Biomedical Ultrasound: Fundamentals of Imaging and Micromachined Transducers

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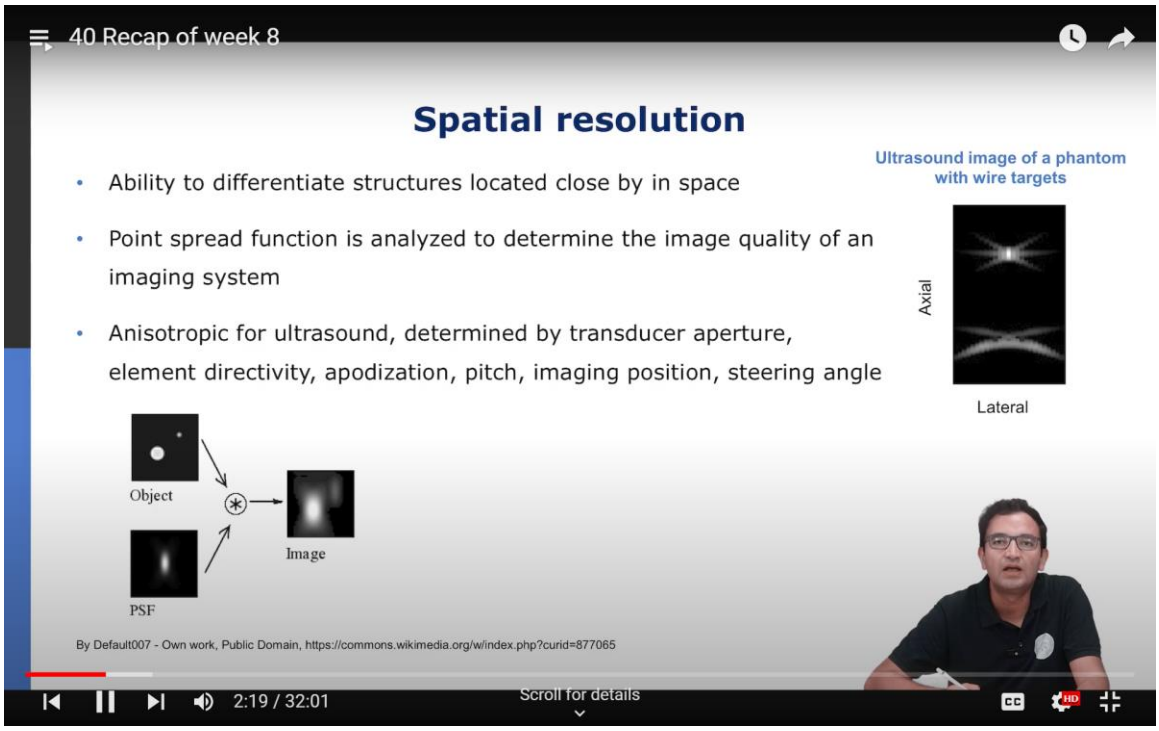
Lecture: 40

Recap of week 8

Hello and welcome to the recap for the lectures of this week. So, let's start off by discussing a few topics here. You'll recall we discussed metrics for image quality. So how do you know that an ultrasound image is good, right? And you'll recall that we discussed that the quality of an ultrasound image is determined by its spatial resolution. In other words, how well resolved are the targets in the image? It's contrast resolution. How good is the contrast? I think you are familiar with these topics because you use your phones, you capture images.




So similar concepts apply in ultrasound imaging as well. What's of interest is the signal to noise ratio. Noise is typically the random signal that originates because of electronic noise, thermal noise, etc. So, it's also a signal but not a signal of interest.

So that's called noise. particularly or in some cases it can also be a spatially varying signal. And then we have artifacts which are, they are also broadly categorized as noise,

but they are different in the sense that they are typically deterministic, and they happen because of a variety of reasons and assumptions that we have about the ultrasound image formation process. Then lastly, you may have a great image with a very good resolution, good signal to noise ratio, but it may not have diagnostic usefulness. Now, this is something that is determined by the clinician.

So, you can talk about metrics, which will tell you the properties of the image or the quality of the image, but diagnostic usefulness, again, is best determined by a clinician or radiologist or a sonographer. So, if you recall, we discussed the concept of point spread function. If you take any imaging system and you give a point target, so typically what's a point? Point is something which doesn't have any area. So, an idealized point doesn't exist. However, you can create a point-like object by selecting a sub-wavelength target.

So, for any type of imaging, if the wavelength is lambda and the scatterer is quite smaller than the wavelength, then it can be considered a point scatterer. So now if you typically have a point, the system introduces a certain blur on that point. It will not be able to recreate the point typically as is if the point is sub-wavelength. So that blur is actually known as the point spread function. So here we are looking at an ultrasound image of two wire targets.

So those wire targets are here and here. These are just dots. but what you see is an extended object here that is because of the point spread function of the ultrasound system and the spread becomes worse here and what you also see that the spread in the axial direction is limited but it's much more in the lateral direction so this tells you that ultrasound has an anisotropic point spread function which is narrower in the axial direction and wider in the lateral direction Also here the imaging performance is better than here and the reason is probably this point is in focus and this point is out of focus. So now, the point spread function has important theoretical as well as practical relevance because point spread function tells you the image quality, the ability to differentiate between different structures. And now, what determines this point spread function? For ultrasound, like we discussed, it is an isotropic point spread function.

It is determined by the aperture of the transducer. How wide is the aperture? Typically, the wider the aperture, you will have a narrower lateral point spread function. How directive is the beam? Meaning, what is the main low width? If the beam is more directive, the main low width will be less, and that will lead to a better lateral resolution. Then, apodization actually also determines the spatial resolution. pitch imaging position steering angle all these have an effect.

So here is an object it's a kind of idealized object and here is the point spread function of a hypothetical imaging system. Now under the assumption of linear shift invariant systems. So, this is an assumption which is often made as a simplification. What you see

is with convolution, which you may have studied in signals and systems courses, with convolution we can get the image. So, the PSF actually blurs out your image. And the sharper the PSF, lesser the blur.

Then we discussed that axial resolution refers to the ability to distinguish two targets which are located axially apart. If the targets come closer and closer, eventually they will blur into each other, and you will not be able to distinguish the targets. So, it depends on the pulse length. We discussed this formula. I believe you remember this.

