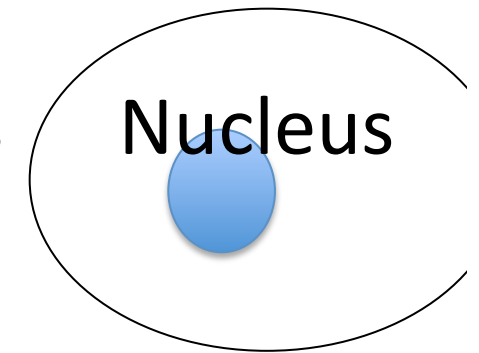


Chromatin Architecture Dynamics and Long-Range Regulatory Control

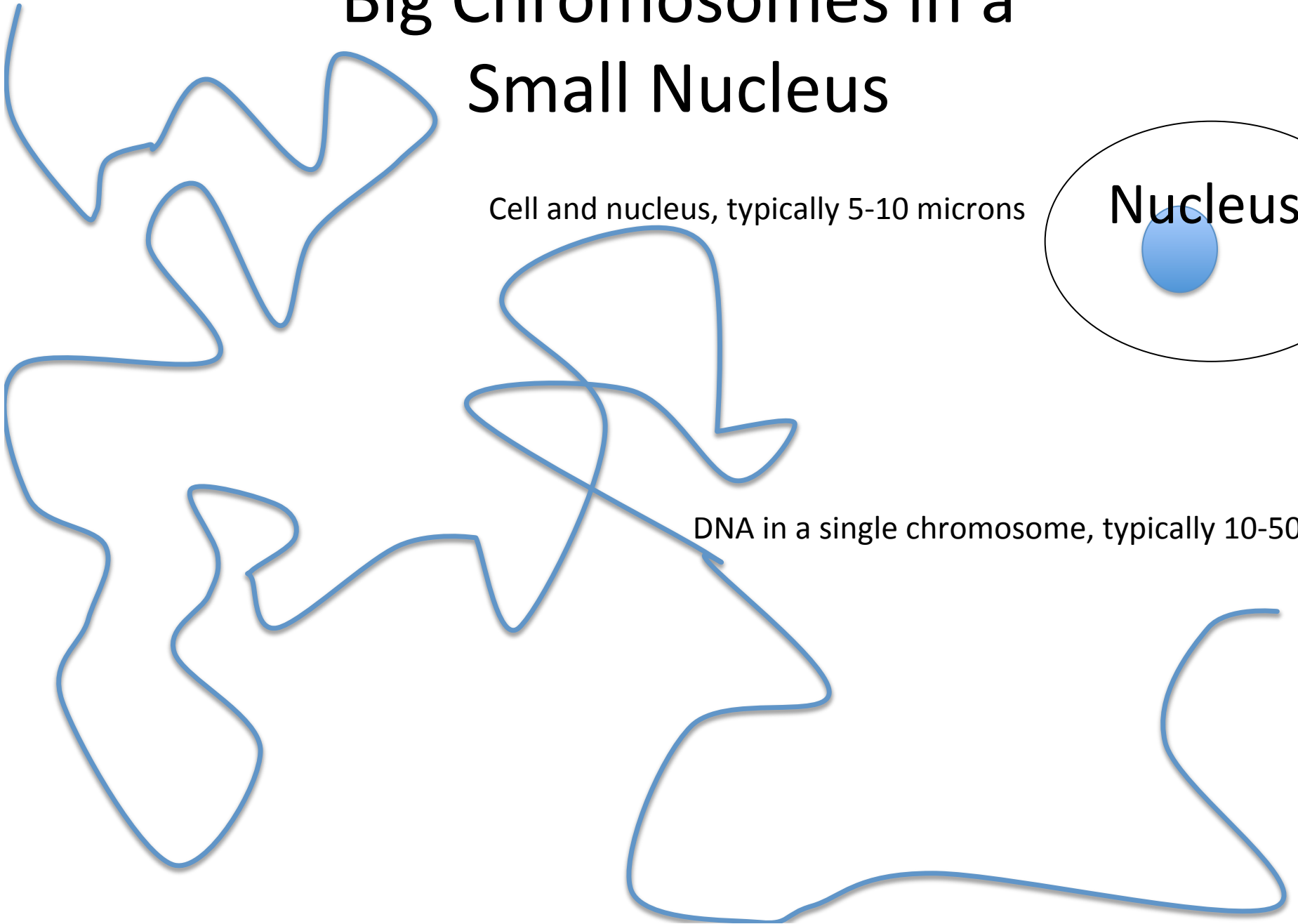
Anirvan Sengupta
Physics and Astronomy
&
BioMaPS Institute
Rutgers University

Big Chromosomes in a Small Nucleus

Cell and nucleus, typically 5-10 microns

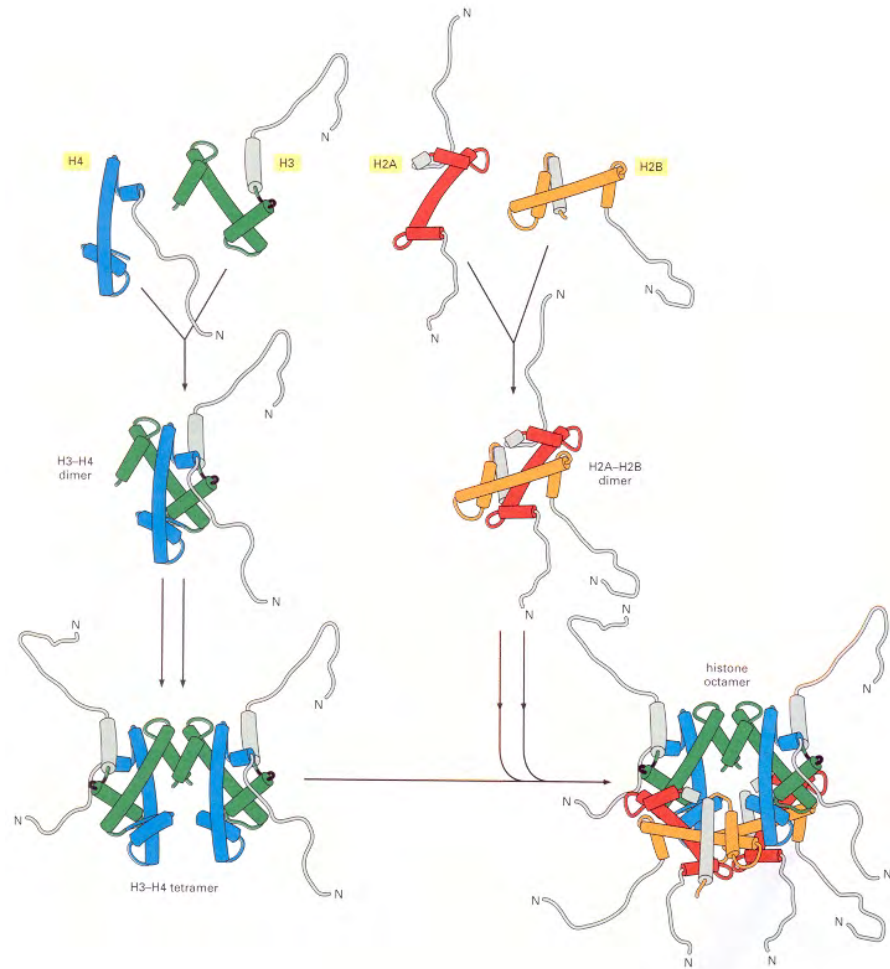
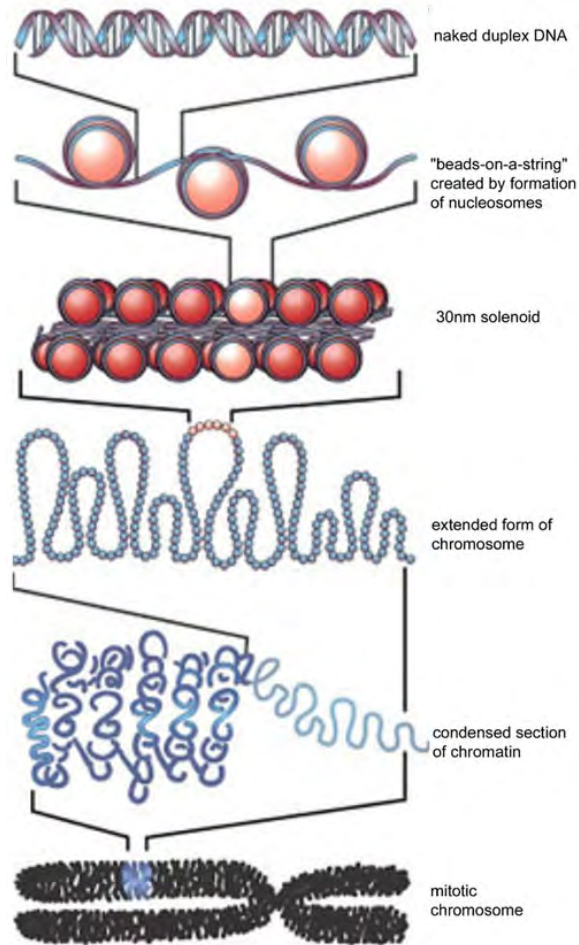


DNA in a single chromosome, typically 10-50mm

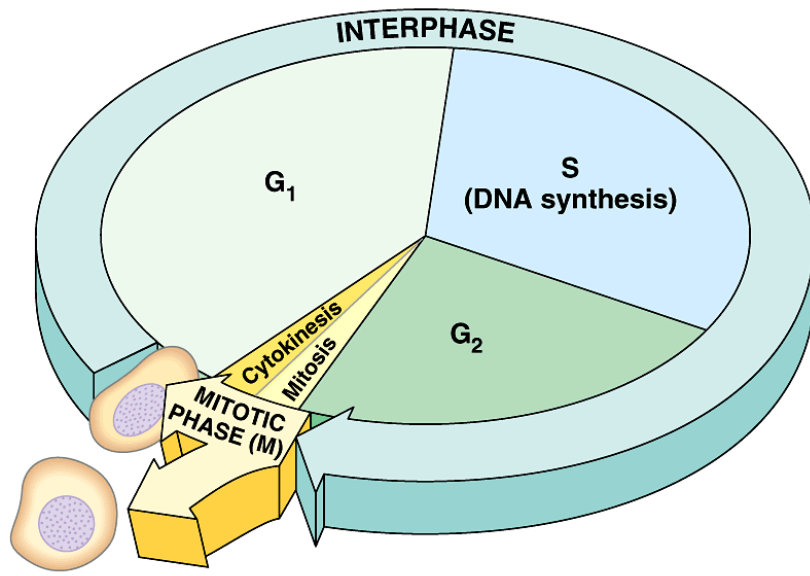


Eukaryotic Chromosomes:

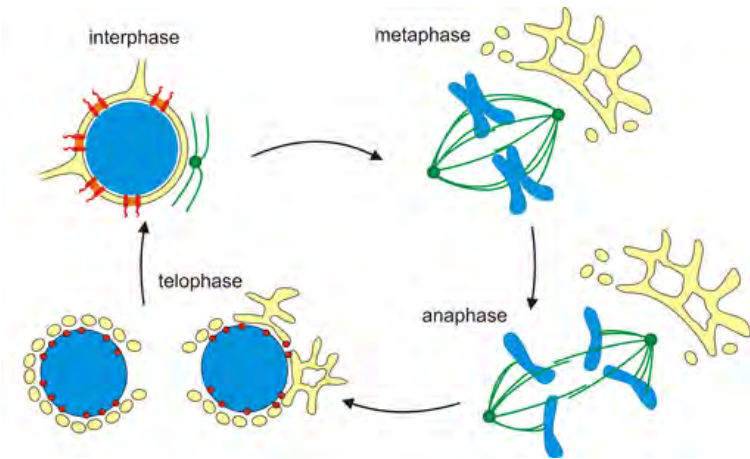
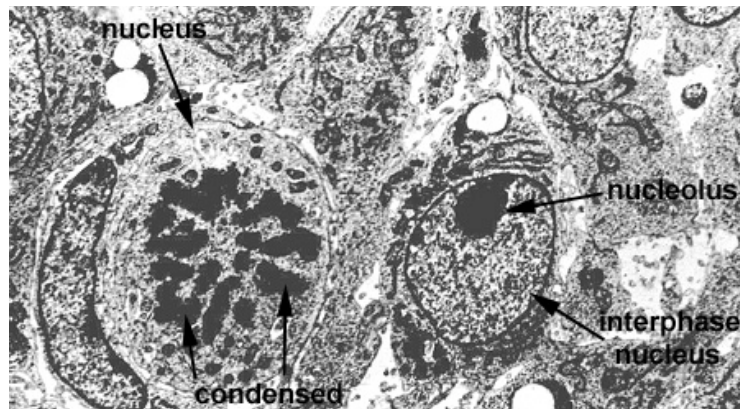
Histone octamers and nucleosomes



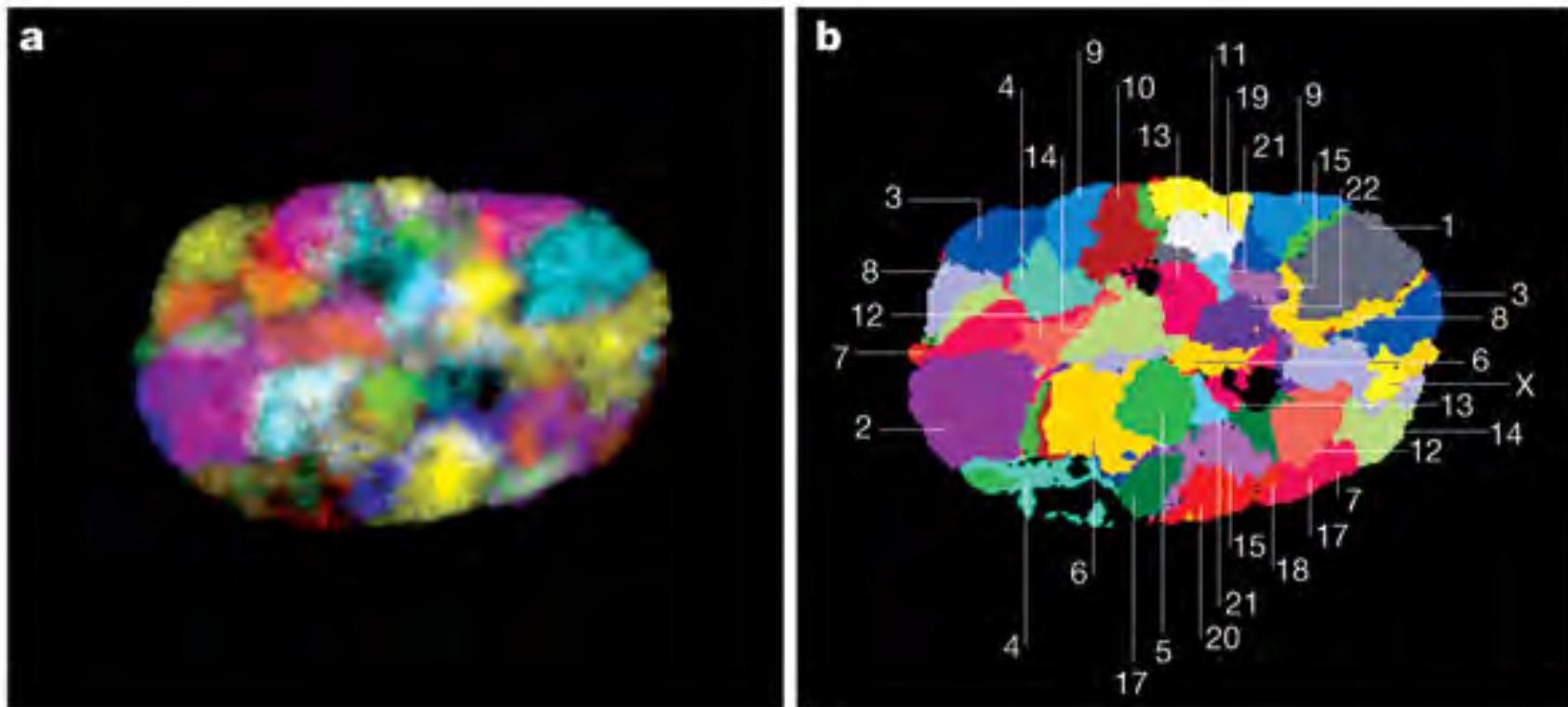
Interphase and Mitotic Phase



Copyright © Pearson Education, Inc., publishing as Benjamin Cummings.



