The Game of Chromosome Organization

WIS Clore 2011

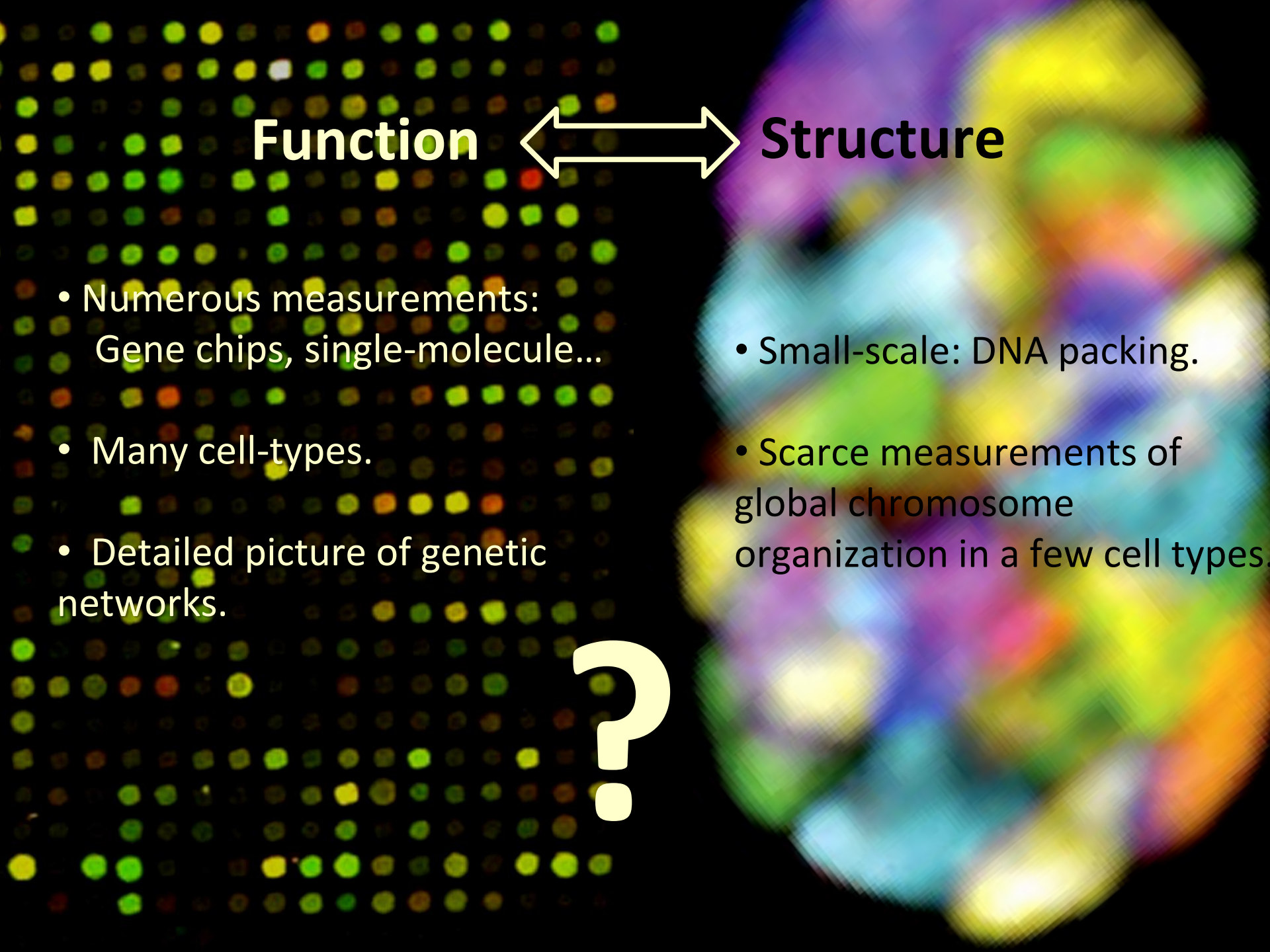
AJ Libchaber (Rockefeller) JP Eckmann (Geneve)

GV Shivashankar, KV Iyer, S Maharana (NUS)

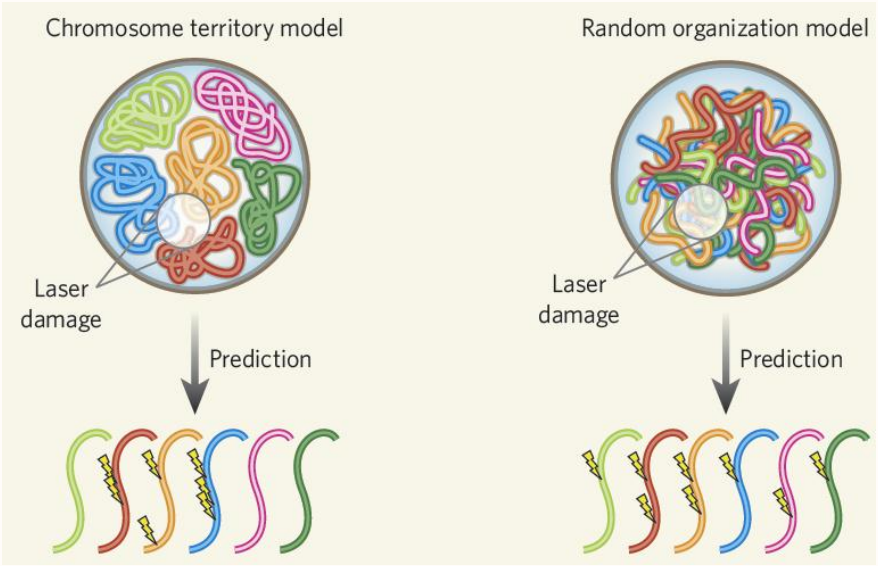
T T (Weizmann)