The shorter the pulse, the better the axial resolution will be. and as you can see it depends on lambda as well so for higher frequencies the lambda is going to be smaller and it also depends on the number of cycles so ideally we should go for lesser number of cycles and higher frequencies to get good axial resolution and to get good axial resolution typically short pulse excitation or impulsive excitation can be used so that you get a very short pulse from your transducer The transducer should also be adequately damped. If you remember, we talked about the backing material of the transducer. If the transducer is adequately damped, the moment your excitation ends, very quickly it will damp out and the spatial pulse length will be narrow. That will lead to good axial resolution.

$$r_A = \frac{\lambda N}{2} = \frac{c\Delta T}{2}$$

But if it is not damped, it will continue ringing for a while and then this kind of degrades your axial resolution because the spatial pulse length increases. Now even if you give an impulse excitation like you know positive impulse or negative impulse you won't have a perfect impulse but let's say a broadband excitation which will be an impulse in the time domain then also because your transducer actually acts as a band pass filter it has a certain resonance frequency and it has a bandwidth centered about that resonance frequency. So, I can draw this. Let's say this is f0 frequency. I'm plotting the frequency versus amplitude, and it will have a certain center frequency and then maybe you can get a range of frequencies in the 3 dB width, and you can call it.

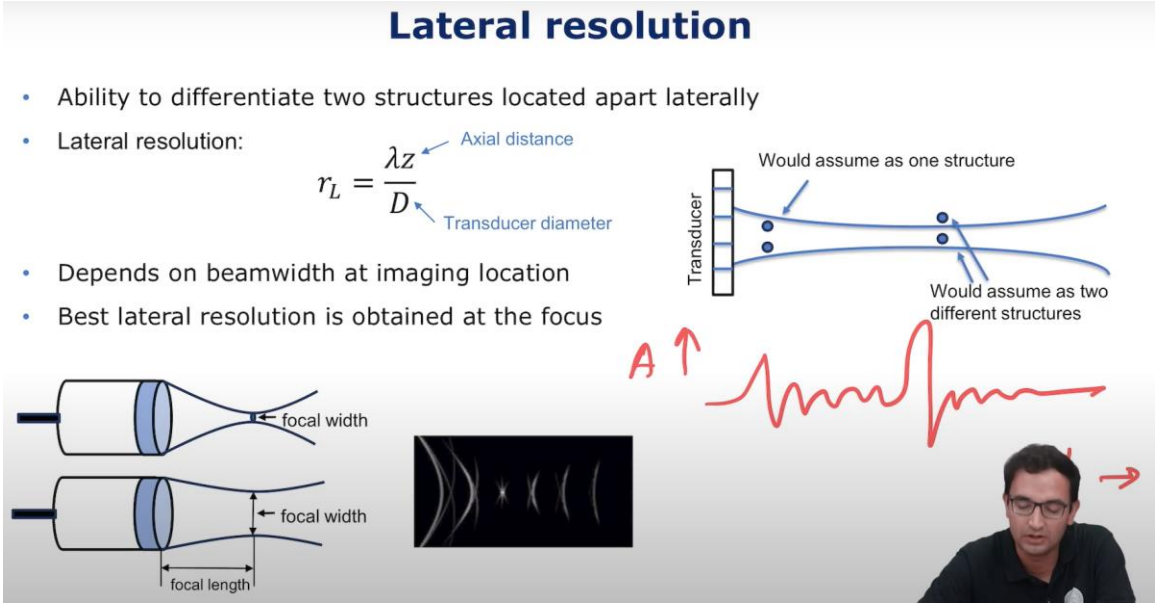
So if it is intensity, then this would be  this would be your full width half maximum bandwidth from this frequency f1 to f2 so f2 minus f1 is your bandwidth right so this transducer as you can see acts as a band pass filter even if you give an impulsive excitation which has a wide range of frequencies only the frequencies in the sensitivity band of the transducer will be selected so essentially you will end up with a sine burst like pulse even if you excite with an impulse because the filtering done by this transducer's bandpass response will result in a sine burst, a modulated sine burst like signal. So, I will just draw a modulated sine burst. This is like a modulated sine burst. Okay, laterally, we would like to have a very narrow beam. If the beam is narrow, then

we can have objects within the beam and the neighboring objects will be outside the beam.

If both objects are within the beam, unfortunately, we cannot distinguish them. Because remember, for each beam that we fire, we only get a single A-line. Like this may be some A-line that we get, right? So, this is my time. Axis and this is my amplitude axis So when we get this single a line remember that the beam is actually two dimensional right this beam is two dimensional and In practice actually it's three dimensional because there's also an elevational dimension for now ignoring it ultimately what I am getting a one is a 1d signal right, so there is a 2D to 1D mapping that's going on and in this some information is lost. So, if both these objects are within the beam, my image formation process almost assumes that a ray is firing, and a ray is being received.

So, if there are two objects, I cannot distinguish them because I'll get some kind of an integrated effect in my received signal. But if one object is in the beam and one object is outside the beam, then I can distinguish them because in this firing only this object will be detected and then when I shift and fire either mechanically or by scanning then I will be able to capture this target. So, we should be able to focus sharply and that determines the lateral resolution. Lateral resolution is given by lambda z by d. This is in the Fraunhofer zone, in the near field we can approximate the lateral resolution as approximately being equal to the aperture diameter with which you are firing.

$$r_L = \frac{\lambda z}{D}$$




So, as you can see this is a sharply focused transducer, this is not so sharply focused and nonetheless you see how well you are able to resolve the point target in the focal zone

and then the lateral resolution becomes much worse in the near field and in the far field. Next is the elevational resolution. So, I would just like to highlight a typo in the last time slides. So, this direction where this is the transducer phase right. So, this direction forward is the axial direction typically we say z axis or z axis and then you have the lateral and elevational direction in the perpendicular directions.

So, elevational resolution allows us to differentiate two structures located apart in the elevational plane. Often, we think of an ultrasound image as 2D, so it is in a single plane. But actually, the ultrasound beam is a three-dimensional object. It has certain thickness in the elevational plane. So even stuff which is slightly outside the plane will sometimes give reflections which can create haze in the image, for example.

So, we would like to have a very tight elevational focus. For example, here if you see, this is the elevational direction. So, if I am at this location, I would have poor elevational focus because there is a certain thickness to the elevational beam here and objects which are out of the plane will also contribute to the signal. But this is the location of the elevational focus. And here the objects which are out of plane will not contribute substantially to the signal.

