Health Informatics

Where we are now, and where we may be going

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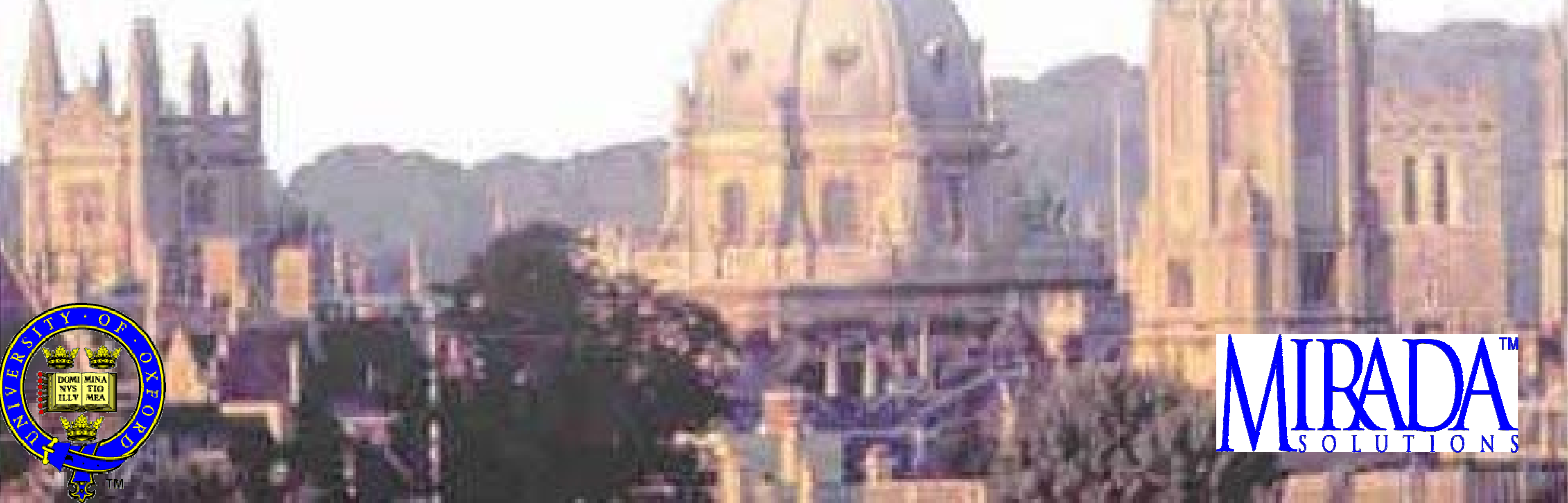


Modern Healthcare

- Continuing surge in knowledge about medicine
  - New ways to diagnose, treat and cure disease
- Continuing ignorance
  - Mental illness, stroke management, arthritis
  - Malaria & other tropical diseases
  - Detect early/cure heart disease and cancer
- Ageing population
  - Life expectancy (in the West) is increasing
  - The body is already outliving the brain
- Social, political, economic challenges
  - Expectation vs reality
  - developed and undeveloped worlds

Health Informatics is changing

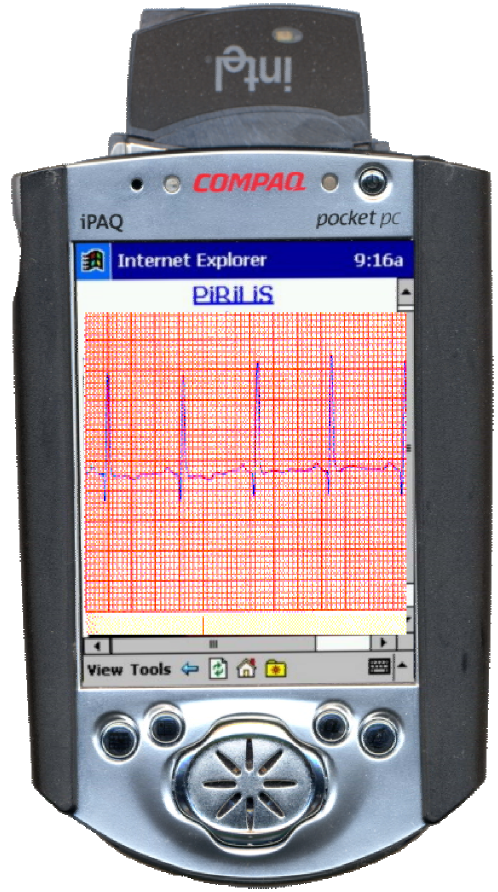
- Move to evidence-based medicine
  - Reasoning becomes explicit
  - Based on signals, images, clinical signs, …
  - (team-based) decision making under uncertainty
- Treatment of disease to anticipation of disease
  - Early diagnosis → better prognosis
  - Prophylactic medicine – the positive role of insurance companies
- Opportunities arising from genomics (and proteomics) to detect and unravel individual variation, stratify patients into disease and treatment groups
  - "Personalised medicines"

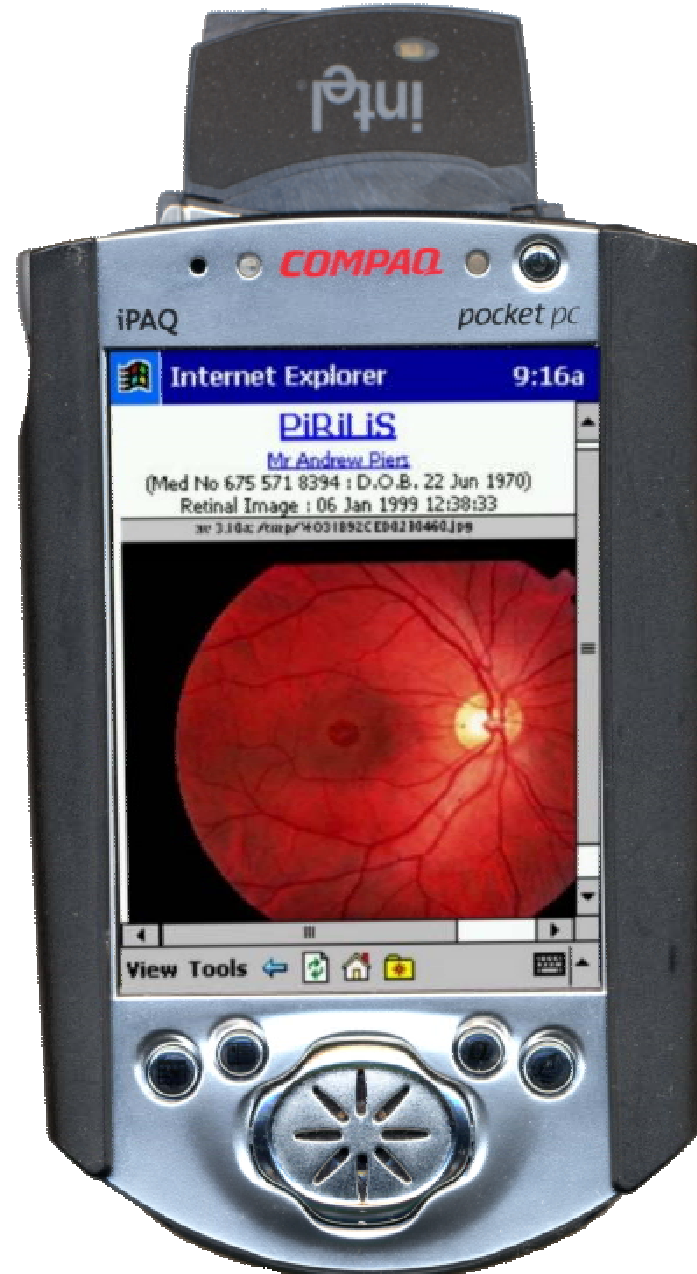
Technological assumptions

- Stream of new, better imaging & signal modalities
- Moore's law will continue, at least for a while
- The emergence of the Grid
- Computers will get smarter
- Health professionals will be increasingly IT literate
  - IT devices will be used
  - IT devices will replace paper & pencil

Waveforms and images anywhere, anytime

The Clinician is always in touch with the full Patient Record



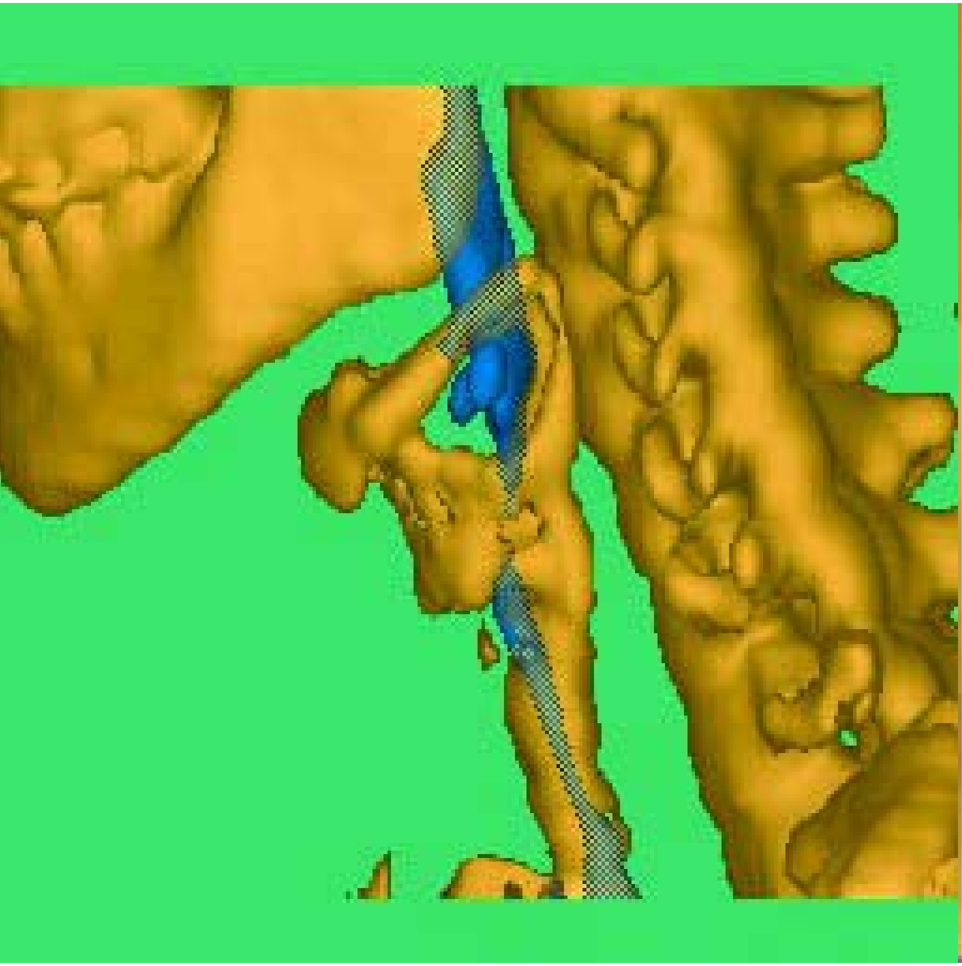


… on the ward round

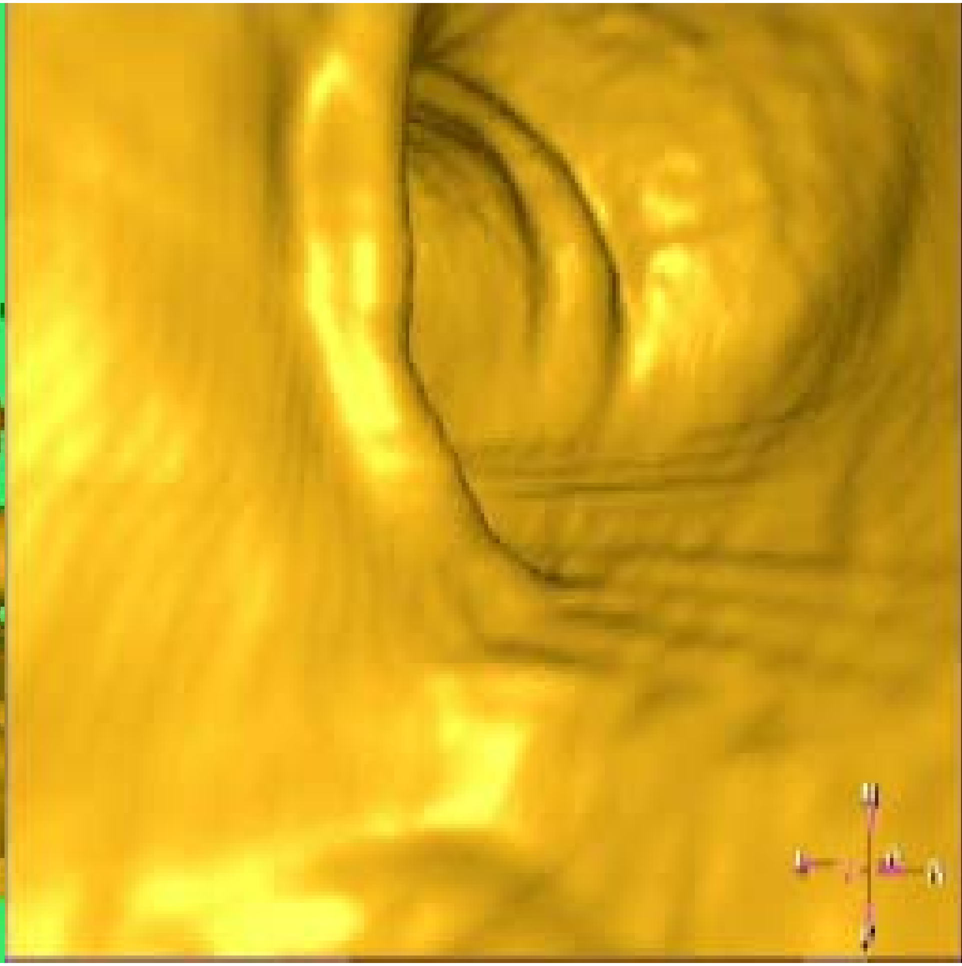
Current reality of health informatics

- Predominantly visualisation, little analysis
  - Registration (CT-PET), overwhelmingly rigid
  - Predominantly manual segmentation
  - Shape analysis is virtually non-existent
- Intensive therapy units are intensively staffed
- PACS – but images only, text separately
- Patient records and BNF on screen for primary physicians
- Teleradiology doesn't exist
- No fielded AI systems
- Surgery has been largely unaffected by Informatics
  - few planning systems, no post-surgical prediction, ...
- Industry is conservative

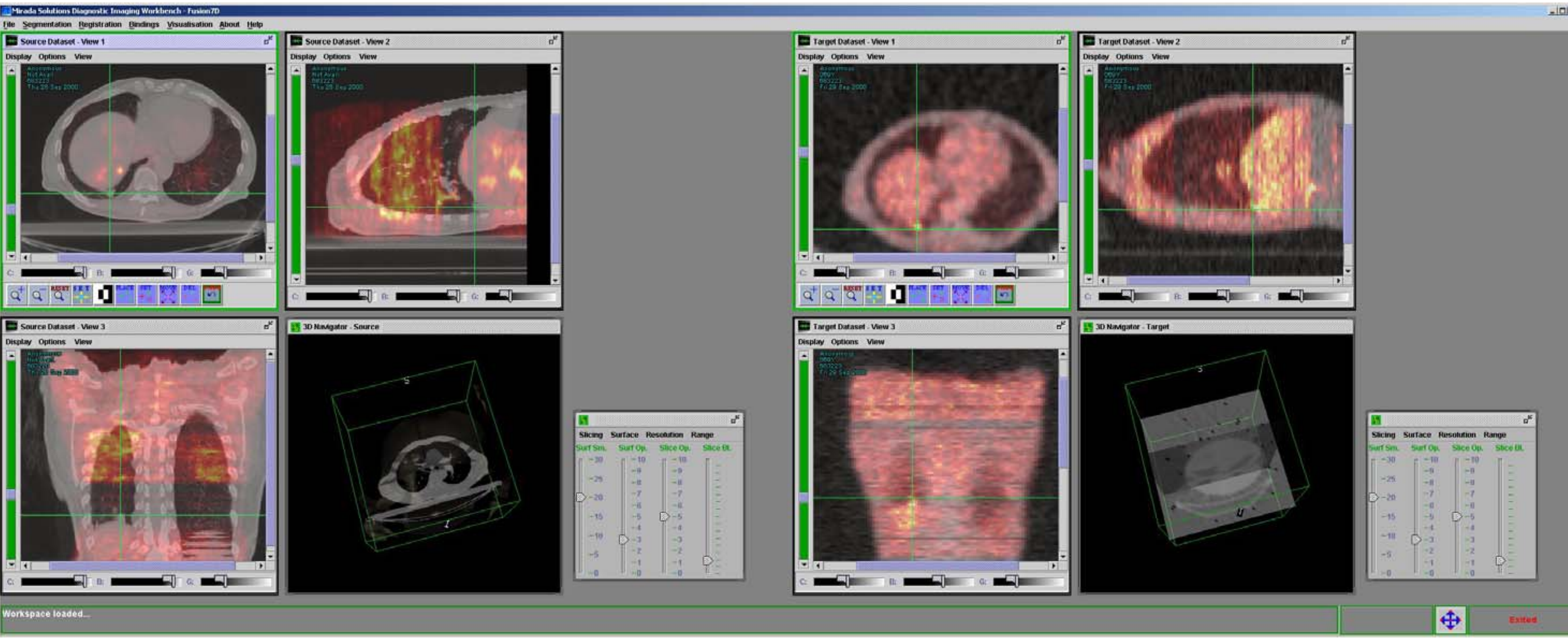
3D visualisation



CT virtual colonoscopy

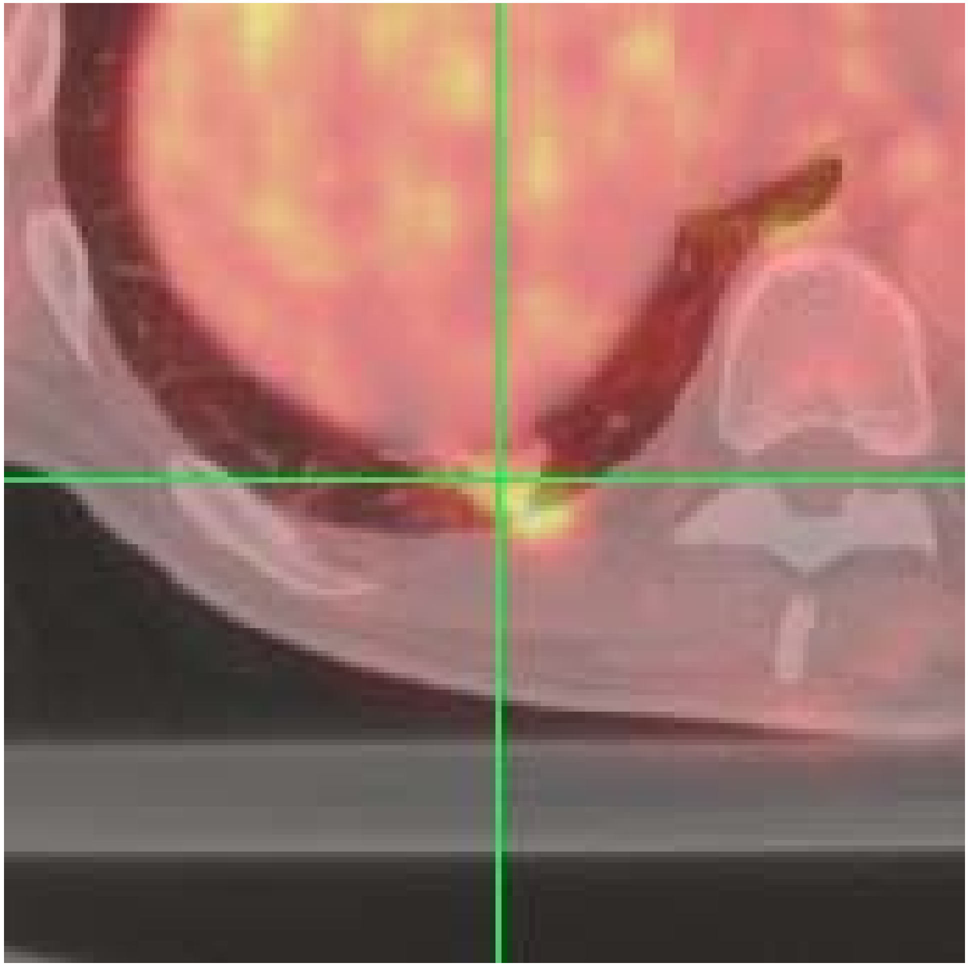


CT – PET registration



Non-rigid registration is necessary

Rigid registration poor



Is the tumour in the lungs or the stomach?

Fusion7D

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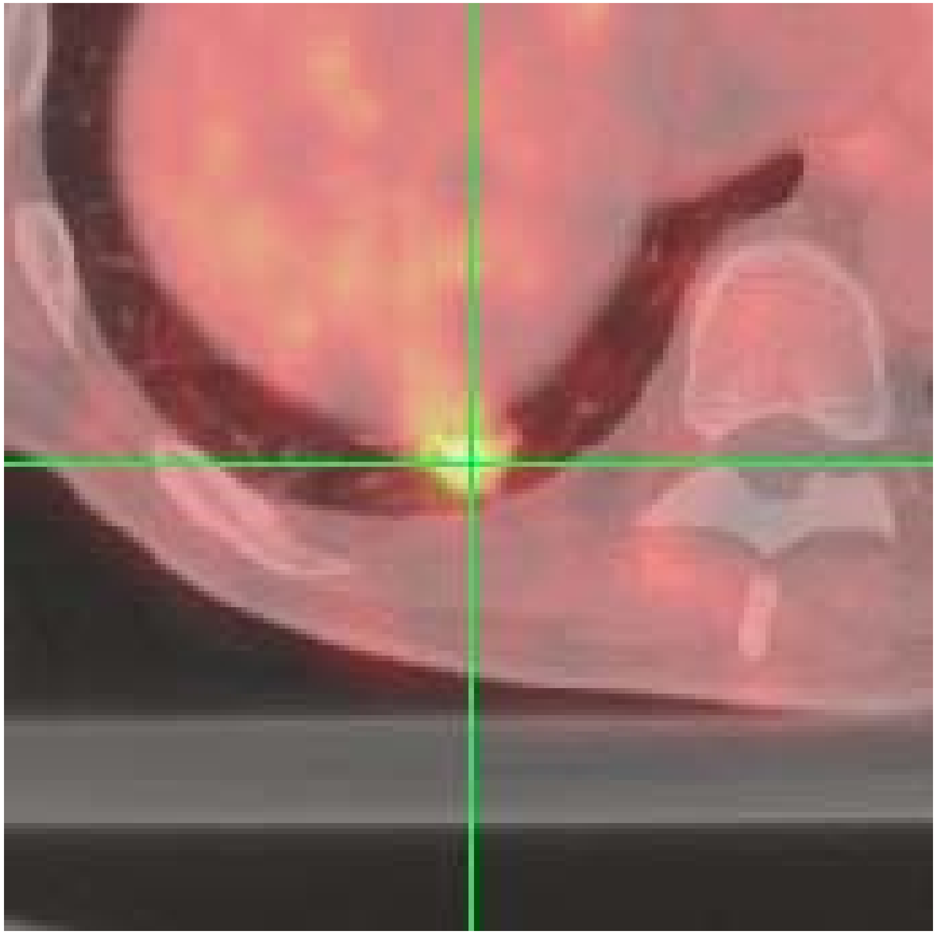
Non-rigid registration



Clinical use implies regulatory approval

Regulatory approval necessitates quality software processes

Researchers do not adhere to quality software processes

Fusion7D

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Glimpses of the future

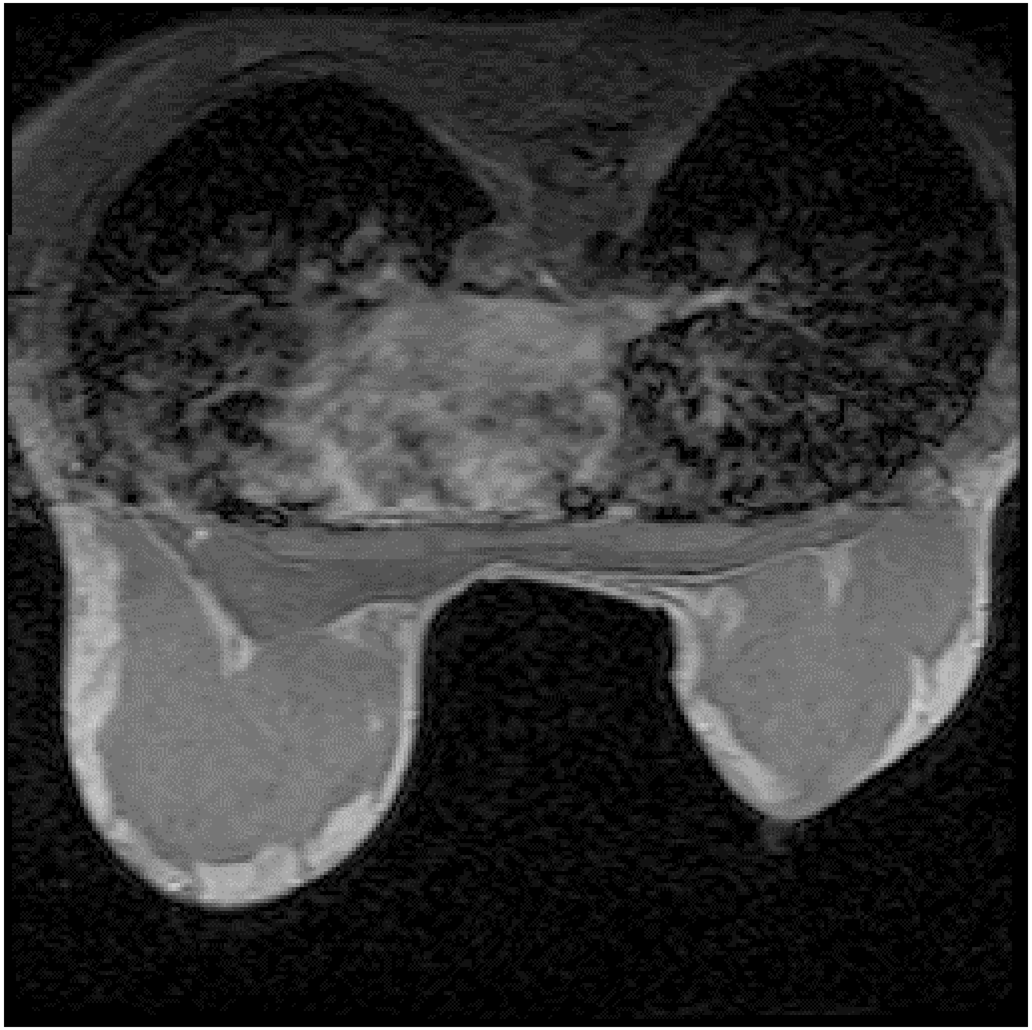
- Functional image analysis
- Multiscale modelling
- Intelligent imaging
- Histopathological image analysis
- Minimally-invasive surgery
- Avoiding surgery
- Molecular imaging
- New ways to image
- Intelligent systems
- The potential of the Grid
- Ubiquitous computing

Functional image analysis

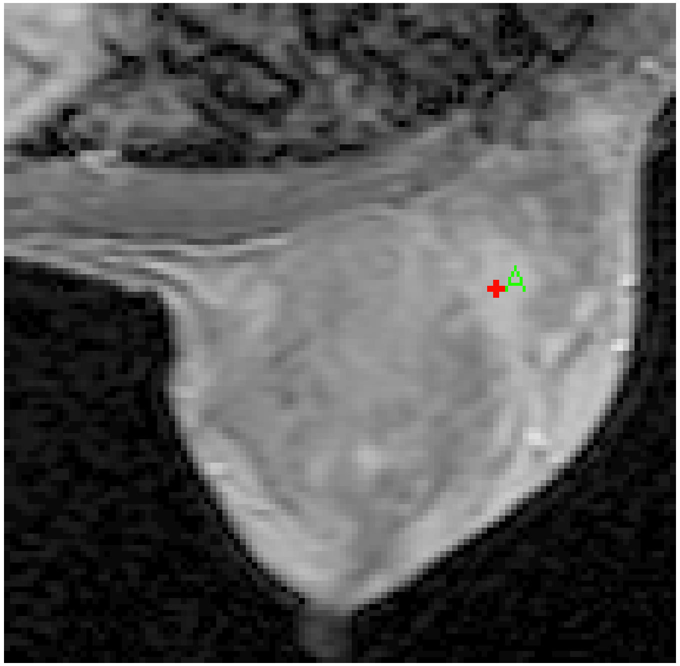
- T_1 imaging of tumours
- BOLD and Probabilistic ICA
- Diffusion-weighted imaging
- PET & MEG

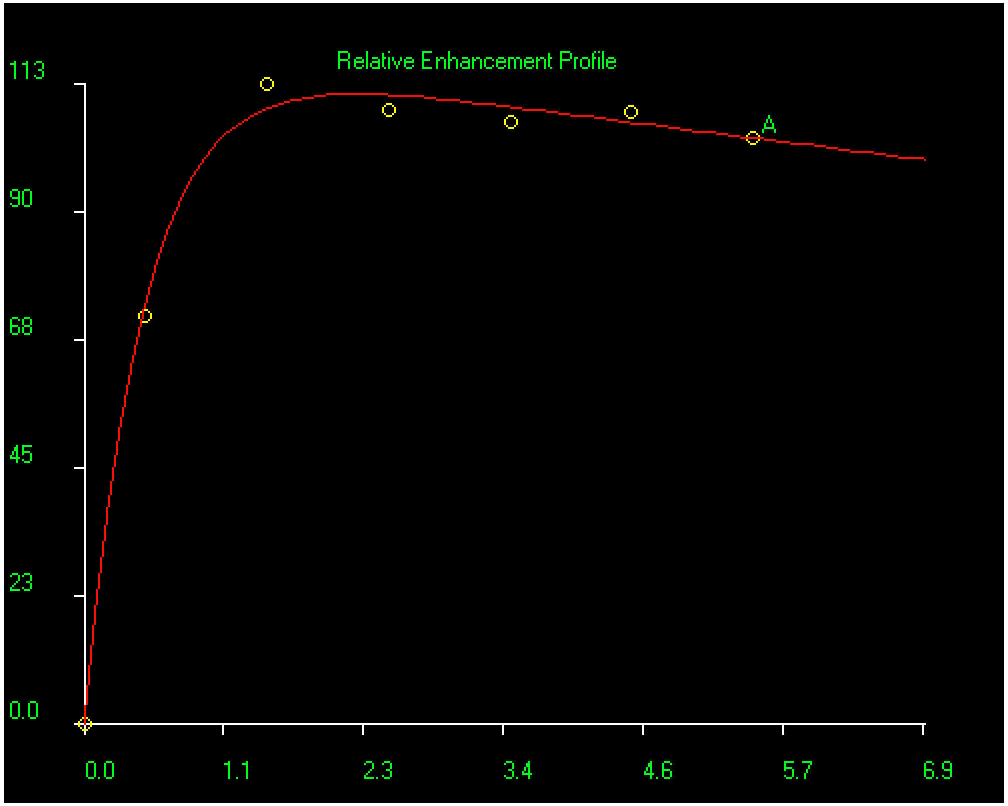
Clinical Procedure.

