Design for Biosecurity

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Lecture 42

Non Enzymatic Glucose Sensor - Part 2

Let's pick up from where we left off in the previous class, continuing our discussion on non-enzymatic glucose sensors. So far, we've covered three key technologies. Before we move ahead, I want to clarify something: while I'm focusing on major research papers, this doesn't mean we are ignoring the rest. Time constraints prevent us from discussing every material used in this field, but the principles we're covering remain the same across many studies.

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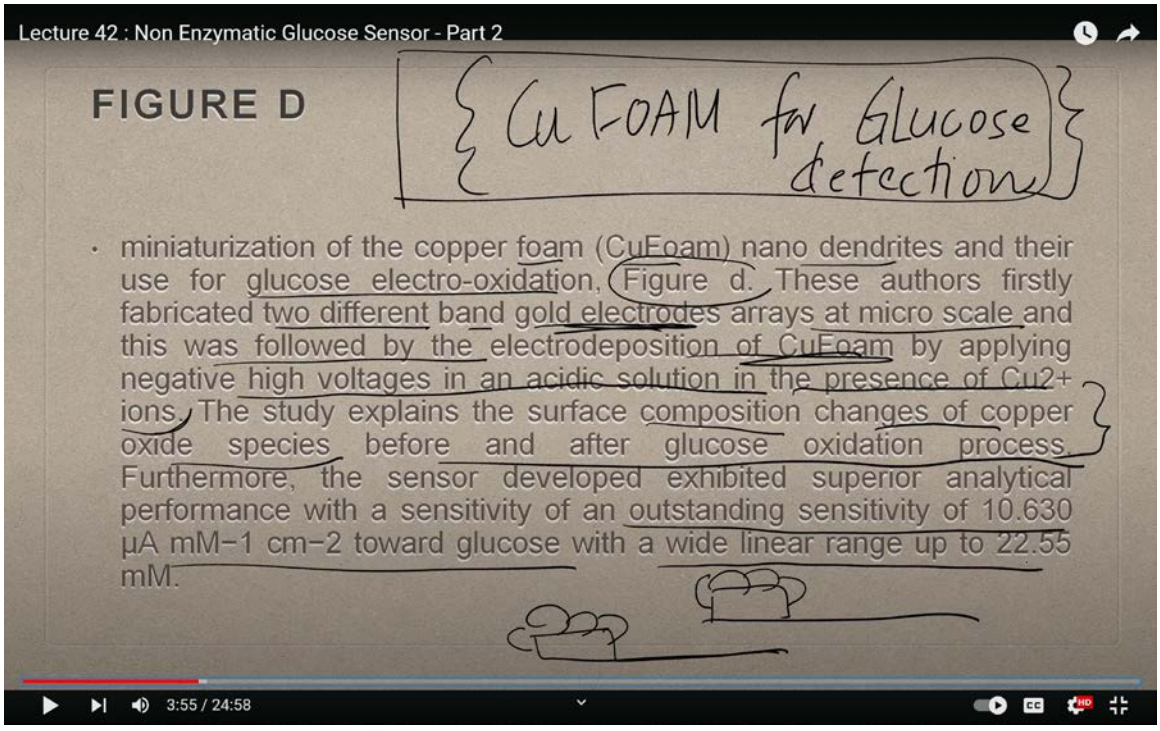

To recap, the first technique we discussed involved using a copper oxide and zinc oxide hybrid material as the electrocatalyst. The second approach featured copper oxide

decorated on top of laser-induced graphene, and the third one introduced a nanograss-like structure protruding from the surface of copper hydroxide. These are the three we've covered so far.

Now, let's move to the fourth approach: using copper foam for glucose detection, which is the focus of today's class. The concept here revolves around miniaturizing copper foam. In Figure D, the researchers fabricated two different gold electrodes for nano-dendrites, which were then used for glucose electro-oxidation.

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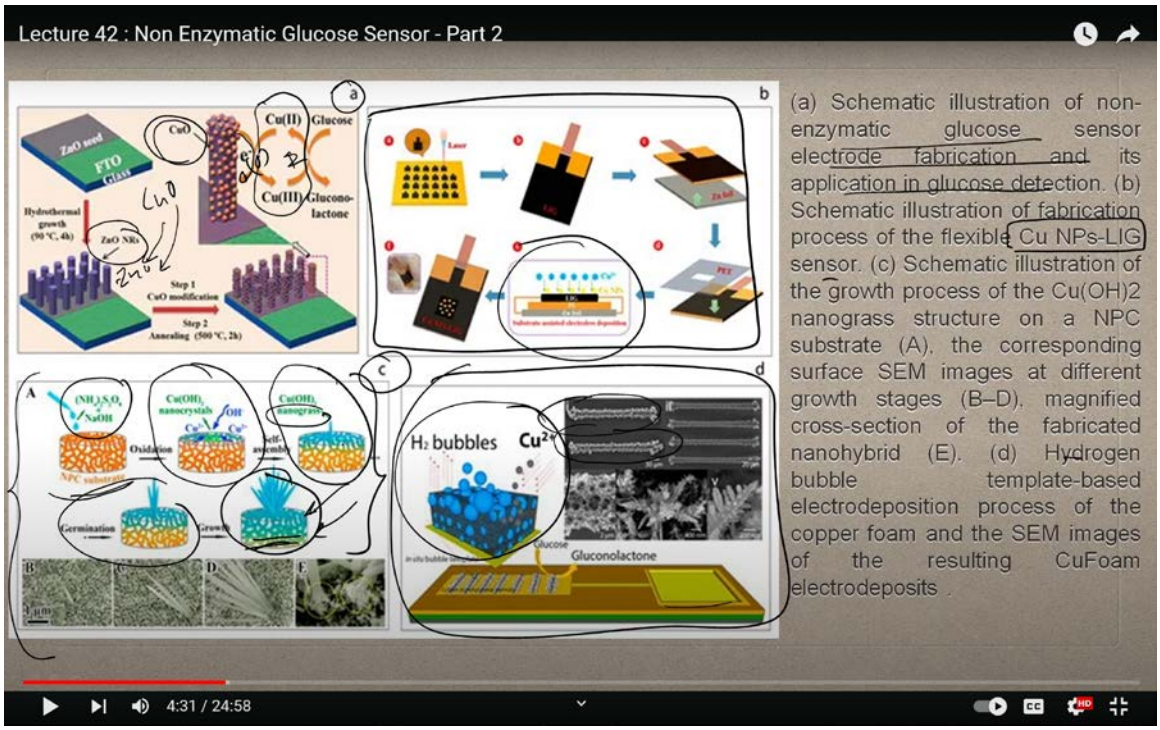

