Arterial Spin Labeling

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Outline

- MRI basics
- ASL Acquisition
- Processing and parameter estimation
- Applications

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Introduction and Motivation

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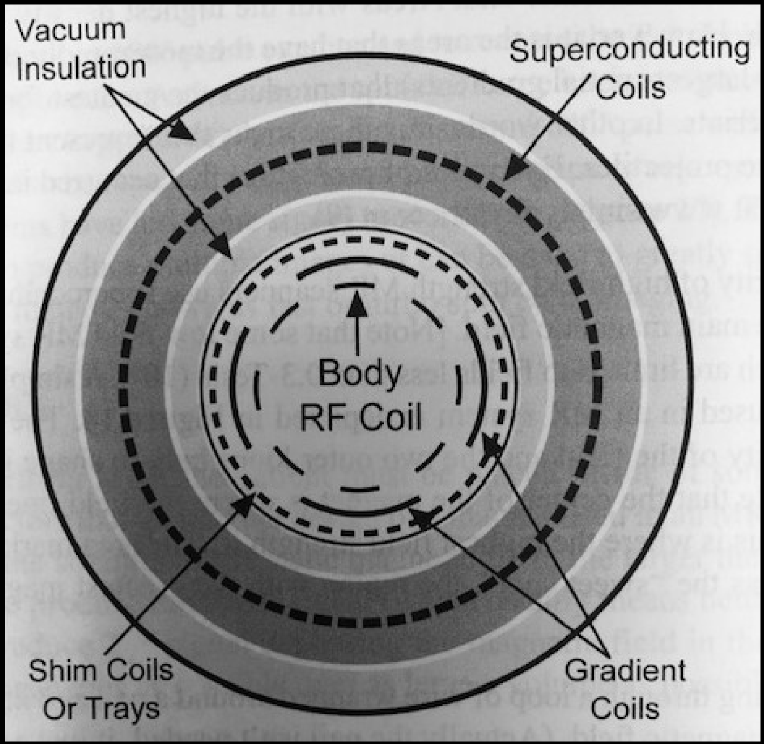
What is MRI?

- Magnetic Resonance Imaging
- Extremely flexible imaging modality
- Uses a static magnetic field and radiofrequency coils
- Probe inherent magnetic properties of tissue

Three Magnetic Fields

- Static Field (B_0 Field)
- Gradient Fields
- Radiofrequency Fields (B_1 Field)

- Additive



NessAiver, M, in: MRI: Bioeffects, Safety, and Patient Management (2014)

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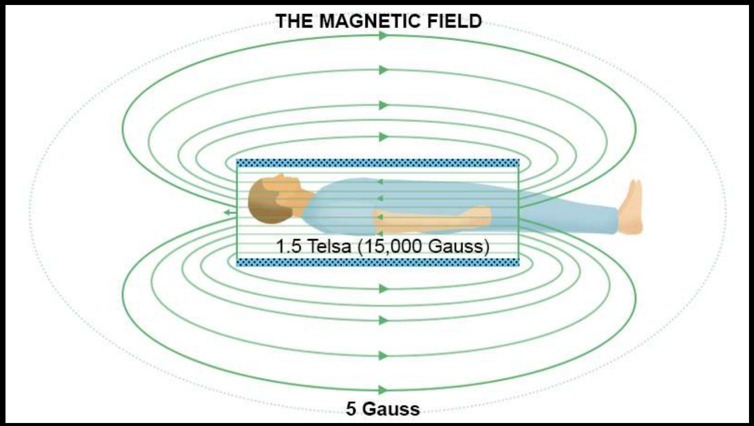
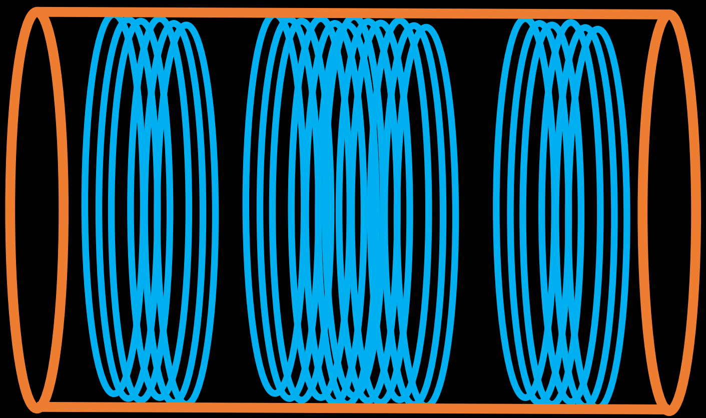
Static Field (B_0)

- Always On
- As homogeneous as possible in bore
- Superconducting coils
  - Cooled with liquid helium
  - Quench
- >1T – 14T



https://www.eeweb.com/mri-machine/



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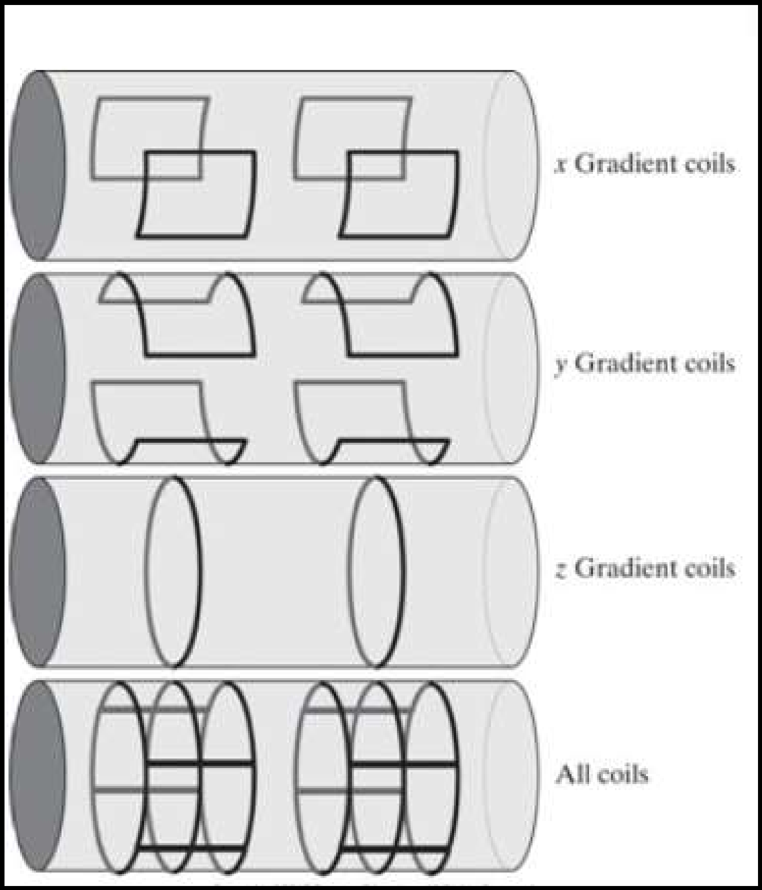
Gradient Fields

- Quickly turned on and off
- Large contribution to noise
- Used in spatial localization
- X, Y, Z gradient coils
- ~5mT/m



http://mriquestions.com/gradient-coils.html

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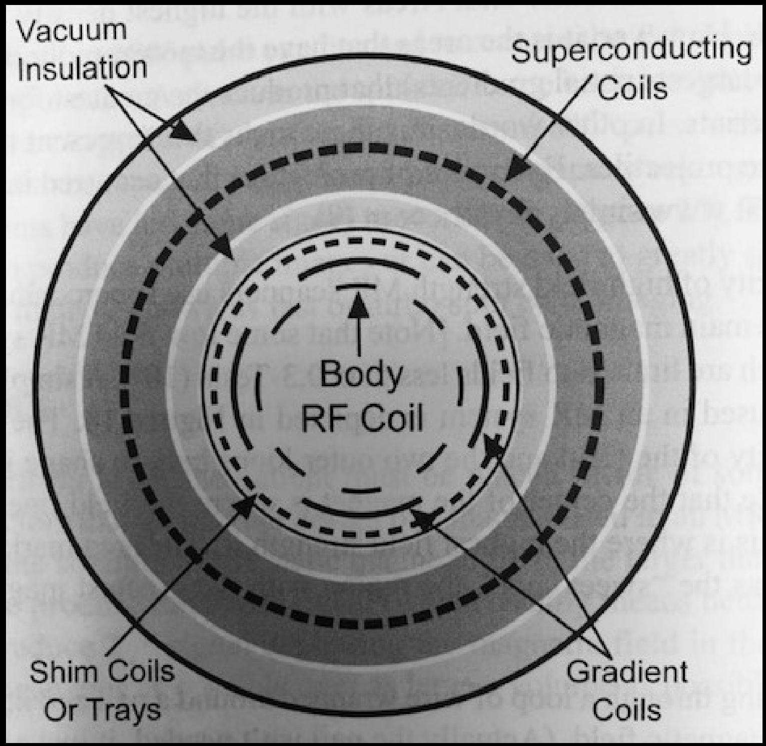
Radiofrequency Fields (B_1)

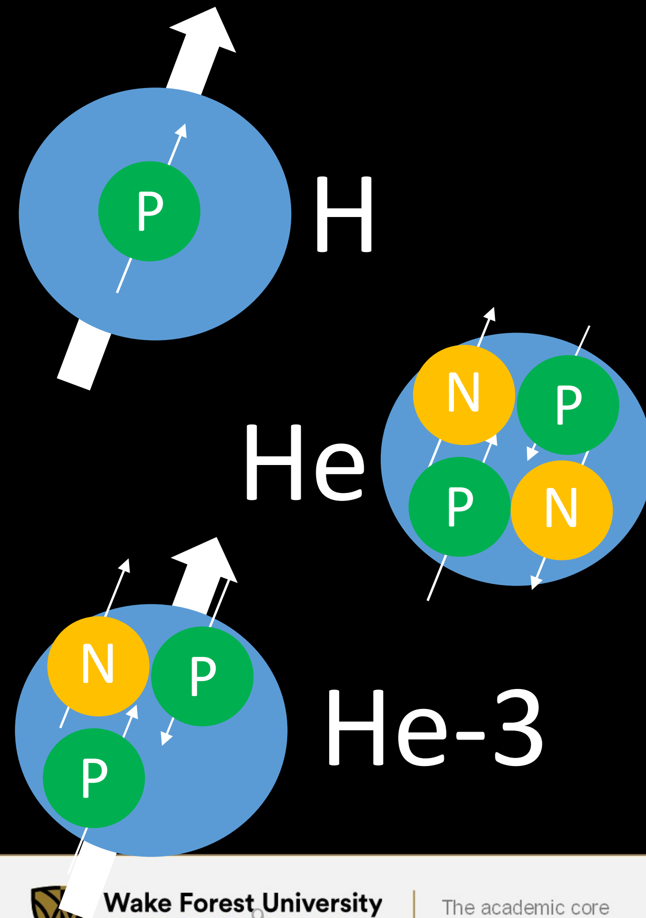
- Excitation
- Turned on and off
- RF coil (body coil)
  - Most interior coil
- 0.01-0.05 mT



NessAiver, M, in: MRI: Bioeffects, Safety, and Patient Management (2014)

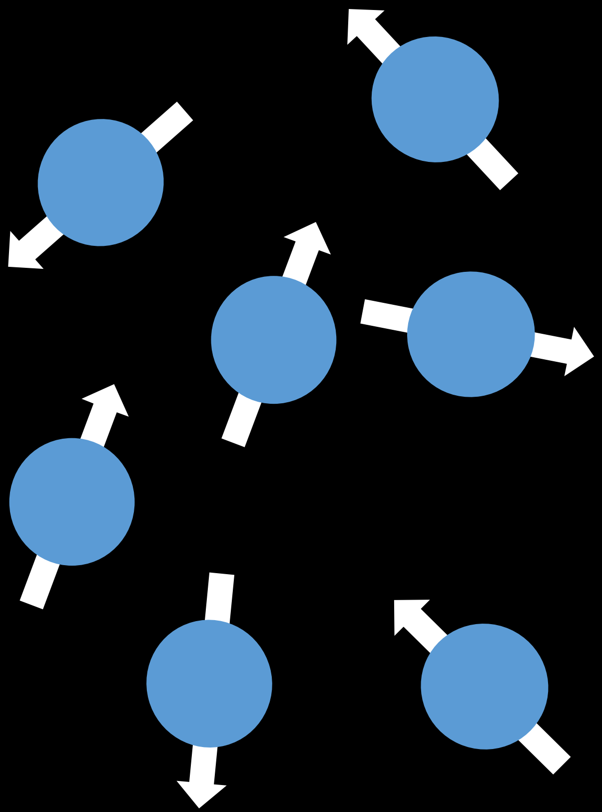
Nuclear Magnetic Moment and Spin

- Nuclei with odd P, odd N, or both have nuclear magnetization
  - Spins, dipoles, magnetic moments
- Spin is a fundamental property
  - Quantized into increments of ½
  - Similar to angular momentum
  - Nuclei with non-zero spin can absorb and emit electromagnetic radiation



Nuclear Magnetic Moment

- In the absence of an external magnetic field, the nuclei are randomly oriented and result in no net nuclear magnetization
- In the presence of a magnetic field, they will orient with or opposed to that field



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Nuclear Magnetic Moment

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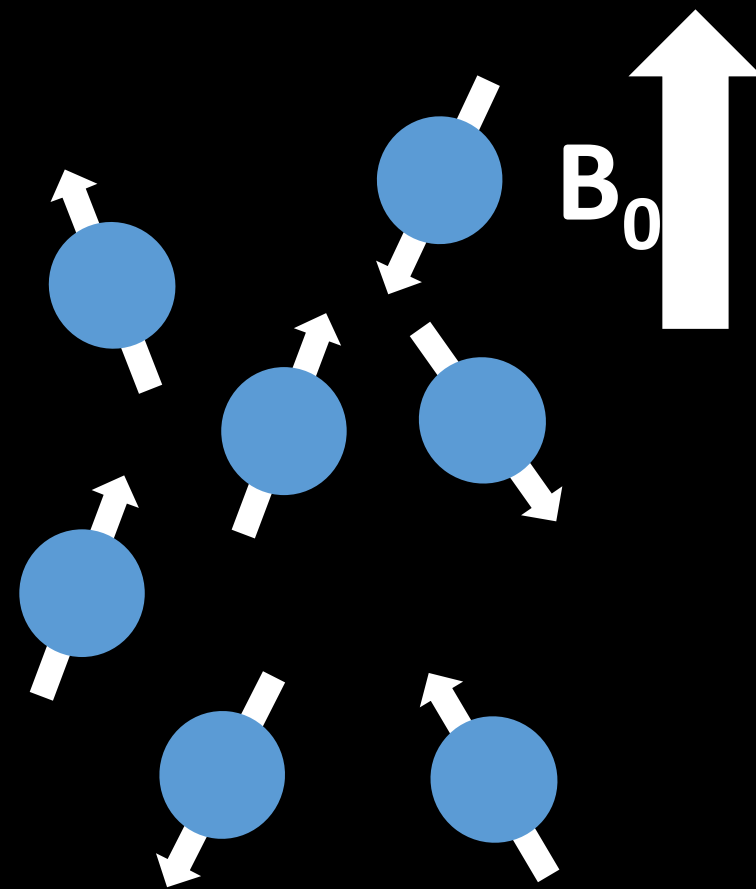
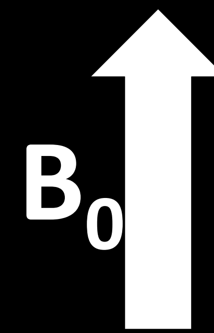
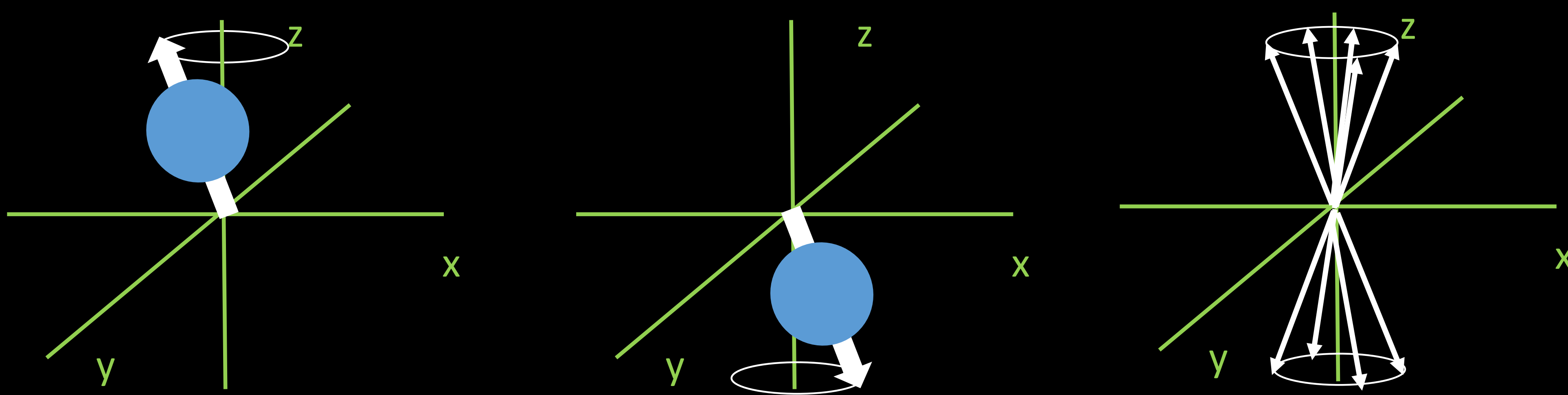


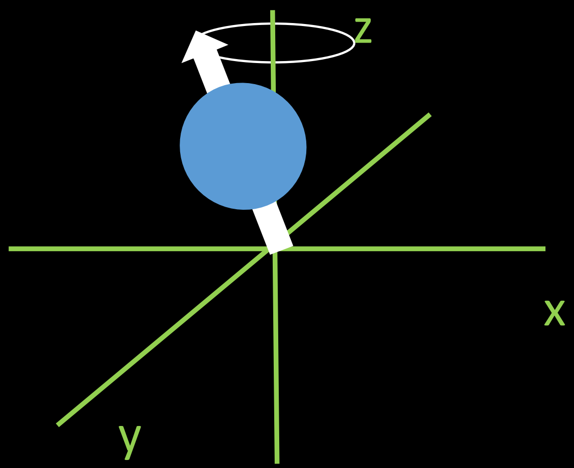
Nuclear Magnetic Moment



- Spins will process around the axis parallel with B_0



Larmor Frequency



- Frequency of procession depends on the element and B_0

$$\boxed{\omega_0 = \gamma\, B_0}$$

- ω is the Larmor Frequency
- γ is the gyromagnetic ratio
  - Different for every element with net nuclear magnetization

