Contrast agents in biomedical imaging

Quantitative and Functional Imaging

BME 4420/7450

Fall 2022

Topics

- What is a contrast agent?
- Why use contrast agents?
- What makes a good contrast agent?
- Contrast agents for
  - CT
  - Ultrasound
  - MRI
- Contrast agent measurements of tissue perfusion

Contrast agents

- A contrast agent is a material that changes the signal in a tissue of interest
  - Increases tissue contrast relative to neighboring tissues
- Delivered by
  - Injection
  - Ingestion
  - Inhalation

Why use contrast agents?

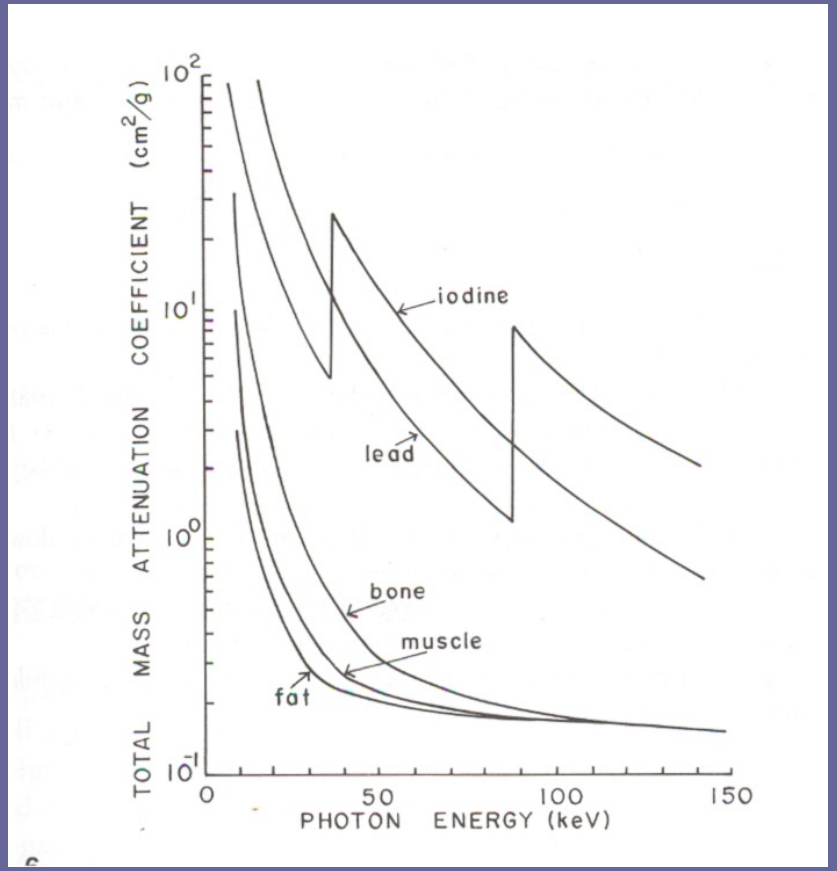
- Low contrast -> poor detectability
- Contrast agents can be used to
  - Improve conspicuity of target tissue
  - Establish exchange between compartments
  - Measure exchange rates
  - Measure flow rates

What makes a good contrast agent?

- Specificity for target tissue
- Efficacy (contrast change / gm of agent)
- Biocompatibility
- Biological half-life
- Cost

I. Contrast agents for CT

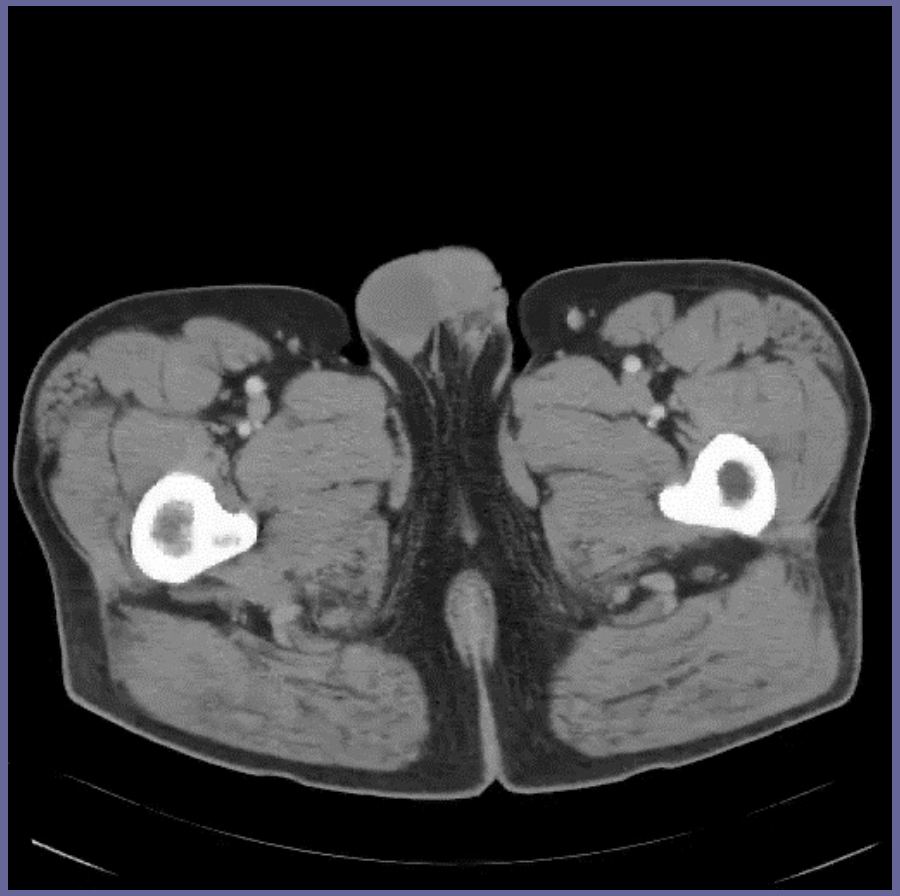
- Goal: increase x-ray attenuation of an anatomical structure
- Commonly contain either
  - Iodine (Z=53)
  - Barium (Z=56)
- Much higher attenuation than soft tissues (Z_{eff}=7.4)
- Both are relatively nontoxic
  - 3% adverse reaction rate to nonionic media



Hendee and Ritenour

Common uses

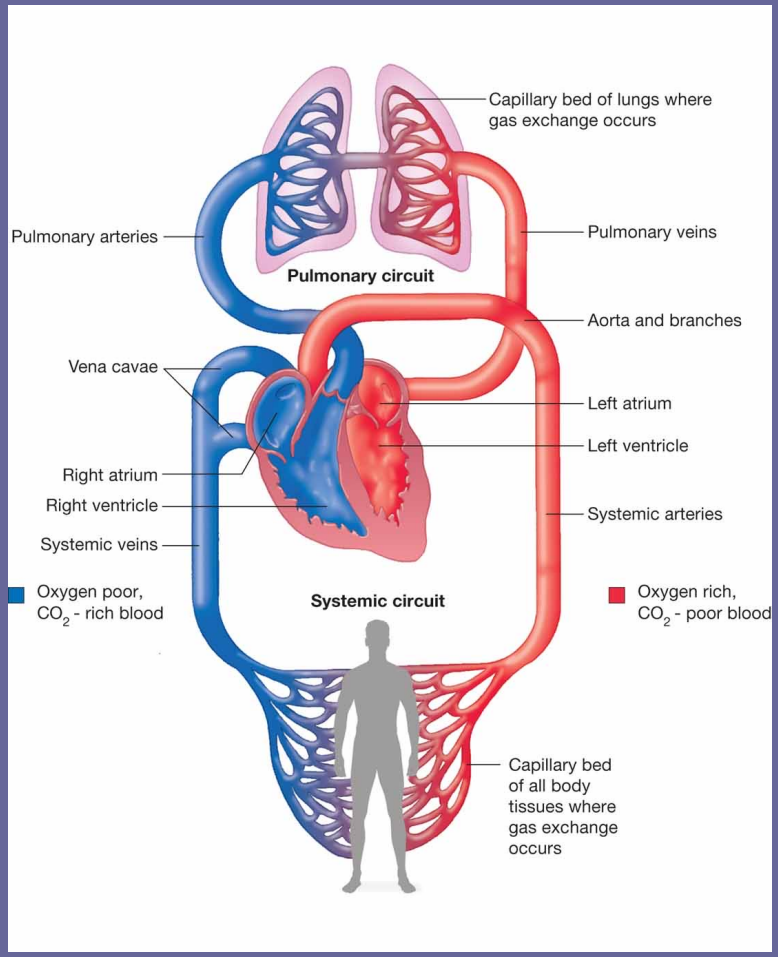
- Gastrointestinal system
  - Stomach, bowel, colon
- Angiography
- Lesion detection
- Urinary tract
- Perfusion analysis



Suetens, 2002

Intravascular injection

- After venous injection, media travel to
  - Vena cava
  - Right side of heart (where mixing with non-opacified blood is completed)
  - Pulmonary circulation
  - Left side of heart
  - Aorta
  - Arterial circulation
  - Capillaries
  - Venous drainage
- Recirculation



