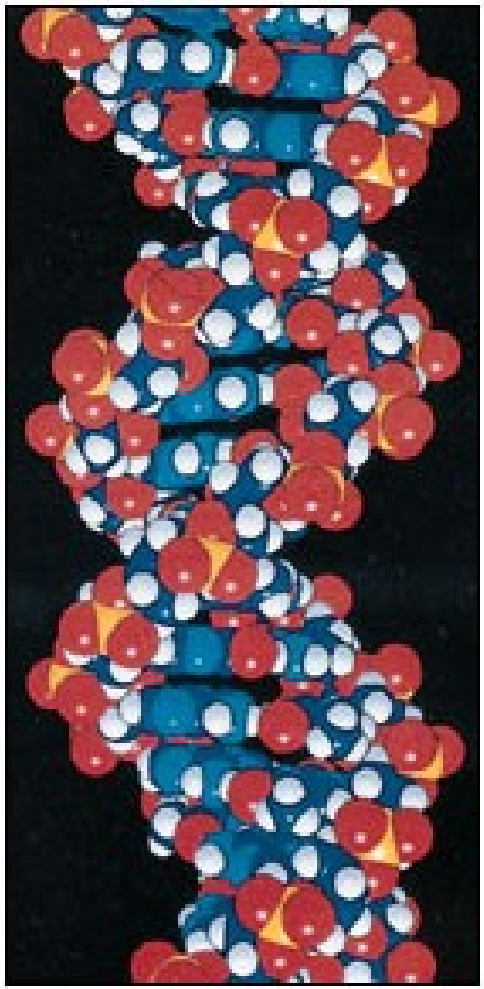
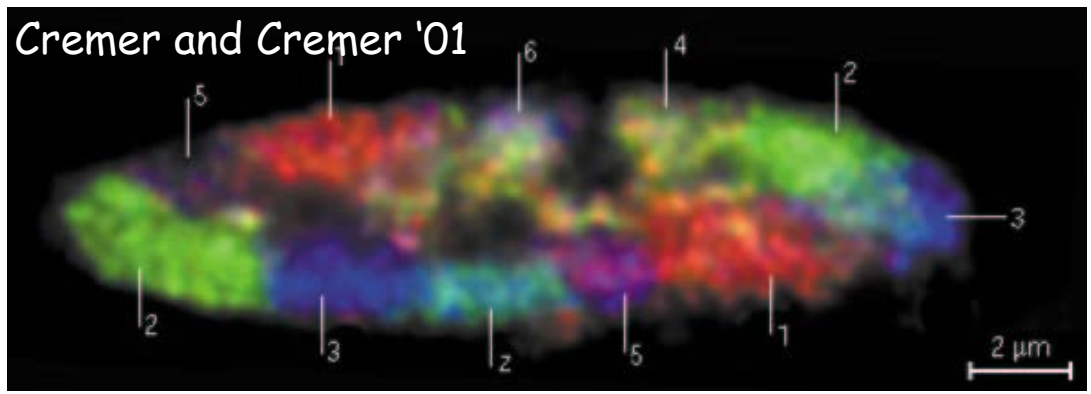
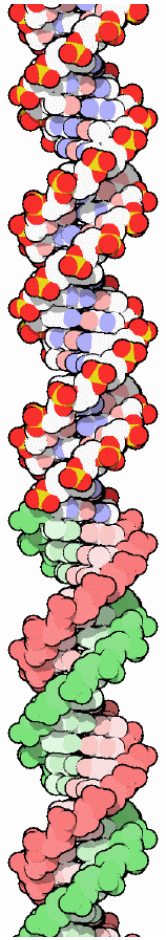
Physics of genome management

J. Kondev - Brandeis University



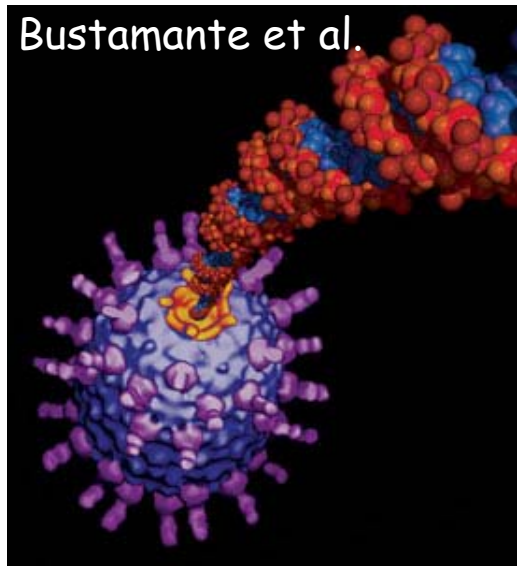


Overview



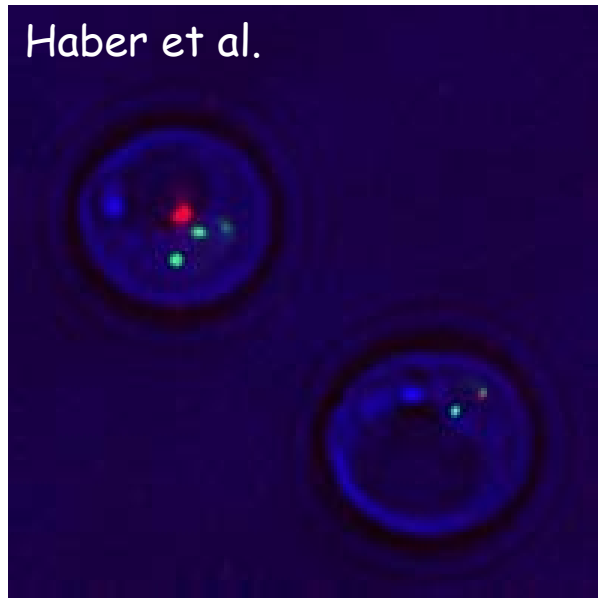
The double helix

- *Central dogma of MB*



Viral DNA Packing

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



Chromosomes in vivo

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

Whither space and time?

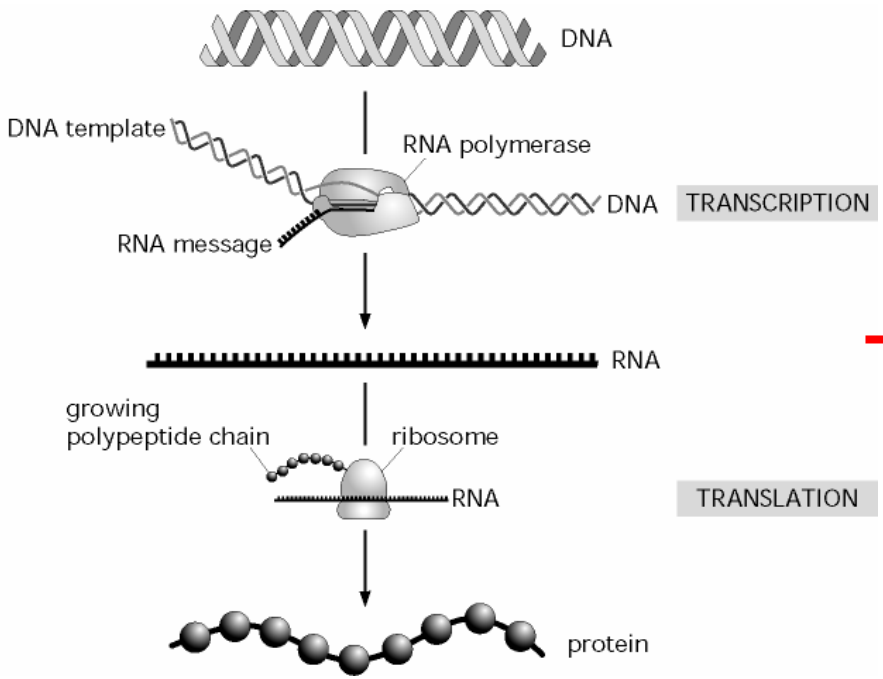
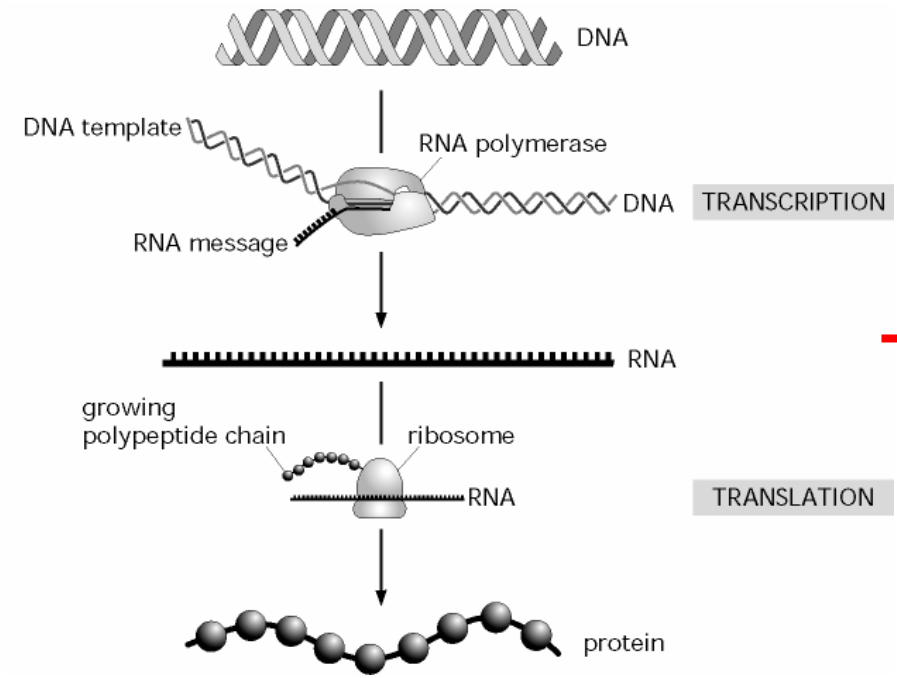
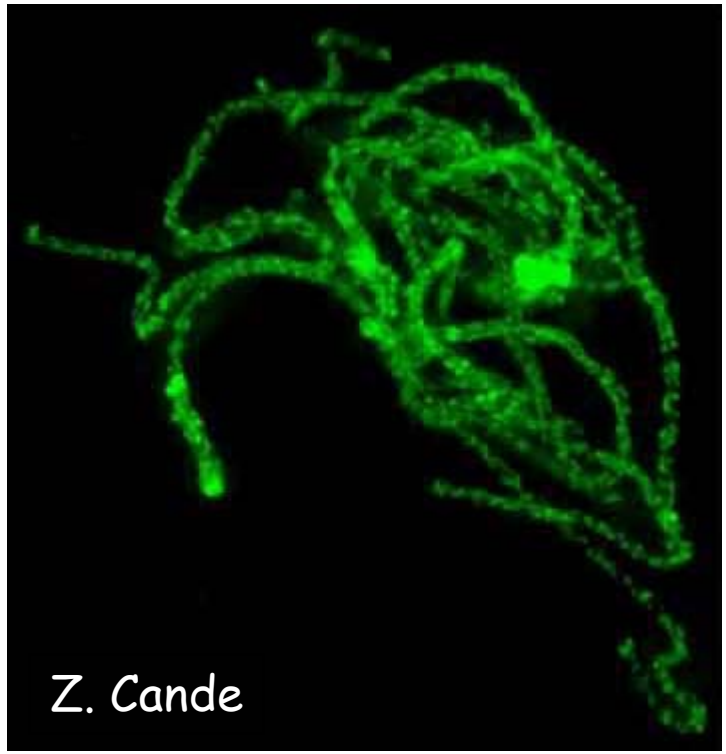


Figure 5-11 Essential Cell Biology, 2/e. (' 2004 Garland Science)

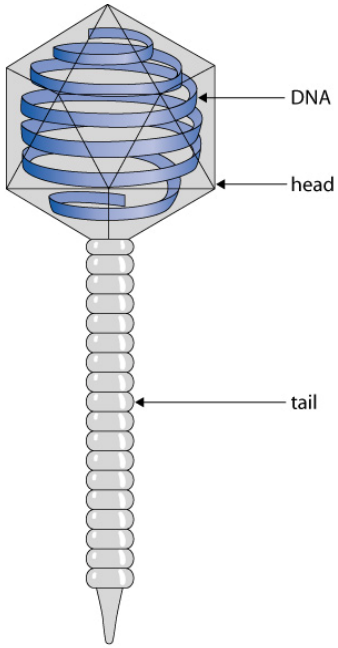
Whither space and time?



