



Classification of tissue variations in X-ray scanning microdiffraction from thin sections of human brain

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Presented by

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Outline

- Problem Statement/ Objective
- Block diagram of stages/ Work Flow
- Human brain tissue preparation at Mass General Hospital (MGH)
- X-ray microdiffraction at Brookhaven National Laboratory (BNL)
- SAXS-WAXS Data pre-processing
- Unsupervised Classification
- Data Visualization using t-SNE
- Conclusion

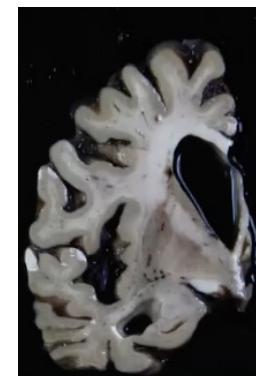


What problem are we trying to solve?

- β -amyloid plaques and neurofibrillary tangles (NFTs) are major hallmarks of pathology in Alzheimer's disease (AD).
- The plaques and NFTs exhibit wide structural variations in different regions of human brain.
- With the use of small (SAXS) and wide (WAXS) angle scattering from histological sections of AD human brain tissue, the underlying fibrillar shape, structure, and types of tissue lesions can be analyzed, detected, and classified over the different parts of individual and multiple human brains from AD subjects.



Normal Human Brain



Alzheimer Disease Human Brain

courtesy: Dr. Derek H Oakley, Mass General Hospital



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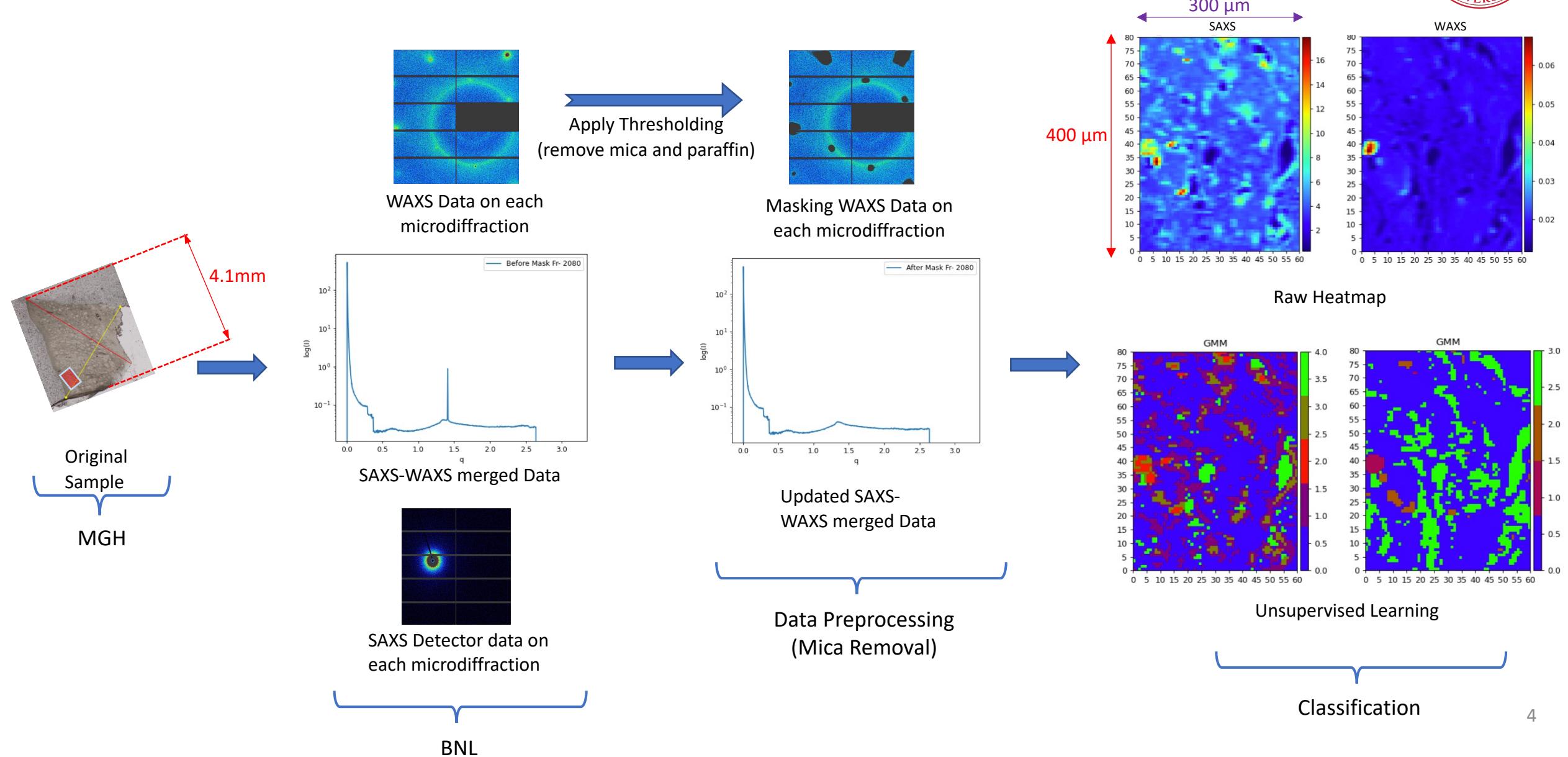


