Aging Effects in the Fornix of the Brain

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ref: Comin, Santos *et al.*, Sci. Rep. 4 (2014)

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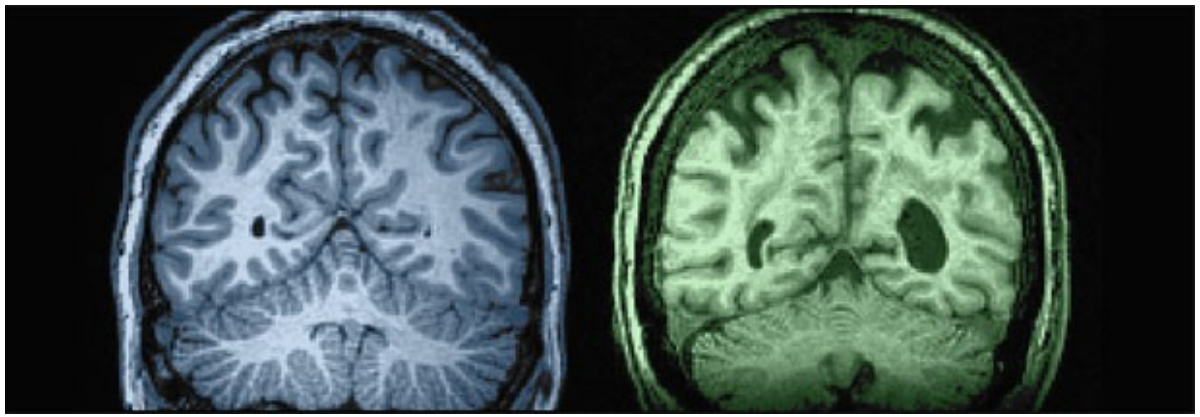
Scientific Question

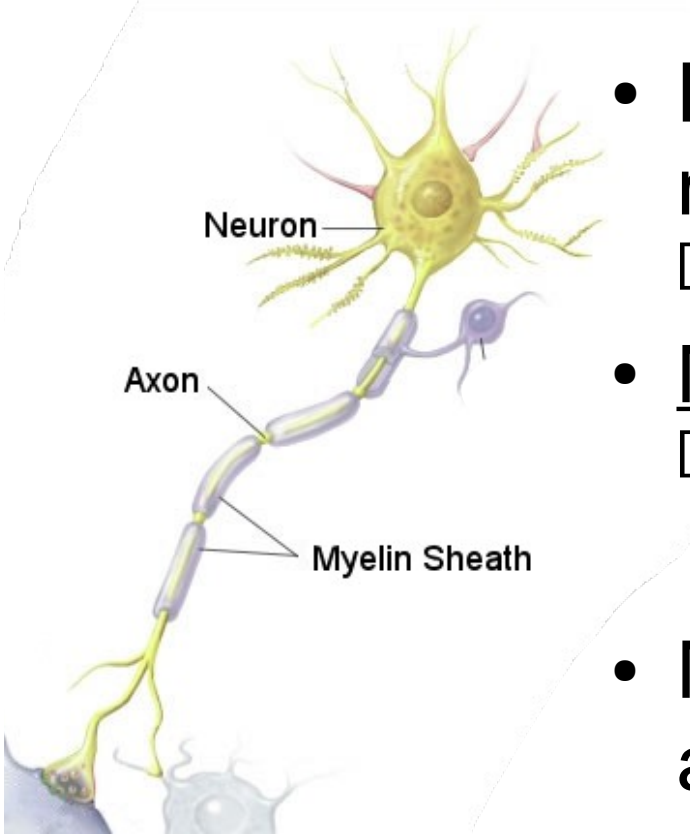
Symptoms of aging are easily recognized



27 year-old 87 year-old

BUT what happens during aging in brains?

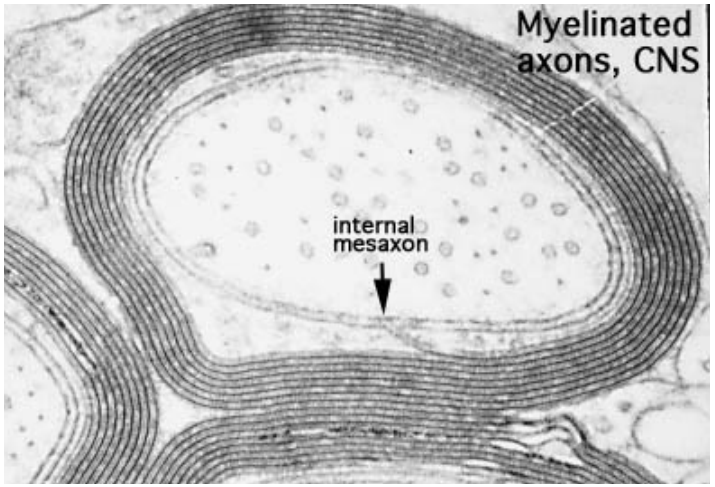
Essential Facts



- No general decrease in number of neurons detected with normal aging
  [Peters *et al.*, Cereb. Cortex **8** (1998)]
- Myelinated axons decrease in number
  [Peters *et al.*, J. Comp. Neurol. **518** (2010)]
  - Little decrease in white matter volume
- Myelin degeneration increases with age [Bowley *et al.*, J. Comp. Neurol. **518** (2010)]

Myelin sheath = insulator

- Higher conduction velocity
- Energy efficiency

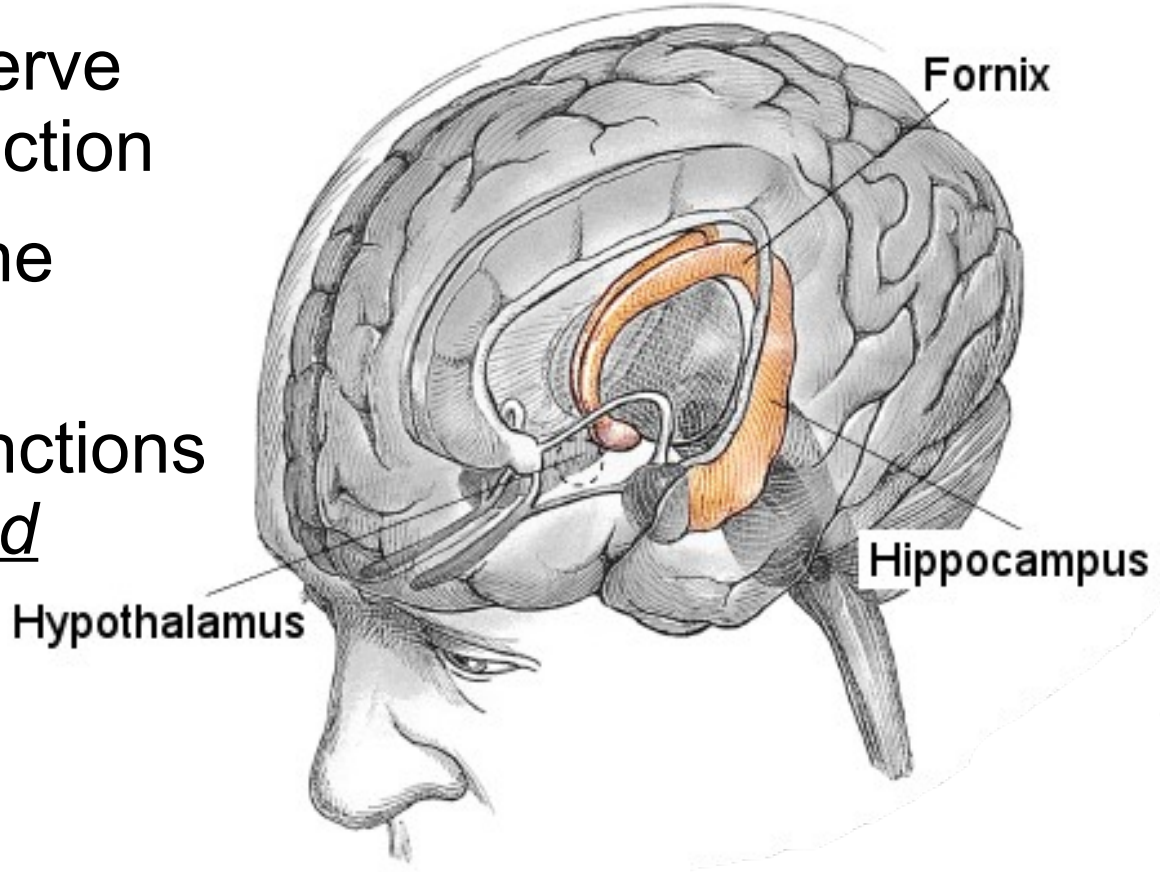


Fornix of the Brain

Why is fornix interesting?

