Design for Biosecurity

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Lecture 46

Far-Infrared Spectroscopy

Welcome back to this week's session! Last week, we wrapped up our discussion by exploring the disadvantages of Raman spectroscopy, which is why I've placed the slide in front of you for reference. We reviewed the Raman spectrometer's functionality, which includes a lens that captures a portion of the scattered radiation and directs it to a filter. This filter ensures that only the Raman-scattered light reaches the detector.

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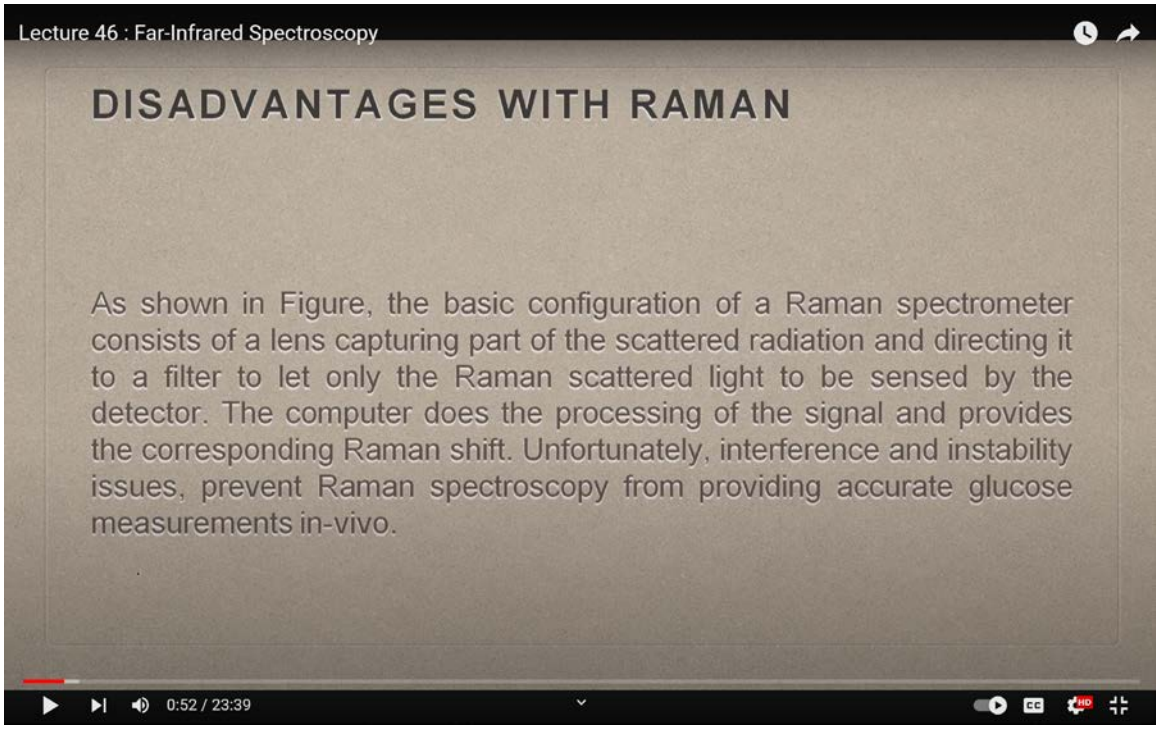

We discovered that while the concept of the Raman shift is fascinating, interference and instability significantly hinder Raman spectroscopy from providing accurate glucose measurements in vivo. Consequently, even though Raman spectroscopy has the potential

to be a powerful tool for in vivo glucose detection, it currently struggles to find its footing in the commercial realm due to excessive noise in the signal.

