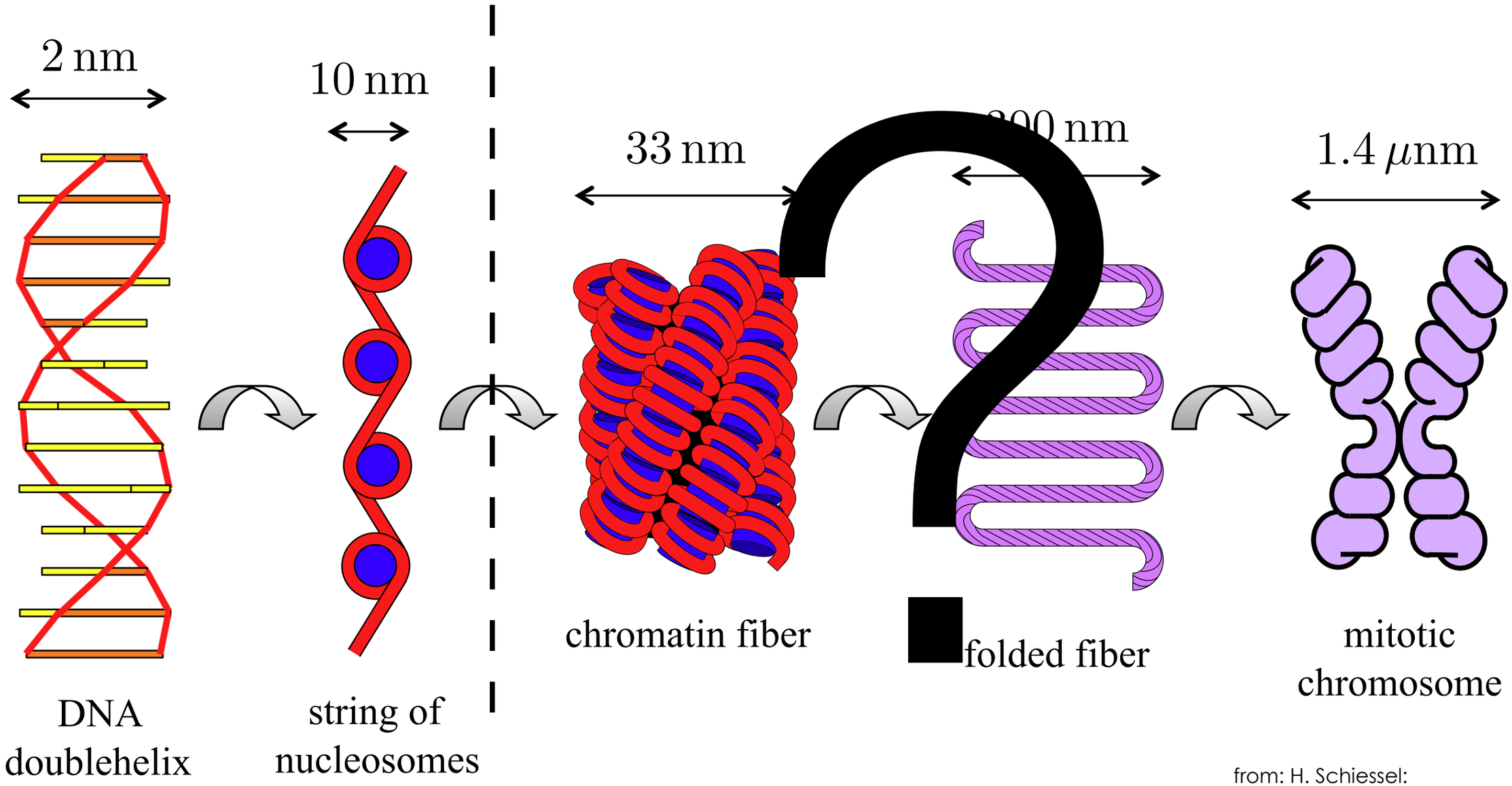
THE MECHANICAL GENOME

Helmut Schiessel
Lorentz Institute
Leiden University

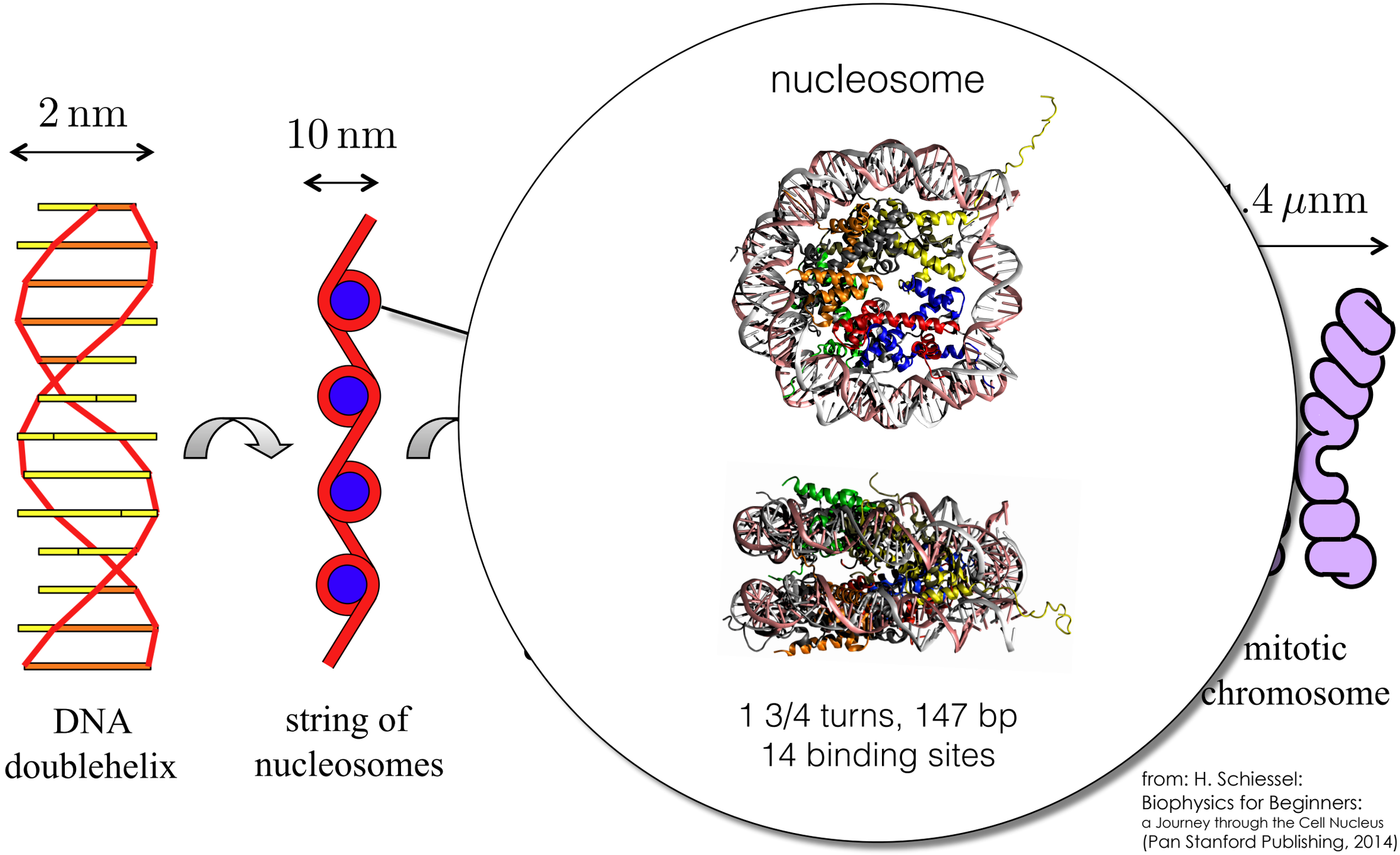
Artwork: Amar van Leewaarde & Marco Tompitak

The chromatin complex



from: H. Schiessel:
Biophysics for Beginners:
a Journey through the Cell Nucleus
(Pan Stanford Publishing, 2014)

The chromatin complex



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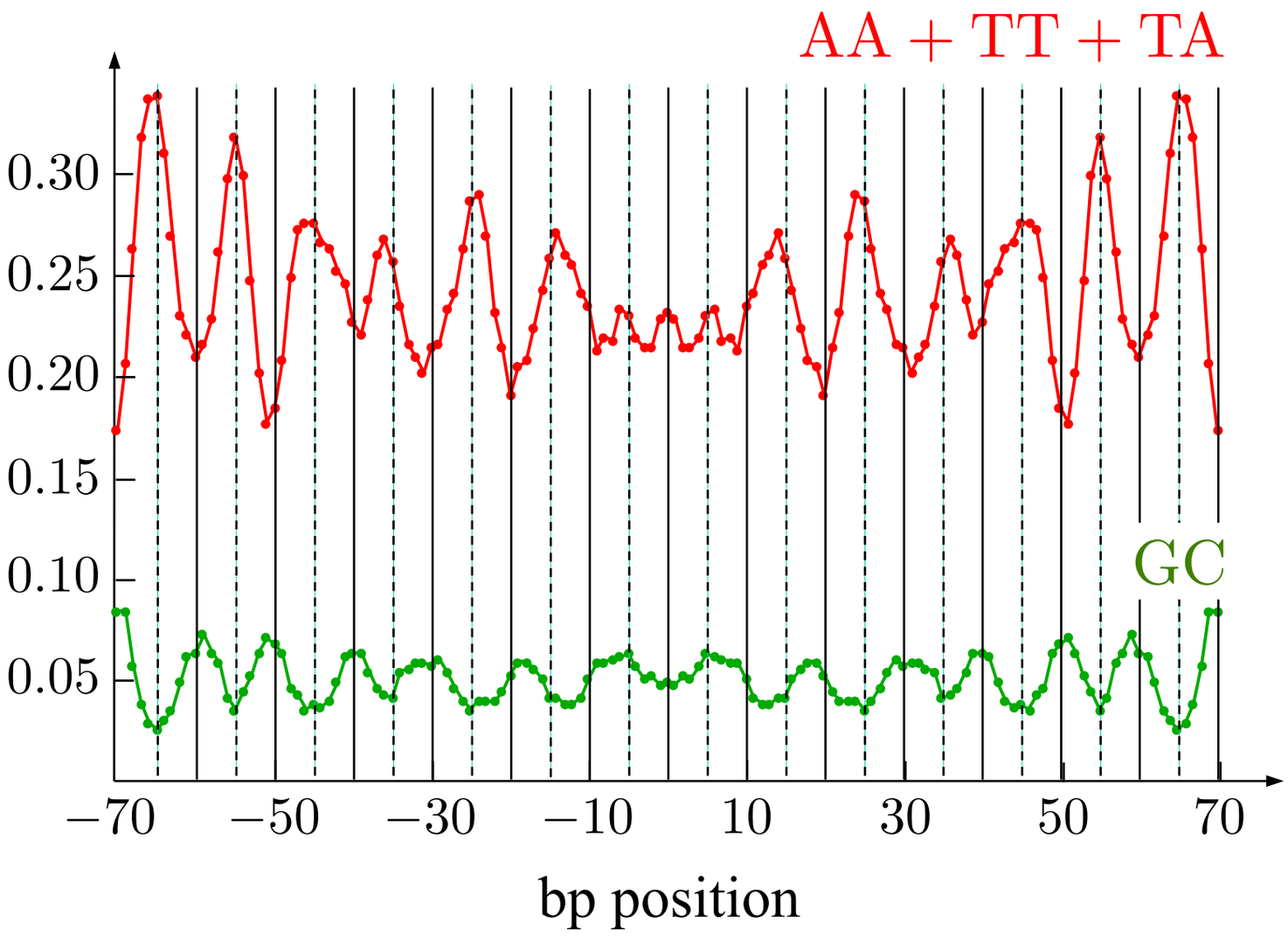
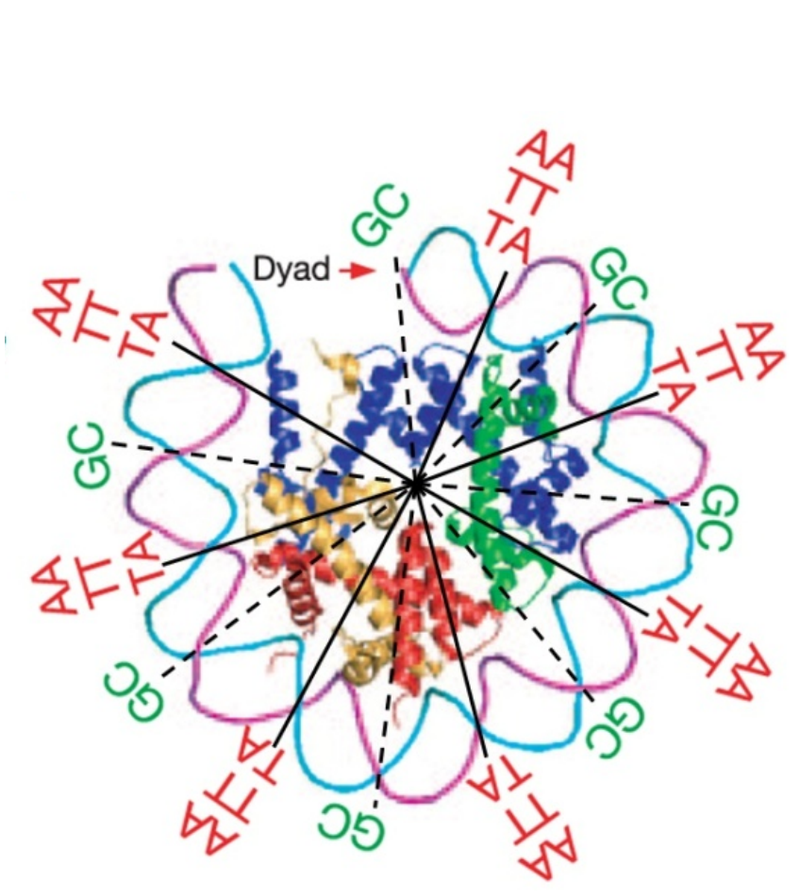
J. Mol. Biol. (1986) **191**, 659–675

Sequence Periodicities in Chicken Nucleosome Core DNA

Sandra C. Satchwell, Horace R. Drew and Andrew A. Travers

Medical Research Council
Laboratory of Molecular Biology
Hills Road, Cambridge CB2 2QH, England





Segal et al., Nature, 2006

J. Mol. Biol. (1986) **191**, 659–675

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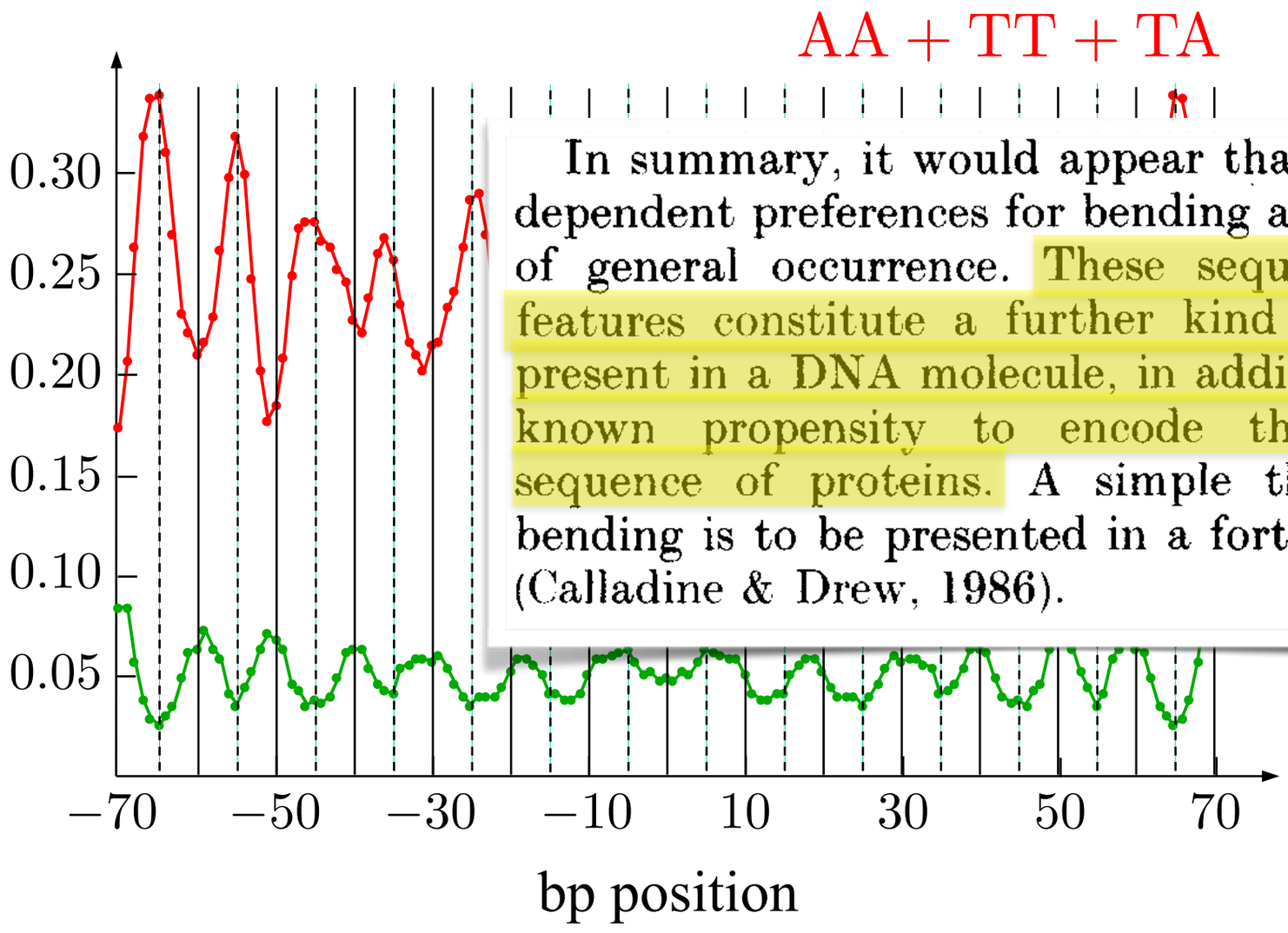
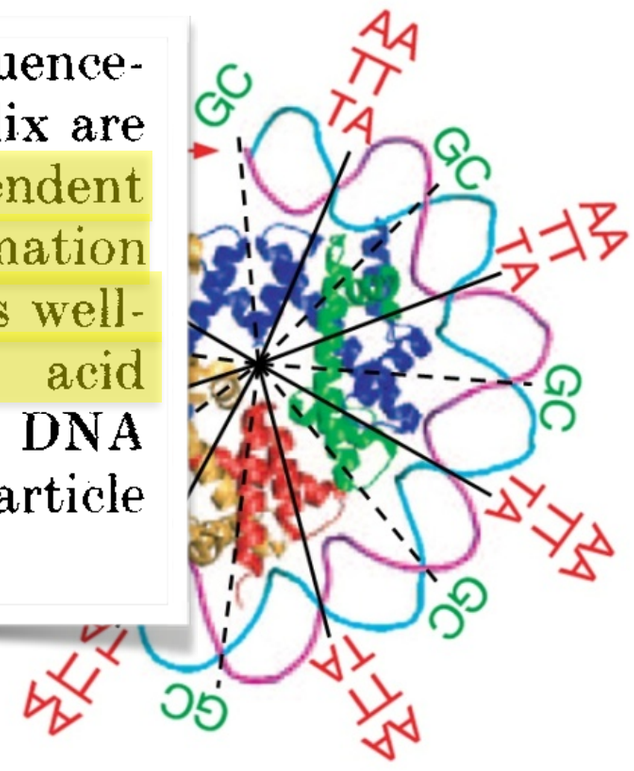


In summary, it would appear that the sequence-dependent preferences for bending a DNA helix are of general occurrence. These sequence-dependent features constitute a further kind of information present in a DNA molecule, in addition to its well-known propensity to encode the amino acid sequence of proteins. A simple theory of DNA bending is to be presented in a forthcoming article (Calladine & Drew, 1986).