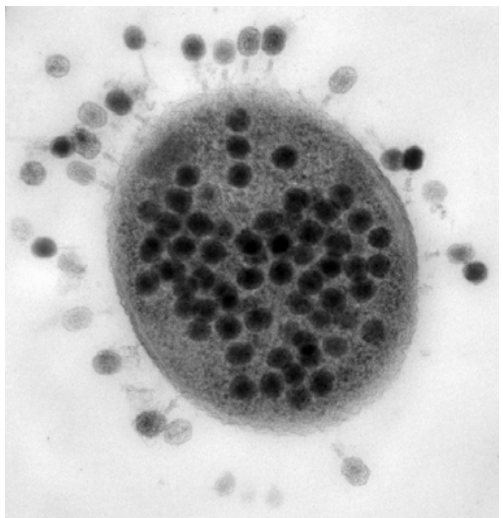


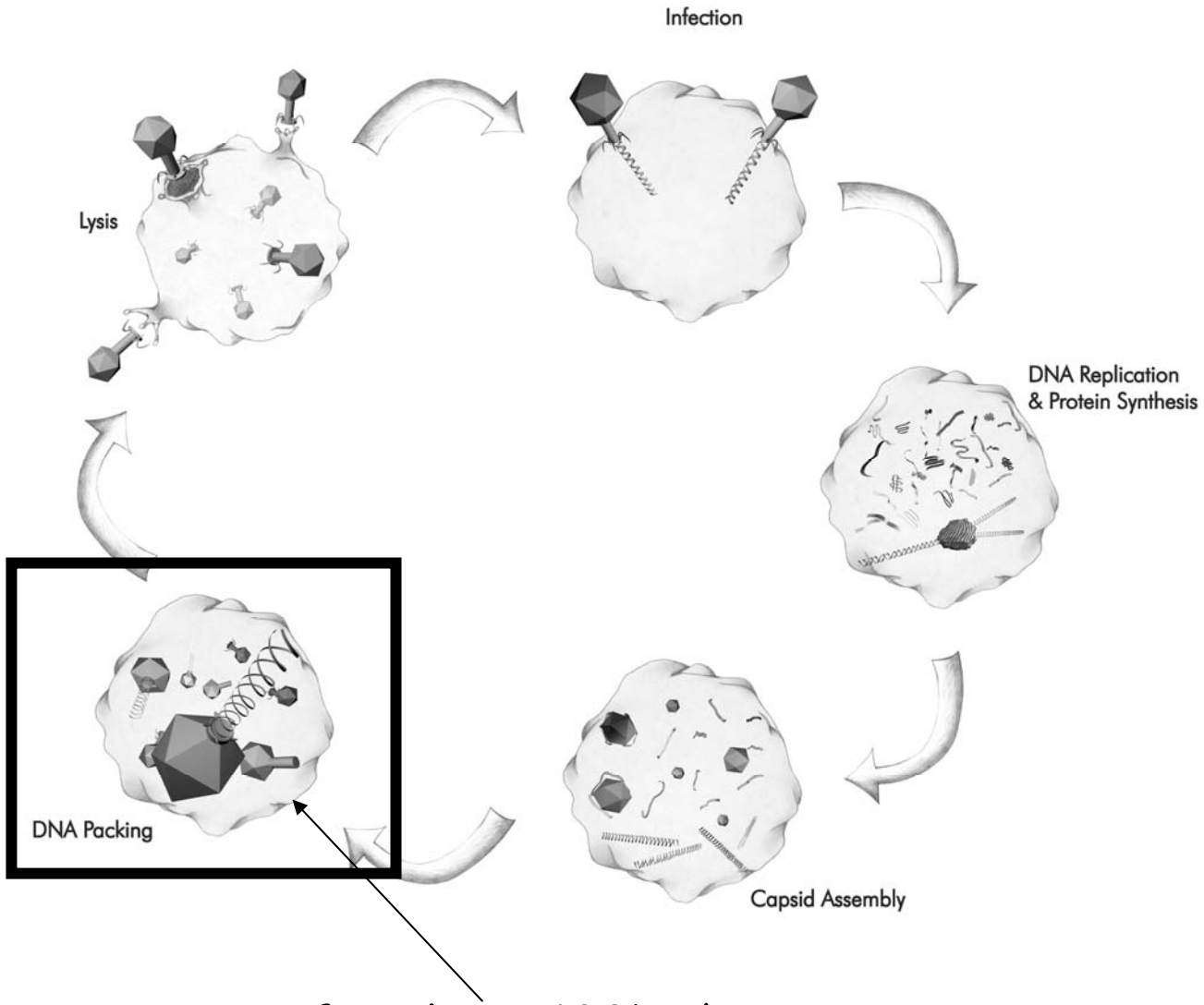
How does the spatial arrangement of DNA in the cell affect the processes of the central dogma?

Case 1: Viral assembly



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

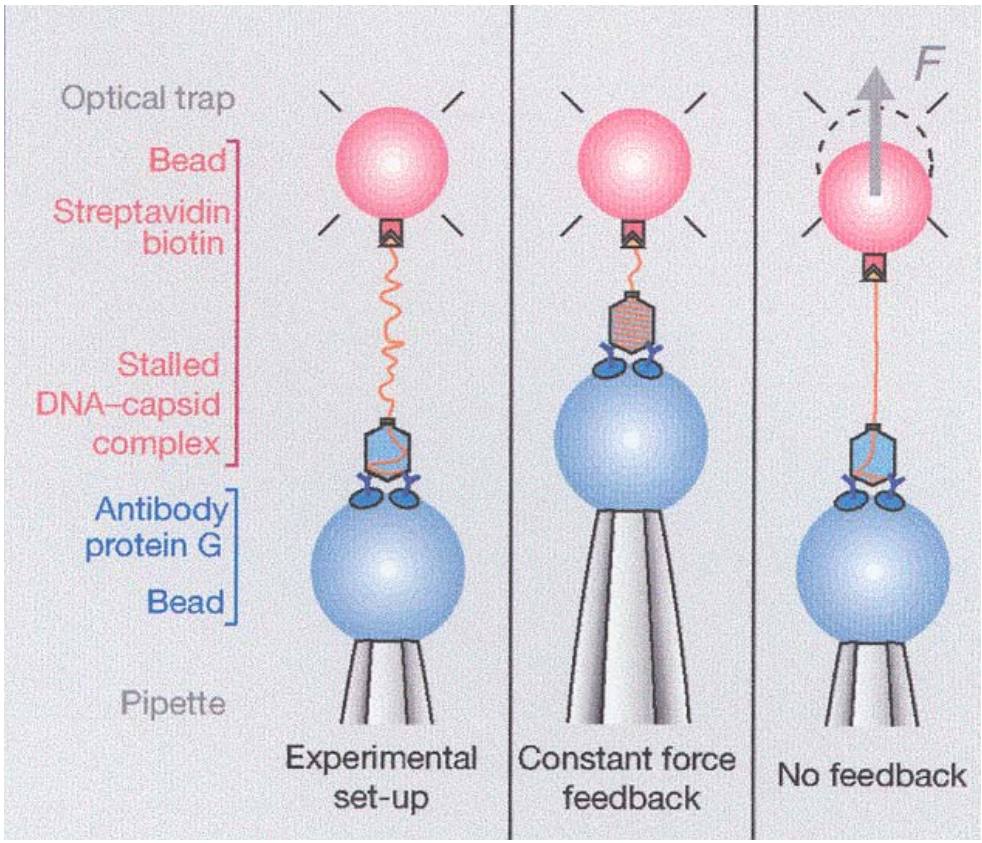


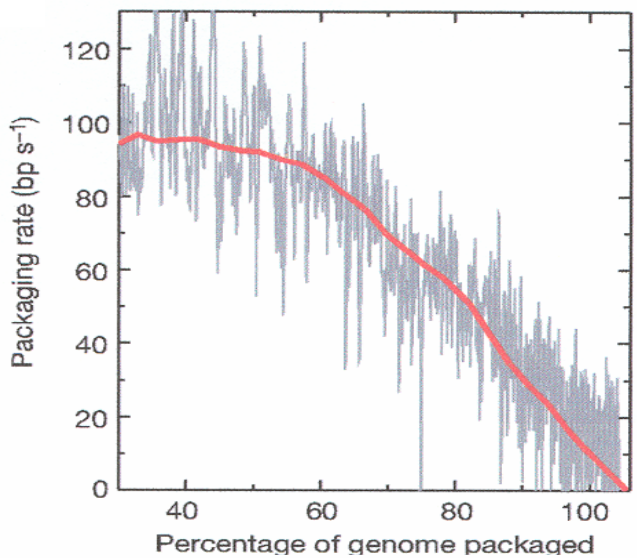


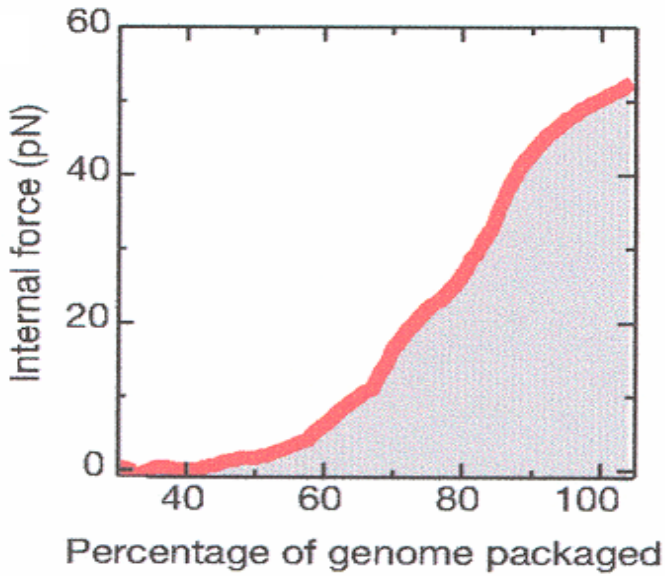
Rate of packing: 100bp/sec

Single molecule studies of viral packing

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





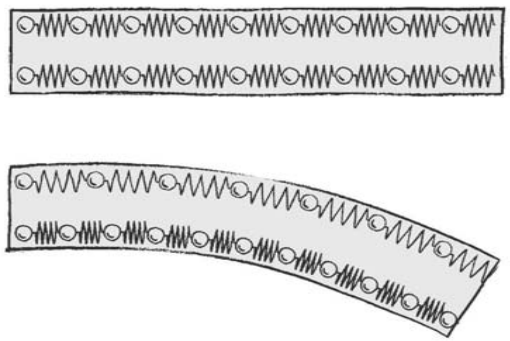


Quantitative data requires quantitative models!

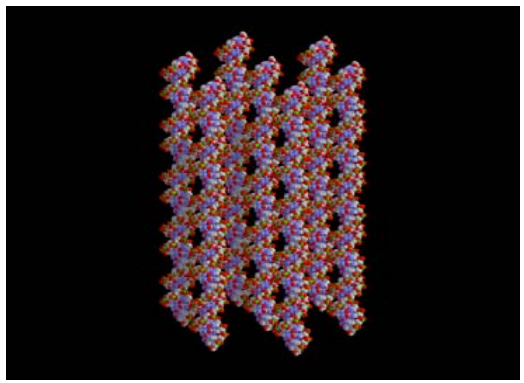
Model of packed DNA

Riemer et al., Odijk, Gelbart et al.

