Nuclear chromodynamics
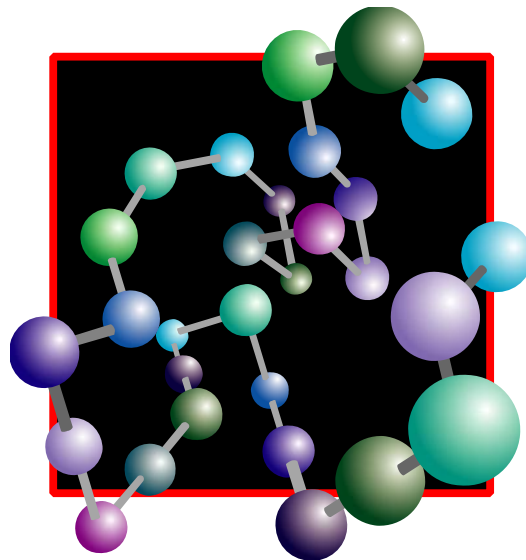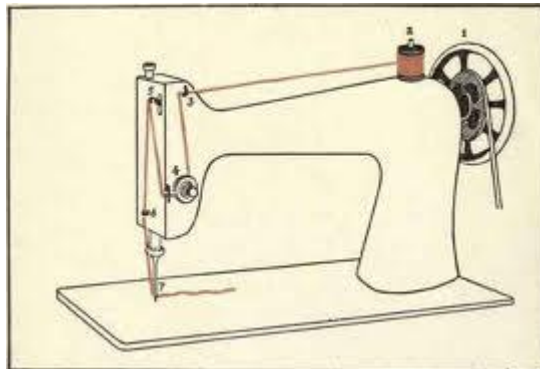
Alexander Grosberg
Center for Soft Matter Research
Department of Physics, New York University

Problem: why is it difficult to manage DNA?

- Human genome length about 2 meters;
- Nucleus size 10 micron;
- Increase all scales by a factor of a million:
  - length 2000 kilometers;
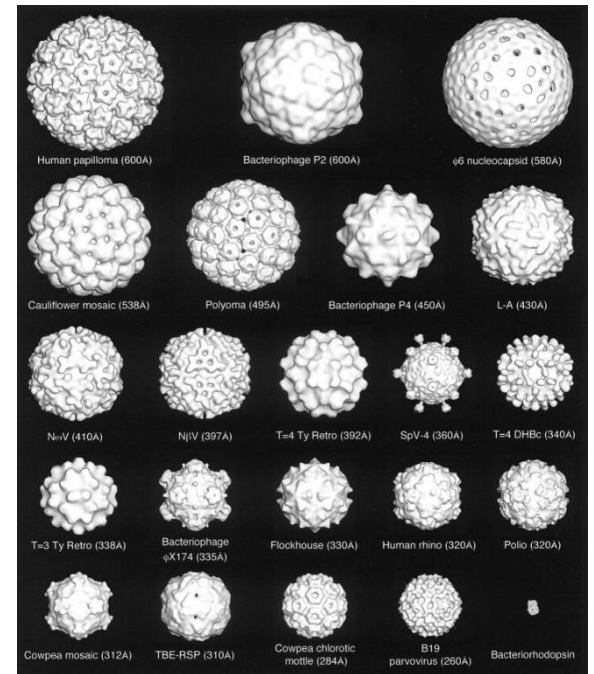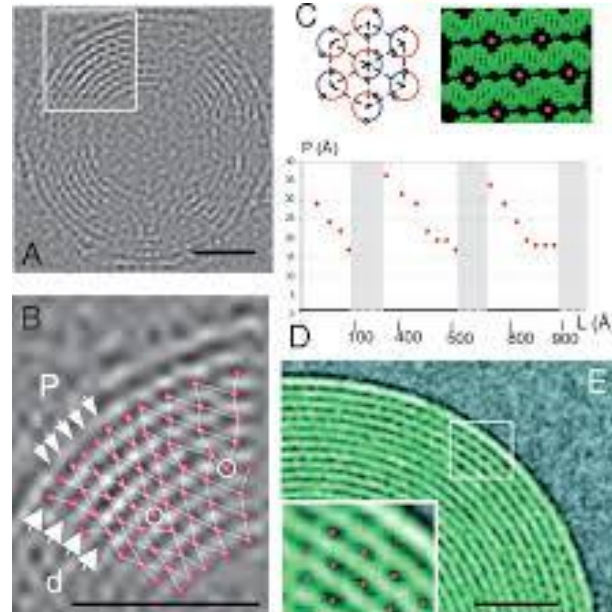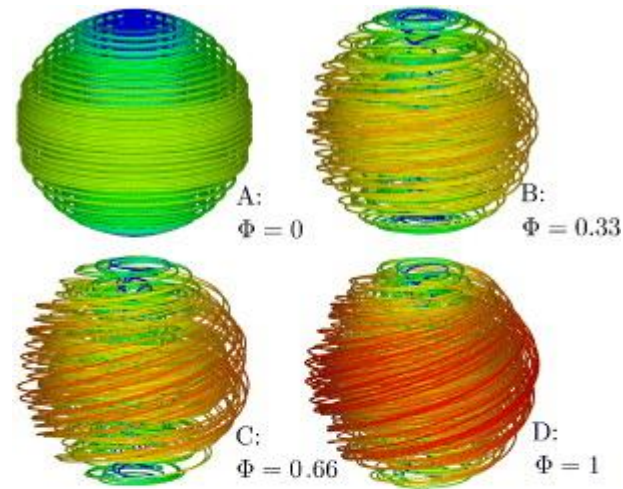 - diameter 2 mm;
  - packed in a few meters sized car...

Ropes, threads, wires...

Viruses do it

Francoise Livolant, ENS Paris

Some examples, with numbers:

Organism	Genome length	Stored in...	Ratio
Human	2 m	10 μm	200,000
Mouse	1.8 m	8 μm	200,000
Fruit Fly	5 cm	5 μm	10,000
Yeast	4 mm	2 μm	2000
Bacteria (E.coli)	1.5 mm	1 μm	1500
Virus (T4)	0.05 mm	0.05 μm	1000

Chromatin and cell nucleus

Interphase:
swollen chromosomes
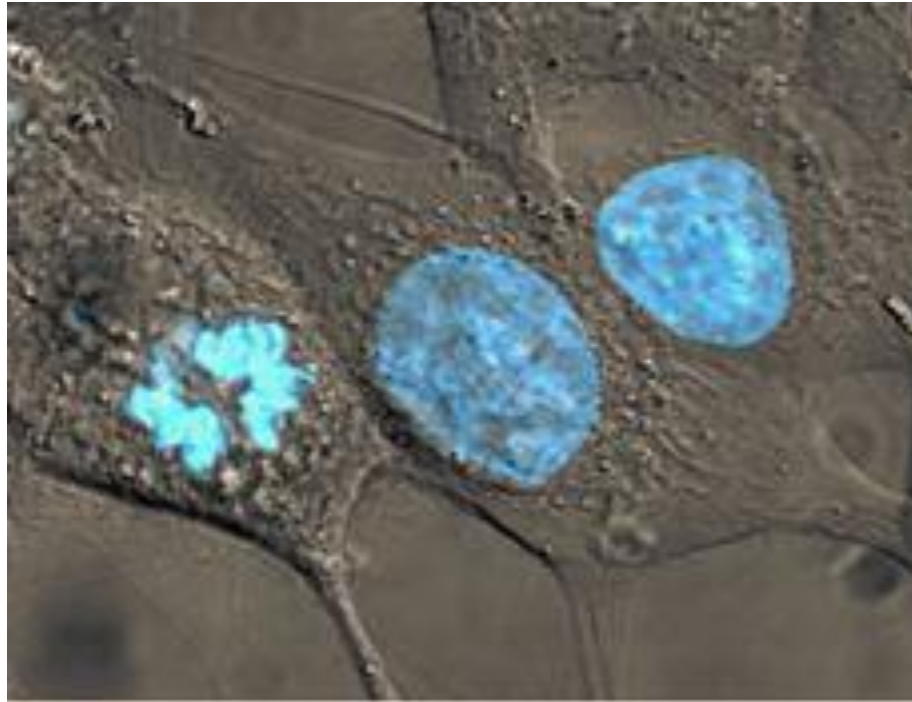
Metaphase:
chromosomes
are condensed
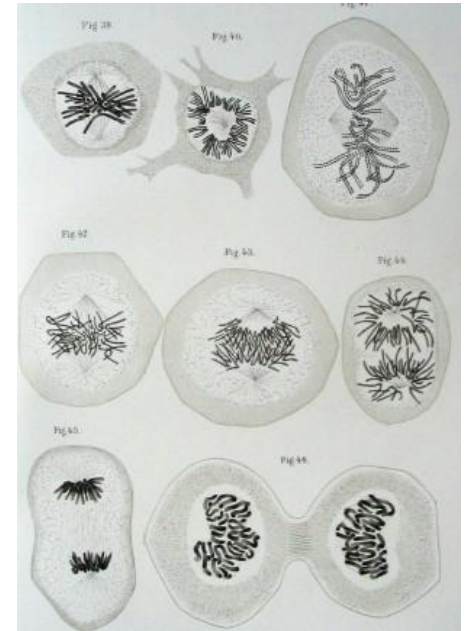
Walther Flemming, 1880

Hierarchial organization

10000 nm

11 nm

30 nm

1 bp, 0.34 nm

Image from the cover of: "Molecular and Cellular Biology," Stephen L. Wolfe, 1993

A NUCLEOSOME

DNA double helix

1-3/4 turns
(146 base pairs)

Histone octamer

10 nm

© 2004 J. Perkins

(A)

(B)

Human mitotic chromosome structure: what happened to the 30-nm fibre?

Jeffrey C Hansen

Department of Biochemistry and Molecular Biology, Colorado State University, Fort Collins, CO, USA.
Correspondence to: jeffrey.c.hansen@colostate.edu

The EMBO Journal (2012) **31**, 1621–1623. doi:10.1038/emboj.2012.66; Published online 13 March 2012
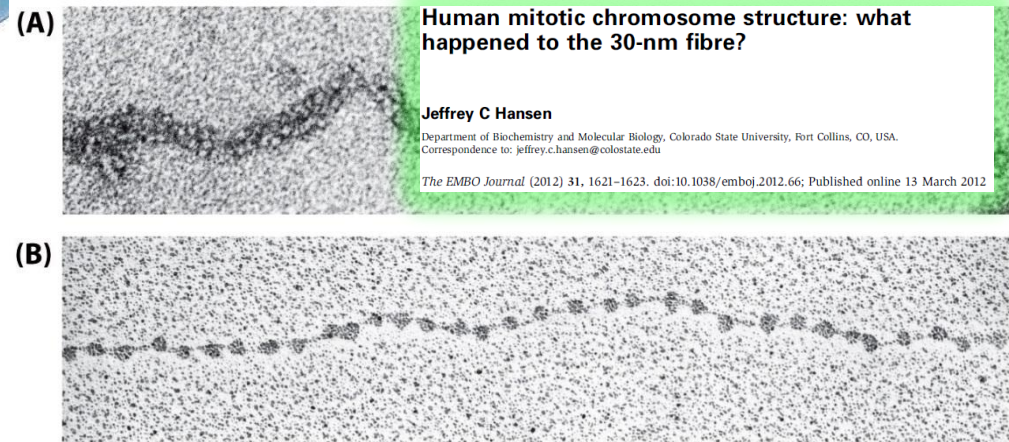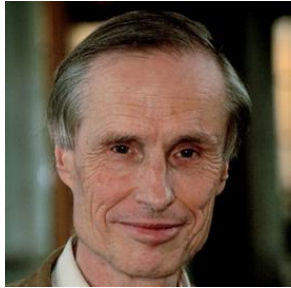
50 nm

Figure 4-22 *Molecular Biology of the Cell* (© Garland Science 2008)
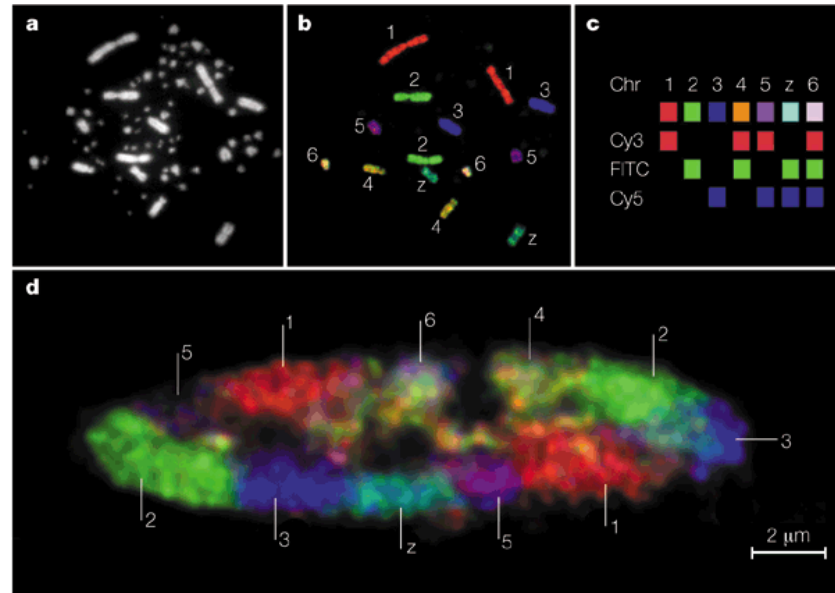
Chromosome territories

Christoph Cremer,
Heidelberg/Mainz

Thomas Cremer,
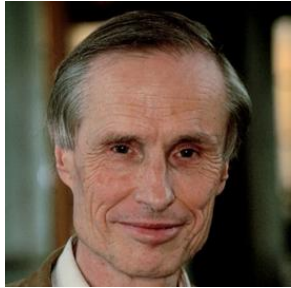LMU Munich

Marion Cremer,
LMU Munich

a | 4,6-diamidino-2-phenylindole (DAPI)-stained, diploid, chicken metaphase spread with macro- and microchromosomes. b | The same metaphase spread after multicolour fluorescence in situ hybridization with pseudocoloured chromosomes. Chicken chromosome paint probes (image courtesy of Johannes Wienberg) were labelled by a combinatorial scheme with oestradiol (1, 4, 5, 6), digoxigenin (2, 4, 6, Z) and biotin (3, 5, 6, Z). c | Oestradiol- and digoxigenin-labelled probes were detected using secondary antibodies labelled with Cy3 and fluorescein isothiocyanate (FITC); biotinylated probes were detected with Cy5-conjugated streptavidin. d | Mid-plane light optical section through a chicken fibroblast nucleus shows mutually exclusive chromosome territories (CTs) with homologous chromosomes seen in separate locations. (Note that only one of the two CTs for each of 4 and 6 is displayed in this section.) (Image courtesy of F. Habermann.)

T. Cremer & C. Cremer "Chromosome territories, nuclear architecture and gene regulation in mammalian cells" Nature Reviews Genetics **2**, 292-301 (April 2001)

T. Cremer & M. Cremer "Chromosome territories" Cold Spring Harbor Perspectives in Biology 2010;2:a003889 (2010)
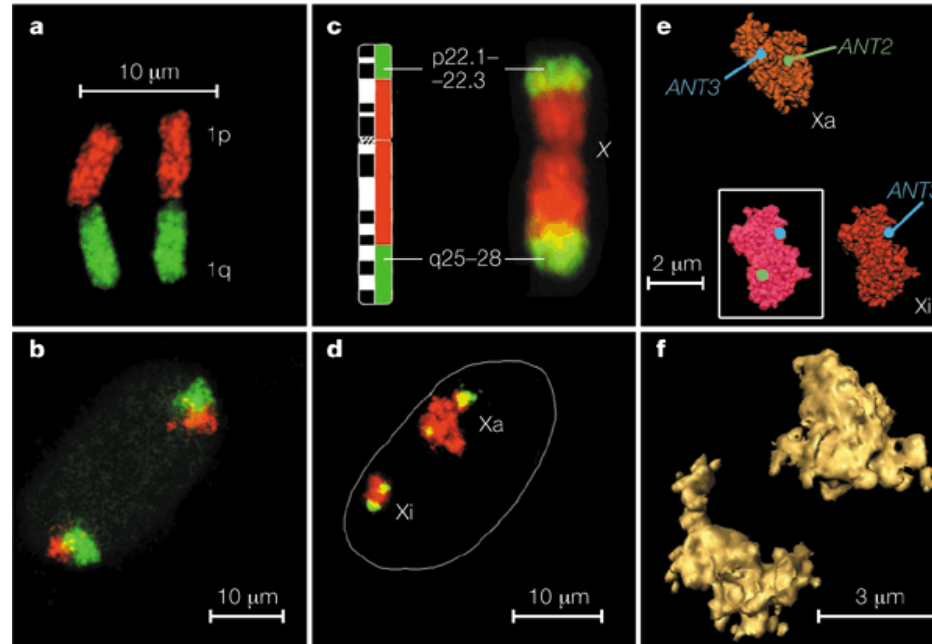
Chromosome territories

Christoph Cremer,
Heidelberg/Mainz

Thomas Cremer,
LMU Munich

Marion Cremer,
LMU Munich

Irina Solovei,
LMU Munich

a | Two-colour painting of the p-arm (red) and the q-arm (green) of human chromosome 1 in a lymphocyte metaphase spread. b | Visualization of the two arms in a light optical section through a human diploid fibroblast nucleus (bottom) shows two distinct, mutually exclusive arm domains[20]. (Image courtesy of Steffen Dietzel). c | Painting of the human X chromosome (red) and several distal bands of its p-arm and q-arm (green) using MICRODISSECTION PROBES[20]. d | Visualization of the active and inactive X-chromosome territories (Xa and Xi, respectively) together with the respective distal-band domains in a light optical section through a female human fibroblast nucleus. (Image courtesy of Joachim Karpf and Irina Solovei). e | Three-dimensional reconstructions of the Xa and Xi territories from a human female fibroblast nucleus (Reproduced with permission from Ref. 22). The three-dimensional positions of the ANT2 and ANT3 (adenosine nucleotide translocase) genes are noted as green and blue spheres, respectively. Note that active ANT genes can be seen at the territory surface (two on Xa and one on Xi). The white box provides a transparent view of the Xi territory (pink), indicating the location of the inactive ANT2 gene in the territory interior. f | Three-dimensonal reconstructions of two chromosome-17 territories, established from light optical serial sections through a human diploid fibroblast nucleus, show complex territory surfaces. (Image courtesy of Irina Solovei.)

T. Cremer & C. Cremer "Chromosome territories, nuclear architecture and gene regulation in mammalian cells" Nature Reviews Genetics **2**, 292-301 (April 2001)

T. Cremer & M. Cremer "Chromosome territories" Cold Spring Harbor Perspectives in Biology 2010;2:a003889 (2010)

Chromosome territories
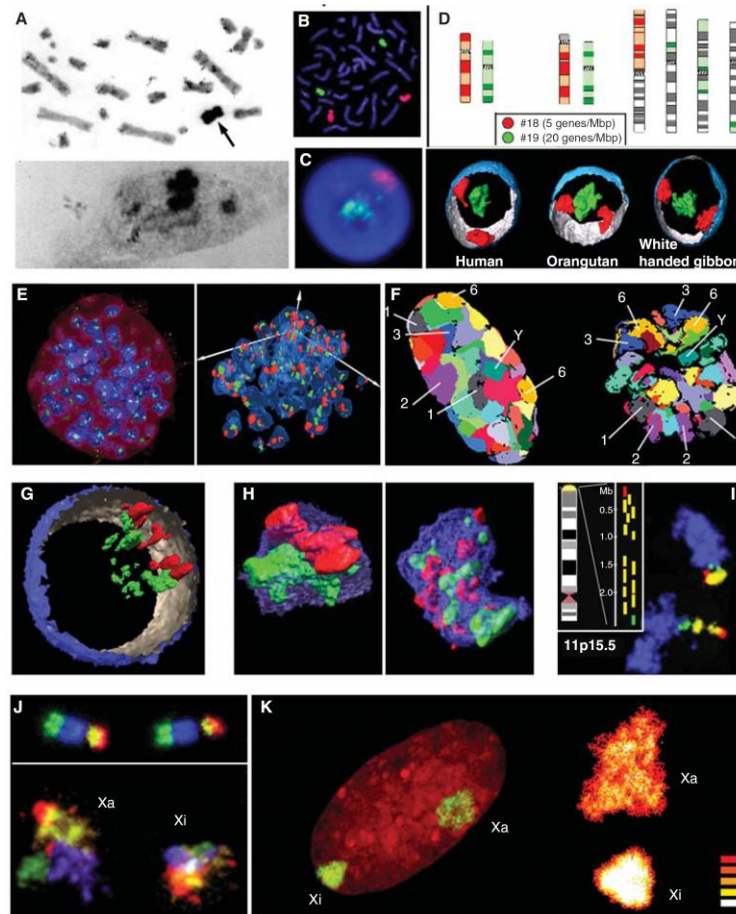
T. Cremer & C. Cremer "Chromosome territories, nuclear architecture and gene regulation in mammalian cells" Nature Reviews Genetics **2**, 292-301 (April 2001)

T. Cremer & M. Cremer "Chromosome territories" Cold Spring Harbor Perspectives in Biology 2010;2:a003889 (2010)

24-Color 3D FISH Representation and Classification of Chromosomes in a Human G0 Fibroblast Nucleus
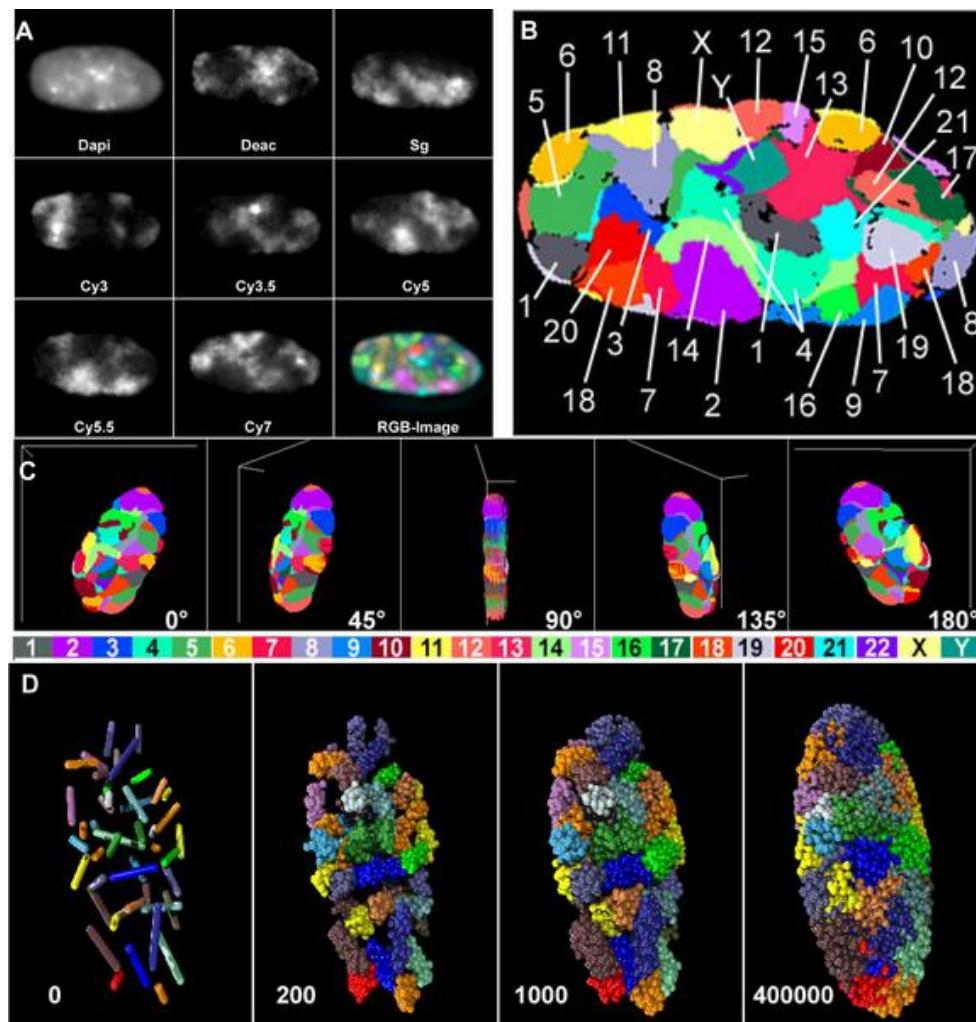
Chromosome territories

1. Chromosomes occupy discrete territories in the cell nucleus and contain distinct chromosome-arm and chromosome-band domains.
2. Chromosome territories (CTs) with different gene densities occupy distinct nuclear positions.
3. Gene-poor, mid-to-late-replicating chromatin is enriched in nuclear compartments that are located at the nuclear periphery and at the perinucleolar region.
4. A compartment for gene-dense, early-replicating chromatin is separated from the compartments for mid-to-late-replicating chromatin.
5. Chromatin domains with a DNA content of approx1 Mb can be detected in nuclei during interphase and in non-cycling cells.
6. The interchromatin compartment (IC) contains various types of non-chromatin domains with factors for transcription, splicing, DNA replication and repair.
7. The CT–IC model predicts that a specific topological relationship between the IC and chromatin domains is essential for gene regulation.
8. The transcriptional status of genes correlates with gene positioning in CTs.
9. A dynamic repositioning of genes with respect to centromeric heterochromatin has a role in gene silencing and activation.
10. Various computer models of CTs and nuclear architecture make different predictions that can be validated by experimental tests.
11. Comprehensive understanding of gene regulation requires much more detailed knowledge of gene expression in the context of nuclear architecture and organization.