Segal et al., Nature, 2006

nature Vol 442|17 August 2006|doi:10.1038/nature04979

ARTICLES

A genomic code for nucleosome positioning

Eran Segal[1], Yvonne Fondufe-Mittendorf[2], Lingyi Chen[2], AnnChristine Thåström[2], Yair Field[1], Irene K. Moore[2], Ji-Ping Z. Wang[3] & Jonathan Widom[2]

Jonathan Widom

1955-2011

"Genomes care where nucleosomes are on average and so genomes encode explicit information to bias [their positions]."

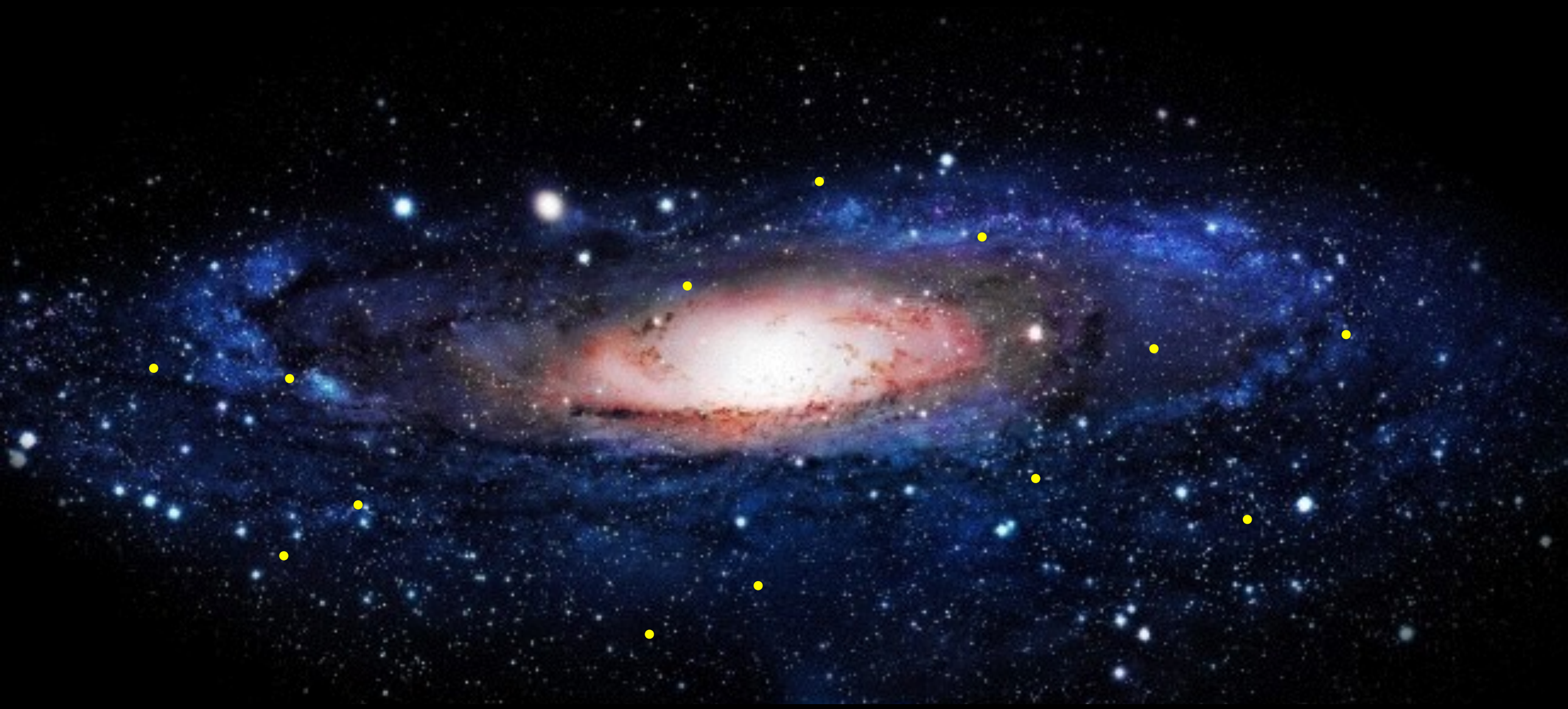
The sequence space

How many sequences can be wrapped around a nucleosome?

$$4^{147}$$

(about 5 times the volume of the Milky Way)

The sequence space

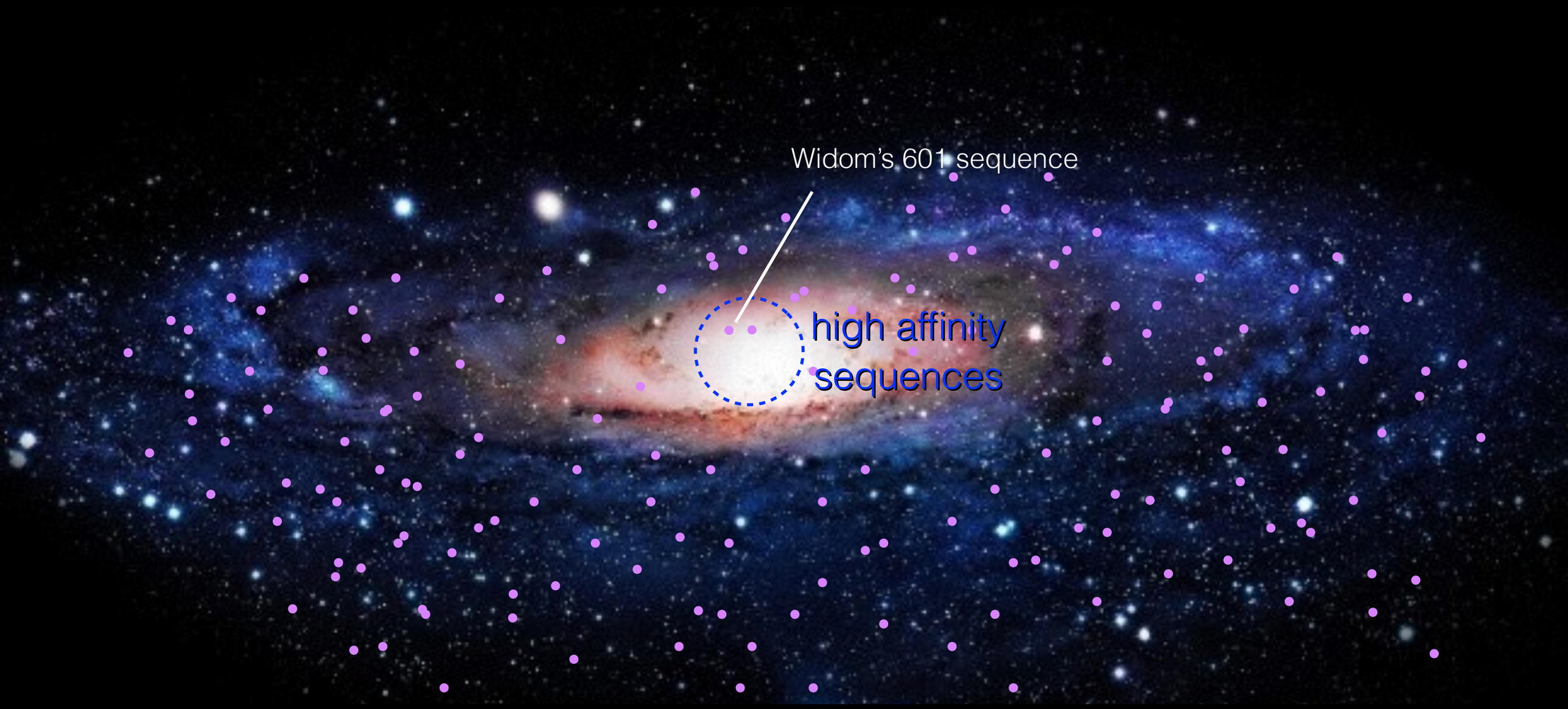


Baker’s Yeast 12 Mb

The sequence space

Human 3.2 Gb

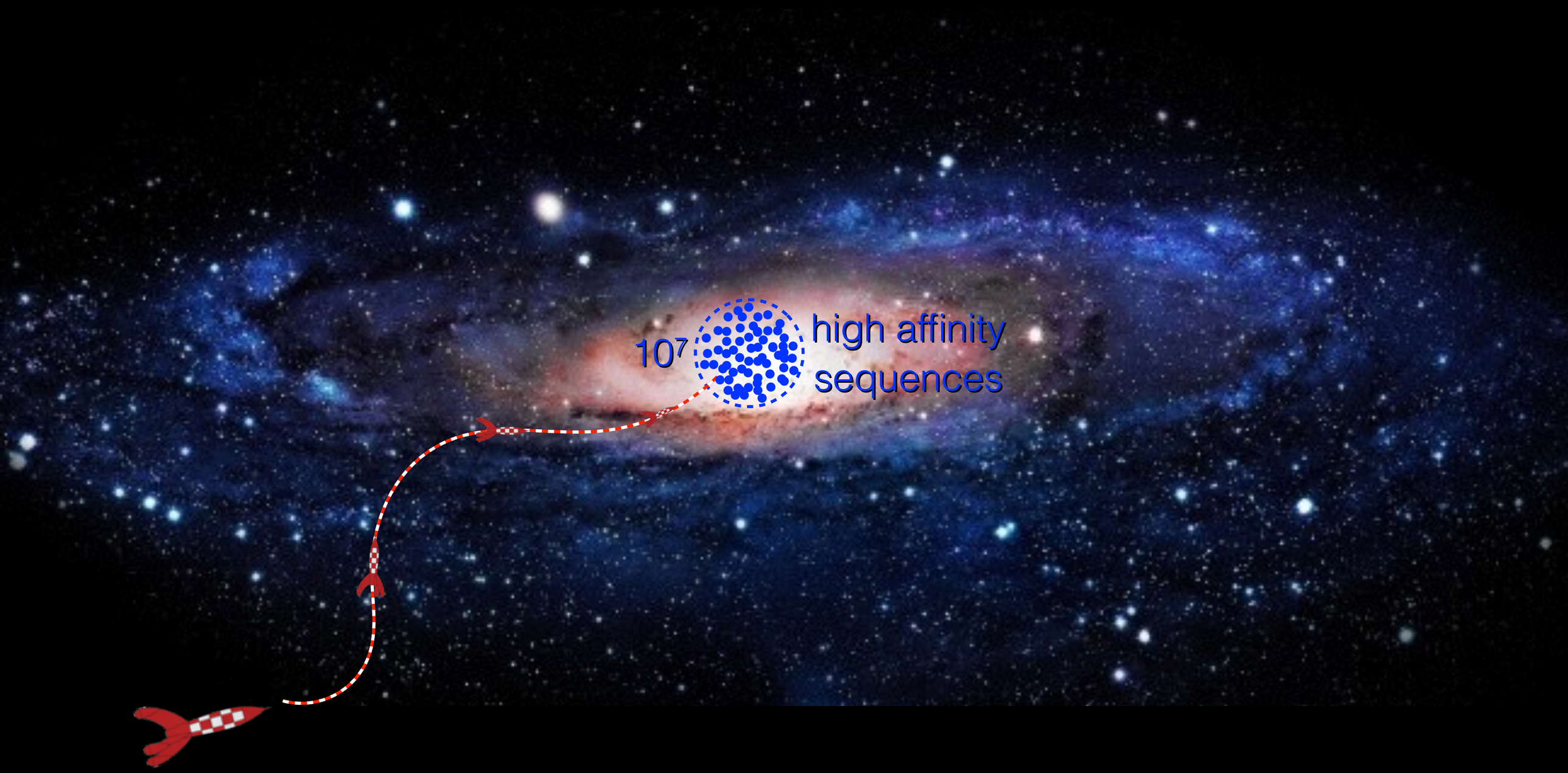
The sequence space



Random Pool 5 Tb

Lowary & Widom 1998

The sequence space



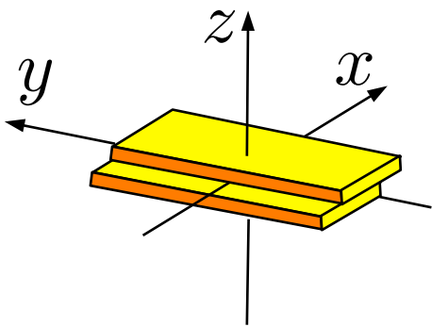
Mutation Monte Carlo method

THE MECHANICAL GENOME

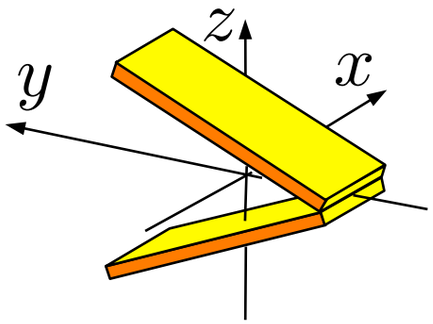
Our questions:

- Can the positioning rules be explained by a purely mechanical model?
- Can mechanical information be multiplexed with classical genetic information?