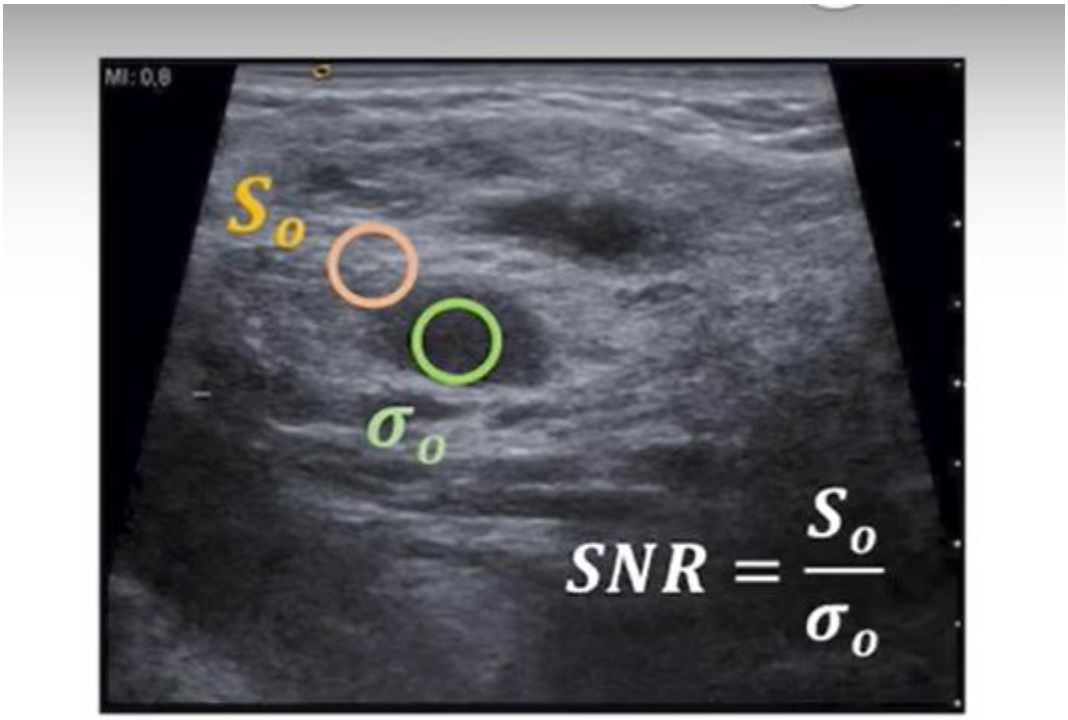
So, we would like to have an elevational focus. And this is done by using a lens for setting the elevational focus. Now the challenge is single lens has a fixed focus. So, what that means is at a given depth, I will have good elevational resolution, but as I move away, both towards the transducer and away from the transducer, my elevational resolution will degrade. So, this is where electronic arrays are used.

There are 1.5D arrays where you may have this type of an array configuration where in one dimension you have more number of elements. So, for simplicity, let's say eight elements in one direction and three elements in the other direction. So, this is the elevational direction where I have drawn three elements. Now this is a gross simplification but now you can provide delays here and by changing those delays you can change the depth at which you are focusing, and you can potentially go for multiple focusing. So by the way this was just an example.

No one would have an array only with eight elements and three elements. Typically in imaging, it's common to have 32, 64, 128, 256 elements, et cetera, in the linear direction, and then probably eight or 16 elements in the other direction. So then in terms of signals to noise ratio, you'll remember the formula. We typically find a target, which is a cyst, which is anechoic. And then we look at the variance within that cyst.

And that typically tells us about the noise because there's no acoustic signature coming out from the cyst. So, the assumption is that that variance is contributed by the noise. And then you can take a region of interest, and you can determine the signal intensity and take

the ratio. So, the way we can use this metric is to assess the quality of an image and typically SNR will improve when you have low noise electronics, you have highly sensitive transducers, you give higher energy, typically higher energy if you fire from the transducer, of course within safety limits and the transducers operating range, then higher energy leads to better signal to noise ratio. If you have better quality piezoelectric crystals, highly sensitive crystals, then you will get better SNR.






And there are other variables here, high number of bits for digitization. So, if the analog to digital converter you use has high number of bits, say 12 or 16, that'll lead to a better performance than say eight bits, for example. Then, of course, there are ways of post-processing, spatial filtering by beamforming, some averaging which leads to improvement in SNR, and things like speckle reduction algorithms, which all contribute to an improved SNR.

Next is contrast resolution so previously we discussed the signal to noise metric this metric tells you about how well you can distinguish two objects which differ in contrast and similarly you will take the regions of interest within the cyst region and the target region and if you take the ratio of the intensities this is a metric of contrast and typically it is reported as a decibel therefore, 20 log 10 Sr by Sb where Sr is the region of interest

and Sb is the region of background which in this case we choose in the cyst and similarly there is contrast to noise ratio. So, as I said, typically it is assumed that the variance is contributed by the noise.

$$Contrast = 20\log_{10}\left(\frac{S_r}{S_b}\right)$$

$$CNR = \frac{|S_r - S_b|}{\sqrt{\sigma_r^2 + \sigma_b^2}}$$

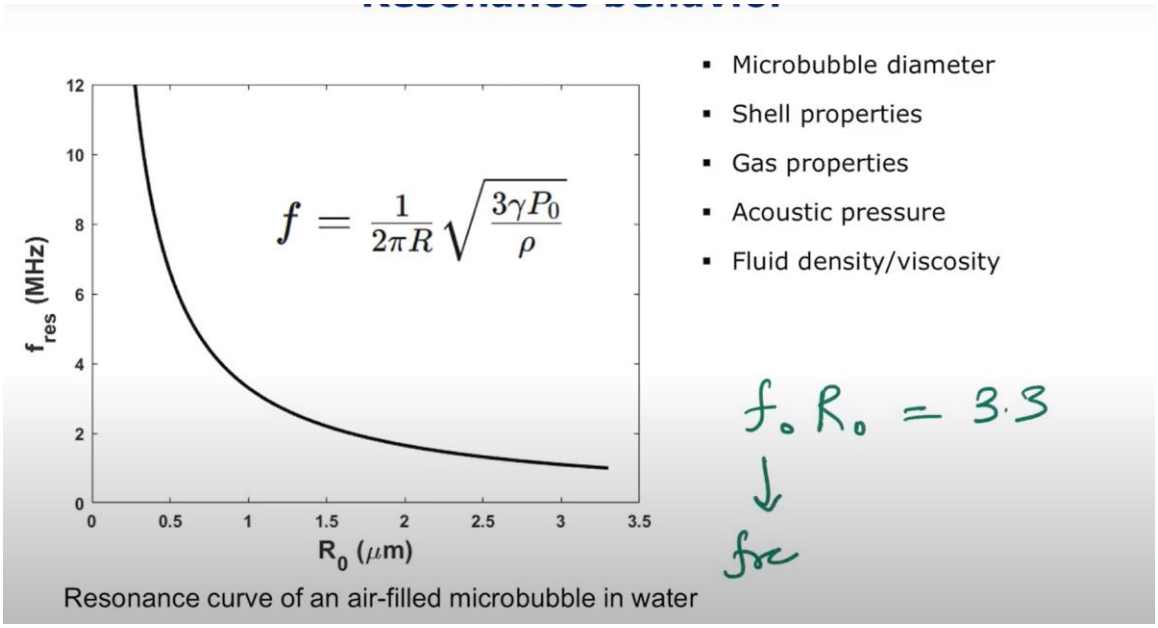
So, you take the difference of the signals in these regions, and you divide by the square root of their variances sum together. Then we discuss ultrasound contrast agents, which are encapsulated microbubbles, typically of mean size around two to three micrometers. They can be injected into the body, and they go and fill up blood filled organs. For example, blood vessels, micro vessels, capillaries, heart, et cetera. And you can visualize the outline of these vessels using ultrasound contrast agent.

