

Shallow and deep learning representations for quantifying spatial heterogeneity in tumours from DCE-MRI

Jola Mirecka

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EPSRC

Engineering and Physical Sciences
Research Council

SciML / CCP-EM
RAL, STFC
&

IBME, University of Oxford



**Science & Technology
Facilities Council**

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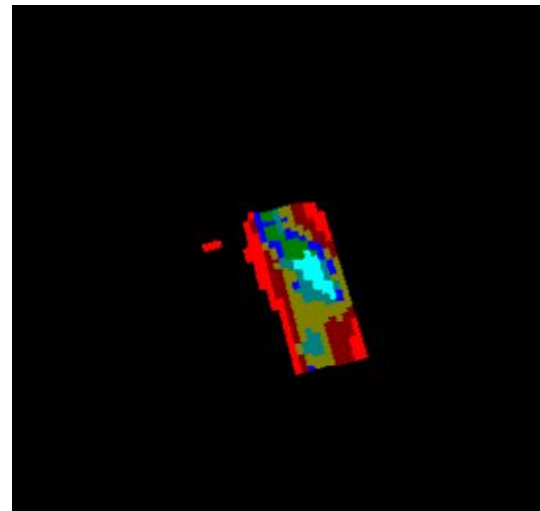
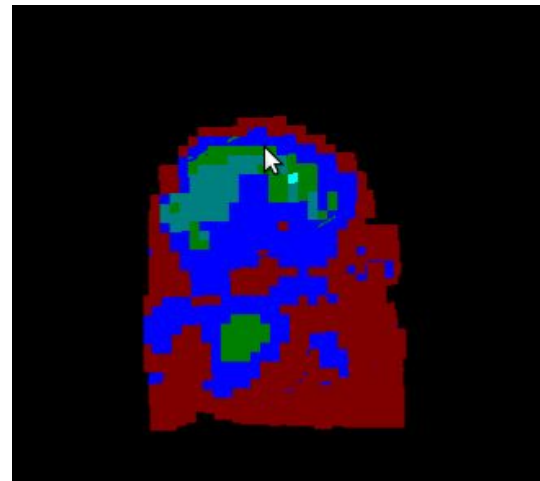


**Science & Technology
Facilities Council**



Presentation outline

1. The problem
2. The question
3. Trial study:
 - 3.1. shallow image representations
4. Methods:
 - 4.1. shallow image representations
 - 4.2. deep image representations
5. Results:
 - 5.1. pre-clinical: tumour progression
 - 5.2. clinical: response to therapy
6. Cryo-EM?

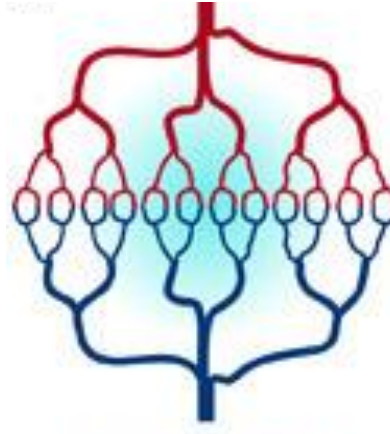




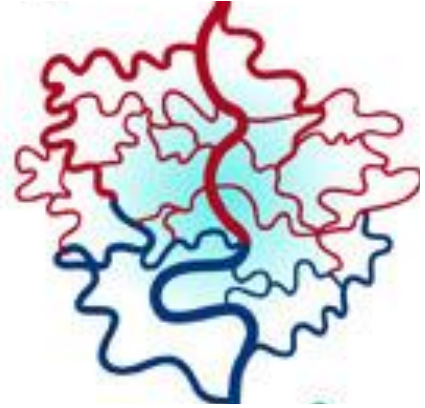
1. The problem

Tumours and heterogeneity

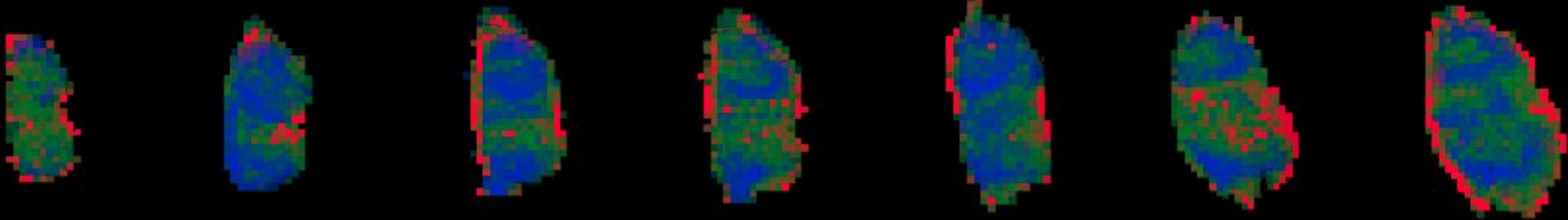
- cancerous tumours are characterized by an increase in heterogeneity
- ★ **heterogeneity** - variation or non-uniformity in composition



normal vasculature



tumour vasculature



CHANGE IN VARIATION

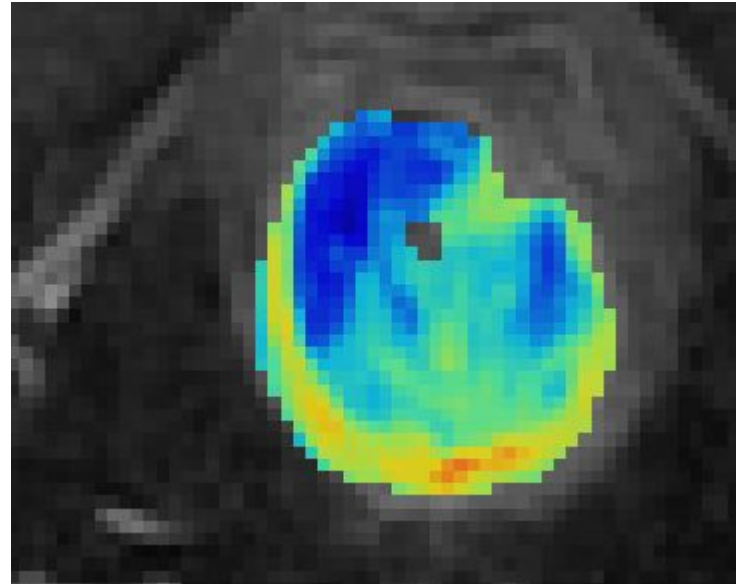
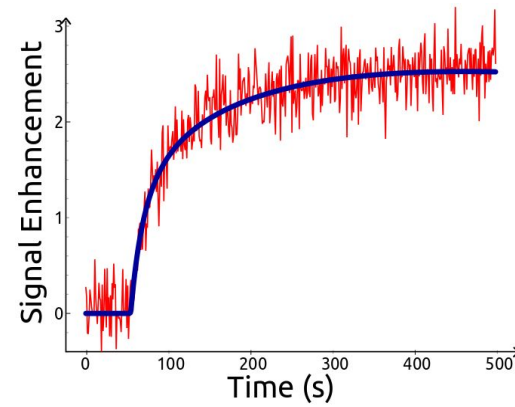




1. The problem

Dynamic Contrast-Enhanced MRI

- capable monitoring and quantifying perfusion





1. The problem

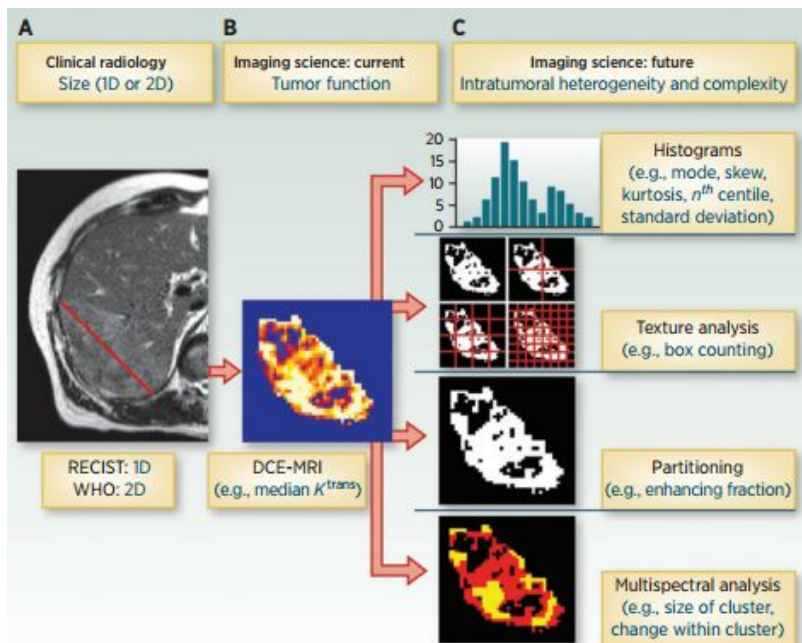
Clinical standards

Review

Clinical
Cancer
Research

Imaging Intratumor Heterogeneity: Role in Therapy Response, Resistance, and Clinical Outcome

James P.B. O'Connor^{1,2}, Chris J. Rose¹, John C. Waterton^{1,3}, Richard A.D. Carano⁴, Geoff J.M. Parker¹, and Alan Jackson¹



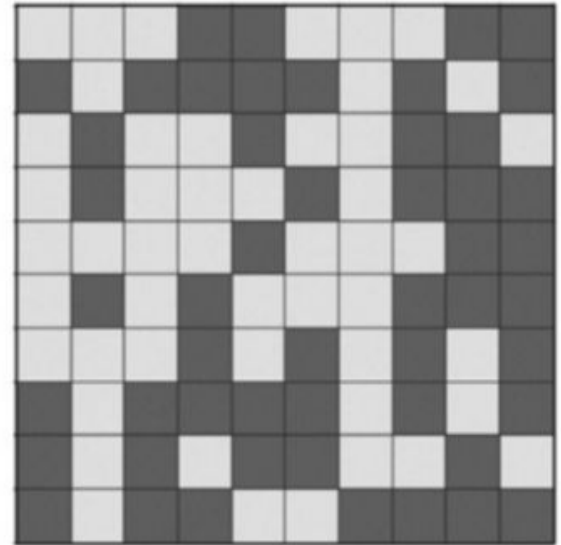
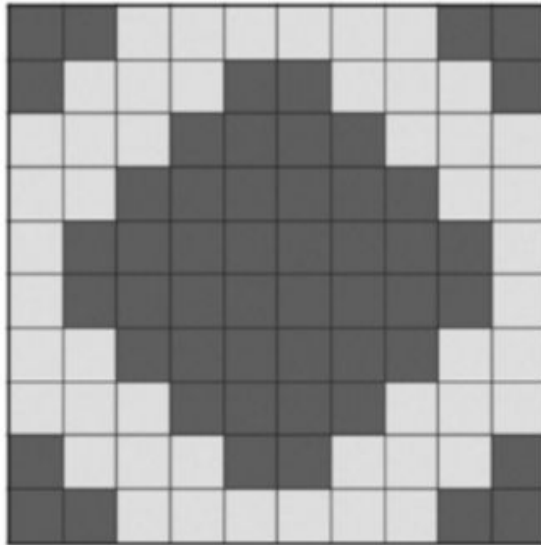
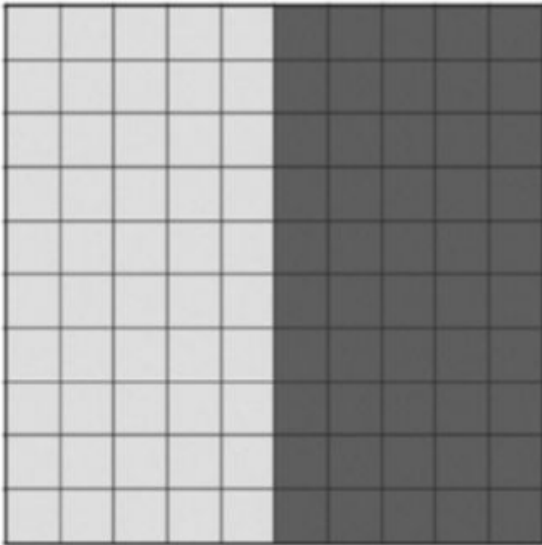
Method	Binary classifier	Threshold value	Multispectral	Geographic
Example	K^{trans}	ADC	K^{trans} and ADC	K^{trans} or ADC
Image				
Distribution				Parameter values unrelated to voxel category
Key	<ul style="list-style-type: none"> Nonenhancing Enhancing 	<ul style="list-style-type: none"> Below median Above median 	<ul style="list-style-type: none"> Cluster 1 Cluster 2 Cluster 3 	<ul style="list-style-type: none"> Inner zone Middle zone Outer zone
Derived BM	Volume or fraction of each tumor subregion	Volume or fraction of each tumor subregion	Volume or fraction of each tumor subregion	Parameter value in each tumor subregion
Segmentation criteria	<i>A priori</i> notion of tumor physiology	Derived from previous data or arbitrary	Data driven	Voxel location



1. The problem

Clinical standards

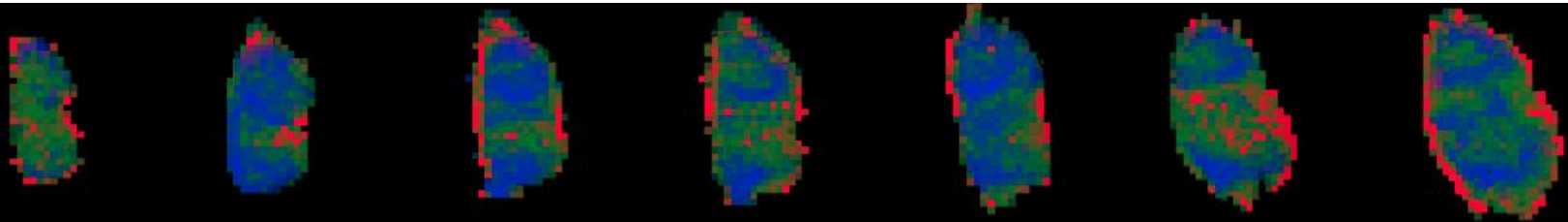
- visual, qualitative or weakly quantitative assessment





2. The question

- Q1) Can we characterize tumour growth with the change in its perfusion heterogeneity?
- Q2) Can we translate such change into clinical application of therapy assessment and prediction?



CHANGE IN VARIATION

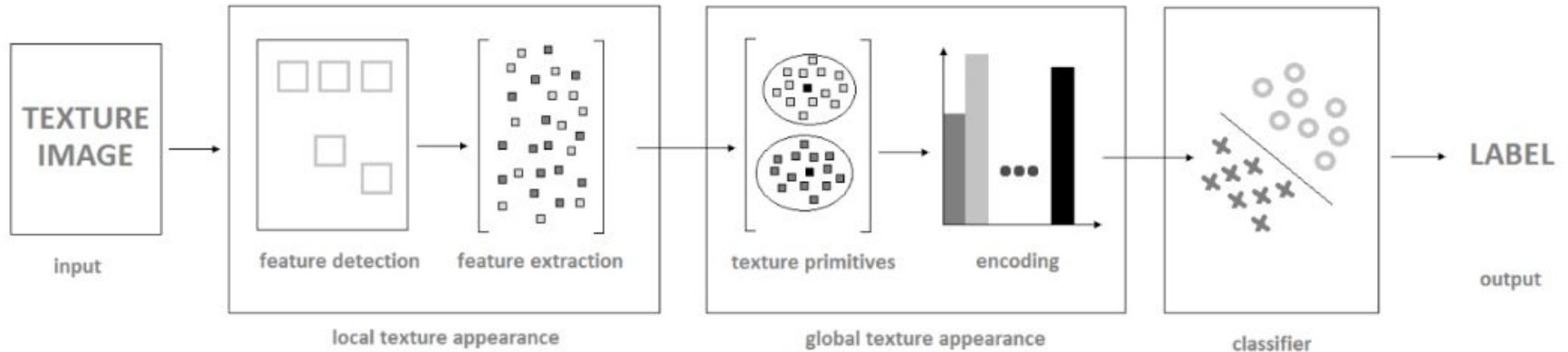




3. Trial study: methods

Shallow texture representations

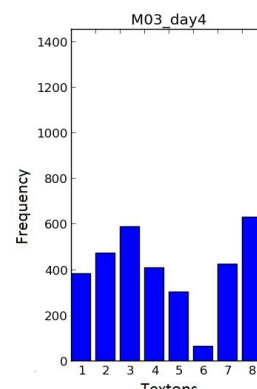
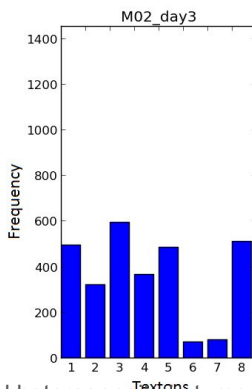
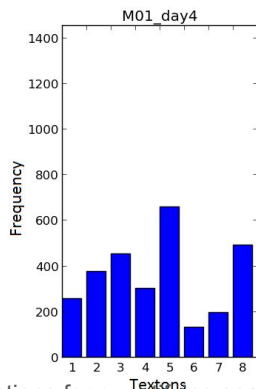
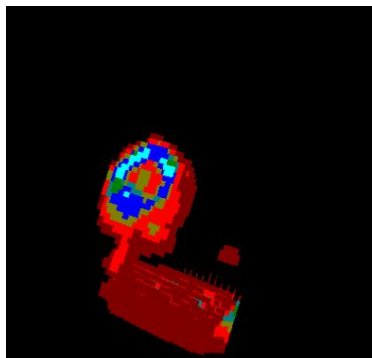
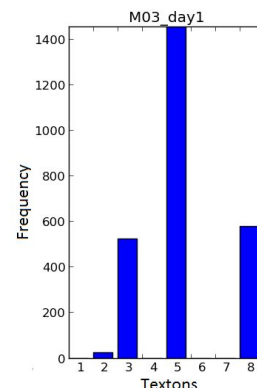
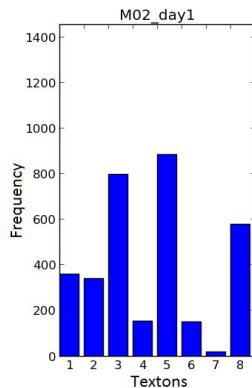
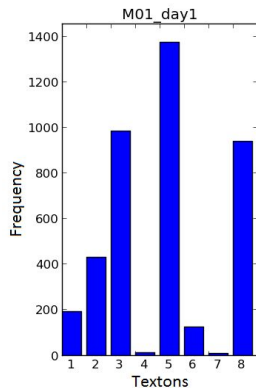
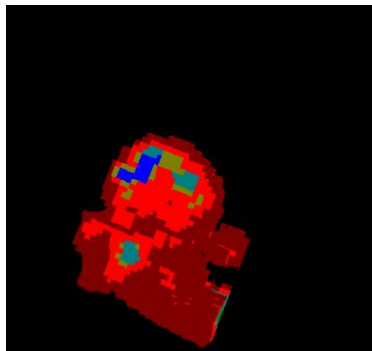
1. allow for training from limited data - **shallow representations**
2. capable of characterizing variation - **texture**
3. some methods robust variation - **patch**





