Beyond Classification: Whole Slide Tissue Histopathology Analysis By End-To-End Part Learning

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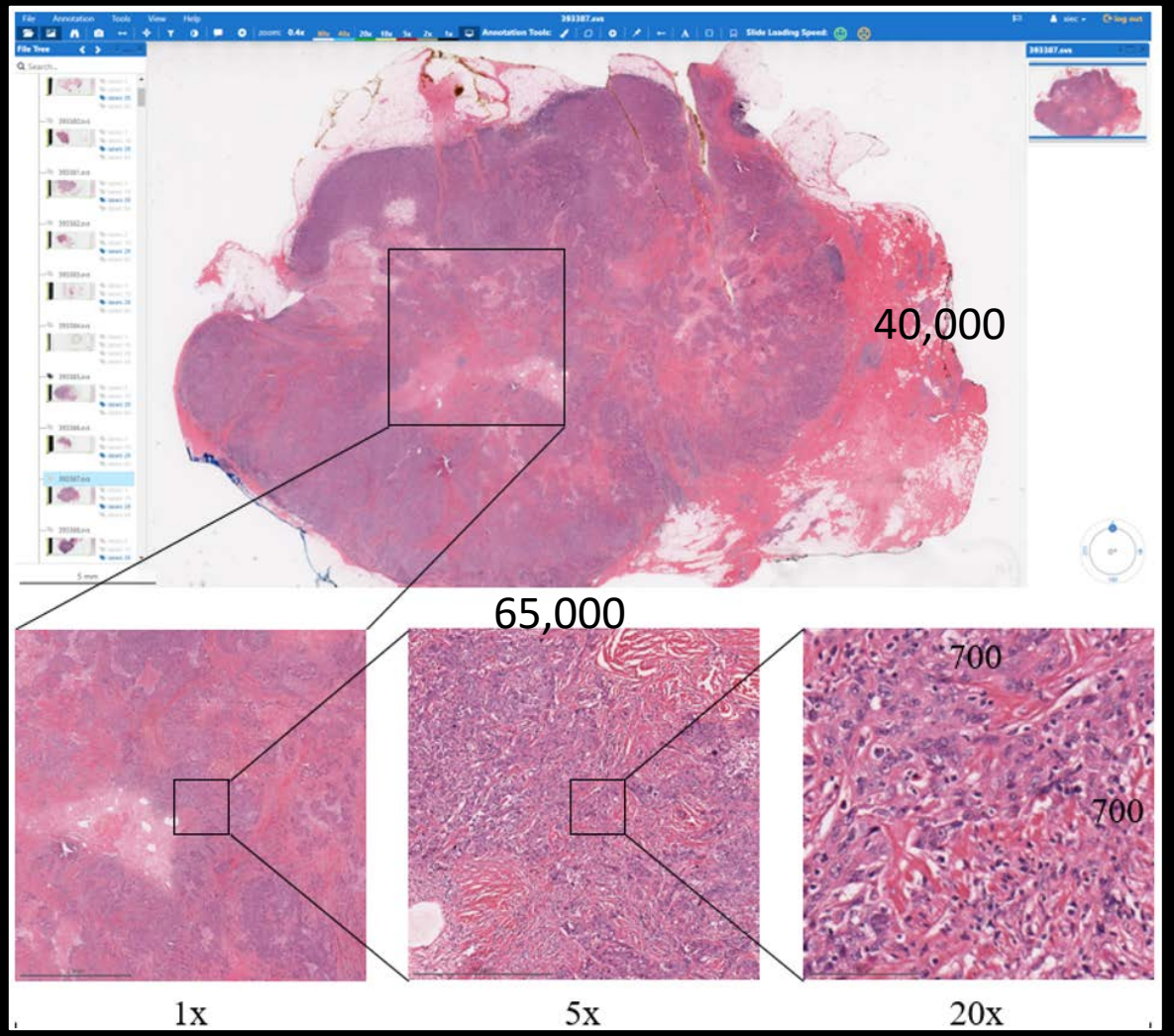
Computational Pathology

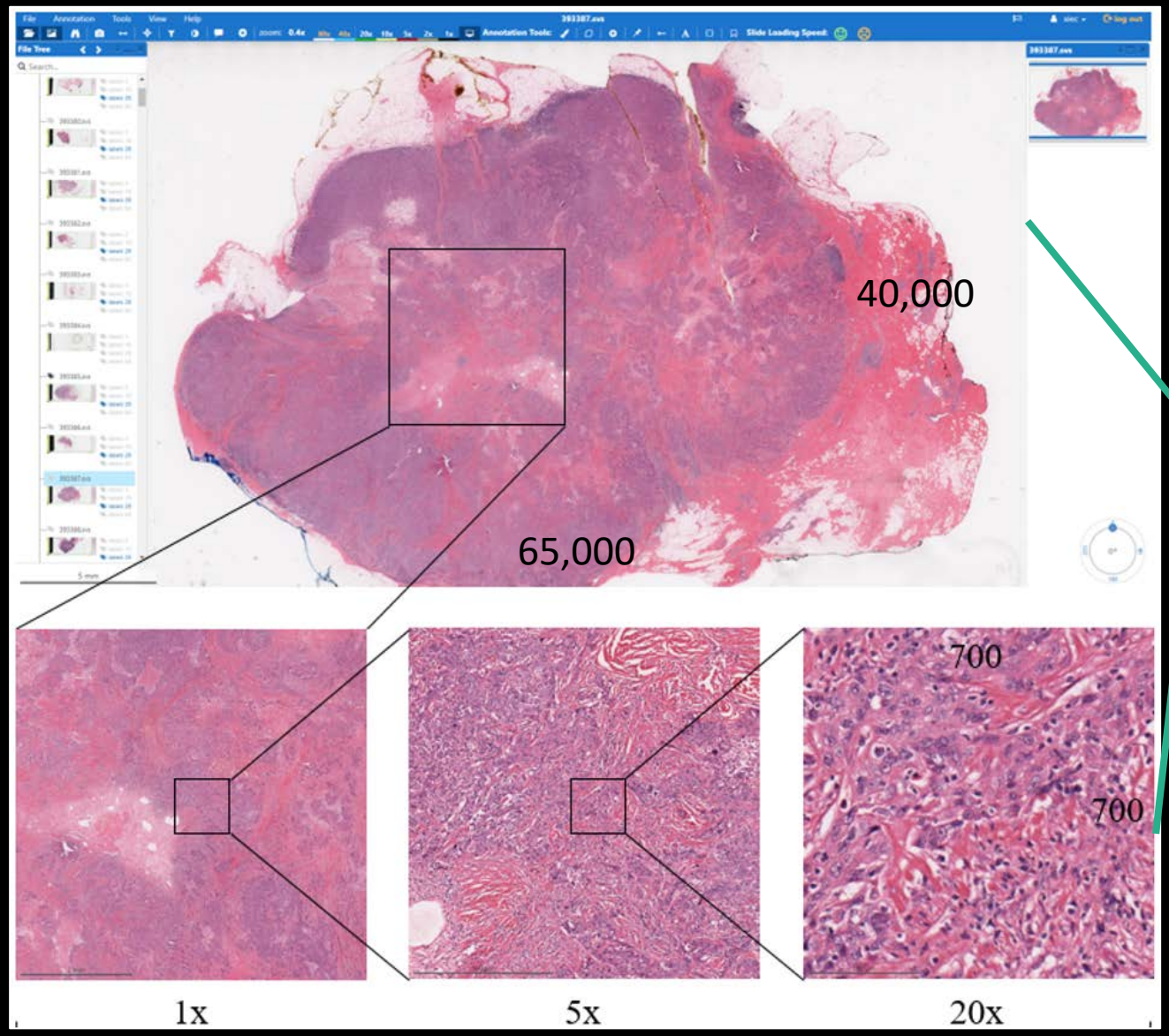
Tissue slide cut, staining, and examination



