Machine Learning Approaches to Biological Research: Bioimage Informatics and Beyond

Lecture 3: Models from images

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September 29-October 1, 2009

Pattern unmixing

- Some proteins may be found in more than one organelle
- Clustering sees each combination of organelles as a new pattern
- Can we “unmix” such mixed patterns?

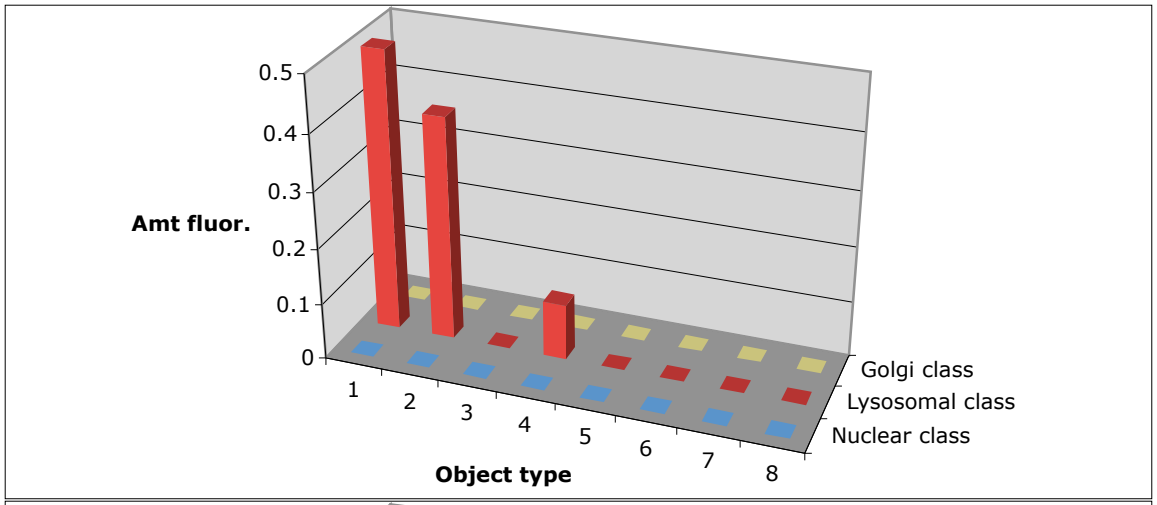
Unmixing approach

- Assume that each fundamental subcellular pattern can be represented by some combination of distinct object types (10% small round objects and 90% long skinny objects)
- Assume that a mixed pattern is formed by adding together the objects from two or more fundamental patterns *and that no new object types are created*

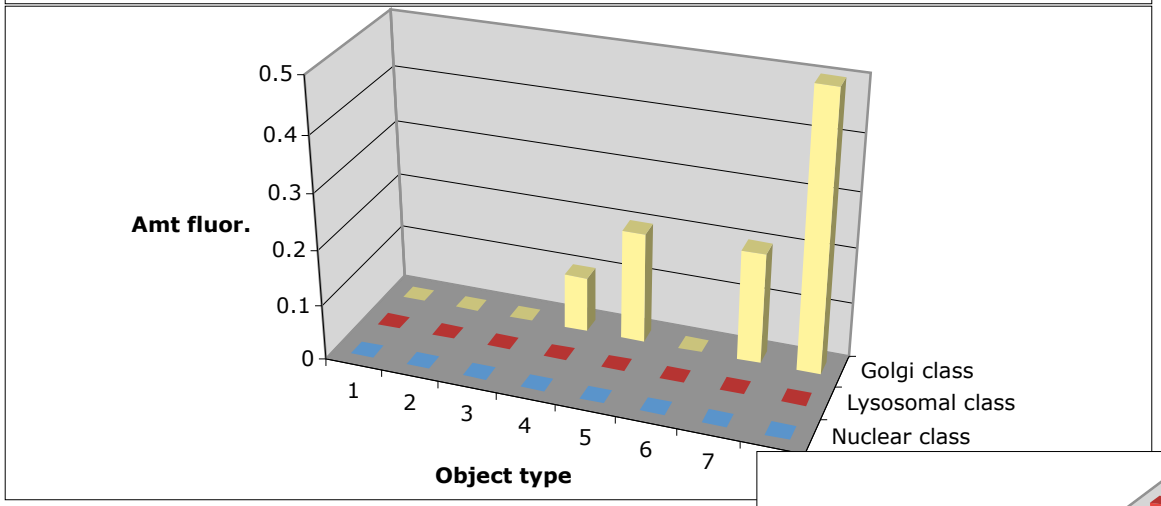
Zhao et al 2005

Learning object types

- Find all objects in all images of fundamental types
- Describe each object by features such as size, ellipticity, distance from nucleus
- Cluster objects to find types
- Represent each fundamental pattern as probabilities of observing each object type