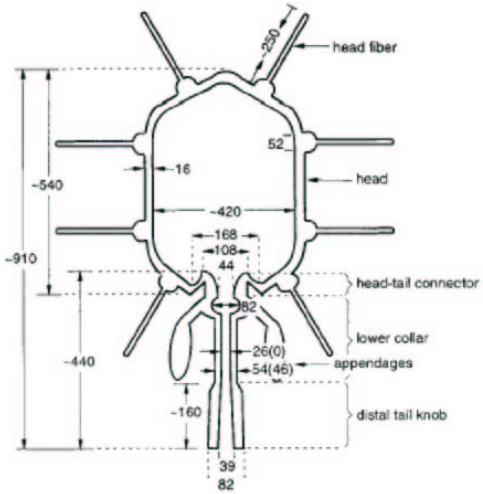
DNA elasticity



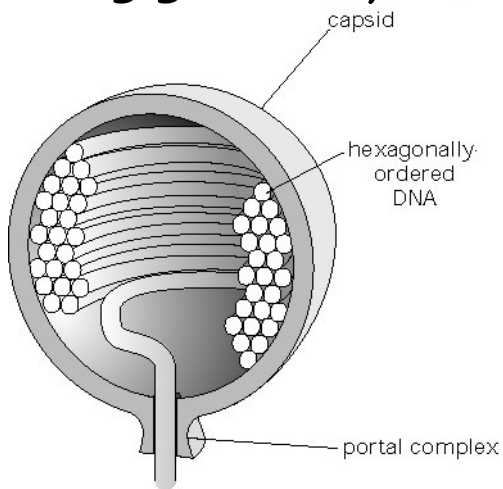
DNA charge



Viral dimensions

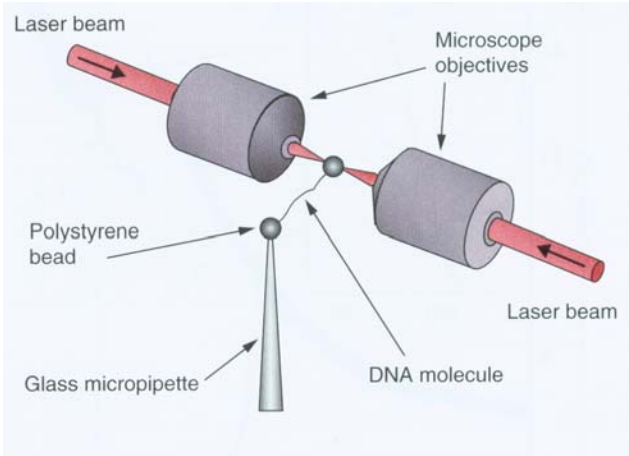


Packing geometry

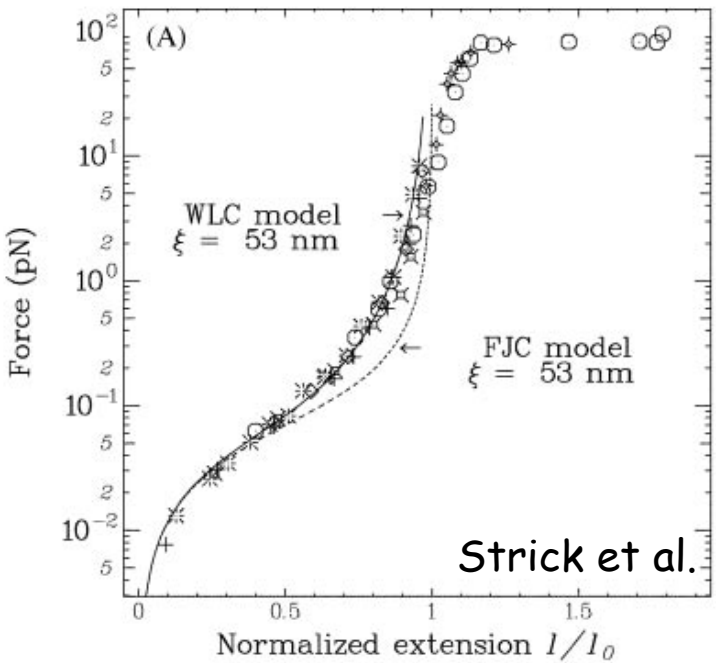


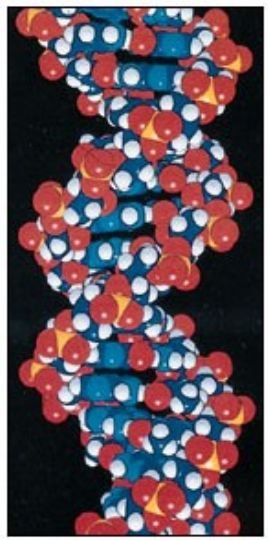
DNA elasticity

Bustamante, Marko and Siggia, Vologodskii, …



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





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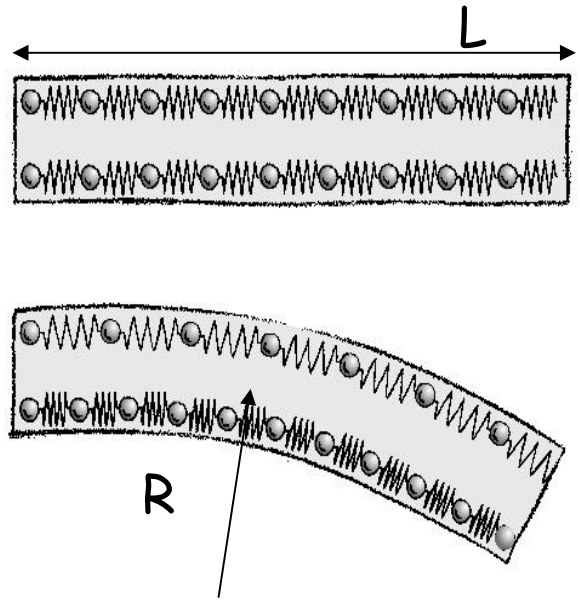
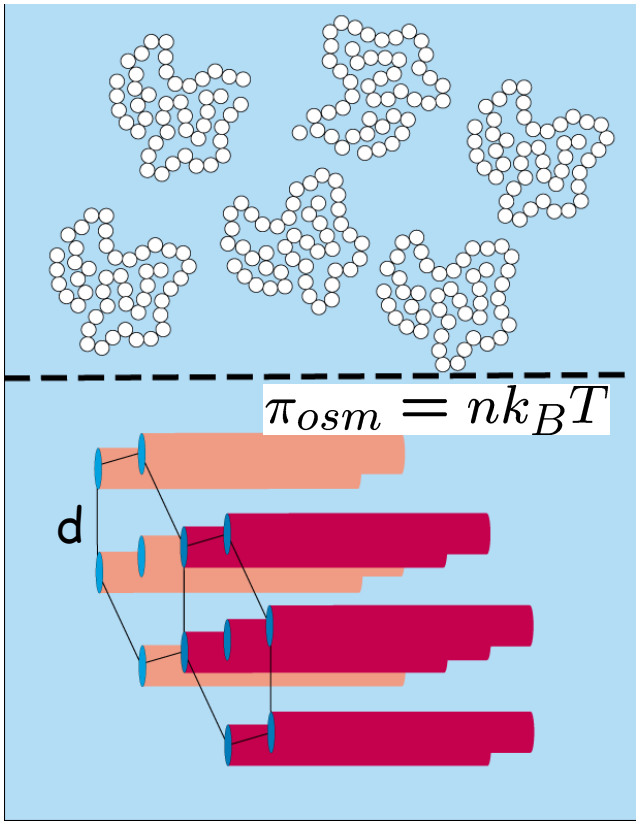


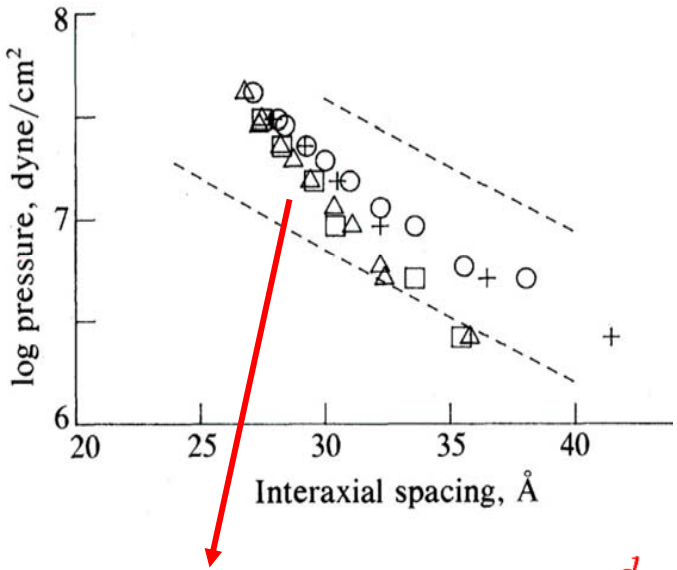
$$E_{\text{beam}} = \frac{\xi_P k_B T}{2} \frac{L}{R^2}$$

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

DNA electrostatics



Rau and Parsegian



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

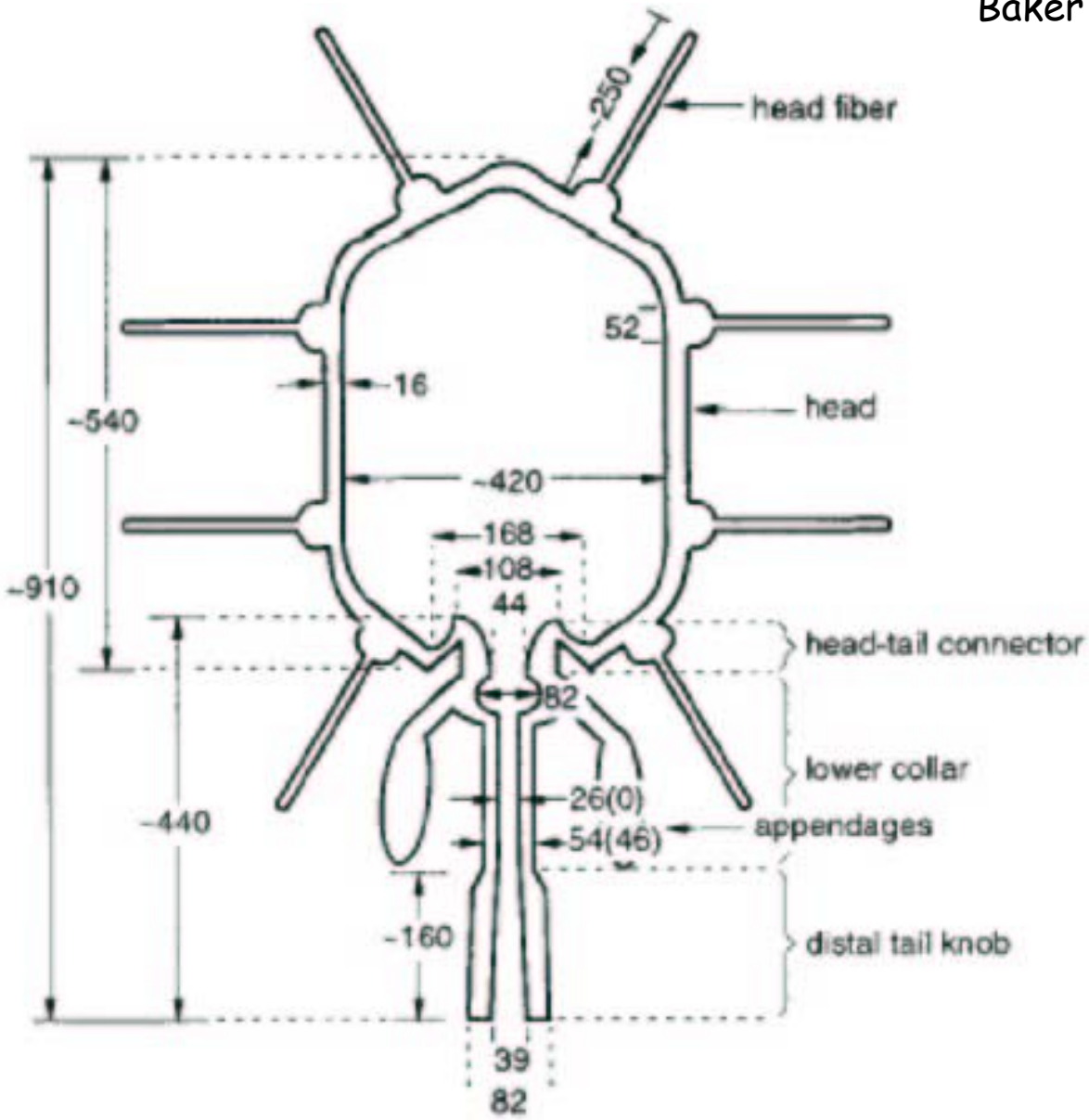
where F_0=55nN/nm^2 and c=.27nm.

