Biomedical Ultrasound Fundamentals of Imaging and Micromachined Transducers

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Lecture – 46

Welcome to the lecture on ultrasound bio-effects. Let us reflect on the birth of medical imaging. Medical imaging was born when X-rays were discovered by William Conrad Röntgen, who also received the Nobel Prize in Physics in 1901 for this discovery. Here in this image, you can see an X-ray image of the hand of William Röntgen's wife, where you can see her wedding ring on her ring finger. It turns out that when you discover something new, it is initially unknown, hence the name "X." The letter "X" was given because it represented an unknown kind of ray.

It is ironic that despite the unknown nature of this wave, it was used extensively for research, entertainment, etc., and caused significant damage. For example, consider this quote by Thomas Edison:

"*But the court says, don't talk to me about X-rays. I'm afraid of them. I stopped experimenting with them two years ago when I came close to losing my eyesight. And Dally, my assistant, practically lost both of his arms. I'm afraid of radium and polonium too, and I don't want to monkey with them.*"

It turns out he was researching X-rays along with his assistant, Clarence Dally, who was a well-known engineer. Both of them suffered significant health damage due to their exposure to X-rays. This underscores the importance of safety in medical imaging is paramount.

When it comes to healthcare, you may be aware that clinicians or physicians take the Hippocratic Oath upon completing their degrees. You may have heard the phrase "do no harm," which is actually an abbreviated version of "I will abstain from all intentional wrongdoing and harm." Even before you aspire to treat a patient, you should ensure that no harm is incurred by the patient because of your treatment approach.

When it comes to ultrasound, just like X-rays, safety is also paramount. You may have thought that ultrasound is safe, and it is. Ultrasound is non-invasive and non-ionizing. Unlike X-rays, it does not use any kind of radiation that can ionize tissue and cause radiation damage. However, safety protocols are as important in ultrasound as in other imaging modalities. It turns out that at certain exposure levels, ultrasound can cause bio-effects that can be either reversible or irreversible.

In terms of diagnostic ultrasound, the safety profile is largely well known, but there is a range of exposure levels that we should understand to use ultrasound safely in the clinic. For example, we know that light is safe; exposure to light is generally safe. But if you have intense light, it can cause significant damage. Even moderate-intensity light, if exposed for a prolonged time, can be harmful. For instance, prolonged sun exposure can cause skin damage. The same principle applies to audible sound. Continuous exposure to loud sounds, such as in a mine where there are frequent dynamite explosions, can cause hearing loss. Similarly, prolonged exposure to moderate sound, such as using headphones, can lead to bio-effects that damage hearing.

The same principles apply in diagnostic ultrasound as well; we want to avoid such bio-effects. Thus, we aim to avoid very intense ultrasound and long-term exposure. Generally speaking, ultrasound bio-effects refer to the biological responses generated in tissue due to exposure to ultrasound energy. These bio-effects can be utilized for therapeutic applications. There is a separate branch of ultrasound called therapeutic ultrasound, which is not the subject of this course, but we will briefly look at it. When these bio-effects are exploited in a controlled manner, they can be clinically useful. However, when it comes to imaging, we would like to avoid these bio-effects.

These bio-effects can be broadly classified as thermal effects and mechanical effects because ultrasound interacts with tissue mainly in two ways: through thermal mechanisms and mechanical mechanisms. Now let me list some potential bio-effects. These include cell lysis, loss of the ability to divide, thermal necrosis (the destruction of cells or tissue by heating), and apoptosis (programmed cell death in response to ultrasound exposure). When cells are exposed to ultrasound and become damaged, they may undergo programmed cell death, known as apoptosis.

Other potential bio-effects include lesioning by cavitation (more on this later), which causes a damaged zone in the tissue, membrane effects (where the cell membrane undergoes physical changes), damage to platelets in the blood, hemorrhage (where a vessel bursts and blood is released), and vessel constriction or occlusion (essentially a blocked vessel) in response to high-intensity ultrasound exposure. This is not an exhaustive list; there are various mechanisms and potential damages that can occur.

When it comes to safety in ultrasound, the exposure levels determine safety, and they can be classified into three regimes ie Diagnostic ultrasound (which includes B-mode, other imaging modes, and Doppler), Therapeutic ultrasound (which may include hyperthermia, such as increasing the temperature of certain body regions by a few degrees to improve healing, or drug delivery in response to ultrasound), and Ultrasound surgery (which involves high intensities, such as in high-intensity focused ultrasound, or high-pressure amplitudes, such as in histotripsy).