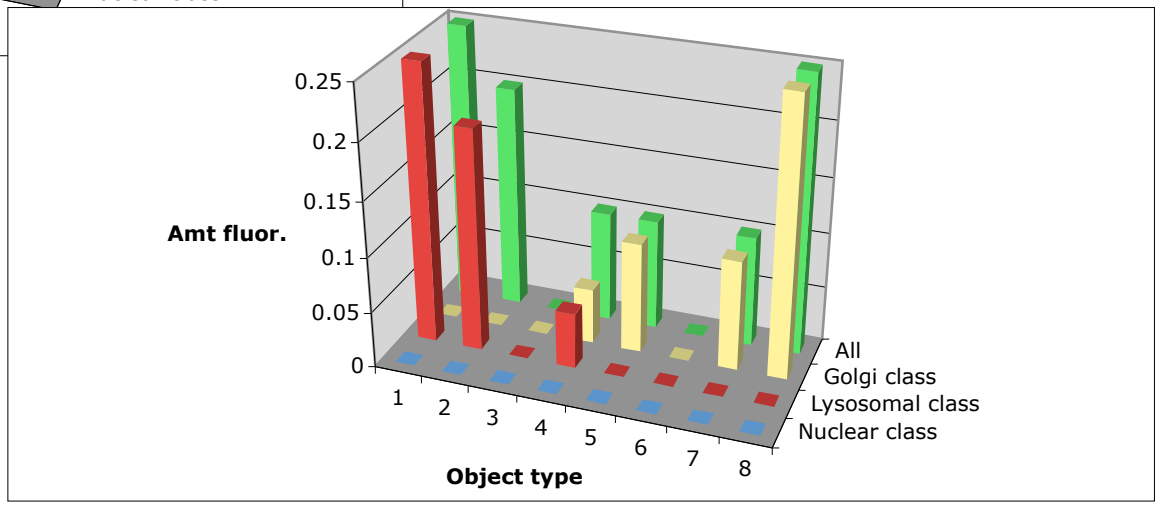


Pure Lysosomal Pattern



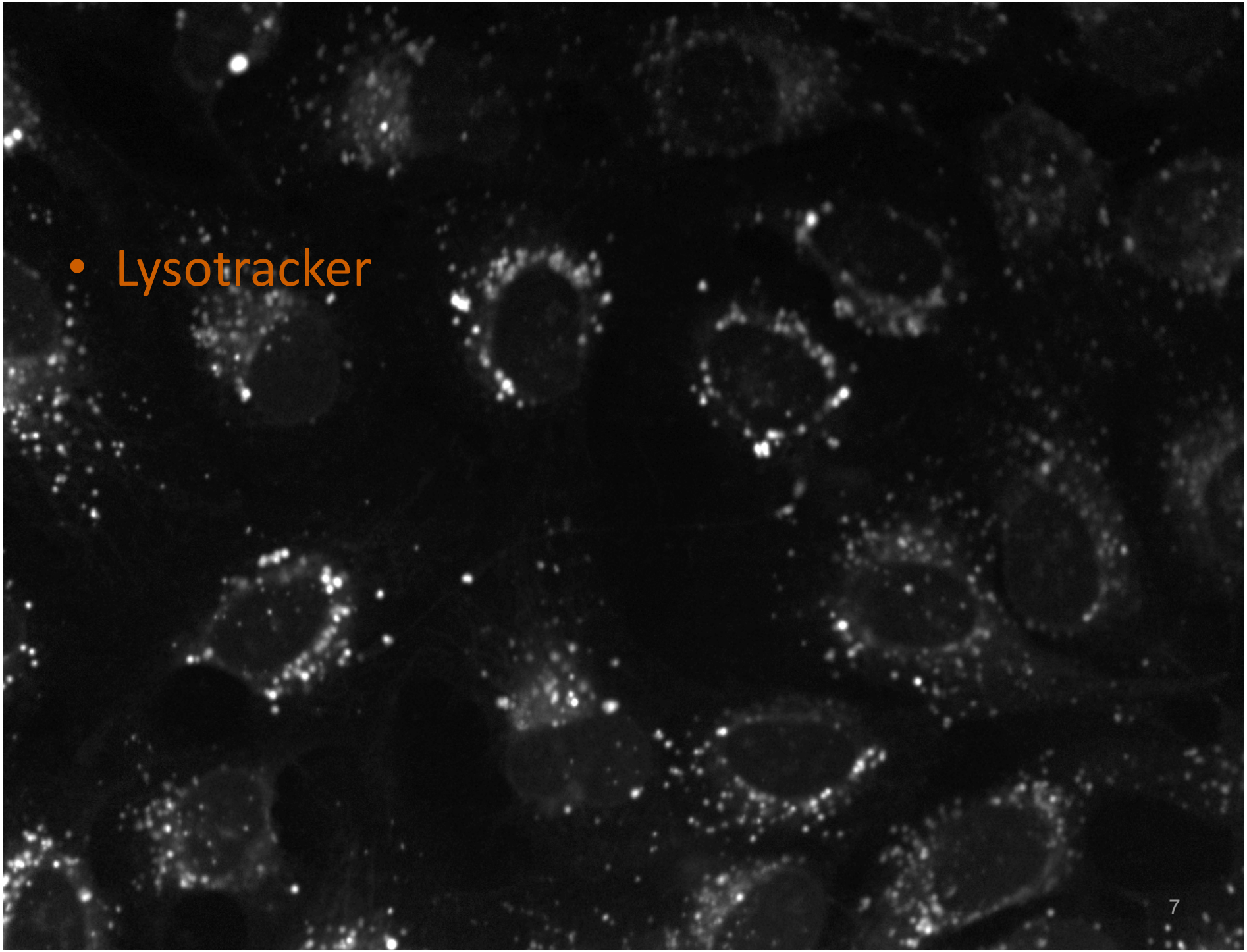
Pure Golgi Pattern

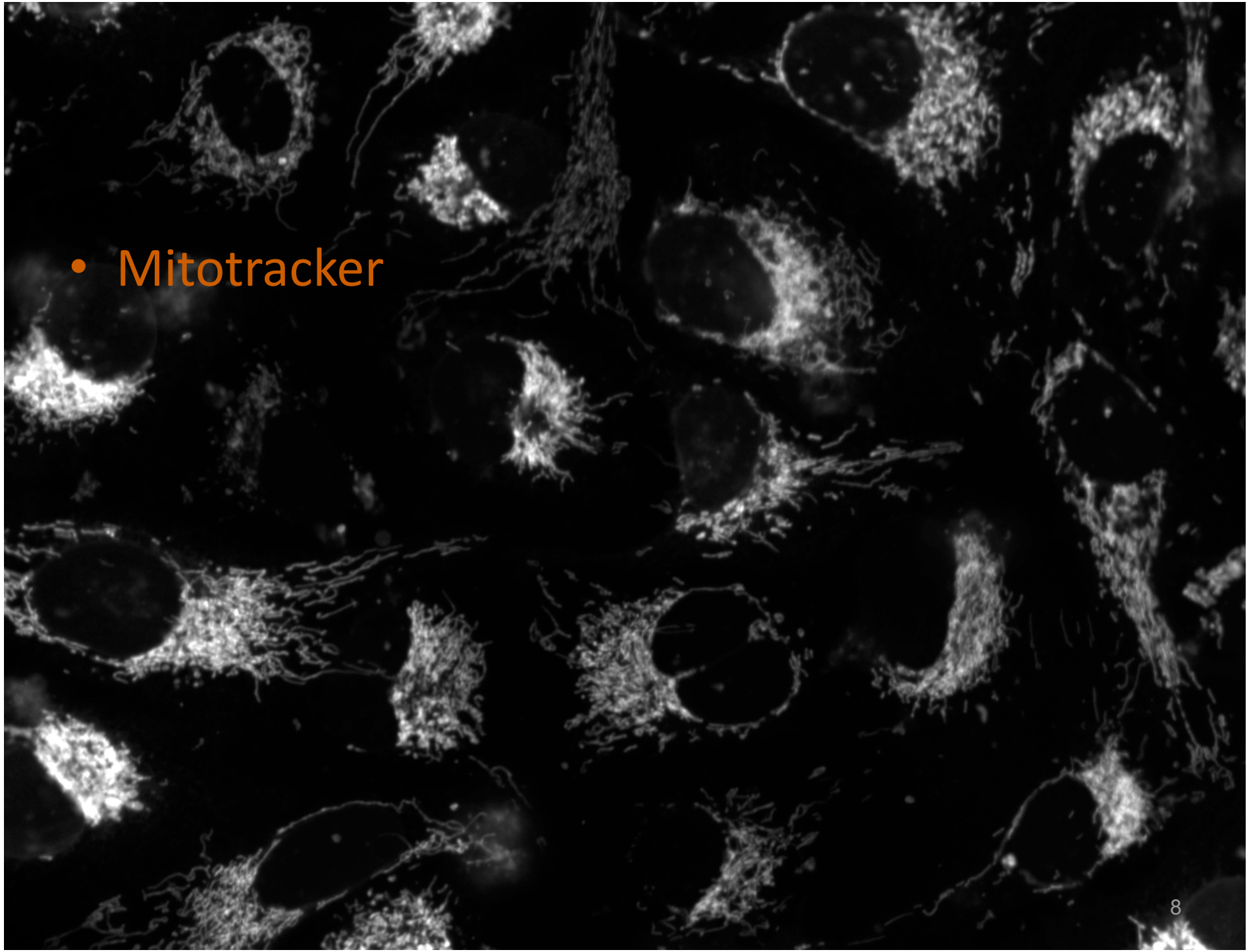
50% mix of each

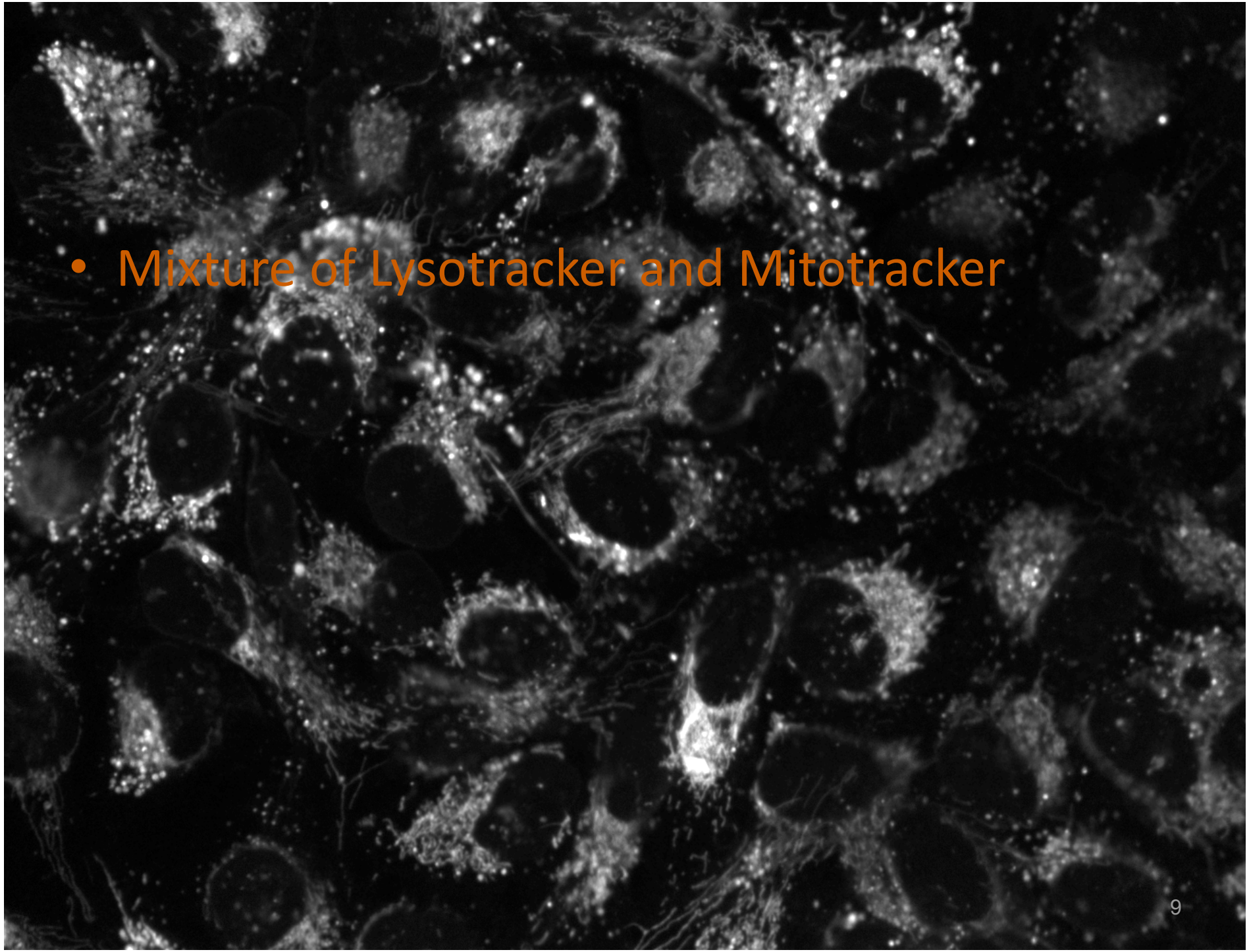


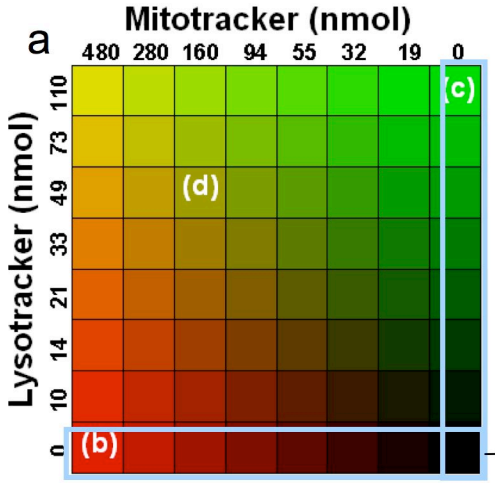
Test samples

- How do we test a subcellular pattern unmixing algorithm?
- Need images of known mixtures of pure patterns – difficult to obtain “naturally”
- Created test set by mixing different proportions of two probes that localize to different cell parts (lysosomes and mitochondria)


