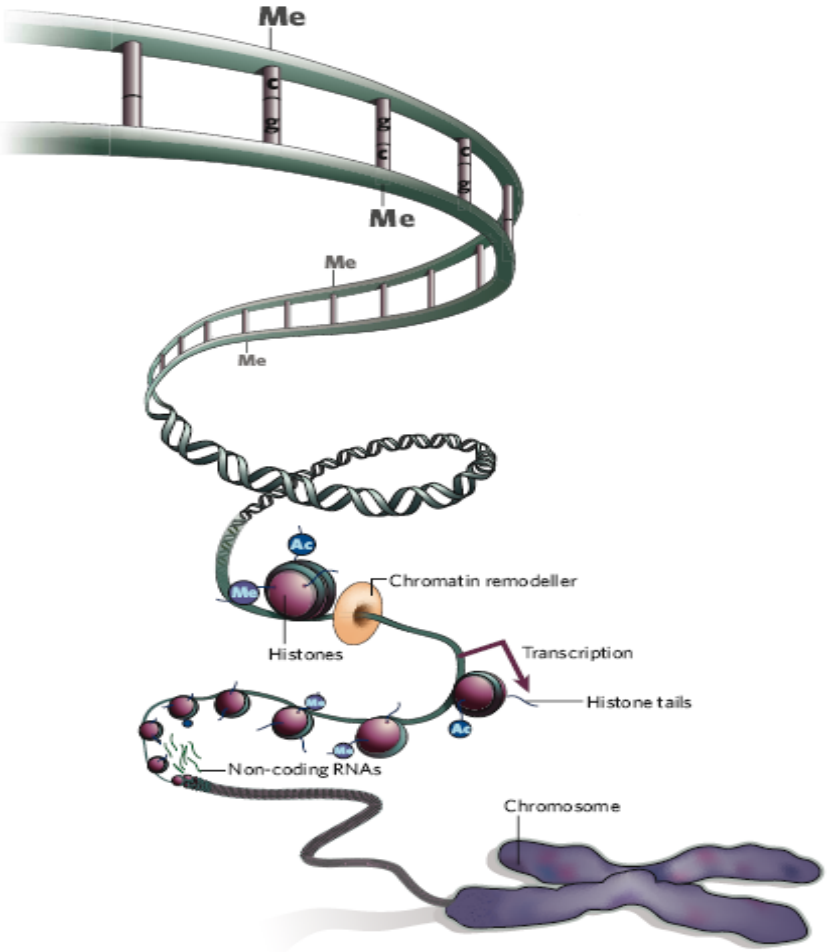
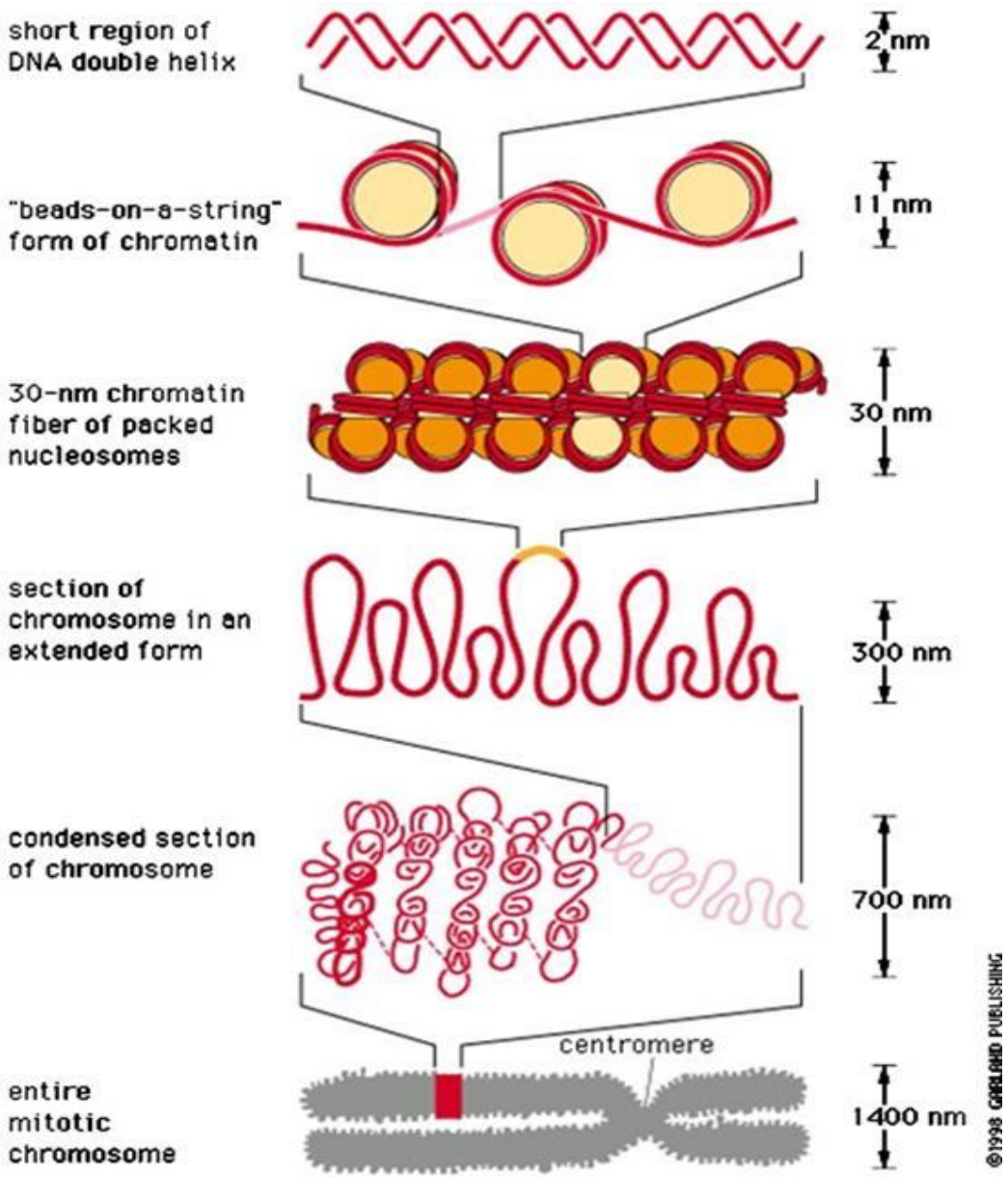
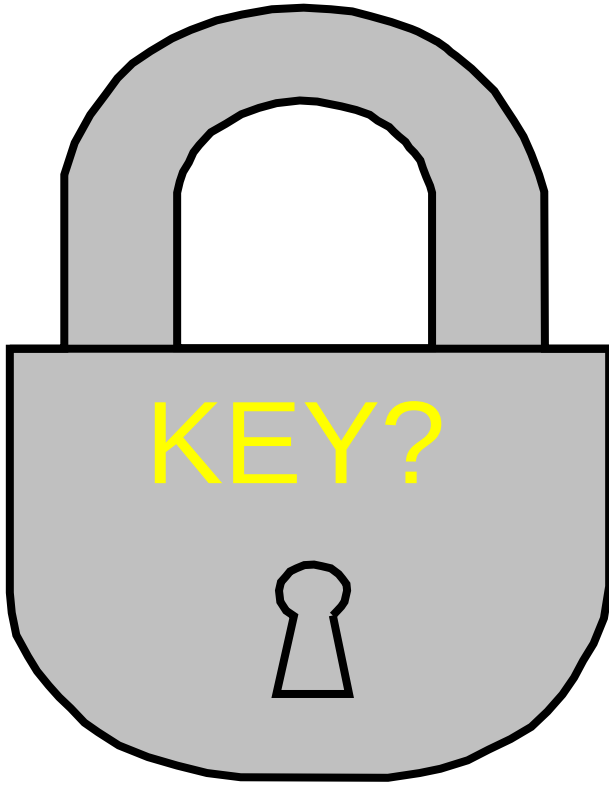
Complexity of chromatin folding is captured by the strings and binders switch model

