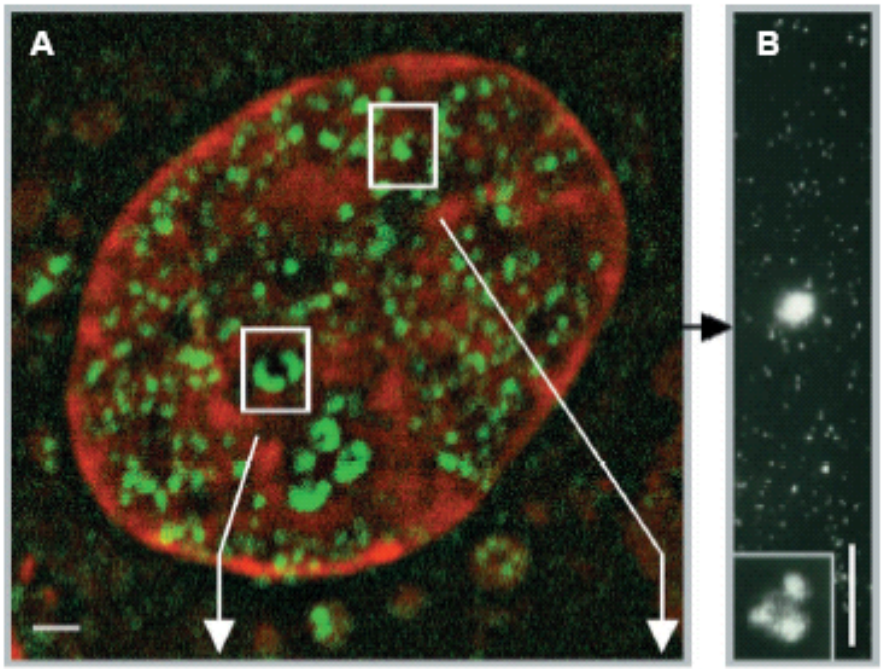
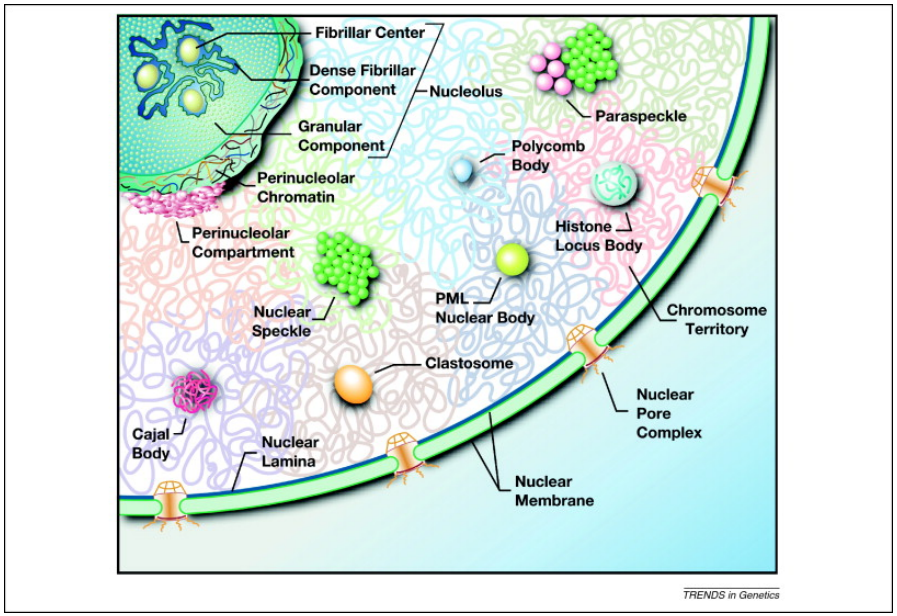
Meet the School of Physics

Coarse grained molecular dynamics simulations





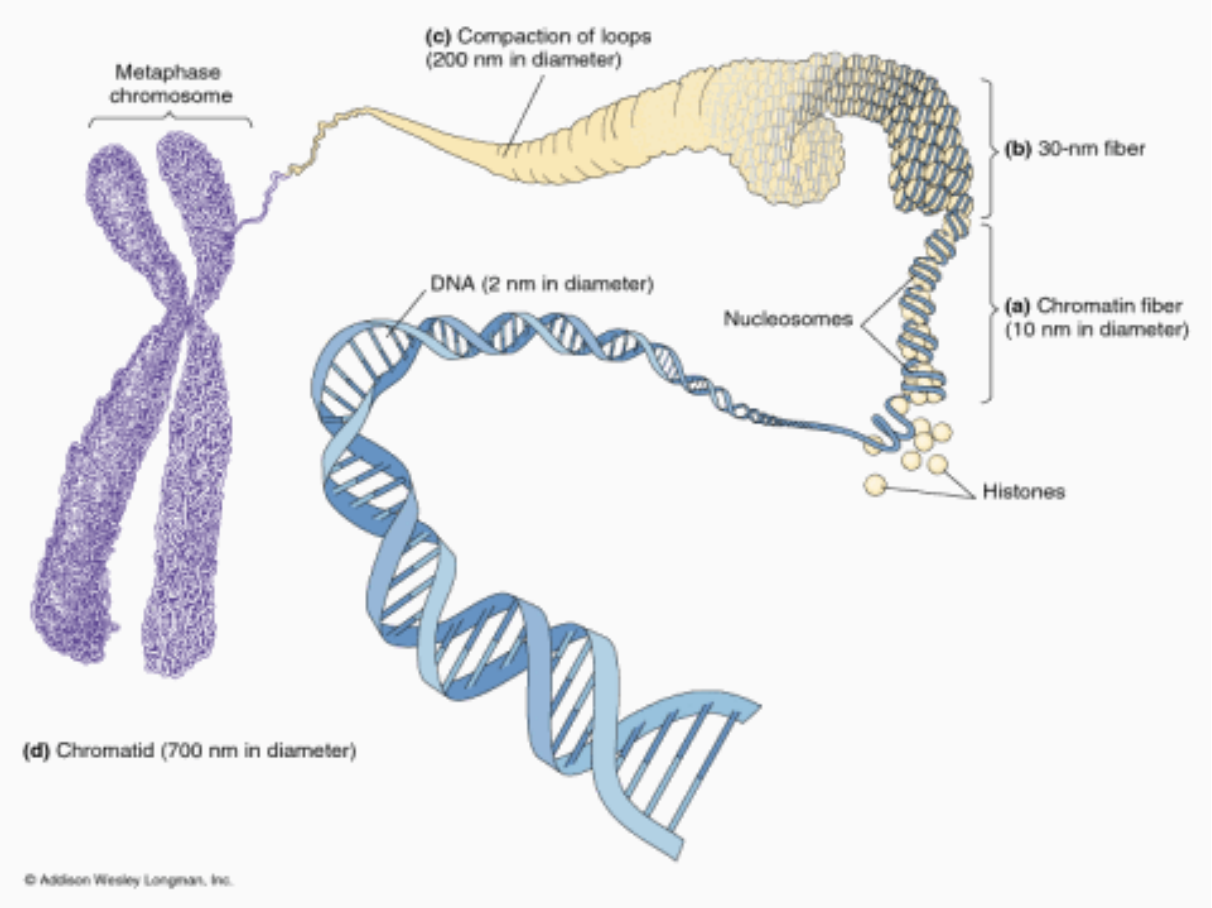
D. Marenduzzo, Edinburgh, May 2017

DNA Collaborators: C. A. Brackley, D. Michieletto, B. Liebchen,

J. Johnson, M. C. Pereira, Y. Fosado, A. Bentivoglio

MD Simulators in Physics: G. J. Ackland, M. Schor, C. MacPhee, R. J. Allen, B. Waclaw, G. Melaugh

Confinement and 3D chromosome organisation



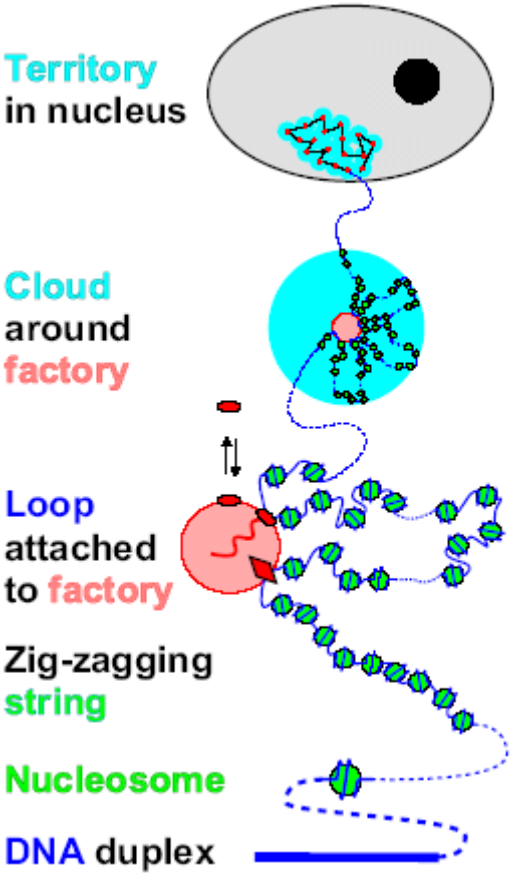
A eukaryotic nucleus (size 10 microns) contains about 2 m of DNA

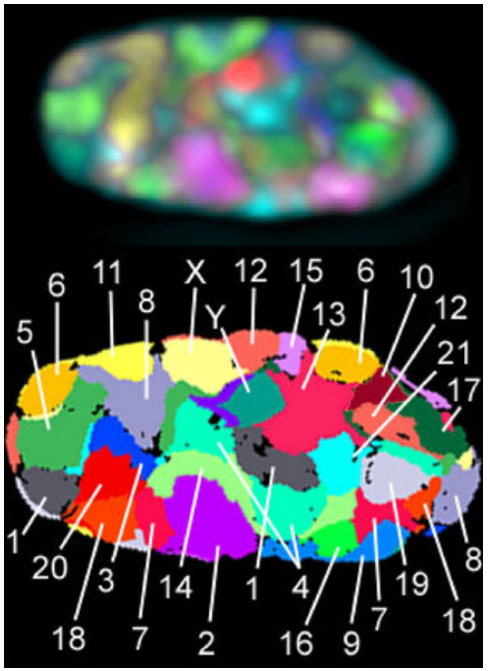
How does the cell solve this confinement problem?

First, DNA is wrapped around histones (size 10 nm) to form "chromatin"

Then, higher order compaction of the chromatin fiber is needed !

