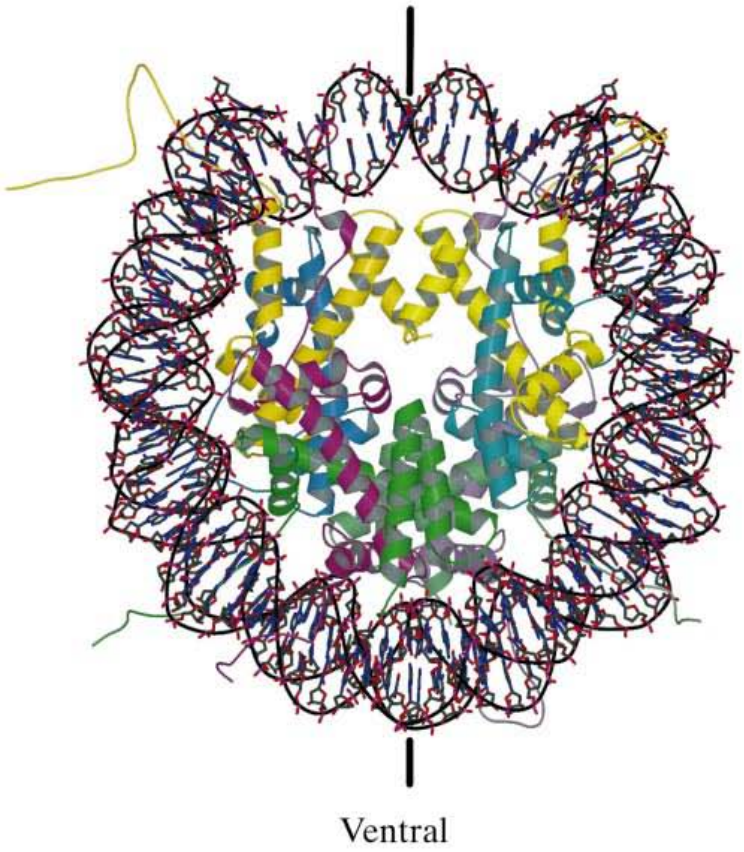
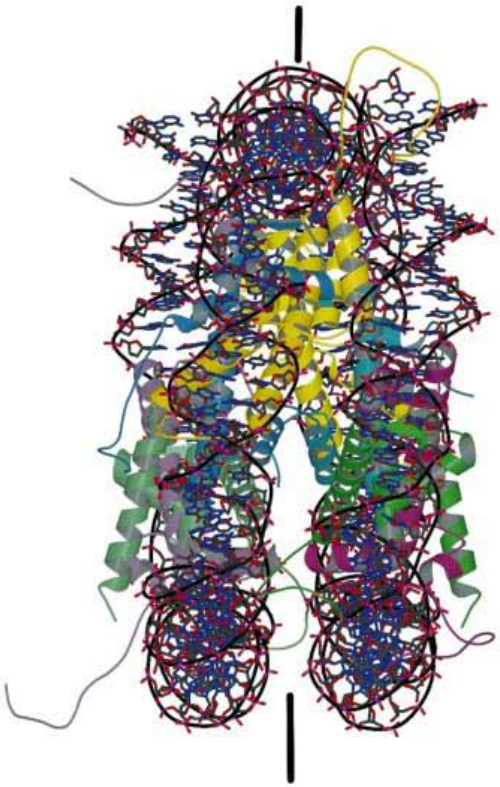
Simple physics and bioinformatics of nucleosome positioning

Edward N. Trifonov
University of Haifa, Israel

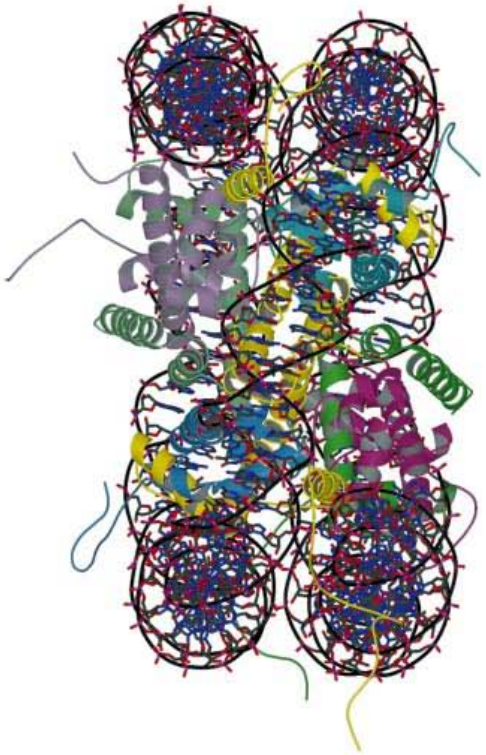
Beograd 2013



Ventral



Side



Dyad

Lab of G. Bunick, 2000

DNA in the nucleosome is severely deformed.

Neighboring base pairs become partially unstacked.

Some of the dinucleotide stacks
may be more deformable than others.
This also depends on their rotational orientations.

The purine-purine • pyrimidyne-pyrimidyne stacks (PuPu•PyPy or RR•YY) are very asymmetric

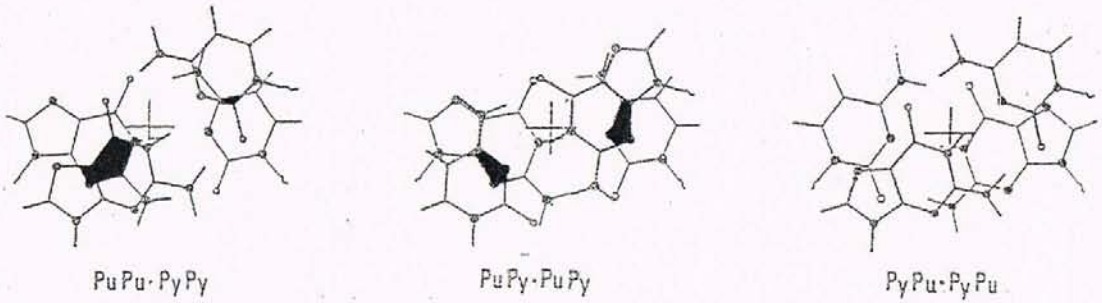


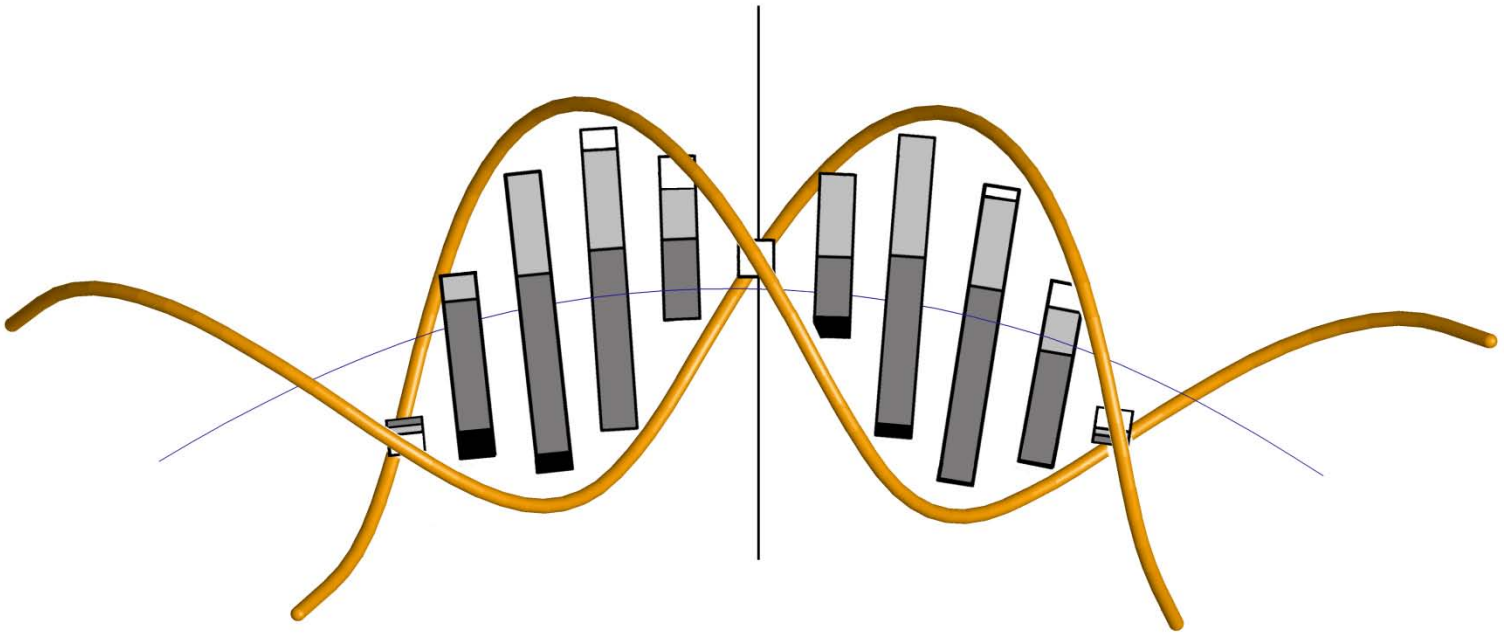
FIGURE 1. Projected views of two successive base-pairs of B DNA. Three possible cases of purine and pyrimidine base overlap are shown. Helix axes (perpendicular to the base-pairs) are indicated by crosses. Overlapping of the heterocyclic rings is shown in black. (From Arnott, S., Dover, S. D., and Wonacott, A. J., *Acta Crystallogr.*, B25, 2192, 1969. With permission.)

E.T.
CRC Crit. Rev. Bioch.
v. 19, 1985

Deformable stacks ("wedges") of the same kind
should be oriented on the surface
of the nucleosome the same way.

Hence - the preferred distances between
certain dinucleotides along the sequence
should be multiples of DNA period (10-11 bases)

5’



5’…YYYRRRRRYYYYYYRRR…

5’…TTTAAAAATTTTTTAAA…

Prediction (1980):

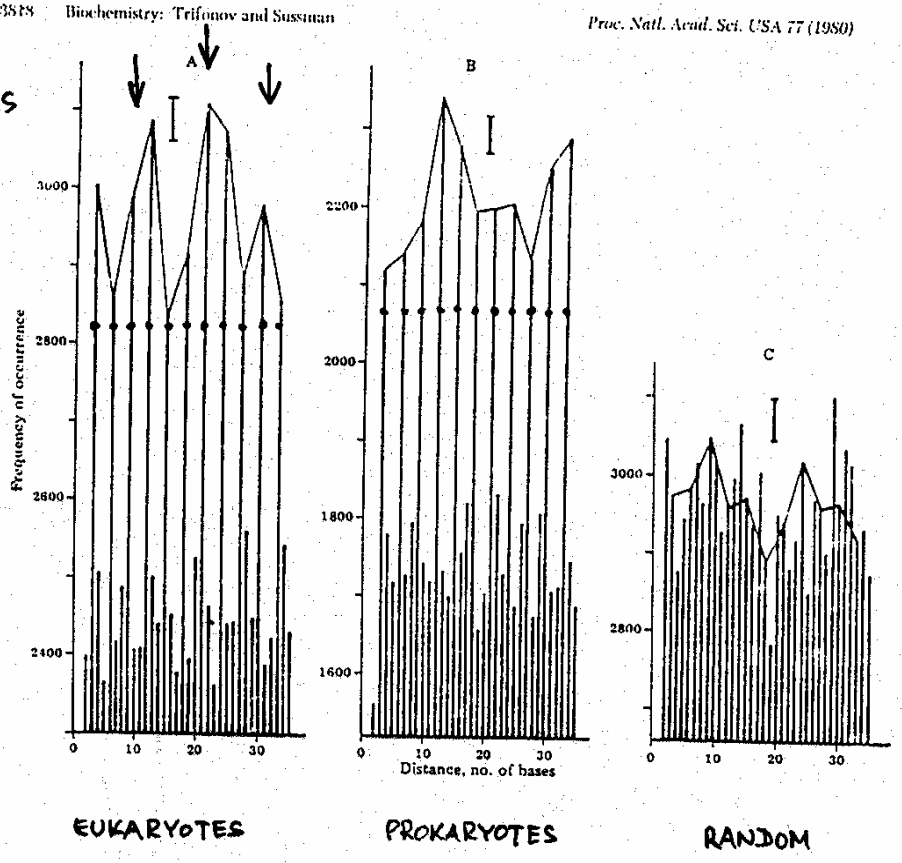
In the fragments of DNA bent in the nucleosome
the sequence should favor periodically positioned
like-named elements, 10-11 bases apart.

Since ~70% of DNA is involved in the nucleosomes -
any long sequence
should also possess the periodicity.

