Determining the parameters of healthy ageing using automated neuron-level analysis of the laminar structure of the human brain

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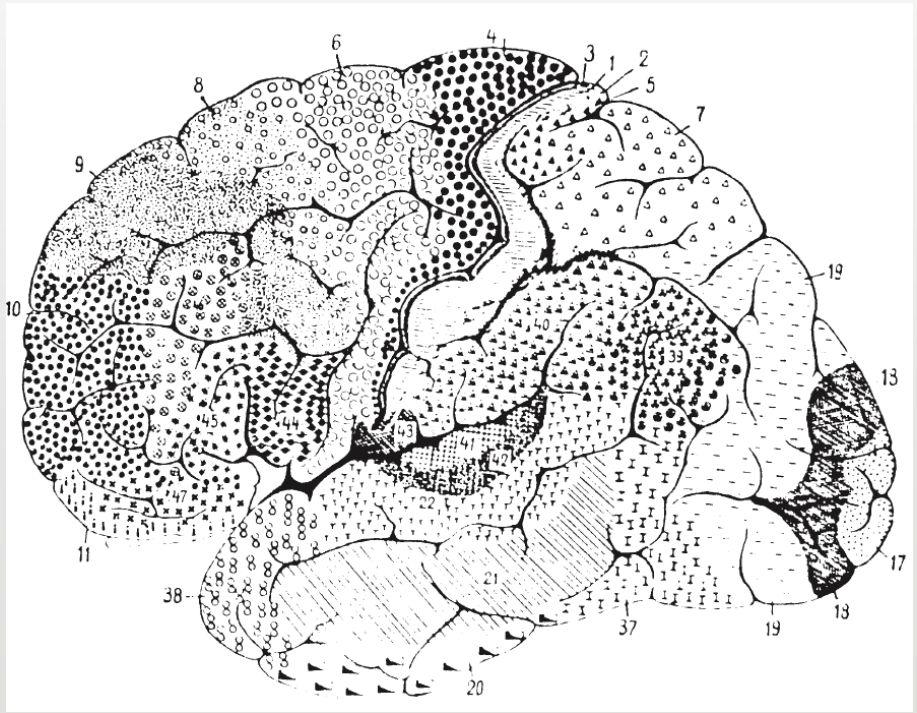
Ageing of the brain

- Characterized by the loss of neuronal elements
- Function defined by structure
- Normal changes or an indication of a disease?
- Subtle histological, cellular and molecular changes
- Dementia: loss of neurons, loss of function
- Many mechanisms not understood
- Can only be detected by quantification



De Strooper, Bart, and Eric Karran. "The cellular phase of Alzheimer's disease." *Cell* 164.4 (2016): 603-615.

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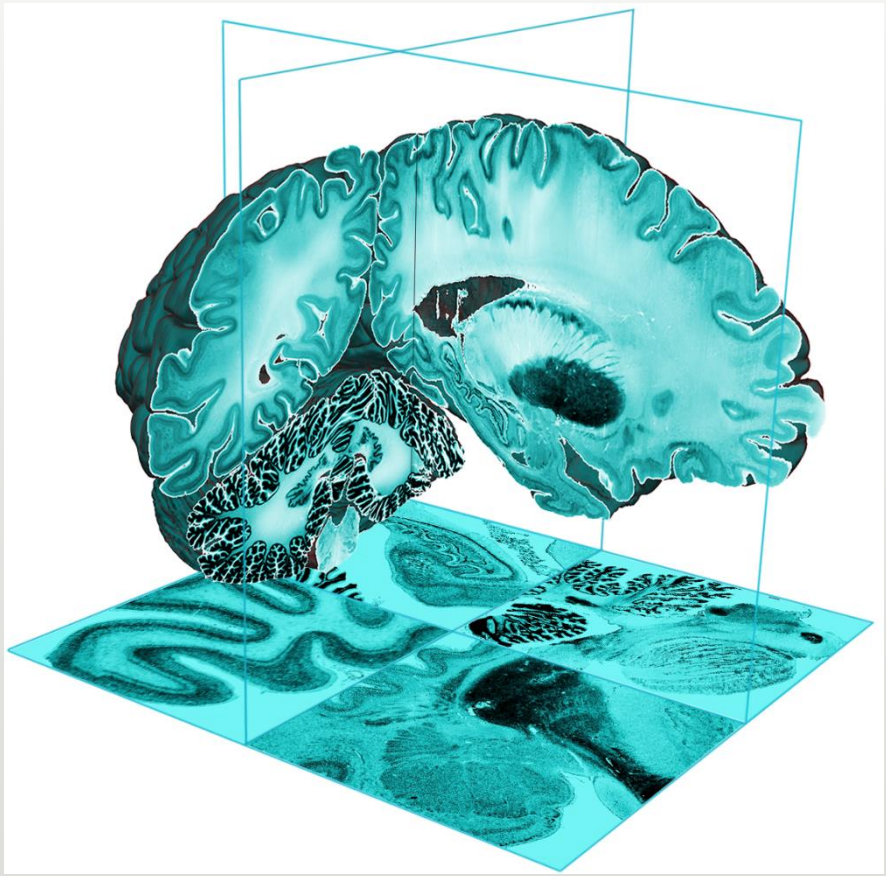
Quantitative characterization

- Precise measurements difficult to make – still in manual domain
- Stereology
  - Subjective
  - Limited capacity
  - ~20% error in estimation
- Need for automation and objective characterization of ageing processes
- Ultra-high resolution imaging
- Framework for fast an objective analysis of histological images of human brain



Amunts, K., Lepage, C., Borgeat, L., Mohlberg, H., Dickscheid, T., Rousseau, M. É., ... & Shah, N. J. (2013). BigBrain: an ultrahigh-resolution 3D human brain model. *Science*, *340*(6139), 1472-1475.

