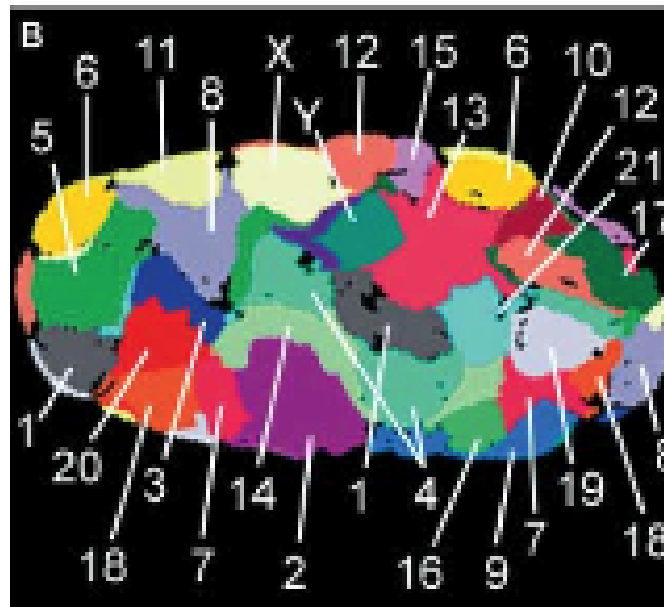


Chromosome packing in cell nuclei



Joint work with Saira Mian

SIAM Conference on Applied Algebraic Geometry

October 9, 2011

Non-random arrangement

- Arrangement of chromosome territories is **non-random**
 - evolutionary conserved in given cell type
 - similar among cell types with similar developmental pathways
 - can change during processes such as cancer, differentiation
- **Radial preference:**
 - In spheric nuclei (e.g. lymphocytes) strong correlation with **gene density** (gene-dense chromosomes in interior)
 - In ellipsoidal nuclei (e.g. human fibroblasts) strong correlation with **chromosome size** (small chromosomes in interior)
- **Neighbor preference:**
 - some evidence (proximity to co-regulated genes might play a role)
 - consequence of non-random radial position?

Goals and questions

- Model for chromosome arrangement
- Map of chromosome arrangements for different cell types
- ? How much of the non-random positioning can be explained by the geometric constraints?
- ? Why are there differences between spherical and flat-ellipsoidal nuclei?
- ? What happens if we alter the number of chromosomes or the ratio between nucleus volume and total chromosome volume?
- ? How are internal cavities distributed?

Outline

- Model for chromosome arrangement based on a sphere packing problem
 - Sphere packing, sphere covering
 - Simulations
 - Number and volume of internal cavities in sphere arrangement
- Interesting math / geometry problems

Model chromosome territory arrangements

- Nucleus ϵ defined by positive definite matrix

$$N = \begin{pmatrix} \frac{1}{E_1^2} & 0 & 0 \\ 0 & \frac{1}{E_2^2} & 0 \\ 0 & 0 & \frac{1}{E_3^2} \end{pmatrix}$$

- Chromosomes: Spheres $S_i, i = 1, \dots, m$ with center X_i and radius R_i . ($X_{m+1} = 0$)
- Preferred distances to other chromosomes and the center represented by $(m + 1) \times (m + 1)$ matrix D
- Variables: Chromosome centers X_i

Model (developed with Dustin Cartwright)

Minimize **overlap** and **deviation** from D
 subject to chromosomes lie inside nucleus

Minimize $L_1 \|\xi\|_2 + L_2 \|\delta\|_2$ (over X, δ, ξ)

subject to $S_i \subset \epsilon$ $\hat{Z}_{ij}^T (X_i - X_j)$ (chr. in nucleus)
 $(R_i + R_j) - \cancel{\|X_i - X_j\|_2} \leq \xi_{ij}$ (overlap)
 $\|X_i - X_j\|_2 \leq (1 + \delta_{ij}) D_{ij}$ (distances)
 $0 \leq \delta_{ij}$
 $0 \leq \xi_{ij}$

