Design for Biosecurity

Prof. Mainak Das

Biotechnology and Bioengineering

Indian Institute of Technology, Kanpur

Lecture 60

Cell Based Biosensors - Part 5

Welcome back to class! As I concluded our last session, I mentioned that today we would explore the challenges associated with the direct contact of cells or any biomolecules with electrodes. We will start by discussing this topic and then wrap up the class by addressing the problems posed by next-generation technologies. The focus of our discussion will be the Electrode Surface and Interaction with Biological Cells, which is crucial for understanding the implications of chemical interactions. This topic is commonly referred to as the cell-electrode interface.

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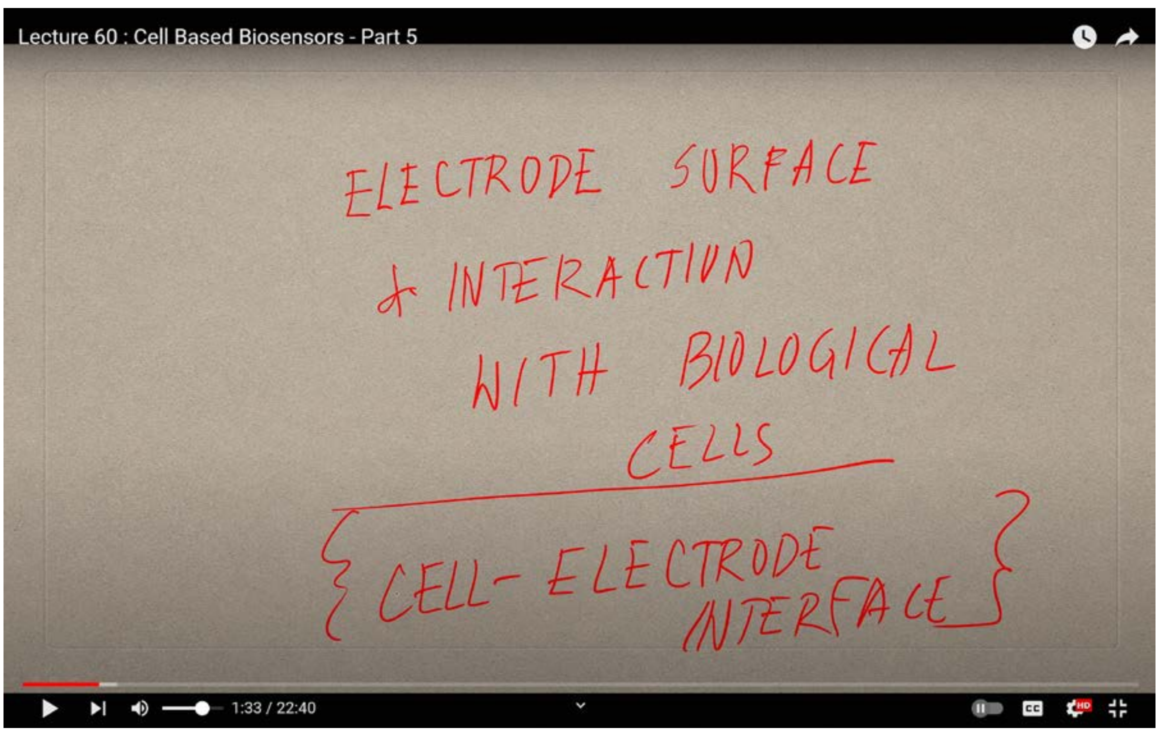

To begin our exploration of the cell-electrode interface, let's visualize it. Imagine we have an electrode surface, and on it, a cell is growing. Here's our electrode surface, and here's the cell. If we zoom in on this interface, what we observe is that the cell surface is not uniform at all. The way we typically depict it is overly simplified; in reality, it looks more like this. In contrast, the electrode surface appears much smoother and more uniform.

