HST.583 Functional Magnetic Resonance Imaging: Data Acquisition and Analysis
Fall 2008

HST.583: Functional Magnetic Resonance Imaging: Data Acquisition and Analysis, Fall 2008
Harvard-MIT Division of Health Sciences and Technology
Course Director: Dr. Randy Gollub.

Part 1: BOLD Imaging II

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Overview

- BOLD in context of MRI physics
- Spatial origin of BOLD signal contribution
- Effects of diffusion on BOLD signal
- BOLD sequence variants
- BOLD imaging parameters

Physics of BOLD

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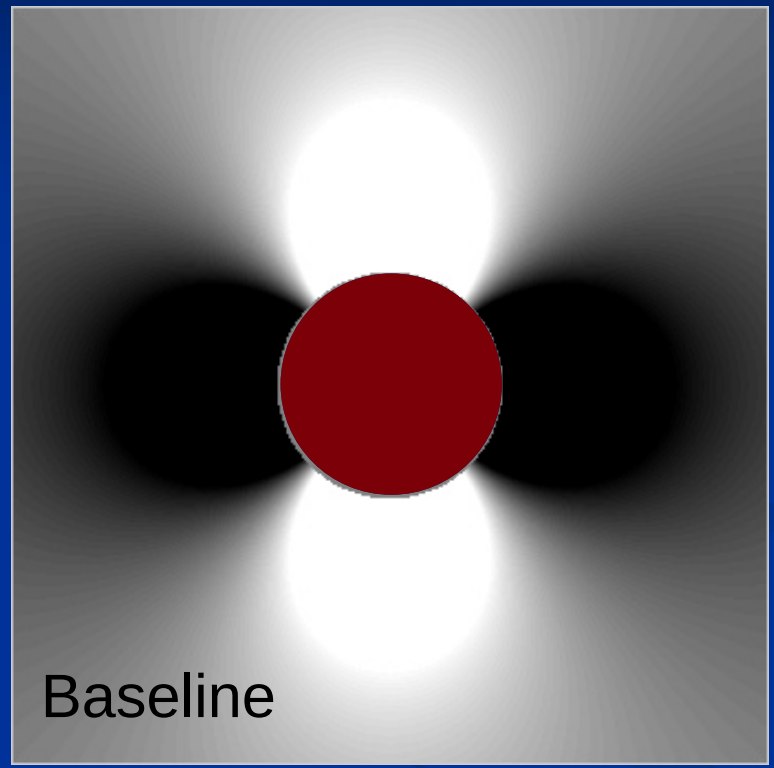
See item # 10 at
http://www.sinauer.com/neuroscience4e/animations1.1.html
(Website for Purves et al. *Neuroscience*. 4th edition. Sunderland, MA: Sinauer Associates, 2008.)



The magnetic field within and surrounding the vessel is perturbed by paramagnetic dHb

Physics of BOLD

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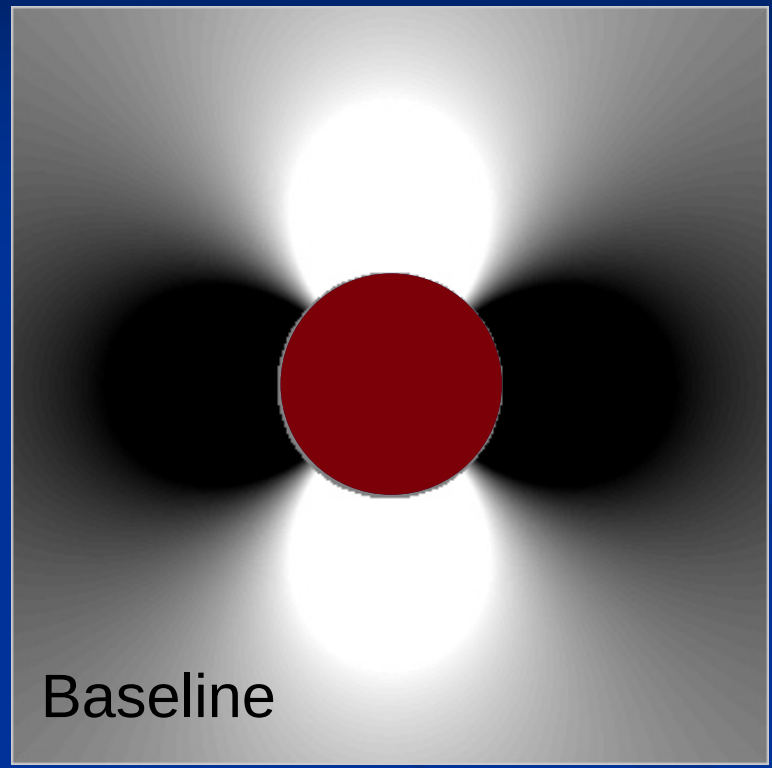

At baseline, late capillary and post-capillary venular blood is substantially deoxygenated (SaO_2 = 60%) and contains dHb

Physics of BOLD

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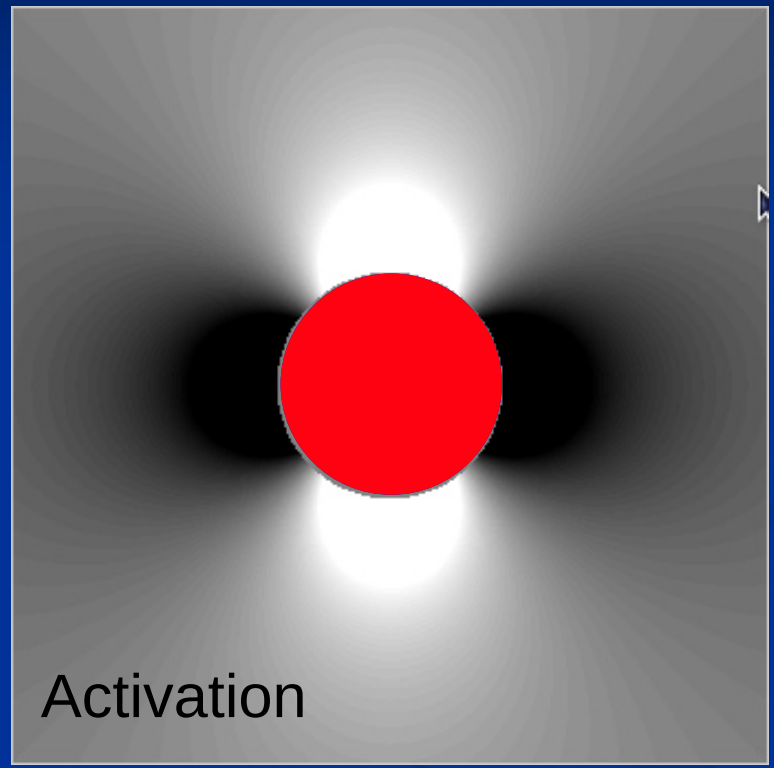

During activation, CBF increases substantially and flushes out dHb. Late capillary and post-capillary venular blood become *more* oxygenated (SaO_2 = 80%)

Physics of BOLD

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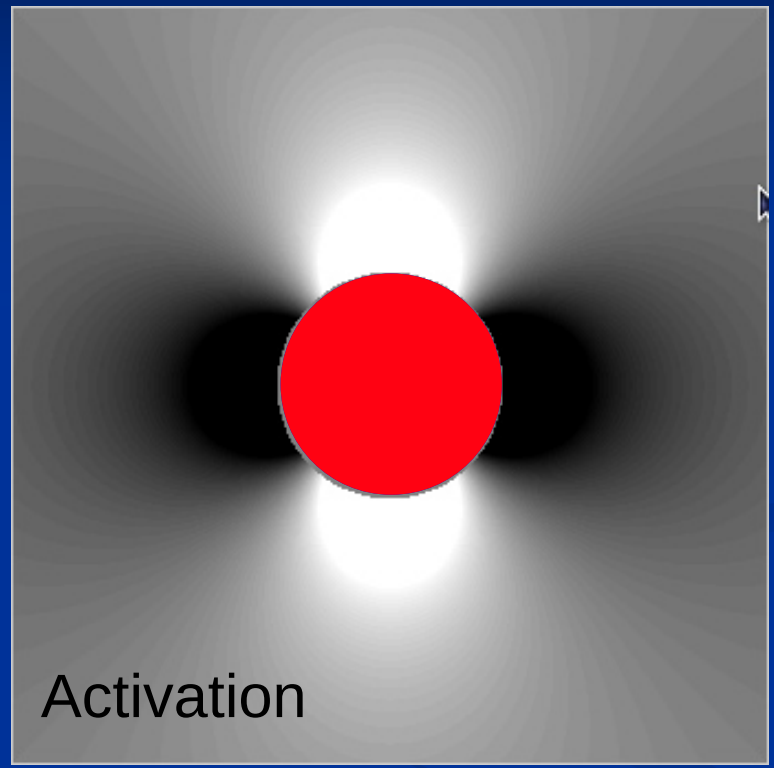

The magnetic field perturbation is substantially attenuated, since there is less paramagnetic dHb

Physics of BOLD

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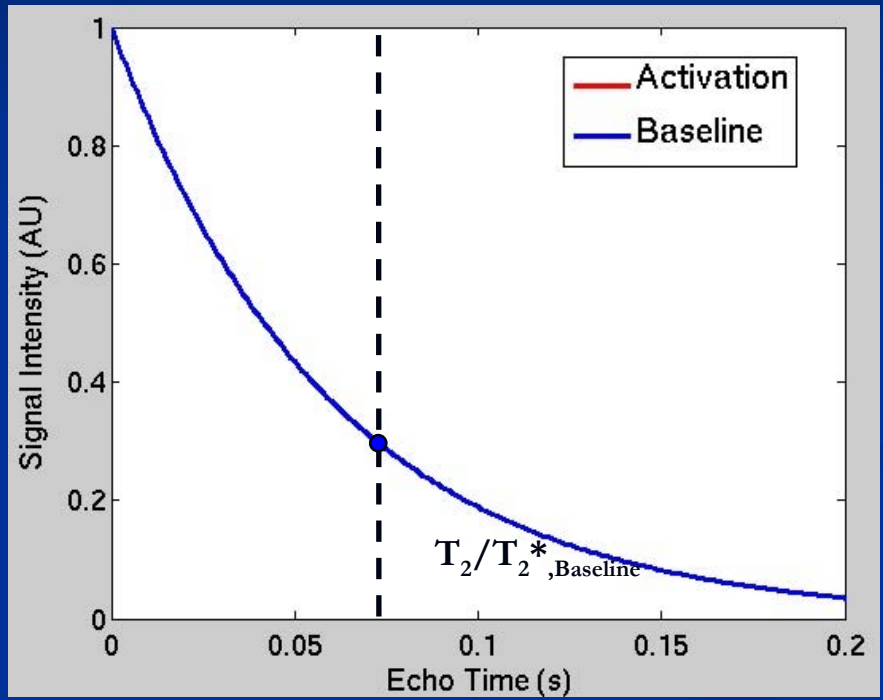

BOLD fMRI involves acquiring data at a certain echo time (TE). At baseline the strong magnetic field perturbations lead to decreased T_2/T_2^*

Physics of BOLD

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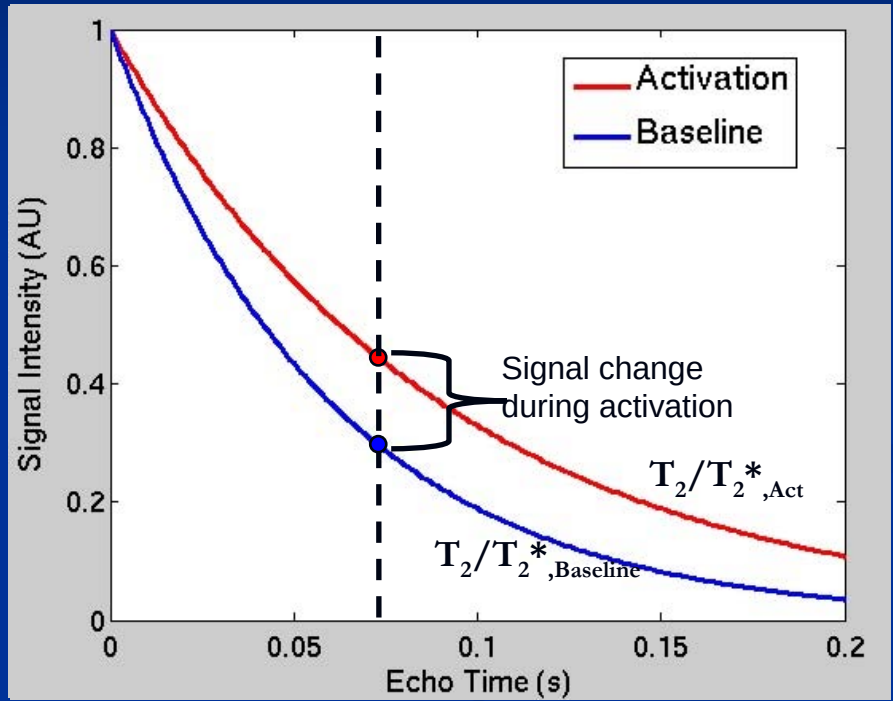

During activation, T_2/T_2^* *increases* due to less dHb. By choosing an optimal TE, this change can be exploited, leading to increased signal

Physics of BOLD

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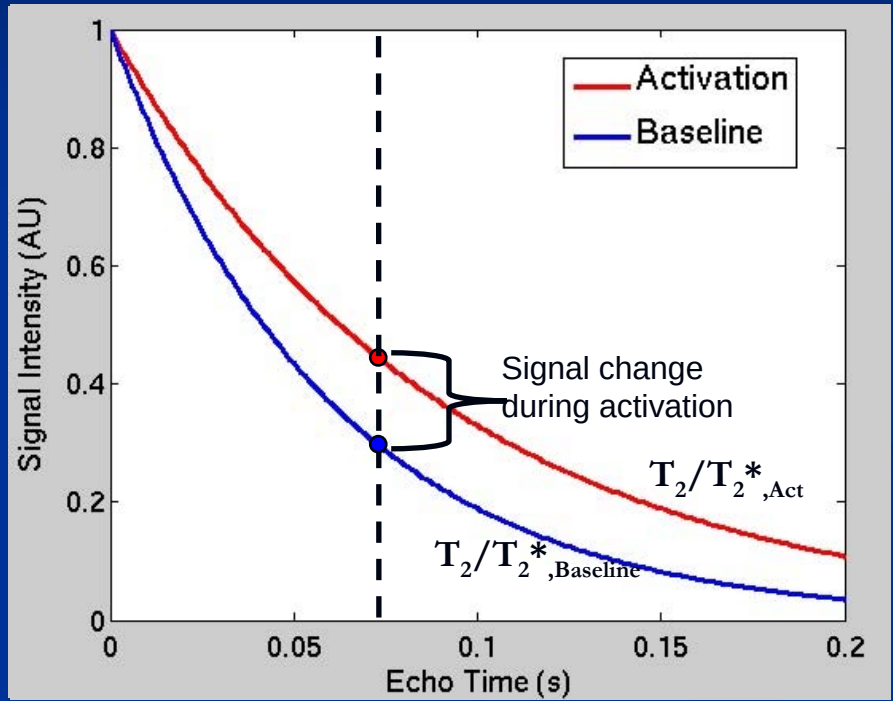


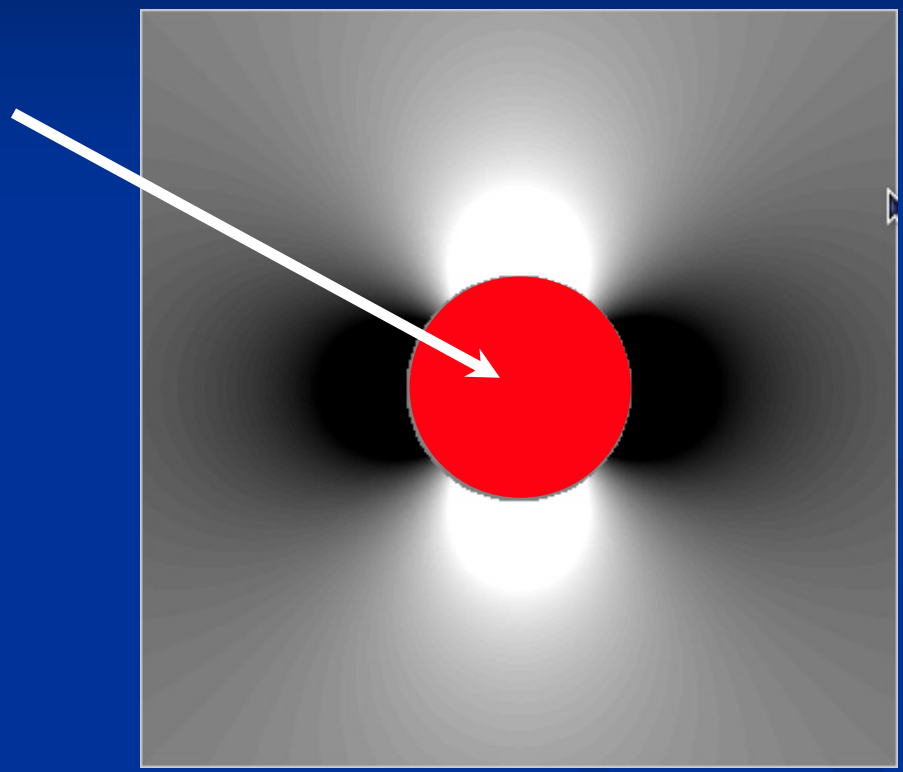
But from where do these changes originate??

Spatial Origin of BOLD

- MRI signal predominantly comes from protons in water
- BOLD signal changes arises from magnetic field perturbations caused by dHb in red blood cells
- Magnetic field gradients are created around:
  - Individual RBCs containing dHb
  - Blood vessels carrying deoxygenated RBC's

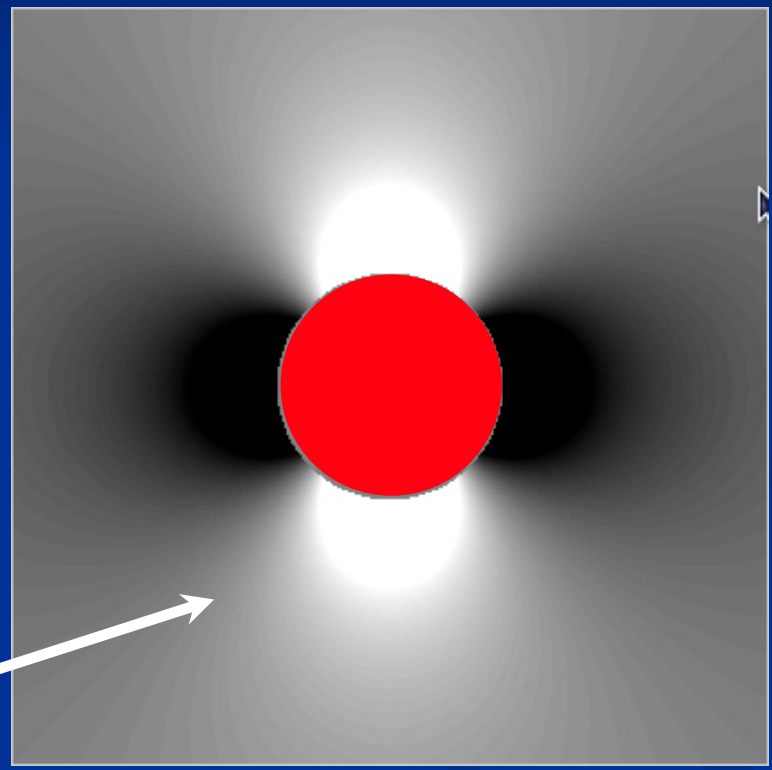
Spatial Origin of BOLD

- Water protons *within* vessels are affected by strong fields around RBCs, leading to an *intravascular* BOLD effect



Spatial Origin of BOLD

- Water protons *within* vessels are affected by strong fields around RBCs, leading to an *intravascular* BOLD effect
- Water protons *around* vessels (i.e. in *tissue*) are affected by field around vessel, leading to an *extravascular* BOLD effect



Spatial Origin of BOLD

See Fig. 1 in van Zijl, P. C. M., et al. “Quantitative assessment of blood flow, blood volume and blood oxygenation effects in functional magnetic resonance imaging.” *Nature Medicine* 4 (1998): 159 – 167. doi:10.1038/nm0298-159.

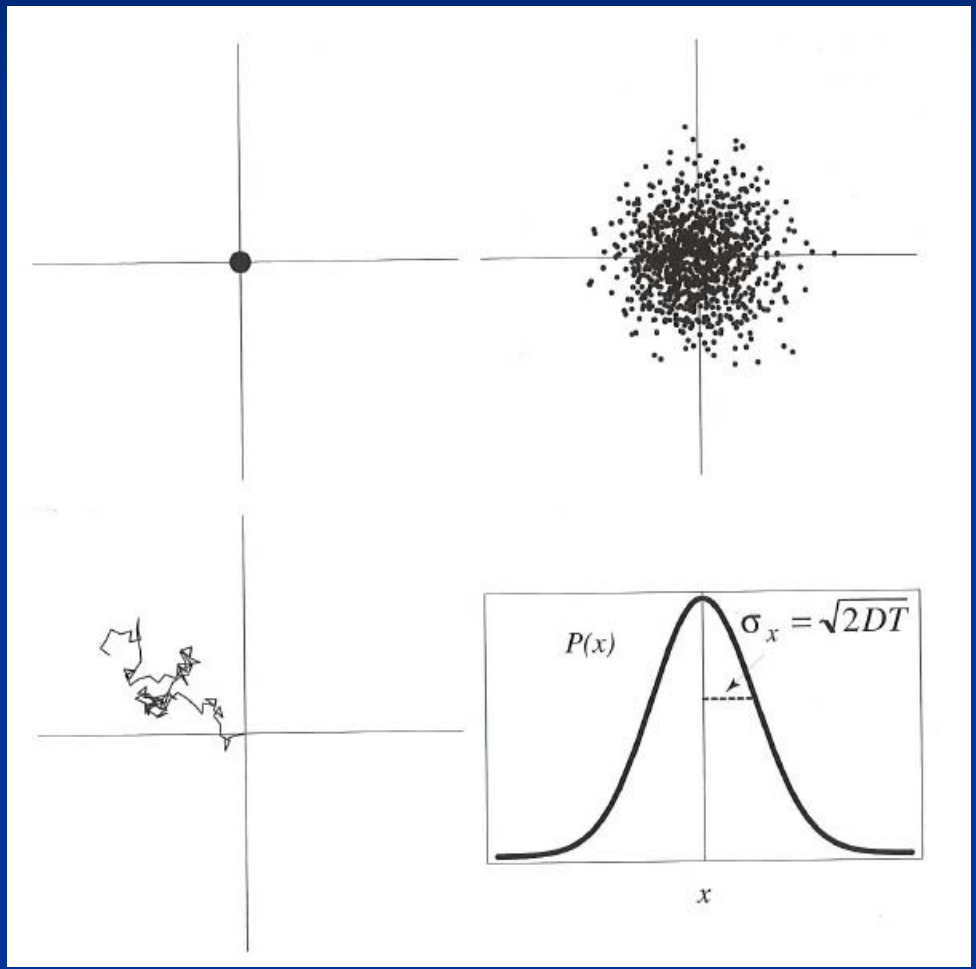
Extravascular BOLD effect

- Extravascular BOLD signal can be further subdivided into:
  - Effects around larg(er) vessels (late venules/ veins)
  - Effects around small microvessels (capillaries, early venules)
- ***Diffusion* heavily influences the degree of contribution**

Diffusion and fMRI

- Due to thermal energy water molecules constantly experience random displacements
- This process is called diffusion
- Since most of the signal in MRI comes from protons in water, diffusion plays critical role in MR signal modulation
- In fact, whole lecture devoted to diffusion imaging!

