

Monte Carlo simulations of densely packed biopolymers

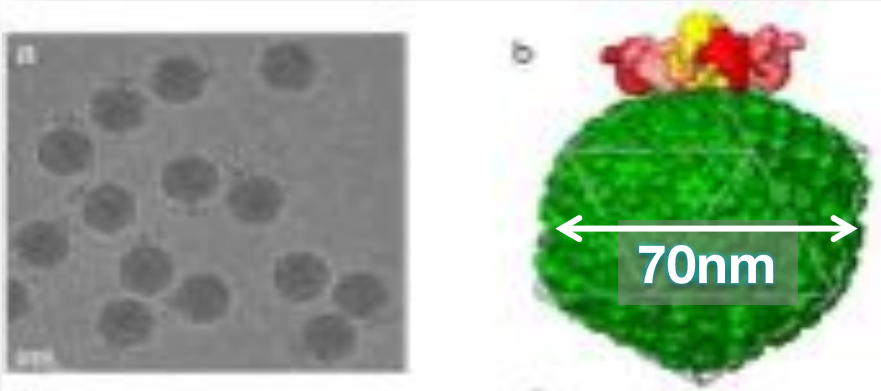
Outline:

Motivation: dense biopolymers are ubiquitous. Prototypical example: DNA packaged inside a viral particle.

Implications of self- and mutual polymer entanglement?

Methodological aspects: Monte Carlo techniques

Generalities on DNA packaging



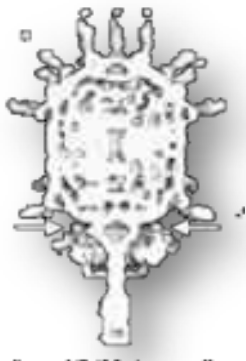
Jiang et al.
Nature 2006

Eukaryotes: *meters* of DNA in a **10 micron** size nucleus

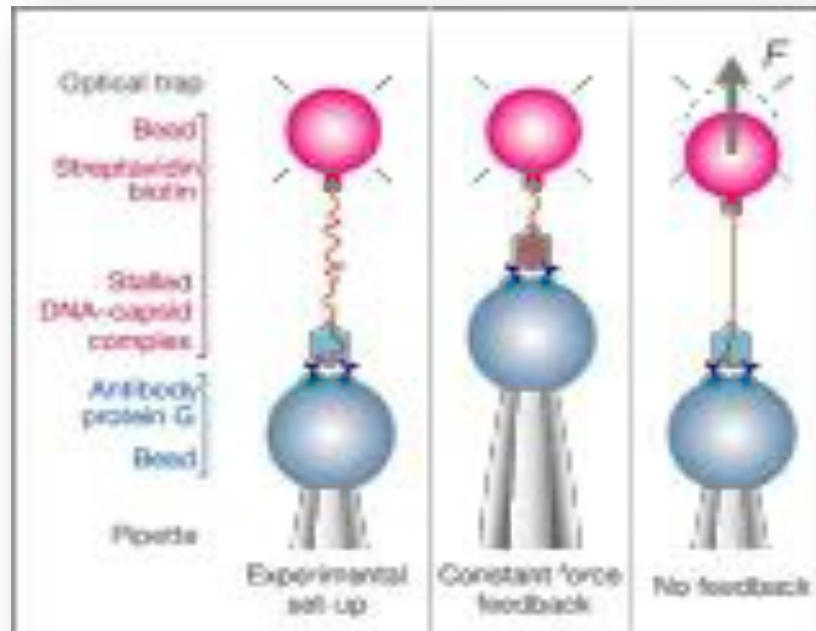
Bacteria: *mm* of DNA in a **micron** size cell

Phages *microns* of DNA in a **50 nm** capsid

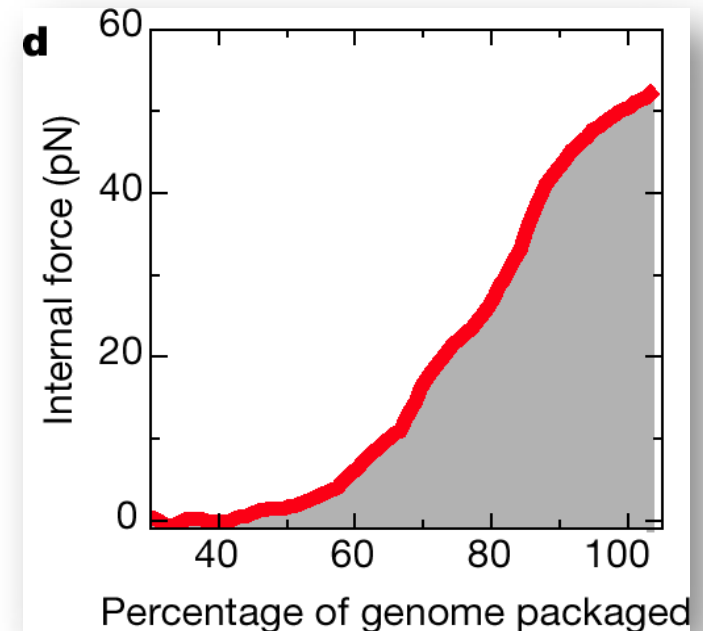
In all cases genome organisation involves a high degree of spatial confinement.



Phi29
capsid

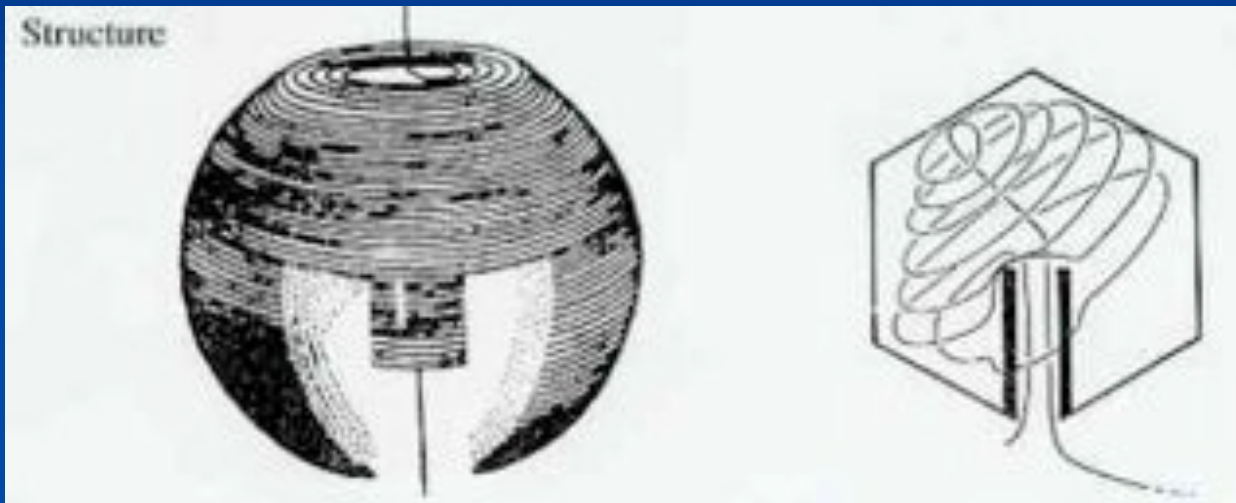


Smith et al., *Nature* 2001



DNA packaging time: 5.5mins

What about the DNA arrangement?



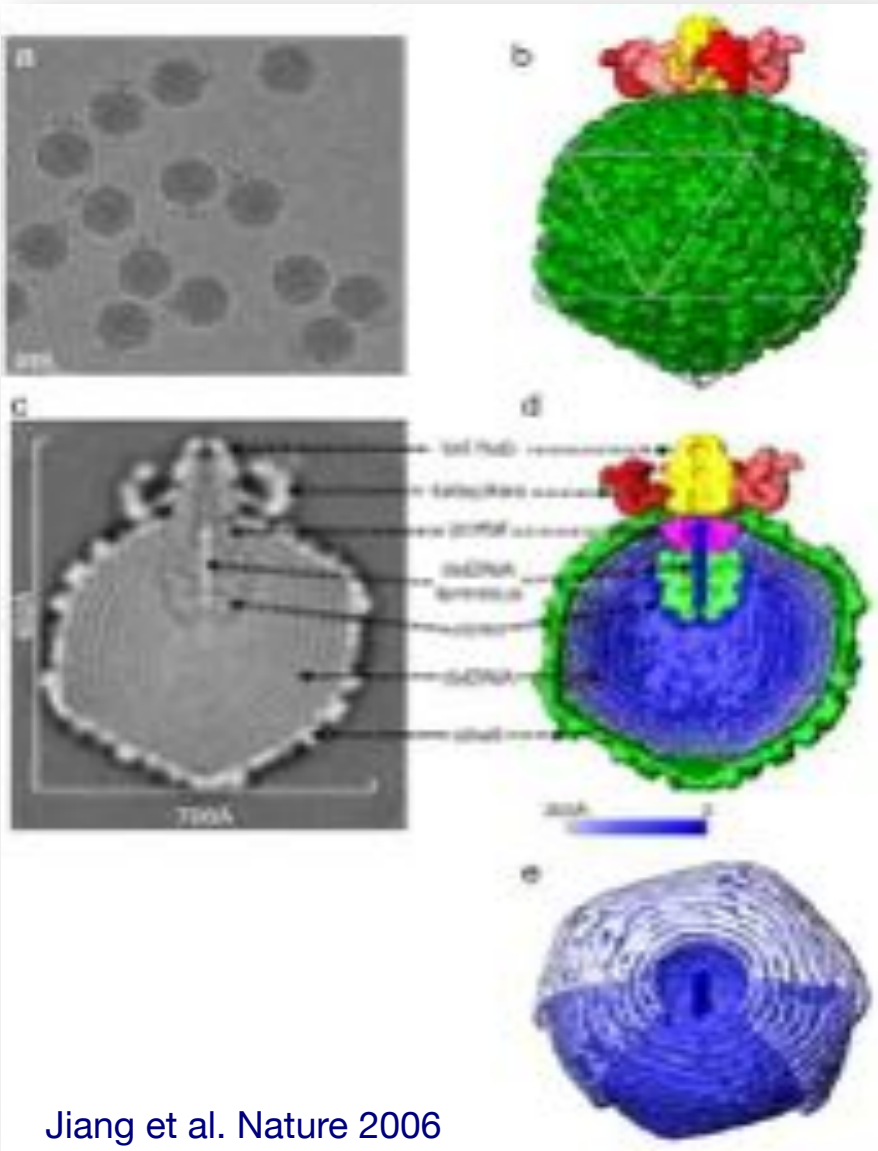
Spooling model,
Richards et al, JMB 1973



Fold model,
Richards et al. JMB 1973

... disordered packing etc.

