Chromosome Packing in Cell Nuclei

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Joint work with Stephen J. Wright (University of Wisconsin-Madison)

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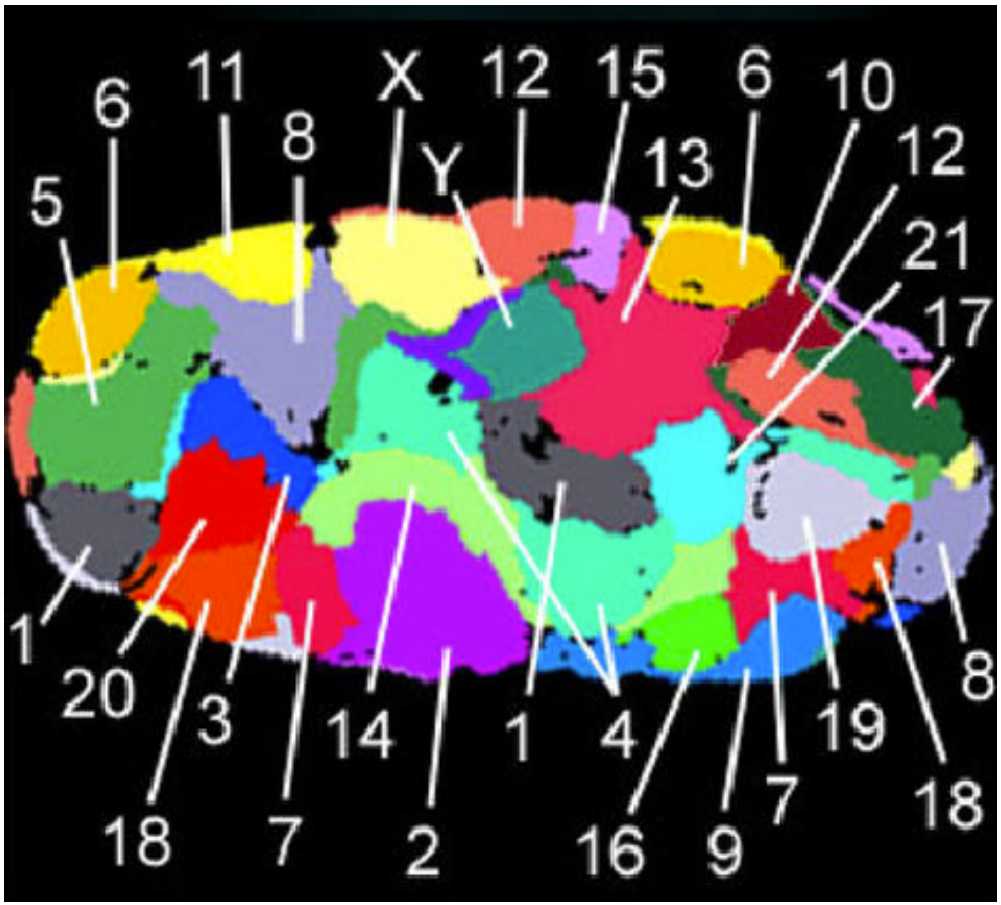
Motivation

Discussion about chromosome territories with Saira Mian (biologist at Lawrence Berkeley Lab)



Nuclear architecture

- **Cell nucleus:** Different cell nuclei have different sizes and shapes
  - Nuclei of human fibroblasts are flat ellipsoidal
  - Nuclei of human lymphocytes are spherical
- **Chromosome territories:** Interphase chromosomes occupy a distinct roughly ellipsoidal domain
- 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 or cell differentiation
  - various locational preferences have been reported

Ref: E.g. publications by the groups of Thomas Cremer (LMU Munich) and Ronald Berezney (University of Buffalo)

Locational Preferences

Locational preferences for CT have been noted experimentally:

- **Radial Preference:**
  - Small chromosomes tend to be in the interior
- **Separated homologs:**
  - Homologous chromosomes tend to be separated further than heterologs
- **Neighbor Preference:**
  - Proximity to co-regulated genes

Cremer and Cremer (2011): *"The search for nonrandom chromatin assemblies, the mechanisms responsible for their formation, and their functional implications is one of the major goals of nuclear architecture research. This search is still in its beginning."*

Goal and Method

Goal: Determine whether the locational preferences can be explained by the purely geometrical considerations of packing

Method: Construct algorithm to identify packings that are "locally optimal" from the purely geometric criterion of minimizing overlap and compare the locational preferences

Find minimal overlap packings of different sized and shaped ellipsoids (the CTs) inside an ellipsoidal container (the cell nucleus)

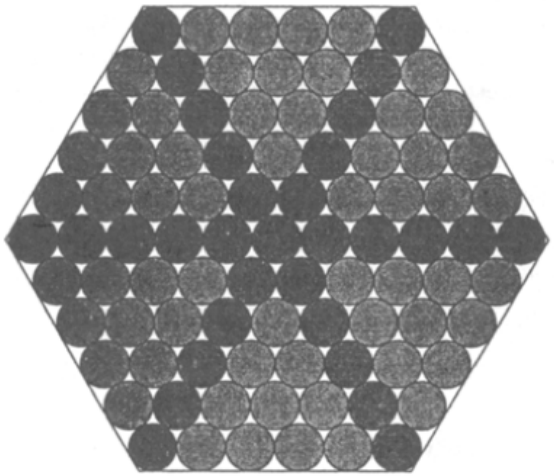
$\rightarrow$ solve easier problem first: **spheres**

Outline

- Classical sphere packing
- Packing spheres with minimal overlap
  - Formulation
  - Algorithm
  - Results
- Packing ellipsoids with minimal overlap
  - Formulation
  - Algorithm
  - Results
- Chromosome organization
  - How important is geometry?
  - Results

Circle Packings Without Overlap

- Pack N identical spheres in enclosing sphere of minimal radius
- In infinite plane hexagonal packing is optimal
- Consider 91 circles arranged hexagonally:



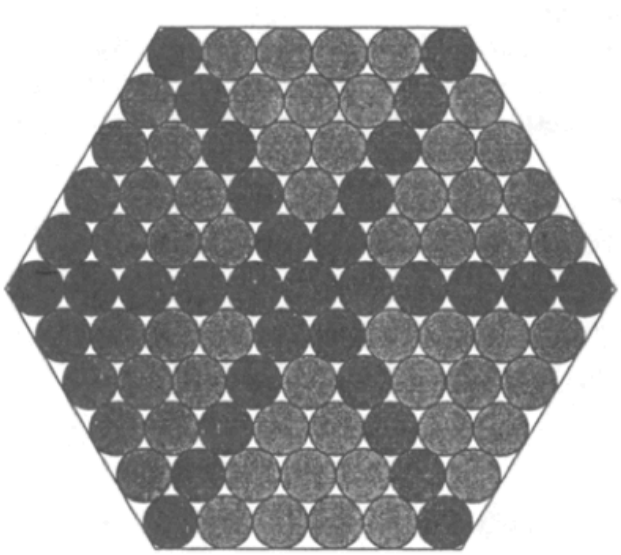
91 disks
density = 0.88434871149353
D/d = 11.154700538379

What is the best arrangement of 91 circles in an enclosing circle?

R. L. Graham, B. D. Lubachevsky et al, *Discrete Mathematics* 181 (1998), pp. 139–154.

Curved Hexagonal Packings

Twisting of hexagonal arrangement allows smaller enclosing circle!



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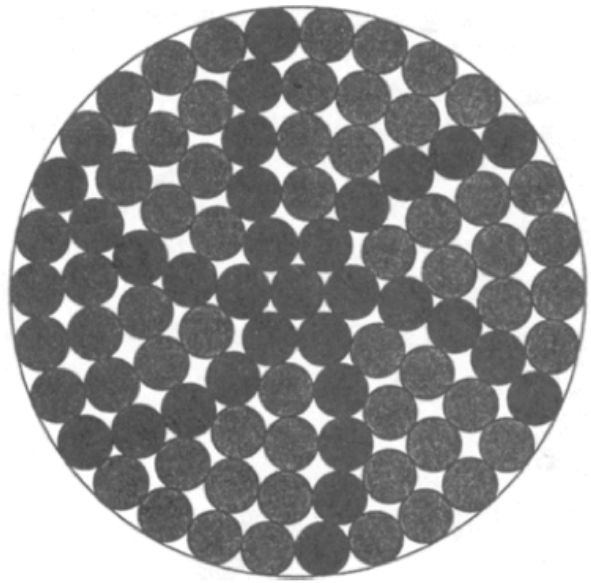

91 disks
density = 0.81499829406214
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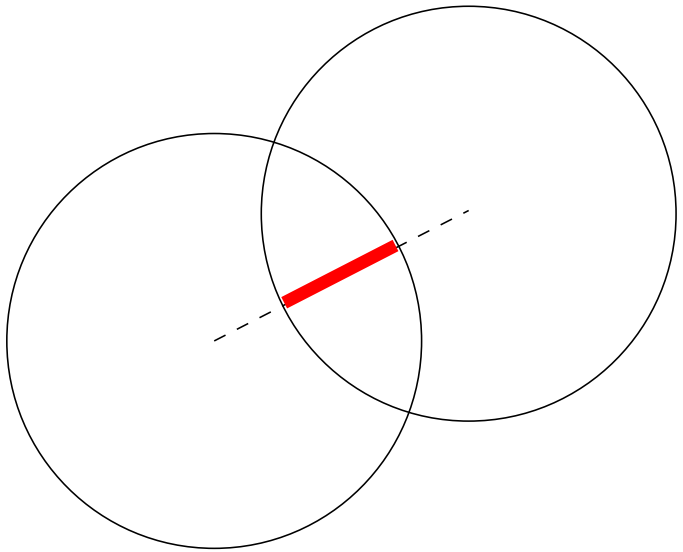
Google "circle packing Magdeburg" for best known packings up to $N = 1100$. (Only $N = 1, 2, \ldots, 13$ and $N = 19$ are proved optimal.)

Packing Spheres with Overlap

- *Given N spheres of prescribed radius r_i, $i = 1, 2, \ldots, N$, and an ellipsoidal container Ω, choose centers $c_i \in \mathbb{R}^3$ so that the spheres lie within Ω and some measure of total overlap is minimized.*
- Simple measure of overlap between two spheres: $r_i + r_j - \|c_i - c_j\|_2$.



Note: This is **diameter of largest sphere inscribed in intersection**.

Formulation

- **Optimization formulation:**

$$\begin{aligned} \min_{c,\xi} \quad & H(\xi) \\ \text{subject to} \quad & (r_i + r_j) - \|c_i - c_j\|_2 \leq \xi_{ij} \qquad \text{for } 1 \leq i < j \leq N \\ & 0 \leq \xi, \\ & c_i \in \Omega_i, \qquad \text{for } i = 1, 2, \ldots, N. \end{aligned}$$

- **Possibilities for H:**
  - ℓ_1 norm: $H(\xi) = \sum_{1 \leq i < j \leq N} |\xi_{ij}|$;
  - ℓ_2 norm: $H(\xi) = \sqrt{\sum_{1 \leq i < j \leq N} \xi_{ij}^2}$;
  - ℓ_∞ norm: $H(\xi) = \max_{1 \leq i < j \leq N} |\xi_{ij}|$;

- Problem is highly non-convex with many local solutions

Key Step

$$
\begin{aligned}
\min_{c,\xi} \quad & H(\xi) \\
\text{subject to} \quad & (r_i + r_j) - \|c_i - c_j\|_2 \leq \xi_{ij} && \text{for } 1 \leq i < j \leq N \\
& 0 \leq \xi, \\
& c_i \in \Omega_i, && \text{for } i = 1, 2, \ldots, N.
\end{aligned}
$$

