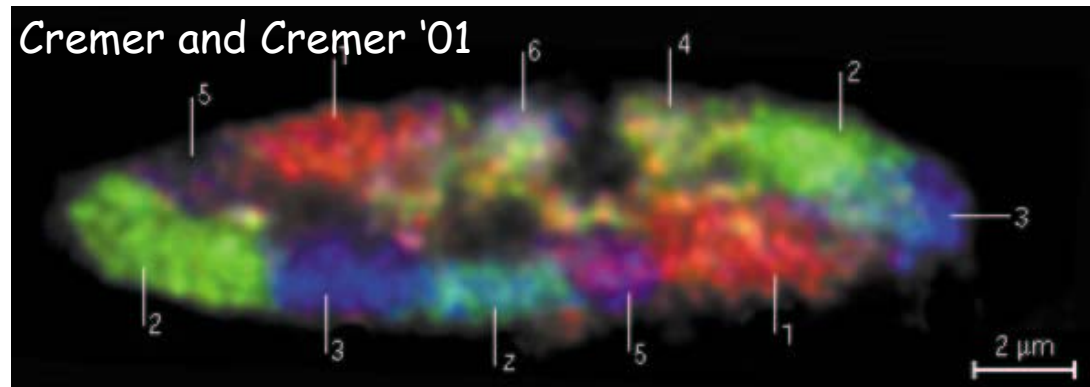
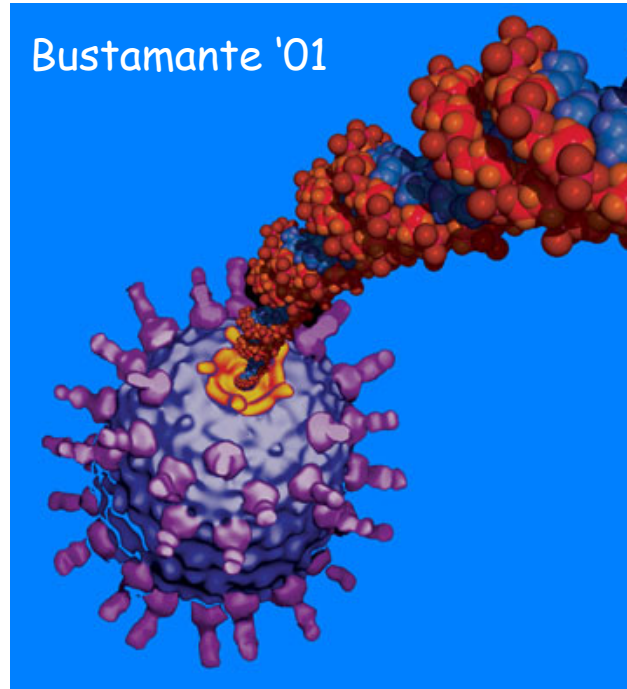
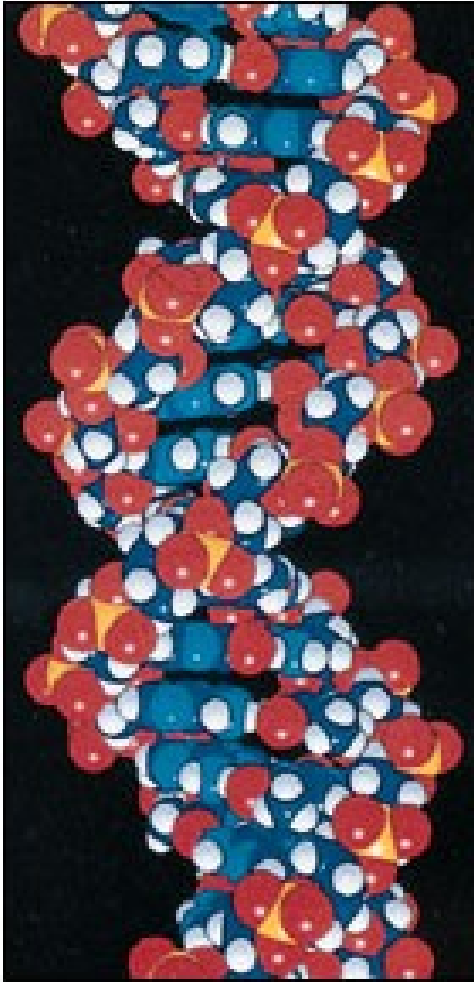
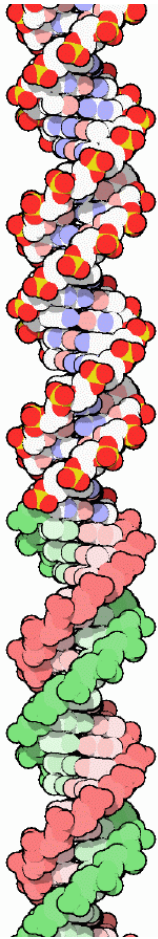


Physics of genome management

J. Kondev - Brandeis University



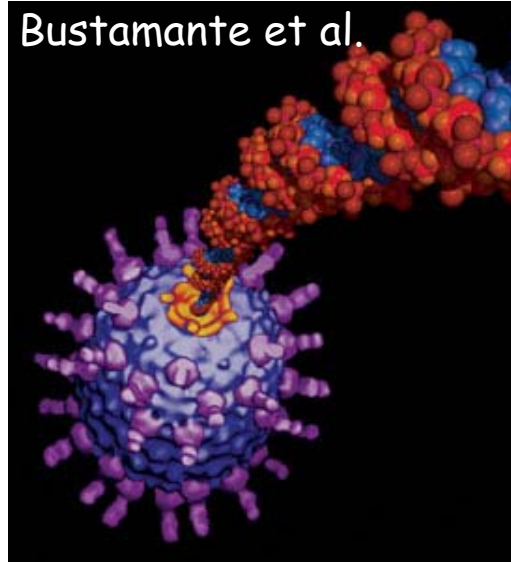
Overview



The double helix

- **Central dogma of MB**

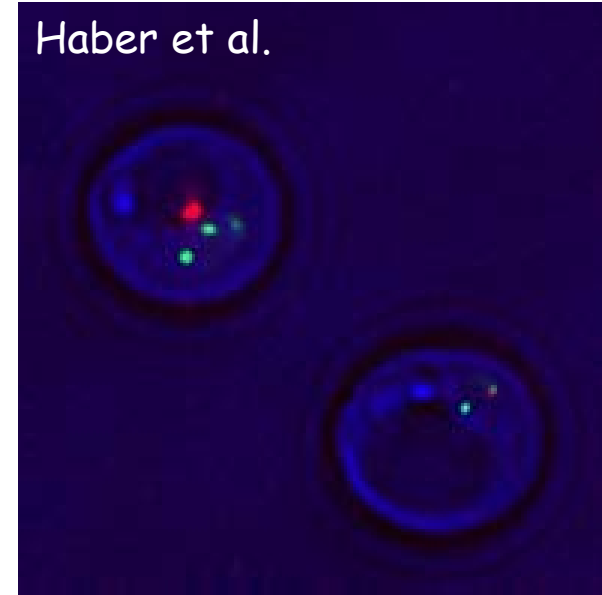
Bustamante et al.



Viral DNA Packing

- **10 microns of DNA confined in a 50nm capsid.**
- **Physical constraints on viral assembly and infection.**

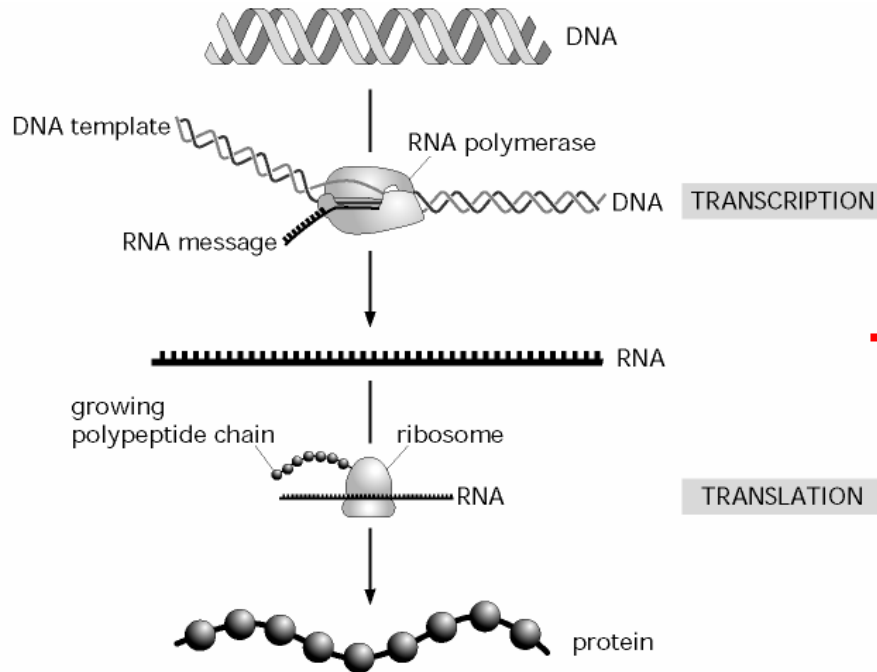
Haber et al.



Chromosomes in vivo

- **Chromosome structure and organization**
- **Tethering of chromosomes and DNA recombination**

Whither space and time?

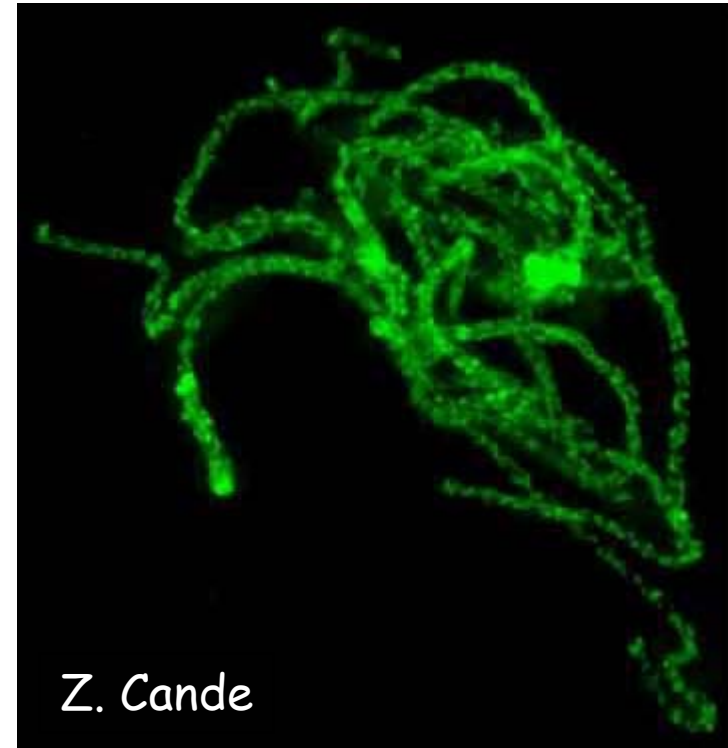
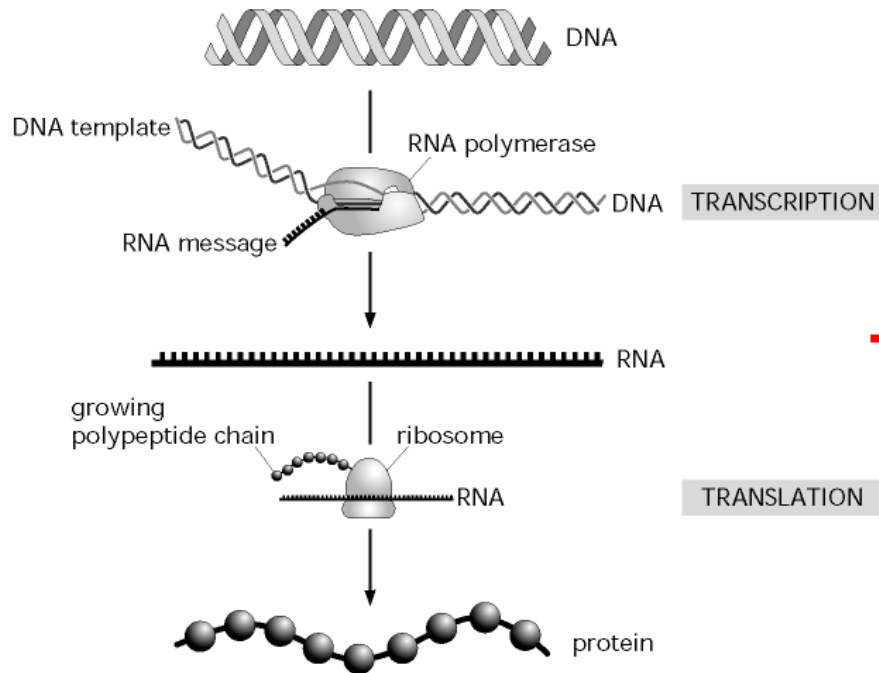


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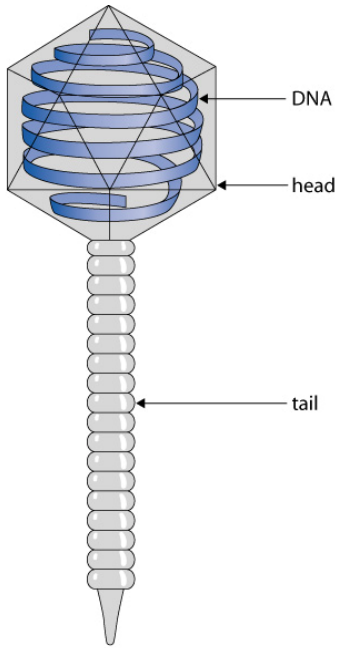
Figure 5-11 Essential Cell Biology, 2/e. (© 2004 Garland Science)

Whither space and time?