Proteins and chromosome organisation



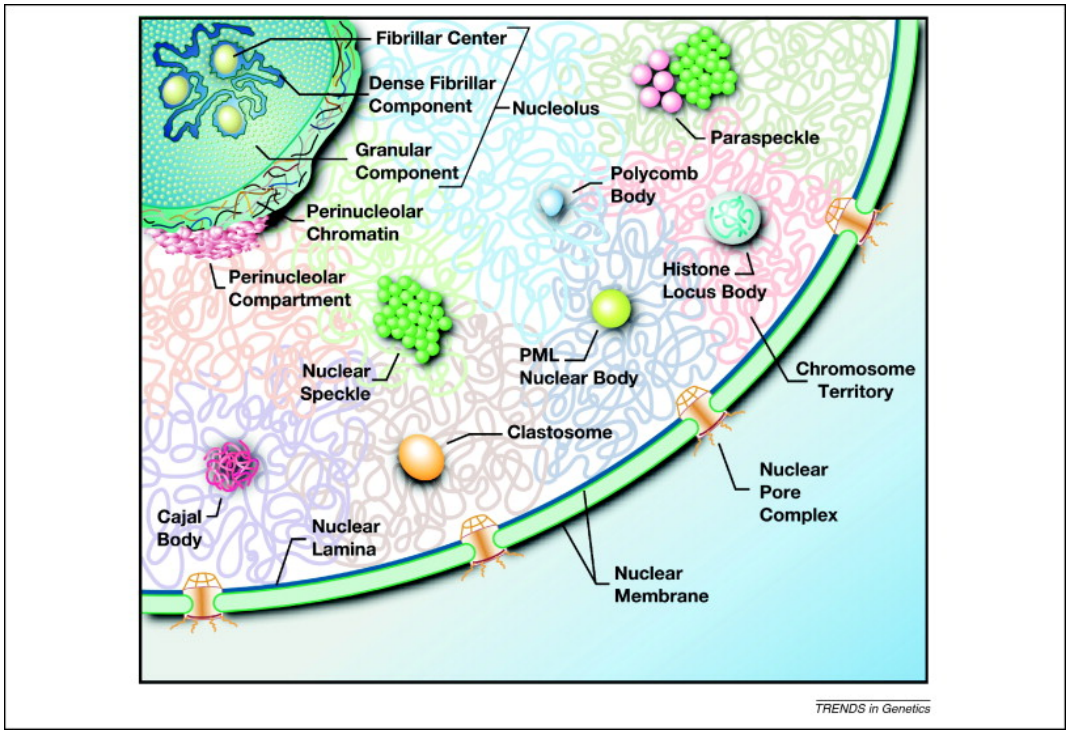


Higher order compaction is also likely achieved by proteins,

which act as **molecular bridges**

Examples are: HP1, CTCF, TFs-RNA Pol complex, etc.

3D protein organisation and nuclear bodies

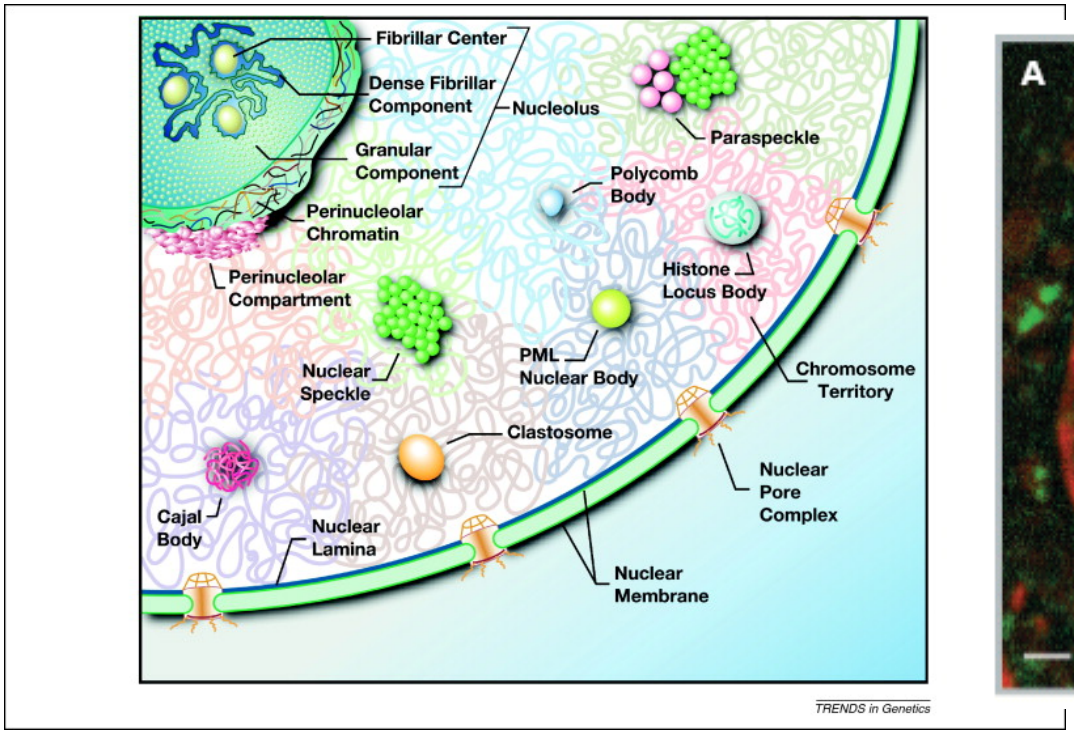


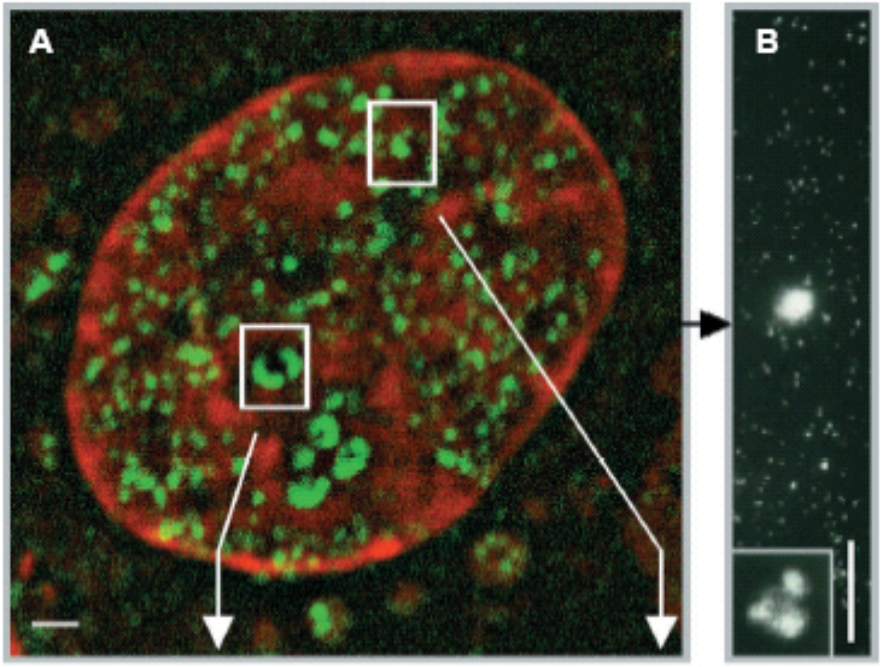
Nuclear proteins are also not organised randomly

They often cluster to form "nuclear bodies"

Examples are nucleoli, Cajal, polycomb and promyelocytic bodies

3D protein organisation and nuclear bodies





Nuclear proteins are also not organised randomly

They often cluster to form "nuclear bodies" (size 0.1-2 microns)

Examples are nucleoli, Cajal, polycomb and promyelocytic bodies

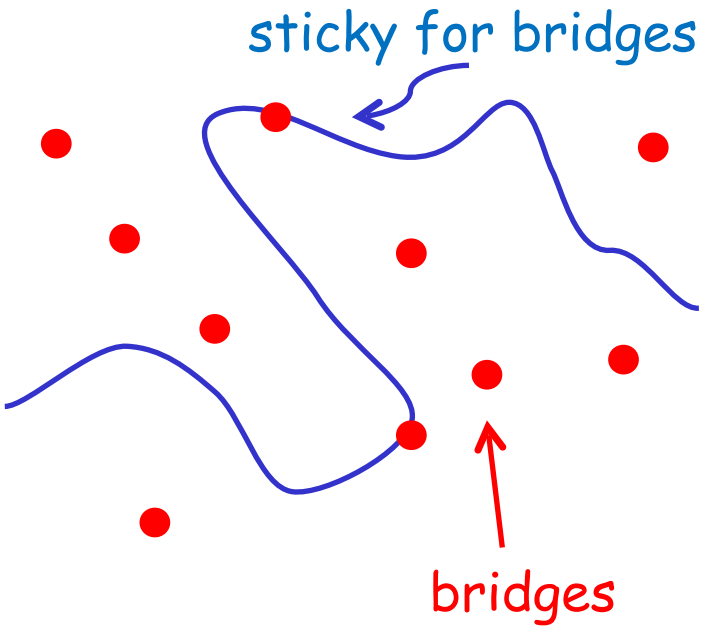
Polymerases also cluster in "transcription factories"

What happens when we consider

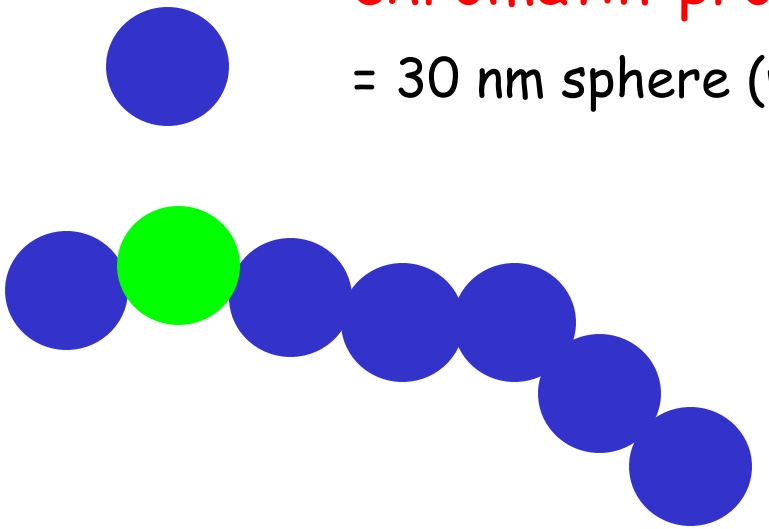
many proteins interacting with DNA?

Start with **non-mutually interacting**

proteins binding **non-specifically** to DNA



How can we set up an MD simulation of chromatin-protein systems ?