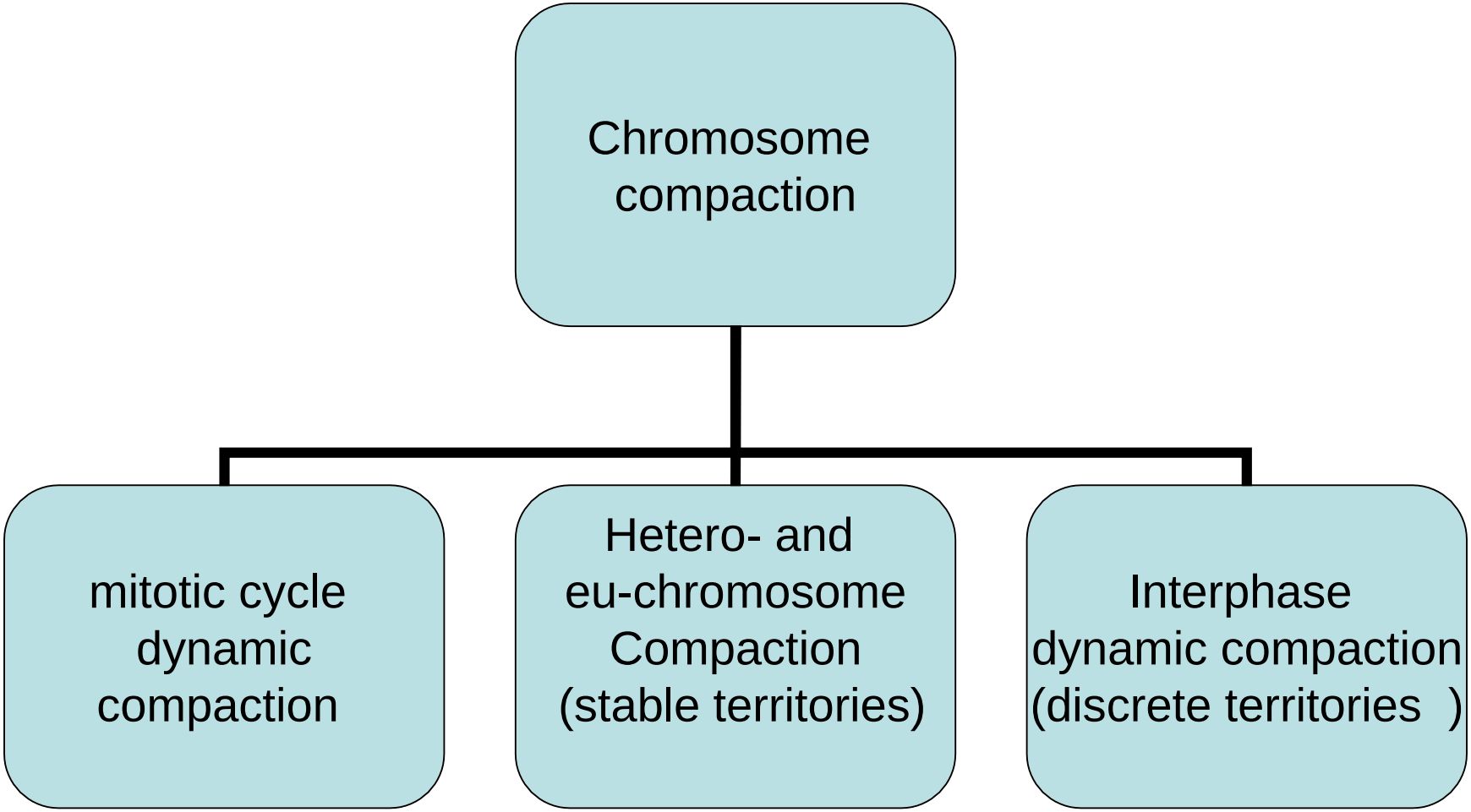


王文韬 周群丰

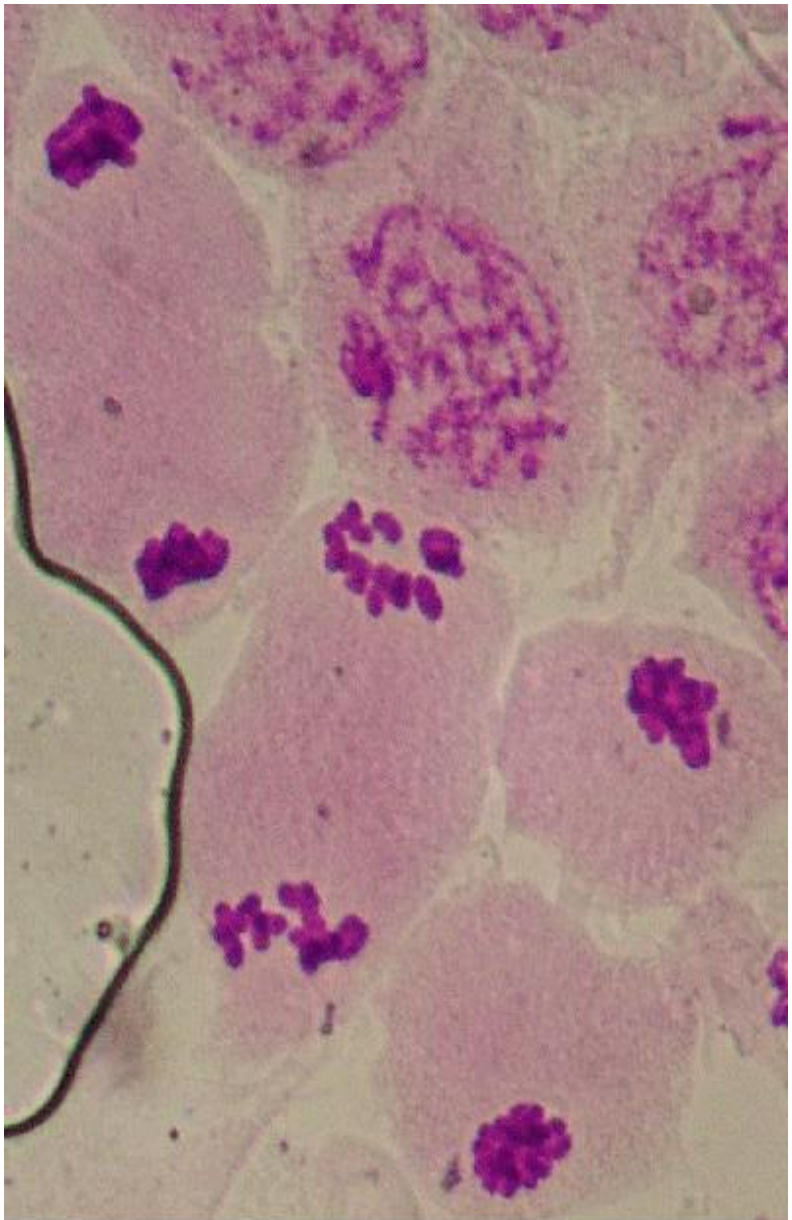

short region of DNA double helix
2 nm
"beads-on-a-string" form of chromatin
11 nm
30-nm chromatin fiber of packed nucleosomes
30 nm
section of chromosome in an extended form
300 nm
condensed section of chromosome
700 nm
centromere
entire mitotic chromosome
1400 nm
©1998 GARLAND PUBLISHING

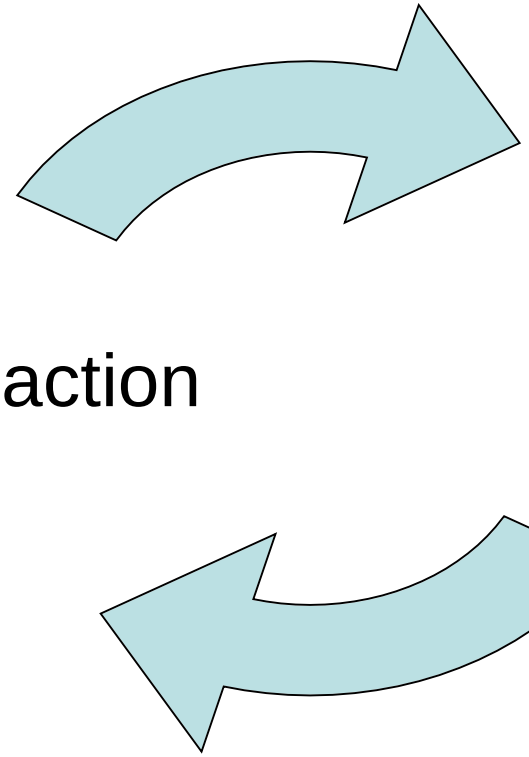

KEY?