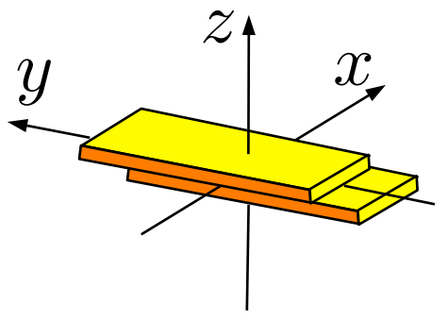
The rigid basepair representation



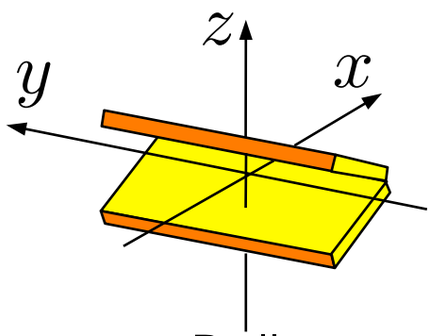
Shift



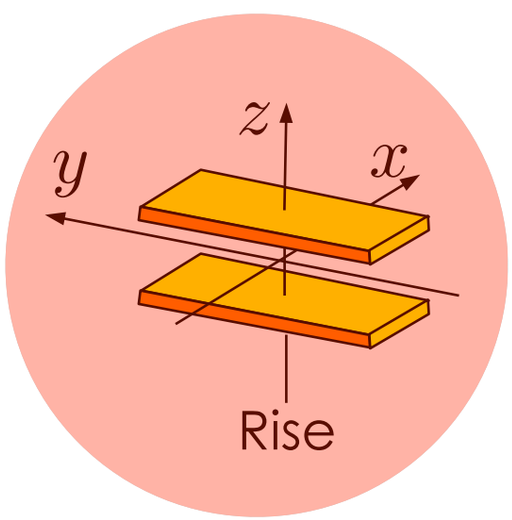
Tilt



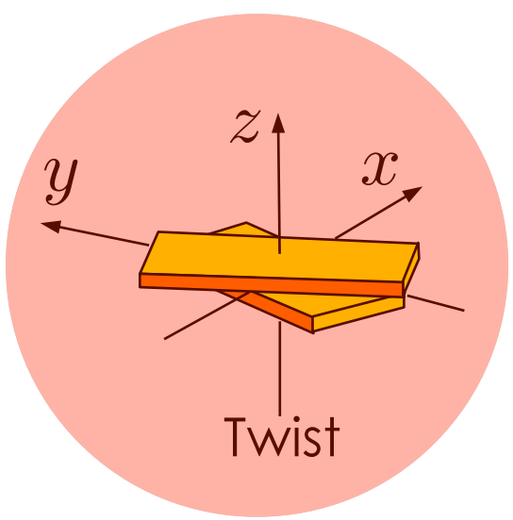
Slide



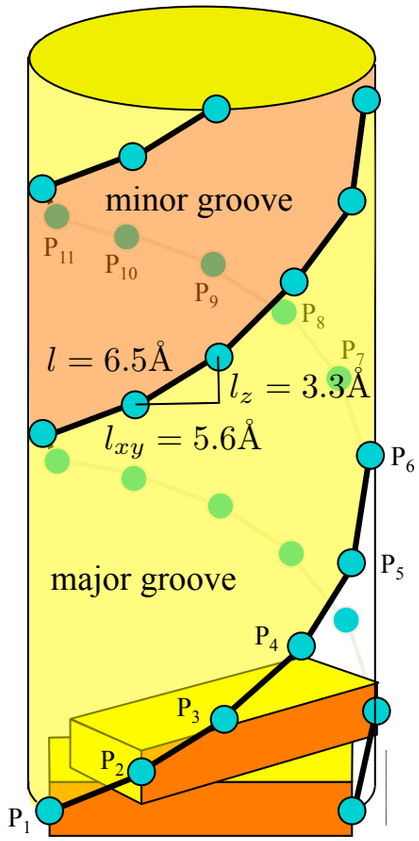
Roll



Rise

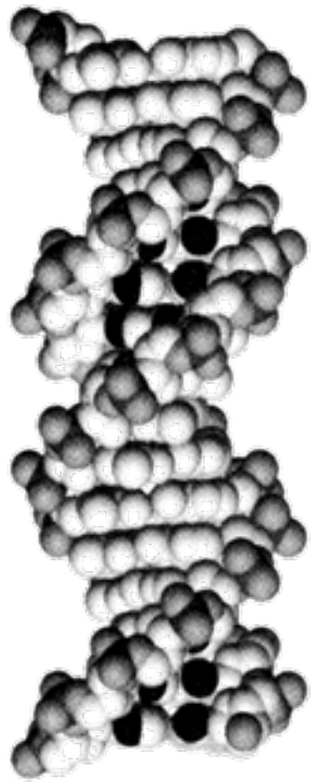


Twist



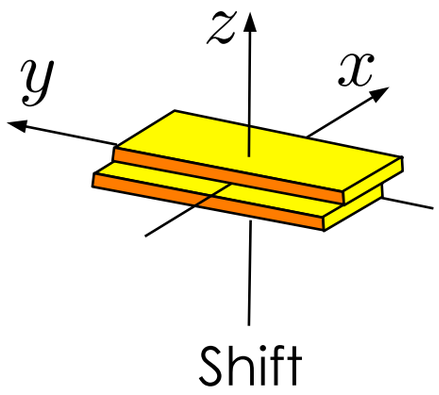
$\text{Rise} = 0.34\,\text{nm}$

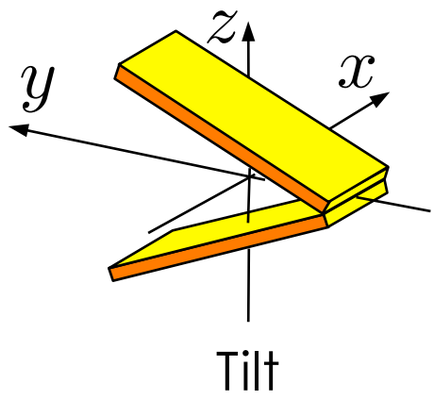
$\text{Twist} = 36°$

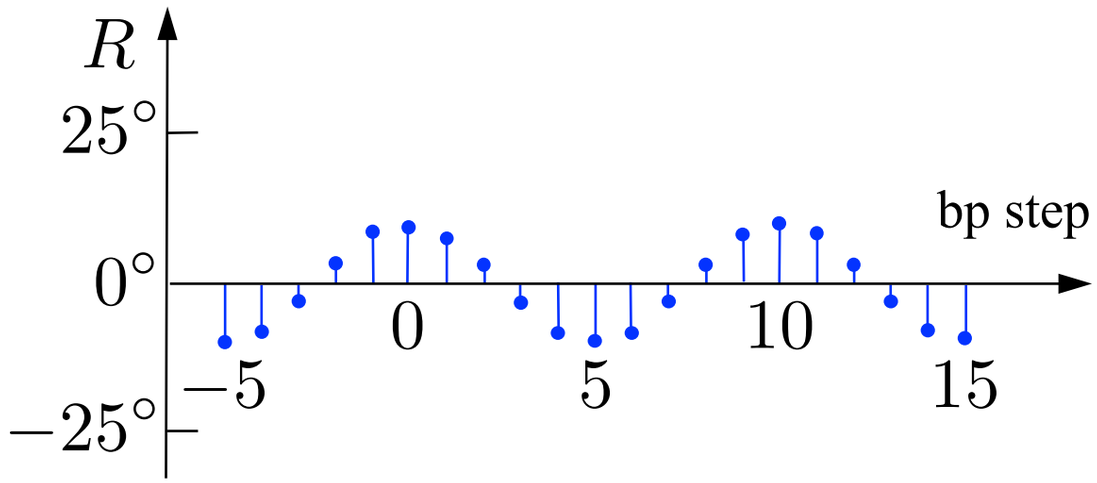


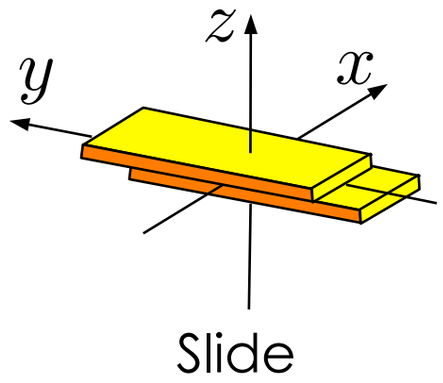
B-DNA

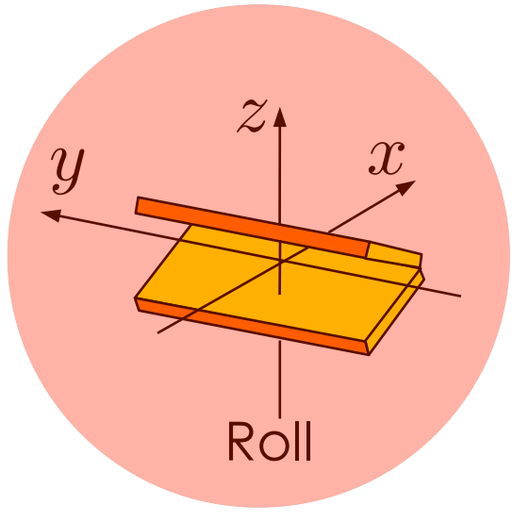
The rigid basepair representation

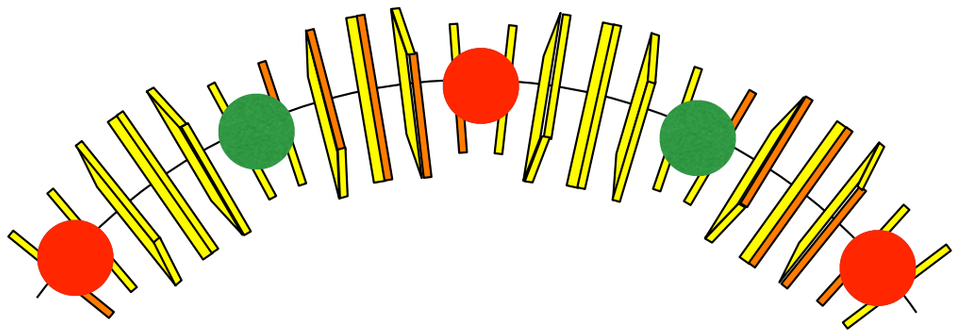


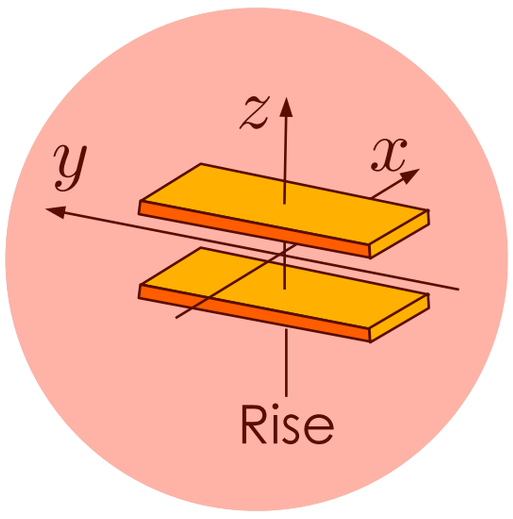


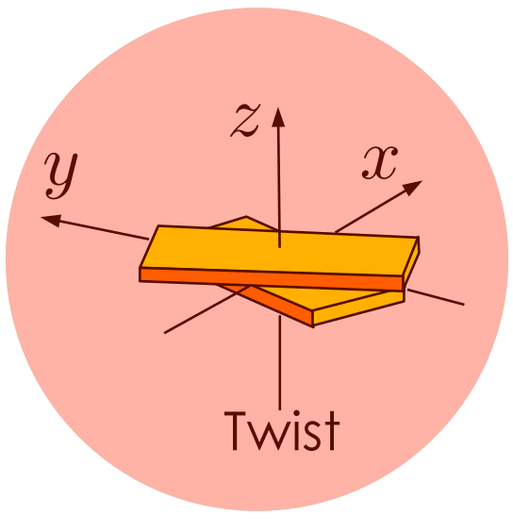


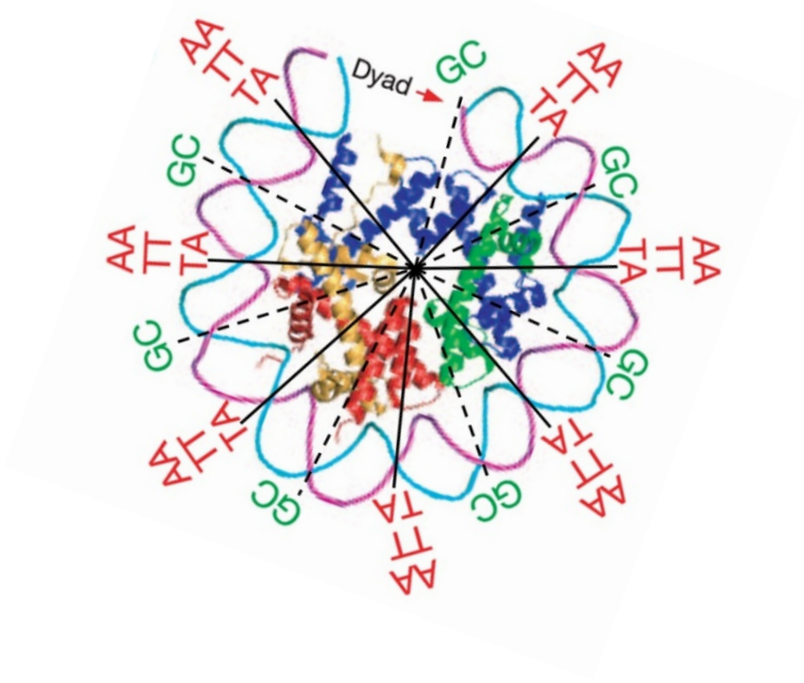




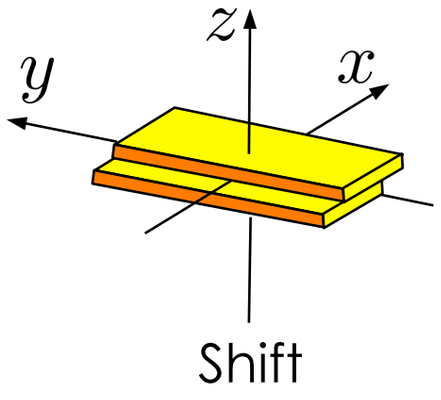


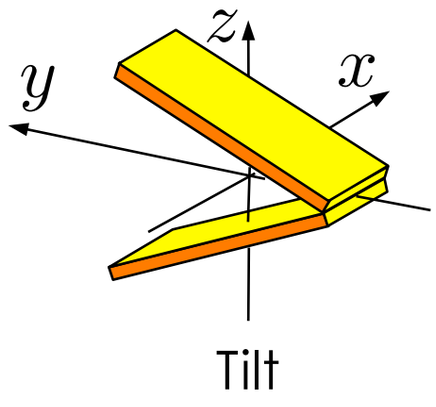




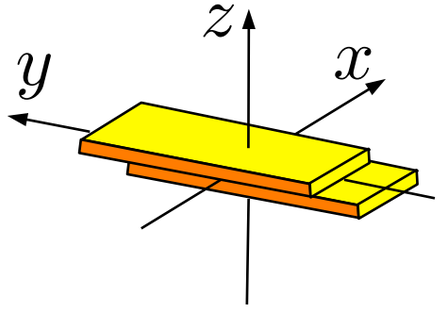


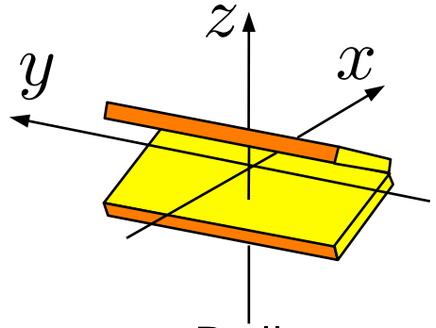
A local harmonic model

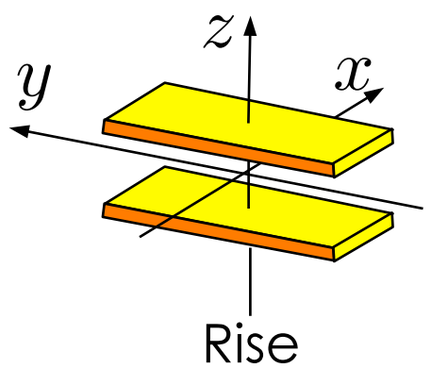


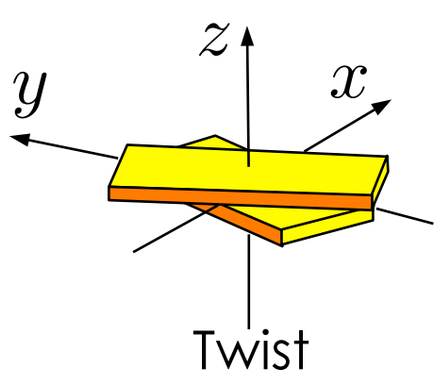


$$\vec{x} = [\text{Tilt},\ \text{Roll},\ \text{Twist},\ \text{Shift},\ \text{Slide},\ \text{Rise}]$$







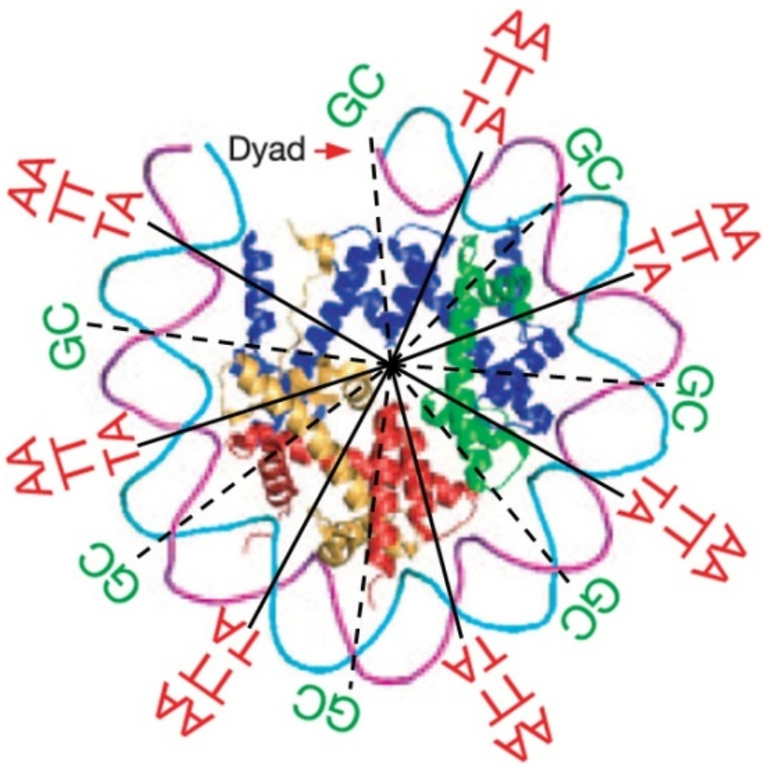


$$E_{\text{step}} = \frac{1}{2}\left(\vec{x} - \vec{x}^{0}\right)^{T} \mathbf{Q} \left(\vec{x} - \vec{x}^{0}\right)$$

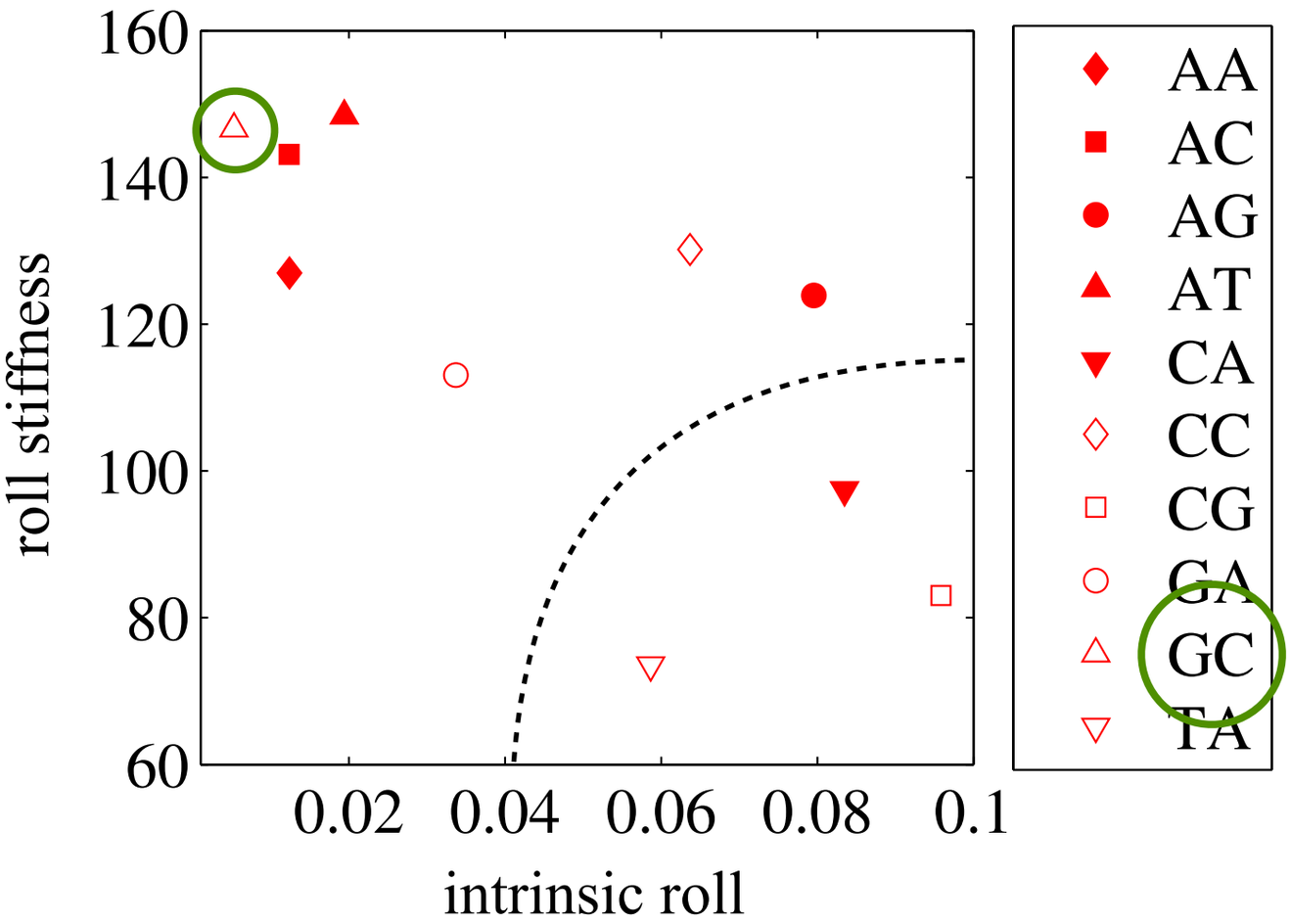
protein-DNA cocrystals
Olson, Gorin, Lu, Hock & Zhurkin
PNAS **95** (1998) 11163

all atom MD simulations
Lavery et al.
Nucleid Acids Res. **38** (2010) 299

The GC step

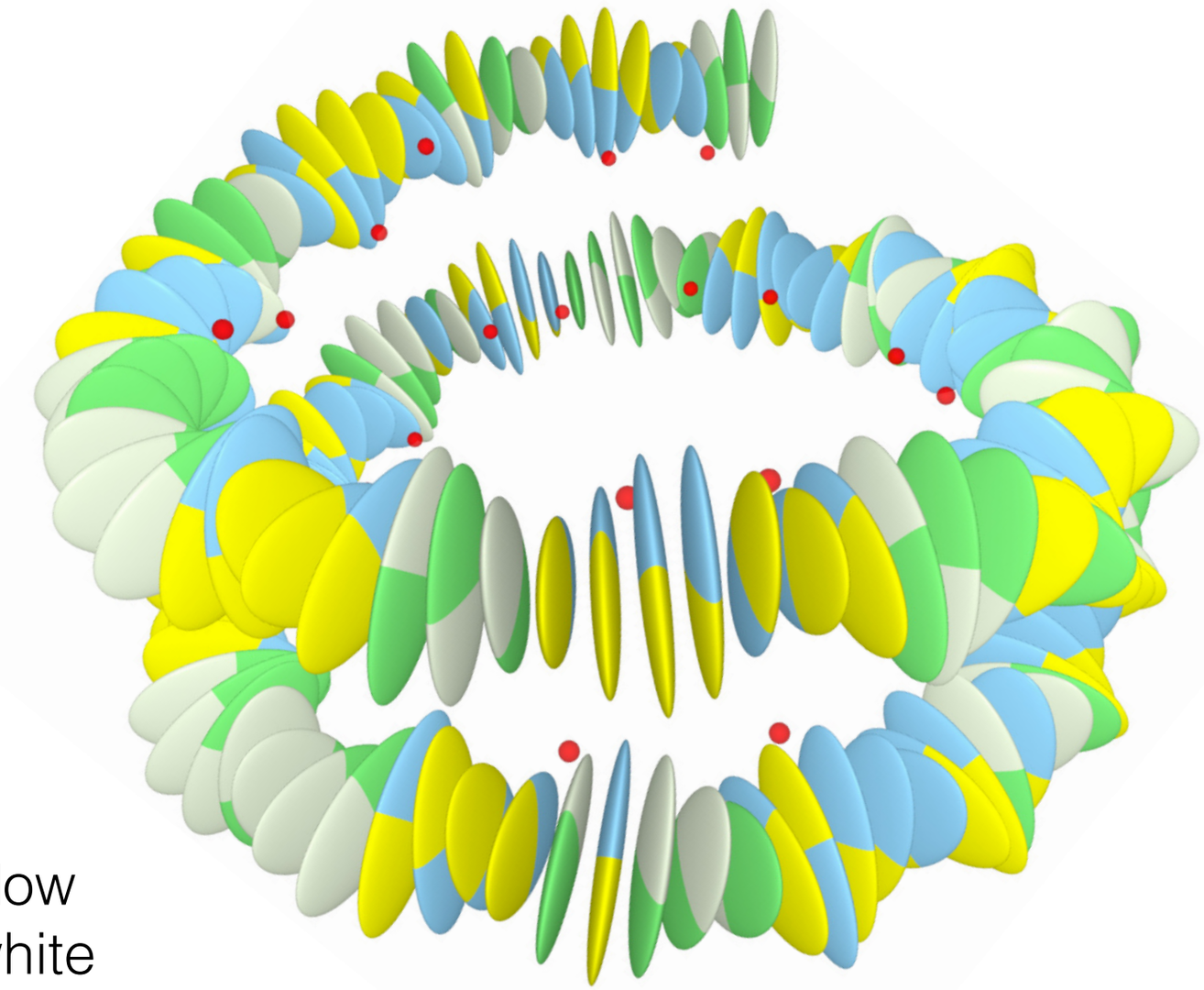


GC peaks at positive roll



Our nucleosome model

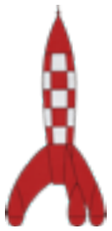
Eslami-Mossalam, Tompitak, Schram, van Noort & Schiessel