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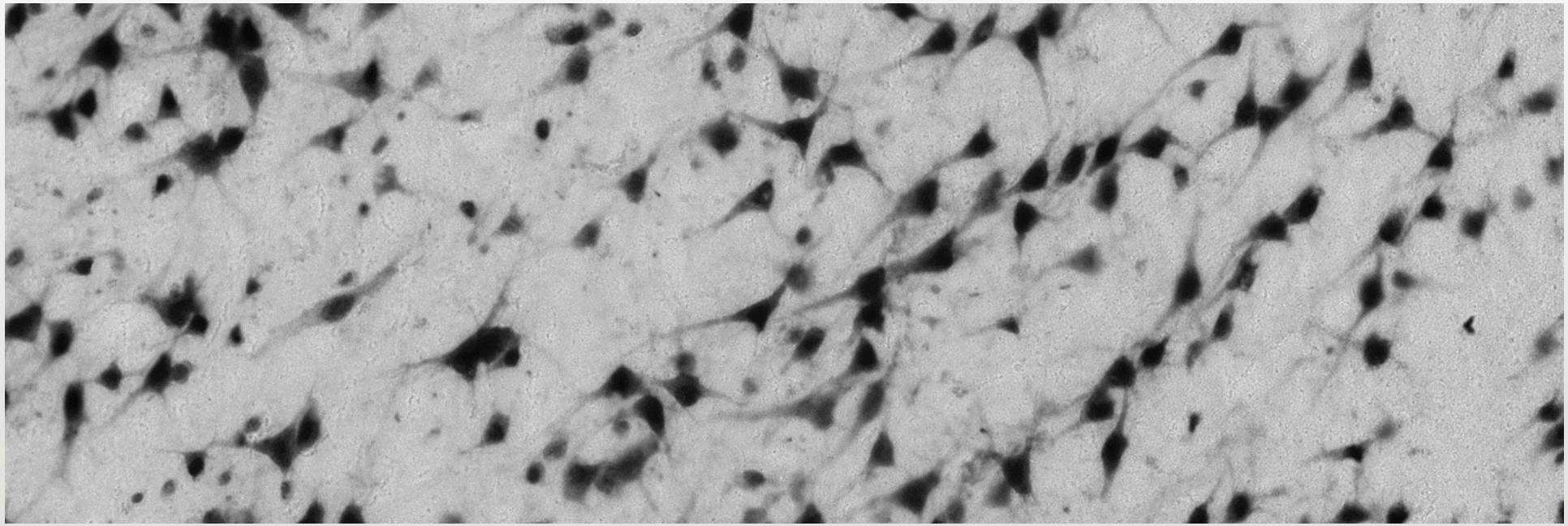
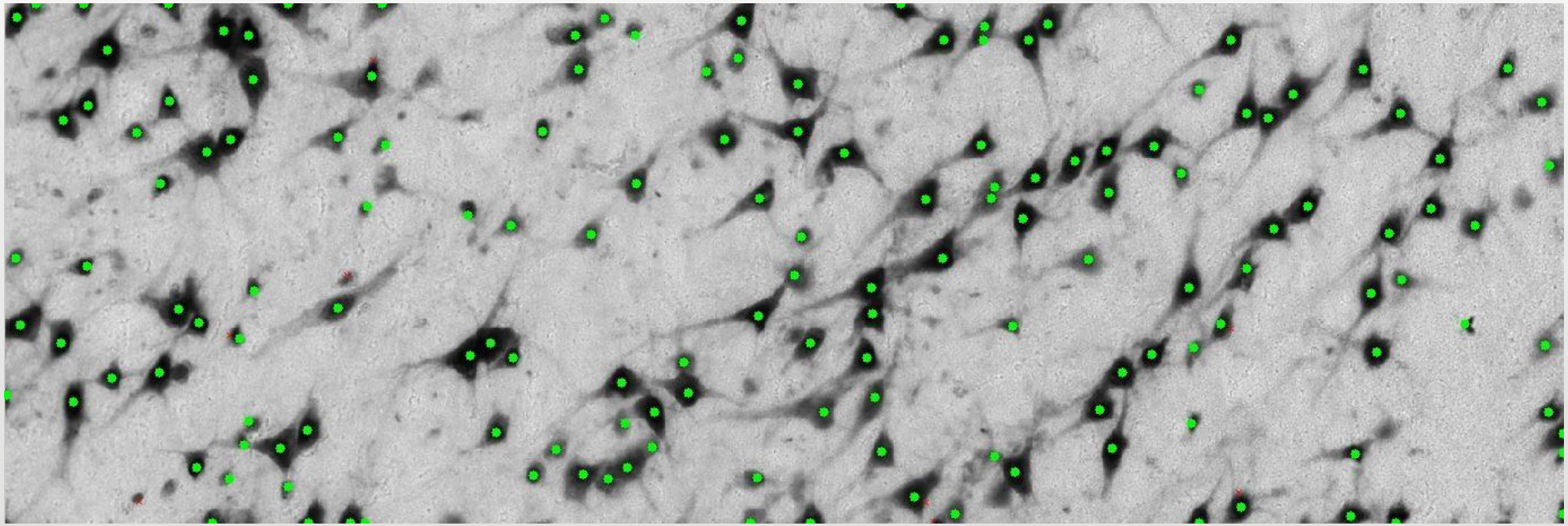
Neuron detection



- NeuN – nuclei antibody, higher dye uptake in cell nucleus
- Local minimum of image intensity – nucleus
- Remove noise, keep local minima

Neuron detection



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PDE-based image processing

- Partial differential equations (PDEs) introduced a new approach in digital image processing with strong theoretical background and development of new filters
- Initial (Cauchy) problem on image doimain

$$\begin{cases} u_t = \Delta u & \Omega \times \langle 0, \infty \rangle \\ u = Im & \Omega \times \{t = 0\} \end{cases}$$

- Perona-Malik model

$$\begin{cases} u_t = \text{div}\left(f(|\nabla u|^2)\,\nabla u\right) & \Omega \times \langle 0, \infty \rangle \\ u = Im & \Omega \times \{t = 0\} \end{cases}$$

$$f(|\nabla u|^2) = e^{-\frac{|\nabla u|^2}{\kappa}}$$

Perona, P., Malik, J., “Scale-space and edge detection using anisotropic diffusion”, IEEE Transactions on pattern analysis and machine intelligence, Vol. 12, No. 7, 1990, str. 629– 639.