T. Cremer & C. Cremer "Chromosome territories, nuclear architecture and gene regulation in mammalian cells" Nature Reviews Genetics **2**, 292-301 (April 2001)

T. Cremer & M. Cremer "Chromosome territories" Cold Spring Harbor Perspectives in Biology 2010;2:a003889 (2010)

Chromosome territories:

"On this, theologians, philosophers, and biologists can agree: we are more than the sum of our genes."
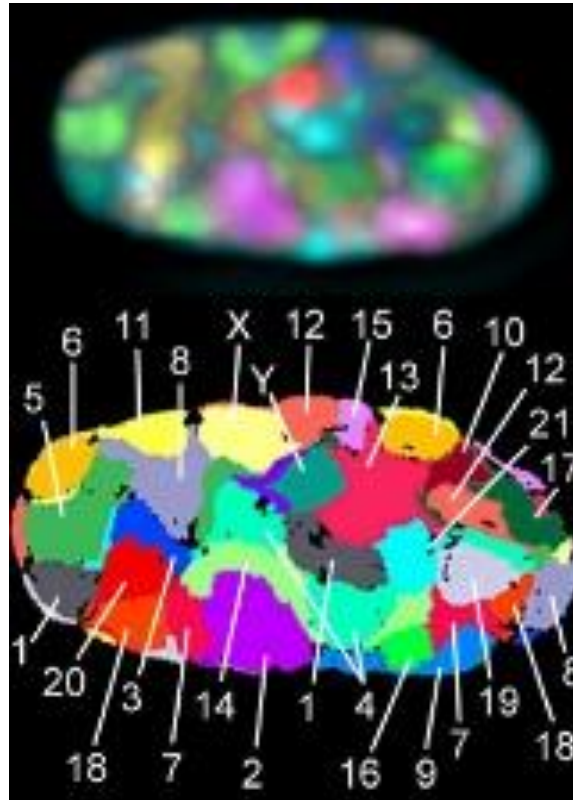

Christoph Cremer, Heidelberg/Mainz

Thomas Cremer, LMU Munich

Marion Cremer, LMU Munich

I think, physicists agree:
More is Different
(P.W.Andersen, 1972)

Fitzgerald: The rich are different from us.
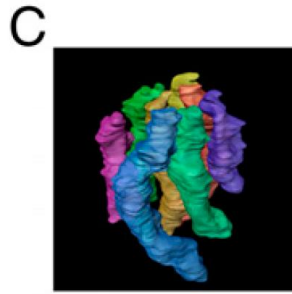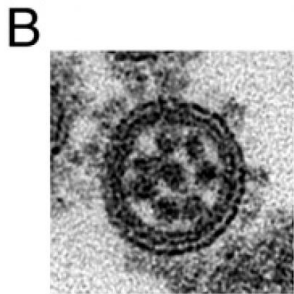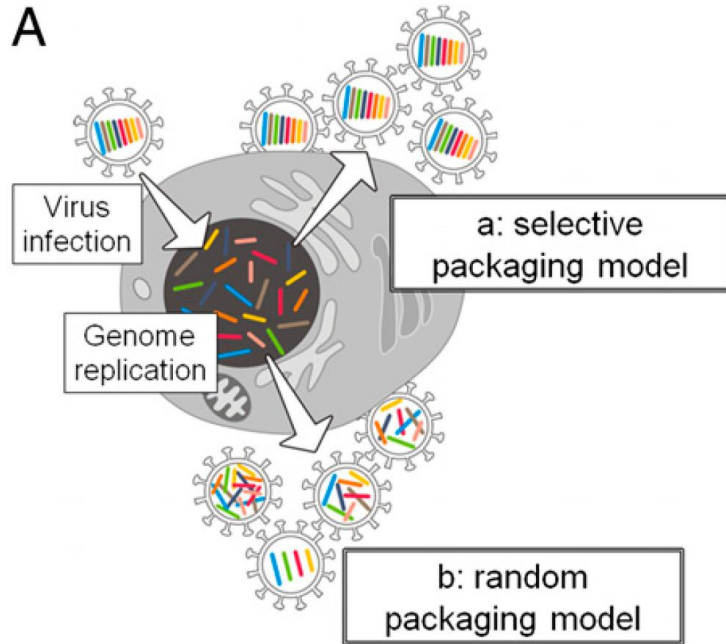Hemingway: Yes, they have more money.

TA.Bolzer, G.Kreth, I.Solovei, D.Koehler, K.Saracoglu, C.Fauth, S.Muller, R.Eils, C.Cremer, MR.Specher, T.Cremer Three-dimensional maps of all chromosomes in human male fibroblast nuclei and prometaphase rosettes. PLoS Biol. 2005 May;3(5):e157.

T. Cremer & C. Cremer "Chromosome territories, nuclear architecture and gene regulation in mammalian cells" Nature Reviews Genetics **2**, 292-301 (April 2001)

T. Cremer & M. Cremer "Chromosome territories" Cold Spring Harbor Perspectives in Biology 2010;2:a003889 (2010)

"Territories" in influenza virus
(genome consists of 8 RNAs)

For a polymer physicist, chromosome territories are surprising
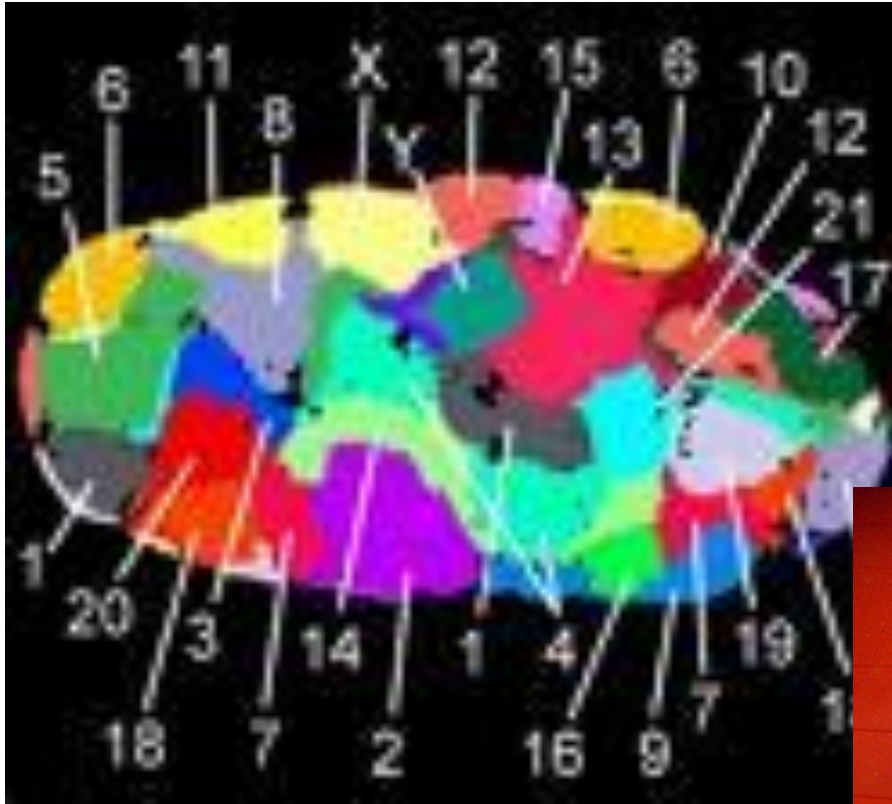
Chromosome Capture experiments:

Step 1: cross-link DNA

Step 2: cut DNA (restriction enzyme)

Step 3: sequence the cross-linked piece of DNA

Step 4: identify cross-linked pieces in DNA
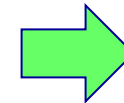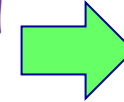
Step 5: repeat many times...

HindIII

AAGCTT
TTCGAA

Job Dekker
U. Mass.
Medical center

Chromosome Conformation Capture data for various species

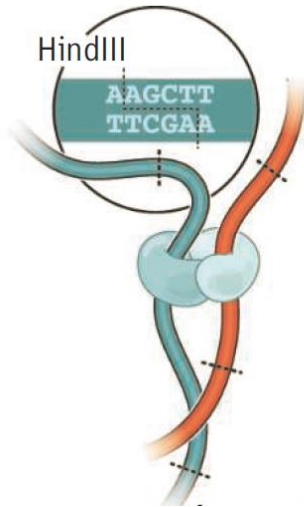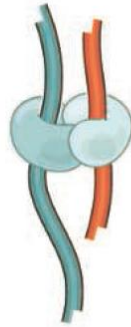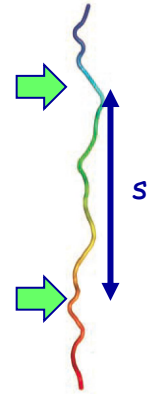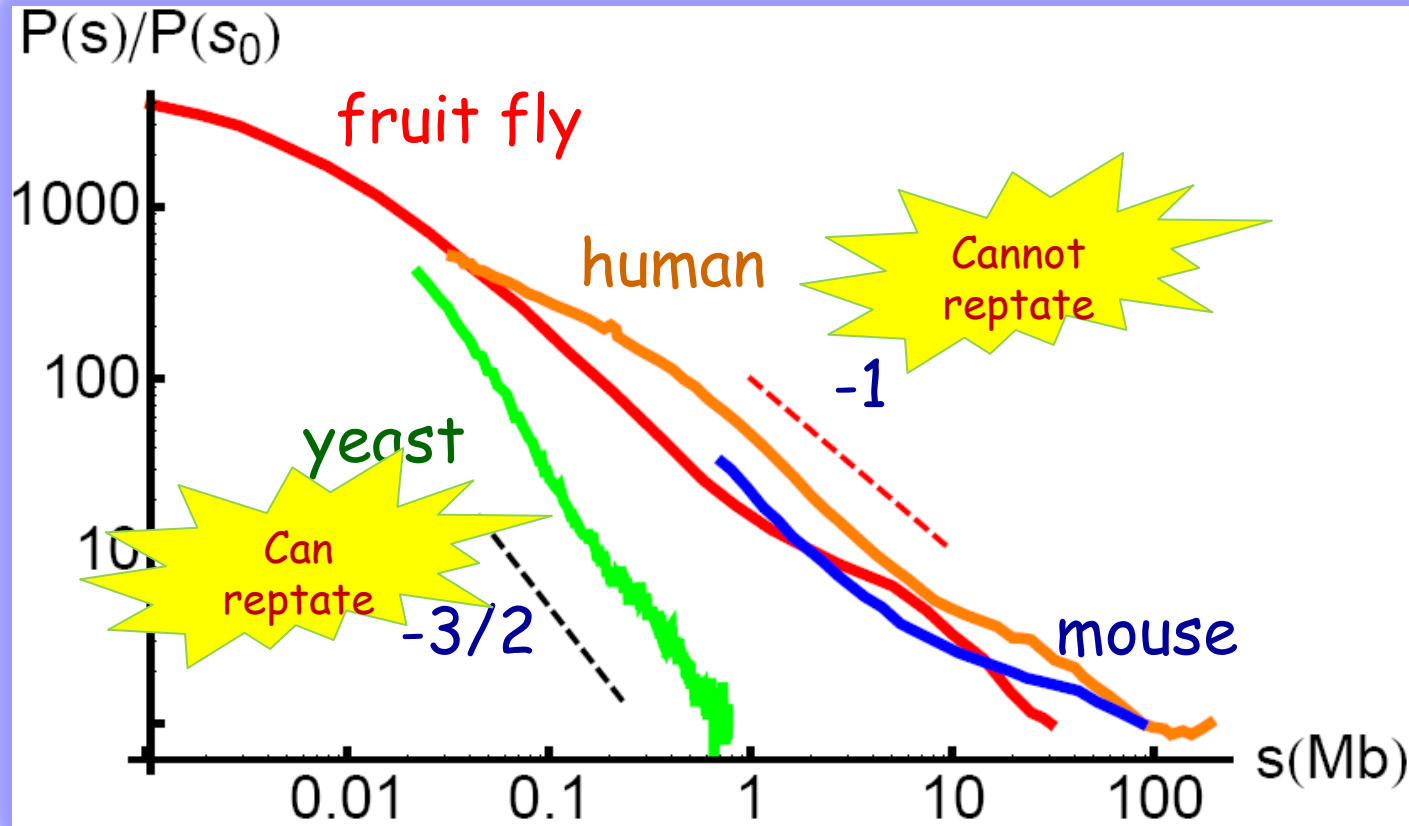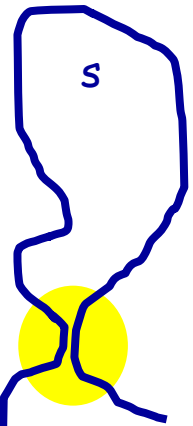E. Lieberman-Aiden, N. L. van Berkum, L. Williams, M. Imakaev, T. Ragoczy, A. Telling, I. Amit, B. R. Lajoie, P. J. Sabo, M. O. Dorschner, et al., Science 326, 289 (2009).

Z. Duan, M. Andronescu, K. Schutz, S. McIlwain, Y. J. Kim, C. Lee, J. Shendure, S. Fields, C. A. Blau, and W. S. Noble, Nature 465, 363 (2010).
Y. Zhang, R. McCord, Y.-J. Ho, B. Lajoie, D. Hildebrand, A. Simon, M. Becker, F. Alt, and J. Dekker, Cell 148, 908 (2012).
T. Sexton, E. Yaffe, E. Kenigsberg, F. Bantignies, B. Leblanc, M. Hoichman, H. Parrinello, A. Tanay, and G. Cavalli, Cell 148, 458 (2012).

Unconcatenated rings are "territorial"

Polymers which don't reptate...   Polymers which do reptate...

Thomas Vettorel, Alexander Y. Grosberg, and Kurt Kremer "
Statistics of polymer rings in the melt: A numerical simulation
study," Physical Biology, v. **6**, n. 2, 025013, 2009.
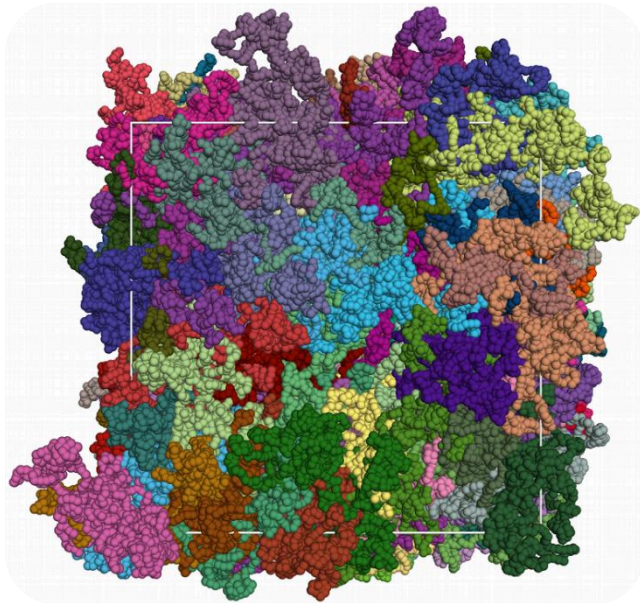
Topological nature of chromosome territories?

Bolzer A, Kreth G, Solovei I, Koehler D, Saracoglu K, Fauth C, Muller S, Eils R, Cremer C, Speicher MR, Cremer T. Three-dimensional maps of all chromosomes in human male fibroblast nuclei and prometaphase rosettes. PLoS Biol. 2005 May;3(5):e157.

back scatter

Territorial polymers
Eukaryotic cells store, manage, and use up to a meter of DNA in a micron-sized nucleus. How that is achieved is not completely understood and, indeed, is not easy to imagine: Consider that in polymer physics, chains packed at a similar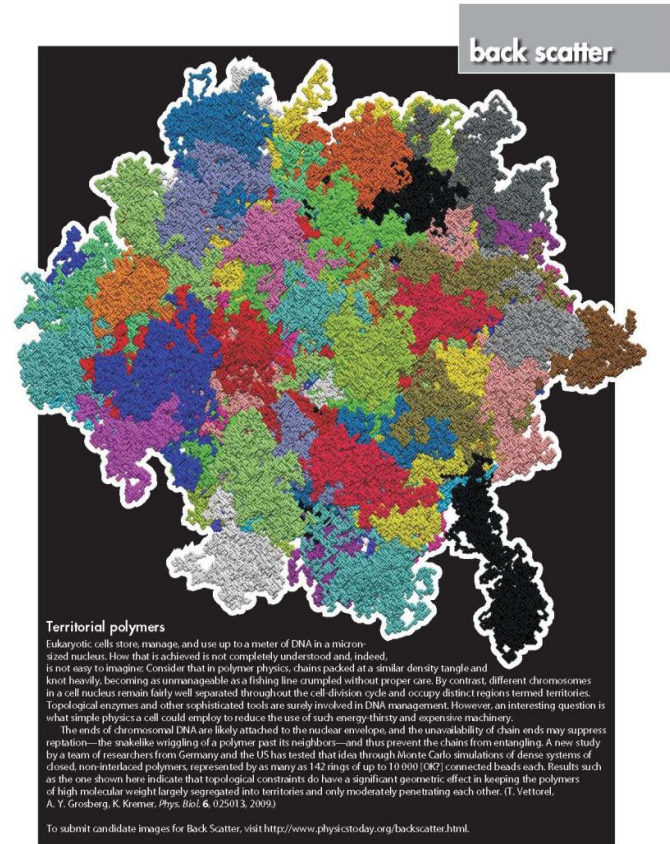 density tangle and knot heavily, becoming as unmanageable as a fishing line crumpled without proper care. By contrast, different chromosomes in a cell nucleus remain fairly well separated throughout the cell-division cycle and occupy distinct regions termed territories. Topological enzymes and other sophisticated tools are surely involved in DNA management. However, an interesting question is what simple physics a cell could employ to reduce the use of such energy-thirsty and expensive machinery.
The ends of chromosomal DNA are likely attached to the nuclear envelope, and the unavailability of chain ends may suppress reptation—the snakelike wriggling of a polymer past its neighbors—and thus prevent the chains from entangling. A new study by a team of researchers from Germany and the US has tested that idea through Monte Carlo simulations of dense systems of closed, non-interlaced polymers, represented by as many as 142 rings of up to 10 000 [OK?] connected beads each. Results such as the one shown here indicate that topological constraints do have a significant geometric effect in keeping the polymers of high molecular weight largely segregated into territories and only moderately penetrating each other. (T. Vettorel, A. Y. Grosberg, K. Kremer, *Phys. Biol.* **6**, 025013, 2009.)

To submit candidate images for Back Scatter, visit http://www.physicstoday.org/backscatter.html.

72   August 2009   Physics Today   www.physicstoday.org

Thomas Vettorel, AYG, and Kurt Kremer " Statistics of polymer rings in the melt: A numerical simulation study," Physical Biology, v. **6**, n. 2, 025013, 2009.