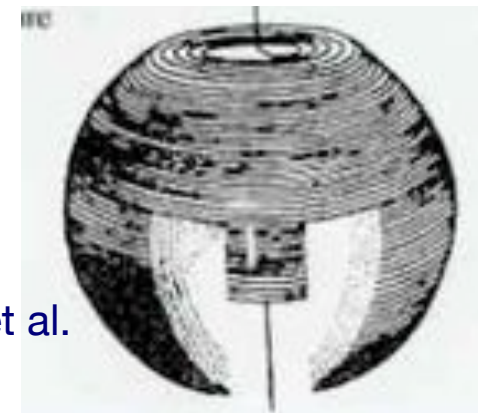
Imaging studies of DNA in bacteriophages



Jiang et al. Nature 2006

Phages *microns* of DNA in a 50 *nm* capsid

Cryo-EM imaging on bacteriophage $\epsilon 15$ indicate that the outer layers of dsDNA have an inverse spool arrangement



Richards et al.
JMB 1973

Self-avoidance and bending rigidity

Growth of a flexible self-avoiding chain in a small sphere ($L_p \gg R$)



See also:

Harvey and coworkers: *Biopolymers* **73** (2004); *Biophys. Chem* (2002)

Marenduzzo and CM. *J. Mol. Biol.* **330** (2003)

Tzill et al. *Biophys. J.* **84** (2003)

Packing a stiff chain

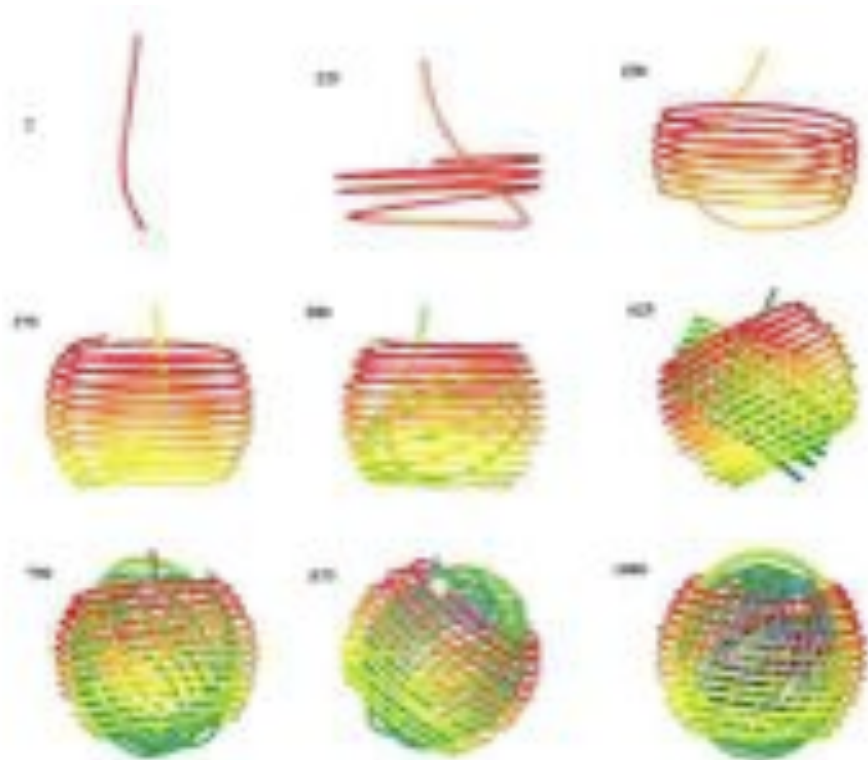


FIGURE 3 Progress of packaging. Colours along the DNA are the same as in FIGURE 1, to facilitate comparison of the two models.

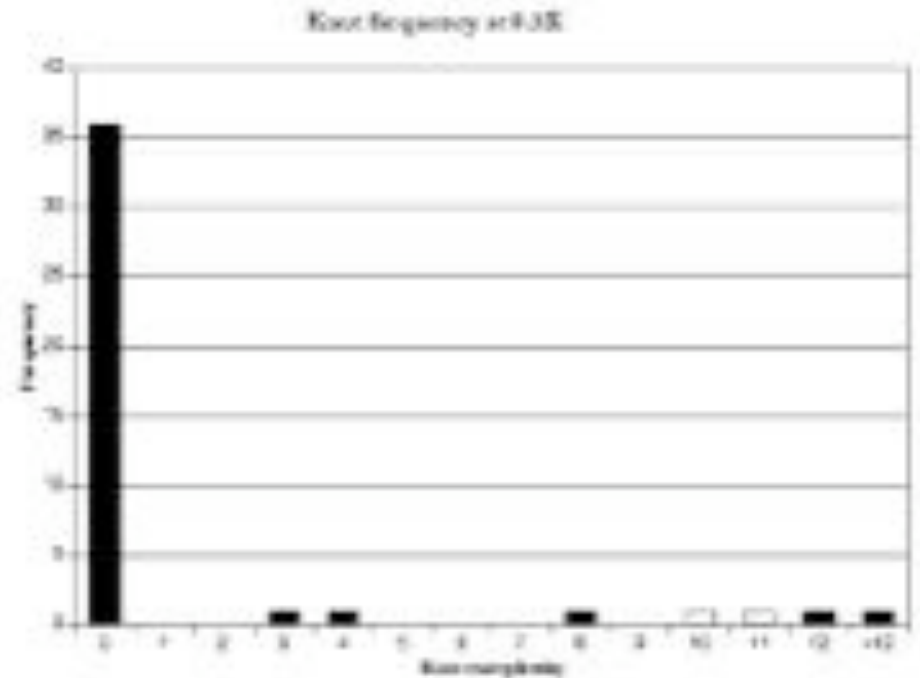


FIGURE 4 Distribution of knots for the ensemble of structures described in FIGURE 3.

LaMarque et al., Biopolymers (2004);
 Arsuaga et al., Biophys. Chem. (2002).

See also:
 Harvey and coworkers: Biopolymers **73** (2004);
 Biophys. Chem (2002)
 Marenduzzo and CM. J. Mol. Biol. **330** (2003)
 Tzill et al. Biophys. J. **84** (2003)

Knots as a probe of DNA organization



P4 bacteriophage

DNA length: 10 kb ~ 3.4 μ m

Capsid diameter: ~ 45 nm

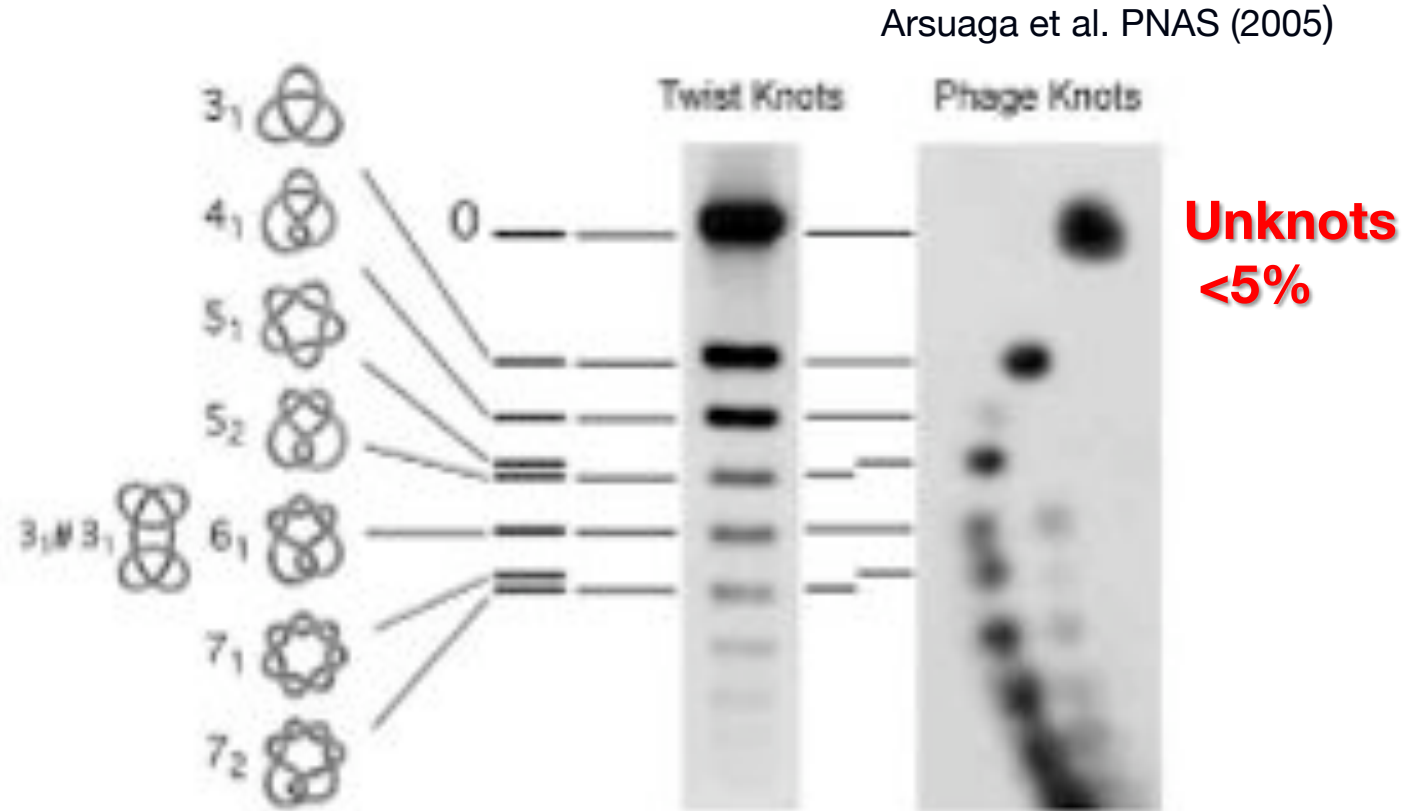


Fig. 2. Identification of specific knot types by their position in the gel. The gel velocity at low voltage of individual knot populations resolved by two-dimensional electrophoresis (Right) is compared with the gel velocity at low voltage of twist knots (3₁, 4₁, 5₂, 6₁, and 7₁) of a 10-kb nicked plasmid (Center)

Knots as a probe of DNA organization

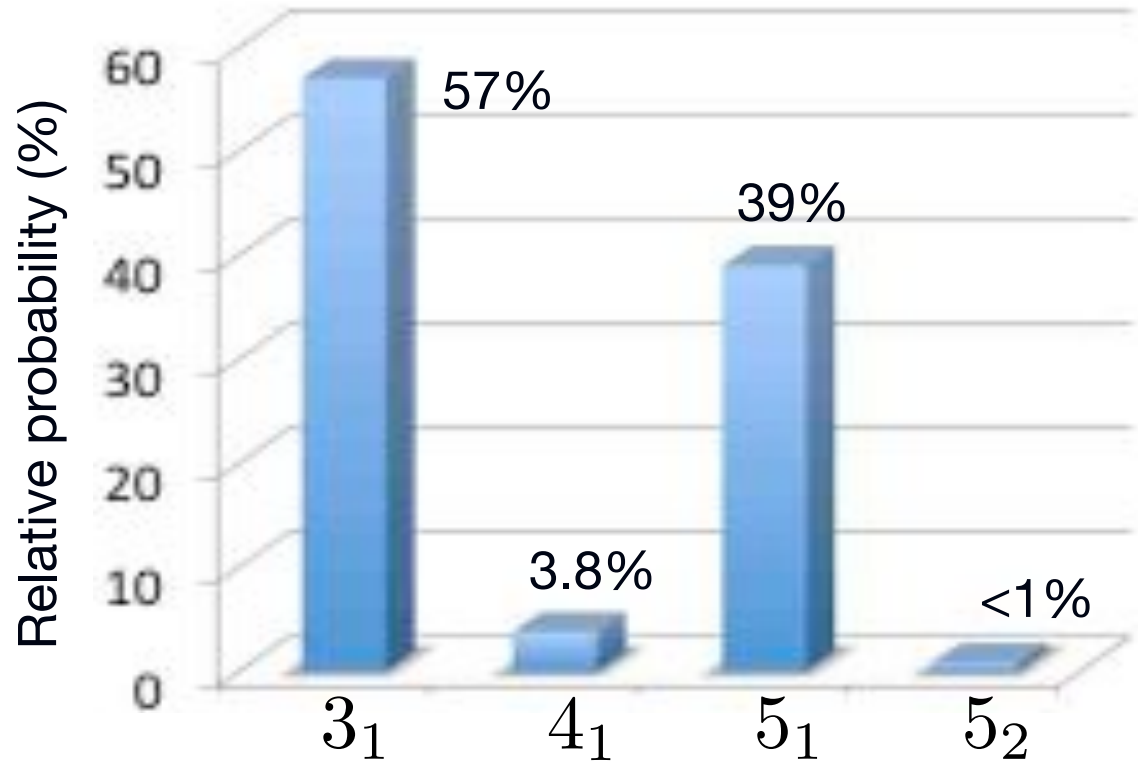


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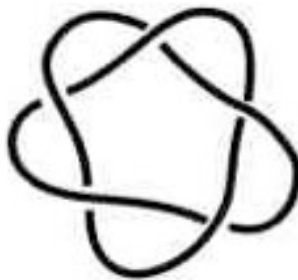
Ref: Arsuaga et al. PNAS 2005



