Multiparametric microvascular MRI: a cluster approach to characterize glioma

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Equipe 5: Neuroimagerie Fonctionnelle et Perfusion Cérébrale

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Context

For solid tumors, several microvascular factors are relevant to:

- tumor diagnosis
- follow-up
- response to treatment

Some parameters can be obtained with MRI:

- apparent diffusion constant (ADC)
- cerebral blood volume (CBV)
- cerebral blood flow (CBF),
- integrity of the vascular wall:
  area under curve after Gd-DOTA injection ($AUC_{Gd\text{-}DOTA}$)
- tissue oxygen saturation (StO_2)
- cerebral metabolic rate of oxygen ($CMRO_2$)

…

Parameter maps accumulation yields however some difficulty for interpretation

cluster-based approach to highlight the tissue structures
that exhibit similar physiological characteristic in two rat models of glioma

Methods – experimental design

Two orthotopic rat models of glioma:

C6 / Wistar rats

- n: 13 rats
- inoculation: 10^5 cells, 5 µL, caudate nucleus
- days of imaging: 21-23 days
- mean tumor size +/- SD: 85.1 +/- 46.4 mm^3

F98 / Fischer rats

- n: 13 rats
- inoculation: 10^3 cells , 5 µL, caudate nucleus
- day of imaging: 22-24 days
- mean tumor size +/-SD: 104.9 +/- 28.0 mm^3

Physiological control

- mechanical ventilation
- blood samples in femoral vein and artery before and after MRI
- similar $p0_2$ and pCO_2 between models

Multiparametric MRI

Magnet 4.7 T (Avance III console; Bruker)

Three regions of interest (ROIs):

- tumor bulk (n=3023 voxels; Wistar-C6=1500, Fischer-F98=1523)
- contralateral striatum (n=579 voxels; Wistar-C6=315, Fischer-F98=264)
- contralateral cortex (n=811 voxels; Wistar-C6=417, Fischer-F98=394)

Methods – MRI parameters

Six MRI parameters:

Apparent diffusion coefficient (ADC)

TR/TE = 3000/28.6 ms, b=900 s/mm^2

Vascular integrity:

DCE imaging approach: *Lemasson et al., Radiology 2010*
- multiple T1-weighted images; n = 60, 15.6 s per image; TR/TE: 800/4.2 ms
- bolus of Gd-DOTA (200µmol/kg)

-> Area Under Curve of Gd-DOTA ($AUC_{Gd\text{-}DOTA}$)

Cerebral blood flow (CBF)

continous arterial spin labeling (CASL) *Clément Debacker*
- spin-echo EPI, TE=17.2 ms
- labeling duration = 4 sec, postlabeling delay = 0.2 sec, 20 pairs

Cerebral blood volume (CBV)

Steady state approach: *Valable et al., NMR Biomed 2008*
- multiple gradient echo sequence; 26 echos TR/TE: 6000/3.5-78.5 ms
- bolus of P904 (200µmol/kg, Guerbet)

.

Tissue oxygen saturation (StO_2)

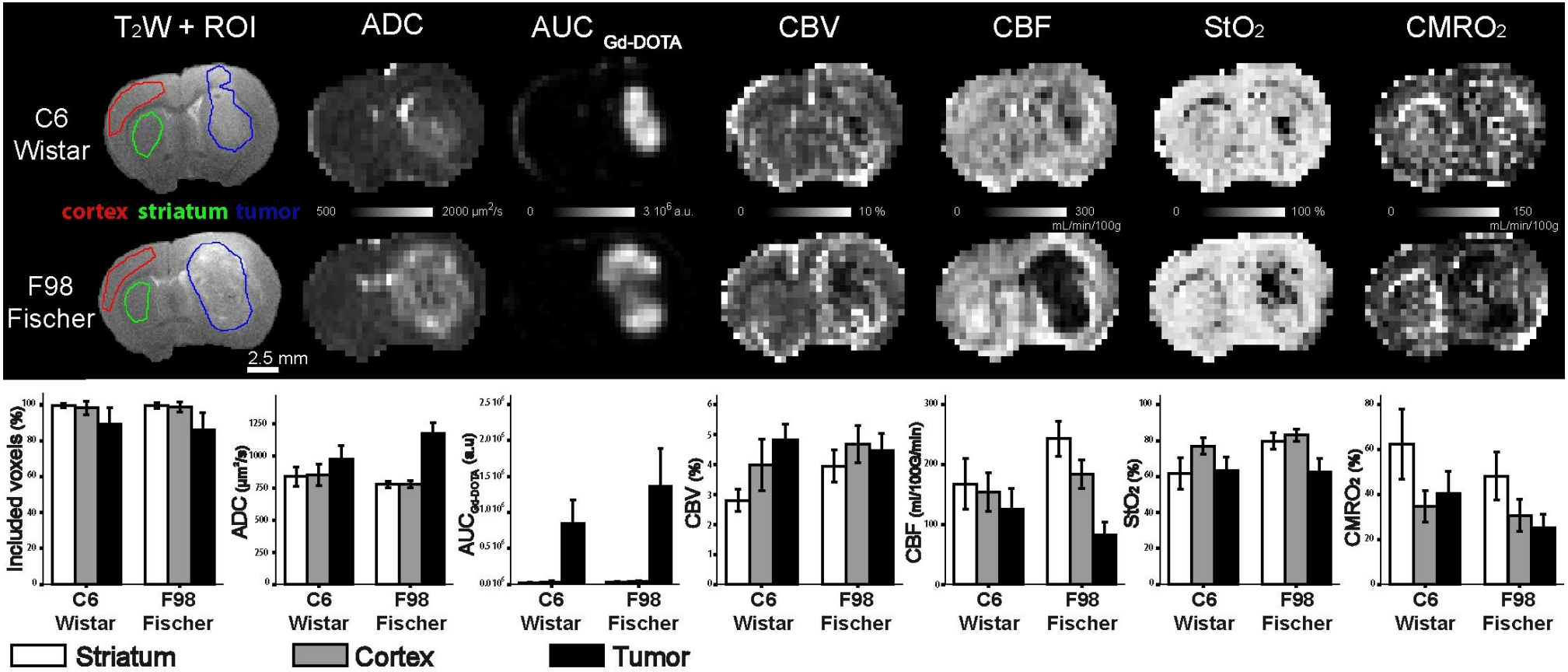
Computation with: *Lemasson et al., Radiology 2012*
- CBV map
- 3D multiple gradient echo sequence; 25 echos TR/TE: 100/3-87 ms
- multiple spin echo sequence; 28 echos TR/TE: 2300/12-336 ms