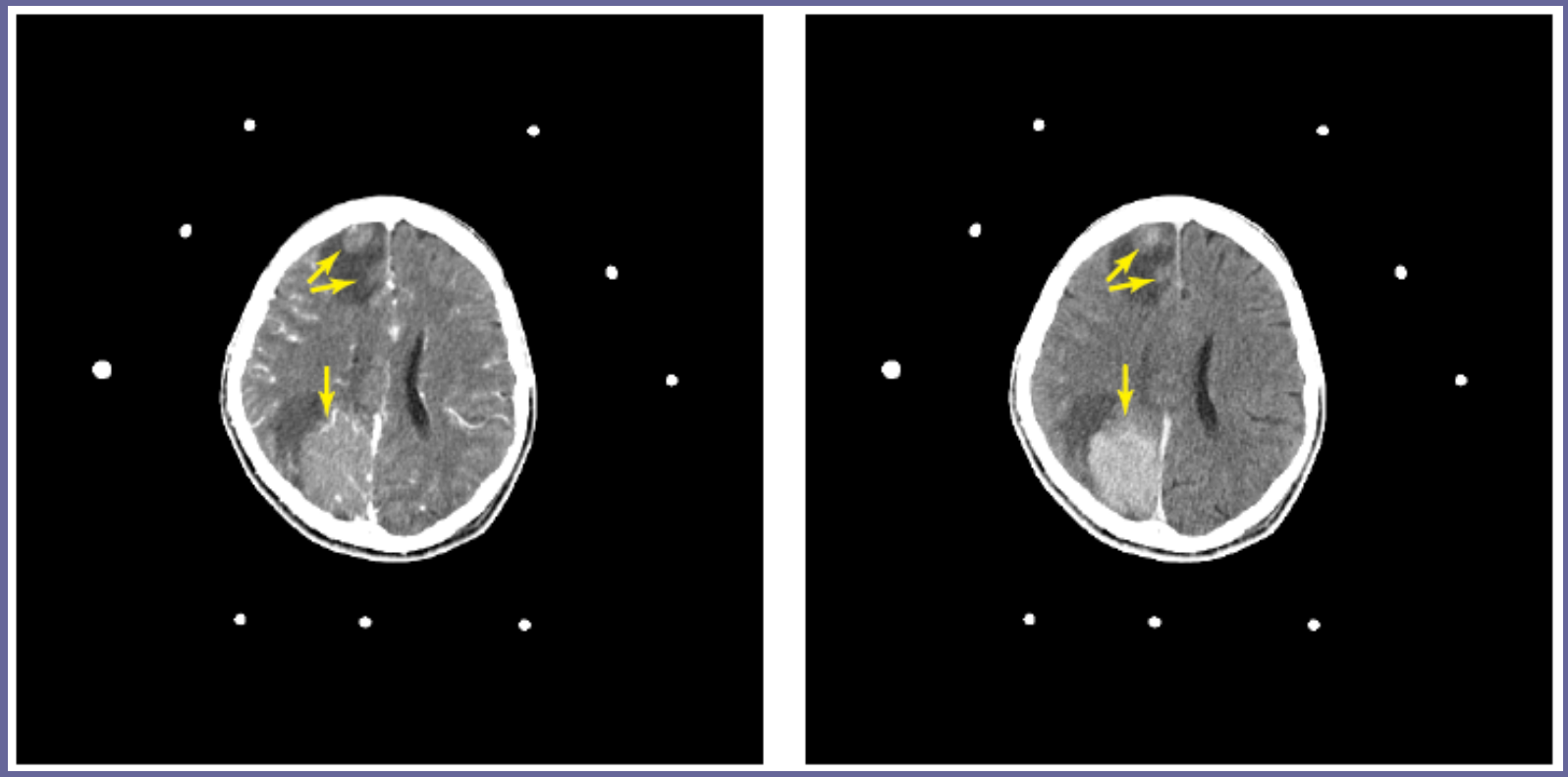
Biology-forums.com

Determinants of enhancement

- Enhancement depends on x-ray attenuation of arterial blood
- Concentration of iodine (for example) in arterial blood is the ratio of
  - Amount of iodine in injected media (typical concentration = 300 mg/ml)
  - Volume of blood the contrast agent mixes with (proportional to duration of injection)
- Enhancement is determined by
  - Amount of iodine (mg) / injection time (s)

Lesion detection

- Tumors with dense capillary networks enhance more than surrounding normal tissue

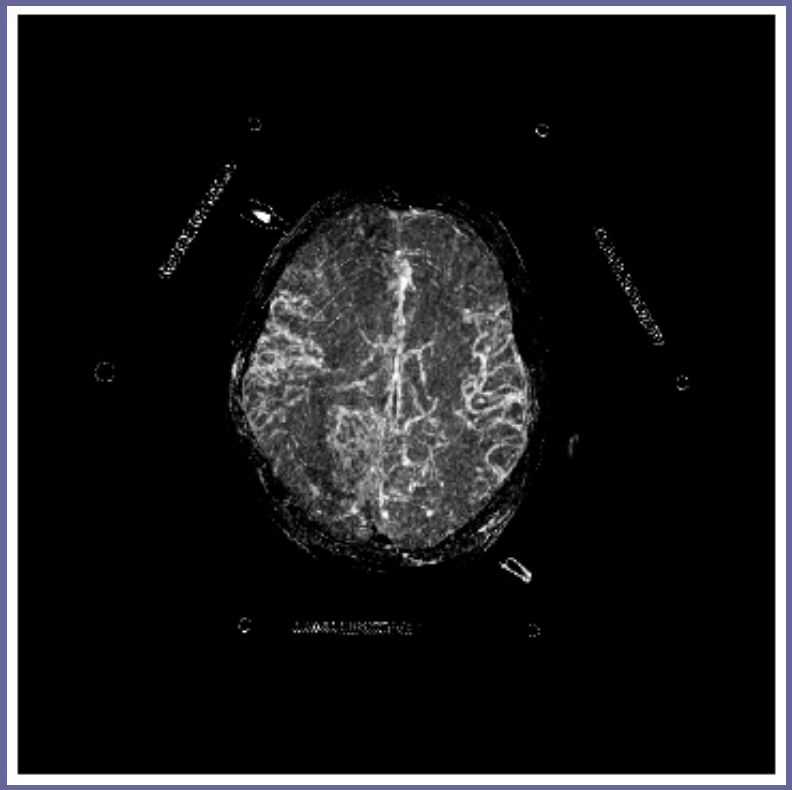


Suetens, 2002

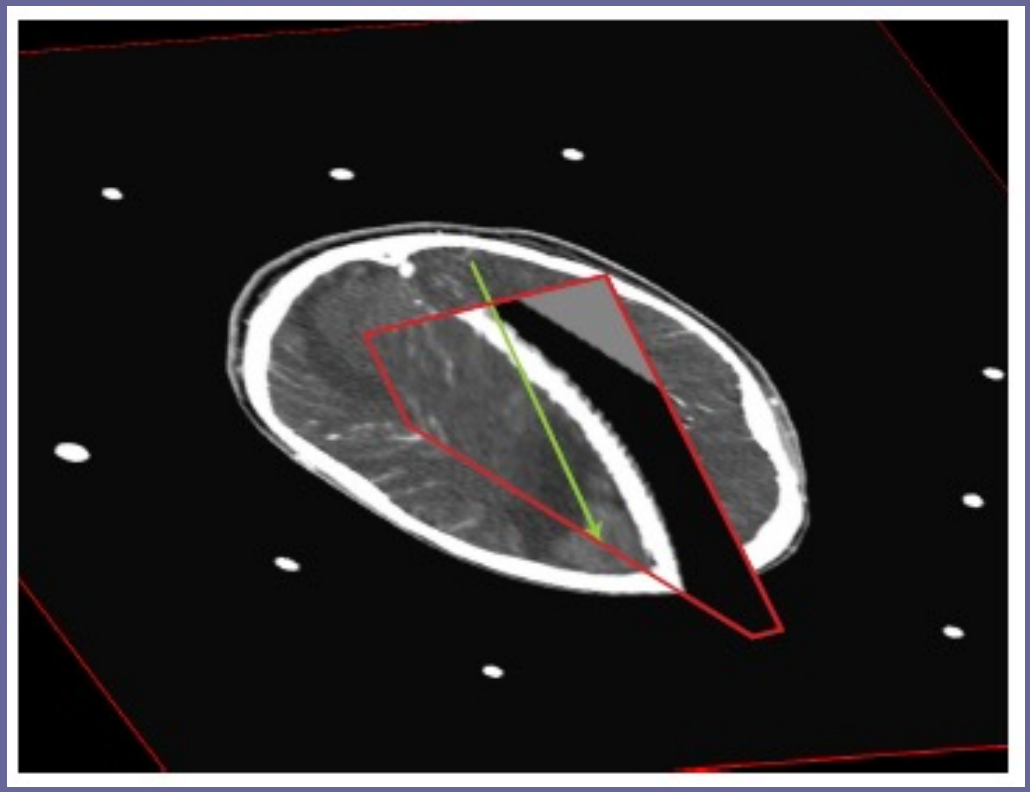
Pre-injection

10 minutes post-injection

Biopsy planning



Immediately post-injection
Arteriogram



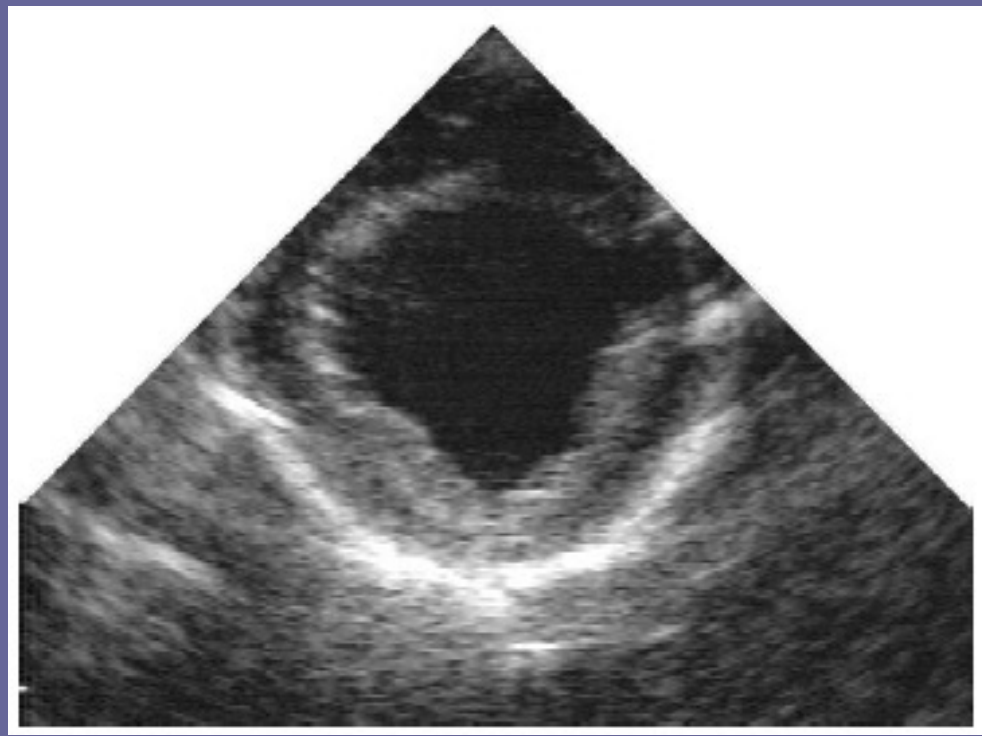
Suetens, 2002

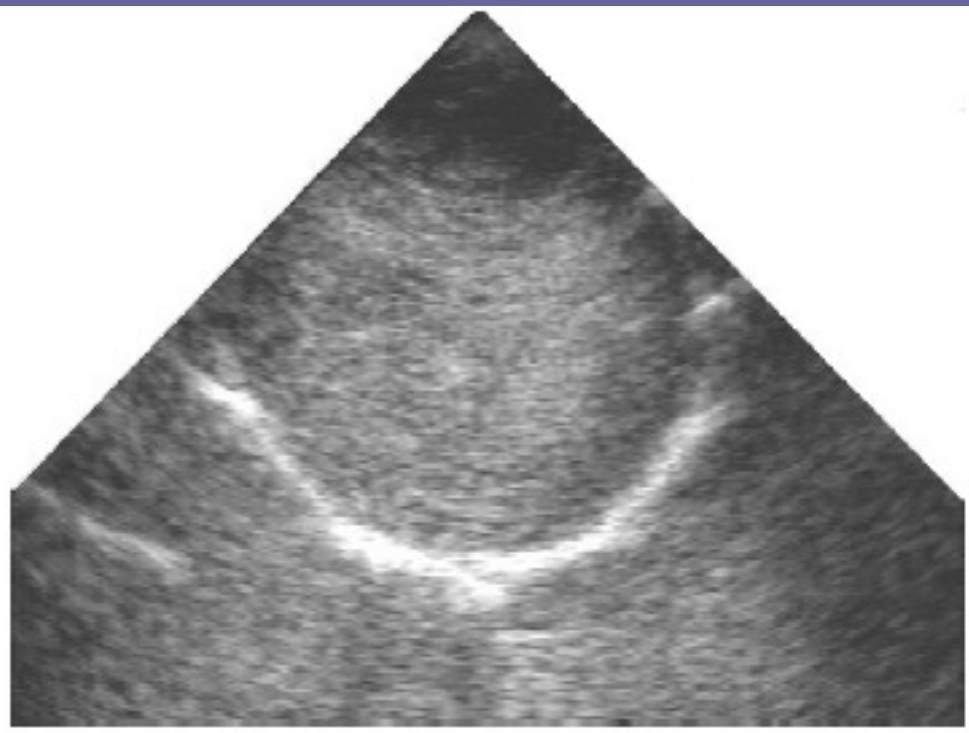
Biopsy approach

II. Contrast agents for ultrasound

- Acoustic impedance of air and tissue are quite different
  - Almost total reflection for tissue/air interfaces
- Blood injected with microbubbles (~4μm in diameter) appears bright on ultrasound
- *Contrast echography*
- Used to assess organ perfusion

