Cancer Detection in Full Field Optical Coherence Tomography Images

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A Multidisciplinary Project

Cancer Diagnosis

rapid tissue analysis

Label-free Imaging

- Full-Field Optical Coherence Tomography (*FFOCT*)
- Dynamic Cell Imaging (*DCI*)

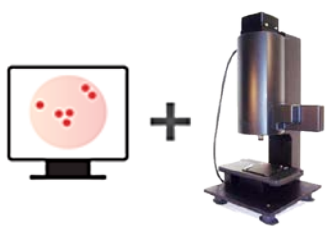
Image Analysis

- exploratory data analysis
- aid-to-diagnosis

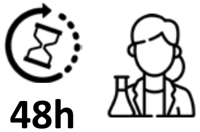
Enable use of novel imaging technique for cancer diagnosis via data analysis.

Clinical Context

- **Cancer** – one of the leading cause of death worldwide
- Gold standard for diagnosis is **tissue analysis** / histopathology
- Standard histopathology is **time** consuming, **labor** intensive
- A need for rapid diagnosis in **interventional** settings
- Pathologists **shortage**

Fix	Embed	Slice	Stain	Visualize	Diagnose
Fresh Tissue		Optical Slicing	Endogenous Contrast		
				novel technique	special training

Gold standard histology



48h

Label-free imaging

10min

Medical personnel needs training to interpret new contrast.

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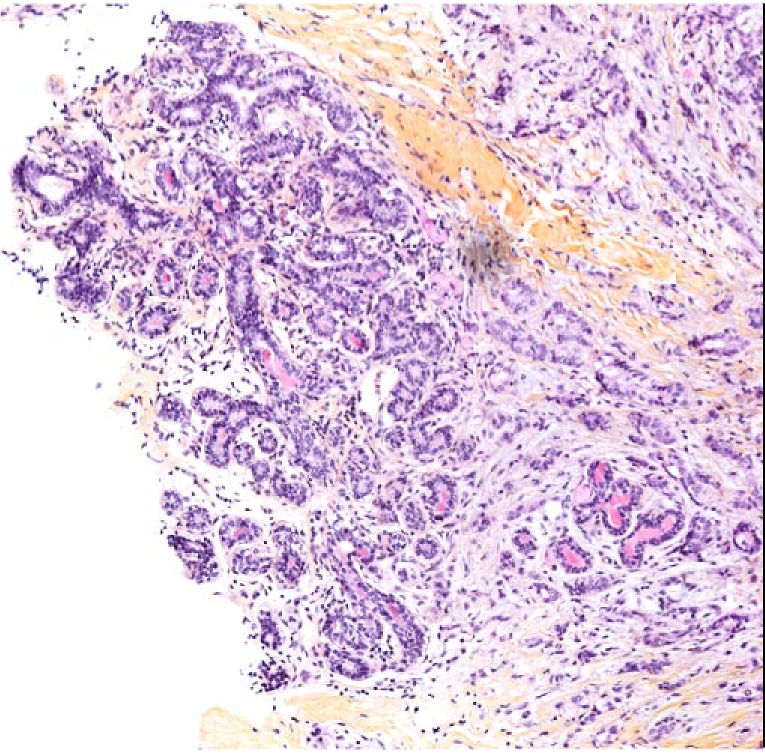
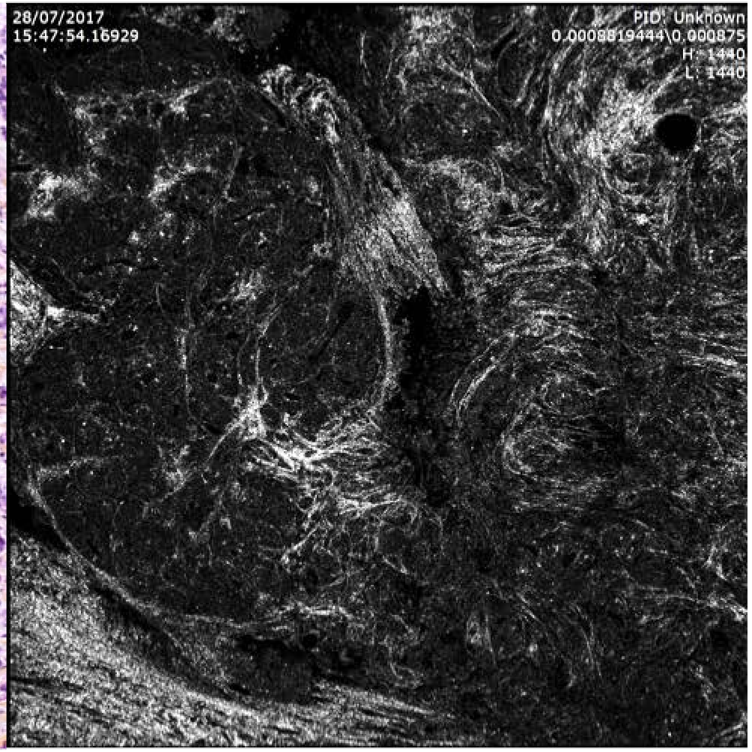
Imaging **Context**

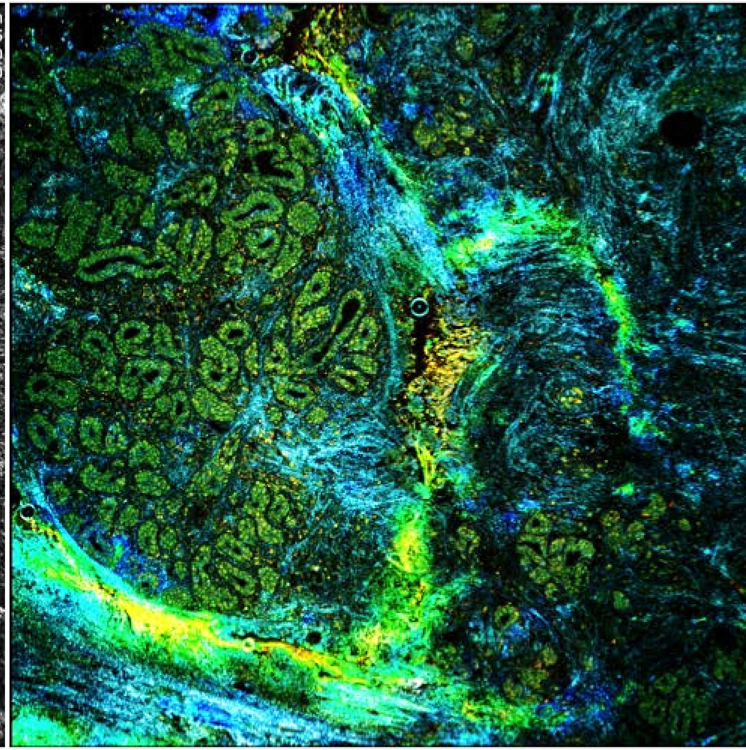
H&E Histology

Full-Field Optical Coherence Tomography **FFOCT**

Dynamic Cell Imaging **DCI**







normal breast lobule

Full-Field Optical Coherence Tomography FFOCT

FFOCT = *en face* OCT

Optical setup : Michelson interferometer

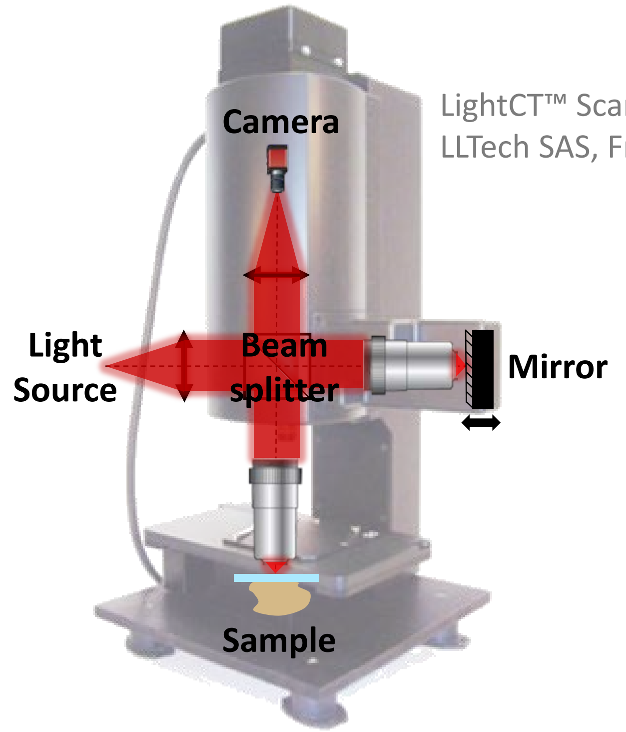
Light interferometry principle :

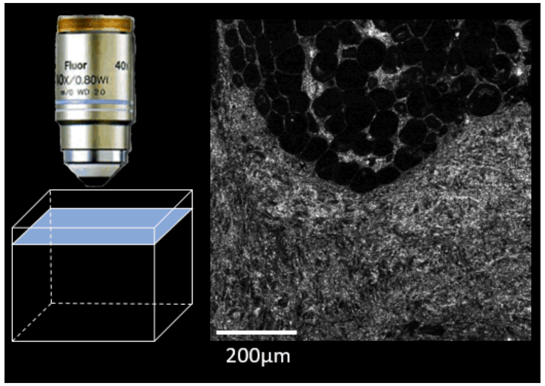
identical waves amplify when in phase, cancel when not

Low coherence interferometry:

large bandwidth = short coherence length ∝ *Z* resolution

PROS	CONS
good **resolution** (1µm)	**no cell information**
fast (seconds)	
reveals **fibers**	





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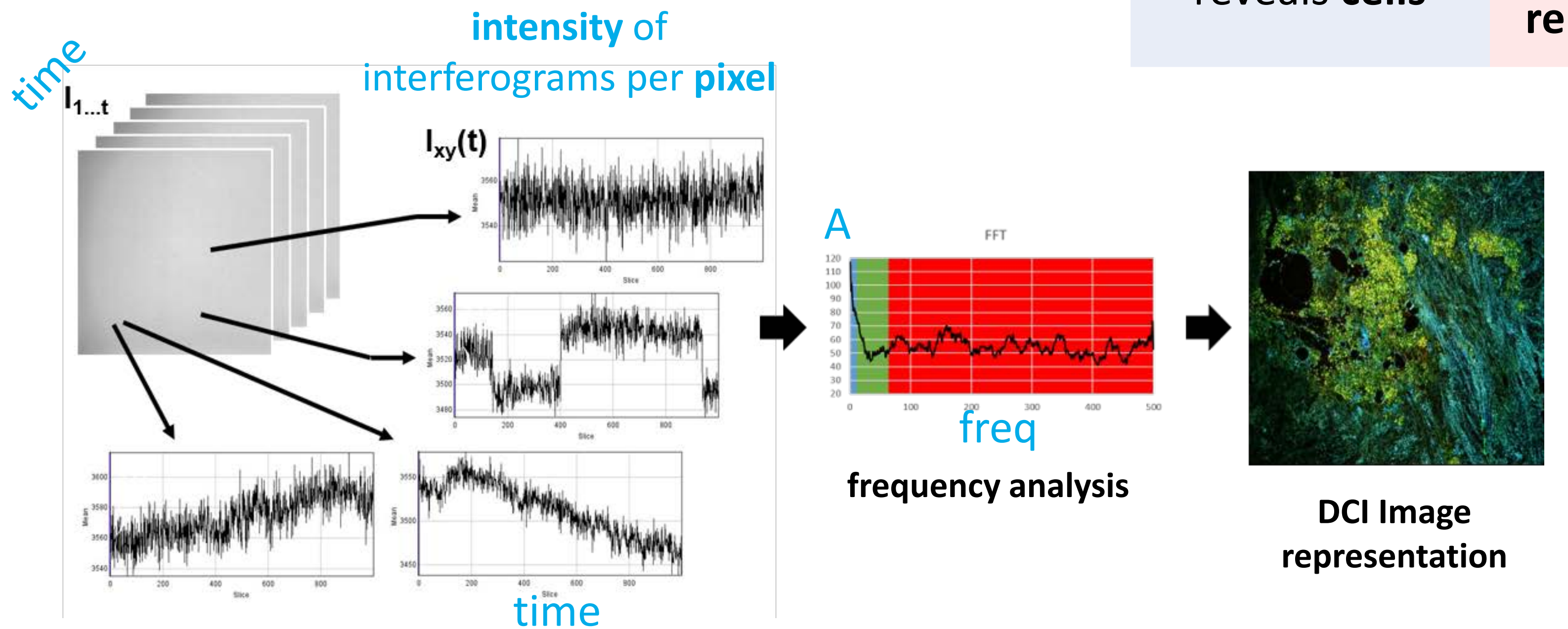
Dubois et al. Applied Optics 2002

Dynamic Cell Imaging DCI

- overcomes **strong** signal from *fibers* and reveals **active** intra-cellular structures
- captures confined micro-displacements of scatterers
- from *10ms* ~~Brownian~~ to *6s* ~~migration~~
- origin of signal presumably *glycolysis* → live tissue

PROS	CONS
good **resolution** (1µm)	motion **artefacts**
fast (minutes)	variable **fiber** contrast
reveals **cells**	image **representation**



DCI acquisition

Apelian et al. Biomedical Optics Express 2016

Methodology Outline

Can we **extract** more info from DCI **signal** ?

