Mathematical aspects of biomedical Electronic System Design
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Near Infrared Spectroscopy and Ultrasound Techniques

So, welcome to the next session of Biomedical Systems and Mathematical Models. In today's session, we will talk about the two multi-model techniques. The first one being near infrared spectroscopy and next is the ultrasound system. And how we can use both of these techniques to actually quantify the bulk properties of the tissue such as in optical we have the optical absorption coefficient and optical reduced scattering coefficient and in the case of ultrasound, we have attenuation coefficient. So, we will see how this bulk properties we can quantify from this extracted tissues from the breast.

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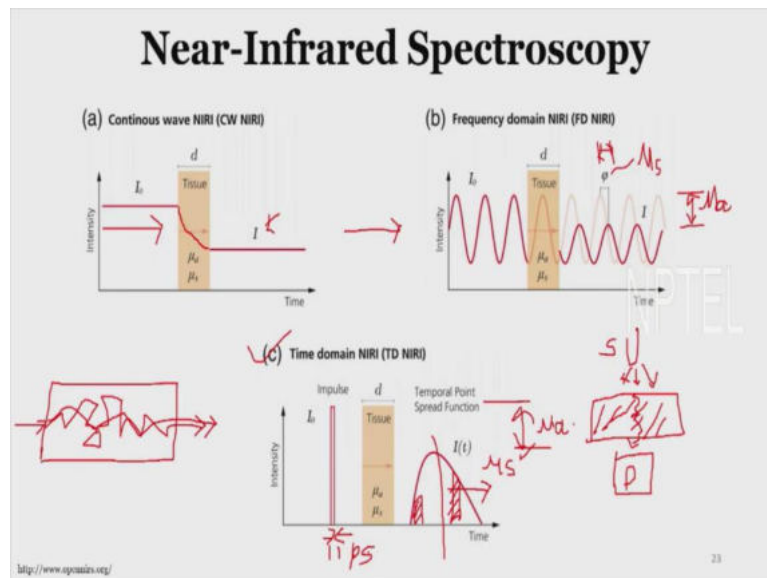
So, as you can see on my screen, in the case of near infrared spectroscopy, there are three different techniques where people use. The first one is the continuous wave near infrared spectroscopy, that is you have the light, which is passing through the tissue. So, you give light inside the tissue with a particular amplitude and it passes through the tissue. There is a certain decrease in the amplitude and you detect this with a detector, the live detector, it could be a silicon photodetector for example or it could be a photomultiplier tube but in the case of continuous wave, you can use this silicon photodetector itself.

When you go ahead to even higher frequencies for example in order of megahertz or so where you are able to distinguish between the phases of the different tissues. So, in that case we are not giving a continuous signal to this tissue but now we are going to give sinusoidal input to

the tissue. So, what we have is if this is the tissue, for example we have the LED placed on top of it, which gives the light. We shine the light. It could be a LED or laser. It shines the light on the tissue and then after it propagates through the tissue we detect it using a photodetector. So, this is the source and this is the detector.

So, in the second case, we use a sine wave or harmonic input to excite the source. And after it passes through the tissue, you can see there are 2 things. The first thing is that the intensity has now reduced so this will give you the information about the attenuation of this light intensity and second is the phase difference of the initial and the observed response of the photodetector.

