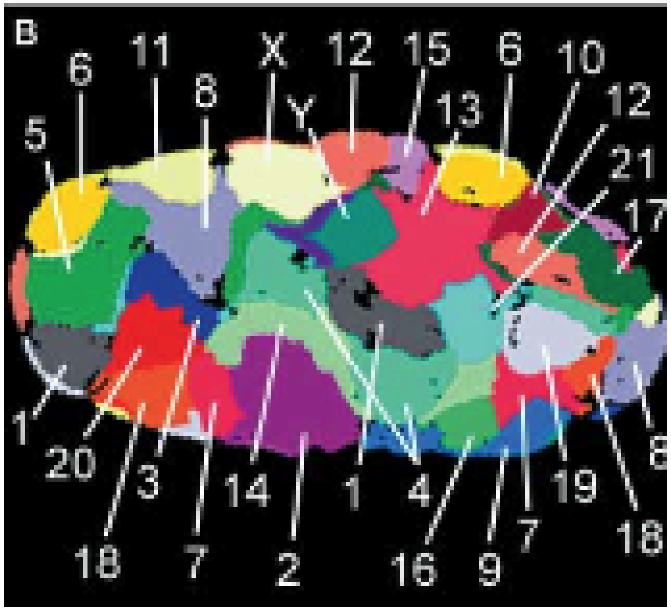
Chromosome packing in cell nuclei



Joint work with Saira Mian

Computational Topology Seminar, Stanford

April 22, 2011

Non-random arrangement

- Arrangement of chromosome territories is **non-random** in eukaryotes
  - 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 flat-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?

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 $S_i, i = 1, \ldots, m$ 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

Minimize **deviation** from D and **overlap**

subject to chromosomes lie inside nucleus

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

subject to

$S_i \subset \epsilon$ (chr. in nucleus)

$||X_i - X_j||_2 \leq (1 + \delta_{ij})D_{ij}$ (distances)

$(R_i + R_j) - ||X_i - X_j||_2 \leq \xi_{ij}$ (overlap)

$\hat{Z}_{ij}^T(X_i - X_j)$

$0 \leq \delta_{ij}$

$0 \leq \xi_{ij}$

Convex relaxation: Iterative procedure

$$||\hat{X}_i - \hat{X}_j||_2 = \max\ Z_{ij}^T(\hat{X}_i - \hat{X}_j) \quad \text{s.t.}\ ||Z_{ij}||_2 \leq 1$$

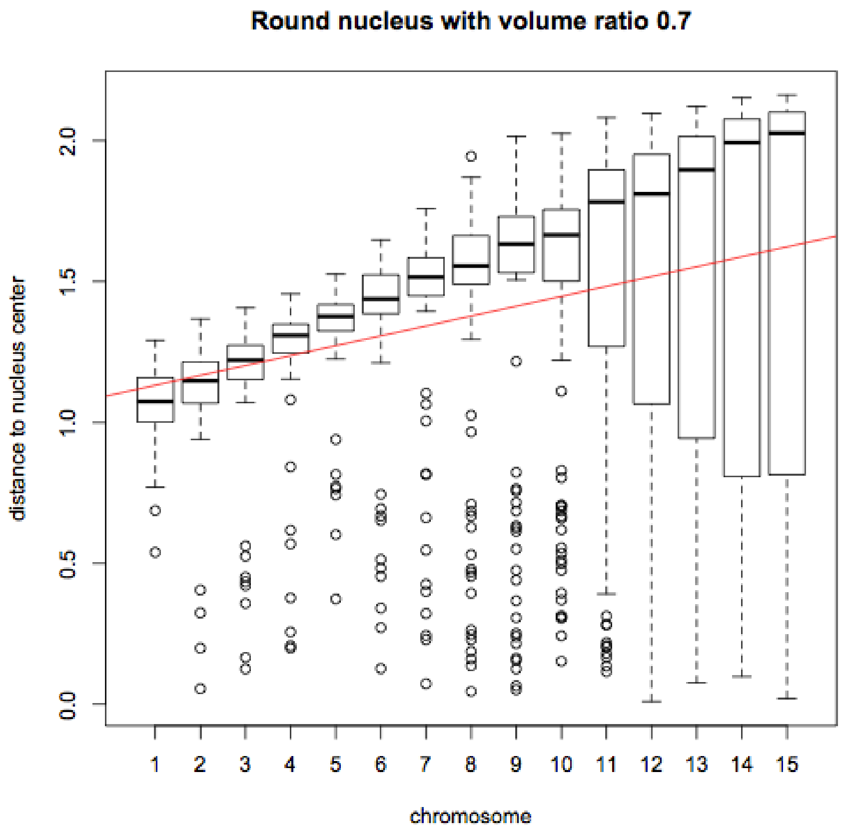
$$\hat{Z}_{ij} = \frac{\hat{X}_i - \hat{X}_j}{||\hat{X}_i - \hat{X}_j||_2}$$