Why use gold electrodes? Yes, gold is costly, but it offers significant advantages. Firstly, it is incredibly inert, making it an ideal choice for sensor applications. Secondly, its high conductivity ensures noise-free recordings, which is why both gold and platinum electrodes are often preferred. However, for commercialization, the focus is shifting towards more economical alternatives, with carbon-based electrodes leading the way due to their affordability and wide applicability.

In this process, gold electrode arrays were created at a micro-scale, followed by the

electrodeposition of copper foam. Imagine you have a gold electrode in place, and on top of that, copper foam is grown through the application of a negative high voltage in an acidic solution containing Cu^{2+} ions. This method enables changes in the surface composition of the copper oxide species before and after the glucose oxidation process. The resulting sensor exhibited exceptional analytical performance, with an impressive sensitivity of 10.6 μA for glucose detection and a wide linear range extending up to 22.5 mM.

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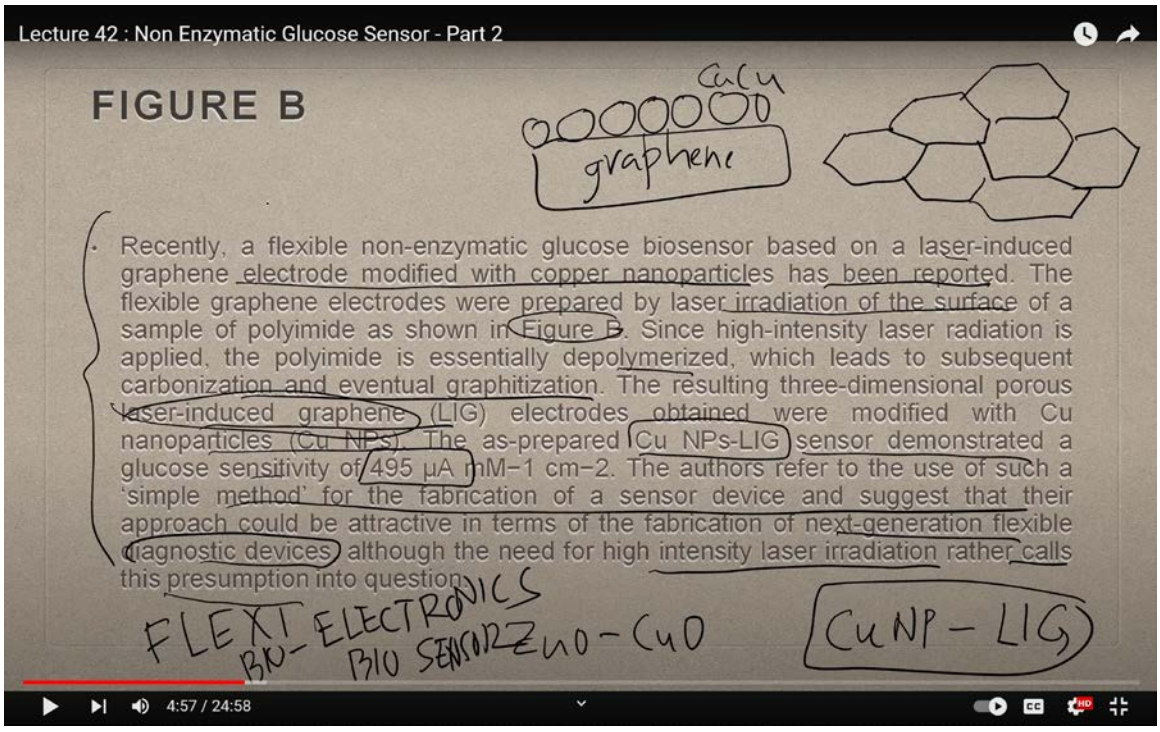