Outline

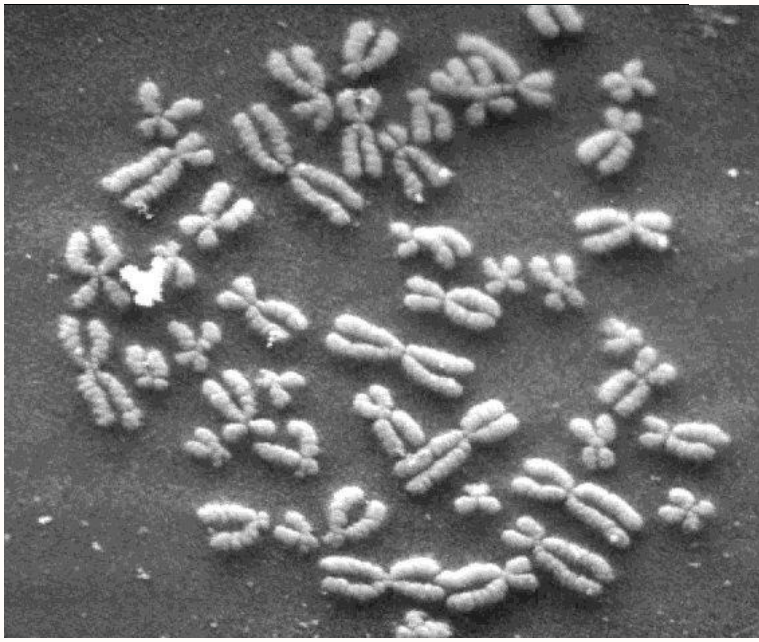
- Intro: Chromosome organization in eukaryotic cells.
- Relation of spatial order to function?
- Combinatorial problem – “game” of chromosome ordering.
- Measured cell-type specific optimality of order.
- …


Function
Structure
• Numerous measurements:
Gene chips, single-molecule…
• Many cell-types.
• Detailed picture of genetic networks.
?
• Small-scale: DNA packing.
• Scarce measurements of global chromosome organization in a few cell types.