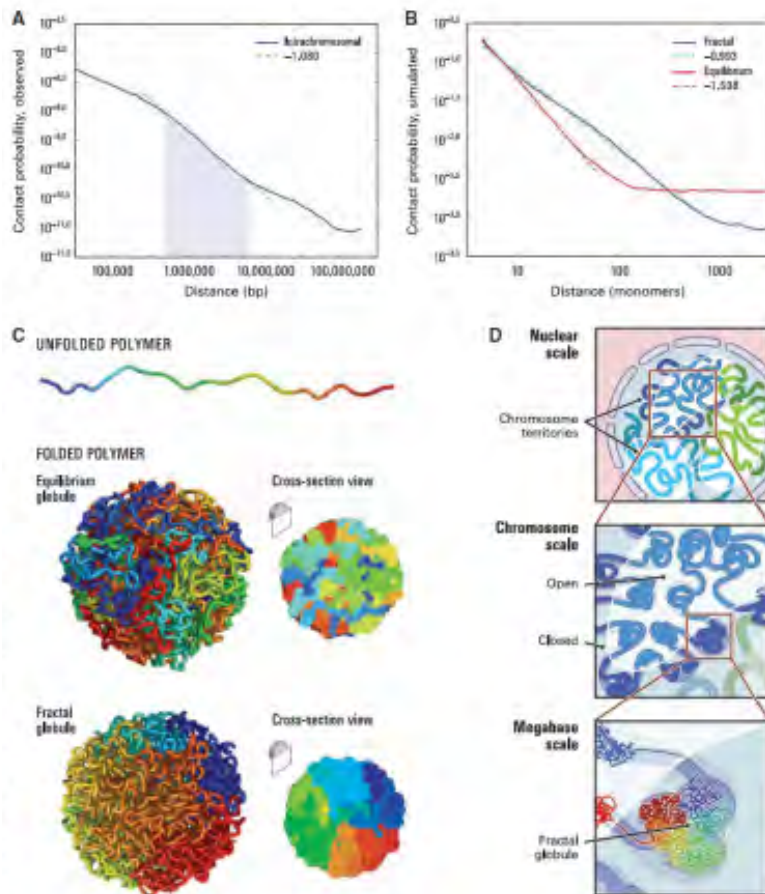
Interphase Organization: Spaghetti or Territories



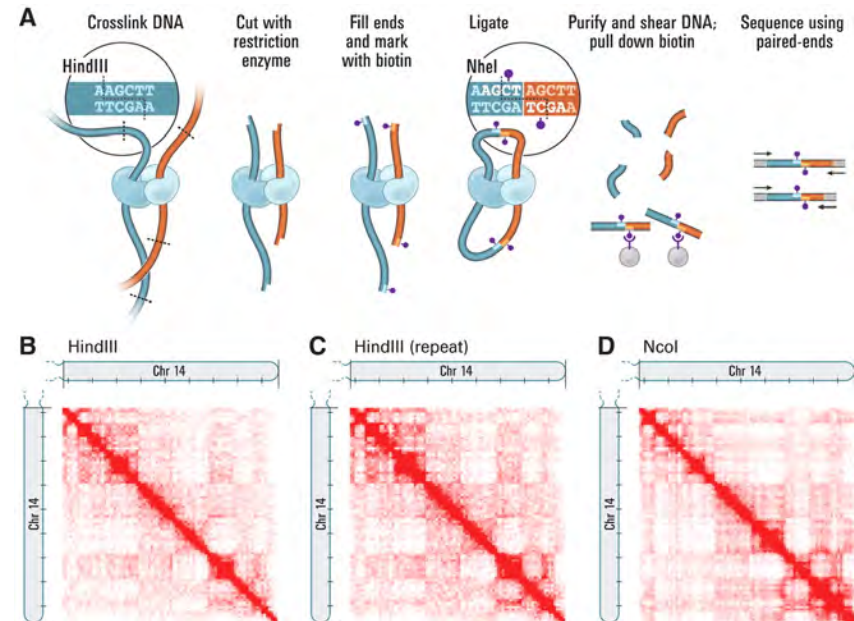
Copyright © 2005 Nature Publishing Group
Nature Reviews | **Genetics**

Speicher and Carter, Nat Rev Gen 2005

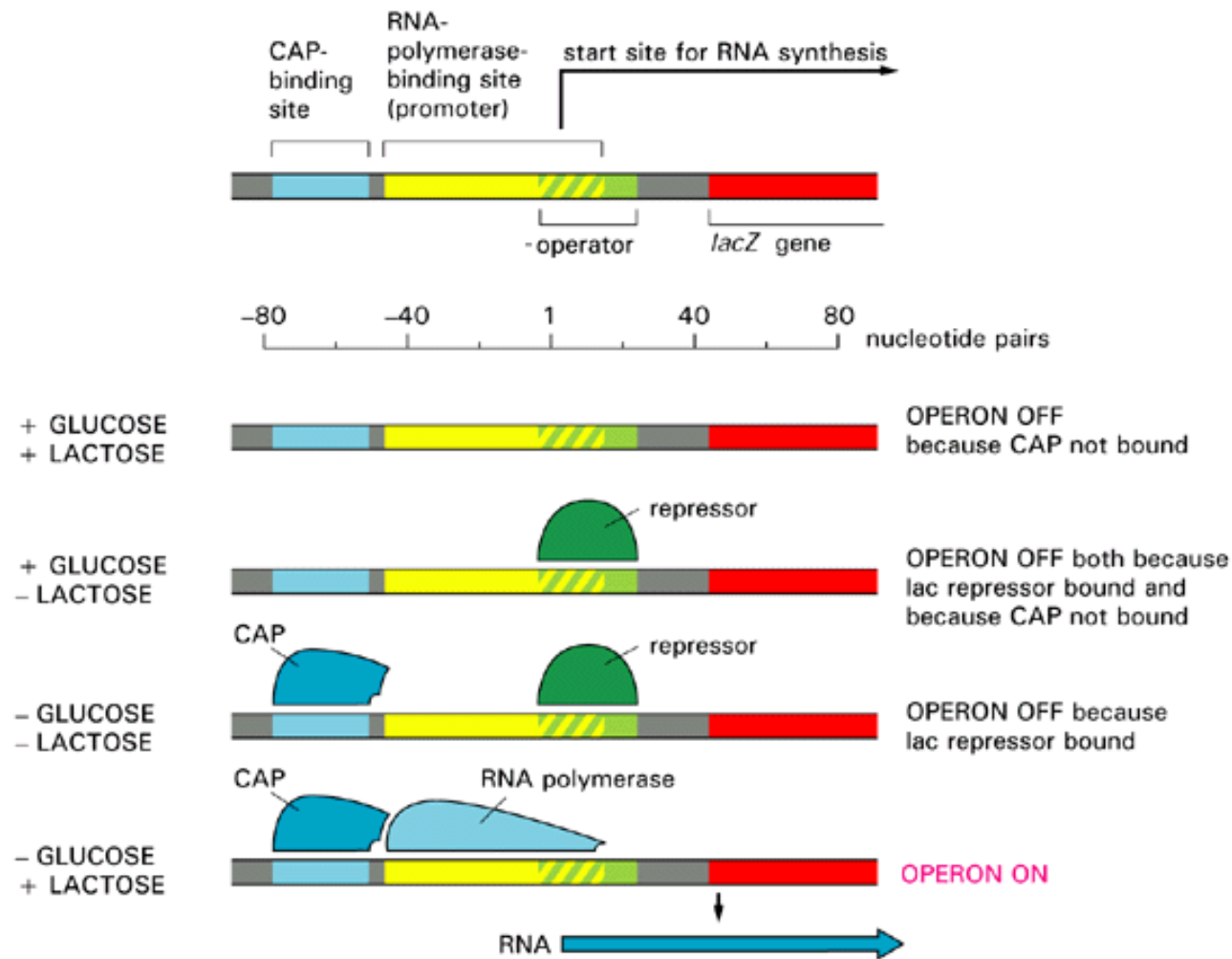
Very Long-range Contact Structure



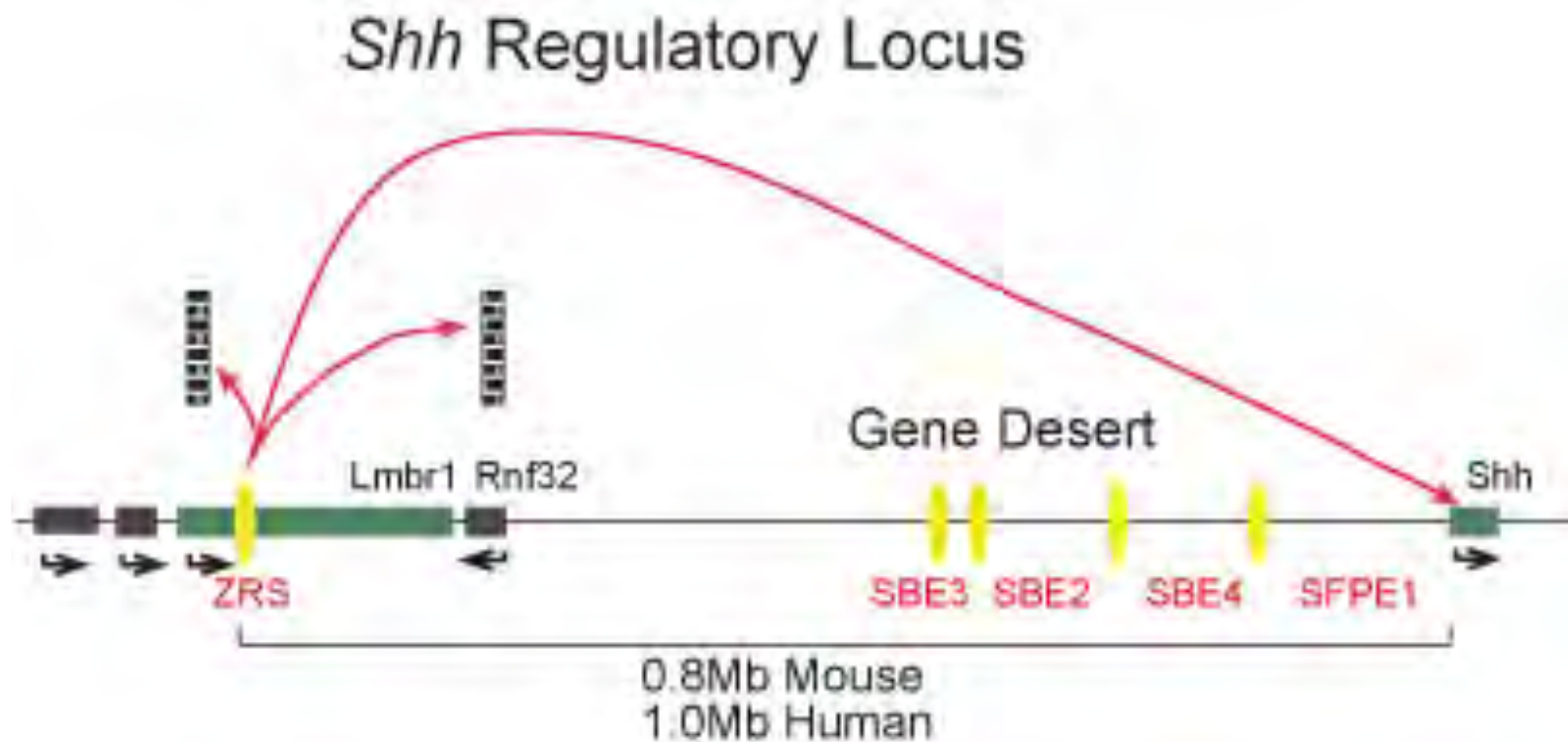
Chromosome consists of a series of fractal globules.



Control of Transcription Initiation in Prokaryotes



Long Range Effects in Higher Organisms



`Discussion'

Biologist: What is the big deal? Why can't chromatin just loop over and make an enhancer promoter contact?

Other biologist : What about specificity of gene regulation, then?

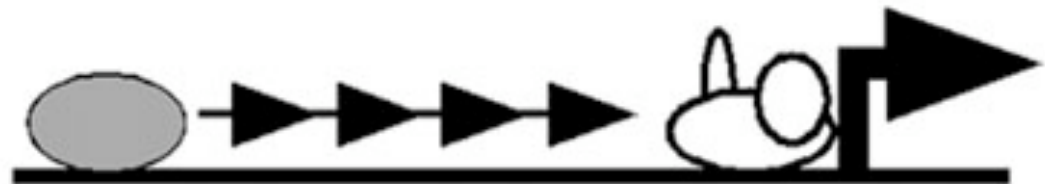
Physicist: Would the efficiency of contact fall off as a power law with genomic separation?