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γ and element selection

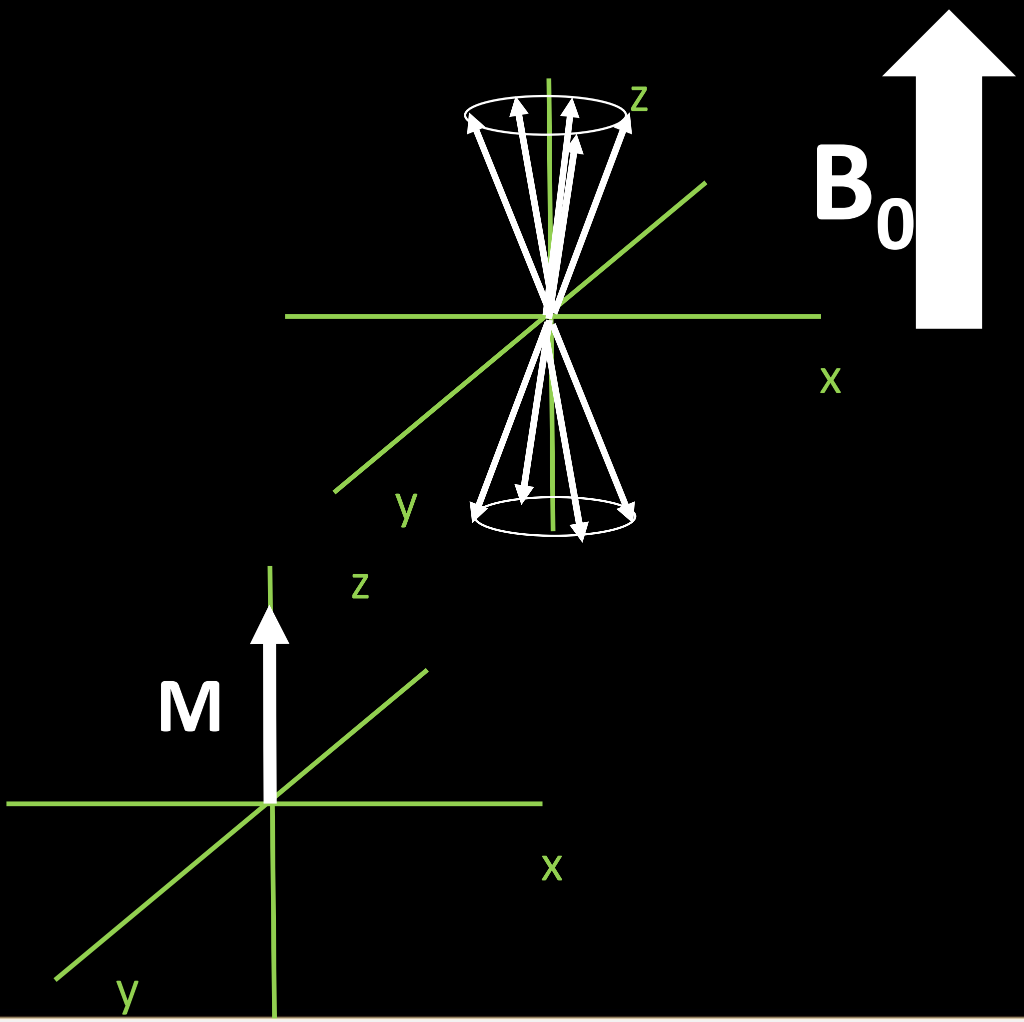
$$\boxed{\omega_0 = \gamma\, B_0}$$

Nuclei	Gyromagnetic ratio (MHz/T)	Spin quantum number	Natural abundance (%)	Relative sensitivity
^{1}H	42.6	1/2	99	1.0
^{13}C	10.7	1/2	1.1	0.016
^{17}O	5.8	5/2	0.1	0.029
^{19}F	40.0	½	100	0.83
^{23}Na	11.3	3/2	100	0.093
^{31}P	17.2	1/2	100	0.07

Humans are 70% water by weight

Bulk Magnetization

- Slightly more nuclei will orient with the B_0 than opposed to B_0
- Results in net bulk magnetization



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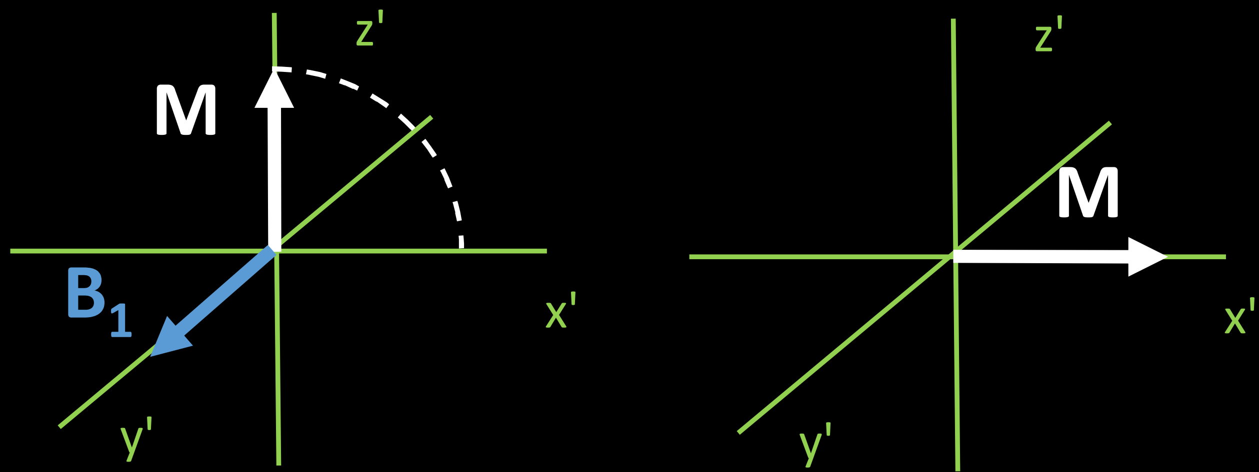
RF pulse – B_1 field

- RF energy input
- M rotates about B_1 for a quarter rotation
- B_1 is turned off
- Here: 90° flip angle



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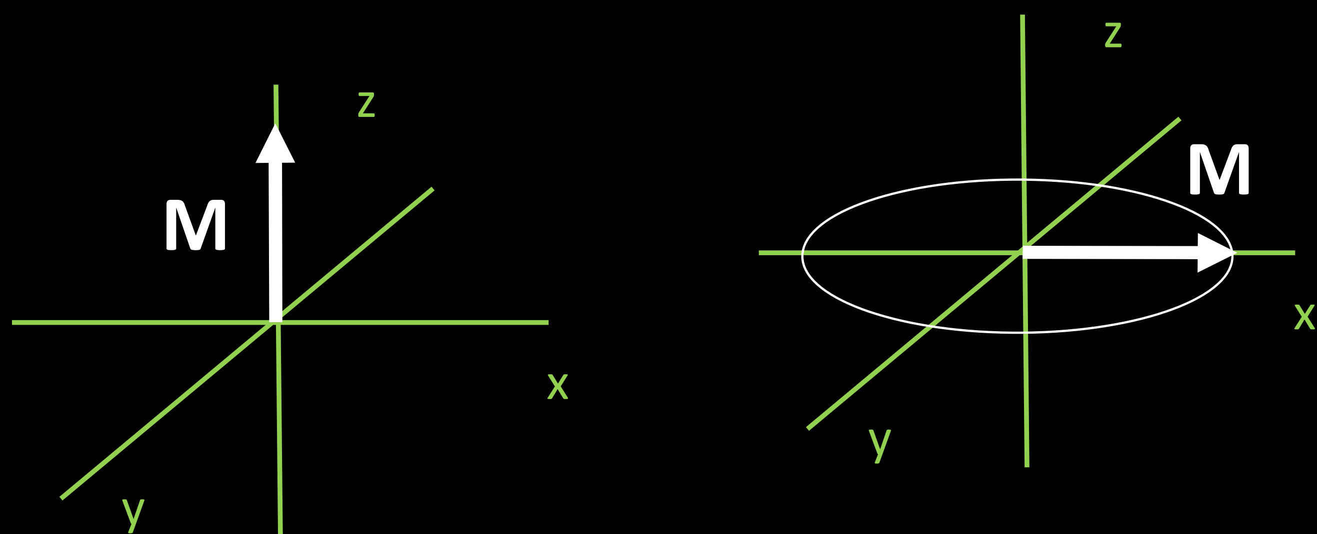
Signal from precessing magnetization

- Equilibrium Magnetization
- Excitation from RF coils



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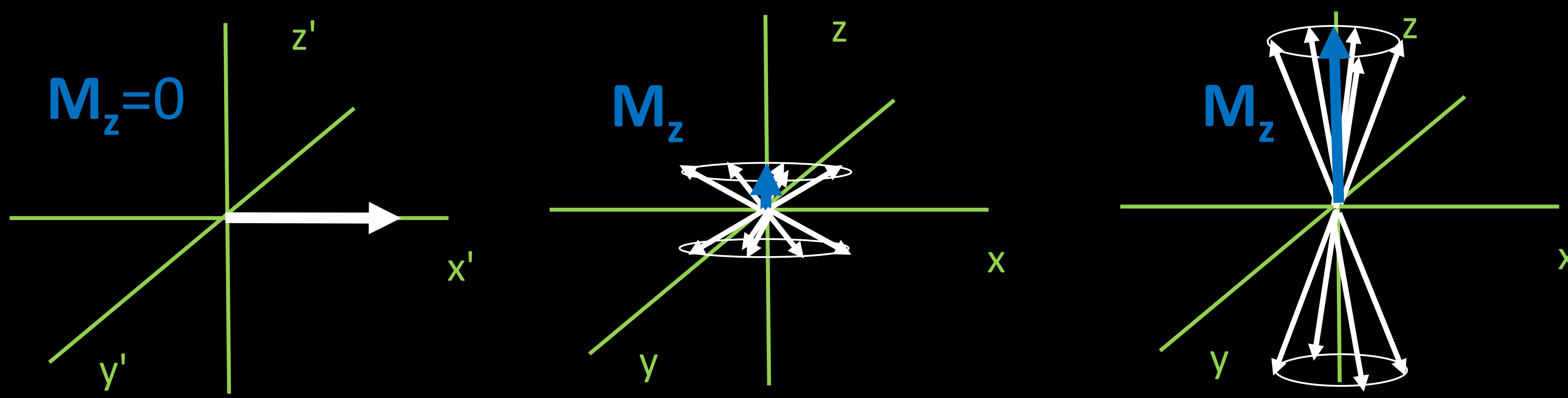
T_1 Recovery

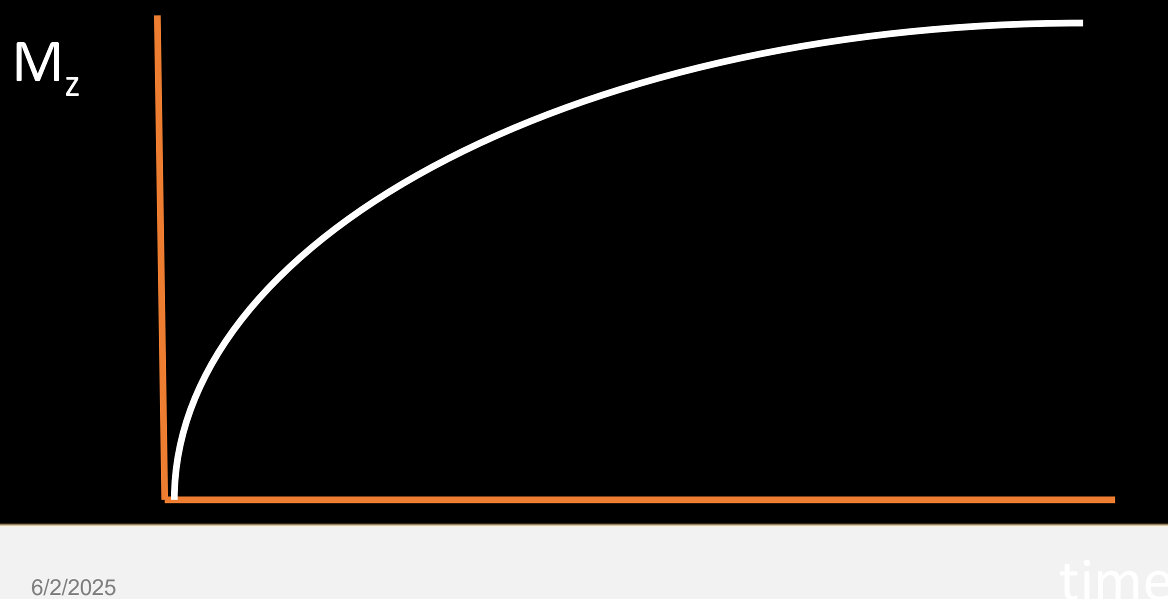
- After RF is turned off, **M** will return to equilibrium



T_1 Recovery (spin-lattice relaxation)

After 90° pulse

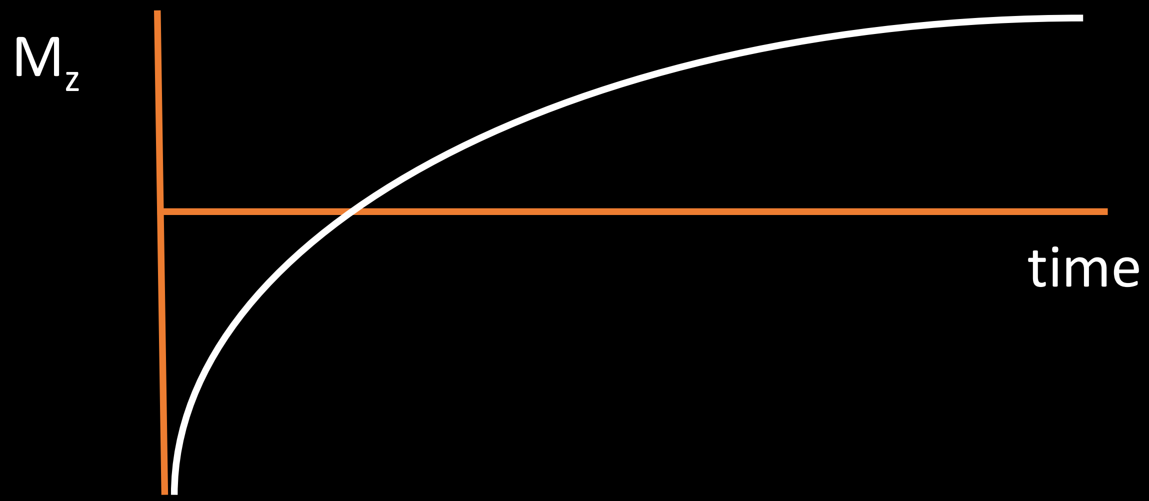
$$\boxed{M_z(t) = M_0(1 - e^{-t/T1})}$$



T_1 Recovery

After 180° pulse

$$\boxed{M_z(t) = M_0(1 - 2e^{-t/T1})}$$



Cerebral Blood Flow Measurement

- Direct measurement of cerebral blood flow (CBF)
- Non-invasive (no contrast agents)
- Quantifiable

Arterial Spin Labeling

- Direct measurement of cerebral blood flow (CBF)
- Non-invasive (no contrast agents) – blood as endogenous contrast agent
- Quantifiable – ml blood/100g tissue/minute

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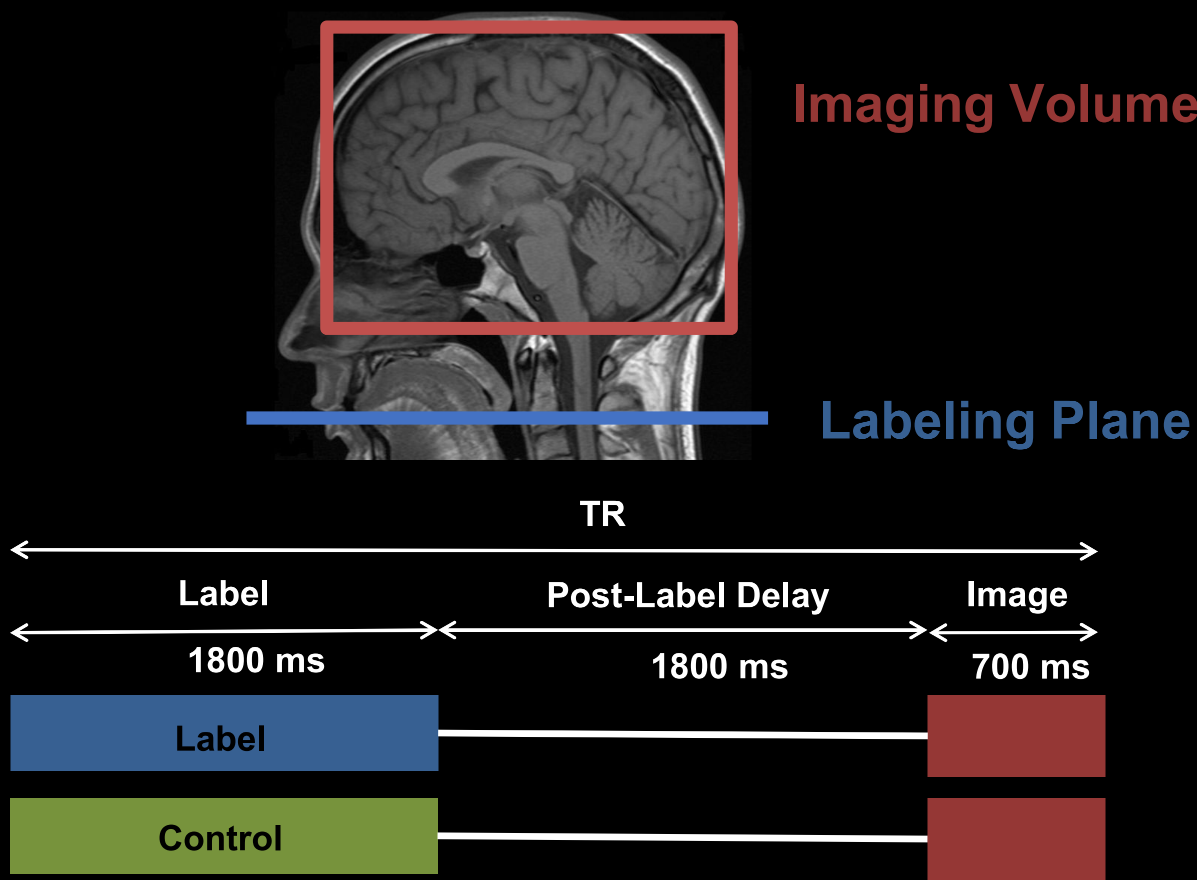
Acquisition

ASL

- Inversion pulse applied at labeling plane
- Wait for labeled blood to perfuse brain
- EPI acquisition or other
- Repeat without inversion (control)



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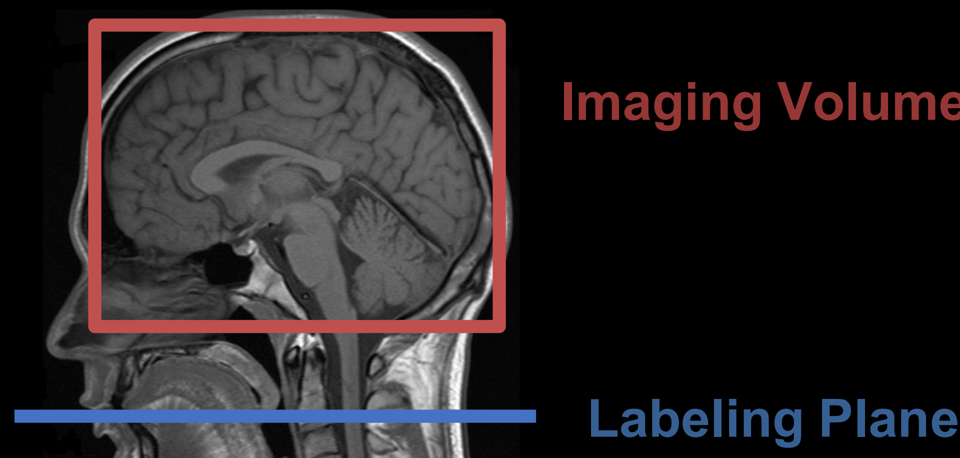
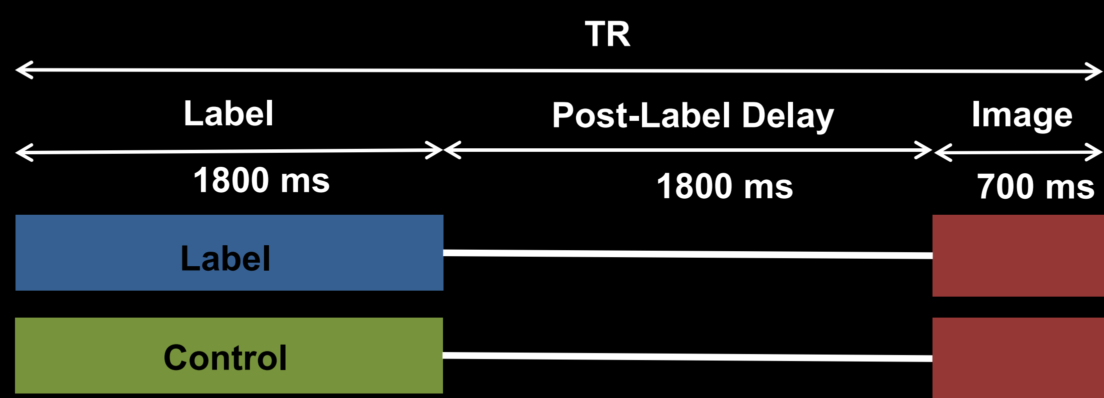
ASL