• Lysotracker


• Mitotracker


• Mixture of Lysotracker and Mitotracker

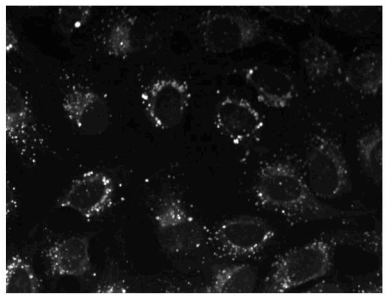


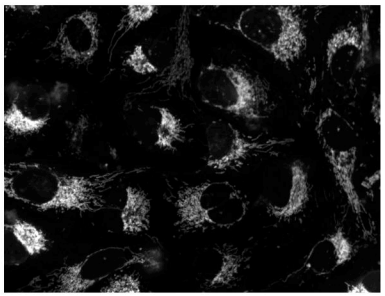
Find objects in each image

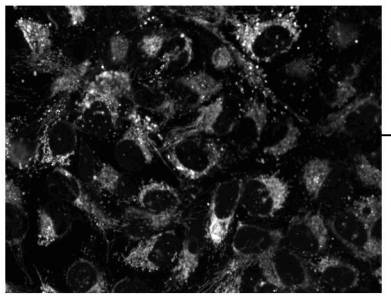
Learn object types from pure samples

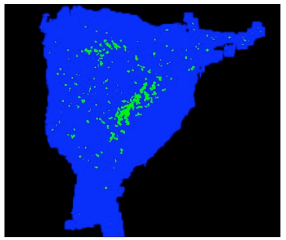
Learn model for distributions of object types in fundamental patterns

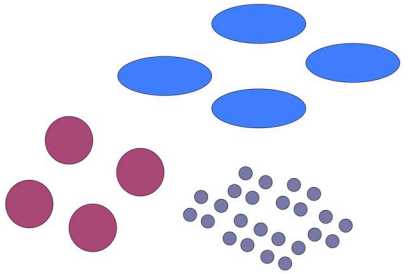
Determine pattern fractions for mixed images

