Computer-Aided Diagnosis for Prostate Cancer using mp-MRI

PhD Defence
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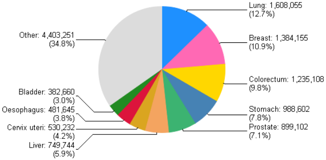
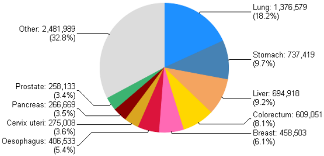
Jordi Freixenet - Paul M. Walker

Statistics



(a) # of cancer cases



(b) # of cancer deaths

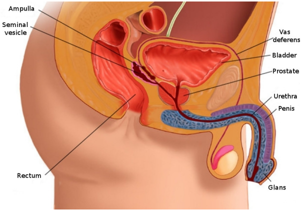
Implications[1]

- 2nd most frequently diagnosed men cancer
- Accounting for 7.1% of overall cancers diagnosed
- Accounting for 3.4% of overall cancers death

[1] J. Ferlay et al. "Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008". In: *Int. J. Cancer* 127.12 (Dec. 2010), pp. 2893–2917.

The prostate organ

Anatomy



Localization of the prostate organ, image source[2]

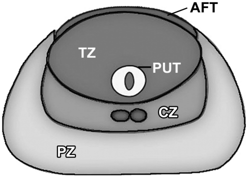
Characteristics

- Height: 3 cm
- Depth: 2.5 cm
- Weight: 7 g to 16 g

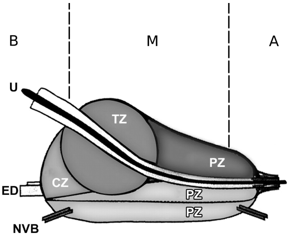
[2] Geckomedia. *Natom Anatomy*. French. June 2011. url: http://www.natomshop.com/.

The prostate organ

Anatomy



(a) Transverse plane

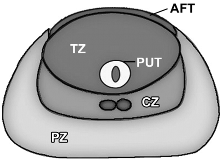


(b) Sagittal plane

Prostate zones - AFT: anterior fibromuscular tissue, CZ: central zone, ED: ejaculatory duct, NVB: neurovascular bundle, PUT: periurethral tissue, PZ: peripheral zone, U: urethra, TZ: transitional zone, B: base, M: median, A: apex; image source[3]

[3] Y. J. Choi et al. "Functional MR imaging of prostate cancer". In: *Radiographics* 27 (2007), pp. 63–75.

Prostate carcinoma (CaP)



CaP development

- Slow-growing $\rightarrow$ 85 %
- Fast-growing $\rightarrow$ 15 %
- CaPs in CG are more aggressive

Zonal predisposition

- PZ $\rightarrow$ 70 % to 80 %
- TZ $\rightarrow$ 10 % to 20 %
- CZ $\rightarrow$ 5 %

What clinicians need?

- Detect CaP
- Distinguish slow- from fast-growing CaP
- Active surveillance *vs.* prostatectomy/other treatments

Screening

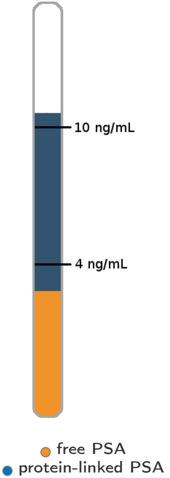
Prostate-specific antigen

- $> 10\,\text{ng}\,\text{mL}^{-1} \rightarrow$ biopsy
- From $4\,\text{ng}\,\text{mL}^{-1}$ to $10\,\text{ng}\,\text{mL}^{-1}$

  $\rightarrow \frac{\bullet}{\bullet + \bullet} > 15\% \rightarrow$ biopsy

"Blind" transrectal ultrasound biopsy

- Take samples from different locations
- Grade using Gleason score



UdG

Screening

UBFC

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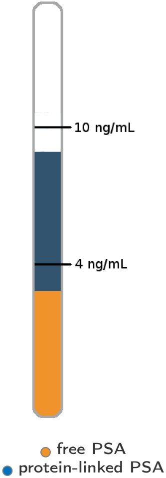

Screening

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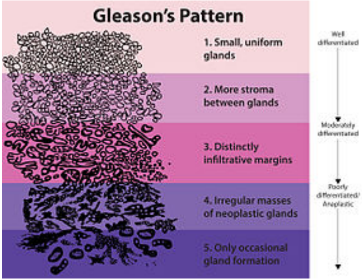


Image source: `https://goo.gl/fEVQXQ`

Screening

Pros

- ✓ Reduce CaP-related mortality between 21 % and 44 %[4]

Cons

- ✗ Up to 30 % of over-diagnosis[5]
- ✗ Up to 35 % of undiagnosed CaP[6]
- ✗ Biopsies are invasive

[4] Fritz H. Schröder et al. "Prostate-cancer mortality at 11 years of follow-up". In: *New England Journal of Medicine* 366.11 (2012), pp. 981–990.

[5] G. P. Haas et al. "Needle biopsies on autopsy prostates: sensitivity of cancer detection based on true prevalence". In: *J. Natl. Cancer Inst.* 99.19 (Oct. 2007), pp. 1484–1489.

[6] A. V. Taira et al. "Performance of transperineal template-guided mapping biopsy in detecting prostate cancer in the initial and repeat biopsy setting". In: *Prostate Cancer Prostatic Dis.* 13.1 (Mar. 2010), pp. 71–77.

UdG

CAD and mp-MRI

UBFC

Current trendy techniques: mp-MRI

✓ Less invasive technique

Human diagnosis using mp-MRI

✗ Need further investigation of the mp-MRI modalities

✗ Low repeatability
- Observer limitations
- Complexity of clinical cases

Emergence of CAD

- CADe $\rightarrow$ detection of potential lesions
- CADx $\rightarrow$ diagnosis regarding those lesions

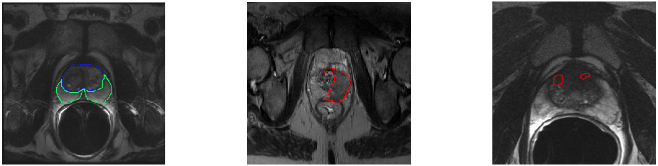
Research objectives

Propose a mp-MRI CAD for CaP

- Study and investigate the state-of-the-art on mp-MRI CAD for CaP
- Identify the scientific barriers
- Design a mp-MRI CAD addressing these issues
- Investigate and analyze the proposed CAD

