

Well, good morning, it's 8:30, so we'll move into the next topic which is the third of the continuing education courses on MRI at this meeting. What we're trying to do in setting up these courses is kind of start with the ACR discussions that Carl Keener presented, move to Geoff Clarke's talk yesterday, which was just, kind of review of the basics, SNR and CNR, and primary pulse sequences and moving today into what I label as advanced MRI, but these are on most of the 1.5 T and higher field strength systems for sure and are for the most part in clinical use, so you can might argue of my choice of the word advanced. Then tomorrow in the fourth session at the same time, same room, Jason Stafford will be discussing high field MR and depending on what week you ask that question, you have to define what high field is, but for this course, that's three Tesla and

higher. So we're kind of moving up the field strengths and moving up the complexity of the studies. So, Geoff Clarke mentioned yesterday a whole list of intrinsic and extrinsic parameters and our game as MR physicists, and medical physicist working in the area of MR, is to basically take the intrinsic parameters that we have, which are not under our control but are set by the patient, and move to the extrinsic parameters that we do have control over, and take advantage of these parameters to make the contrast in the image reflect the intrinsic parameters that are of the clinical question. So we're going to continue doing that today. Geoff started that process yesterday in discussion, and today we're gonna talk about four quote/unquote, advanced topics. So what are those four? The first is techniques that are being used to what I call assess the microvascular

environment, so we're not looking at macroscopic vessels, which we would do with angiographic studies, but looking at smaller vessels like capillaries and venules and how do those change either as an effect of treatment or how can we use those to aid us in differential diagnosis. The other is looking at diffusion and this is a very commonly used technique in magnetic resonance imaging today and is basically just looking at the brownian, or thermal motion of protons in different tissues, primarily brain for now (for clinical operations), but that is changing. And then how do we look at areas of neuronal activation? We don't do that directly but we look at indirect responses of neuronal activation to map areas of the brain that are active in certain tasks, and do that for primarily treatment planning but also for basic research. And also, how can we assess

biochemical changes non-invasively? And again, virtually all of the certainly state of the art 1.5 T and higher systems have capabilities of doing all of these things. So let's take them one at a time and talk about assessing the microvascular environment. Well, as I mentioned, we can do angiographic studies with MRI both non contrast enhanced, these two were with no exogenous contrast agents injected, or we can inject and do basically first pass bolus angiography much like CT angio, and we can do that virtually throughout the body from head to toe, these are draining vessels in arterial phase and mixed arterial venous phase going from a giant cell tumor in the foot, for example. So we can look at vessel sizes down to about one millimeter or so using the both contrast enhanced and non contrast enhanced techniques, so I would consider that to be kind of macroscopic

vascular morphology changes. However, certainly in the oncologic setting, it's the

microvascular changes that we're very interested in and so when tumors begin to grow, it's typically true they can't grow beyond two millimeters without making a change in their vascular environment; that is either recruiting the growth of new vessels or modifying existing vessels to be more permeable to provide more nutrients for the growing tumor and they certainly can't metastasize without making such modifications. So if we can assess this, we can both look at effects for treatment of tumors that are based on anti-angiogenic or anti-vascular responses or just use this information to aid in differential diagnosis of malignant versus non-malignant tumors, for example, or lesions, for example. So if we want to assess this vascular change in MRI, we have to use very

high speed imaging techniques and that's why these techniques were more recently added to the armamentarium of MRI. So the most common ways to do that is to use what's known as dynamic contrast agent enhanced MRI, or DCE MRI, or dynamic susceptibility change MRI, or DSC MRI, and we're gonna talk briefly about each of those techniques. Both of them require very rapid sampling. For DCE MRI, we typically like to be able to acquire sets of images at five to ten seconds per image set. You can do coarser sampling, but it's nice to be able to acquire at this high temporal resolution. If you want to look at the dynamic susceptibility change techniques, as we'll see in moment, that's the first pass bolus capture, and you need to have temporal resolutions on the order of one to two seconds. So both of them also require infusion of exogenous contrast agents and Geoff

Clarke talked some about this yesterday, and mentioned the three most common contrast agents we use in MRI. All of them are based on the gadolinium atom. It's a paramagnetic atom and basically affects, as we'll see in a moment, the T1 and T2 relaxation times. The good news about these contrast agents is their osmotic loads are much, much less than iodinated contrast agents we use in CT and R&F and so you have much less likely adverse reactions, and these contrast agents can be used even in compromised kidney function patients. So these agents affect both T1 and T2 relaxation times, in fact they shorten both and demonstrated here is the effect of the increasing concentration gadolinium on the T1 relaxation time and similarly for the T2 relaxation time and the thing that varies among the contrast agents is the relaxivities of these

contrast agents that describe how much effect these agents have as a function of concentration on the relaxation parameters. Clinically, we always focus on the T1 shortening, but there's also a T2 shortening as Geoff mentioned yesterday. The day-in-day-out practice of using contrast agents is to use T1 weighted images before and after contrast as static views. So we acquire an acquisition before we inject contrast, inject contrast and, in a spin echo sequence here, small increases in gadolinium cause a huge increase in contrast in the areas where this contrast agent leaks out. Geoff mentioned yesterday that the blood/brain barrier's impermeable to this agent but when that blood/brain barrier is partially or completely destroyed, it leaks out and you see the uptake. So this has been used clinically for many years. What we do differently now is

image rapidly before, during and after this bolus injection of contrast agent. So again, most of these are based on sequences that Geoff discussed yesterday, fast spoiled gradient echo sequences, FSPGR's on GE systems, FLASH sequences on Siemens, etc. The

