Medical Imaging Informatics

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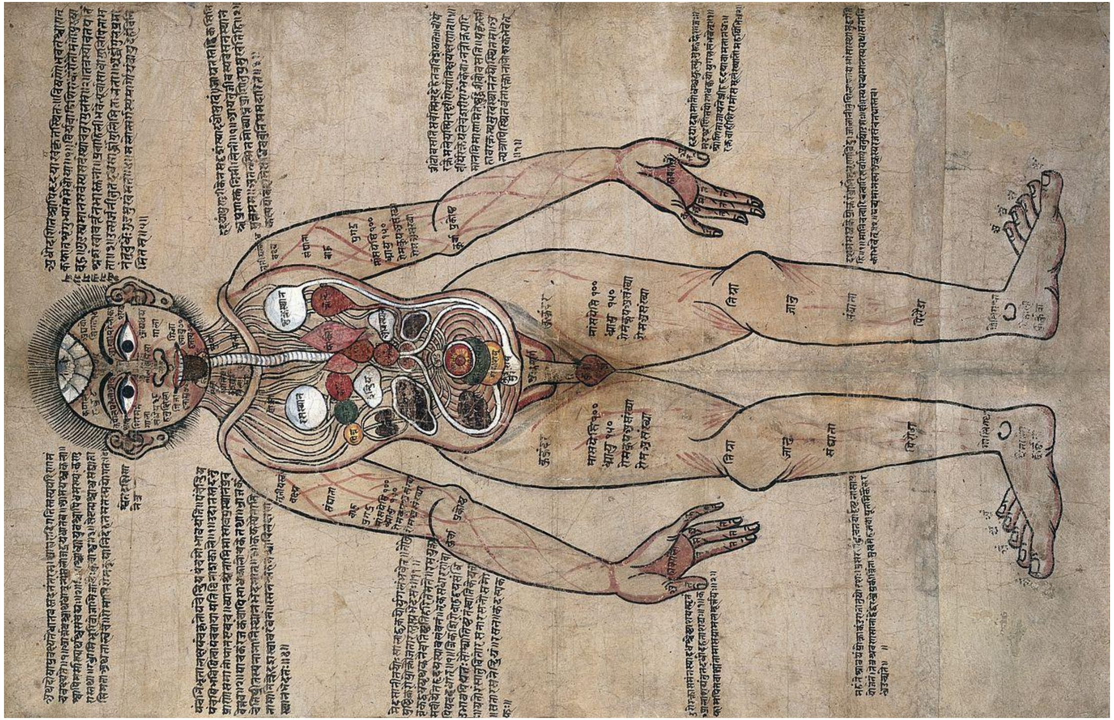
First Nepal Winter School in AI
Kathmandu, Nepal
28 December 2018

Looking Inside The Human Body

The Ayurvedic Man Nepal c. 18th century



https://en.wikipedia.org/wiki/History_of_anatomy

Looking Inside The Human Body

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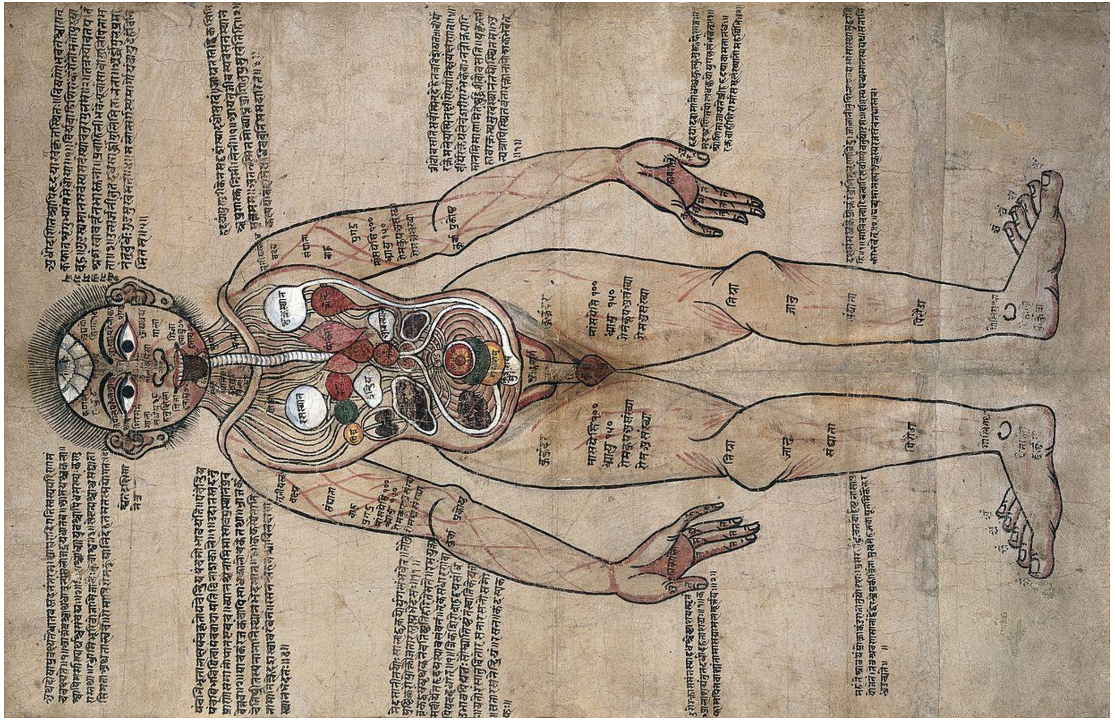

https://en.wikipedia.org/wiki/History_of_anatomy

Vedic Literature

Chinese Medicine

Ancient Egypt

Greek ...

Looking Inside The Human Body

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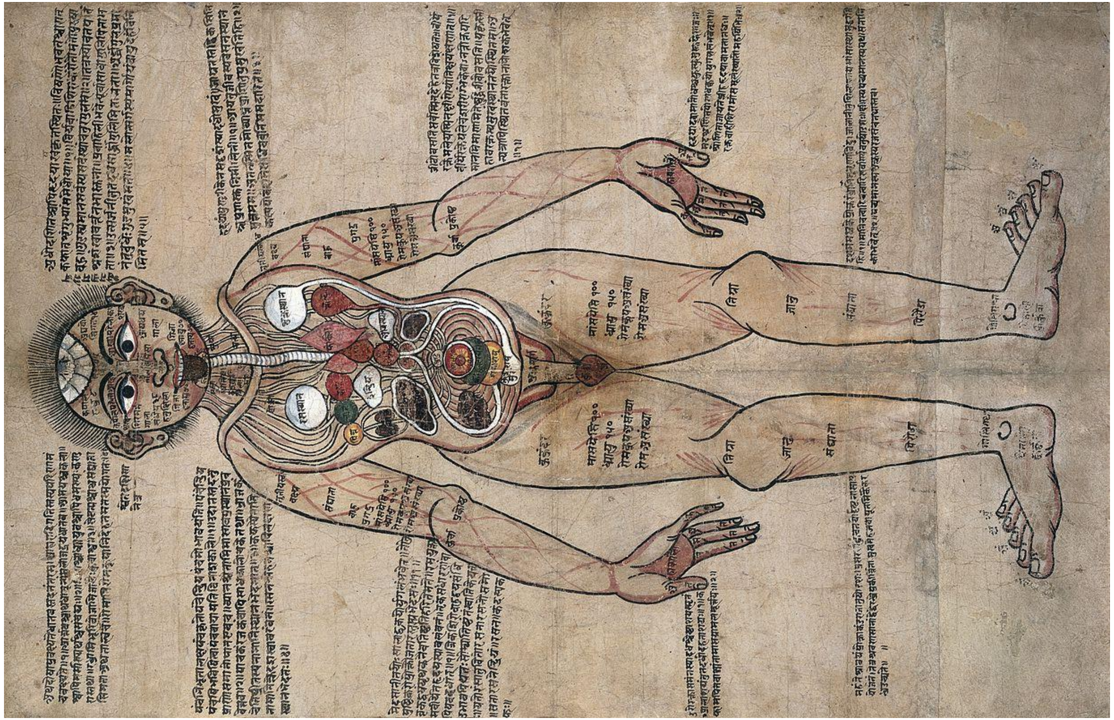

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Vedic Literature

Chinese Medicine

Ancient Egypt

Greek ...

Invasive Approach

Peeking Non-Invasively Into Our Body

The First X-ray Image: Wilhelm Conrad Roentgen, 1895.

“Hand mit Ringen” [Wellcome Library, London/CC BY 4.0]

Peeking Non-Invasively Into Our Body

The First X-ray Image: Wilhelm Conrad Roentgen, 1895.

"Hand mit Ringen" Wellcome Library, London/CC BY 4.0

First Nobel Prize in Physics!

Peeking Non-Invasively Into Our Body

CT-Scan

MRI

PET

Ultrasound

Nicholas Ayache, INRIA. Medical Image Computing for Computational Medicine, ICM 2015.

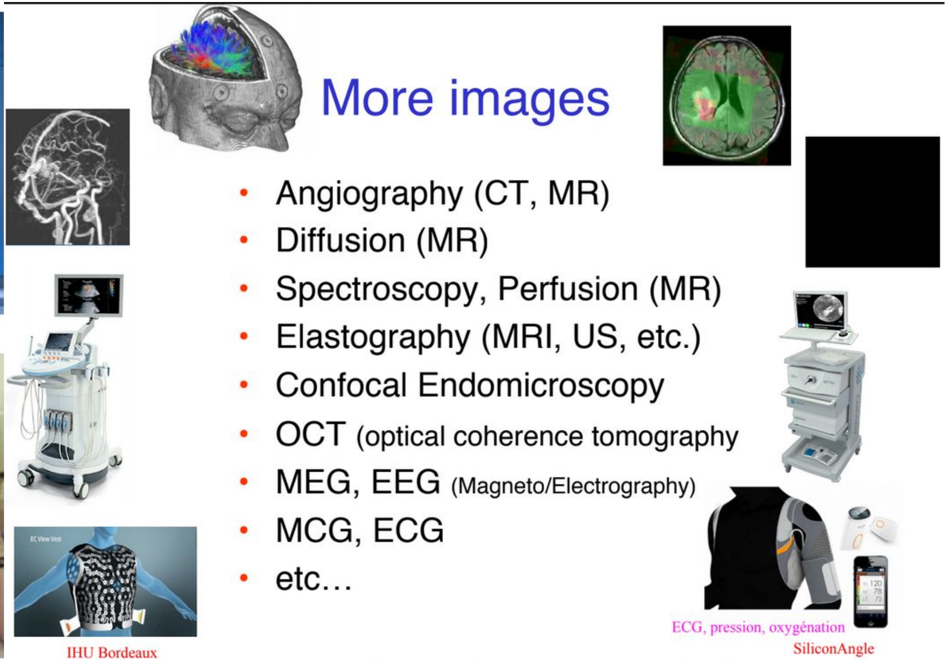
Peeking Non-Invasively Into Our Body

CT-Scan

MRI

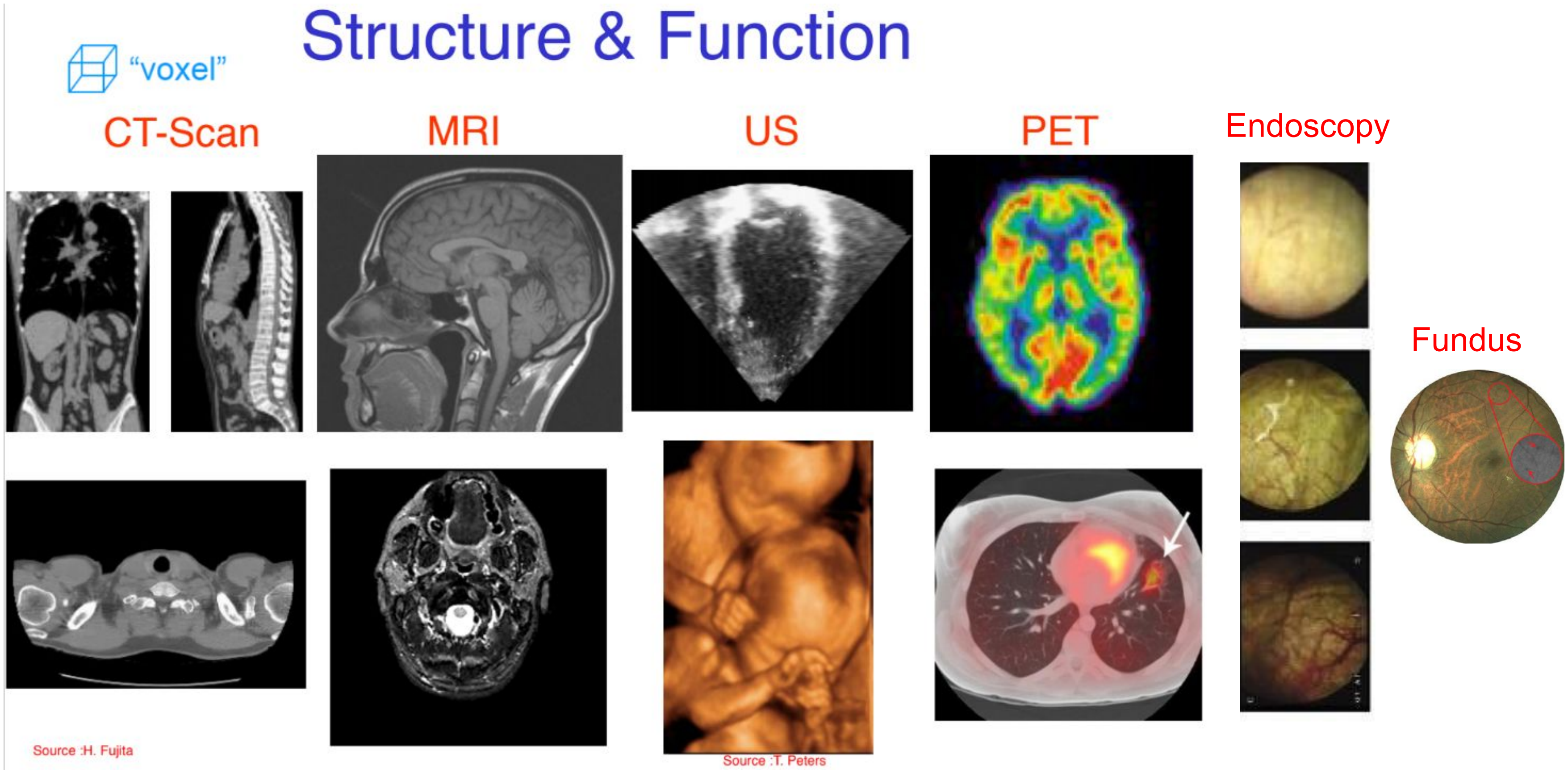
PET

Ultrasound



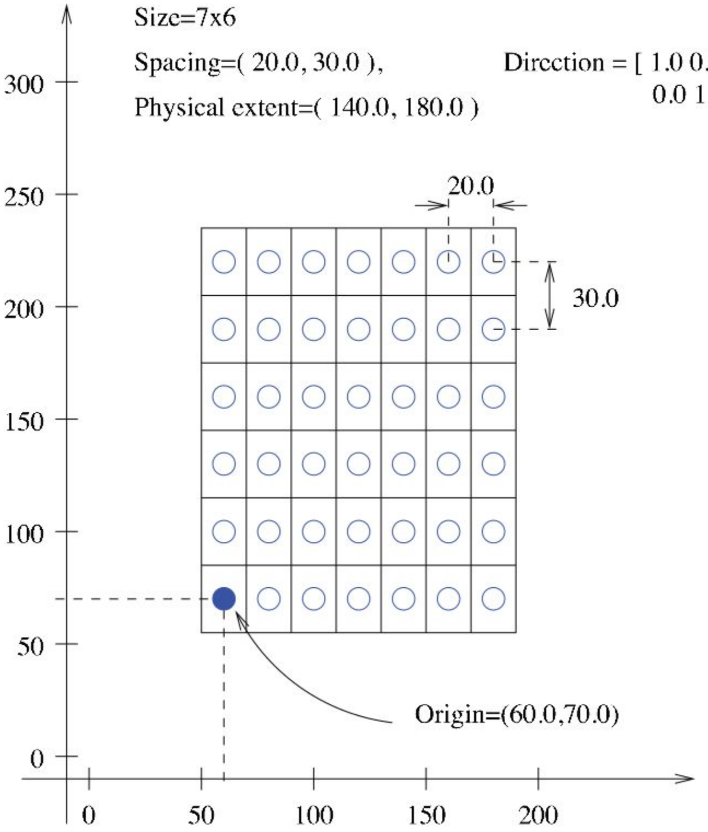
Nicholas Ayache, INRIA. Medical Image Computing for Computational Medicine, ICM 2015.

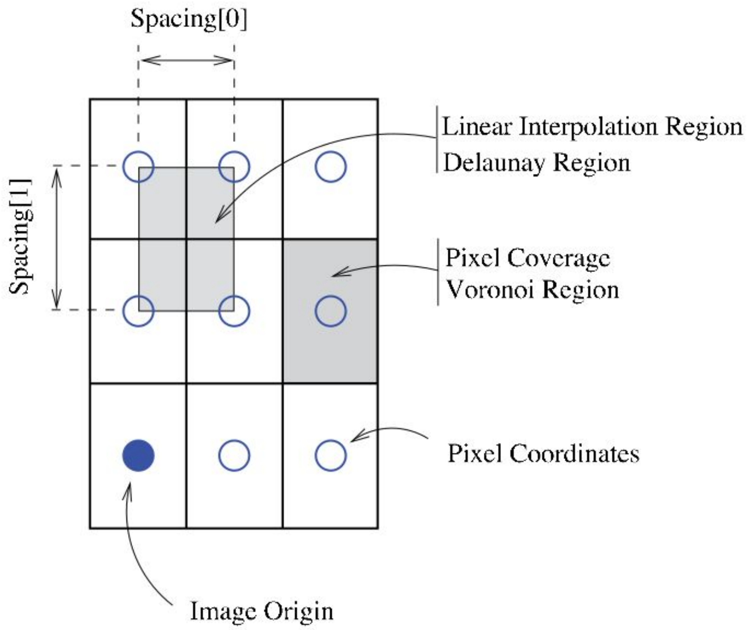
Peeking Non-Invasively Into Our Body



Nicholas Ayache, INRIA. Medical Image Computing for Computational Medicine, ICM 2015.