MRI modalities

T_2W-MRI



(a) Healthy (b) CaP PZ (c) CaP CG

Healthy

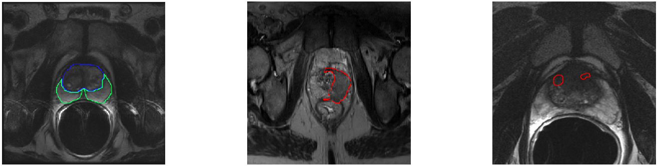
- Intermediate to high-signal intensity (SI) in PZ
- Low-SI in CG

CaP

- Low-SI
- Round and ill-defined mass in PZ
- Homogeneous with ill-defined edges in CG

MRI modalities

T_2W-MRI



(a) Healthy (b) CaP PZ (c) CaP CG

Pros

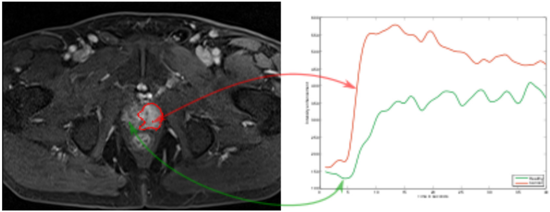
- Highest spatial resolution
- Anatomy nicely depicted

Cons

- Low sensitivity in CG
- Lower specificity due to outliers

MRI modalities

DCE-MRI



Green: healthy - Red: CaP

Healthy

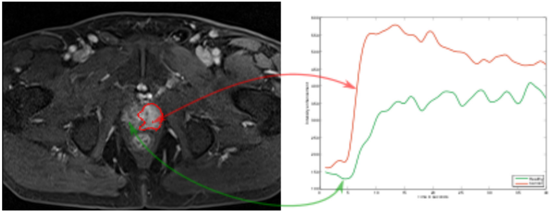
- Slower wash-in, wash-out, time-to-peak enhancement
- Lower integral under the curve, max SI

CaP

- Faster wash-in, wash-out, time-to-peak enhancement
- Higher integral under the curve, max SI

MRI modalities

DCE-MRI



Green: healthy - Red: CaP

Pros

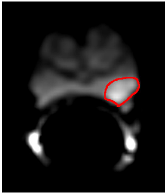
- Information about vascularity

Cons

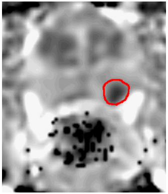
- Spatial mis-registration
- Lower spatial resolution than T_2W-MRI
- Difficult detection in CG

MRI modalities

DW-MRI - ADC



(a) DW MRI



(b) ADC

Healthy

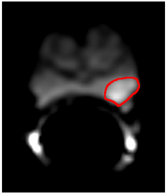
- DW-MRI: lower SI
- ADC: higher-SI

CaP

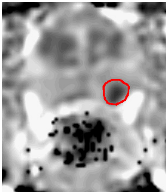
- DW-MRI: higher SI
- ADC: lower-SI

MRI modalities

DW-MRI - ADC



(a) DW MRI



(b) ADC

Pros

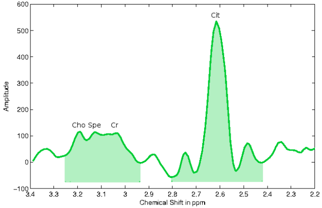
- Information about tissue structure
- ADC correlated with Gleason score

Cons

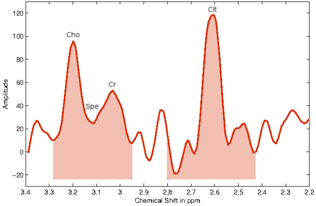
- Poor spatial resolution
- Variability of the ADC coefficient

MRI modalities

MRSI



(a) Healthy



(b) CaP

Healthy

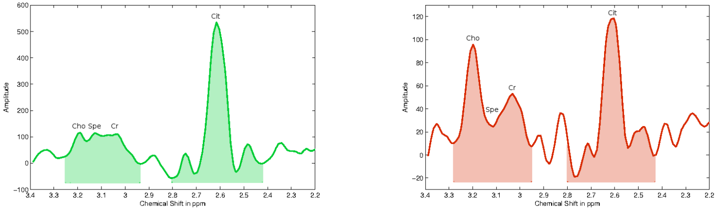
- High citrate concentration
- Moderate choline and spermine concentrations

CaP

- Decrease of citrate and spermine concentrations
- Increase of choline concentration

MRI modalities

MRSI



(a) Healthy

(b) CaP

Pros

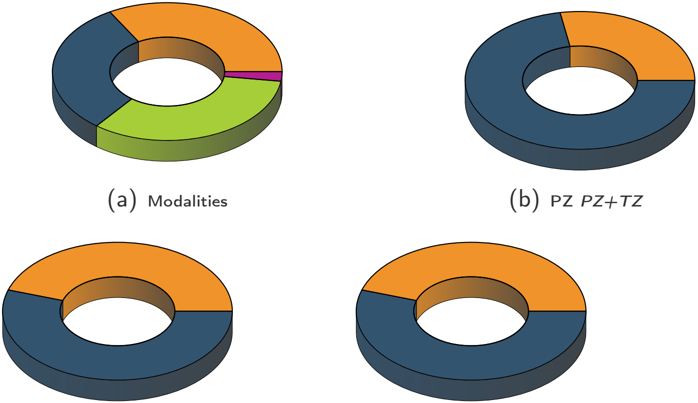
- Citrate correlated with Gleason score

Cons

- Low spatial resolution
- Variation inter-patients

CAD for CaP

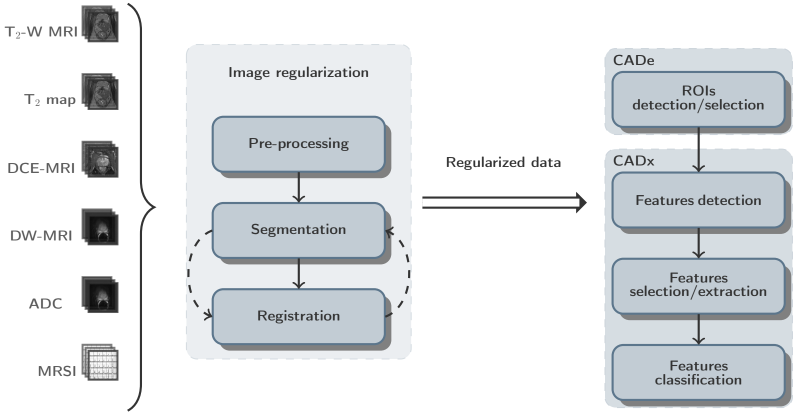
block



(a) Modalities (b) PZ *PZ+TZ* (c) 1.5 T *vs.* 3 T (d) CADe

CAD for CaP

Full CAD for detection and diagnosis of CaP

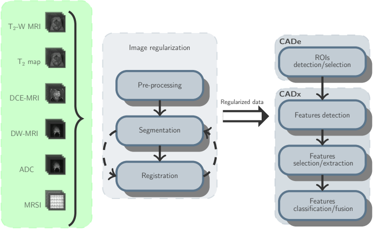


Common CAD framework based on MRI images used to detect CaP

CAD for CaP

Conclusions

- ✓ 3 modalities better than 2
- ✓ Texture and edge features are predominant
- ✓ Features selection/extraction tends to improve performance
- ✓ Pre-eminence of SVM and ensemble classifier (i.e., AdaBoost, RF, etc.)