So, there would be some phase difference between the actual input signal and the signal which has been detected after it has propagated through the tissue. And this Φ over here, so this Φ over here can help you calculate the scattering coefficient. This reduction in the amplitude will help you to get you the absorption coefficient. So, this is the bulk properties with which you can actually quantify with the frequency domain stimulation.
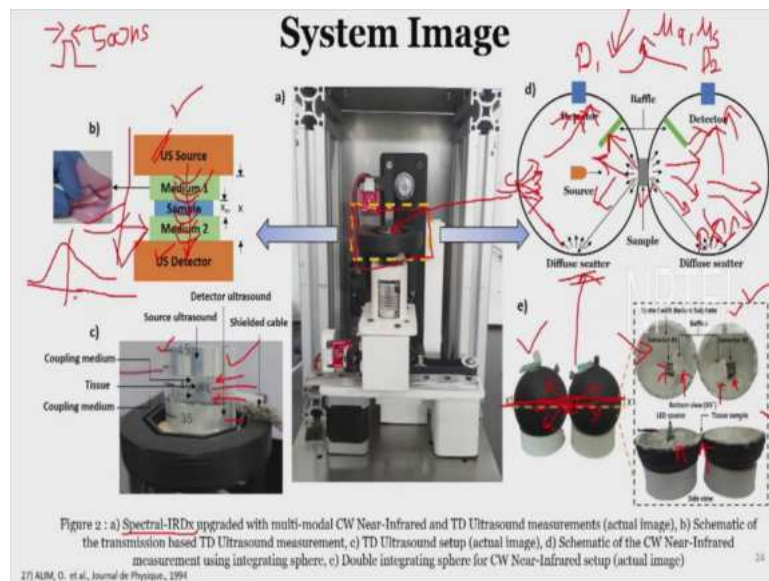
In the case of time domain simulation as you can see in the C part over here, instead of giving a sinusoidal input, we give a pulse which is of very small duration, which is in order of picoseconds ideally and once it pass through the tissue. So, you can see that as you have already seen in my earlier lecture as the light passes or the photons actually passes through the tissue it goes under large number of scattering before it passes through and goes through this tissue.

There are some tissues – some photons which are having more scattering and there are some tissue which are having less scattering. So, some of them which undergo less scattering. They reach very quickly. So, these are these photons which reach very quickly and then there are some photons which scatters very high and they reach very late to the detector. So, there what you observe is not just rectangular function but you see some kind of a Gaussian peak which with a long tail.

So, you see that the tail is stretched out on the one side and from there, you can actually quantify what, so how much is the stretching of this tail from that you can quantify this scattering coefficient for example. So, if this is most stretching of this tail which means there is more scattering which means you can quantify the scattering coefficient. Again you can quantify the amplitude of the received signal and from there you can quantify the absorption coefficient.

So, there are different techniques which you can use to quantify the different, different bulk optical coefficients such as absorption and the reduced scattering coefficient.

Figure 2 : a) Spectral-IRDx upgraded with multi-modal CW Near-Infrared and TD Ultrasound measurements (actual image), b) Schematic of the transmission based TD Ultrasound measurement, c) TD Ultrasound setup (actual image), d) Schematic of the CW Near-Infrared measurement using integrating sphere, e) Double integrating sphere for CW Near-Infrared setup (actual image)

27) ALIM, O. et al., Journal de Physique, 1994

So, let us come to this system that we developed at IISc. So, the system is spectral IRDx system and this we incorporated only near infrared spectroscopy technique earlier that is a transmitters based near infrared spectroscopy but we updated the system with multi-model technique that is now it is having the capability to quantify both the ultrasound as well as the near infrared spectroscopy.

So, let us go into these topics one by one. The first topic is the ultrasound. So, what you see over here is the assembly where this is the sample where the sample needs to be kept and the other regions actually are for the placement of the technology or the modules. For example in this case we have the ultrasound module. Second we will talk about the near infrared spectroscopy module.

In this case what we do is we keep the ultrasound source. So, this is a piezoelectric sensor as you can see over here. So, this is the piezoelectric sensor, the same piezoelectric sensor and then we have the coupling medium. So, the ultrasound transducer which incorporates piezoelectric sensor, it gives ultrasound waves which passes though the medium and then it passes through the sample and then it again passes through medium and gets detected by the detector over here.

So, this propagation through the combination of medium one couple of medium sample that is tissue sample and again the coupling medium is being provided over here. The coupling medium is required because you need to have low impedance between the coupling of ultrasound transducer and the sample; tissue sample. So, they have a different impedance. So,

to minimize this reflection due to impedance mismatch, we use the medium, a coupling medium.

And this coupling medium needs to be again be used once you want the ultrasound wave to propagate from the sample to the detector and that is why we need this coupling medium over here. In this case we use this coupling medium which is proprietary of the company with which we bought the ultrasound transducer. What we do is we actually give impulses, short pules in order of few hundreds of nanoseconds.