3. Trial study: results

Shallow texture representations

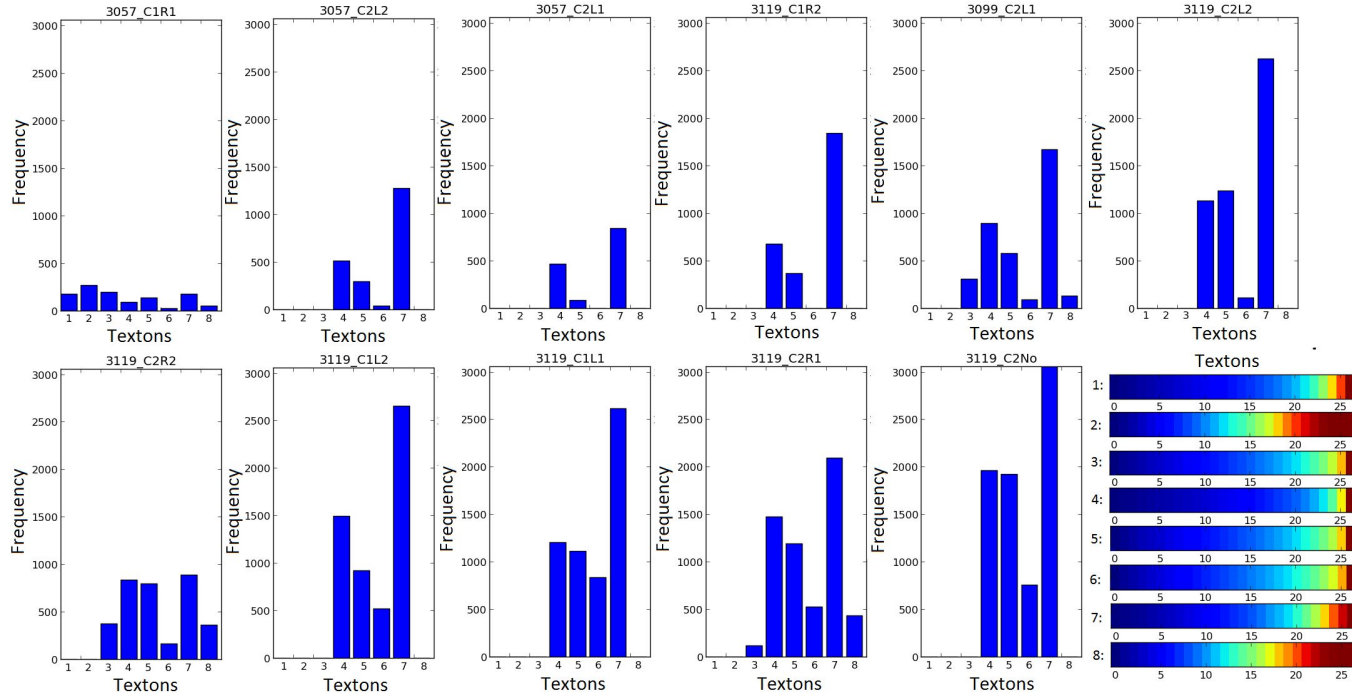


89% acc.
with SVM



3. Trial study: results

Shallow texture representations



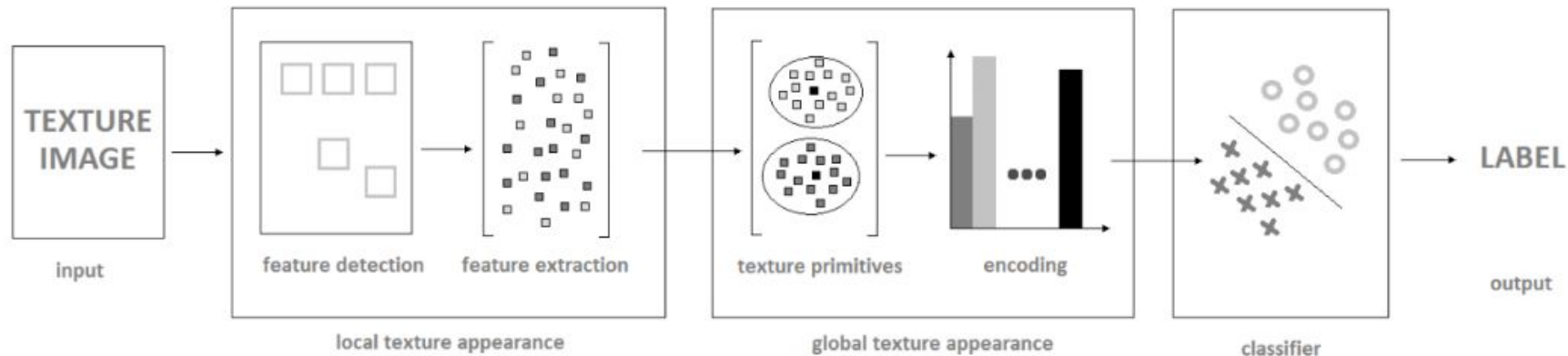


4. Methods

Shallow texture representations

- allow for training from limited data
- capable of characterizing variation

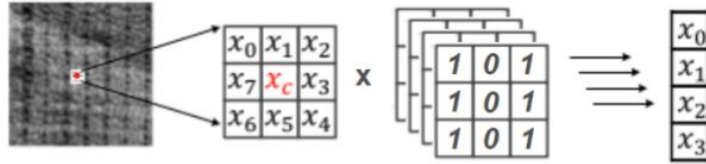
1. **Feature detection:** dense
2. **Feature descriptors:** Voxels, Gabor, Patch, LBP
3. **Visual vocabulary:** KMeans, GMM
4. **Encoding:** BoV
5. **Classifier:** SVM



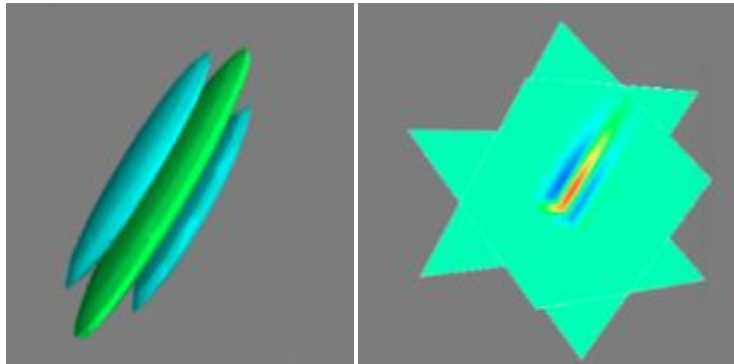


4. Methods: Gabor

Shallow texture representations



a) filter bank
feature descriptor



$$\phi_{\theta, \sigma, \gamma, \lambda, \varphi}(x, y) = \exp\left(-\frac{x'^2 + (\gamma y')^2}{2\sigma^2}\right) \cos\left(2\pi \frac{x'}{\lambda} + \varphi\right)$$

$$\phi_{\theta, \sigma, \gamma, \lambda, \varphi}(x, y, z) = \exp\left[-\frac{1}{2}\left(\frac{x'^2}{\sigma_x^2} + \frac{(\gamma y')^2}{\sigma_y^2} + \frac{(\gamma z')^2}{\sigma_z^2}\right)\right] \cos\left(2\pi \frac{x'}{\lambda} + \varphi\right)$$

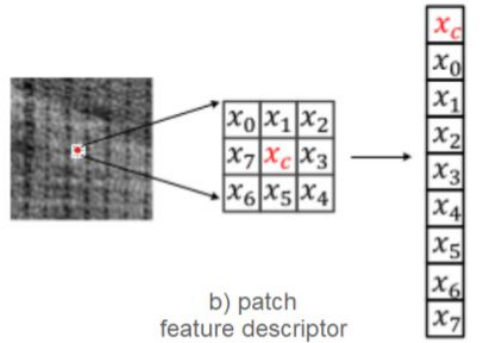
$$\begin{bmatrix} x' \\ y' \\ z' \end{bmatrix} = R(\theta) \begin{bmatrix} x \\ y \\ z \end{bmatrix} \quad R(\theta) = R_x R_y R_z$$

$$R_x = \begin{bmatrix} 1 & 0 & 0 \\ 0 & \cos \theta_x & -\sin \theta_x \\ 0 & \sin \theta_x & \cos \theta_x \end{bmatrix} \quad R_y = \begin{bmatrix} \cos \theta_y & 0 & \sin \theta_y \\ 0 & 1 & 0 \\ -\sin \theta_y & 0 & \cos \theta_y \end{bmatrix} \quad R_z = \begin{bmatrix} 0 & \cos \theta_z & -\sin \theta_z \\ 0 & \sin \theta_z & \cos \theta_z \\ 0 & 0 & 1 \end{bmatrix}$$



4. Methods: Patch

Shallow texture representations

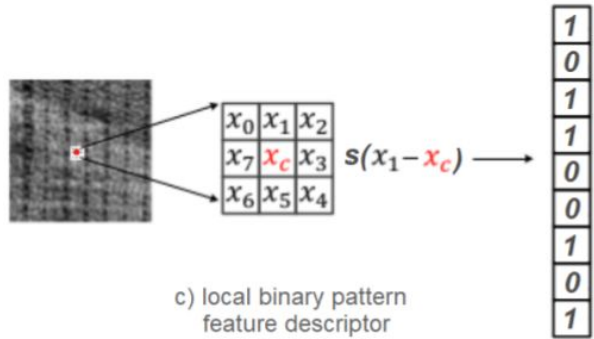




4. Methods: LBP

Shallow texture representations

$$LBP(i, j, k) = \sum_{p=-n/2}^{n/2} \sum_{r=-n/2}^{n/2} \sum_{s=-n/2}^{n/2} s(I(i-p, j-r, k-s) - I(i, j, k)) 2^{prs}$$



$$s(x) = \begin{cases} 1 & x \geq 0 \\ 0 & x < 0 \end{cases}$$

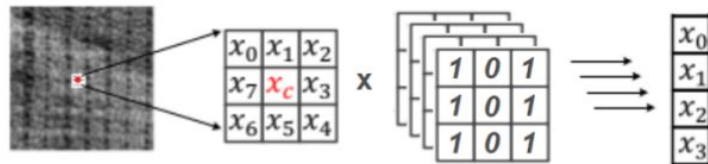
$$ELBP_CI_p(x_c) = s(x_c - \beta)$$

$$ELBP_NI_p(x_c) = \sum_{i=1}^{n^3} s(x_i - \beta_p) 2^i$$

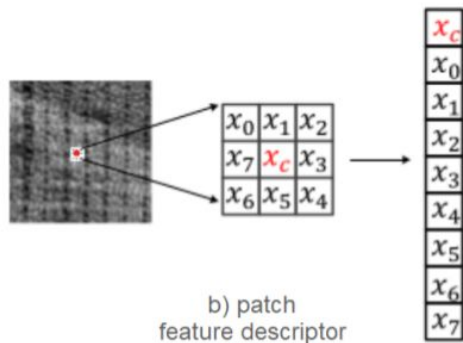


4. Methods: feature descriptors

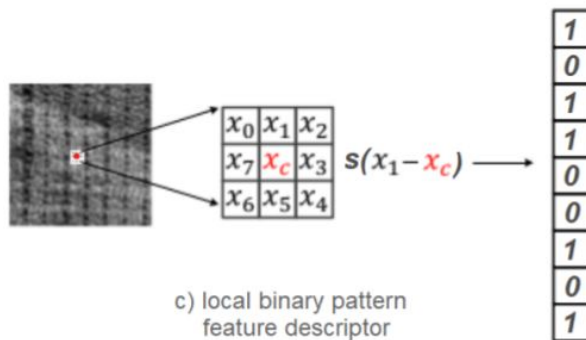
Shallow texture representations



a) filter bank
feature descriptor



b) patch
feature descriptor



c) local binary pattern
feature descriptor



4. Methods

Deep texture representations

- allow for training from limited data
- capable of characterizing variation

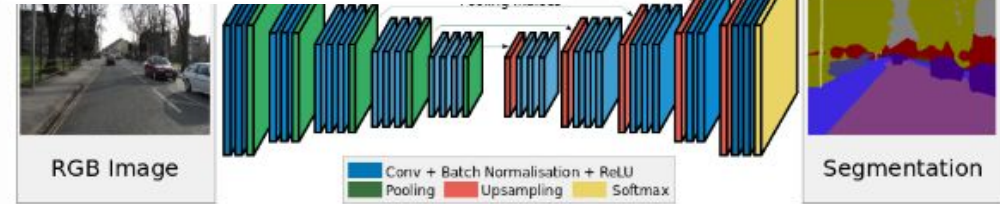
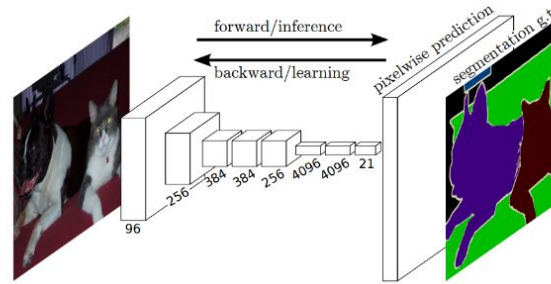
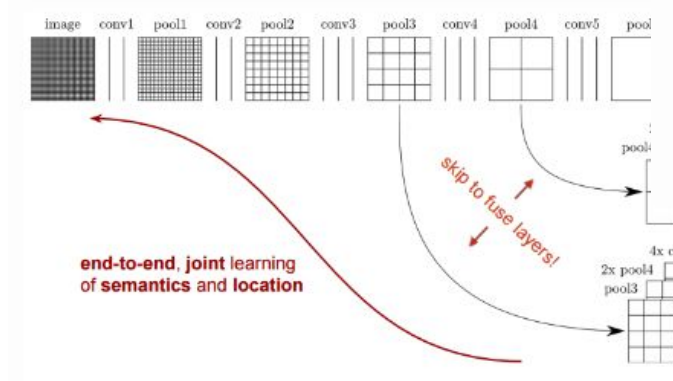
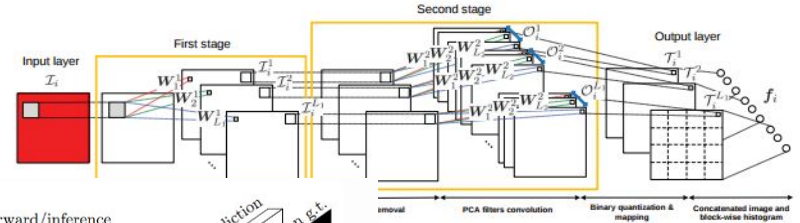
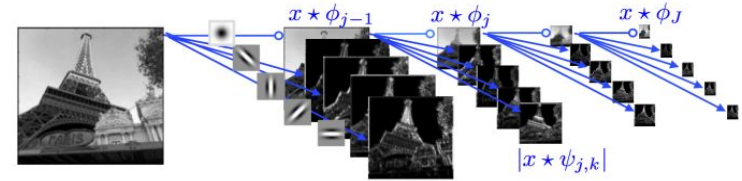


Figure : The SegNet Architecture



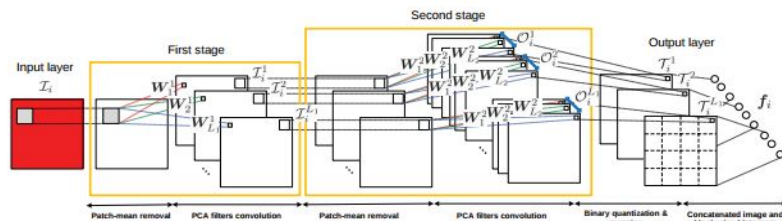
4. Methods

Deep texture representations

1. **transfer learning**: feature extractor
2. **hand-crafted nets**: random projections

PCANet: A Simple Deep Learning Baseline for Image Classification?