Fornix (latin: *arch)*

- C-shaped bundle of nerve fibers going same direction
- Carries signals from the Hippocampus
- Crucial in cognitive functions (*<u>memory formation and recall</u>*)

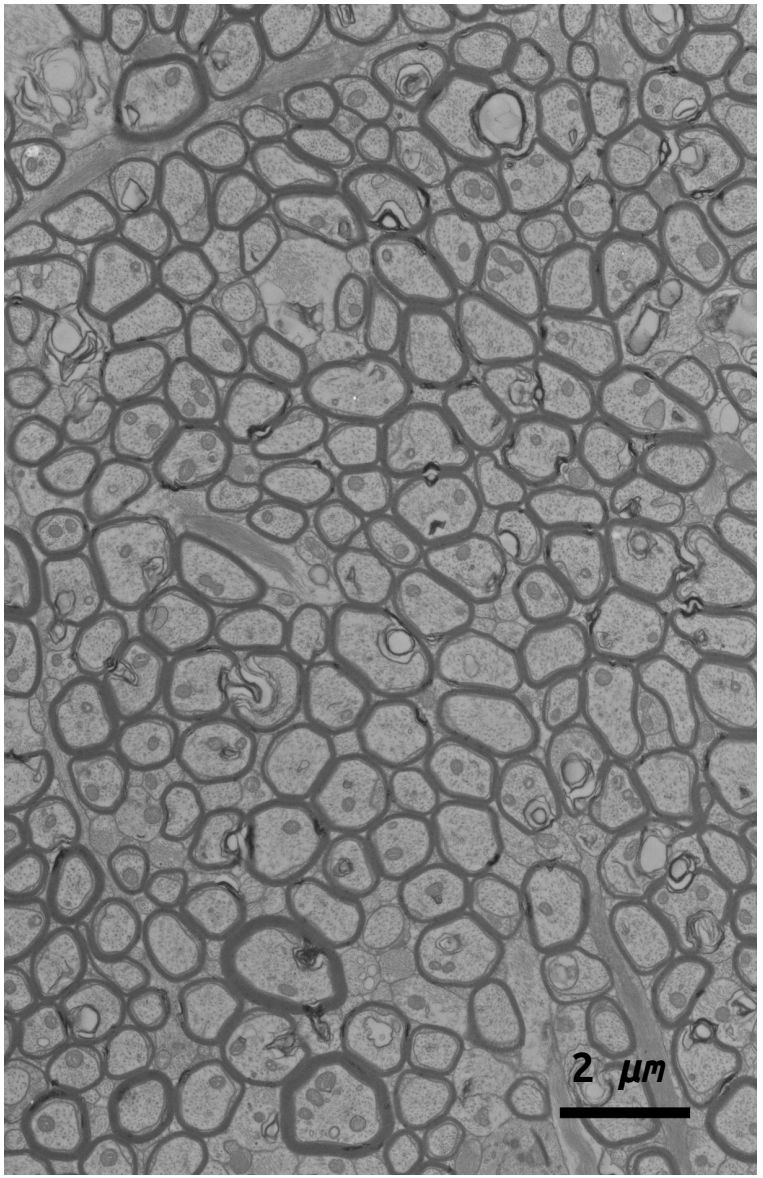


Scientific Question:

Differences in the fornix between young and old subjects?

Subjects

EM image of the Fornix
of a young subject



25 rhesus monkeys

- 14 males & 11 females
- ages from 3.8 to 33.1 years old

(1 monkey year ≈ 3 human years)

328 electron micrographs (EM)

Results

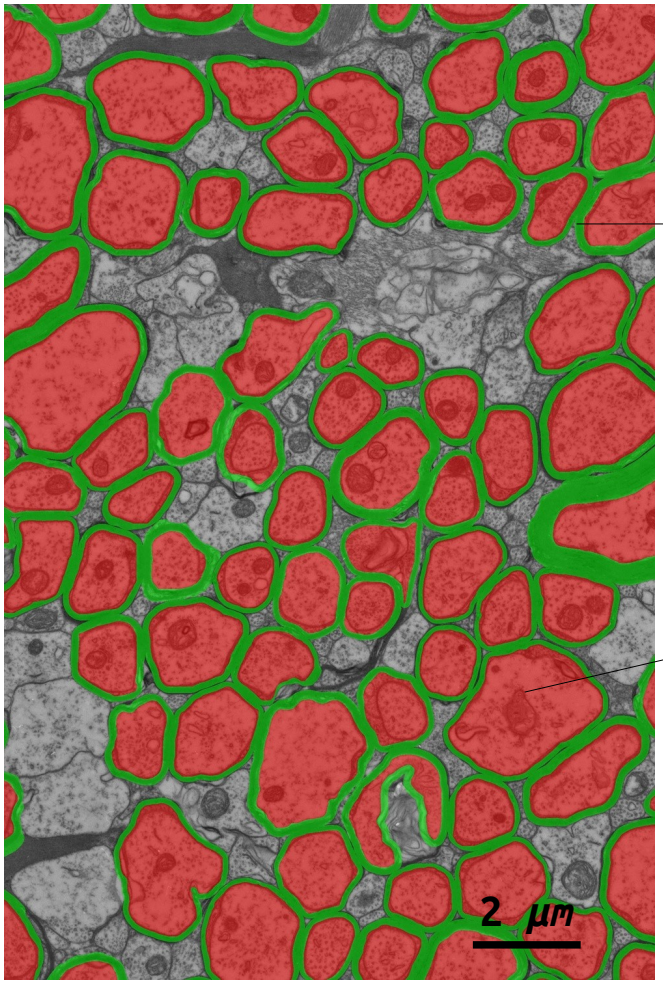
1. ***Axon Recognition Algorithm***
2. Macroscopic Changes with Age
3. Morphological Changes with Age
4. Structural Changes with Age
5. Feature Selection
6. Myelin Sheath

Axon Recognition Algorithm

[Comin, Santos *et al.*, Sci. Rep. **4** (2014)]

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

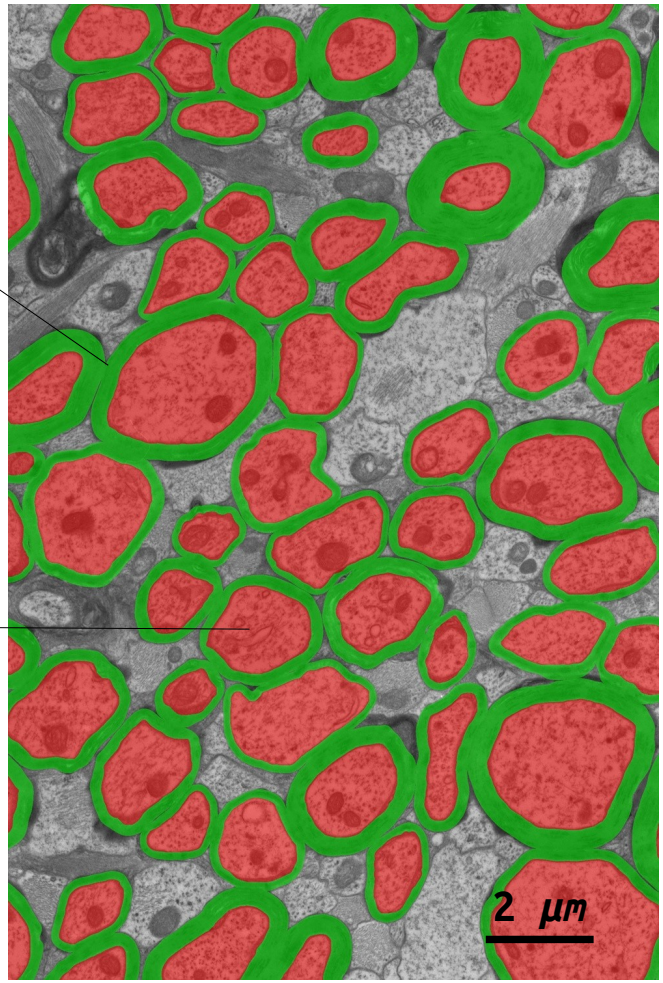
Young subject EM image



Myelin Sheath (green)

Axon (red)

Old subject EM image

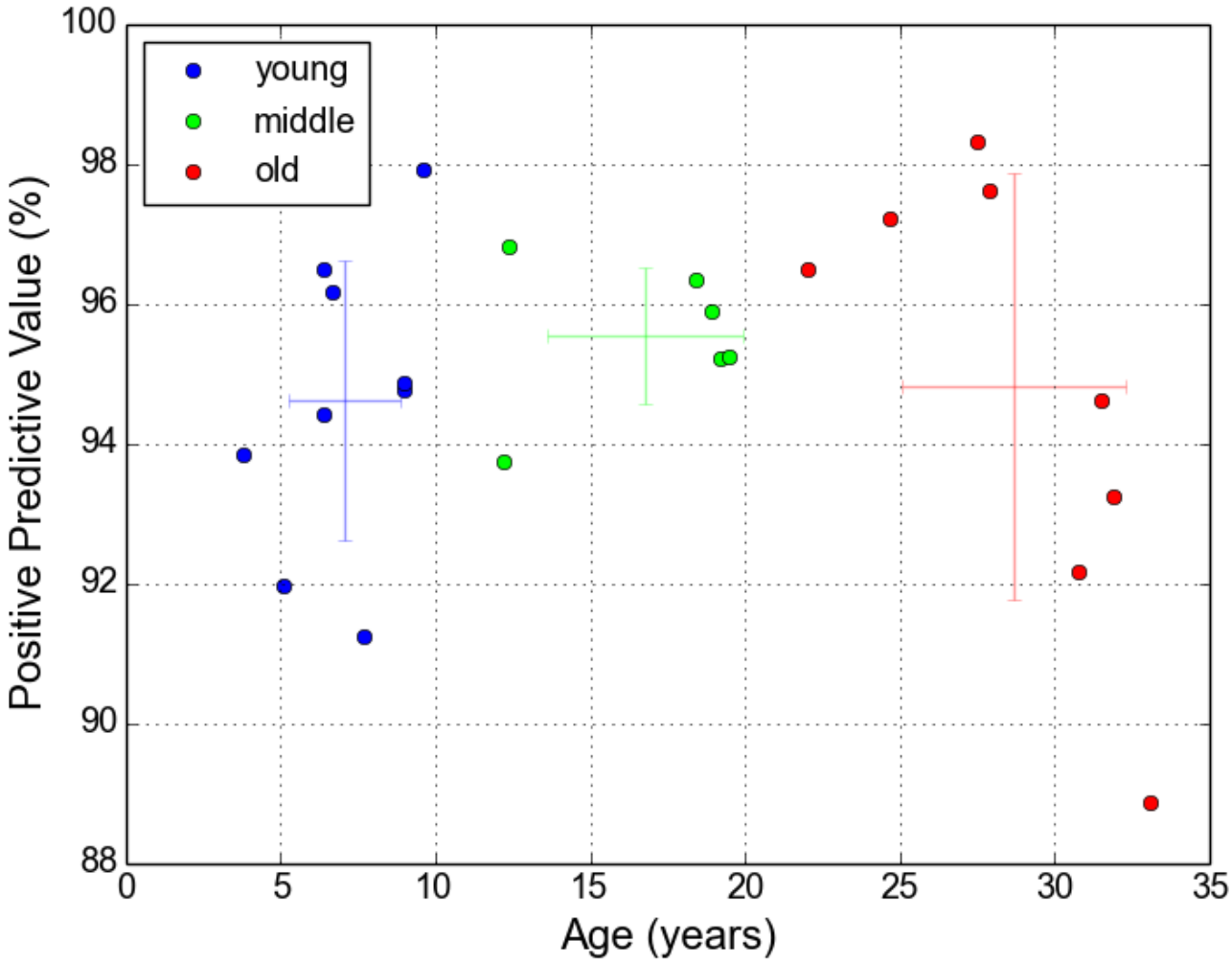


Recognition Rates

Positive Predictive Value (or precision): fraction of recognized axons that are actual axons