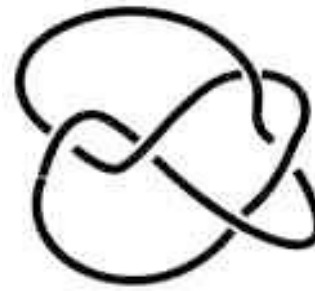
3_1



4_1



5_1

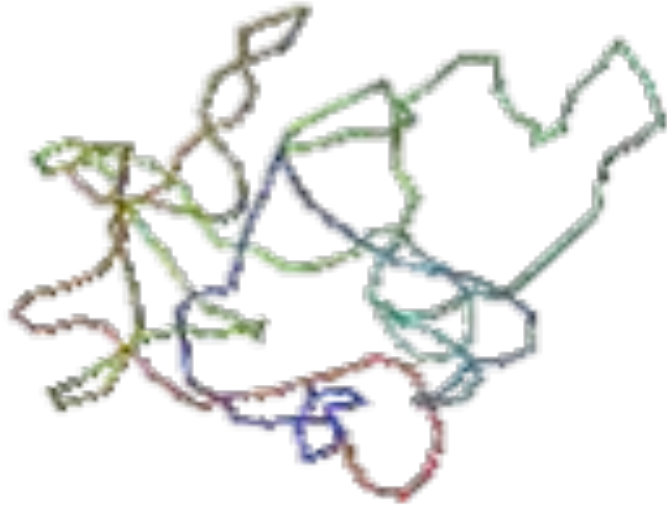


5_2

Some of these knots occur in proteins too!

see Wallin *et al.*
J. Mol. Biol. 2007

Model for circular DNA



Flexible ring of N cylinders

(Vologodskii and coworkers)

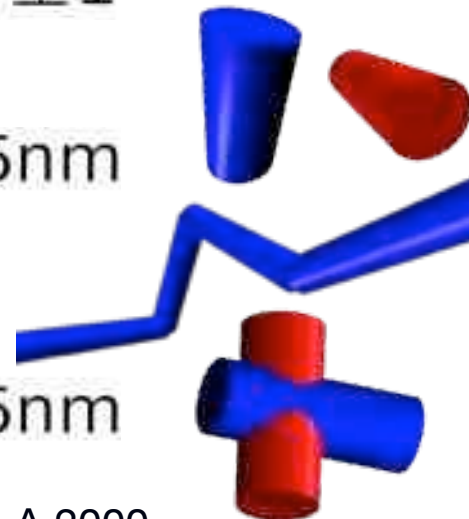
Diameter of cylinders: 2.5 nm

Contour length: $N a = 3.4 \mu\text{m}$

Persistence length: 50 nm

$$\mathcal{H} = \sum_i V_{br}(i) + \sum_{i \neq j, j \pm 1} V_{hc}(i, j)$$

$$\vec{V}_{br}(i) \equiv \begin{cases} 0 & \text{if } d_{ij} > 2.5\text{nm} \\ \alpha(1 - \vec{t}_i \cdot \vec{t}_{i+1}) & \\ +\infty & \text{if } d_{ij} \leq 2.5\text{nm} \end{cases}$$

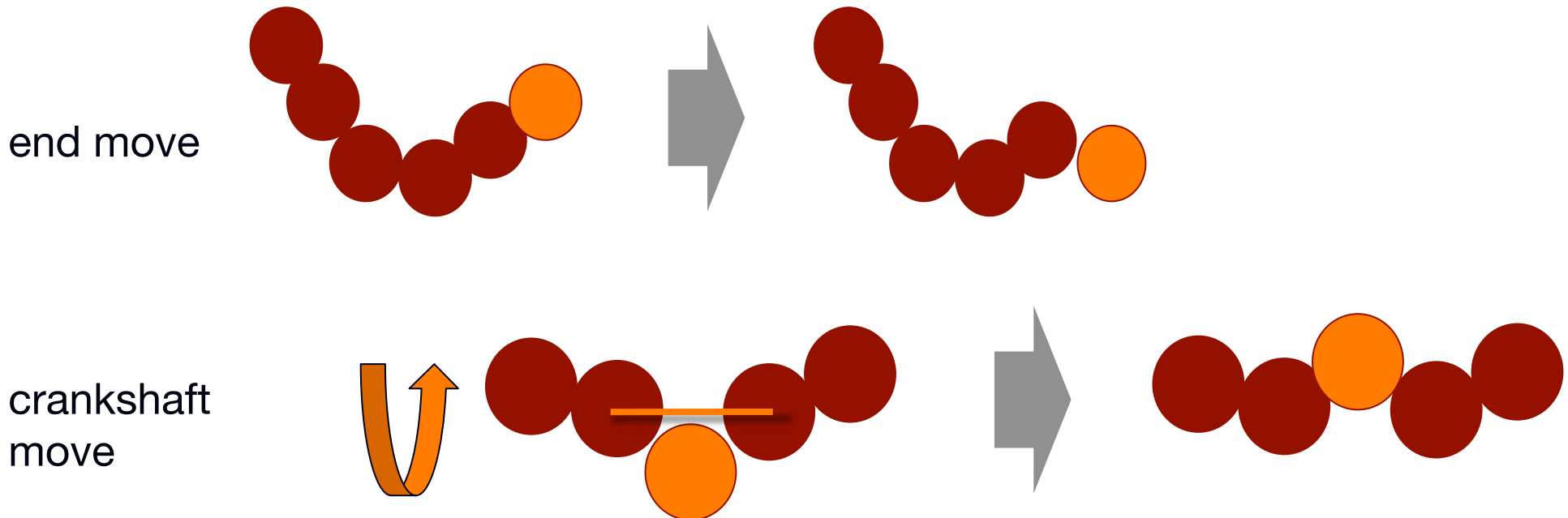


Monte Carlo sampling

MC is used to produce a sequence of system snapshots sampled with **canonical weight**. Key prescriptions:

- (1) at each time step obtain a trial system configuration by changing the current one using random moves.
- (2) Accept the trial configuration or retain the current one using a suitable rule. The accepted/retained configuration becomes the new system configuration.

(1) Monte Carlo moves for polymer chains



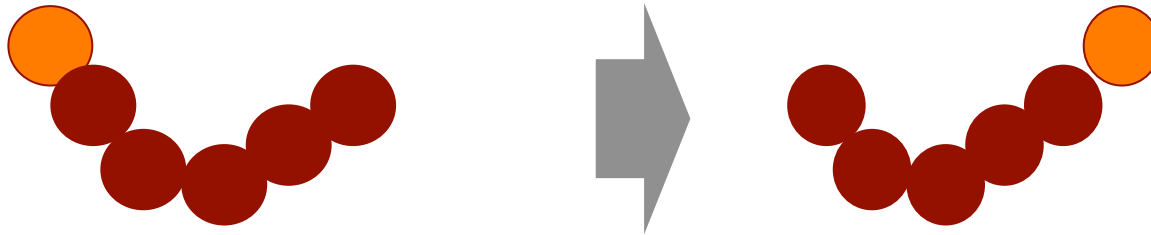
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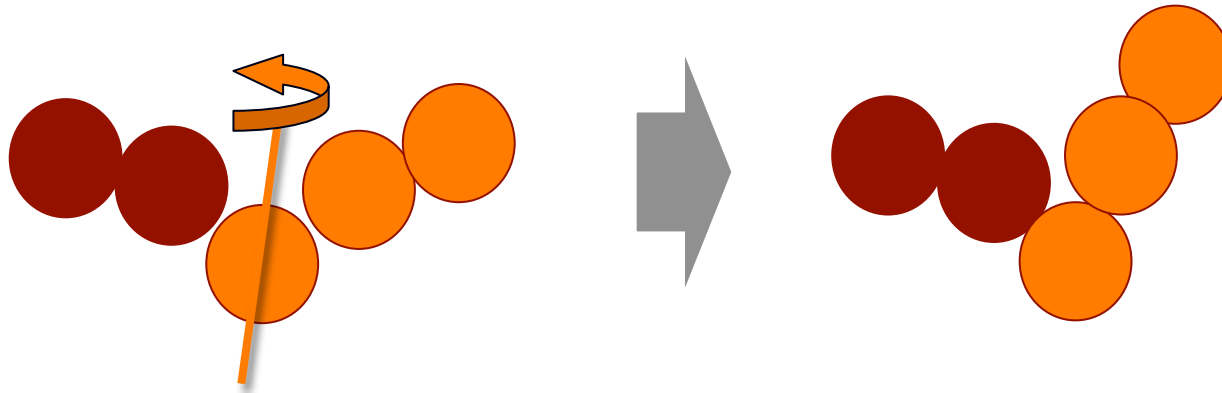
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(1) Monte Carlo moves for polymer chains

slithering
move



pivot
move



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(2) Acceptance-rejection rule

We wish that in the long run, configurations are picked with canonical probability

$$P_{eq}(\Gamma) \propto e^{-E(\Gamma)/K_B T}$$

This condition is satisfied if the rates of going from configuration A to B (and vice versa) obey the detailed balance prescription:

$$P_{eq}(\Gamma_A)W_{A \rightarrow B} = P_{eq}(\Gamma_B)W_{B \rightarrow A}$$

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$$W_{A \rightarrow B} = \begin{cases} 1 & \text{if } E_B < E_A \\ e^{-(E_B - E_A)/K_B T} & \text{otherwise} \end{cases}$$

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Cons:

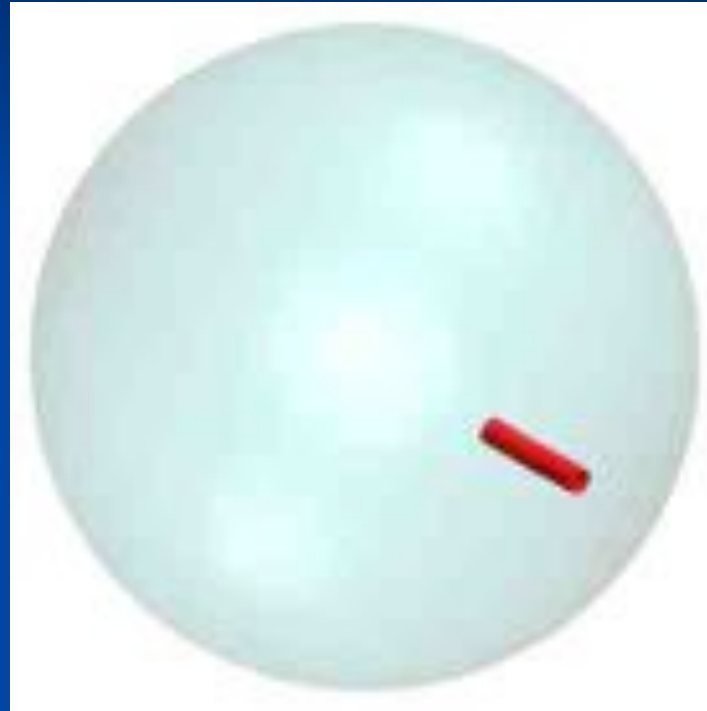
- No viable information about system kinetics. However, if one uses only **local** moves, then MC trajectories can be a viable stochastic system dynamics.