What can we **learn** from DCI **images** ?

Can we learn **fiber representation** in DCI from FFOCT ?

Can DCI be **routinely** used in **clinical** applications ?

Data Exploration

DCI Signal

- Source separation

DCI Images

- Fully-supervised classification

Multi-modality

- FFOCT/DCI cross-modal representation learning

Clinical application

- Multiple Instance Learning classification

Breast Surgical Excisions Dataset

Breast Biopsies Dataset

Breast Surgical Excisions Dataset

Goal : feasibility study to discern **pathological** from **healthy** tissue in DCI

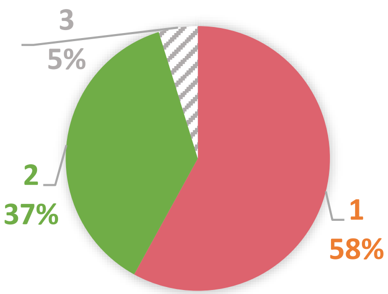
Cohort :

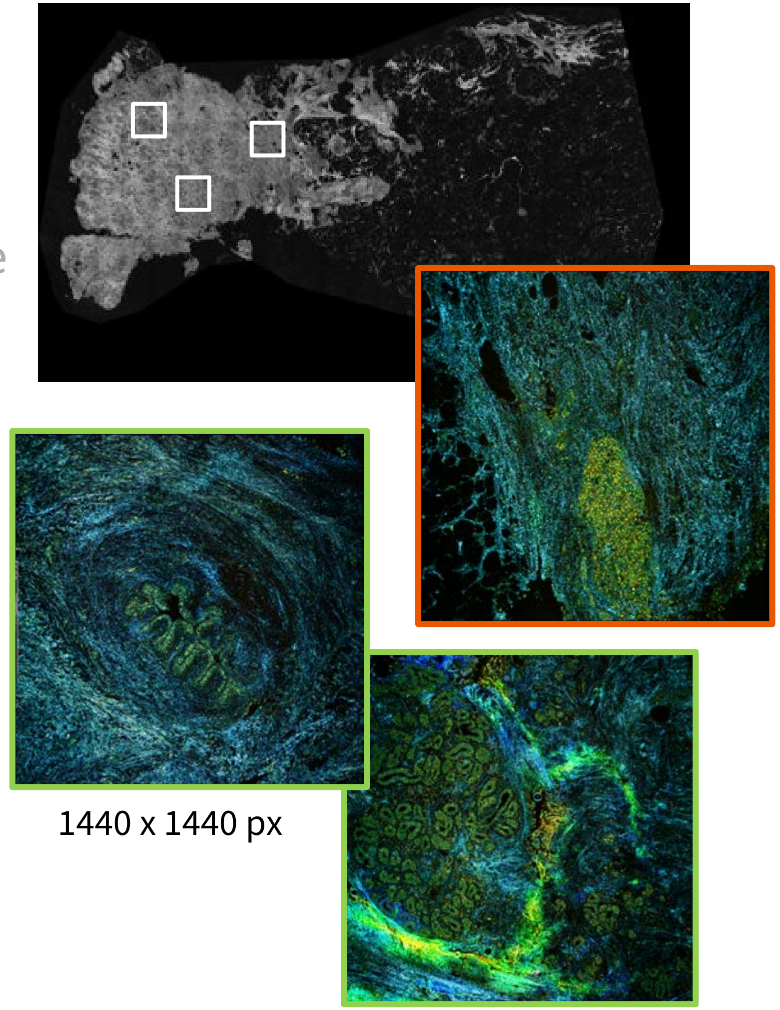
- 33 patients, **mastectomies**
- 47 samples, 11 **healthy** and 36 **tumoral**
- several ROIs per sample ~10 (3 to 16) ROIs / sample

Diagnostic : per ROI with H&E correlations, by pathologist

Dataset :

- ROIs:
    - 279 cancer
    - 179 normal
    - 23 uncertain





1440 x 1440 px

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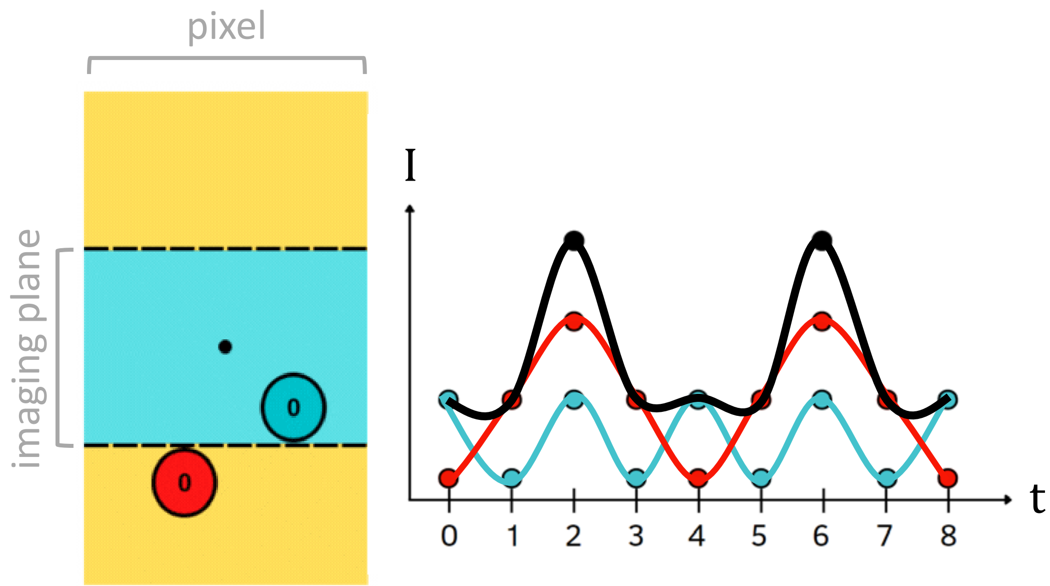
1 Exploring DCI Signal

Hypothesis

- multiple **oscillatory behaviors** present
- **overlapping** scatterers per pixel

Strategy

signal separation



Two scatterers moving inside a pixel relative to the focal plane & the acquired pixel **intensity**

$$\boldsymbol{I(t) = I_1(t) + I_2(t)}$$

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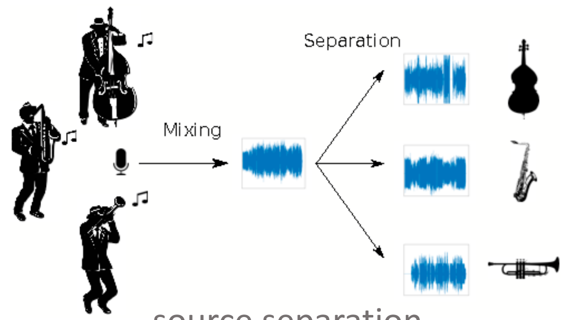
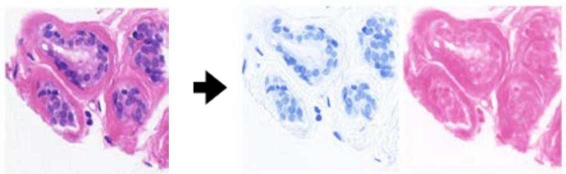
1 Exploring DCI Signal

Signal Separation

- recover the **independent** component signals from a **mixture** signal
- non-negative matrix factorization (**NMF**)



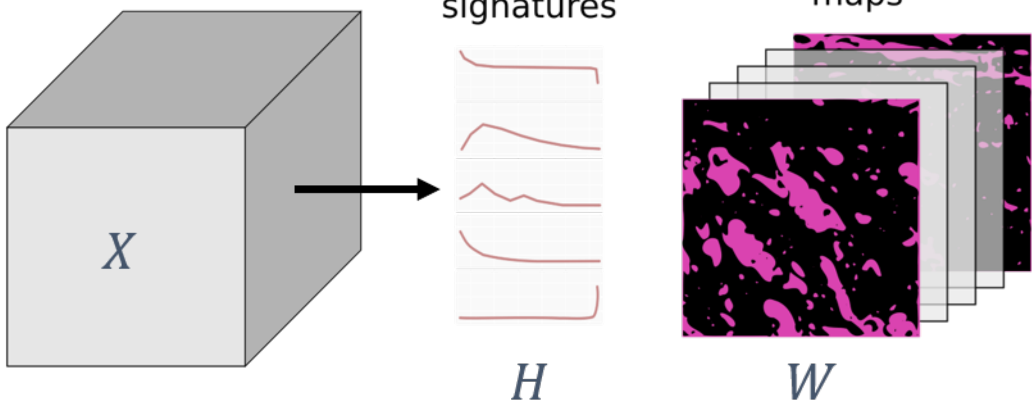
source separation



stain separation

$$\min_{W\in\mathbb{R}^{n\times k}, H\in\mathbb{R}^{k\times f}} \|X - WH\|_F^2 \; s.t. \; W \geq 0, H \geq 0$$

- positive **part-based** decomposition
- **dynamic** and **spatial** components
- empiric choice or rank *k =5*



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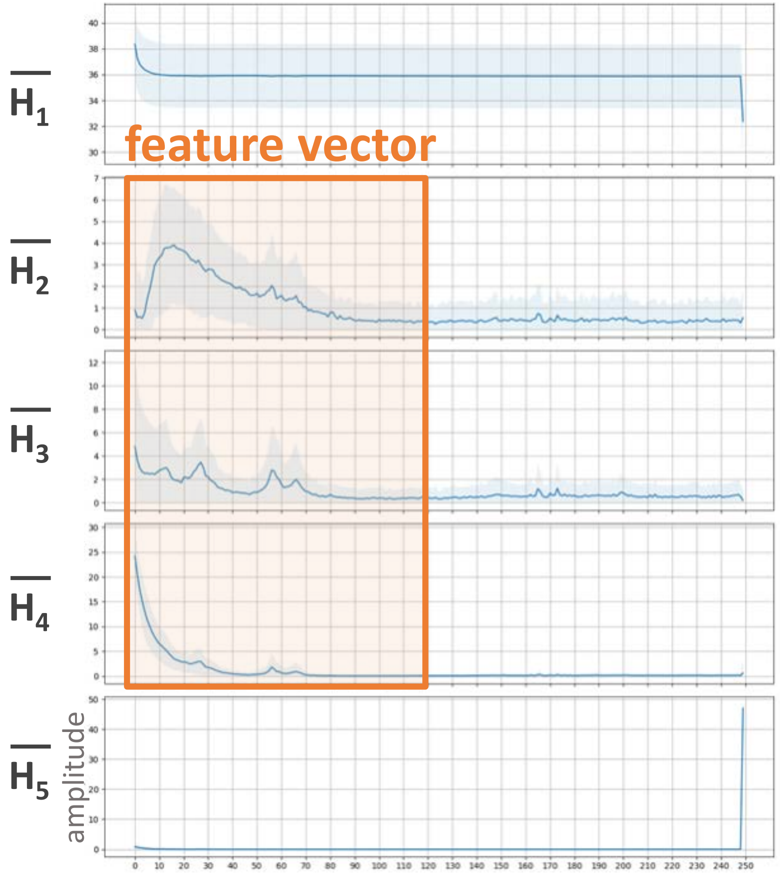
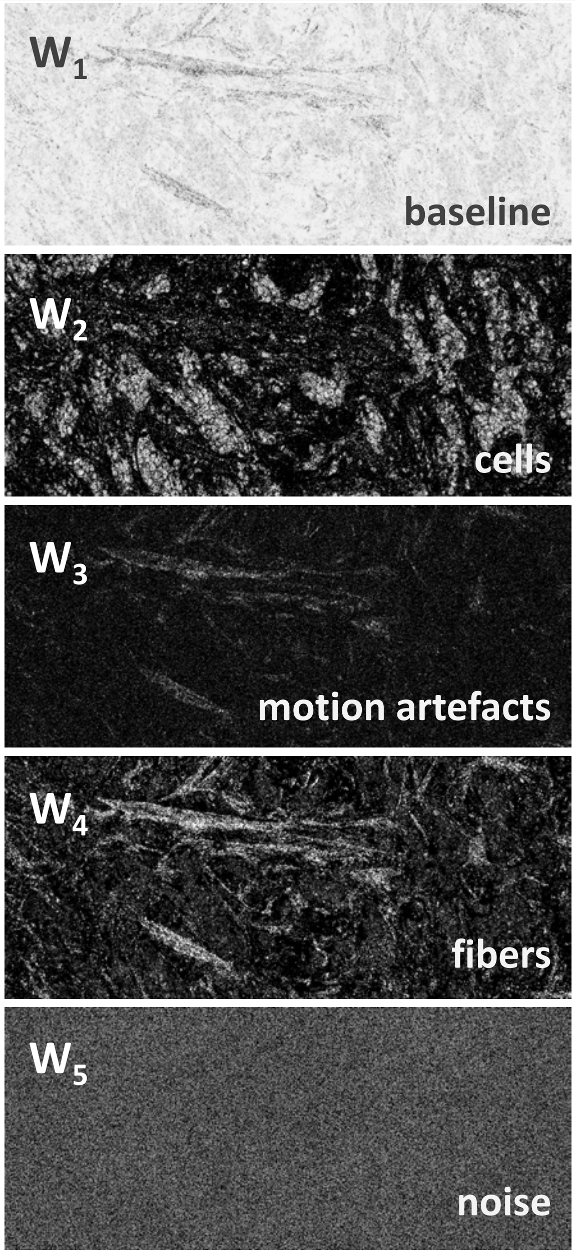
1 Exploring DCI Signal NMF Decomposition Results

