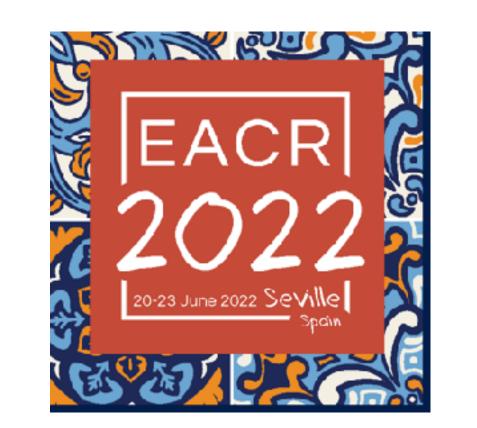
MUNI RECETOX



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The impact of tumor morphology landscape on molecular signatures

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Hypothesis/motivation: i) Tumour molecular profiles are correlated with tumour morphology, ii) intratumoural morphological heterogeneity is a thing, iii) sampling matters!

Objective: study the intra-tumoral heterogeneity in terms of morphology-driven transcriptomics

Background

- intra-tumoral heterogeneity (ITH) and tumor sampling strategies impact on consensus molecular subtypes [1,2]
- molecular subtypes correlate with tumor morphology patterns [3,4]
- molecular features can predict CMS [4,5]
- should we take morphology in consideration when sampling for molecular profiling?

Materials and Methods

- 110 tumors: morphological patterns annotated by expert pathologist and macro dissected
- 203 whole-genome good quality expression profiles (Clariom D Affy chips); 30 whole-tumor, 173 morphological parts
- CMScaller was used for subtype assignment, xCell for estimating the cell population mixture

CIN

Morphology had the strongest effect of gene expression (modules) and cellular composition (PERMANOVA: p < 0.001) followed by patient effect (p = 0.017)

		Morphotypes									
		CT	DE	MU	PP	SE	TB	NR	ST	PY	Total
	CMS1	13	1	3	1	3	4	0	1	0	26
CMS	CMS2	16	1	0	5	11	0	2	0	1	36
<section-header></section-header>	CMS2	5	1	3	3	9	0	13	0	1	35
	CMS4	3	5	14	1	4	1	1	7	0	36
Total assigned		37 (71.2%)	8 (72.7%)	20 (95.2%)	10 (91%)	27 (65.6%)	5 (55.6%)	16 (94%)	8 (88.9%)	2 (100%)	133