(Since the nucleosomes generally are not phased,
the periodicity would span only the nucleosome sequence size)

TRIFONOV, SUSSMAN, 1980

DISTANCE ANALYSIS (Autocorrelation)

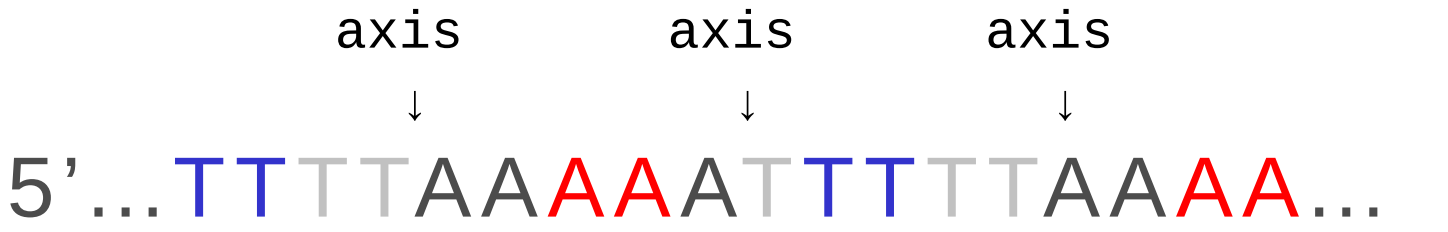


One more important prediction:

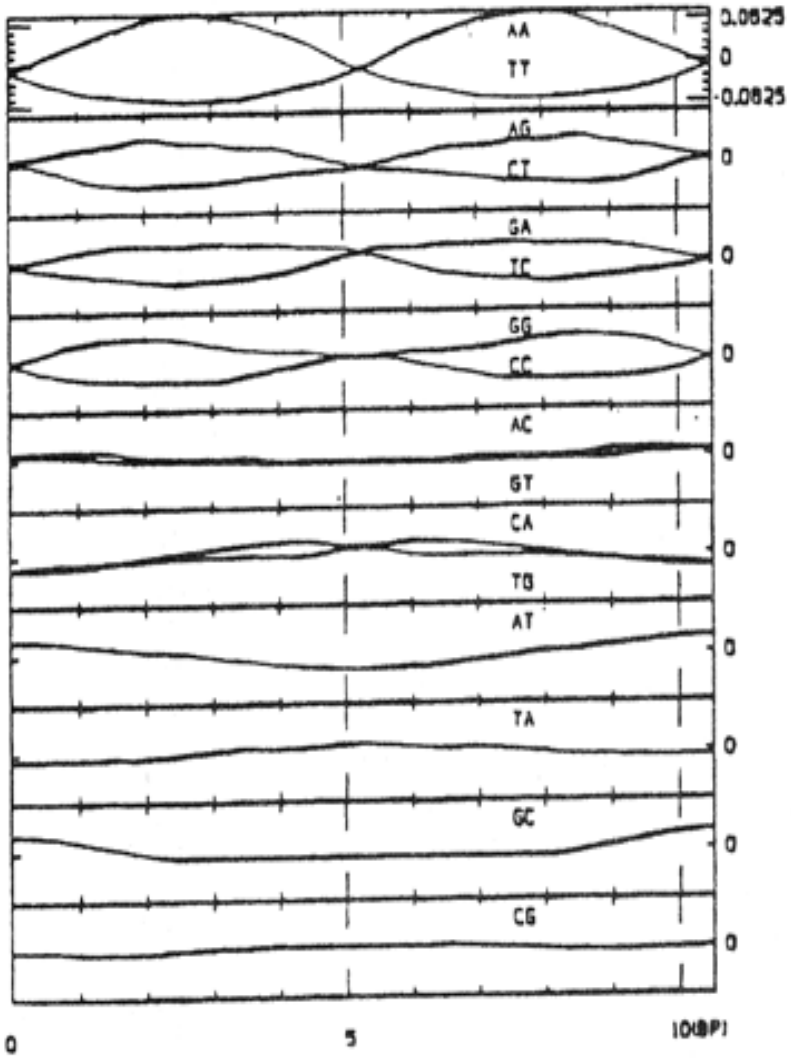
The deformation (bending) should follow the *dyad symmetry* of DNA molecule.

So should the dinucleotide elements (stacks).

Thus, within the sequence period
AA and **TT** elements should be
on opposite sides from the axes, at the same distance



5′…RRRYYYYYYRRRRRRYYY…

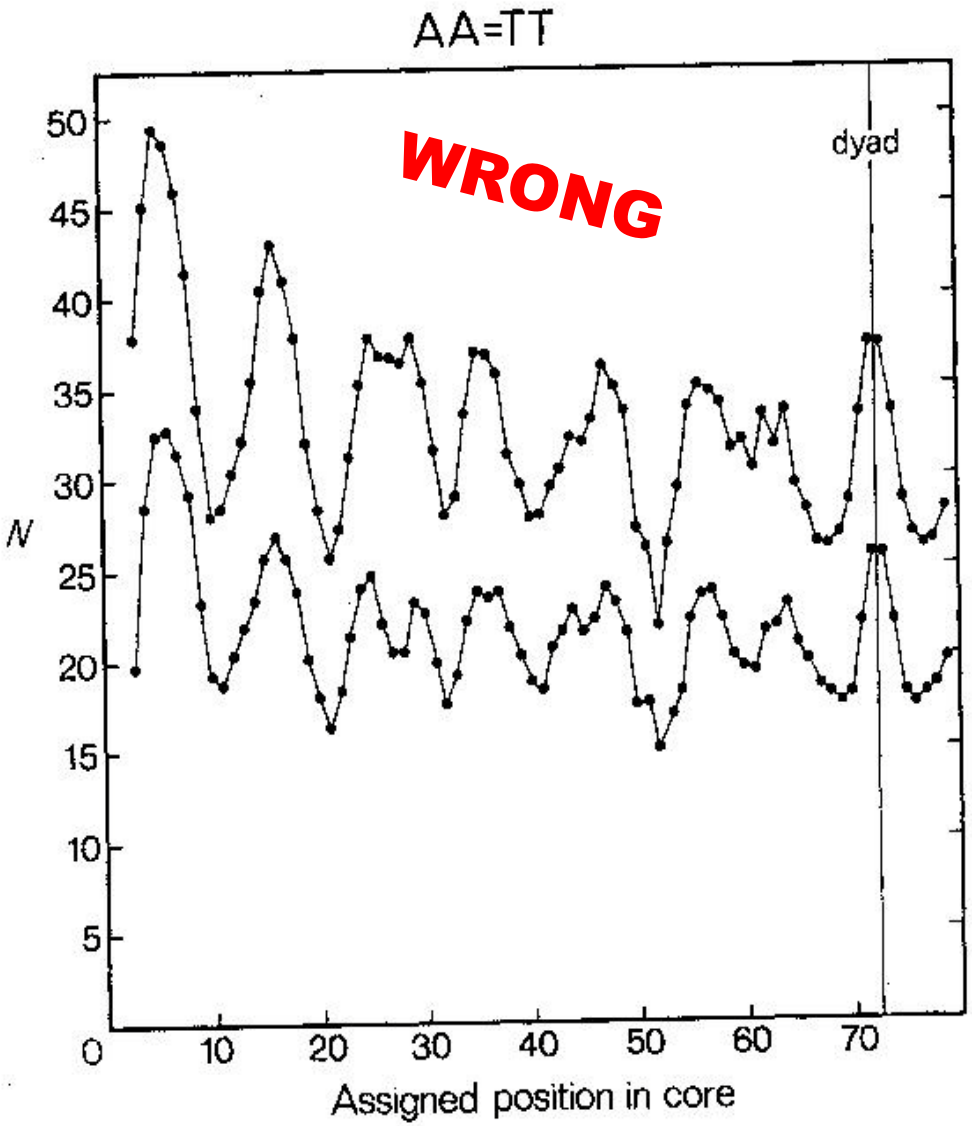


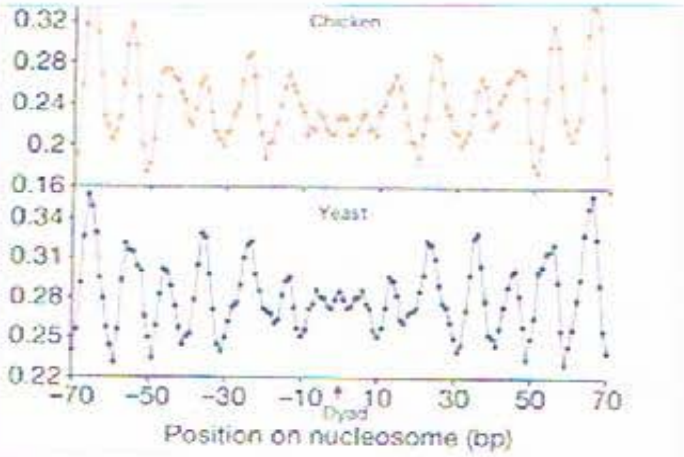
First matrix of nucleosome DNA bendability

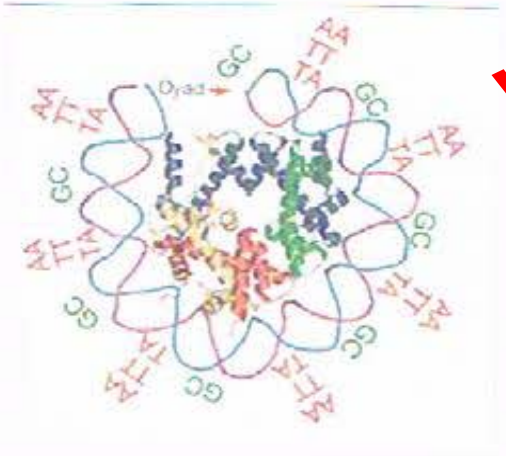
Mengeritsky and ENT, 1983

The ***dyad symmetry*** of the DNA in the nucleosome has been mistaken in 1986 by a reputed team of scientists for a ***mirror symmetry***.
("Errare humanum est")

This had catastrophic consequences for trustful naïve chromatin community (biologists), causing major confusion worldwide, still in effect


AA=TT
WRONG
dyad
N
50
45
40
35
30
25
20
15
10
5
0
10
20
30
40
50
60
70
Assigned position in core





WRONG

Segal,⋯, Widom, Nature 2006

Yet another confusion reigned in the community:

The periodic signal in the nucleosome DNA sequence is very weak, and it is rather hard task to find out what would be the true nucleosome positioning sequence.

Actually, none of the experimentally extracted nucleosome DNA sequences
shows any visible periodicity.

The periodic hidden signal can be only revealed by one or another signal processing procedure applied to large amount of sequences.

The idea of the periodicity has been accepted, but none of suggested sequence patterns has been trusted

Lowary and Widom (1998) took large ensemble of synthetic DNA fragments with random sequences, and selected those of them which formed

strong nucleosomes

The sequences demonstrated rather strong periodicity of TA dinucleotides

Clone 601,

from collection of Lowary and Widom (1998)

...CAGCGCG**TA**CGTGCGTT**TA**AGCGGTGC**TA**GAGCTGTC**TA**C...

TACGTGCGTT**TA**
TAAGCGGTG**C**TA
TAGAGCTGT**C**TA

We took all **TA**nnnnnnnn**TA** segments
from the collection of Lowary/Widom,
and analysed which dinucleotides
are most frequently located in the
interval between **TA**, and in which positions.

Bendability matrix for strong nucleosome DNAs of Lowary and Widom collection

	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**0**
AA	0	16	3	0	0	1	0	0	0	0	0
AC	0	5	2	5	2	3	5	3	1	0	0
AG	0	**25**	11	**9**	2	4	1	1	1	0	0
AT	0	2	0	3	1	1	3	1	2	0	0
CA	0	0	1	0	2	4	3	1	0	0	0
CC	0	0	0	0	5	4	7	3	6	0	0
CG	0	0	4	4	4	4	4	5	3	0	0
CT	0	0	0	2	1	2	1	9	11	**22**	0
GA	0	0	**12**	4	3	3	0	0	0	0	0
GC	0	0	4	7	6	7	5	10	5	0	0
GG	0	0	7	4	3	3	7	0	1	0	0
GT	0	0	2	7	6	4	5	6	2	6	0
TA	**48**	0	1	1	4	1	2	3	0	0	**48**
TC	0	0	0	0	1	1	1	4	10	0	0
TG	0	0	0	1	8	6	4	2	1	0	0
TT	0	0	1	1	0	0	0	0	5	20	0

C T A G A G x x x x **C T A G** – manually from the matrix
C T A G x x x x x x C T A G – from Lowary & Widom paper
C T A G A G G C C T C T A G – by dynamic programming

Y R R R R R Y Y Y Y Y R

T A G A G G C C T C T A

A T C T C C G G A G A T

The periodical pattern hidden in the sequences of Lowary and Widom is selfcomplementary (that is, displays *dyad symmetry*), and manifests alternation of RRRRR and YYYYY

HALF

Taking the elegant idea of Lowary and Widom as a lead

we extracted *natural* strong nucleosomes

from whole genomes *computationally.*

We looked for periodical sequences in genomes

The exact value of the period of DNA in the nucleosome has been matter of bitter argument between two schools during last 30 years:

Close to 10.0 bp per turn - Crick, Klug, Richmond
(torsional constraint for unfolding of the nucleosome)

Close to 10.4 bp per turn - our works
(no torsional constraint)

Structural (sequence) periodicity of nucleosome DNA

DNase I digestion of chromatin	10.30-10.40 bp	Prunell, Kornberg, Lutter, Klug, Levitt, Crick, **1979**
Beat effect, DNase I	10.33-10.40 bp	Bettecken, **1979**
Analytical geometry of nucl. DNA	10.30-10.50 bp	Ulanovsky, **1983**
DNA path in nucleosome crystals	10.36-10.44 bp	Cohanim, **2006**
CG periodicity, honey bee	10.36-10.44 bp	Bettecken, **2009**
DNase I digestion of chromatin	10.30-10.40 bp	Boyle et al., 2008 Winter et al., **2013**