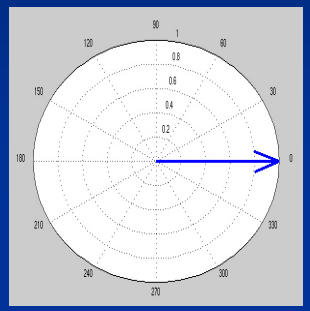
Basics of water diffusion



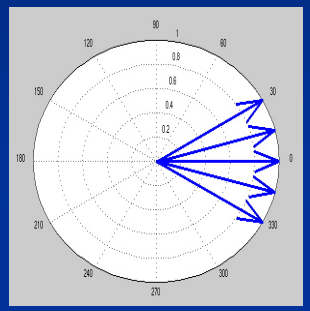
- Water molecules start from center
- Over time, these molecules spread out (*think ink*)
- Each molecule undergoes a *random walk*
- Mean of *all* molecule displacements is still zero
- Variance increases as a function of time

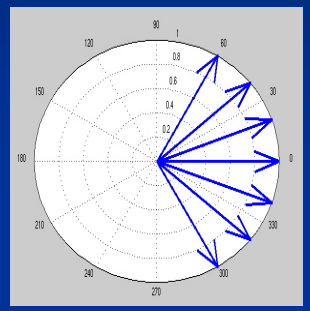
GRE/ SE Review

Gradient Echo: Dephasing, no refocus, ***T_2* decay***

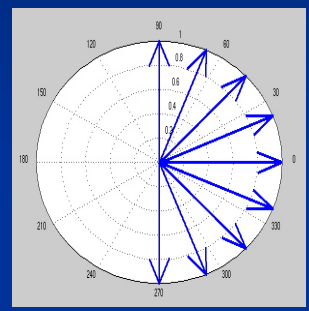


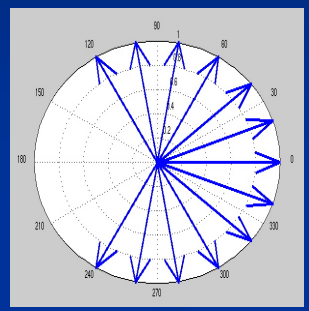
t = 0





t = TE/2

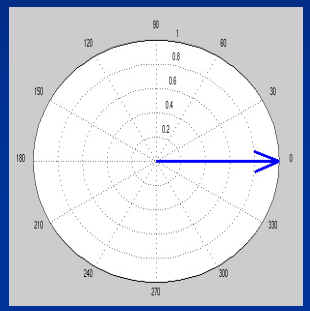




t = TE

GRE/ SE Review

Gradient Echo: Dephasing, no refocus, ***T_2* decay***



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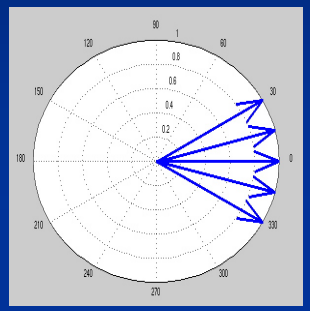
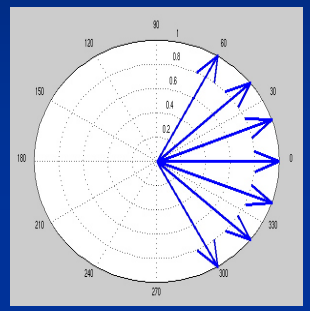
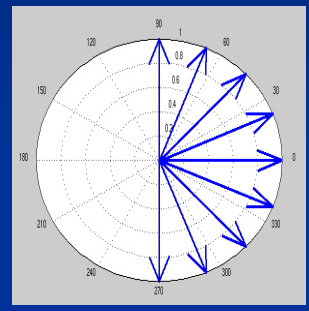
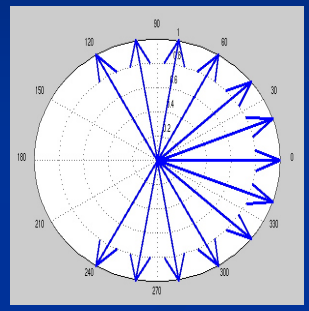




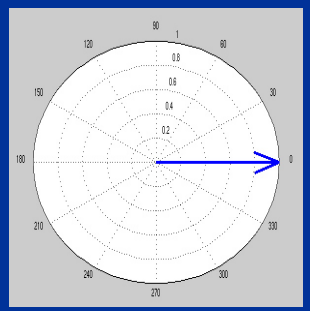
t = TE/2



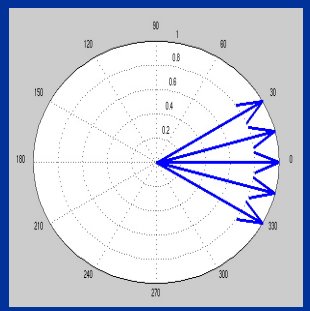


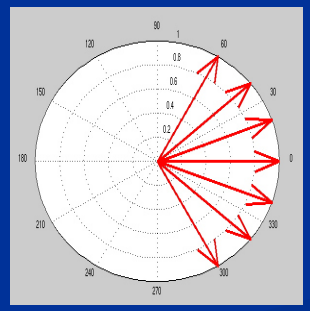
t = TE

Spin Echo: Dephasing, 180 pulse at t = TE/2, ***T_2 decay***

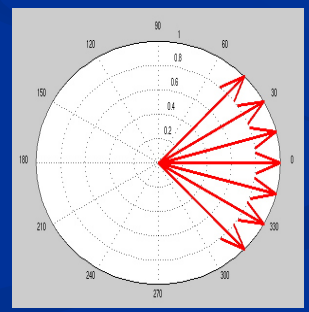


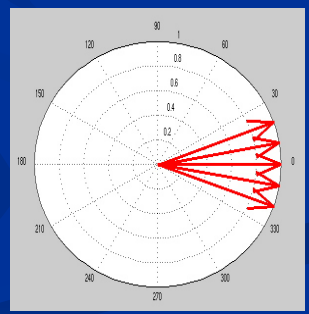
t = 0





t = TE/2, 180 pulse

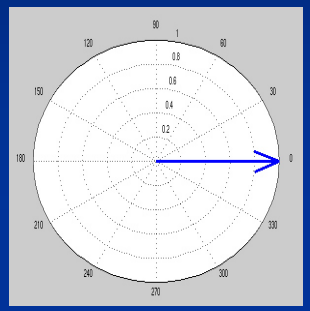




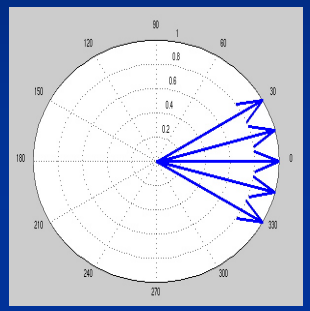
t = TE

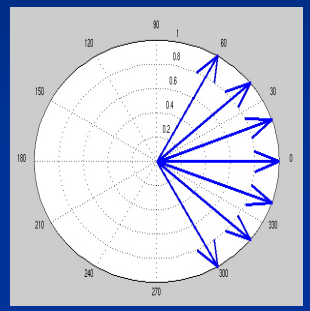
GRE/ SE Review

Gradient Echo: Dephasing, no refocus, ***T_2* decay***

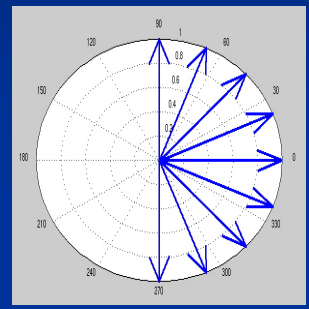


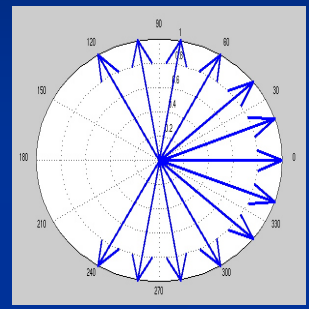
t = 0





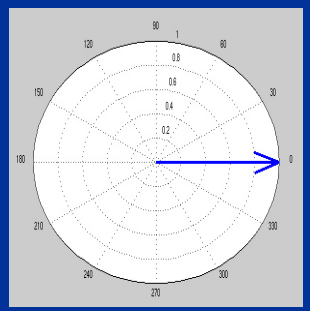
t = TE/2





t = TE

Spin Echo: Dephasing, 180 pulse at t = TE/2, ***T_2 decay***



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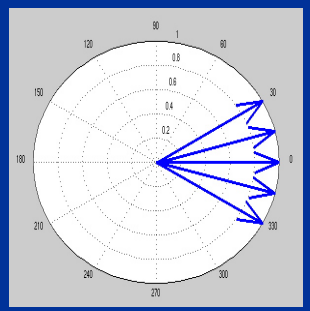
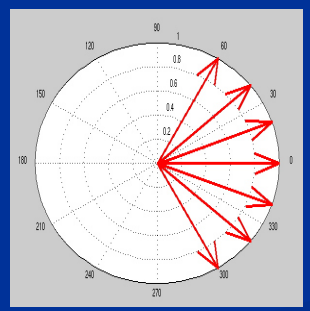
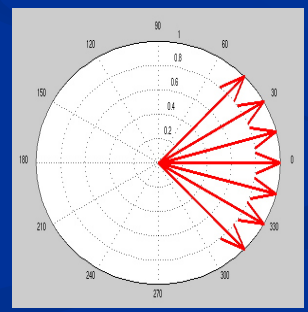
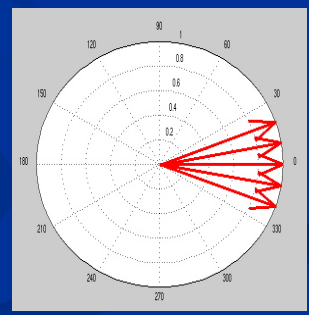




t = TE/2, 180 pulse





t = TE

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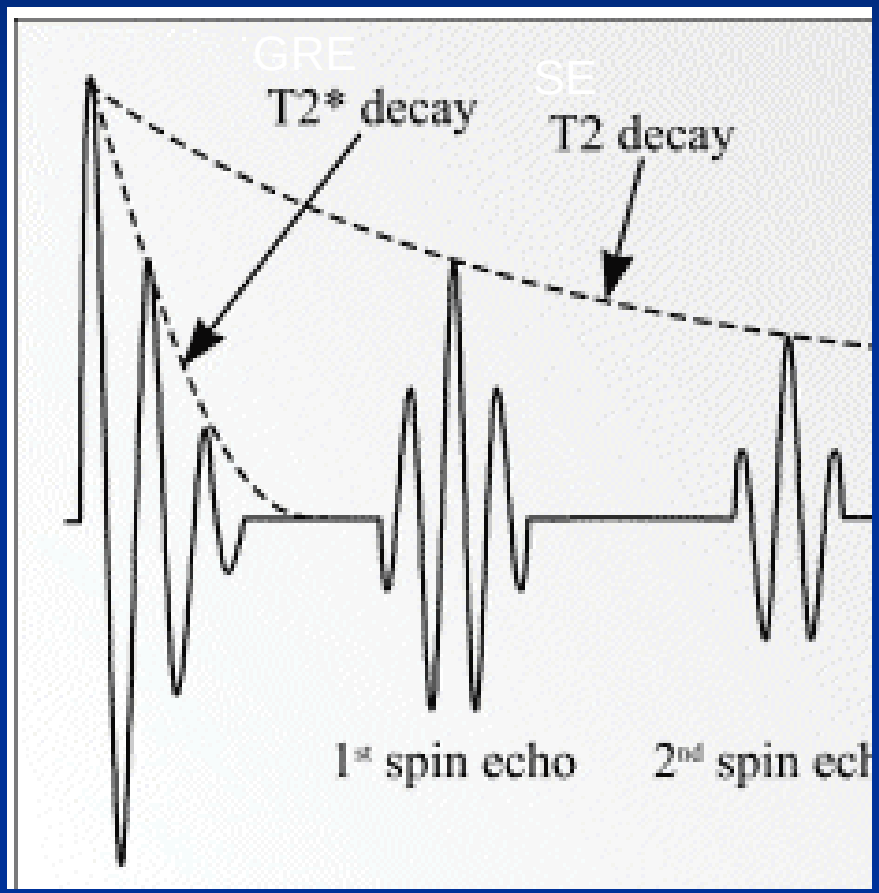
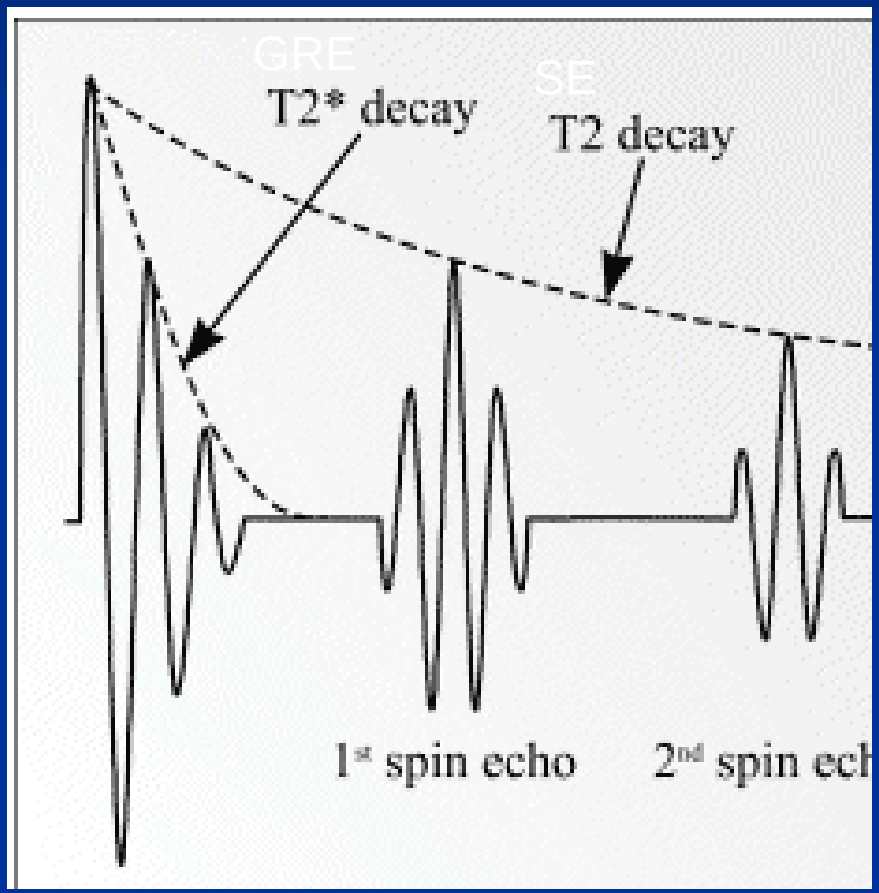
GRE/ SE Review



from *http://www.easymeasure.co.uk/principlesmri.aspx*

- Because of dephasing, GRE decay (T_2*) is considerable

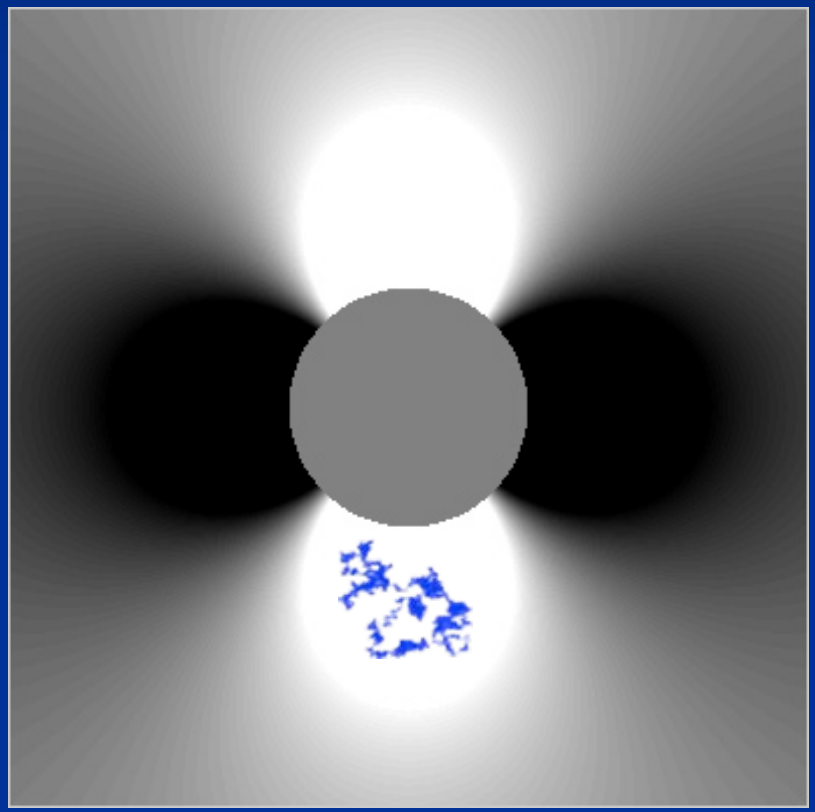
GRE/ SE Review



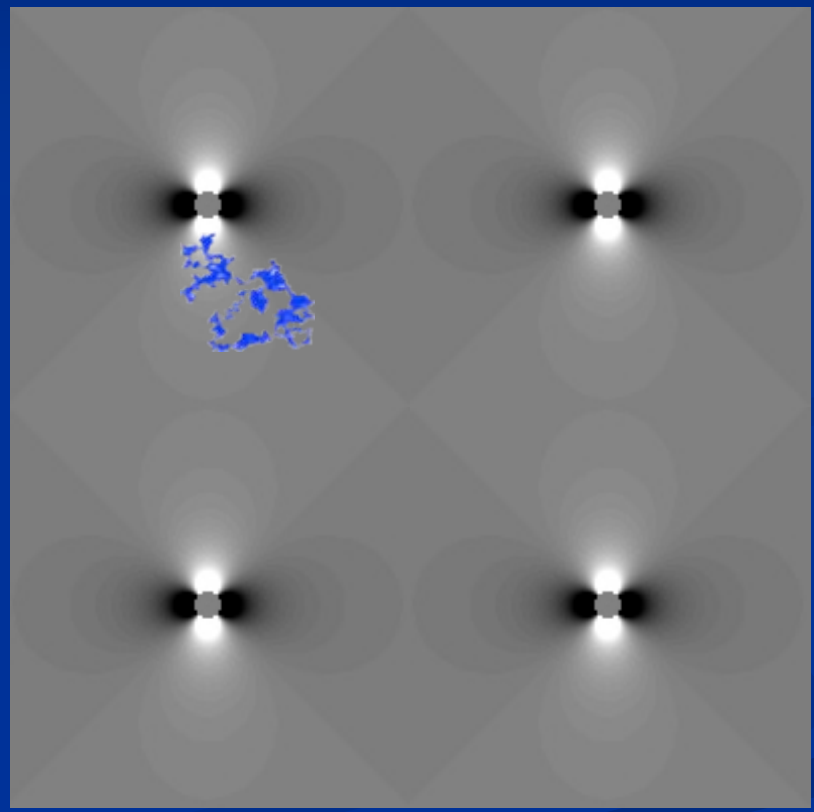
from *http://www.easymeasure.co.uk/principlesmri.aspx*

- Because of dephasing, GRE decay (T_2*) is considerable
- Because of SE refocusing, some signal is recovered and decays with a T_2 time constant

Diffusion around vessels and the MR signal



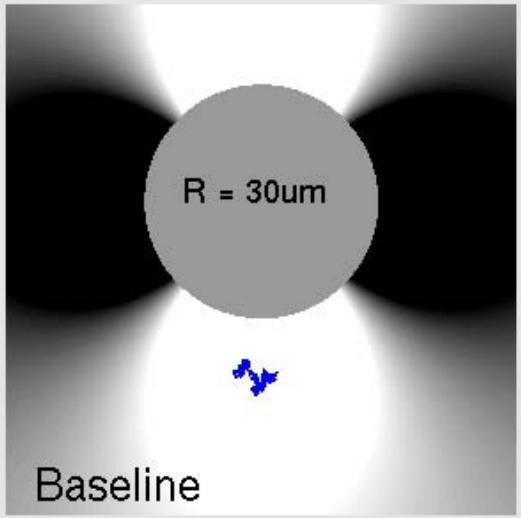
Large* Vessel (30 um)

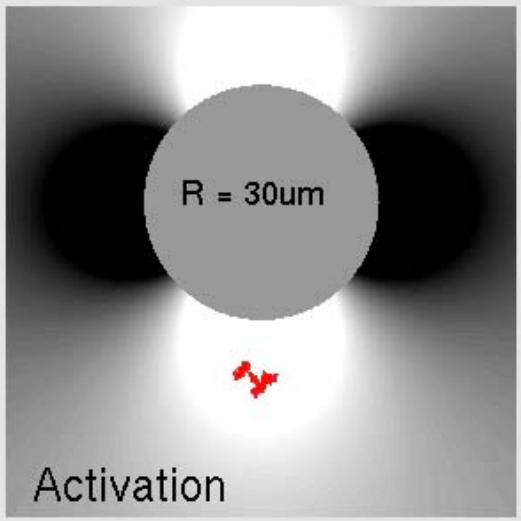


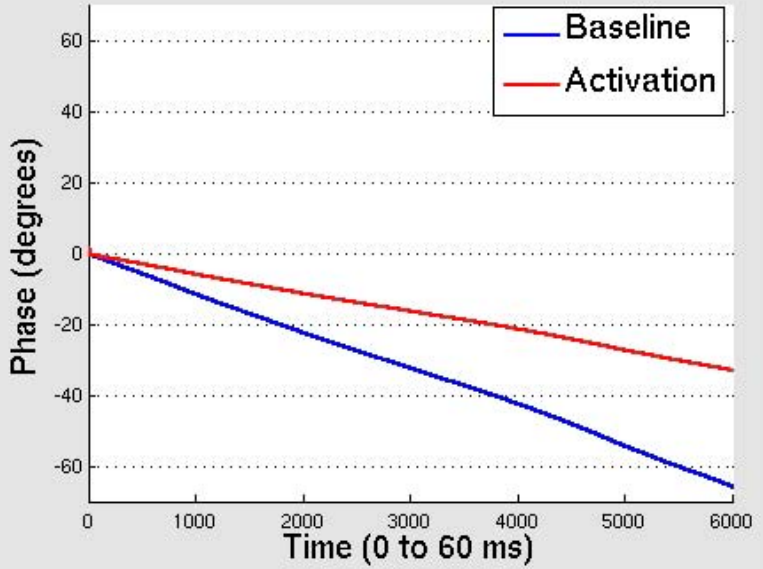
Small Vessels (3 um)

**** Keep in mind "large" is a relative term here! 30 um is still quite small!!***

Diffusion around large vessels: GRE

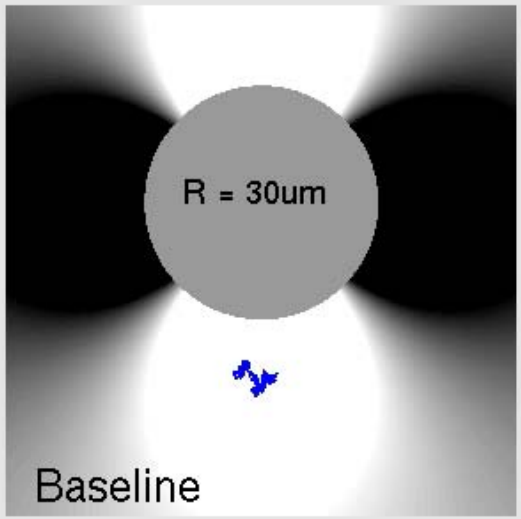


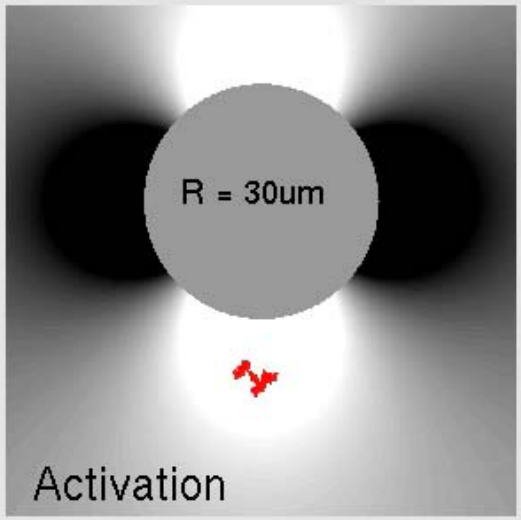


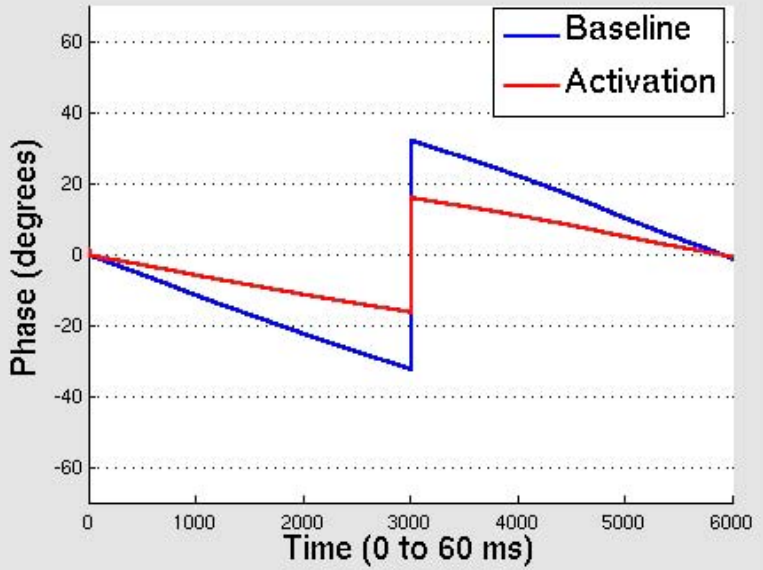


- Diffusion is small compared to venule or vein
- Water molecule therefore feels a relatively large, constant field
- Leads to *linear* phase accrual
- Magnitude of dephasing is large
- **Large change in GRE-BOLD via T_2*!**