Microbubbles viewed in the left ventricle



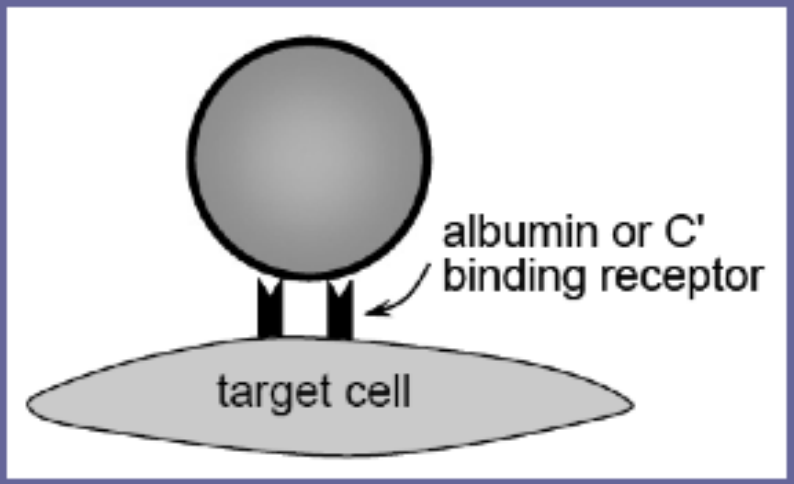


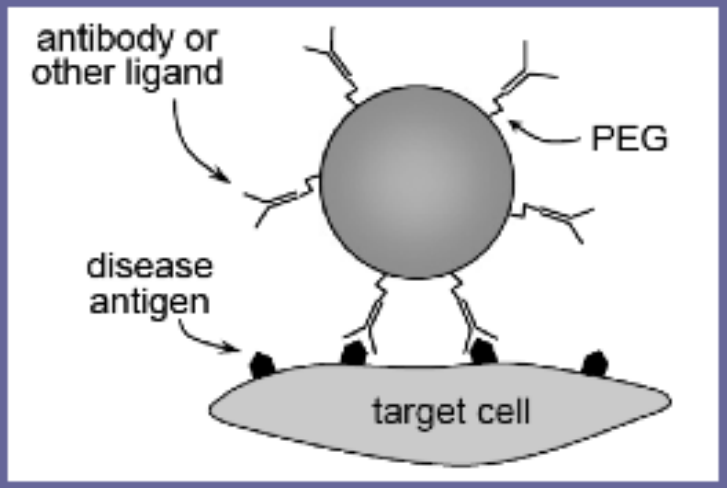
Suetens, 2002

Before injection

After injection

Targeting strategies





Behm and Lindner, 2006

Shell material has high affinity for target

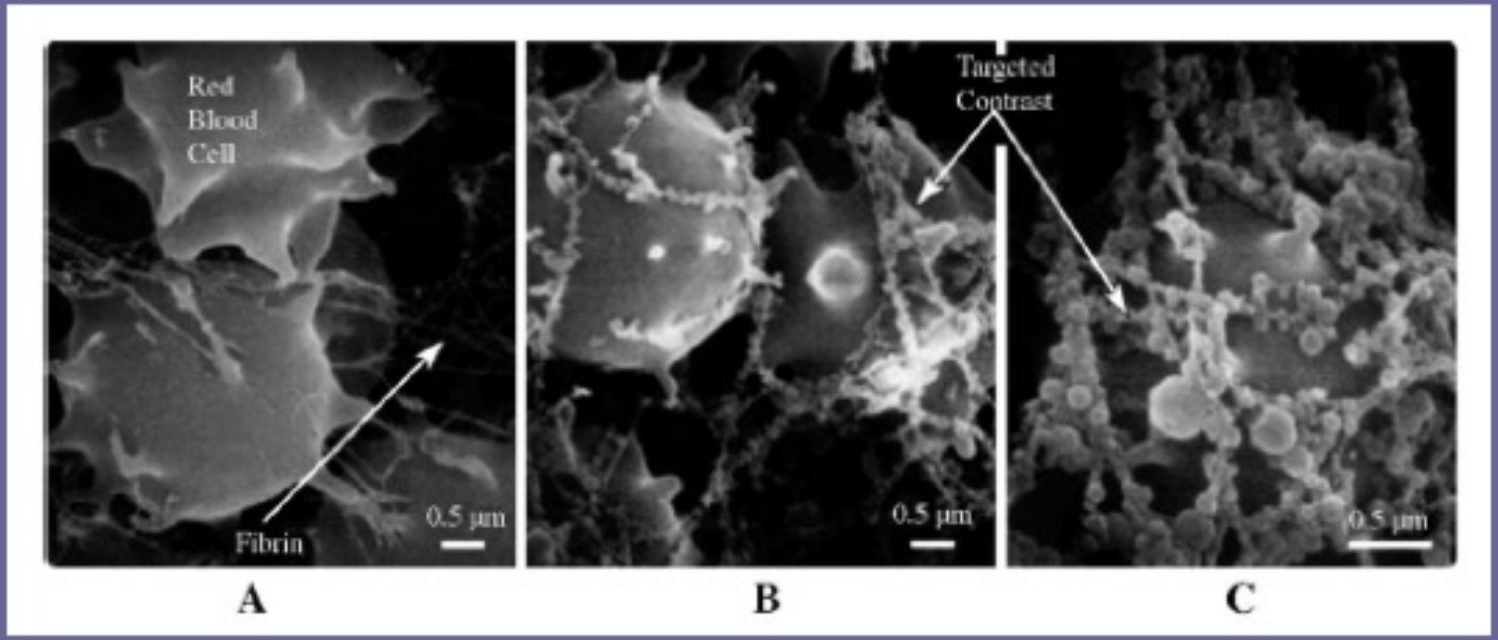
Example: phospholipids that attach to activated leukocytes

Attach specific antibody or peptide to microbubble shell.

Up to 10^4-10^5 ligands per bubble

Thrombus imaging

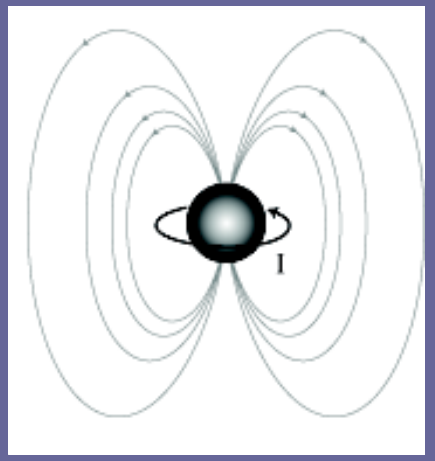
- Use microbubbles with high affinity for fibrin
- Microbubbles adhere to blood clots



Liu et al (2006)

III. Contrast agents for MRI

- Magnetic particles
  - Strongly magnetized by the B_0 field
  - Disturb field in particles' environment
  - Enhance relaxation
    - Shorten T_1, T_2
- Two basic types
  - Paramagnetic atoms
    - Gadolinium (7 unpaired electrons)
  - Iron Oxide nanoparticles

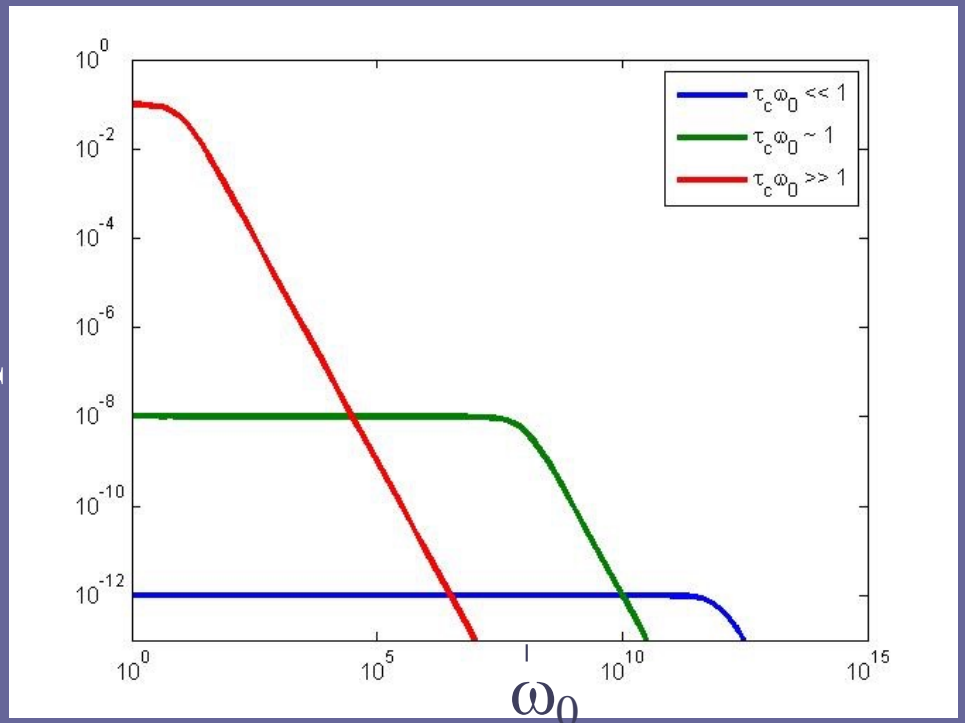


Review: Determinants of R_1

- A transverse magnetic field at frequency ~ω_0 flips spins
- Spins are influenced by fields generated by neighboring spins
  - Larger magnetic moments have greater effect
- Tumbling molecules produce and experience time-varying magnetic fields, $b_1(t)$, in their neighborhoods
- Frequency components of $b_1(t)$ at ~ω_0 drive magnetization towards equilibrium
- Frequency spectrum of $b_1(t)$ depends on molecular motion