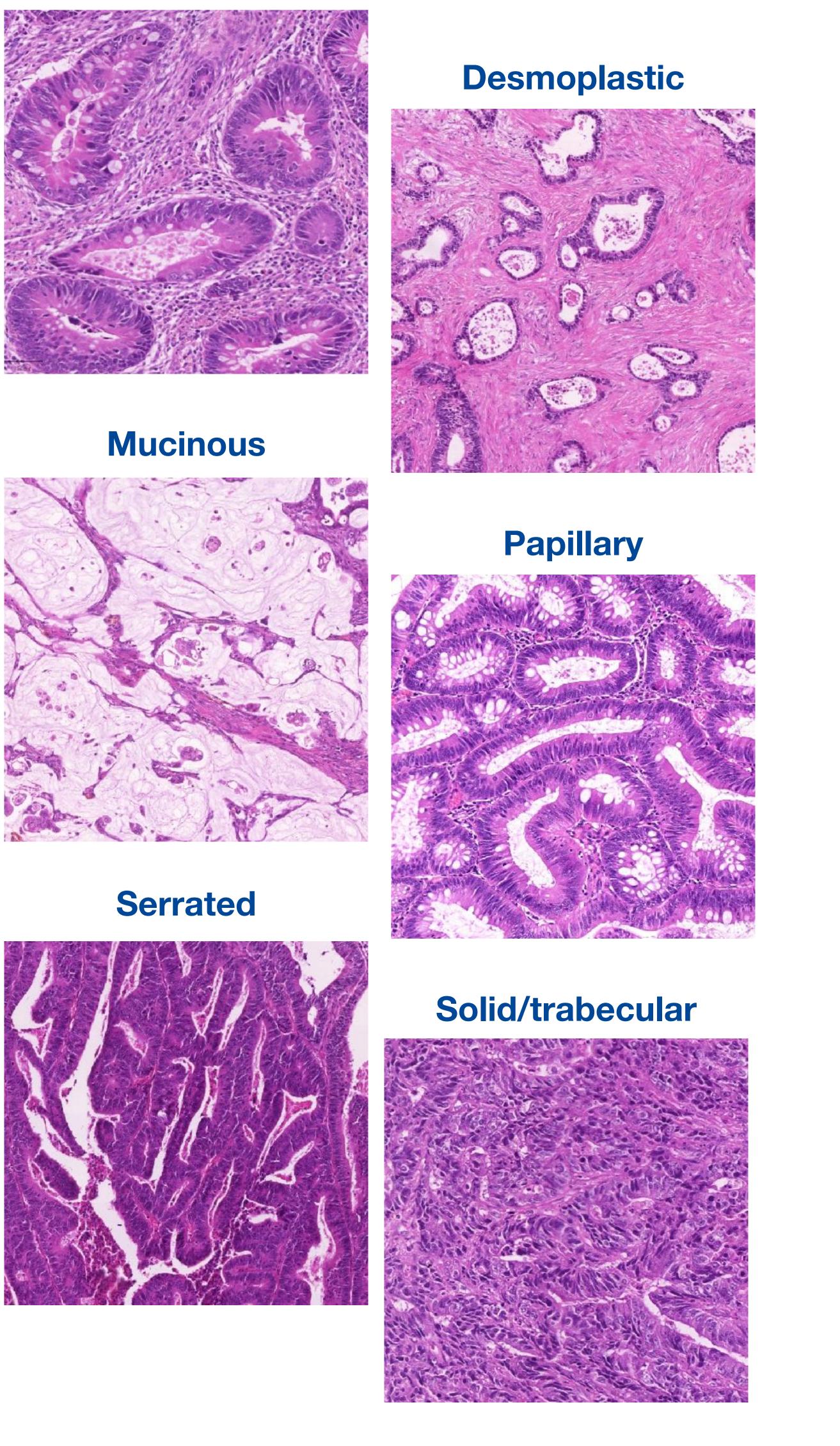
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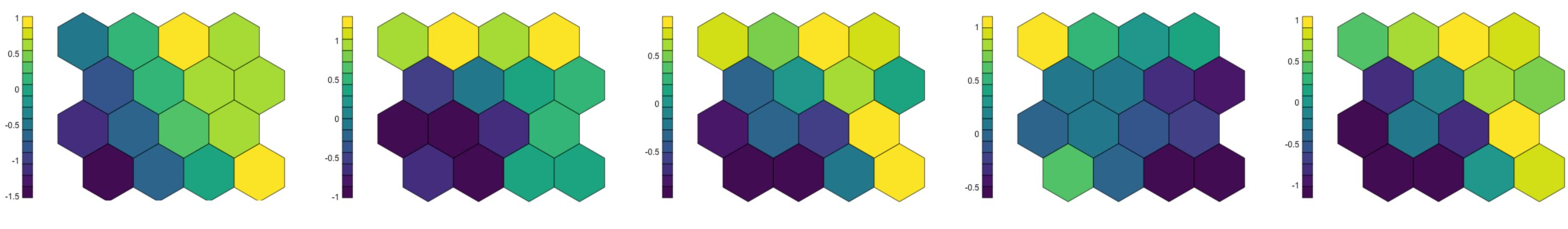
- GSVA for pathway scoring
- PERMANOVA to estimate effects of tumour vs morphology
 Complex tubular