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

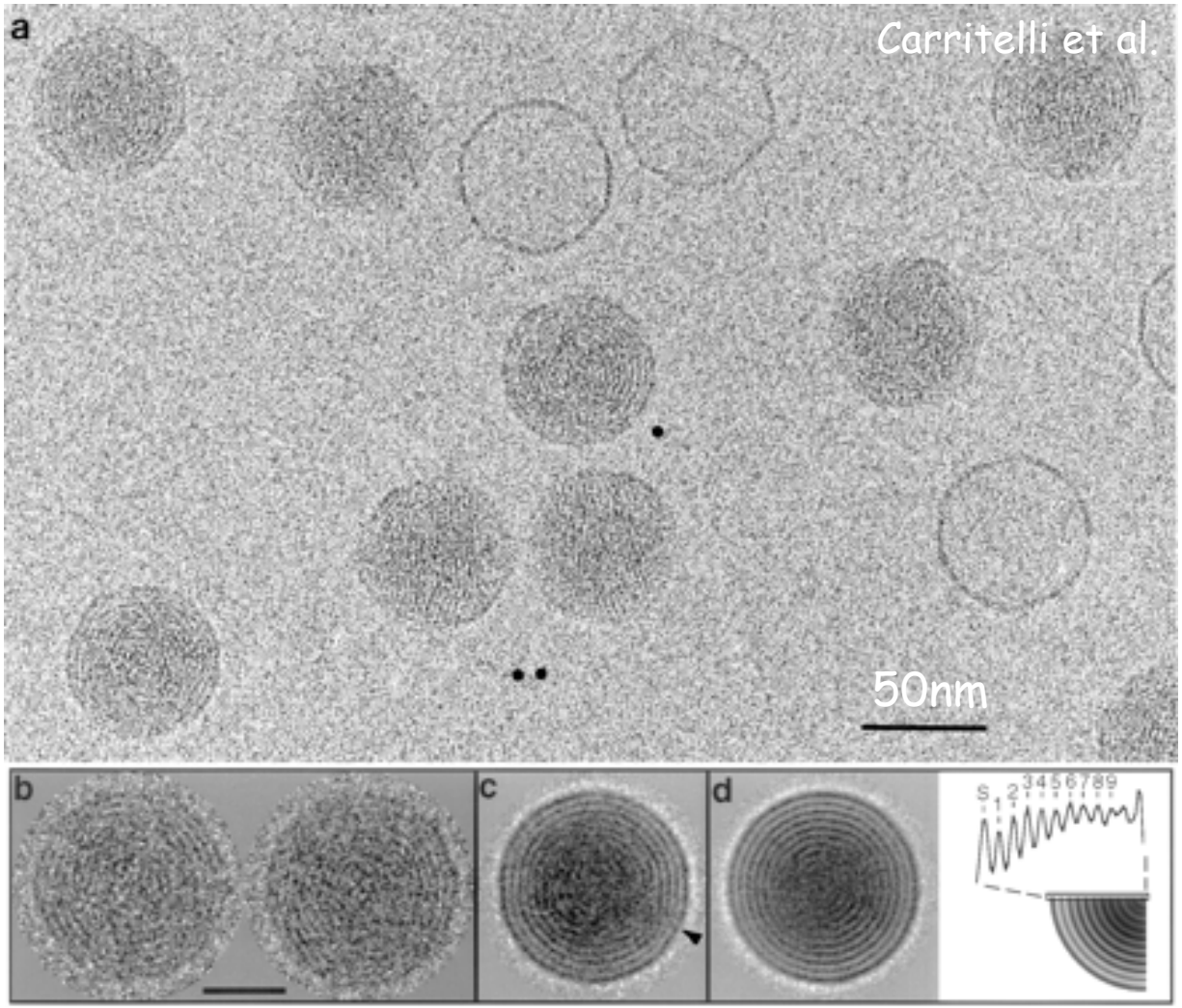
$$e(d) = \sqrt{3}\int_{\infty}^{d} x\pi_{osm}(x)dx = \sqrt{3}F_0(c^2 + cd)e^{-\frac{d}{c}}$$

ϕ29 dimensions

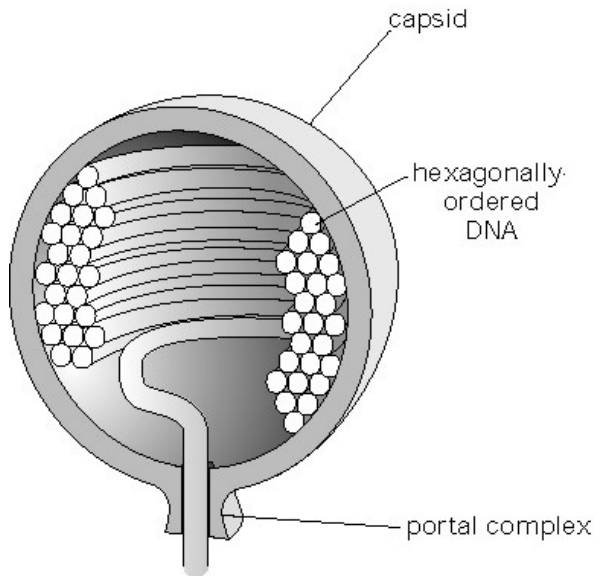
Baker et al.



