LECTURE 7

T1, T2, T2* CONTRAST

Lecture Notes by Assaf Tal

T_1, T_2 and T_2^* in Pathology

Motivating the Need for T_1, T_2, T_2^* Contrast

The MRI signal at each point is proportional to the number of protons at that point, and, by extension, to the density of water. While density changes hold **some** diagnostic value, they are usually not very informative in and of themselves. It turns out that the T_1, T_2 and T_2^* time constants are often much more sensitive than water density to pathological tissue changes, and so many imaging sequences aim to either directly measure them (at each point), or at least produce weighted images. In other words, many of the sequences in MRI try to make the signal as sensitive as possible to T_1, T_2, T_2^*, or a combination thereof. This lecture will concern itself with such sequences, and the next one will look at the mechanistic models that link T_1, T_2 and T_2^* to underlying processes on the cellular and sub-cellular levels.

Since T_1, T_2 and T_2^* are time constants, they are measured by introducing **delays.** For example, T_2 and T_2^* govern the signal decay, so exciting the magnetization, waiting a certain amount of time, and then observing it will make the signal sensitive to T_2 and/or T_2^*, depending on the exact details. This will produce signals that are T_2-weighted or T_2^*-weighted. Similarly, if we excite the magnetization from thermal equilibrium, wait a certain amount of time for it to build up due to T_1 relaxation – but not quite return to equilibrium – and then excite it again, we will get a signal intensity that will depend on how fast the magnetization built itself back up; that is, a T_1-weighted signal.

How Pathology Changes T_1 and T_2

The main usefulness of T_1, T_2 and T_2^* in MRI comes from their sensitivity to microscopic pathological changes in tissue. This is a very interesting and important point:

> T_1, T_2 and T_2^* can reveal microscopic pathologies on a much smaller scale than the voxel size (although these pathologies must permeate a macroscopic region on the order of the voxel size to be detected, due to MRI's low sensitivity).

Pathologies can appear as either **hypointense** (dark) or **hyperintense** (bright) on T_1 or T_2 (or T_2^*) relative to healthy tissue on weighted images. Pathologies which are **isointense** (same as surroundings) are invisible, although a pathology might be isointense on a T_1 weighted image but hyper/hypo intense on a T_2 weighted image!

The following tables summarize some typical pathologies and their associated appearances:

Hypointense (Longer) T_1	Hyperintense (Shorter) T_1
Edema	Fat
Tumor	Subacute hemorrhage
Infarction	Melanin
Inflammation	Protein-rich fluid
Hyperacute hemorrhage	Slowly-flowing blood
Chronic hemorrhage	Paramagnetic substances (gadolinium, manganese, copper, etc)
Low proton density	Calcification
Calcification	Laminar necrosis of cerebral infarction
Flow void	
Tissue loss	

Hypointense (Shorter) T_2	Hyperintense (Longer) T_2
Low proton density	Edema
calcification	Tumor
fibrous tissue	Infarction
protein-rich fluid	Inflammation
flow void	Hyperacute hemorrhage
paramagnetic substances (iron, ferritin, melanin, deoxyhemoglobin, etc)	Chronic hemorrhage
	Extracellular methemoglobin
	subacute hemorrhage

The above are just rules of thumb and should never be used to make any sort of conclusive diagnosis. Leave those to the trained radiologists! We are not in the business of medical diagnosis, but rather in the business of creating images which are sensitive to T_1, T_2 and T_2^*.

T_1 Hyperintensity Usually Means A Shorter T_1. T_2 Hyperintensity Usually Means A Longer T_2.

CSF, which has a long T_1, appears dark on T_1-weighted images. This is not a "law of nature" but has to do with the way T_1 contrast is usually created in MRI images, via rapid pulsing or inversion recovery. For both, high T_1 values appear darker, as discussed in the lecture dealing with creating T_1 and T_2 contrast.

On the other hand, T_2-weighted sequences often rely on some form of spin-echo, which has a signal dependence of the form

$$s \propto e^{-TE/T_2}.$$

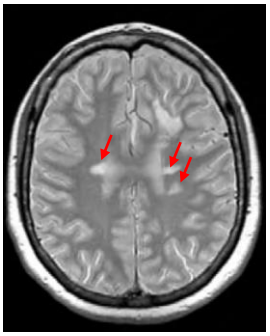
As T_2 is increased, the signal decays more slowly, which results in hyperintensity (compared to normal, non-increased T_2). This means that hyperintensity corresponds to longer T_2s. It's very important not to automatically assume that hyperintensity means there is "more" of something. It all depends on the signal equation and type of contrast!

A Brief Example: Multiple Sclerosis

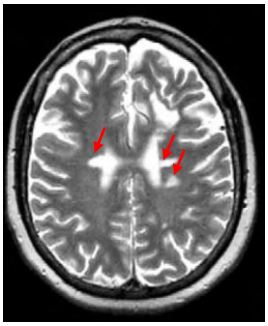
Multiple Sclerosis (MS) is an inflammatory disease of the central nervous system which affects about 2 million people worldwide. In MS, prologed inflammation leads to **demyelination** of neuronal axons[1], resulting in symptoms ranging from impaired vision and fatigue to depression and musculoskeletal weakness. There are two major theories for why inflammation occurs: either via an autoimmune response, or via failure of myelin producing cells. There is no cure for MS, but drugs can delay its onset and effects[2].

The diagnosis of MS is often done by combining clinical evaluation with MRI imaging. The hallmark of MS is the appearance of **lesions** on the MRI scans. These are small round/oval structures that result from the underlying damage to brain tissue through the inflammatory processes. Most lesions appear hyperintense on T_2-weighted images and hypointense on T_1-weighted images. It is fairly common to see hyper-T_2/hypo-T_1 pathologies in MRI, and we will explain why in a bit. This means that the T_1 and T_2 images sometimes contain the same information

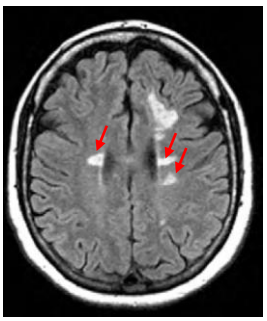
The problem with T_2 images is that hyperintense lesions are hard to tell apart from the cerebrospinal fluid (CSF). A sequence known as **FLAIR (FLuid Attenuated Inversion Recovery)** precedes the T_2-weighting imaging with an inversion recovery designed to null the CSF signal based on its long T_1.



In this Proton Density (PD) image, as little T_1 and T_2 contrast is created (e.g. by taking long TRs and short TEs). "Typical" MS lesions appear hyperintense.



In this T_2-weighted image, the same lesions also appear hyperintense. However, they are difficult to identify due to the bright CSF. This is why FLAIR is used (next).



The FLAIR image is T_2-weighted, but it uses the long T_1 value of the CSF to null its signal with a special pulse sequence. This makes identifying the T_2-hyperintense lesions much easier.

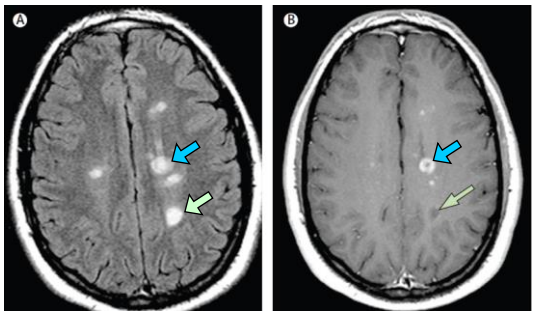
Images taken from Sahraian and Eshaghi, Clin. Neurol. Neurosurg. 112:609-615 (2010)

Another image type often used is a T_1-image after the injection of a contrast agent such as

[1] This means the myelin sheeth that surrounds the neurons is somehow damaged or completely stripped. This, in turn, for leaves the neuron vulnerable to damage, as well as impairs its ability to conduct electrical impulses.

[2] Weizmann holds the patent rights for Copaxone, one of the most influential drugs on the market for treating MS.

gadolinium (Gd-DTPA, or Gd for short). The effect of Gd is to shorten T_1 substantially. As we have seen, rapid pulsing tends to saturate long T_1, which is why CSF appears dark on T_1 weighted images. Gd therefore causes hyperintensity wherever it reaches in the brain. Not all hyperintense T_2 lesions are also hyperintense on T_1 weighted contrast enhanced scans, but not always!

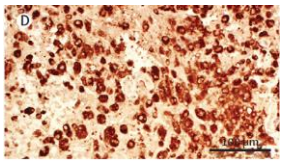


FLAIR Contrast Enhanced T_1

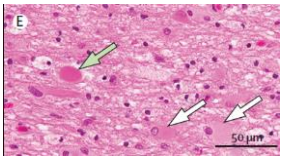
Most MS lesions are hyperintense on both image types (blue arrow). Some are hypointense, and are also known as **black holes**; those are usually older lesions in which inflammatory activity has somewhat declined. (image from Filippi et. al., Lancet Neurol

The brain is special in having a **blood brain barrier** (BBB) which prevents contrast from entering the brain under normal circumstances. Lesions tend to "light up" whenever there is a breakdown of this barrier due to the inflammatory processes and the immune response at the site.