See also J.**Arsuaga** , Y.Diao, M.Vazquez "DNA topology in recombination and chromosome organization". (Book Chapter) Mathematics of DNA Structure, Function and Interactions (eds C.J. Benham, S. Harvey, W.K. Olson, D.W. Sumners and D. Swigon), Springer (2009)

Data vs Theory:

If you need a theory…
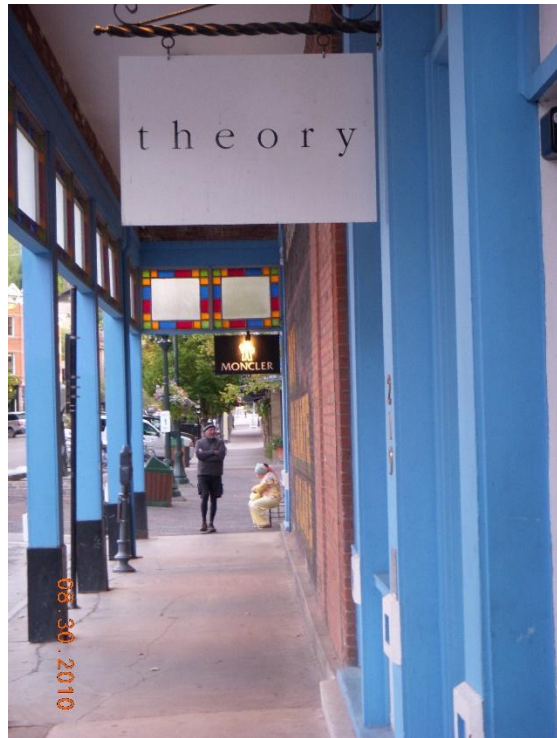
If your experiment does not work, and your data is so-so…

- **Theory Return & Exchange Policies:**
  We will happily accept your return or exchange of … when accompanied by a receipt within 14 days … if it does not fit

Chromatin fiber as a polymer:

Regular polymer in Gauss regime: $R^2 = \ell L$,
Effective Kuhn segment ℓ, nm,
Contour length L, nm;

For dsDNA, Kuhn segment: $\ell = 100$ nm

For chromatin fiber, Kuhn length is not well understood, usually assumed around 300 nm

Contour length is usually known as the number of base pairs, N:
L = N B
contour density 1/B bp/nm is
POORLY KNOWN,
Usually estimated between 40 and 120 bp/nm

Estimate of entanglement
length from 4 kbp to 1300 kbp

Some examples, with numbers:

Organism	Length of genome N, bp	Diameter of domain, D, μm	L/D L = Nx0.34 nm/bp	Volume fraction of DNA	Volume fraction with "tight" proteins	
					lower	upper
Bacteriophage (T4)	1.7×10^5	0.05	$\sim 10^3$	50%	Not applicable	
E. coli	4.6×10^6	1	1500	$\sim 1\%$	Not known	
Yeast, haploid	1.2×10^7	2	$\sim 2 \times 10^3$	$\sim 0.3\%$	0.6%	10%
Drosophila, diploid	1.5×10^8	10	$\sim 10^4$	$\sim 0.05\%$	0.1%	1.5%
Chicken, diploid	1.2×10^9	2	$\sim 2 \times 10^5$	$\sim 4\%$	$\sim 8\%$	100%
Mouse, diploid	2.8×10^9	9	$\sim 2 \times 10^5$	$\sim 1\%$	$\sim 2\%$	$\sim 30\%$
Human, diploid	3.3×10^9	10	$\sim 2 \times 10^5$	$\sim 1\%$	$\sim 2\%$	$\sim 30\%$

Some arithmetic:

As a Gaussian coil, every single chromosome would be about $R \approx (L \ell)^{1/2} = (N \ell/B)^{1/2} \approx 25 \ \mu m$, twice bigger than the whole nucleus.
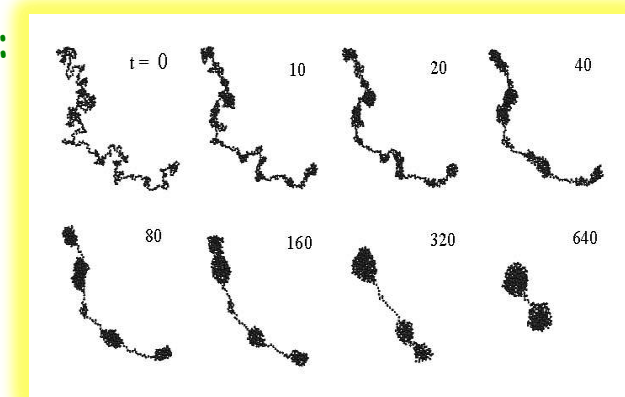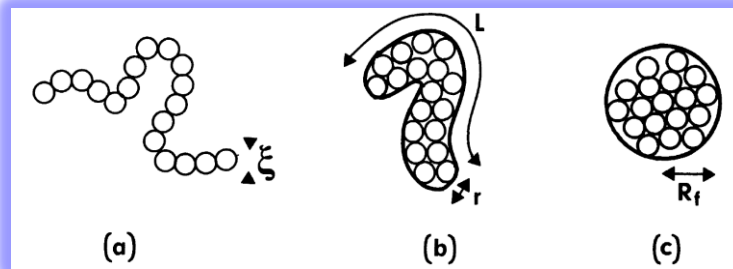
What are the compressing forces?
- "poor solvent", e.g., two handed proteins (cross-linkers)?
- Osmotic pressure of the nuclear envelope?
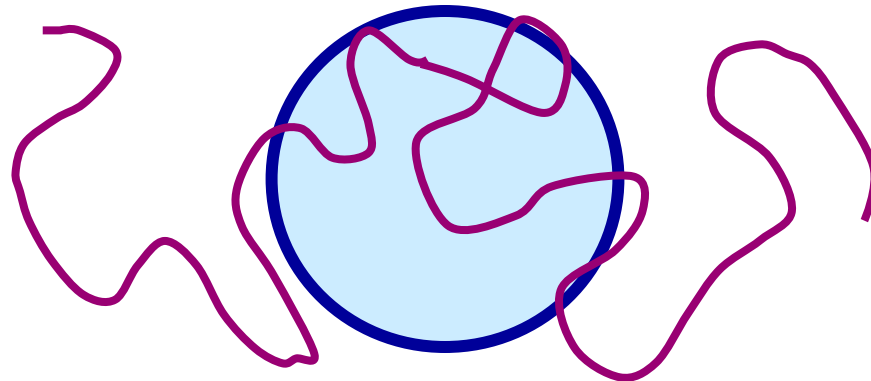
Rapid coil collapse: puzzling problem

P.-G. de Gennes (1985) hierarchical collapse scenario:

P.G. de Gennes "Kinetics of Collapse for a Flexible Coil", Journal de Physique Lettres, v. **46**, p. L639-42, 1985.

C.F.Abrams, N.K.Lee, S.P.Obukhov "Collapse dynamics of a polymer chain" Europhys. Lett., v. **59**, p. 391-397, 2002

Crumpled globule = chain collapsed too rapidly to make knots, assumed "territorial"
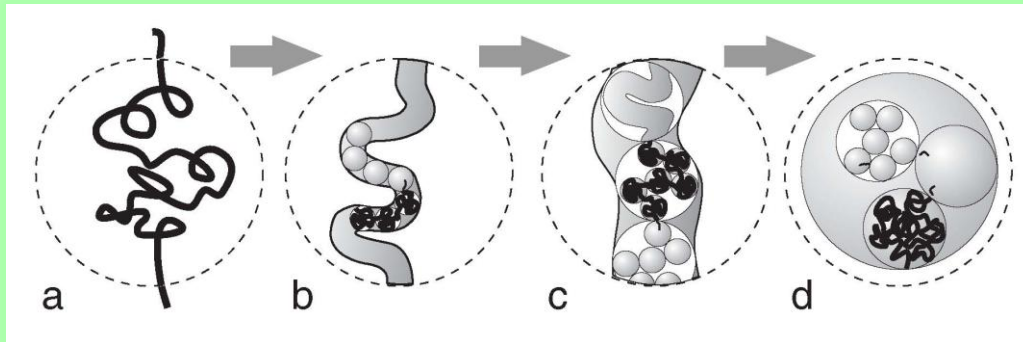
AYG, S.K.Nechaev, E.I.Shakhnovich "The Role of Topological Constrains in the Kinetics of Collapse of Macromolecule", Journal de Physique, v. **49**, p. 2095-2100, 1988

Recent contribution

G.Bunin, M.Kardar "Coalescence Model for Crumpled Globules Formed in Polymer Collapse", Phys. Rev. Lett. **115**, 088303 (2015)

Rosa & Everaers (2008):

Structure and Dynamics of Interphase Chromosomes

Angelo Rosa[1,2*], Ralf Everaers[1,3]

1 Max-Planck-Institut für Physik Komplexer Systeme, Dresden, Germany, 2 Institute for Biocomputation and Physics of Complex Systems (BIFI), Zaragoza, Spain, 3 Université de Lyon, Laboratoire de Physique, École Normale Supérieure de Lyon, CNRS UMR 5672, Lyon, France
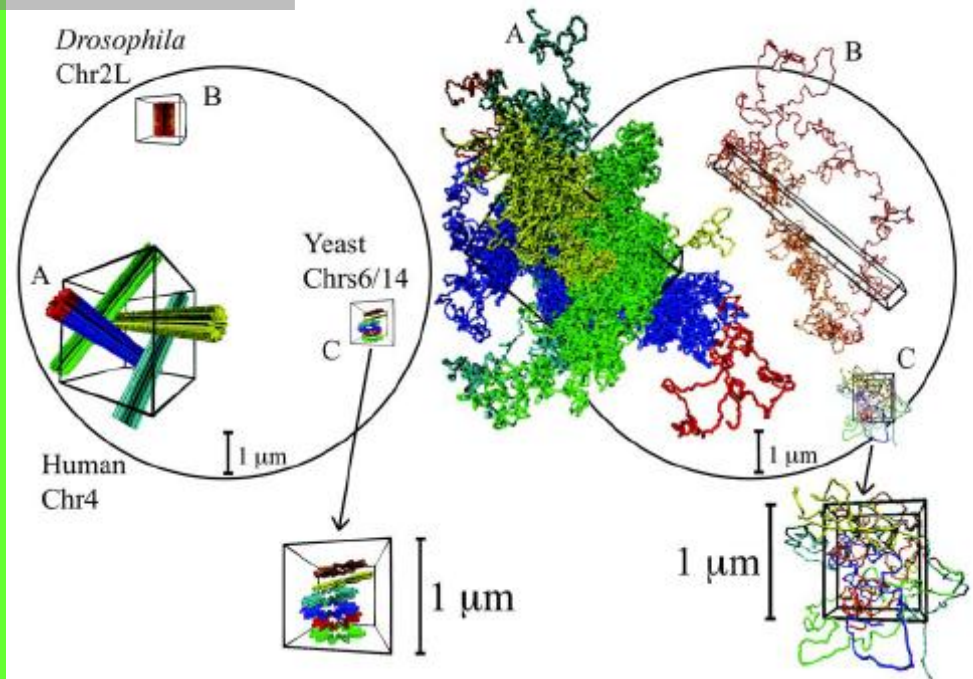
Figure 3. Initial ('metaphase-like', left) and final (right) configurations of human Chr4 (A), of *Drosophila* Chr2L (B) and of yeast Chr6 and Chr14 (C) shown together with the spherical nucleus (black circle) of 10 μm in diameter and the corresponding simulation boxes (in black). For the blue configuration in A and for the configuration B, we have highlighted in red the two terminal parts up to 4.5 Mbp. In Chr4, this corresponds to the terminal 4p16.3 region [17]. (A) Simultaneous decondensation of 4 model chromosomes half the size the human Chr4. (B) Decondensation of 1 model chromosome the size the *Drosophila* Chr2L. The final elongated shape qualitatively resembles a Rabl-like territory. (C) Simultaneous decondensation of 6 model chromosomes the size the yeast Chr6 and Chr14. Arrows points at magnified versions of the same configurations. Lack of chromosome territoriality is evident.
doi:10.1371/journal.pcbi.1000153.g003

<u>Unconcatenated</u> loops

- ## Exactly solvable model:
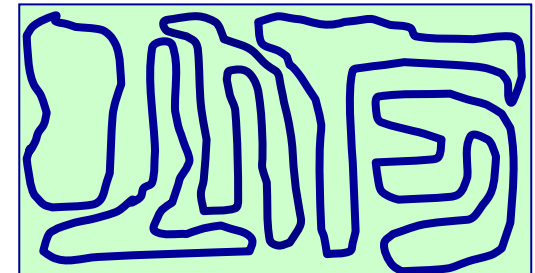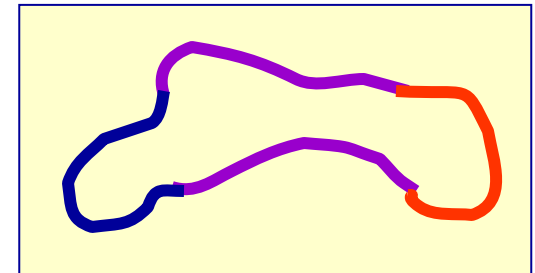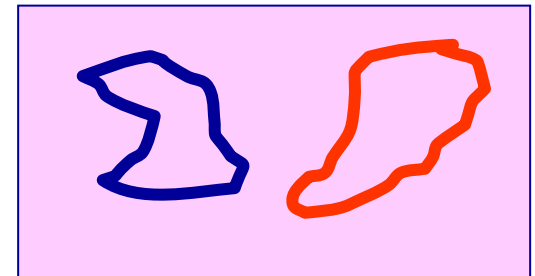 (F.Spitzer, 1960; S.F.Edwards, 1967;
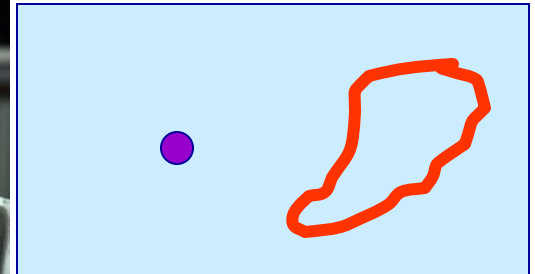 S.Prager, H.L.Frisch, 1967)

- ## For two rings, $A_2 \sim R_g^3$
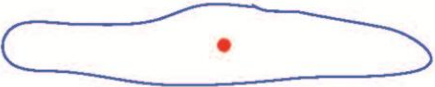 ## even in θ-solvent
  (M.Frank-Kamenetskii et al, 1973)

- ## Parts of the same loop:
  - $R_g \sim N^{\nu}$ (des Cloizeaux, 1981; AYG 2000)

- ## Concentrated system of loops, a melt or a globule (subchains <-> loops)

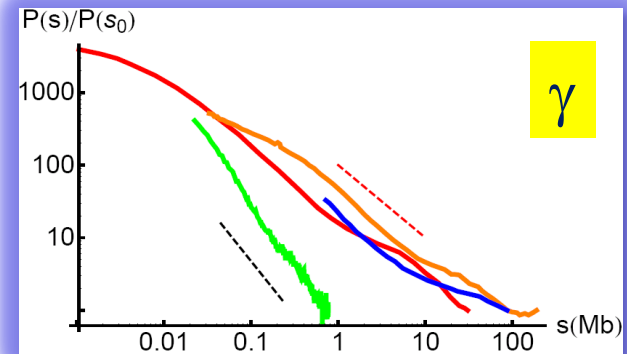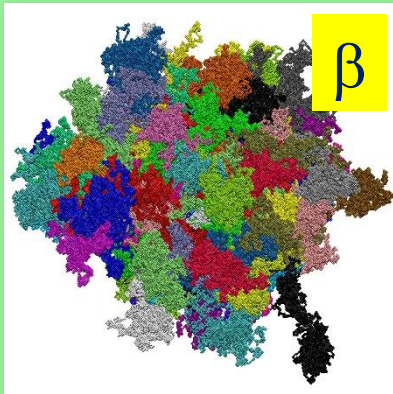# $d_1+d_2+1 \geq D$

d_1	d_2	D	
0	0	1	
0	1	2	
0	2	3	A point is either inside or outside a sphere; I cannot draw it...
1	1	3	
1	2	4	Somebody's world line may be either entangled or not entangled with a 2d sphere; I cannot draw it...
2	2	5	2d surface in 5d may be "knotted" or "unknotted"; hard for me to imagine...

Exponents for rings

- Ring size $R \sim N^{\nu}$, or subchain size $r(s) \sim s^{\nu}$; territories suggest $\nu=1/3$
- Surface fractal dimension, or surface roughness: $N_{surf} \sim N^{\beta}$; $\beta=d_b/d$;
- Contact probability: $P(s) \sim s^{-\gamma}$
- # conformations: $z^N N^{\text{"other } \gamma\text{"} - 1}$;
- Minimal surface $A \sim N^{x}$;
- # ring threading.

β

x

$P(s)/P(s_0)$

γ

1000

100

10

0.01 0.1 1 10 100 $s(Mb)$

Theoretically exact relations for infinite system:
$\beta+\gamma=2$ and γ = other γ

Finite size corrections to scaling are hugely important, but poorly understood

# Melt of rings: opinions about ν (R~N^{ν})

- Khokhlov, Nechaev: ν=1/3 (1985);
- Cates and Deutsch: ν = 0.4 (1986);
- Vilgis et al: ν=0.45 (1987);
- AYG, Nechaev, Shakhnovich: ν = 1/3 (1988)
- Mueller, Wittmer, Cates: (1996, 2000)

....

- Nowadays ν=1/3 is postulated, because it is considered obvious... Sakaue (2011), Rubinstein (2012)

- Experimental evidence: A.R.Bras, S.Gooßen, M.Krutyeva, A.Radulescu, B.Farago, J.Allgaier, W.Pyckhout-Hintzen, A.Wischnewskia, and D.Richtera, "Compact structure and non-Gaussian dynamics of ring polymer melts," Soft Matter, 2014, **10**, 3649

Individual ring in the sea of others:
$\nu = 1/3$
space-filling curves
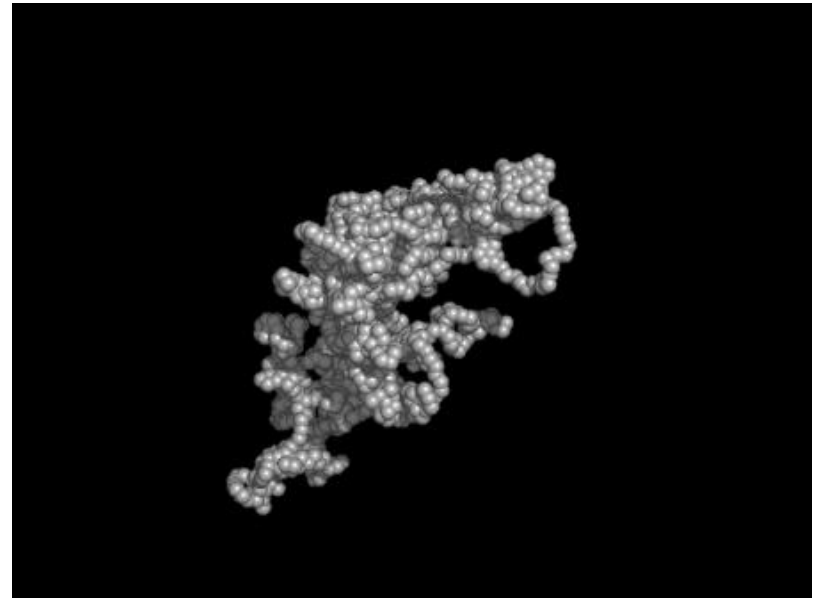

(a) Linear $N = 800$

(b) Ring $N = 1600$
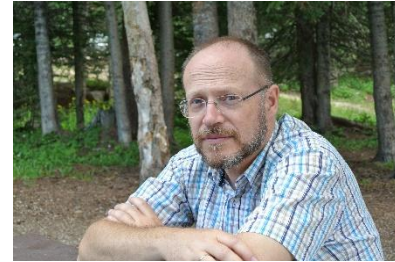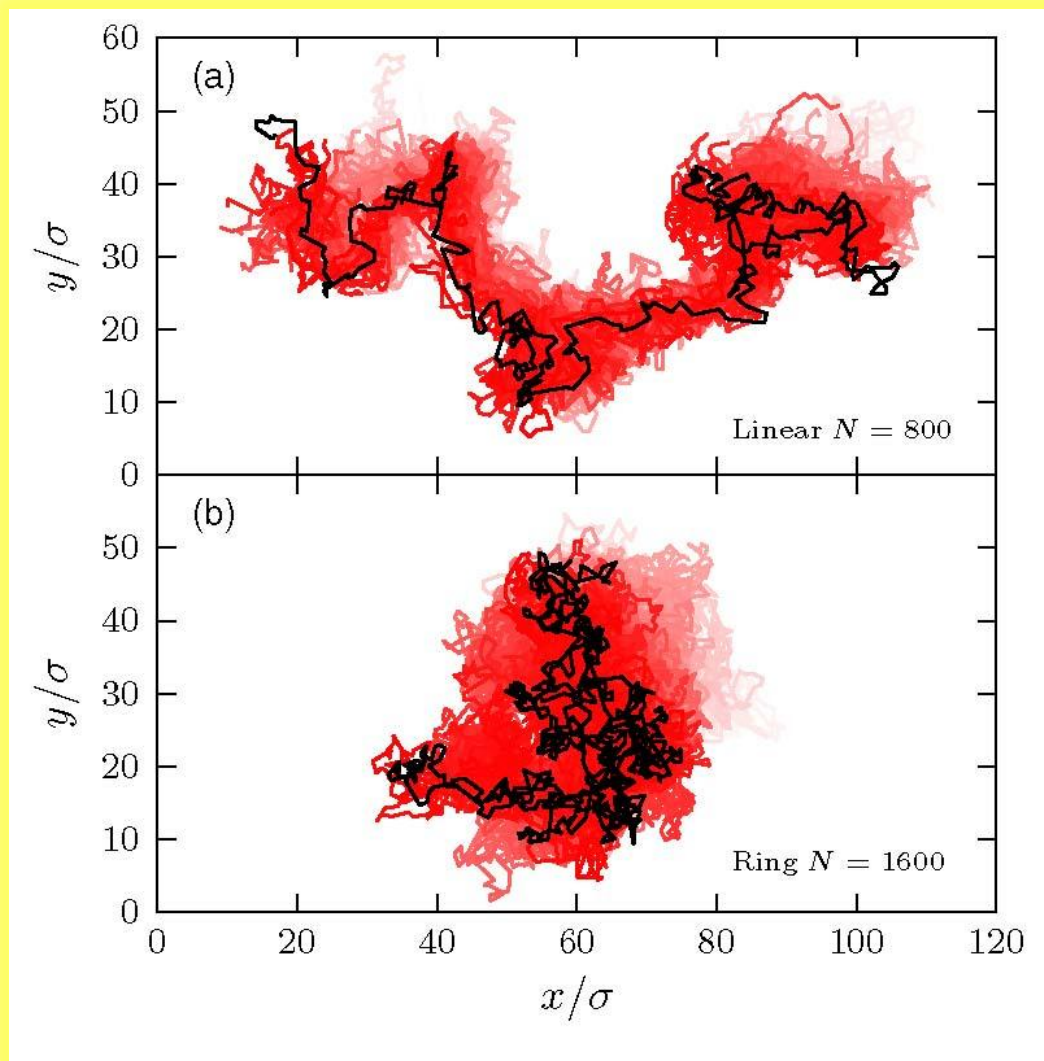
Simulation: J.Halverson and K.Kremer
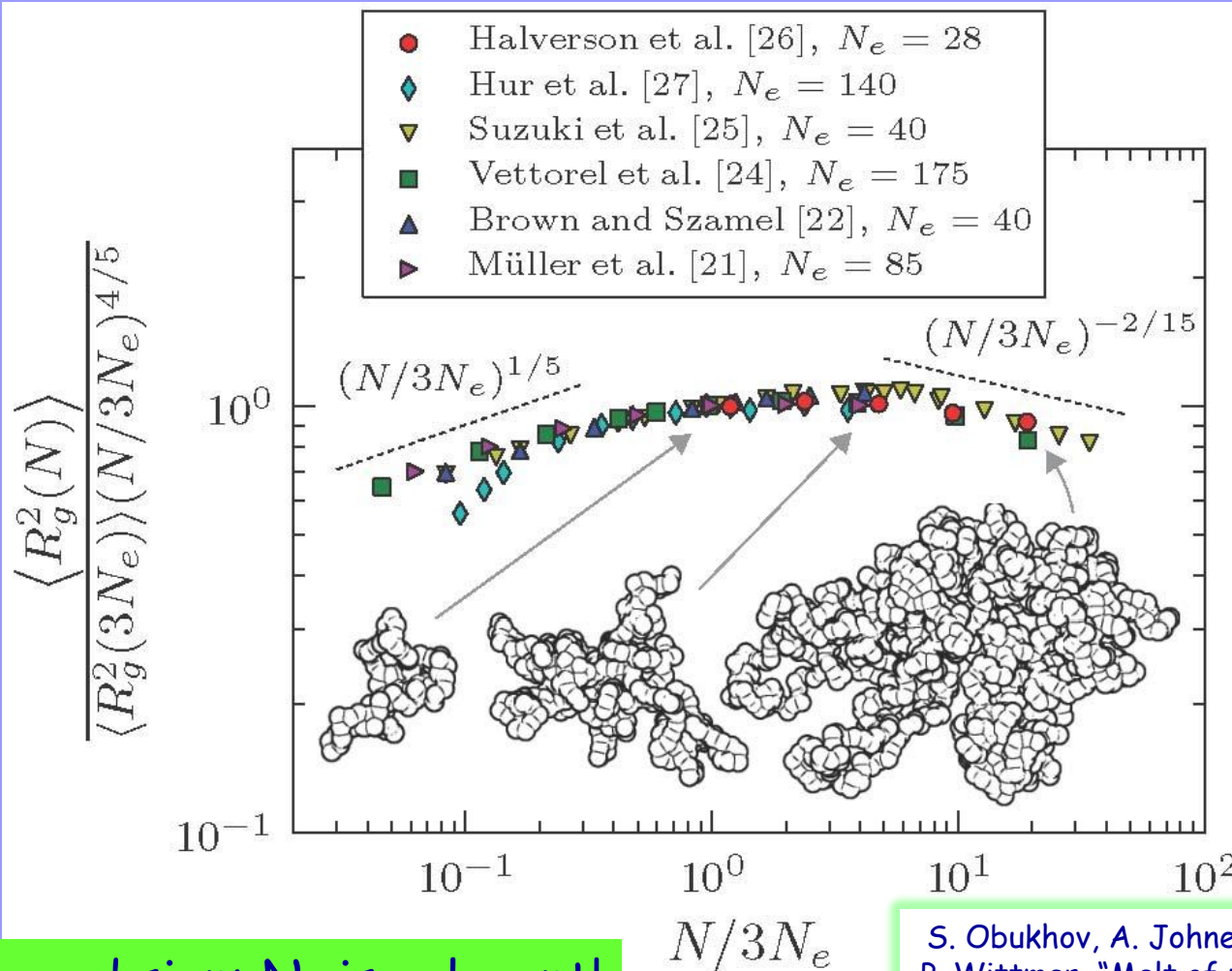
Chains or rings in the sea of others
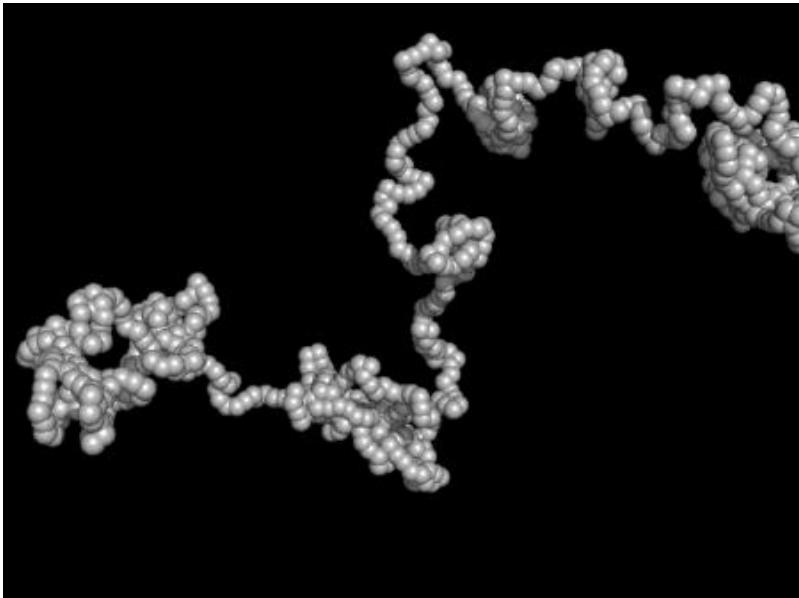
Linear chain in the melt of linear chains, N=800
$R_g/\langle R_g \rangle$ changes from 0.82 to 1.36.