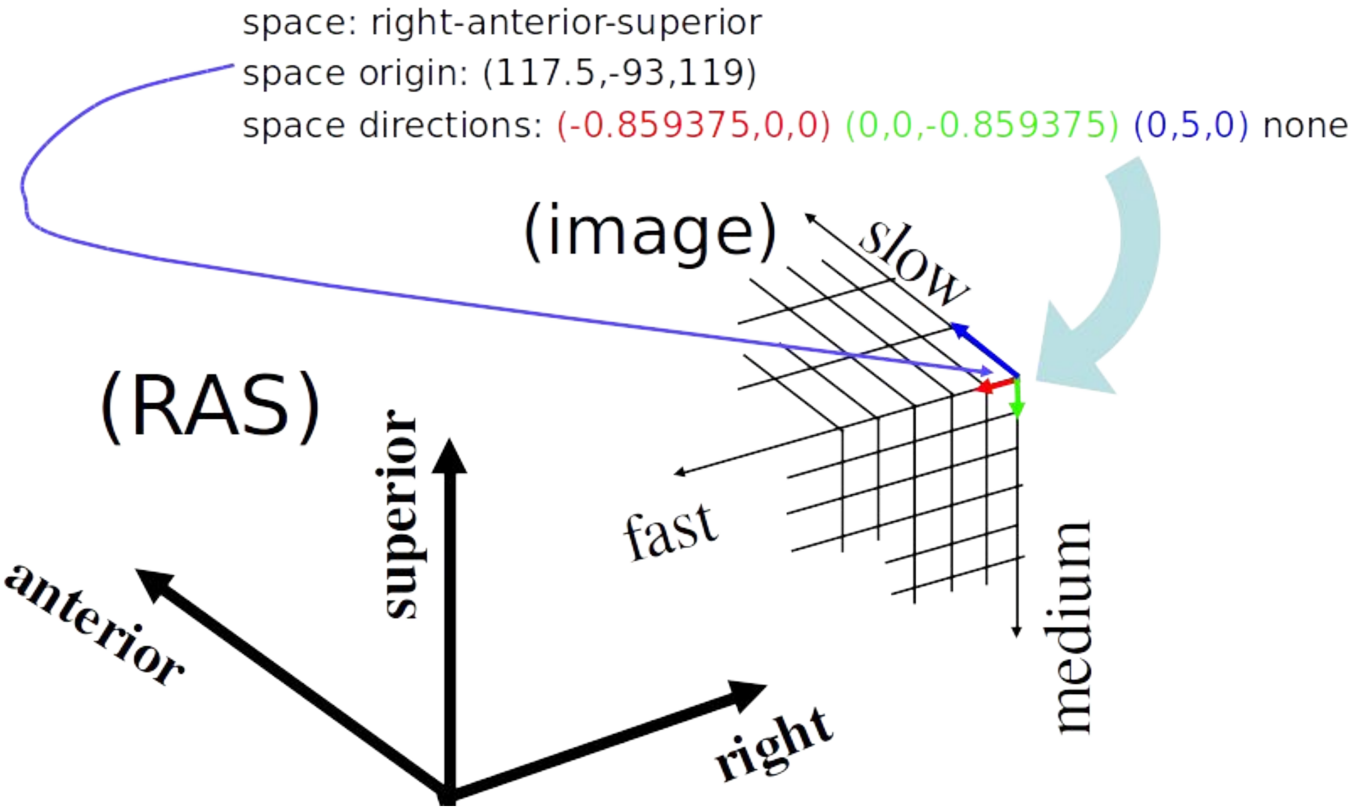
Coordinate System and Units Matter





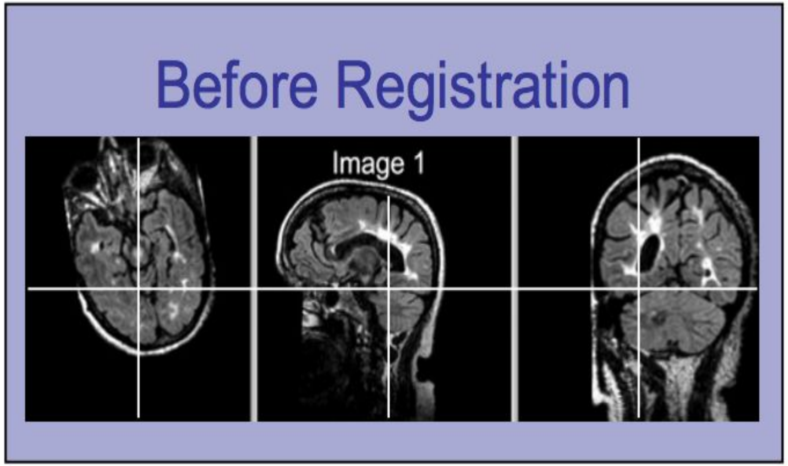
Source: ITK Software Guide

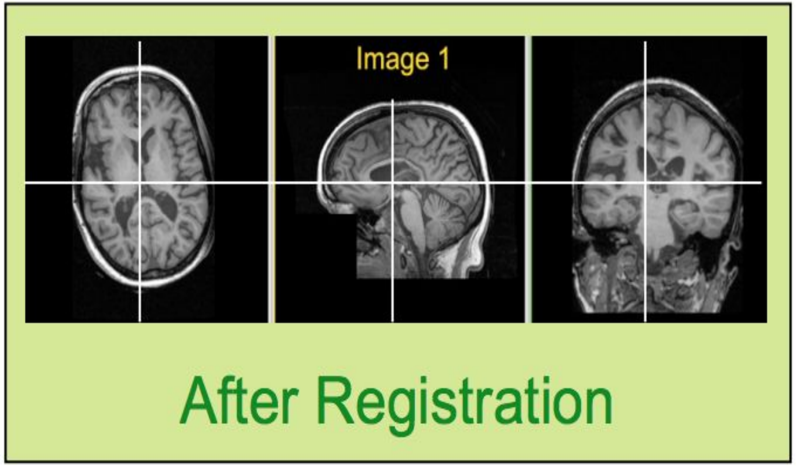
Location, Orientation and Spacing



Source: National Alliance of Medical Image Computing http://na-mic.org

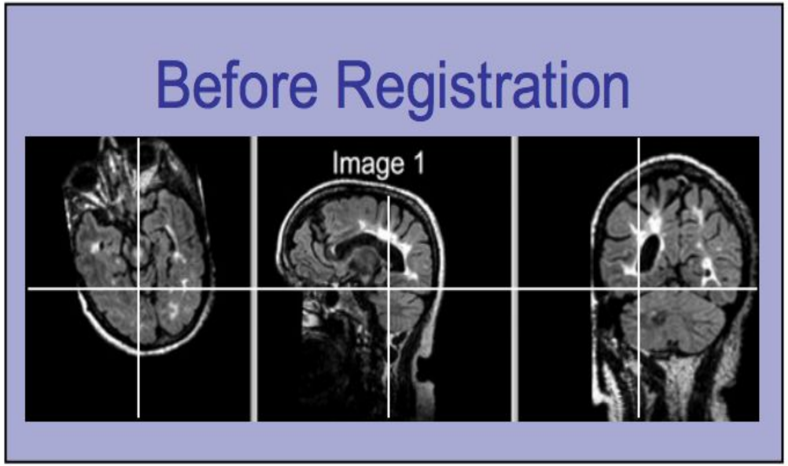
Registration

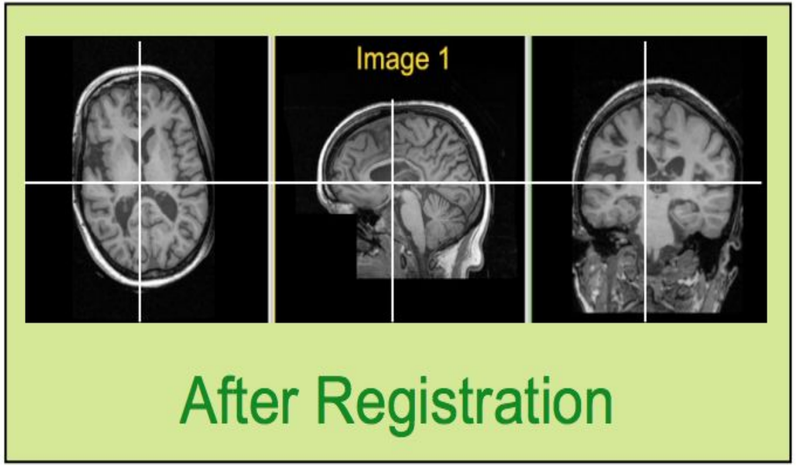


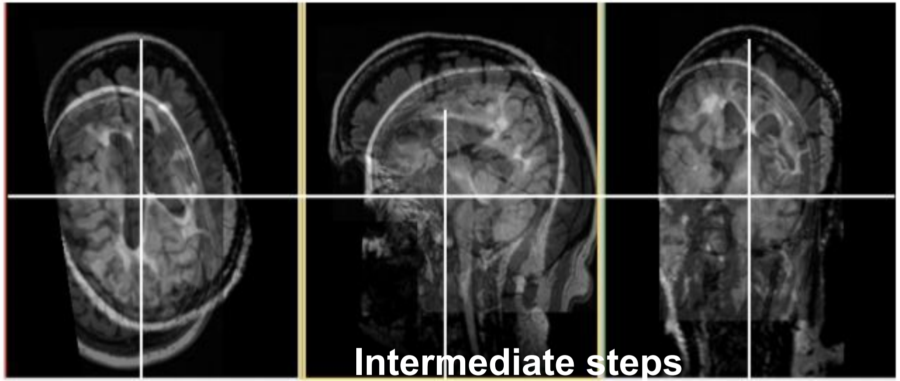


Source: 3Dslicer

Registration

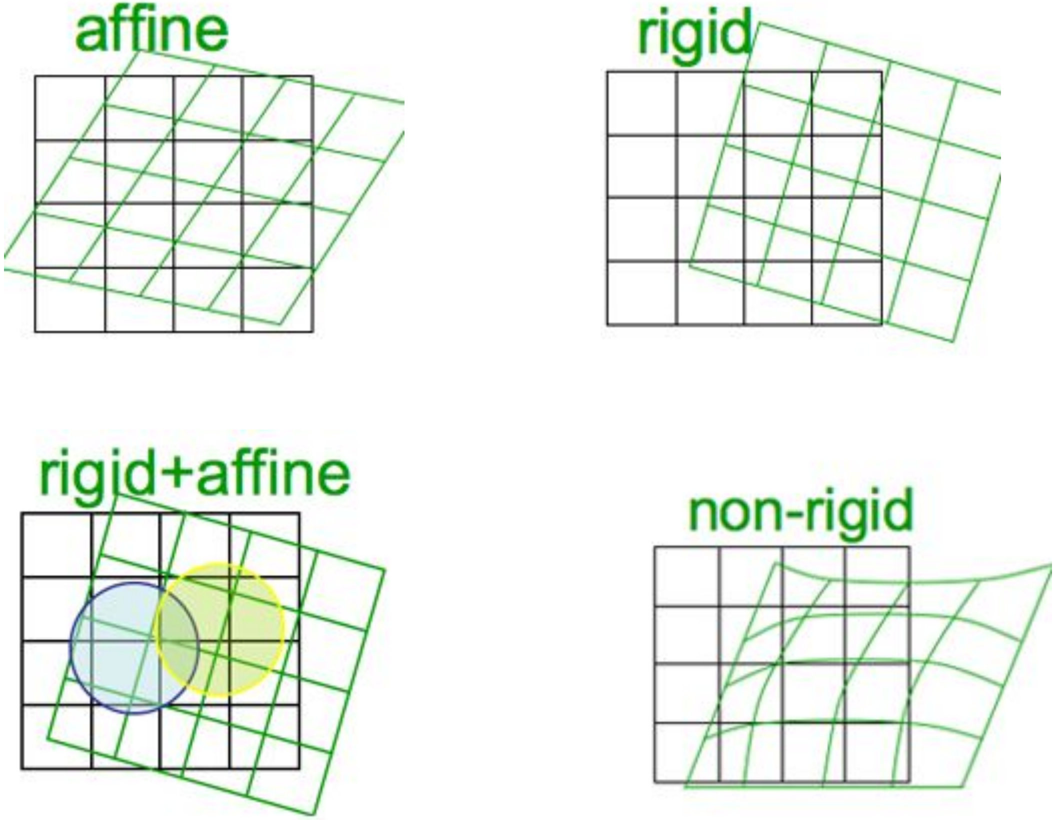






Source: 3Dslicer

Types of Registration



Source: 3Dslicer

Image Formats and Header Information

Format	Header	Extension	Data types
Analyze	Fixed-length: 348 byte binary format	.img and .hdr	Unsigned integer (8-bit), signed integer (16-, 32-bit), float (32-, 64-bit), complex (64-bit)
Nifti	Fixed-length: 352 byte binary format[a] (348 byte in the case of data stored as .img and .hdr)	.nii	Signed and unsigned integer (from 8- to 64-bit), float (from 32- to 128-bit), complex (from 64- to 256-bit)
Minc	Extensible binary format	.mnc	Signed and unsigned integer (from 8- to 32-bit), float (32-, 64-bit), complex (32-, 64-bit)
Dicom	Variable length binary format	.dcm	Signed and unsigned integer, (8-, 16-bit; 32-bit only allowed for radiotherapy dose), float not supported

Not all the software support all the specified data types. Dicom, Analyze, and Nifti support color RGB 24-bit; Nifti also supports RGBA 32-bit (RGB plus an alpha-channel)

Source: Larobina et al. Medical Image File Formats. J of Digital Imaging, 2013.

Medical Imaging Informatics

Extract clinically pertinent information for:

Diagnosis

Prognosis

Therapy planning

Overview

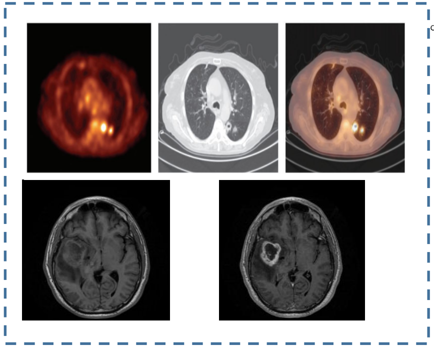
Medical imaging → Image processing → Machine learning → Outcome

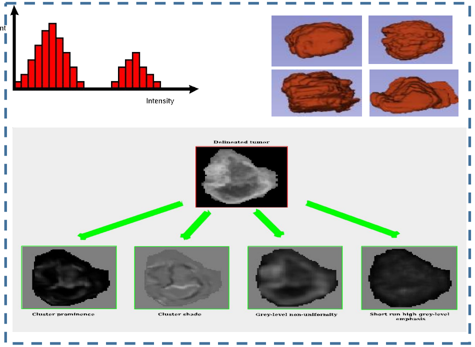
Medical imaging
- Pathology
- Imaging

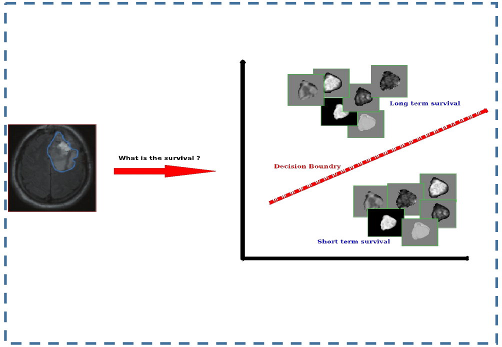
Image processing
- Pre-processing
- Radiomics feature extraction

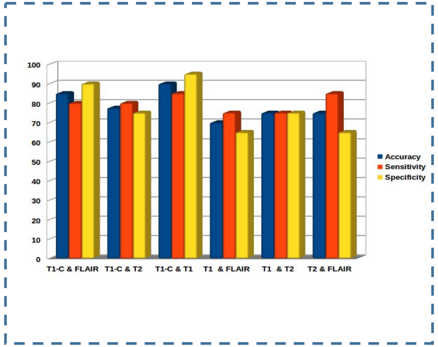
Machine learning
- Predictive and Prognostic model building

Outcome
- Decision support

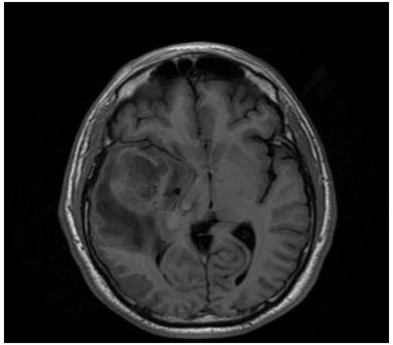




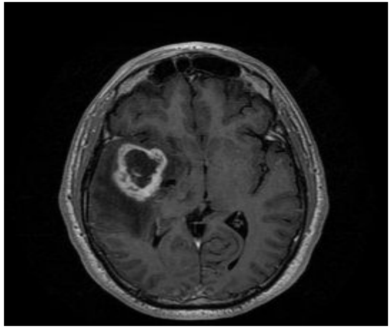




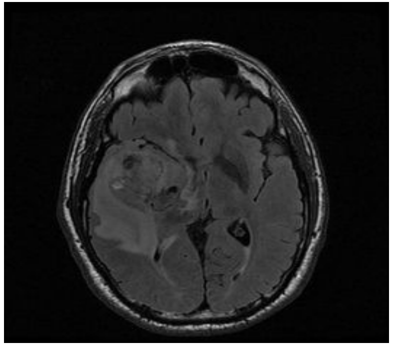
Multimodal Images: Complementary Information



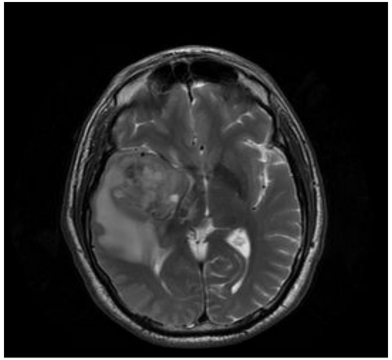
T1 pre-contrast



T1 post-contrast



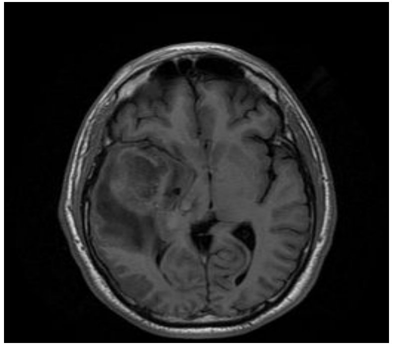
FLAIR



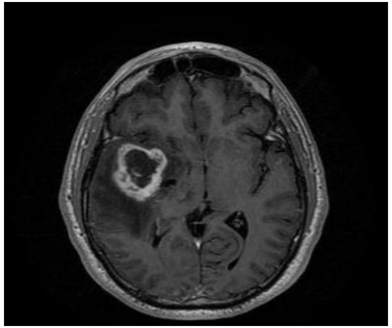
T2

What is this imaging ?

Multimodal Images: Complementary Information

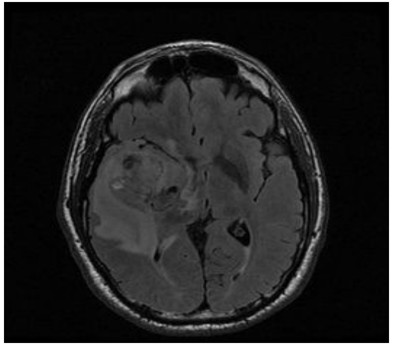


T1 pre-contrast

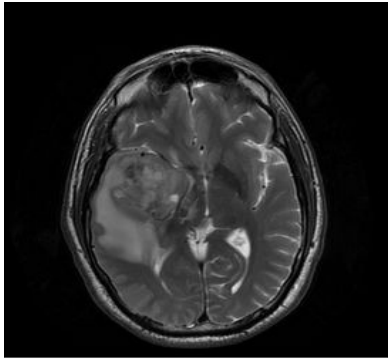


T1 post-contrast

Brain Tumor

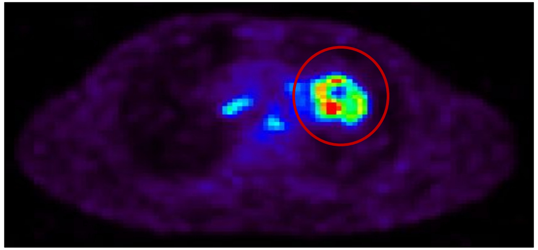


FLAIR



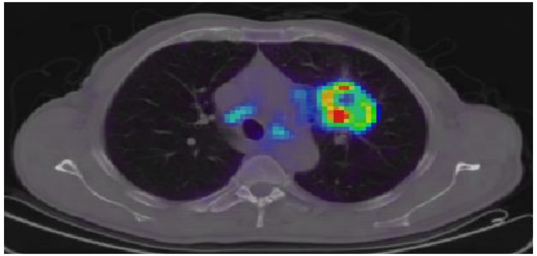
T2

Multimodal Images: Imaging Lung Cancer



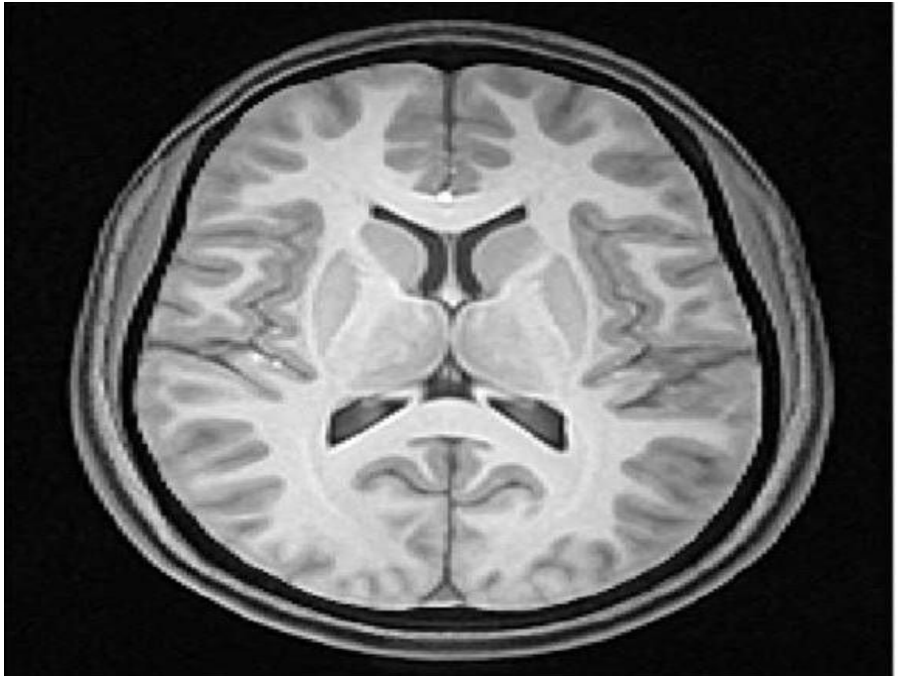
Positron emission tomography (PET)