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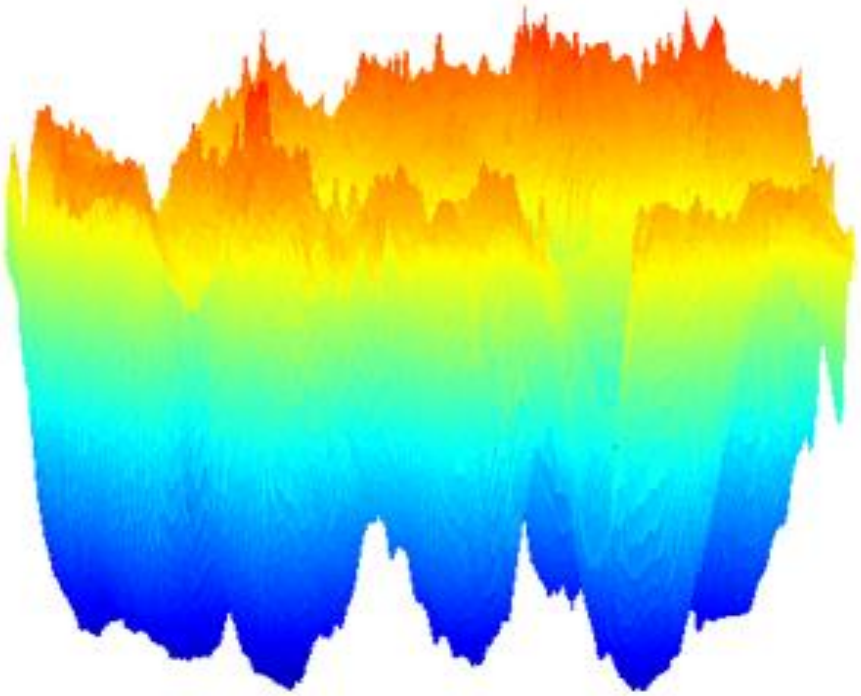