- Continuous ASL (CASL) – one long RF pulse at labeling plane
- Pseudo-continuous ASL (PCASL) – series of RF pulses have same effect, less SAR





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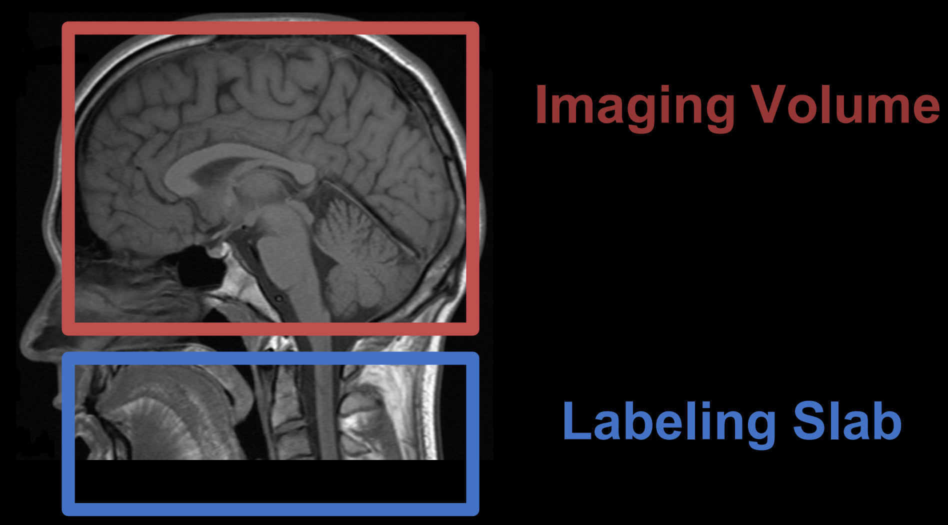
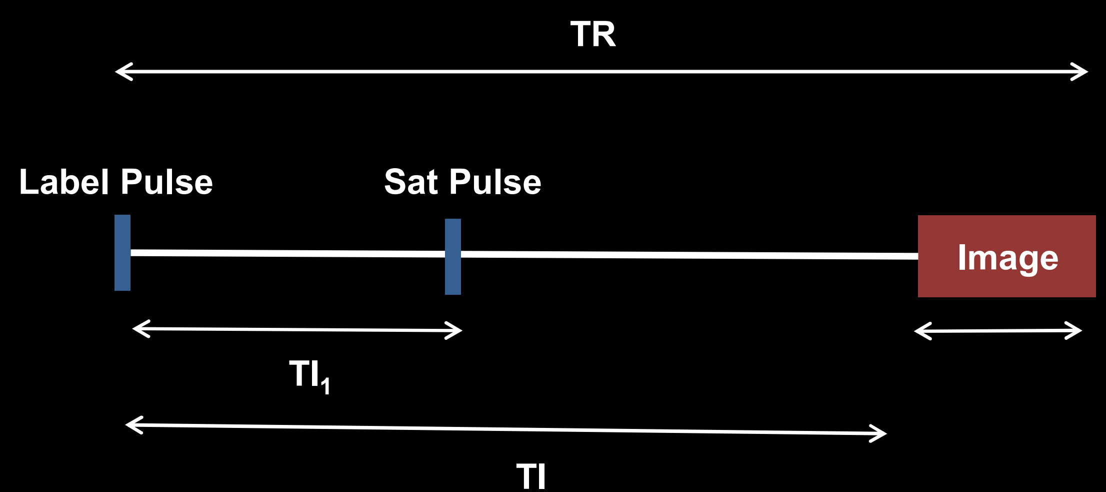
ASL

- Pulsed ASL (PASL)
- Inversion pulse over slab of tissue
- Many method variations of PASL
- QUIPSS-II uses saturation pulse to define end of bolus





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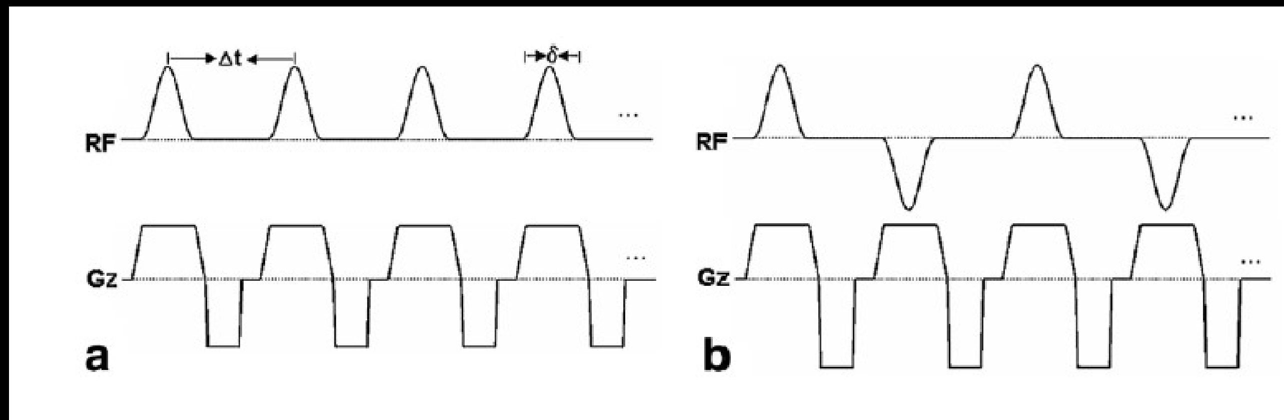
Dai et al. MRM 60:1488-1497 (2008)

PCASL

Label **Control**



Labeling Plane

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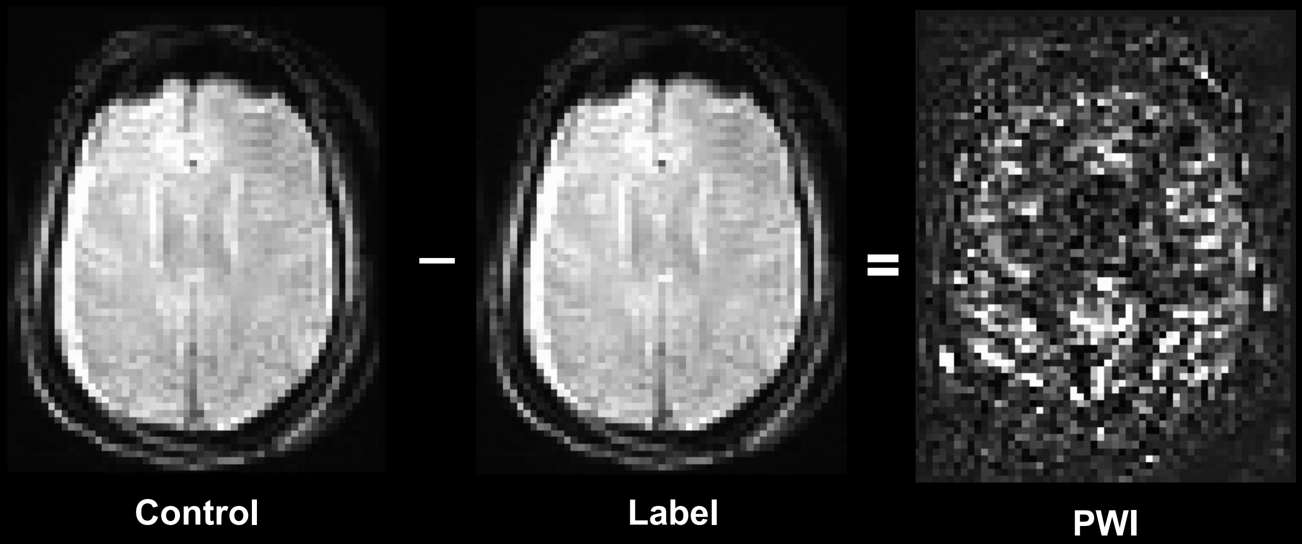
Acquisition

- 2D EPI (Echo Planar Imaging)
- 3D TGSE (Turbo Gradient Spin Echo)
  - Also called GRASE (GRadient And Spin Echo)

ASL

- Control image = brain tissue + fully relaxed blood
- Label/Tag image = brain tissue + blood effected by inversion pulse
- Perfusion weighted image = control - label



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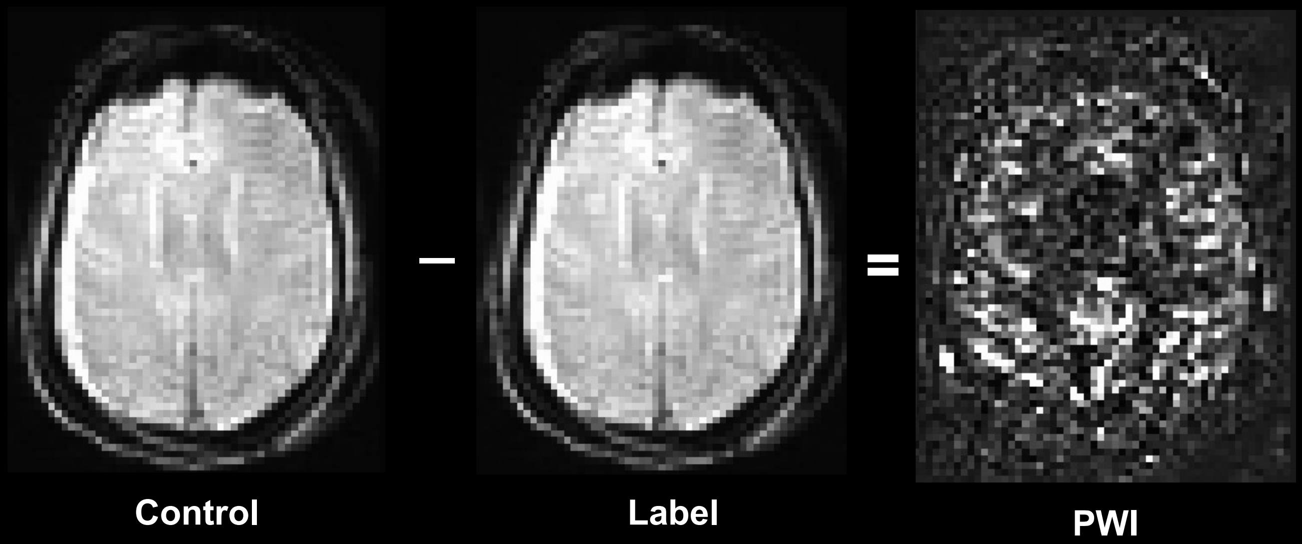
ASL

- Blood is 1% by volume
- Perfusion-weighted image is low SNR
- Must repeat acquisition to increase SNR
- Average after pair-wise subtraction



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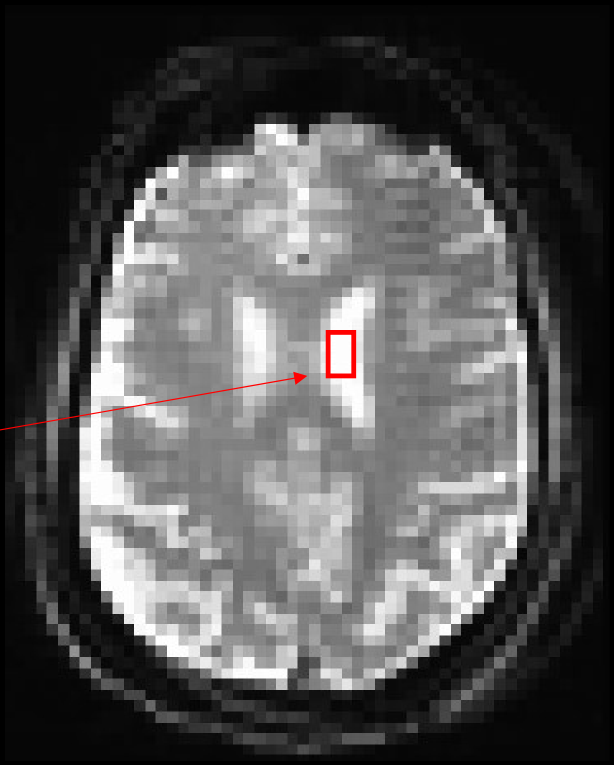
ASL

- M_0 image is acquired at beginning after 3 TRs
  - Fully relaxed magnetization
- Extract M_0 from CSF



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Processing and Parameter Estimation

Image processing

- Rigid realignment of time series
- Remove volumes with excessive motion
- Generate perfusion weighted image (PWI)
- Extract M_0 value from CSF
- Calculate CBF
  - With slice timing correction for 2D (changes effective PLD)

Image processing

- Rigid realignment of time series

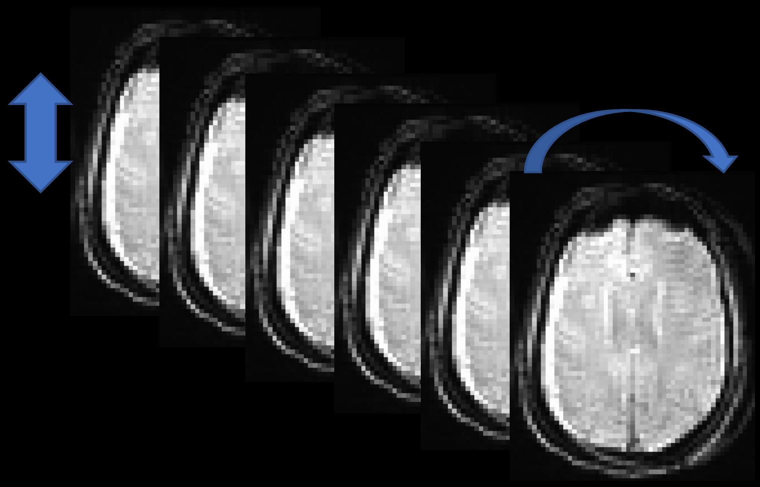

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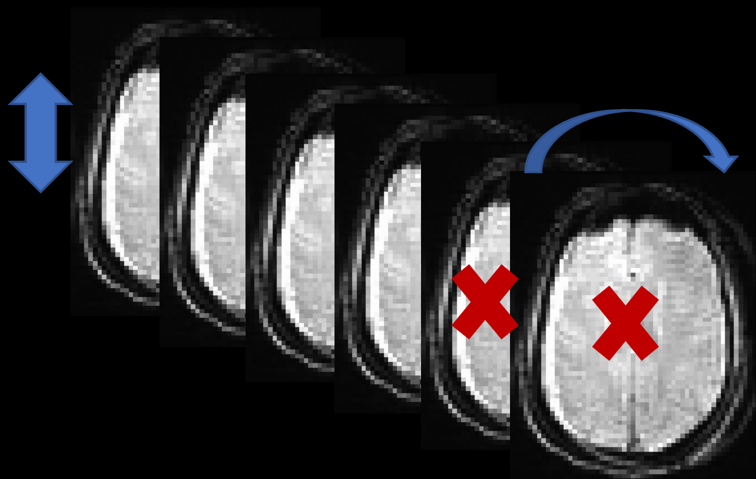
Image processing

Rigid realignment of time series



Remove volumes with excessive motion

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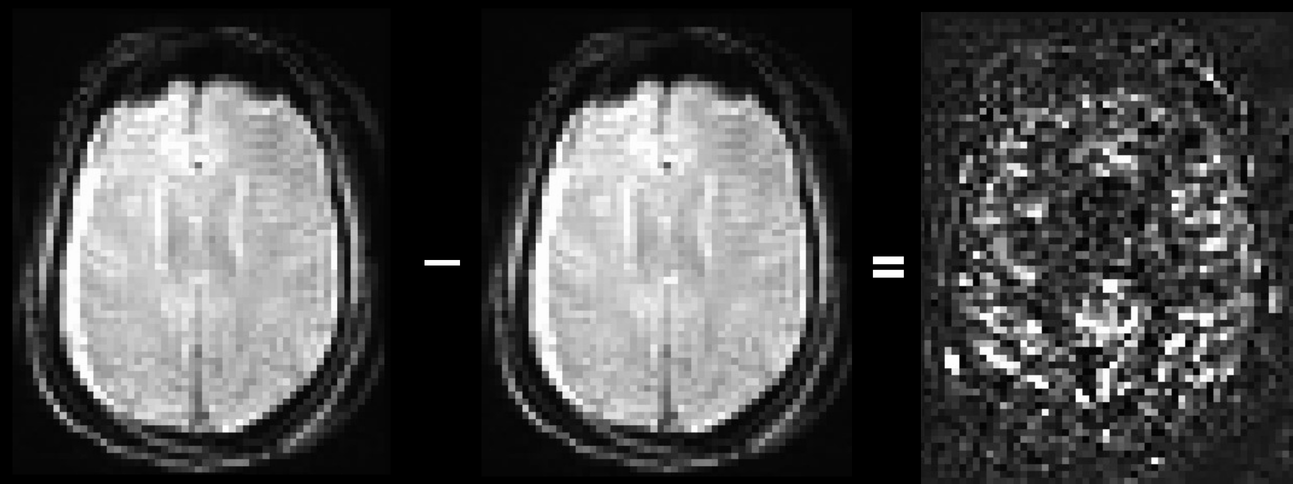
Image Processing

Generate perfusion weighted image (PWI)



Control − Label = PWI

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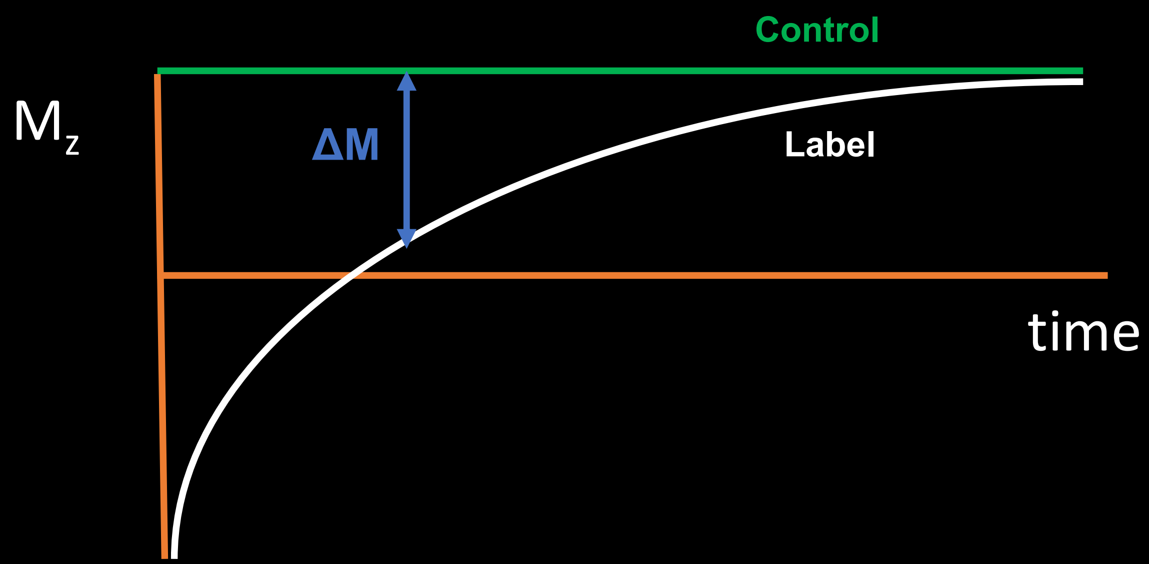
Blood inversion recovery