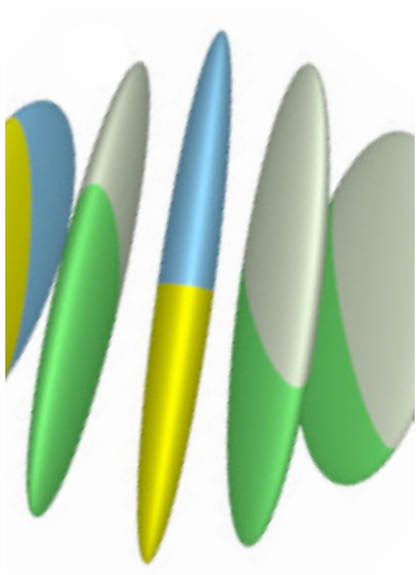
AT: blue/yellow
GC: green/white

similar models:

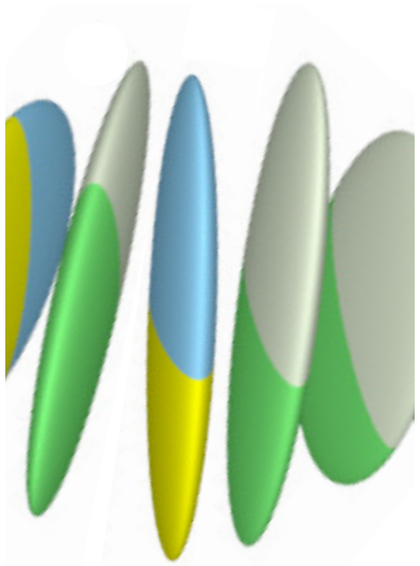
Tolstorukov et al., J. Mol. Biol. 2007
Vaillant, Audit & Arneodo, 2007
Morozov et al., Nucl. Acids Res. 2009
Becker & Everaers, Structure 2009
Fathizadeh, Besya, Ejtehadi & Schiessel, EPJE 2013

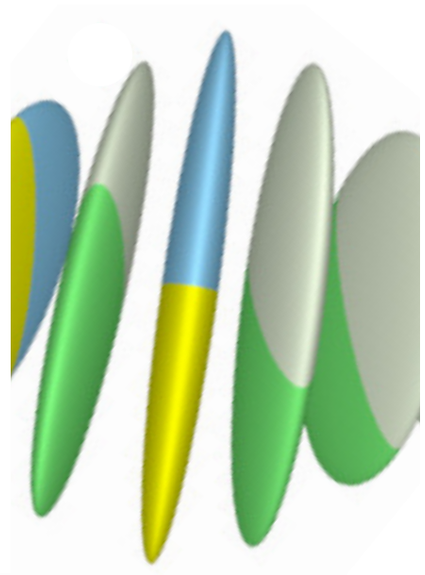


Mutation Monte Carlo method

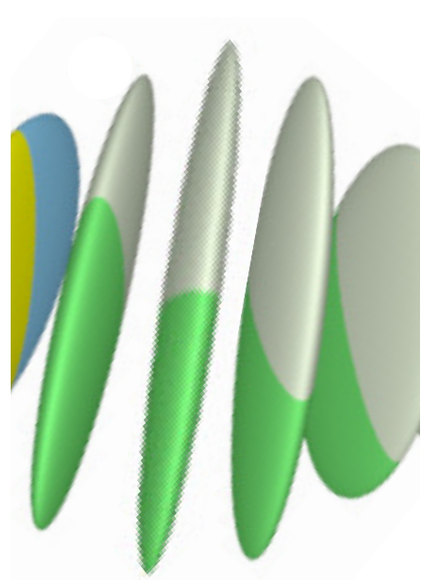


conformation

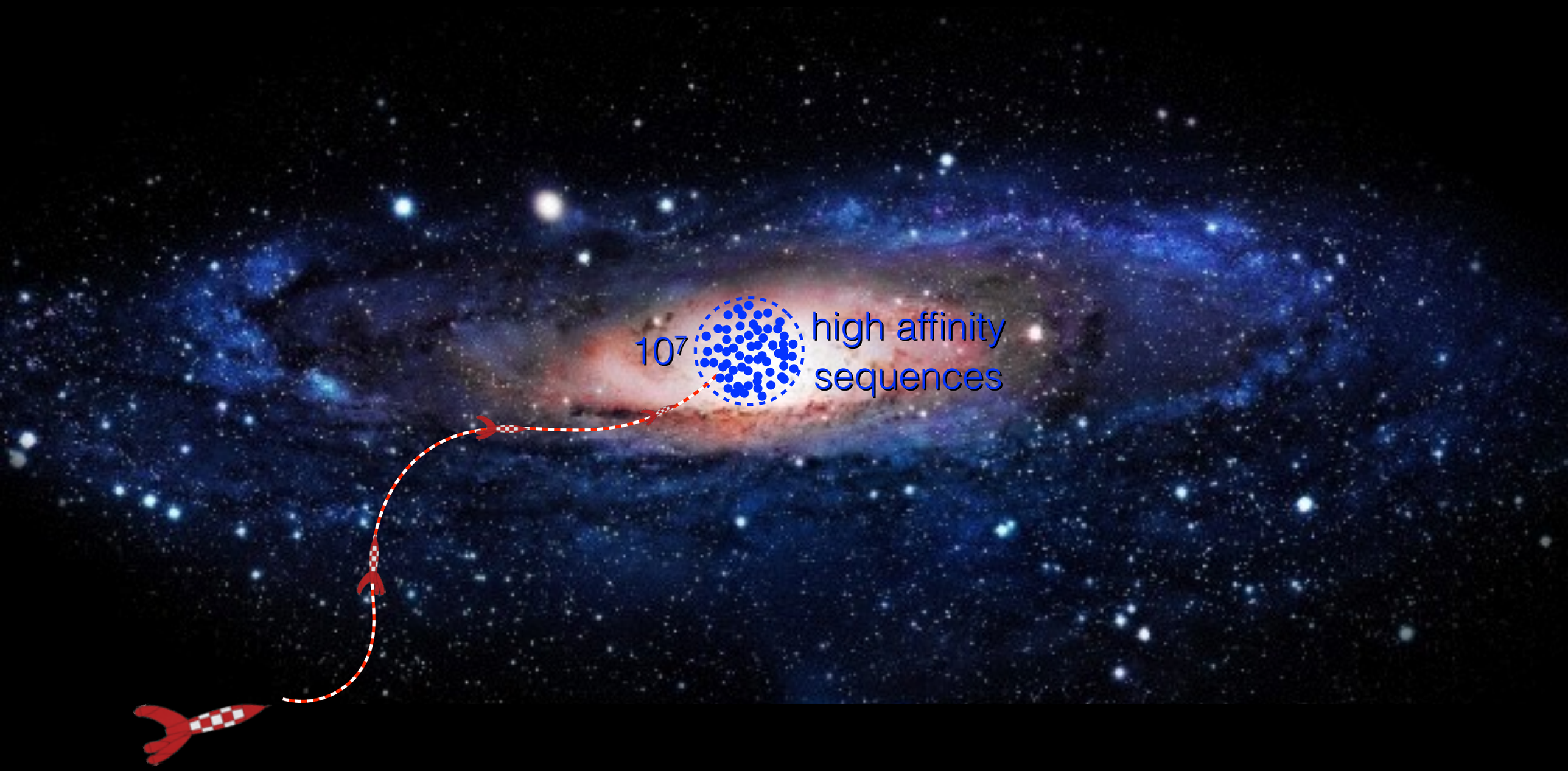




mutation

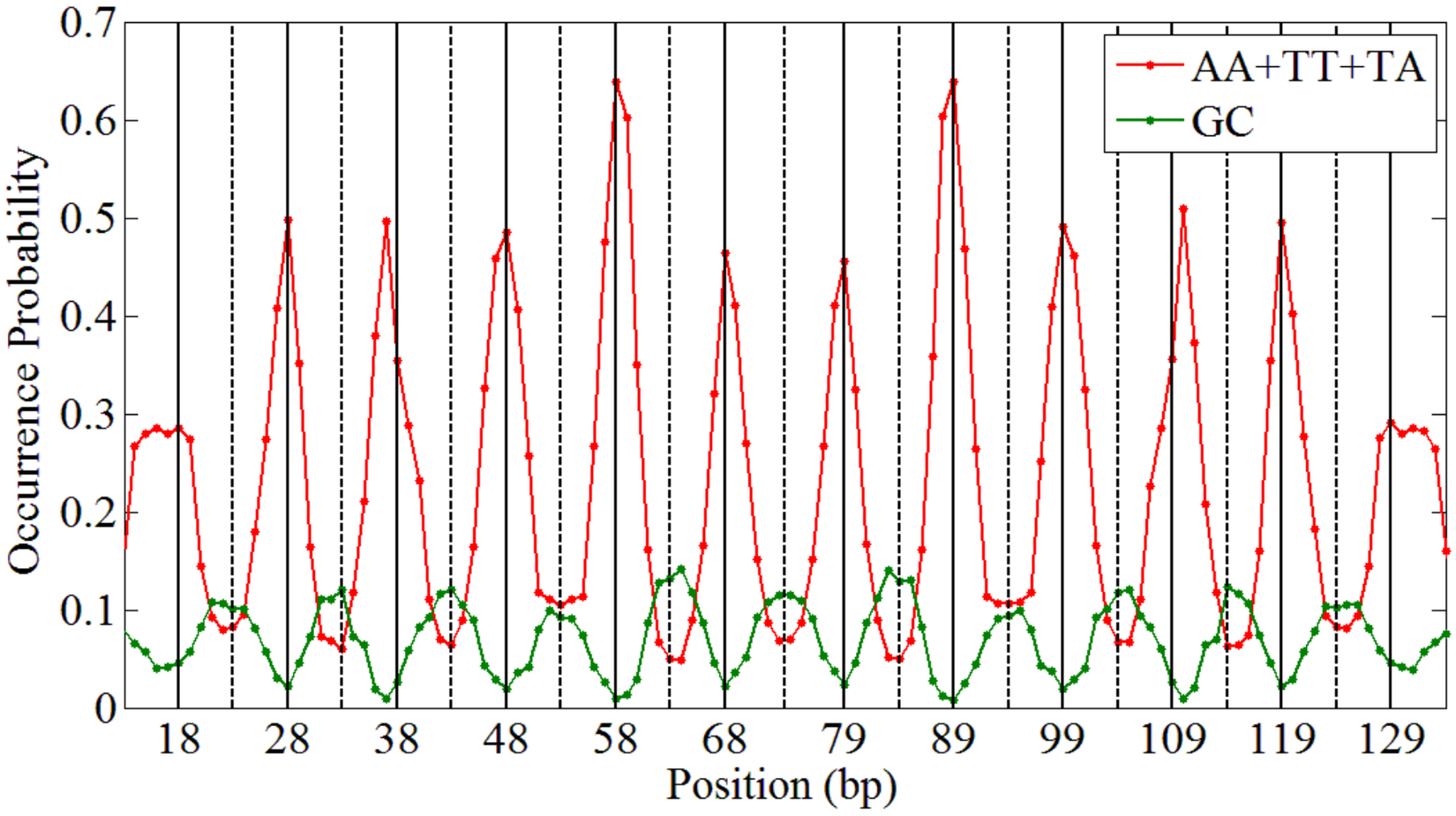


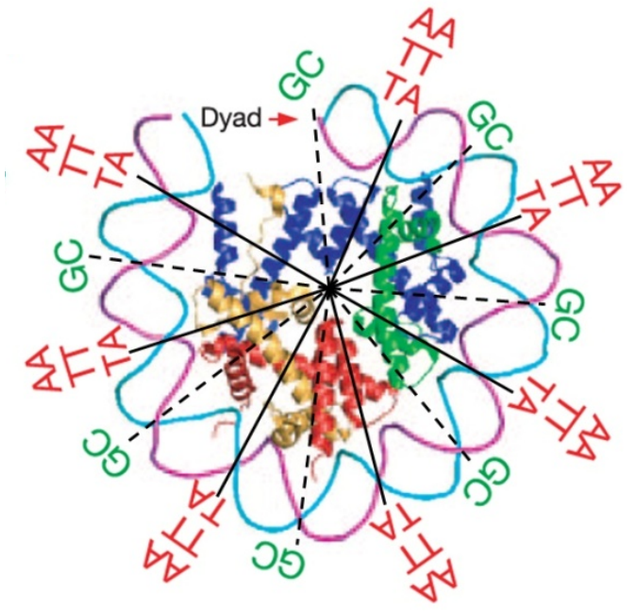
Mutation Monte Carlo method



Recovering the positioning rules

10 million sequences at 100 K





GC steps peak at their least favorite positions. Why?

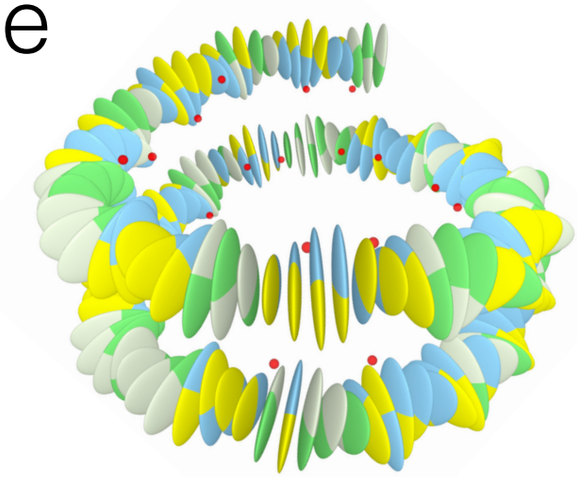
GC brings in good neighbors, e.g. AGCT

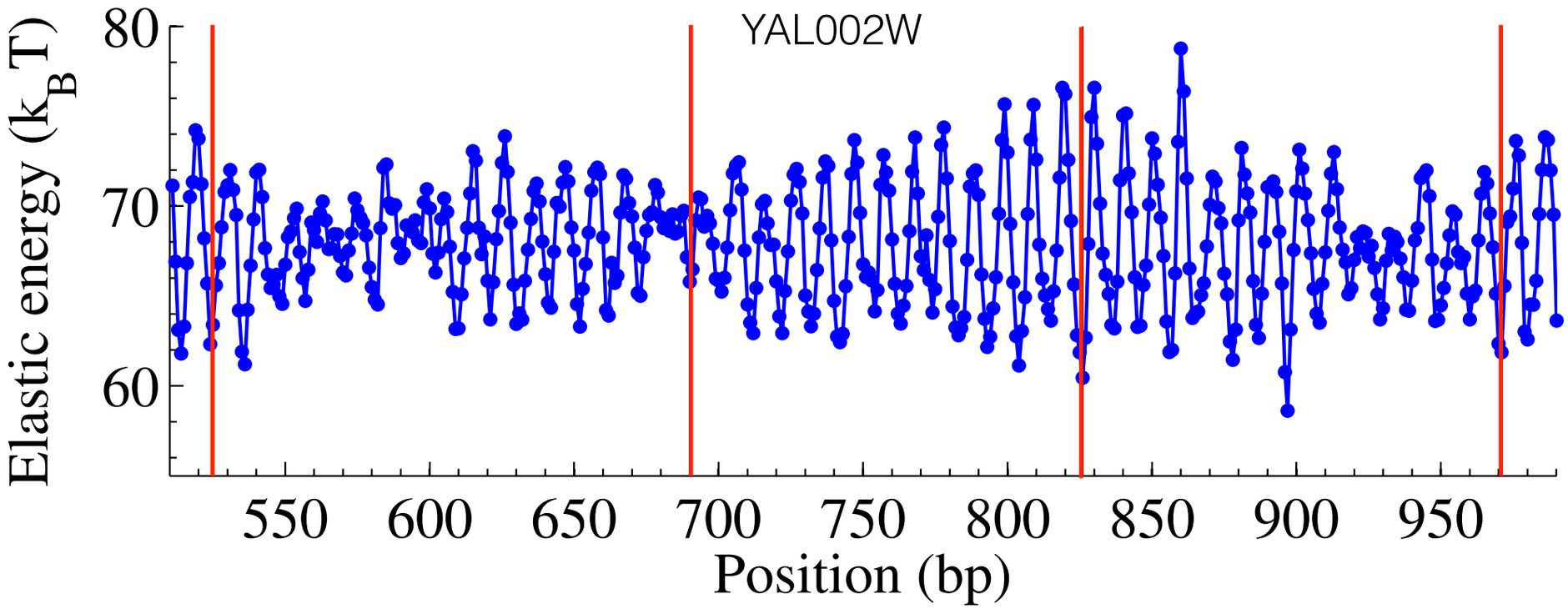
THE MECHANICAL GENOME

Our questions:

- Yes, the positioning rules can be explained by a purely mechanical model.
- Can mechanical information be multiplexed with classical genetic information?

The energy landscape of a gene





Nucleosome mapping at basepair resolution in *Saccharomyces cerevisiae*

Brogaard, Xi, Wang & Widom

Nature **486** (2012) 496

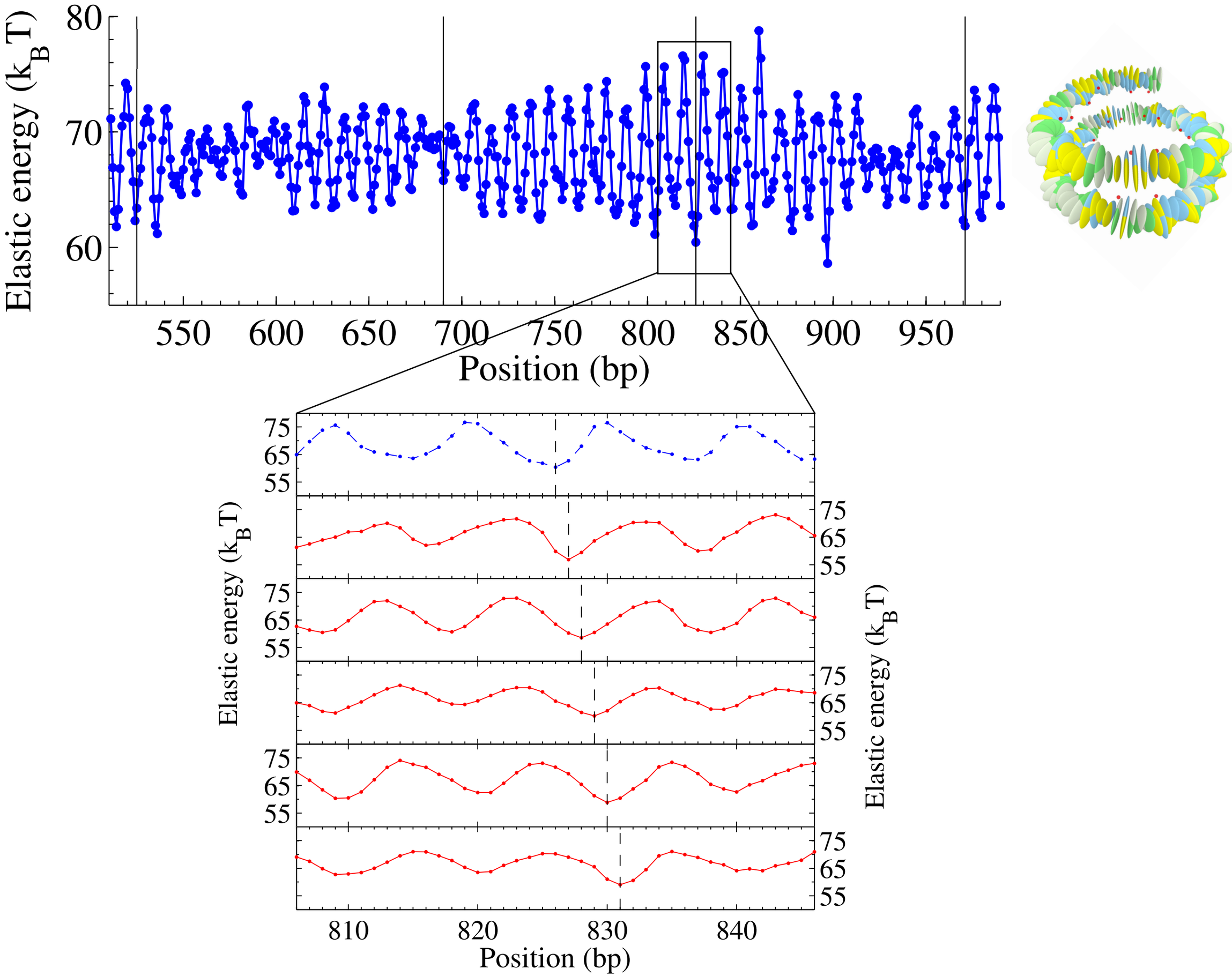
Synonymous Mutation Monte Carlo

… GTA CTC ACA ACT ACA CAT TTT GCC CTT ATT …

… Val Leu Thr Thr Thr His Phe Ala Leu Ile …

allowed mutations

GTA	TTA	ACA	ACA	ACA	CAT	TTT	GCA	TTA	ATA
GTT	TTG	ACT	ACT	ACT	CAC	TTC	GCT	TTG	ATT
GTG	CTA	ACG	ACG	ACG			GCG	CTA	ATC
GTC	CTT	ACC	ACC	ACC			GCC	CTT	
	CTG							CTG	
	CTC							CTC	


Elastic energy (k_BT)
80
70
60
550
600
650
700
750
800
850
900
950
Position (bp)
75
65
55
Elastic energy (k_BT)
810
820
830
840
Position (bp)

THE MECHANICAL GENOME

Our questions:

- Yes, the positioning rules can be explained by a purely mechanical model.
- Yes, mechanical and genetic information can be multiplexed together.