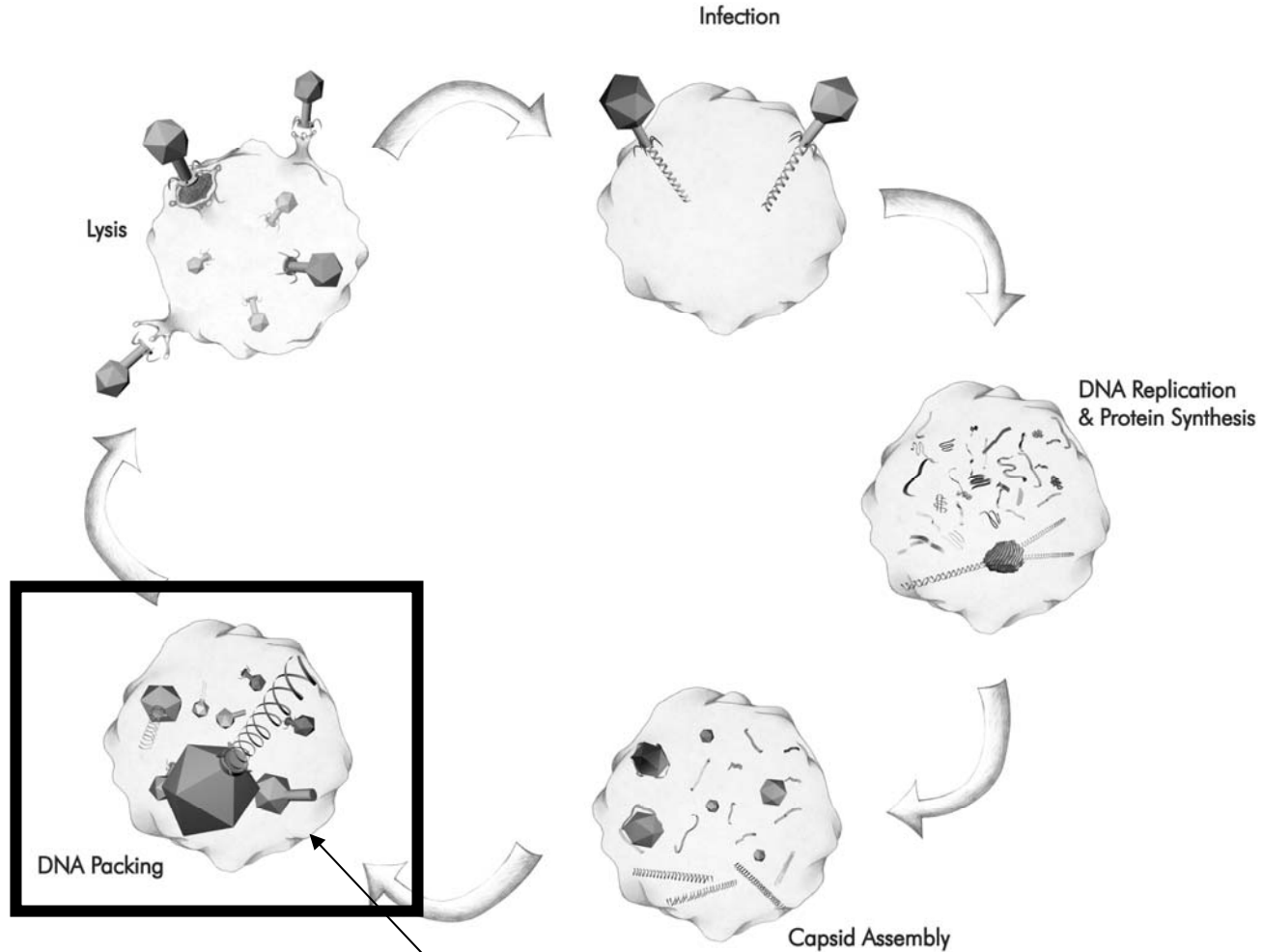


How does the spatial arrangement of DNA in the cell affect the processes of the central dogma?

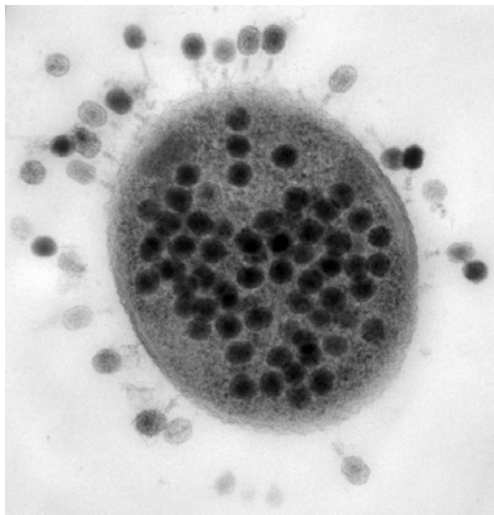
Case 1: Viral assembly



A Genetic Switch, 3rd edition, 2004
© Cold Spring Harbor Laboratory Press
Chapter 1, Figure 2

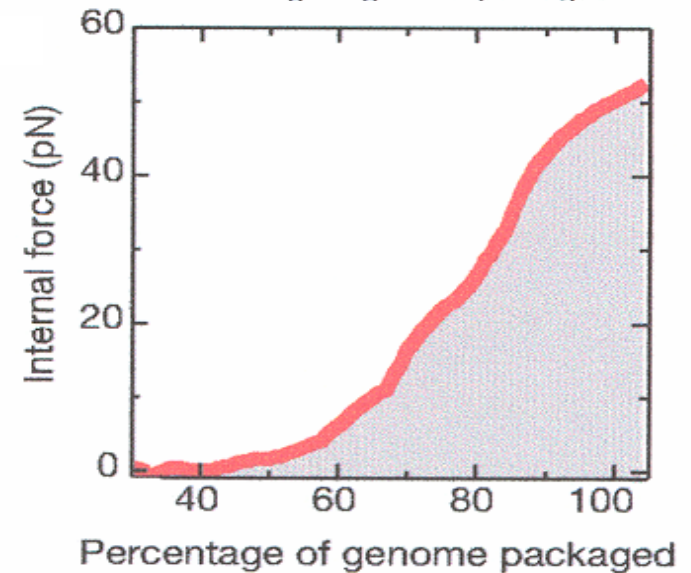
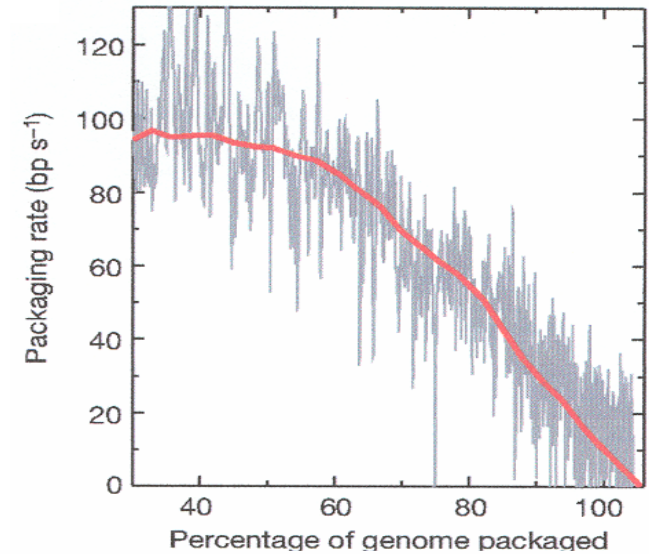
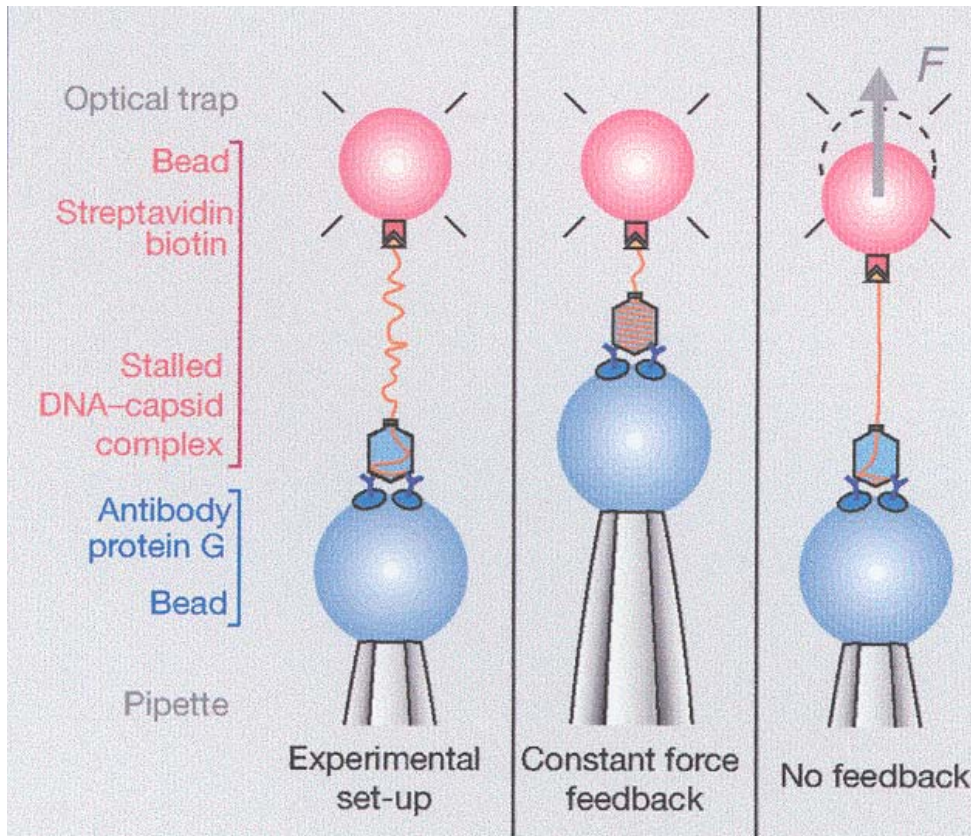


Rate of packing: 100bp/sec



Single molecule studies of viral packing

Smith et al., Nature **413**, 748 (2001).

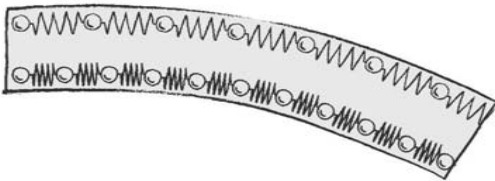


Quantitative data requires quantitative models!

