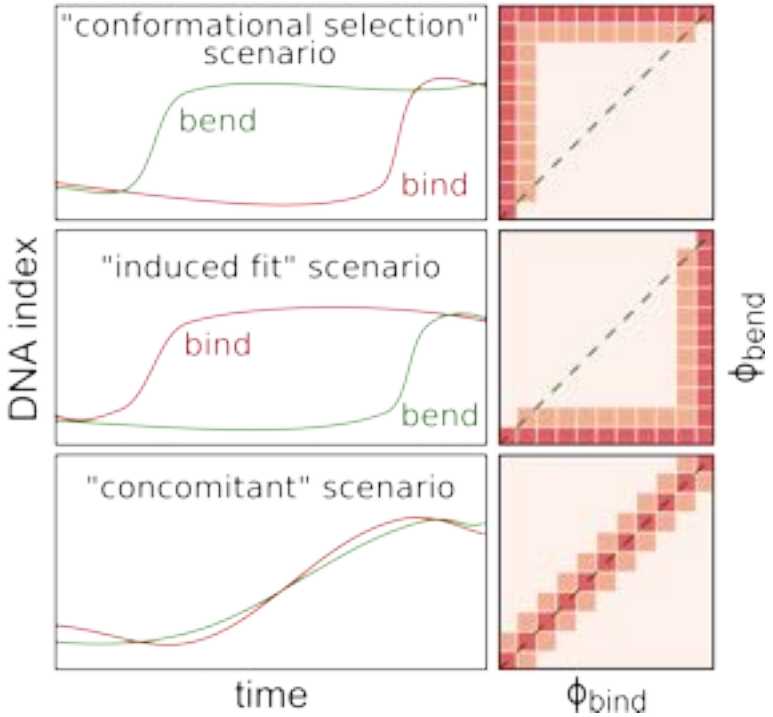
Scenarios of Different Mechanism



“Concomitant”