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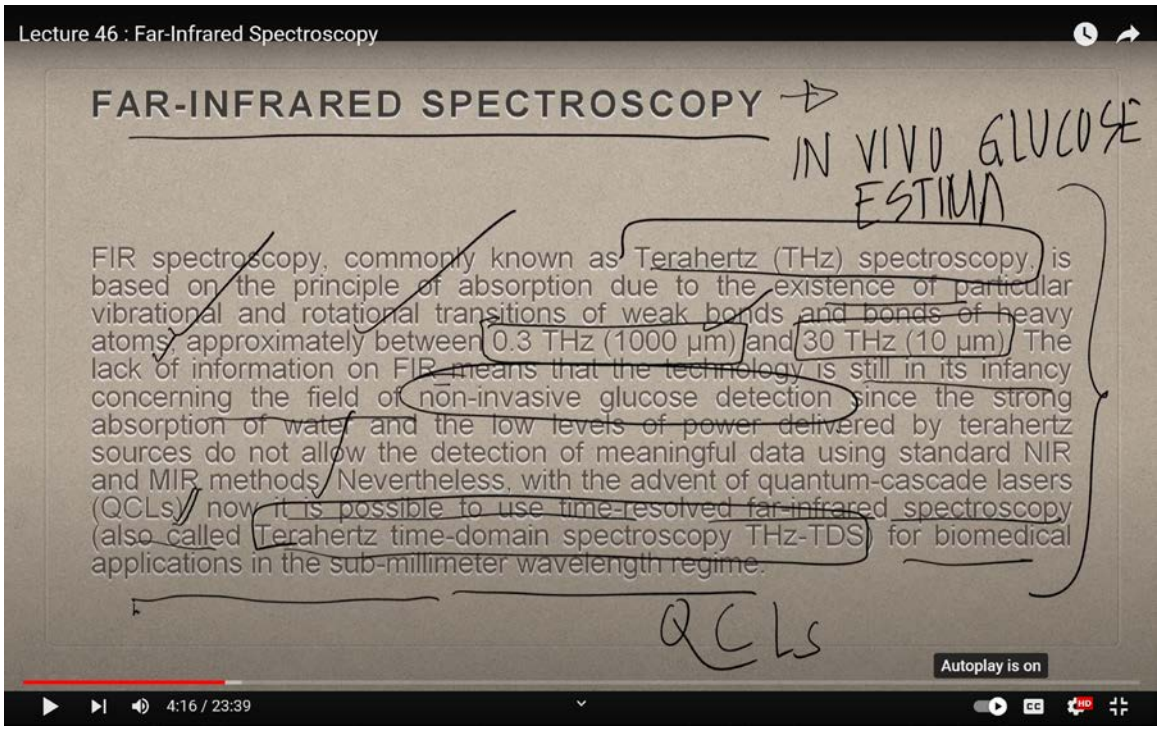

Continuing along this theme, last week, I mentioned we would delve into far-infrared spectroscopy. It’s crucial to understand that when we discuss the far infrared, we are attempting to detect weak bonds and subtle vibrational and rotational motions, which are common in biological systems. Achieving this from an external source, essentially in vivo measurements, requires a unique signature.

When you take a pure sample and analyze it using a spectrophotometer, the scenario is quite different. However, when you're trying to obtain these readouts directly from a living subject, whether human, animal, or any other moving biological system, numerous interferences come into play.

As we explore infrared spectroscopy, also known as terahertz spectroscopy, we find that it operates on the principle of absorption related to specific vibrational and rotational transitions of weak bonds and bonds involving heavy atoms. The relevant frequency range

to keep in mind is from approximately 0.3 terahertz (which corresponds to about 1000 micrometers) to 30 terahertz (around 10 micrometers).

It's important to note that the current lack of information regarding far-infrared (FIR) spectroscopy means that this technology is still in its infancy regarding non-invasive glucose detection. The substantial water absorption and the low power levels produced by terahertz sources hinder meaningful data collection when using standard near-infrared (NIR) and mid-infrared (MIR) methods.