- Iterative procedure: **linearize overlap constraint**

$$
\begin{aligned}
\|c_i - c_j\|_2 = \max \quad & z_{ij}^T (c_i - c_j) \\
\text{s.t.} \quad & \|z_{ij}\|_2 = 1
\end{aligned}
$$

$$
\hat{z}_{ij} = \frac{c_i - c_j}{\|c_i - c_j\|_2}
$$

Algorithm: Successive Linearization

$$
\begin{aligned}
\min_{c,\xi} \quad & H(\xi) \\
\text{subject to} \quad & (r_i + r_j) - z_{ij}^T (c_i - c_j) \leq \xi_{ij}, \quad \text{for } 1 \leq i < j \leq N, \\
& 0 \leq \xi, \\
& c_i \in \Omega_i, \quad \text{for } i = 1, \ldots, N,
\end{aligned}
$$

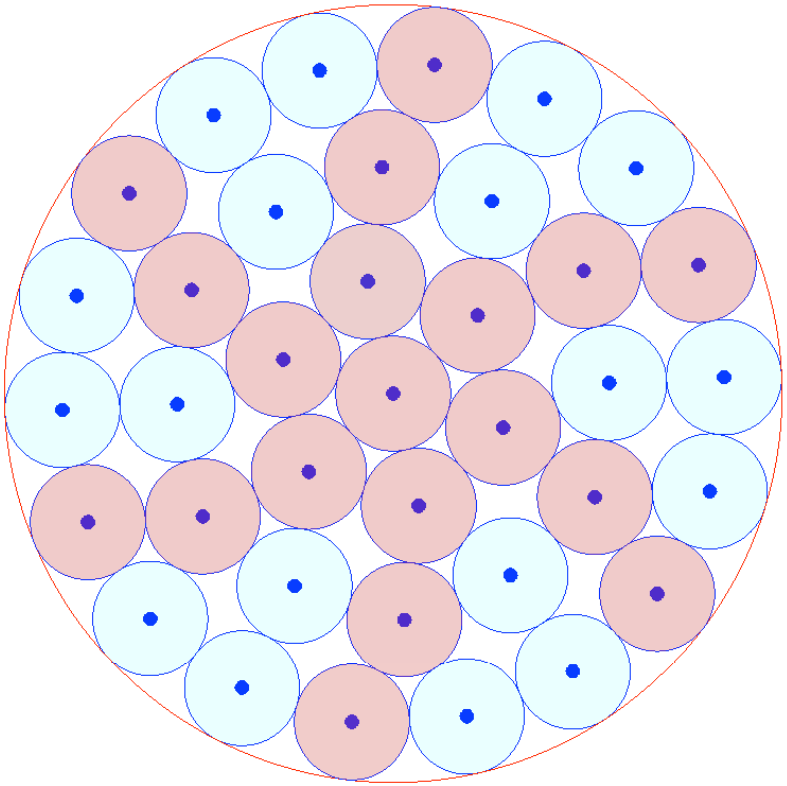
$$
\text{where} \quad z_{ij} := \begin{cases} \frac{(c_i^- - c_j^-)^T}{\|c_i^- - c_j^-\|} & \text{when } c_i^- \neq c_j^- \\ 0 & \text{otherwise.} \end{cases}
$$

Theorem

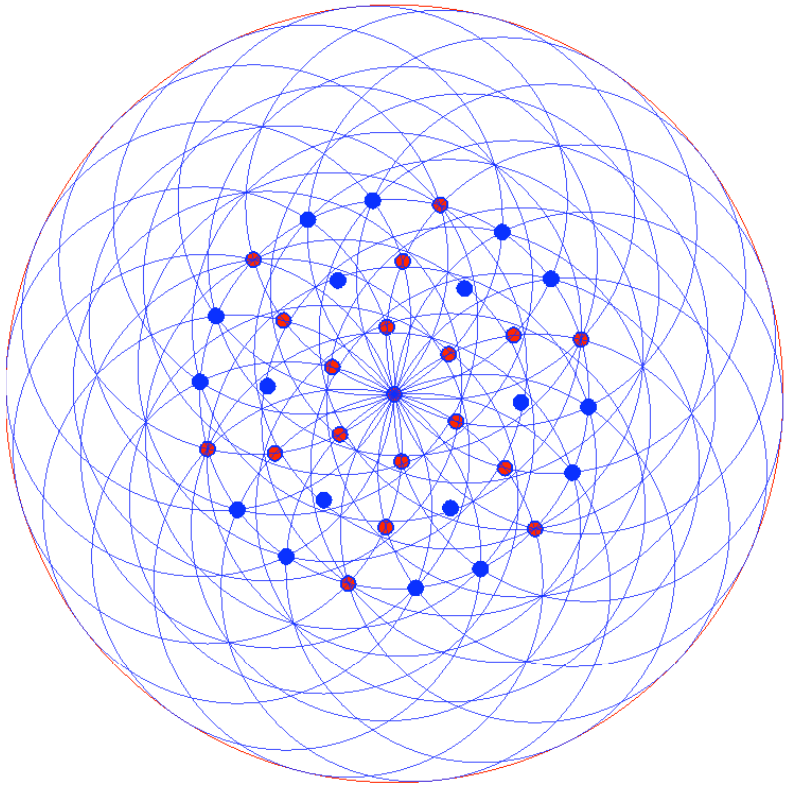
H decreases at every iteration. Accumulation points are either stationary or degenerate (i.e. $\hat{c}_i = \hat{c}_j$ for $i \neq j$).

Results: Curved Hexagonal Packings

We can recover the curved hexagonal packings by solving a min-max overlap problem with the appropriate number of circles ($N = 19, 37, 61, 91$, etc.) for arbitrary radius inscribed in a larger outer circle.