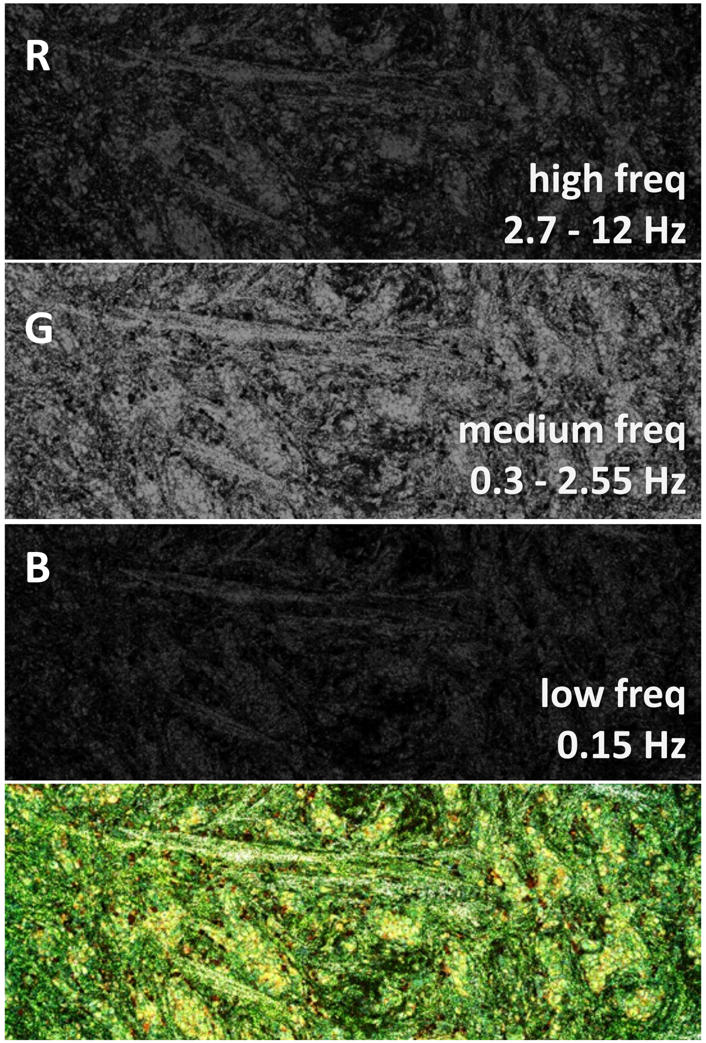
$$X \approx WH$$

NMF **dynamic** and **spatial** components





DCI processed image and RGB channels

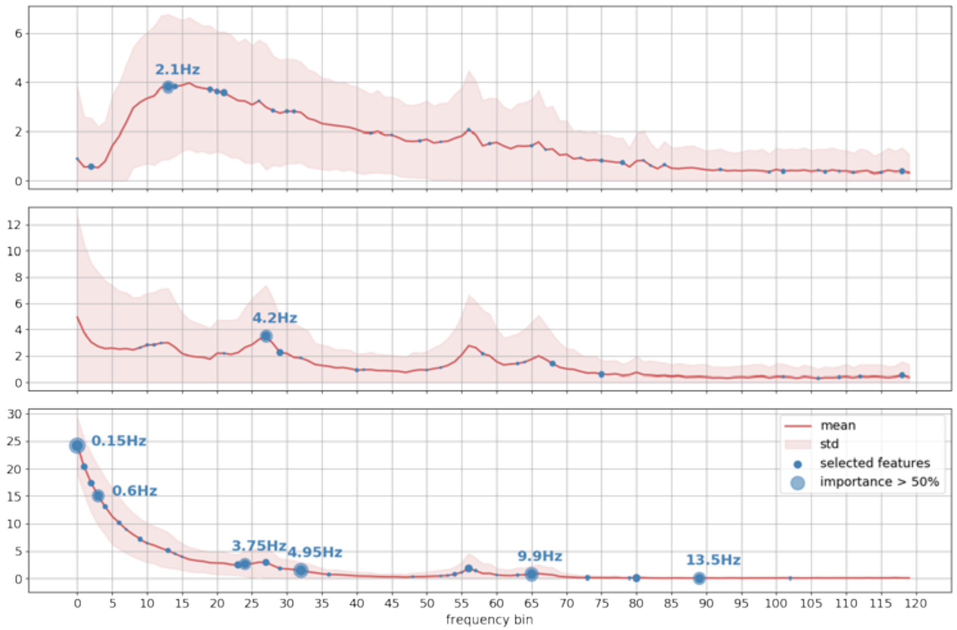


1 Exploring DCI Signal A Promising Direction

Diagnosis

- train tree-based classifiers (eg. *XGBoost, AdaBoost*) on dynamic components only
- normal vs cancer discrimination accuracy ≤ 70%
- reveal feature importance

tree-based models
rule-based decision tree models which represent how different input variables can be used to predict a target value.



Conclusion

- a **framework** for quantitative analysis of oscillatory behaviors in DCI

What information can be learned from spatial DCI data ?

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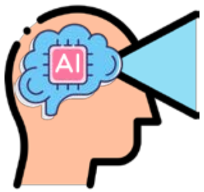
Mandache et al. ISBI 2021

2 Normal *vs* Breast Cancer in DCI Images

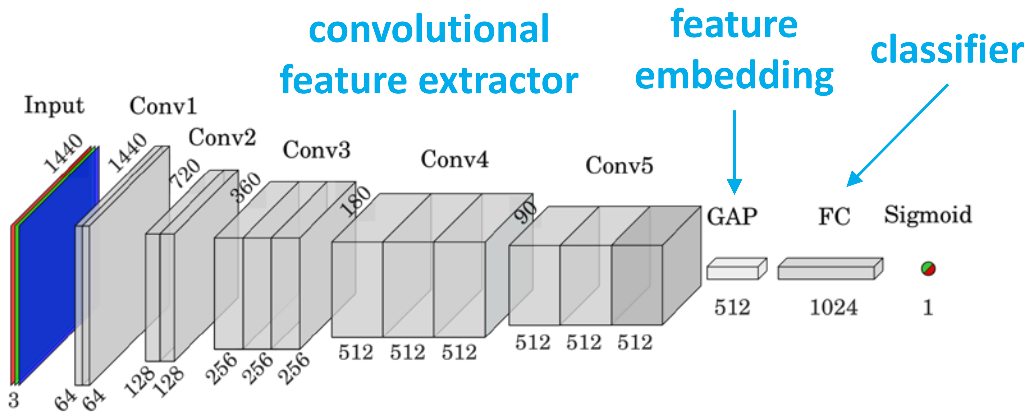
Goal: predict pathologist diagnosis from DCI images.



Convolutional Neural Networks (CNN)

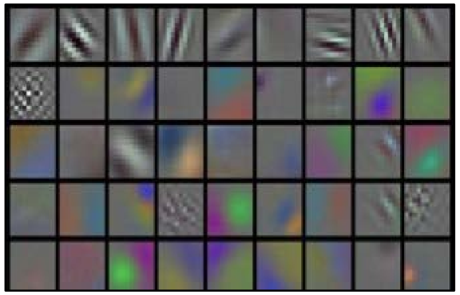
ML models inspired by the human vision mechanism

- Learn **patterns** from image examples
- Input image > feature extractor > embedding > classifier > output prediction

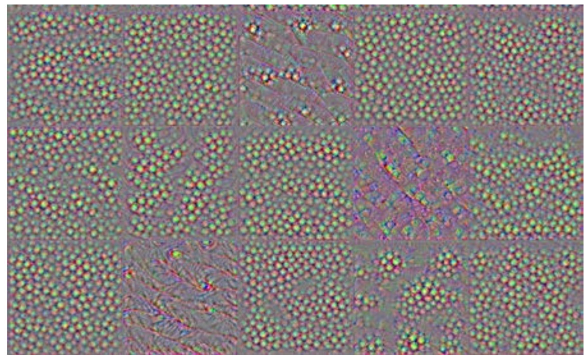


Our Training Strategy:

- ensure **convergence** : limited data → transfer learning, VGG16 / ImageNet
- ensure **generalization** → narrow bottleneck, GAP embedding, dictionary-like



low-level features
(e.g. edges, colors)

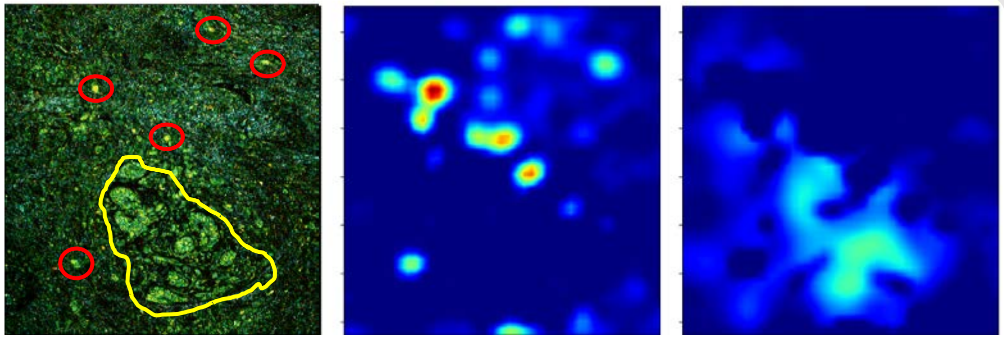


high-level features
(e.g. cell organization)

2 An interpretable diagnosis

localization maps - *GradCAM*

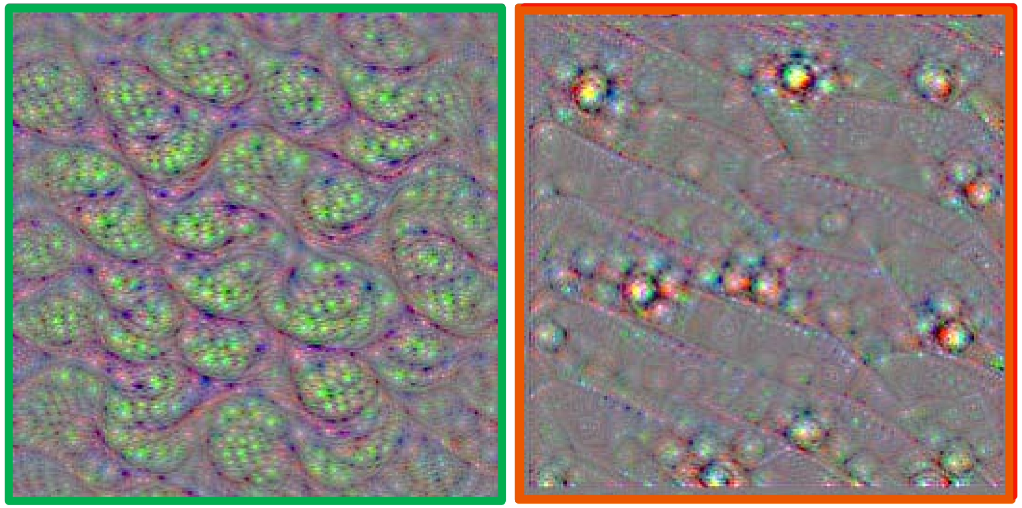
learned patterns - *synthetic input, gradient ascent*



DCI crop of FOV correctly classified as tumoral

Tumor-positive localization map **isolated cancer cells**

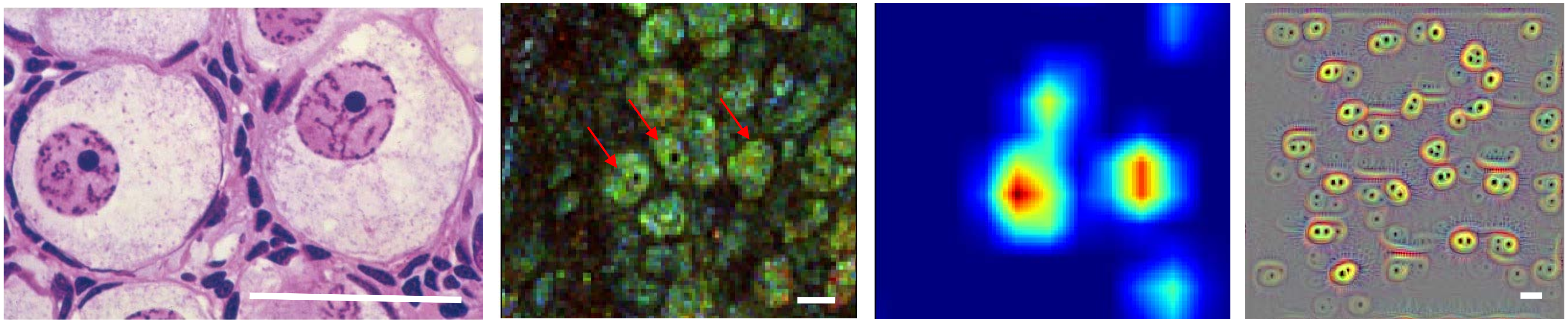
Tumor-negative localization map **healthy breast lobule**



negative evidence

positive evidence

Example of learned ***filters*** in the last convolutional layer showing different **cell sizes, shapes and organization**, proper to each **class**



Enlarged **nucleoli** as **biomarker** in DCI: appearance in H&E and DCI, qualitative evidence

2 Fully-supervised Classification Results

Quantitative Results

- Algorithm **surpasses** pathologist performance

  Possible explanation:

  ↗**Sensitivity** : pathologist missed *low contrast isolated* invasive cancer cells

  ↘**Specificity** : normal *vs* in-situ cancer

- **Error agreement** between algorithm (3) and pathologists (6)
  - Model *appropriates* **medical reasoning**.
  - Model *overcomes* **human limitations**.
- Performance is robust to adding images with **uncertain** diagnosis
  - Model is *robust* to **ambiguity**.