Models of Enhancer Action

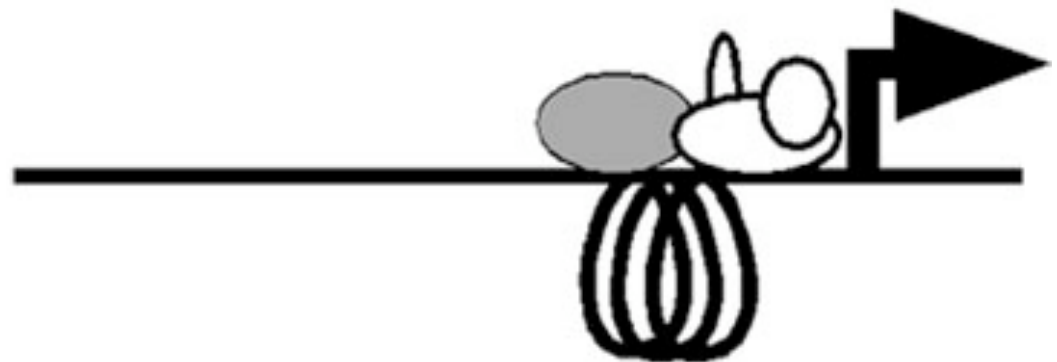
A Looping



B Tracking

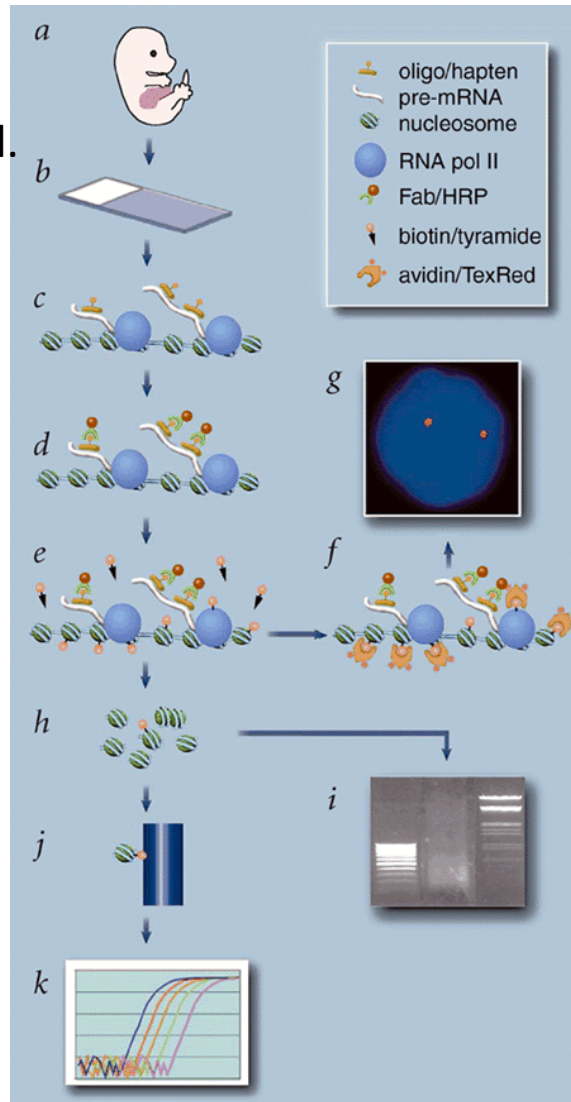


C Linking

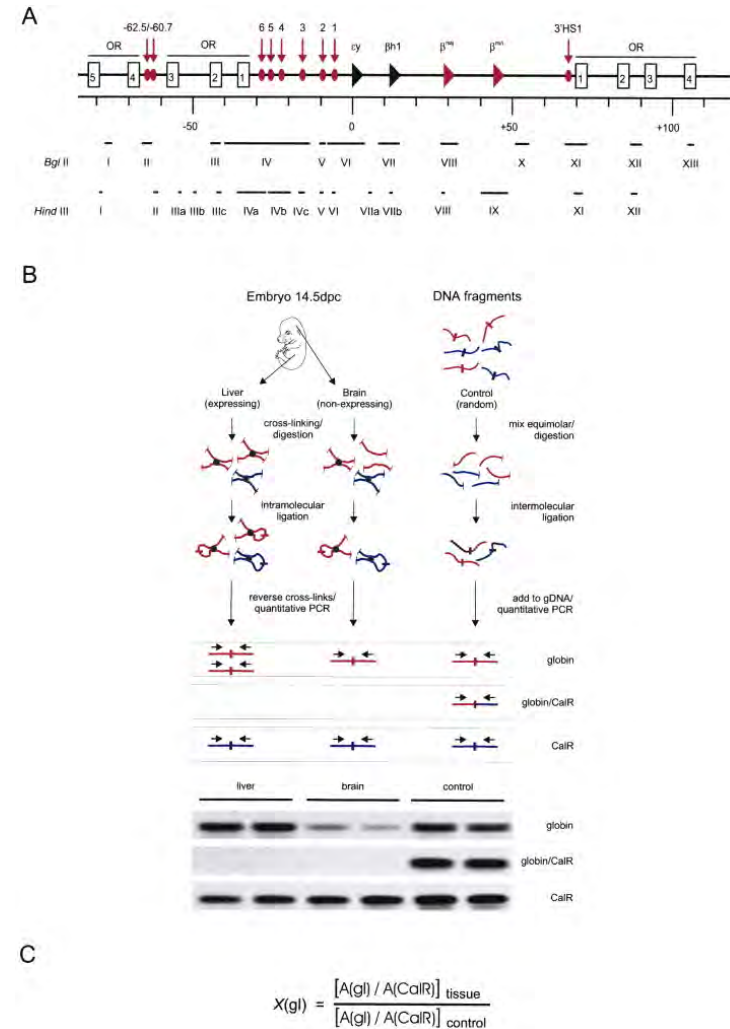


Probing long-distance interaction

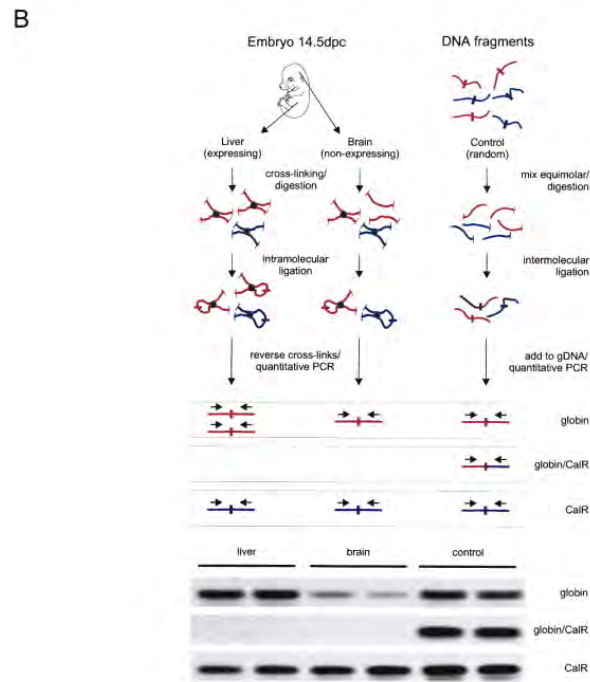
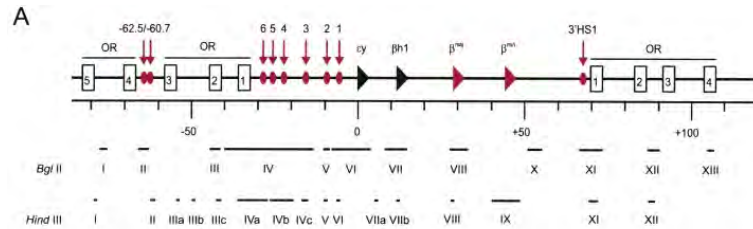
RNA trap:
Carter et al.
Nature
Genetics,
2002



3C:
Tolhuis
et al.
Mol.
Cell,
2002

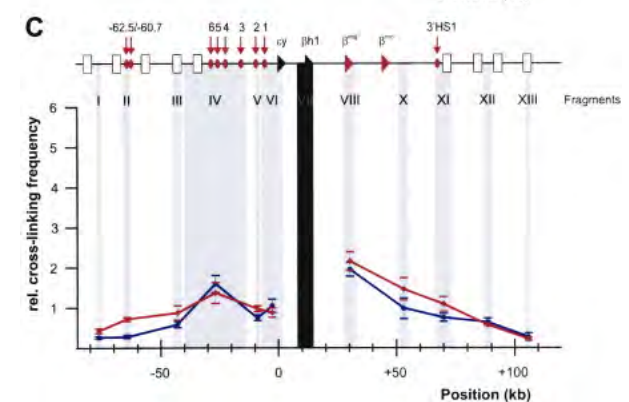
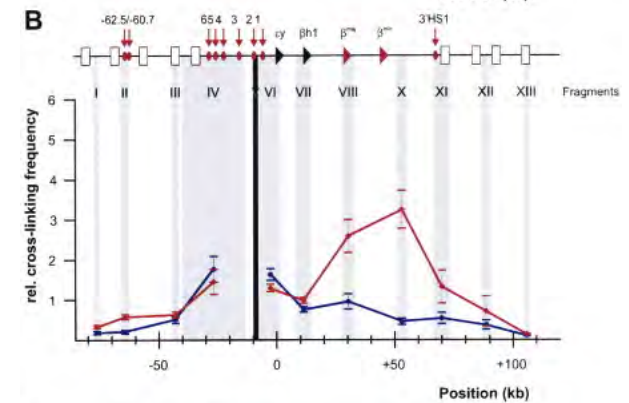
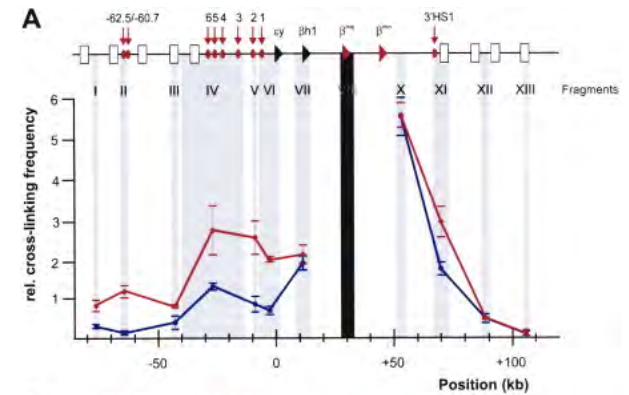


Probing long-distance interaction

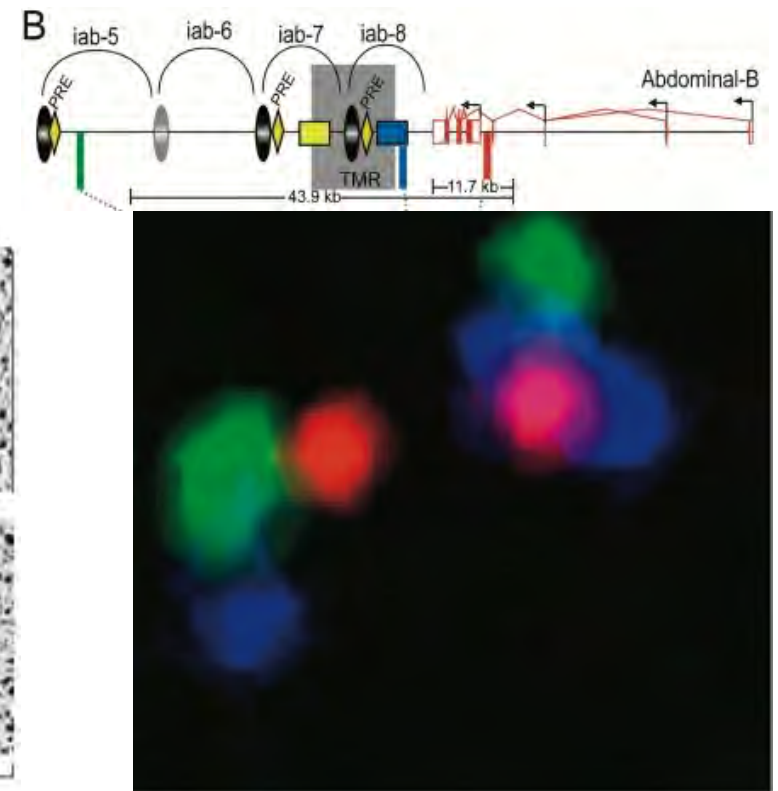
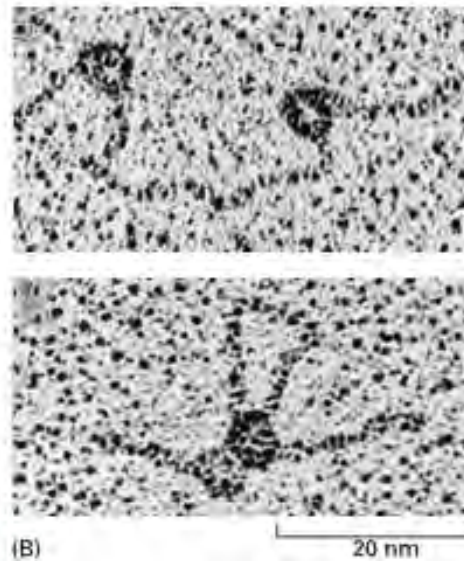
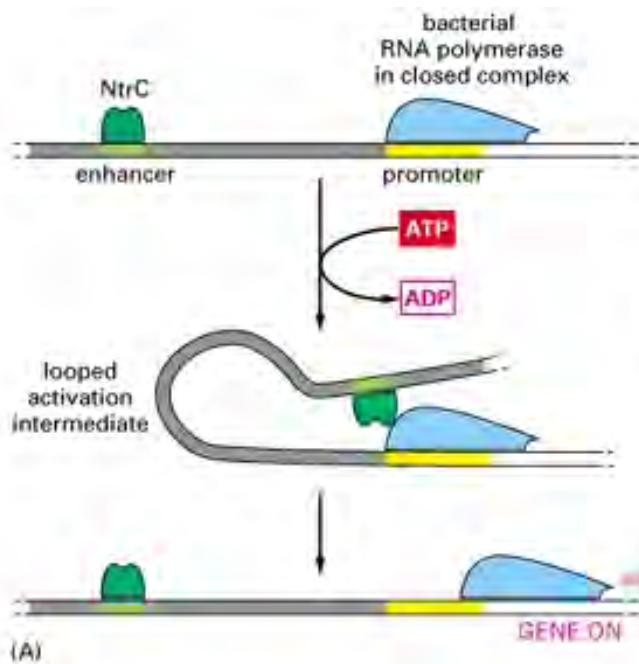


C

$$X(\text{gl}) = \frac{[A(\text{gl}) / A(\text{CalR})]_{\text{tissue}}}{[A(\text{gl}) / A(\text{CalR})]_{\text{control}}}$$