spoiling here maintains T1 weighting even with very short TR's, which is our goal, to go to short TR's to get fast sampling. And there's always a tradeoff between the need for good temporal resolution, because we want to capture these dynamic processes, and adequate spatial coverage. And both 2-D and 3-D acquisition modes are commonly used in clinics. More recently you might see systems that have fast spoiled gradient echo sequences with what's known as echo train readout so we, much like a fast spin echo sequence that Geoff discussed yesterday, we acquire more than one echo per TR and that

speeds up the acquisition rates even more, and that can be used to increase temporal resolution or to improve our anatomic coverage. So this is an application of dynamic imaging in breast, which was one of the very first applications clinically back in the early 90's, actually, and so what you can see is, over time, the contrast agent fills in not only the lesion, but the normal parenchymal tissue of the breast. So the idea behind all these dynamic imaging techniques is you look at different regions of interest as a function of time, look at change in signal intensity, and you can see very different characteristics; the area that "lit up first", so to speak, was the tumor area, so it has very rapid uptake of contrast agent, whereas the normal surrounding parenchyma increased more slowly. But if you wait out here to the very end, virtually everything's enhanced so it's very hard to

tell about the different tissue types making up this breast tissue. It's not only true in breast, these are examples from brain tumors and lesions so this is a primary brain tumor, a metastatic brain tumor, a meningioma, and radiation necrosis (there's no active tumor here), and what you see is as a function of time, the uptake characteristics vary. And it looks sort of like this; if you have changes in blood volume, (these are simulated uptake curves of contrast agent versus time), so if an increase in blood volume locally occurs, such that the blood volume here in one is higher than two, higher than three, what you see is what you would expect. The uptake curves are much larger in the higher blood volume cases and the area under these curves would reflect that and that's often commonly used to assess dynamic imaging techniques. The other things is if the vessels are leakier, so in

the pink here is the highly leaky vessel going down toward blue which is a much less leaky vessel, the permeability's much less, then you can see the slopes of these curves all change where the more leaky vessels, higher permeable vessels, have very rapid uptake of this contrast agent, which is what we saw in that breast case. And the benign tissue, or lower grade lesions typically have very slow uptake and that's again, is what we saw in the normal breast tissue. So these curves have been looked at since the mid 90's, both qualitatively, just visually looking at these curves and saying "this tissue took up contrast very rapidly therefore it's probably tumor" People have also looked at semi-quantitative, as I call them, techniques, time to peak enhancement (things that enhance faster typically are more malignant), maximum rate of uptake (looking at the slope of that uptake again),

and in these, as I mentioned, the area under the curve and the initial area under the curve, which is basically again in proportion to the slope. And then more recently there's been a lot of moves to go to quantitative imaging, or quantitative analysis data, particularly for drug clinical trials with agents that are targeted at the vasculature. And to just briefly mention that technique, because we're seeing it used more and more commonly, the idea

here is that if you have a lesion, this happens to be a mouse, but if you have a lesion and you can sample the contrast uptake over time in the lesion, you can also sample the uptake in the major vessels, so that's the vascular response to the contrast agent in administration. So you measure those two parameters, the contrast in the lesion (contrast concentration) and the contrast concentration in the plasma and then you know that in this

region of interest, the contrast that you see is due to that part of this ROI that's vascular, so there's the vascular volume fraction, and the contrast agent that's in the vasculature, and the part that we call the interstitial space (these contrast agents can't get into the cells). So this is the stuff that's outside the vessel, but also outside the cells. So you can't measure this directly, and that's where you use the pharmacokinetic modeling and it's much more straight forward than maybe it looks here, you have contrast coming into the blood vessels that goes through the blood/barrier or the capillary endothelial cells into this interstitial space and eventually that comes back to the plasma and is eliminated, for these contrast agents, by the kidneys. So the rate that this goes across is basically proportional to how permeable these vessels are. So now you're getting a measure of the

vascular volume by using these equations and also how permeable the vessel is. So that's the idea, if you can extract these three quantitative measures, you can say a great deal about changes in the microvascular environment. And if you're gonna do that, there are basically several regimes. There's what we call the flow limited case, where basically of all the contrast that comes in, a high fraction passes right through the blood/brain barrier or the endothelial cells first pass, so it's very, very leaky. You can also have permeability limited areas. So this is low permeability, and then mainly we're working in between. And the measures that came out were in that previous slide, 1) K-trans, which is what you see in the literature called endothelial transfer coefficient, that basically tells you something about the permeability, 2) the vascular volume fraction and 3) the reflex rate.

So these techniques are being used to provide quantitative information and we can do that either in a region of interests approach as I had a shown before, or you can calculate it pixel by pixel and see how this lesion varies - the heterogeneity of this lesion in both its plasma volume as well as its permeability. And these techniques, again, are being used very frequently in clinical trials for testing new therapeutic techniques, but also is useful in both the differential diagnosis of lesions, and also targeting the area of the lesion that might be the prime target for biopsy, and that's actually the example here where you can see the fiducial markers around the individual's brain. This was used to basically target the most suspect region based on the maximum vascular volume and the endothelial transfer coefficient. So these techniques are being used not only for clinical trials and

advanced applications. Very frequently, if you go to a center, they're doing dynamic imaging of the liver, it's again used to help in the differential diagnosis of lesions in the liver, they may not be doing the quantitative analysis, but they very commonly do an early phase, mid phase, late phase. So this is basically taking that approach, we're doing that in CT as well now, taking that approach and moving it out to a higher temporal sampling regime. Another technique for looking at microvascular changes is what we call dynamic susceptibility change MRI and here, very similarly, we inject a bolus of

contrast agent, for now all gadolinium based. The other contrast agents that we would like to use, as Geoff mentioned yesterday, are still on the FDA pipeline. So we inject the common contrast agents that we use clinically now, but we inject it very rapidly and we