These contrast agents are stabilized by coating. They are filled with high molecular weight gas, which has low solubility in the solution. And then once you excite them with ultrasound, they undergo volume pulsation. They can also be destroyed at will. So, if you want to pop the bubbles, you give a slightly higher amplitude ultrasound, and they will disappear.

So, you can bring and get rid of contrast using ultrasound. These are also very well established in terms of their safety profile because they have been in use since the late 90s. Okay, so we discussed why these bubbles are so effective because of their high compressibility and high acoustic impedance mismatch. They scatter ultrasound strongly and not only do they scatter ultrasound strongly, but they also give out unique acoustic signatures which are not common to the background tissue. So, using those unique acoustic signatures, you can actually distinguish between the response of these bubbles and the response of the tissue.

So, in a way, it's like background free imaging, because if you get rid of the background, then you can visualize the target very nicely. This is similar to fluorescence imaging or second harmonic imaging in microscopy, which you may have heard of. Next let us discuss micro bubble ultrasound interaction. So, just like we discussed a harmonic oscillator oscillates under an external sinusoidal harmonic force and it has a spring constant and a mass, and you can calculate the resonant frequency of the system. Similarly, a bubble which is being driven by a sinusoidal pressure and it has a surrounding fluid which has a certain mass.

You can also assume that the gas in the bubble, it provides a certain stiffness because if you try to deform the bubble, it will provide resistance. So, a spring constant k can be assumed. So now a resonance frequency can also be defined for this bubble system. and here is the plot of the resonance behavior as you can see as the radius of the micro bubble increases. So, on the x axis we have a radius resonant radius in micrometers right.



Resonance curve of an air-filled microbubble in water

$$f_o R_o = 3.3$$

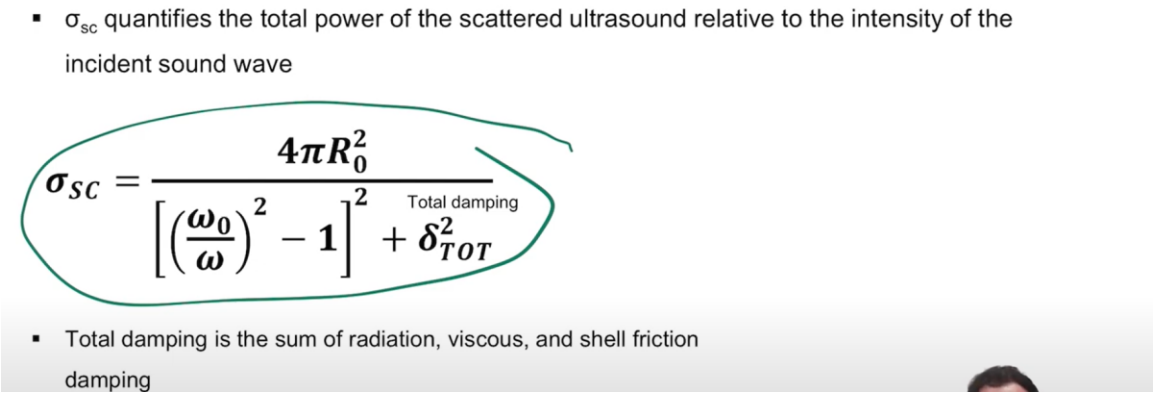
$$f_o \rightarrow Resonant\ freqeuncy\ (MHz)$$

$$R_o \rightarrow Resonant\ radius\ (\mu m)$$

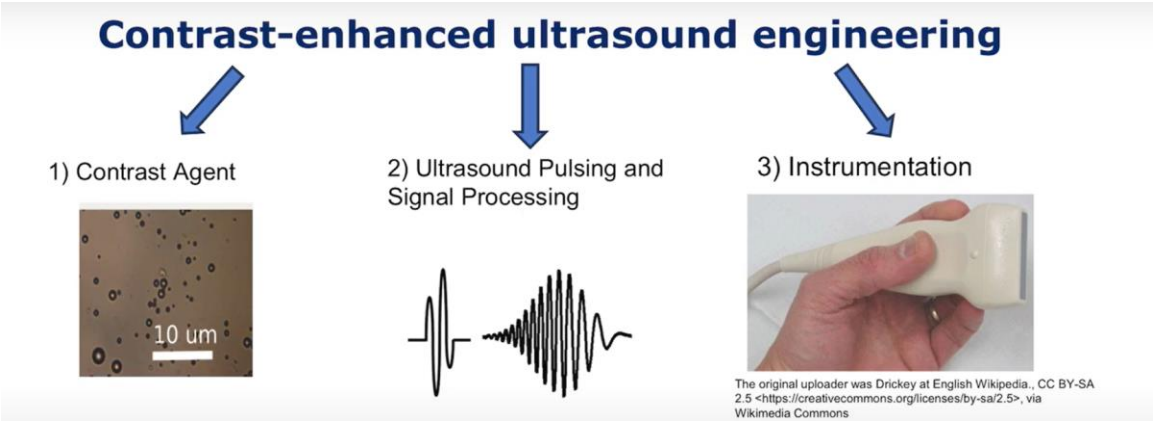
So, if we assume that this bubble is resonant and then we change the radius then what will change is the resonant frequency. So, here we see that if the resonant radius is around 1.5 micrometers resonant frequency is around 2 megahertz. This is a simplification, this is derived you know this is called the Minert's formula and this roughly simplifies to f naught times r naught is equal to 3.3, where f naught is the frequency resonance frequency in megahertz and r naught is the resonant radius in micrometers.

So, once you fill in these values of these constants etcetera you get this, and this is the famous Minert's equation. So, there are other factors also which you know effect the resonance, but this is a simplification here. Now this is the scattering cross section which is the quantification of the total power of scattered ultrasound relative to the intensity of the incident ultrasound wave. So, a strong scatterer will have a high scattering cross section, and this is the formulation for the scattering cross section of the bubble. So, there is a term in the denominator which is a frequency dependent term when your frequency is

a resonant frequency this term will be cancelled right and now the amplitude of oscillation is only determined by damping. I am sure you have seen you know resistance capacitance inductance and in a LRC circuit you may have seen resonance. So just there, only the resistance dictates the amplitude when a resonance is happening. Similarly, here, this damping dictates the amplitude and this damping can be calculated as a sum of radiation damping, viscous damping and shell friction damping when a shell bubble is oscillating. So, moving on, we discussed that you could get non-linear signatures. So, if you are firing at 10 megahertz to an ultrasound contrast agent suspension using your transducer, when you receive the signal, you may get lower frequencies, in this case a subharmonic, you may get higher frequencies, ultra harmonics and harmonics.