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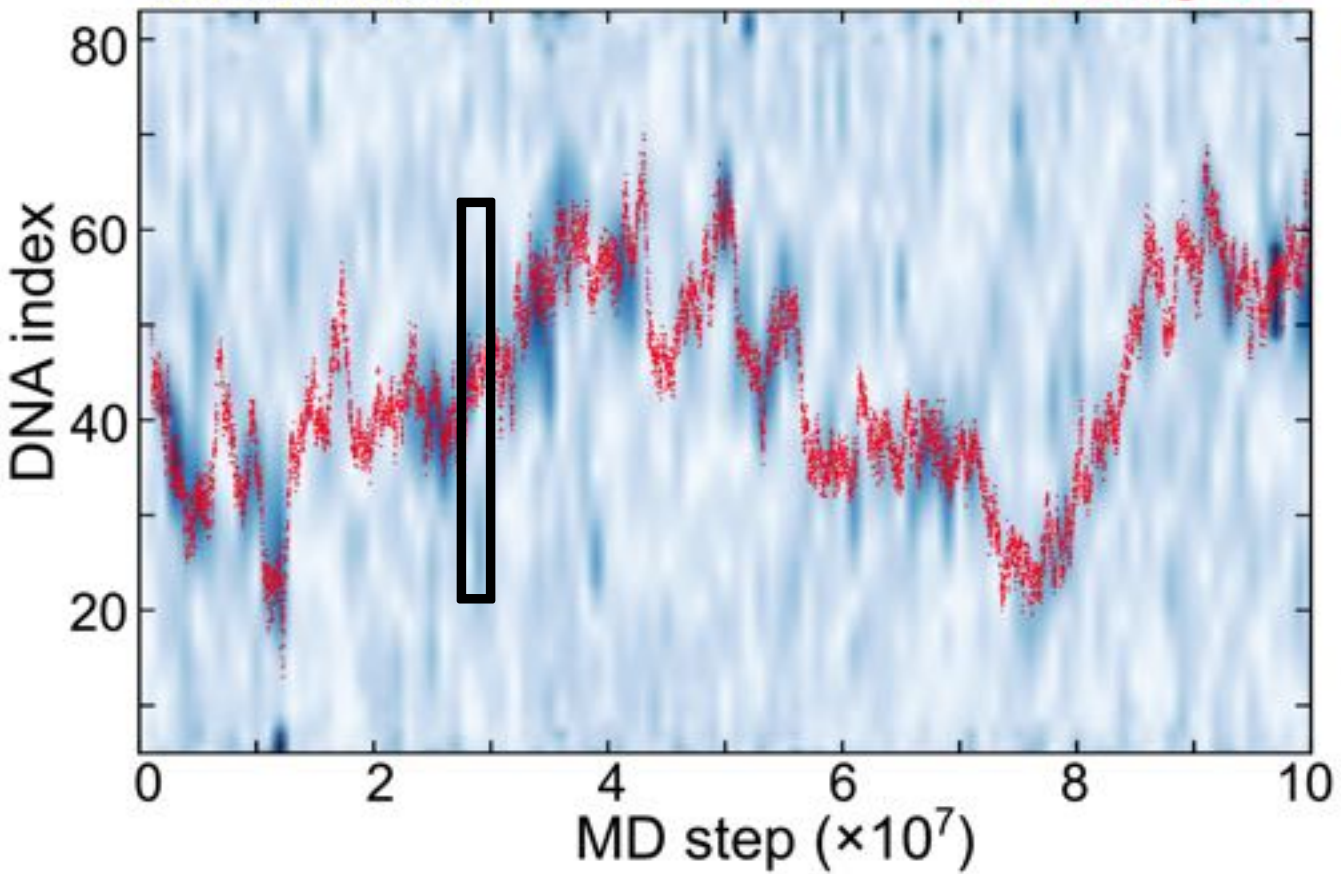
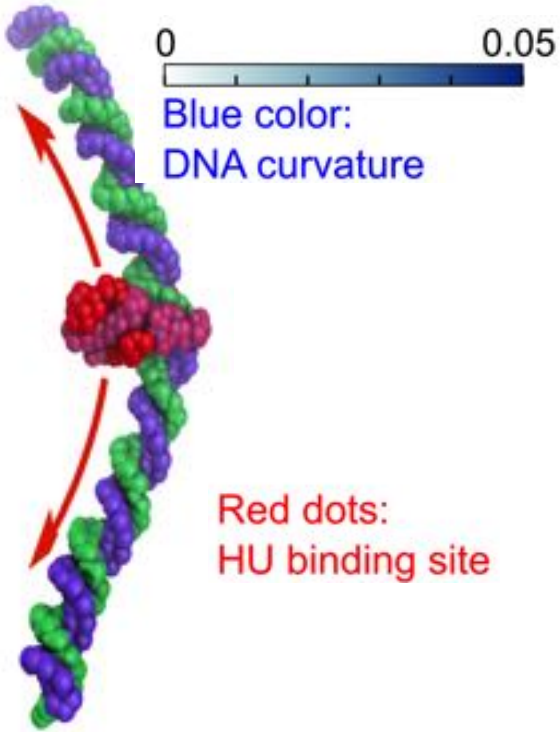
Coupling of HU Binding and DNA Bending