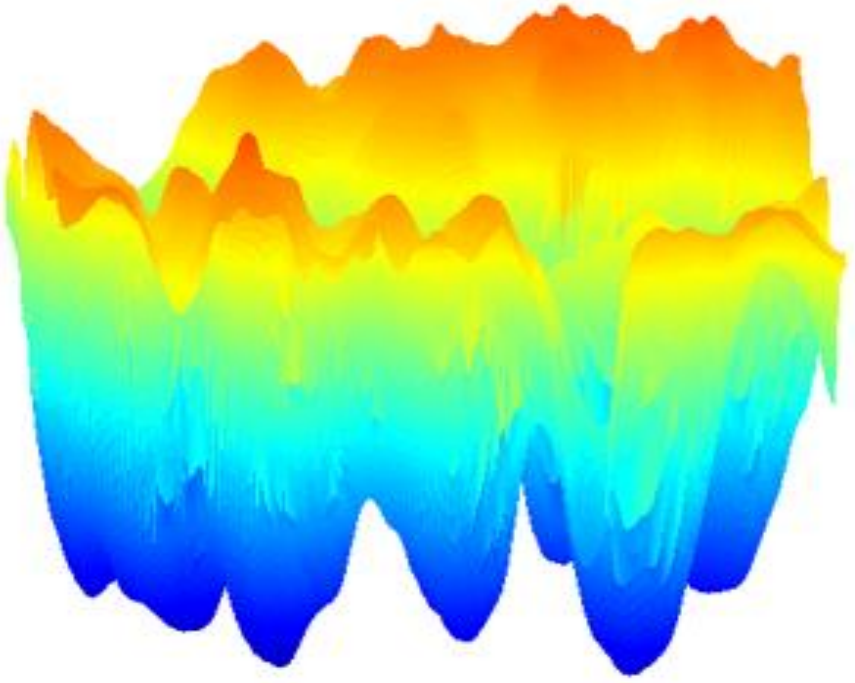

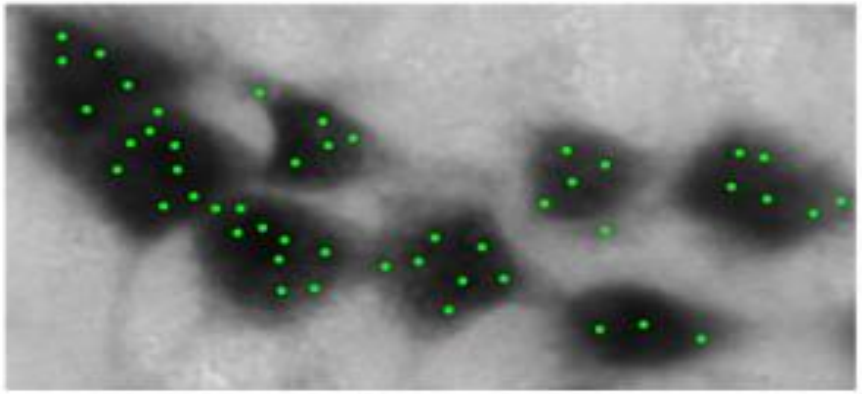

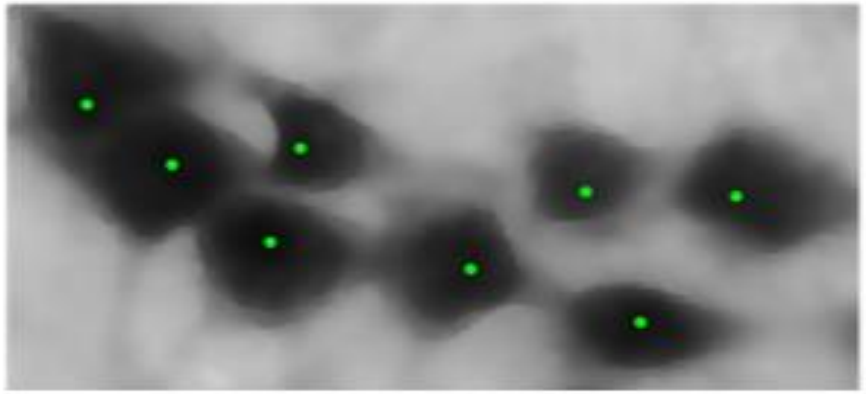

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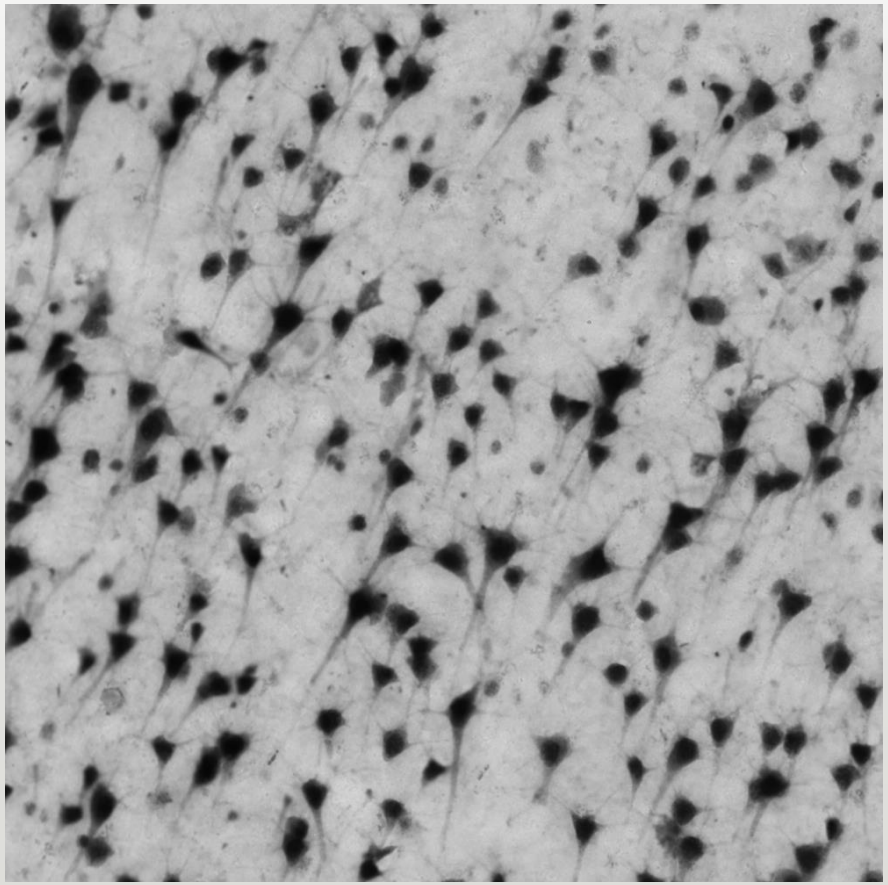
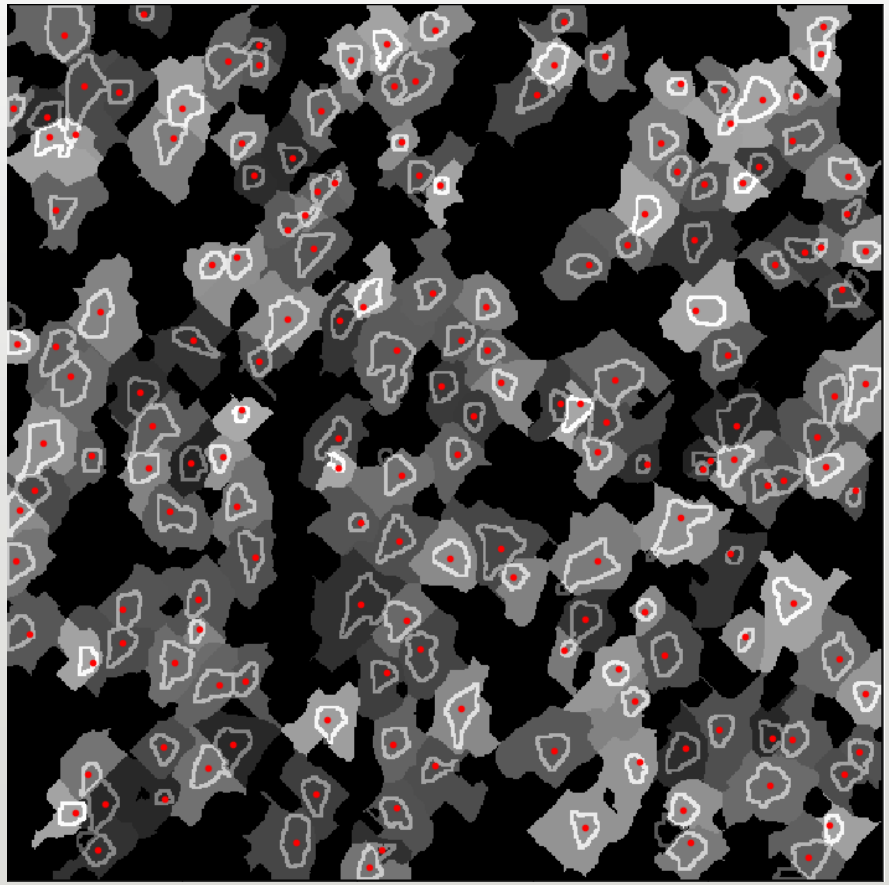
3D localization and segmentation