Convex relaxation: Iterative procedure

$$\|\hat{X}_i - \hat{X}_j\|_2 = \max Z_{ij}^T (\hat{X}_i - \hat{X}_j)$$

$$\text{s.t. } \|Z_{ij}\|_2 \leq 1$$

$$\hat{Z}_{ij} = \frac{\hat{X}_i - \hat{X}_j}{\|\hat{X}_i - \hat{X}_j\|_2}$$

Iterative method

- Seems to perform well and fast
- Optimal value in iterative method never increases from one iteration to the next
- Allows to explore different optimal configurations of chromosome arrangements

Sphere packing / covering

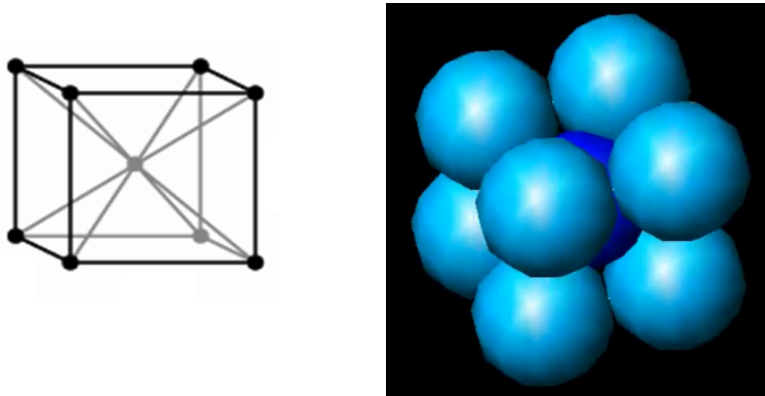
Sphere packing problem: Find densest arrangement of spheres inside container with NO overlapping

Sphere covering problem: Find finest arrangement of spheres which fills the whole space (overlapping allowed)

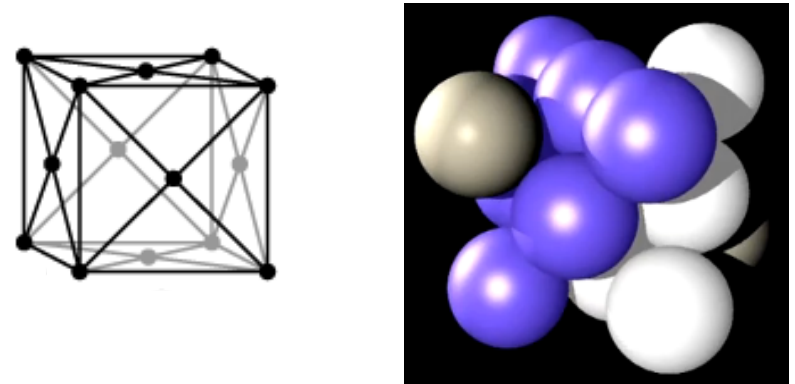
- **Density** (d): ratio of total sphere volume to total lattice volume
- 2D: optimal sphere packing and sphere covering is given by **hexagonal lattice**
- 3D: optimal sphere packing given by **BCC lattice**, optimal sphere covering given by **FCC lattice !!!**