Diffusion around large vessels: SE

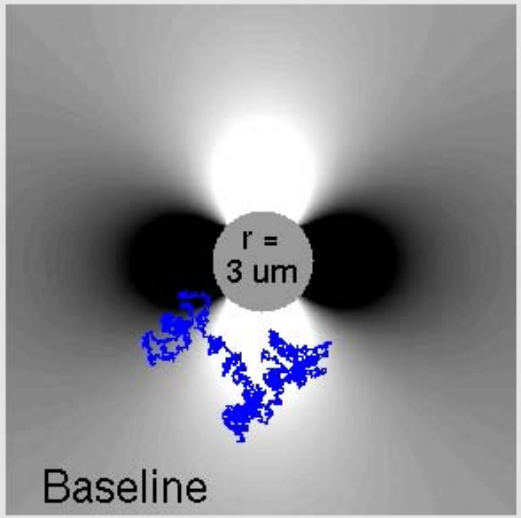


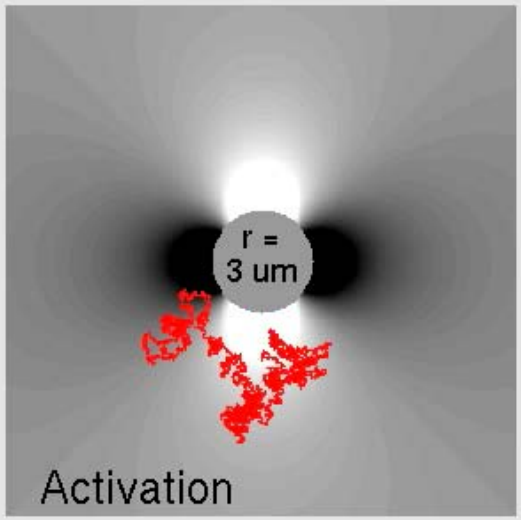


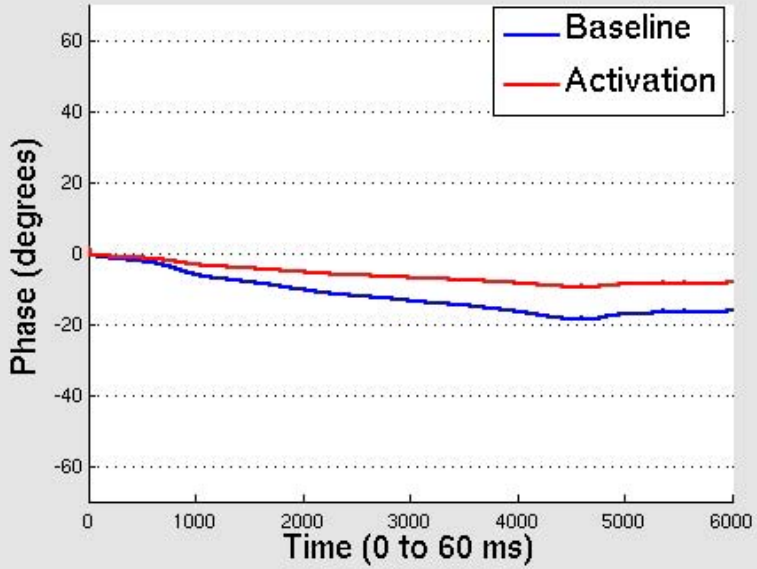


- In a spin echo sequence, a 180-pulse *inverts* spins to *refocus* linear phase accrual
- Dephasing is refocused; there is little change in T_2 during activation!!
- **There will be almost zero signal change around large vessels in SE-BOLD!**

Diffusion around small vessels: GRE

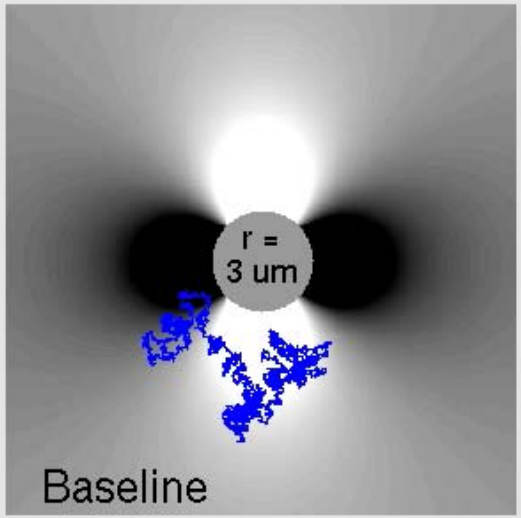


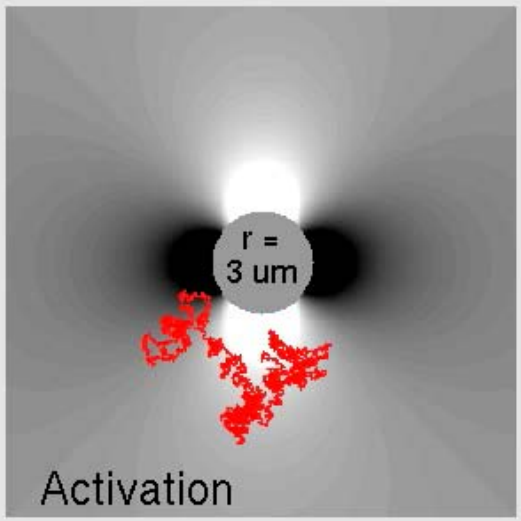


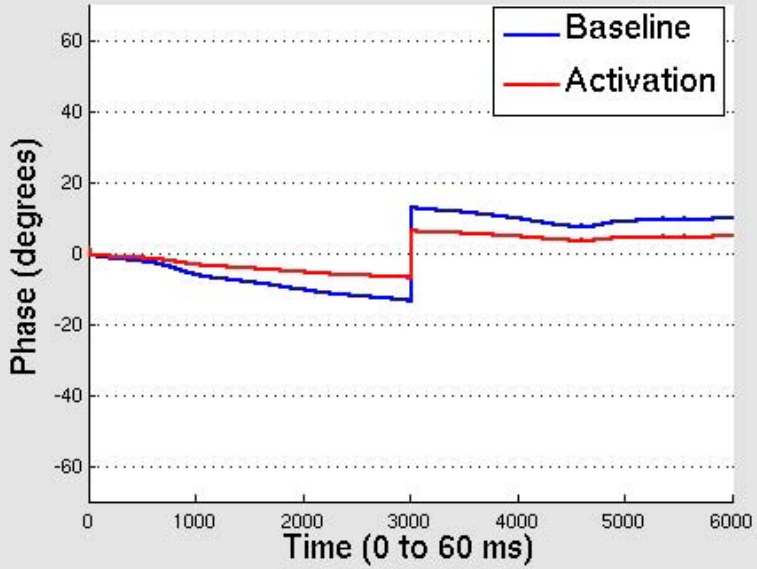


- Diffusion distance is larger or of comparable size to vessel
- Water molecules experience a *range* of field offsets
- The net phase experienced by a water molecule diffusing will reflect the average of these fields
- *This reduces the phase dispersion of all diffusing spins*
- The phase difference between activation and baseline is smaller than the large vessel situation
- **This results in a modest change in GRE-BOLD via T_2* effect**

Diffusion around small vessels: SE







- Because of diffusion through a ***range*** of fields, a water molecule will see a ***different*** set of phase offsets in **first** and **second half** of echo time
- Phase offsets acquired during the first half will thus ***not*** be completely reversed by a spin echo
- There ends up being a net phase at TE, and a phase difference between the activated and inactivated state
- ***Activation changes T_2, resulting in a modest contribution to the total SE-BOLD signal***

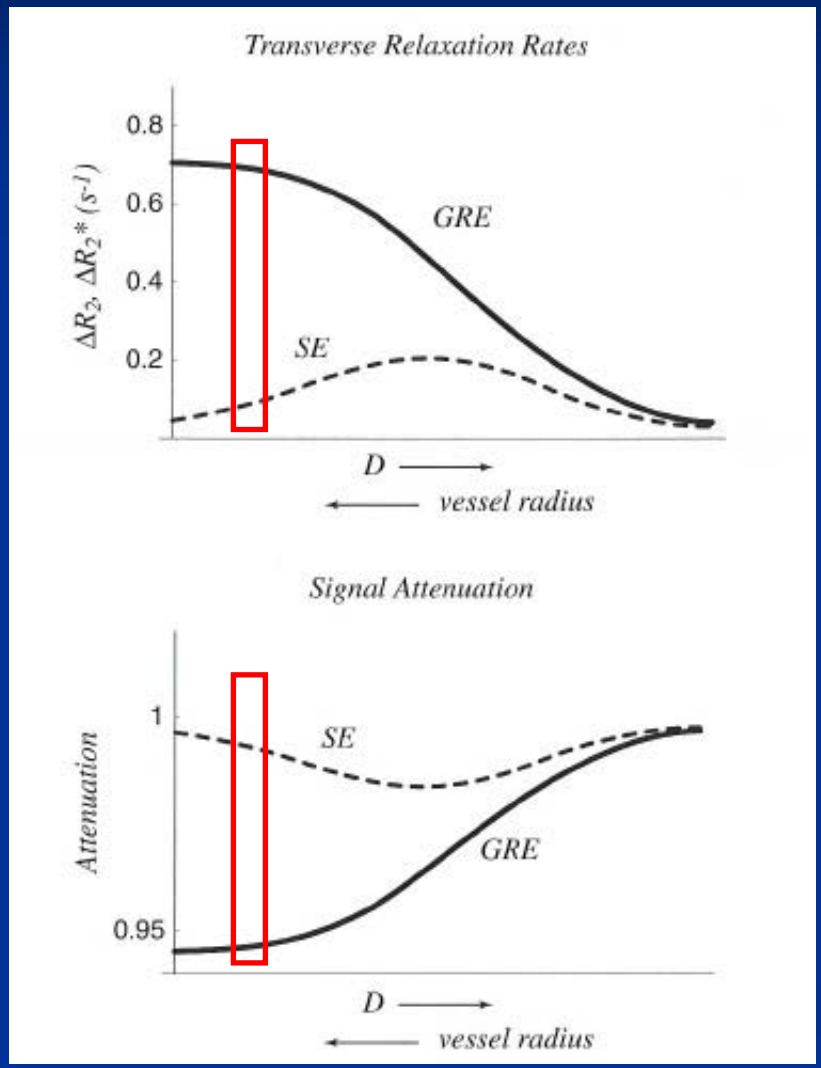
Extravascular Effect Summary

- Around larger vessels
- Includes late venules and veins
- Diffusion size is much smaller than vessel diameter
- Water molecules feel large, constant field, leading to *static dephasing*
- Produces **large** T_2* change and GRE-BOLD effect
- Static dephasing effects can be refocused via SE; T_2 change is **negligible**

Around smaller vessels

- Includes capillaries, early venules
- Diffusion size is on the order or slightly larger than vessel diameter
- Water molecules feel small, varying field, leading to *dynamic dephasing*
- Produces **modest** T_2* change and GRE-BOLD effect
- Dynamic dephasing effects *cannot* be refocused via SE; therefore T_2 effects are also **modest**

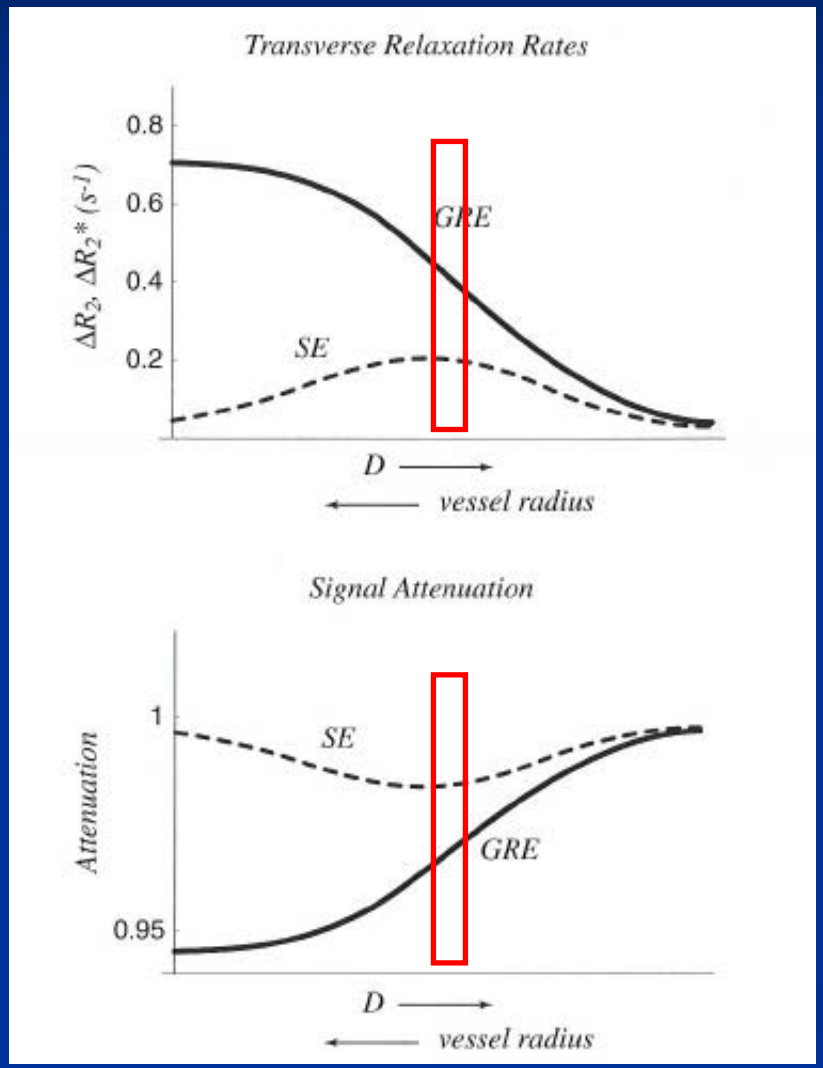
Extravascular Contribution to BOLD



- During activation there is a large T_2^* (solid) but small T_2 change (dotted) around large vessels

HST.583, Div Bolar, 2008

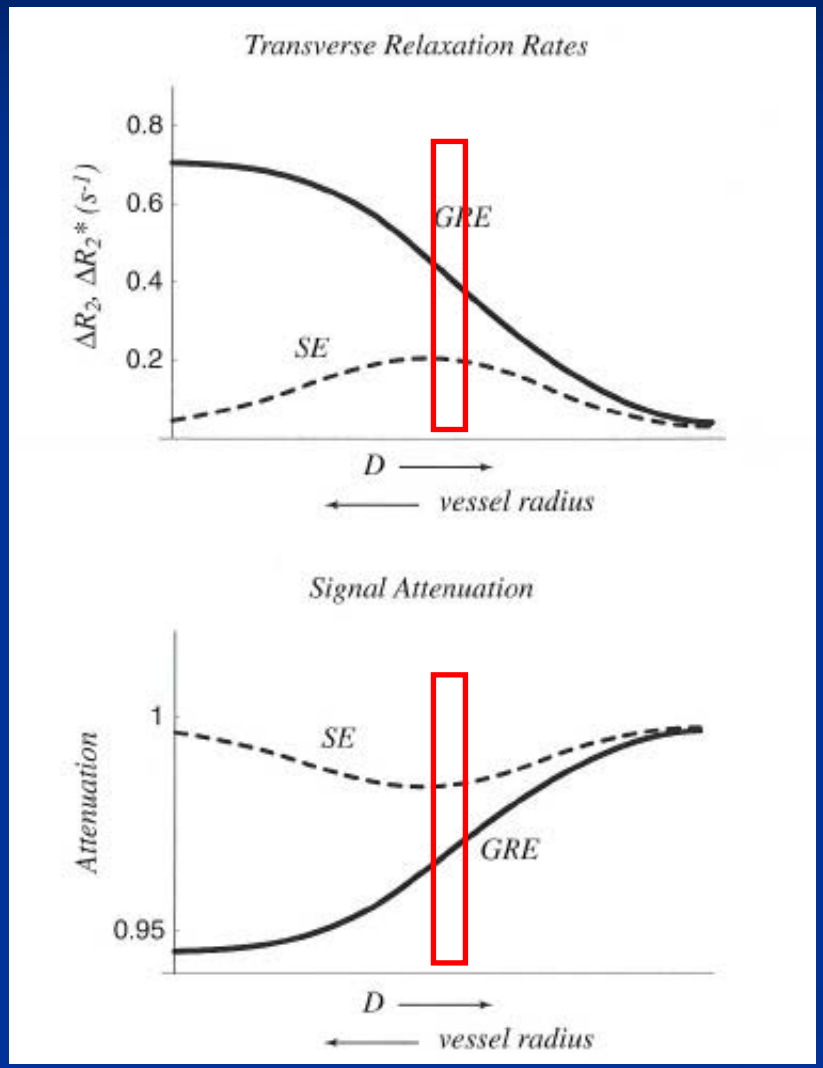
Extravascular Contribution to BOLD



- During activation there is a large T_2^* (solid) but small T_2 change (dotted) around large vessels
- During activation there is a modest T_2^* (solid) and a modest T_2 (dotted) change around small vessels

HST.583, Div Bolar, 2008

Extravascular Contribution to BOLD



- During activation there is a large T_2^* (solid) but small T_2 change (dotted) around large vessels
- During activation there is a modest T_2^* (solid) and a modest T_2 (dotted) change around small vessels
- GRE and SE allow us to target T_2^* or T_2

HST.583, Div Bolar, 2008

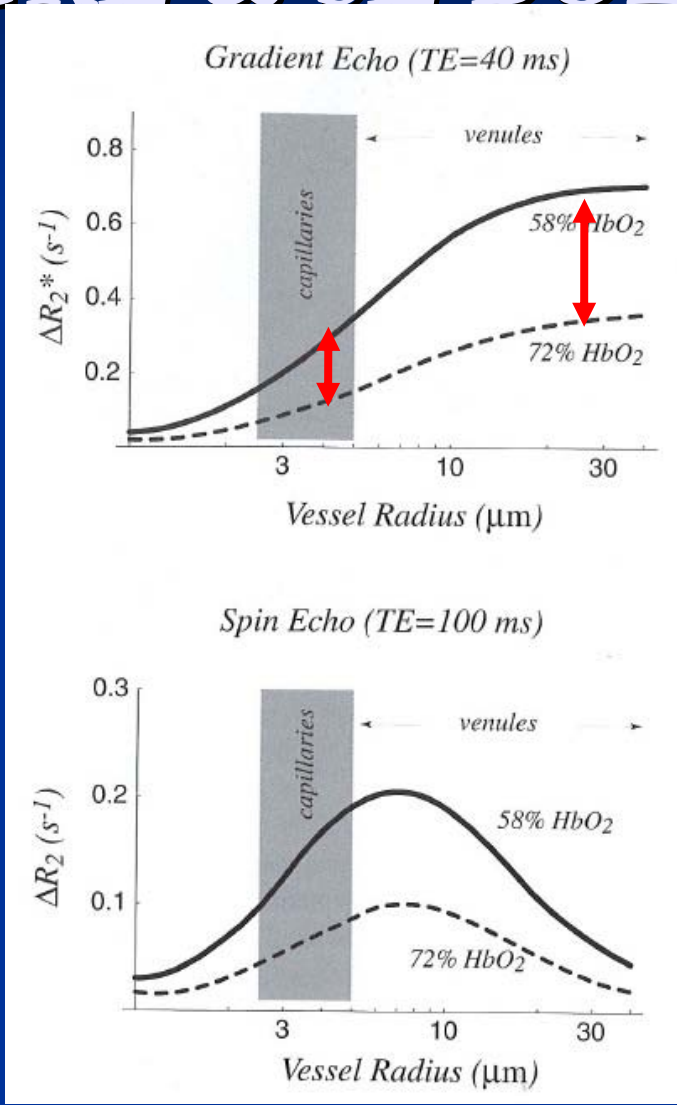
GE versus SE BOLD

- Gradient Echo BOLD
- Contrast based on changes in T_2*
- Water molecules around large vessels contribute substantially
- Water molecules around small vessels contribute modestly
- ***Based on extravascular contribution alone, GRE-BOLD is weighted towards late venules and veins during activation***

Spin Echo BOLD

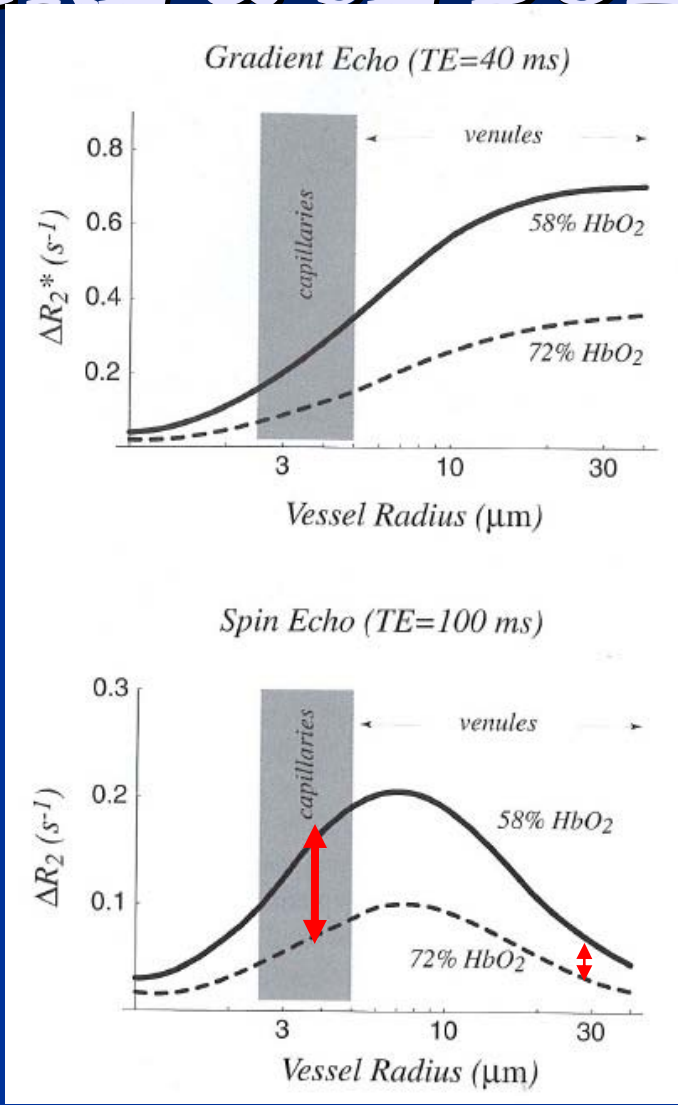
- Contrast based on changes in T_2
- Water molecules around large vessels have negligible contribution
- Water molecules around small vessels contribute modestly
- ***Based on extravascular contribution alone, SE-BOLD is weighted towards capillaries, early venules during activation***