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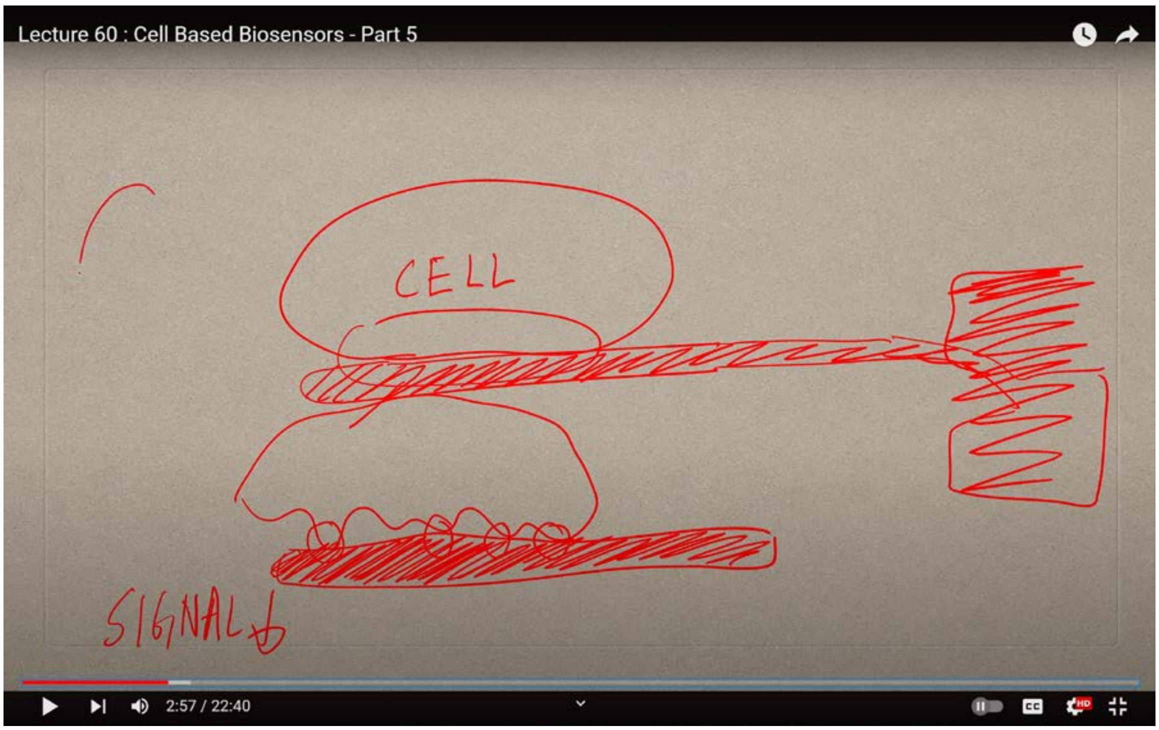

Upon magnifying this entire setup, you will notice that the contact points between the cell and the electrode are quite limited. For instance, you have one contact point here, another one there, and so forth. With such a small number of contact points, the fidelity of the signal will inevitably be lower, resulting in fewer signals being transmitted.

This presents a fundamental challenge: how can we enhance this interaction? The critical question we must address is how to modify the electrode surface, as we cannot change the cell surface, it is beyond our control. Our focus, therefore, is on altering the geometry of the electrode surface. This is particularly important because we are interested in extracellular recordings, which aim to collect maximum signals in a non-invasive manner.

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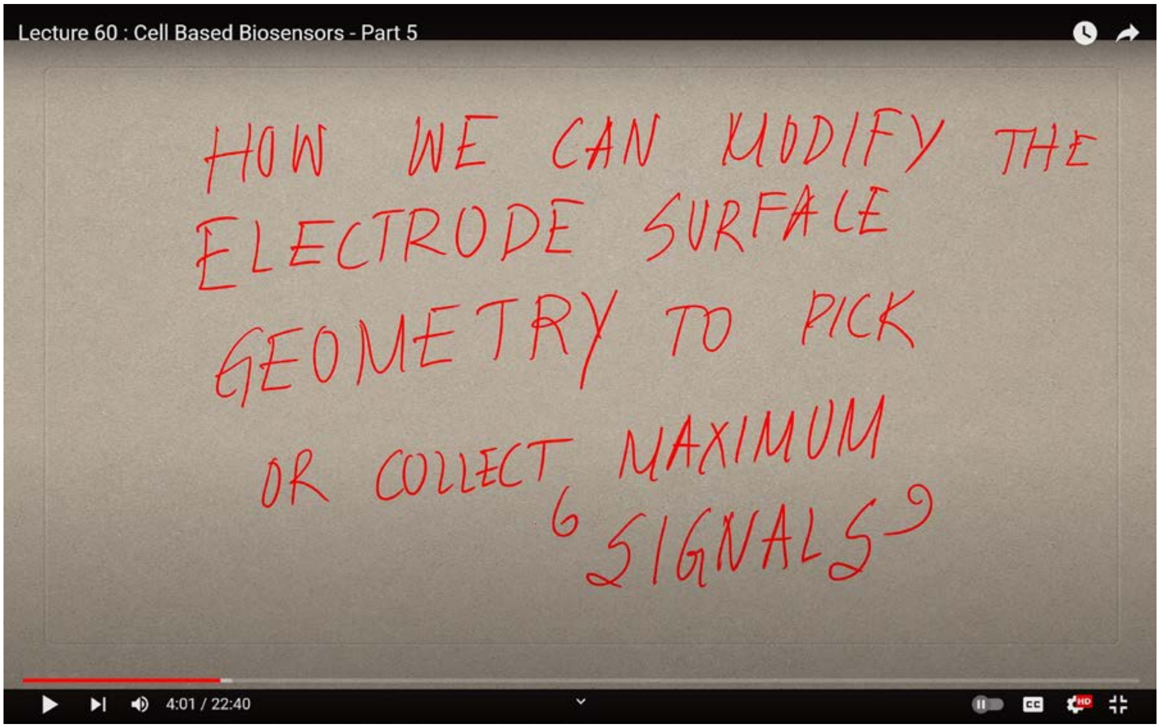