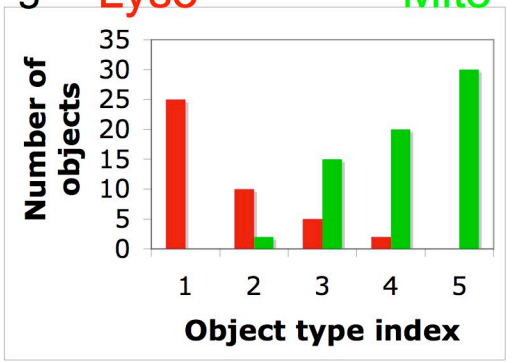


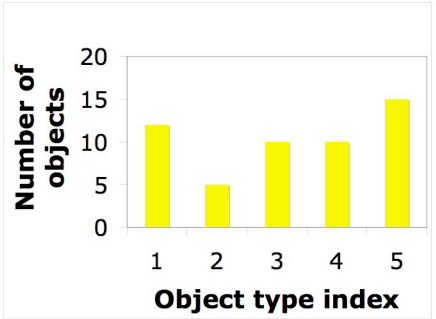






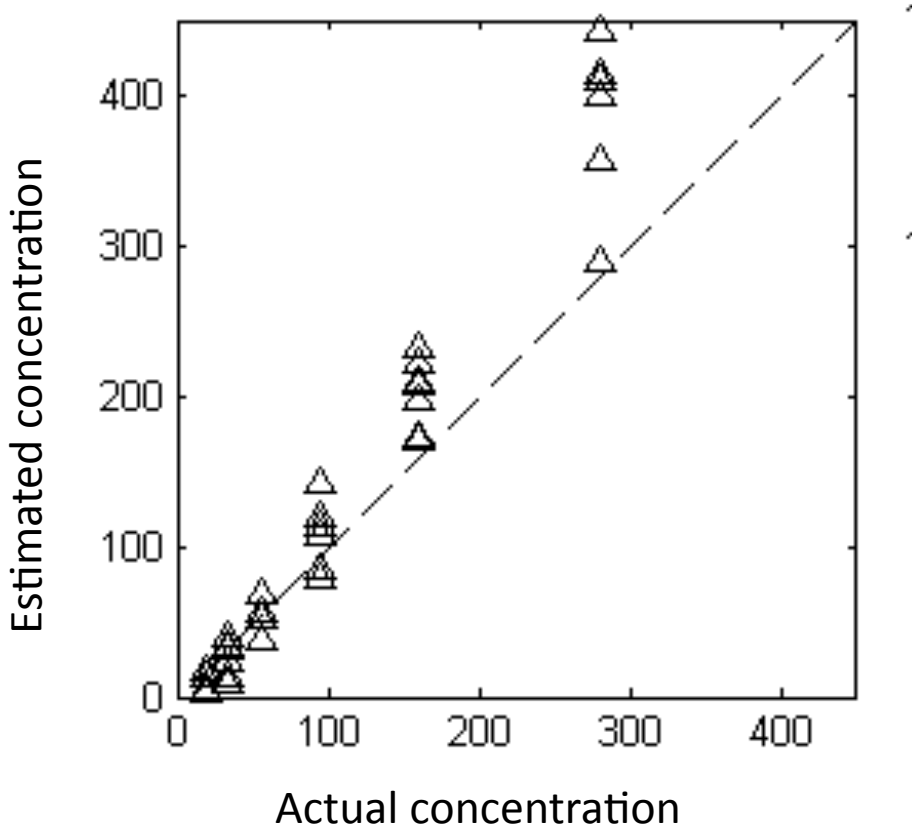






%lyso=0.45

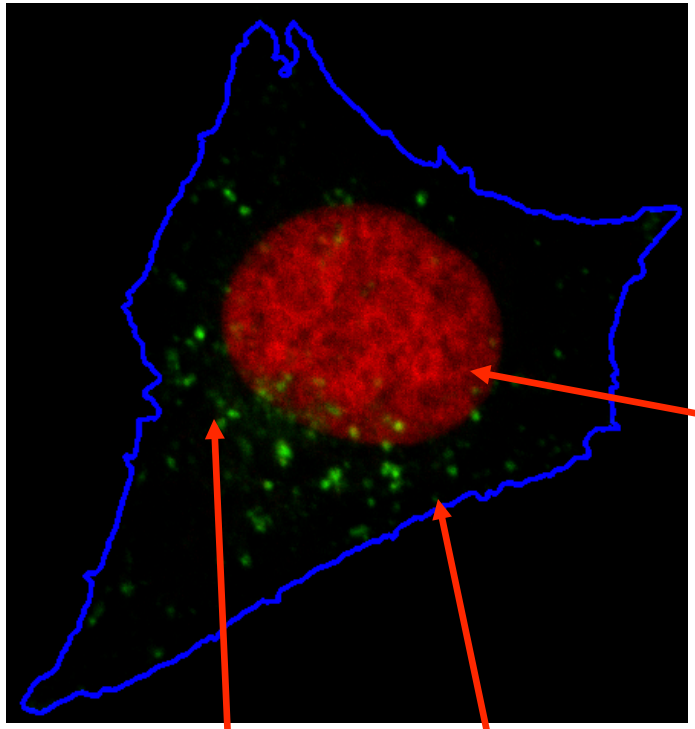
Pattern unmixing results



Communicating patterns

- How do we communicate results learned about subcellular patterns?
- Proposal: Use generative models learned from images to capture pattern and *variation* in pattern

Generative Model Components



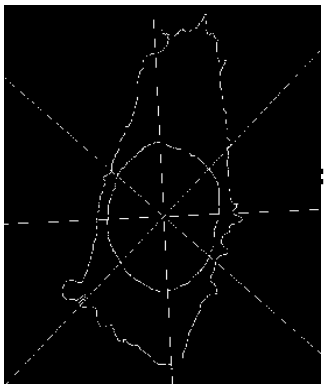
Nucleus

Cell membrane

Protein objects

width

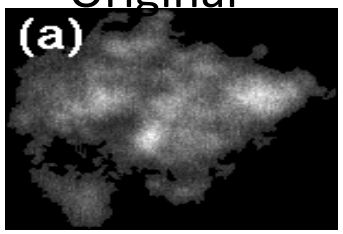
Medial axis



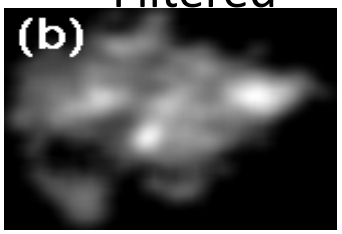
$$\frac{d_1 + d_2}{d_2}$$

Model parameters

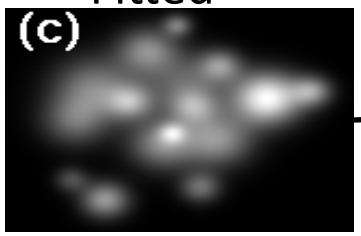
Original



Filtered



Fitted

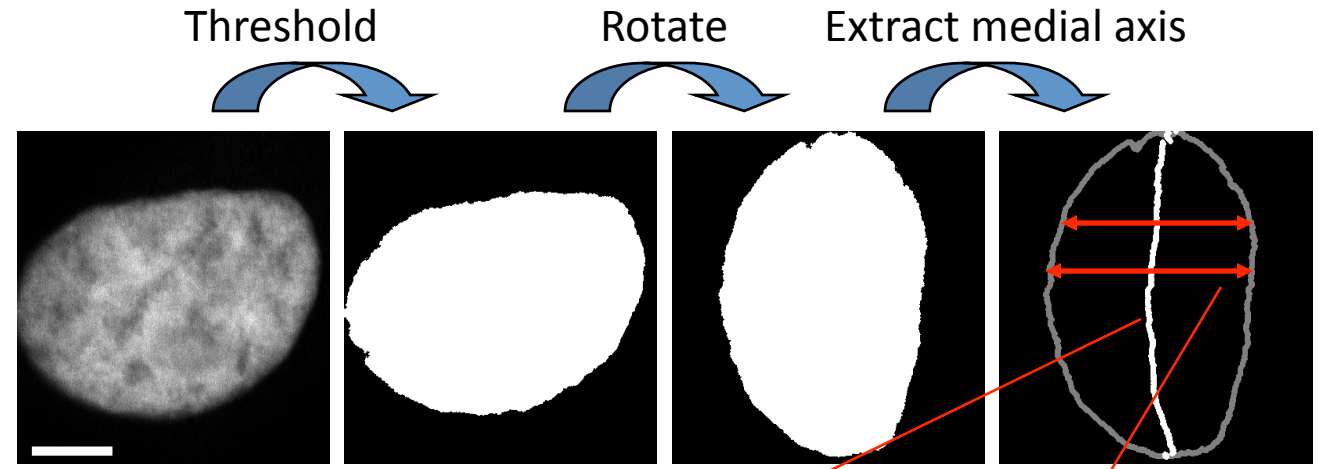


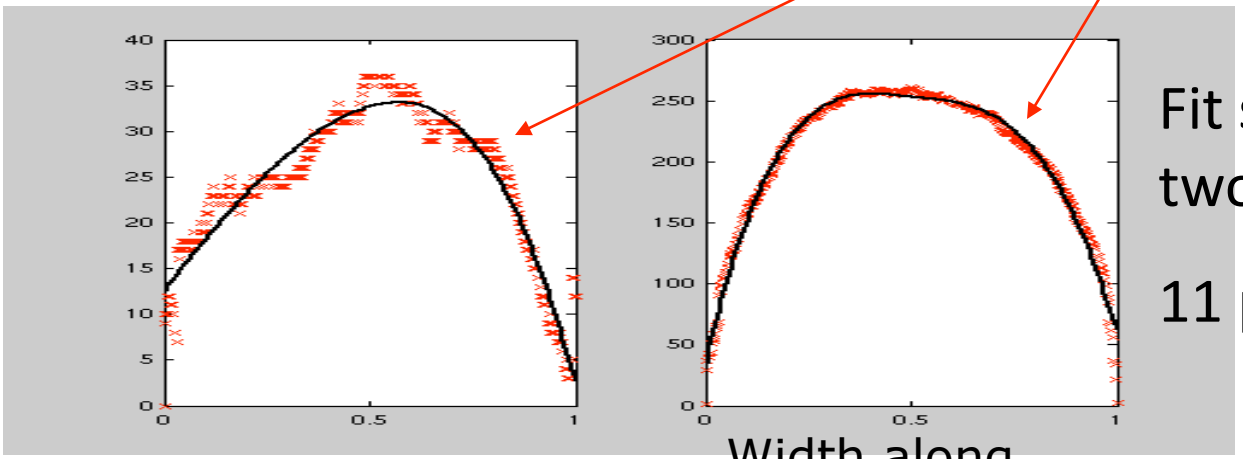
Zhao & Murphy 2007

Nuclear shape models

- Modified medial axis model
- Diffeomorphic model
  - S. Yang, D. Köhler, K. Teller, T, Cremer, P. Le Baccon, E. Heard, R. Eils, and K. Rohr, MICCAI 2006, LNCS 4190, pp. 907–914, 2006