For example, 500 nanoseconds we observed at 500 nanoseconds there was a very good delineation between normal and cancer tissues. So, we propagate very short pulses of ultrasound input from the source and which passes through this mediums and what we observed is that we get a signal like this, similar to what we observed in the pan domain analysis of the near infrared spectroscopy but this is the case of the ultrasound technique.

So, the actual experiment system looks like this. So, this is the first ultrasound transducer which acts as a source. This is the coupling medium. This is the actual sample. This is again the second coupling medium and the finally we have the detector ultrasound; detector. You can see the detected wire, the wire which is coupling these detected ultrasound is actually shielded so that there is very less EMI interference between the input and the output signals over here. So, this is the case of the ultrasound detector.

So, let us go ahead with the continuous wave near infrared spectroscopy. To quantify the absorption and this scattering coefficient in the case of near infrared spectroscopy people have already used the double integrating sphere approach. A double integrating sphere is what you see in the bottom over here.

So, it involves 2 different spheres which are connected to each other through this input and exit ports over here. You keep the samples somewhere over here and your LED light is over here and you shine this light through the tissue which actually back scatters as well as forward scatters. And the same thing you can see over here in the schematic.

So, if I do the cross section and viewing the schematic over here what do you see is the source is placed inside the center and then this is the tissue, tissue sample and which scatters the light both backward as well as forward scattering. This light which interacts with the inner surface of this sphere, which again gets diffuse scattered. And this diffuse scattered light is then scattered again.

So, this light which comes over here which again scatters over here and then there is again a diffuse scattering which is taking place over here and goes through multiple diffuse scattering with very low losses or less absorption and finally it actually gets detected by the detector. So, we assume that there is a very low loss after it gets hit by the surface over here.
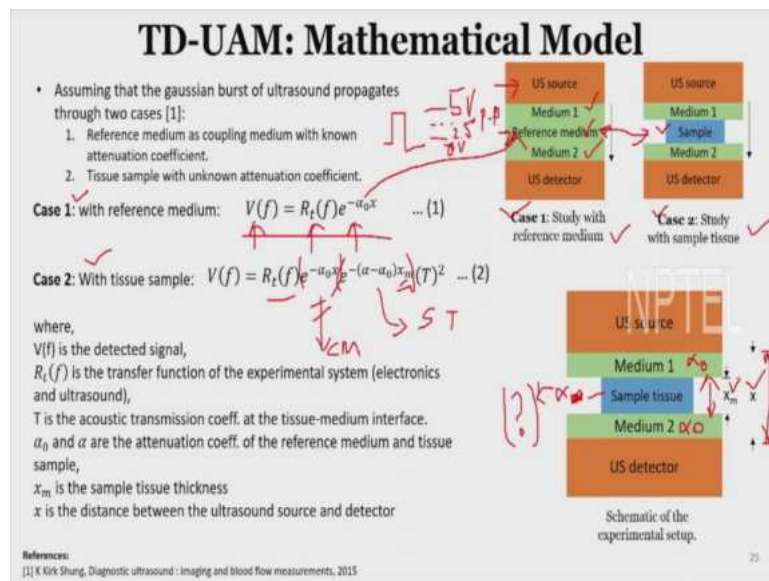
The same case happens once it gets the light which is actually going through this forward scattering. So, it goes through the forward scattering and what you see is again the light gets diffusely scattered and then gets absorbed by the detector. So, we gave the detected voltage 1 from the first detector and detected voltage 2 from the second detector and then we can use these 2 to actually quantify the bulk optical property such as μ_a and μ_s.

And the bottom what you see is the actual experimental setup where you have the detector - so this is the - again we cut slice this open, the integrating spheres and this is the top view. So, this is the bottom view in the top and then we have the side view over here. So, what we see from the bottom view is that this is the detector, first detector, this is the second detector and this is the baffle so that there is no direct interaction from the light which is getting scattered to this detector. So, only the diffused light should actually go through this detector.

What you see over here is this LED lamp; LED light over here and this tissue, tissue sample over here and you can see that the inner surface of this integrating sphere is actually coated with barium sulfate. Barium sulfate has the property to reflect 98 percent of the near infrared light which is incident on that particular surface. And as the name suggest itself that it is actually a integrating sphere so it integrates the light which gets scattered from the tissue from all the sites and it gets detected by the detector.