chromosome compaction

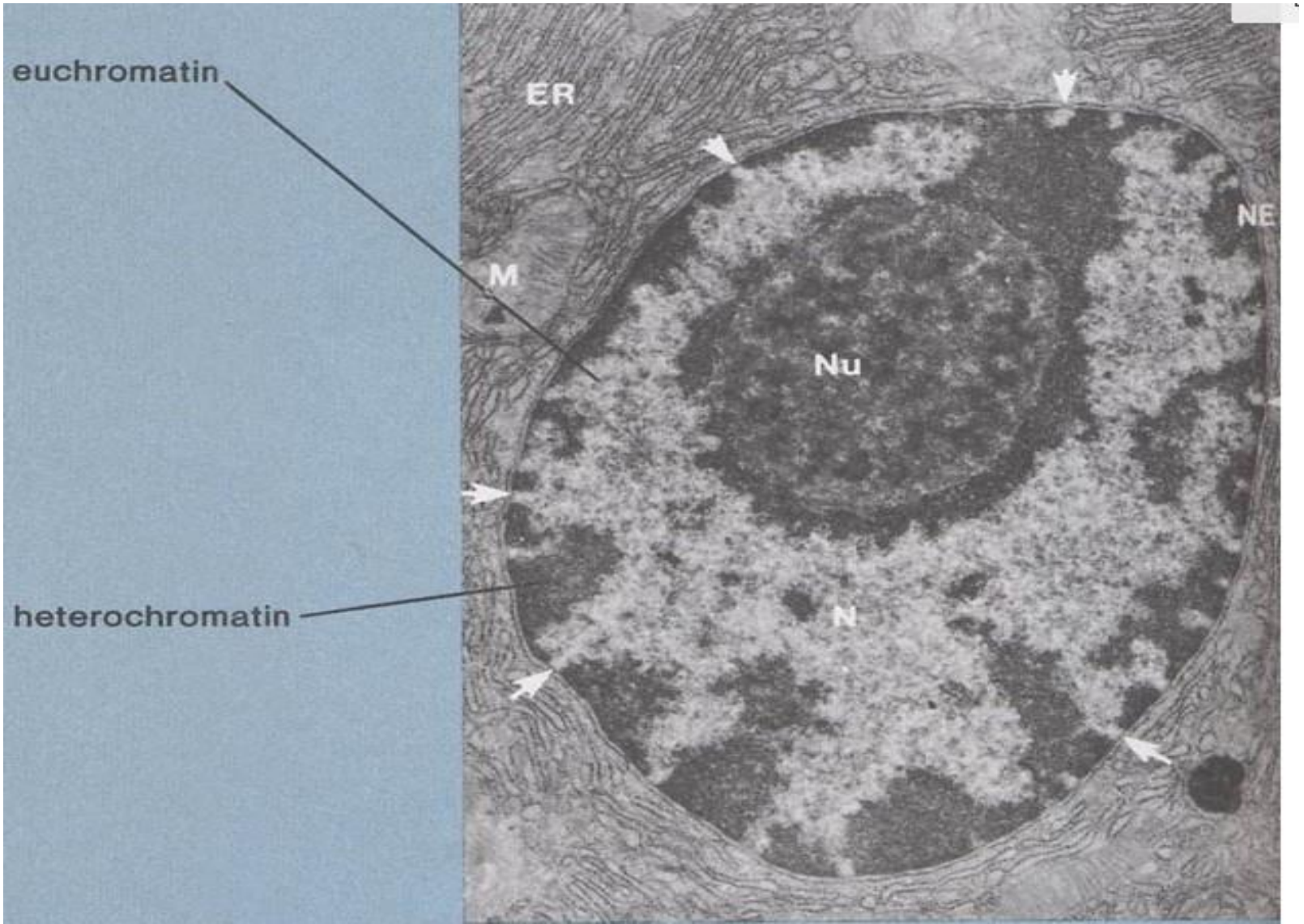


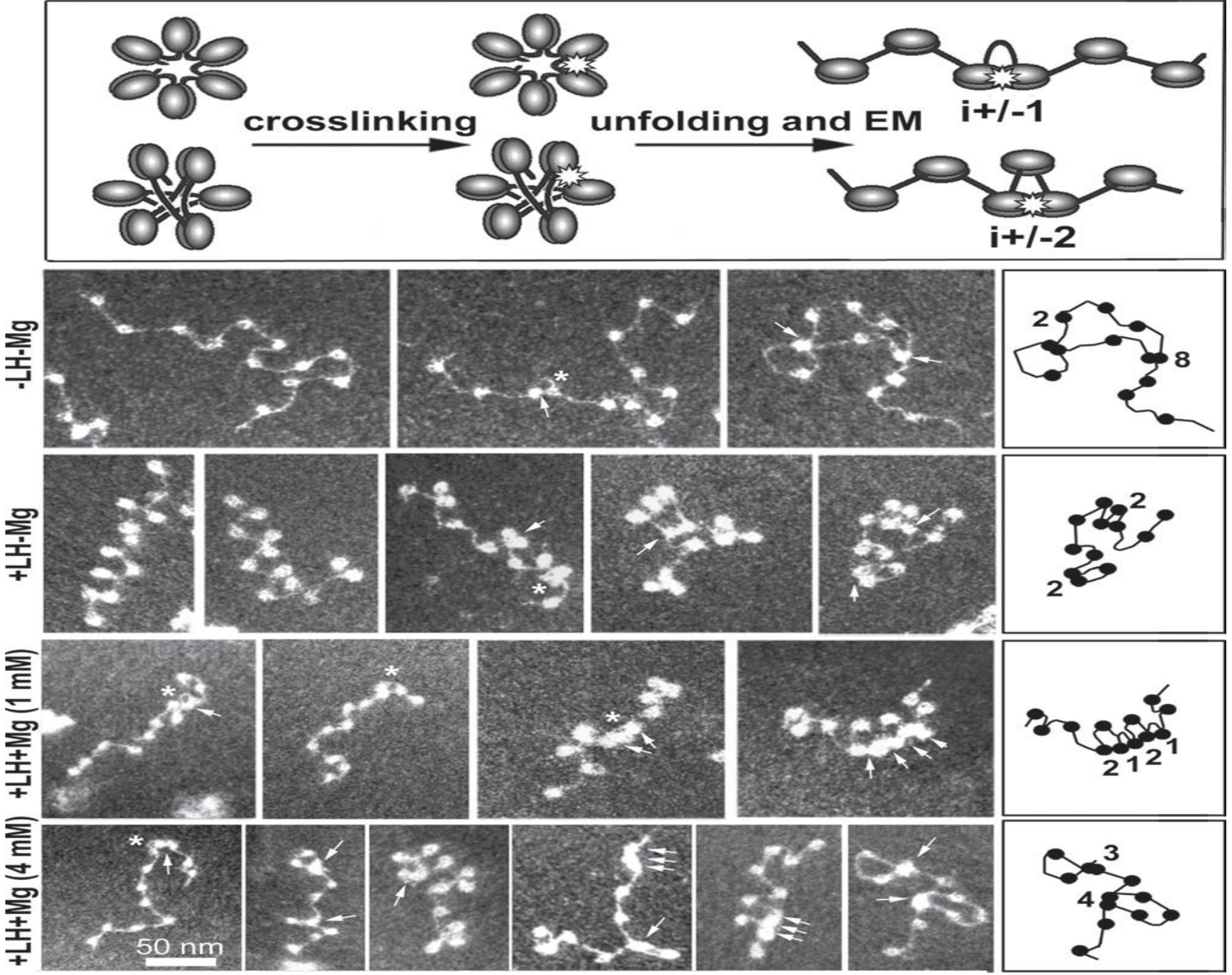
mitotic cycle dynamic compaction





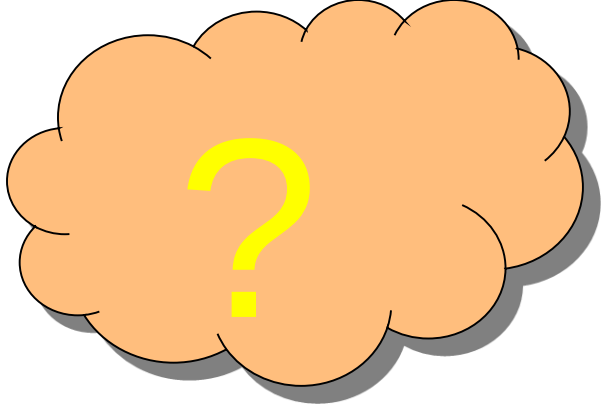
Hetero-chromomatin and euchromamtin ----stable compaction





Grigoryev et al.2009

- Spatial genome organization is guided by intra-and inter -chromosomal interactions mediated by nuclear components that include transcription factors, transcription and replication factories, Polycomb bodies, and contacts with the lamina.



How binding of diffusible factors to specific genomic regions drives chromatin folding remains poorly understood.

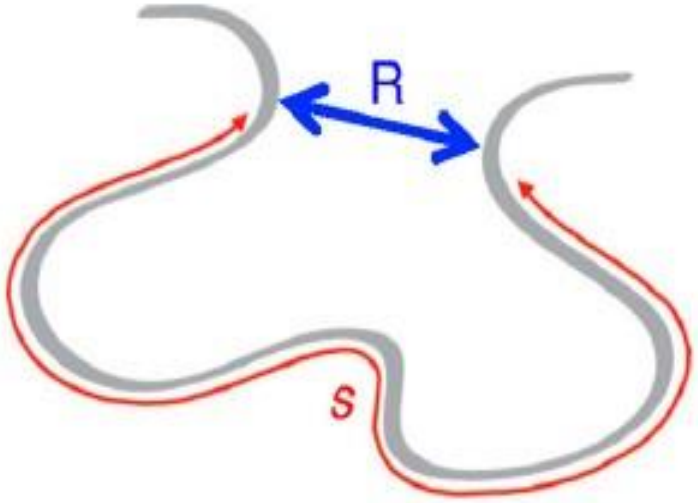
Three key tech. to analysis compaction

FISH: Imaging of single loci

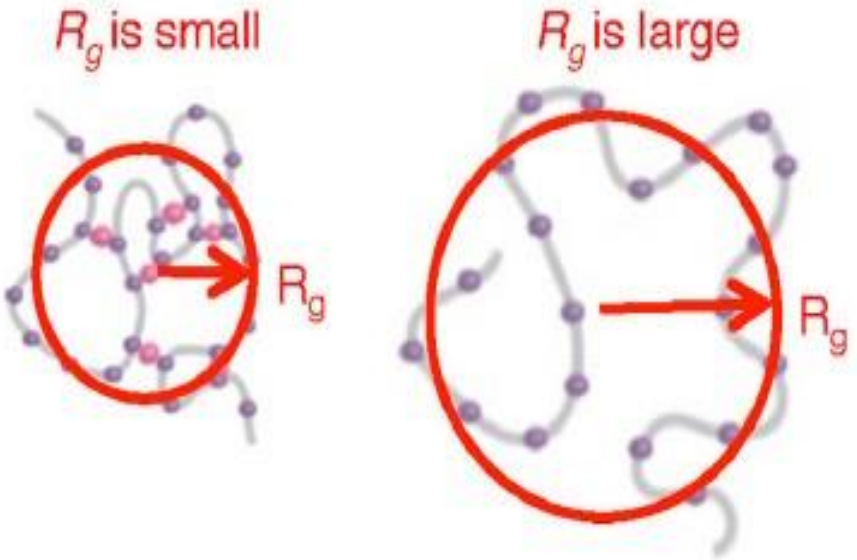
3C (chromosome conformation capture approaches): genome-wide mapping of chromatin interactions