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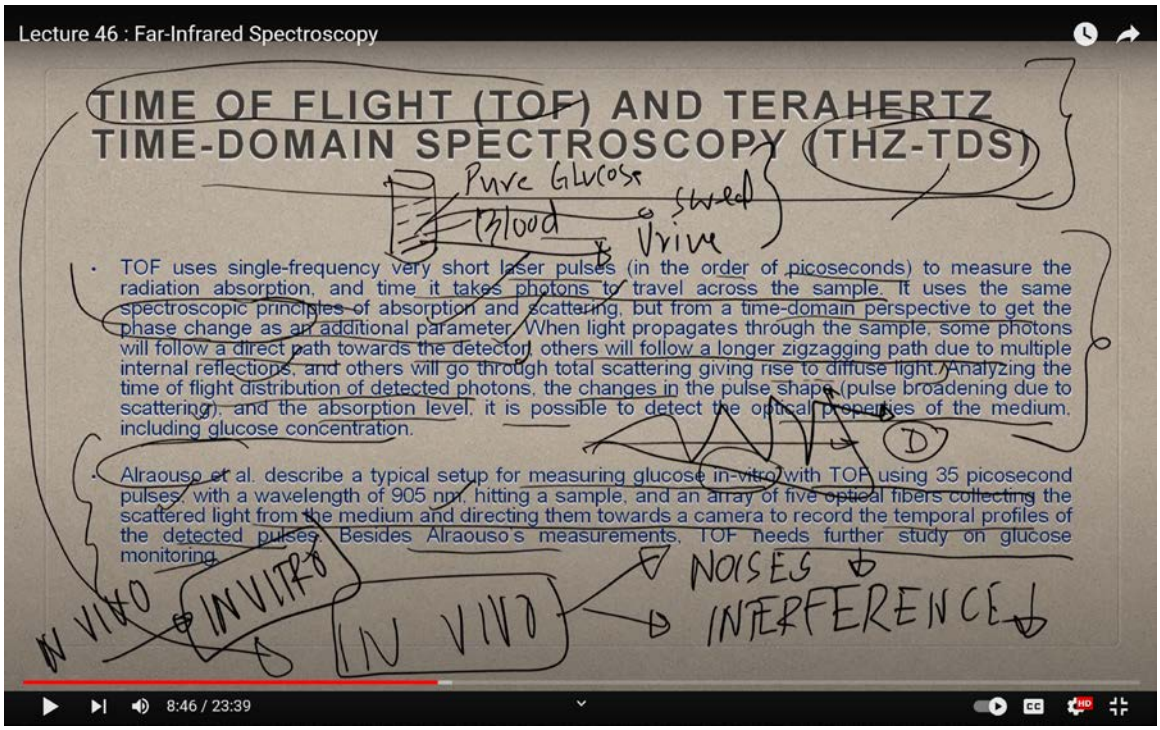

However, the advent of quantum cascade lasers (QCLs) opens exciting possibilities. With these lasers, we can utilize time-resolved far-infrared spectroscopy, also known as terahertz time-domain spectroscopy, for biomedical applications in the sub-millimeter wavelength range. This marks a significant advancement in our capacity to apply quantum cascade lasers in this field!

It is indeed possible to achieve time-resolved far-infrared spectroscopy, and this exciting development in laser technology has opened up numerous opportunities for utilizing far-

infrared spectroscopy in the near future for in vivo glucose estimation, not through traditional methods, but by employing quantum cascade laser (QCL) techniques.

Another area bustling with research is the realm of time-of-flight (TOF) mass spectrometry and terahertz time-domain spectroscopy (THz-TDS). To clarify, TDS stands for time-domain spectroscopy, while THz refers to terahertz, and TOF is simply the acronym for time of flight. The TOF method uses single-frequency, very short laser pulses, typically in the order of picoseconds, to measure radiation absorption and the time it takes for photons to traverse the sample.

These incredibly brief laser pulses allow us to assess both the radiation absorption and the time taken for photons to travel through the sample. The fundamental principles of absorption and scattering remain unchanged; however, we approach them from a time-domain perspective, which enables us to capture phase changes as an additional parameter. This phase change is significant because, as light propagates through the sample, some photons will take a direct path to the detector, while others will navigate a longer, more convoluted zigzag path due to multiple internal reflections.

