

Computer based platform for automated classification of brain tumor types-Glioblastomas, brain Metastases and CNS Lymphomas for co-registered MRI sequences



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Motivation

- **Conventional MR Imaging** (e.g. T1, Flair Imaging) is limited in making distinction between different types of tumors
- **Accurate preoperative diagnosis** is crucial in the different types of cancer treatment
- **Verify** that combination of DTI (FA,MD,CI,Cs,Cp) and Perfusion MRI (rCBV, **CBF, MTT**) can assist in the differentiation of Glioblastomas, brain Metastases and CNS Lymphomas

MRI Sequences

- **T1 with Gadolinium (Gd) Infusion** - responsible for tumoral area enhancement
- **T1 Flair without Gd Infusion** – non-contrast T1 image
- **T2 Flair** - responsible for peritumoral edema area enhancement
- **Diffusion MRI** - describes the microscopic motion of water molecules (diffusion) in biological tissue. Gives details about tissue architecture, either normal or in a diseased state (e.g. acute ischemic stroke, cancer)
- **Perfusion MRI** –measures delivery of blood to a capillary bed in the biological tissue.

Intoduction

Related works

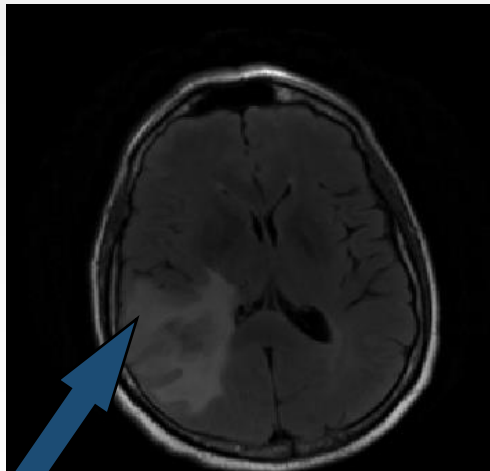
- P.B. Kingsley (2006) reviewed in three-part series the mathematical aspects of Diffusion Tensor MRI and the measurement of the Diffusion Tensor
- L.Østergaard, et al. (1996) reviewed theoretical basis of determination of cerebral blood flow (CBF)
- C. Lorenz (2004) presented a new method described calculates perfusion metrics by defining an arterial input function (AIF)
- S. Wang, S. Kim, et al. (2010) found that a combination of DTI and rCBV can help in the differentiation of Glioblastomas, Brain Metastases, CNS Lymphomas

Classification Brain Tumor

MRI Dataset

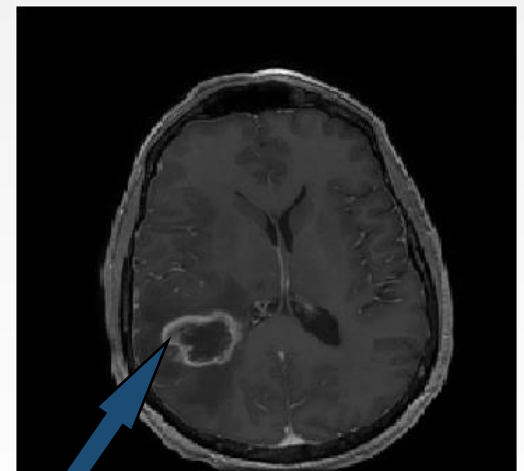
- CNS Lymphomas (10 cases)
- Glioblastomas (21 cases)
- Brain Metastases (5 cases)

T2 Flair



Edema

T1 with Gd Infusion



Tumor

Preprocess MRI data: Diffusion Tensor

•**Definition:** the Diffusion Tensor D is a symmetric positive definite matrix (3x3)

$$D = \underbrace{\begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{pmatrix}}_{\text{estimated from Diffusion MRI}} = \lambda_1 v_1 v_1^t + \lambda_2 v_2 v_2^t + \lambda_3 v_3 v_3^t$$

estimated from Diffusion MRI

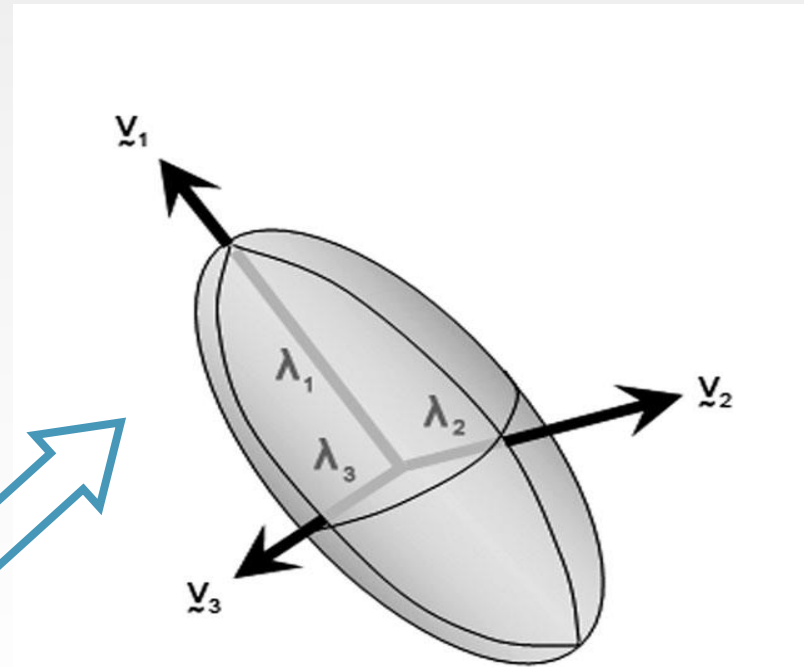
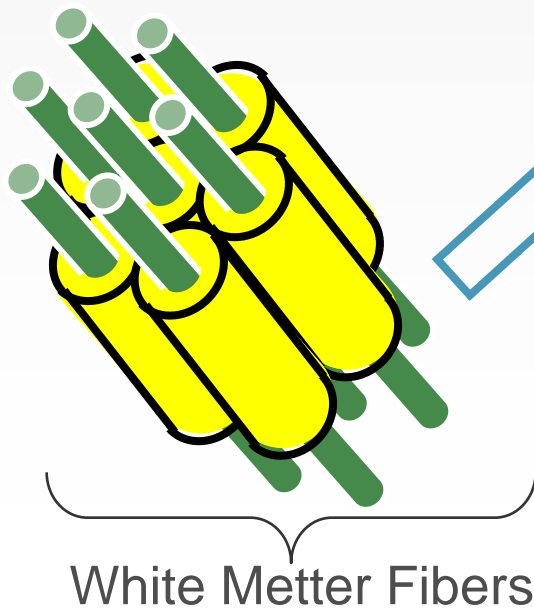
where:

v_i - the orthogonal eigenvectors (3x1), $i=1,2,3$

λ_i - the eigenvalues (diffusivity), $i=1,2,3$

Classification Brain Tumor

Preprocess MRI data: Geometric Shape of Diffusion Tensor



Preprocess MRI data: Diffusion MRI Metrics

- **Mean Diffusivity (MD)** - the average of the diffusion in the different directions

$$\hat{\lambda} = (\lambda_1 + \lambda_2 + \lambda_3) / 3$$

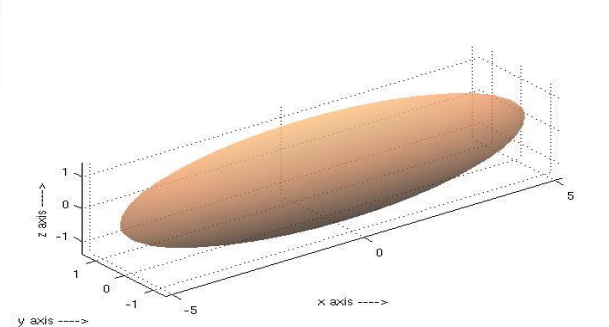
Classification Brain Tumor

Preprocess MRI data: Diffusion MRI Metrics

- **Fractional Anisotropy (FA)** - degree of anisotropy of a diffusion process

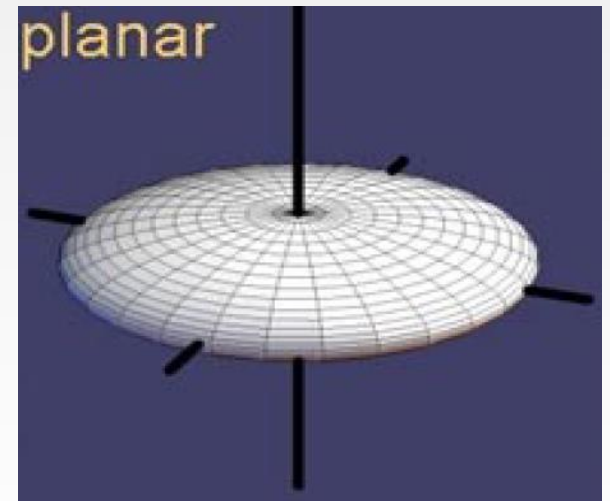
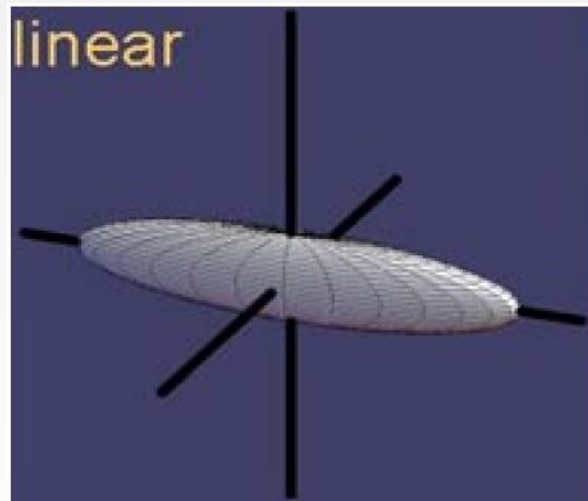
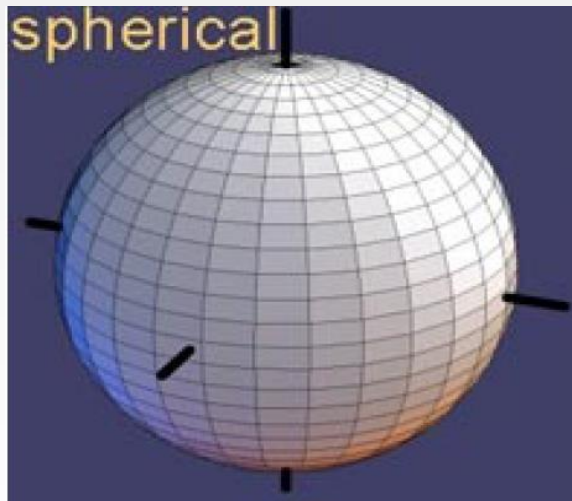
$$FA = \sqrt{\frac{3}{2}} \frac{\sqrt{(\lambda_1 - \hat{\lambda})^2 + (\lambda_2 - \hat{\lambda})^2 + (\lambda_3 - \hat{\lambda})^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$

- **Example** – FA value of 0.9209, DT matrix is diagonal ([27 2 2])



Classification Brain Tumor

Preprocess MRI data: Diffusion MRI Metrics



$$c_s = \frac{3\lambda_3}{\lambda_1 + \lambda_2 + \lambda_3}$$

$$c_l = \frac{\lambda_1 - \lambda_2}{\lambda_1 + \lambda_2 + \lambda_3}$$

$$c_p = \frac{2(\lambda_2 - \lambda_3)}{\lambda_1 + \lambda_2 + \lambda_3}$$

Preprocess MRI data: Kinetic Model for Blood Flow

- The rate of change in concentration in tissue is equal to the rate of tracer entering the tissue minus the rate of tracer leaving the tissue per unit volume

$$\frac{dC_T(t)}{dt} = fC_a(t) - fC_T(t) \Rightarrow \text{First Order Differential Equation}$$

$$C_T(t) = C_a(t) \otimes e^{-ft} f \Rightarrow \text{Discretization}$$

$$C_T(t_j) = \Delta t \sum_{i=0}^j C_a(t_i) e^{-f(t_j-t_i)} f, \quad t_j = t_{j-1} + \Delta t \quad (\text{Eq.1})$$
$$1 \leq t_j \leq N-1$$

where f :Cerebral Blood Flow (CBF) (ml/min/g)