Extrvascular Effects: GRE & SE BOLD



- GRE sensitizes us to T_2* changes and thus weights us to larger vessels (although there is small vessel contribution)

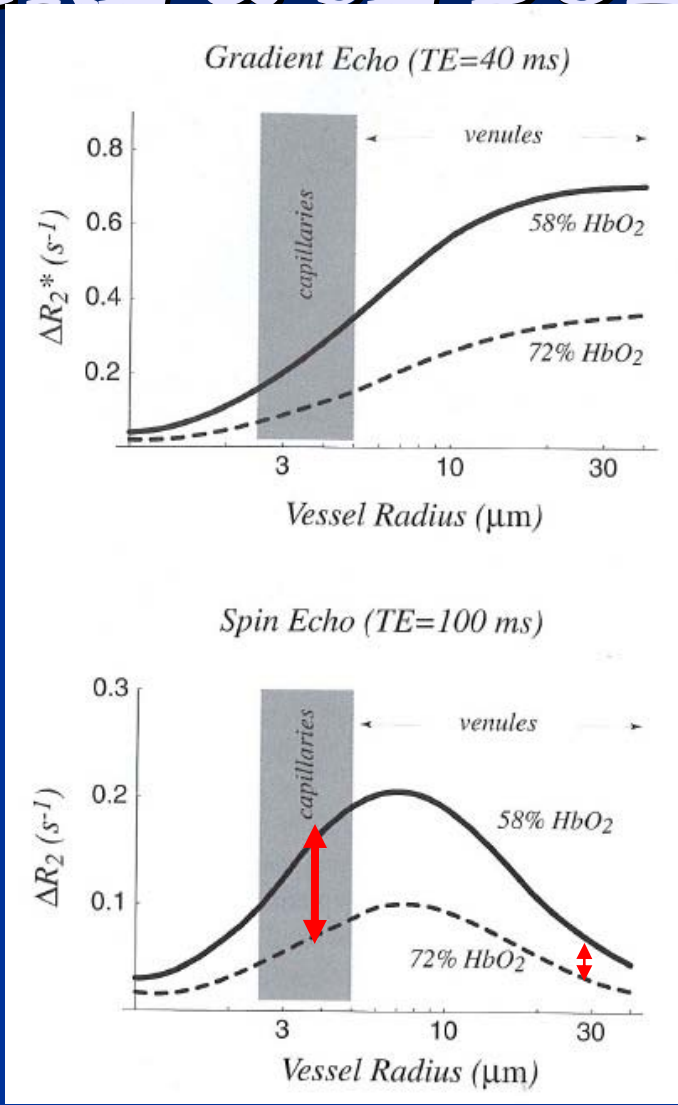
Extrvascular Effects: GRE & SE BOLD



- GRE sensitizes us to T_2* changes and thus weights us to larger vessels (although there is small vessel contribution)
- SE sensitizes us to T_2 changes and thus weights us to smaller microvessels (capillaries, early venules)

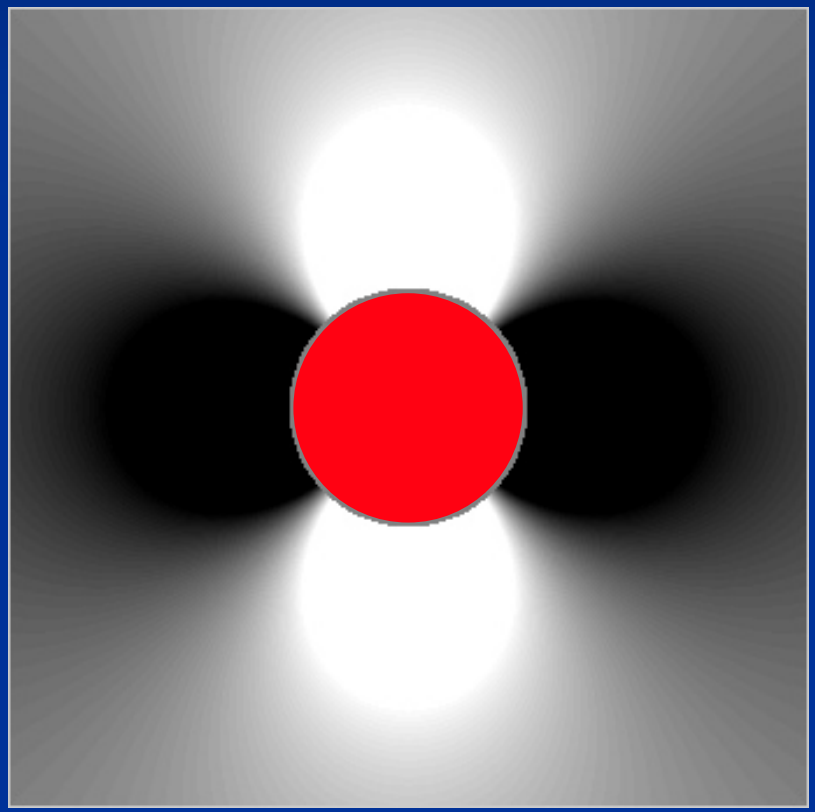
HST.583, Div Bolar, 2008

Extrvascular Effects: GRE & SE BOLD

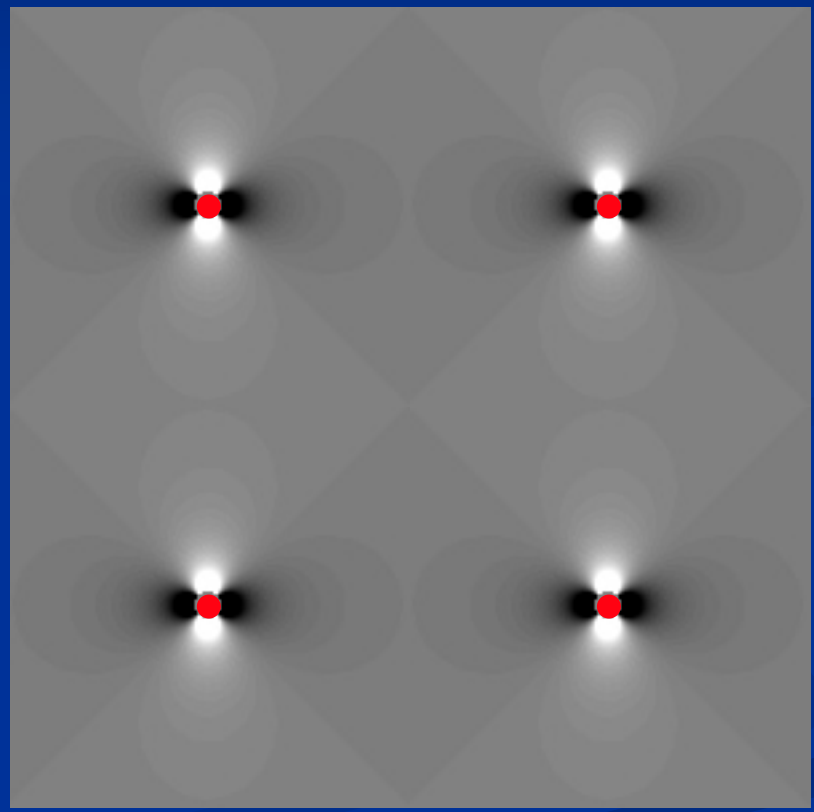


- GRE sensitizes us to T_2* changes and thus weights us to larger vessels (although there is small vessel contribution)
- SE sensitizes us to T_2 changes and thus weights us to smaller microvessels (capillaries, early venules)
- ***Okay, but now what about intravascular contributions??***

Intravascular contribution



Large Vessel (30 um)

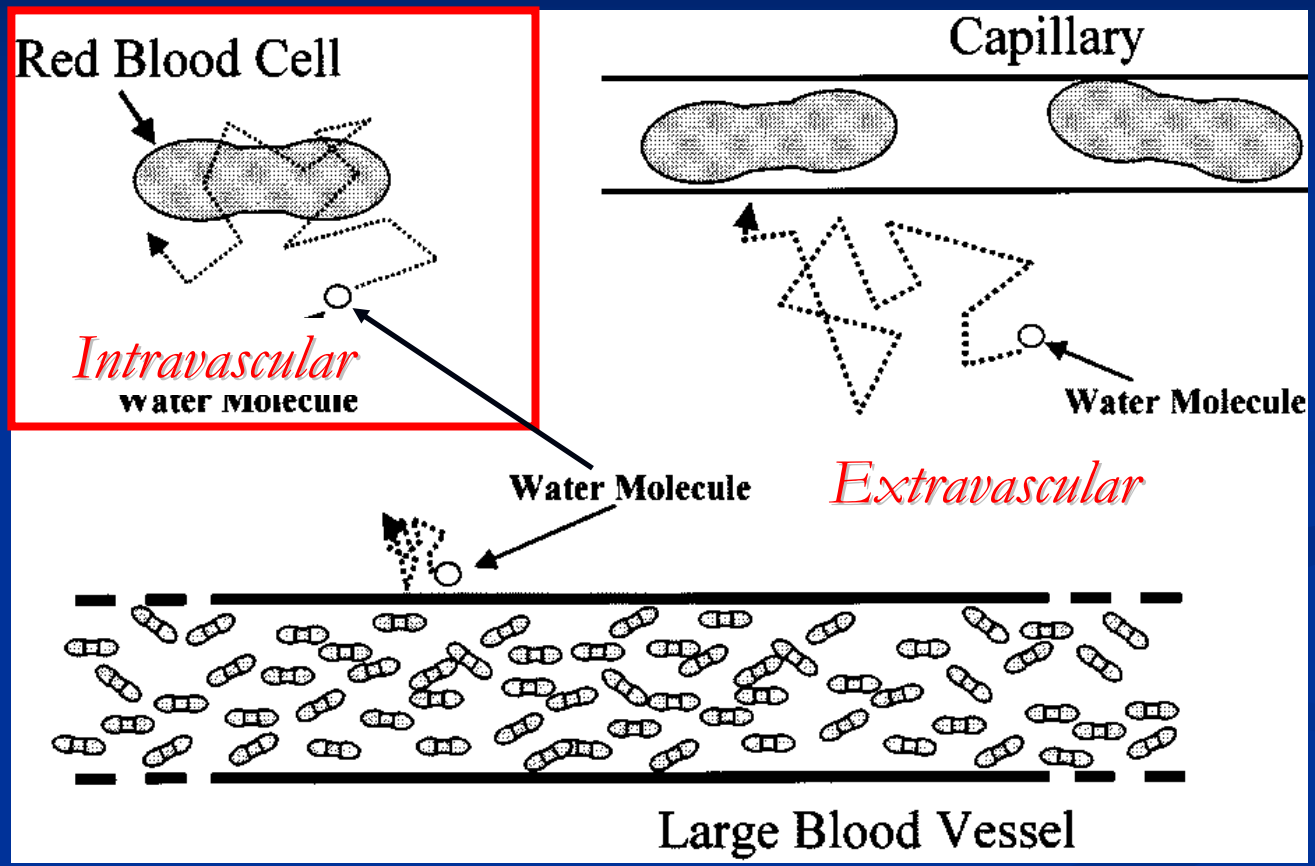


Small Vessels (3 um)

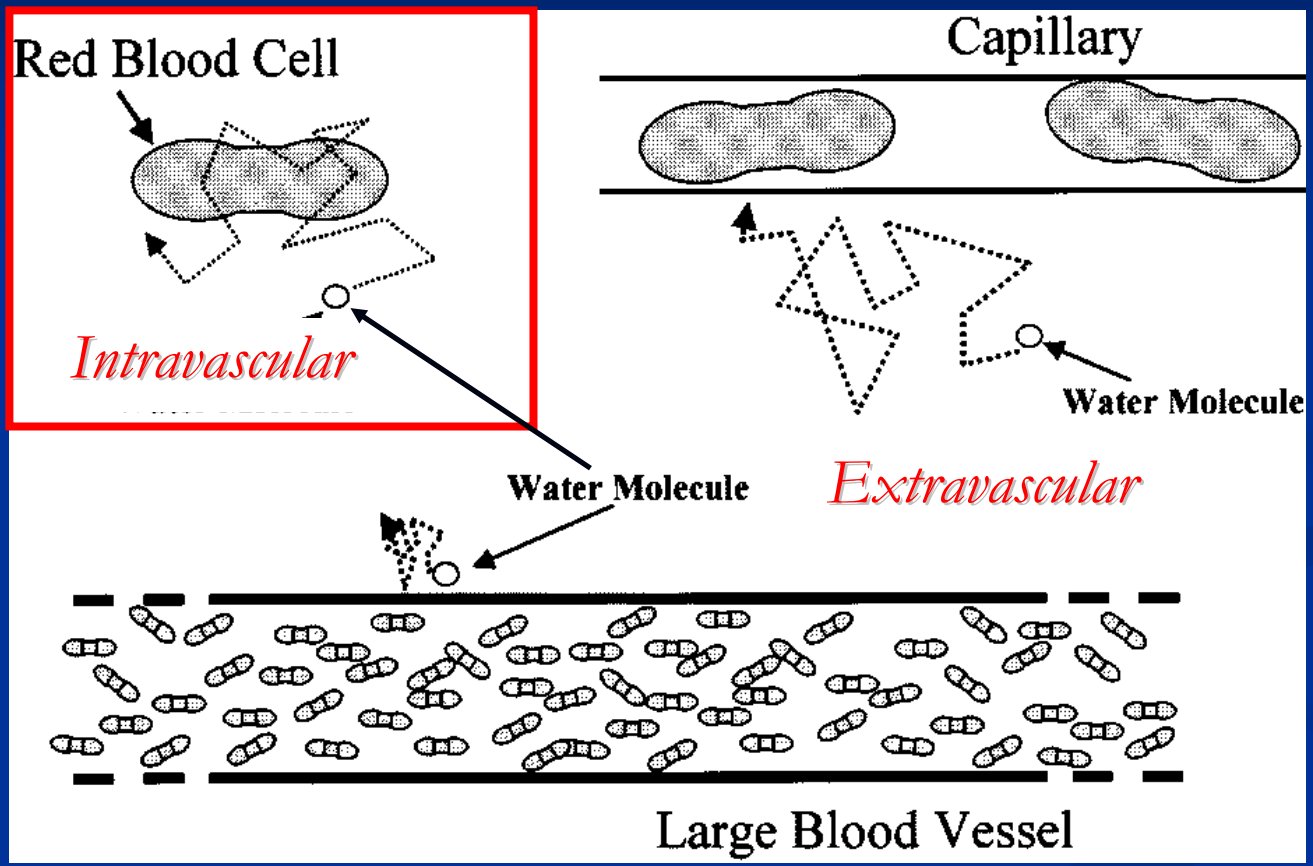
Intravascular Effects

- Despite small intravascular volume, intravascular signal contribution is *large*
- This is due to large gradient fields around RBCs containing dHb.
- T_2/T_2^* of *blood itself* changes during activation
- Intravascular signal contribution is comparable to extravascular contribution, despite the small volume fraction

Intravascular & Extravascular



Intravascular & Extravascular



- *So is intravascular dephasing static or dynamic??*

GE versus SE BOLD

- Gradient Echo BOLD
- Contrast based on changes in T2*
- Water molecules around large vessels contribute substantially
- Water molecules around small vessels contribute modestly
- ***Intravascular water molecules contribute substantially!***

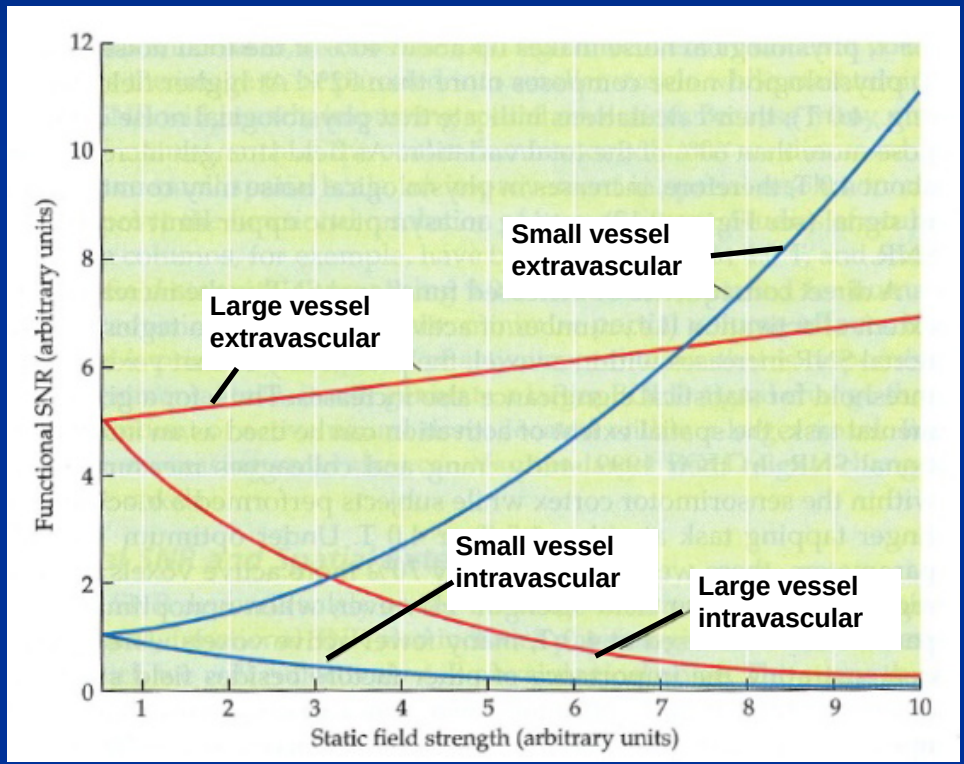
Spin Echo BOLD

- Contrast based on changes in T2
- Water molecules around large vessels have negligible contribution
- Water molecules around small vessels contribute modestly
- ***Intravascular water molecules contribute substantially!***
- *Dynamic dephasing effects cannot be refocused!*

Spatial specificity to neuronal activity?

- Small microvessels (capillaries, early venules) are more likely to co-localize with neuronal activity
- Signal changes around larger vessels (late venules, veins) may be artifactual; i.e. may be well downstream of true neuronal activity
- So-called ***"Brain versus Vein"*** problem of BOLD imaging
- Possible ways to reduce large vessel contribution?

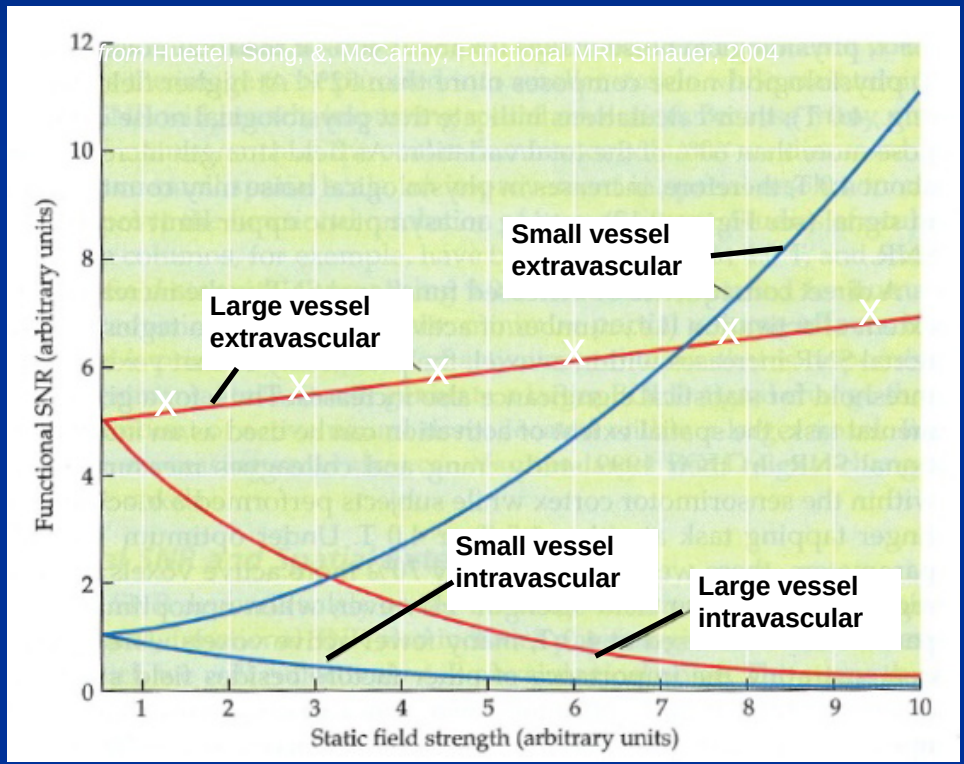
Spatial specificity of large and small vessels



Functional Sensitivity versus Field Strength

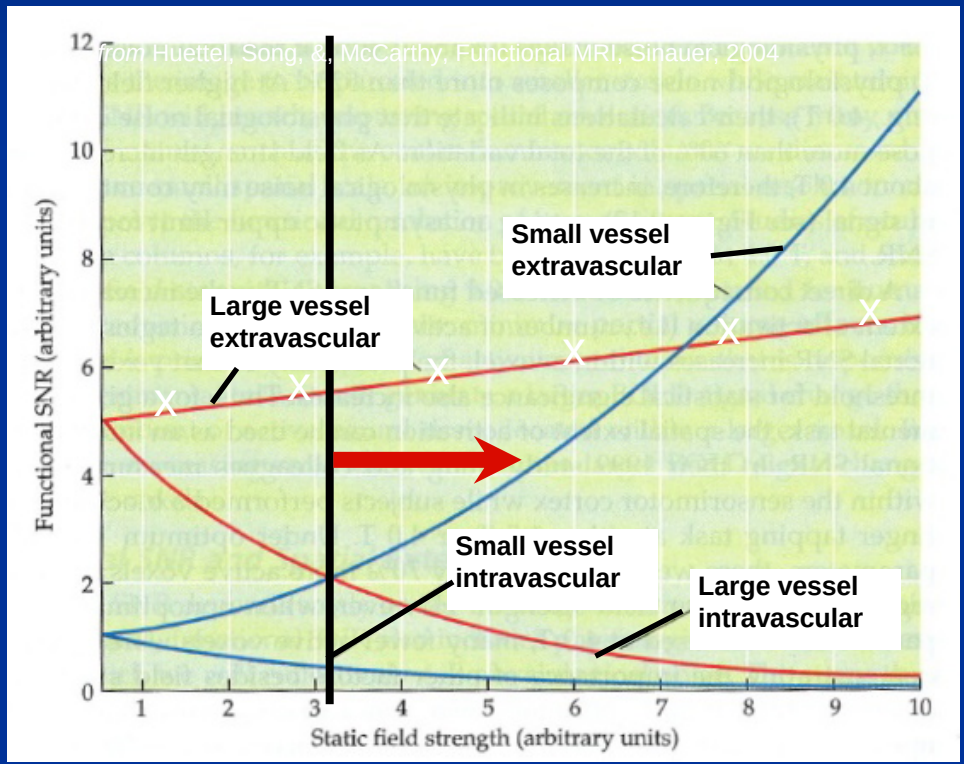
Spatial specificity of large and small vessels