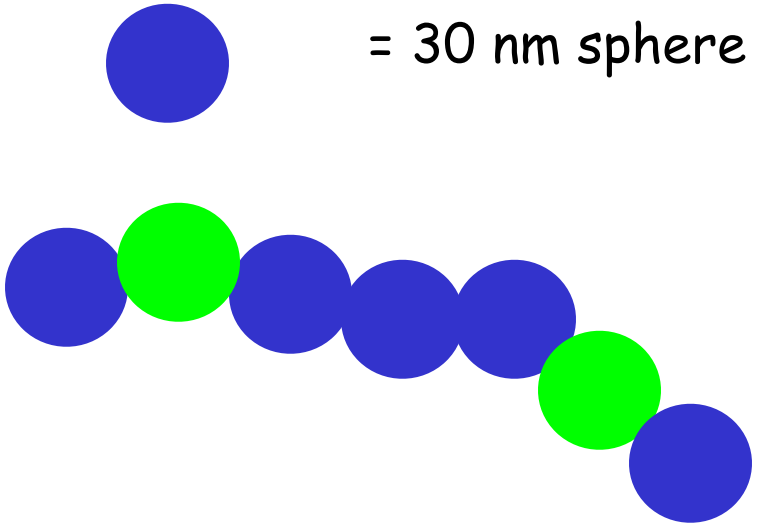
= 30 nm sphere (width of chromatin fibre)

Many "monomers" make up the chromatin; each of these satisfies a Langevin equation

$$m\frac{d^2\mathbf{x}_i}{dt^2} = -\nabla_i V - \gamma\frac{d\mathbf{x}_i}{dt} + \sqrt{2k_B T\gamma}\,\boldsymbol{\eta}(t)$$

$$\langle \boldsymbol{\eta}(t) \rangle = 0 \;;\; \langle \eta_\alpha(t)\eta_\beta(t') \rangle = \delta_{\alpha\beta}\delta(t-t')$$

$$D = \frac{k_B T}{\gamma} \quad \text{(Fluctuation - Dissipation Theorem)}$$



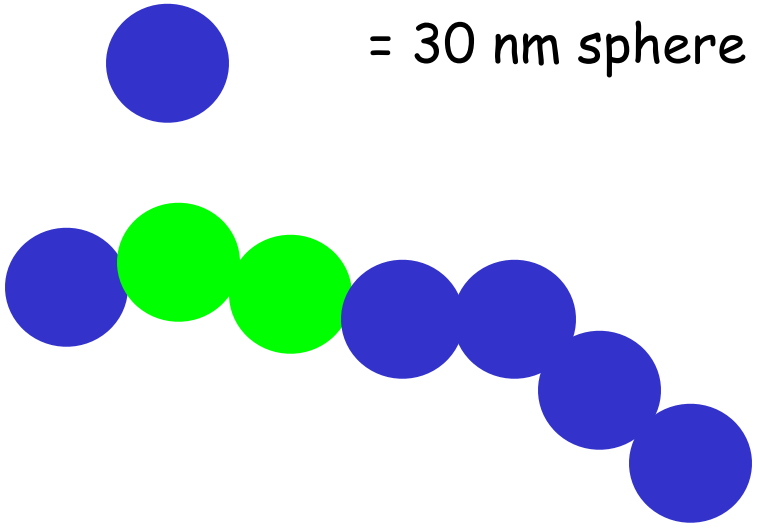
= 30 nm sphere (width of chromatin fibre)

Any two monomers

interact with steric repulsion

(e.g. truncated-shifted LJ)

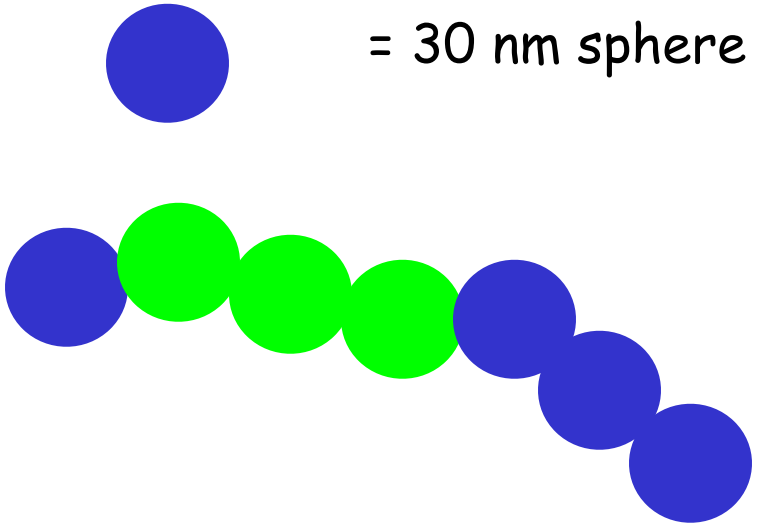
$$V_{LJ}(r_{ij}) = \begin{cases} 4\varepsilon\left[\left(\frac{\sigma}{r_{ij}}\right)^{12} - \left(\frac{\sigma}{r_{ij}}\right)^{6}\right] + \varepsilon & \text{if } r_{ij} < 2^{1/6}\sigma \\ 0 & \text{otherwise} \end{cases}$$



= 30 nm sphere (width of chromatin fibre)

Two neighbouring monomers also interact through a bonding potential (e.g. FENE)

$$V_{\mathrm{FENE}}\left(r = \left|\mathbf{r_{i+1}} - \mathbf{r_i}\right|\right) = -\frac{K_{FENE} R_0^{\,2}}{2} \log\left[1 - \left(\frac{r}{R_0}\right)^2\right]$$

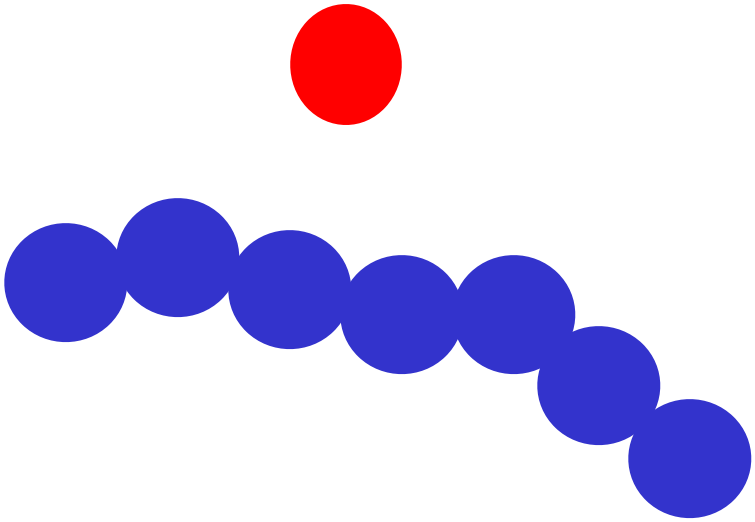


= 30 nm sphere (width of chromatin fibre)

Two neighbouring links feel a bending rigidity potential (e.g. Kratky-Porod, persistence length 40-200 nm)

$$V_{\text{bending}}(\theta = a\cos(\mathbf{t}_i \cdot \mathbf{t}_{i+1})) = K_b(1 - \cos(\theta))$$