Whole Slide Image (WSI)

Diagnosis | Treatment | Prognosis

Challenges of Computational Pathology

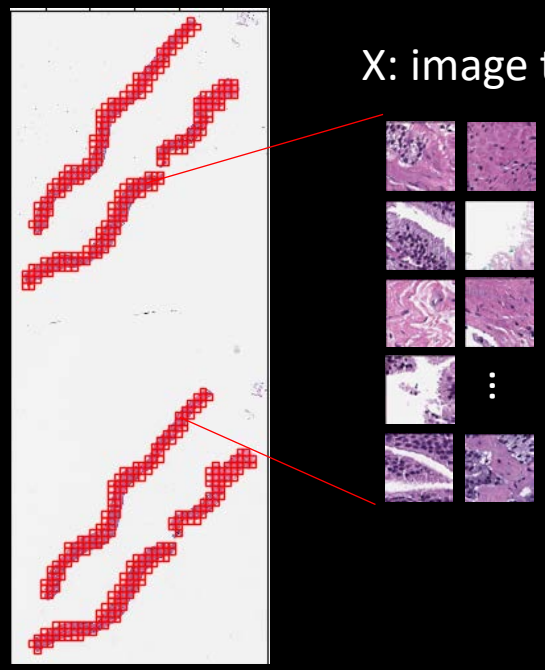


Giga-pixel images
Information at cellular level

Lack of local annotation
Only slide-level labels

Slide label
- Cancer classification
- Treatment response
- Survival

Two-stage approaches for WSI classification



X: image tiles

θ_e

Z: latent variable
- Tile score
- Tile feature

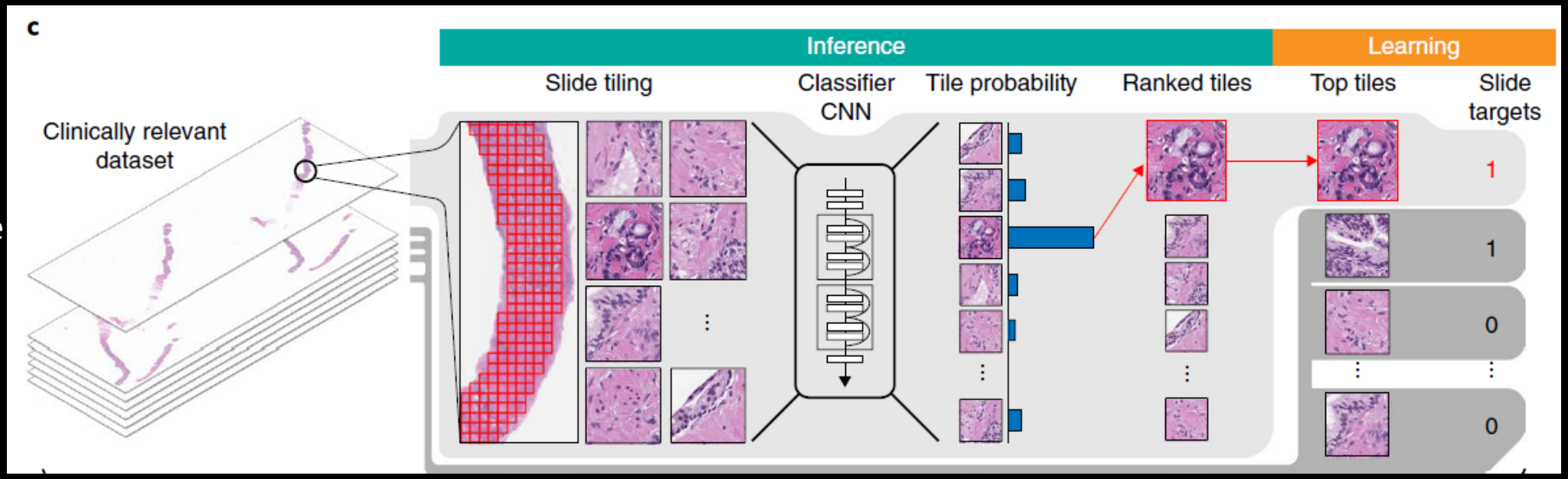
θ_a

Y: Slide label
- Cancer classification
- Treatment response
- Survival

Two-stage approaches for WSI classification

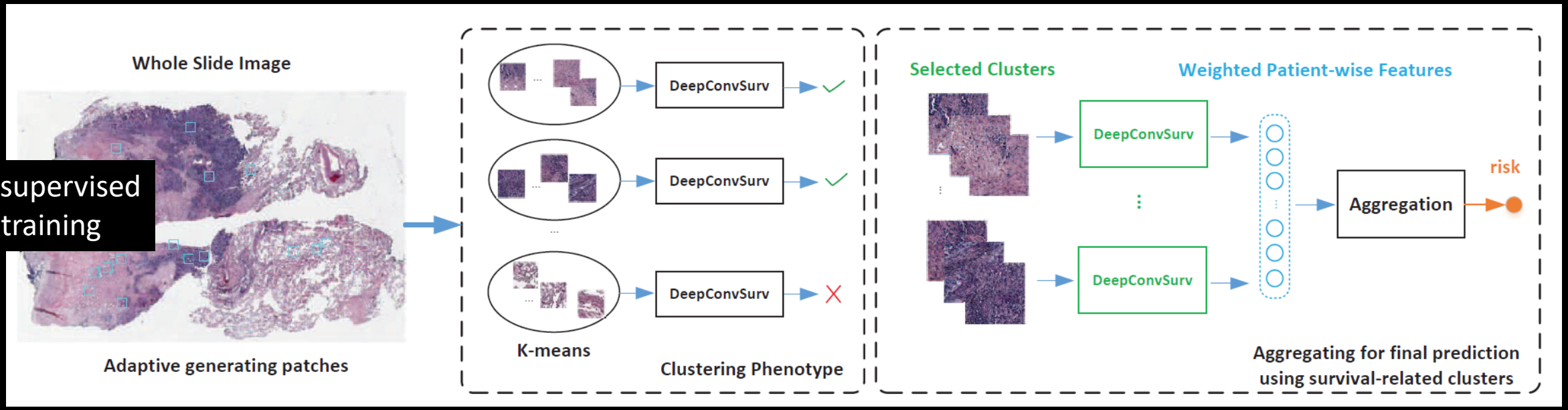
	X: image tiles	θ_e	Z: latent variable	θ_a	Y: Slide label
	With local annotation	X: labeled tiles		Z: tile scores • Tile label	Cancer classification
Weakly-supervised	Multiple instance learning (MIL)	X: Negative slides: all tiles Positive slides: tiles with score Z > t		Z: tile scores • Tile "pseudo" label • Assumption: ***Z = Y***	Cancer classification
Weakly-supervised	Unsupervised θ_e training	X: all tiles		Z: tile features • Reconstruction • Self-supervision	Cancer classification Survival regression

Multiple instance learning (MIL)



Campanella, G., Hanna, M.G., Geneslaw, L. *et al.* Clinical-grade computational pathology using weakly supervised deep learning on whole slide images. *Nat Med* **25,** 1301–1309 (2019) doi:10.1038/s41591-019-0508-1

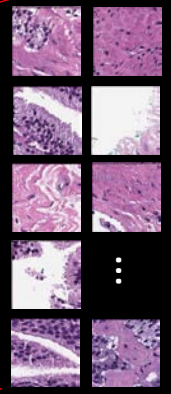
Unsupervised θ_e training



Zhu, Xinliang, et al. "Wsisa: Making survival prediction from whole slide histopathological images." *Proceedings of the IEEE Conference on Computer Vision and Pattern Recognition*. 2017.