Computed Tomography (CT)



Fusion PET/CT

Image processing: Bias Field Inhomogeneity Correction



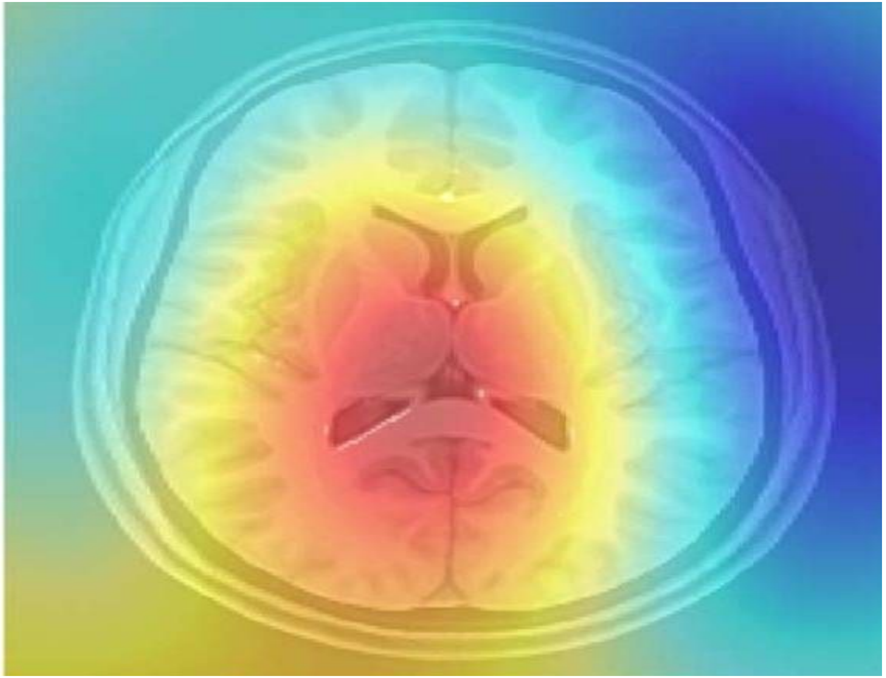


Image processing: MRI Multimodal 3D Registration

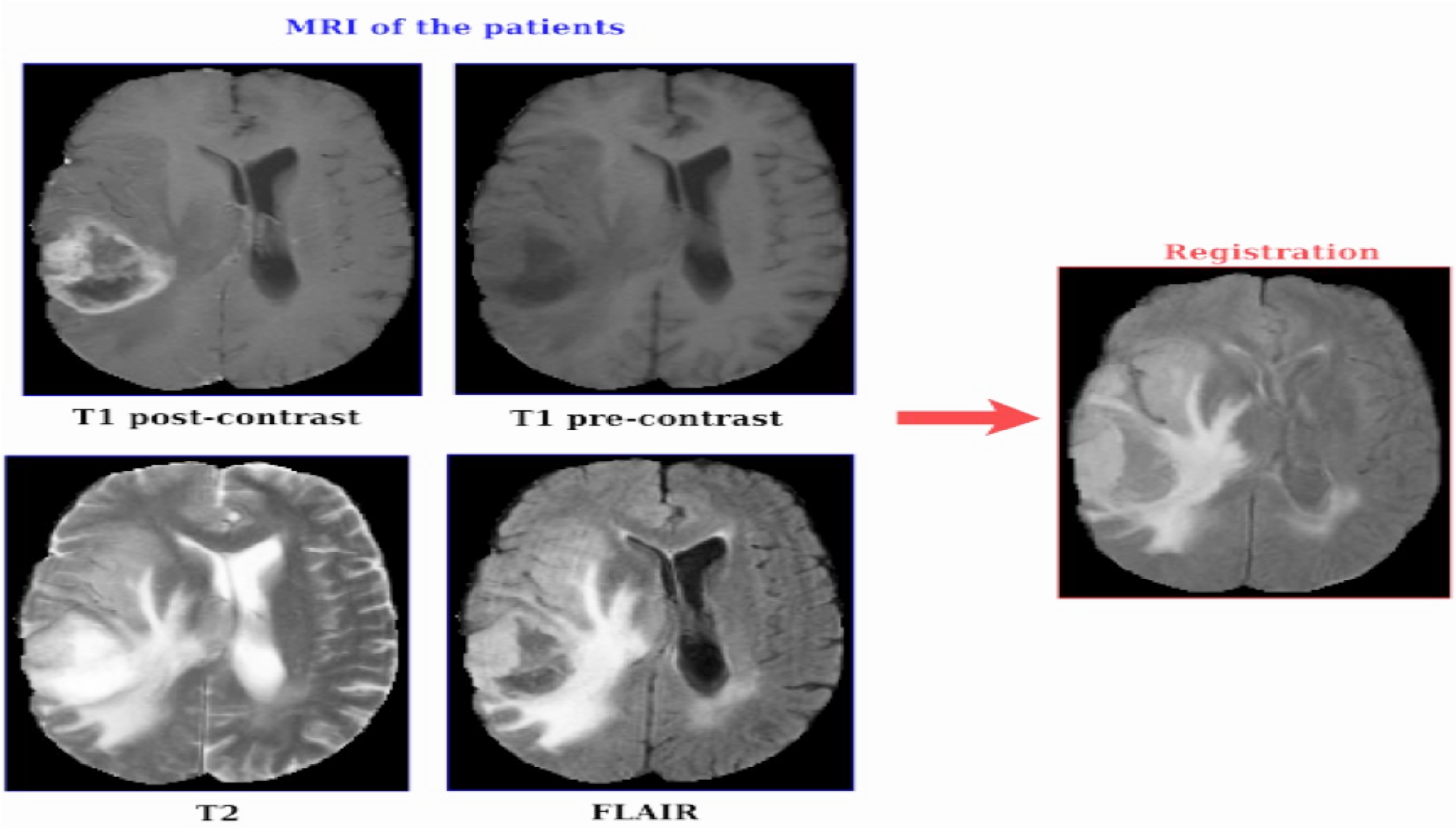


Image processing: PET/CT 3D Registration (Multi-modal)

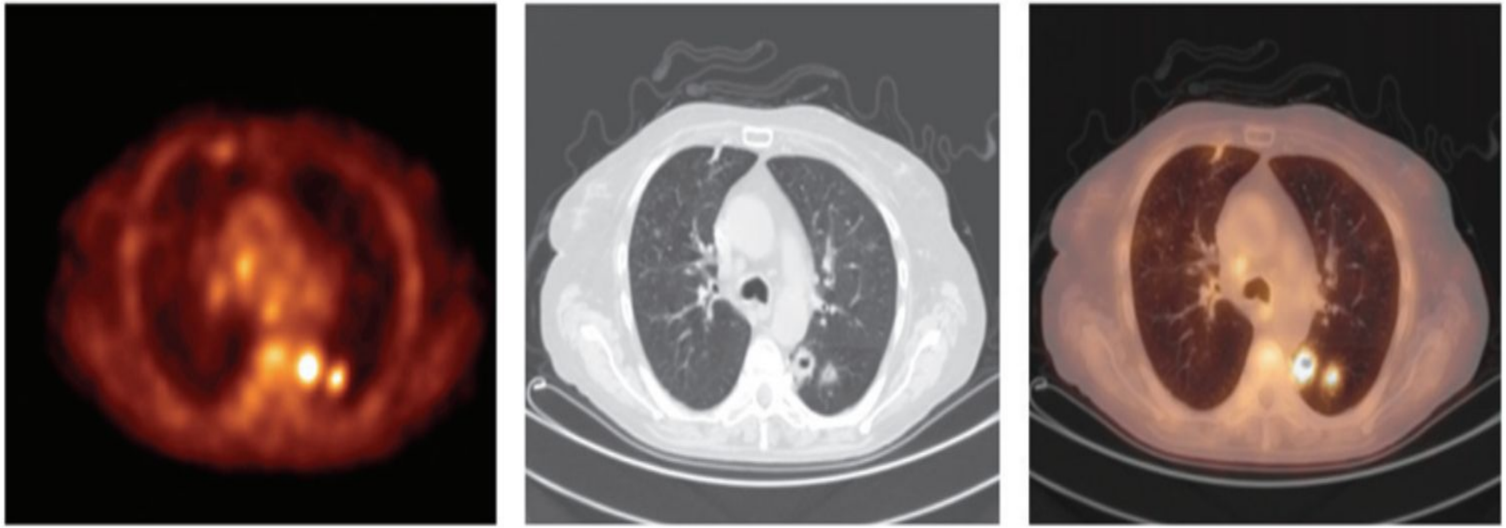
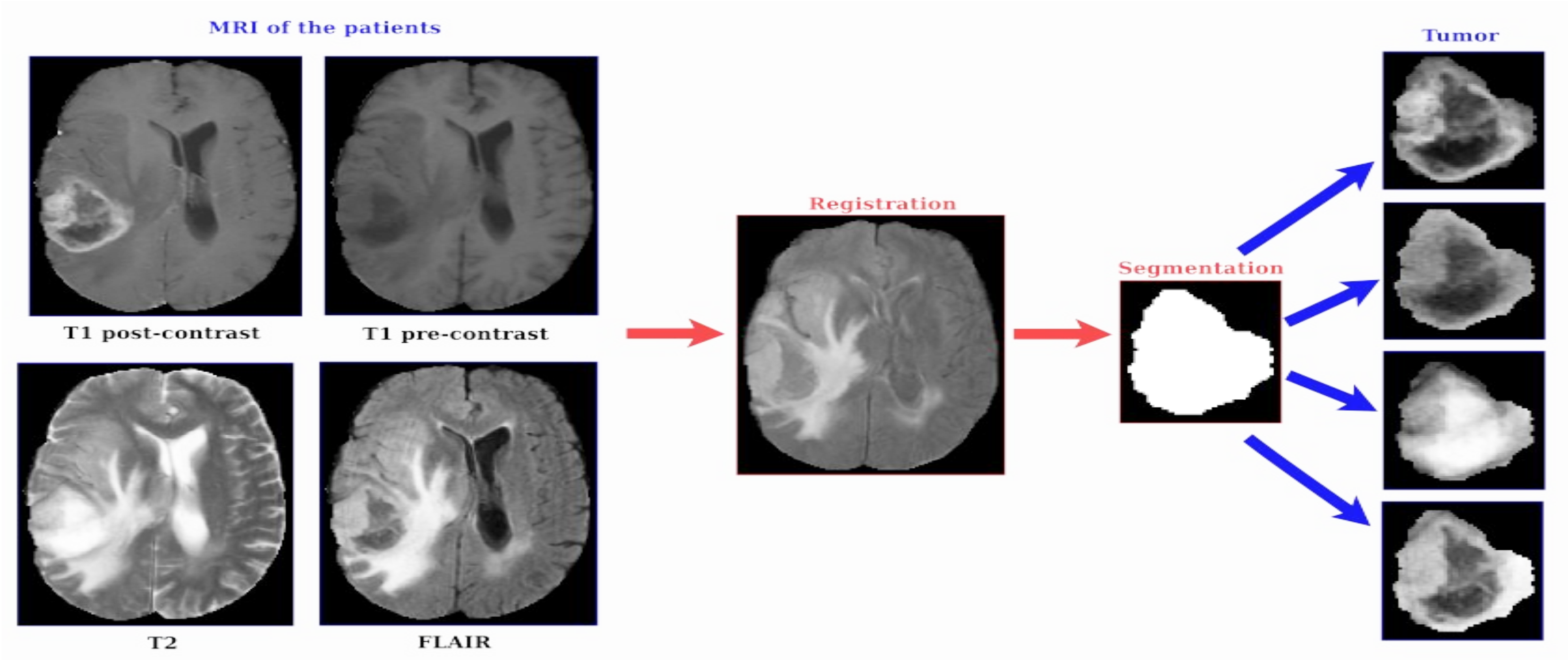
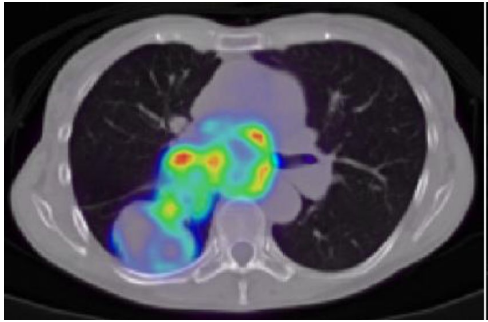


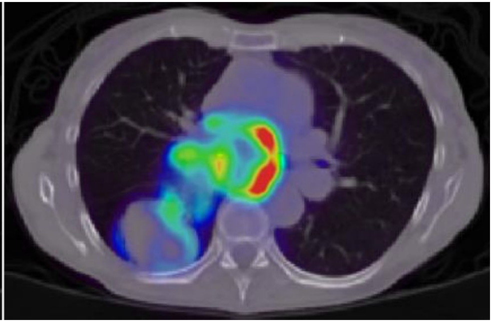
Image processing: Segmentation



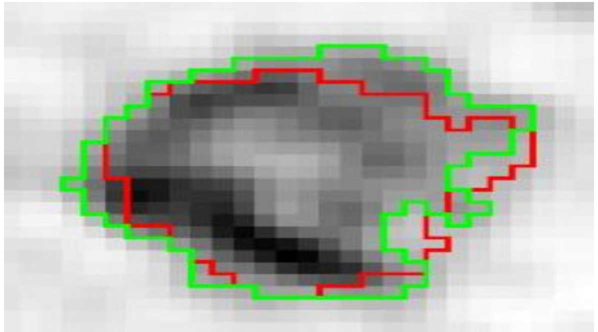
Challenges and issues: robustness/reliability



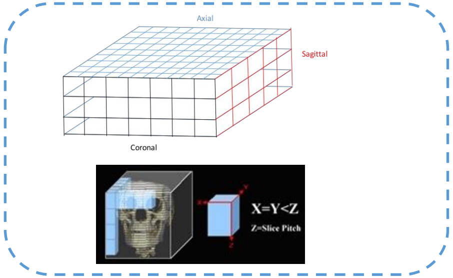
Test PET/CT



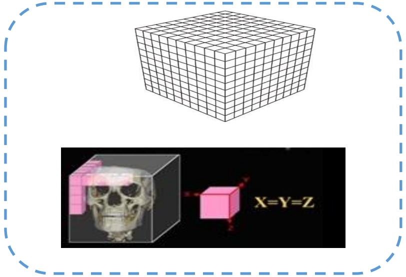
Re-test PET/CT



Tumor delineation



Anisotropic voxels



Isotropic voxels

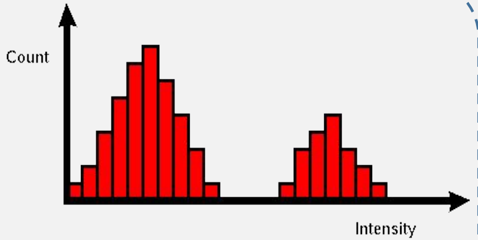
Reconstruction algorithm, ..

https://www.youtube.com/watch?v=Tq980GEVP0Y&t=2s

Radiomics

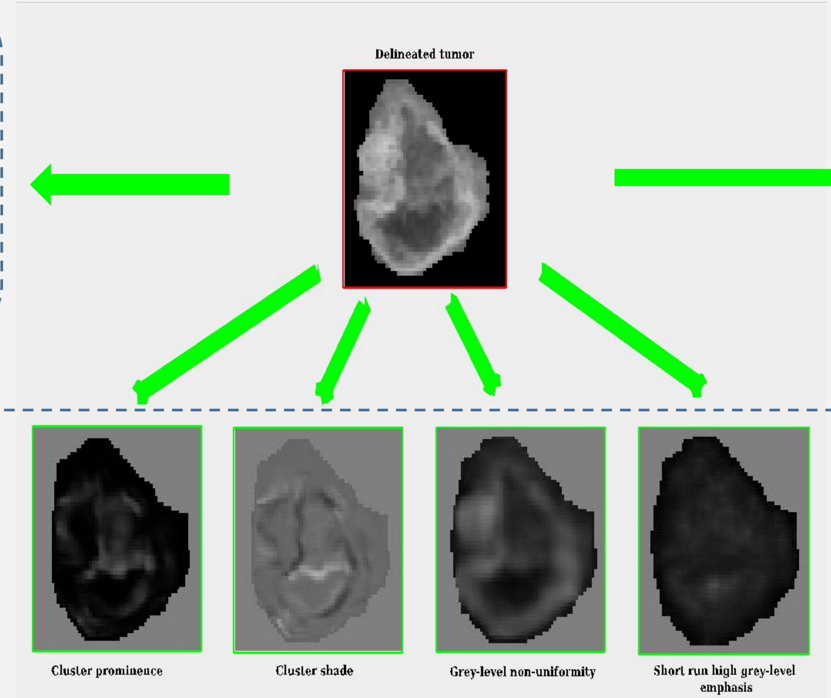
Radiomics is a field of medical study that aims to extract large amount of quantitative features from medical images using data-characterisation algorithms.