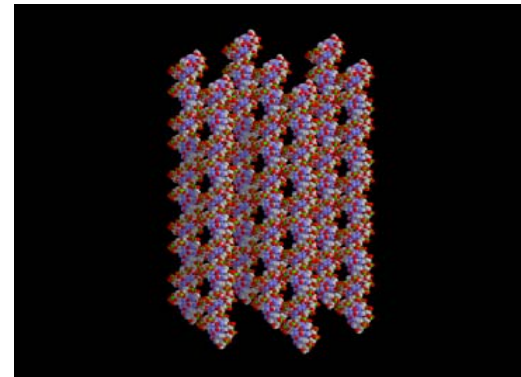
Model of packed DNA

Riemer et al., Odijk, Gelbart et al.

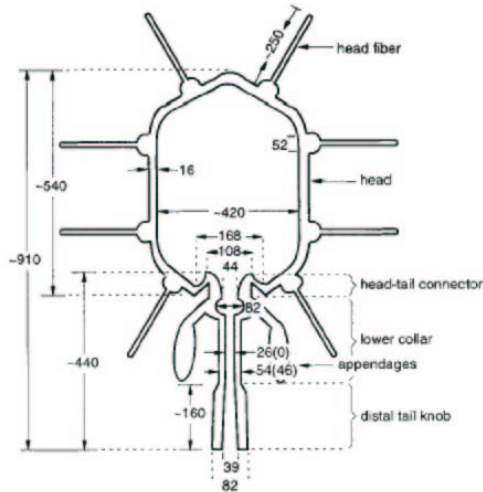
DNA elasticity



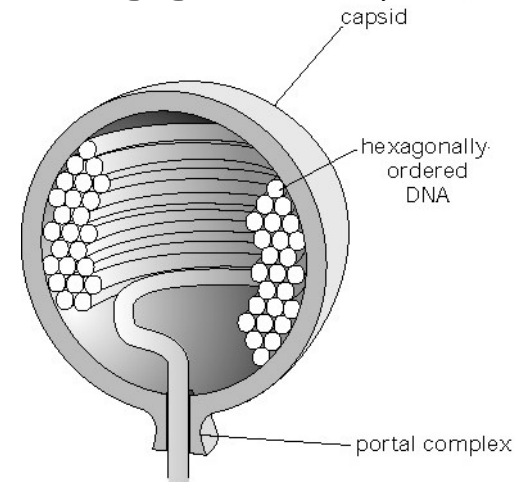
DNA charge



Viral dimensions

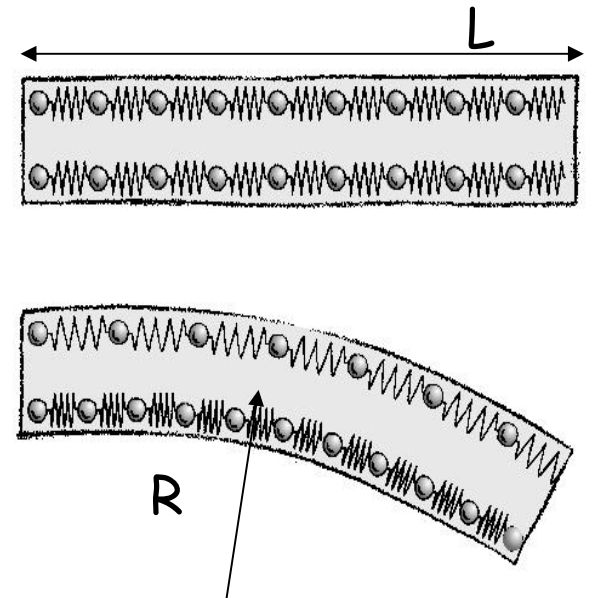
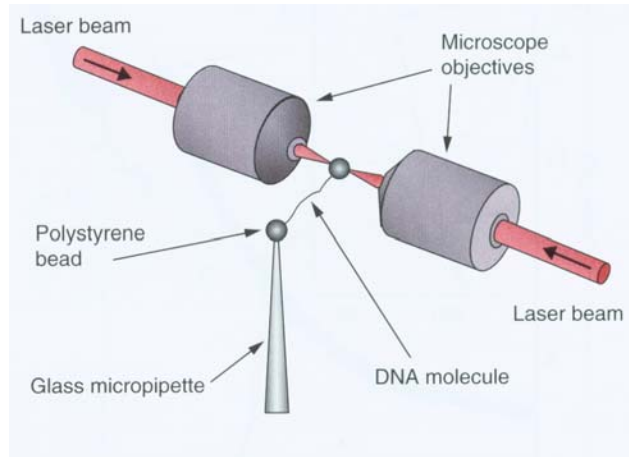


Packing geometry

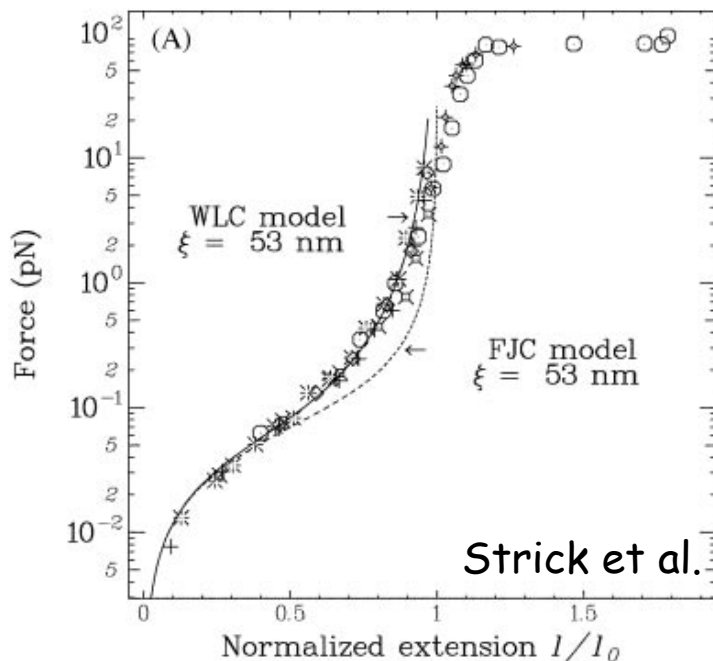


DNA elasticity

Bustamante, Marko and Siggia, Vologodskii, ...



$$k_B T \approx 4 \text{ pNnm}$$

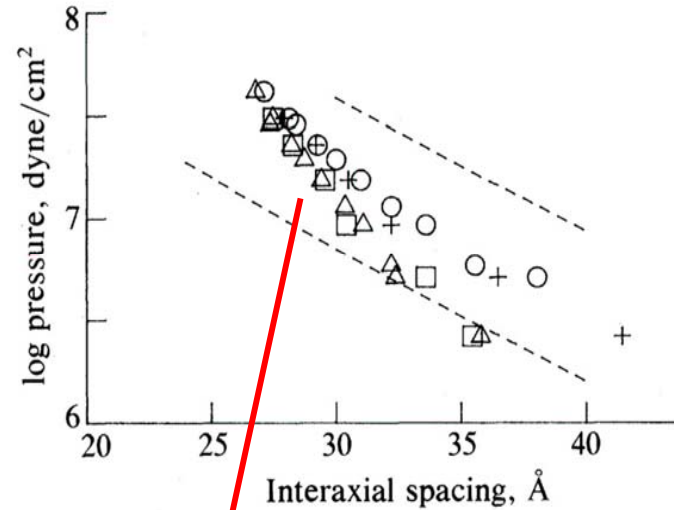
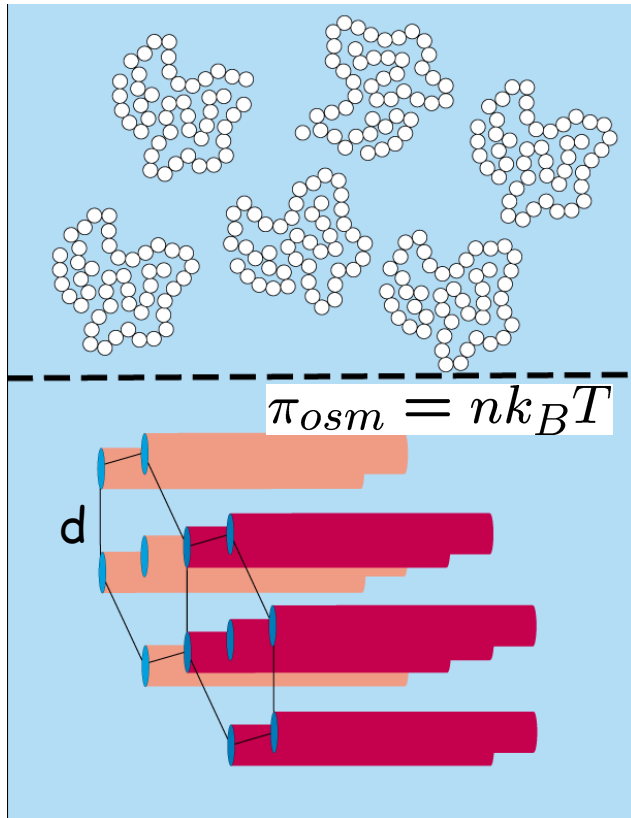


$$E_{\text{beam}} = \frac{\xi_P k_B T}{2} \frac{L}{R^2}$$

Persistence length: $\xi_P \approx 50 \text{ nm}$

DNA electrostatics

Rau and Parsegian



$$\pi_{osm}(d) = F_0 e^{-\frac{d}{c}}$$

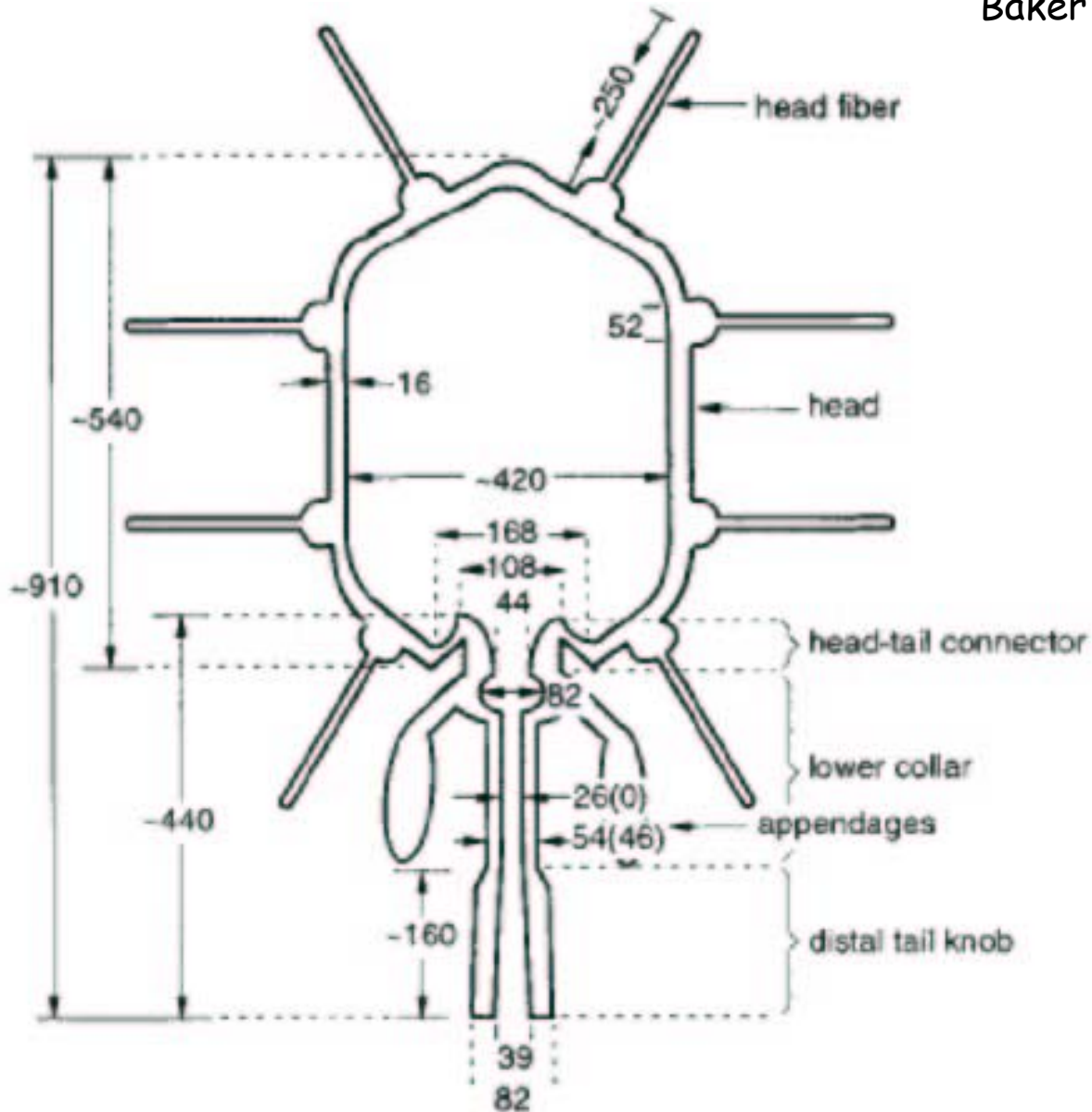
where $F_0 = 55 \text{ nN/nm}^2$ and $c = .27 \text{ nm}$.