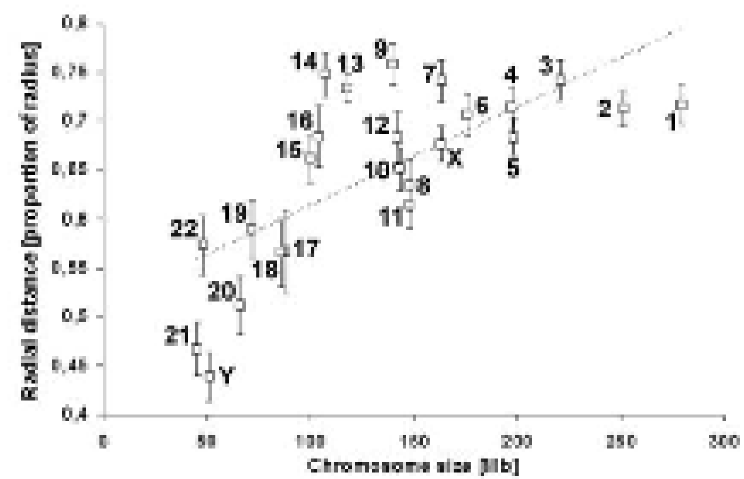
Iterative method

- Seems to perform well and fast
- Optimal value in iterative method decreases from one iteration to the next
- Allows to explore different optimal configurations of chromosome packings

Simulation study: Round nucleus 2D

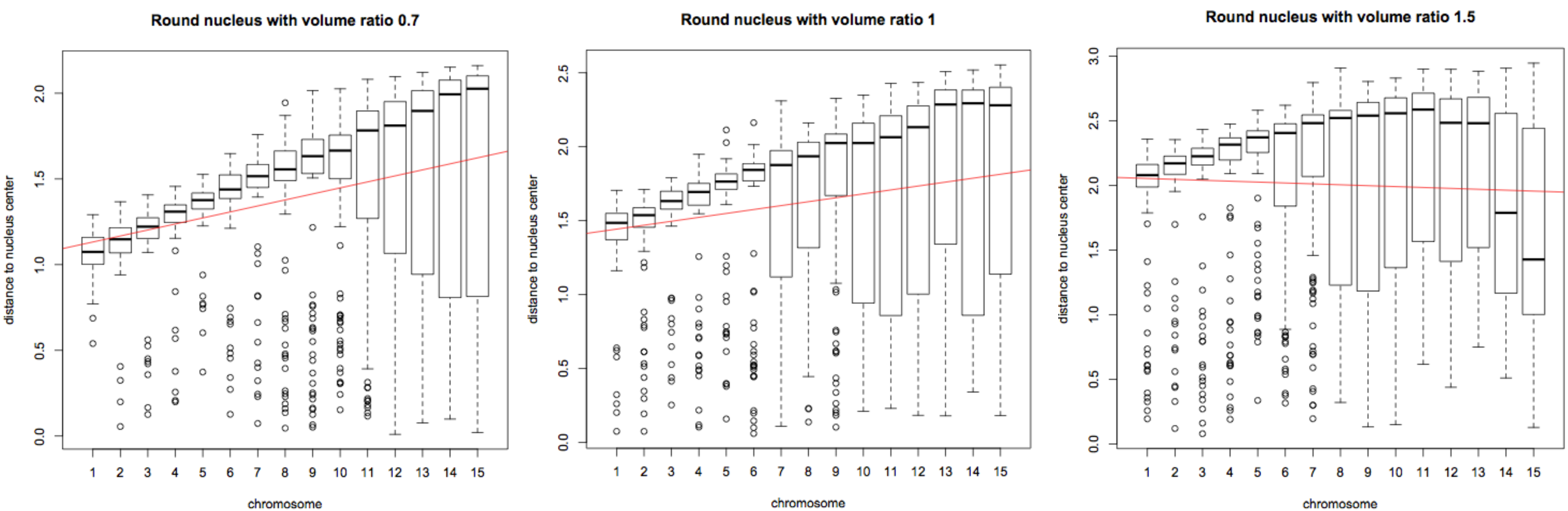
- Sample chromosomes with fixed ratio of nucleus volume to total chromosome volume in simplest model with no distance constraints