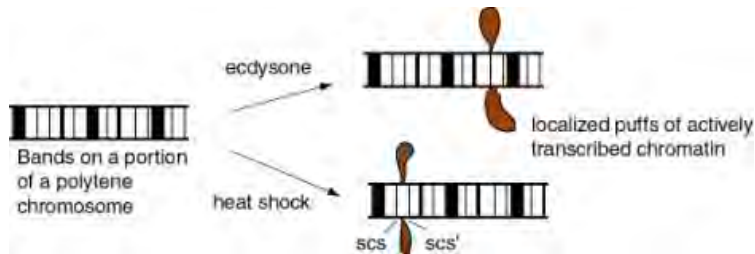


`Direct' Visualization of Activating Loops

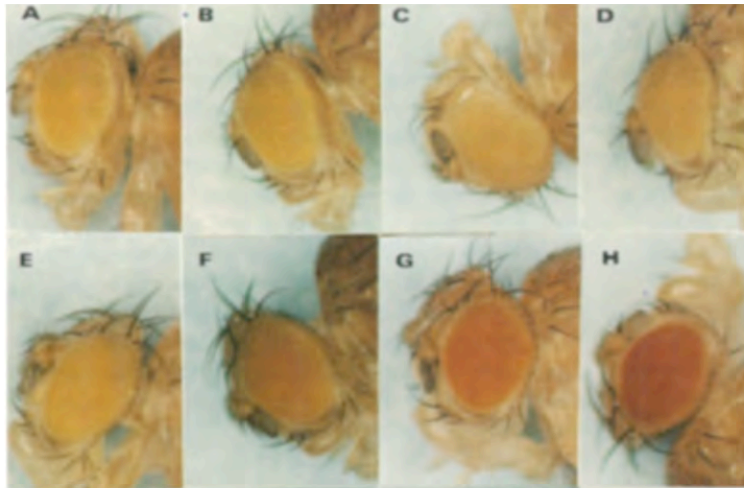
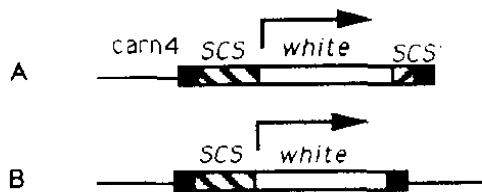


Levin group

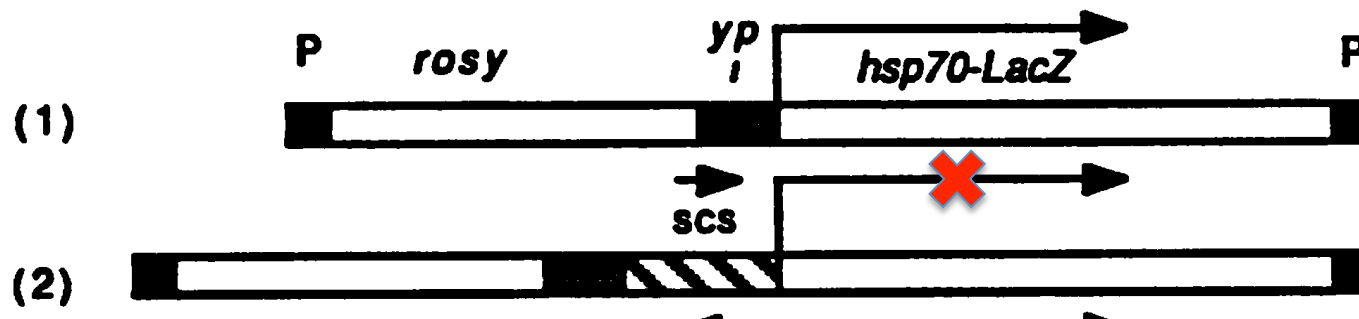
Specificity and Insulators



Udvadry, Maine and Schedl, JMB, 1985

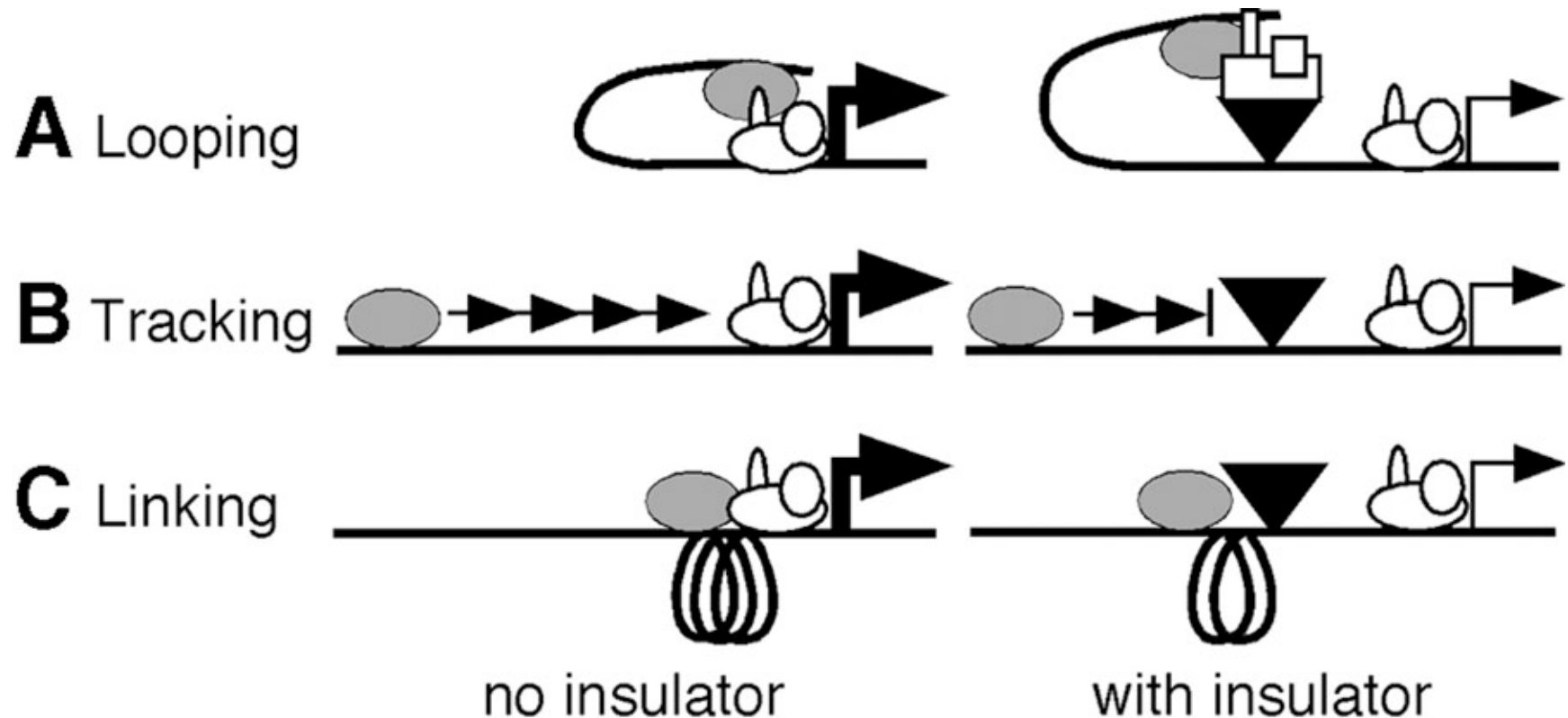


Kellum and Schedl, Cell, 1991

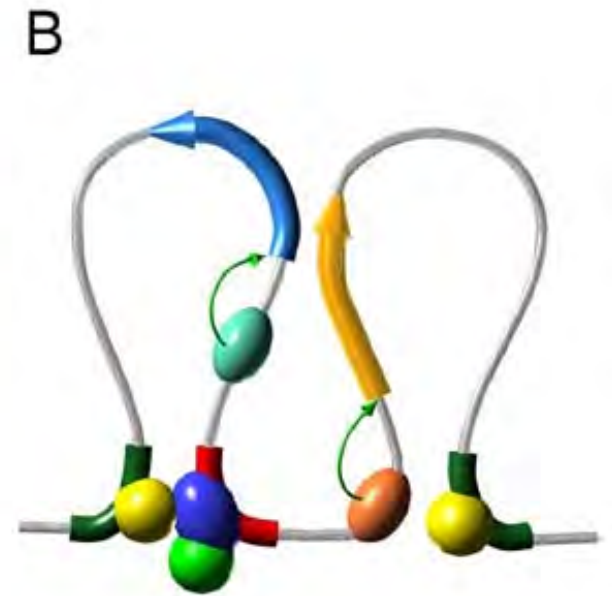
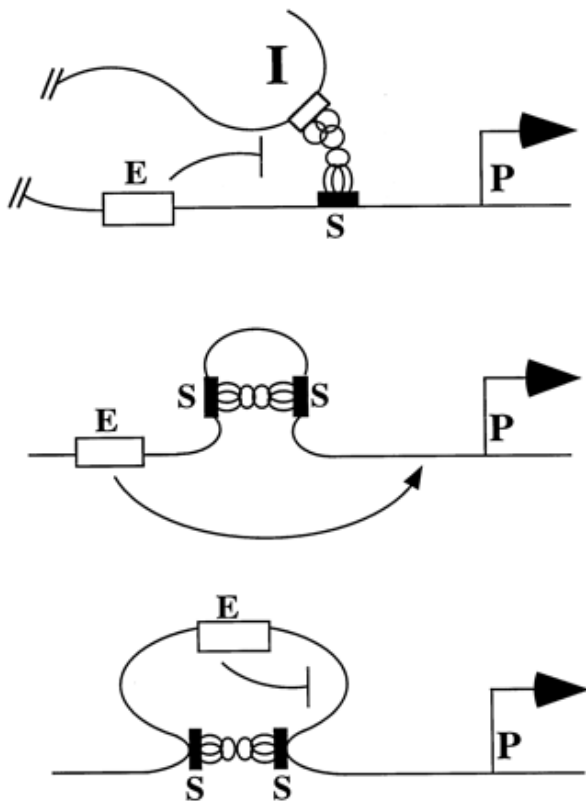


Kellum and Schedl, MCB, 1992

Early Models of Insulator Action



'Repressive' Loops forming Topological Domains



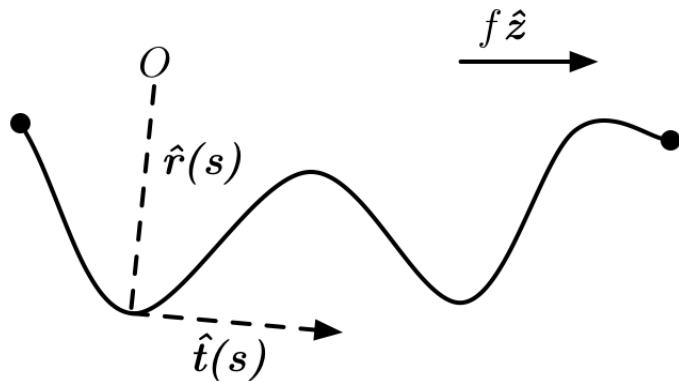
`Discussion' contd.

Biologist: Loop domains made by insulators seems to be a neat hypothesis that explains most genetics experiments.

Other biologist : It seems somewhat non-intuitive that two flopping loops don't touch each other.

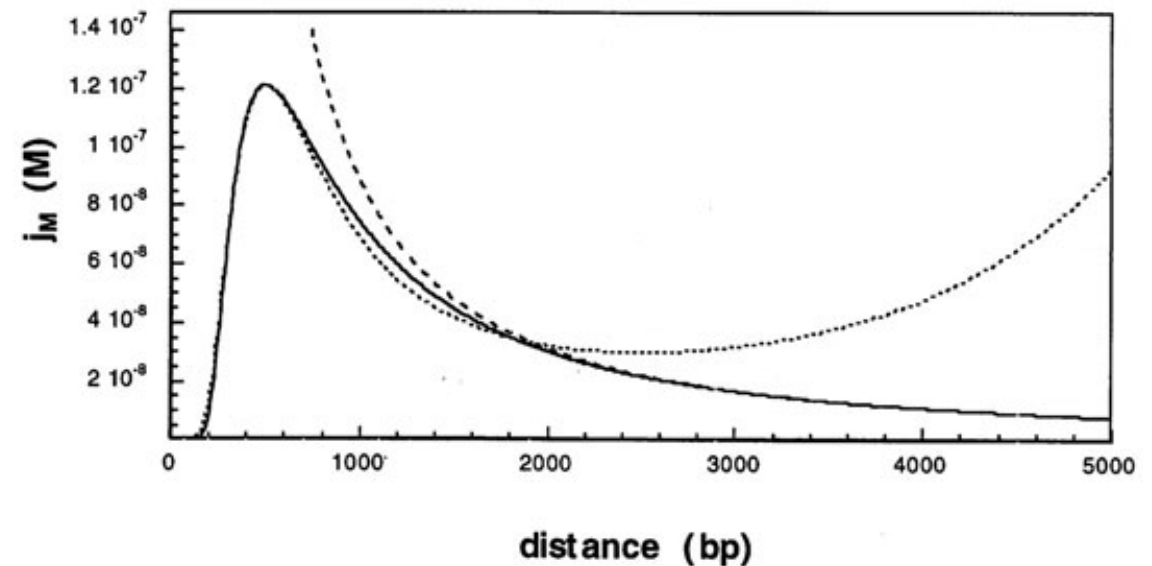
Physicist : Perhaps dual problems of inefficiency of long-distance contact and of the non-intuitiveness of insulation via loop formation points to something beyond the simple picture.