Two-stage approaches for WSI classification

X: image tiles



θ_e

Z: latent variable
- Tile score
- Tile feature

θ_a

Y: Slide label
- Cancer classification
- Treatment response
- Survival

Unsupervised θ_e training:
- Combining diverse information over whole slides
- Decoupled training of θ_e and θ_a
- Theoretically applicable to any learnable tasks, e.g. survival prediction

Multiple instance learning (MIL):
- Selecting most predictive tiles
- Assumption: ***Z=Y***
- Only applicable to cancer classification
- θ_a is usually voting

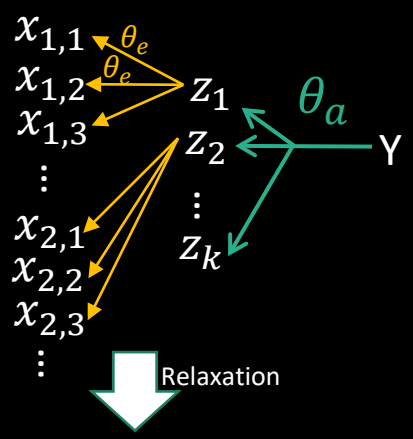
How do we combine diverse information of all tiles and learn slide label end-to-end?

Ideal end-to-end learning :

$$maximize \quad P(Y|\theta_a, \theta_e, X)$$

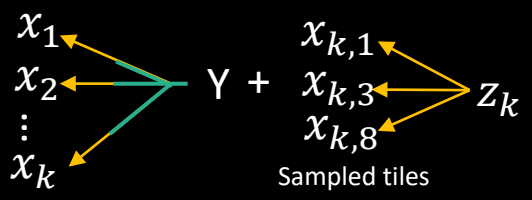
Represent the whole slides as K tile clusters in feature space so that θ_a only needs to learn aggregation over K centroids rather than all tiles:

$$maximize \quad P(Y|\theta_a, Z),\ where\ Z = \{z_1, ..., z_k\},\ z_k = 1/N_k \sum_{N_k} \theta_e(x_{k,i})$$



Relaxation: calculating centroids -> approximating each centroid by the nearest tile

$$maximize \quad P(Y|\theta_a, \theta_e, \{x_1, ..., x_k\}) + P(Z|\theta_e, \{x_1, ..., x_k\})$$

