Aging Effects in the Fornix of the Brain

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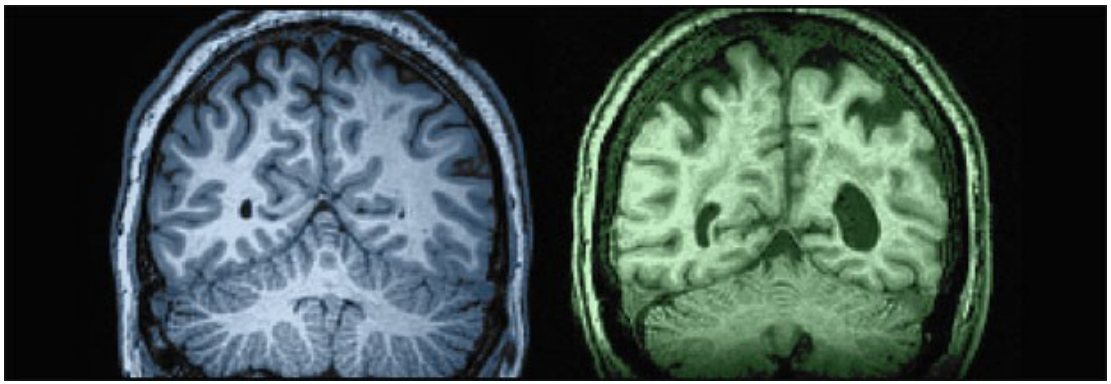
Scientific Question

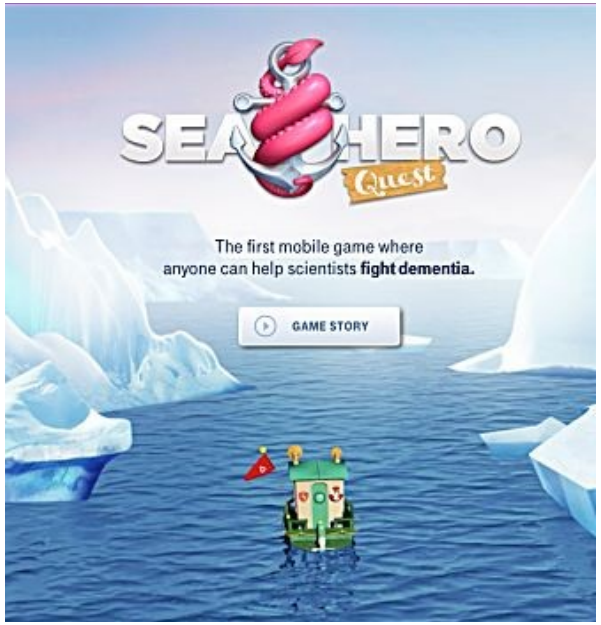
How to quantify aging?
And aging effects?



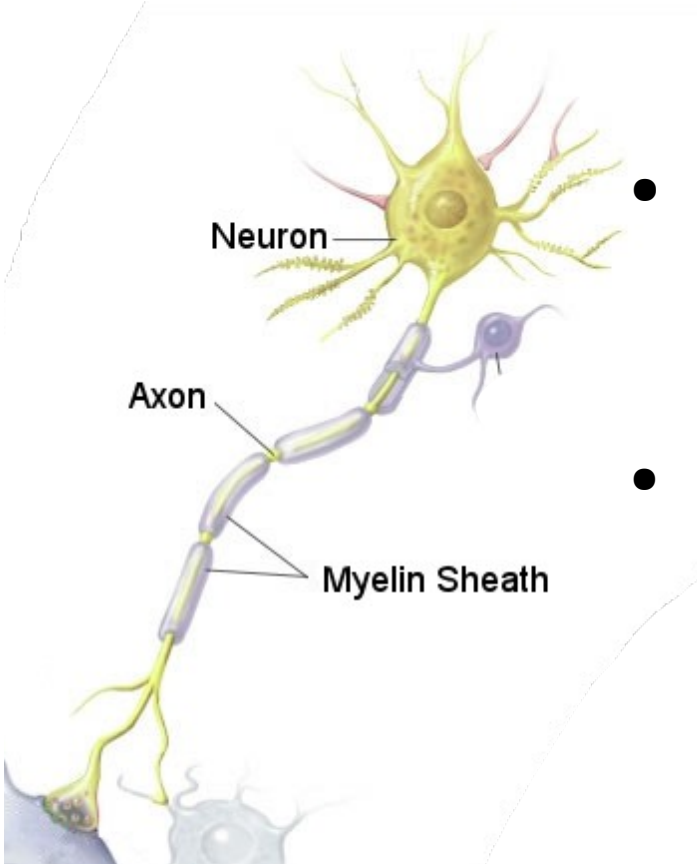
27 year-old

87 year-old

What changes occur in the brain during aging?



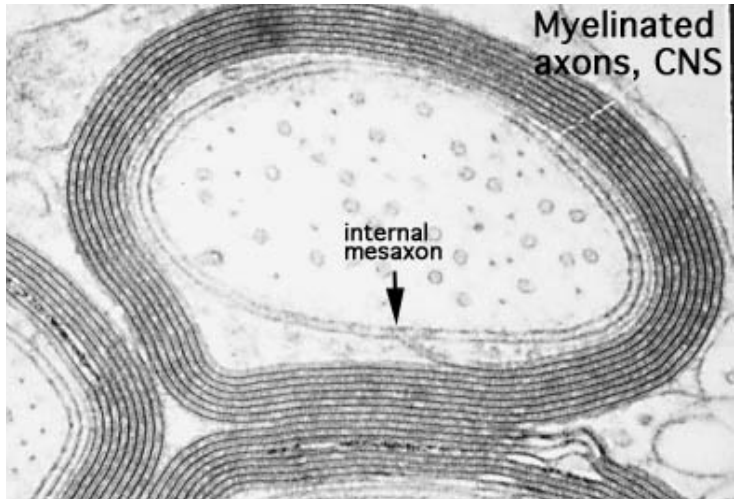
Essential Facts



- 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 sheath = insulator

- Higher conduction velocity
- Energy efficiency

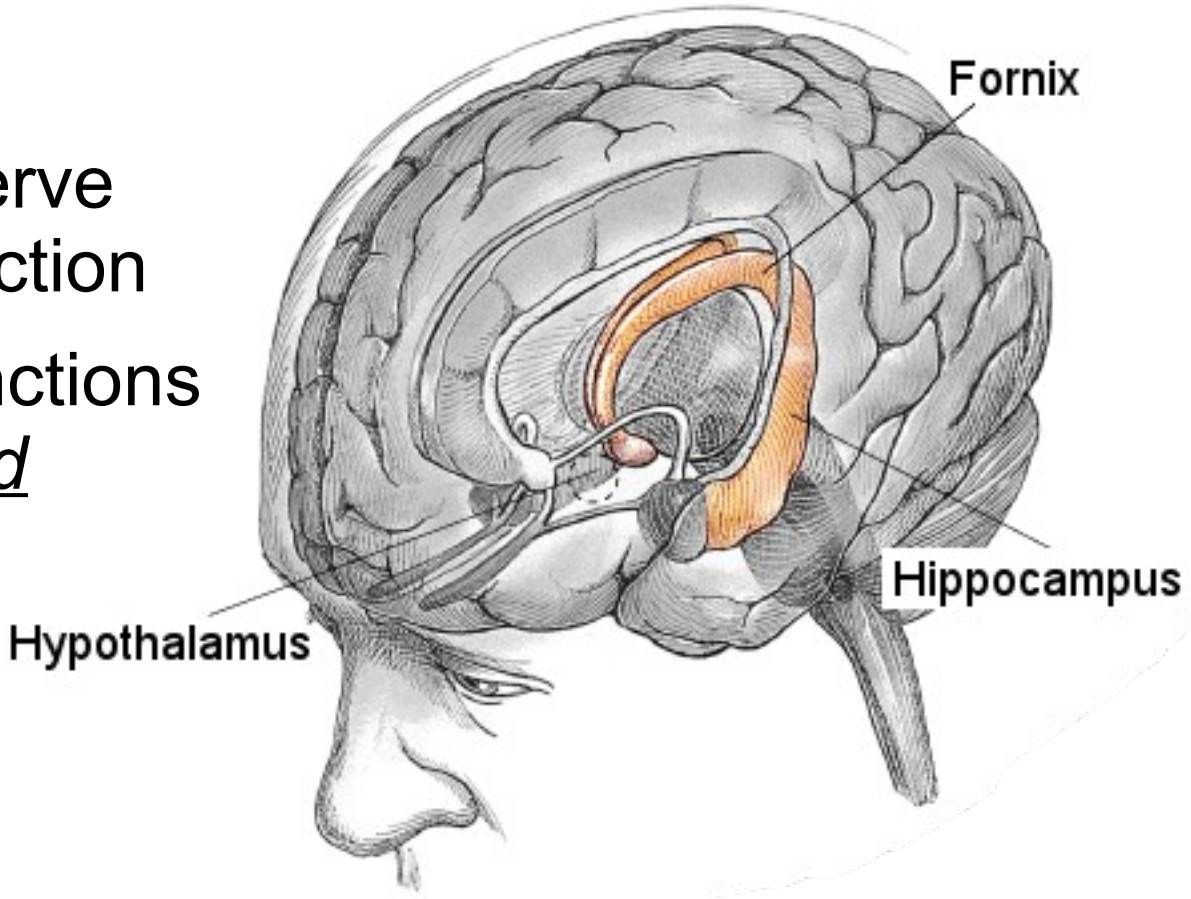


Fornix of the Brain

Why is fornix interesting?

Fornix

- C-shaped bundle of nerve fibers going same direction
- Crucial in cognitive functions (*memory formation and recall*)



Differences in the fornix between young and old subjects?

Subjects

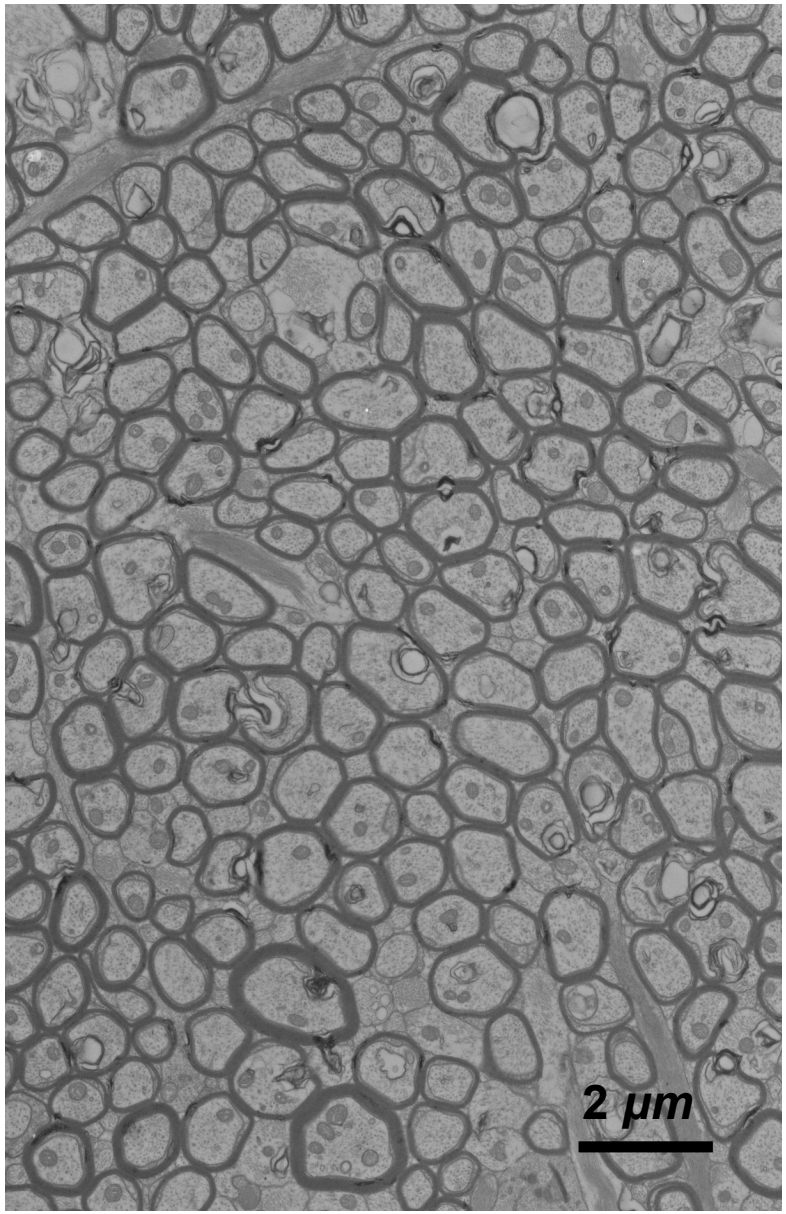
25 rhesus monkeys

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

(1 monkey year ≈ 3 human years)

328 electron micrographs (EM) from Dr. Peters collection

EM image of the Fornix of a young subject



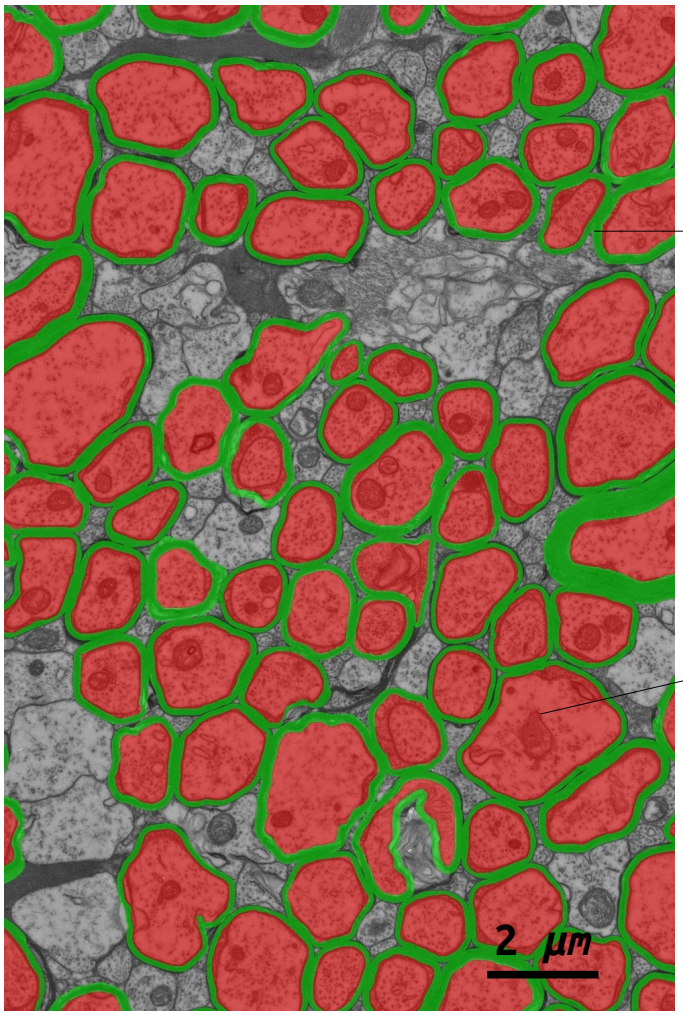
Results

1. ***Axon Recognition Algorithm***
2. Macroscopic Properties
3. Morphological Properties
4. Myelin Sheath Properties
5. Structural Properties
6. Feature Selection in Young vs. Old