Tsung-Han Chan, Kui Jia, Shenghua Gao, Jiwen Lu, Zinan Zeng, and Yi Ma

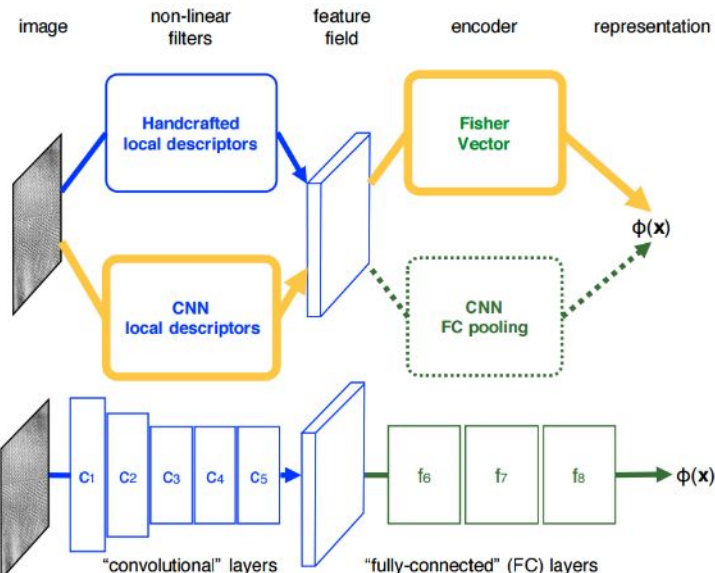


Deep Filter Banks for Texture Recognition and Segmentation

Mircea Cimpoi
University of Oxford

Subhransu Maji
University of Massachusetts, Amherst

Andrea Vedaldi
University of Oxford

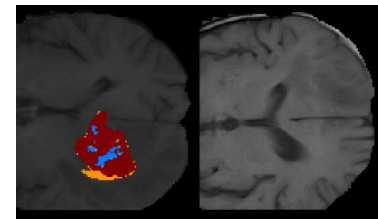
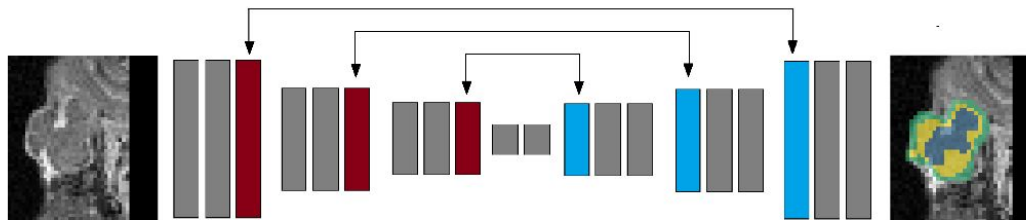




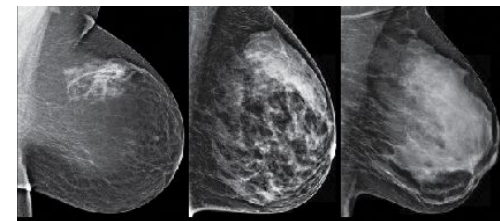
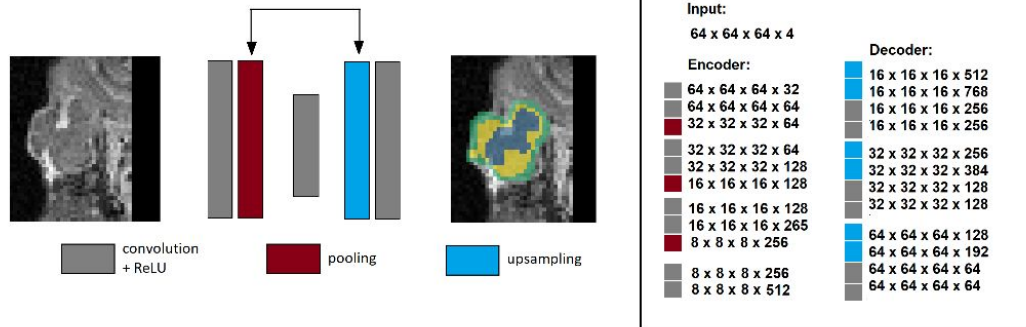
4. Methods

Deep texture representations

T-UNet



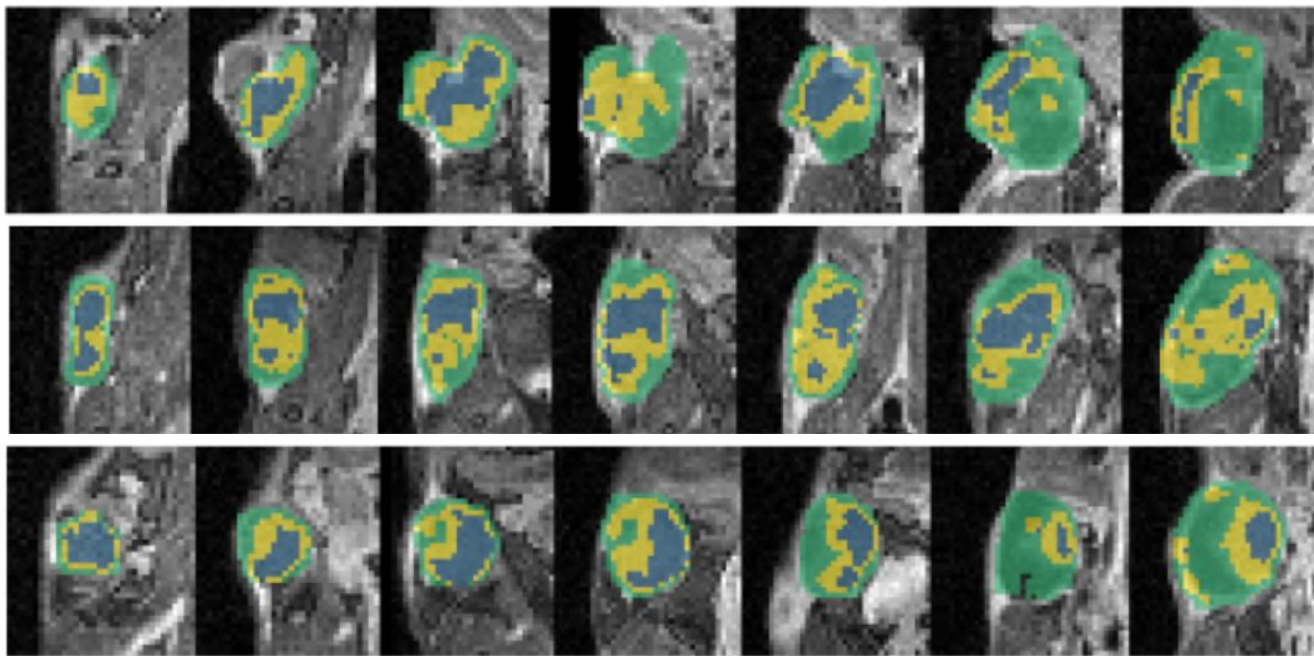
Rand-UNet



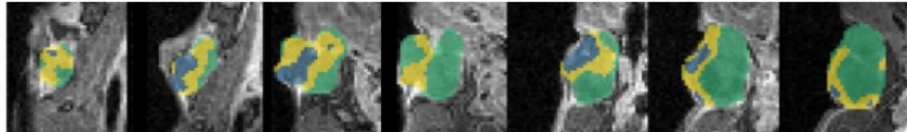


5. Results: segmentations

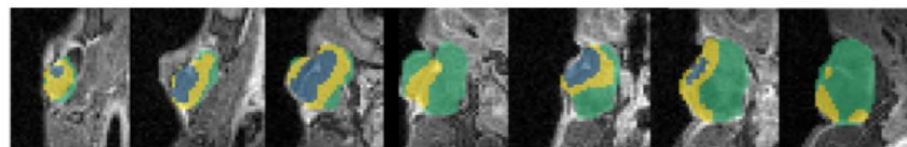
Pre-clinical: tumour progression



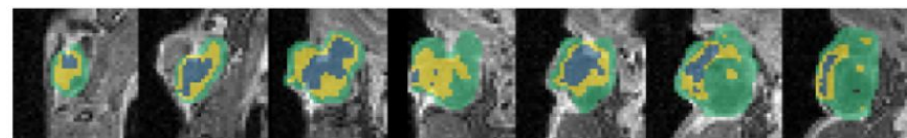
T-UNet+KM



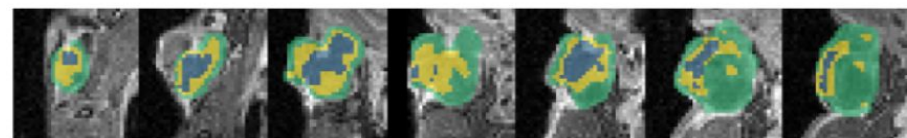
Rand-UNet+KM



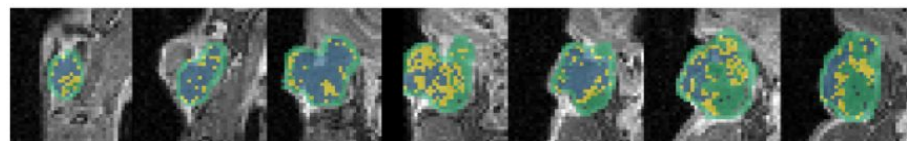
LBP+KM



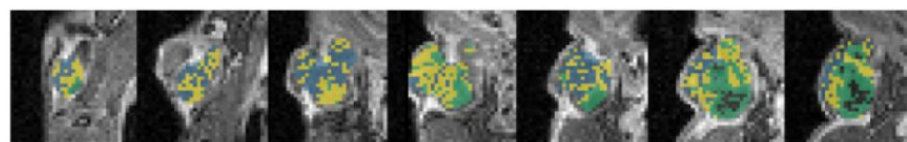
Patch+KM



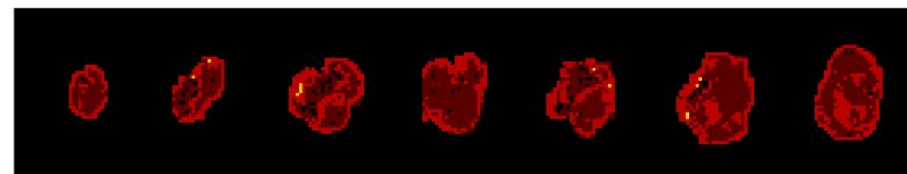
Gabor+KM



Vox+KM



confidence





5. Results: classifications

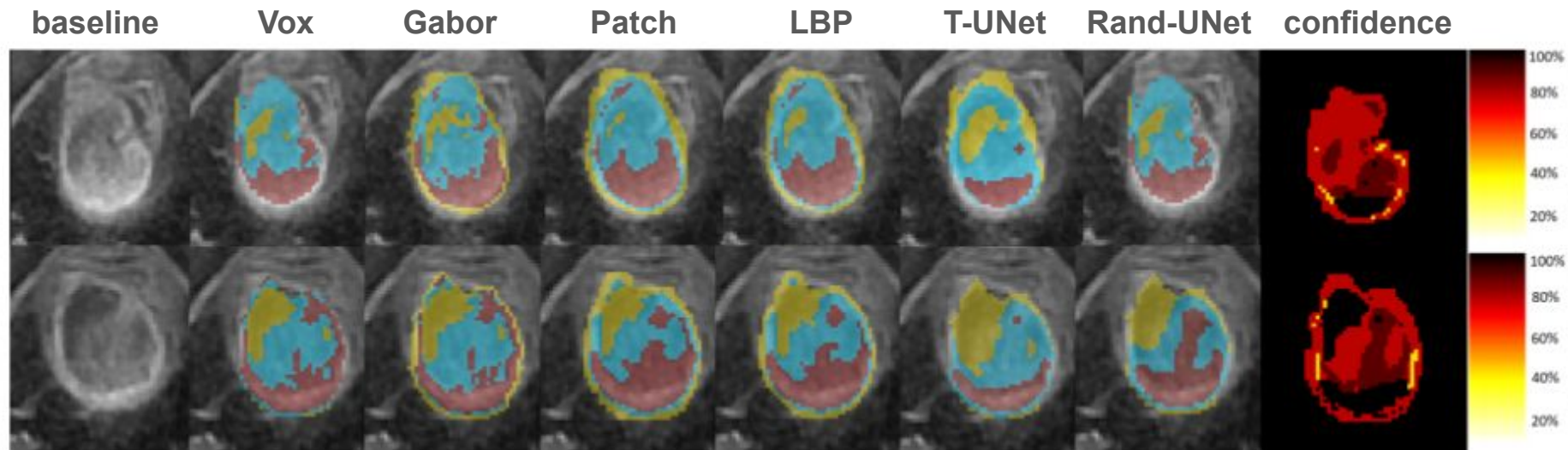
Pre-clinical: tumour progression

	Vox	Filters	Patch	LBP	UNet	RandUNet
	Acc. DICE	Acc. DICE	Acc. DICE	Acc. DICE	Acc. DICE	Acc. DICE
KM	65% 0.599	70% 0.604	70% 0.715	75% 0.723	80% 0.825	75% 0.729
GMM	82.5% 0.516	70% 0.754	70% 0.958	70% 0.963	77.5% 0.783	75% 0.715



5. Results: segmentations

Clinical: therapy response

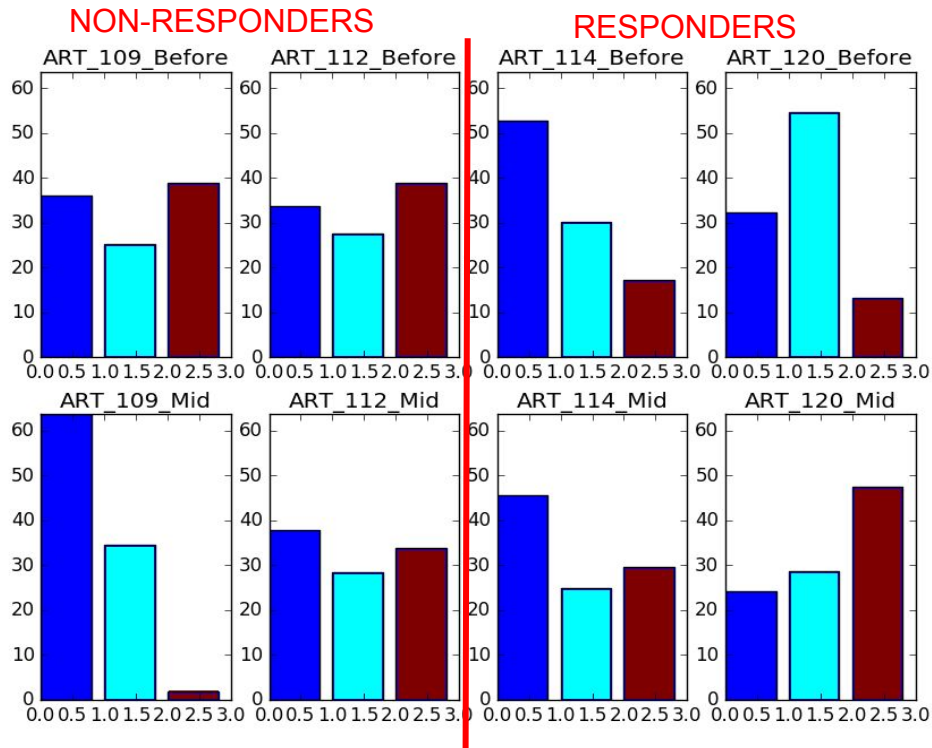
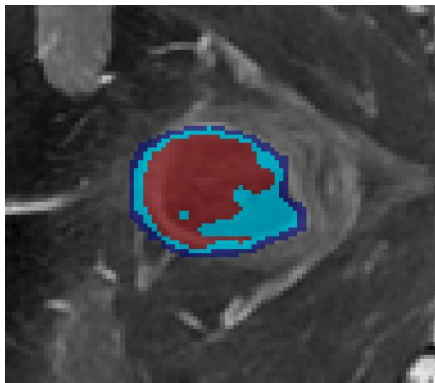
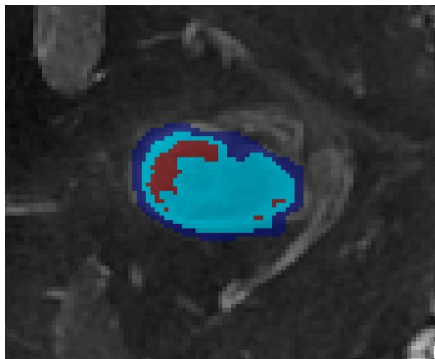