So, let us go through the mathematical model, which requires to be used to quantify the acoustic coefficient and the optical coefficient. The first is the acoustic coefficient.
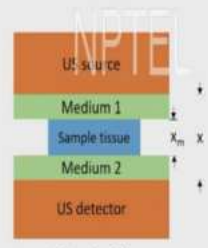
TD-UAM: Mathematical Model

- Assuming that the gaussian burst of ultrasound propagates through two cases [1]:
  1. Reference medium as coupling medium with known attenuation coefficient.
  2. Tissue sample with unknown attenuation coefficient.

Case 1: with reference medium: $V(f) = R_t(f)e^{-\alpha_0 x}$ ...(1)

Case 2: With tissue sample: $V(f) = R_t(f)e^{-\alpha_0 x}e^{-(\alpha-\alpha_0)x_m}(T)^2$ ...(2)

where,
V(f) is the detected signal,
$R_t(f)$ is the transfer function of the experimental system (electronics and ultrasound),
T is the acoustic transmission coeff. at the tissue-medium interface.
α_0 and α are the attenuation coeff. of the reference medium and tissue sample,
x_m is the sample tissue thickness
x is the distance between the ultrasound source and detector

References:
[1] K Kirk Shung, Diagnostic ultrasound : imaging and blood flow measurements, 2015

Schematic of the experimental setup.

In the first case what you observe is – what we give an input is the pules over here. So, this is the voltage pulse which is 5 volt peak to peak to the ultrasound transducer and having a VDC of around 2.5. So, this is actually 0 volt, the bottom part. So, to quantify the acoustic attenuation coefficient, we come up with 2 different cases.

The case 1 is the we assume that the reference medium is there in the center. In the case 2 where we assume that the sample is the actual tissue sample is there in the center domain, instead of the reference medium. So, we have the voltage detected with this reference medium and the voltage detected using the sample tissue both.

In the case of reference medium, in this case the reference medium is the same as the coupling medium. Over here we actually can calculate the detected voltage, this is the detected voltage, over here. As a product of transfer function of the system and the product with $e^{-\alpha_0 x}$ where x is the total distance over here.

So, over here you can see this is the x that is the complete distance from starting from the medium one, tissue sample or the reference medium and the medium 2. So, this is the x the total distance over here and α_0 is the attenuation coefficient of the reference medium. This α_0 is the same for medium one, reference medium and the medium 2.

In the second case with the tissue sample you have a different equation that represents. You have RT and then there is a product of 2 terms. The first term is for the coupling medium, so this is for the coupling medium and second is that is x_m that is the thickness of the sample medium and this is for the sample tissue.

So for the medium, coupling medium the attenuation coefficient is α_0 and we know this α_0. While for the sample tissue it is assumed as α over here but this is what we do not know. So, we still do not know what is α over here. That is the attenuation coefficient of the sample tissue. We know the α_0 of this coupling medium 1 and coupling medium 2 but we know the rest of the values. So, for example, we know this x we know the x_m. So, let us see how we come across and how do we calculate this α from this other equations.

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So, now if we have the 2 equations we mentioned over here, equation 1 and equation 2, we can take a ratio of them and we can do away with this transfer function, which is related to this experimental set up. So, that actually goes, so RTF actually goes away and we have only the $e^{-(\alpha-\alpha_0)x_m}(T)^2$.

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TD-UAM: Mathematical Model

- Assuming that the gaussian burst of ultrasound propagates through two cases [1]:
    1. Reference medium as coupling medium with known attenuation coefficient.
    2. Tissue sample with unknown attenuation coefficient.