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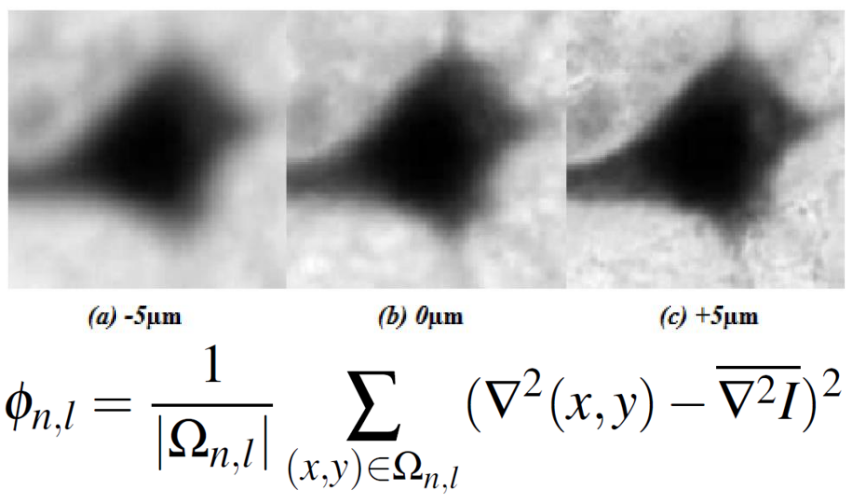
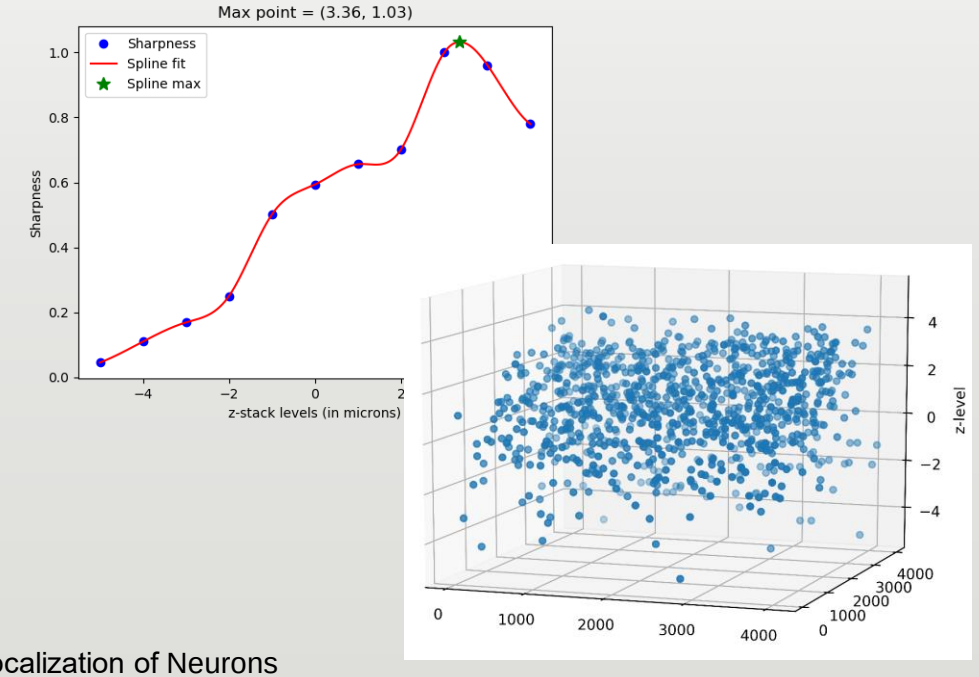
3D localization and segmentation

- Scanning in multiple focal planes, measuring variation of Laplacian
- Spline interpolation for more realistic 3D visualization



$$\phi_{n,l} = \frac{1}{|\Omega_{n,l}|} \sum_{(x,y)\in\Omega_{n,l}} (\nabla^2(x,y) - \overline{\nabla^2 I})^2$$



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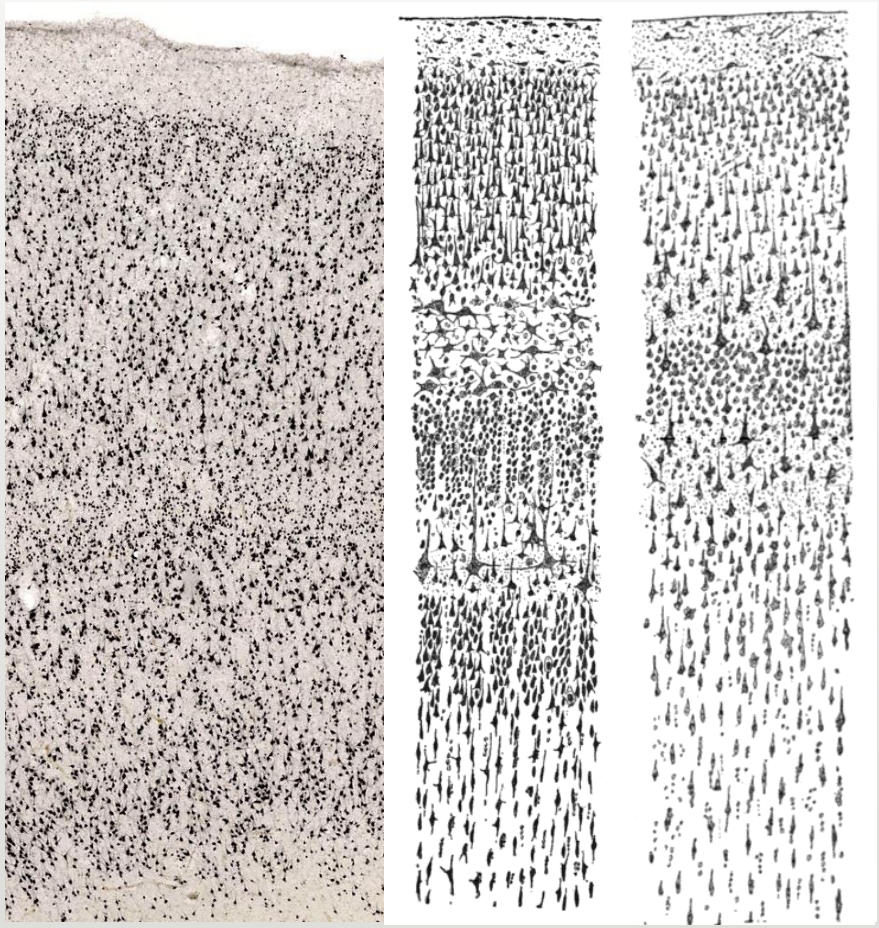
Analysis of laminar structure of the cortex