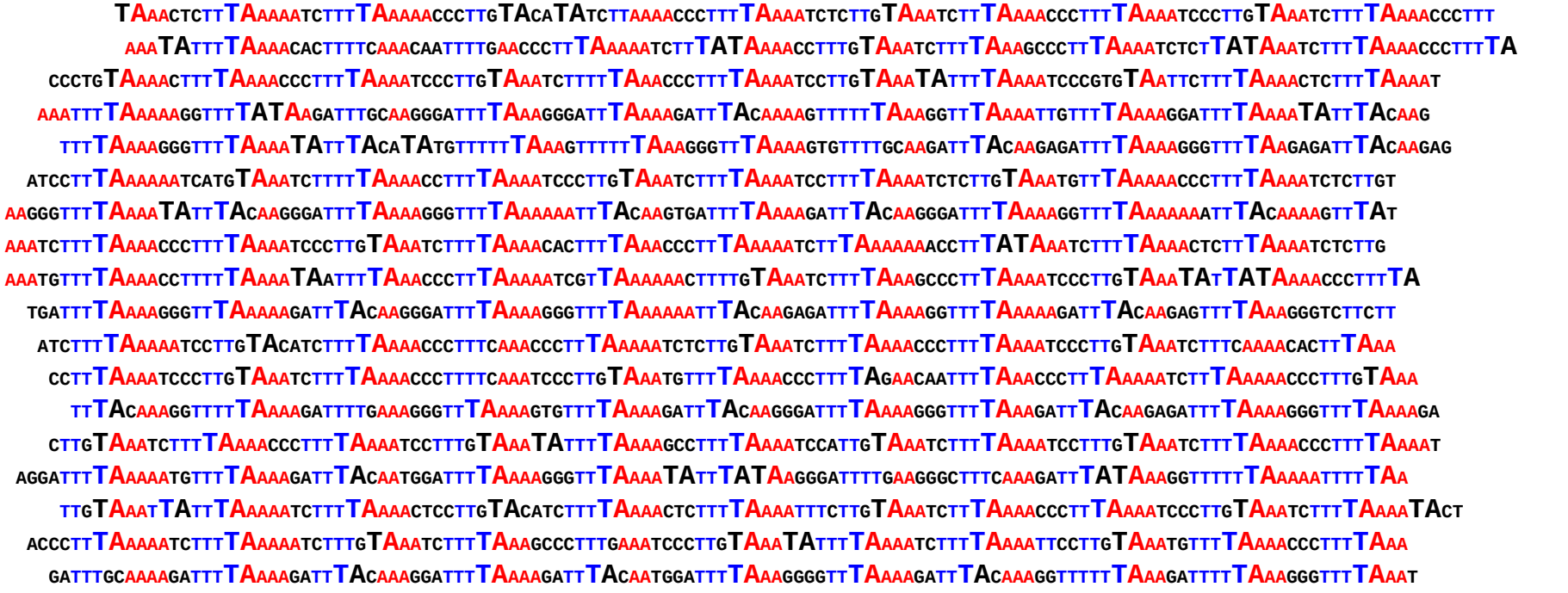
Common range 10.36-10.40 bp

Magic distances, 10.4•n bases

	nearest integers
10.4	10
20.8	21
31.2	31
41.6	42
52.0	52
62.4	62
72.8	73
83.2	83
93.6	94
104.0	104
114.4	114

The ideal nucleosome positioning sequence
would contain some periodically repeating motif,
and all the distances between the same dinucleotides
would be magic distances.
Strong nucleosome DNA would show many magic distances.

The strongest nucleosomes of *A. thaliana* display very clear though still imperfect periodicity



The consensus pattern for *A.thaliana* is repetition of TAAAAATTTTTA, again, alternation of RRRRR and YYYYY, and complementary symmetry

Before this picture was generated

(Dec. last year) nobody ever had seen

that the nucleosome sequences

look, indeed, periodical

From the bendability matrices

for the strong nucleosomes:

```
T AGAGG CCTCT A   Lowary and Widom
T AAAAA TTTTT A   A.thaliana
T AAAAA TTTTT A   C.elegans
T AAAAA TTTTT A   H.sapiens
T AAAAA TTTTT A   isochores L1, L2, H1 and H2
C GGGGG CCCCC G   isochores H3

Y RRRRR YYYYY R   common for all
```

(and complementarty symmetry)

Previously detected patterrns, species:

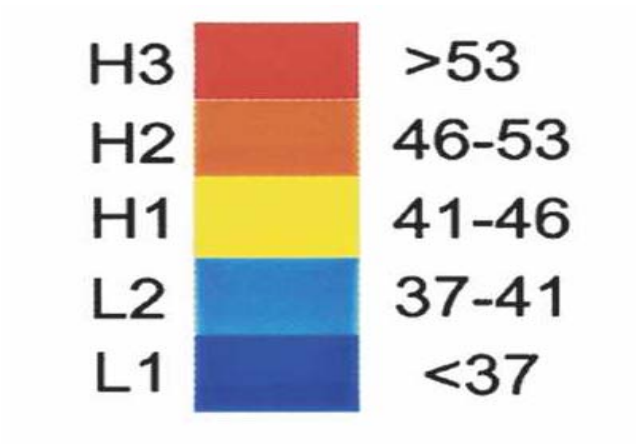
	species	authors	method
C GRAAA TTTYC G	*C. elegans*	Gabdank, 2009	A
C AAAAA TTTTT G	*C. elegans*	Rapoport, 2011	B
C AAAAA TTTTT G	*A. gambiae*	same	B
C AAAAA TTTTT G	*C. albicans*	same	B
C AAAAA TTTTT G	*D. melanogaster*	same	B
C AAAAA TTTTT G	*S. cerevisiae*	same	B
T AAAAA TTTTT A	*A. mellifera*	same	B
T AAAAA TTTTT A	*A. thaliana*	same	B
T AAAAA TTTTT A	*D. discoideum*	same	B
T AAAAA TTTTT A	*D. rerio*	same	B
T AAAAA TTTTT A	*G. gallus*	same	B
T AAAAA TTTTT A	*H. sapiens*	same	B
T AAAAA TTTTT A	*M. musculus*	same	B
c GGGGG CCccc G	*C. reinhardtii*	same	B
Y RRRRR YYYYY R	consensus		

A – signal regeneration, nucleosomes
B – Shannon N-gram extension, whole genome

Nucleosome positioning patterns of various isochores (Frenkel et al., 2011) by N-gram extension