(a) 37 disks



(b) 37 disks, larger radii

Packing Ellipsoids: M&Ms

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Improving the Density of Jammed Disordered Packings Using Ellipsoids

Aleksandar Donev,[1,4] Ibrahim Cisse,[2,5] David Sachs,[2] Evan A. Variano,[2,6] Frank H. Stillinger,[3] Robert Connelly,[7] Salvatore Torquato,[1,3,4*] P. M. Chaikin[2,4]

Packing problems, such as how densely objects can fill a volume, are among the most ancient and persistent problems in mathematics and science. For equal spheres, it has only recently been proved that the face-centered cubic lattice has the highest possible packing fraction $\varphi = \pi/\sqrt{18} \approx 0.74$. It is also well known that certain random (amorphous) jammed packings have $\varphi \approx 0.64$. Here, we show experimentally and with a new simulation algorithm that ellipsoids can randomly pack more densely—up to $\varphi = 0.68$ to 0.71 for spheroids with an aspect ratio close to that of M&M's Candies—and even approach $\varphi \approx 0.74$ for ellipsoids with other aspect ratios. We suggest that the higher density is directly related to the higher number of degrees of freedom per particle and thus the larger number of particle contacts required to mechanically stabilize the packing. We measured the number of contacts per particle $Z \approx 10$ for our spheroids, as compared to $Z \approx 6$ for spheres. Our results have implications for a broad range of scientific disciplines, including the properties of granular media and ceramics, glass formation, and discrete geometry.

The structure of liquids, crystals, and glasses is intimately related to volume fractions of ordered and disordered (random) hard-sphere packings, as are the transitions between these phases (*1*). Packing problems (*2*) are of current interest in dimensions higher than three

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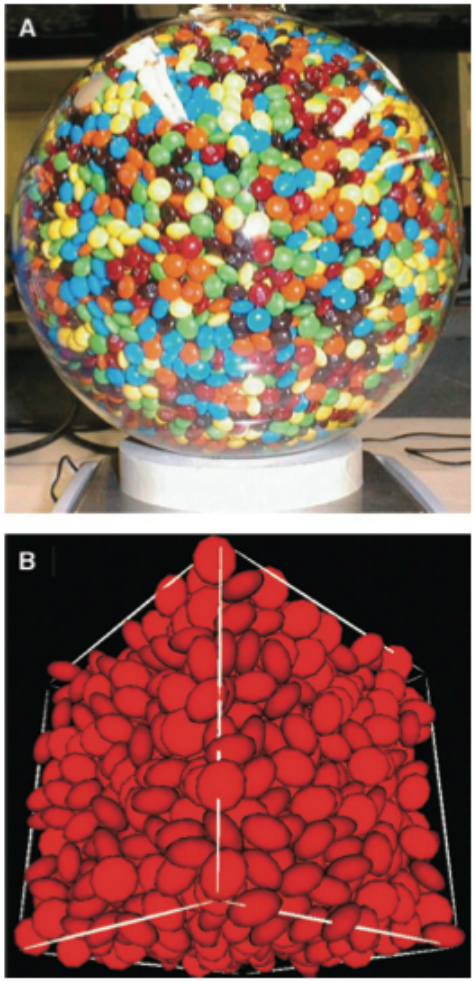


Fig. 1. **(A)** An experimental packing of the regular candies. **(B)** Computer-generated packing of 1000 oblate ellipsoids with $\alpha = 1.9^{-1}$.

Packing 3D Ellipsoids: Results (from Science 2004 paper)

- Ellipsoids pack denser than spheres
- Among prolate and oblate ellipsoids, best packing is attained by ellipsoids with aspect ratio similar to M&Ms; density $\approx .71$ with about 10 contacts per ellipsoid (sphere packings have density $\approx .64$, with average about 6 contacts per sphere)
- Verified by measurements with actual M&Ms and a molecular-dynamics algorithm

Ellipsoids: Measuring Overlap

- *Given N ellipsoids $\mathcal{E}_i$ with prescribed half-axes r_{i1}, r_{i2} and r_{i3}, and an ellipsoidal container Ω, choose centers $c_i \in \mathbb{R}^3$ and orientations Σ_i so that the ellipsoids lie within Ω and some measure of total overlap is minimized.*
- Quantify the overlap $\hat{O}(c_i, c_j, \Sigma_i, \Sigma_j)$ between two ellipsoids $\mathcal{E}_i$ and $\mathcal{E}_j$ by the **largest sum of principal axes of any ellipsoid inscribed in the intersection**.
- Computing the overlap $\hat{O}(c_i, c_j, \Sigma_i, \Sigma_j)$ between two ellipsoids can be done efficiently: it's a convex problem

Optimization Formulation

Min-max-overlap packing:

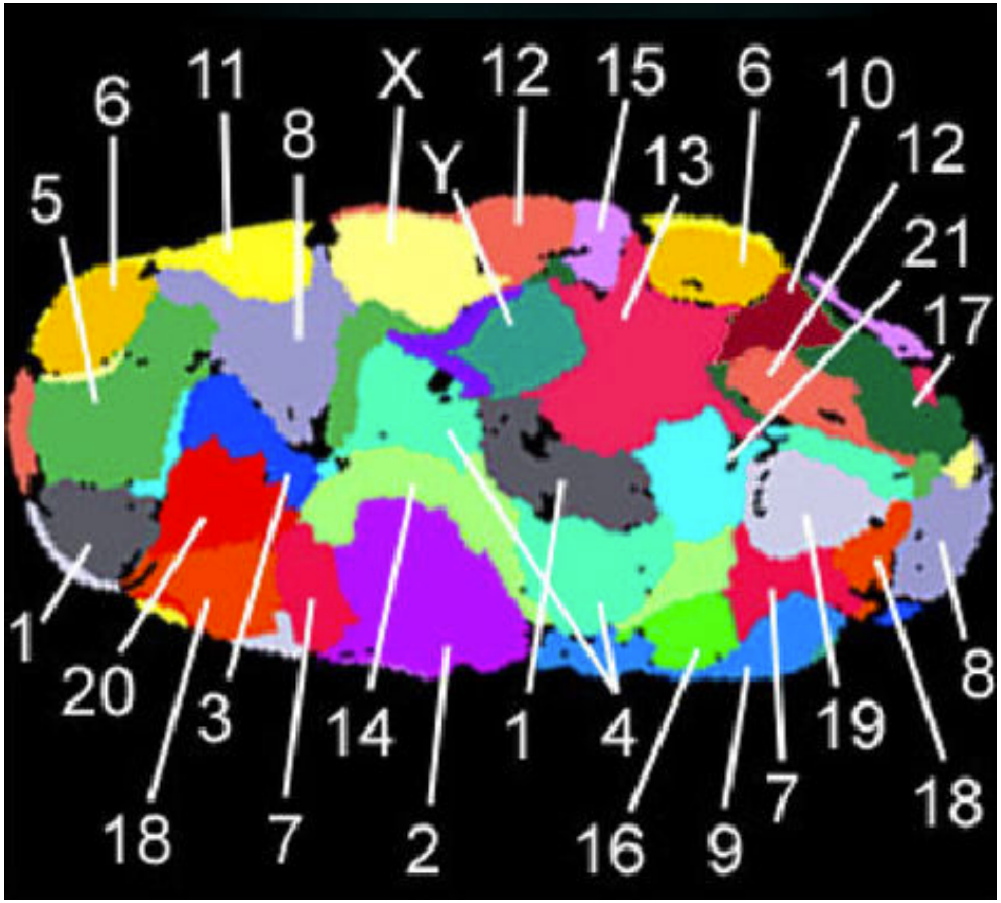
$$\min_{\xi,(c_i,\Sigma_i),i=1,2,\ldots,N} \xi$$

$$\begin{aligned} \text{subject to} \quad & \xi \geq \hat{O}(c_i, c_j, \Sigma_i, \Sigma_j), && 1 \leq i < j \leq N, \\ & \mathcal{E}_i \subset \mathcal{E}, && i = 1, 2, \ldots, N, \\ & \text{semi-axes of } \mathcal{E}_i \text{ have lengths } r_{i1}, r_{i2}, r_{i3}, && i = 1, 2, \ldots, N. \end{aligned}$$

- Problem is **highly nonconvex**, because of
  (a) overlap constraint
  (b) semi-axis constraints.
- **Solution:** (a) bilevel optimization strategy with successive linearization using dual variables
  (b) relax to convexify
- Implemented in Matlab and `cvx`.

Chromosome Packing

Study arrangement of chromosome territories in cell nuclei



Locational preferences

Locational preferences for CT have been noted experimentally:

- **Radial Preference:**
  - Small chromosomes tend to be in the interior
- **Separated homologs:**
  - Homologous chromosomes tend to be separated further than heterologs
- **Neighbor Preference:**
  - Proximity to co-regulated genes

Goal: Determine whether the locational preferences can be explained by the purely geometrical considerations of packing

