Application of Statistical Physics Methods to Quantify the Aging Process in the Brain

João Ricardo Santos

Advisor: H. E. Stanley

Boston University

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Scientific Question?

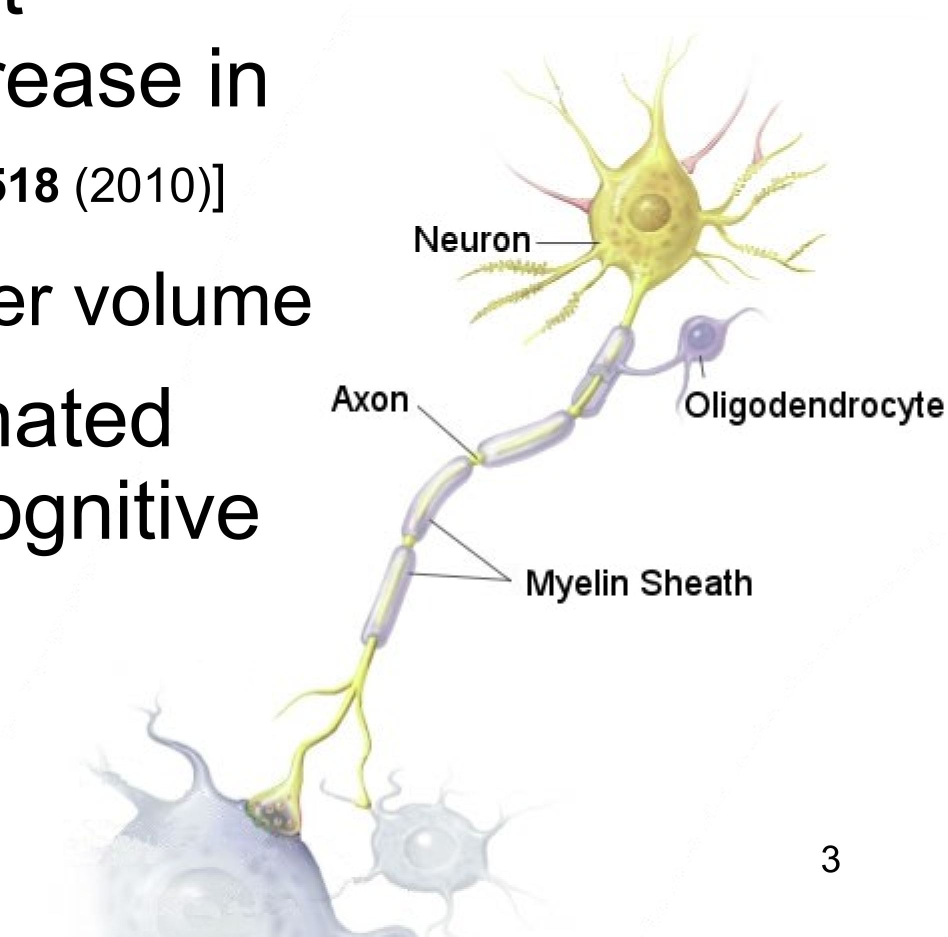
We recognize the symptoms of aging

BUT what happens during aging?

Background

- No general decrease in number of neurons detected [Peters *et al.*, Cereb. Cortex **8** (1998)]

- One observed change is that myelinated nerve fibers decrease in number [Peters *et al.*, J. Comp. Neurol. **518** (2010)]
  - Little decrease in white matter volume
- Observed changes of myelinated nerve fibers correlate with cognitive decline

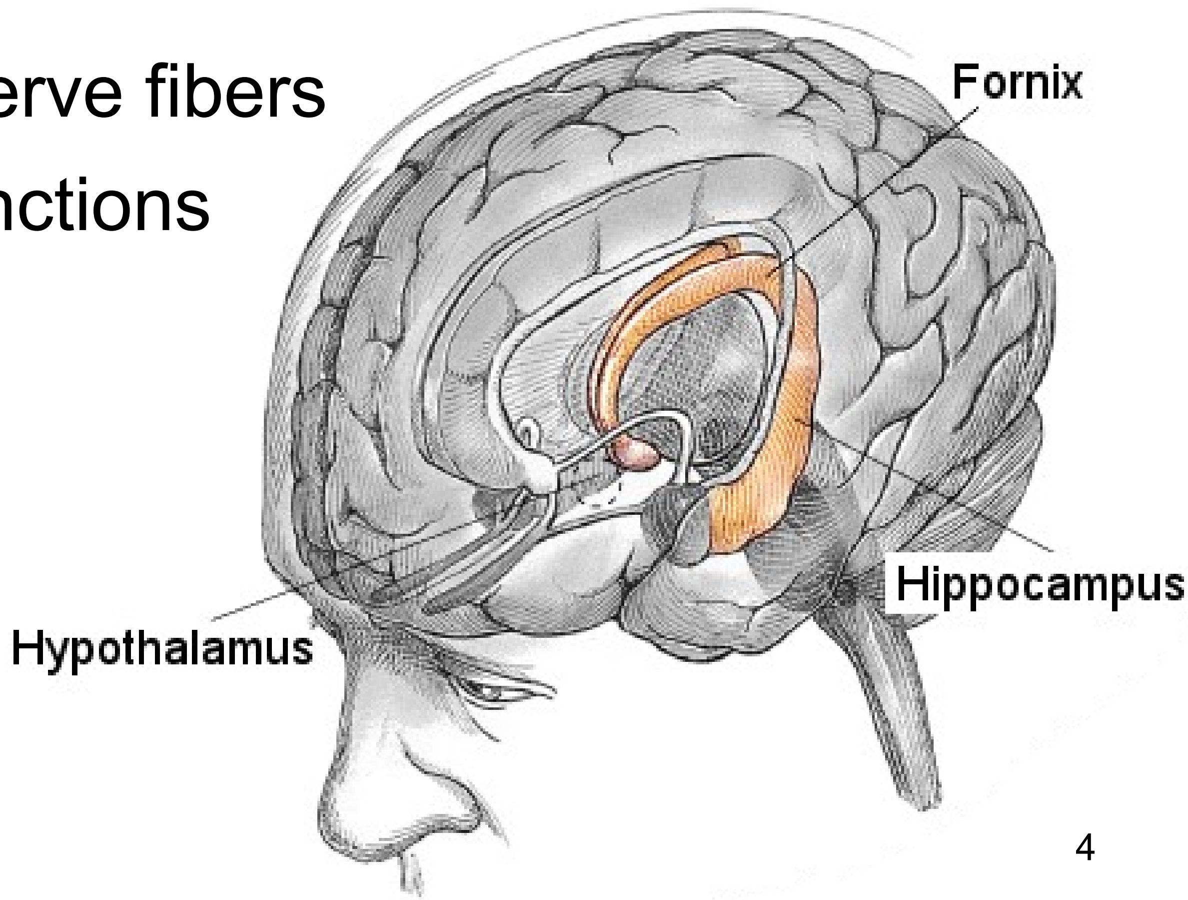


Fornix of the Brain

Why is Fornix interesting?