'Trouble' with Looping Model



$$\frac{E}{k_B T} = \int_0^{L_{tot}} \left[\frac{A}{2} \left| \frac{d \hat{t}(s)}{ds} \right|^2 - \frac{f}{k_B T} \hat{t}(s) \cdot \hat{z} \right] ds$$

A



Persistence length:

DNA

50nm=150bp

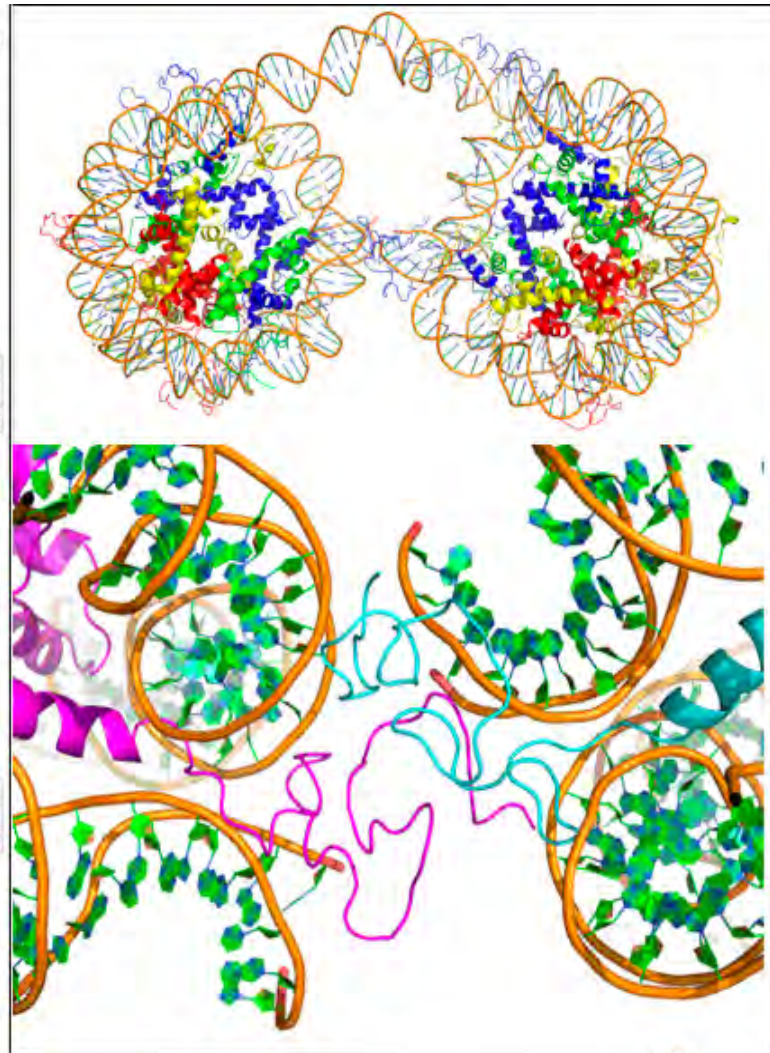
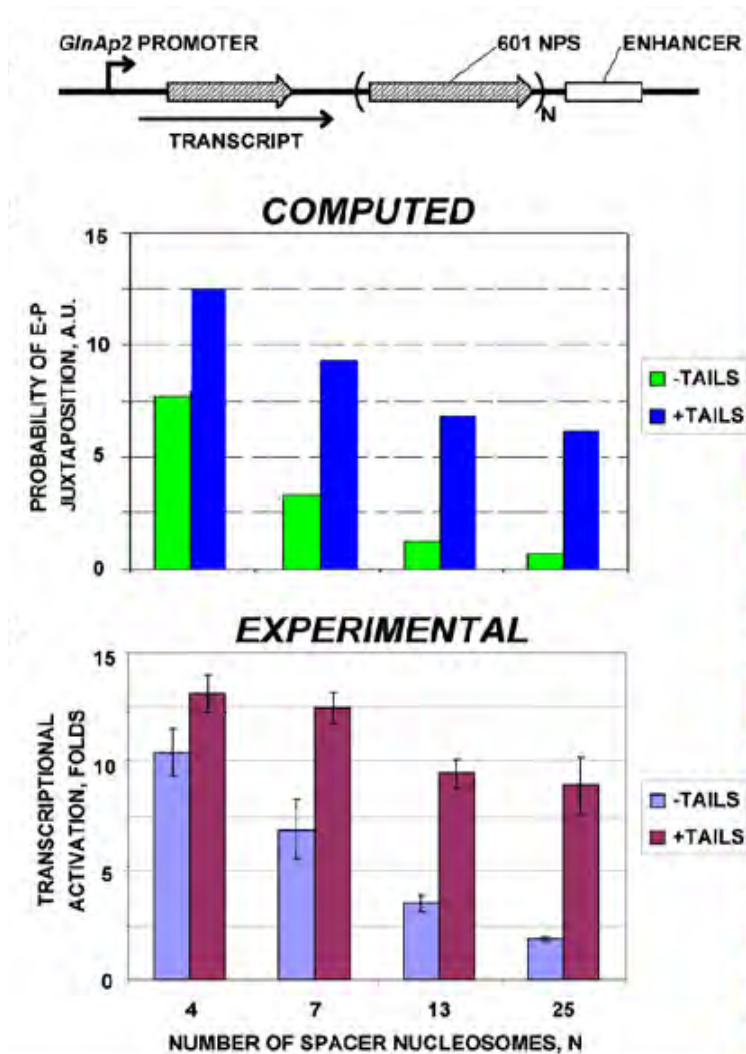
Chromatin

30-200 nm

Or 1-10Kbp

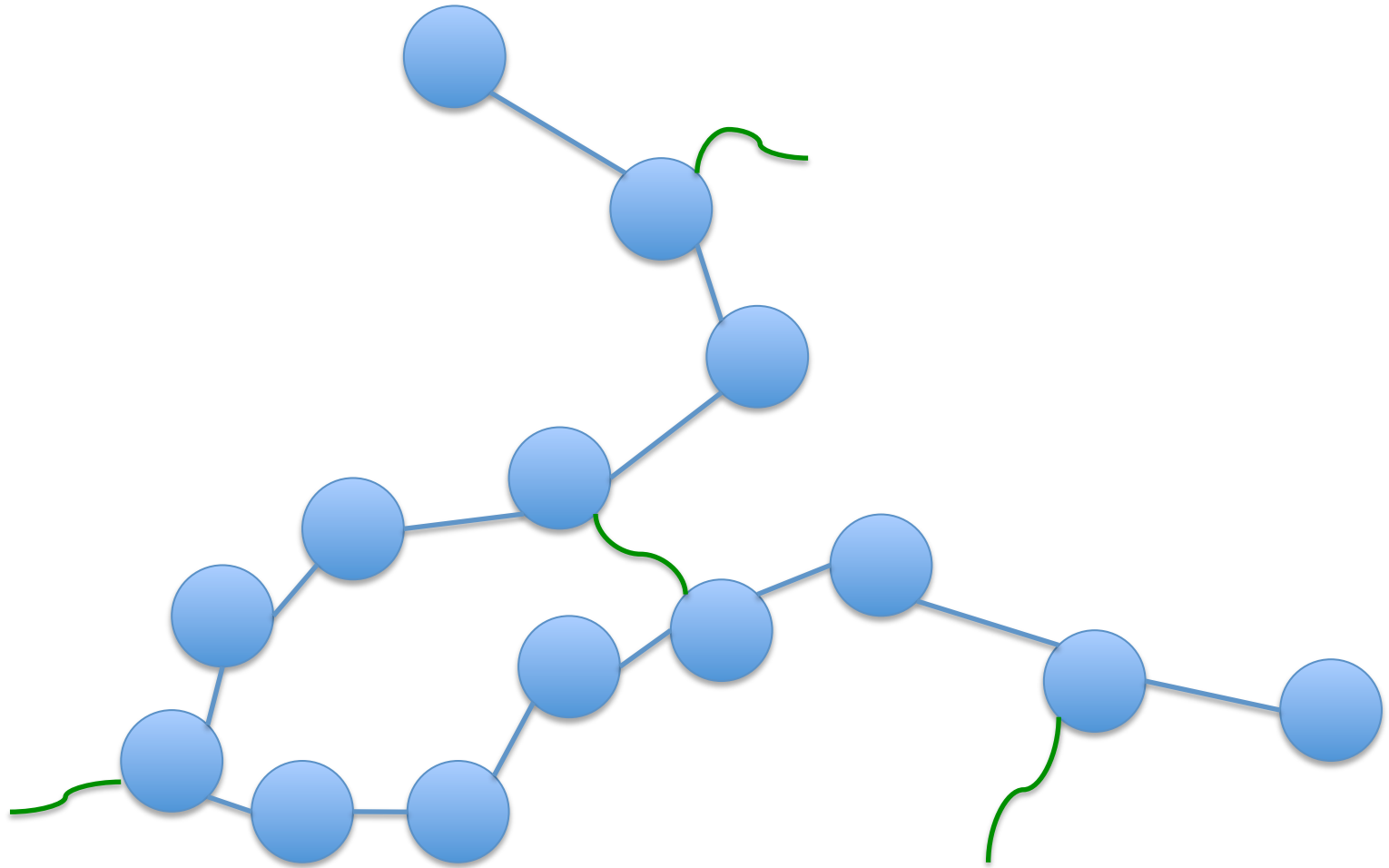
Ringrose 1999, Rippe, 1995/2001

Tail-induced Chromatin-Chromatin Interaction

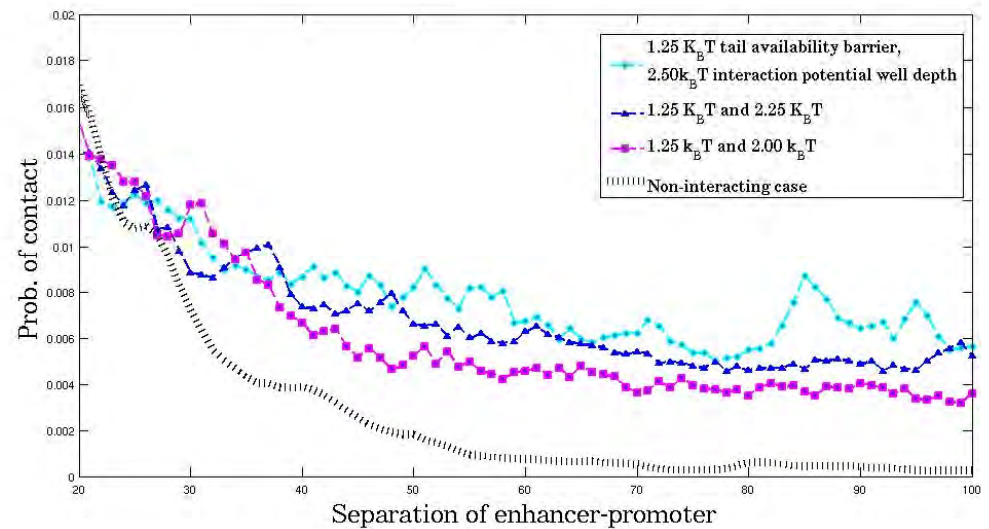
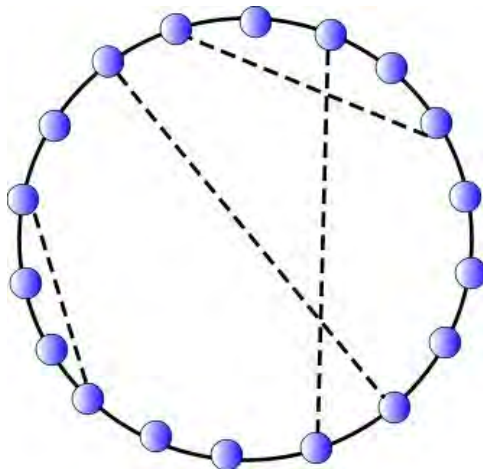
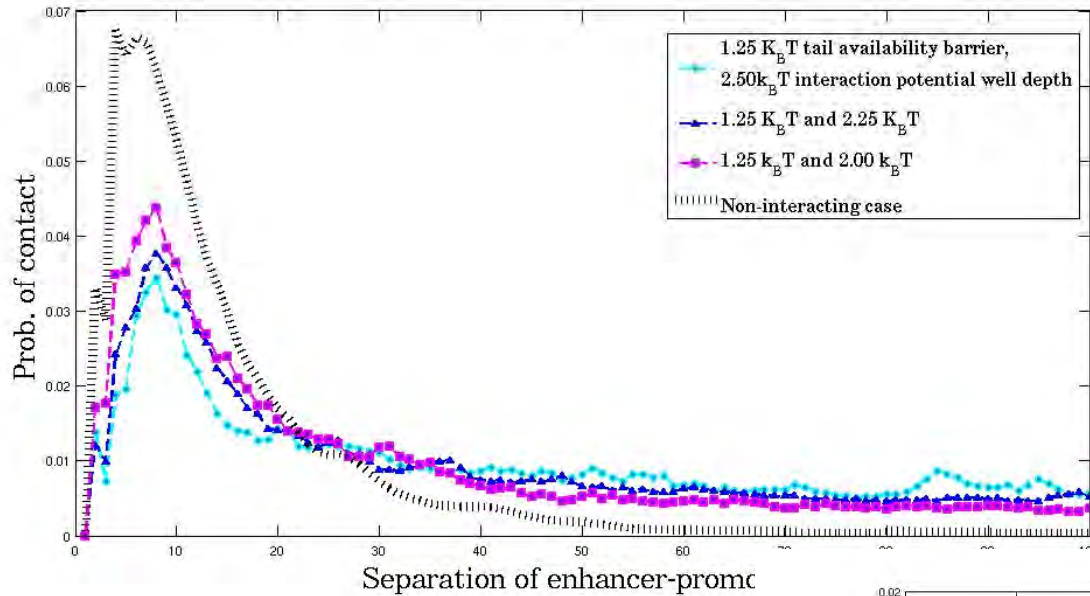


Studitsky
Group
Case Group

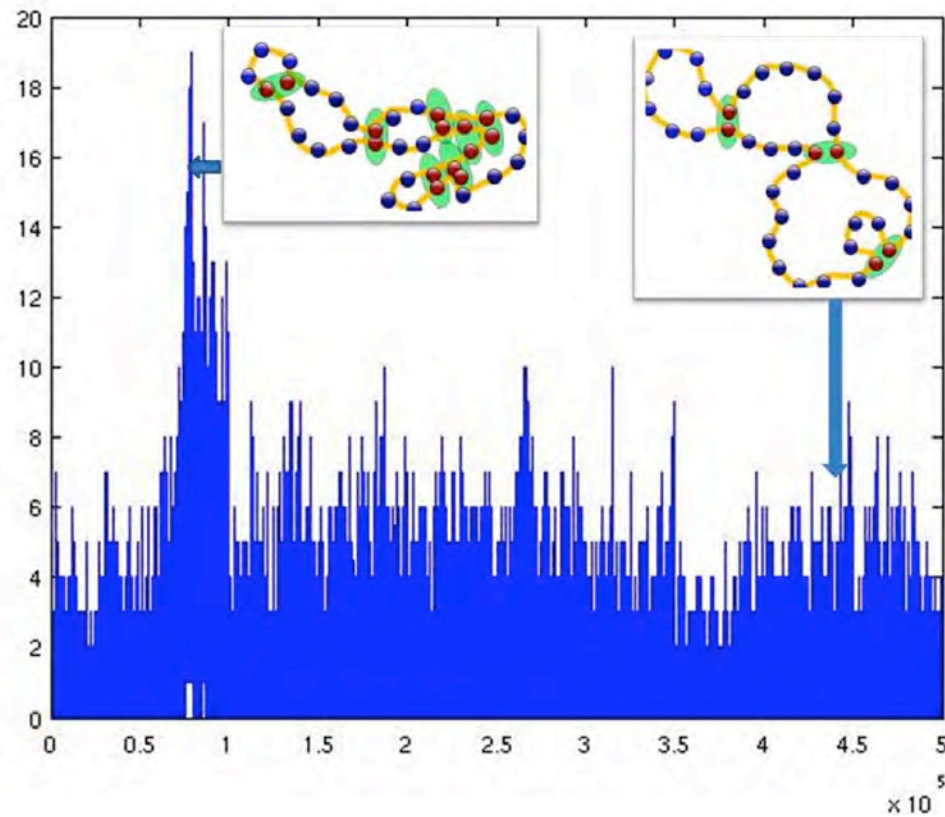
Modeling Interacting Chromatin: Bead-spring Model with Sticky Tails