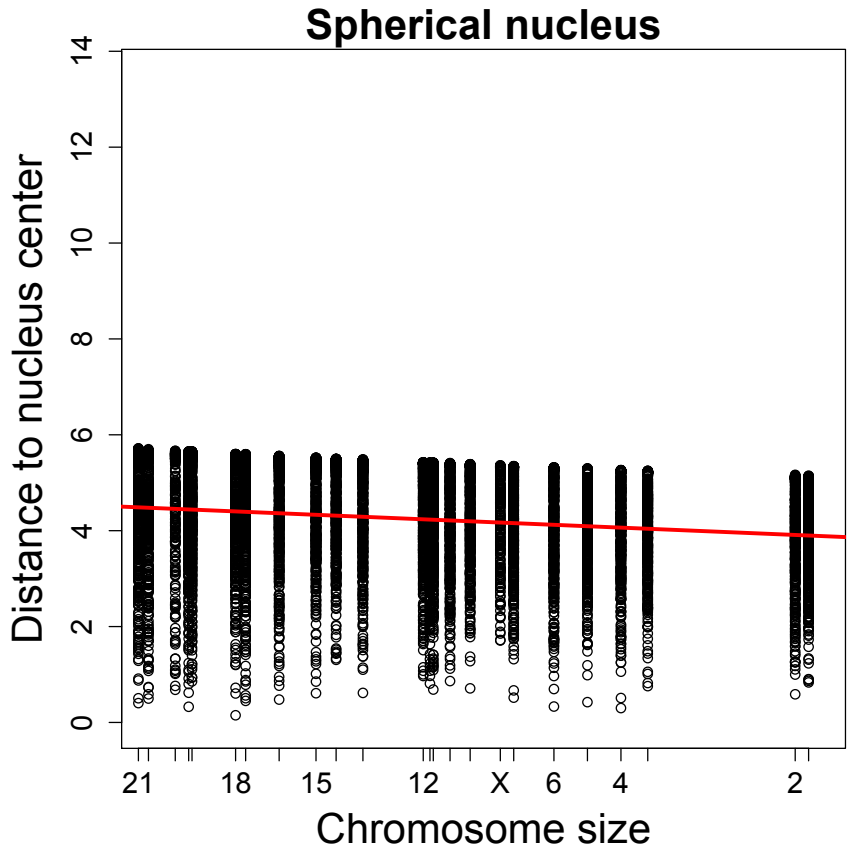
Setup

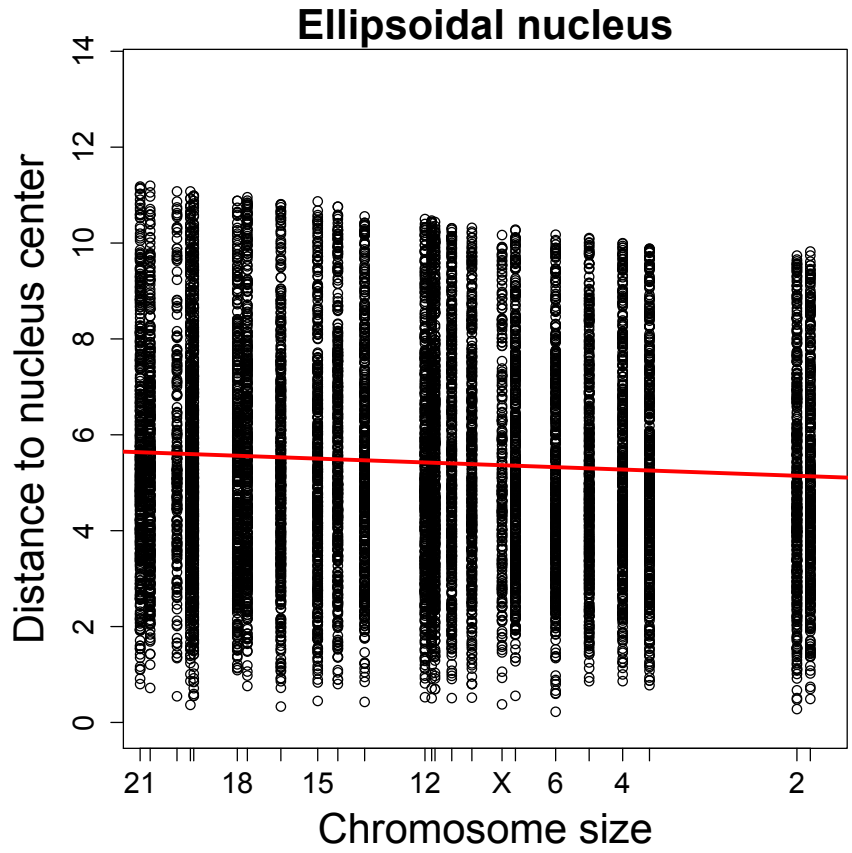
- Three different nucleus sizes: 500, 1000, 1600 $\mu\mathrm{m}^3$
- Two nucleus shapes: spherical, and ellipsoidal (axes $1:2:4$)
- Volumes of CTs based on known number of base pairs in each, and chromatin density
- Shapes of CTs based on observations of mouse chromosomes: approximate axis ratios $1:2.9:4.4$
- Generated 200 problems (by sampling axis ratios of the various shapes, and CT volumes) and ran 100 iterations of the algorithm

CT	1	2	3	4	5	6	7	8
volume	37.05	36.45	29.85	28.65	27.15	25.65	23.85	21.90
CT	9	10	11	12	13	14	15	16
volume	21.00	20.25	20.10	19.80	17.10	15.90	15.00	13.35
CT	17	18	19	20	21	22	X	Y
volume	11.85	11.40	9.45	9.30	7.05	7.50	23.25	8.70