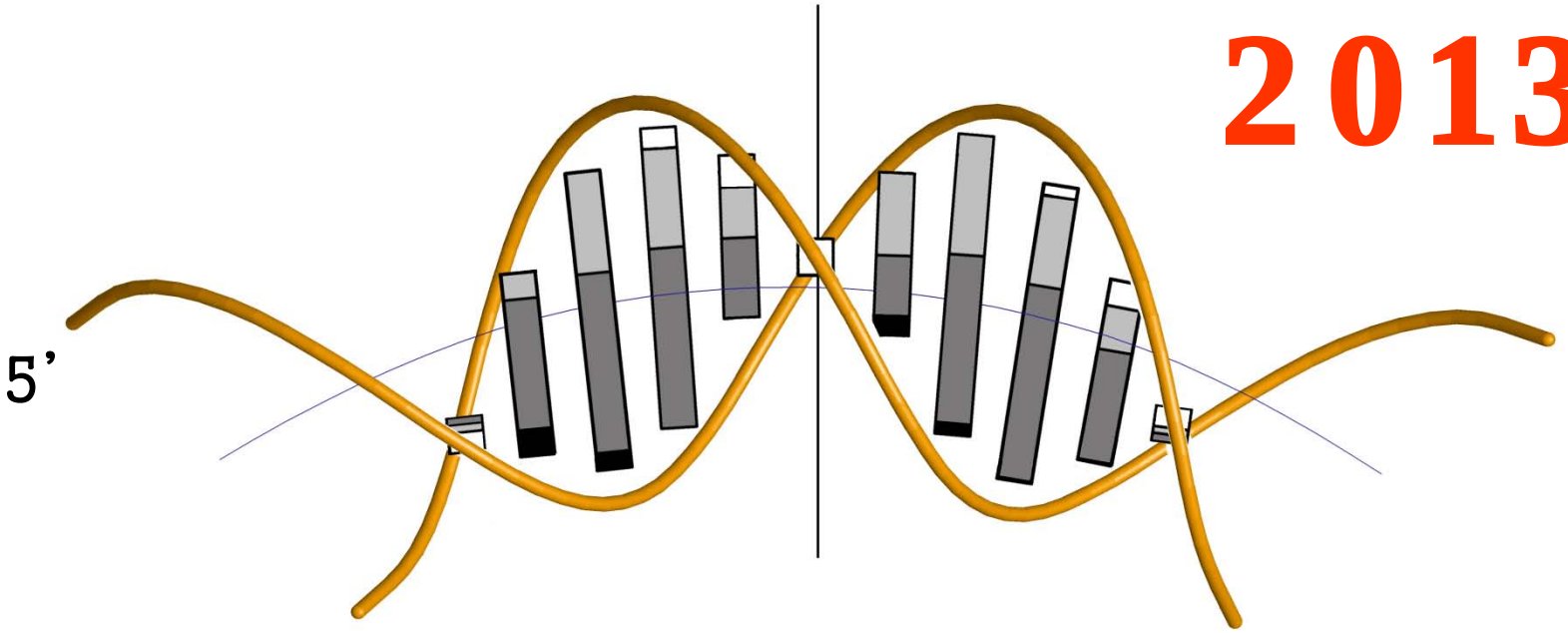
C AGGGG CCCCT G
C GGGGA TCCCC G
C AGAAA TTTCT G
T AAAAA TTTTT A
T AAAAA TTTTT A

Y RRRRR YYYYY R



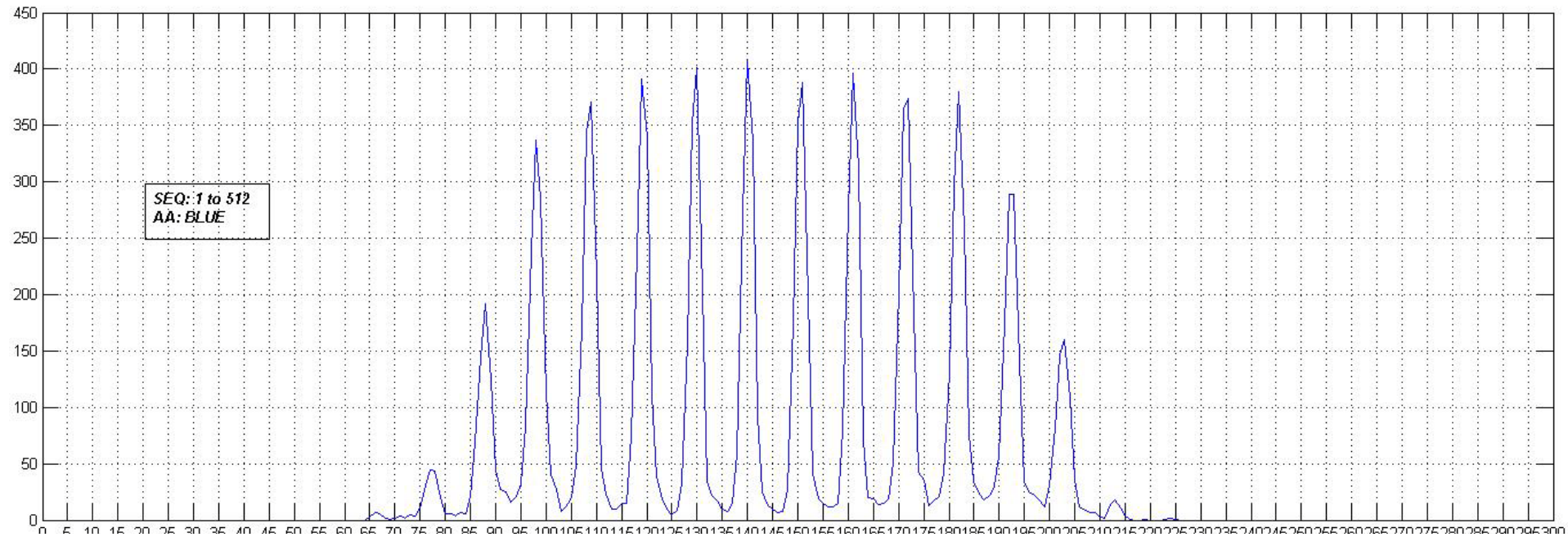
Nucleosome positioning pattern

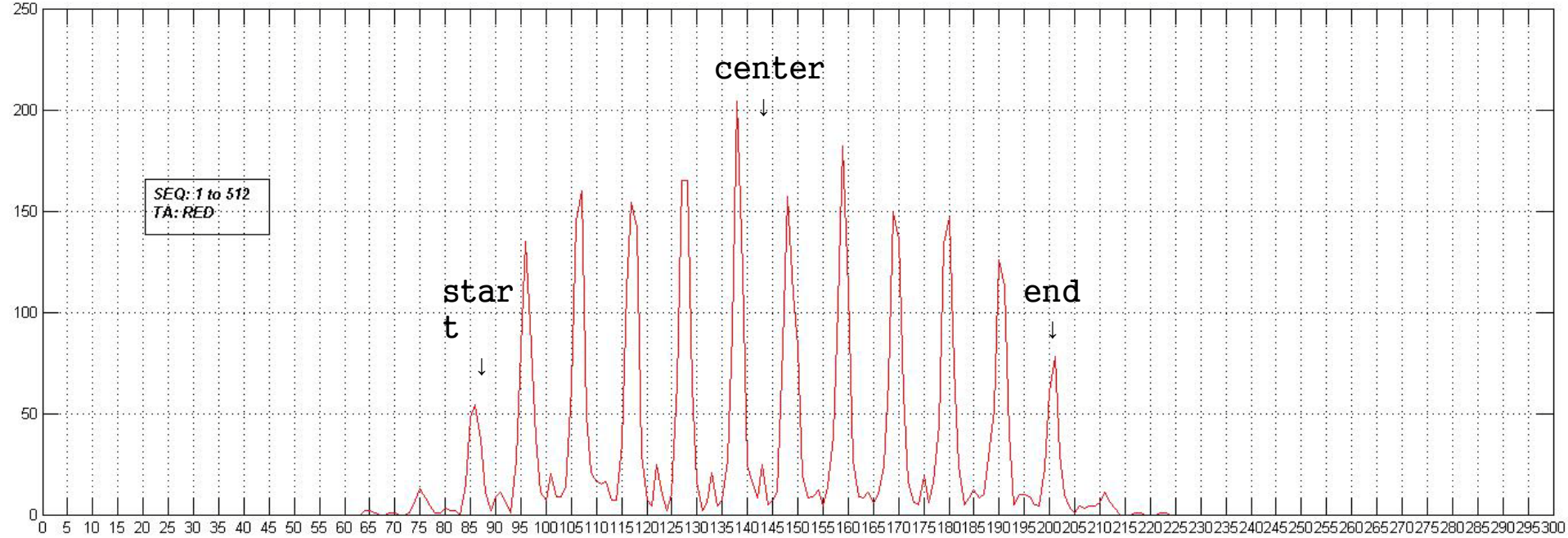
2013

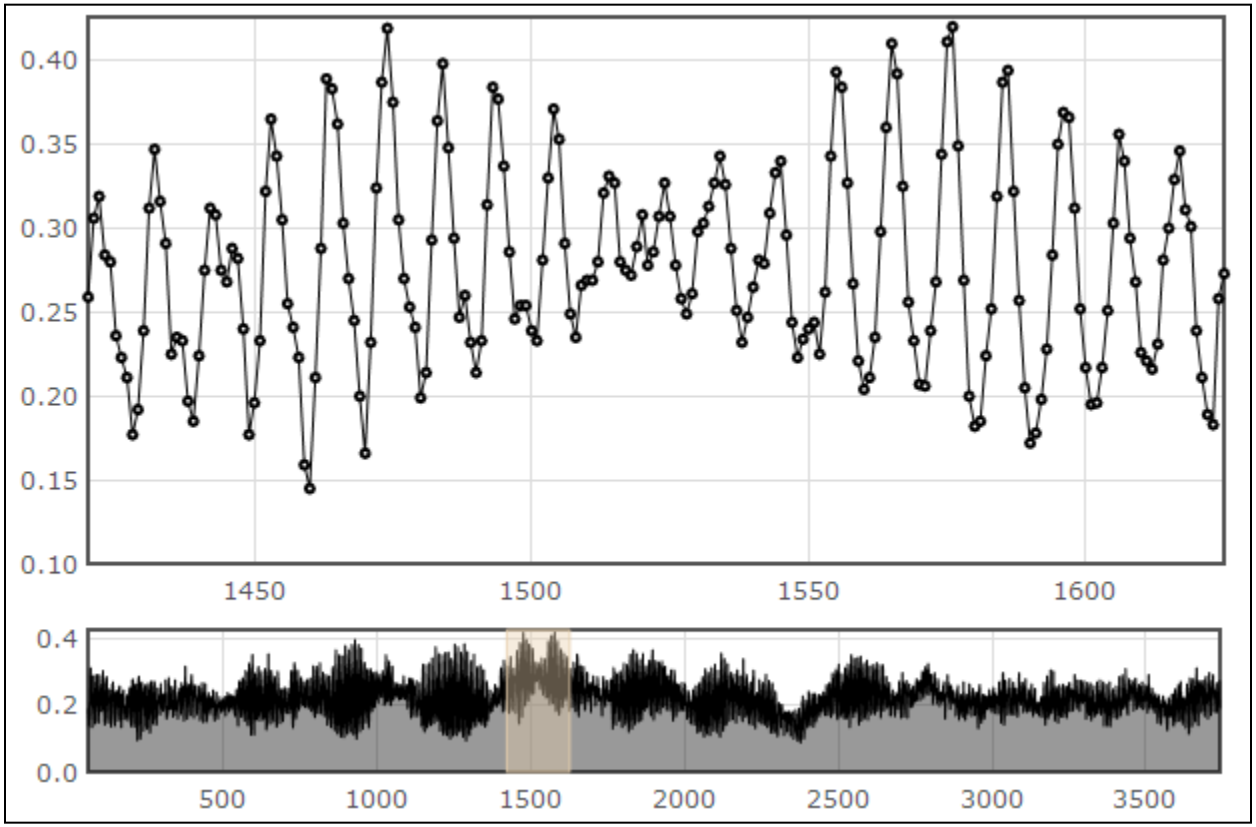


5’…YYYRRRRRYYYYYYRRR…

TA	AT	TA
CG	GC	CG
TG	AC	TG
CA	GT	CA
Contact with arginines	Exposed	

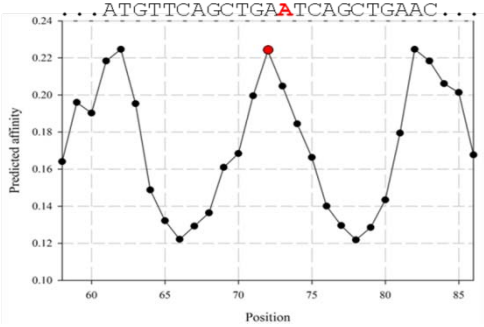

SEQ: 1 to 512
AA: BLUE

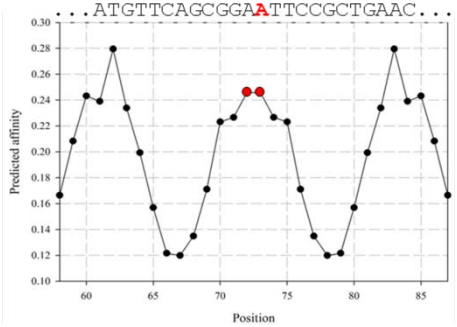

SEQ: 1 to 512
TA: RED
center
start
end

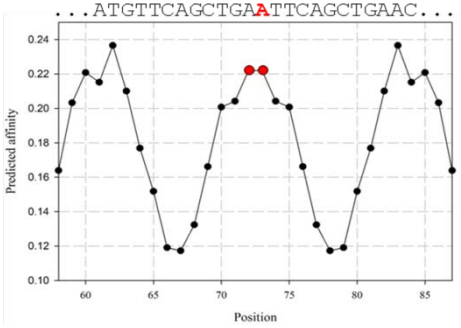


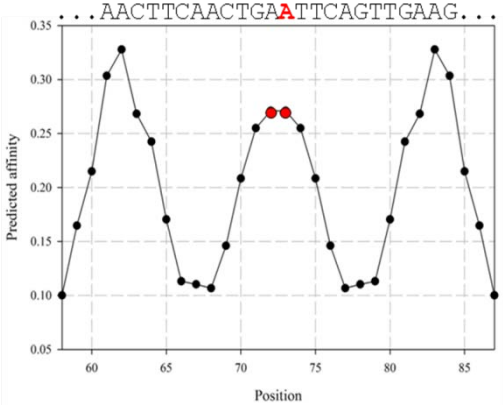
Example of the output from the nucleosome mapping server http://www.cs.bgu.ac.il/~nucleom (Google “finestr”)

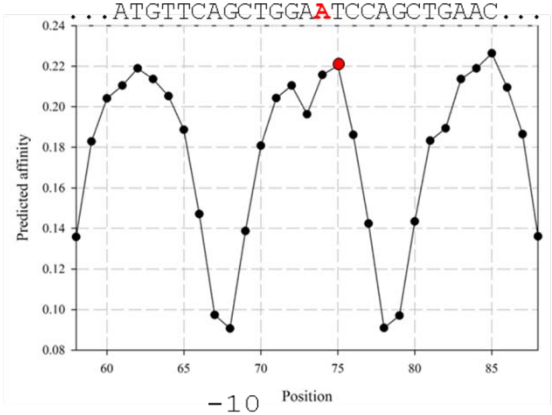
Mapping of sharply positioned nucleosomes