Pros:

- Efficient exploration of phase space
- Information about system equilibrium properties
- Potential energy needs not be differentiable
- Constraints can be efficiently implemented

Self-avoidance and bending rigidity

Growth of a flexible self-avoiding chain in a small sphere ($L_p \gg R$)



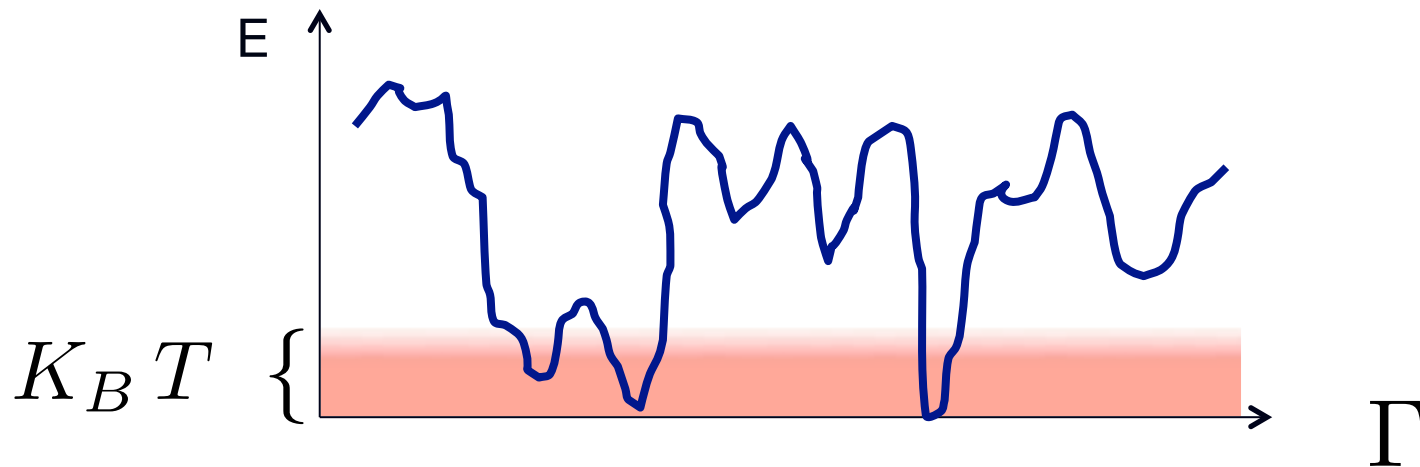
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Harvey and coworkers: *Biopolymers* **73** (2004); *Biophys. Chem* (2002)

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Advanced sampling techniques: parallel tempering

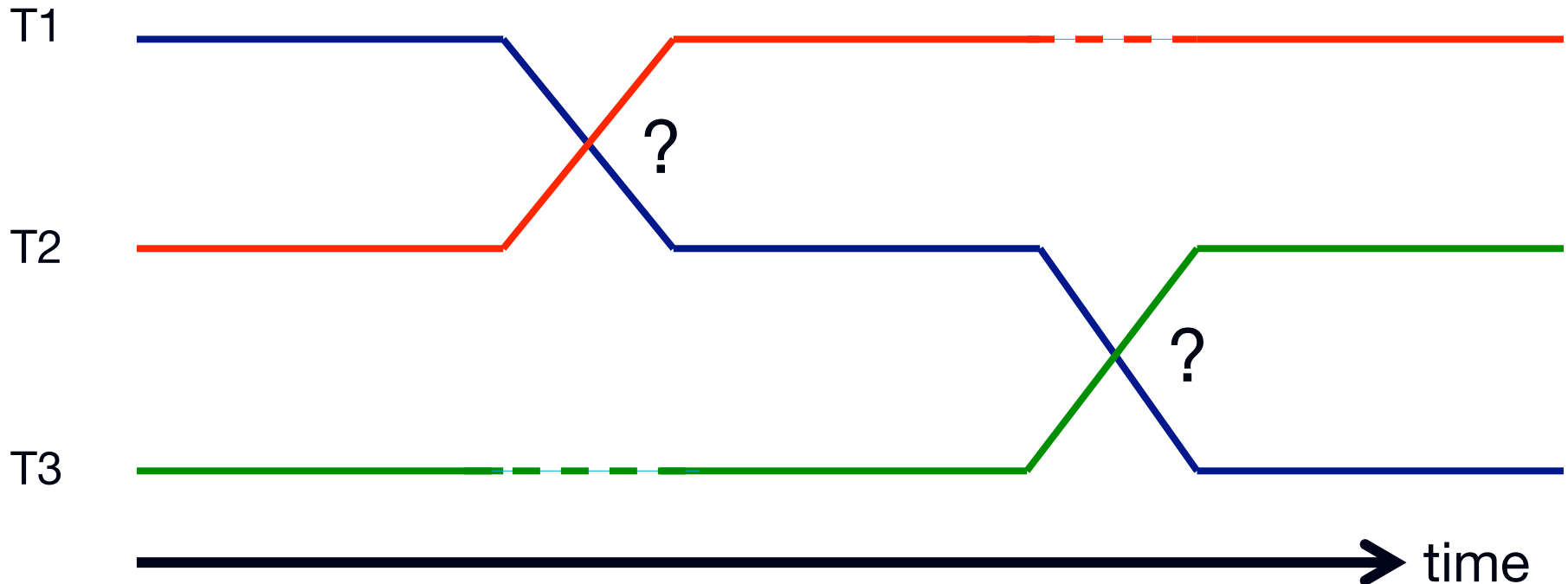


Sampling the relevant phase space is impractical due to large (free) energy barriers.

How can we overcome the problem?

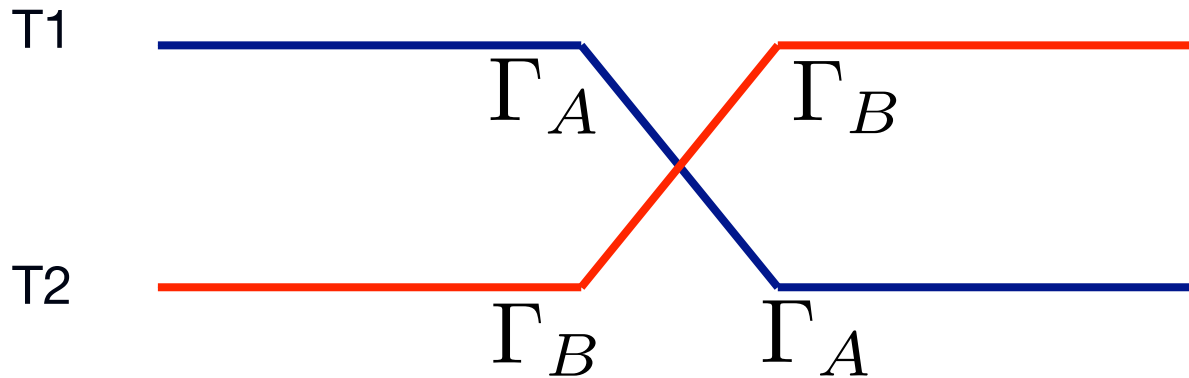
Advanced sampling techniques: parallel tempering

Run several MC trajectories at additional (higher and lower) temperatures and occasionally propose swaps between systems at nearby temperatures.



Advanced sampling techniques: parallel tempering

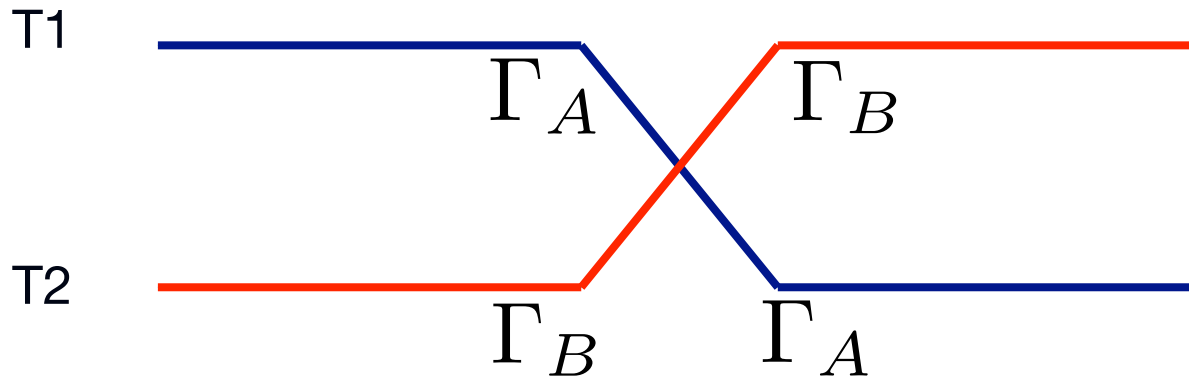
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Q: With what probability should we accept the swap?

Advanced sampling techniques: parallel tempering

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Q: With what probability should we accept the swap?

$$\min \left(1, \frac{e^{-E_B/T_A - E_A/T_B}}{e^{-E_A/T_A - E_B/T_B}} \right)$$

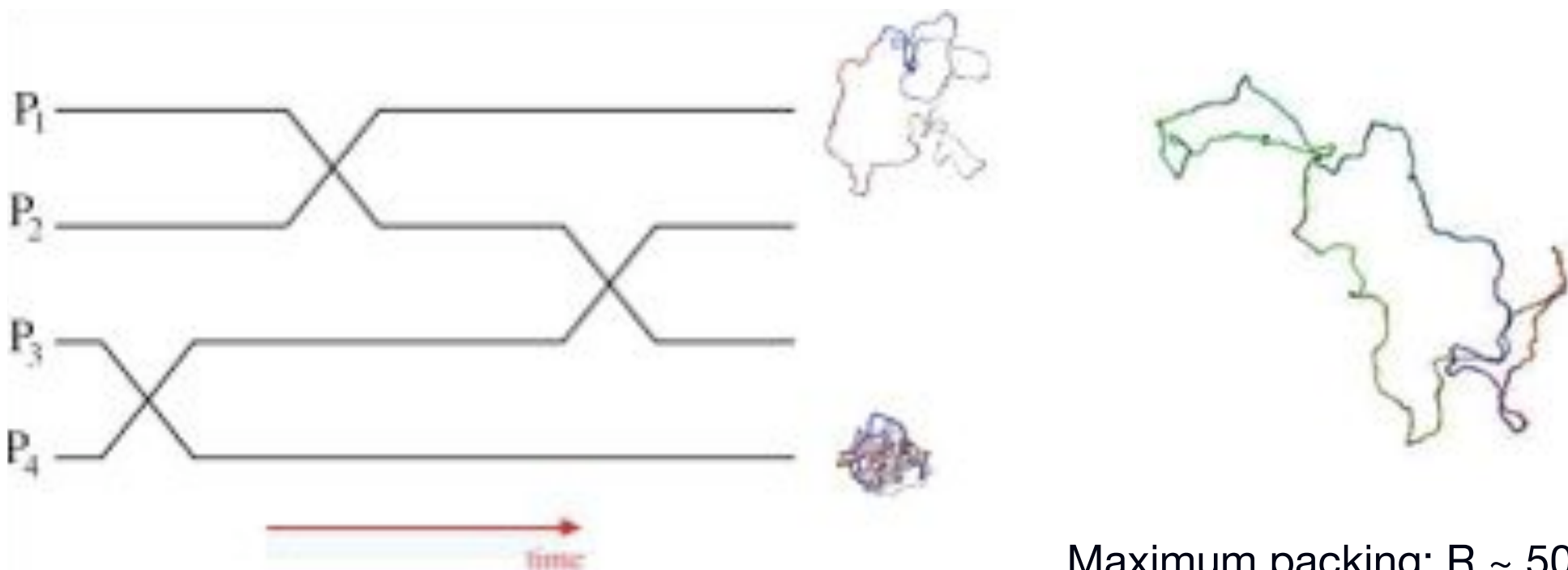
Stochastic sampling of compact rings

Use Metropolis scheme to sample rings with weight $w \equiv e^{-P R^3 - \beta \mathcal{H}}$