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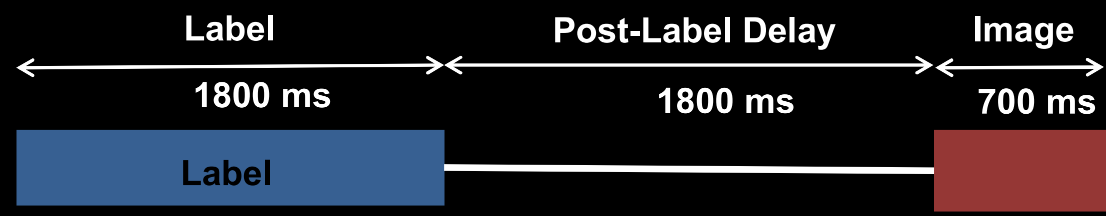
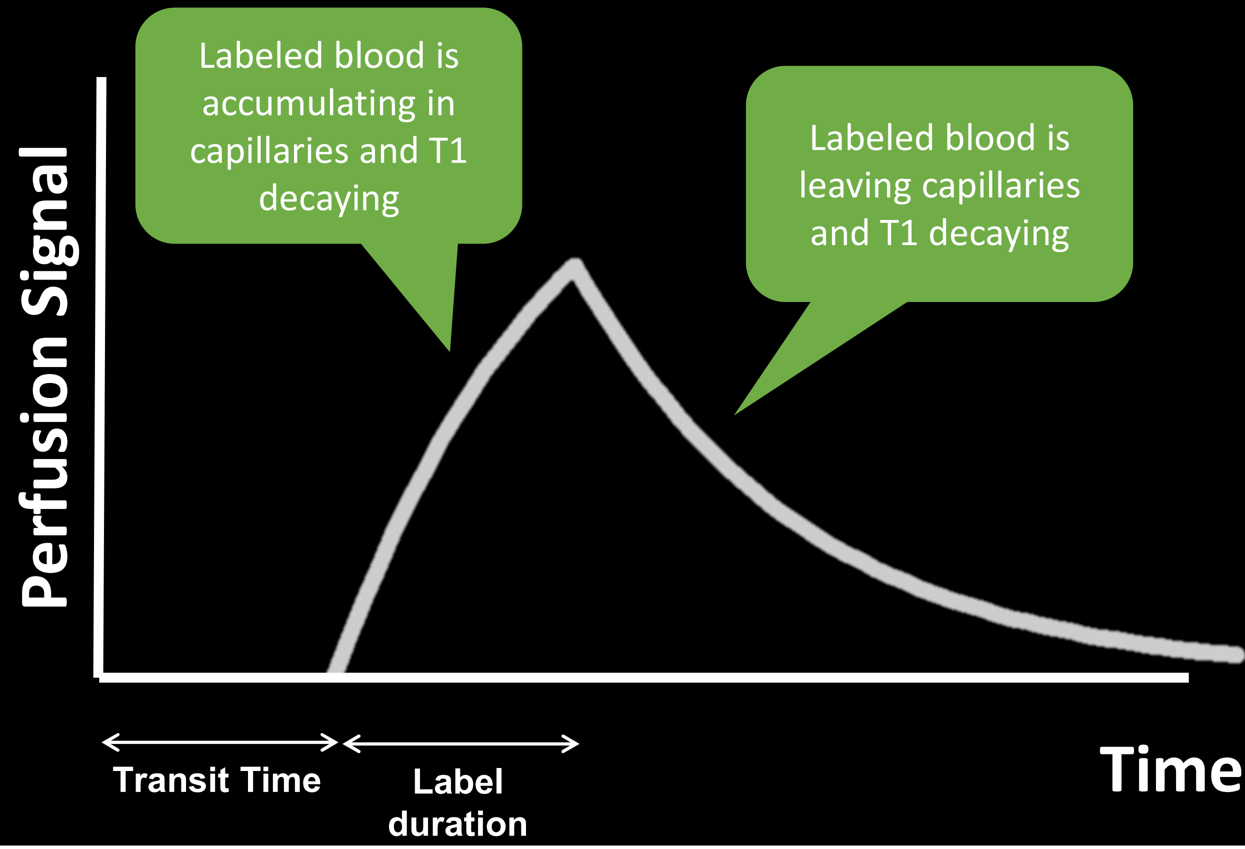
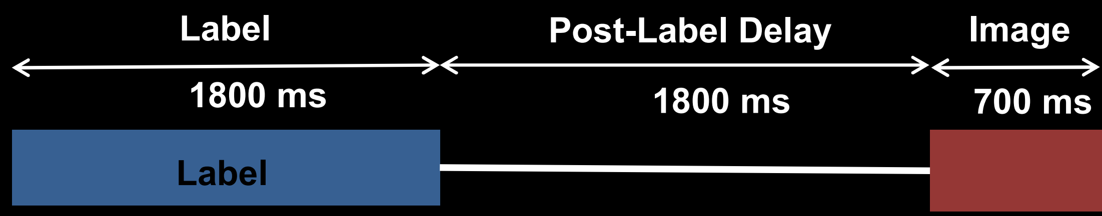
CBF estimation

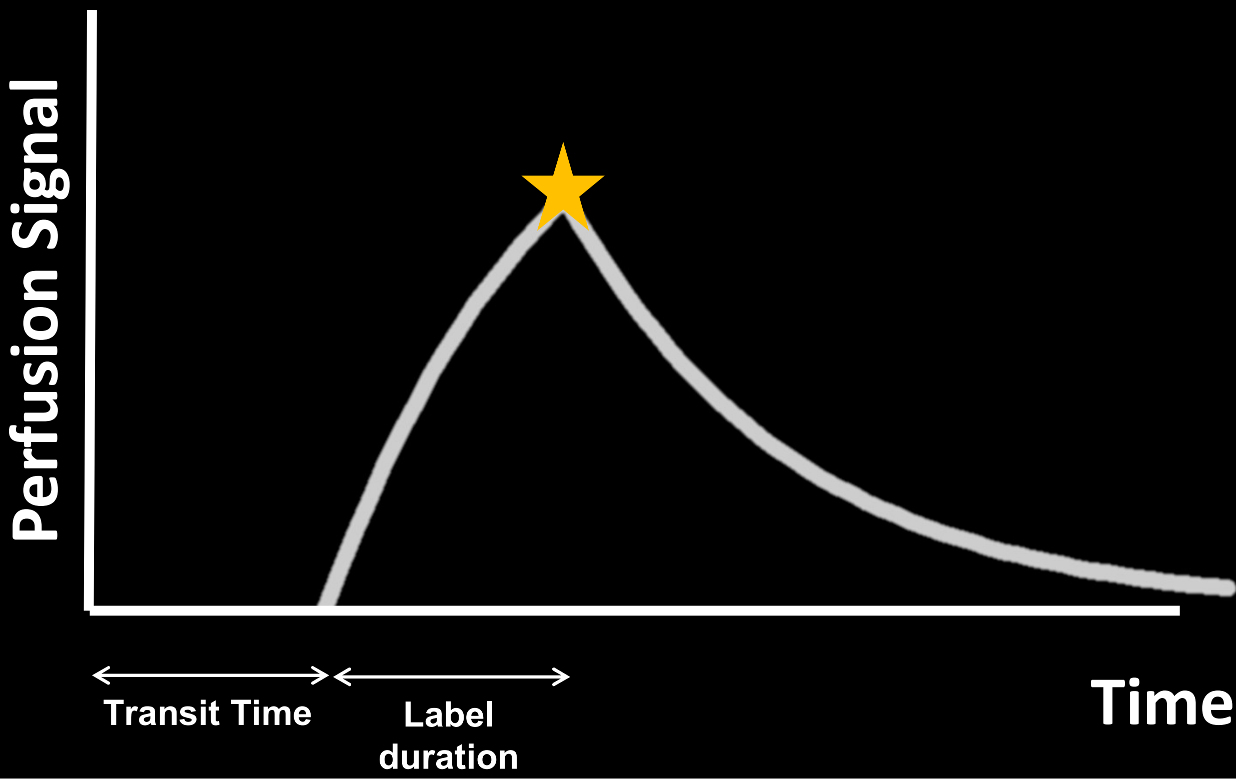




- Need PLD to account for Arterial Transit Time (ATT)

CBF estimation





- Assume we perfectly captured the peak signal
- Select PLD for match study/patient population

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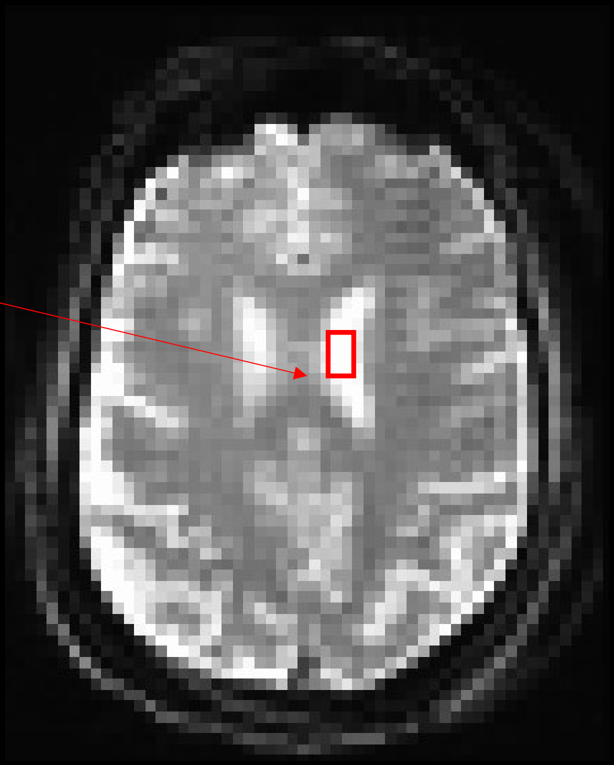
ASL

- Extract M_0 from CSF



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CBF estimation

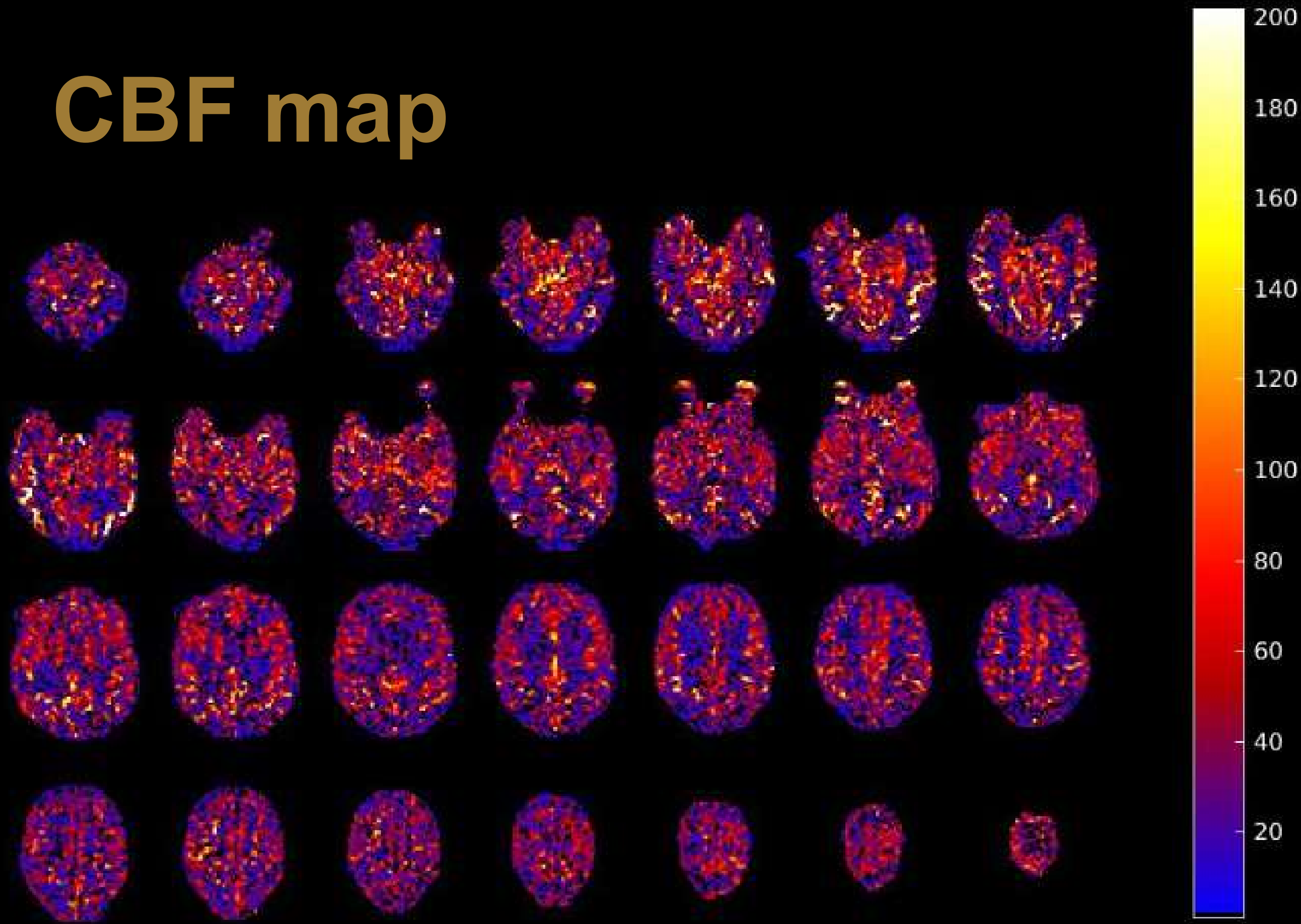
“Buxton Model”
Buxton et al. MRM 40:383-396 (1998)

- PCASL:

$$CBF = \frac{6000 * \lambda * (\Delta M) * e^{PLD/T1\,blood}}{2 * \alpha * T1\,blood\ * M0\,blood\ * (1 - e^{-\tau/T\quad blood})}$$

ΔM = PWI, λ = brain/blood partition coefficient (mL/g), α = labeling efficiency, τ = labeling duration, 6000 allows for conventional units

CBF map



ml blood/100g tissue/min

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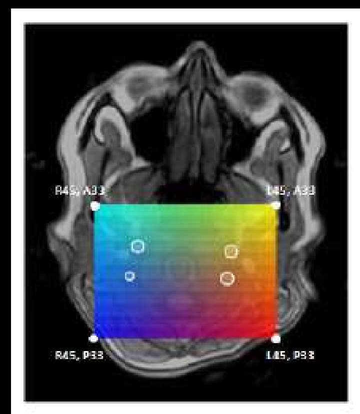
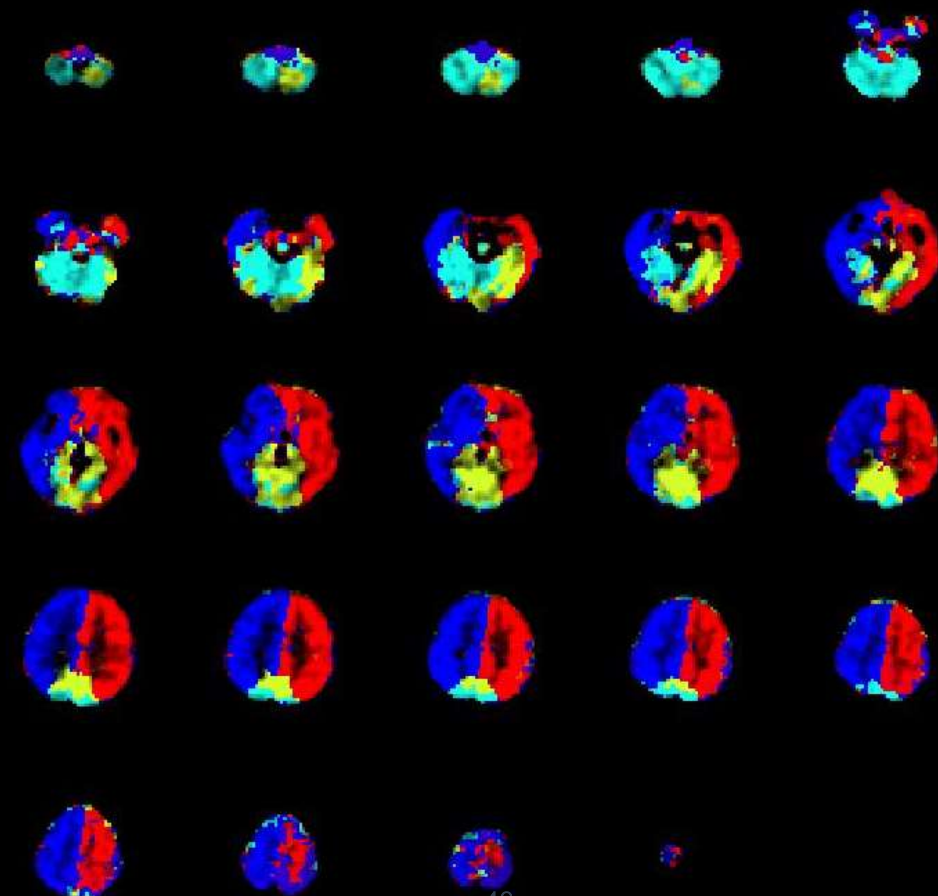
Vascular Territory Mapping

- Similar to gradients used for spatial encoding, apply gradients at labeling plane
- Can decode the source of PWI





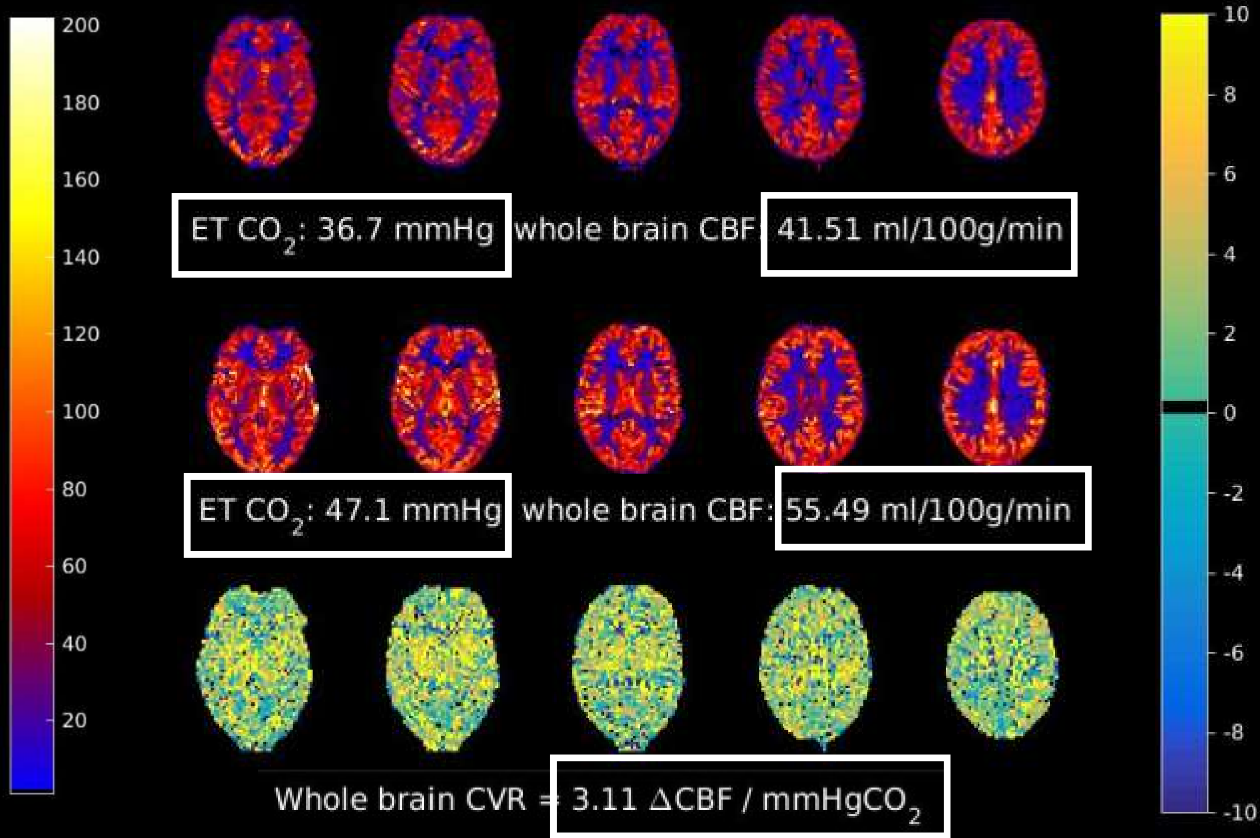
Jung, ISMRM 20 (2012) 581

Cerebral Vascular Reactivity

RespirACT

Control end-tidal CO_2 and O_2

Cerebral Vascular Reactivity



Baseline CBF

Hypercapnia CBF

CVR

Image analysis

- Mask GM and examine whole brain GM CBF only

- Align to template (MNI space)
- Apply AAL atlas for ROI based analysis
- Voxel-wise analysis