Hi-C(A global analysis of genome-wide 3C)

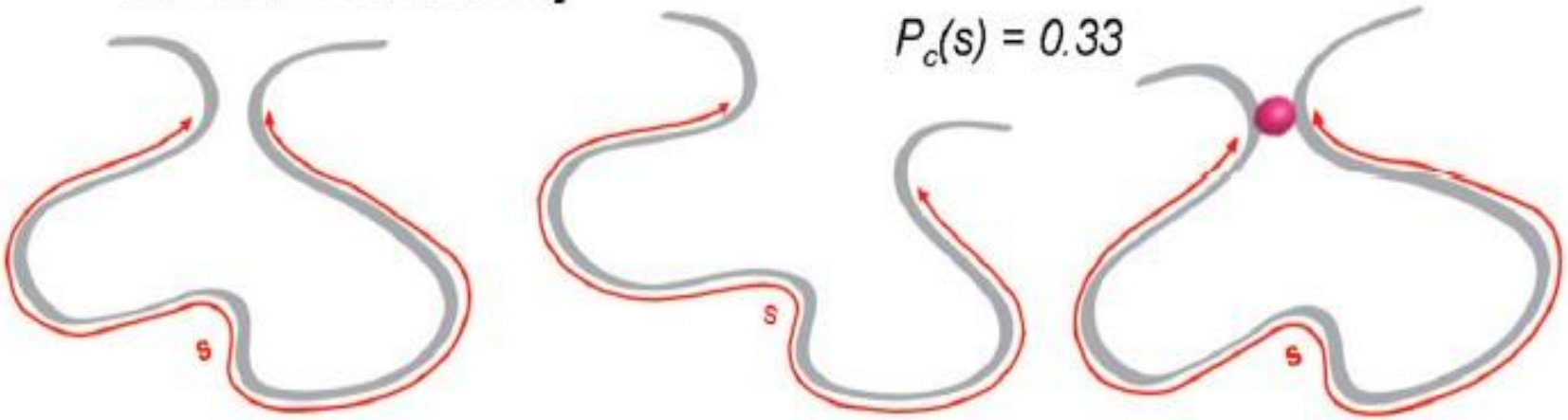
Mean spatial distance



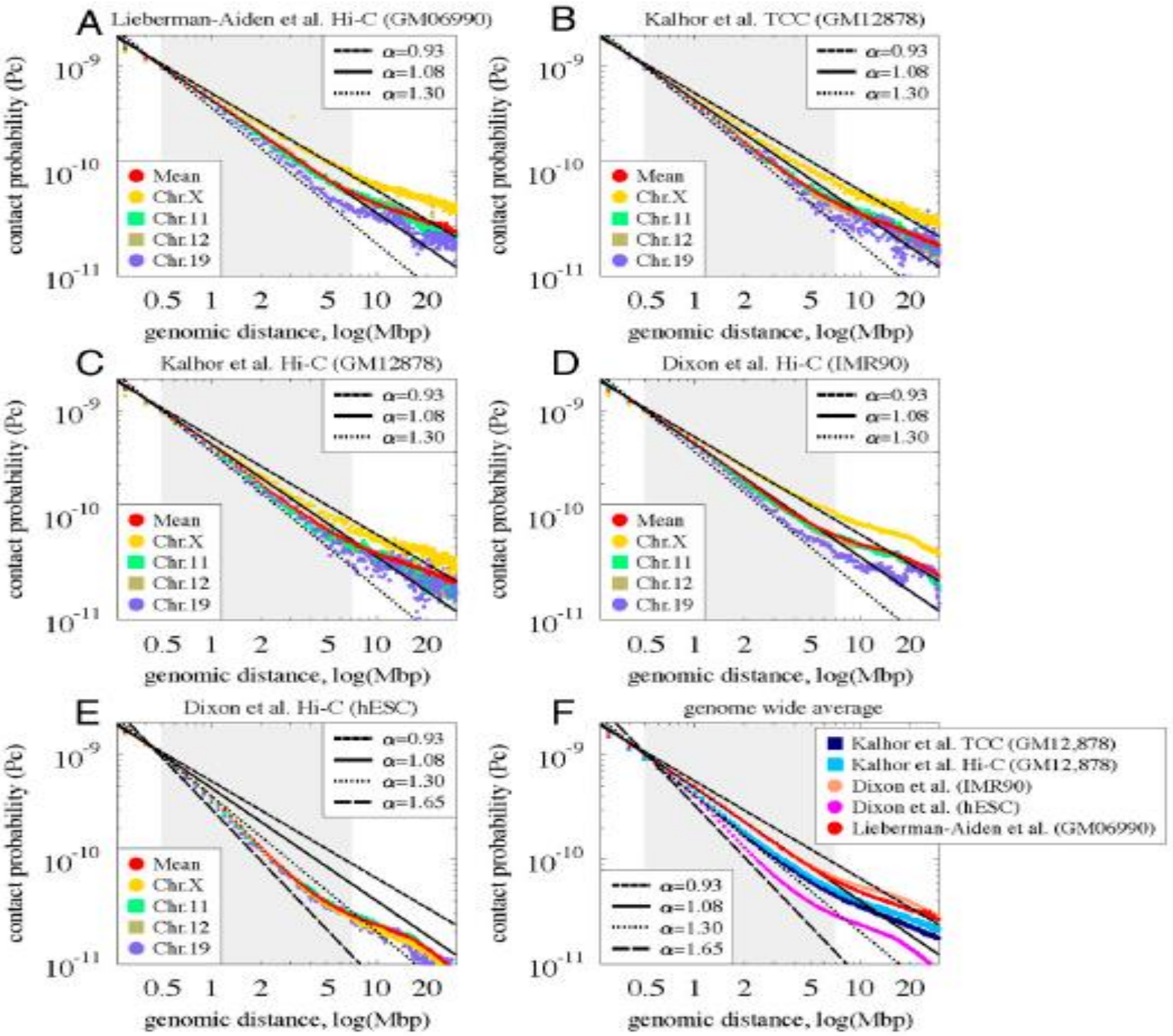
Gyration Radius



Contact Probability



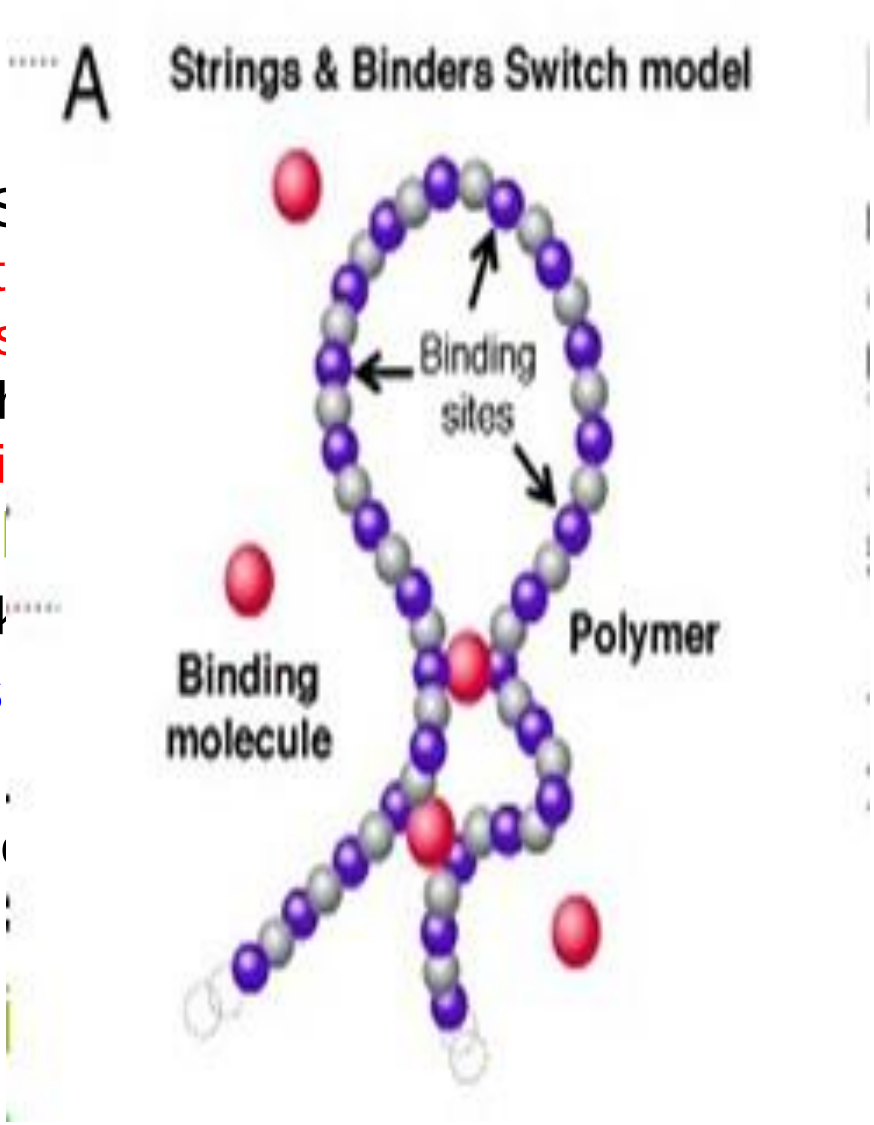
Cellular material	Technique	Genomic region analysed (resolution)	Mean square spatial distance, $R^2(s)$, as a function of genomic separation, s	Contact probability, $P_c(s)$, as a function of genomic separation, s	Ref.
Human female fibroblast cells	3D-FISH	Chr1q, 27Mb (~1Mb) and Chr11q, 75Mb (~3Mb)	s = 0.4-2Mb, $R^2(s)$ increases (ν = 0.33) s >10Mb, $R^2(s)$ reaches a plateau (ν = 0)	N/A	*9*
Mouse pre-pro-B cells ($E2A^{-/-}$) and pro-B cells ($RAG^{-/-}$)	3D-FISH	Igh locus, 3Mb (~300kb)	s <0.5Mb, $R^2(s)$ increases (ν = 0.25 for pre-pro-B cells, ν = 0.1 for pro-B cells) s >0.5Mb, $R^2(s)$ reaches a plateau (ν = 0; both cell types)	N/A	*10*
Mouse NIH-3T3 fibroblasts	3D-FISH	Chr14, 4.3Mb (200kb)	s <3.5Mb, $R^2(s)$ increases ($\nu \sim 0.5$) s >3.5, $R^2(s)$ may plateau	N/A	*11*
Human male fibroblast cells	2D-FISH	Chr4 (10Mb)	s <50Mb, $R^2(s)$ increases ($\nu \sim 0.5$) s >50Mb, $R^2(s)$ increases ($\nu \sim 0.3$)	N/A	*12*
Human lymphoblastoid cell line	Hi-C	Genome-wide (1Mb)	N/A	s = 0.5-7Mb, $P_c(s)$ decreases approximately as a power law, with exponent α = 1.08	*13*
Drosophila embryos	Simplified Hi-C	Genome-wide and Repressive epigenetic classes	N/A	Genome wide: contact frequencies decrease approximately as a power law, with exponent $\alpha \approx 0.85$ Repressive epigenetic classes: contact frequencies decrease approximately as a power law, with exponent $\alpha \approx 0.70$	*14*