Cerebral metabolic rate of oxygen ($CMRO_2$)

$CMRO_2 = CBF \times (1 - StO_2/100)$

Multiparametric MRI

Classical ROI-based analysis



-Similarities or heterogeneities between Wistar/Fischers rats, C6/F98 tumor models
-Mean measurement do not reflect disparities within ROI
-Loss of spatial information

Mclust-based Clustering approach

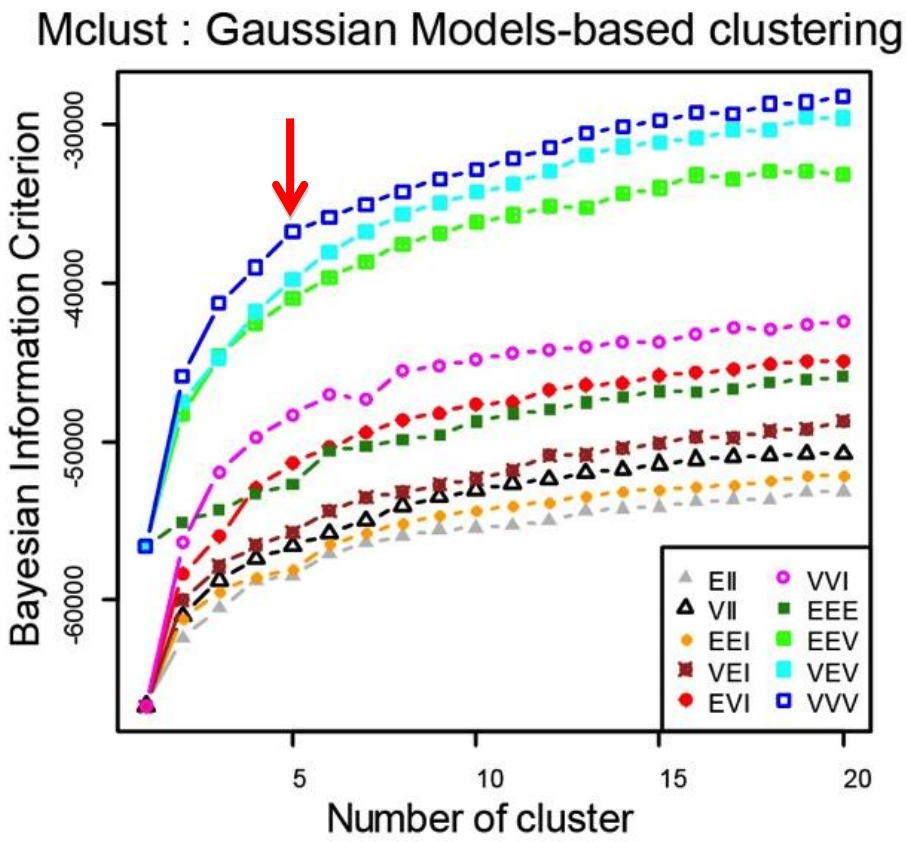
Cluster-based analysis

C. Fraley and A. E. Raftery (2002). Journal of the American Statistical Association

Normal mixture modeling: Mclust
Values standardization for scale effect minimization between parameters
Allows prediction of new data set from built model
Model choice / optimal number of clusters > Bayesian Information Criterion (BIC)