- SE-BOLD can substantially reduce large vessel *extravascular* contribution



Functional Sensitivity versus Field Strength

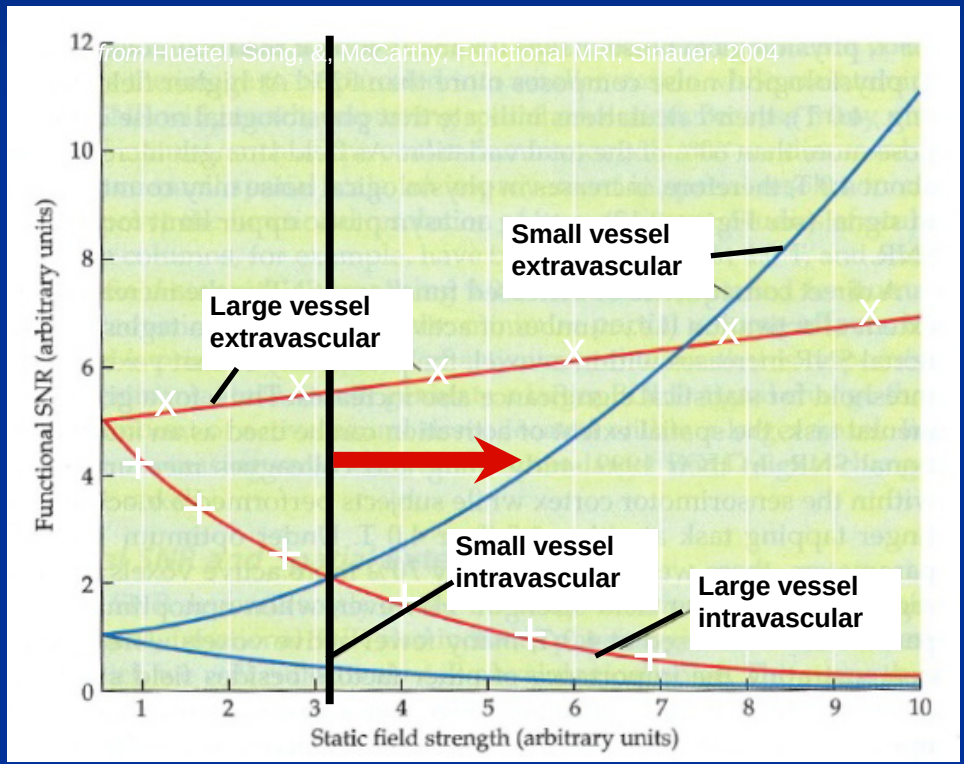
Spatial specificity of large and small vessels



Functional Sensitivity versus Field Strength

- SE-BOLD can substantially reduce large vessel *extravascular* contribution
- T_2/T_2^* of blood both decrease significantly with increasing field; can reduce large vessel *intravascular* contribution

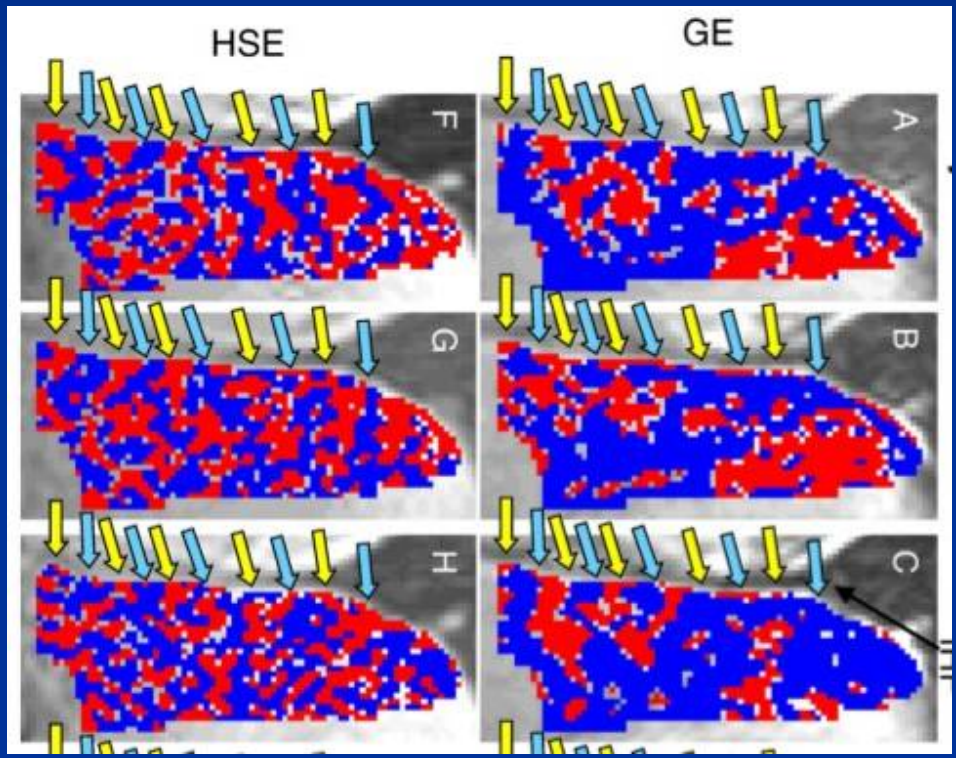
Spatial specificity of large and small vessels



Functional Sensitivity versus Field Strength

- SE-BOLD can substantially reduce large vessel *extravascular* contribution
- T_2/T_2^* of blood both decrease significantly with increasing field; can reduce large vessel *intravascular* contribution
- Can also employ modest diffusion weighting* to eliminate large vessel *intravascular* signal

Spatial specificity of large and small vessels



from Yacoub et. al., *NeuroImage* 37 no. 4 (2007): 1161-1177.

- SE-BOLD at 7T show robust detection of ocular dominance columns
- Superior to GE-BOLD, which was not able to resolve columns

Pulse sequences

- GRE-EPI (*EPI = echo planar imaging = fast*)
  - Most commonly used at 1.5T, 3.0T
  - Provides large signal changes; very sensitive to activation
  - Large vessel artifacts (*brain versus vein* problem)

Pulse sequences

- SE-EPI
  - Will attenuate large vessel extravascular signal, but at 1.5T/3.0T large vessel *intravascular* signal will become dominant
  - Lose SNR with SE due to refocusing and longer TE
  - ***May be ideal at 7T and above***
    - T_2/T_2^* blood shortens: intravascular effect will be substantially reduced
    - SNR increases linearly with field strength
  - Reduces distortions! If imaging frontal lobe, this may be worth considering

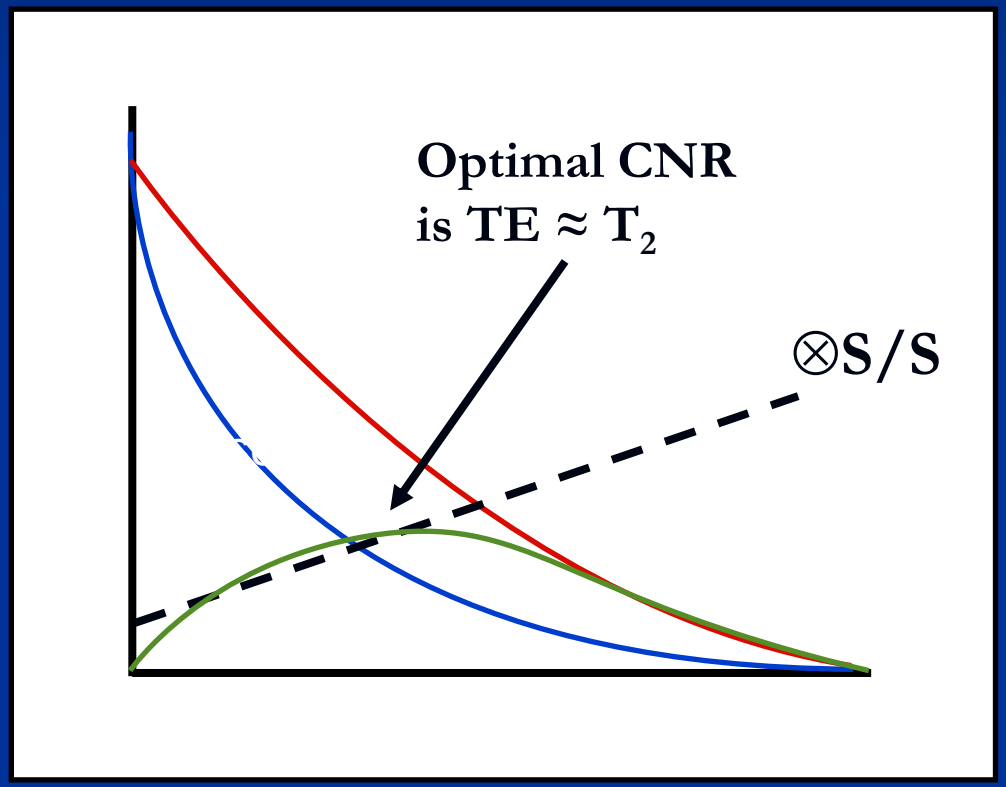
Pulse sequences

- Diffusion-weighted GRE-EPI
  - Will reduce large vessel intravascular effects, but will be prone to large vessel extravascular effects
- Diffusion-weighted SE-EPI
  - Will reduce large vessel intravascular and extravascular effects
  - Will lose considerable sensitivity; longer TE
  - May be possible at 1.5T/3.0T in targeting small vessel intravascular and extravascular effects

Pulse sequences

- Spiral Imaging
  - As fast (or faster) than EPI, but not prone to distortions
  - Non-trivial image reconstruction
- HASTE, FLASH, TSE, etc.
  - Used for very high resolution imaging, but speed is sacrificed
  - Typically not amenable to whole cortex/ brain coverage (~20-30 slices) with short TR
  - If specific region-of-interest eliminates necessity for whole brain acquisition, these approaches may be useful

BOLD Acquisition Parameters: TE choice



- Optimal CNR is a trade off between SNR and relative signal change (⊗S/S)
- This ends up being close to TE=T_2, but not exactly
- There are many other factors that come into play, e.g. distortion, motion, etc.

BOLD Acquisition Parameters: TE choice

- Optimal GE-BOLD TE:
  - 50 – 60 ms at 1.5T
  - 45 ms at 3.0T
    - Fera et. Al (2004), JMRI 19, 19-26
- Optimal SE-BOLD TE:
  - 74 ms at 3T
  - 45 ms at 7T
    - Schafer, MAGMA
- Both empirically determined; not set in stone!

Example Acquisition Parameters for BOLD

- *Sensitivity* increases with larger voxels
- *Specificity* decreases with larger voxels
  - There is a limit of course; specificity is ultimately limited by spatial coarseness of hemodynamic response
- Typical parameters at 3T:
  - 24 slices, 64x64 matrix, voxel size = 3.5x3.5x3.5 mm^3, BW = 2998 Hz, TE = 40 ms, TR = 2000 ms
- Take that with a grain of salt! It all depends on the question *you* want to ask! Will explore this more during Experimental Design Block

Part 2:
Beyond BOLD: Novel techniques for imaging activation

Why BOLD?

- Highest CNR and sensitivity compared to all other functional MRI techniques
- High temporal resolution (compared to speed of response)
- High spatial resolution possible, but not with standard approaches
- Feasible on nearly all MRI scanners (including clinical machines) without special hardware or software
- BOLD has been one of the largest success stories in the past decade!

Why *not* BOLD?

- As we've learned, there are fundamental spatial and temporal limitations in BOLD fMRI
- Temporal:
  - Considerable delay and dispersion after stimulus onset and cessation
  - Response lags stimulus and neuronal response by seconds
- Spatial:
  - BOLD not exclusively sensitive to microvasculature; difficult to separate larger vein effects (*brain versus vein*).
  - Fundamental limitation of hemodynamic response; *watering garden* analogy…

Why *not* BOLD?

- Remember that BOLD is a *relative* technique; moreover, it is not a real physiological parameter
- No direct knowledge of any absolute physiological parameters like CBF, CBV, $CMRO_2$, etc.
- BOLD relative change often depends on baseline state, which can vary from scan to scan, person to person
- Results can be highly variable
  - Same person, same task, different day: different results
  - Can lose statistical power over course of study

Novel approaches

- CBF: Arterial Spin Labeling
- Calibrated BOLD (relative $CMRO_2$)
- CBV: Vascular Space Occupancy

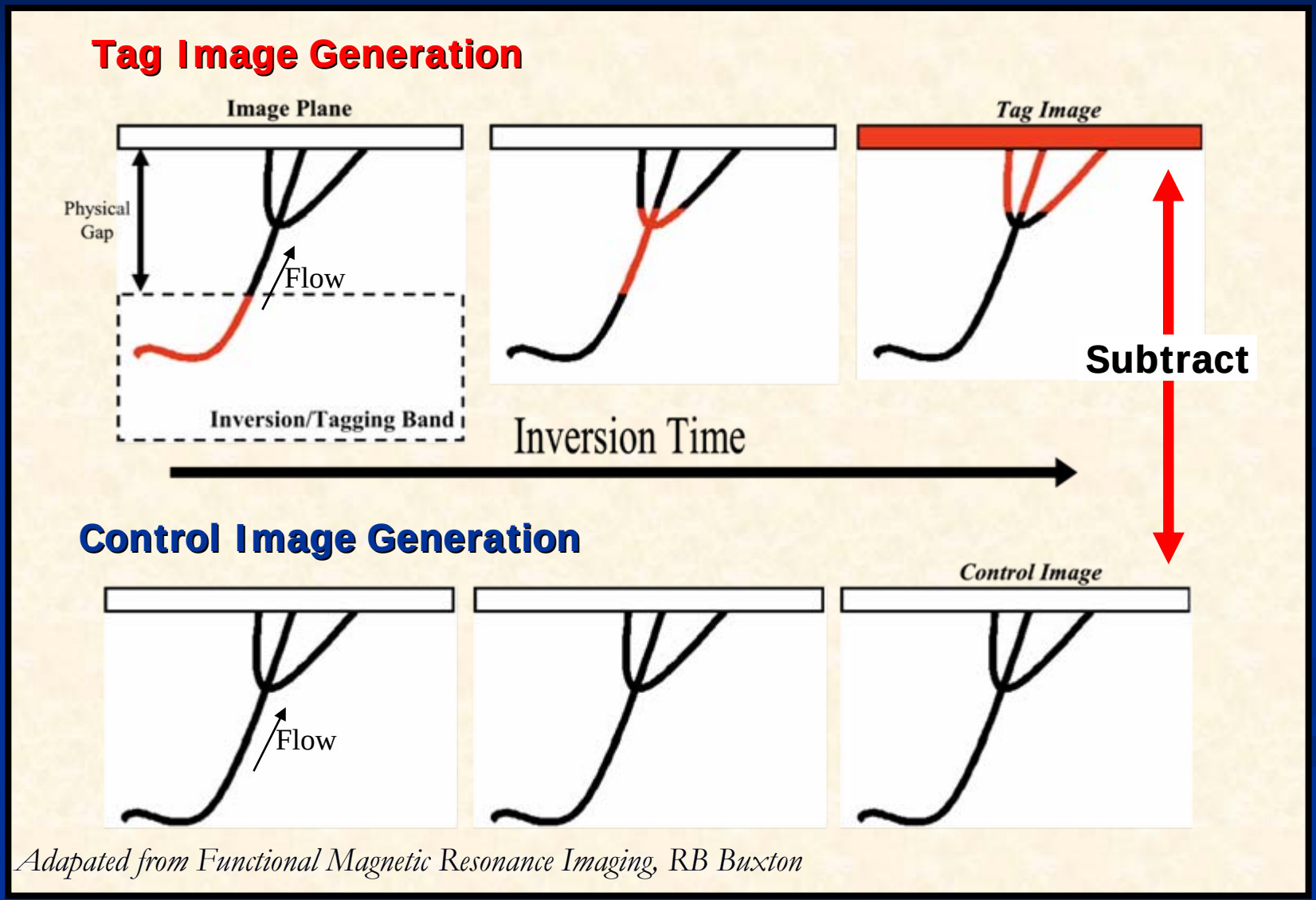
Arterial Spin Labeling (ASL)

- Non-contrast MR technique used to image CBF directly, i.e. tissue perfusion (microvascular flow)
- Involves creating a “magnetic” bolus by using RF energy to invert proton spins of water in arterial blood
- Inverted spins act as an endogenous contrast agent
- Imaging spins as they traverse the vascular tree generates perfusion maps
- *CBF quantification in absolute units, ml/ (mg-min)*

ASL: Advantages over BOLD

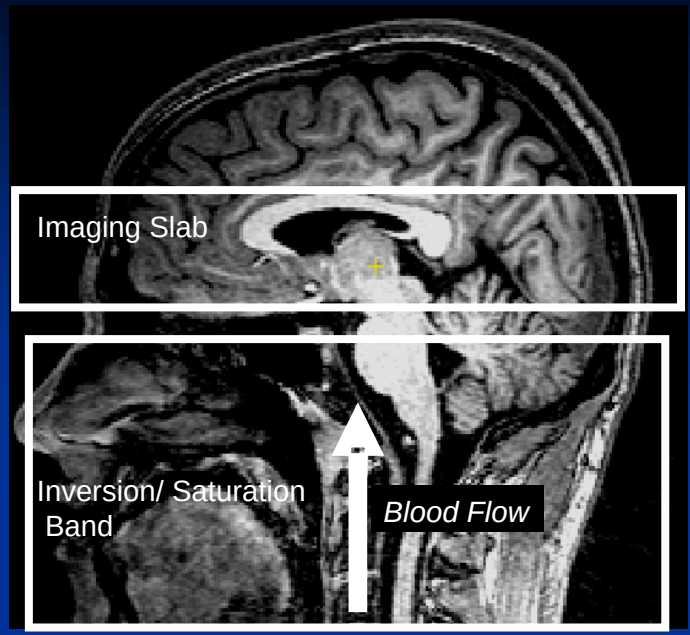
- More stable than BOLD time course signal
- *Absolute* technique; can quantify absolute CBF; calibrate changes with baseline CBF
- Is sensitive to arterial/ capillary flow; should be more tightly localized to site of neuronal activity
- Ideal for longitudinal studies
- Simultaneous BOLD/ ASL; BOLD is free!
- CBF is a fundamental, clinically meaningful physiological parameter

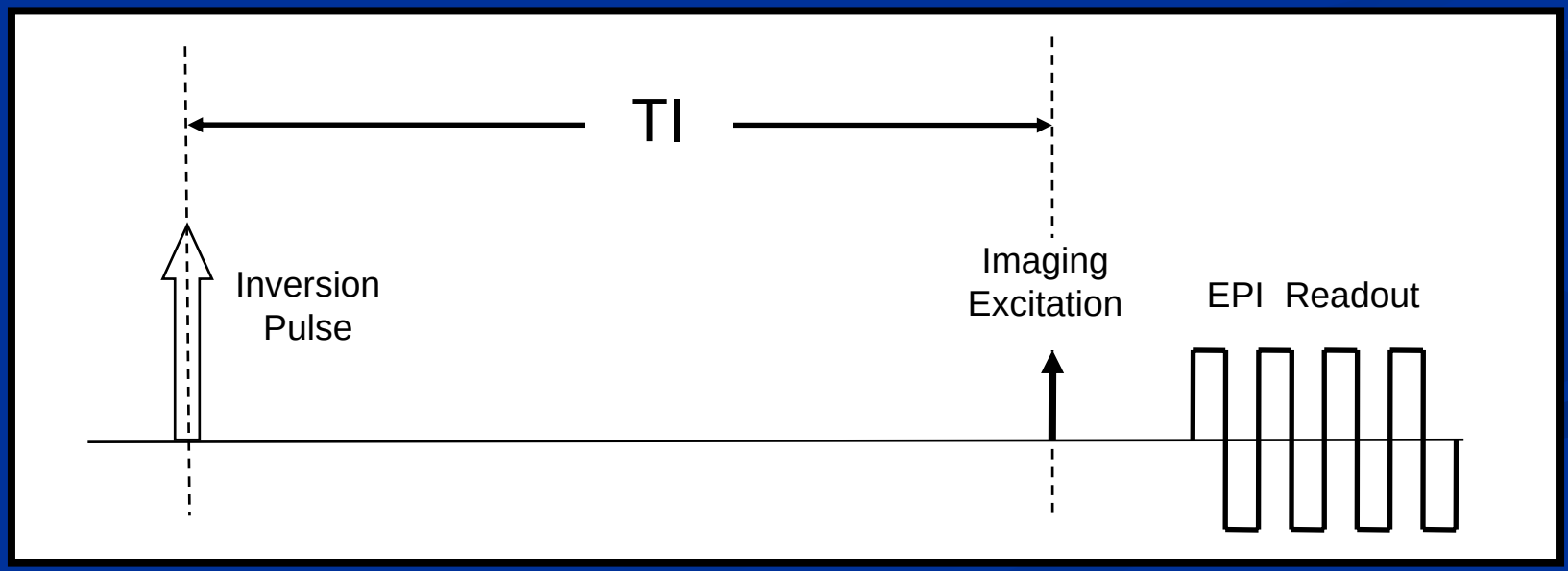
ASL: General Pulsed Approach



Adapated from Functional Magnetic Resonance Imaging, RB Buxton

Pulsed ASL Anatomical Diagram & Pulse Sequence Timing





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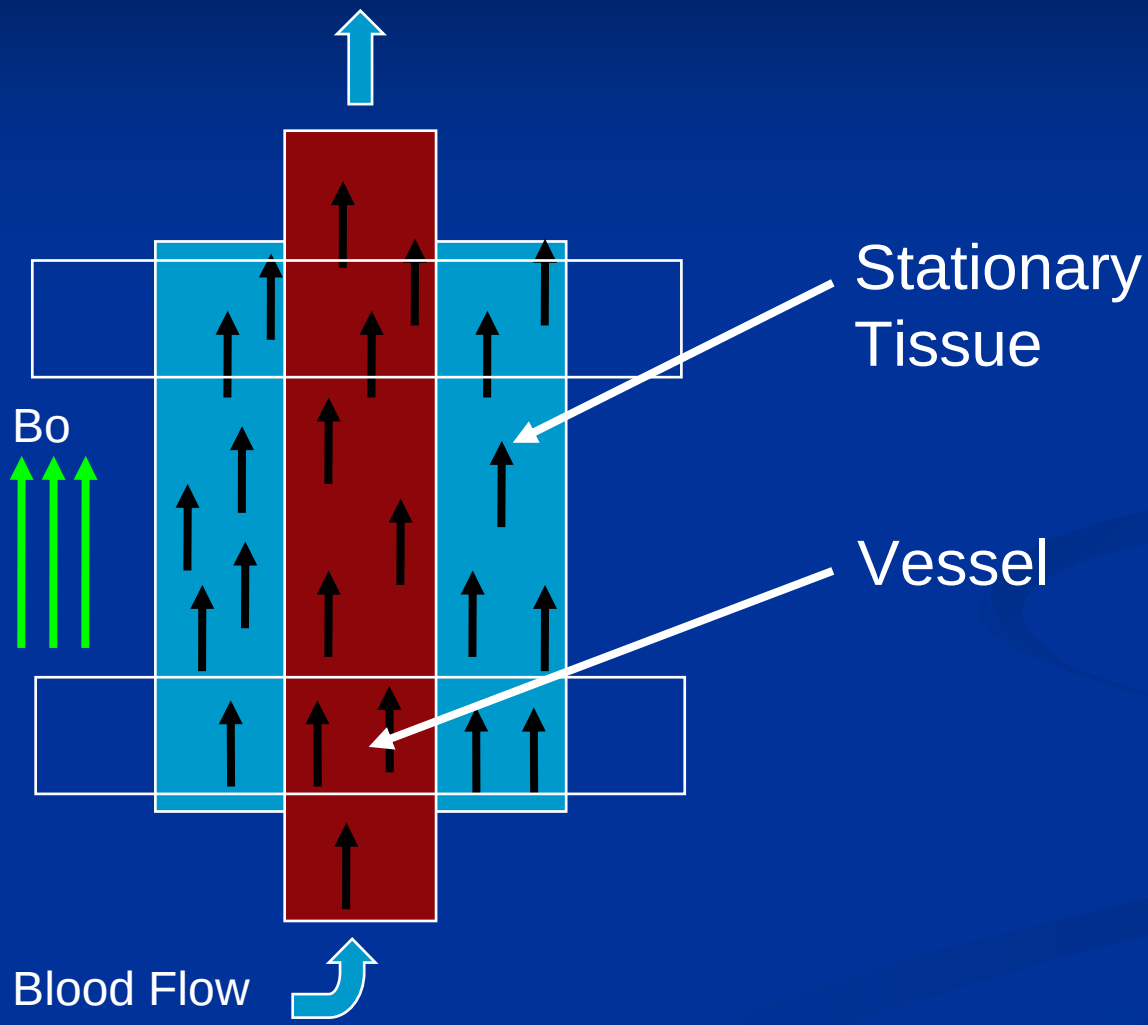