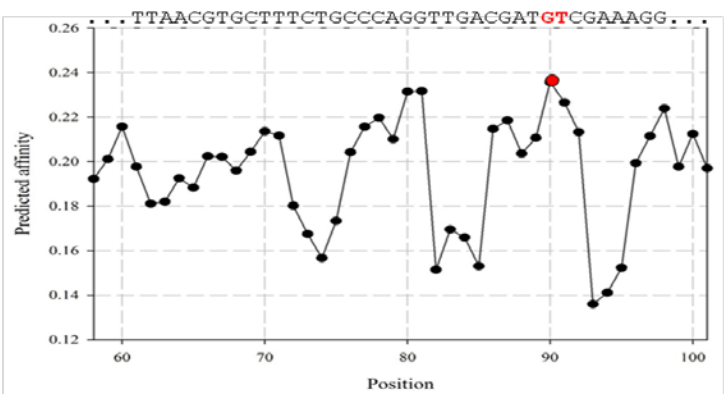


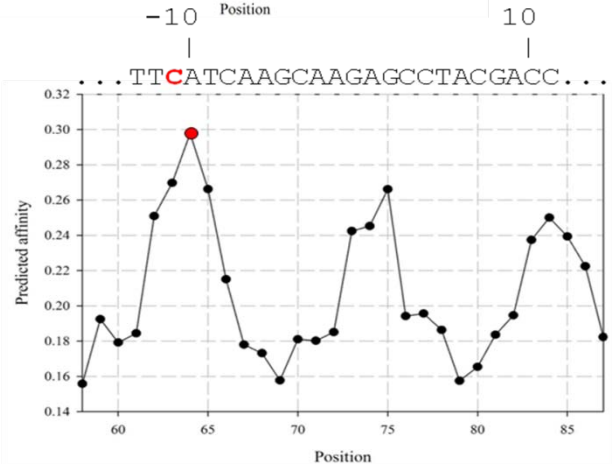


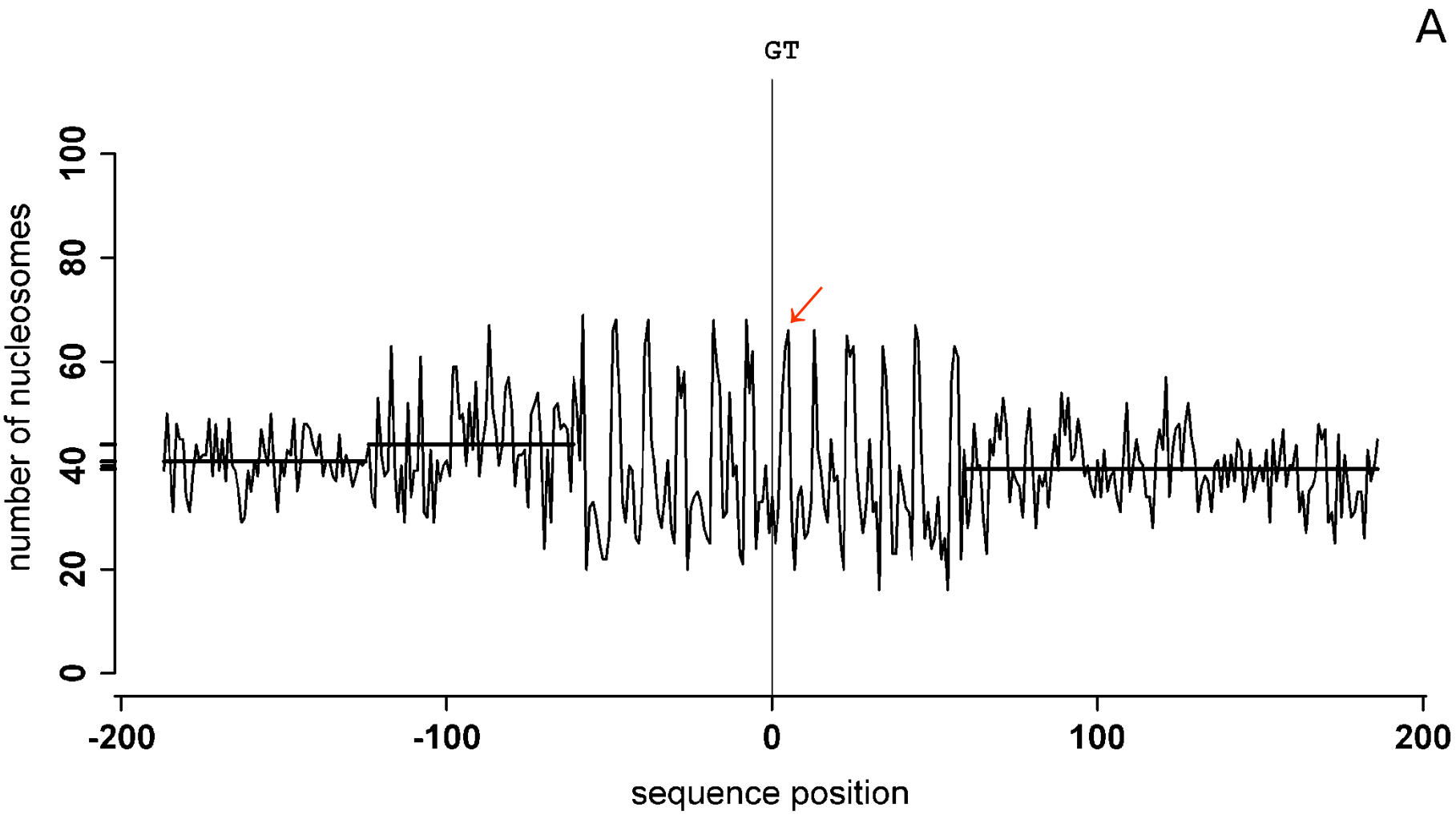








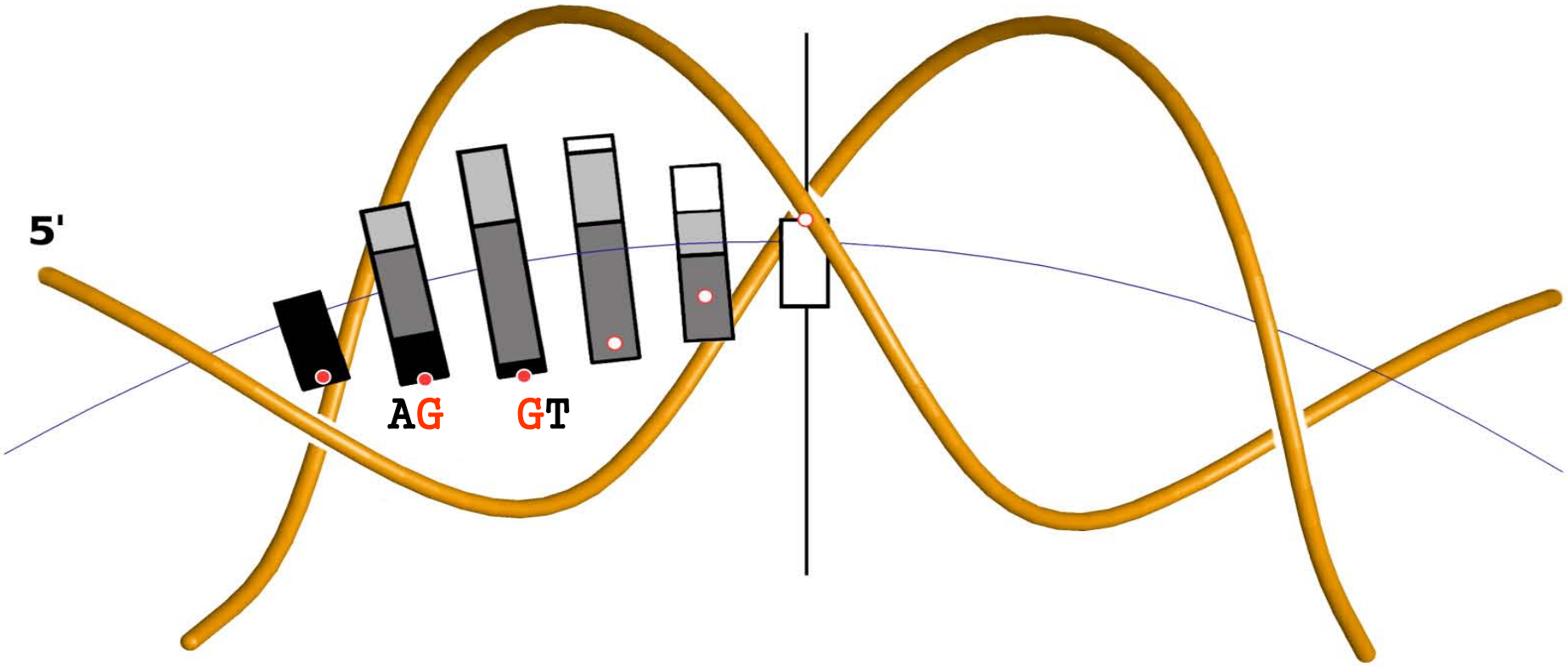




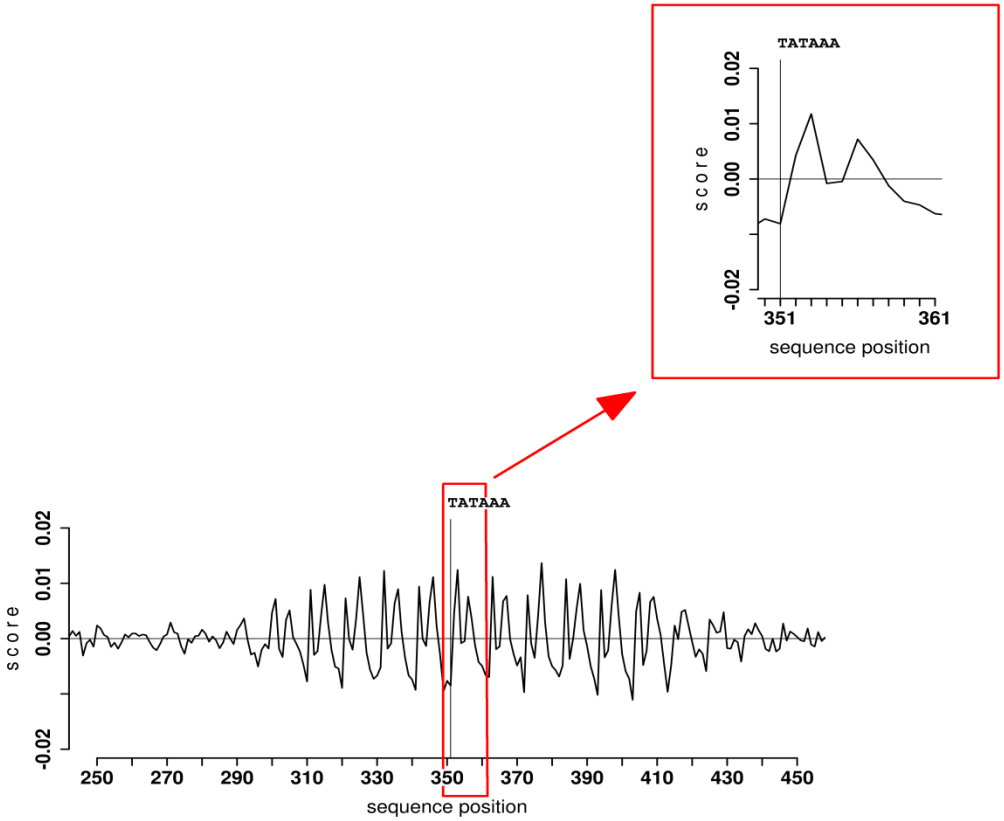
Nucleosomes around the GT splice junctions

Hapala J, ENT, Gene 2011

Splice junctions are hiding on the surface of histone octamers



Dots • – N9 atoms of guanines



Nucleosome DNA which carries promoter TATAAA box has two rotational settings encoded in the sequence (two peaks within one period).

Jan Hapala & ET, in press

TATA-switch

Two alternative positions of TATAAA box
in the promoter nucleosomes
are separated by 140 (220) degrees,
which corresponds to exposed and inaccessible
orientations of the box.

By shifting the DNA along its path by 4(6) bases,
the promoter is switched **ON** or **OFF.**

The switch (shift) may be triggered by remodelers or transcription factors.

ACKNOWLEDGEMENTS

Recent colaborators (2009-2013):

Idan **Gabdank** (Beer Sheva, Israel)
Zakharia **Frenkel** (Haifa, Israel)
Alexandra **Rapoport** (Haifa, Israel)
Thomas **Bettecken** (München, Germany)
Jan **Hapala** (Brno, Czech Republic)
Bilal **Salih** (Haifa, Israel)
Vijay **Tripathi** (Haifa, Israel)

Earlier colaborators (1979-2008)

Thomas **Bettecken**
Joel **Sussman**
Galina **Mengeritsky**
Levy **Ulanovsky**
Alex **Bolshoy**
Ilya **Ioshikhes**
Amir **Cohanim**
Fadil **Salih**
Simon **Kogan**

Funding (2009–2012)
Israel Science Foundation,
and South Moravian Program

From FHC Crick & A Klug, Kinky helix, Nature 255, 530–533, 1975

We have found it very difficult to estimate just how much energy is required to bend DNA "smoothly" to a small radius of curvature, say 30–50A, bearing in mind that these numbers are not many times greater than the diameter of the DNA double helix, which is about 20A, and that bending a helix destroys its symmetry. We have formed the impression that the energy might be rather high. **We therefore asked ourselves whether the folded DNA may consist of** relatively straight stretches joined by **large kinks**. This paper describes a certain type of kink which can be built rather nicely and has interesting properties.

In other words:

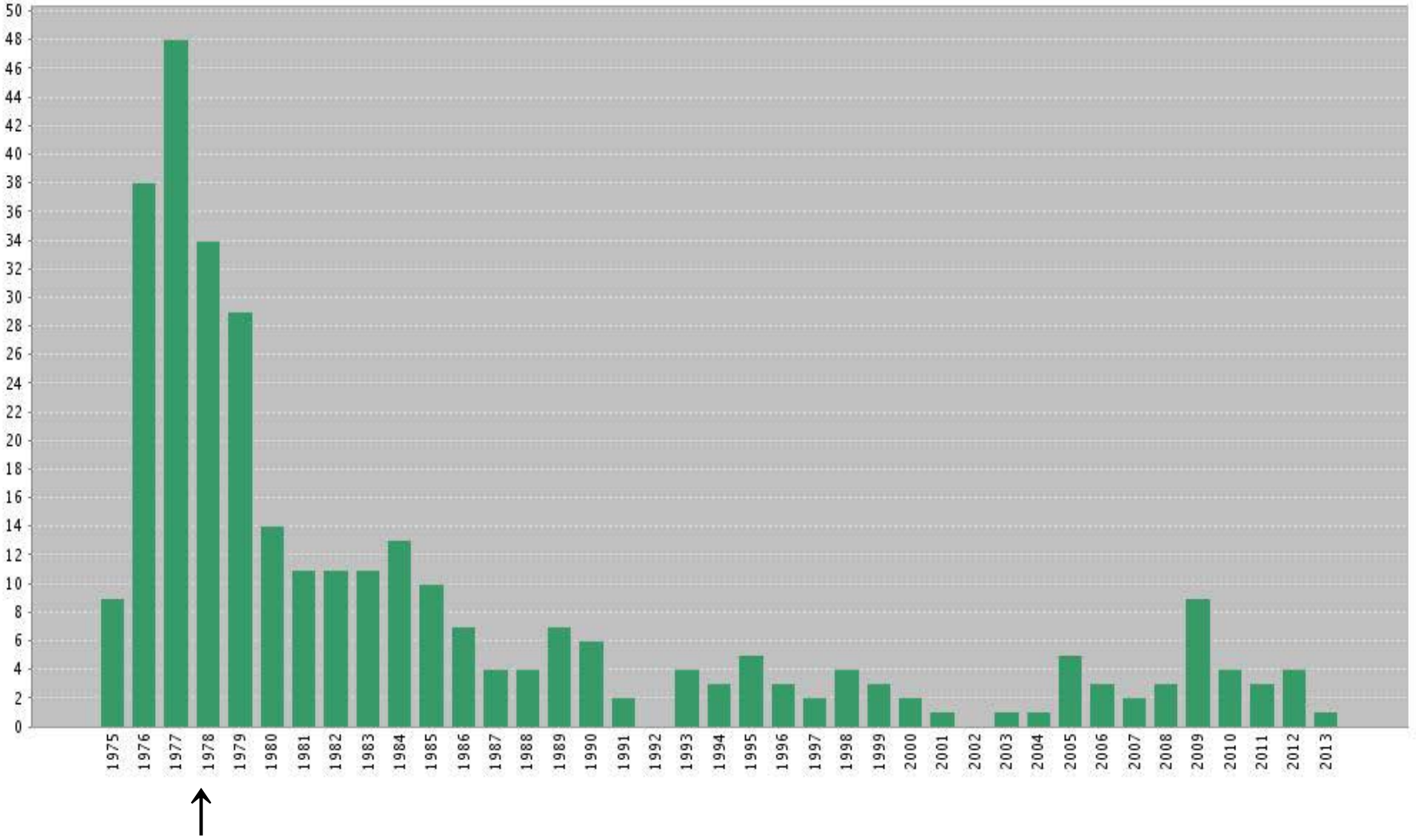
Smooth bending is difficult to calculate. We therefore thought about large kinks

.

Possibility of nonkinked packing of DNA in chromat

JL Sussman, EN Trifonov
Proc Natl Acad Sci U S A 75, 103-107, 1978

Citation of “kinky helix” paper (from SCI)



↑

our paper

Pattern of **1980-1983**

yrRRRryYYYyr
xxAAAxxTTTxx

is self-complementary

Trifonov, Sussman , 1980
Trifonov, 1980
Mengeritsky, Trifonov, 1983

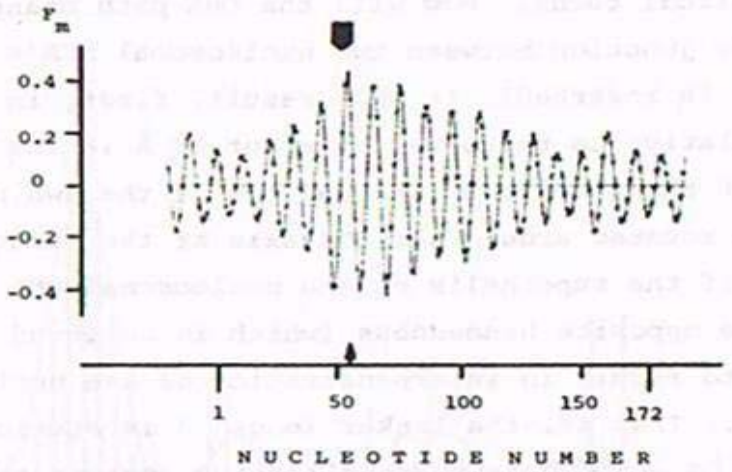


Fig. 5: The mapping function calculated for the nucleotide sequence of green monkey α-satellite. The numbering of the nucleotides is the same as used by Rosenberg *et al.*[13] The small arrow indicates position of the major maximum of the mapping function. The bigger arrow on the top points to the middle of the nucleosome found experimentally.[8,9] The width of the arrow corresponds to the error of the experimental mapping.