When we talk about the detector, represented here as D, it is important to note that while some photons will experience total scattering, resulting in diffuse light, others will reach the detector more directly. By analyzing the time-of-flight distribution of the detected photons, including changes in pulse shape and pulse broadening due to scattering and absorption, we can extract valuable information about the optical properties of the medium, including glucose concentration.

However, as I illustrated in the drawings, you must have noticed that when conducting such analyses in vivo, we encounter substantial noise and interference. If we could mitigate these interferences, it would be possible to obtain a very unique signature from the readings.

The authors describe a typical setup for measuring glucose in vitro. Here, they employ TOF with 35 picosecond pulses at a wavelength of 905 nanometers. This setup directs the laser at the sample and utilizes an array of five optical fibers to collect the scattered light from the medium, ultimately directing it toward a camera to record the temporal profile of the

detected pulses.

While TOF is a promising measurement method, further studies are necessary for effective glucose monitoring. For instance, when discussing samples such as a pure glucose solution, blood, urine, or sweat, the laser light can easily access these fluids within a cuvette. The direct accessibility is advantageous; however, when we consider conducting measurements through the skin, the scenario becomes more complex.

The skin presents multiple layers, including the epidermal and subepidermal layers, that the light must penetrate before reaching the blood vessels. During this process, a significant amount of interference and noise is generated, which poses a major challenge. Whenever we discuss time-of-flight and time-domain spectroscopy at the terahertz level, it becomes clear that all these techniques are susceptible to these interferences.

Thus, while many spectroscopic techniques provide some of the most refined signatures, translating results from in vivo measurements to in vitro conditions fundamentally alters the equation.

If there were a method to correlate in vitro data with in vivo measurements using the same signature, these techniques could potentially revolutionize daily glucose monitoring practices. Now, let’s shift our focus to another fascinating form of spectroscopy known as thermal emission spectroscopy, or TESS for short. We all understand that due to the myriad metabolic activities occurring in our bodies, we naturally generate heat or heat radiation. This heat signature is essentially a cumulative reflection of all the biochemical reactions taking place within us.

Imagine if we could detect glucose levels from that heat signature. Essentially, the heat generated is a summation of numerous metabolic processes in the body. For instance, if this heat signature is influenced by ten different parameters, and we could isolate the glucose contribution, we could obtain valuable insights into glucose levels.

Thermal emission spectroscopy operates on the principle that the human body inherently emits energy as heat within the far-infrared bands, specifically between 8 micrometers and 14 micrometers. Interestingly, many animals utilize similar far-infrared sensing

capabilities to detect humans, snakes, for example, employ this technology to sense their prey.

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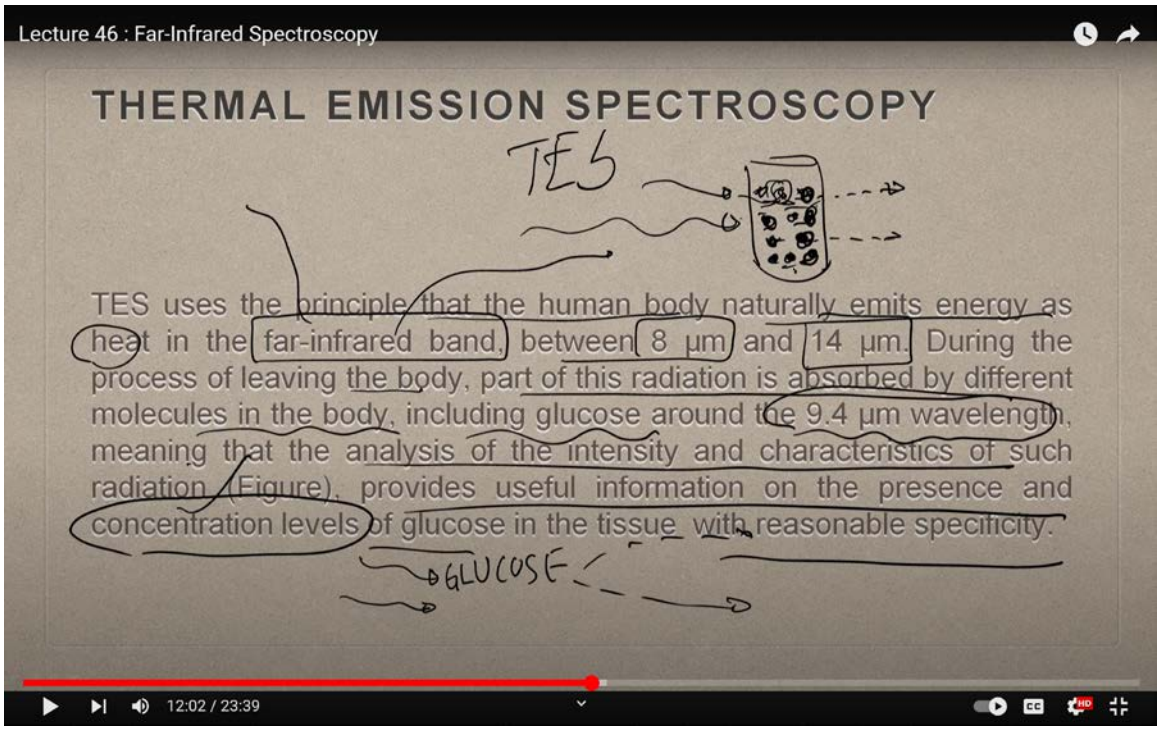