- Analyze neuron distribution across layers of the cortex
- Include neighborhood
- Develop new neuron descriptors
- Automatically segment cortical layers
- Learn from manual segmentations



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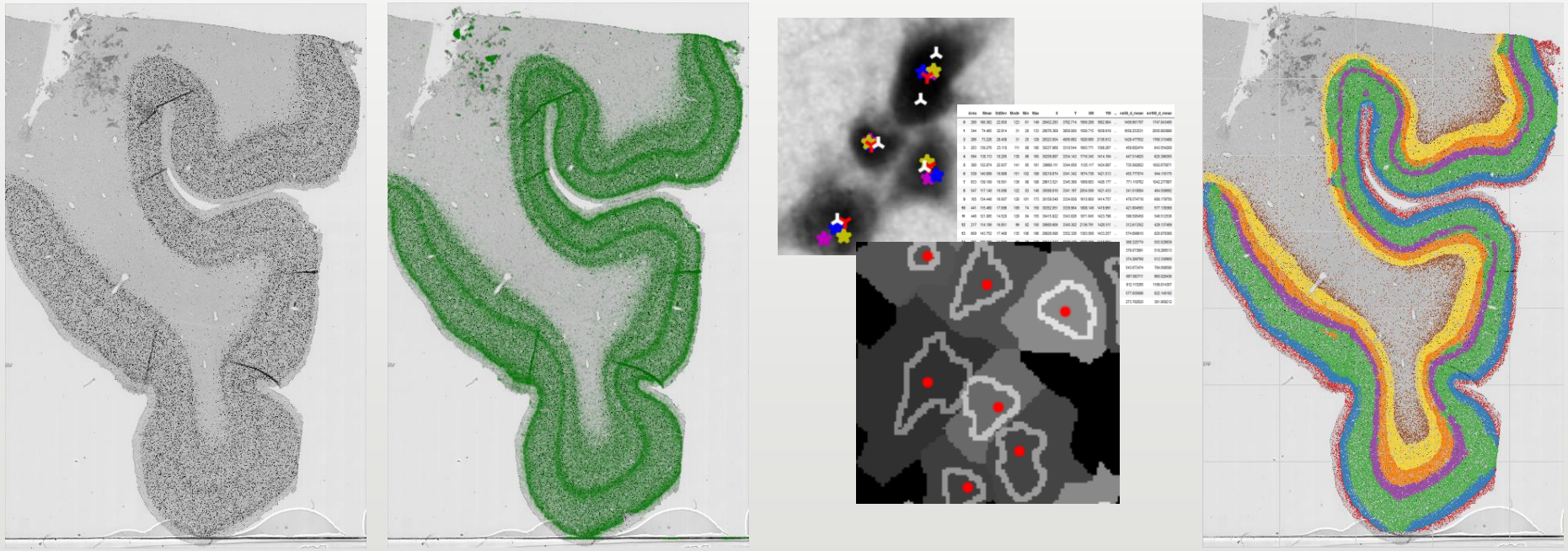
Neuron-level layer segmentation



Input → Feature engineering → Mapping from features → Output

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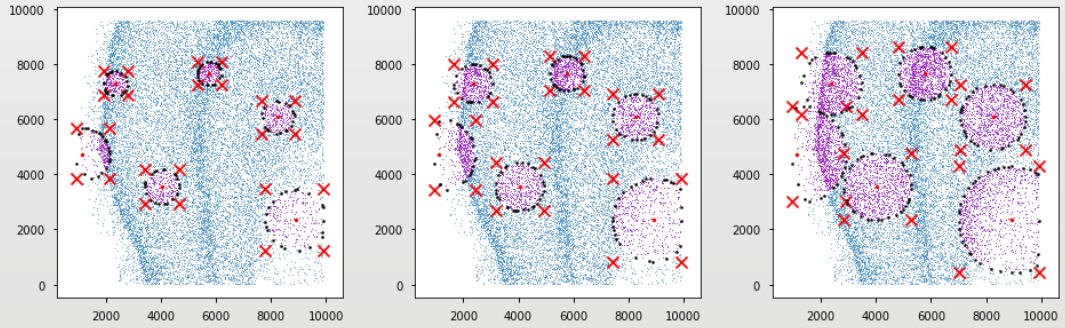
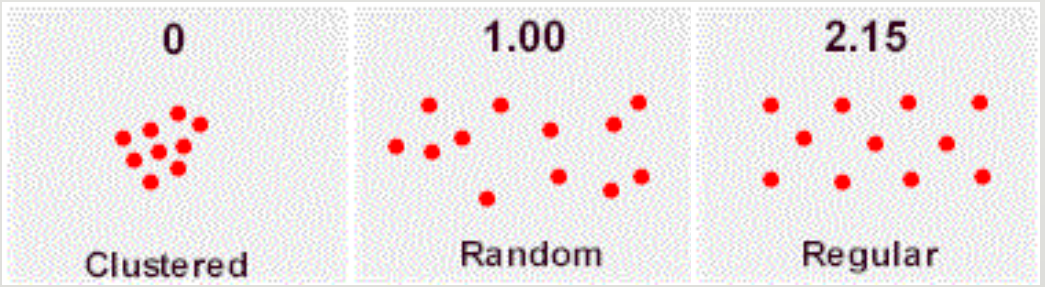
Feature engineering