$C_T(t)$:tissue time activity curve

$C_a(t)$:arterial time activity curve

Classification Brain Tumor

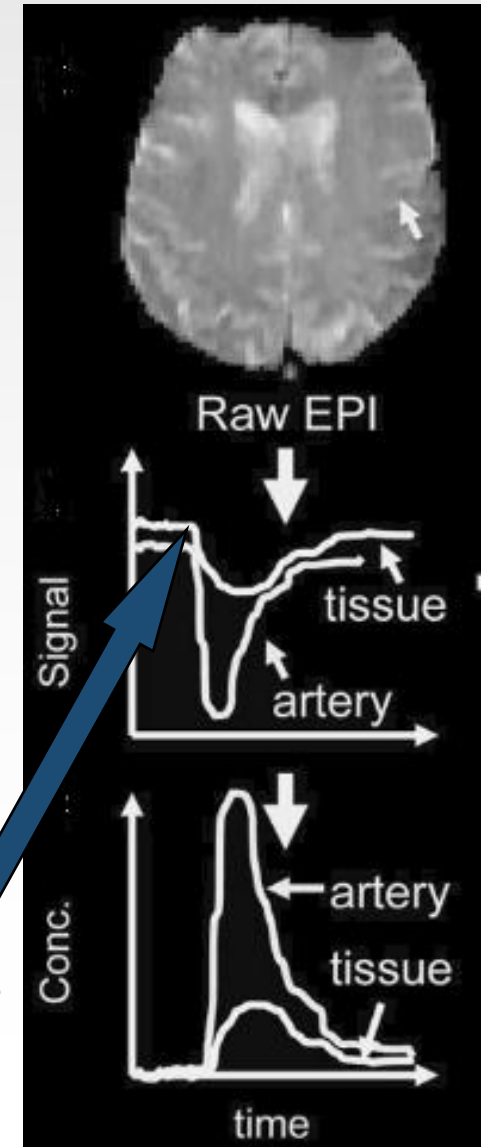
Preprocess MRI data

- Tissue Time Activity Curve

$$C_T(t) \propto \Delta R_2(t) = \frac{1}{TE} \ln\left(\frac{S(t)}{S_0}\right)$$

where TE :echo time
 $S(t)$:pixel intensity at time t
 S_0 :baseline MRI intensity
 $\Delta R_2(t)$:change in T2 relaxation rate

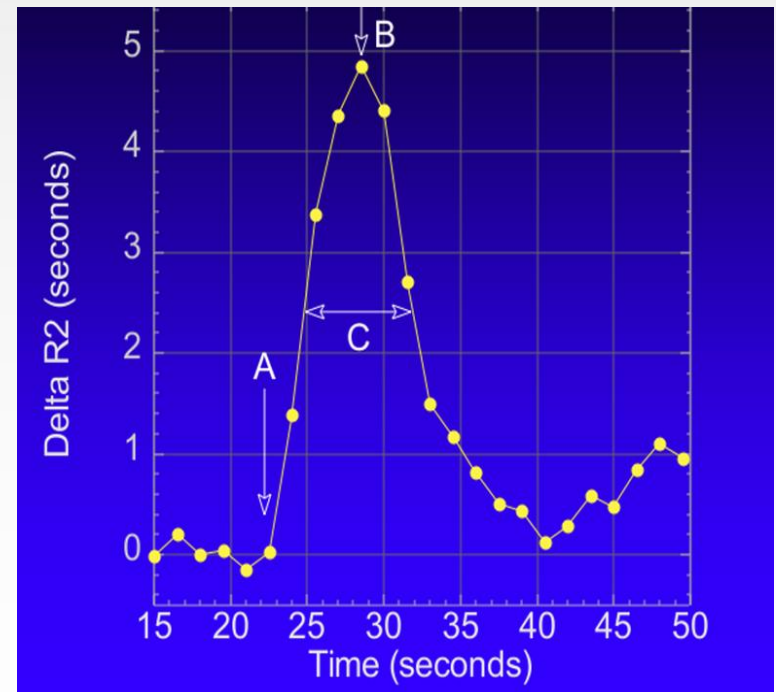
Gd reaches the brain



Classification Brain Tumor

Preprocess MRI data: Arterial Time Activity Curve

- Point **A** is the baseline region of the signal before the contrast arrives and it should be near zero
- Point **B** is the peak concentration value.
- Point **C** is the full width at half maximum value



Estimated from $C_T(t)$ (C.Lorentz)

PresentationPoint

Preprocess MRI data: Perfusion MRI Metrics

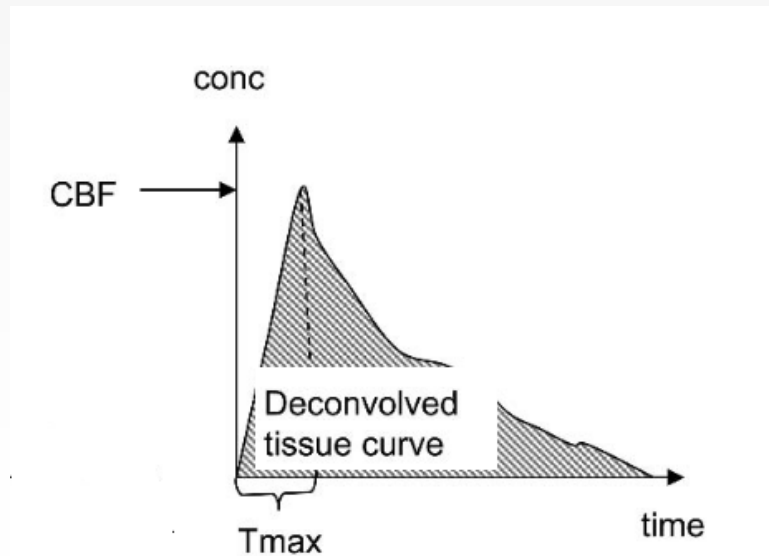
- **Definition:** The Cerebral Blood Volume CBV is the total volume of blood traversing a given region of brain (ml/100 g of brain tissue)
- **Relative CBV Computation**

$$rCBV = \int C_T(t) dt$$

Classification Brain Tumor

Preprocess MRI data: Perfusion MRI Metrics

- Definition:** The Cerebral Blood Flow CBF is the volume of blood traversing a given region of brain per unit time (ml/100 g of brain tissue/min)
- CBF estimation:** deconvolution of [\(Eq.1\)](#) using SVD approach