$$K_b = k_B T \frac{l_p}{\sigma}$$

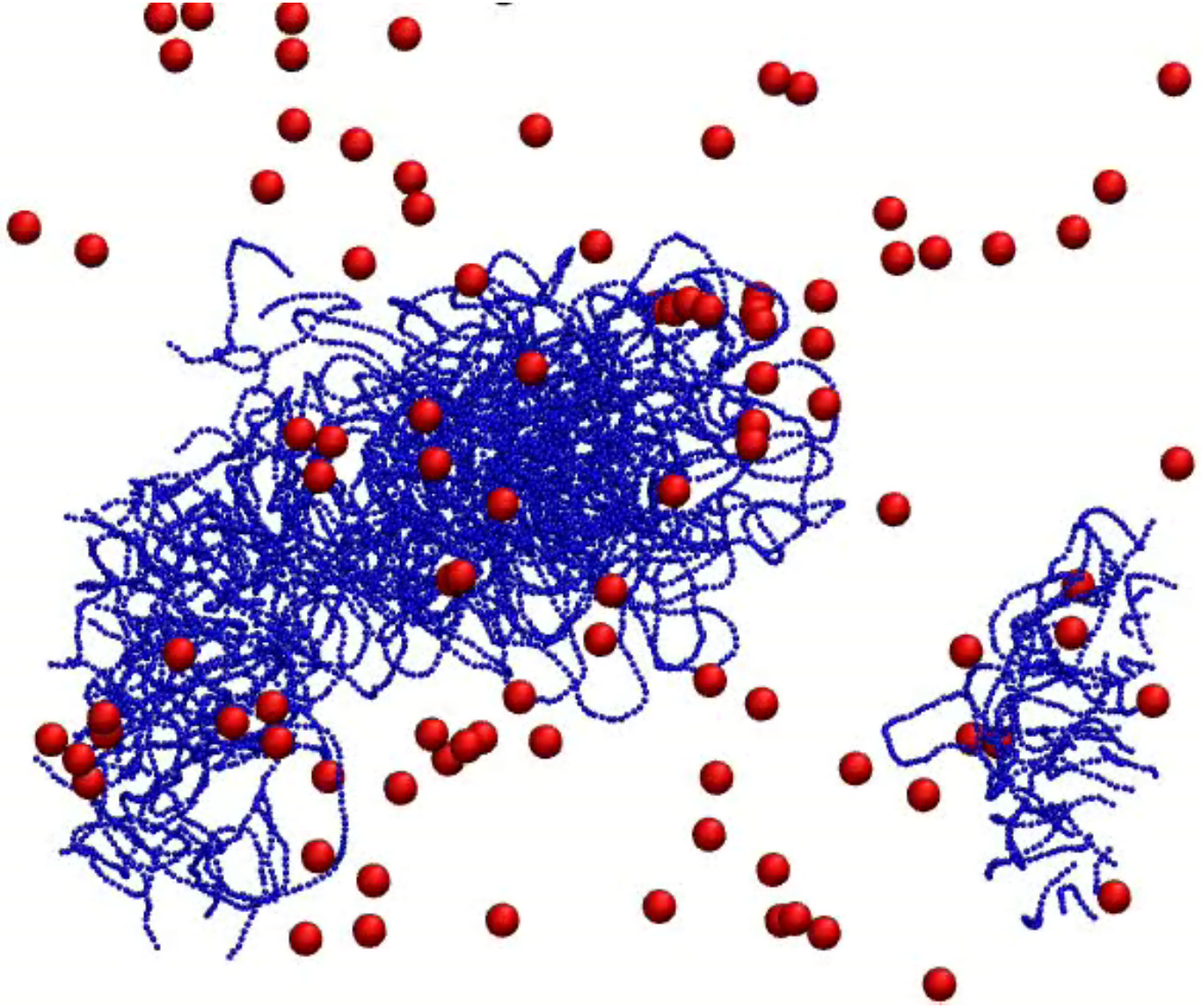


Protein modelled as a sticky sphere

via a chromatin:protein
Lennard-Jones potential

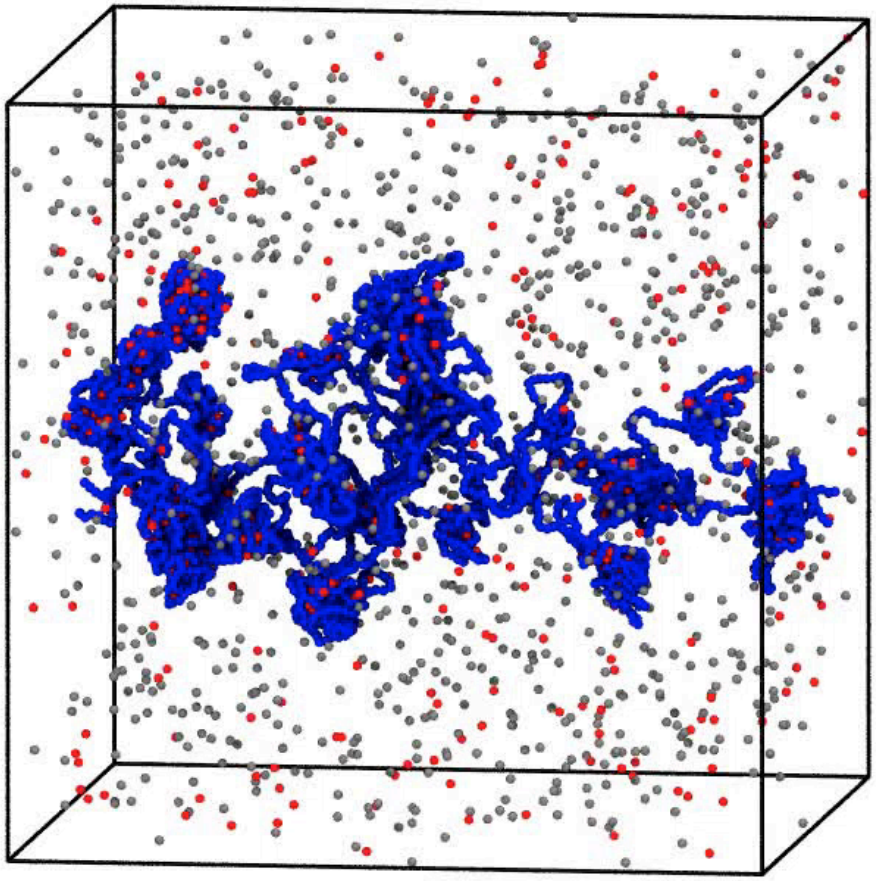
whereas chromatin:chromatin
and protein:protein
interactions are repulsive (steric repulsion)

$$V_{LJ}^{ab}(r_{ij}) = \begin{cases} 4\varepsilon_{ab}\left[\left(\frac{\sigma_{ab}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ab}}{r_{ij}}\right)^{6} - \left(\frac{\sigma_{ab}}{r_{thr}}\right)^{12} + \left(\frac{\sigma_{ab}}{r_{thr}}\right)^{6}\right] & \text{if } r_{ij} < r_{thr} \\ 0 & \text{otherwise} \end{cases}$$



Proteins cluster due to a 'bridging-induced' positive feedback:

proteins bridge the DNA, local DNA concentration increases, more bridges bind, etc.



This thermodynamic 'bridging-induced attraction' provides a simple model for the biogenesis of a model nuclear body.

In the simplest version, clusters coarsen

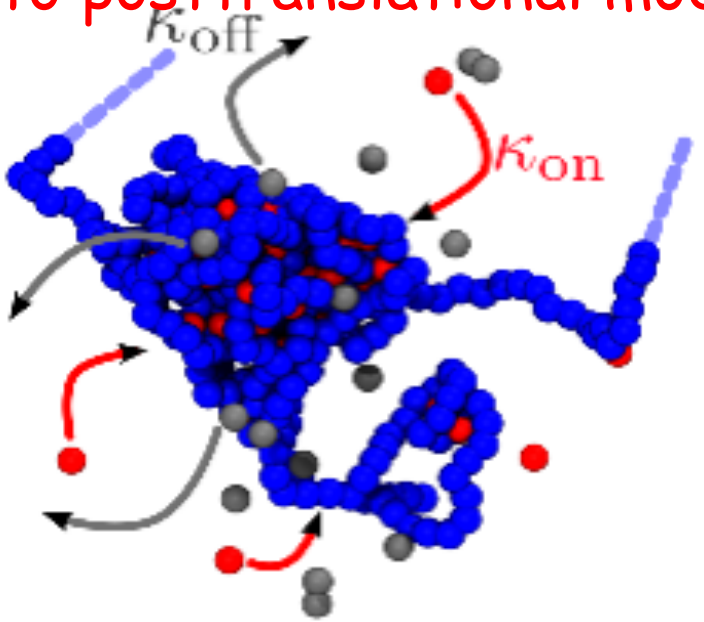
Consider again non-interacting bridges

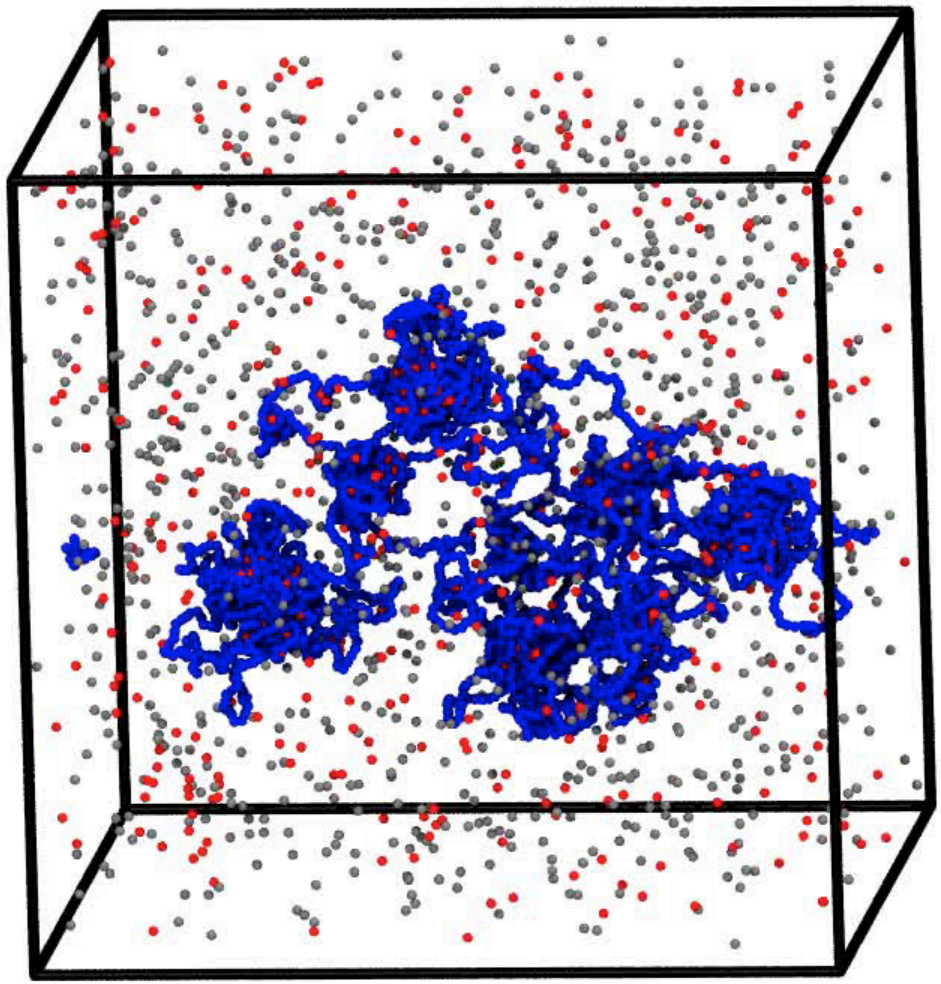
binding non-specifically to DNA,

but where now bridges can 'switch'

between binding and non-binding

(e.g. due to posttranslational modifications)





Now the clusters/nuclear bodies which form do not coarsen indefinitely

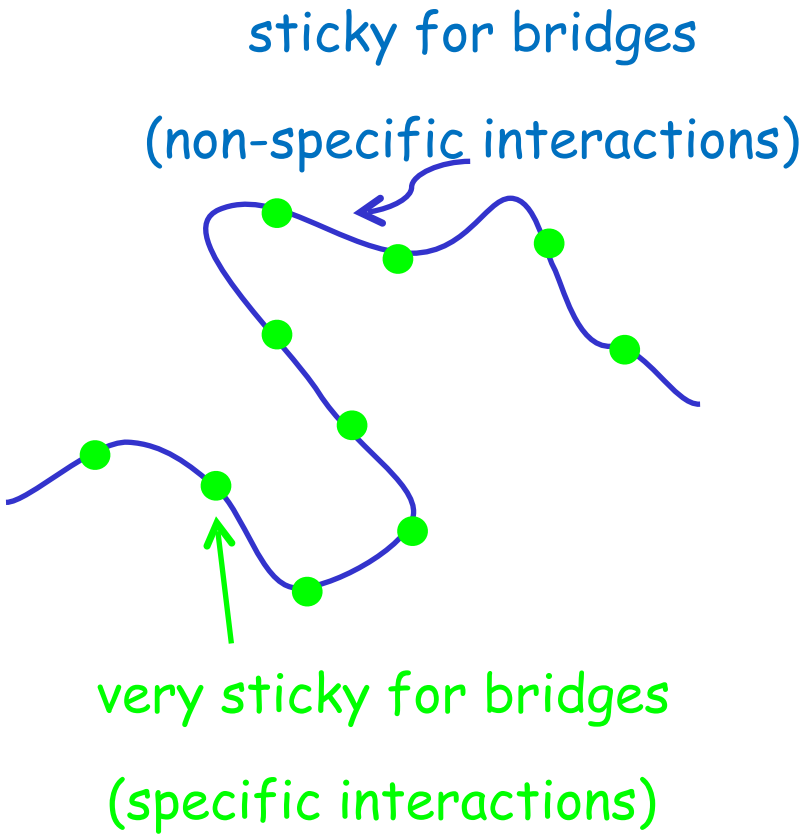
and the cluster size in steady state can be controlled by reaction rates

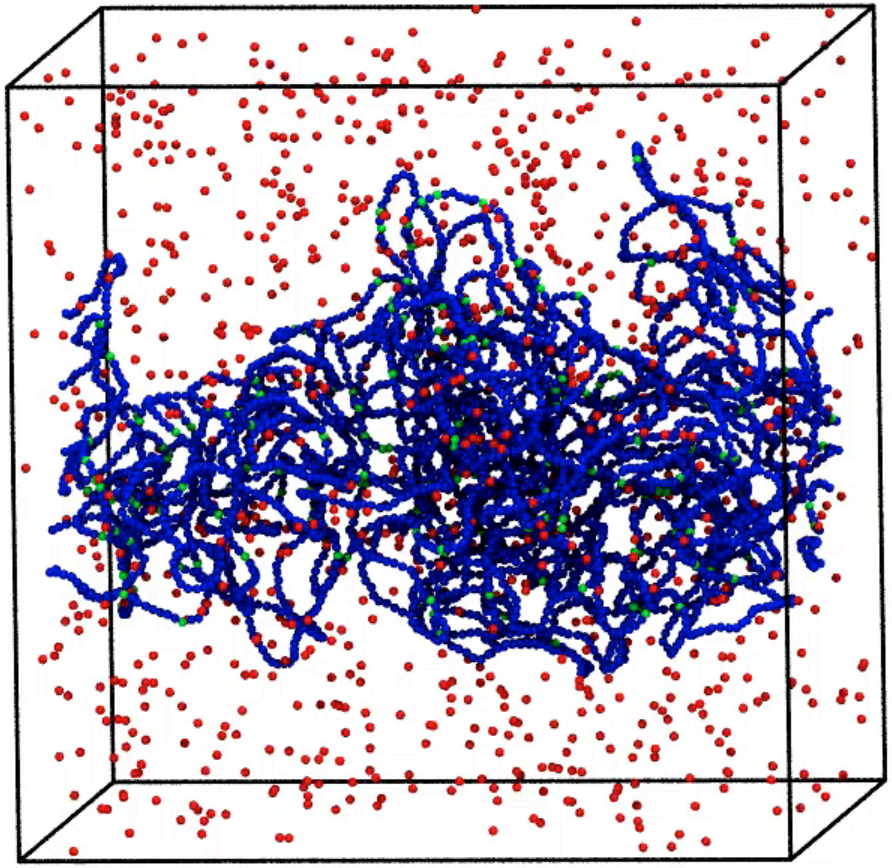
Brackley Lieberman Michieletto Mouvet Cook Marenduzzo, Biophys J (2017)