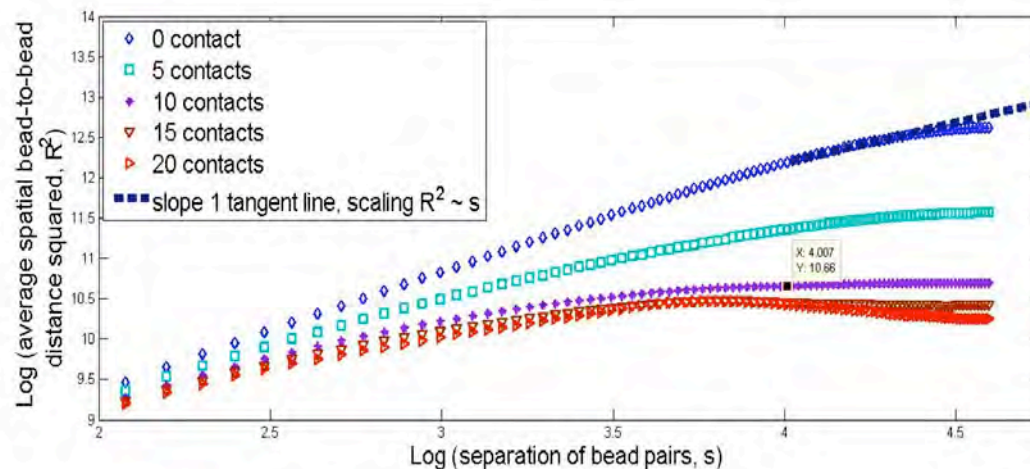
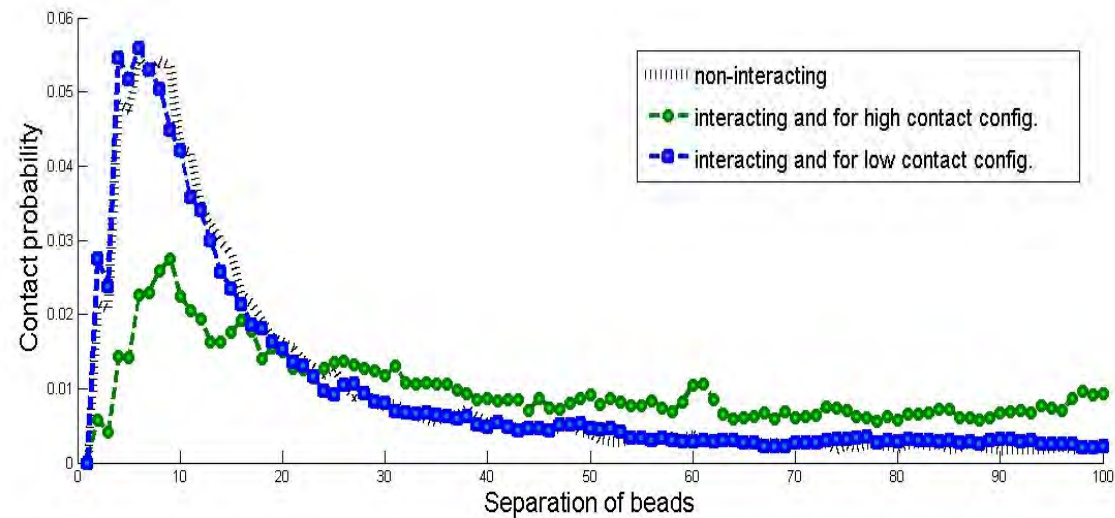
Enhancer Promoter Contact



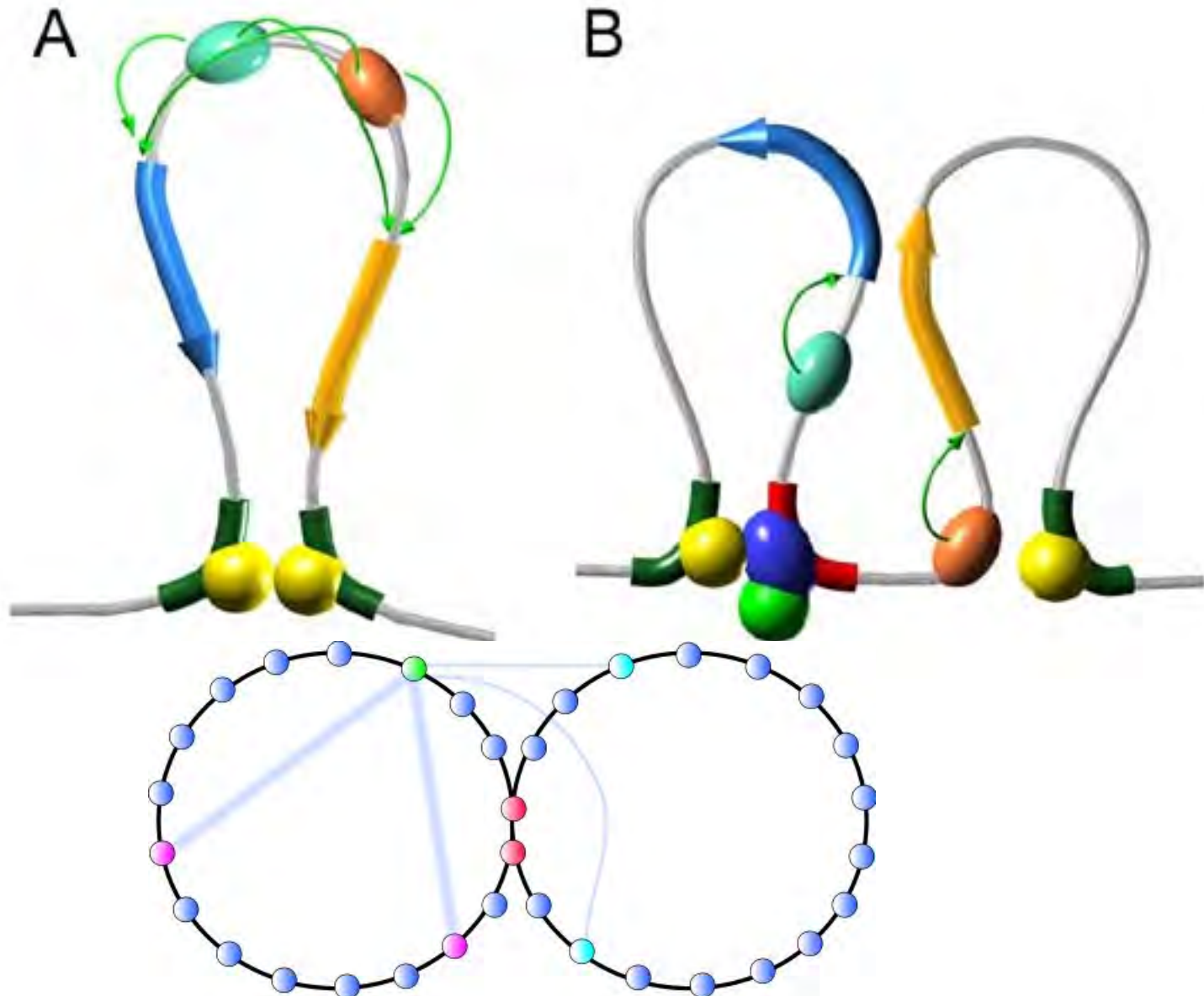
Transient High Contact Configurations



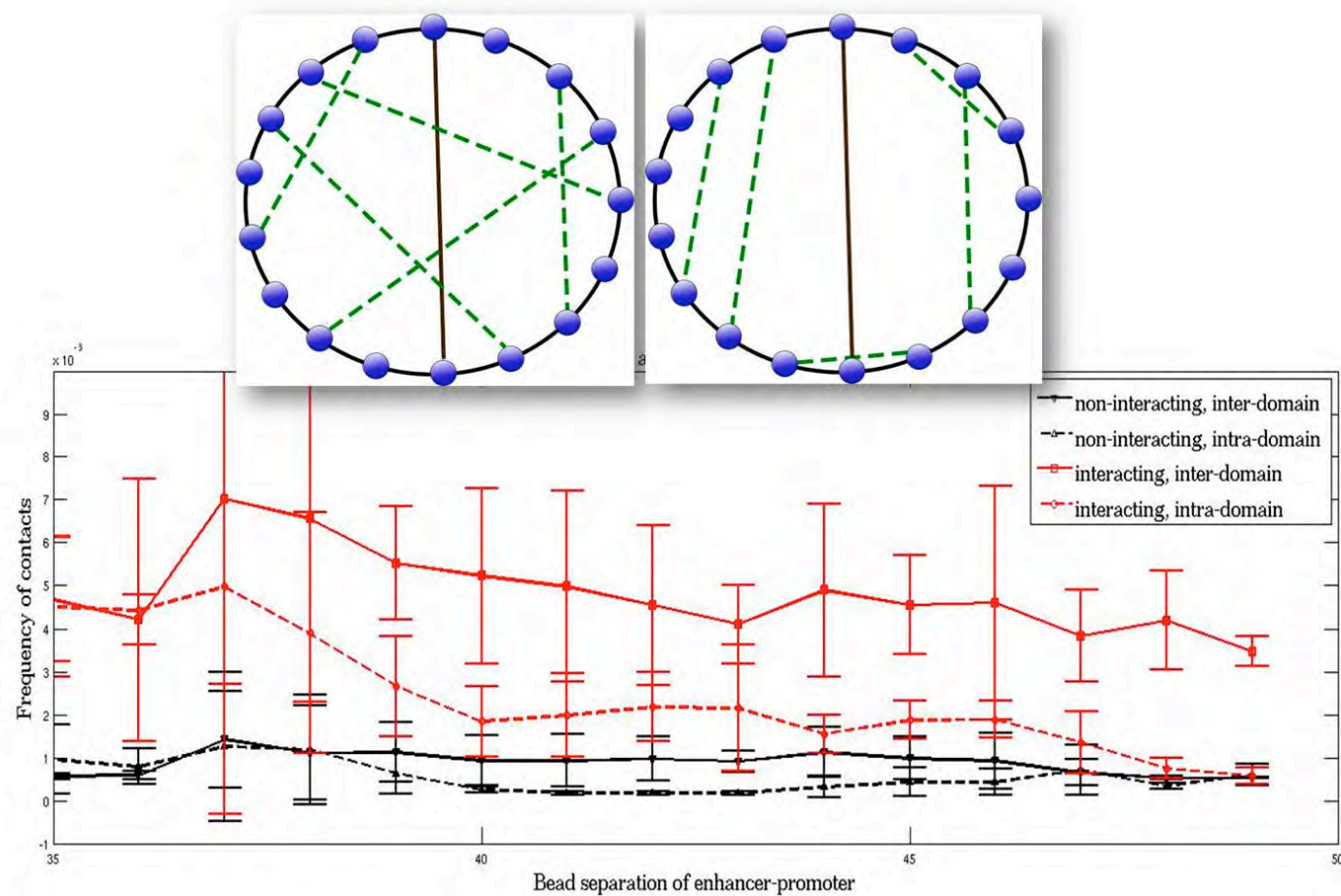
The Long-range Interaction is from the High-contact Transients



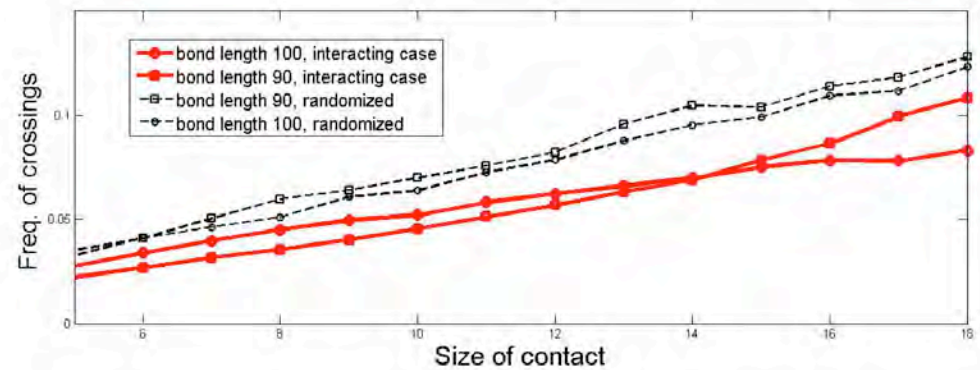
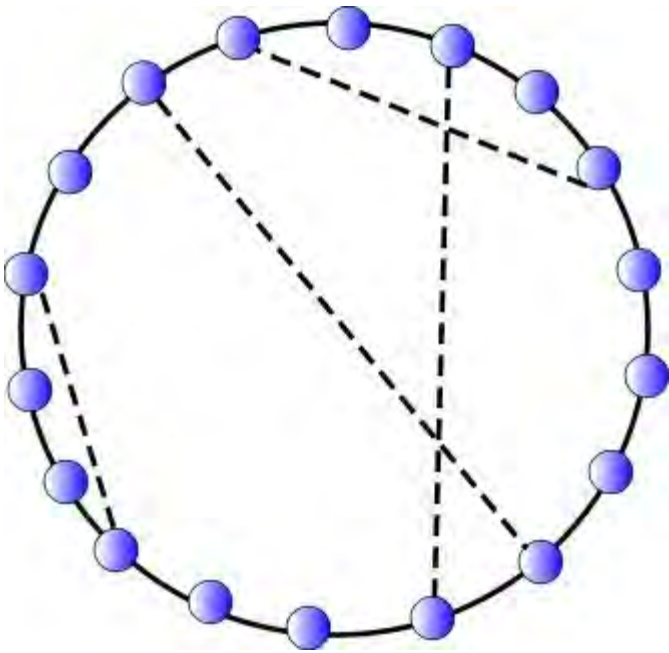
Simulation of Pinched Rings



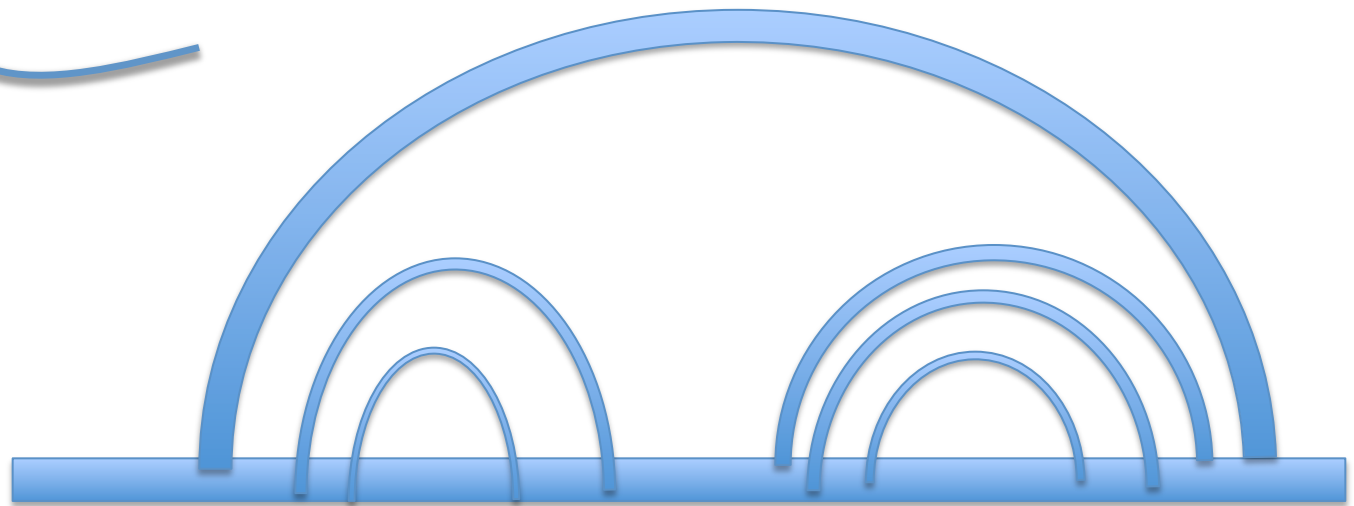
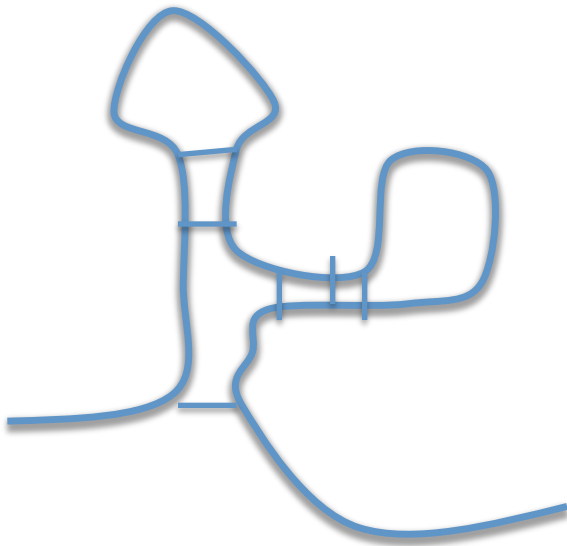
Simulation of Pinched Rings: Results



“Quasi-planar” contact maps?