Preprocess MRI data: Perfusion MRI Metrics

- **Definition:** The Mean Transit Time MTT is the average time (sec) it takes for blood to traverse between arterial inflow and venous outflow

$$MTT = \frac{rCBV}{CBF} \quad (\text{Central Volume Theorem})$$

Preprocess MRI data: Co-Registration

- Algorithm based on Mattes Mutual Information Registration Metric

Algorithm 1 Rigid co-registration of MRI sequences

FixedImage = T1 with gadolinium

for each seq in {T1 Flair, T2 Flair, FA, MD, Cl, Cp, Cs, rCBV, CBF, MTT} **do**

MovingImage = seq

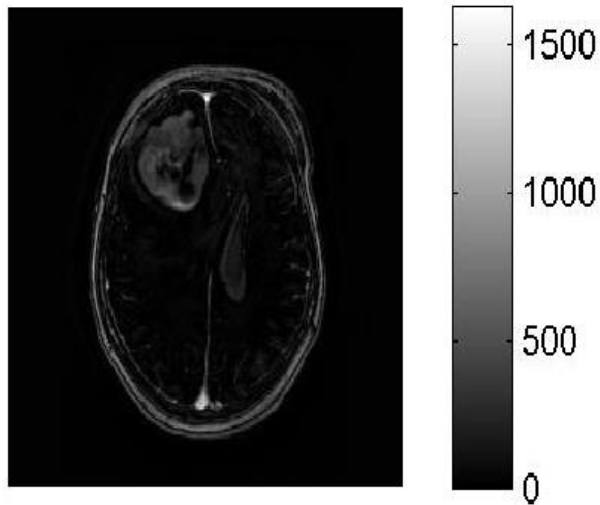
ResampledImage = *RigidRegistration*('MattesMIMetric', *FixedImage*, *MovingImage*)

end for

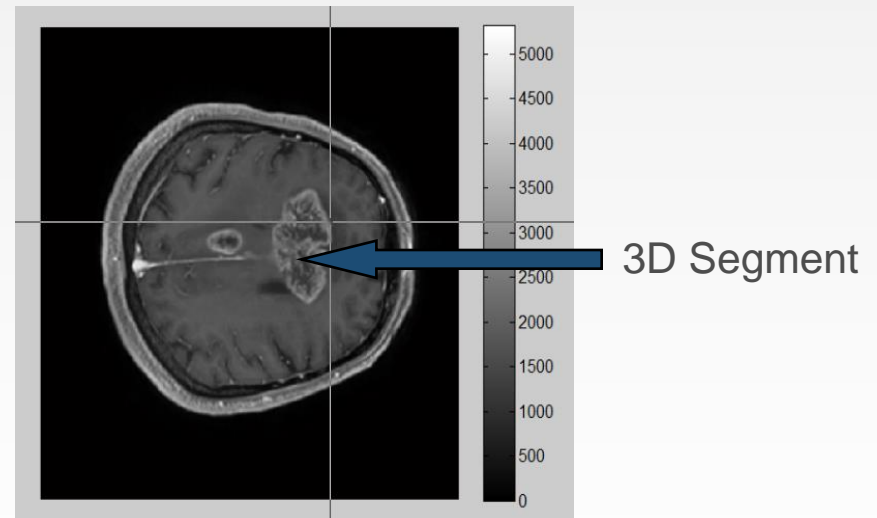
Feature Extraction (slide 1 of 2)