Chromosomes reside in well-defined territories

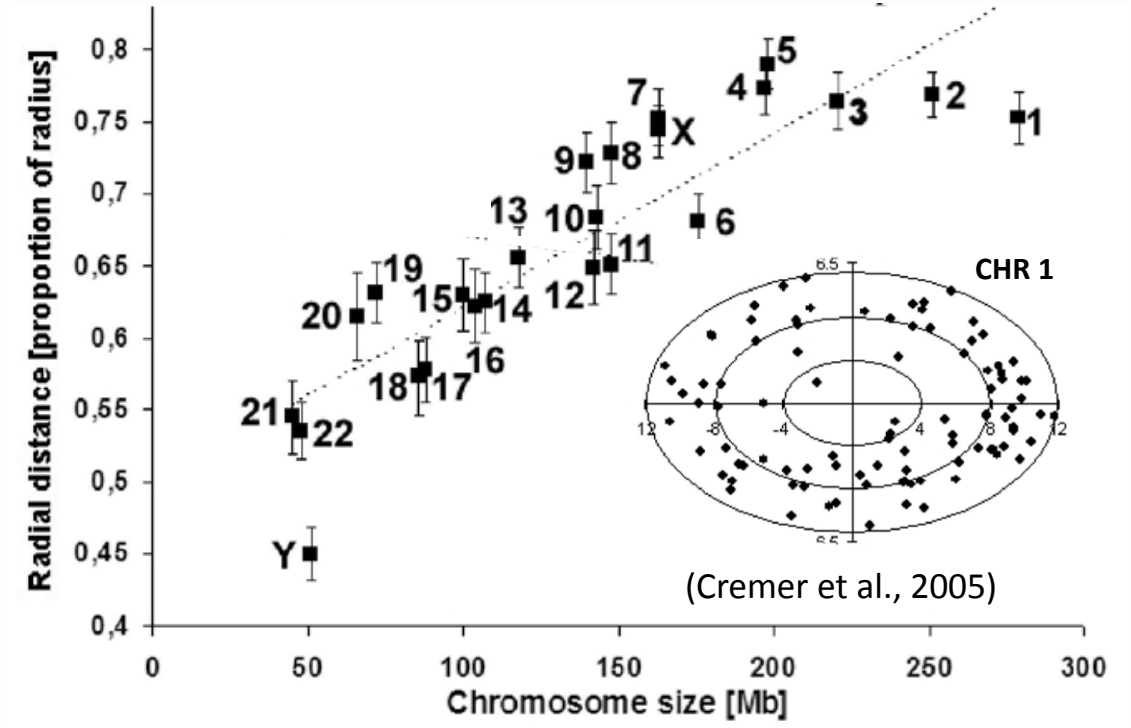


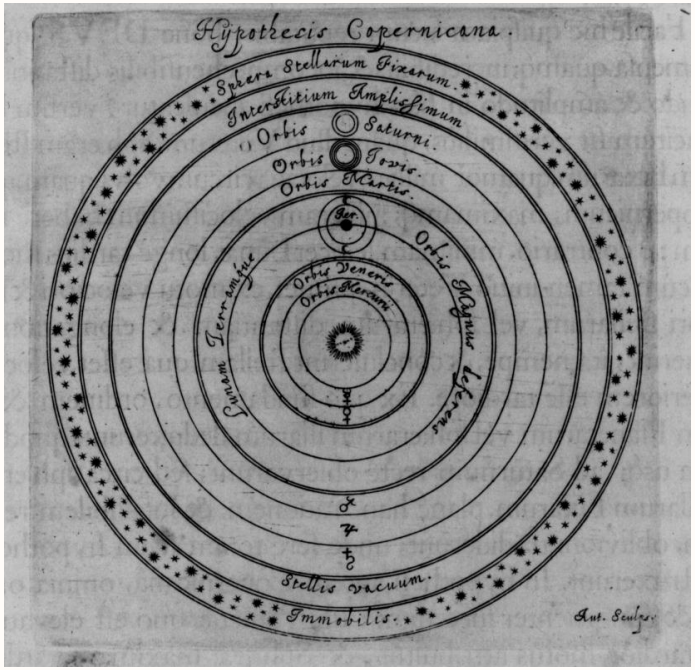
Cremer & Cremer (80s)



- Eukaryote nucleus is divided into **chromosome territories.**
- Chromosome structure hierarchal “sponge”, accessible to regulation.

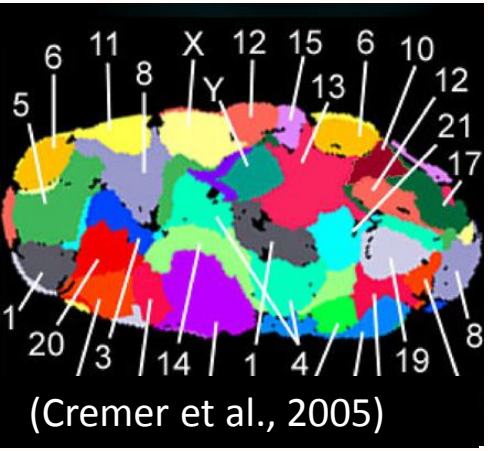
Chromosomes are radially ordered.





- Mammalian chromosomes have preferential radial position.
- Radial order is *probabilistic*
  and *cell-specific* (chromosomes move during differentiation).
- Order with respect to nucleus coordinate.

The puzzles of chromosomes



(Cremer et al., 2005)

- What is the optimal (?) number?

- Why organization?
- What is the optimal (?) spatial order?
- More than radial order? **relative** order?
- Relation to cell-type and function?

(Hint: cell-type specific positions in across species)

- Mechanisms of positioning and interaction among chromosomes?

Organism	# chr
M. pilosula (ant)	2
Fruit fly	8
Arabisdopsis	10
C. elegans	12
Rye	14
Corn	20
Chinese hamster	22
Budding yeast	32
Earthworm	36
Cat	38
Syrian Hamster	44
Human	46
Tobacco	48
Silkworm	56
Horse	64
Dog	78
Goldfish	100
Adder's tongue	1400

Mapping between 3D organization and expression

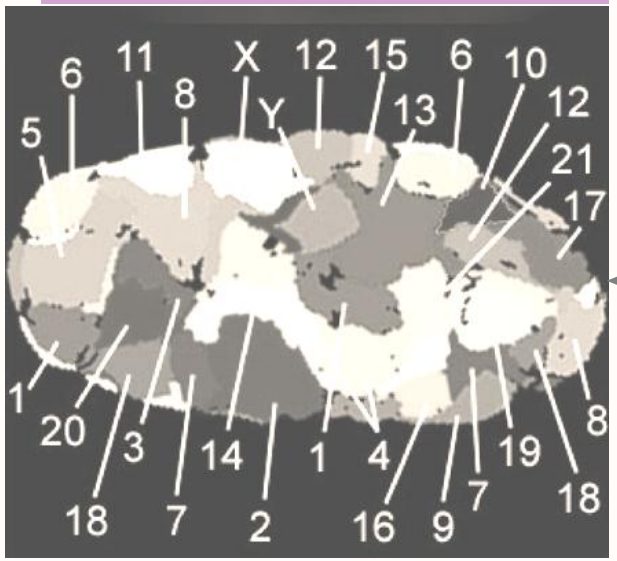
Real Space

Cell Types

"Function Space"