1. A pre-image is taken,
2. Contrast agent is injected (Gd-DTPA)
3. Post contrast Images are acquired as fast as possible



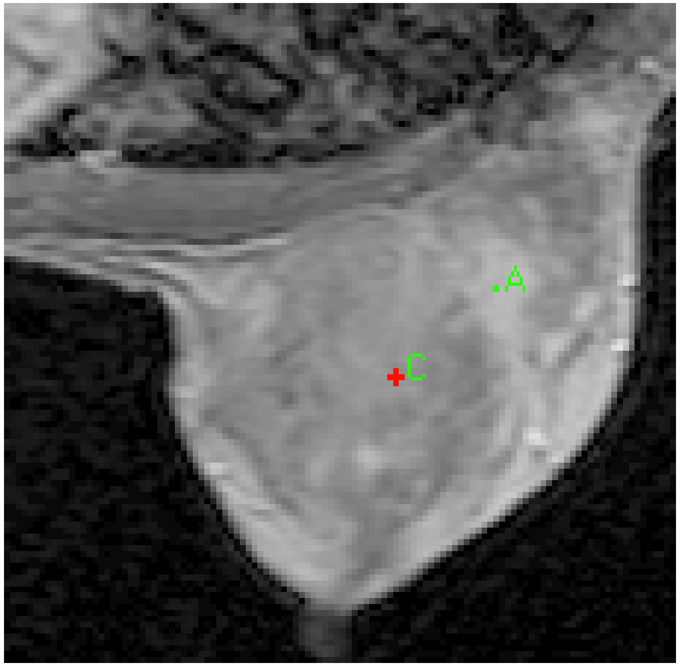
Contrast agent take-up

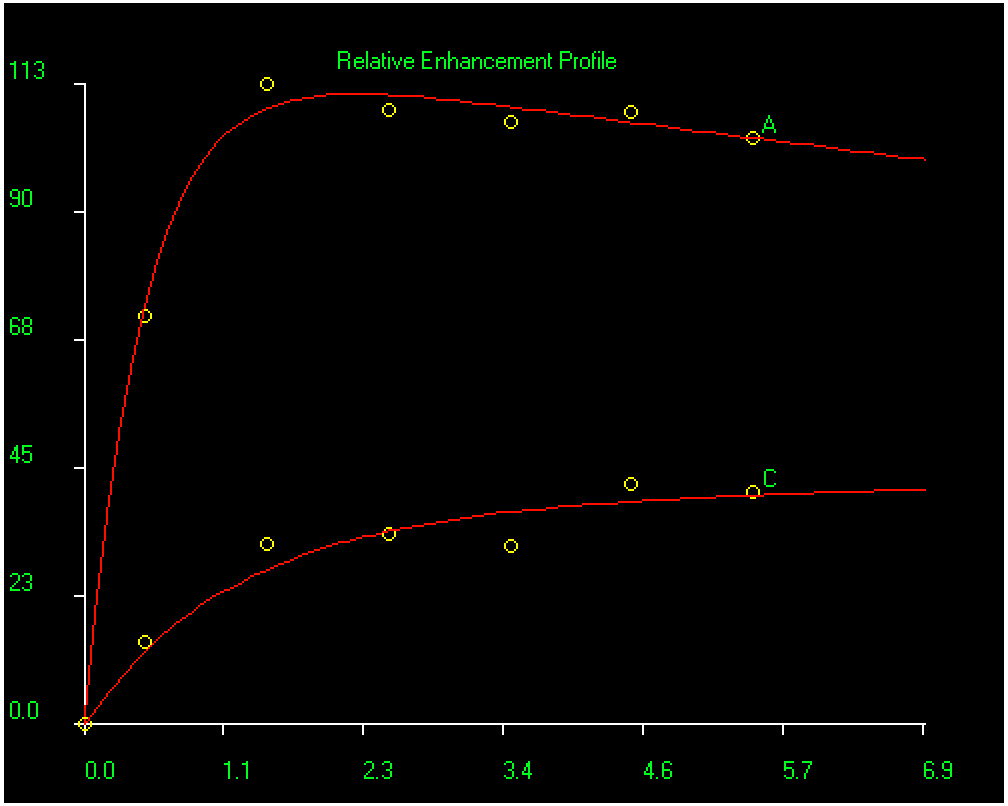




Inside the tumour, the enhancement is high & fast

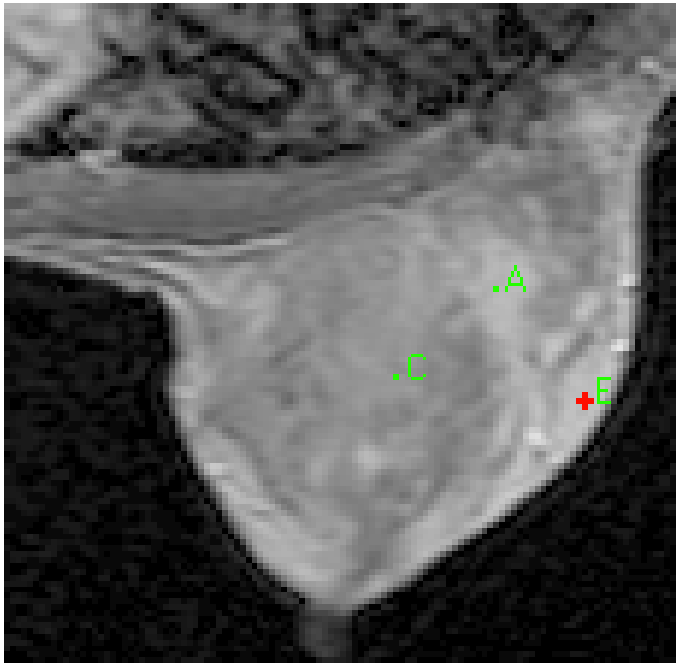
Contrast agent take-up

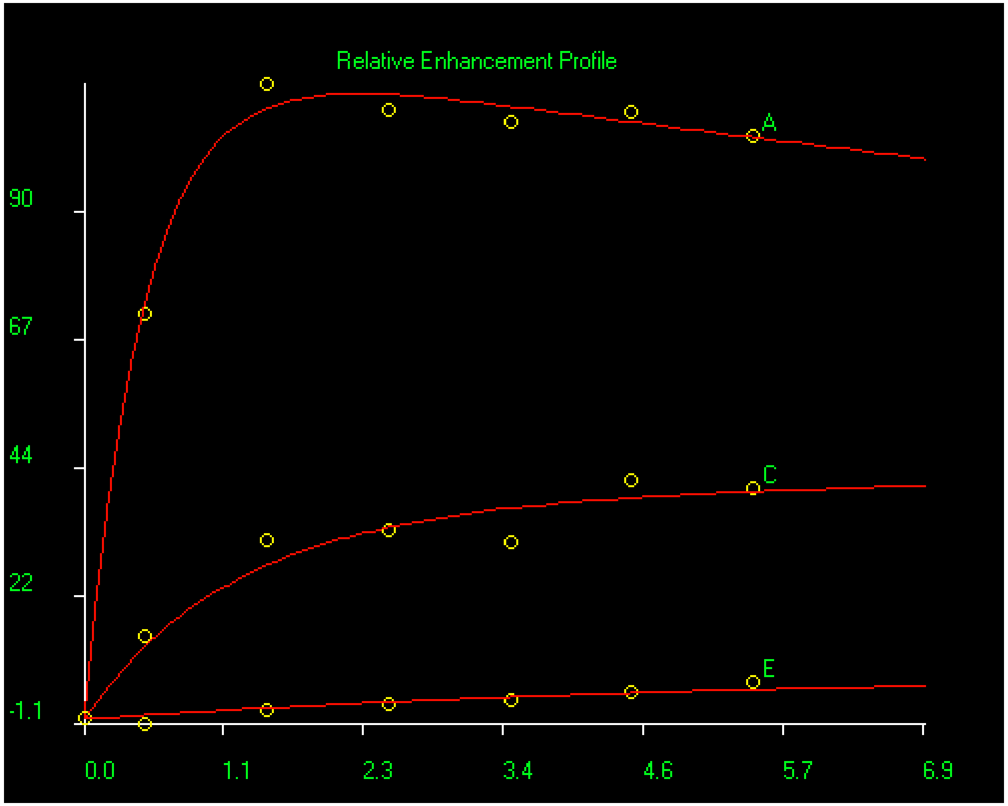




.. Normal tissue enhances less …usually

Contrast agent take-up

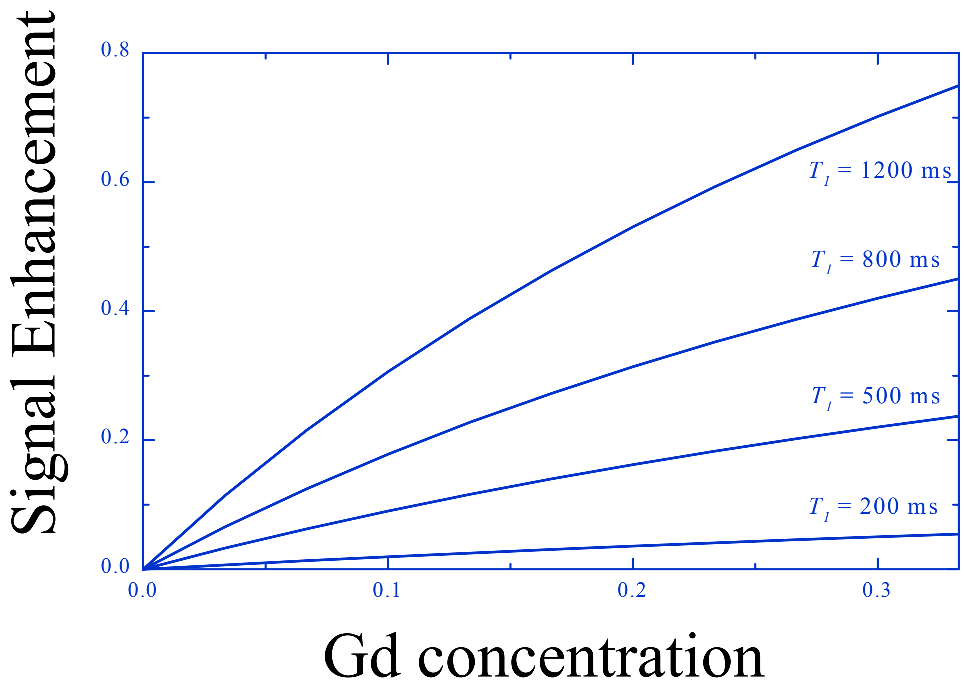




.. Whereas fat barely enhances at all (no perfusion)

Signal Enhancement vs Gd concentration

$$E(C_t) = \frac{S(C_t)}{S(0)} = e^{-TER_2C_t}\left(\frac{1 - e^{-TR\left(\frac{1}{T_1}+R_1C_t\right)} - \cos\alpha\left(e^{-TR/T_1} - e^{-TR\left(\frac{2}{T_1}+R_1C_t\right)}\right)}{1 - e^{-TR/T_1} - \cos\alpha\left(e^{-TR\left(\frac{1}{T_1}+R_1C_t\right)} - e^{-TR\left(\frac{2}{T_1}+R_1C_t\right)}\right)}\right)$$

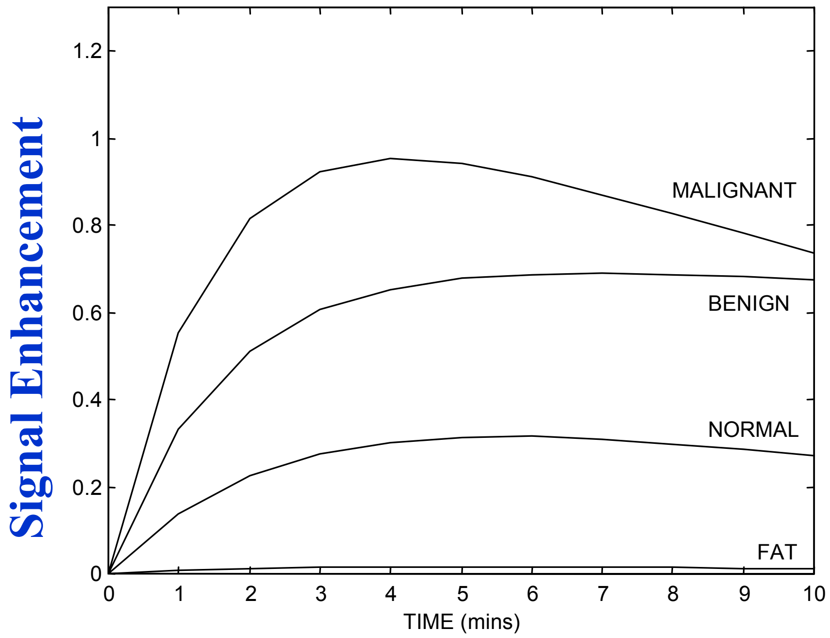


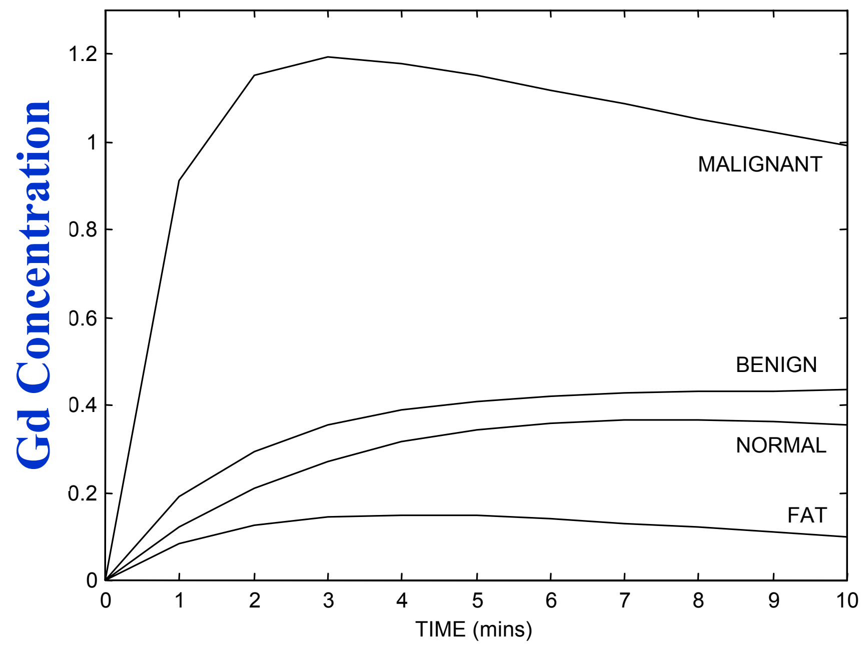
Nonlinear variation with T_1

⇨ T_1 must be measured

Three low flip angle acquisitions prior to Gd enable T_1 and its change to be measured

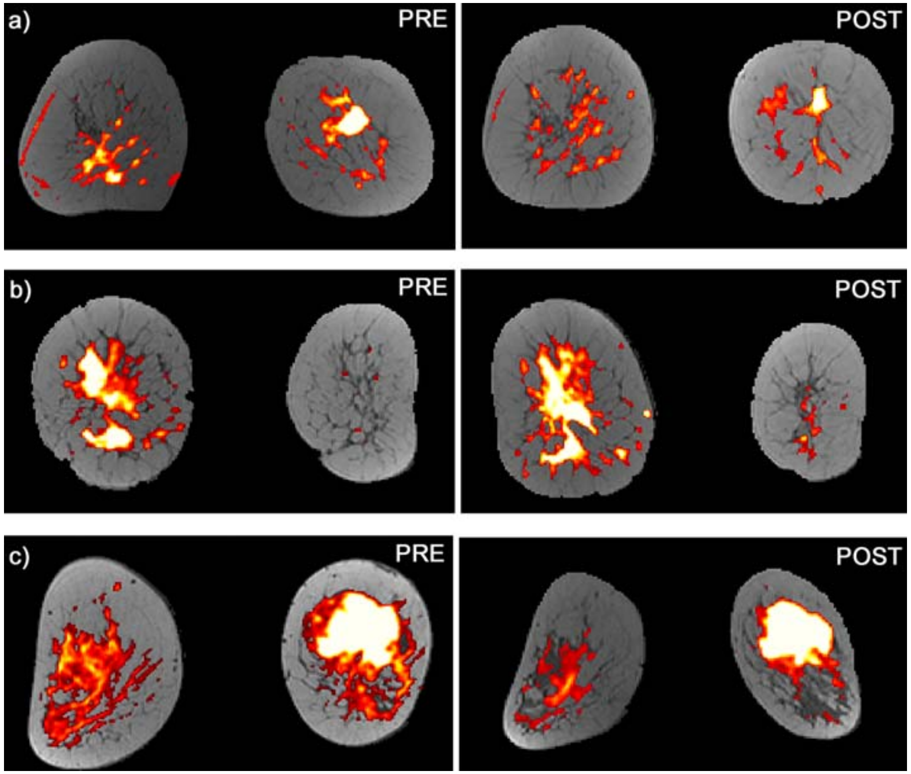
From Signal Enhancement to Gd Concentration



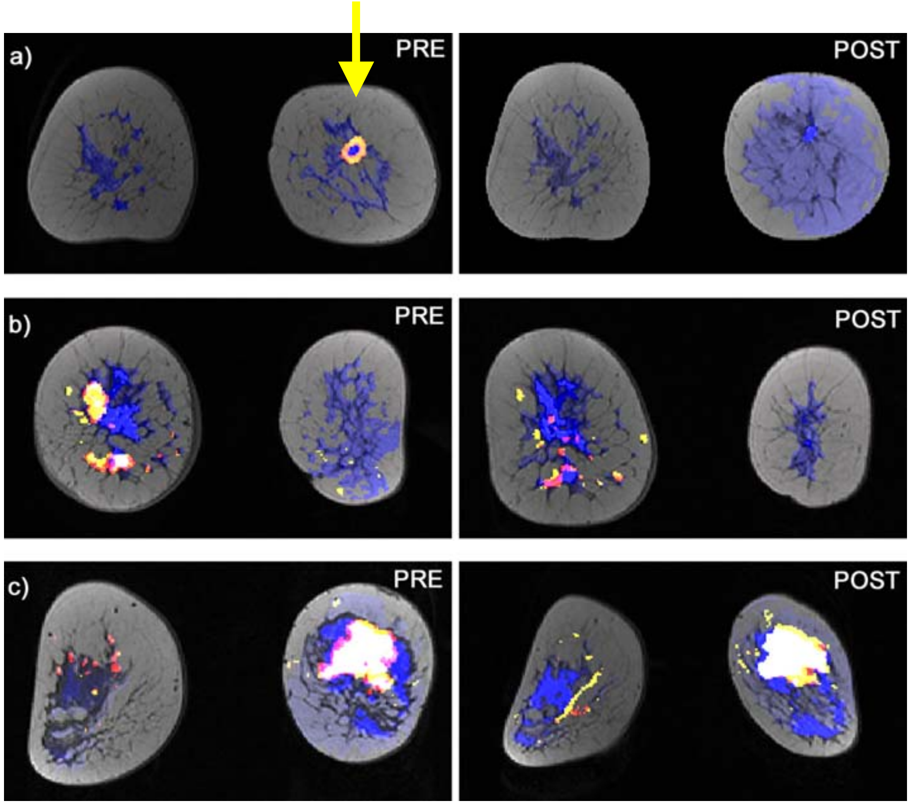


Malignant to benign distinction is improved using concentration based analysis

Quantifying effect of chemotherapy

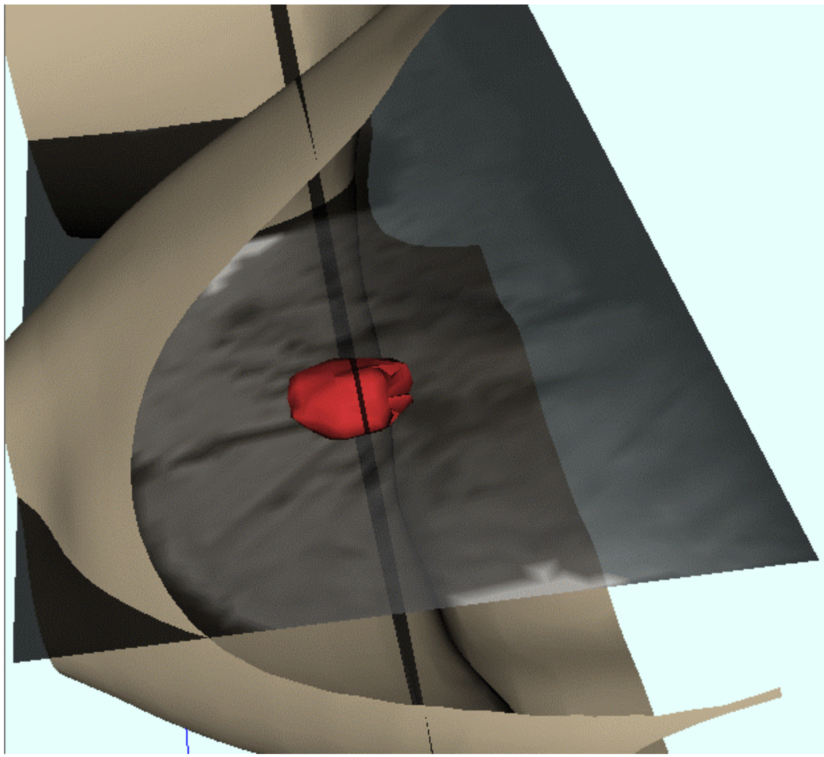


Pre- (left) and post-chemotherapy (right) Percentage increase in intensity

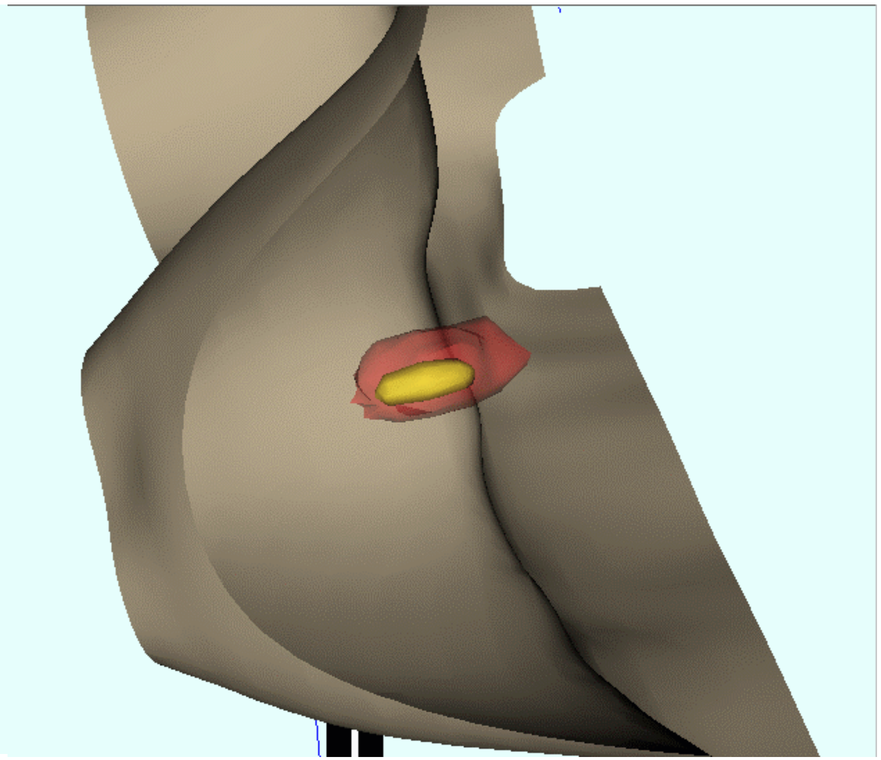


Pre- and post-chemotherapy ΔT_1

Pre- and post-chemotherapy



Pre-chemotherapy

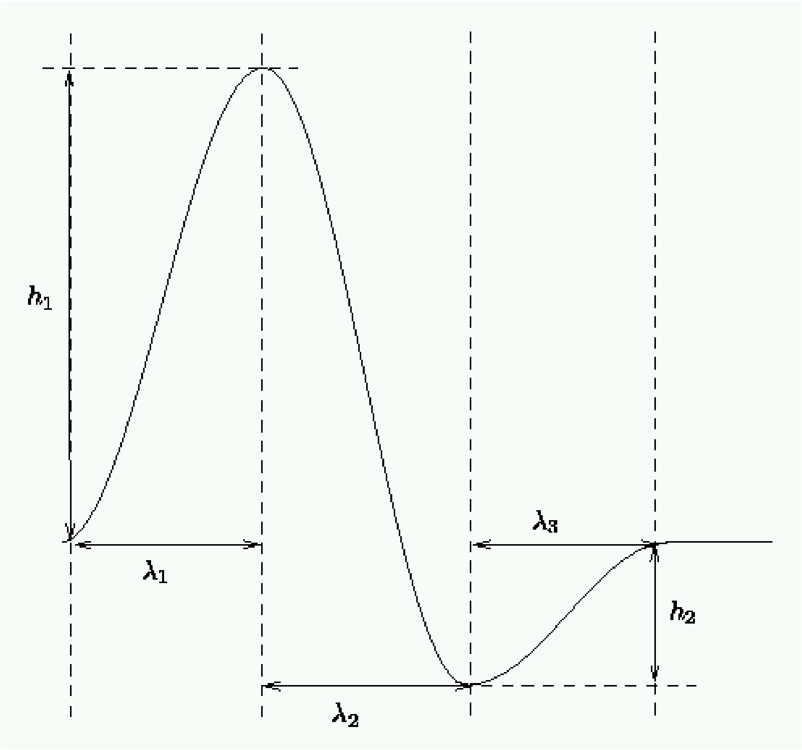


Post-chemotherapy after registration with pre-chemo

"The viable part of the tumour has reduced by 31%"

Functional MRI: BOLD effect

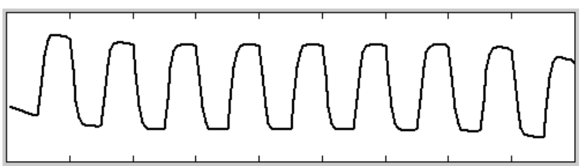
- Blood Oxygenation Level Dependent
- Haemodynamic response function
  - Parametric form assumed
  - Assumed constant
- HRF varies temporally and spatially

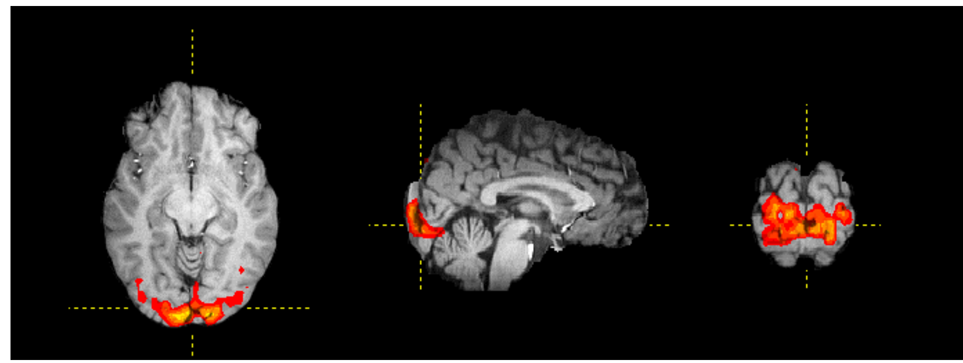


General Linear Model and PICA

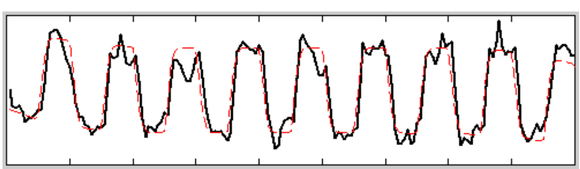
audio-visual data - GLM with assumed and estimated model time course

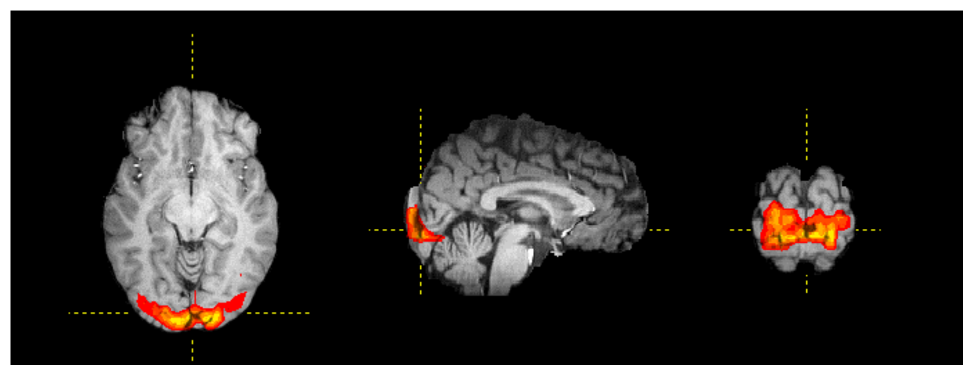
GLM model time course





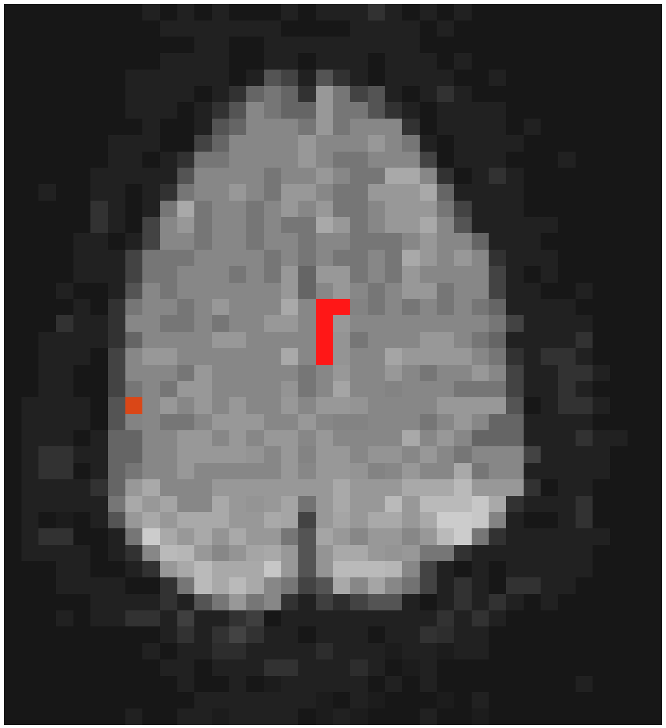
ICA time course



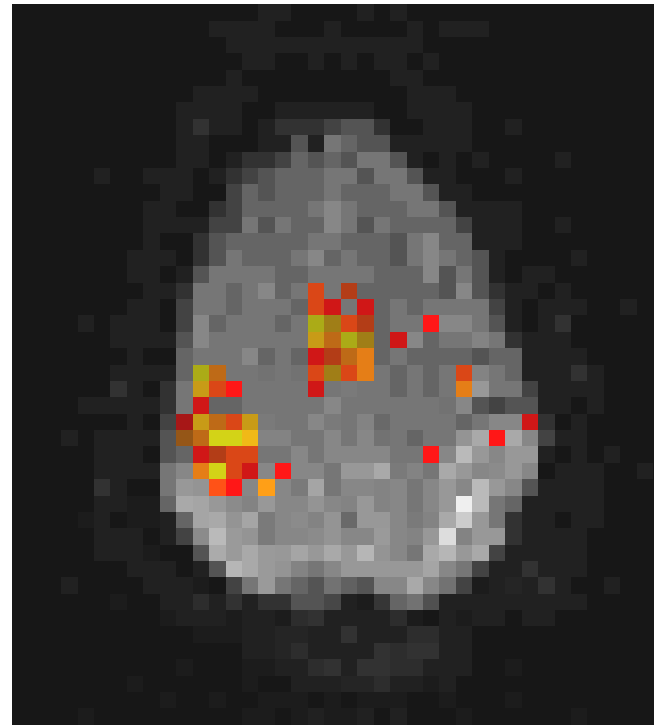


Probabilistic ICA enables adaptive estimation of spatial and temporal changes to HRF

Recent research suggests that FMRI may be able to define the brain changes responsible for recovery after stroke



There is little brain activation with movement after stroke...