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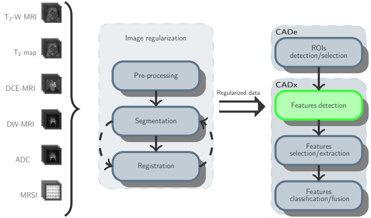

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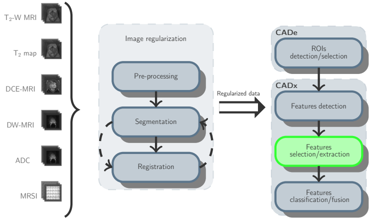

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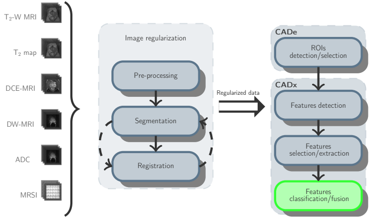

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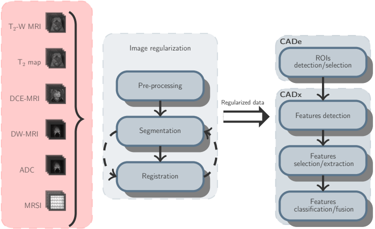
Scientific and technical challenges

- ✗ No publicly available mp-MRI dataset
- ✗ Only 1 study used 4 MRI modalities
- ✗ Limited work on data normalization
- ✗ A lot of features are extracted in 2D
- ✗ Limited work regarding selection/extraction
- ✗ No work regarding data balancing
- ✗ No source code available of any CAD

CAD for CaP



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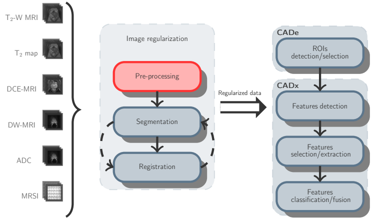

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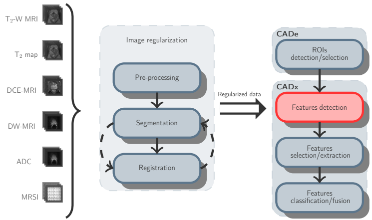

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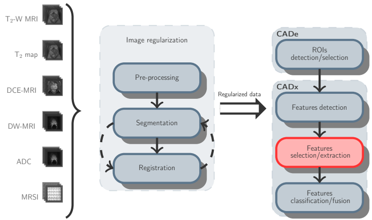

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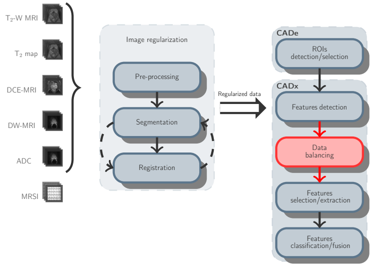

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CAD for CaP

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Research objectives

- Collect a mp-MRI dataset
- Design a CAD for CaP using all mp-MRI modalities
- Investigate normalization, feature selection/extraction, data balancing
- Implement 3D features
- Release source code and dataset

UdG

Mp-MRI prostate datasets

UBFC

1.5 T General Electric scanner

- T_2W-MRI, DW-MRI, DCE-MRI, and MRSI
- Ground-truth (GT) for CaP, PZ, and CG associated to T_2W-MRI modality
- Healthy: 4 *vs.* CaP: { PZ: $14 + 3$, CG: $0 + 3$ }

3 T Siemens scanner

- T_2W-MRI, ADC, DCE-MRI, and MRSI
- GT for CaP, PZ, and CG associated to T_2W-MRI modality
- Additional GT of the prostate for DCE-MRI and ADC
- Healthy: 2 *vs.* CaP: { PZ: $12 + 2$, CG: $3 + 2$ }

UdG

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UBFC

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Open source initiative

protoclass toolbox

- Data management
- Features detection

imbalanced-learn toolbox[7]

- Part of the `scikit-learn-contrib` projects

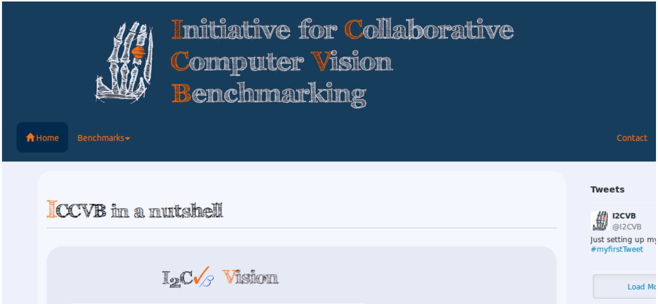
Third-party toolboxes

NumPy, SciPy, matplotlib, IPython Interactive Computing, SimpleITK, scikit-image image processing in python, scikit learn

[7] Guillaume Lemaitre et al. "Imbalanced-learn: A Python Toolbox to Tackle the Curse of Imbalanced Datasets in Machine Learning". In: *Journal of Machine Learning Research* (2017).