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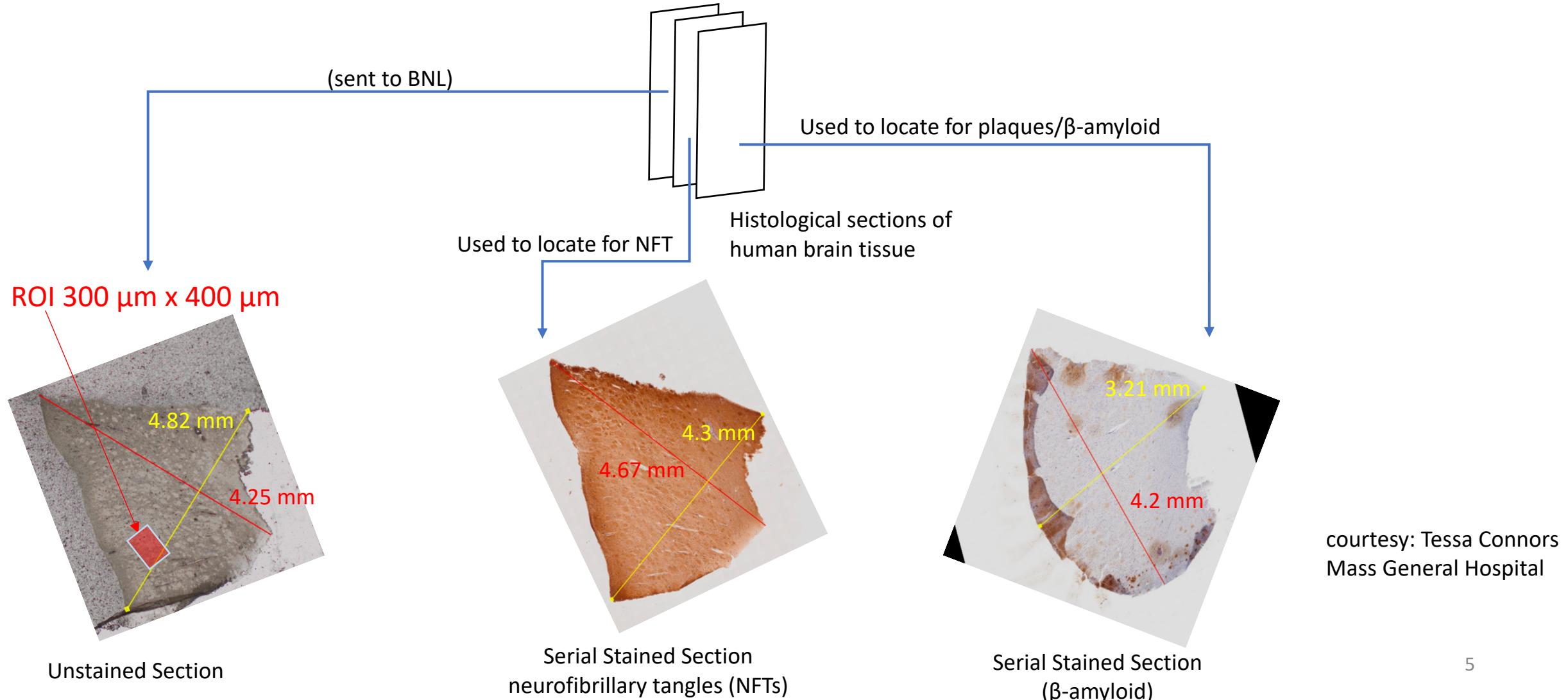
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How can we solve this classification problem?

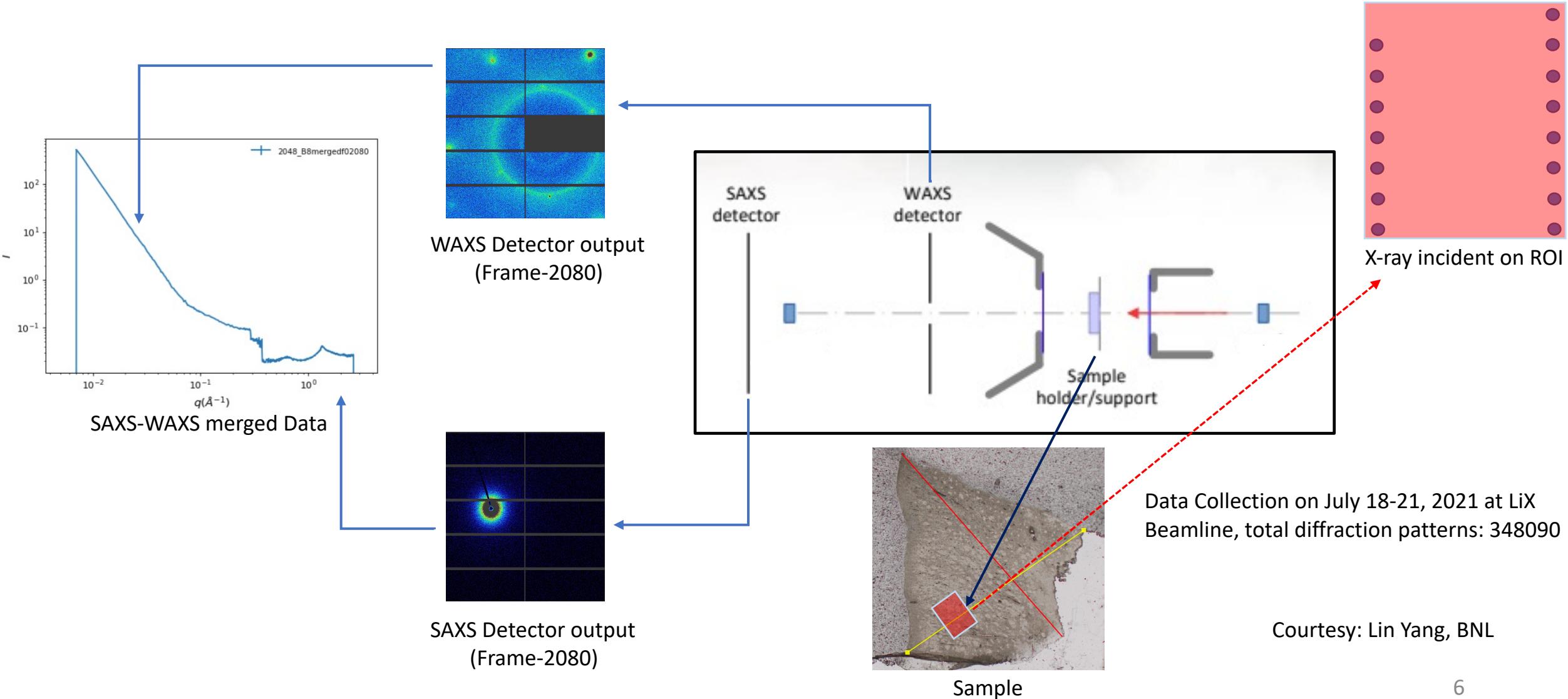


Histological sections of human brain tissue with AD

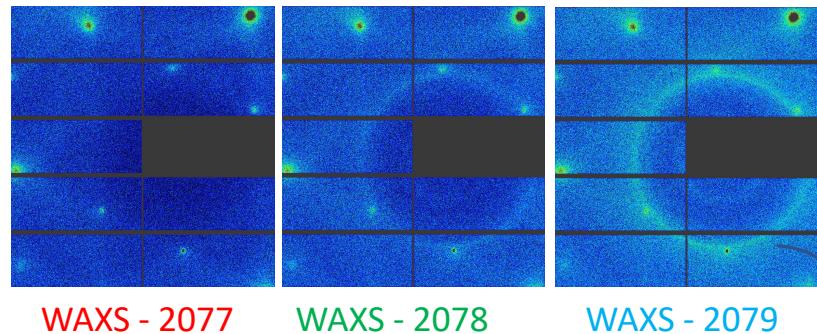
- Sample prepared by Mass General Hospital
- Sample placed on a 12 μm thick Mica substrate