From a histopathological point of view, active lesions are a site of myelin breakdown. They are filled with macrophages, lymphocytes, and other cells, as well as myelin debris (taken up by the macrophages). Chronic (T_1-hypointense) inactive lesions have reduced cellular density, reduced inflammation and no active demyelination.



"Sea of macrophages" in an active MS lesion, obtained by staining for myelin proteolipid protein within macrophages (hyperintense on T_1-Gd).



Axonal swelling (green arrow) and reactive astrocytes (white arrow) in active MS lesion.

From: Filippi et. al., Lancet Neurol 11:349-60 (2011))

The above is by no means an exhaustive or even completely accurate treatment of MS in MRI, but was provided just to give the reader a feeling for how T_1 and T_2 might vary in a real-life pathology.

T_2* Requires Extra Care

We will defer discussion of T_2* to a later point in this lecture, for the simple reason that it is a very tricky parameter to measure. A large part of it comes from hardware imperfections which are obviously uninteresting and patient-independent. However, some T_2* decay is intrinsic to the tissue and is interesting. T_2* is created by field inhomogeneities, and these are induced on a microscopic scale whenever one magnetic material interfaces with another having a different magnetic susceptbility. The greatest inhomogeneity is created at air-tissue interfaces. These so-called **susceptibility artifacts** can be on either a macroscopic scale – as is near the air filled sinuses – in which case they are uninteresting and lead mainly to image artifacts; or they can be on a mesoscopic scale, much smaller than the voxel size, as can be at the interface between microscopic tissue in the brain. Such **mesoscopic susceptibility artifacts** can generate interesting and viable tissue contrast which is also sensitive to many changes. Extra care is needed to isolate the mesoscopic susceptibility effects from field imperfections and macroscopic susceptibility artifacts, since they all lead to a distortion in B_0.

T_1 Contrast

Waiting For The Magnetization To Return To Thermal Equilibrium Takes Too Much Time

Let's do a simple calculation. Suppose we want to acquire an image with 256×256×192 points, not uncommon in MRI. The T_1 of water in GM and WM in the brain is about 1 second, so after each excitation we would need to water about $5 \cdot T_1$ for the magnetization to return to thermal equilibrium along the z-axis, meaning

$$\begin{aligned} \text{TR} &\equiv \text{Time to repeat} \\ &\approx 5 \cdot T_1 \approx 5 \text{ sec} \end{aligned}$$

One of the directions would use a readout gradient, so we don't have to "pay" for it with a scan, meaning we acquire all of the points in one shot after the excitation by applying a readout gradient. This still leaves us with 256×192 scans (256 phase encoding steps and 192 slices), leading to a total scan time of

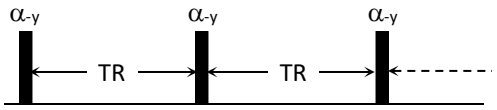
$$256 \times 192 \times \text{TR} = 68 \text{ Hours.}$$

Obviously not a very practical protocol. This can be shortened considerably by either reducing the resolution or reducing TR. We will explore what happens during the latter. As we'll see, this will not only shorten the measurement but will also introduce T_1-weighting which is in many times desirable.

Pulsing At A Rate TR~T_1 And Below Introduces T_1 Weighting

Imagine a static bucket with water. The water is said to be in *static equilibrium*, because nothing's happening to it. Next, imaging (i.) poking a hole in the bottom of the bucket, so water start running out, and (ii.) opening a tap just above the bucket, letting water flow in at a constant rate. What will happen? The water may rise or fall, but will eventually reach a new state of equilibrium (remember, the more water there is, the faster it drips out due to pressure; and the less water there is, the slower, so eventually the water flowing in will equilibrate with the water flowing out, even if at first the rates are different). This new equilibrium is termed **dynamic equilibrium**. Something is continuously happening to the system (in and out flow of water), so it's not static anymore, and yet its state doesn't change.

A similar thing happens in MRI when we use rapid pulsing. Consider a train of pulses of flip angle α (that is, $\gamma B_{RF} t = \alpha$) around, say, the –y axis. Let's call the time between pulses TR (for "Time per Repetition"):



The spins get acted upon by two "forces": the pulses, which repetitively try to take them out of equilibrium, and relaxation, which tries to get them back to equilibrium. There's also precession going on. It can be shown (I won't do it here, but it's not that difficult really) that the spins eventually settle into dynamic equilibrium, regardless of their initial state; that is, after enough pulses have been given, the state of the spins after each pulse is identical. In other words, the magnetization vector at points A, B, C, ... below is the same:

This state will depend on the variables of the system: TR, T_1, T_2 and α, and also the offset of the spins, $\Delta\omega$.

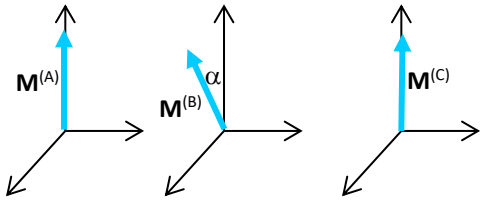
We will assume that TR>>T_2 for the time being. This serves to ensure the transverse magnetization decays to 0 before the next pulse, so we can assume M_{xy}=0 just before any of the pulses. In MRI jargon we say that the transverse magnetization is **spoiled** before each excitation.

Denote by $\mathbf{M}^{(A)}, \mathbf{M}^{(B)}, \mathbf{M}^{(C)}$ the magnetization vectors at A, B and C, respectively in the following diagram:

We're interested in computing $\mathbf{M}^{(B)}$ right after the excitation and, subsequently, the magnetization's evolution between the pulses. Note that:

1. By assumption of dynamic equilibrium, $\mathbf{M}^{(A)} = \mathbf{M}^{(C)}$.
2. Since we're assuming the magnetization is spoiled, $M_{xy}^{(A)} = M_{xy}^{(C)} = 0$.

So:



Since $\mathbf{M}^{(B)}$ is a tipped version of $\mathbf{M}^{(A)}$ by an angle α, we have:

$$M_z^{(B)} = M_z^{(A)}\cos(\alpha)$$
$$M_x^{(B)} = M_z^{(A)}\sin(\alpha)$$
$$M_y^{(B)} = 0$$

So $M_{xy}^{(B)} = M_z^{(A)}\sin(\alpha)$. However, we're not interested in the transverse magnetization (yet). We know that the longitudinal component of **M** relaxes back to equilibrium with a time-constant T_1. Between points B and C the longitudinal magnetization will relax with a time constant T_1 and evolve as:

$$M_z^{(C)} = M_z^{(B)}e^{-TR/T_1} + \left(1-e^{-TR/T_1}\right)M_0$$

where M_0 is the thermal equilibrium value of the magnetization (it's in general **not** equal to $M_z^{(A)}$!). Since $M_z^{(C)} = M_z^{(A)}$ and $M_z^{(B)} = M_z^{(A)}\cos(\alpha)$, we can plug these into the above equation,

$$M_z^{(A)} = M_z^{(A)}\cos(\alpha)e^{-TR/T_1} + \left(1-e^{-TR/T_1}\right)M_0$$

and solve for $M_z^{(A)}$:

$$M_z^{(A)} = \frac{1-e^{-TR/T_1}}{1-\cos(\alpha)e^{-TR/T_1}}M_0.$$

From this we can compute $M_{xy}^{(B)} = M_z^{(A)}\sin(\alpha)$:

$$M_{xy}^{(B)} = \frac{\left(1-e^{-TR/T_1}\right)\sin(\alpha)}{1-\cos(\alpha)e^{-TR/T_1}}M_0.$$

Thus, our transverse magnetization $M_{xy}(t)$ following excitation for any time between the pulses (t=0 corresponds to the time right after a pulse):

$$M_{xy}(t) = M_{xy}^{B}\, e^{-2\pi i \mathbf{k}\cdot\mathbf{r}}\, e^{-\frac{t}{T_2^*}}$$

which equals

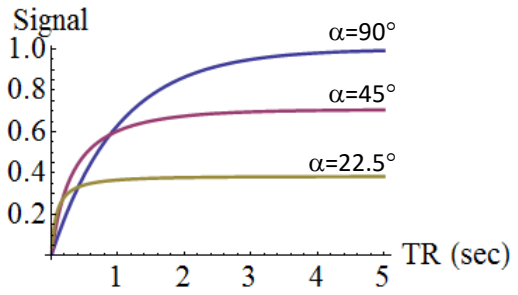
$$M_{xy}(t) = \frac{\left(\left(1-e^{-\frac{TR}{T_1}}\right)\sin\alpha\right)}{1-\cos\alpha\; e^{-\frac{TR}{T_1}}} M_0 e^{-2\pi i \mathbf{k}\cdot\mathbf{r}}\, e^{-\frac{t}{T_2^*}}$$

Understanding the DEF (#1): Pulsing At A Rate TR<<T_1 Saturates The Signal

Let us plot the intensity of the **dynamic equilibrium factor**,

$$DEF\left(\tfrac{TR}{T_1},\alpha\right) = \frac{\left[1-e^{-TR/T_1}\right]\sin(\alpha)}{1-\cos(\alpha)e^{-TR/T_1}},$$

as a function of TR for T_1=1 sec and for several values of α:



As we take TR to be shorter and shorter three things happen:

1. Our acquisition becomes shorter (good!).
2. We get more T_1 weighting, meaning the intensity becomes more sensitive to T_1, albeit only in a certain range. This is usually good.
3. The signal diminishes (bad).