This achievement in the single-base accuracy mapping of the nucleosomes has not been accepted by chromatin research community.

The reasons:

1. Mistrust. The physics of the phenomenon and multiple alternative positions of the nucleosome centers are hard to grasp for non-physicists, and the sequences did not show any obvious periodicity

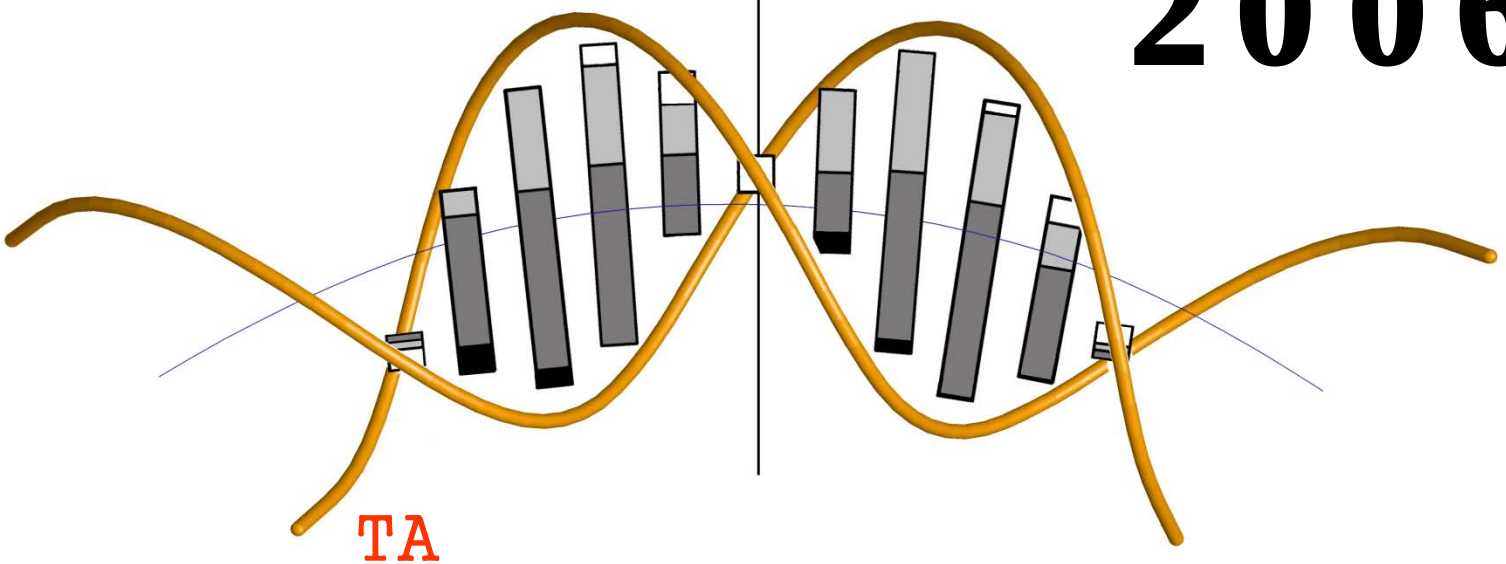
2. The chromatin research community was not ready yet methodologically to conduct high resolution experimental studies

GG
CC
GC
CG

Suggestion of an approximate pattern by Segal,…,Widom, Nature 442, 772

2006

5’



TA
AA
TT

The work of Segal et al., 2006, was
the first high throughput whole-genome analysis.

It drew a lot of attention, and the approach
became very fashionable in the chromatin community.

But the emphasis was still on low resolution studies,
maps of “occupancy”, where the alternative positions
of the nucleosomes and rotational setting of DNA
are not seen.

No attempts were made in that work to derive an exact
nucleosome positioning sequence pattern
from the whole genome sequences.

THE SALK INSTITUTE

September 15, 1978

Dr. Edward N. Trifonov
Polymer Department
The Weizmann Institute of Science
Rehovot, ISRAEL

Dear Dr. Trifonov,

Thank you for the preprint of your paper about the nuclease digestion of nucleosomal DNA. The idea is ingenious and the agreement with experiment rather striking, but I am reluctant to accept it for the following reason. Your mechanism, as I understand it, would predict very sharp bands on the gels. Now Len Lutter has improved the gels so that chains differing by one nucleotide in length are resolved so one can see the true width of the bands seen on the earlier gel. The results show that those bands were not sharp. For example, the band at 83 on the new gels is flanked by bands at 82 and 84 and also, to a lesser extent, by ones at 81 and 85.

For this reason I pick to think of the nucleases as attacking not at a narrow angle but over a fairly wide angular range. However I agree that this does not itself explain why the cuts are strong at some places and not at others. I suspect we shall have to wait for the solution of the crystal structure before the matter is finally resolved.

Yours sincerely,

Francis Crick

F. H. C. Crick
Kieckhefer Research Professor

FHCC/bml

From 1979 until 2008 the value 10.0 dominated in liter

It is now gradually replaced by 10.4

It was admitted by Richmond at the conference in 200
that “everybody knows that the period is 10.4”

Не иначе как бес попутал кристаллографов

```
5′…Y Y Y R R R R R Y Y Y Y Y R R R…
       T A       A T
       C G       G C
       C A       A C
       T G       G T
```

strong nucleosomes

```
5′…Y Y Y R R R R R Y Y Y Y Y R R R…
       T A       G C
       A A       G G
       T T       C C
                 C G
```

Segal et al. 2006

We now entered a new era
of single-base resolution chromatin research.

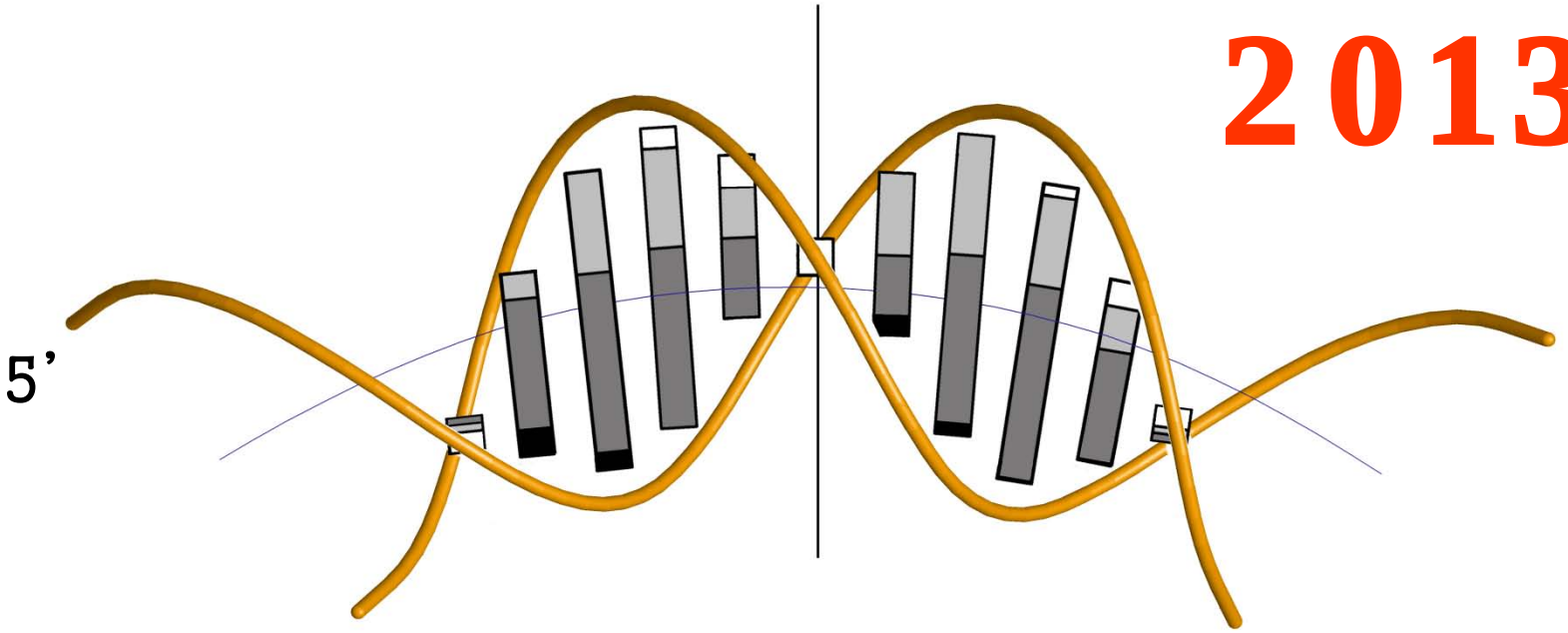
None of experimental techniques provides today
the single-base resolution.

The computational mapping of the nucleosomes,
quick and accurate,
is waiting for sceptic experimentalists
to join and enjoy.

Но поезд уходит: мы первыми пожнем плоды

Nucleosome positioning pattern

2013



5’…YYYRRRRRYYYYYYRRR…

TA	AT	TA
CG	GC	CG
TG	AC	TG
CA	GT	CA
Contact with arginines	Exposed	

СПАСИБО ЗА ВНИМАНИЕ!

When we joined the high throughput efforts our primary task was to derive the detailed nucleosome positioning sequence pattern

This involved three original techniques

A. Signal regeneration from its parts
B. Shannon N-gram extension
C. Extraction and analysis of strong nucleosomes

Regeneration of signal from its incomplete versions:

AA

positional autocorrelation

AAnnnnnnnnAA

regeneration
(all occurrences of AAnnnnnnnnAA are aligned, and other dinucleotides counted within the period)

AAnnnnCCnnAA

Gabdank, 2009

A. thaliana	T AAAAA TTTTT A	strong nucleosomes
	T AAAAA TTTTT A	Shannon extension
C. elegans	T AAAAA TTTTT A	strong nucleosomes
	c grAAA TTT**yc g**	signal regeneration
isochores L1, L2	T AAAAA TTTTT A	strong nucleosomes
	T AAAAA TTTTT A	Shannon extension
isochores H1	T AAAAA TTTTT A	strong nucleosomes
	c A**g**AAA TTT**c**T **g**	Shannon extension
isochores H2	T AAAAA TTTTT A	strong nucleosomes
	c ggggA T**cccc g**	Shannon extension
isochores H3	C GGGGG CCCCC G	strong nucleosomes
	C **a**GGGG CCCC**t** G	Shannon extension

Y RRRRR YYYYY R – all,
and all with complementary symmetry

The dinucleotide stacks are placed in such positions within the nucleosome DNA period to ensure best possible bending.

The better the bending – the stronger the nucleosome.

But the bulk of the nucleosomes are only marginally stable.

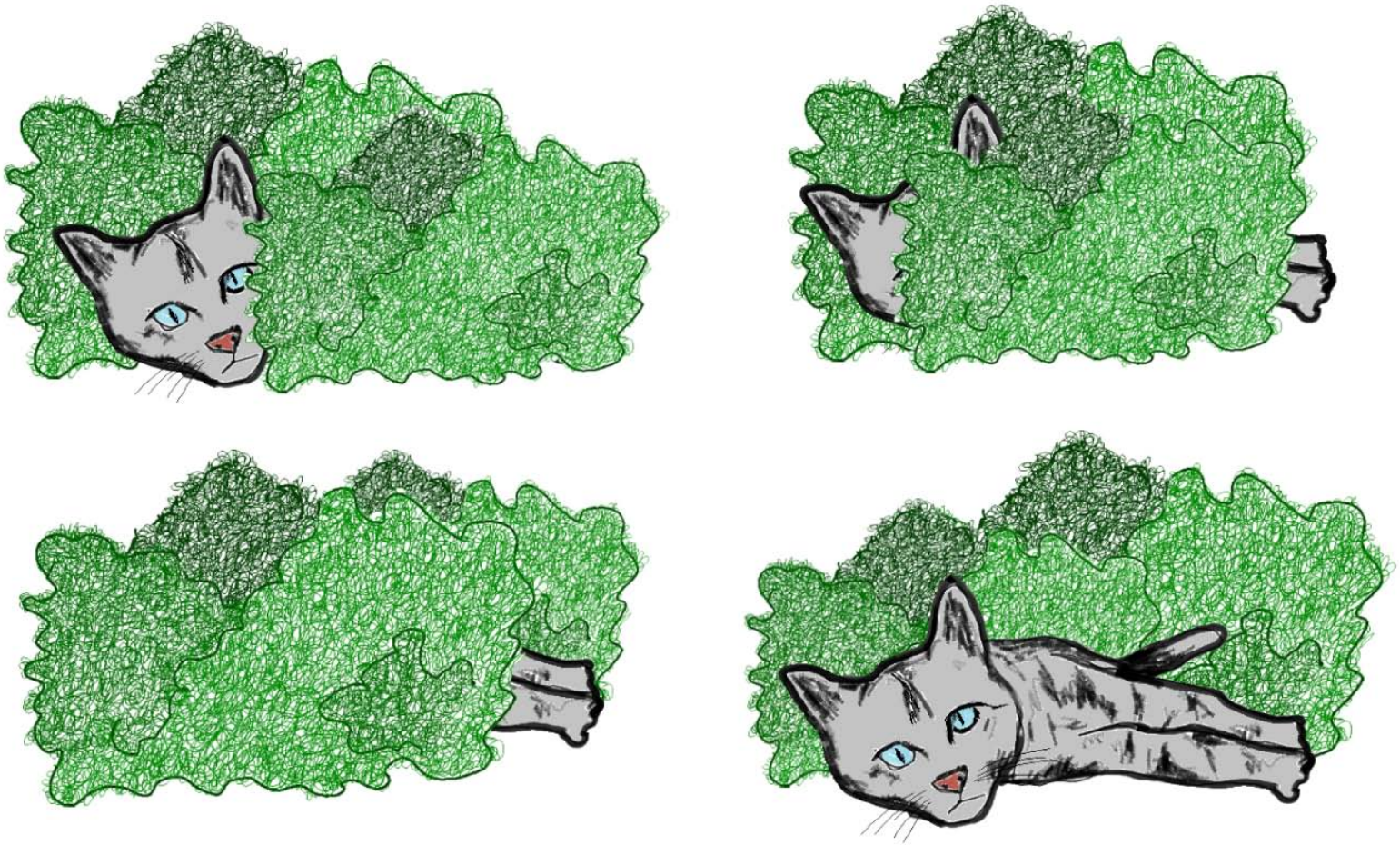
Only a fraction of properly positioned dinucleotides
is present in any given nucleosome DNA sequence.