A web platform

I$_2$C$\sqrt{B}$ platform



Hub for our different resources

- GitHub for our source codes
- Zenodo for our datasets
- HAL, arXiv, ResearchGate for our publications

Toward a mp-MRI CAD for CaP

Mp-MRI CAD for CaP

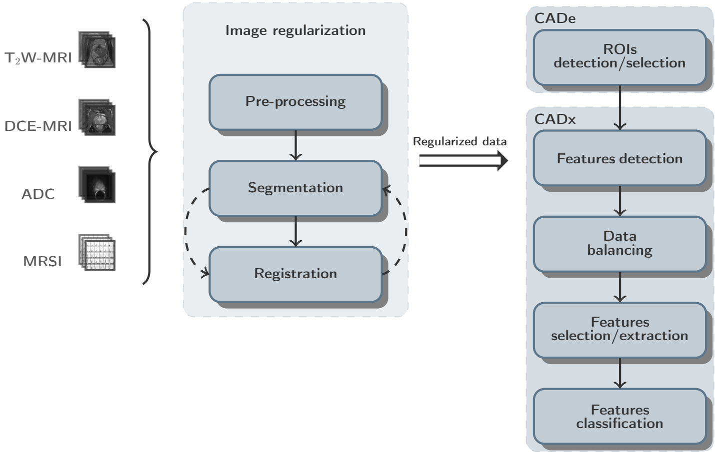
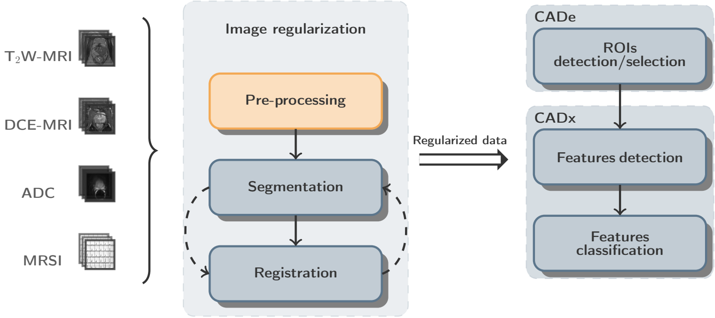


Image regularization

Pre-processing



Pre-processing

T_2W-MRI normalization

- Rician normalization[8]

DCE-MRI normalization

- Graph and deviation based normalization[9]

ADC normalization

- Piecewise-linear normalization

MRSI normalization

- Phase correction[10]
- Frequency alignment
- Baseline correction[11]

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[9] Guillaume Lemaitre et al. "Automatic prostate cancer detection through DCE-MRI images: all you need is a good normalization". In: *Medical Image Analysis - Submitted* (2017).

[10] Guillaume Lemaitre et al. "Normalization of T2W-MRI Prostate Images using Rician a priori". In: *SPIE Medical Imaging*. International Society for Optics and Photonics. 2016, pp. 978529–978529.

[11] Li Chen et al. "An efficient algorithm for automatic phase correction of {NMR} spectra based on entropy minimization ". In: *Journal of Magnetic Resonance* 158.1–2 (2002), pp. 164–168.

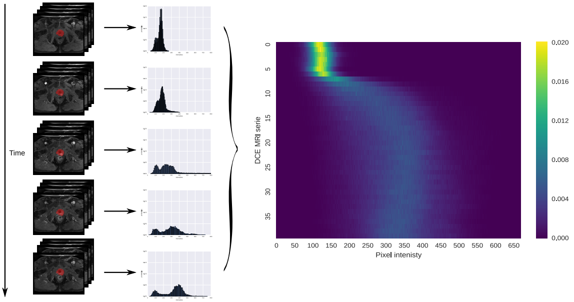
[12] Yuanxin Xi and David M Rocke. "Baseline correction for NMR spectroscopic metabolomics data analysis". In: *BMC bioinformatics* 9.1 (2008), p. 1.

DCE-MRI normalization

Contribution[13]

- Propose a method to normalize DCE-MRI data

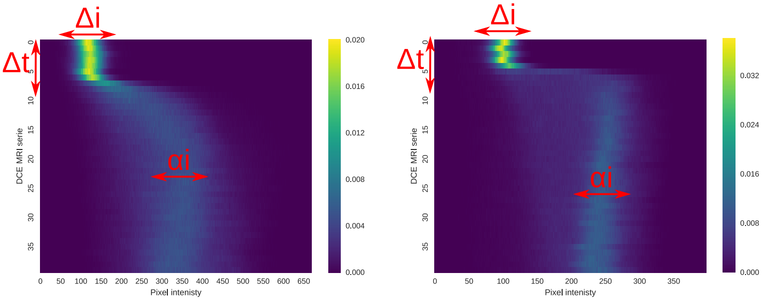
Heatmap representation



[13] Lemaitre et al., "Automatic prostate cancer detection through DCE-MRI images: all you need is a good normalization".

DCE-MRI normalization

Inter-patients variations



(a) Patient #1 (b) Patient #2

Variations driven by Δ_i, Δ_t, and α_i

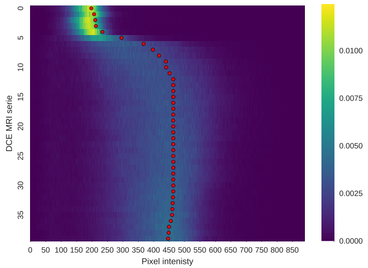
DCE-MRI normalization

Correction of Δ_i

- Estimate with smooth transitions
- Estimate the closest of the PDF peak

→ Find the shortest path in a directed weighted graph, with the edge weight w_{ij}:

$$w_{ij} = \begin{cases} \alpha \exp(1 - \frac{H(i)}{\max(H)}) & \text{if } x_j = x_i + 1 \text{ and } y_j = y_i, \\ (1-\alpha) \exp(1 - \frac{H(i)}{\max(H)}) & \text{if } x_j = x_i \text{ and } y_j = y_i + 1, \\ 0 & \text{otherwise}, \end{cases} \quad (1)$$



DCE-MRI normalization

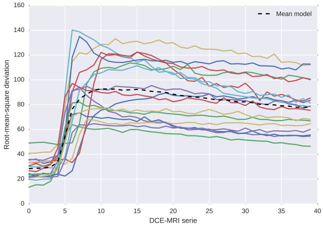
Correction of Δ_t and α_i

Register all RMSD to a mean model such that:

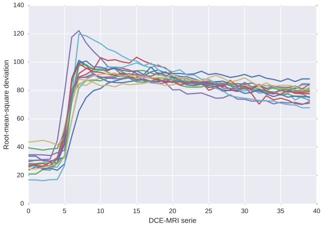
$$\underset{\alpha,\tau}{\arg\min} = \sum_{t=1}^{N} \left[T\left(\alpha, \tau, f(t)\right) - \mu(t) \right]^2 , \quad (2)$$

$$f(t) = \sqrt{\left(\frac{\sum_{n=1}^{N} x(t)_n^2}{N} \right)}, \quad (3)$$

$$T(\alpha, \tau, f(t)) = \alpha f(t - \tau). \quad (4)$$



(a) RMSD before correction



(b) Registered RMSD

DCE-MRI normalization

Evaluation through pharmacokinetic models

- Brix's model
- Hoffmann's model
- Tofts' model
- PUN model

Other approaches

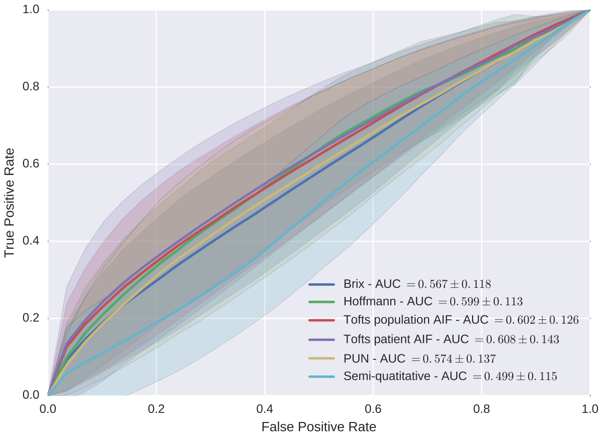
- Semi-quantitative model
- Entire enhanced signal