The first is obvious. We will take a look at the second in a moment. The diminishing intensity is called **saturation**. When we excite the magnetization from thermal equilibrium we diminish the M_z by an amount $\sin(\alpha)$. After we do so, M_z will start building up towards thermal equilibrium during TR with a time constant T_1. This means there are two "forces" acting on M_z: T_1 relaxation, which builds it up, and our pulsing, that reduces it. If $TR<<T_1$ the pulsing wins and M_z reduces to 0 (that is, we saturate the signal). If $TR>>T_1$, M_z has sufficient time to build towards thermal equilibrium and we start up from the full intensity before the next pulse.

It is not uncommon to see sequences with TR=5 ms. We can repeat our calculation of the sequence's duration and get:

$$256\times192\times TR\approx 4 \text{ minutes}.$$

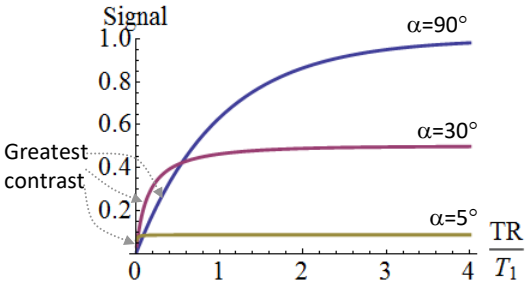
A significant reduction compared to our previous 68 hours, and also a reasonable scan time.

Understanding the DEF (#2): Lowering The Flip Angle Reduces Maximal SNR

The dynamic equilibrium factor really depends only on two parameters: the flip angle and the ratio TR/T_1:

$$DEF\left(\frac{TR}{T_1},\alpha\right)=\frac{\left[1-e^{-TR/T_1}\right]\sin(\alpha)}{1-\cos(\alpha)e^{-TR/T_1}}.$$

Let us plot it as a function of the ratio, for several different flip angles:



The **maximal signal** is obtained when the signal becomes independent of T_1. Naively, it looks like this might happen when $TR>>T_1$, which is true, since then $e^{-TR/T_1}\approx 0$ and

$$DEF_{\max}=\sin(\alpha)\qquad\begin{pmatrix}\text{for fixed}\\ \text{flip angle}\end{pmatrix}.$$

However, the above plots show this happens even before that for small α! How so? Let's take the degenerate case $\alpha\approx0$, at which $\cos(\alpha)\approx1$ and:

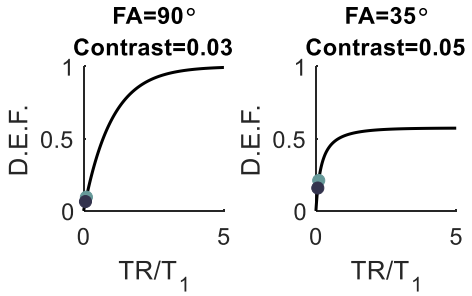
$$DEF\left(\frac{TR}{T_1},\alpha\right)\approx\frac{\left[1-e^{-TR/T_1}\right]\sin(\alpha)}{1-e^{-TR/T_1}}=\sin(\alpha).$$

So, the smaller α, the more similar the nominator $(1-e^{-TR/T1})$ and denominator $(1-\cos(\alpha)e^{-TR/T1})$ become and consequently the less dependent on TR/T_1. The true criterion is:

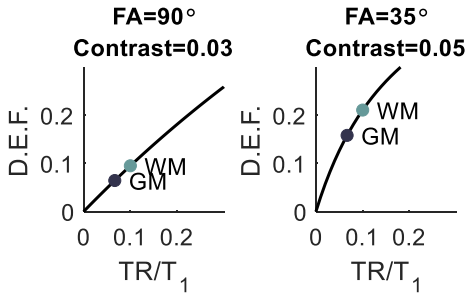
$$\frac{TR}{T_1}>>-\log\left(\cos(\alpha)\right)\equiv\left(\frac{TR}{T_1}\right)_0$$

Understanding the DEF (#3): If You Want Faster Sequences, Use Lower Flip Angles

If you wish to minimize the total sequence time you should use short TRs. To maintain good contrast, you should pick a TR which places the tissues of interest in the regime where the DEF is most sensitive to T_1. **The shorter your TR, the lower the flip angle should be to make the DEF sensitive to T_1.**To see this, a visual demonstration would help. Set TR=100 ms, and assume T_1=1500 ms (GM), T_1=1000 ms (WM). Drawn below are two DEF plots, with two different flip angles:



The two points correspond to WM (bright blue) and GM (dark gray). It is a bit difficult to see clearly, so we can zoom in on both axes:



The DEF has a larger slope in the FA=35° case in the region where TR/T_1 is small, which leads to a larger difference in signal (0.03 for FA=90°, compared to 0.05 for FA=35°).

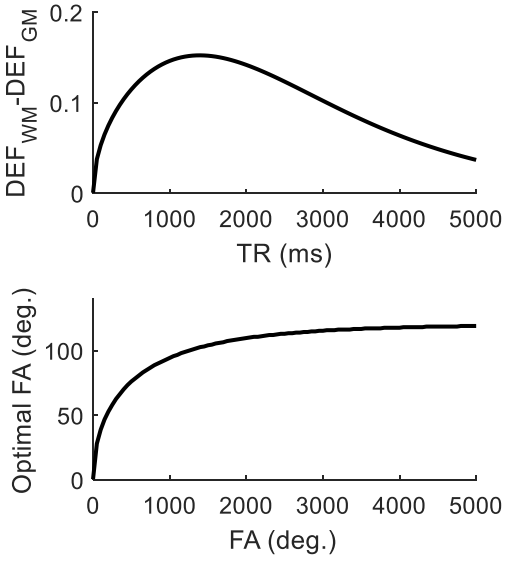
Of course, this entire discussion **assumed** that TR must be short. However, if you want to **maximize contrast** and don't care about shortening the scan time, you should pick long TRs and optimize the flip angle accordingly, as we show next.

Understanding the DEF (#4): Higher Relative CNR Is Obtained At Lower Flip Angles. Higher Absolute CNR Is Obtained At Higher Flip Angles.

We return again to the example of two tissue types (GM, T_1=1500 ms; WM, T_1=1000 ms). Let's say we wish to maximize their signal difference, for some fixed noise level – that is, maximize the CNR:

$$CNR = \frac{\left(DEF\left(\frac{TR}{T_{1,GM}}, FA\right) - DEF\left(\frac{TR}{T_{1,WM}}, FA\right) \right)}{\sigma_{noise}}$$

For each TR, we find the flip angle for which this difference is maximal, and write down the maximal CNR. We when plot the maximal CNR, and the corresponding optimal flip angle, as a function of TR:

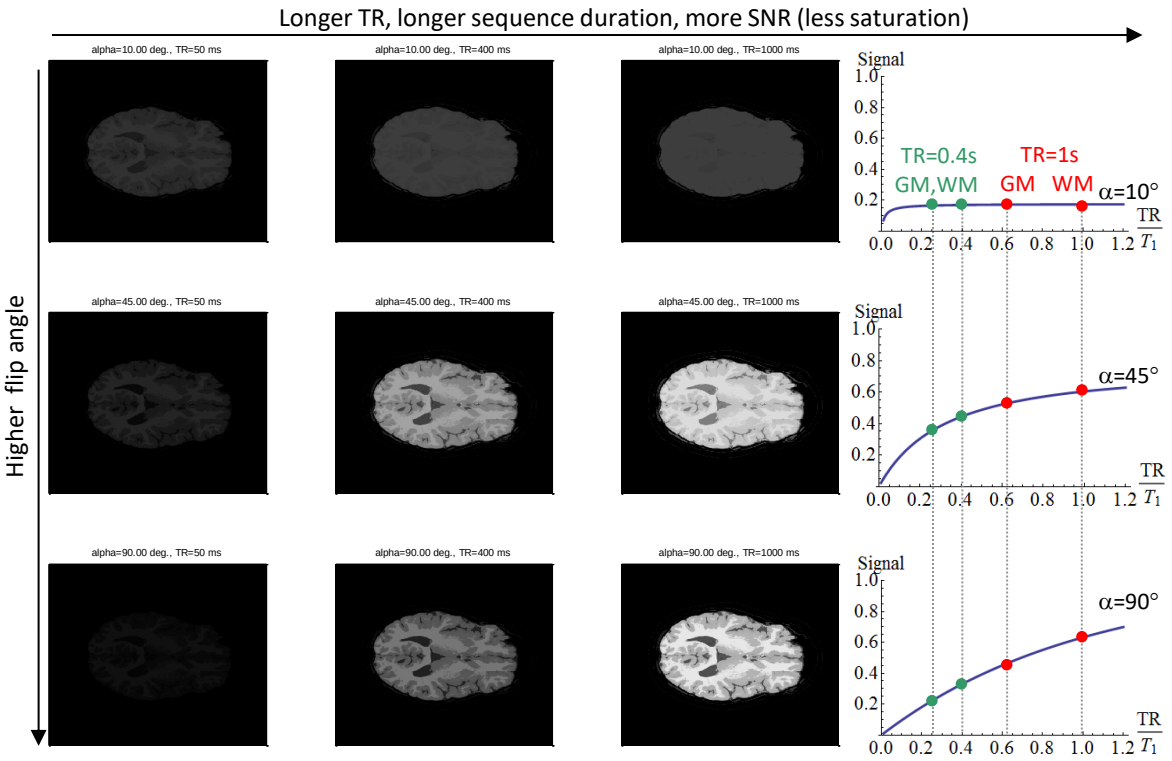


This simple optimization problem teaches us two things:

1. Optimal contrast is obtained when TR≈1400 ms, which is on the order of the T_1 value of both tissue types. So, to get the best possible contrast, we need fairly long sequences.
2. As TR becomes shorter (and CNR becomes worse), the optimal angle becomes lower and lower, again in line with our conclusion from the previous section.