Nuclear Shape - Medial Axis Model





Medial axis

Width along the medial axis

Fit splines to two curves :

11 parameters

Shape generation

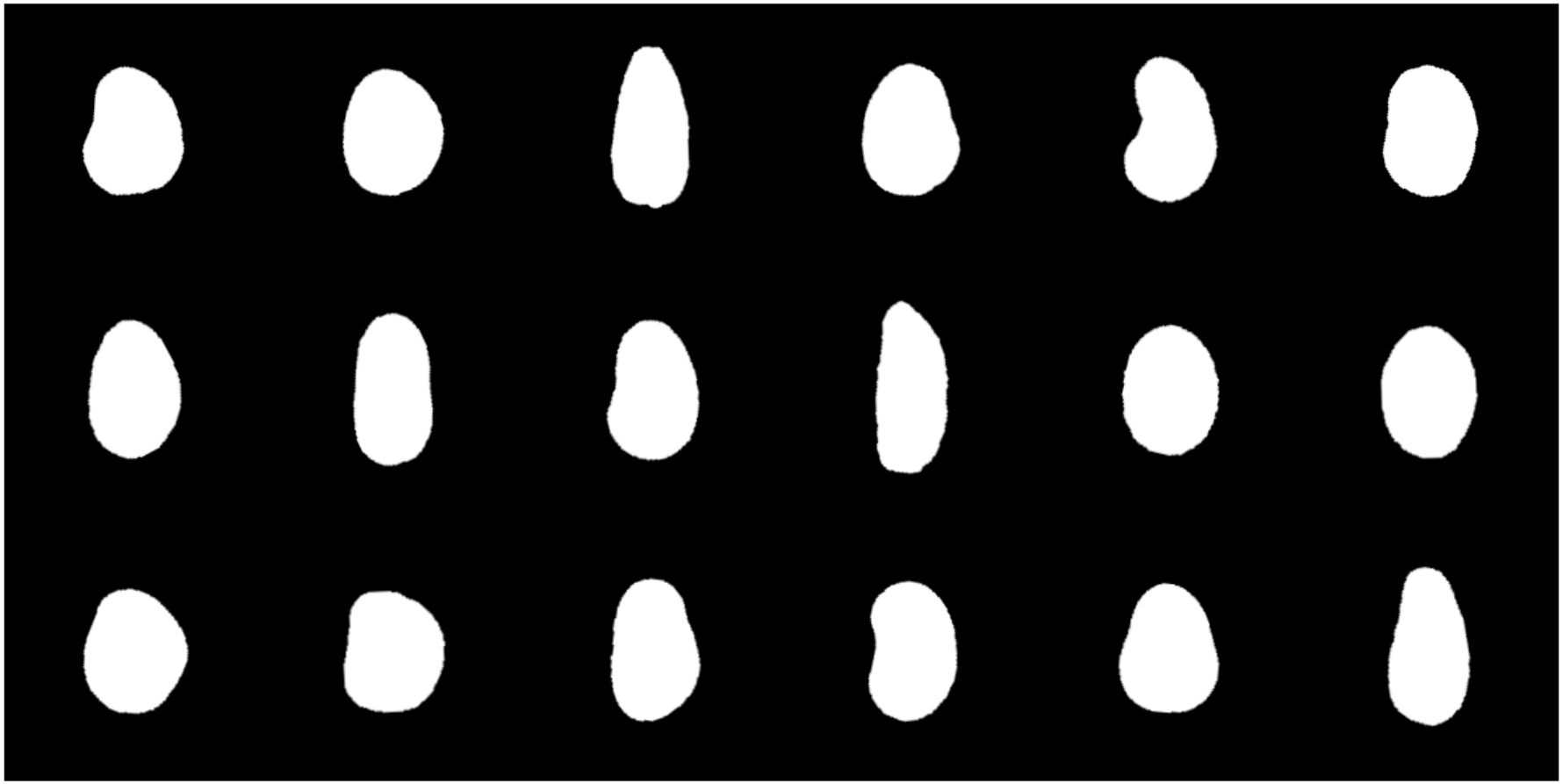
- 11 parameters for each object
  - 5 parameters for each curve
  - the length of the medial axis
- Learn the distribution of parameters over many nuclei
  - Assume multivariate normal
- Randomly sample parameters from distribution
- Construct nuclear shape using the sampled parameters

Synthesized nuclear shapes

Diffeomorphic analysis of nuclear shape

- Can use distance between shapes to characterize shape space instead of parameters of model – Gustavo Rohde

Concept: measure distances between all examples as means of characterizing shape space



LDDMM references

Miller MI. Computational anatomy: shape, growth, and atrophy comparison via diffeomorphisms. Neuroimage 2004;23 Suppl 1:S19-33.

Beg MF, Miller MI, Trouve A, Younes L. Computing large deformation metric mappings via geodesic flows of diffeomorphisms. International Journal of Computer Vision 2005;61:139-157.

Miller MI, Trouve A, Younes L. On the metrics and euler-lagrange equations of computational anatomy. Annu Rev Biomed Eng 2002;4:375-405.

Finding deformation field

- Goal: Find a function g(x,t) which smoothly transforms an image I_n into an image I_m as t goes from 0 to T
- Choose g(x,t) to minimize sum of
  - Total deformation in g from 0 to T
  - Distance between I_m and $I_n(g(x,T))$

Finding deformation field

Solve differential describing evolution from x to g(x)

$$\begin{cases} \dfrac{dg(x,t)}{dt} = v\big(g(x,t),t\big) \\ g(x,0) = x \end{cases}$$

$$v = \arg\min_{v(x,t)} \left(\int_0^T \|v(x,t)\|_V^2 \, dt + \left\| I_n(x) - I_m\big(g(x,T)\big) \right\|_{L^2}^2 \right)$$