Cluster number determination

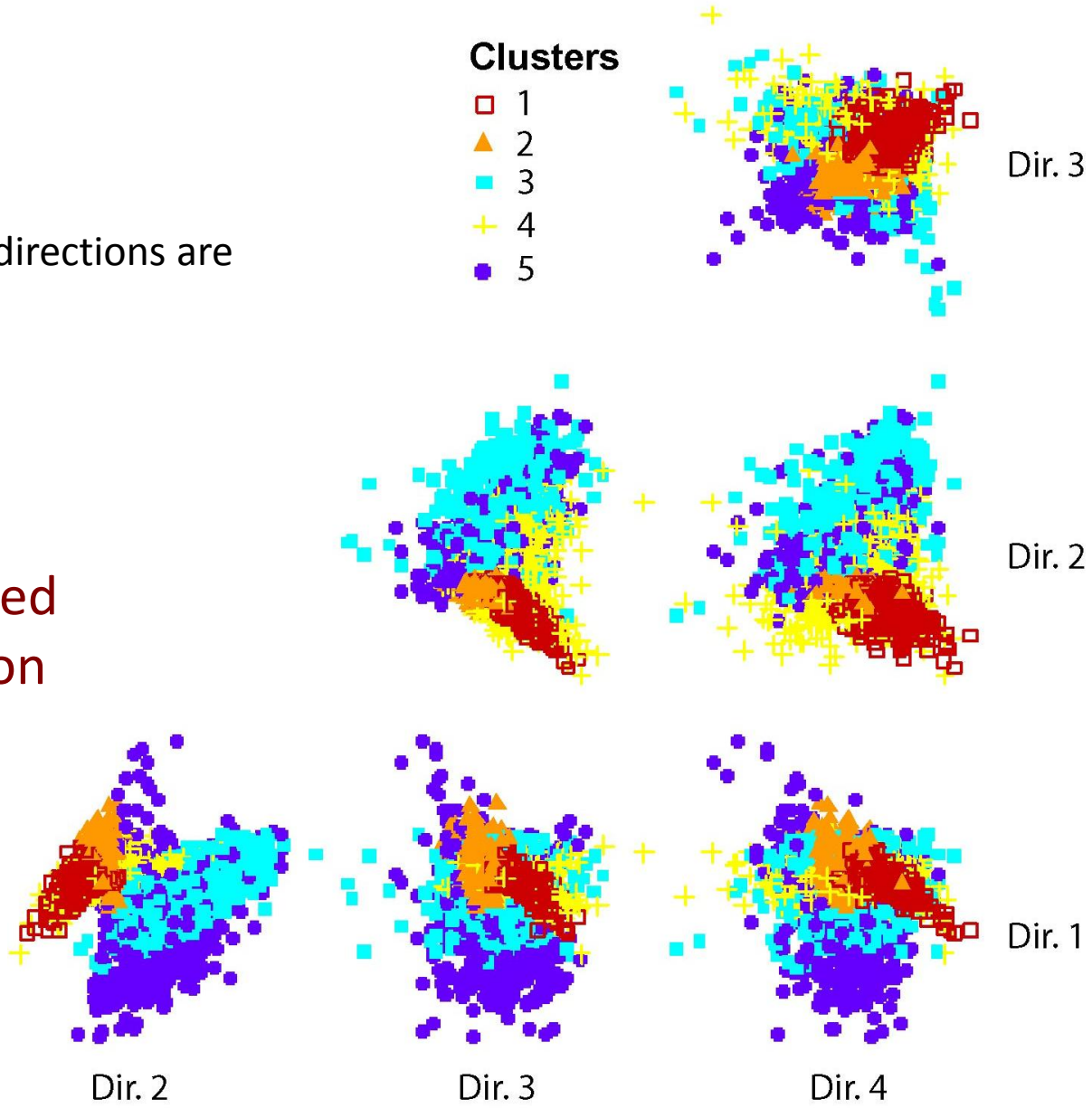
5 clusters are sufficient
to explain variability of the
data set



Mclust-based Clustering approach

Clusters separation

Data reduction after clustering
Total of 6 directions
Cluster distribution in the 4 first directions are depicted



> Clusters are well grouped
> Good clusters separation

Cluster description #1

	Healthy		Pathological		Excluded
	mMRI parameters in each cluster (mean +/- SD of absolute values)				
cluster	1	2	3	4	5
voxel number	875	837	758	805	637
ADC ($\mu m^2/s$)	797.7 +/- 56.7	925.2 +/- 143.5	1188.2 +/- 242.0	1012.6 +/- 148.9	1102.3 +/- 216.7
$AUC_{Gd\text{-}DOTA}$ (10^5 a.u).	1.2 +/- 2.7	8.7 +/- 10.6	177.8 +/- 85.9	65.5 +/- 58.9	131.4 +/- 92.8
CBV (%)	4.0 +/- 1.2	3.3 +/- 0.9	5.0 +/- 2.5	6.1 +/- 2.6	3.4 +/-1.6
CBF (mL/min/100g)	197.3 +/- 54.1	151.0 +/- 45.1	36.8 +/- 19.4	170.2 +/- 57.6	78.8 +/- 47.5
StO_2 (%)	83.0 +/- 6.8	64.1 +/- 11.7	65.4 +/- 13.9	81.0 +/- 8.4	36.6 +/- 20.2
$CMRO_2$ (mL/min/100g)	33.8 +/- 17.4	54.5 +/- 24.7	12.6 +/- 7.7	31.9 +/- 17.5	47.0 +/- 33.0