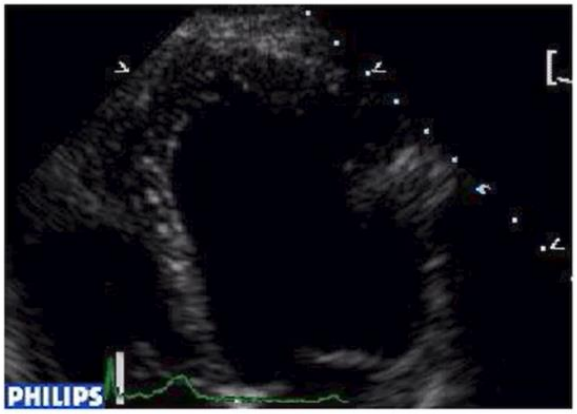

Subharmonic is at half the frequency; ultra harmonic is at 1.5 times the frequency. And these specific signatures, because they are specific to the microbubbles, they don't occur in tissue. These can be used to detect bubbles with high sensitivity and specificity. So, in the field of contrast-enhanced ultrasound engineering, you can either engineer better contrast agents with better stability, stronger resonant behavior, better biocompatibility, which is a chemical engineering endeavor, and chemistry, of course.

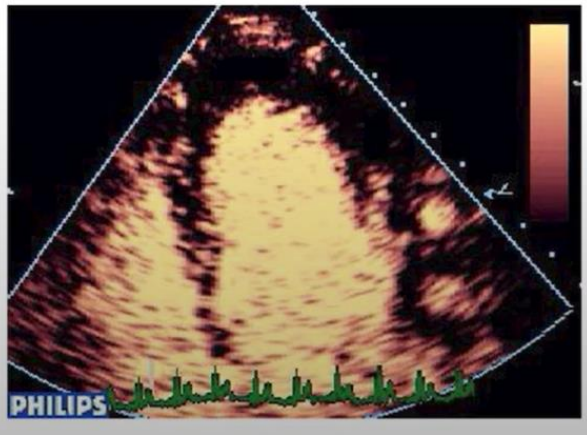



Or you can design ultrasound pulsing and signal processing approaches. Or you can develop better instrumentation, wider bandwidth transducers, more sensitive crystals, et

cetera. So here is the most common application of contrast agents, left ventricular opacification. Here probably in an obese patient what you see that the chamber walls are not very clearly visible.

So, we don't know what is going on here, here. here but when you add ultrasound contrast agents these areas light up and now the wall is very clearly visible as you can see the wall is very clearly visible and from this you can calculate the ejection fraction how much blood is being pumped but that is only possible if you have a good estimate of the wall right which can be wall location which can be obtained by using ultrasound contrast agents.



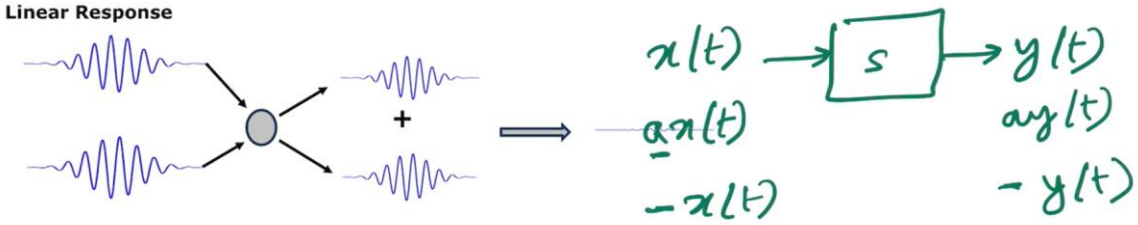





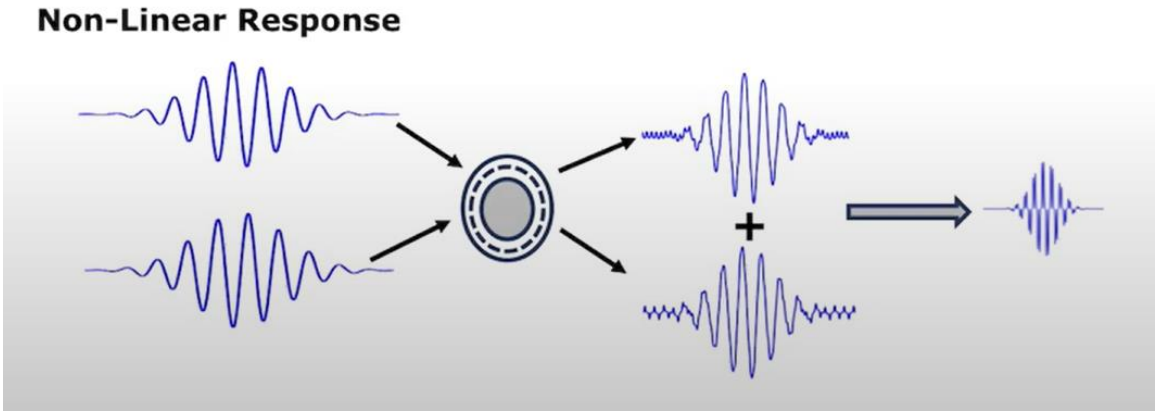

Now let us discuss how to isolate these non-linear signals. So, one example is pulse inversion. Let us assume that a signal s x of t passes through the system s and the output is y of t. So, if I scale the input and I make it a x of t for linear systems, what do we get? we should get a y of t right because if you scale the input output gets scaled. So, this a can be any constant right let me choose a as minus 1.

So, if I put minus x t as the input the output should be minus y of t right. Now, if I sum the inputs right x t plus minus x t I will get 0 right, but similarly if I sum the outputs y t