Looking at this scenario, one potential solution is to roughen the electrode surface. Instead of having a smooth surface like this, imagine if the electrode surface had a configuration resembling this. With a roughened surface, the cell might settle in such a way that it establishes more contact points.

Roughening the electrode surface is one of the technological advancements that several research groups around the world are pursuing. By modifying the geometry of the electrode, we can potentially enhance signal collection. This approach is one of many strategies to address the challenges we face in the cell-electrode interface.

The second approach involves a different strategy altogether. Instead of simply roughening the electrode surface, we can alter the interface by incorporating electrical connectors. For instance, imagine introducing electroactive polymers into the design. Picture this: we have our electrode, and on top of it, we are layering some form of electroactive polymer. The cells will then grow on this modified surface, allowing for a more effective interface.

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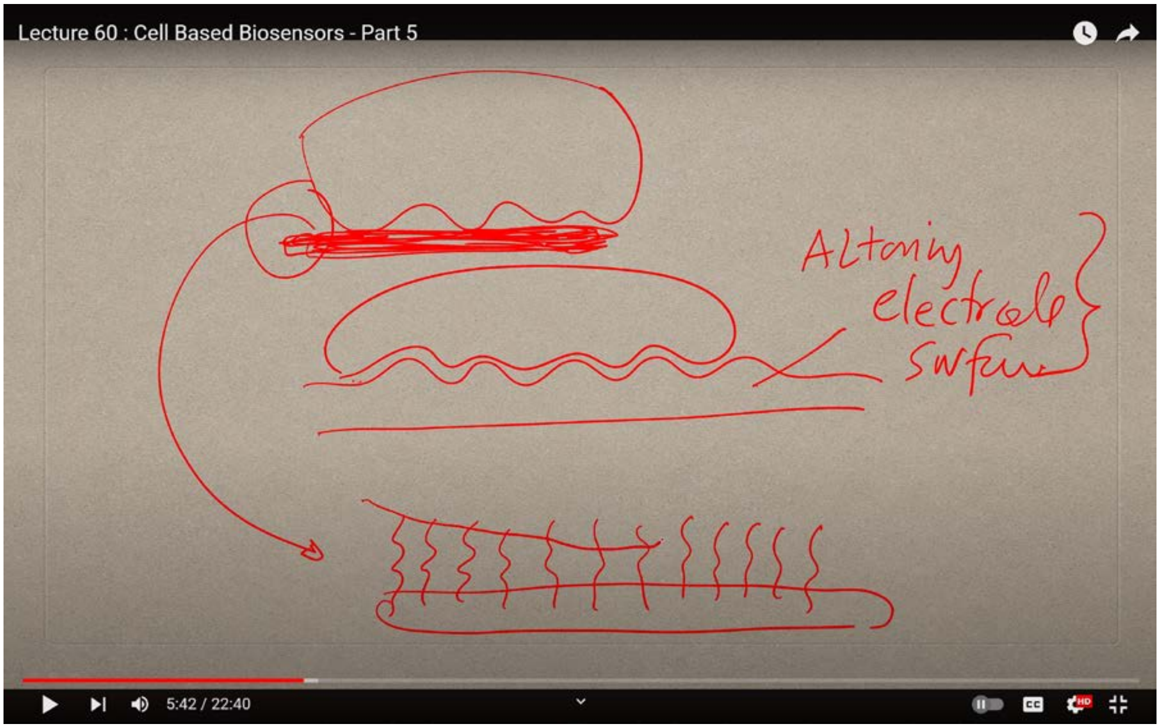