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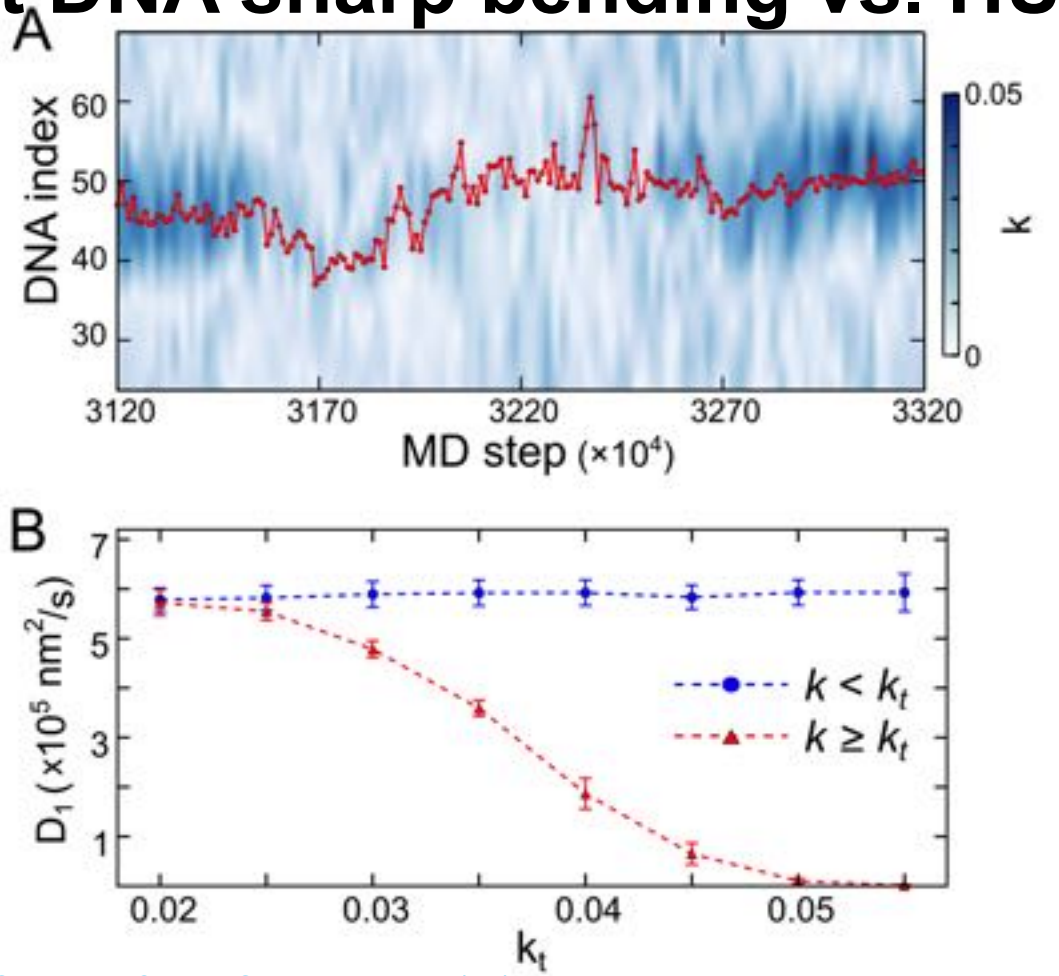
Transient DNA sharp bending vs. HU sliding