Rings are deformed by crankshaft moves

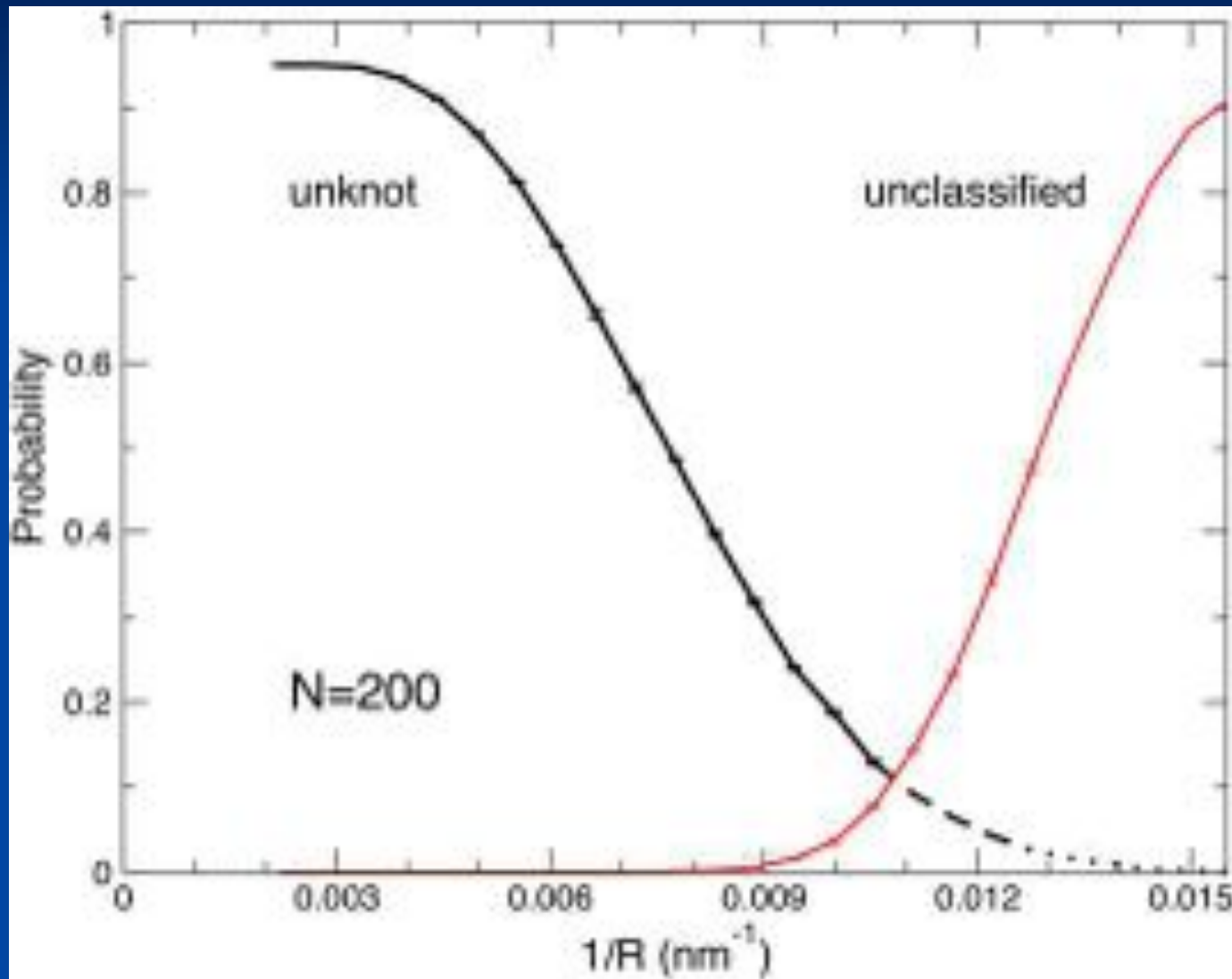
Occasional swapping of rings at various values of P (Tesi et al. J, Stat. Phys 1996)

Recover canonical statistics by undoing pressure bias (Ferrenberg and Swendsen, PRL 1989)

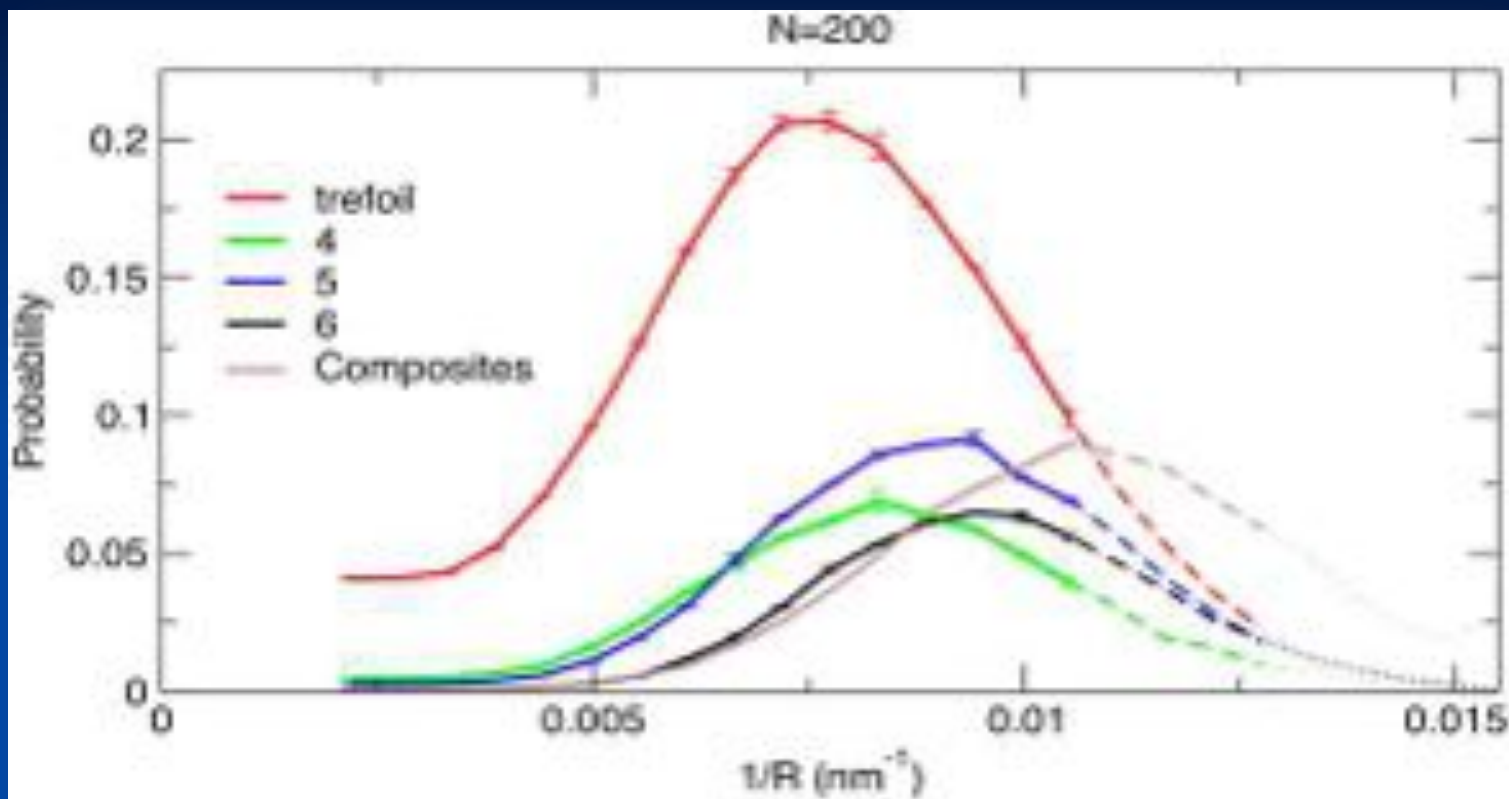


Maximum packing: $R \sim 50\text{nm}$

Confinement and knot complexity



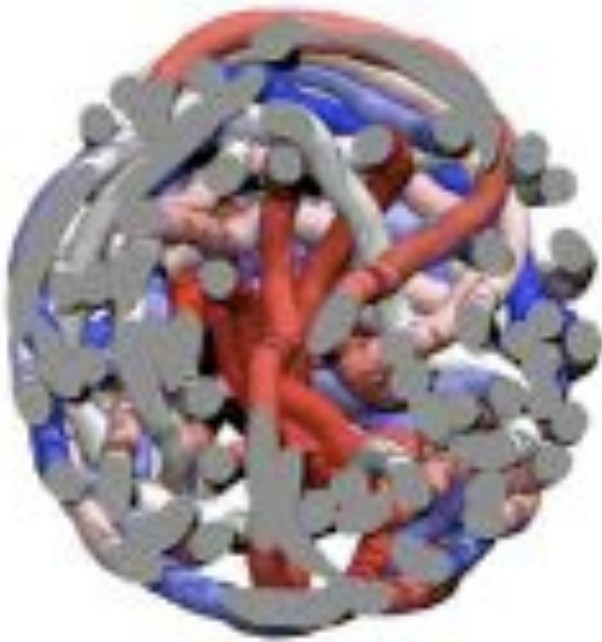
Simple knots



Unconstrained case:

Knot type	Probability	Experiment (*)
3	3.8%	3.5%
4	0.46%	0.44%
5	0.27%	0.25%

* 1M NaCl
Rybenkov et al. PNAS 1993

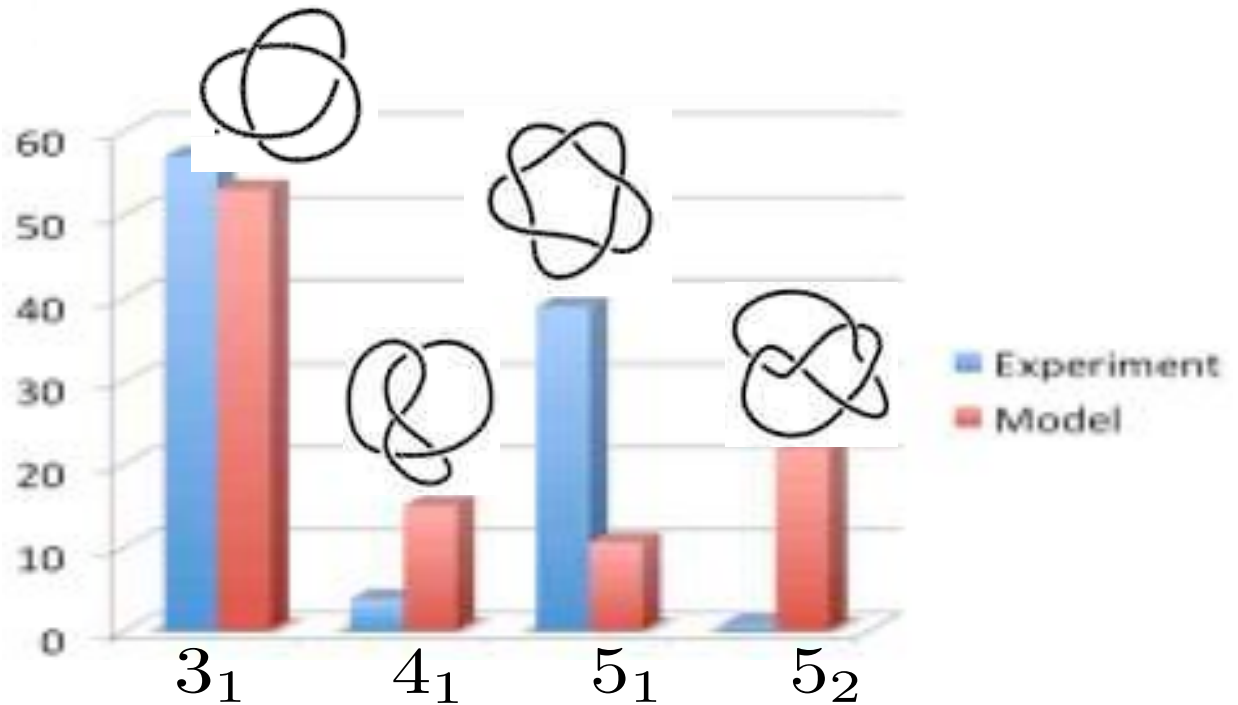


Packing of half P4 genome (4.7Kb)