Ring chain in the melt of un-concatenated rings, N=1600
$R_g/\langle R_g \rangle$ changes from 0.74 to 1.28.

Simulation: J.Halverson and K.Kremer

Many simulation & experimental works agree for R_g versus N/N_e

Legend:
- Halverson et al. [26], $N_e = 28$
- Hur et al. [27], $N_e = 140$
- Suzuki et al. [25], $N_e = 40$
- Vettorel et al. [24], $N_e = 175$
- Brown and Szamel [22], $N_e = 40$
- Müller et al. [21], $N_e = 85$

Axis labels: $\frac{\langle R_g^2(N) \rangle}{\langle R_g^2(3N_e) \rangle (N/3N_e)^{4/5}}$ versus $N/3N_e$

$(N/3N_e)^{1/5}$ $(N/3N_e)^{-2/15}$

... large N data converge on $R_g \sim N^{1/3}$, consistent with territories although cross-over is surprisingly broad

A good sign: N_e is relevant!

S. Obukhov, A. Johner, J. Baschnagel, H. Meyer and J. P. Wittmer, "Melt of polymer rings: The decorated loop model," EPL, **105**, 48005, 2014

$R_g = N^{1/3}(1 + \underline{\text{finite size correction}})$
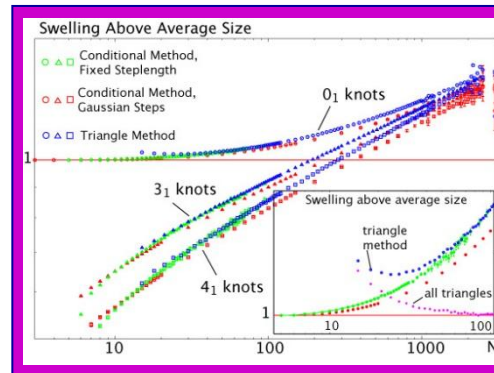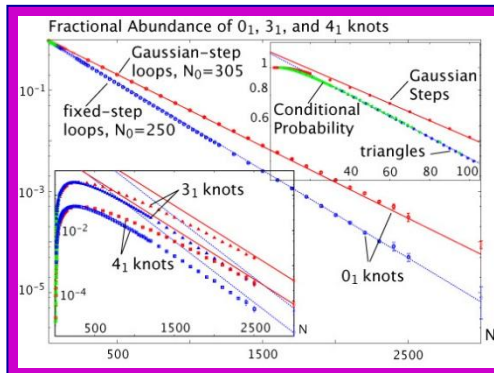
N_0 and N_e: two scales or one?

N_0 is a static property

- N_0 enters in annealed knots questions ($W \sim \exp(-N/N_0)$);
- N_0 enters quenched knots questions (topological swelling at $N > N_0$);
- Studied in computations;
- From ~150 to 2×10^7 for models known (5 decades).

N_e is a dynamic property

- N_e enters in dynamics, e.g., melt viscosity $\sim N^3/N_e^2$ or plateau modulus $1/N_e$;
- N_e is believed to feature in statics for melt of rings;
- Both simulations and expts;
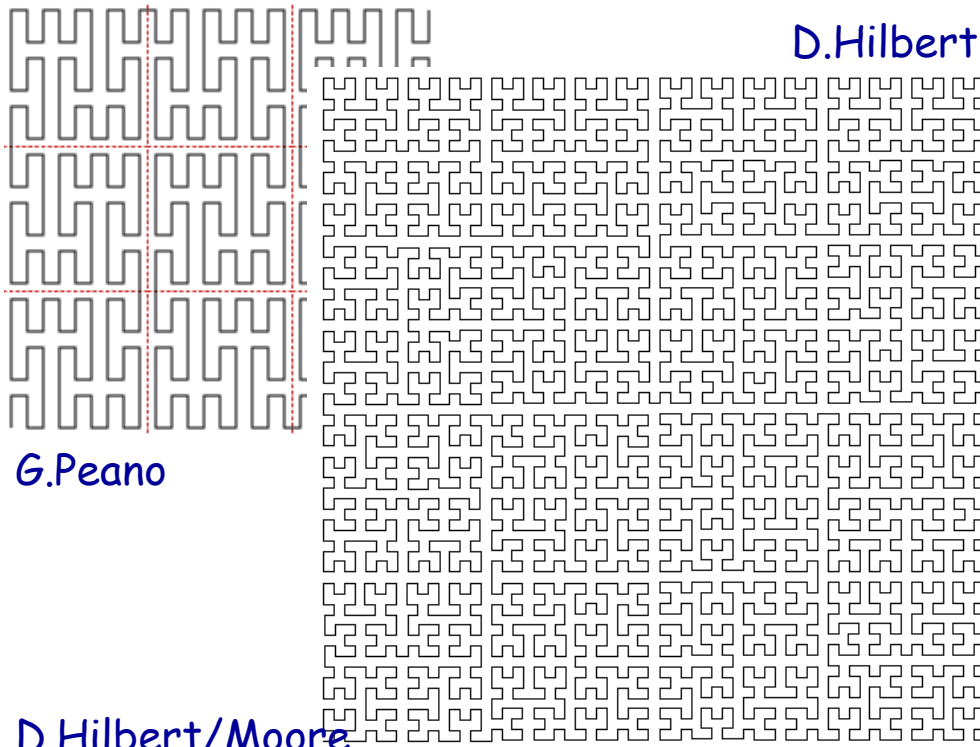- L_e/l_K from 0.02 to ~10^5 for systems known (7 decades).

J. Qin, S. T. Milner "Counting polymer knots to find the entanglement length" Soft Matter, v. 7, 10676 -- 10693, 2011.
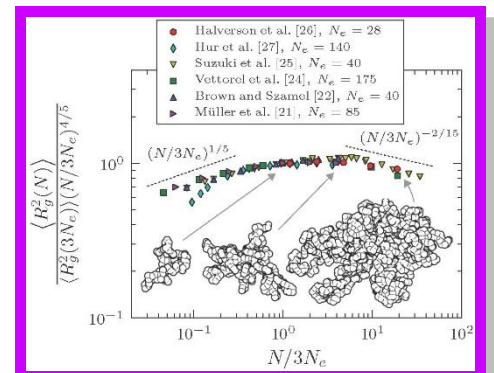
Entanglement length of chromatin fiber

Linear density	$D = 5\,\mu\mathrm{m}$	$D = 10\,\mu\mathrm{m}$	$D = 15\,\mu\mathrm{m}$
$\frac{1}{B} = 40\,\mathrm{bp\,nm}^{-1}$	$L_e = 0.1\,\mu\mathrm{m}$ $N_e = 4\,\mathrm{kbp}$	$L_e = 0.35\,\mu\mathrm{m}$ $N_e = 14\,\mathrm{kbp}$	$L_e = 1.6\,\mu\mathrm{m}$ $N_e = 64\,\mathrm{kbp}$
$\frac{1}{B} = 80\,\mathrm{bp\,nm}^{-1}$	$L_e = 0.15\,\mu\mathrm{m}$ $N_e = 12\,\mathrm{kbp}$	$L_e = 0.7\,\mu\mathrm{m}$ $N_e = 56\,\mathrm{kbp}$	$L_e = 5\,\mu\mathrm{m}$ $N_e = 400\,\mathrm{kbp}$
$\frac{1}{B} = 120\,\mathrm{bp\,nm}^{-1}$	$L_e = 0.2\,\mu\mathrm{m}$ $N_e = 24\,\mathrm{kbp}$	$L_e = 1.3\,\mu\mathrm{m}$ $N_e = 156\,\mathrm{kbp}$	$L_e = 11\,\mu\mathrm{m}$ $N_e = 1320\,\mathrm{kbp}$

$$L_e = l_K \left[\left(\frac{1}{c_\xi \rho_K l_K^3} \right)^{2/5} + \left(\frac{1}{c_\xi \rho_K l_K^3} \right)^2 \right]$$
$c_\xi = 0.06$

The value of the linear density for chromatin fiber is not known very well, while the nucleus diameter can be different from cell to cell. Accordingly, we present the whole spectrum of entanglement length estimates, based on the total size of the human genome. In all cases the calculations are done using formula above for entanglement length L_e, while the number of base pairs between entanglements is calculated as $N_e = L_e/B$. The case $1/B = 120$ bp/nm and $D = 10\,\mu$m was used by Rosa and Everaers (PLOS, 2008). The Kuhn segment was assumed to be $l_K = 300$nm.

Nariya Uchida, Gary S. Grest, and Ralf Everaers "Viscoelasticity and primitive path analysis of entangled polymer liquids: From F-actin to polyethylene", The Journal of Chemical Physics, v. **128**, n. 4, 044902, 2008.

Unlike mathematical toys, real boundaries are not smooth

D.Hilbert
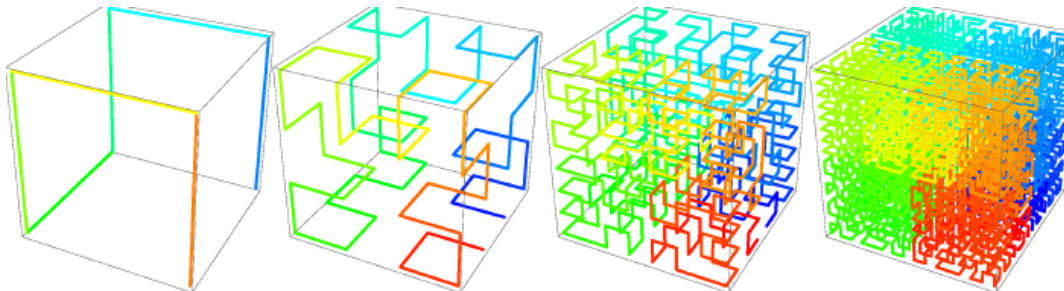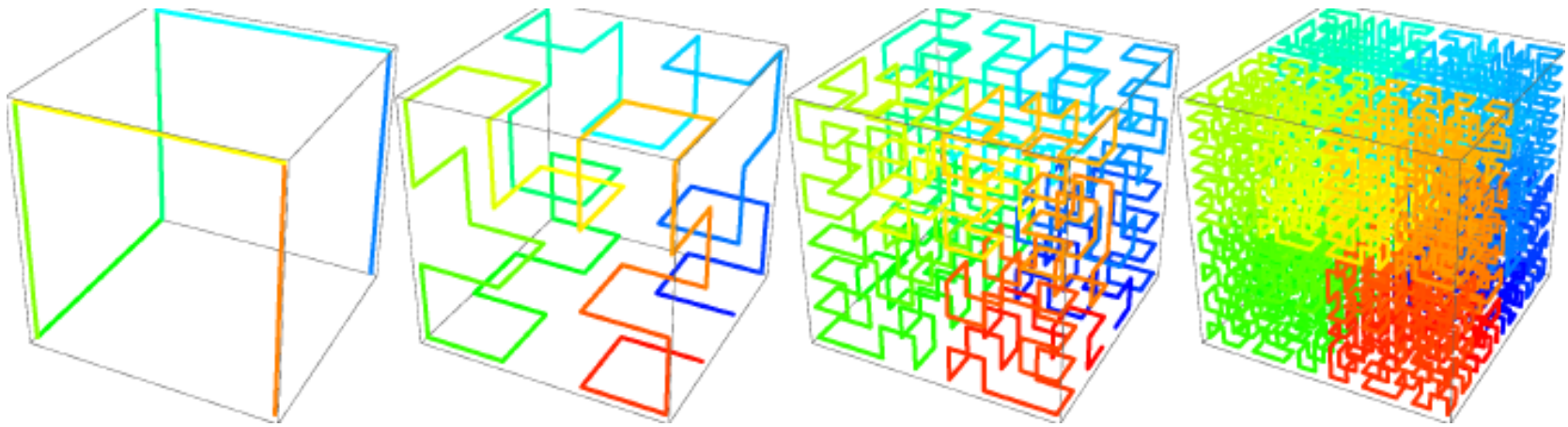
G.Peano

D.Hilbert/Moore

Territorial polymers

Eukaryotic cells store, manage, and use up to a meter of DNA in a micron-sized nucleus. How that is achieved is not completely understood and, indeed, is not easy to imagine: Consider that in polymer physics, chains packed at a similar density tangle and knot heavily, becoming as unmanageable as a fishing line crumpled without proper care. By contrast, different chromosomes in a cell nucleus remain fairly well separated throughout the cell-division cycle and occupy distinct regions termed territories. Topological enzymes and other sophisticated tools are surely involved in DNA management. However, an interesting question is what simple physics a cell could employ to reduce the use of such energy-thirsty and expensive machinery.

The ends of chromosomal DNA are likely attached to the nuclear envelope, and the unavailability of chain ends may suppress reptation—the snakelike wriggling of a polymer past its neighbors—and thus prevent the chains from entangling. A new study by a team of researchers from Germany and the US has tested that idea through Monte Carlo simulations of dense systems of closed, non-interlaced polymers, represented by as many as 142 rings of up to 10 000 [OK?] connected beads each. Results such as the one shown here indicate that topological constraints do have a significant geometric effect in keeping the polymers of high molecular weight largely segregated into territories and only moderately penetrating each other. (T. Vettorel, A. Y. Grosberg, K. Kremer, *Phys. Biol.* **6**, 025013, 2009.)

To submit candidate images for Back Scatter, visit http://www.physicstoday.org/backscatter.html.

72   August 2009   Physics Today

www.physicstoday.org

Space Filling Unknots (Hilbert/Moore)

Enumeration of all Hilbert curves, $\sim\gamma\exp[\sigma N]$, $\gamma\approx0.873$ and $\sigma\approx0.304908$
(J.Smrek, AYG, J. Phys. A: Math. Theor. **48** 195001, 2015)

For comparison, total number of Hamiltonian walks $\sim\exp[\sigma'N]$, with $\sigma'\approx0.609766$

Existence theorem (J.Smrek):

- There exist space filling unknots with surface roughness exponent β arbitrarily close to 1 from below (or with surface fractal dimension arbitrarily close to 3 from below).

J. Smrek, AYG "A novel family of space-filling curves in their relation to chromosome conformation in eukaryotes", Physica A, v. **392**, n. 24, pp. 6375 - 6388, 2013
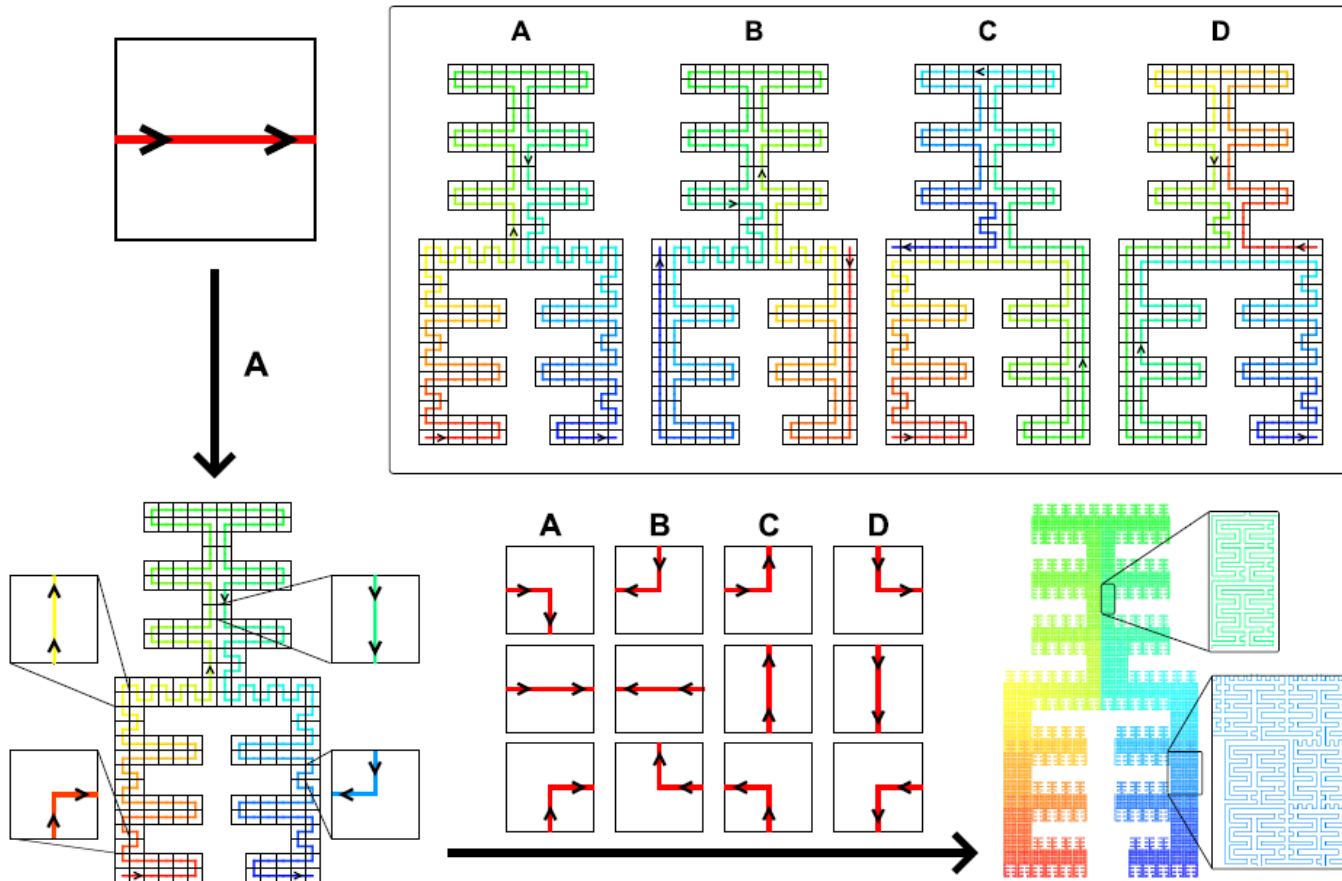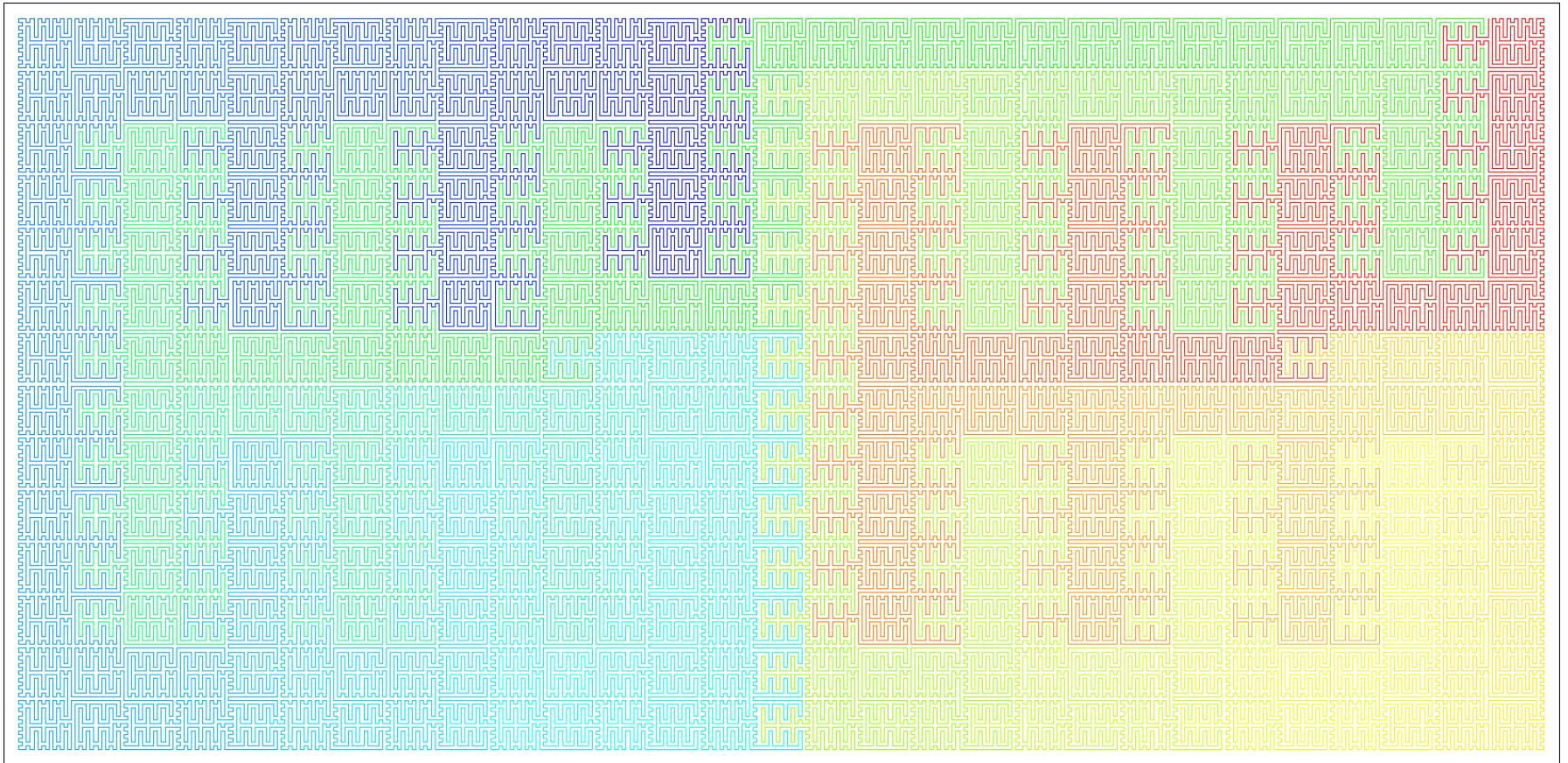
Jan Smrek
(formerly at NYU,
presently in MPIP Mainz)