Medium nuclei

Plot distance of CT to nucleus center versus size of CT



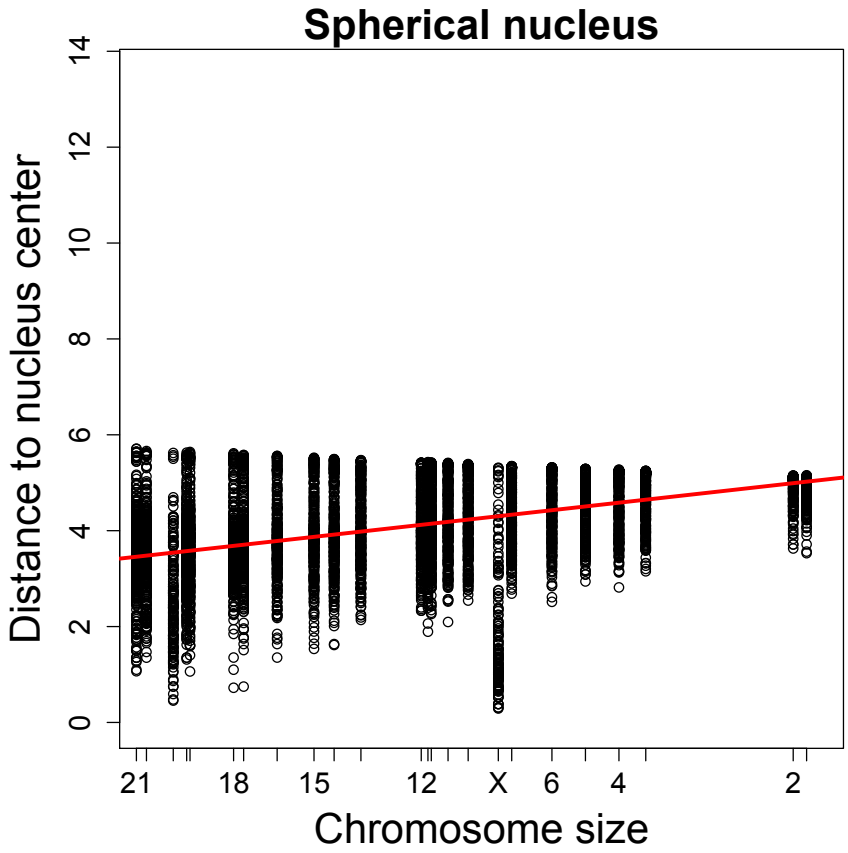


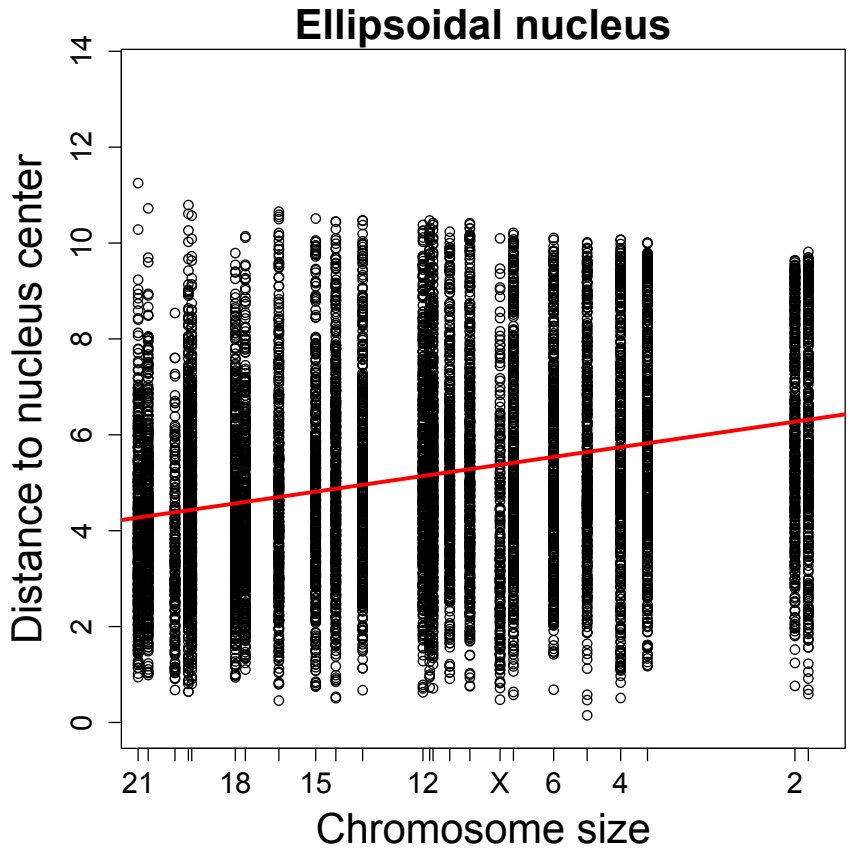
Observations, Modified Formulation

- Radial preference for packing larger CTs toward the center — opposite to biological observations so far
- Suggests that observed radial preference cannot be explained by geometric constraints. Biological explanation?
- Change formulation by adding extra penalty for overlap of homologs
- Possible bio explanations for separated homologs:
  - avoiding DNA recombination between homologs
  - avoiding co-regulation of genes