Fornix (latin: *arch)*

- C-shaped bundle of nerve fibers
- Crucial in cognitive functions (memory)



Scientific Objective

- Study effects of aging in the fornix
  - Describe myelinated axons
  - Differences between young and old subjects
    - Macroscopic changes (e.g. axon density)
    - Morphological changes (e.g. area, shape)
    - Structural changes (e.g. disorder)

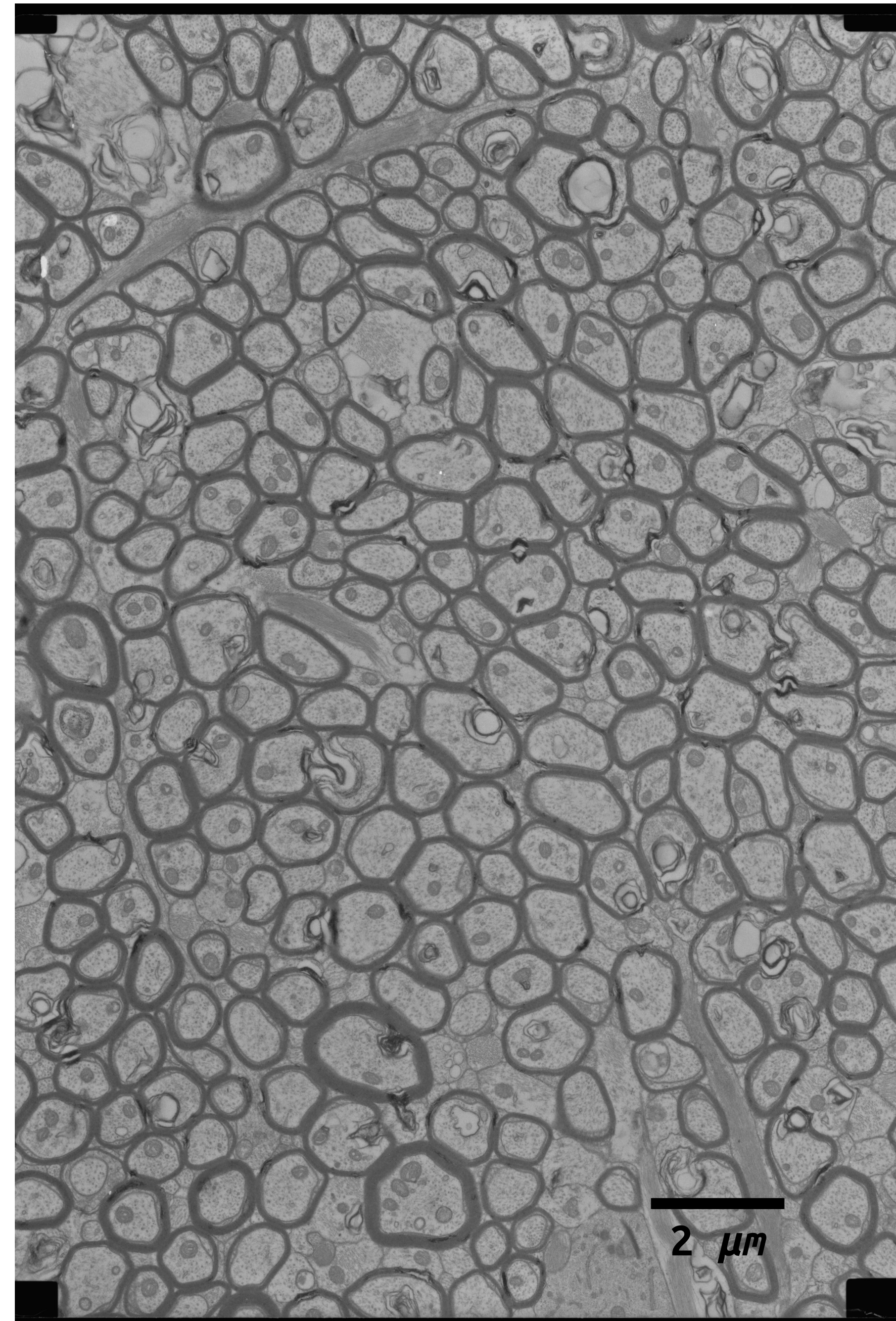
Subjects

6 female specimens (rhesus monkey)

- 3 young females
  - aged 6 to 8 years
- 3 old females
  - aged 25 to 32 years

67 slides analyzed from Dr. Peters collection

EM image of the fornix of a young subject



Results

1. ***Axon Recognition Algorithm***
2. Macroscopic Changes
3. Morphological Changes
4. Structural Changes

1. **Axon Recognition Algorithm**

[development by Will Morrison]

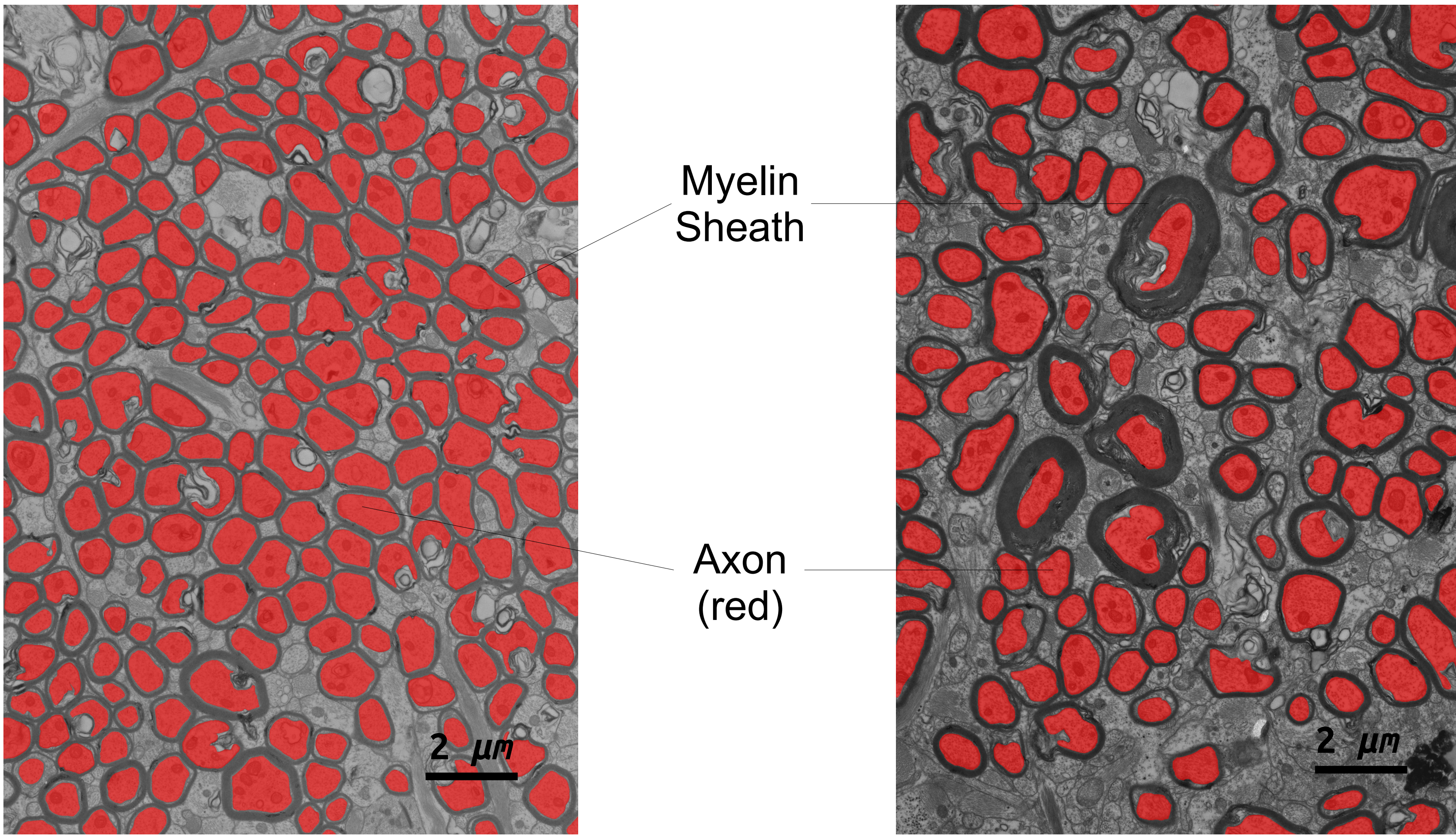
Recognition via contrast between convex light region (axon) surrounded by dark region (myelin sheath)

- Smooth image
- Threshold image
- Find edges
- Reduce false positives
  - area cut, eccentricity cut, uniformity cut, convex curvature cut
- Manual check

1. **Axon Recognition Algorithm**

Axon Recognition examples:

Young subject EM image | Old subject EM image

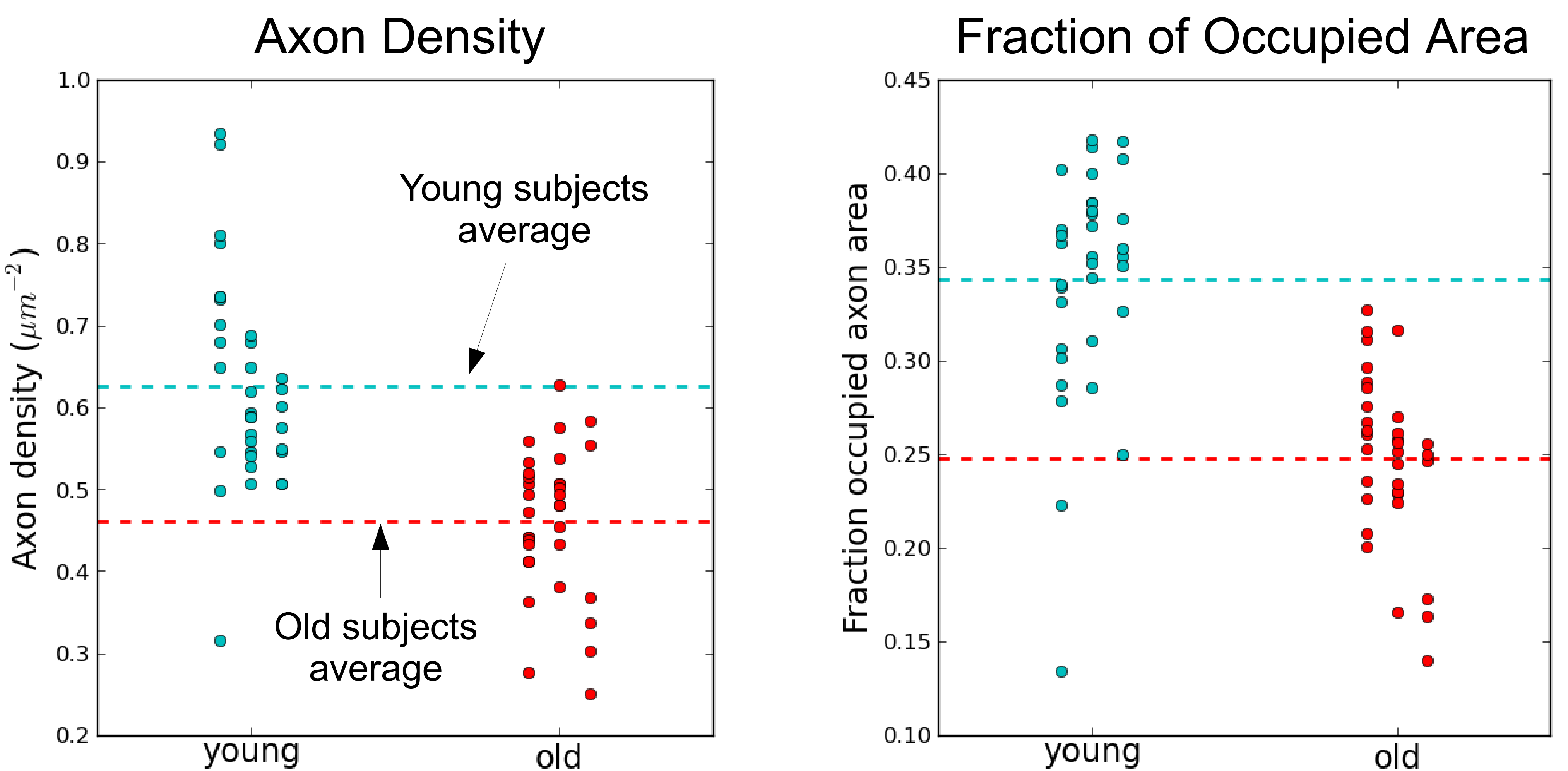


9024 recognized axons in 67 slides

Results

1. Axon Recognition Algorithm
2. ***Macroscopic Changes***
   a) **Axon Density**
3. Morphological Changes
4. Structural Changes

2a) **Myelinated Axon Density**

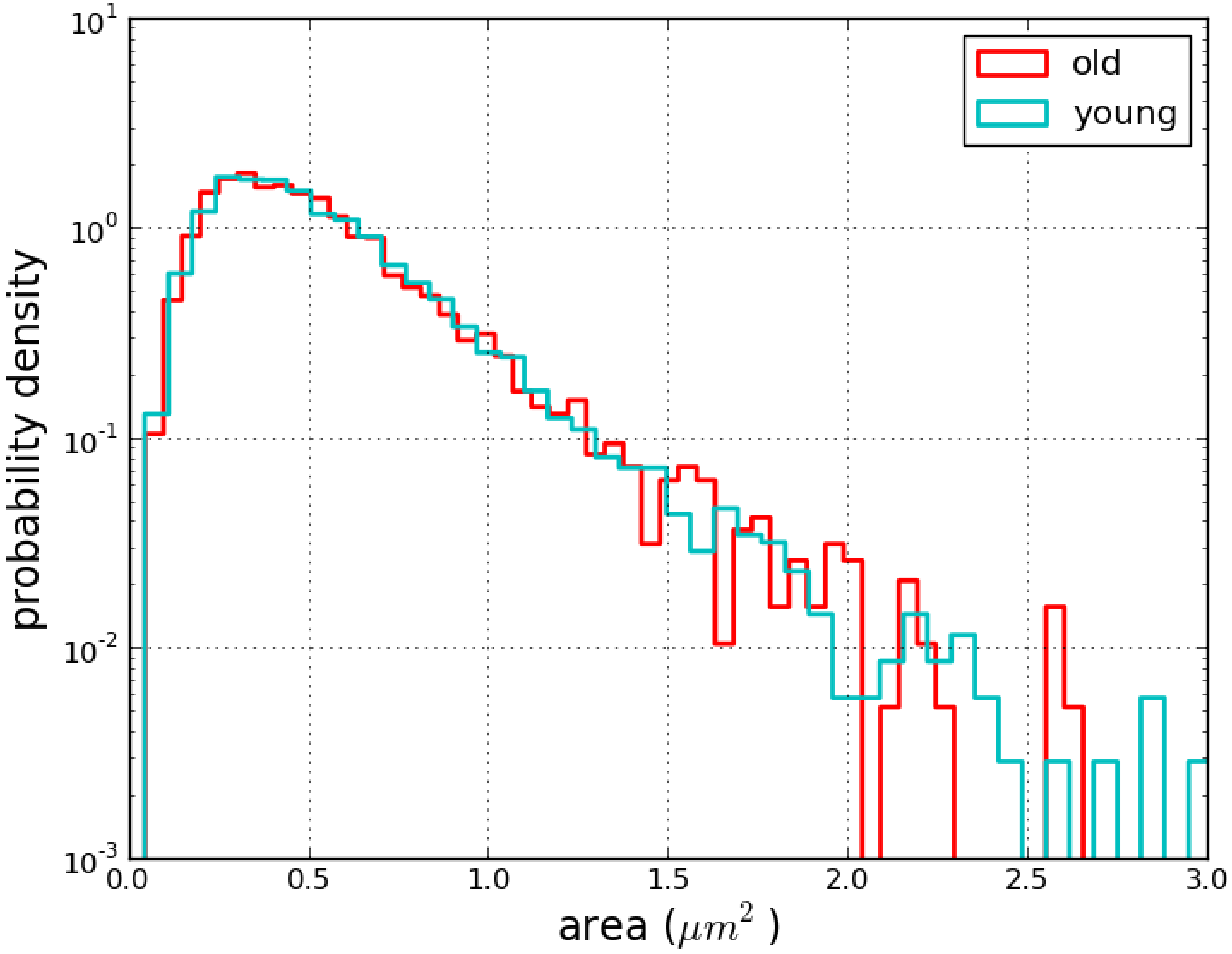


Young and Old specimens are statistically distinguishable

Results

1. Axon Recognition Algorithm
2. Macroscopic Changes
3. ***Morphological Changes***
   a) **Axon Area**
   b) **Shape Parameters**
4. Structural Changes