X-ray microdiffraction at Brookhaven National Laboratory

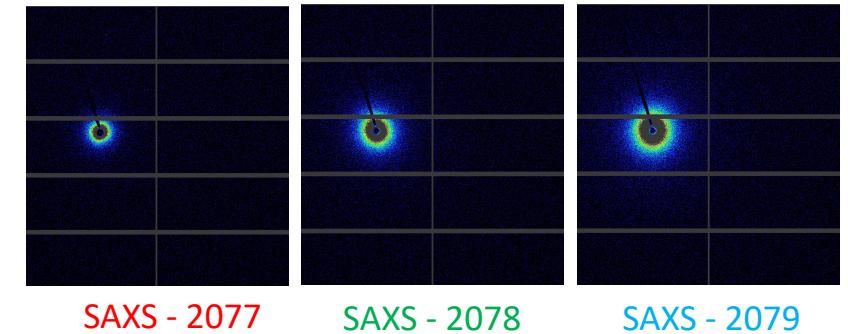
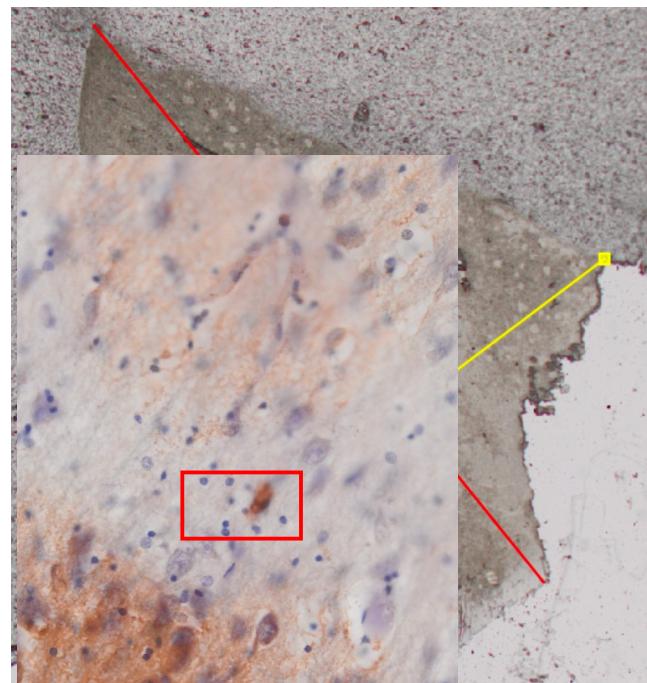


What happens when X-ray hits plaque?



WAXS - 2077 WAXS - 2078 WAXS - 2079

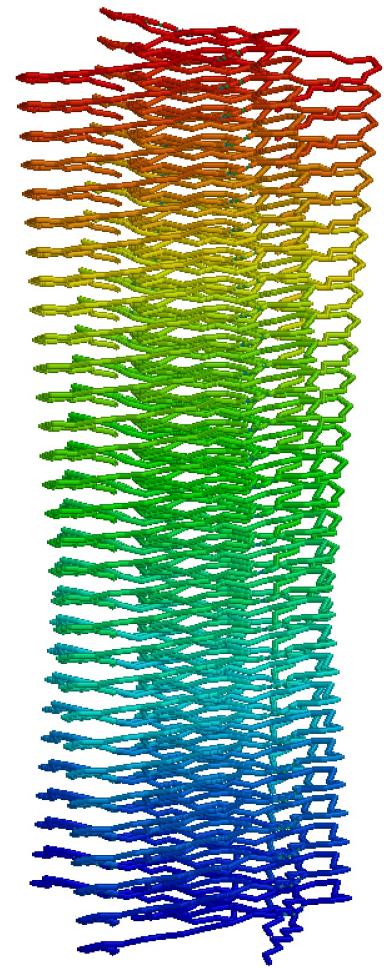
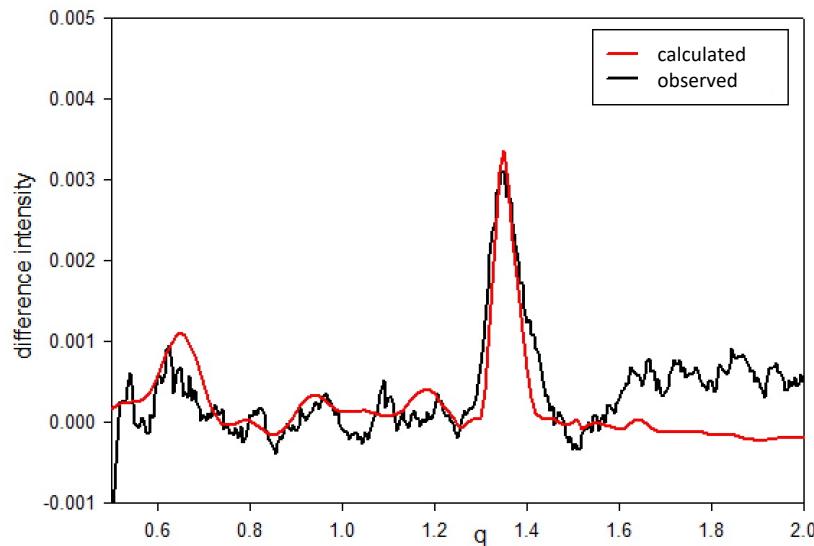
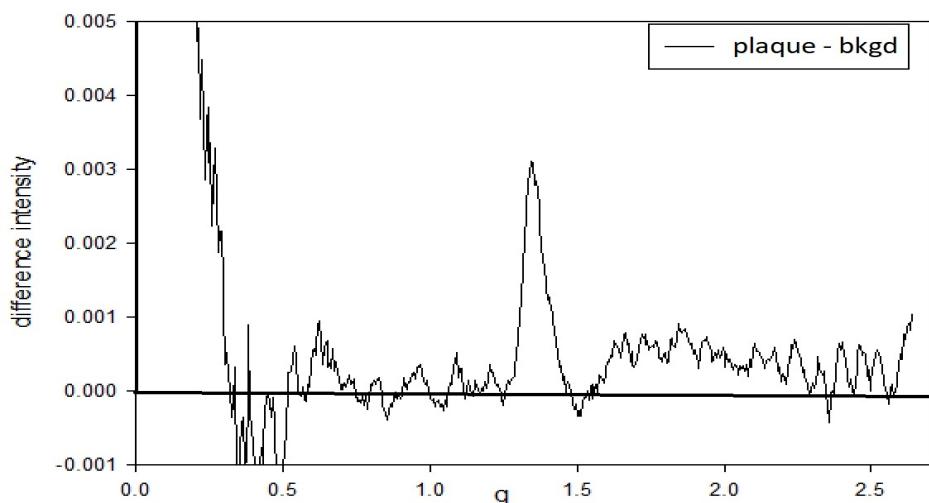
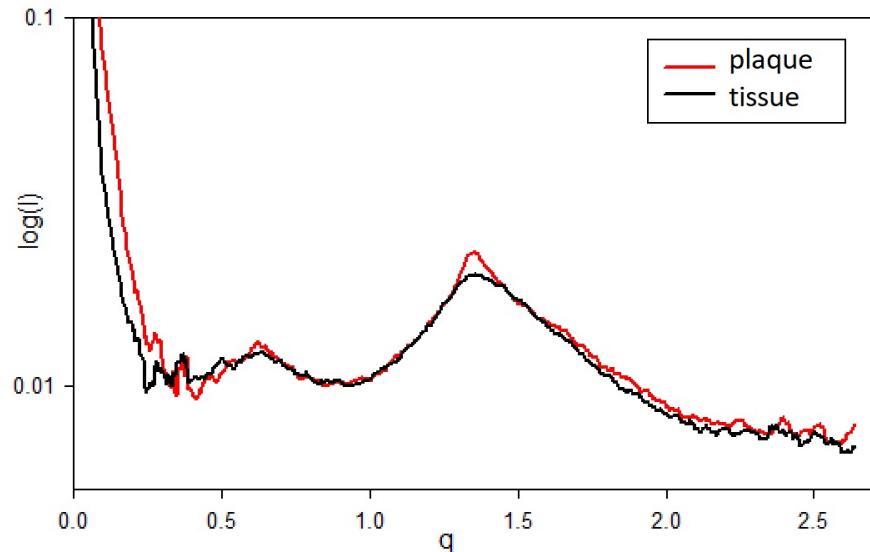
Pronounced 4.7 \AA ring while X-ray hits amyloid