To visualize this, look at the corresponding image: you'll see the electrode deposition process, with the gold electrode forming the base, and the copper foam growing on top of it, where the glucose oxidation reaction takes place. This is the foundation of this particular electrode system. So, to summarize, we've now covered four approaches:

1. Copper oxide and zinc oxide hybrid.

2. Copper nanoparticles on laser-induced graphene.

3. Copper hydroxide nanograss.

4. Copper foam on a gold electrode.

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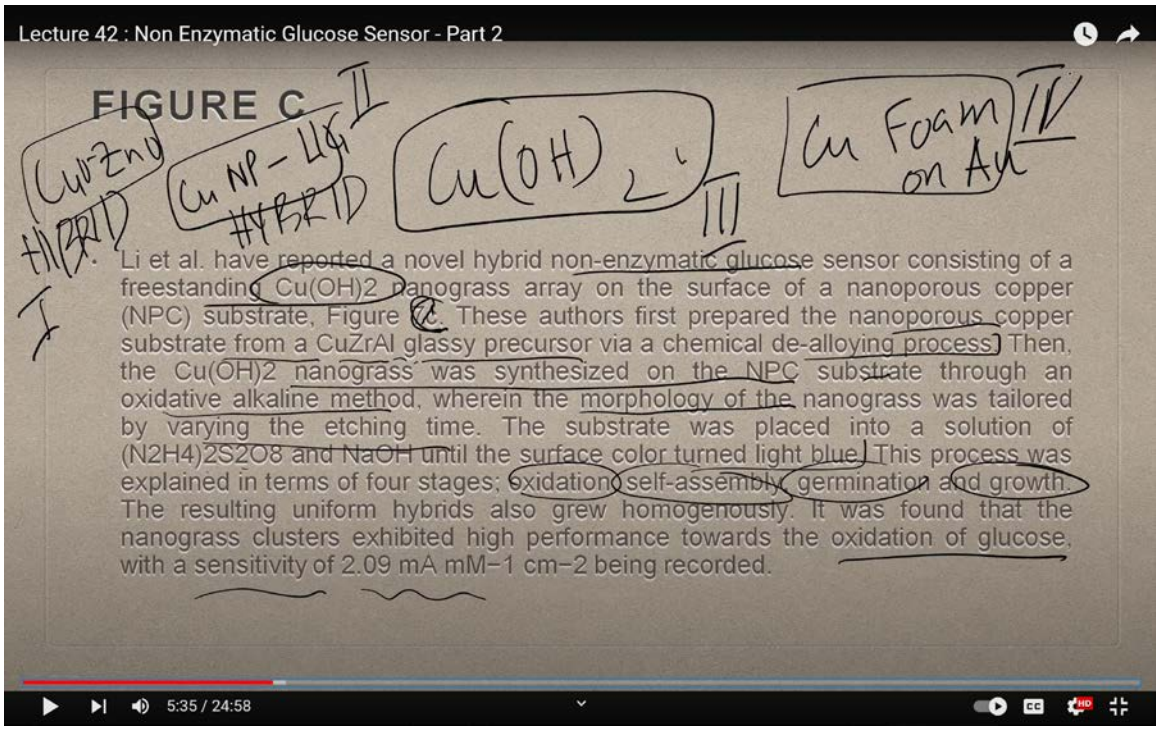

These four examples highlight different non-enzymatic methods for glucose detection, allowing us to bypass the use of glucose oxidase enzymes.

Now, let’s touch on another emerging field: wearable, non-invasive electrochemical glucose sensors. This is a highly promising area that’s seeing an increase in research and technological development. The idea is that people shouldn’t need to wear bulky devices or invasive equipment to monitor their glucose levels. Imagine having a wearable device, like a wristwatch, that can tell you your glucose levels in real-time, similar to how a thermometer reads your body temperature. You could place a device under your arm, and based on the sweat it collects, it could predict the glucose levels in your bloodstream. Alternatively, a smart contact lens could measure the glucose concentration in your tears.

These non-invasive methods are rapidly gaining traction, and they could revolutionize the way glucose monitoring is done in the near future.