New question:

How do you multiplex those two types of genetic information?

Three mechanisms allow for multiplexing

1 protein sequences highly degenerate

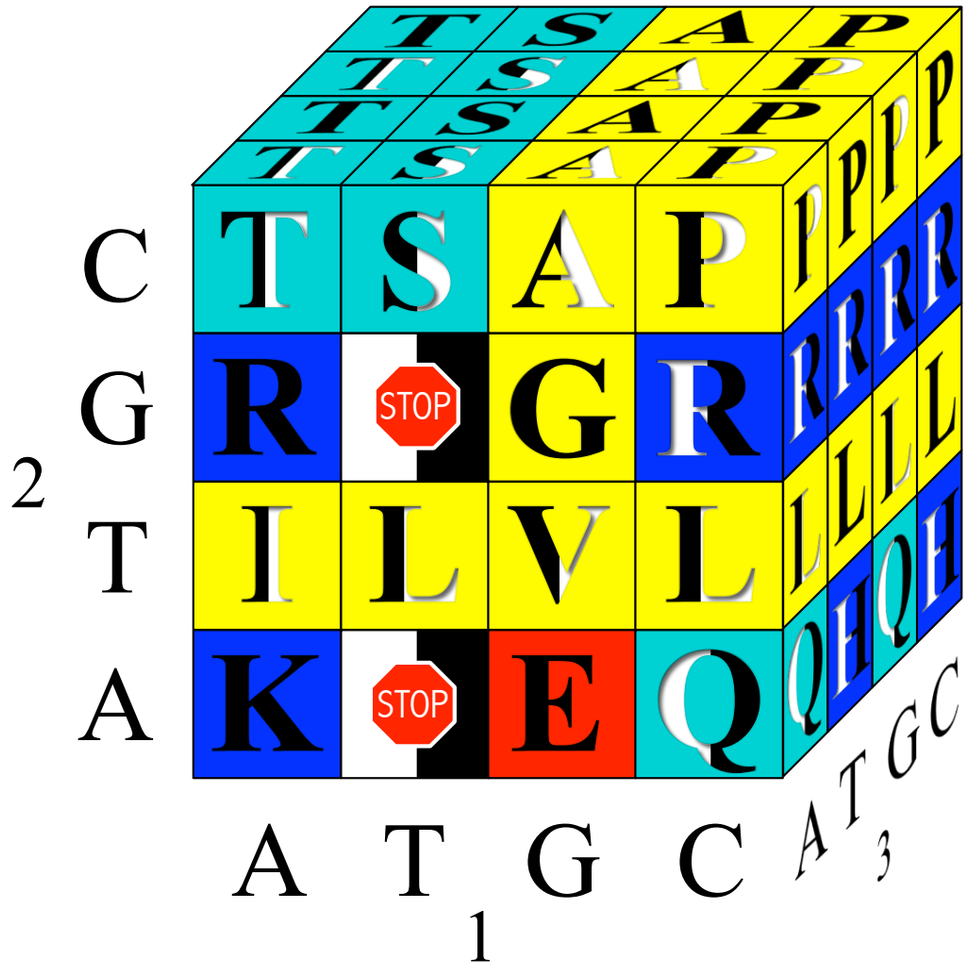
2 genomes not selected for highest affinity

3 plasticity due to mechanical nature of DNA readout

Jonathan Widom
"Nucleosome positioning" at the KITP conference
"Soft Matter Physics Approaches to Biology"
Santa Barbara, May 23rd 2011

Three mechanisms allow for multiplexing

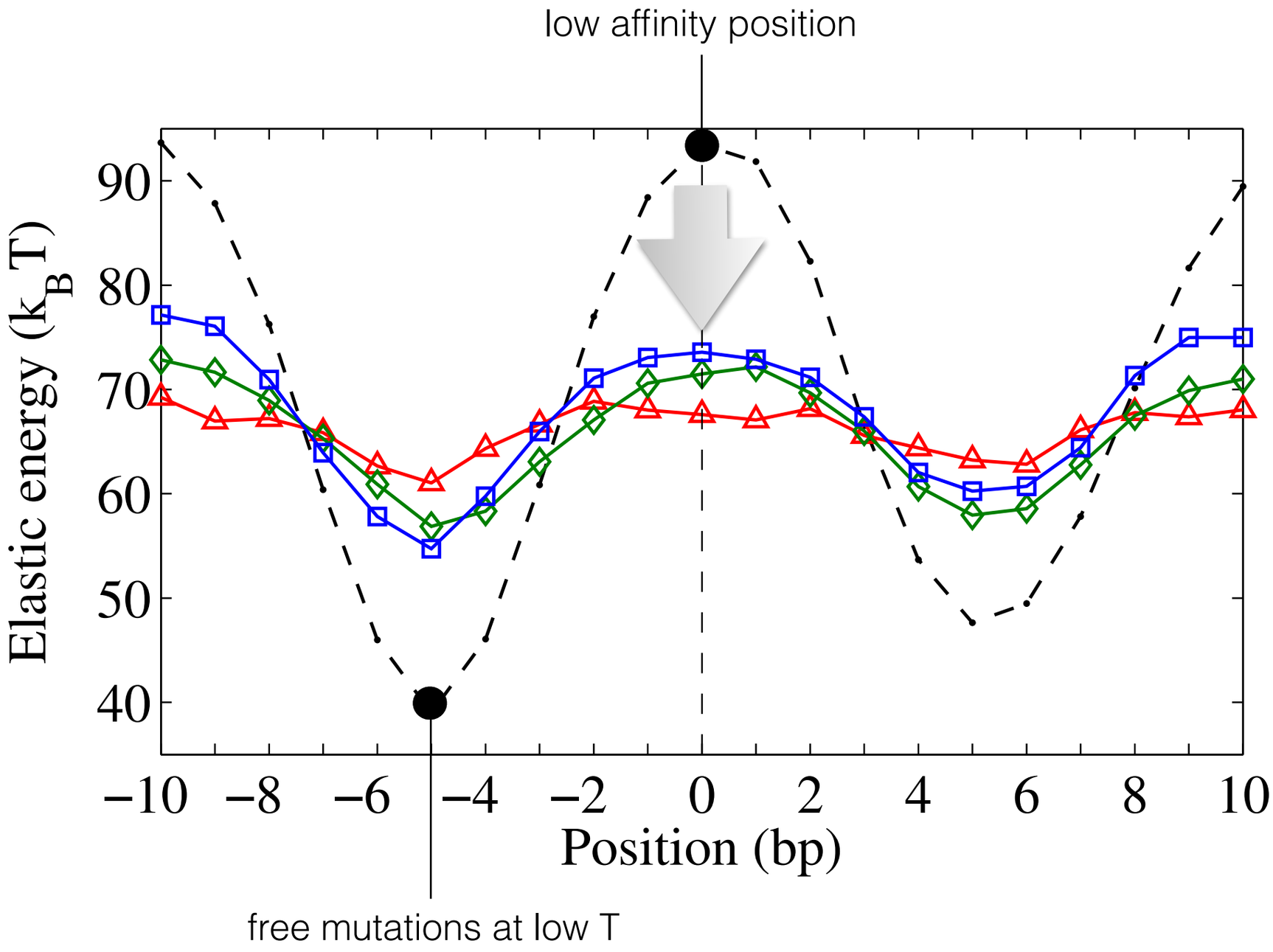
1 protein sequences highly degenerate



from: H. Schiessel:
Biophysics for Beginners:
a Journey through the Cell Nucleus
(Pan Stanford Publishing, 2014)

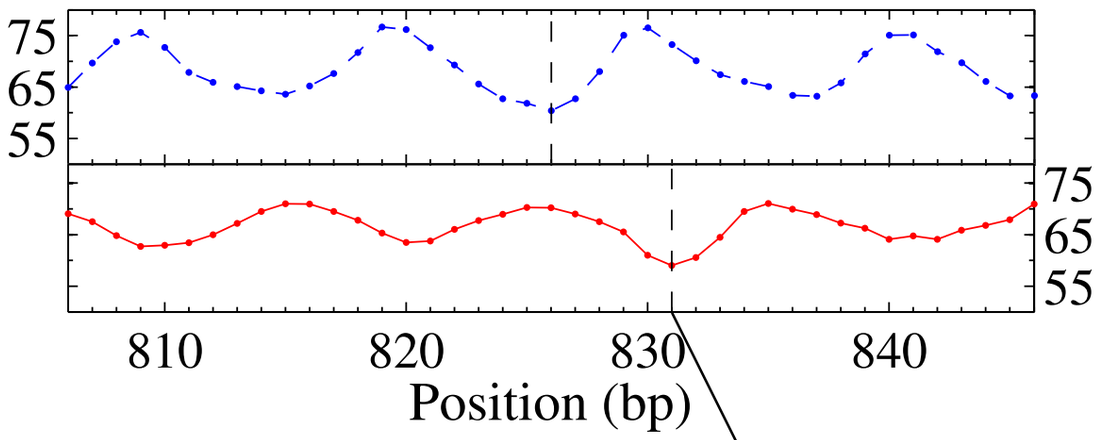
Three mechanisms allow for multiplexing

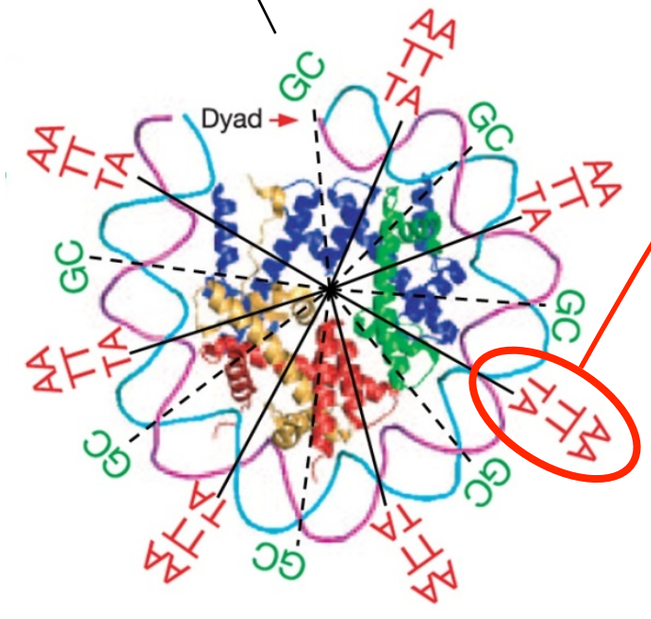
2 genomes not selected for highest affinity



Three mechanisms allow for multiplexing

3 plasticity due to mechanical nature of DNA readout





… GAA ACT …

… Glu Thr …

GAA ACA
GAG ACT
ACG
ACC

suboptimal location of a good basepair step

Three mechanisms allow for multiplexing

1 protein sequences highly degenerate

2 genomes not selected for highest affinity

3 plasticity due to mechanical nature of DNA readout

Jonathan Widom
"Nucleosome positioning" at the KITP conference
"Soft Matter Physics Approaches to Biology"
Santa Barbara, May 23rd 2011

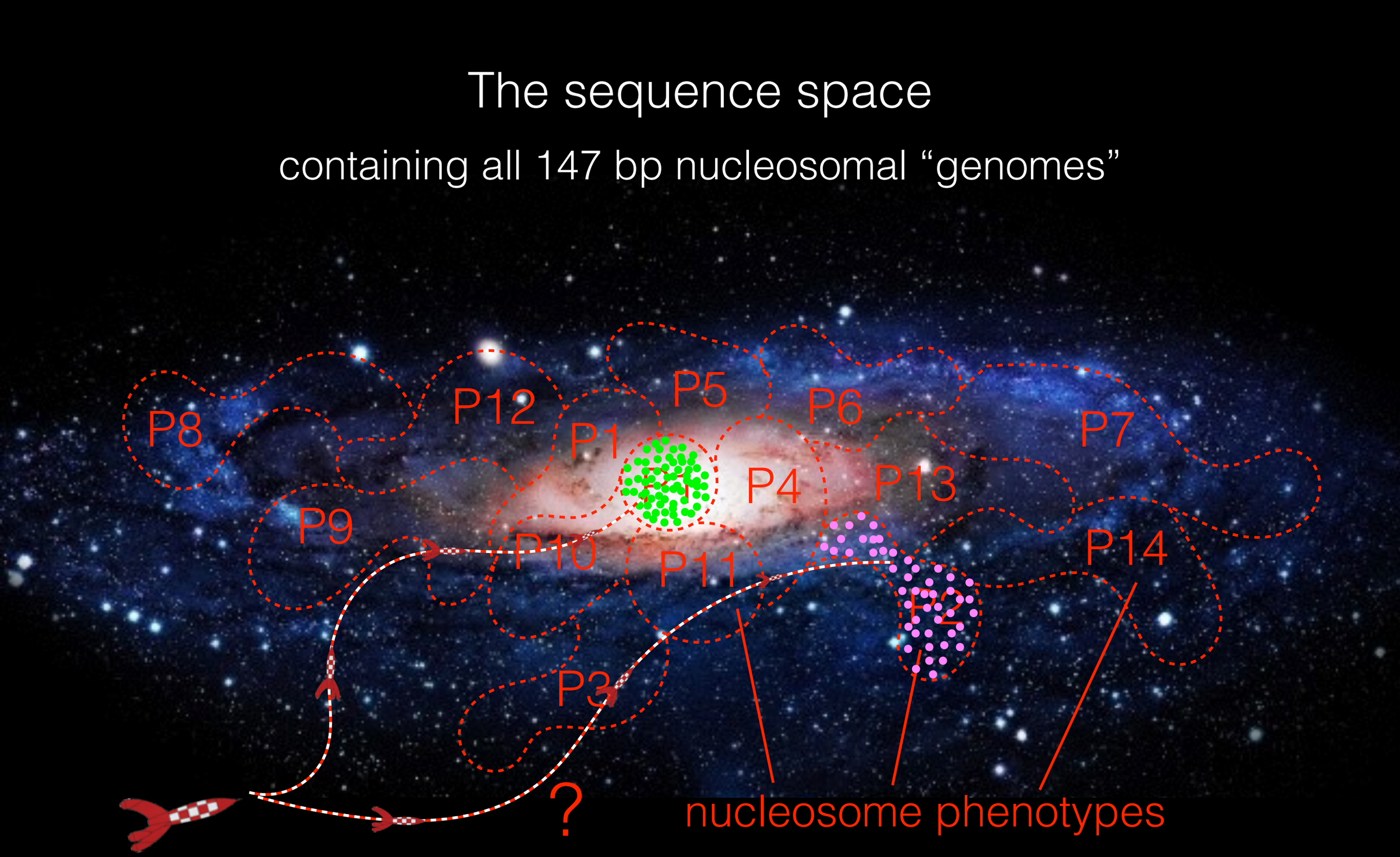
THE MECHANICAL GENOME

Question:

Can DNA mechanics affect nucleosomes beyond their positioning?

The sequence space

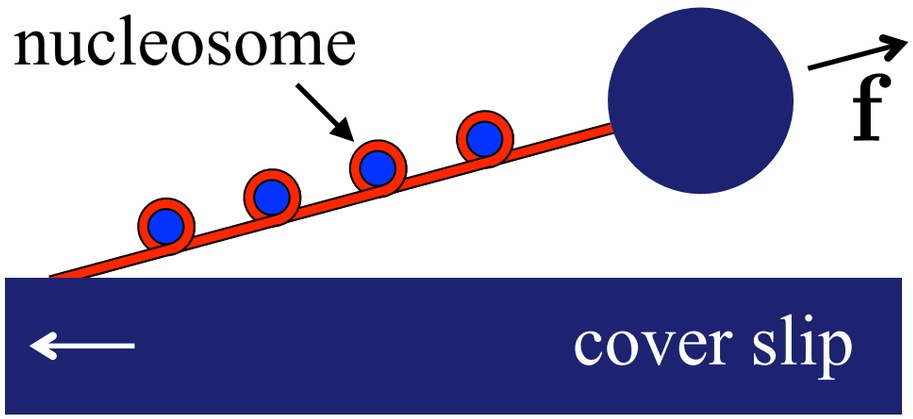
containing all 147 bp nucleosomal “genomes”

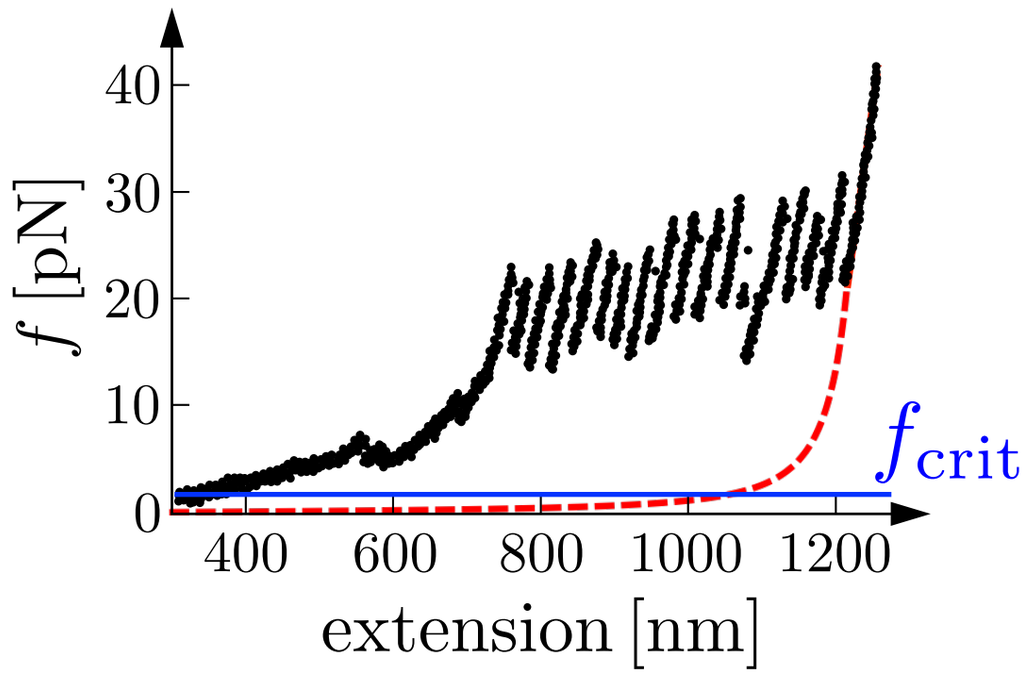


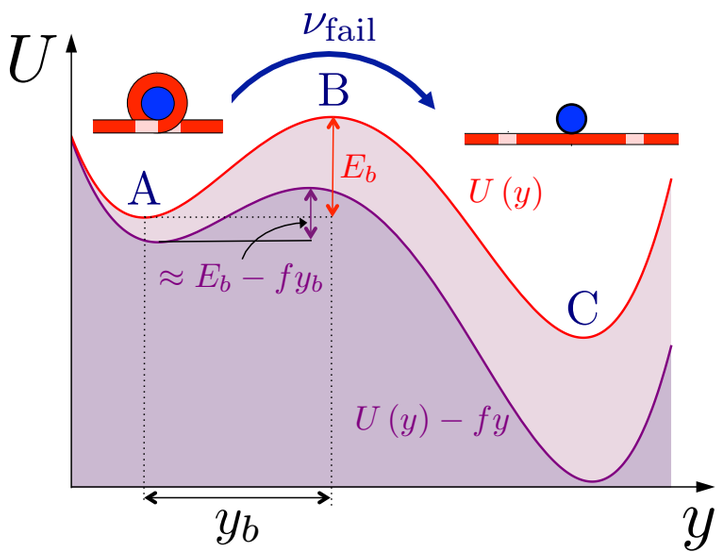
mutation Monte Carlo

17 nucleosomes under tension

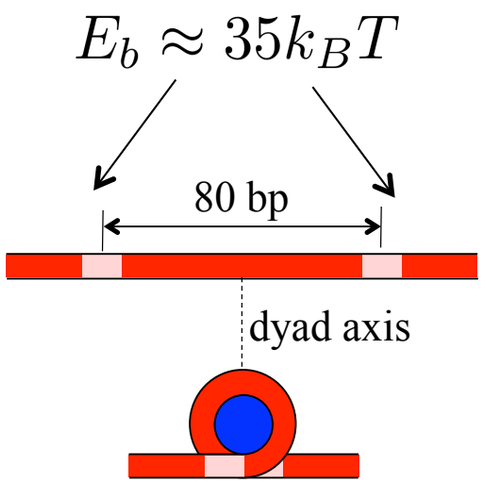
Brower-Toland et al., PNAS **99** (2002) 1960