•Tumoral ROI

LMSE difference between T1 and T1Flair

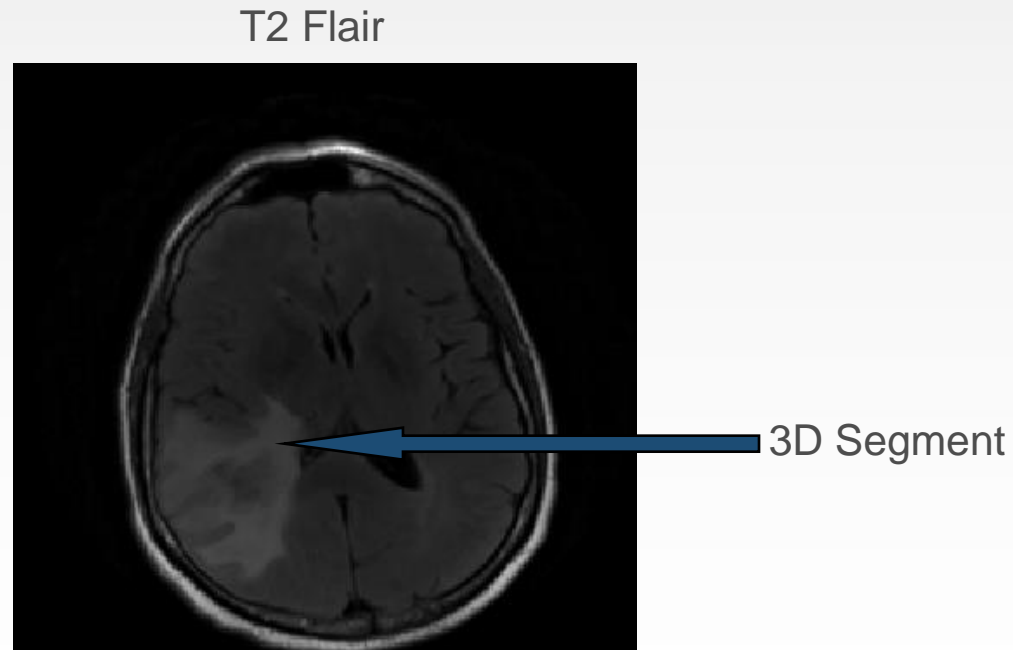


T1 with Gd Infusion



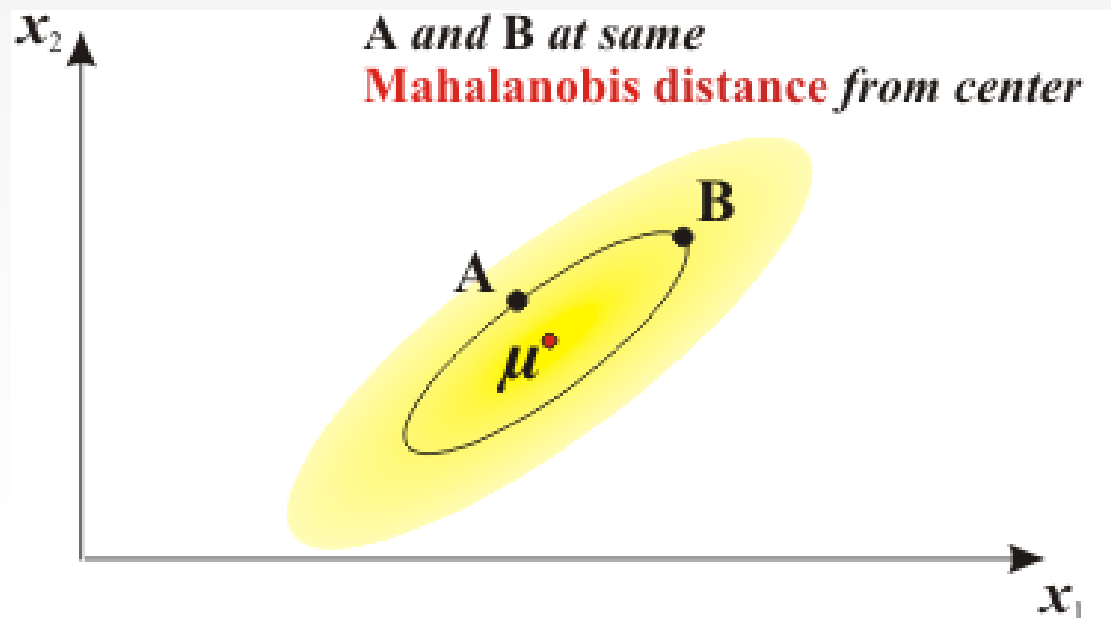
Feature Extraction (slide 2 of 2)

- Peritumoral edema ROI



Mahalanobis distance

- **Definition:** The Mahalanobis distance between two points $x, y \in R^p$ is defined as $d_s(x, y) = \sqrt{(x - y)^t D^{-1} (x - y)}$ where D^{-1} is the inverse of the covariance matrix



Feature Selection (slide 2 of 3)

- The Mahalanobis distance method is used as a feature selection technique to find a set of the most uncorrelated features

Algorithm 2 Features selection using Mahalanobis distance

```
1:  $BRan \leftarrow \{1stClassDS\}$ 
2:  $GRan \leftarrow \{2ndClassDS\}$ 
3:  $n \leftarrow \#features$ 
4:  $IDX \leftarrow \{1, 2, \dots, n\}$ 
5: for  $i = 1 \rightarrow n$  do
6:    $q \leftarrow IDX - \{i\}$ 
7:    $Br \leftarrow BRann(:, q)$ 
8:    $Gr \leftarrow GRann(:, q)$ 
9:    $bdis(i) \leftarrow mean(mahal(Gr, Br));$ 
10: end for
11:  $[bb, ib] \leftarrow sort(bdis, 'ascend')$ 
12: Select first k features manually
13:  $redu \leftarrow \{ib(1 : k)\}$ 
14:  $redu \leftarrow sort(redu, 'ascend')$ 
15:  $BRan_{red} \leftarrow BRan(:, redu)$ 
16:  $GRan_{red} \leftarrow GRan(:, redu)$ 
```

T-statistics

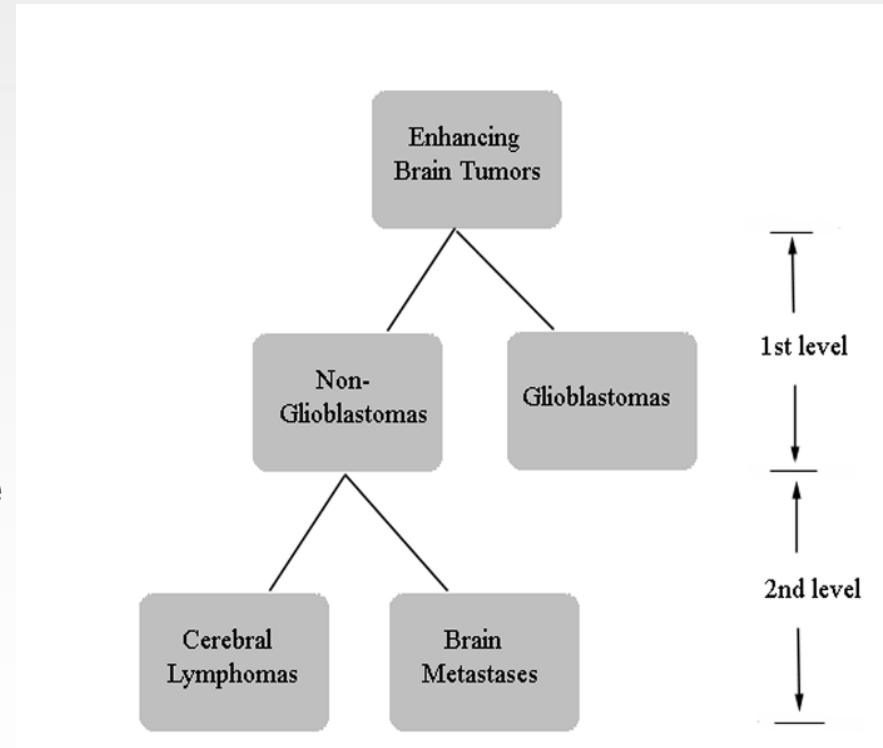
T-test was used to define the discriminative power of DTI/perfusion metrics by applying a cutoff p-values $< \alpha$ where α is the significant level for rejecting the null hypothesis