Let us now consider what happens when bridges can bind in two modes:

non-specific (low affinity) and specific (high affinity)

This is typical for most DNA-binding proteins (e.g. RNA Polymerase)



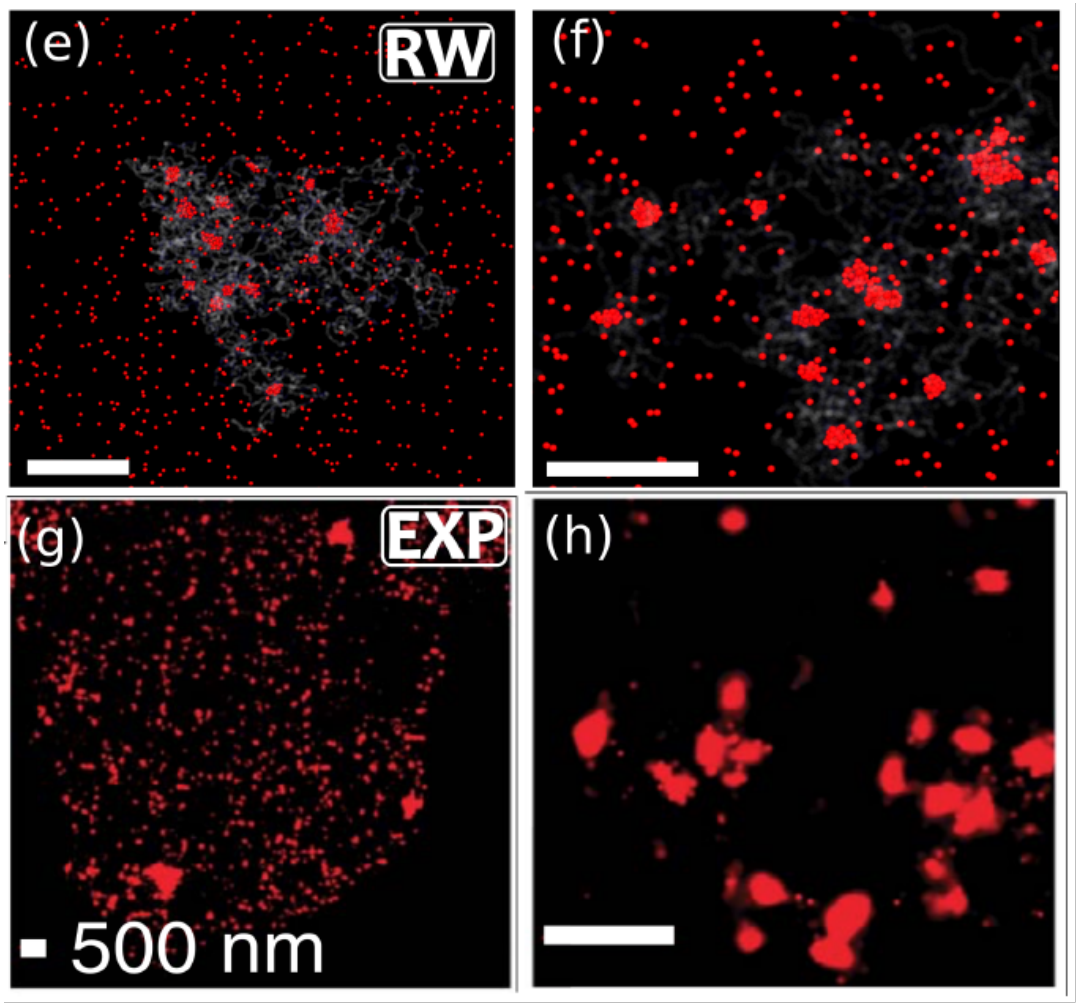


Now the clusters forming due to the 'briding-induced attraction'

reach a limiting size even if bridges are in thermal equilibrium

This is because clusters create loops, and these keep clusters apart

An application: polycomb bodies in Drosophila

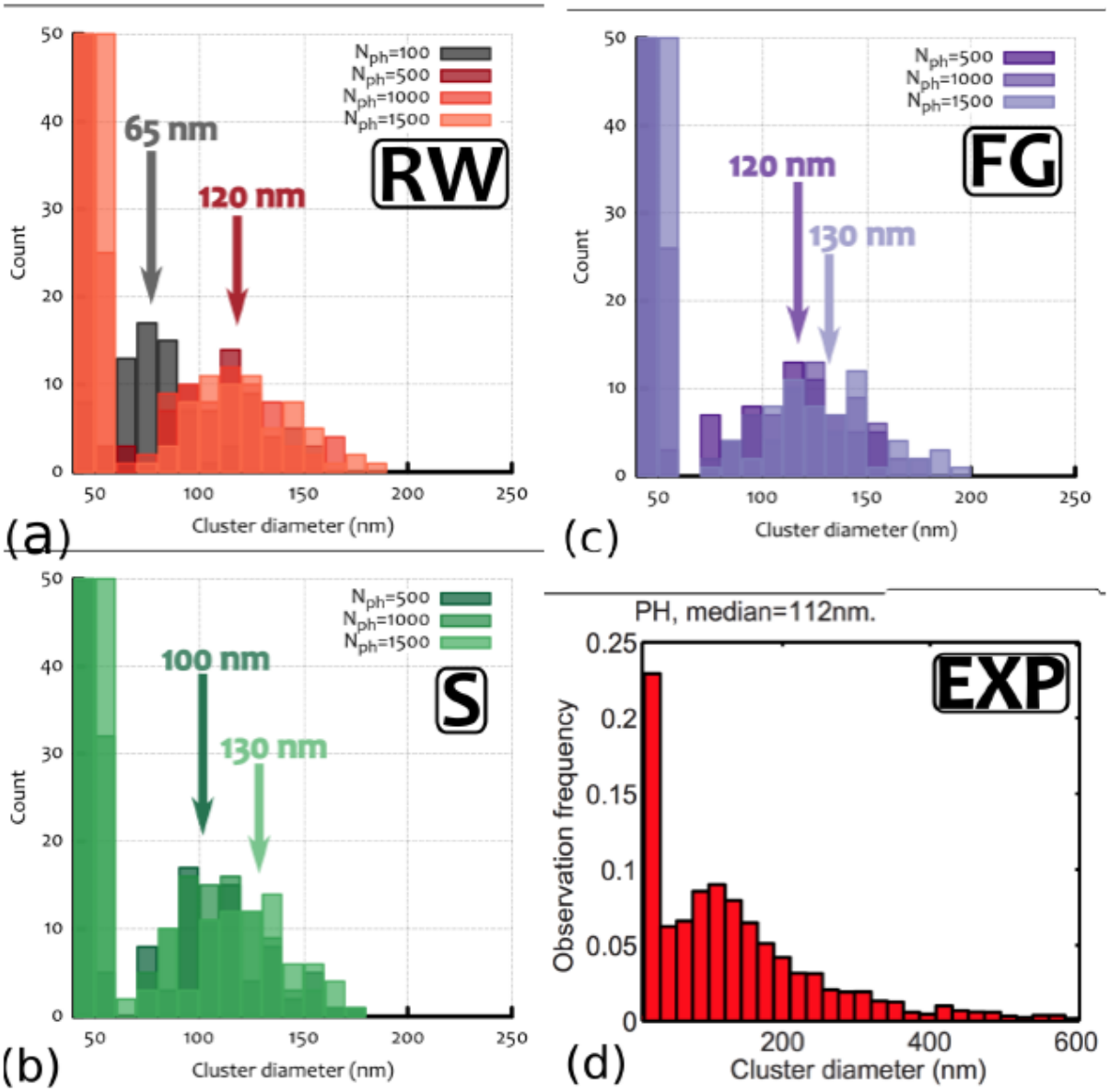


Non-specific and specific binding sites for polycomb bridges (PH)

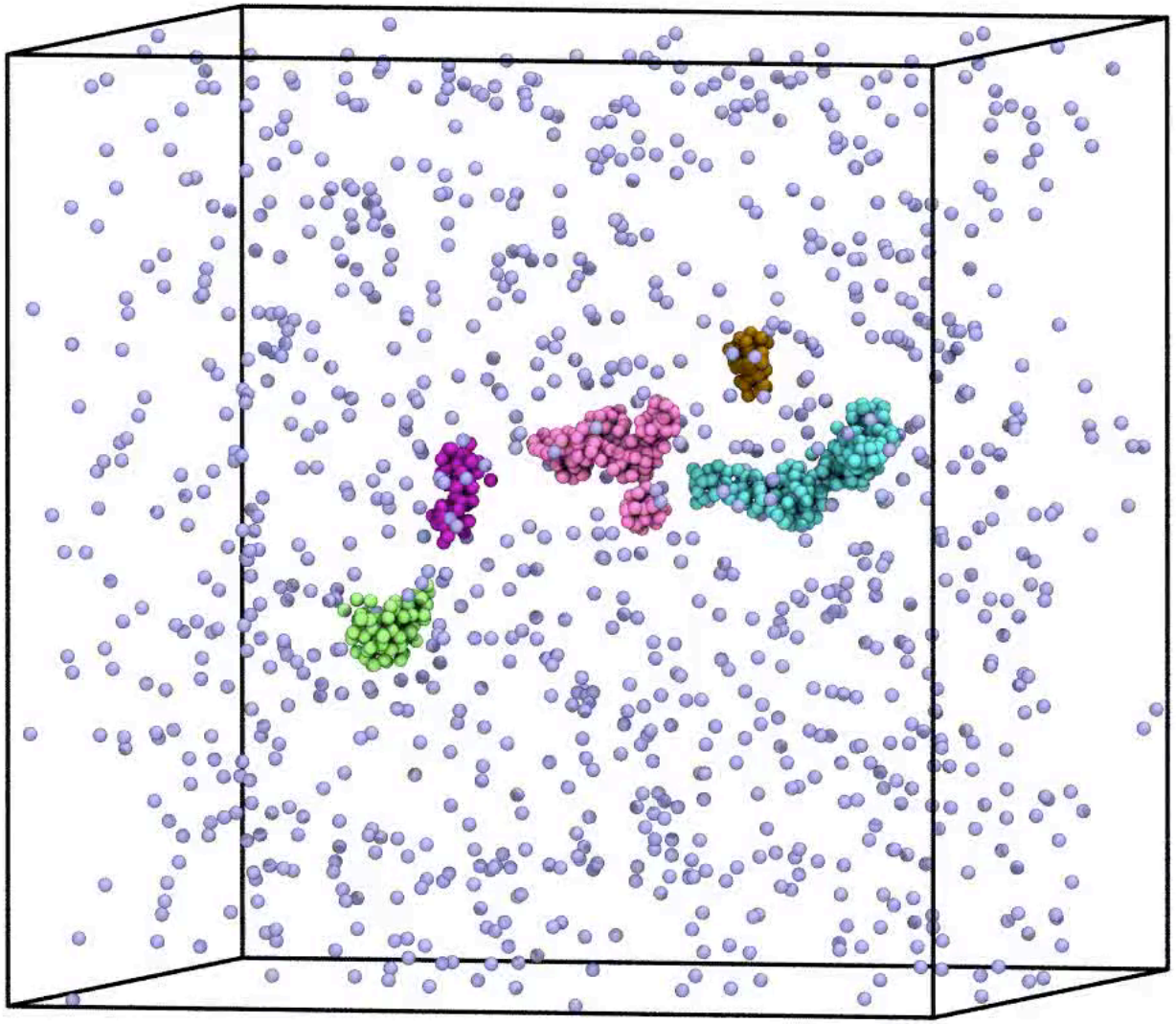
were selected on the basis of (chromosome immunoprecipitation) experiments