	Accuracy	Sensitivity	Specificity
pathologist P1	91 %	91 %	**92 %**
pathologist P2	89 %	94 %	75 %
avg(pathologists)	90 %	93 %	83 %
algorithm[1]	**94 %**	**97 %**	85 %
[1] aggregated 5-fold CV test pred	+ 4%	+ 4%	+ 2%

Fully-supervised learning is powerful for diagnosis and cell feature extraction.

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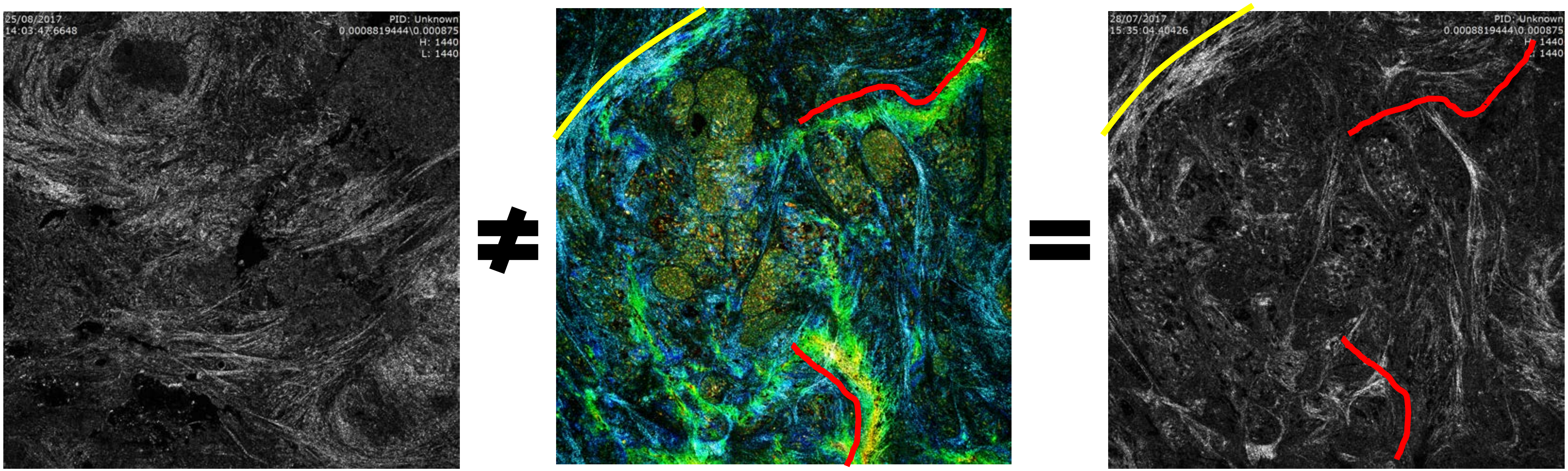
3 FFOCT/DCI Cross-Modal Representation

Goal : better characterize **fiber orientation** from DCI

Strategy

- akin to human agent, learn by **contrast** FFOCT / DCI
- train model to **match** corresponding images – contrastive learning

contrastive representation learning
ML paradigm for building an embedding space in which similar sample pairs stay close to each other while dissimilar ones are far apart.



Cross-modal matching = pretext task for robust fiber representation in DCI.

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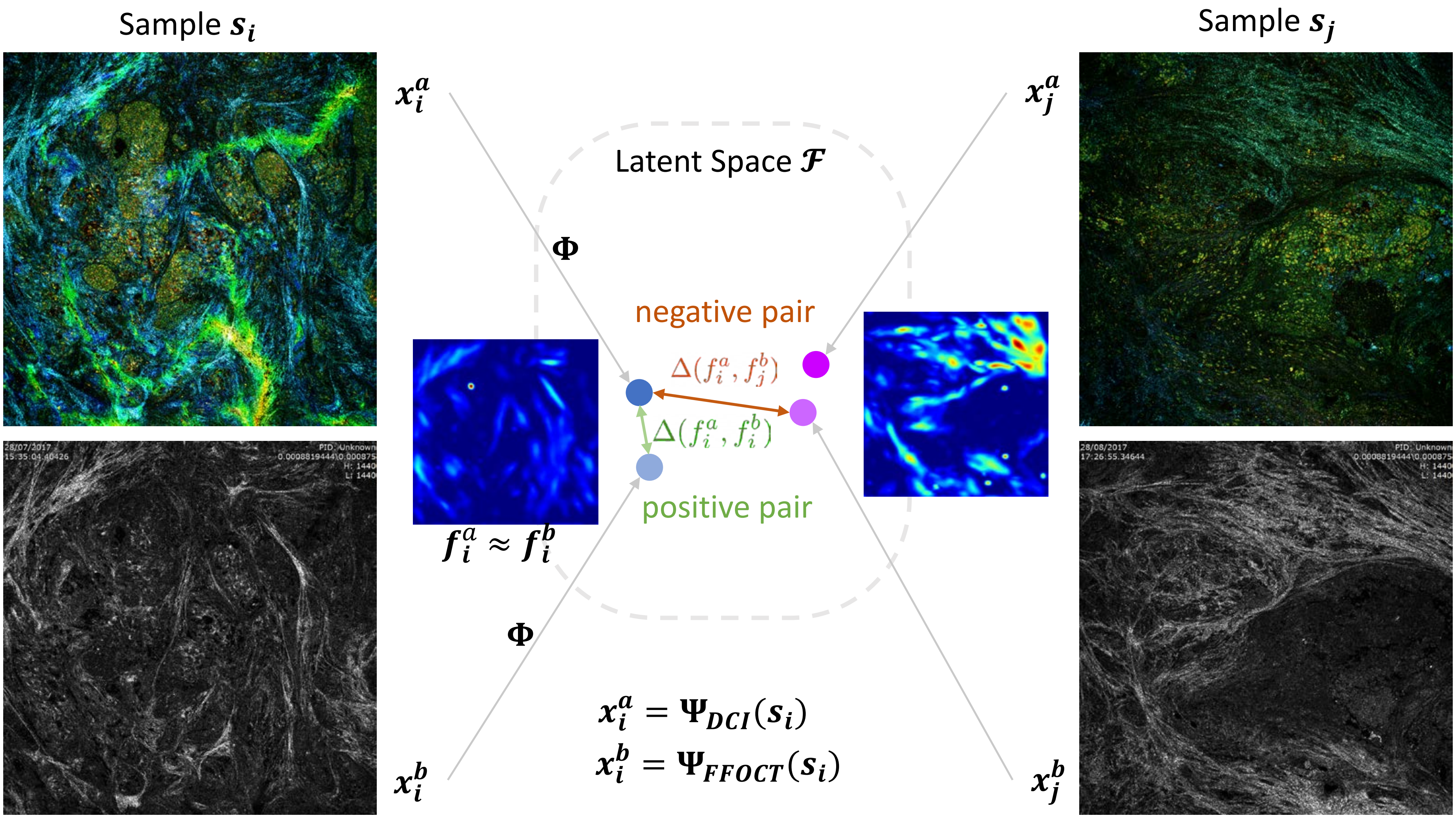
3 Concept



$\exists\ \Phi, f_i^a = \Phi(x_i^a)$ and $f_i^b = \Phi(x_i^b)$ s.t. $f_i^a \approx f_i^b$

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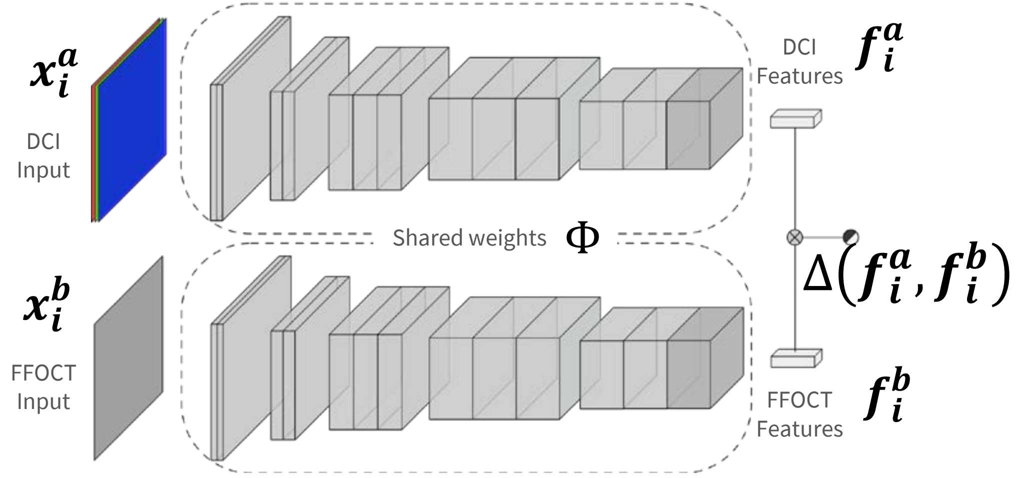
3 Implementation

- Siamese CNN encodes $\boldsymbol{\Phi}$ embedding function
- Δ function is **cosine distance** :
  - not sensitive to amount of activation
  - bounded [0,1] → binary formulation:

$$L(\theta,\hat{\theta}) = \begin{cases} -\log(\cos(\hat{\theta})) & \text{if } \theta = 0 \\ -\log(1-\cos(\hat{\theta})) & \text{if } \theta > 0 \end{cases}$$

- "Infinite" dataset generation
  - exploit **registered** images
  - artificially **augment** dataset by extracting corresponding sub-images (480px patches)
  - **online** batch generation (new data every epoch)

siamese neural network
an artificial neural network containing identical sub-networks working in tandem on different inputs.



$$\Delta(f_i^a, f_i^b) = 1 - \cos\Theta(f_i^a, f_i^b)$$

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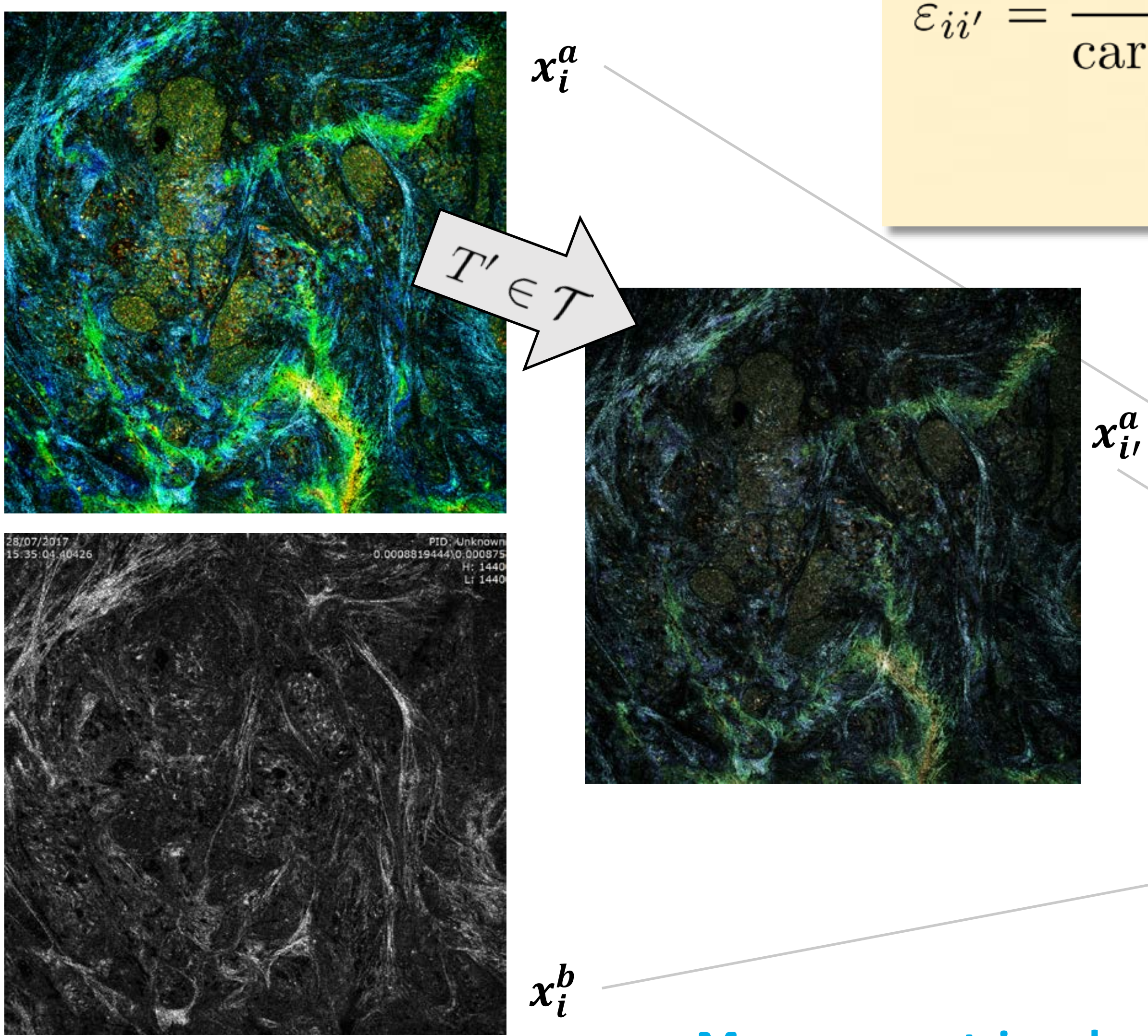
3 Validation Identity Error