5. Results: classifications

Clinical: therapy response

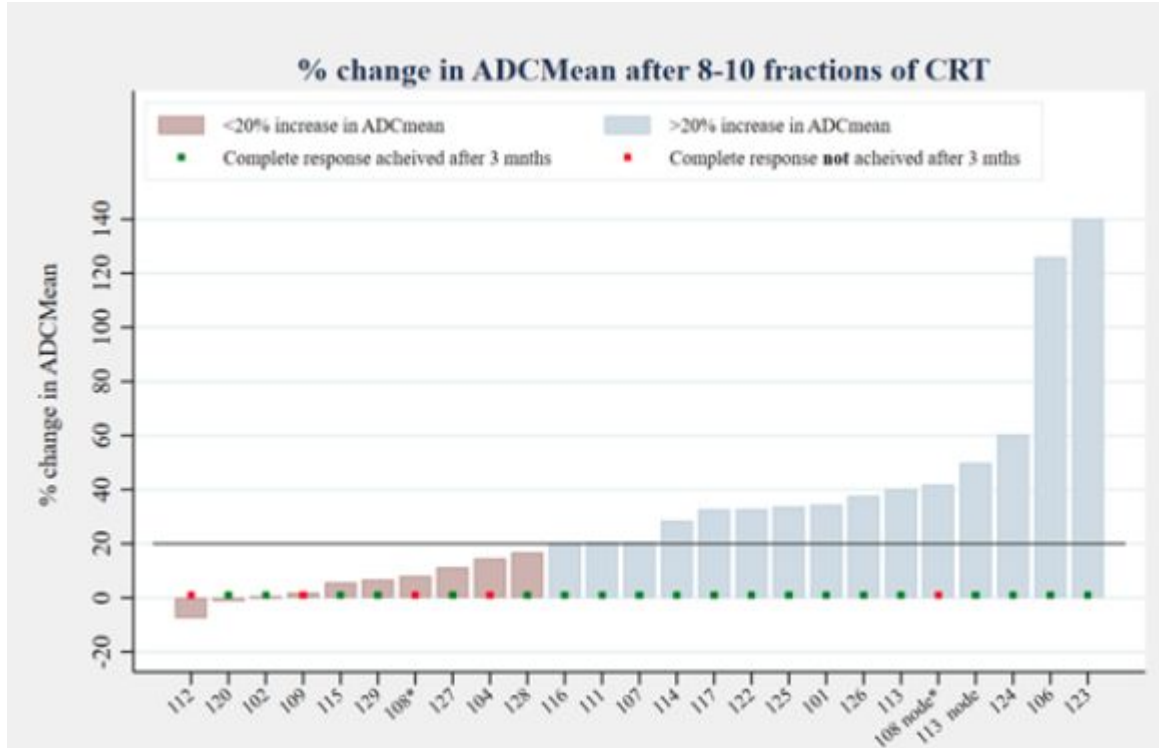
$$J_SAD = \sum_{j=1}^6 \sum_{i=0}^k abs(h_{j,1}(i) - h_{j,2}(i))$$





Part 1: Results

Question 2: Clinical application - therapy assessment



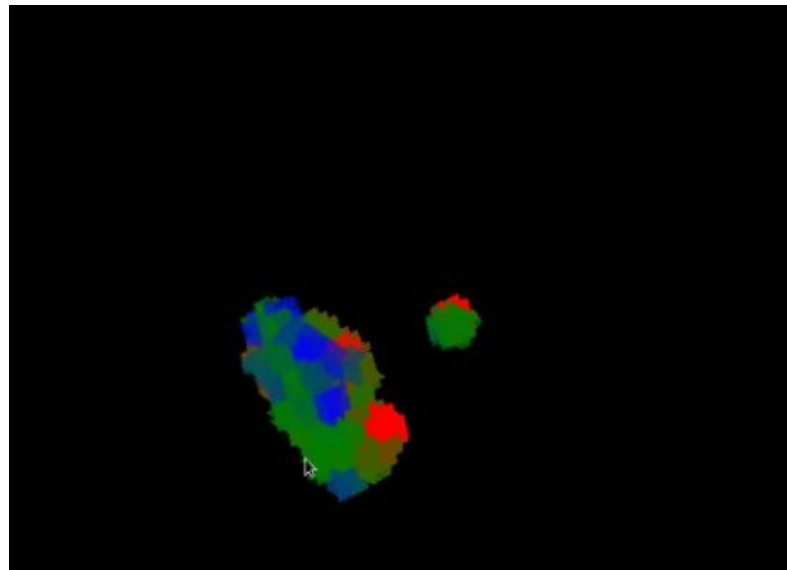


Quantifying Spatial Perfusion Heterogeneity in Tumours from DCE-MRI

Jola Mirecka

(jolanta.mirecka@eng.ox.ac.uk)

- ★ Collaborators: **Bartek Papiez, Benjamin Irving**
- ★ Pre-clinical collaborators: **Pavitra Kannan, Ana Gomes, Veerle Kesermans, Danny Allen, Paul Kinchesh, Sean Smart**
- ★ Clinical collaborators: **Ben George, Maria Hawkins**
- ★ Supervisors: **Mark Jenkinson, Julia Schnabel** and **Michael Chappell, Mike Brady** (advisory)



Questions?



CANCER
RESEARCH
UK

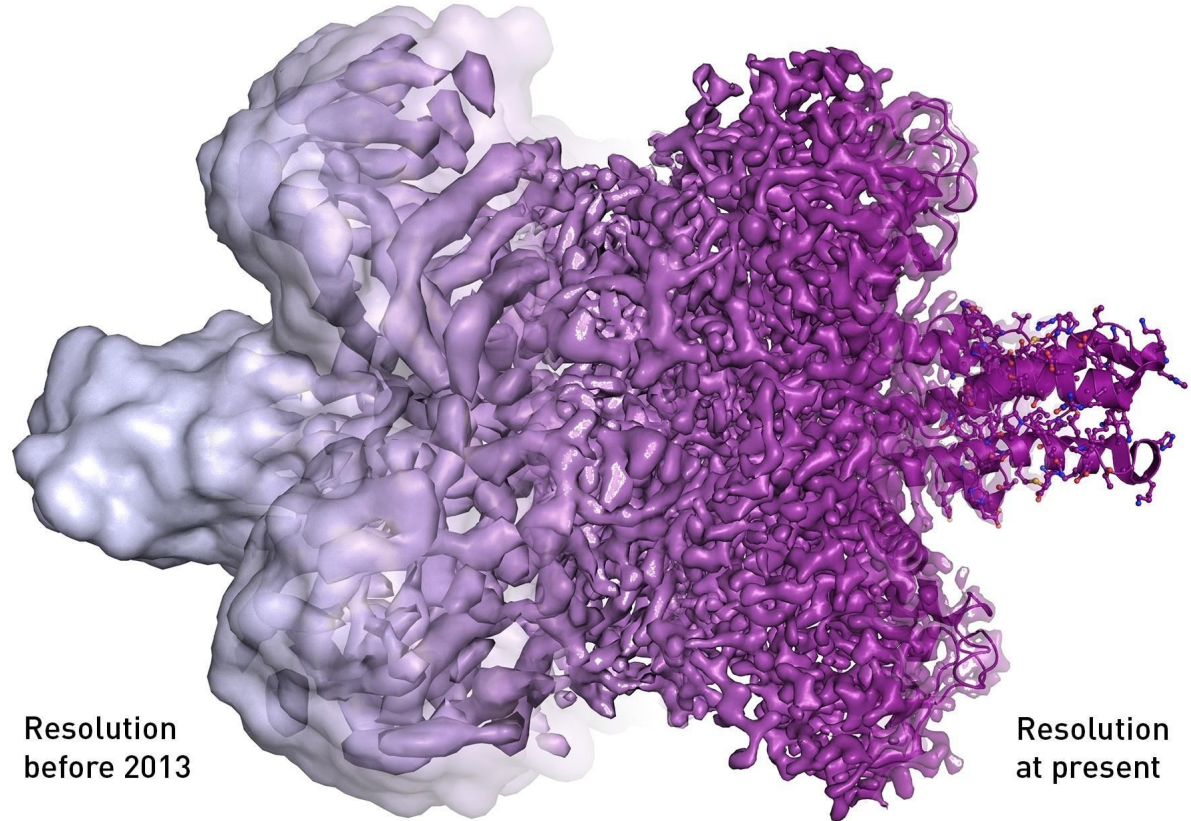




Cryo-EM?

- structure to function
- resolution revolution
- pharmaceutical implications

eBIC facilities



**Resolution
before 2013**

**Resolution
at present**

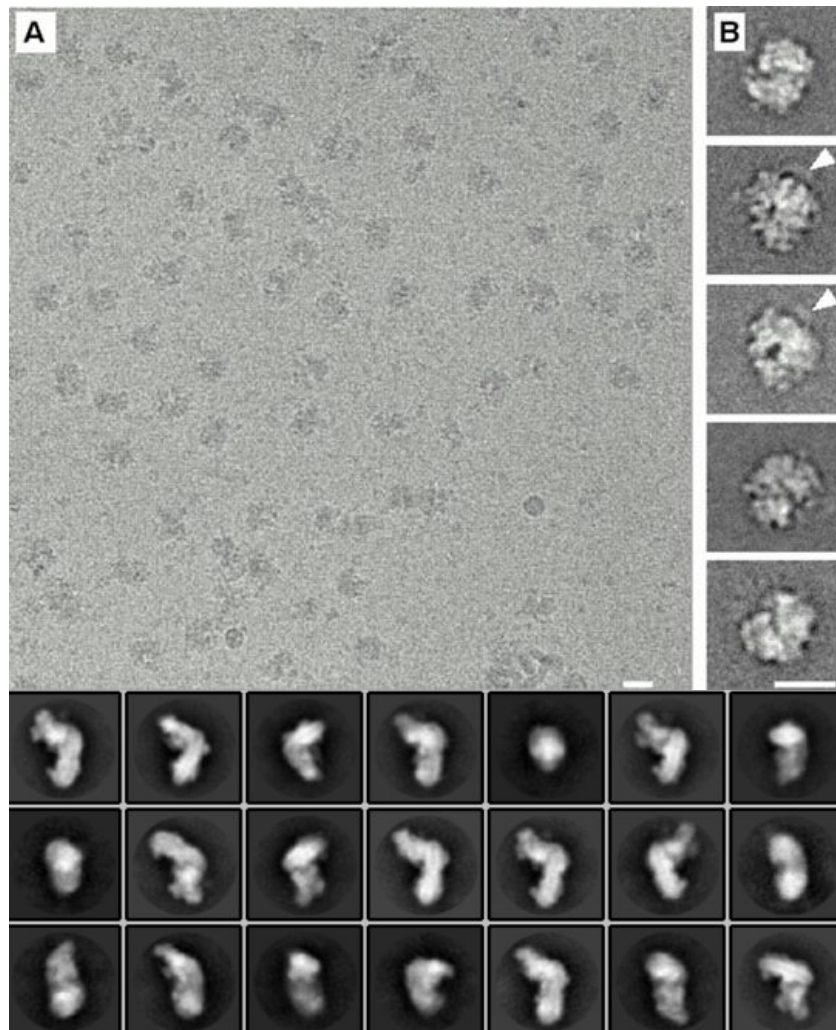
Illustration: ©Martin Högbom/The Royal Swedish Academy of Sciences



Cryo-EM?

Particle picking:

- noisy micrographs
- picking particles
- 2D classification

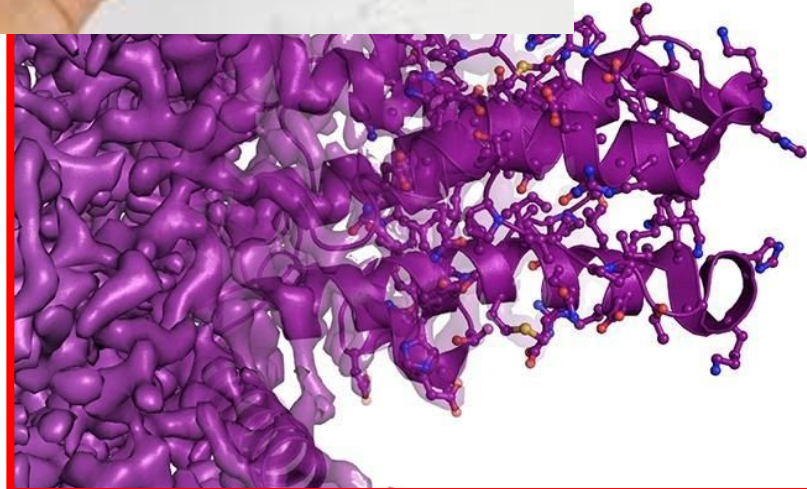




Cryo-EM?

Model building:

- density segmentation
- secondary structure
- side chains



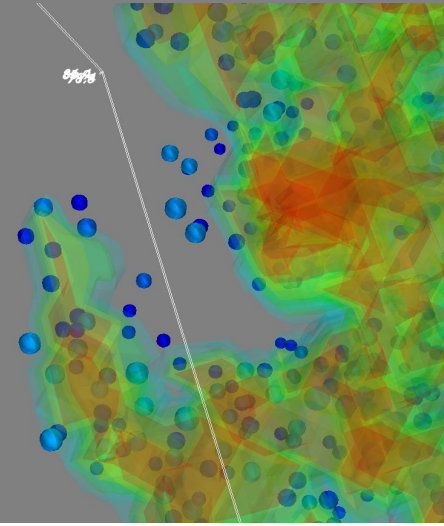
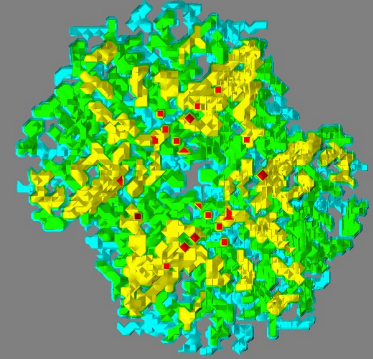
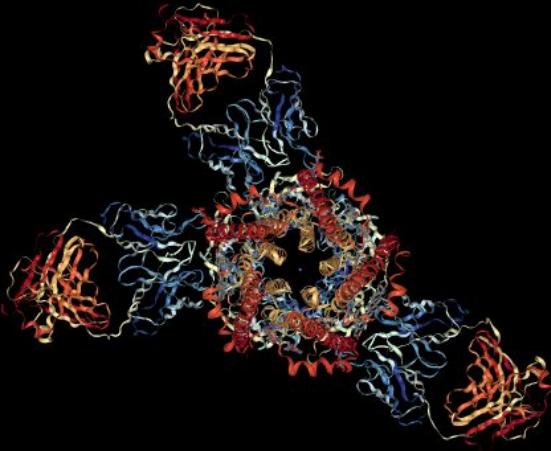


Cryo-EM?

Model building:

- density segmentation
- secondary structure
- side chains

Ribosome: 100 000 atoms





Cryo-EM?

Pipeline automation:

- automatic parameter selection
- data model

File Jobs Autorun I/O Auto-sampling Compute Running

Import
Motion correction
CTF estimation
Manual picking
Auto-picking
Particle extraction
Particle sorting
Subset selection
2D classification
3D initial model
3D classification
3D auto-refine
3D multi-body
Movie refinement
Particle polishing
Mask creation
Join star files
Particle subtraction
Post-processing
Local resolution

Consensus refinement optimiser.star: 001/run_it032_optimiser.star ? Browse
Continue from here: ? Browse
Body STAR file: 3bodies_repairedmasks.star ? Browse
Reconstruct subtracted bodies? Yes ?

Print command Schedule Run now!

Job actions Current job: Give_alias_here Display: ?

Finished jobs	Running jobs	Input to this job
PostProcess/evec1_ftm14_overall/ PostProcess/evec1_ltm14_overall/ PostProcess/multibody_HEAD/ PostProcess/multibody_SSU/ PostProcess/multibody_LSU/ PostProcess/consensus_LSU/ PostProcess/consensus_SSU/ PostProcess/consensus_HEAD/ PostProcess/consensus_overall/ LocalRes/job023/ Refine3D/evec1_ltm14/ Refine3D/evec1_gtm14/ PostProcess/repairedmask_HEAD/	MultiBody/job039/	
	Scheduled jobs	Output from this job

stdout will go here; double-click this window to open stdout in a separate window



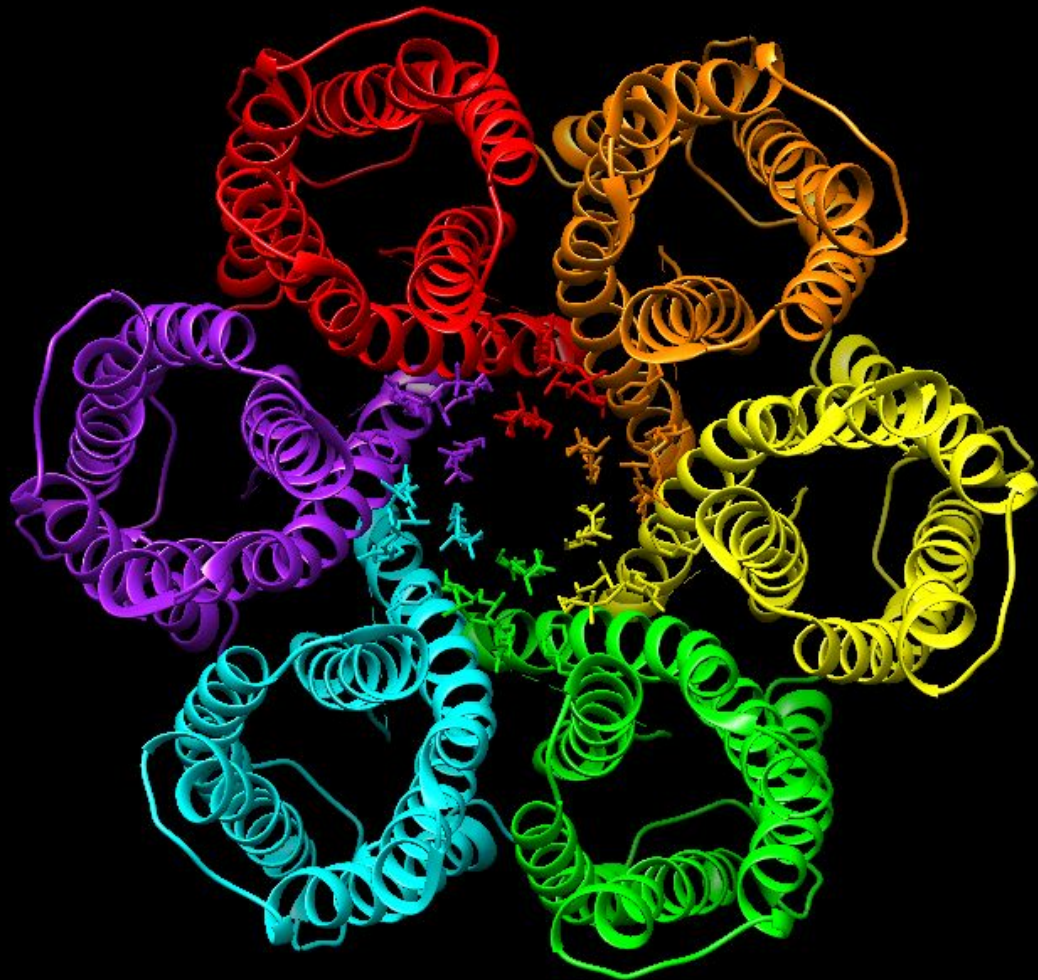
Questions?