DNA packing: insights from cryoEM

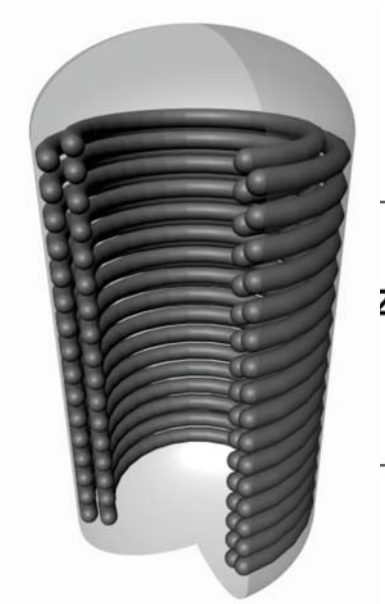


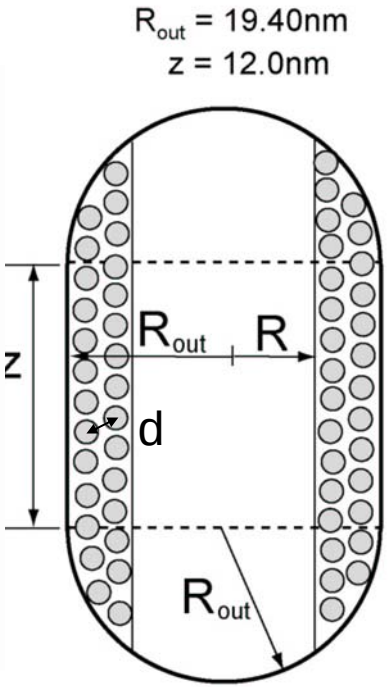
Inverse spool configuration

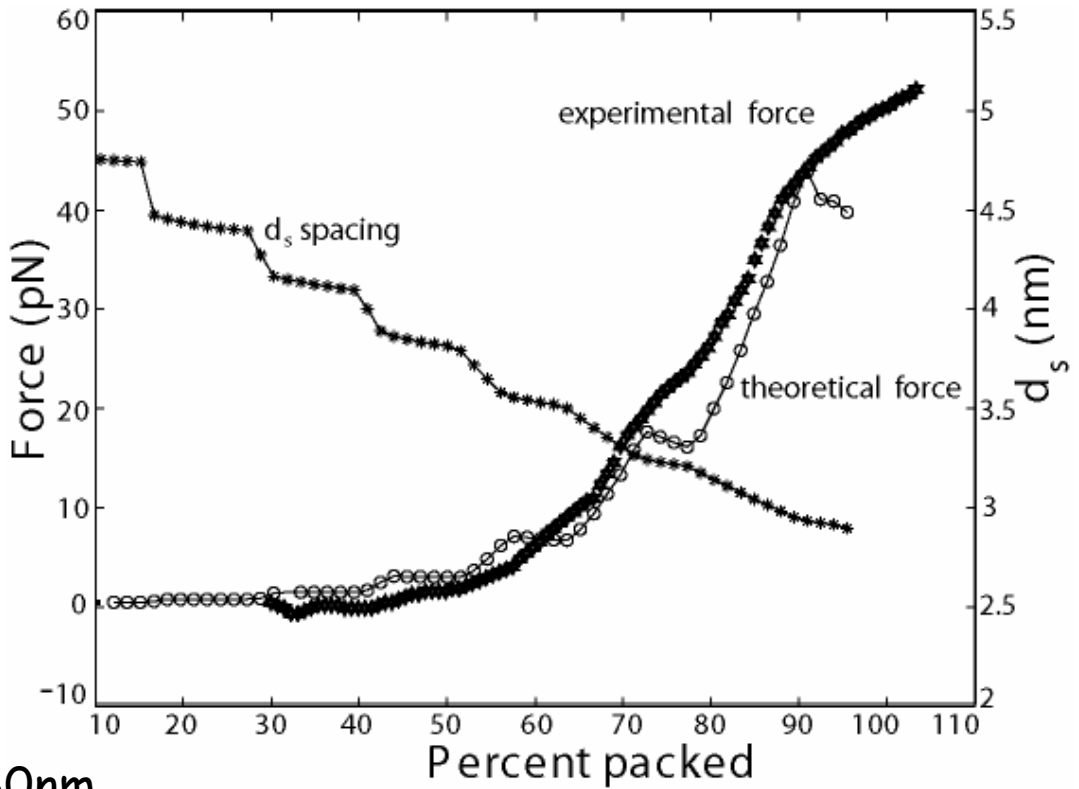


Model of packed DNA

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





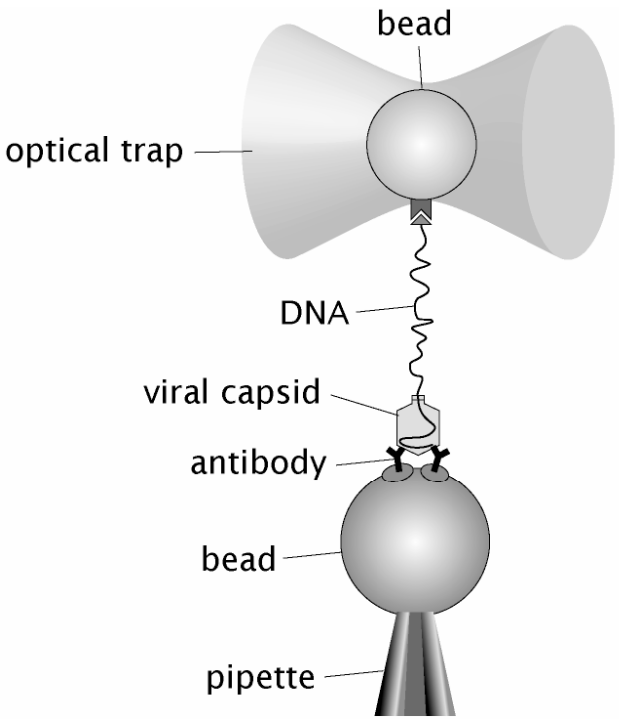


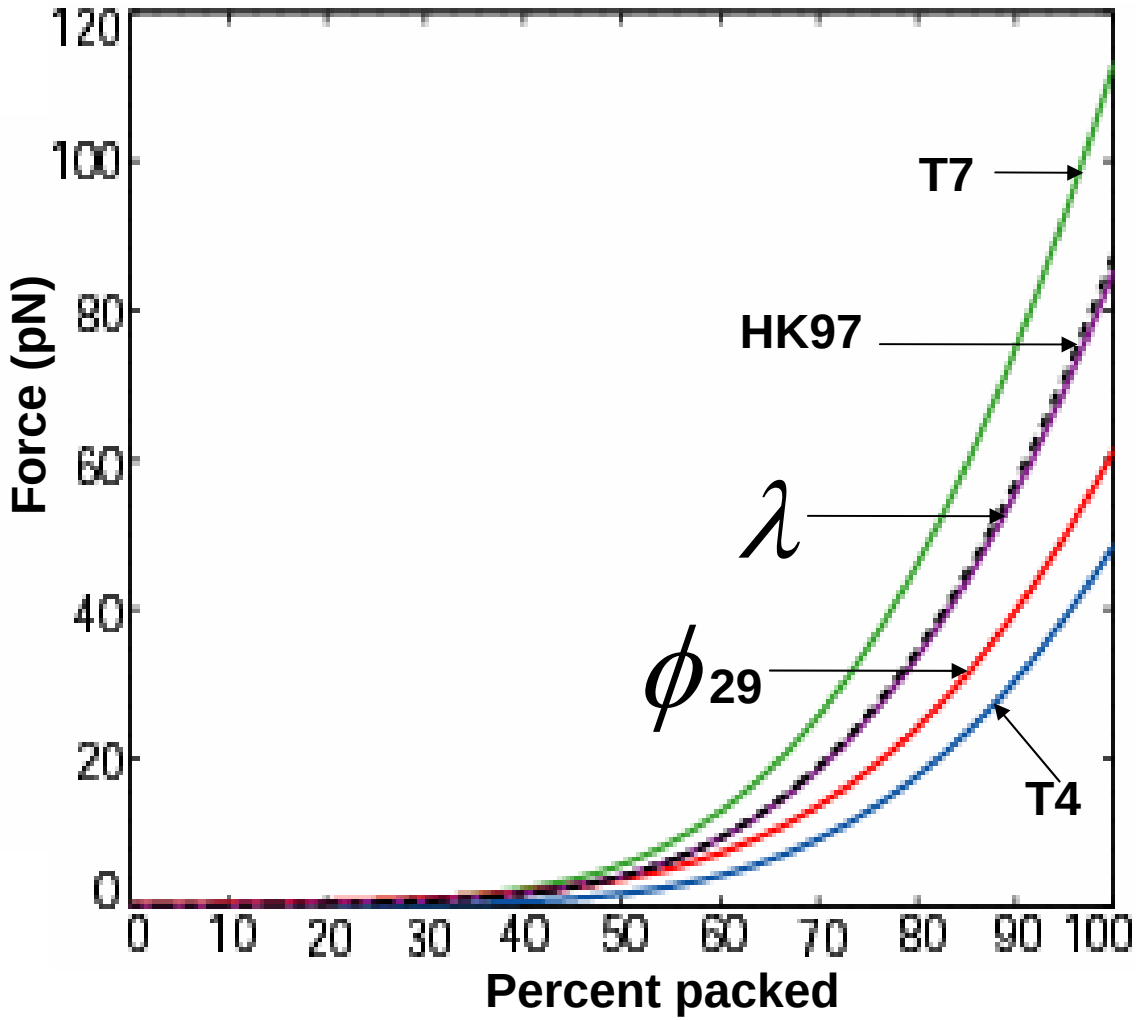
R_{out}=19.4nm, z=12nm, and L_{gen}=6580nm.

Models must make predictions!

Prediction: Different phages

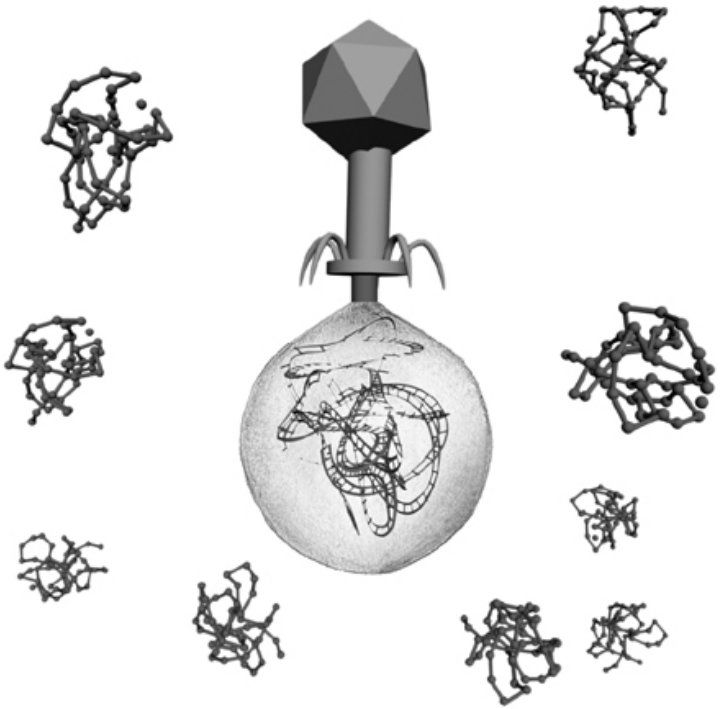
The legth of the viral genome and the size of the capsids vary among phages.

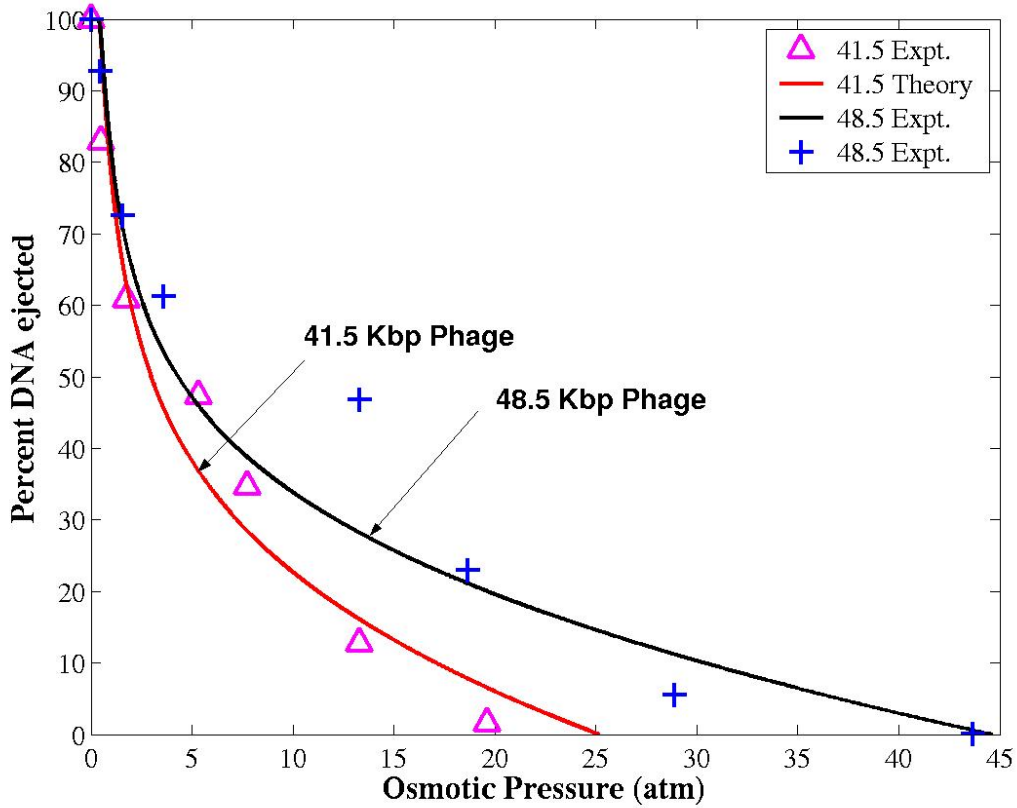




Prediction: Ejection inhibition

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

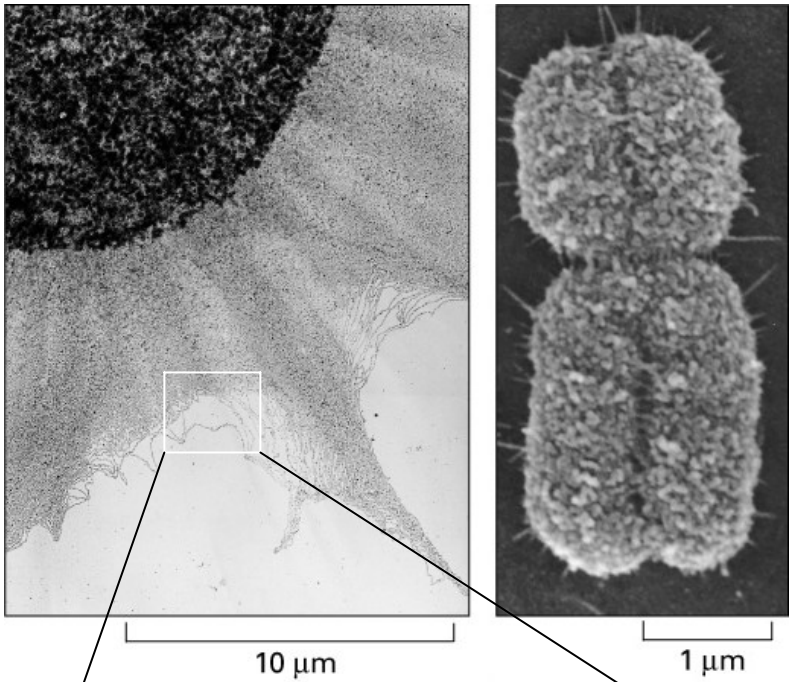




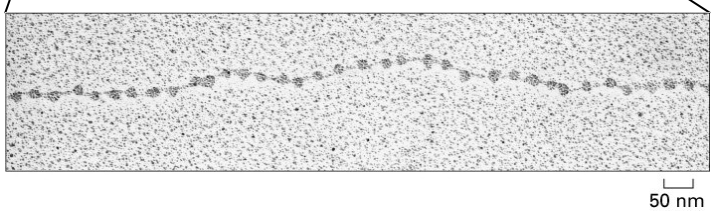
$$\underbrace{\frac{\partial E_{in}}{\partial L}(L_{\text{genome}} - L)}_{\text{packing model}} = \underbrace{\frac{\partial E_{out}}{\partial L}(L)}_{\text{osmotic pressure}}$$

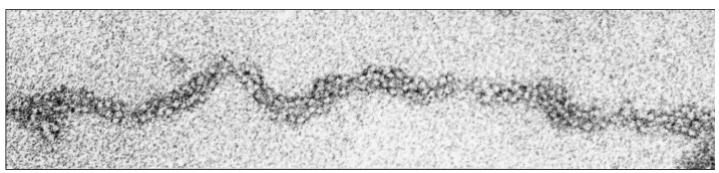
Filled capsids are pressurized!

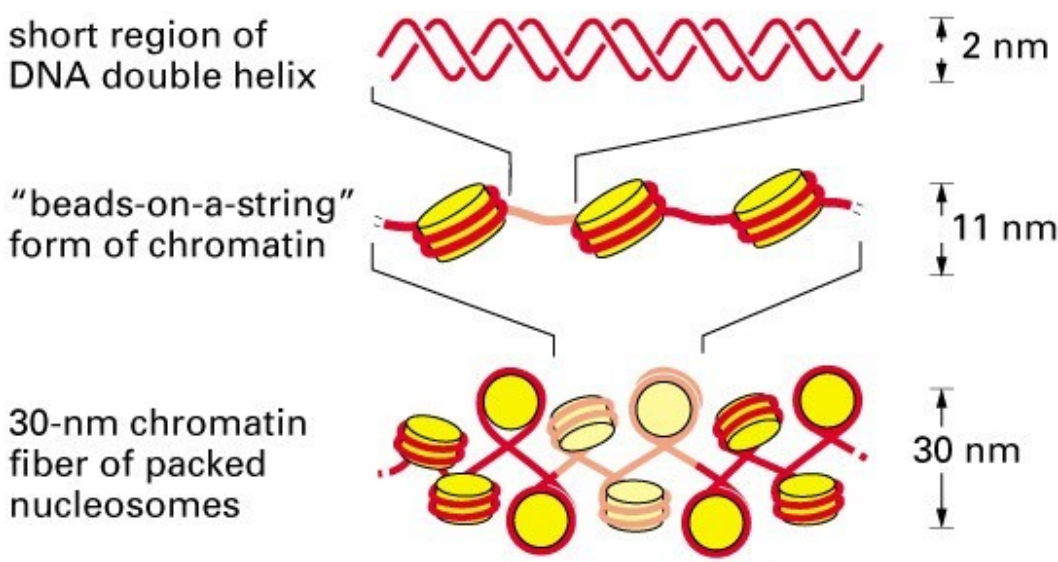
Case 2: Eukaryotic chromosomes



Interphase chromosomes are less condensed than their metaphase counterparts.

