

5/9/2018

Chromatin 2.

1) Sizes of random coils of chromatin

For DNA

$$CR^2 = 2Ll_p$$

$$2l_p = b \leftarrow \text{Kuhn's length}$$

$$l_p = 150 \text{ bp} = 50 \text{ nm} ; b = 100 \text{ nm}$$

For nucleosomal fiber

l_p is unknown but can be estimated
 one linker: 20-50 bp \Rightarrow 3-6 linkers of DNA
 $\approx l_p$ of DNA

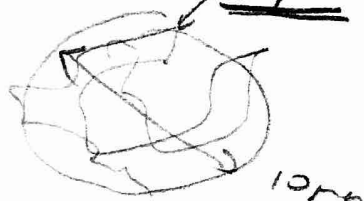
$$\Rightarrow l_p \approx 3-6 \text{ nucleosomes}$$

$$\approx 1,000 \text{ bp} \dots b \dots$$

$$\approx 50 \text{ nm of the fiber} \quad b \approx 100 \text{ nm}$$

o Bacteria $L = 5 \cdot 10^6 \text{ bp} \approx 2 \cdot 10^6 \text{ nm}$ $R = \sqrt{2 \cdot 10^6 \cdot 10^2} \approx 10^4 \text{ nm} = 10 \mu\text{m}$

Size of Bacteria $\sim 1 \mu\text{m}$



o Human cell $L = \frac{2.3 \cdot 10^9 \text{ bp}}{5} = 4.6 \cdot 10^8 \text{ bp} = 4 \cdot 10^8 \text{ nm}$

$\frac{1}{2}$ fold shorter due to nucleosomes

$$R = \sqrt{4 \cdot 10^8 \cdot 100} = 2 \cdot 10^5 \text{ nm} = 200 \mu\text{m}$$

One chromosome: ~ 50 times shorter than whole (diploid genome)

$$R_{\text{chrom}} = 30 \mu\text{m}$$

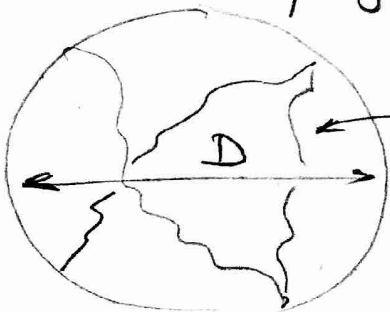
$$D_{\text{nucleus}} \approx 70 - 25 \mu\text{m}$$

↑ ↙

somatic cells oocytes

comparable for oocytes

2) Confined polymer (without other interactions) $N = L/b$
 = confined RW of length



Random walks that bounce off the walls
 $K \cdot b^2 = D^2 \leftarrow$ each walk of K steps

②

Free energy of such system:

$$F = T f(RKD) = T f(b\sqrt{N}/D)$$

↑ the only energy unit ← only two length scales

F must be additive, i.e. linear in N

$$F = T \frac{b^2 N}{D^2} = T \frac{N}{K} \quad \text{i.e. one unit of } kT \text{ per random walk}$$

Pressure on the walls

$$P = - \frac{dF}{dV} = - \frac{dF}{D^3 dD} = \frac{T b^2 N}{D^5} = \frac{T}{V} \frac{N}{K}$$

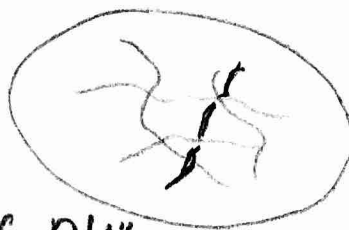
⇒ Ideal gas of $\frac{N}{K}$ random walk!

$$PV = T \frac{N}{K}$$

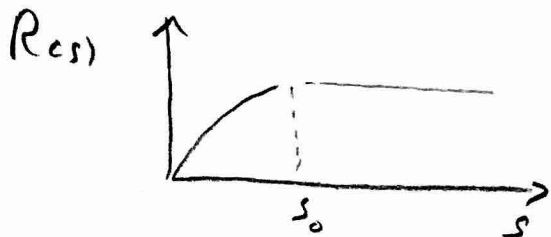
A polymer with excluded volume interactions that is collapsed due to pairwise interactions: $R^3 \sim N$ i.e. space filling: $R \sim N^{1/3}$ is equivalent to RW confined into $D \sim N^{1/3}$. This is because any subchain fills other chains as much as it self

and hence subchains experience external pressure that exactly compensates for excluded volume