- Hundreds of features developed for each neuron
- Area, gray value statistics, circularity, perimeter, roundness, solidity, …
- Measures of neighboring neurons
- Convex hull of neighborhoods
- Nearest neighbor index



$$NNI_i = \frac{\frac{1}{n}\sum_{j=1}^{n} d(i,j)}{0.5\sqrt{HullArea(i)/n}}$$



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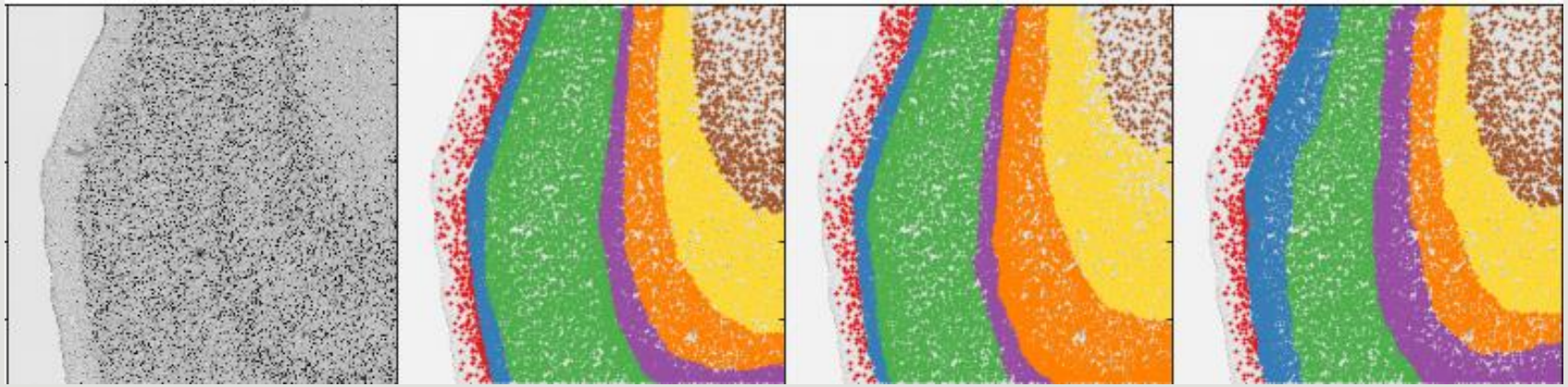
Relating neuron features with cortical layers

- No single feature provides clear segmentation of layers
- Goal: learn mapping from manual segmentations!
- Strong interrater variability – underlines the necessity for objective analysis



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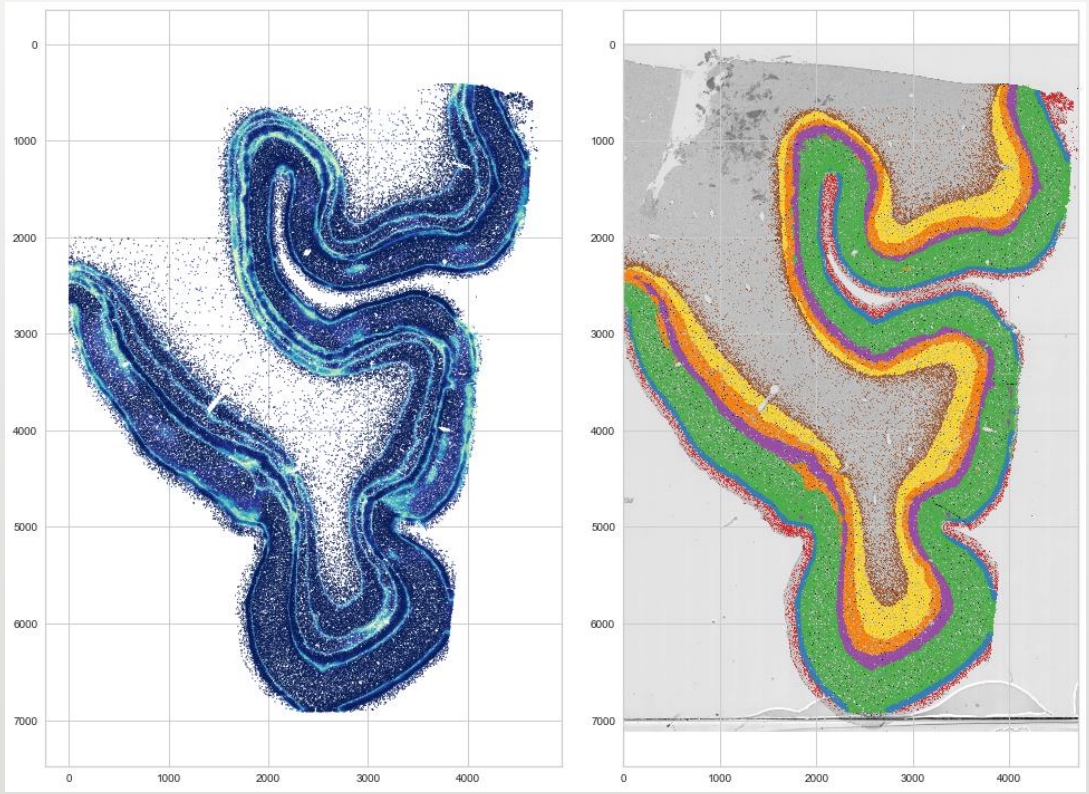
Machine learning models

- Ensembles of tree classifiers
  - No data preprocessing
  - Good performance without large dataset
  - Small computational cost
  - Simple to understand and interpret
  - Statistical, computational, representational reasons
- CATBoost Classfier