A
Lieberman-Aiden et al. Hi-C (GM06990)
B
Kalhor et al. TCC (GM12878)
C
Kalhor et al. Hi-C (GM12878)
D
Dixon et al. Hi-C (IMR90)
E
Dixon et al. Hi-C (hESC)
F
genome wide average
contact probability (Pc)
genomic distance, log(Mbp)
0.5 1 2 5 10 20
α=0.93
α=1.08
α=1.30
α=1.65
Mean
Chr.X
Chr.11
Chr.12
Chr.19
Kalhor et al. TCC (GM12,878)
Kalhor et al. Hi-C (GM12,878)
Dixon et al. (IMR90)
Dixon et al. (hESC)
Lieberman-Aiden et al. (GM06990)

SBS

- In “strings and binders switch” (S
  conformations are established t
  factors (binders) to binding sites
  give rise to a variety of stable ch
  coexist in the nucleus. Chromati
  changes in binding site distri
  binding affinity, in a switch-lik
  values via thermodynamics

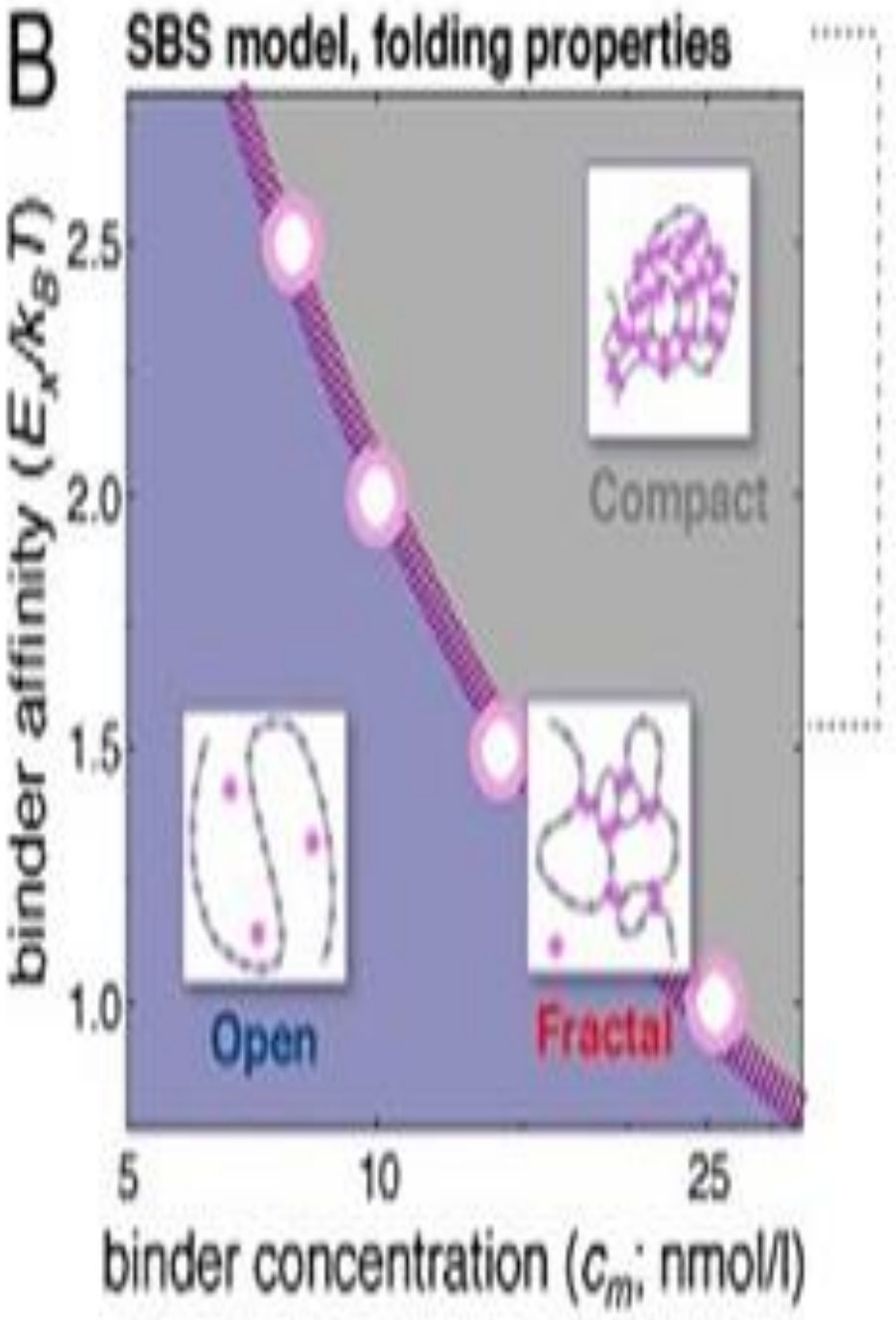
- More important**ly,** SBS mod
  all current experimental data on
  FISH, Hi-C and 3C approaches



- SBS mode evaluated the dyr
  the polymer using extensive
  known range of the biochemi
  binders ） and E_X.(binders affi
- $E_X=2K_BT$ (kB is the Boltzma
- in kelvin)

E_x change with the C_m

- C_{tr} (threshold concentration)