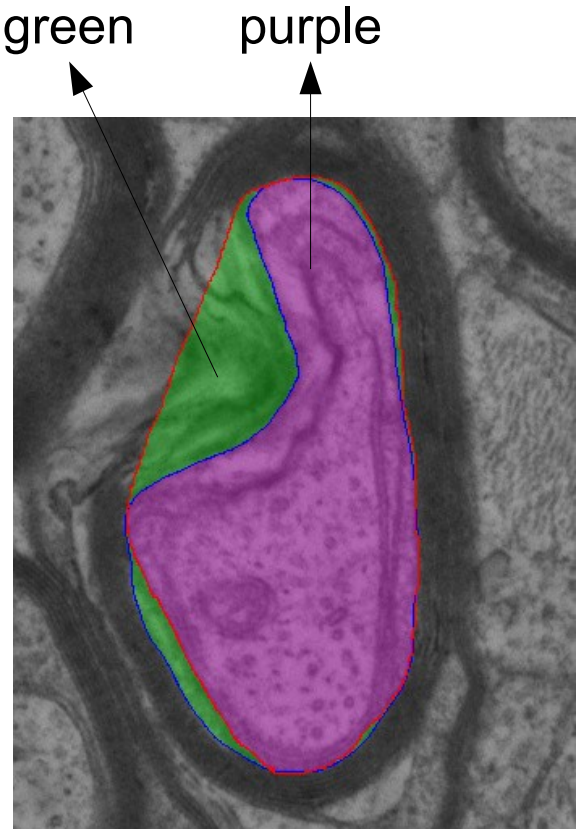
$$\frac{\mathrm{TP}}{\mathrm{TP} + \mathrm{FP}}$$

TP – True Positives
FP – False Positives

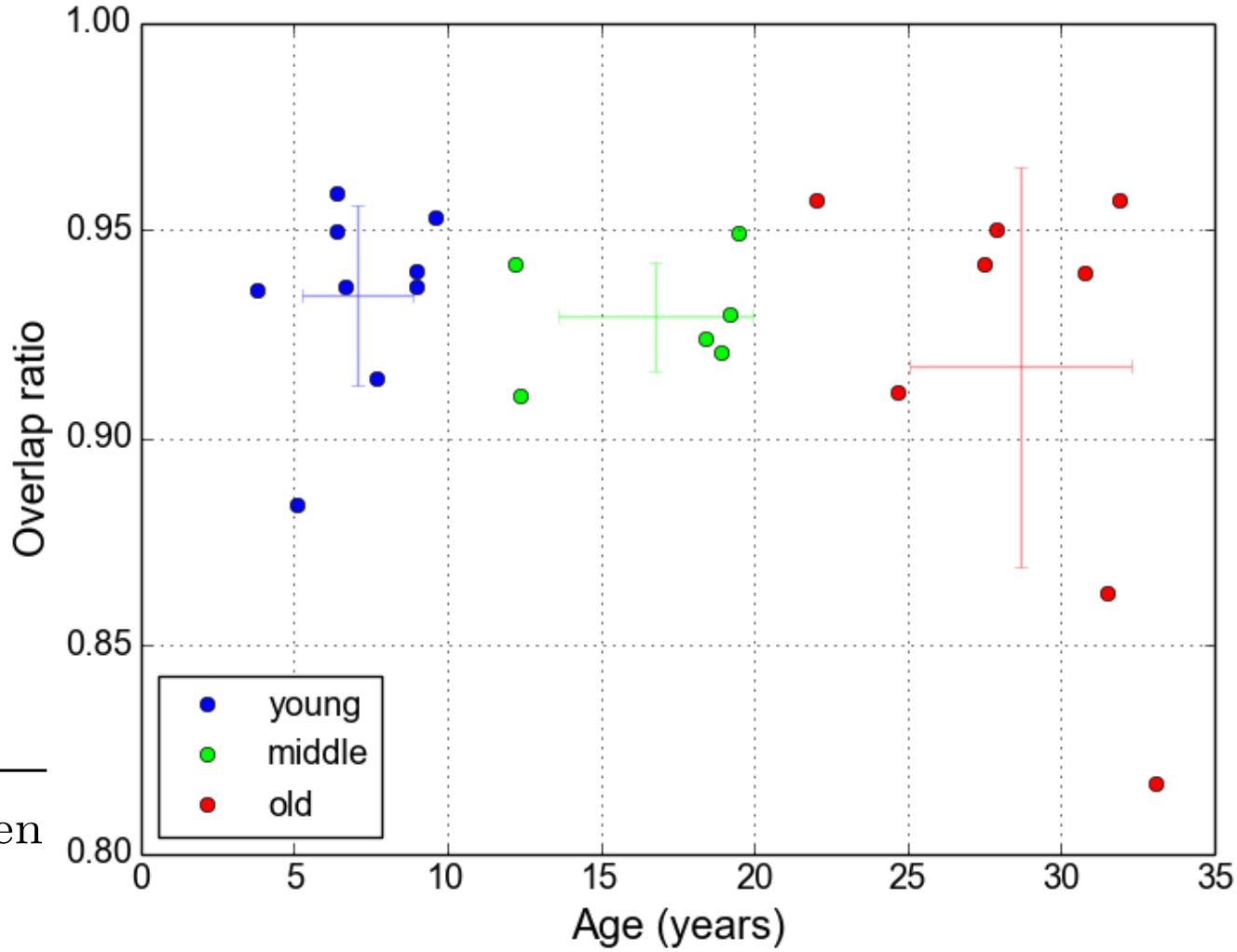


- The recognition rates are similar for all age groups

Overlap Ratio



$$\text{ratio} = \frac{A_{\text{purple}}}{A_{\text{purple}} + A_{\text{green}}}$$

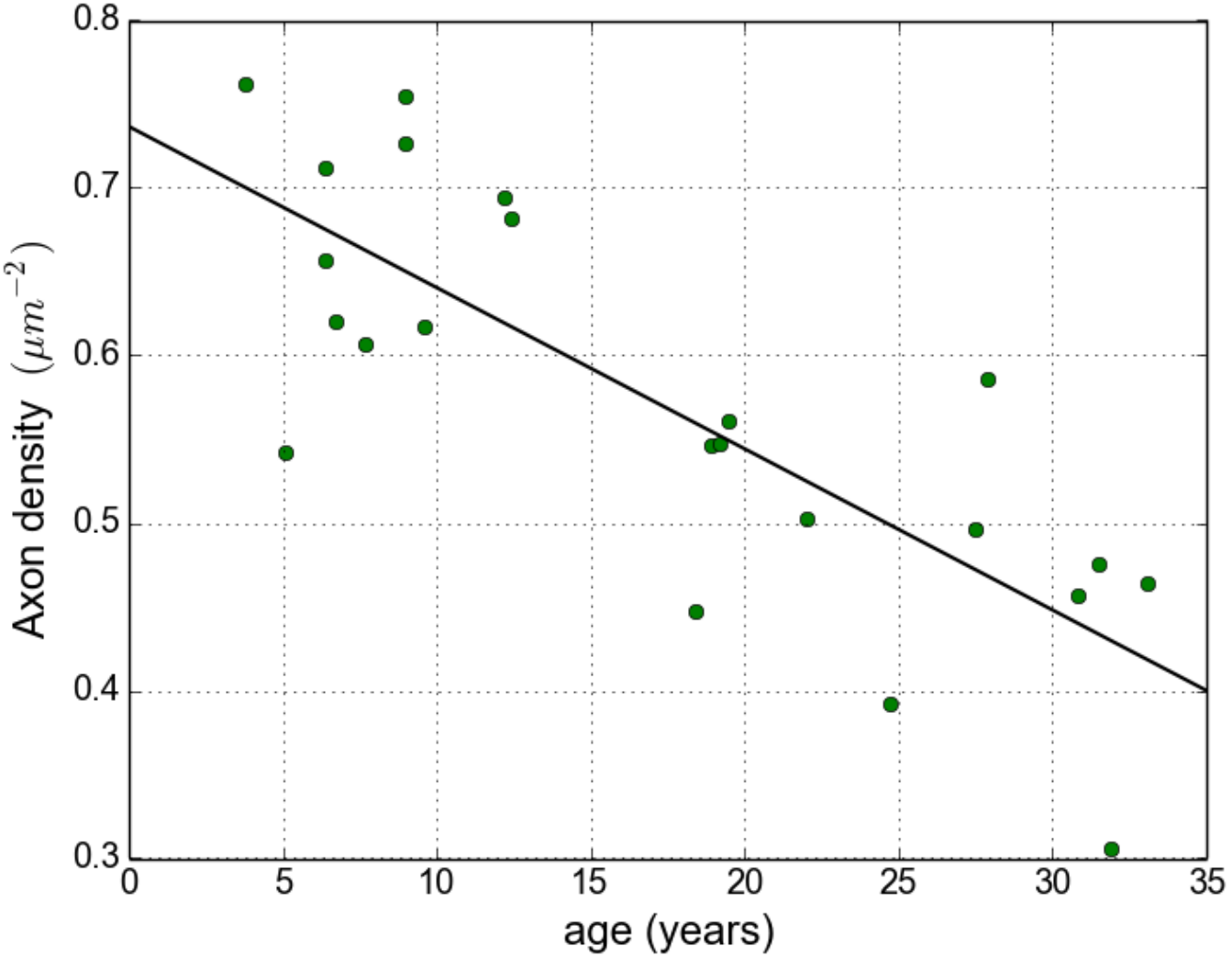


- The overlap ratios for the algorithm are similar to the overlap ratios between 2 humans