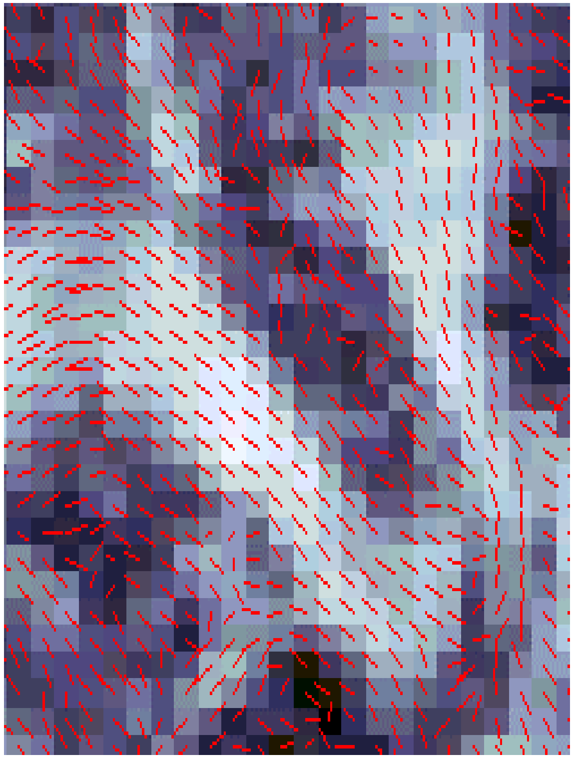
But activation is increased after physiotherapy and further recovery

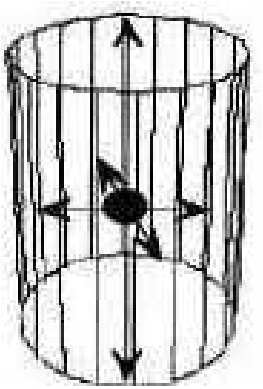
Analysis of fMRI data should be spatio-temporal but most analysis makes the naïve assumption that voxels are independent signals

Recent work by Habibi at ISERM (La P-S) show how better networks from AI can be combined with fMRI analysis

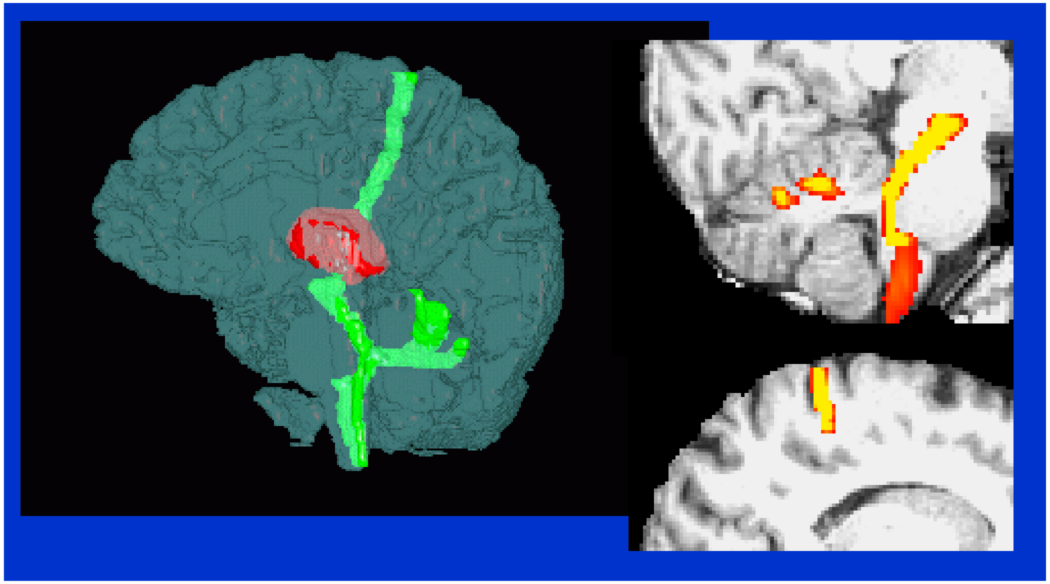
Diffusion Imaging

- Measure self diffusion of protons in every voxel.
- In white matter areas – more diffusion in fibre direction.

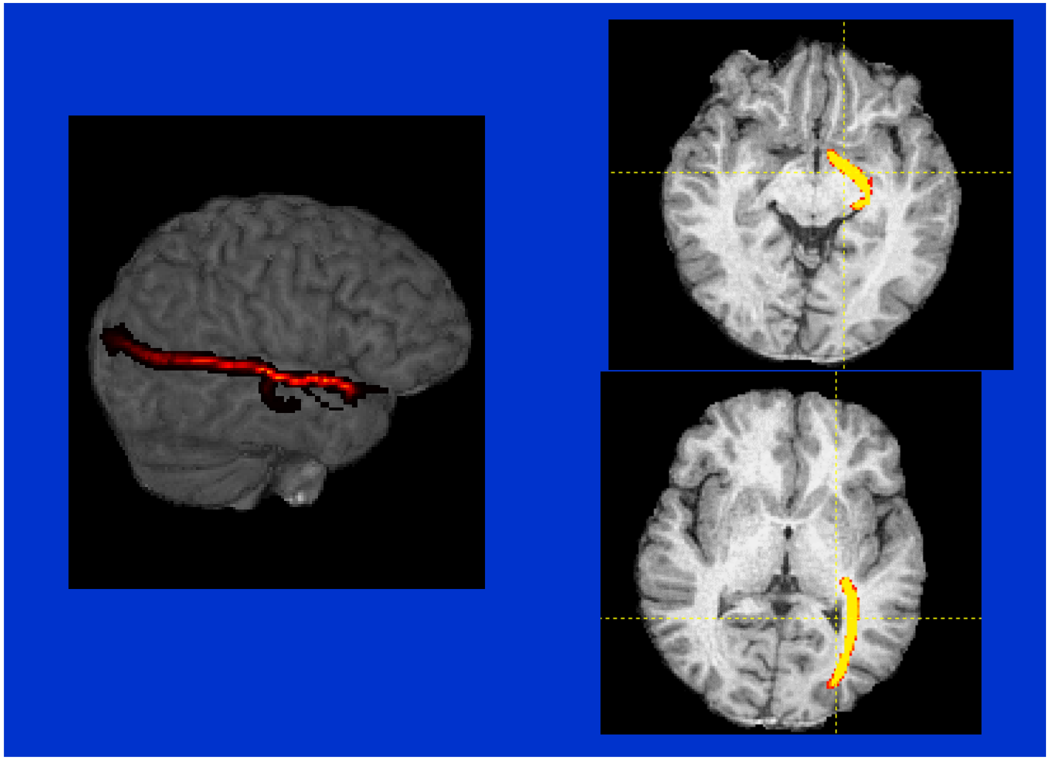




We can measure e.g. principle fibre direction and “anisotropy” (Strength of fibre direction).



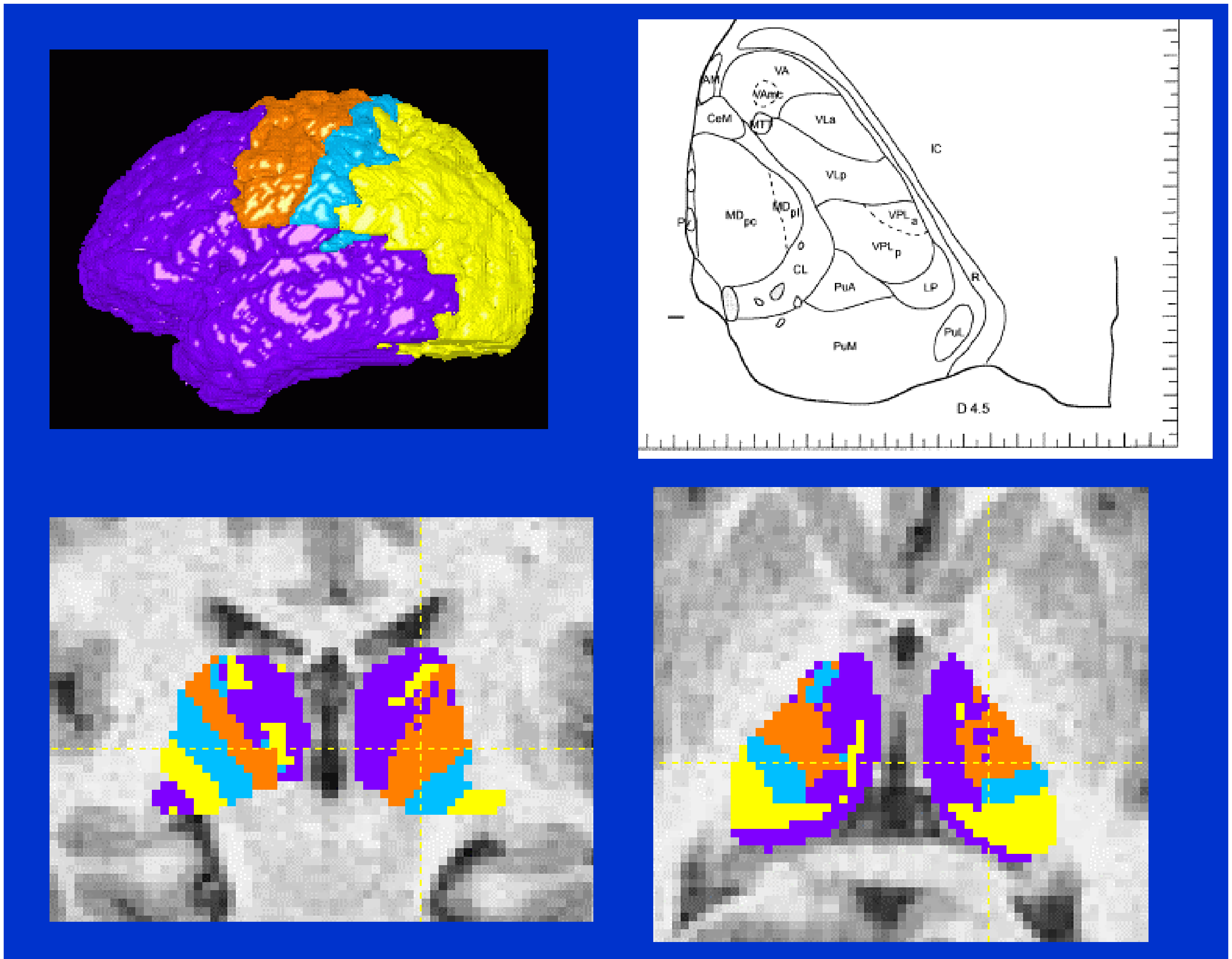
White matter tract from Ventral Lateral nucleus going to M1, cerebellum and brainstem



White matter tract from LGN going to optic tract and visual cortex

“Tractography”

Segmentation of left and right thalami, based on projections to 4 cortical zones.

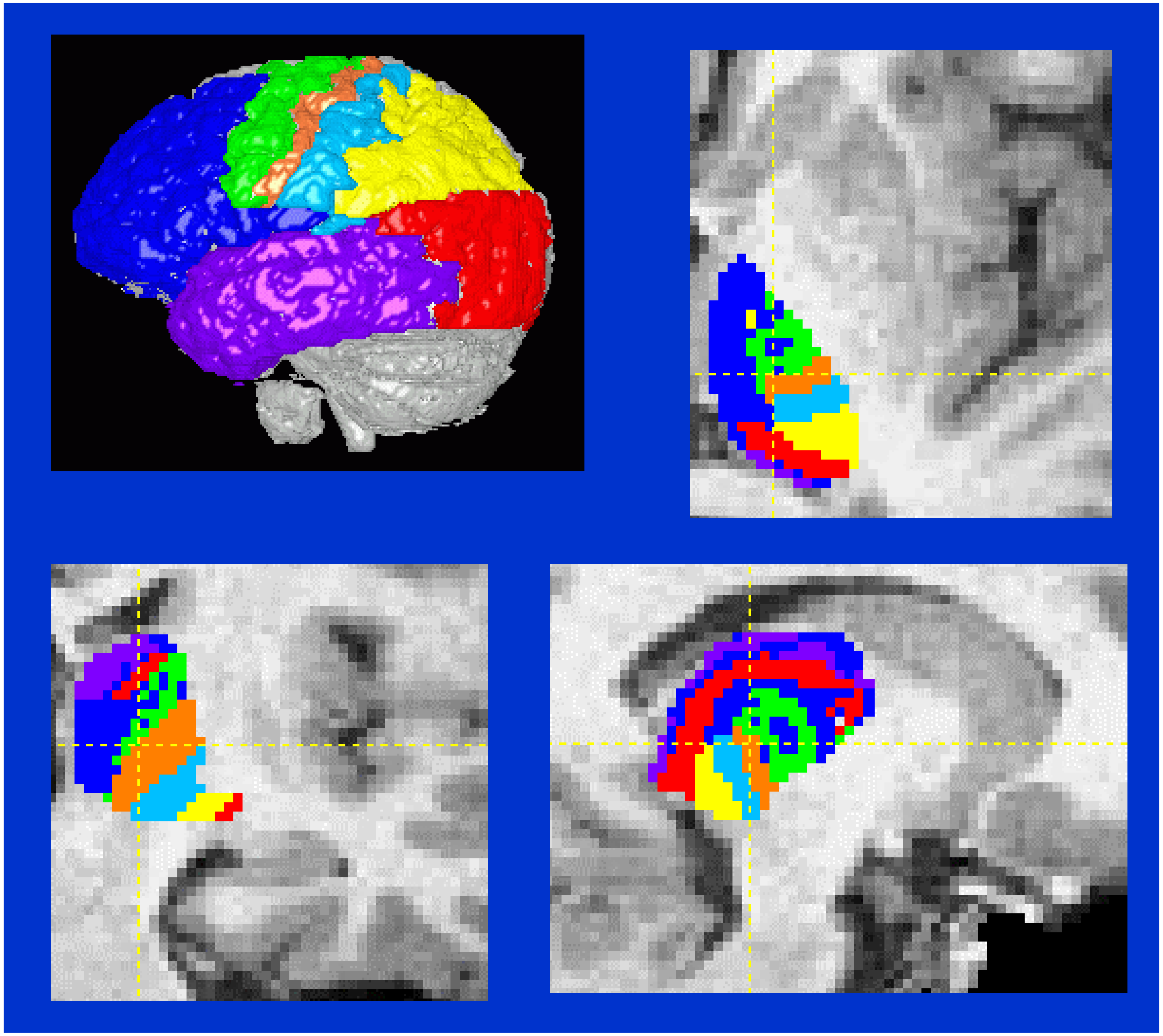


Purple: Mediodorsal nucleus
Projects to PFC, receives from temporal lobe

Blue: Ventral posterior nucleus, projects to S1/S2

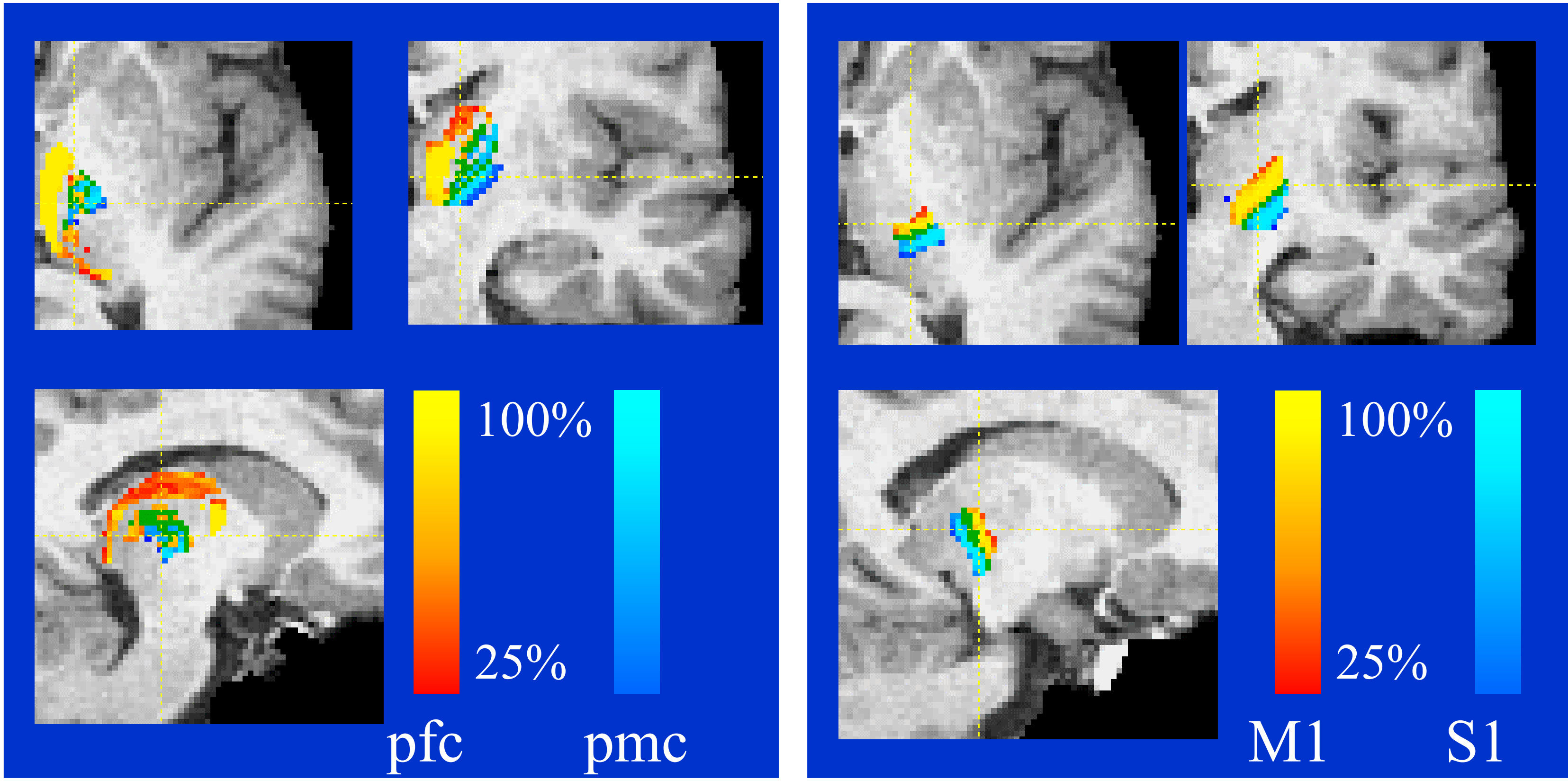
Orange: Ventral lateral and ventral anterior nuclei.
Project to M1 and PMC/SMA

Yellow: Pulvinar, projects to PPC and extrastriate cortex.



Subdivisions of right thalamus based on connections to 7 cortical zones

Blue: PFC; Purple: temporal; Green: PMC/SMA; Orange: M1; Light blue: S1/S2; Yellow: PPC; Red: occipital lobe/optic tract



Probabilistic mapping of connections

Functional image analysis

Take home message:

need to understand the physics of image formation

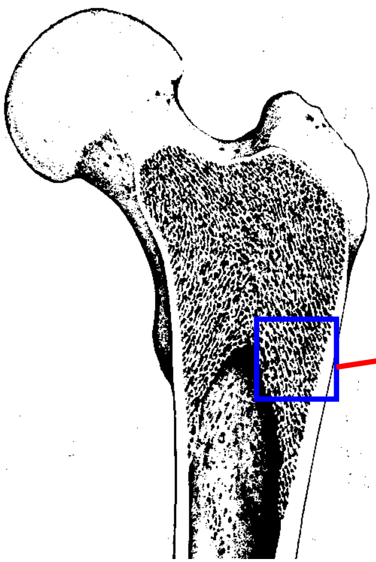
and its interaction with biology and physiology

Theme for the 21st century: Convergence of physics, Informatics and Biology

Multidimensional modelling

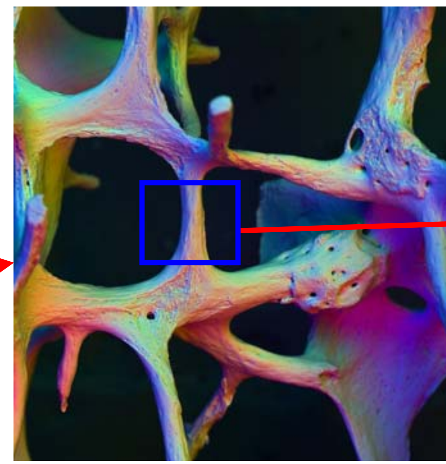
- Multi-scale modeling
  - cell to organ and whole system
  - over a wide range of timescales
- Development/synthesis of physiologically-based models of cerebral physiology
  - haemodynamics, auto-regulation and metabolism
- Model $\Leftrightarrow$ signals/images
  - obtained continuously/intermittently

Changes to bone structure are given at multiple scales: leading to explanations that range from arthritis to cancellous bone



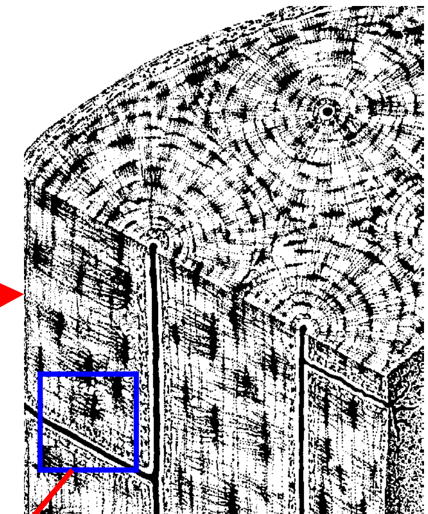
Mega scale ✓

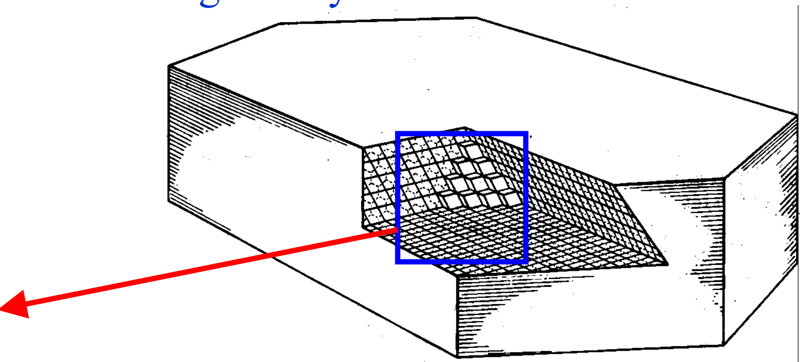
Rigid body mechanics



Macro scale: trabeculae ✓

Finite element analysis

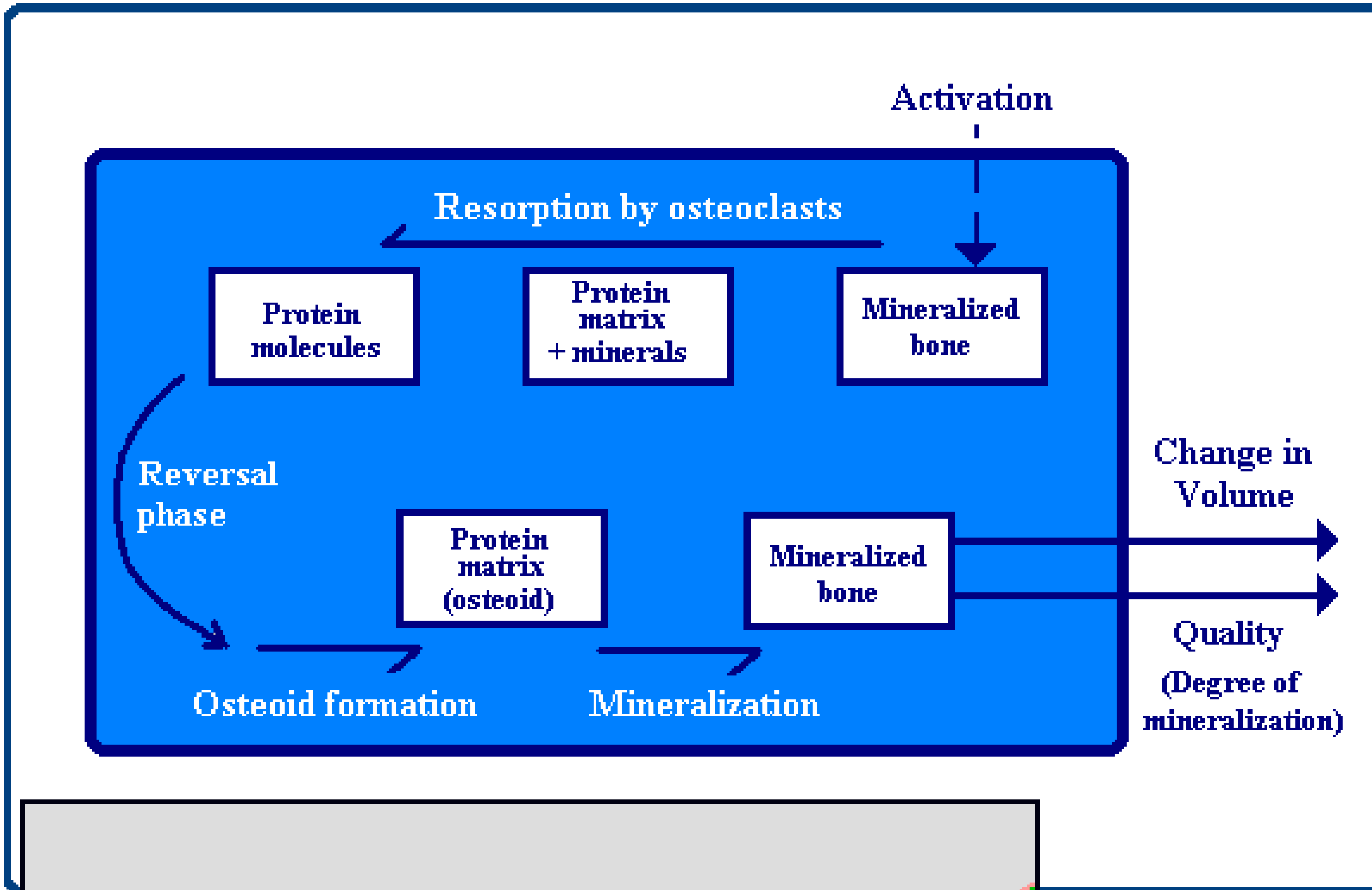




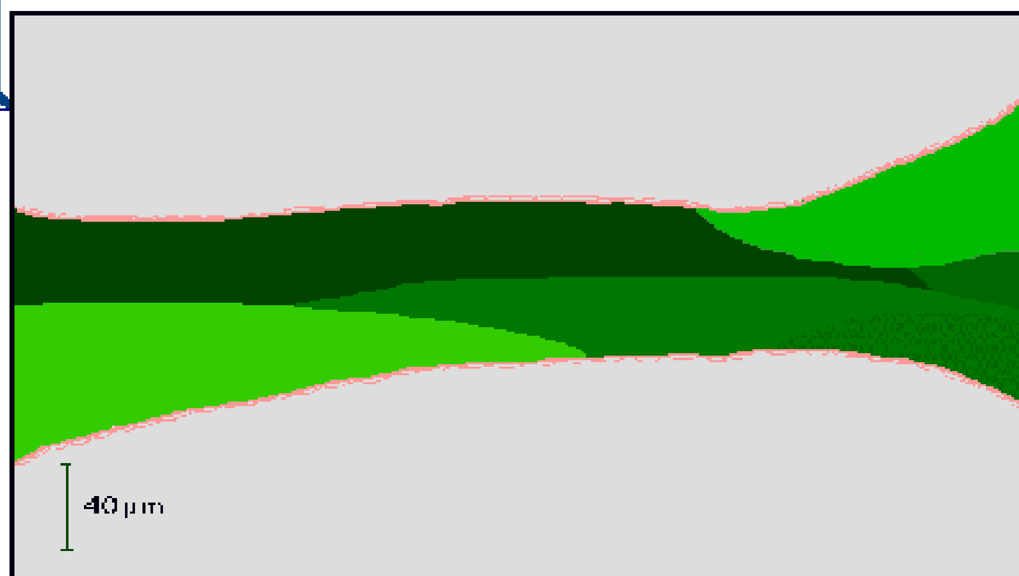
Micro scale: each trabecula is a complex biochemical structure