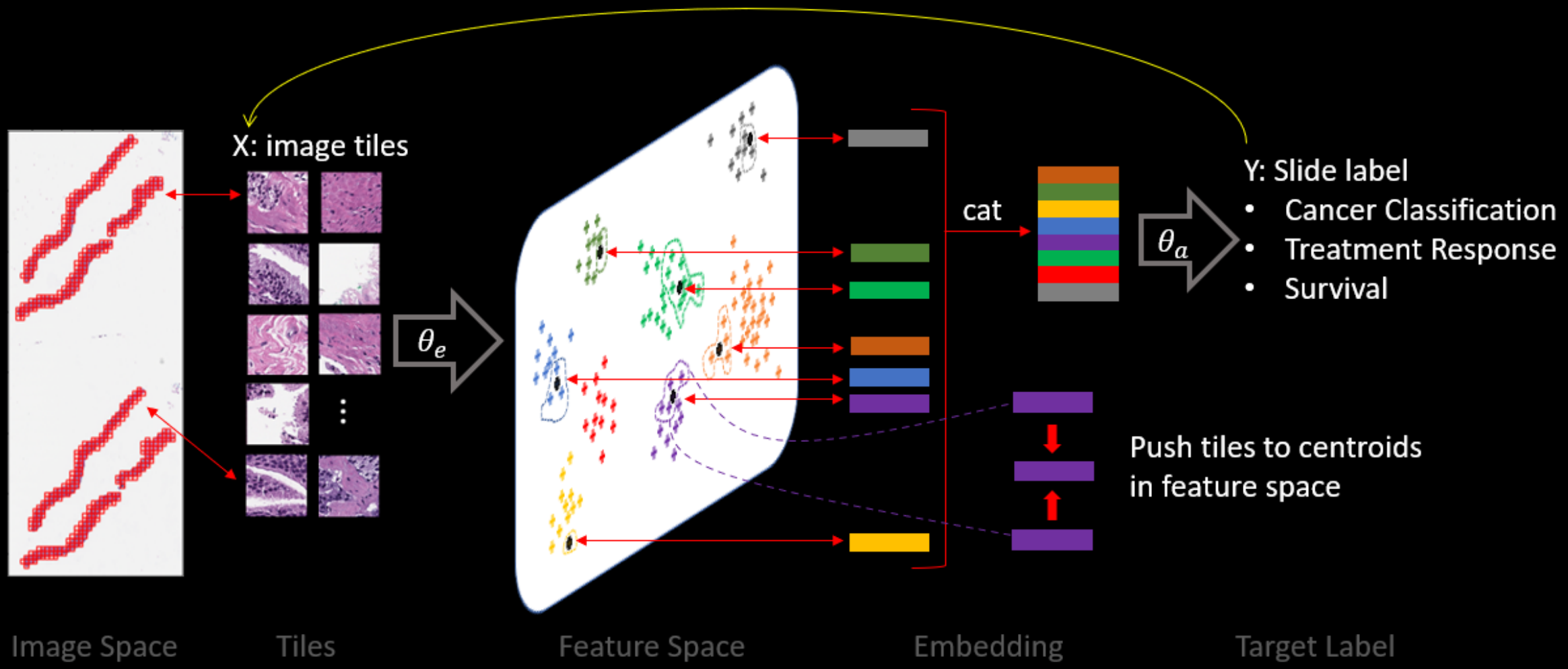


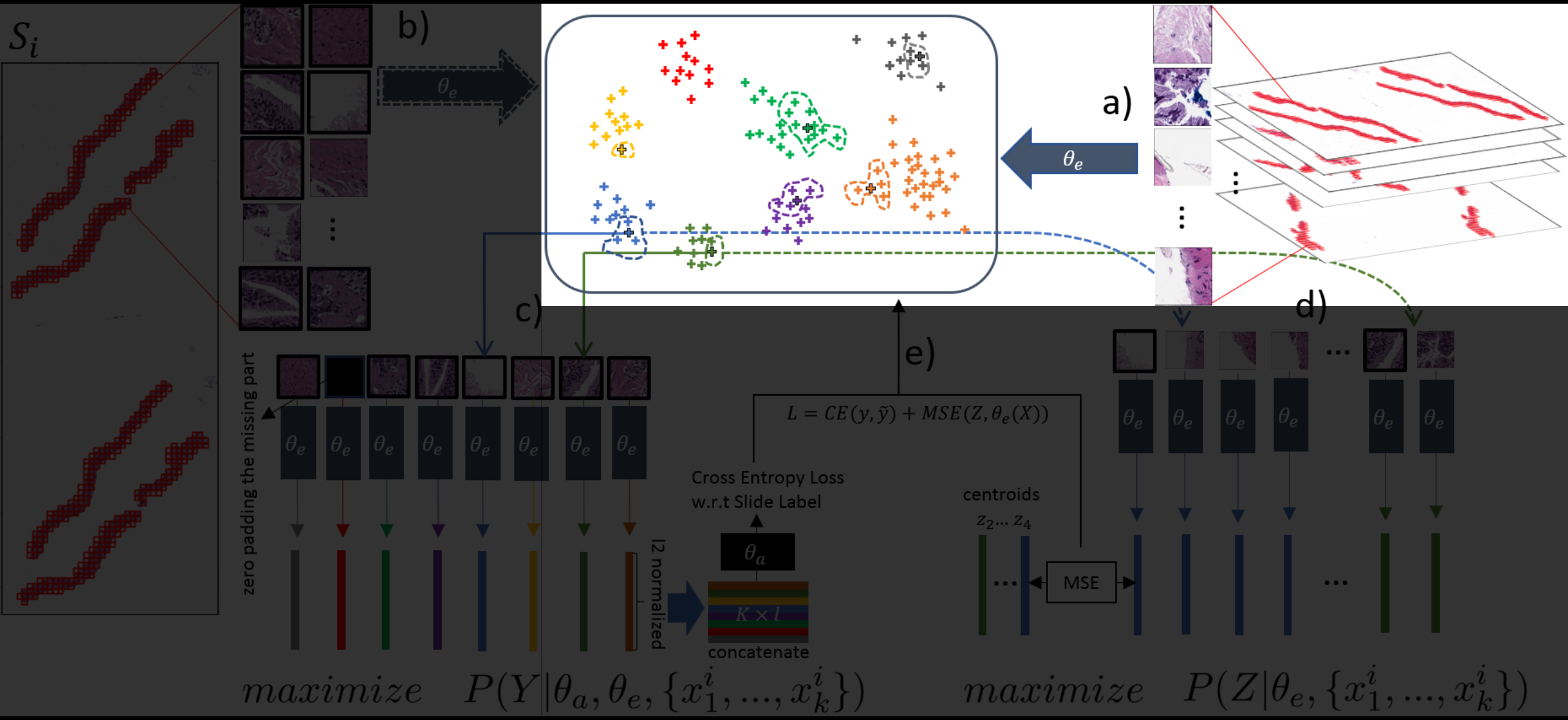
- Approximating each centroid by the nearest tile in feature space and minimizing the Euclidean distance between tiles and their centroids.
- The whole model consisting of K tile encoders θ_e, which share parameters, and 1 aggregation module θ_a can be optimized from end-to-end w.r.t any learnable target Y.

End-to-end Part Learning (EPL) For Whole Slide Image Analysis

Chensu Xie @ FuchsLab

[Xie et al., MIDL 2020]





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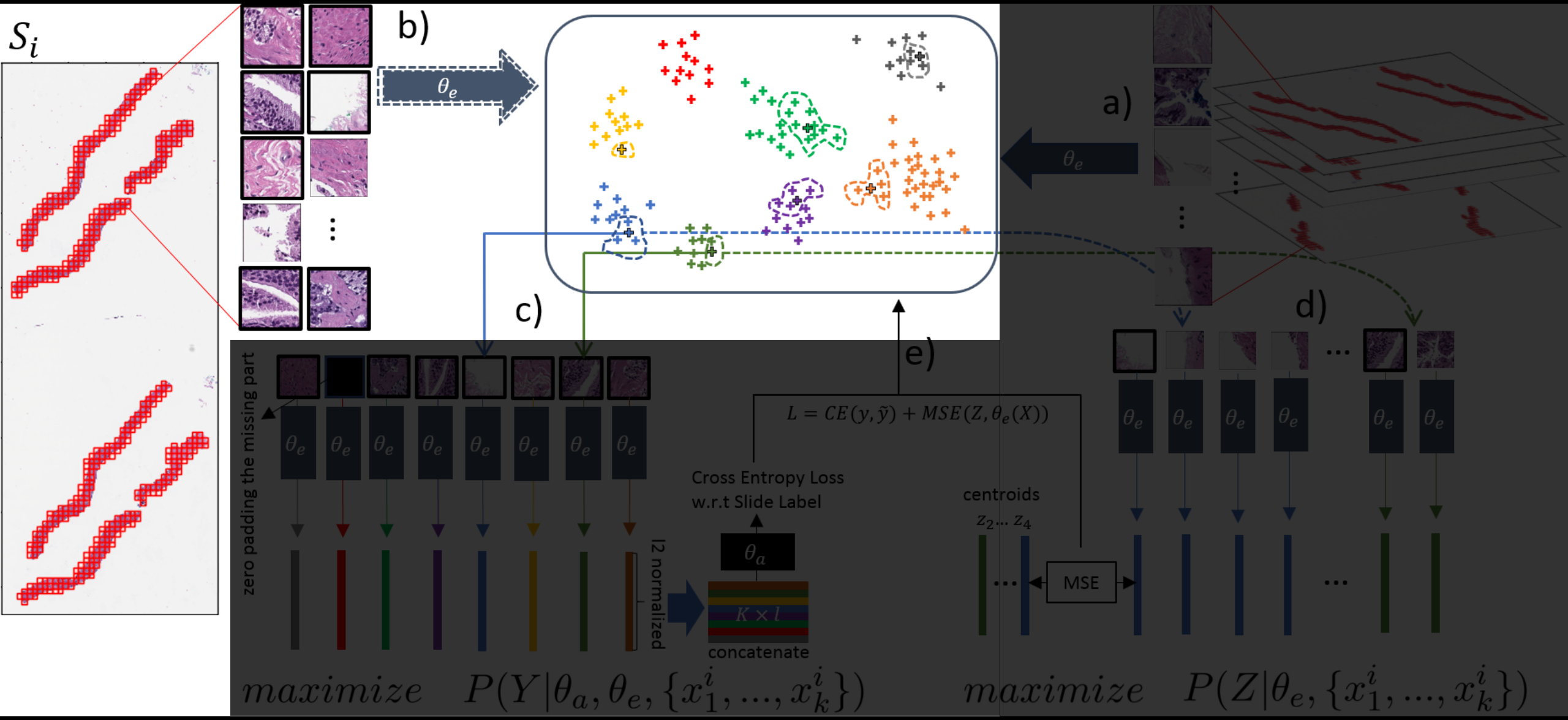