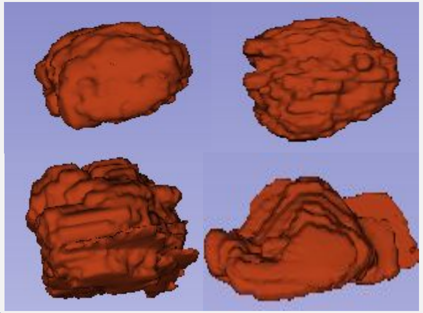
Radiomics



Histogram

First order statistics





3D Shape complexity

3D heterogeneity textural features

Second and higher order statistics

Image Biomarker Standardization Initiative (ISBI)

20 research groups, 8 countries

Cardiff University
Philip Whybra, Emiliano Spezi

Dana Farber Cancer Institute and **Brigham and Women's Hospital, Harvard University**
Andriy Fedorov, Hugo Aerts

Gemelli ART, Università Cattolica del Sacro Cuore
Jacopo Lenkowicz, Luca Boldrini, Nicola Dinapoli, Vincenzo Valentini

German Cancer Research Center (DKFZ)
Michael Götz, Nils Gählert, Fabian Isensee, Klaus H. Maier-Hein

INSERM Brest, University of Brest
Marie-Charlotte Desseroit, Taman Upadhaya, Mathieu Hatt

The Netherlands Cancer Institute (NKI)
Joost van Griethuysen, Cuong Viet Dinh, Uulke van der Heide

Universitätsklinikum Tübingen, Eberhard Karls University Tübingen
Jairo Socarras Fernandez, Daniela Thorwarth

University Hospital Zürich, University of Zürich
Marta Bogowicz, Stephanie Tanadini-Lang, Matthias Guckenberger

Leiden University Medical Center
Floris H.P. van Velden

MAASTRO clinic, Maastricht University
Ralph T.H. Leijenaar, Philippe Lambin

McGill University
Martin Vallières, Issam El Naqa

Memorial Sloan Kettering Cancer Center
Aditya Apte

Moffitt Cancer Center
Mahmoud A. Abdalah, Robert Gillies

OncoRay – National Center for Radiation Research in Oncology and **NCT Dresden**
Alex Zwanenburg, Stefan Leger, Esther Troost, Christian Richter, Steffen Löck

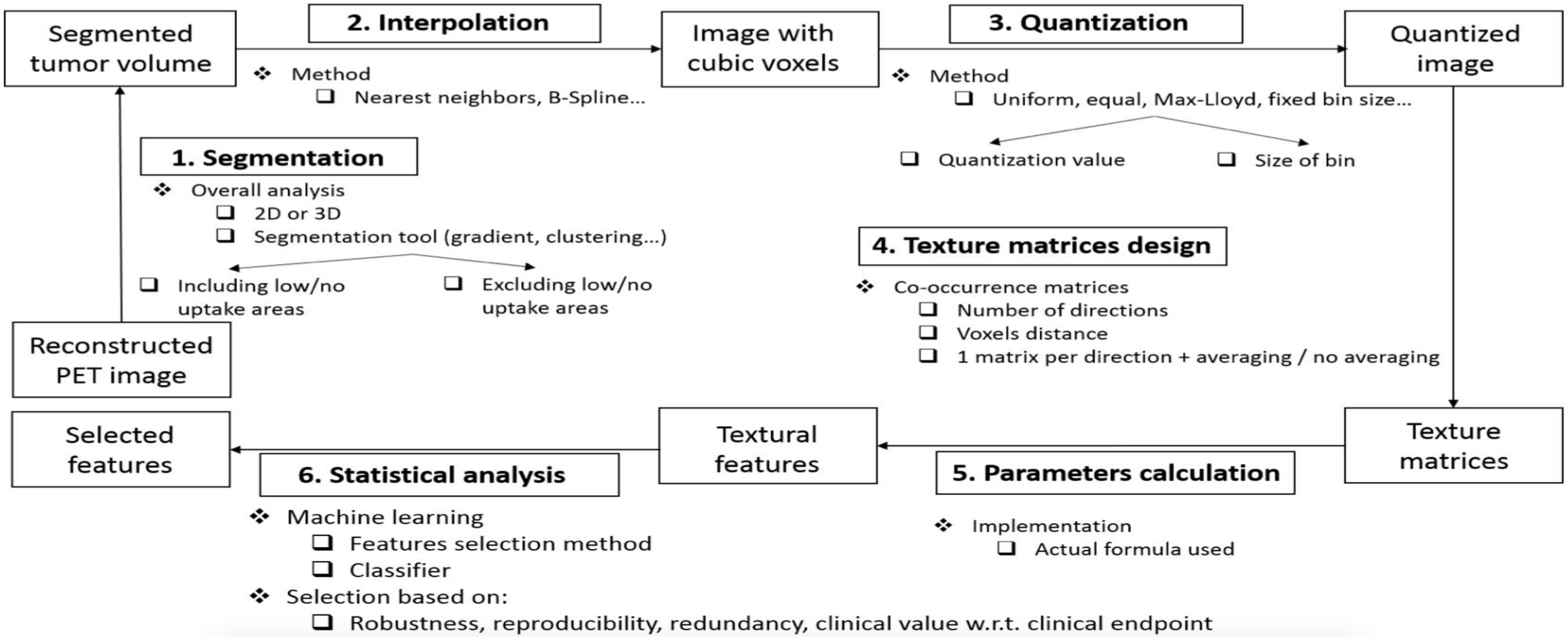
University of Bergen
Are Losnegård

University of California, San Francisco
Olivier Morin

University of Groningen, University Medical Center Groningen
Lisanne V. van Dijk, Jorn Beukinga, Nanna M. Sijtsema, Roel J.H.M. Steenbakkers, Ronald Boellaard

Radiomics

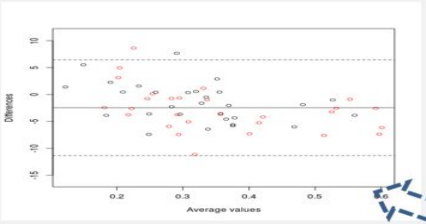
Challenges and issues: the complexity of textural features



Framework

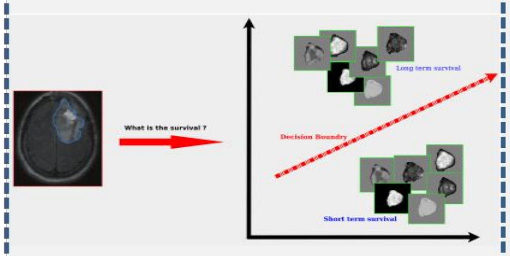
Robustness analysis

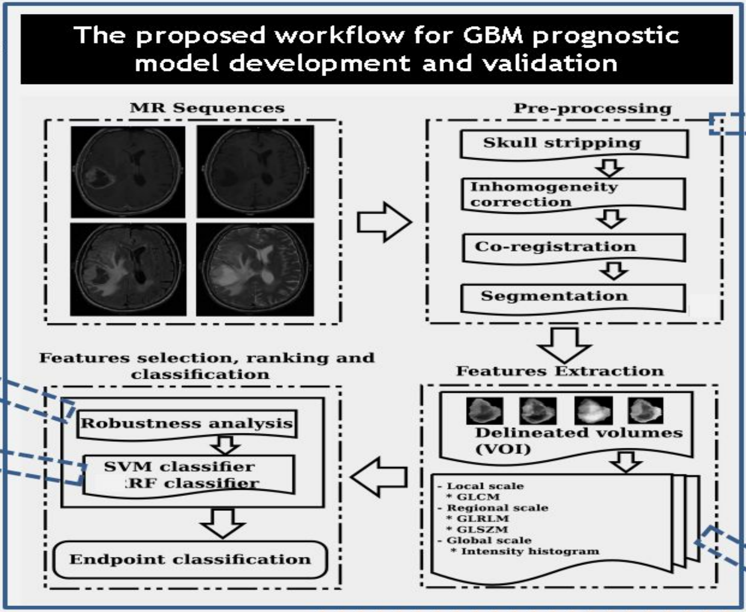
- Bland-Altman analysis of "Radiomics"
- Categorizing into four groups: very reliable, reliable, moderately reliable and unreliable



Features selection, ranking and classification

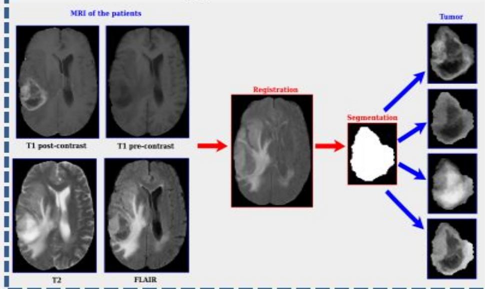
- Support Vector Machine-Recursive Feature Elimination (SVM-RFE) and
- Random Forest (RF)



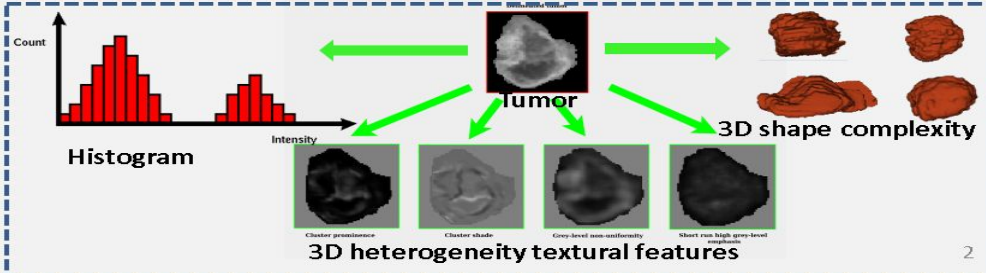


Pre-processing

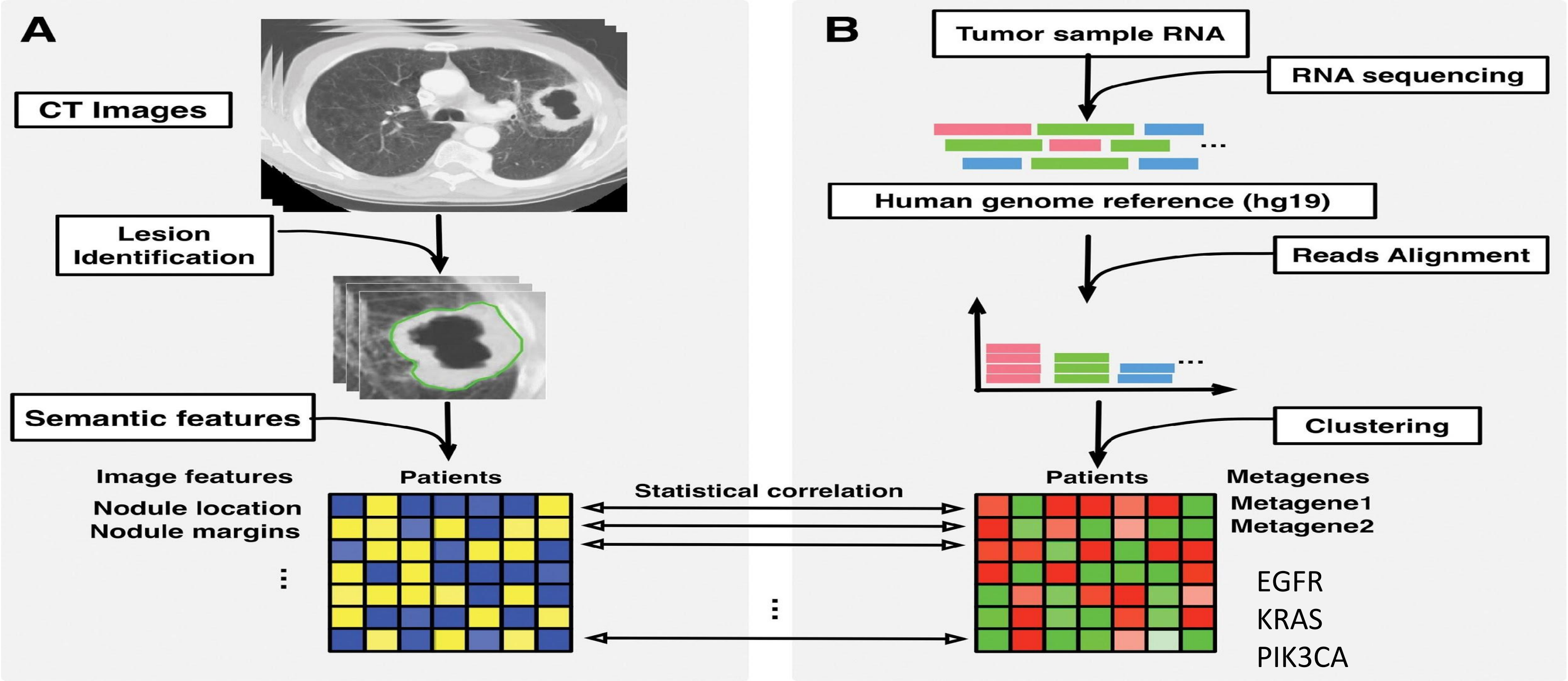
- Skull striping
- Inhomogeneity correction
- Co-registration
- Tumor segmentation



Radiomics

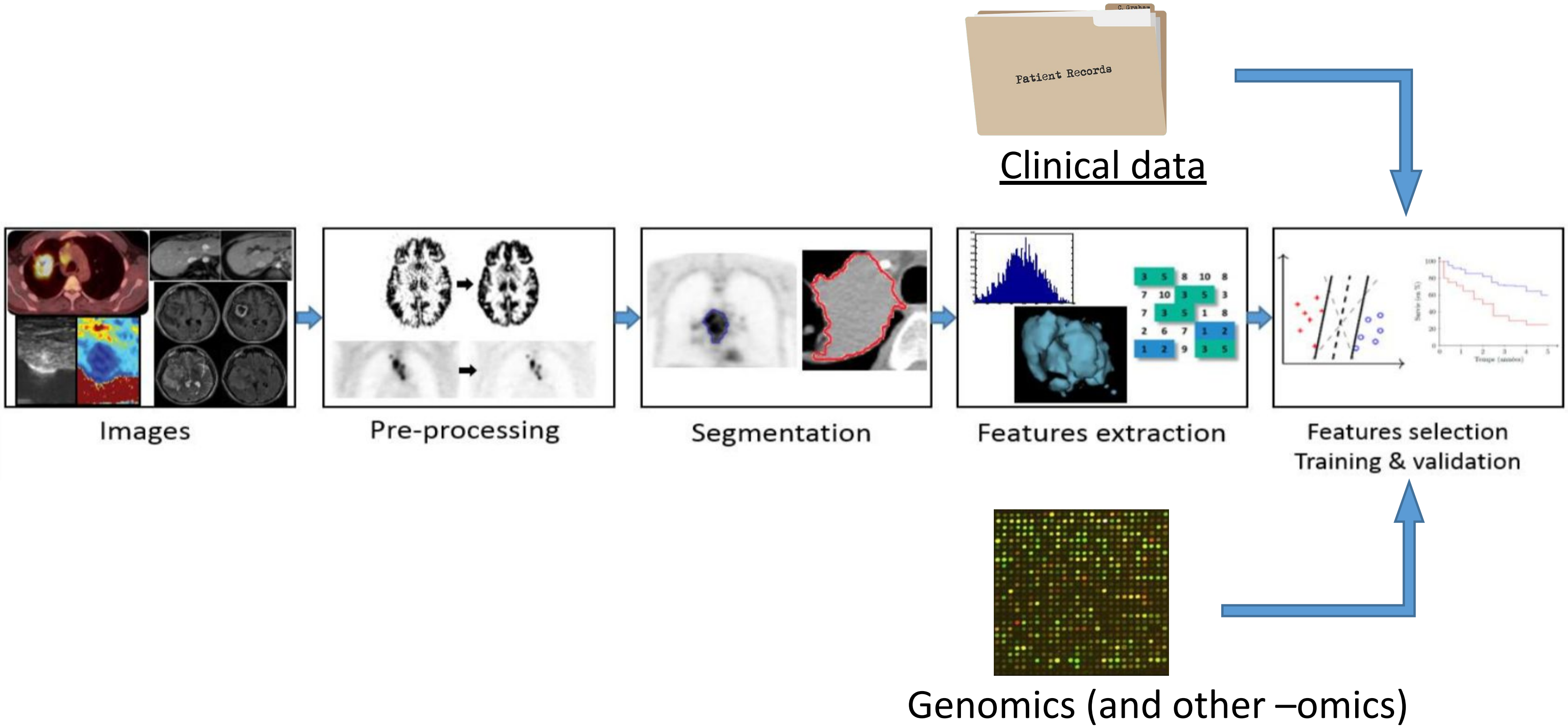


Radiogenomics

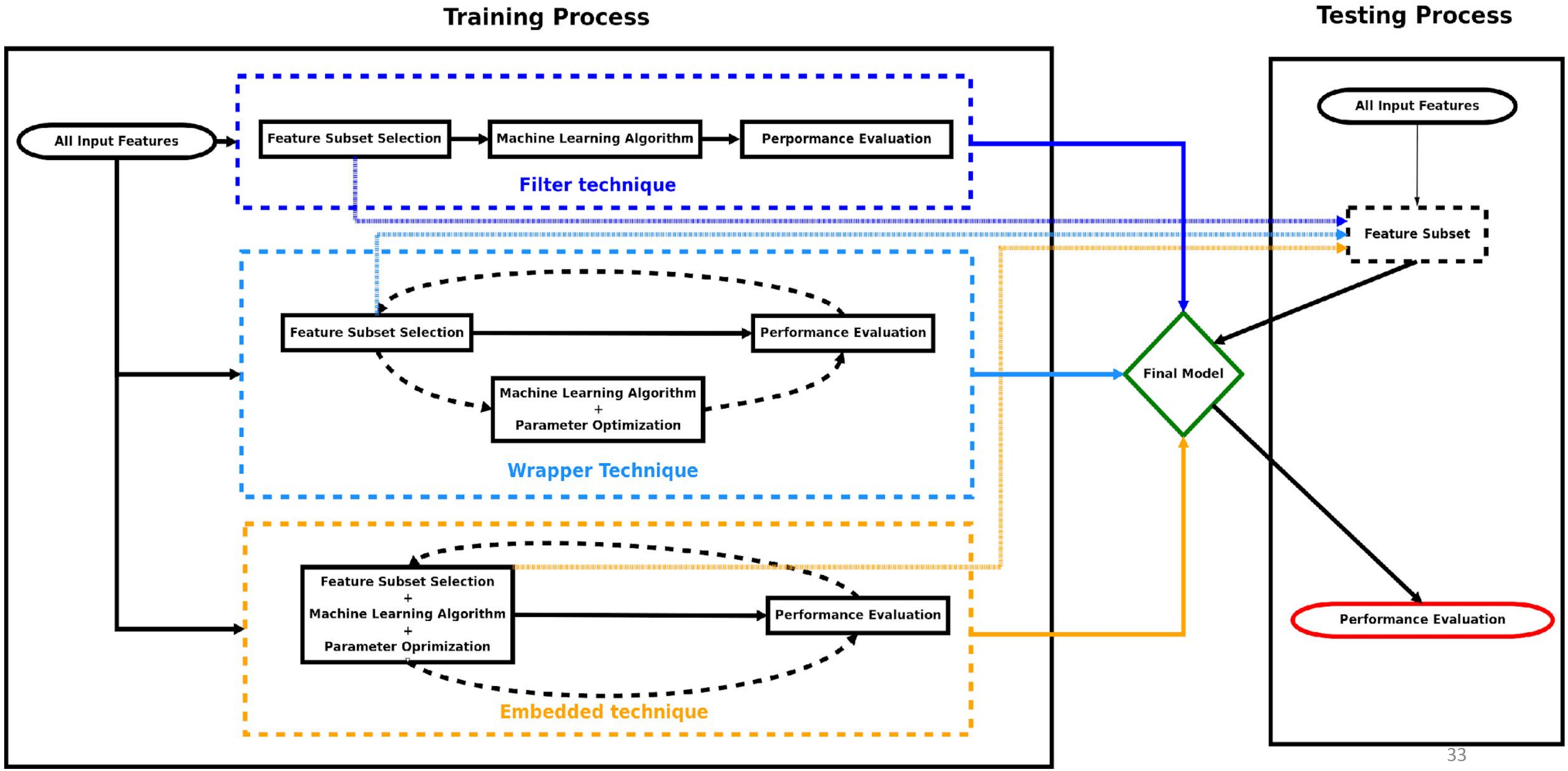


Overview of radiogenomic analysis to identify associations between (*A*) semantic features at CT and (*B*) RNA sequencing data.