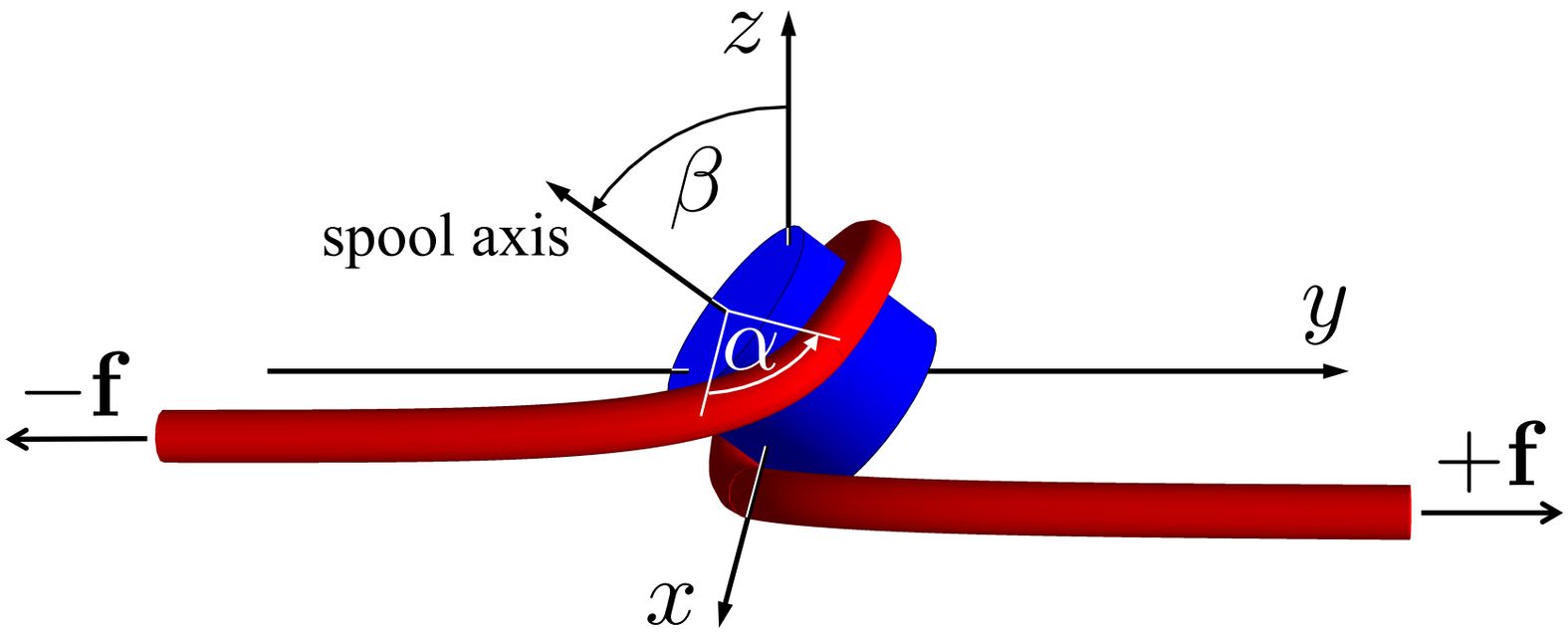


dynamical force spectroscopy



Model

Kulic & HS, Phys. Rev. Lett. **92** (2004) 228101



α : unwrapping angle

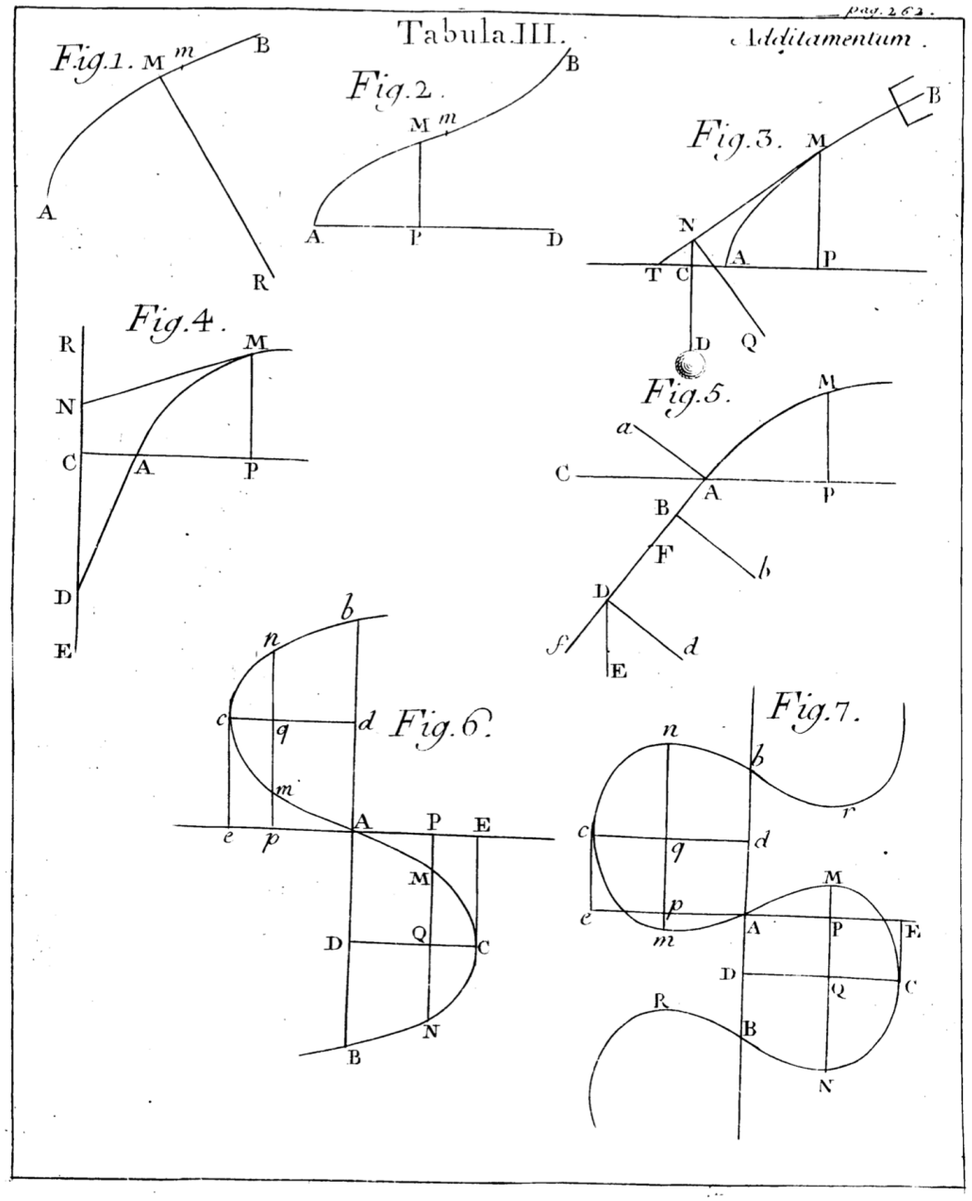
β : tilting angle

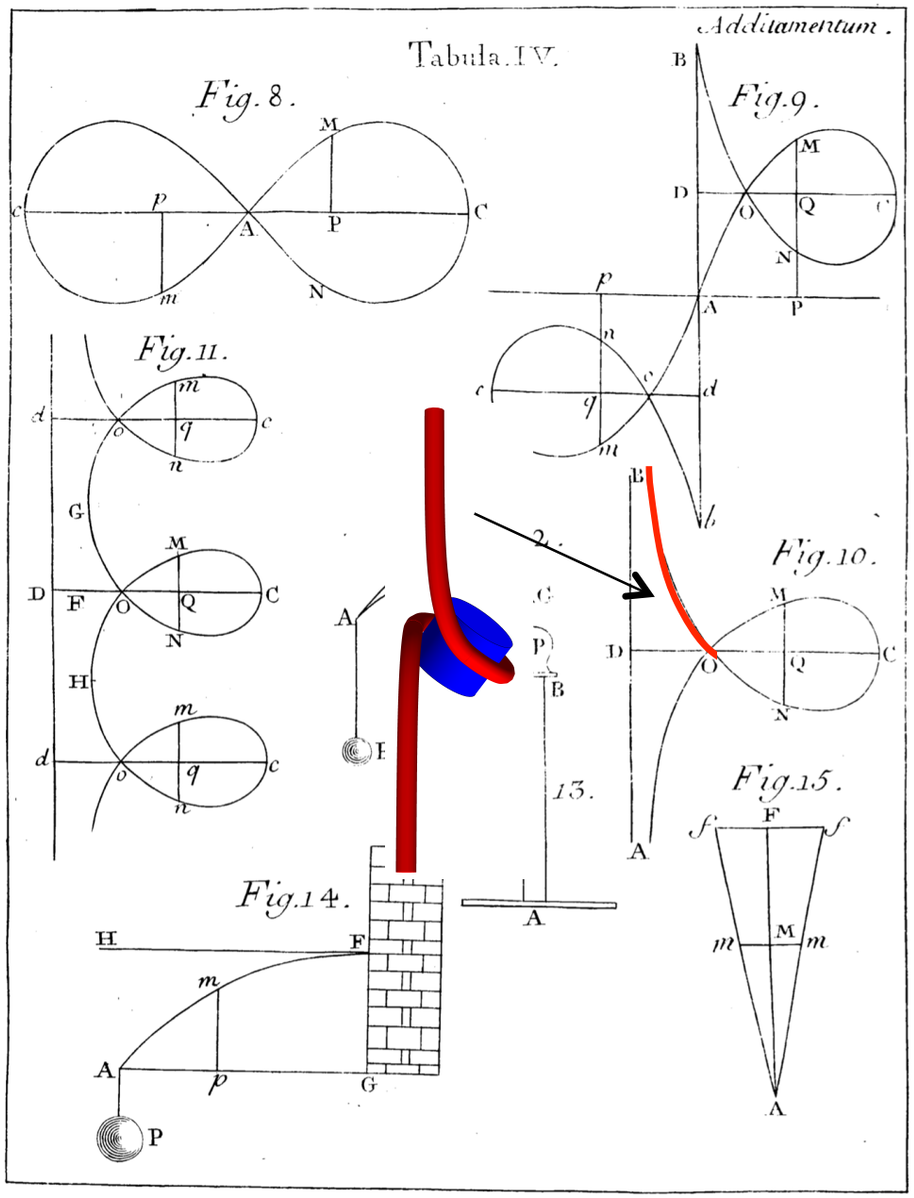
total energy:

$$E_{\mathrm{tot}} = \underbrace{\frac{A}{2}\int_0^L ds \left(\frac{1}{R(s)}\right)^2}_{\text{DNA bending}} \underbrace{- f L_{EE}}_{\text{external force}} \underbrace{+ 2R_0 f_{\mathrm{crit}} \alpha}_{\text{DNA adsorption}}$$