≈

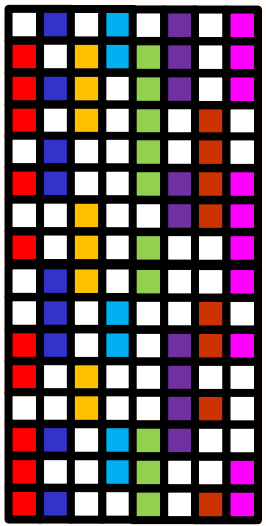
Spatial organization



Expression

Cell type

genes

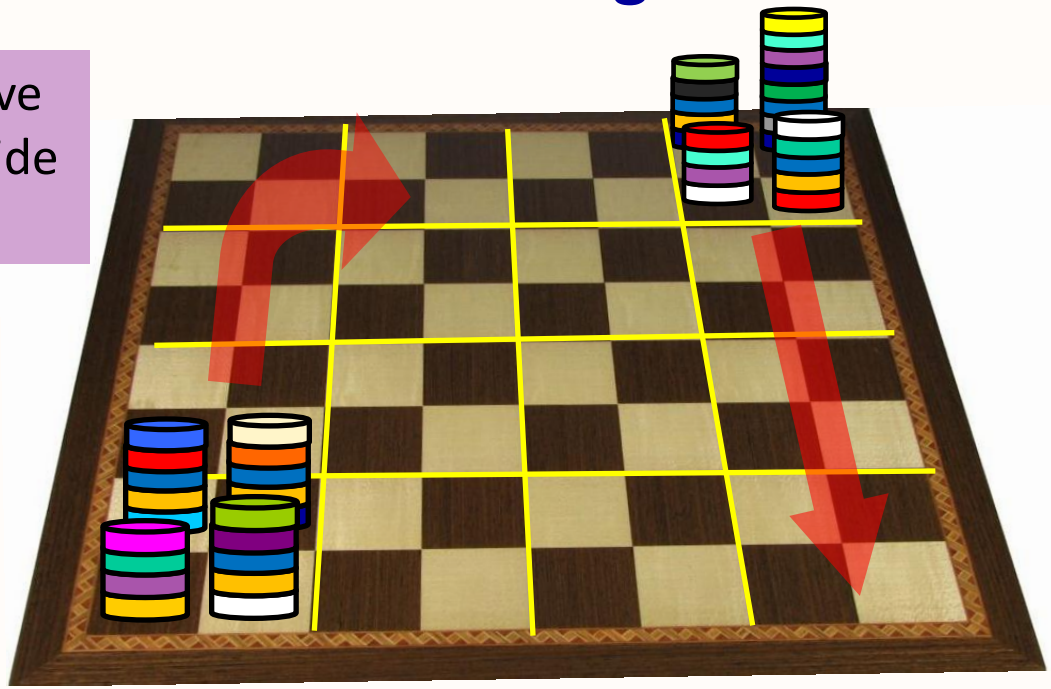


?

Hypothesis: relation between real space and function space based on **optimality**

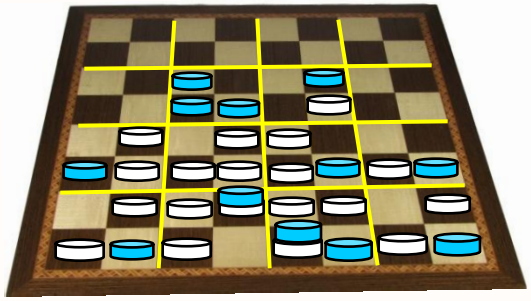
The combinatorial game of chromosome Organization

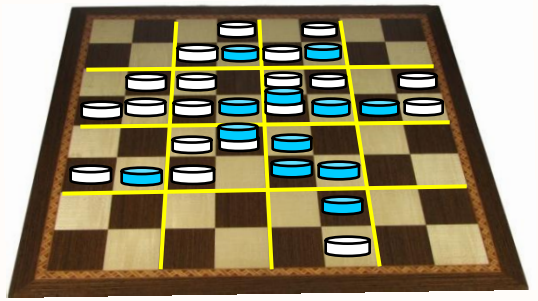
Hypothesis: co-expressed genes or active genes with similar function tend to reside in the same or in close chromosomes.



"Casino chip shuffling"

(A) Given stacks of multi-color Chips.
(B) Divide chessboard into "Blocks".
(C) Cover board with stacks.
(D) For each color: Shuffle the Blocks such that all chips of this color will be close as possible to each other.



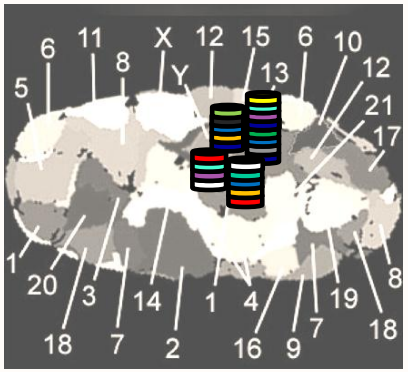


Optimal chromosome organization?

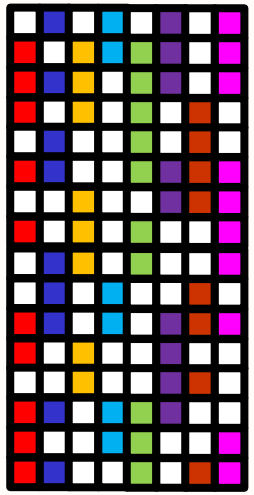
Hypothesis: co-expressed genes or active genes with similar function tend to reside in the same or in close chromosomes.

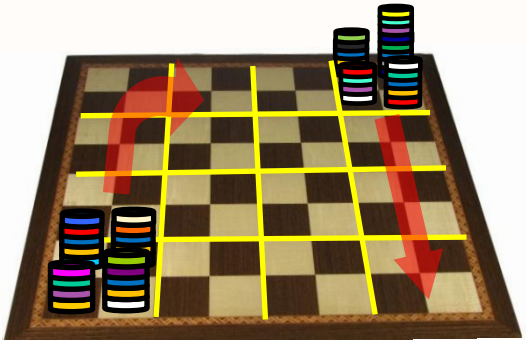
Optimal organization	Casino chip shuffling
Cell type/function	color
Gene	Chip stack
Chromosome	Block
Nucleus	Chessboard
Chrom. reorganization	Block shuffling
Close active genes	Close Same color chips