By utilizing these electroactive polymers, we aim to enhance the contact points with the cells, thereby maximizing the signal we can capture. This method becomes particularly valuable when we are employing biomolecules for sensing applications. Initially, we discussed the option of modifying the electrode surface itself to create a rougher texture. Now, we are introducing the concept of electrical "brushes," akin to the bristles of a toothbrush. Envision each bristle as an electroactive polymer; the design allows cells to become trapped within these structures.

It's essential to highlight that throughout this process, we must ensure biocompatibility. Without biocompatibility, integrating these technologies would be impossible.

Another fascinating option is to develop an electroactive sponge coating. This flexible coating is applied over the electrode, enabling the cells to adhere more effectively. This spongy extracellular matrix (ECM) provides yet another means to modify the cell-electrode interface.

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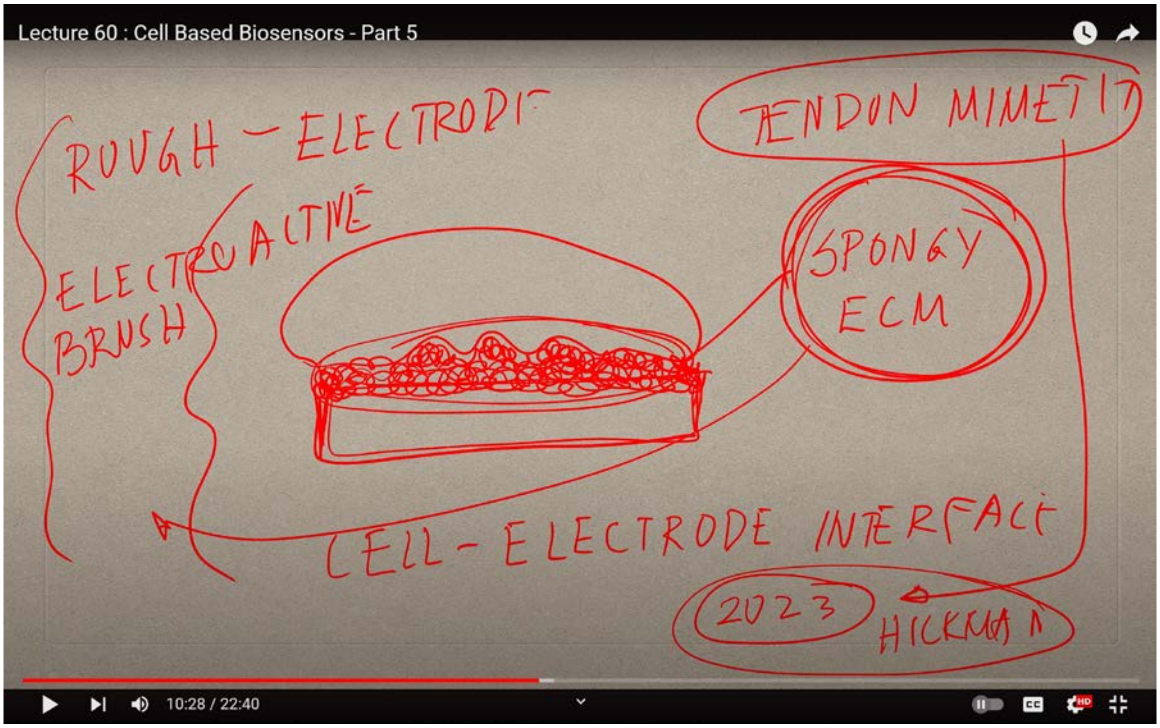

As you can see, there are numerous strategies at our disposal. The ones I've mentioned are just a few examples; there are many more potential approaches. To recap, we have discussed rough electrodes, electroactive brushes, and spongy ECMs. I encourage you to explore recent literature, such as the paper on tendon mimetics in biomaterials science, specifically published in 2023 by the Hickman group. The paper titled "Tendon Mimetic Study for Skeletal Muscle and Cantilever," authored by Zhang and Hickman, is particularly noteworthy. It showcases strategies similar to those we've discussed today.