microscale model…

Cancellous bone and osteoclasts



Individual trabecula & mineralisation



Example: auto-regulation in the brain

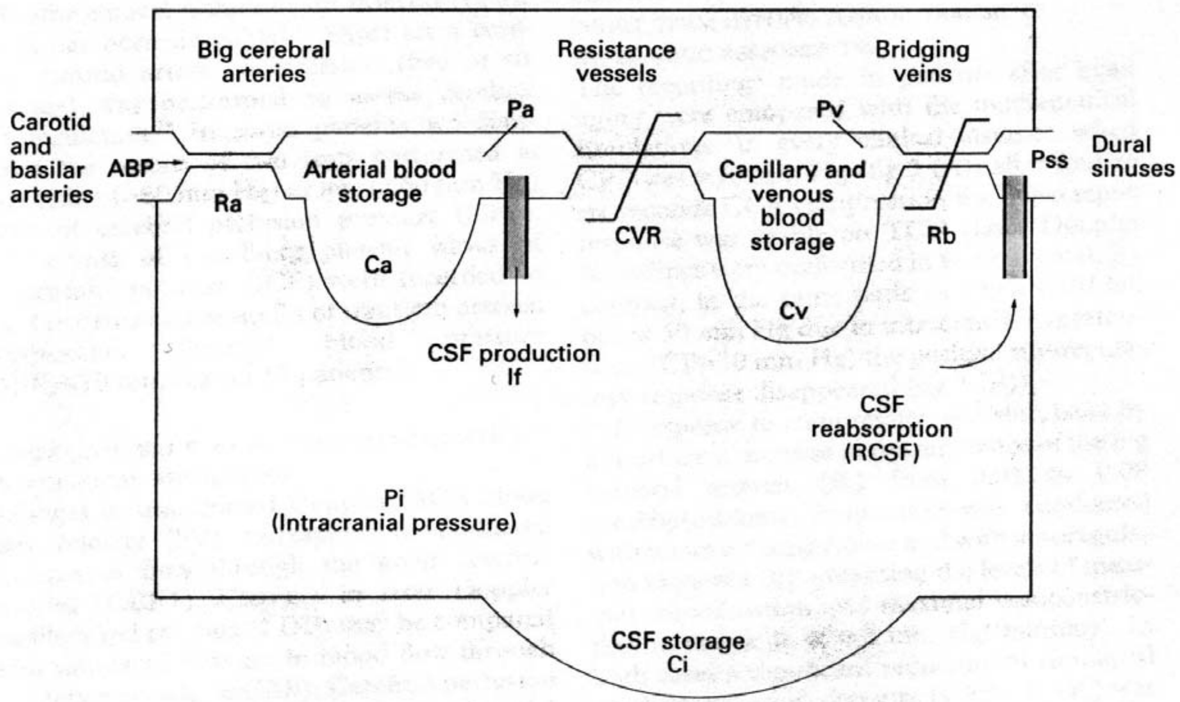
Investigation of novel methods based on these models to study auto-regulation, function and metabolism in:

- cerebral trauma
- systemic cardiovascular disease
- diffuse brain disease.
- (neonatal hypoxic-ischaemic injury)

NIR & vital signs monitoring

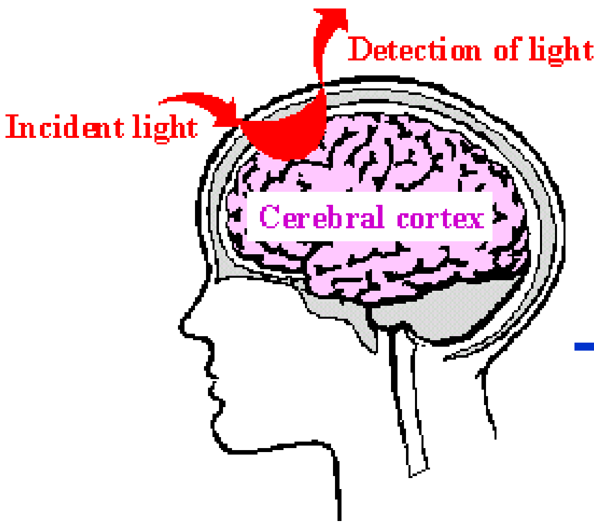
Physiological models

- hydrodynamic model of the blood flow passing through a series of vessels and compartments.



Model this using electrical components, control theory, and automatic parameter setting relevant to different patient settings

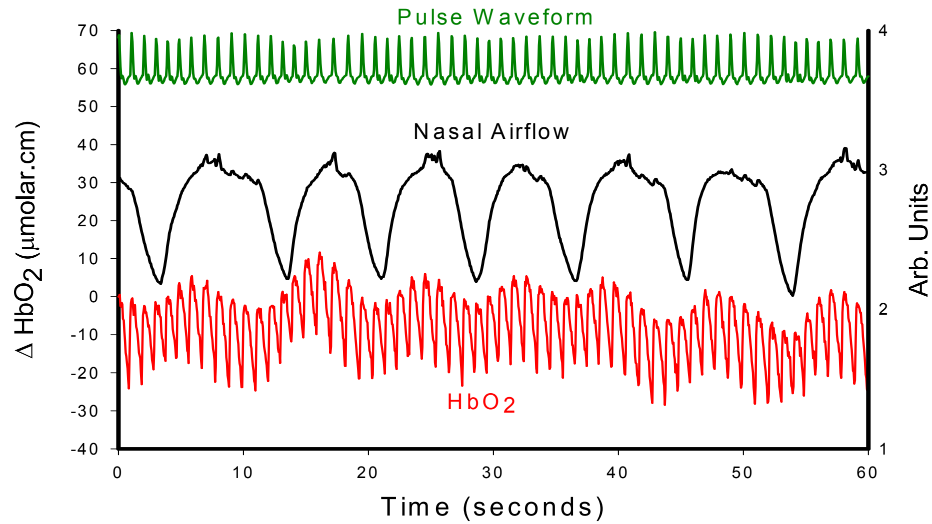
NIR topography principles



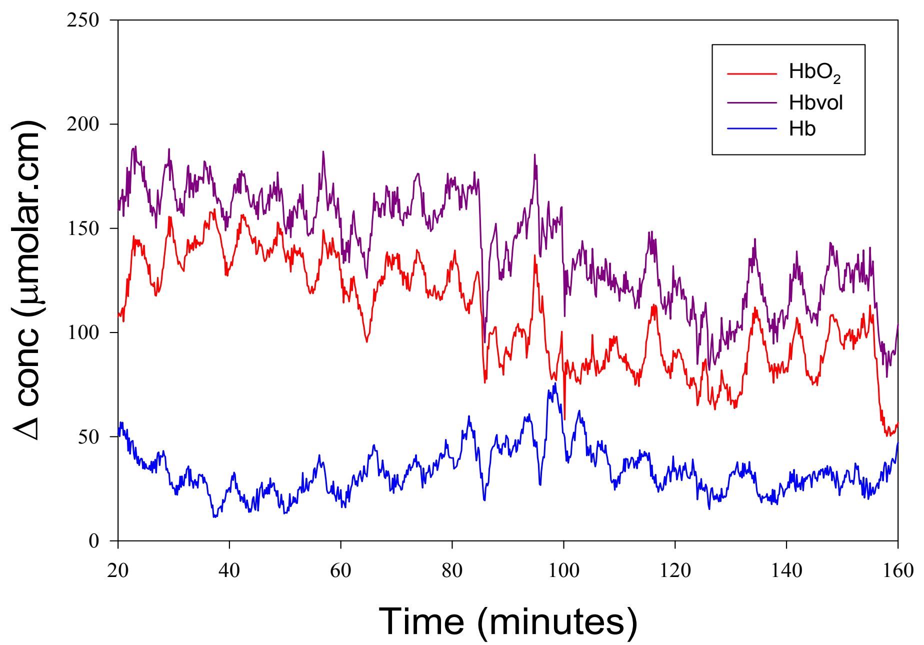
fetus

hydrocephalus

Cerebral NIR (red), Respiratory (black), and Cardiac Oscillations (green)



Long term Cerebral NIR Oscillations



Multidimensional modelling

Take home messages:

No single representation suffices: PDEs, belief networks, …

The full repertoire of engineering modelling techniques are needed

Agent architectures offer a novel way to integrate very different representations across a wide range of scales

Reprise of the main theme: state-of-the-art Informatics combined with Physics and Biology

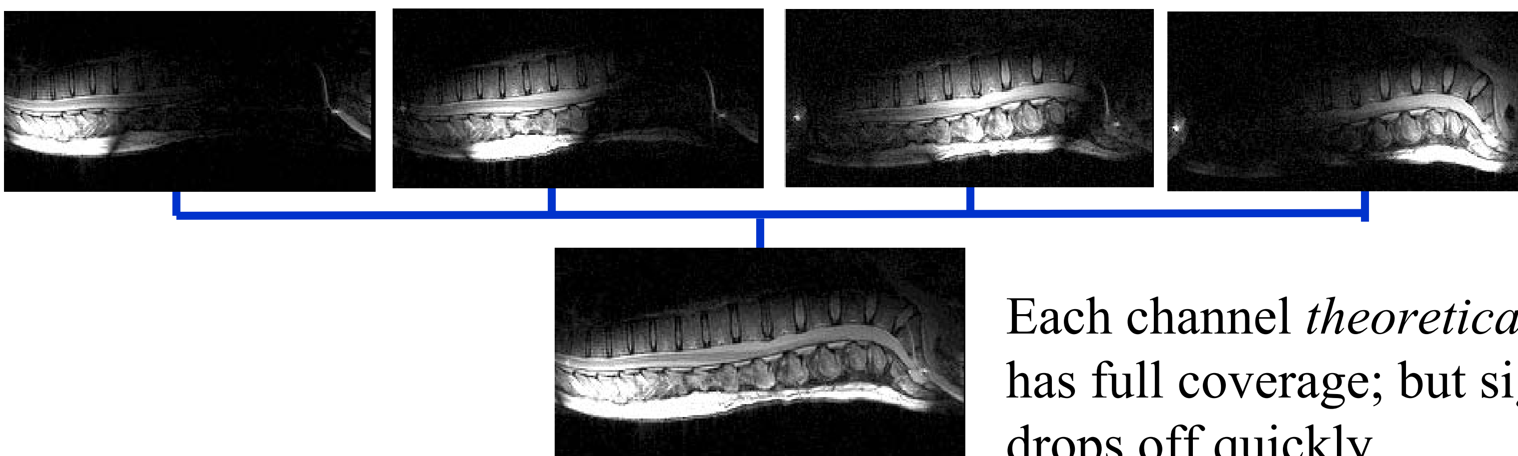
Intelligent imaging

- Closing the loop:
  - Bandwidth of communications from imager to computers is such that image formation can be adapted to *this* patient
  - Example: Parallel k-space imaging in MRI
- Contrast agents
  - Adaptive acquisition protocols

Parallel (k-space) imaging: PPI

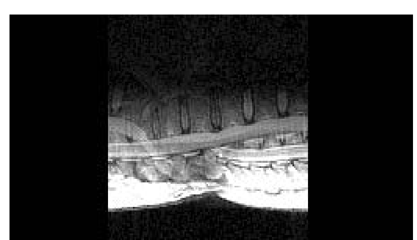
- Array coils

- Multiple independent receiver channels



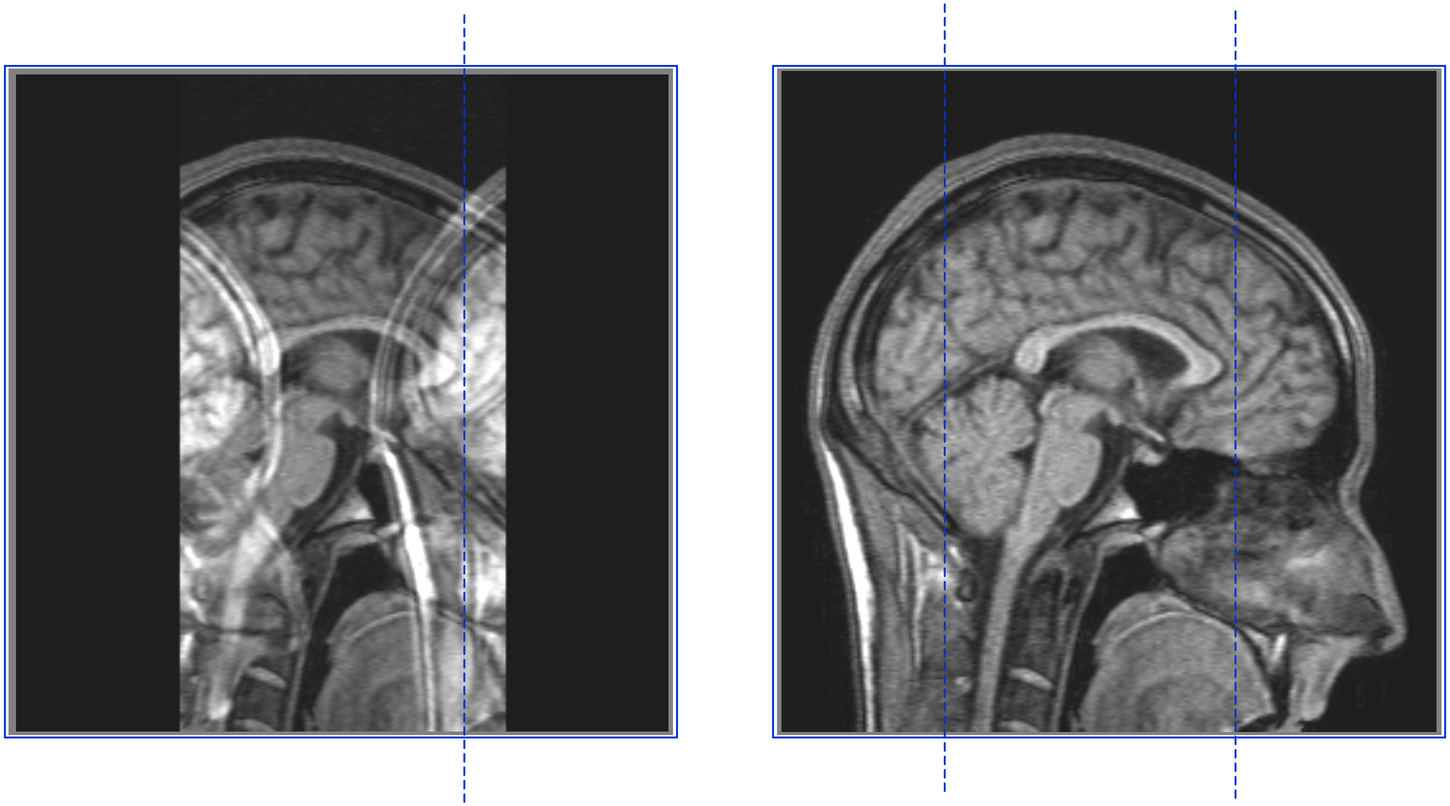
Each channel *theoretically* has full coverage; but signal drops off quickly

- vs conventional



Fourier theory

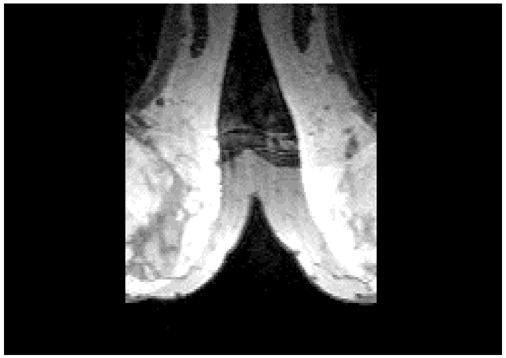
parallel image acquisition

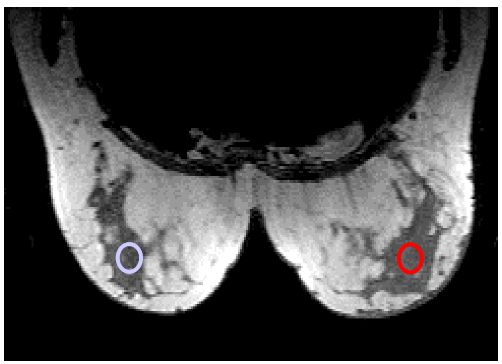


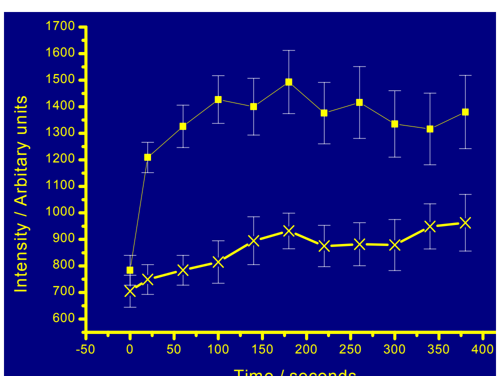
Potential applications include: faster imaging (eg contrast enhancement, EPI, …); motion correction; distortion reduction; ..

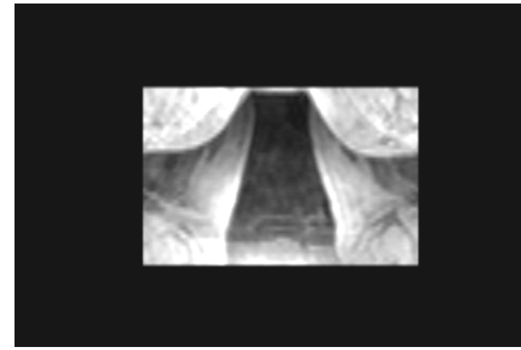
increasing application to cardiovascular disease…

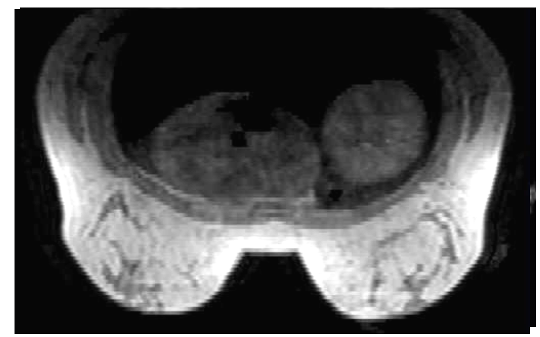
Improving temporal resolution in Dynamic Contrast Uptake imaging

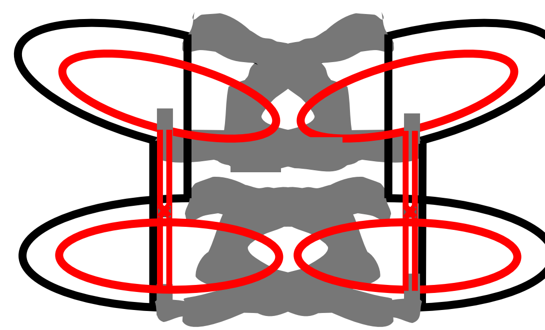








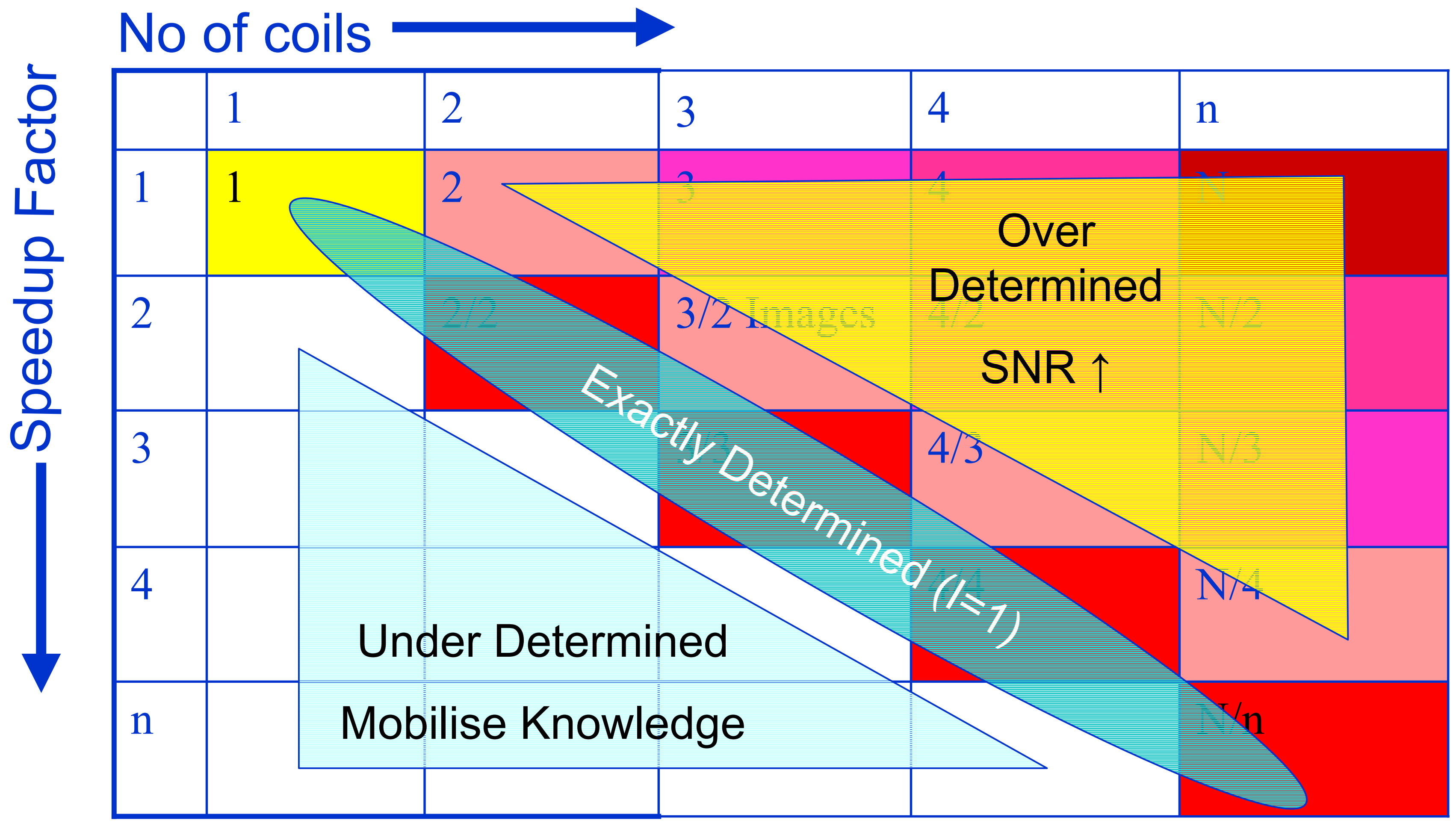




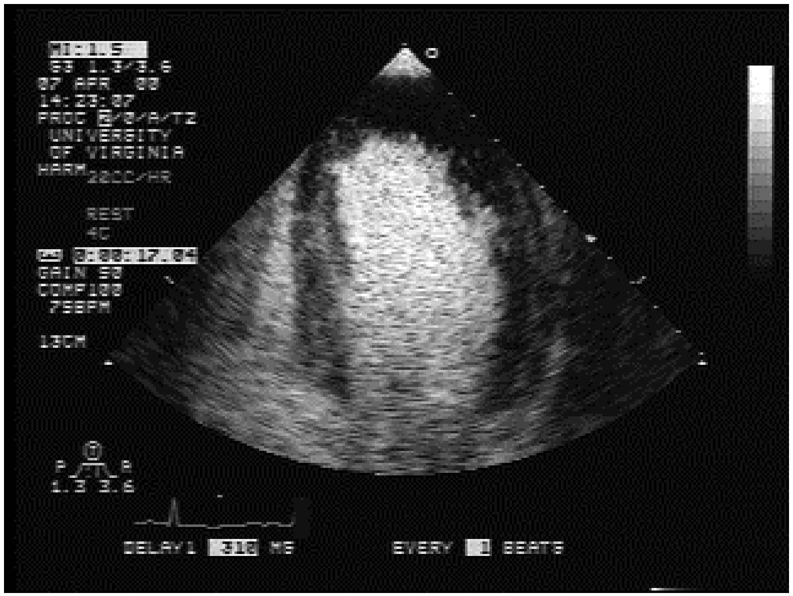
Doubling temporal sampling of contrast take-up

PPI Information content, expanded data space

For better images, to gain speed, error detection, integrate with motion model, …



Ultrasound contrast agents



Focus to date has been on: Stable contrast agents and Developing and modifying imaging protocols

Opportunity: model bubble/ultrasound interactions and computation of quantitative information from time sequences

adaptive acquisition protocols, eg triggered vs real-time: simultaneous registration and (spatio-temporal) model-based segmentation?