- Change in CBF over time / due to intervention

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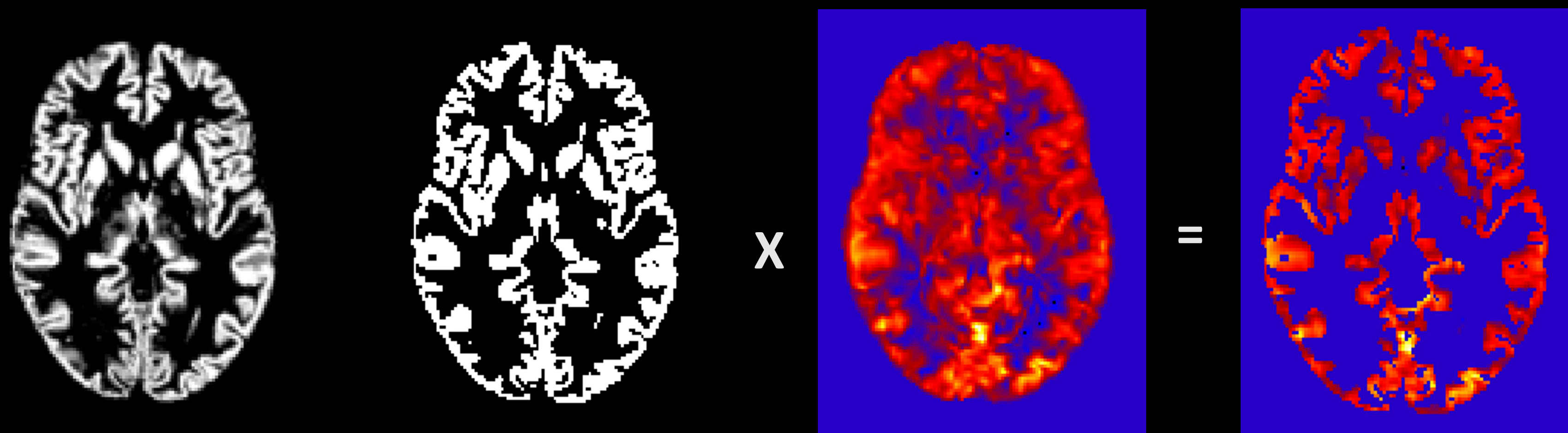
Image analysis

- Mask GM and examine whole brain GM CBF only



GM segmentation | Threshold to 0.5 | CBF map | Multiplied by GM mask

Image analysis

- Align to template (MNI space)
- Apply AAL atlas for ROI based analysis
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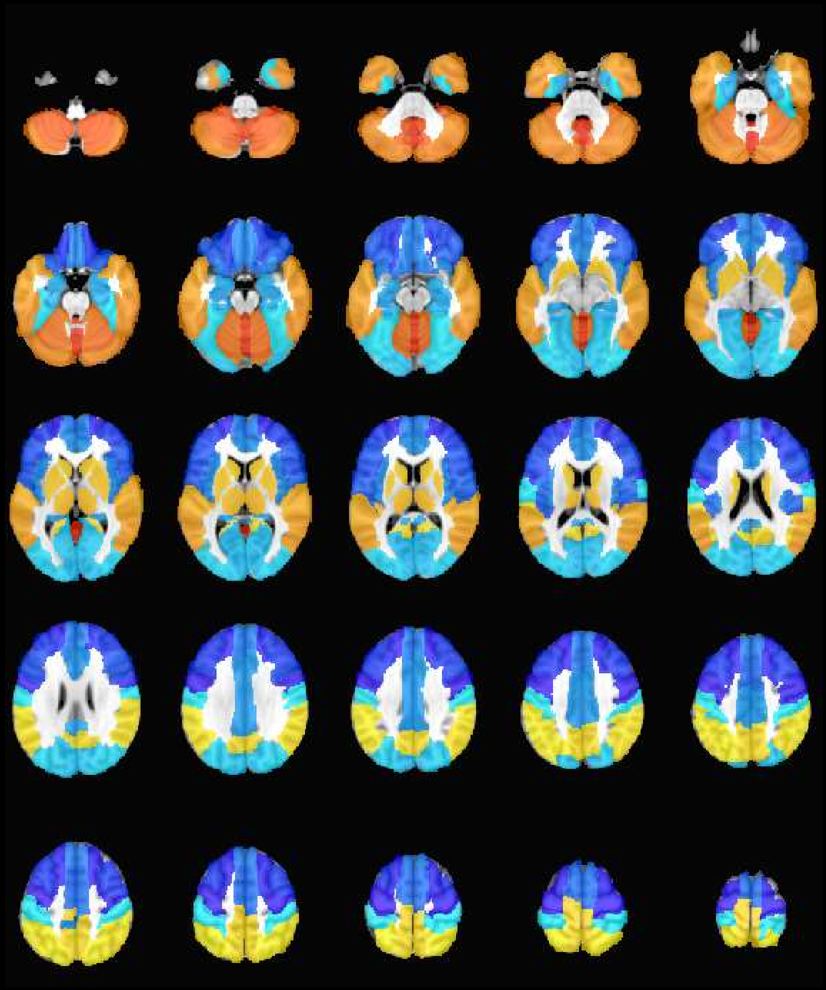

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Applications

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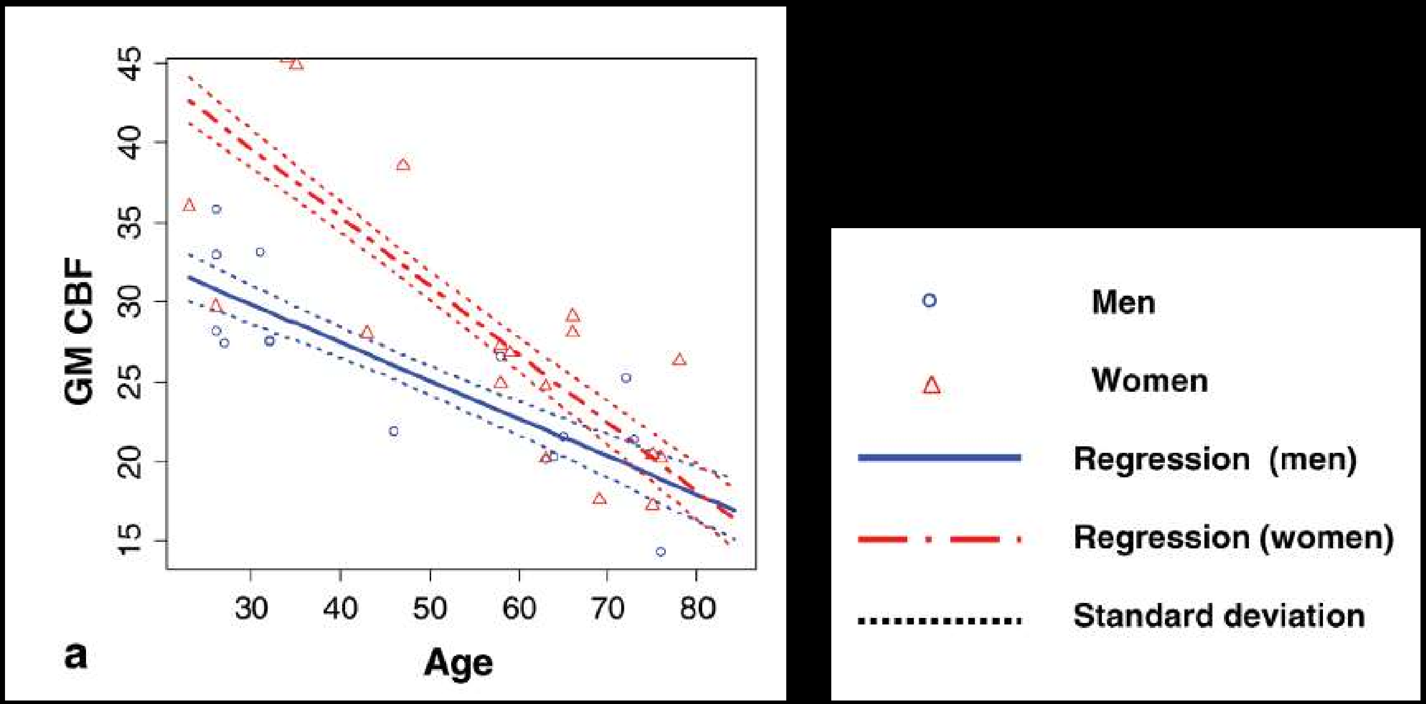
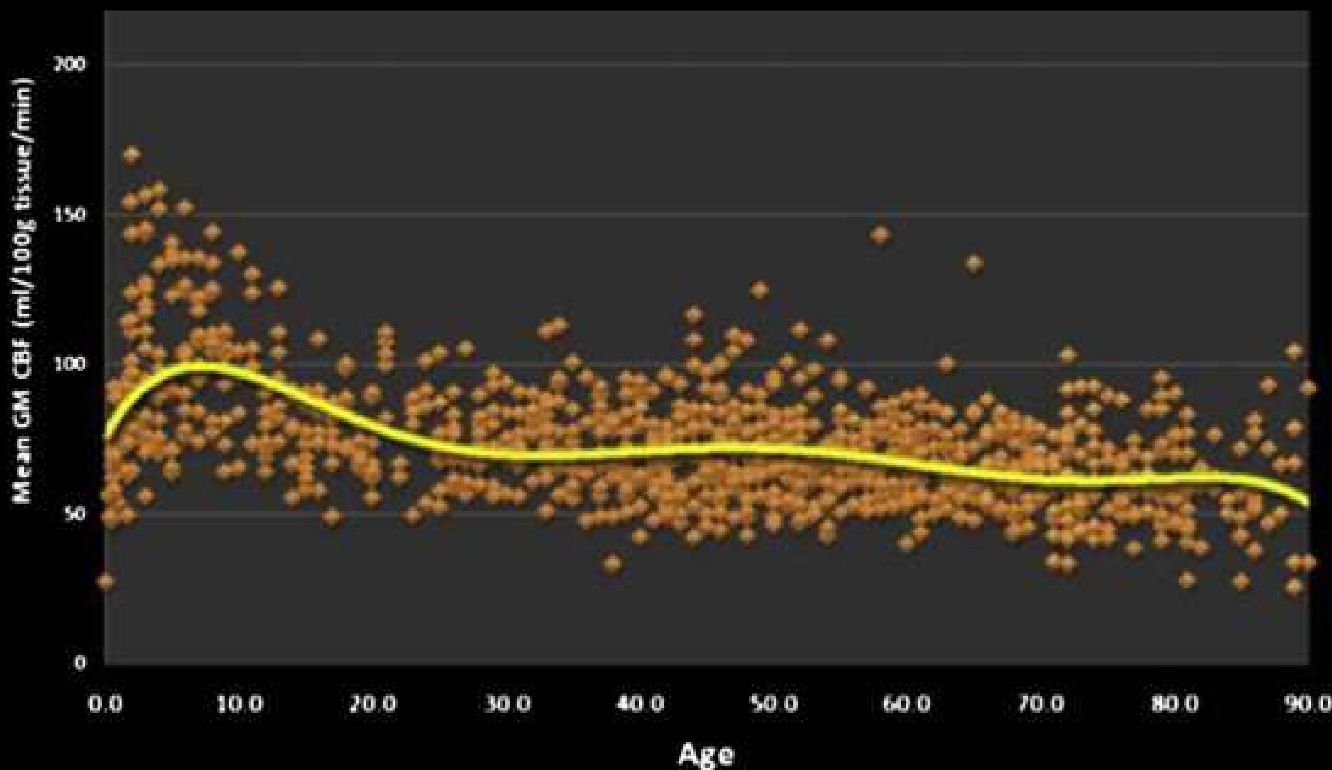
CBF differences with gender and age



Liu et al. MRM 68: 912-922 (2012)

CBF over the life span



- Peak around age 8
- Wide variety for 'normal/healthy'

Pollock et al. Magn Reson Imaging Clin N Am 17 pp 315-338 2009

Brain

- Aging and Dementia
- Traumatic Brain Injury
- Vascular damage / disease
- Tumors
- Stroke

- General indicator of brain metabolism and health

Other body regions

- Kidney
- Eye
- Placenta

- Organs with large feeding artery for labeling

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Thank you

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Imaging Bootcamp: An Intro to Quantitative Imaging

Jared Weis, PhD

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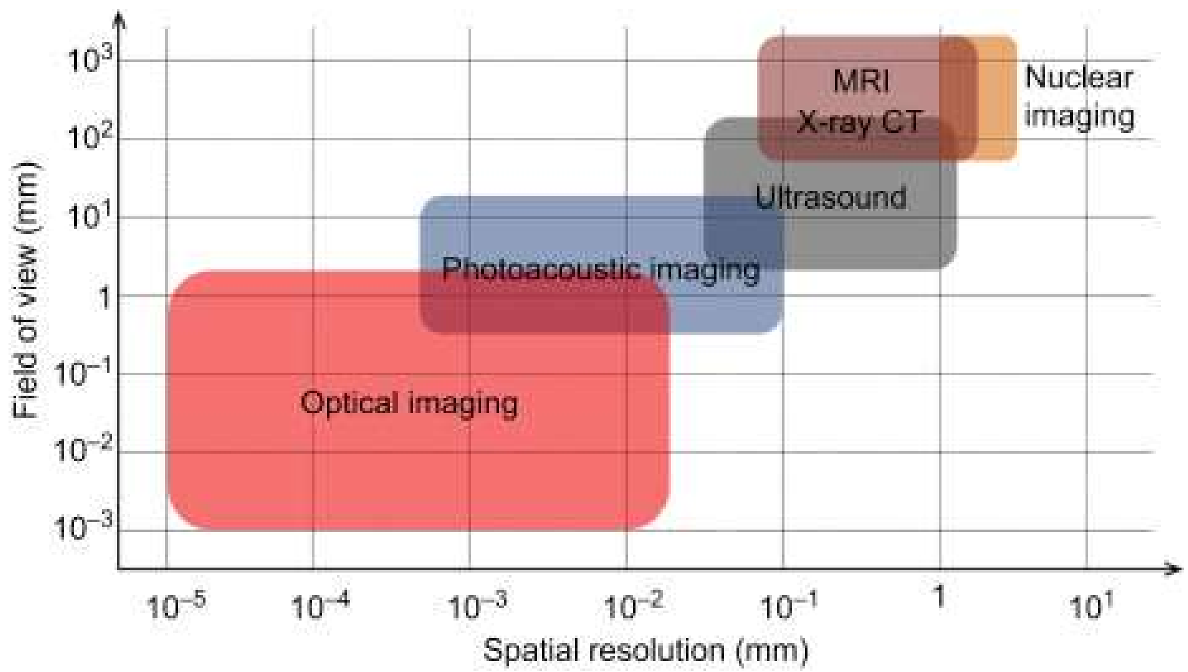
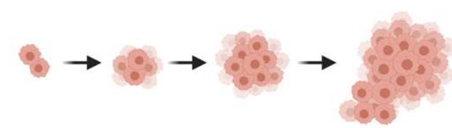
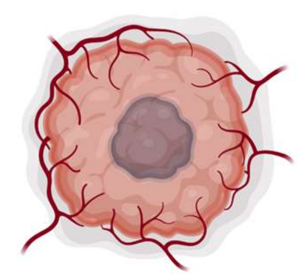
Imaging Length Scales



Targeting imaging to disease: cancer

- Imaging techniques combine a contrast mechanism (exogeneous or endogenous) and an instrument to measure that contrast
- Cancer imaging involves the development, implementation, and application of techniques which exploit cancer-specific contrast mechanisms to assess tumor characteristics
- Cancer has a number of traits to target for imaging:
  - Cancer is characterized by unchecked cell proliferation, and this can be quantified by metrics that assess cell density and cell metabolism
  - Tumors cannot grow beyond a few mm^3 without developing a vascular network – imaging techniques sensitive to vascular structure





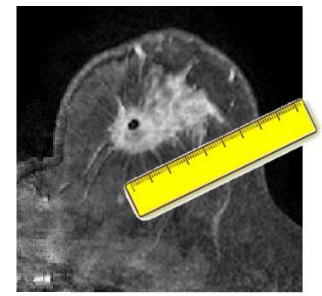
Use of imaging in cancer

- **Screening:** Detect suspicious areas or abnormalities that might be cancerous.
- **Diagnosis/staging:** Find out where a cancer is located in the body, if it has spread, and how much is present. Can help determine what stage the cancer is, and if the cancer is in, around, or near important organs and blood vessels. Imaging may be used to help guide biopsy and/or surgery.
- **Guiding treatment:** To make cancer treatments less invasive by narrowly focusing treatments on the tumors.
- **Determining if a treatment is working:** To see if a tumor is shrinking or if the tumor has changed and is using less of the body's resources than before treatment.
- **Monitoring for recurrence:** To see if a previously treated cancer has returned or if the cancer is spreading to other locations.

Quantifying Cancer Imaging

- Response Evaluation Criteria In Solid Tumors (RECIST)
  - Measurement of lesion longest diameter

- Many investigators, cooperative groups, industry, and government authorities have adopted these criteria in the assessment of treatment outcomes
- Idea: simple, reproducible method to assess the response of tumors to treatment
  - Change in tumor burden is an important feature of the clinical evaluation of cancer therapeutics
  - Tumor shrinkage and disease progression are useful endpoints in clinical trials
- Phase II clinical trials show that, for many solid tumors, agents which shrink tumors in a high proportion of patients have a reasonable chance of subsequently demonstrating an improvement in overall survival



Response Assessment	Criteria
Complete response	Disappearance of lesion
Partial response	Decrease ≥ 30%
Progressive disease	Increase ≥ 20%
Stable disease	Otherwise

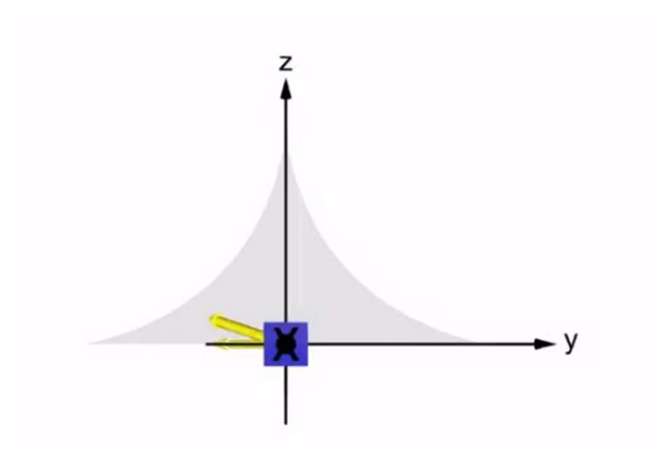
Key concepts

- Cancer imaging—need a contrast mechanism to separate healthy tissues from diseased; what can we measure that is substantially different within a tumor than within healthy tissue?