The measured pressure can be turned into an interaction energy between pairs of DNA strands. This energy, per strand length is:

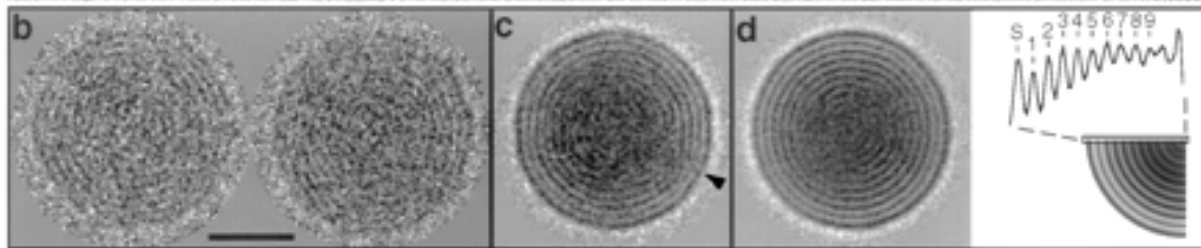
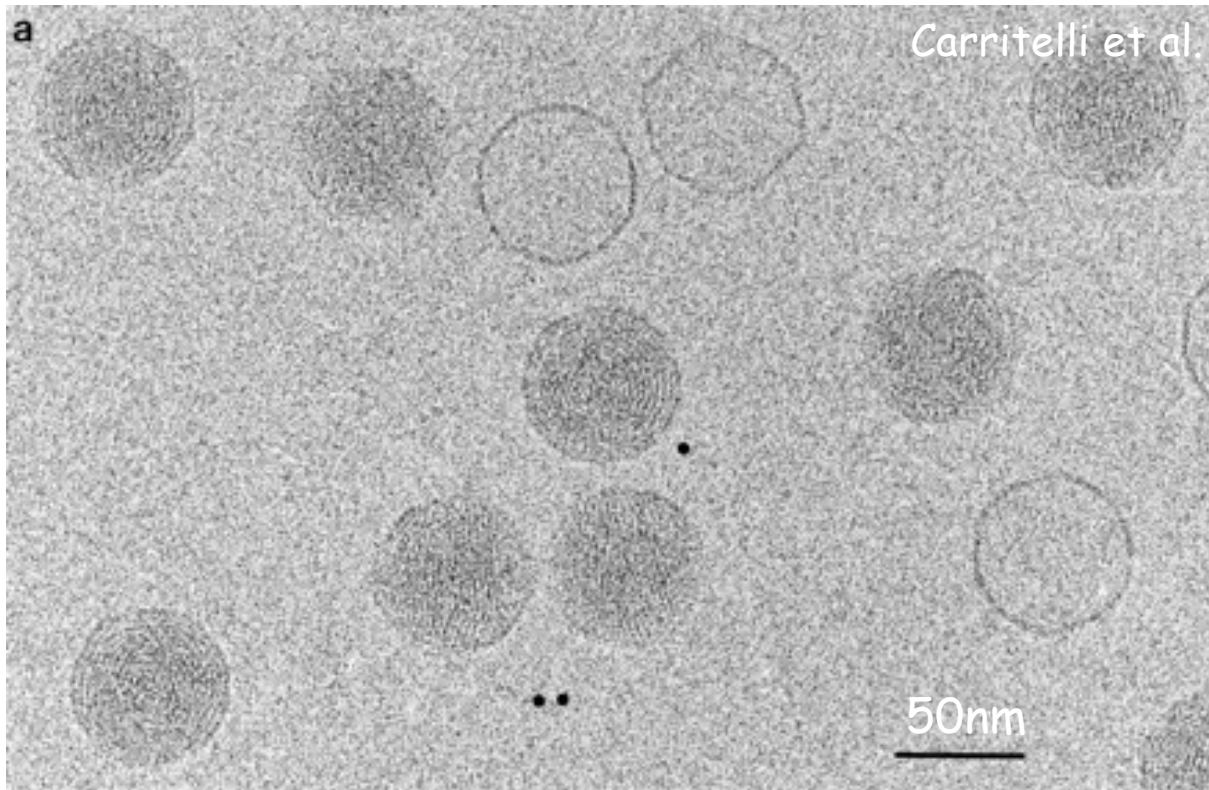
$$e(d) = \sqrt{3} \int_0^d x \pi_{osm}(x) dx = \sqrt{3} F_0 (c^2 + cd) e^{-\frac{d}{c}}$$

$\phi 29$ dimensions

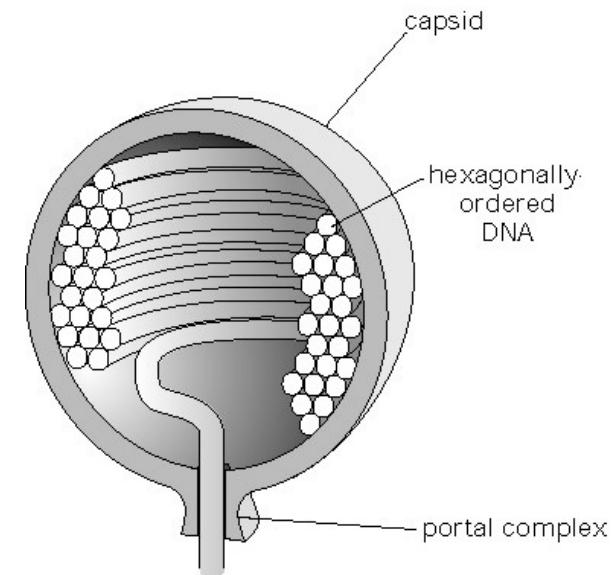
Baker et al.



DNA packing: insights from cryoEM

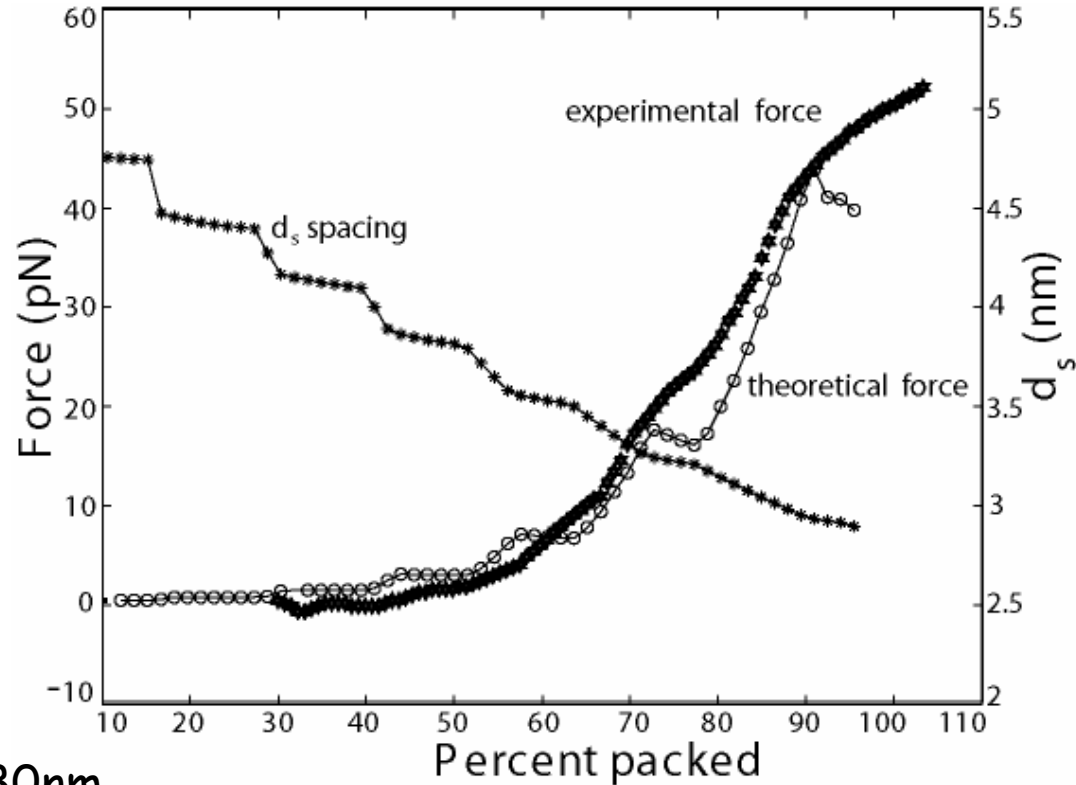
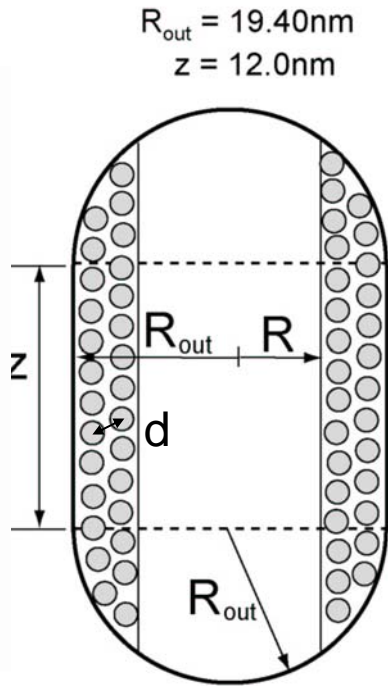


Inverse spool configuration



Model of packed DNA

$$E_{tot}(d, L) = \pi \xi_P k_B T \sum_i \frac{N(R_i)}{R_i} + L \sqrt{3} F_0 (c^2 + dc) e^{-d/c}$$