[experiment: Trigueros and Roca BMC biotech. 2007]

1. No order at surface
2. No bias in favour of torus and chiral knots

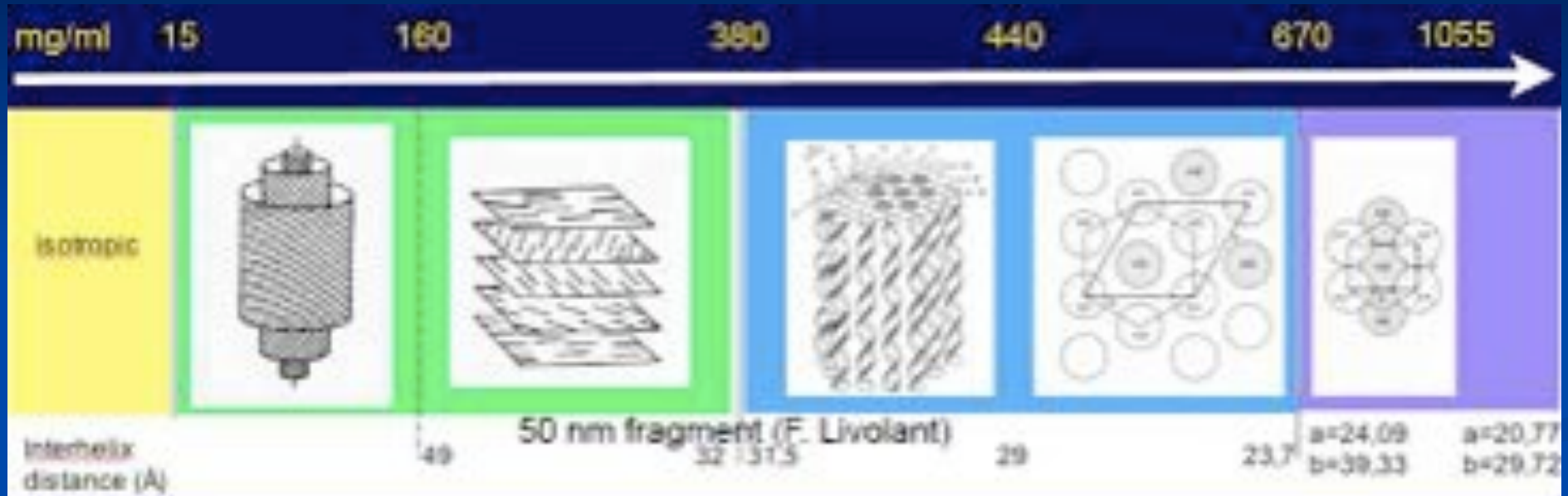
Configuration obtained with
“growth” simulations (kink-
jump dynamics)



What is the missing ingredient?

Dense phases of DNA segments

adapted from R. Podgornik, Taiwan lectures



blue phases

cholesteric

hexatic

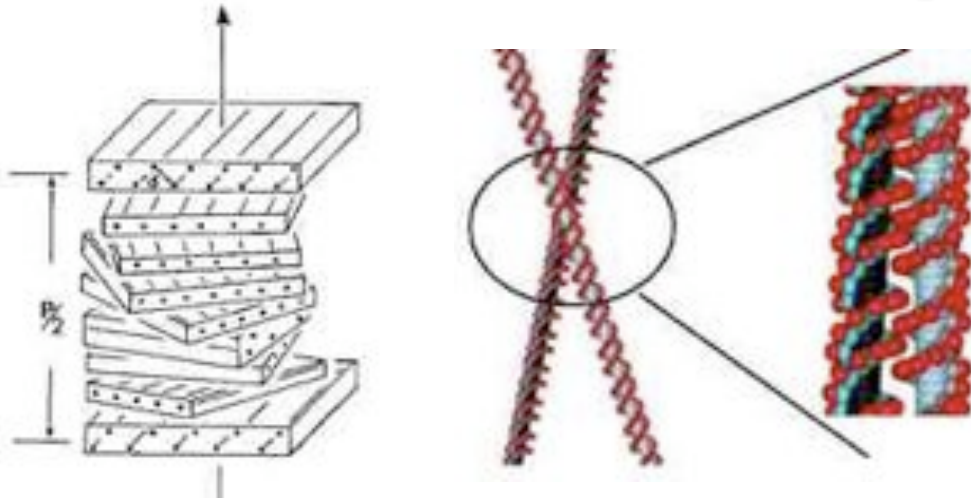
Pelta et al.
Biophys. J. 1996

Estimated P4 DNA density (packaging model of Purohit et al. PNAS 2003)

Full genome (10kb) : 270 mg/ml

Half-genome (4.7kb): 200 mg/ml

Cholesteric phases of DNA

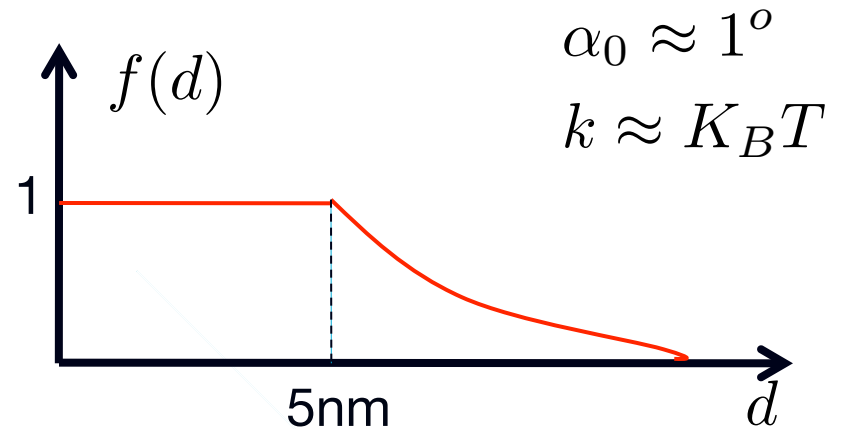
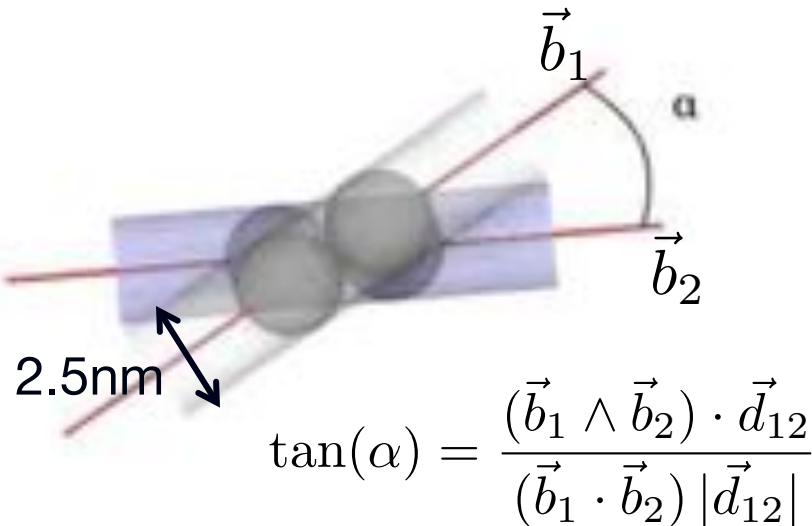


DNA strands form a preferential angle (steric hindrance + electrostatics)

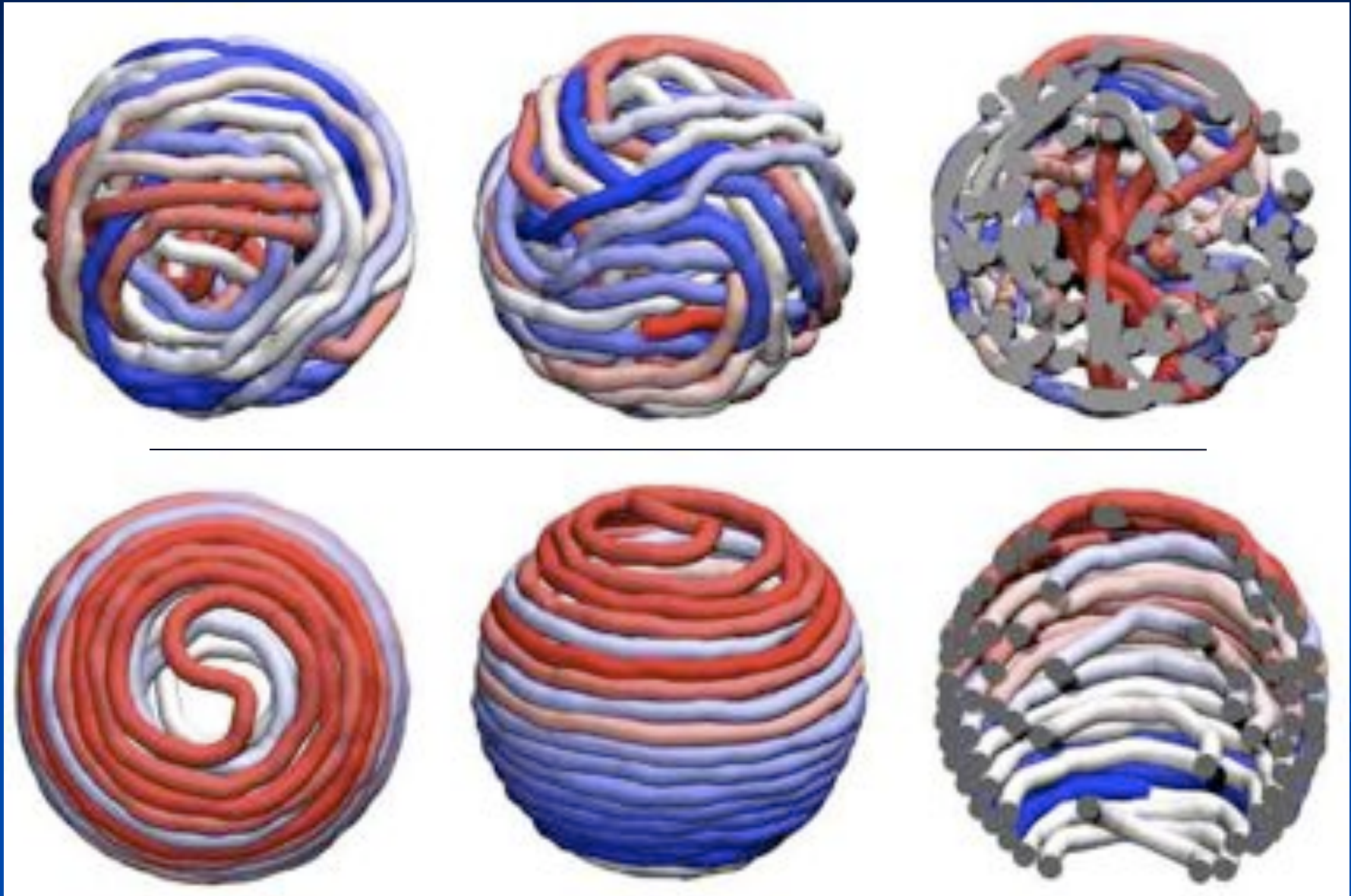
Leforestier et al. C. Rendu Chimie (2008)
Kornishev et al. Phys. Rev. Lett. 2007;
Ferrarini et al. J Chem. Phys (2005);