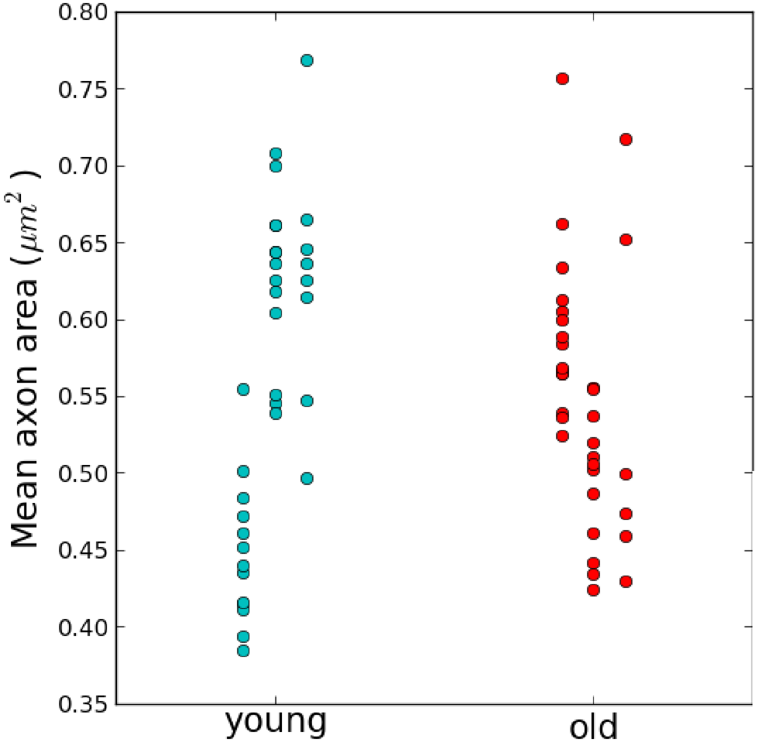
3a) **Axon Area Distribution**



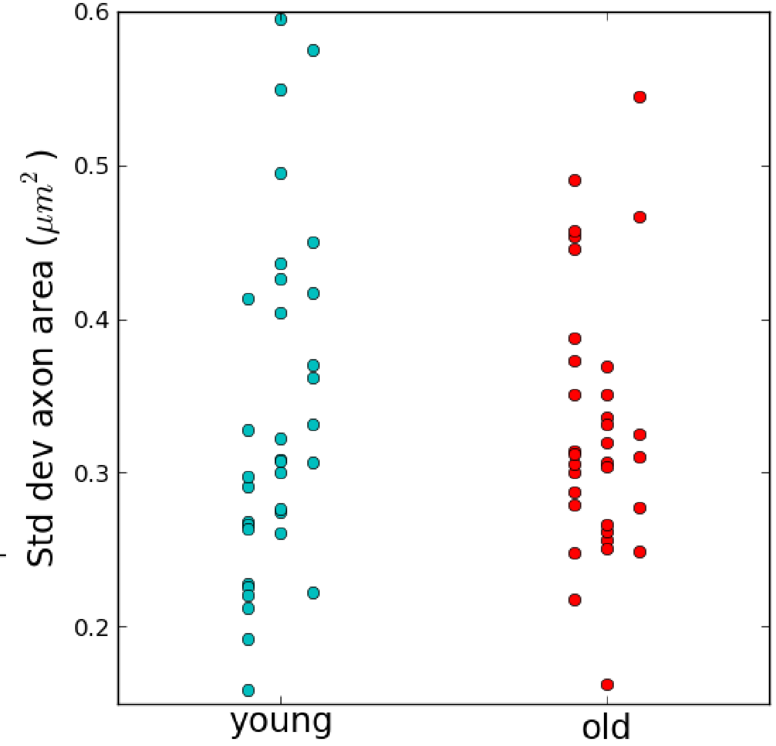
Similar area distribution profile
(statistically NOT different)

3a) **Axon Area Distribution**

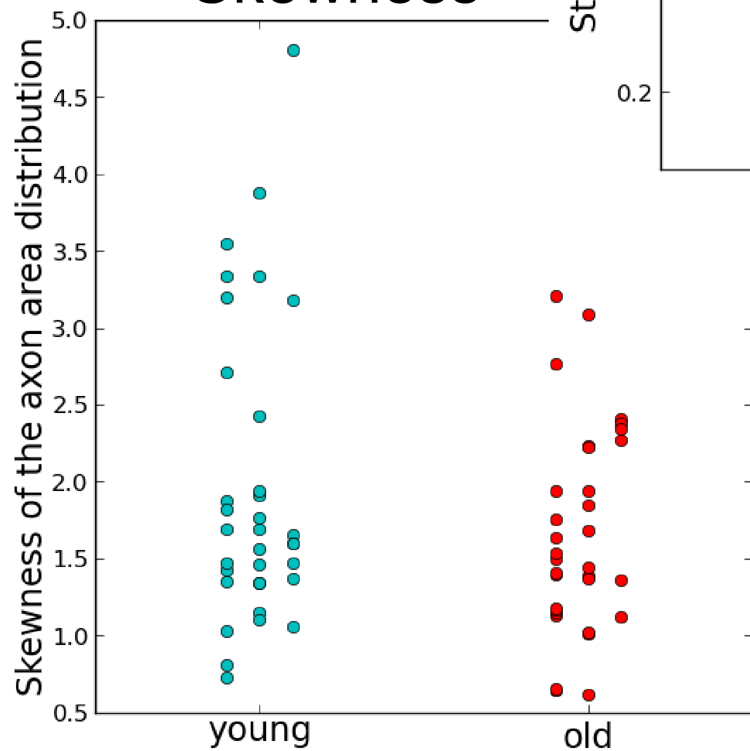
Mean Axon Area



Standard Deviation



Skewness

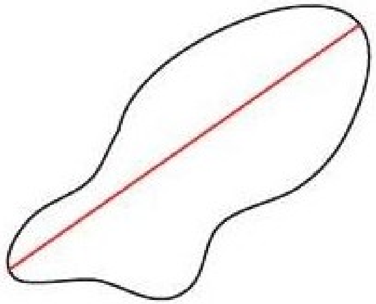


Individual area properties not enough to distinguish between age groups

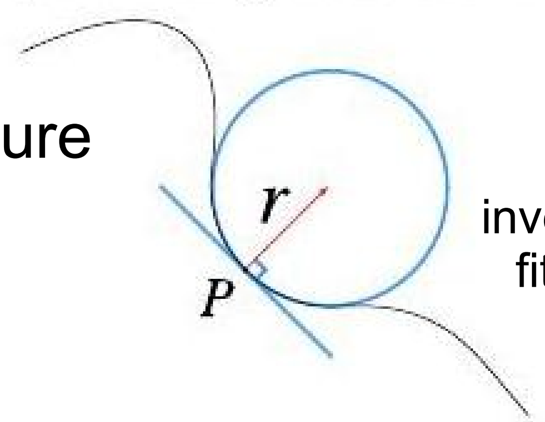
3b) **Shape Parameters**

[calculations by César Comin]

- Other shape parameters are also not enough to distinguish between age groups
  - Perimeter
  - Circularity $= 4\pi \frac{Area}{Perimeter^2}$ For a circle, circularity=1
  - Diameter – Largest distance between 2 contour points



  - Curvature



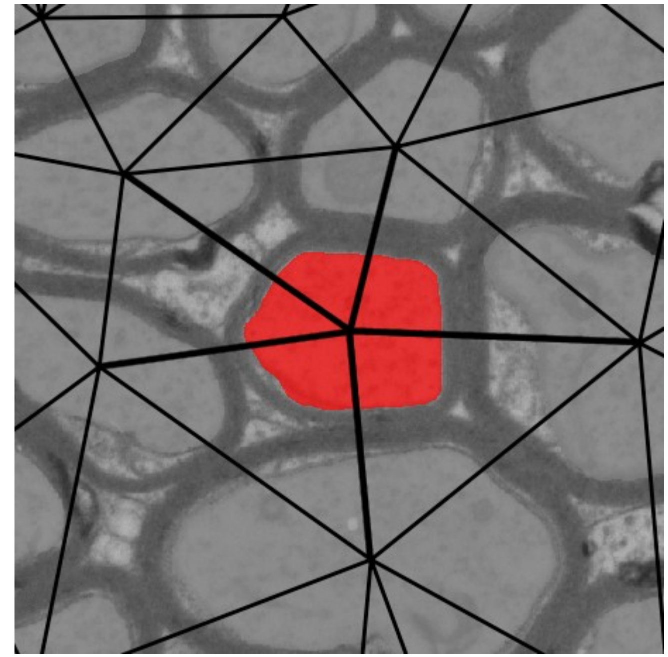
Curvature of point P is inverse of radius of the circle fitting the curve at point P