Cluster description #2

	Healthy		Pathological		Excluded
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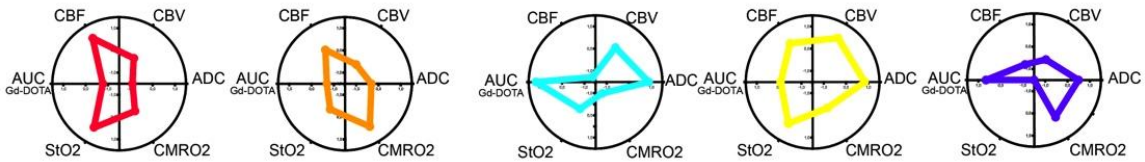
mMRI parameters in each cluster (mean of standardized values)



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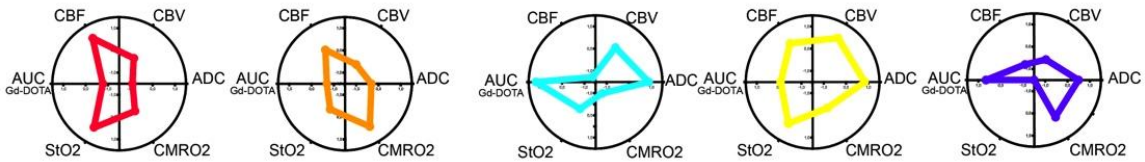

ROIs distribution in each cluster ?

Cluster description #3

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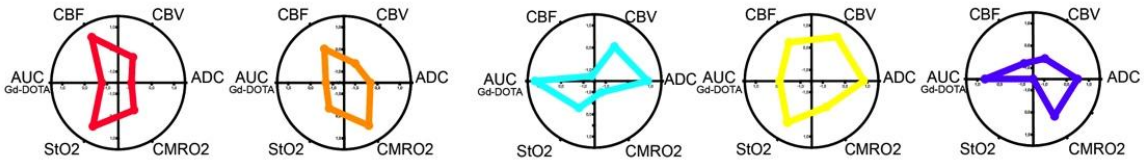
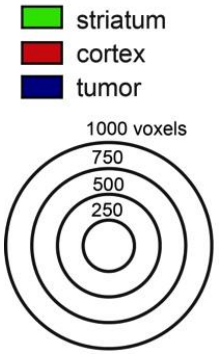
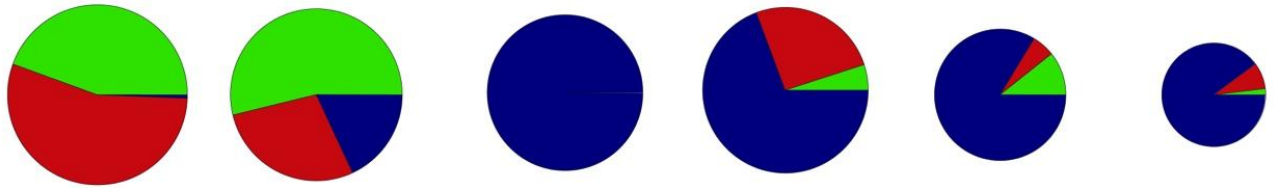


ROI distribution in each cluster





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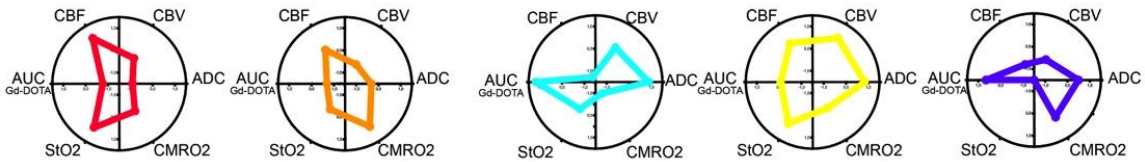
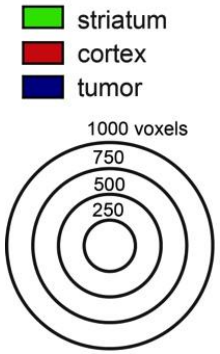
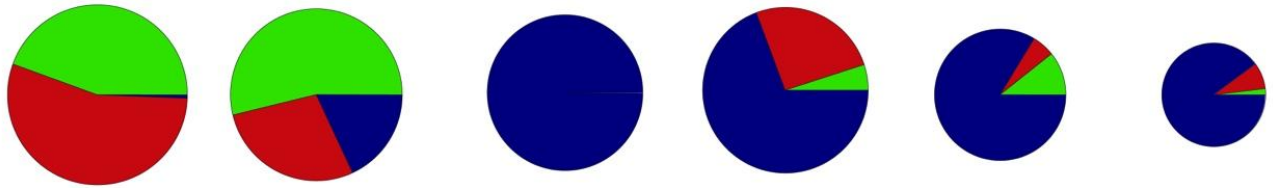


ROI distribution in each cluster





Rat stem distribution in striatum and cortex ROIs?