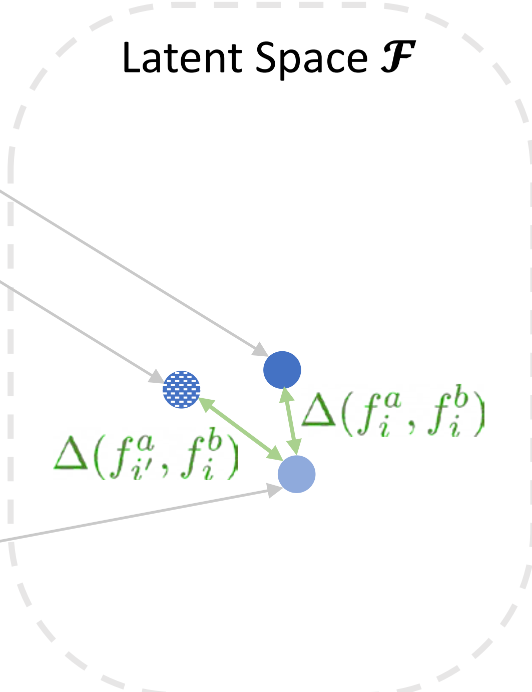
$$\varepsilon_{ii'} = \frac{1}{\mathrm{card}(\mathcal{T})} \sum_{i'} \left| \Delta(f^a_{i'}, f^b_i) - \overline{\Delta(f^a_{i'}, f^b_i)} \right|$$

$$\text{where } x^a_{i'} = T'(x^a_i) \text{ and } T' \in \mathcal{T}$$

$\overline{\varepsilon_{ii'}} = 0.004 \pm 0.008$

Sample $\boldsymbol{s_i}$





Measure metric robustness to slight transforms.

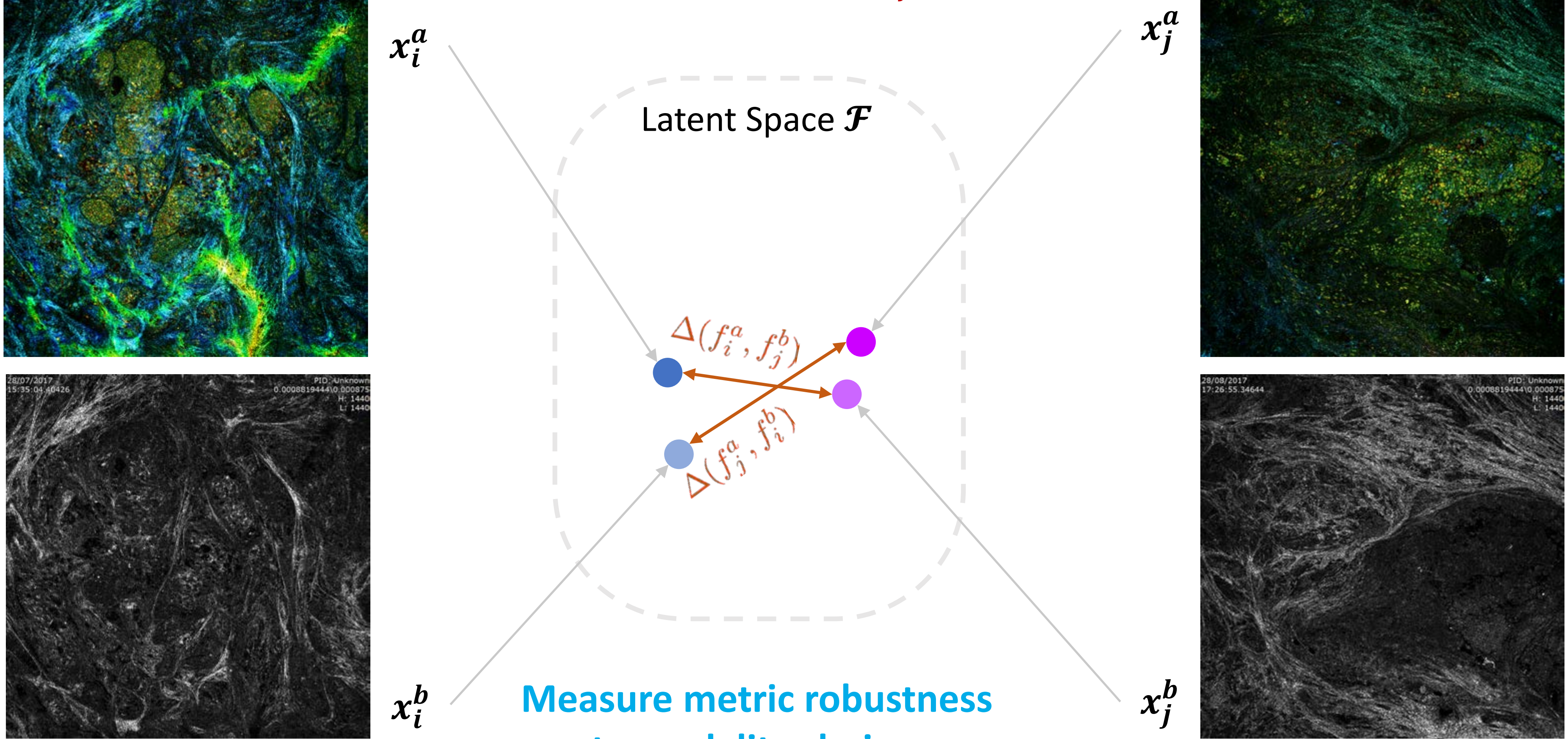
3 Validation Symmetry Error

$$\varepsilon_{ij} = \left|\Delta(f_i^a, f_j^b) - \Delta(f_j^a, f_i^b)\right| \text{ where } i \neq j$$

Sample $\boldsymbol{s_i}$

Sample $\boldsymbol{s_j}$

$\overline{\varepsilon_{ij}} = 0.009 \pm 0.012$



Measure metric robustness to modality choice.

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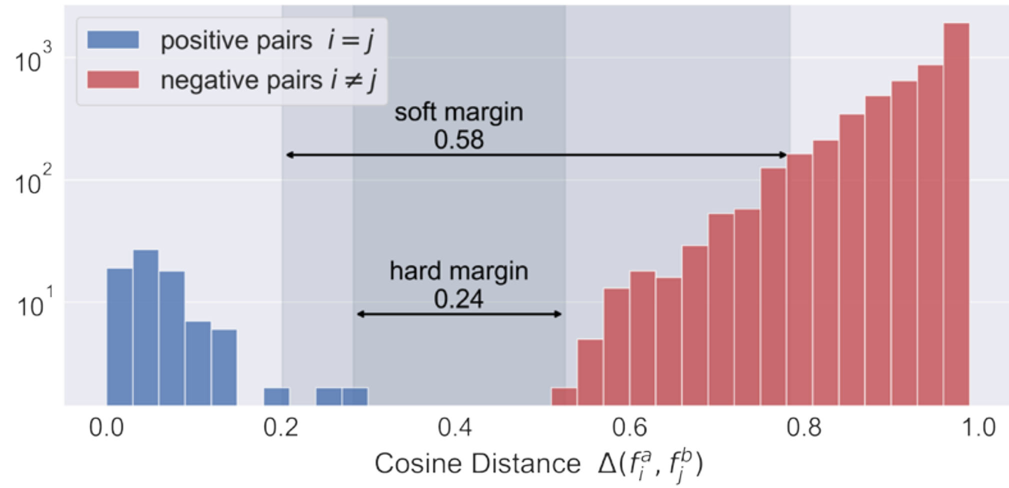
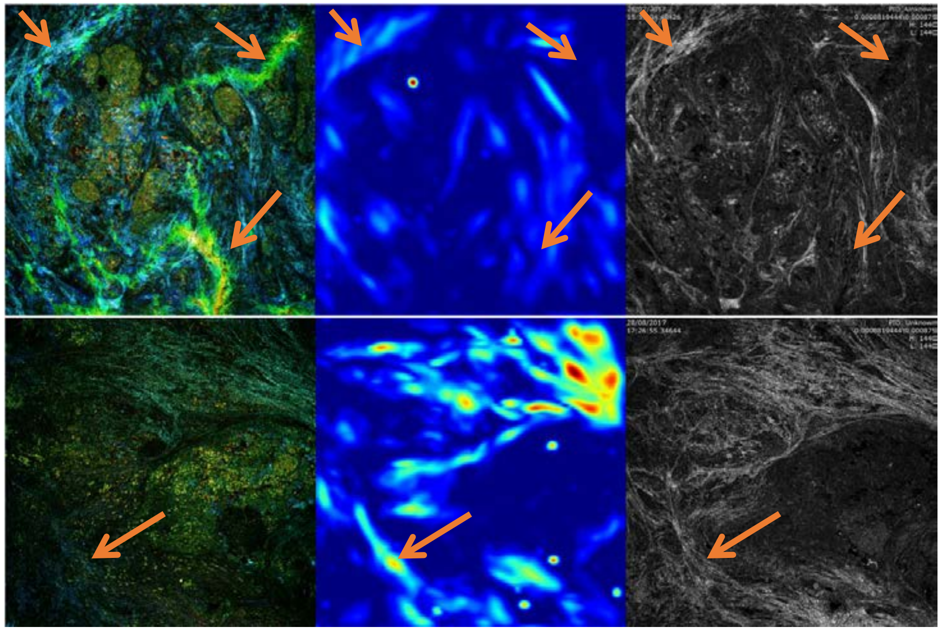
3 Cross-Modal Representation Results

Robust fiber characterization

- **Quantitative** :
  - *identity* & *symmetry* **errors** <1%
  - implicit **margin** learned
- **Qualitative** :
  - imaging **artifacts** are understood by the network and discounted
  - **low contrast** fibers are captured by the network

Universality : agnostic to dataset → build **general** fiber representation in DCI





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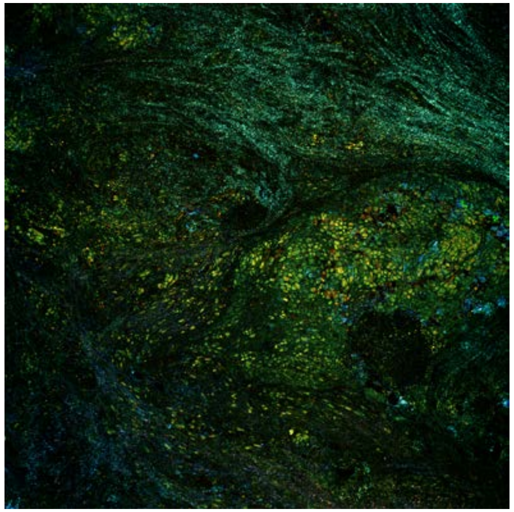
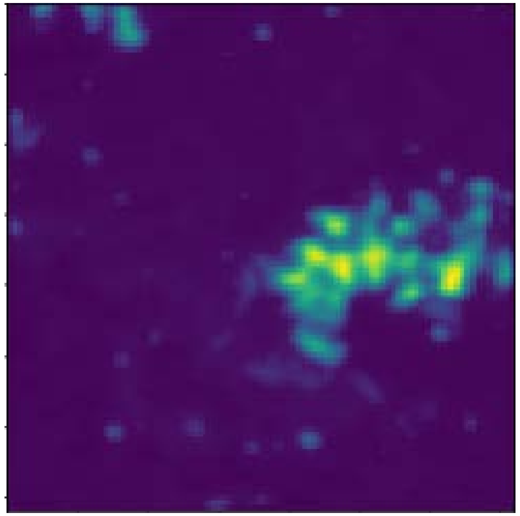
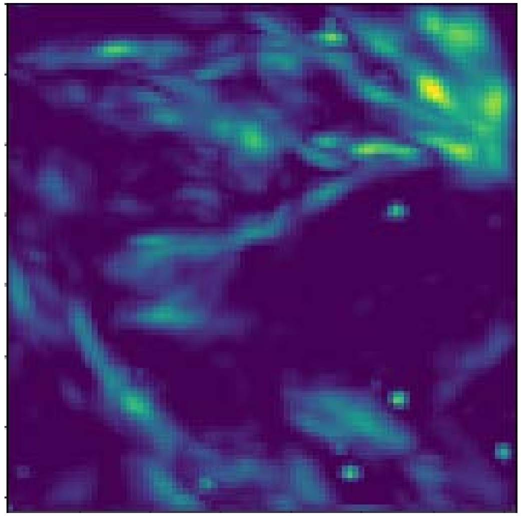
A Complete Characterization of DCI Images

tumor classification model
+
cross-modal matching model
=
full (*cells* + *fibers*) image **representation**
↓
serve **downstream** tasks
(image coding, signal analysis, diagnosis…)