Finding deformation field

Geodesic distance between two images

$$d(I_m, I_n) = \int_0^T \left\| v(x,t) \right\|_V dt$$

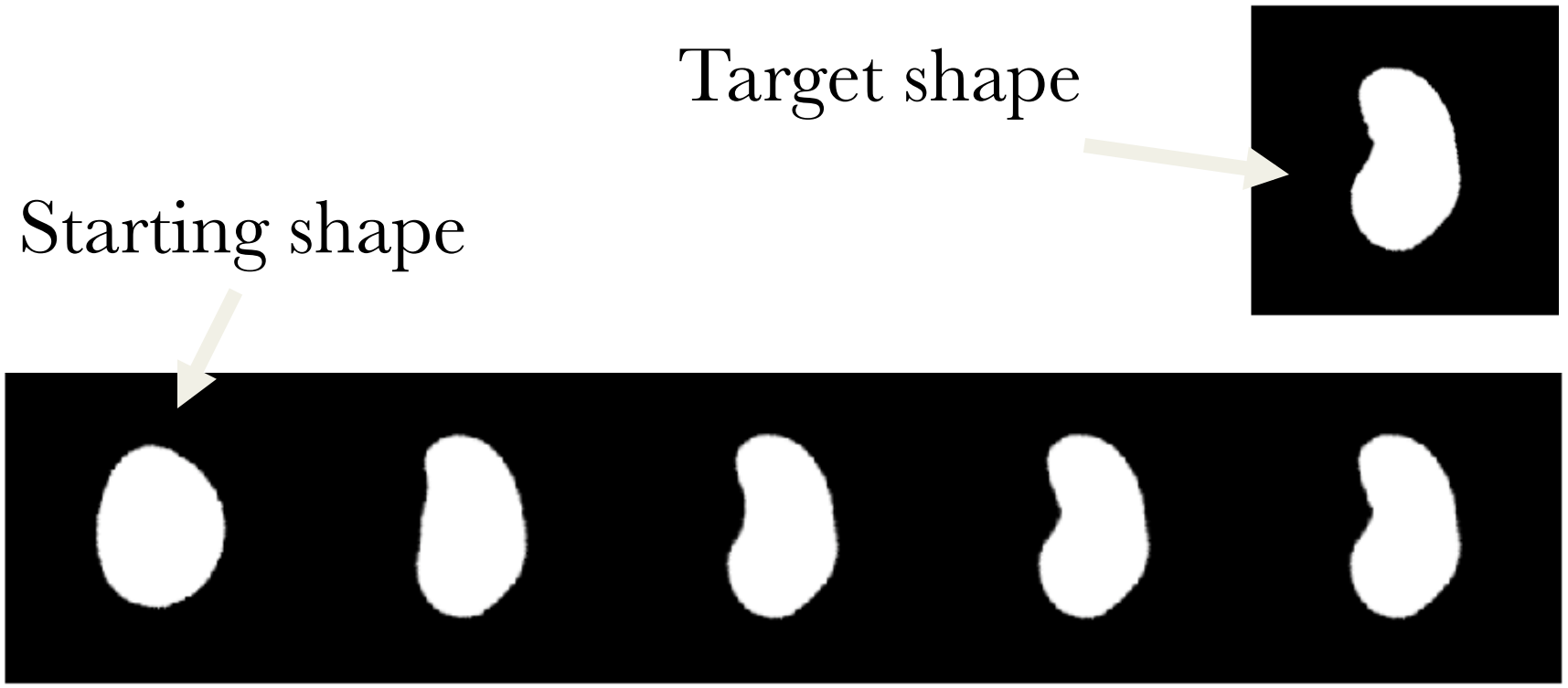
Where

$$\left\| v(x,t) \right\|_V = \left\| Lv(x,t) \right\|_{L^2}$$

for some operator *L*

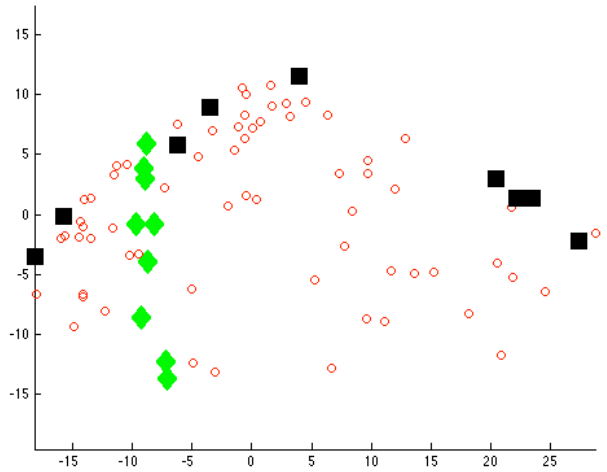
…

Mapping two shapes to each other

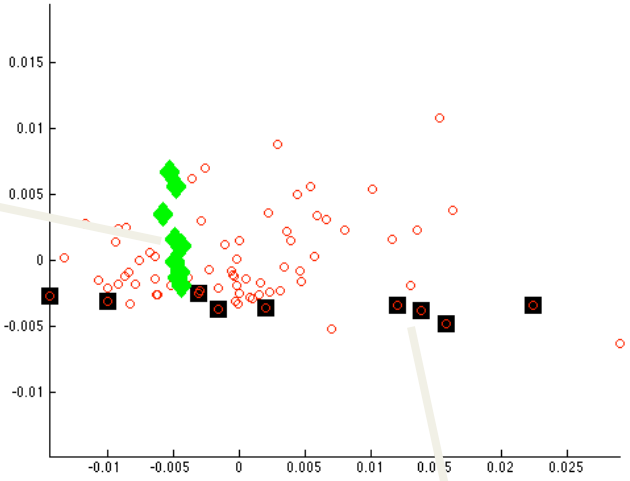

Target shape
Starting shape
0
0.0165
0.0191
0.0194
0.0195
Distance

Characterizing shape space

- Find deformation fields from each image to every other image
- Calculate distance between each pair of images as total deformation required between them
- Use multidimensional scaling (MDS) to find variables (principal components) that compactly represent variation



First 2 components from MDS directly on perimeter coordinates



First 2 components from MDS on distance matrix from LDDMM

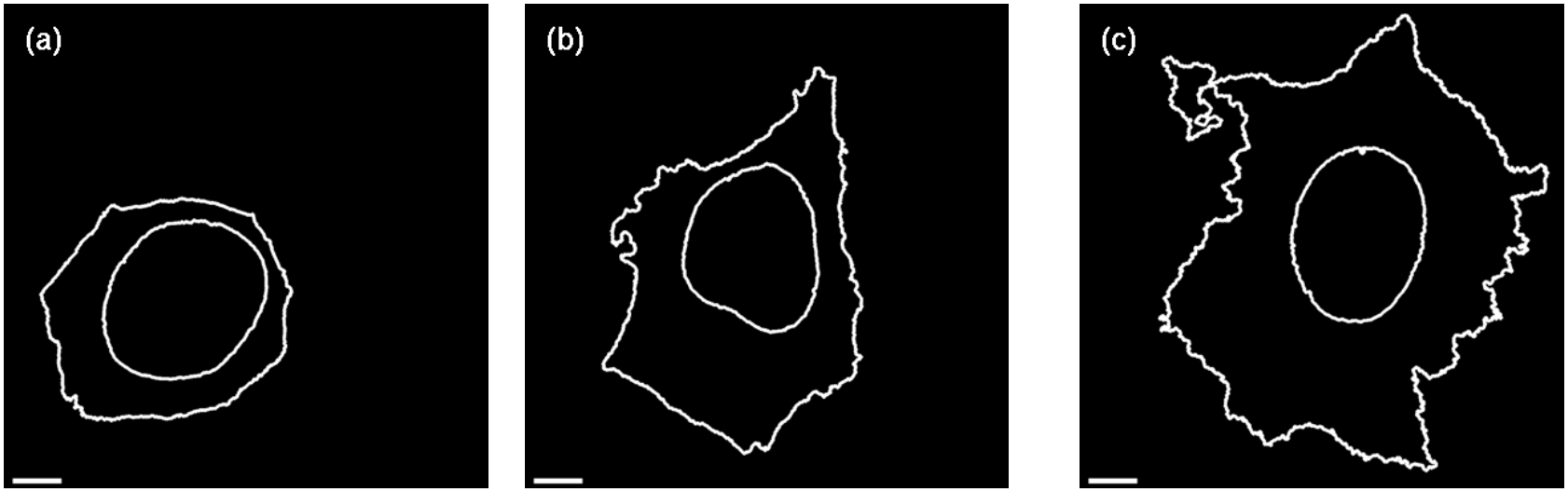
Finding mean shape

- For a population of images/shapes, find mean shape as that from which all shapes can be generated with minimum total deformation