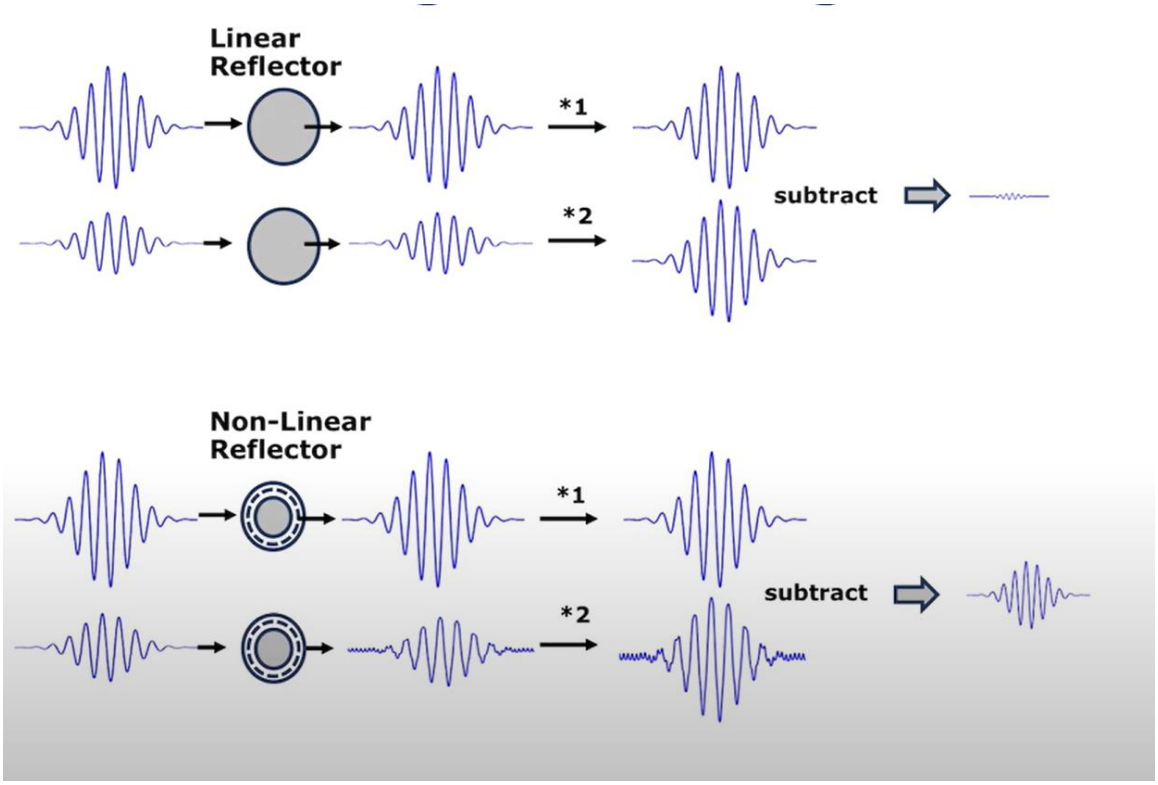
plus minus of y t I will again get 0. So, now using this principle if you see here what you observe is there are two signals that are phase inverted. So, this signal versus this signal actually there is a negative sign you multiply by minus 1.



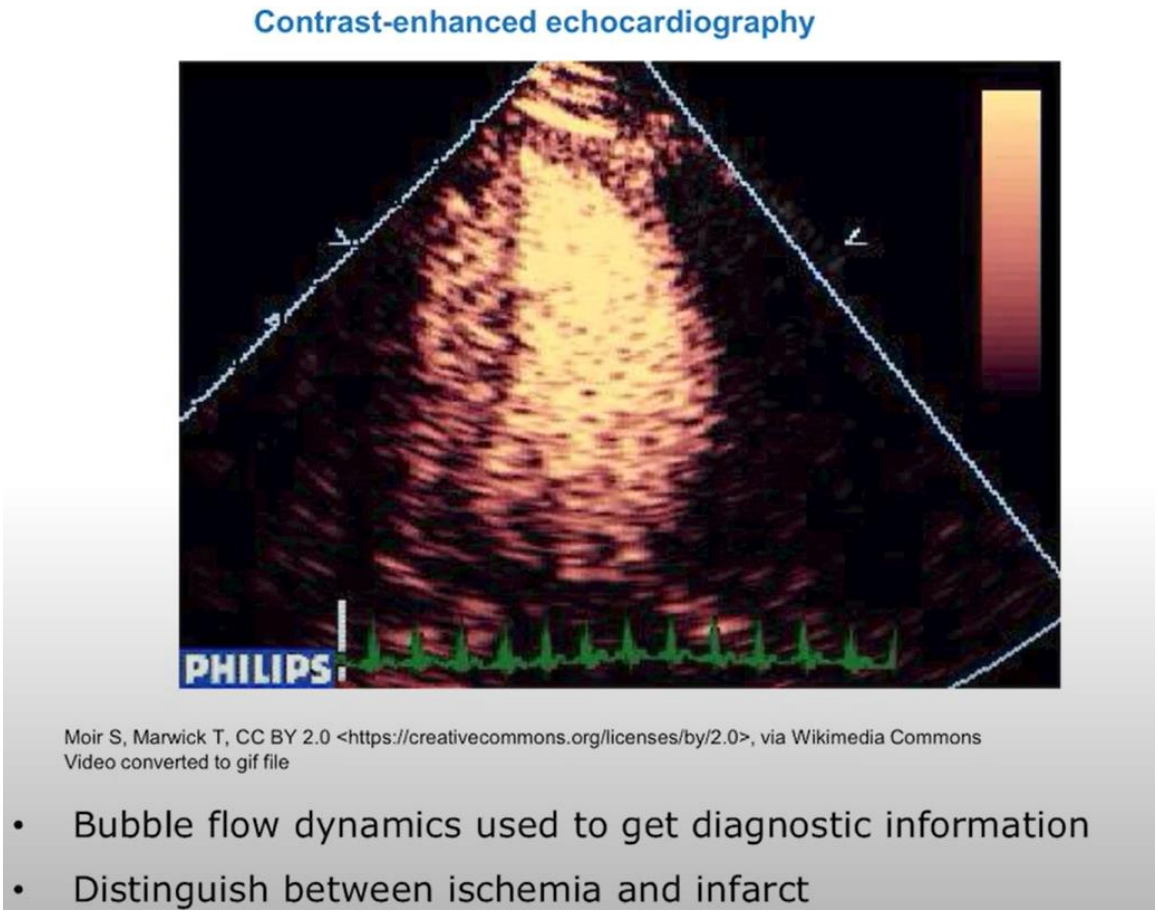

So, there will be a phase inversion. Now, if you pass it through a linear system let us say tissue which can be approximated as a linear system at moderate pressure amplitudes. Then what is going on is whatever was the output initially, if you scale by minus 1, the output should also get scaled by minus 1. And when you sum these outputs, the output will be 0, almost 0 because it is not going to be perfect. There will be probably some artifacts, some motion, some noise, but it will be close to 0. Now, this will suppress the tissue background, but if you have an oscillating bubble which is highly non-linear, then just scaling will not actually cancel the outputs. So, even after summing the output and the scale output by minus 1, you still get a residual signal that will help you find the bubbles.




So, there is another technique, power modulation. I think you remember it. This is also based on scaling, but the scaling factors are 1 and 2, not 1 and minus 1. This is also used to detect the bubbles and suppress the background.