The PH clusters formed in simulations (e,f)

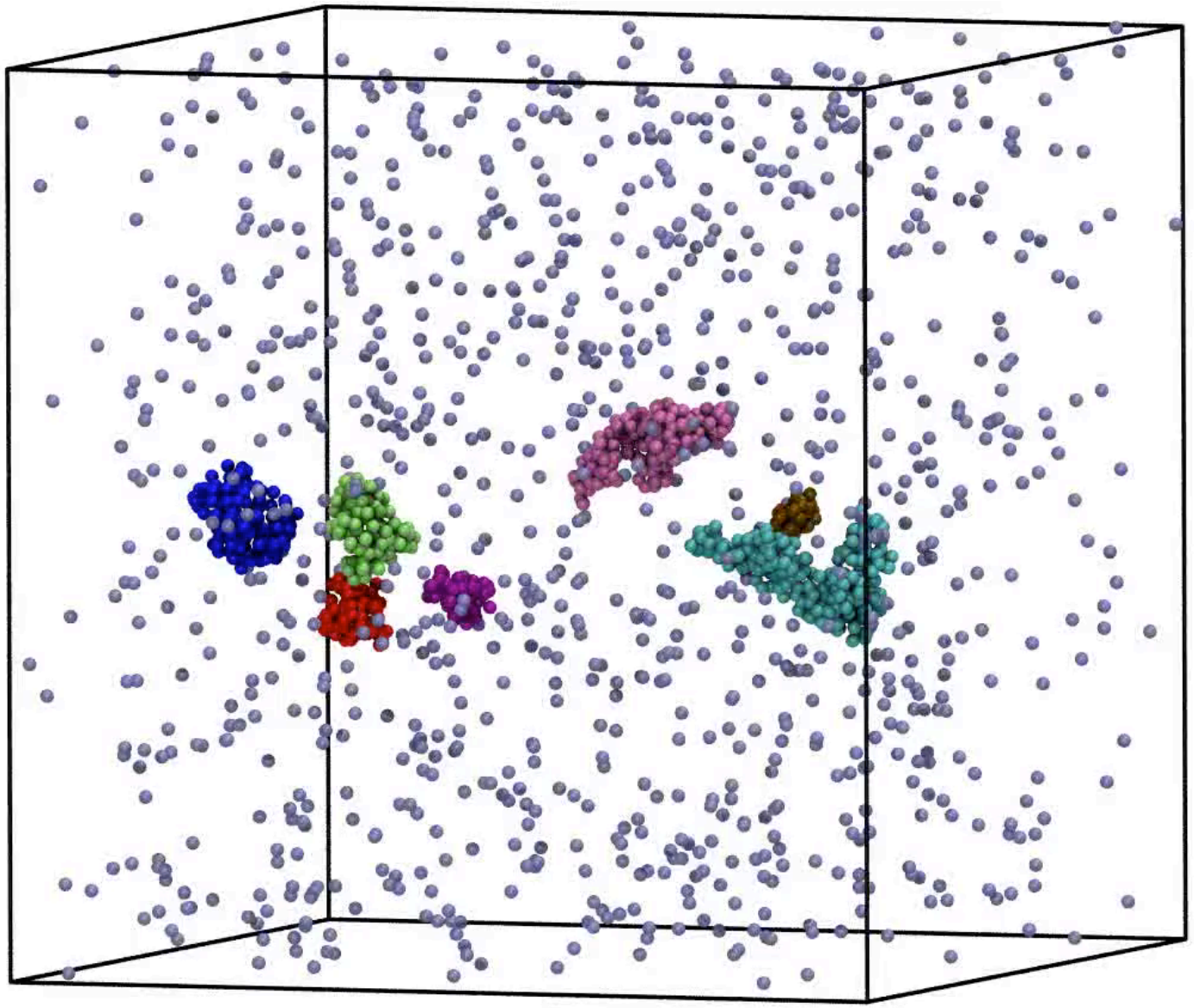
resemble polycomb bodies found via STORM microscopy (g,h)



The cluster size distribution found in simulations with different initial conditions matches well the experimental one

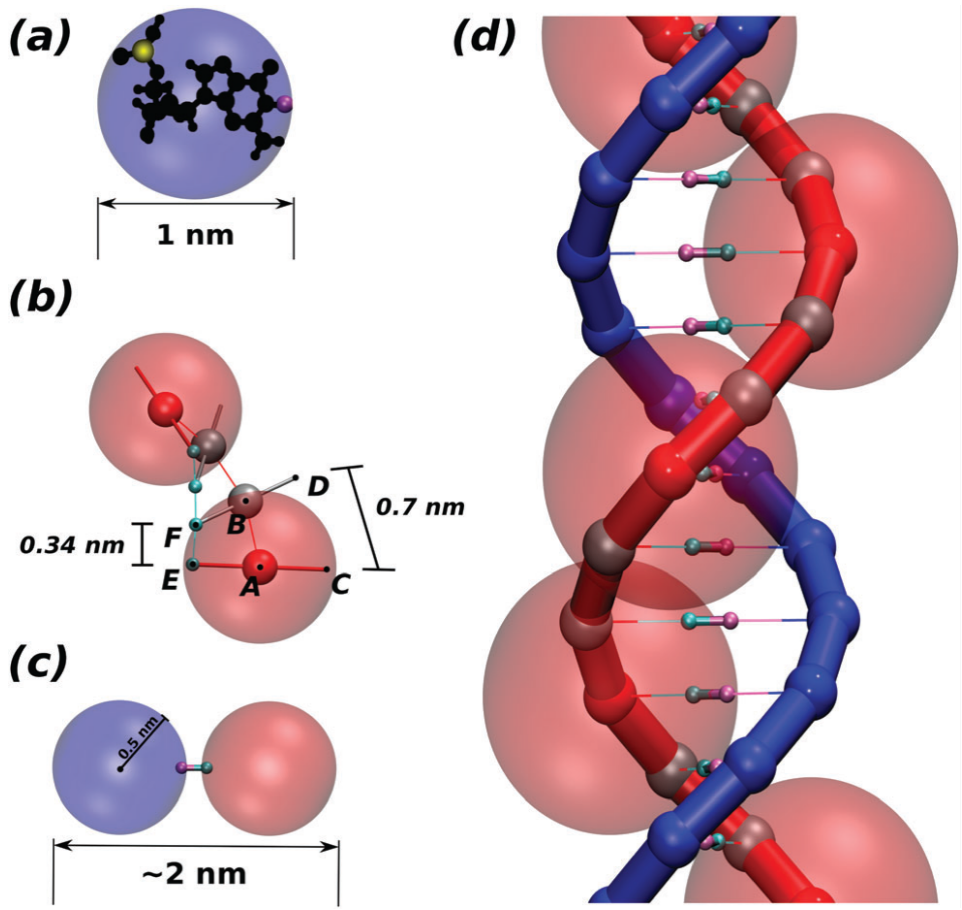


There is a problem though: the clusters formed in this way are static, while photobleaching finds highly dynamic clusters (fast FRAP recovery)



Considering switching (rather than thermodynamic) bridges,

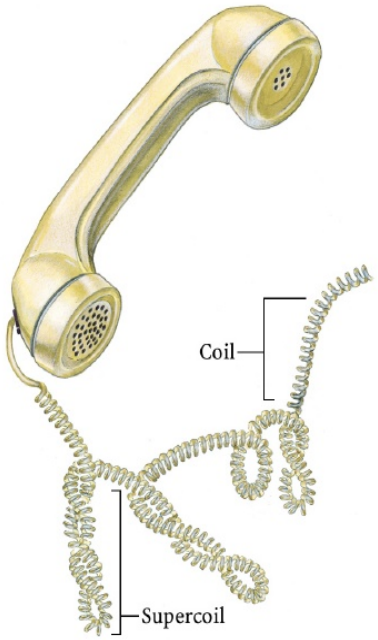
clusters are instead dynamic and continuously recycle their components

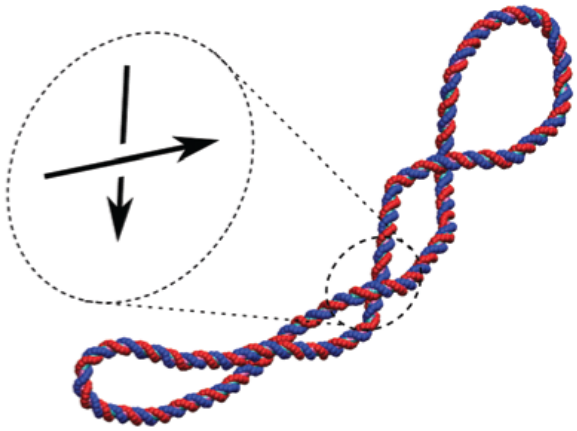


Coarse grained MD of DNA can be also made at much smaller resolution

(here there are two beads for each base in the DNA)