Tumor models distribution in tumor ROI ?

Cluster description #4

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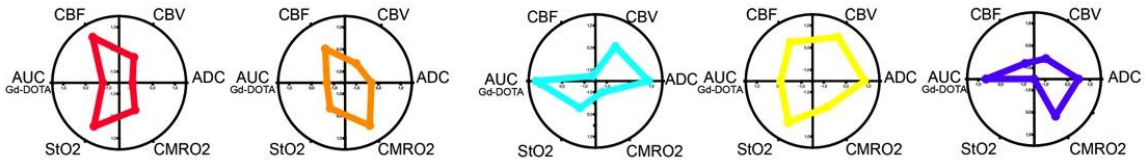
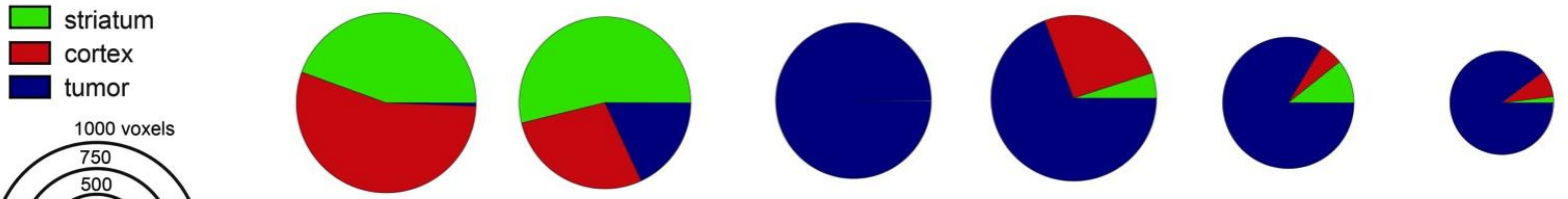
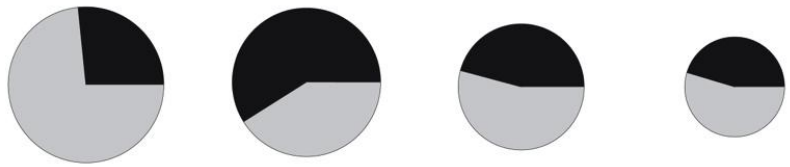