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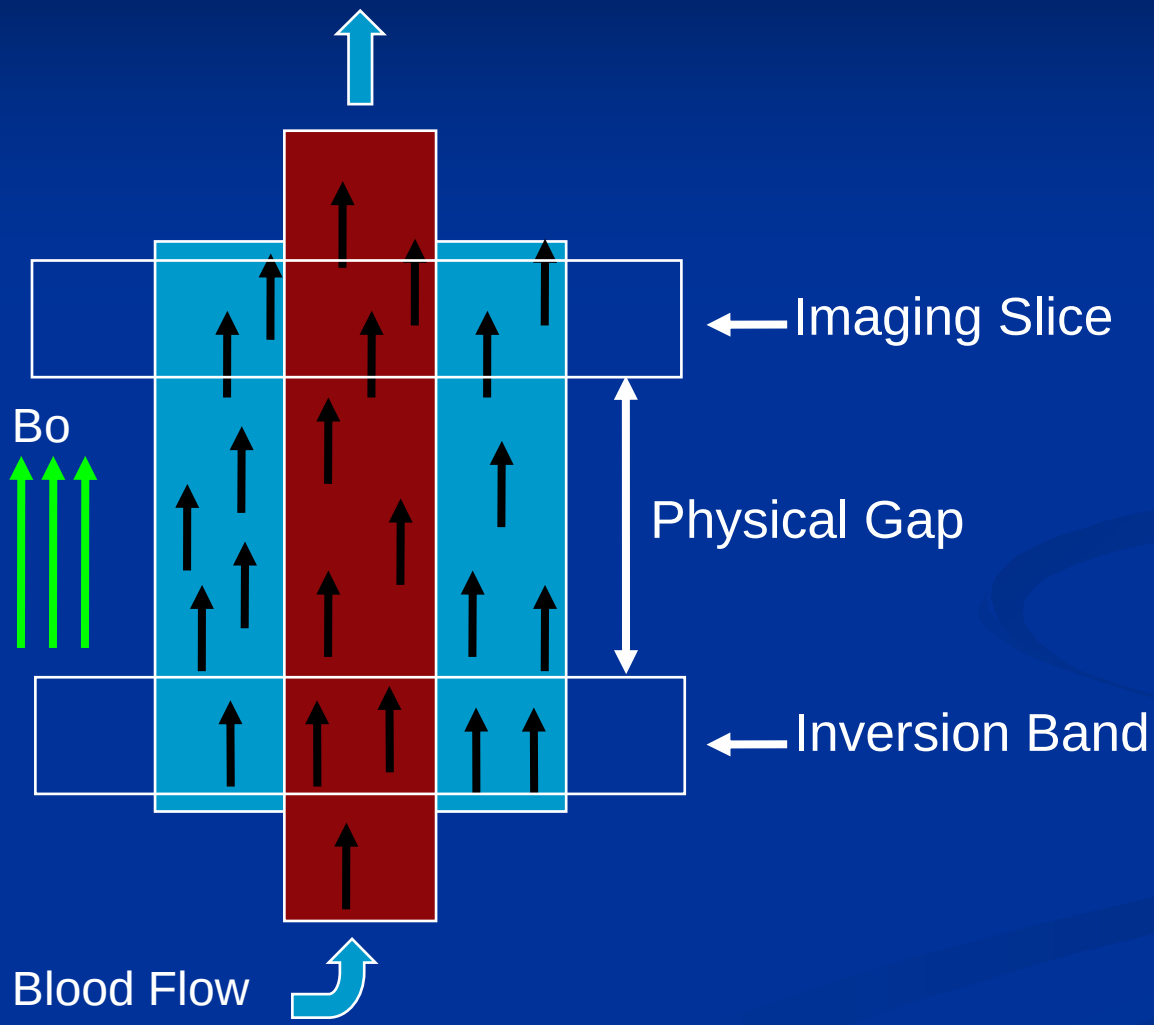

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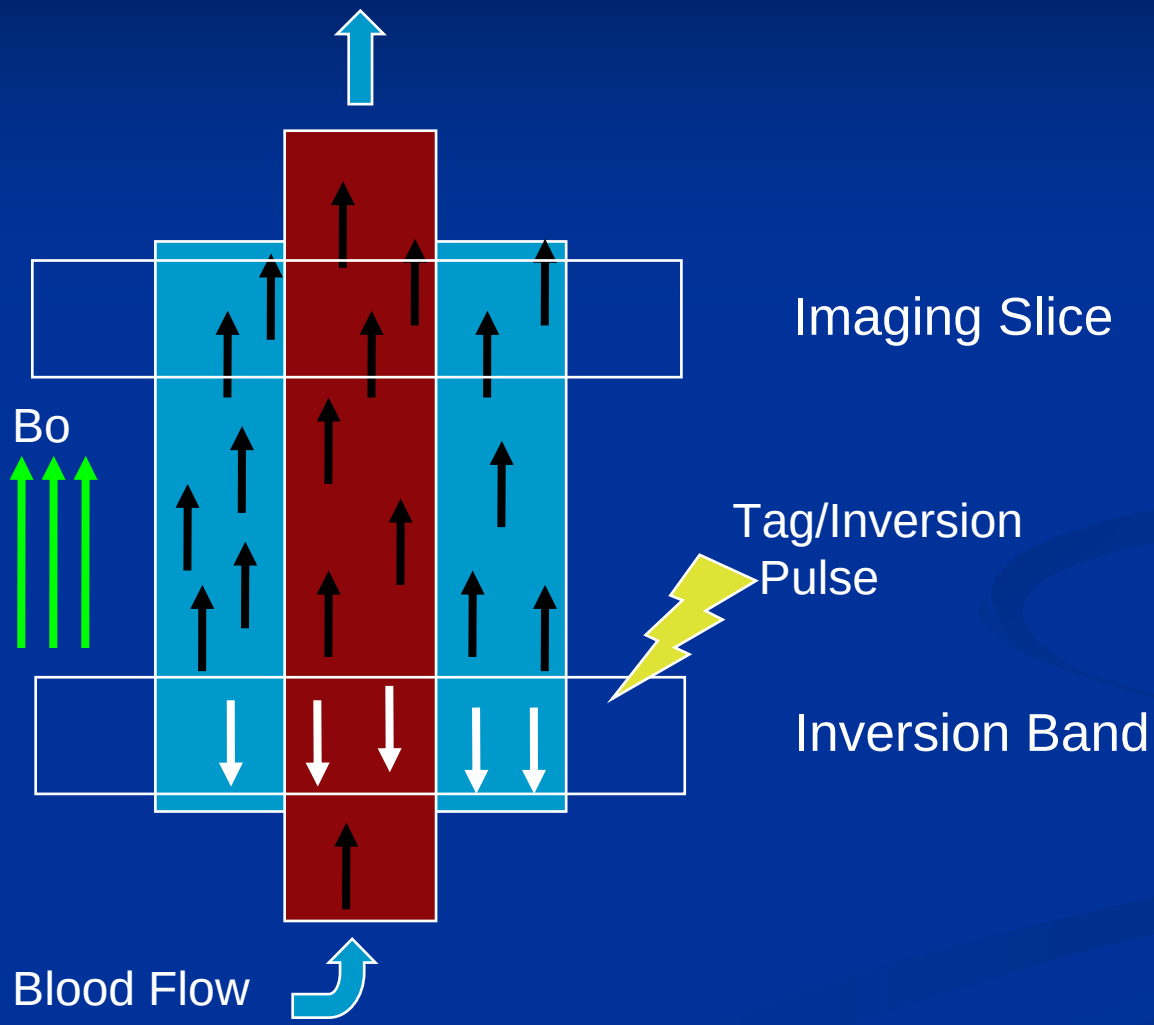

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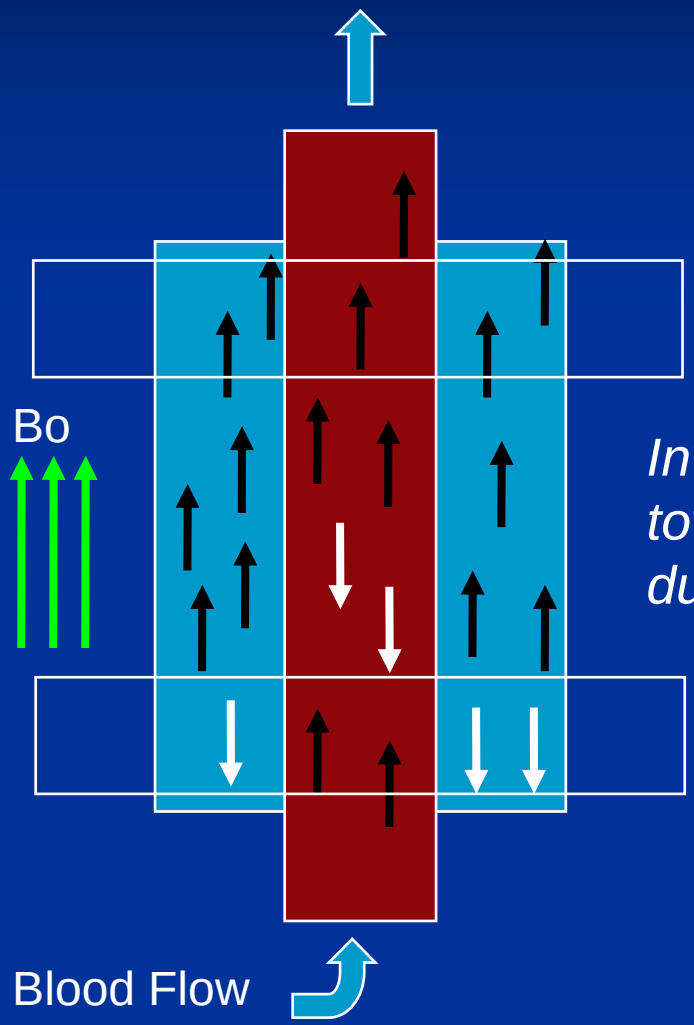
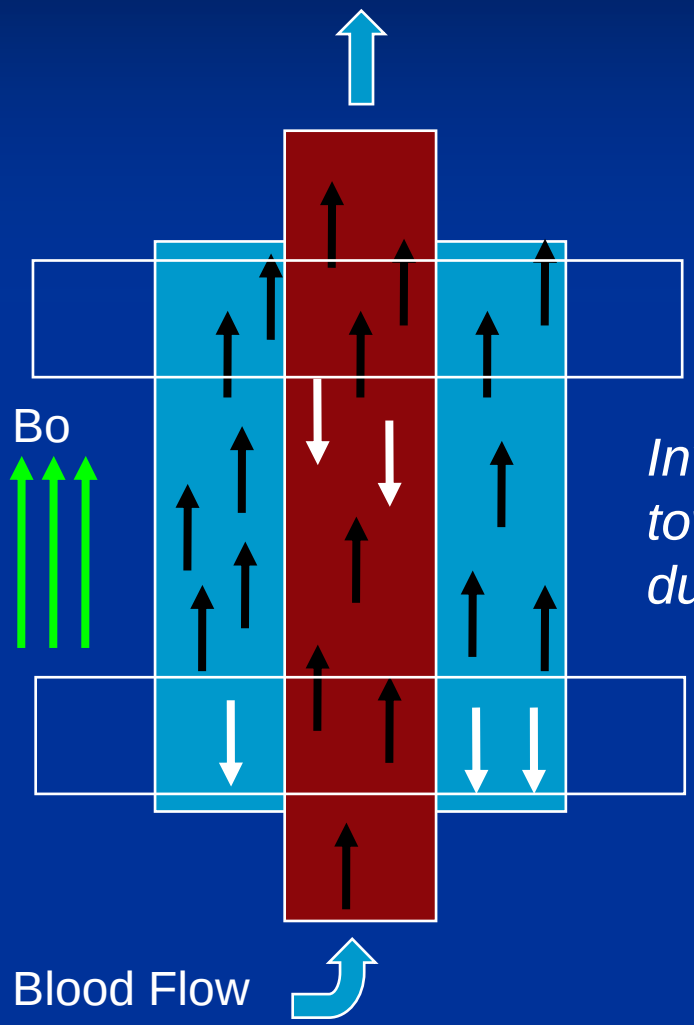


Imaging Slice

Inverted spins flow towards imaging slice during inversion time, TI

Inversion Band

Tag Image Generation



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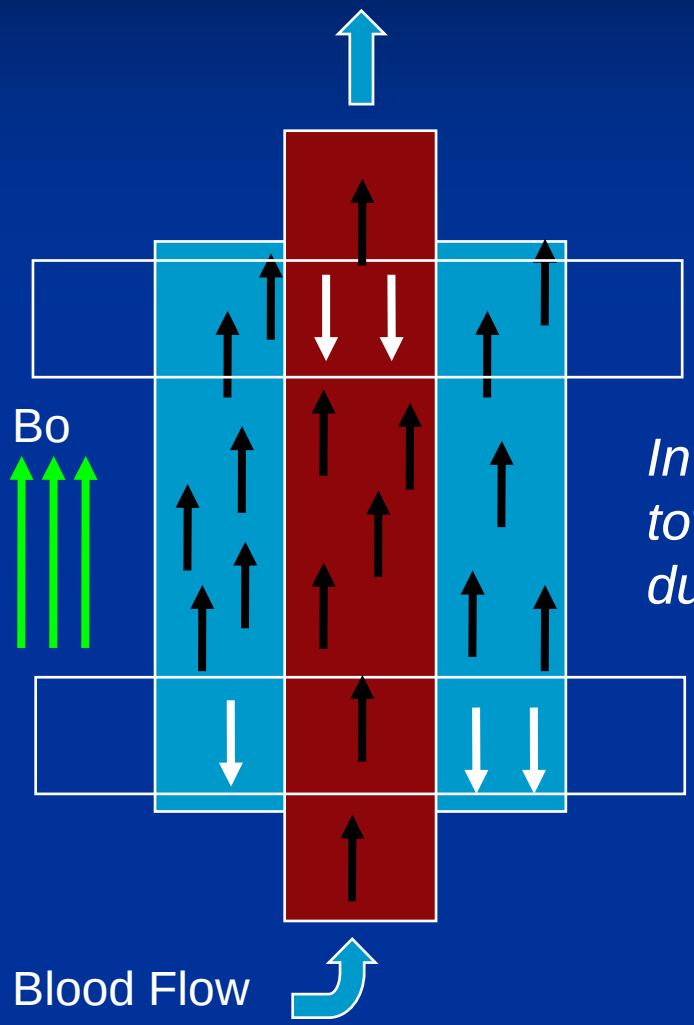

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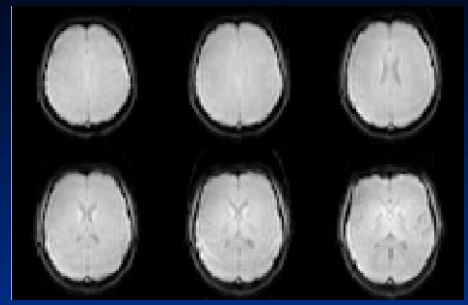

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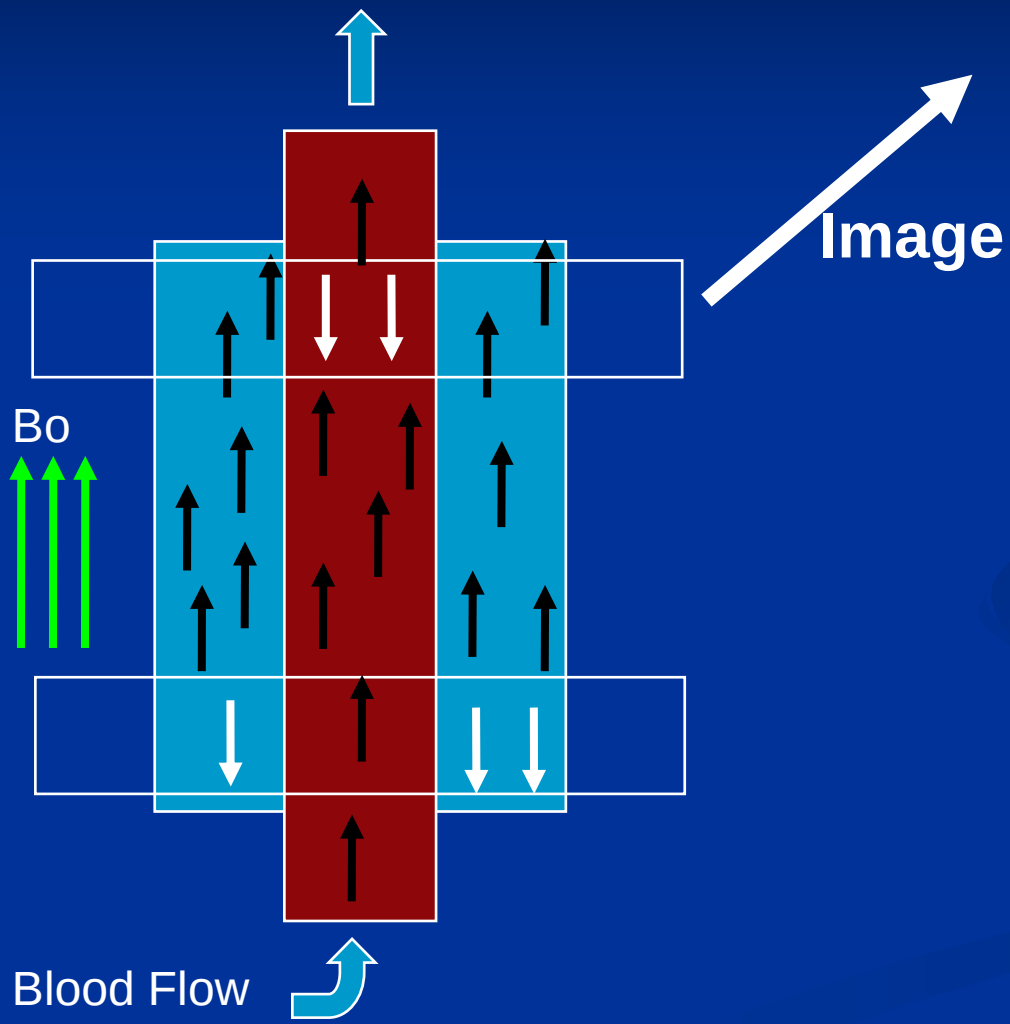

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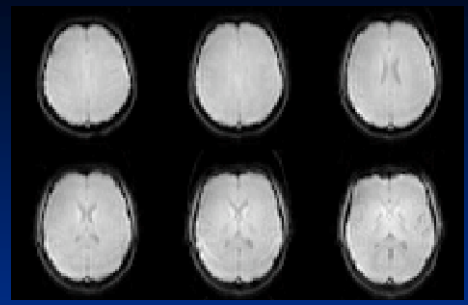

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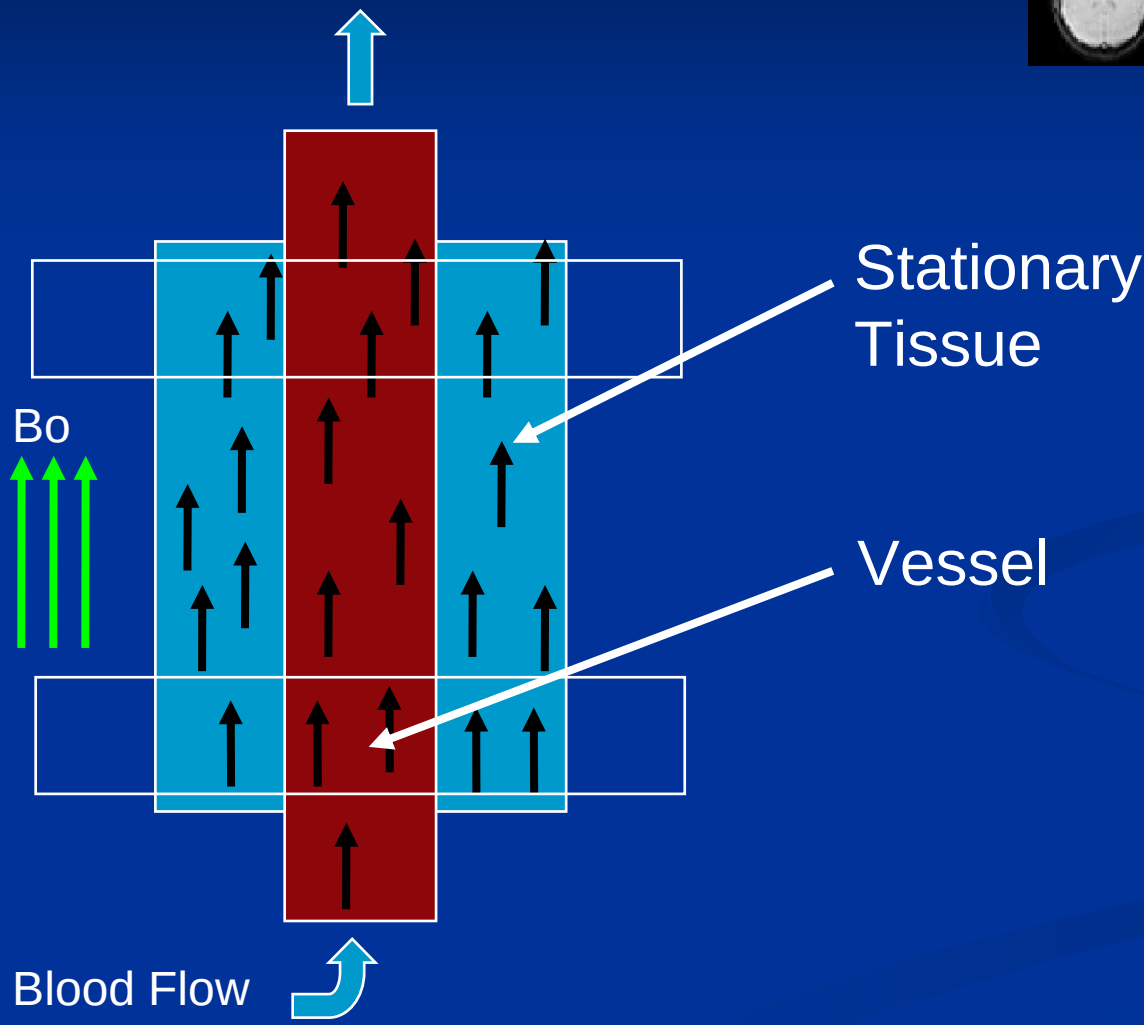

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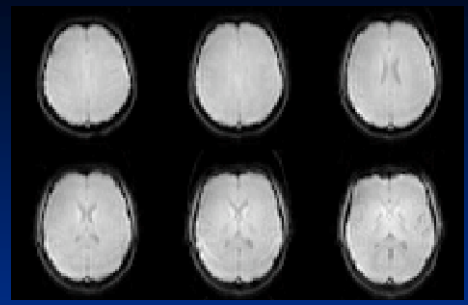