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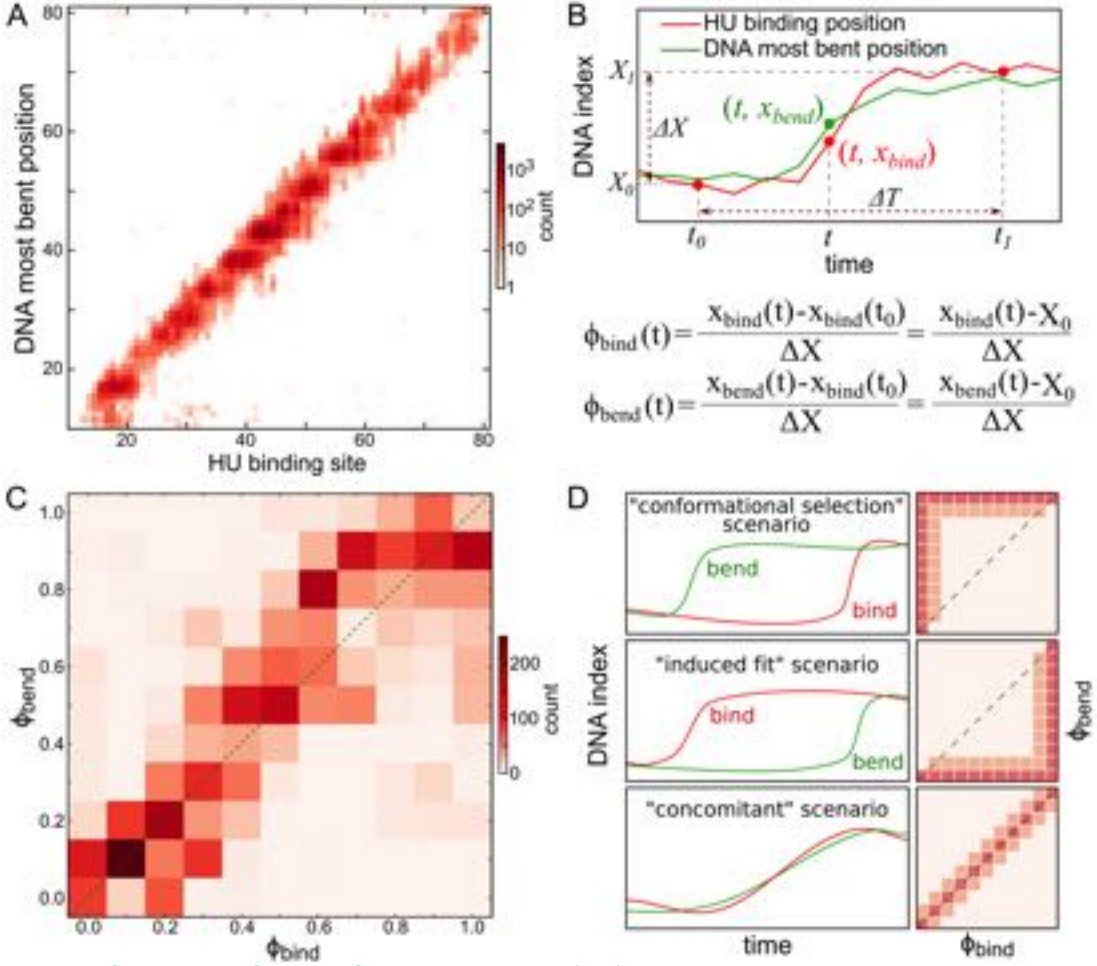
Dynamic Coupling between Binding and Bending