SAXS - 2077 SAXS - 2078 SAXS - 2079

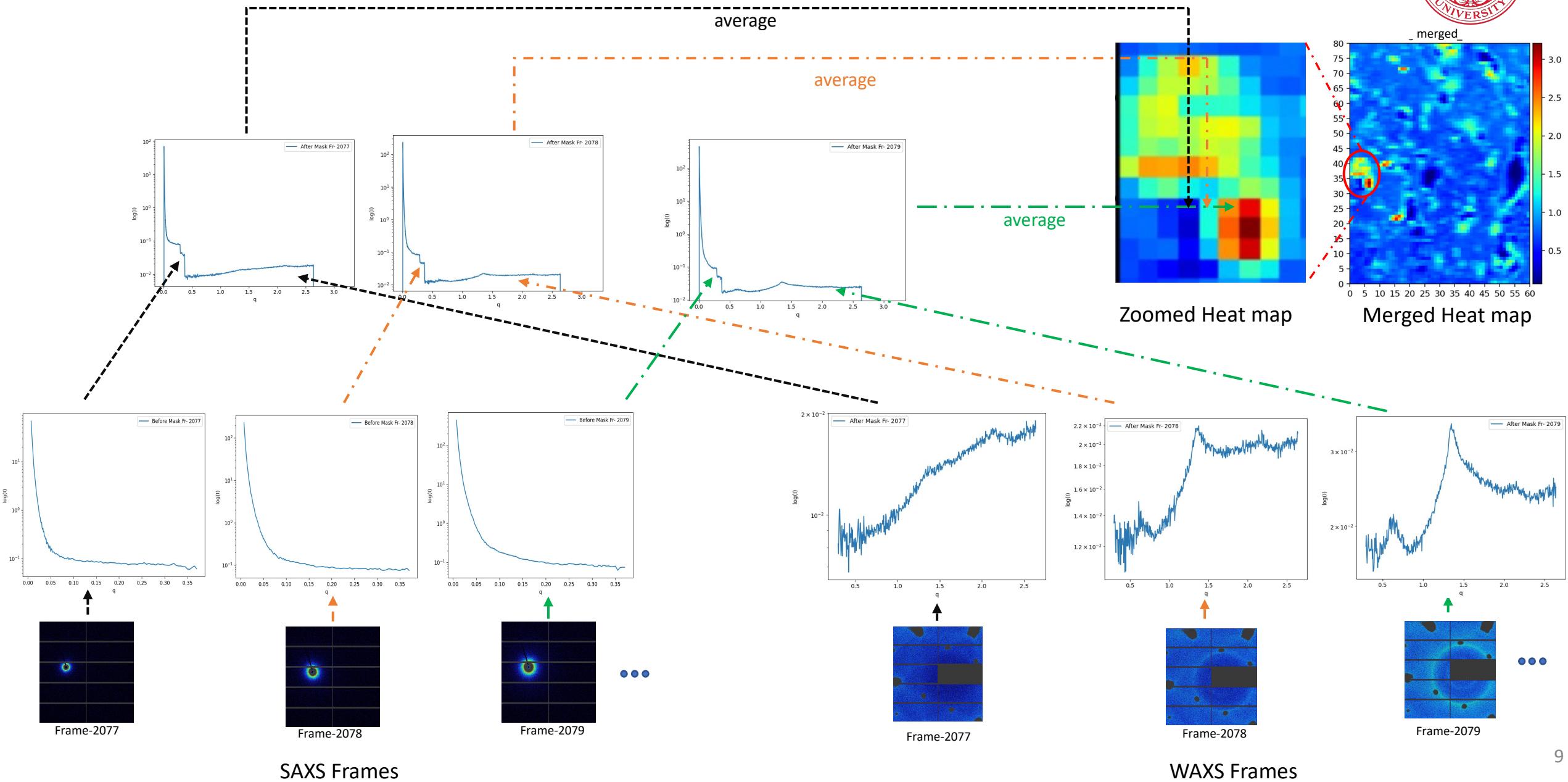
Xray incident on tissue sample

Micro diffraction from Amyloid

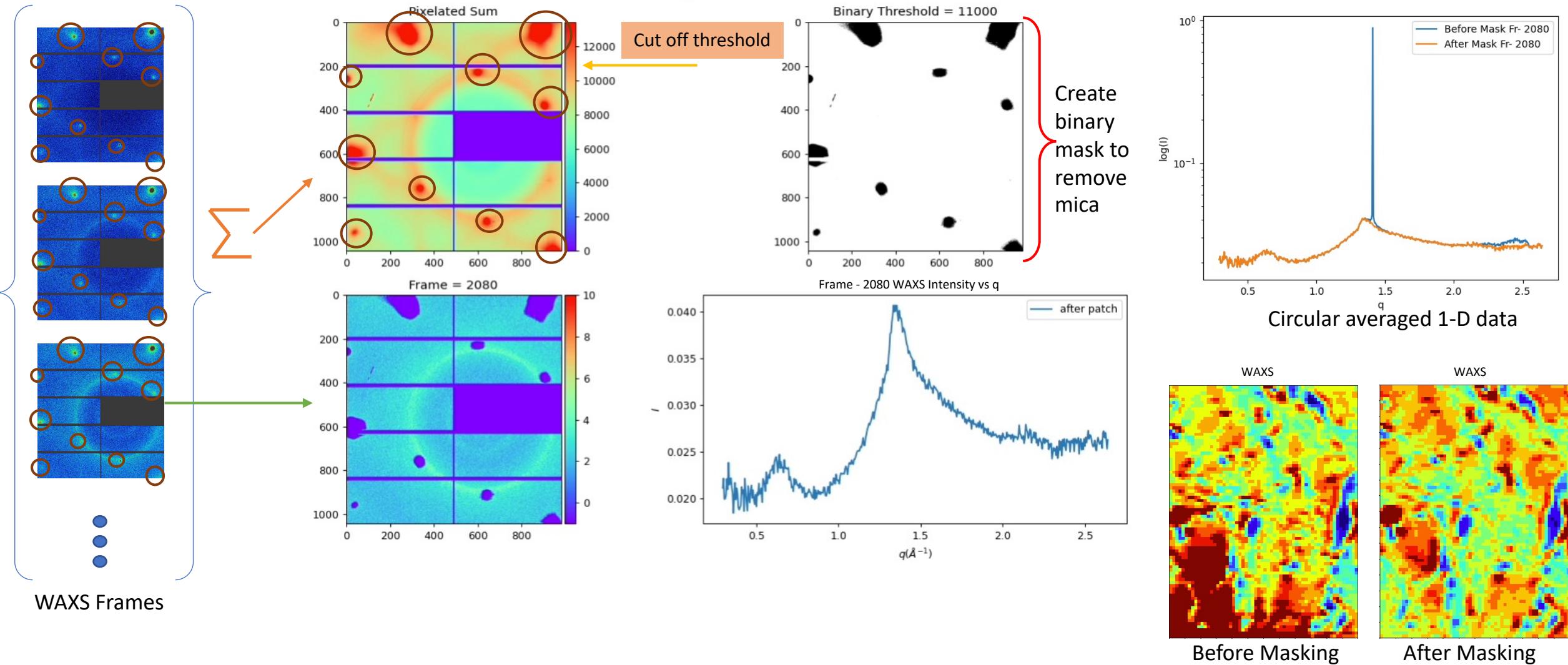


courtesy: Deepti Murthy

How to generate a Heatmap/reconstruct ROI?



Removal of mica and paraffin scattering using thresholding