acquire images very rapidly. Because here we're wanting to look at changes in the first pass, as the bolus of contrast agent passes through region of interest, it causes a dephasing of the signal because you've got this contrast agent that's a paramagnetic substance passing through a region of interest. As it does that, it will perturb the magnetic field, you'll get increased dephasing and signal loss. Normally that's a bad thing, but one of the goals of doing MRI is to turn everything that's bad into something good if you can. So this is a case where we're losing signal but we're using that for our advantage. So as an illustrative point, here's a single slice from a cine frame, where we've injected this contrast agent. So we're scanning along at baseline, and we inject contrast agent. As that contrast agent goes through the microvascular space, you see a

loss of signal intensity, particularly in the gray matter. And that's because the gray matter vascular volume's twice that, roughly, of the white matter so you see a signal decrease and then it's transient as that tight bolus passes out and then mixes through the bloodstream, you get a recovery back to baseline again. Well, it so happens that this is a curve basically taken from a gray matter region here, showing that signal loss and then if we mathematically manipulate that signal loss curve, we can basically show that the area under that curve is proportional to the blood volume. So if we can measure this curve and then if we want to convert that into absolute terms, we have to basically manipulate things a bit here where S_0 is the baseline intensity, $S(t)$ is the signal intensity as function of time and TE is just the echo time. So we can get this relaxation curve here, or change

in relaxation curve, and, again, the area under that first pass bolus is proportional to the microvascular blood volume. So this allows us to look at changes in blood volume and by calculating what's known as the mean transit time of this bolus through the vascular space, also the blood flow. This is a directly analogous technique to what you may be seeing in multi-slice CT in terms of functional CT which is now actually a commercial package on some platforms so it's a direct analogy to the CT approach. So by doing this, these are the source images that we use, these are the types of blood volume maps that can be created and this is in a normal appearing brain at least. This is a patient with a glioblastoma multiforme so you can see the contrast leakage into that using just standard clinical imaging. You can also see that there are different areas of this that have higher

blood volume that you can't really distinguish in just the static pre/post contrast views and these areas are at the higher blood volume, more likely to be the malignant and higher grade tumor. So that's some of the things that are going on in assessing microvascular environment using these techniques. Something that's very, very commonly used now is diffusion imaging and Geoff introduced this topic yesterday so I'd just like to follow up on that. At our center, for example, every patient that gets a brain scan gets a diffusion scan. This really started as we'll see in just a few moments, in screening for acute stroke but has branched into many other areas. So how does this

work? Well as Geoff pointed out yesterday, if you appropriately modify even a spin echo sequence, the contrast can be made to depend on the rate of random brownian motion -

just diffusion of protons due to thermal motion. Now the range of proton motion due to diffusion processes is very, very small, microns to millimeters depending on how long you assess the diffusion. And every time your heart beats, your brain moves that much. Just blood flow coursing through causes that. Physiologic motion and gross patient motion are much larger time scales than that so we have to be able to scan exceedingly rapidly so typically these acquisitions acquired using echo planar imaging that Geoff discussed yesterday, which are currently the most rapid acquisition techniques on clinical scanners, with spiral acquisition techniques coming out as well. These techniques allow us to acquire images in the 50 to 100 millisecond per image time scale. So again, what happens, as Geoff pointed out, is you might have a spin echo sequence - so here's your 90

degree pulse, your 180 degree pulse - and you sandwich two very large gradient pulses on either side of the 180, symmetrically about that. So for protons that are sitting still, basically there is no effect on the signal from those protons because this gradient pulse, after the 180, is basically counteracted by the other gradient pulse. But you can show that protons that are moving due to either macroscopic flow or even microscopic diffusional processes will have a different signal characteristic following this because they weren't in the same place at this point in time but they are at this point in time, so these don't balance out. So what that gives rise to is to a loss of signal intensity compared to baseline that's proportional to the rate of diffusion D here and something we call the b -value that Geoff mentioned yesterday, and you'll see this on scanners; you can tune, you

can select the b -value and it has a maximum value that basically tells you how much area is under these diffusion sensitizing gradients. So the higher the b -value you can use, the larger the effect, it's an exponential relationship here. But the higher the b -value, the stronger you're driving these gradients and typically the bigger the area the gradients and the longer these pulses are, and that has an important point that we'll get to in just a moment. So the b -value is something you select, the larger the b -value the more diffusion sensitization this image will have. Now if you look at a region of interest in a tissue, it's comprised of the extracellular space and the intracellular space so you've got the cells floating around in this interstitial space here and, of course, you've got proton pools in each and even though the interstitial, well, the intracellular volume's actually

larger than the extracellular volume, the protons can move around randomly much more freely out here in just basically pure fluid than they can inside the cells, because inside the cells there's all kind of organelles and things for the protons to basically bump into and limits their diffusional path. In the surrounding fluid, they're very freely diffused so the extracellular diffusion rate is roughly ten times what it is inside the cell. But what you measure is a combination of both, and that is an important point when we start talking about stroke, for example. So, let's take the case where we have baseline normal tissue function. So you have your normal diffusion rate that you measure and let's assume for some reason the cells begin to swell. If that happens, then what you can imagine would happen is the measured diffusion rate would drop here and that's because

the intracellular volume is increasing but the diffusion rate inside the cells is much lower so your rate of diffusion will drop if you cause these cell to swell for any reason. We'll come back in just a moment and illustrate that in stroke this is exactly what happens acutely, in acute stroke ischemic conditions the cells swell and that causes a change in diffusion and that's why it's such a useful technique for screening for stroke. Now the diffusion, as was mentioned in the present symposium on Monday if you got the chance to see that, is basically described by a tensor and it's a symmetric tensor and the things that we measure are the on-diagonal elements and the off-diagonal elements. If diffusion is isotropic, so it doesn't matter what direction the protons move, it's freely isotropic, then this tensor just decreases to three terms only, the X, and the Y, and the Z diagonal