$$\phi_{bind}(t) = \frac{x_{bind}(t) - x_{bind}(t_0)}{\Delta X} = \frac{x_{bind}(t) - X_0}{\Delta X}$$

$$\phi_{bend}(t) = \frac{x_{bend}(t) - x_{bind}(t_0)}{\Delta X} = \frac{x_{bend}(t) - X_0}{\Delta X}$$

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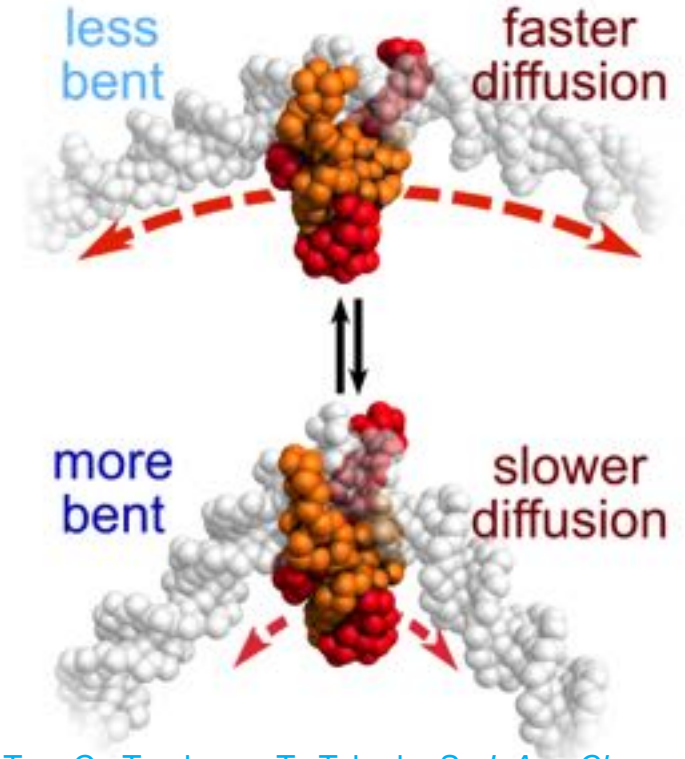
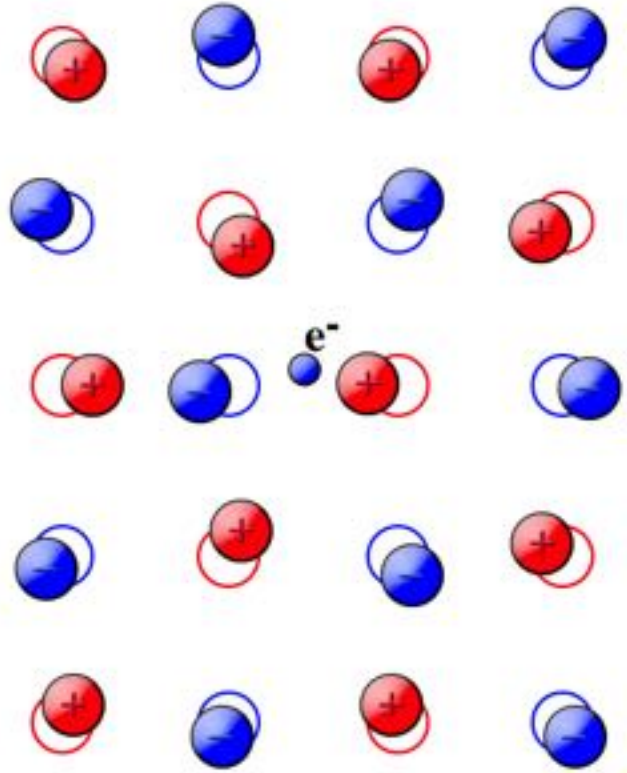
Relation between protein binding and DNA bending