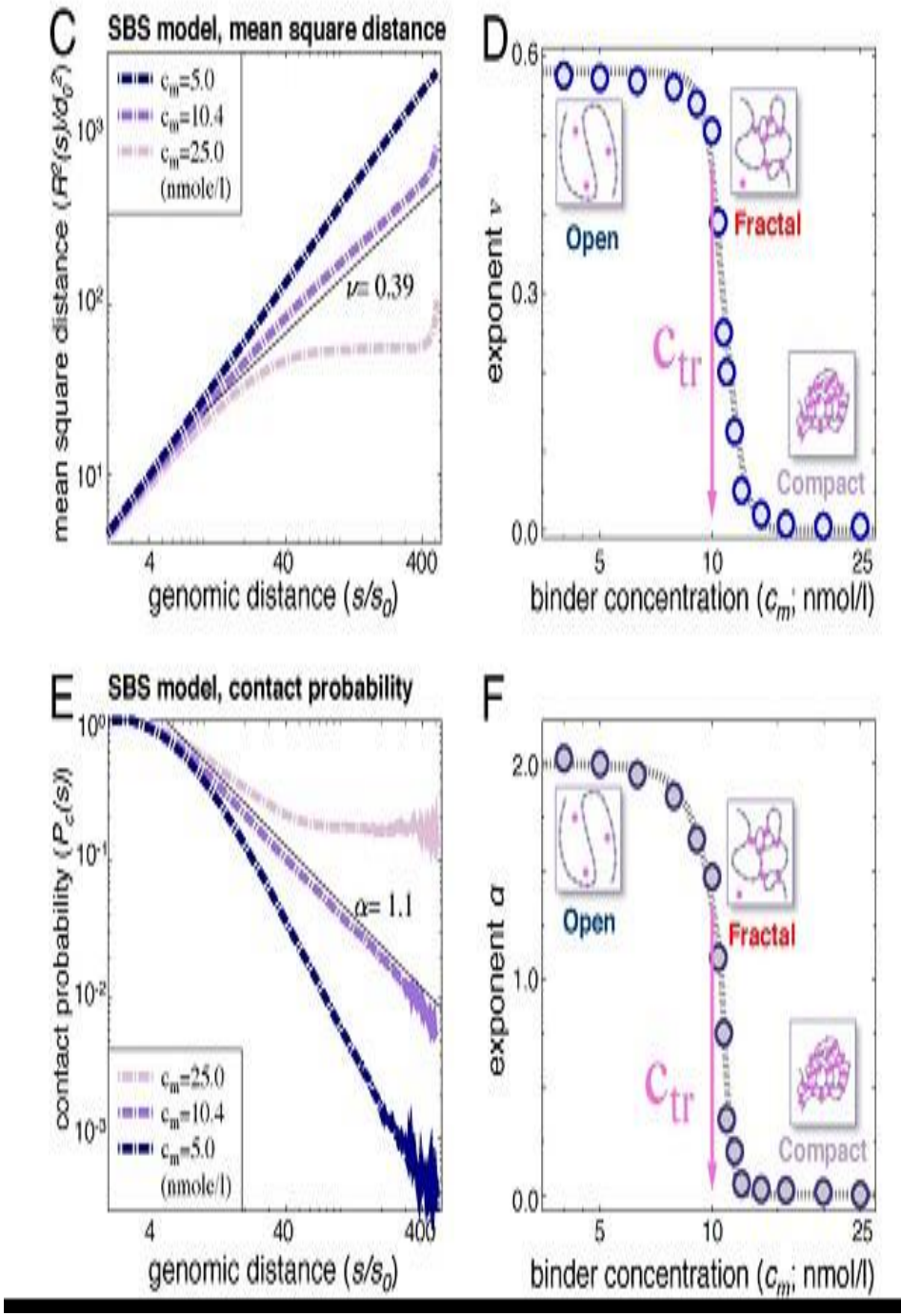


In the SBS model, the shape of the two functions $R_2(s)$ and Pc(s) is sensitive to the concentration of binding molecules, C_m

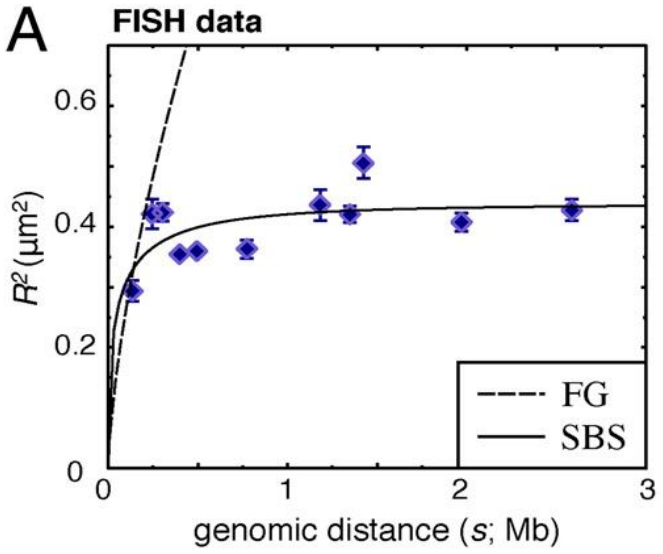
$Pc(s) \sim 1/S\alpha$

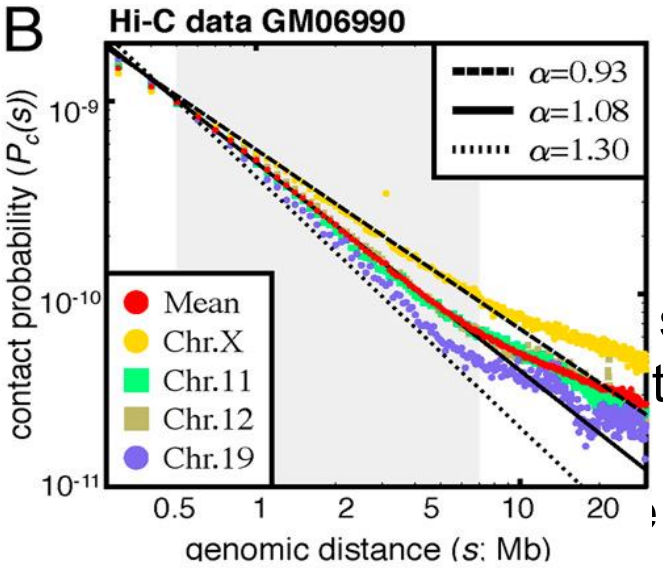
C_m & C_{tr}

$R^2(s) \sim S_{2v}$



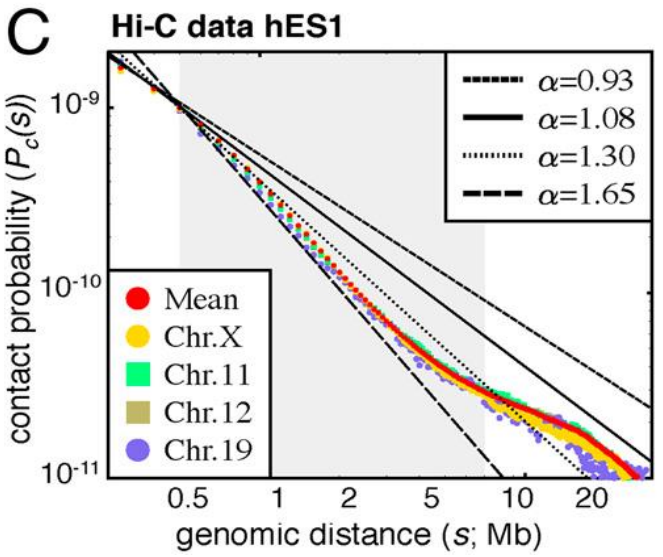
Comparison of the SBS and Other Models Against

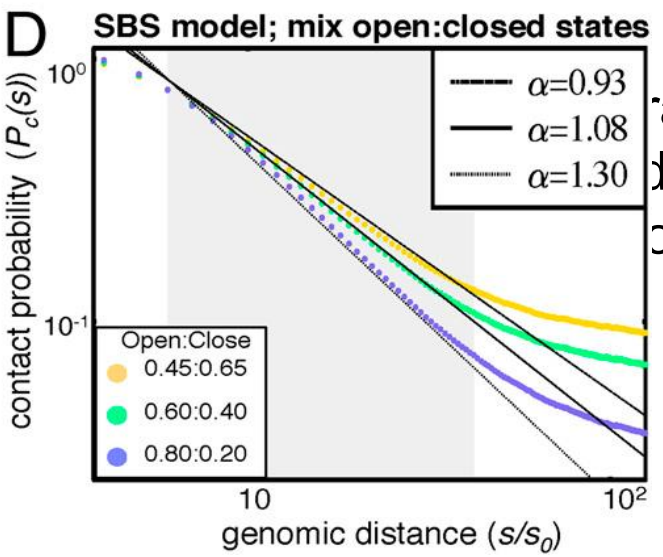




same cell)
t α.