As this thermal radiation exits the body, it is partially absorbed by various molecules within, including glucose, which notably absorbs radiation at around a wavelength of 94.4 micrometers. Thus, by analyzing the intensity and characteristics of this emitted radiation, we can glean useful information regarding the concentration levels of glucose present in the tissue with reasonable specificity.

To illustrate this concept further, imagine a cuvette containing glucose molecules suspended in solution. As far-infrared radiation passes through, these molecules absorb some of the energy, which is then re-emitted after the absorption process. The extent of absorption is directly related to the number of glucose particles present: the greater the concentration, the more energy will be absorbed. This relationship underscores the capability of thermal emission spectroscopy to provide meaningful insights into glucose concentration levels.

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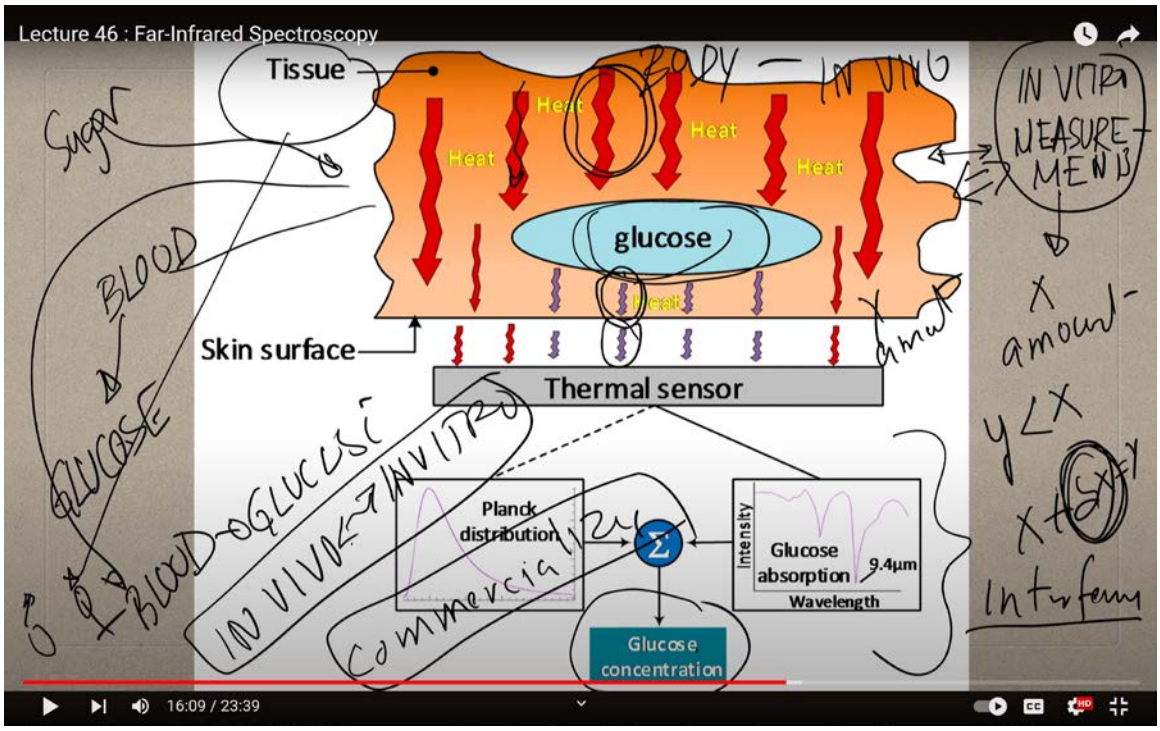