Introduce additional cholesteric potential (besides chain connectivity, bending energy and screened electrostatic interactions):

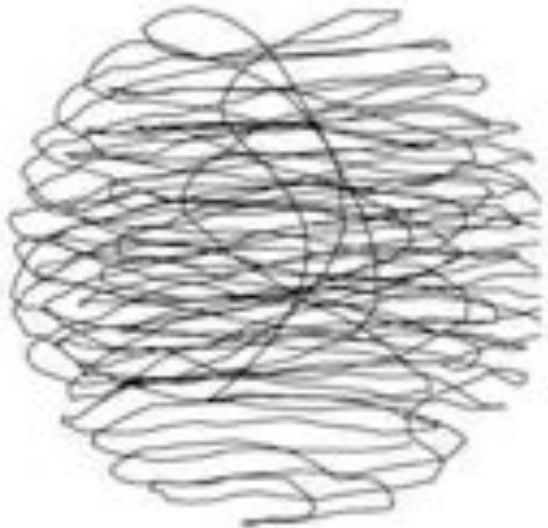
$$V = k(\alpha - \alpha_0)^2 f(d_{ij})$$



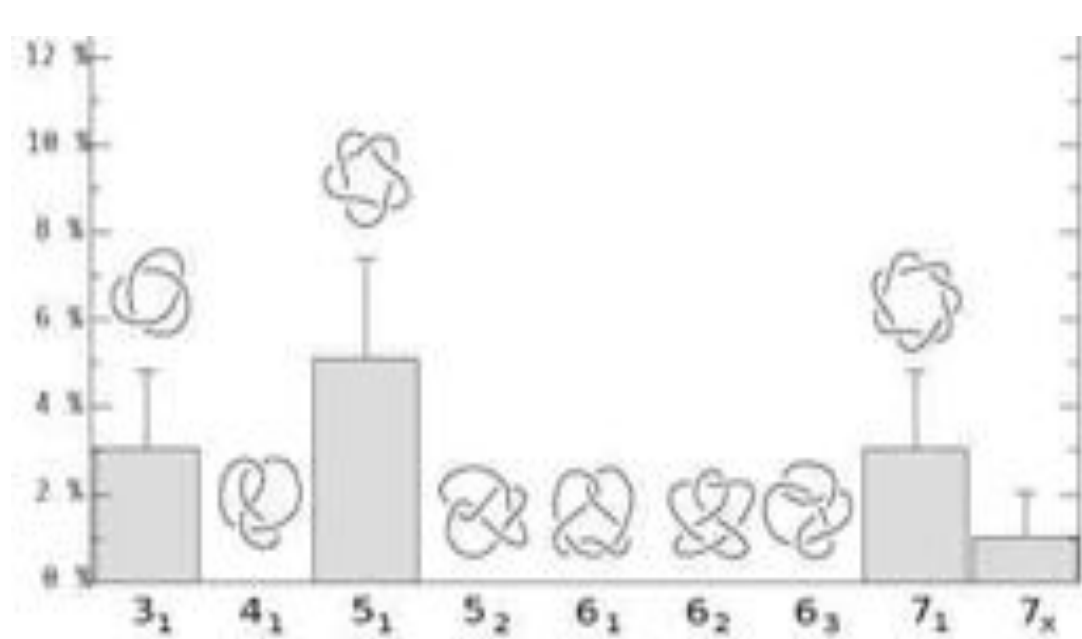
Ordering effect of the cholesteric potential



Ordering effect

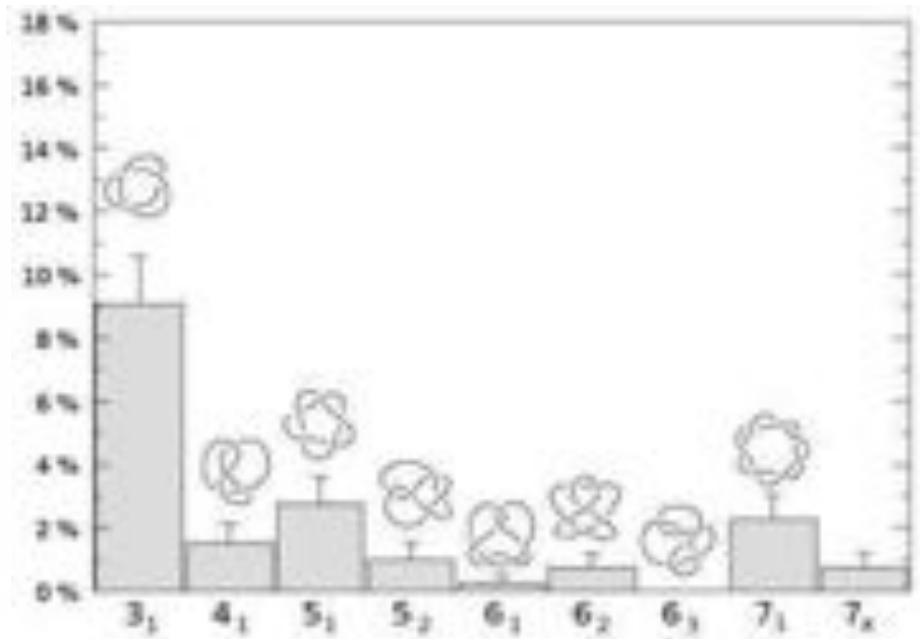


Knot spectrum (after circularization)



$$\alpha_0 = 1^\circ$$

$$k = 2 K_B T$$

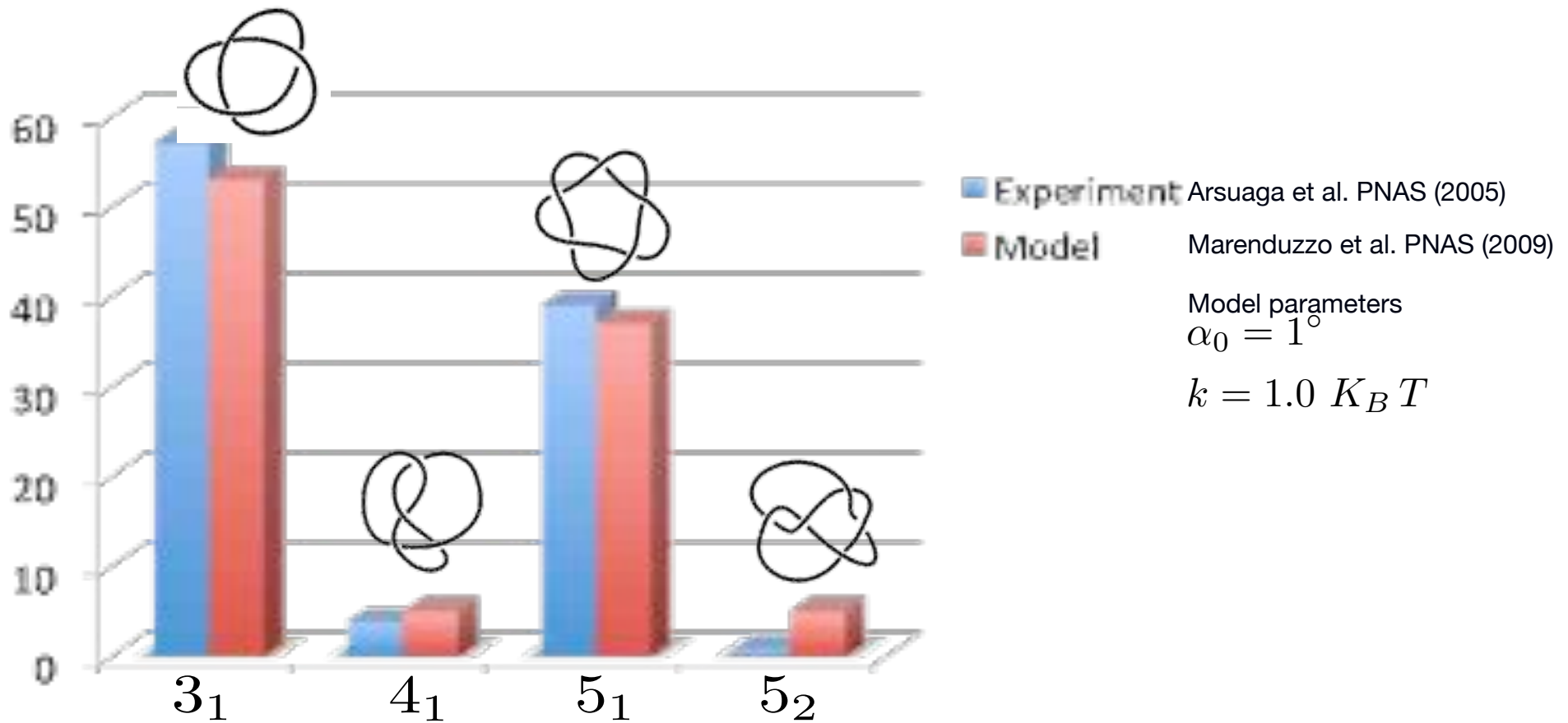


$$\alpha_0 = 10^\circ$$

$$k = 1.0 K_B T$$

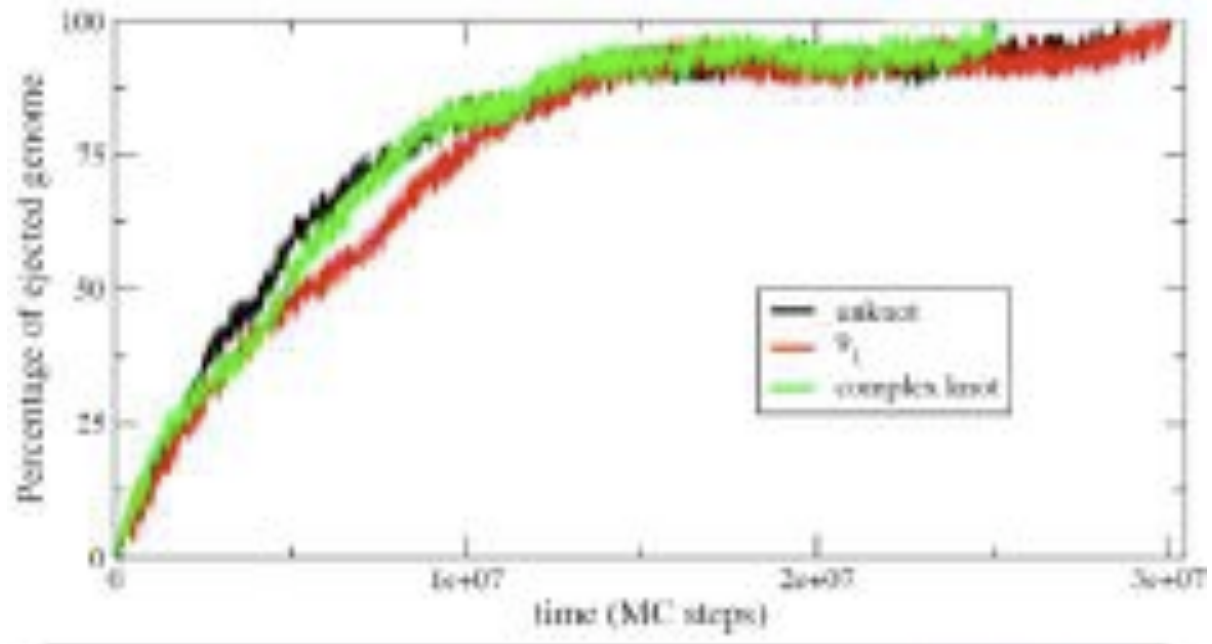
Bias towards torus and chiral knots over a good range of parameters