Now, there is a famous principle to avoid any unwanted effects during diagnosis (we are talking about diagnosis and not therapy). This is the principle of ALARA, which stands for "As Low As Reasonably Achievable." The idea is that the exposures used in diagnosis should be as low as

reasonably achievable and not higher. The ALARA principle limits the escalation of ultrasound exposure and also avoids scans that do not produce any additional diagnostic information.

Generally, if you use a higher pressure pulse, it will improve the penetration depth and enhance the contrast and signal-to-noise ratio. However, we are making this ultrasound image for clinical use and not for cosmetic purposes. Therefore, there is a limit to how much diagnostic information is contained in the image based on these parameters. Beyond a certain signal-to-noise ratio, further enhancement through increased pressure may not serve a purpose and can increase the risk of adverse bio-effects.

There are cases where increasing exposure levels does not add significant value in the clinical context; hence, it is discouraged. For instance, here is a very impressive 3D ultrasound image, and you can also create a 4D video in which the fetus can be seen in three dimensions. Here is the standard two-dimensional image of the fetus. You may wonder why the 2D image is still so popular when we can make such beautiful three-dimensional images. It turns out that this 4D scan or 3D scan in time actually requires more ultrasound exposure and longer exposure times. Therefore, it is better to avoid a 4D scan when a 2D scan will suffice. A 4D scan should only be recommended if the 2D scan indicates something and more diagnostic information is needed. However, a 4D scan should not be used casually or for cosmetic reasons.

The clinician will assess the risk-benefit ratio when using any kind of diagnostic imaging or mode, considering the benefits to the patient in terms of improved diagnostic information and the associated risks, if any. Based on this assessment, they will make an informed decision, keeping ALARA in mind.

When it comes to thermal bio-effects, the main reason is energy deposition and heating. When energy is deposited into tissue, part of it gets absorbed, while other parts are reflected or refracted. However, some of it gets absorbed due to the tissue medium's viscous properties. Typically, absorption is harder to measure, while attenuation is easier to measure because you can measure attenuation directly using the insertion loss method.

You can measure attenuation, and it turns out that absorption is the dominant contributor to attenuation. Essentially, if you measure attenuation, you almost have an absorption measurement because absorption is the dominant contributor to the attenuation coefficient. Thus, the attenuation coefficient is often used as a surrogate for the absorption coefficient.

Now, the thermal bio-effects depend on the temperature elevation. For example, if I take a certain tissue region and I am doing imaging, there will be heat deposition, and therefore there will be a temperature elevation. But if the temperature elevation is less than 1.5°C, then it is considered acceptable and low risk. However, if the temperature elevation is more than 4°C for more than 5 minutes, it can cause tissue damage and may be considered sensitive for regions such as the fetus,

which are extraordinarily sensitive. Also, it depends on how sensitive the tissue is to heat deposition. For example, the absorption coefficients vary with tissue. Hence, the bio-effects incurred by tissue in response to a certain amount of heat will also depend on the type of tissue.

For example, acoustic absorption is frequency dependent. Recall the power law relation discussed by Professor Karla. If the beam is non-linear, having the fundamental signal as well as the harmonics, then the attenuation will increase because these high-frequency components in the form of harmonics will be absorbed more.

Also, consider that certain tissues absorb more heat than others. For example, bone and cartilage absorb more heat and experience temperature elevation very quickly. So all these factors should be kept in mind while performing imaging.

According to the AIUM, or the American Institute of Ultrasound in Medicine, which is a professional society that provides oversight in this region, the temperature elevation:

$$\Delta T_{max} \leq 6 - \log_{10}(t) / 0.6$$

where t is the exposure time in minutes. If you increase the exposure time, then typically the temperature elevation is higher. Therefore, this formula tells you that if your exposure time is longer, you will probably have to reduce your intensity or amplitudes so that this ΔT_{max} remains lower than this value. Also, while considering thermal dose, analogous to the dose of drugs or medicines, there is a concept of thermal dose in which, if you have a temperature of 43°C maintained for 240 minutes, it is considered lethal for the tissue. The human body can tolerate elevated temperature for short times. For example, we can drink high-temperature drinks, and we can also have fever temperature elevations of a few degrees for a short period of time, and it is not lethal. But if the temperature exceeds 43°C for a long time (240 minutes), then it is considered lethal.