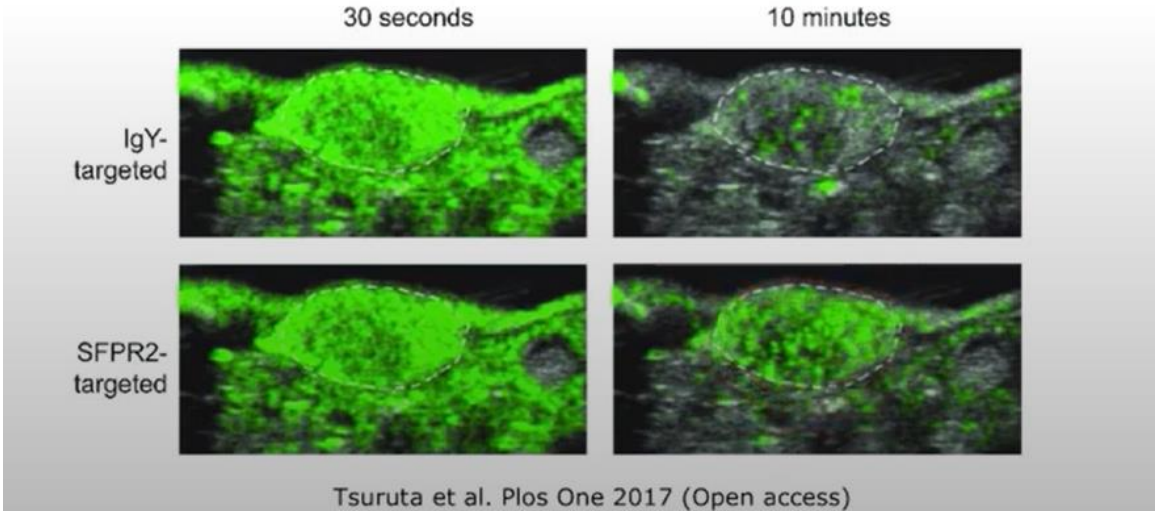

There are other techniques called flash contrast imaging. Here you send a pulse and destroy all the bubbles. And actually, what we are interested in is this wall. This is the heart wall. And when you destroy, then this heart wall will become dark. But then slowly, the bubbles will start flowing into the wall as well.




The wall has several small blood vessels. So, this region, which is actually the chamber of the heart, this gets lit up because of the presence of the bubbles. But the bubbles also go into the heart wall and start perfusing the wall. So essentially the wall also starts lighting up, although not as much as the chamber. So, if the regions of the wall don't light up, that suggests that those regions are not getting any flow. So then that can help in making some diagnostics whether that tissue is experiencing ischemia which is limited flow or whether that tissue is infarcted or the tissue is already dead.

This kind of information's can be obtained by the doctor using this flash contrast imaging. So, we have written this review article which discusses different techniques to detect microbubbles. I hope you look it up if you have some time.

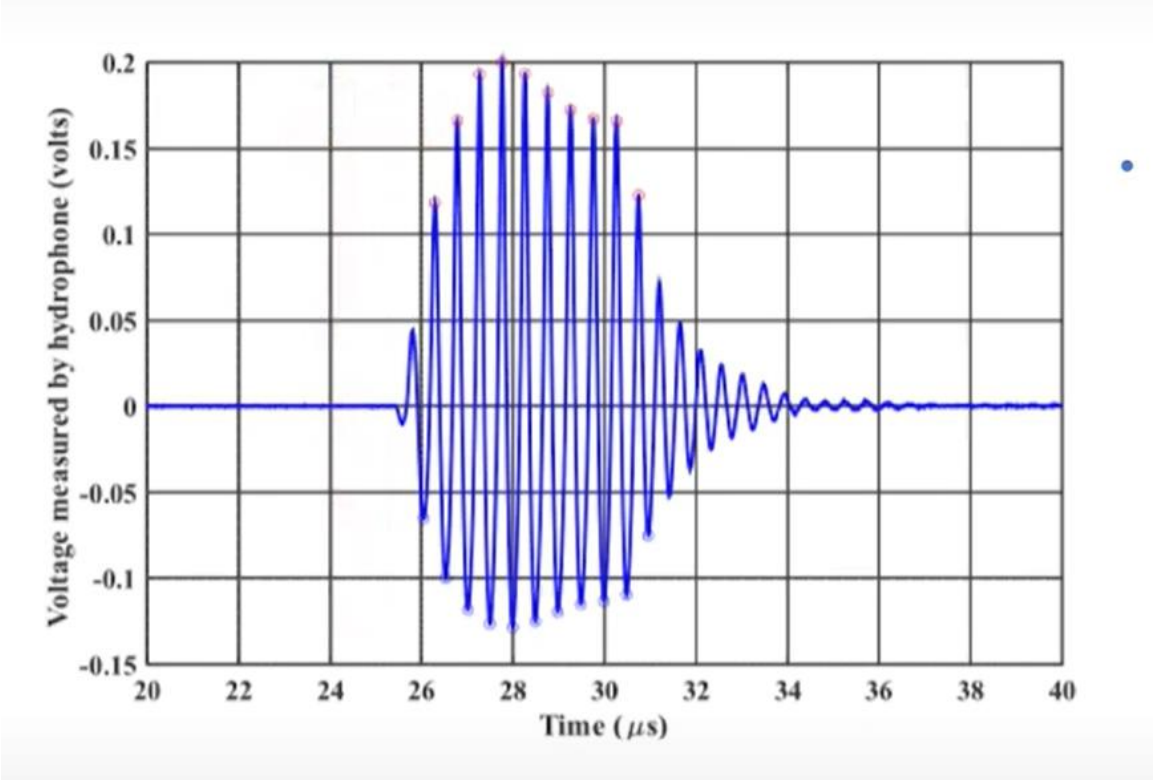
Next let's discuss ultrasound molecular imaging in which you have a bubble this bubble is actually targeted by putting a ligand which will help it attach to certain biomolecules of interest or certain biomarkers.




These could be biomarkers of inflammation, angiogenesis, etc., which will provide clinical information. Once you send these bubbles, they adhere to the target. So, here's an example. If you have non-specific targeting, meaning these are just for control as control bubbles, then after some time, they just flow out because they are not adhering at the target.

But these targets have specific interaction. So, they adhere and even after some time, the bubbles that are freely floating, they are gone. But the bubbles which are adhered are visible. And therefore, you can say that this tumor actually shows the expression of SFPR2, which is a biomarker.

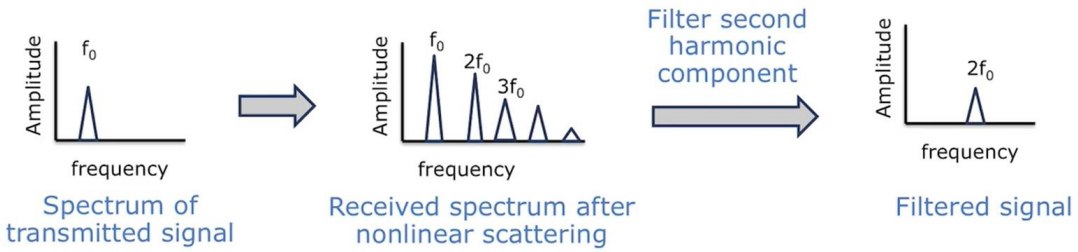
Then we discussed non-linear propagation. So, here is a pulse which has an amplitude in the diagnostically relevant range, but this pulse is showing some asymmetry, some non-linearity and you can see that the peak compressional pressure here goes from well this is not a pressure axis, but this is proportional to pressure because this is voltage.