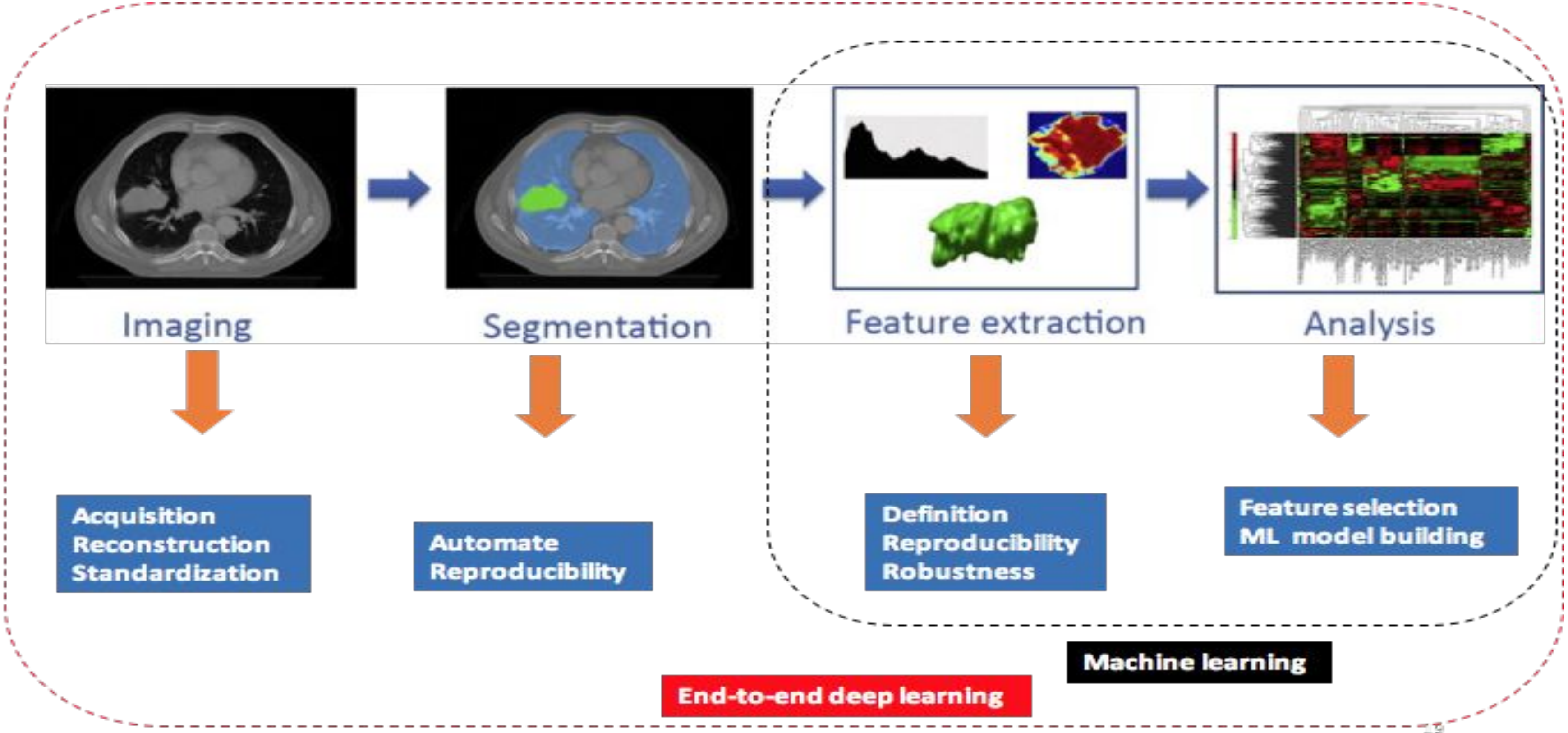
Radiomics: Standard Workflow



Machine Learning: Challenges and Issues

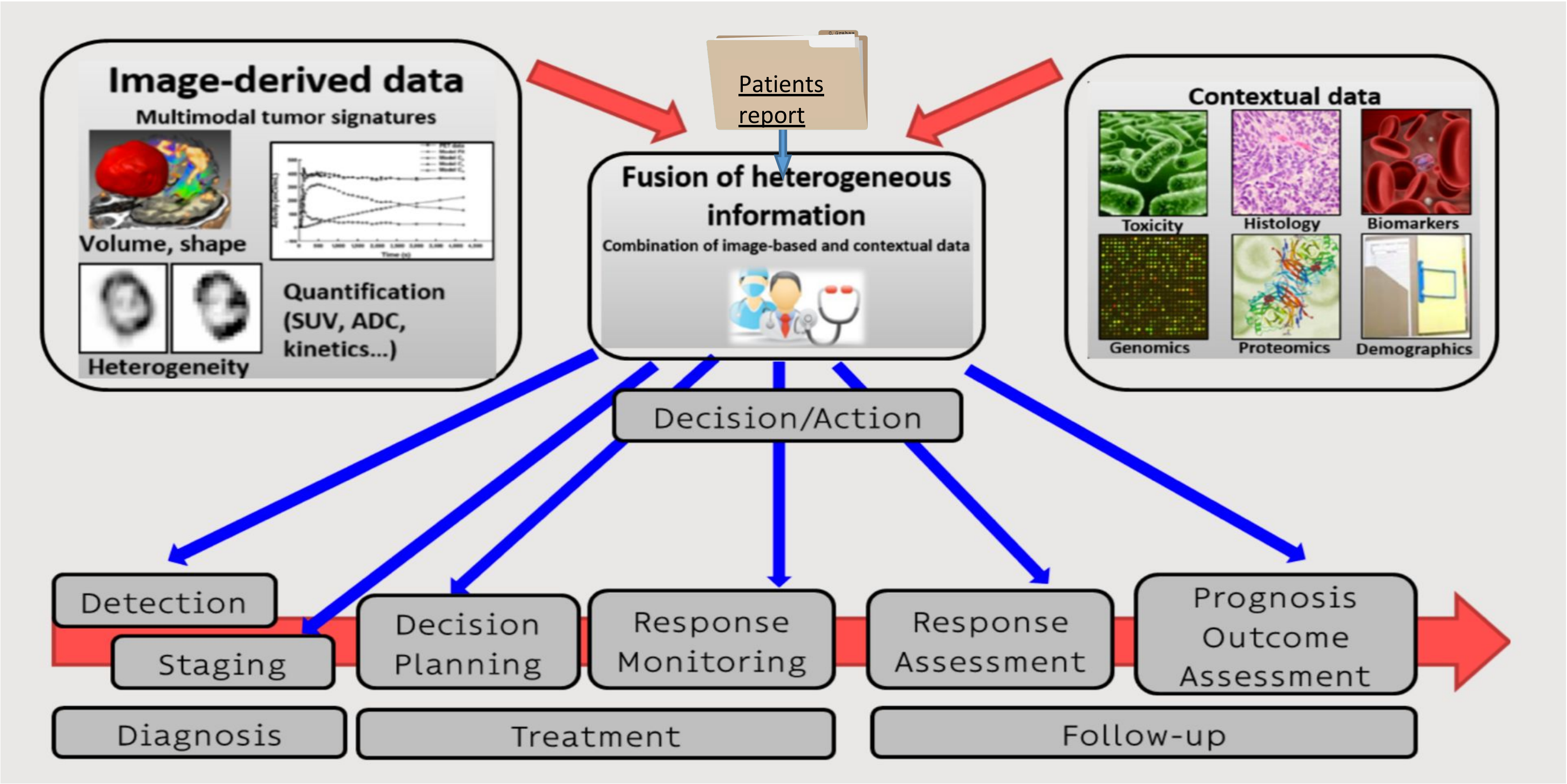


Workflow and challenges



Lambin P, *et al*. *Radiomics: extracting more information from medical images using advanced feature analysis.*

Precision Medicine: decision support system



Applications in multi-scale modeling for complex diseases

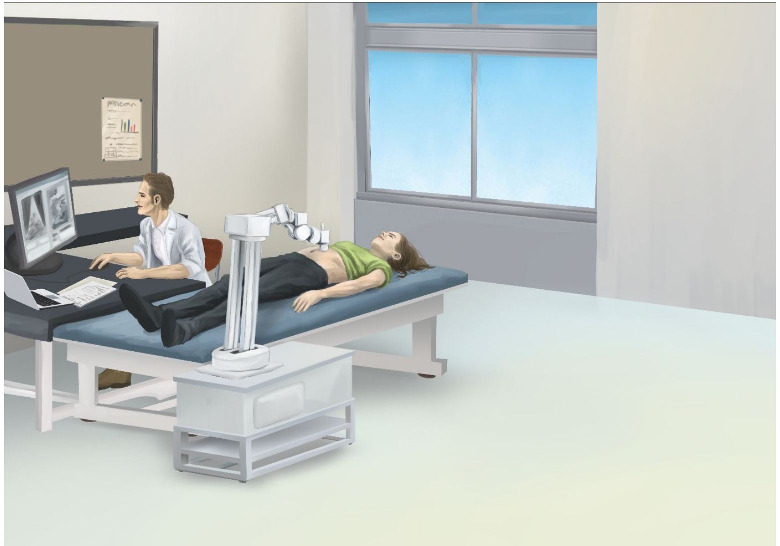
iFIND
intelligent Fetal Imaging and Diagnosis

2D, 3D and 4D imaging data
Up to 60 images/sec at ~1mm^2 resolution

- ➔ **500+ subjects**
- ➔ **50’000 labelled images per subject**

iFIND
intelligent Fetal Imaging and Diagnosis

“dramatically improving fetal anomaly **screening** by improving fetal **imaging**, from **acquisition** to **analysis**”



iFIND
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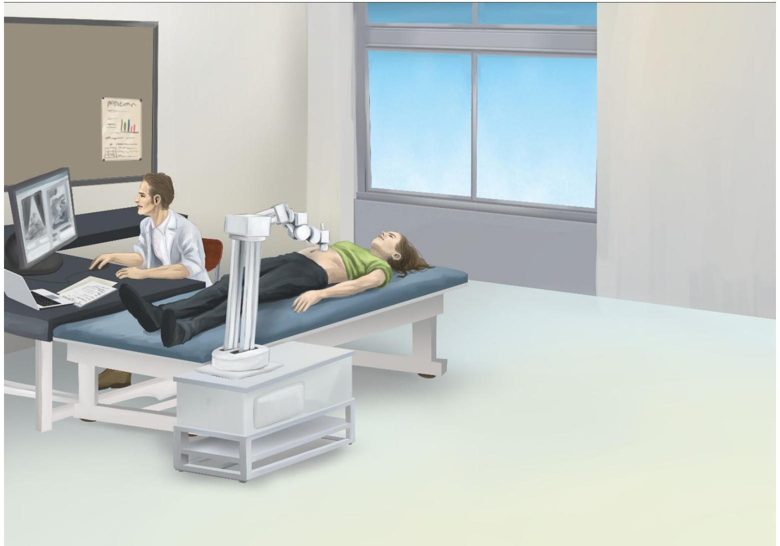
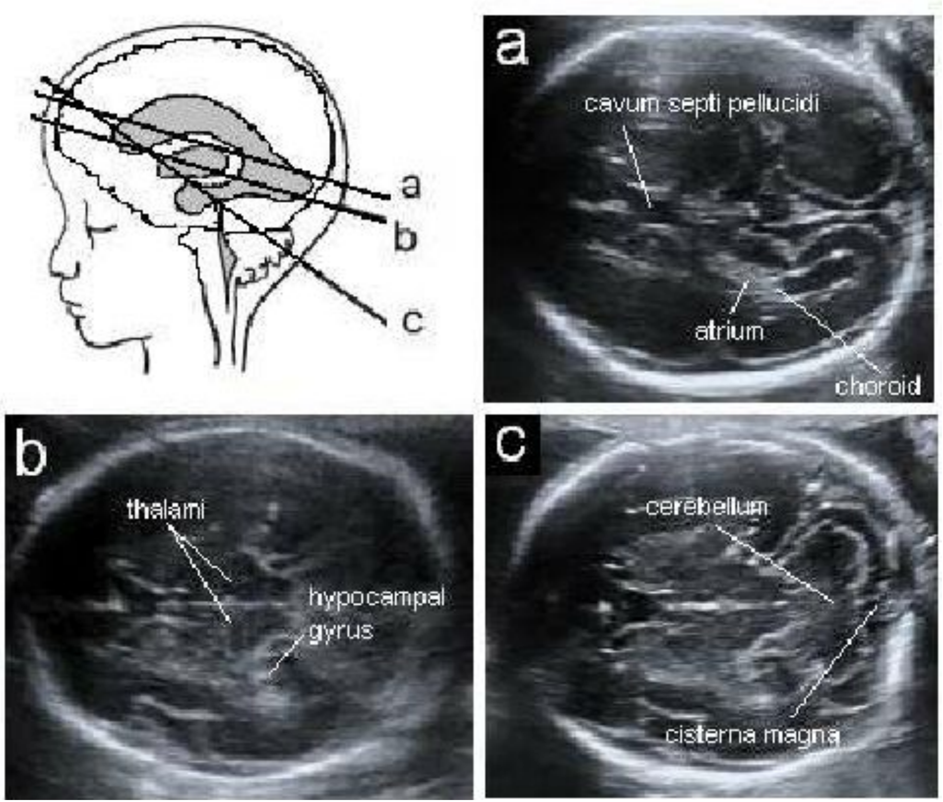
“dramatically improving fetal anomaly **screening** by improving fetal **imaging**, from **acquisition** to **analysis**”



My personal interest:
Automated Guided Scanning for non-expert sonographers + Machine Learning based basic diagnostics
Retrospective (potentially remote) examination by experts

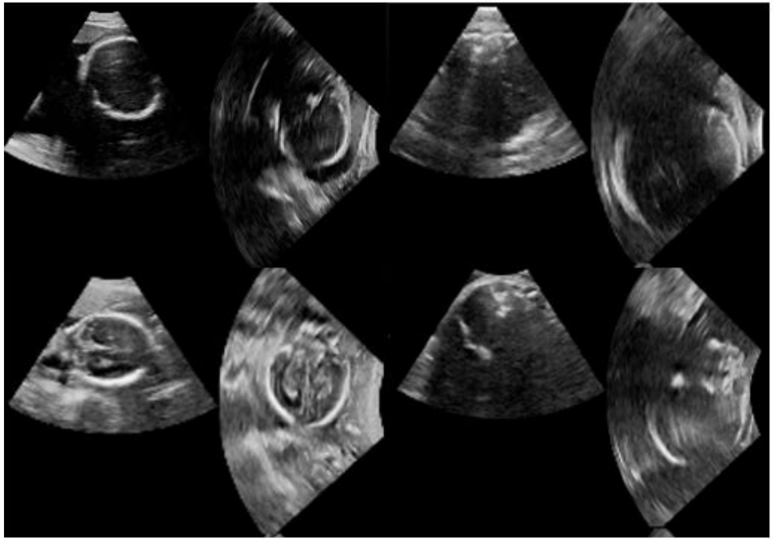
Challenges with Ultrasound



(a) Transventricular plane; (b) transthalamic plane; (c) transcerebellar plane.
Source: Carneiro et al. Semantic-based indexing [...]. CVPR 2008.

iFIND project

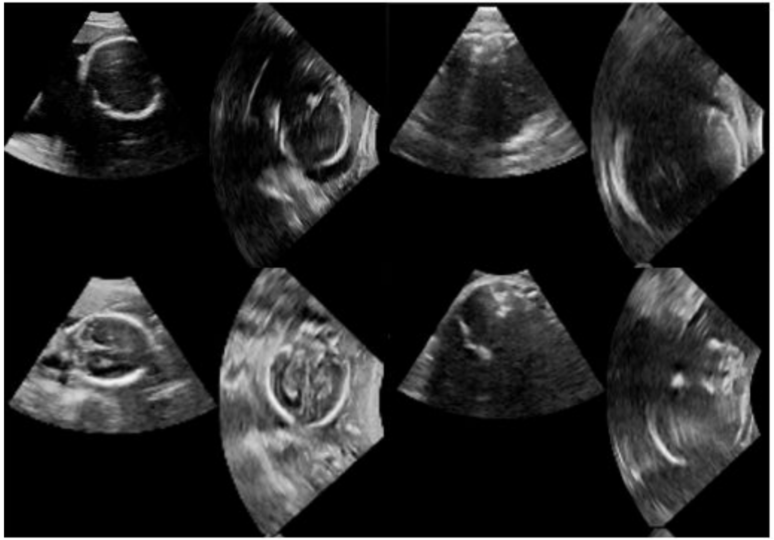
Challenges with Ultrasound



- Limited field of view (FoV)
- Probe pose dependant image appearance

- Operator dependant image quality
- Fetal position dependant image quality
- Operator dependant diagnosis
- Lack of experts in rural areas limits the potential of low-cost nature of US

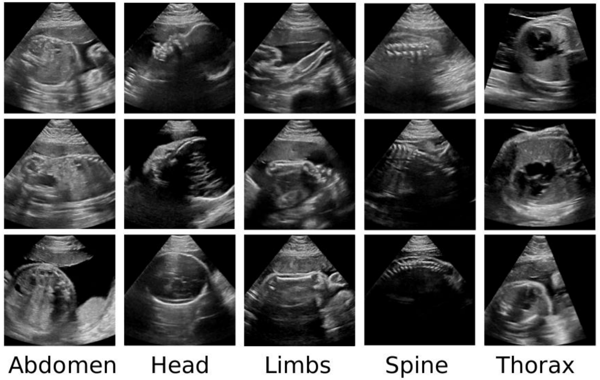
Navigation and Standard US Image Acquisition

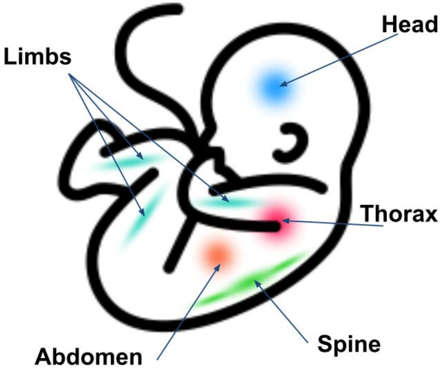


- Limited field of view (FoV)
- Probe pose dependant image appearance

- Identify Standard Views
- Estimate probe transformation w.r.t. Fetus
- Extend FoV and compound multiple images
- Create atlas for population studies

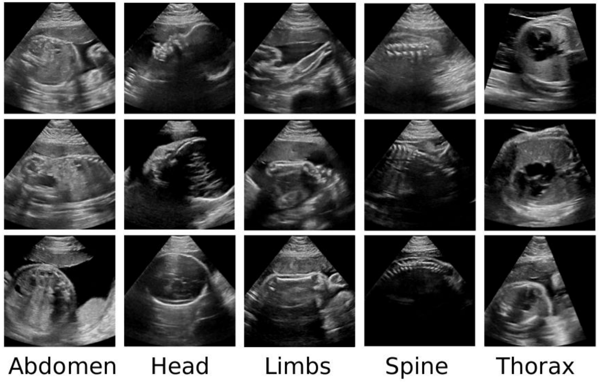
Fetal Region Detection and Localization in 2D US

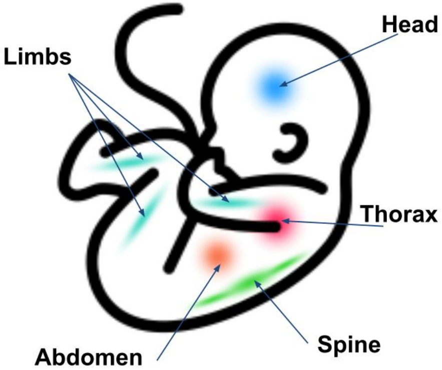


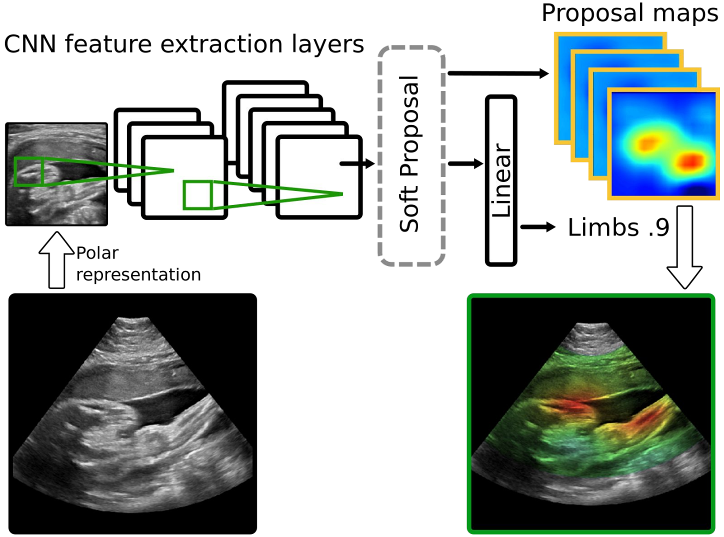


N. Toussaint, **B. Khanal,** *et al*. Weakly Supervised Localisation for Fetal Ultrasound Images. *MICCAI Workshop DLMIA 2018*.