Axon Recognition Algorithm

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

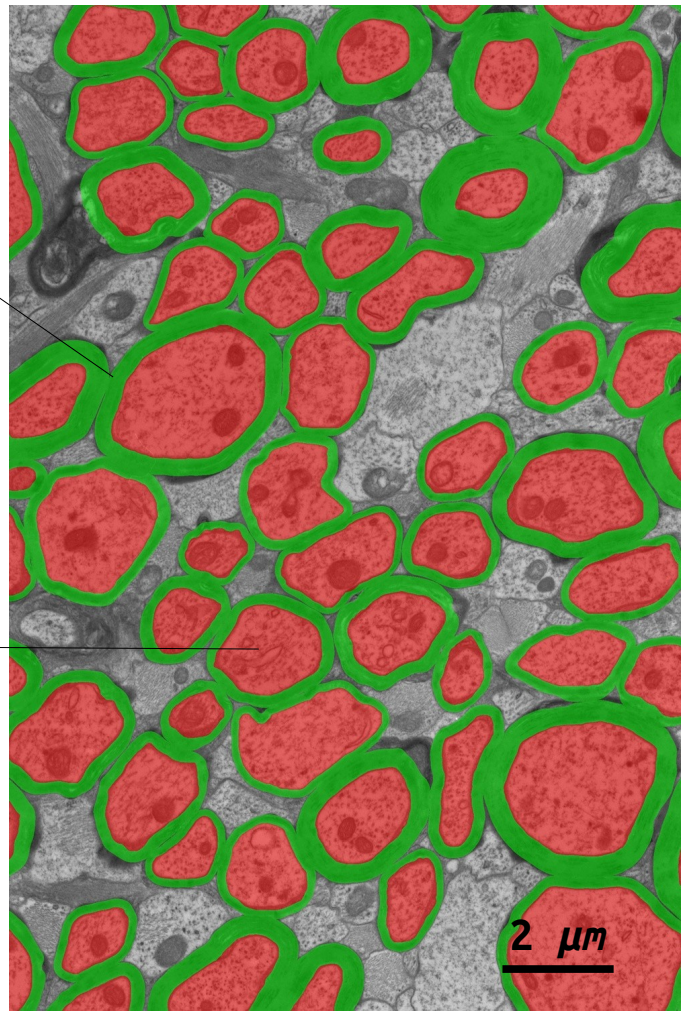
Young subject EM image



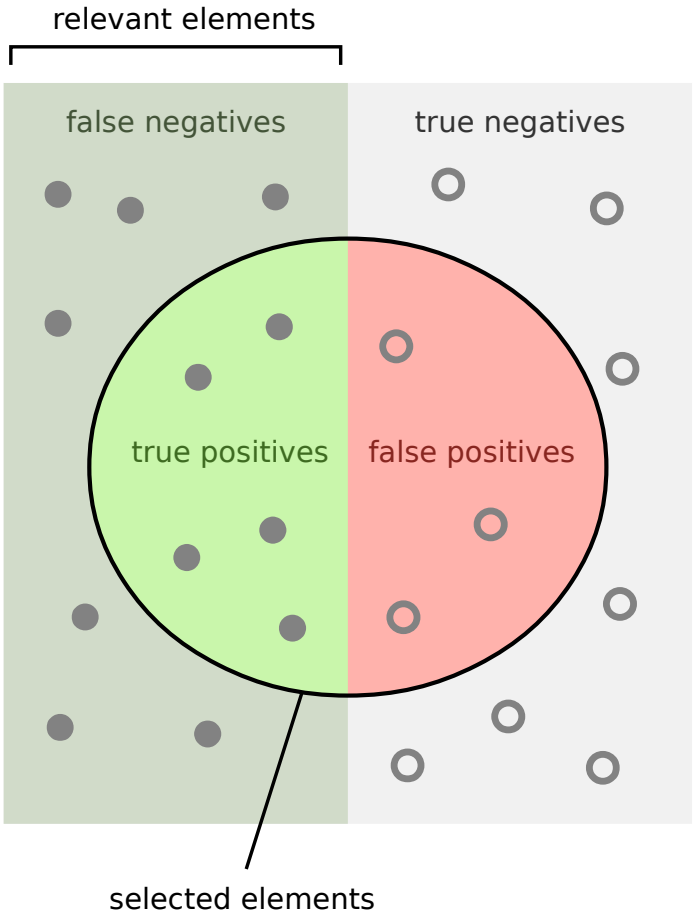
Myelin Sheath (green)

Axon (red)

Old subject EM image



Recognition Evaluation



http://en.wikipedia.org/wiki/Precision_and_recall

- Positive Predictive Value (PPV)

  95% average

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

- True Positive Rate (TPR)

  90% average

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

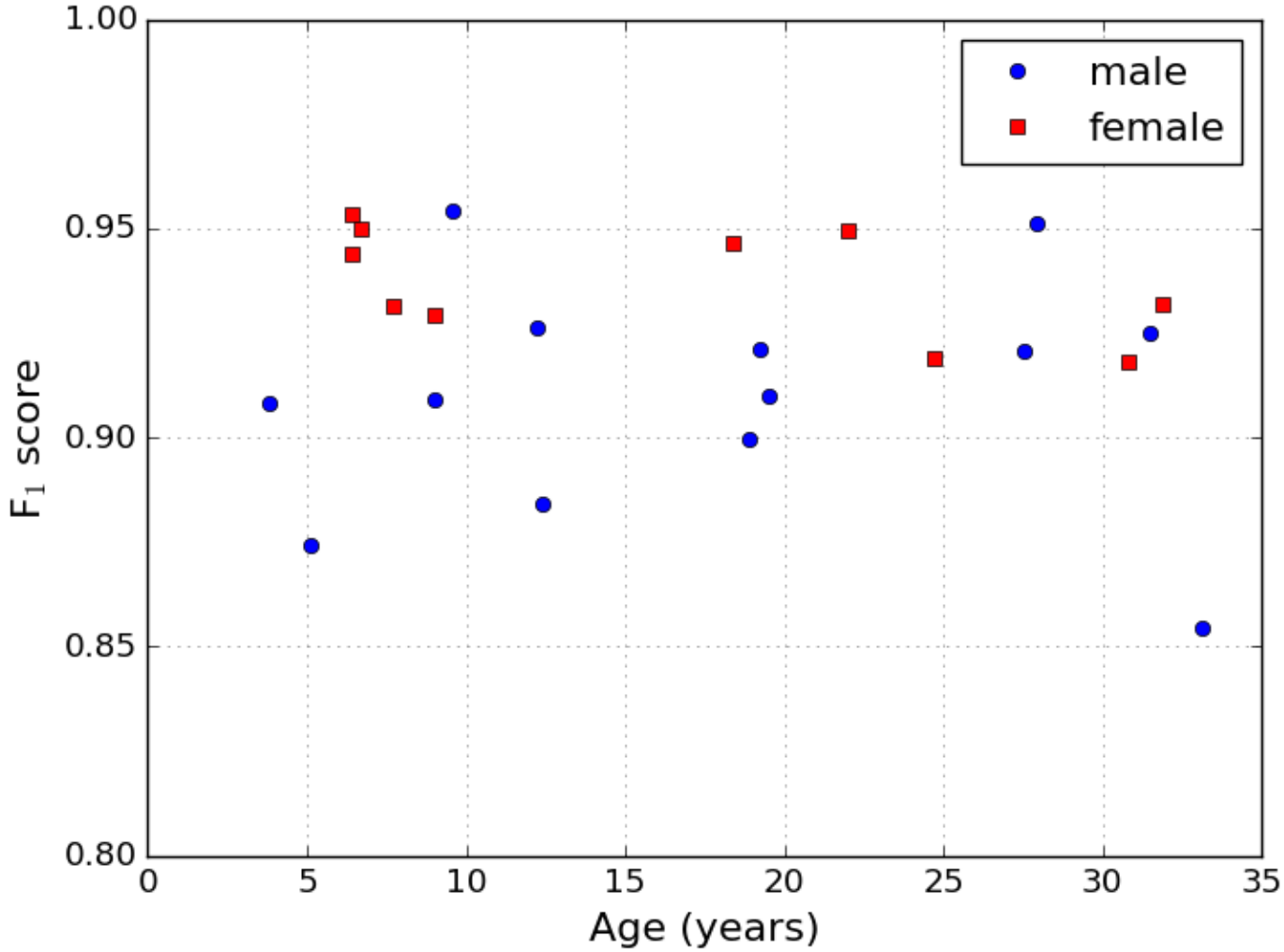
- F1 score: harmonic mean

  0.922 average

$$F_1 = 2\,\frac{\mathrm{TPR} \times \mathrm{PPV}}{\mathrm{TPR} + \mathrm{PPV}}$$

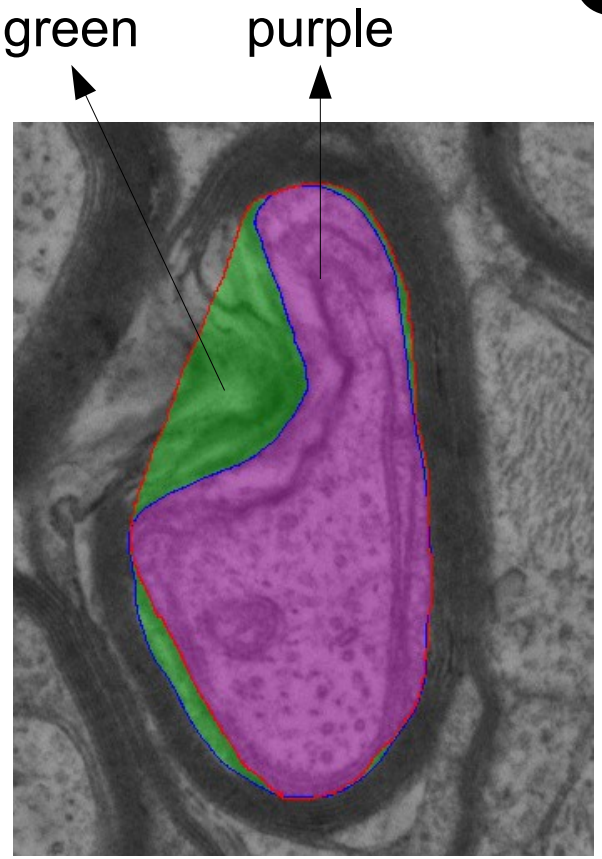
TP – True Positives
FP – False Positives