Smrek curve
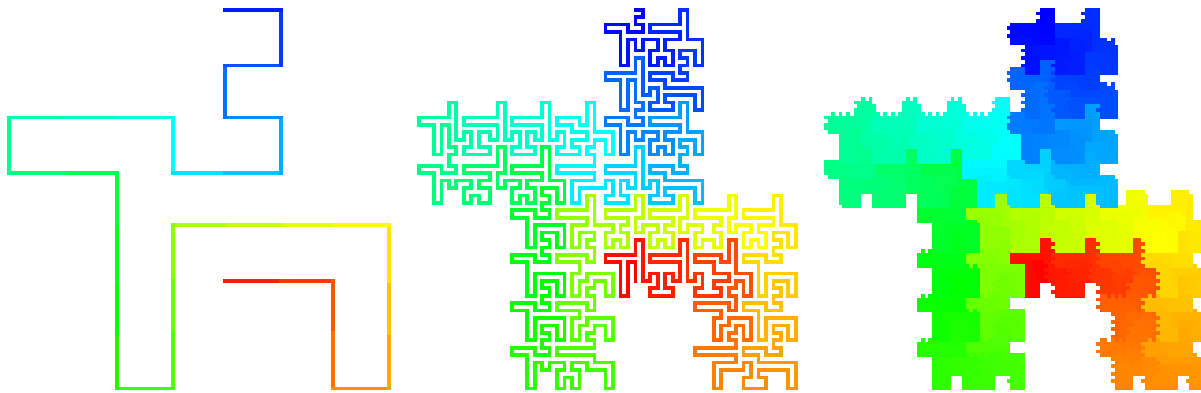
$\beta = 1/\ln(36) \approx 0.64 > 0.5$

J. Smrek, AYG "A novel family of space-filling curves in their relation to chromosome conformation in eukaryotes", Physica A, v. **392**, n. 24, pp. 6375 - 6388, 2013

Inspirations
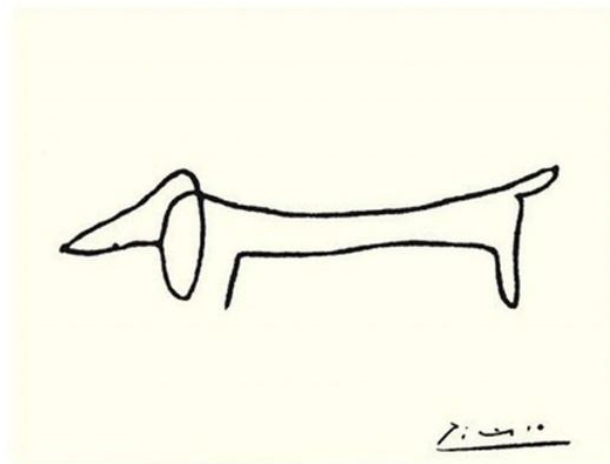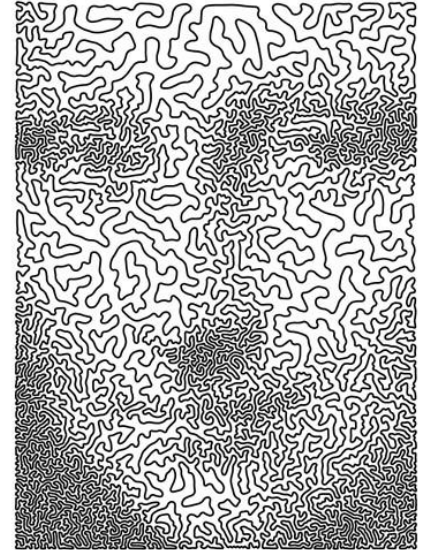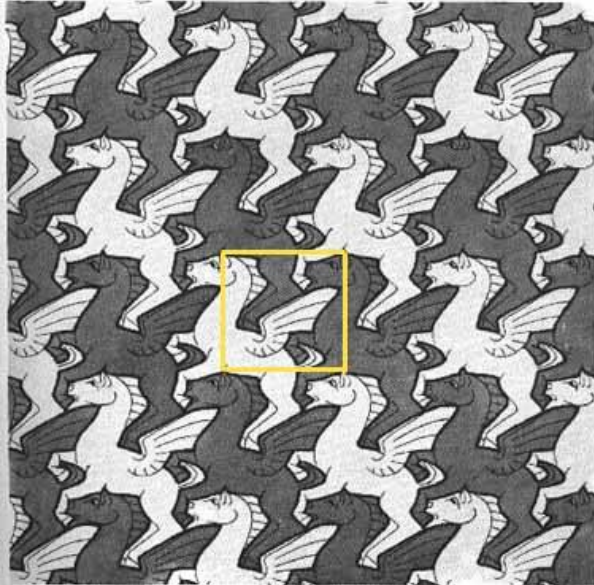
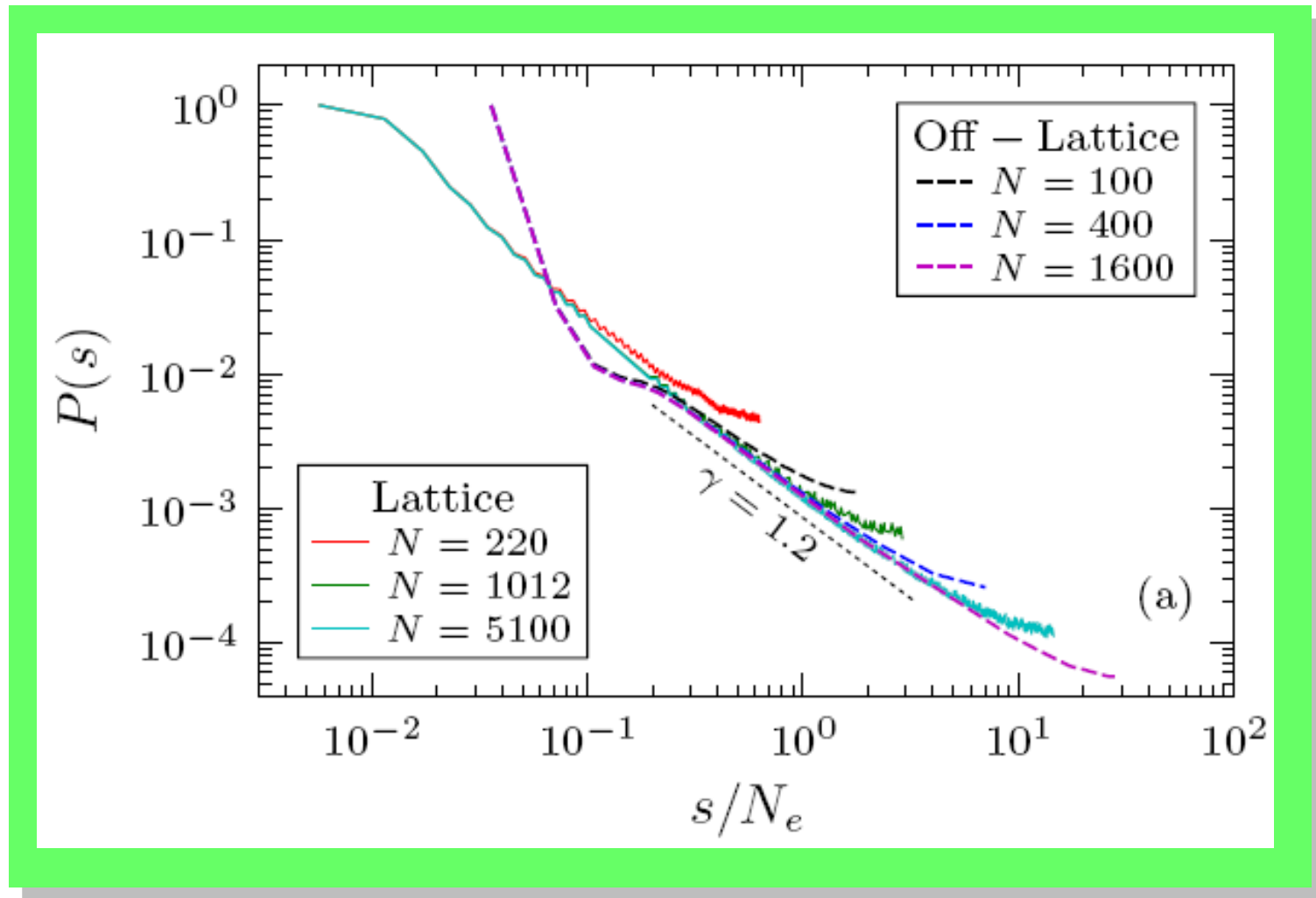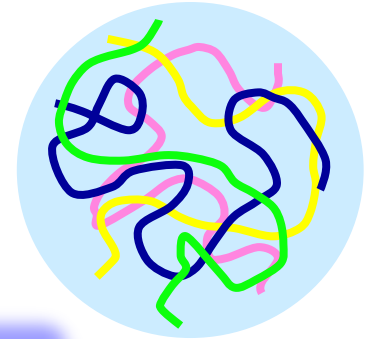# New family of curves:
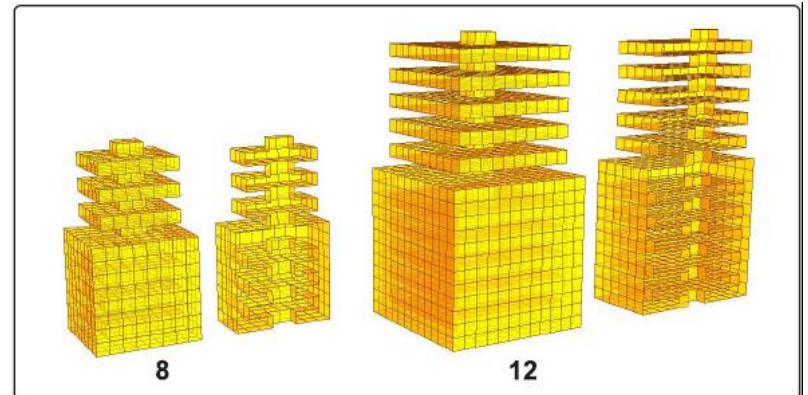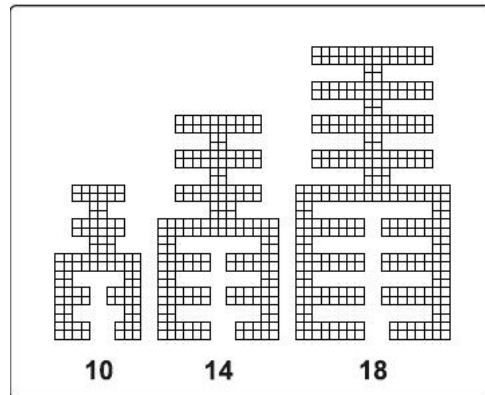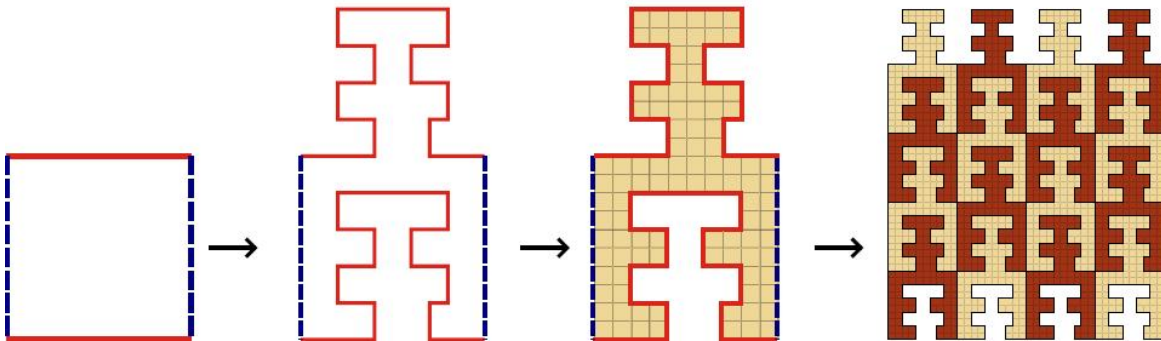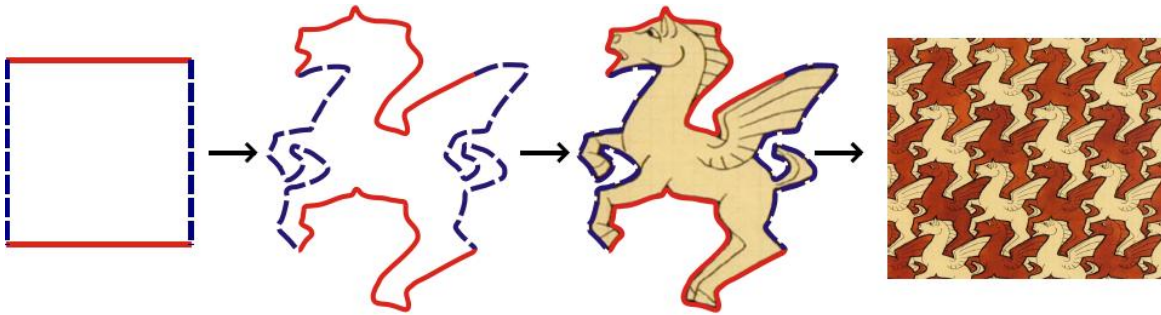
New family of curves:

Smooth outer boundary, β arbitrarily close to 1

Contact probability:

Indices β_1, β_2, and γ

Consider a sub-chain of length s:

   $\#$ all contacts except with itself s^{β_1}

   $\#$ contacts with a similar blob s^{β_2}

$\beta_1 = \beta_2 + \nu d - 1 \quad \Rightarrow \quad$ since $\nu = 1/3$, $d=3$, so $\beta_1 = \beta_2$

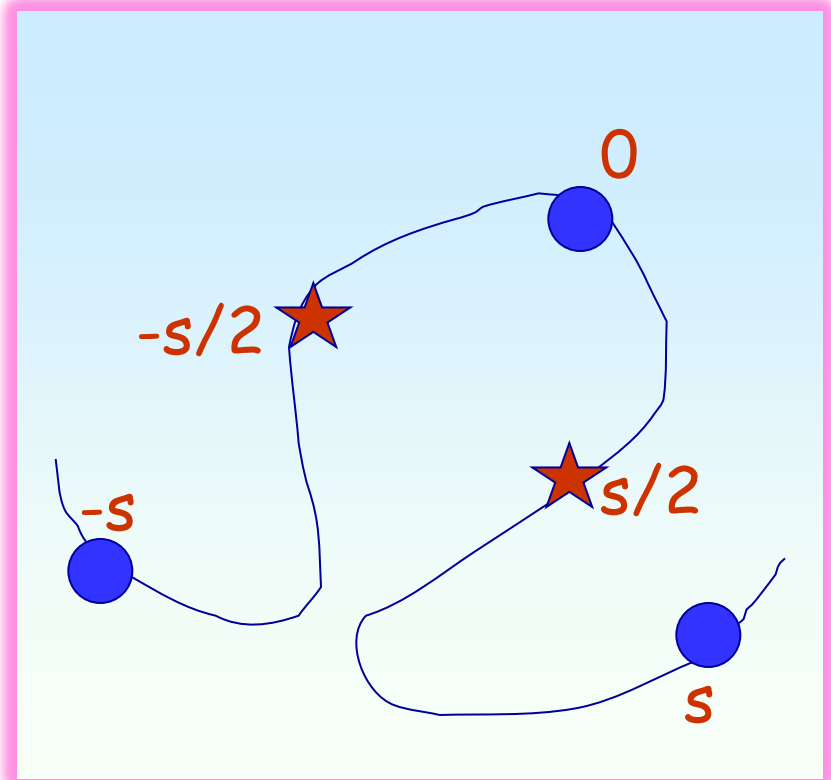Proof: $s^{\beta_1} = s^{\beta_2} \times (\# \text{ overlapping blobs}) = s^{\beta_2} (s^{\nu d}/s)$

For a sub-chain of length s, one end is smeared through the volume $\sim s^{\nu d}$ around the other (mean field) $\Rightarrow s^{-\gamma} = s^{-\nu d} \Rightarrow \gamma = \nu d = 1$

$\beta_1 = \nu d + 1 - \gamma \quad \Rightarrow \quad$ since $\nu = 1/3$, $d=3$, so $\beta_1 = 2 - \gamma$

Proof: $s^{\beta_1} = s \ast \text{Sum}_{|s'| > s} |s'|^{-\gamma} \sim s^{2-\gamma}$

β+γ=2: derivation

- # contacts between blobs (-s,0) and (0,s): s^{β_2};

- Probability of contact between monomers s/2 and –s/2: $\sim s^{\beta_2}/s^2$;

- Same probability must be $\sim s^{-\gamma}$;

- $s^{\beta_2}/s^2 = s^{-\gamma}$ yields $\beta_2 + \gamma = 2$

Alternative (but equivalent) self-similarity argument:
$$N/s^\gamma = [(N/g)/(s/g)^\gamma] * g^{\beta_2}/g$$

Pompous mathematical proof: A.Sanborn, S.Rao, et al, PNAS, v. 112, n. 47, p. E6456-E6465, 2015

Example: β_1, β_2, and γ for a melt of linear chains (or equilibrium globule)

$$\beta_1 = \beta_2 + \nu d - 1 \quad ; \quad \beta_1 = \nu d + 1 - \gamma \; ; \; \beta_2 = 2 - \gamma$$
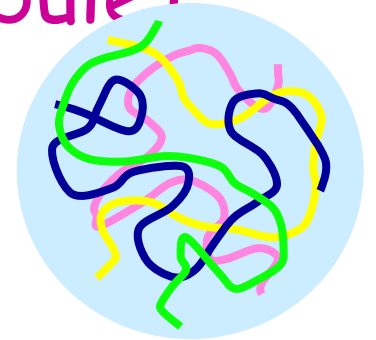
In Gaussian case, $\beta_1 = 1$; $\nu = 1/2$; $\gamma = d/2$; $\beta_2 = (4-d)/2$

Consider a sub-chain of length s:
all contacts except with itself s^{β_1}
contacts with a similar blob s^{β_2}

Indices β_1, β_2, and γ: estimates

$$\beta_1 = \beta_2 + \nu d - 1 \quad ; \quad \beta_1 = \nu d + 1 - \gamma \; ; \; \beta_2 = 2 - \gamma$$
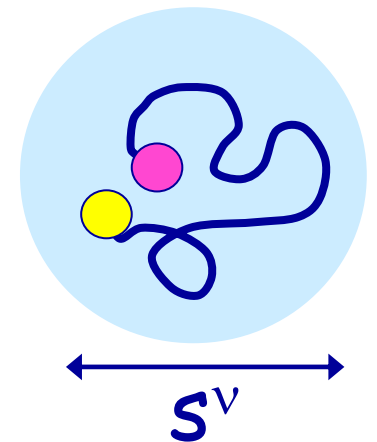
Trivial bounds:
- $1/d \leq \nu \leq 1$;
- $(d-1)/d \leq \beta_1 \leq 1$;
- $\beta_1 \geq \beta_2$;
- $1 \leq \gamma \leq 2$;
- $1 \leq \gamma \leq 1+1/d$ if $\nu = 1/d$

Strict(?) bound:
$\text{Sum}_s s^{-\gamma} = (\#\text{contacts})$
must converge =>

$\gamma > 1$
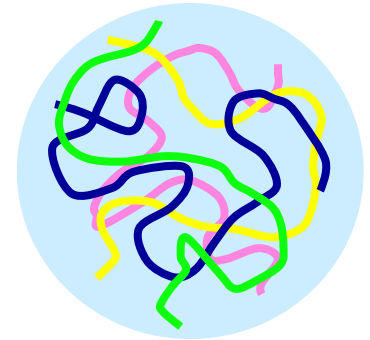
Mean field: For a sub-chain of length s, one end is smeared through the volume $\sim s^{\nu d}$ around the other => $s^{-\gamma} = s^{-\nu d}$ => $\gamma = \nu d = 1$

Consider a sub-chain of length s:
 # all contacts except with itself s^{β_1}
 # contacts with a similar blob s^{β_2}

Structure factor scaling

$$S(q) \sim \frac{n^{\beta-1}}{q^{(2-\beta)/\nu}}$$

Imagine that we labeled (for instance, deuterated) some n monomers. The static structure factor is defined by the formula:

$$S(q) = \frac{1}{n} \sum_{i \neq j}^{n} \exp\left(\imath q \cdot \left(r_i - r_j \right) \right). \tag{22}$$

For the moment let us assume that the labeled part is either one entire ring ($n = N$) or some part of it ($n < N$). In this case, the static structure factor (22) has the following properties. First, at $q = 0$ we always obtain $S(q = 0) = n$. Second, in the intermediate range of q we expect some power law dependence $S(q) \sim q^x$, where the power x is to be found. Moreover, since the overall size $R \sim bn^\nu$ is the only relevant length scale (since we deal with one ring or its part), we can write $S(q) \sim n(qR)^x \sim q^x n^{1+\nu x}$. Third, and this is the most delicate part of the argument, the only place where scattering can take place is the surface of the labeled part. Therefore, the total scattered intensity, which is equal to $nS(q)$, must depend on the number of labeled monomers as n^β. Comparing, we conclude that $2 + \nu x = \beta$. Therefore, the structure factor scales as

Experiment, theory, and simulation: $\gamma+\beta=2$

	Contact probability, γ	Surface roughness, β
HiC, human (experiment)	1.08	
HiC, mouse (experiment)	1.05	
"ε"-expansion (annealed tree model, theory)	1.09	
Contact probability, melt of rings (simulation)	1.2	
Structure factor (melt of rings, simulation); criticized!		0.93
Surface roughness (melt of rings, simulation)		0.97

Minimal surfaces spanned
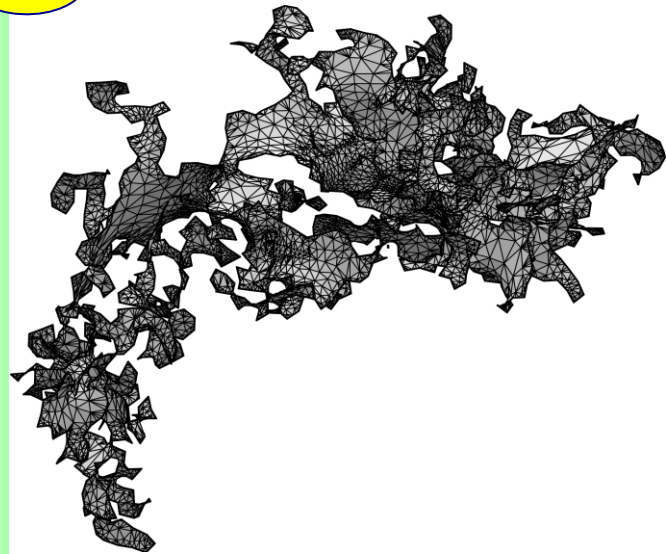
Unknotted ring from
unconcatenated melt
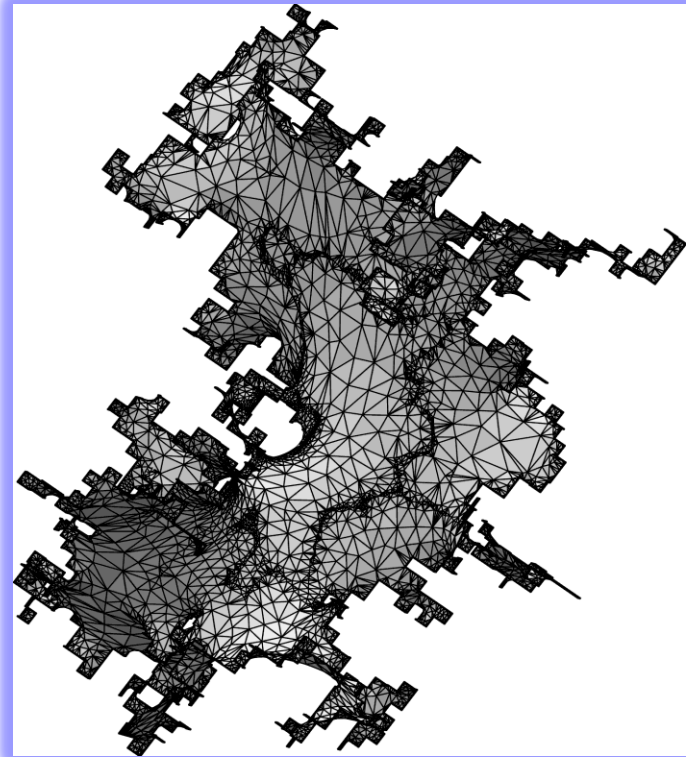
Unknotted ring in
free space