Intelligent acquisition

Take home messages:

Computer technology is opening new opportunities

Modelling the details of image acquisition provides massive new opportunities

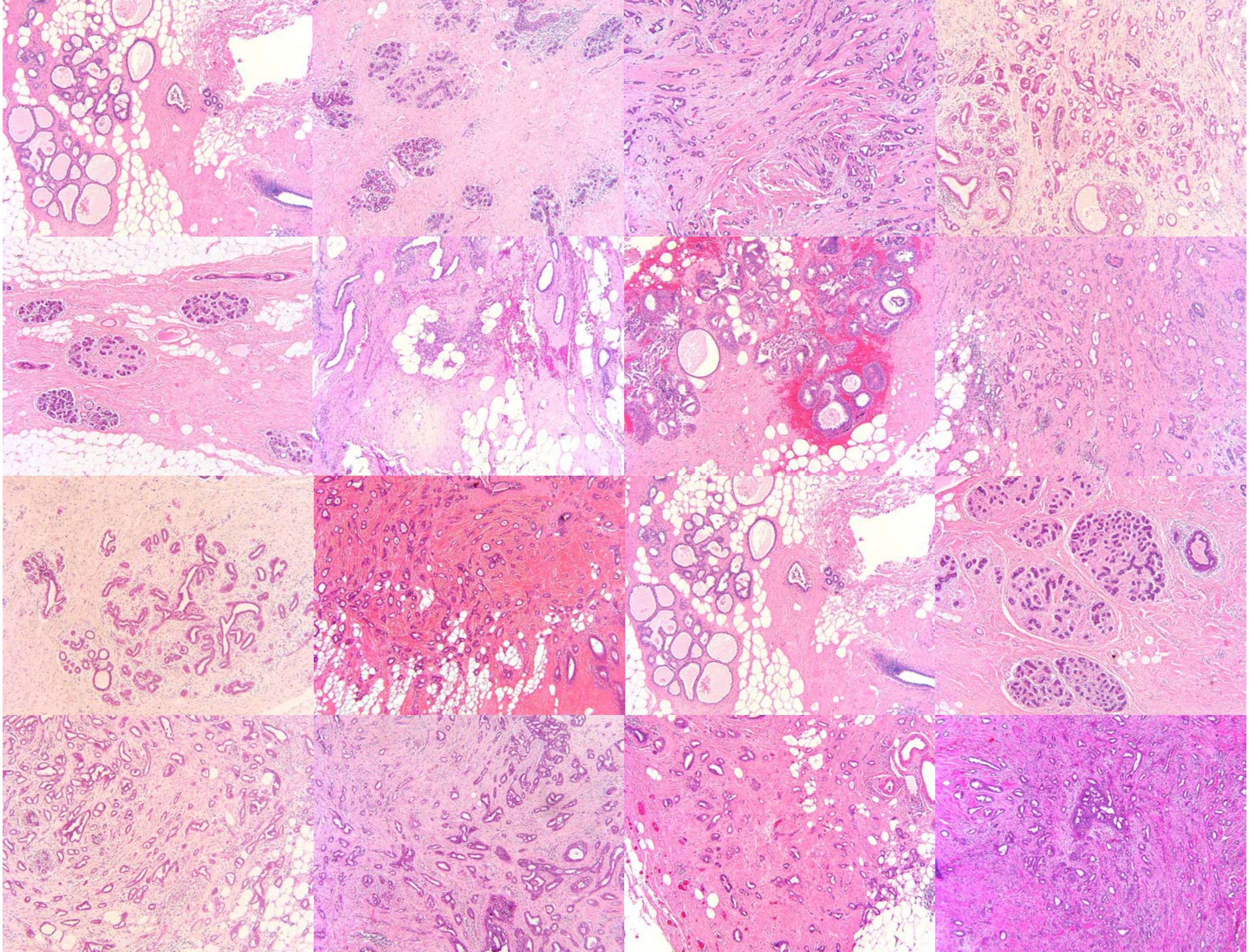
New solutions to old problems: motion correction

Time and space can be treated equally

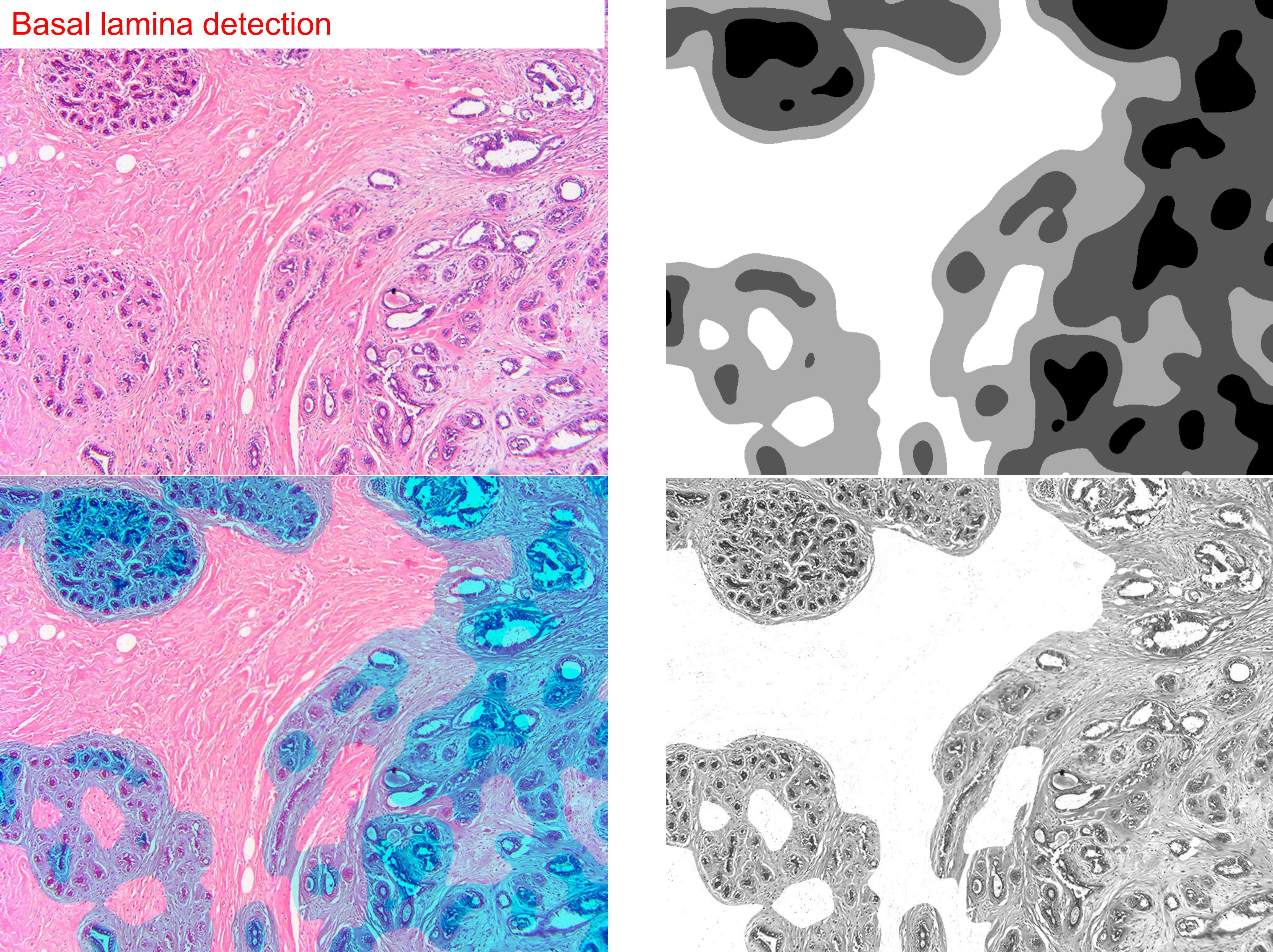
That same old theme …

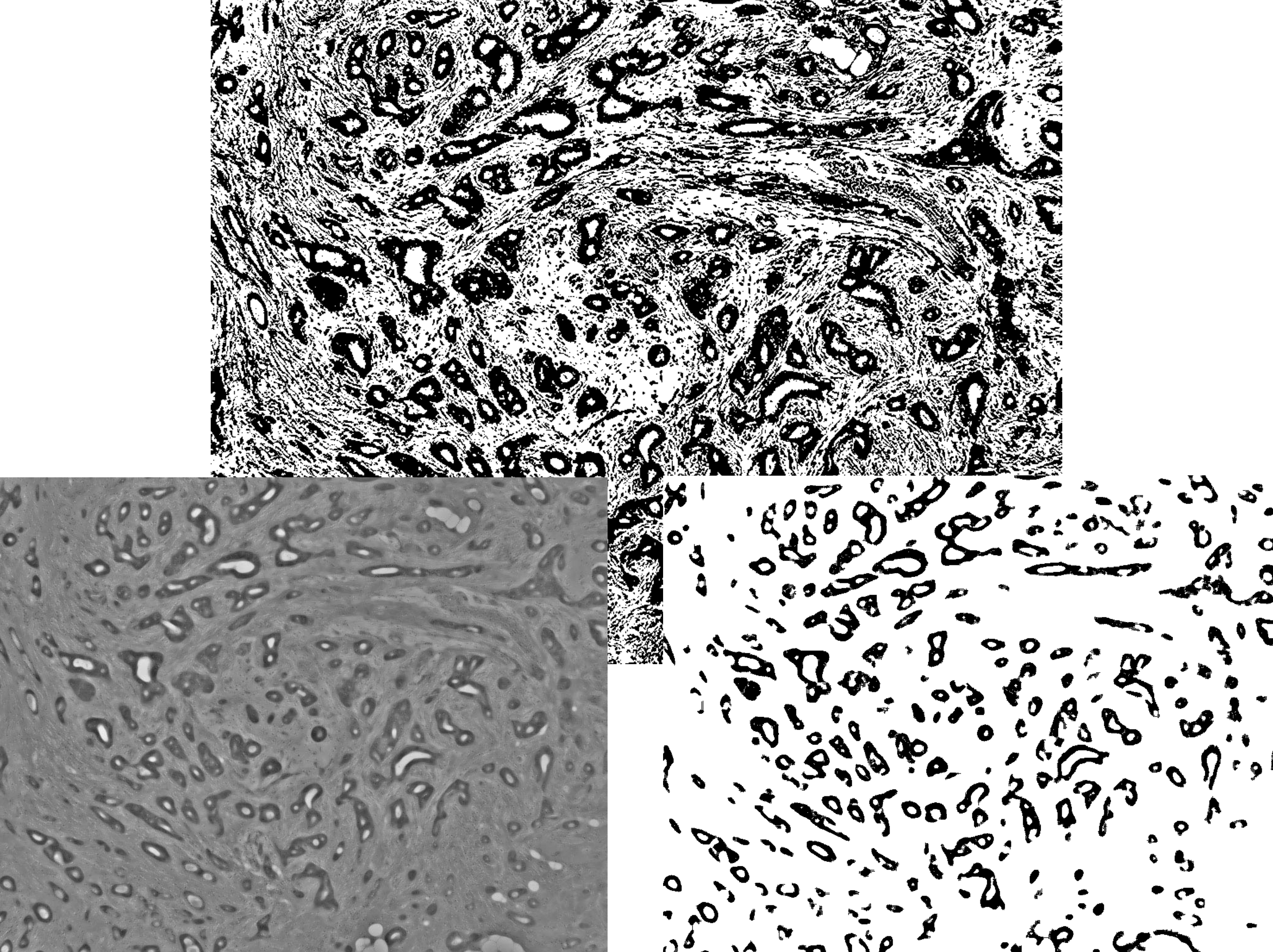
Histopathological image analysis

- Though histopathology is image-based, there is negligible image analysis
- The images are complex, even by medical image analysis standards!
- Histological images are ***not*** radiological images
  - Image fusion is not appropriate



Basal lamina detection





Histopathological image analysis

Take home message:

This is essentially an open field, whose time is coming with the Grid

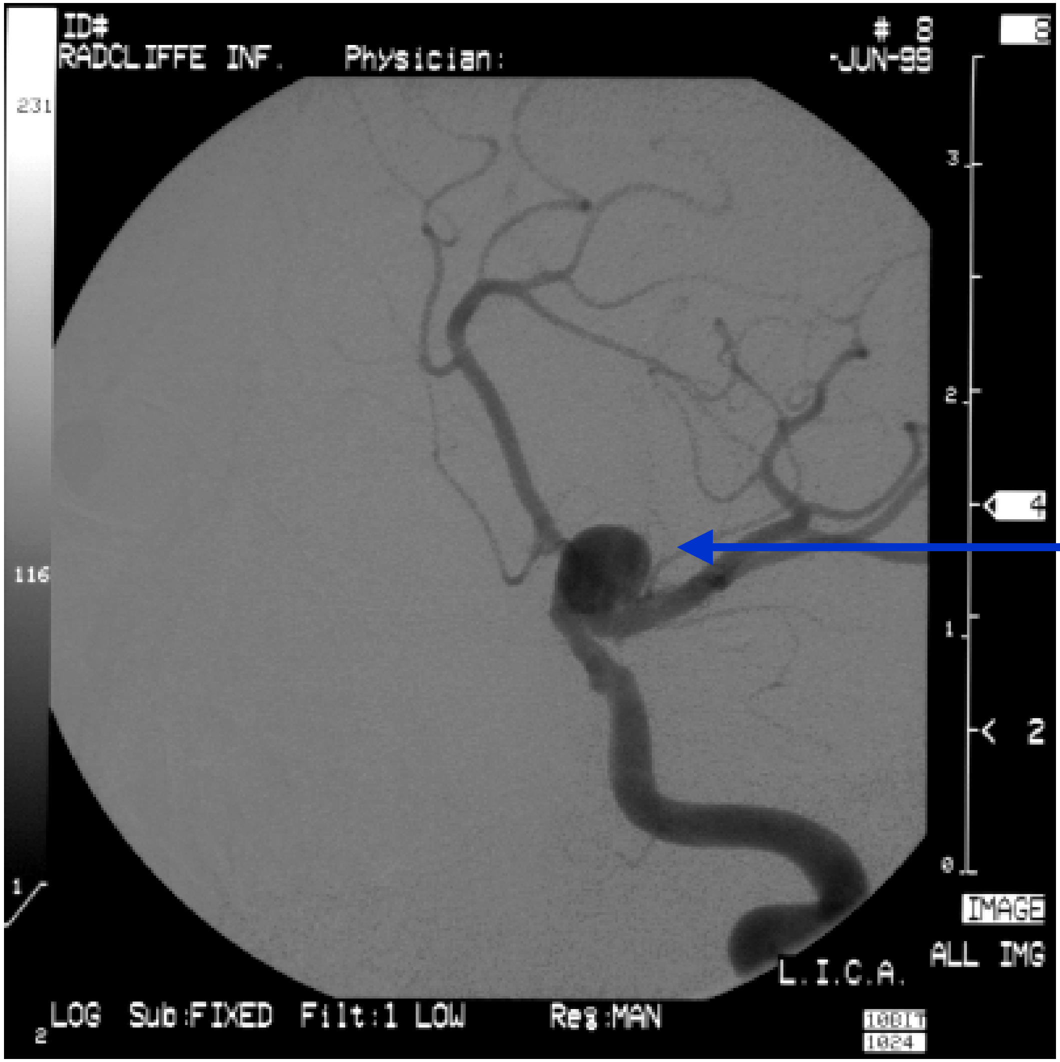
registration is infeasible, reasoning is feasible but hard

basis of an improved *Triple Assessment* process of patient management (*vide inf.)*

Minimally-invasive surgery

- Coil Embolisation
- CHIR and general context
  - the next talk!

Surgical planning system for brain surgery

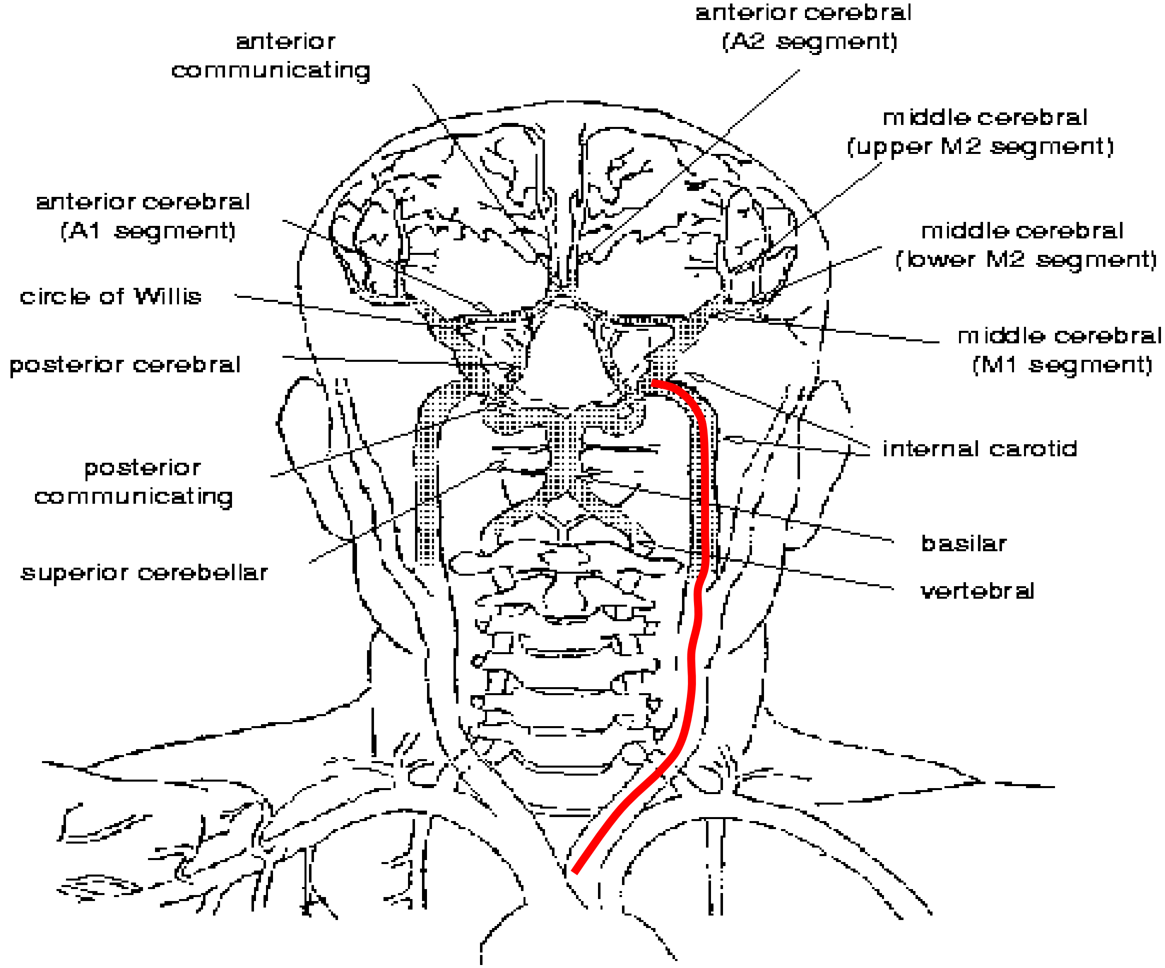


Digital subtraction angiography

aneurysm

Surgeons plan and carry out complex brain operations using only 2D information!!!

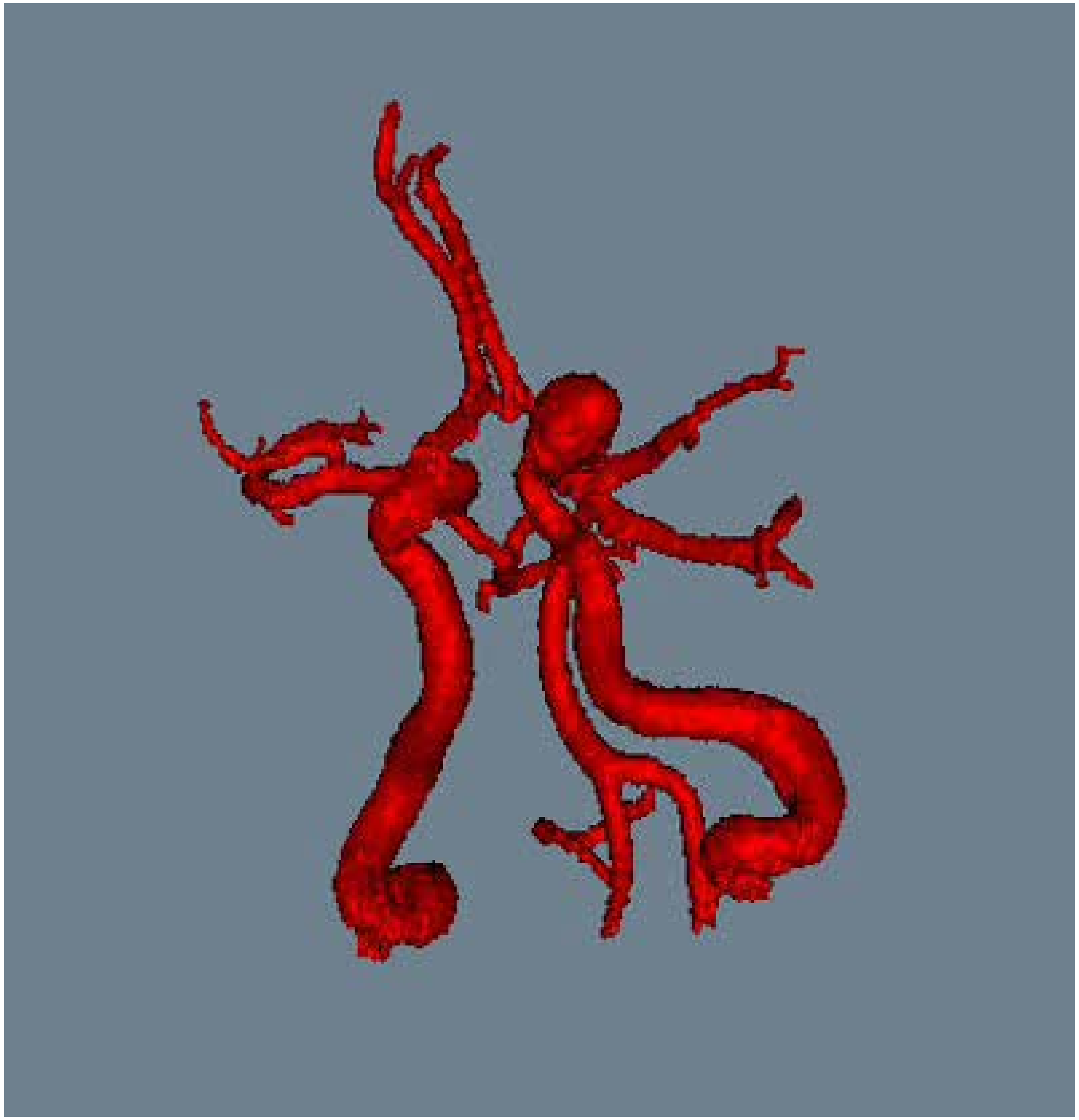
Surgical path



During the operation, coils are used to pack the aneurysm to spoil the blood flow

During the operation, coils are used to pack the aneurysm to spoil the blood flow

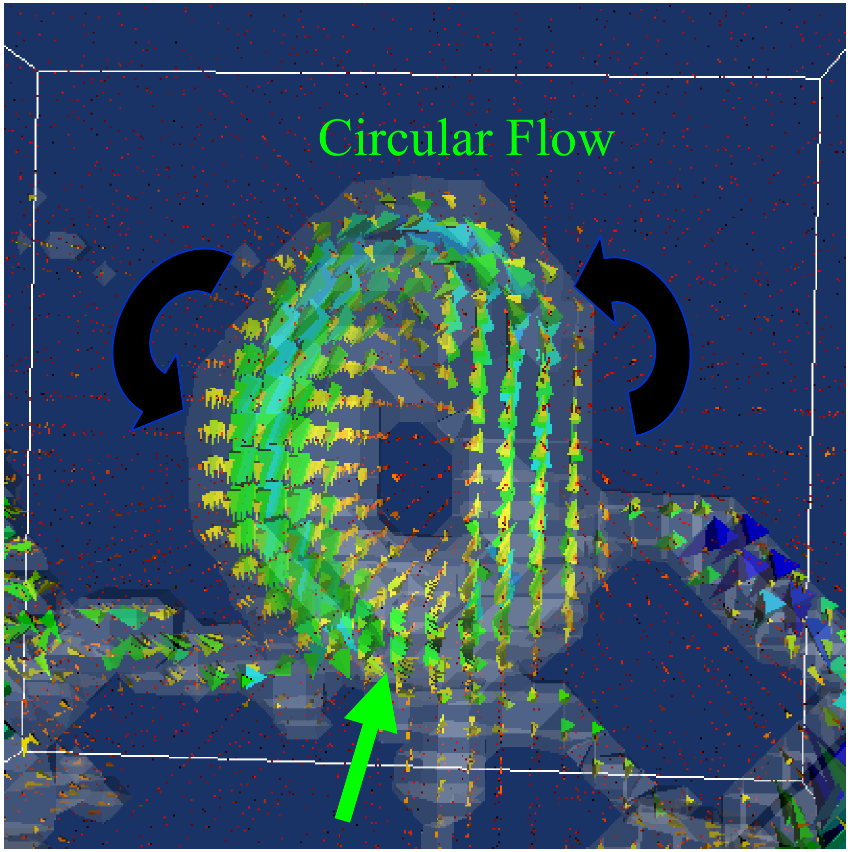
Minimally-invasive surgical system for brain surgery



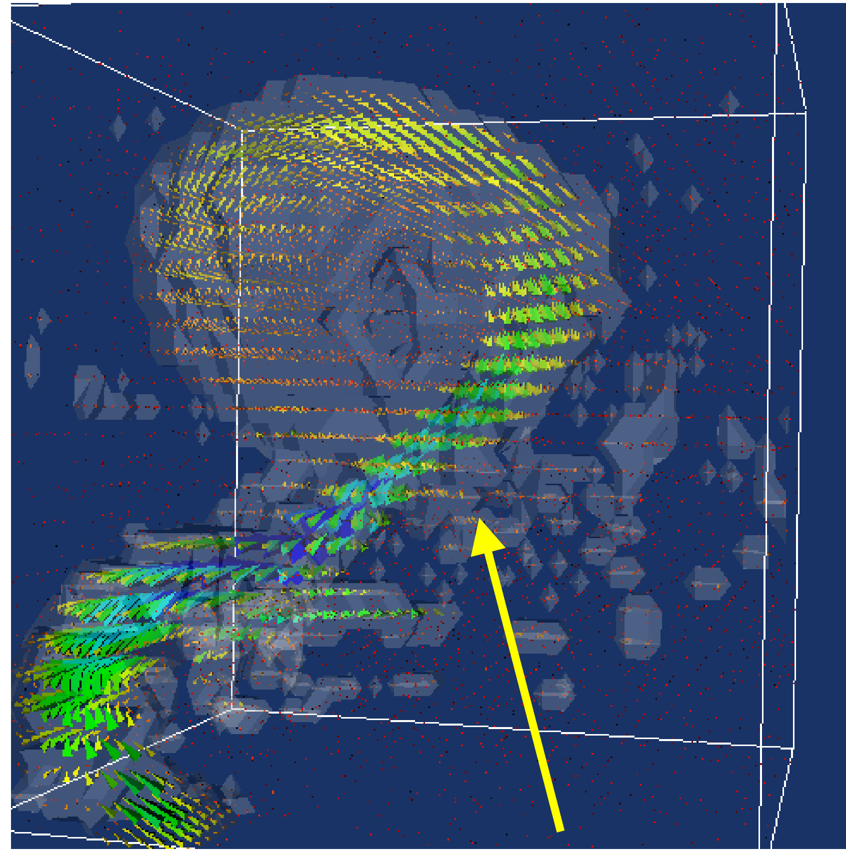
3D Model of the type used routinely in Oxford for planning and execution of brain surgery

Over 70% of operations in Oxford now utilise this technique

3D Flow

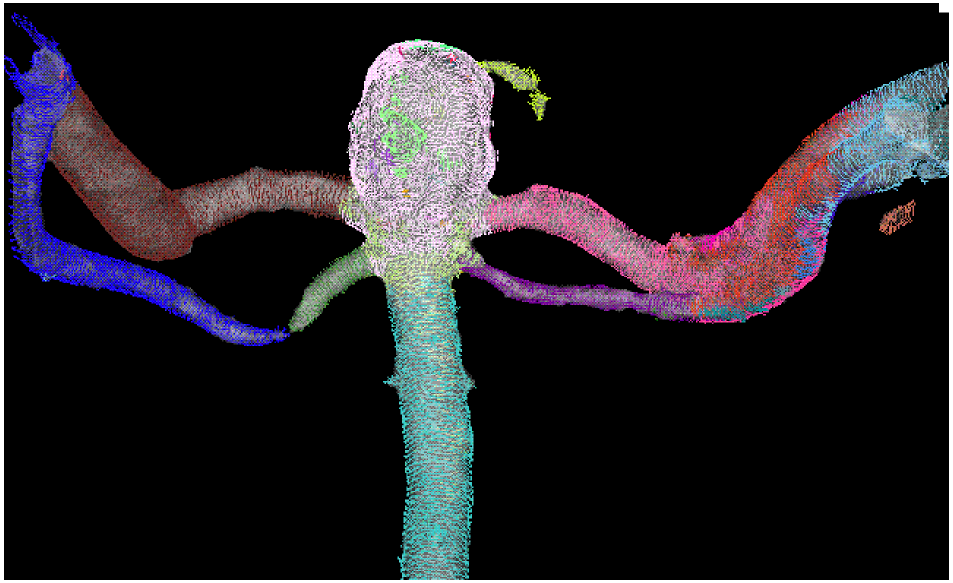
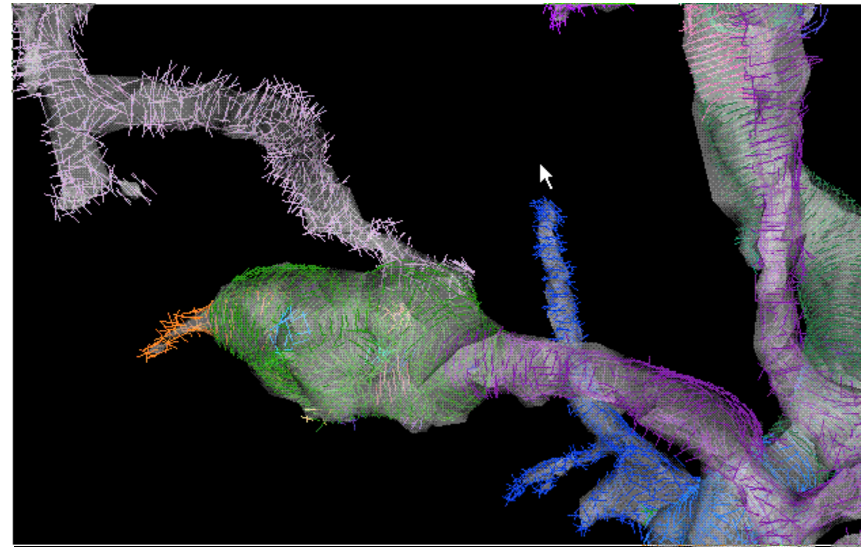
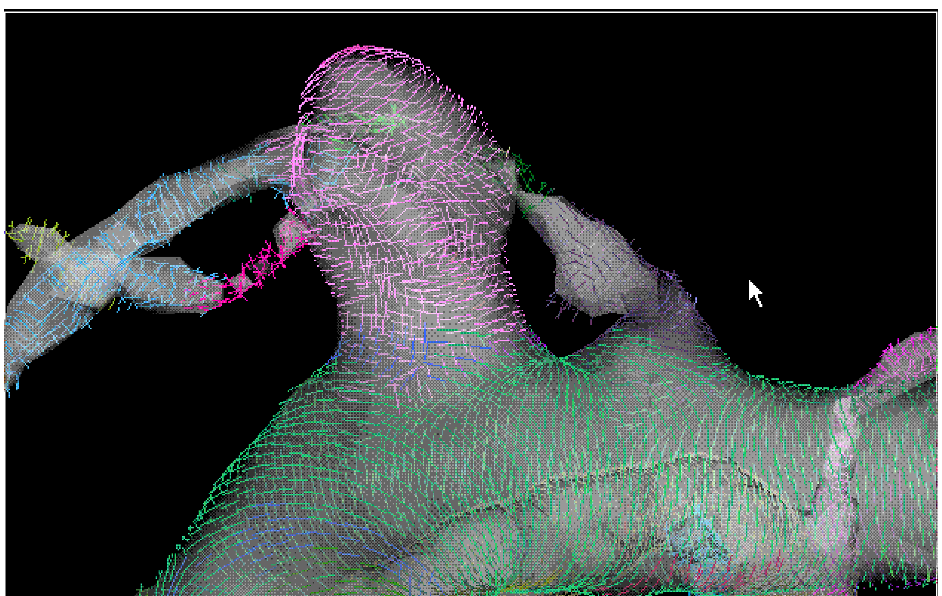
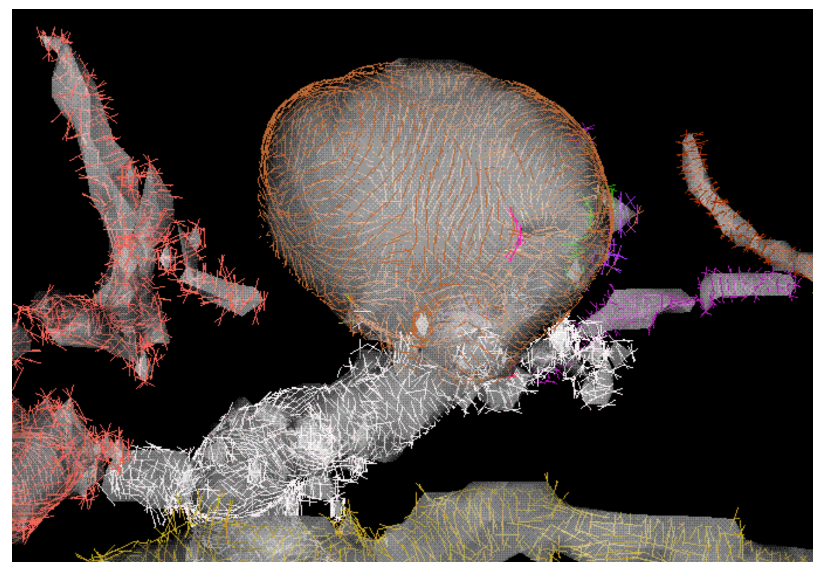