Classification

- Classification with random forest (RF)
- Leave-one-patient-out cross-validation (LOPO)
- Receiver operating characteristic (ROC) analysis
- Area under the ROC curve (AUC)

DCE-MRI normalization

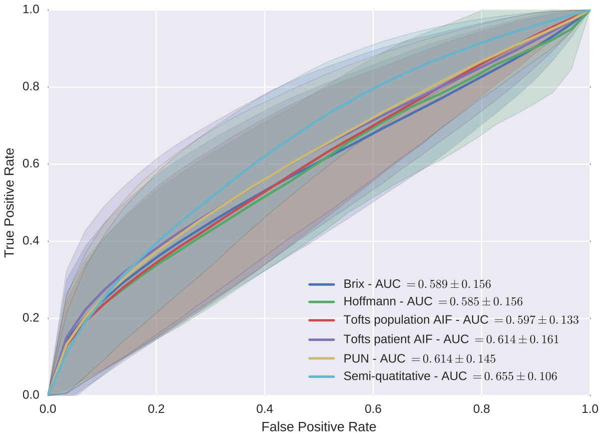
Quantitative and semi-quantitative models



ROC analysis without normalization

DCE-MRI normalization

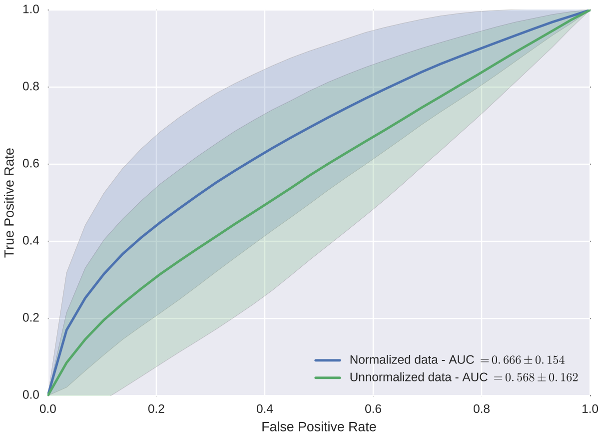
Quantitative and semi-quantitative models



ROC analysis with normalization

DCE-MRI normalization

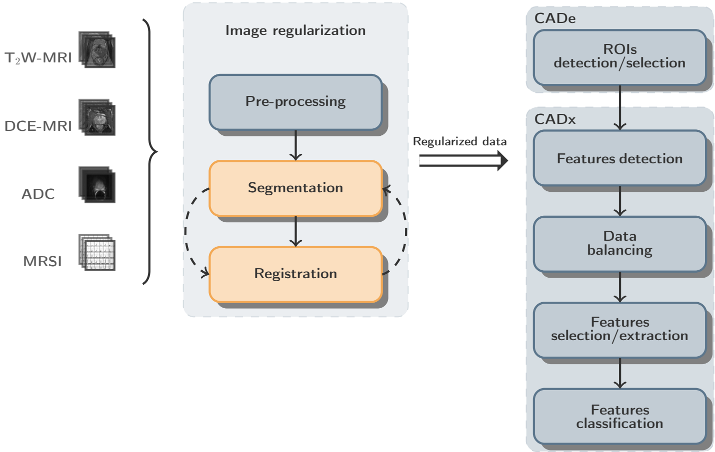
Entire signal



ROC analysis with entire enhanced signal

Image regularization

Segmentation & registration



Segmentation & registration

Resampling

- ADC and DCE-MRI are resampled to the T_2W-MRI resolution

Segmentation

- Manual prostate segmentation available for T_2W-MRI, DCE-MRI, and ADC
- CaP, PZ, and CG manual segmentation available for T_2W-MRI

Registration

- Intra-patient motions correction in DCE-MRI: rigid registration using mutual information
- DCE-MRI is registered to T_2W-MRI using the prostate segmentation
- ADC is registered to T_2W-MRI using the prostate segmentation

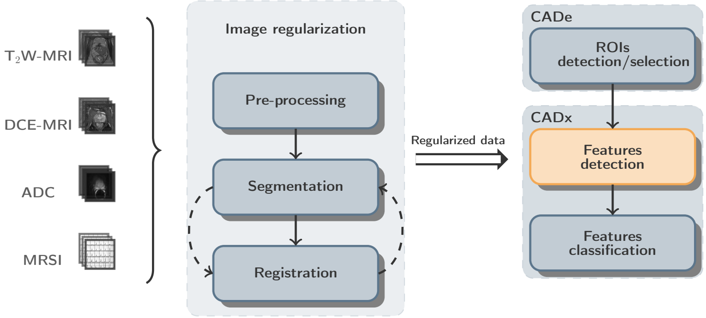
CADe-CADx

Summary of experiments

- Investigate the performance of features from each standalone modality
- Investigate the performance of the combination of features: *coarse combination*
- Investigate the effect of data balancing
- Investigate the effect of selection/extraction
- Investigate the performance of the combination of features: *fine-tuned combination*

CADe-CADx

Features detection



Feature detection

T_2W-MRI and ADC features

- Intensity
- Kirsch filter
- Laplacian filter*
- Prewitt filter*
- Scharr filter*
- Sobel filter*
- DCT decomposition*
- Gabor filters*
- Phase congruency filter
- Haralick filter*
- LBP filter*

DCE-MRI features

- Brix's model
- Hoffmann's model
- Tofts' model
- PUN model
- Semi-quantitative model
- Entire enhanced signal