Minimal surfaces for N<N$_e$: M. Lang, J. Fischer, and J.-U. Sommer *Effect of Topology on the Conformations of Ring Polymers*, Macromolecules, v. **45**, p. 7642-7648, 2012; M.Lang *Ring Conformations in Bidisperse Blends of Ring Polymers*, Macromolecules, v. **46**, p. 1158-1166, 2013

Scaling of minimal surfaces

... it scales like a tree...
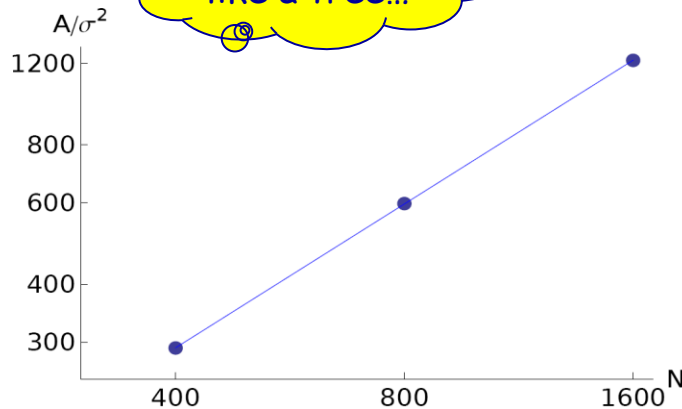
FIG. 4. The mean area of minimal surface of the rings in the melt as function of N in log log scale. Symbols: data, Line: best fit with slope

x=1.02, i.e. A~N$^{1.02}$

FIG. 6. The mean area of minimal surface of the swelled rings as function of N in log log scale. Symbols: data, Line: best fit with slope

x=1.25, i.e. A~N$^{1.25}$

Unknotted rings from unconcatenated melt

Unknotted rings in free space

Compare the 2D theorem (Area ~ N):
E.J.J.van Rensburg, and S.G.Whittington, "Punctured discs on the square lattice," Journal of Physics A, **23** 1287,1990

Important caveat: our minimal surface finder may be trapped in a local minimum

My current tentative theory: x=2ν=1.76

Annealed tree model:

$$\frac{\Delta F}{k_B T} \sim \frac{R^2}{L N_e^{1/2}} + \frac{L^2}{N} + \frac{1}{N} N_e^{pd/2} \left(\frac{N/N_e}{R^d}\right)^{p+1} R^d$$

Collisions of order p, in dimension d, 1/N due to screening, in the end p goes to infinity.

Competition between ring compaction and penetration through others

Long rings are "compact"

$$R \sim \begin{cases} N^{1/2} & \text{for} \quad N \ll N_e \\ N^{1/3} N_e^{1/6} & \text{for} \quad N \gg N_e \end{cases} \quad \text{or} \quad \nu = 1/3 \ ,$$

$$L \sim \begin{cases} N^{1/2} & \text{for} \quad N \ll N_e \\ N^{5/9} N_e^{-1/18} & \text{for} \quad N \gg N_e \end{cases} \quad \text{or} \quad \rho = 5/9 \ .$$

$$R \sim \begin{cases} L & \text{for} \quad L \ll N_e^{1/2} \\ L^{3/5} N_e^{1/5} & \text{for} \quad L \gg N_e^{1/2} \end{cases} \quad \text{or} \quad \frac{\nu}{\rho} = 3/5 \ .$$

More and better on this:
- A.Rosa, R.Everaers "Ring polymers in the melt state: The physics of crumpling" PRL, v. **112**, 118302, 2014
- S.Obukhov, A.Johner, J.Baschnagel, H.Meyer, J.P.Wittmer "Melt of polymer rings: The decorated loop model", EPL, v. **105**, 48005, 2014.
- T.Ge, S.Panyukov, M.Rubinstein, Macromolecules, to appear in 2016

"Backbone" behaves like a Flory self-avoiding walk!

AYG "Annealed lattice animal model and Flory theory for the melt of non-concatenated rings: towards the physics of crumpling" v. **10**, p. 560-565, Soft Matter, 2014

Order parameter and generalized Kramers theorem
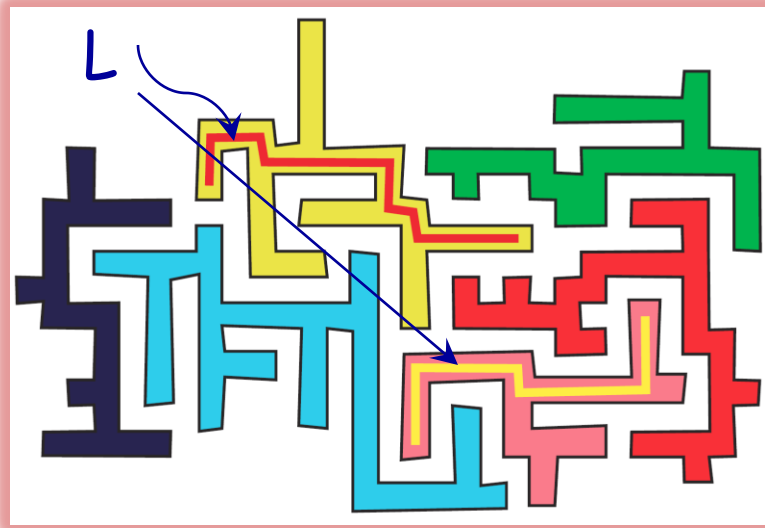
Why is stretching entropy for a tree $\sim R^2/L \sim R^2/\langle R^2\rangle$?

M. Daoud, P. Pincus, W. H. Stockmayer, and T. Witten, Macromolecules **16**, 1833 (1983).
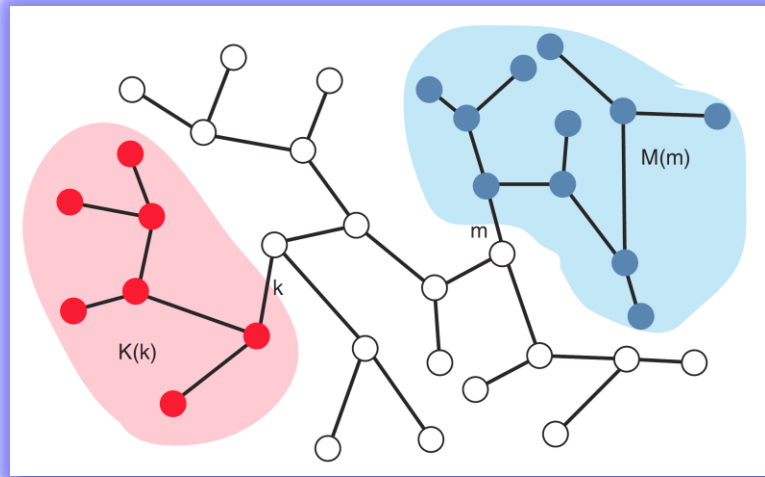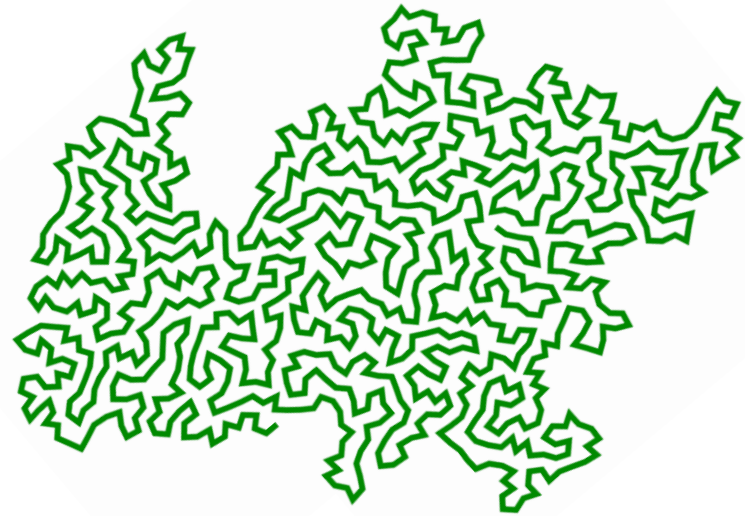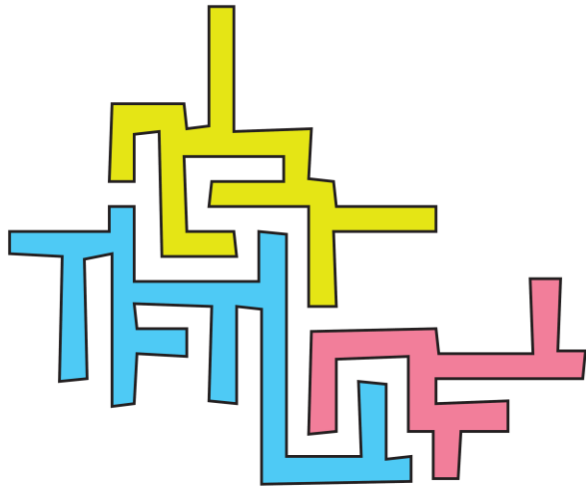
Probability distribution for gyration radius of a Gaussian tree, at large R $\exp[-R^2/\lambda]$, with λ the leading eigenvalue of $G(k,m)=K(k)M(m)/N^2$

H.A.Kramers (1946): $\langle R^2\rangle=\mathrm{Tr}[G]$

For most trees, $\lambda \sim \langle R^2\rangle$

Does it work for ring melt in 2D?

- In 2D, "non-concatenated" naturally becomes "not nested";
- Annealed branched animal certainly exists;
- Flory theory gives backbone~perimeter~r(N)~$N^{3/4}$;
- Exact Duplantier theory (assuming it is applicable for rings!) predicts <u>loop-erased random walks </u>r(N) ~$N^{4/5}$;
- Out of curiosity, LERW in 3D gives $\nu\approx0.61$ instead of 0.58.

Bertarnd Duplantier "Statistical mechanics of polymer networks of any topology" J. Stat. Phys., 54, 3/4, 581 - 680, 1989

Single compact ring: subchain size, sensitivity to boundary conditions

$$
r_{\text{torus}}(s) \simeq
\begin{cases}
s^{1/2} & \text{for} \quad s < N_e \\
s^{1/3} N_e^{1/6} & \text{for} \quad s > N_e
\end{cases}
$$

$$
r_{\text{cavity}}(s) \simeq
\begin{cases}
s^{1/2} & \text{for} \quad s < N_e \\
s^{1/3} N_e^{1/6} & \text{for} \quad N N_e^{-1/2} > s > N_e \\
N^{1/3} & \text{for} \quad N > s > N N_e^{-1/2}
\end{cases}
$$

- The system is surprisingly sensitive to boundary conditions
- For the ring in a "cavity" (smooth boundaries), the window of crumpled behavior is pretty narrow and exists only if $N \gg N_e^{3/2}$; or $N^{2/3} \gg N_e$ (entangled globular blob)

a Unknotted globule   b Knotted globule
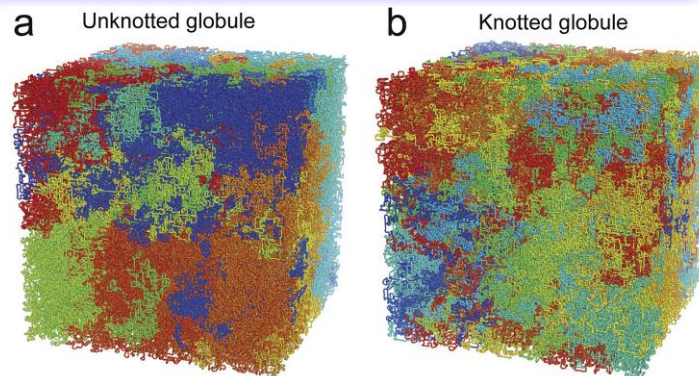
Compare simulations:
- M.Imakaev, K.Tchourine, S.Nechaev, and L.Mirny, "Effects of topological constraints on globular polymers," Soft Matter v. **11**, 665-671, 2015.
- A. Chertovich and P. Kos "Crumpled globule formation during collapse of a long flexible and semiflexible polymer in poor solvent," J. Chem. Phys., **141**, 134903, 2014.

About index γ: $P(s) \sim s^{-\gamma}$ (important for HiC)

$$P(s) = N^{-\gamma_{\text{contact}}} \phi(s/N)$$

$$\phi(x) \simeq x^{-\gamma_{\text{contact}}} \text{ when } 1/N \ll x \ll 1/2$$
$$(1-x)^{-\gamma_{\text{contact}}} \text{ when } 1/N \ll 1-x \ll 1/2$$

$$P_{\text{opposite}} = P(N/2) \sim N^{-\gamma_{\text{contact}}}$$

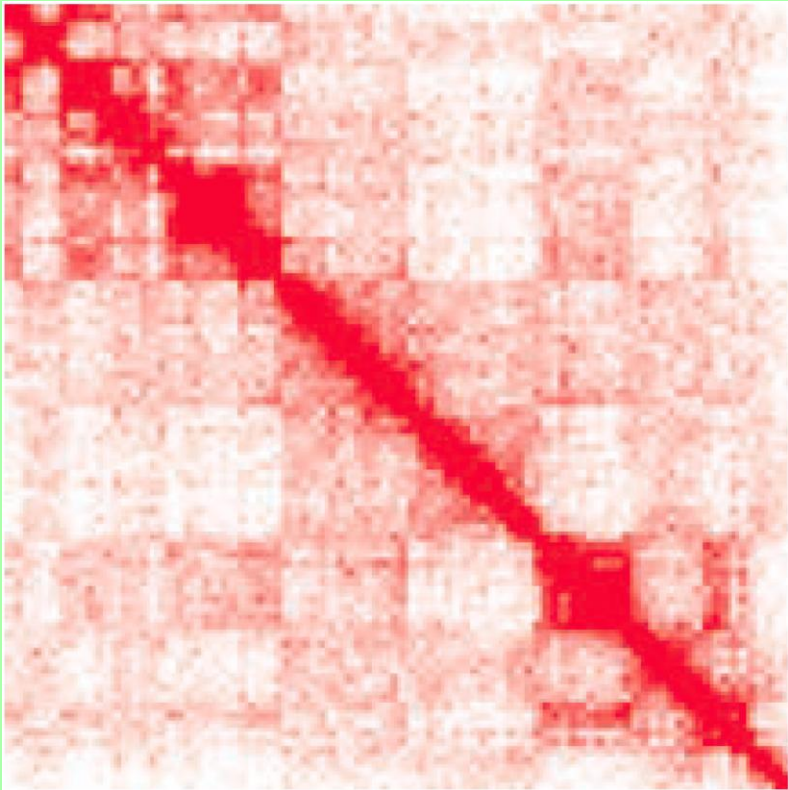$$P_{\text{opposite}} \sim \frac{1}{R^3} \frac{\Omega_\rho(N)}{\Omega_\rho^2(N/2)}$$

Decisive step
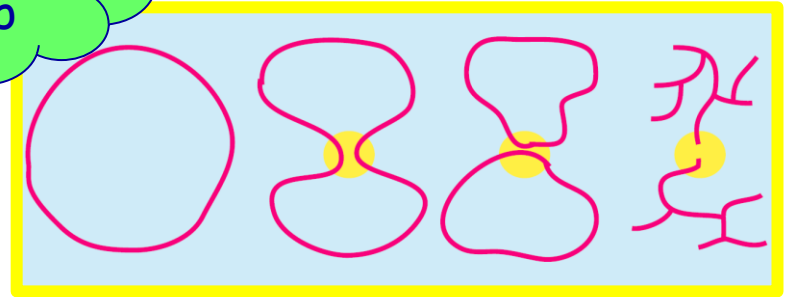
$$\Omega_\rho = z^N N^{\gamma_\rho - 1}$$

$$P_{\text{opposite}} \sim \frac{1}{N^{3\nu}} \frac{z^N N^{\gamma_\rho - 1}}{z^{2(N/2)}(N/2)^{2(\gamma_\rho - 1)}} \sim N^{-\gamma_\rho + 1 - 3\nu}$$

Result: "our" γ is just the usual "old" γ

$$\gamma_{\text{contact}} = \gamma_\rho - 1 + 3\nu = \gamma_\rho$$

HiC entropy and TADs

- How many conformations are there consistent with a given HiC contact map? ("Entropy of the map");
- How to generate and/or understand conformations producing checker-board patterns (TADs, transcription factories, etc.); entropy of that;

Loop extrusion model

E.Alipour, J.F.Marko "Self-organization of domain structures by DNA-loop-extruding enzymes" Nucleic Acids Research, 40, 11202-11212, 2012

Switch gears: dynamics

Single site/particle tracking

- Corralled diffusion, ~10^{-4} μm^2/s (Sedat et al, 1997-2001);
- Sub-diffusion of telomeres, up to 10-100s, with power 0.4: r(t) ~ $t^{0.4}$ (Garini et al, 2009);
- Lac-operator sites: long periods of constrained diffusion, followed by ~1s super-diffusive leaps of ~150nm (only with ATP; Gratton et al, 2005);
- Injected ~1 μm size particles – 250 nm cage (Shivashankar et al, 2012).

Subdiffusion of a particular locus

Nonthermal ATP-dependent fluctuations contribute to the in vivo motion of chromosomal loci

Stephanie C. Weber[a,b,1], Andrew J. Spakowitz[c,d], and Julie A. Theriot[a,b,d,e,2]

[a]Department of Biochemistry, [b]Howard Hughes Medical Institute, [c]Department of Chemical Engineering, [d]Biophysics Program, and [e]Department of Microbiology and Immunology, Stanford University, Stanford, CA 94305
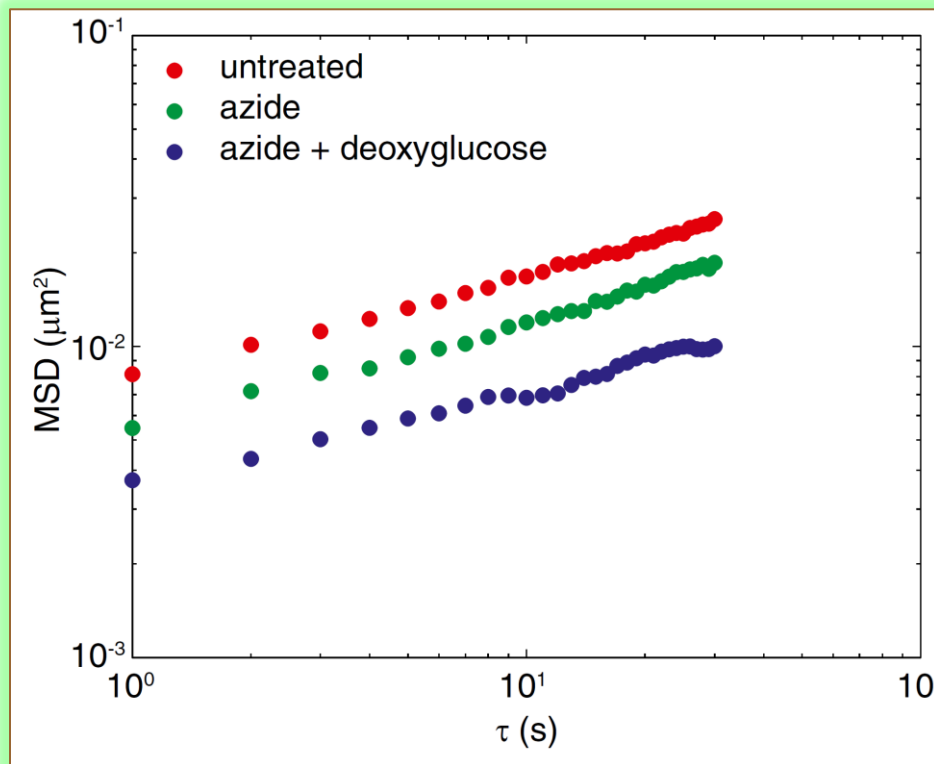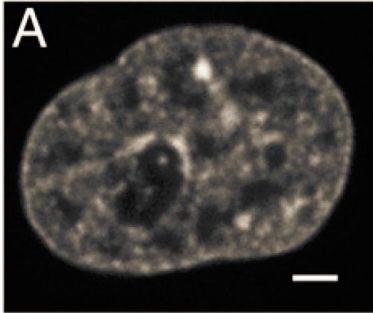
- This data for bacterial cell;
- Similar data exist fore eukaryotic cell (yeast);
- $\langle r^2 \rangle \sim t^{0.4}$
- ATP supply increases intensity of fluctuations, but does not seem to change the character of subdiffusion;
- What happens at earlier times is not clear.

Chromatin dynamics:
Zidovska et al, 2013

Chromatin structure and dynamics control all aspects of DNA biology yet are poorly understood, especially at large length... own, powered by different ATP-dependent nuclear enzymes (e.g., RNA polymerase, helicase, etc.). Clearly, chromatin dynamics...

color = direction (e.g. green = + x; orange = + y)

- Interphase HeLa cells;
- GFP-tagged histone H2B;
- Displacement correlation;
- Measure mean velocities
  $(\mathbf{r}(t+\Delta t)-\mathbf{r}(t))/\Delta t$;
- Dependence on Δt.
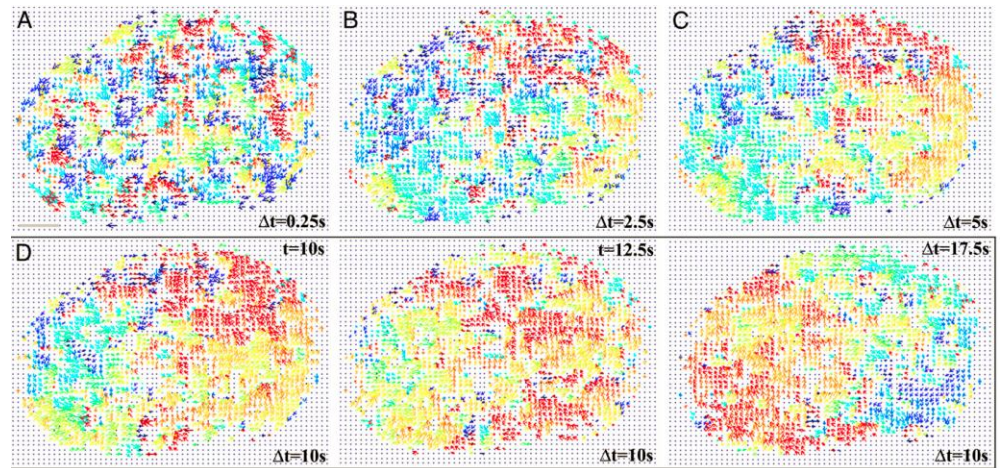
- Velocity domains: Size $\Delta L \approx$ µm; Lifetime $\approx$ 10 seconds.
- Coherent motion regions **not** correlated with chromosome territories.