terms. However, if there's non isotropic or anisotropic diffusion as it is in white matter tracks for example, then the off-diagonal elements are non-zero. They're still symmetric, generally, but they're non-zero. So you can apply these diffusion sensitizing gradients in multiple directions and clinical systems now allow you to go up to 55 or more directions to encode this. To fill out this diffusion tensor matrix, whether you need that much information or not, depends on your clinical applications as we'll see in just a moment. So, diffusion anisotropy, what happens if the protons can't diffuse in all directions and same rate? If that's the case, then you have multiple terms here, the on-diagonal and off-diagonal elements, and it's hard to know if changes that you see in each of these images that you've diffusion sensitized in a different direction are due to anisotropy or if they're

due to actual physiologic tissue damage. So what's commonly done on clinical scanners is to calculate what's known as a trace of the tensor and basically it just takes the diagonal here and it takes the geometric average of that or sometimes they use just the average of that divided by three but this is the actual correct form so you get an average value of the diffusion. Just to illustrate that, these are diffusion sensitized images with a b-value of 800 where we've set the diffusion gradients to go along the superior-inferior axis, head to foot of the patient, and you can see the areas where the protons diffusion rapidly in that direction become dark, that exponential signal loss. If you then turn the sensitizing gradients right/left, you see that different regions become dark here and those are the white matter tracks that run right/left because water can go freely along the white matter

track but it can't easily go across a white matter track because of the myelination of the white matter. If we now go anterior/posterior you see the white matter tracks that go from the front of the face to the back of the head become dark. So you wouldn't know if you just looked at these three images, well what's pathology, what's just normal tissue anisotropy. If you take the trace of all this information though, you're left with an image that doesn't have all this anisotropic information in it. So just to show that in a clinical case, this is a, a patient with an acute stroke that had sensitization AP, and you see this bright object there, then they turn the gradients superior/inferior. Well now what's going on, that thing's still there, but what is this? These things weren't, oops, these weren't in that image, and then if you go right/left, other things light up. So which of these is real

and "which is Memorex" or which is just absolutely nothing? Well if you take the trace

of the image, the average image, you're left with the true lesion here which is an acute infarct, so that's the advantage of this technique. Now if your site is doing diffusion weighted imaging, or diffusion imaging, there's two ways to display the images. There's the diffusion weighted images of which what comes up directly on the scanner and in these images, regions where there is a free diffusion, unrestricted diffusion, are dark because of the exponential signal loss. Areas of where the protons are restricted from diffusion, are bright so where the cells swell, you'll get bright signal intensity on a diffusion weighted image just like this, the area of stroke, the cells swell, it becomes bright. The advantage to this is its very fast, you don't have to do any post processing, it

can come up immediately off the scanner. The disadvantage is something known as T2 shine through, and what this means is in order to apply these large gradient pulses that we showed, we typically have a very long echo time, 100 milliseconds or so, in order to get those pulses in there. Because of that, your images are automatically T2 weighted, very heavily T2 weighted, and so if you have fluids there, you can get T2 signal increase because you do that in all T2 weighted images, that has nothing to do with diffusion and it can mask what's going on. To get rid of that, you can use apparent diffusion coefficient imaging, or ADC imaging, and many scanners, in fact, most scanners that have diffusion capability, can reconstruct the images in ADC maps. And it's somewhat confusing initially because here areas of unrestricted diffusion are now bright and areas of restricted

diffusion are dark so they're opposite in contrast to the diffusion weighted images. So if you're at a site doing this, be sure to understand which mode they're displaying the images in and some sites calculate both. To do this, however, you have to acquire more than one b-value because you basically have to do a linear regression to this equation, signal intensity as a function of an acquisition acquired without any diffusion sensitization, and then you acquire images with multiple b-values, the minimum of course being two, it's easy to fit a straight line with two. The good news is this T2 shine through is eliminated because you basically take that out, the T2 shine through will be the same regardless of b-value. It'll always be there so you eliminate it by this process. The bad news is you have to acquire at least two different images and that's okay, because you

almost always get two. But better, you acquire more than two b- values over range of b-values and then do linear regression as shown here. Just to illustrate that, this is a case of a patient with a large brain tumor, a lot of edema, fluid build-up, you can see that in the T2 images. One component of that lesion is cystic, which you can see here, one component is just the edema. Of course edema is going to be bright on T2 as you see as well as the cyst, and in the diffusion weighted image, the cyst, where you have very free diffusion, turns dark. That's exactly what you expect, the CSF turns dark, that's all perfect. But all the area around it is a little bit bright actually compared to the contralateral region. And that's due to the T2 shine through here, this fluid being bright, the edema being bright. The ADC image much more clearly represents what's going on,

the cystic component is now bright because I said on ADC, high diffusion rate substances are bright, but now you can see the edema around it as well where there's increased diffusion. That's much more hard to, to visualize here and in fact you would expect this

increased diffusion to be darker here, but it's not and that's because of the underlying T2 shine through. So sites that do diffusion imaging very frequently will do both. I mentioned that acute stroke is one of the big applications and here's why, we alluded to it earlier. If you have normal tissue, you measure some normal diffusion rate or apparent diffusion coefficient, as the cells swell as I mentioned, that measured diffusion rate will drop because the intracellular volume goes up. The extracellular volume goes down and the extracellular volume is where the high diffusion rate is so your diffusion measures

decrease. As that tissue moves forward and remains ischemic, the cells lyse and so, effectively, the extracellular volume now increases so the diffusion will actually increase compared to normal later. So this gives you a way to kind of temporally evaluate lesions using diffusion imaging and it became very common, initially done by Mass General in Boston, in cases of acute stroke patients where the density weighted image, the T2 weighted image and even the FLAIR images, our mainstays of neuroimaging, none of them show the pathology. Whereas the diffusion imaging, diffusion weighted image here, these areas of restricted diffusion become very hyperintense, so it's a very useful technique for screening for stroke. That is not its only application. We're an oncologic center; we use it routinely for improved differential diagnosis of lesions based mainly on