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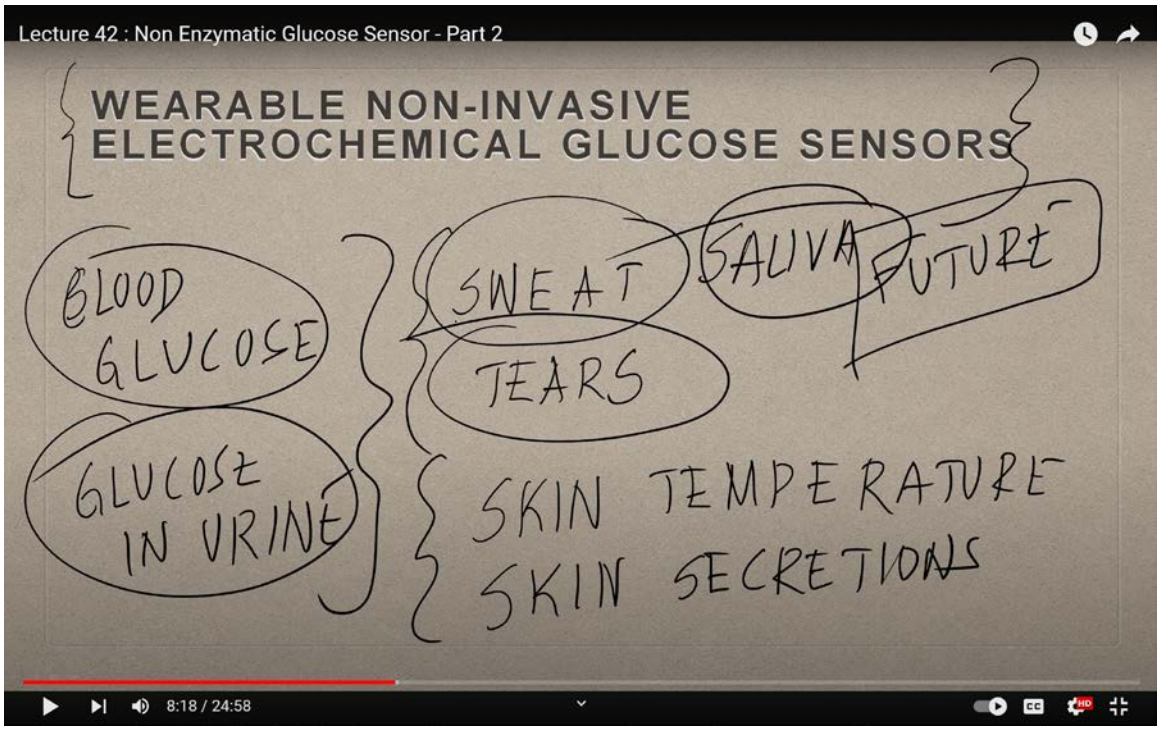

Some of these non-invasive methods focus on analyzing sweat, tears, and other surface fluids of the body, including skin temperature and secretions, aside from sweat. These fluids act as the primary analytes for glucose detection. Up until now, we've been discussing glucose monitoring in blood and urine, but we are now delving into scenarios where glucose levels are much lower and more difficult to measure, such as in surface fluids. This shift represents the future of non-invasive sensors, which are becoming the forefront of research in bio-defense detection. The goal is to develop methods that don't require drawing blood or saliva and instead rely on sweat, tears, skin secretions, and even interstitial fluids, though the latter is still somewhat invasive.

So, what are the challenges? Most current detection methods for determining glucose concentration are based on blood or serum analysis, but it is also possible to detect glucose from bodily fluids like sweat, saliva, and tears. This makes non-invasive glucose sensing platforms a particularly promising area for diabetes management. These sensors, since they don't come into contact with blood, avoid being exposed to the immune system in the way implantable sensors are.

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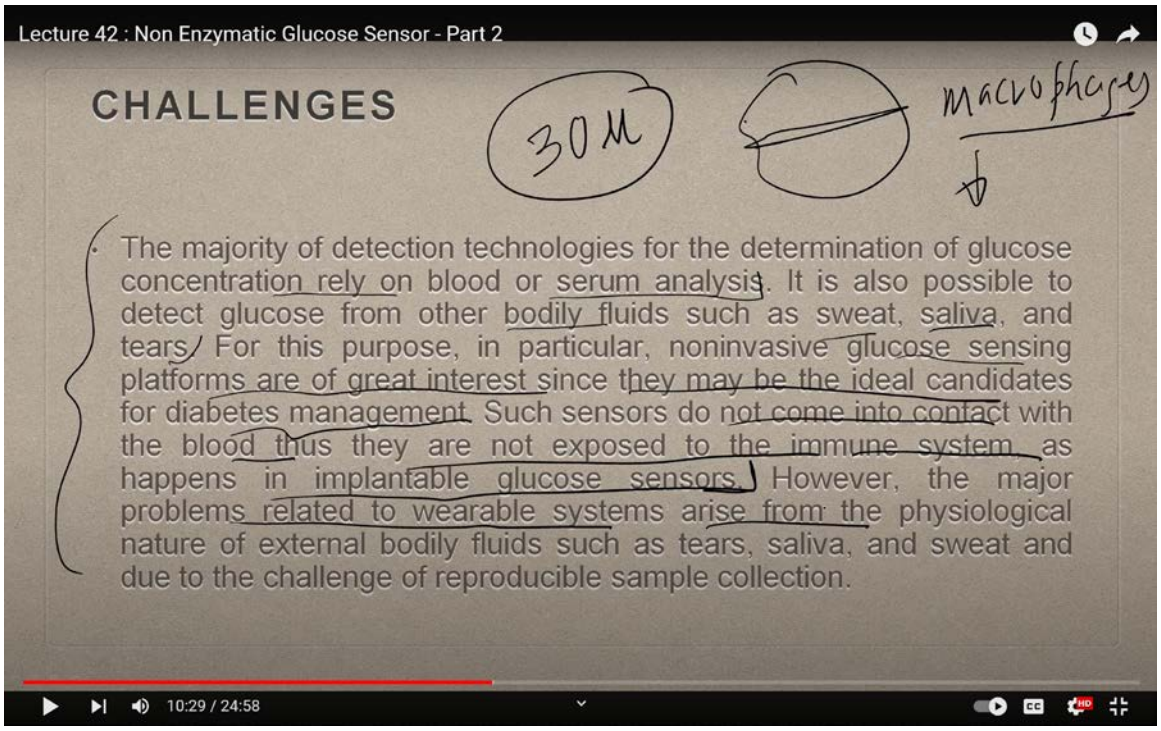

It's important to realize that when you're drawing blood, you're dealing with large cellular components, mammalian cells, for instance, are around 30 microns in diameter. Blood contains immune cells like macrophages, which can act as barriers, lowering detection efficiency. The same challenges arise in detecting viruses or microbes, which are also complex and heterogeneous mixtures. I'm spending time here to highlight how challenging this field is, given the vast number of interfering molecules that can complicate the detection process.