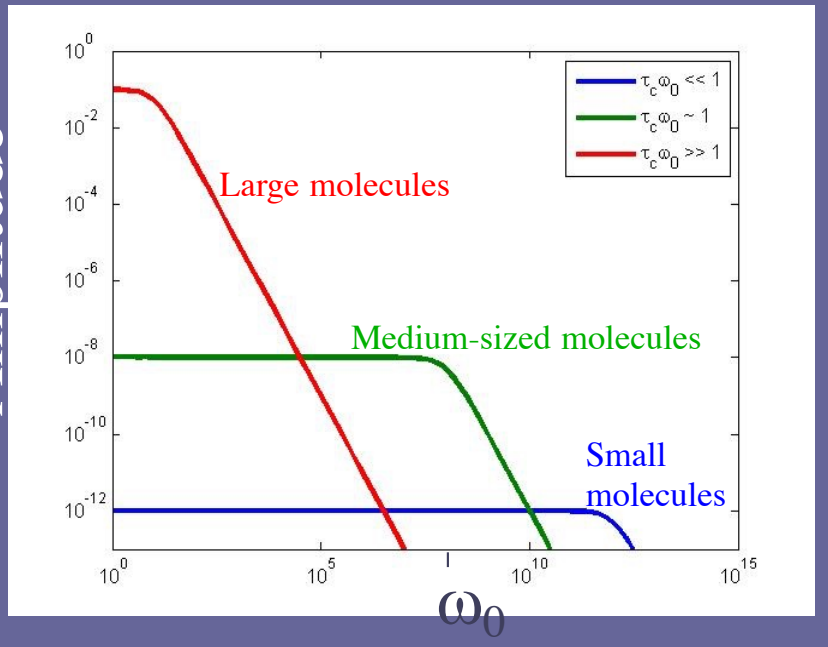
Molecular motion

- The *correlation time*, τ_c, is the interval required for a molecule to change orientation or position appreciably
- The frequency spectrum of $b_1(t)$ depends on τ_c:

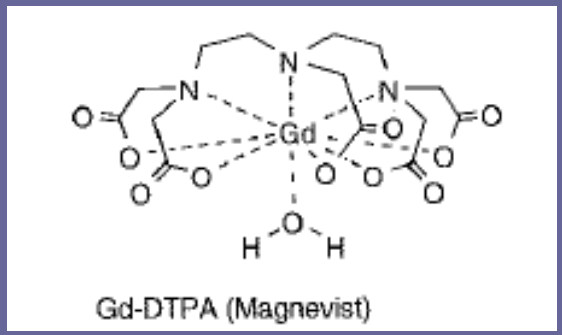


Determinants of R_2

- Two ways to dephase spins
  - Different precession rates
  - Tip out of, then back into the transverse plane
- Speed of tumbling motion (τ_c^{-1})
  - b_z component at ~0 Hz
  - $b_1(t)$ at frequency ~ω_0

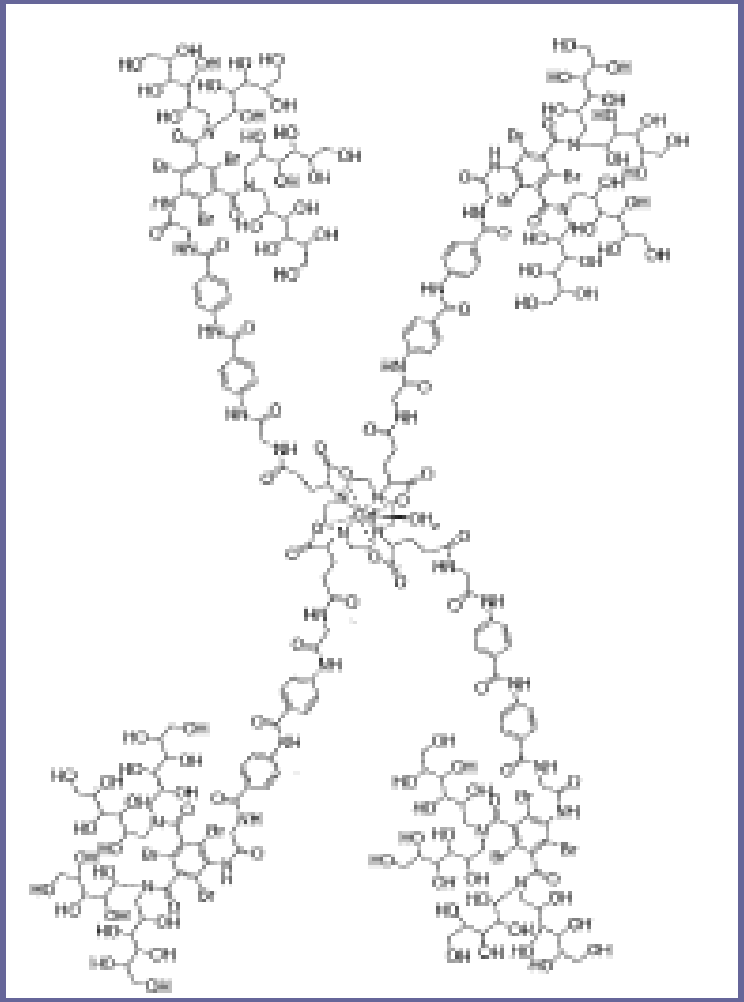


Tuning correlation times



Edelman et al, 2005

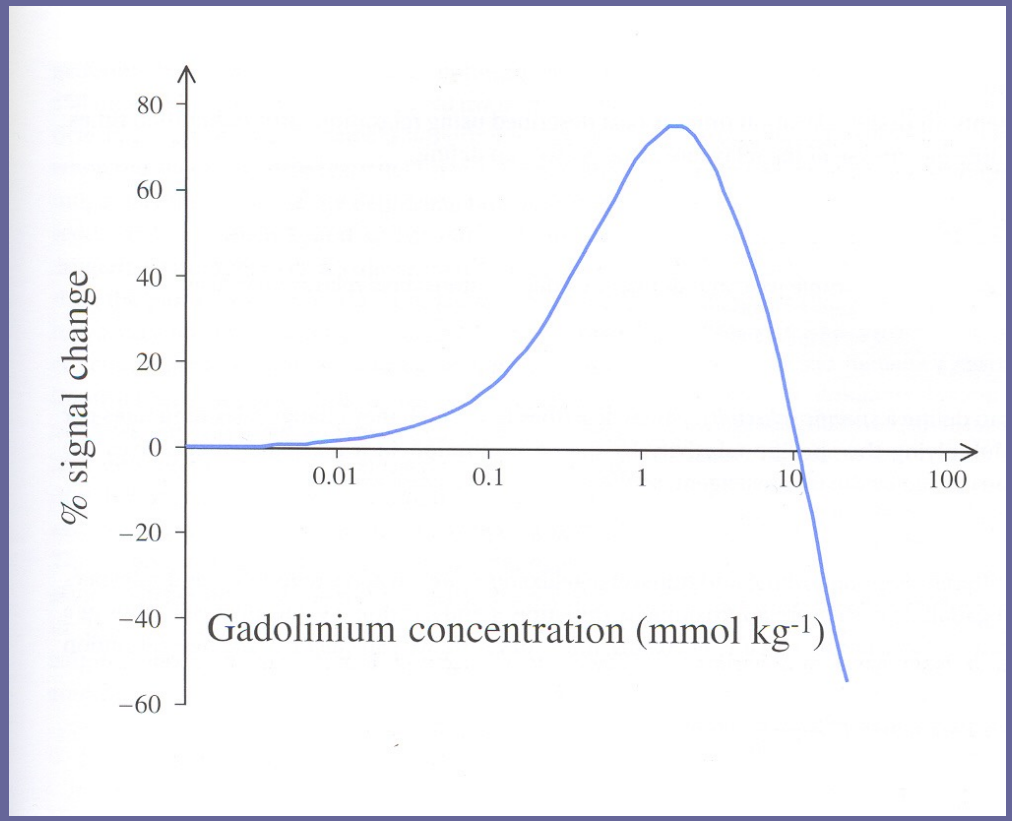
Larger molecules -> larger τ_c



Edelman et al, 2005

Gadolinium

- At low concentrations, T_1 reduction dominates
- At higher concentrations, T_2 losses reduce the signal
- Typical dose is 0.1 mmol / kg body weight
- Biological half life is ~1.5 h
- Gd is toxic, so it is chelated (to DTPA) to prevent interaction with anything but water
- T_1 of tissue is



McRobbie et al, 2003

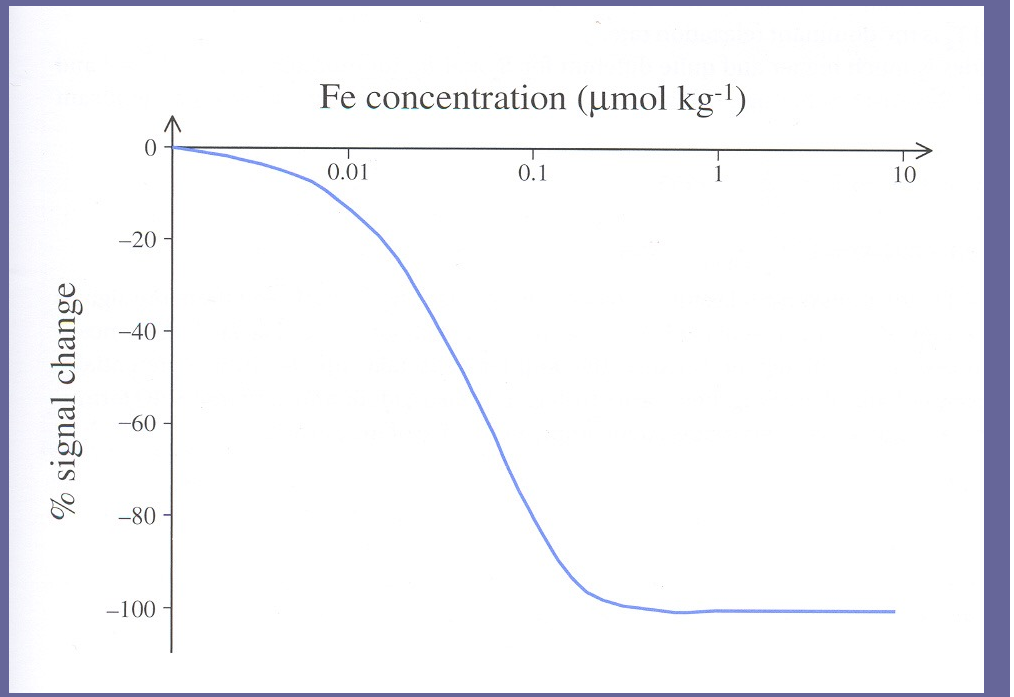
$$\frac{1}{T_{1,\,post}} = \frac{1}{T_{1,\,pre}} + R_1 \cdot [C_A]$$