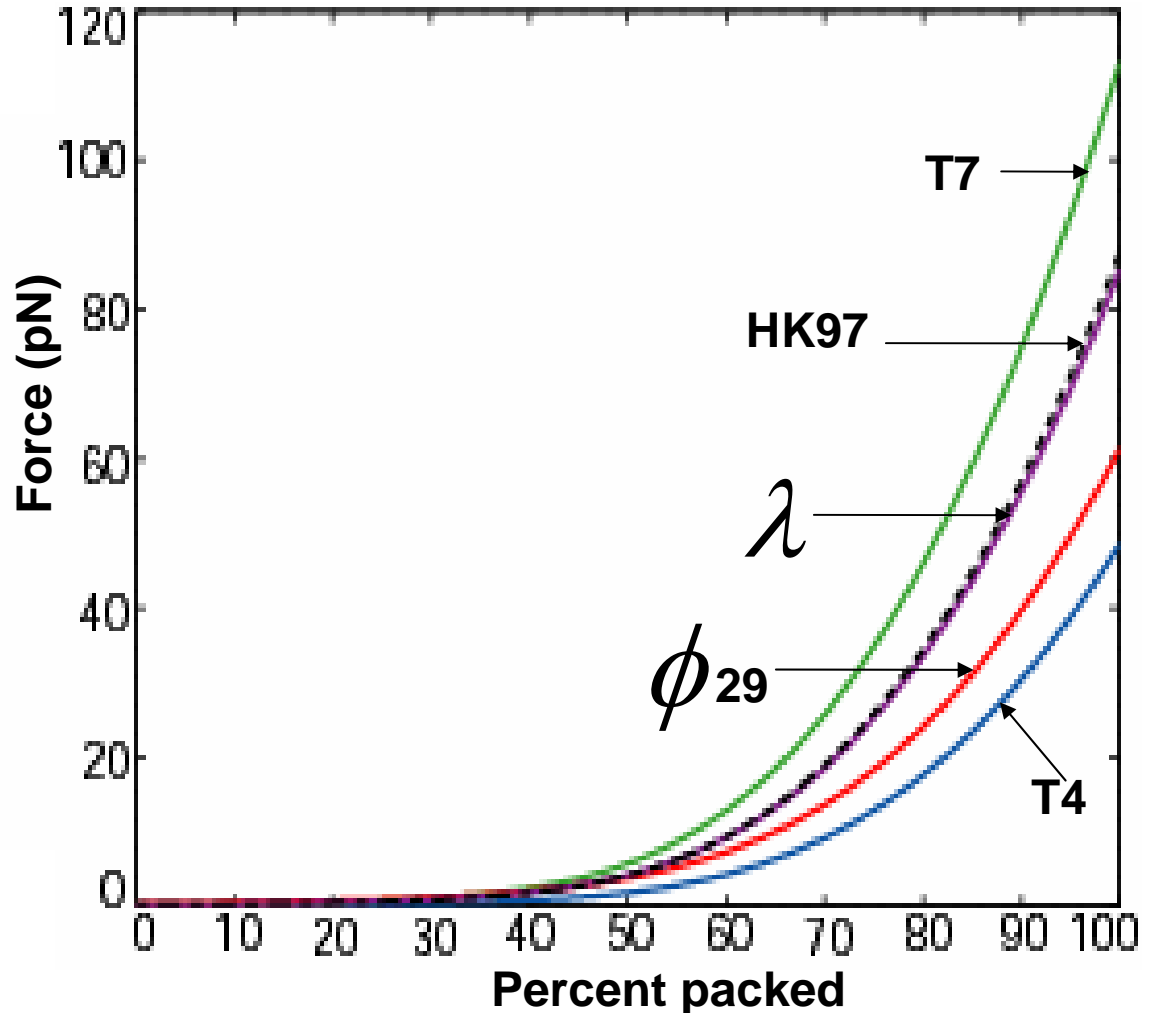
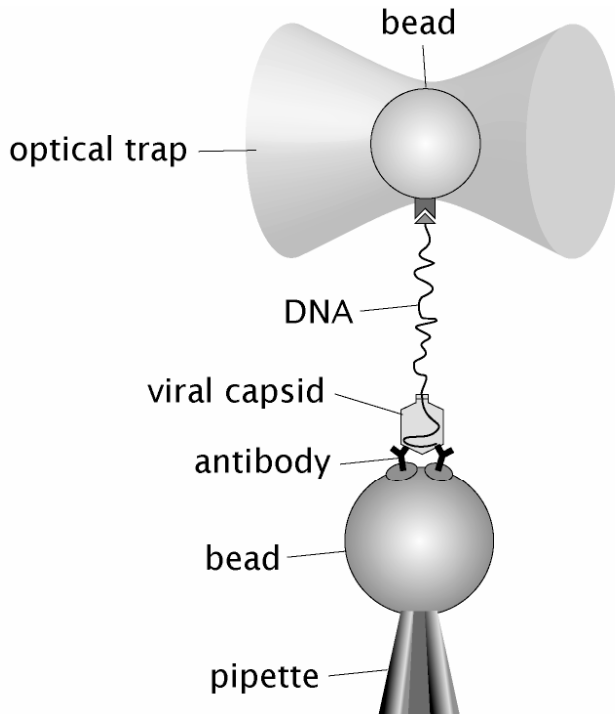


$R_{out} = 19.4 \text{ nm}$, $z = 12 \text{ nm}$, and $L_{gen} = 6580 \text{ nm}$.

Models must make predictions!

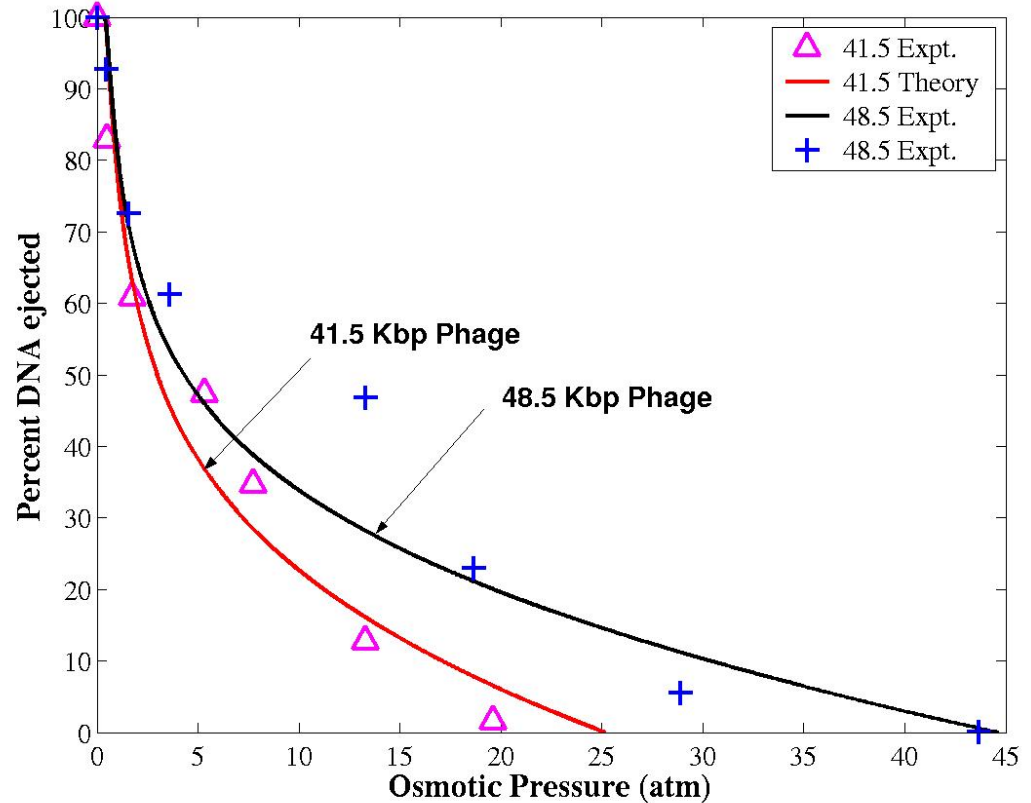
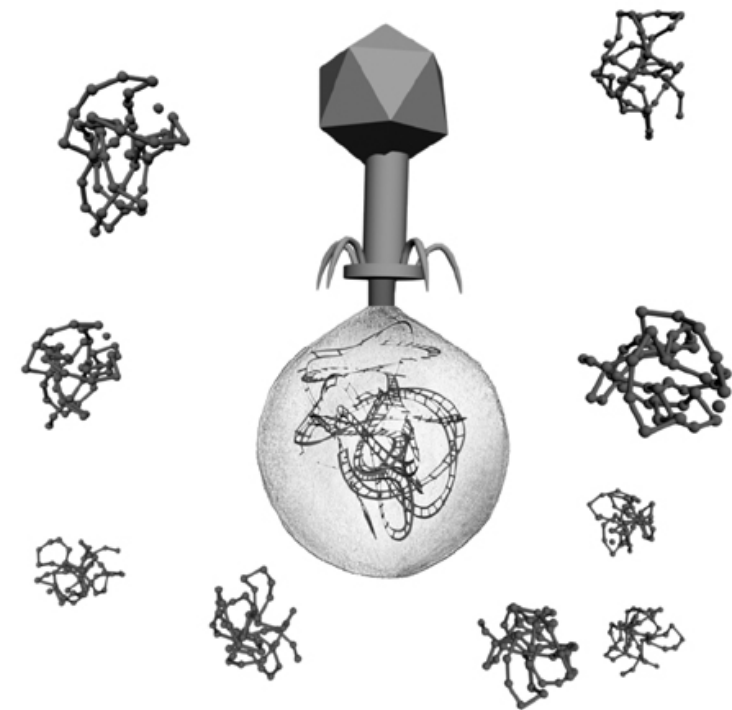
Prediction: Different phages

The length of the viral genome and the size of the capsids vary among phages.



Prediction: Ejection inhibition

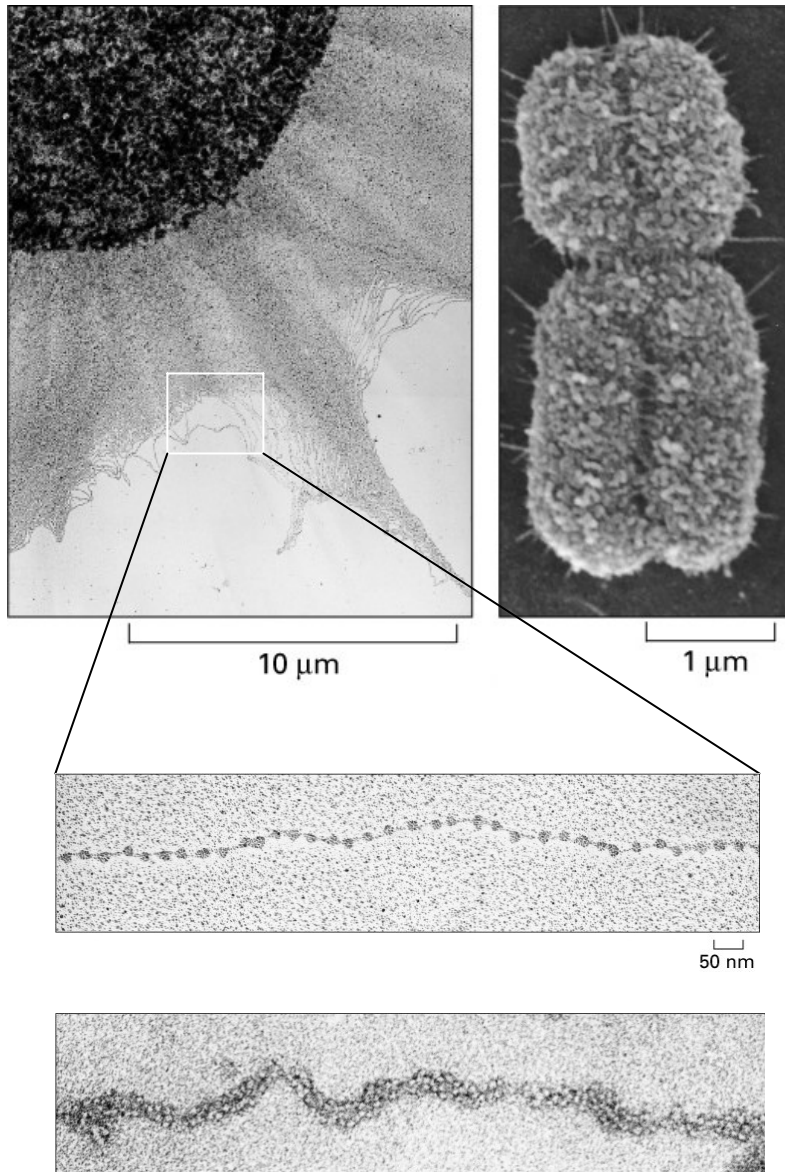
W. Gelbart, A. Evilevitch, C. Knobler (UCLA) and R. Phillips, P. Grayson (Caltech)



$$\underbrace{\frac{\partial E_{in}}{\partial L}(L_{\text{genome}} - L)}_{\text{packing model}} = \underbrace{\frac{\partial E_{out}}{\partial L}(L)}_{\text{osmotic pressure}}$$

Filled capsids are pressurized!