⇒ gas of RWs



③ Testing Experimentally: $R(s) \sim s^{1/2}$ for RW

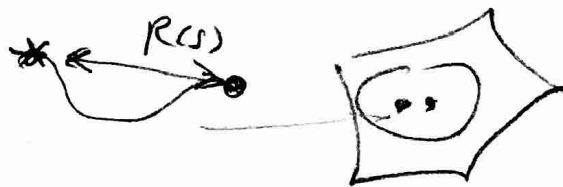
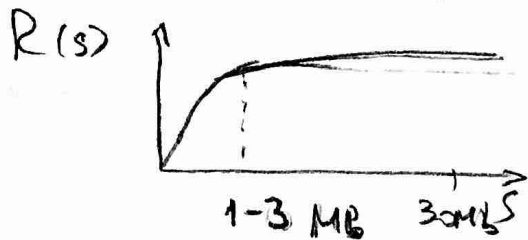


$$R(s) \sim \begin{cases} s^{1/2} & \text{for } s \leq s_0 \\ \text{const} & \text{for } s \geq s_0 \end{cases}$$

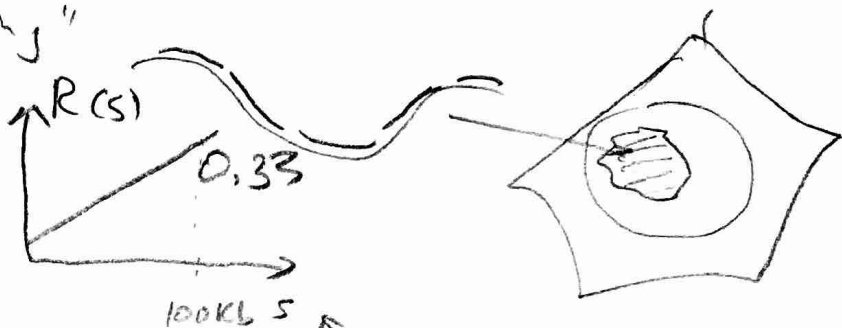
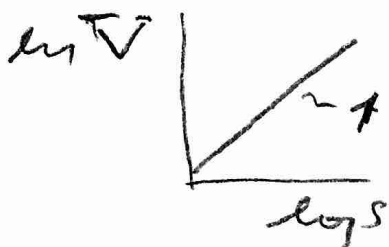
$$s_0^{1/2} = D \sim N^{1/3} \quad s_0 \sim N^{2/3}$$

③ Experiments

1) "FISH" two probes



2) DNA "staining"



compacted: $R \sim s^{1/3}$
at all scales!

4) Hi-C measures contact frequency

$P_c(s) \sim s^{-\alpha}$ $\alpha = 1.1-1.2$

What are our expectations?

Random walk:

$$P(r) = A f\left(\frac{r}{R}\right) \quad \int P(r) d^3r = 1 \Rightarrow A \int f\left(\frac{r}{R}\right) \frac{d^3r}{R^3} \cdot R^3 = 1$$

contact radius (a)

$\rightarrow a$

$$P(r) = \frac{1}{R^3} f\left(\frac{r}{R}\right)$$

$$P_c(s) = \int_0^a P(r) (R(s))^3 d^3r$$

$$AR^3 = 1 \quad A \sim \frac{1}{R^3}$$

$$= \frac{1}{R(s)^3} \int_0^a f\left(\frac{r}{R(s)}\right) d^3r \approx \frac{a^3}{R^3(s)} f\left(\frac{a}{R}\right)$$

$$\sim R^{-3}$$

for $a \ll R$
replace $f\left(\frac{r}{R(s)}\right)$ with $f\left(\frac{a}{R}\right)$

For RW: $P_c(s) \sim s^{-3/2}$

For compact polymer $P_c(s) \sim \begin{cases} s^{-3/2} & s < s_0 \\ \text{const} & s > s_0 \end{cases}$

④ But this doesn't give $\alpha \approx 1$

However $R(s) \sim s^{0.33}$ as observed experimentally
 is consistent with $P(s) \sim s^{-1}$ ($\alpha=1$)

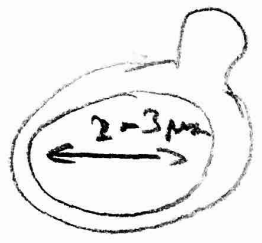
Notes: Yeast chromosomes & human in oocytes show $P(s) \sim s^{-3/2}$!