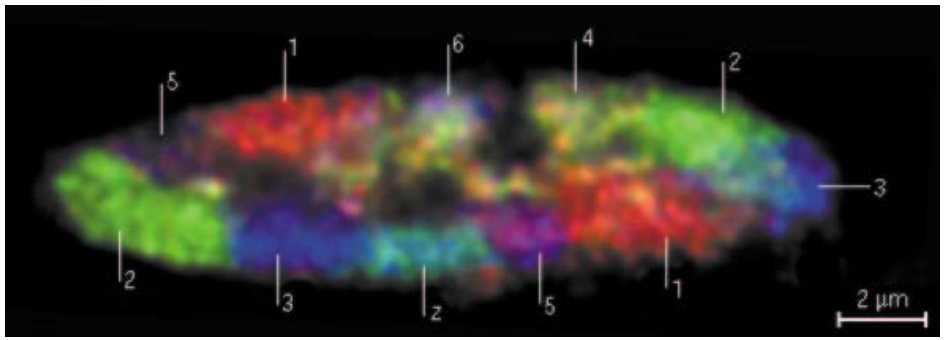




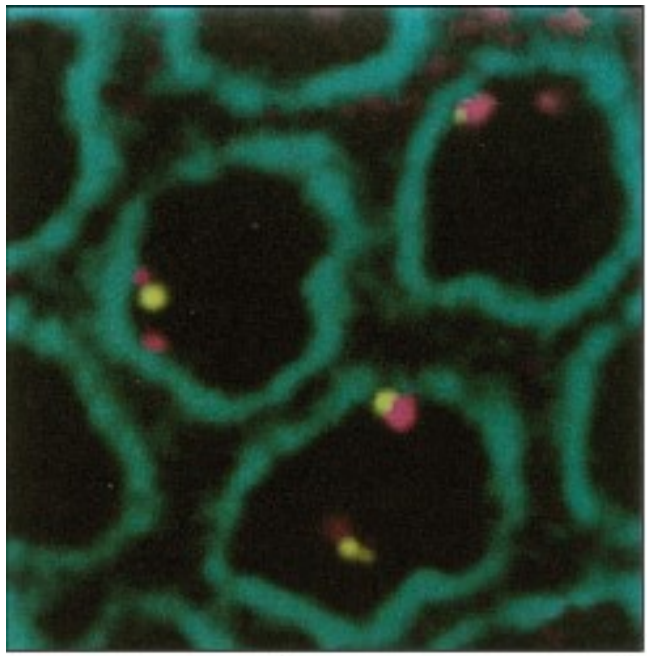


Molecular Biology of the Cell, 4th Edition

Chromosome organization



Cremer and Cremer '01



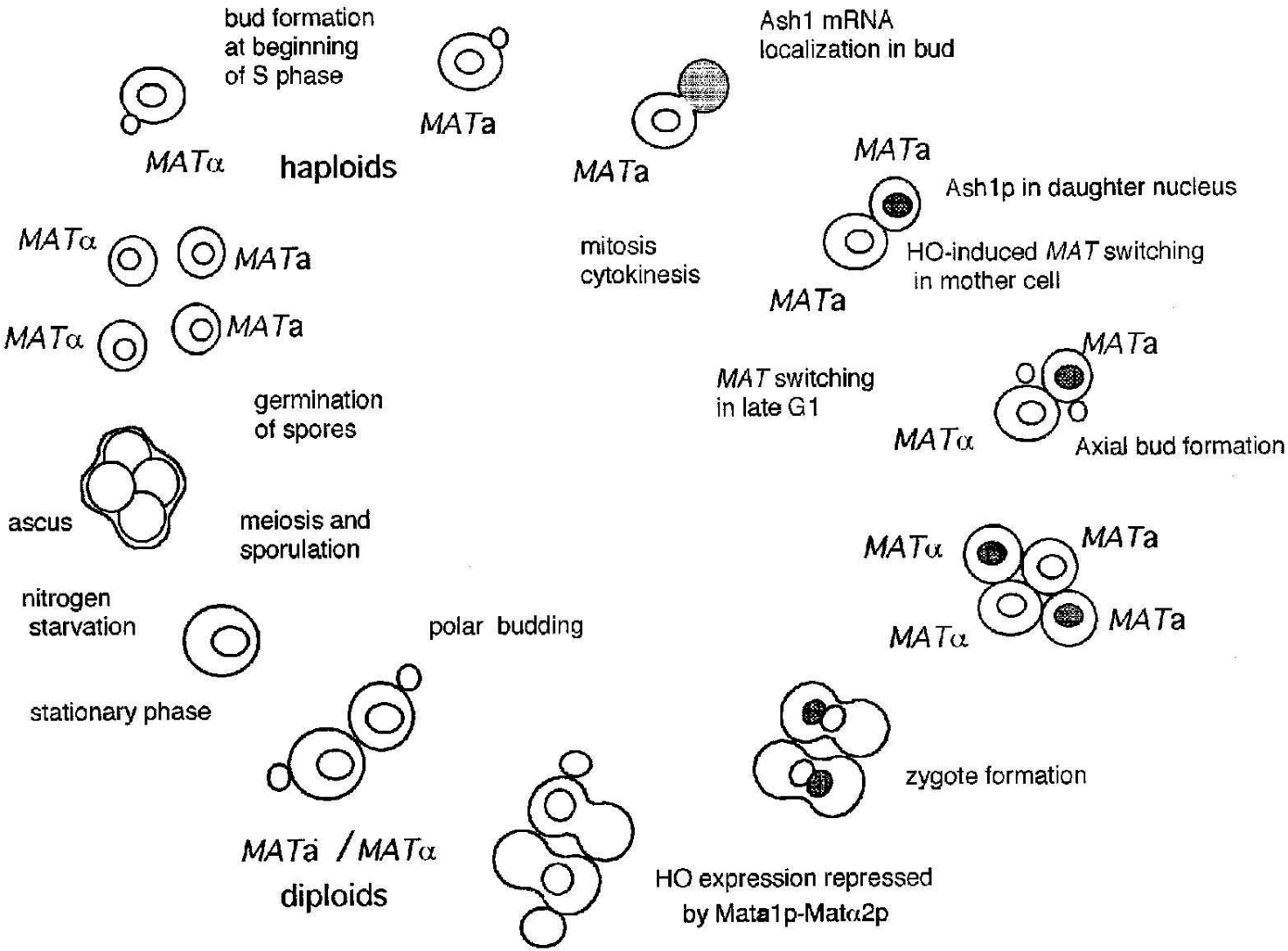
Marshall et al. '96

Interphase chromosomes assume well defined territories.

Chromosomal loci are associated with the nuclear membrane.

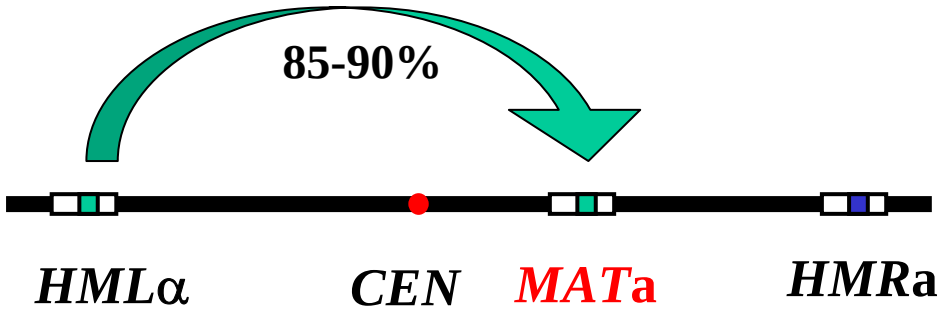
Chromosome structure and organization regulate gene expression.