Case 2: Eukaryotic chromosomes



Interphase chromosomes are less condensed than their metaphase counterparts.

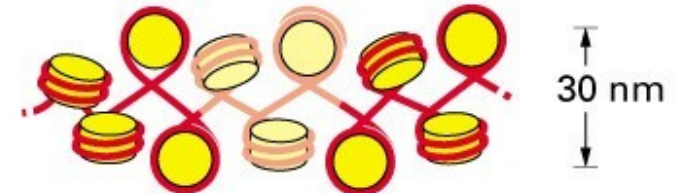
short region of DNA double helix



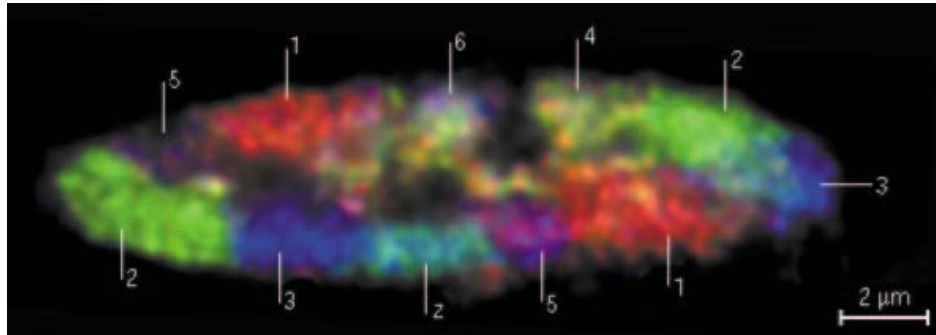
"beads-on-a-string" form of chromatin



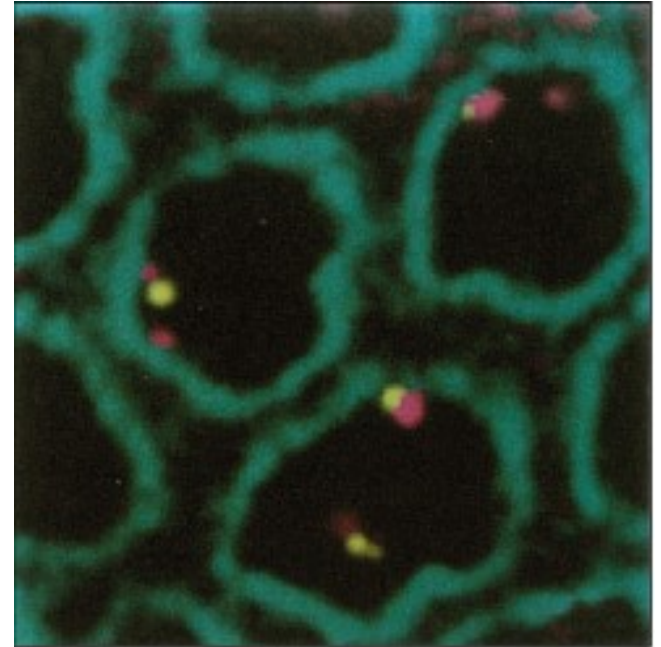
30-nm chromatin fiber of packed nucleosomes



Chromosome organization



Cremer and Cremer '01



5 μm

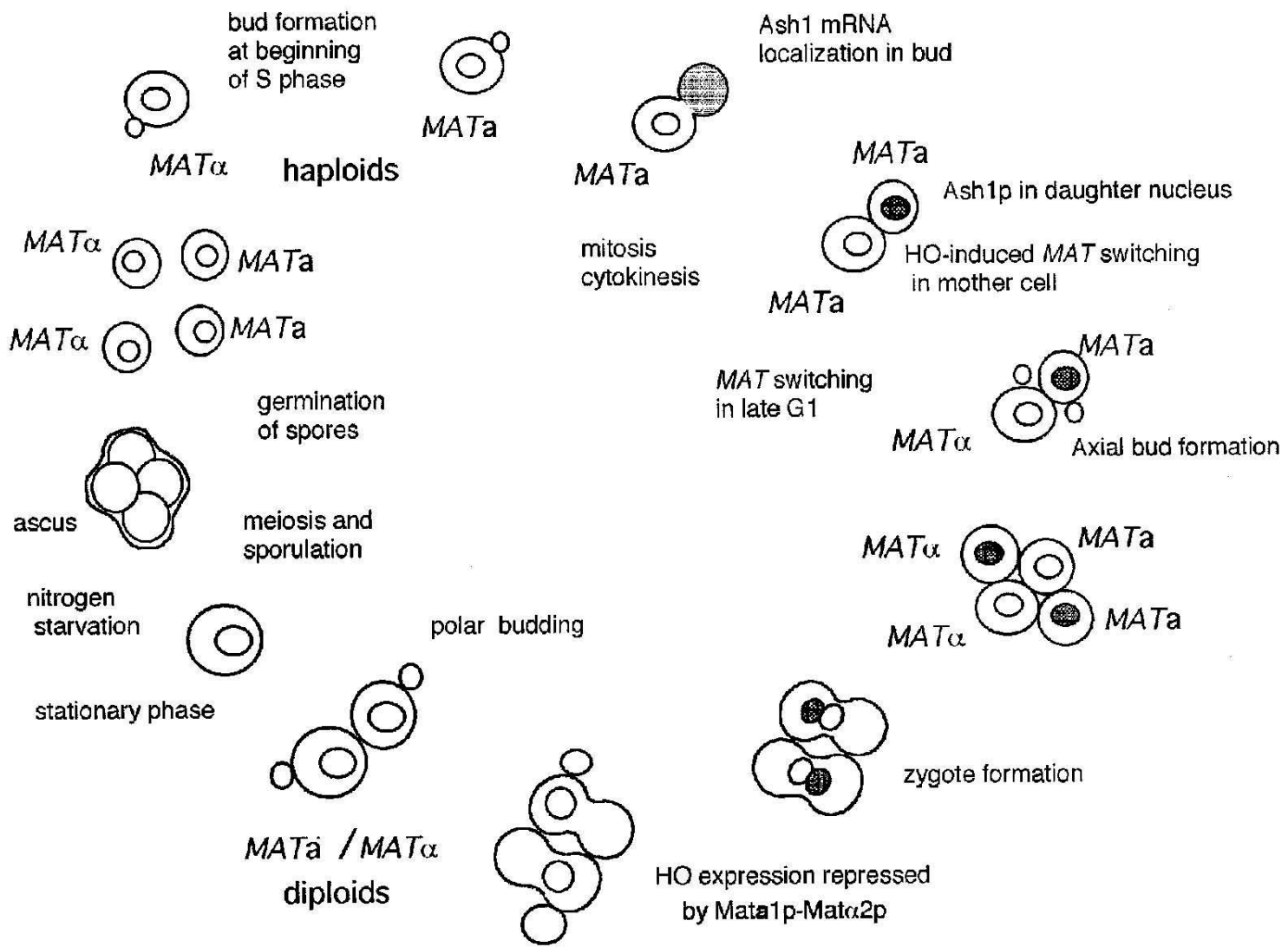
Marshall et al. '96

Interphase chromosomes assume well defined territories.

Chromosomal loci are associated with the nuclear membrane.

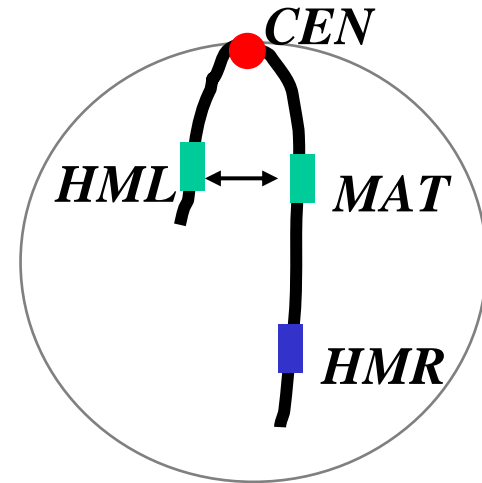
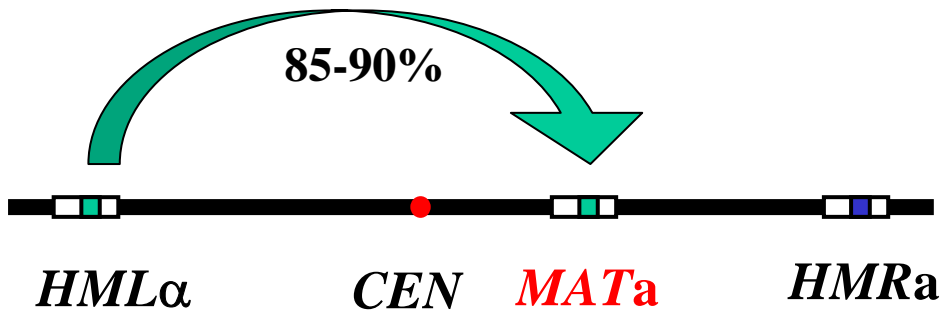
Chromosome structure and organization regulate gene expression.

The life and times of yeast

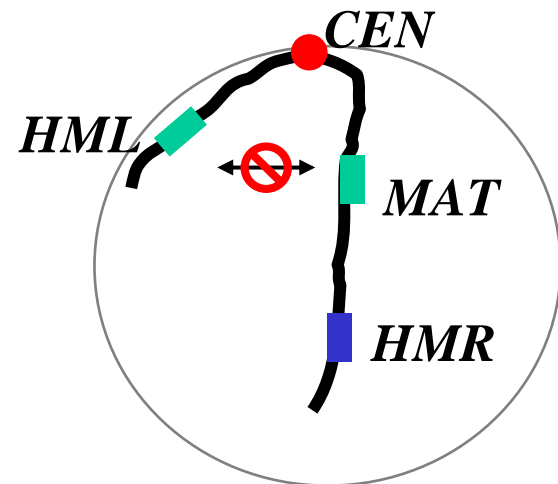
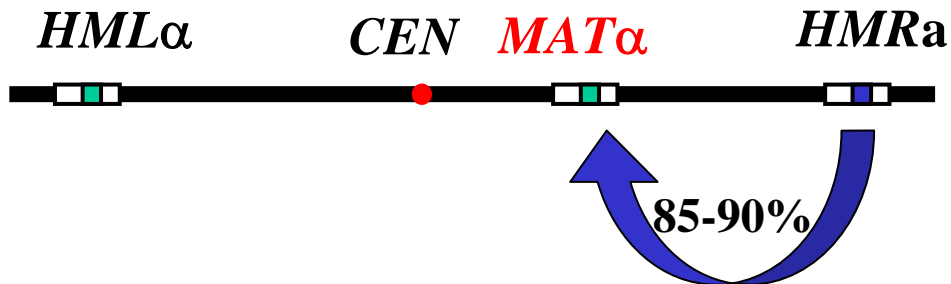