Results

1. Axon Recognition Algorithm
2. ***Macroscopic Changes with Age***
   - **a) Axon Density**
3. Morphological Changes with Age
4. Structural Changes with Age
5. Feature Selection
6. Myelin Sheath

Myelinated Axon Density

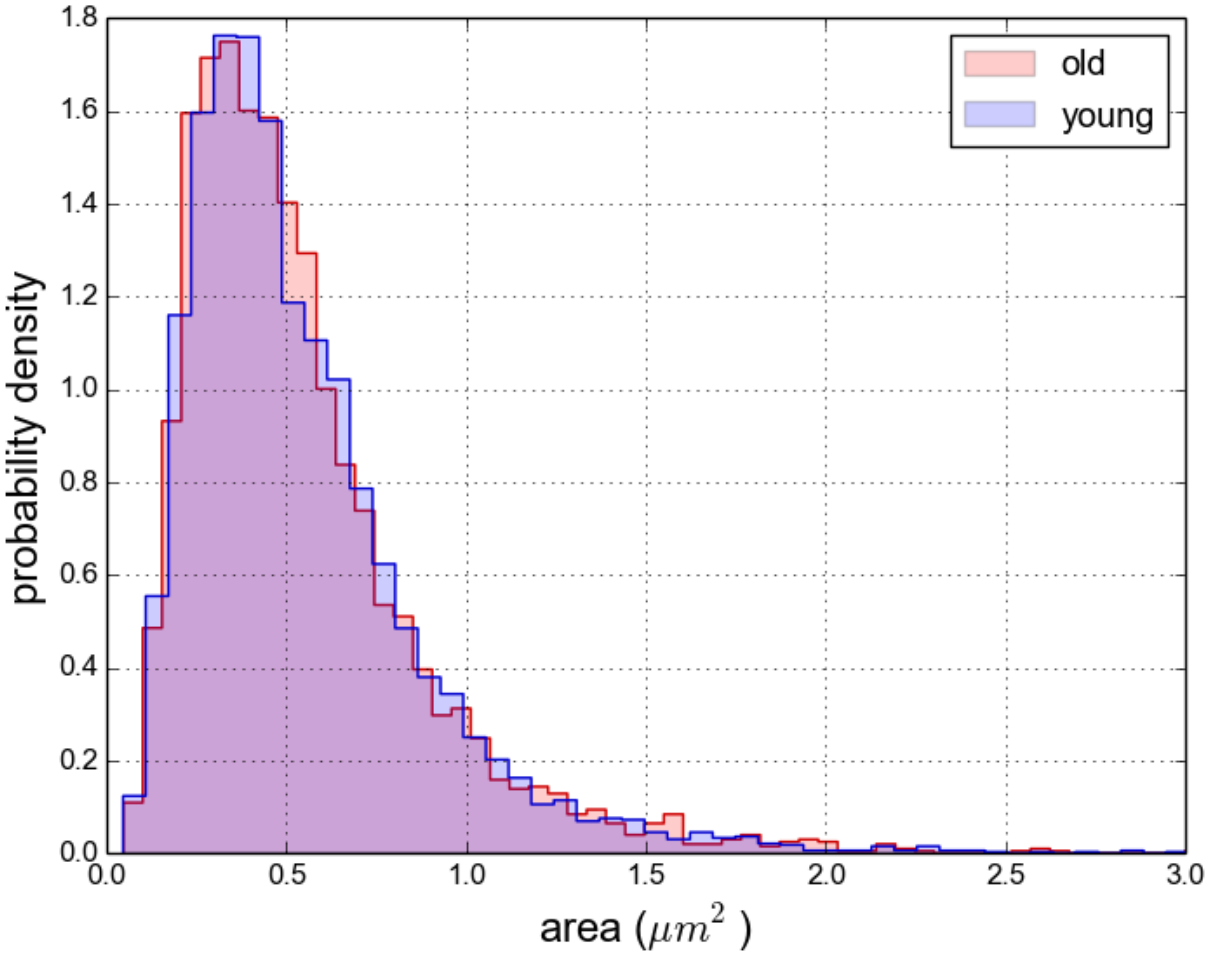


- Axon density decreases with age
- Myelinated axons lost with age

Results

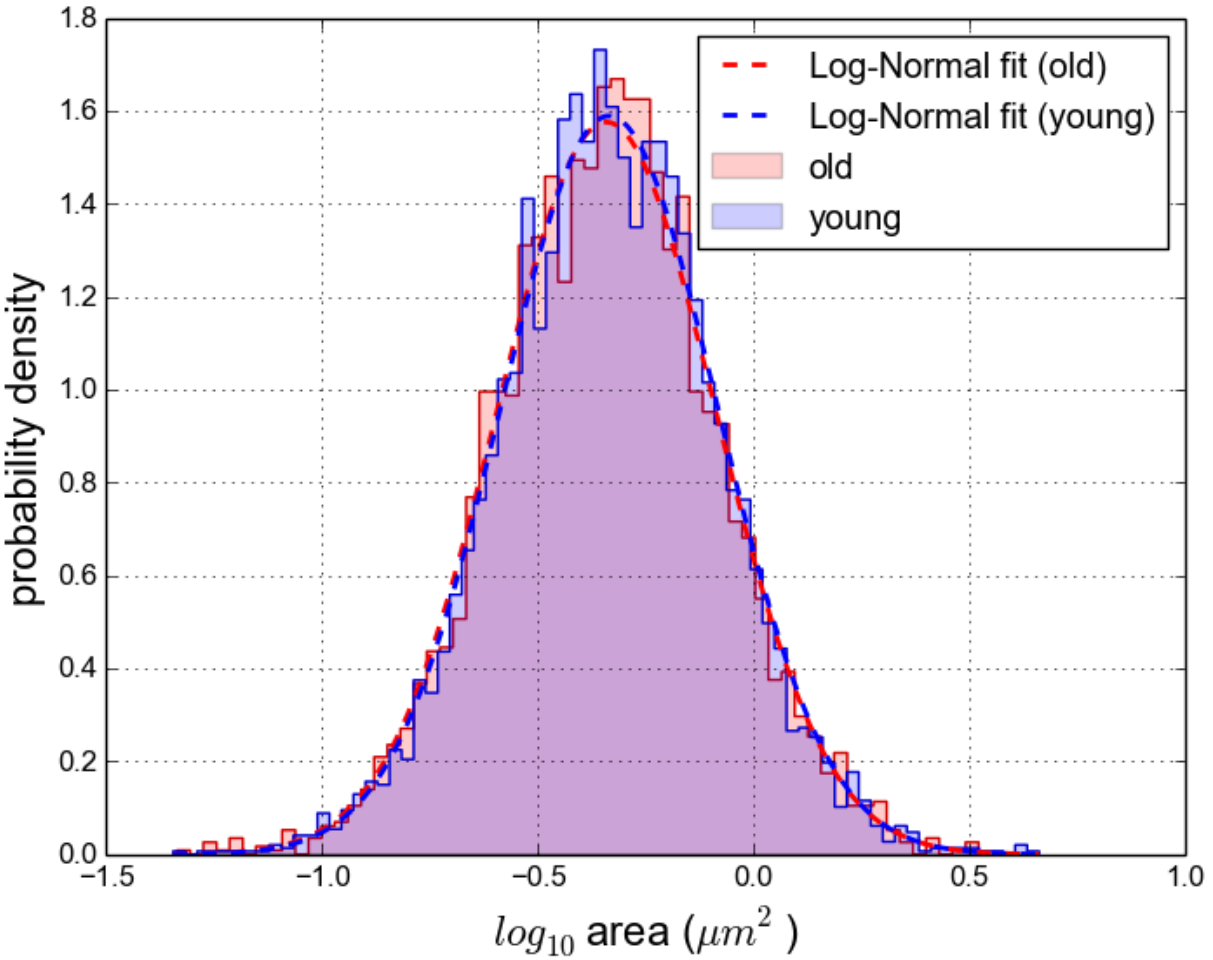
1. Axon Recognition Algorithm
2. Macroscopic Changes with Age
3. ***Morphological Changes with Age***
   - **a) Axon Area**
4. Structural Changes with Age
5. Feature Selection
6. Myelin Sheath

Axon Area Distribution



- Same axon area distribution for young and old
- Myelinated axons lost independently of their areas

Axon Area Distribution



→ Log scale

- Axon area distribution is heavy-tailed
  - Matches a Log-Normal distribution
- Hypothesis: stochastic geometric growth of axons?