CCP-EM:

Tom Burnley
Colin Palmer
Agnel Joseph
Martyn Winn

SciML:

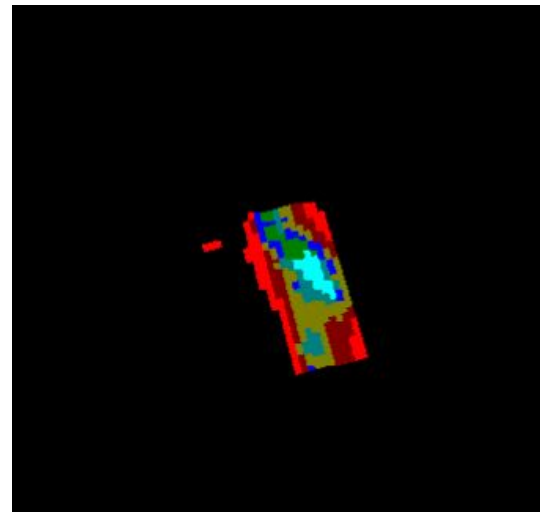
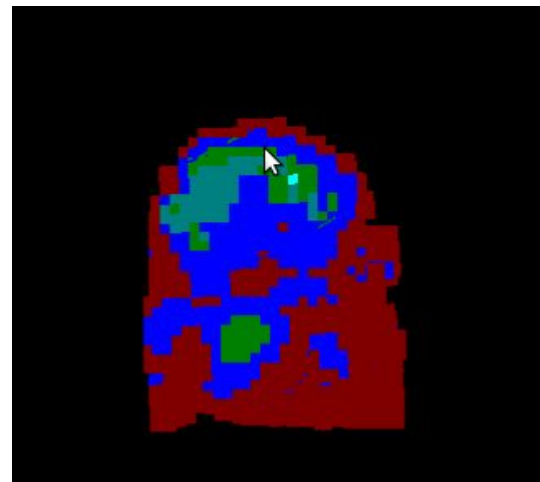
Tony Hey
Jeyan Thiyagalingam





Presentation outline

1. The problem
2. The question
3. Trial study:
 - 3.1. shallow image representations
4. Methods:
 - 4.1. shallow image representations
 - 4.2. deep image representations
5. Results:
 - 5.1. pre-clinical: tumour progression
 - 5.2. clinical: response to therapy
6. Cryo-EM?

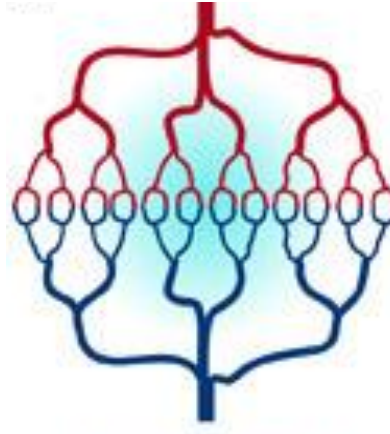




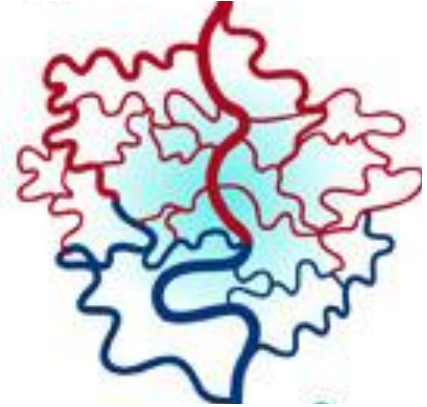
1. The problem

Tumours and heterogeneity

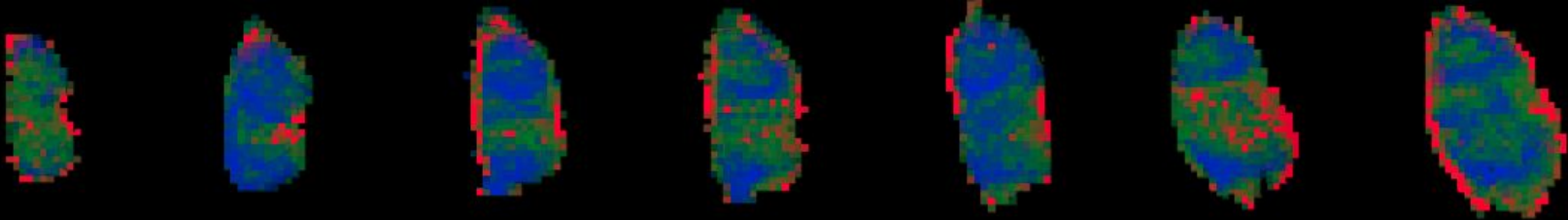
- cancerous tumours are characterized by an increase in heterogeneity
- ★ **heterogeneity** - variation or non-uniformity in composition



normal vasculature



tumour vasculature



CHANGE IN VARIATION

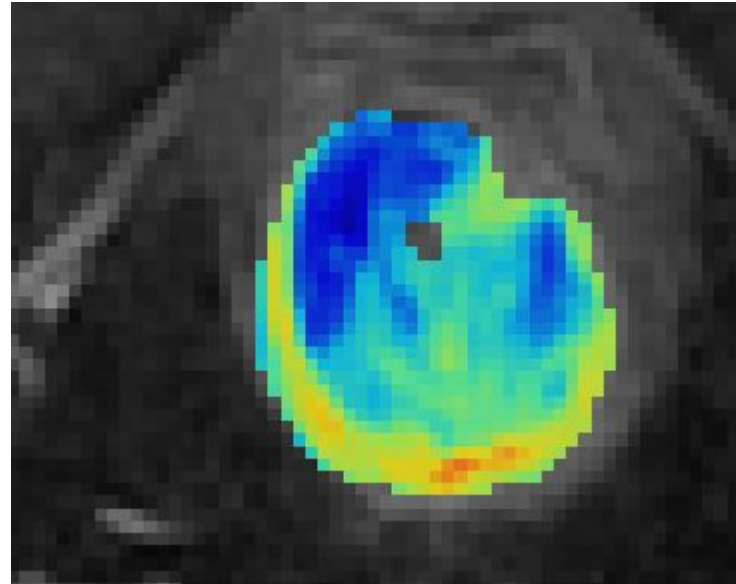
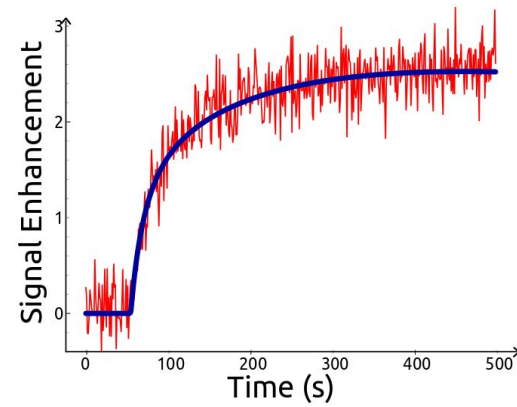




1. The problem

Dynamic Contrast-Enhanced MRI

- capable monitoring and quantifying perfusion





1. The problem

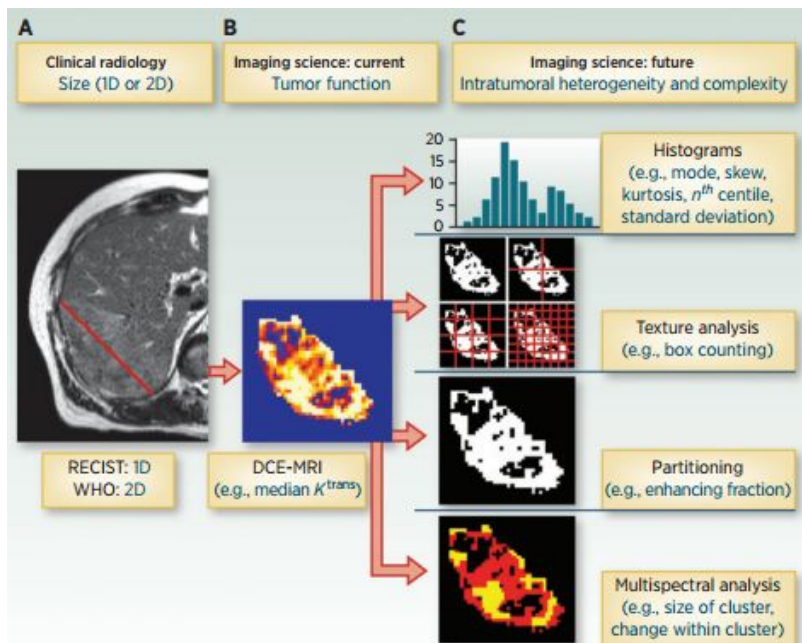
Clinical standards

Review

Clinical
Cancer
Research

Imaging Intratumor Heterogeneity: Role in Therapy Response, Resistance, and Clinical Outcome

James P.B. O'Connor^{1,2}, Chris J. Rose¹, John C. Waterton^{1,3}, Richard A.D. Carano⁴, Geoff J.M. Parker¹, and Alan Jackson¹



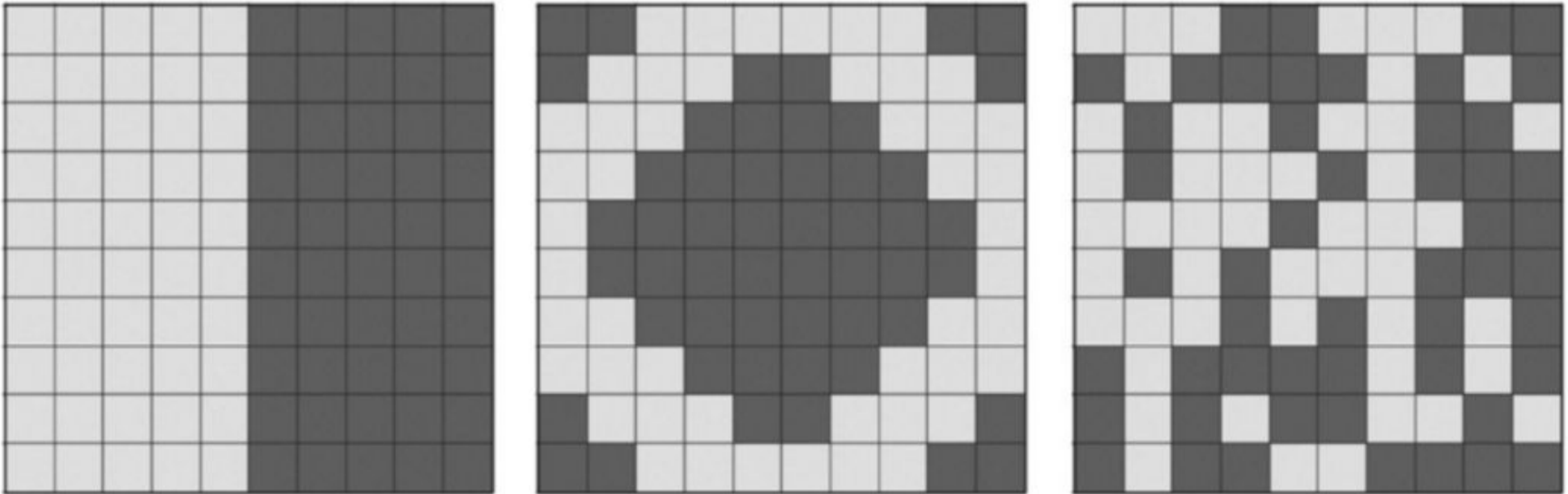
Method	Binary classifier	Threshold value	Multispectral	Geographic
Example	K^{trans}	ADC	K^{trans} and ADC	K^{trans} or ADC
Image				
Distribution				Parameter values unrelated to voxel category
Key	<ul style="list-style-type: none"> Nonenhancing Enhancing 	<ul style="list-style-type: none"> Below median Above median 	<ul style="list-style-type: none"> Cluster 1 Cluster 2 Cluster 3 	<ul style="list-style-type: none"> Inner zone Middle zone Outer zone
Derived BM	Volume or fraction of each tumor subregion	Volume or fraction of each tumor subregion	Volume or fraction of each tumor subregion	Parameter value in each tumor subregion
Segmentation criteria	<i>A priori</i> notion of tumor physiology	Derived from previous data or arbitrary	Data driven	Voxel location



1. The problem

Clinical standards

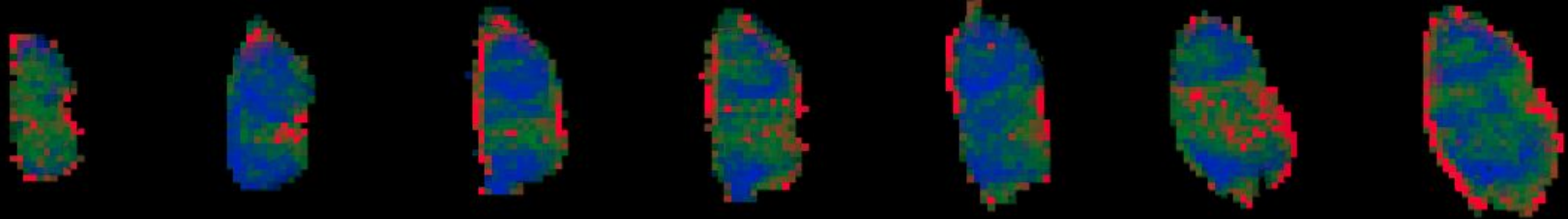
- visual, qualitative or weakly quantitative assessment





2. The question

- Q1) Can we characterize tumour growth with the change in its perfusion heterogeneity?
- Q2) Can we translate such change into clinical application of therapy assessment and prediction?