changes in cell volume. Now I shared this slide before and mentioned that typically we'll wanna get rid of these anisotropic effects and basically give our average image here, but you can use that information, and this is a little more of a research application, but I thought I'd show it anyway, something known as diffusion tensor imaging, and Andrew Maidment at the Presidential Symposium on Monday showed some applications of this too, but again here we basically use that diffusional direction information to determine what is the principle diffusion direction. And so you can see a very large brain tumor here pushing against the white matter tracks that are very easily visualized using this diffusion direction information. And if we move to high field systems, my plug for tomorrow's talk, many of the techniques we're talking about today only improve, both

signal noise, resolution and everything so you can see, well not everything, there are some caveats here. If you get 1.5 T imaging versus 3 T imaging, just how much better the diffusion trace or tensor imaging is. And then, more in the research application, we can start combining this information to make some truly confusing but pretty images that show basically all the directional information in one picture and if you can kind of mentally get through all of that, you're a pretty impressive character. But you can encode for right/left directional diffusion in one color, AP in another and superior and inferior in the other direction and teasing all this information out is an active area of research. Now that's kind of the white matter tracks, and I'm basically going to segue from that into what goes on in the gray matter. One of the applications of very high speed imaging is to

look at areas of the brain that are, are activated in certain tasks. That can be either a sensory motor task, like me sitting here, you know, making my duck sounds or whatever. Or expressive speech, or cognitive thought, which hopefully I'm doing some of both while I'm up here. But how can we look at these effects? This has been the domain of PET imaging using 0-15 water flow initially, but for most sites, this has now moved into

MRI. The most common technique for looking at areas of the brain that are activated in certain tasks is what's known as blood oxygen level dependent contrast, or BOLD. (If you hadn't figured out by now, if you can't come up with a cute name for your MR technique, it'll never get published much less be used.) So we have BOLD imaging. The basic idea is relatively straight forward and just shows how fortunate and lucky we are

sometimes. The basic principle is that oxyhemoglobin and deoxyhemoglobin have different magnetic properties. Oxyhemoglobin is diamagnetic, has minimal effect on what we measure. Deoxyhemoglobin turns out to be paramagnetic, that has a measurable effect on MR imaging and actually can cause a loss of signal as we saw in the contrast agent DSC technique. So, it's very fortuitous for us that this, these two states exist and they have different magnetic properties and we're doing magnetic resonance so we should be able to pick that up. If we can measure the difference in this, then we can actually look at areas where there's a change in oxyhemoglobin and deoxyhemoglobin ratio, as I'll show you in just a moment. And we can do it totally non invasively, we don't have to inject anything here, we're using blood essentially as our contrast agent.

That's the good news. Bad news is, at 1.5 T, these changes are very small which is another reason many sites are very, very interested in going to higher field systems, 3 T and above. So, schematically, how does this work? Well, if this is meant to be a capillary or venule and the other things here are oxyhemoglobin and the dark things are deoxyhemoglobin, then in our normal basal metabolic resting state, you're mentally at bliss, then basically in these venules 60 percent of the hemoglobin here is in the oxyhemoglobin state. And you have some normal oxygen extraction fraction that's feeding the brain cells and there's a relatively large susceptibility affect there, this is the paramagnetic effect that I talked about. So you have some signal loss due to the fact that you have a fair amount of deoxyhemoglobin here in addition to the oxyhemoglobin, 40

percent of its deoxy. So that gives you baseline signal intensity. Now as I start doing some task, like tapping my fingers together here, there's an area in my brain, about right here, that is being activated to do that. And in that area there's a local increase in blood volume and flow and so there's an increase in the amount of oxyhemoglobin being delivered, so that's one thing. The other thing is that we overcompensate, we greatly overcompensate, providing a lot more oxyhemoglobin than we increase in oxygen extraction so there's a 15 percent roughly increase in oxyhemoglobin, only a five percent increase in the extraction of that oxygen. So what does that mean to us in the MR world? Well it means that there's a lot more oxyhemoglobin to deoxyhemoglobin ratio here. We said that the oxyhemoglobin doesn't have a negative effect on signal intensity in MR but

deoxyhemoglobin does so if we decrease the amount of relative amount of deoxyhemoglobin, you get an increase of signal intensity here. Again, that's a very fortuitous thing, we're lucky in two ways. There's difference in magnetic properties in these different types of hemoglobin, and also we way overcompensate. Both of those allow us to actually look at the areas of the brain that are activated, not directly, but indirectly. We look at the hemodynamic response, we're not looking at the neuronal activity, the electromagnetic activity that MEG and EEG look at, but we do it with

images. They have to figure out where those signals came from. So basically, if a patient's sitting there and tapping their fingers together like this for some period of time and then we tell them to stop and they do that again, we tell them to stop, we know what

we told them to do and when we told them to do it. If we go through and look at the signal intensity measured in every pixel in these images over time and we basically do a cross correlation here and say okay, we know this is when we told them to do the task, which pixels in this image have a signal intensity that follow that signal, cross correlation. Then we basically code those pixels that correlate closely with this waveform, bright signal intensity. Now again I have to stress we're not measuring the electromagnetic neuronal phenomenon itself. We're measuring a delayed effect, the hemodynamic response to that. The cells start needing nutrients, the microvascular space agrees, compensates that by increasing blood volume and flow. So if we have a bright flash of light at time zero here, the occipital region of the brain, you'll see response in