We define a concept of ultrasound dose. The thermal dose per unit time is defined as D, and it is given as:

$$D = \int_{0}^{\Delta t} R^{[43 - T(t)]} dt$$

where T(t) is the temperature profile and R is given as 0.25 if the temperature is lower than 43°C and 0.5 if the temperature is greater than 43°C. Δt is the heating period, and T(t) is the temperature profile.

Now, this is an empirically derived formula. This is not derived from first principles, but it is useful for calculating the thermal dose per unit time. These thermal effects can be used for therapy, although they are not exactly imaging or diagnostics.

So the common therapeutic applications based on thermal effects are hyperthermia or diathermia, and this diathermia is very common for healing certain tissues, and high-intensity focused ultrasound therapy, which is a form of ultrasound-based surgery.

So hyperthermia, literally speaking, "hyper" means more and "thermia" means temperature. Essentially, it will increase the temperature locally in the body, which increases blood flow. Now, you may have experienced that when you get injured, sometimes you put a hot pack on that region, or you may have put a hot water bottle on your abdomen. But ultrasound allows us to do the same thing, essentially to induce hyperthermia, but it can focus deeper into the body and reach regions that you cannot access with a hot pack.

Now, the ultrasound that is used here is low-intensity ultrasound, but it is used for a longer period of time and generally elevates the temperature by 2-4°C only, and the intensity used is generally 1 to 2 W/cm^2 for tens of minutes. This hyperthermia is commonly used in sports medicine for healing fractures, tendons, loosening muscles, etc. The frequency used is typically 1-3MHz. It is also a range of intensities that leads to cell membrane permeability, meaning the cell membrane becomes more permeable, making drug uptake more efficient. Therefore, hyperthermia has also been used with chemotherapy in cancer. First, cause hyperthermia in the tissue that you want to target, and then perform chemotherapy. This approach works better than either hyperthermia alone or chemotherapy alone.

And it turns out hyperthermia also reduces cell division at elevated temperatures, which can be used for cancer treatment in addition to radiation therapy.

Now, let's discuss high-intensity focused ultrasound surgery (HIFU). So HIFU therapy uses a highly focused, high-intensity ultrasound beam, which can be 100-10,000 W/cm^2 to thermally treat diseases.

HIFU transducers are very large in size compared to a traditional ultrasound imaging array, and these transducers are able to generate a sharply focused beam that can have high intensities. Just by exposing the tissue for a few seconds, these transducers can actually enhance the temperature of the tissue by 60-70°C. Because of this, the tissue undergoes thermal necrosis and is destroyed. So effectively, it is like destroying a certain region, just like you would excise a certain tumor.

Here, without any scalpel, without cutting open the tissue, you can destroy a certain region from outside or non-invasively, which is the most interesting aspect of HIFU surgery.

So in HIFU, when you are treating the tissue with this very high intensity, sometimes the temperature elevation can be on the order of 30-70°C. If the temperature exceeds 100°C, it causes boiling in the tissue, and bubbles are created. While these bubbles can enhance heating, which is good for damaging tissue, they can also cause off-target tissue damage. Essentially, if you are trying to destroy a tumor, you may also destroy some adjacent normal tissues because of this uncontrolled heating. These bubbles also have the effect of shielding the target. So, let's assume that you would like to destroy this region. Assume that some bubbles are formed here. These bubbles have a high impedance mismatch, and they will reflect the sound to a large extent. They will also modify the ultrasound beam and shift the focus, causing sometimes the distal regions not to be properly ablated, resulting in asymmetric lesions.

Nonetheless, HIFU is being used for some applications in western countries and in some Asian countries, including India. HIFU is being used for uterine fibroid ablation. This is a common problem in the uterus where you can have fibrous development called fibroids, which can cause problems. They can be treated non-invasively using HIFU. Another application is in the brain, where you can treat motor symptoms or tremors caused by a disease called essential tremor. You can also treat the motor symptoms of Parkinson's disease. While it is not a cure for the disease itself, the disability experienced by the patient because of the motor symptoms is reduced when HIFU is used in the brain. Many other tumors are also being treated by HIFU, and they are under research and development. Another approved application by the US FDA is treating metastasis in the bone. So when you have a tumor originating from some other source and forming in the bone, they can be treated using HIFU to provide relief to the patient.

HIFU is not the only ablation technique. Ablation refers to localized tissue damage that is done for medical reasons. There are other options. For example, the physician can surgically resect the tumor. Cryoablation can be performed, in which very low-temperature liquid or gas is used to destroy the localized tissue. RF ablation can be performed, where electricity is used to destroy the tissue. Electrodes are placed, and current is passed, which destroys the tissue locally. There can also be laser ablation, but they have their own strengths and limitations.