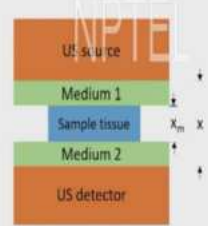**Case 1**: with reference medium: $\quad V(f) = R_t(f)e^{-\alpha_0 x} \qquad \dots (1)$

Case 2: With tissue sample: $\quad V(f) = R_t(f)e^{-\alpha_0 x}e^{-(\alpha-\alpha_0)x_m}(T)^2 \quad \dots (2)$

Diving the Eqn. 1 by Eqn. 2.: $\quad \dfrac{V_a(f)}{V_b(f)} = e^{-(\alpha-\alpha_0)x_m}(T)^2 \quad \dots (3)$

Assuming, the Transmission coefficient (T) at the interface of coupling medium and tissue sample approaches 1

Eqn. 3 can be simplified as: $\quad \dfrac{V_a(f)}{V_b(f)} = e^{-(\alpha-\alpha_0)x_m}$

Evaluate the unknown attenuation coefficient of the tissue sample

References:
[1] K Kirk Shung, Diagnostic ultrasound : imaging and blood flow measurements, 2015

US source
Medium 1
Sample tissue x_m x
Medium 2
US detector

Schematic of the experimental setup.

The transmission is, so transmission coefficient is actually, we can assume it to be 1 in the case where we assume that the acoustic wave propagation is transmitted completely from the medium 1 to the sample tissue for example and from sample tissue to the medium. So, this is an assumption over here.

So, if we assume that it the transmission actually approaches 1, in that case, the equation can be simplified to this equation over here and in this case all of the components unknown for example V_a is known V_b is known, α_0 is known, x_m is known. The only unknown is the α. That is the attenuation coefficient of that sample tissue. So, we do multiple experiments. We repeat it for three times and we then quantify the average α value for each of the sample tissue.

Now let us go for the near infrared spectroscopy mathematical model. So, what do we have over here is the double integrating sphere as we discussed earlier, and the light which gets scattered back scattered from the tissue gets detected by the detector 1. So, you get the values of detector 1 and you get the values of the detector 2. These two values of voltage that is VD_1 and VD_2 are performed for different, different tissues and from there you come up with the value of M_R. M_R is the measurement reflectance and M_T is the measurement transmittance. And equation over here represents the different, different cases for example the first one represents for the actual case like what you detect over here.

So, R(r,r,t,t) is for the detector 1. Over here this one the T(r,r,t,t) is for detected one that is transmitted. Similarly, if you remove the sample over here if you remove the sample over here and keep this port empty, you get this value from the detected one. And if you remove the sample over here and you calculate the transmitted power you get this T(0,0,0,0).

So, from this M_R and M_T value that we get we input it into Monte Carlo method over here. So, that is inwards adding the doubling software that we used over here so yes mentioned over here and the reference is also mentioned so it is from S Prahl in the bottom you can see. And this software is available freely on the internet. You can download it and use it.

What we need to mention is the diameter of this – of the spheres, equal spheres. The refractive index of the tissue. You need to mention and once you mention this you also need to mention this wave length that is operating wave length. In our case we measured it for 850 nanometers 940 nanometers and 1060 nanometers and from this we quantified the absorption coefficient

and the scattering coefficient. So, you input these values in this software and you get this μ_a and μ_s'.

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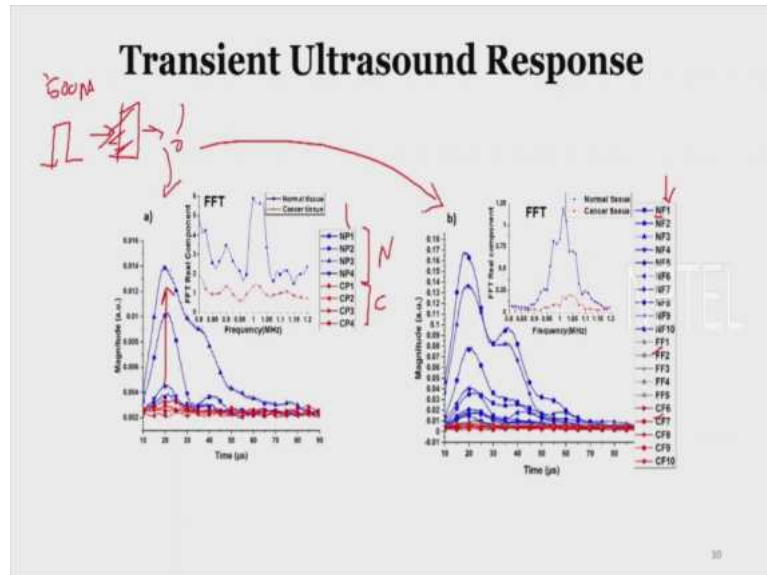
So, this is how this transient ultrasound response looks like. So, here you can see this in the case of normal, so you can see the blue curves are for the normal and the red one are for cancer, cancer and P actually signifies the paraffinized embedded tissue sample. So, there are different ways to store the tissue whether it could be either paraffin embedded, which needs to be de-paraffinized and second is the F is actually stands for this formalin-fixed tissues, the second letter that suggests over here