- RECIST—simple way to assess treatment response (change in longest dimensions); limiting—why?
  - Changes in morphology may not happen for many cycles of therapy; we want to know early that a therapy is not working
  - There are underlying pathophysiological changes precede changes in tumor size
  - Current and next generation of anti-cancer drugs are targeted—specific, changes in tumor volume are downstream from where the drug may be acting.
    - Drug may be working, but won't know by looking at changes in longest dimension (at least you may not know for awhile)

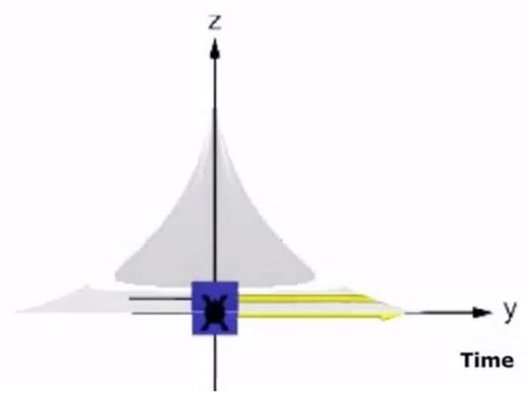
A very brief intro to MRI

- Based on magnetization properties of atomic nuclei
- MRI scanners employ a powerful, uniform, external magnetic field to align protons (normally randomly oriented) within the water nuclei of tissue
- Alignment (magnetization) is perturbed by introducing an external RF pulse. Nuclei return to their resting alignment through various relaxation processes



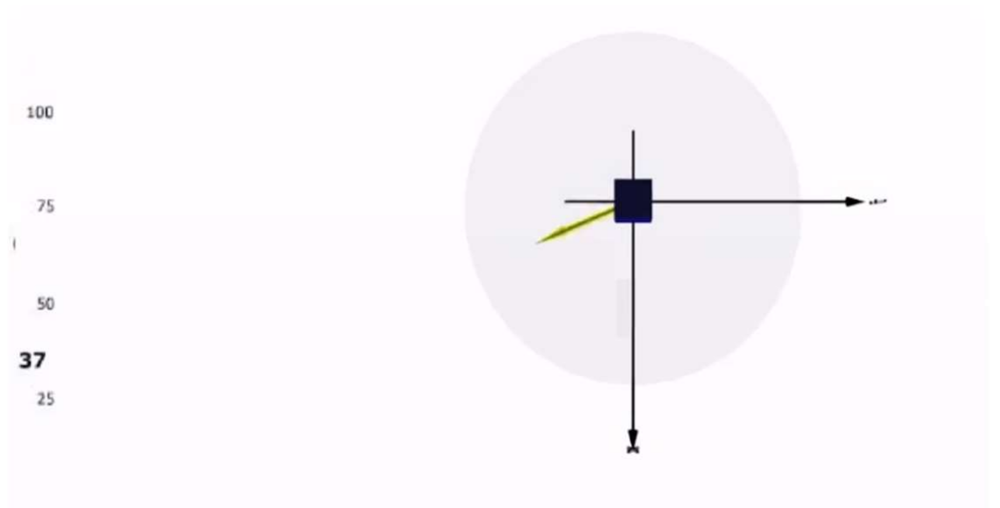
A very brief intro to MRI

- T1 weighted image
  - Sensitive to differences in the T1 relaxation times of tissue
  - Depends on longitudinal relaxation of tissue’s net magnetization vector
    - Spins aligned in a magnetic field are put into the transverse plane by a RF pulse. Tissue T1 relaxation time reflects the amount of time for protons’ spins to realign with the magnetic field
    - Fat – quick longitudinal realignment
      - bright in T1 weighted image
    - Water – slow longitudinal realignment
      - dark in T1 weighted image
    - T1-weighted sequences provide great contrast for paramagnetic contrast agents
      - Shortens relaxation times

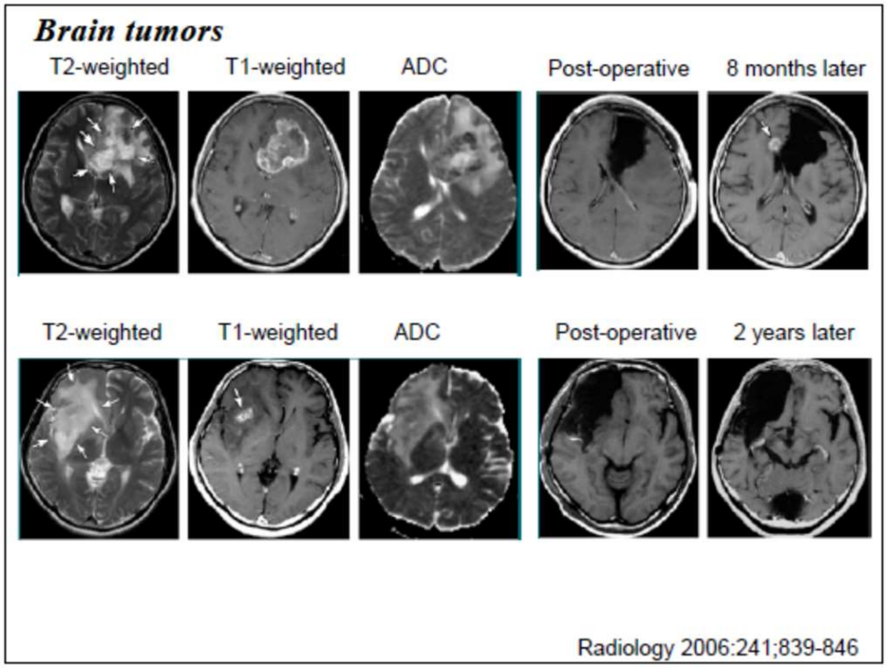


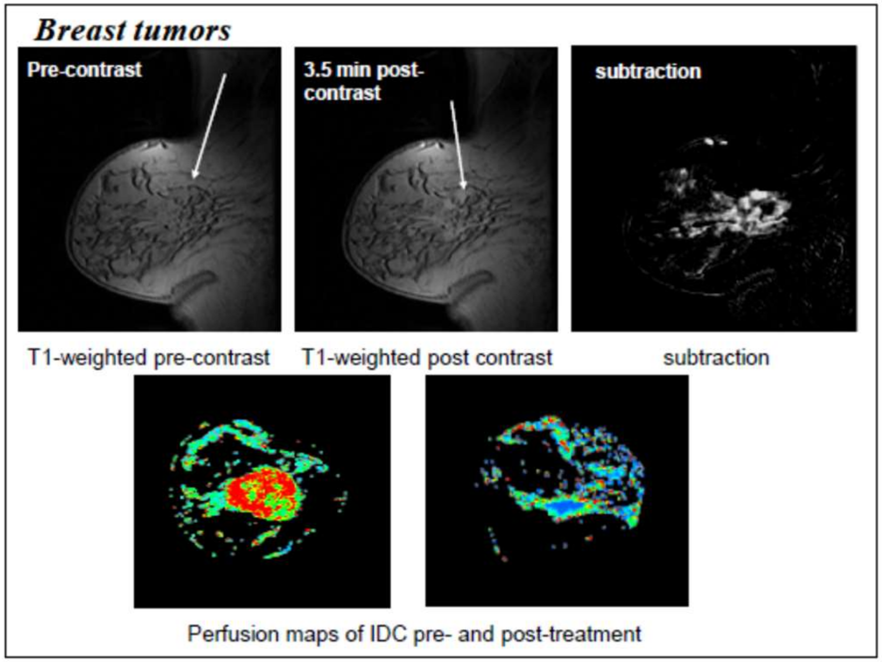
A very brief intro to MRI

- T2 weighted image
  - Sensitive to differences in the T2 relaxation times of tissue
  - Depends on transverse relaxation of tissue’s net magnetization vector
    - Thinking back to T1 discussion…
      after RF pulse, relaxation of spins from the transverse plane toward the main longitudinal magnetic vector (T1). But at the same time, spins are decaying from the aligned precession in the transverse plane.
    - T2 captures differences in this decay.



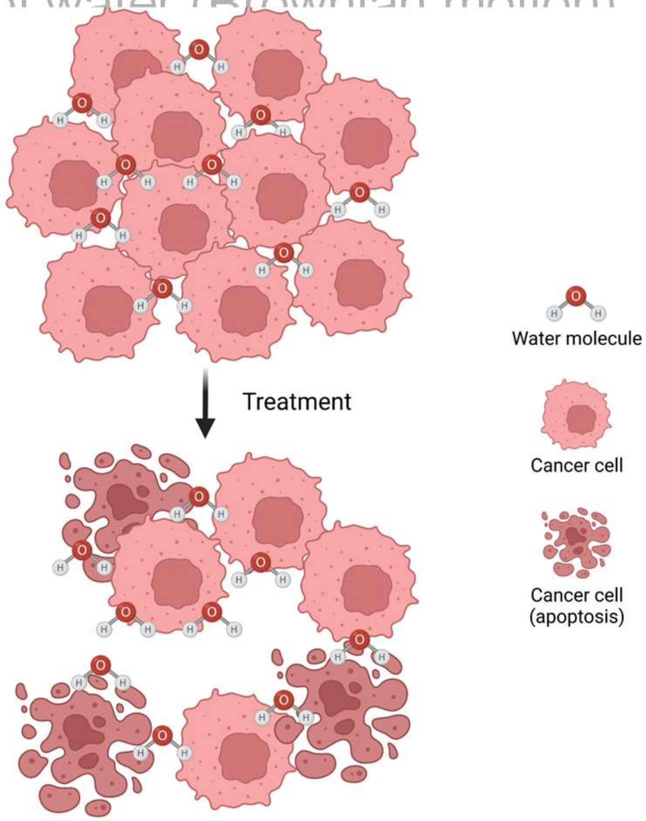
Clinical cancer MRI





Diffusion-weighted MRI

- Based on self-diffusion of water (Brownian motion)
  - Apparent diffusion coeffi
- DW-MRI reflects effecti ecules within a time interval
- Diffusion in cellular tissı liffusion
  - Scales inversely and lin



↑ ADC
↓ Cellularity

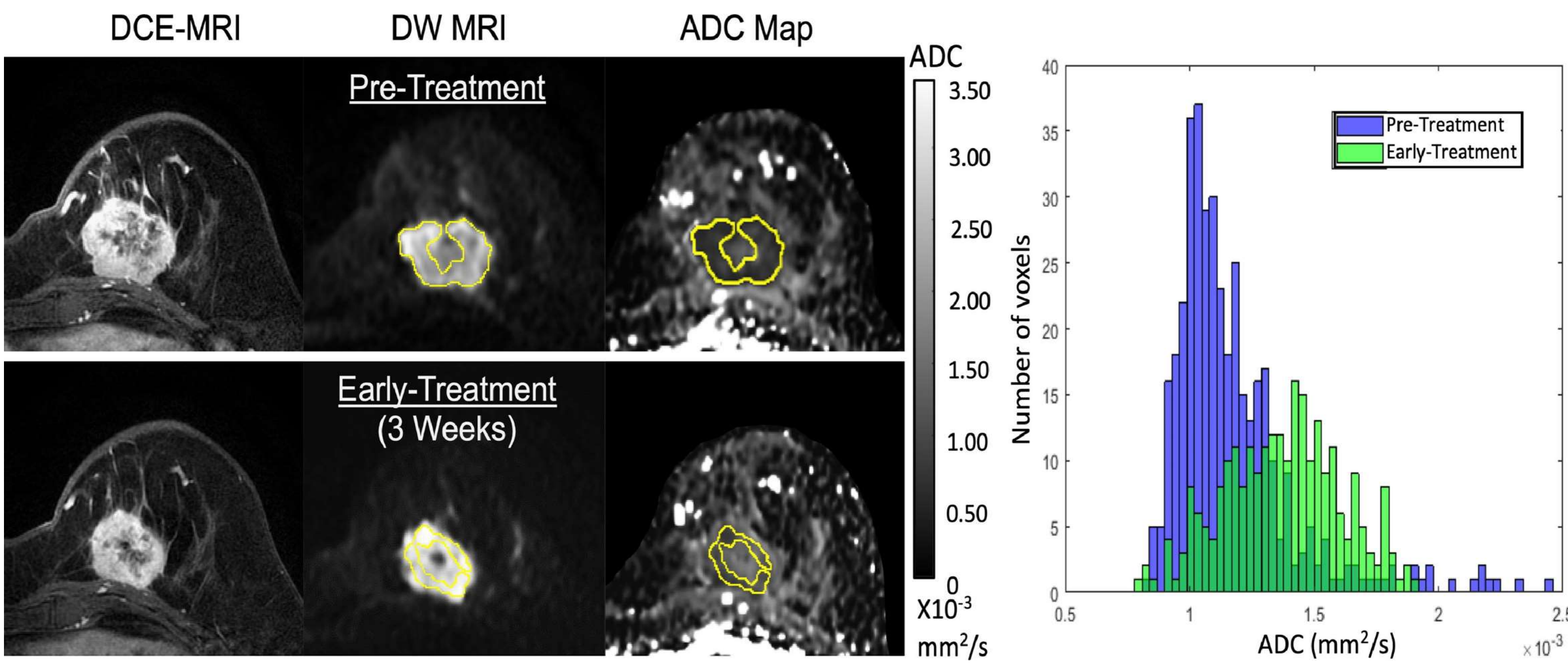
↓ ADC
Cellularity

$ADC = \frac{\sum_{i=x,y,z} 1}{}$

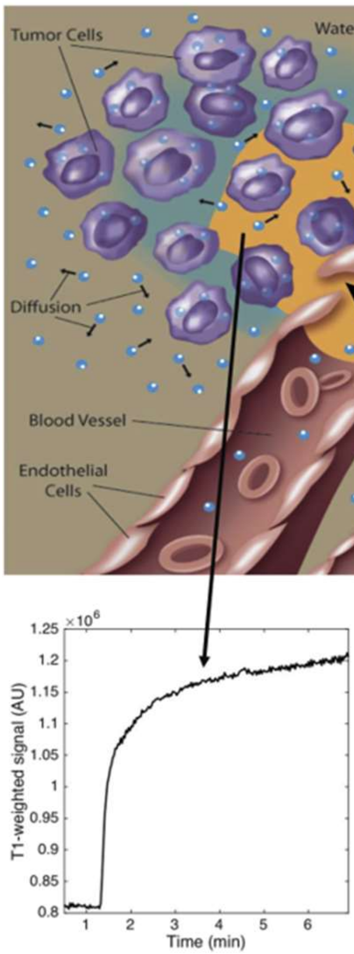
$- ADC(\bar{x},t)$
$- ADC_{\min}$

Atuegwu NC, et al., Phys Med Biol, 2012. Anderson AW, et al., *Magn Reson Imaging*, 2000

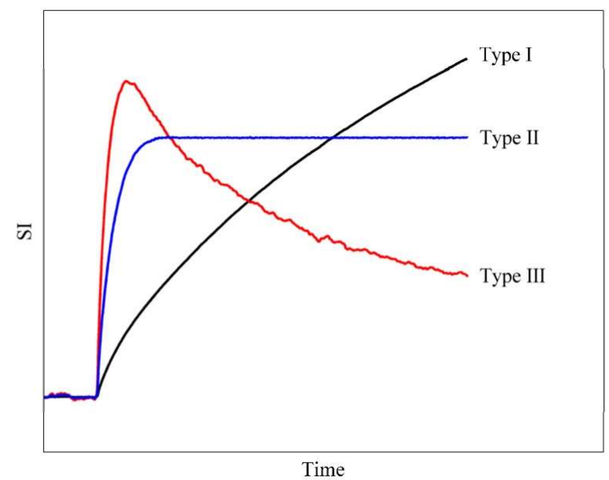
Diffusion-weighted MRI



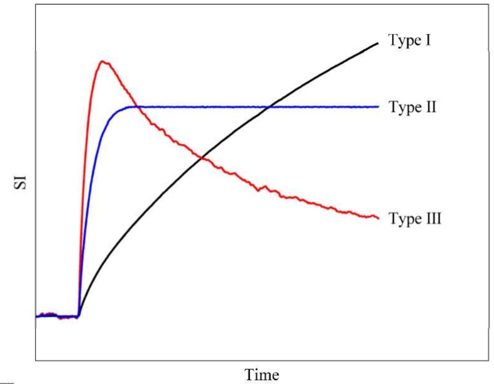
Dynamic contrast enhanced MRI (DCE-MRI)



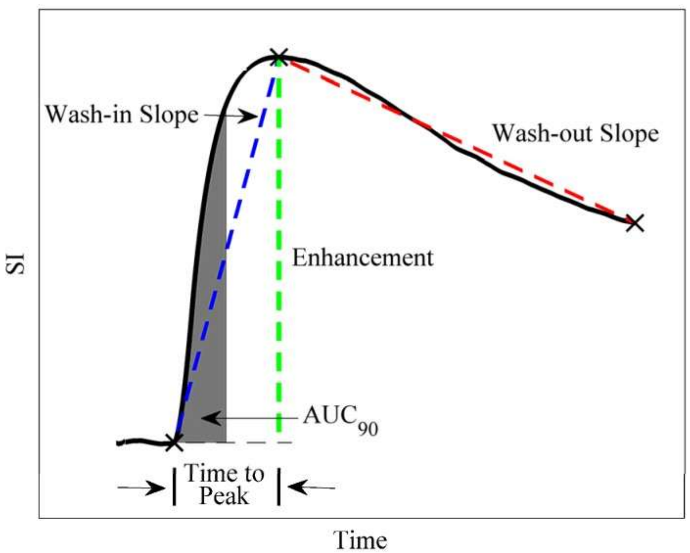
- Dynamically acquire sequential images before, during, and after the administration of a bolus of contrast agent.
- Examine voxel-wise signal intensity time course over the course of the dynamic scan to observe wash-in/wash-out kinetics



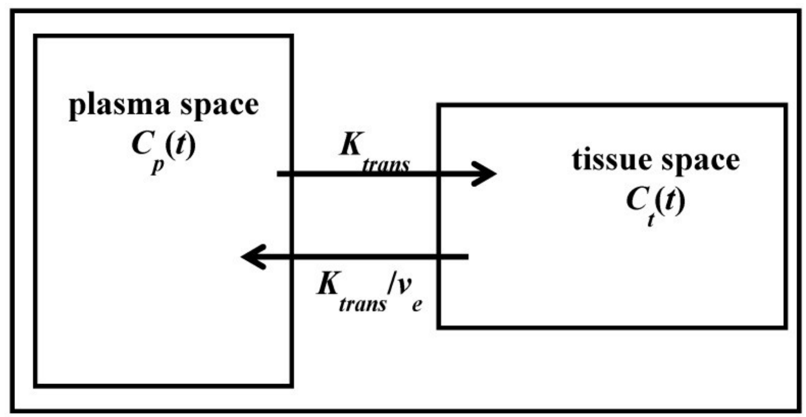
Analyzing the DCE signal intensity time course