Recognition Rates

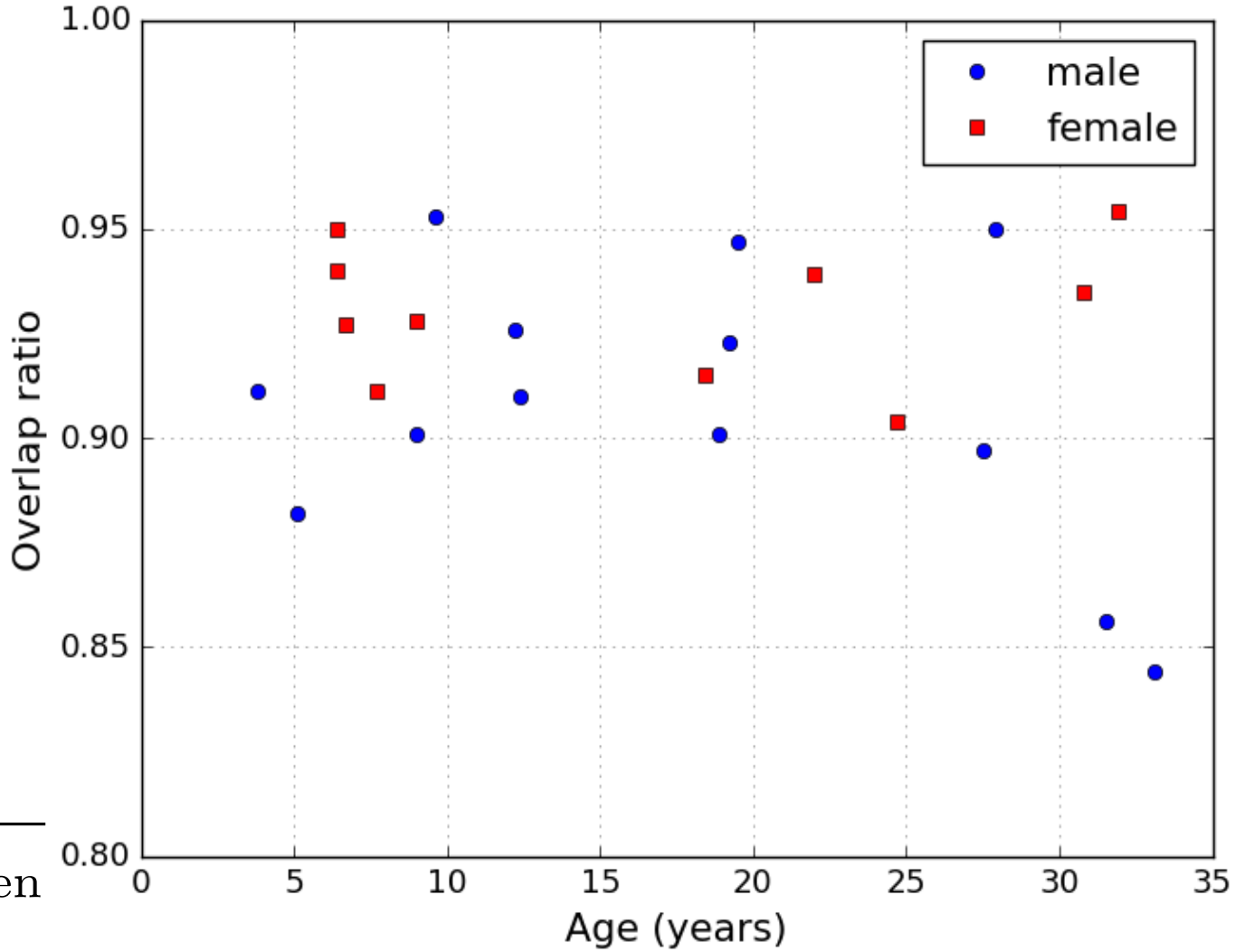


- The recognition rates do not depend on age

Overlap Ratio



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

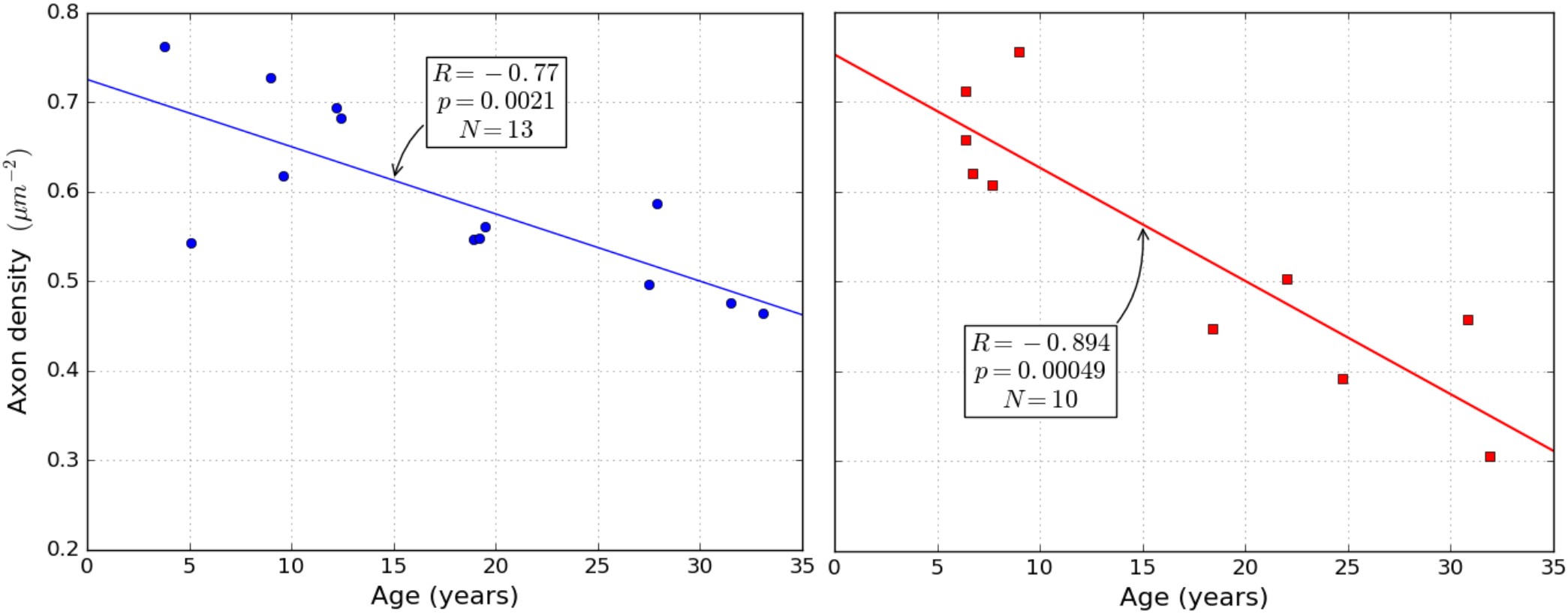


- Average overlap ratio of 0.92
- Similar to overlap ratios between contours marked by 2 persons (0.93-0.94)

Results

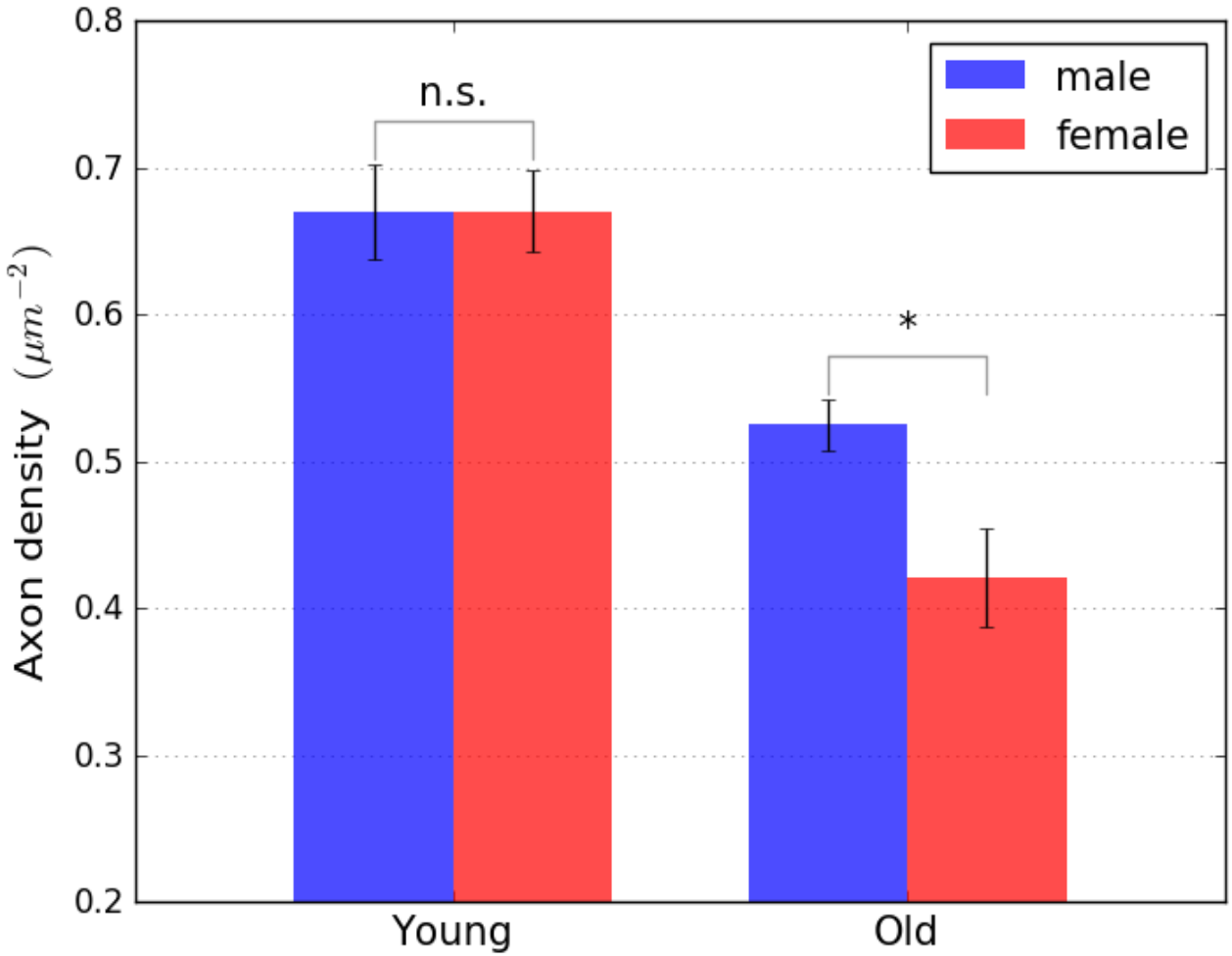
1. Axon Recognition Algorithm
2. ***Macroscopic Properties***
    a) **Axon density**
    b) **Fraction of occupied axon area**
3. Morphological Properties
4. Myelin Sheath Properties
5. Structural Properties
6. Feature Selection in Young vs. Old

Myelinated Axon Density



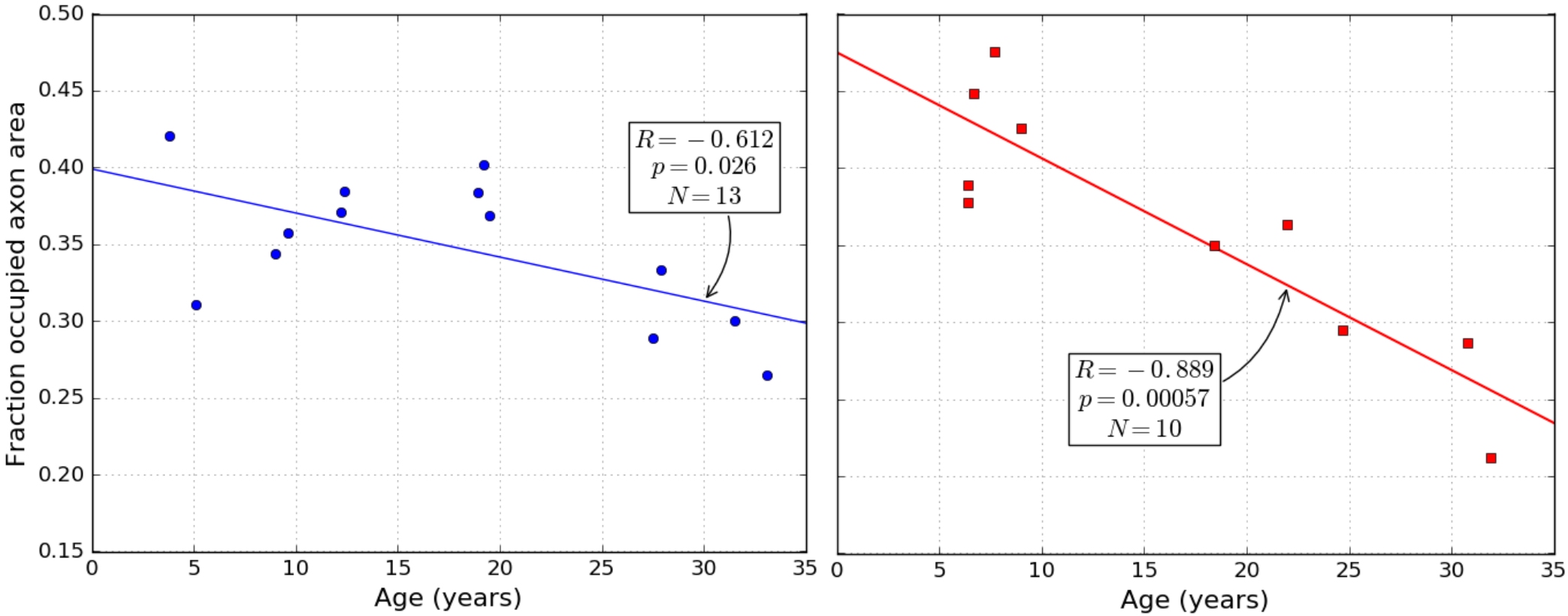
- Axon density decreases with age, for both male subjects and female subjects
- Myelinated axons lost with age

Myelinated Axon Density



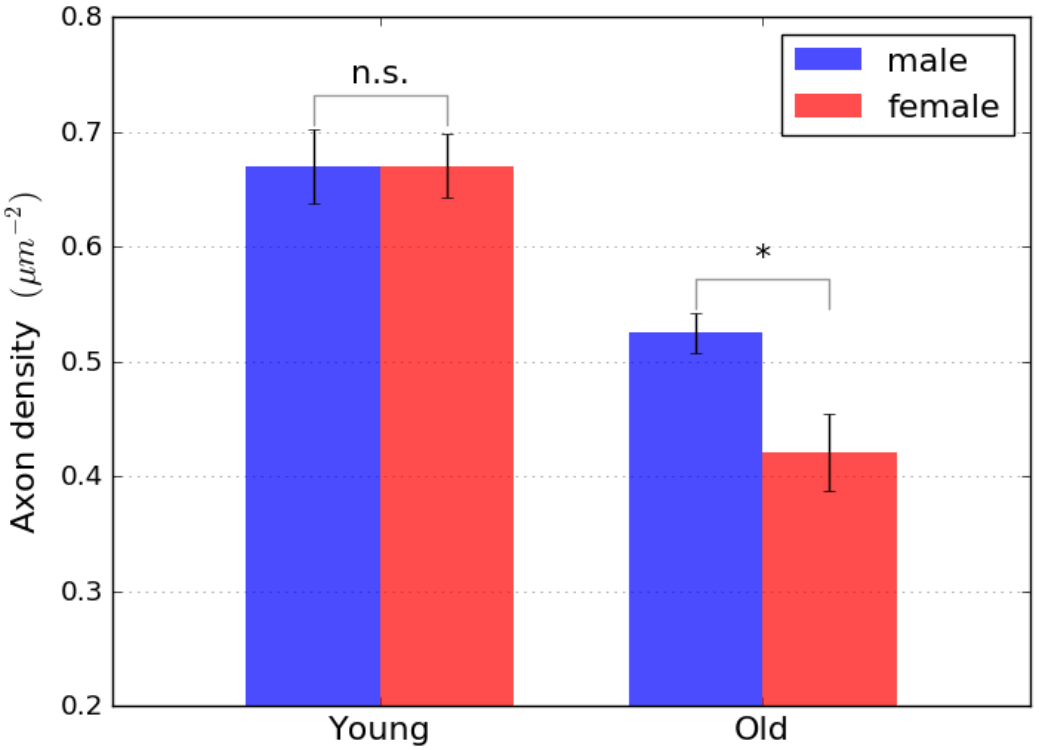
- Axon density is different for old male vs. old female subjects (p=0.023)
- Females lose more myelinated axons than males