The major challenge with wearable non-invasive sensors, however, stems from the physiological nature of external body fluids like tears, saliva, and sweat, and the difficulty of achieving reproducible sample collection. Our bodies are constantly interacting with external elements. For example, we all use deodorants, perfumes, lotions, creams, and other skincare products. These products alter the chemical composition of tears, sweat, and other external fluids, making it difficult to ensure that what is being detected is from the body and not a result of an external product. This is where the complexity really starts to unfold, it's not just about detecting glucose; it's about distinguishing between what's naturally

occurring in the body and what might have been applied externally.

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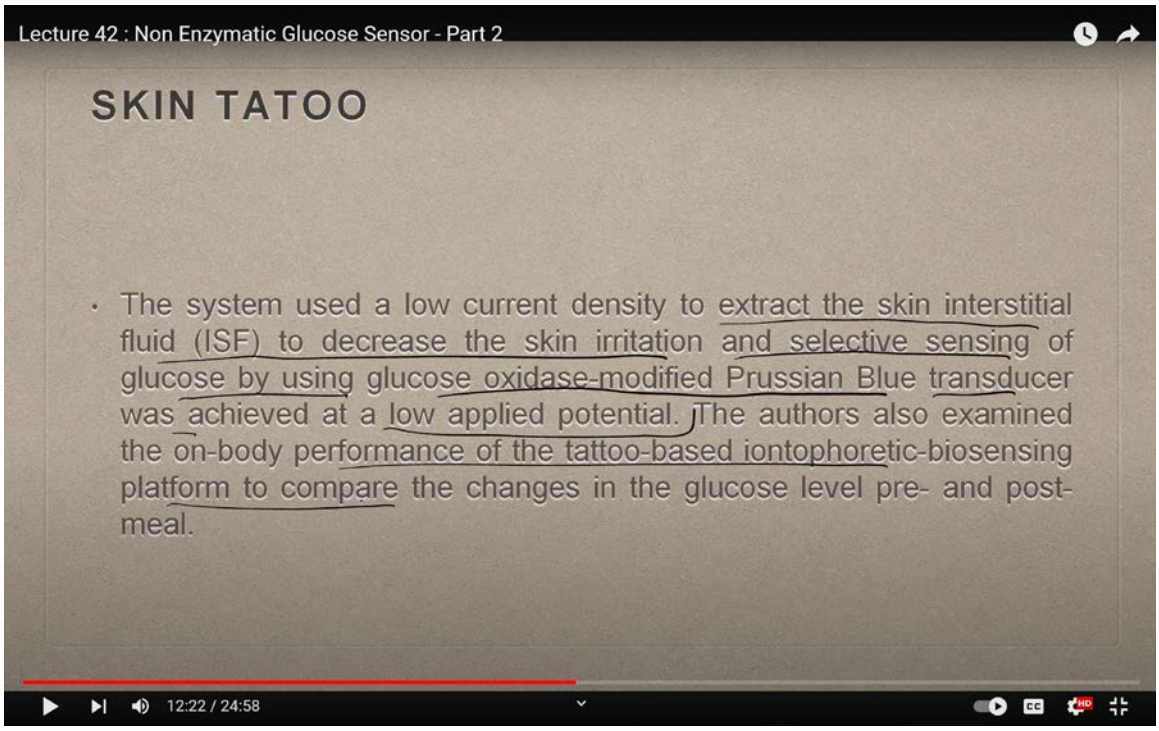

One promising approach is the use of a skin tattoo for glucose detection. This system applies a low current density to extract interstitial fluid from the skin, minimizing irritation, and then uses a glucose oxidase-modified Prussian blue transducer to selectively sense glucose at a low applied potential. Researchers have studied the performance of this tattoo-based ionophoretic biosensing platform and compared glucose levels pre- and post-meal.

This is where the tattoo comes into play, a non-invasive, wearable glucose sensing platform. You can see a schematic image of the printable ionophoretic sensing system, as well as a photograph of the tattoo-based glucose sensor applied to a human subject. The study also includes a timeline to show the glucose monitoring process over time. Essentially, this method relies on enzymatic assays, detecting glucose from the surface layer of bodily fluids.

In addition to the tattoo-based system, there's another method involving a microfluidic device. This device is a flexible, epidermal, microfluidic detection platform designed for

continuous glucose and lactate monitoring. It's fabricated using lithography and screen-printing technologies to effectively collect sweat and measure glucose levels. These two methods, the tattoo-based platform and the microfluidic device, are both cutting-edge approaches to non-invasive glucose detection, each showing great potential for real-world application in diabetes management and beyond.