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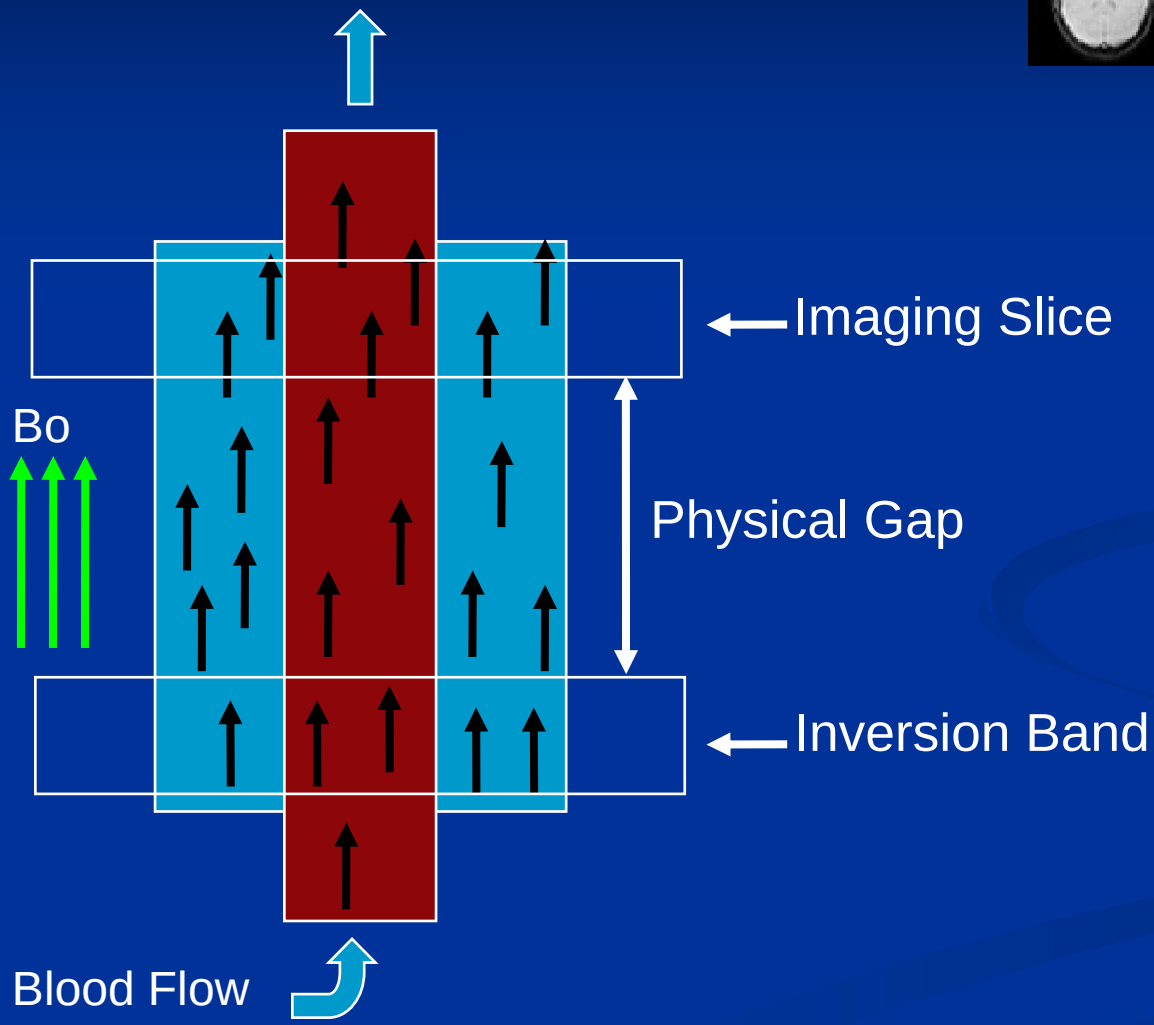

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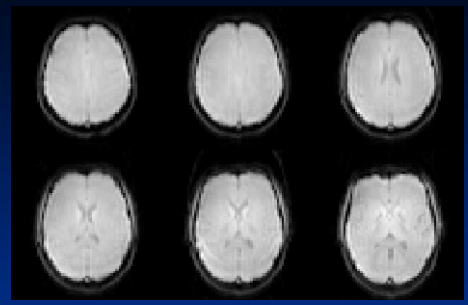

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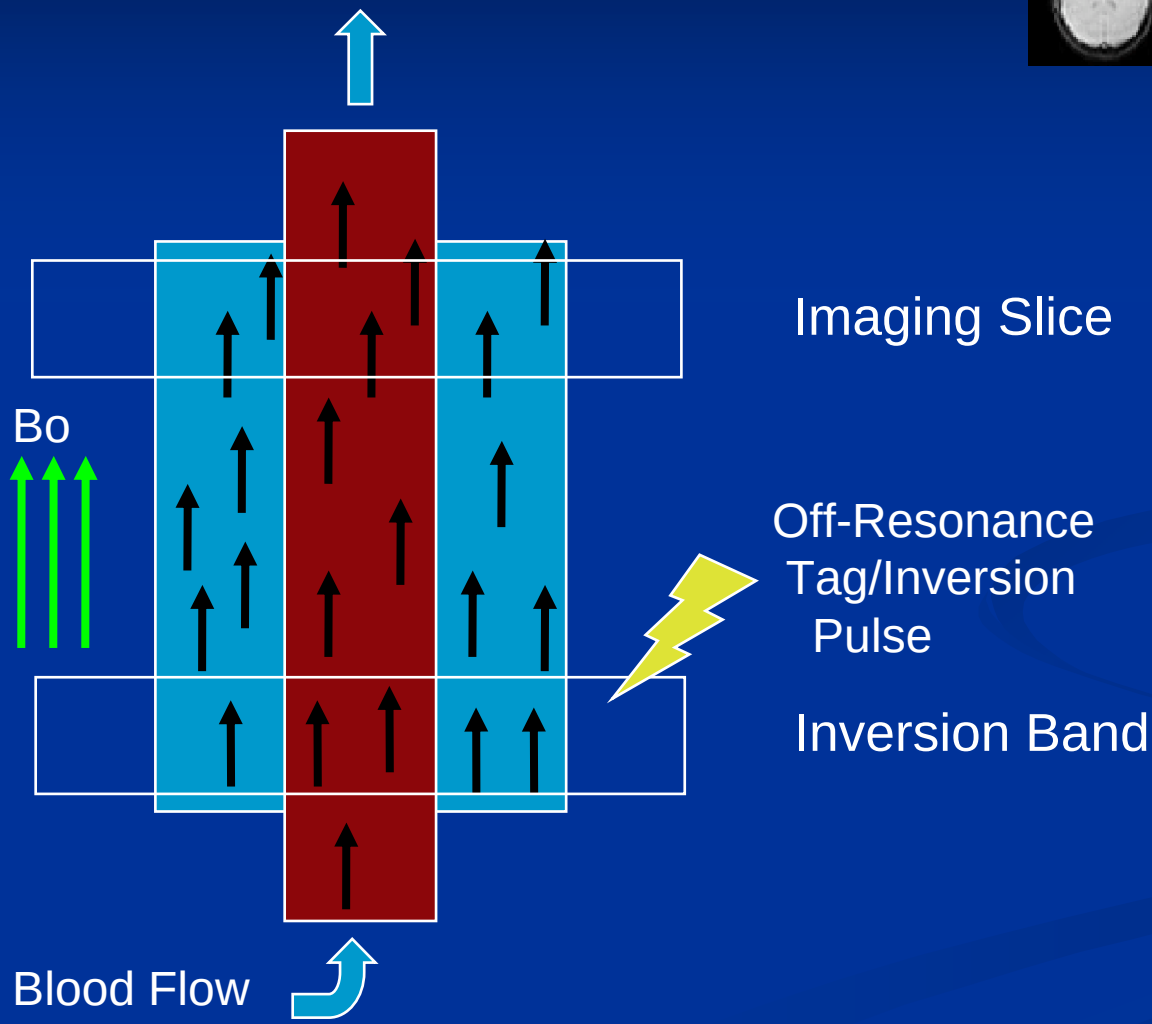
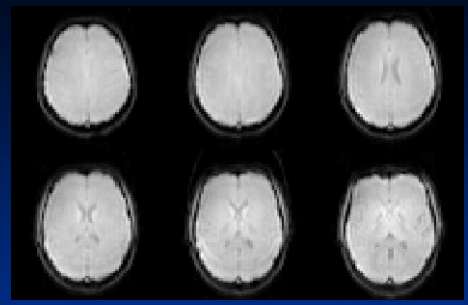


Control Image Generation



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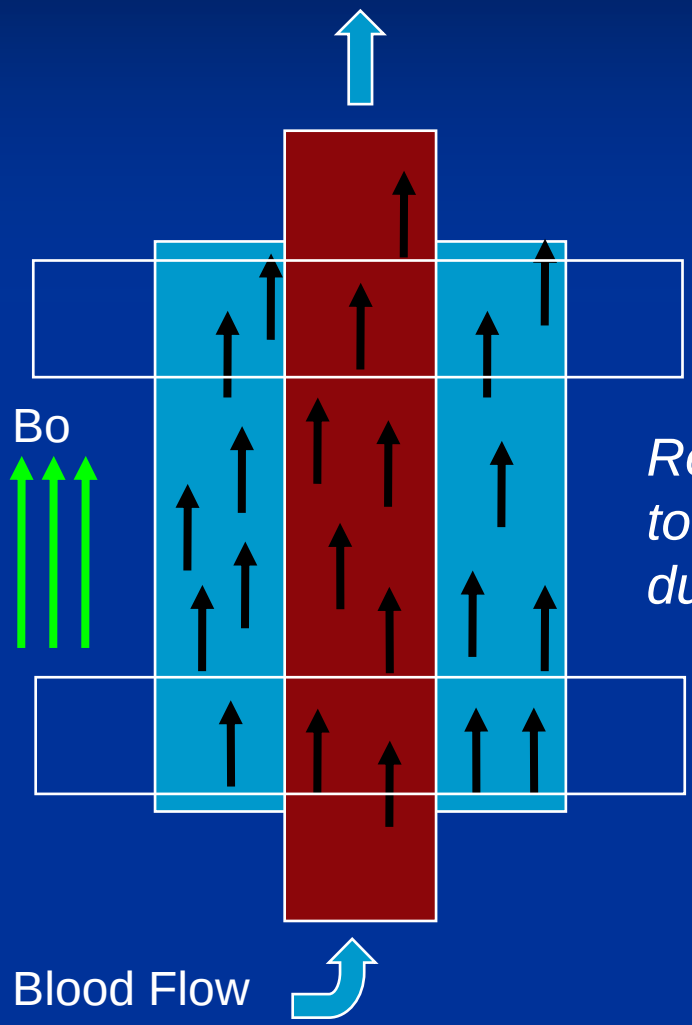
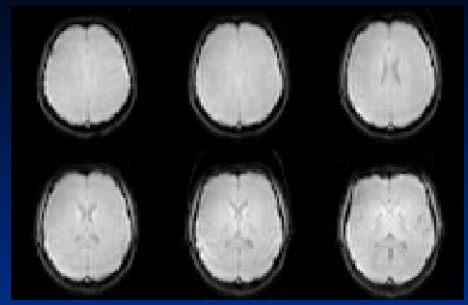


Imaging Slice

Relaxed spins flow towards imaging slice during inversion time, TI

Inversion Band

Control Image Generation



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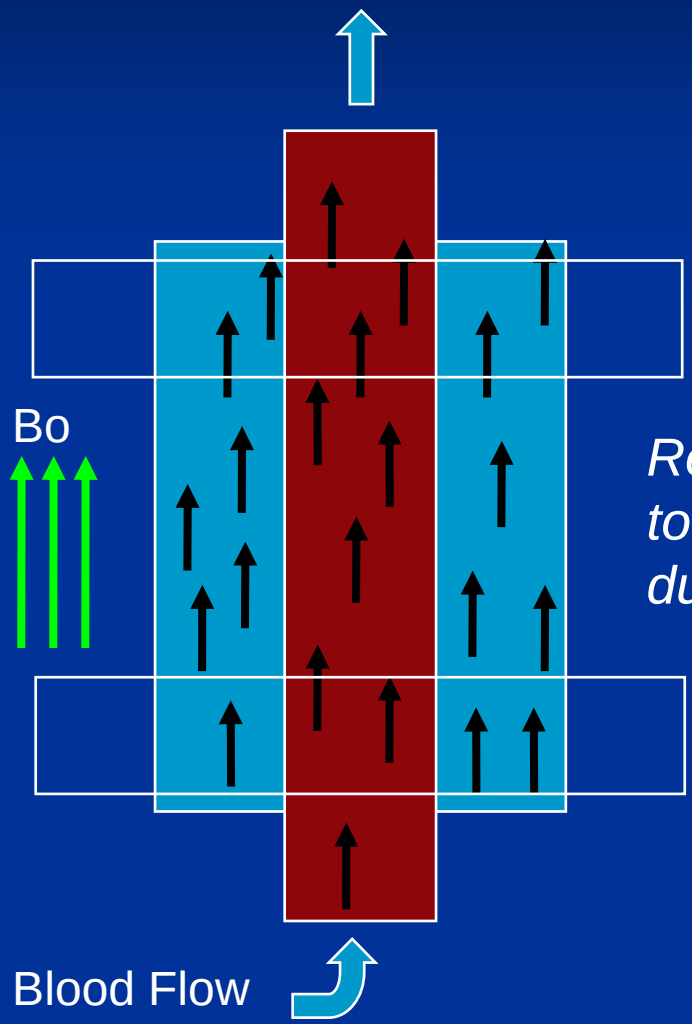
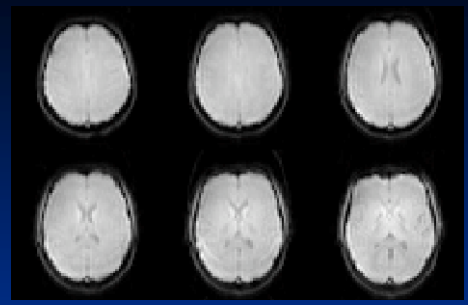


Imaging Slice

Relaxed spins flow towards imaging slice during inversion time, TI

Inversion Band

Control Image Generation



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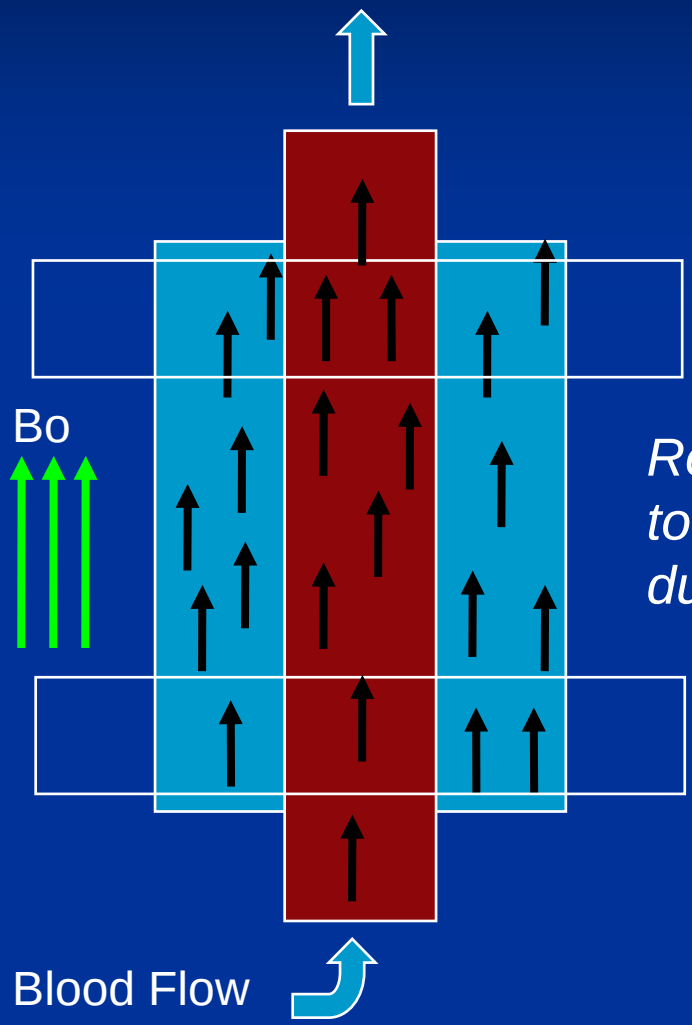
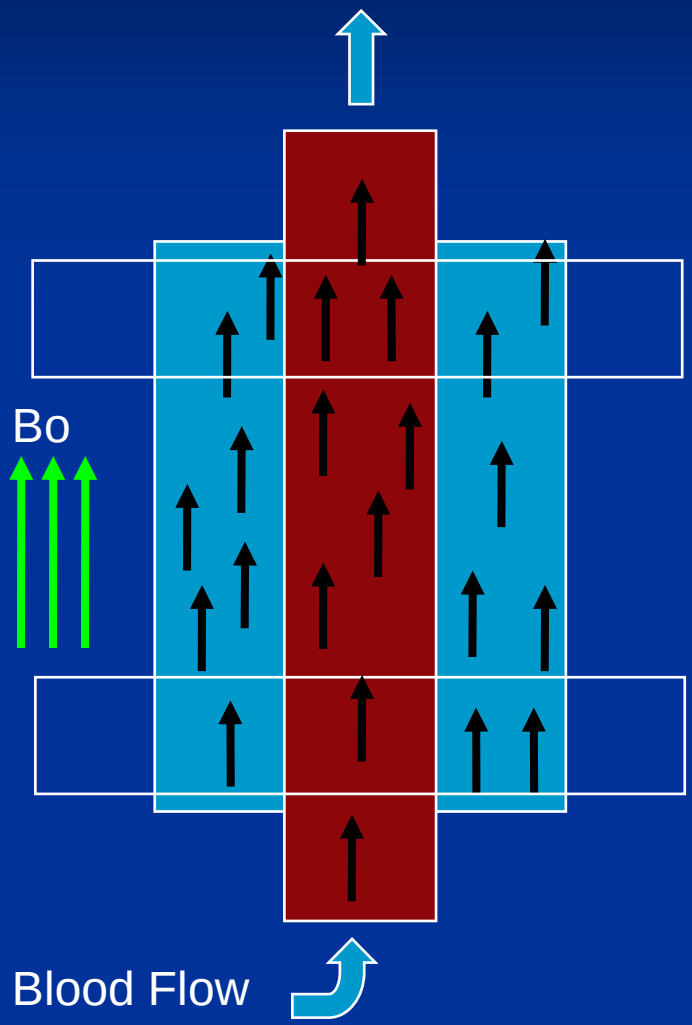


Imaging Slice

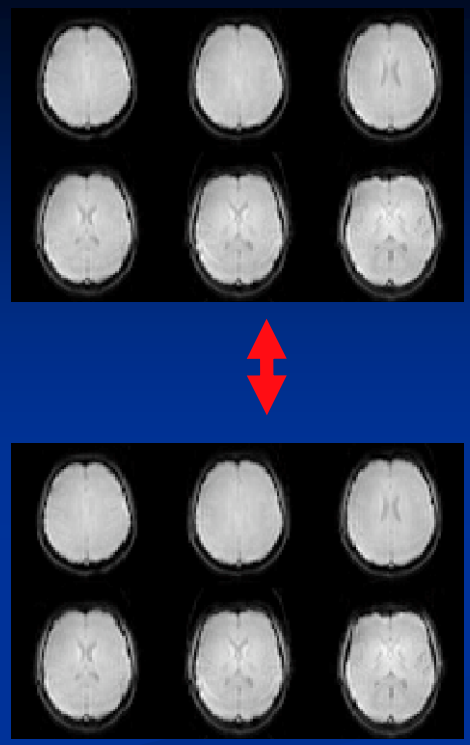
Relaxed spins flow towards imaging slice during inversion time, TI

Inversion Band

Control Image Generation



Image



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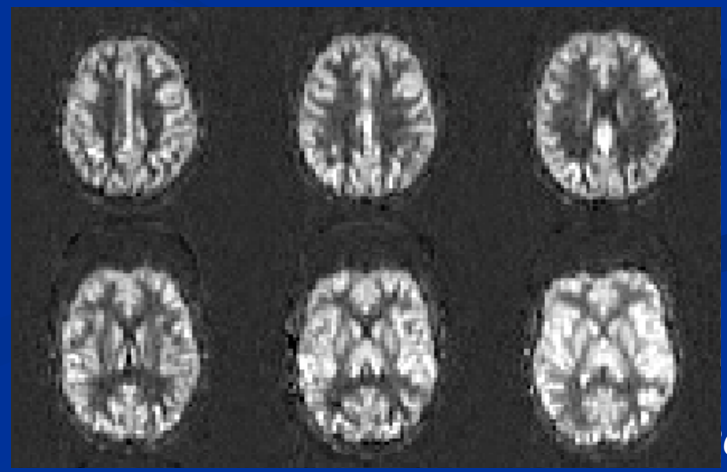
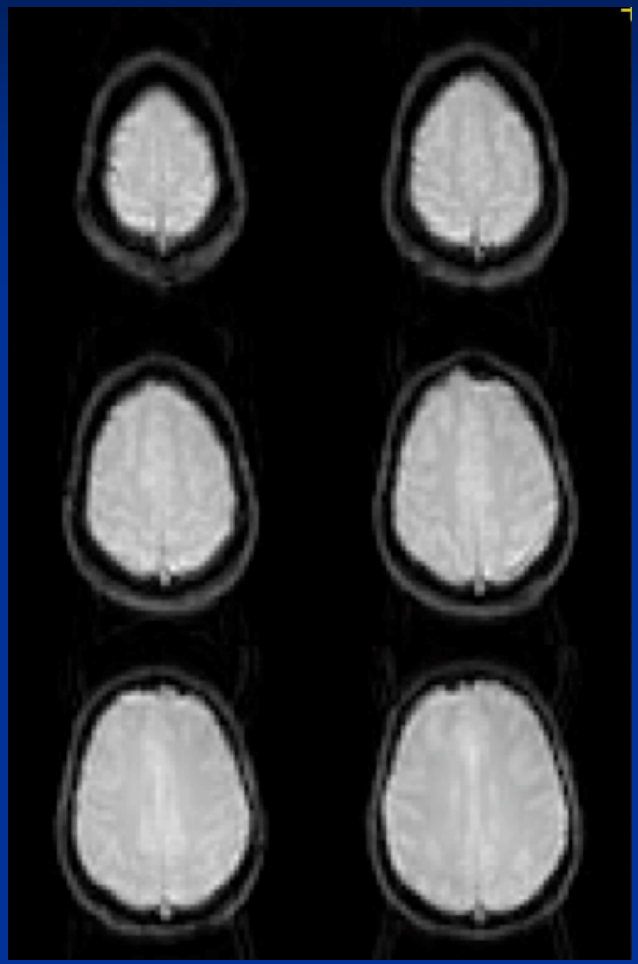
Control



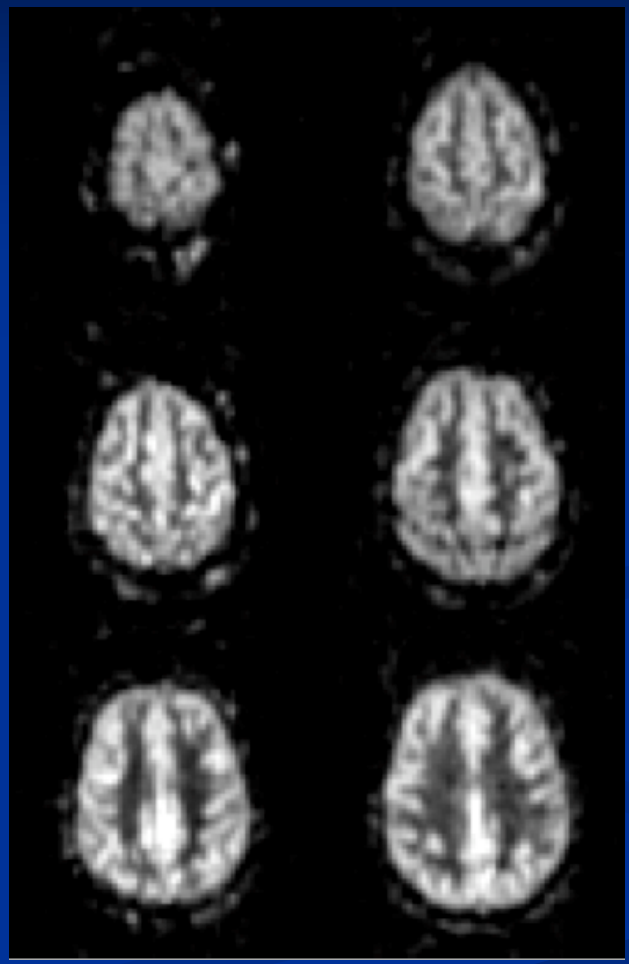
Mean PWI

olar, 2008

ASL: EPI & Perfusion Images



Anatomical EPI images



Perfusion-weighted images (averaged and smoothed)