Now, let’s visualize a scenario where we have the heat generated by body tissue containing varying amounts of glucose. Depending on the glucose concentration, the level of absorbed radiation will change. For instance, a thermal sensor can measure this radiation absorption in relation to the body’s glucose level.

To validate this method, you could draw blood from a tissue sample and measure glucose levels using another in vivo or in vitro technique. Similarly, if you were to feed an animal sugar and subsequently draw blood for glucose measurement, you would have two distinct sets of data: one representing glucose levels before sugar intake and the other following it.

The thermal sensor will exhibit different absorption characteristics based on these two conditions, allowing us to assess glucose levels against the sensor's sensitivity. This presents a compelling avenue for leveraging thermal emission spectroscopy in glucose monitoring, providing a unique and non-invasive method of measurement.

This concept forms the foundation of thermal sensing through thermal emission spectroscopy, making it yet another profound technique in the field. However, this kind of

technology necessitates extensive testing, both in vivo and in vitro. When we quantify these measurements together, we observe the deviations that occur when comparing in vitro data with in vivo results.

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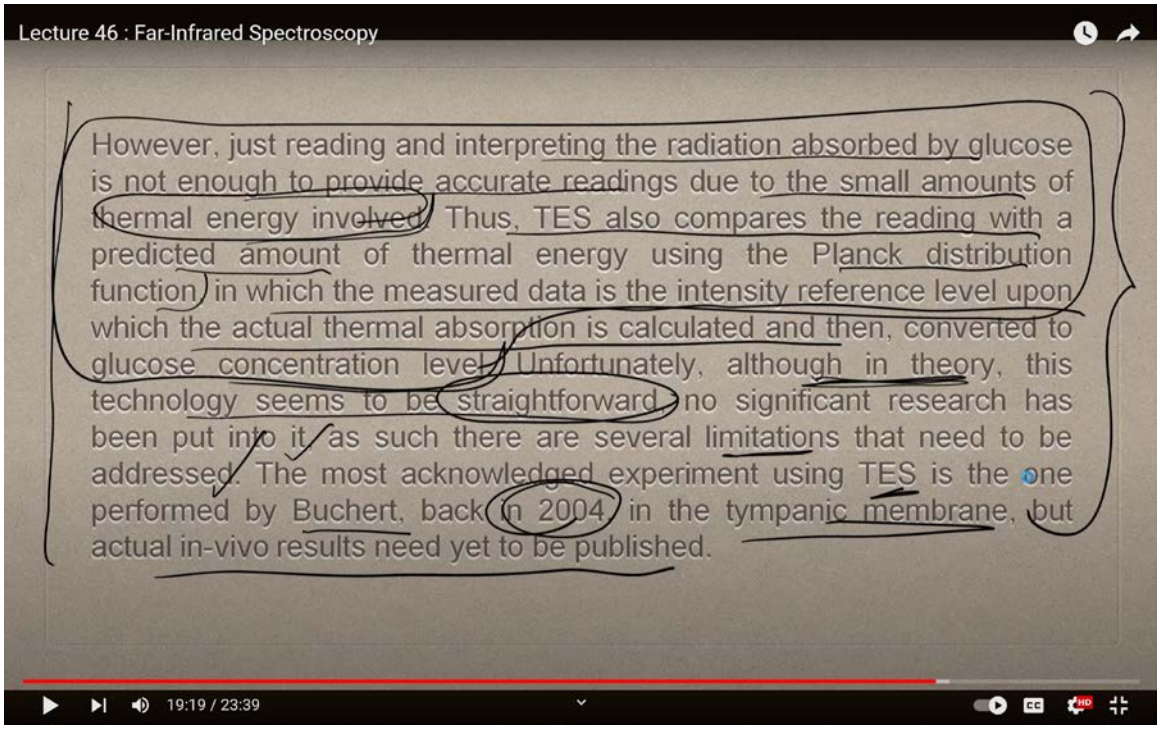