ROI distribution in each cluster

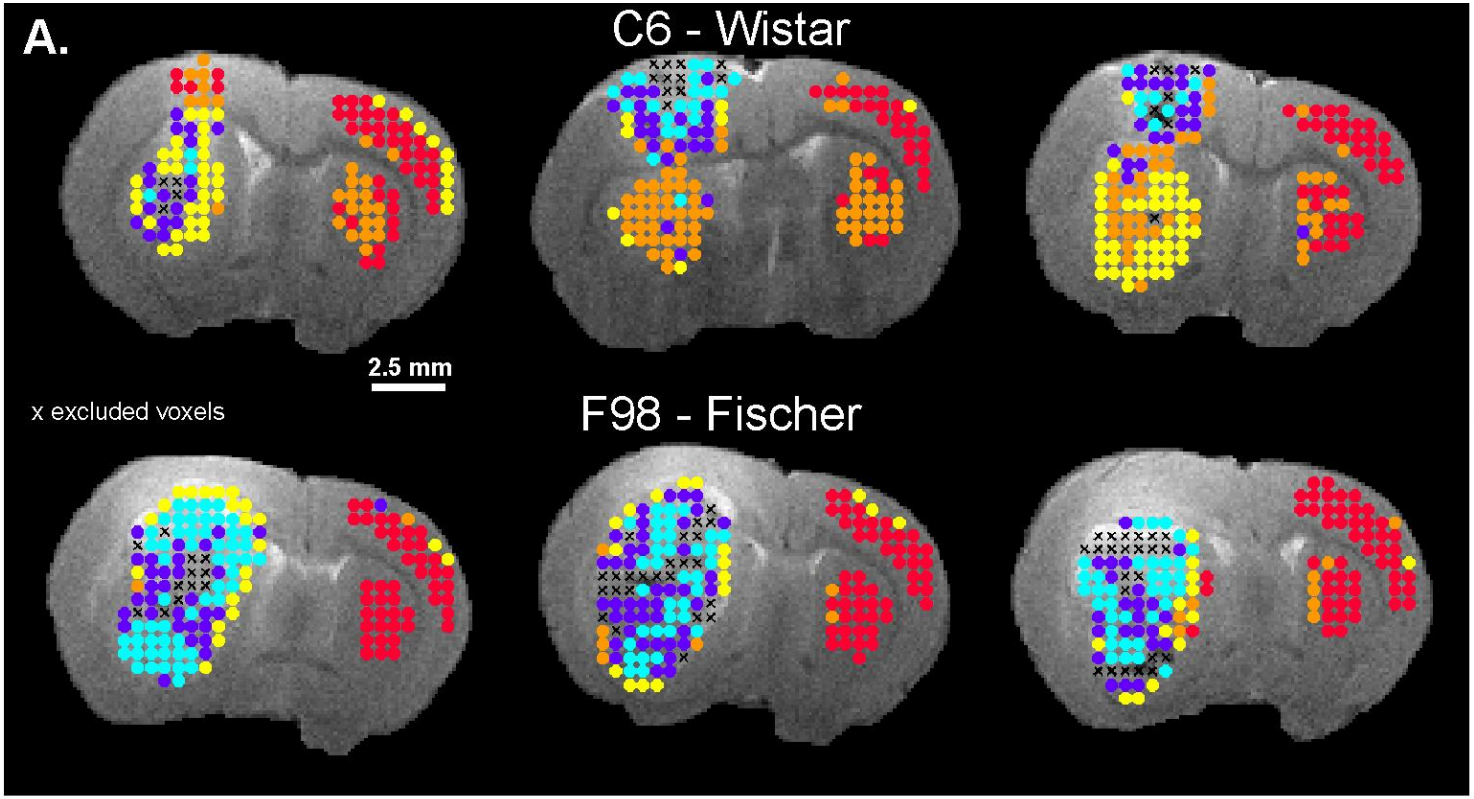


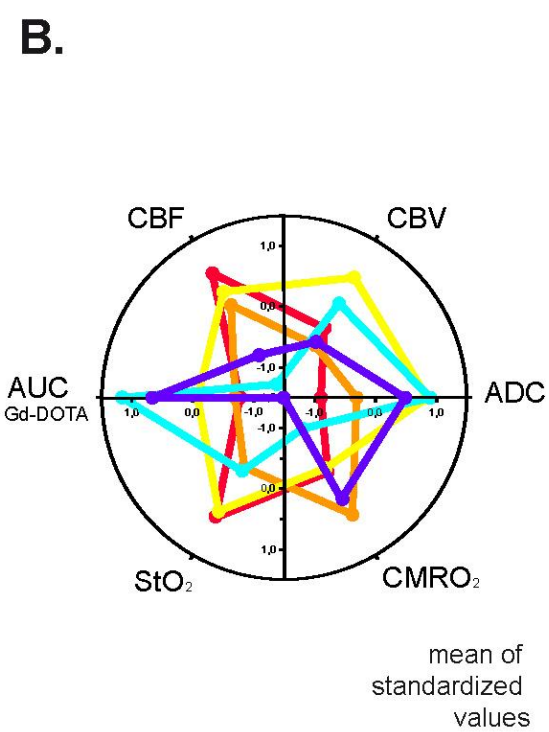
striatum and cortex

tumor



Cluster maps comparison





Clusters

- 1: Healthy spécific
- 2: Healthy/Wistar specific
- 3: Tumor/F98 specific
- 4: Tumor specific (tendency toward C6 specificity)
- 5: Tumor specific

-Rat stem differences highlighted. Cluster 2 (orange) mostly presents in Wistar rat striatum
-Some healthy clusters present in drawn tumor ROI: partial volume, false positive tumor voxels
-Spatial organization of cluster in tumor

Conclusion/Perspectives

Conclusion

Normal Mixture model-based clustering:

- separates tumor tissue from healthy tissue
- shows cluster composition differences between C6 and F98 glioma models
- explain rat brain variability between rat stem
- highlight the spatial distribution of clusters within tumor

Perspectives

Preclinical research: effect of treatments on cluster composition
…detection of responsive/non responsive clusters

Clinical research (Julien Bouvier, PhD student):
- tumor localization
- diagnosis
- grades

Merci pour votre attention

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GIN
Equipe 5 : Neuroimagerie Fonctionnelle et Perfusion Cérébrale

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Blandine Chanteloup-Forêt
Emmanuelle Grillon