Alexandra Zidovska, David A.Weitz, Timothy J.Mitchison "Micron-scale coherence in chromatin interphase dynamics, Proc. Natl. Acad. Sci. USA, v. **110**, n. 39, 15555-15560, 2013

Passive dynamics of rings: three approaches

- J.Smrek, AYG J Phys Cond Mat **27** 064117, 2015:
- Displacement of a monomer $\langle x^2 \rangle \sim t^\alpha$, with $\alpha = (2/d_f)/(2+1/3\nu_F)$ close to 0.26 at $d_f=3$ and $\nu_F=0.6$.
- We compute many other quantities (viscosity, self-diffusion, relaxation time, stress relaxation…)

- M.Tamm, L.Nazarov, A.Gavrilov, A.Chertovich, Phys. Rev. Lett. **114**, 178102, 2015
- Mean squared displacement of a monomer $\langle x^2 \rangle \sim t^\alpha$, with $\alpha = 2/(2+d_f\beta)$ about 0.4 at $d_f=3$ and β close to 1.
- Present simulation of their own.

- T.Ge, S.Panyukov, M.Rubinstein Macromolecules, 2016 (to appear)
- Mean squared displacement of a monomer $\langle x^2 \rangle \sim t^\alpha$, with $\alpha = 2/(2d_f+1)$ about 0.29 at $d_f=3$.
- Compute many other quantities.

- Simulation by Halverson & Kremer seems to give α about 0.3
- Garini group reports sub-diffusion of telomeres (chromosome ends) with α close to 0.4.
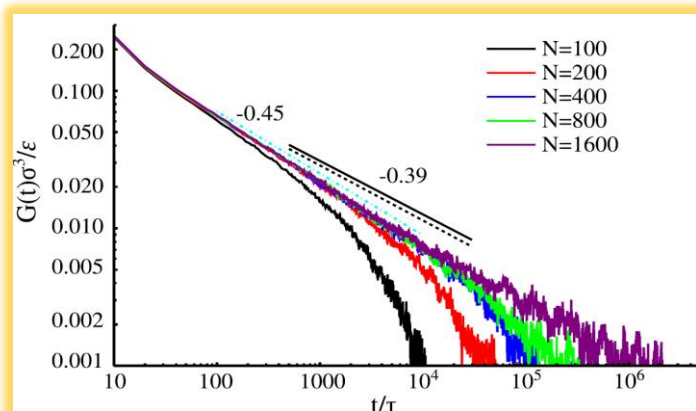- Overall the matter is not settled (in my opinion).

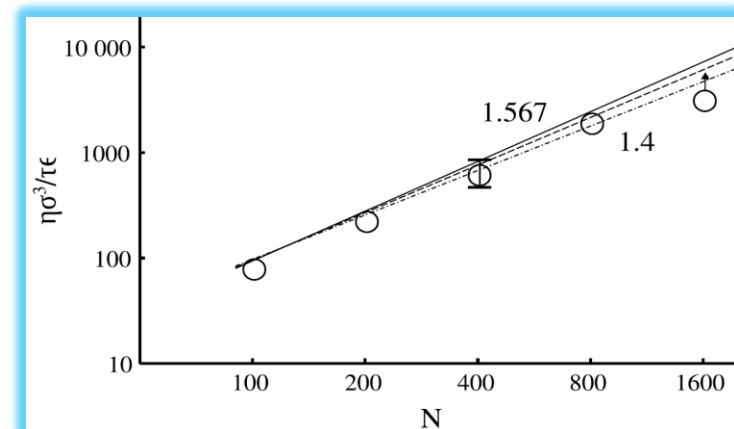# Passive dynamics in the annealed tree model
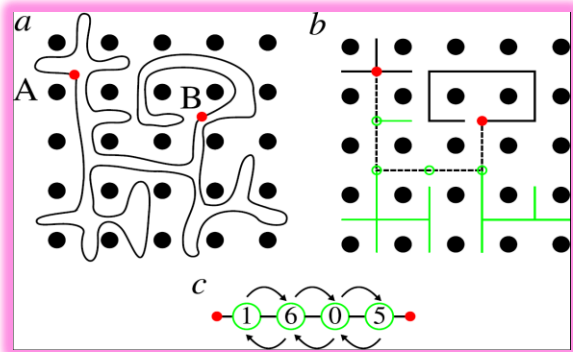
Approach similar to: Sergei P. Obukhov, Michael Rubinstein, and Thomas Duke "Dynamics of a Ring Polymer in a Gel", PRL, v. **73**, 1263--1266, 1994
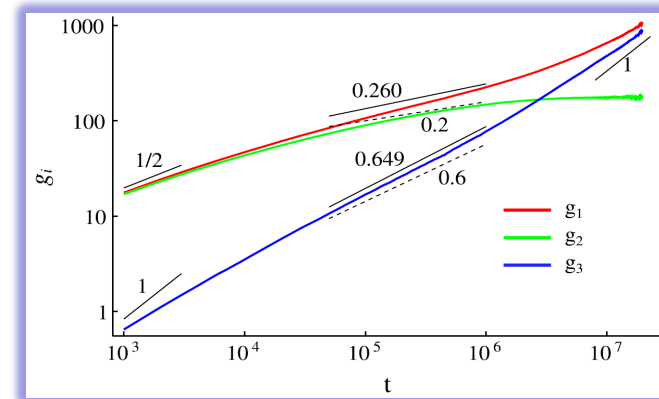
Subdiffusion

Stress relaxation

Viscosity against chain length

Looks good, but not good enough to make any judgment

R.Pasquino, T.C.Vasilakopoulos, Y.C.Jeong, H.Lee, S.Rogers, G.Sakellariou, J.Allgaier, A.Takano, A.R.Brás, T.Chang, S.Gooßen, W.Pyckhout-Hintzen, A.Wischnewski, N.Hadjichristidis, D.Richter, M.Rubinstein, and D.Vlassopoulos, "Viscosity of Ring Polymer Melts," ACS Macro Lett. 2013, **2**, 874–878

Passive dynamics: q-dependent viscosity
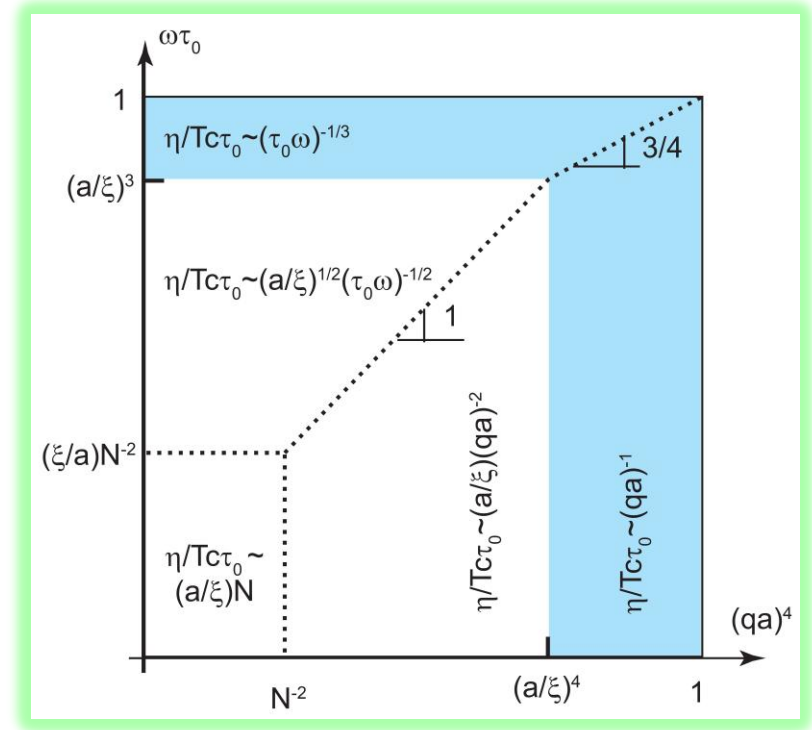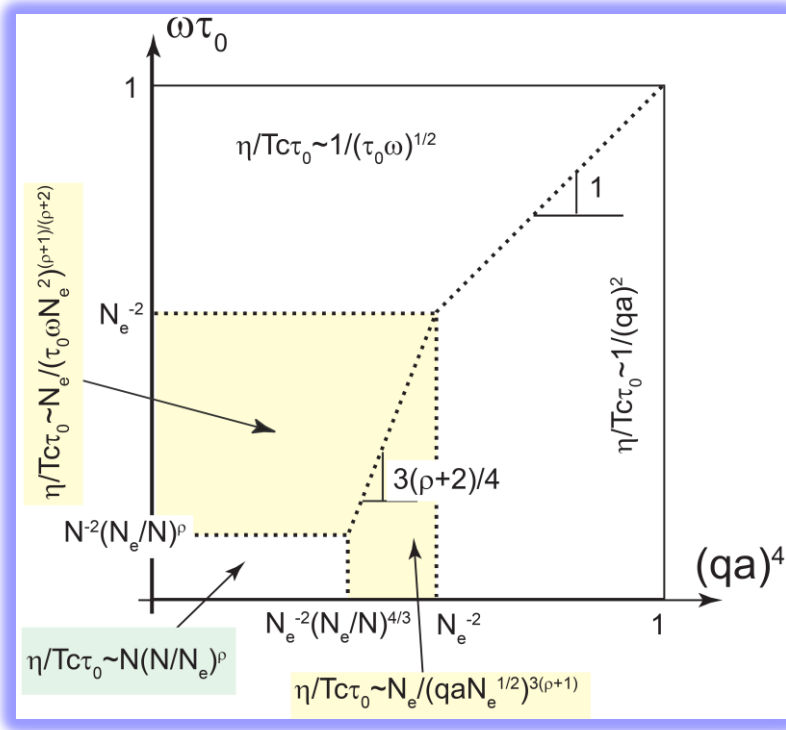
Y.Rabin and W.Srinin

Anelloni

Topological glass?

S.Obukhov
KITP talk
1997

D.Michieletto, D.Marenduzzo, E.Orlandini, G.Alexander, and M.Turner "Threading Dynamics of Ring Polymers in a Gel", ACS Macro Lett., v. **3**, n. 3, p. 255-259, 2014.

D.Michieletto, D.Marenduzzo, E.Orlandini, G.Alexander, and M.Turner "Dynamics of self-threading ring polymers in a gel", Soft Matter, v. **10**, n. 32, p. 5936-5944, 2014

D.Michieletto, and M.Turner, "A Topologically Driven Glass in Ring Polymers", ArXiv 1510.05625, 2015

E.Lee, S.Kim, and Y.Joon Jung, "Slowing Down of Ring Polymer Diffusion Caused by Inter-Ring Threading", Macromol. Rapid Commun., v. **36**,n. 11, p. 1115-2111, 2015

AYG, Y.Smrek (under review)

Chromatin dynamics: <u>Active</u> hydrodynamics theory
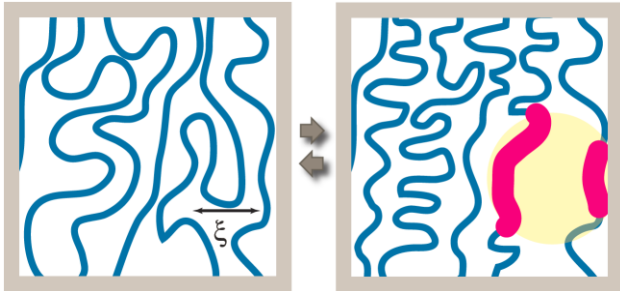
Scalar active source

R.Bruinsma, UCLA

Y.Rabin, Bar Ilan

A.Zidovska, NYU
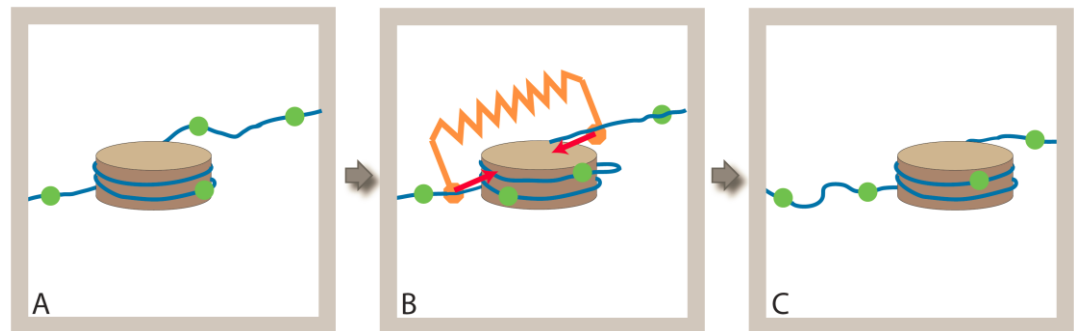
Vector active source

What drives chromatin dynamics?

- <u>Passive</u> Brownian motion;
- <u>Active</u> ATP dependent "chromatin remodeling" (e.g., nucleosome repositioning, gene transcription, etc)

Image from Wikipedia http://en.wikipedia.org/wiki/Chromatin_remodeling
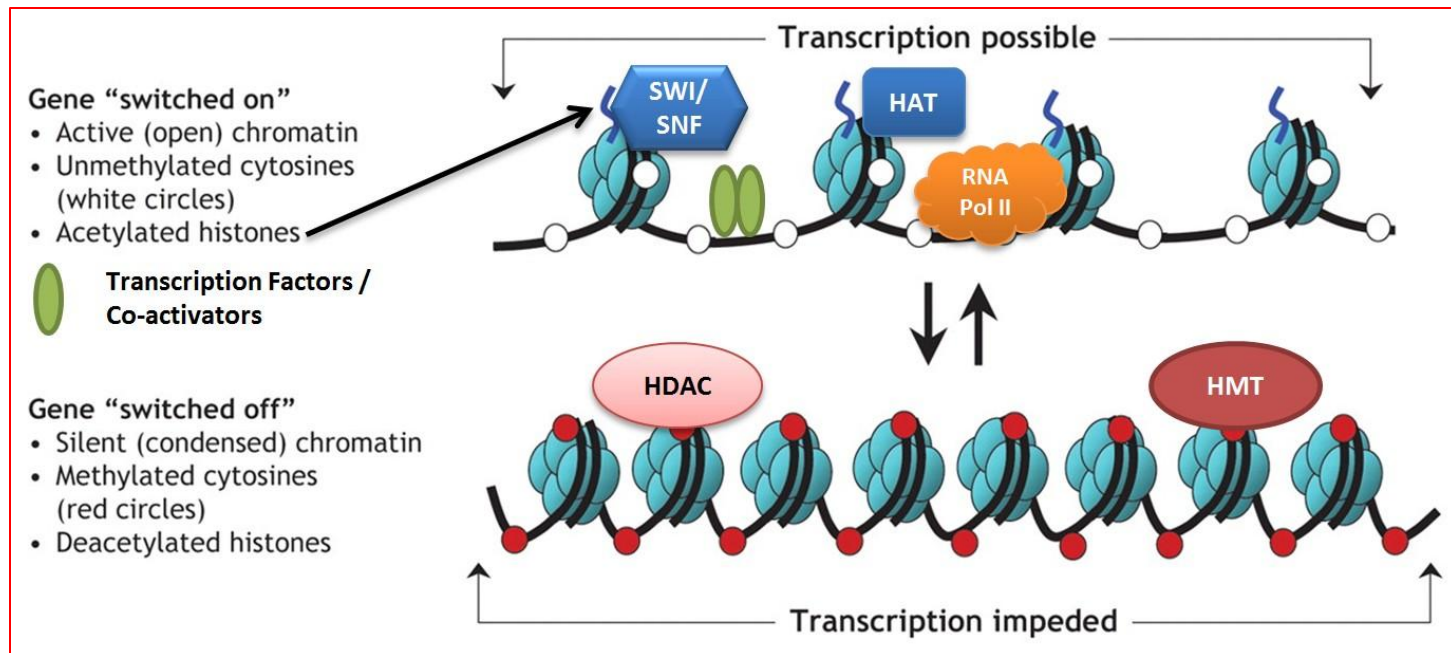
Active two-fluid hydrodynamis:
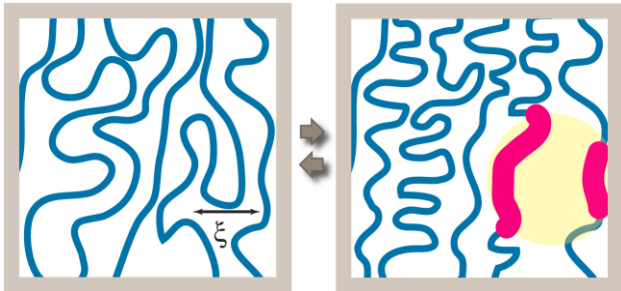
$$\Pi = K\delta\phi + \Pi^{\text{active}}; \qquad \Pi^{\text{active}} = -\alpha(\mathbf{r}, t)$$

Scalar active source,
no force and no ten...

... active source,
force dipole

$$\zeta\left(\mathbf{v}^p - \mathbf{v}^s\right) = \nabla \cdot \overleftrightarrow{\sigma} - \nabla\Pi - \phi_0 \nabla p$$
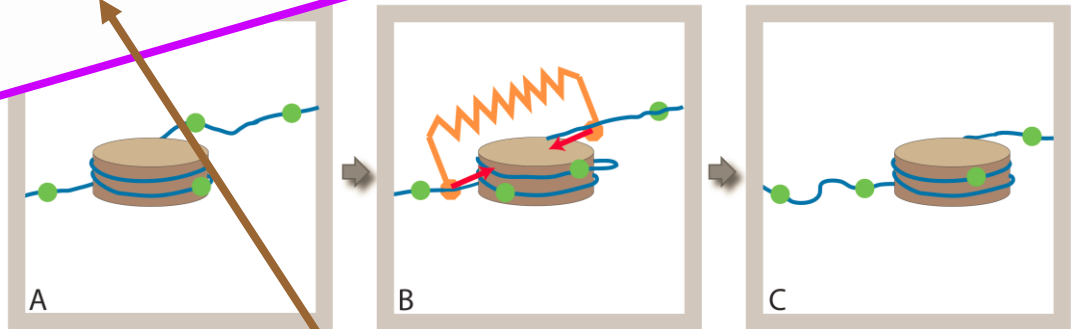
$$\overleftrightarrow{\sigma} = \overleftrightarrow{\sigma}^{\text{viscoelastic}} + \overleftrightarrow{\sigma}^{\text{active}} ; \qquad \overleftrightarrow{\sigma}^{\text{active}} \propto \beta(\mathbf{r}, t)$$

Linear response

Longitudinal velocity responds to scalar sources

$$\delta\phi(\vec{q},\omega) = \chi(q,\omega)\alpha(\vec{q},\omega)$$

$$\chi(q,\omega) = \frac{iq^2\phi_0}{\omega\left[\frac{\zeta}{(1-\phi_0)^2} + \frac{4}{3}E(q,\omega)q^2\right] + iq^2K\phi_0}$$

$$\left(v_\parallel^2\right)_{\vec{q},\omega} = \frac{\omega^2}{q^2\phi_0^2}\left|\chi(q,\omega)\right|^2\left(\alpha^2\right)_{\vec{q},\omega}$$

Transverse velocity responds to vector sources

$$\vec{v}_\perp(\vec{q},\omega) = \frac{1}{qE(q,\omega)}\vec{\beta}(\vec{q},\omega)$$

$$\left(\vec{v}_\perp^2\right)_{\vec{q},\omega} = \left|\frac{1}{qE(q,\omega)}\right|^2\left(\vec{\beta}^2\right)_{\vec{q},\omega}$$

In active case, fluctuations are controlled by the spectrum of sources – scalar (α) and vector (β): input from biology is needed

$$\left(\delta\phi^2\right)_{\vec{q},\omega} = \frac{2k_BT}{\omega}\mathrm{Im}\left[\chi(q,\omega)\right]$$

$$\left(\vec{v}_\perp^2\right)_{\vec{q},\omega} \simeq \frac{4k_BT}{q^2}\mathrm{Re}\left[\frac{1}{E(q,\omega)}\right]$$

In thermal case, it is all k_BT

Without ATP…

- Assume FDT applicable (may be wrong, because of
    1. remaining activity, and/or
    2. "glassiness" effects):

$$\left(v_\perp^2\right)^2_{\mathbf{q},\omega} \simeq \frac{4k_B T}{q^2}\mathrm{Re}\left[\frac{1}{E(q,\omega)}\right]$$

- Assume Maxwell model (may be wrong, because there is no reason for it to be right):

$$E(q,\omega) = \frac{\eta}{1+\imath\omega\tau} \implies \left(v_\perp^2\right)^2_{\mathbf{q},\omega} \simeq \frac{4k_B T}{\eta q^2}$$

$$\left.\frac{S(q,\Delta t)}{ck_B T}\right|_{\Delta t \text{ is large}} \simeq \frac{\text{mess}}{q^2\Delta t^2} + \frac{4}{q^2\Delta t}$$

Data, no ATP

$S(q,\Delta t)\Delta t^2$ is practically independent of Δt, meaning B is very nearly zero: Concentration fluctuations dominate in ATP-off case!
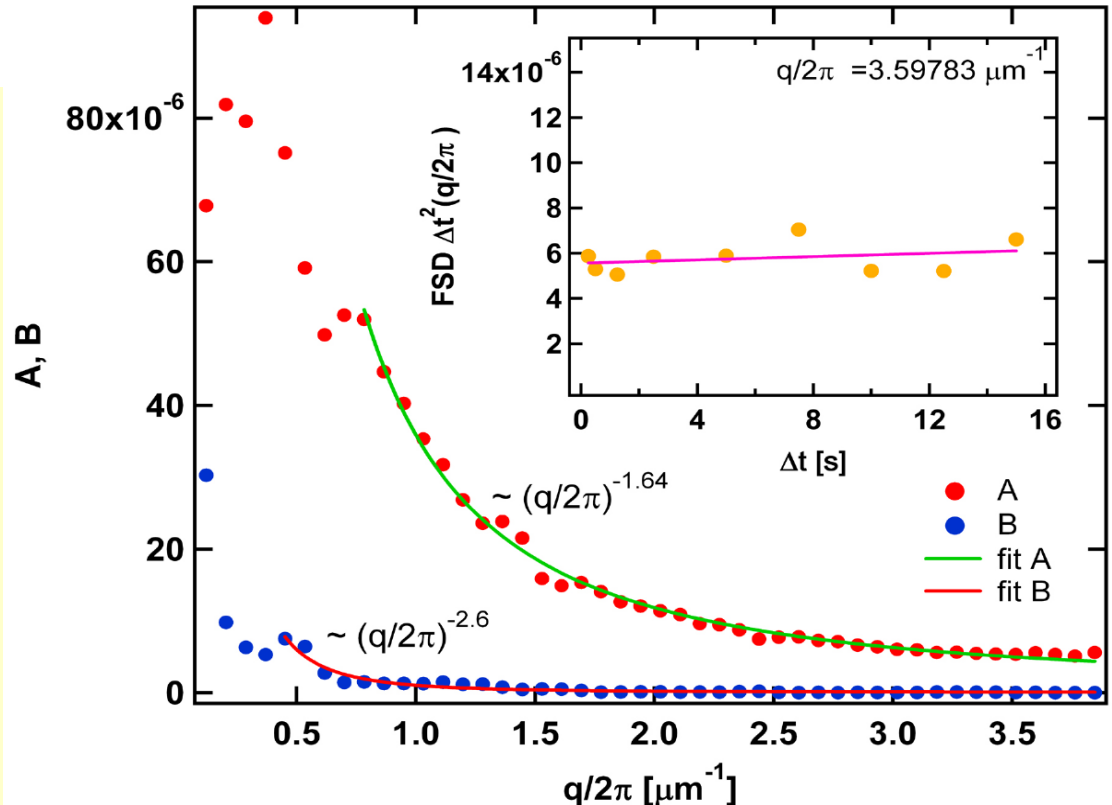
$$S(q, \Delta t) \simeq c \int \frac{1 - \cos\omega\Delta t}{(\omega\Delta t)^2} \left(\vec{v}^2\right)_{\vec{q},\omega} \frac{d\omega}{\pi}$$

$$S(q, \Delta t) = A(q)/\Delta t^2 + B(q)/\Delta t$$

With ATP…

$$\left(v_\parallel^2\right)^2_{\mathbf{q},\omega} = \frac{\omega^2}{q^2\phi_0^2}\left|\chi\left(\mathbf{q},\omega\right)\right|^2\left(\alpha^2\right)_{\mathbf{q},\omega}$$

$$\left(v_\perp^2\right)^2_{\mathbf{q},\omega} = \left|\frac{1}{qE\left(q,\omega\right)}\right|^2\left(\beta^2\right)_{\mathbf{q},\omega}$$

- We need to know sources α and β;
- Reverse the logic: can we learn about sources from observations of flow?