- **Binding-induced-bending-regulated-sliding?**



Polaron-like diffusion?



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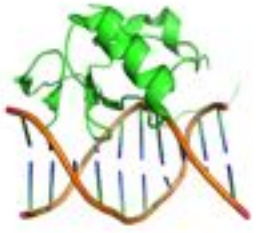
More examples

1a1l
+4 (+6)
29

1ca6
+6 (+18)
66

1gcc
+7 (+13)
63

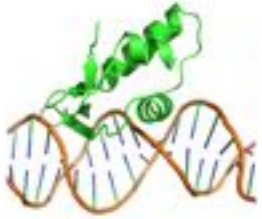


3kde
+12 (+15)
74

1if1
+6 (+18)
105

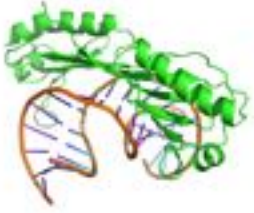
1gat
+11 (+13)
60

1srs
+19 (+30)
164



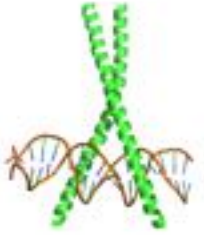
1dp7
+6 (+11)
76

1nk3
+13 (+18)
63



1cdw
+16 (+29)
179

1bc8
+9 (+15)
93



1nwq
+14 (+34)
120

1mdy
+19 (+33)
127

1ihf
+8 (+36)
190

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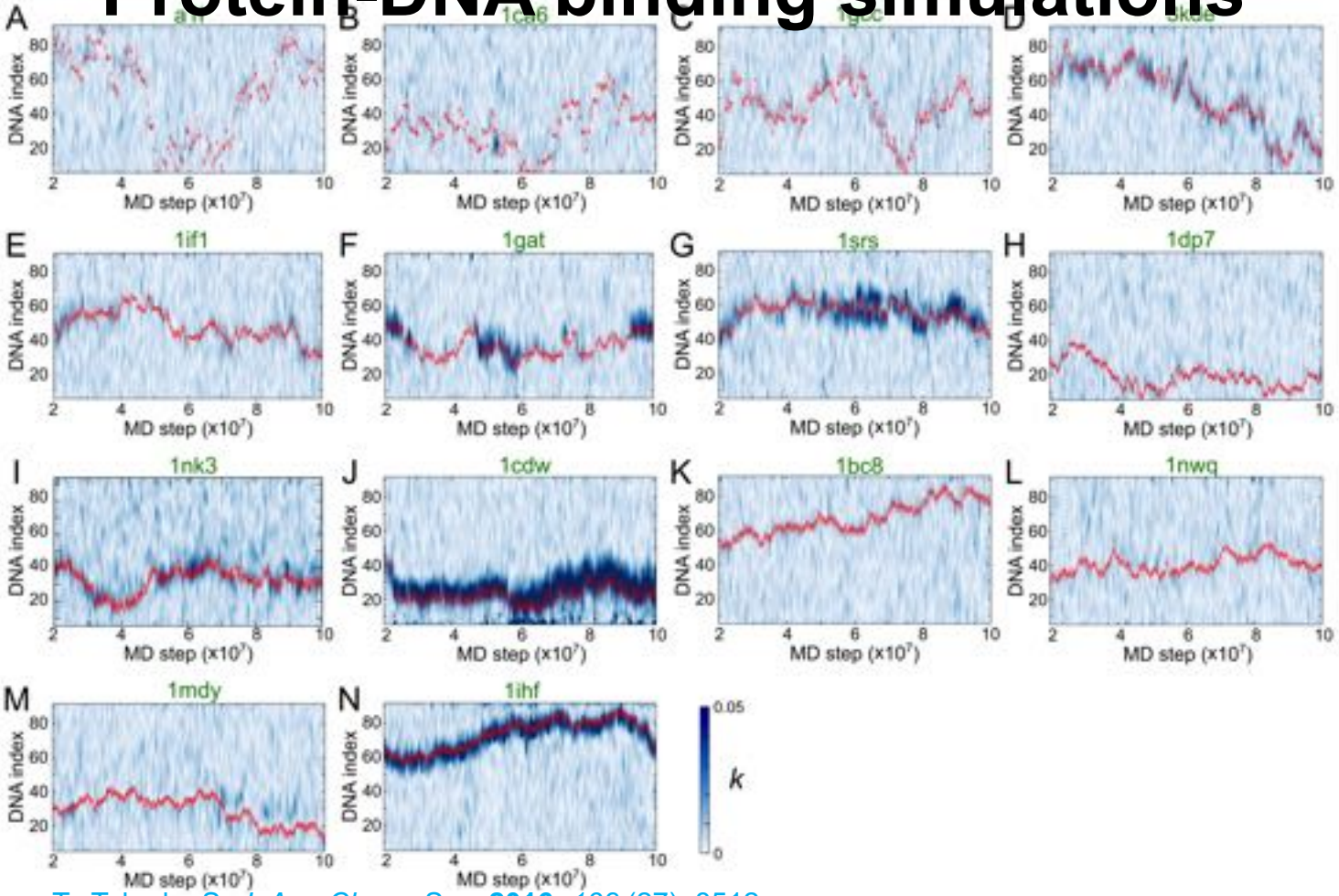
Protein-DNA binding simulations