terms of hemodynamic response that comes much later, two to three seconds later before anything happens, about six seconds before it peaks and then it falls off as this kind of gamma variant function. So what it means is when we tell a person to do a task in the lines that are indicated in blue here, that's when they're doing whatever task we're asking them to do. There is a lag behind in the measured signal. So what we get is a red line here and it's essentially a convolution of this signal with the blue dashed lines here. And that's okay as long as there's plenty of space between the tasks, we let them rest for a while between. But if we start trying to get that too fast, of course, these signals are gonna bunch up on one another and you have to try to deconvolve this information and that makes it a little bit trickier, but possible. The other thing you have to be able to do is

get stimuli into the magnet, how do you do that? You've got a very large magnetic field, you can't really put your TV or your stereo headphones in there, so there has to be equipment to do that, but that's readily available these days and I just wanna talk about a couple of applications. One is an application oncology, there are lots and lots of applications to basic neuroscience here that we certainly don't have time to discuss so I'm just going to zero in on one for oncology and that is for neurosurgical planning, where the goal is to maximize the resection volume, for the best prognosis later, while preserving quality of life of the patient. You don't want to touch what neurosurgeons like to call "eloquent centers". So the benefits is you get presurgical planning, the neurosurgeon can decide where they wanna do the craniotomy, how big does it need to be, how they wanna

approach it and what areas do they want to avoid. You get decreased operating room time, because the way that we measure the, surgeons measure this now, for a motor map (and we're not right after lunch or before lunch so here's my gross picture). Here's a patient with a craniotomy, there's a grid of electrodes that are see here, but it's laying right on the surface of the brain and if a surgeon wants to know where the motor strip is in the brain, where this action occurs, this is state of the art. You align a grid of electrodes on top of the brain surface, this goes off to a recording device and then you electrically stimulate typically the median nerve, if you're looking upper extremity, and

you look for electrical activity and you can do this while the patient's asleep, they never know it happened, and you can map out where you see a phase change in this. But you

can imagine this is fairly invasive, you have to do a fairly large craniotomy if you're not sure where the motor strip is, and it's relatively invasive and it certainly takes OR time. Even worse than that, if you're going to look at things like speech, this doesn't work, you have to wake the patient up in the OR, ask them to do some kind of speech task and electrically stimulate the brain until they go into this temporary speech arrest. Or you do what's known as a Wada procedure, which is done under fluoro-guidance and you basically put a catheter up into one of the two carotid arteries, inject sodium amytal and put half of your brain to sleep at a time, and find out which side of the brain this activity occurs on. So you can see there's probably a good role for trying to this non-invasively. Now, for many years, neuroscientists and neurosurgeons have known very well what

areas of the brain reflect activity of different parts of the body. But this is only true in a normal brain and neurosurgeons don't frequently see normal brains - why would they be in there? So when you have things like this, this organization gets changed very frequently either due to just mass effect, being pushed out of the way, or what we call plasticity - particularly in younger patients where this neuronal function gets re-mapped to another part of the brain that's non-diseased. So just a few applications of this. This is a patient with a non-enhancing frontal brain tumor here. The question is how far back can the surgeon go without striking the motor cortex? In other words, could they, how far can they resect this before they hit tissue that would basically cause the patient to have paralysis of the, in this case, the upper end, certainly the upper extremity. So you can see

in orange here and in blue, the two parts of the brain that are activated when you're doing right-hand and left-hand, just simple sensory motor tasks like this. This is another case showing displacement of that motor activity relative to the contralateral side just due to mass effect of this very large temporal lobe lesion here. And then expressive speech, when you're forming words and getting ready to say those, where does that activity occur? And you have to develop paradigms that are specific to this activation and you have to be able to visualize that. You can see in this mass here, that that activity is right behind this mass, so it's very important to know that and this is very difficult to do in the OR, again, you would have to wake the patient up, ask them to do some kind of task and then put them to sleep again while you actually do the resection. Receptive speech, your

comprehension, this is a task that activates both the auditory cortex from just, these are audibly presented tasks, but where is this activation occurring with regard to these temporal lobe lesions? And you can display this now also in three dimensional views, and the neurosurgeons absolutely love this so that they can see their brain surface, which is their guidance, and also the brain vessels which are kind of the road map for neurosurgeons. The vessels there and these sulci on the brain surface and you can overlay this information and in fact, send that information to the OR where they use image guided surgery devices in the OR where they can track their probes, register that to images, you see the blue probe here is the surgeon's probe, and know exactly where the underlying activation is. So this is not, you know, in the future, this is now actually in

quite a few centers. And then the last thing I have put in the listing that we would discuss, is a little bit about assessing biochemical changes and that's done in MR using spectroscopy and that's nothing new, spectroscopy was actually the first major application of the MR phenomenon. It went from physics very quickly to chemists and stayed there for many years, still used, very commonly. And the chemists use it because the Larmor frequency that a given nucleus resonates at, depends of course on the gyromagnetic ratio, as Geoff mentioned yesterday, but also in the magnetic field felt by the nucleus and very frequently you'll always see this mentioned as just B_0 , the applied magnetic field and that's the Larmor frequency and we're done. Well, we're not quite done because there are variations in the magnetic field at each given nucleus and that's

due to the fact that the electronic environment that a proton finds itself in, affects the magnetic field at that given nucleus. There's something known as a shielding phenomenon, electronic shielding phenomenon, that modifies the applied magnetic field, the static magnetic field which you put in with a magnet, based on the local electronic or nuclear shielding by the electrons and this varies by proton, depending on what chemical environment they are in and this is what was used, still is used very frequently by chemists to work out the structure of a molecule or even now proteins based on the spectrum because the, the peaks that you get in the spectrum are kind of coded to what the local electronic environment is for that nucleus. Now, you'll always see spectra come up on all scanners in terms of chemical shift, parts per million. And all it means is there's