Medium Nuclei, no homolog overlap

Plot distance of CT to nucleus center versus size of CT





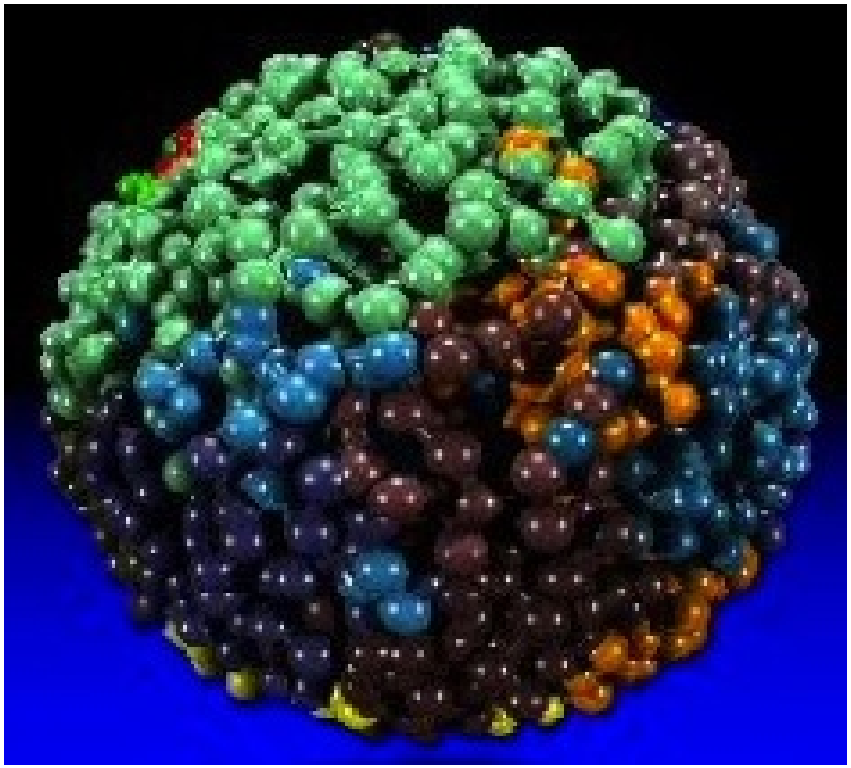
Conclusions

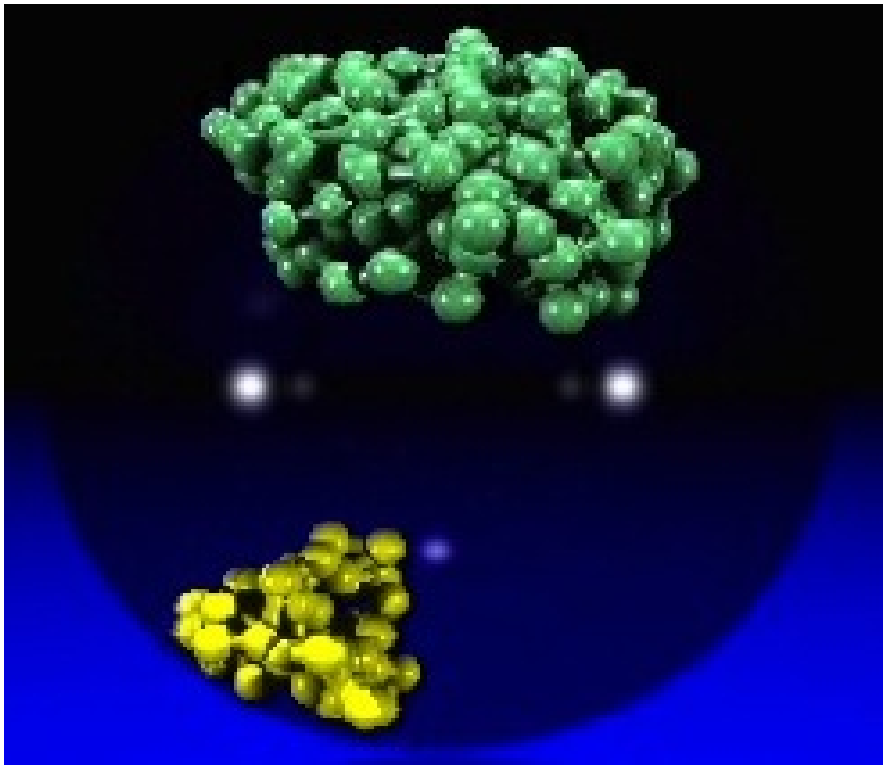
- Described bilevel optimization procedure based on convex sub-problems to find minimal overlap packing of ellipsoids of different size and shape
- Used our algorithm to analyze chromosome organization in cell nucleus:
  - Geometric constraints alone cannot explain radial preferences: opposite trend
  - With extra condition on homologs, smaller CTs tend to be nearer to the center: in line with experiments
- We believe that algorithms like this will help in understanding CT arrangement, in particular, its dependence on basic principles

Outlook

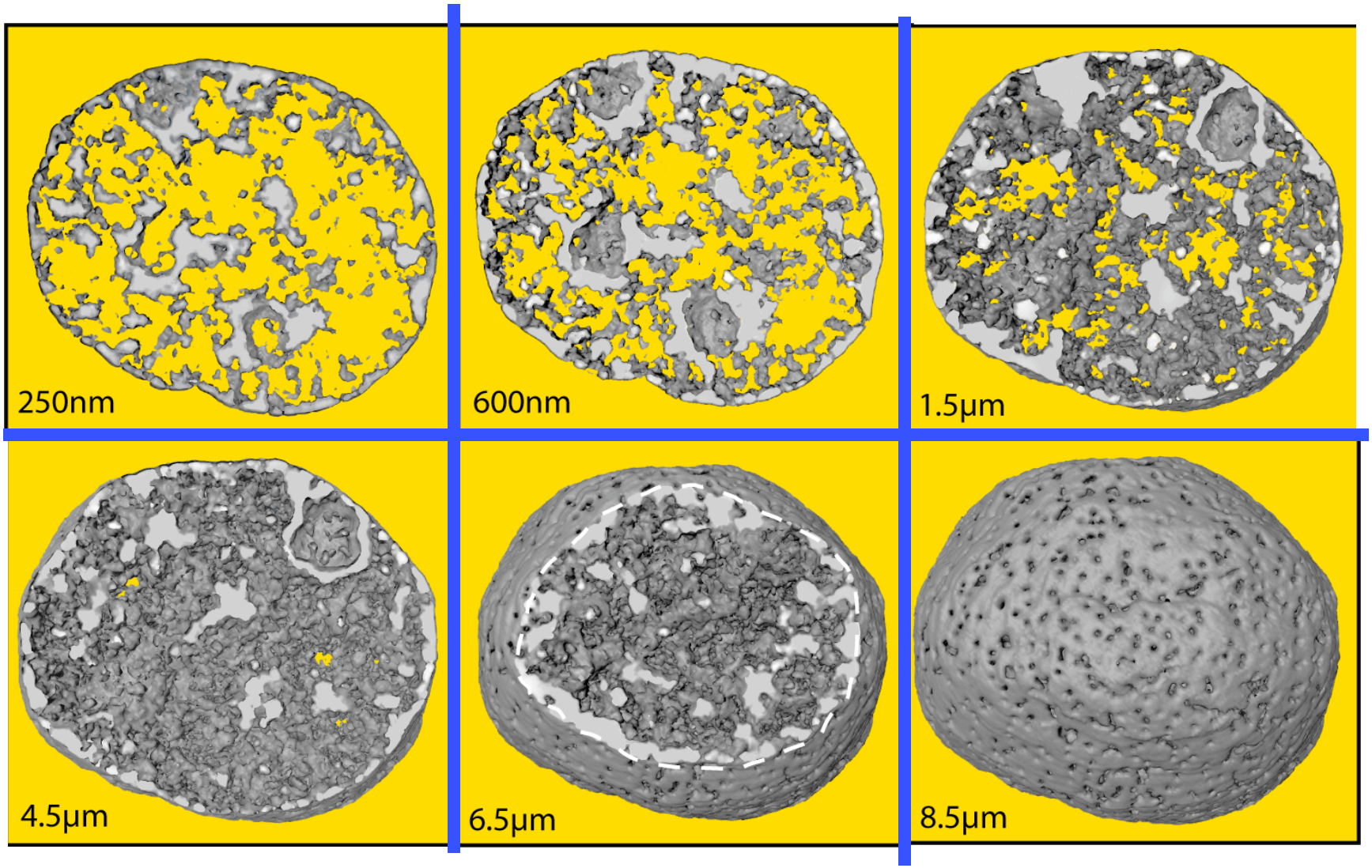
- Get ML estimates for the repulsion of homologous chromosomes in different cell types, do goodness-of-fit analyses, test our hypothesis in C. elegans (*ongoing collaboration with Christian Lanctot*)
- Dynamic model of whole cell cycle including mitosis
- Extend algorithm to model topological domains and study nucleus pores and interchromatin compartments

Topological Domains





Interchromatin Compartments



U. & Wright: Packing ellipsoids with overlap (to appear in *SIAM Review*)

Thank you!