Sample characteristics

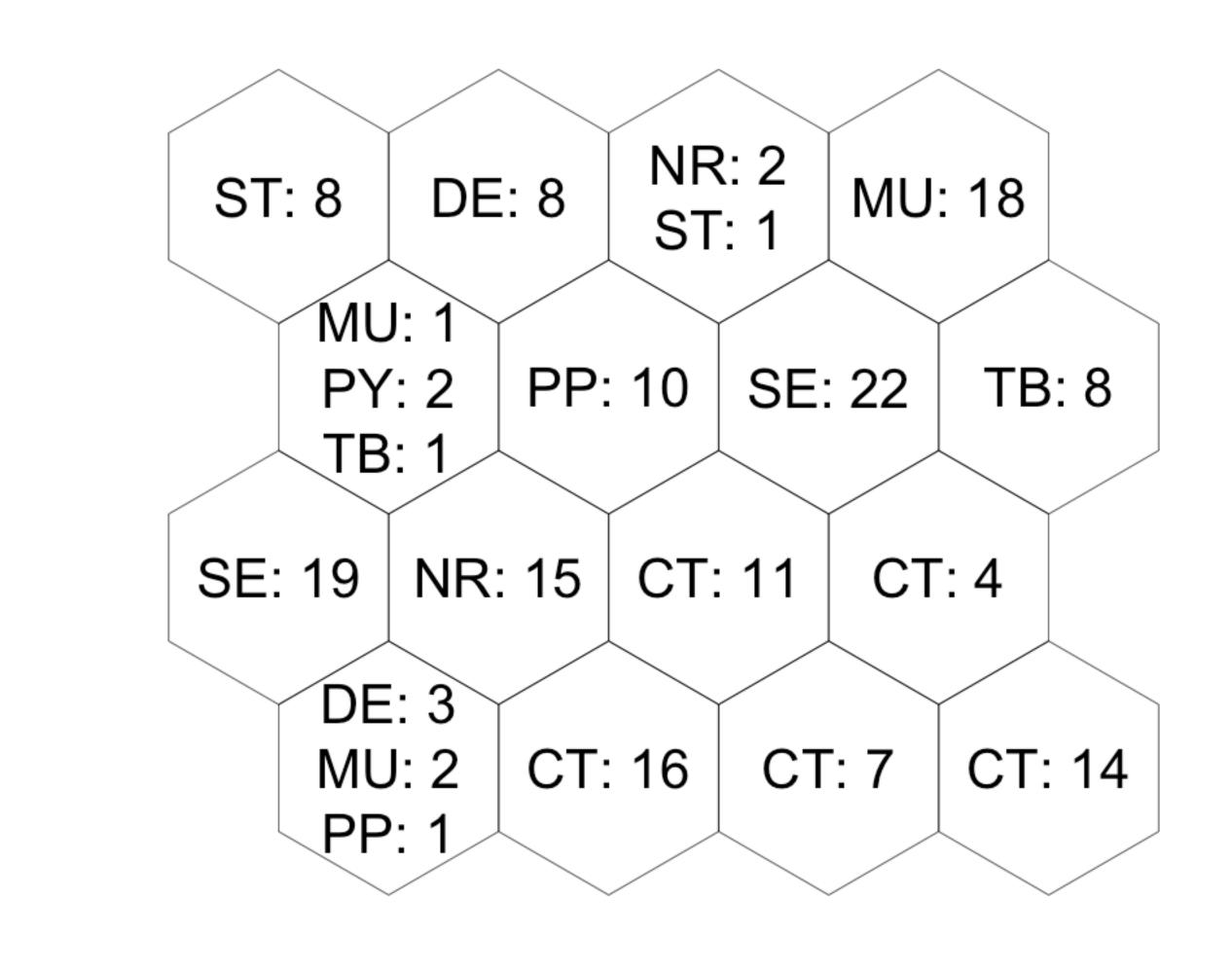
Age	33-87 (Mean: 66.6, Median: 69
Stage	II: 47; III: 32; IV: 20
Grade	1: 11; 2: 52: 3: 36
TNM	T1: 1; T2: 5; T3: 85; T4: 8 N0: 49, N1: 32; N2: 18 M0: 79; M1: 20

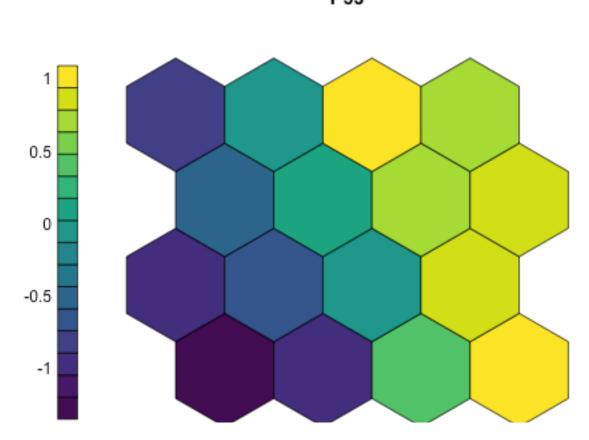
Morphological Complex tubular (CT): 52 regions Desmoplastic (DE): 11 Mucinous (MU): 21 Papillary (PP): 11 Serrated (SE): 41 Solid/trabecular (TB): 9 Tumor-adjacent normal (NR): 17 Polyp (PY): 2