Semi-quantitative

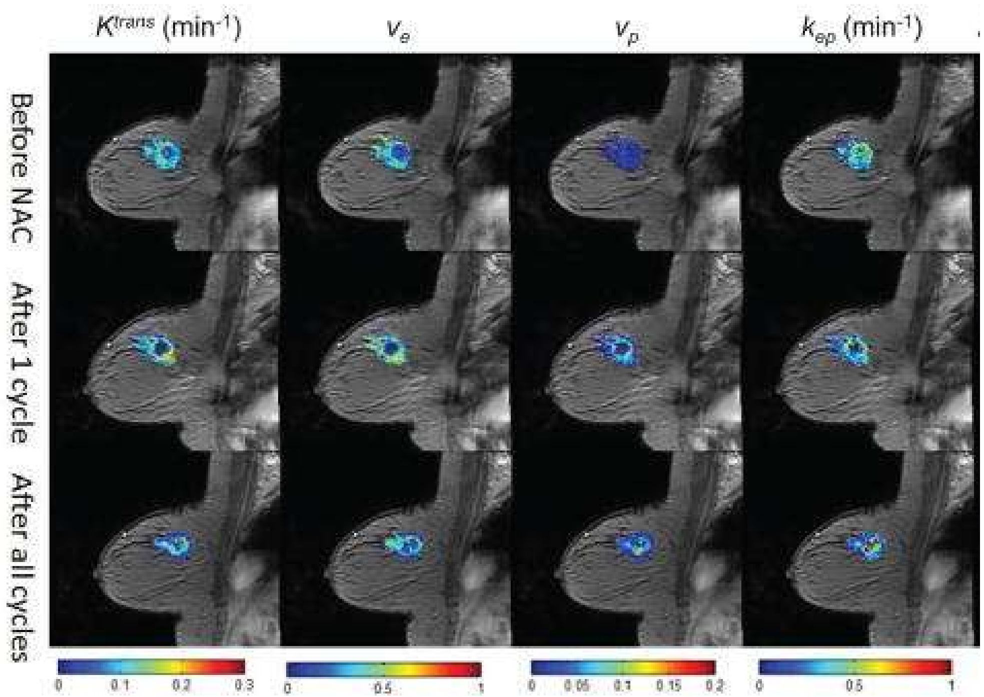


Compartmental model



$$\frac{dC_t(t)}{dt} = K^{trans} \cdot C_p(t) - \frac{K^{trans}}{v_e} C_t(t),$$

Dynamic contrast enhanced MRI (DCE-MRI)

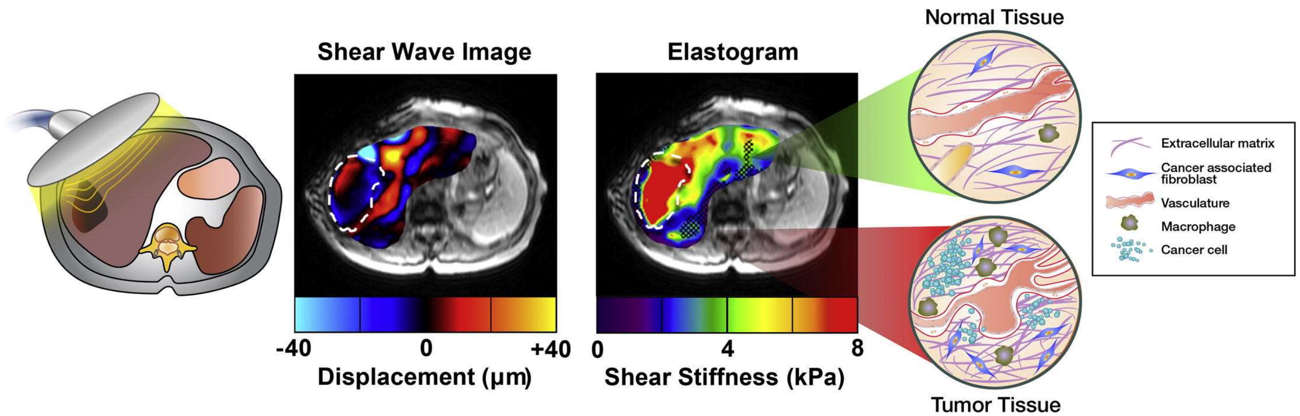


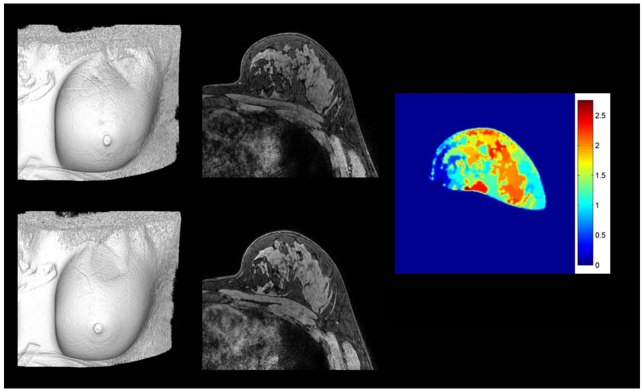
- K^{trans} – Volume transfer coefficient between blood plasma and extravascular extracellular space (EES)
- v_e – Volume of EES per unit volume of tissue
- k_{ep} – Rate constant between EES and blood plasma (backflux exchange rate)

- $k_{ep}=K^{trans}/v_e$

Elasticity Imaging

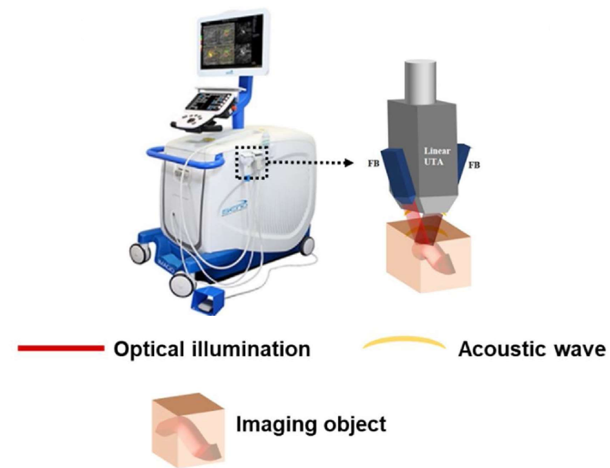
- Cancer progression is associated with significant desmoplasia that results in ECM remodeling, leading to enhanced collagen, fibronectin, and proteoglycan deposition, along with enhanced protease cleavage and matrix crosslinking.
- These ECM remodeling events result in a dramatic increase in tumor stromal stiffness and interstitial fluid pressure.
- Elasticity imaging (elastography) measures tissue mechanical stiffness by imaging the propagation of mechanical shear waves (MRE) or pre/post deformation (quasi-static) and using biomechanical models to estimate mechanical stiffness



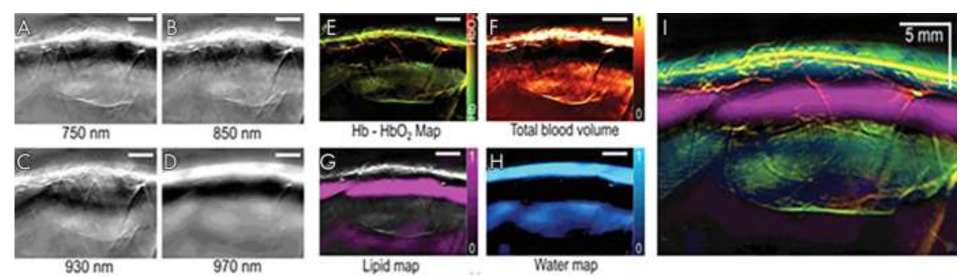


Photoacoustic/Optoacoustic Imaging

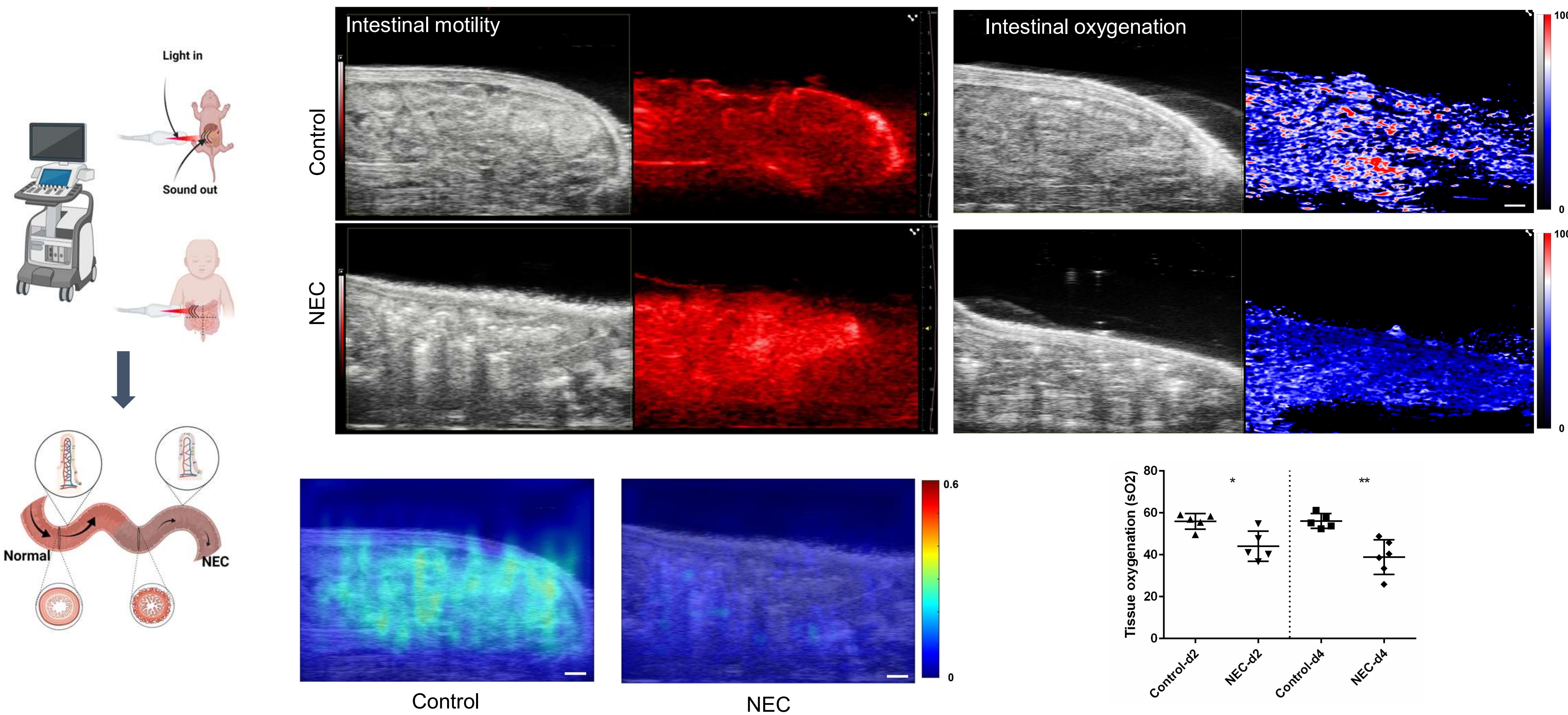
- Light in / sound out
  - Photoacoustic effect – generation of mechanical pressure waves from light absorption and subsequent thermoelastic expansion
  - Ultrasound transducer to detect pressure wave



- Near-infrared (NIR) light – mitigate photon scatter in tissue to allow for increased-depth penetration
- Endogenous contrast – Oxy/de-oxy hemoglobin, melanin, lipid, water, collagen, etc.
- Exogenous contrast – NIR dyes tagged to probes (molecular, pH, etc.)
  - Can multiplex using spectral unmixing techniques with spectrally-distant probes



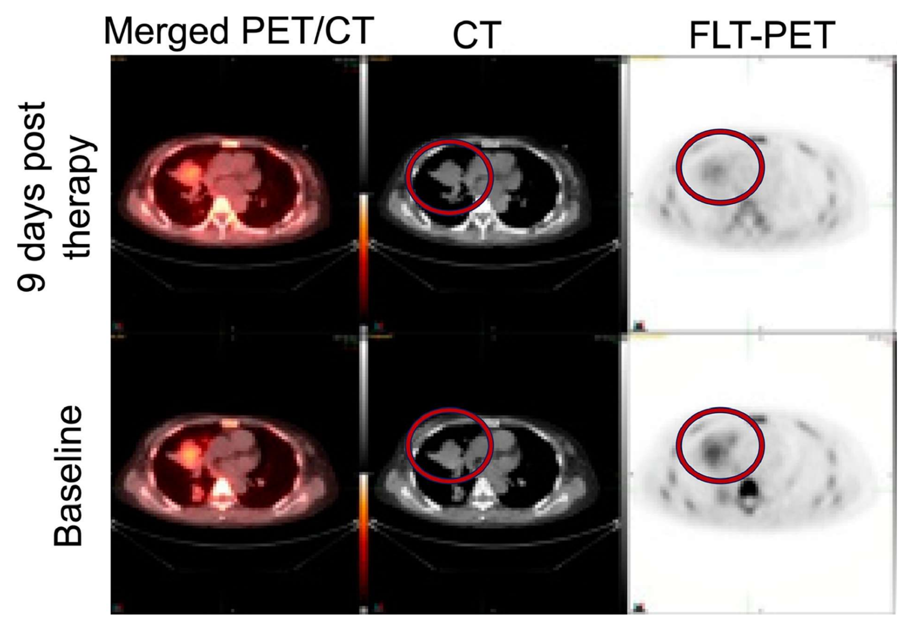
Photoacoustic imaging to measure biophysical physiological biomarkers of intestinal disease (necrotizing enterocolitis) in premature infants

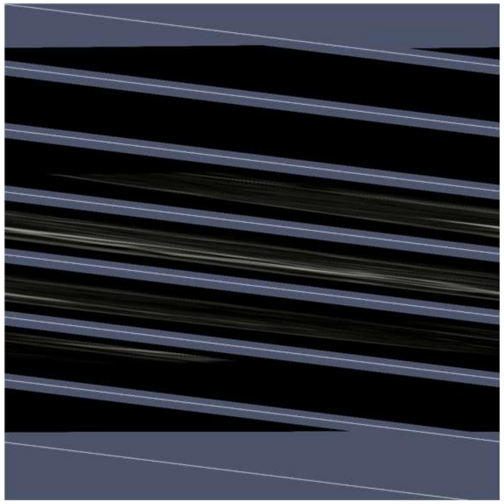


PET

- Detection of radioactivity emitted after a small amount of a radioactive tracer is injected into a peripheral vein

- FDG-PET – glucose consumption
- FLT-PET – cell proliferation
- FMISO-PET – hypoxia
- Antibody- and Peptide-based PET Imaging



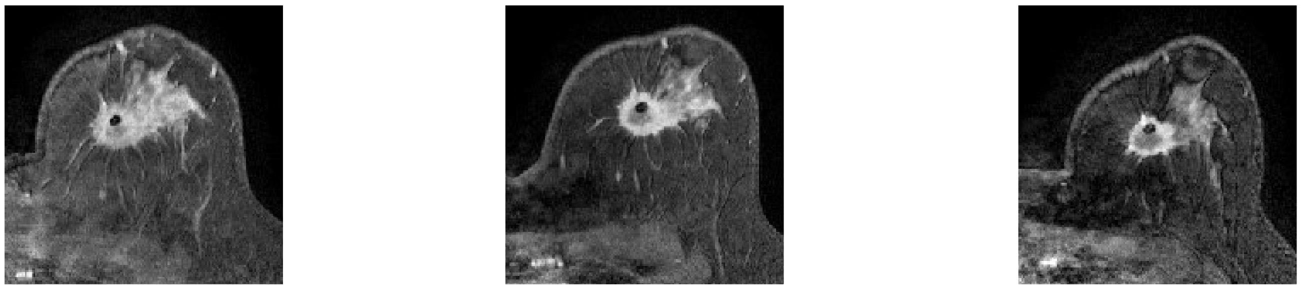


Imaging-driven biophysical profiling of breast cancer therapy response

Predicting drug response in the neoadjuvant setting

- Breast Cancer Neoadjuvant Therapy (NAT)
  - Reduce tumor burden, downstage prior to surgery
  - Response is prognostic for recurrence risk
- Patients are prescribed predetermined anti-neoplastic therapy based on major breast disease subtypes (HR+, HER2+, TNBC)
- Individualized patient response is highly heterogeneous
  - *Some patients need only a portion for complete tumor eradication*
  - *Other patients would significantly benefit from alternative therapy*
- Avoid unnecessary side effects/toxicities of ineffective or unnecessary therapy

Challenging existing paradigms in breast cancer NAT response assessment



Before starting NAT

Early cycle NAT

Conclusion of NAT (~12-16 cycles)

12-16 weeks

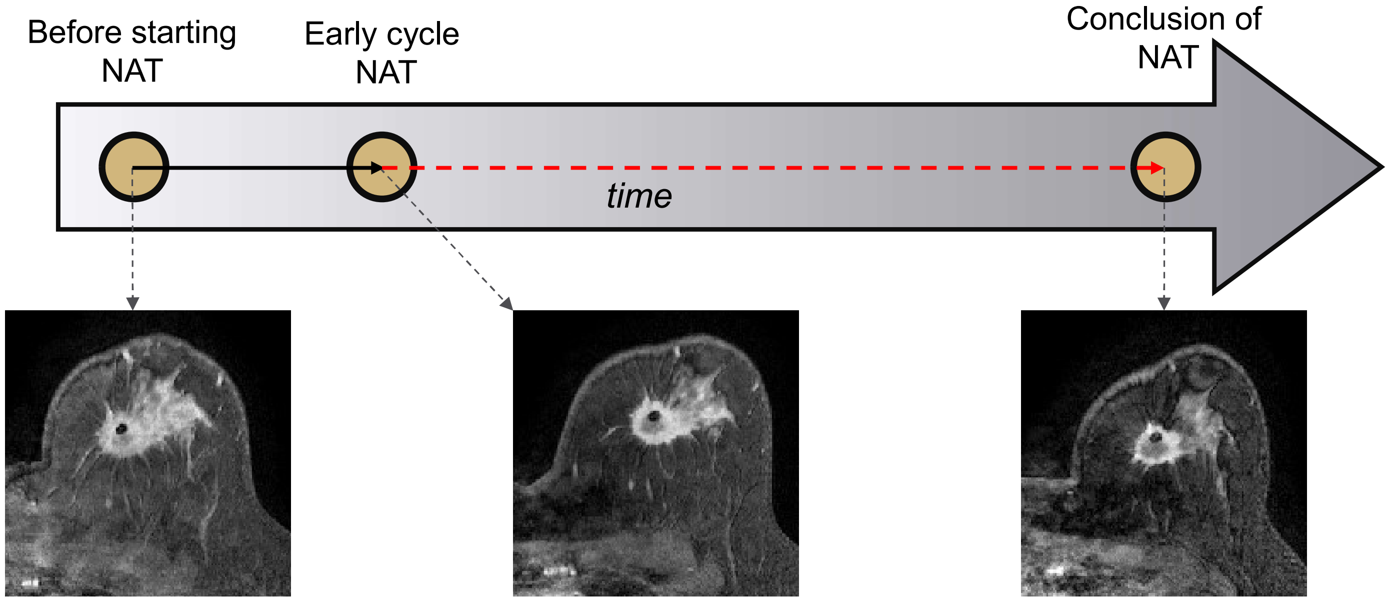
1 - 4 weeks

before

- Long clinical evaluation period
  - Observable changes are ***downstream*** of cell-level therapeutic effects
  - Limited opportunity for therapeutic intervention
- Can we predict/monitor patient response ***during*** therapy?