Basilar Bifurcation Aneurysm



Saccular Aneurysm

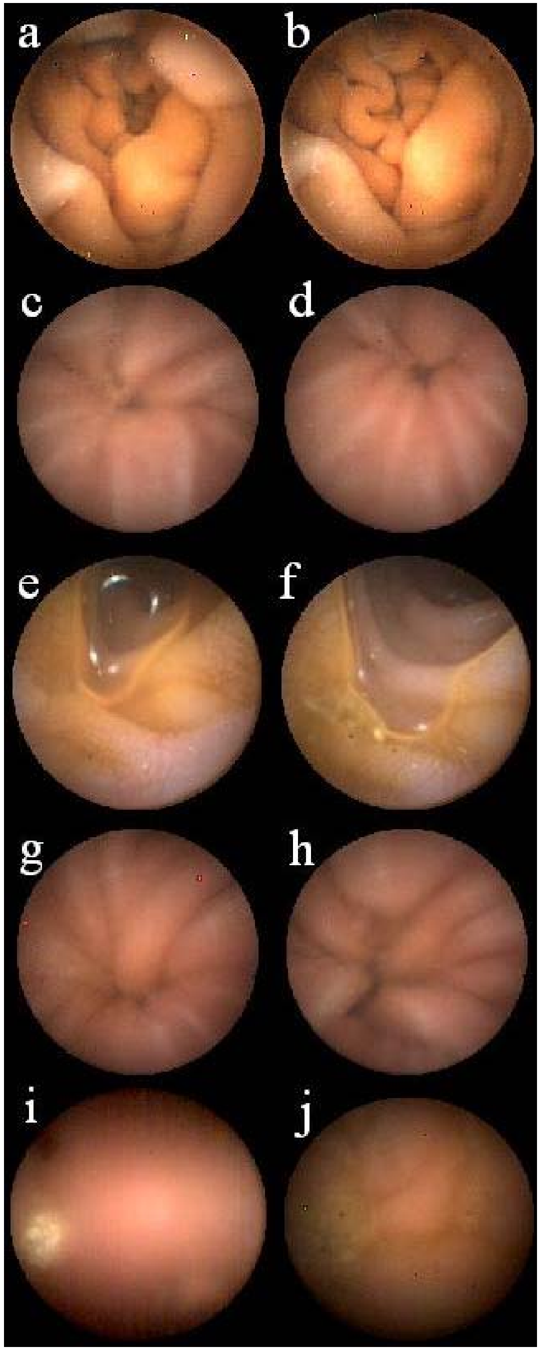
Observation : within vessels, velocities of the neighbouring voxels tend to be coherent - local phase coherence

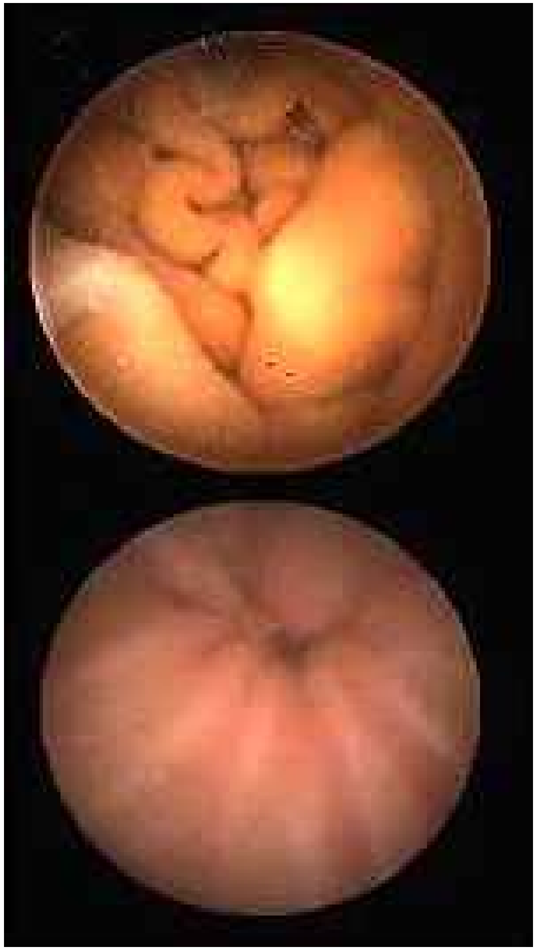
Avoiding surgery

- Radiation therapy planning
- Microwave heating
- Pellets
- Collateral damage and targeted therapy

The endoscopy "pill"



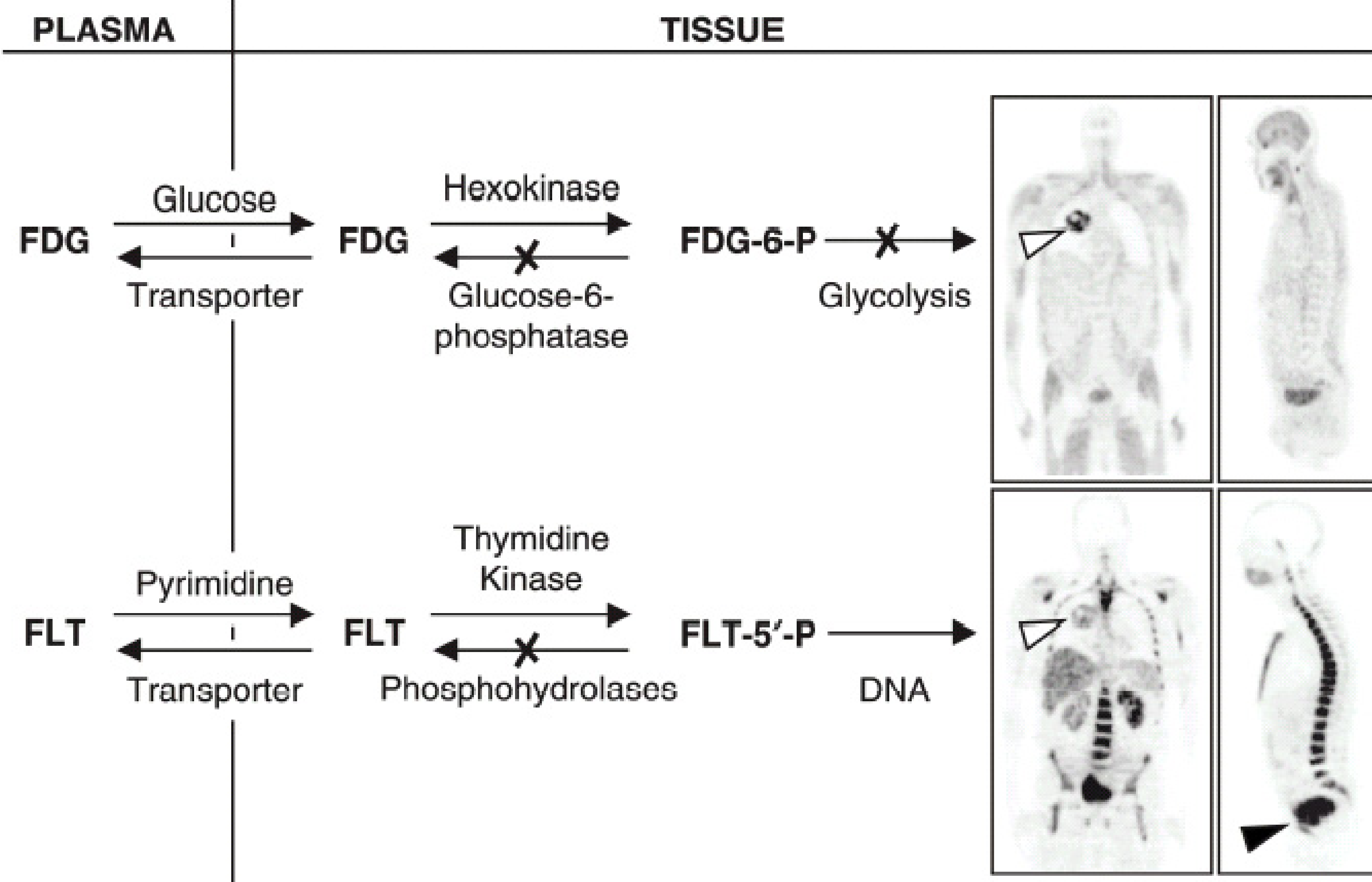
Images obtained when passing through the bowel (Given Imaging System)



Molecular imaging

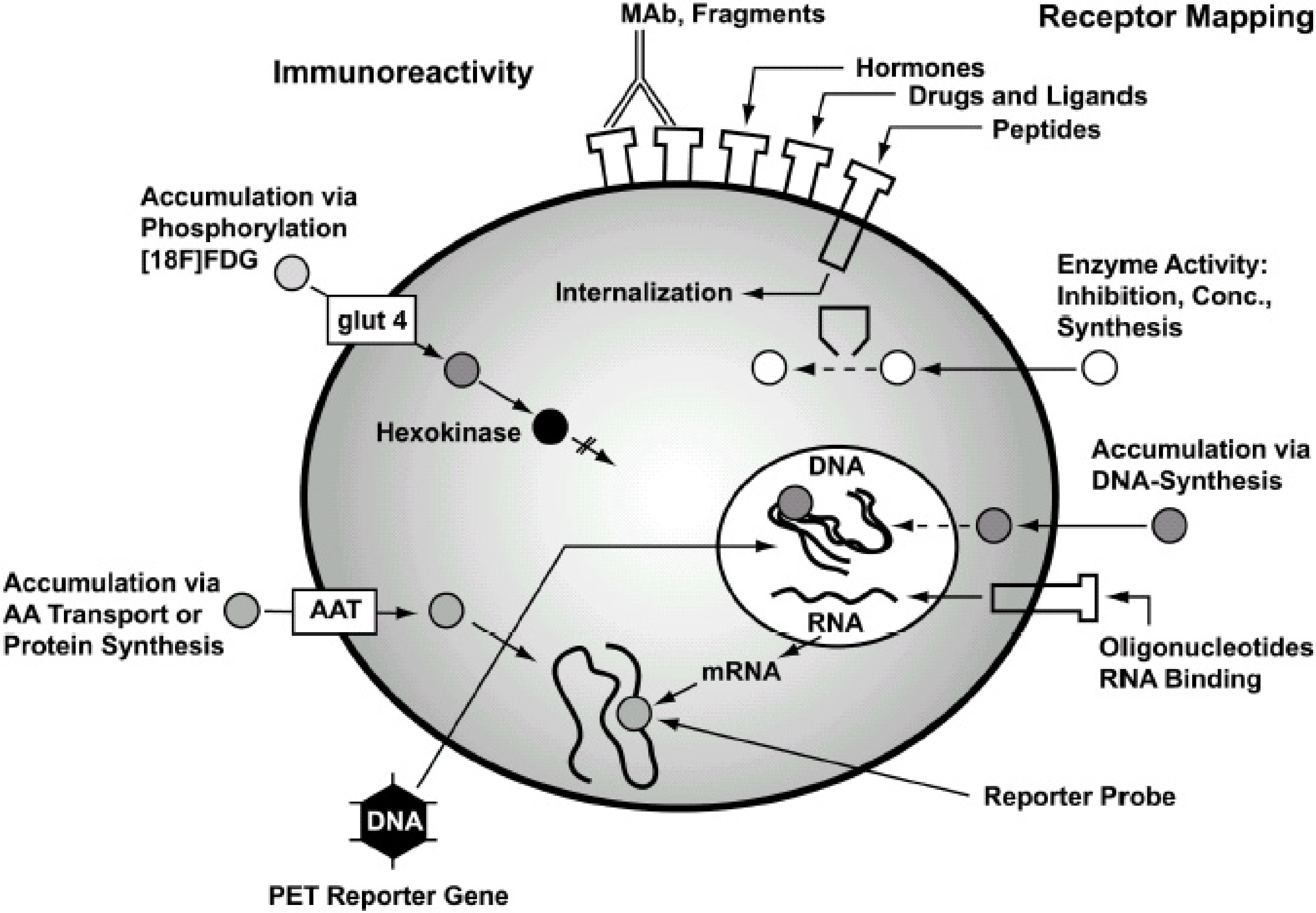
- What it is:
  - Use of molecular probes, or
  - Generation of signals from specific molecules
- Uses:
  - Fuse with anatomical images to examine biological processes (CT/PET;PET/fMRI;…)
  - Fuse two molecular images to differentiate disease

This is set to transform medicine; but realisation is profoundly hard



Top row: fluorodeoxyglucose – as used most frequently in PET

Bottom: deoxy-fluorothymidine: gives DNA replication rate in region of high glycolysis



Molecular therapeutics: image the presence and function of a target and use the same molecule to modify the function (e.g. zap it)

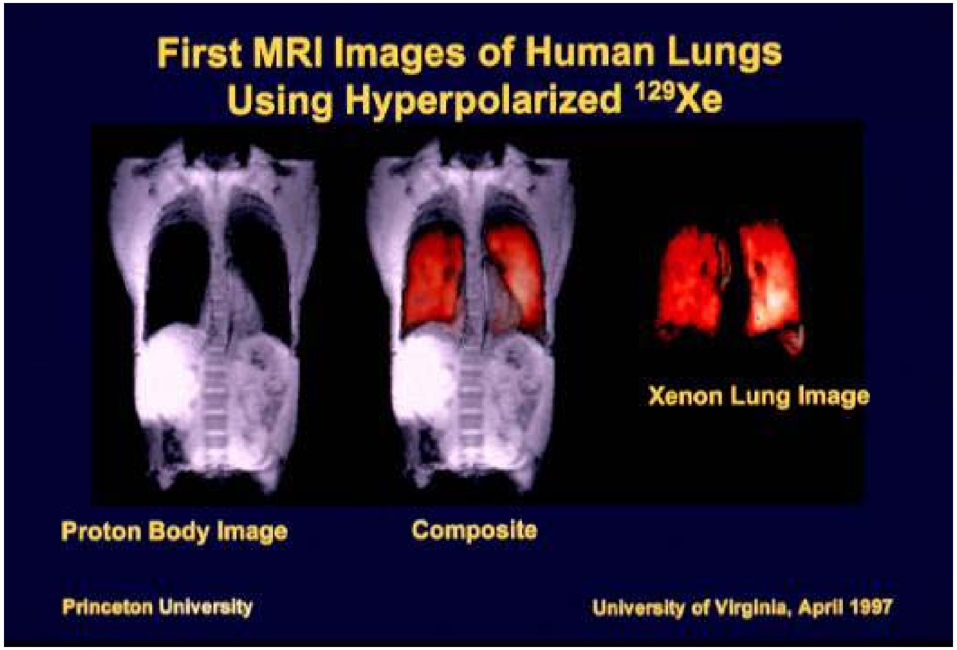
Opportunities to probe and image cellular processes – targeted therapies

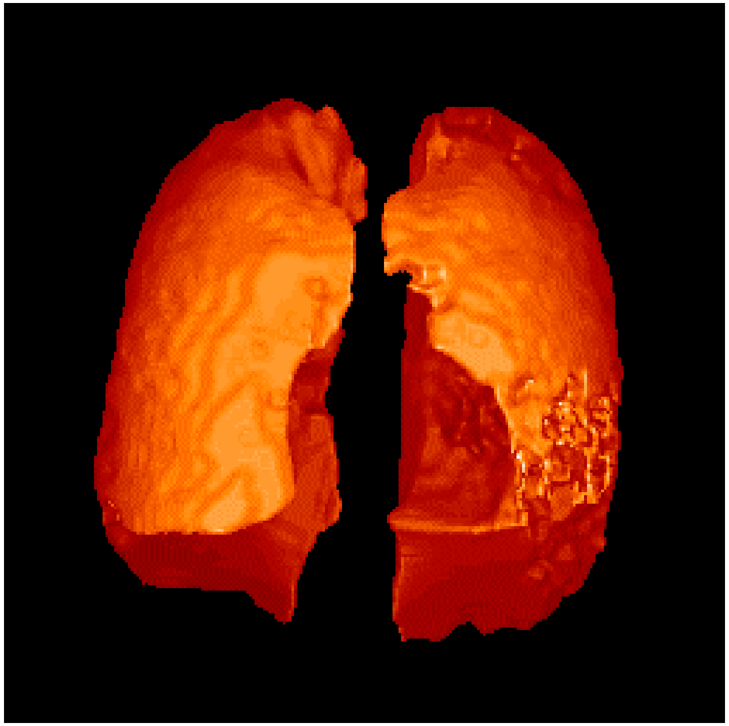
New ways to image

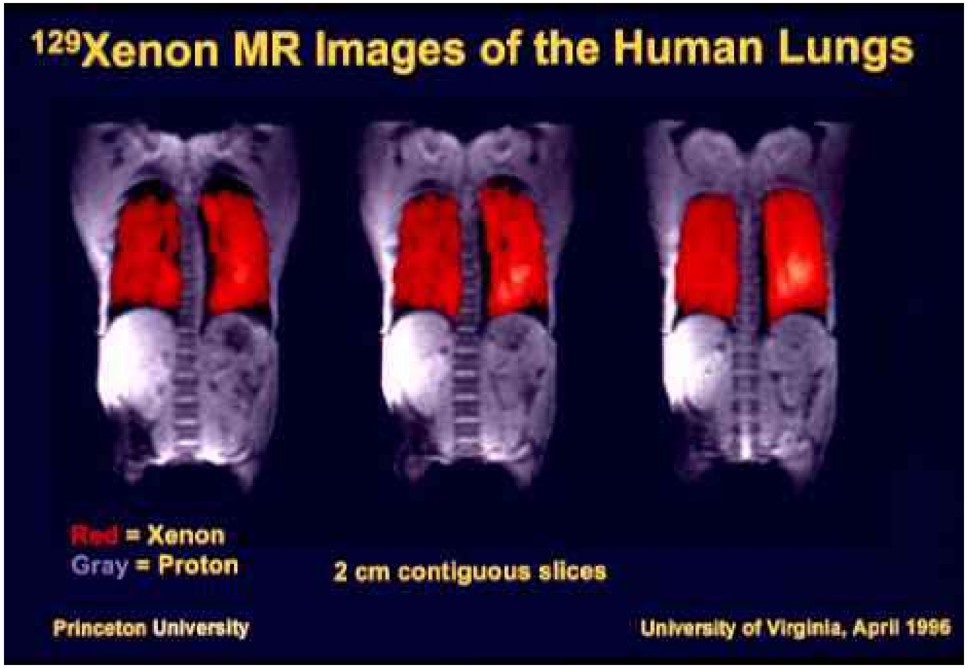
- Exogenous fluorophones
- Thermoacoustics
- Terahertz imaging 3D ultrasound
- Tissue biomechanics from ultrasound
- NIR topography & tomography
- Optical Coherence Tomography
- …

Lung MR imaging with Hyperpolarised ^{129}Xe

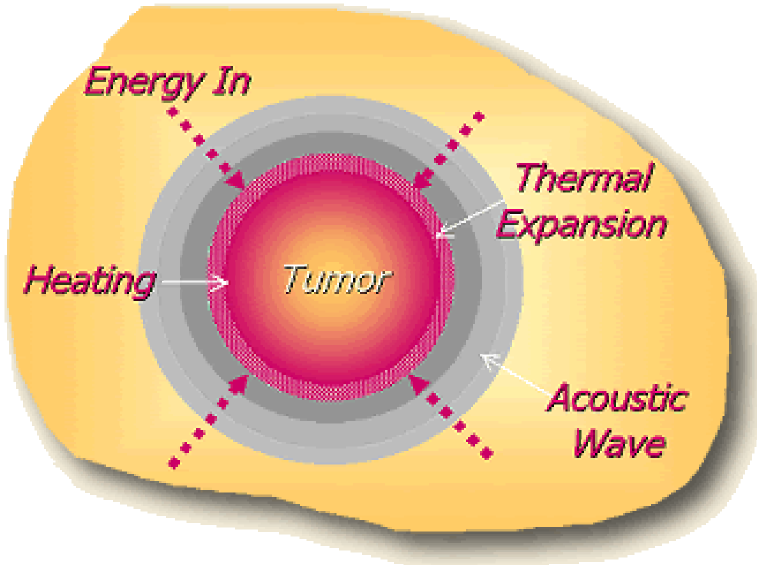
Other inert gases are being developed



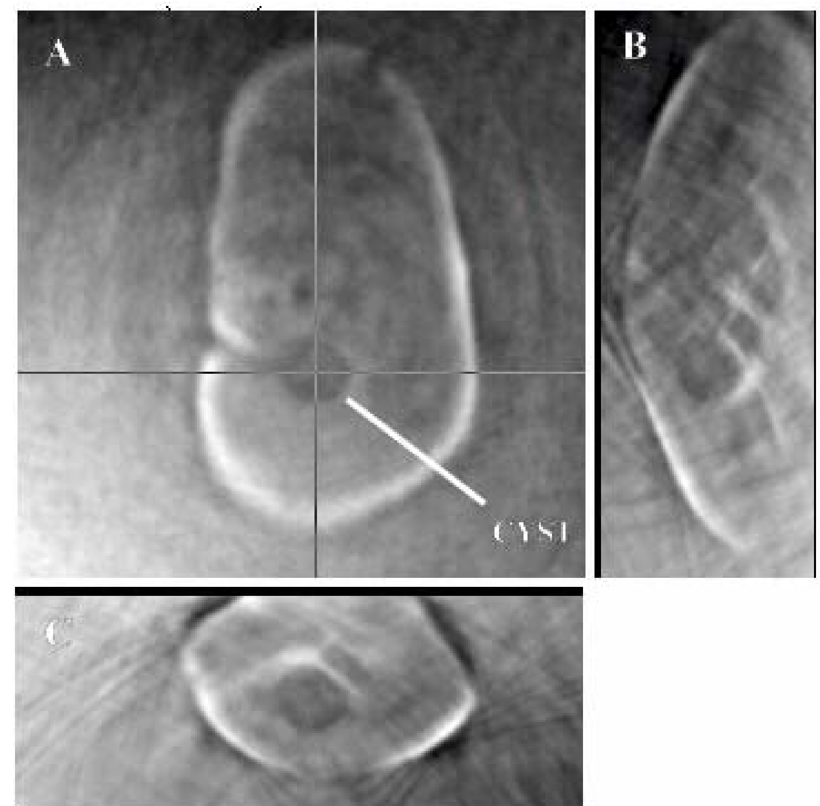




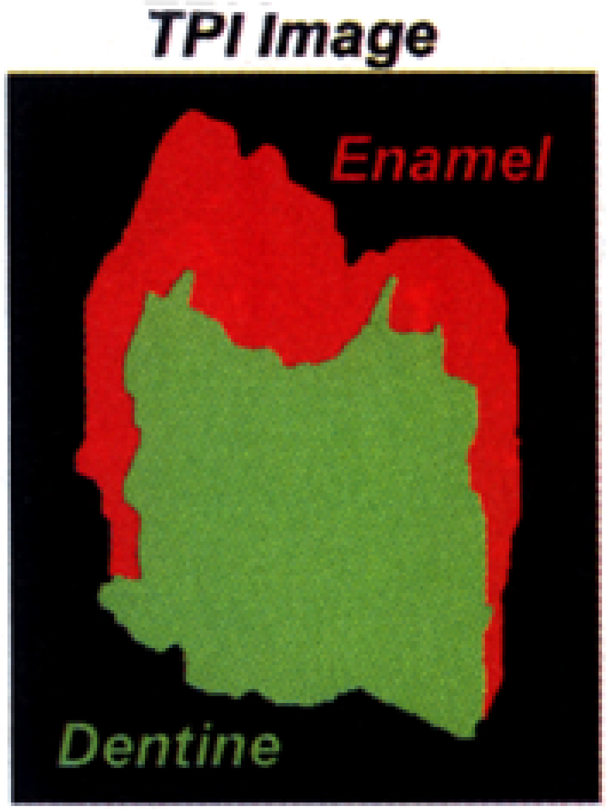
Thermoacoustic imaging of kidney with cyst



Attenuated ultrasound energy manifests as heat which is sensed
Contrast depends on absorption of particular energy type

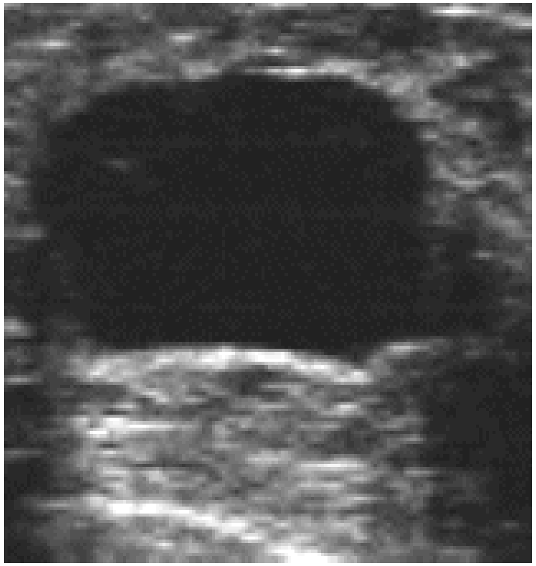


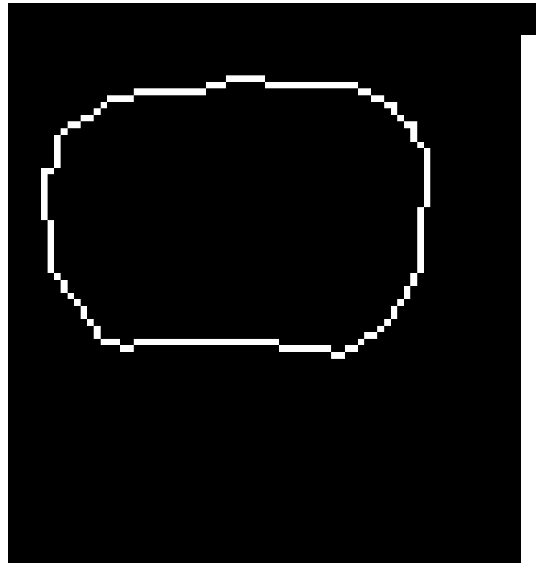
Terahertz imaging

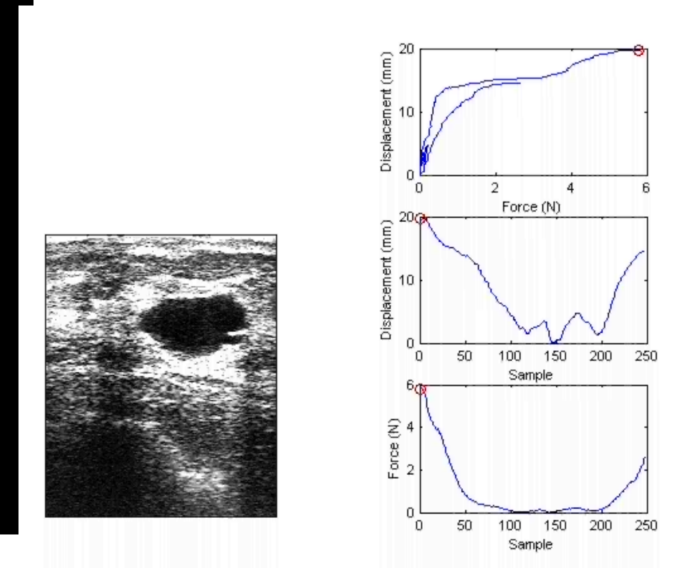


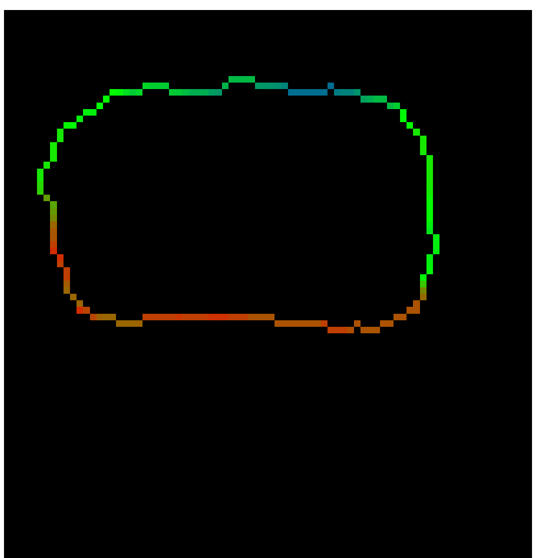
Non-ionising radiation that has frequency greater than 100 GHz