What is the purpose of unsupervised learning/classifier ?

- Mapping the variability of scattering into multiple classes

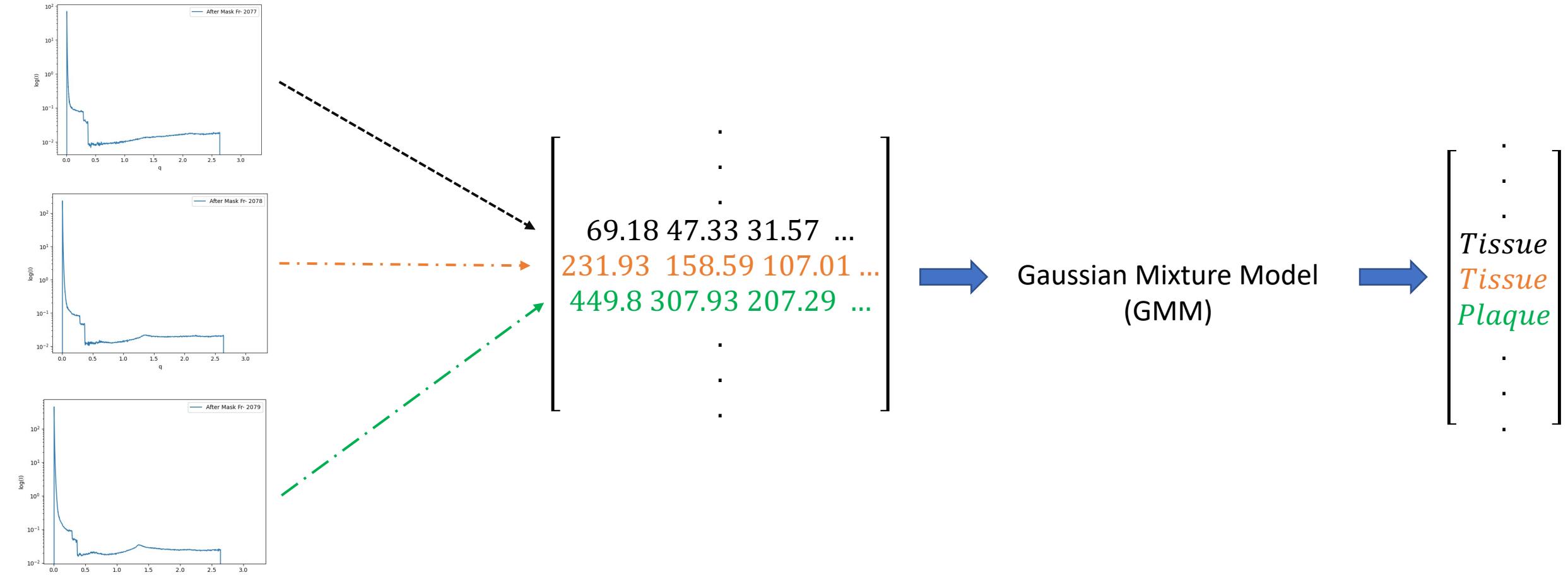
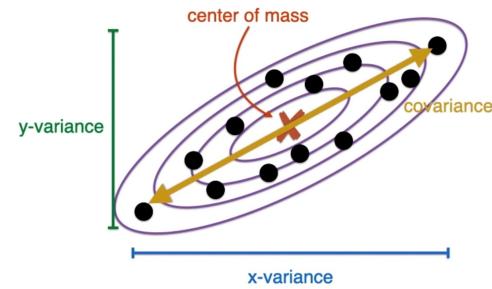


Fig: Structure of an unsupervised learning algorithm



Gaussian Mixture Model (GMM)