Yair Fosado





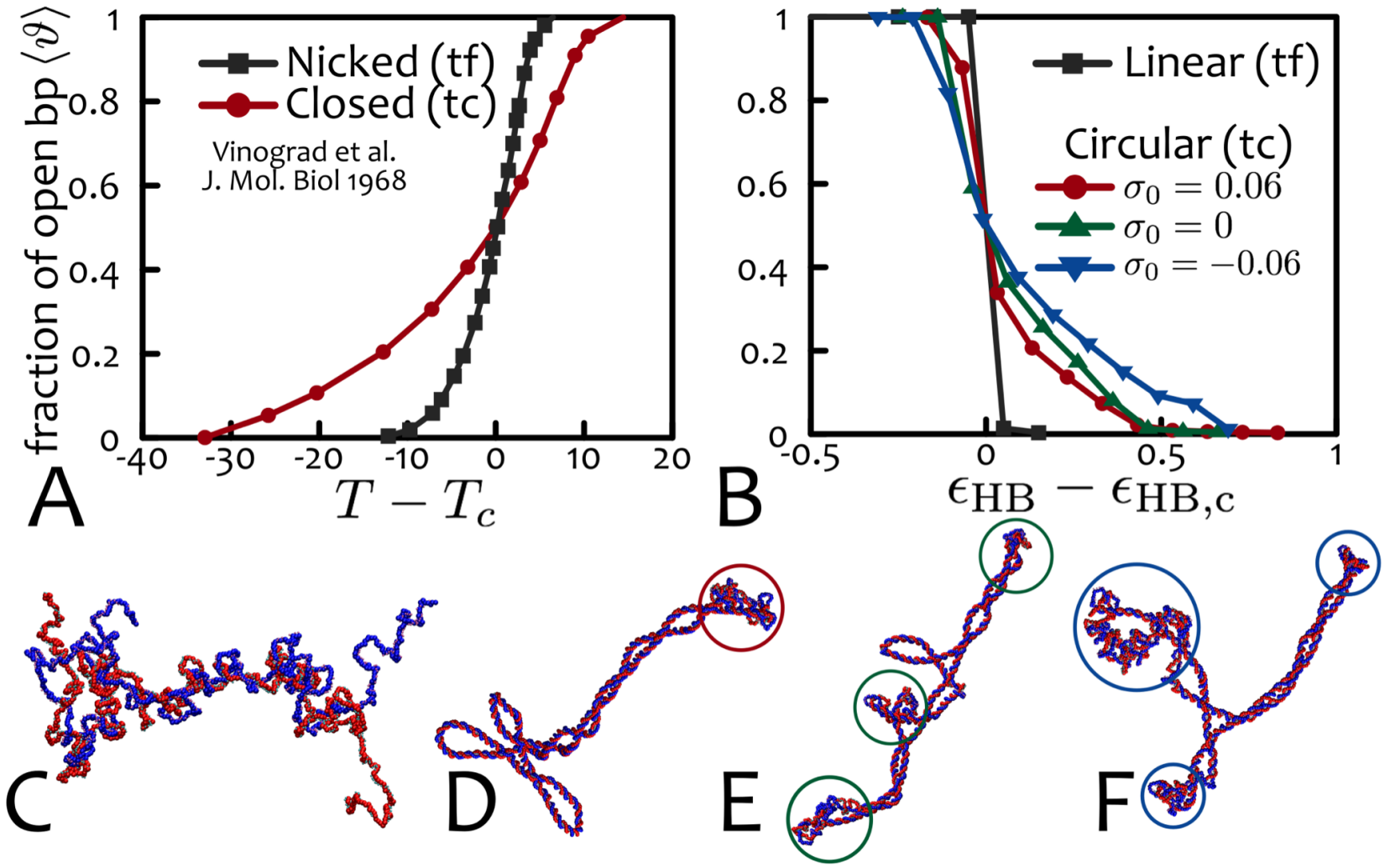
Lk = 47

Tw = 50

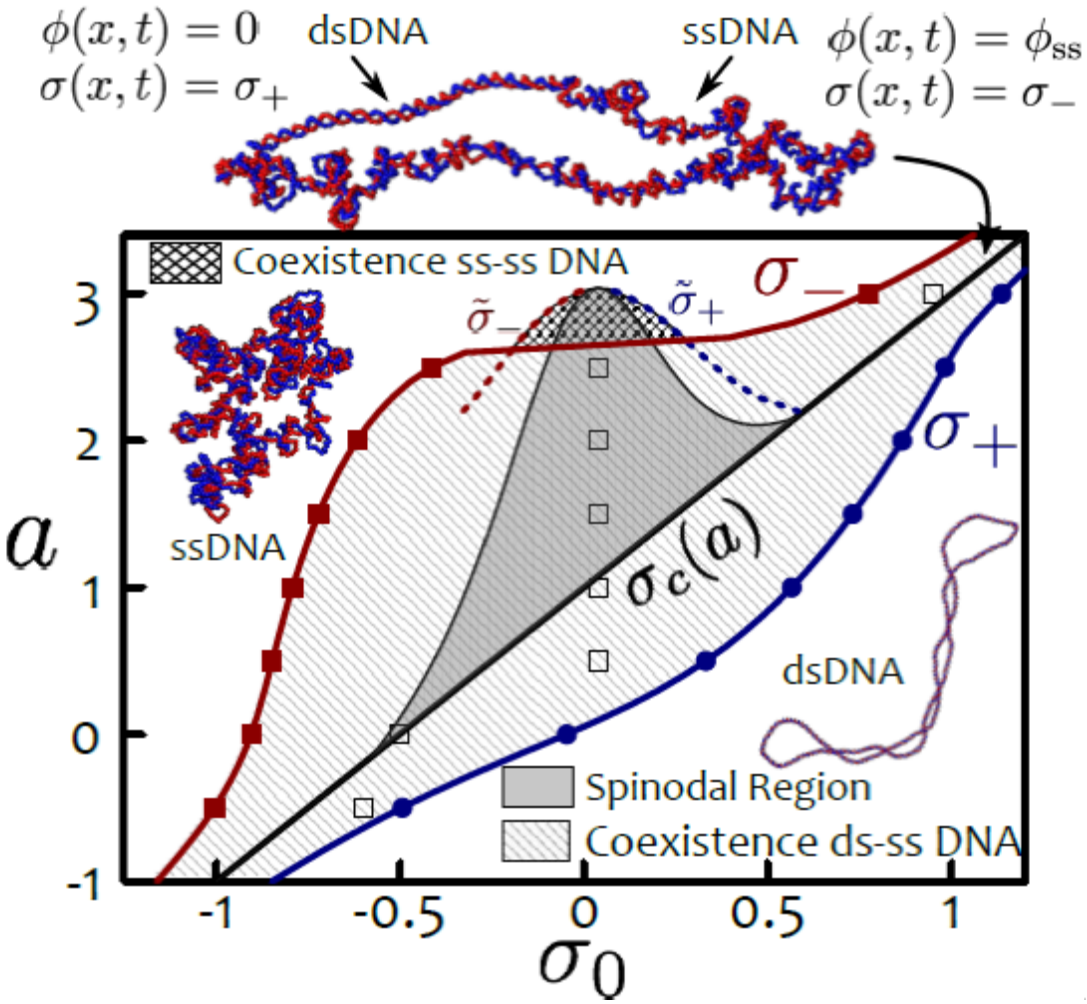
Wr = -3

This was recently used to study the melting dynamics of supercoiled DNA

Fosado Michieletto Marenduzzo, 2017



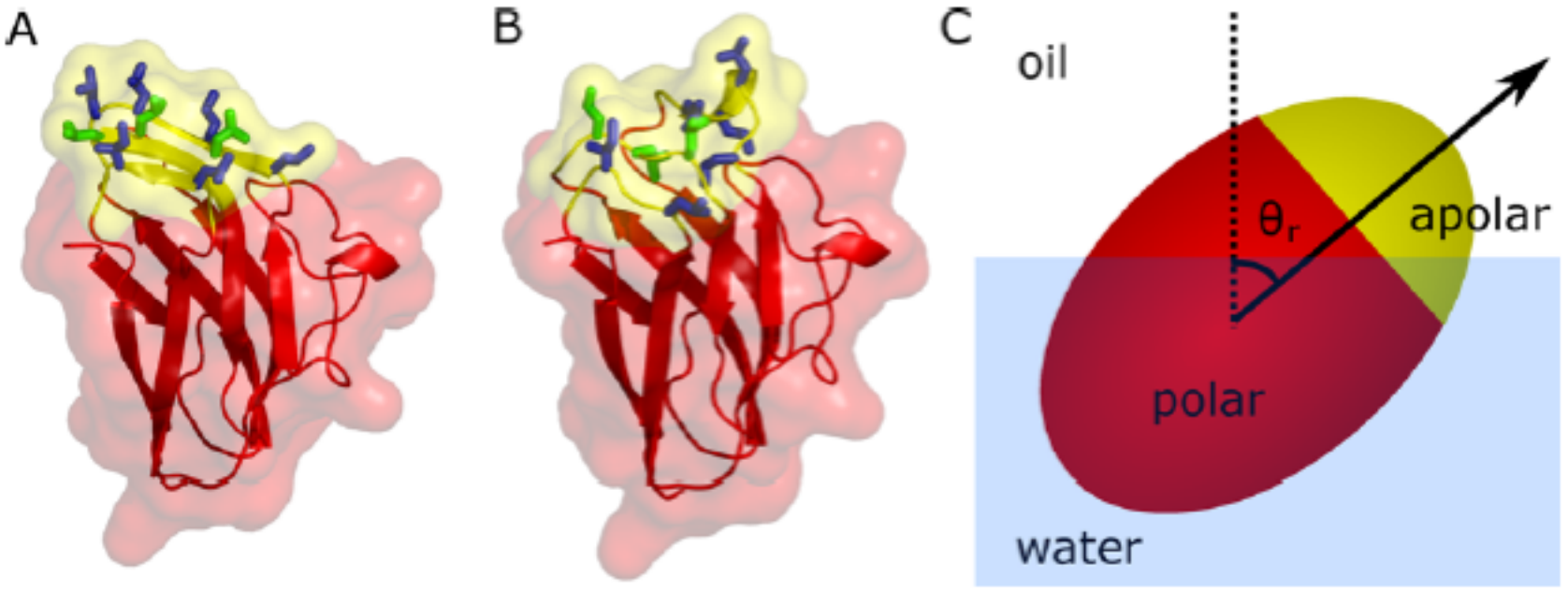
MD simulations show that supercoiled DNA unwinds differently, and much more smoothly, with respect to linear DNA



The mechanism can be understood by field theoretical methods:

the transition is smoother as the critical point

is substituted by a phase coexistence region



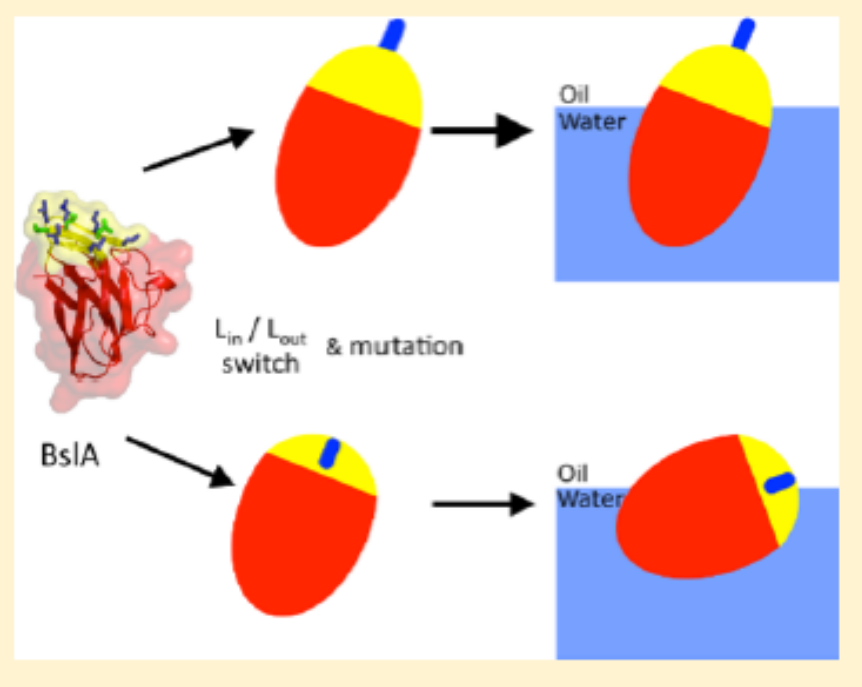
Different coarse graining can also be used within the same study.