Nucleus



Expression

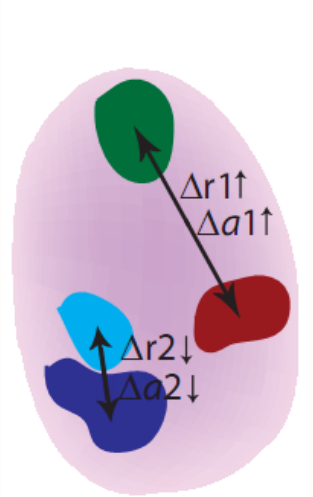


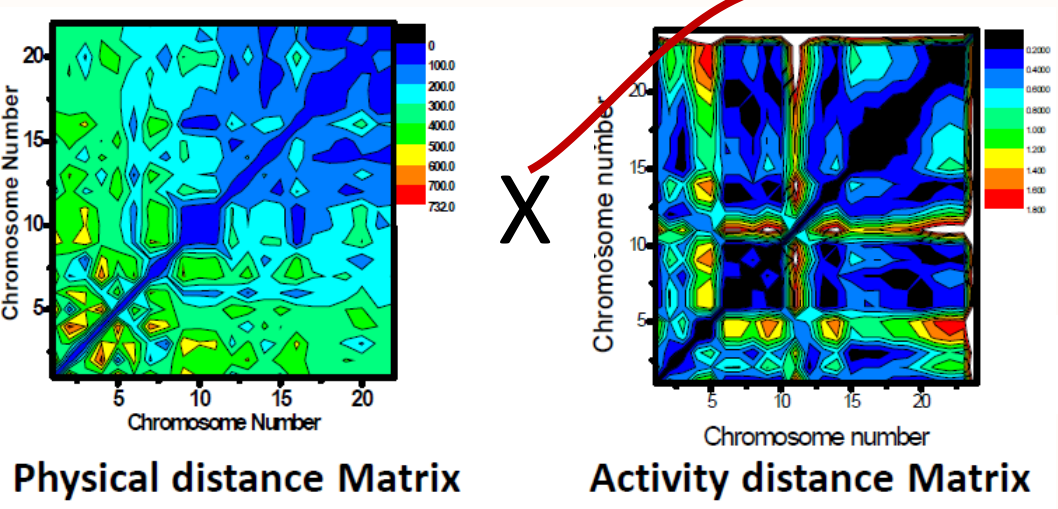


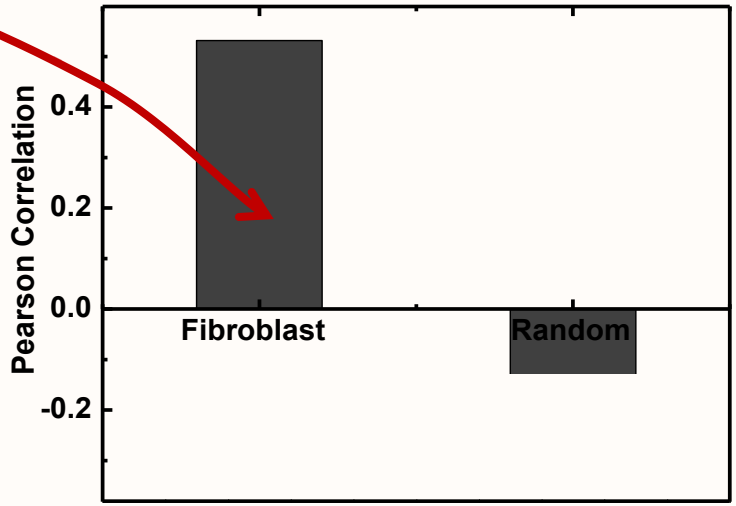
Spatial organization and expression are correlated

- Expression distance $IAD = \left| \ln \frac{\langle \text{activity/gene} \rangle_i}{\langle \text{activity/gene} \rangle_j} \right|$
- Physical distance $IPD = \left| \langle r_i - r_j \rangle \right|$
- Average over 54 nuclei yields significant correlation

  (fibroblast measurements by Cremer et al.)





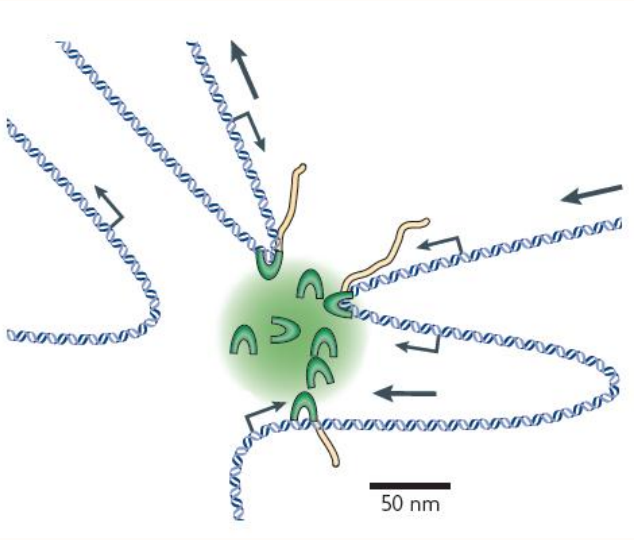


Possible mechanisms of chromosome interaction and positioning

- Order is statically conserved throughout cell division.
- Anchoring to nuclear scaffolding?
- Radial ordering by size and gene density?