Our combined insights allow us to understand the following figure, which shows the brain using a "model" with WM (T_1=1 s), GM (T_1=1.5 s) and CSF (T_1=4 s) for different TRs (50, 400, 1000 ms) and flip angles (10°, 30°, 90°):

1. Best overall contrast is observed for TR=1000 ms, with a large flip angle (90°).
2. As TR is reduced to 400 ms, and then 50 ms, the best contrast is observed for smaller and smaller flip angles (45° at TR=400 ms, and 10 deg. At TR=50 ms).



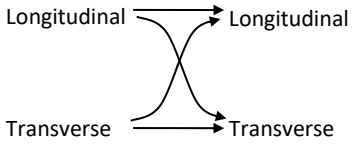
Simulated brain images with WM (T_1=1000 ms), GM (T_1=1500 ms) and CSF (T_1=4000 ms) for three different values of FA (10°, 45° and 90°) and repetition times (50, 400 and 1000 ms). The signal plots on the right show the DEF for the three different flip angles. The red dots represent WM and GM DEF for TR=1000 ms, and the green dots represent WM and GM for TR=400 ms (in both cases, GM is to the "left", because it experiences more saturation).

The Need for Spoiling, and Non-Spoiled Sequences

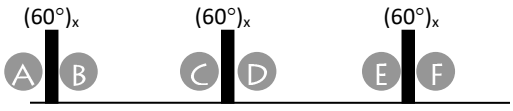
Spoiling Fails When TR~T_2 Or Shorter

All of our discussion up to this point assumed that our sequence is spoiled; namely, that M_{xy}=0 prior to each excitation pulse. This occurs naturally when TR>>T_2 so the transverse magnetization decays to 0 due to T_2 relaxation before the next pulse in the train is applied.

Any unspoiled transverse magnetization prior to the next α excitation pulse will be partially **stored** - that is, converted to longitudinal magnetization - and partially remain in the xy plane. Any longitudinal magnetization will be partially excited and partially remain along the z-axis. The effect of each pulse can be described as:

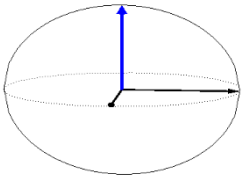


This complicates the analysis and understanding of the sequence considerably; even more so when the flip angle is not 90°. Just to provide a visual picture, here is what happens to an ensemble of spins when the inter-pulse spacing is 50 ms, with α=60°, T_1=500 ms, T_2=100 ms:

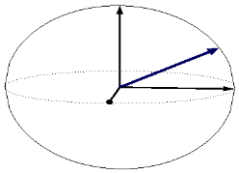


Below I've simulated what happens to an ensemble of spins with a distribution of offsets (different hues of blue correspond to different offsets):

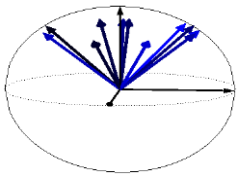
Before 1st pulse (A)



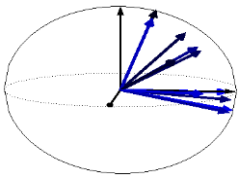
After 1st pulse (B)



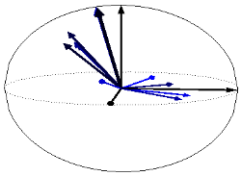
Before 2nd pulse (C)



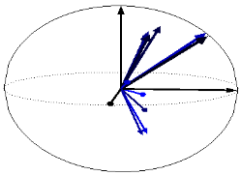
After 2nd pulse (D)



Before 3rd pulse (E)



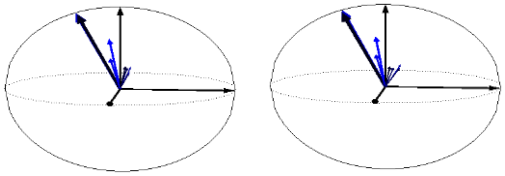
After 3rd pulse (F)



At point (C), just before the second pulse, we still have transverse magnetization – this is the meaning of a **non-spoiled sequence**.

It is quite clear that any attempt to visualize the spins' individual trajectories is impossible after 2-3 pulses. Some spins spend time in the xy-plane and are affected by T_2, while others spend time along z and are affected by T_1, and each spin rotates by a different amount.

What happens if we keep on giving pulses? Below I've simulated the state of the spins just before the 12th (left) and 13th (right) pulses:



It is clear that the two states are very similar. Even though our sequences are non-spoiled, they still converge to a state of **dynamic equilibrium**.

Because unspoiled sequences with TR~T_2 or shorter contain transverse magnetization from the previous excitation, it shouldn't come as a surprise that the signal in a non-spoiled steady state sequence with "short" TRs (i.e. on the order of T_2 or shorter) are weighted by **both** T_1 and T_2.

Spoiling Can Still Be Achieved Even At TR<<T_2 Via Either Spoiler Gradients Or RF Pulse Phases

Before taking a look at non-spoiled sequences we note that we can create "effective spoiling" via two mechanisms at our disposal: by introducing **spoiler gradients** at the end of each TR, or by incrementing the phases of the RF pulses between successive excitations. The first approach is called **gradient spoiling** and the second approach is called **RF spoiling**.

The basic idea you should grasp is the following:

If the transverse components of spins inside a voxel are randomly and/or evenly distributed in the xy plane then their transverse vector sum will add up to zero and we will have effective spoiling. In MRI jargon we say that we're **dephasing** the **intra-voxel magnetization**.

The question now becomes: how can we make sure the spins inside a voxel point in different directions in the xy-plane?

One answer to that would be: apply a strong gradient! A strong (constant, for simplicity) gradient applied for a time t will create a phase of the form:

$$\phi(\mathbf{r}) = \gamma(\mathbf{G}\cdot\mathbf{r})t\ .$$

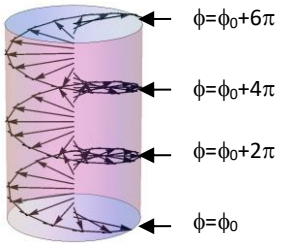
The signal from the voxel (assuming an ideal boxcar PSF) will be:

$$s = \int_{\text{voxel}} M_{xy}(\mathbf{r}) e^{-i\gamma(\mathbf{G}\cdot\mathbf{r})t} d\mathbf{r}\ .$$

Let's suppose we have just a z-gradient, so

$$\phi(z) = \gamma G z t\ .$$

We've already plotted the shape of the spins as a function of z:



Each "winding" in this helix corresponds to a phase difference of 2π, and means the spins belonging to that helix are evenly distributed in the xy-plane. Adding up the spins will give zero signal if the spins are all equal magnitude. This may or may not be a good approximation, which is why we want as many windings as we can possibly get to null the signal:

$$\Delta\phi_{voxel} \gg 2\pi$$

or

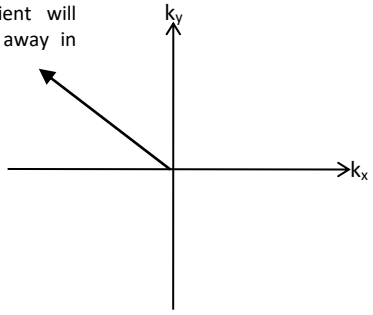
$$\gamma G \Delta z_{voxel} t \gg 2\pi$$

This would ensure that

$$s = \int_{voxel} M_{xy}\ \boldsymbol{r}\ e^{-i\gamma\ \boldsymbol{G}\cdot\boldsymbol{r}\ t} d\boldsymbol{r} \approx 0$$

There is another way of viewing this: by applying a constant gradient we're getting farther and farther away from the center of k-space, and we've already remarked that the farther out we go in k-space the smaller our signal (in the following diagram we assume the strong gradients are applied along the x- and y-axes, not the z-axis):

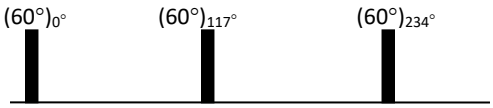
Wherever we start, a strong gradient will take us far away in k-space



[3] Readers interested in the details are referred to Zur et. al., Magn. Reson. Med. 21(2):251-263 (1991)

Spoiler gradients are an effective and simple way of ensuring effective spoiling, but they can be tricky to design since they might refocus unwanted signals (see homework assignment).