So, in the case of normal tissues you can see that the amplitude of the response is very high as compared to the cancerous tissue. So, what is – you can see is that the cancerous tissue have are able to absorb these signals time domain acoustic ultrasound response, very quickly but in the case of normal, it is able to allow this ultrasound radiation to pass through the tissue.

Same is the case seen in this formalin-fixed tissues. Here, N stands for this normal adjacent normal. F stands for this formalin-fixed and C actually stands for the cancerous tissue, so you can see that normal tissue has very high amplitude of a signal. Please note that the input that goes into the system is this pulse which is having 500 nanosecond pulse. So, this is the system which goes through this tissue, give this pulse of ultrasound to the tissue and what we detect is the results that you see over here.
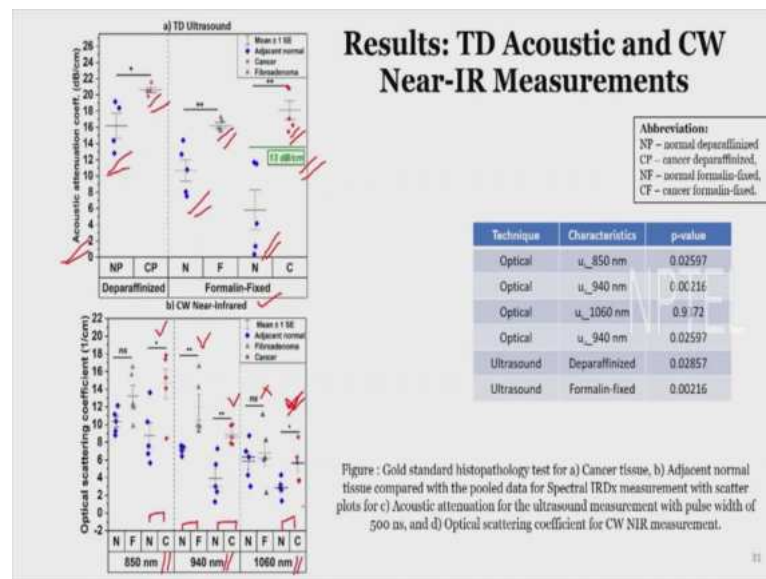
From this we quantify this attenuation coefficient over here and what we see is that for cancerous tissue the attenuation coefficient is like very high as compared to the normal tissues. If you also observe for the fibro-adenoma the attenuation coefficient is higher than this normal tissue and for the cancerous tissue, it is even higher for as compared to the normal tissue. And for this there was clear delineation if you use this factor or this value from 13 dB per centimeter, you can easily distinguish between normal and cancer.

In the case of near infrared spectroscopy, we needed for 3 different wavelengths that is 850 nanometers, you have 940 nanometers and 1050 nanometers. So, here you can see that there is a very good delineation in the case at 940 nanometers for both between normal and fibroadenoma tissues and normal and cancerous tissue.

In the case of 850 nanometers, we can see that there are good delineation between normal and cancer at 850 nanometers but not so much for 1060 nanometers, so not much in the case of 1060 nanometers over here, slightly significance at between normal and cancer at 1060 nanometers what we can see over here.

So, this is what we have observed when we performed this multi-model. Multi-model is known as because we combine the acoustic measurements or the ultrasound measurement along with the near infrared spectroscopy measurements. So, that is it with this session. The next session we will talk about another technique, which we used to quantify the thermal properties of the tissues.