Fitting a Gaussian



μ = Average

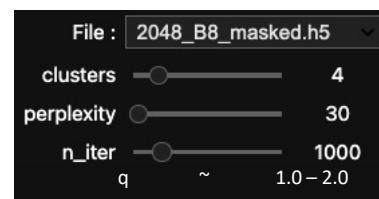
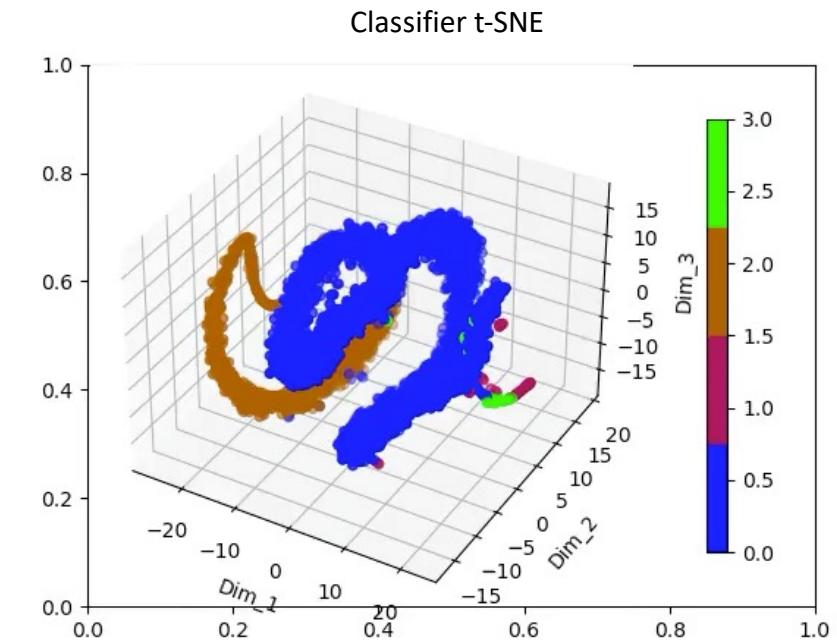
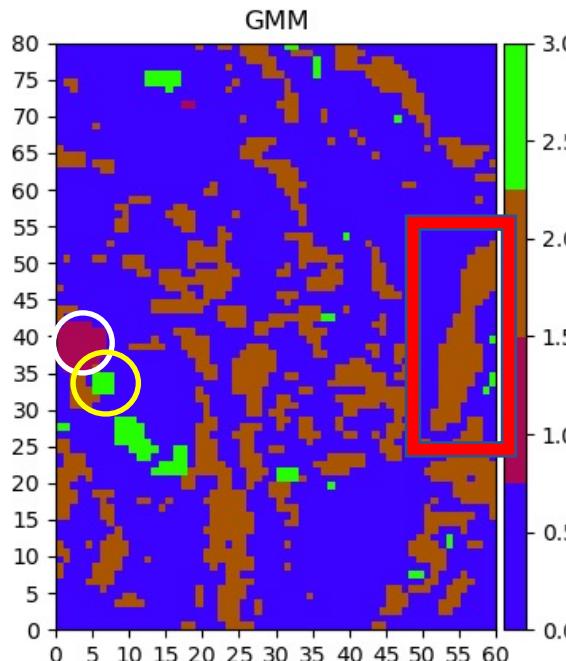
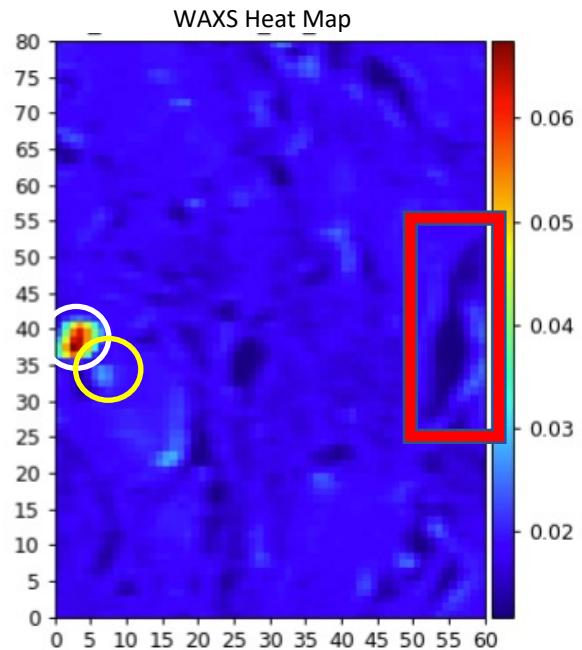
$$\Sigma = \begin{pmatrix} Var(x) & Cov(x, y) \\ Cov(x, y) & Var(y) \end{pmatrix}$$

$$f(x) = \frac{\exp(-\frac{1}{2}(x - \mu)^T \Sigma^{-1} (x - \mu))}{2\pi\sqrt{|\Sigma|}}$$

$$f(x) = \frac{1}{\sqrt{2\pi}\sigma} e^{(-\frac{1}{2}(\frac{x-\mu}{\sigma})^2)}$$

Summary

Gaussian Mixture Model for WAXS



Classification attributes

unpublished



Conclusion/Take away

- Binary thresholding helps masking mica and paraffin
- SAXS-WAXS diffractions from tissue can be distinguished by unsupervised machine learning algorithm
- t-SNE is a powerful tool to visualize the classified categories
- Background Subtraction may produce even cleaner categorization
- GMM algorithm can produce relative good correspondence with Raw heatmaps
- Next Step - Interpretation of the diffraction patterns in terms of the spatial distribution of amyloid and NFT polymorphs in brain tissues.