Relaxivity of contrast agent

Concentration of contrast agent

Iron oxide particles

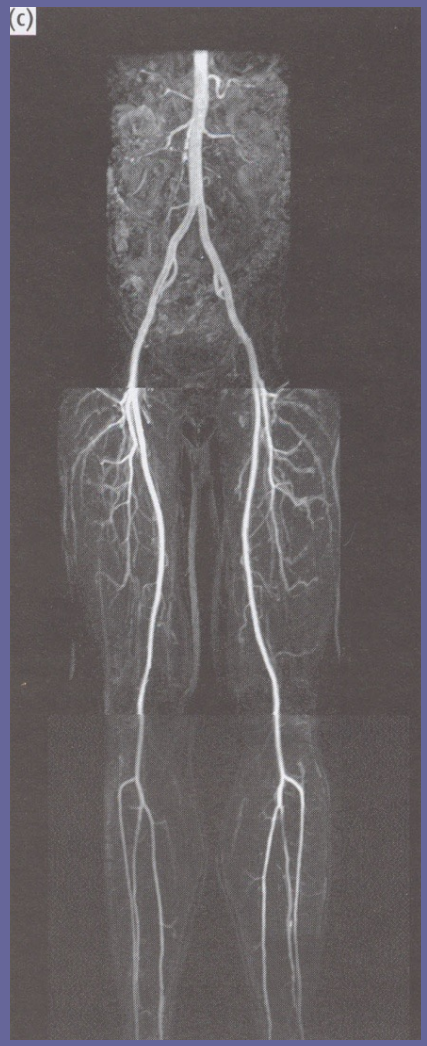
- Particles are much larger than Gd-DTPA
  - Field extends farther
  - Effective dose is smaller (8-16 μmol Fe/kg)
- T_2 shortening dominates T_1 effects
- Particles are coated with a carbohydrate layer to improve biocompatibility



McRobbie et al, 2003

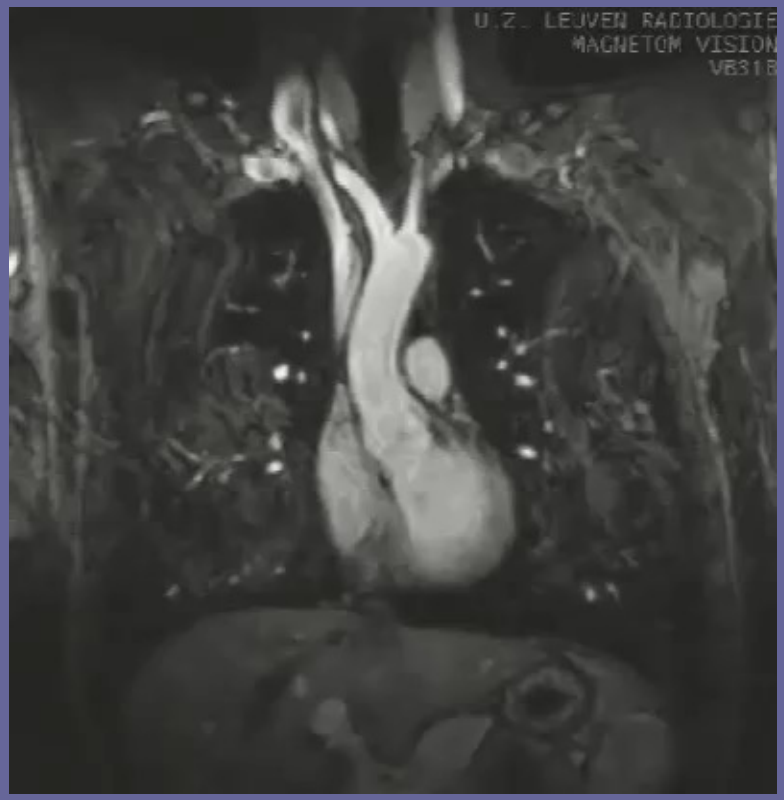
MR angiography

- Visualize vascular system
- Steps
  - Inject T_1 contrast agent
  - Wait for distribution to vessels of interest (e.g., arteries)
  - Acquire images with heavy T_1 weighting

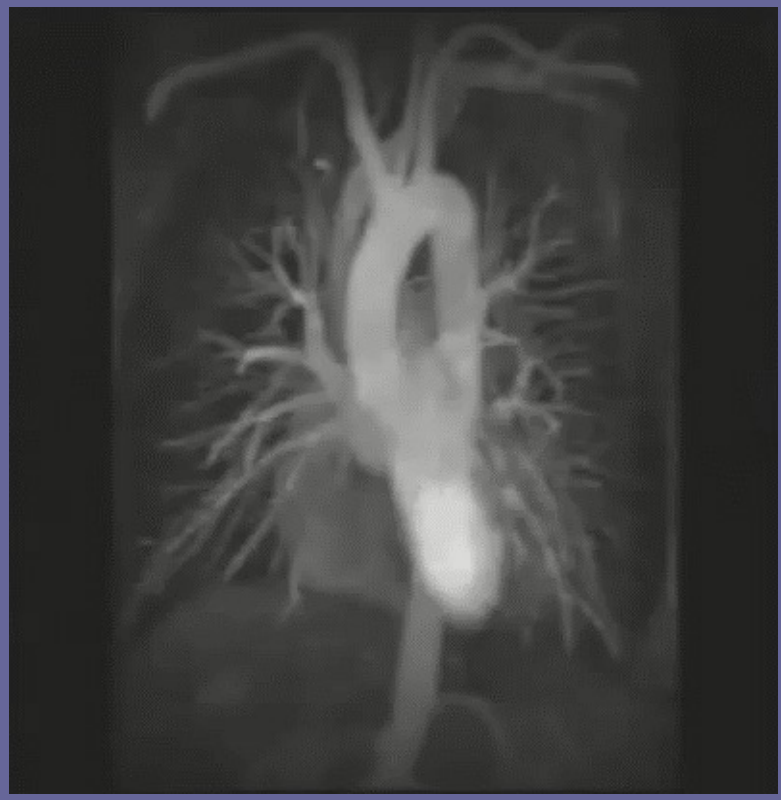


McRobbie et al, 2003

Visualizing thoracic vessels



Suetens, 2002

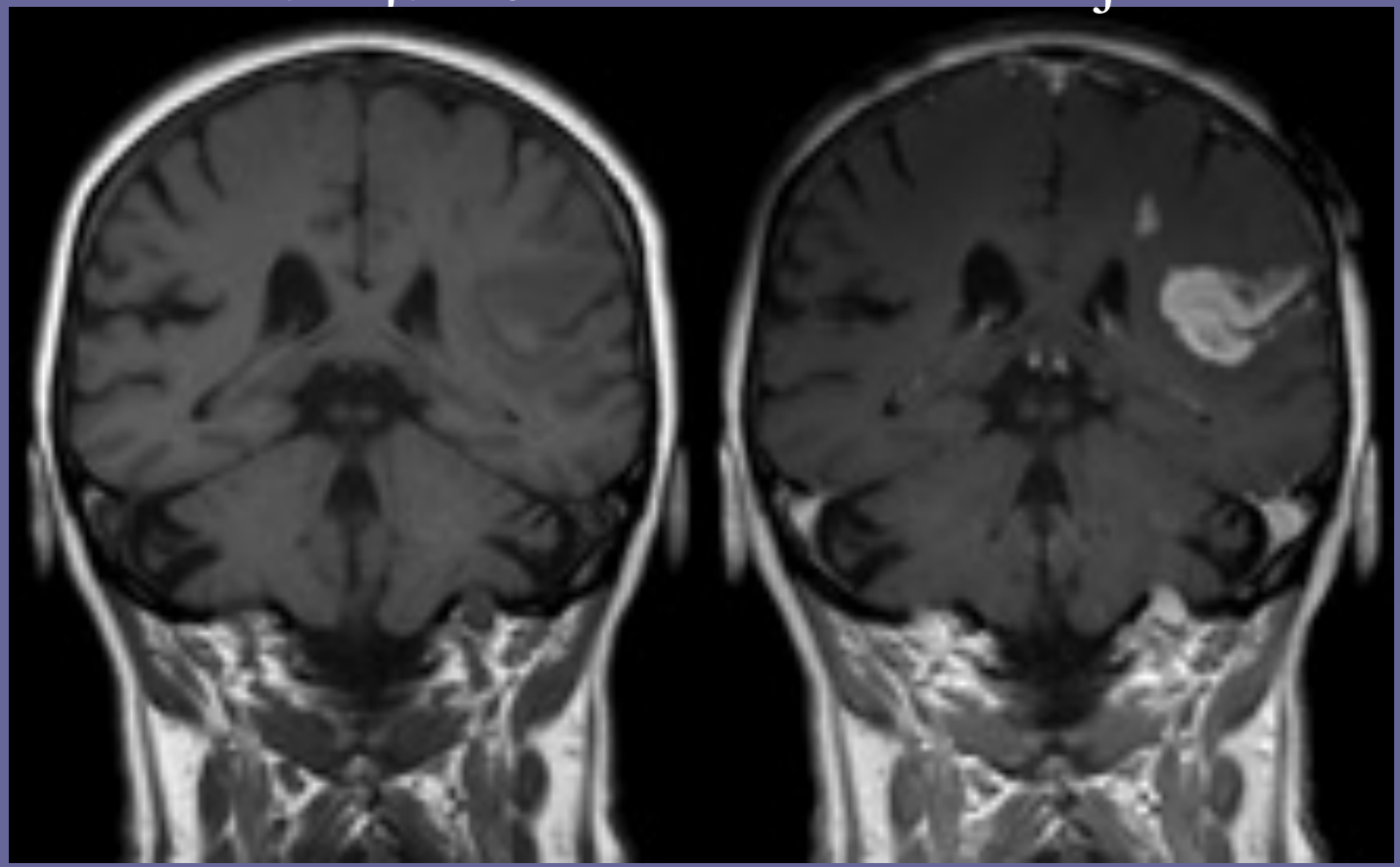


Suetens, 2002

Vessel wall integrity

- Blood-brain barrier disruption following stroke—vessel walls become leaky

Pre-injection Post-injection



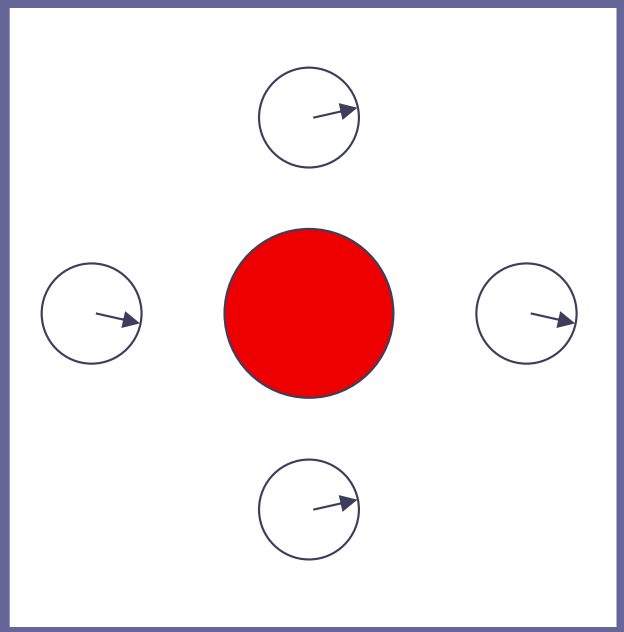
en.wikipedia.org/wiki/MRI_contrast_agent