Mating-type switching in yeast

a cell

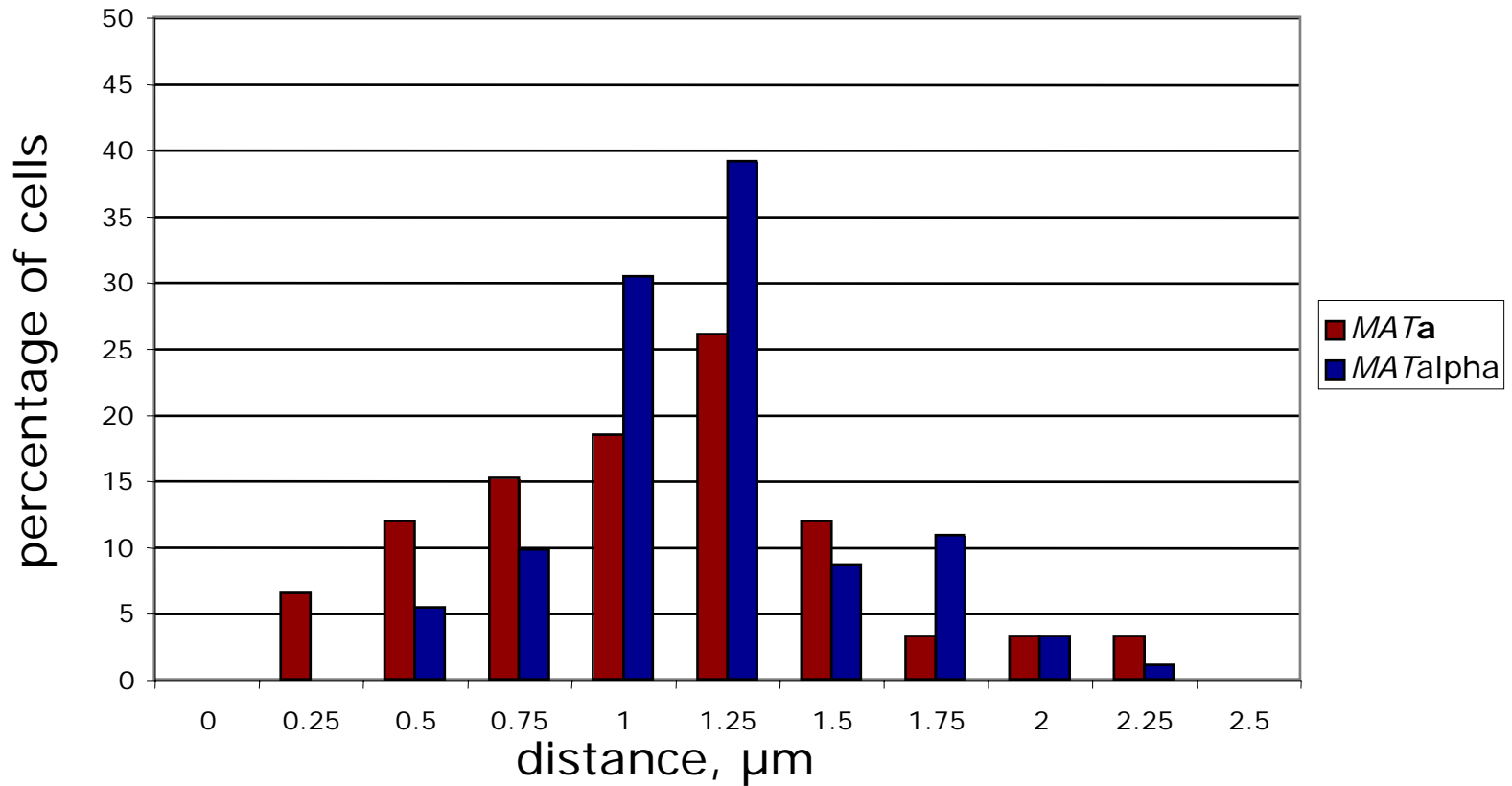
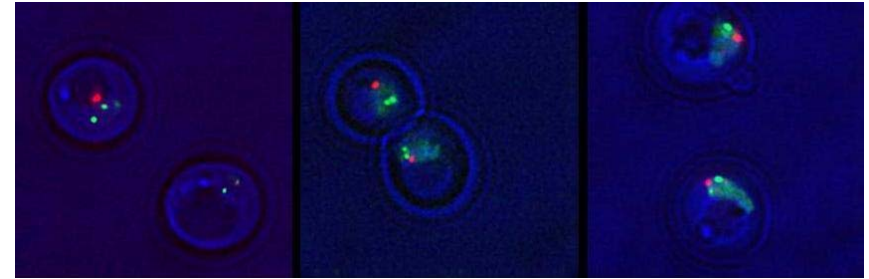
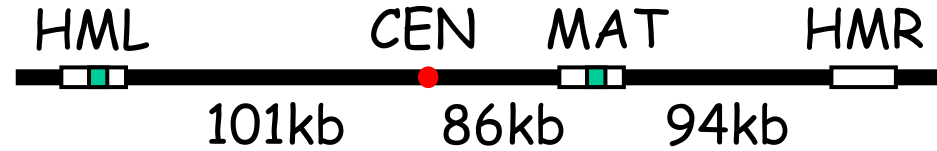


α cell



What is the physical mechanism of donor preference?

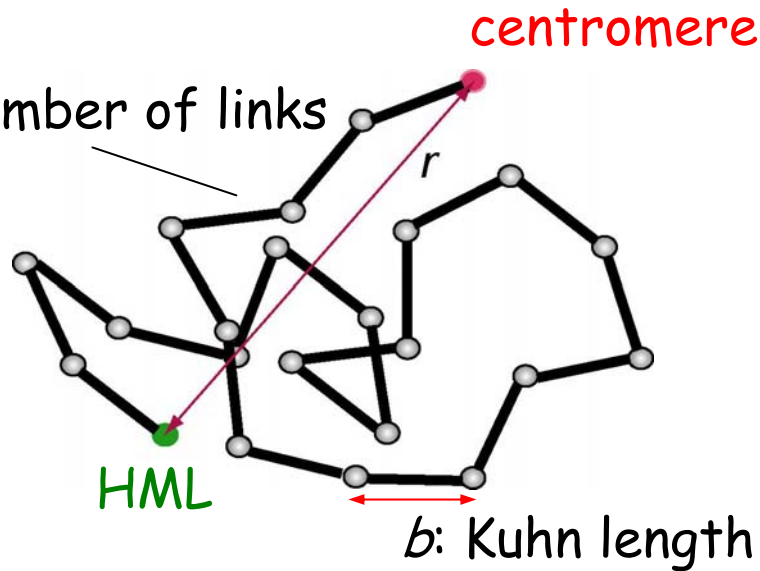
HML-CEN distance distributions



Does tethering account quantitatively for the difference in distributions?

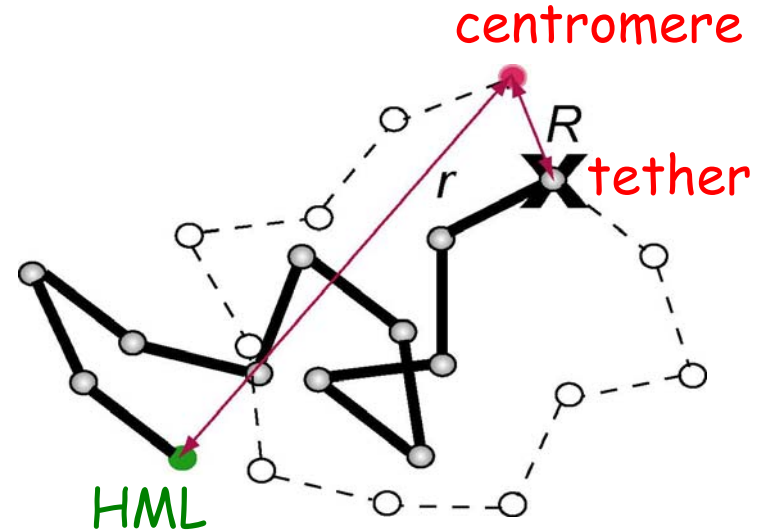
Polymer models of chromosome III

a cell



$$P(r) = \mathcal{N} r^2 e^{-\frac{3r^2}{2Nb^2}}$$

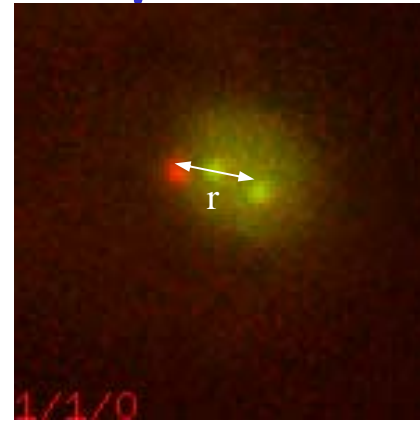
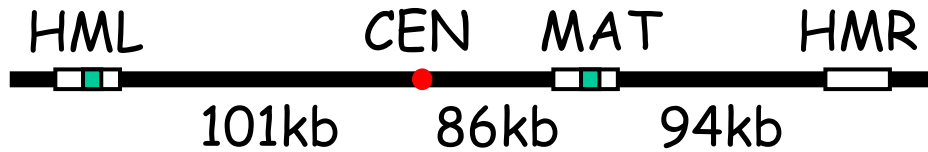
α cell



$$P(r) = \mathcal{N} \frac{r}{R} \left[e^{-\frac{3(r-R)^2}{2Nb^2}} - e^{-\frac{3(r+R)^2}{2Nb^2}} \right]$$

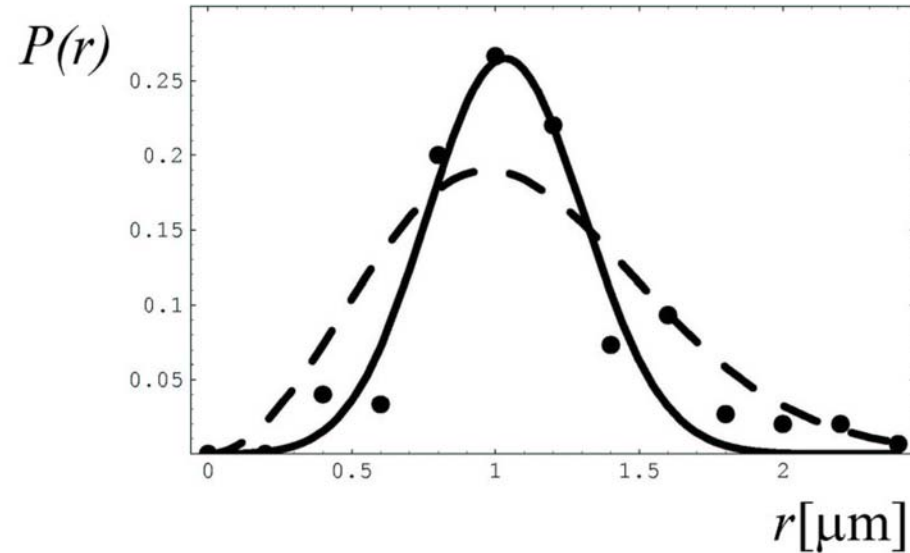
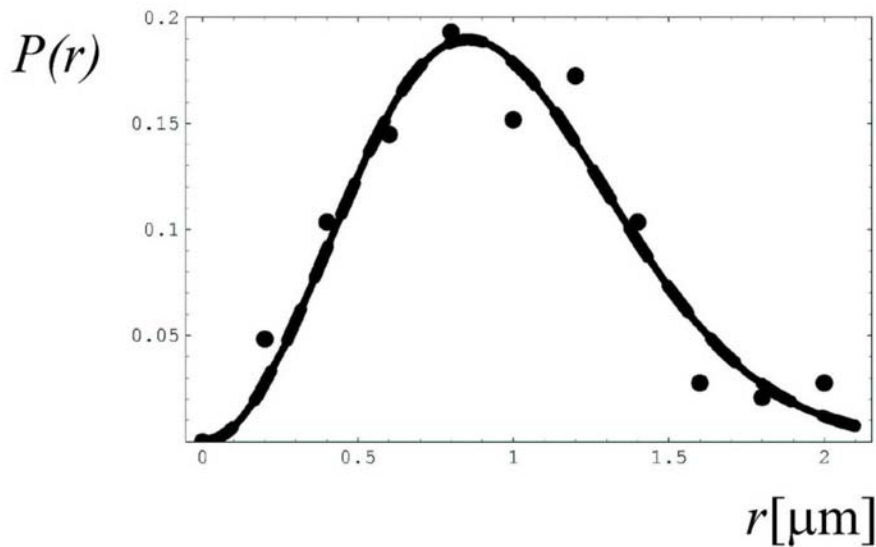
A tethering site between HML and centromere leads to a change in the functional form of the distance distribution.