MRSI features

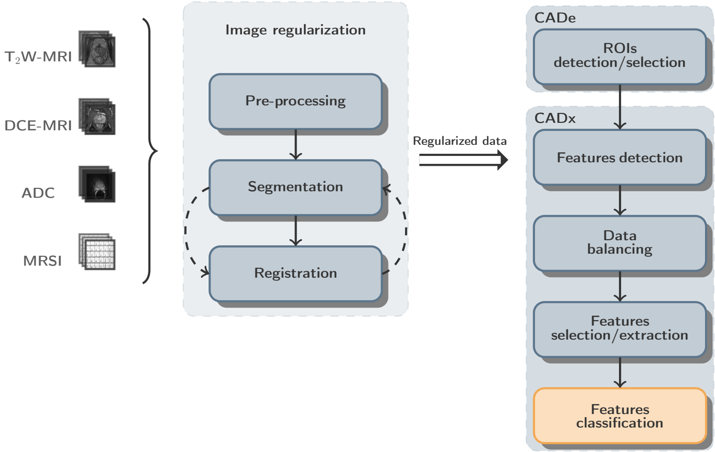
- Quantification with fixed bounds
- Quantification by fitting some modeled signal
- Entire spectra

Spatial information

- Relative distance
- Relative position
- Prostate zone

CADe-CADx

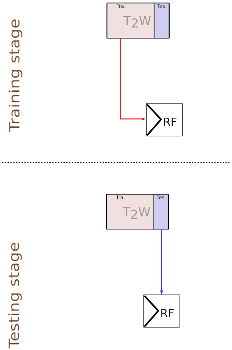
Features classification



Features classification

Classification as fusion

- Single RF → features of one modality
- Single RF → aggregated features of modalities
- Stack of RF with an adaboost and gradient-boosting meta-classifier



Validation

- LOPO CV
- ROC analysis
- AUC

Features classification

Classification as fusion

- Single RF → features of one modality
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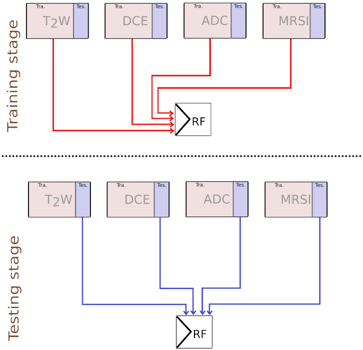
- Stack of RF with an adaboost and gradient-boosting meta-classifier



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Features classification

Classification as fusion

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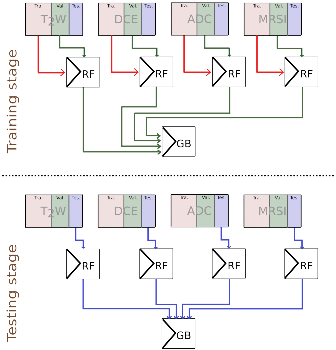
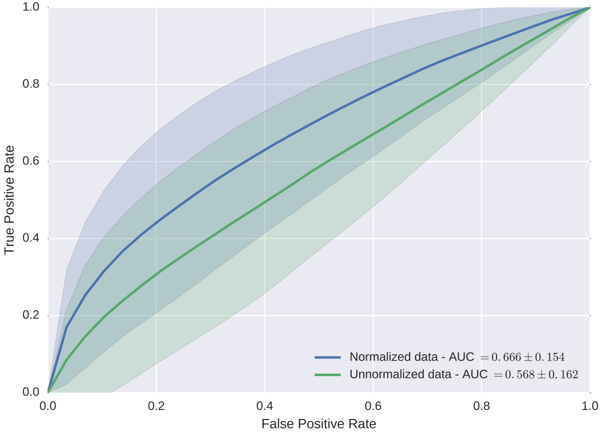


Validation

- LOPO CV
- ROC analysis
- AUC

DCE modality

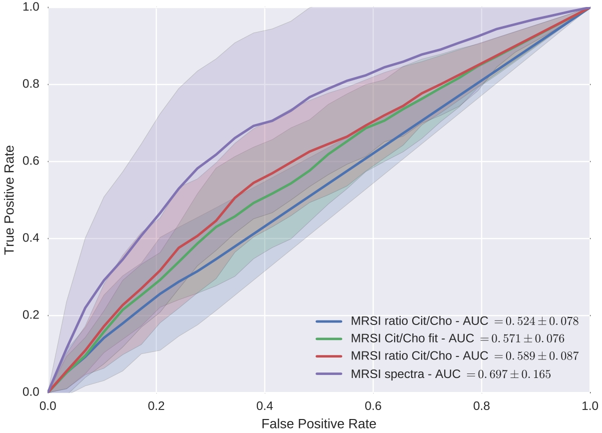
Entire signal



ROC analysis for the entire enhanced signal

MRSI modalities

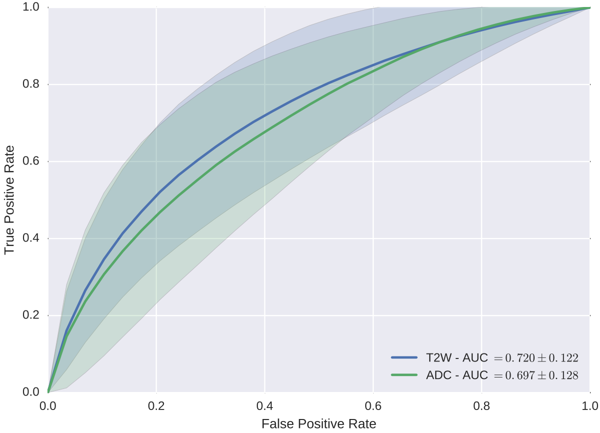
ROC analysis



ROC analysis for the MRSI modality

T_2W-MRI, ADC, and MRSI modalities

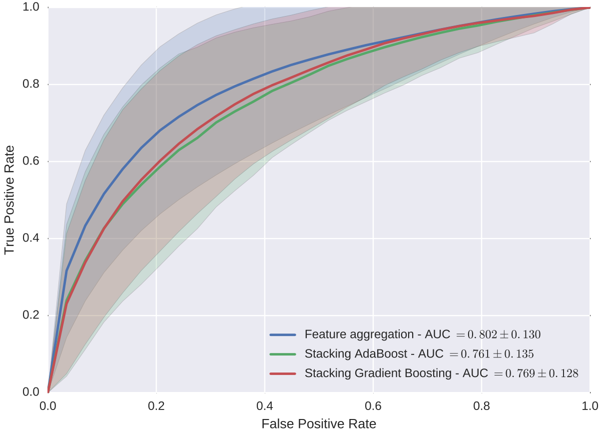
ROC analysis



ROC analysis for T_2W-MRI and ADC modalities

Coarse combination

Aggregation *vs.* stacking



ROC analysis for the fusion strategies

T_2W-MRI, ADC, and MRSI modalities

Overall best performance

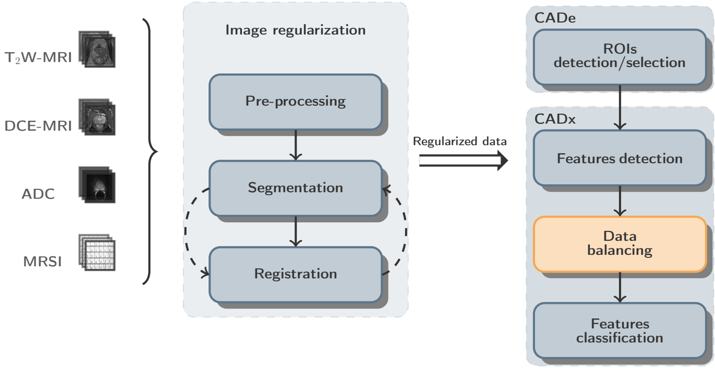
AUC	T_2W-MRI	DCE-MRI	ADC	MRSI	Aggregation
Mean	0.720	0.666	0.697	0.697	0.802
Std	0.122	0.154	0.128	0.165	0.130