Application: contrast agent measurements of perfusion

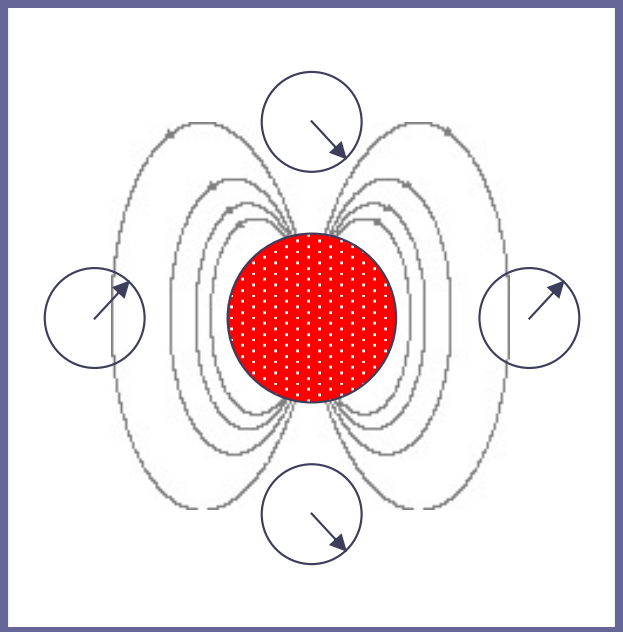
Effects of MRI contrast agents

- Large magnetic moment
  - Gadolinium (7 unpaired electrons)
- Increase relaxation rate of neighboring water molecules
  - T_1 relaxation (M_z)
  - T_2 relaxation (M_{xy})
- When confined to vessels, concentrated magnetic moments shift the field around the vessels

Magnetic field surrounding a vessel



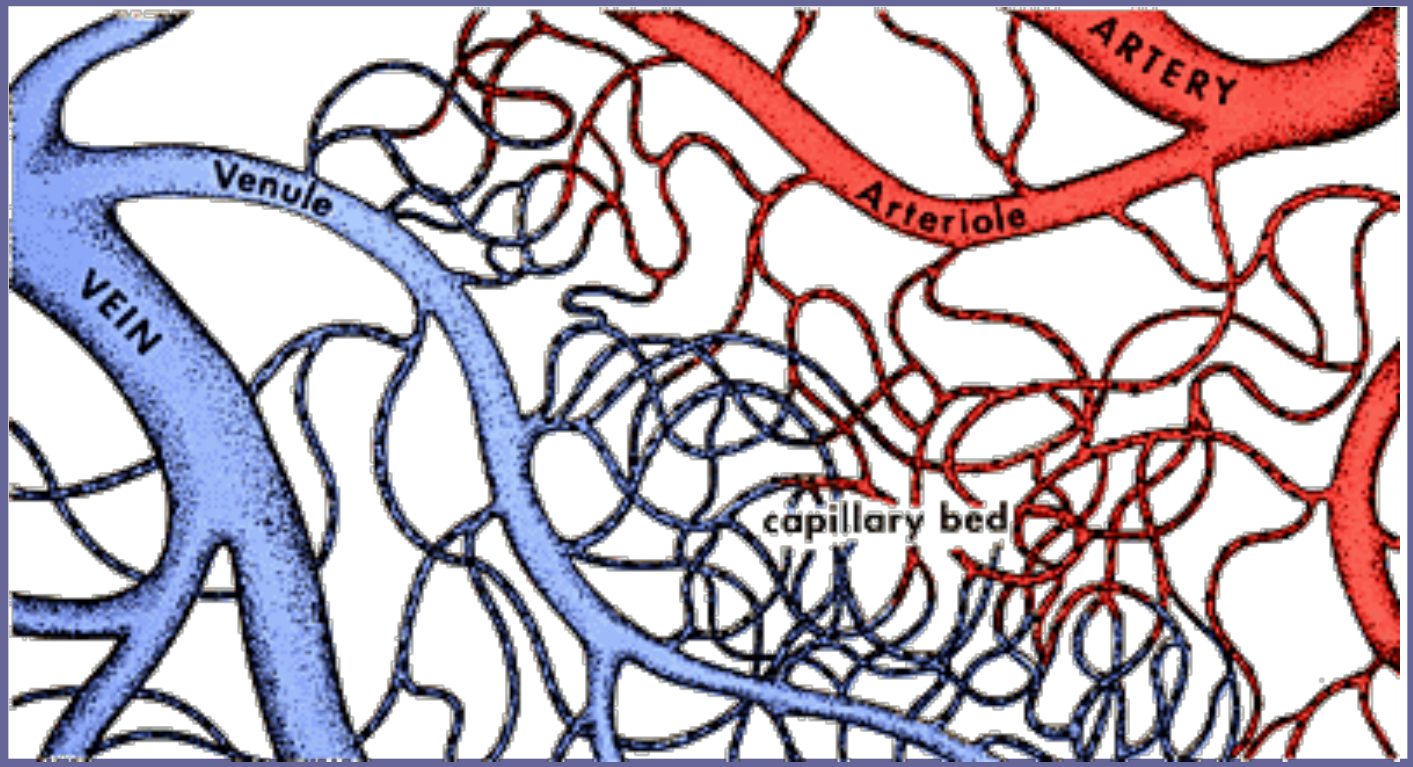
B_0



Normal blood

Blood with contrast agent

Capillary networks



Buxton, 2002

Blood susceptibility and tissue transverse relaxation

- Field shifts dephase spins: $\delta\omega = -\gamma \cdot \delta B_z$
- Relaxation rate increases
  - depends on tissue contrast agent density, $C_T(t)$
- Signal drops

Dependence of relaxation rate on tissue contrast agent concentration

- Relaxation rate is the inverse of the time constant

$$R_2^* = \frac{1}{T_2^*}$$

$$R_2^*(\text{with contrast}) = R_2^*(\text{without contrast}) + \Delta R_2^*$$

Dependence of relaxation rate on tissue contrast agent concentration

- Relaxation rate is the inverse of the time constant

$$R_2^* = \frac{1}{T_2^*}$$

$$R_2^*(\text{with contrast}) = R_2^*(\text{without contrast}) + \Delta R_2^*$$

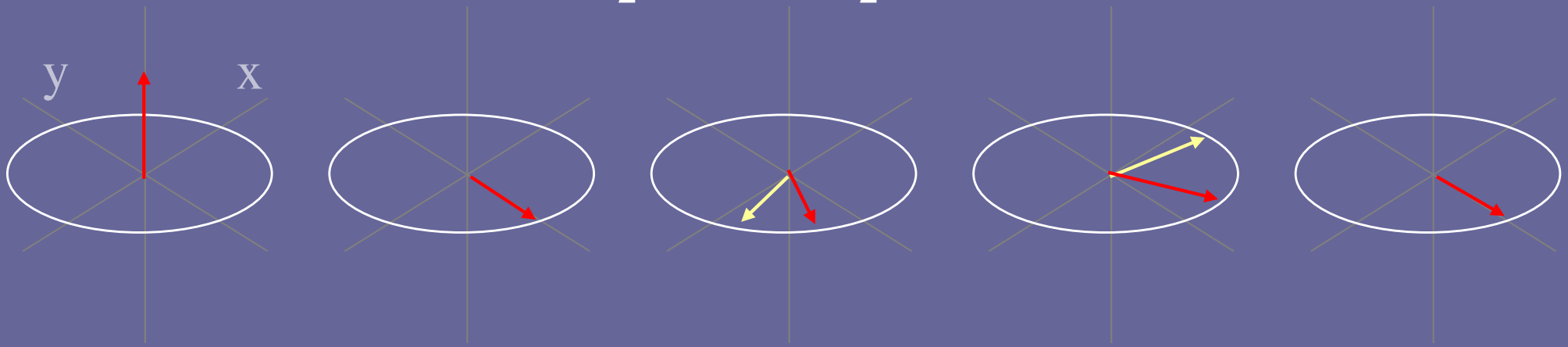
- Tissue relaxation due to contrast agent

$$\Delta R_2^* = k \cdot C_T(t)$$

T_2 vs T_2^* relaxation

- A 180° refocusing pulse cancels time-independent frequency differences between spins— the 'spin echo'
  - Only time-varying b(t) fields contribute to T2 relaxation
  - Time-independent B_z also contributes to T2* relaxation

$$\frac{1}{T_2^*} = \frac{1}{T_2} + \frac{1}{T_2'}$$



90_x ϕ_z 180_y ϕ_z

- Signal intensity prior to contrast agent injection

$$S_0 = A \cdot e^{-T_E \cdot R_2^*(\text{no contrast})}$$

- Signal intensity prior to contrast agent injection

$$S_0 = A \cdot e^{-T_E \cdot R_2^*(\text{no contrast})}$$

- Signal intensity with contrast agent

$$\begin{aligned} S &= A \cdot e^{-T_E \cdot R_2^*(\text{contrast})} \\ &= A \cdot e^{-T_E \cdot R_2^*(\text{no contrast})} \cdot e^{-T_E \cdot \Delta R_2^*} \\ &= S_0 \cdot e^{-T_E \cdot \Delta R_2^*} \end{aligned}$$