Fetal Region Detection and Localization in 2D US







ResNet or VGG CNN architecture, Multi-label soft margin loss

Soft Proposal layer for class-aware maps

Training time: 35 epochs / 4h

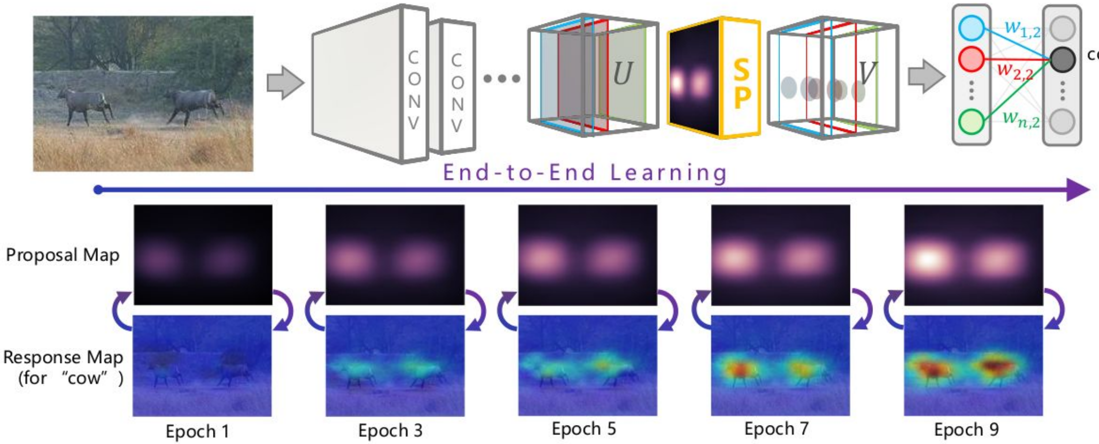
Augmentation: horizontal flips

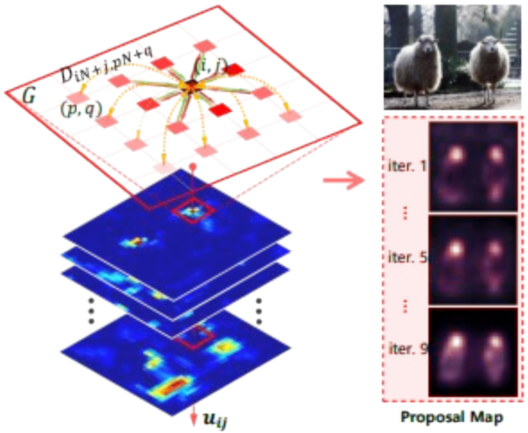
$$L(x,y) = -\sum_i y_i \log \frac{1}{1+\exp(-x_i)} + (1-y_i) \log \frac{\exp(-x_i)}{1+\exp(-x_i)}$$

Training: 18 subjects (85,000 images) Test: 25’000 images

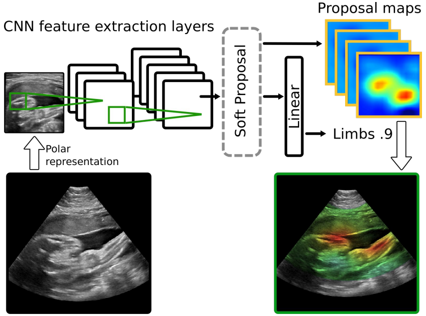
N. Toussaint, **B. Khanal,** *et al*. Weakly Supervised Localisation for Fetal Ultrasound Images. *MICCAI Workshop DLMIA 2018*.

Fetal Region Localization with Soft Proposal Map





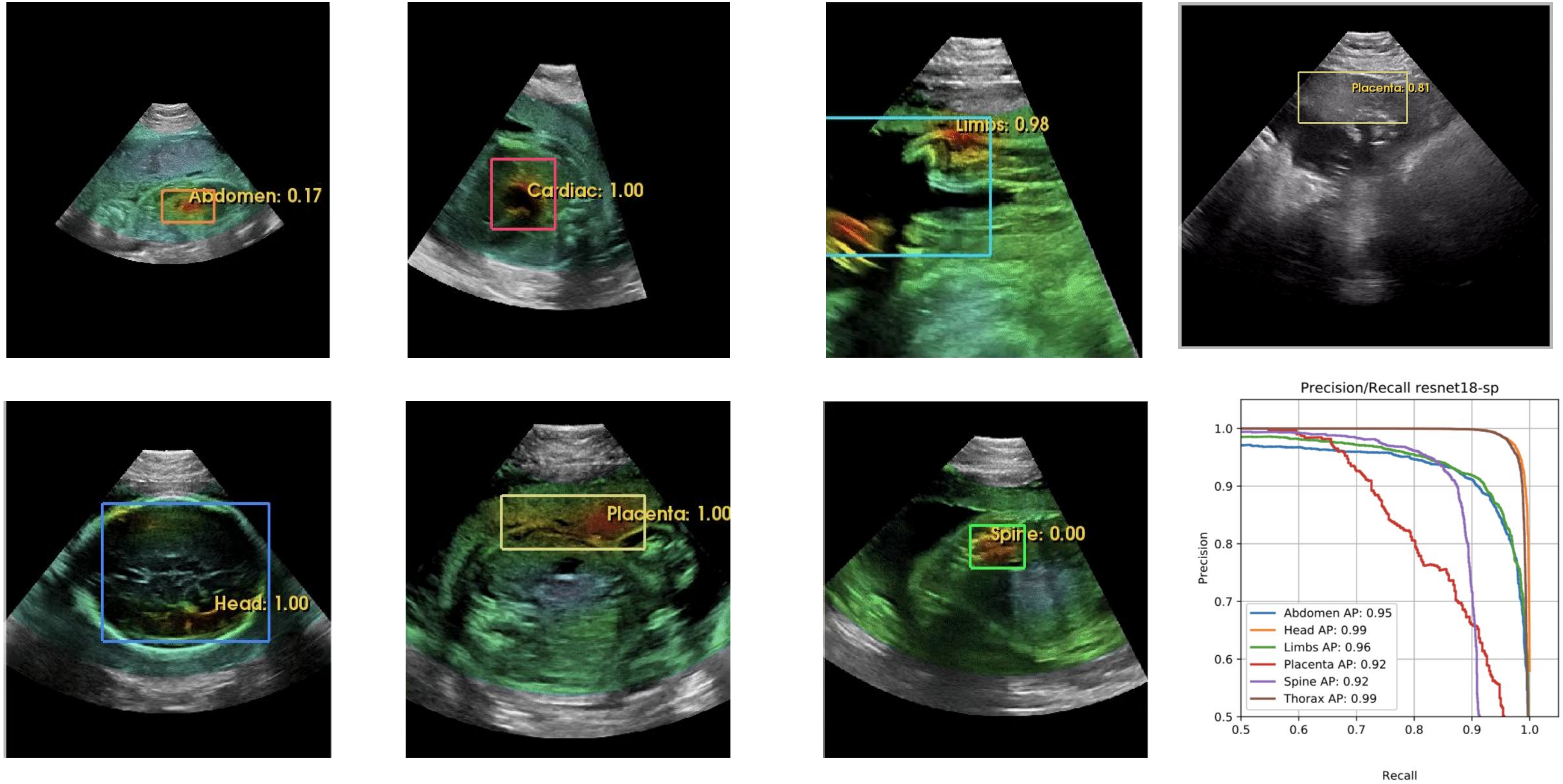
Soft Proposal Generation in single SPN feedforward pass



Fully connected directed graph G over the feature map
Weight matrix D with "objectness measure": spatial closeness + feature similarity
Graph propagation with random walk to generate proposal map M
Hadamard product coupling of feature map with proposal map

1. N. Toussaint, **B. Khanal,** *et al*. Weakly Supervised Localisation for Fetal Ultrasound Images. *MICCAI Workshop DLMIA 2018*.
2. Y. Zhu *et al*. Soft Proposal Networks for Weakly Supervised Object Localization. *ICCV, 2017*.

Fetal Region Detection and Localization in 2D US



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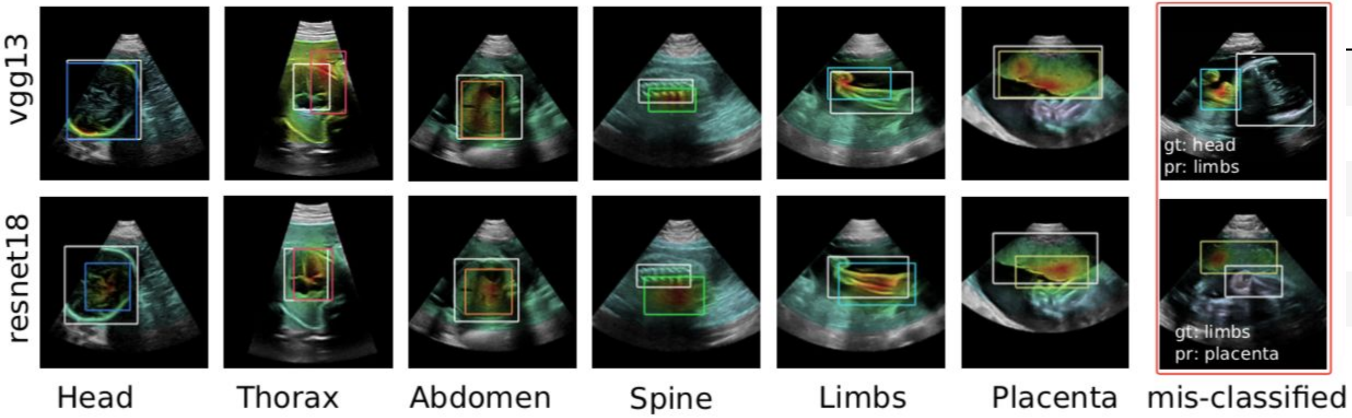
Fetal Region Detection and Localization in 2D US



	Label	IoC	sigma	Corr.	Rel.
0	Abdomen	0.40	0.12	0.48	0.63
2	Head	0.56	0.22	0.72	0.74
3	Limbs	0.51	0.17	0.70	0.78
4	Placenta	0.60	0.18	0.82	0.89
5	Spine	0.51	0.10	0.84	0.97
6	Thorax	0.32	0.12	0.25	0.30

Ground truth box manually by experts

N=3800 frames (~150 frames x 6 regions x 4 subjects)

<u>Metrics</u>:

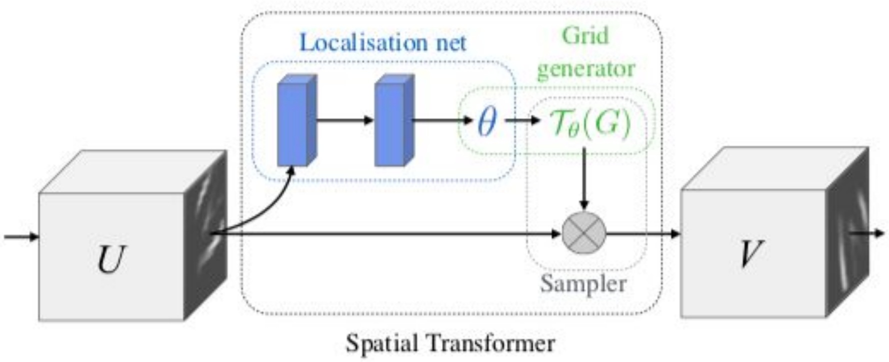
- IoC: intersection over union of boxes
- sigma: standard dev. of IoC
- Correctness: % of frames with IoC > 0.4

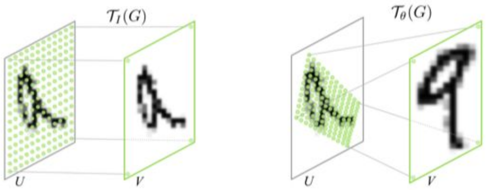
Region	ResNet18-SP	ResNet34-SP	VGG13-SP	VGG16-SP
Abdomen	97 %	99%	94 %	95 %
Background	97 %	96%	96 %	96 %
Head	95 %	91%	86 %	90 %
Limbs	88 %	83%	89 %	92 %
Spine	85 %	85%	85 %	86 %
Thorax	91 %	94%	99 %	96 %
Average	**92.2 %**	**91.3 %**	**91.5 %**	**92.5 %**

N. Toussaint, **B. Khanal,** *et al*. Weakly Supervised Localisation for Fetal Ultrasound Images. *MICCAI Workshop DLMIA 2018*.

3D and 4D Ultrasound

Spatial Transformer Networks

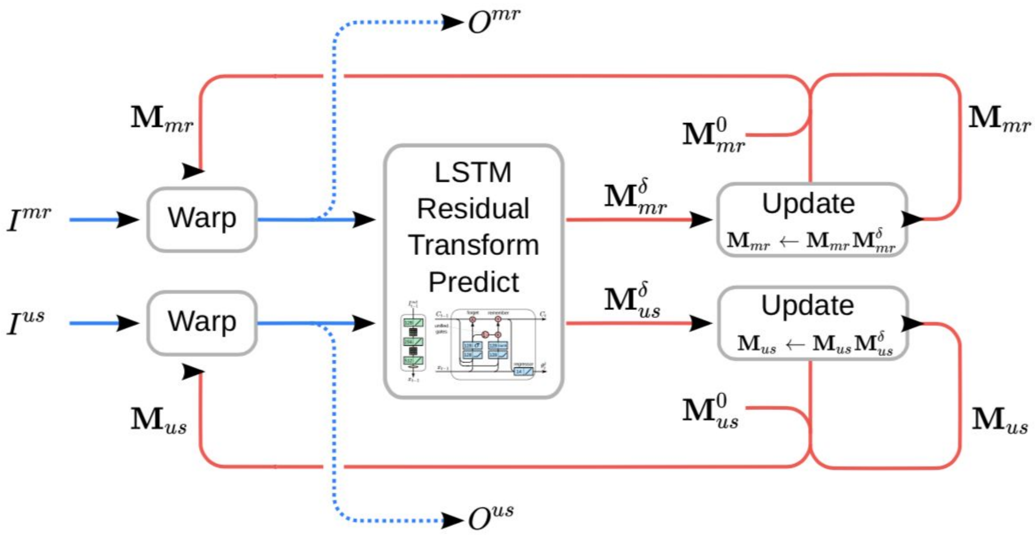


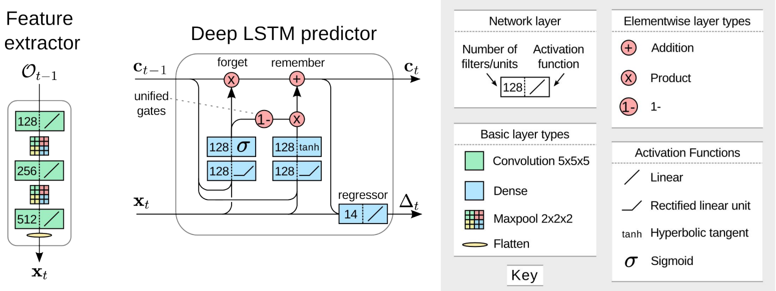


Explicit spatial manipulation of feature maps within CNNs
Resulting models learn invariance to translation, scale, rotation and more generic warping
Localisation network: Provides transformation conditional on the input.
Grid generator: Creates image sampling grid
Sampler: Generates output sampled from the input at the grid points

M Jaderberg et al. Spatial Transformer Networks. NIPS 2015

Fetal MR- 3DUS Joint Alignment





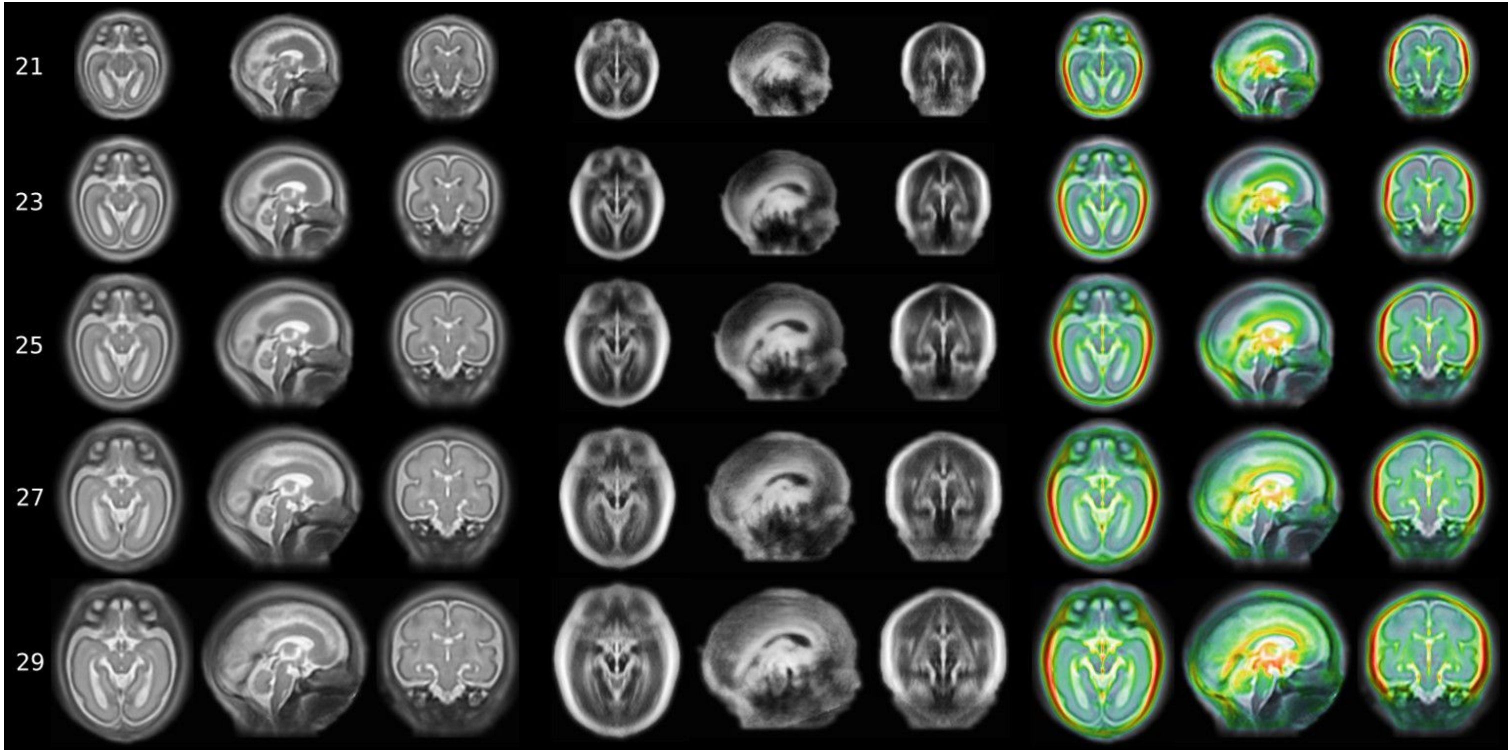
$$\mathcal{L} = \sum_{i=1}^{N} \sum_{t=1}^{k} d(\mathbf{M}^i_t\, \mathbf{D}^i)/d(\mathbf{M}^i_{t-1}\, \mathbf{D}^i) + \lambda \frac{t}{k}\, d(\mathbf{M}^i_t\, \mathbf{D}^i).$$

Flow of image intensities is shown in blue while flow of transformation parameters is shown in red.
LSTM network predicts residual transformations Mδmr, Mδus conditioned on the current warped images O^us, O^mr, iteratively refining their alignment.

Select image tuple and transform each by randomly generated matrix D and feed into the network
D incorporates affine augmentation + initial rigid transformation

R. Wright, **B. Khanal,** *et al*. Lstm spatial co-transformer {…} registration of 3d fetal us-mr images. *MICCAI Workshop PIPPI 2018*.

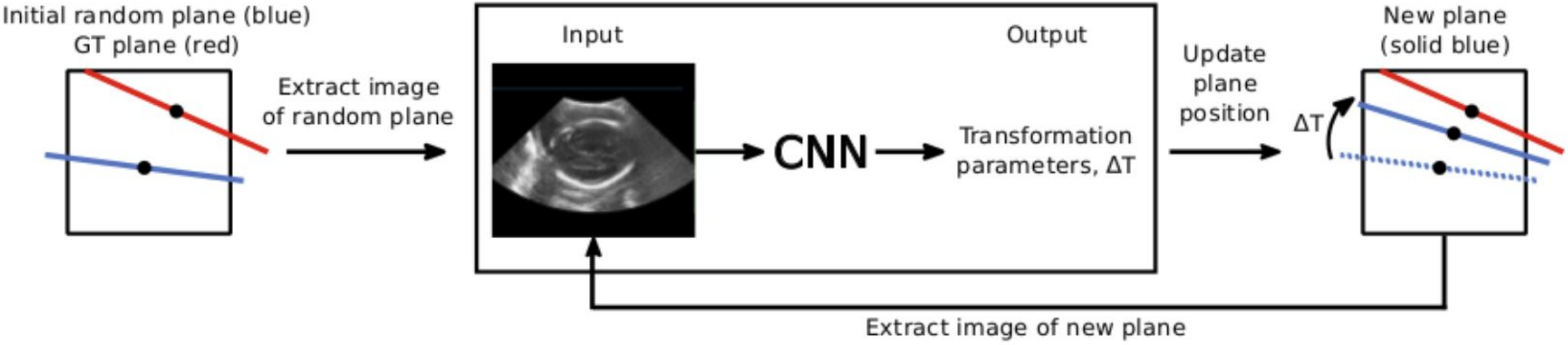
Fetal MR- 3DUS Joint Alignment

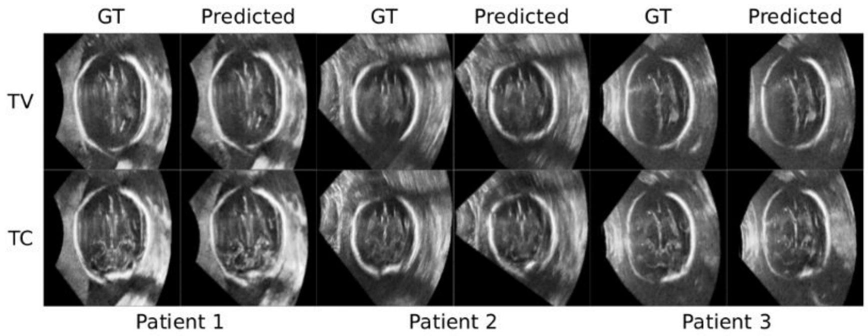


Average image intensity templates for each week of gestation (20 - 31 weeks), from 166 3D reconstructed MR / 3D US image pairs

R. Wright, **B. Khanal,** *et al*. Lstm spatial co-transformer {…} registration of 3d fetal us-mr images. *MICCAI Workshop PIPPI 2018*.