RF spoiling can also be used to dephase the intra-voxel transverse magnetization. The ideas here are significantly more complex than gradient spoiling, so we will not go into the details[3], but the philosophy is very straightforward: can we cause the newly excited magnetization after each pulse to cancel out the magnetization from all of the previous excitation? The answer is yes. One way to do this is increment the phase of the RF pulses by 117° between excitations:



How to Analyze Steady State Sequences (Advanced Topic; Not for Exam)

The general approach to steady state sequences involves a bit more math than that we've employed so far. Let's take the same sequence as before:

By virtue of dynamic equilibrium,

$$\boldsymbol{M}_A = \boldsymbol{M}_C.$$

The effect of the pulse going from $A \rightarrow B$ can be modeled using a rotation matrix:

$$\boldsymbol{M}_B = R\boldsymbol{M}_A$$

$$R = \begin{pmatrix} 1 & 0 & 0 \\ 0 & \cos(\alpha) & \sin(\alpha) \\ 0 & -\sin(\alpha) & \cos(\alpha) \end{pmatrix}$$

The time evolution $B \rightarrow C$ is then again modeled using a matrix equation:

$$\boldsymbol{M}_C = E\boldsymbol{M}_B + P\boldsymbol{M}_0$$

where B embodies the decay of the signal due to T_1 and T_2,

$$E = \begin{pmatrix} \exp\left(-\frac{TR}{T_2}\right) & 0 & 0 \\ 0 & \exp\left(-\frac{TR}{T_2}\right) & 0 \\ 0 & 0 & \exp\left(-\frac{TR}{T_1}\right) \end{pmatrix},$$

and P is the buildup matrix:

$$P = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & \left(1 - \exp\left(-\frac{TR}{T_1}\right)\right) \end{pmatrix}$$

$$\boldsymbol{M}_0 = \begin{pmatrix} 0 \\ 0 \\ M_0 \end{pmatrix}$$

M_0 is the thermal equilibrium magnetization value. In a spoiled sequence, the $\exp\left(-\frac{TR}{T_2}\right)$ factors in the matrix E are assumed zero, making solution much simpler.

Putting everything together, we then have:

$$\boldsymbol{M}_A = \boldsymbol{M}_C = E\boldsymbol{M}_B + P\boldsymbol{M}_0 = ER\boldsymbol{M}_A + P\boldsymbol{M}_0,$$

or

$$(I - ER)\boldsymbol{M}_A = P\boldsymbol{M}_0.$$

The matrix $(I - ER)$ (where I is the identity) is a diagonal matrix and has in inverse. We can multiply by it to obtain:

$$\boldsymbol{M}_A = (I - ER)^{-1}P\boldsymbol{M}_0.$$

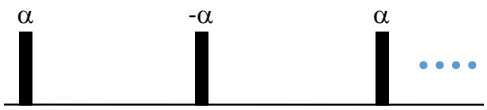
The actual calculation is doable and people have analyzed it to obtain explicit analytical expression for $\mathbf{M}_A$ (and, more importantly, $\mathbf{M}_B$=R$\mathbf{M}_A$). We're not going to attempt it now, but you should see this is definitely doable (if a bit painful algebraically).

Why Use Non-Spoiled Sequences?

There are two reasons for using non-spoiled sequences:

1. First, by spoiling the signal we're throwing it away! Non-spoiled sequences aim to make use of more signal and generate greater SNR.
2. The T_1 and T_2 contrast curves for non-spoiled sequences are different. That may be good or bad, depending on the choice of parameters.

Non-spoiled sequences have names such as balanced steady state free precession (bSFFP), steady state free precession (SSFP), FISP, trueFISP and so forth. The different sequences differ by whether their total gradients are balanced or not (i.e. whether **k**=0 before each excitation or not); some sequences also use a "two-pulse unit", where the phase of the excitation pulse is alternated:



The analysis of balanced sequences will take us a bit further than we'd like to go this course so we will leave it to a more advanced offering.

T_2, T_2' and T_2^*

The Main (B_0) Magnetic Field is Never Fully Spatially Homogeneous

The main field is never truly spatially homogeneous. You should always imagine there's an additional term in there (that might be small or large, depending on the situation):

$$B_0 + \Delta B\ \boldsymbol{r}$$

Spatial inhomogeneities might come about from several sources:

1. **Magnet imperfections**. It's impossible to build an actual magnet that is perfectly spatially homogeneous. Superconducting magnets can be made homogeneous to within ~10 part-per-billion, meaning $\frac{\Delta B\ \boldsymbol{r}}{B_0} \sim 10^{-8}$. This might sound like a great feat, and it is, but remember that $\gamma B_0 \approx 100\ \mathrm{MHz}$, meaning that $\gamma \Delta B_0 \approx \mathrm{Hz}$. Such inhomogeneities, while small, can be non-negligible when dealing with delicate sequences such as diffusion, chemical exchange and spectroscopy, which we'll encounter down the line. Furthermore, not all magnets are superconducting! Attempts to build magnets using magnetized metals have been made to drive costs down. Such magnets are much less homogeneous

spatially, because magnetized metals are "alive" – they expand and shrink due to temperature changes just enough to create spatial inhomogeneities that are very sizable *and changing in time* (yikes).

2. **Sample diamagnetism**. Biological tissue is diamagnetic, meaning that if you put a person inside a perfectly homogeneous B_0 field they will distort the B_0 lines around them, diminishing the field strength leading to inhomogeneities can be on the order of kHz ($\gamma\Delta B \sim \mathrm{kHz}$). What happens here is that the electrons in the atoms in the external field will get slowed down due to the external field and form non-zero magnetization, which will serve to *shield* the nucleus from the external field. Diamagnetism is a small effect, but still large enough to make a big difference in MRI.
3. **Implants**. Certain metallic (non-magnetic) implants out of, say, titanium, are used routinely in surgeries. When imaged in an MRI they distort the field around them and can lead to inhomogeneities that can reach tens of kHz over a very small region.

Signal Decays due to Spatial B_0 Inhomogeneities with a Time Constant T_2'

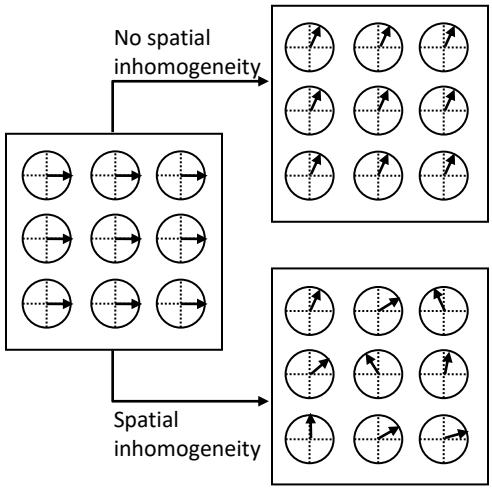
Let's think about what happens to the spins in the transverse plane due to spatial inhomogeneity of B_0: $B_0 + \Delta B\ \boldsymbol{r}$. We will argue that this leads to a decay of the signal with a time constant which we'll call T_2', **even if there is no microscopic T_2 induced thermal relaxation**. For simplicity, we'll only deal with $\Delta B\ \boldsymbol{r}$ that are temporally stable – e.g. due to tissue diamagnetism. Furthermore, in the rotating frame, B_0 will disappear and the effective field will appear as

$$\boldsymbol{B}_{eff} = \begin{pmatrix} 0 \\ 0 \\ \Delta B\ \boldsymbol{r} \end{pmatrix}$$

If our inhomogeneities are time-independent, $\Delta B(\mathbf{r})$, then spins at **r** will have an offset $\gamma\Delta B(\mathbf{r})$ and accumulate a phase $\phi(\mathbf{r},t) = \gamma\Delta B(\mathbf{r})t$ after a time t. Our transverse magnetization will behave as:

$$M_{xy}(\mathbf{r},t) = M_{xy}(\mathbf{r},0)e^{-i\gamma\Delta B(\mathbf{r})t}$$

This means that if all of our spins start out in-phase at time t=0 (along the same axis), they end up dephasing at later times:



The acquired signal at point **r** will simply be the result of convolving M_{xy} with the PSF centered at that point:

$$\begin{aligned} s(\mathbf{r},t) &= \int PSF(\mathbf{r}'-\mathbf{r})M_{xy}(\mathbf{r}',t)d\mathbf{r}' \\ &= \int PSF(\mathbf{r}'-\mathbf{r})M_{xy}(\mathbf{r}',0)e^{-i\gamma\Delta B(\mathbf{r}')t}d\mathbf{r}' \end{aligned}$$

Let's suppose for simplicity the PSF is a cube (or rectangle) the size of the voxel, so

$$s(\mathbf{r},t) \approx \int_{\text{voxel}} M_{xy}(\mathbf{r}',0)e^{-i\gamma\Delta B(\mathbf{r}')t}d\mathbf{r}'$$

Without knowing the exact form of $\Delta B(\mathbf{r}')$ we cannot make any exact claims, but we can see that overall two effects will occur:

1. **Dephasing**: The spins will go out of phase, leading to a loss of signal.
2. **Net phase accumulation**: The spins might accumulate some average non-zero phase which would create a non-zero phase for the signal s(**r**,t).