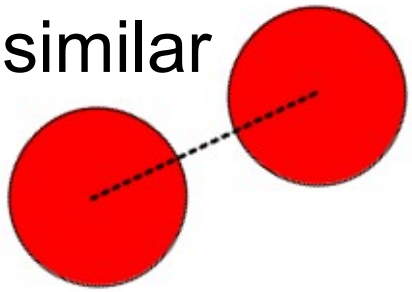
Results

1. Axon Recognition Algorithm
2. Macroscopic Changes with Age
3. Morphological Changes with Age
4. ***Structural Changes with Age***
    a) **Axon Area Correlations**
5. Feature Selection
6. Myelin Sheath

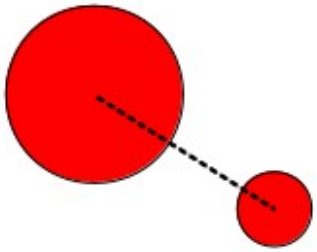
Axon Area Autocorrelation

Measure similarity of axon areas in function of distance:

- Autocorrelation > 0 → axon areas are similar

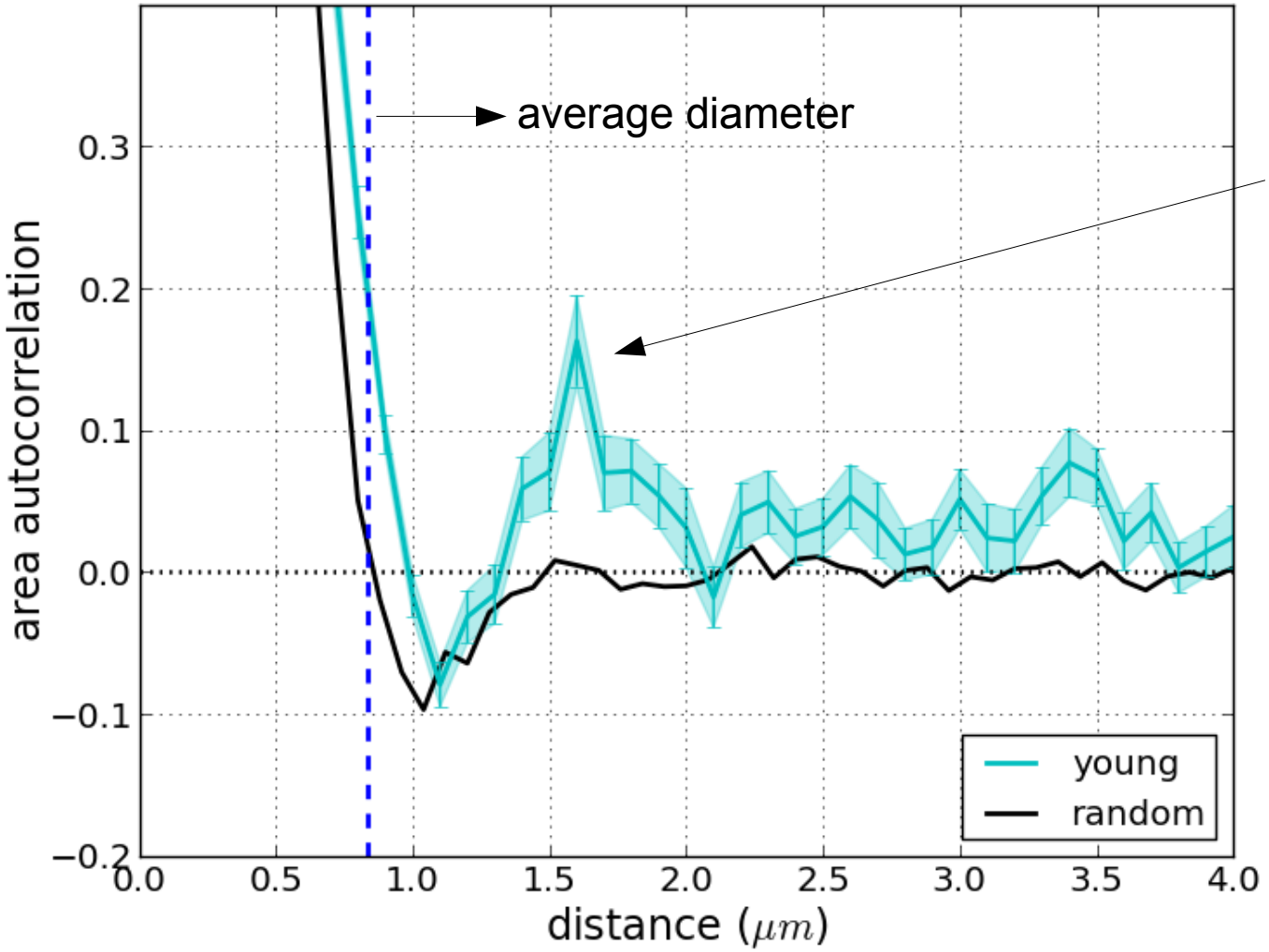


- Autocorrelation < 0 → axons have different areas



Axon Area Autocorrelation

(i) young subjects



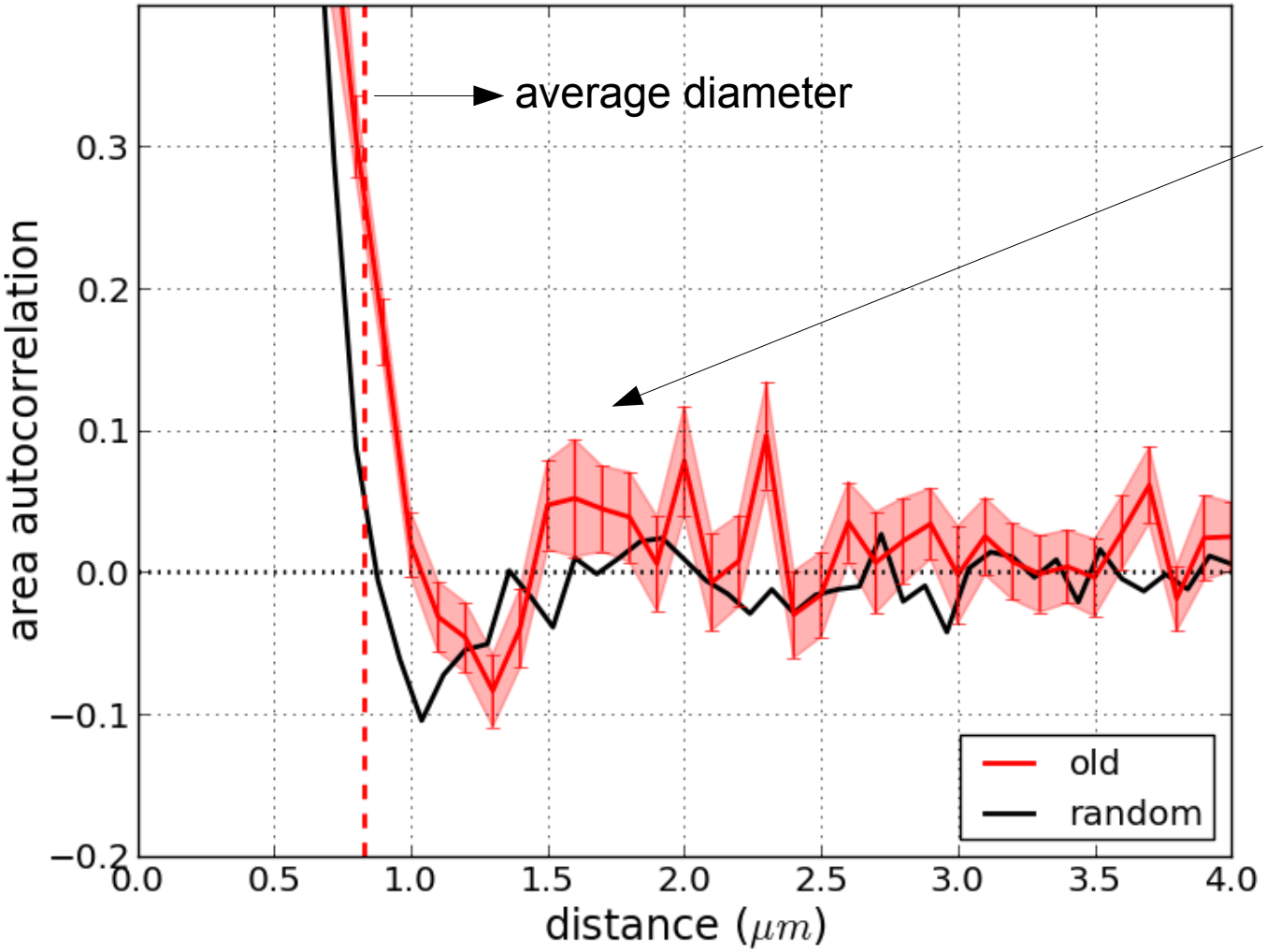
higher than random case

no long-range correlation

Axons with similar areas are clustered

Axon Area Autocorrelation

(ii) old subjects



lower peak compared to young plot

no long-range correlation

No clustering of axons with similar areas

Results

1. Axon Recognition Algorithm
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5. ***Feature Selection***
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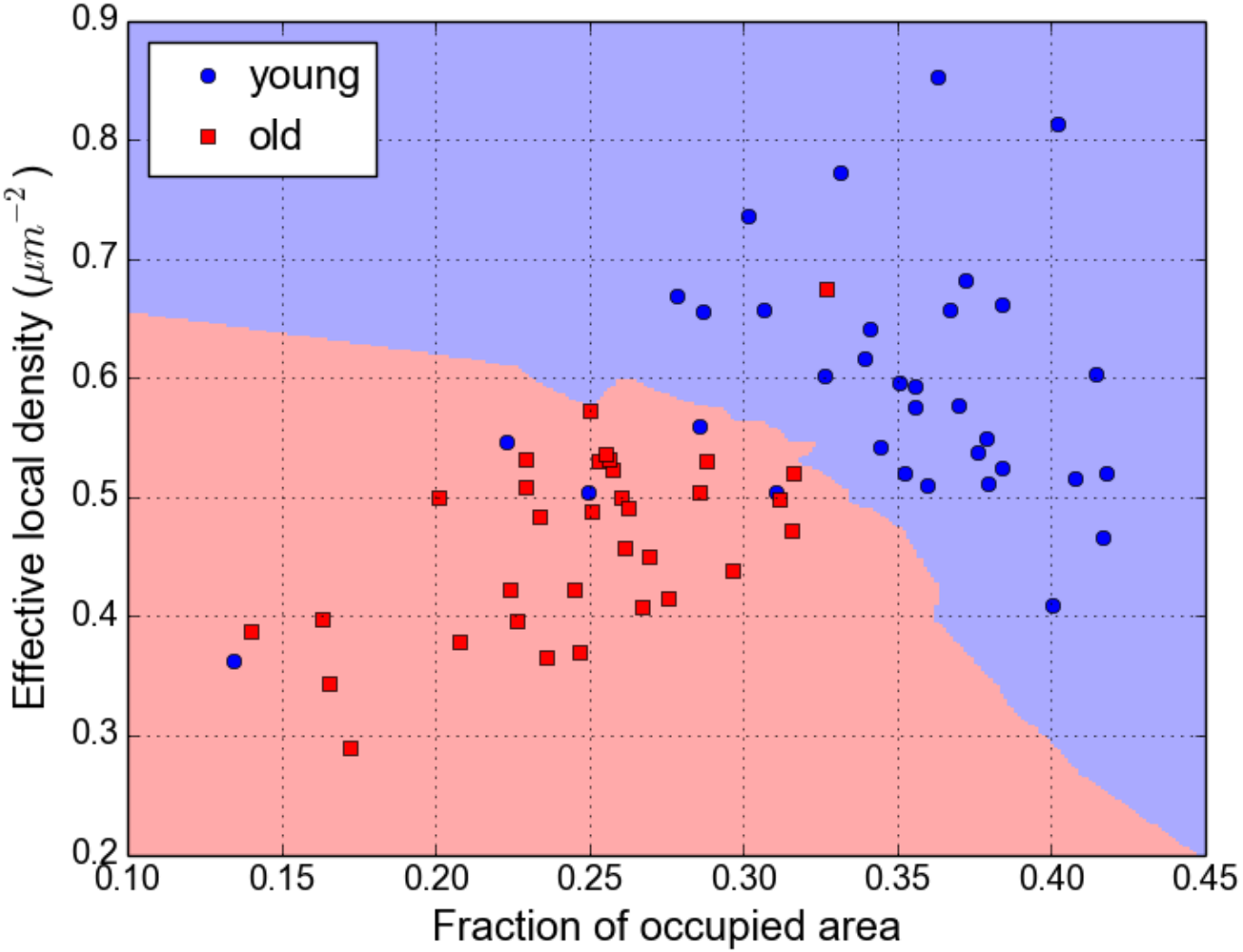
Feature Selection