Planarity of Contacts: Pseudoknot 'Free' Folding



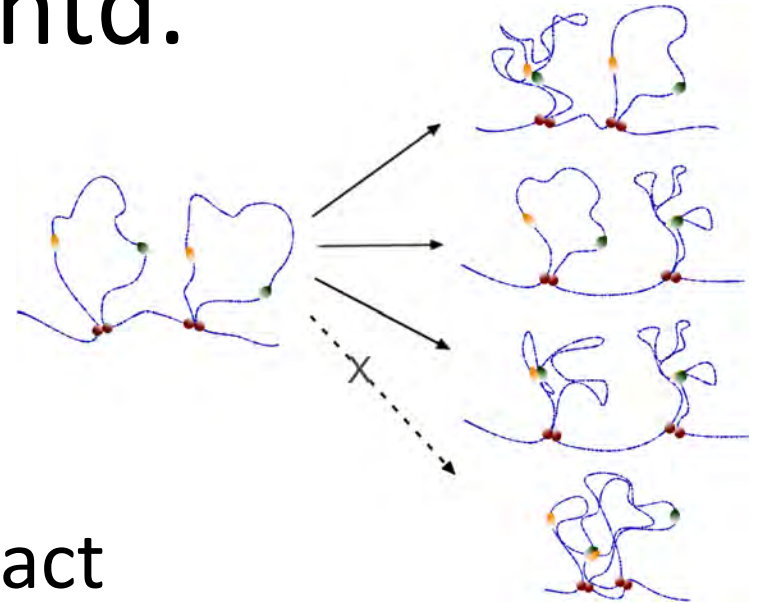
Dialogues contd.

Biologist: This looks very much like what happens in RNA. Why is chromatin not having too many pseudoknots?

Physicist: For large number of contacts too many crossings lowers configurational entropy.

Other biologist: Back to my original discomfort with the loop domain model: why do two flopping loops not touch each other?

Dialogues contd.

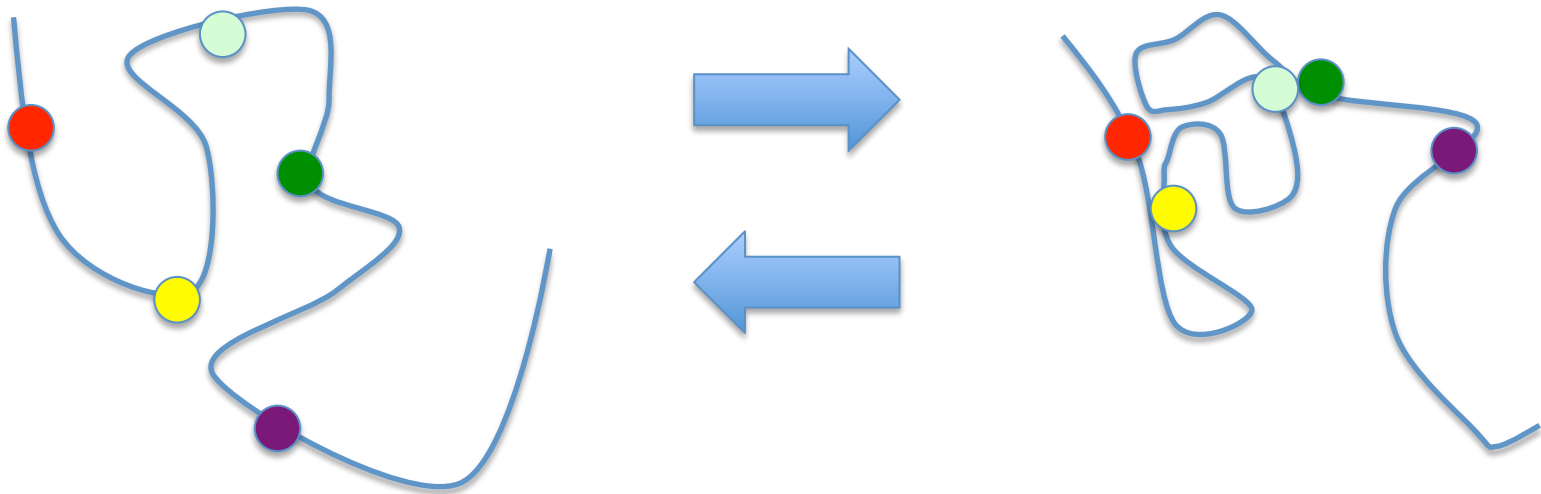


Physicist: They do! With low contact configurations, those contacts are as rare as long range enhancer action within the loop. You have to look at the structure of the temporarily collapsed configurations for the solution.

Biologist: What predictions does this theory make? Does this sort of model have any use beyond providing the `big picture`?

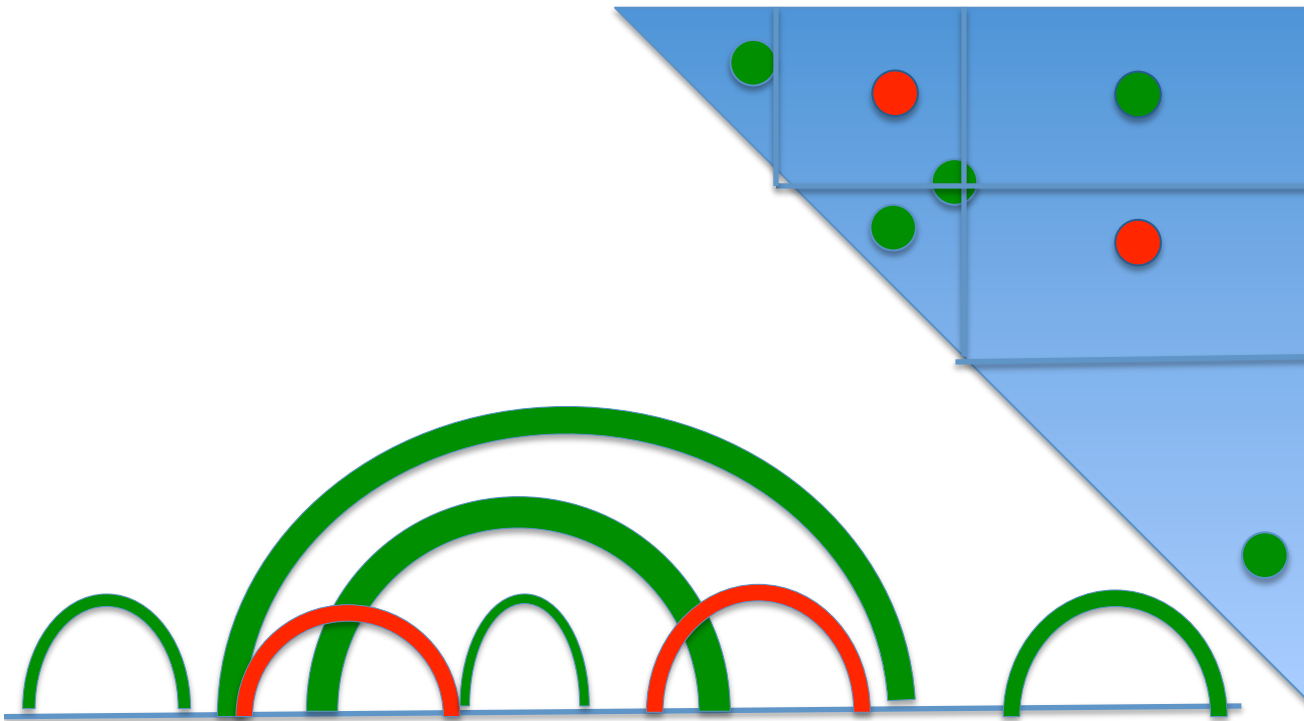
Prediction I

Direct visual observation of the rare collapsed states by FISH.



Prediction II

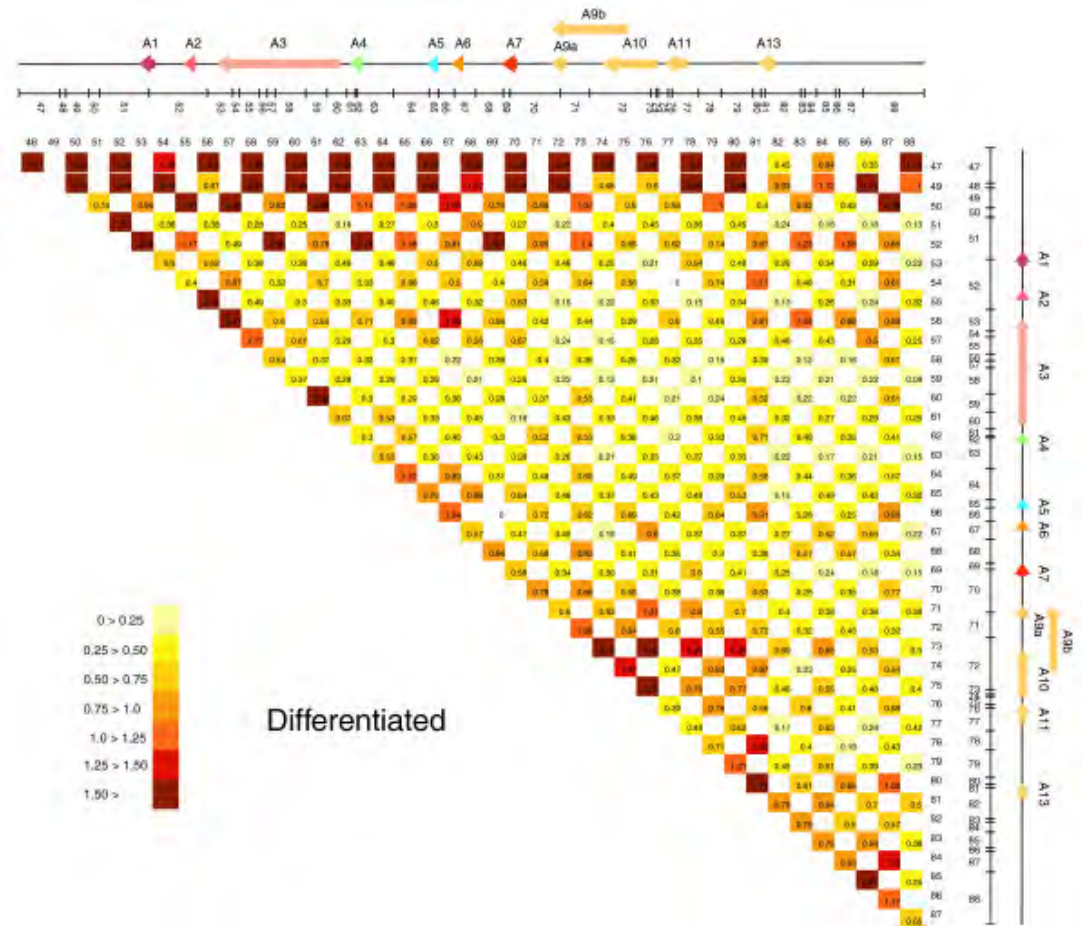
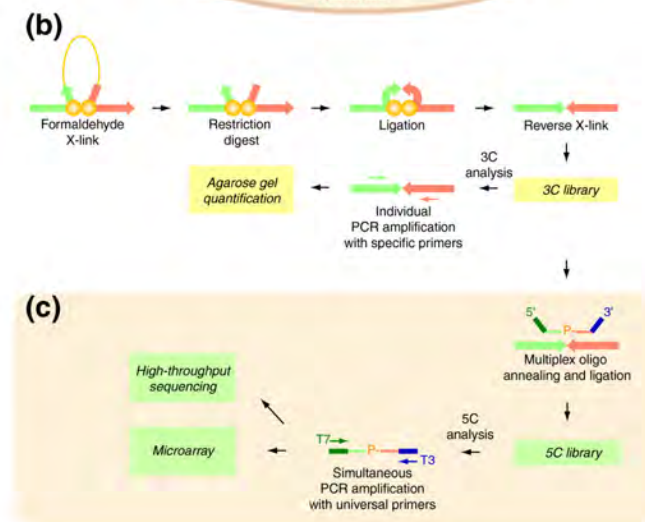
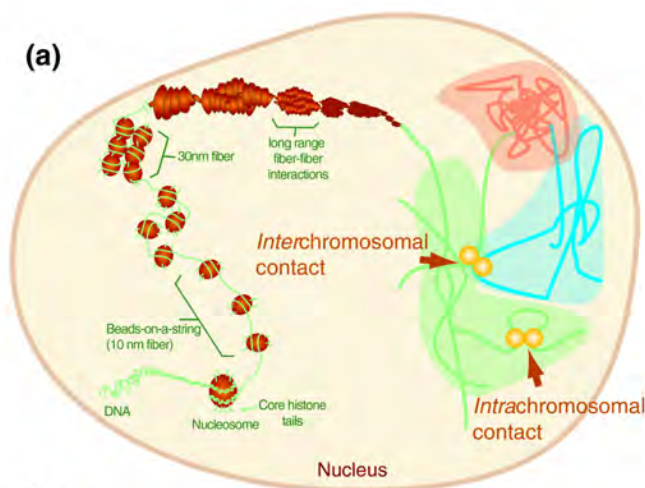
Single cell 3C/High C experiments should show signatures of non crossing.