Match of the BamHI nucleosome (typical semistable nucleosome) to the standard nucleosome probe $(GAAAATTTTC)_n$

CGGAAATTTTCCGGAAATTTCCGGAAATTTCCGGGAAATTTCCGGAAATTTCCGGAAATTTTCCGGAAATTTCCGGGAAATTTCCGGAAATTTTCC
Cagaggagcttcctgggga**TCC**a**GA**c**AT**gataagataca**TT**gat**GA**gt**TT**ggaca**AA**ccacaactag**AAT**gcagt**GAAA**aaaatgctttA**TTT**gtga**AA**t**TT**gtgatgcta**TT**gct
YRRRRRag**YYYY**ct**RRR**ga**YYYRRR**c**RY**gata**RRR**taca**YY**gat**RRR**t**YY**ggac**RRR**ccacaact**RRRRY**gcagt**RRRR**aaaa**YR**ctttRYYYgt**RRRR**t**YY**gtgatgcta**YY**g**YY**

The strongest nucleosomes of *A. thaliana* display very clear though still imperfect periodicity

The ideal pattern for *A. thaliana* is repetition of TAAAAATTTTTA, again, alternation of RRRRR and YYYYY, and complementary symmetry



Cat in bushes. Courtesy of I. Gabdank

Guanines of GT- and AG-ends of introns are oriented towards the surface of the histone octamer, away from exterior.

Such orientation is the best for guanines to minimize spontaneous depurination and oxidation

The most frequent spontaneous damages to DNA bases:

depurination of G (N9 atoms)

oxidation of G

deamination of C

History of the chromatin code. Pre-genomic studies 1980-2006

~10.5 base periodicity of some dinucleotides Trifonov, Sussman (1980)

...T T A A A A A T T T T T A A A A A T T...	Mengeritsky, Trifonov (1983)
...Y Y R R R R R Y Y Y Y Y R R R R R Y Y...	Mengeritsky, Trifonov (1983)
...x Y R x x x R Y x x x Y R x x x R Y x...	Zhurkin (1983)
...W W W W x S S S S x W W W W x S S S S...	Satchwell *et al*. (1986)
...x W W W x x S S S x x W W W x x S S S...	Shrader, Crothers(1989), Tanaka et al.,(1992)
...C C x x x x x C C C C C x x x x x C C...	Bolshoy (1995)
...V W G x x x x x x x V W G x x x x x x...	Baldi *et al*. (1996)
...x x G G R x x x x x x x G G R x x x x...	Travers, Muyldermans (1996)
...C T A T A A A C G C C T A T A A A C G...	Widlund *et al*. (1997)
...C T A G x x x x x x C T A G x x x x x...	Lowary, Widom (1998)
...S S A A A A A S S S S S A A A A A S S...	Fitzgerald, Anderson (1998)
...C C G G G G G C C C C C G G G G G C C...	Kogan *et al*. (2006)

Today the single-base resolution nucleosome mapping is the only practical tool to study fine structure of chromatin and its role in

factor binding,
transcription,
replication,
DNA repair,
transposition,
recombination,
apoptosis,
chromatin domains,
and more

Immediate questions:

Where in genomes the strong nucleosomes are located?

What they are doing there?

Tentative answer:

Strong nucleosomes are chromatin organizers.

Why DNA binds to histone octamers
by one side?

It could be either intrinsic DNA curvature

or better bending in one specific direction
(deformational anisotropy of DNA)

Both should be sequence-dependent

Nucleosome positioning sequence pattern is very weak

(as the nucleosomes should be easy to unfold)

The weak pattern overlaps with other messages (“noise”).

That makes the signal/noise ratio very low.

VERY large

database of the nucleosome DNA sequences is needed,

to extract and fully describe the signal

It is easy, however, to detect the signal

DISTANCE ANALYSIS (Autocorrelation)

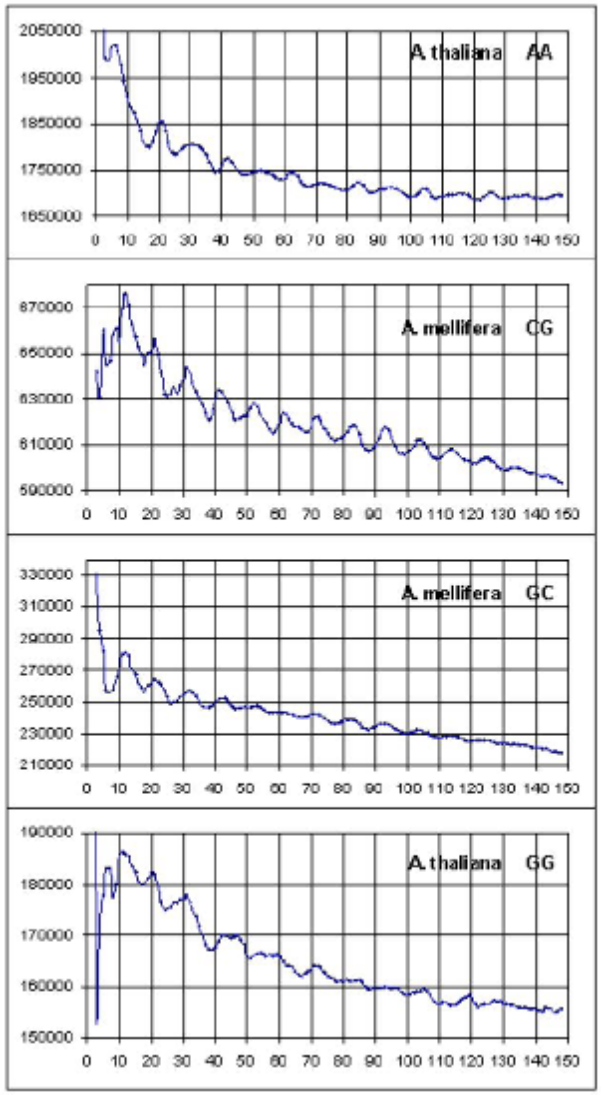
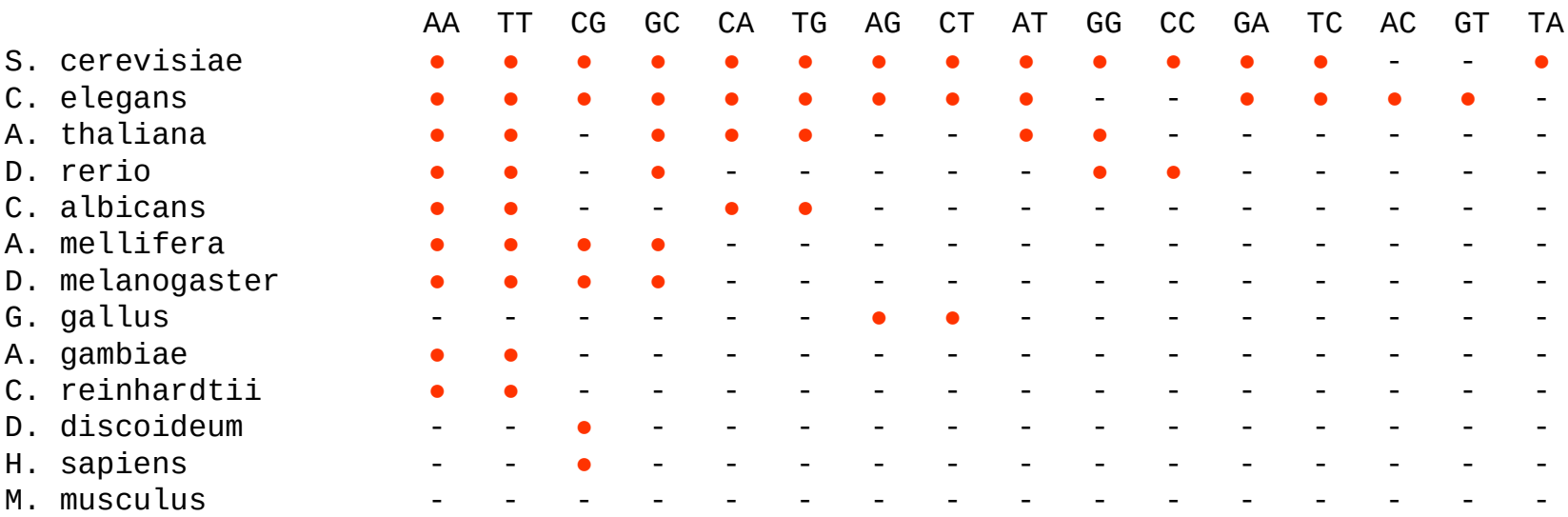


Figure 1

Whole-genome periodicities (distance analysis)



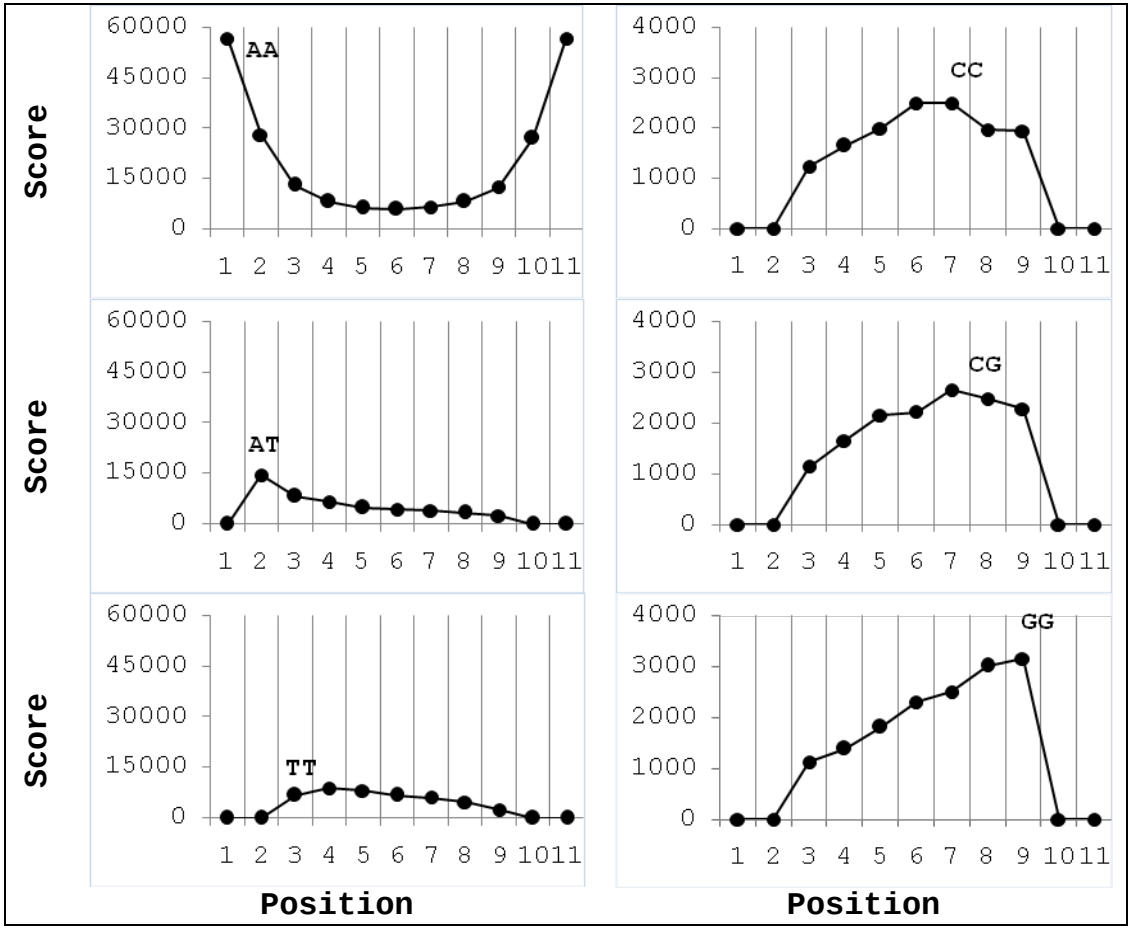
T.Bettecken, E.N.T., 2009

Nucleosome positioning patterns, isochores
(Frenkel, 2011, 2012)

			isochore	method
T	AAAAA	TTTTT A	L1 (<37% G+C)	B
T	AAAAA	TTTTT A	same	A
T	AAAAA	TTTTT A	L2 (37-41% G+C)	B
C	AGAAA	TTTCT G	H1 (41-46% G+C)	B
C	GGGGA	TCCCC G	H2 (46-53% G+C)	B
C	AGGGG	CCCCT G	H3 (>53% G+C)	B
C	AGGGG	CCCCT G	same	A
Y	RRRRR	YYYYY R	consensus	

A signal regeneration, nucleosomes
B Shannon N-gram extension, whole genome

AAnnnnnnnnAA repeat structure (*C. elegans*)



Regenerated pattern (AAATTTCCGG)(AAAT…

Positional matrix of bendability(C.elegans)

1	2	3	4	5	6	7	8	9	0	1	2
C	G									C	G
	G	G									
	G	A									
		G	A								
		A	A								
			A	A	A						
					A	T					
						T	T	T			
								T	T		
								T	C		
									T	C	
									C	C	
										C	G

LINEAR FORM OF THE POSITIONAL MATRIX OF BENDABILITY (*C.elegans*):

CGRAAATTTYCG

(YRRRRRYYYYYR)

Trinucleotides of *C. elegans* genome

		counts
1	**AAA**	4162266
2	**TTT**	4160750
3	**ATT**	2488998
4	**AAT**	2486813
5	**GAA**	1873844
6	**TTC**	1871673
7	CAA	1667120
8	TTG	1663842
9	TCA	1498069
10	TGA	1496493
.....		.....