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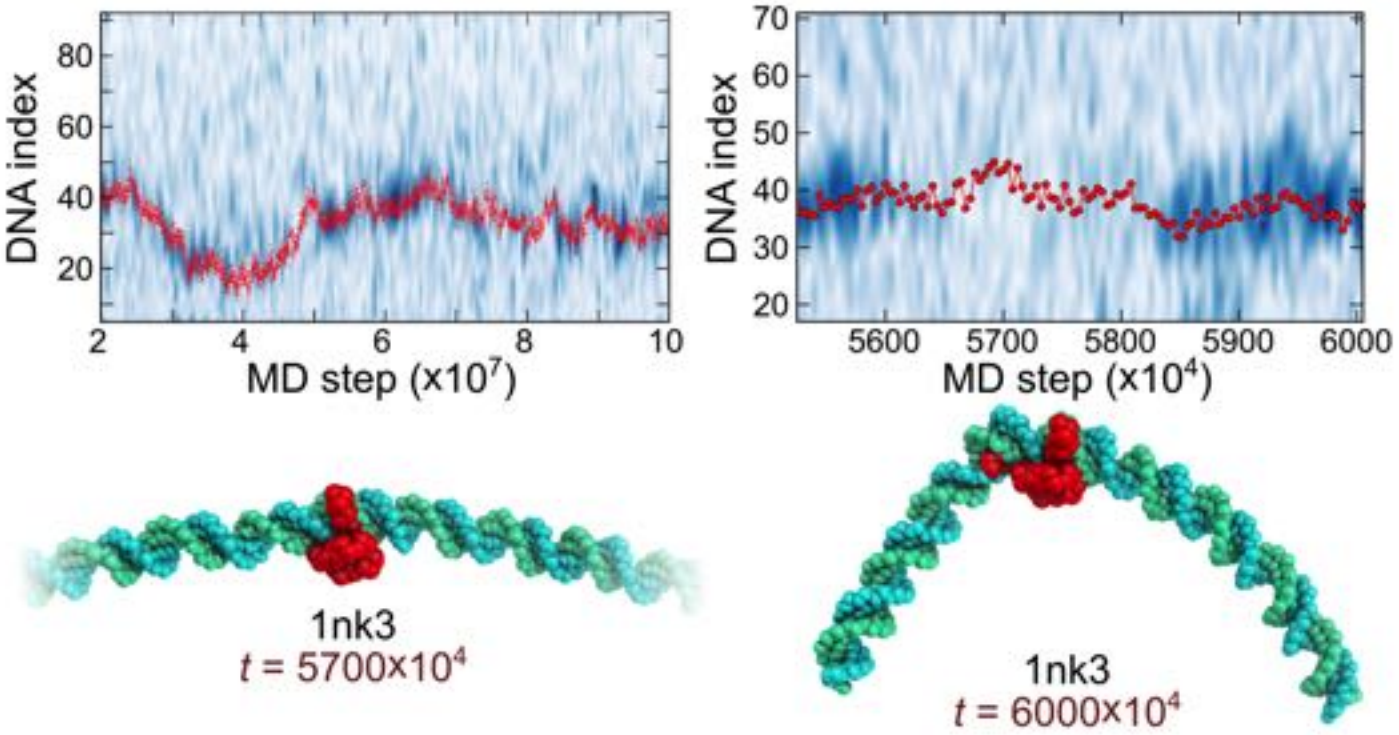
DNA bending and protein binding of 1nk3 (homeodomain)



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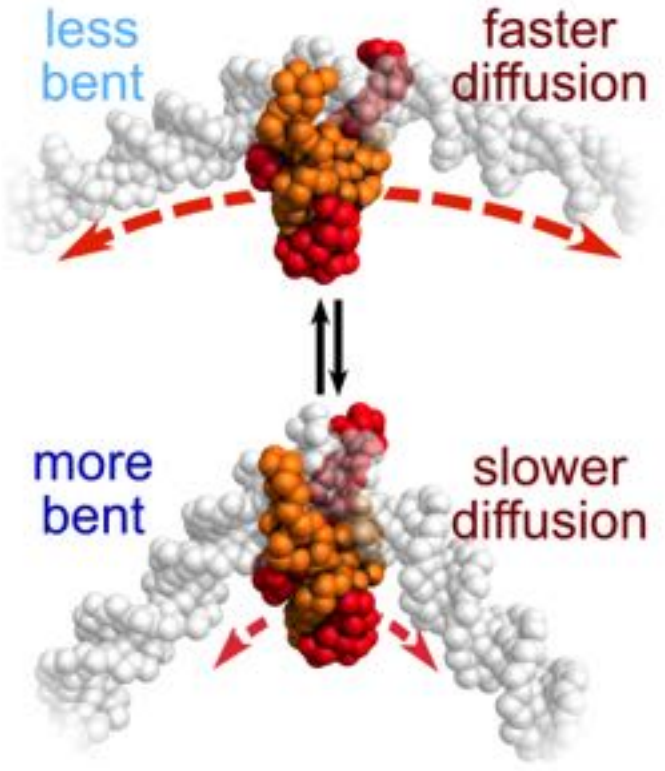
Conclusions

- Bendability of DNA affects the preference of HU binding.
- HU binding facilitates DNA bending; DNA bending modulates HU sliding.
- **Curvature of DNA affects protein diffusion speed.**
- **The “Polaron-like” sliding: protein moves together with the induced local bending of DNA.**



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Acknowledgements

- Dr. Hiroo Kenzaki
- Dr. Daniel Duzdevich
- Dr. Tsuyoshi Terakawa
- Prof. Shoji Takada

Thank you for your attention!

Molecule in a **Café** cup.

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