Yeast $L_{chr} = 12 \text{ Mb} / 12 \text{ chromosomes} = 1 \text{ Mb}$

$L_{chr} = 10^6 \text{ bp} / 5 \cdot 3 \frac{\text{bp}}{\text{nm}} = 6 \cdot 10^4 \text{ nm}$

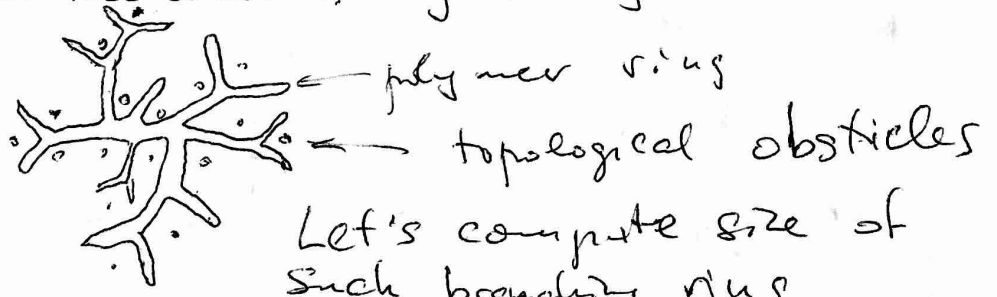
$R = \sqrt{6 \cdot 10^4 \cdot 10^2} = 2.5 \cdot 10^3 \text{ nm} = 2.5 \mu\text{m}$

$D = 2-3 \mu\text{m} \leftarrow \text{fits!}$



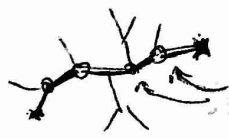
5) Topological constraints can create a structure that is compact on all scales

One model of how topological constraints act on the chain is by creating random obstacles in 2D:



Let's compute size of such branching ring

It's size is the same as that of a randomly polymer



m - # of branchings between to leaves
 and n is the number of Khun segments between two branching points

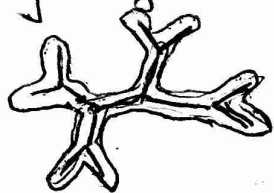


$\langle R^2 \rangle \sim m n a^2$

(5) then length of the chain between two leaves is $m \cdot n$ and $R^2 \sim m n a^2$

Now we need to compute m .

- Consider a randomly branching polymer that consists of $P = N/n$ segments and branches after every segment (on Cayley tree = Bethe tree)



How is P related to m ?

- Consider a contour that goes around the tree it has length $2P$.
- Relative to some leaf 1 - it's a random walk with every step going either towards or away from 1 , but the RW returns to 1 i.e. ADRW with length $2P$ and displacement m

$$\Rightarrow m \sim P^{1/2} \sim N^{1/2} / n^{1/2}$$

$$R^2 \sim m n a^2 \sim N^{1/2} n^{1/2} a^2 \quad (\text{Zimm \& Stockmayer '49})$$

$$\boxed{R \sim N^{1/4}} \leftarrow \text{very compact:}$$

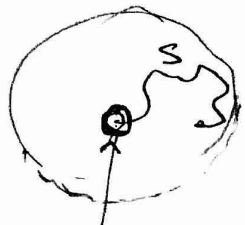
$$V \sim R^3 \sim N^{3/4} \quad \rho = \frac{N}{V} \sim N^{1/4} \rightarrow \infty \text{ for } N \rightarrow \infty$$

density is growing
i.e. it cannot be the case in 3D!

The most compact possible: $\boxed{R \sim N^{1/3}}$
Same for all subchains $R(s) \sim s^{1/3}$

\Rightarrow Topological constraints create chains compact on all scales
(crumpled globule)

⑥ * Let's compute $P(s)$ for crumpled globule



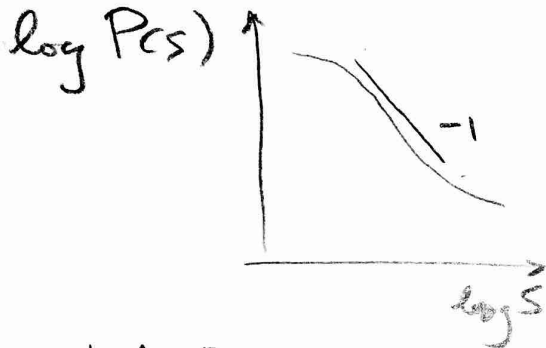
a contact radius

$$P(s) \sim \frac{a^3}{R(s)^3} \sim s^{-1}$$

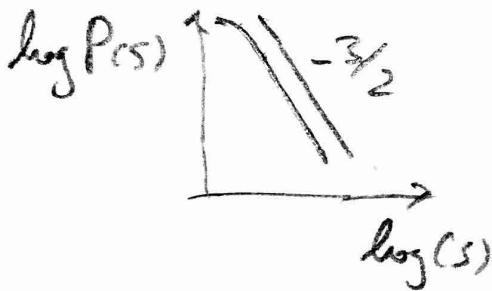
because $R(s) \sim s^{1/3}$

very close
to experiment!
in mammals

⇒ chromosomes are compact crumpled globules in human/mouse cells



but RW chains in yeast or large human cells



6) Domains, compaction & loop extrusion

theory
(following Goloborodko et al
Biophys J 2016)