For example, if the inhomogeneity only varies weakly in the voxel, we can use a Taylor expansion, keeping things in 1D and assuming the voxel's center coincides with *x*=0 for simplicity:

$$\Delta B(x) \approx \Delta B(0) + \left(\frac{d\Delta B}{dx}\right)_0 x$$

Substituting this into the signal, and assuming we have a homogeneous voxel (again, for simplicity):

$$\begin{aligned} s(\mathbf{r},t) &= \int_{-\Delta x/2}^{\Delta x/2} e^{-i\gamma\Delta B(x)t}\,dx \\ &= e^{-i\gamma\Delta B(0)t}\int_{-\Delta x/2}^{\Delta x/2} e^{-i\gamma\left(\frac{d\Delta B(x)}{dx}\right)_0 xt}\,dx \\ &= \underbrace{e^{-i\gamma\Delta B(0)t}}_{\substack{\text{overall}\\ \text{constant}\\ \text{phase}}} \underbrace{\Delta x \cdot \operatorname{sinc}\left[\gamma\left(\frac{d\Delta B(x)}{dx}\right)_0 \frac{\Delta x}{2} t\right]}_{\text{signal decay due to dephasing}} \end{aligned}$$

We see that for a linear inhomogeneity the signal does not decay exponentially with time but rather as a sinc function.

While a linear approximation over a voxel might be a good approximation for the macroscopic fields, that is not the case for the microscopic ones. In a macroscopic ~ 1 mm^3 voxel there is significant heterogeneity and the microscopic fields are very complicated. Their average effect is not a linear gradient over the voxel, but some statistical distribution of fields, leading to a statistical distribution of spin phases inside the voxel. This statistical distribution leads more naturally (although not always!) to a more exponential decay. The time constant of this decay is termed T_2':

$$M_{xy}(t) \propto e^{-\frac{t}{T_2'}}$$

This decay is **in addition to any T_2 related decay**, meaning the total decay of the signal as a function of time will be

$$\begin{aligned} M_{xy}(t) &\propto e^{-\frac{t}{T_2}} e^{-\frac{t}{T_2'}} \\ &\equiv e^{-\frac{t}{T_2^*}} \end{aligned}$$

The combined decay constant is called T_2^* and is given by:

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

Although both of these effects lead to approximately exponential decays, you should keep in mind they originate from two **totally different mechanisms**: T_2 comes from microscopic fluctuating fields, while T_2' comes from spatial static inhomogeneities in the effective field along the z-axis (e.g. due to tissue diamagnetism, B_0 imperfections, or surgical implants).

T_2^* Contrast

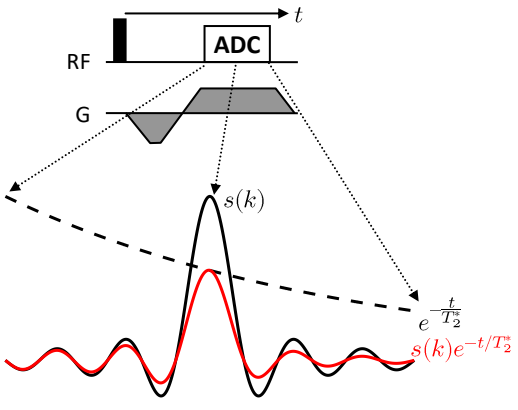
The Gradient-Echo Sequence Produces T_2^* Weighting

In the previous lecture we explained how reading data our symmetrically in k-space produces a gradient echo. Our description did not include relaxation, but mentioned that an echo is formed as we cross the center of k-space.

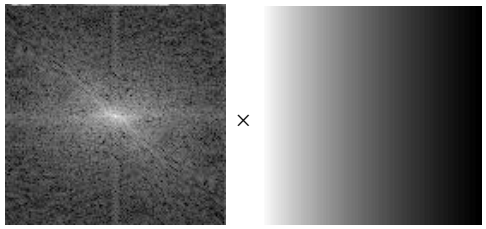
We now include relaxation, which occurs via T_2^* - the combined result of microscopic T_2 and macroscopic T_2' effects. Relaxation "kicks in" right after excitation. Let us denote by **TE** the **Time to Echo**; that is, the time between the center of the excitation pulse to the point at which the gradient echo forms at the center of the ADC event (when we cross k_x=0). Then we have:

$$s(\boldsymbol{k}(t),t) = e^{-\frac{t}{T_2^*}} \int_{body} M_0(\boldsymbol{r})\, e^{-2\pi i \boldsymbol{k}(t)\cdot\boldsymbol{r}}\, d\boldsymbol{r}$$

We assumed T_2^* does not vary spatially, which is not true in the brain. However, if it does we can just break up our integral into sub-regions in which T_2^* is constant. As a result of T_2^* relaxation, the sinc-like appearance of the echo in k-space will be weighted by an exponential decay (solid red line):



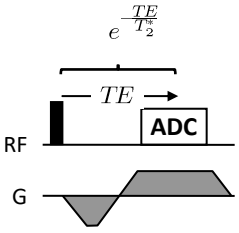
We now generalize to 2D: When viewed in 2D **k**-space, the T_2* decay happens along the readout direction (say, the x-direction). Thus we can think of our signal in **k**-space as being the result of multiplying the non-decaying signal, s(**k**), by the additional decay ξ(**k**) along the readout axis accrued due to the T_2* decay:



s(**k**) ξ(**k**)

Hence the "decay function" ξ(**k**) is only a function of k_r, the k-coordinate along the readout direction (here it's the horizontal direction). The actual extent of decay will depend on the ratio between T_{ADC}, the total acquisition time, and T_2* (t=0 corresponds to the **center** of the ADC):

$$\xi\ k_r\ = \underbrace{e^{-\frac{TE}{T_2^*}}}_{\substack{\text{decay until}\\ \text{ADC center}}} \times \underbrace{e^{-\frac{t\ k_r}{T_2^*}}}_{\text{decay during ADC}}$$



Because we set t=0 at the center of the ADC (at the echo), we have

$$k_r\ t\ = \frac{t}{T_{ADC}} \cdot k_{max}$$

so k(0)=0, k(-T_{ADC}/2) = -k_{max}/2 and k(T_{ADC}/2)=k_{max}/2. This is a slightly unusual choice of t=0 but it makes subsequent calculations easier. Inverting,

$$t\ k_r\ = \frac{T_{ADC}}{k_{max}} \cdot k_r$$

Plugging this back into our decay equation, we get:

$$\xi\ k_r\ = \underbrace{e^{-\frac{TE}{T_2^*}}}_{\substack{\text{decay until}\\ \text{ADC center}}} \times \underbrace{e^{-\frac{T_{ADC}}{k_{max}T_2^*}k_r}}_{\text{decay during ADC}}$$

The Effect of T_2* Decay on the Echo is (Usually) A Simple Scaling

How can we understand the above figure? Well, if the readout is short enough – short compared to T_2* - then we can neglect T_2* to a first approximation during the readout and just assume it causes our signal to decay up until the gradient echo (the center of k-space). This decay is given by

$$\exp\left(-\frac{TE}{T_2^*}\right)$$

This approximation is quite good for most practical cases, since T_2^* is indeed often longer than most readouts.

If The Readout is Long Enough, T_2* Decay Also Blurs the Image

If T_2^* decay is substantial during readout, it will blur the image along the readout direction. This is a general feature of Fourier transforms: constraining the signal to a region of width X in one domain will cause the signal to widen by an amount 1/X in the Fourier domain. In our case, the signal will decay with a time constant T_2* as it is read out in k-space. If the readout gradient strength is G, then $k\ t\ = \gamma\!\!\!^{-}Gt$ and, in terms of the variable k:

$$e^{-\frac{t}{T_2^*}} = e^{-\frac{k}{\gamma\!\!\!^{-}GT_2^*}}$$

This means that the signal decays with a scale $\gamma\!\!\!^{-}GT_2^*$ in k-space. As a result, once it is Fourier transformed back to real space it will have a width (i.e. blurring!) given by

$$\Delta x_{blur} \sim \frac{1}{\gamma\!\!\!^{-}GT_2^*}$$

For most practical purposes this blurring is too small to have an effect on the image. For example, putting typical values of G=10 mT/m, T_2*=50 ms, we obtain $\Delta x_{blur} \sim 50\ \mu m$. This is

much smaller than most in-vivo human voxel sizes, which are usually on the order of 1.0 mm.

T_2^* Contrast Application: The BOLD Effect

Oxygenated blood and non-oxygenated blood have different magnetic properties, because tying up oxygen to the heme group in blood cells shields the iron atoms in the heme group. As a result, oxygenated blood is **diamagnetic**, and does not appreciably distorts B_0 around it; while non-oxygenated blood is **paramagnetic**, and distorts B_0 more heavily. Consequently, oxygenated blood has a longer T_2^* compared to non-oxygenated blood. This is used as the cornerstone of **functional MRI (fMRI)**.

In fMRI, a subject is scanned initially at rest (usually using a T_2^*-weighted sequence) and then subsequently during the application of an external stimulation. Regions that show a signal change (usually an increase, due to the inflow of oxygenated blood) are regions which are involved in the neural processing of the stimulation input.

> BOLD contrast refers to the change in signal in voxels in "activated" brain regions seen using (usually) T_2^* weighted (GRE) images.

This idea of functional imaging lets us study the *functional parcellation* of the brain: assigning different functions to different regions, and studying how these regions interact. This is a very powerful approach to "understanding" the brain.