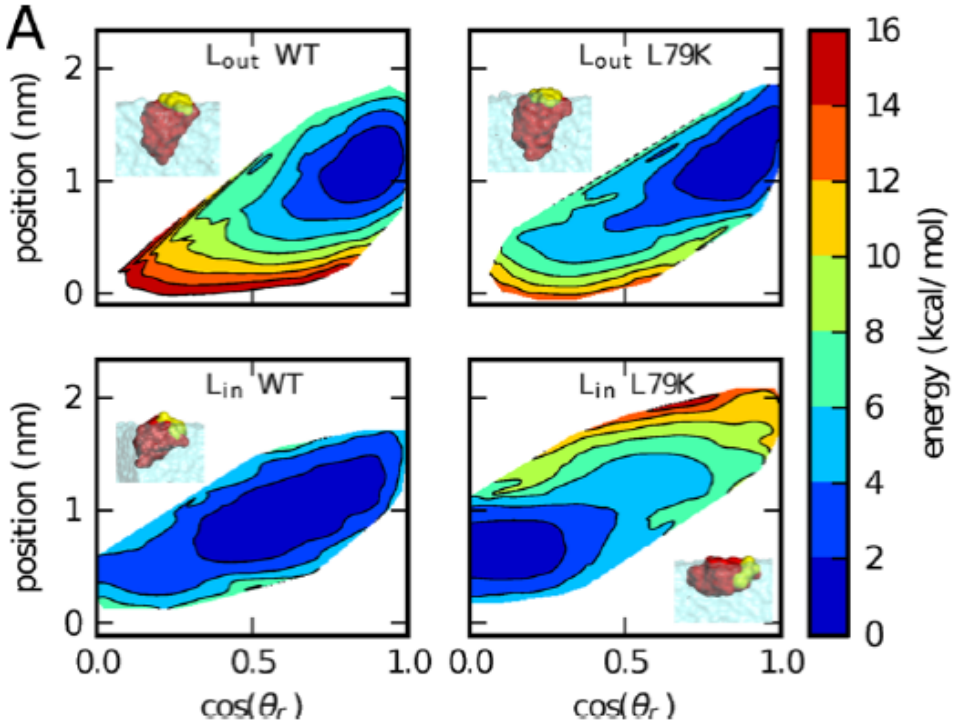
For instance recently we used atomistic simulations and

coarse-grained Monte-Carlo simulations

to study the physical behaviour of BslA at an interface

Brandani, Schor, Morris, Stanley-Wall, MacPhee, Marenduzzo, Zachariae, Langmuir (2015)





It was found that BslA behaves as

a switchable Janus colloids at an oil/water interface.

The wild type sits up straight at the interface due to hydrophobic interactions;

mutants (with the hydrophobic cap disrupted) lie on

the side to minimise surface tension.

The MD results can be recapitulated by a simple model with ellipsoid and a surface.

Example of other work not covered in talk

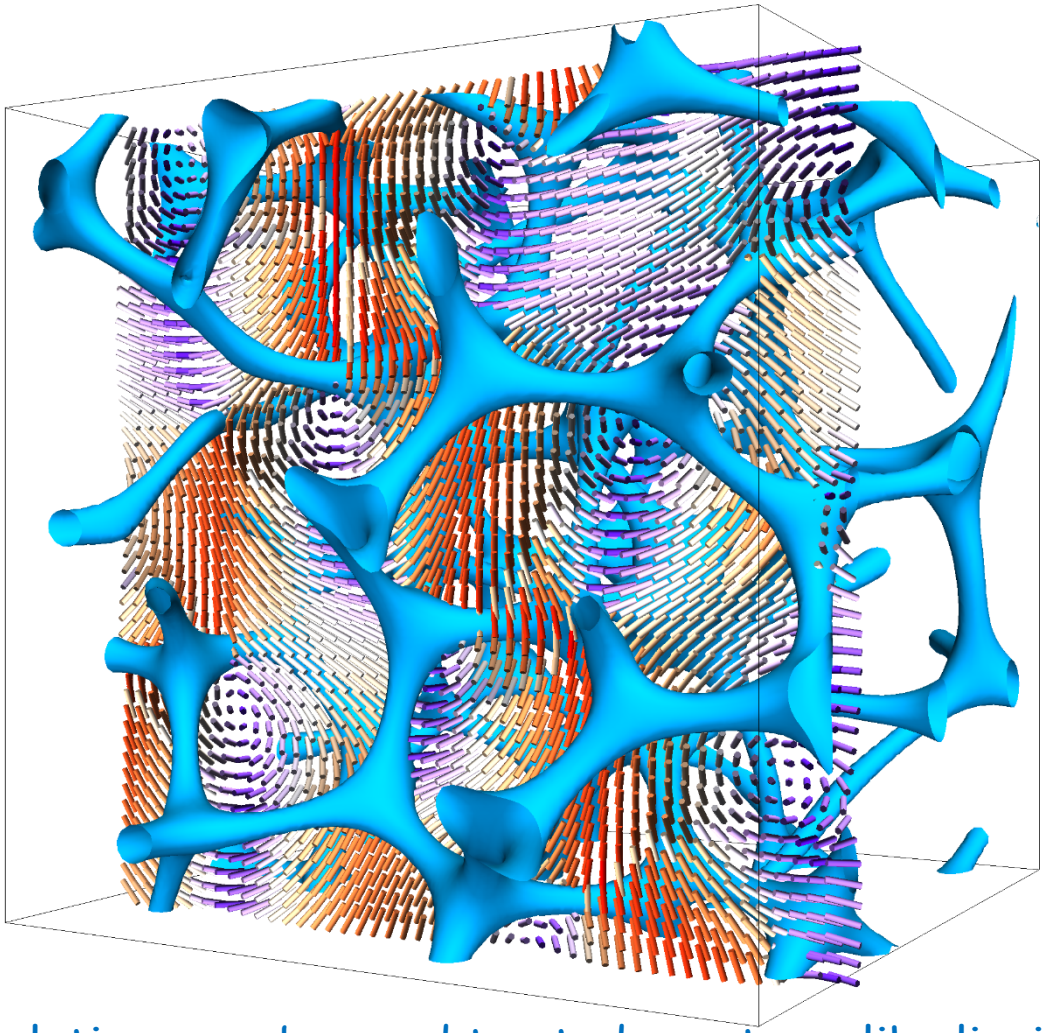
Fully atomistic MD simulations of protein folding (Schor, Macphee)

MD simulations of metals, alloys and other condensed matter systems (Ackland, includes work under high pressure)

MD simulations of bacterial biofilms and of

growing cell/bacterial colonies (Allen, Melaugh, Waclaw)

LB simulations of colloidal particles or droplets in fluids

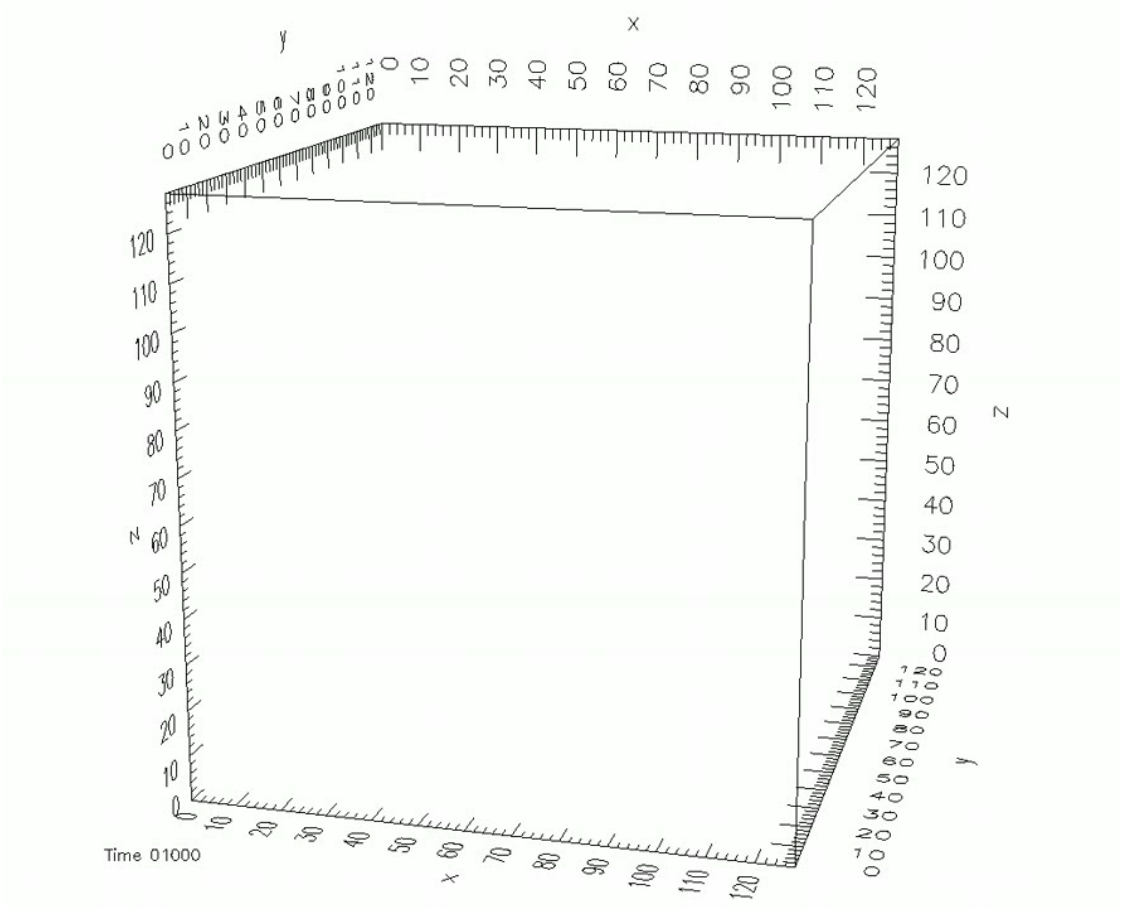


LB simulations can be used to study systems like liquid crystals

Without molecular detail (via continuum theory).

This is a structure for blue phase III which we proposed via LB simulations.

Henrich Stratford Cates Marenduzzo, PRL (2011); Henrich Marenduzzo, Physics World (2017)



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