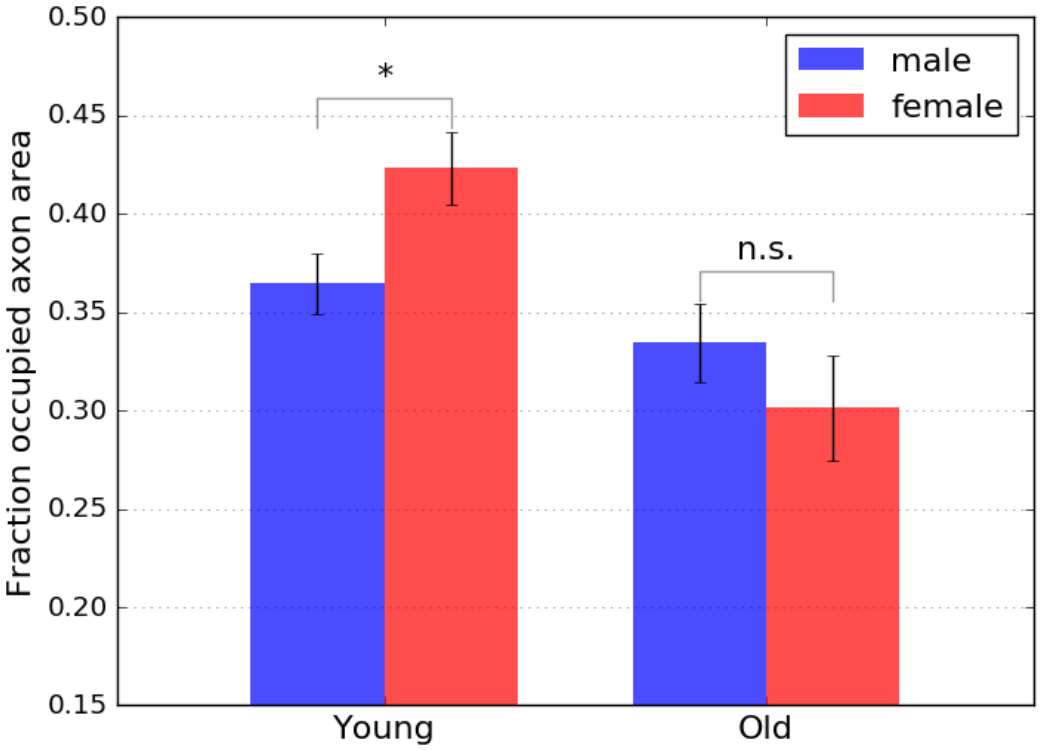
Fraction of Occupied Axon Area



- Fraction of occupied axon area decreases with age, for both male and female subjects

Male vs. Female



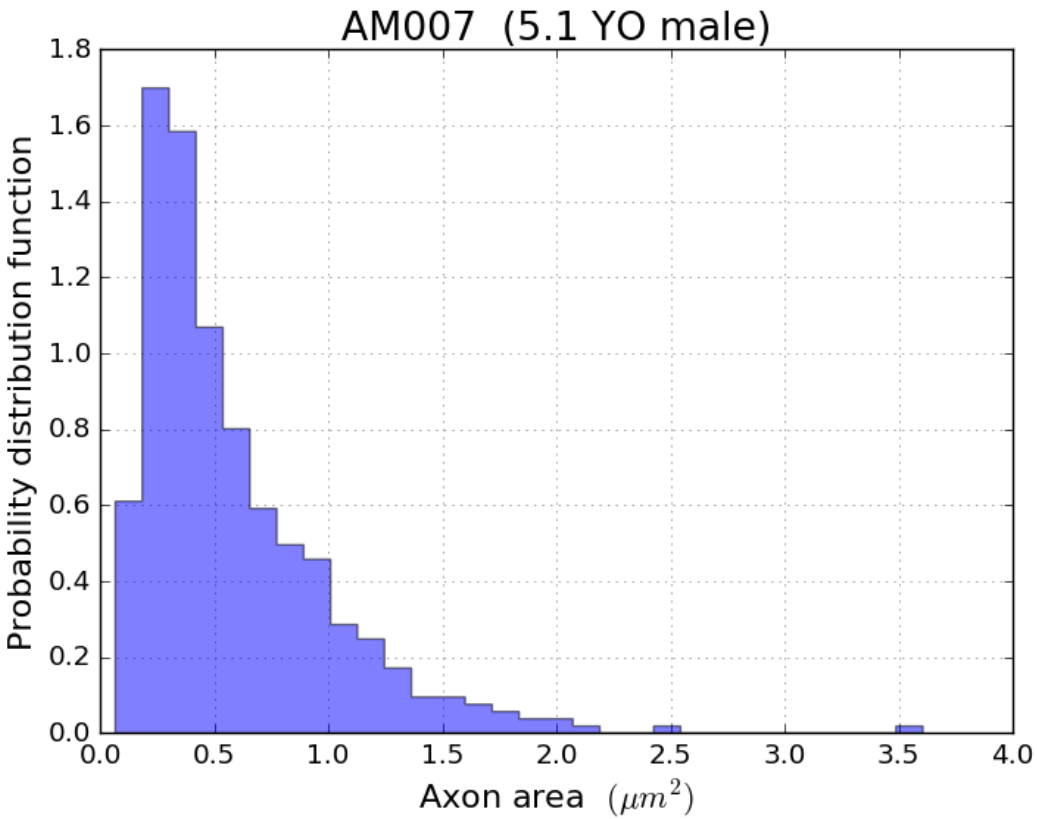


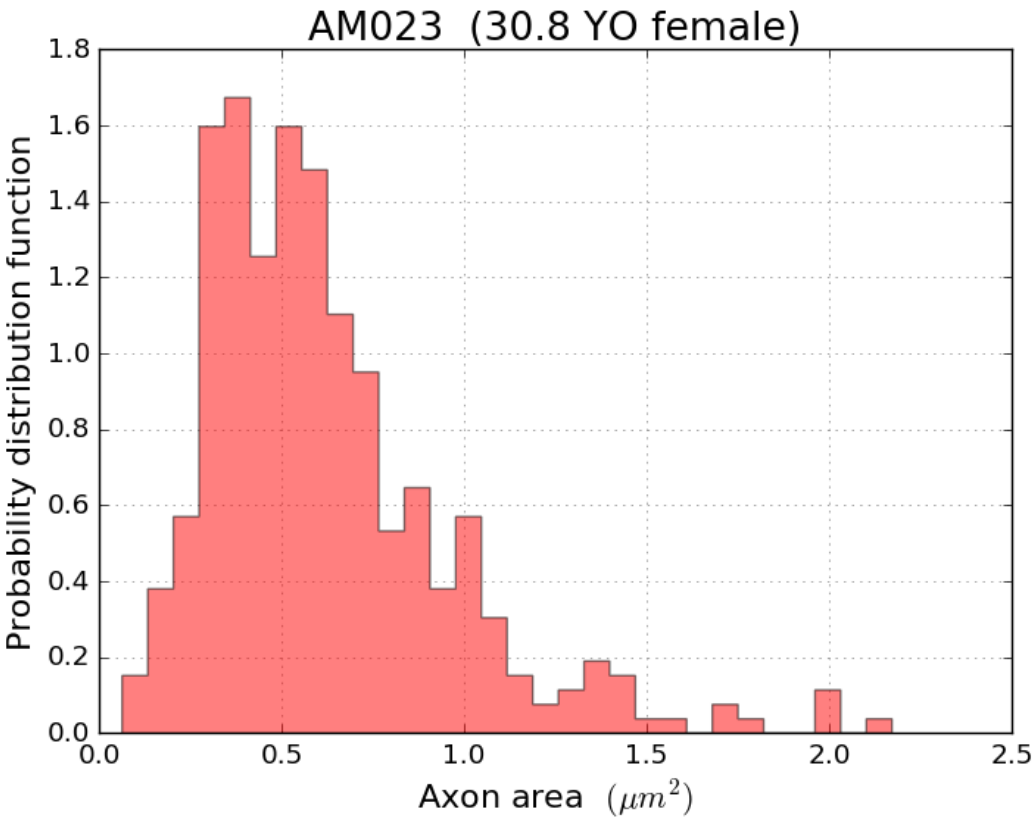
- Are axon areas different for males vs. females?

Results

1. Axon Recognition Algorithm
2. Macroscopic Properties
3. ***Morphological Properties***
    a) Axon Area
4. Myelin Sheath Properties
5. Structural Properties
6. Feature Selection in Young vs. Old