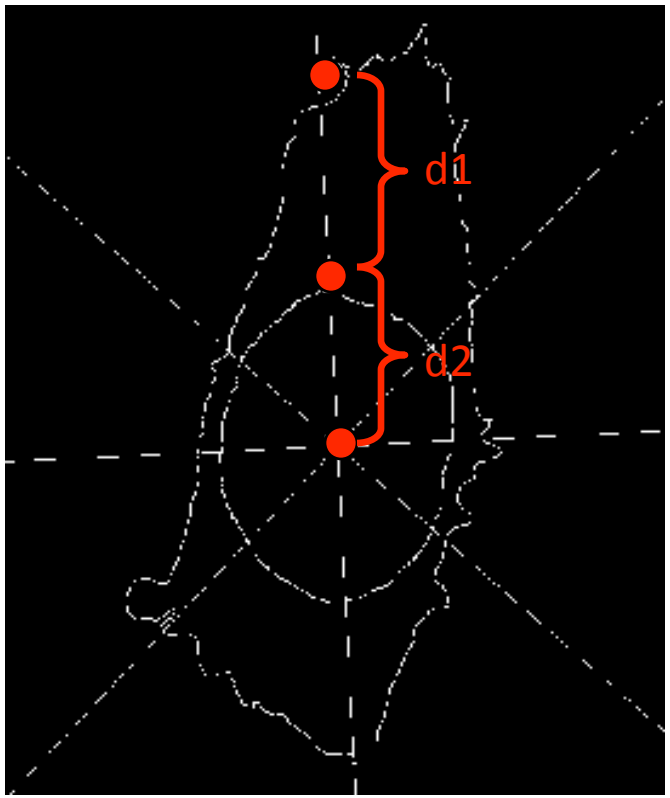
Cell shape models

- Conditional radial distance ratio model
- Diffeomorphic model (in progress)

Examples of natural variation in cell shape



Cell Shape
Description: Distance Ratio



$$r = \frac{d_1 + d_2}{d_2}$$

Represent single shape as vector of ratios for *n* angles and represent variation using PCA

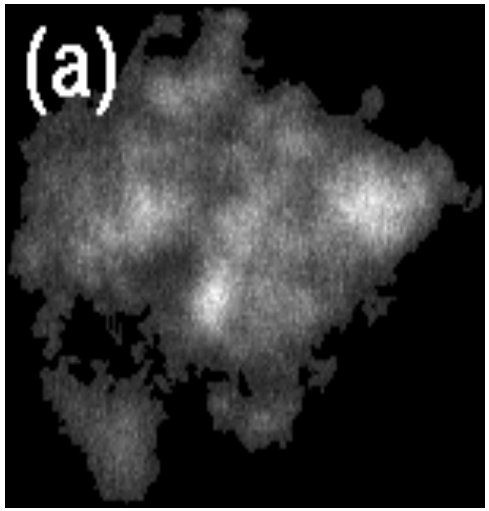
Diffeomorphic analysis of cell shape

Models for protein-containing objects

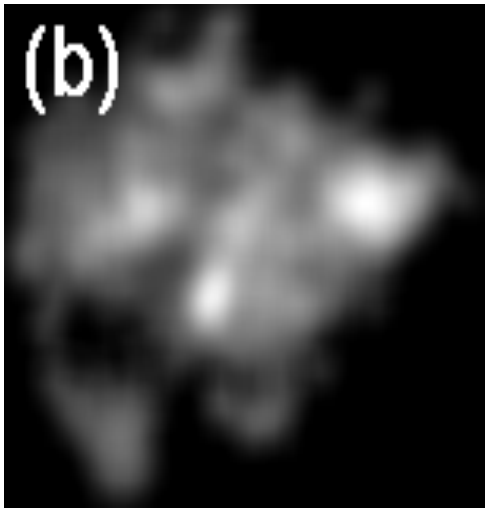
- Object library
- Gaussian objects
  - Mixture of Gaussians with number of objects determined from number of local minima
  - Learn distributions for number of objects and object size
  - Learn probability density function for object position relative to nucleus and cell shape