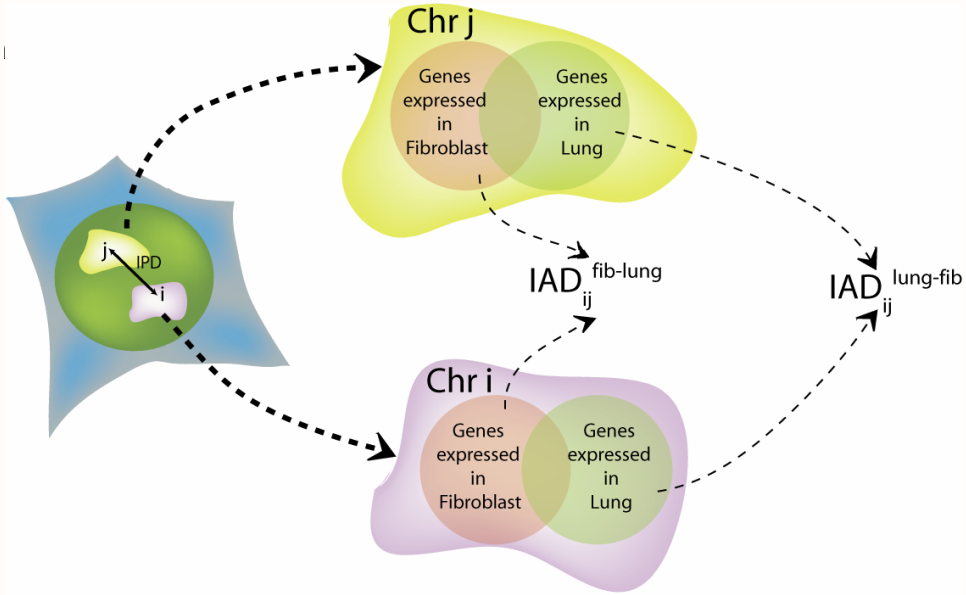
self organization by activity and function

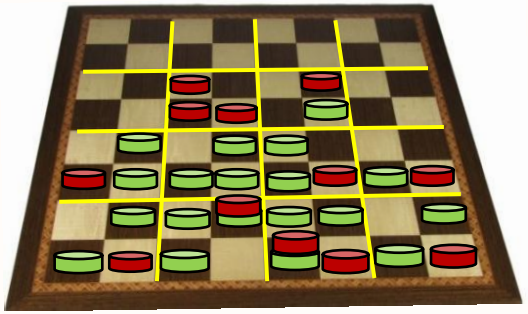
- Proximity boosts efficiency of *transcription factories*?
- Active\inactive regions are de-condensed\condensed?
- Interactions between genes and regulatory regions?

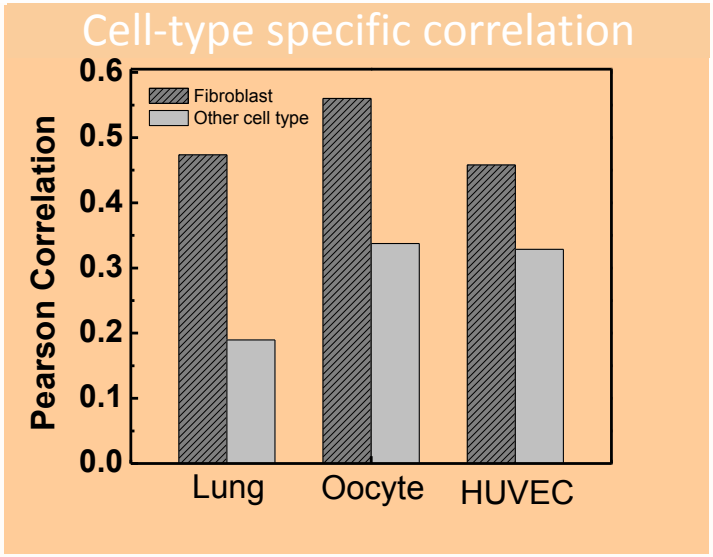


Transcription factories: Genes from different chromosomes associate with polymerases in the same factory. (Sutherland & Bickmore, *Nat Rev Gen* 2009)

Is chromosome organization cell specific?