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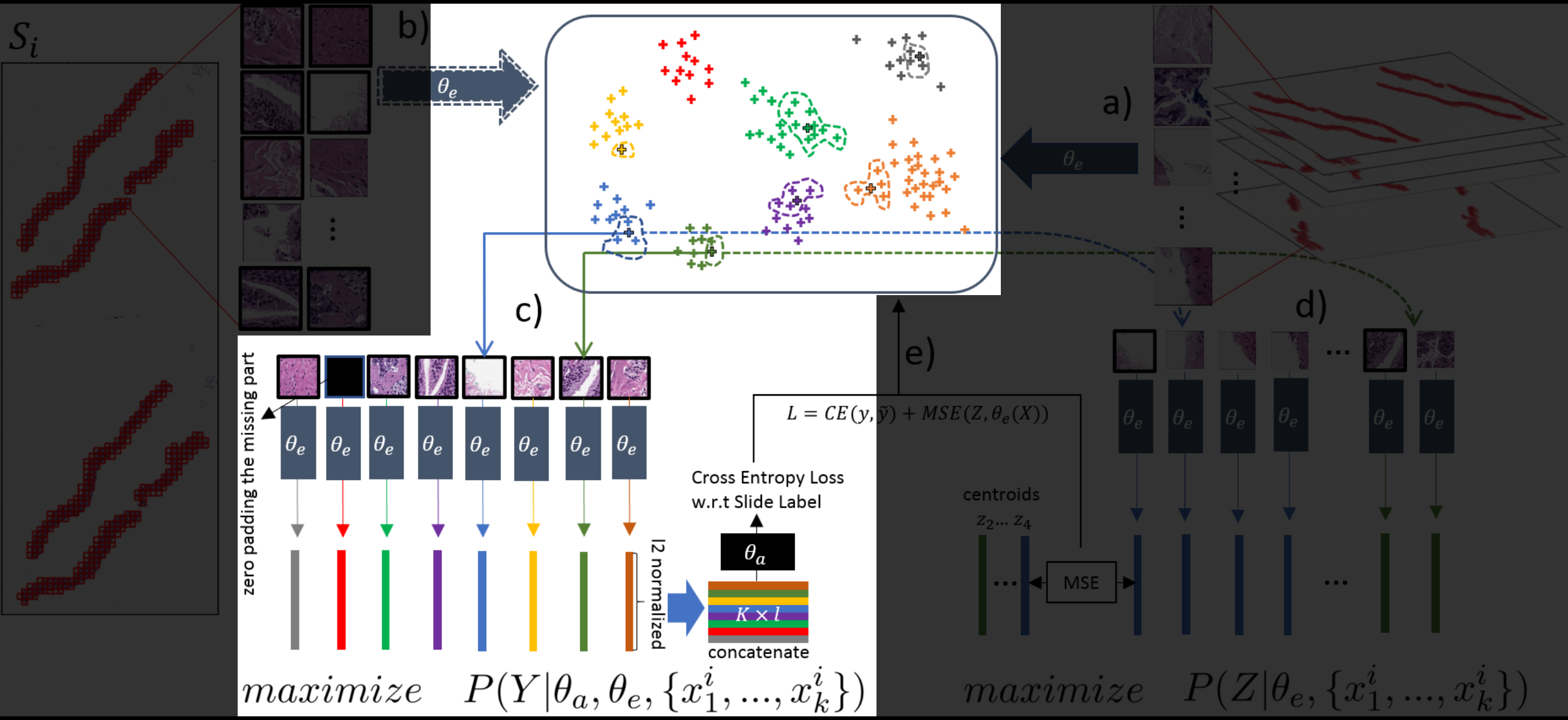

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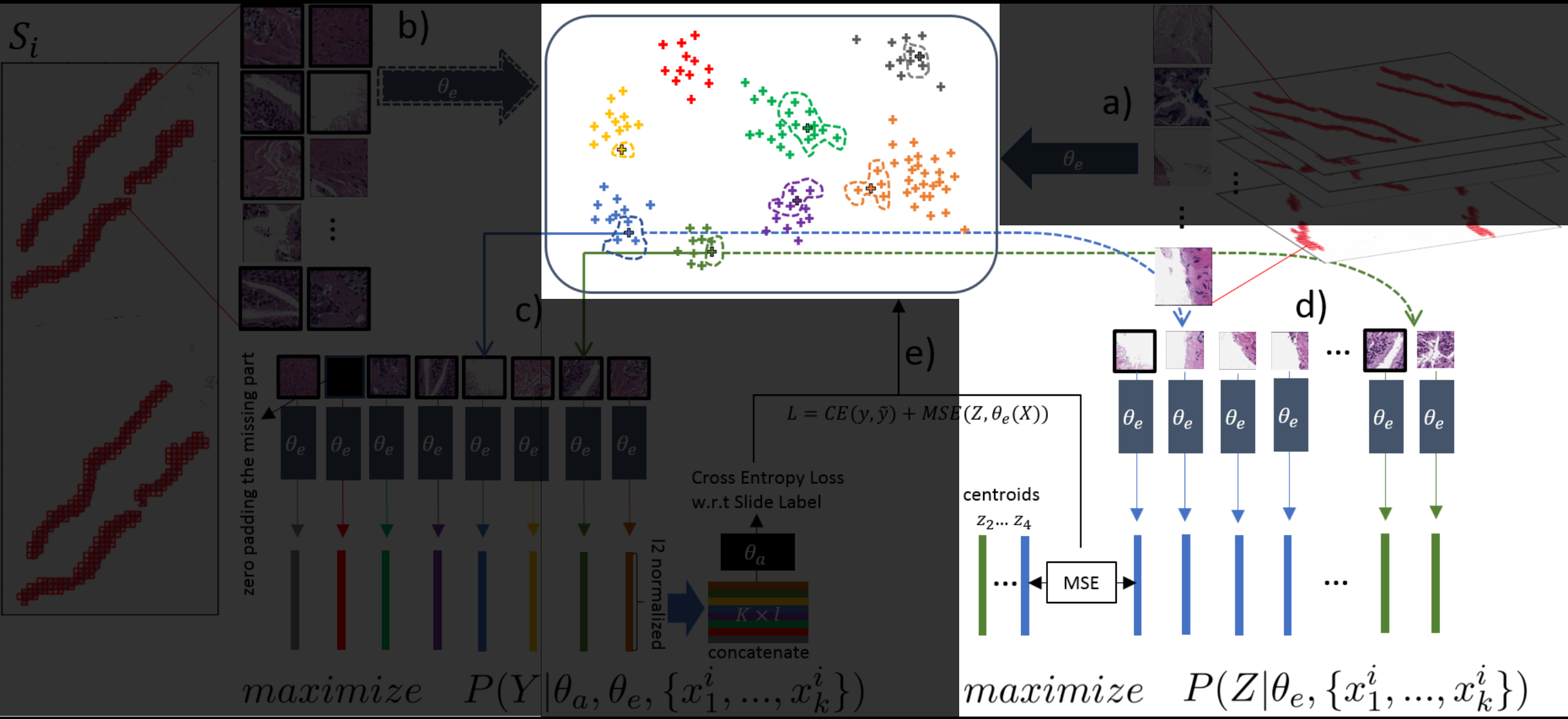