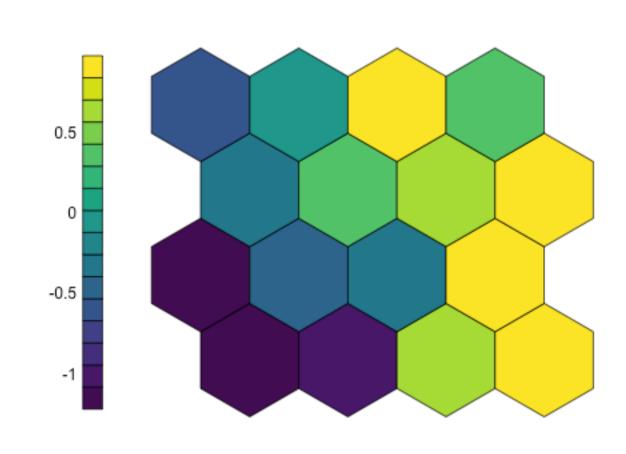


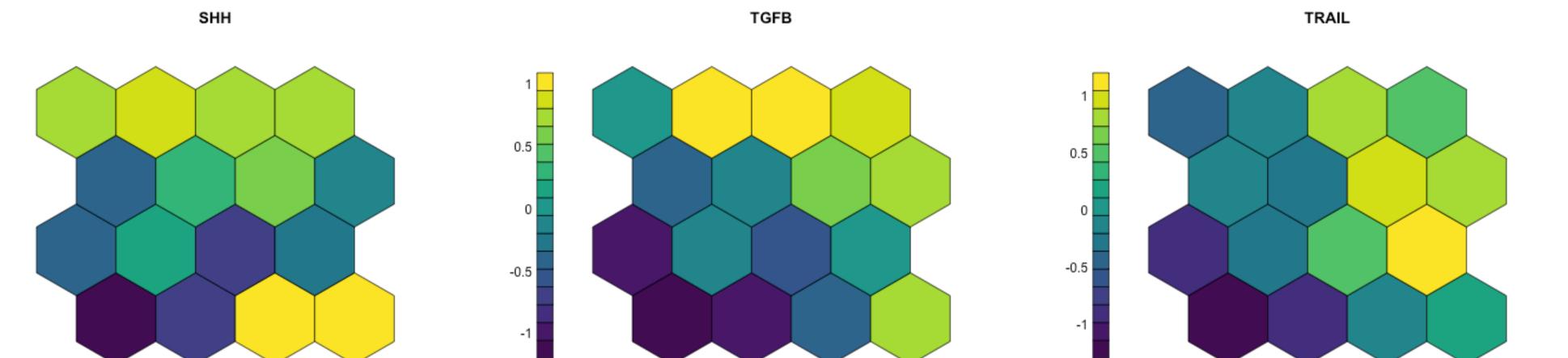


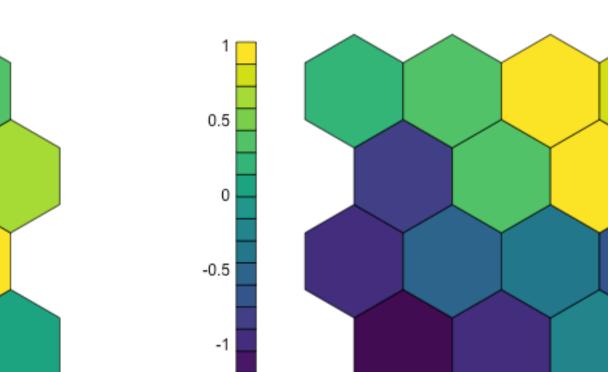
Clustering: Kohonen mapping











Tumor-adjacent stroma (ST): 9

Conclusions

- molecular signatures vary across regions of the same section
- a whole tumor is better represented through a set of region-based signatures (e.g. CMS)
- ITH affects both prognostic signatures and expressionbased classifiers
- multi-region sampling provides a cost-effective means of addressing ITH

References

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Intra-tumoral heterogeneity