Standard Plane Detection in 3D US





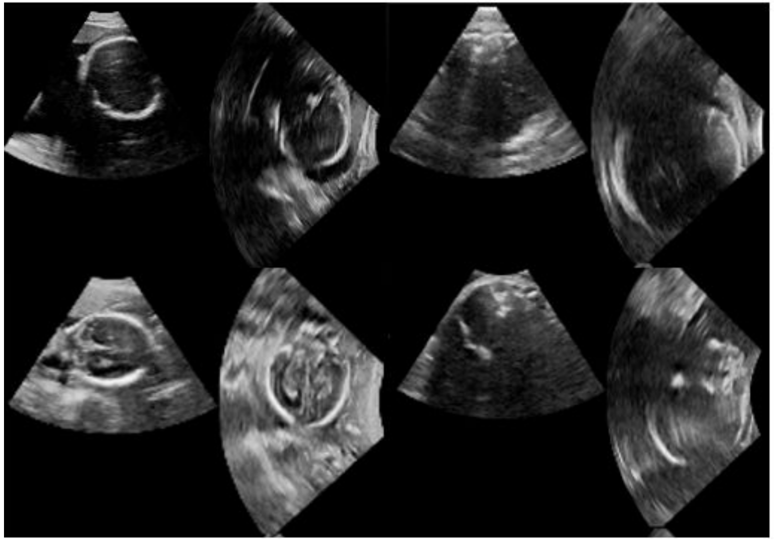
3D Volume without precise plane --> less expertise

- Acquisition by Female Health Volunteers
- Retrospective (remotely) analysis by experts

Y. Li, **B. Khanal**, *et al.* Standard Plane Detection in 3D Fetal Ultrasound Using an Iterative Transformation Network. *MICCAI, 2018*.

Challenges with 4D US

- Limited field of view (FoV)
- Probe pose dependant image appearance



- Operator dependant image quality
- Fetal position dependant image quality
- Operator dependant diagnosis
- Lack of experts in rural areas limits the potential of low-cost nature of US

Goals and Challenges

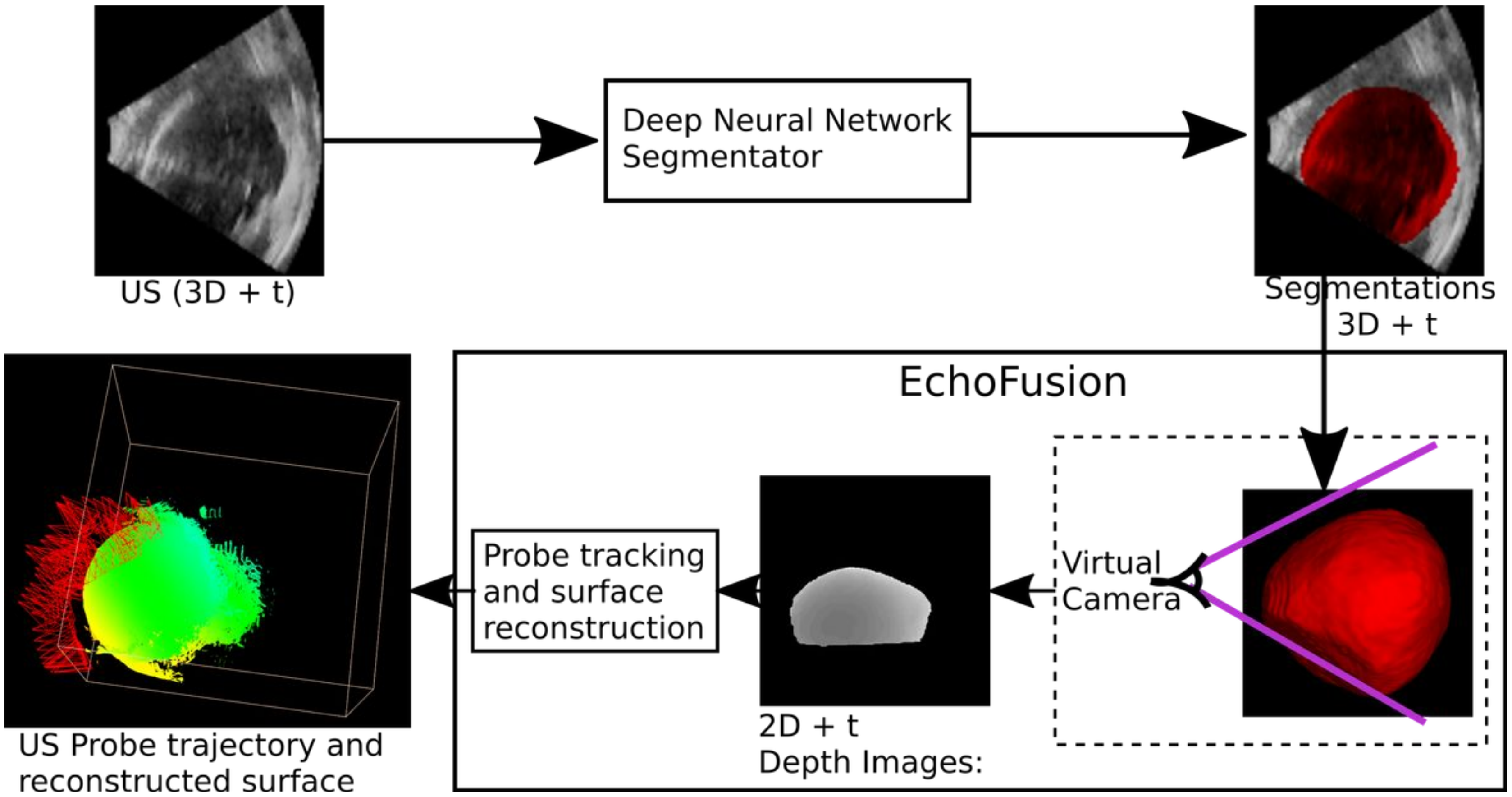
Goals

- **Compound** multiple US volumes, in real time, scanned potentially by non-experts to enlarge FoV, remove artefacts and improve image quality.
- **Compound:** Align volumes + Fuse Intensity Information
- Track pose w.r.t fetus and align all fetal volumes in real-time

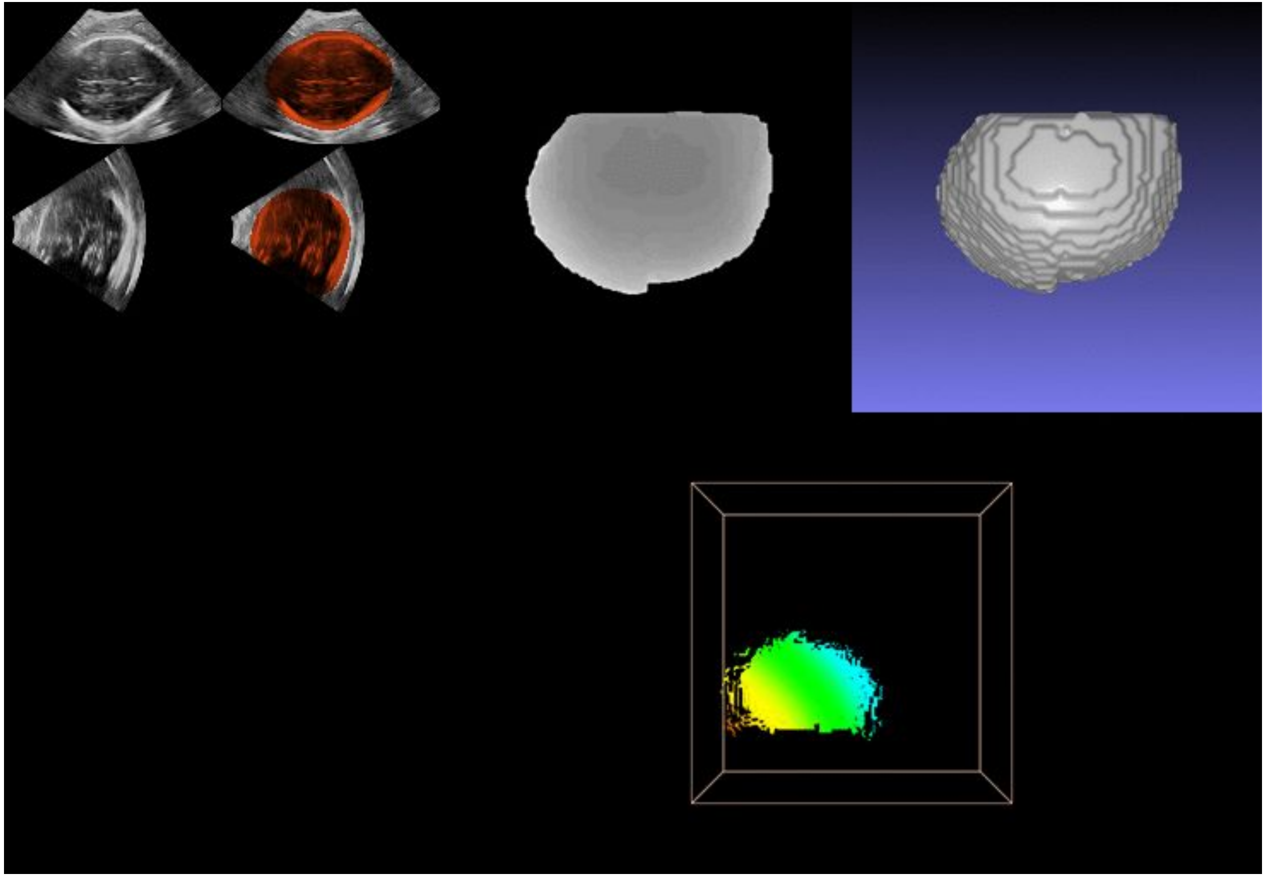
Challenges

- Limited FoV and transformations between images unavailable
- External trackers: not always practical; not w.r.t. fetus
- Pose dependant image appearance due to artefacts such as shadows
- Features not repeating in different volumes, changing maternal tissues

EchoFusion: Compounding and Reconstruction from 4D US



Segmentation and Tracking US Probes



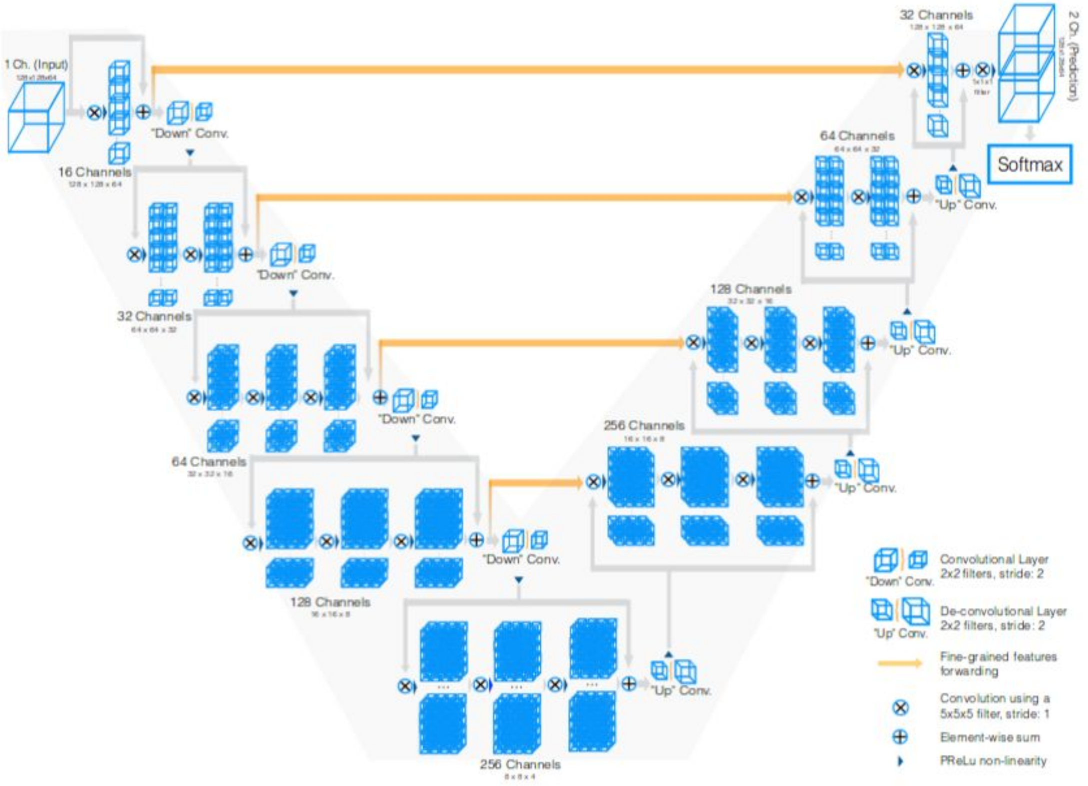
Top Left: Segmentation

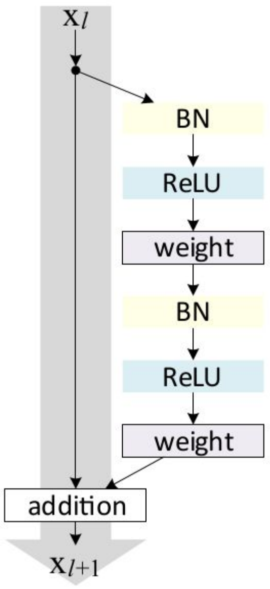
Top Middle: Depth Map

Top Right: Head Surface

Bottom: Tracked Probe and Reconstructed Surface

Segmentation with Residual 3D U-Net





He, K. et al. Identity mappings in deep residual networks. ECCV 2016.
Milletari, F. et al. V-Net: fully convolutional neural networks for volumetric medical image segmentation. 3DV 2016.
Ronneberger, O. et al. U-Net: convolutional networks for biomedical image segmentation. MICCAI 2015

Segmentation with Residual 3D U-Net

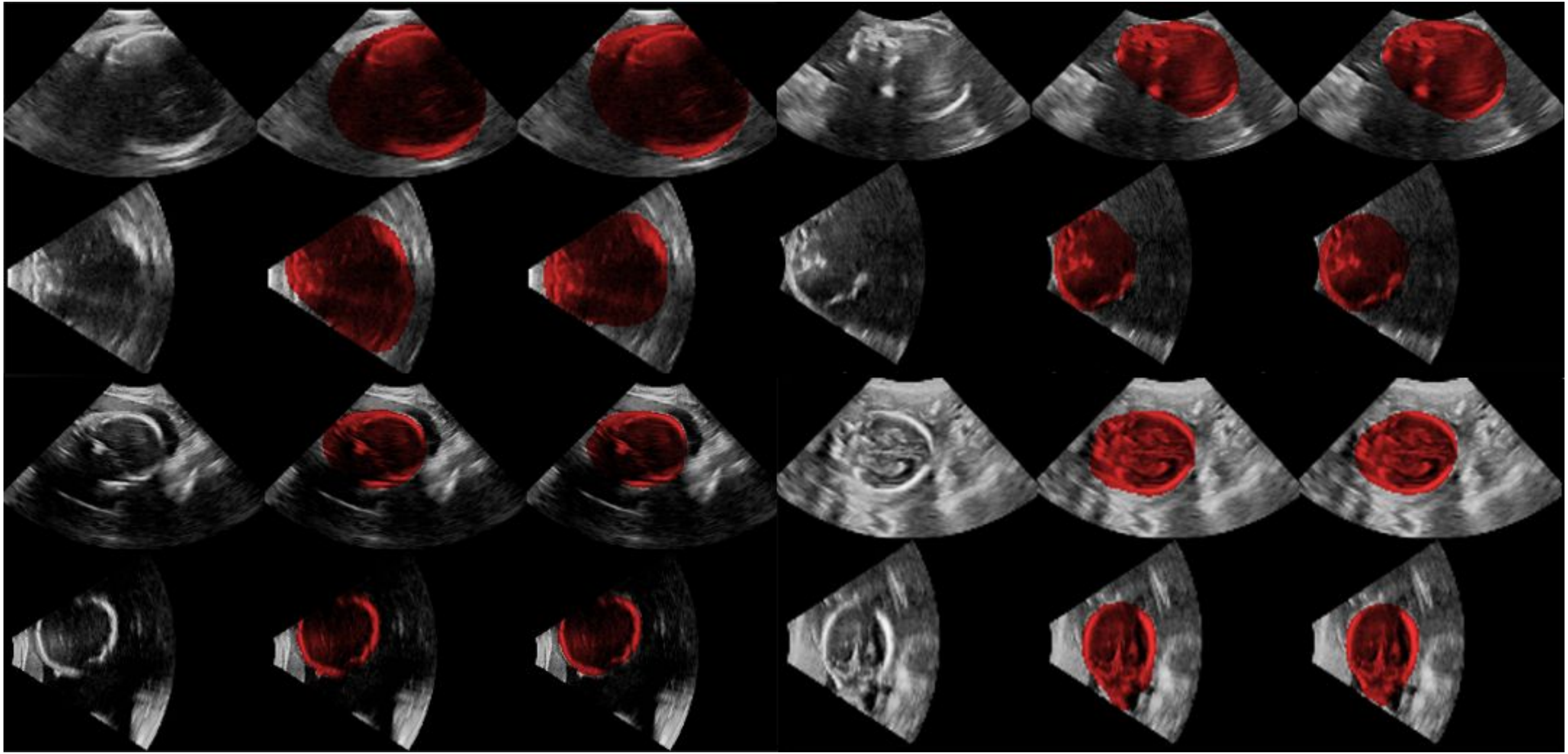
- Residual 3D U-Net, all conv. Layers with residual-units
- Features in each layer: 16, 32, 64, 128
- Batch normalization, ReLUs and zero-padding
- 64×64×64 voxels, standard cross-entropy loss
- Adam optimization, learning rate of 0.001 and L2 regularization.
- Augmentation: Gaussian additive noise ($\sigma = 0.02$), image flipping in each axis.

- 19 fetuses; Gestational age: 23–34 weeks; mean (std) 30 (2.842) wks.