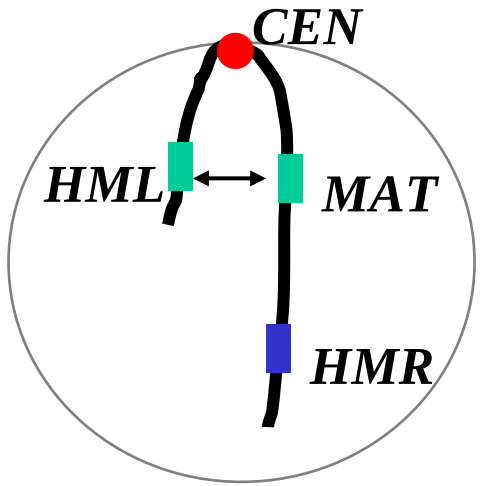
The life and times of yeast



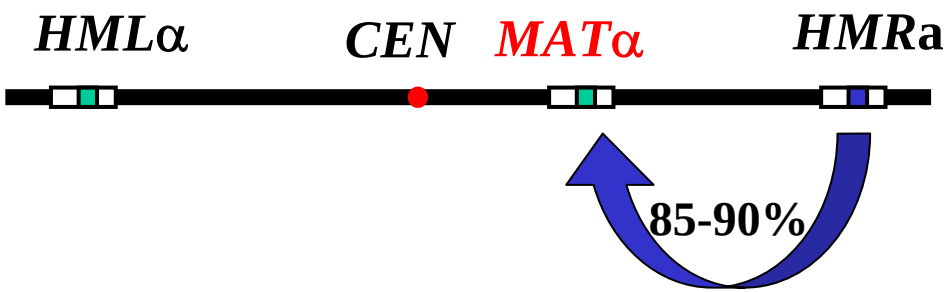
Mating-type switching in yeast

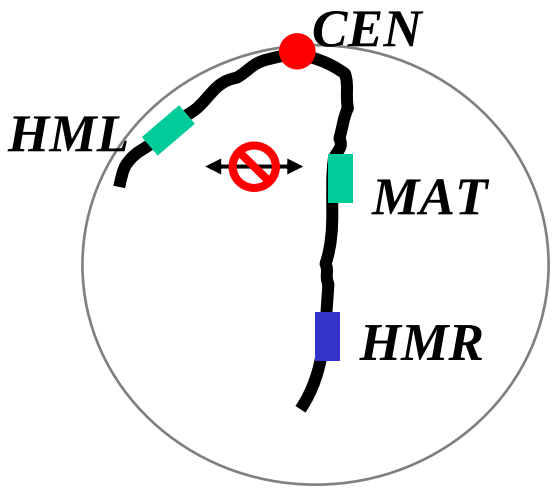
a cell





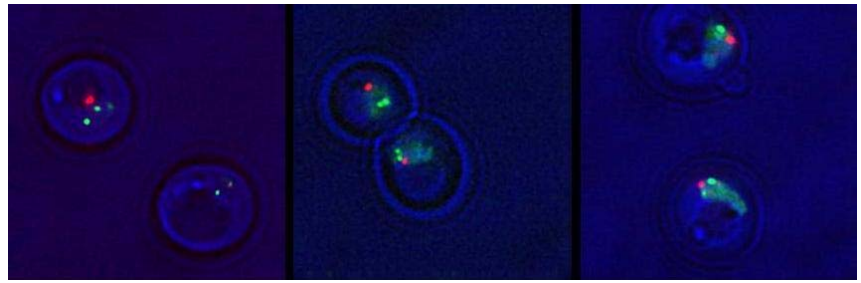
α cell

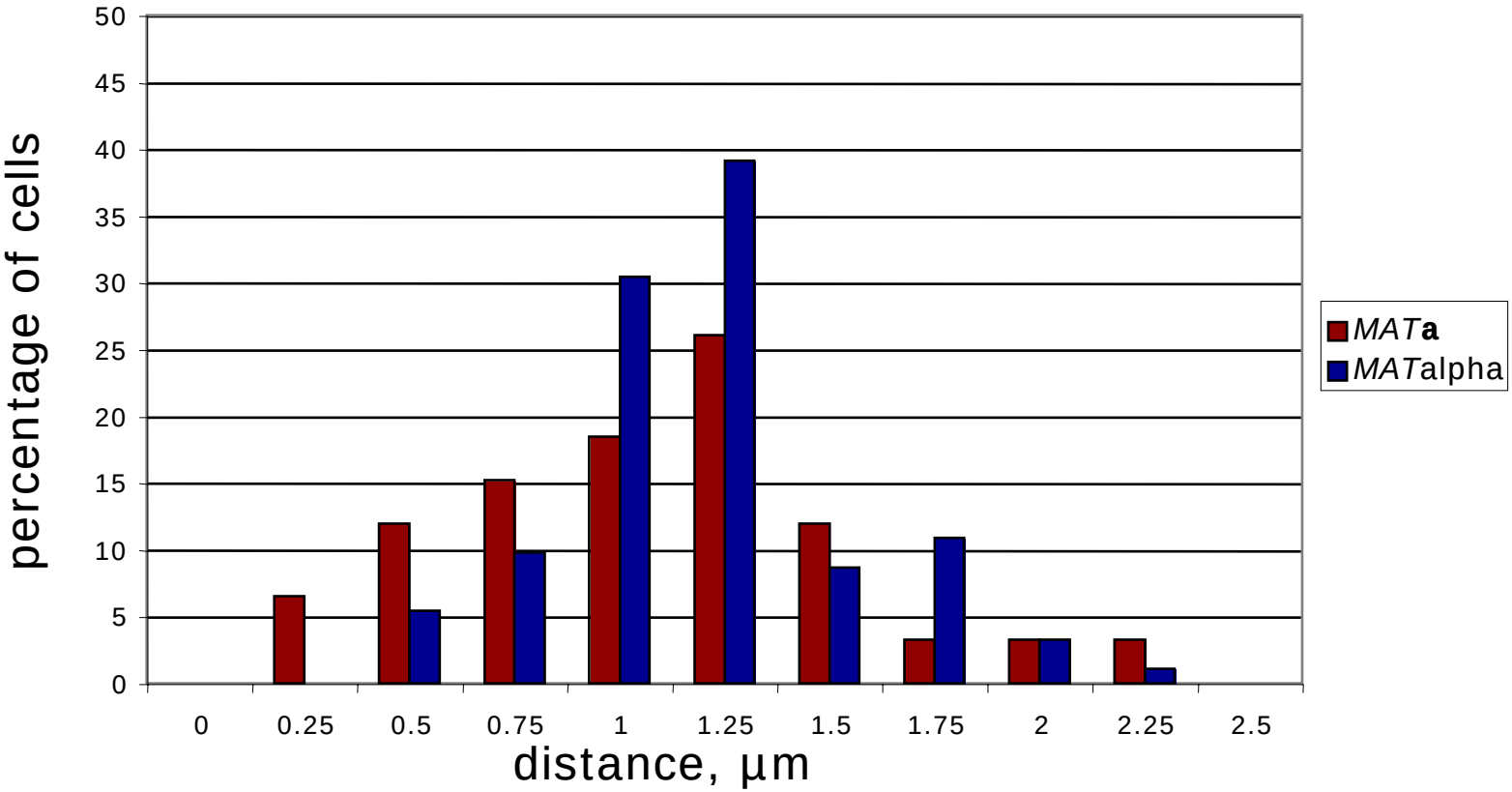




What is the physical mechanism of donor preference?

HML-CEN distance distributions

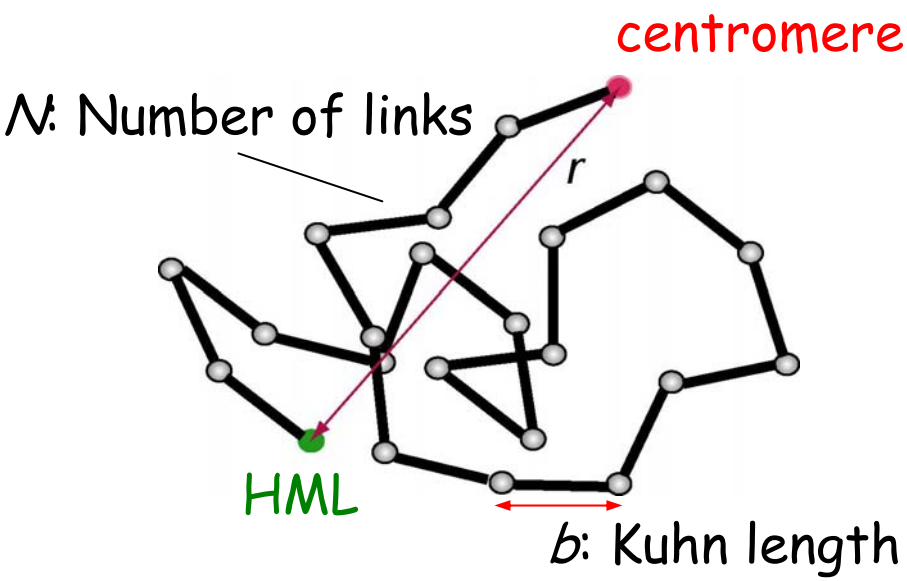




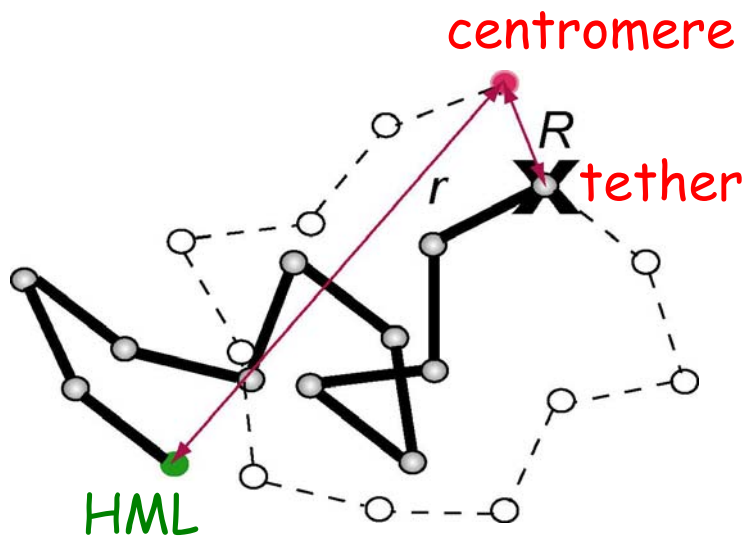
Does tethering account quantitatively for the difference in distributions?

Polymer models of chromosome III

a cell



α cell

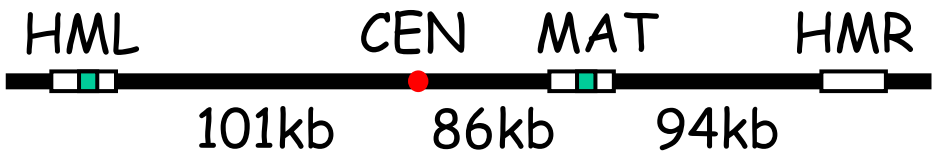


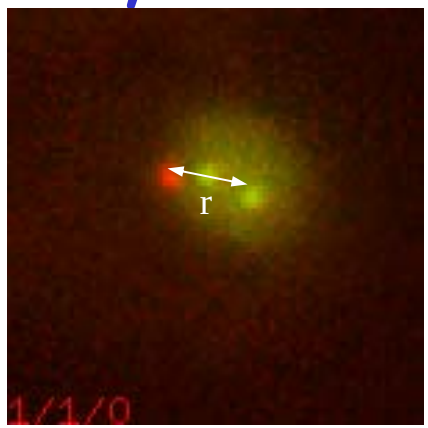
$$P(r) = \mathcal{N} r^2 e^{-\frac{3r^2}{2Nb^2}}$$

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

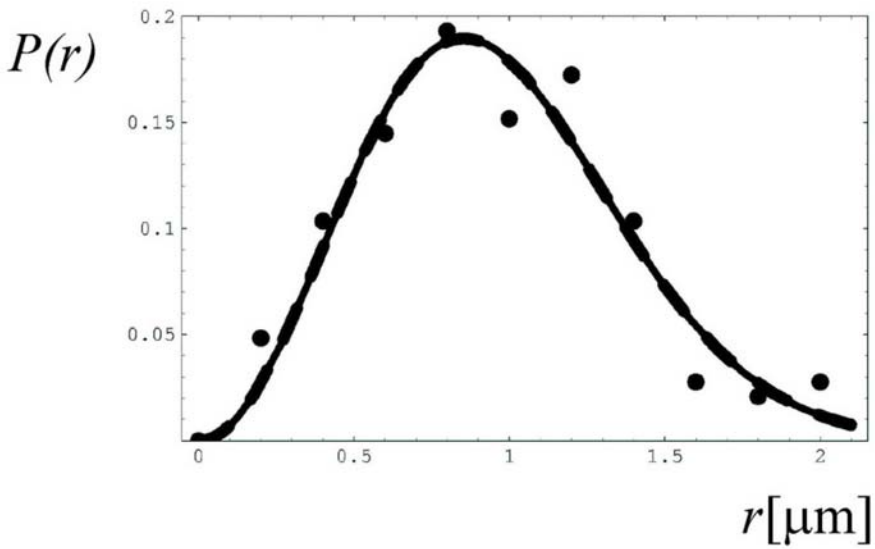
A tethering site between HML and centromere leads to a change in the functional form of the distance distribution.

Distance distributions: experiment meets theory



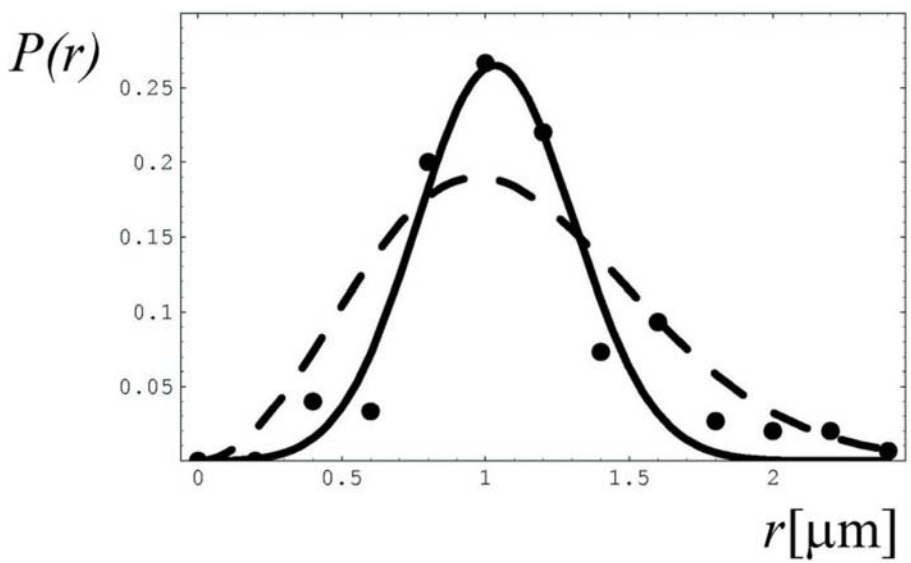


a cell



Chromosome III is not tethered.

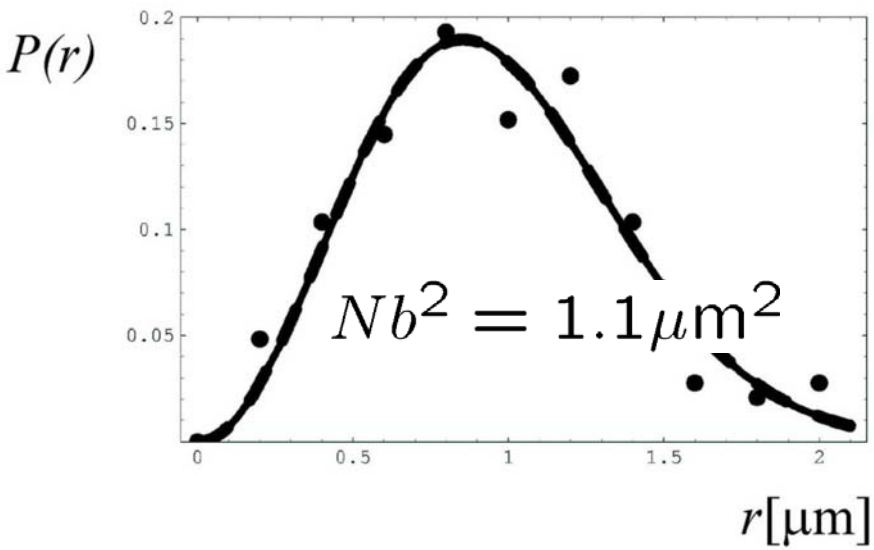
α cell

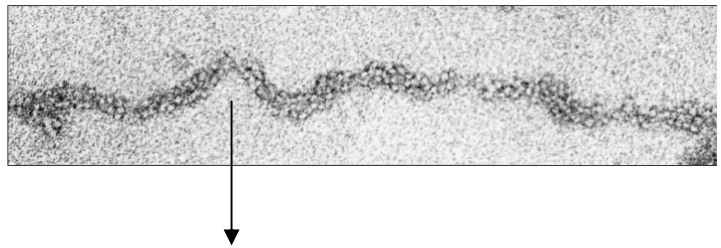


Chromosome III is tethered.