To illustrate, let's say your in vitro measurement indicates an amount of glucose X, while your in vivo measurement shows Y. Assuming that Y is less than X, we can express this relationship as $X + \Delta X = Y$, where ΔX represents the loss of glucose detection due to interference and other absorbing molecules present in the sample. Until these two values, the in vivo and in vitro measurements, are closely correlated and the error margins are well-defined, these sensors will require considerable refinement before they can be commercialized.

It's comparable to the development of a mercury thermometer. This device has undergone decades of meticulous improvement, allowing us to confidently associate specific rises in mercury with precise temperature changes. Similarly, we must understand how variations in glucose levels affect radiation absorption in this context.

The physiological status of the tissue being measured plays a significant role as well. For example, we need to consider whether the individual is male or female, as well as racial differences that may influence metabolic rates and heat generation. A Caucasian subject may exhibit different thermal signatures compared to an Asian subject, or someone with darker skin tones. Additionally, environmental factors, such as whether they are from a cold, icy region or a hot climate, or if they have recently engaged in strenuous activities like underwater exercises or are operating in a submarine, can drastically alter heat generation in the body. Professionals in sports medicine are well aware of these variations.

Thus, without a wealth of in vivo data corroborated by in vitro findings, it becomes incredibly challenging to paint an accurate picture of glucose levels in the body. While these techniques are theoretically fascinating, their practical applications are hampered by numerous challenges that must be addressed over the coming decades.

Moreover, merely reading and interpreting the radiation absorbed by glucose is insufficient for providing an accurate reading due to the minimal amount of thermal energy involved. This brings us to another critical point: thermal emission spectroscopy (TES) also involves comparing the readings obtained with the predicted amount of thermal energy, using Planck's distribution function. In this context, the measured data serves as a reference intensity level upon which the actual thermal absorption is calculated and subsequently converted into glucose concentration levels.

As we delve into the details of Planck's distribution, the intricacies of this process will become clearer. Essentially, you are measuring the intensity of a very small amount of radiation, and understanding this complex relationship is key to unlocking the full potential of thermal emission spectroscopy.

Although this technology appears straightforward in theory, the reality is quite different. Limited research has been conducted in this area, leading to several significant limitations that must be addressed. The most notable experiment using terahertz gas spectroscopy (TGS) was carried out by Bouchard in 2004, focusing on the tympanic membrane. However, we are still awaiting the publication of actual in vivo results, which is certainly something worth keeping an eye on.

While this technique is theoretically beautiful, it encounters numerous challenges in practical applications. Unless these issues are addressed and rectified, the commercial viability of these technologies remains uncertain. This is similar to our discussion about time-of-flight and terahertz domain spectroscopy, as far-infrared spectroscopy faces the same hurdles. Most of these technologies, although crucial, present significant challenges.