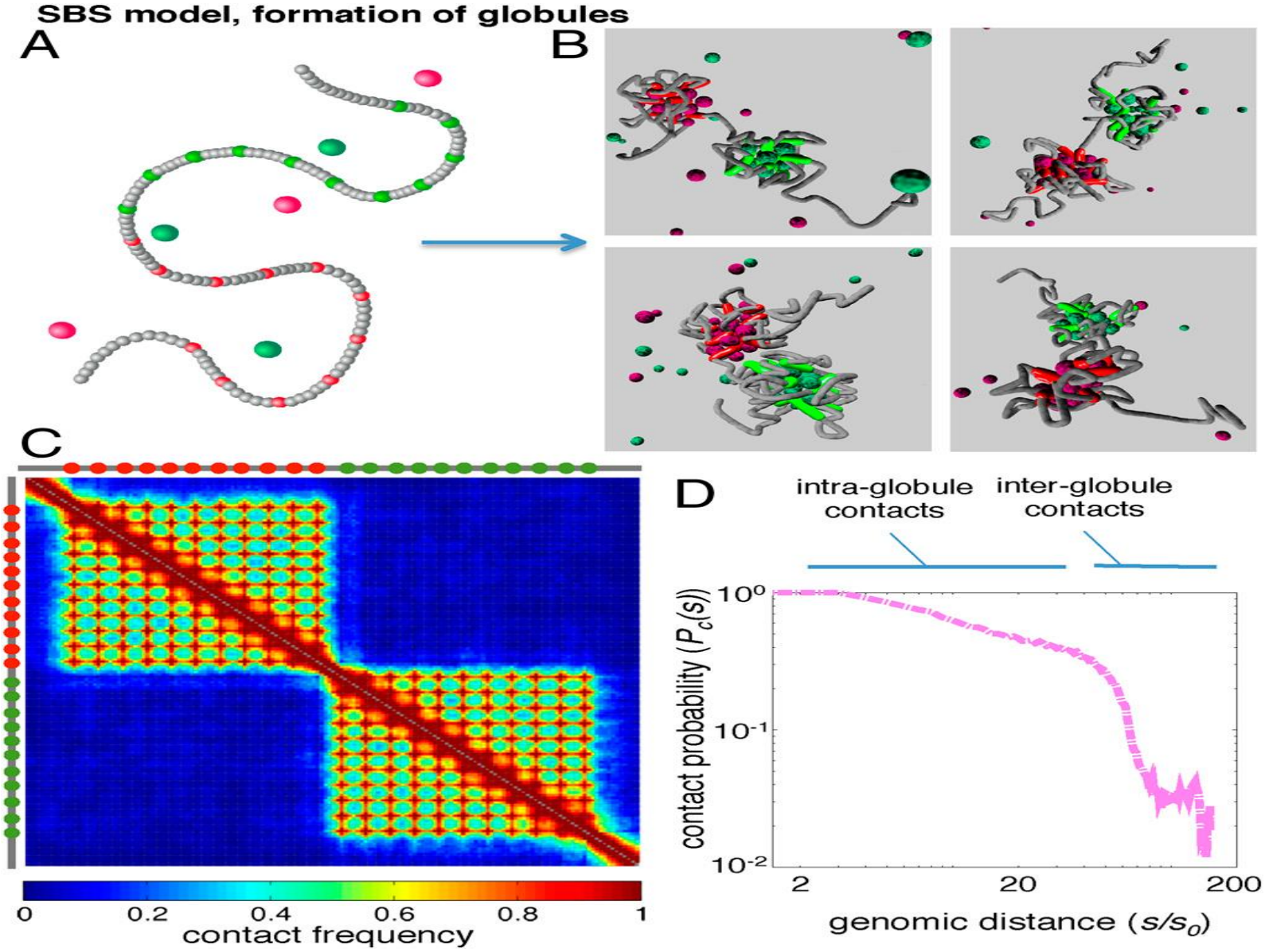
of α



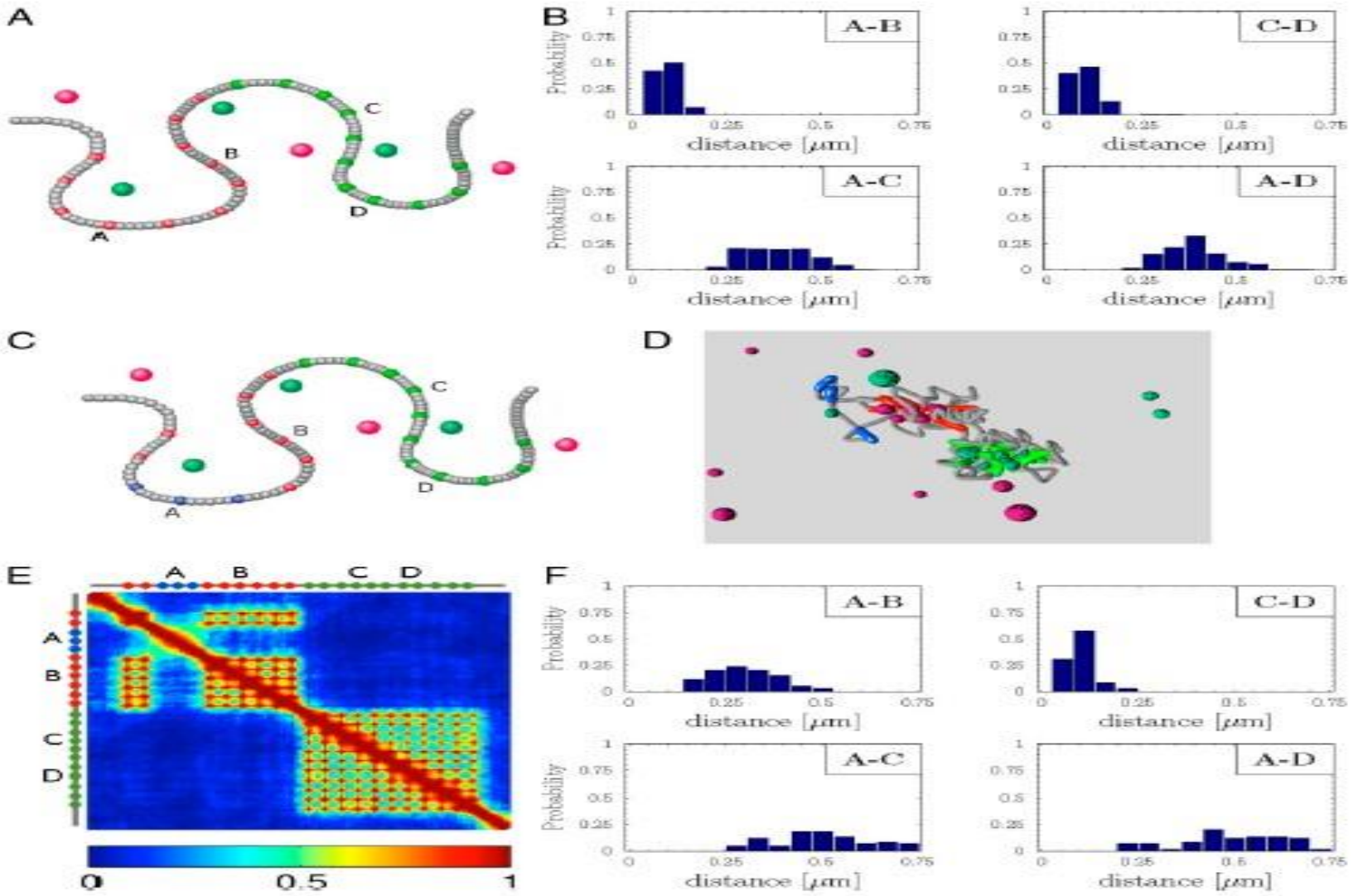


ransitional
d chromatin
ome

The SBS Model Reproduces the Organization of Chromatin in Topological Domains.



changed the state of three contiguous sites from binding the red binders to no longer having affinity to binders



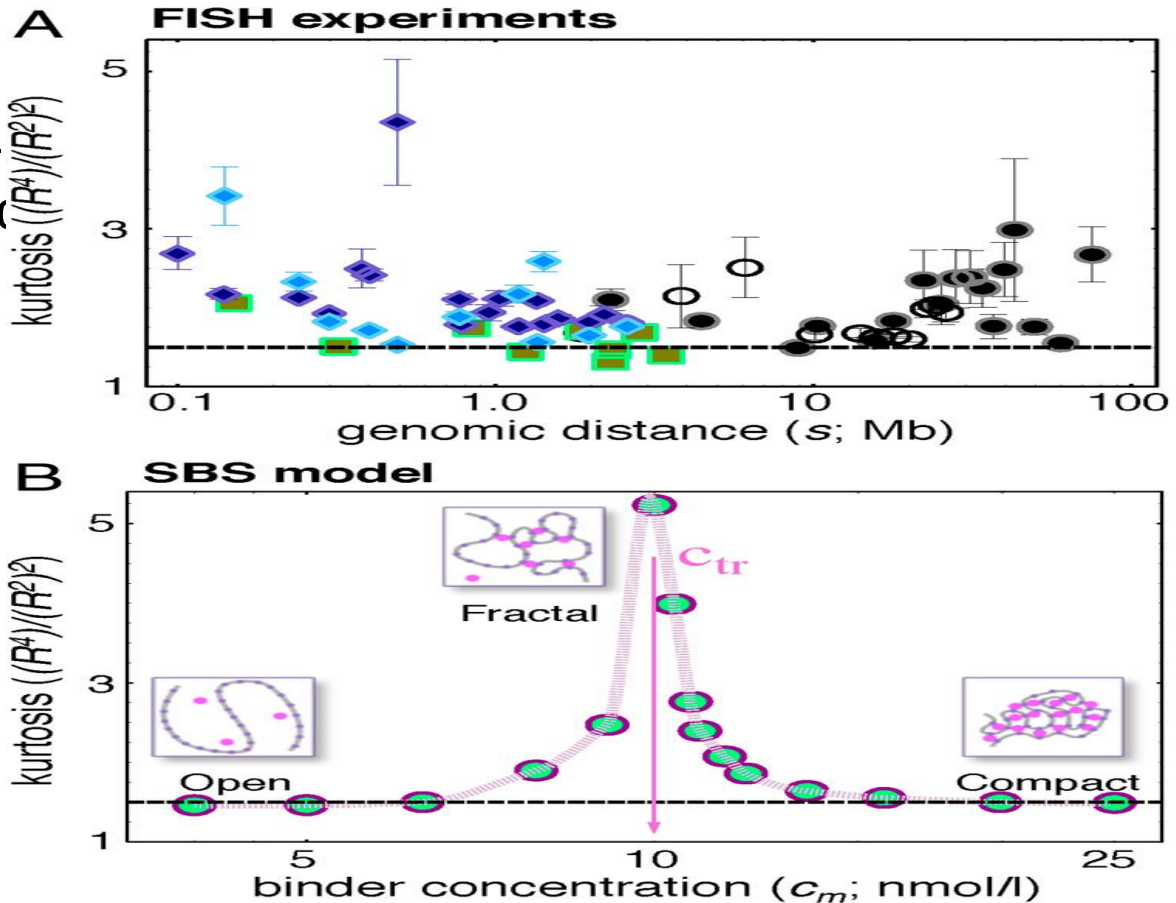
The SBS Model Reproduces the Dynamic Folding Behaviors of Chromatin.

- As a final test to the power of the SBS model, researcher investigated the kurtosis $K = \langle R^4(s) \rangle / \langle R^2(s) \rangle^2$, which is the ratio of the fourth and second moment of the spatial distance.