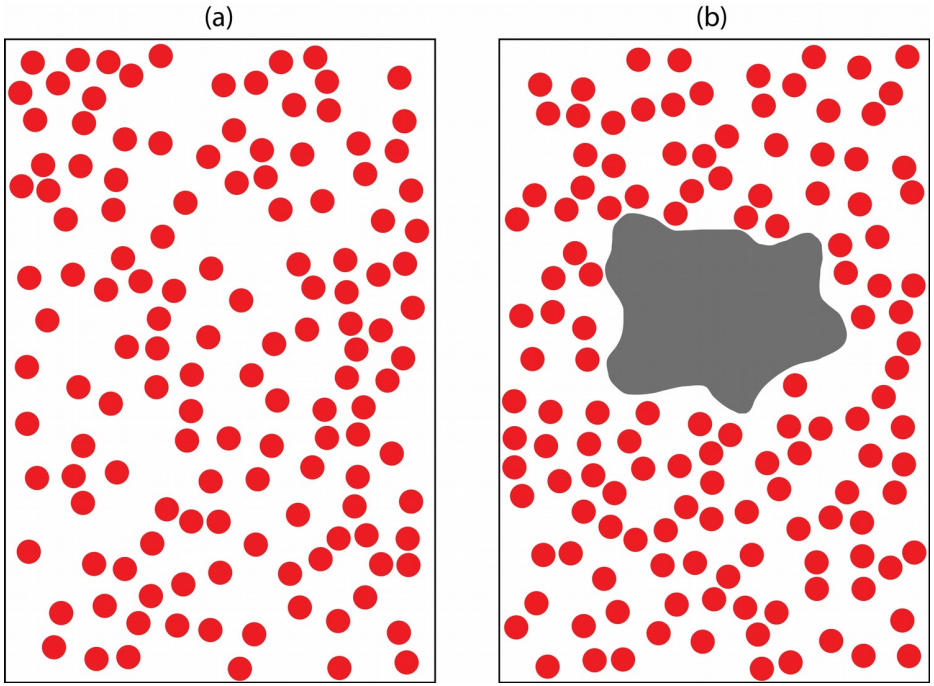
[Comin, Santos *et al.*, Sci. Rep. **4** (2014)]

Effective local density around axons (measured from nearest neighbor distances)



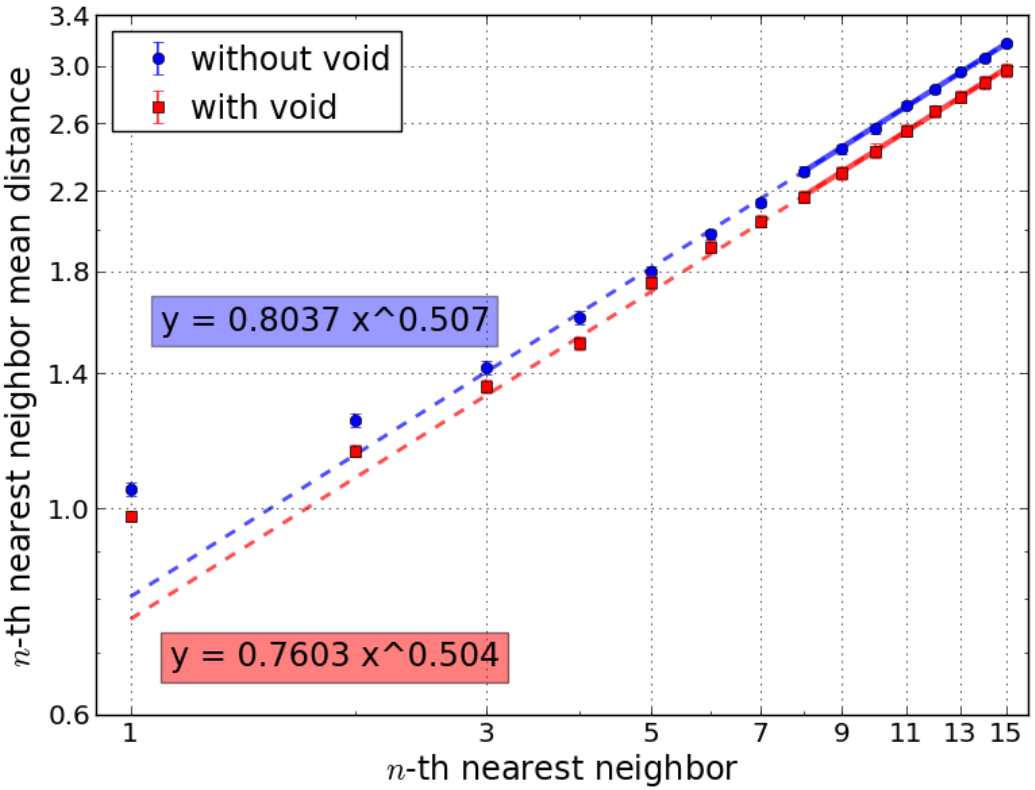
Taking ONLY these 2 features:
90% accuracy of images

Effective Local Density



$\rho = 0.50$ $\rho = 0.50$

$\rho_{eff} = 0.49$ $\rho_{eff} = 0.55$



- Effective Local Density is a better age discriminant than the actual axon density

Results

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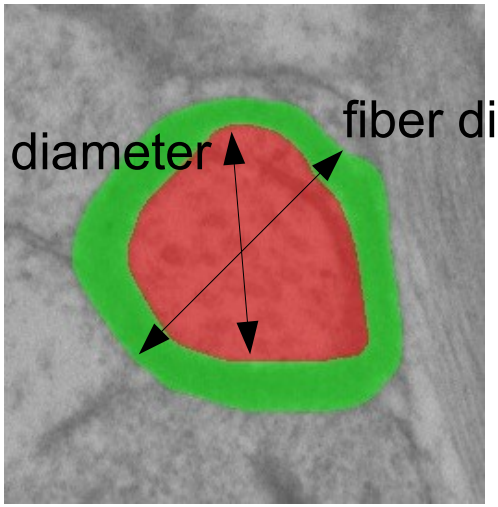
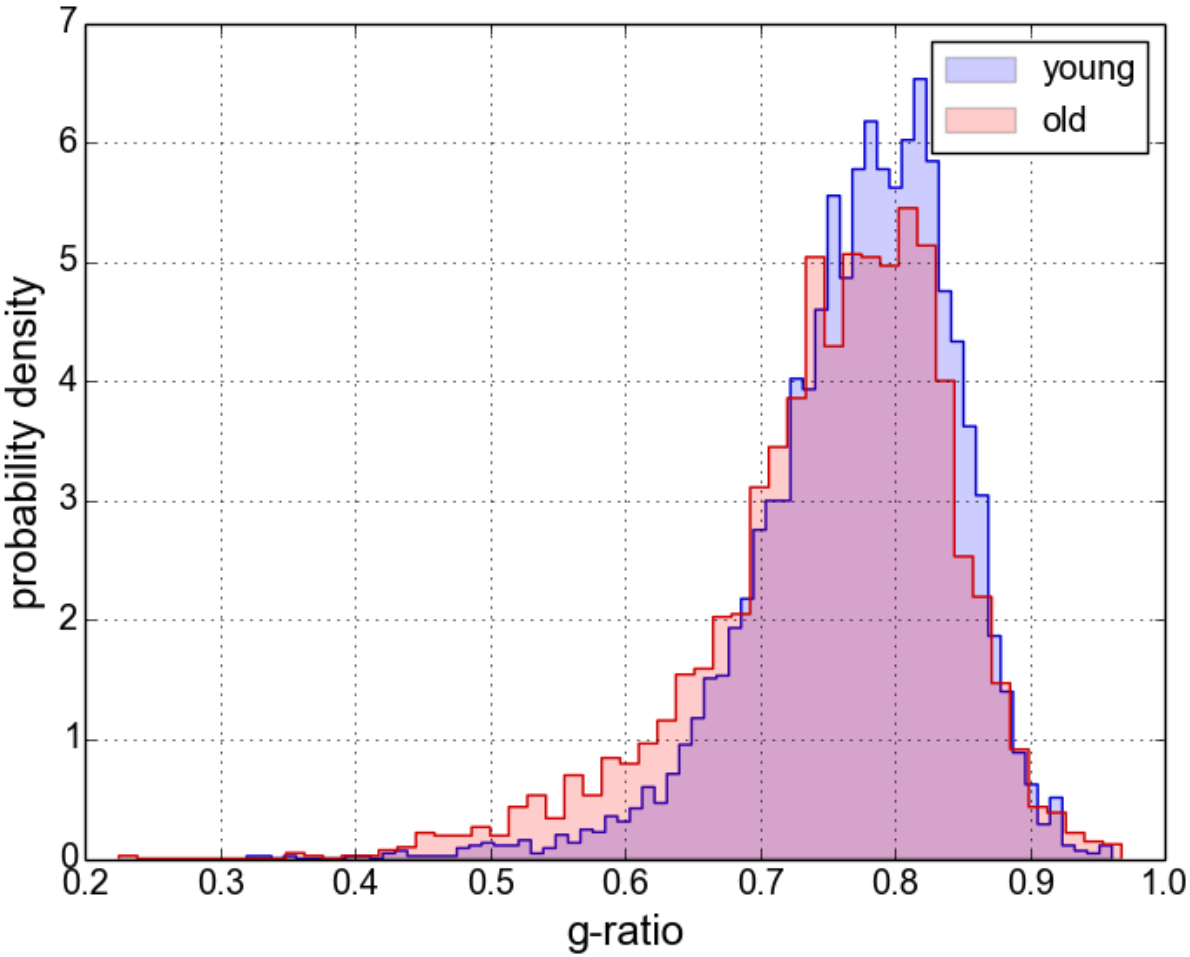
Myelin Sheath