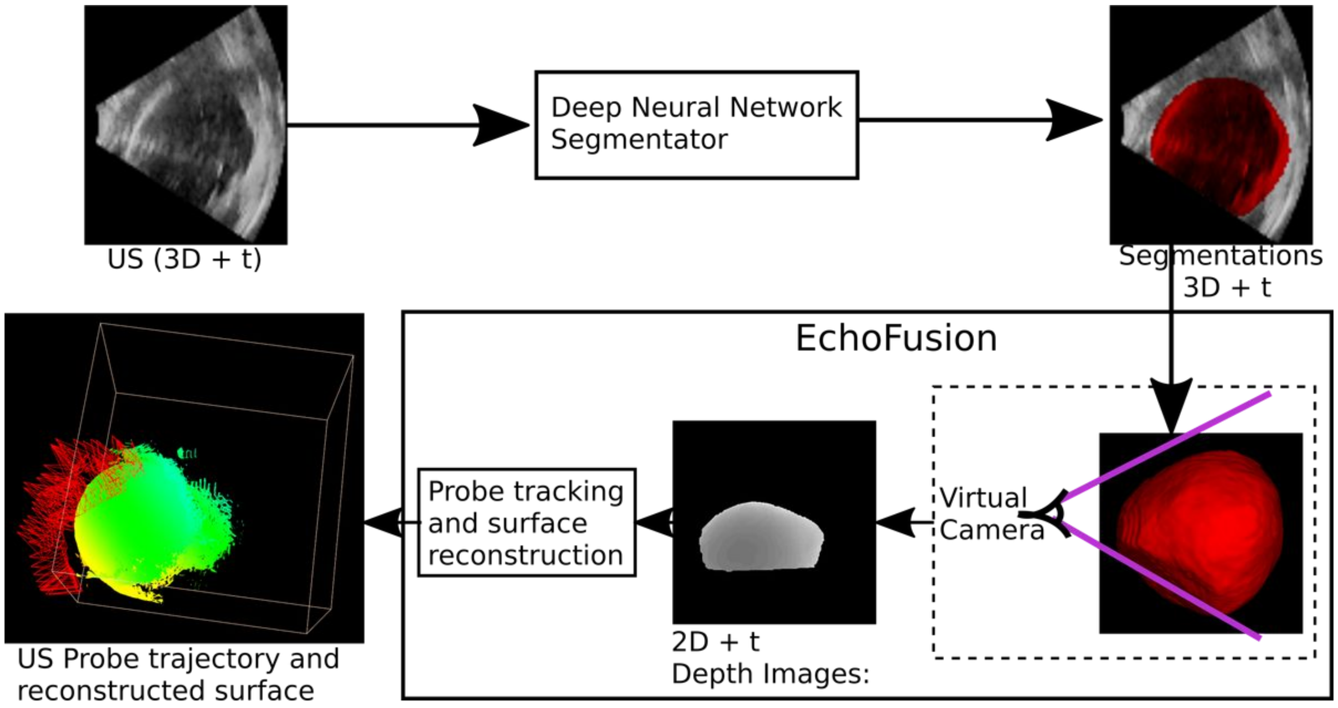
Dice scores

Set	images(real)	mean(std)	images(Phantom)	mean(std)
Train	178	0.9408(0.0389)	24	0.9735(0.0125)
Validation	8	0.9217(0.0212)	4	0.9267(0.0074)
Test	26	0.8942(0.0671)	-	-

Segmentation with “weak” supervision



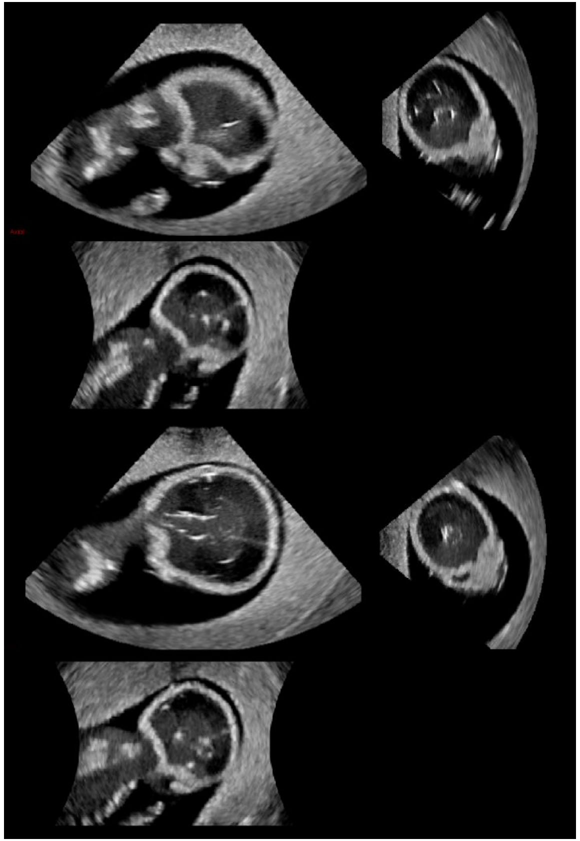
Set up a virtual camera



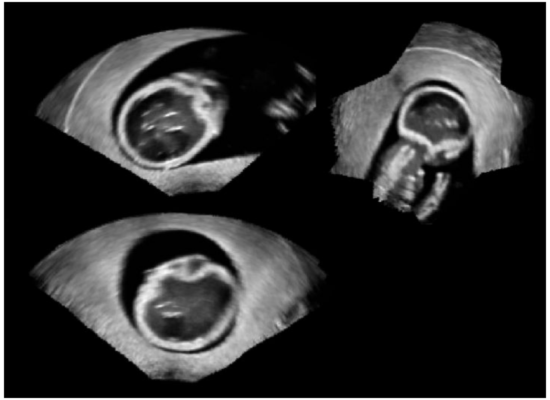
- Extract sector lines with Hough transform on orthogonal central slices
- Estimate "virtual camera position" as the intersection point closest to the image

Phantom Whole-Body Compounding Result

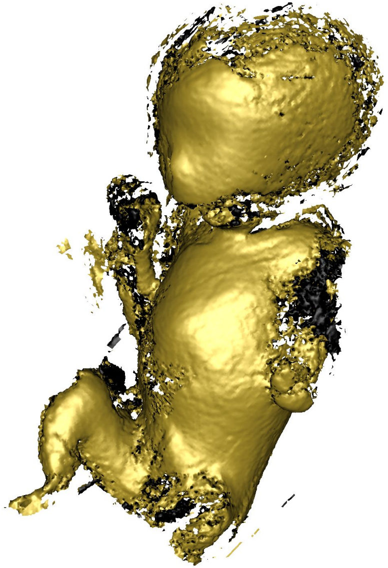
Input volume examples



Compounded (10 vols)



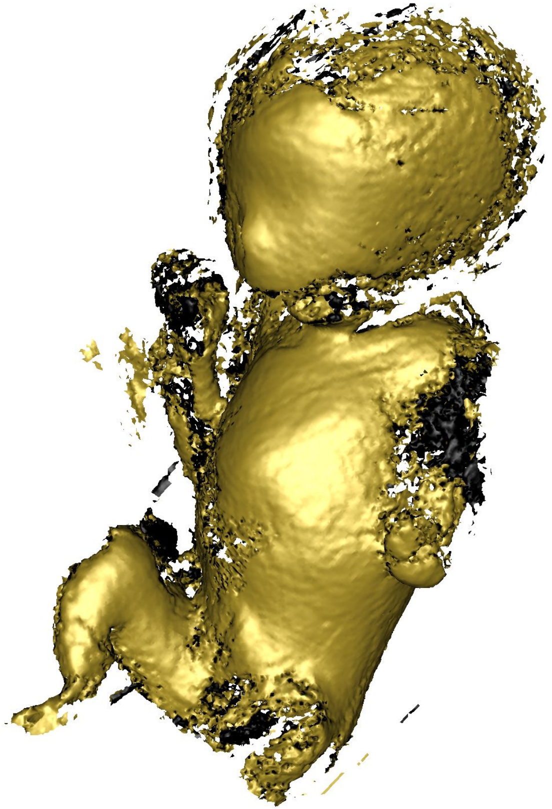
Reconstructed Surface



Phantom Whole-Body Compounding Result

Tracked Probe Trajectory

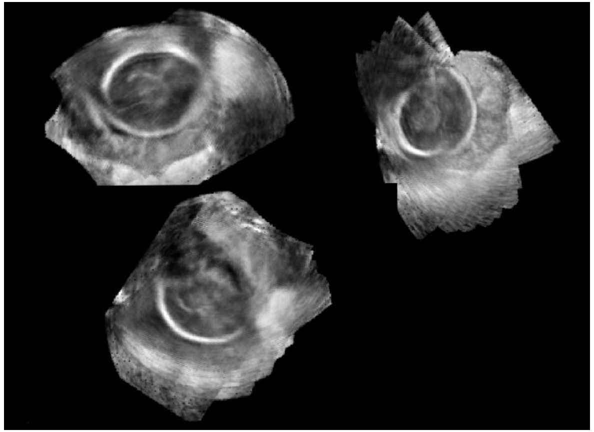
Reconstructed Surface



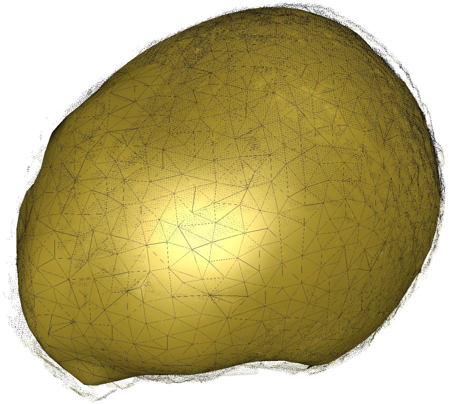
Real Fetus Head Compounding Result

Input volume examples

Compounded (10 vols)

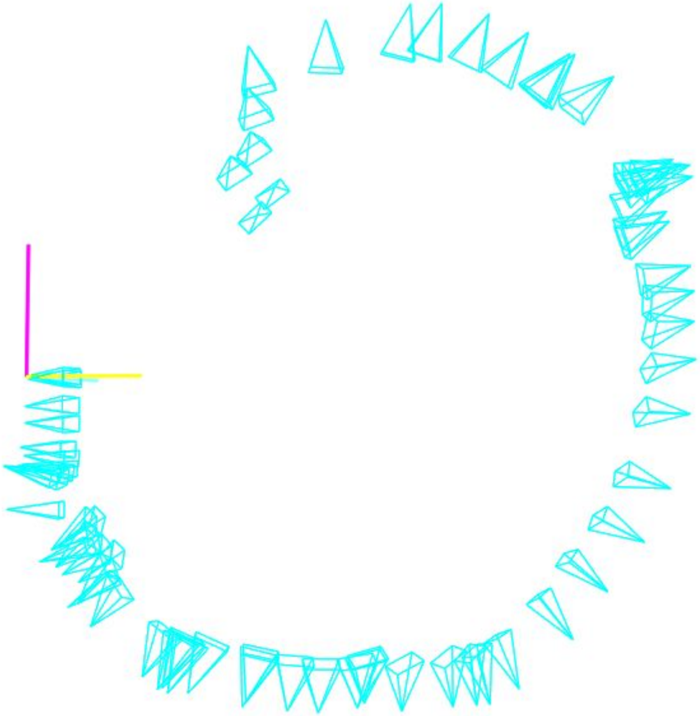


Reconstructed Surface

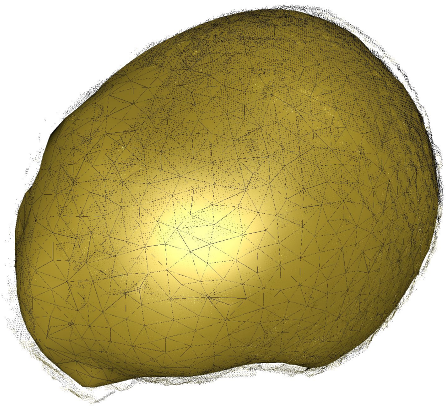


Real Fetus Head Compounding Result

Tracked Probe Trajectories



Reconstructed Surface

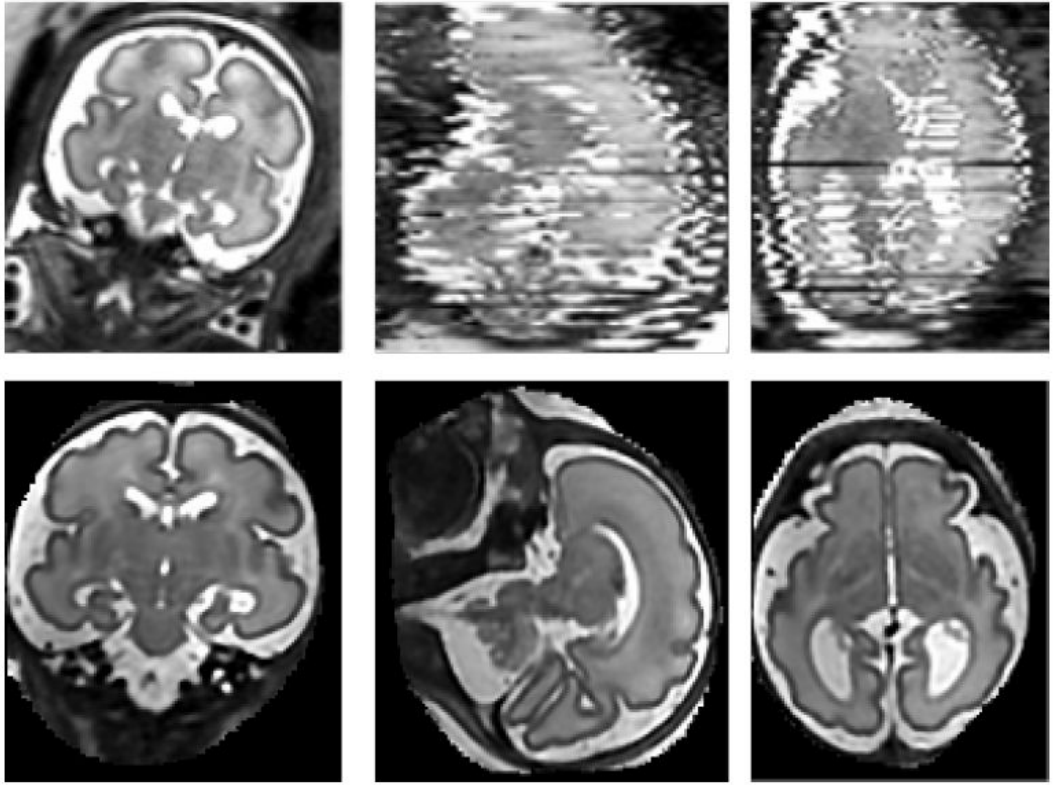


Biomedical Engineering, Computer Science & AI

Democratizing Innovation in Medicine: Three Key Themes

- Frugal Innovation & Disruptive Innovation
- Enable new ways (or efficient ways) of imaging from existing devices
- Fundamental research and novel biomarker discovery from population based studies of diverse demographic cohorts

Fetal MRI and Slice to Volume Reconstruction



- Congenital brain defects
- Study brain development
- Population based studies

Kainz et al. Fast Volume Reconstruction from Motion Corrupted Stacks of 2D Slices. TMI 2015.
Hou, **Khanal** et al. 3d reconstruction in canonical co-ordinate space from arbitrarily oriented 2d images. TMI 2018.

Cardiac Arrests in South Asia

Stanford
HEALTH CARE

Doctors | Clinics & Locations | Conditions & Treatments | Patients

Stanford Health Now

South Asians and Heart Disease Q&A

05.18.2015

Are South Asians at higher risk for heart disease?

People from South Asia—India, Pakistan, Bangladesh, Nepal, Bhutan, Maldives and Sri Lanka—have a four times greater risk of heart disease than the general population and have a much greater chance of having a heart attack before age 50.

Heart attacks strike South Asian men and women at younger ages and the attacks are more deadly compared to any other ethnic group. Almost one in three in this group will die from heart disease before age 65.

In India, cardiovascular disease remains the No. 1 cause of death. One study found that South Asians developed heart disease 10 years earlier than other groups.

What is causing this heart disease phenomenon in South Asians?

Why these heart attacks occur is only partially answered with traditional risk factor assessment. South Asians tend to be smokers, and the typical South Asian diet tends to be high in sugar, refined grains, and fatty foods.

- 4X greater chance of heart attack
- Why: not exactly known
- Population based morphological studies
- Imaging genetics
- Novel Biomarkers from heterogeneous data

https://stanfordhealthcare.org/stanford-health-now/2015/south-asians-heart-disease-qa.html Accessed 30 July, 2018

Global Impact and Potential of Engineering

‘God of sight’ has restored the vision of 100,000+ people in poverty-stricken areas worldwide

http://www.ntd.tv/inspiring/life/god-sight-restored-vision-100000-people-poverty-stricken-areas.html Accessed on: 2018-04-09

39 million blind, half because of cataracts.
80% treatable if patients can afford - WHO

"In 5 minutes, he lets the blind see"
https://www.nytimes.com/2015/11/08/opinion/sunday/in-5-minutes-he-lets-the-blind-see.html

Sanduk Ruit, Eye Surgeon, Nepal

Pioneered small-incision cataract surgery

Global Impact and Potential of Engineering

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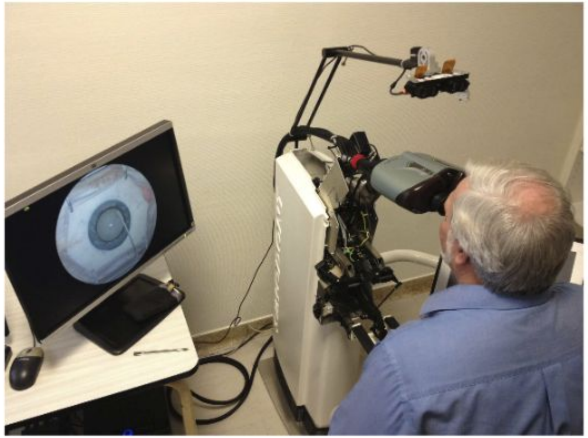
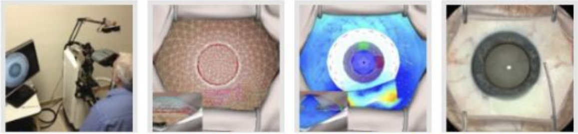
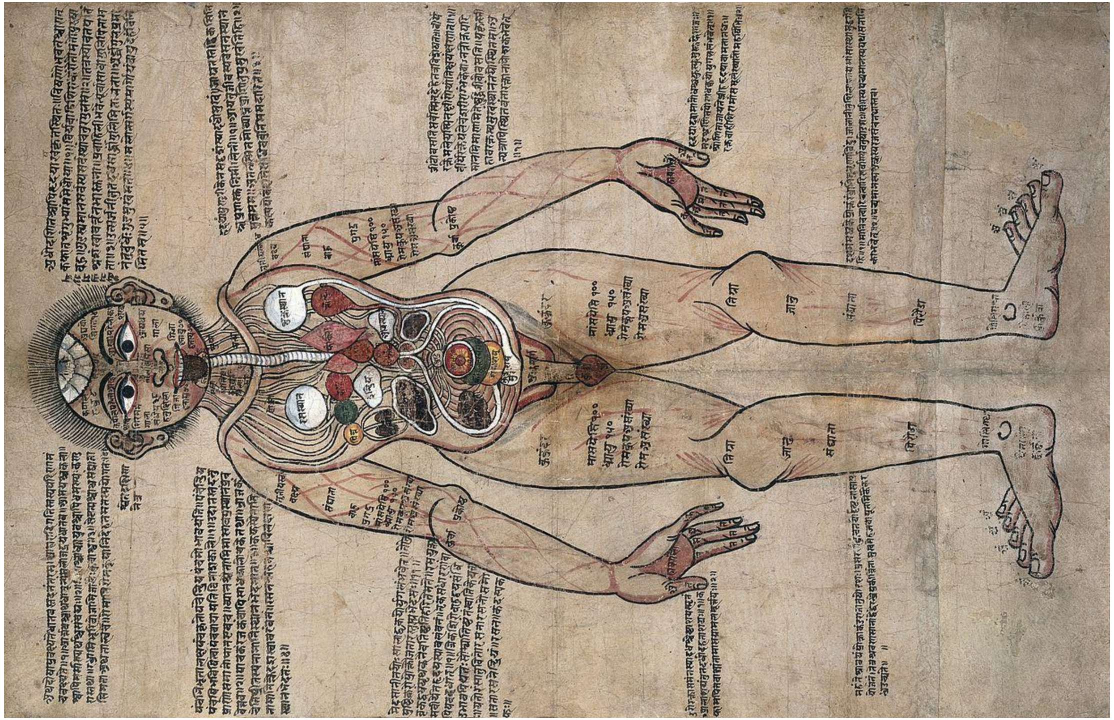




MIMESIS, INRIA, IHU Stratsbourg http://mimesis-dev.loria.fr/projects/help-me-see-cataract-surgery/

Look Inside & Understand Everything Non-Invasively

The Ayurvedic Man Nepal c. 18th century



https://en.wikipedia.org/wiki/History_of_anatomy