K carry information of genomic locus and cell – cell variation ,and depen(on Cm

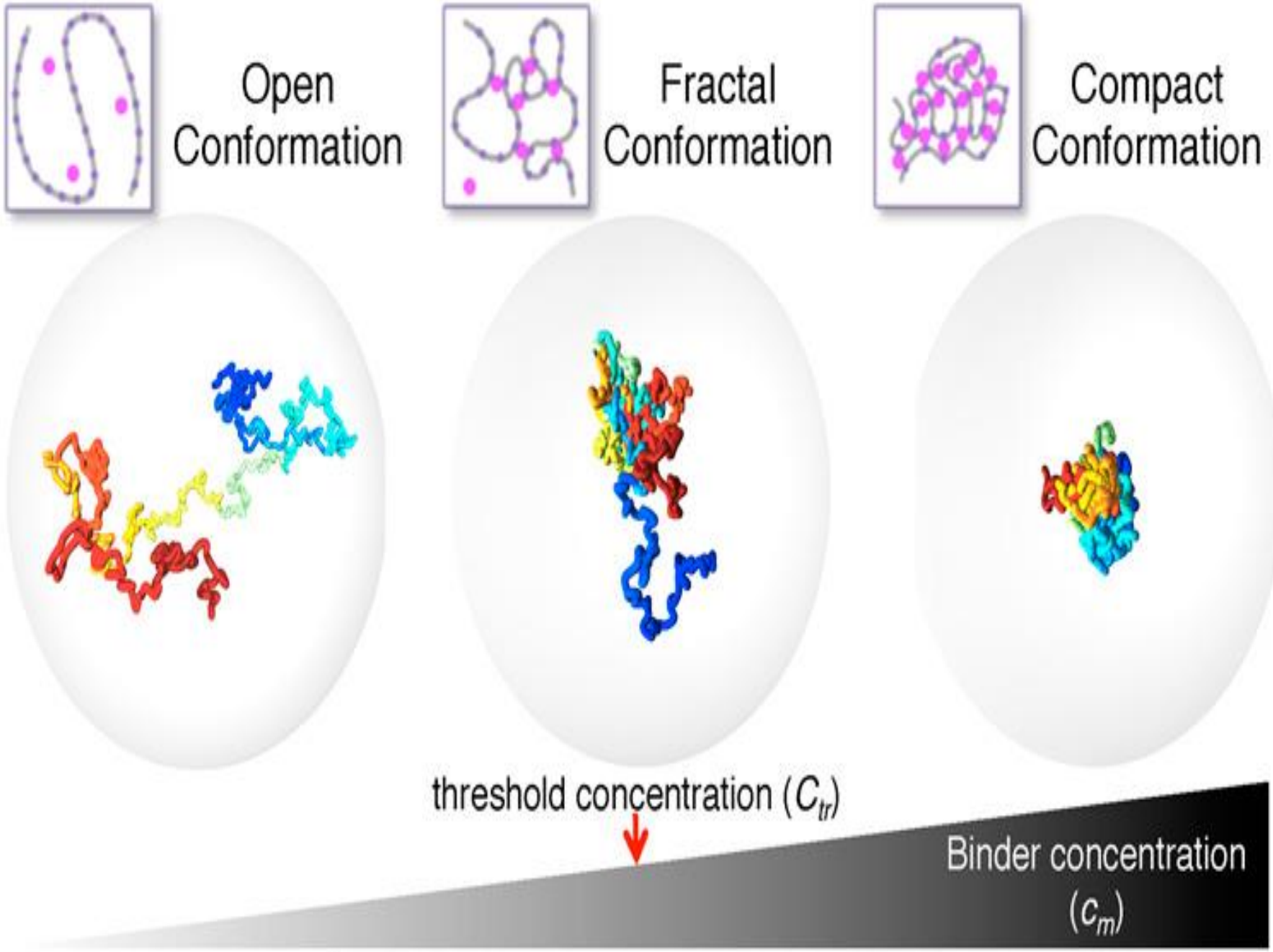
K=1.5,corresponding is compact and open

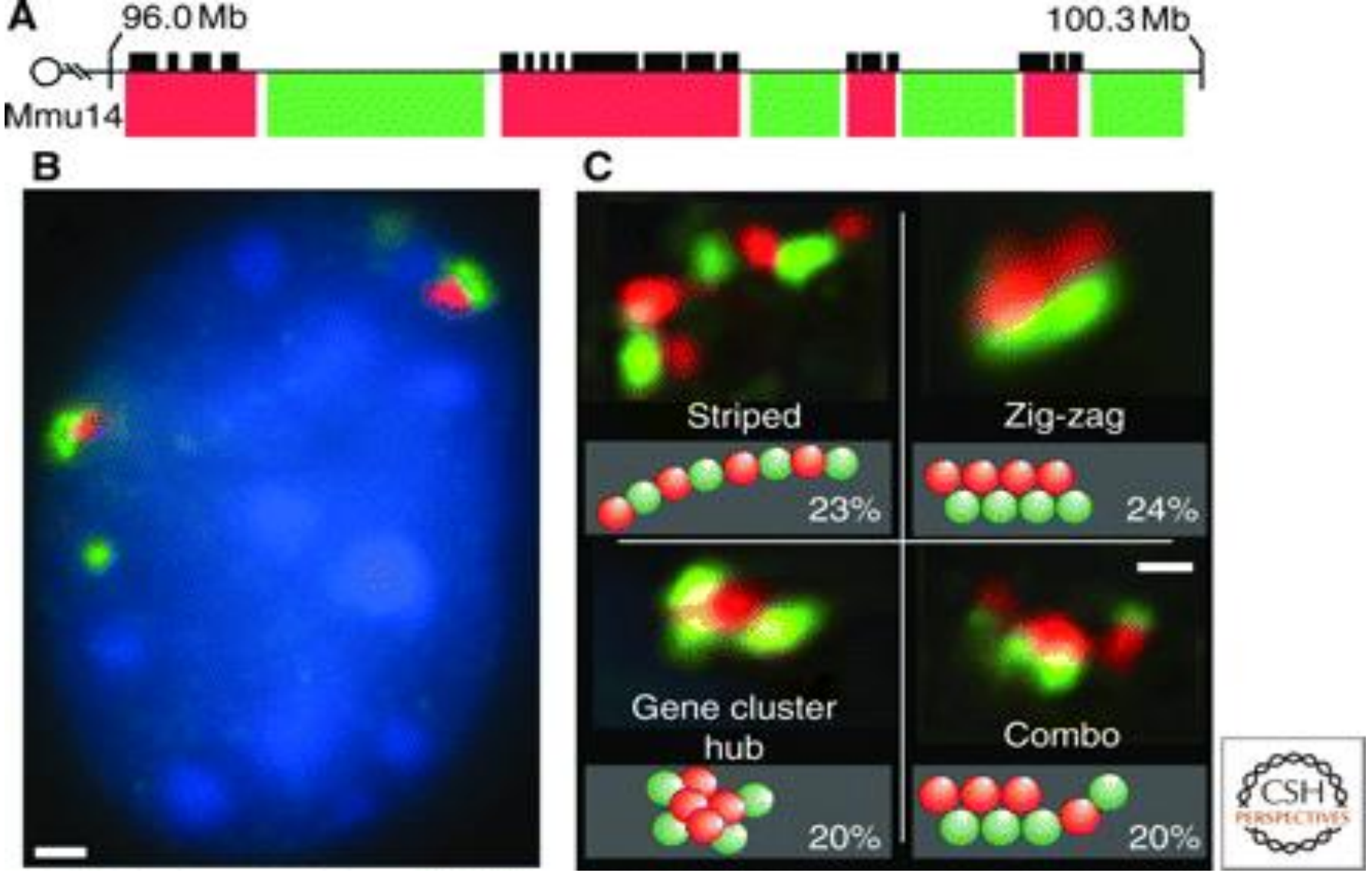
K=5,corresponding region is transition



Discussion

- 1. Interphase nuclei exhibit dynamic chromatin structures that change in response to cellular signals and influence patterns of gene expression.
  2 . genomic architectures sharp regulation of nuclear architecture can be obtained reliably by simple strategies, such as protein up-regulation or modification, without the need to fine tune these specific parameters.
- 3. SBS mode analysis strongly supports the conclusion that the principles of chromatin folding in interphase nuclei cannot be recapitulated by a single "universal" conformational state (and its given α).
  4. SBS model illustrates key physical concepts and basic required ingredients to explain chromatin folding in a variety of states identified in living systems, a variety of specific binding factors exist, where different regions can spontaneously fold into different chromatin states
- 5. polymer scaling theory ensures that the exponents in R^2 and Pc are independent of the minute details of the system considered and reflect universal properties
- 6The thermodynamic mechanisms discussed, which are robust and independent of specific molecular details, will be relevant to many cellular and nuclear processes requiring spatial organization
  7.SBS mode is a powerful mode to analysis chromatin structure organization.


Open Conformation
Fractal Conformation
Compact Conformation
threshold concentration (C_{tr})
Binder concentration (c_m)



(*A*) A large locus consisting of ~4-Mbp region containing regions of gene "deserts" (red fluorescence) and gene clusters (green fluorescence) is seen in the nucleus in multiple configurations (*C*). In general, gene deserts are more closely associated with the heterochromatin at the nuclear periphery (*B*). Scale is 1 μm. From Shopland et al. 2006.

Thanks for your attention