Inserm
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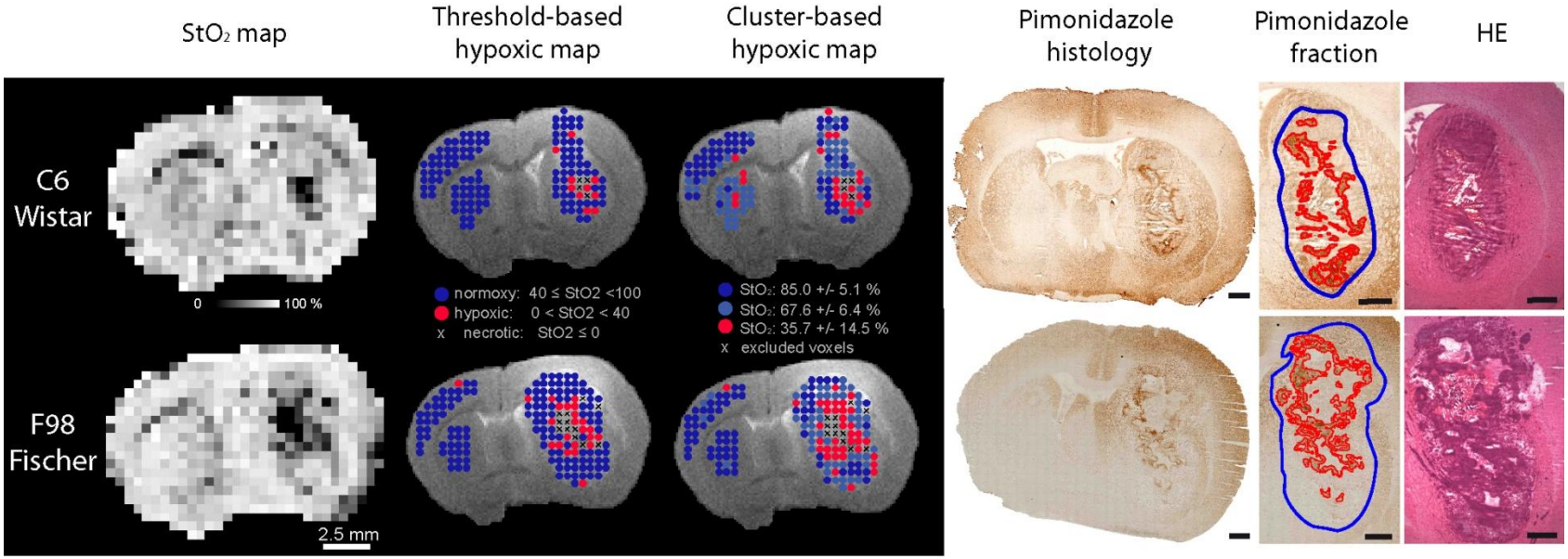
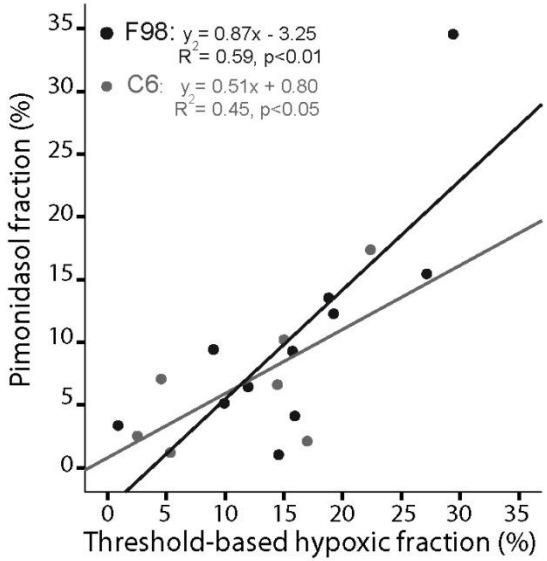
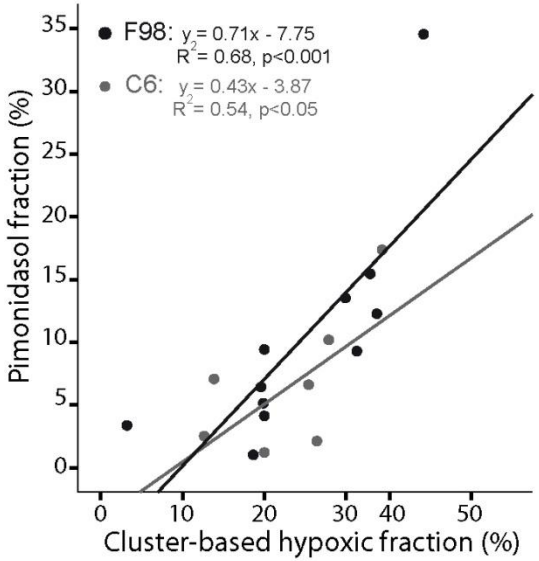
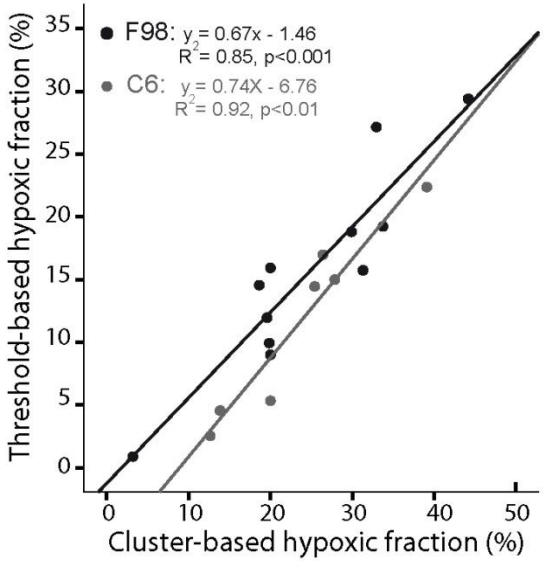
Cluster-based approach validation on StO2 map vs Pimonidazol histology