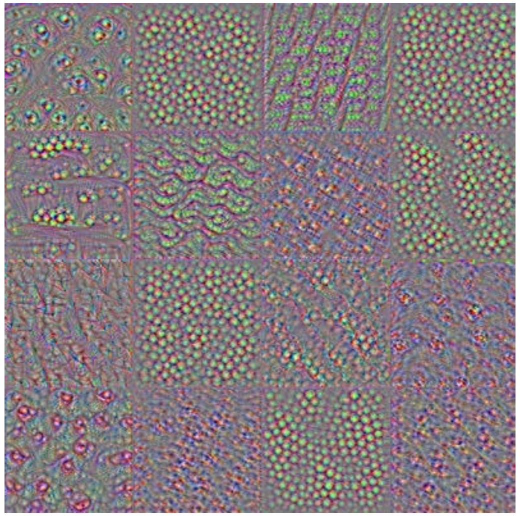


DCI image

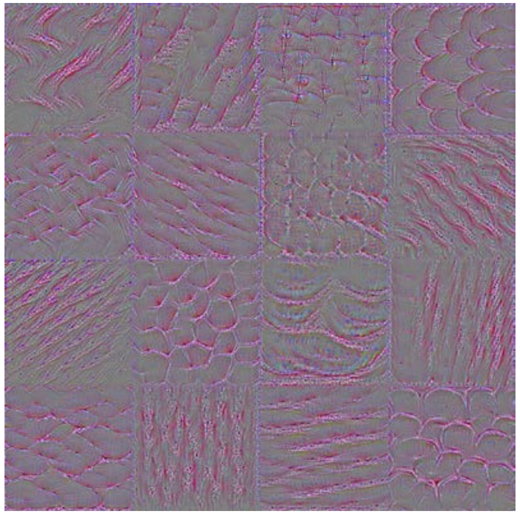




localization maps



tumor classification model (cell features)



cross-modal matching model (fibers features)

learned filters

Methodology Outline

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What can we **learn** from DCI **images** ?

Can we learn **fiber representation** in DCI from FFOCT ?

Can DCI be **routinely** used in **clinical** applications ?

Data Exploration

DCI Signal

- Source separation

DCI Images

- Fully-supervised classification

Multi-modality

- FFOCT/DCI cross-modal representation learning

Clinical application

- Multiple Instance Learning classification

Breast Surgical Excisions Dataset

Breast Biopsies Dataset

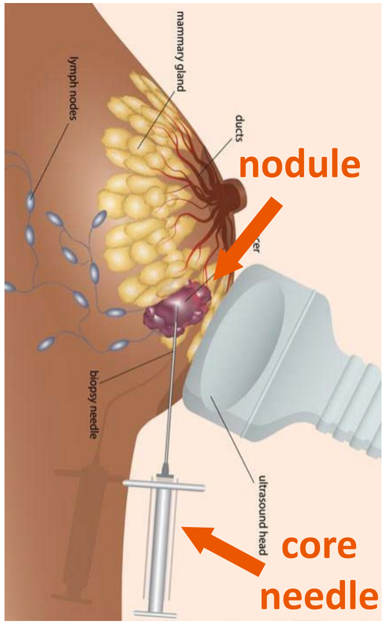
Breast Biopsy Procedure

biopsy = sample tissue from suspect nodule to diagnose malignancy

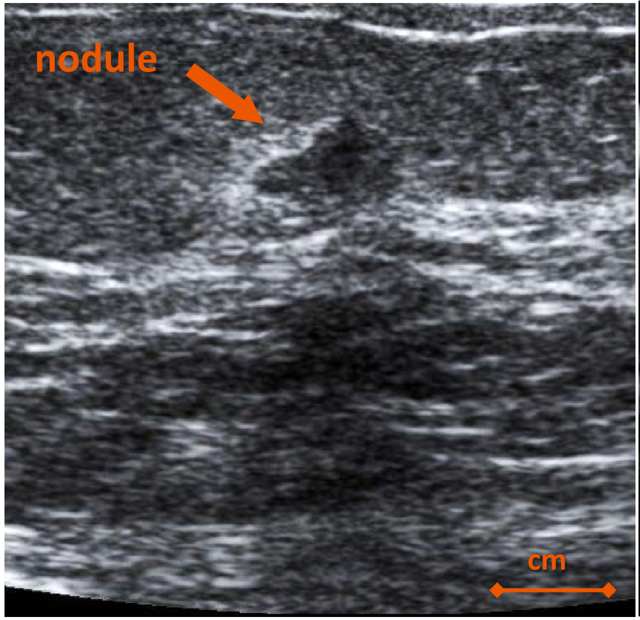
DCI use-cases :

- biopsy **quality assessment** → **minimize** number of biopsies excised
- **rapid** diagnosis → **comfort** patient (80% biopsies not malignant)

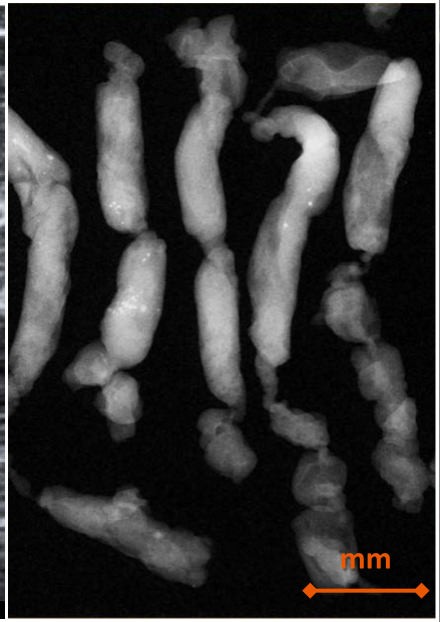
breast biopsy



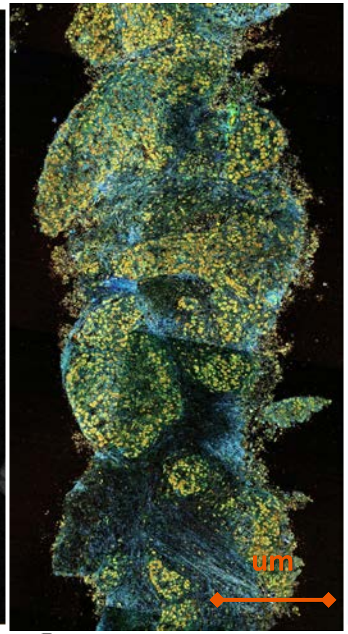
ultrasound guidance



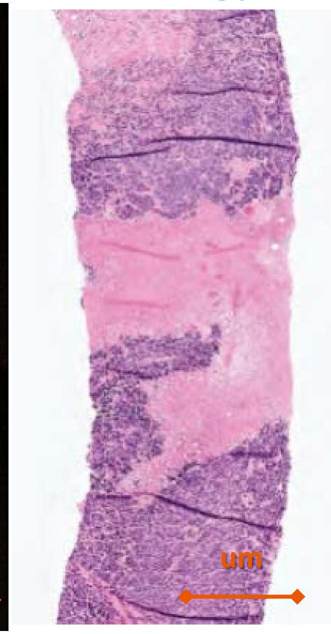
multiple biopsies per nodule



biopsy in DCI



biopsy in H&E histology



minutes **days**

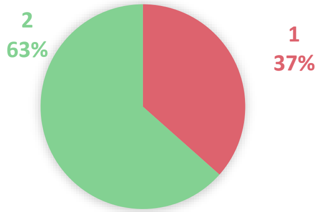
Breast Biopsies Dataset

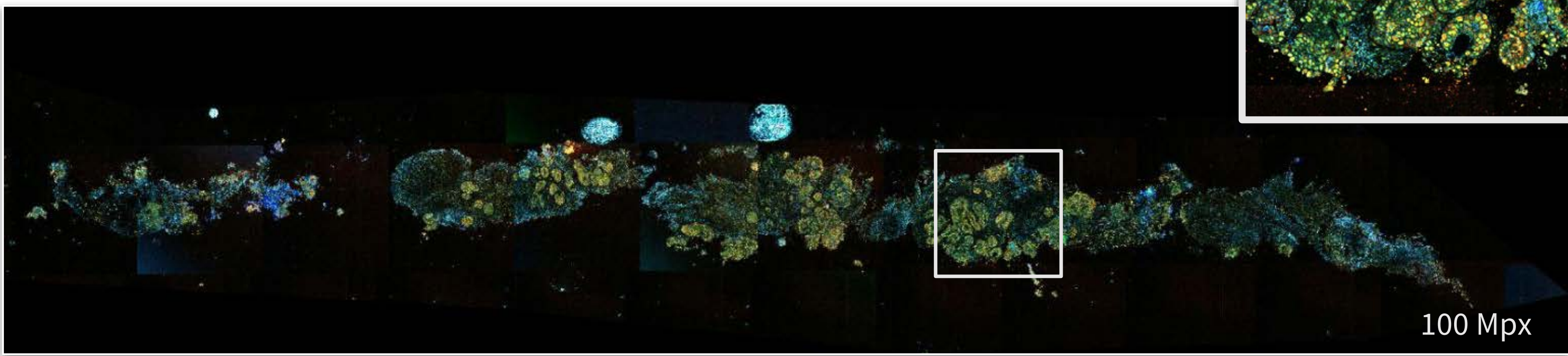
Cohort : 71 breast nodules

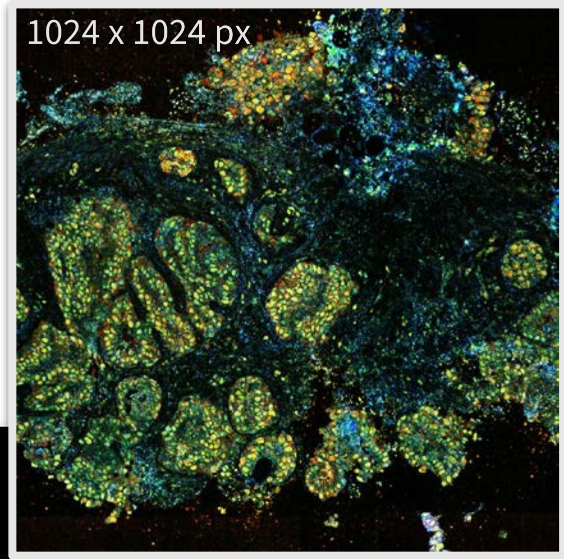
Diagnostic : a histopathology report per nodule, based on H&E

Dataset :