Results

1. Axon Recognition Algorithm
2. Macroscopic Changes
3. Morphological Changes
4. ***Structural Changes***
   a) **Hexagonality Index**
   b) **Nearest Neighbor Distances**
   c) **Axon Area Correlations**

4. **Order and Regularity**

How to quantify regularity?



a) compare to a regular lattice → Hexagonality Index

b) study behavior of nearest neighbors

c) measure regularity of axon areas

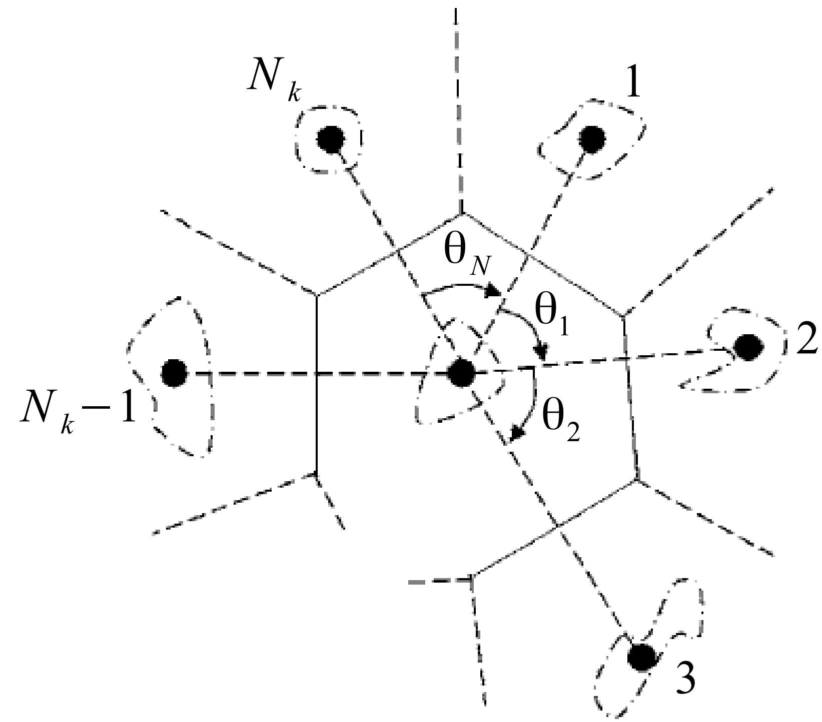
4a) **Hexagonality Index** (HI)

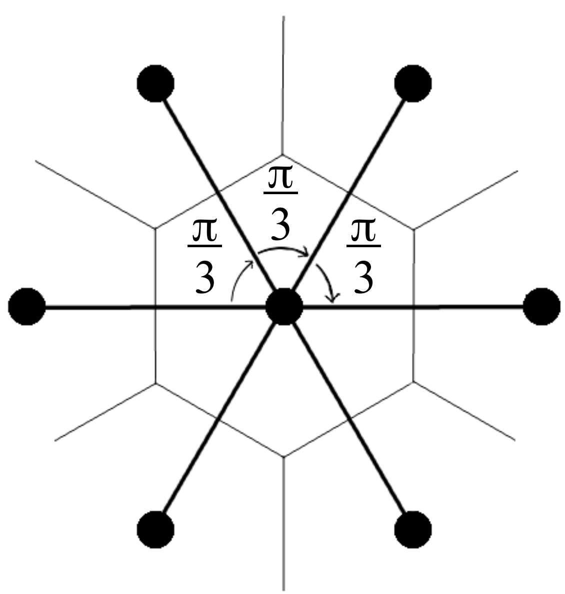
[Costa *et al.*, Phys. Rev. E **73** (2006)]

How ordered is a structure?