CHANGE IN VARIATION

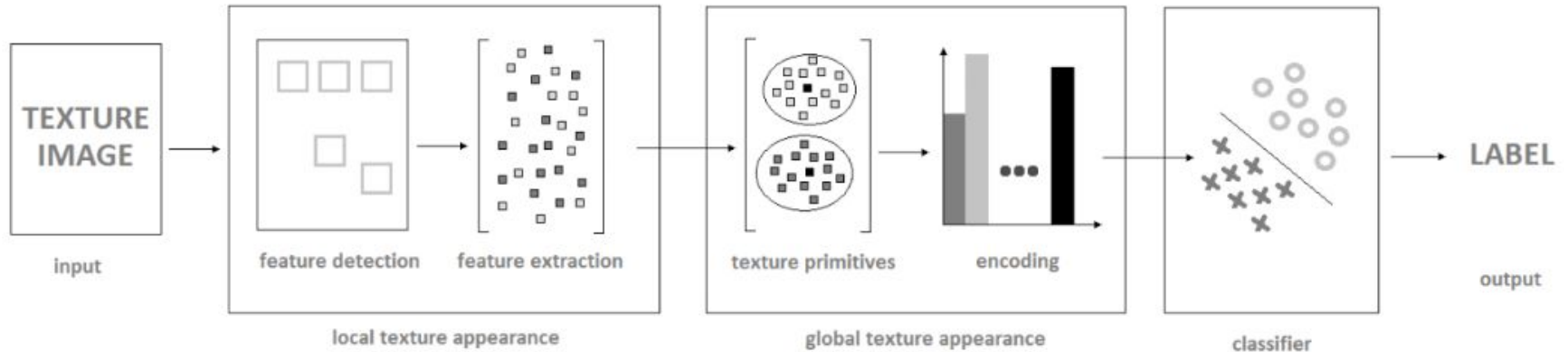




3. Trial study: methods

Shallow texture representations

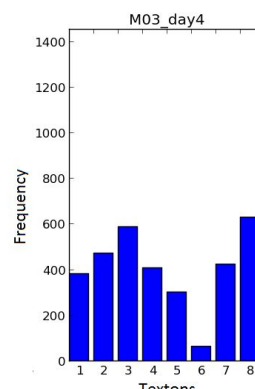
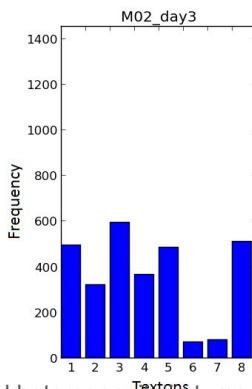
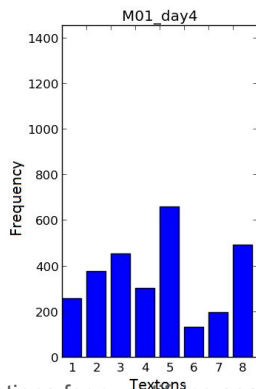
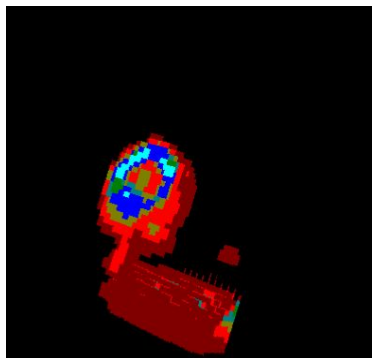
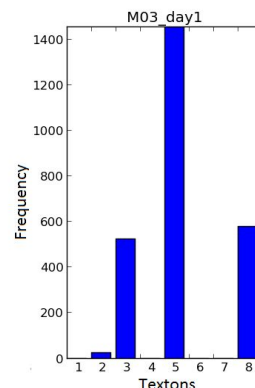
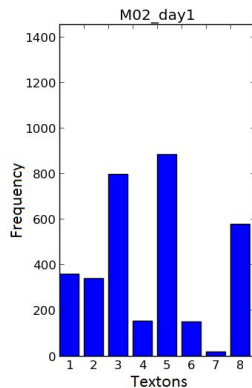
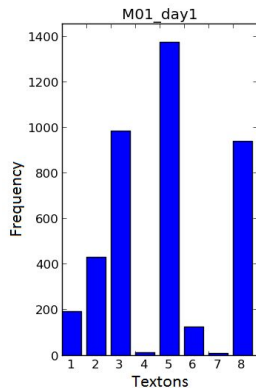
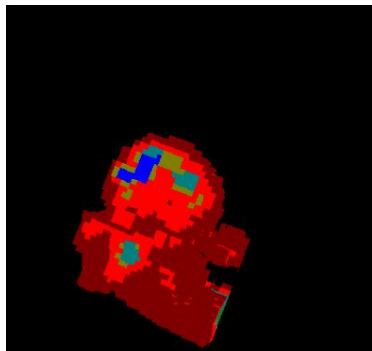
1. allow for training from limited data - **shallow representations**
2. capable of characterizing variation - **texture**
3. some methods robust variation - **patch**





3. Trial study: results

Shallow texture representations

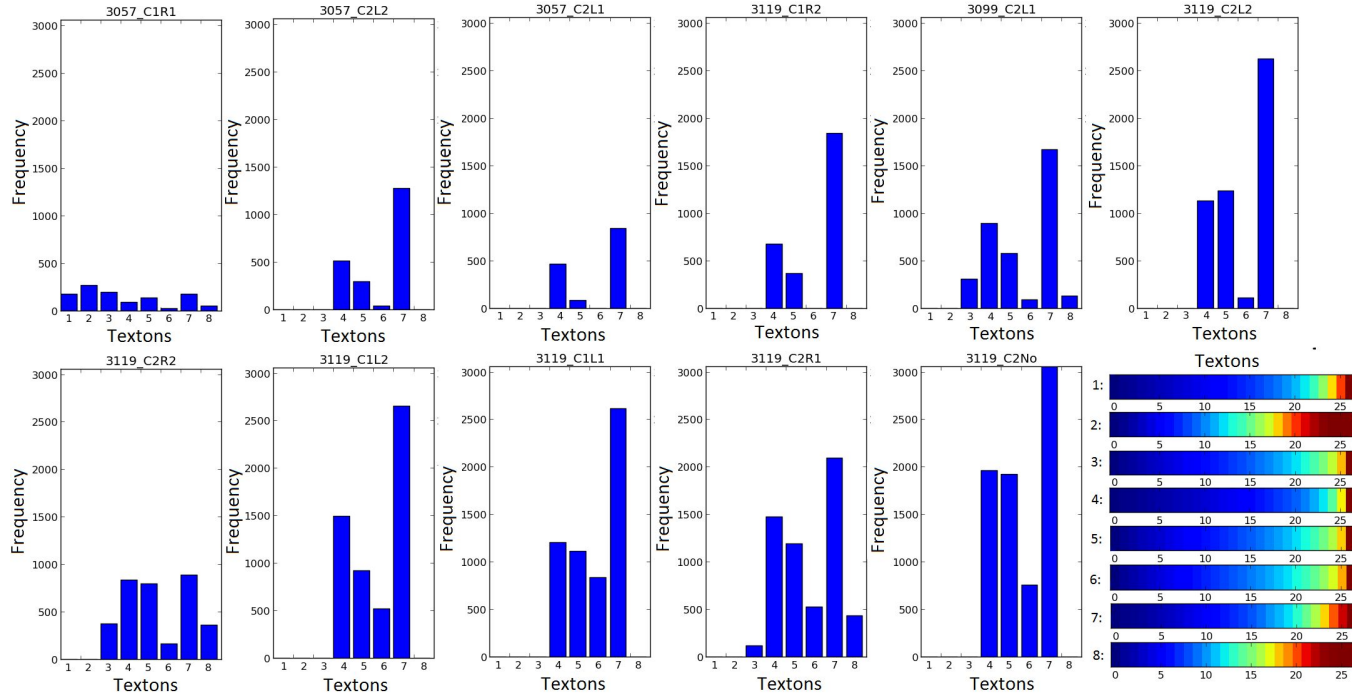


89% acc.
with SVM



3. Trial study: results

Shallow texture representations



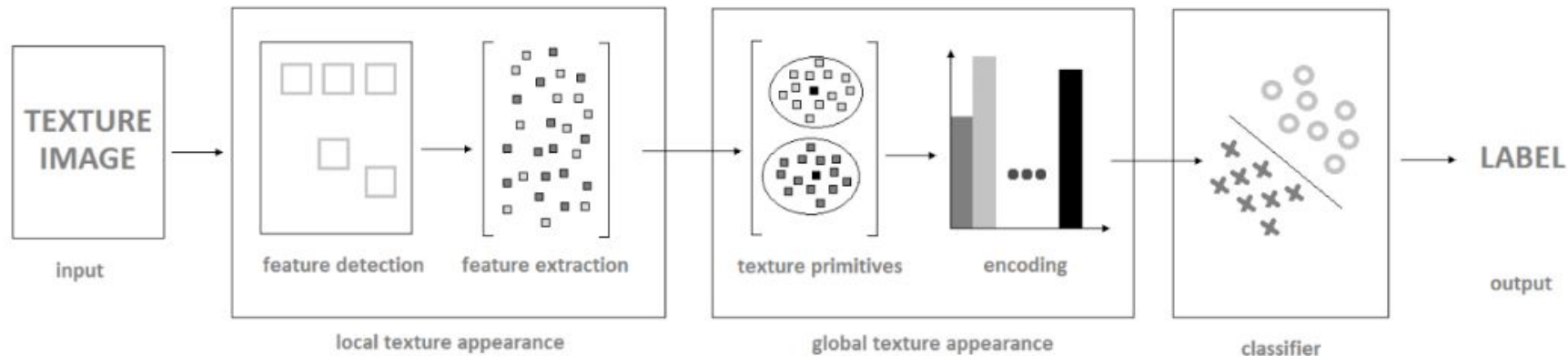


4. Methods

Shallow texture representations

- allow for training from limited data
- capable of characterizing variation

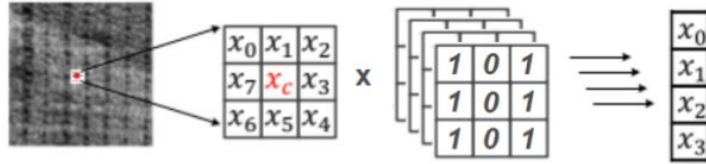
1. **Feature detection:** dense
2. **Feature descriptors:** Voxels, Gabor, Patch, LBP
3. **Visual vocabulary:** KMeans, GMM
4. **Encoding:** BoV
5. **Classifier:** SVM



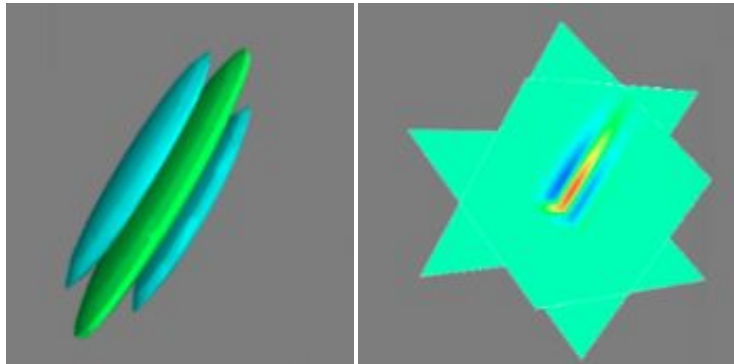


4. Methods: Gabor

Shallow texture representations



a) filter bank
feature descriptor



$$\phi_{\theta, \sigma, \gamma, \lambda, \varphi}(x, y) = \exp\left(-\frac{x'^2 + (\gamma y')^2}{2\sigma^2}\right) \cos\left(2\pi \frac{x'}{\lambda} + \varphi\right)$$

$$\phi_{\theta, \sigma, \gamma, \lambda, \varphi}(x, y, z) = \exp\left[-\frac{1}{2}\left(\frac{x'^2}{\sigma_x^2} + \frac{(\gamma y')^2}{\sigma_y^2} + \frac{(\gamma z')^2}{\sigma_z^2}\right)\right] \cos\left(2\pi \frac{x'}{\lambda} + \varphi\right)$$

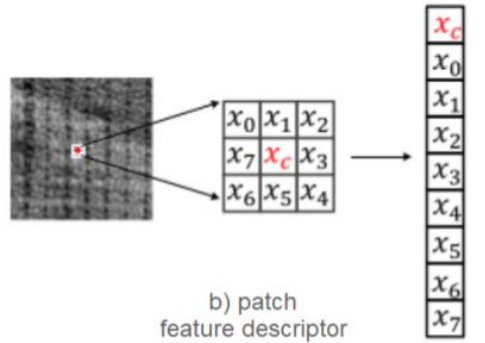
$$\begin{bmatrix} x' \\ y' \\ z' \end{bmatrix} = R(\theta) \begin{bmatrix} x \\ y \\ z \end{bmatrix} \quad R(\theta) = R_x R_y R_z$$

$$R_x = \begin{bmatrix} 1 & 0 & 0 \\ 0 & \cos \theta_x & -\sin \theta_x \\ 0 & \sin \theta_x & \cos \theta_x \end{bmatrix} \quad R_y = \begin{bmatrix} \cos \theta_y & 0 & \sin \theta_y \\ 0 & 1 & 0 \\ -\sin \theta_y & 0 & \cos \theta_y \end{bmatrix} \quad R_z = \begin{bmatrix} 0 & \cos \theta_z & -\sin \theta_z \\ 0 & \sin \theta_z & \cos \theta_z \\ 0 & 0 & 1 \end{bmatrix}$$



4. Methods: Patch

Shallow texture representations

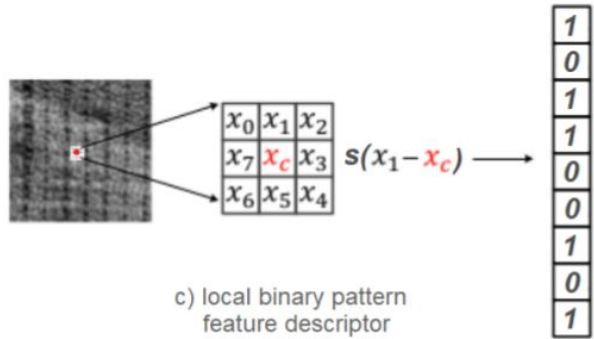




4. Methods: LBP

Shallow texture representations

$$LBP(i, j, k) = \sum_{p=-n/2}^{n/2} \sum_{r=-n/2}^{n/2} \sum_{s=-n/2}^{n/2} s(I(i-p, j-r, k-s) - I(i, j, k)) 2^{prs}$$



$$s(x) = \begin{cases} 1 & x \geq 0 \\ 0 & x < 0 \end{cases}$$

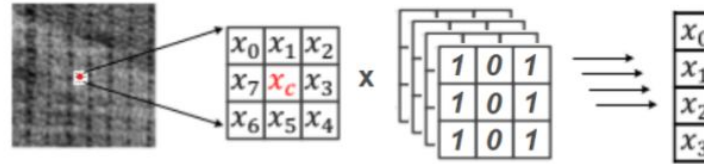
$$ELBP_CI_p(x_c) = s(x_c - \beta)$$

$$ELBP_NI_p(x_c) = \sum_{i=1}^{n^3} s(x_i - \beta_p) 2^i$$

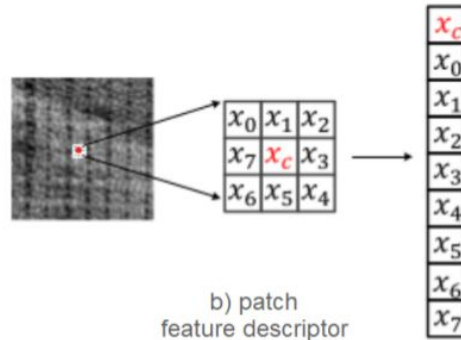


4. Methods: feature descriptors

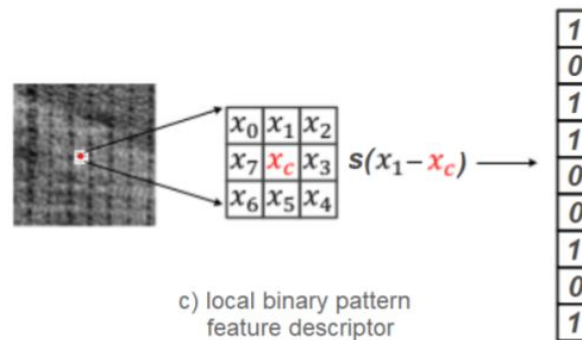
Shallow texture representations



a) filter bank
feature descriptor



b) patch
feature descriptor



c) local binary pattern
feature descriptor



4. Methods

Deep texture representations

- allow for training from limited data
- capable of characterizing variation

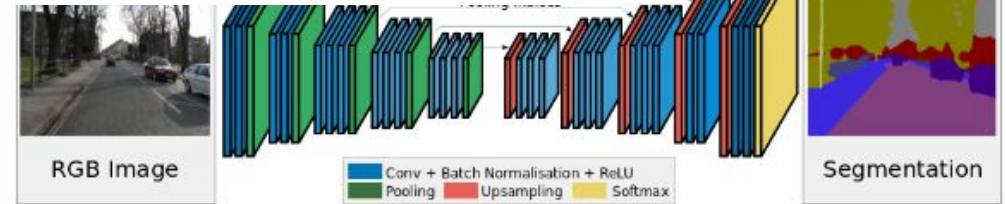
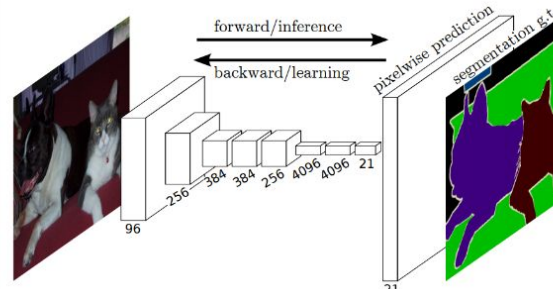
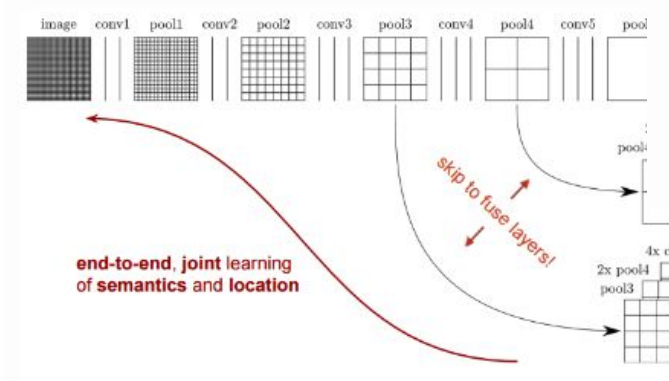
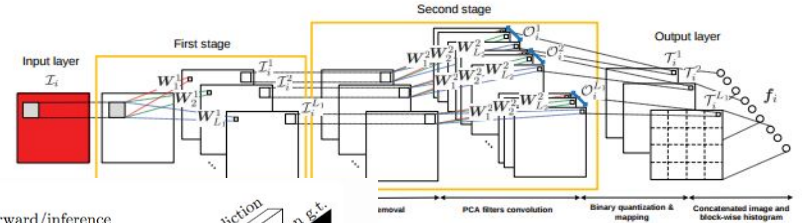
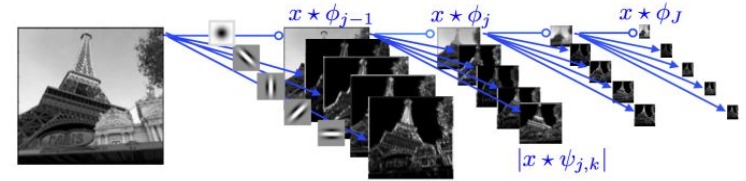


Figure : The SegNet Architecture



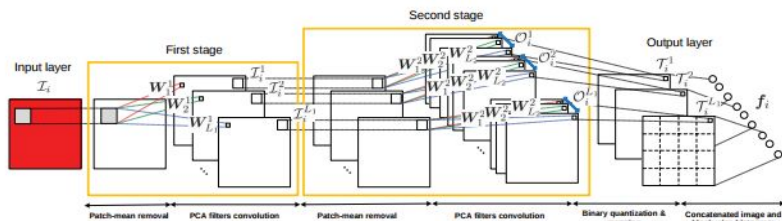
4. Methods

Deep texture representations

1. **transfer learning:** feature extractor
2. **hand-crafted nets:** random projections

PCANet: A Simple Deep Learning Baseline for Image Classification?