not an absolute reference. In chemistry you inject something that you know what the resonant frequency is and that's your internal standard; you can't do that in patients. So you'd use an internal reference and most commonly that internal reference for proton spectroscopy, which is why it's FDA approved, is water. So we have the reference frequency for water and anything else we look at, we refer to water in parts per million and that's called a chemical shift. The advantage of this normalization is it doesn't matter what field strength you acquire a spectrum at, 0.2 T which you probably would never do, 1.5 T, 3 T, 7 T, the chemical shift will always be the same. The separation of the peaks in absolute frequency units, however, increases directly the field strength and that's another driving force for going to 3 T, 7 T, for 9.4 T field strengths. And also the

spectral resolution improves and also, fortunately, so does the signal and noise ratio and that'll be talked about more in tomorrow's talk on high field applications. So you get a spectrum, and again, it depends on where the protons are. The methyl protons resonate a different place than the benzyl attached protons which are way down here because there's a lot more electronic shielding in a benzene ring than there is in a methyl molecule. So enough chemistry. The bottom line is that depending on where these peaks occur in a spectrum, it tells you something about what kind of proton gave rise to that signal. To do this in a patient requires that we have to have high quality localization and we have to know where the signal's coming from. We have to have a very good homogeneous magnetic field and one thing I should mention is, both the echo planar imaging

techniques and spectroscopy techniques, have to have very high homogeneous magnetic

fields and you have to be able to get rid of the water signal that we so desperately like having for all of our imaging applications. So we have to suppress that because all the information we want to see is well below the signal of the water protons. And we typically need to have some way to analyze these spectrum. So, how do we do water suppression? Well Geoff talked about fat suppression techniques and chem-sat techniques yesterday, where we basically apply a frequency dependent pulse before we acquire our data with say, a spin echo sequence and we basically saturate the signal we don't want to see as Geoff mentioned yesterday. So we have to do that very efficiently here, because everything we want to look at, all these chemicals we want to look at, have

concentrations that are maybe 8,000 times less than what water is. So we need to get rid of that water signal. To illustrate that, this is a spectrum actually from my gastroc muscle some years ago, there's more fat now. So without water suppression, here's the water, here's the lipid, and that's all you can see. If you have water suppression, however, now lipid becomes bigger but you also see all these other metabolites that we're acutely interested in. Similar things happen in brain, which is the most common use of spectro, for now. So, to do the water suppression, again, we usually apply three saturation pulses, very similar to the fat-sat pulses you use in clinical imaging and we use three to improve the efficiency of the water suppression. So it looks something like this; we have some kind of localization technique that we'll talk about in just a moment. Here's our water

suppression pulses out front. So, that's how we suppress the water. Now we have to localize where the signal comes from, and there's two basic ways that this is done on clinical systems. One is what's known as single voxel volume localization, here the volume of interest that we're gonna get signal from, is basically acquired from the inner section of three slices and I'll show you a schematic of that in a minute and the inner section of those three slices, is the volume of interest from which you get the signal. So that's single voxel technique. You get it from one region at a time, if you need to get it from somewhere else; you need to acquire a whole different acquisition. Spectroscopic imaging techniques, which are now the most prevalent in use clinically, actually go beyond that and they use phasing encoding techniques to encode the information in plane

and I'll show you a picture of this in a moment. And you can get spectra from multiple voxels in one shot. Takes longer than this, but you get a lot more information and the signal to noise per unit time is actually higher here. And then there's more commonly, hybrids, I'll show you that in a moment. So again, you need to be able to basically go in an image, draw a box, and say "I want a spectrum from the tissue that's only in this box, from nowhere else". So here's schematically those two representations in the single voxel technique you get a, you select a slice first through plane here, and then you do two other slices, the intersection of all three of those slices to find your volume of interest. The spectroscopic imaging techniques typically still select a big box here instead of a small one, and then they phase encode in the X and the Y directions in this image, to get

information from multiple small boxes inside the big box. There are two techniques that are commonly used for this; one is based on something known as STEAM, or stimulated echo acquisition mode, the other is based on something known as PRESS, or point

resolved spectroscopy. The difference between it is STEAM uses three 90 degree selective pulses to select these volumes and these slices here, and PRESS uses a 90-180-180. There are some advantages and disadvantages of both, by far the most common in clinical use right now is PRESS-based techniques. The reason for that is, in general, there's a two 2X increase in SNR in this technique relative to STEAM, that's not exactly true for peaks that couple, but that's for a question later. But you can get to shorter echo times with STEAM, so most scanners do have both modes, as if there weren't enough

options on scanners already. So just graphically, what does this do, here's a single voxel acquisition technique, here's the water suppression pulses, for STEAM there are three 90 degree pulses, each of those are slice selective, combination of a bandwidth limited RF pulse and a gradient selects a slice and our section of three slices gives you your volume of interest. If you use PRESS, just change those two 90's, the, the second two 90's to 180's, the philosophy is the same otherwise. Spectroscopic imaging techniques, these come in variety as well, most commonly is 2-D techniques where you acquire a slice of data at a time. But there are actually 3-D techniques out there now as well. In terms of pulse sequence, it looks sort of like this; you do water suppression again, you select a volume using three pulses, RF gradient pulse combinations, that selects a big volume and

then you do phase encoding techniques shown here, to now subdivide that big voxel into multiple voxels so you can get a spectrum from each of these little dash line boxes. This is nice, and it let's you look at lesion heterogeneity or compare a lesion to a normal appearing tissue. It may be on the other side of the brain, for example. Now spectroscopic imaging, that's the big advantage. You get spectra from more than vol-, one volume of interest in a given acquisition. These, these, these volumes can also be smaller in spectroscopic imaging techniques, than single voxel techniques and since you get a spectra from multiple boxes, you can go backwards and say I've got the spectrum from each of these boxes, I can now produce kind of maps of the distribution of these different chemicals so if this is a spectrum, this is what's known as N-acetylaspartate,