ROC analysis

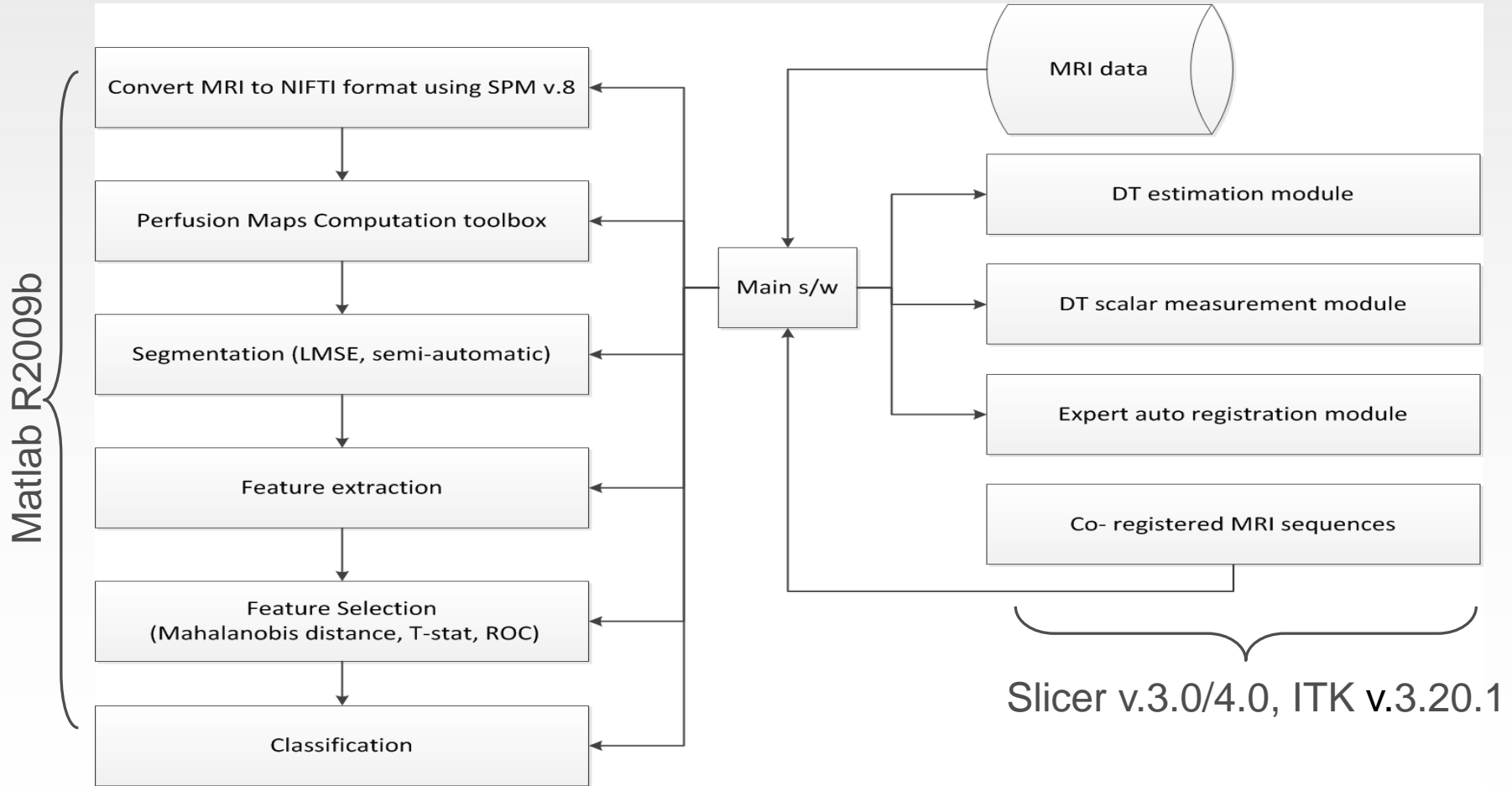
ROC analysis technique was used to possibly select optimal models and to analyze the discriminative power of DTI/perfusion metrics to achieve better classification

Classification

- **Dataset** – $\{x_1, \dots, x_{36}\} \in R^{32}$
- **Model** – Multivariate Logistic Regression Analysis with Cutoff
- **Discrimination** – Two Level Decision Tree
- **Cross-Validation** – Leave-One-Out

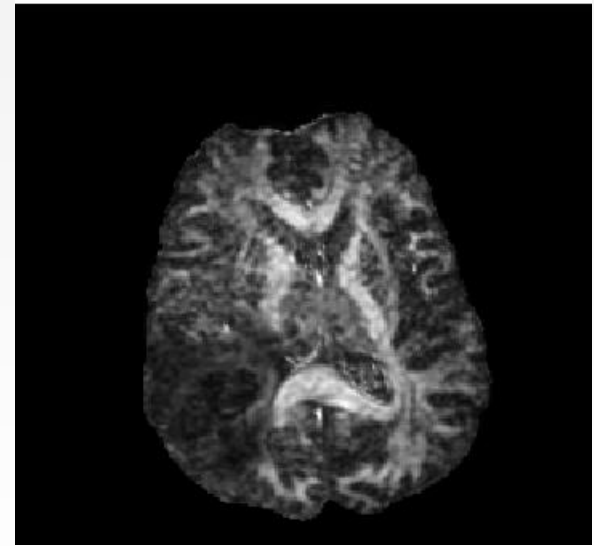
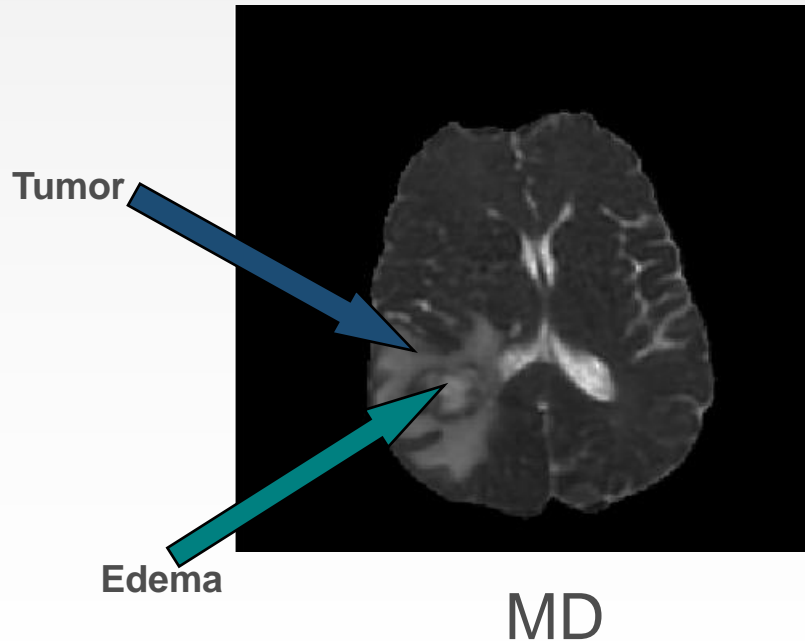