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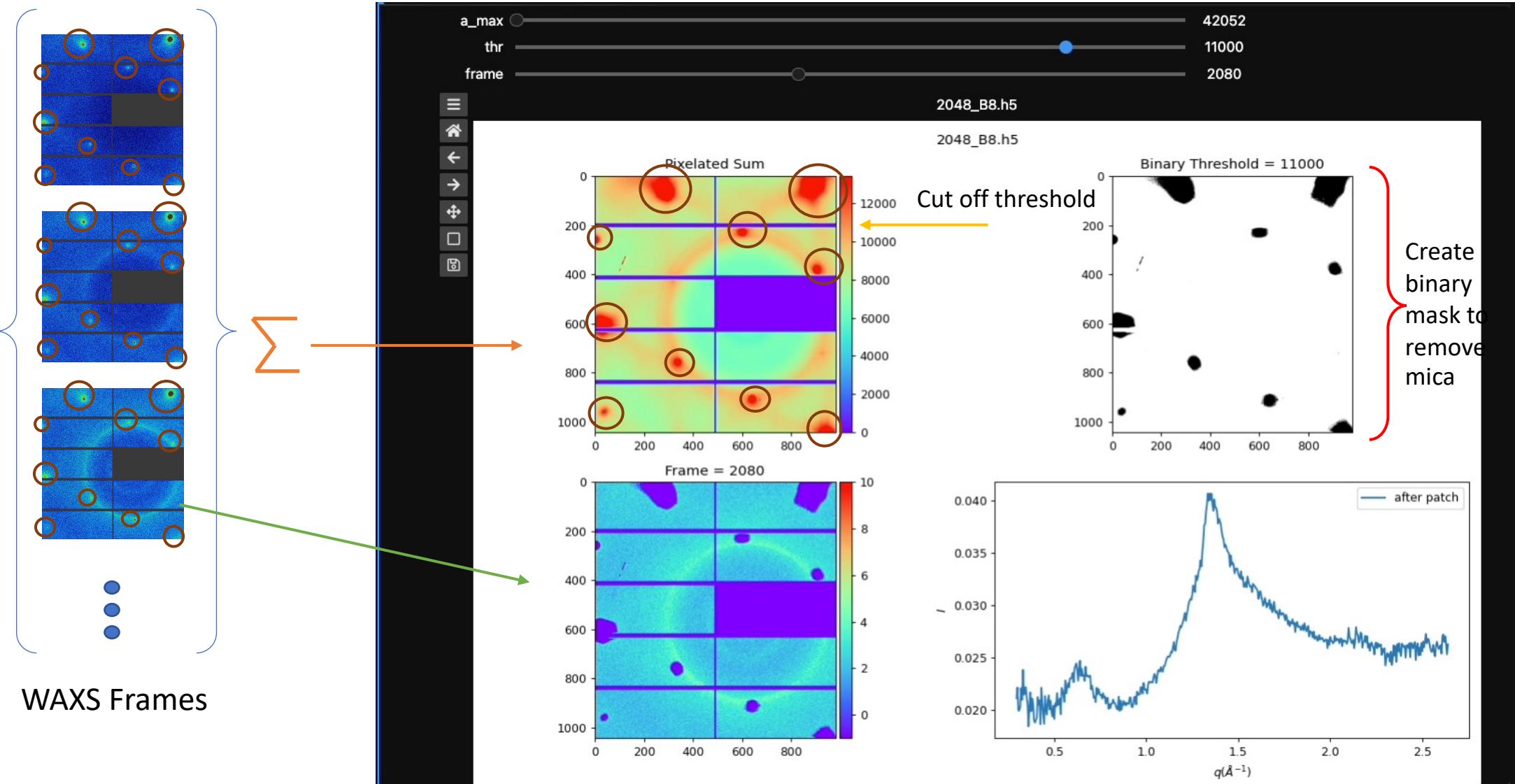


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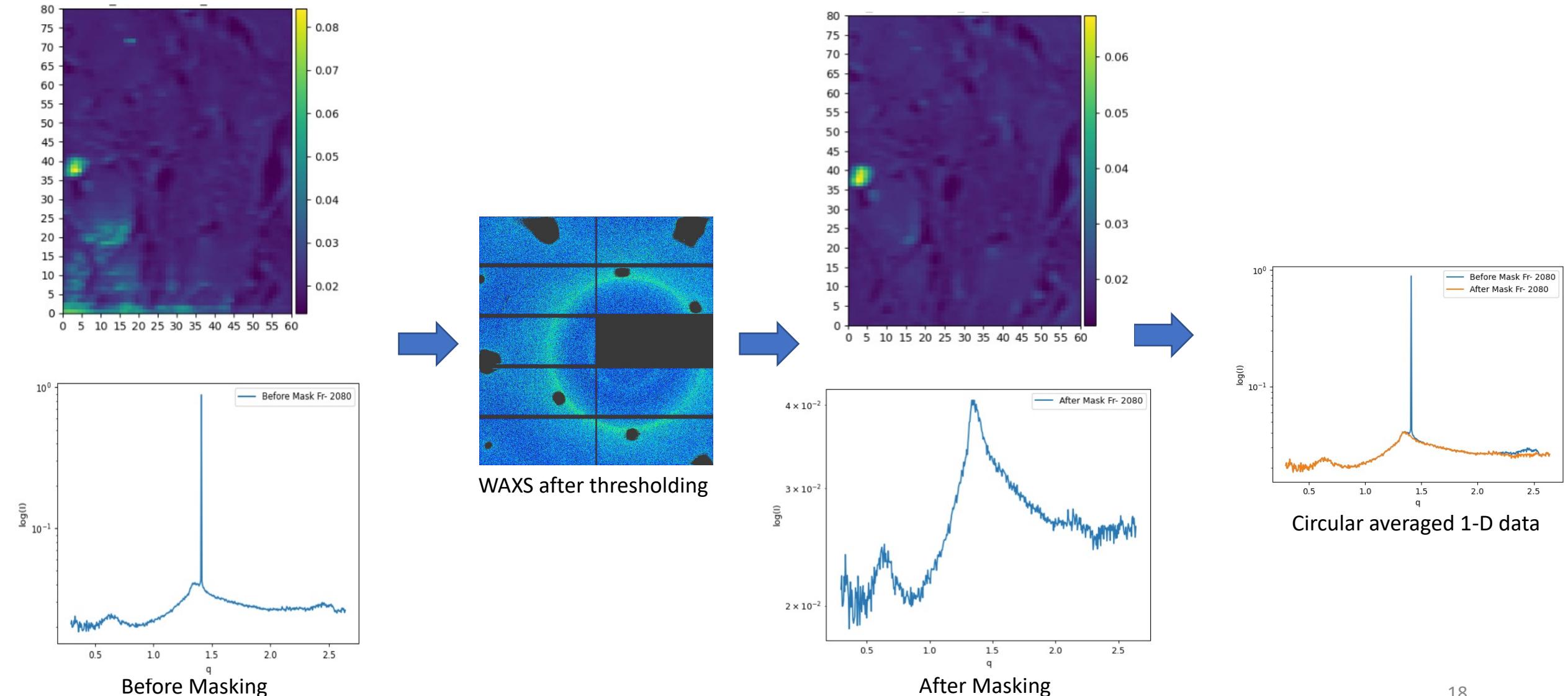


Thank You!
Questions

Removal of mica and paraffin scattering using thresholding



Removal of mica and paraffin scattering using thresholding (cont'd)