Tsung-Han Chan, Kui Jia, Shenghua Gao, Jiwen Lu, Zinan Zeng, and Yi Ma

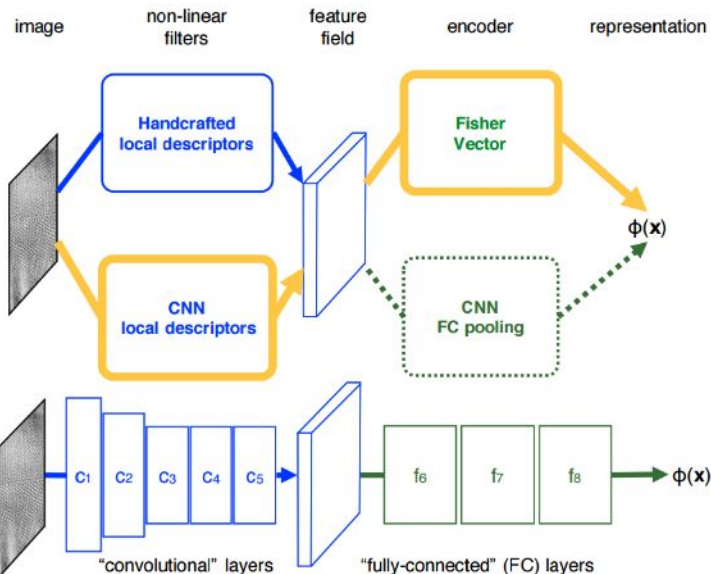


Deep Filter Banks for Texture Recognition and Segmentation

Mircea Cimpoi
University of Oxford

Subhransu Maji
University of Massachusetts, Amherst

Andrea Vedaldi
University of Oxford

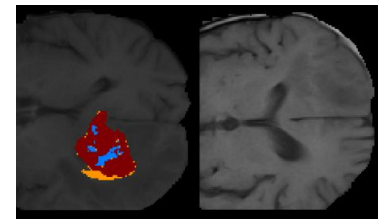
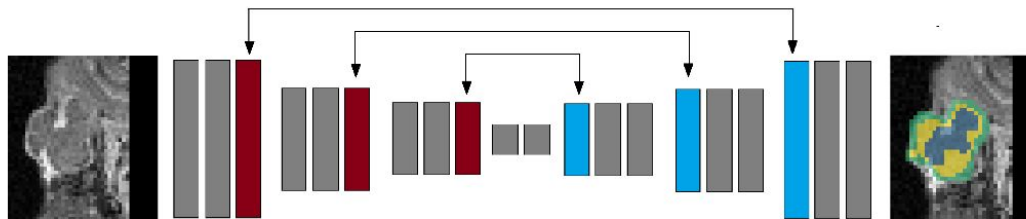




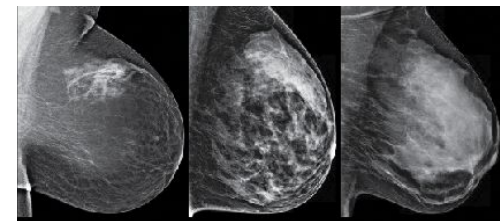
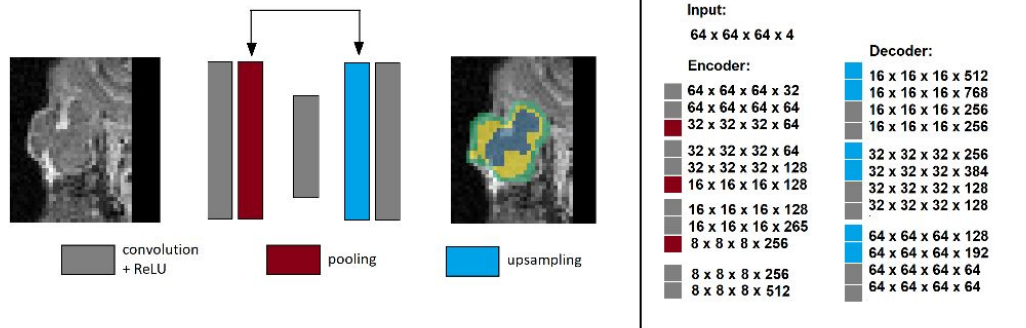
4. Methods

Deep texture representations

T-UNet



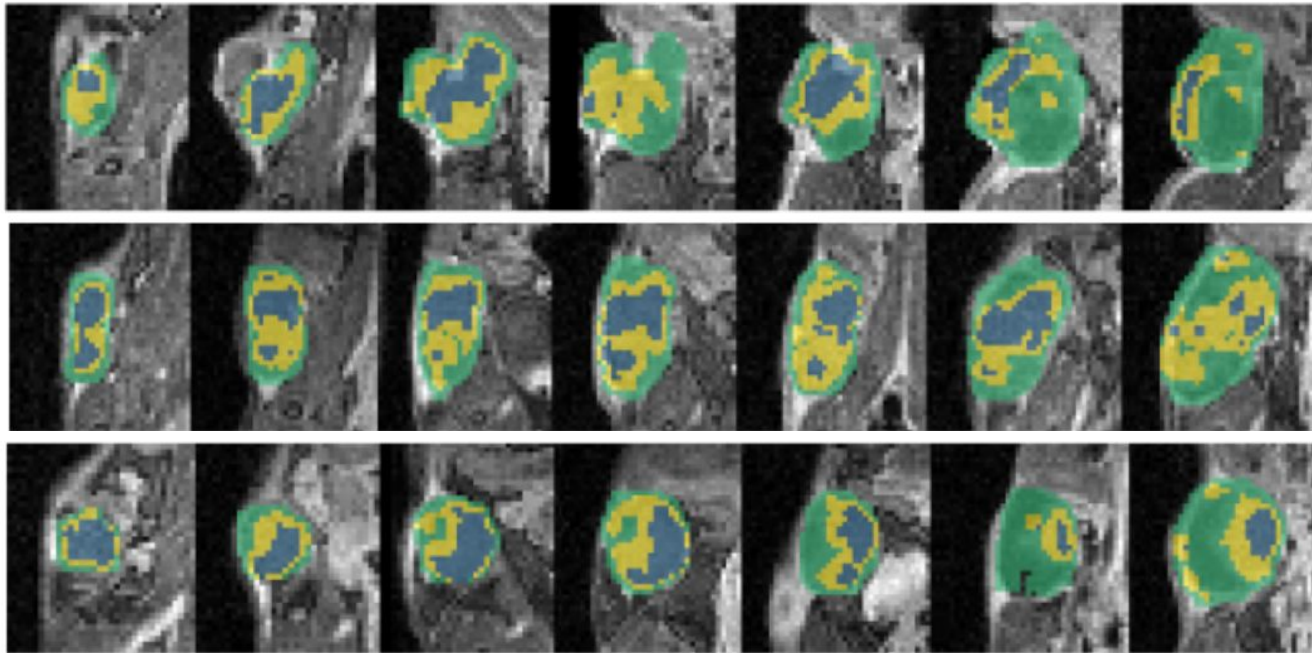
Rand-UNet



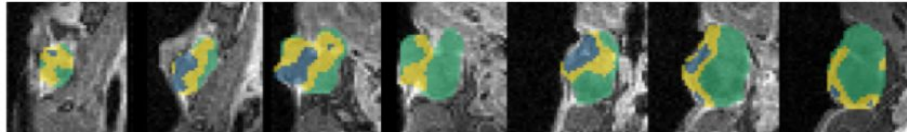


5. Results: segmentations

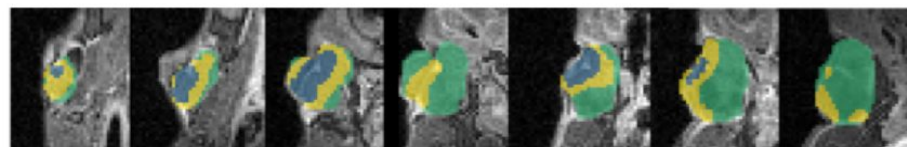
Pre-clinical: tumour progression



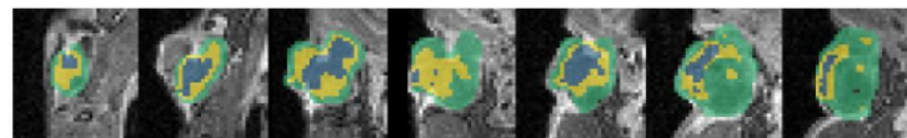
T-UNet+KM



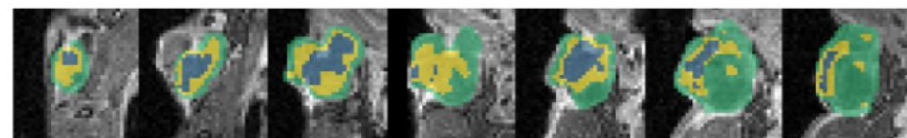
Rand-UNet+KM



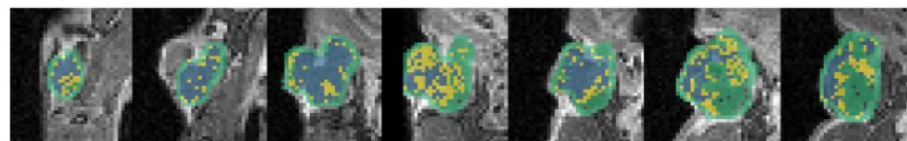
LBP+KM



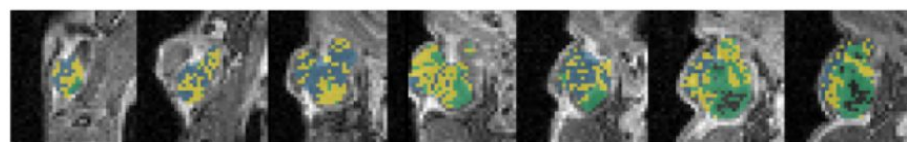
Patch+KM



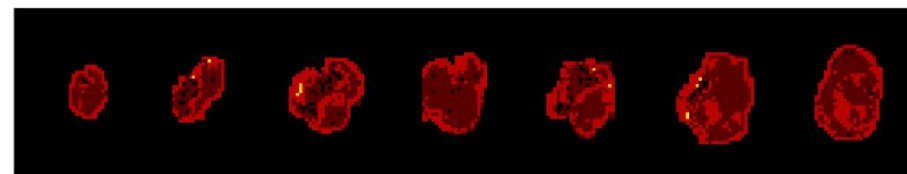
Gabor+KM



Vox+KM



confidence





5. Results: classifications

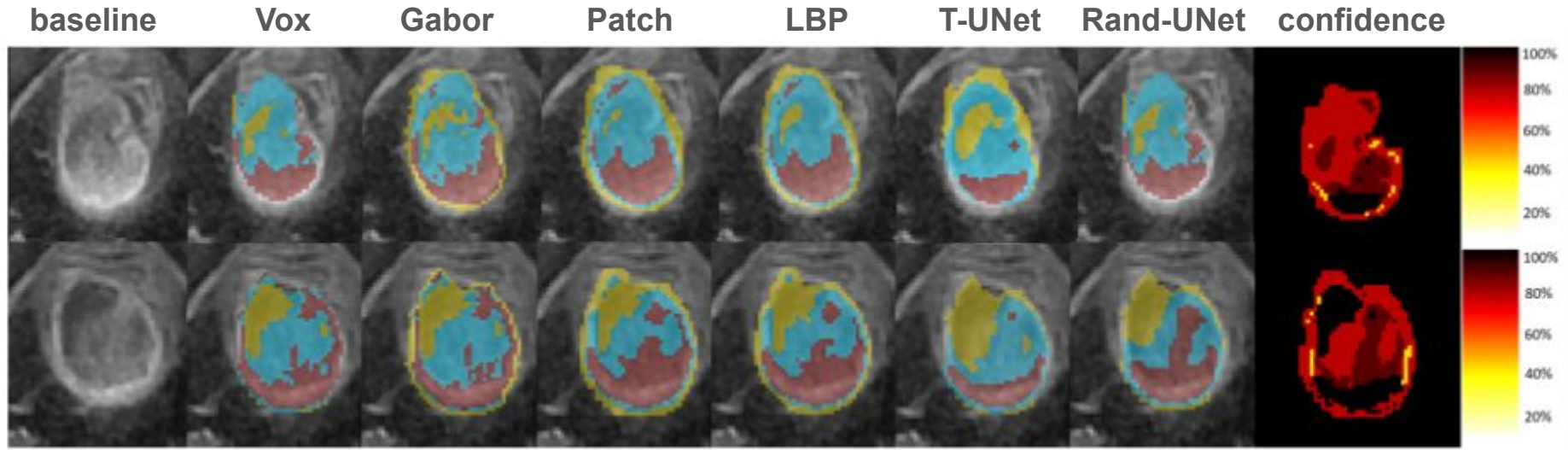
Pre-clinical: tumour progression

	Vox	Filters	Patch	LBP	UNet	RandUNet
	Acc. DICE	Acc. DICE	Acc. DICE	Acc. DICE	Acc. DICE	Acc. DICE
KM	65% 0.599	70% 0.604	70% 0.715	75% 0.723	80% 0.825	75% 0.729
GMM	82.5% 0.516	70% 0.754	70% 0.958	70% 0.963	77.5% 0.783	75% 0.715



5. Results: segmentations

Clinical: therapy response

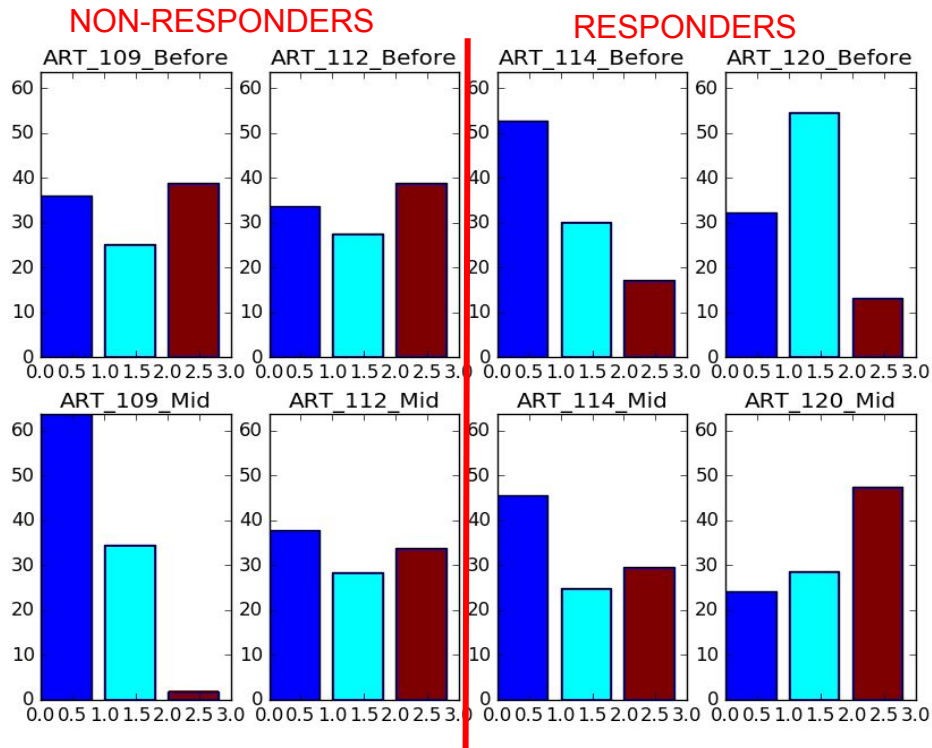
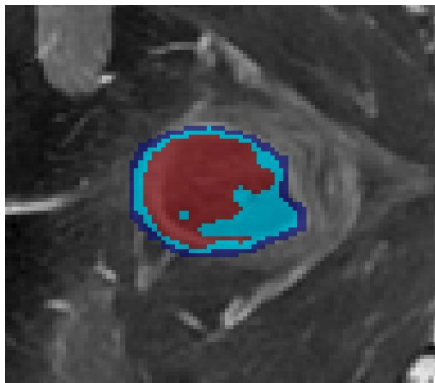
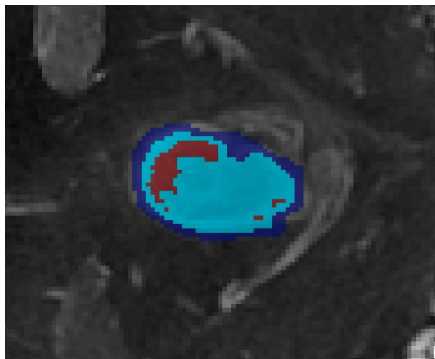