Distance distributions: experiment meets theory



a cell

α cell

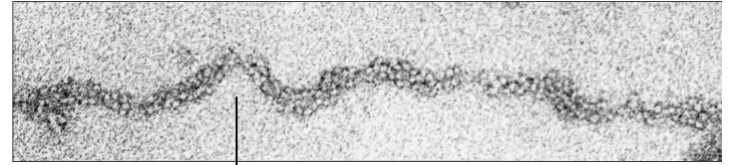
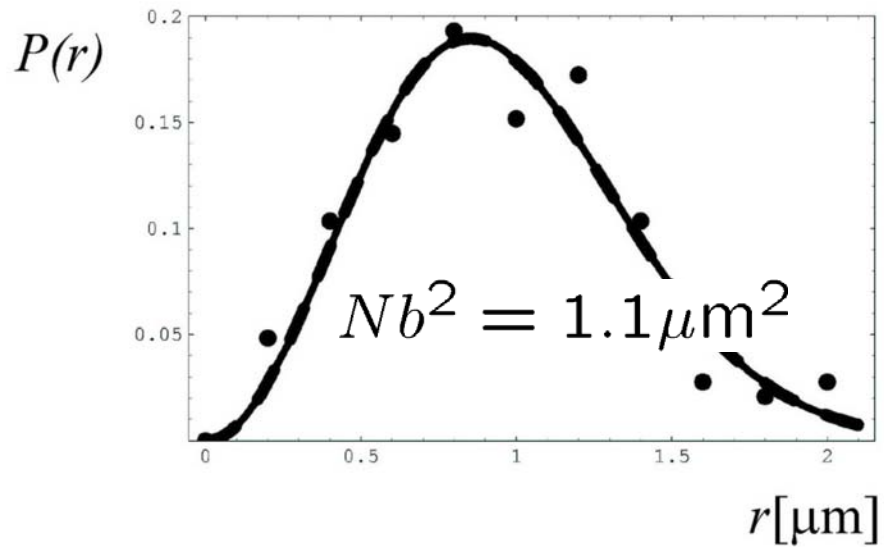


Chromosome III is **not tethered**.

Chromosome III is **tethered**.

Interphase chromatin structure

a cell

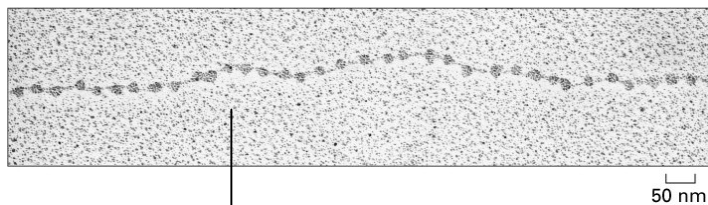
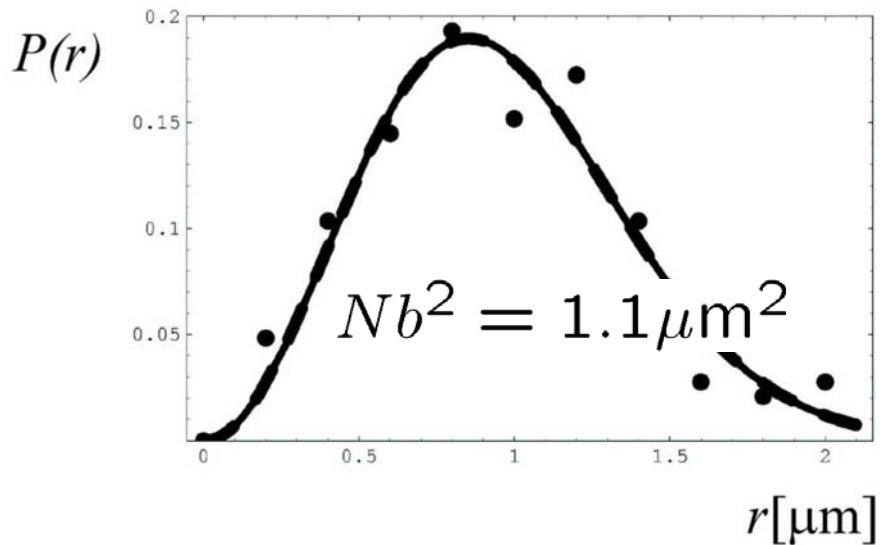


$$\nu \approx 10\text{nm/kb}$$

$$Nb = 100\text{kb} \times \nu \approx 1\mu\text{m}$$

Interphase chromatin structure

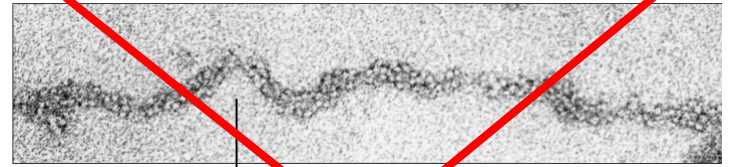
a cell



$$\nu \approx 125 \text{ nm/kb}$$

$$Nb = 100 \text{ kb} \times \nu \approx 12.5 \mu\text{m}$$

$$\Rightarrow N \approx 140 \quad b \approx 90 \text{ nm}$$



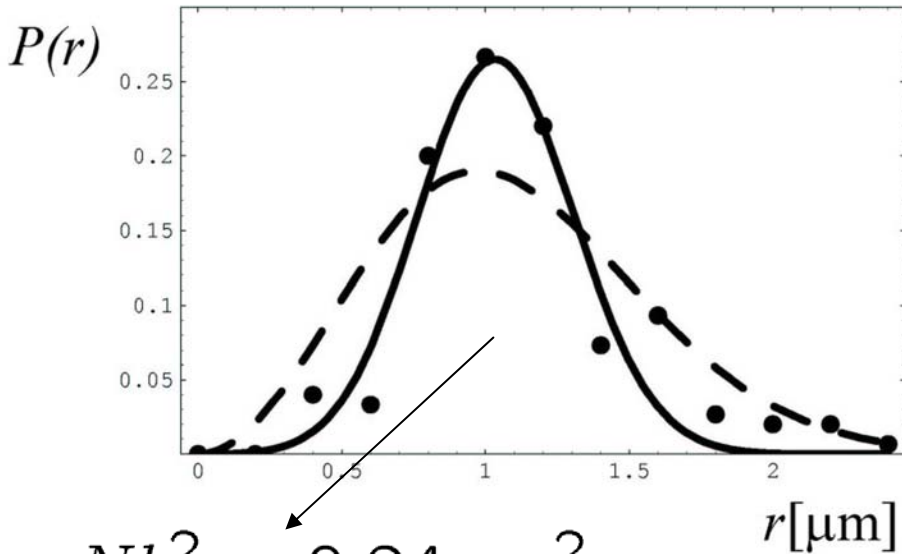
$$\nu \approx 10 \text{ nm/kb}$$

$$Nb = 100 \text{ kb} \times \nu \approx 1 \mu\text{m}$$

The left arm of chromosome III in yeast can be modeled as a 10nm fiber.

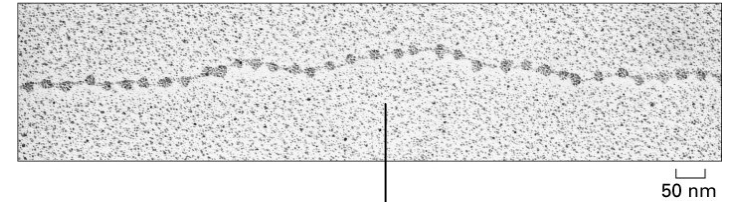
Tethering of chromosome III

α cell



$$Nb^2 = 0.24 \mu\text{m}^2$$

$$R = 0.96 \mu\text{m}$$

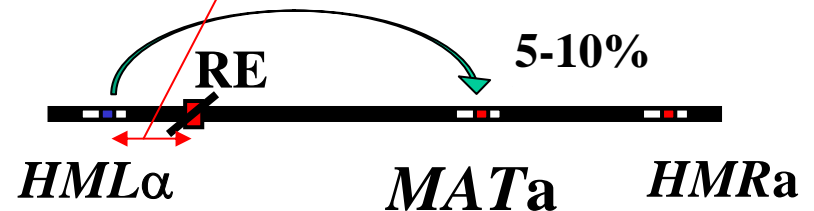


$$\nu \approx 125 \text{ nm/kb} \quad b = 90 \text{ nm}$$

$$Nb = \frac{0.24 \mu\text{m}^2}{90 \text{ nm}} = 2.6 \mu\text{m}$$

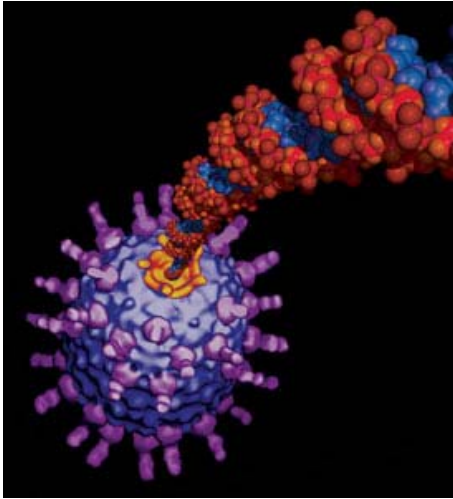
$2.6 \mu\text{m} / \nu = 21 \text{ kb}$ is the distance between HML and the tether site.

Prediction: The left arm of chromosome III in α cells is tethered 21kb away from HML.

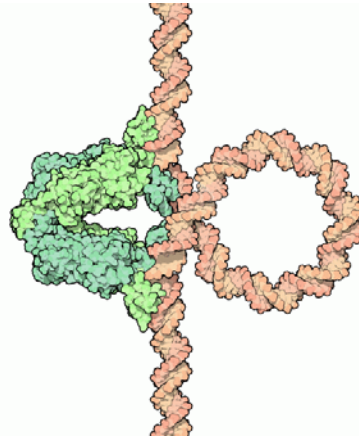


DNA confinement and cell biology

Viral life cycle

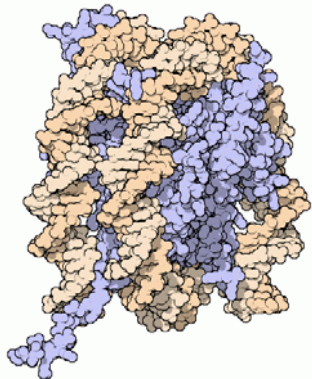


Transcriptional regulation

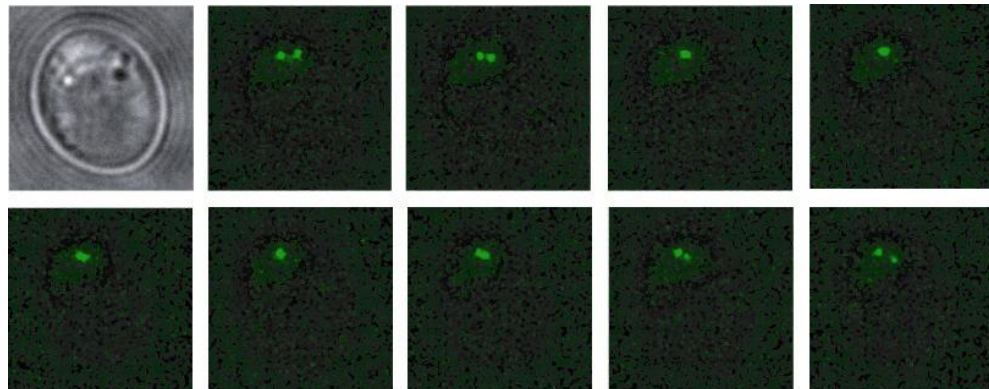


Life's processes are profoundly influenced by the spatial organization of DNA inside the cell.

Nucleosomes



DNA recombination



Acknowledgements



Josh Martin



Jim Haber



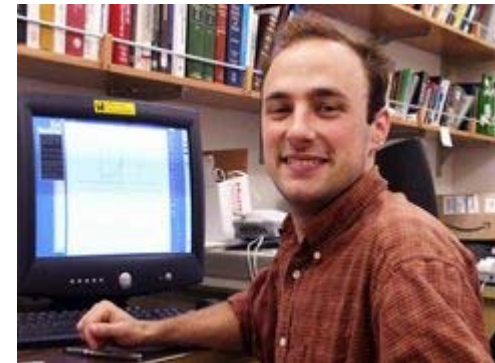
Deb Bressan



Prashant Purohit



Rob Phillips



Paul Wiggins

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It's not just about the DNA



Frey, Manella '03