Modeling Vesicular Organelles

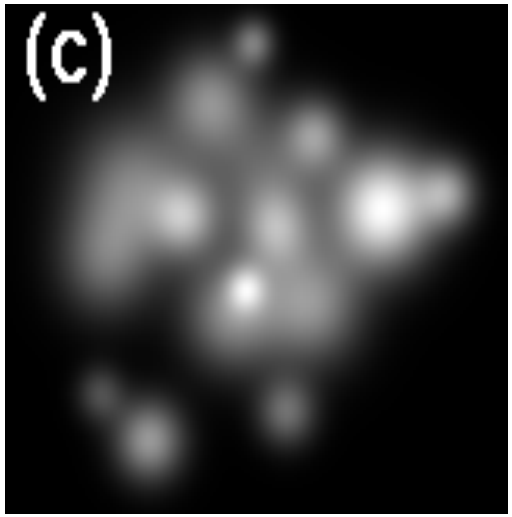
Original



Filtered

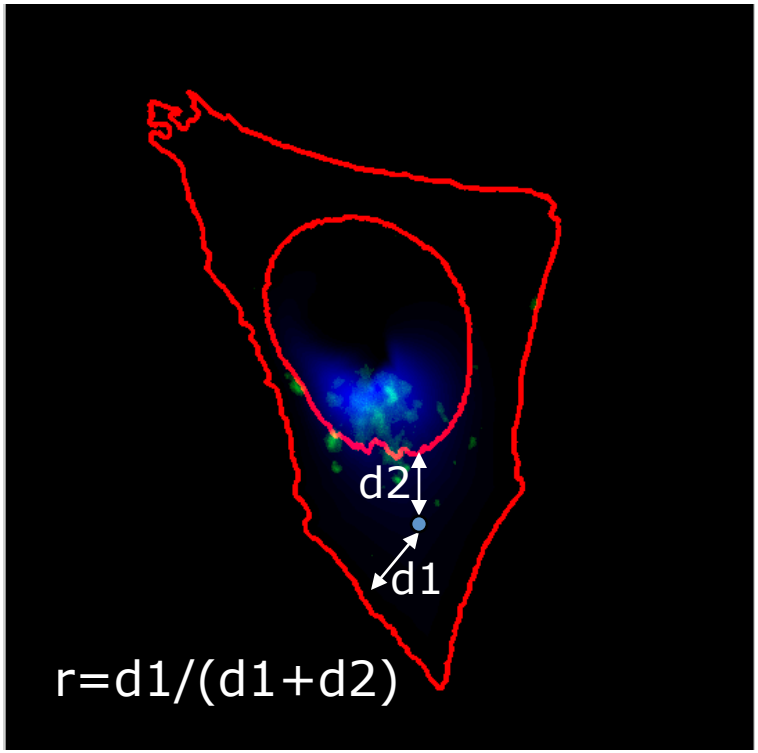


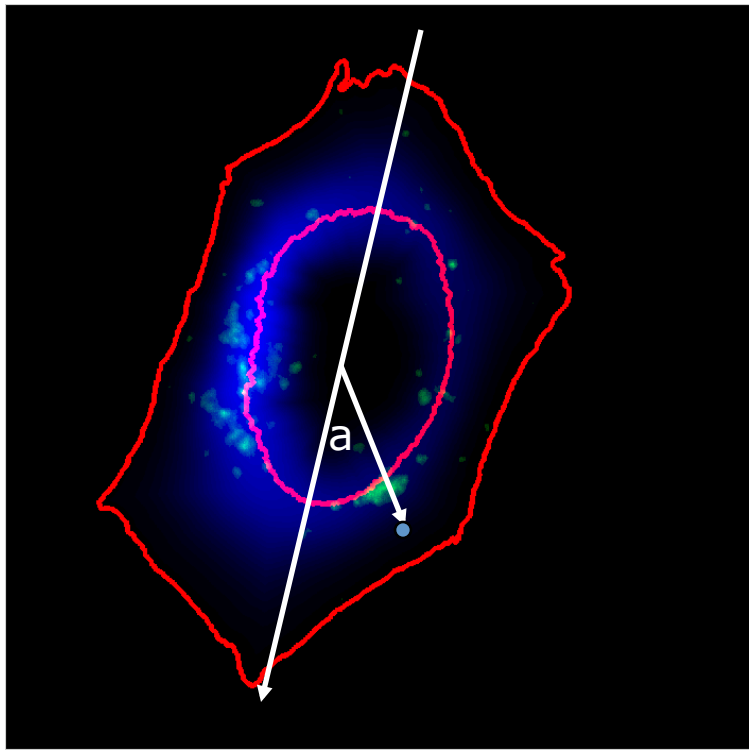
Fitted Gaussians



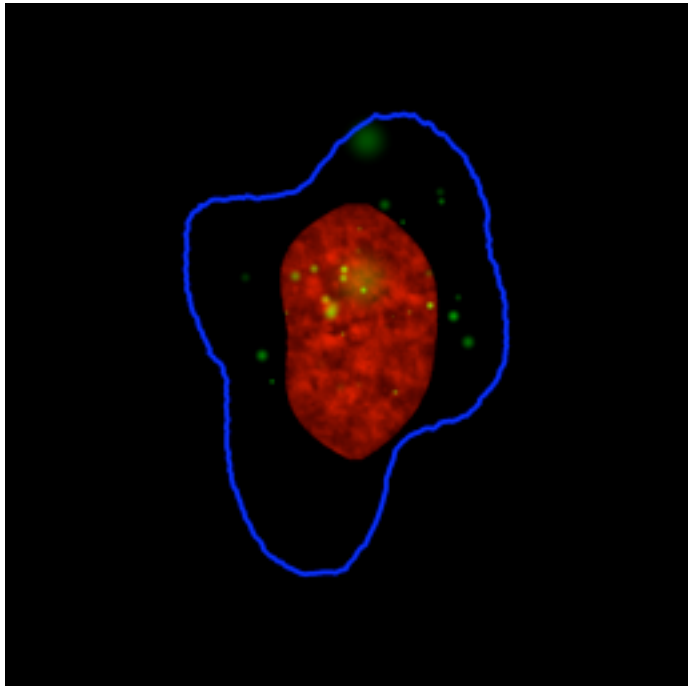
Position Model

r: normalized distance, a: angle to major axis

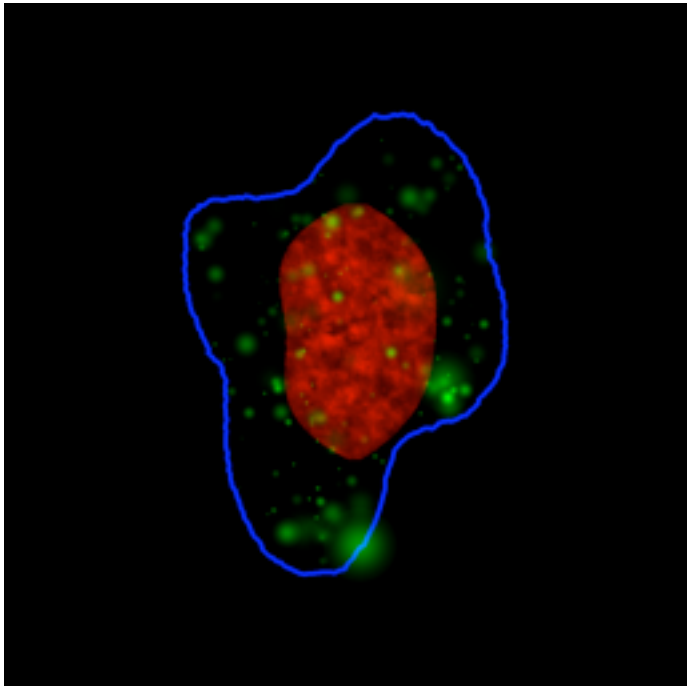




Synthesized Images



Lysosomes



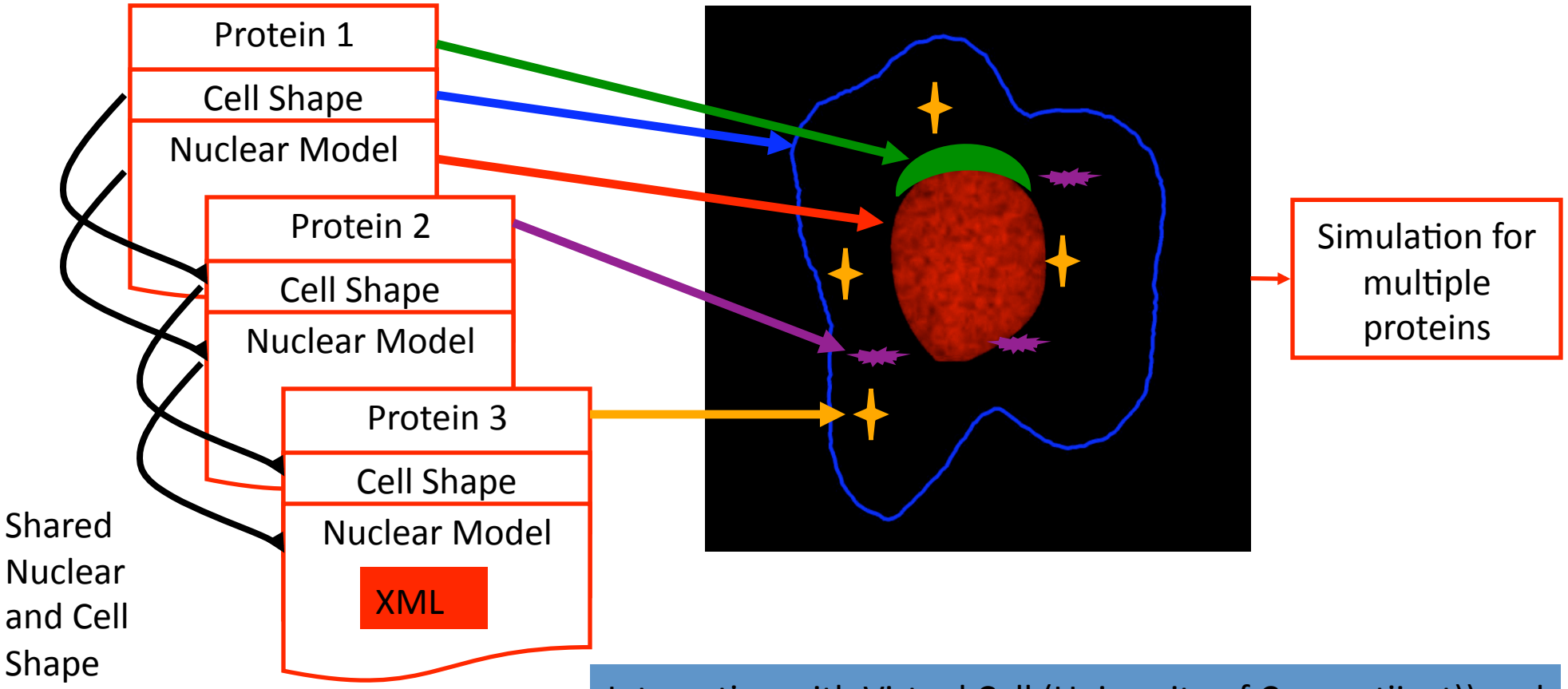
Endosomes

- SLML toolbox - Ivan Cao-Berg, Tao Peng, Ting Zhao
- Have portable tool for generating images from model

Framework for conditional subcellular location models

- SLML: slots for different parts of cell model
  - Nucleus
  - Plasma membrane
  - Specific protein
- Each slot can hold one of multiple types of models, each of which is probabilistic
- Each slot's model can be conditional (dependent) on another

Combining Models for Cell Simulations



Integrating with Virtual Cell (University of Connectiicut)) and M-Cell (Pittsburgh Supercomputing Center)