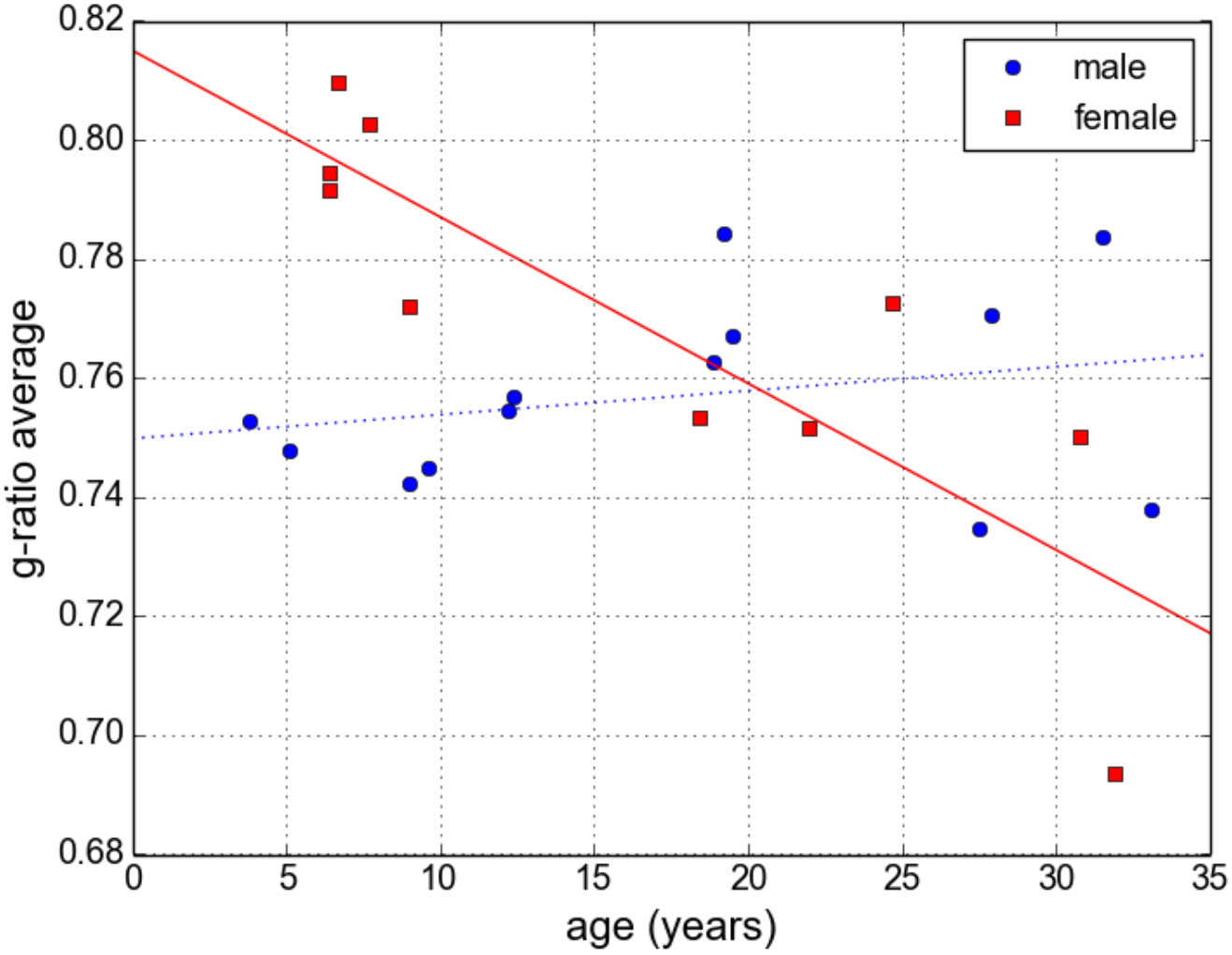


$$\text{g-ratio} = \frac{\text{axon diameter}}{\text{fiber diameter}}$$



- The distribution of g-ratio values is relatively identical for each image of a particular subject

G-ratio dependence with age



- G-ratio depends on sex & age

Conclusions

- Myelinated axons are lost with age
  - This process happens independently of the axons area
- Myelinated axons in fornix have regularity
  - Older subjects have a more disordered fornix
- Simple random axon loss does not explain age differences
- The g-ratio (axon to fiber diameter) depends on the sex of the subjects

Current Work

1) Myelin Sheath properties with age
2) Expansion of feature selection to include myelin data
   - determine which parameters that, *taken together*, can better separate the two age groups
3) Model of aging process
   - compare to random cases

Acknowledgements

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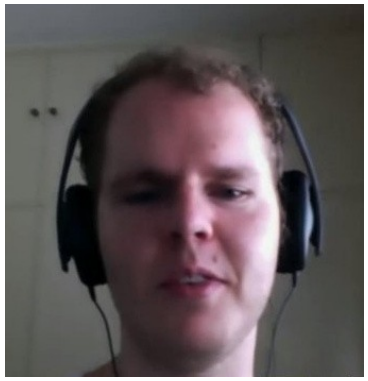

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Universidade de São Paulo

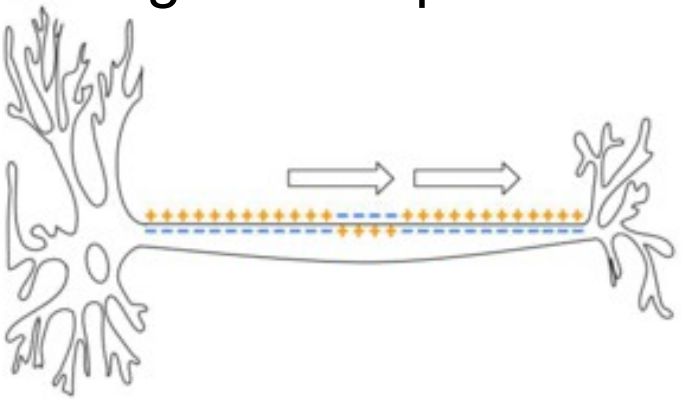
Thank you!

Questions?