Conclusions

- DCE-MRI: normalized data $\rightarrow$ best performance
- DCE-MRI: entire signal better than models
- MRSI: fitting better than bounds approach
- MRSI: entire spectra better than others
- T_2W-MRI $>$ ADC $=$ MRSI $>$ DCE
- Performance at an "acceptable" level of discrimination - AUC $\in [0.7, 0.8]$
- Aggregation better than stacking

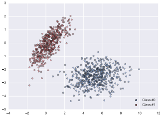
CADe-CADx

Data balancing

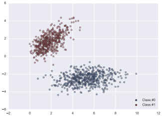


Data balancing

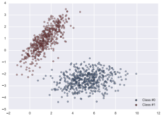
Under-sampling



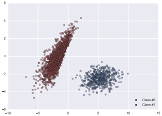
(a) NM1



(b) NM2

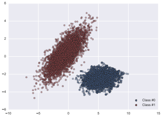


(c) NM3

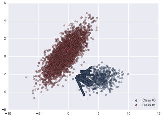


(d) IHT

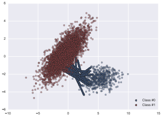
Over-sampling



(e) SMOTE



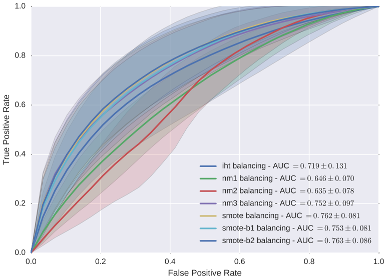
(f) SMOTE-b1



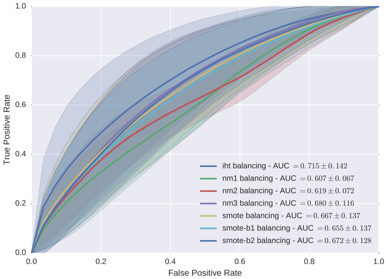
(g) SMOTE-b2

Data balancing

T_2W-MRI and ADC



(a) T_2W-MRI

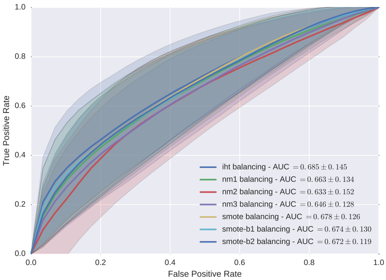


(b) ADC

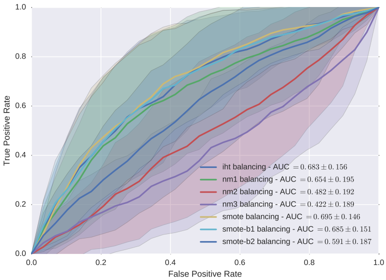
ROC analysis for T_2W-MRI and ADC

Data balancing

DCE-MRI and MRSI



(a) DCE-MRI

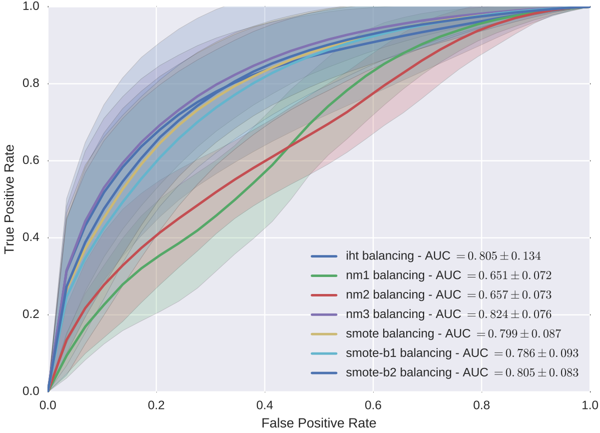


(b) MRSI

ROC analysis for DCE-MRI and MRSI modalities

Data balancing

Aggregation



ROC analysis while aggregating the features

Data balancing

Conclusions

- ✓ IHT → ADC and DCE-MRI
- ✓ SMOTE → T_2W-MRI and MRSI
- ✓ NM3 → aggregate feature

Before data balancing

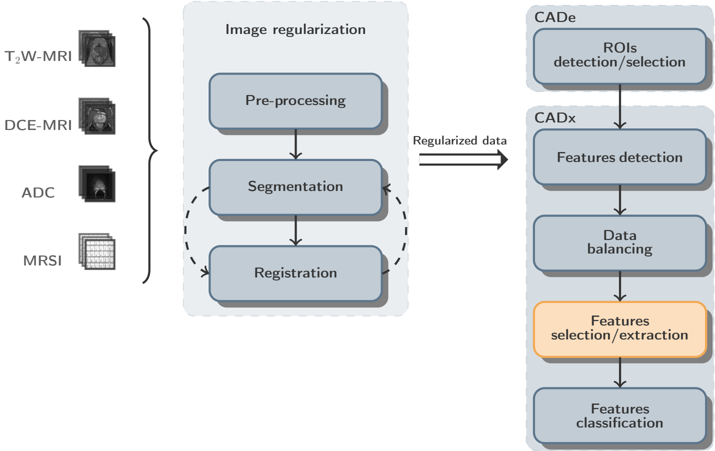
AUC	T_2W-MRI	DCE-MRI	ADC	MRSI	Aggregation
Mean	0.720	0.666	0.697	0.697	0.802
Std	0.122	0.154	0.128	0.165	0.130

After data balancing

AUC	T_2W-MRI	DCE-MRI	ADC	MRSI	Aggregation
Mean	0.762	0.685	0.715	0.695	0.824
Std	0.081	0.145	0.142	0.156	0.076
Tendency	✓	✓	✓	=	✓