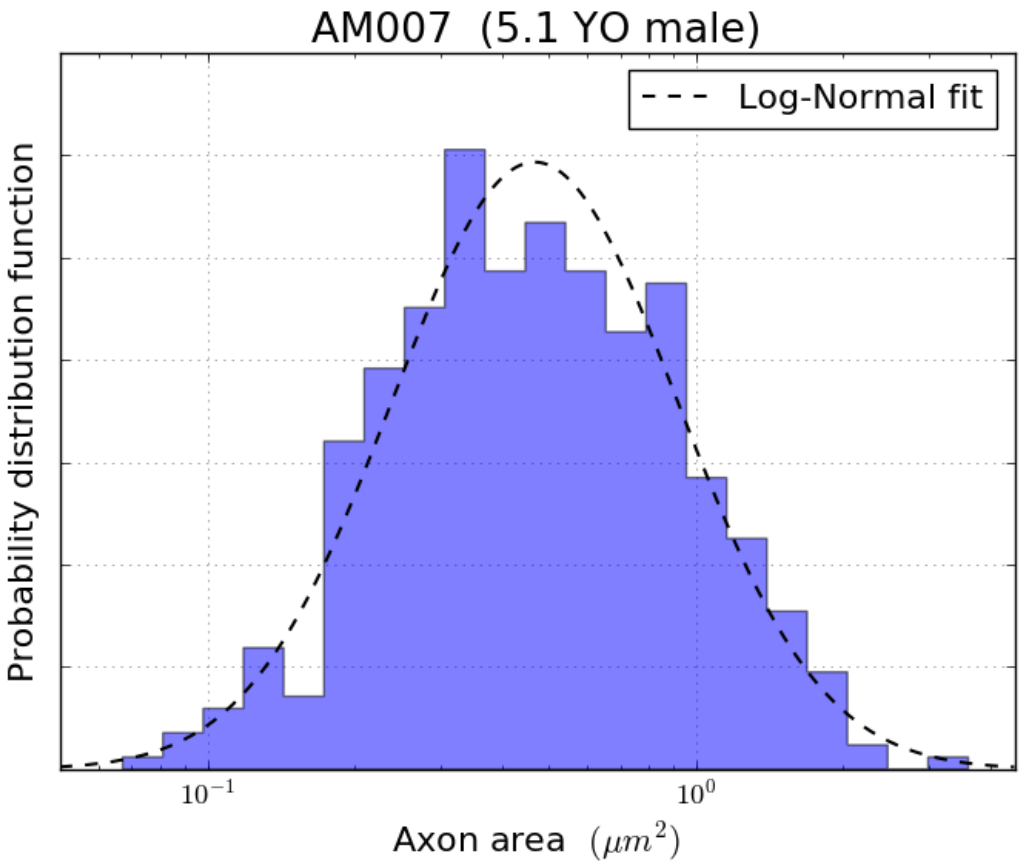
Axon Area Distribution

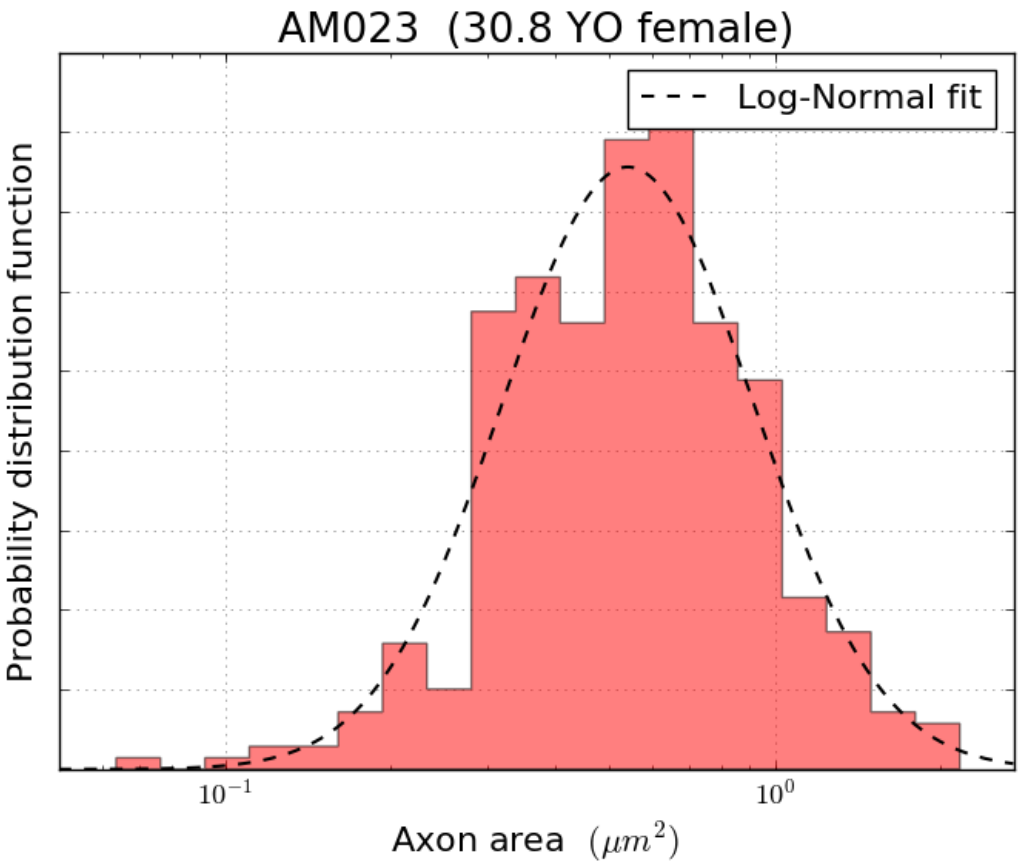




- Axon area distribution of each subject is heavy-tailed

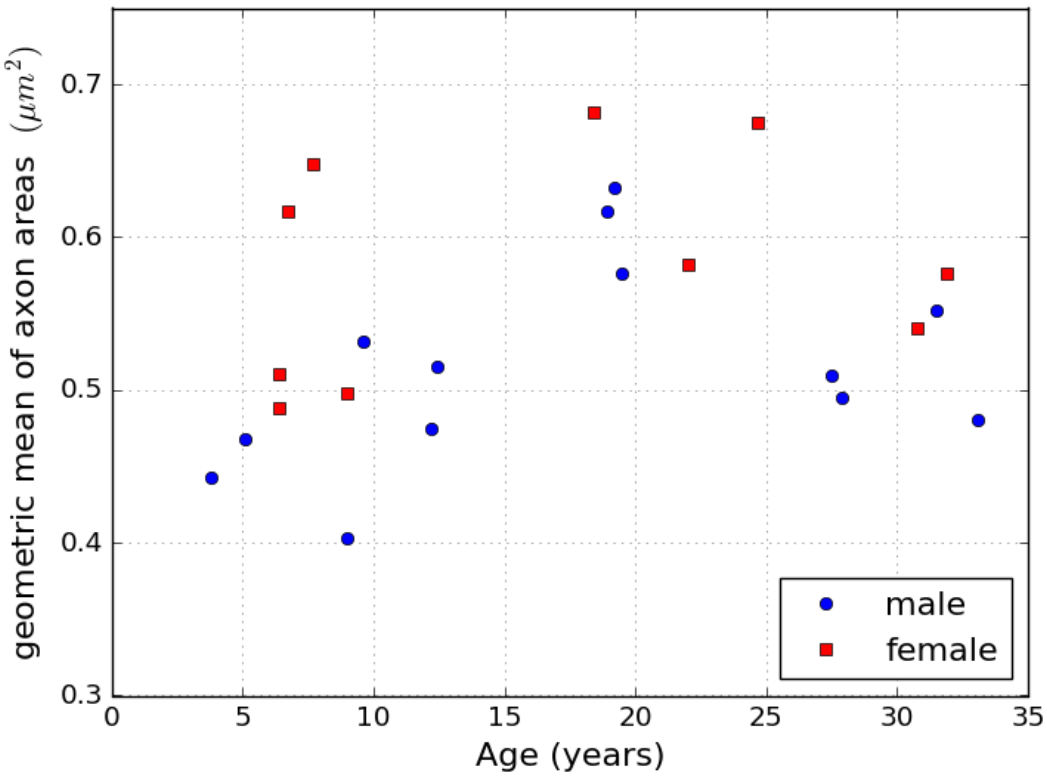
Axon Area Distribution

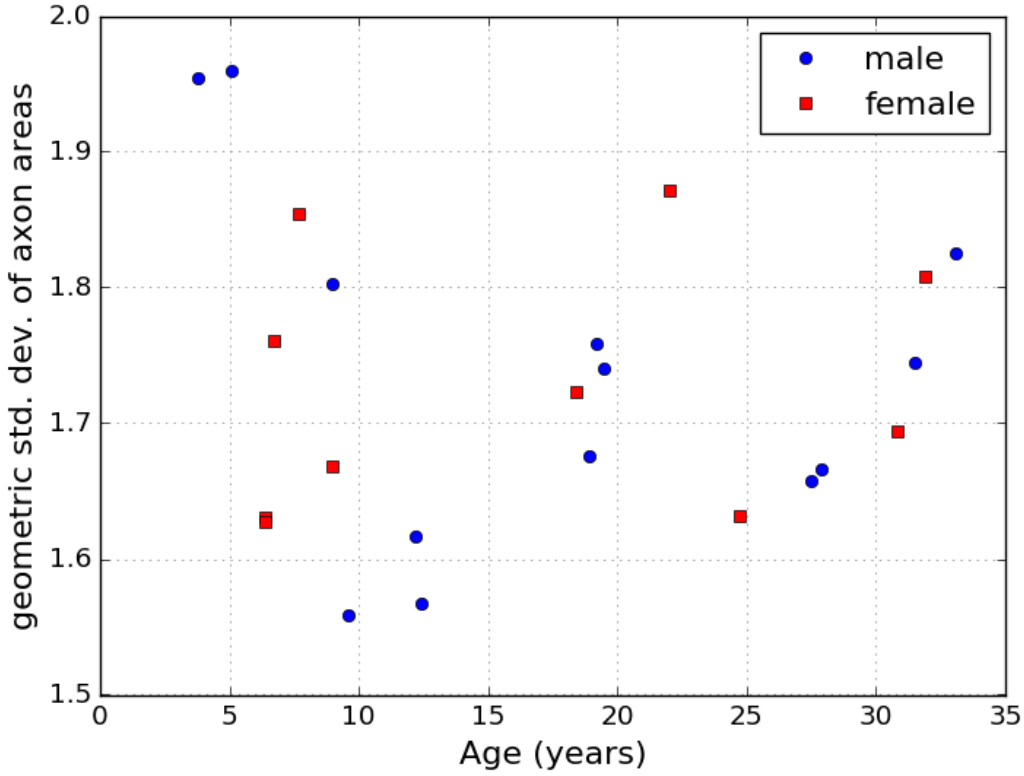




- Axon area distribution follows a Log-normal distribution
- Hypothesis: stochastic geometric growth of axons, i.e., geometric random walk

Axon Areas



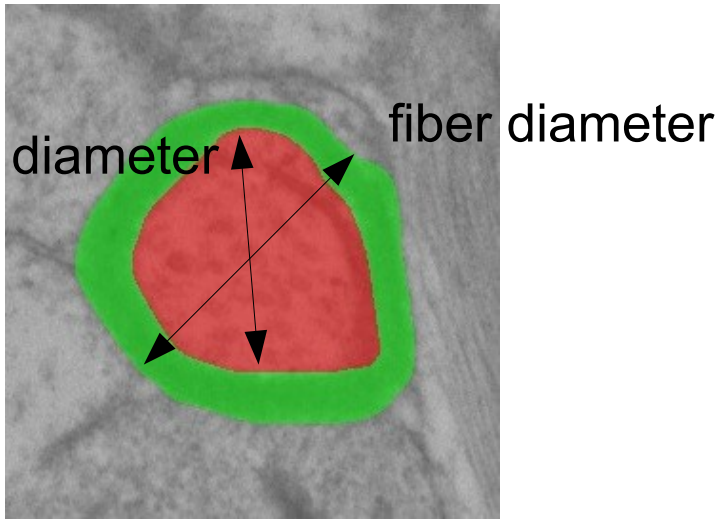


- Axon area parameters do not depend on age for both male and female subjects
- Myelinated axons lost independently of their areas
- There is a difference in the geometric mean axon area between male and female subjects (p=0.038)

Results

1. Axon Recognition Algorithm
2. Macroscopic Properties
3. Morphological Properties
4. ***Myelin Sheath Properties***
5. Structural Properties
6. Feature Selection in Young vs. Old

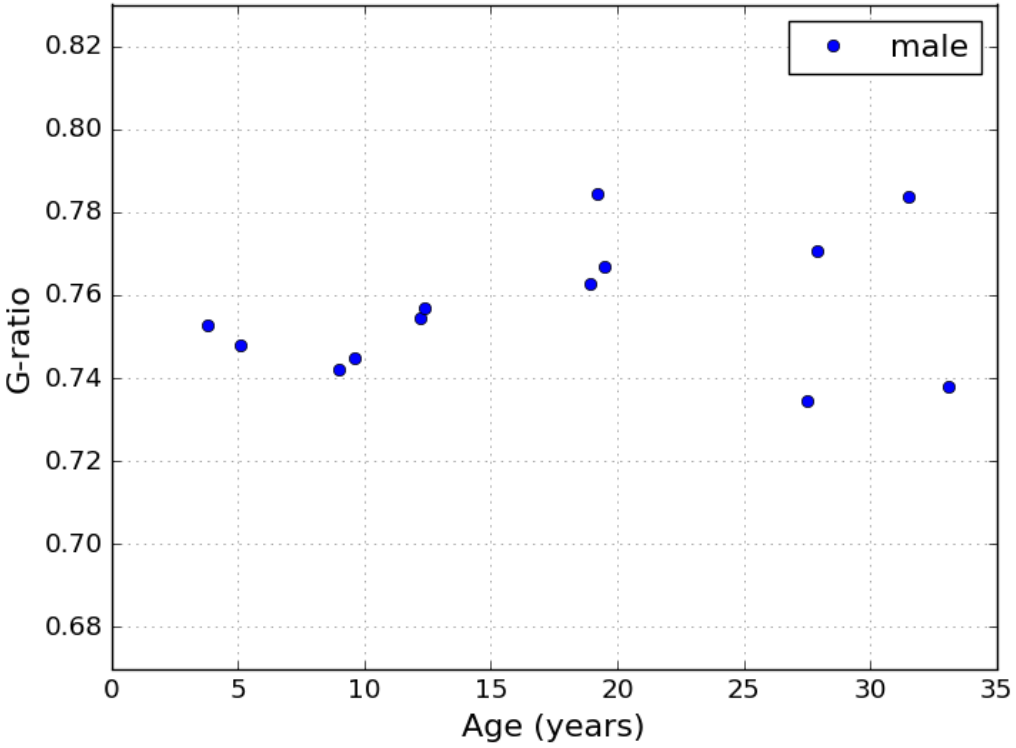
Myelin Sheath

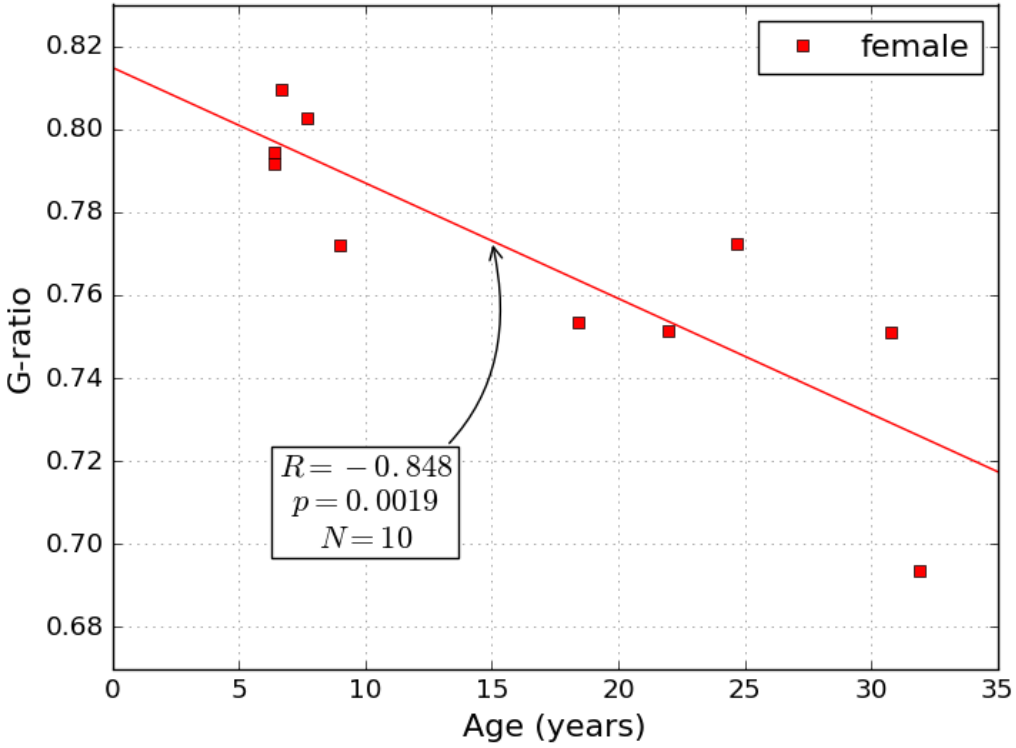


$$\text{g-ratio} = \frac{\text{axon diameter}}{\text{fiber diameter}}$$

- Axons with g-ratios close to 1 have thin myelin sheaths
- Axons with lower g-ratios have thicker myelin sheaths, compared to the axon size
- Conduction models of myelinated axons depend on g-ratio