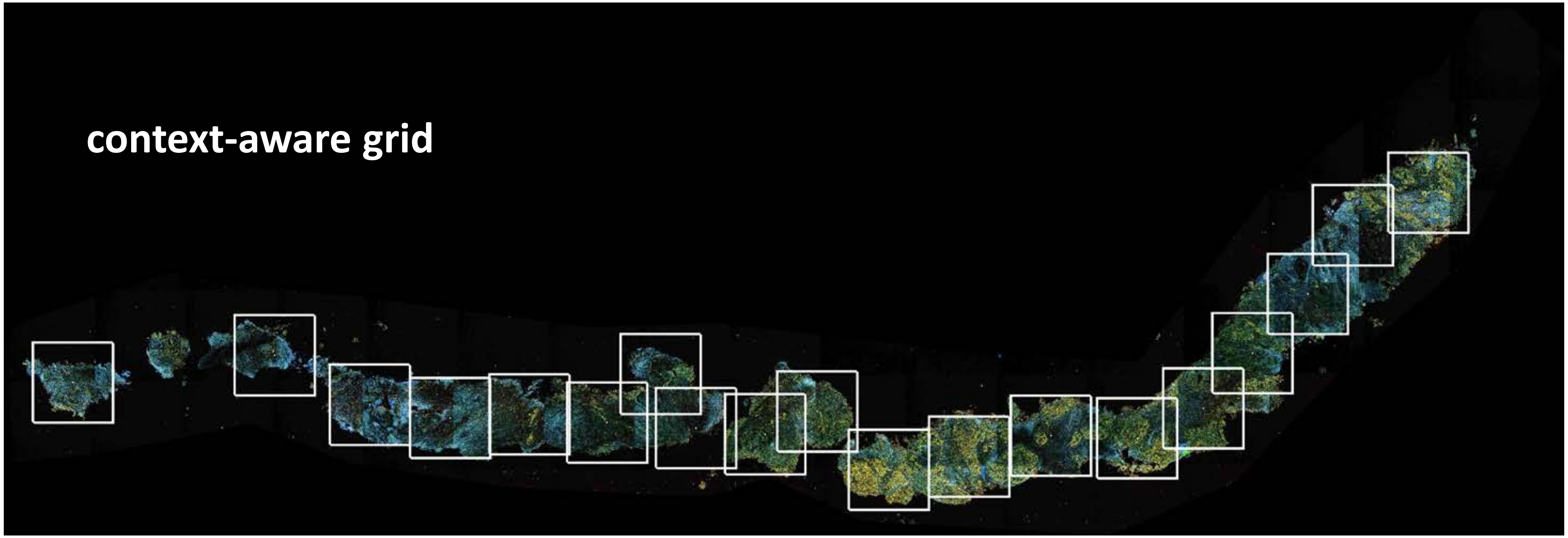
- 71 breast nodules + pathology reports
  - 27 malignant
  - 44 benign
- 145 biopsies in DCI
  - 53 from malignant
  - 92 from benign





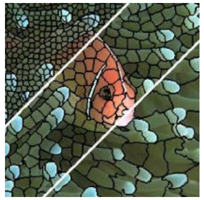


Breast Biopsies Dataset Image Sampling



- sub-sample image optimally :
  - minimal **fragmentation**
  - avoid splitting **homogenous** structures
- *SoSleek* - context-aware sampling with SLIC superpixel segmentation

⇨ 2K patches of 1024 x 1024 px / 145 biopsies



Simple Linear Iterative Clustering (SLIC) image segmentation method that groups pixels according to their spatial and color proximity.

Sample Optimally with SLIC (*SoSleek*) Python package for optimally sampling big images with texture awareness, based on SLIC superpixels.
github.com/dmandache/sleek-patch

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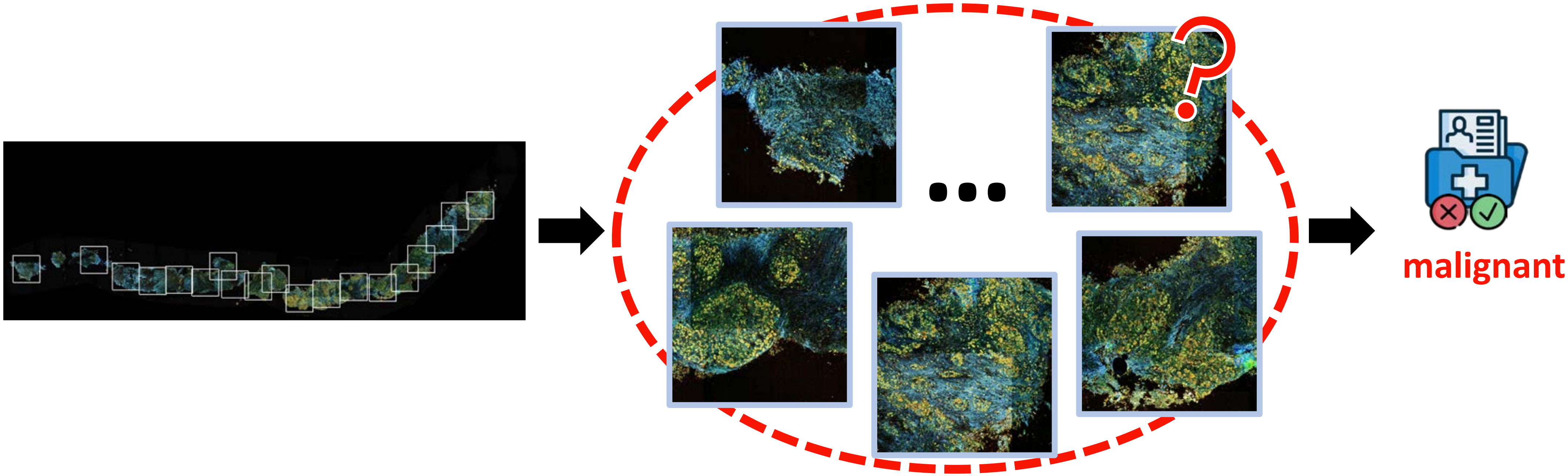
Cancer Detection *via* Multiple Instance Learning



one diagnostic per **group** of patches → MIL training paradigm

MIL Assumptions:

- A malignant biopsy contains at least **one** malignant instance.
- A benign biopsy does not contain **any** malignant instances.

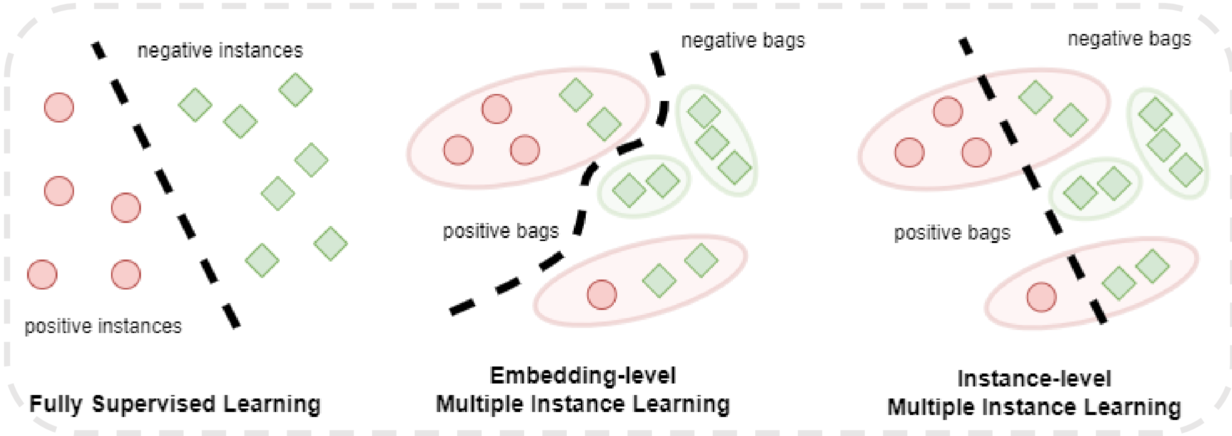
Multiple Instance Learning (MIL)
supervised method for learning from labeled groups (bags) of instances and the individual labels are unknown.

Goal: predict **global** (biopsies) and **local** (patches) diagnosis

Multiple Instance Learning

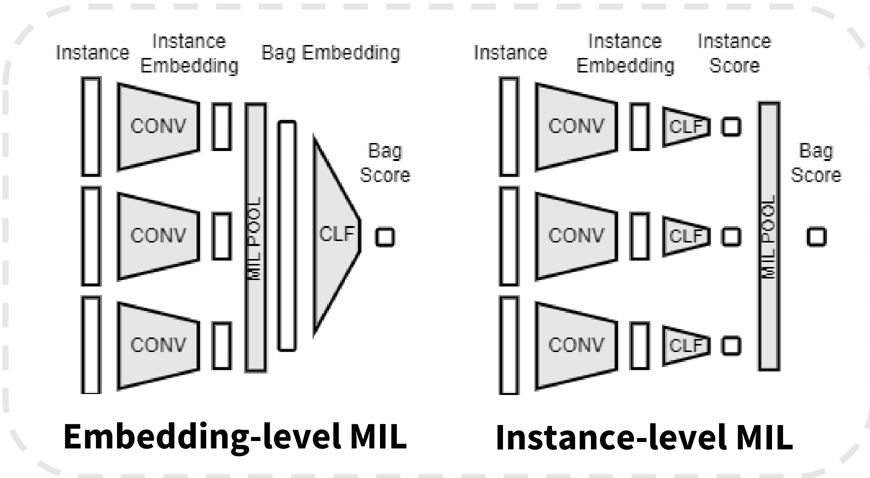
MIL formulations

- Embedding-level MIL
  - global embedding
- Instance-level MIL
  - local scores



Implementation = multi-branch CNN

- computationally heavy
- cannot train end-to-end
- transfer weights (not task-specific)



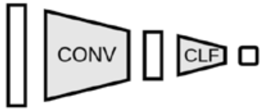
Most MIL applications are embedding-level with transferred feature extractors.

Favor interpretability and task-specific knowledge encoding in MIL.

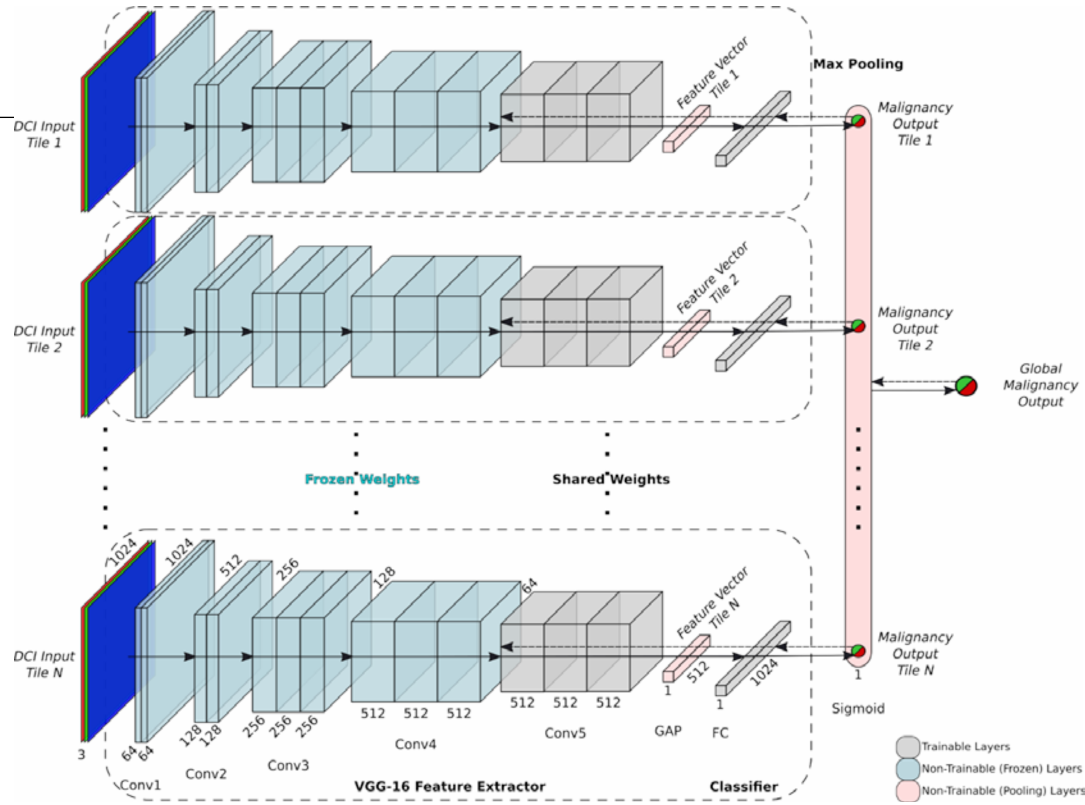
Implementation

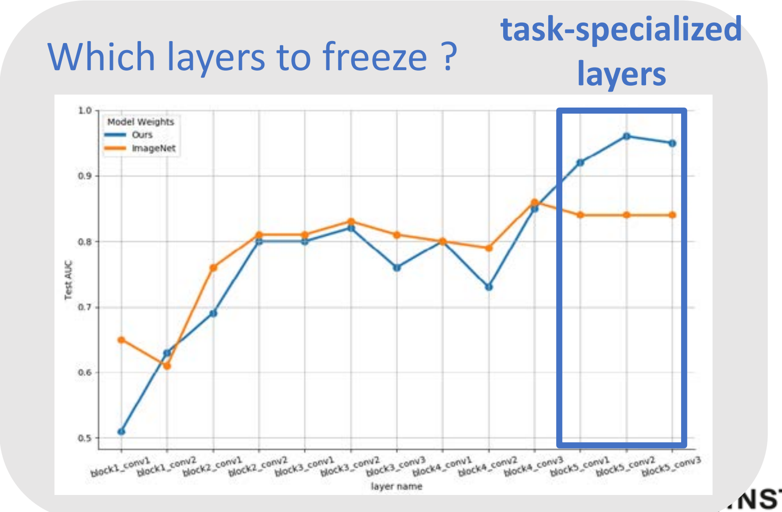
Architecture

- instance-level MIL with max aggregation implements MIL assumptions $\boldsymbol{\widehat{Y} = max_i(\hat{y}_i)}$
- **main branch** *transferred* from our prior diagnostic task