BCC and FCC lattice

BCC lattice



FCC lattice



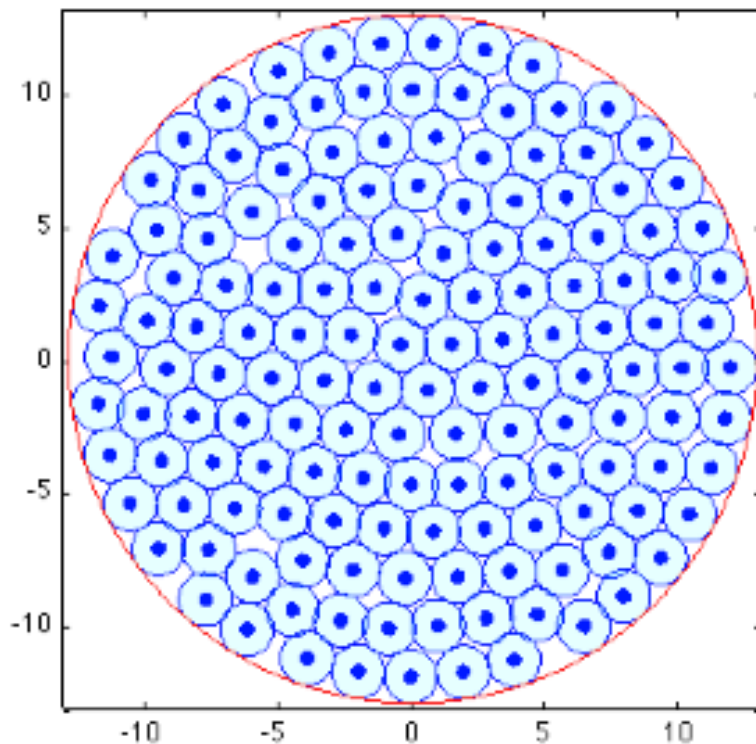
- Optimal covering ($d = 1.463$)
- 8 neighbors in packing
- 14 neighbors in covering

- Optimal packing ($d = 0.740$)
- 12 neighbors in packing
- 18 neighbors in covering

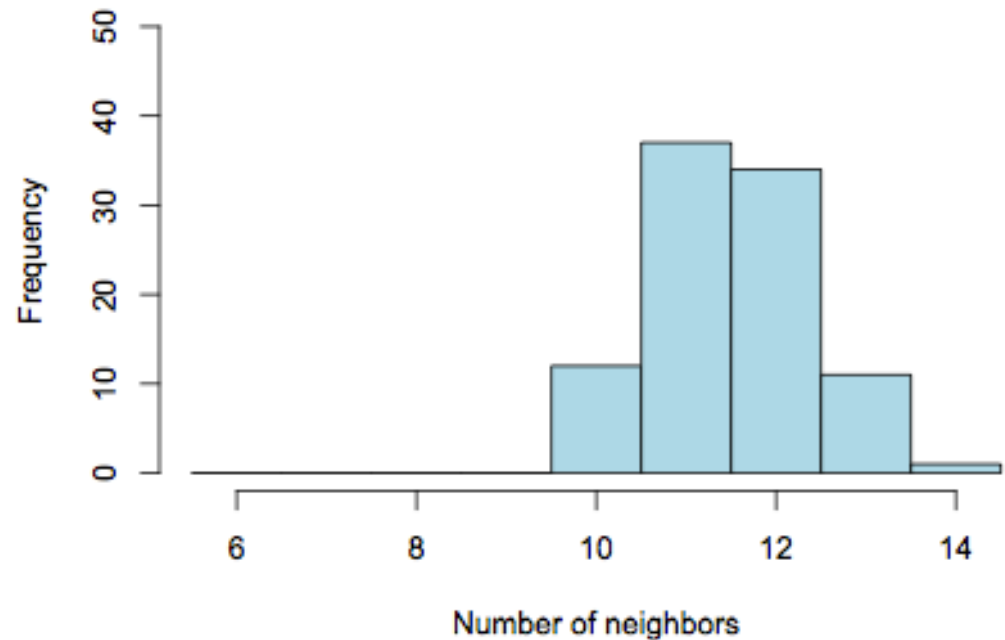
Sanity check

- Run algorithm on large collection of spheres in a spheric container satisfying optimal sphere packing density:

2D:



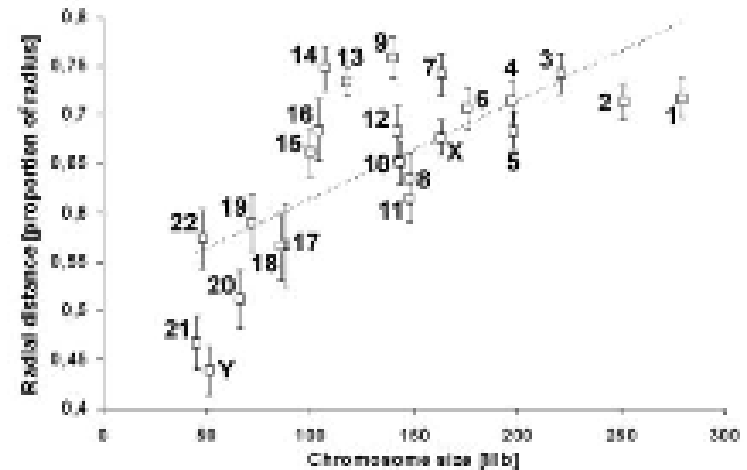
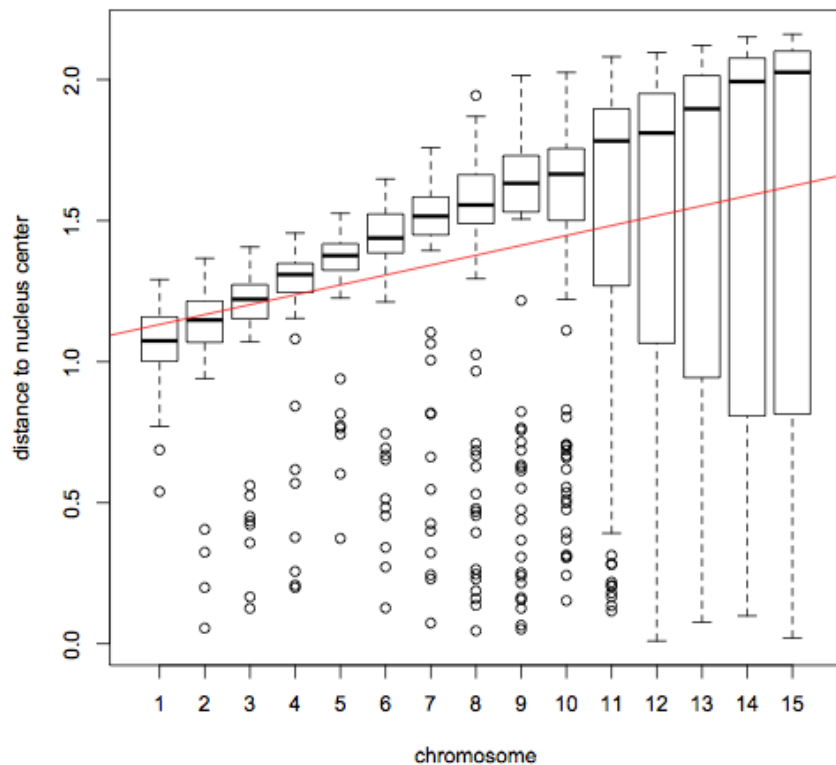
3D:



Simulation study: Round nucleus 2D

Sample chromosomes with fixed ratio of total chromosome volume to nucleus volume in simplest model with no distance constraints

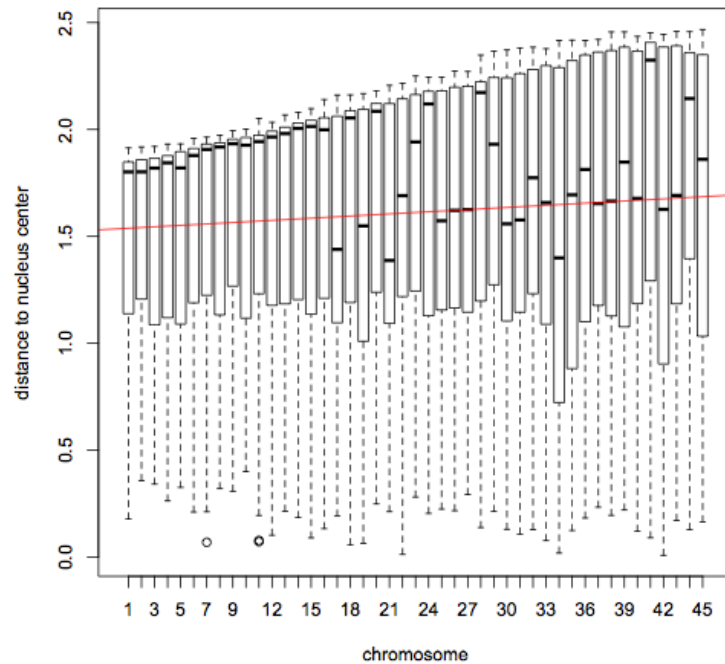
Round nucleus, $d=1.0$:



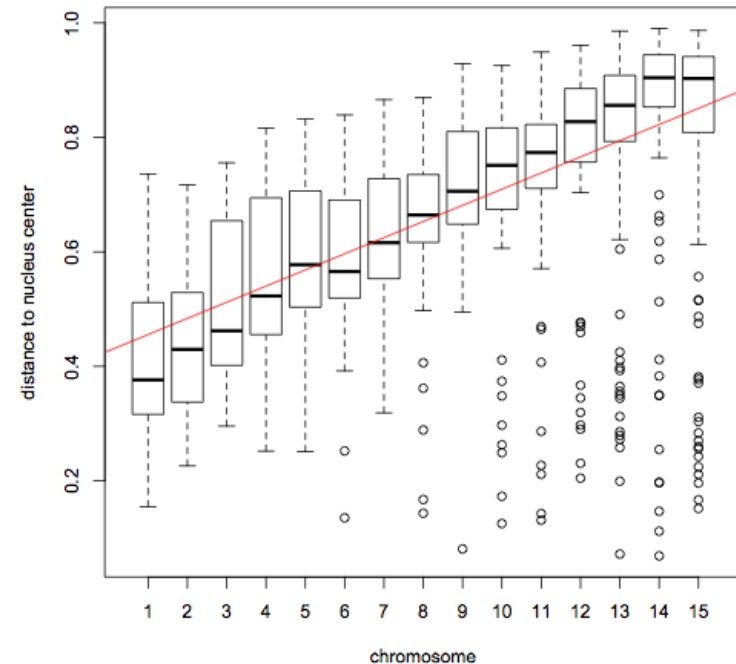
- ➔ Not what I expected!
- ➔ Interesting math problem?
- ➔ Additional forces are present!

Simulation study: Round nucleus 2D

Round nucleus, $d=1$:



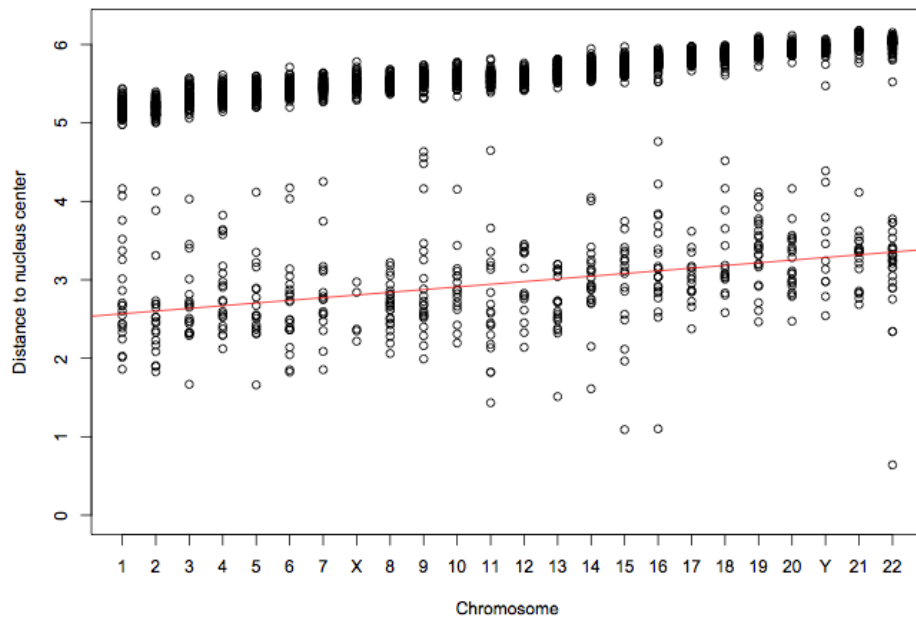
Ellipse, axes 3:1, $d=1$:



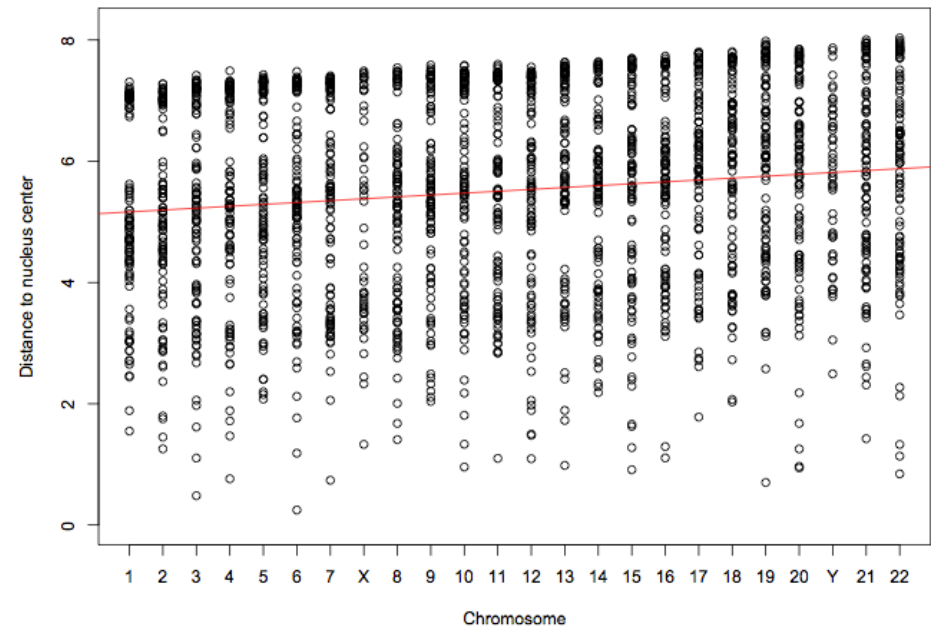
- Same behavior for larger number of chromosomes
- Same behavior for ellipse-formed nuclei
- Can we extrapolate the 2D results to 3D?

Simulation study: Round nucleus 3D

Spheric nucleus, $d=0.6$:



Oblate nucleus, axes 2:2:1, $d=0.6$:



➤ Same behavior for 3D

Internal cavities

- **Interchromatine compartments:**

- DNA free, contiguous space of channels, which start at the nuclear pores and expand into the interior of the nucleus
- make chromosomes accessible to regulatory factors
- release of RNA transcripts

- Measure internal cavities using the software **Pocket** (Edelsbrunner Faciello and Liang, 1995; Patrice Koehl)

- Using alpha shape theory **Pocket** computes volume / surface area of pockets, number of mouths, which spheres are involved,...

Internal cavities: Observations

- For decreasing nucleus volume, total volume of pockets decreases but total number of pockets increases
- 1-2 large pockets make for at least 95% of the total pocket volume
- These main pockets have 1-2 mouths for medium to large sized nuclei: **interchromatine compartments**
- For small sized nuclei the main pockets have no mouths. Regulation less important?

Summary

- Model for chromosome arrangements
 - allows to sample different chromosome territory configurations
 - no distance constraints: small chromosomes outside
 - ➔ Geometric constraints are not sufficient to describe biological observations
- Analysis of chromosome arrangements based on pockets
 - Interchromatine compartments which connect most chromosomes
 - Build maps based on pockets?
- Interesting math / geometry problems:
 - Configuration with small spheres outside: global optimum?
 - Optimal packing for fixed overlap? 2D: hexagonal? 3D?
 - Generalize alpha shape theory to ellipsoids