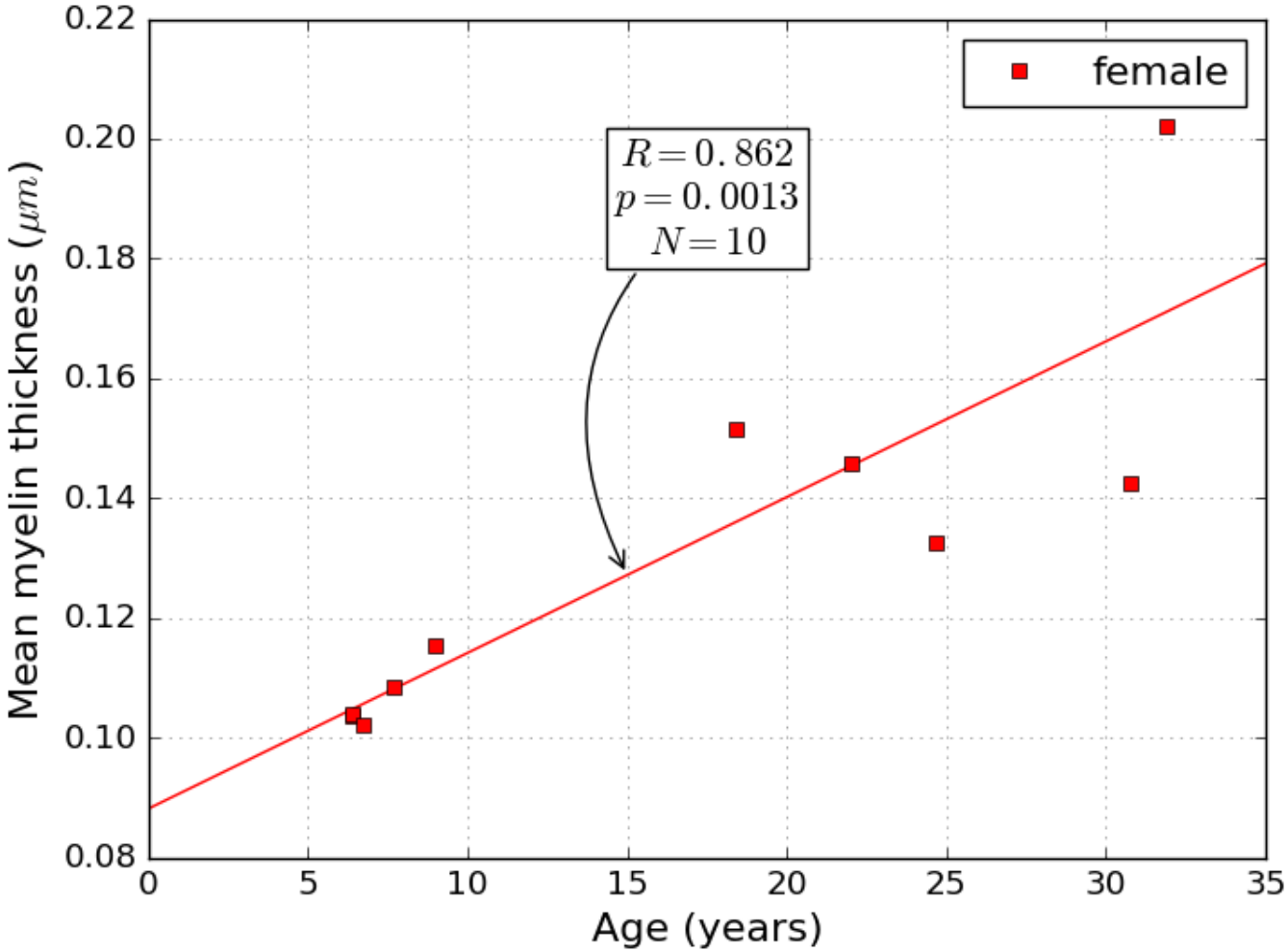
G-ratio dependence with age





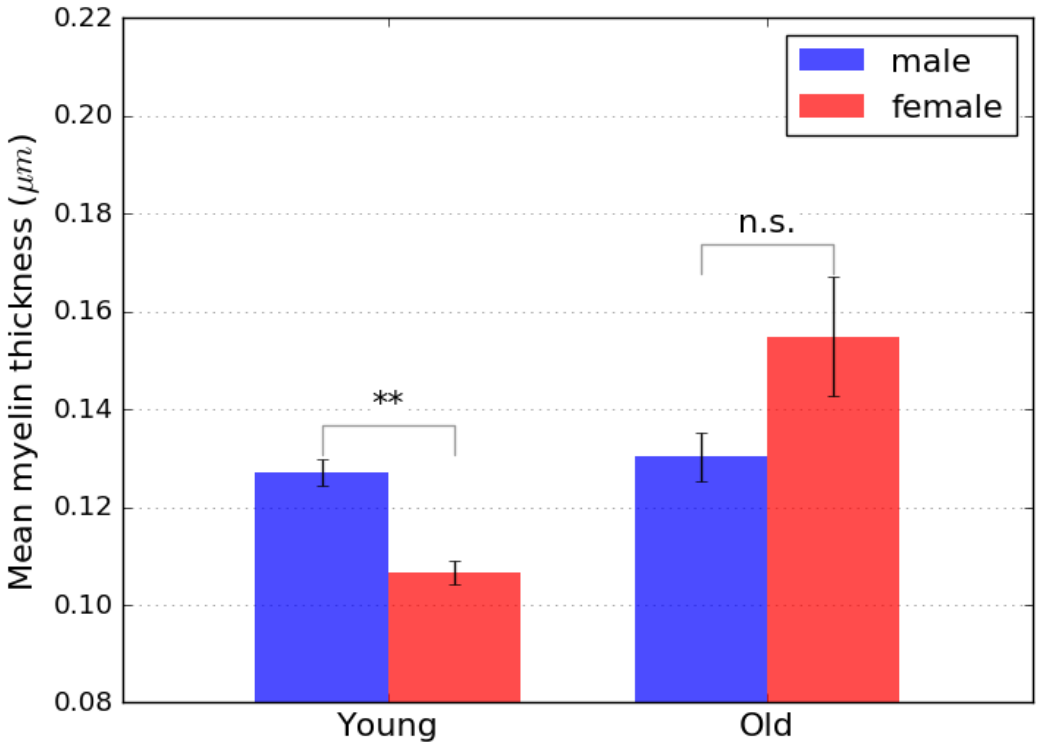
- G-ratio remains relatively constant with age for male subjects
- G-ratio decreases with age for femle subjects

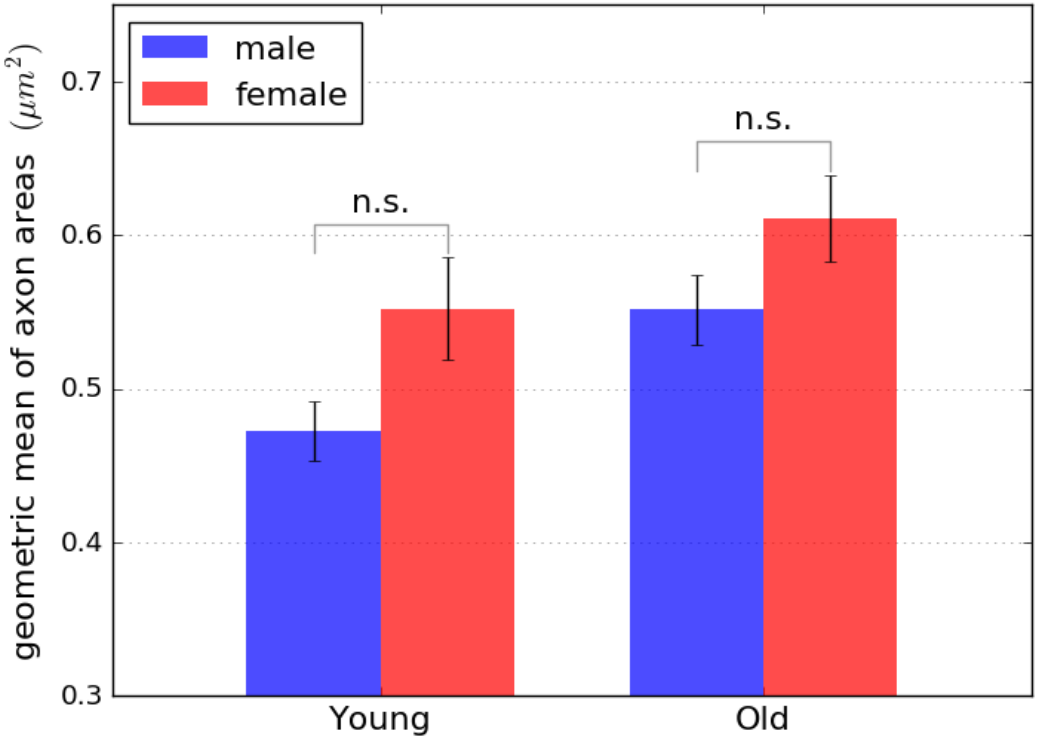
Myelin thickness



- Myelin thickness behavior with age mimics the behavior observed for g-ratio

Myelin thickness





- G-ratio behavior is dictated by the behavior of the myelin thickness
- Higher rate of remyelination in female subjects?
- Axons with higher g-ratio die at higher rates?

Results

1. Axon Recognition Algorithm
2. Macroscopic Properties
3. Morphological Properties
4. Myelin Sheath Properties
5. ***Structural Properties***
   - **a) Axon Area Correlation**
6. Feature Selection in Young vs. Old

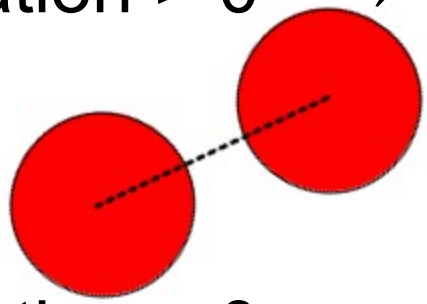
Axon Area Autocorrelation

How similar are the areas of neighboring axons?

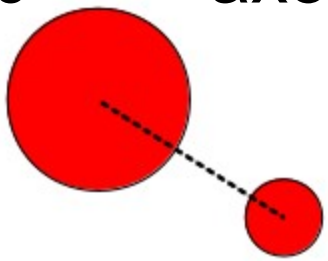
What about for axons separated by larger distances?