For example, cryoablation and RF ablation are not non-invasive; they are minimally invasive. Laser ablation has limited depth, so it is used for certain applications such as in the eye, where a very clear optical window is present, but it cannot be used deep in the body, which is where HIFU has its own advantages.

Next, let's discuss mechanical bio-effects. Just like thermal bio-effects, ultrasound also interacts with tissues mechanically. Mechanical bio-effects can be due to the interaction of pressure waves with the tissue medium. Some common mechanical bio-effects include cavitation, acoustic radiation force, and acoustic streaming.

Cavitation can be due either to contrast agent bubbles that are injected into the body for some imaging application or because of bubbles that are generated in the body itself because of ultrasound exposure. Cavitation refers to bubble activity in response to ultrasound.

How can we generate bubbles in situ inside the body? This is because of ultrasound exposure. Before we try to understand how ultrasound exposure can cause bubbles to form, consider the example of soda. If you take a can of soda and open the can, you will see a large number of bubbles being nucleated. It turns out these bubbles were actually dissolved at high pressure in the fluid, and when you release the pressure by opening the can, bubbles are nucleated and bubble out. The same effect happens in tissue because ultrasound is actually a pressure wave that has phases of high pressure (compression) and low pressure (rarefaction). So in this low-pressure phase, where the ultrasound causes the pressure to drop, the solubility of gas in the tissue also drops, and bubbles can be nucleated. So that is how you would be able to generate bubbles in situ in the body, and then these bubbles would interact with the incoming ultrasound beam and cause some bio-effects.

So here is an image that shows bubble compression and expansion in response to pressure. These are actually depicting moderate amplitude oscillations. However, there can also be more violent oscillations in cavitation, which we will discuss further. Cavitating microbubbles can exert mechanical forces into the surrounding medium and cause tissue damage. They can also have other bio-effects, such as transiently increasing membrane permeability in cell membranes and promoting drug uptake through barriers in the body, such as the endothelial barrier.

Cavitation can be broadly categorized as stable cavitation and inertial cavitation. Stable cavitation is broadly defined as the oscillation of bubbles at low pressures, in which there is repeatable bubble activity. The bubbles undergo moderate oscillations and have a unique acoustic signature, which we will discuss in the next slide. In contrast, inertial cavitation refers to the violent collapse of a bubble after rapid growth. It is akin to the implosion of the bubble, and it also has a unique spectral signature. In stable cavitation, the ultrasound signal that is scattered exhibits specific frequency components.

It essentially forms a line spectrum, wherein you will have the fundamental frequency component. For example, if you are exciting the bubble at 2MHz, you will have a 2MHz peak, but you will also have a large number of $f_0/2$ components, for example, 1 MHz (which is $f_0/2$), 1.5 MHz (which is called ultra-harmonic), and $f_0/2$ is called sub-harmonic. You will also have harmonic frequencies.

This kind of line spectrum is characteristic of stable cavitation. In inertial cavitation, you will have the growth of the bubble and its implosion.

Because of this impulsive collapse, as we know, an impulse corresponds to a broadband signal. If you take the FFT of an impulse signal in the time domain, you get a broadband signal. Therefore, the implosion of these bubbles in an impulsive manner creates a broadband spectrum. Here are some spectral signatures. In blue, you can see the spectrum of very low amplitude oscillations. We shouldn't say there is no cavitation, but rather that there is very weak cavitation occurring. It is mostly a linear response from the bubbles at 50 kilopascals of peak negative pressure.

Now, as you increase the pressure, you undergo stable cavitation in this case, largely stable cavitation, although there can be a mix of stable and inertial cavitation when there are polydispersed bubble populations. You have the 2 MHz component, but you also have a 1 MHz component, a 1.5 MHz component, a 4 MHz component (which is the second harmonic), a 6 MHz component, and so on. This line spectrum is characteristic of primarily stable cavitation. As you go to much higher pressures (4.5 MPa), you see that the line spectrum becomes very weak, and primarily you get a broadband signal increase, which is due to impulsive bubble collapse, characteristic of inertial cavitation.

This is a very exciting development because just by listening to the bubble activity, we can determine whether primarily stable cavitation or inertial cavitation is occurring, or both. This listening can be performed by a cavitation detector, which is another piezoelectric transducer that is listening to the signals coming from these cavitating bubbles.