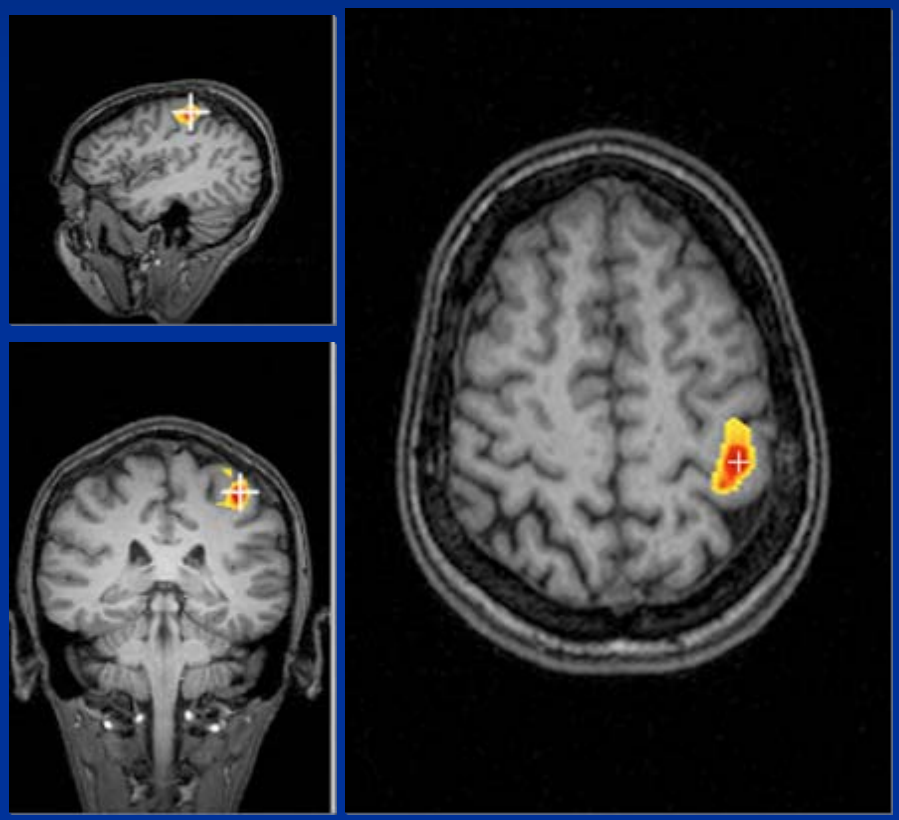
ASL: CBF Quantification

- CBF is calculated by simply dividing the volume of inverted spins delivered (V_{ASL}) , by the delivery time (|)*
- Volume of spins delivered (V_{ASL}) proportional to perfusion map signal intensity
- Delivery time (|) equal to inversion time, TI
- An additional 10 sec calibration scan is required for final conversion of SI in arbitrary units to CBF in ml/(g of tissue – min)

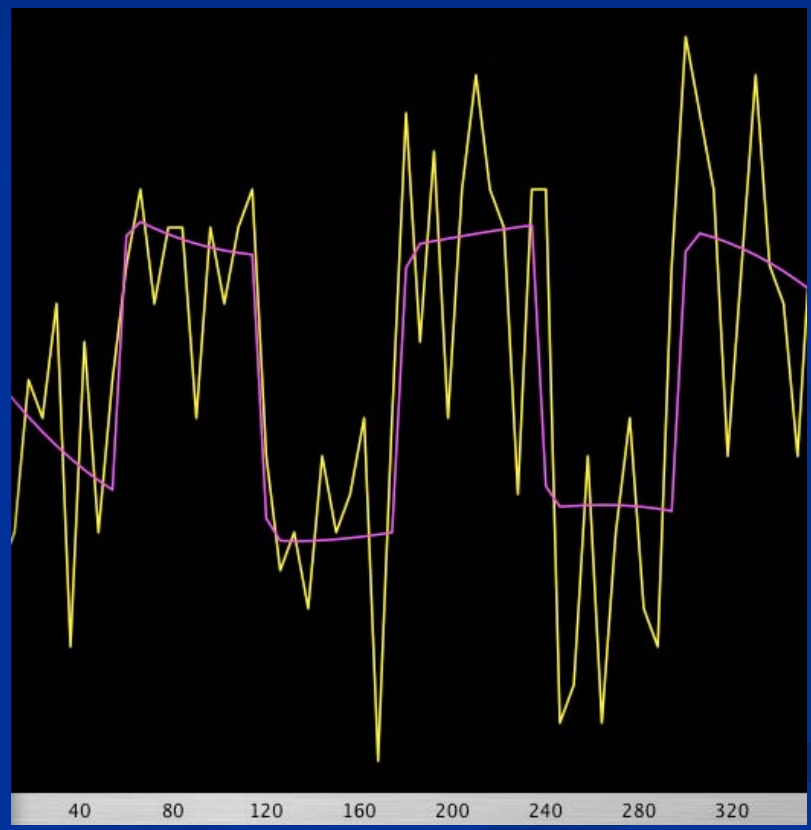
Limitations of ASL

- Low signal-to-noise ratio (SNR); activation change is ~1% of total signal (versus BOLD which is 3-5%)
  - Perfusion map from single-subtraction takes ~4 seconds; mean perfusion map requires ~6 min (90 averages)
  - Limited to low-resolution and few-slice acquisitions
  - ***Considerably less sensitive than BOLD!***
- Tricky technique! Requires careful parameter optimization

ASL: Motor Cortex Activation



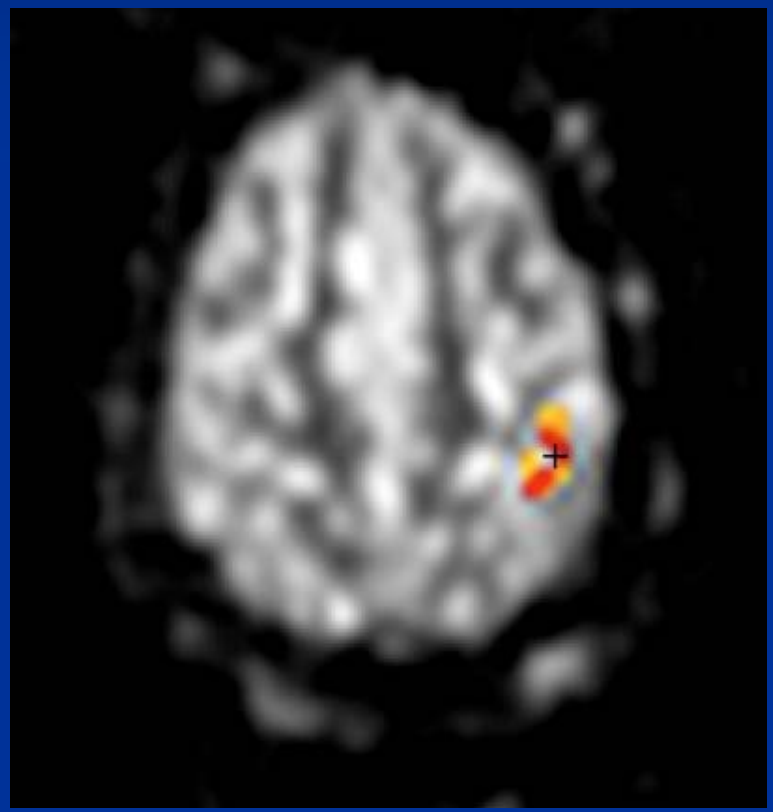
Overlay on anatomical T1-weighted image – Primary Motor Cortex –



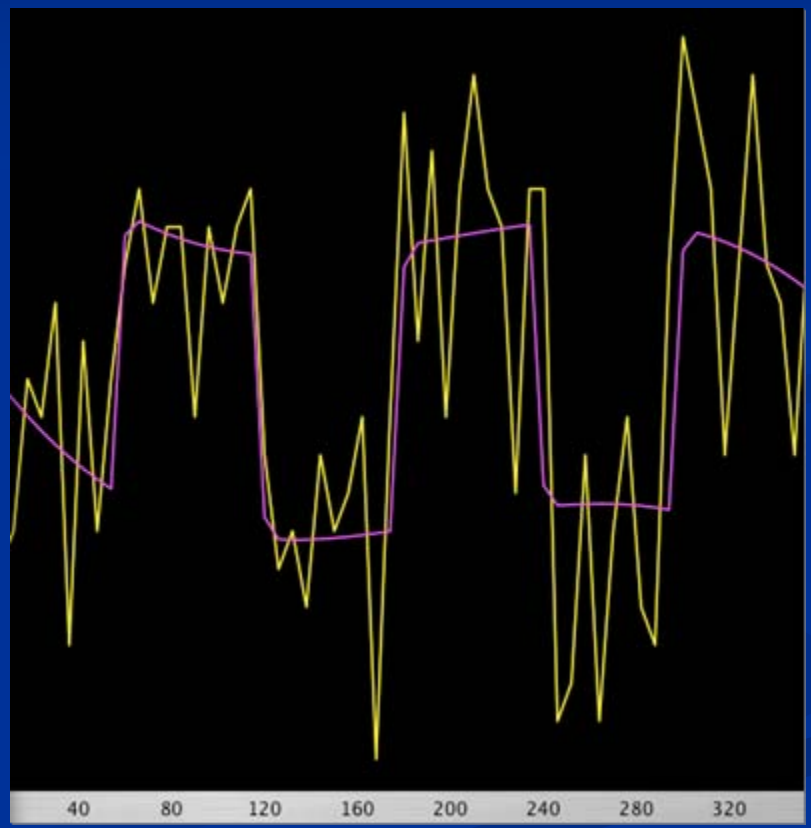
Time series Blood flow to marked voxel over time

HST.583, Div Bolar, 2008

ASL: Motor Cortex Activation



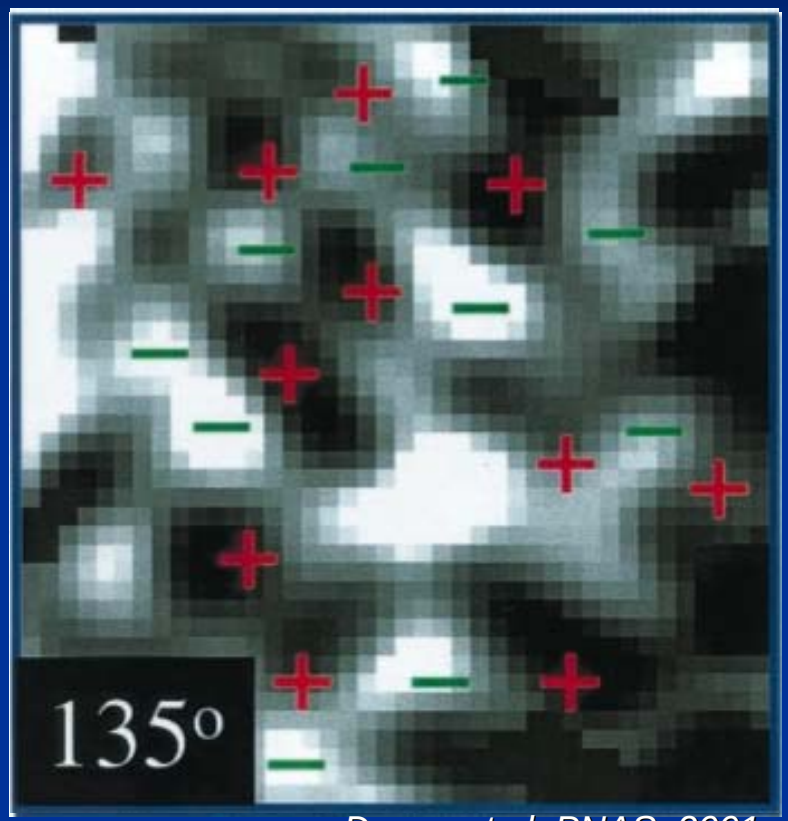
Overlay on perfusion-weighted image



Blood flow to marked voxel over time

HST.583, Div Bolar, 2008

ASL: Highly specific to activation



Duong et al, PNAS, 2001

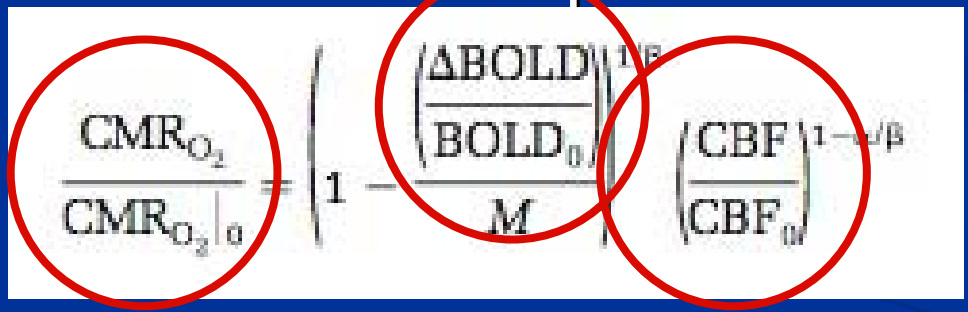
- Duong and colleagues used CBF-mapping MRI (ASL) to delineate orientation columns in cat visual cortex
- Showed that hemodynamic-based fMRI could indeed be used to individual functional columns
- ASL not prone to BOLD venous large-vessel contribution

ASL: Summary

- Becoming a popular addition to BOLD, especially as imaging hardware improves (and alleviates SNR limitations)
- Can be done simultaneously with BOLD, to to *calibrate* BOLD signal
- Major MR scanner manufacturers now offer ASL as a produce sequence

Calibrated BOLD

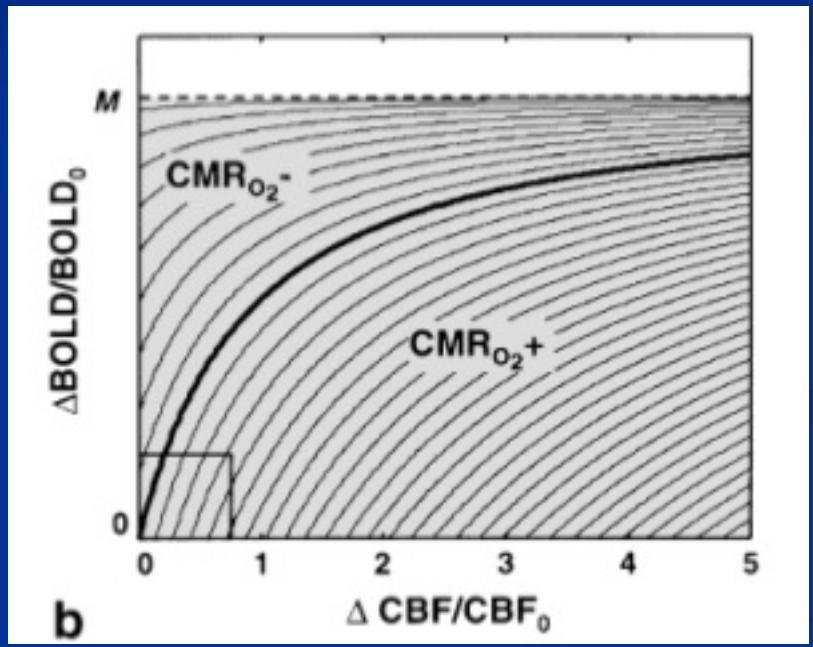
- Use BOLD-ASL to calculate *relative $CMRO_2$* changes during activation (Davis, PNAS, 1998, Hoge, PNAS/MRM, 1999)
- Based on the derivable equation:



- If we know relative change in BOLD and CBF, we can compute relative change in $CMRO_2$
- Assume alpha, beta, need to calculate ***M***

Calibrated BOLD

- ***M*** represents the maximum possible BOLD change



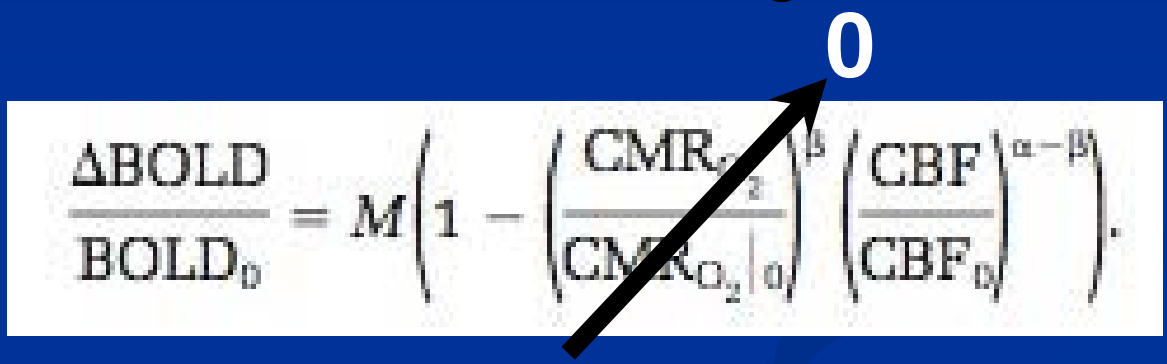
Hoge et al, MRM, 1999

- At the limit, CBF will increase so much that *ALL dHb gets washed out!* ***Beyond this point, any additional increase in CBF will not change dHb content or BOLD signal!***

HST.583, Div Bolar, 2008

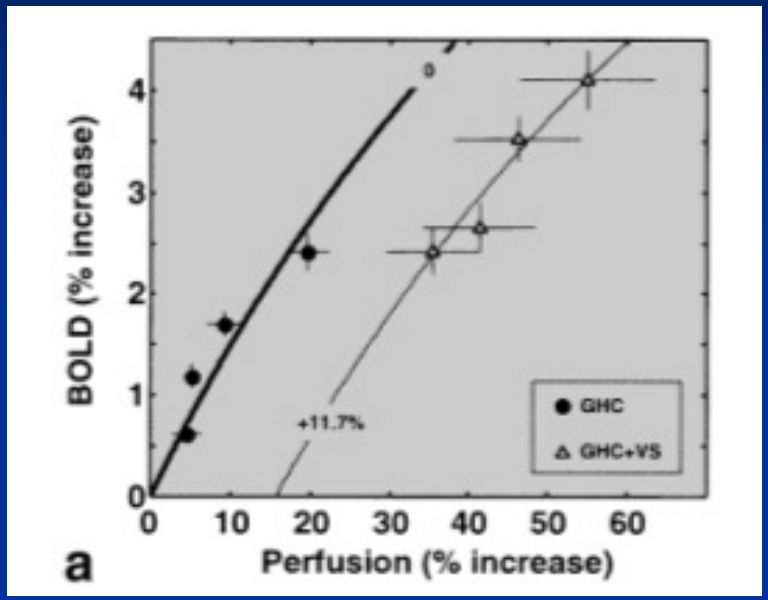
Calibrated BOLD

- To calculate ***M*** from CBF and BOLD, we need to make relative $CMRO_2$ change *zero*



- We can do this by inducing ***hypercapnia***; i.e. inhalation of CO_2 causes CBF/ BOLD change via vasodilation, but no $CMRO_2$ change*

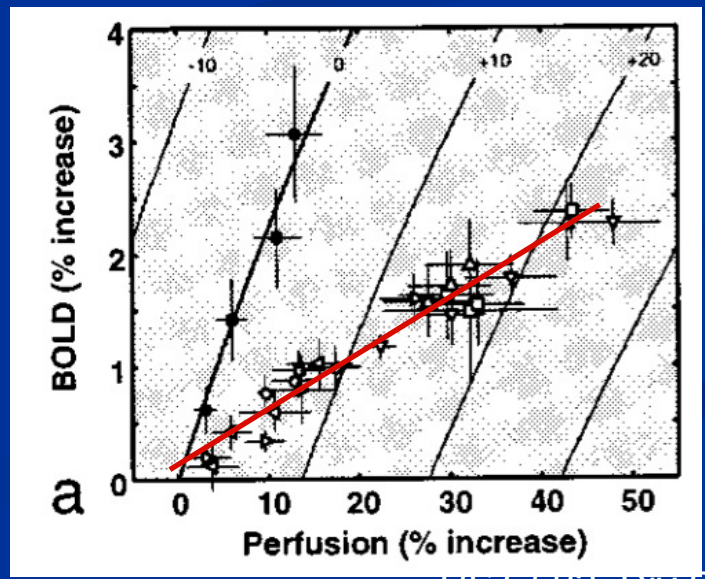
Calibrated BOLD



Hoge et al, MRM, 1999

- We can see how $CMRO_2$ changes by plotting BOLD versus CBF for a task
- Data points should go *across* isocontours, giving us relative $CMRO_2$

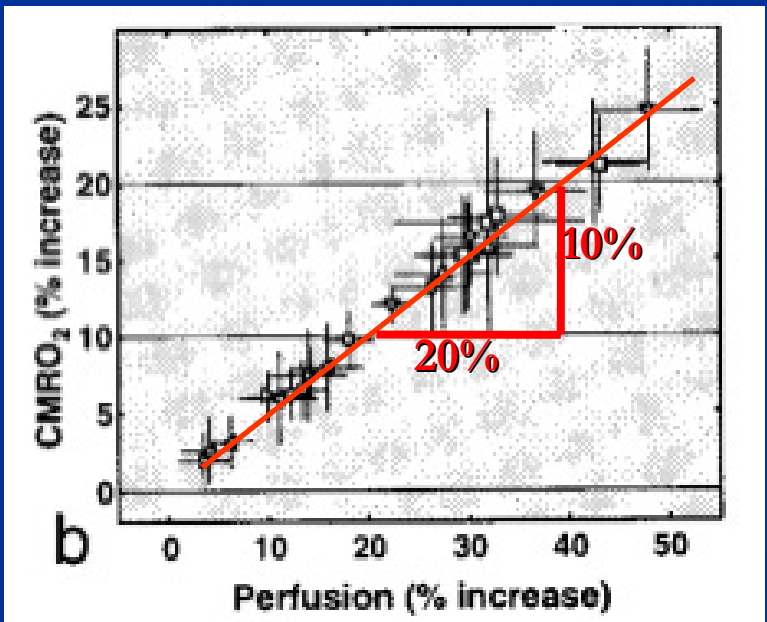
- Using graded hypercapnia it is possible to create isocontours of $CMRO_2$



Hoge et al, PNAS, 1999

Calibrated BOLD

- Allows calculation of *coupling index, n* (i.e. relative $CMRO_2$ change versus relative CBF change)

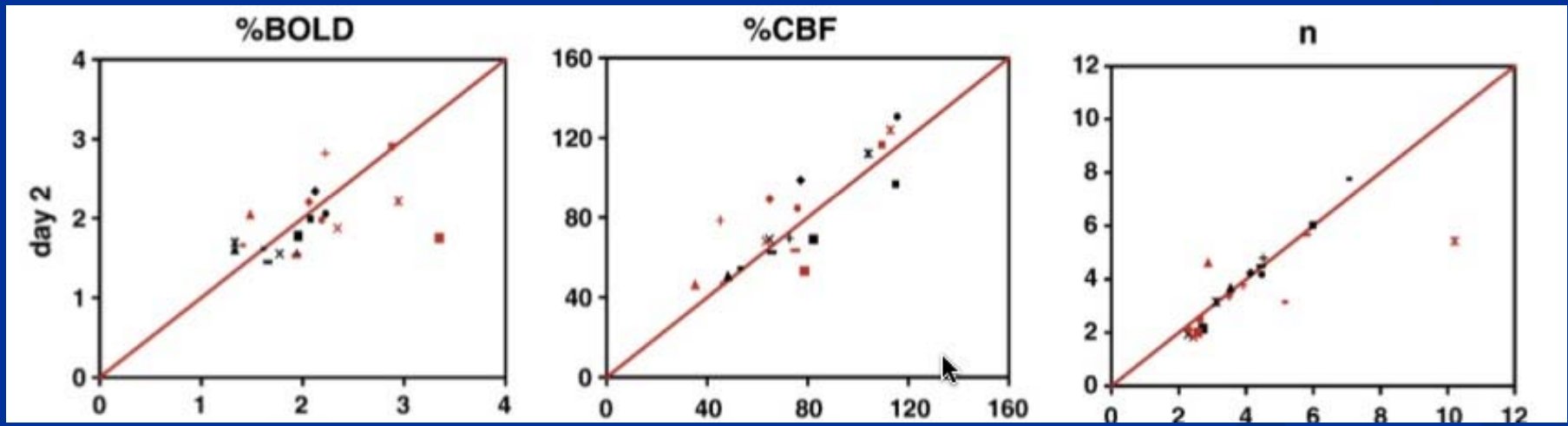


Hoge et al, PNAS, 1999

n = 2

Calibrated BOLD

- Coupling index (n) shows higher reproducibility than BOLD or CBF alone



Leontiev et al, NeuroImage, 2007

Day 1

Summary: Calibrated BOLD

- Theoretically, only one grade of hypercapnia is needed to define ***M***, $CMRO_2$ isocontours
- Even without hypercapnia, can simply assume ***M***
- Using coupling index (n) as actvation measure may reduce intrasubject and intersubject variability of BOLD/CBF signal
  - For example, given the same task in different sessions, the calibrated change will be less variable
  - Could increase power of your study (i.e. via group statistics, etc.)