So, higher voltage in the peak positive side and lower voltage in the peak negative side which shows this asymmetry and shows non-linear propagation. We discussed that Goldberg number tells you whether the propagation is attenuation dominant or nonlinearity dominant because certain media are more nonlinear but then they also have high attenuation. So, the nonlinearity never builds up because the attenuation suppresses it. On the other hand, there can be media. which have a lower nonlinearity coefficient but very low attenuation and that will lead to effectively stronger nonlinear propagation. So, taking a ratio of two parameters this Goldberg number was derived, and this Goldberg number tells you effectively how strong the nonlinear propagation is.

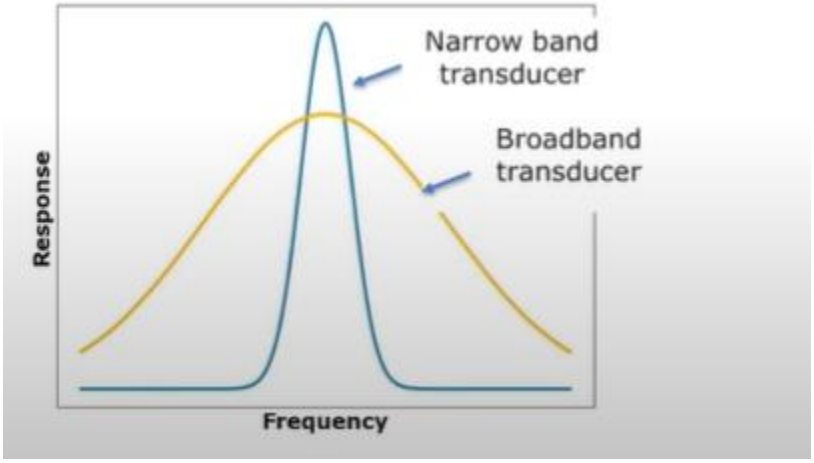
| Type of Medium | Gol'dberg number |
|---|---|
| Breast | <14 |
| Liver | <14 |
| Muscle | <14 |
| Blood | 14 |
| Water | 266 |

There's also been the development of a technique called tissue harmonic imaging in which you just send a pulse of a certain frequency or a certain range of frequencies. And as the wave propagates, then you get certain harmonics. And those harmonics can be filtered, and imaging can be done at 2F0, for example, second harmonic imaging, in which you are visualizing twice the frequency preferentially. And this leads to better resolution as well as lower side lobes.

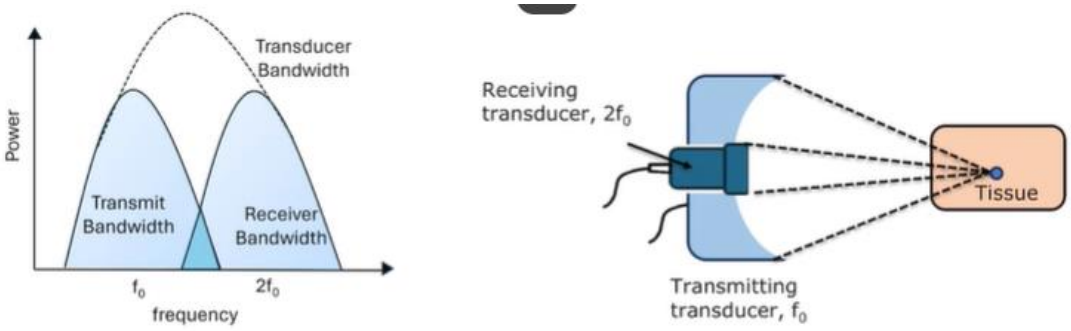



It has better penetration depth compared to fundamental signal at 2F0. So, suppose if I was to send signal at 2F0 directly instead of relying on non-linear propagation, I would have to propagate two-way distance at 2F0 frequency that will lead to high attenuation, but if 2F0 is generated by nonlinear propagation at a certain depth, then only in the way backwards, I will have high attenuation because of the higher frequency. So that is the advantage of tissue harmonic imaging. These are some examples, although it's not that clear here, but certain walls are better visible, and some artifacts are less visible in tissue harmonic imaging.

Then of course for non-linear imaging you need transducers with appropriate bandwidth. You should be sensitive at the fundamental frequency as well as the non-linear frequency of interest and that's why the requirement from the transducer design perspective increases substantially.



So, you need transducers where you have adequate sensitivity at the transmit as well as the receive frequency. And this is typically done by taking the bandwidth of the transducer and exploiting the lower part of the bandwidth for transmission and higher part of the bandwidth for reception at the harmonic frequency. and then you can create certain specialized transducers where there is some kind of overlay between the two different types of crystals, one for transmission and one for receive. Now let's discuss contrast-enhanced harmonic imaging, which is also called contrast-enhanced second harmonic imaging.




Why I brought this up? Because this is related to nonlinear propagation as well. Because if we are imaging at 2F0, relying on the second harmonic signal coming out from contrast agents, it is important to remember that second harmonics can also be generated in tissue because of nonlinear propagation. So, for second harmonic imaging to be successful, where I am talking about successful visualization of contrast agent and suppression of the background, that's only possible if the second harmonic in tissue is not very strong or essentially non-linear propagation is not very strong. To reduce nonlinear propagation, we ought to reduce the pressure amplitude of the transmitted signal. At those lower pressure amplitudes, you won't have very significant nonlinear propagation.

But you still get strong nonlinearity from contrast agents. And it is possible to improve the contrast to tissue ratio. So that's important because these are confounding factors for second harmonic imaging. And I hope you followed this point. also to avoid the challenges with second harmonic imaging one modality that has been proposed is sub harmonic imaging and it turns out that non-linear propagation does not generate appreciable levels of sub harmonic signal and in this case what I mean by sub harmonic is f0 by 2 and then there are also n of 0 by 2 essentially with higher n's which lead to 1.5 f0 and other fractional order harmonics which are called ultra harmonics these are more specific to the bubbles.

So, they are not generated substantially by non-linear propagation and therefore, they can be used to get better contrast when non-linear propagation is involved and they are highly specific to the bubbles, but the challenge is these are threshold phenomena. So,

essentially the pressure has to exceed a certain threshold only then these sub and ultra harmonics are formed and that leads to lower sensitivity. So, I hope you enjoyed this summary of the past few lectures, and we discussed topics ranging from image quality metrics to nonlinear acoustics and imaging. Please revise these topics and I'll see you in the next lecture.

Thank you.