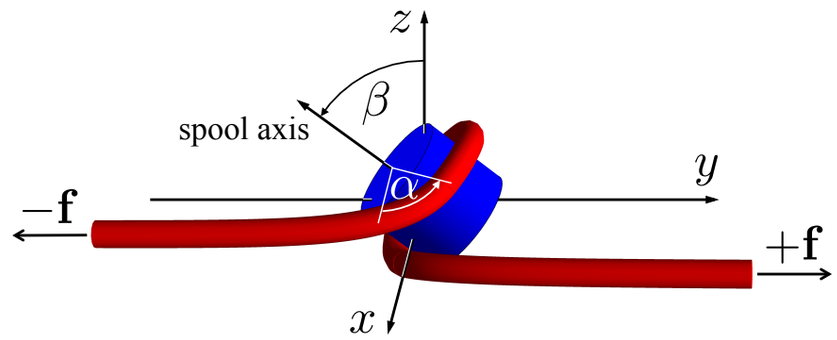
Euler elasticas

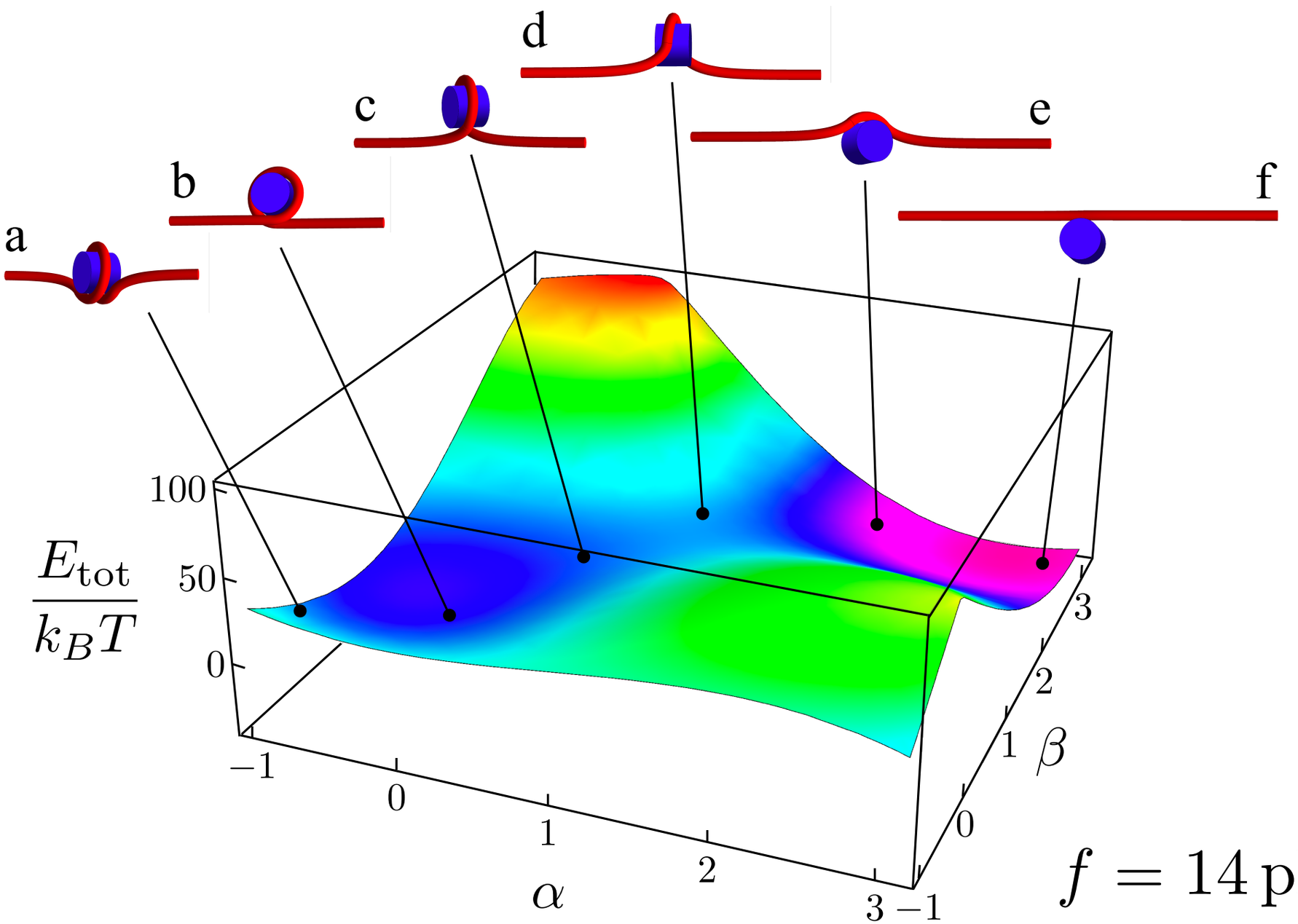
Leonard Euler, Methodus, 1744





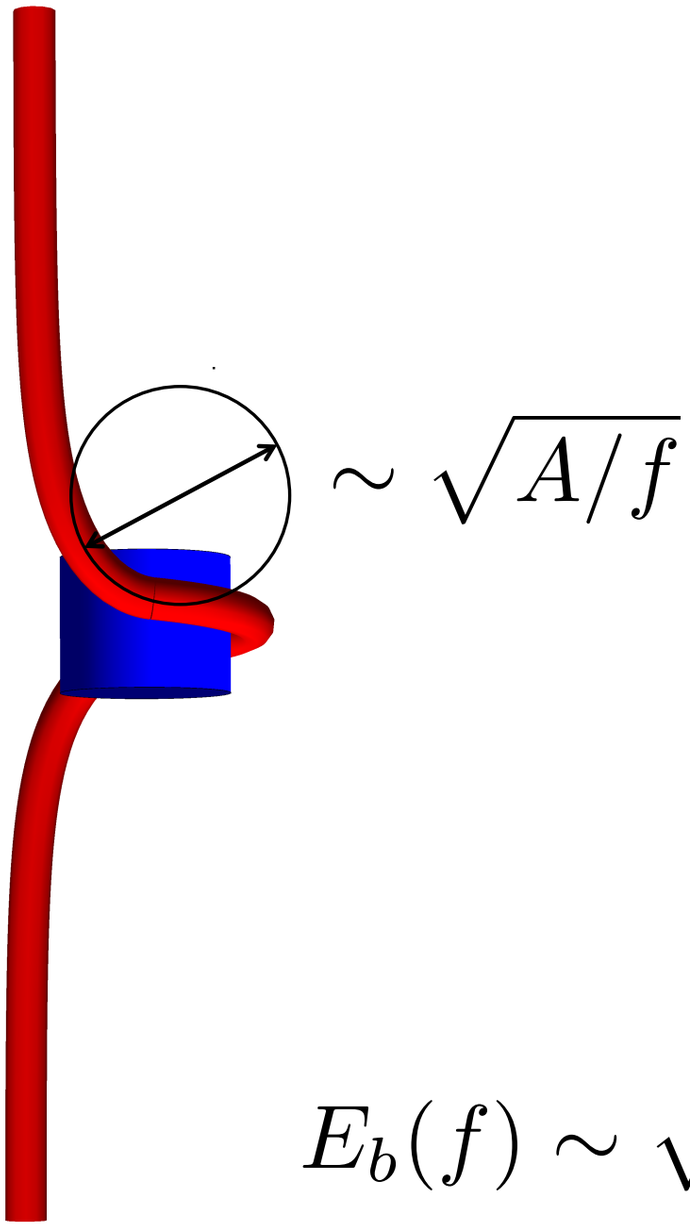
Energy landscape





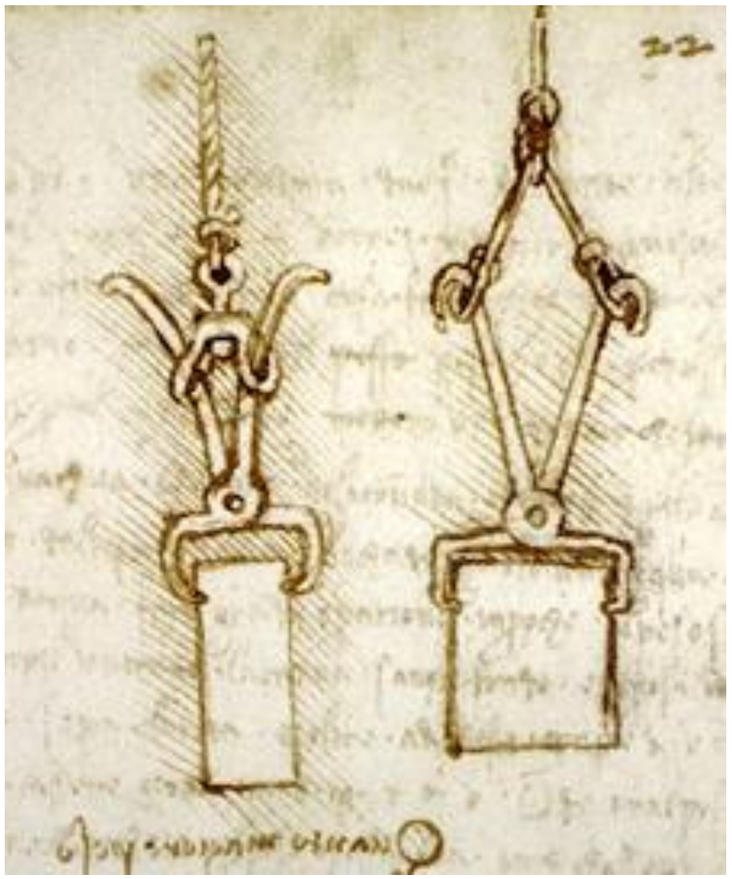
$f = 14\,\mathrm{pN}$

The origin of the barrier



$$E_b(f) \sim \sqrt{Af}$$

force-induced strengthening

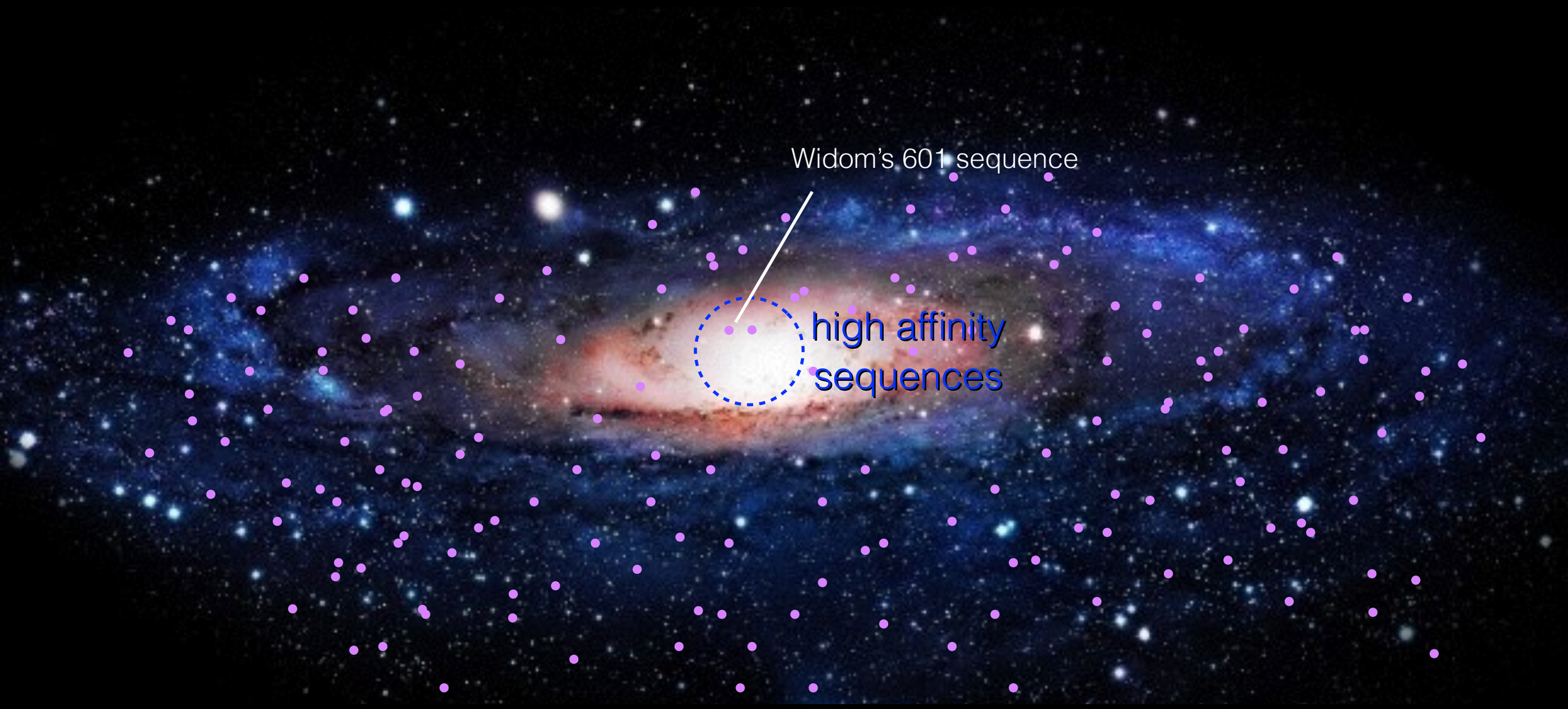


Leonardo da Vinci:

"The greater the weight held by this lifting tong, the better and stronger it will be supported."

Madrid Ms. I (BNM), fol. 22r

The sequence space

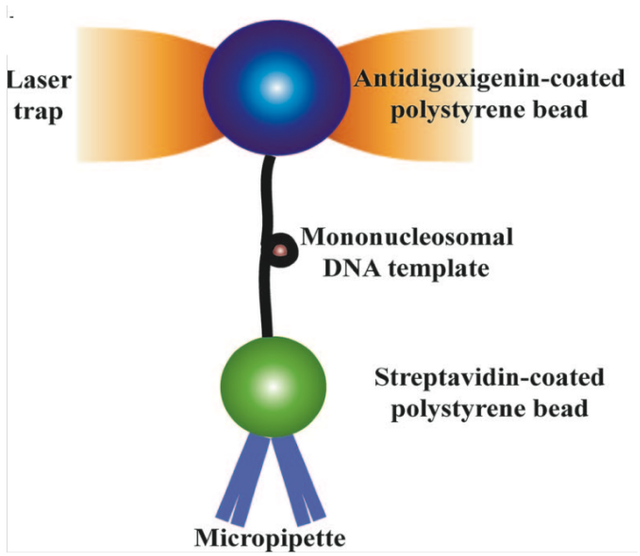


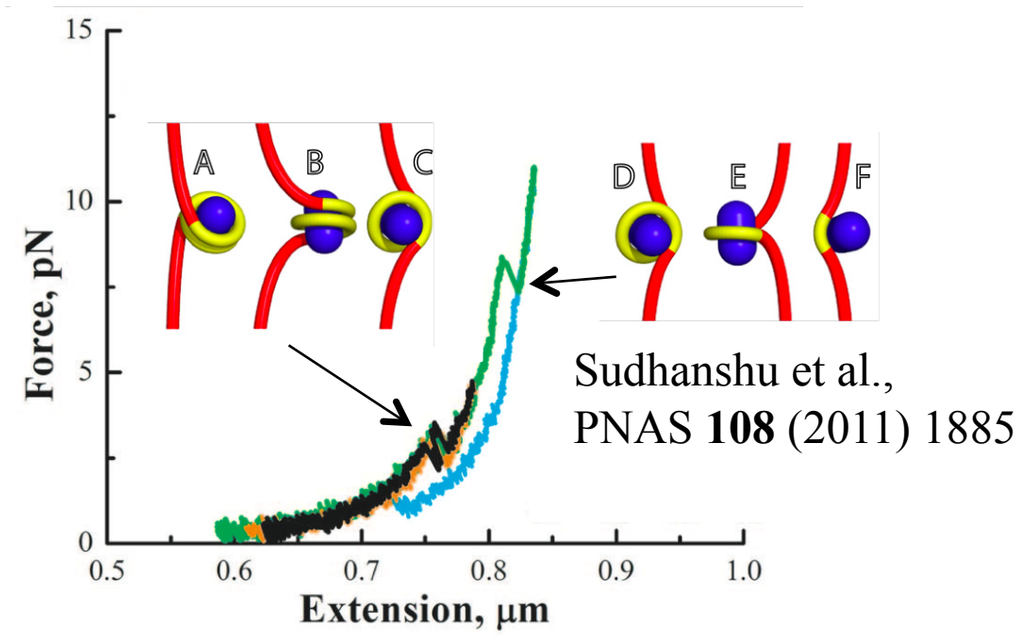
Random Pool 5 Tb

Lowary & Widom 1998

Single nucleosome under tension

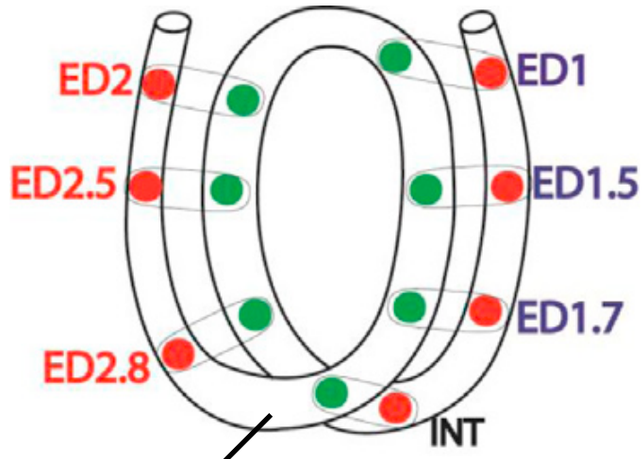
Mihardja, Spakowitz, Zhang, Bustamante
PNAS **103** (2006) 15871



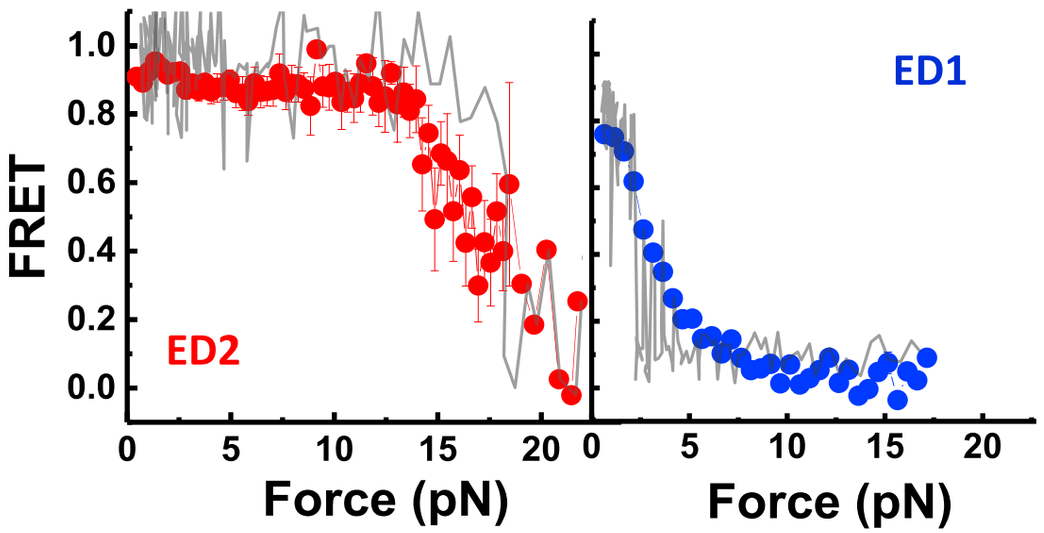


Sudhanshu et al.,
PNAS **108** (2011) 1885

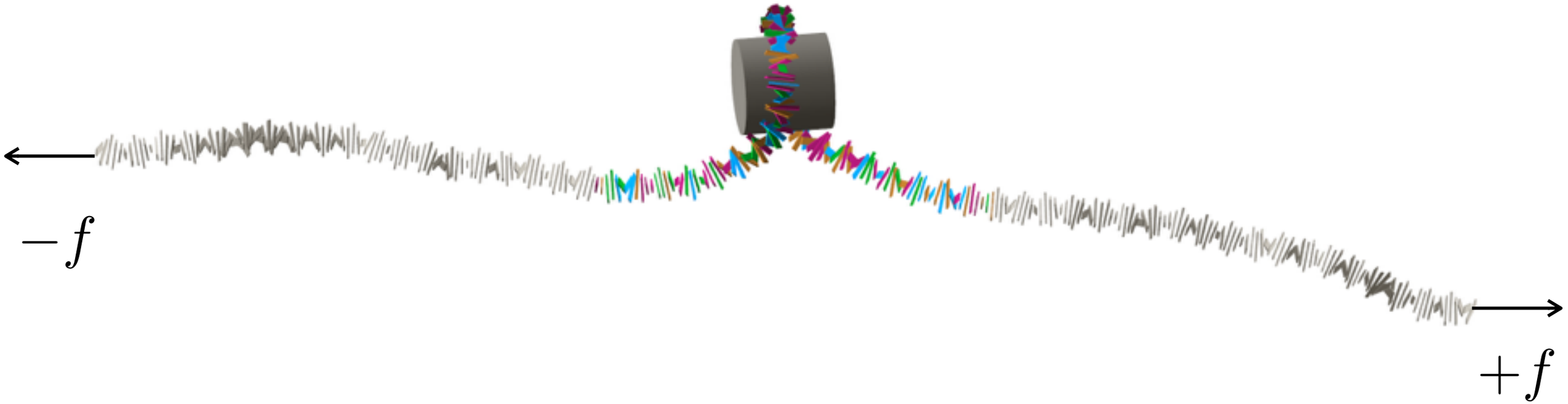
Ngo, Zhang, Zhou, Yodh, Ha
Cell **160** (2015) 1135