Axon Area Autocorrelation

- Autocorrelation > 0 → axon areas are similar

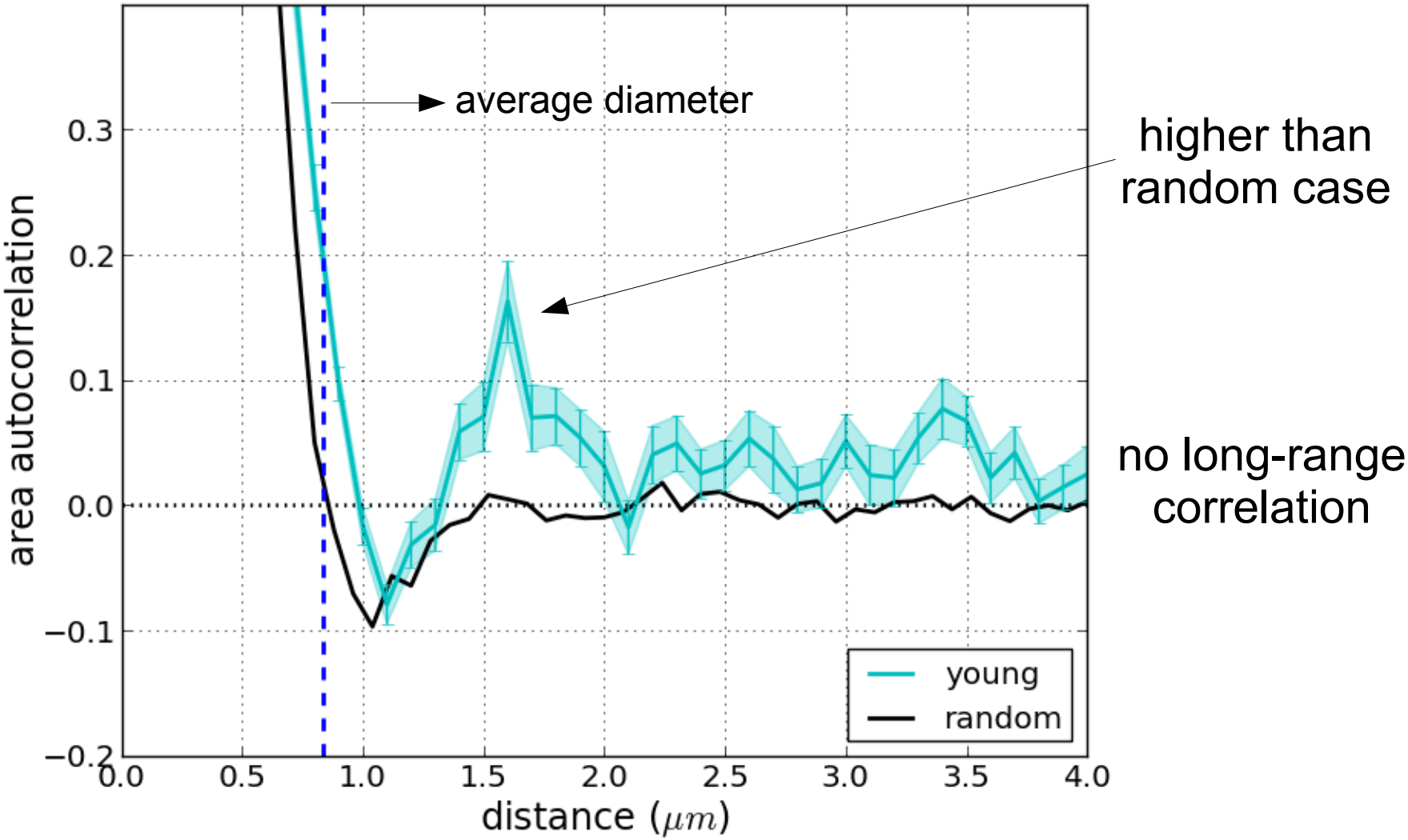


- Autocorrelation < 0 → axons have different areas



Axon Area Autocorrelation

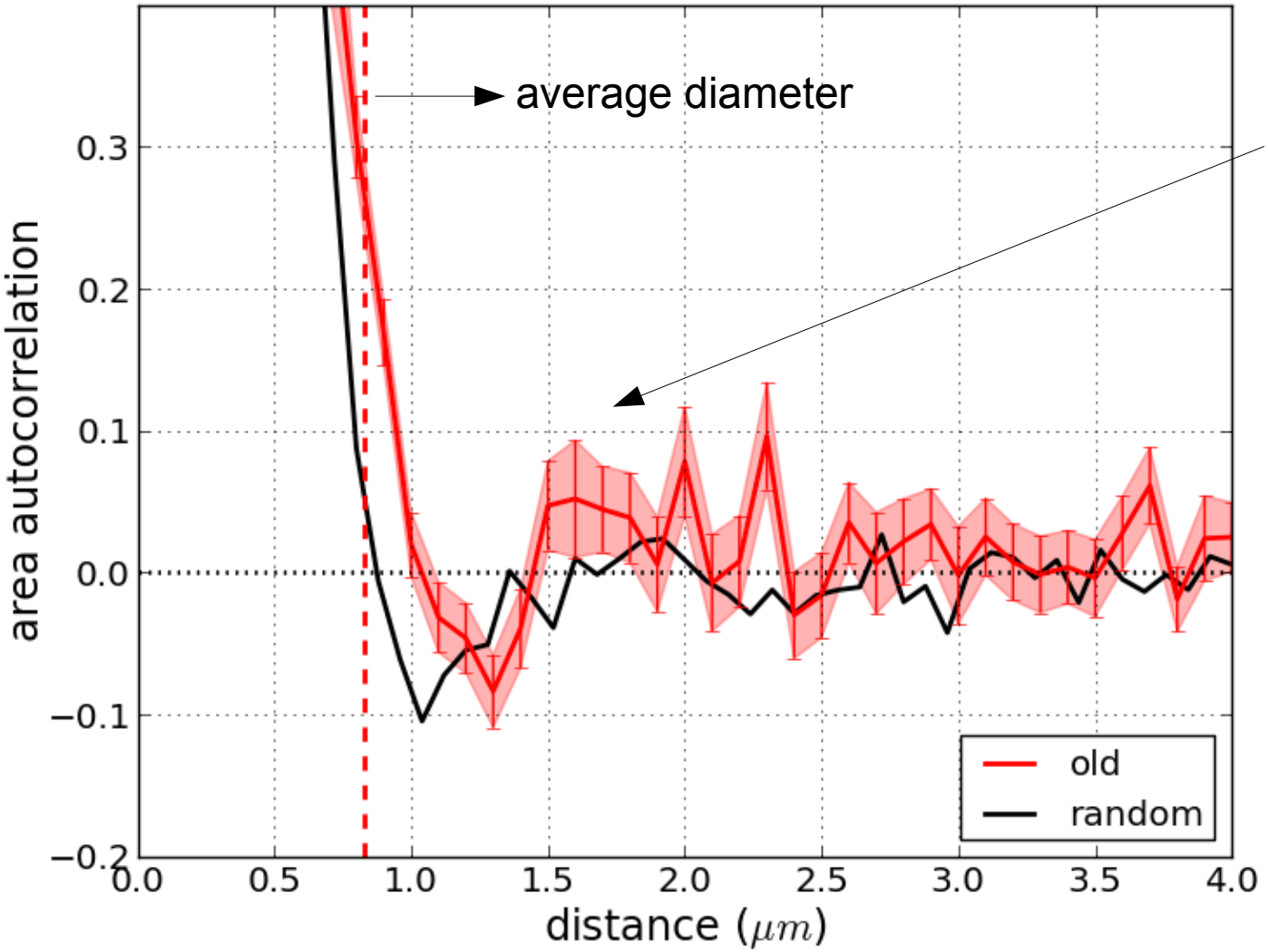
(i) young subjects



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

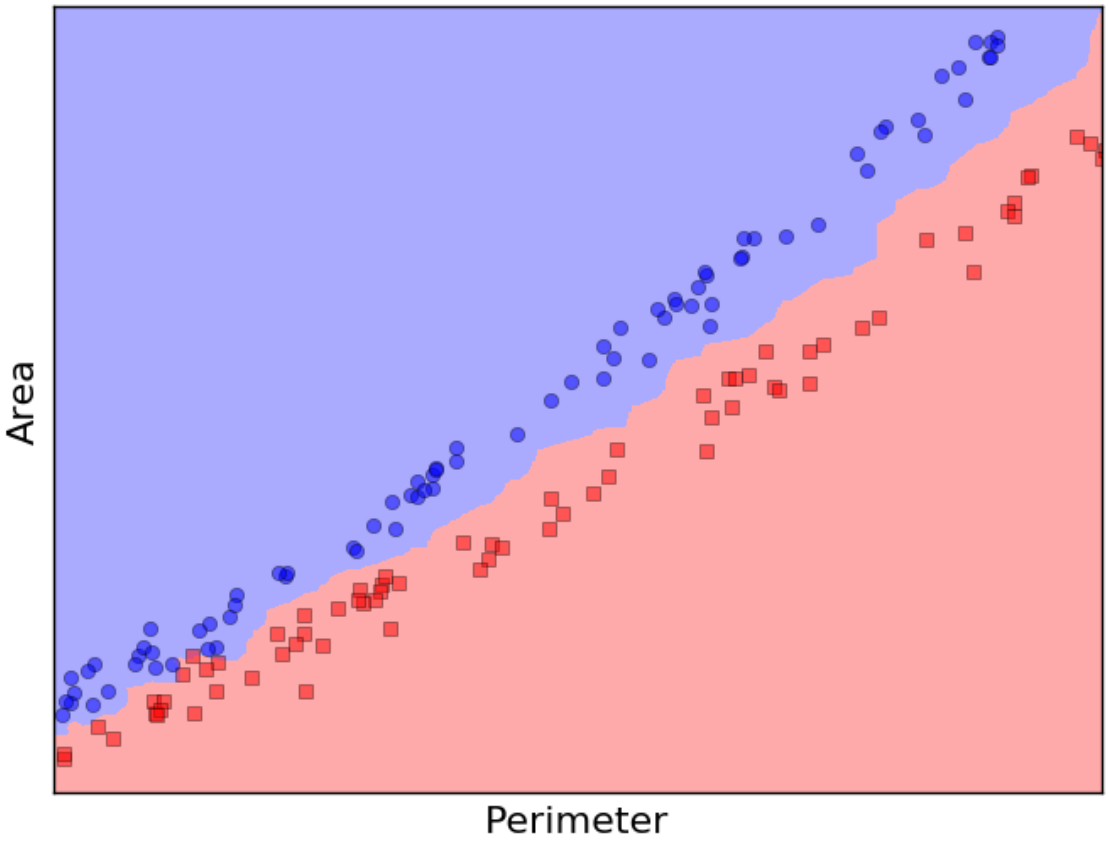
Results

1. Axon Recognition Algorithm
2. Macroscopic Properties
3. Morphological Properties
4. Myelin Sheath Properties
5. Structural Properties
6. ***Feature Selection in Young vs. Old***

Feature Selection

How to distinguish between two groups?

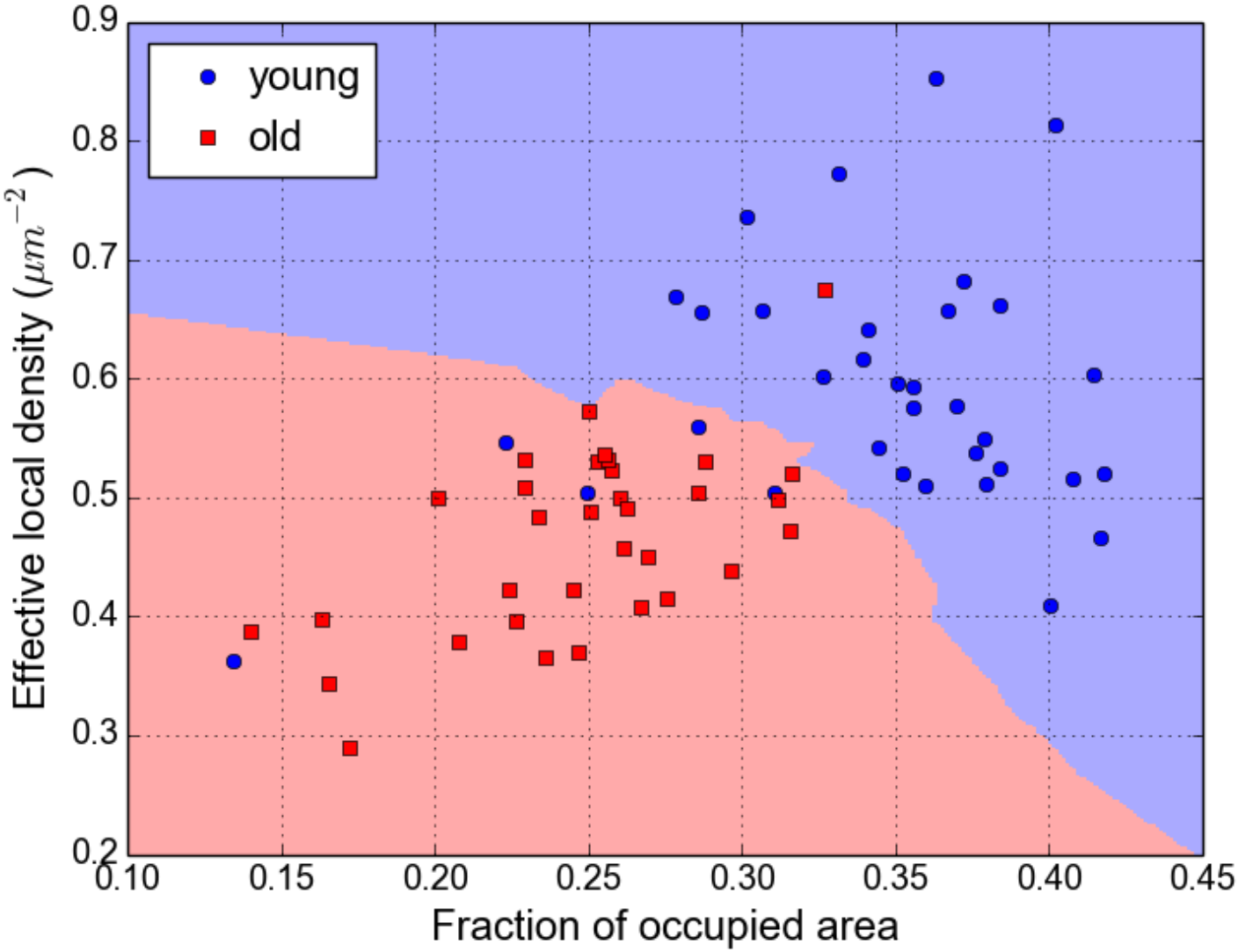
Find the subset of features that, *when combined*, gives a good separation between groups



Feature Selection

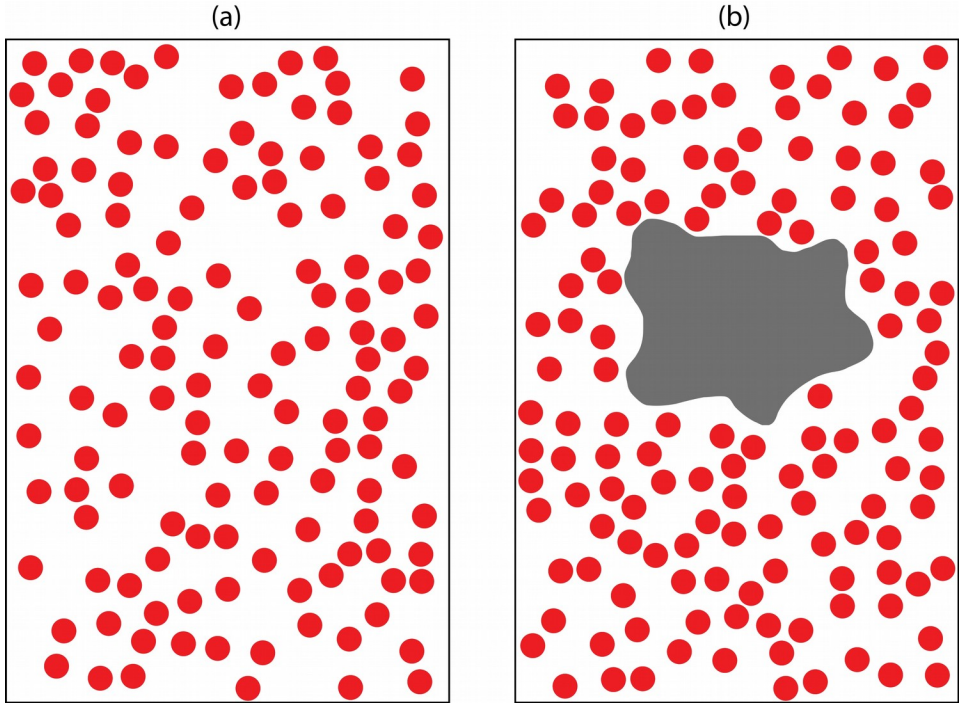
[Comin, Santos *et al.*, Sci. Rep. **4** (2014)]

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



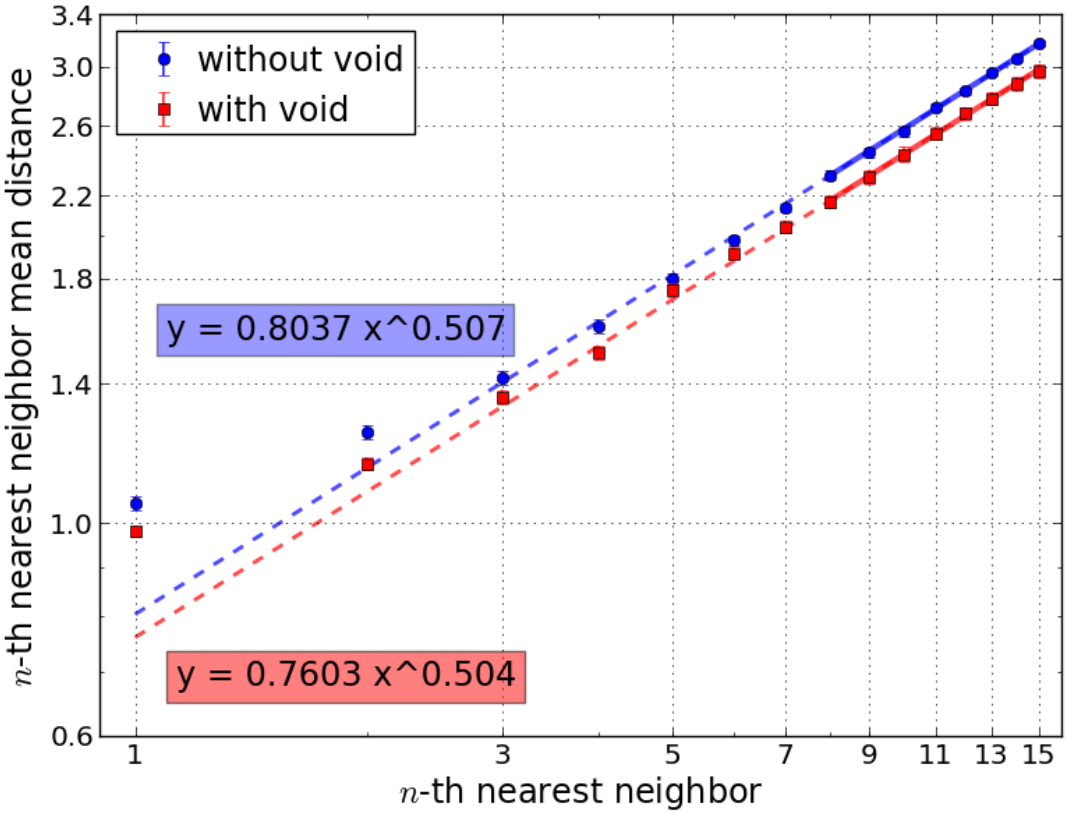
Taking ONLY these 2 features:
90% accuracy of images

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

Conclusions

- Myelinated axons are lost with age
  - This process happens independently of the axons area
- The correlations of myelin properties with age depend significantly on the sex of the subjects
  - The g-ratio correlation with age depends on sex
- Myelinated axons in fornix have regularity
  - Older subjects have a more disordered fornix
- Simple random axon loss does not explain age differences

Future Directions

1) Inclusion of myelin data to improve the feature selection
2) Model of aging process
   - Which axons are more likely to die, compared to random cases
3) Diffusion models in myelinated axons
4) Enable recognition in other areas as well as for changes caused by brain pathologies or by developmental disorder

Acknowledgements

Will Morrison
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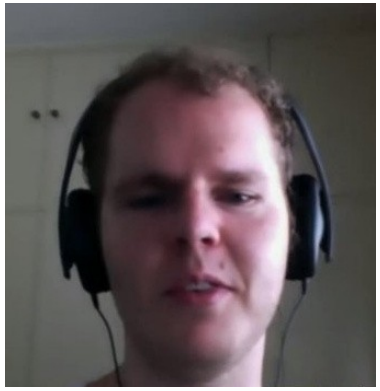
Boston University



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Boston University

Luciano Costa
Universidade de São Paulo

Thank you!