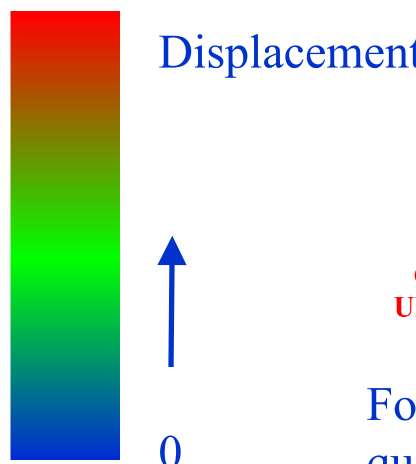
Example 1: A Cyst

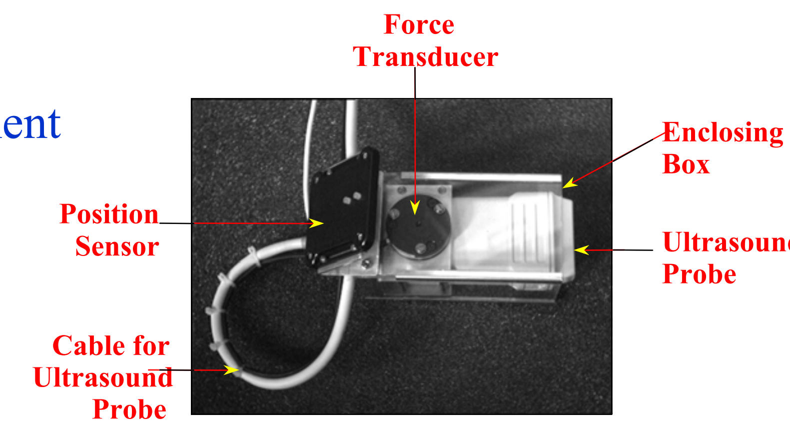






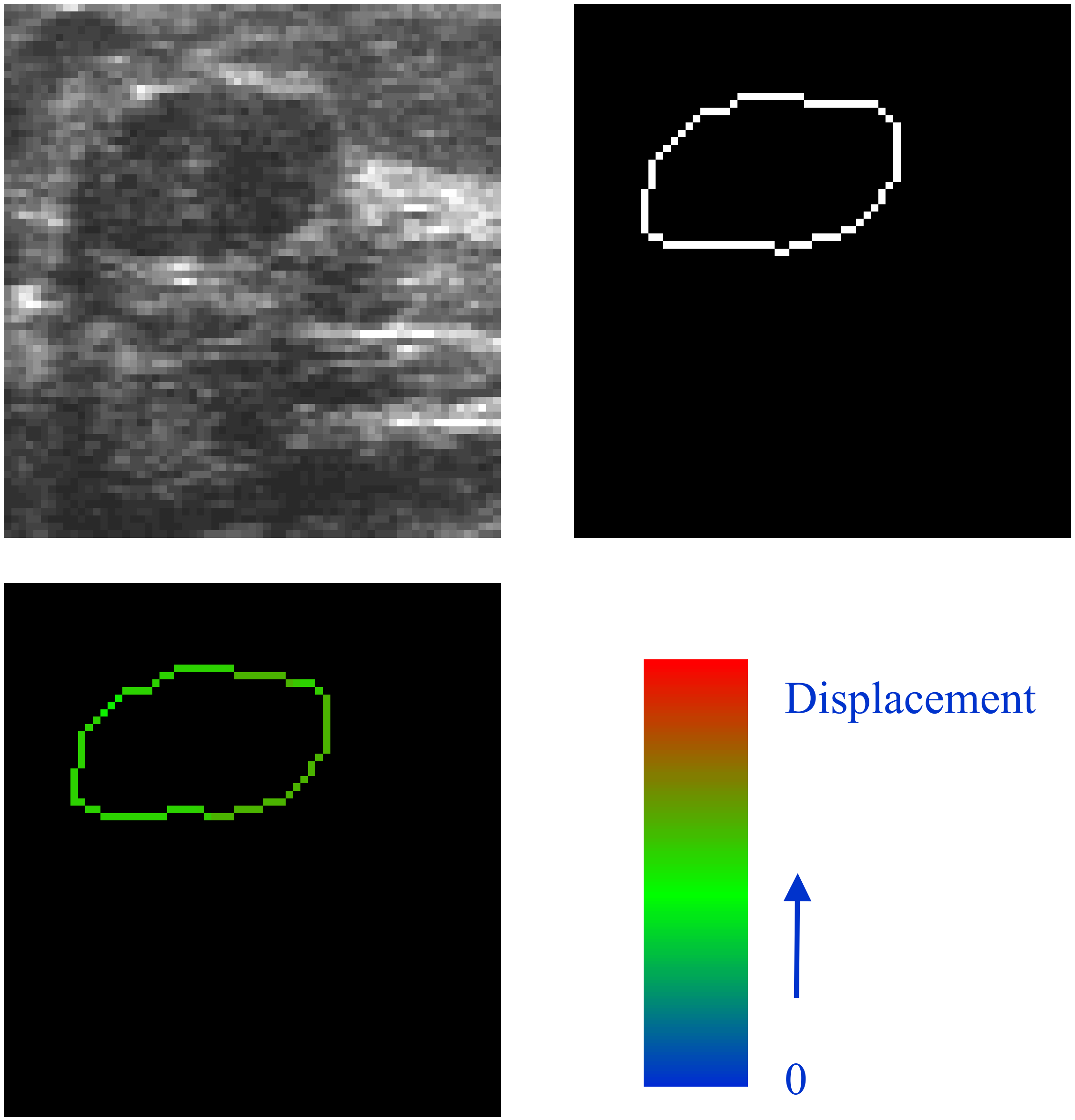






Force instrumentation provides quantitative measurement of tissue density (Noble and Burcher, 2002)

Example 2: A Fibroadenoma



Intelligent systems

- The key role of systems architecture
  - “islands of automation” to actual use
  - CHIR
- The role of AI
  - CREDO
- Towards triple assessment

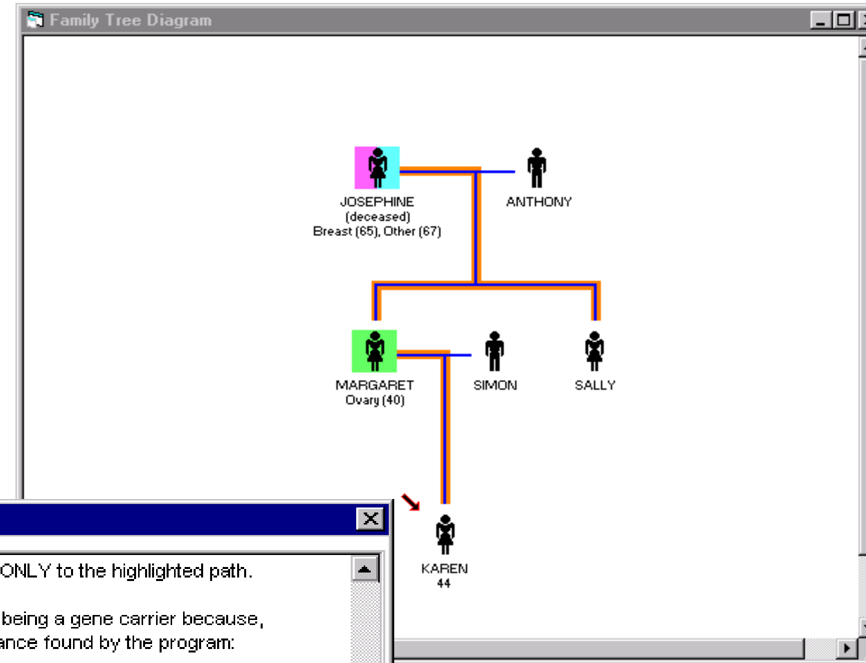
CREDO : Supporting clinical practice and the NHS cancer plan

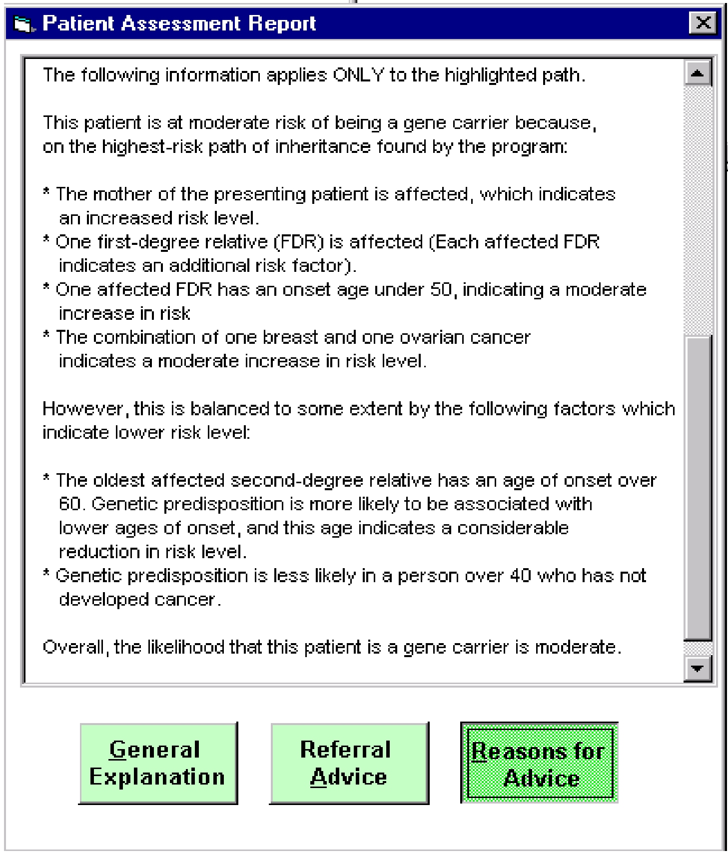
- Improving prevention
- Cutting waiting times
- Improving treatment
- Better palliative care
- Empowering the patient

CREDO system based on Pro*forma* : The first notation for describing clinical and other processes in a form that can be understood by a computer

Improving Prevention

Risk Assessment in Genetics

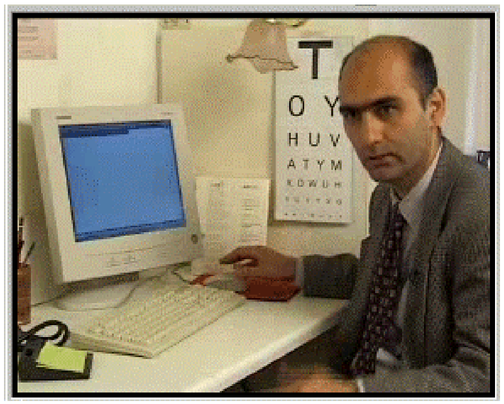


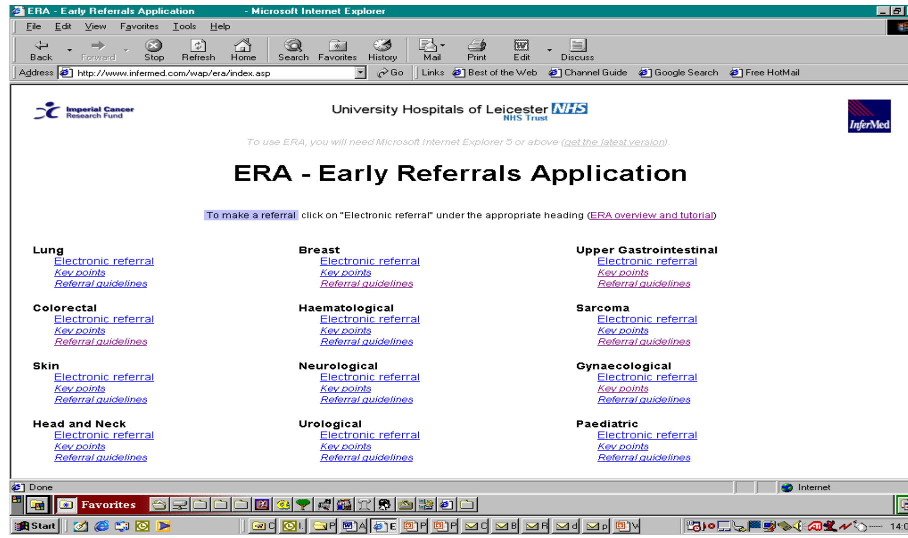


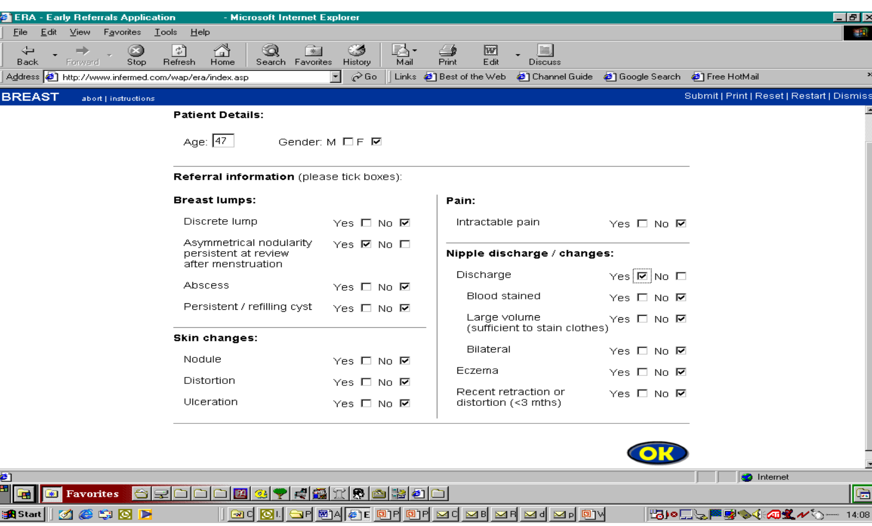
CANCER RESEARCH UK

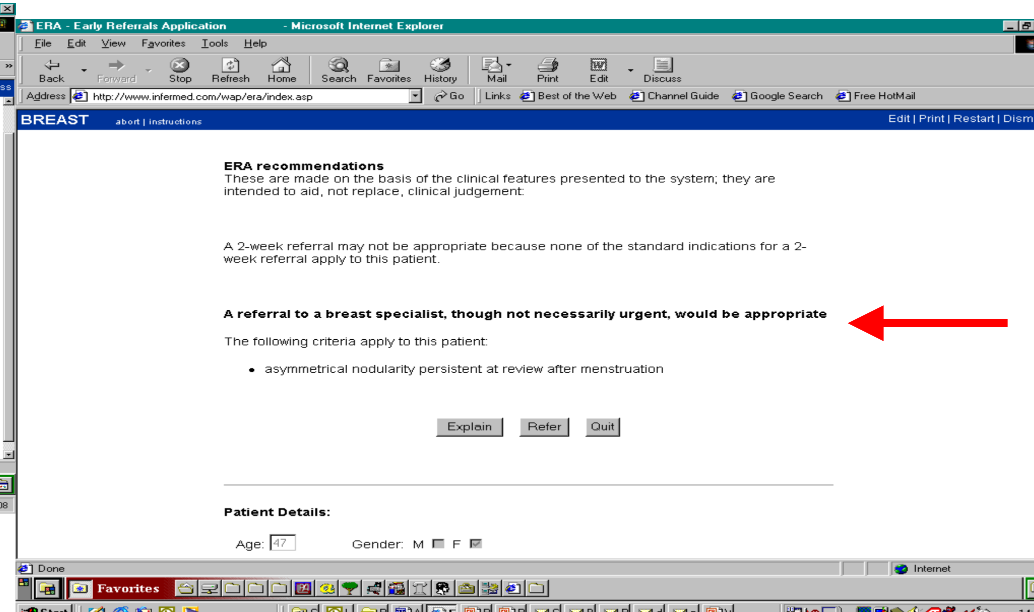
Cutting Waiting Times

Helping primary care physicians make referrals

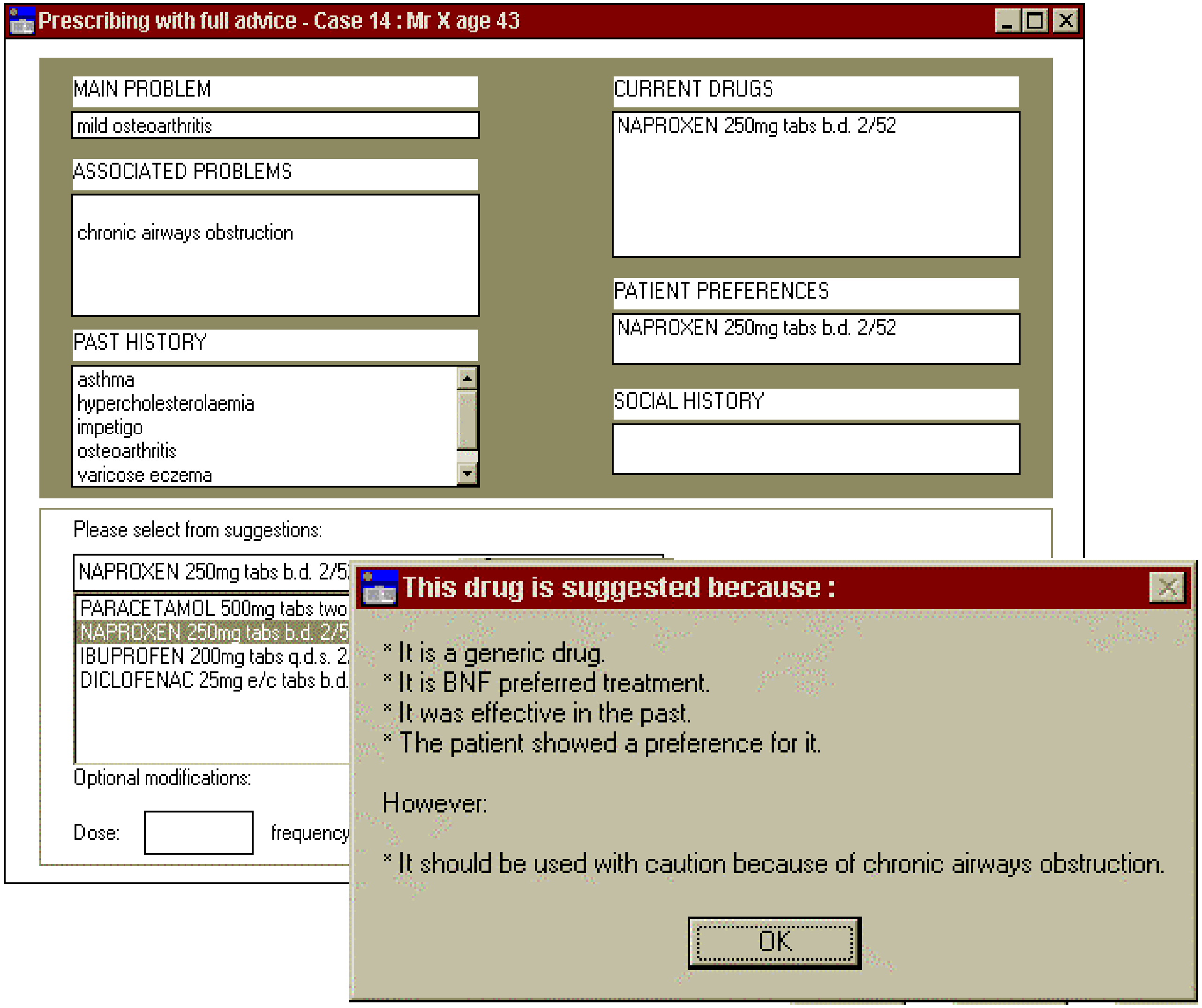








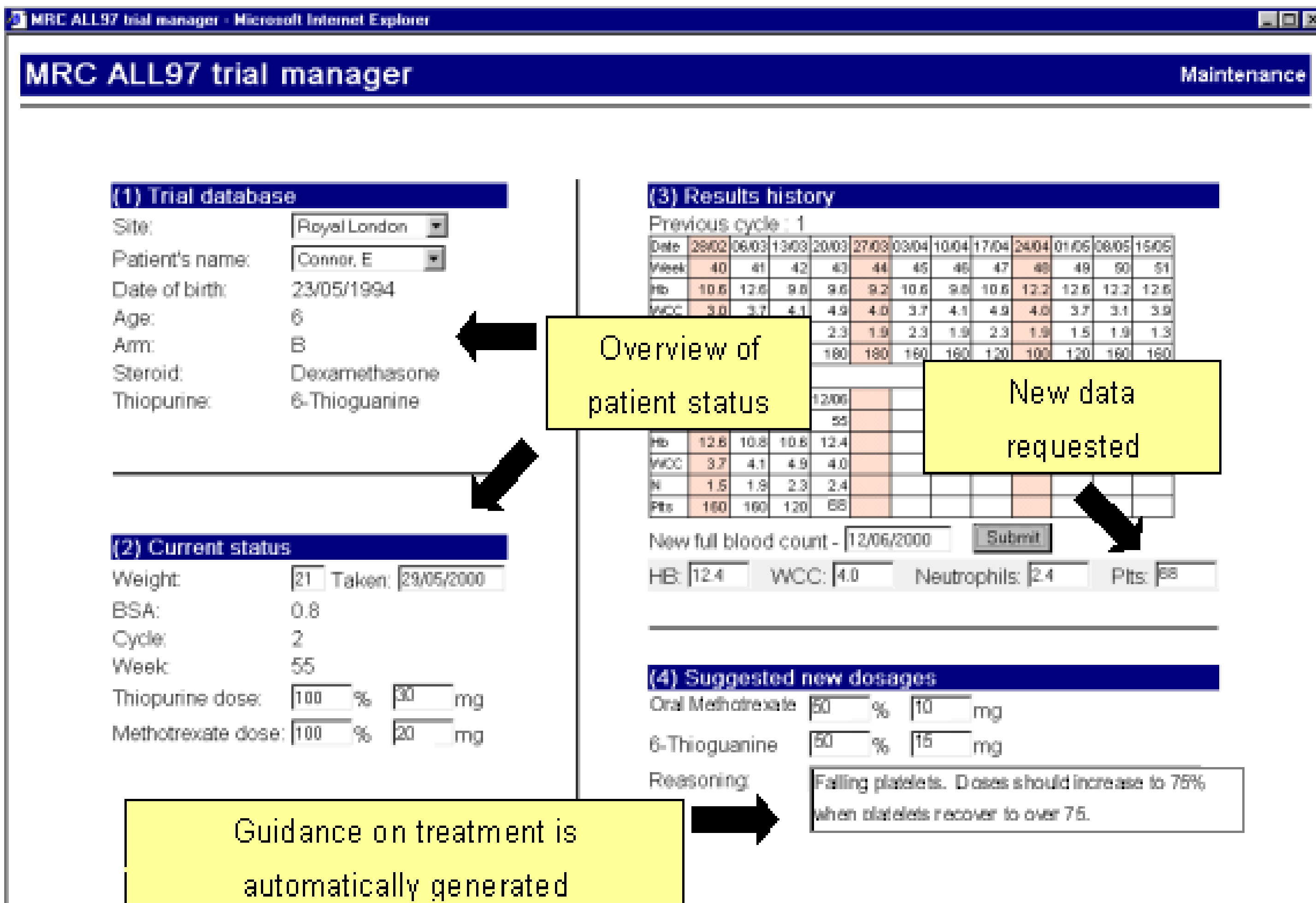
Improving Treatment
Drug prescribing



CANCER RESEARCH UK

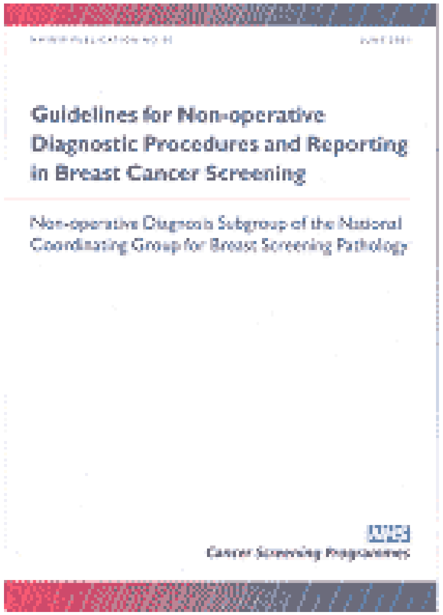
Improving Treatment

Leukaemia in children



CANCER RESEARCH UK

Triple assessment

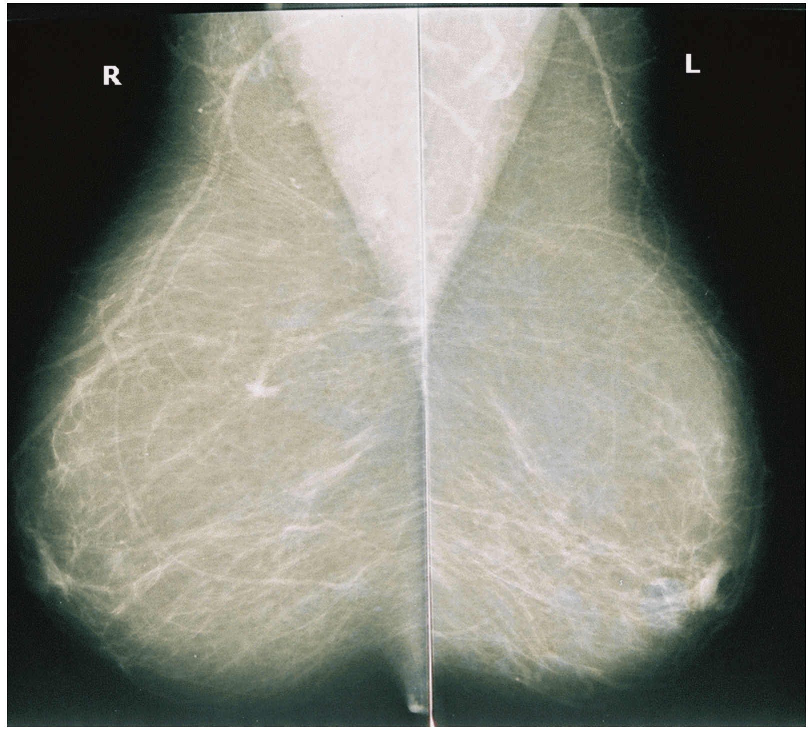


Guidelines for Non-operative Diagnostic Procedures and Reporting in Breast Cancer Screening

Non-operative Diagnosis Subgroup of the National Coordinating Group for Breast Screening Pathology