It's crucial to remember that these strategies are all aimed at minimizing current loss. If there is insufficient contact, we won't be able to record any meaningful data.

Electrodes certainly have their limitations. However, the next frontier in this field is the potential to integrate excitable cells with semiconductors. This innovation could lead to what we might call a true neuron-electronic interface. Back in the 1990s, a groundbreaking paper from Germany explored the integration of field-effect transistors, commonly referred to as FETs, with excitable cells derived from leeches. This work was incredibly fascinating!

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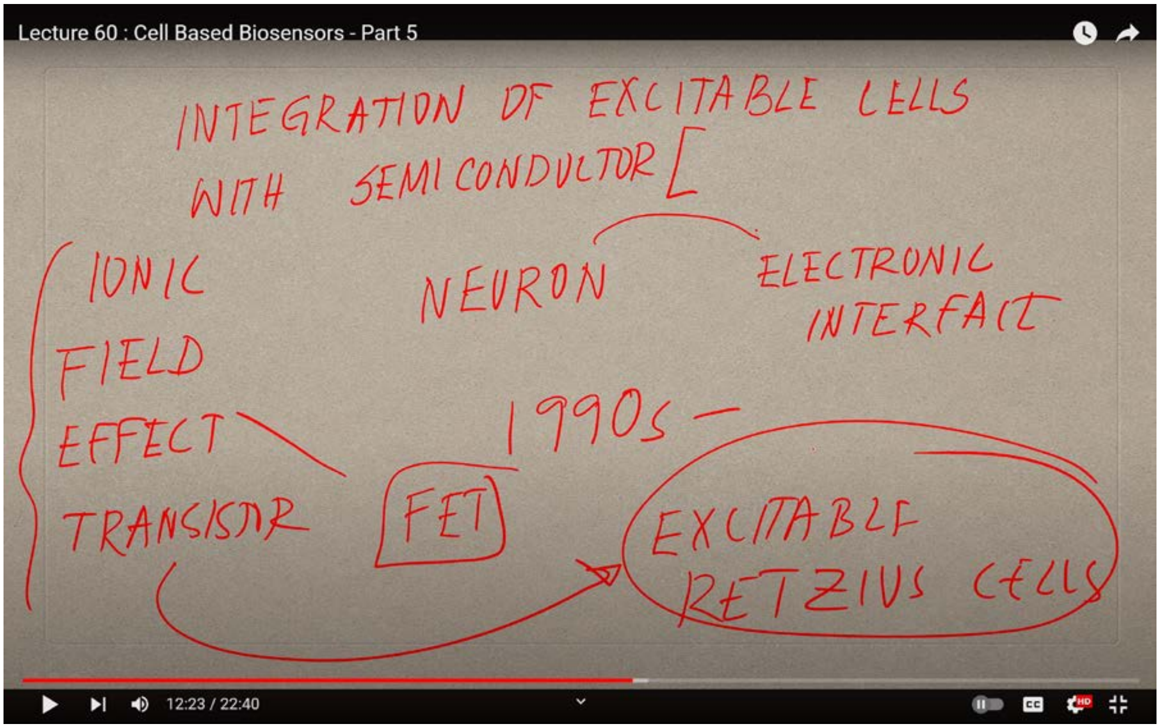

When we discuss semiconductor devices, we're referring to their gates, specifically, N-type and P-type materials. As you might recall, N-type materials have an excess of electrons, while P-type materials have a deficiency. These fundamental properties dictate the flow of electrons through the material. Visualize this: imagine two gates, these are semiconductor gates, within a very small dimensional space.

So, what are field-effect transistors? Essentially, if there's a change in the electric field beneath the gate, it induces a current flow. That's the crux of the concept. For instance, if you have one gate positioned here and another gate positioned there, and if there's a shift in the electric field potential across them, you'll see a corresponding current flow. This forms the foundation of field-effect transistors, where the electric field influences the transistor's activity.

In the studies from the 1990s, they took this concept to a whole new level. We're talking about electrodes in the millimeter range, but the gates were fabricated on a scale that is not visible to the naked eye. They created micro-fabricated transistors, complete with multiple gates. Now, if you place an excitable cell on top of this intricate setup, this single cell above those tiny gates, you can begin to appreciate how many gates could potentially be involved, even if I can only illustrate a few.