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

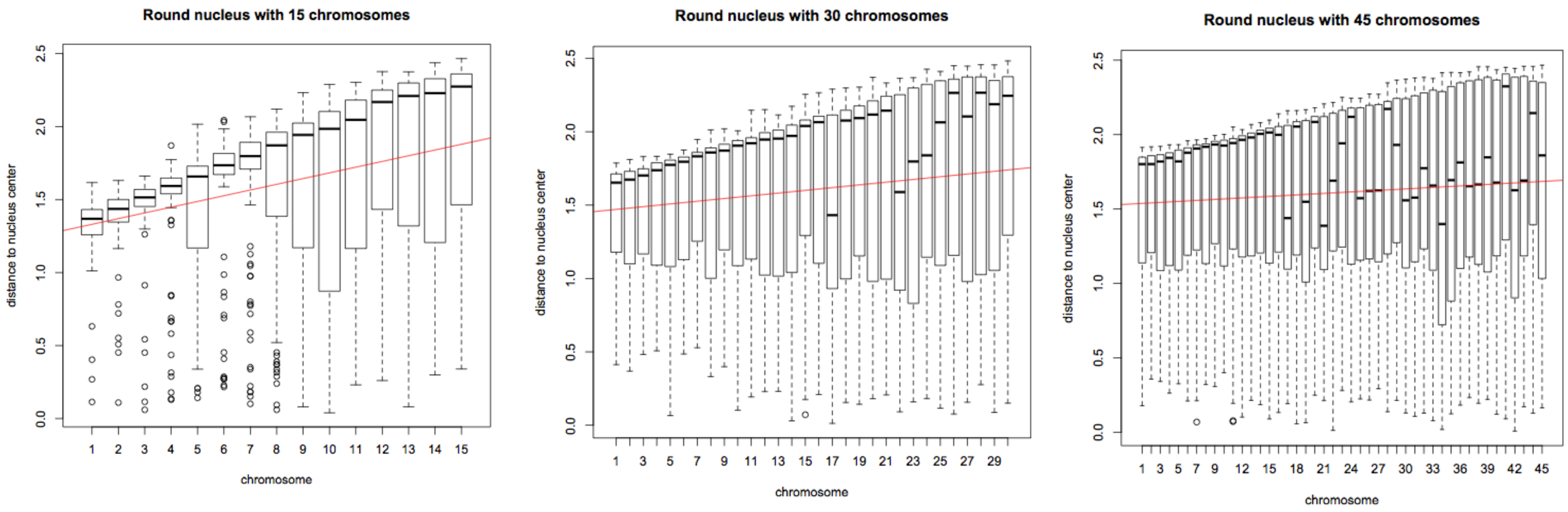
Simulation study: Round nucleus 2D



- Trend breaks down at a certain volume ratio
- Overlap is no constraint anymore

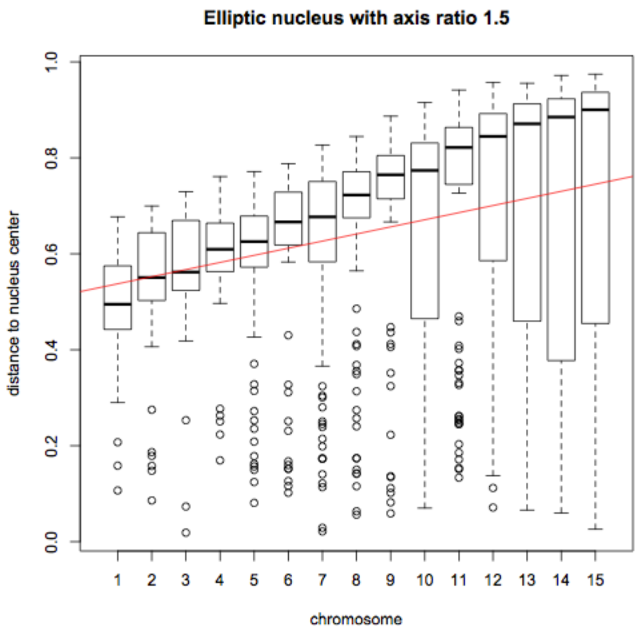
Simulation study: Round nucleus 2D

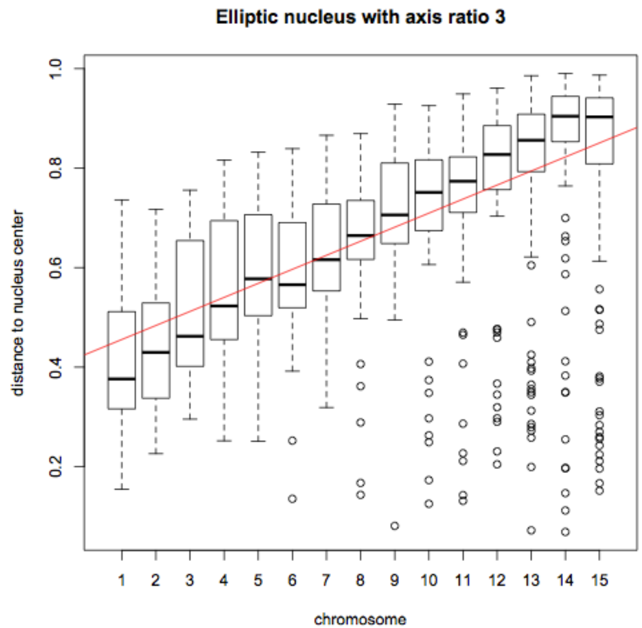
- Vary chromosome number with fixed ratio of nucleus volume to total chromosome volume in model with no distance constraints

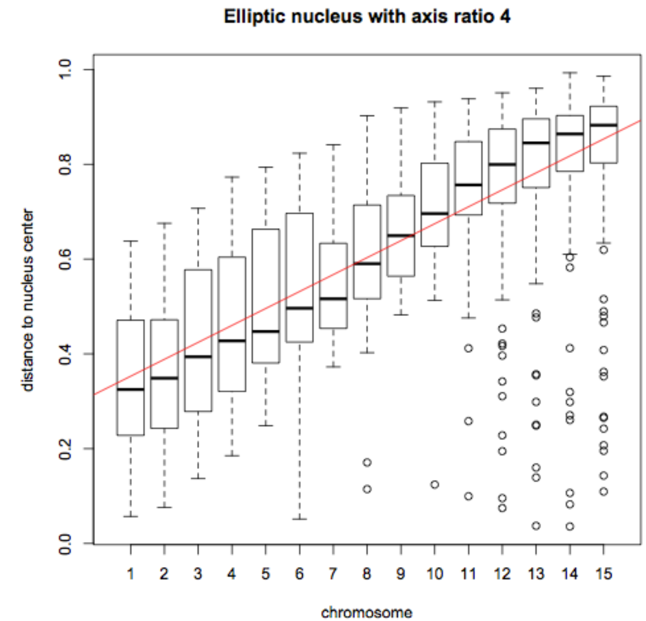


- No surprises

Simulation study: Elliptic nucleus 2D







- Similar behavior

Simulation study: 3D

- Human cell nuclei:

  - volume ranging from 500μm^3 to 1600μm^3

  - Chromatine packing in living cells is about 0.15μm^3/Mb

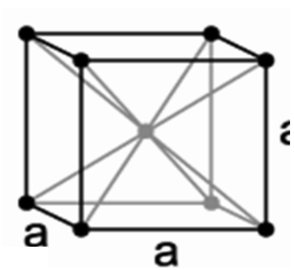
  - This results in a total chromosome volume of 462μm^3 and a nucleus to chromosome volume ratio of 1 to 3.5.

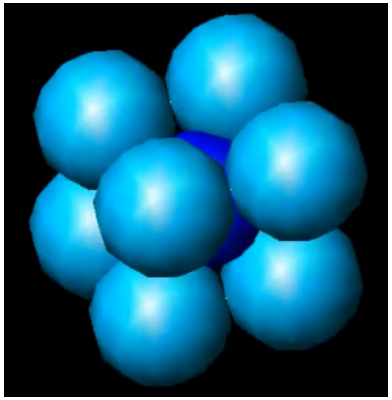
- Can we extrapolate the 2D results to 3D?