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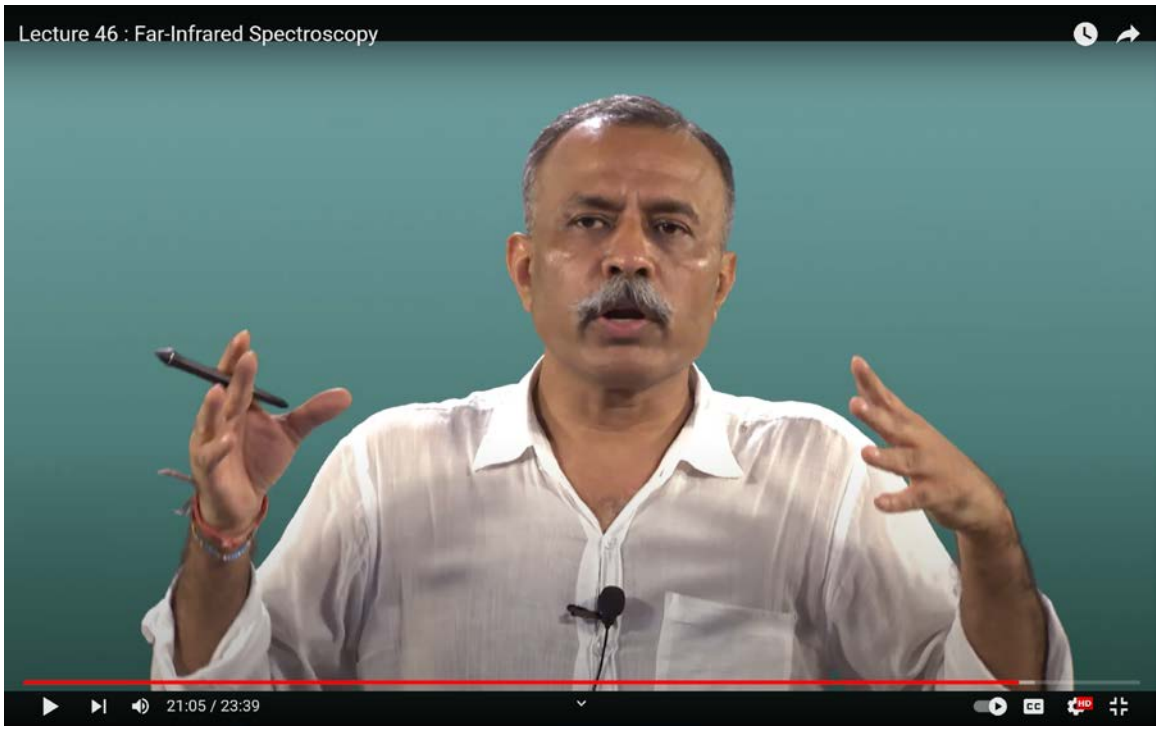

Yet, there are scenarios where these technologies could be applied in unique contexts. Consider situations like desert warfare or high-altitude operations. In these cases, the data generated can be incredibly valuable, as they provide insights into the extreme conditions faced by individuals. Imagine being able to gather critical information about human subjects in such demanding environments.

Looking ahead, it's conceivable that in 20 years, these technologies could represent breakthroughs that yield data from extreme conditions. They hold potential for generating insights in hyperbaric and hypoxic situations, such as low-pressure environments or underwater expeditions, including scuba diving and deep-sea diving. Additionally, they

could be useful in space missions or specialized military operations in desert warfare.

Furthermore, it’s essential to verify this data across different races and ethnicities to ensure its applicability. This extensive level of data collection is crucial to achieving a clear understanding of how we can utilize this information for the long-term commercialization of these technologies. This is especially relevant when considering sensor-integrated suits for warfare and biowarfare applications.

Individually, these technologies may not seem impactful; however, when integrated with various other technologies, their value becomes apparent. For instance, picture a suit equipped with multiple integrated sensors. In this suit, thermal sensors could be paired with embedded software that analyzes Planck's distribution to estimate glucose levels. Other types of sensors would also be present within the system.

It’s important to note that much of this sensor technology will rely on printed electrodes, a topic we will delve into in the coming weeks. The trends toward miniaturization and bodily integration will play a significant role in advancing sensor technology for in vivo recording.

As we conclude this discussion, I look forward to exploring more about in vivo glucose sensing technologies in our next class. Thank you!