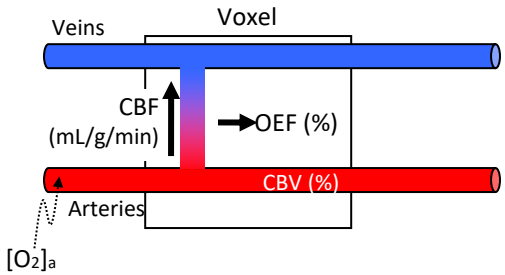
An ideal functional imaging experiment would map some sort of **physiological quantity**, such as neuronal firing rates, blood flow, or anything that has a biological meaning. BOLD-fMRI, as we'll see in a bit, is not an idea imaging experiment, because the signal change depends in a complicated manner on multiple physiological parameters. However, it is an **easy** experiment to do, and it offers good spatial (~mm) and temporal (~sec) resolutions, making it one of the most powerful tools in human neuroscience.

The Concept of Functional Activation

Even when we are at complete rest our brain consumes an incredible amount of energy. 20% of our caloric energy intake are used by the brain alone, despite comprising only 2% of the body's weight. However, when presented with an external stimulus, certain regions become more "engaged", resulting in increased types of activity:

1. Increased electrical activity, stemming from neurons conducting electrical currents along their axons, happens on timescales of milliseconds.
2. Increased hemodynamic activity, in which oxygenated blood flows to different areas is regulated, happens on a timescale of seconds.
3. Increased metabolic activity, in which the consumption of metabolic products such as oxygen and glucose is regulated, happens on a timescale of seconds.

The three are heavily inter-related. Increased energy demands in neurons sends signals to astrocytes which then interact with the endothelial cells which line the capillaries and dilate them, causing increased blood flow. There are several associated quantities with these changes, illustrated in the following diagram:



1. **Increased Cerebral Blood Flow (CBF)**: Pretty much most of the early functional studies were concerned with the flow of blood to the brain. Initial experiments measured **global CBF** by letting patients breath in NO, which is inert, and measure its outflow concentration in the jugular vein - not a pleasant experiment. CBF is stated in volume per unit time and can be either a local (to a particular tissue or organ) or a global quantity (to the entire brain). When described as a local quantity, it is given in blood volume per unit time per gram of tissue; e.g., mL/min/g. We note here that **CBF, as used in fMRI and seen in MRI, quantifies the amount of blood extracted to capillaries in the imaging voxel**. This is slightly different than the more physiological

use in which one would quantify the total blood flowing through the voxel.

2. **Increased Cerebral Metabolic Rate of Oxygen ($CMRO_2$):** This is the rate at which oxygen is removed from the blood. It is given usually in μmol/(gram·min).
3. **Increased Cerebral Metabolic Rate of Glucose (CMRGlu)**: This quantity is similar in meaning to $CMRO_2$, only it pertains to glucose utilization for the purpose of either aerobic or anaerobic respiration in cells.
4. **Decreased Oxygen to Glucose Index (OGI)**: Aerobic respiration uses glucose and oxygen at a ratio of 1:6. If cells used completely aerobic respiration their CMRGlu would be six times larger than $CMRO_2$. This ratio, called the OGI, is in fact slightly lower at rest (about 5.3), and becomes slightly lower during activation, indicating that energy production becomes slightly anaerobic.
5. **Increased Cerebral Blood Volume (CBV)**: This is the amount of volume blood (in blood vessels) occupies within either the brain as a whole or within an organ or voxel or any other unit of volume. It is therefore not a volume per-se but a percentage or fraction. This is a surprisingly small number in "average" brain tissue, around a few percent.
6. **<u>Decreased</u> Oxygen Extraction Fraction (OEF)**: The OEF is the amount of oxygen that leaves the blood and is metabolized in the cells. It is specified in percentage. If we have a certain oxygen concentration in the arteries going into some brain tissue, $[O_2]_a$, and CBF liters of this blood go into the tissue per gram per unit time, and a certain percentage of it is extracted by the tissue, then $CMRO_2 = OEF \cdot CBF \cdot [O_2]_a$, or

$$OEF = \frac{CMRO_2}{CBF \cdot [O_2]_a}$$

What do you think happens to the OEF during functional activation? Contrary to intuition it actually goes **down**. This is because during activation $CMRO_2$ and CBF both increase, but the CBF increases more than $CMRO_2$. Less OEF means a larger oxygenated hemoglobin concentration, which means blood becomes more diamagnetic, which means a signal increase - which is indeed what we see in BOLD imaging.

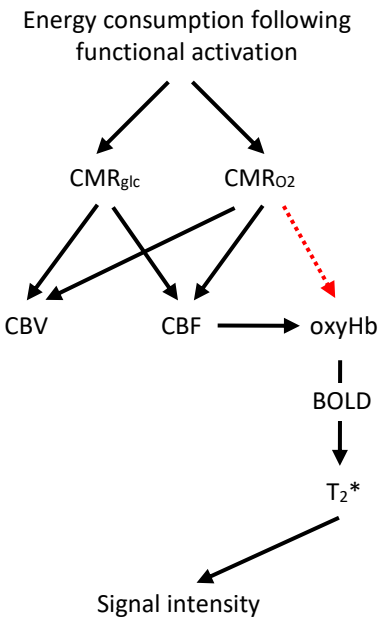
The following table summarizes typical resting brain and "activated brain" values:

Quantity	Typical Value (Resting Brain)	Typical Change in Activation
CBF	0.5 mL/g/min	50%↑
CBV (GM)	3-5%	5% ↑
CBV (WM)	2%	5% ↑
λ (brain avg)	0.9	None
$CMRO_2$	1.6 μmol/g/min	10%-50% ↑
CMRGlu	8.5 μmol/g/min	50%-100% ↑
OGI (Glu/O_2)	~5.3	Decreases slightly
OEF[4]	40%	20% ↓
$[O_2]_a$	8 μmol	Increases slightly
Energy usage (brain avg)	21 μmol/g/min	

Functional Activation Prolongs T_2*

The following diagram summarizes the changes during functional activation, and show how they lead to increased T_2*:

[4] Interestingly, OEF is almost constant throughout the brain (at rest). For example, oxygen consumption in GM is about 4 times as large as in WM, but the OEF for both is very similar!



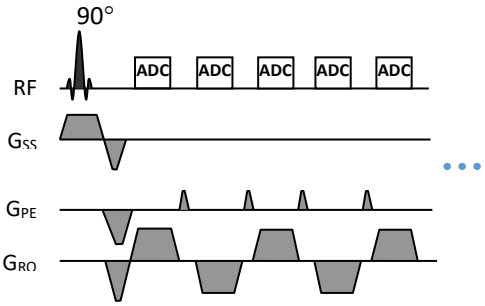
Black solid lines: increase
Red dashed lines: decrease

Briefly: the increased oxygen metabolic rate ($CMRO_2$) increase the cerebral blood flow (CBF), but also removes more oxygen from the red blood cells. However, there are more oxygenated blood cells coming into the voxel than "used up" deoxygenated blood cells, resulting in an overall increase in oxygenated blood cells and an increase of T_2*. This is the basis of BOLD.

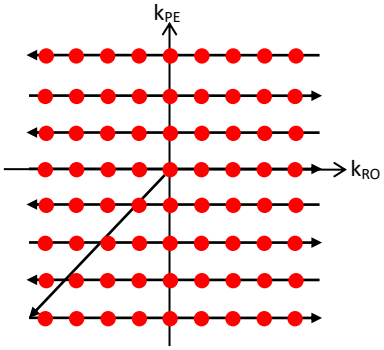
There are other functional imaging methods. Cerebral Blood Flow (CBF) can be assessed using special sequences which use radiofrequency pulses to do Arterial Spin Labeling (ASL). CBV changes can be imaged using special contrast agents which affect T_2. CMRGlc and $CMRO_2$ can be imaged directly using radioactive tracers and positron emission tomography (PET). Direct neuronal activity can be imaged by measuring the electrical (EEG) or magnetic (MEG) fields outside the brain. We will not discuss these methods in this course, and just mention them in passing so you know they're out there.

Fast T_2*-Weighted Images Can Be Acquired Using an Echo Planar Imaging Sequence

The blood flow changes that lead to T_2* changes happen on the order of seconds. It is possible to acquire full 2D slices of the brain with a temporal resolution on the order of seconds by using a special sequence called an **Echo Planar Imaging** (EPI) sequence. Here is its schematic pulse sequence:



This sequence excites the spins in a given slice, and they start at the center of k-space. The initial rewinder gradients along the PE and RO axes move you to a corner in k-space. Then each RO gradient reads out a line in k-space – positive, then negative, then positive, then negative, and so forth. The small "blips" along the PE direction between each successive line nudge you slightly up in k-space in small steps. The resulting trajectory in k-space is illustrated below:



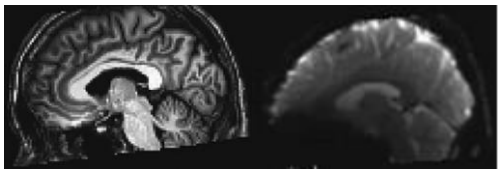
All k-space sampling constraints apply to EPI as well: the distance between points along a certain direction equals the field of view along that direction, and the extent of sampling along that direction equals the nominal voxel size.