System Architecture



DTI Metrics Computation

- **Example:** patient diagnosed with brain metastasis

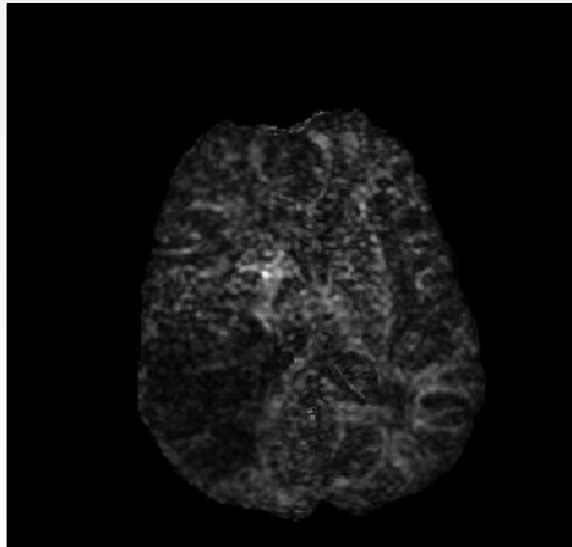


DTI Metrics Computation

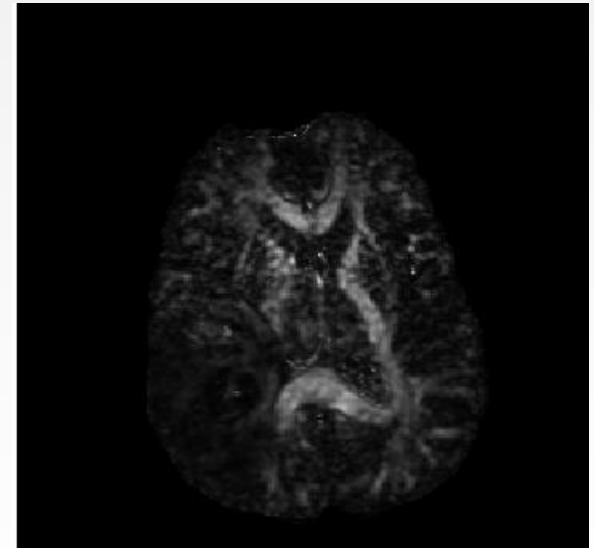
- **Example:** patient diagnosed with brain metastasis



Cs



Cp

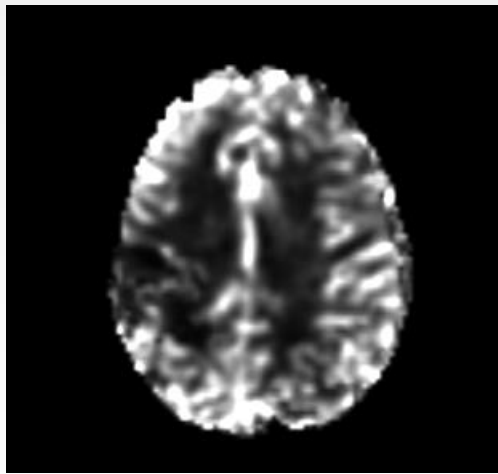


Cl

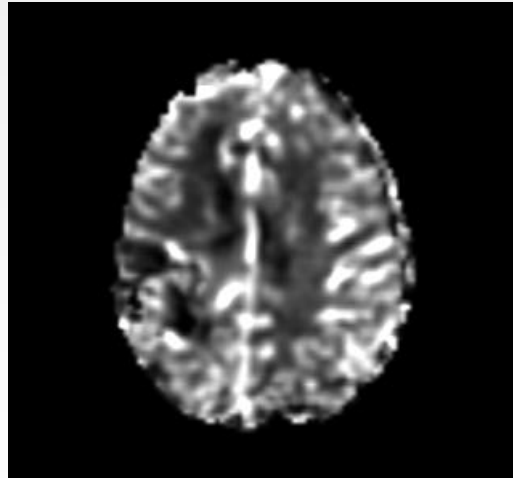
Experimental Results

Perfusion Metrics Computation

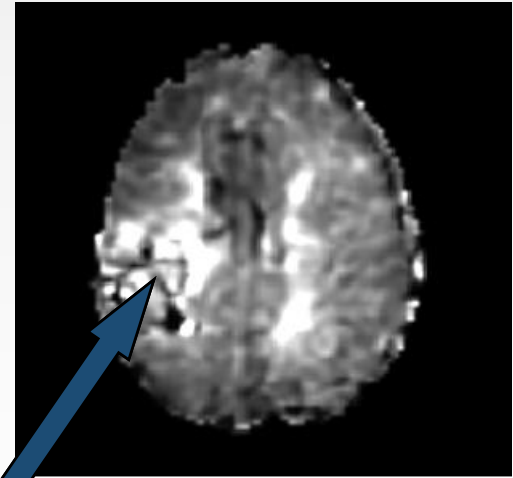
- **Example:** patient diagnosed with brain metastasis



CBF



rCBV

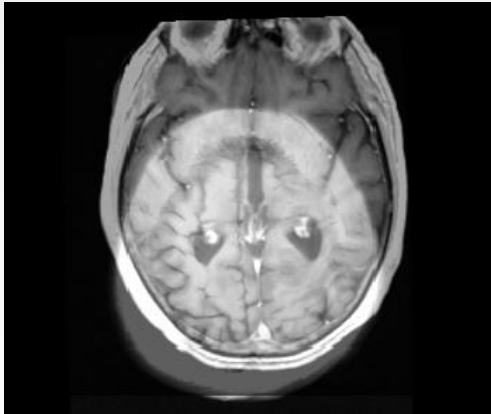


Tumor/Edema MTT

Experimental Results

Co-Registration

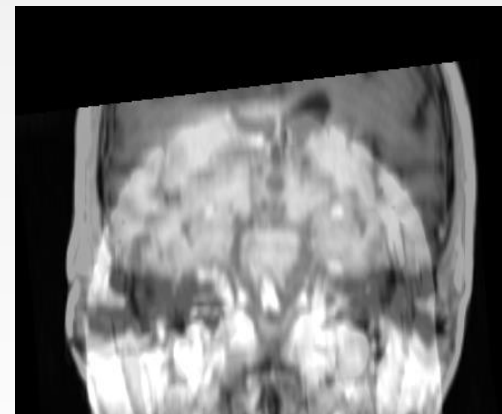
- **Example:** unregistered T1 with Gd Infusion and T1 Flair