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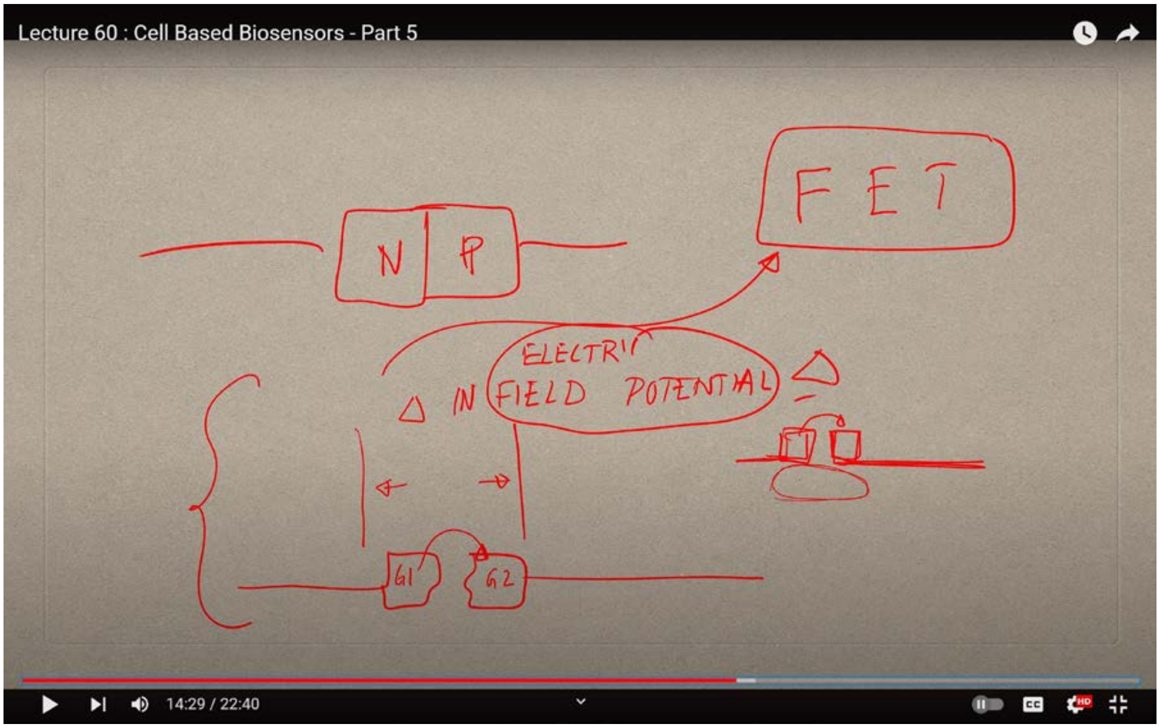

When the cell gets excited, an important phenomenon occurs: there will be a change in the electric field due to the movement of ions within the cell. These gates are designed to sense such changes. To clarify the structure, beneath the visible portion of the setup, there's a black layer where all the gates are located. Above this black layer is an insulating layer, represented in white, and the cells sit atop this insulation.

The key point is that while the insulating layer prevents fluids from contacting the gates directly, it must be sensitive enough to detect any changes happening above it. This intricate design is crucial for ensuring that the gates can accurately sense the ionic mobility triggered by cell excitation. This level of integration between biological systems and electronic components holds incredible promise for the future!

If the gate detects that change, you will observe a current flowing through the system. This marks a historic milestone in human innovation, the first integration of electronic components with neurons. It was a groundbreaking discovery! However, despite its significance, this technology at the cellular level has not gained widespread popularity yet, largely due to the numerous challenges that must be overcome before it can take center stage. This is precisely where we are headed: we are striving to integrate these technologies to bypass the significant challenges posed by the cell-electrode interface.

The cell-electrode interface is indeed a considerable hurdle. Just consider the scale we are discussing, there's a massive cell positioned above a minuscule electrode. If we were to scale down from the electrode dimensions to the gate dimensions, we're talking about a reduction factor of 1,000 to 2,000 times! In that minuscule area, we could potentially fit 100 or 200 gates, with each gate serving as a sensor element.