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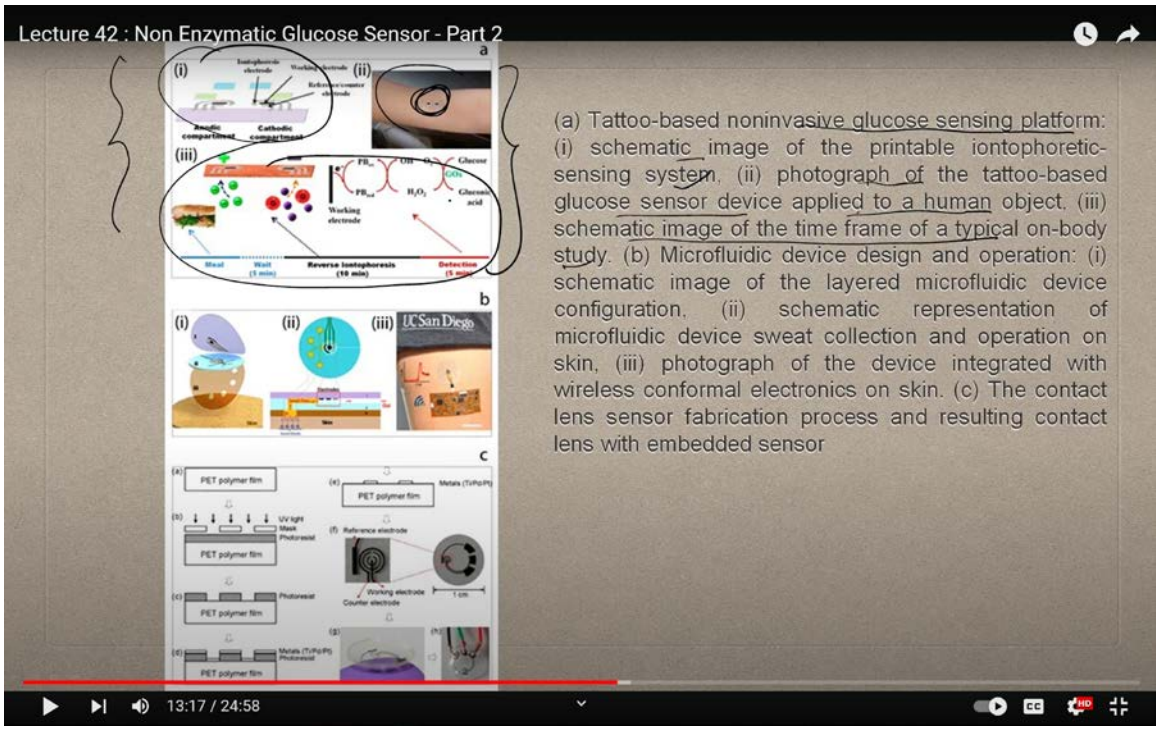

Sweat sampling is also being explored for detecting viruses and other microbial agents. Most of the research in sensors and biosensors has historically revolved around glucose because it serves as the benchmark for developing other kinds of sensors. This is why I am placing such a strong emphasis on glucose biosensors. Now, moving on to the second type of sensor we're discussing, the microfluidic-based system. Here, you can see a schematic image of the layered configuration of a microfluidic device. The device's sweat collection and operational functions are shown in a photograph, which also displays its integration with wireless conformal electronics worn on the skin. This particular system was developed at the University of California, San Diego, as indicated by the logo on the device.

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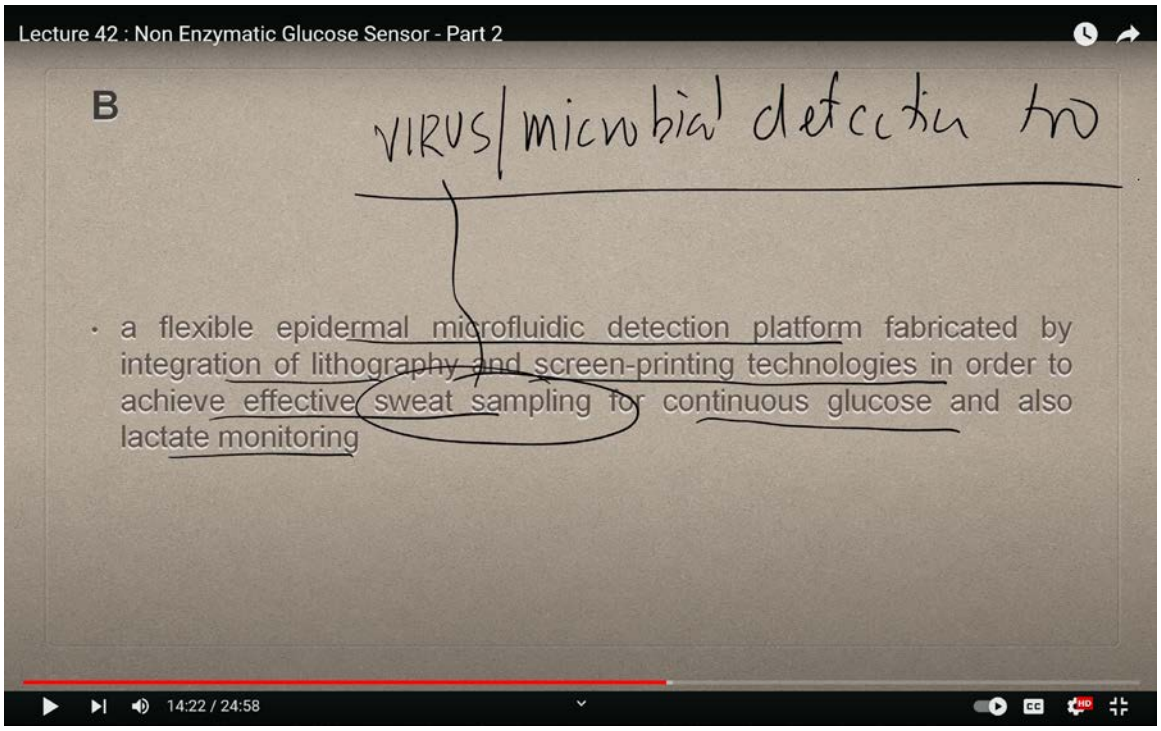