5. Results: classifications

Clinical: therapy response

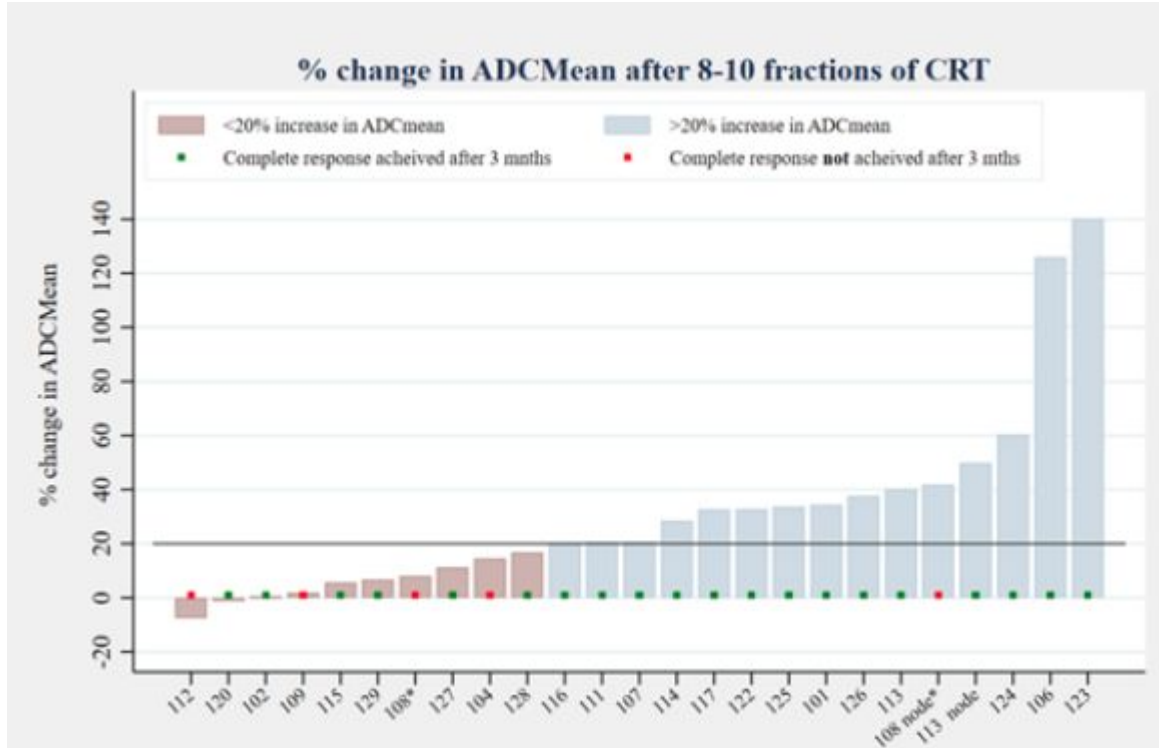
$$J_SAD = \sum_{j=1}^6 \sum_{i=0}^k abs(h_{j,1}(i) - h_{j,2}(i))$$





Part 1: Results

Question 2: Clinical application - therapy assessment



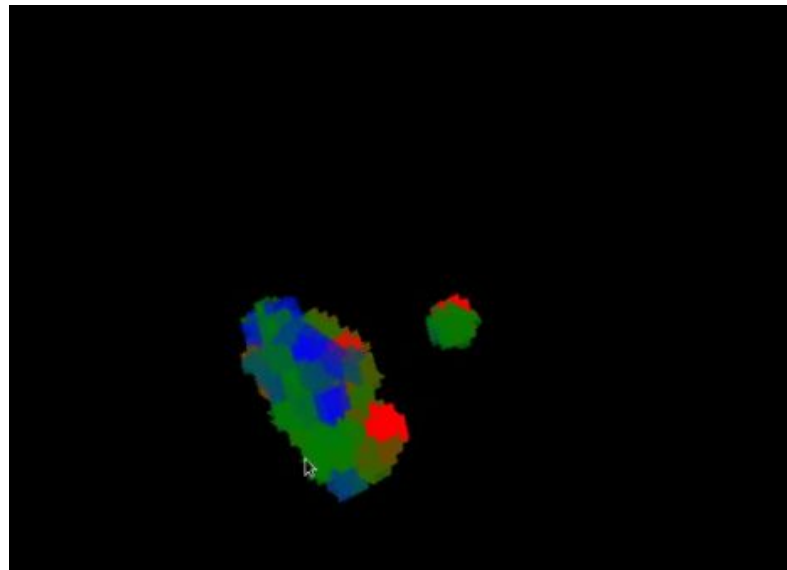


Quantifying Spatial Perfusion Heterogeneity in Tumours from DCE-MRI

Jola Mirecka

(jolanta.mirecka@eng.ox.ac.uk)

- ★ Collaborators: **Bartek Papiez, Benjamin Irving**
- ★ Pre-clinical collaborators: **Pavitra Kannan, Ana Gomes, Veerle Kesermans, Danny Allen, Paul Kinchesh, Sean Smart**
- ★ Clinical collaborators: **Ben George, Maria Hawkins**
- ★ Supervisors: **Mark Jenkinson, Julia Schnabel** and **Michael Chappell, Mike Brady** (advisory)



Questions?



CANCER
RESEARCH
UK

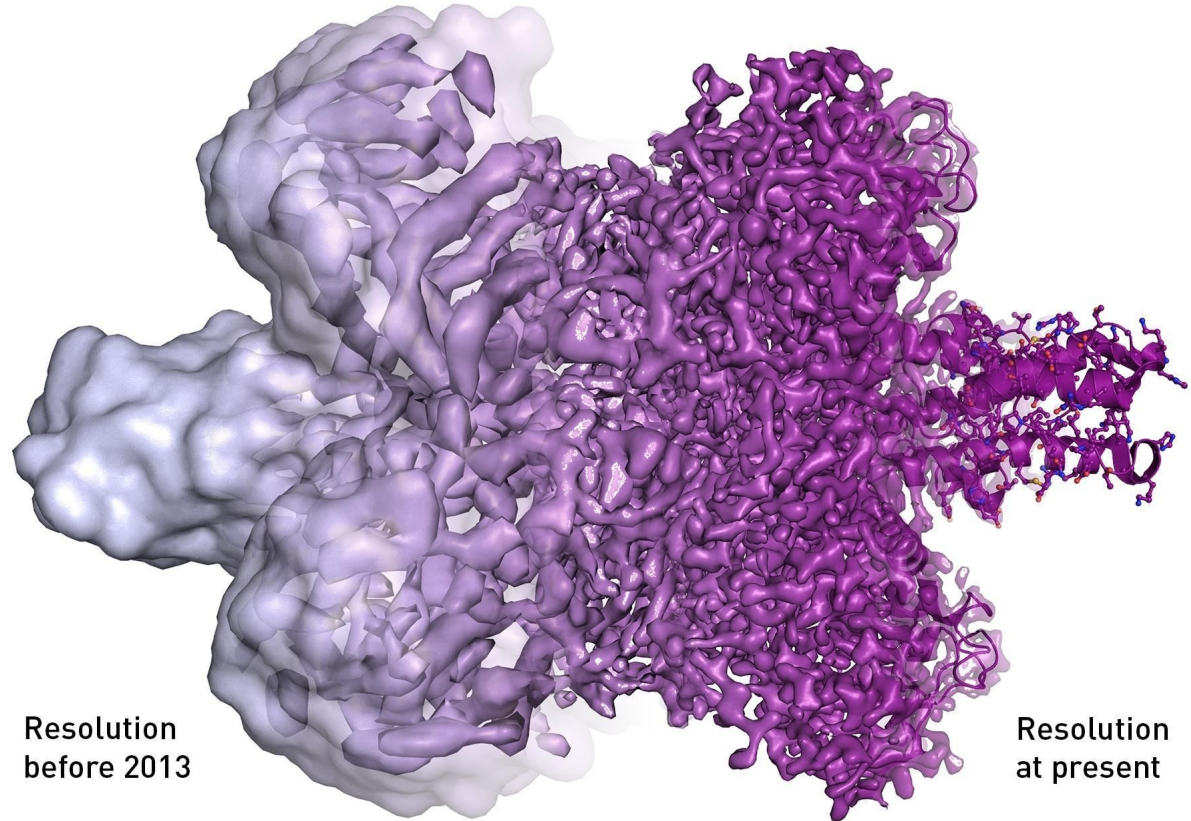




Cryo-EM?

- structure to function
- resolution revolution
- pharmaceutical implications

eBIC facilities



**Resolution
before 2013**

**Resolution
at present**

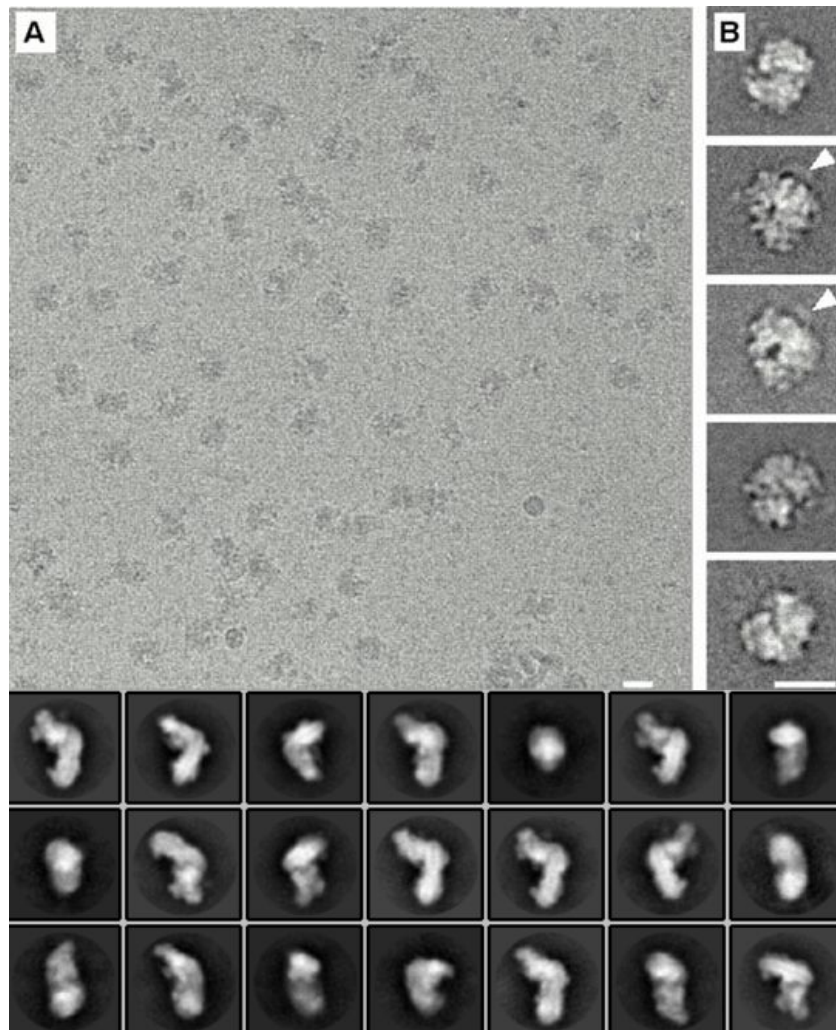
Illustration: ©Martin Högbom/The Royal Swedish Academy of Sciences



Cryo-EM?

Particle picking:

- noisy micrographs
- picking particles
- 2D classification

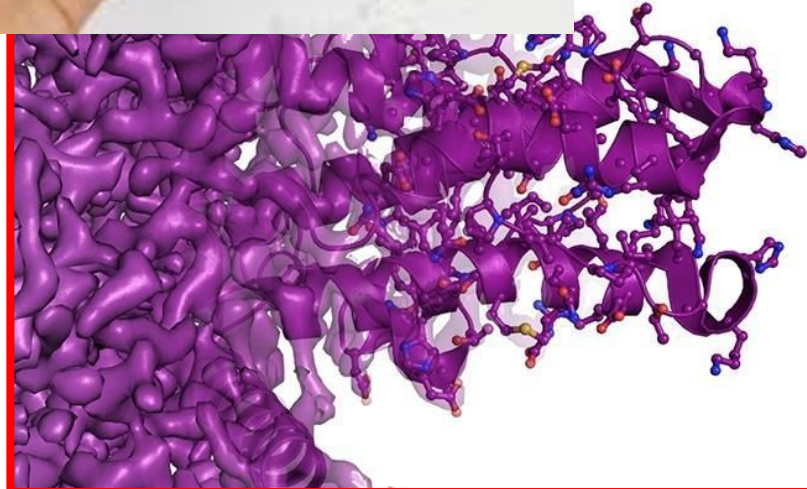




Cryo-EM?

Model building:

- density segmentation
- secondary structure
- side chains



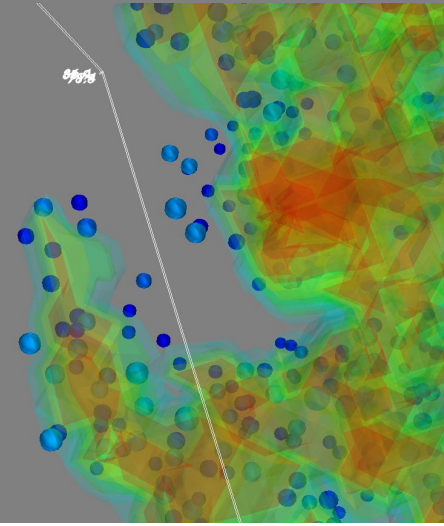
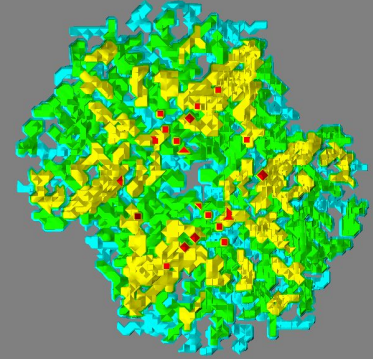
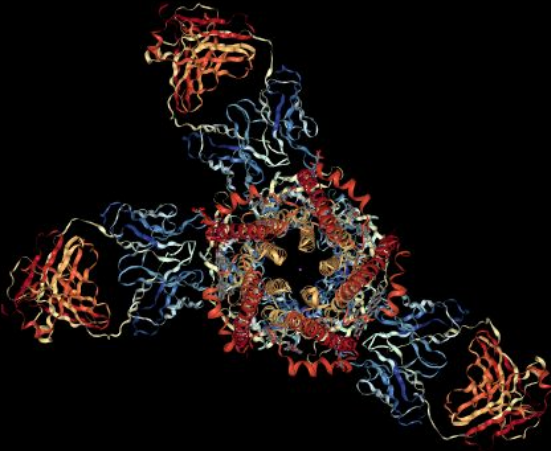
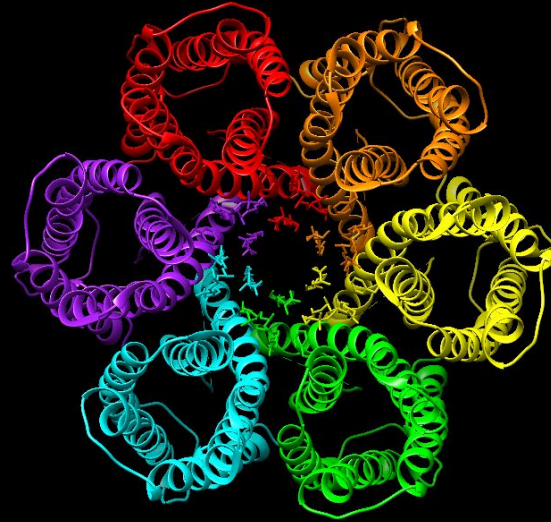


Cryo-EM?

Model building:

- density segmentation
- secondary structure
- side chains

Ribosome: 100 000 atoms





Cryo-EM?

Pipeline automation:

- automatic parameter selection
- data model

File Jobs Autorun I/O Auto-sampling Compute Running

Import
Motion correction
CTF estimation
Manual picking
Auto-picking
Particle extraction
Particle sorting
Subset selection
2D classification
3D initial model
3D classification
3D auto-refine
3D multi-body
Movie refinement
Particle polishing
Mask creation
Join star files
Particle subtraction
Post-processing
Local resolution

Consensus refinement optimiser.star: 001/run_it032_optimiser.star ? Browse
Continue from here: ? Browse
Body STAR file: 3bodies_repairedmasks.star ? Browse
Reconstruct subtracted bodies? Yes ?

Print command Schedule Run now!

Job actions Current job: Give_alias_here Display: ?

Finished jobs	Running jobs	Input to this job
PostProcess/evec1_ftm14_overall/ PostProcess/evec1_ltm14_overall/ PostProcess/multibody_HEAD/ PostProcess/multibody_SSU/ PostProcess/multibody_LSU/ PostProcess/consensus_LSU/ PostProcess/consensus_SSU/ PostProcess/consensus_HEAD/ PostProcess/consensus_overall/ LocalRes/job023/ Refine3D/evec1_ltm14/ Refine3D/evec1_gtm14/ PostProcess/repairedmask_HEAD/	MultiBody/job039/	
	Scheduled jobs	Output from this job

stdout will go here; double-click this window to open stdout in a separate window



Questions?

CCP-EM:

Tom Burnley
Colin Palmer
Agnel Joseph
Martyn Winn

SciML:

Tony Hey
Jeyan Thiyagalingam