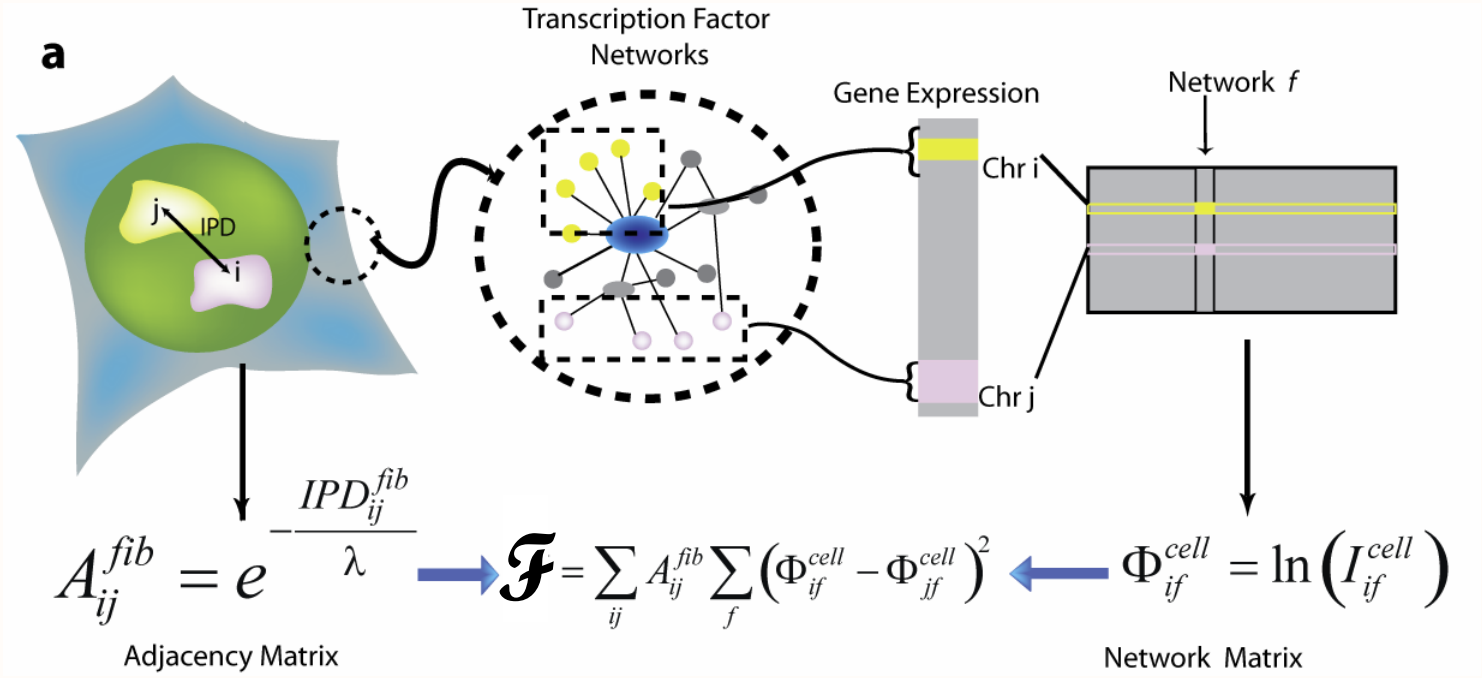






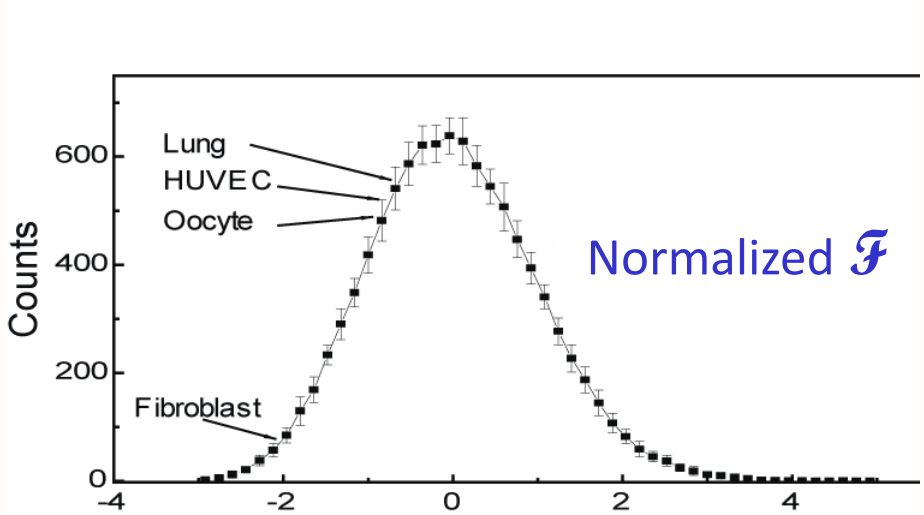
- HUVEC - human umbilical cord vein endothelial cell.
- Oocyte – female germ cells.
- Fibroblast – connective tissue.
- Lung – epithelial cells.

“Fitness” of chromosome organization



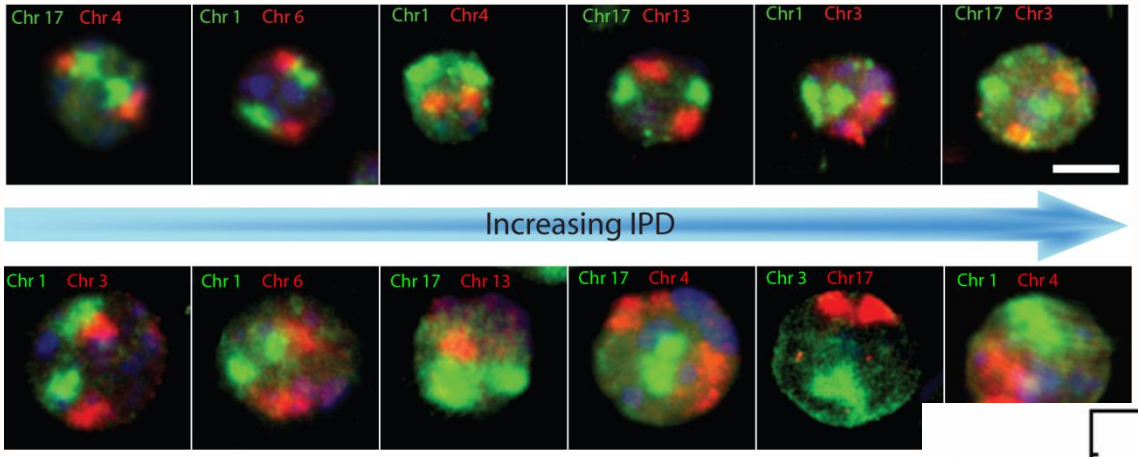
- $\mathcal{F}$ is “Smoothness” measure :