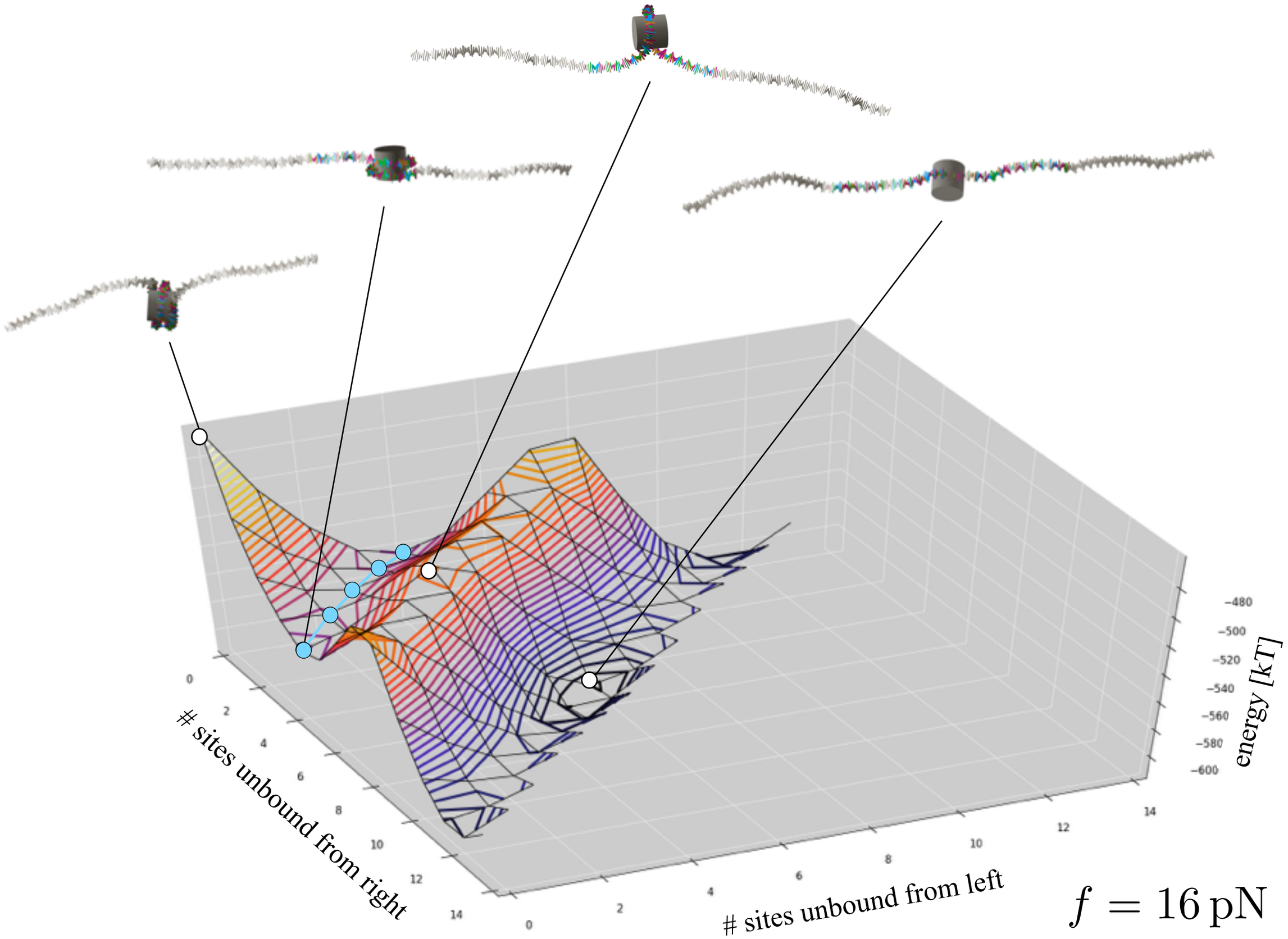


601 sequence

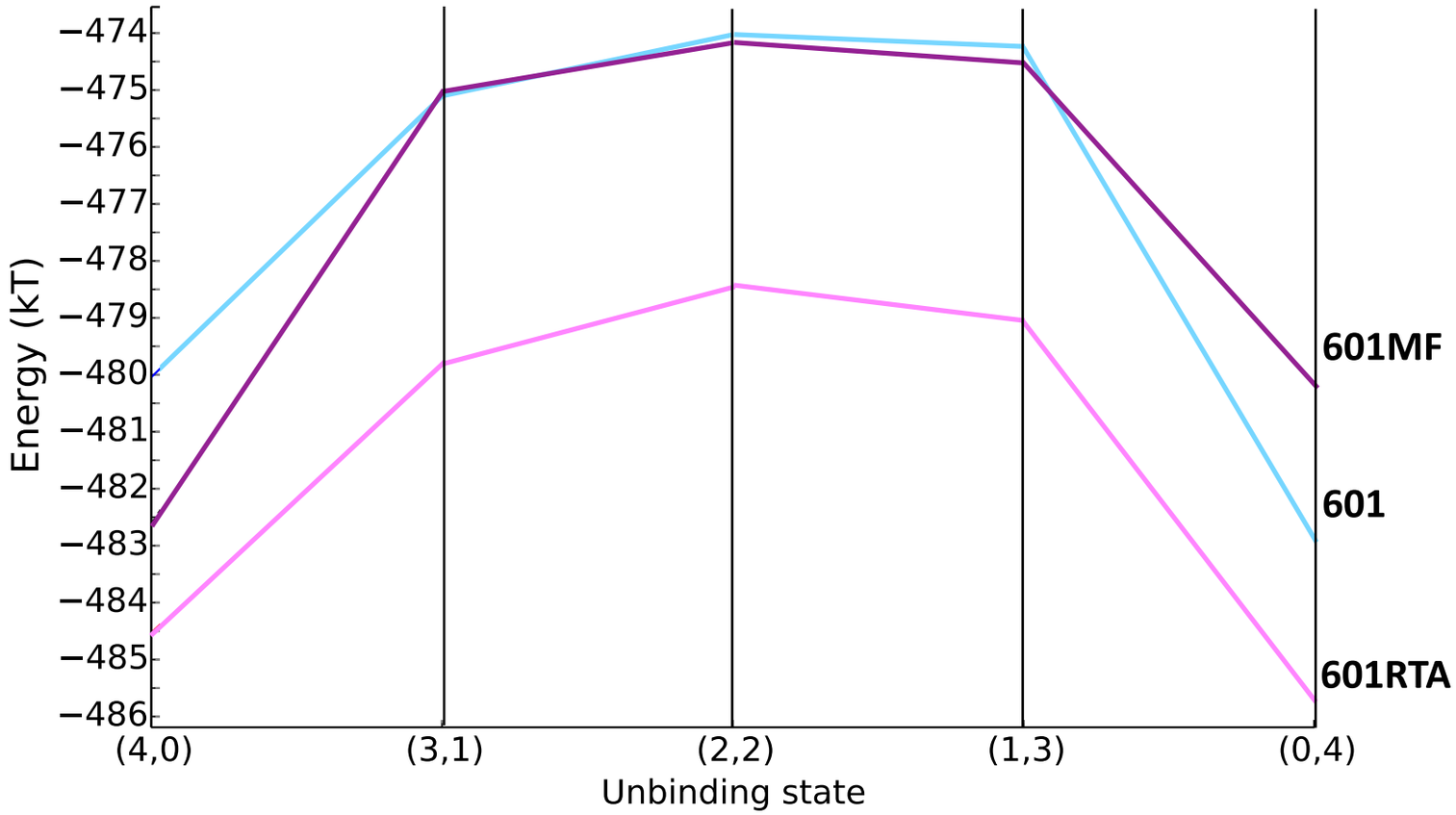


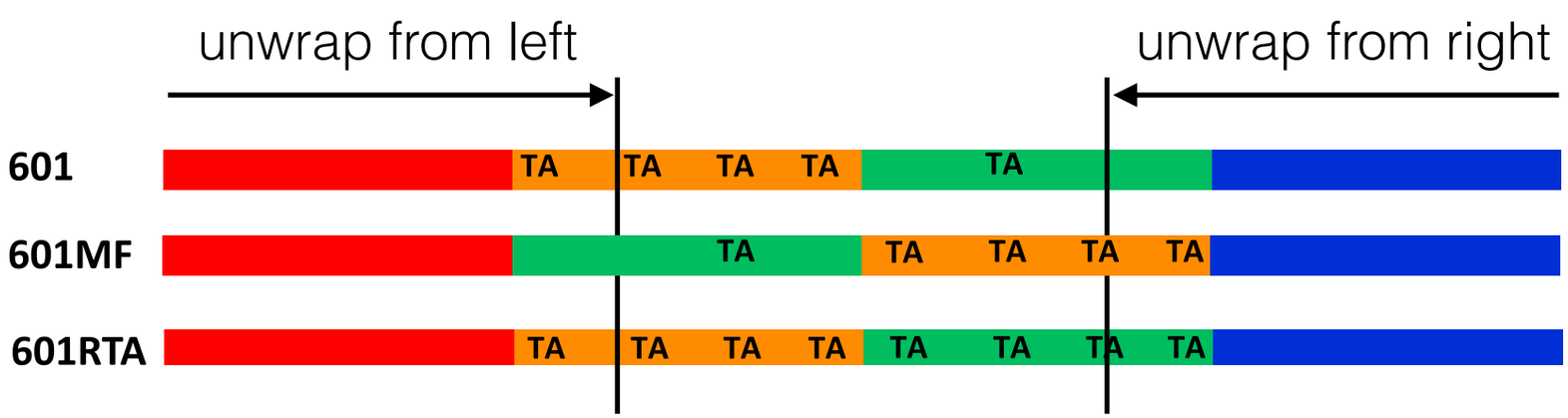
Why does the 601 nucleosome unwrap asymetrically?




0
2
4
6
8
10
12
14
sites unbound from right
0
2
4
6
8
10
12
14
sites unbound from left
−480
−500
−520
−540
−560
−580
−600
energy [kT]
$f = 16\,\mathrm{pN}$

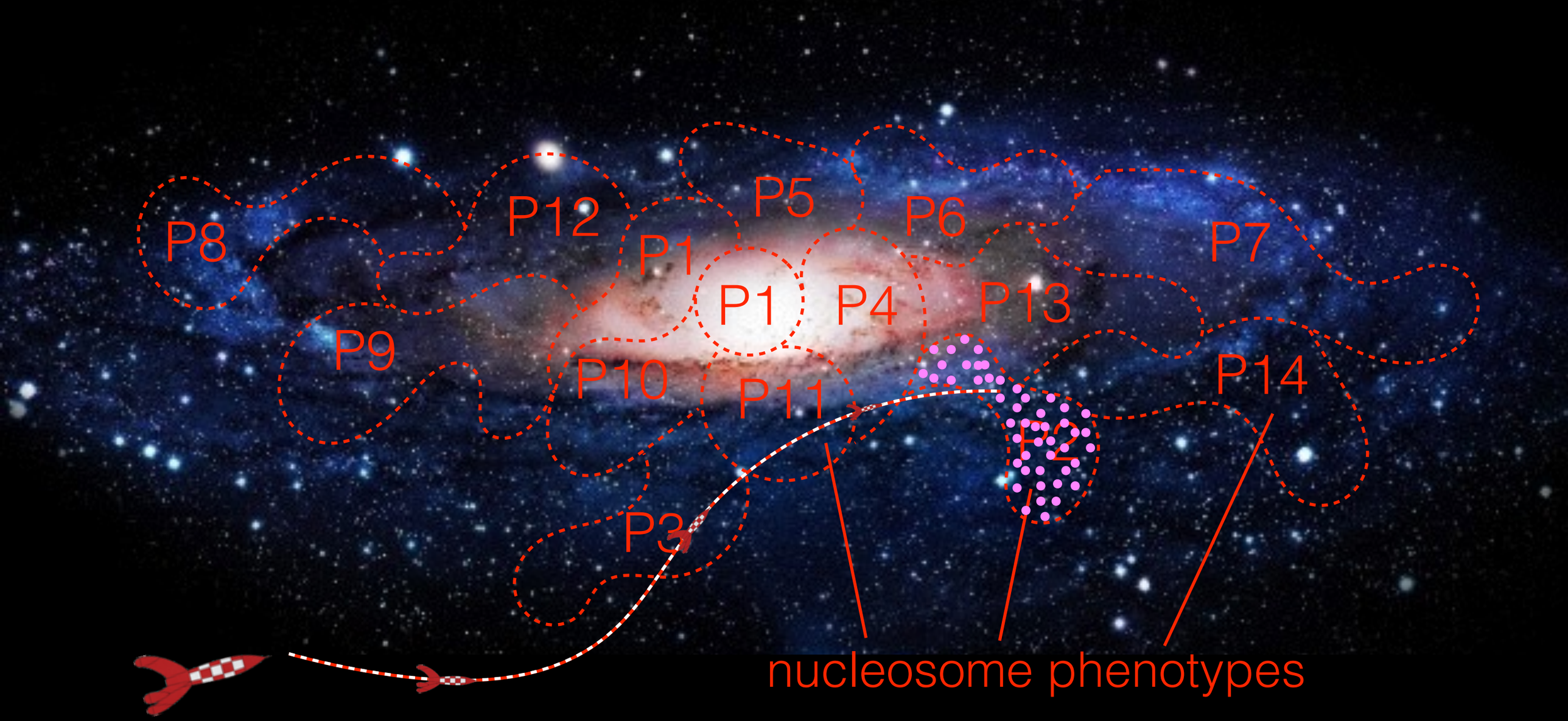
The metastable state is asymmetrical



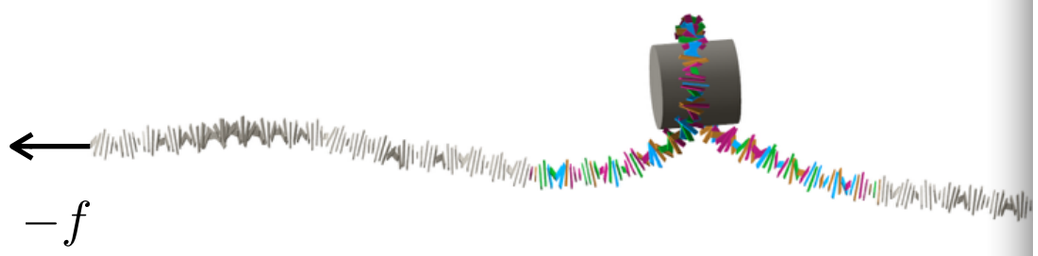


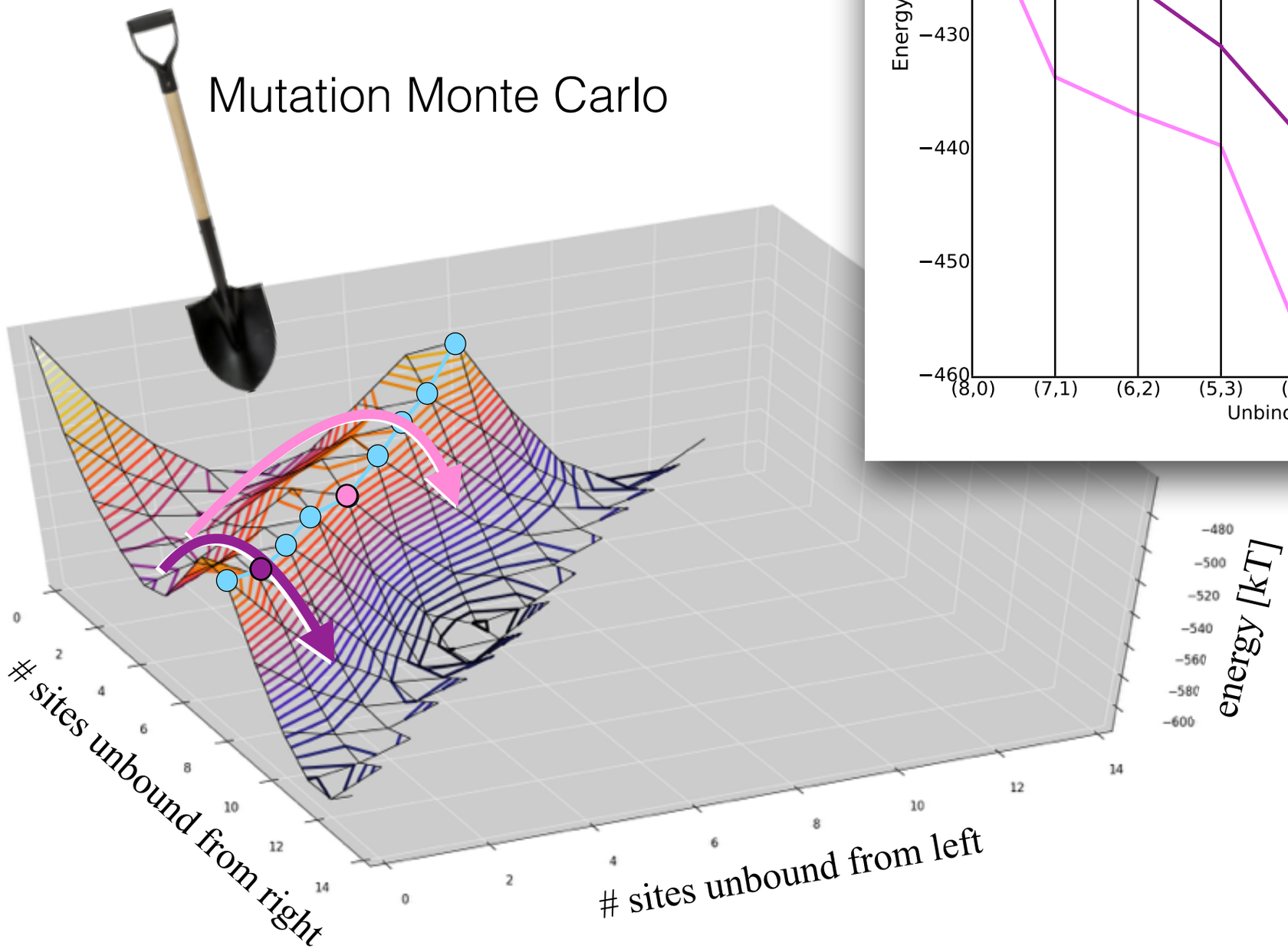
The sequence space

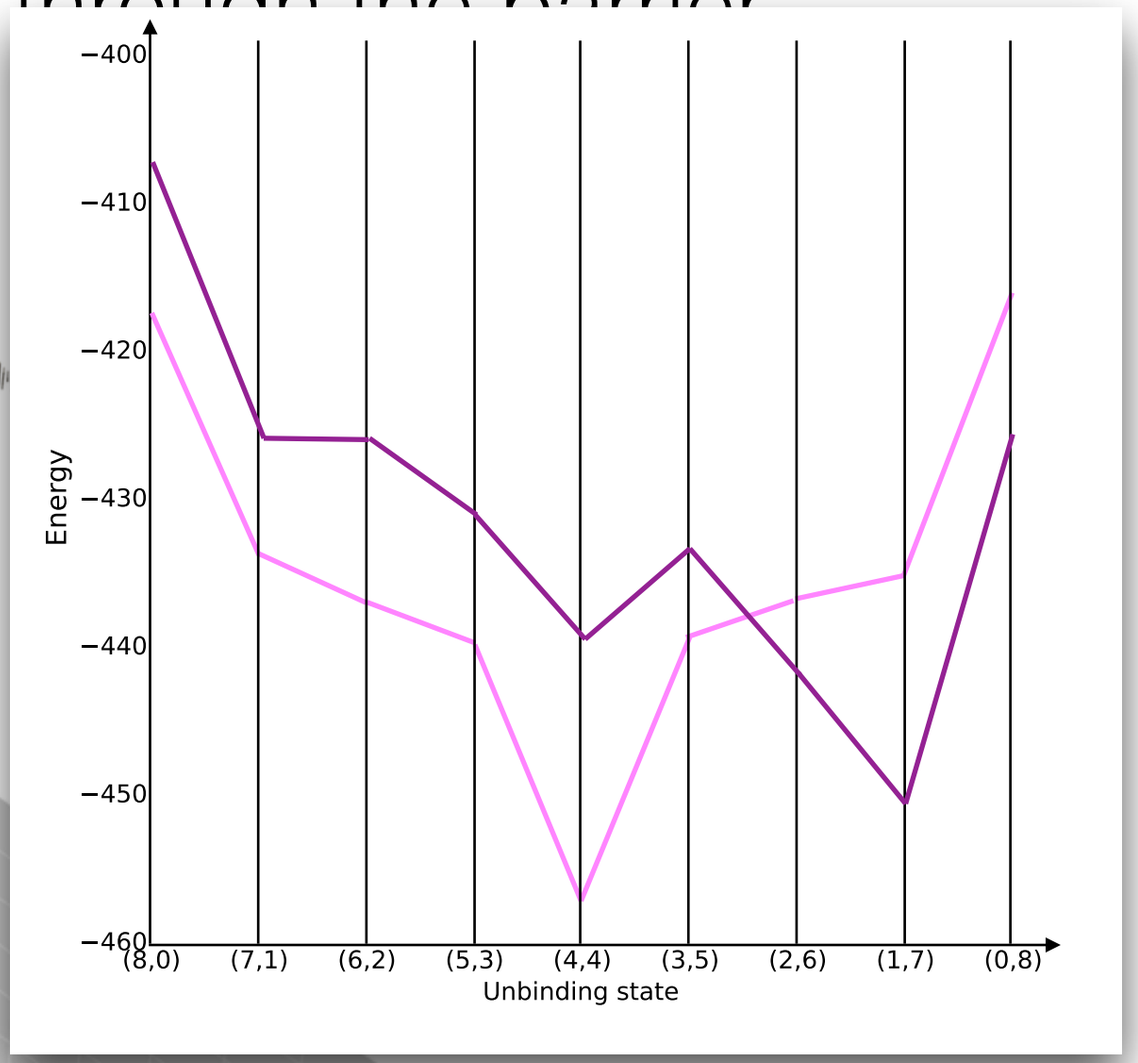
containing all 147bp nucleosomal genomes



Cutting a trench through the barrier







THE MECHANICAL GENOME

Summary:

Mechanical information can be used to

- position nucleosomes
- create various nucleosome phenotypes

Mechanical and genetic information can be multiplexed.

THE MECHANICAL GENOME

Some of the questions we would like to address:

- What nucleosomal phenotypes can we create and do they exist and have a specific function in real mechanical genomes?
- Can we simulate a mechanical evolution that leads to energy landscapes with statistical features as in real genomes?
- Can we find hints for the structures beyond the nucleosome from the mechanical landscape?

Acknowledgements

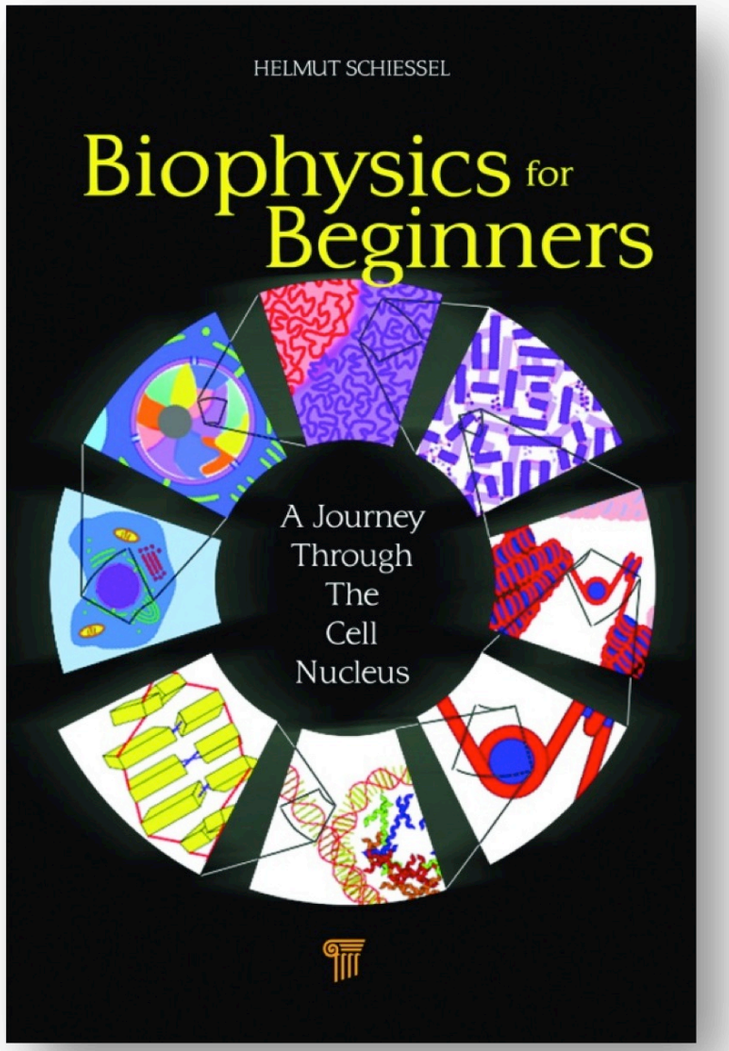
Behrouz Eslami-Mossalam

Raoul Schram

Marco Tompitak

Lennart de Bruin

John van Noort



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