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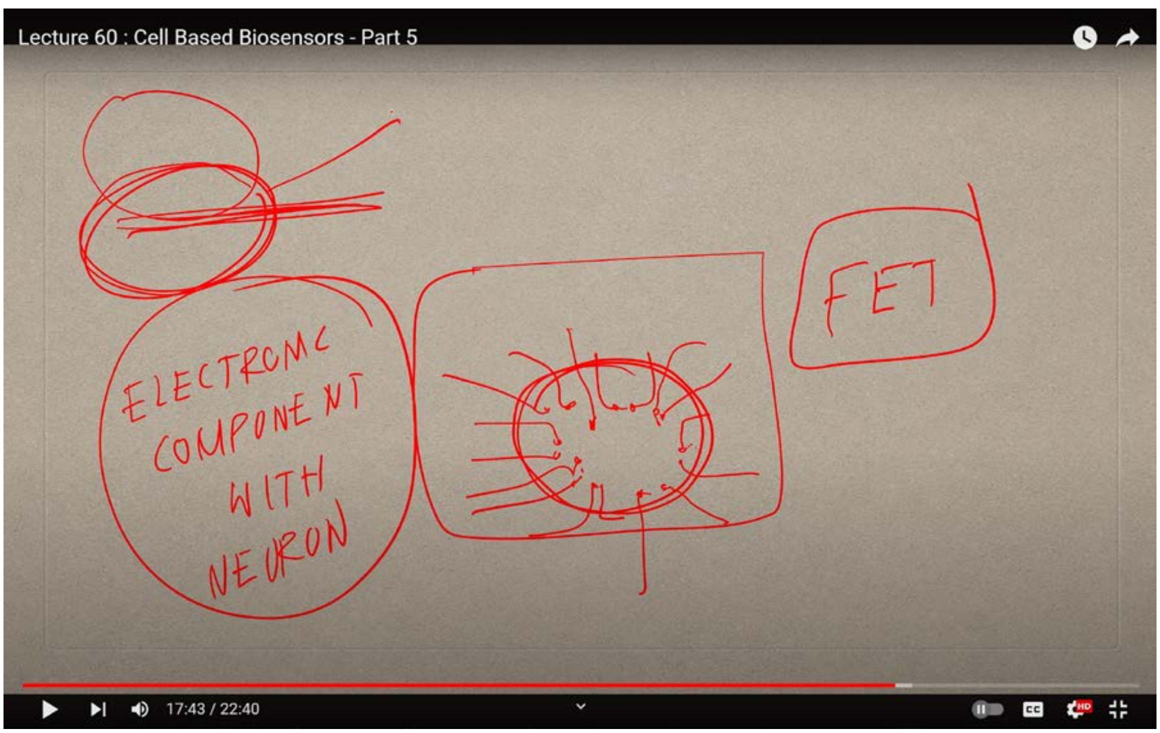

Consequently, the quantity of signals we can gather from this integration of electronics and cells is vastly different from that of an electrochemical system. This discrepancy highlights the real challenge: how can we develop a technology that is not only economical but also maximizes output from the cells? If we succeed in the future, we could directly integrate such systems into the brain or body, allowing electronic systems to provide real-time data.

In this context, we would not merely implant electrodes; we would be implanting a semiconductor chip. Now, looking at this from a reverse angle, consider how we can synthetically create fascinating interactions. When we talk about a chip with gates, changing the voltage across the cell modifies the electrical field, which the gate can sense. Imagine a scenario where we synthetically alter the gate voltage externally. This capability would allow us to perform reverse experiments, observing the electrical activity of the cell while monitoring it from above with a patch electrode.

In our journey, we are moving towards two dimensions. First, extensive research will focus on human-on-a-chip platforms. Simultaneously, a smaller team will dedicate its efforts to integrating cells with electronics. The entire field of biosensors, particularly in biodefense, is advancing along both these pathways. We need enhanced detection tools at multiple levels, compound, molecular, cellular, and even at the level of whole organisms. While human-on-a-chip technologies may eventually replace animal systems due to their precision, significant work will continue in the integration of electronics with cells. In particular, we can expect a tremendous amount of advancement in field-effect transistors, especially ion-selective field-effect transistors, over the next 50 years, leading to entirely new dimensions in this field.

With that, I will conclude this class. I look forward to sharing this journey with all of you, and I believe that through our discussions, we have both enriched our understanding. Thank you!