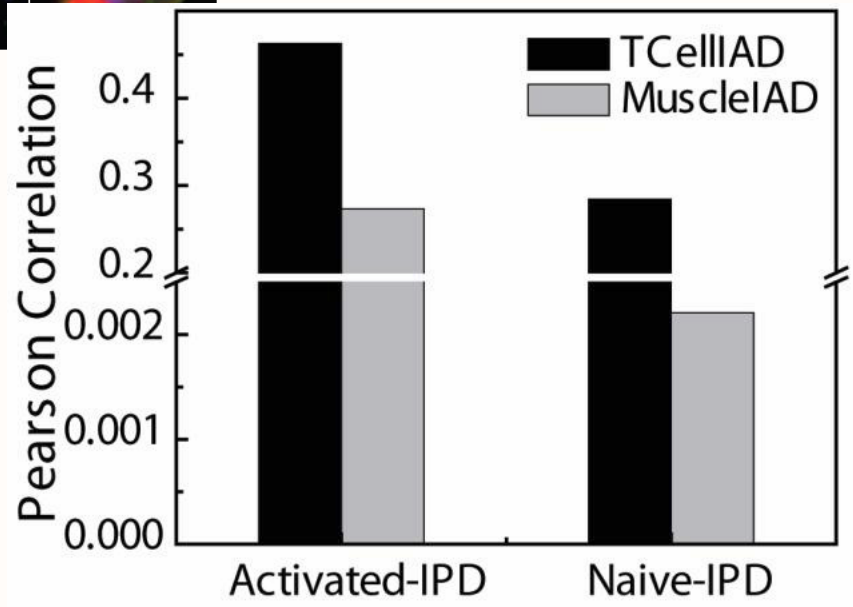
  How close are gene that perform the same function in given cell type?



Evidence from T-cells measurements

- Other cell types (preliminary evidence from T cells).

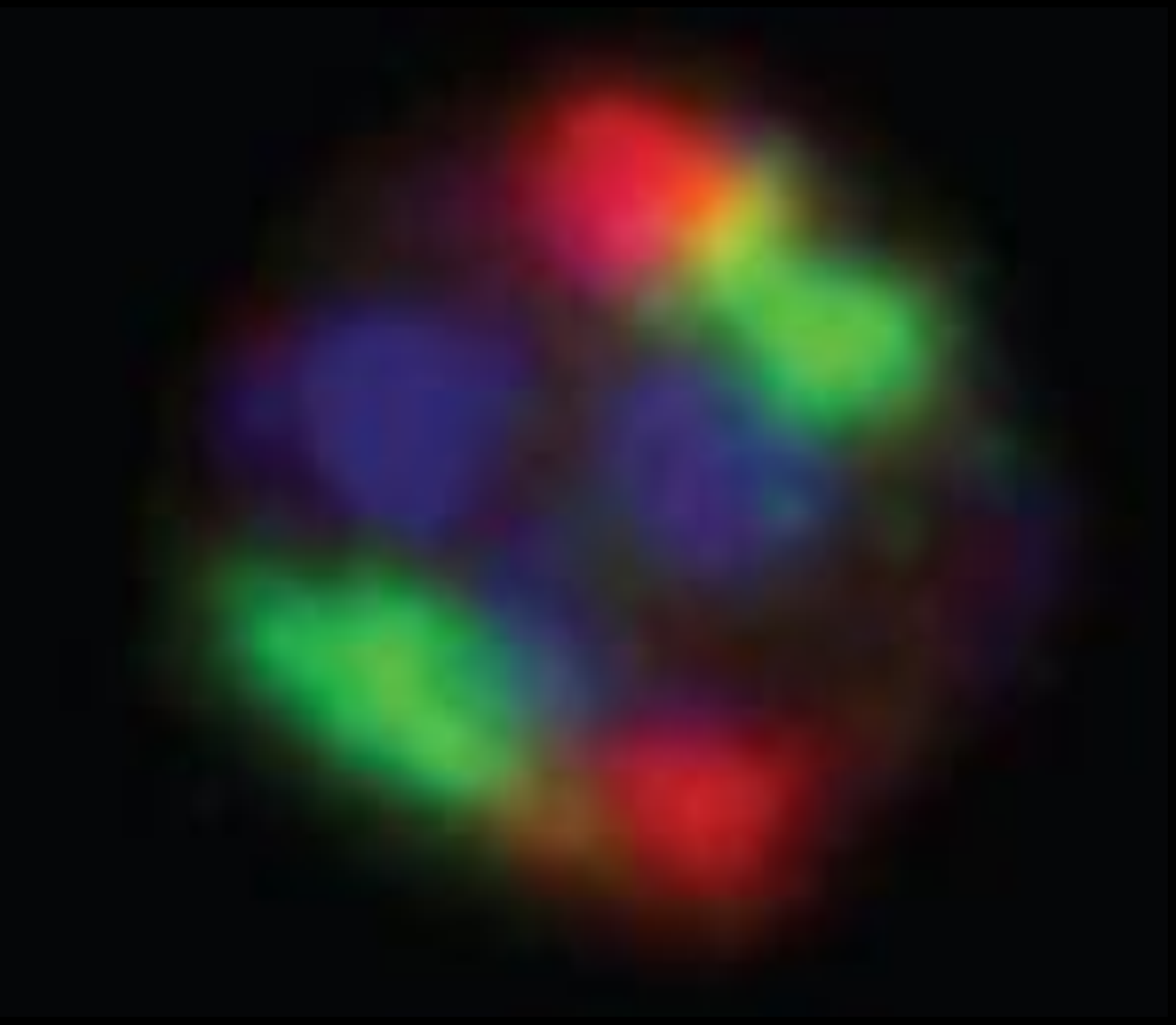




Questions and directions

- Better optimality measures (transcription factories).
- Optimality transition as a function of chromosome #.
- Relations to the topology of the chromosome graph (A_{ij}).

THANKS



Rockefeller
Albert Libchaber

NUS, NCBS
G.V. Shivashankar
S. Maharana
V.K. Iyer

Geneva
Jean-Pierre Eckmann

T cell measured by the Shivashankar group NUS