Questions?

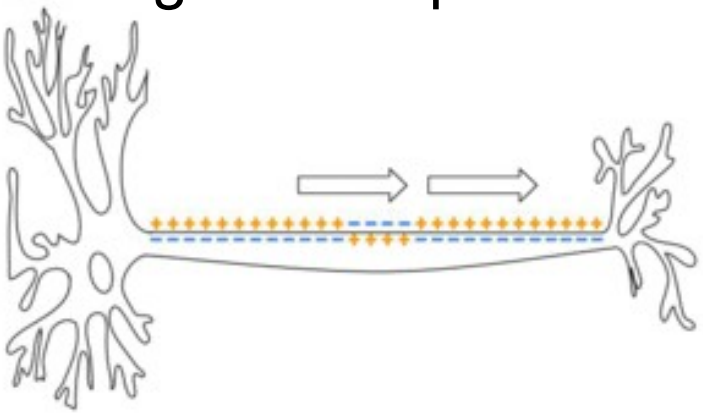
É Sexta-feira
Suei a semana inteira
No bolso não trago um tostão
Alguém me arranje emprego
Bom bom bom bom
Já já já já
- Boss AC

It's Friday
I've sweated all week long
Ain't got a penny in my pocket
Someone get me a job
Good good good good
Now now now now
- Boss AC

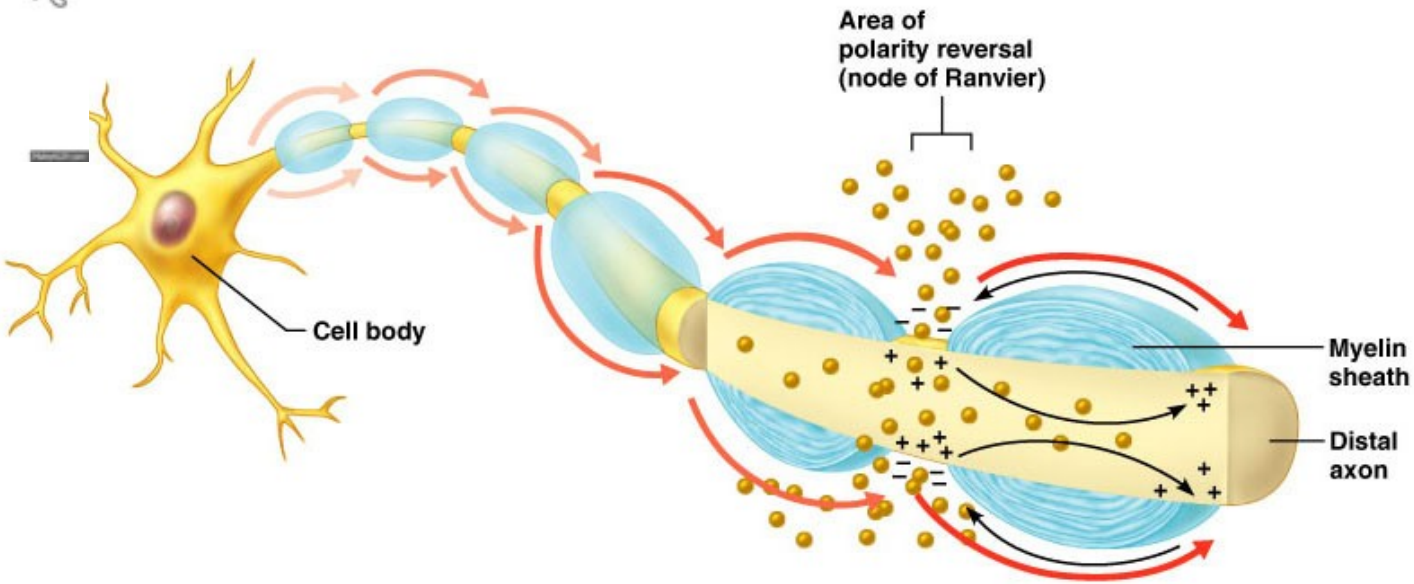
Conduction in Axons

- Axons are projections of neurons conducting electrical signals

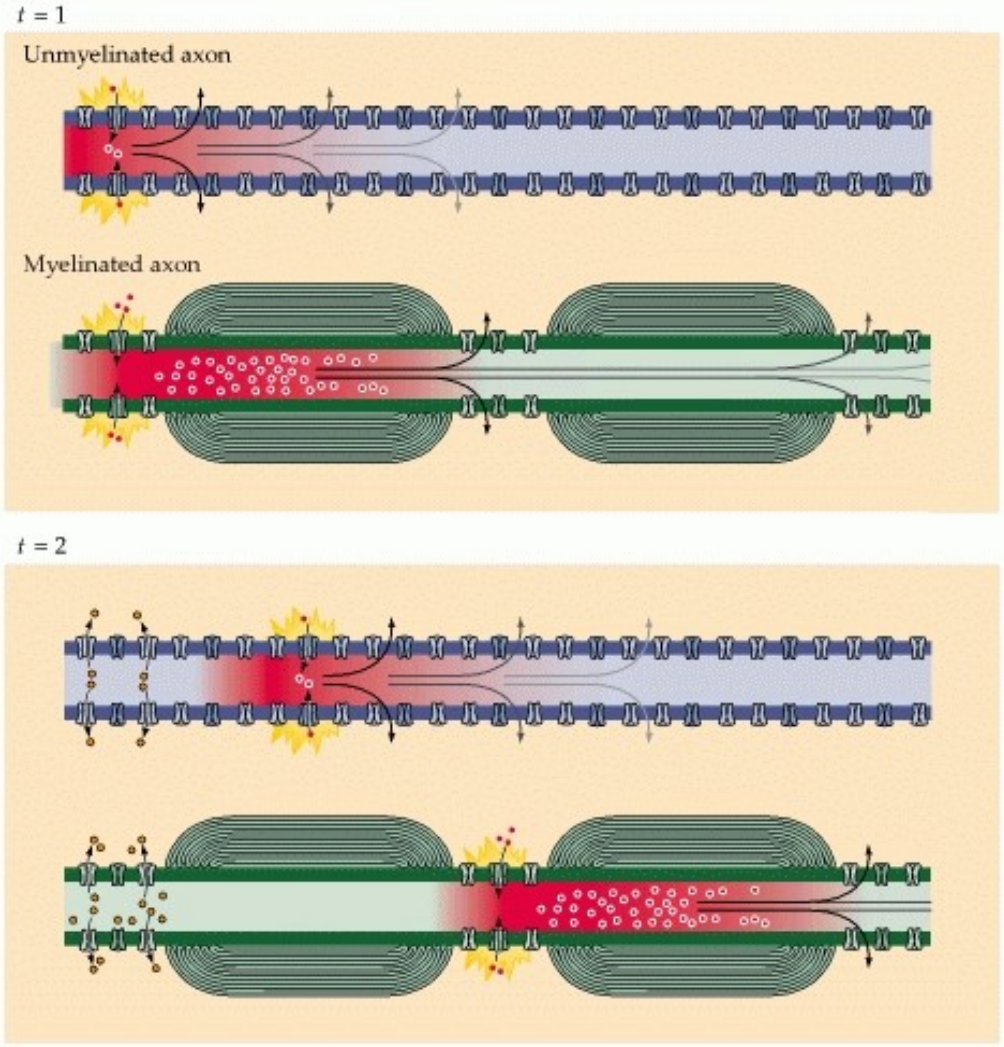
Signals travel in unmyelinated axons through action potentials

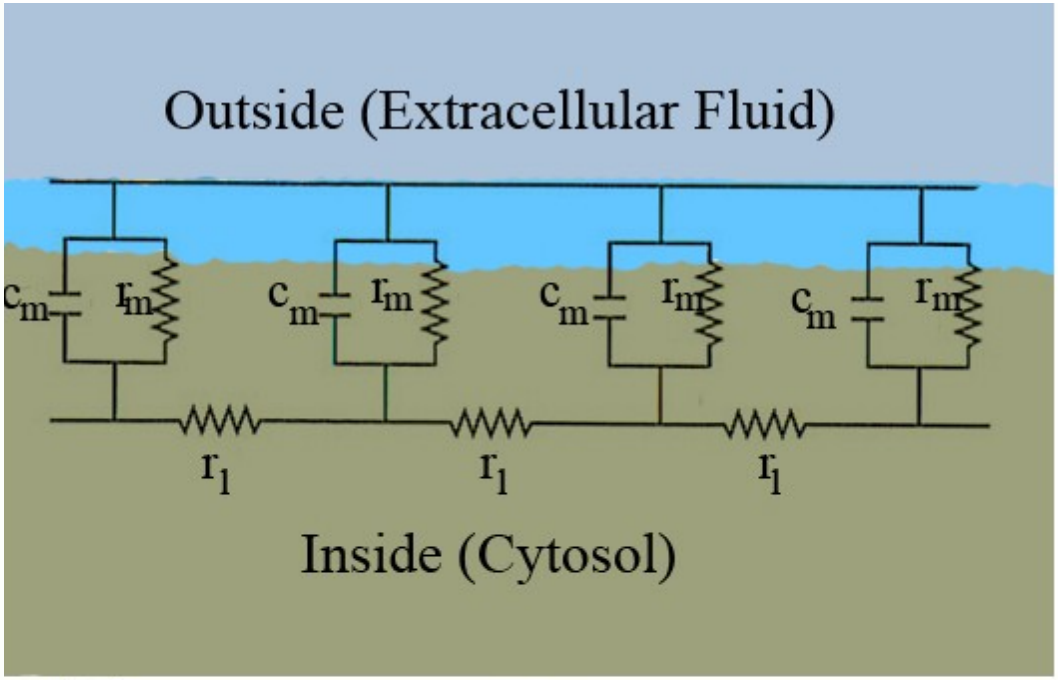


In myelinated axons, the conduction occurs through saltatory conduction



Conduction in Axons





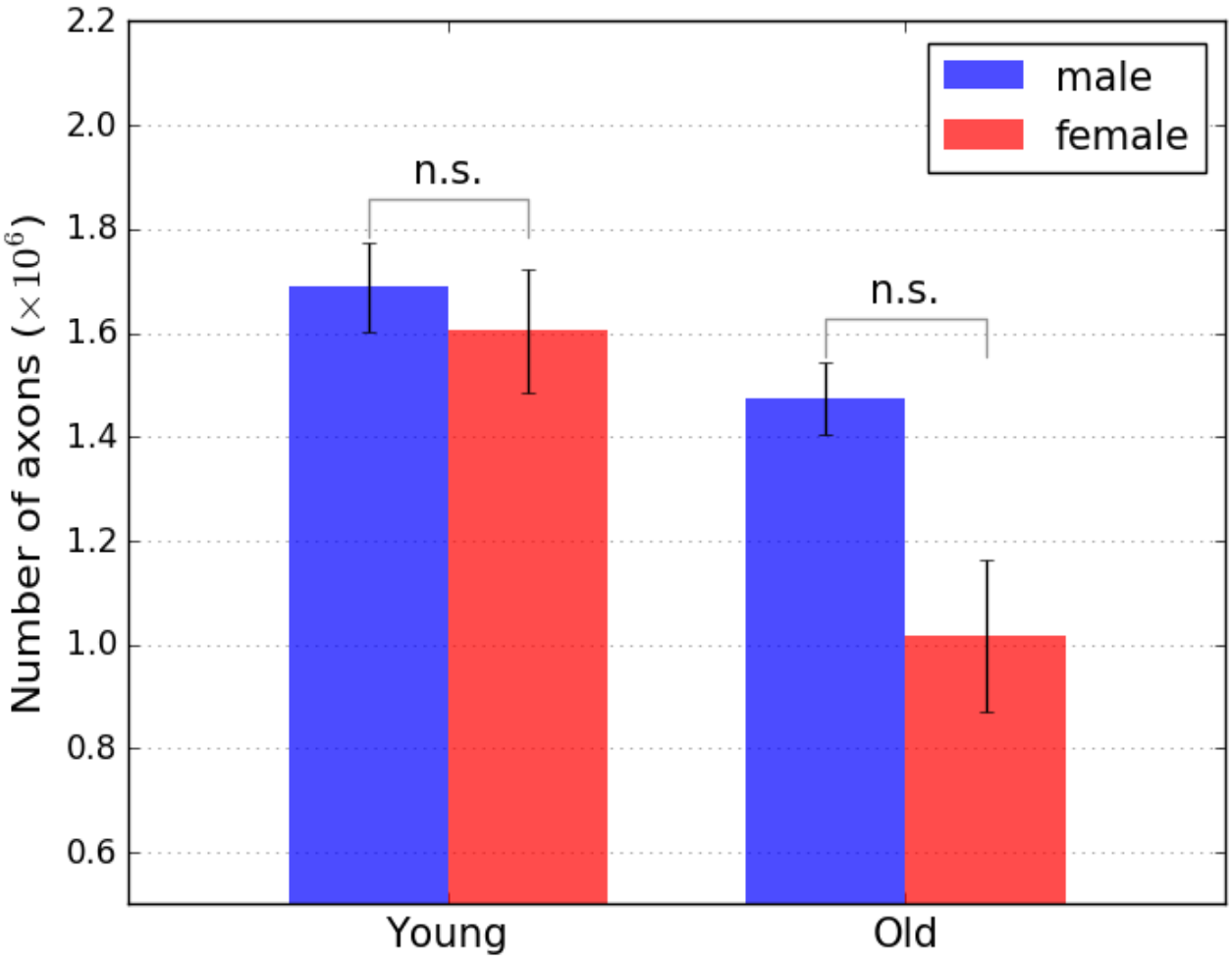
Capacitance

Resistance

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

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

Number of Axons



- Lower number of myelinated axons for old females, compared to old male subjects (p=0.026 one-side U-test)
- Females lose more myelinated axons than males