NHS

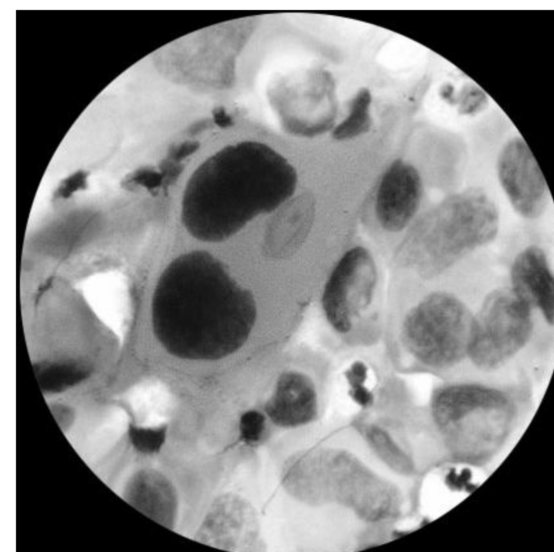
Cancer Screening Programmes



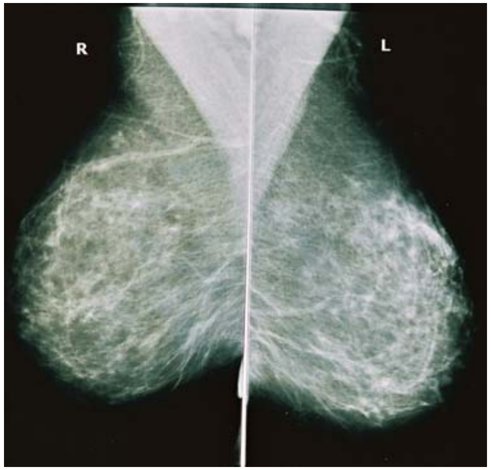
Radiological images

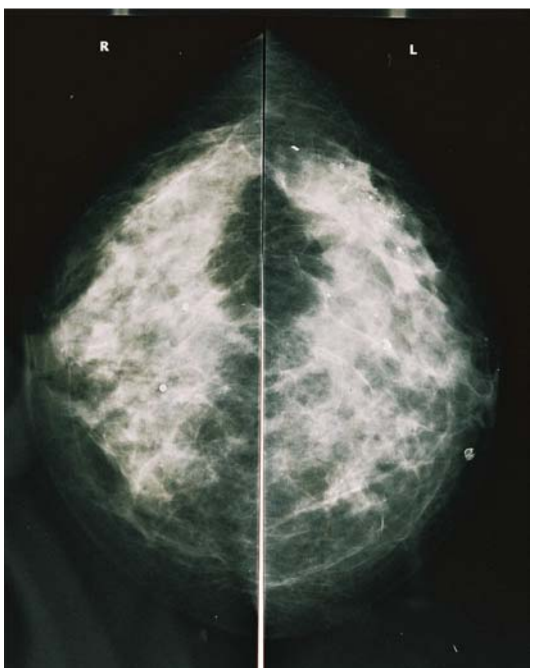
Clinical data

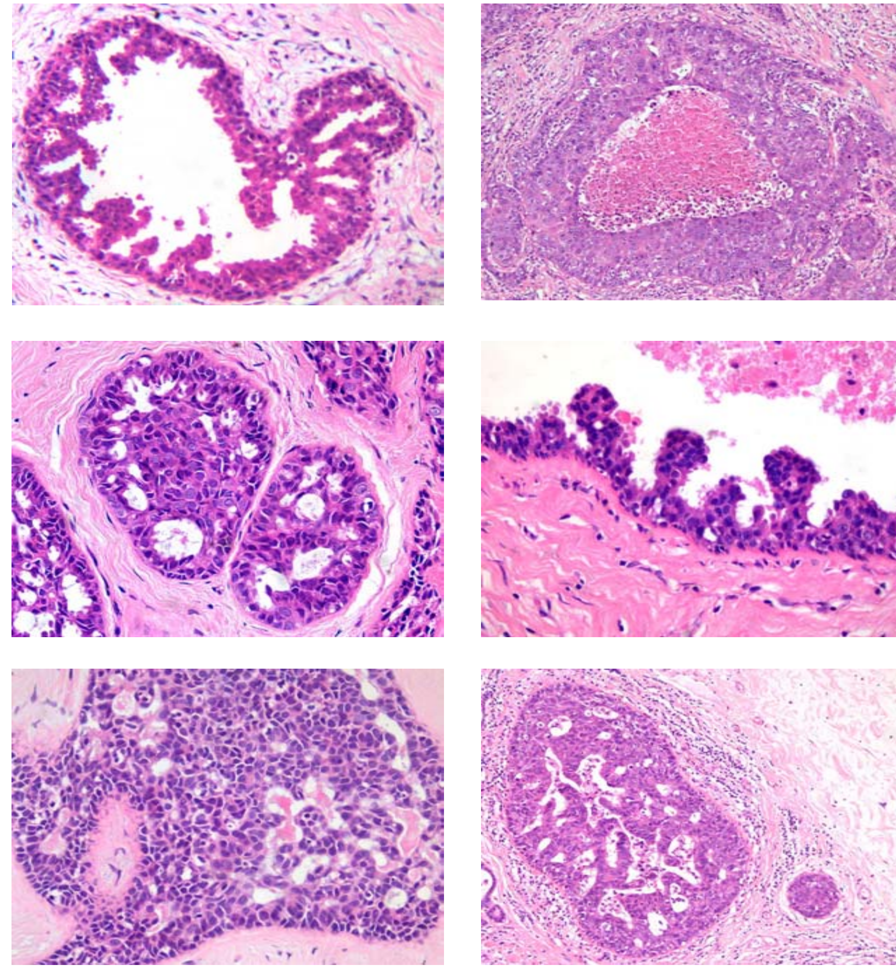
Histopathology slides



Histopathology images are quite different from radiological images







Appearance is very different, so is scale of analysis

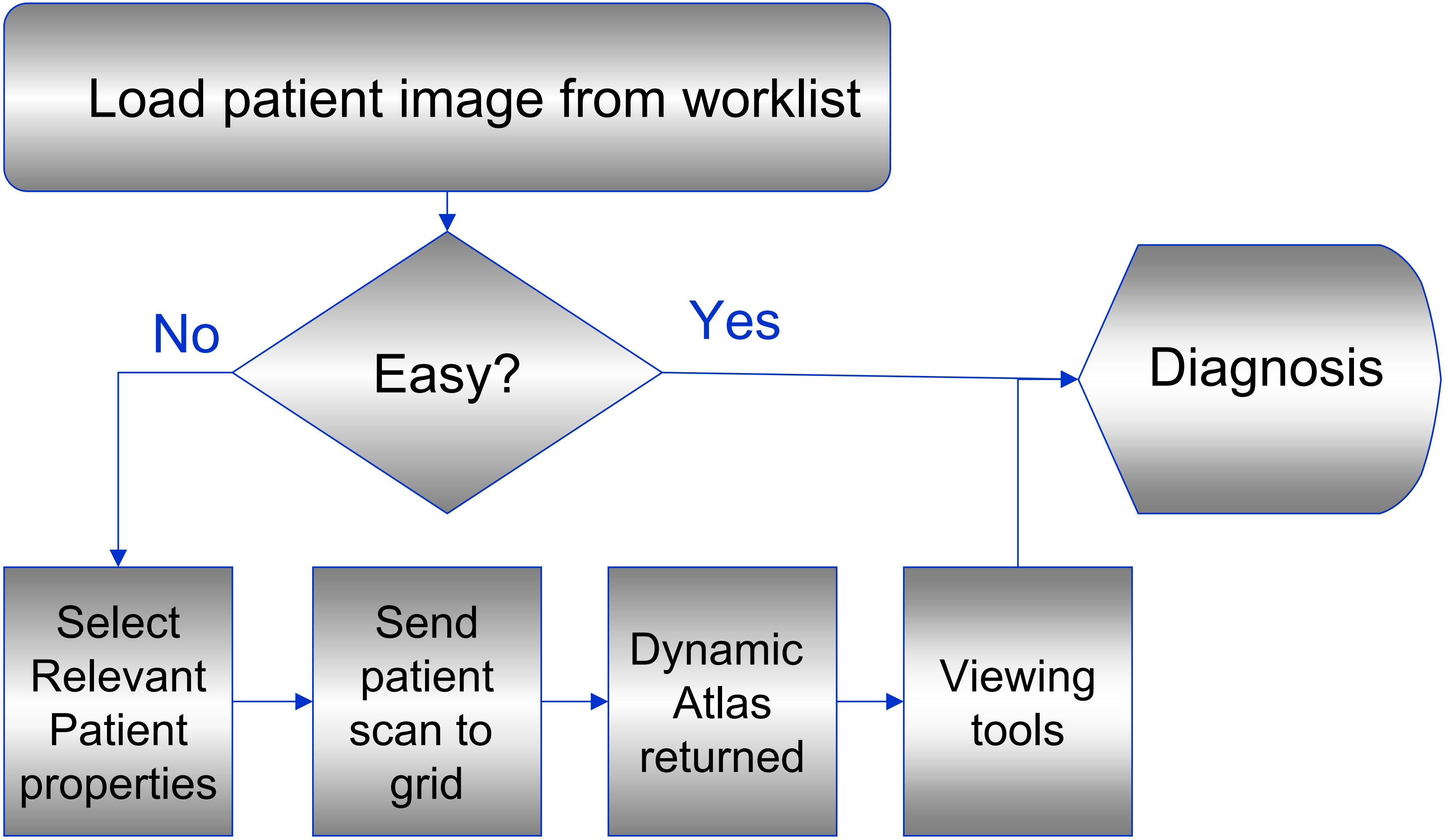
Registration infeasible over widely different scales …reasoning implies shared ontology

The potential of the Grid

- Web services & high bandwidth + grid security interface
- A dynamic atlas
- Mammogrid/eDiamond
  - Federated database of mammograms
  - Normalised images SMF
- UK BioBank
  - Clinical, environmental, genomic information

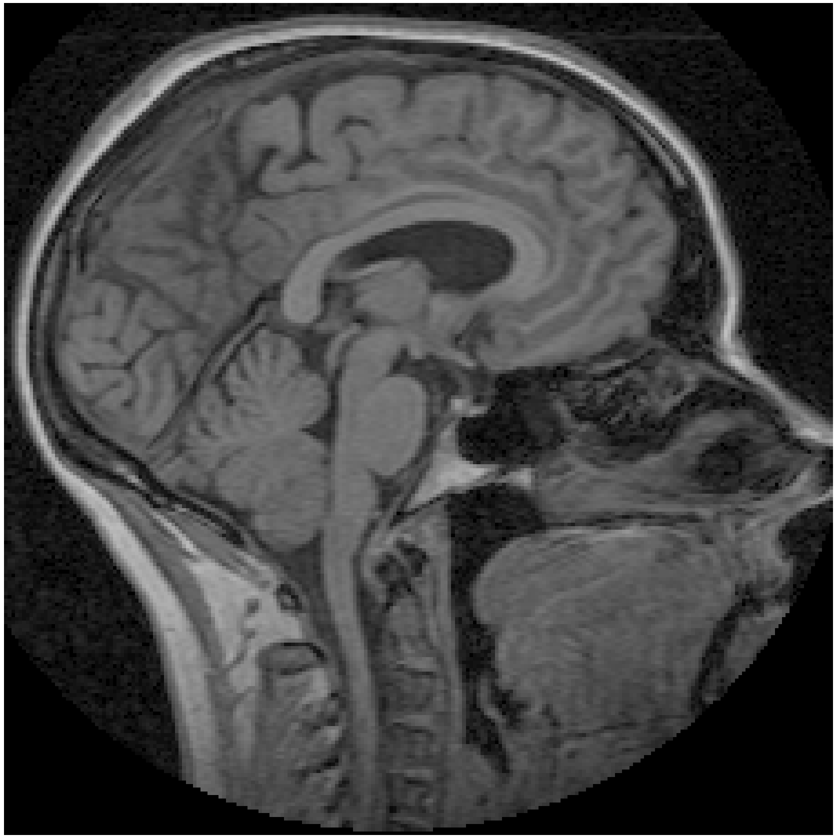
Ontologies are key to keeping the database live

Workflow of a Busy Radiologist… 2005



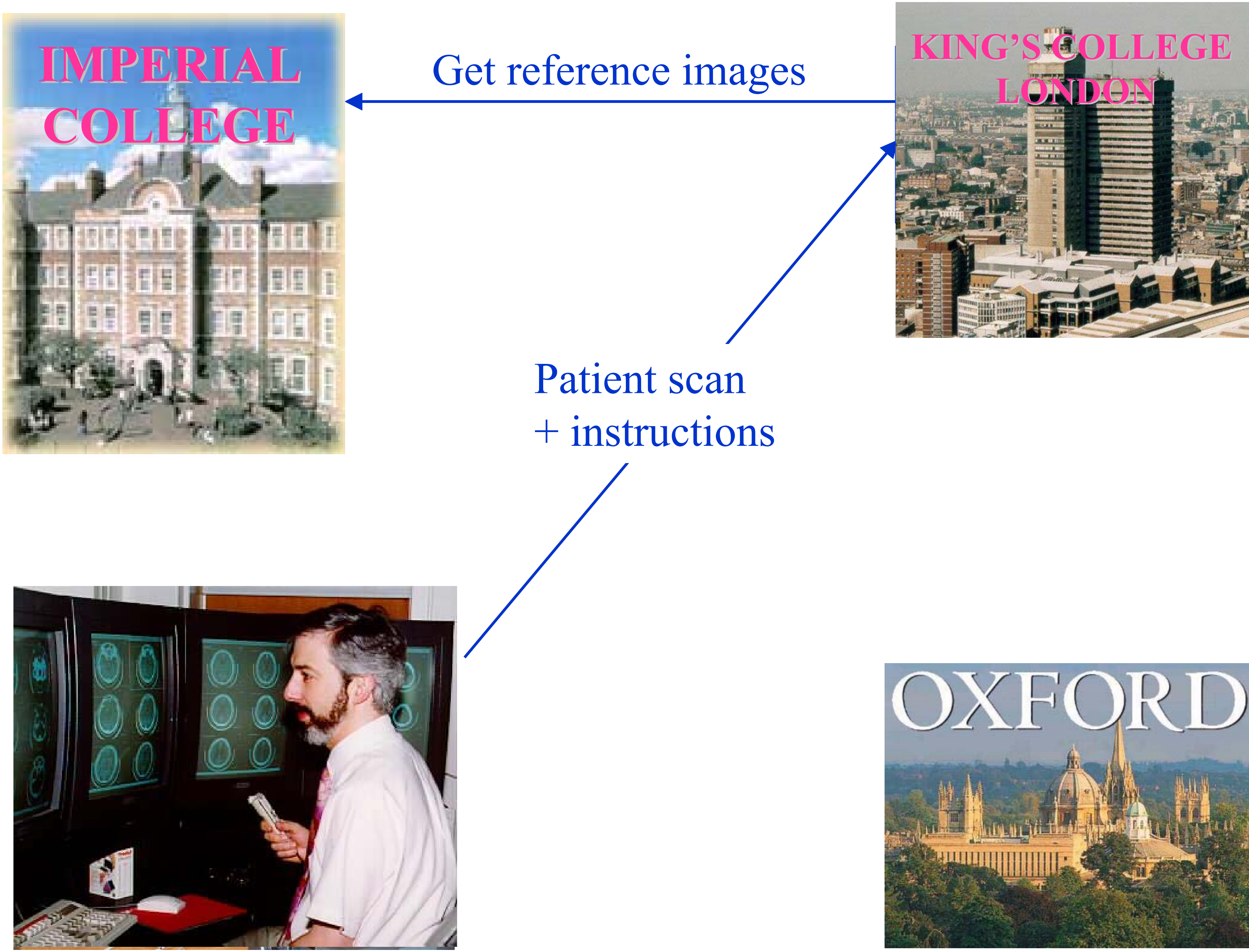
Original Data From 200 Subjects

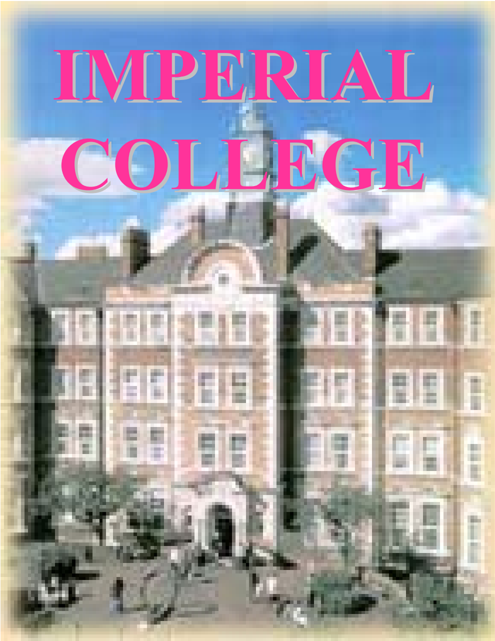
Used to create an atlas – the "average" brain, so that differences between *this* brain and the average can be noted



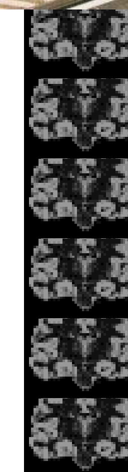
Can we dynamically create an atlas that is relevant for *this* patient?

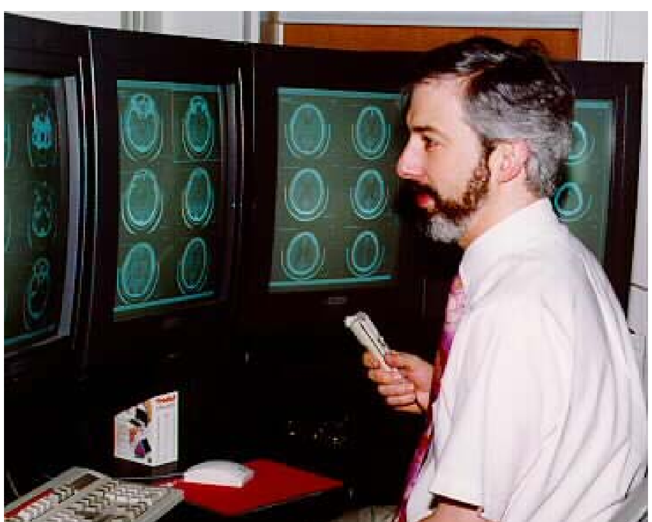
The "average" may comprise young/old; normal/many diseases; …

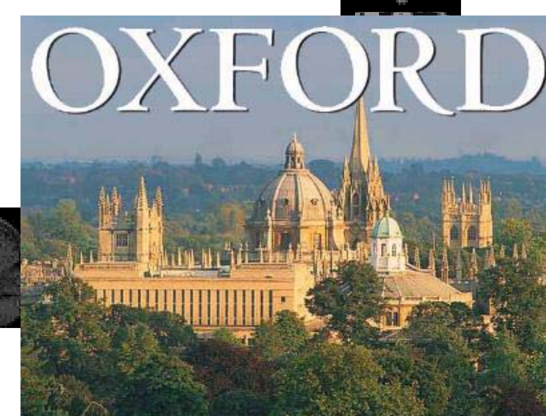

IMPERIAL COLLEGE
Get reference images
KING'S COLLEGE LONDON
Patient scan
+ instructions
OXFORD

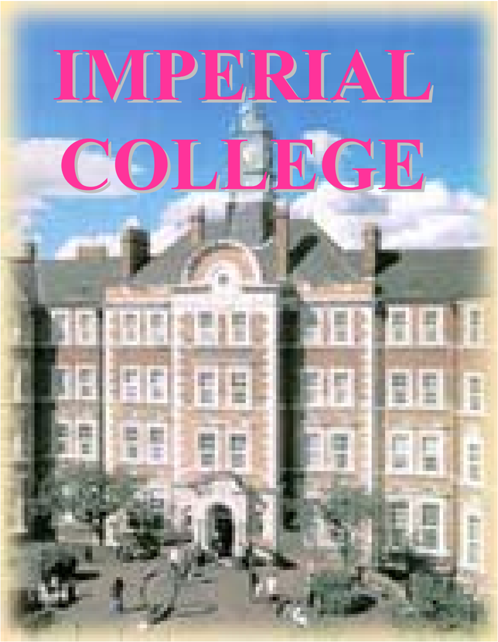

IMPERIAL
COLLEGE


KING'S COLLEGE
LONDON



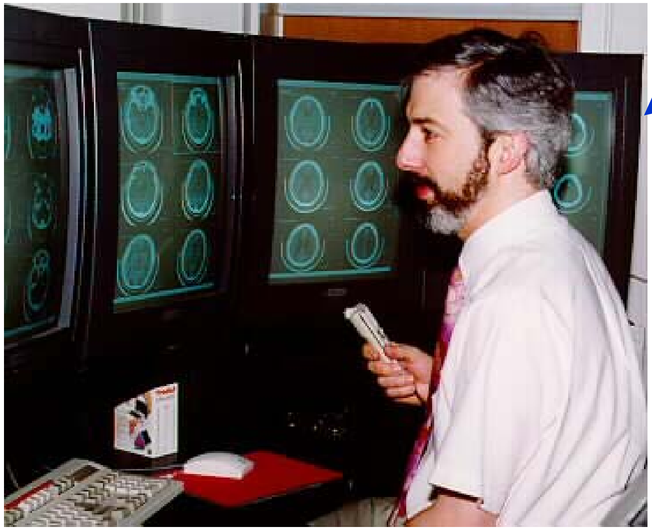


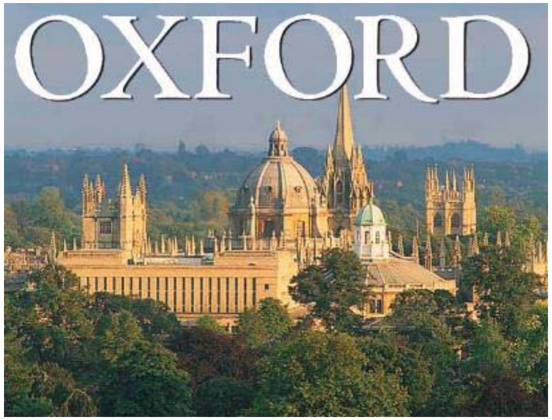

OXFORD


IMPERIAL
COLLEGE


KING'S COLLEGE
LONDON
Create atlas

atlas




OXFORD

A UK database of mammograms

- Currently one view taken of each breast → 3,000,000 images per year in UK (26M in Europe)
- Increasing to 2 views per breast over the next 2-5 years
- Digitised at 50μ each mammogram yields 25-40Mbytes
- Total annual potential is 240×10^{12} bytes
- Compression must be lossless

… and there are 11,000,000 mammograms in the UK backlog!

The eDiamond project

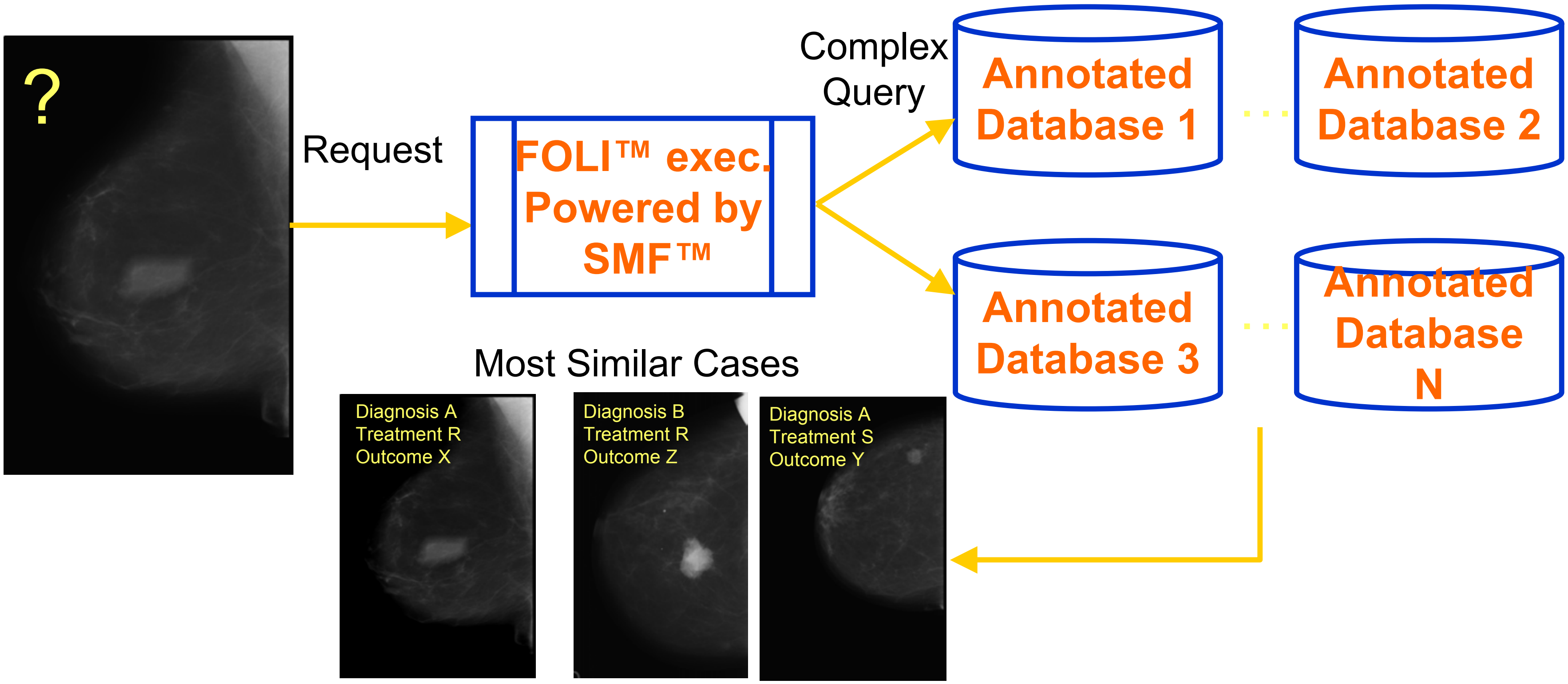
- ✓ Teaching & Continuing Professional Development
- ✓ Tele-diagnosis: second opinions from an expert
- ✓ Automated Quality control
- ✓ Epidemiology
- ✓ Algorithm development: data mining

Massively supported by industry and UK government

Grid challenges: database

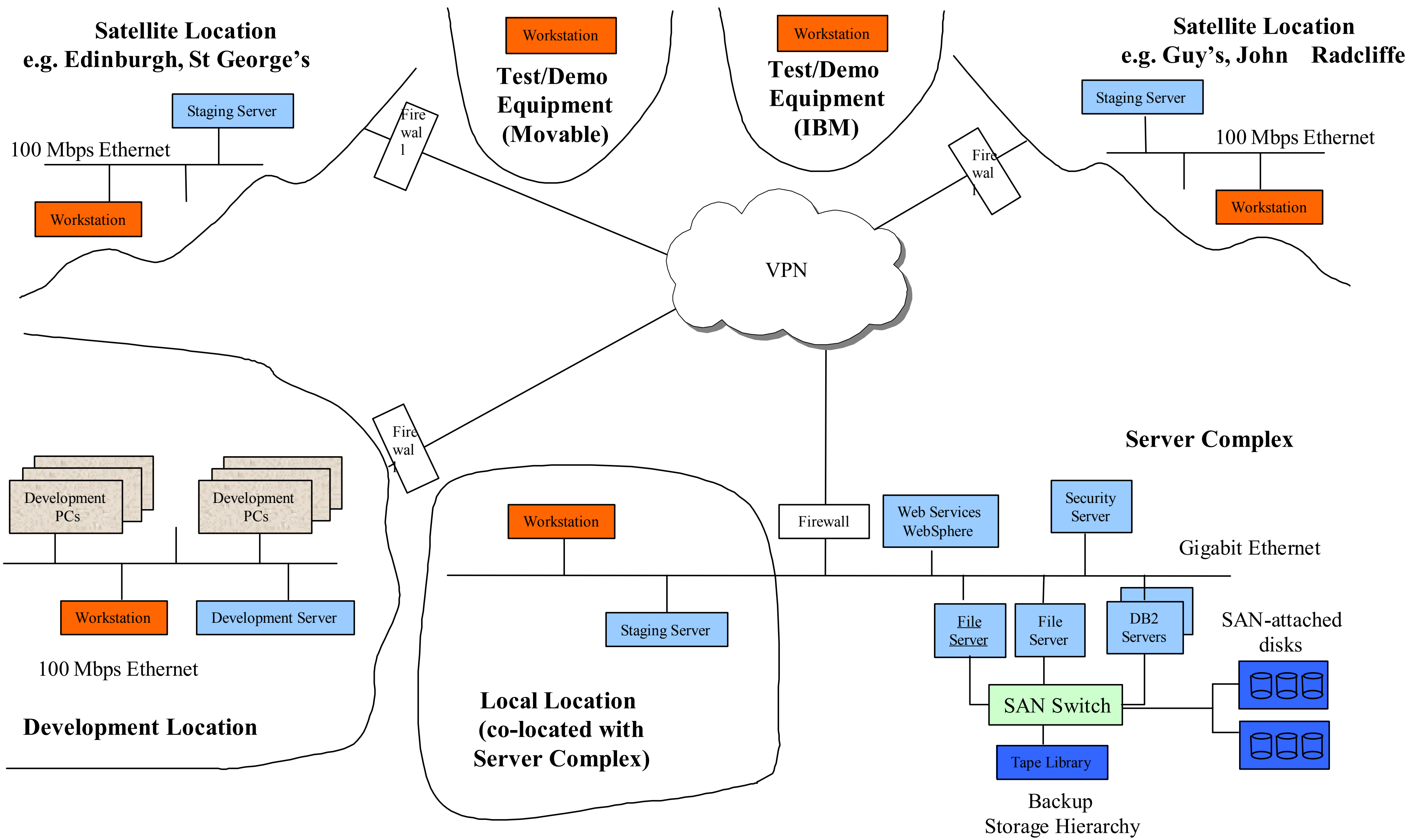
- Large federated databases
  - Images and metadata
- Ontologies and metadata
  - Image formation parameters
  - Image features
  - Clinical information
  - Demographic data
- Effective data mining of a rapidly growing database
- Allow for complex queries involving executables
  - e.g. “give me breast densities for all women >45 with HRT”
  - e.g. “… and those with a suspect mass like this”

Find one like it (data mining)



- "*Find one like it*" improves diagnostic confidence, can be used to monitor diagnostic quality and teaching
- Interaction with LTU

The architecture



Ubiquitous computing

- Electronic devices are getting smaller and cheaper
- PDAs replace clip-boards on the ward round
  - Ask the patient his/her identity
  - And confirm by asking the bed which patient is in it
- Most doctors can't type, those that can do it slowly
  - Speech, gestures, …
- Smart ingested devices?

The changing world of ultrasound

- Technological advances in image acquisition technology (frame-rate, portability,modes)

?

1995 2002 2010

Ubiquitous computing

- Electronic devices are getting smaller and cheaper
- PDAs replace clip-boards on the ward round
  - Ask the patient his/her identity
  - And confirm by asking the bed which patient is in it
- Most doctors can't type, those that can do it slowly
  - Speech, gestures, …

Themes for FP6

- Decision support for diagnosis, treatment & patient management
- Portable communications
  - Direct contact from patient to primary care/hospital
  - Continuous intelligent surveillance
- Systems to provide patients with more active role in managing their own treatment
- Constant monitoring: disease to prevention
- Intelligent Biomedical Clothes
  - Wearable systems (intelligent fabrics, nanotechnology sensors, …)

Future Health Informatics INRIA's technical base

Existing world-class efforts:

- Image analysis
- Modelling (geometry, biomechanics, …)
- Robotics
- AI
- Large-scale software development
- W3C & Grid
- …

Good news: INRIA has world-class efforts in many of the required Informatics technologies

Future Health Informatics challenges for INRIA

- "Fortress" INRIA (etc) vs multidisciplinary working
  - multidisciplinary research
  - MRC + EPSRC + BBSRC
  - Inserm + CNRS + INRIA?
  - Are these barriers too high for INRIA?
- Leading the way vs following
  - All innovations in image and signal analysis have come from physics and biology, not from Informatics
- Health informatics vs Informatics with medical data
- Team working vs personal credit
- Systems engineering/architecture vs the theorem culture