Neoadjuvant Response Category	Criteria
Complete response	Disappearance of lesion
Partial response	Decrease ≥ 30%
Progressive disease	Increase >20%
Stable disease	Otherwise

Biophysics and mathematics offer compelling opportunities to profile therapeutic response using imaging data

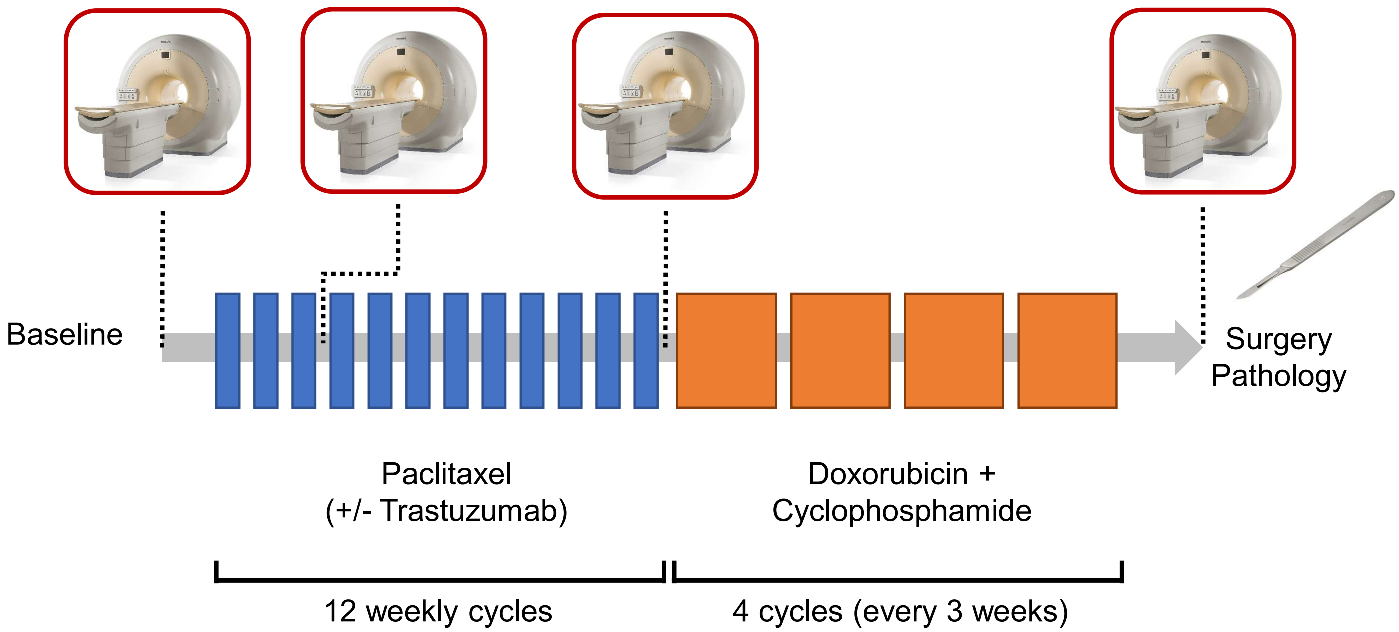


$$\frac{\partial N(\bar{x},t)}{\partial t} = \underset{\textit{Diffusion}}{\nabla\cdot\left(D\nabla N(\bar{x},t)\right)} + \underset{\textit{Proliferation}}{k(\bar{x})\,N(\bar{x},t)}\left(1-\frac{N(\bar{x},t)}{\theta}\right)$$

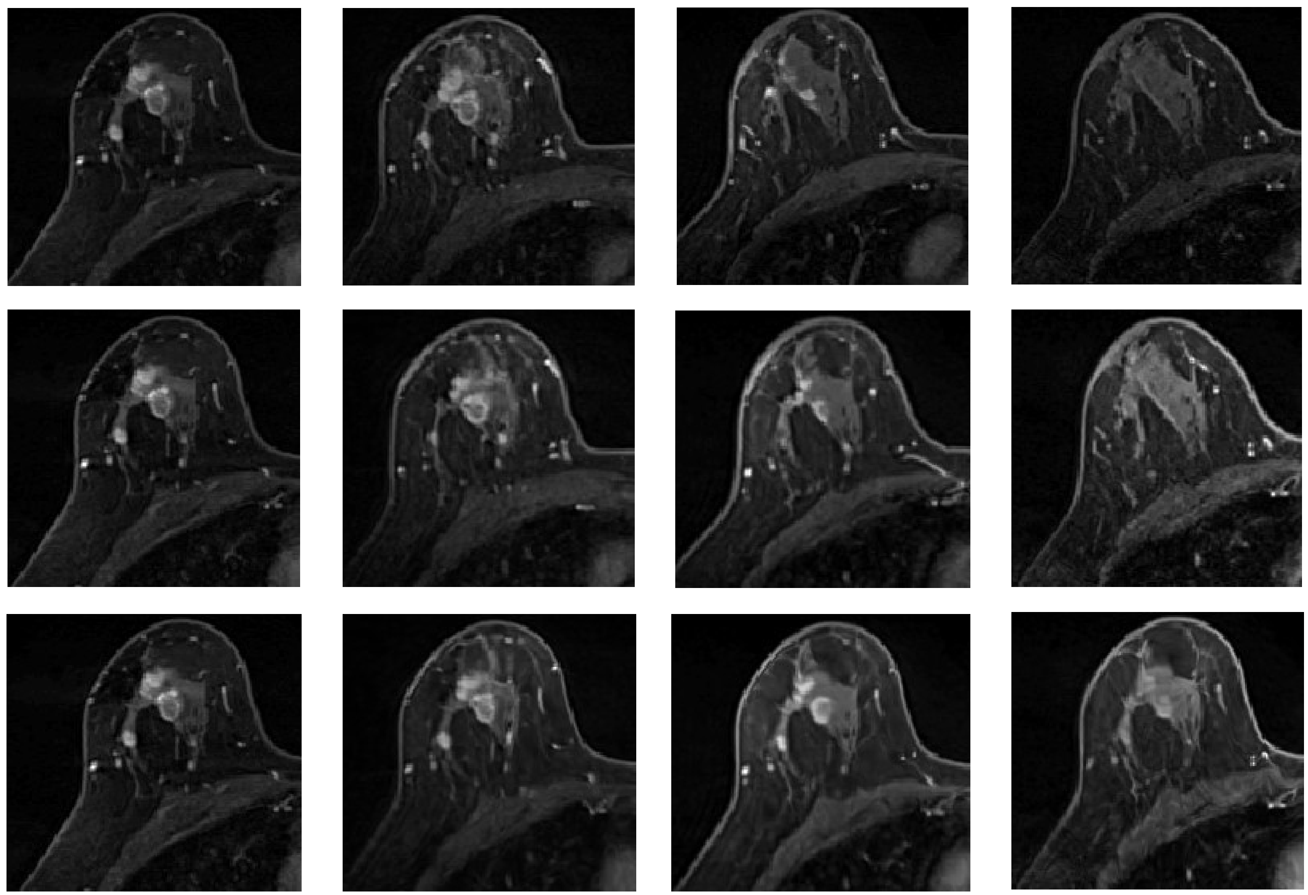
$$\underset{\textit{Mechano-inhibitive diffusion}}{D = D_0 e^{-\gamma\sigma_{vm}(\bar{x},t)}}$$

$$\underset{\substack{\textit{Mechanical equilibrium /}\\ \textit{Mass effect}}}{\nabla\cdot\sigma-\lambda\nabla N(\bar{x},t)=0}$$

Early-cycle evaluation of imaging data

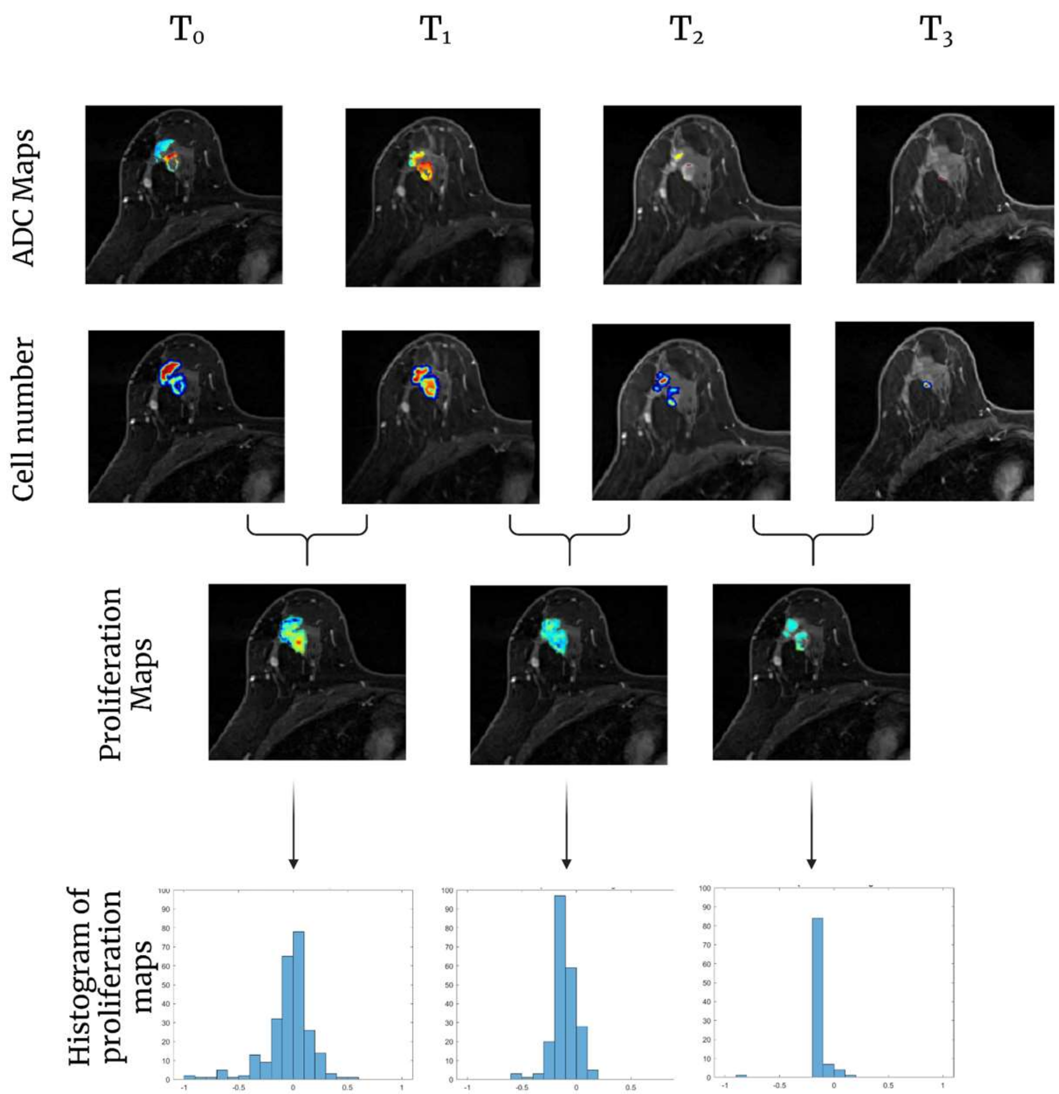


Registration



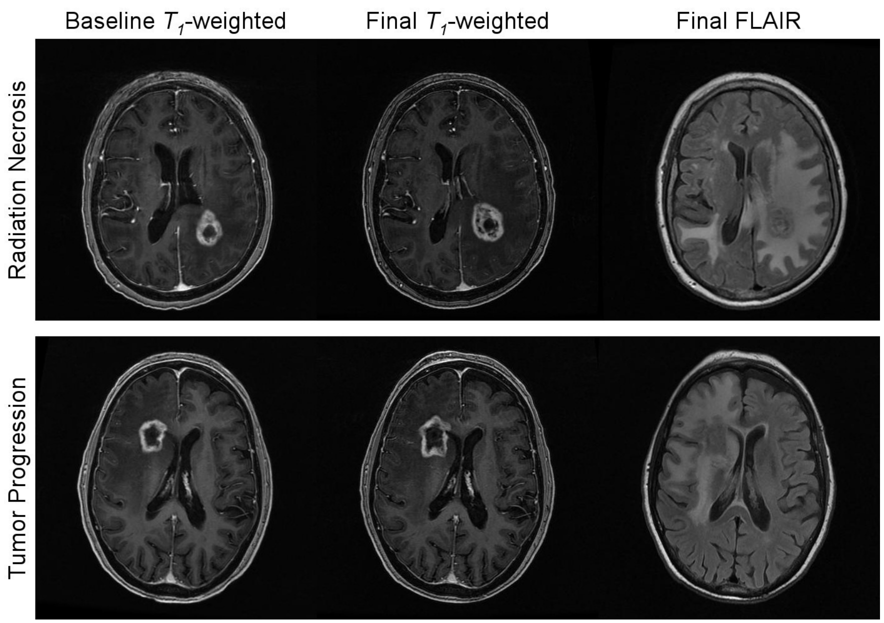
Rigid Registration

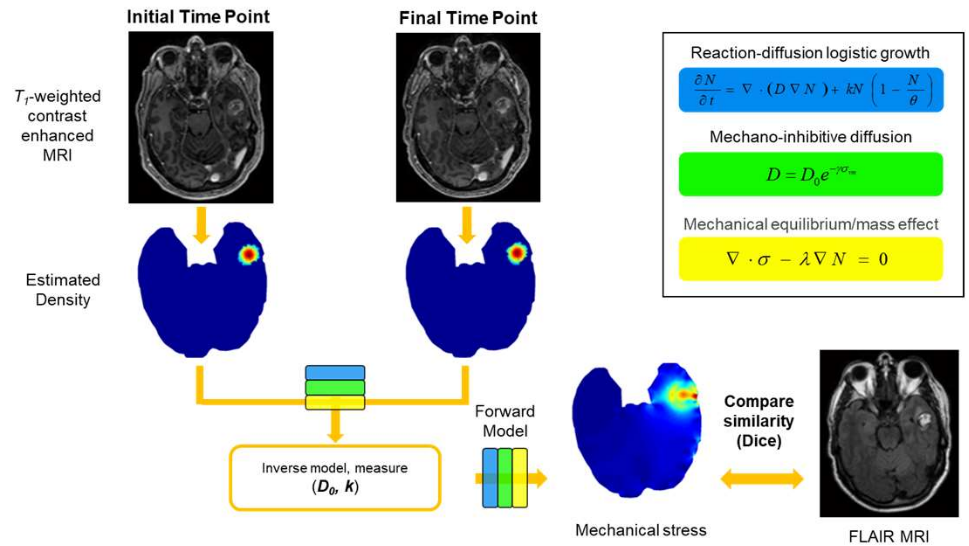
Non-Rigid Registration



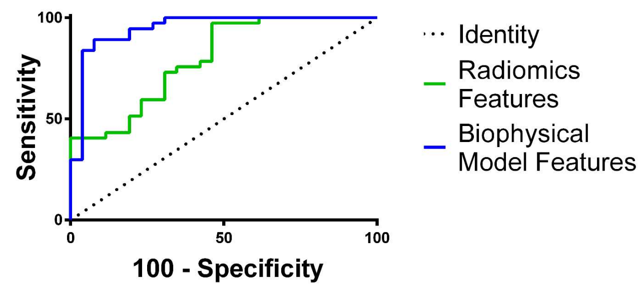
T0
T1
T2
T3
ADC Maps
Cell number
Proliferation Maps
Histogram of proliferation maps

Biophysical modeling to distinguish tumor progression and radiation necrosis following radiosurgery

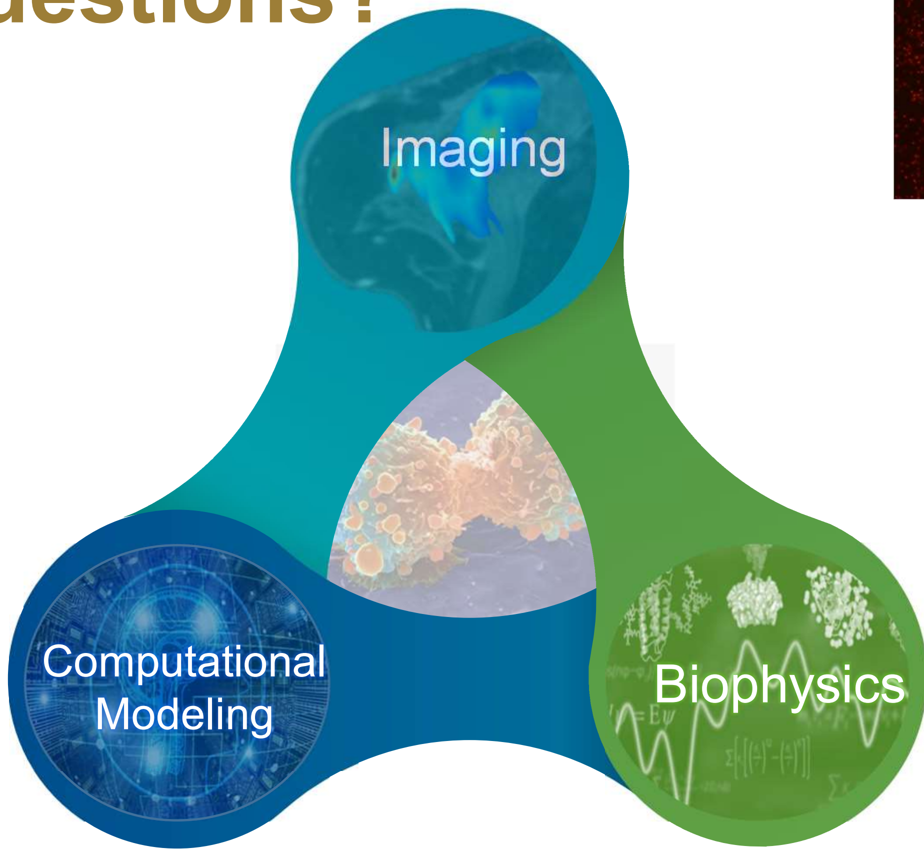


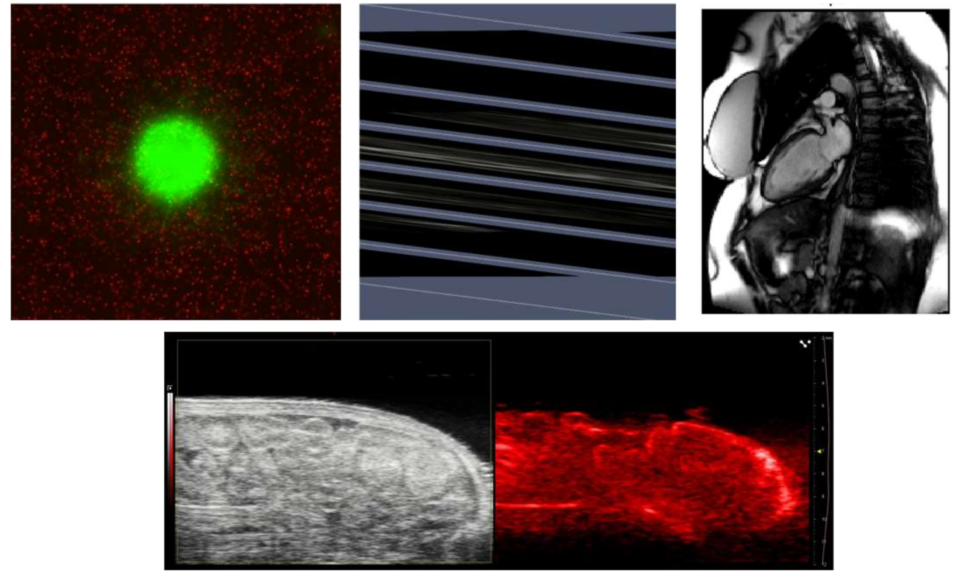


78 lesions (31 radiation necrosis / 47 tumor progression)
Routine T1-weighted and FLAIR MR imaging
Mechanistic model: ROC AUC 0.97
Radiomics features: ROC AUC 0.74



Questions?





Studying disease at the intersection of imaging science, biophysics, and computational modeling

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