- Assume no correlations between active events;
- Assume abrupt onset/switch off ($|\alpha|^2 \sim |\beta|^2 \sim 1/\omega^2$);
- Assume Maxwell model:

$$\left.\frac{S(q,\Delta t)}{ck_BT}\right|_{\Delta t \text{ is large}} \simeq \frac{\text{mess}(q)}{\Delta t^2} + \frac{\text{mess}'}{q^2\Delta t}$$

Data, with ATP

S(q,Δt)Δt² is practically linear in Δt, meaning B is important at small q: Transverse flow dominates at small q in ATP-on case!
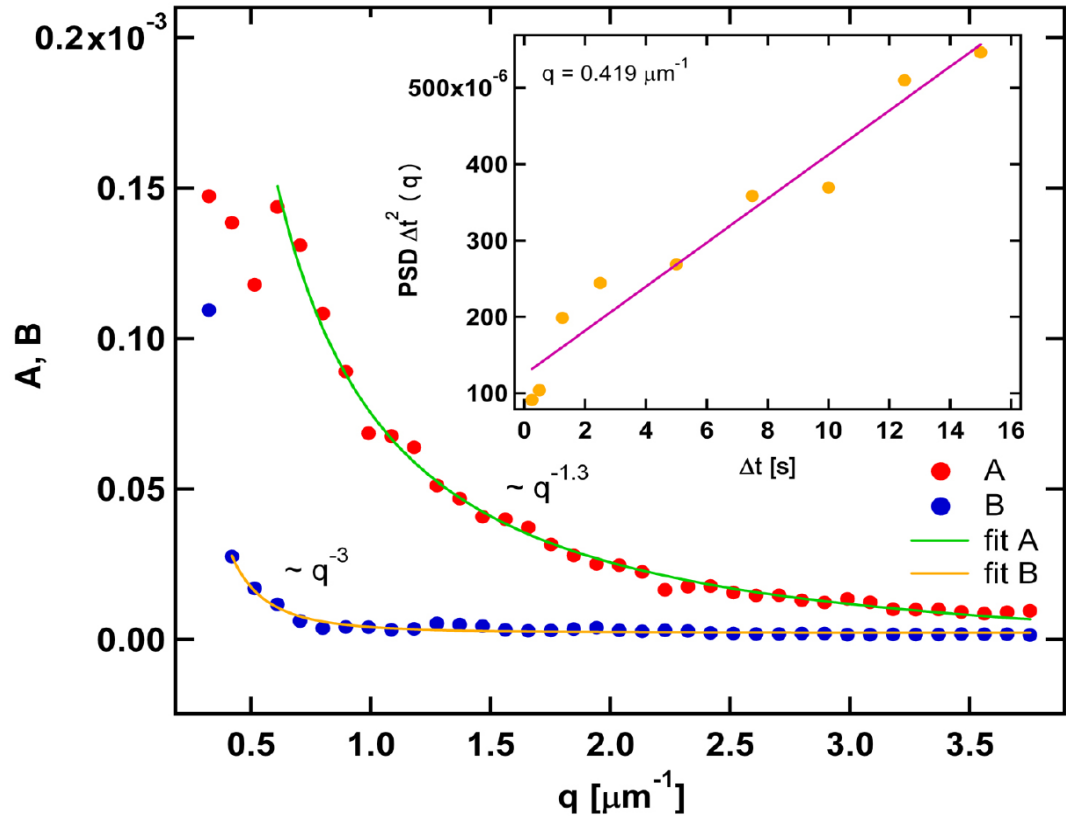
$$S(q, \Delta t) \simeq c \int \frac{1 - \cos \omega \Delta t}{(\omega \Delta t)^2} (\vec{v}^2)_{\vec{q}, \omega} \frac{d\omega}{\pi}$$

$$S(q, \Delta t) = A(q)/\Delta t^2 + B(q)/\Delta t$$

Longitudinal and transverse flow fluctuations

For "longitudinal" flow fluctuations, power spectrum $\propto$ Power spectrum of scalar sources

$$\left(v_\parallel^2\right)^2_{\mathbf{q},\omega} = \frac{\omega^2}{q^2\phi_0^2}\left|\chi\left(\mathbf{q},\omega\right)\right|^2\left(\alpha^2\right)_{\mathbf{q},\omega}$$

$$\chi(q,\omega) = \frac{\imath q^2\phi_0}{\omega\left[\frac{\zeta}{(1-\phi_0)^2} + 4/3E(q,\omega)q^2\right] + \imath q^2 K\phi_0}$$

For "transverse" flow fluctuations, power spectrum $\propto$ Power spectrum of vector sources

$$\left(v_\perp^2\right)^2_{\mathbf{q},\omega} = \left|\frac{1}{qE\left(q,\omega\right)}\right|^2\left(\beta^2\right)_{\mathbf{q},\omega}$$

Back to the data...

What is measured for N labeled histones is $r_j(t)$:

$$\vec{F}(\vec{q}, \Delta t) = \sum_{j}^{N} \frac{\vec{r}_j(t + \Delta t) - \vec{r}_j(t)}{\Delta t} e^{i\vec{q} \cdot \vec{r}_j(t)}$$
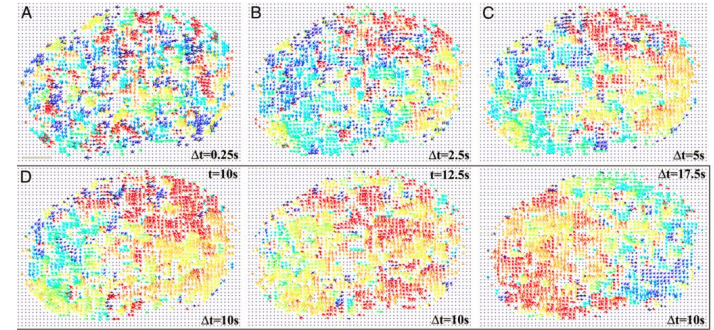
Flow spectral density $S(q, \Delta t)$ is defined as $\langle |F(q, \Delta t|^2 \rangle / N$:

$$S(q, \Delta t) \simeq c \int \frac{1 - \cos \omega \Delta t}{(\omega \Delta t)^2} (\vec{v}^2)_{\vec{q}, \omega} \frac{d\omega}{\pi}$$

Missing part:

- Eventually one would have to compute generalized viscosity based on some version of polymer theory
    - crumpled globule,
    - melt of rings,
    - annealed animals,
    - insights from Rosa & Everaers,
    - "loopy globule" of Rubinstein,
    - "decorated loops" of Obukhov et al …

Chromosome territories: gene-poor vs. gene-rich
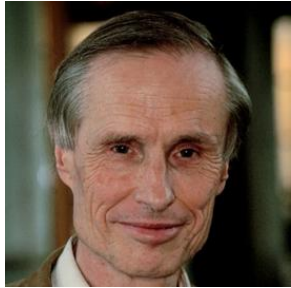
Christoph Cremer, Heidelberg/Mainz

Thomas Cremer, LMU Munich

Marion Cremer, LMU Munich

Irina Solovei, LMU Munich
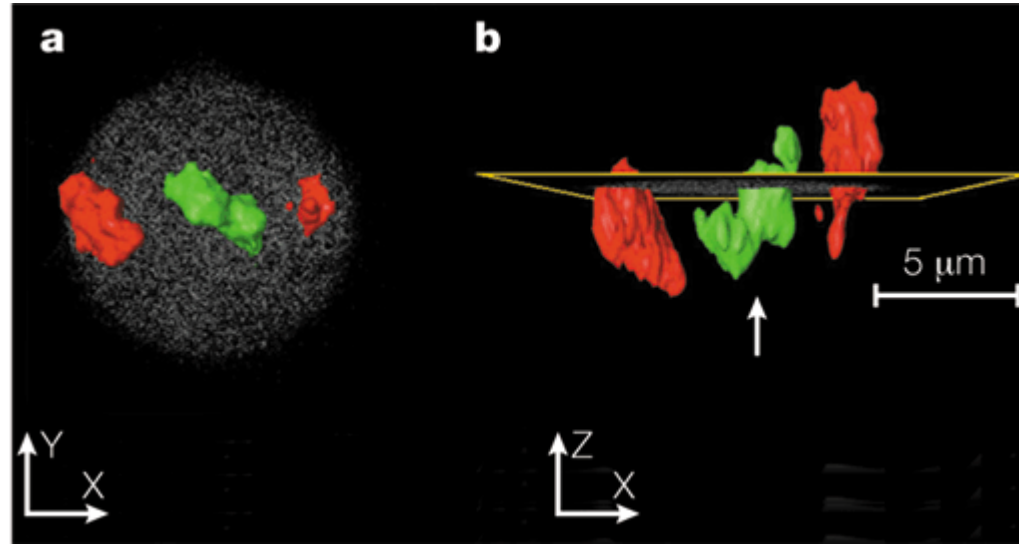
Three-dimensional reconstructions of chromosome 18 (red; gene-poor) and 19 (green; gene-rich) territories painted in the nucleus of a non-stimulated human lymphocyte. (Image courtesy of Marion Cremer and Irina Solovei.) Chromosome 18 territories were typically found at the nuclear periphery, whereas chromosome 19 territories were located in the nuclear interior[42]. a | X,Y view: a mid-plane section of the nucleus is shown as a grey shade. Only the parts of the territories below this section can be seen. b | X,Z view: the arrow marks the side from which the section in part a is viewed.

T. Cremer & C. Cremer "Chromosome territories, nuclear architecture and gene regulation in mammalian cells" Nature Reviews Genetics **2**, 292-301 (April 2001)

T. Cremer & M. Cremer "Chromosome territories" Cold Spring Harbor Perspectives in Biology 2010;2:a003889 (2010)

Territories and translocations

DSB formation | Repair factor recruitment | Partner search | Pairing | Joining

Hetero- and eu-chromatin

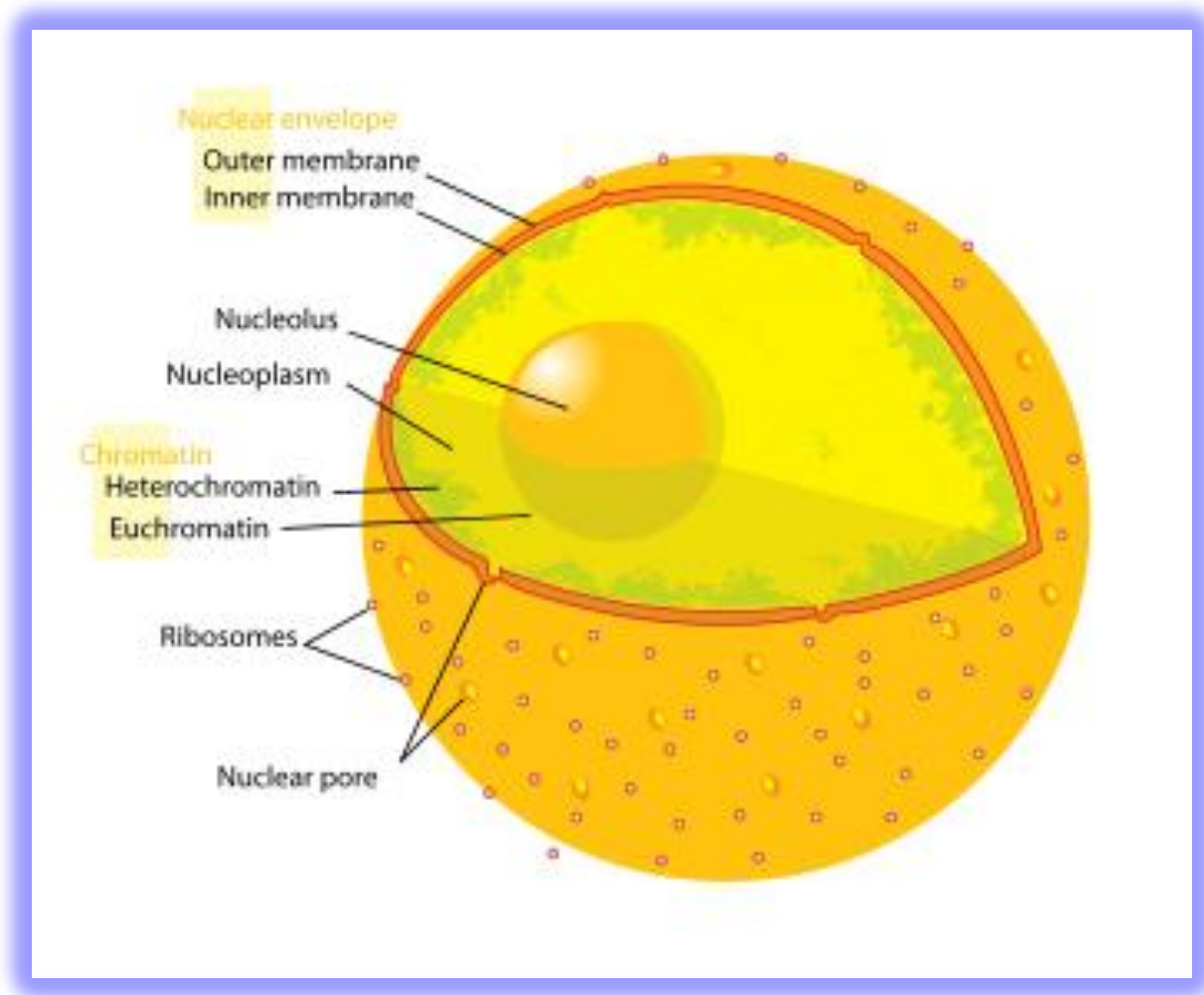# Hetero- and Eu-chromatin

Chromosome positioning from activity-based segregation

Nirmalendu Ganai[1], Surajit Sengupta[2,3] and Gautam I. Menon[4,5,6,*]

[1]Department of Physics, Nabadwip Vidyasagar College, Nabadwip, Nadia 741302, India, [2]TIFR Centre for Interdisciplinary Sciences, 21 Brundavan Colony, Narsingi, Hyderabad 500075, India, [3]Centre for Advanced Materials, Indian Association for the Cultivation of Science, Jadavpur, Kolkata 700032, India, [4]The Institute of Mathematical Sciences, C.I.T. Campus, Taramani, Chennai 600 113, India, [5]Mechanobiology Institute, National University of Singapore, T-Lab, #10-01, 5A Engineering Drive 1, Singapore 117411, Singapore and [6]Department of Biological Sciences, National University of Singapore, 14 Science Drive 4, Singapore 117543, Singapore
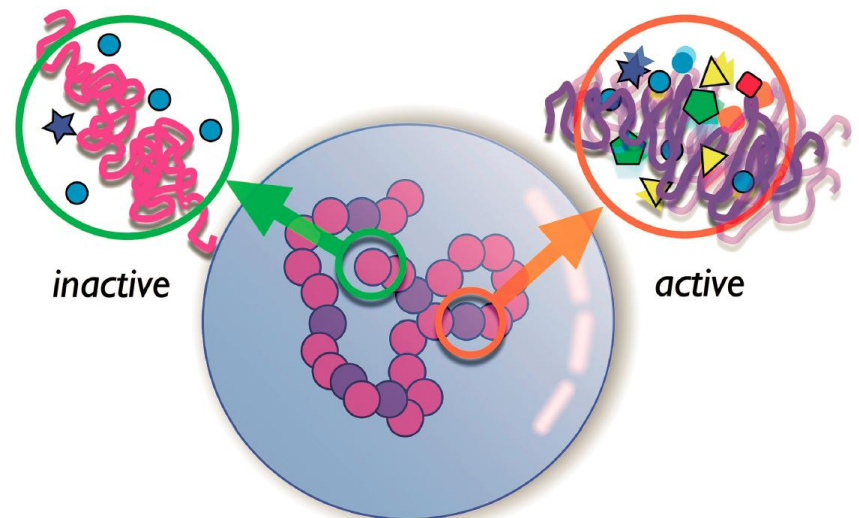
inactive

active

Take it seriously:
activity based segregation

This brings analogies with physics of active swimmers...

<u>Idea:</u> mixture of particles with two levels of activity as exposed to two different thermostats

J.-F.Joanny, ESPCI

$$\zeta \dot{x}_{\mathcal{A}} = -\partial_{\mathcal{A}} U + \sqrt{2\zeta T_{\mathcal{A}}} \xi_{\mathcal{A}}(t)$$

$$\zeta \dot{x}_{\mathcal{B}} = -\partial_{\mathcal{B}} U + \sqrt{2\zeta T_{\mathcal{B}}} \xi_{\mathcal{B}}(t)$$

Two particles:

$$\zeta \dot{x}_\mathcal{A} = -\partial_\mathcal{A} U + \sqrt{2\zeta T_\mathcal{A}} \xi_\mathcal{A}(t)$$

$$\zeta \dot{x}_\mathcal{B} = -\partial_\mathcal{B} U + \sqrt{2\zeta T_\mathcal{B}} \xi_\mathcal{B}(t)$$

$$r = x_\mathcal{A} - x_\mathcal{B}$$

$$\zeta \dot{r} = -2\nabla U + \sqrt{2\zeta \left(T_\mathcal{A} + T_\mathcal{B}\right)} \xi_r(t)$$

$$P(r) = z^{-1} \exp\left[-\frac{U(r)}{\left(T_\mathcal{A} + T_\mathcal{B}\right)/2} \right]$$
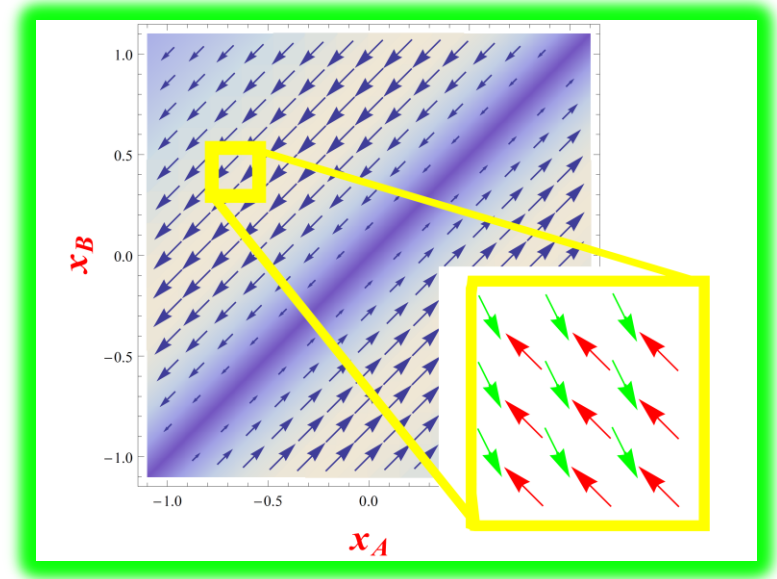
J.-F.Joanny, ESPCI

Mixture, second virial approximation:

Hierarchy of equations (like BBGKI)

$$\frac{\partial p_1^{\mathcal{A}}(\mathbf{r})}{\partial t} = \frac{N_{\mathcal{A}}}{\zeta_{\mathcal{A}}} \partial_{\mathbf{r}} \left[\int \frac{\partial u^{\mathcal{AA}}}{\partial \mathbf{r}} p_2^{\mathcal{AA}}(\mathbf{r}, \mathbf{r}') d\mathbf{r}' \right] +$$

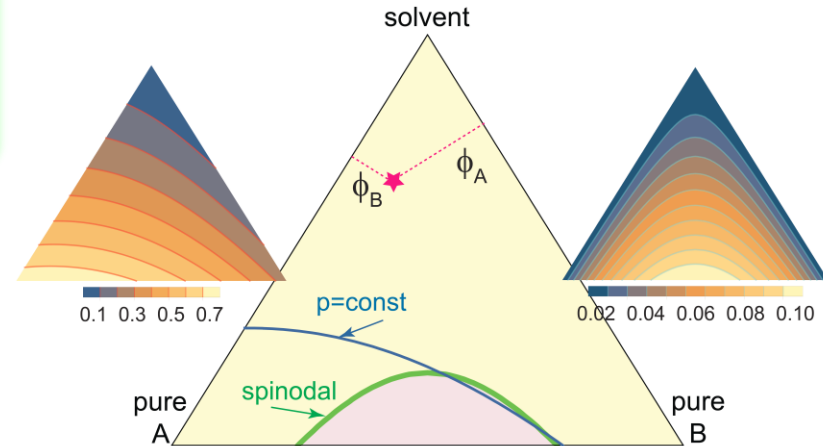$$+ \frac{N_{\mathcal{B}}}{\zeta_{\mathcal{B}}} \partial_{\mathbf{r}} \left[\int \frac{\partial u^{\mathcal{AB}}}{\partial \mathbf{r}} p_2^{\mathcal{AB}}(\mathbf{r}, \mathbf{r}') d\mathbf{r}' \right] + \frac{T_{\mathcal{A}}}{\zeta_{\mathcal{A}}} \nabla_{\mathbf{r}}^2 p_1^{\mathcal{A}}(\mathbf{r})$$

$$p_2^{ij}(\mathbf{r}, \mathbf{r}') = p_1^i(\mathbf{r}) p_1^j(\mathbf{r}') \exp\left[-u^{ij}(\mathbf{r} - \mathbf{r}')/T_i\right]$$

T_i: either T_A, or T_B, or $\langle T \rangle$

Energy transfer:

$$w = c^{\mathcal{A}} c^{\mathcal{B}} \frac{T_{\mathcal{A}} - T_{\mathcal{B}}}{T_{\mathcal{A}} \zeta_{\mathcal{B}} + T_{\mathcal{B}} \zeta_{\mathcal{A}}} \int \left(\frac{\partial u^{\mathcal{AB}}}{\partial \mathbf{r}}\right)^2 e^{-\frac{u^{\mathcal{AB}}(\mathbf{r})}{\overline{T}}} d^3\mathbf{r}$$

J.-F.Joanny, ESPCI

Acknowledgements:

Conclusions = Open questions:

- Are N_0 and N_e the same or different?
- What is the role of slip knots in chromatin?
- Animals, decorated loops, etc? What are the powers β and γ? What are the corrections to scaling?
- Is it possible to separate explicitly longitudinal and transverse flow fields, to get information about scalar and vector activities.
- What happens with active fluctuations when it comes to a metaphase? Concentration fluctuations grow, K ->0?
- How does nematic order of vector sources arise?
- What is the role of activity based segregation in hydrodynamic description?

Thank you!