- *freeze* **domain specific** feature extractors
- *fine-tune* **task specialized** feature extractors + **classifier**





Training

- $\mathcal{L}(\hat{Y}, Y) = \mathcal{L}(max_i(\hat{y}_i), Y)$
- Focal Loss
  - focus on hard examples $FL = -(1-P)^{\gamma}\log(P)$
  - **8%** accuracy gain vs CE $CE = -\log(P)$

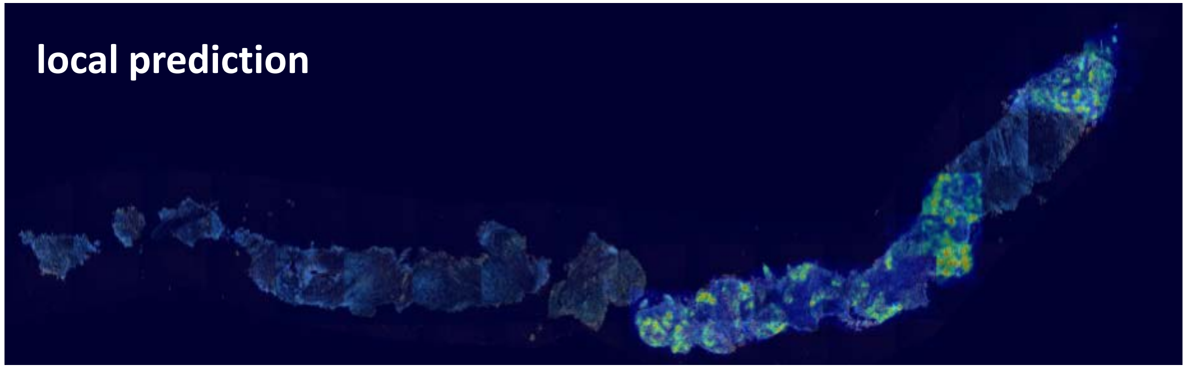
Results

- intra-domain pre-training allows **convergence**
- relevant metric assessment:

***Not all biopsies** of same nodule might be **malignant**.*

  - specificity at **biopsy** level **90 %**
  - sensitivity at **nodule** level **89 %**

- **clinical acceptability criteria**:
  - specificity > **90%**
  - sensitivity > **80%**
- improve with local ground truth *OR* embedding-level MIL



Intra-domain *vs* Extra-domain pre-training

	Datasets	Test Metrics		
		Accuracy	Sensitivity	Specificity
Extra	*ImageNet + BiopsyData*	72 %	57 %	82 %
Intra	*SurgeryData + BiopsyData*	**86 %**	**89 %**	**84 %**
		+ 14 %	+ 32 %	+ 2 %

	Test Metrics		
	Accuracy	Sensitivity	Specificity
biopsy	85 %	76 %	**90** %
nodule	86 %	**89** %	84 %

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Prediction Analysis

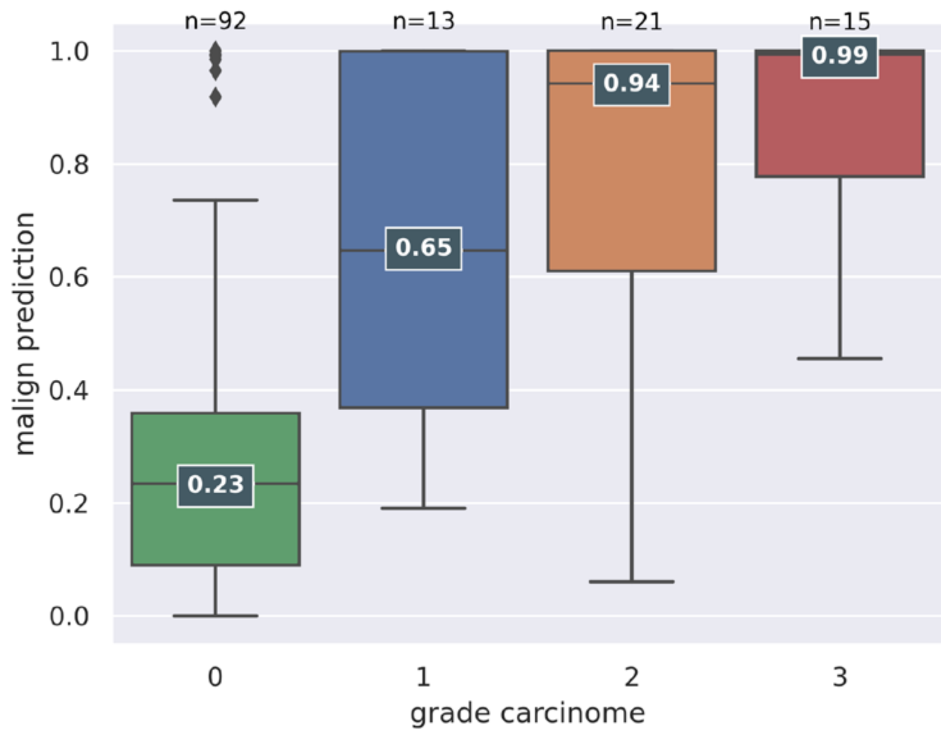
Benign tumors and **high grade** cancers have more chance to be identified.

Malignancy Grade	True Prediction
1	70 %
2	76 %
3	87 %
1+2+3	75 %
0	90 %

emergency intervention

screening

prediction accuracy according to **malignancy grade**



sample prediction according to **malignancy grade**

Find best use-case for DCI: screening, emergency intervention.

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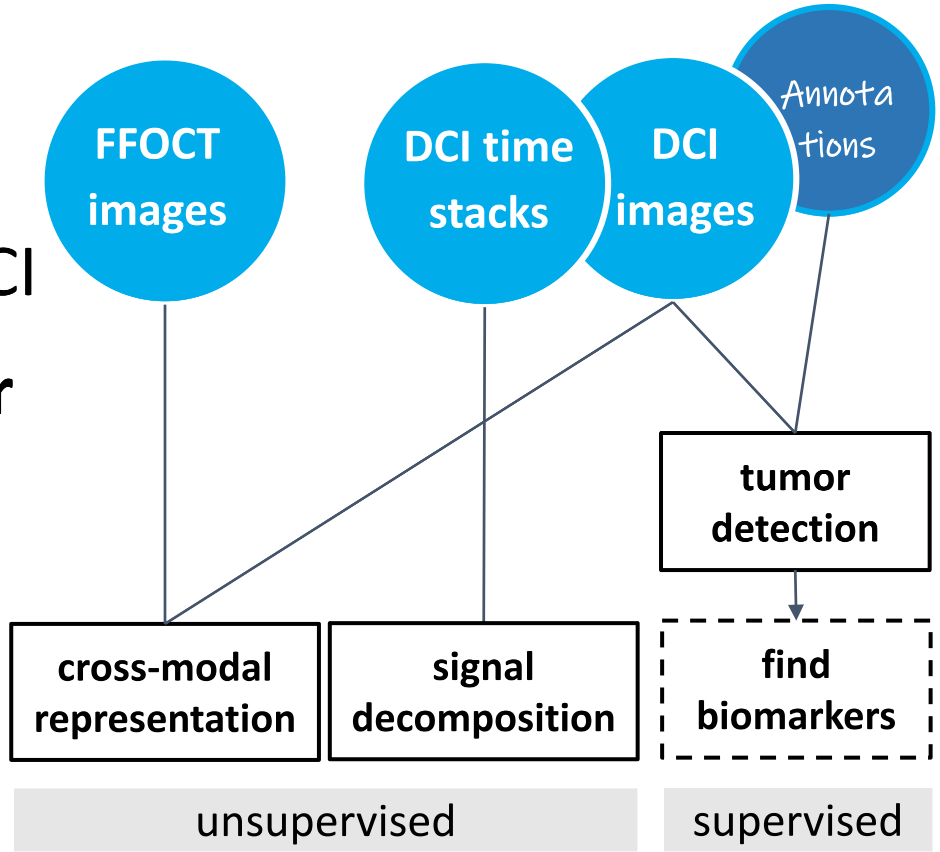
Conclusions Data Exploration

- ✓framework for extracting **oscillatory signatures**
- ✓*robust* **fiber characterization** in DCI
- ✓*interpretable* CNN **tumor classifier** which *surpasses* pathologist performance
- ✓*evidence* towards considering enlarged **nucleoli** as cancer **biomarker** in DCI



Better characterization of DCI data.

Conclusions Clinical Application

diagnosis method for real-world **clinical** application :

- ✓ *remove* expert **annotation** bottleneck
- ✓ *predict* **local** diagnosis without explicit training
  → interpretability
- ✓ *facilitate* **datasets** and **aid-to-diagnosis model** development

Efficient aid-to-diagnosis model development without disturbing clinical protocol.

Speed-up the adoption of DCI.

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Perspectives

- **dynamic** signal analysis + cell/fiber **localization maps** as ground truth
  - supervised source separation
- include corresponding **histology images**
  - preparation protocol correlated with DCI acquisition
  - multi-modal contrastive learning
- **metabolic** analysis + dynamic signal analysis
  - 10x glycolysis rate in cancer cells (Warburg effect)

Efforts towards better image representation and biological understanding.

Thank you ! Merci ! Mulțumesc !

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Bioimage Analysis Unit

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INCEPTION

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♥ *all BIA members 2017-2022* ♥
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Hôpital Sainte-Anne
Dr Bertrand Devaux

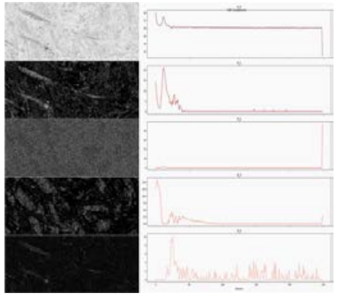
Institut Gustave-Roussy
Dr Marie-Christine Mathieu

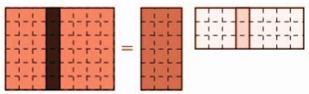
Timeline

Proof of concept

- FFOCT skin cancer detection
- Pixel annotations
- Custom CNN

Mandache et al. ISBI 2018

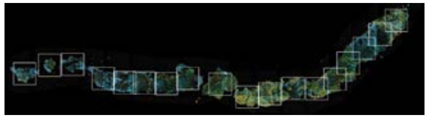


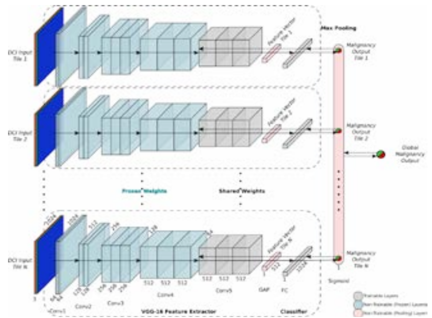


DCI Images

- Fully supervised classification normal vs malignant
- Overcome pathologist performance with 92% and tumor localization with attention

Mandache et al. ISBI 2021

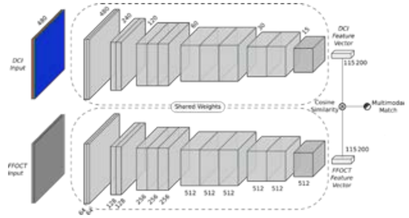


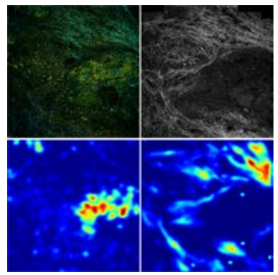


Multimodality

- Cross-modal matching
- Learn common latent space in contrastive learning framework

Mandache et al. ISBI 2023





DCI Signal

- Characterize DCI signal, clustering / decomposition on raw signal (unsupervised)
- *paper : NMF decomposition of DCI signal*

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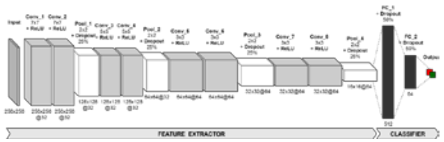

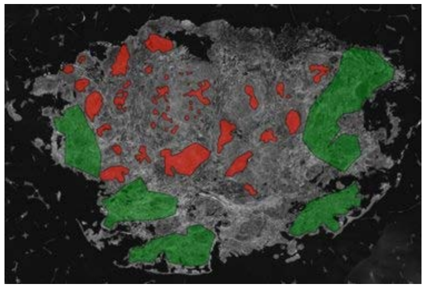

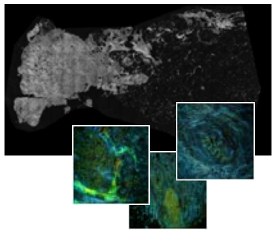

Clinical Data

- Annotation scarcity
- Multiple Instance Learning (MIL) based classification benign vs malignant
- paper :

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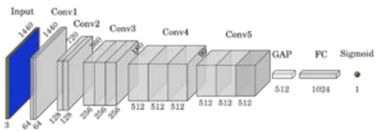

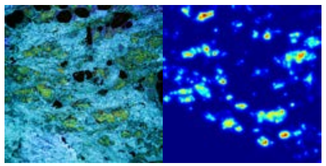

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