➔ Distances to nucleus center behave similarly as for 2D

BCC and FCC lattice

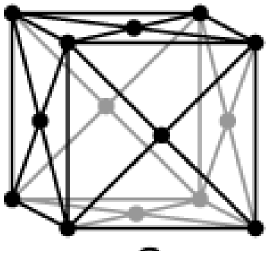
BCC lattice

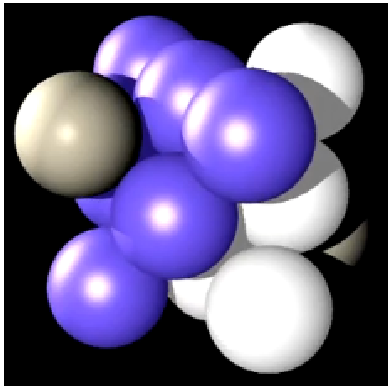




optimal covering

FCC lattice





optimal packing

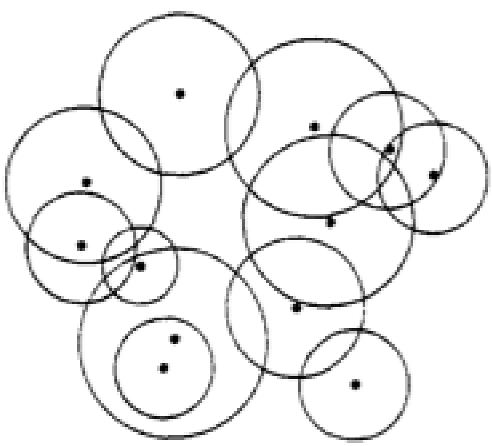
1-parameter family of distortions of integer grid: $e_i \mapsto e_i + \frac{\delta - 1}{n} \mathbb{1}$

$$\delta = \frac{1}{\sqrt{n+1}}$$

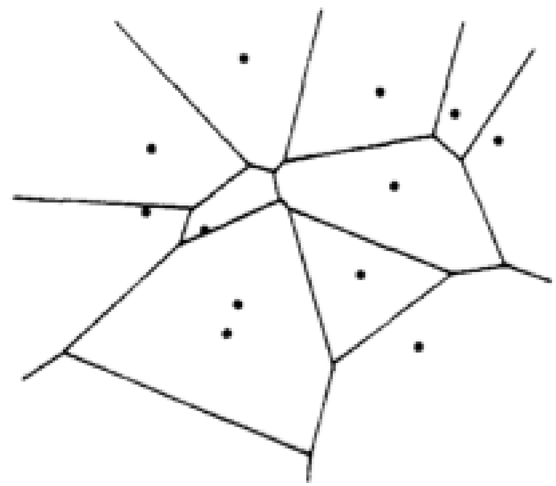
$$\delta = \sqrt{n+1}$$

Delaunay triangulation and Voronoi diagram

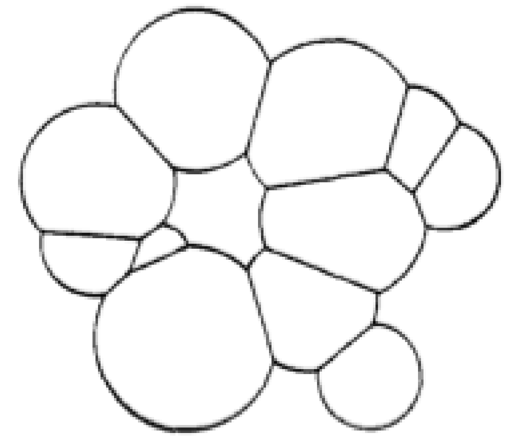
Union of 12 disks



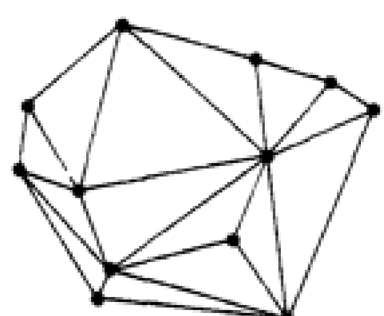
Voronoi cells



Voronoi diagram



Delaunay complex



Delaunay triangulation