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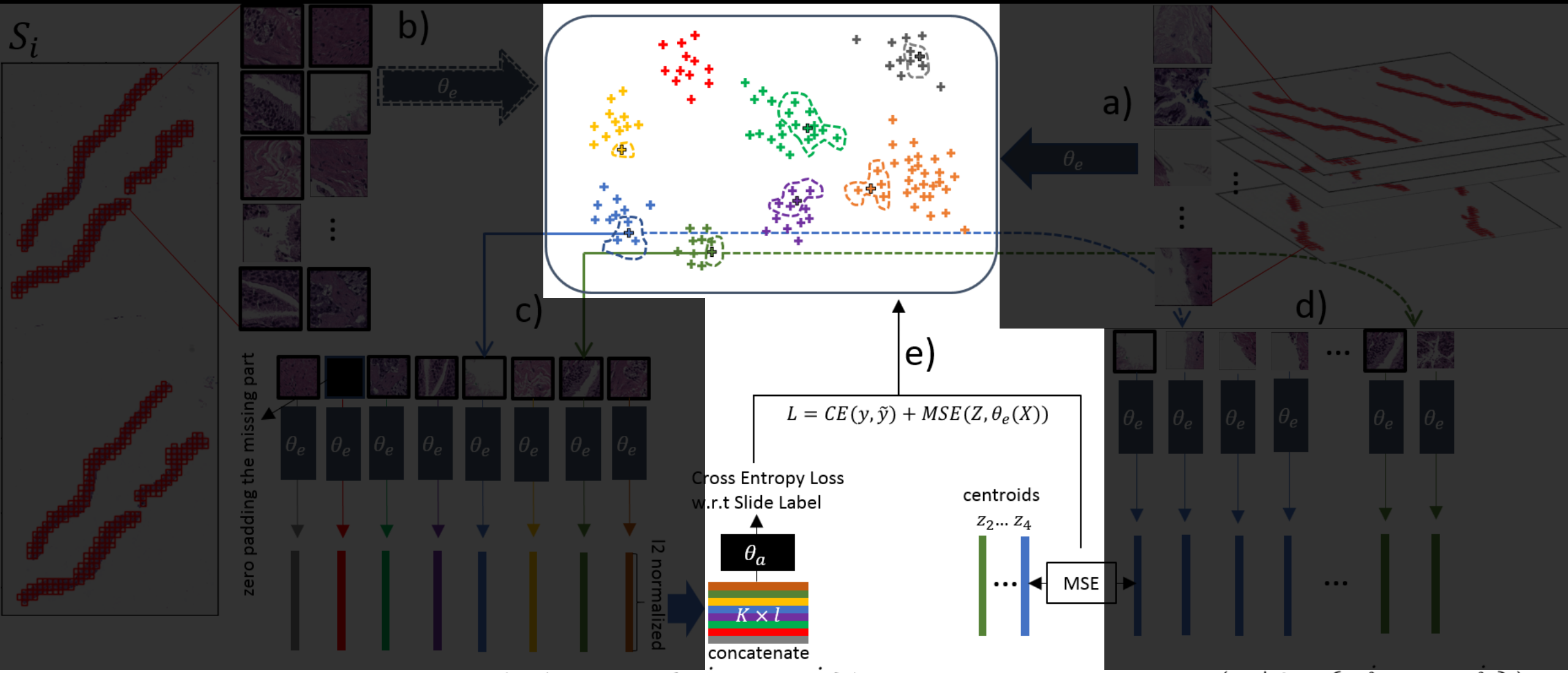

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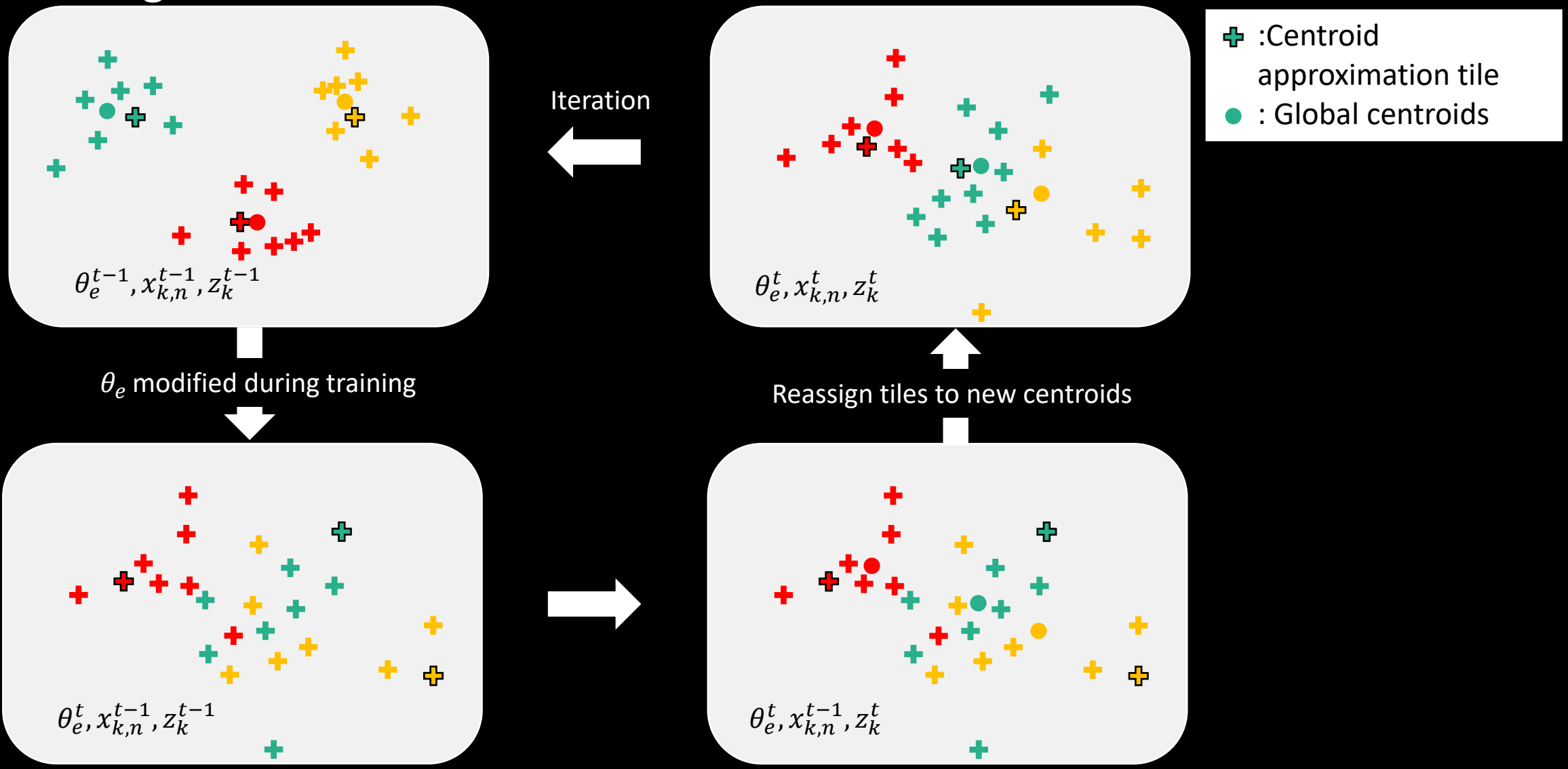
Part reassignment