Interesting Mesoscopic Polymer Physics

- Attractive polymer \leftrightarrow Quantum particle in non-gaussian disordered potential
- Q Mech in disordered potential \leftrightarrow large N expansion
- Large N methods \leftrightarrow Genus of contact maps
- Potential non-equilibrium contributions
- Data Analysis: Conformation capture data to 'statistical' topology

Analyzing 3D Geometry of Chromatin.



Dostie group

Opportunities_A

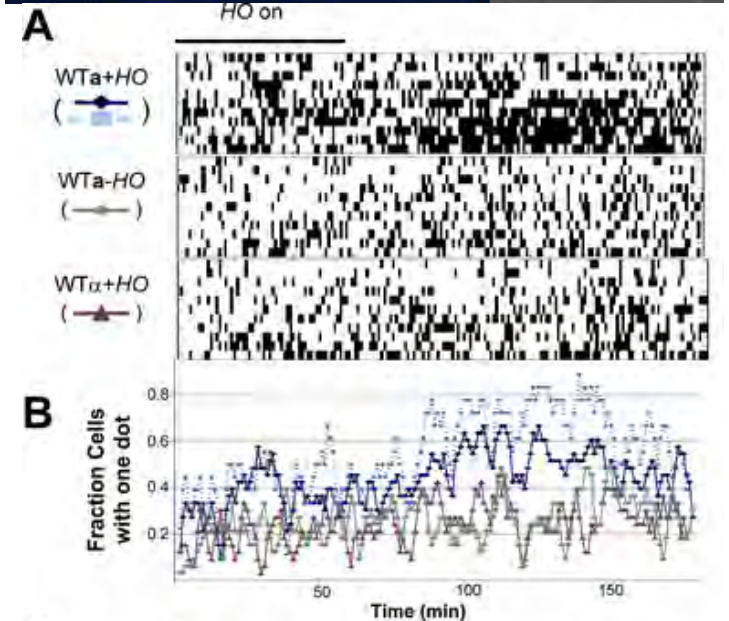
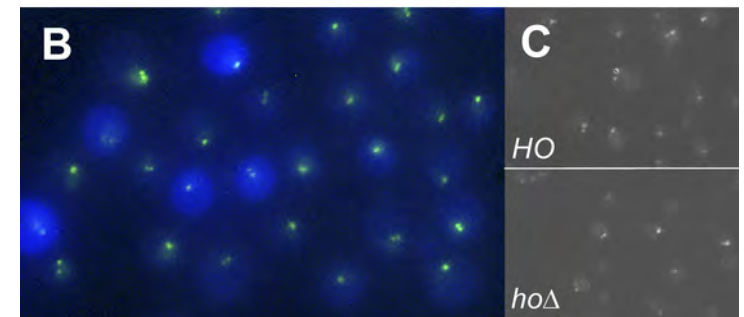
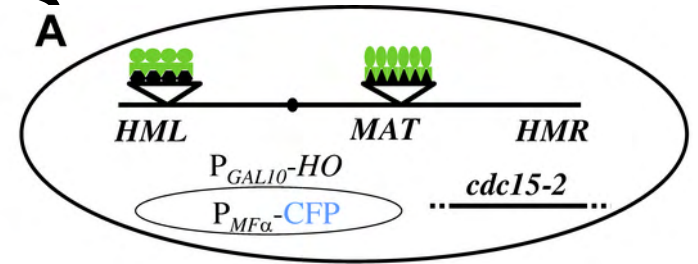


Job Dekker

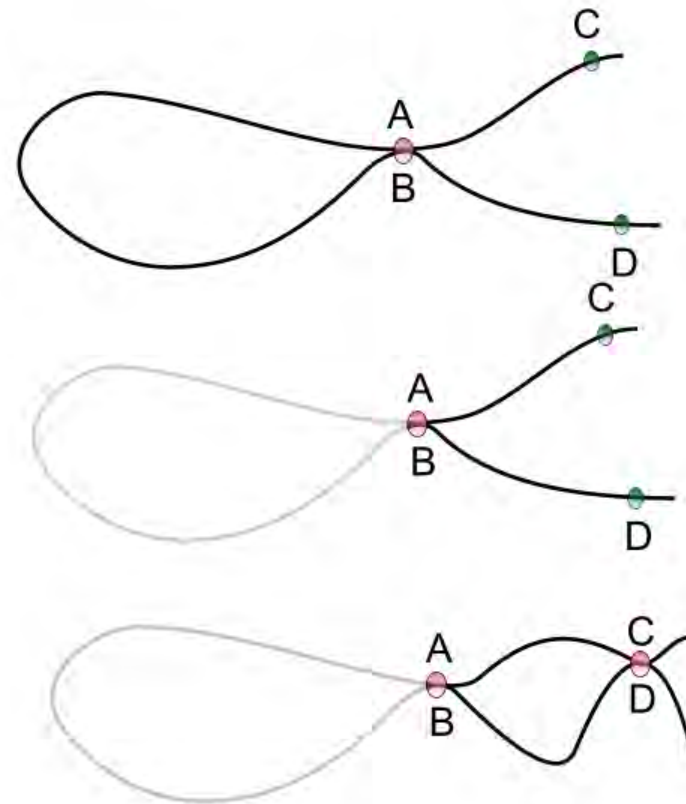
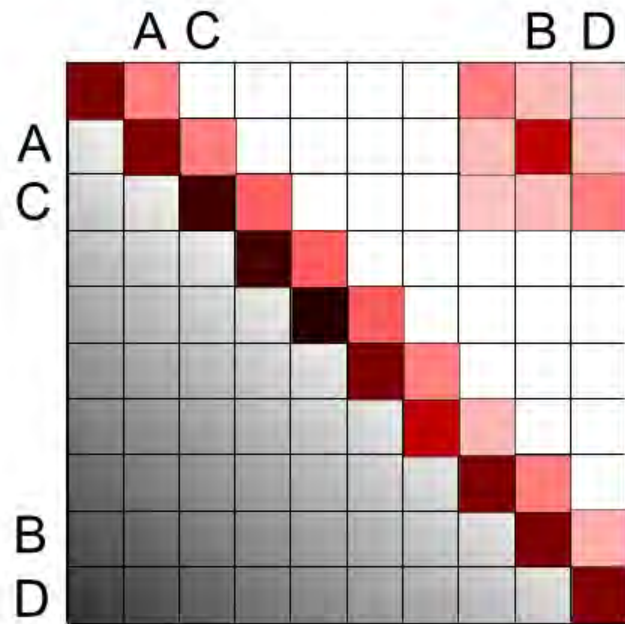


Dynamics, anyone?

Houston and Broach,
PLoS Genetics, '06



Intuition



Contact Data to Probability Model

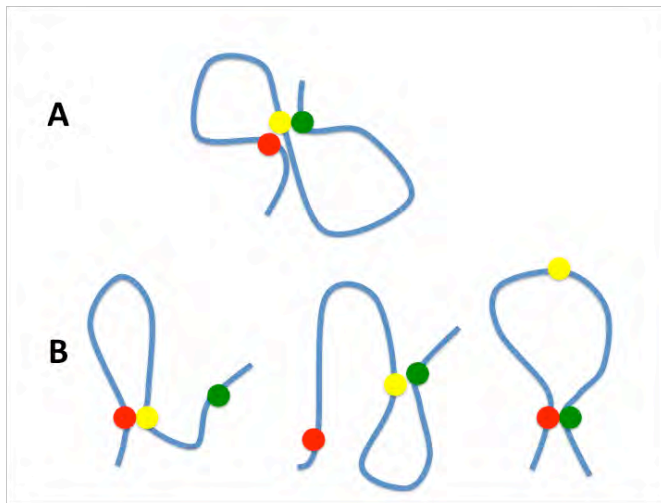
$$C_{ij} = \langle \delta(x_i - x_j) \rangle = \int Dx P(x) \delta(x_i - x_j)$$

&

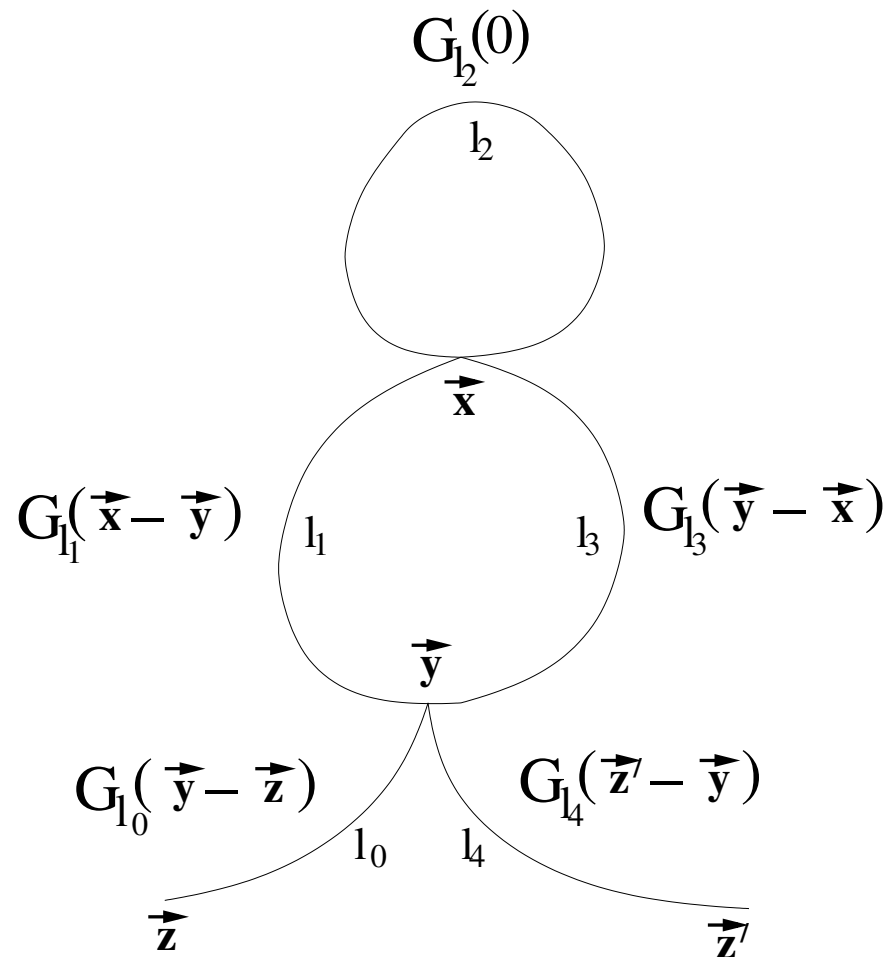
$$\min \int Dx P(x) \ln \{P(x) / P_0(x)\}$$

$$\Rightarrow P(x) \propto P_0(x) \exp[-\sum_{ij} v_{ij} \delta(x_i - x_j)]$$

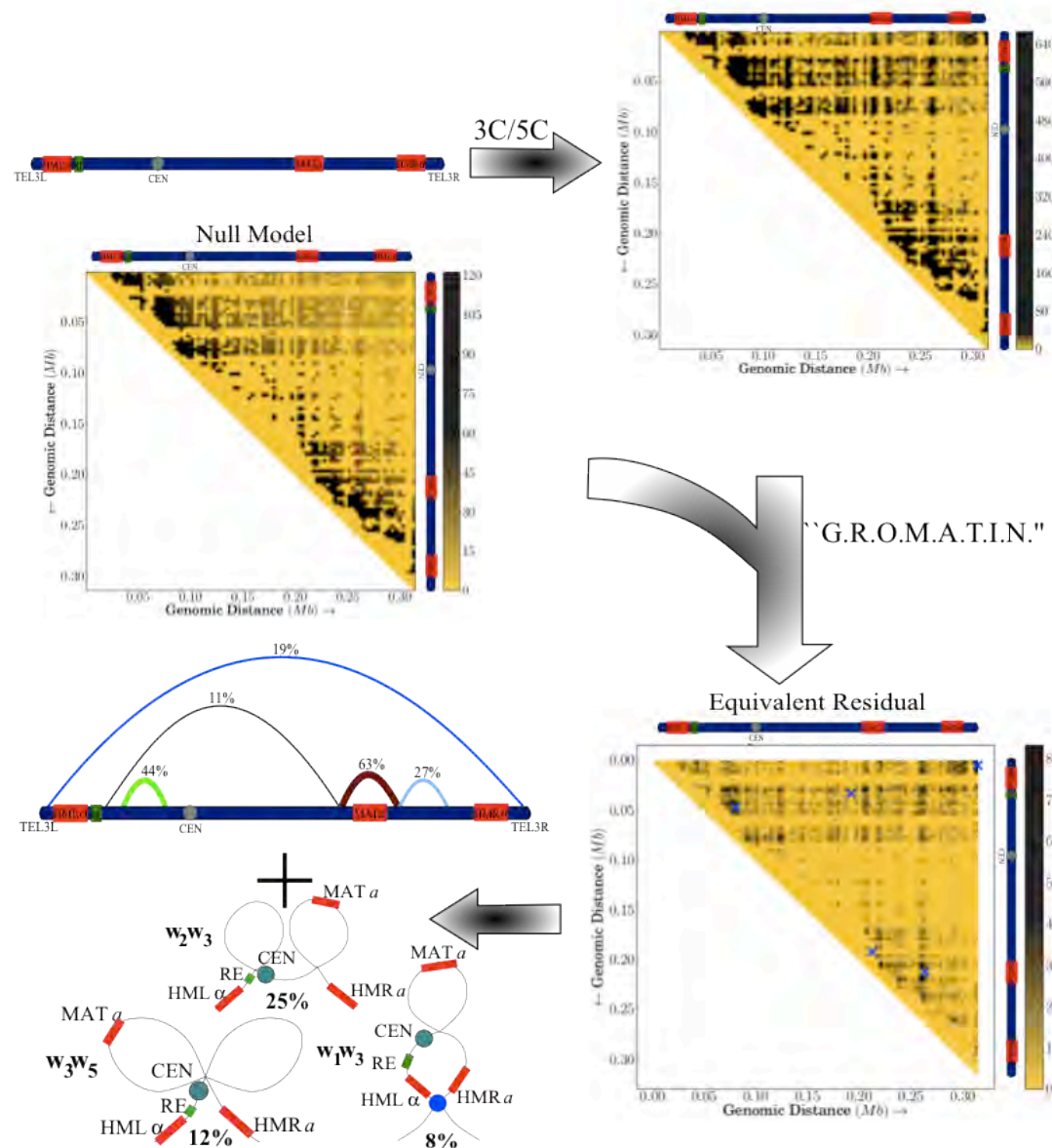
$$\propto \exp[-\sum_i (x_{i+1} - x_i)^2 - \sum_{ij} v_{ij} \delta(x_i - x_j)]$$



Green functions



Yeast Chromosome III



Summary

- Pseudoknot suppression explains insulator action
- Analyzing topology of contact
- Analysis of 3C/FISH Data using polymer models

Collaborators

Swagatam Mukhopadhyay
Manjul Apratim
Dave Hassan
Mohammad Ramezanali

Vasily Studitsky
Paul Schedl

Wilma Olson's group

Lourdes Serrano's group