CADe-CADx

Features selection/extraction



UdG

Features selection/extraction

UBFC

Features extraction

- Independent components analysis (ICA)
- Principal components analysis (PCA)
- Sparse-PCA

Features selection

- One-way analysis of variance (ANOVA)
- Gini importance

Conclusions

✓ T_2W-MRI: ANOVA-based selection with 25 % of features

✓ ADC: Gini importance-based selection with 5 % of features

✓ DCE-MRI: ICA with 24 components

✓ MRSI: ICA with 36 components

✓ Aggregation: Gini importance with 17.5 % of features

UdG

Data balancing

UBFC

Before features selection/extraction

AUC	T_2W-MRI	DCE-MRI	ADC	MRSI	Aggregation
Mean	0.762	0.685	0.715	0.685	0.824
Std	0.081	0.145	0.142	0.156	0.076

After features selection/extraction

AUC	T_2W-MRI	DCE-MRI	ADC	MRSI	Aggregation
Mean	0.784	0.691	0.743	0.677	0.836
Std	0.067	0.158	0.139	0.171	0.083
Tendency	✓	✓	✓	✗	✓

Features selection

Selected features in T_2W-MRI and ADC

T_2W-MRI	ADC
8/12 edges 155/256 Gabor filters 2/169 Haralick features 1/1 intensity 4/6 LBP 2/3 phase congruency	1/243 DCT 32/256 Gabor filters 1/3 phase congruency
172 features	34 features

Selected features with aggregation

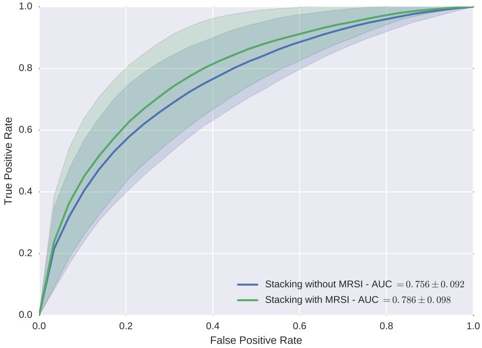
T_2W-MRI	ADC	DCE-MRI	MRSI
113/256 Gabor filters 1/3 phase congruency 4/12 edges 1/1 intensity	53/256 Gabor filters 2/3 phase congruency	14/40 samples	78/101 samples
267 features			

MRSI benefit

Importance of MRSI in aggregation

- Features from MRSI are the most selected features

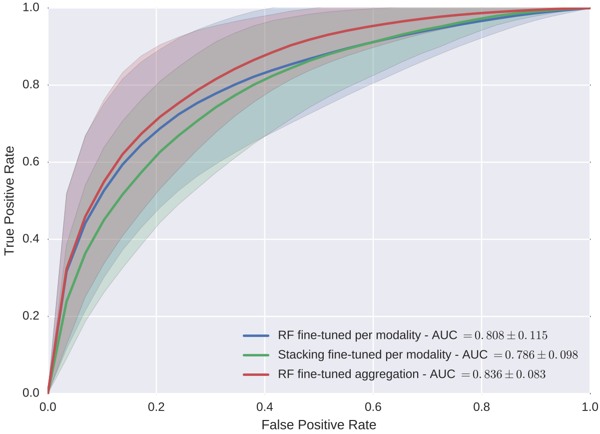
Stacking with/without MRSI



ROC analysis with/without MRSI

Fine-tuned combination

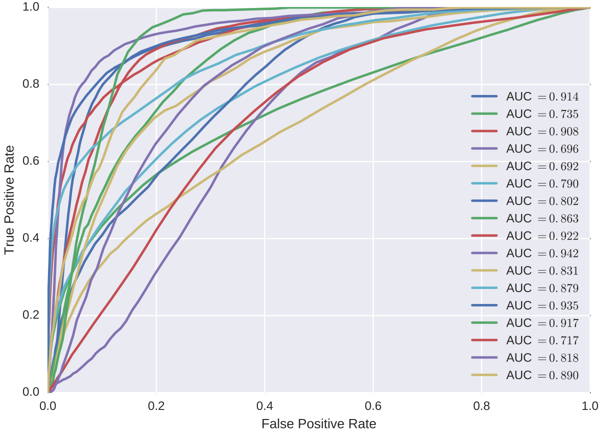
Aggregation *vs.* stacking



ROC analysis with the different fusion strategies

Fine-tuned combination

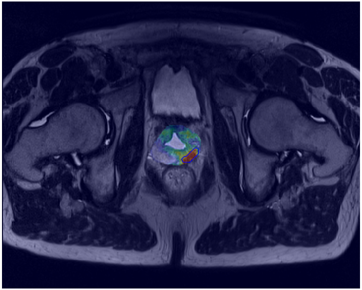
ROC for each patient



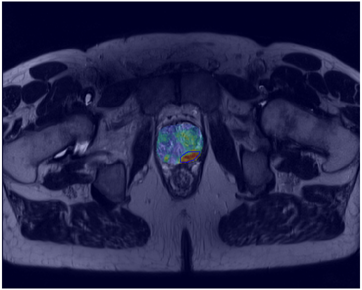
ROC analysis for each patient

Fine-tuned combination

"Outstanding" discrimination level



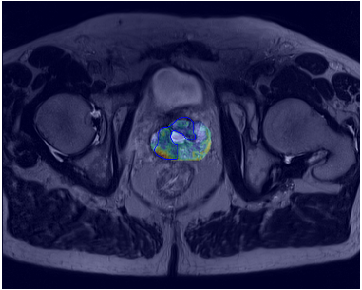
(a) AUC $= 0.922$



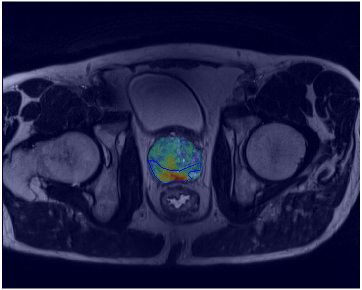
(b) AUC $= 0.914$

Fine-tuned combination

"Acceptable" discrimination level



(c) AUC $= 0.692$



(d) AUC $= 0.735$

Contributions & future works

Research objectives

- Collect a mp-MRI dataset
- Design a CAD for CaP using all mp-MRI modalities
- Investigate normalization, feature selection/extraction, data balancing
- Implement 3D features
- Release source code and dataset

Contributions & future works

Contributions

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Avenue for future research

- ✗ Incorporate spatial connectivity in classification using super-voxels
- ✗ Dissociate classifiers for the PZ and CG regions
- ✗ Explore the features from PI-RADS v.2
- ✗ Investigate the benefit of deep-learning

Timeline