Moving forward to the third type of sensor, contact lenses embedded with glucose sensors. These contact lenses are designed to measure glucose levels from tears. Imagine this: if you place a contact lens on your eye, where it comes into contact with your tears, and that lens is embedded with a sensor, it can then detect the amount of glucose present in your tears. The construction process for these lenses is shown in Figure C, where a polyethylene terephthalate (PET) polymer is used as the substrate, which is spin-coated with a resist. After that, metal deposition is performed, followed by a lift-off process in acetone. The electrodes are fabricated, cut into small pieces about 1 cm in diameter, and heat-molded into the shape of a contact lens.

These contact lenses effectively function as electrodes, and the glucose oxidase enzyme is immobilized on them. The enzyme solution is drop-cast onto the electrode surface, and then the lens is suspended vertically above a solution of titanium isopropoxide in a sealed dish. This creates a glucose oxidase titania sol-gel membrane on the surface. The sol-gel membrane is then covered with Nafion, which is widely used in such applications. The developed system for non-invasive glucose monitoring has been studied using

amperometry, with glucose sensors fabricated on the polymer contact lenses demonstrating excellent sensitivity, 240 µA, to be exact.

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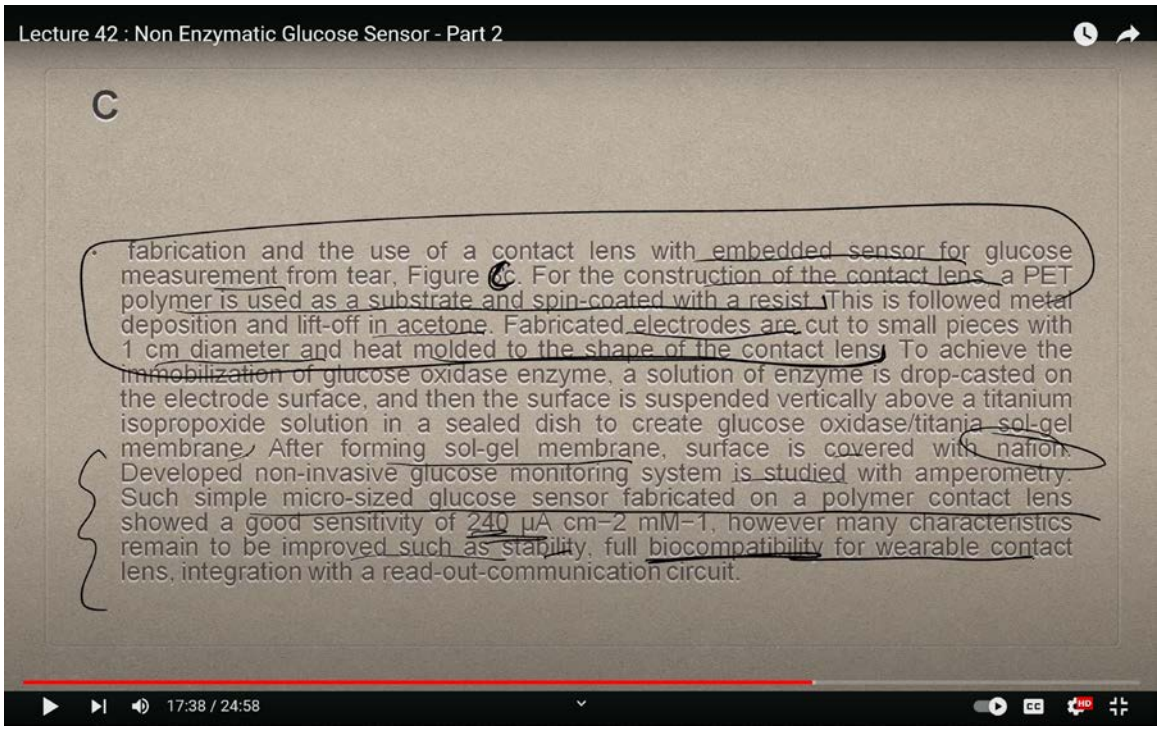

However, despite these advancements, there are still challenges to overcome, such as improving the stability and full biocompatibility of the wearable contact lenses, integrating them with readout communication circuits, and ensuring seamless integration into wireless systems for direct data transmission. This figure shows the entire process: from the electrode configuration to the reference electrode, all the way to the contact lens ready for application.