It only listens but does not send any pulses; that’s why the word “passive.” A passive cavitation detector can tell you what kind of bubble activity is going on. It turns out that stable cavitation and non-inertial cavitation are sometimes used interchangeably, but non-inertial cavitation is a bit broader than stable cavitation. This type of cavitation produces a certain kind of bio-effects, while inertial cavitation produces separate bio-effects.

Now I will give an example of a cavitation-mediated ablation therapy called histotripsy, in which a bubble cloud is formed in the focal region. Very high amplitude pulses are used to nucleate a bubble cloud, and this bubble cloud oscillation causes lesions in a very localized fashion, allowing tumors to be treated.

Excitingly, just last year, probably less than 8 or 9 months ago, this technique received FDA approval for treating liver tumors. The beams are very sharply focused here, so if the tumors are large in size, the tumor volume is ablated by scanning the histotripsy focus mechanically. Here’s an example image where you can see an array of histotripsy transducers.

Each of these structures is a separate transducer, and this array can be controlled, with each element being controlled individually. In the center, there is an imaging probe for image guidance because

you would like to see where you are delivering your therapy pulse, and you would like to passively receive the signal from there as well as create an image of the region to target your pulse. Here is an image of the treated region, where a cavitation cloud is visible in the ablated tumor. In this manner, you can achieve image guidance while simultaneously treating the tumor.

This is an example where there is a certain region that has to be treated, showing some echogenicity. As you treat it, a bubble cloud forms, and bubbles are very good scatterers of ultrasound, as we learned about in the ultrasound contrast agent chapter. These bubbles are hyper-echoic here, and after the whole tissue is treated, it becomes anechoic because the tumor is completely destroyed.

Histotripsy needs to be performed under image guidance to avoid any collateral damage or off-target effects. Typically, it relies on the presence of a hyperechoic bubble cloud in B-mode images. Here, there is a hyperechoic bubble cloud, indicating that ablation is occurring. You would need to mechanically scan to ensure that the entire tumor is destroyed by changing the location of this hyperechoic bubble cloud.

Another technique, which has been in existence since the late 1980s and 1990s, is lithotripsy, which is used to break kidney stones or gallbladder stones. This technique uses a high-intensity focused beam directed onto the stone, breaking it into small parts that can then be passed in urine.

This technique has a faster recovery time compared to regular surgery because it is largely non-invasive, and it is being used extensively in clinics, including in India. Now, let me talk about a couple of other mechanical effects. Acoustic streaming is a kind of fluid flow induced by the bulk motion of fluid when tissue is treated by ultrasound. The velocity of this fluid streaming is proportional to the acoustic power of the transducer.

This kind of fluid motion can have significance in terms of bio-effects because it can cause fluid mixing and convection. Then there is a closely related effect called microstreaming. An oscillating bubble can cause flow patterns around it. As you can see here, this bubble is undergoing radial oscillations. These fluid flow patterns are being introduced near this bubble in response to exposure by a transducer, and this is called microstreaming.

This microstreaming enables these bubbles to act like small micropumps. The fluid flow caused by these microbubbles can generate shear stresses. So if there are cells nearby or if there are endothelial layers nearby, it can have an effect on them and can also cause fluid mixing; hence the name micropump.

Another prominent mechanical effect is acoustic radiation force. In acoustic radiation force, a focused ultrasound beam exerts a pushing force at a focus. You may be familiar with the concept of radiation pressure as it applies to a comet. A comet's tail always faces away from the sun because the radiation pressure of the photons pushes the tail away. In a similar manner, when an ultrasound

beam is fired at tissue, there is a finite push or force that causes small local deformations. This is called acoustic radiation force.

This acoustic radiation force causes the transfer of momentum at the location, and this can produce some bio-effects. You will learn more about acoustic radiation force when you discuss elastography with Professor Karla.

We discussed why it is important to be safe in medical imaging diagnostics, specifically for ultrasound. We reviewed the thermal and mechanical bio-effects of ultrasound, including heating, cavitation, streaming, and acoustic radiation force, as well as the various means by which ultrasound interacts with tissue. We examined the spectral signatures of cavitation: for stable cavitation, we observed a line spectrum, while for inertial cavitation, we noted a broadband response. We also discussed a few applications, including hyperthermia, HIFU surgery, histotripsy, and lithotripsy.

Next, we will focus on quantitative metrics for ultrasound bio-effects in the next lecture.