TOPMOST TRINUCLEOTIDES MAKE TOGETHER THE DOMINANT PATTERN

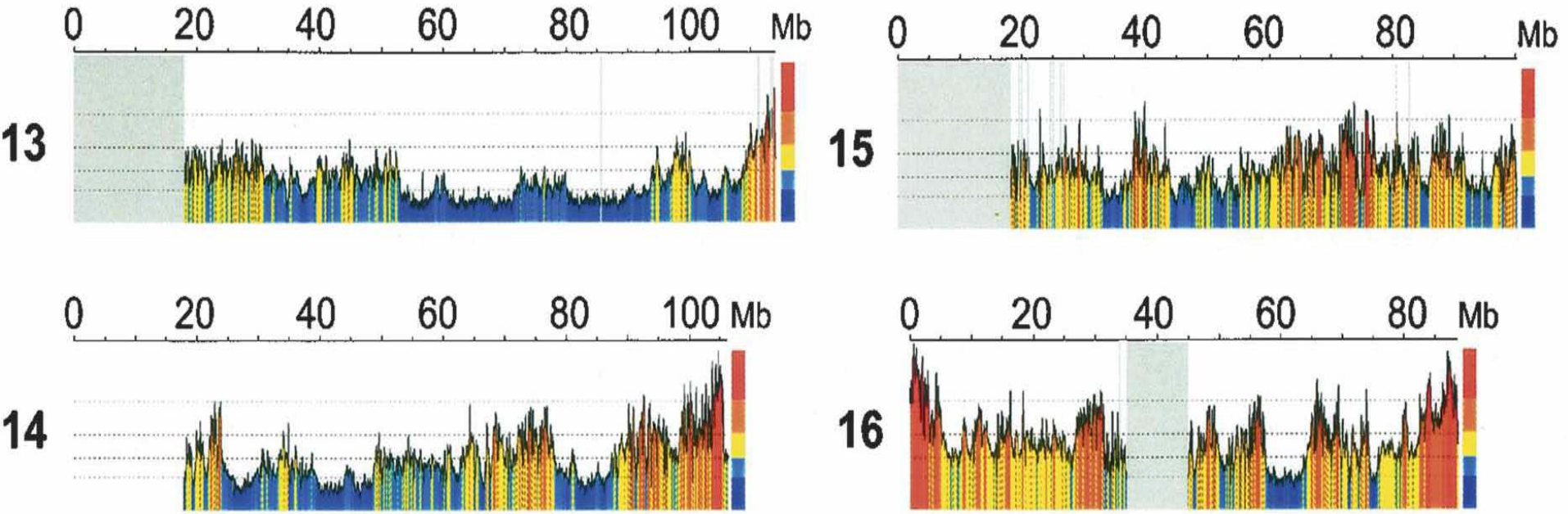
GAAAATTTTC:

GAAAATTTTC
GAAAATTTTC
GAAAATTTTC
GAAAATTTTC
GAAAATTTTC
GAAAATTTTC
GAAAATTTTC
GAAAATTTTC

This technique is known since 1948 -

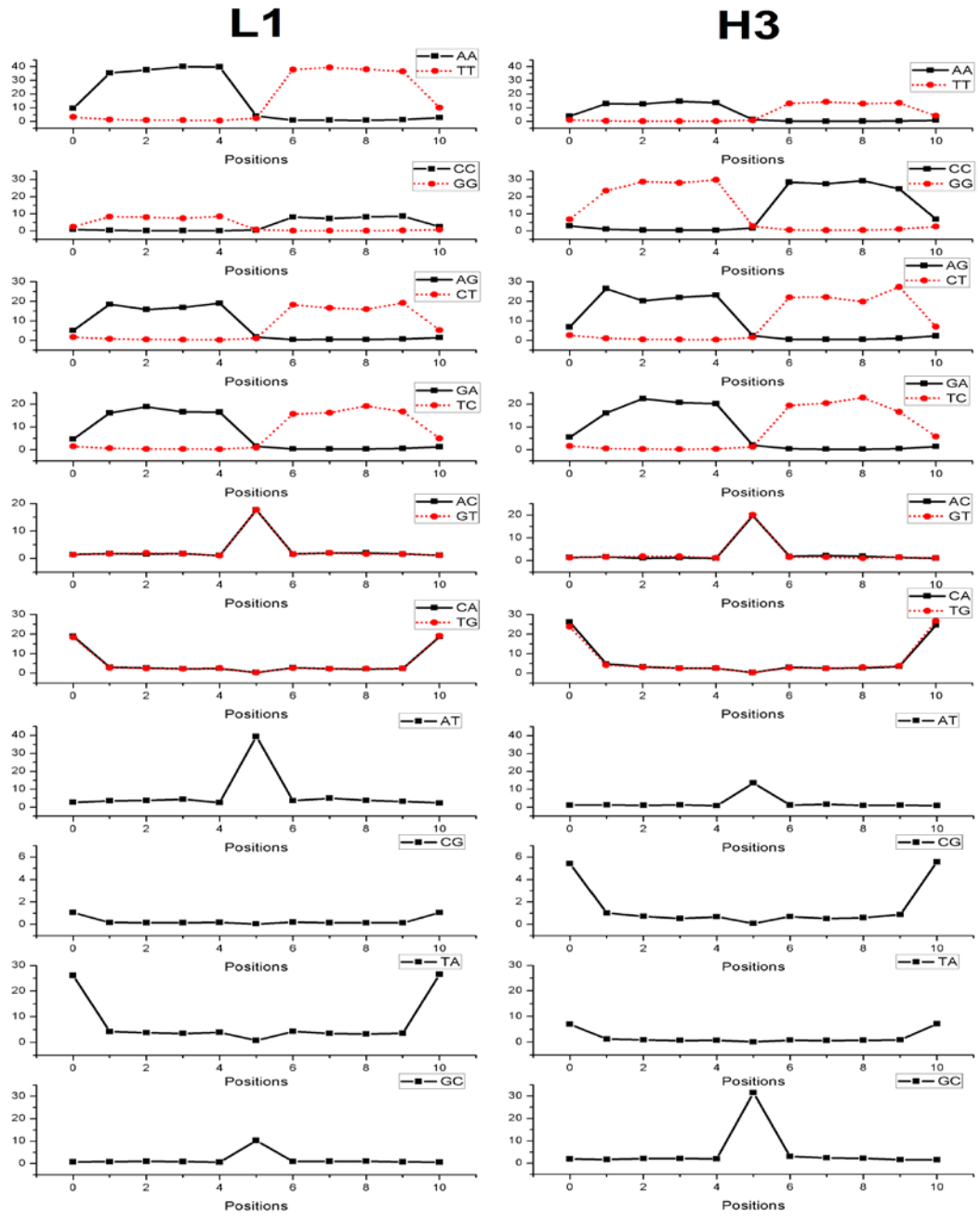
Shannon N-gram extension

It has been very helpful
in further studies
of the nucleosome positioning patterns



Human isochores

Lab of G. Bernardi, 2006



Nucleosome positioning patterns for human isochores L1 and H3 derived by signal regeneration from apoptotic nucleosomes:

L1: T AAAAA TTTTT A
H3: C AGGGG CCCCT G

Frenkel et al., 2011

Shannon N-gram reconstruction of linkers

TTTTATTTTAAATAAAA	human linkers
AAAATAAAATATTTTATTTT	yeast linkers
TAAAgTAcTTTA	human, apoptotic cuts

consensus:

TAxxxTAxxxTAxxx

(B. Salih, T. Bettecken, Z. Frenkel)

TTAAAAATTTTTAAAAATTTTTAA	human L1 isochores, nucleosomes

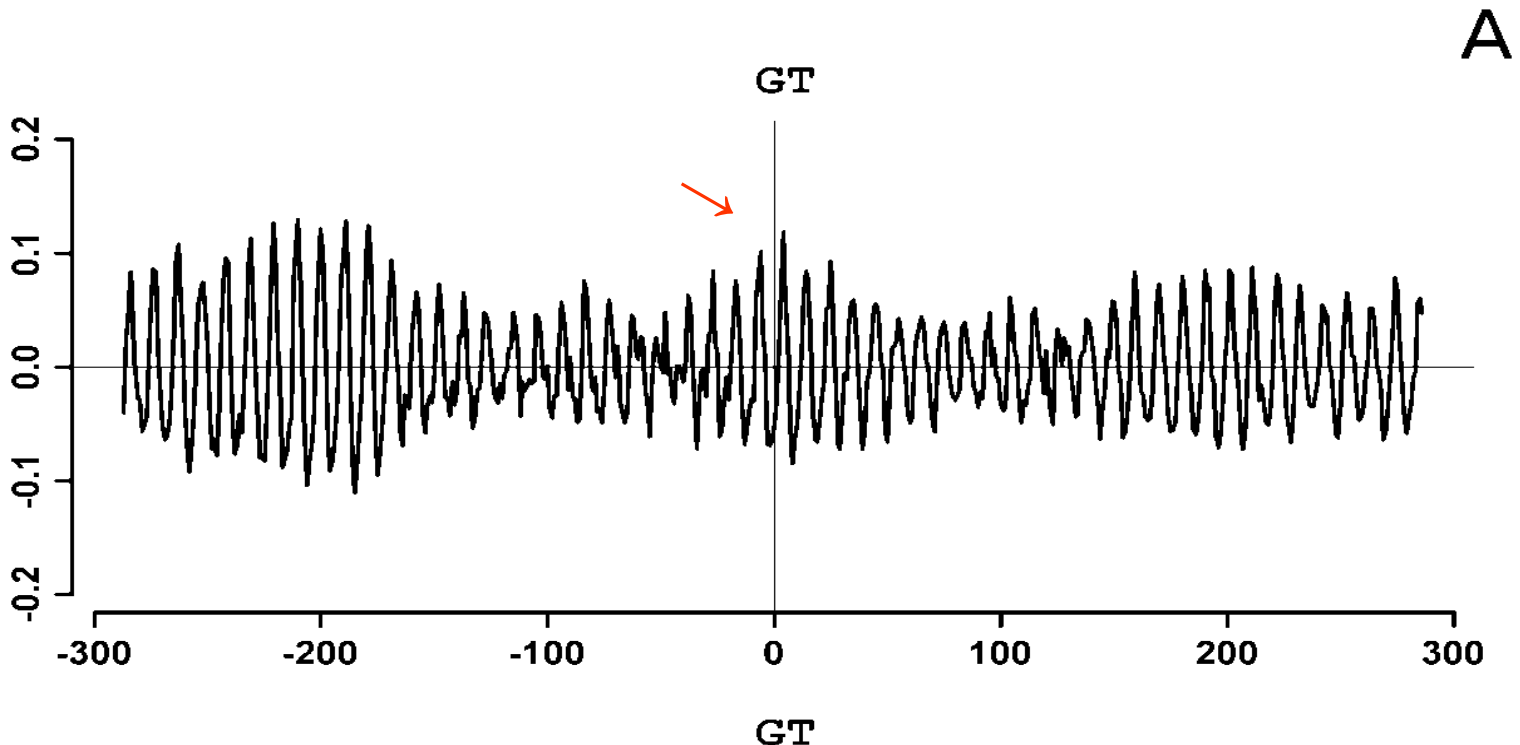
BamHI nucleosome of Ponder and Crawford, 1977

BamHI fragments of BamHI nucleosome DNA

Calculated	Observed in the gel	
24		
34		
43		
54	~53	misfit ± 1 base
64	~63	
(73)	(~73)	
82	~83	
92	~93	
103		
112		
122		

Example of the nucleosomes at and around GT splice junction

Hapala, 2011



Plenty of various other nucleosome positioning patterns have been suggested during 30 years since the first observation of sequence periodicity.
At the best they provide occupancy maps (resolution of ~15 bases).

The (GRAAATTTYC)n and (RRRRRYYYYY)n are the only patterns that generate maps with single-base resolution, verified by crystal data.

The future of the chromatin structure/function is with the high resolution studies.