Transverse



Coronal

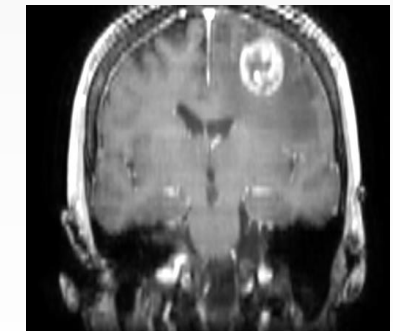
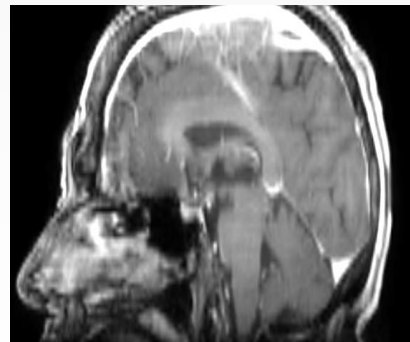
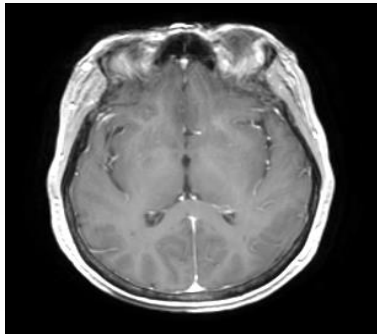
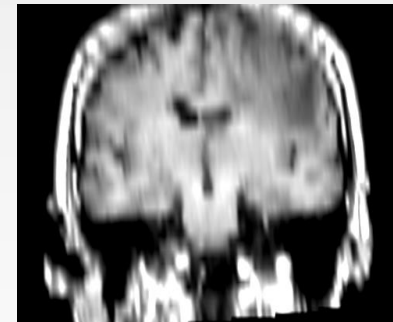
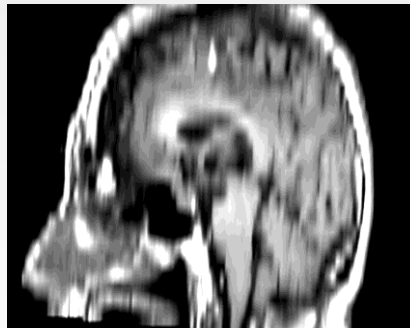
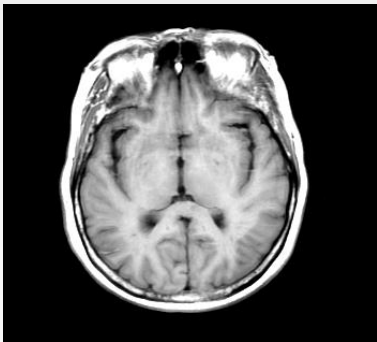


Sagittal

Experimental Results

Co-registration (Mattes Mutual Information Registration Metric)

- **Example:** co-unregistered T1 with Gd Infusion and T1 Flair



Transverse

Coronal

Sagittal

Mahalanobis Distance Feature Selection Algorithm

- **Glioblastomas vs. Non-glioblastomas**
 - accuracy = 78% (LRM leave-one-out)
 - sensitivity = 85.8%
 - specificity = 66.7%
 - cutoff = 0.5
- **The most uncorrelated median parameters**
CI, Cs, MTT in tumoral area and FA in peritumoral edema

T-Statistics (p-value<0.05)

•Glioblastomas vs. Non-glioblastomas

- accuracy = 78% (LRM leave-one-out)
- sensitivity = 95%
- specificity = 46%
- cutoff = 0.57
- MTT ($p<0.025$) in tumoral, FA ($p<0.049$) in peritumoral edema

•Brain Metastases vs. CNS lymphoma

- accuracy = 80% (LRM leave-one-out)
- sensitivity = 90%
- specificity = 60%
- cutoff = 0.54
- Cs ($p<0.0184$) in peritumoral edema

Results Comparison

	Wang S., Kim S., Chawla S., et al.		Our study	
	Glioblastomas vs. Non-glioblastomas	Brain Metastases vs. CNS lymphomas	Glioblastomas vs. Non-glioblastomas	Brain Metastases vs. CNS lymphomas
Accuracy	89.6%	81.6%	78%	80%
Sensitivity	89%	77%	95%	90%
Specificity	93%	94%	46%	60%
Selected Features (tumoral)	ADC Cs rCBV	ADC rCBV(max)	MTT	
Selected Features (peritumoral edema)		FA	FA	Cs
DataSet	26 Glioblastomas 25 brain Metastases 16 CNS lymphomas		21 Glioblastomas 5 brain Metastases 10 CNS lymphomas	

ROC analysis

•Brain metastases vs. Non-metastases

- accuracy = 82% (LRM leave-one-out)
- sensitivity = 70%
- specificity = 85%
- cutoff = 0.78
- CBF max (AUC=0.83) in tumoral area

•Glioblastomas vs. CNS lymphoma

- accuracy = 85% (LRM leave-one-out)
- sensitivity = 90%
- specificity = 60%
- cutoff = 0.62
- CBF, Cs median, rCBV max (AUC=0.98) in tumoral area

Discussion

- **Tensor shape** measurement provides additional information about diffusion characteristics and assisted in tumor classification
- **rCBV** was found to be significant in differentiation of glioblastomas from CNS lymphomas due to tumor neovascularization absence in CNS Lymphomas
- **CBF/MTT**, which has not been previously observed in the brain tumor classification study were found to be significant in differentiating analysis. From the biological point of view CBF measurements have been shown to correlate with tumor grade

Conclusions

- **Combination of DTI and Perfusion Metrics** can assist in the differentiation between three observed tumors types
- **Apparent Diffusion Coefficient (ADC)** may contribute to differentiate between different types of tumors as it shown by Wang S., Kim S., Chawla S., et al.
- **Fully Automated Computer-Based Platform** that consists of co-registered MRI sequences could contribute to the future research done in the MR field

- **Repeat** the experiments with more pathological cases of brain Metastases and CNS Lymphomas added to the observed dataset
- **Apparent Diffusion Coefficient (ADC)** feature to be included
- **Automatic** segmentation of tumoral tissue and peritumoral edema to be done
- **Biological** characteristics (tumor grade, patient age) of three observed tumors types should be studied more thoroughly
- **Unsupervised Learning** to analyze DTI/Perfusion metrics and to find hidden structures between different types of tumors or even tumor grades

Thank you