Now, let’s summarize what we’ve covered so far. We began by discussing diabetes and its management, initially touching on insulin as an agent that could potentially be harmful. We then transitioned into exploring glucose detection within the body, and from there, we broke down the basic reaction involved: glucose reacts with oxygen in the presence of glucose oxidase to form gluconolactone and hydrogen peroxide. From this, we moved on to Clark’s electrode, which detects oxygen consumption during the oxidation of glucose,

this became the cornerstone for glucose detection. This process was then further refined with electrocatalysis, where the hydrogen peroxide formed was oxidized on the electrode, regenerating oxygen while releasing two protons and two electrons. The amount of peroxide was directly proportional to the amount of glucose oxidized, forming the basis for many glucose sensors.

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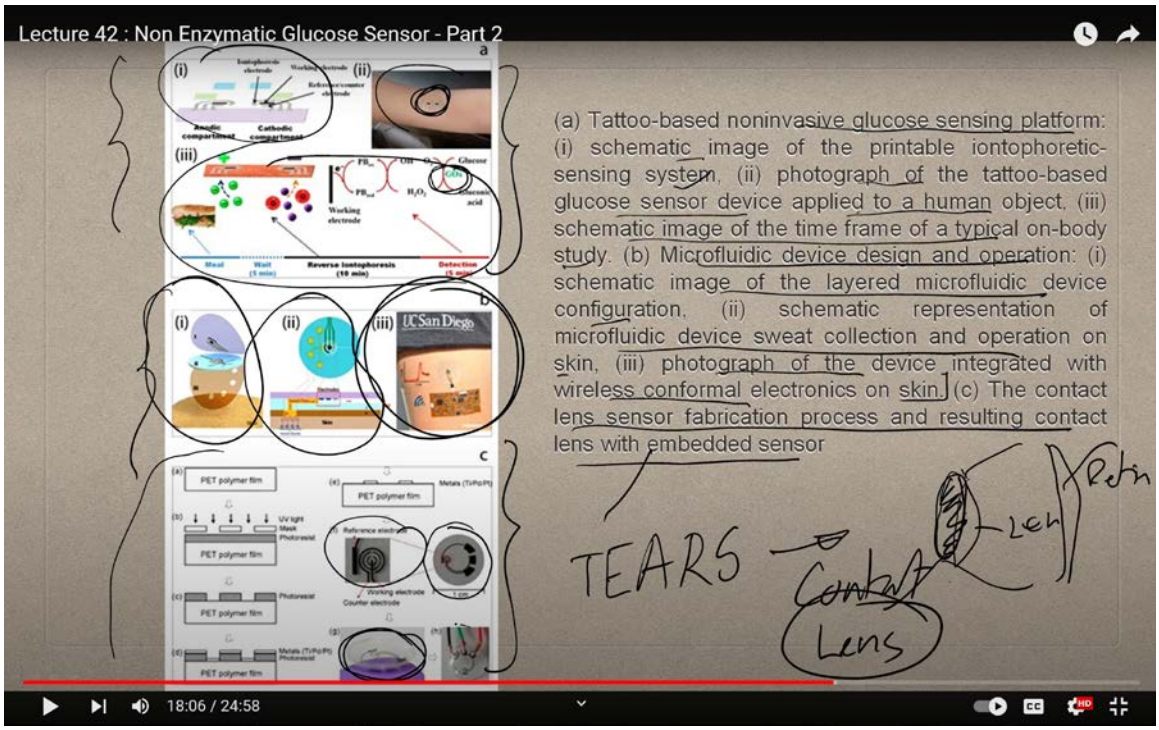

We explored how this fundamental reaction was used to develop a wide range of glucose sensors, particularly enzymatic arrays, and we discussed the complexities of detecting glucose in various bodily fluids, including serum, urine, sweat, and tears. These fluids pose challenges for enzymatic detection due to interfering molecules and the difficulty of getting glucose to reach the enzyme surface for an accurate reaction. This led us to advancements in non-enzymatic detection methods, which we explored both in this class and in previous ones.

We also examined non-invasive methods, such as devices that can be implanted on the skin or integrated into contact lenses. Looking ahead, it’s clear that we are moving toward a

future where surface detection methodologies, like skin-implanted or wearable devices, will become the norm. In the next class, we'll summarize the different technologies developed so far for glucose sensing, providing a comprehensive revision of all the methods we've studied.

It's important to understand why this knowledge is critical, glucose detection serves as the foundation for much of the work being done in the world of biosensing. If you can successfully detect glucose, it's widely believed that you can then apply that knowledge to other sensors, as glucose detection is thoroughly documented in the literature.

One more thing worth mentioning is the significant role nanotechnology is playing in biosensing. Nanomaterials such as copper oxide, zinc oxide hybrids, graphene-copper oxide hybrids, and copper hydroxide have gained enormous popularity for non-enzymatic detection. These materials, along with flexible biosensors and carbon-based electrode materials, are powerful candidates in electrocatalysis. The most troublesome materials remain copper and aluminum, as they oxidize quickly. As a result, carbon-based systems, such as carbon quantum dots, graphene oxide, and graphene-based materials, are gaining popularity because they are more stable and offer a more economical alternative to gold electrodes.

We are at a fascinating juncture where electronics are merging with biological systems for detection, therapy, and surveillance. In the next class, we will consolidate all the glucose measurement systems we've discussed so far, offering a comprehensive review. Thank you.