Calculate new global centroids $\{z_1, z_2, \ldots, z_k\}^t$ by averaging the new feature of each part of tiles assigned in the previous epoch $t-1$:

$$z_k^t = 1/N \sum_n \theta_e^t(x_{k,n}^{t-1})$$

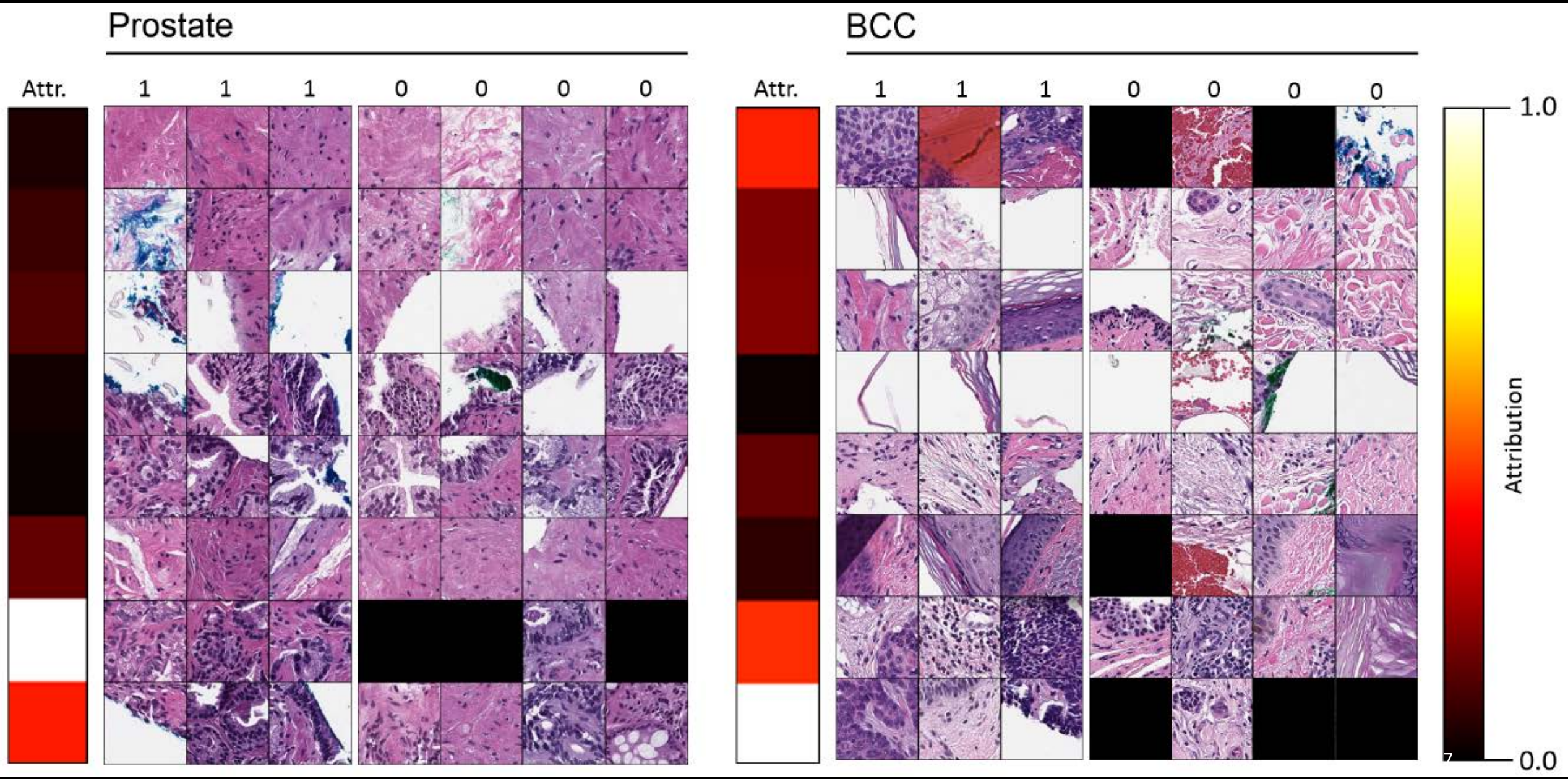
Benchmark against traditional task

Method	Cancer Classification		Lung Cancer Architectural Subtyping			
	Prostate	BCC	Lepidic	Papillary	Solid	Micropapillary
MIL[1]	0.986	0.986	-	-	-	-
MIL-RNN[1]	0.991	0.988	-	-	-	-
EPL	0.986	0.986	0.654	0.533	0.781	0.627
EPL-NA	0.984	0.987	-	-	-	-
EPL-k1	0.734	0.930	0.585	0.518	0.648	0.530

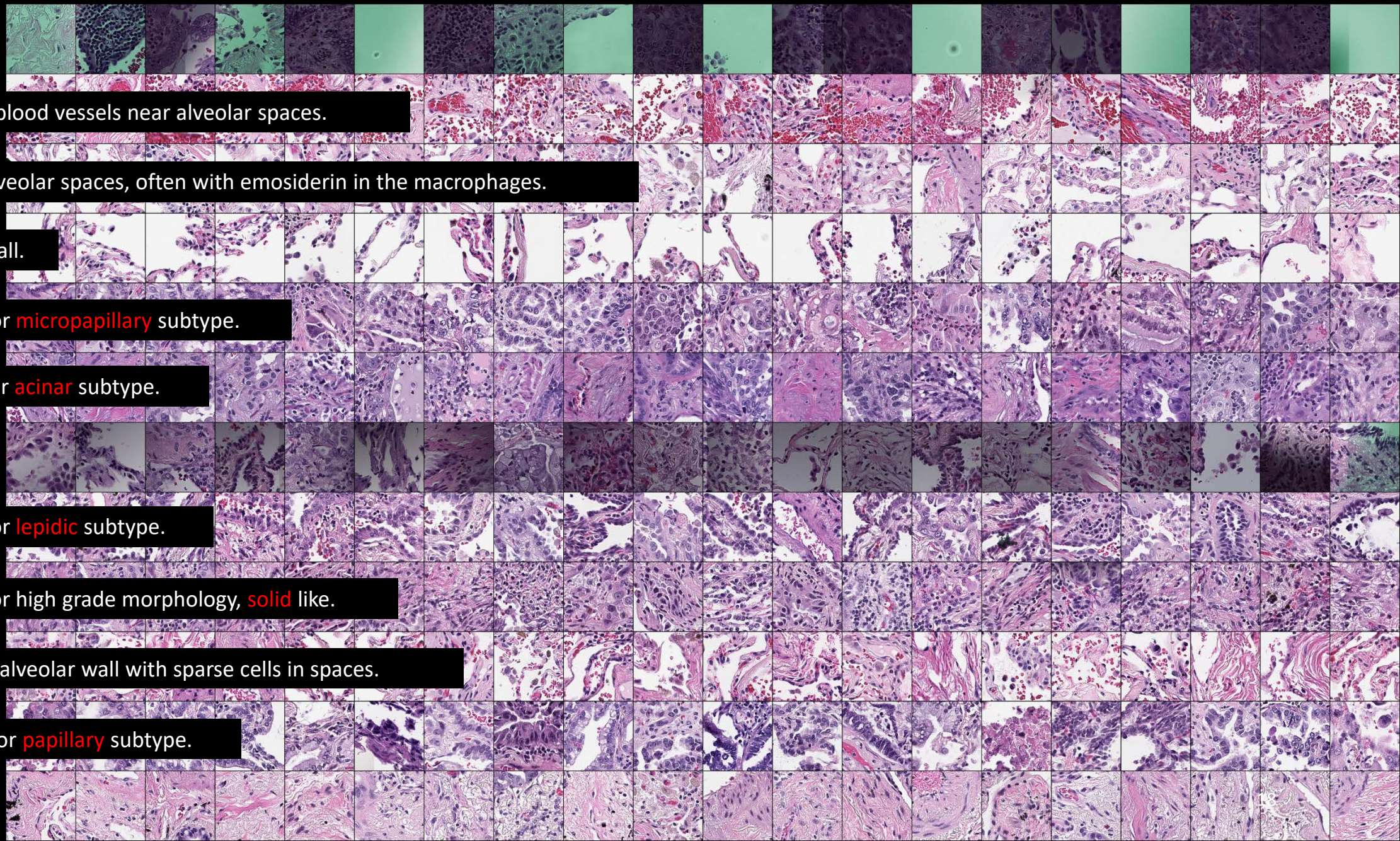
- Traditional cancer classification: S → {0,1}
  - Clinical-grade classification: only 4 and 6 false negative slides (undetected cancer cases) out of the 1500+ test slides respectively
- Multi-label lung cancer architectural subtyping: S → <1,0,0,1>
  - MIL is not applicable