- Signal reflects tissue contrast agent concentration:

$$S(t) = S_0 \cdot e^{-k \cdot T_E C_T(t)}$$

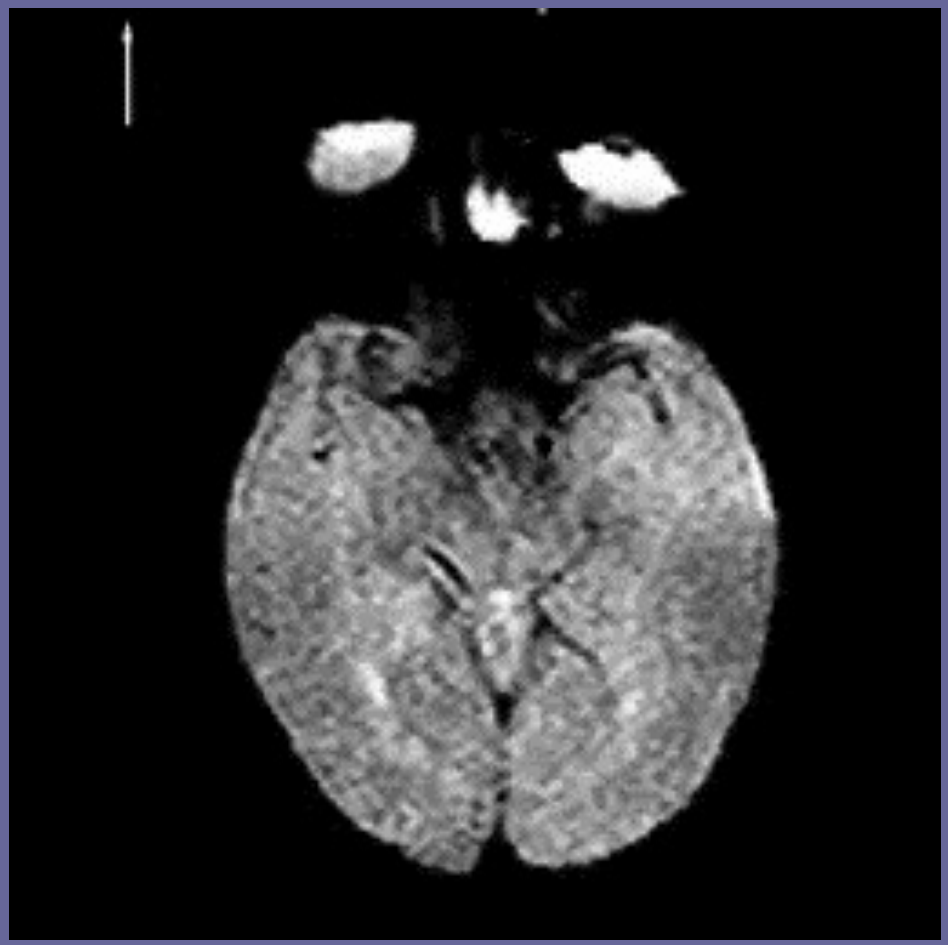
$$\ln(S/S_0) = -k \cdot T_E C_T(t)$$

$$C_T(t) = \frac{-\ln(S/S_0)}{k \cdot T_E}$$

Image acquisition

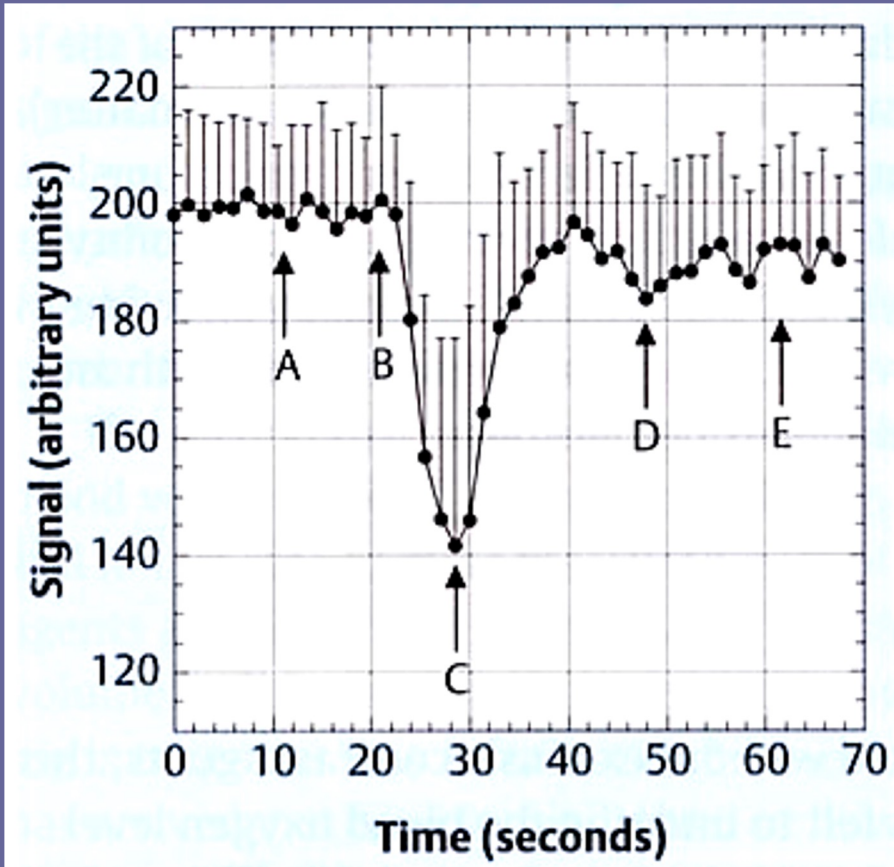
- Single shot imaging
- T_R = 1-1.5 seconds (to capture 1st pass)
- T_E = 65 ms (to detect T_2^* changes)
- Total imaging time ~ 1 minute
- Time of injection ~ 10 sec
  - Started 10 seconds after imaging
- Amount of contrast agent ~0.4 mmol/kg
  - 40 mmol for 100 kg person
  - Followed by 25mL saline flush

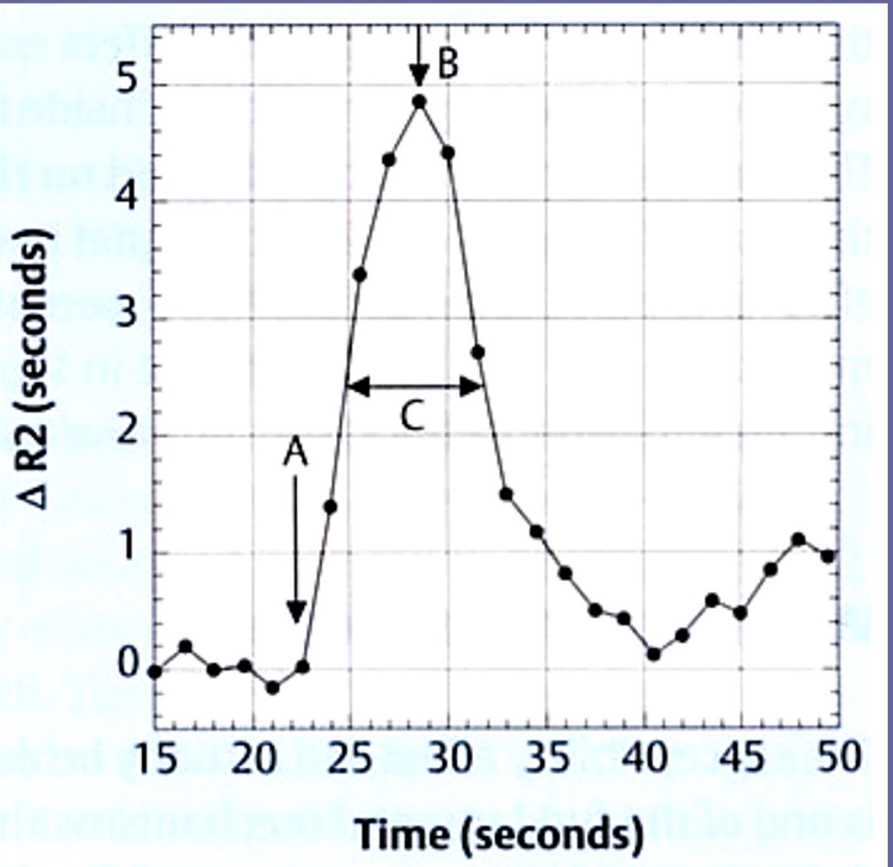
Example: normal perfusion



Sorensen, 2000

Signal time course





$$\Delta R_2^* = -\frac{\ln(S/S_0)}{TE}$$

Sorensen, 2000

Goals of image analysis

- Relative cerebral blood volume (rCBV)
  - "relative" means a proportionality constant is unknown (but the same for all pixels)
- Mean transit time (MTT)

Measuring CBV using a short bolus injection

- Integrating the convolution relation for tissue concentration,

$$C_T(t) = f \cdot \int_0^\infty C_A(t') \cdot r(t-t') \cdot dt'$$

$$\int_0^\infty C_T(t) \cdot dt = f \cdot \int_0^\infty C_A(t') \cdot \left[\int_0^\infty r(t-t') \cdot dt \right] \cdot dt'$$

$$= f \cdot \tau_{MT} \cdot \int_0^\infty C_A(t') \cdot dt'$$

$$= \lambda \cdot \int_0^\infty C_A(t') \cdot dt'$$

so

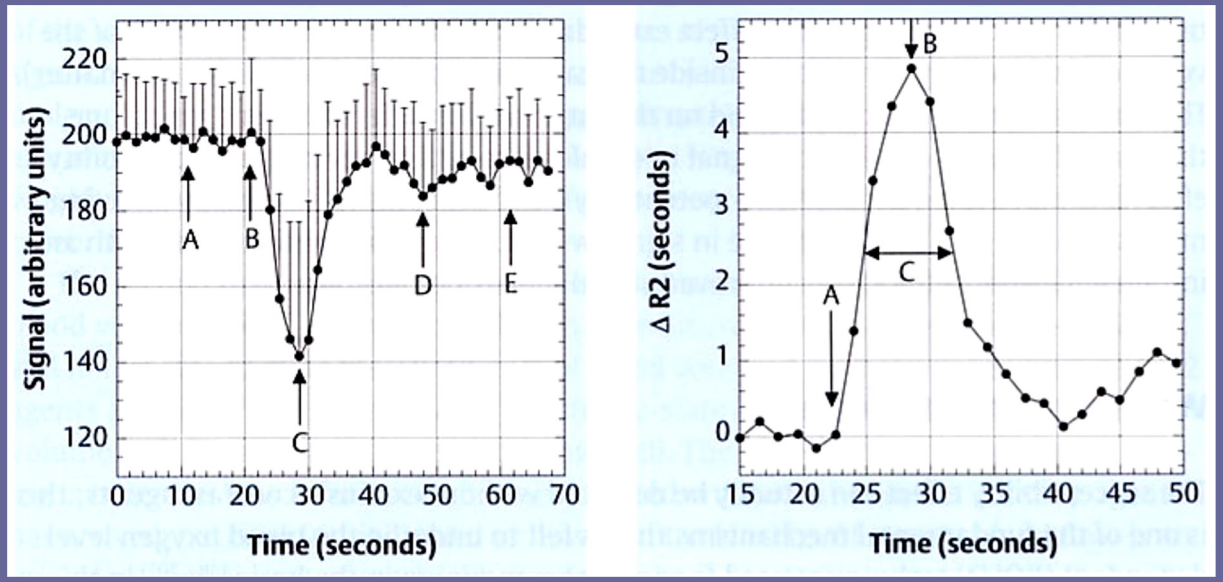
$$\lambda = \frac{\int_0^\infty C_T(t) \cdot dt}{\int_0^\infty C_A(t') \cdot dt'}$$