EPI sequences yield T_2* contrast. The echo time in EPI sequences is defined as the time that elapses from the excitation pulse (or, more accurately, the center of the excitation pulse), up until the center of k-space. You must read through several k-space "lines" before reaching the center of k-space, and therefore the typical TEs in EPI tend to be on the order of several tens

of milliseconds. This can help create excellent T_2* contrast. However, EPI also has several drawbacks:

1. The long evolution time of the spins in the xy plane allows for more time for any field inhomogeneities to evolve, which distorts the image and leads to signal loss.
2. The limited time (~T_2*) available to acquire all points in "one-go" means that EPI images often acquire fewer points and offer lower resolution compared to approaches that acquire one line "at a time".

This is why EPI sequences are not often used in clinical settings.

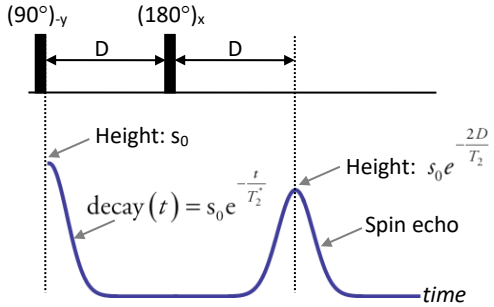


Left: T_2* and T_1 weighted gradient echo sequence. Right: EPI from same slice (taken from: Radiology 2020; 294:149–157). Notice the signal dropout in EPI near the sinuses and mouth, where air-tissue interfaces lead to a discontinuity in the magnetic susceptibility and large B_0 inhomogeneities.

T_2 Contrast

The Spin Echo Refocuses T_2' And Leaves Us Solely With T_2 Related Signal Decay

We now come to the next class of sequences known as **spin echo sequences**, which are T_2-weighted. These sequences rely on a basic element known as a spin echo. Imagine the following simplified pulse sequence, in which the spins are excited, precess around, and then subjected to a 180° pulse – also called a **π-pulse** in MR jargon for obvious reasons. If we run this sequence and plot the signal as a function of time, we will obtain



We will now analyze what happens to the signal as a function of time. The π-pulse inverts the phase of the spins in the xy-plane. Focusing on a small, mesoscopic subregion, the offset of those spins due to spatial, constant field inhomogeneities will be $\omega(\mathbf{r},t)=\gamma\Delta B(\mathbf{r})$. Its time evolution will be

$$M_{xy}(\mathbf{r},t)=M_{xy}(\mathbf{r},0)\,e^{-\int_0^t \omega(\mathbf{r},t')dt'}.$$

At time D, right before the 180° pulse, it will have accumulated a phase

$$\phi(D)=\gamma\Delta B(\mathbf{r})\,D.$$

What is the effect of the $(180°)_x$-pulse on it? This can be deduced via a simple calculation: if we write the magnetization vector as

$$\mathbf{M}=\begin{pmatrix}\cos(\phi)\\ \sin(\phi)\\ 0\end{pmatrix}$$

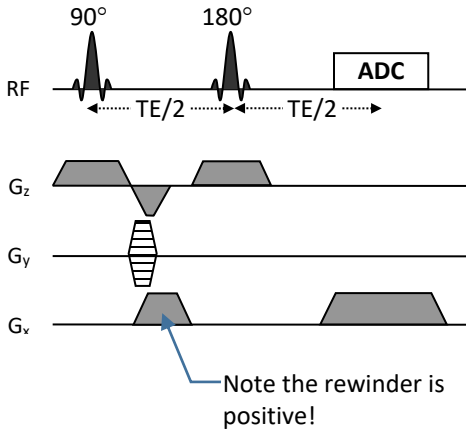
and use the form of a rotation matrix about x:

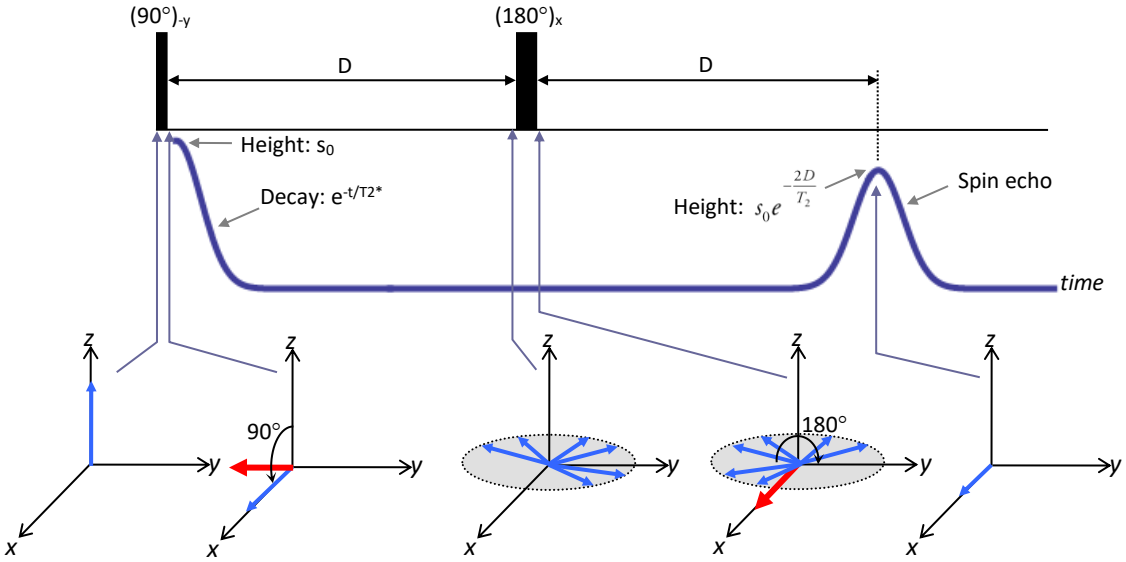
$$R_x(\theta)=\begin{pmatrix}1 & 0 & 0\\ 0 & \cos(\theta) & \sin(\theta)\\ 0 & -\sin(\theta) & \cos(\theta)\end{pmatrix}$$

we get

$$R_x(\pi)\mathbf{M}=\begin{pmatrix}1 & 0 & 0\\ 0 & -1 & 0\\ 0 & 0 & -1\end{pmatrix}\begin{pmatrix}\cos(\phi)\\ \sin(\phi)\\ 0\end{pmatrix}=\begin{pmatrix}\cos(-\phi)\\ \sin(-\phi)\\ 0\end{pmatrix}$$

namely, the phase of the spin will be flipped $\phi \to -\phi$. Since in the subsequent delay D it will acquire again the same phase $\phi(D) = \gamma \Delta B(\mathbf{r}) D$, these two will cancel out and the spin will return to the x-axis, **regardless of its constant offset**. This experiment is one of the most important experiments in the history of NMR, first carried out by Erwin Hahn in 1950 (in a slightly different variation). Even though the π-pulse negates T_2' decay due to constant inhomogeneities, it does not negate the microscopic T_2 decay due to the microscopic fluctuations of the fields. We thus say that the π-pulse has **refocused** T_2' but not T_2.





t=0⁻
All the spins start out from thermal equilibrium.

t=0⁺
Following the initial $(90°)_{-y}$ hard pulse, all spins are tilted to the transverse plane.

t=D⁻
The spins dephase due to different spatial offsets (T_2') and microscopic decay (T_2).

t=D⁺
A $(180°)_x$ flips the spins about the y axis and reverses their phases, $\phi \to -\phi$.

t=2D
All of the spins refocus along the y-axis and the signal "revives", forming a **spin echo**. Some signal is lost due to intrinsic, irreversible T_2 decay.

π-Pulses Allow Us To Replace T_2* Contrast With T_2 Contrast

180° pulses can be used to turn the basic T_2* based gradient echo (GRE) sequence we've encountered previously into a T_2 based spin echo (SE) sequence as follows:

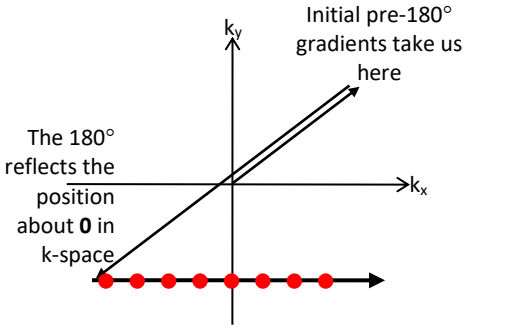
Note several changes compared to the GRE sequence. First, the rewinding gradient lobe along x is now positive. This is because the effect of the 180° is to invert the phase of the spins. This means that spins with a particular **k**-space position,

$$M_{xy}^{(rot)}(\mathbf{r},t) = M_0(\mathbf{r}) e^{-2\pi i \mathbf{k}(t)\cdot\mathbf{r}}$$

will get their phase flipped by the 180° pulse:

$$M_{xy}^{(rot)}(\mathbf{r},t) = M_0(\mathbf{r})e^{-2\pi i\mathbf{k}(t)\cdot\mathbf{r}} \xrightarrow{180^\circ} M_0(\mathbf{r})e^{-2\pi i\mathbf{k}(t)\cdot\mathbf{r}}$$

which is equivalent to replacing **k** by -**k**. Thus, the corresponding trajectory in **k**-space for a given scan looks like this:



Our simplistic analysis can now be repeated: our signal decays and to a first approximation we need only take its value at the echo time, TE, into account. The decay is now governed by T_2 and not T_2* thanks to the 180° pulse; This means **our signal in each voxel will be multiplied by** $\exp\left(-\frac{TE}{T_2}\right)$.