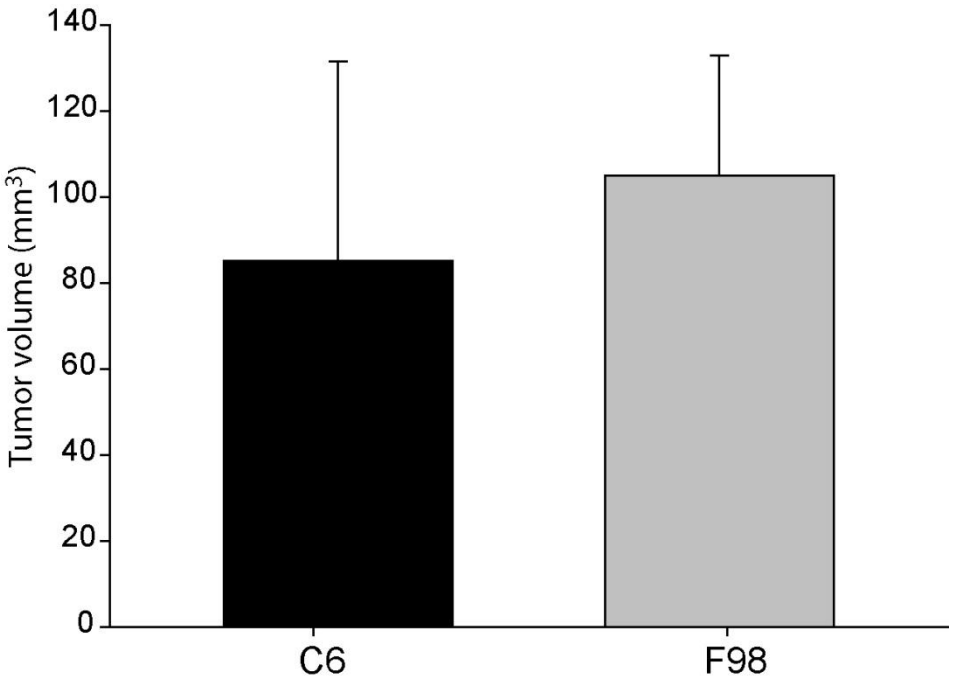
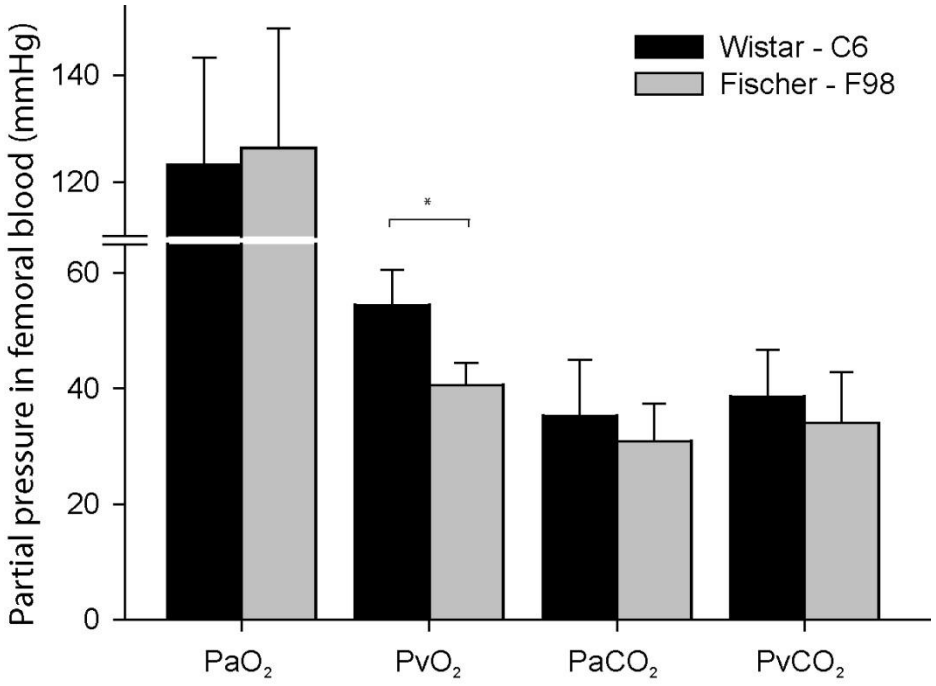






Physiologic controls

Tumor Volume



Systemic oxygenation