- Compare angles to nearest neighbors to those of a triangular lattice

$$HI_k = \frac{1}{\sum_{i=1}^{N_k} \left|\theta_i - \frac{\pi}{3}\right| + 1}$$



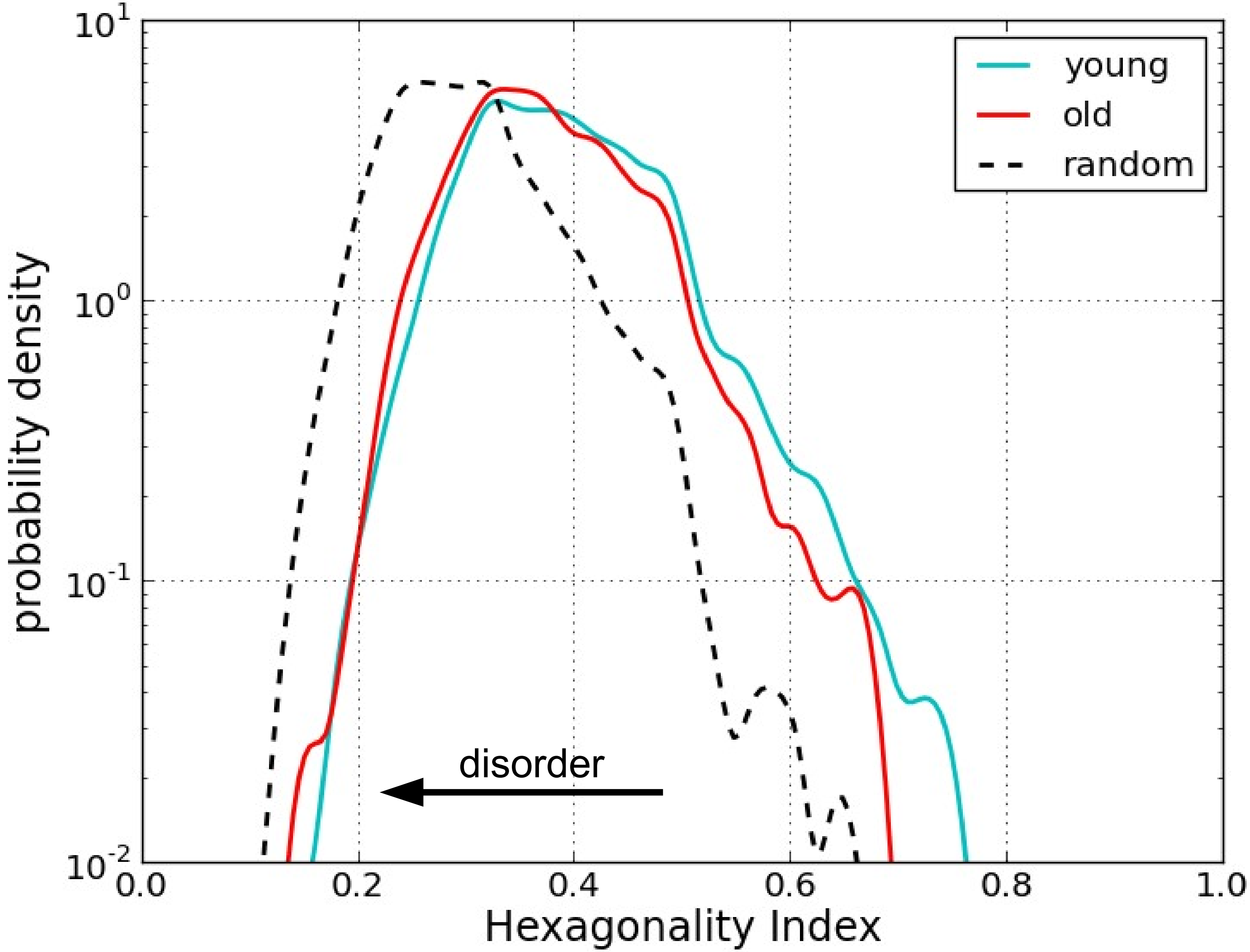


HI = 1 for a perfect triangular lattice

HI → 0 for more disordered systems

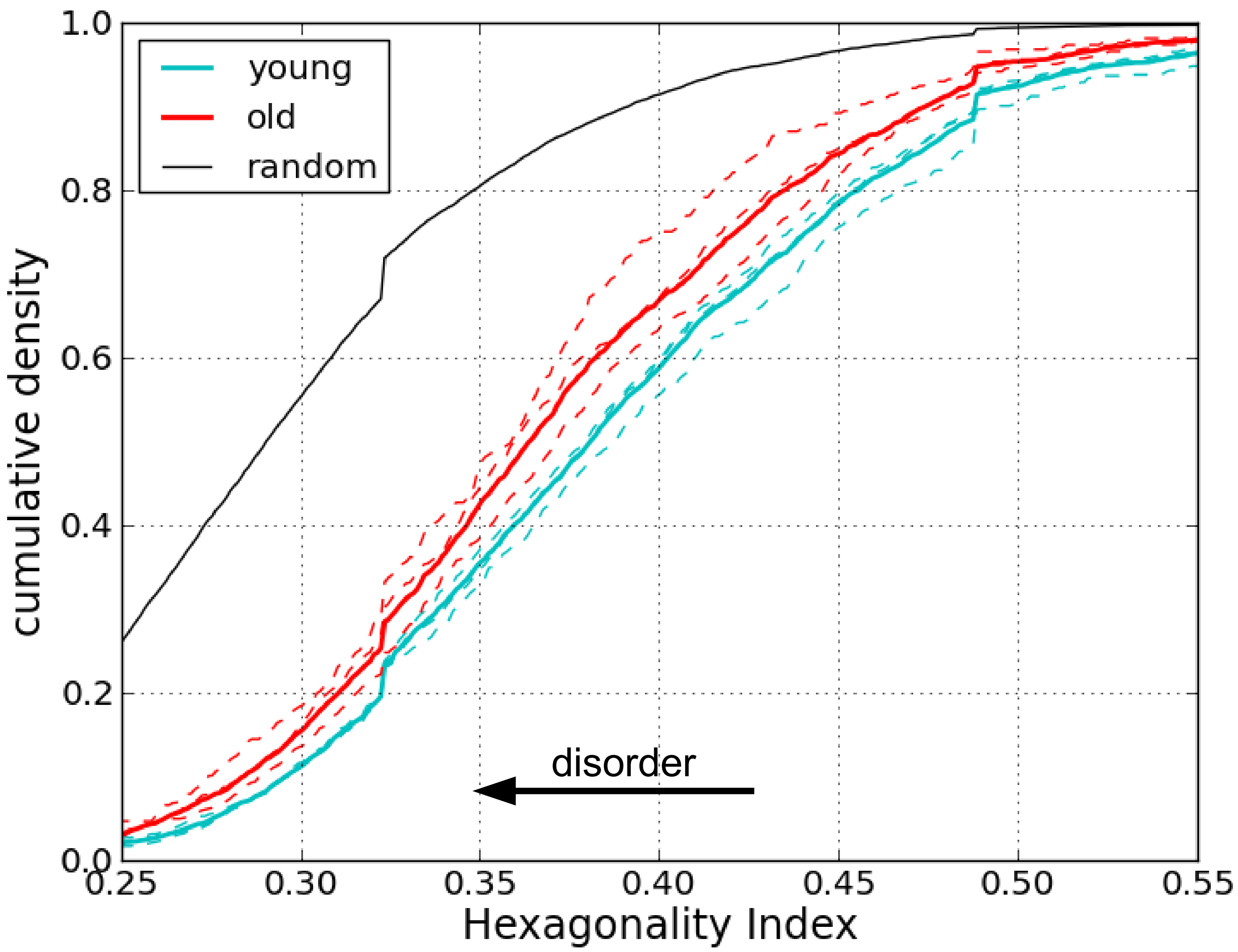
4a) **Hexagonality index**

[calculations by Chester Curme]



Both age groups display angular regularity

4a) **Hexagonality index**



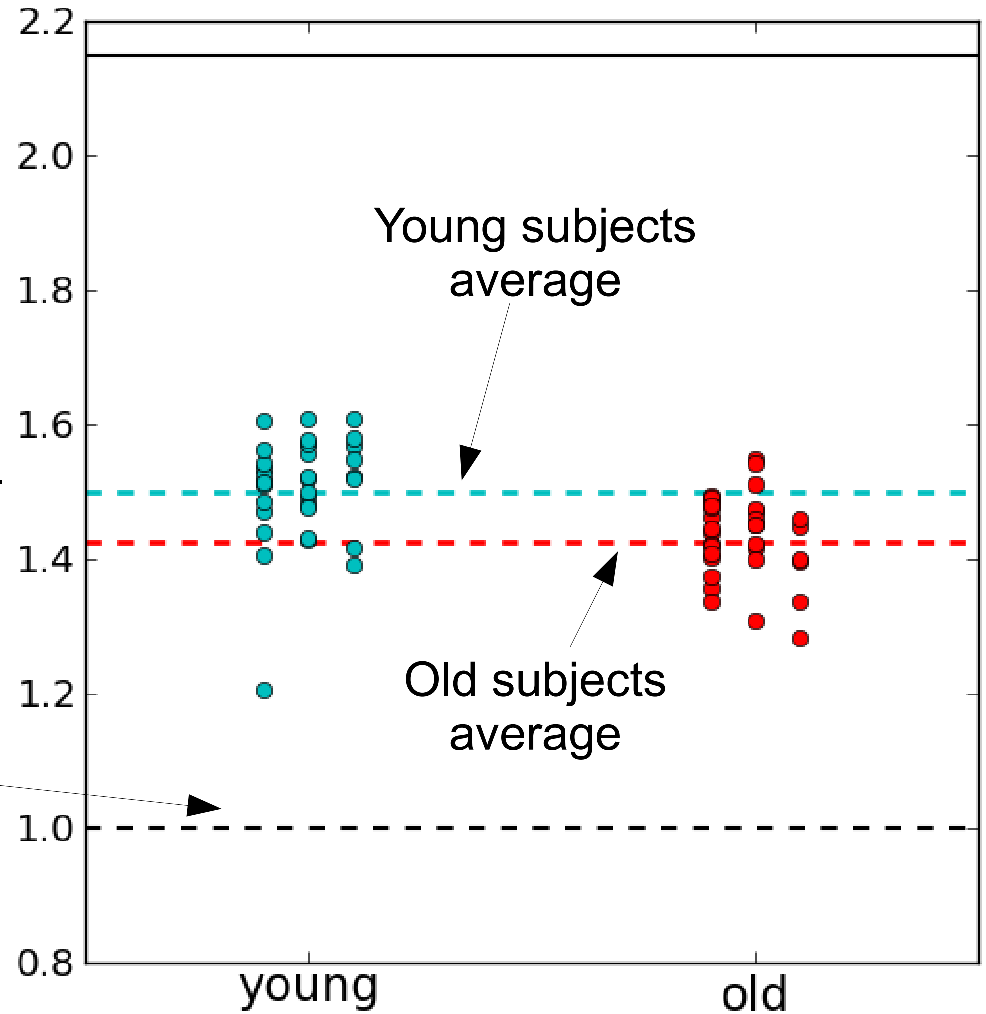
Old subjects more disordered

4b) Nearest Neighbor Distances

Measure spatial order through mean distance to nearest neighbor [Clark et al., Ecology **35** (1954)]

normalized distance to nearest neighbor

$$\frac{\langle d_1 \rangle}{d_1^{rand}}$$



triangular lattice:

$$d_1^{tri} = \sqrt{\frac{2}{\sqrt{3}\rho}}$$

random set of points:

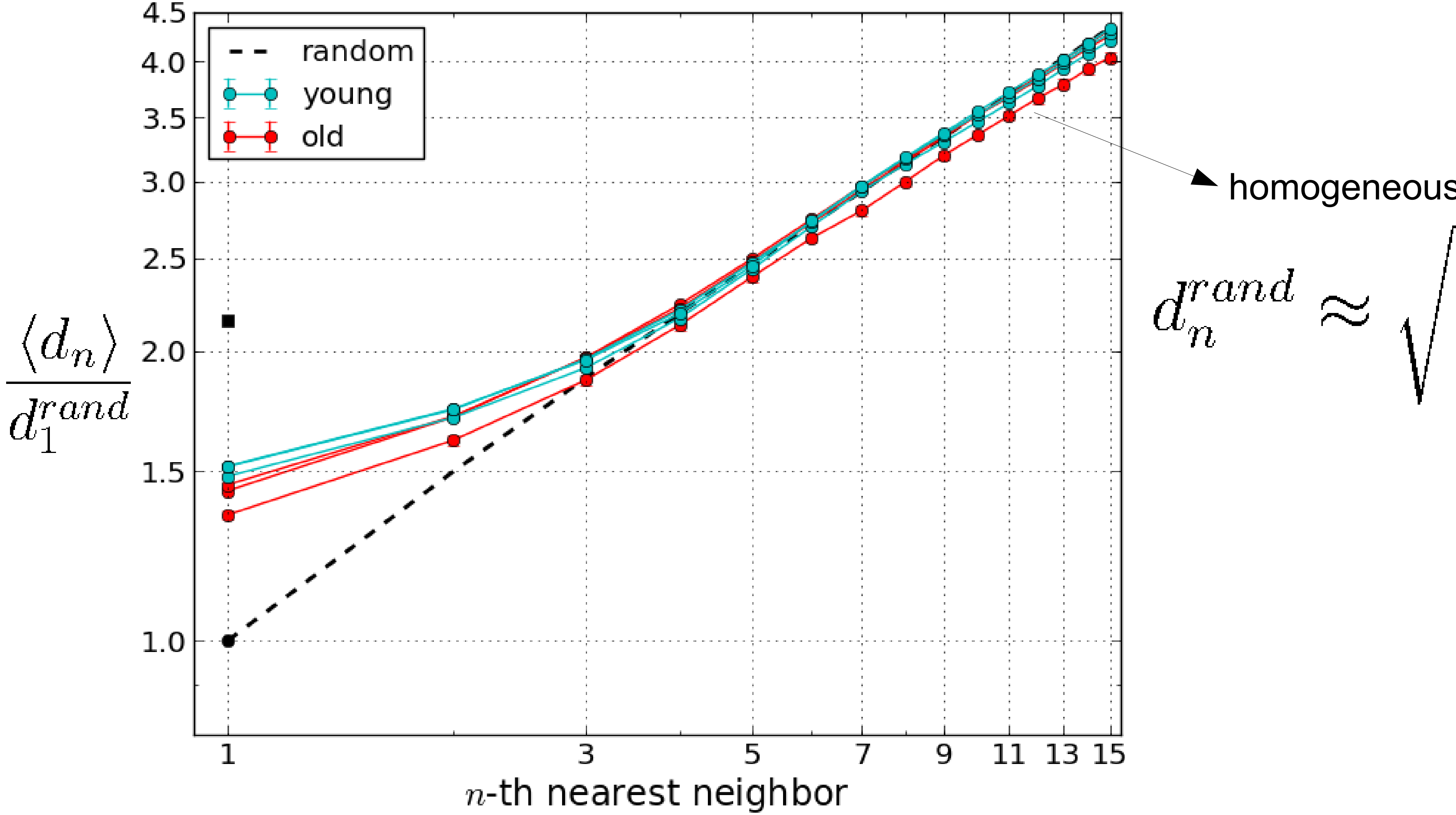
$$d_1^{rand} = \frac{1}{2\sqrt{\rho}}$$

Young subjects more regular

order

clustering

4b) **Nearest Neighbor Distances**

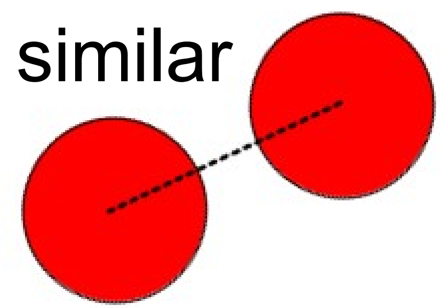


$$d_n^{rand} \approx \sqrt{\frac{n}{\pi \rho}}$$

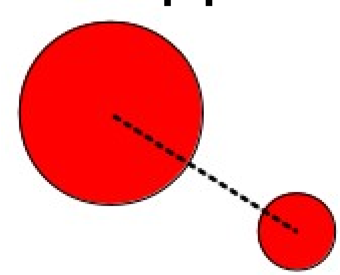
4c) Axon Area Autocorrelation

Measure similarity of axon areas in function of distance:

- Autocorrelation > 0 → axon areas are similar

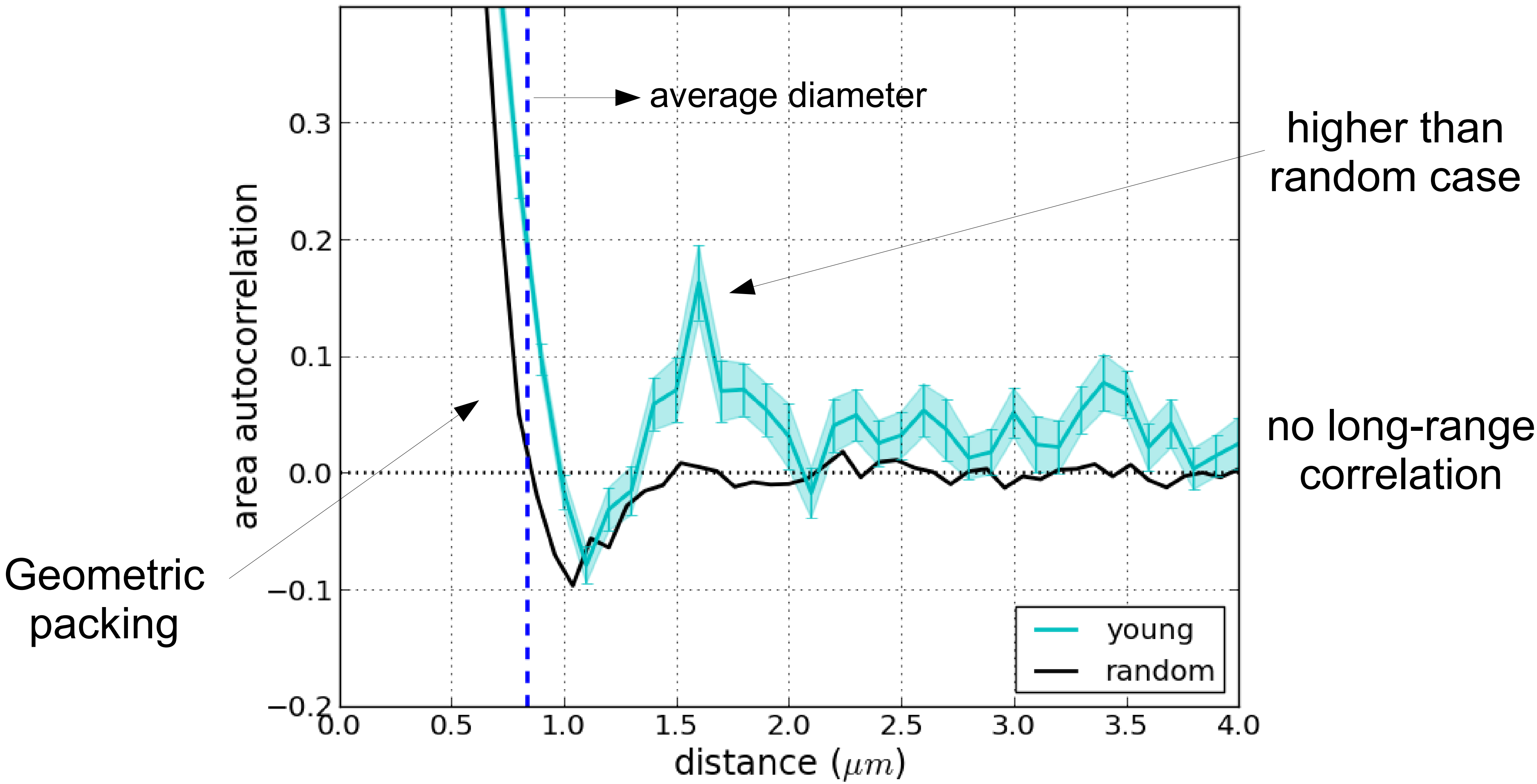


- Autocorrelation < 0 → axons have opposed areas



4c) **Axon Area Autocorrelation**

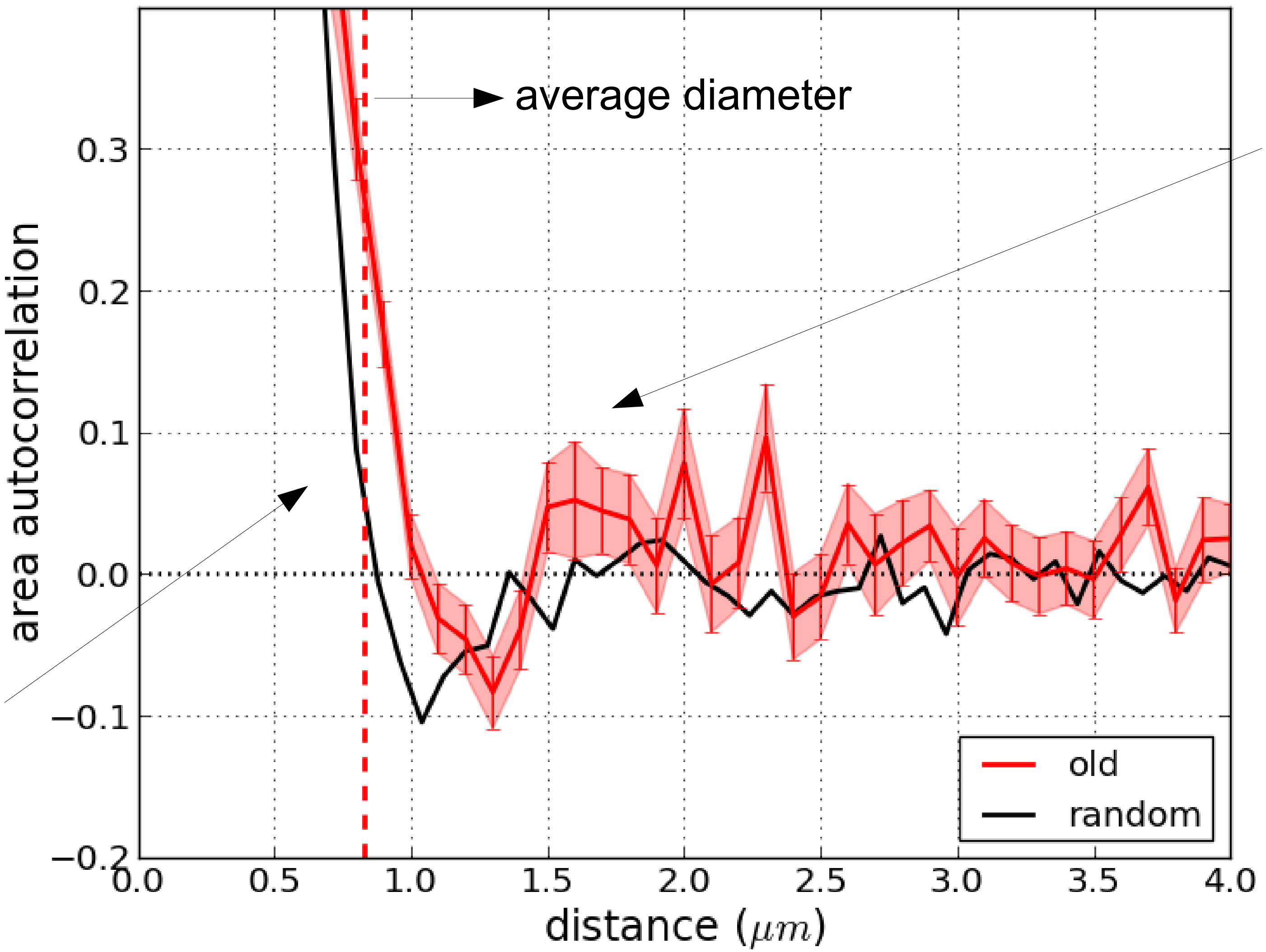
(i) young subjects



Axon areas have regularity

4c) **Axon Area Autocorrelation**

(i) old subjects



lower peak compared to young plot

no long-range correlation

Geometric packing

Old subjects less regular

Conclusions

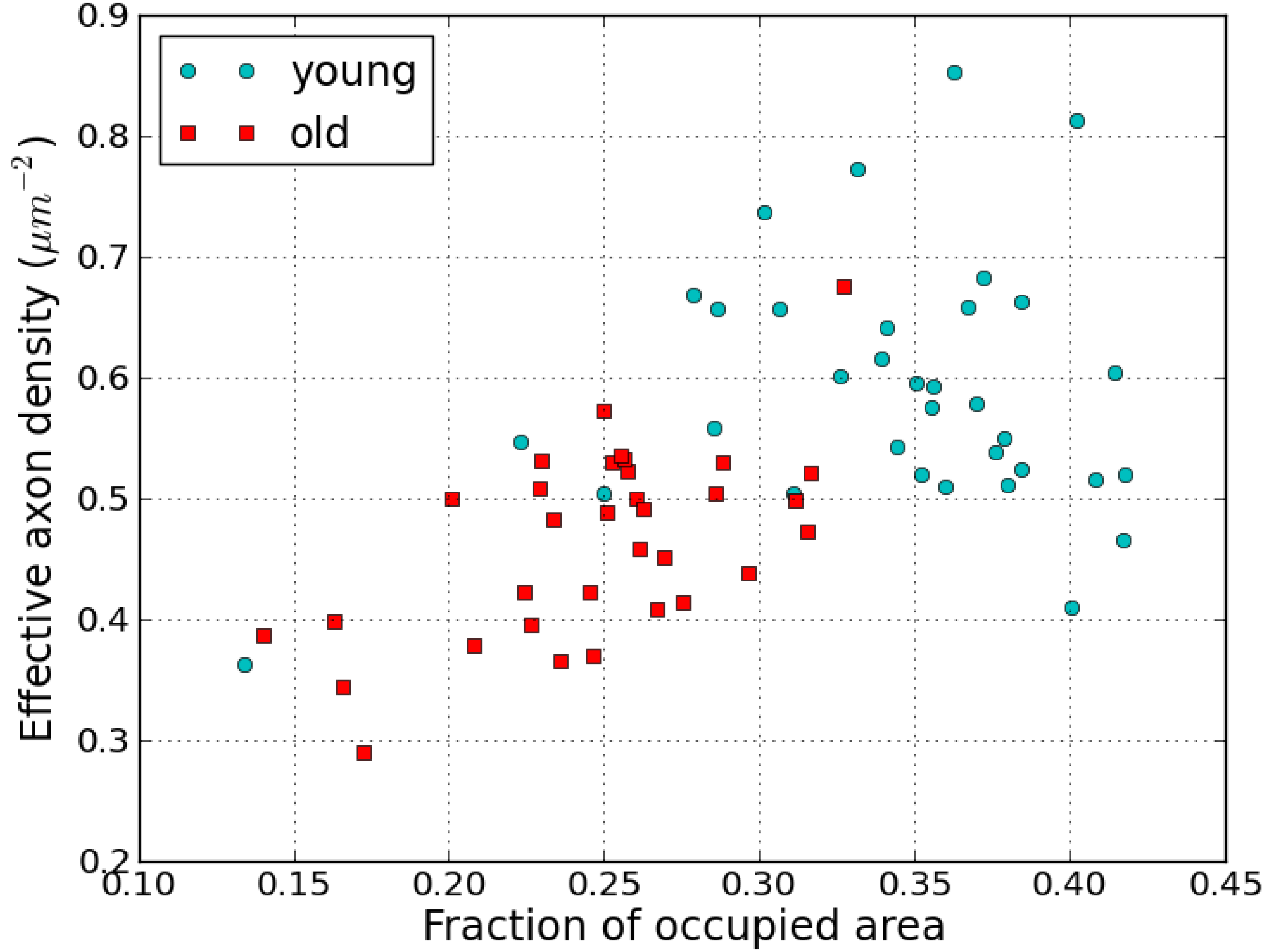
- Myelinated axons have regularity
- Older subjects have more disordered systems
  - Regularity of myelinated axons in the fornix decreases with age

Hypothesis: Loss of regularity is reason for decrease in cognitive functions

Future work

1) Feature selection
   - determine which parameters that, *taken together*, can better separate the 2 age groups
2) Modeling of aging process
   - compare to random cases
3) Study changes in the myelin sheath

1) **Feature Selection**



Taking ONLY these 2 features: 90% accuracy

Questions?