creatine, choline, you can now basically go backwards and say in each of these boxes, tell me what the area this, this peaks is, and that tells me something about the relative concentration of the N-acetylaspartate in each of these boxes and you can kind of map out the images where the pixel intensity is proportional to the area of each of these peaks. And this is a very commonly used approach, radiologists like this because it's a visual representation, not all the squiggly lines. But the truth is just like in angiography techniques. There the truth is in the source images; here the truth is in the individual spectra. So the disadvantage of spectroscopic imaging techniques is these techniques are relatively long, these techniques at 1.5 T typically take maybe on the order of eight minutes, that can drop as you go to higher field strength because the boost in SNR and

you don't do a lot of, of phase encodings here and if you think about that, what that means is, is that your point spread function is relatively poor and you can get spectral bleed from one voxel into the next, because you don't have an adequate point spread function to spatially distinguish these boxes and there are ways to minimize these problems. So what do you get in a spectrum? And I'm gonna show brain only here,

although as you've probably seen at this conference or other conferences, a big developing application particularly for oncology applications of spectroscopy, as in prostate, where we're looking at citrate as a very sensitive technique it appears, for determining malignant tissue versus benign prostate hyperplasia, for example. And there are multi-center trials looking at that as well but the biggest applications so far, is in

brain. Prostate and breast are developing applications. So in brain, you can see a variety of peaks and we won't go into the physiology of this, I'm sure you're glad to hear that, but what I want to point out that is important is the echo times that you choose for these acquisitions are very important. Short echo times are very useful for getting, allowing you to see more peaks and the reason is, the, each of these different metabolites or biochemicals, have different T1's and T2's, some of them have very short T2's, so if you increase the echo time, their signal goes away and you never even see them. To illustrate this, these are spectra from a spectroscopy phantom, acquired at a short echo time, you see a lot of different peaks, and then increasing echo times and you see the spectra becomes much simpler here, and that makes it actually easier to acquire and so this is

probably a very common acquisition time, echo time actually, but you notice that some of the peaks like the inositol peak here, is completely gone and that's because the T2 of inositol is much shorter as you increase the echo time, the signal decays, dephases. Also I want to point out, and this is the important fact that's not frequently mentioned, is because each of these chemicals have a different T1 and T2 value, the peak ratios change as you go from short echo time to long echo time. You can see that the, here is the creatine and choline ratio is much higher here than the creatine to choline ratio here. So if you're gonna compare spectra against what's in the literature or among patients, you have to be very careful to look at the echo times and make sure those are matched or taken account of. So this is what you can kind of see in normal brain, in a pathologic

brain, this is a patient with an anaplastic astrocytoma, relatively high grade lesion and the hallmark is that the choline is elevated, creatine is dropped. This is a primary application in both brain and developing application in breast, high elevations in choline typically indicate a malignancy. You might see lactic acid form because of the hypoxia and then any time there's a destruction of normal brain cells you see N-acetylaspartate drop. Those are the, the big changes you see. Again you can map out the distribution of those, this is a case of meta-, metastatic lesion where we're looking at the choline to creatine ratio so where the choline is elevated, this is probably still active tumor. Where the lipids have built up, that usually describes the necrotic core and you can see that here in the individual spectra where this is the lipid peak is very well seen inside this necrotic core.

So how do you, how do you analyze these things? You present your radiologist with a bunch of squiggly lines, basically you look at ratios of different compounds because it's hard to do absolute quantitation, it's very hard to make accurate, it can be done, but it's tedious and fraught with technical difficulties to say that you have this many millimole of NAA in this, in this voxel. So most commonly you look at ratios of compounds. The disadvantage, of course, is that either of these could change in pathologic conditions. So again, one last thing about spectro, it's very important you look at the TE and TR, and

I've mentioned this already, but some scan systems didn't even put TE and TR in their spectro that went to, images that went to PAC systems and that, in my opinion, can be very misleading. So, I picked neuro imaging for most of these applications, this is going

to be in other areas as well, but this was our mainstay for many years, and still is at many places, T1 without contrast, T1 with contrast, T2 and FLAIR and Geoff talked about this yesterday, what I tried to do is show, okay, we can expand that and Geoff kind of alluded that MR can do a lot more than just non-enhanced/enhanced imaging. So now we can look at diffusion processes, we can look at tractography and see how these lesions are affecting white matter tracks, we can look at the chemical information, we can look at the functional information. And so MRI has basically evolved, in my opinion, and continues to do so rapidly, from being exquisite way of looking at anatomy and angiography without injection of contrast agent, with injection contrast agents. Now looking at physiology, blood volume and flow, diffusion processes, diffusion tensor imaging,

looking neuronal activation indirectly by looking at hemodynamic response, changes in microvascular environment, changes in the chemical environment and then the Holy Grail, where we're in animal models now, but hoping to go in humans someday, pending FDA, of course, is molecular imaging with MR. It's not only the domain of nuclear medicine, although that was the first and still is by far the biggest, there are approaches to doing molecular imaging MR and I hope that we see this at this meeting, some time in the fairly near future. And then, the last thing I want to say is again, these techniques are on clinical systems, there's nothing I'm showing here that's not on state of the art, certainly 1.5 T, very definitely 3 T, these are techniques being used many places clinically. Not all of these, but subsets of these in different clinical applications. I think we as medical

physicists need to start thinking about that and our quality assurance. It's not just ACR quality control, although that's what we focus on. These techniques are out there. I think we need to be thinking about quality control methods for these techniques because we're using them in patient care. So, with that, it's slightly past, so I'll shut up and thank you for coming and I encourage you, if you can, to come to tomorrow's talk on high field MR and thank you for your interest in the MR continued education course. Thanks.