1. Campanella, G., Hanna, M.G., Geneslaw, L. *et al.* Clinical-grade computational pathology using weakly supervised deep learning on whole slide images. *Nat Med* **25,** 1301–1309 (2019) doi:10.1038/s41591-019-0508-1

Cancer classification

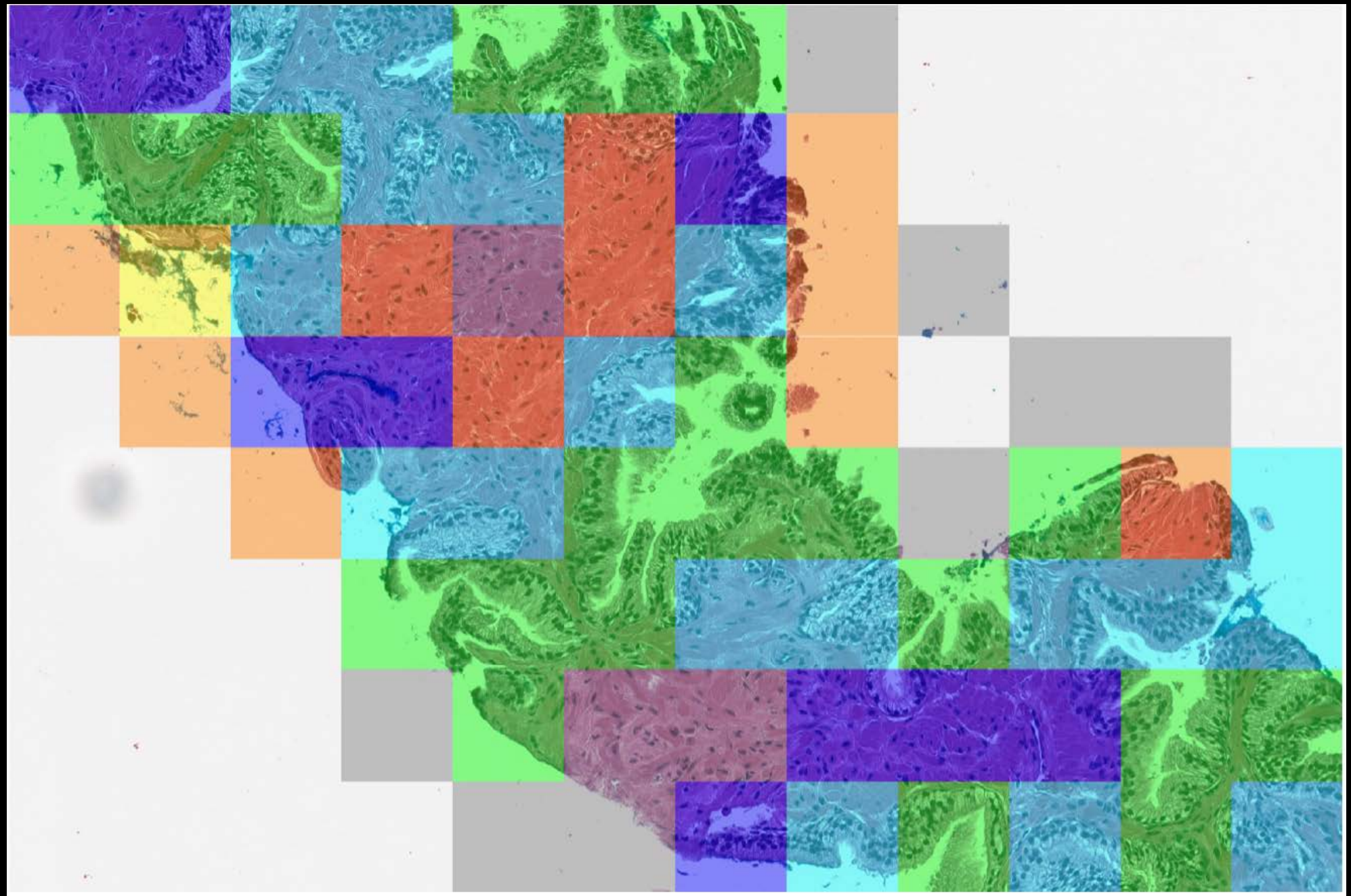


Multi-label lung cancer subtypes prediction



1. Green ink.
2. Red blood cells in blood vessels near alveolar spaces.
3. Macrophages in alveolar spaces, often with emosiderin in the macrophages.
4. Normal alveolar wall.
5. Cancer enriched for micropapillary subtype.
6. Cancer enriched for acinar subtype.
7. Black ink.
8. Cancer enriched for lepidic subtype.
9. Cancer enriched for high grade morphology, solid like.
10. Blood vessel and alveolar wall with sparse cells in spaces.
11. Cancer enrichedfor papillary subtype.
12. Stroma.

Tissue type localization and region importance scoring



EPL: a general framework for the future of end-to-end WSI assessment

- A general weakly-supervised WSI prediction algorithm; theoretically applicable to any learnable target Y.
  - Ongoing projects in the lab (with promising results):
    - EPL for survival regression
    - EPL prediction of lung cancer patient response to immunotherapy

- Easy to be combined with tile-level proxy tasks.
  - Simply adding concurrently trained loss
  - E.g. tile labels, self-supervision targets etc.

- Various tile encoder θ_e
  - θ_e as graph neural network (GNN) for WSI classification based on cell graph built from nuclei detection results of VOCA[1]

1. Xie, C., Vanderbilt, C.M., Grabenstetter, A. & Fuchs, T.J.. (2019). VOCA: Cell Nuclei Detection In Histopathology Images By Vector Oriented Confidence Accumulation. Proceedings of The 2nd International Conference on Medical Imaging with Deep Learning, in PMLR 102:527-539

Thanks to Fuchs’ lab!