Solution scattering vs tissue scattering

- Tissues are heterogeneous
- During sample preparation tissues are partially dehydrated
- But, some constituents are denatured
- Cross beta amyloid structures largely preserved
- Our primary interest is in relative position of plaques and NFTs
- As brain is polymorphic in every scale – that is what we want to explore

t-distributed Stochastic Neighbor Embedding (t-SNE)

$$p_{j|i} = \frac{\exp(-\|x_i - x_j\|^2 / 2\sigma_i^2)}{\sum_{k \neq i} \exp(-\|x_i - x_k\|^2 / 2\sigma_i^2)},$$

$$q_{ij} = \frac{(1 + \|y_i - y_j\|^2)^{-1}}{\sum_{k \neq l} (1 + \|y_k - y_l\|^2)^{-1}}.$$

$$C = \sum_i KL(P_i || Q_i) = \sum_i \sum_j p_{j|i} \log \frac{p_{j|i}}{q_{j|i}},$$

$$\frac{\delta C}{\delta y_i} = 2 \sum_j (p_{j|i} - q_{j|i} + p_{i|j} - q_{i|j})(y_i - y_j).$$

$$\mathcal{Y}^{(t)} = \mathcal{Y}^{(t-1)} + \eta \frac{\delta C}{\delta \mathcal{Y}} + \alpha(t) (\mathcal{Y}^{(t-1)} - \mathcal{Y}^{(t-2)})$$

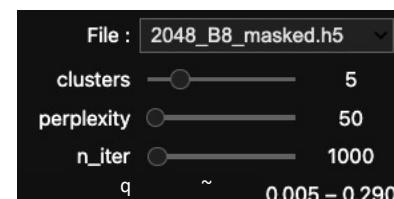
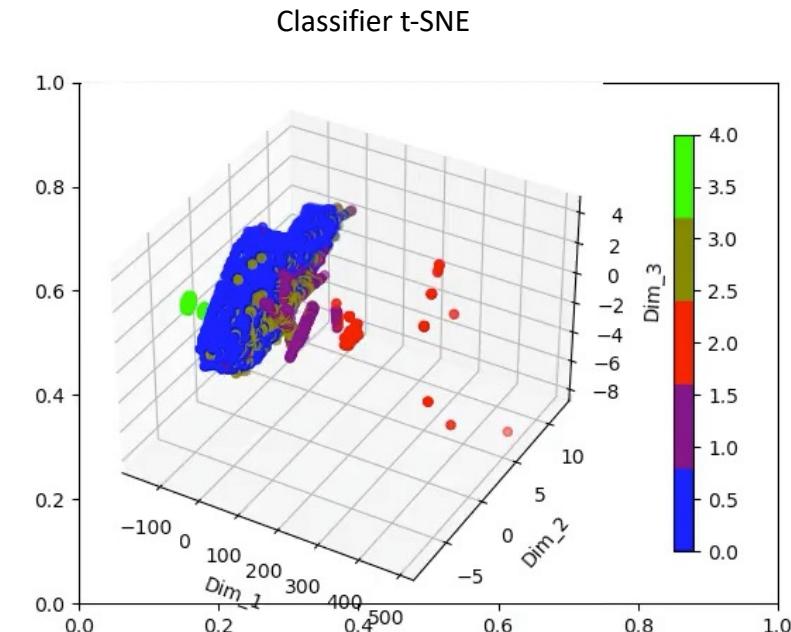
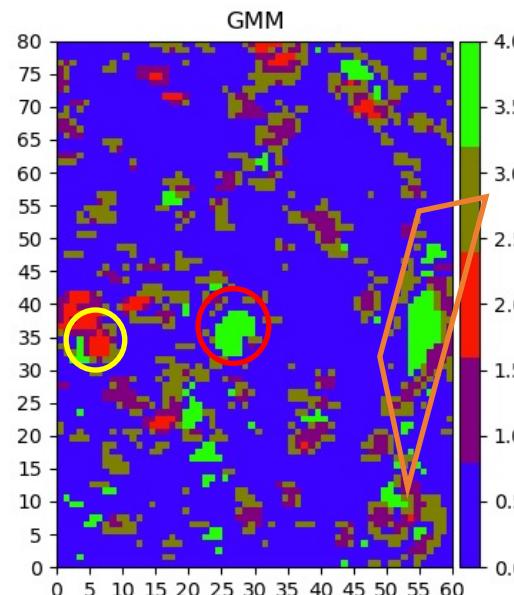
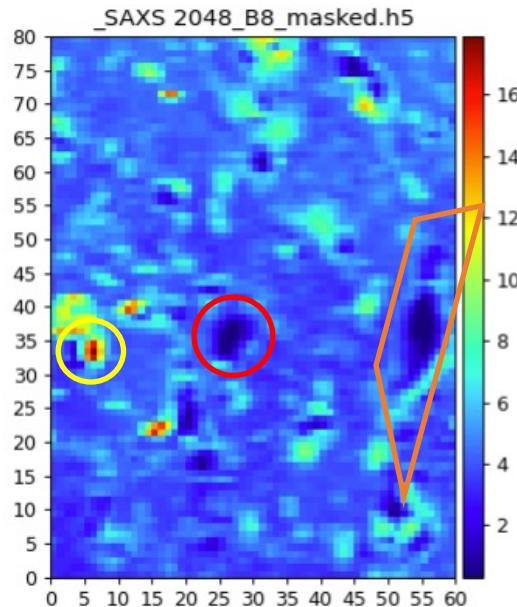
Algorithm 1: Simple version of t-Distributed Stochastic Neighbor Embedding.

Data: data set $\mathcal{X} = \{x_1, x_2, \dots, x_n\}$,
cost function parameters: perplexity $Perp$,
optimization parameters: number of iterations T , learning rate η , momentum $\alpha(t)$.
Result: low-dimensional data representation $\mathcal{Y}^{(T)} = \{y_1, y_2, \dots, y_n\}$.

begin

- compute pairwise affinities $p_{j|i}$ with perplexity $Perp$ (using Equation 1)
- set $p_{ij} = \frac{p_{j|i} + p_{i|j}}{2n}$
- sample initial solution $\mathcal{Y}^{(0)} = \{y_1, y_2, \dots, y_n\}$ from $\mathcal{N}(0, 10^{-4}I)$
- for** $t=1$ **to** T **do**
- compute** low-dimensional affinities q_{ij} (using Equation 4)
- compute** gradient $\frac{\delta C}{\delta \mathcal{Y}}$ (using Equation 5)
- set** $\mathcal{Y}^{(t)} = \mathcal{Y}^{(t-1)} + \eta \frac{\delta C}{\delta \mathcal{Y}} + \alpha(t) (\mathcal{Y}^{(t-1)} - \mathcal{Y}^{(t-2)})$
- end**
- end**

Gaussian Mixture Model for SAXS



Classification attributes