Interphase chromatin structure

a cell



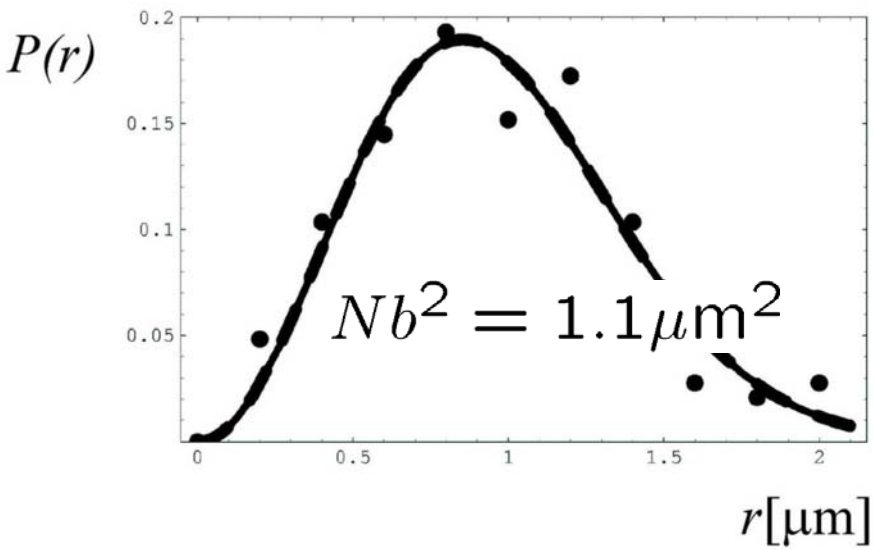


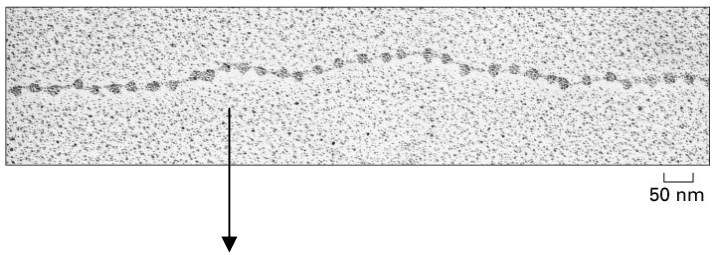
$\nu \approx 10\text{nm/kb}$

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

Interphase chromatin structure

a cell

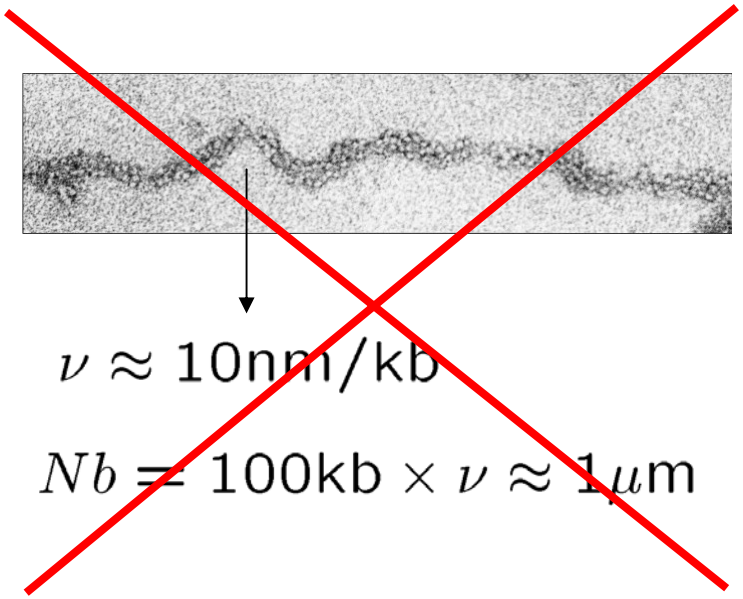




$\nu \approx 125\text{nm/kb}$

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

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



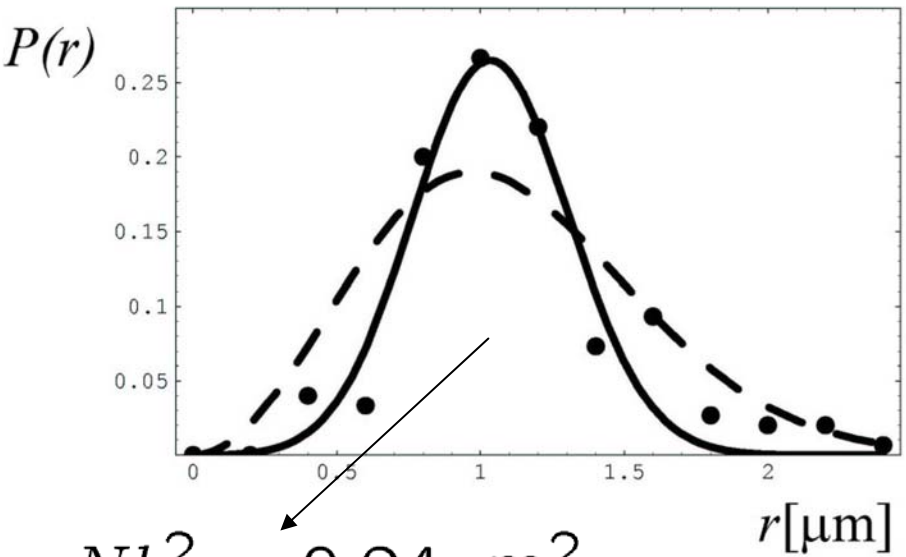
$\nu \approx 10\text{nm/kb}$

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

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

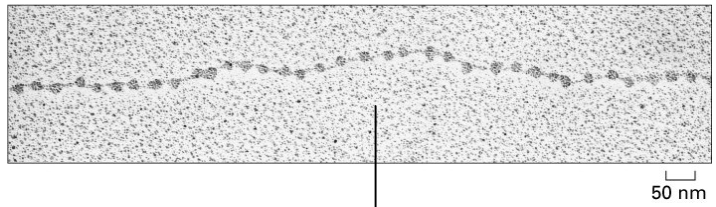
Tethering of chromosome III

α cell



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

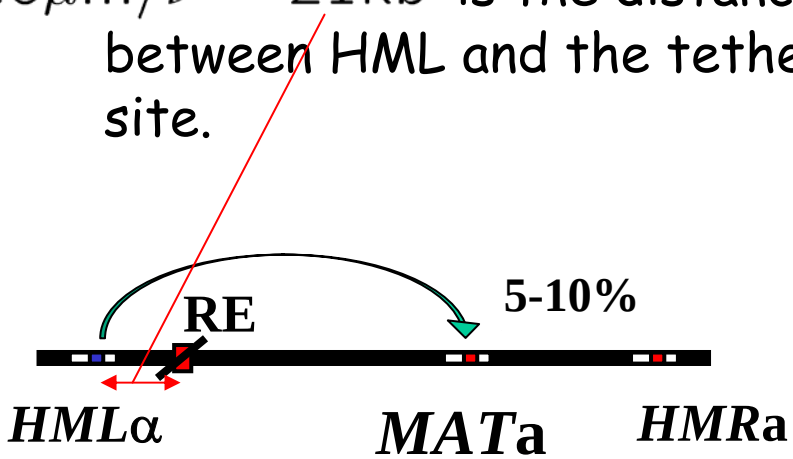
$R = 0.96\mu\text{m}$



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

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

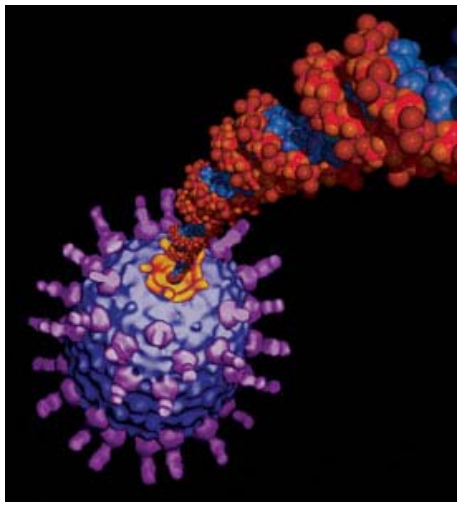
$2.6\mu\text{m}/\nu = 21\text{kb}$ is the distance between HML and the tether site.



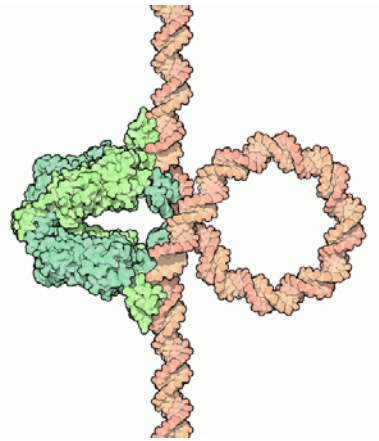
Prediction: The left arm of chromosome III in α cells is tethered 21kb away from HML.

DNA confinement and cell biology

Viral life cycle

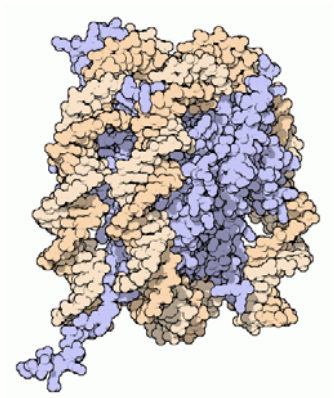


Transcriptional regulation

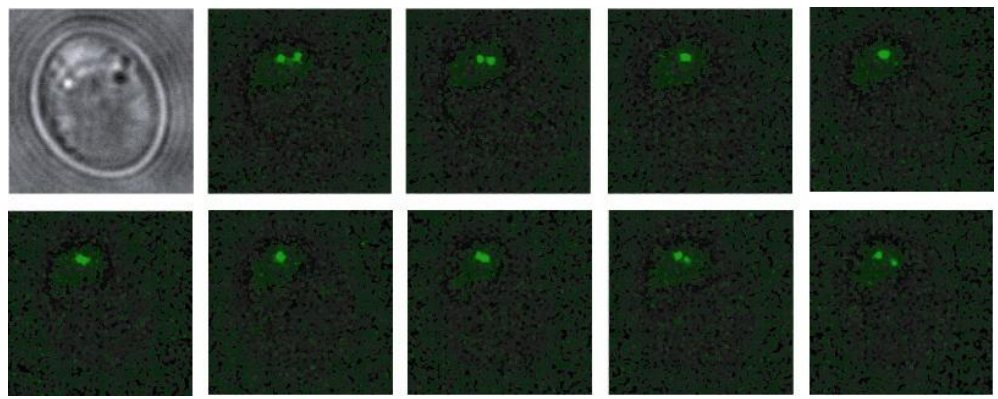


Life's processes are profoundly influenced by the spatial organization of DNA inside the cell.

Nucleosomes



DNA recombination



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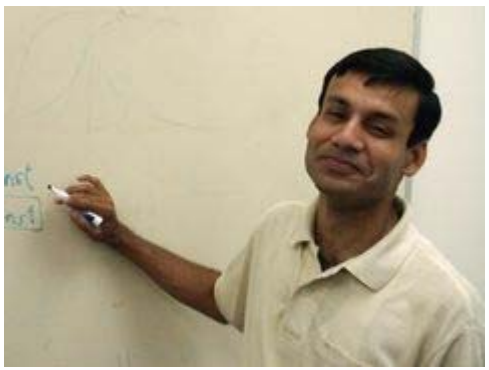
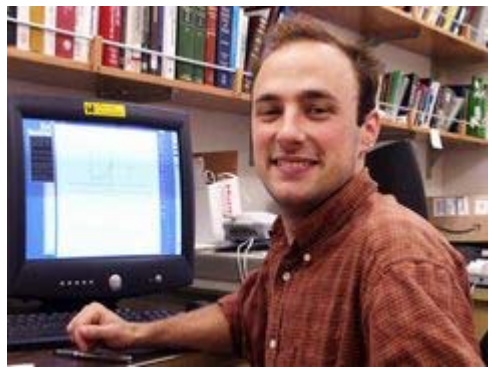


Prashant Purohit

Rob Phillips



Paul Wiggins

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It's not just about the DNA

Frey, Manella '03