Potential strength tuned to reproduce experimental data on full P4 genome



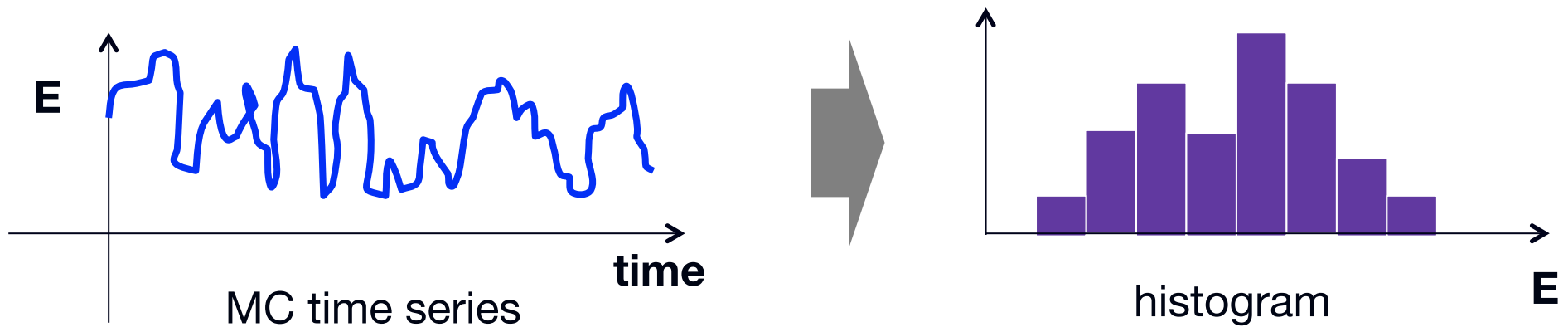
Knots are delocalised; on average they occupy 60% of the chain.

Ejection of entangled DNA



... and one more thing: thermodynamic reweighting

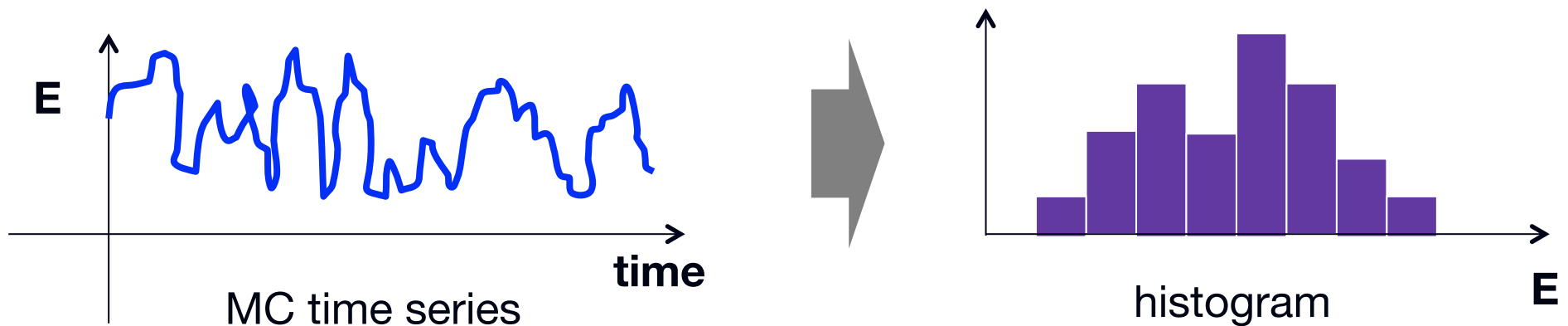
MC simulations at a given temperature can give us equilibrium properties at different (nearby) temperatures!



The height of the i th bin is proportional to:

... and one more thing: thermodynamic reweighting

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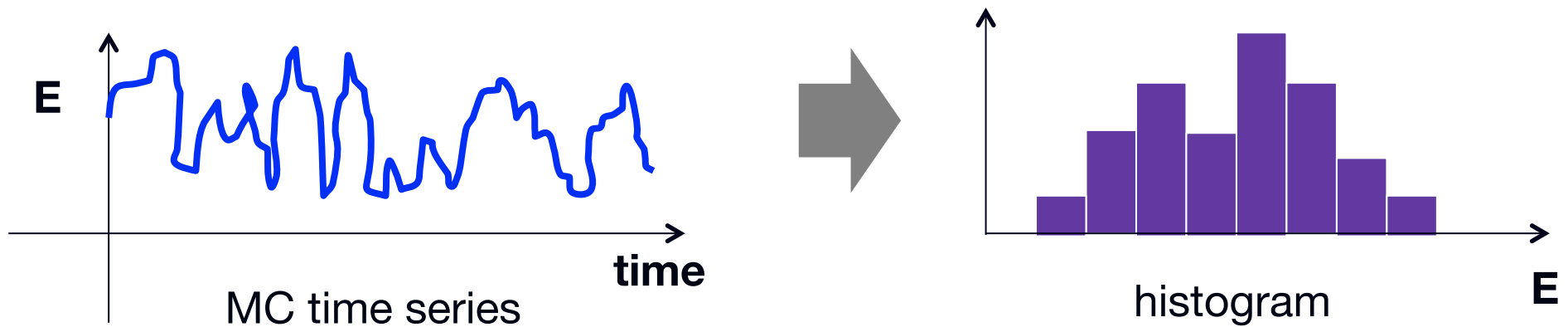
The height of the i th bin is proportional to:

- N , the total number of MC snapshots
- $\exp(-E_i/T)$, the canonical weight
- W_i , The number of microstates with energy E_i

$$h_i \propto N W_i e^{-E_i/T}$$

... and one more thing: thermodynamic reweighting

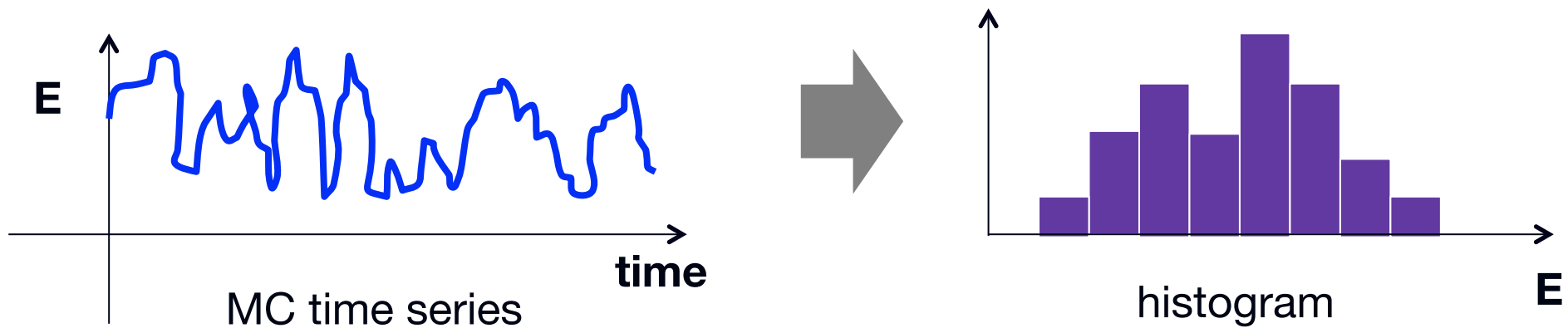
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$$W_i \propto \frac{h_i}{N} e^{+E_i/T}$$

... and one more thing: thermodynamic reweighting

MC simulations at a given temperature can give us equilibrium properties at different (nearby) temperatures!



$$\langle E(T') \rangle = \frac{\sum_i E_i W_i e^{-E_i/T'}}{\sum_i W_i e^{-E_i/T'}} \quad \leftarrow \quad W_i \propto \frac{h_i}{N} e^{+E_i/T}$$

Summary

- Monte Carlo as a general tool to characterize equilibrium properties of systems
- Advanced sampling techniques: Parallel tempering
- Thermodynamic Reweighting techniques

Application to a challenging system: densely packed DNA

Useful references (based on my own taste...):

- Itzykson & Drouffe, Statistical field theory
- Newman and Barkema, Monte Carlo methods in Statistical Physics
- K. Binder, Lecture notes of Varenna summer school
- + material available at <http://people.sissa.it/~michelet/Lund>

Acknowledgements

- Pietro Faccioli (UniTN)
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- Ken Millett (UCSB)
- Enzo Orlandini (Padova)
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- Luca Tubiana (SISSA)
- Javier Arsuaga
- Giovanni Dietler
- Eric Rawdon
- Ngo Mihn Toan



The Abdus Salam
International Centre for Theoretical Physics



Workshop on Physical Virology
(24 - 28 September 2012)
Trieste - Trieste, Italy

The Abdus Salam International Centre for Theoretical Physics (ICTP, Trieste, Italy) is organizing a Workshop on Physical Virology to hold in the ICTP from 24 - 28 September 2012.

DESCRIPTION:

The workshop on Virology and polymerase will discuss the fundamental questions that address a high efficiency of their replication cycle by harnessing various genetic and/or physical mechanisms.

The Workshop aims at gathering researchers from different disciplines to discuss the recent theoretical and experimental advancements on the character of these physical mechanisms, particularly those with a technical bias.

The main topics will be:

1. self-assembly and organization of viral capsids
2. packaging and ejection of the viral genome from the capsid
3. interaction between the host DNA/RNA and viral coat proteins
4. virus based nanocomposites
5. genome based modelling of epidemic outbreaks

PARTICIPATION: Scientists and students from all countries that are members of the United Nations Organization (UN) are invited. As the Workshop will be conducted in English, participants should have an adequate working knowledge of this language. Although the main purpose of the Centre is to help research workers from developing countries through a programme of training activities within a framework of international cooperation, a limited number of research and post-graduate students from developing countries are also welcome to attend.

An air fare, travel and subsistence allowance of the participants should be borne by their home institutions. Travel will be provided to study by candidates to receive support for their fees. There are very limited funds available for partial support of some participants who are students of, and working in, a developing country and who are not more than 40 years old. Such support is available only to those who attend the entire Workshop. There is no registration fee for attending this workshop.



ORGANIZERS:

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Giuseppe LORIANI
ICTP & University Bicocca, Milan, Italy

Cinzia MICHIELLI
ICTP, Trieste, Italy

Wahid PERKUMBEK
University of Jember, Indonesia

LOCAL ORGANISER:

Matteo MARINI
ICTP, Trieste, Italy

INVITED SPEAKERS/CALLERS:

- Shantanu ADATI (ICTP, Trieste)
- Enrique ORSINI (ICTP, Trieste)
- Paul STELLINGSMA (ICTP, Trieste)
- Alex STREBLOVICH (ICTP, Trieste)
- Walter PONDANI (ICTP, Trieste)
- Flavia DE PISTIS (ICTP, Trieste)
- ANDREW HART (ICTP, Trieste)
- Thomas HANSEN (ICTP, Trieste)

ICTP Workshop on Physical Virology

Application deadline:

June 20