Image analysis

- Find signal time course in a region of interest (ROI)

Image analysis

- Find signal time course in a region of interest (ROI)
- Convert signal changes to R_2^* changes

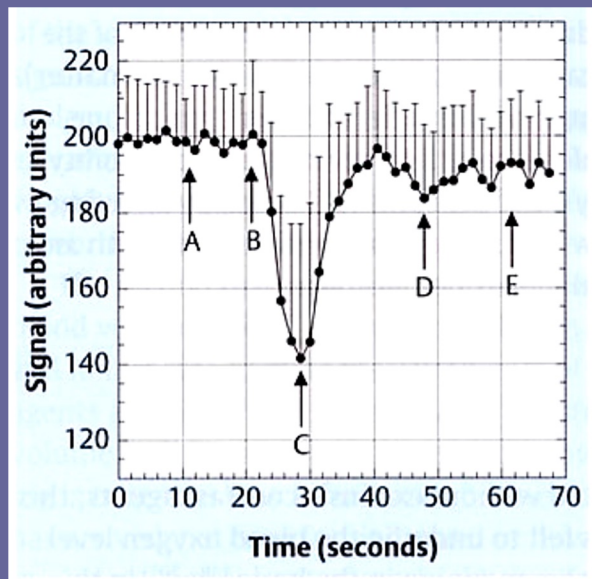


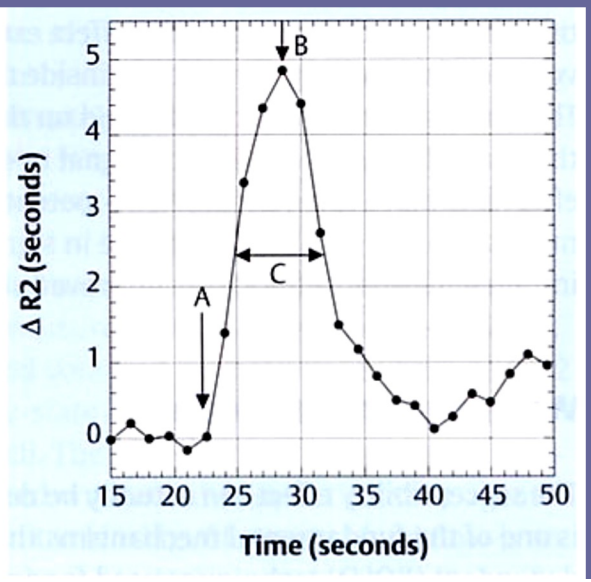
$$\Delta R_2^* = -\frac{\ln(S/S_0)}{TE}$$

Sorensen, 2000

Image analysis

- Find signal time course in a region of interest (ROI)
- Convert signal changes to R_2^* changes
- Identify the baseline (pre-contrast R_2^*)





$$\Delta R_2^* = -\frac{\ln(S/S_0)}{TE}$$

Sorensen, 2000

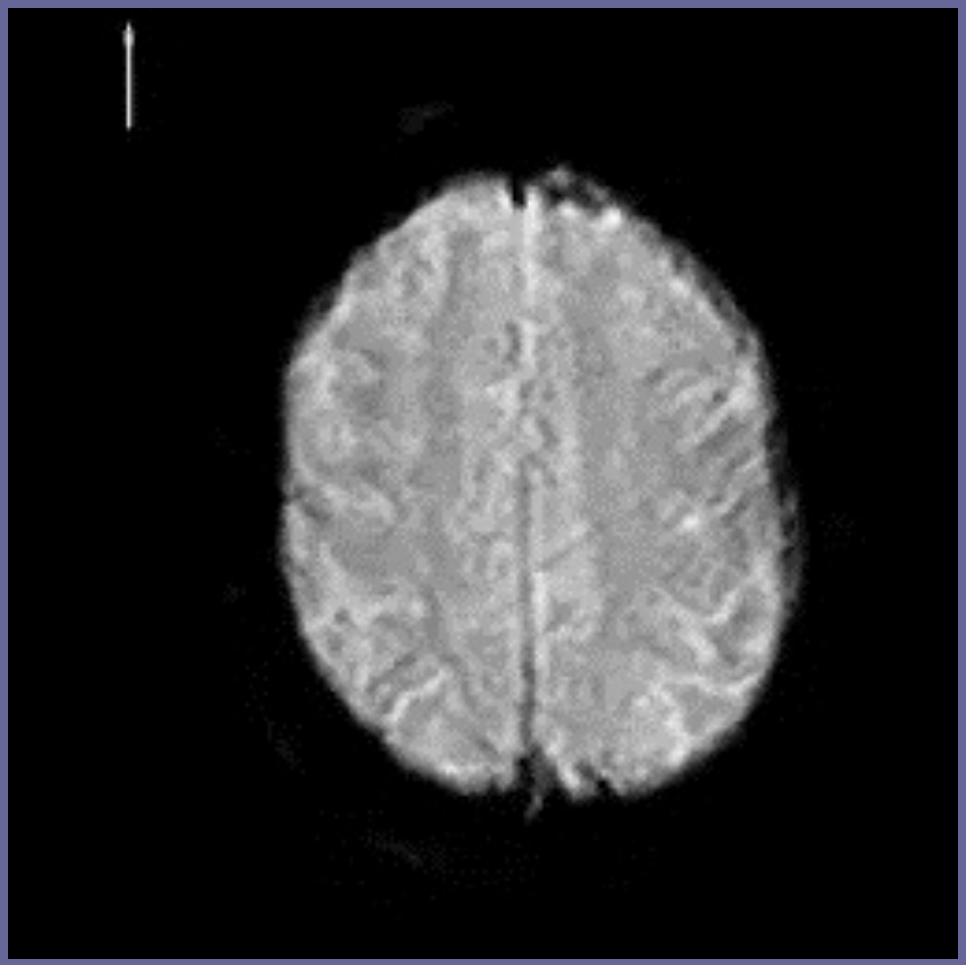
Image analysis

- Find signal time course in a region of interest (ROI)
- Convert signal changes to R_2^* changes
- Identify the baseline (pre-contrast R_2^*)
- Integrate the changes in R_2^*

$$CBV = \frac{\int_0^\infty C_T(t)dt}{\int_0^\infty C_A(t)dt} = c \cdot \int \Delta R_2^*(t)dt$$

Same for all voxels

Mean transit time in ischemic stroke

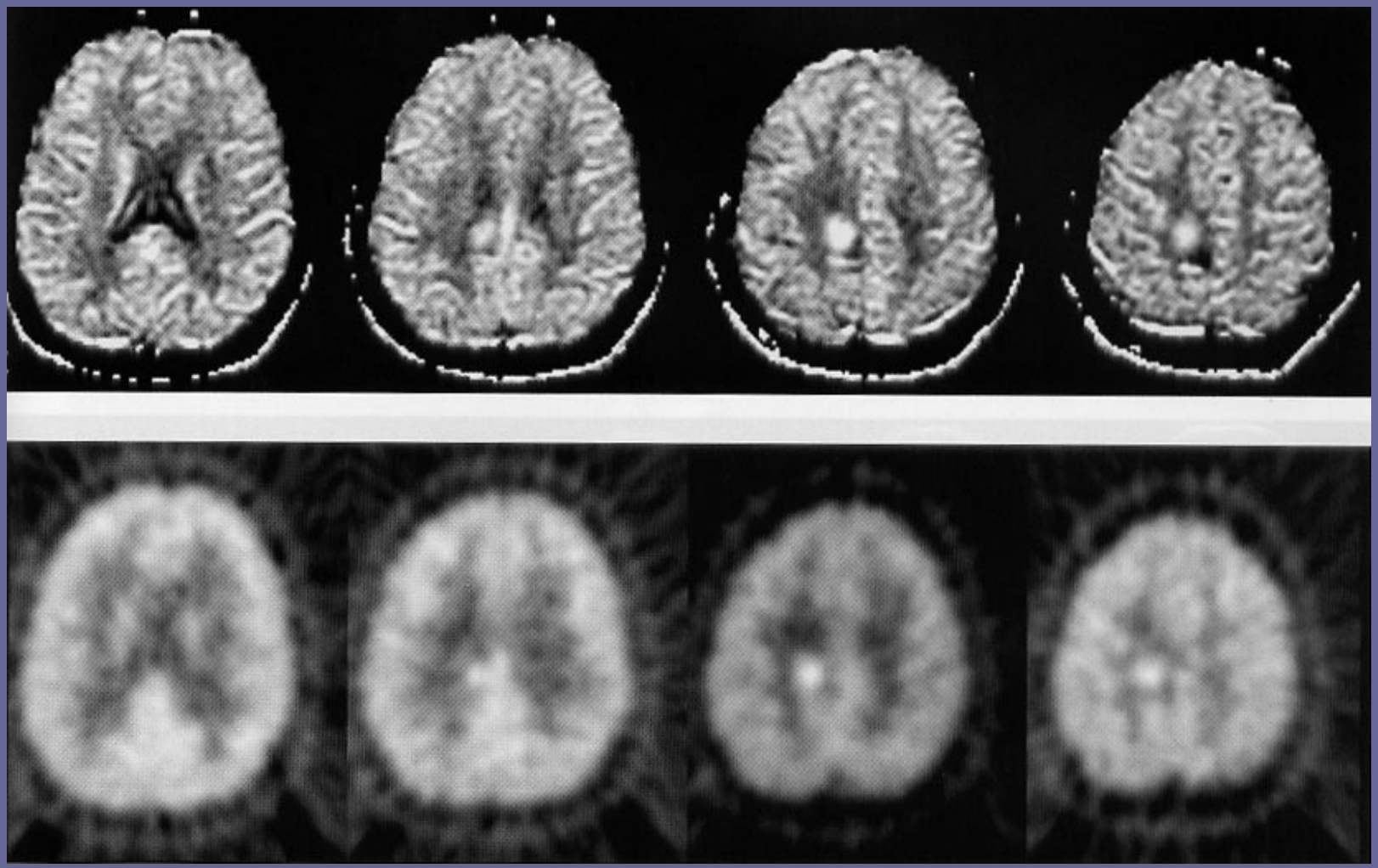


Left side lags right, reflecting lower flow

$$\tau_{MT} = \frac{\lambda}{f}$$

Sorensen, 2000

rCBV reflects capillary density in high grade tumors



rCBV

PET FDG

Sorensen, 2000

Summary

- Contrast media exist for CT, MRI, and ultrasound
- These agents expand the applications of imaging methods by providing contrast based on structure and/or function
- Magnetic susceptibility contrast agents are used in MRI to measure
  - Volume of distribution of the agent
  - Mean transit time
  - Blood perfusion
- Applications in neurology, cancer, neuroscience

References

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