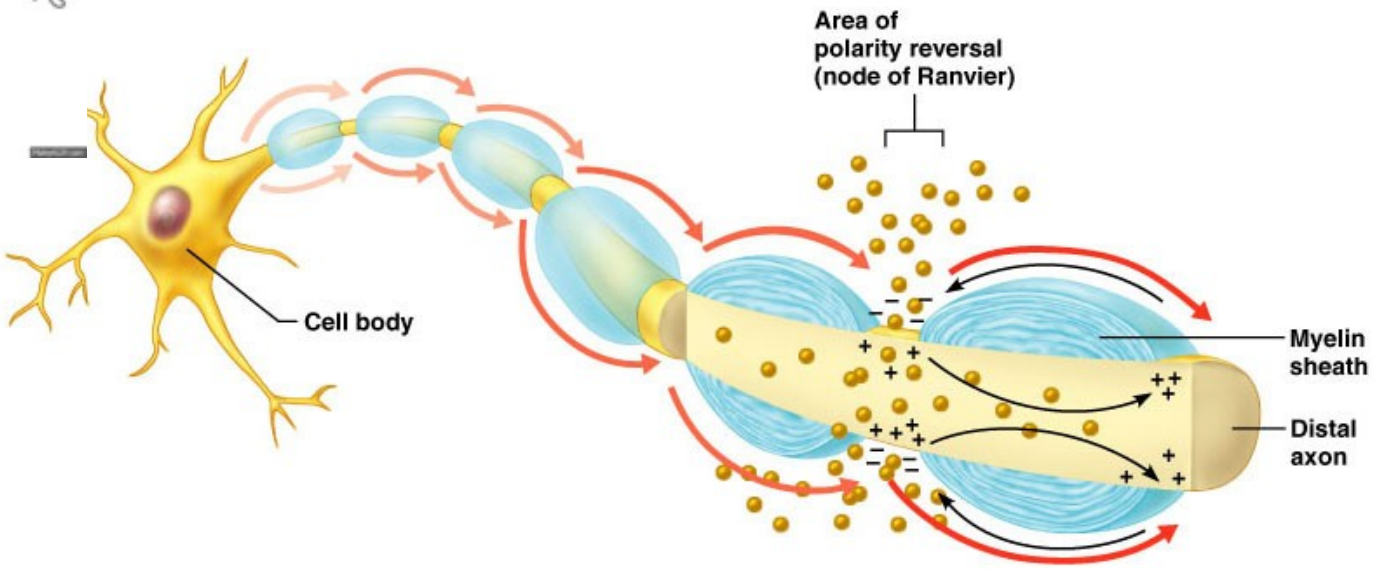
Conduction in Axons

- Axons are projections of neurons conducting electrical signals

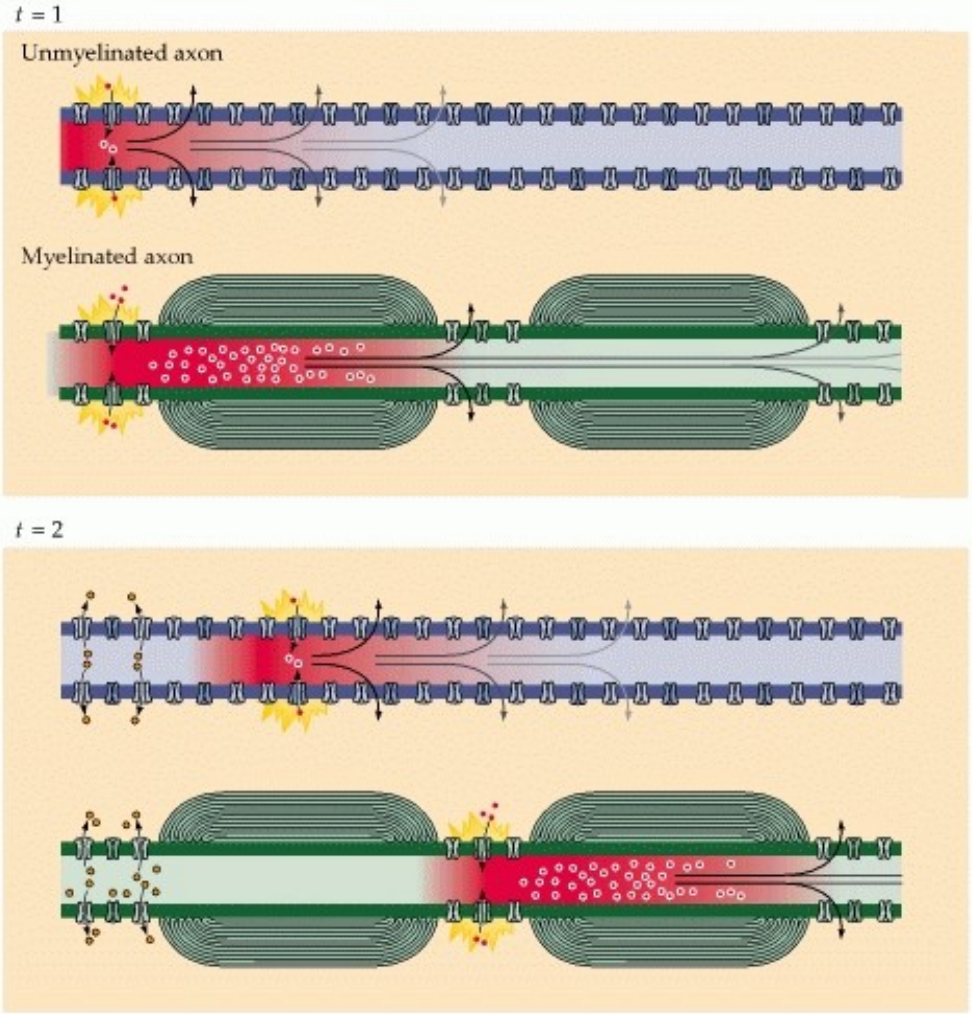
Signals travel in unmyelinated axons through action potentials

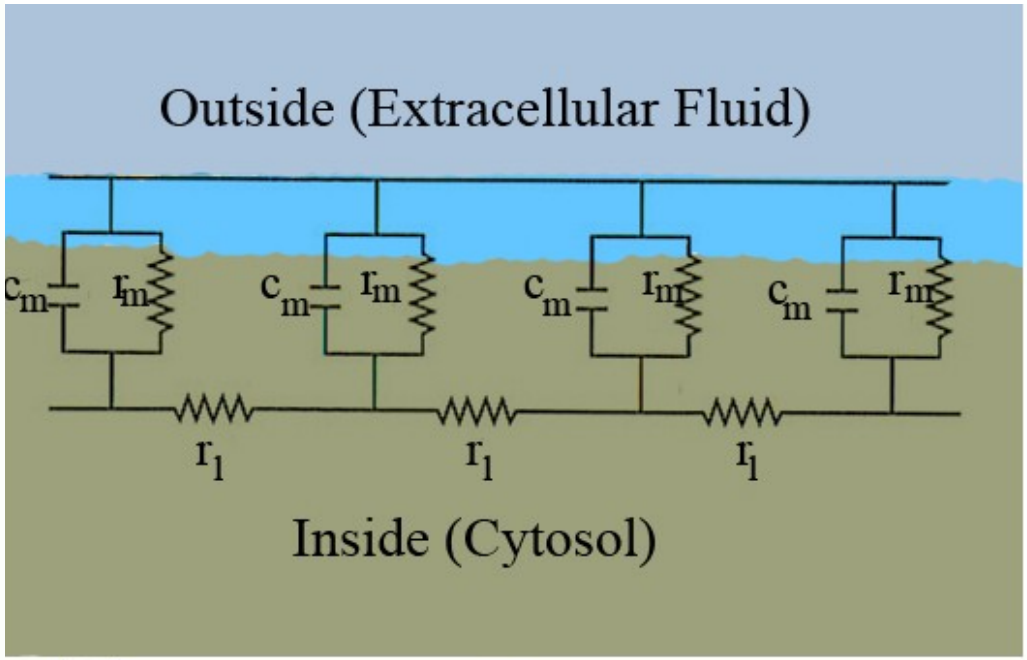


In myelinated axons, the conduction occurs through saltatory conduction



Conduction in Axons

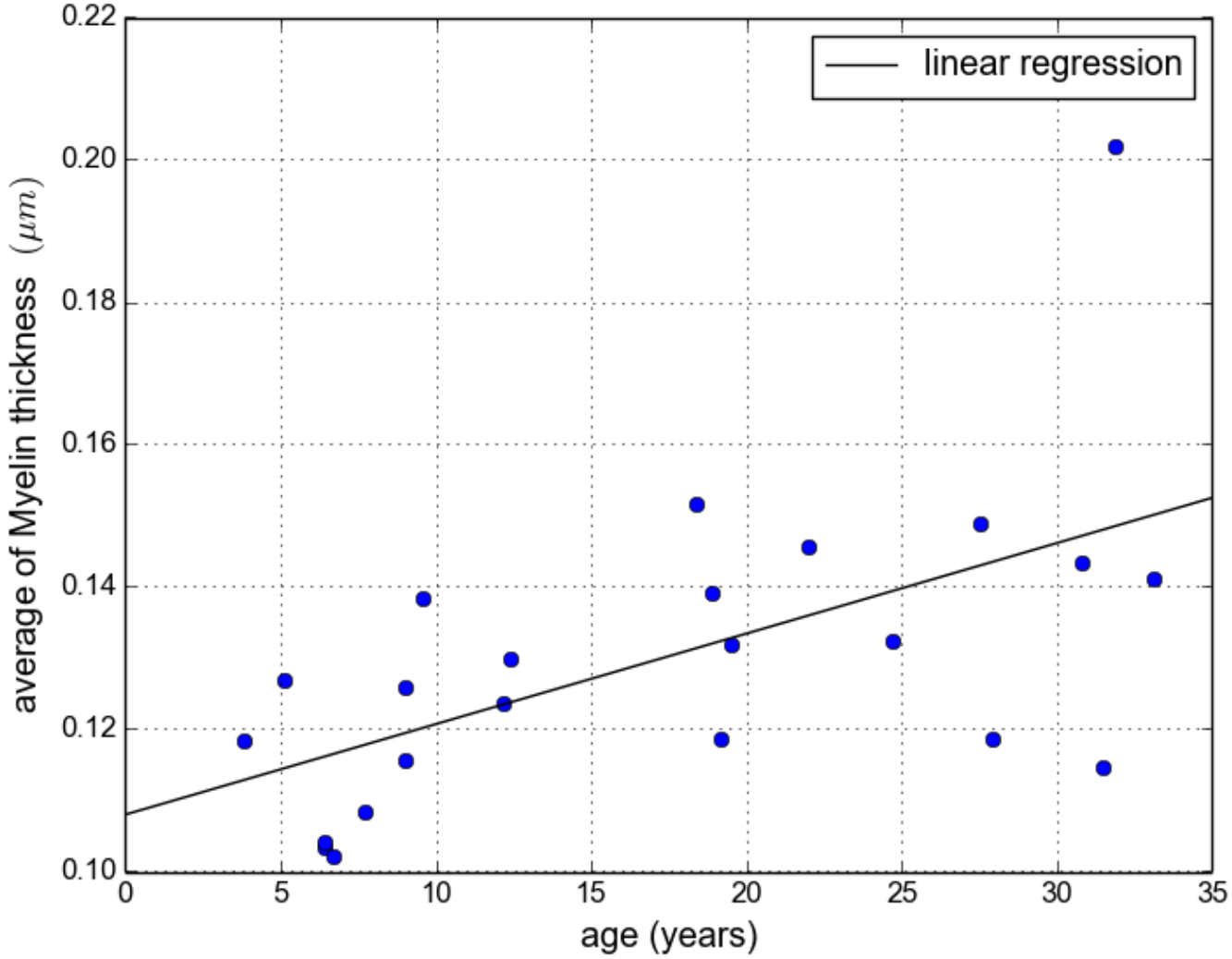




r_m: Membrane resistance
r_l : Longitudinal resistance
c_m: Capacitance due to electrostatic forces

- Myelin sheath advantages:
  - Higher conduction velocity
  - Energy efficiency

Myelin Thickness



- Myelin sheath thickness increases with age