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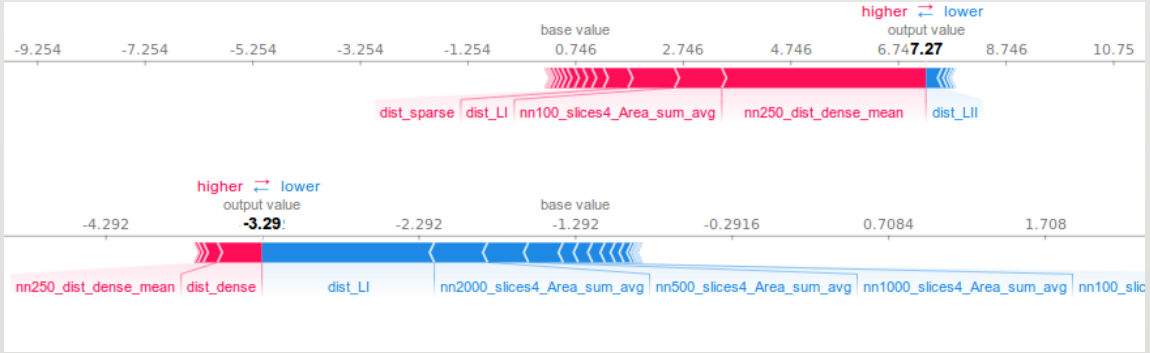
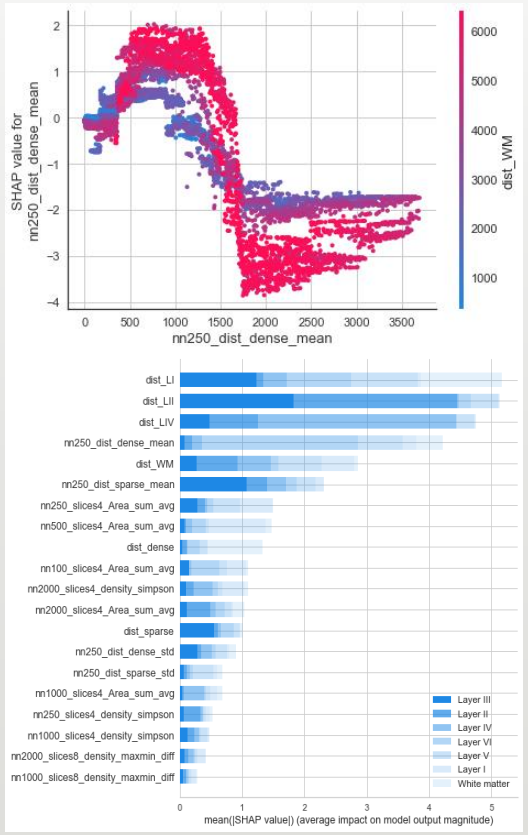
Analysis of feature distribution

- SHAP analysis
  - Model-agnostic
  - Accurate and interpretable
  - Feature interaction effects
  - Model- and instance-level analysis





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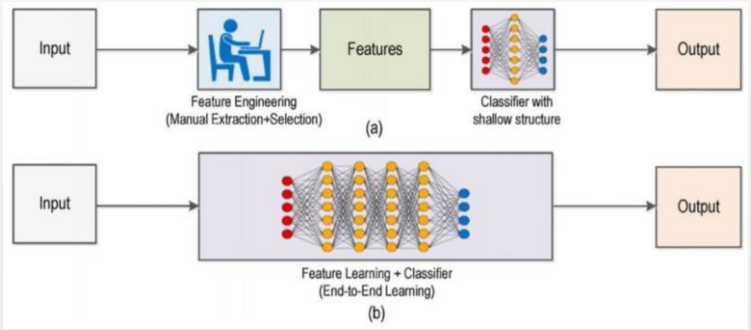
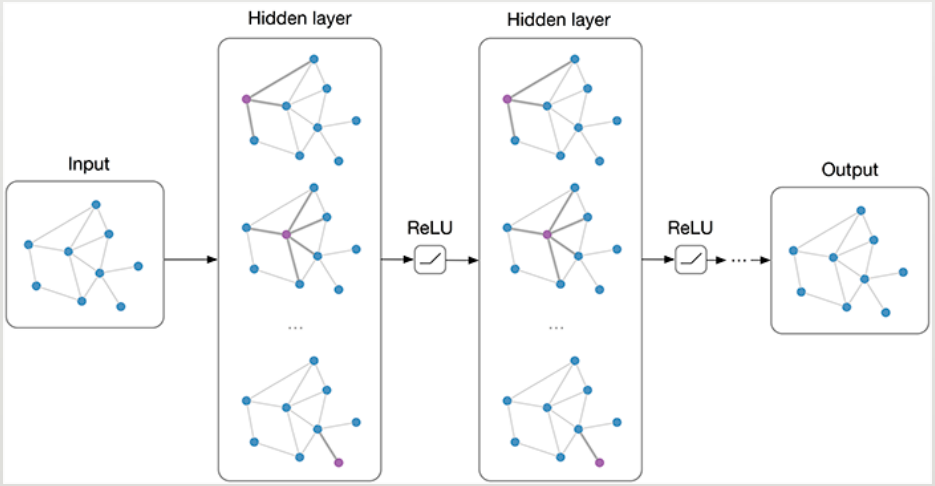
Future work

- End-to-end learning
- Graph convolutional neural networks





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Summary

- Framework for automatic detection of neurons yields precise neuron locations and segmentations
- First *bottom-up* methodology based on tissue features provides capacity for automatic segmentation of cortical layers and interpretation of cortical tissue features
- Introduction of computational methods to the field of histology sets path to bias-free, objective and explainable quantitative investigations

- This research helps shed light on following questions:
  - How are neurons rearranging with age?
  - Which changes are specific for normal ageing?
  - How does loss of neuronal elements affect neuronal populations in different brain areas?
  - Which changes in cytoarchitecture occur in different aging-related neurodegenerative diseases

Thank you

Thank you for your attention.

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presentation slides
github.com/astajd/BFHA

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